Synthesis of natural and non-natural terpenoid natural products

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‘There is just one little snag. I have no idea where the Tower of the Swallow is.’

‘Perhaps I’ll find a remedy for that. Do you know, Ciri, what university studies give a person?’

‘No. What?’

‘The ability to make use of sources.’

from

‘The Tower of the Swallow’ by Andrzej Sapkowski

Kurzzusammenfassung

Synthese von Natürlichen und Unnatürlichen Terpenoiden Naturstoffen

Malte Moeller

Schlagworte: Totalsynthese, Terpene, Naturstoffe, STC, Biotransformation, NMR-Spektroskopie

Terpene stellen die größte und strukturell vielfältigste Gruppe von Naturstoffen dar. Sesquiterpene sind für ihren charakteristischen Geruch und Geschmack bekannt und werden in großem Umfang in der Parfüm- und Lebensmittelindustrie verwendet. Sie bestehen aus sich wiederholenden Isopreneinheiten, die durch Kondensation der biosynthetischen Bausteine Isopentenyl- und Dimethylallylpyrophosphat aufgebaut werden. Die einfachen linearen Vorstufen werden dann durch Terpenzyklasen in verschiedene polyzyklische Produkte umgewandelt. In diesen Kaskadenreaktionen durchlaufen die Vorstufen mehrfache Veränderungen in der Konstitution, Hybridisierung und Stereochemie. Diese komplexe Kaskade ist für jede Zyklase einzigartig und führt zu einer großen Vielfalt an möglichen Strukturen.

In dieser Arbeit sollte ein aus Biotransformationsuntersuchungen eines nicht natürlichen FPP-Derivats mit der STC Bot2 gewonnenen Trizyklus synthetisiert werden, um seine Stereochemie zu verifizieren und weitere Eigenschaften durch Derivatisierung zu untersuchen. Zum anderen wurden Farnesylderivate synthetisiert, die Oxidationen an den terminalen Methylgruppen tragen. Damit sind Oxidationen an Positionen gemeint, die später üblicherweise durch enzymatische Folgereaktionen oxidiert werden. Diese Substrate wurden mit Hilfe verschiedener chemischer Verfahren um Doppel- und Dreifachbindungen herum synthetisiert, um die erforderliche Regioselektivität zu gewährleisten. Neue Produkte aus Biotransformationsexperimenten wurden isoliert und ihre Strukturen wurden aufgeklärt.

Abstract

Synthesis of Natural and Non-natural Terpenoid Natural Products

Malte Moeller

Keywords: total synthesis, terpenes, natural products, STC, biotransformation, NMR-spectroscopy

Terpenes represent the largest and most structurally diverse group of natural products. Sesquiterpenes are well known by their distinctive smells and tastes and are used extensively in the perfume and food industries. These are comprised of repeating isoprene units that are constructed by condensation of the biosynthetic building blocks isopentenyl- and dimethylallyl pyrophosphate. The simple linear precursors are then transformed by terpene cyclases to diverse polycyclic products. In these cascade reactions the precursors undergo multiple changes in bonding, hybridization and stereochemistry. This complex cascade is unique for each cyclase leading to a huge variety of different possible structures.

In this thesis, a from biotransformation experiments with unnatural FPP-derivatives utilizing STC Bot2 isolated tricyclus was waimed to be synthesized to verify its stereochemistry and explore further properties *via* derivatization. On the other hand, farnesyl derivatives that bear oxidations at the terminal methyl groups were synthesized. By this, oxidations at positions which would usually be later on oxidized by follow up enzymatic reactions are included. These substrates were synthesized using different kinds of chemistry around double and triple bonds to ensure the necessary regioselectivity. New products from biotransformation assays were isolated and their structures were elucidated.

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List of Abbreviations

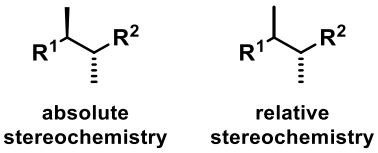
Ac	acyl
aq.	aqueous
Bn	benzyl
brsm	based on recovered starting material
calc.	calculated
cat.	catalytic
CH_2Cl_2	dichloromethane
CI	chemical ionisation
cod	(*cis*, *cis*)-1,5-cyclooctadiene
comb.	combined
conc.	concentrated
Cp	cyclopentadienyl
COSY	correlation spectroscopy
CSA	camphorsulphonic acid
CTP	cytidintriphosphat
DBE	1,2-dibromoethane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
decomp.	decomposition
DHP	dihydropyrane
DIAD	di*iso*propyl azodicarboxylate
DIBAL-H	di*iso*butylaluminium hydride
DIPA	di*iso*propylamine
4-DMAP	4-dimethylaminopyridine
DMAPP	dimethylallylpyrophosphate
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DXP	1-deoxy-D-xylulose 5-phosphate
EE	ethoxyethyl

EI-GCT-HRMS	electron ionization gas chromatography time of flight high resolution mass spectrometry
engl.	English
eq	equivalents
ESI-LCT-HRMS	electron spray ionization liquid chromatography time of flight high resolution mass spectrometry
Et	ethyl
EtOAc	ethyl acetate
Et_2O	diethylether
FPP	farnesylpyrophosphate
GFPP	geranylfarnesylpyrophosphate
GGPP	geranylgeranylpyrophosphate
GPP	geranylpyrophosphate
hex	hexanes
HMBC	heteronuclear multiple bond correlation
HMDS	hexadimethylsilazane
HMPA	hexamethylphosphoric triamide
HSQC	heteronuclear single quantum coherence
imid.	Imidazole
*i*Pr	*iso*propyl
LC-MS	liquid chromatography mass spectrometry
LDA	lithium di*iso*propylamine
LiDBB	lithium di*tert*-butylbiphenylide
*m*CPBA	*m*-chloroperoxybenzoic acid
MEP	methyl-D-erythritol 4-phosphate
Ms	mesylate
NBS	*N*-bromosuccinimide
*n*Bu	*n*-butyl
n.c.	no conversion
NCS	*N*-chlorosuccinimide
n.d.	not determined
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy

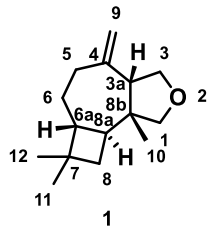
NPs	natural products
o/n	overnight
org.	organic
PE	petrol ether
PG	protection group
Ph	phenyl
pin	pinacolate
PMB	*p*-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
PT	5-phenyl-1*H*-tetrazol
ref	reference
R_f	retention factor
rf	reflux
RNA	ribonucleic acid
rt	room temperature
s.	see
sat.	saturated
soln.	solution
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
*t*Bu	*tert*-butyl
TES	triethylsilyl
Tf	triflyl
Th	thiophenyl
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	tri*iso*propylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TPP	thiaminpyrophosphate
Trt	trityl

Preliminary Remarks

In the schemes and figures in this thesis the following definition of absolute and relative stereochemistry is used. Wedged bonds show the absolute configuration of a stereocenter, bar-type bonds show the relative configuration of a stereocenter.

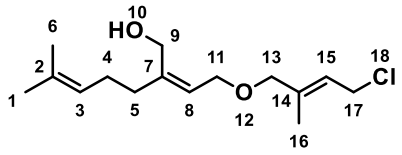


The numbering of the molecules in the following synthesis follows the numbering by the IUPAC-rules for the final compound **1**.



1

The numbering of the molecules in the following synthesis of the biosynthesis precursors follows the numbering by the IUPAC-rules for the final compound **2**.



2

1 Introduction

1.1 On the History of Total Synthesis

Since ancient times the medicinal use of herbs and plants was known among all major human cultures. Already used in the traditional Chinese medicine, it was realized that different parts of a plant contain different substances which can be used for various treatments. The common method was to extract aetheric oils from the plants which then were administered as a tea or other forms of treatments. One example is the use of licorice root against indigestions or bronchitis.[1–3] With increasing knowledge of natural sciences and technology, the interest in creating biologically active compounds grew. On one hand, alchemy mostly focused on creating metal-based compounds, for example gold. On the other hand, entering the 19th century industrial revolution brought chemistry in a brighter light and the success story of organic chemistry begun. Most chemists focused on identifying and then creating those active compounds from known medicinal plants, now well known as total synthesis – art and science at the same time. In order to understand the great importance of this field, the development of chemistry can be demonstrated examining natural products which were synthesized during the last three centuries.[4] Starting in the early 19th century, Friedrich Wöhler was the first to describe a chemical synthesis, here of urea (**3**) in 1828 (s. figure 1). He used cyan acid and liquid ammonia to form artificial urea which, as he described, has the same properties as the one isolated from urine.[5] Later in, 1845 Kolbe was the first to use the word "synthesize", when he made artificial acetic acid (**4**).[6] 45 years later Emil Fischer synthesized glucose (**5**) as the first molecule containing stereogenic centers.[7] Entering the 20th century, more and more molecules were synthesized, also accessing more complex structures which were offered by the natural products classes of terpenes and alkaloids. For example, two syntheses of camphor (**6**) were published in 1903 and 1904, respectively by two independent groups, namely of Komppa and Perkin.[8,9] **6** is a very interesting target as it is the first molecule which contains a stereocenter and a bridged ring system which is formed in both syntheses. Almost at the same time, alkaloid tropinone (**7**) was synthesized by Willstätter and Robinson facing similar challenges.[10,11] Robinson's synthesis is worth an extra note, as it was proposed in a single step synthesis of **7** starting from succindialdehyde, methylamine, and the calcium salt of acetonedicarboxylic acid.[11] The Pre-World War II era was then closed with the outstanding syntheses of haemin (**8**) by Fisher in 1929[12] and a synthesis of the steroid hormone equilenin (**9**) by Bachmann in 1939.[13] Already three chemists from this era were awarded with a Nobel Prize: E. Fischer in 1902, H. Fischer in 1930 and R. Robinson in 1947.[14] After the Second World War, the era of two masters of synthesis begun. Starting with R. Woodward who was a Professor at Harvard university and later also a Nobel laureate[14] for developing the Woodward-Hoffmann-rules.[15–18] He was a great mind who understood to transform his observations into general rules thus bringing total synthesis onto a

new level. Furthermore, he also started using synthesis as a method for structural elucidation for which it is used still today.[4]

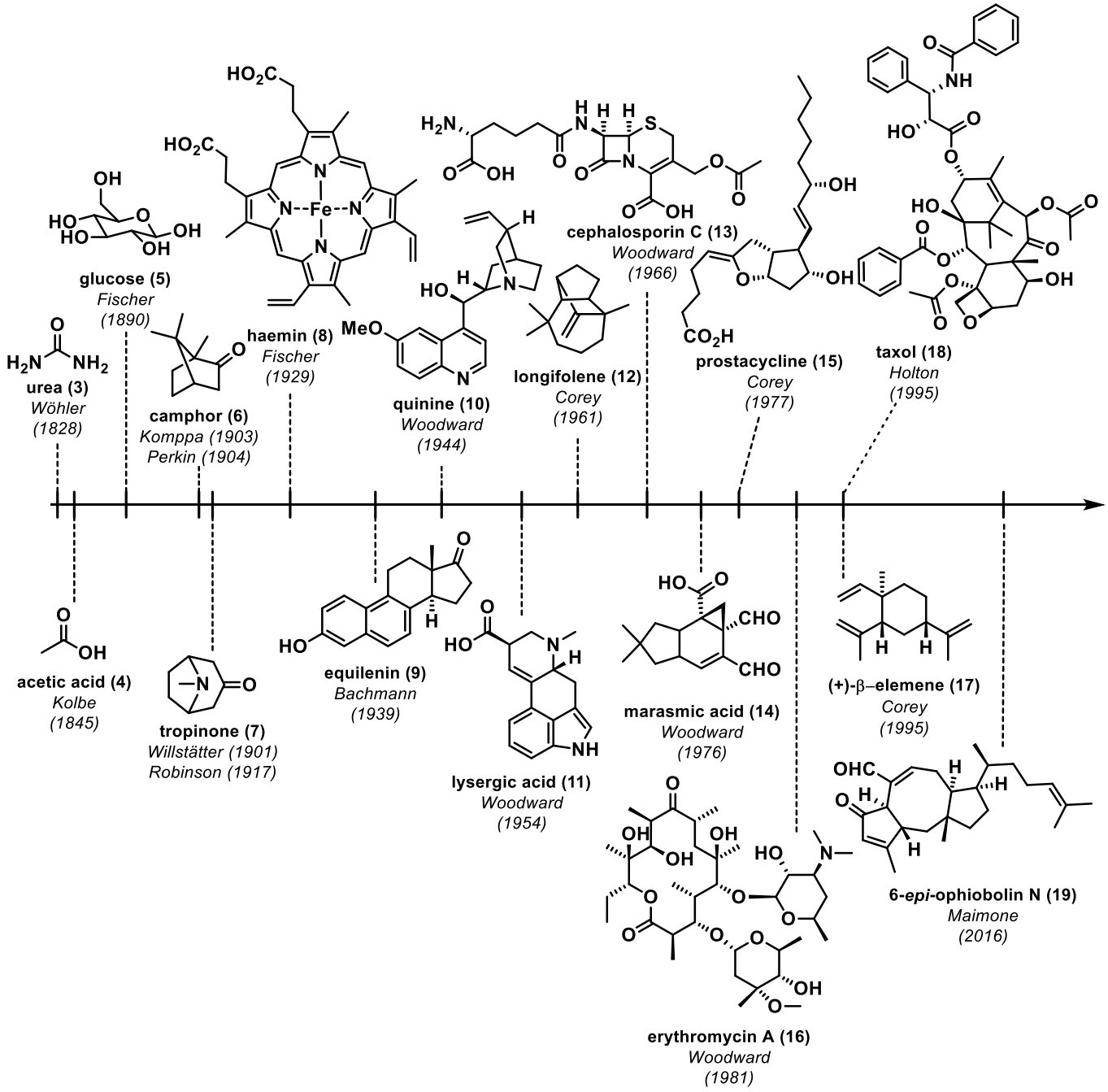


Figure 1: Timeline showing selected landmark total syntheses of the last two centuries.

Woodward's first accomplishment was the synthesis of the alkaloid quinine (**10**) which marks the beginning of his career.[19] After that he finished several total syntheses, including alkaloid lysergic acid (**11**) in 1954,[20] β-lactam antibiotic cephalosporin C (**13**) in 1966,[21,22] terpene marasmic acid (**14**) in 1976[23–25] and polyketide erythromycin A (**16**) in 1981[26–28] as one of his last landmarks, contributing syntheses to all major natural product classes. One of the main themes in his syntheses is the use of rings to control stereoselectivity.[4] Overlapping in the same time a second incredible

mind started his professional career at Harvard University, E.J. Corey. His work was determined by sharp retrosynthetic analysis for which he defined specific rules[29] and he invented several new synthetic methods.[30] For the first time, he applied his own rules in the synthesis of longifolene (**12**) in 1961.[31] Around 100 total syntheses, e.g. his famous prostacycline (**15**) synthesis in 1977[32], were published under his guidance in the 30 years of hard work starting from his first synthesis until 1990, the year of his Nobel prize.[14] Corey did not stop at this point, he continued synthesizing more and more compounds, also complex terpenes like (+)-β-elemene (**17**) in 1995.[33]

In all these years, both styles and knowledge were transferred into other groups applying these ideas of chemical synthesis leading to the accomplishment of more and more complex synthetic targets. The first and famous synthesis of taxol (**18**) by the Holton group is only one example of many to be mentioned.[34,35] Nowadays, still new synthesis of novel and long known structures are published but also of already synthesized compounds applying new methodologies. One example is here the synthesis of 6-*epi*-ophiobolin N (**19**) by Maimone in 2016 whereas he reduced the step count to nine steps in total. This is a remarkable result in the field of complex natural product synthesis.[36]

Thus, improving scientific skills and technique lead to novel beautiful results similar to painting an old majestic picture again just by looking from a different perspective and angle using new materials recreating the original as a better version of itself.

1.2 Natural Products

In the section above the story of synthesis of natural products was told. The reader though might have the following question: What is a natural product and why are they of interest for mankind?

Natural products (NPs) are molecules containing an intrinsic biological functionality. Generally, there are two classes of NPs, primary and secondary metabolites which can be divided into further subclasses. While primary metabolites are necessary to sustain the viability of the organism, secondary metabolites are not needed for the direct survival of the organism.[37] An overview of the different classes is shown in figure 2. On the one hand, there are primary metabolites like fatty acids, nucleobases, sugars and amino acids as the individual building blocks. Each for itself or as combination of those form larger organic compounds like nucleic acids (DNA or RNA), carbohydrates, lipids and proteins (blue part in figure 2). These are all compounds a cell depends on to maintain and replicate. On the other hand, there are secondary metabolites (red part in figure 2) like phenylpropanoids, alkaloids, polyketides and terpenes. These classes of molecules strongly distinguish themselves in structure and size making them a large library of compounds generated from different intermediates of the

metabolism. Each class has a unique building block which can be found in any NP generated in this subclass. For example, alkaloids frequently bear a tertiary nitrogen atom.[38]

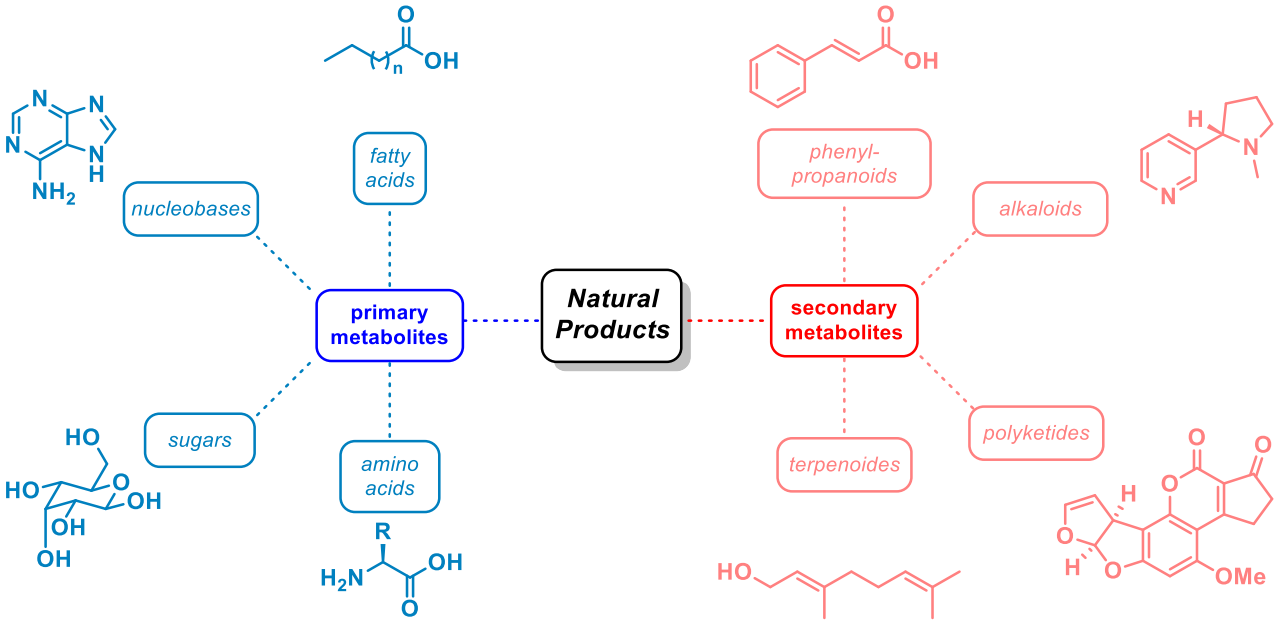


Figure 2: Classification of NPs with examples for every subclass.

Herein, the focus is set on NPs which are secondary metabolites produced by different kind of sources, e.g. animals, micro-organisms and plants thus leading to very versatile structural motives.[39] They are a result of the interaction of the organism with its environment, as these metabolites assist and improve the producing organism to survive, therefore giving it an advantage against competing organisms. These properties can be used in the development of pharmaceuticals. Often directly NPs or derivatives of it are used as agents. These derivatives contain the pharmacophore – which is the part of the molecule which is necessary for the pharmaceutical activity[40] - and are designed by total synthesis.[41–44] One of these classes are the terpenoids mostly produced by plants featuring more than 50,000 entities making them very interesting as a synthetic target.[45] Hence, this thesis will focus on this kind of NPs.

1.3 Natural Terpenoids

1.3.1 General

The word terpene is derived from the German word "*Terpentin*" (*engl*. terpentine or turpentine) which describes a fluid isolated from trees, primarily pines. It was at first used by German chemist August Kekulé in 1866.[46] This fluid contained different hydrocarbons all having the general formula of $(C_5H_8)_n$ in common. Next to terpenes, there are also terpenoids which also cover terpenes bearing heteroatoms mainly oxygen derivatives. Unfortunately, both terms are often used interchangeably.

Nevertheless, terpenoids and terpenes often have similar biological functionalities. Mostly, these secondary metabolites are either used to create fragrances, scents, tastes or bioactive compounds like steroids. A selection of some terpenes and terpenoids is shown in figure 3.[47] The smallest terpene is called isoprene (**20**), it is also the building block which forms all other terpenes (s. below). The classic smell of pine wood is generated by α-pinene (**21**) but it can be also found in other plants. Carvone is an interesting example for the effects of stereochemistry on biology, as both enantiomers have a very distinct scent: While (+)-carvone (**23**) has the smell of caraway seeds, (-)-carvone (**24**) smells like spearmint. Terpenoid arteminsinine (**24**) is produced by the plant sweet wormwood (*Artemisia annua)* used as a malaria treatment.[48] Lanesterol (**25**) is the precursor for most tetracyclic steroids. Most of these terpenes and terpenoids are obtained by extracting the ethereal oils from the plants.

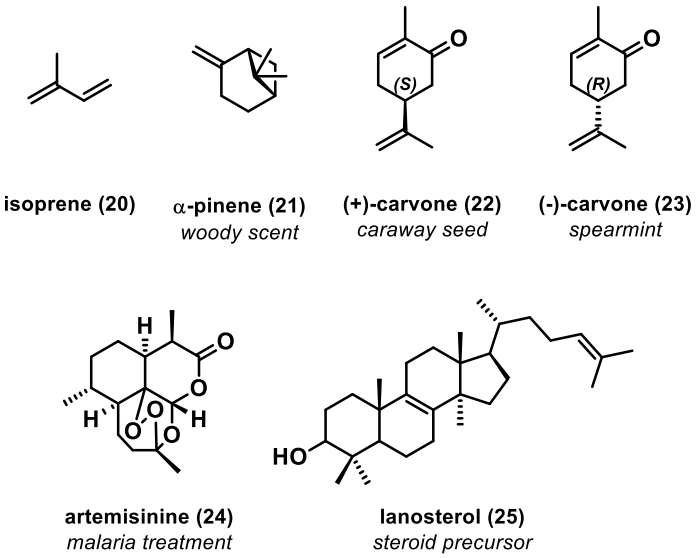


Figure 3: Selected examples of terpenes and terpenoids with their use.

As mentioned above, terpenes are built up by combination of isoprene subunits. German chemist Otto Wallach was the first to observe this pattern in 1909.[49] Later on, Leopold Ružička framed the so called isoprene-rule "*which states that the carbon skeleton of the terpenes is composed of isoprene units linked in regular or irregular arrangement*."[50] Sometimes in the biosynthesis of these cyclic terpenes, methyl shifts or Wagner-Meerwein-rearrangements can occur leading to very divers structures starting from the linear precursors.[50] The general pyrophosphates which are needed to build up these terpenes are shown in figure 4 with the containing isoprene units marked in red.

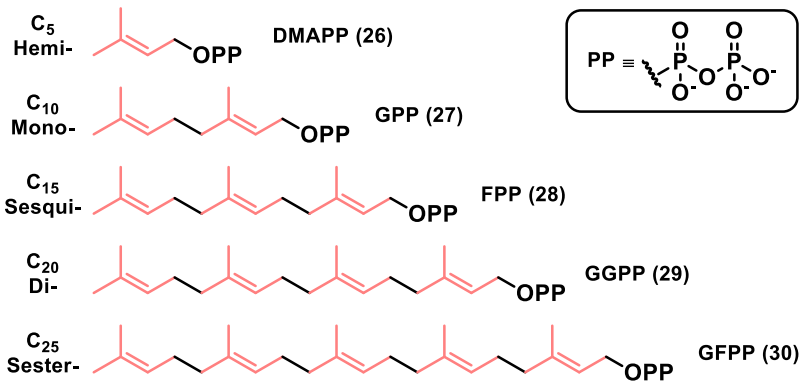


Figure 4: Linear pyrophosphate precursors with the marked isoprene units in red (DMAPP = dimethylallylpyrophosphate, G = geranyl, F = farnesyl, PP = pyrophosphate).[51]

Based on the number of isoprene units, terpenes are divided into classes, regarding hemiterpenes for C_5-based ones, mono- for C_{10}, sesqui- for C_{15}, di- for C_{20} and ester- for C_{25}. These elongated terpenes are formed in nature by combination of DMAPP (**26**) with IPP (**31**) catalyzed by prenyltransferases. The linkage takes place by combination of the head, which is the dimethyl-end, and the tail, which is the ethylpyrophosphate-end, of a hemiterpene, so called *head to tail* elongation (s. figure 5).[47,51]

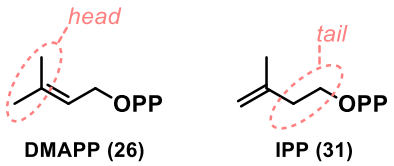
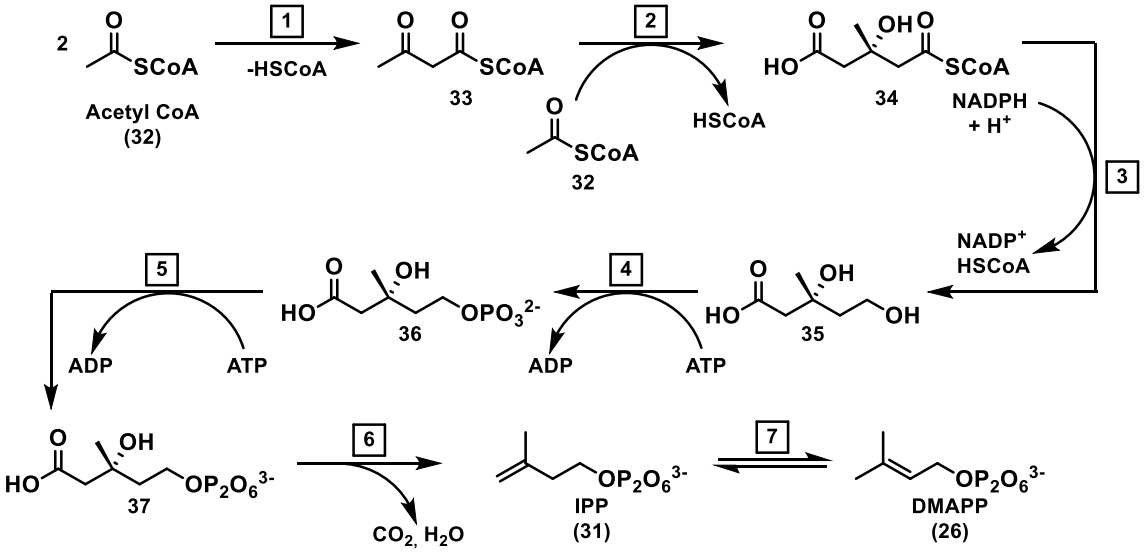


Figure 5: Structures of general terpene building blocks DMAPP (**26**) and IPP (**31**) with the marked ends in red.

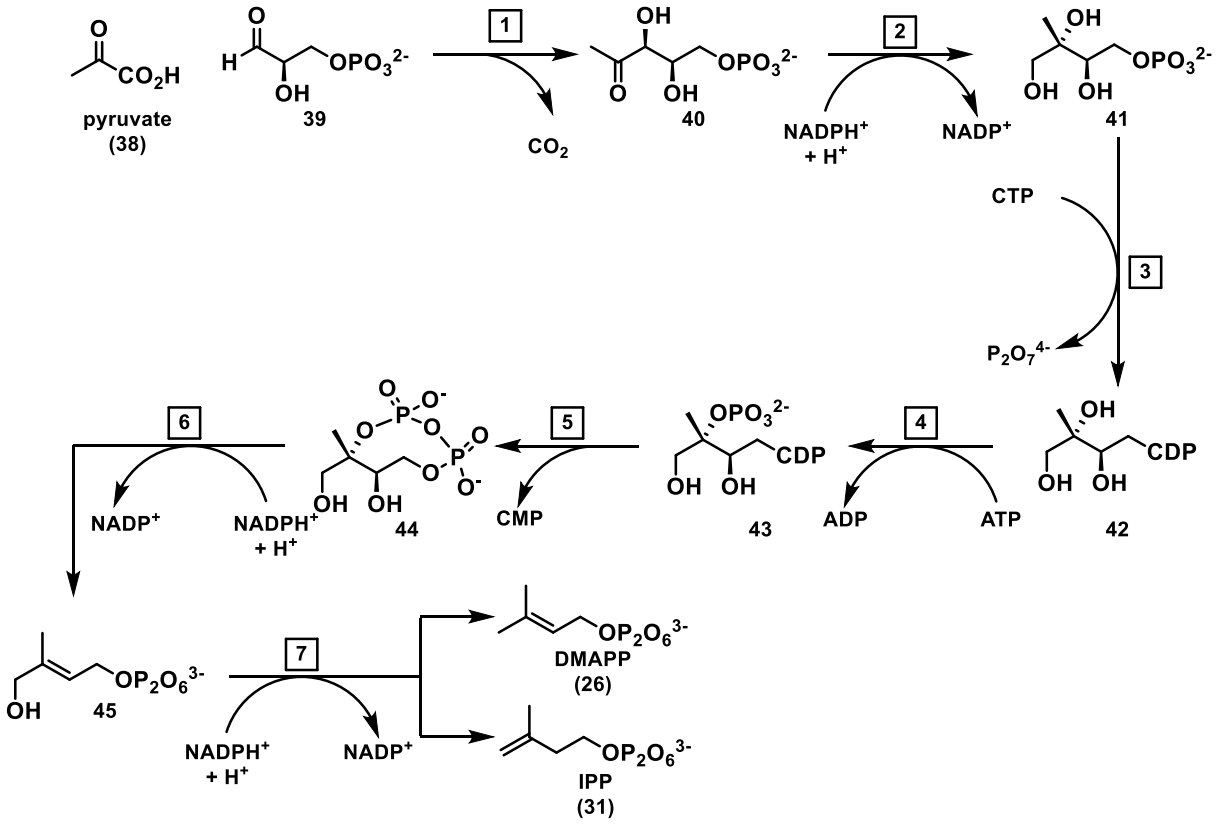
1.3.2 Biosynthesis of Farnesol



Scheme 6: Overview of the mevalonat pathway: 1) acetoacetyl-CoA-thiolase, 2) HMG-CoA-synthase. 3) HMG-CoA-reductase, 4) mevalonate-5-kinase, 5) phosphomevalonate kinase, 6) mevalonate pyrophosphate decarboxylase, 7) isopentenyl pyrophosphate isomerase.

As mentioned above, basic linear terpenes are produced by the combination of DMAPP and IPP. These C_5-bodies can be formed by two different pathways, mainly through the cytosolic mevalonate pathway or additionally in some bacteria, plants or green algae through the methyl-D-erythritol 4-phosphate pathway (MEP-pathway).[51–53]

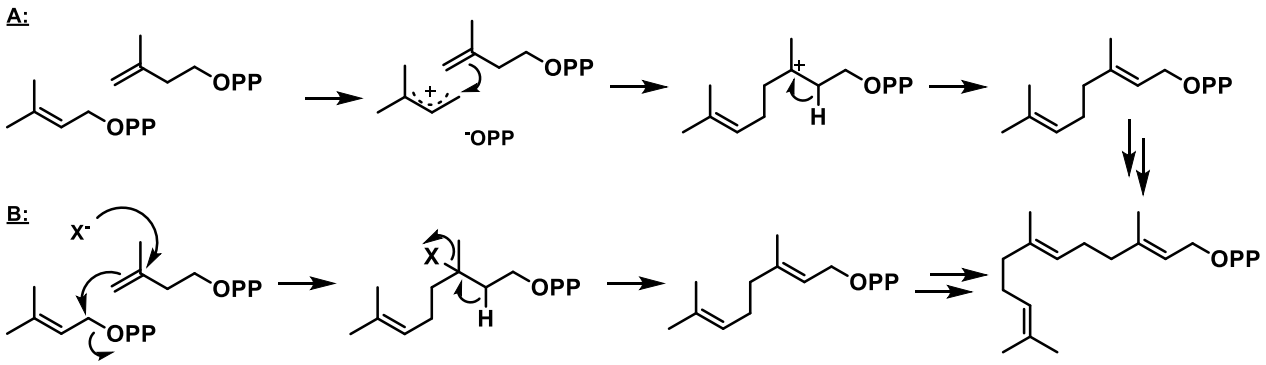
The mevalonate pathway is shown in scheme 6. It starts with a Claisen condensation of two molecules of acetyl-CoA (**32**) that is catalyzed by the acetoacetyl-CoA-thiolase to from acetoacetyl-CoA (**33**). **33** is then condensed with another molecule acetyl-CoA to form HMG-CoA (**34**) by the HMG-CoA-synthase. **34** is reduced to mevalonic acid (**35**) by the HMG-CoA reductase under consumption of one equivalent of NADPH + H^+. The generated primary alcohol is then phosphorylated in two steps to yield pyrophosphate **37** via phosphate **36**, each with consumption of one equivalent of ATP. In the end, **37** is decarboxylated with elimination of water to form IPP (**31**). The isomerization between IPP and DMAPP is catalyzed by the isopentyl pyrophosphate isomerase.



Scheme 7: Overview over the MEP-pathway: 1) DXP synthase, 2) DXP reductoisomerase, 3) 2-C-methyl-D-erythritol 4-phosphate cytidylyltransferase, 4) 4-diphosphocytidyl-2-C-methyl-D-erythritol kinase, 5) 2-C-methyl-D-erythritol 2,4-cyclodiphosphate synthase, 6) (*E*)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate synthase, 7) (*E*)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate reductase.

Alternatively, the MEP-pathway starts with a thiaminepyrophosphate (TPP) catalyzed reaction when pyruvate (**38**) and glyceraldehyde 3-phosphate (**39**) are combined to yield 1-deoxy-D-xylulose 5-phosphate (**40**) after decarboxylation. **40** is then transformed into 2-C-methylerythritol 4-phosphate (**41**) using one quivalent of NADPH. Next, the phosphate is activated by converting it into the CDP-analogon **42**. **42** is transformed into cyclic pyrophosphate **44** by phosphorylation with an equivalent of ATP to allow the subsequent elimination to access (*E*)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (**45**) with consumption of one equivalent of NADPH. In the end **45** is transformed either into DMAPP (**26**) or IPP (**31**) by a reductase and conversion of a final equivalent of NADPH.[54–56]

The combination of IPP and DMAPP is enabled by isoprenyl diphosphate synthases or so called prenyltransferases. For example, the farnesyl diphosphate synthetase (FPPSase) is a classic member of this family as it accepts DMAPP as the initial allylic building block. Then two quivalents of IPP are attached in head to tail fashion to form all-*trans* farnesol. The chain elongation either proceeds in an ionization-condensation-elimination mechanism (A) or alternatively a condensation-elimination mechanism (B, s. scheme 8). In an iterative process FPP is obtained.[57,58]

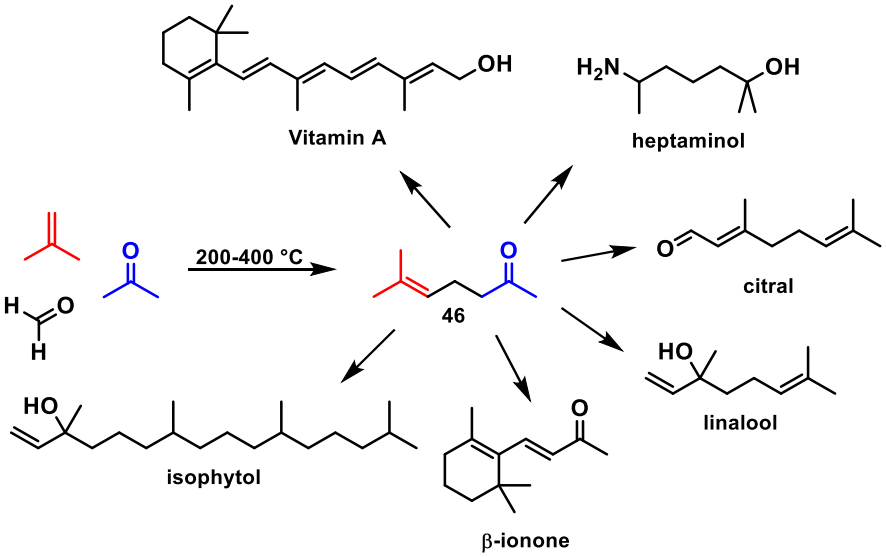


Scheme 8: Possible mechanisms of the synthesis of FPP.

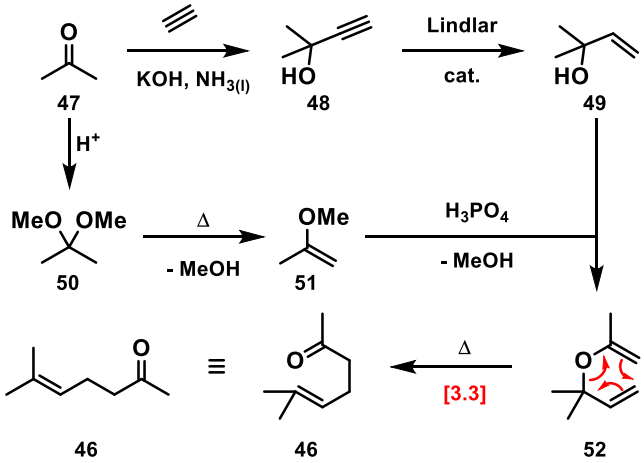
1.3.3 Industrial Synthesis of Terpenes

After learning how nature produces terpene precursors, it is interesting to understand how mankind generates smaller terpenes. Until now different synthesis of farnesol and its double bond isomers were described by various groups. The methods reach from Wittig-olefinations to cross coupling reactions of vinyl triflates and sigmatropic rearrangements.[59–62] The letter is interesting as sigmatropic rearrangements are also part of several industrial syntheses of terpene building blocks. A few examples will be explained next. One of the major building blocks is methylheptylketone that can be transformed to a variety of possible products (s. scheme 9).[63,64] It is generated in a multi component reaction from acetone, *iso*butene and an aqueous solution of formaldehyde. Another possibility to

synthesize **46** is the La Roche-Hoffmann process that is depicted in scheme 10. This sequence uses a mixture of acetone and acetylene to form alcohol **48** under Faworski-Babayan conditions or in a high pressure reaction followed by reduction to 3-methyl-1-buten-3-ol (**49**) using the Lindlar catalyst. On the other hand, acetone is transformed into enolether **51** using methanol and *p*TsOH as a catalyst. Both fragments are combined under acidic catalysis of phosphoric acid to furnish allyl vinyl ether **52** that undergoes a [3.3]-sigmatropic rearrangement upon heating at 200 °C to from methylheptylketone.[65]



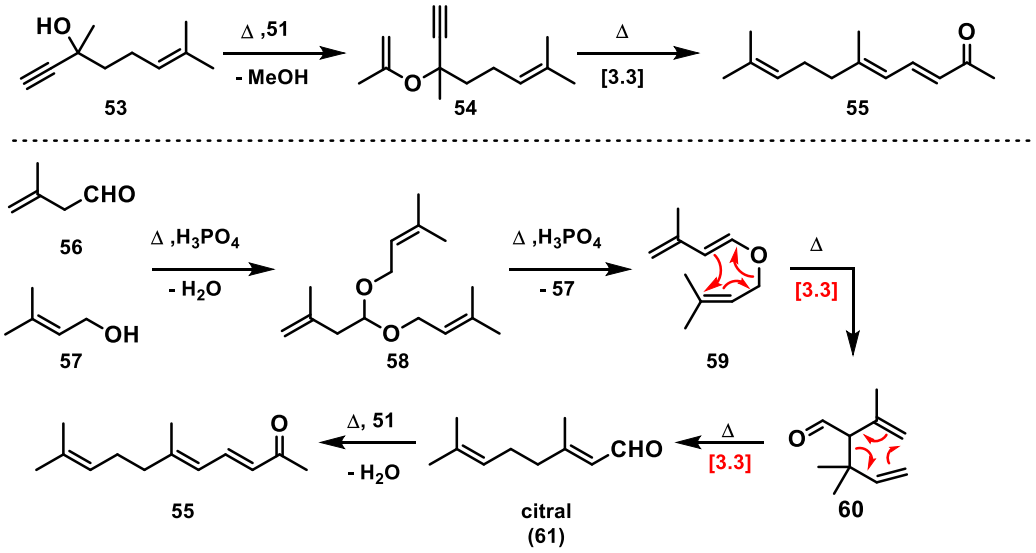
Scheme 9: Synthesis of methylheptenone which is finalized by a double bond isomerization with a nobel metal catalyst and products formed from it.



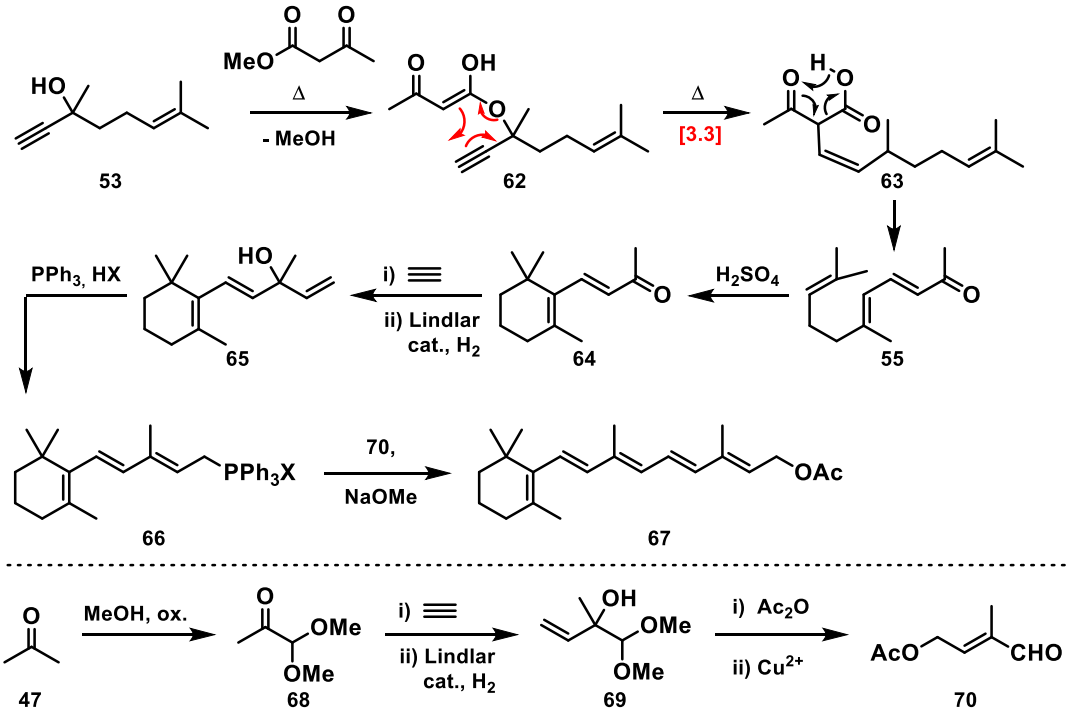
Scheme 10: Overview over the Hoffman-La-Roche process to synthesize methylheptylketone.

When this process is performed iteravely, at first linalool is obtained and then later on farnesol.[65] Also, when the reduction with the Lindlar catalyst is skipped, dehydrolinalool (**53**) is obtained which is transformed again with an enolether to precursor **54** that undergoes a sigmatropic rearrangement to

yield pseudoionone (**55**).[66] Another interesting approach containing a series of sigmatropic rearrangements is the BASF synthesis of citral (**61**) as shown in scheme 11. In the beginning, an acetal is formed that undergoes a 1,2-cleavage (or 1,4-cleavage when its isomeric acetals are used) to generate vinyl allyl alcohol **59** under acid catalysis. Now, the Claisen rearrangement takes place to give **60** which undergoes the Cope rearrangement to yield citral (**61**). In the end, a condensation with acetone takes place to yield **55**.[67,68]



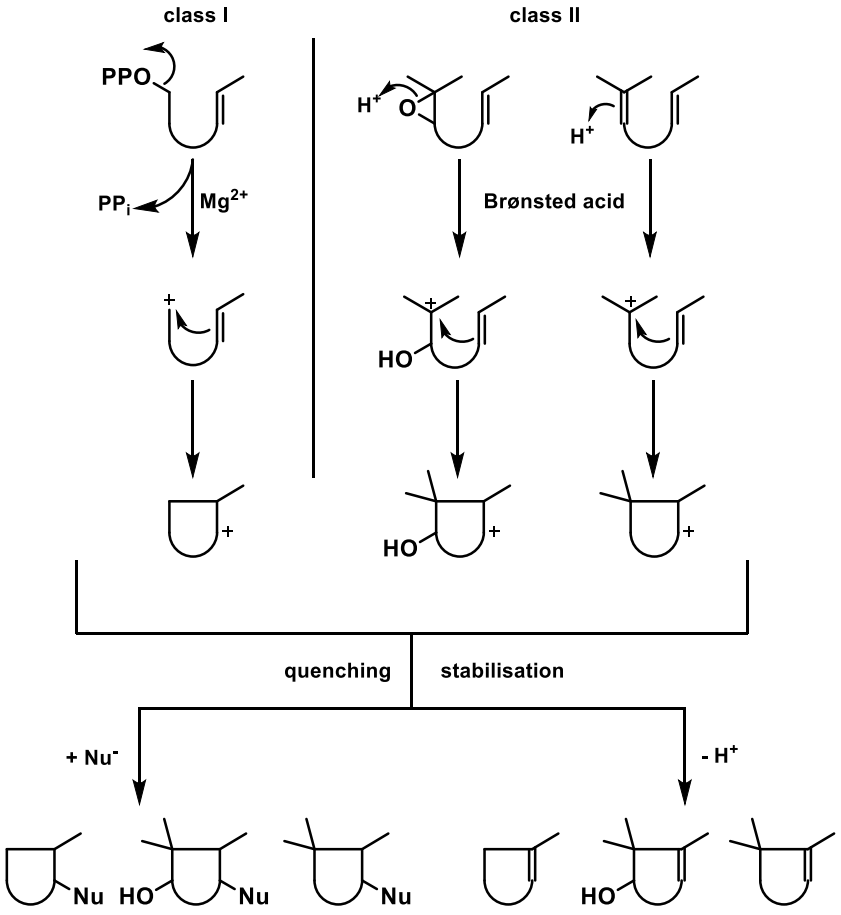
Scheme 11: Syntheses of pseudoiodonone *via* sigmatropic rearrangements.



Scheme 12: Synthesis of pseudoiodonone (**55**) *via* a Carroll reaction and synthesis of vitamin A acetate *via* BASF's procedure containing a Wittig-reaction.

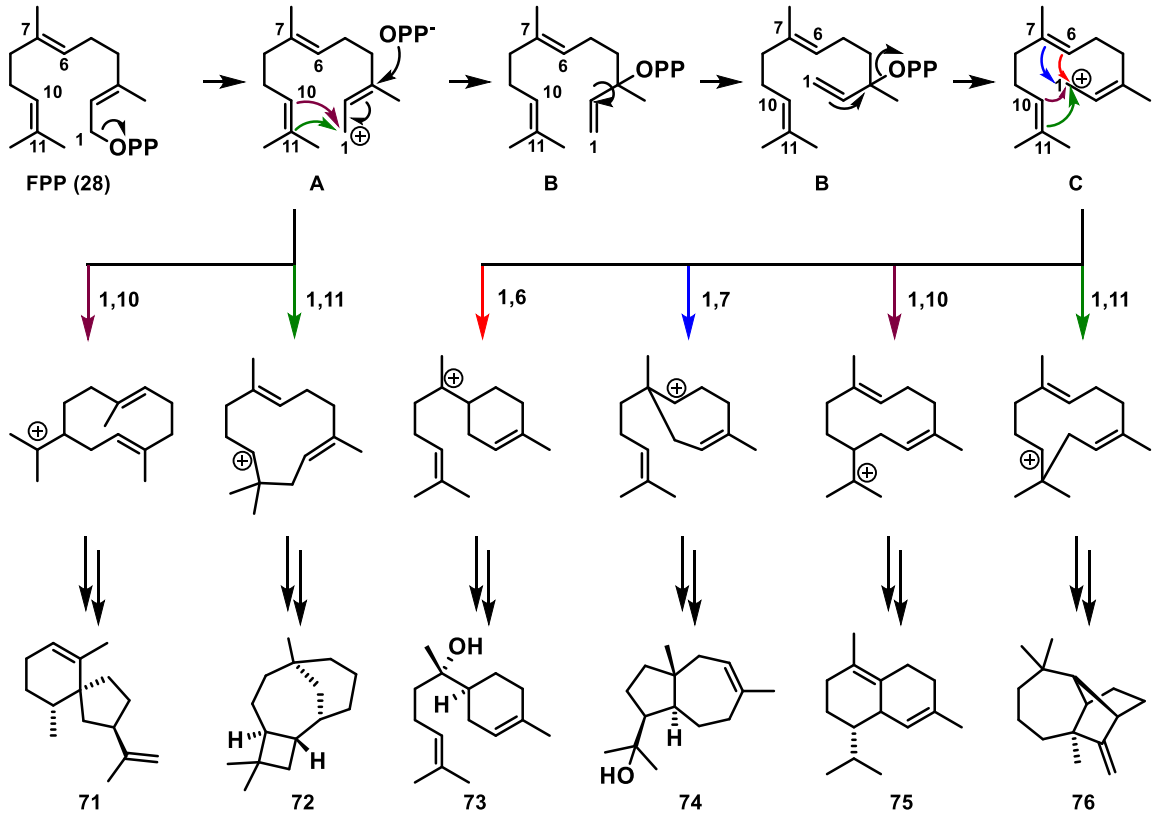
Alternatively, **55** can be obtained by a Carroll reaction of **53** with acetoacetate (s. scheme 12). Hereby, CO_2 is liberated to give pseudoiodonone (**55**) after a sigmatropic rearrangement.[63,69] Then, **55** is cyclized to β-iodonone (**64**) *via* H_2SO_4 catalysis. Ketone **64** is transformed into C_{15}-salt in a few steps involving addition of acetylene followed by partial reduction with hydrogen gas and rearrangement of vinylalcohol **65** under acid catalysis in the presence of triphenylphosphine to yield salt **66**. This was purified to remove side products which could not be removed by distillation in the previous steps of this synthesis. On the other hand, C_5-acetate **70** is generated by oxidation of acetone in the presence of methanol and a nitrosation reagent to give **68**. Again, addition of acetylene under high pressure conditions and partial reduction results in C_5-alcohol **69**. This is acetylated followed by rearrangement using Cu^{2+}-ions and upon acetal cleavage C_5-ester **70** is obtained. The Wittig olefination is performed with sodium methylate as a base giving a 7:3 ratio of *trans/cis*-products. The undesired *cis*-isomer can be isomerized to the corresponding all-*trans* isomer **67** using iodine. This is necessary to guarantee an economic process.[63,68,70]

1.3.4 Products of Terpene Cyclases



Scheme 13: Principle mechanism of cyclzation of class I and II terpene cyclases.

After a small digression on industrial synthesis methods of terpenes, the focus is back on how nature produces complex terpenes from its simple precursors. Generally, enzymes so called terpene cyclases transform pyrophosphates into terpenes creating a large structural diversity. Mainly, there are two types of cyclases: While mono- and sesquiterpene cyclases belong to class I and the cyclization cascade is initiated by activation of the pyrophosphate with Mg^{2+} ions leading to the formation of the initial carbocation. Triterpene cyclases on the other hand belong to class II and the cyclization cascade is initiated by protonation of an epoxide or olefinic double bond using a Brønsted acid, often promoted by an aspargic acid residue. Both principal mechanisms are shown in scheme 13. [51,71] After formation of the initial cation an attack of another double bond occurs leading to the formation of a new tertiary cation. Before the cascade is terminated by addition of water or elimination of a proton leading to either an alcohol or an alkene. An addition, methyl- or hydride shifts can occur in between. In the following the focus is based on class I TCs, specifically as sesquiterpene cyclases play the main role in this thesis.



Scheme 14: Overview over the cyclization cascade, catalyzed by STCs and possible skeletons.

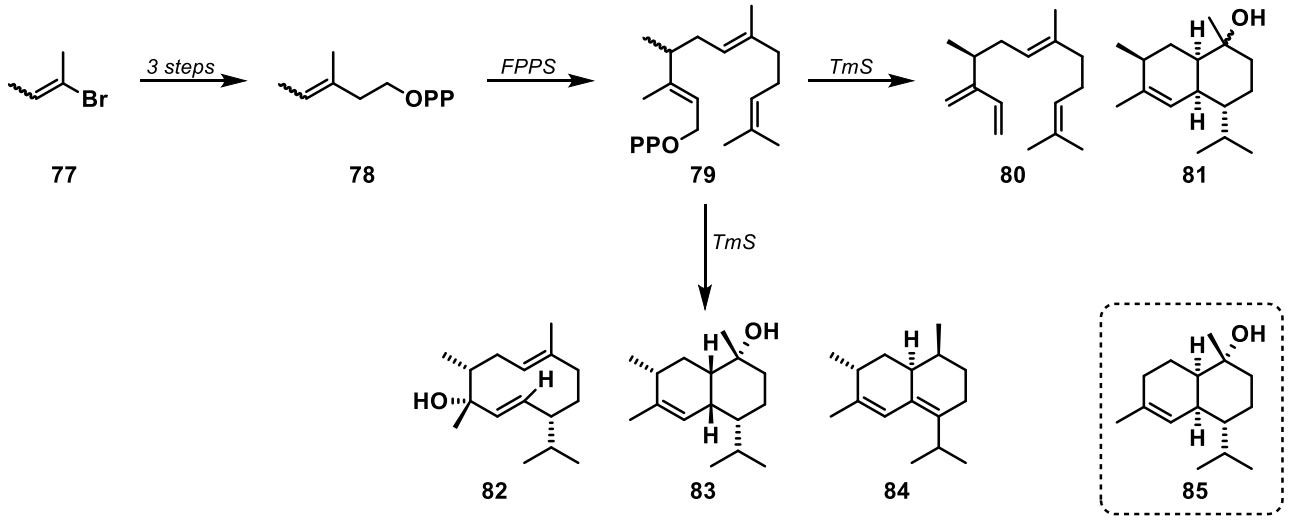
In scheme 14, the basic cyclization mechanism of FPP is shown. Initially, the allylic farnesylcation (**A**) is formed by abstraction of the pyrophosphate under catalysis of Mg^{2+} ions. This cation can undergo a 1,10- or 1,11-cyclization leading to different cations. Alternatively, the pyrophosphate moiety can attack the cation at the C3-position leading to (*E*)-nerolidyl pyrophosphate (**B**). The free rotation

of the single bond allows the formation of a *cis*-configured farnesylcation (**C**) which can undergo also 1,6-, 1,7-, 1,10- or 1,11- cyclizations depending on the STC. This forms also either tertiary or secondary cations whereas the latter results from *anti*-Markovnikov cyclizations. Further attacks of double bonds, hydride or methyl shifts as well as Wagner-Meerwein rearrangements can occur leading to a variety of structural motives. The amino acid residues facing the inside of the enzymatic active pocket determine the outcome of this cyclization cascade. In the end, the cyclization is terminated either by addition of water or elimination of a proton. Depending on the size of the pocket and the choice of amino acid residues, different products are formed as the intermediates can take various conformations reaching from simple mono-, bi- or tricycles and even more complex bridged or spirocycles.[51,71–75]

1.4 Unnatural Terpenoids

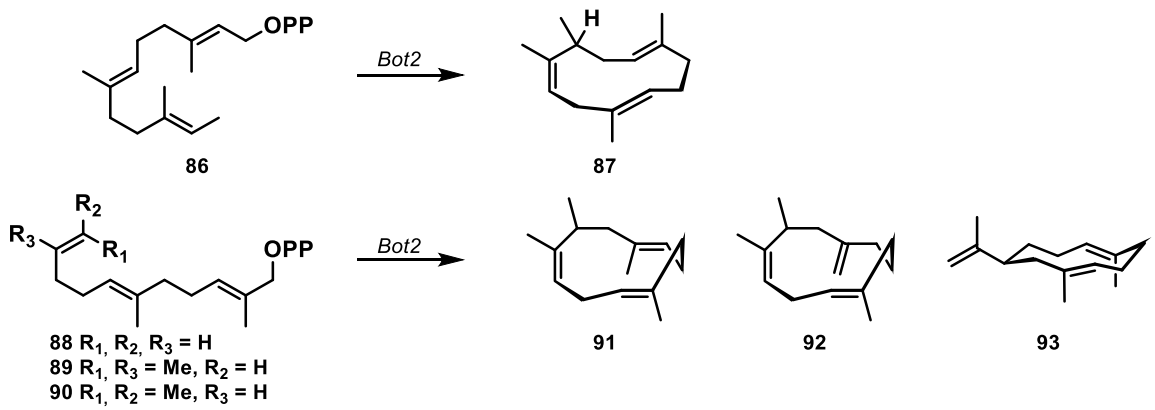
Production of novel terpenoids is of great interest. Therefore, several groups applied the idea of synthesizing new farnesyl analogs which were then transformed by various STCs to explore the synthetic potential of those. Mostly, analogs with shifted methyl groups or additional heteroatoms were tested.[76]

One interesting approach was performed by Dickschat and co-workers who synthesizied a methylated IPP-derivative **78** that was elongated using a FPPSase to achieve the synthesis of FPP analog **79** that were transformed using the T–muurolol synthase (TMS).[77] Depending on the stereochemistry of the novel methyl residue, different products were obtained reaching from (almost) those that are identical analogues to the natural product **85** up to structurally simpler products (s. scheme 15).



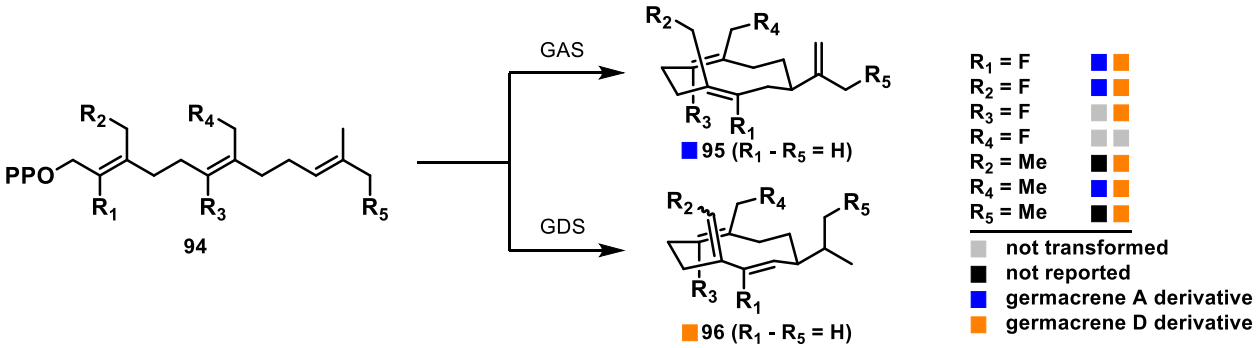
Scheme 15: Dickschat's synthesis of novel methylated terpenoids using a methylated IPP-derivative **78**.

A series of analogs with shifted methylgroups or double bonds was synthesized by our group and tested with a set of STCs. Here, STC Bot2 showed the most promising results and best acceptance for farnesyl analogs. The products are macrocycles arising from either 1,10- or 1,11-cyclizations. Only **89** resulted in a comlex mixture of low yielding products, not allowing to isolate and elucidate their structures. Interestingly, for **87** three macrocyclic conformers were found.[78]



Scheme 16: Kirschning's novel terpenoids by transformation of methyl-shifted FPP-analogs.

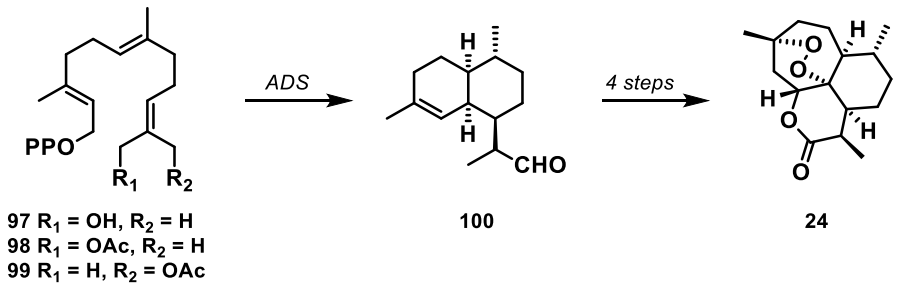
Allemann and co-workers also synthesized a series of analogs including three which bear a homologated methyl group in the allylic position. Next, several analogs with fluorine substituents either in the vinylic or allylic position were synthesizied and all analogs were transformed with the germacrene A and D synthases (GAS, GDS).[79,80] The results are shown in scheme 17 are based on GC-MS analysis.



Scheme 17: Results from Allemann's transformation of methylated and fluorinated analogs with GAS and GDS.[76]

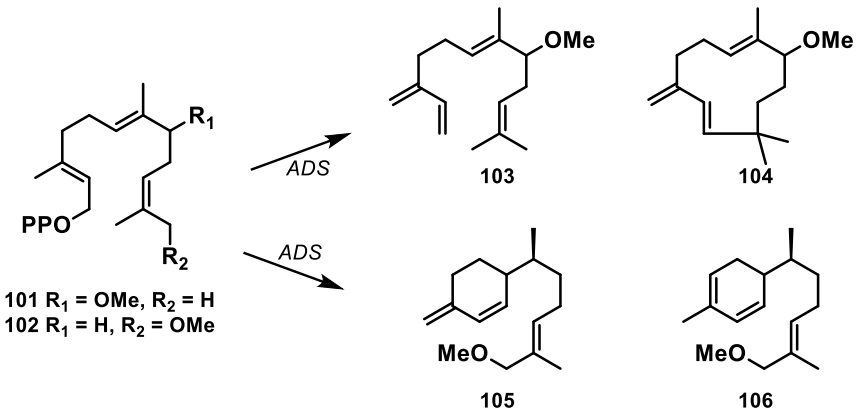
Furthermore, other groups explored the transformation of fluoriantеd derivatives with various STCs. All results have in common that mostly macrocycles were formed due to the strongly disactivative effect of the fluorine atom. Since these substrates are applicable to allow a better understanding of a cyclization mechanism and the promiscuity of STCs, there is still a need for novel terpenoids with

olfactoric favourable or other properties.[76] One interesting example is Allemann's work on his chembiosynthetic aproach towards the anti-malaria drug artemisinin (**24**). Three different oxygenated FPP-analogs were transformed with the amorphadiene synthase (ADS) to achieve the synthesis of dihydroartemisinic aldehyde (**100**) which is an intermediate in the biosynthesis of **24**. The synthesis was then completed by four chemical transformations (s. scheme 18).[81,82]



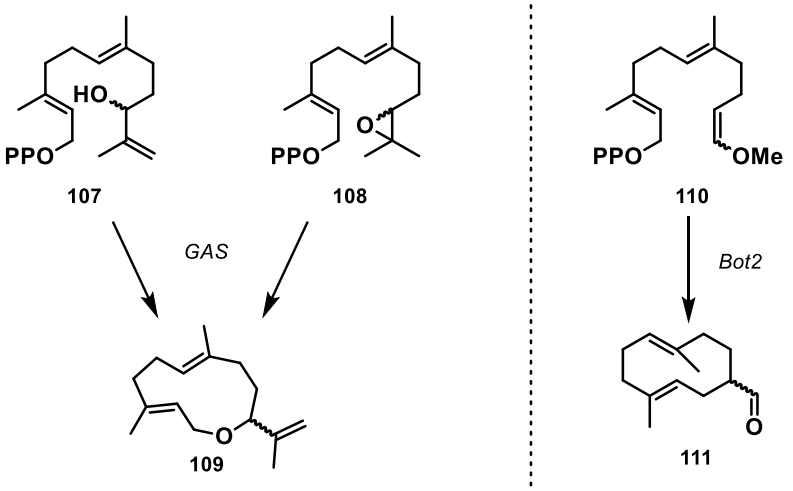
Scheme 18: Allemann's chembiochem-synthesis of artemisinin (**24**).

Allemann also synthesized similar substrates only with a methylether at two positions in these farnesyl analogs, obtaining different products using the ADS. When the methylether was positioned in an internal position, a β-cyryophyllene similar terpenoid (**104**) was obtained or its corresponding not cyclized form **103**. On the other hand, when the methylether was installed at the terminal position two monocycles with a conjugated π-system were generated.[83]



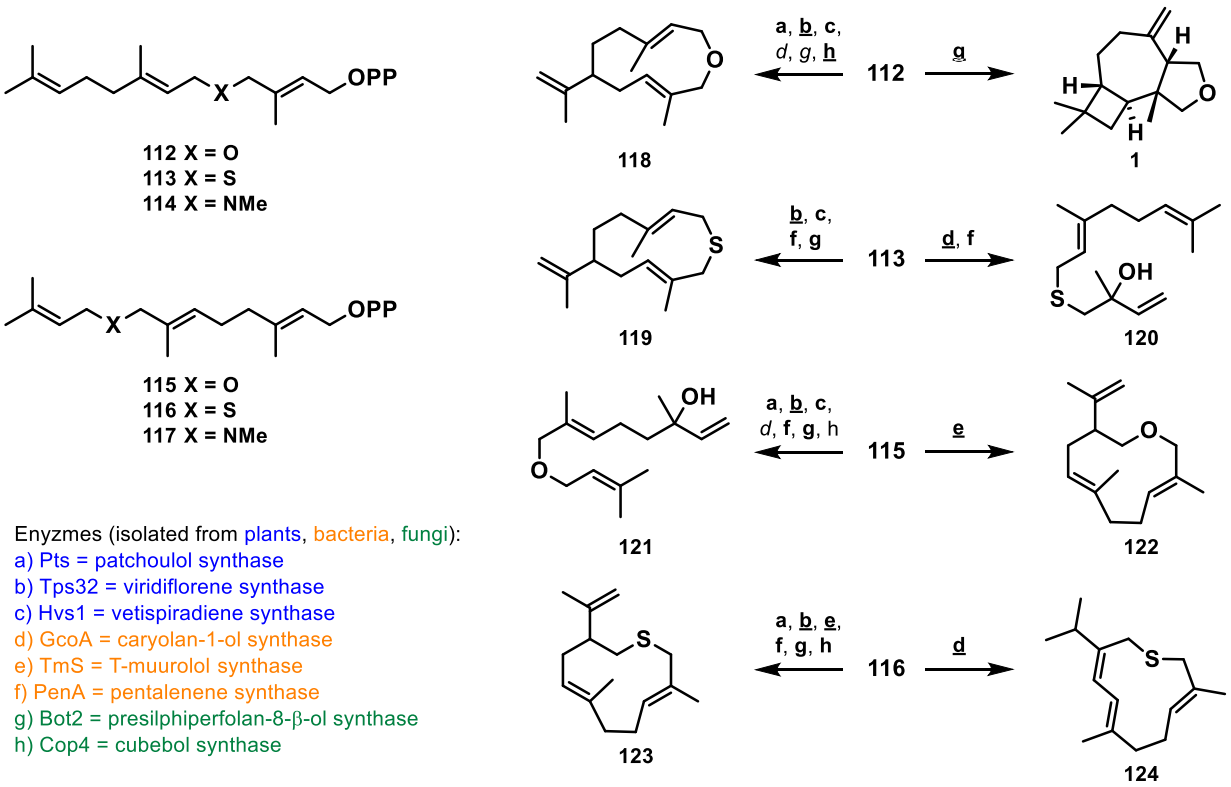
Scheme 19: Synthesis of novel terpenoids with methylether substituted farnesyl analogs.

Also, a variety of other oxygen functionalized farnesyl analoga were synthesized and tested by several groups. Mostly, different macrocycles were obtained from their biotransformation using several STCs. For example, terminal epoxide **108** and allylic alcohol with the shifted double bond **107** were transformed both to the same diallylether **109**.[84] One interesting analog, is enolether **110** which was transformed into macrocyclic aldehyde **111**.[85]



Scheme 20: Formation of novel macrocyclic ethers using the synthetic potential of STCs.

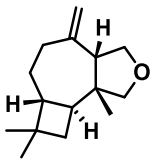
But not only oxygen can be inserted as a heteroatom but also nitrogen and sulfur. Kirschning and co-workers synthesized a library of different compounds, this time also including heteroatoms within the backbone chain of the farnesyl analogs. A set of eight different STCs was used to transform the analogs into novel terpenoids. From all eight obtained products, **1** was the most interesting one based on its structural motif with the unusual *trans*-configured four-membered ring and its olfactometric property. This is determined as ethereal, peppery and camphor scent, similar to rutondone.[86]



Scheme 21: Novel terpenoid products produced by selected STCs *via* a biotransformation of unnatural heteroatom-modified FPP-analogues (enzymes gave **main product**, used for preparative scale, *traces of product*).

2 Aim of this Thesis

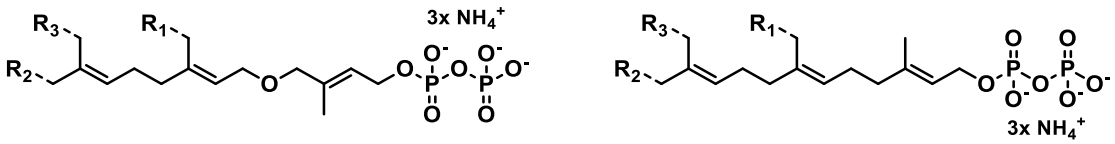
This work is divided into two topics with the first part dealing with synthetic access to tricycle **1** and pursuing different retrosynthetic concepts. A synthetic approach to tricycle **1** should make different analogs accessible and thus further (olfactory) properties should be investigated (s. figure 22).



1

Figure 22: Target of total synthesis: Tricycle **1**.

In the second part, a series of farnesyl derivatives bearing oxa-containing functional groups at the terminal methyl groups will be synthesized. Consequently, the promiscuity of STCs can be further explored by biotransformation experiments and new oxa-bearing terpenoids can be accessed and their structures elucidated. The structures of the pyrophosphates targeted are shown in figure 23.



R_1 = OH, R_2, R_3 = H 125
R_1 = OMe, R_2, R_3 = H 126
R_2 = OH, R_1, R_3 = H 127
R_2 = OMe, R_1, R_3 = H 128
R_3 = OH, R_1, R_2 = H 129
R_3 = OMe, R_1, R_2 = H 130

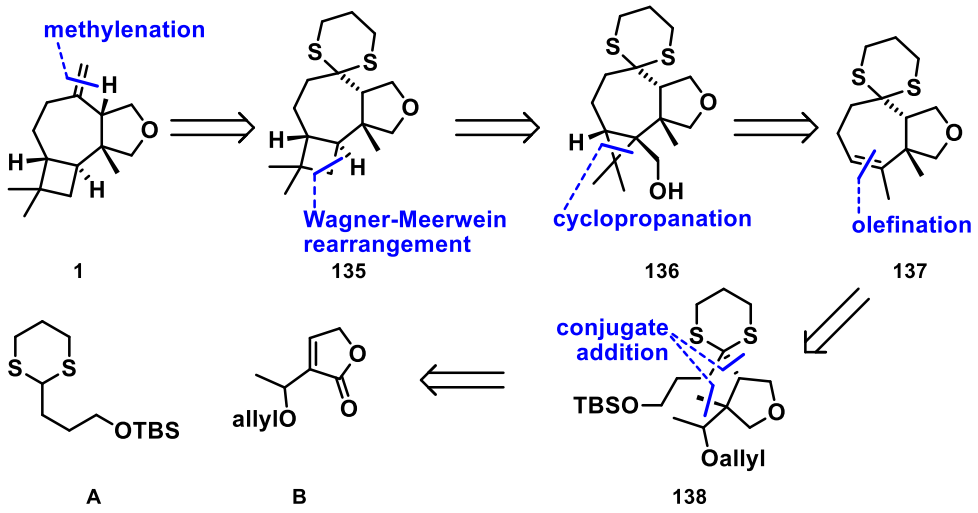
R_1 = OH, R_2, R_3 = H 131
R_1 = OMe, R_2, R_3 = H 132
R_2 = OH, R_1, R_3 = H 97
R_2 = OMe, R_1, R_3 = H 133
R_3 = OH, R_1, R_2 = H 134
R_3 = OMe, R_1, R_2 = H 102

Figure 23: Envisioned Oxa-Farnesyl Derivatives with R = OH and OMe.

3 First Synthetic Approach

3.1 Retrosynthesis

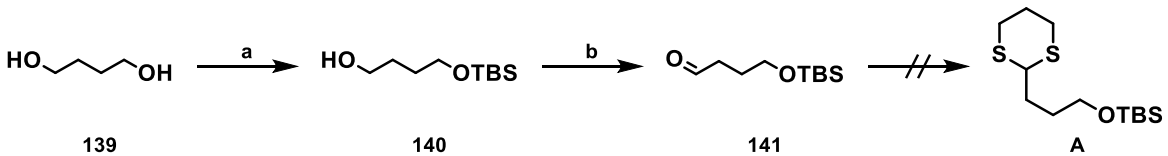
The envisioned retrosynthetic analysis is shown in scheme 24. The first step would be the introduction of the exomethylene group by using the Tebbe reagent or related olefination methods which would lead to compound **135** by transforming the ketone to the corresponding dithiane. This molecule can be synthesized by asymmetric hydrogenation at positions 8 and 8a and a Wagner-Meerwein rearrangement starting from cyclopropane **136**. The cyclopropane moiety should then be introduced by an asymmetric cyclopropanation reaction controlled by the allylic alcohol. This should be accessible by allyl oxidation of compound **137**. The double bond can be incorporated through intramolecular olefination of compound **138**, which should be prepared by an asymmetric conjugated addition of fragment **A** to fragment **B**.



Scheme 24: Retrosynthetic analysis of **1**.

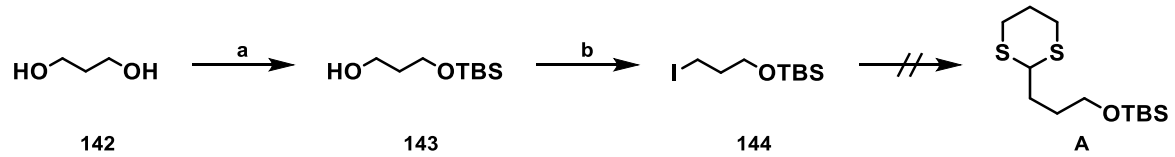
3.2 Synthesis of Fragment A

In a first attempt, fragment **A** was to be synthesized starting from 1,4-butanediol (**139**) according to the reaction sequence shown in scheme 25. Selective monoprotection of one alcohol and oxidation of the remaining hydroxyl group employing the Swern oxidation was achieved in good to quantitative yields. Treatment of the aldehyde **141** with 1,3-propanedithiol and various Lewis acids did not yield the desired product but only the deprotected starting material or traces of the deprotected fragment **A**.



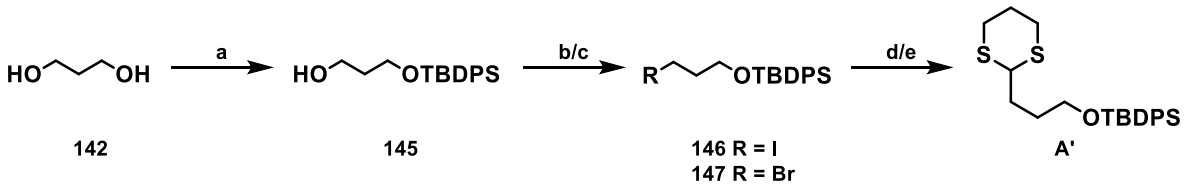
Scheme 25: First attempt towards fragment **A**: a) NaH, THF, 0 °C, 30 min, *then* TBSCl, *to* rt, 1 h, 52%; b) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, 10 min, *then* **140**, CH_2Cl_2, -78 °C, 15 min, *then* NEt_3, *to* rt, 30 min, *quant.*

In a second experiment, the desired fragment **A** was to be synthesized starting from 1,3-propanediol (**142**), which was converted to the singly protected alcohol **143** while the remaining hydroxyl group was converted to iodide **144** in moderate to quantitative yield using the Appel reaction (s. scheme 26). In the α-alkylation of 1,3-dithiane with iodide **144** the same results were found as in the previous dithiane formation reaction. Thus, it can be concluded that the TBS group is not stable enough under strongly acidic or basic Lewis conditions, so consequently it was exchanged for a TBDPS group in the following leading to the new fragment **A'**.



Scheme 26: Second attempt towards fragment **A**: a) NaH, THF, 0 °C, *to* rt, 45 min, *then* TBSCl, rt, 1 h, 60%; b) imid., PPh_3, I_2, CH_2Cl_2, rt, 4 h, exclusion of light, *quant*.

Following the same idea, iodide **146** and bromide **147** were synthesized almost quantitatively in two steps starting from 1,3-propanediol (**142**) using the mono-protection protocol followed by the Appel reaction. Alternatively, the Appel reaction to bromide **147** could also be carried out with pyridine as base. Finally, the α-alkylation of 1,3-dithiane succeeded for both electrophiles under optimized conditions, including the addition of HMPA as a co-solvent (s. scheme 27).



Scheme 27: First attempt towards new fragment **A'**: a) *n*BuLi, TBDPSCl, THF, -78 °C, 15 min, *to* rt, 30 min, *then* reflux, 3 h, *quant.*; b) imid., PPh_3, I_2, CH_2Cl_2, rt, 4 h, exclusion of light, *quant.*; c) imid., PPh_3, Br_2, CH_2Cl_2, rt, 4 h, exclusion of light, 83%; d) *n*BuLi, 1,3-dithiane, Et_2O/HMPA (4:1), -30 °C, *then* -20 °C, 1.5 h, *then* **146**, Et_2O, *to* rt, 30 min, *quant.*; e) *n*BuLi, 1,3-dithiane, Et_2O/HMPA (4:1), -30 °C, *then* -20 °C, 1.5 h, *then* **147**, Et_2O, *to* rt, 30 min, *quant*.

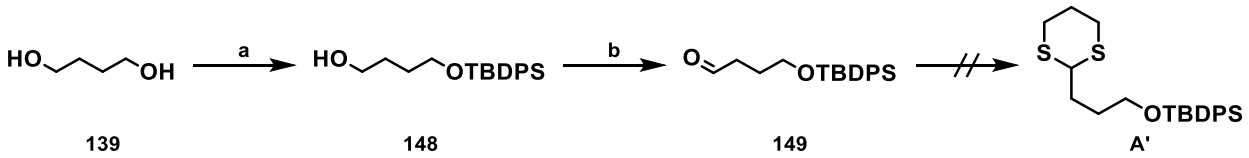
As part of an optimization study, it was found that the addition of HMPA as a co-solvent was necessary for successful alkylation (s. entry 6 in Table 1). Initially, the reaction was carried out in THF without co-solvent which did not yield the desired product. By changing the solvent to diethyl ether, a trace of the product was identified as judged by TLC and LC-MS. To test whether it is at all possible to deprotonate in the α-position of dithiane under the conditions, a deuteration experiment was performed. A small amount of 1,3-dithiane was treated with *n*BuLi or *t*BuLi in Et_2O at -30 °C for 1.5 h, then MeOH-d_4 was added to the mixture and subjected to ^{1}H NMR analysis. The data showed that

the integral for the α-CH_2 group was reduced from two to one indicating that deprotonation at this position was possible in principle. This led to the conclusion that deprotonation itself is not the problem but either the lack of nucleophilicity of the dithiane moiety or the electrophilicity of the leaving group. It is known that organolithium species can form clusters that exhibit lower reactivity and co-solvents such as DMPU and HMPA can break these clusters by chelating the lithium, thereby increasing the carbanion reactivity. As shown in table 1, the addition of HMPA gave the desired result while the addition of DMPU did not increase the yield.

Table 1: Optimization of the conditions for the α-alkylation towards fragment **A**'.

entry	solvent	electrophile	result
1	THF	**146**	no conversion
2	THF	**147**	no conversion
3	Et_2O	**146**	trace **A'**
4	Et_2O	**147**	trace **A'**
5	Et_2O/DMPU (4:1)	**146**	trace **A'**
6	Et_2O/HMPA (4:1)	**147**	*quant.* **A'**

Since HMPA is classified as a carcinogen, an alternative route *via* the aldehyde **149** was pursued. Starting from 1,4-butanediol (**139**) it was synthesized in good yields in two steps *via* a mono protection protocol followed by a Swern oxidation (s. scheme 28). Unfortunately, under the same conditions as described above for accessing fragment **A** (s. scheme 25) only a trace amount of the desired product could be isolated. Presumably, the same reasons as above can be blamed for the failure of this route. Therefore, the first route was reverted to.

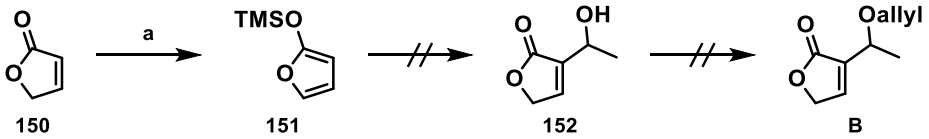


Scheme 28: Second attempt towards new fragment **A'**: a) *n*BuLi, TBDPSCl, THF, -78 °C, *to* rt, *then* reflux, 3 h, 89%; b) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, 10 min, *then* **149**, CH_2Cl_2, -78 °C, 15 min, *then* NEt_3, *to* rt, 30 min, 82%.

3.3 Synthesis of Fragment B

In a first attempt to prepare fragment **B**, furanone **150** was converted to the silyl ether **151** in good yield. This compound can react in the α-position in a Mukaiyama aldol reaction with small Lewis acids and subsequent shift of the double bond to yield the conjugated enone 152.[87] Unfortunately,

the desired product could only be isolated in poor yields. Presumably, it is lost during the aqueous workup or the column chromatography.



Scheme 29: Synthesis towards fragment **B**: a) NEt_3, TMSOTf, CH_2Cl_2, 0 °C *to* rt, o/n, 59%.

Analysis of the crude product revealed that the deconjugated product was present. Various workup protocols were attempted (s. table 2) but none of these approaches could increase the product yield.

Table 2: Tested workups for the Mukaiyama aldol reaction.

entry	work up	result
1	hydrolysis with a sat. aq. NH_4Cl-soln., extract with EtOAc	trace **152**
2	hydrolysis with a sat. aq. $NaHCO_3$-soln., extract with EtOAc	trace **152**
3	hydrolysis with water, extract with EtOAc	trace **152**
4	dry loading onto silica, column chromatography	14 % of **152**
5	dry loading onto silica, short plug column chromatography	18 % of **152**
6	dilute THF	byproduct

With the material in hand, the introduction of the allyl protecting group was subsequently tested. However, when the enone **152** was added to a solution of NaH in THF, the material decomposed. No transformation was observed even when milder conditions were chosen. Therefore, an alternative protecting group was sought. For this purpose, conjugate addition test reactions were performed first as described below to verify the feasibility of the main step in this synthesis.

3.4 First Conjugate Additions

Seebach and co-workers summarized the chemistry of dithiane, including their versatile use in conjugate addition reactions.[88] In a first attempt, the 2-lithiodithiane was added to furanone **150** according to the procedure described by Medarde and co-workers.[89] They described 2-heteroaryl-1,3-dithiane as good nucleophiles for such conjugate additions. Unfortunately, no conversion could be obtained for fragment **A'** (s. table 3) under these and similar conditions.

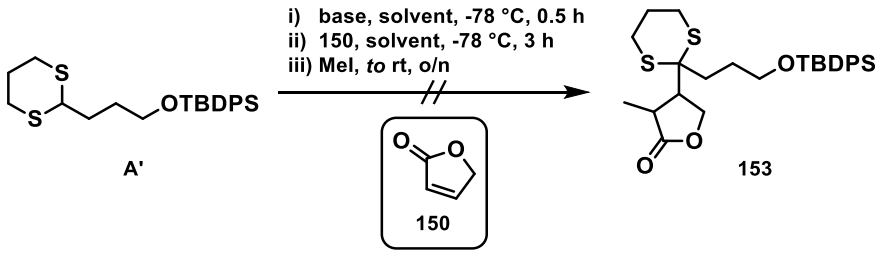
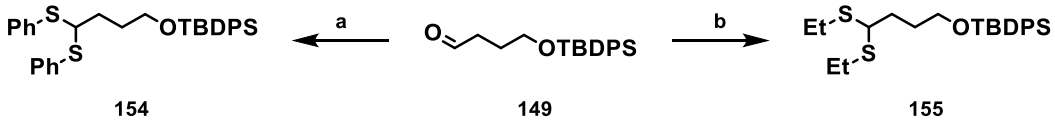


Table 3: First test conjugate additions with fragment **A'**.

entry	solvent	base	result
1	THF	*n*BuLi	no conversion
2	Et_2O	*n*BuLi	no conversion
3	Et_2O/HMPA (4:1)	*t*BuLi	no conversion

Thus, it was concluded that the nucleophilicity of this dithiane is to less pronounced or the deprotonation failed. To rule out the second hypothesis, a deuteration experiment was again performed. A small amount of the dithiane **A'** was treated with *n*BuLi and *t*BuLi in THF at -30 °C for 1.5 h and then MeOH-d_4 was added and subjected to ^{1}H NMR analysis. If the α-position were deprotonated, the triplet would disappear at 4.03 ppm because the proton was replaced by deuterium which does not couple with protons in the neighborhood. As the experiments showed, deprotonation in the α-position is possible with *n*BuLi, since the triplet disappears in the ^{1}H NMR spectrum. When *t*BuLi is used, the triplet was still present, leading to the conclusion that the anion does not have sufficient stability at the high temperatures over a period of 1.5 h or the *tert*-butyl group is too bulky. Either a shorter reaction time or lower temperatures must be selected if *t*BuLi is chosen as the base for this reaction. Ultimately, this experiment proves the hypothesis that dithiane **A'** is not nucleophilic enough for conjugate addition, as deprotonation in the α-position is principally possible. Based on these results, a deeper literature search was carried out which revealed that anion stabilizing groups favor conjugate addition, but in the present case a substituent is present with the alkyl side chain which does not enhance the nucleophilicity of dithiane **A'**. Therefore, new thioacetals were synthesized that are known to exhibit enhanced nucleophilicity in these conjugate addition reactions.[88]



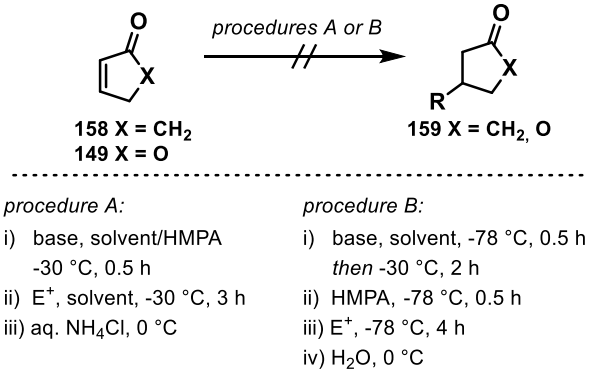
Scheme 30: Synthesis of new thioacetals: a) $BF_3{\cdot}OEt_2$, HSPh, $CHCl_3$, 0 °C, 1 h, 90%; b) $AlCl_3$, HSEt, DCE, rt, 15 min, *quant*.

Following two different procedures, *bis*-thiophenyl acetal **154** and *bis*-thioethylacetal **155** could be synthesized in very good yields. Another possibility are chiral sulfoxides which are easily prepared from fragment **A'** in an enantioselective oxidation with a chiral oxidant or alternatively with $NaIO_4$ only if the racemate is to be prepared.[88] Sulfoxides possess increased nucleophilicity as an anion stabilizing group which is desirable for conjugated additions. In addition, the sulfoxide acts as a chiral inducer which eliminates the need for an external chiral inducer e.g. derived from Lewis acids.

Figure 31: Further synthesized dithianes: a) $NaIO_4$, MeOH, 0 °C, 16 h, 44%; b) *n*BuLi, THF, -20 °C, 1.5 h, *then* CO_2, -20 °C, 1 h, *to* rt, 2 h, 59%.

3.5 Tested Conjugate Additions

Once these dithiane **154-157** were available, they were tested in the conjugate additions with either cyclopentenone (**158**) or furan-2(5*H*)-one (**149**) as Michael acceptor. Regardless of different procedures published and pursued for similar systems[90,91], either no conversion or decomposition was observed (s. table 4). It was concluded that such conjugate additions are not feasible for the chosen system. Either the dithiane is not reactive enough to add to the Michael acceptor, or the Michael acceptor is too reactive, leading to decomposition products. Deuteration experiments showed that the deprotonation of dithiane **154-157** is in principal possible under the same conditions as found in step 1 of methods A and B. This means that decomposition occurs when heated to temperatures above -78 °C. Therefore, a new strategy had to be developed.



Scheme 32: Overview of the carried out conjugate additions.

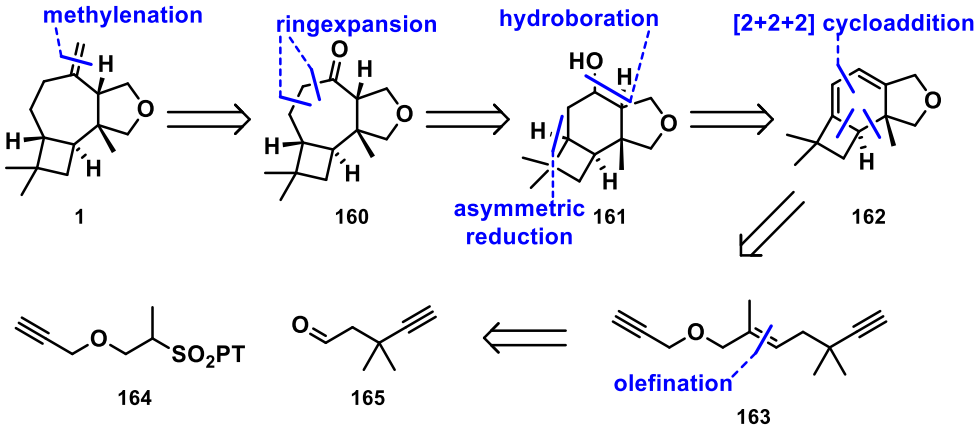
Table 4: Tested conjugate additions.

entry	procedure	conditions	result
1	A	**154**, *n*BuLi, Et_2O, **149**	decomposition
2	A	**156**, *t*BuLi, Et_2O, **149**	decomposition
3	A	**155**, *n*BuLi, Et_2O, **149**	decomposition
4	A	**155**, *t*BuLi, Et_2O, **149**	decomposition
5	B	**156**, *n*BuLi, THF, **158**	no conversion
6	B	**155**, *n*BuLi, THF, **158**	no conversion
7	B	**154**, *n*BuLi, THF, **158**	no conversion
8	B	**157**, *n*BuLi, THF, **158**	no conversion
9	B	**156**, *n*BuLi, Et_2O, **158**	no conversion
10	B	**155**, *n*BuLi, Et_2O, **158**	no conversion
11	B	**154**, *n*BuLi, Et_2O, **158**	no conversion
12	B	**156**, *n*BuLi, Et_2O, **158**	no conversion

4 Second Synthetic Approach

4.1 Retrosynthesis

In the next retrosynthetic analysis, the exomethylene group was to be introduced as one of the last functional units. The seven-membered ring was to be established by a ring extension leading to ketone **160**. The necessary hydroxy group was planned to be installed by asymmetric hydroboration and the stereocenter in the four-membered ring could be introduced by asymmetric reduction, leading to precursor **162**. This had to be generated in a [2+2+2] cycloaddition from the enedine **163** derived from the sulfone **164** and the aldehyde **165** *via* an (*E*)-selective Julia-Kocienski olefination.

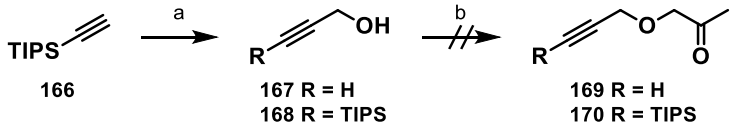


Scheme 33: New retrosynthetic approach with a [2+2+2] cycloaddition as a key step.

4.2 Synthesis of the Western Fragment

4.2.1 First Approach towards the Western Fragment

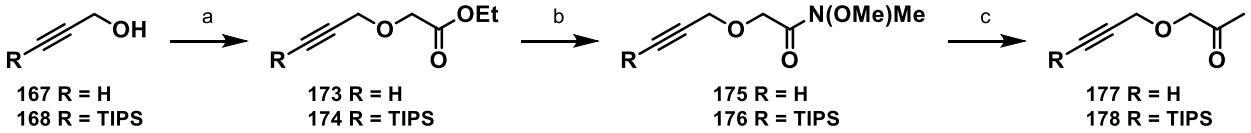
In a first effort, the ether was prepared from propargyl alcohol **167** and the TIPS-protected derivative **168** and α-chloroacetone (**171**) by a Williamson synthesis. Unfortunately, only decomposition could be observed.



Scheme 34: First approach towards the western fragment **164**: a) *t*BuLi, THF, -40 °C, 0.5 h, *then* $(CH_2O)_n$, -40 °C, 20 min, 79%; b) NaH, THF, 0 °C, *then* rt, 1 h, *then* **171**, 0 °C, *to* rt, 3 h, *decomp*.

In a second approach the known transformation[92] was successful with α-bromoethyl acetate (**172**) and two propargyl alcohols **167** and **168** giving desired ethers **173** and **174**. These were converted to the Weinreb amides **175** and **176**, respectively, in moderate to poor yields. Application of various standard conditions[92,93] to introduce the Weinreb moiety did not lead to higher yields. Next, two

amides **175** and **176** were converted to ketones **177** and **178** in good yield by nucleophilic addition of methylmagnesium bromide.

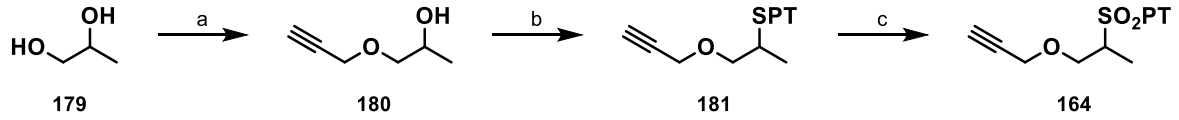


Scheme 35: Second Approach towards the western fragment **164**: a) NaH, THF, 0°C *to* rt, 1 h, *then* **172**, rt, 3 h, 61-72%; b) *i*PrMgCl, HN(OMe)Me·HCl, THF, -20 °C, 0.5 h, 16-52%; c) MeMgBr, THF, 0 °C, 1 h, 83-92%.

Due to the moderate yields and large number of individual steps, an alternative and faster approach was developed for the synthesis of the western fragment starting from 1,2-propanediol (**179**).

4.2.2 Second Approach Towards the Western Fragment

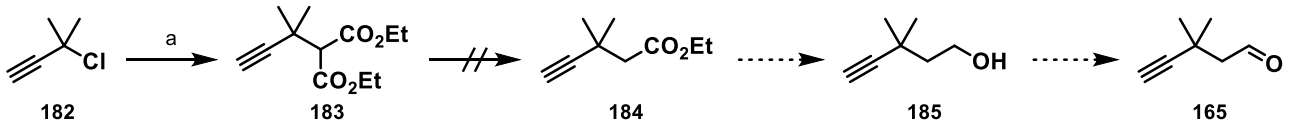
Finally, western fragment (**164**) could be synthesized in three steps starting from 1,2-propanediol (**179**) according to the reaction sequence shown in scheme 36. The propargylation of the alcohol units is carried out in a ratio of 6:1 in terms of the desired product **180**. The non-separable mixture was subjected to a Mitsunobu reaction and allowed the introduction of the phenyltetrazole ring which is a standard residue for the (*E*)-selective Julia-Kocienski olefination.[94] The resulting mixture could be separated by column chromatography and desired thioether **181** was obtained. Subsequently, product **181** was oxidized to the sulfone so that western fragment **164** became available in good yield in only three steps.



Scheme 36: Synthesis of the western fragment **164**: a) NaH, THF, 0 °C, 2 h, *then* propargyl bromide, 0 °C, *then* **179**, rf, 5 h, 75% (6:1 for desired); b) PPh_3, DIAD, HS-PT, THF, rt, o/n, 95%; c) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, H_2O_2, EtOH, rt, o/n, 83%.

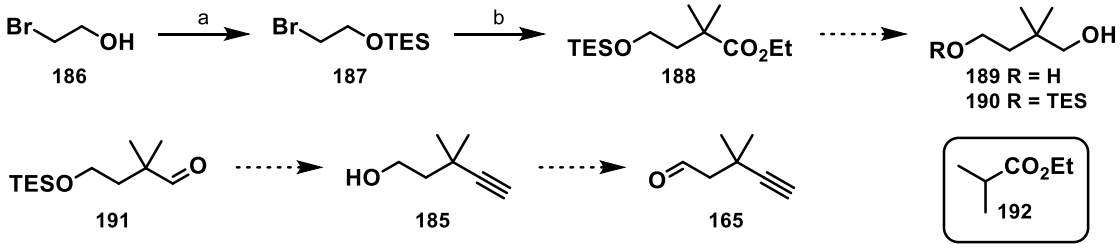
4.3 Synthesis of the Eastern Fragment

The synthesis of the eastern fragment has already been published via two different routes.[95,96] When both routes were investigated, it turned out that only one route proved to be reproducible.



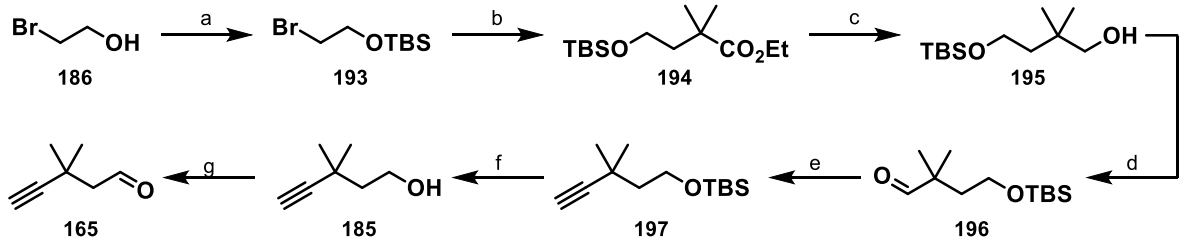
Scheme 37: First route towards the eastern fragment **165** which could not be reproduced: a) Na, EtOH, 10 °C, 10 min, *then* **182 & 183**, rt, *to* 65 °C, 4 h, 17%.

In addition to the problems concerning reproducibility, the protecting group proved to lack sufficient stability under the specified conditions. Therefore, it was exchanged from TES to TBS.



Scheme 38: Second approach with the reported protection group which could not be reproduced: a) NEt_3, TESOTf CH_2Cl_2, 0 °C to rt, *quant.*; b) *n*BuLi, DIPA, THF, -78 °C, 10 min, *then* **192**, THF, -78 °C, 1 h, *then* **187**, *to* rt, o/n, 43%.

Finally, the final eastern fragment was synthesized starting from 2-bromo ethanol (**186**) which was TBS-protected and then used as an alkylating agent to yield ester **194** following then the same route as published by Li and coworkers.[96]



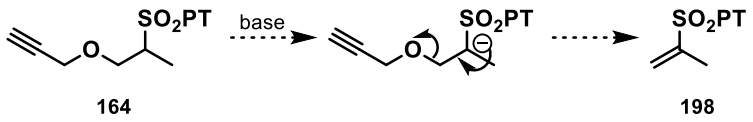
Scheme 39: Third approach with the improved protection group strategy towards the eastern fragment **165**: a) NEt_3, TBSCl, 0 °C *to* rt, o/n, 84%; b) *n*BuLi, DIPA, THF, -78°C, 10 min, *then* **192**, THF, -78 °C, 1 h, *then* **193**, *to* rt, o/n, *quant.*; c) $LiAlH_4$, Et_2O, -78 °C, 0.5 h, *quant.*; d) $(COCl)_2$, DMSO, CH_2Cl_2 -78 °C, 10 min, *then* **195**, CH_2Cl_2, -78 °C, 15 min, *then* NEt_3, *to* rt, 30 min, 93%; e) *n*BuLi, $TMSCHN_2$, THF, -78 °C, 1 h, *then* **196**, -78 °C *to* rt, o/n, 57%; f) TBAF, THF, 0 °C *to* rt, o/n, 52%; g) $(COCl)_2$, DMSO, CH_2Cl_2 -78 °C, 10 min, *then* **185**, CH_2Cl_2, -78 °C, 15 min, *then* NEt_3, *to* rt, 30 min, n.d.

A reduction-oxidation sequence led to aldehyde **196**. While the classical Swern conditions gave **196** in very good yields, the prior reduction led to a variety of difficulties. Initially, DIBAL-H was used as the reducing agent. Even the replaced protecting group did not appear to be stable at -78 °C. Same diol **189** was found on a small-scale as by-product and when carrying out the reaction on a large scale

it is formed as major product. Presumably, a Lewis acid which is a byproduct of DIBAL-H reduction may lead to this deprotection. This happens mainly when the dropwise addition on a larger scale takes too long. Thus, a rapid addition of DIBAL-H precooled to -78 °C was carried out, which succeeded in good yields on a small scale. However, on a larger scale diol **189** is the main product formed. Therefore, the reducing agent was replaced to $LiAlH_4$ which acted readily at -78 °C and desired alcohol **195** was formed alone. Swern oxidation led to aldehyde **196** which was used for alkyne homologation. Again, the published results could not be reproduced. Neither the Gilbert-Seyferth reagent[97] nor the optimized Bestmann-Ohira reagent[96] nor various Corey-Fuchs conditions.[98,99] succeeded in homologation. Only Colvin's modified version of the Corey-Fuchs reaction with TMS-diazomethane and *n*BuLi [100] afforded desired alkyne **197**. The synthesis of the eastern fragment was completed with deprotection of the TBS group with TBAF followed by Swern oxidation. The crude product of aldehyde **165** was subsequently used for Julia-Kocienski olefinations.

4.4 First Olefinations

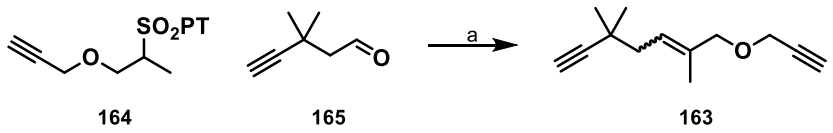
Test reactions of the Julia-Kocienski reaction could be carried out with the crude product of aldehyde **165** and sulfone **164**.[94] Under published standard conditions, no formation of the product was found, but only decomposition products and the starting aldehyde were detected. Thus, a side reaction resulting from premixing of the sulfone with the base may occur. It was suggested that after deprotonation in the α-position to the sulfone, an α-elimination of the propargyl residue occurred, leaving the non-reprotonatable sulfone **198** and the propargyl alcoholate. However, sulfone **198** could not be isolated, and deuteration experiments showed that sulfone **164** decomposed before a deuterated sulfone was formed. This observation also applies to very short reaction times of less than one minute.



Scheme 40: Undesired side reaction after deprotonation of sulfone **164** applying standard conditions.

It can be concluded that the reaction should be carried out under Barbier conditions due to the instability of sulfone **164**. Interestingly, it was found that when this reaction was carried out using the standard bases LiHMDS, KHMDS and NaHMDS, the first bases gave the best results. After some optimization steps in the purification, an inseparable mixture of *E/Z* isomers of olefin **163** could be isolated. It can be imagined that **163** is rather volatile. Therefore, the reaction was carried out in THF (decomposition products were mainly found in ether), a pentane/ether mixture was used for column chromatography and concentration on the rotary evaporator was carried out in the absence of light

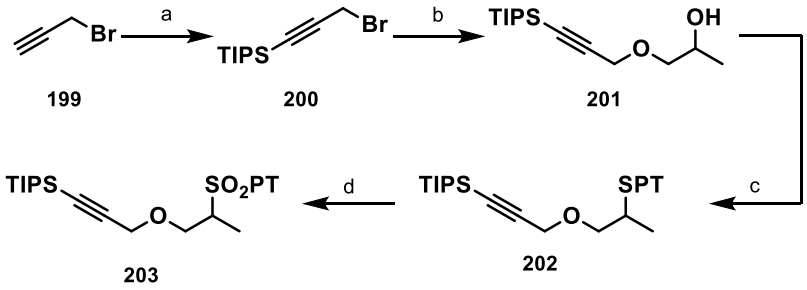
and at 30 °C. Under these non-optimized conditions, it was considered to prepare additional western fragments bearing a silyl protecting group at the terminal alkyne to reduce the volatility of the enediins. It is known that these types of compounds can also be used for [2+2+2] cycloadditions.[101–103]



Scheme 41: First unoptimized conditions towards enediyne **163**: a) LiHMDS, -78 °C *to* rt, o/n, 45% (4:1 *E/Z*); the *E/Z*-ratio was determined by NMR analysis.

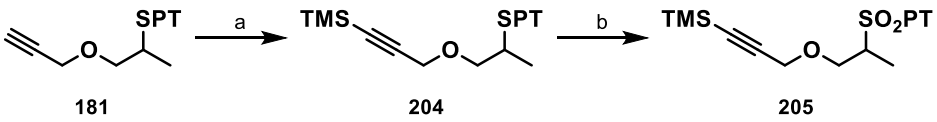
4.5 Optimized Western Fragments

TIPS-protected sulfone **203** was synthesized in the same way as described for sulfone **164**. The only difference represents the TIPS protection of propargyl bromide right at the beginning of the synthetic route. The synthesis could then be reproduced in similar yields and sulfone **203** was obtained.



Scheme 42: Synthesis of the new TIPS-protected sulfone **203**: a) *n*BuLi, THF, -78 °C, 1 h, *then* TIPSCl, THF, *to* rt, 2 h, 98%; b) NaH, THF, 0 °C, *then* **179**, rf, 5 h, 89% (3:1 mix for desired); c) DIAD, PPH_3, HS-PT, THF, 0 °C *to* rt, o/n, 57%; d) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, EtOH, H_2O_2, rt, o/n, 77%.

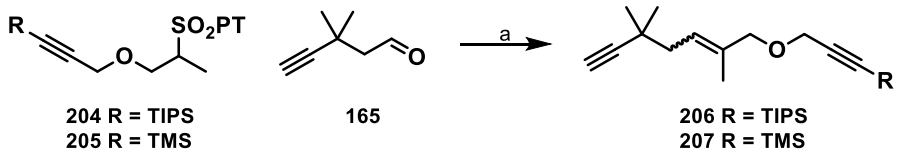
TMS protection of propargyl bromide is also possible but the TMS group proved too unstable in the subsequent ether synthesis. Therefore, the TMS derivative was synthesized starting from advanced intermediate **181**, which was deprotonated at the terminal alkyne and then oxidized. Thus, final sulfone **205** was obtained. With this new compound in hand, further olefinations could be tested.



Scheme 43: Synthesis of the new TMS-protected sulfone **205**: a) LiHMDS, THF, -78 °C, 1 h, TMSCl, THF, -78 °C, 2 h, 82%; b) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, EtOH, H_2O_2, rt, o/n, 95%.

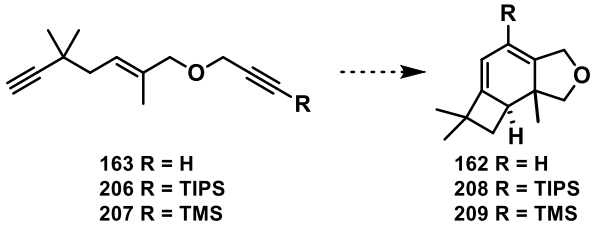
4.6 Second Generation of Olefinations and Cycloadditions

The new substrates were transformed under the reaction conditions found for the synthesis of the first substrate. While TIPS-protected enediin **206** was prepared in a yield of 45% (*E*/*Z*= 3:1), TMS-protected enediin **207** could be isolated in 42% (*E*/*Z*= 5:1).



Scheme 44: Unoptimized conditions applied to the new substrates **204** and **205**: a) LiHMDS, THF, -78 °C *to* rt, o/n, 45% (3:1 *E*/*Z*) or 42% (5:1 *E*/*Z*).

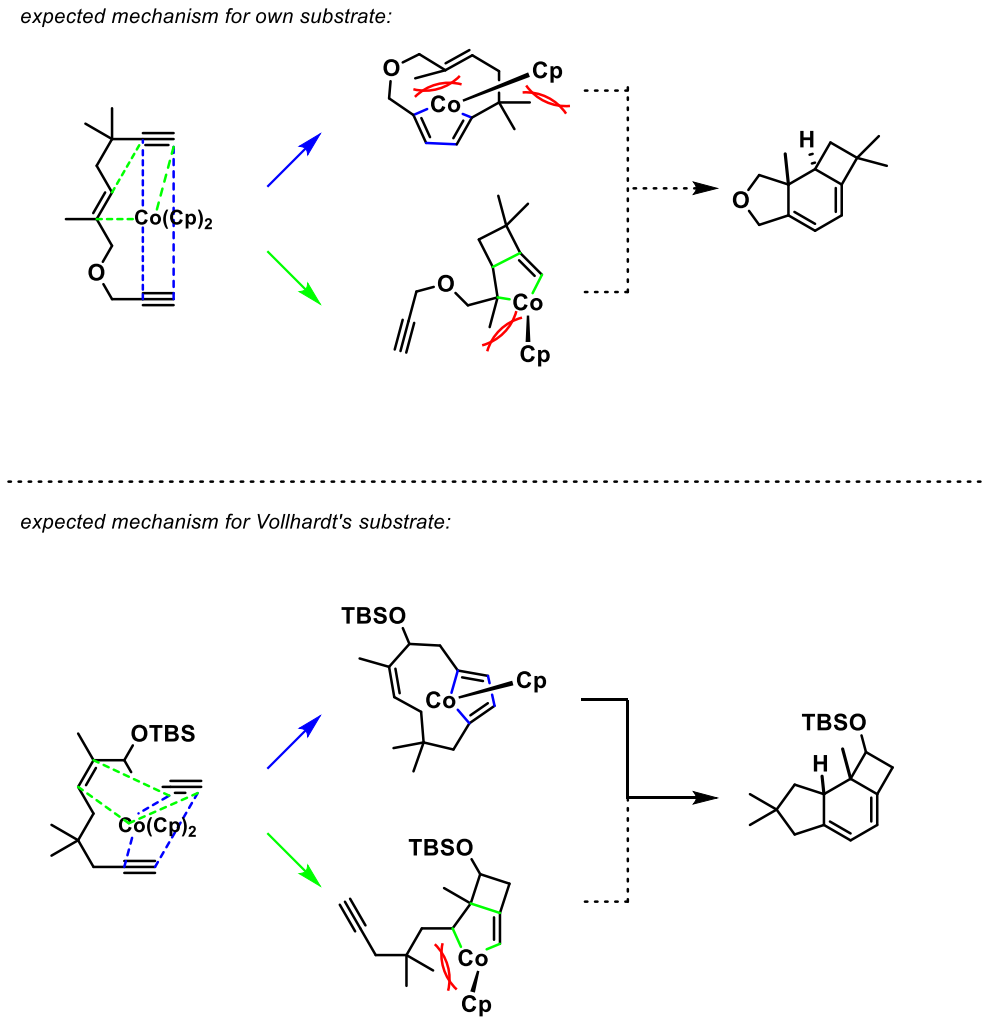
The first experiments on [2+2+2] cycloadditions were carried out with these three enediynes. Since this reaction has been well studied by many different groups under the leadership of its founder Vollhardt, the conditions developed by his group were first tested. Since sound additional material was lacking in his early work on illudol[104], it was difficult to find the correct conditions for achieving a successful transformation.[105–107]



Scheme 45: Overview reaction of the carried out [2+2+2]-cycloadditions using $CpCo(CO)_2$ as a catalyst.

Table 5: Performed screening for the [2+2+2]-cycloaddition.

entry	sm (R =)	lamp	solvent	time	temperature	result
1	H	365 nm, 150 W	PhMe	5 h	110	decomp
2	H	365 nm, 150 W	PhMe	o/n	110	decomp
3	H	200-400 nm, 100 W	PhMe	o/n	110	sm
4	H	vis light, 50 W	PhMe	o/n	110	sm
5	H	vis light, 300 W	THF	o/n	70	sm
6	H	vis light, 300 W	PhMe	o/n	110	sm
7	H	vis light, 300 W	*iso*octane	o/n	110	sm
8	TIPS	vis light, 300 W	PhMe	o/n	110	sm
9	TIPS	365 nm, 150 W	PhMe	o/n	110	sm
10	TIPS	200-400 nm, 100 W	PhMe	o/n	110	sm

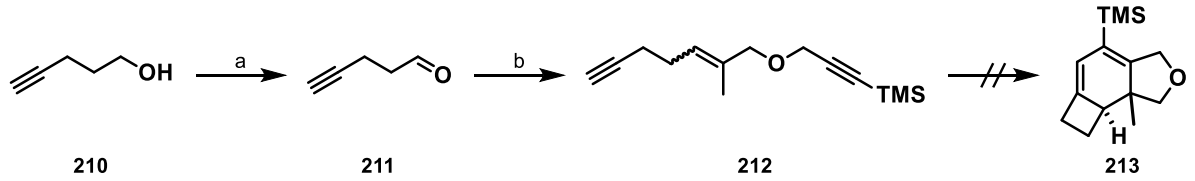


Scheme 46: Proposed intermediates during the [2+2+2]-cycloaddition.

One can imagine that reactions that require a light source have a larger number of parameters to be optimized, or various additional possible sources of error exist to perform them in the best possible way. The first problem we encountered was the setup of the reaction. The detailed description by Mulzer and co-workers gave the first indication that dilution and slow addition of the cobalt catalyst is necessary for successful conversion.[108] Another problem is the light source chosen. Often this was not specified and so either lamps with emission in the ultraviolet spectral range or in the visible light range were used. Another problem is the power of the lamp and the distance between the lamp and the flask. Therefore, a small optimization study was performed testing different lamps and solvents. Mostly toluene was used as the solvent of choice because it has the highest boiling point. As can be seen, all experiments either furnished decomposition or only the starting material was recovered. This led to the conclusion that the steric hindrance of the gem-dimethyl group adjacent to the alkyne moiety was too pronounced and therefore hindered a reaction mediated by the cobalt center of the catalyst. Therefore, a brief explanation of the mechanism of a [2+2+2] cycloaddition is helpful here. In general, two different routes can be followed when an enediyne is used: Either both alkyne moieties can form

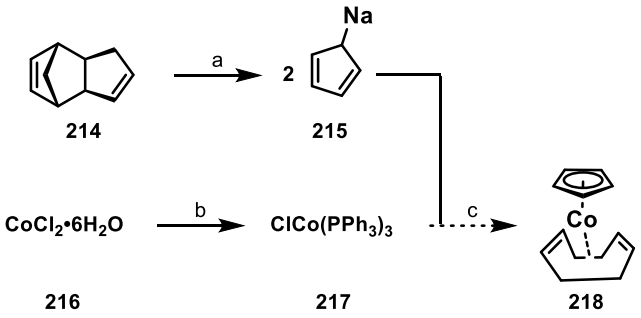
a cobalt pentadiene (blue pathway) or one alkyne and one alkene form a cobalt cyclopentene species in one step (green pathway).[105]

In the latter case, the metal is usually eliminated to form cyclobutene, since the insertion of the remaining alkyne moiety is sterically hindered due to the presence of the gem-dimethyl group at the carbon center to which the cobalt is also attached. On the blue pathway, there is again a gem-dimethyl group in the α-position to the metal center of the cyclopentadiene. There could also be an unfavourable interaction between the methyl group of the (*E*)-configured double bond and the metal center. Therefore, a comparison with Vollhardt's precursor from his illudol synthesis might be of interest.[104] Again, two different routes are conceivable. The green pathway, in which again a cobalt cyclopentene is formed, is less likely, since again the hinderance induced by the gem-dimethyl group may take place. If the blue pathway is followed, two major differences from the substrate to be used here are obvious: First, the double bond of the internal alkene is (Z)-configured. Therefore, there are fewer steric hindrances with the methyl group and the metal center of the pentadiene moiety. However, the work of Vollhardt has shown that the geometry of the internal double bond is not crucial for the success of the [2+2+2] cycloaddition.[109] Thus, the problem could be that there is no gem-dimethyl group in the alpha position to the metal center to enable the reaction. To rule out the last assumption, new enediin **212** was synthesized in two steps to perform the cycloaddition again. The route follows the same steps as before and leads to enediin **212**.



Scheme 47: Synthesis of new enediyne **212** and tested cycloaddition: a) $(COCl)_2$, DMSO, CH_2Cl_2 -78 °C, 10 min, *then* **210**, CH_2Cl_2, -78 °C, 15 min, *then* NEt_3, *to* rt, 30 min, *quant*.; b) LiHMDS, THF, -78 °C *to* rt, o/n, 20% (3:1 *E*/*Z*).

Unfortunately, when reaction conditions according to entries 8-10 from table 5 were applied, only starting material was isolated. One possible explanation is that the necessary ligand exchange of the carbon monoxide ligands by the alkynes did not occur. Therefore, a new catalyst should be synthesized carrying ligands that are more weakly bound to the metal center.[110,111] Common possibilities include the use of (*cis, cis*)-1,5-cyclooctadiene or ethene.[112,113] Initially, a single conversion of the readily available catalyst was carried out without success,[114] so the full synthesis was carried out starting from cobalt hexachloride which also included the synthesis of sodium cyclopentadienide.



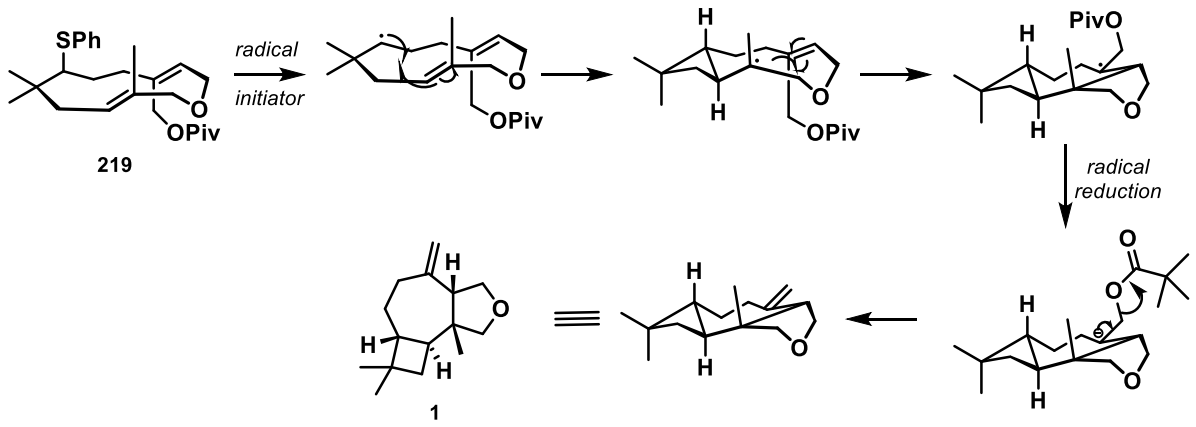
Scheme 48: Synthesis of the new cobalt catalyst for [2+2+2]-cycloadditions: a) Na, 160 °C, 6 h, *quant*.; b) PPh_3, $NaBH_4$, EtOH, 65 °C, 0.5 h, 84%; c) NaCp, THF, -78 °C, *then* warm *to* rt, cod, rf, 0.5 h.

Unfortunately, this sequence was not successful. While the first reaction steps worked well and all described color changes occurred, the last exchange with cyclooctadiene did not succeed. Another problem was revealed by the ^{1}H NMR analysis of the generated sodium cyclooctadienide. It revealed no impurities, although the solution basically turned black instead of remaining colorlessly clear. Since this anion is also commercially available, it was ordered, but the companies delayed delivery for several months. Therefore, a new strategy was started until the chemicals arrived to try further cycloaddition reactions in the meantime.

5 Third Retrosynthetic Approach

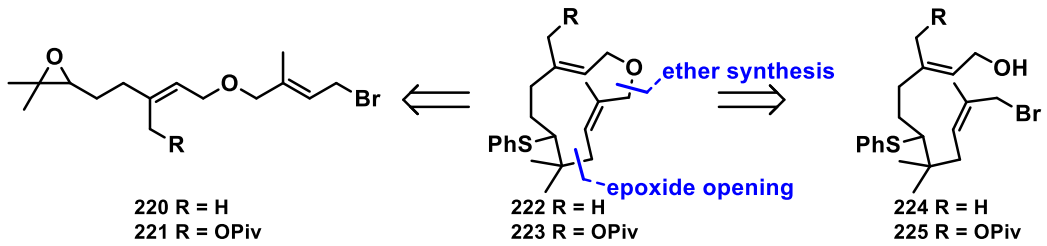
5.1 Retrosynthesis

The next retrosynthetic analysis pursues the cut of the strategic bonds according to a biomimetic pathway. The final step should be a radical cascade to build up the fused ring bonds and also the exomethylene double bond in a single transformation. This transformation would produce a mixture of enantiomers which may be of interest because the other enantiomer may have new olfactoric properties worth knowing. Only one set of diastereoisomers is expected to form since the precursor should have the same fold as proposed by our group for the biotransformations.[86] (s. scheme 49)



Scheme 49: Biomimetic radical cascade to build the framework of the final tricycle **1**.

The synthesis of required precursors **222** and **223** can be done *via* two different routes. To explore both routes, simplified precursors **220** and **224** should first be synthesized without the pivalate moiety.

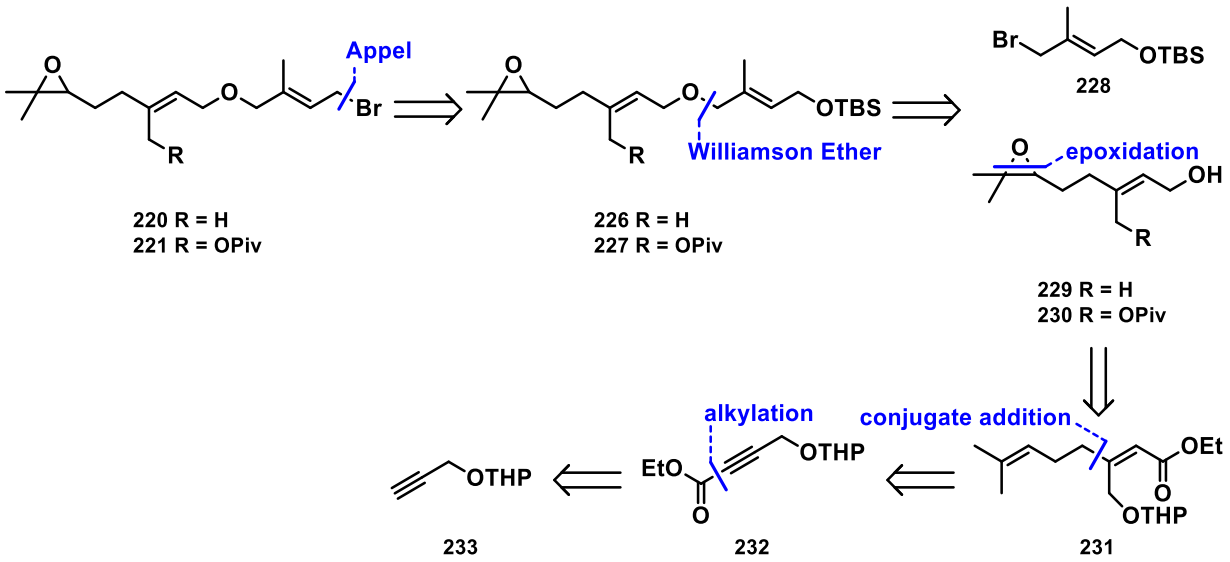


Scheme 50: Overview of both possible retrosynthetic pathways.

5.1.1 Epoxide Opening Pathway

The synthesis of the required precursors **222** and **223** can be achieved *via* two different routes. To explore both routes, simplified precursors **220** and **224** that lack the pivalate moiety should first be synthesized. In this retrosynthetic analysis, final bromides **220** and **221** used for macrocyclization were introduced *via* a sequence of Appel reaction and TBS deprotection to lead to precursors **226** and **227** that are derived from a Williamson ether synthesis of known compounds **228** and **229**. While **228**

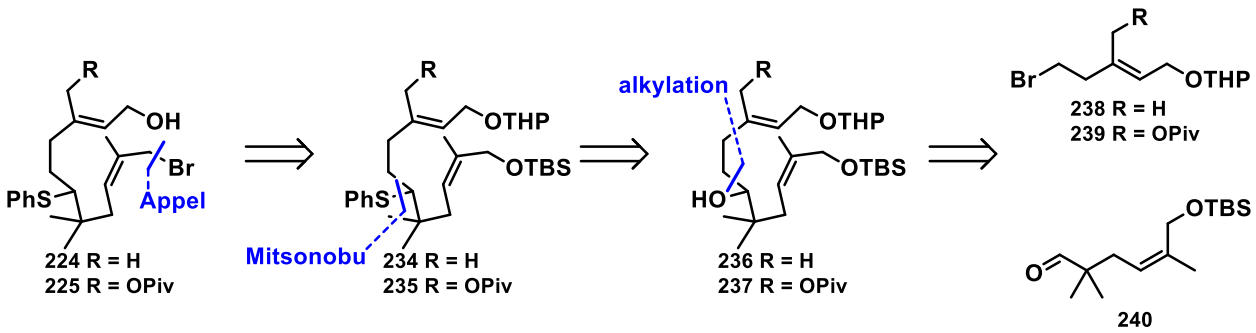
can be synthesized in three steps from isoprene (**20**), **229** must be synthesized from geraniol (**246**) following a previously published route for the simplified precursor. In the retrosynthetic analysis of geraniol bearing the leaving group, reduction followed by epoxidation led to precursor **231**. This compound is also known and can be obtained from THP-protected propargyl alcohol **233** *via* a sequence of conjugate addition and alkylation.



Scheme 51: Retrosynthetic analysis *via* the epoxidation pathway.

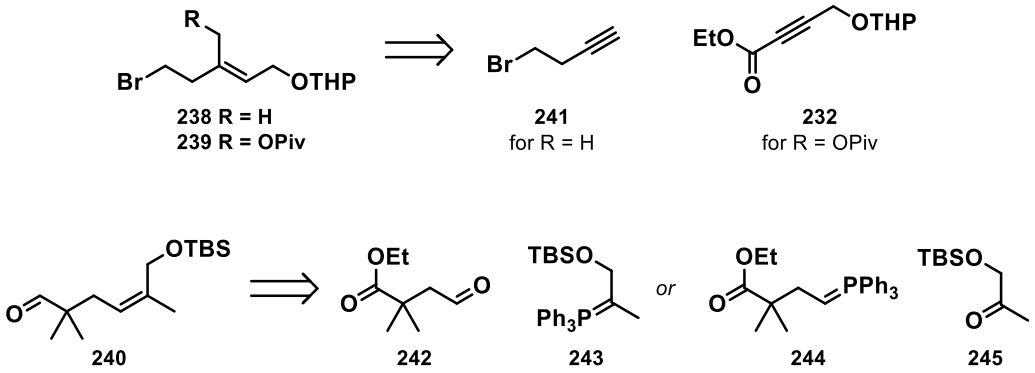
5.1.2 Ether Synthesis Pathway

In this retrosynthetic analysis, macrocyclization occurs *via* an intramolecular Williamson ether synthesis leading to precursors **224** & **225**.[115] A sequence of Appel reaction and deprotection steps leads to **234** & **235** which can be synthesized from alcohols **236** & **237** by a Mitsonobu reaction that introduces the thioether. Alcohols **236** and **237** are formed by a 1,2-addition of bromides **238** and **239** to aldehyde **240**.



Scheme 52: Retrosynthetic analysis *via* the macrocyclic ether synthesis.

For the simplified precursor, northern fragment **238** can be synthesized in a few steps from alkyne **241** *via* zirconium-catalyzed carboalumination followed by protection. For advanced derivative **239**, a similar route as previously described was envisaged; here then using TBS-protected bromoethanol as the nucleophile in the conjugated addition. The southern fragment was to be synthesized *via* a (*Z*)-selective Wittig reaction between ylide **243** and aldehyde **242** or ylide **244** and ketone **245**.



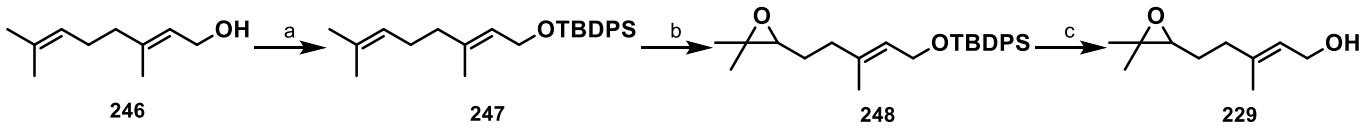
Scheme 53: Retrosynthetic analysis of the northern and the southern fragment.

5.2 Synthesis *via* the Epoxide Pathway

5.2.1 Synthesis of the Simplified Precursor

5.2.1.1 Synthesis of Epoxy-geraniol

The synthesis of epoxygeraniol begins with TBDPS protection of geraniol (**246**). Resulting silyl ether **247** is then epoxidized with *m*CPBA. Since the formation of the sterogenic center generated is not of interest, a non-chiral peroxide source can be used. The synthesis is completed by deprotection with TBAF with good to quantitative yields over three steps.

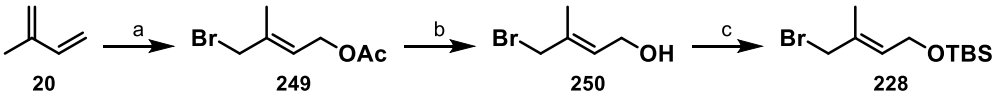


Scheme 54: Synthesis of epoxy-geraniol **229**: a) TBDPSCl, imid., DMF, 0 °C, *to* rt, 2 h, *quant*.; b) *m*CPBA, CH_2Cl_2, 0 °C, 1.5 h, 70%; c) TBAF, THF, 0 °C *to* rt, 3 h, 77%.

5.2.1.2 Synthesis of the Isoprene Derivative

The synthesis of isoprene derivative **228** follows the route also used by our group, except that a TBS group instead of a THP protecting group is incorporated at the end which is thought to be more easily cleaved under slightly basic conditions in the presence of the epoxide. First, isoprene (**20**) is reacted with NBS in acetic acid to give acetate **249**. The resulting crude product, a mixture of *E*- and *Z*-

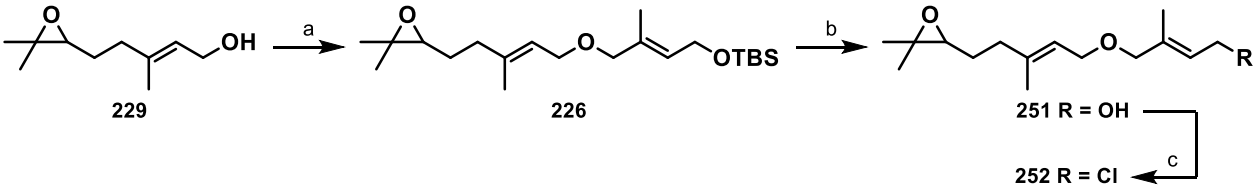
isomers, is submitted to deprotection to give alcohol **250** in good yield. Careful workup and purification in the absence of light gave the desired pure *trans* alcohol **250** which was TBS-protected in moderate yield to furnish final product **228**. A small optimization study of the TBS-protection process finally gave maximum yields of around 50%.



Scheme 55: Synthesis of isoprene derivative **228**: a) NBS, AcOH, 0 °C *to* rt, o/n; b) K_2CO_3, MeOH/H_2O, rt, 1 h, 25% *o2s*; c) TBSCl, imid., DMF, 0 °C *to* rt, 1 h, 48%.

5.2.1.3 Towards the Final Simplified Precursor

When the Williamson ether synthesis was carried out under typical reaction conditions, the product afforded **226** in 11% yield but by changing the solvent to DMF the yield could be increased to 70%. Subsequent deprotection with TBAF again afforded desired alcohol **251** and an Appel reaction was then tested to convert **251** to an iodide. TLC analysis showed complete conversion but isolation was difficult because the product is very sensitive to light and temperature. Therefore, conversion to chloride **252** turned out to be the better solution which could be carried out in good yield under the established standard conditions. Thus, chloride **252** was subjected to various attempts to close the macrocycle. When different lithium bases were added, it was found that even at low temperatures (< -78 °C) the opening of the epoxide was faster than the replacement of the halogen metal. Therefore, the macrocyclization approach was pursued.



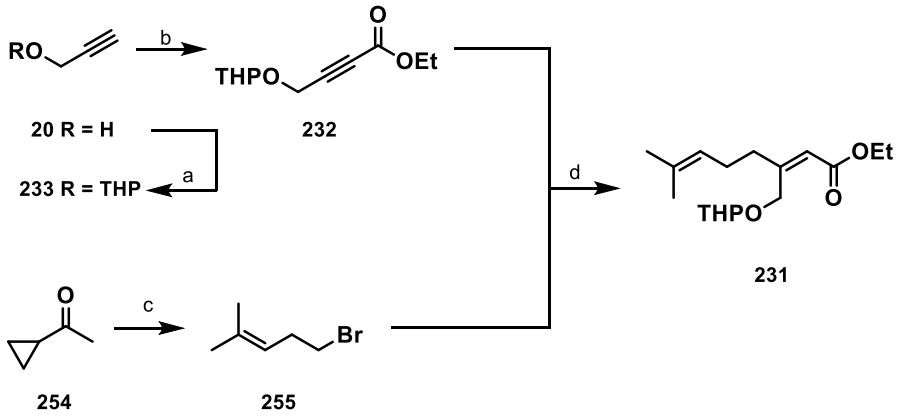
Scheme 56: Synthesis towards the final precursor of the epoxide opening macrocyclization: a) NaH, DMF, 0 °C *to* rt, 1 h, *then* **228**, rt, o/n, 70%; b) TBAF, THF, 0 °C *to* rt, 2 h, 87%; c) NCS, DMS, CH_2Cl_2 0 °C, 5 min, *then* **251**, CH_2Cl_2, 0 °C, *to* rt, 4 h, 65%.

5.2.2 Synthesis of the Advanced Precursor

5.2.2.1 Synthesis of the Advanced Epoxy-geraniol

The synthesis of the advanced precursor follows a known procedure for the selective introduction of oxygen at the primary methyl group.[116] It begins with THP protection of propargyl alcohol **253** in good yield, followed by acylation to afford alkynoate **232**. Bromide **255** was readily available by conversion of ketone **254** and conjugate addition was tested. Unfortunately, a 5:1 E/Z mixture of the

two double bond isomers resulted and together with the results from the experiments with the simplified precursor, this idea was eventually discarded.

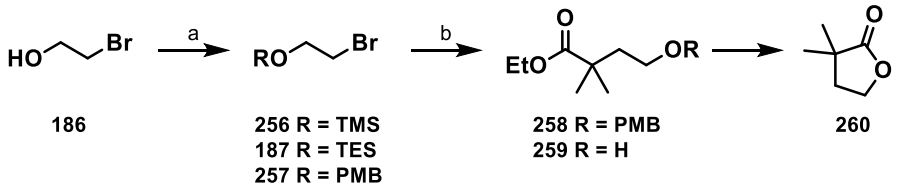


Scheme 57: Synthesis towards the advanced precursor for the macrocyclisation via the epoxide opening: a) *p*TsOH·H_2O, DHP, CH_2Cl_2, 0 °C *to* rt, 1 h, 85%; b) *n*BuLi, THF, -78 °C, 1 h, *then* ClCOOEt, -78 °C, *to* -10 °C, 2 h, 92%; c) MeMgBr, THF, rf, 0.5 h, *then* H_2SO_4/H_2O, 10 °C, 0.5 h, 51%; d) **255**, Mg, I_2 (cat.), THF, rt, 2 h, cool *to* -50 °C, CuBr·DMS, THF, -50 °C, cool *to* -78 °C, **232**, -78 °C, 1 h, 72% (5:1 *E*/*Z*).

5.3 Synthesis *via* the Williamson Ether Macrocyclization

5.3.1 Synthesis of the Southern Fragment

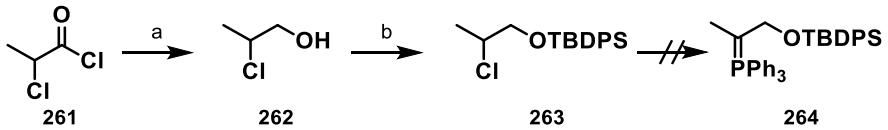
In a first experiment, aldehyde **242** and ylide **243** were selected. Starting with TMS- and TES-protected bromoethanol (**186**), two bromides **256** and **187** were synthesized. These were submitted for alkylation with ester **192**. It was intended to cleave off the protecting group *in situ* under acidic conditions to form alcohol **259**. However, only lactone **260** could be isolated in moderate yield. Interestingly, the ring opening to desired alcohol **259** was published but could not be reproduced in the present work.[117] Therefore, the protecting group was exchanged for PMB to ensure milder deprotection conditions; however, the same results were observed in this case as well.



Scheme 58: Failed Synthesis of aldehyde **242**: a) HMDS, 0 °C to rt, o/n, *or* NEt_3, TBSCl, 0 °C *to* rt, o/n, 84% *or* PMB-$NHCCl_3$, CSA, CH_2Cl_2, rt, o/n, 71%; b) *n*BuLi, DIPA, -78 °C, 10 min, *then* **192**, -78 °C, 1 h, *then* **256**, **187** or **257**, *to* rt o/n, then 2 M HCl, n.d. or 70%.

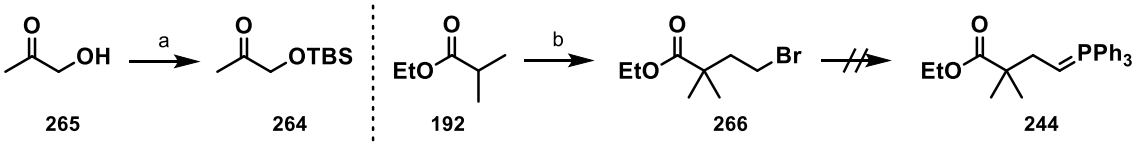
On the other hand, 2-chloropropanoyl chloride (**261**) was reduced and alcohol **262** was obtained in good yield which was then to be transferred to the TBDPS ether to form silyl ether **263**. However,

TBS protection of alcohol **262** failed. This proved to be unstable on the silica gel column and so it was used directly for the S_N2 reaction to introduce the phosphine and subsequent deprotonation to ylide **264**. Unfortunately, attempting to perform other conditions or two-step procedures according to the Finkelstein reaction resulted only in recovery of the starting material.



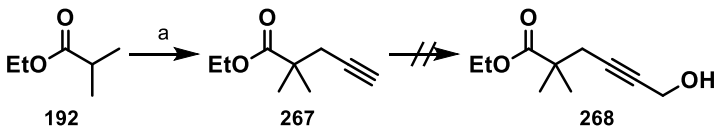
Scheme 59: Failed synthesis of ylide **264**: a) $LiAlH_4$, Et_2O, rf, 3 h, then cool to 0 °C, **261**, 0 °C, 30 min, 70%; b) TBDPSCl, imid., DMF, 0 °C, *then* rt, 1.5 h, *quant*.

Therefore, the other pair consisting of ketone **245** and ylide **244** was chosen. α-Hydroxyacetone could be protected in very good yield as TBS ether. On the other hand, ester **192** was alkylated with 1,2-dibromoethane as alkylating agent and bromide **266** was obtained. However, the same problems occurred here as with the other halide. Therefore, a new strategy had to be devised.



Scheme 60: Failed synthesis with the second chosen pair for the (*Z*)-selective Wittig reaction: a) TBSCl, imid, CH_2Cl_2, 0 °C, *to* rt, 2.5 h, 90%; b) *n*BuLi, DIPA, THF, -78 °C, 10 min, *then* **192**, THF, -78 °C, 1 h, *then* DBE, *to* rt, o/n, 58%.

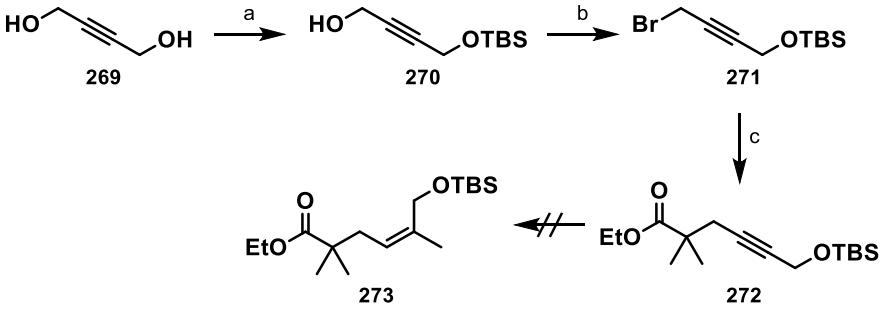
The next consideration was to build up the (*Z*)-olefin *via* zirconium-catalyzed carboalumination after the alkyne was attached to the ester. Therefore, two different approaches were chosen. First, ester **192** was alkylated with propargyl bromide, then the terminal position was deprotonated and extended by addition of formaldehyde. Unfortunately, the deprotonation only led to decomposition products when using standard bases such as LDA, LiHMDS, *n*BuLi or *t*BuLi.



Scheme 61: Failed approach towards the internal carboalumination: a) *n*BuLi, DIPA, THF, -78 °C, 10 min, *then* **192**, THF, -78 °C, 1 h, *then* propargylbromide -78°C, warm *to* rt, o/n, 72%.

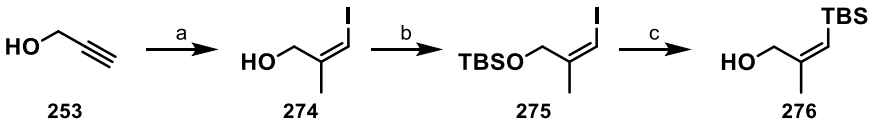
The second approach starts from diol **269** which is first mono-protected in moderate yield followed by a two-step Appel-like reaction to form bromide **271** which is then used as an alkylating agent to

finally target ester **272**. This was submitted for the internal carboalumination reaction. According to the literature, this transformation is not widely used because it must be carried out under harsh conditions and regioisomers are often formed.[118] In this case, no reaction was observed when the mixture was heated under refluxing conditions for several hours. Presumably, the temperature or pressure was not high enough to cause the alkyne to react with the active species.



Scheme 62: Failed approach *via* the internal carboalumination reaction to build up the (*Z*)-selective olefin: a) TBSCl, imid., DMF, rt, o/n, 29%, b) *i.* MsCl, NEt_3, THF, 0 °C, 1 h, *then* rt, 30 min, *ii.* LiBr, THF, rt, 30 min, 54%; c) *n*BuLi, DIPA, THF, -78 °C, 10 min, *then* **192**, THF, -78 °C, 1 h, *then* **271**, -78 °C, *to* rt, o/n, 86%.

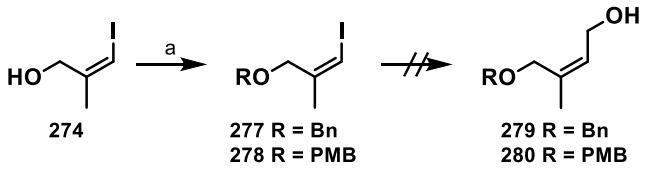
The next approach found was a procedure in which, starting from propargyl alcohol, (*Z*)-vinyl iodide **274** was obtained by adding CuI and methylmagnesium bromide which was then protected with TBS to obtain iodide **275** in good yield. The reaction with various lithium bases followed by addition of paraformaldehyde gave the product of a [1,4]-*retro*-Brook rearrangement in good yields rather than the homologous alcohol. This is interesting in that this reaction was described only once briefly in another paper.[119] However, this method has not previously been reported to construct trisubstituted (*Z*)-vinylsilanes which can be used for a variety of chemical reactions such as Hiyama coupling.[120,121] The synthesis of (*E*)-vinylsilanes, on the other hand, has been studied in greater depth.[122]



Scheme 63: Unexpected synthesis of vinylsilanes **276**: a) CuI (10 mol%), MeMgBr, THF, -20 °C, *then* warm *to* -10 °C, -10 °C, 30 min, *then* I_2, THF/Et_2O (1:1), rt, 30 min, 70%; b) TBSCl, imid., CH_2Cl_2, 0 °C *to* rt, o/n, 84%; c) *n*BuLi, THF, -78 °C, 1 h, then $(CH_2O)_n$, rt, 1 h, 76%.

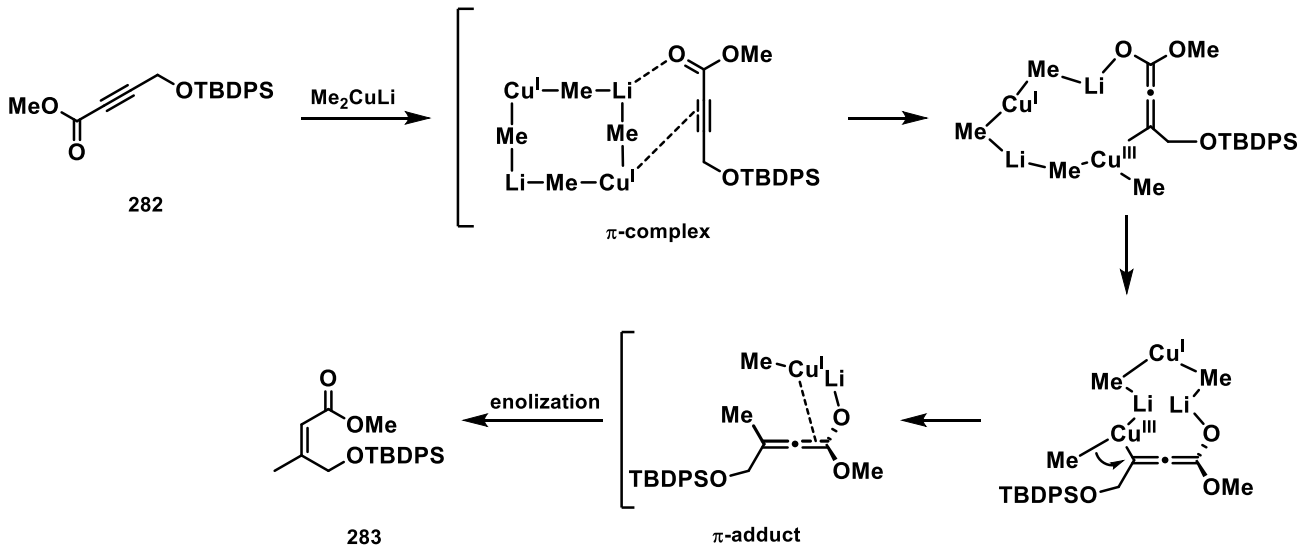
To avoid this side reaction, the protecting group was exchanged for benzyl or PMB. Both iodine compounds **277** and **278** could be synthesized in moderate yield for PMB and in good yield for Bn. The formation of a mixture of E/Z isomers in a 10:1 ratio was also observed upon incorporation of

the PMB group. Unfortunately, lithium-halogen exchange employing various procedures[123,124] and trapping of the carbanion with paraformaldehyde only led to many compounds. Since only electrophiles other than paraformaldehyde were used in the literature, this could also be a critical issue.



Scheme 64: Tested protection groups for the one carbon homologation: a) NaH, THF, 0 °C, 1 h, *then* BnBr, rt, 1 h, 91% or NaH, THF, 0 °C, 1 h, *then* PMBCl, rt, 1 h, 56%.

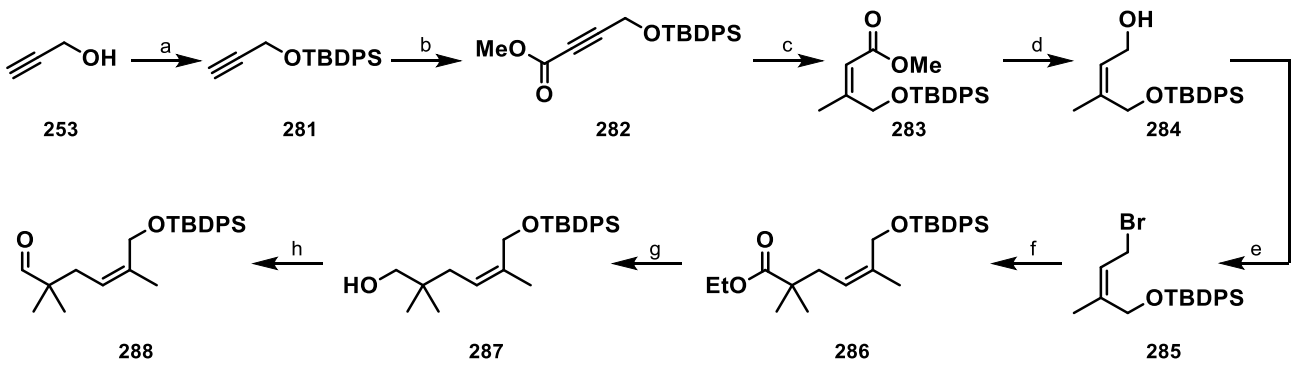
Again, a new strategy was planned in which a conjugated addition to an acetylenic ester is carried out. Formation of the desired (*Z*)-configured double bond is guaranteed by stabilization of the alkene-ketene acetal intermediate with the help of the copper ion (scheme 65). The exact mechanism is still part of controversial debates but one possible explanation is associated with the formation of a copper(III) intermediate. After formation of the π-complex and attack of the copper species in the β-position, the copper(III) intermediate is obtained. This alkene intermediate allows the attack of the methyl radical on one side, while the copper radical bound on the opposite side shields it, since the double bonds of the allene are orthogonal to each other and the copper is complexed by the oxyanion. The π-adduct then formed enolizes to the final product, yielding only the desired (*Z*)-alkene.[125]



Scheme 65: Stereochemical rational of the conjugate addition to ynoates.

Starting from propargyl alcohol **253**, acetylenic ester **282** could be synthesized in near quantitative yield after TBDPS ether protection and then acylation. The subsequent conjugate addition was carried

out using MeLi as a nucleophile giving desired enone **283** which eventually carried the (*Z*)-configured double bond. Reduction of the ester to alcohol **284** was carried out in excellent yield and this was followed by an Appel reaction which afforded bromide **285**. This was used without further purification for the subsequent alkylation with ethyl isobutyrate **192** which gave ester **286** in good yield. Presumably, the yield can be increased after purification of bromide **285**. The synthesis of southern fragment **288** was completed *via* a reduction-oxidation sequence in excellent yields. Overall, the southern fragment was synthesized in 8 steps with a total yield of 48%.



Scheme 66: Final synthesis of the southern fragment **288** *via* the conjugate addition method: a) TBDPSCl, imid., CH_2Cl_2, 0 °C *to* rt, o/n, *quant.*; b) *n*BuLi, THF, -78 °C, 1 h, *then*, $ClCO_2Me$, -78 °C, *to* rt, 2 h, 91%; c) MeLi, CuI, THF, 0 °C, 30 min, cool *to* -78 °C, **282**, THF, -78 °C, 2 h, 93%; d) DIBAL-H, CH_2Cl_2, -78 °C, 5 min, 98%; e) PBr_3, Et_2O, 0 °C *to* rt, 30 min; f) *n*BuLi, DIPA, THF, -78 °C, 10 min, *then* **192**, THF, -78 °C, 1 h, *then* **285**, -78 °C *to* rt, o/n, 65% *o2s*; g) DIBAL-H, CH_2Cl_2, -78 °C, 5 min, 97%; h) DMSO, $(COCl)_2$, CH_2Cl_2, -78 °C, 10 min, *then* **287**, CH_2Cl_2, -78 °C, 15 min, *then* NEt_3, -78 °C *to* rt, 30 min, 91%.

To confirm the configuration of the double bond NOE and NOESY measurements were performed with ester **286**, which confirmed the desired (*Z*) configuration of the double bond. In figure 67 the resonance signals are depicted.

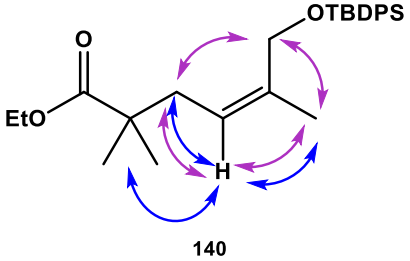
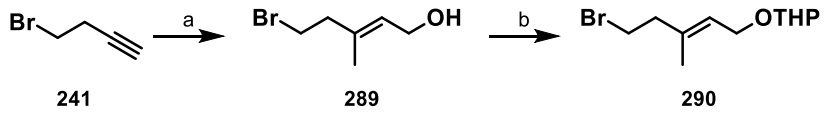


Figure 67: Results of the NOE- and NOESY-experiments on ester **286**: purple arrows for signals in NOE and blue arrows for signals in NOESY.

5.3.2 Synthesis of the Northern Fragment

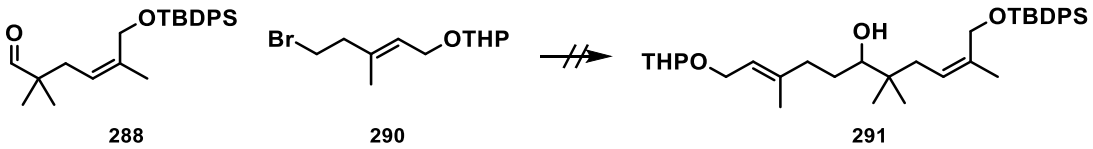
5.3.2.1 Synthesis of the Simplified Northern Fragment

The structurally simplified northern fragment **290** was synthesized in good yield in two steps. First, alkyne **241** was subjected to a carboalumination reaction terminated by the addition of formaldehyde. It afforded alcohol **289** in a very good yield for this complex transformation. The free alcohol was then THP-protected yielding simplified northern fragment **290**.



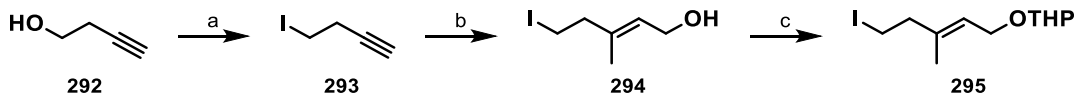
Scheme 68: Synthesis of the simplified northern fragment **290**: a) Cp_2ZrCl_2, $AlMe_3$, CH_2Cl_2 0 °C, 30 min, *then* **241**, CH_2Cl_2, *to* rt o/n, cool *to* 0 °C, $(CH_2O)_n$, 0 °C, 3 h, 68%; b) DHP, *p*TsOH, CH_2Cl_2, 0 °C, 30 min, 81%.

Now that both fragments were available, initial test coupling reactions were performed. The use of a standard procedure[126] to convert the Grignard reagent derived from bromide **290** did not result in conversion. Extending the time to form the reagent also did not result in the formation of the organometallic species. After termination of the reaction by addition of water, both fragments could be reisolated in quantitative yield. Therefore, corresponding iodide **295** was planned to be synthesized in the following, as it can be readily converted to various organometallic reagents including the organo-lithium species.



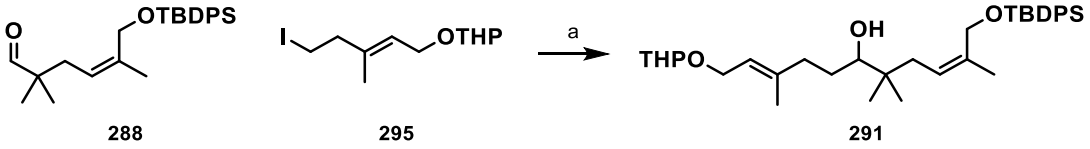
Scheme 69: Tested 1,2-addition of southern **288** and simplified northern fragment **290**.

The new northern fragment was synthesized according to the same concept as described for bromide **290**. Starting with alcohol **292**, a two-step procedure was employed to obtain iodide **293** in moderate yield. Presumably, the yield could be increased by working under light exclusion and heating under refluxing conditions overnight. Carboalumination gave alcohol **294** in good yield which was protected as a THP acetal and thus completed the synthesis of new northern fragment **295**.



Scheme 70: Synthesis of improved simplified northern fragment **295**: a) *i.* MsCl, NEt_3, CH_2Cl_2, 0 °C, 1 h, *ii.* NaI, acetone, rf, 4 h, 31%; b) Cp_2ZrCl_2, $AlMe_3$, CH_2Cl_2 0 °C, 30 min, *then* **293**, CH_2Cl_2, *to* rt o/n, cool *to* 0 °C, $(CH_2O)_n$, 0 °C, 3 h, 42%; b) DHP, *p*TsOH, CH_2Cl_2, 0 °C, 30 min, 85%.

In a first test reaction, the formation of the desired coupling product was detected. Using *t*BuLi in Et_2O and direct addition of the aldehyde, a yield of 26% was obtained. The exact mass of the product was also determined in an ESI-LCT-HRMS experiment. It should be noted that hydroiodination or β-hydride elimination after halogen-metal exchange are possible side reactions that would drastically lower the yield.[127]

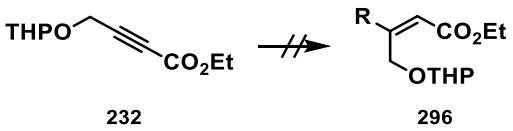


Scheme 71: First test of the addition towards the macrocycle: *t*BuLi, Et_2O, -78 °C, *then* **288**, Et_2O, -78 °C, 5 min, 26%.

5.3.2.2 First Approach towards the Northern Fragment

The first approach is based on the same idea as already described for the southern fragment. It was assumed that a conjugate addition of an organo-copper species to known alkynoate **232** should provide the desired (*E*)-configured double bond. An overview of the synthesis carried out is summarized in scheme 72. Although several reaction conditions are known for this transformation, this reaction proved to be very difficult. First, TBS-protected bromoethanol or dibromoethane were used as halides which were converted to the appropriate Grignard reagents (entries 1-3). Indeed, these organometallic reagents are not stable at low temperatures as they tend to undergo β-hydride elimination giving rise to the corresponding vinyl species. Therefore, direct addition of the desired functionalities was not possible. Next, an attempt was pursued to install a vinyl group which could subsequently be converted to the primary alcohol by hydroboration. Initially, the same promising conditions as applied for the synthesis of the southern fragment were employed to install the vinyl group (entries 4-6). Various solutions of the already available Grignard reagent derived from vinyl bromide were used for this purpose. In all cases, no conversion was found which can be attributed to decompositions of the solutions containing the Grignard reagents. Interestingly, no conversion was observed even when a fresh bottle of vinyl magnesium bromide (entry 7) was chosen. Therefore, transmetallation to the lithium species which can be considered the appropriate metal species was performed next. Here, a different procedure was tried in which the $CuBr{\cdot}Me_2S$ complex served as the copper source (entries

8-10). The copper salt was dissolved in various solvents known to give clear solutions of the salt. No conversion was observed when using old solutions of the readily available vinyl bromide. The intense yellow color of the solutions was noticeable indicating decomposition of the bromide and this was confirmed by ^{1}H NMR analysis. Therefore, a new bottle was used (entries 11-13) but only the same results were found again. Repeating the previous conditions did not lead to a transformation either. A fresh solution of vinyl bromide in diethyl ether was then prepared by condensing the gaseous bromide into the solution. The problem here may have been side reactions, since all commercially available solutions are based on THF. This freshly prepared solution was also subjected to ^{1}H NMR analysis to determine the stability of the solution itself, which indeed showed no signs of decomposition within two weeks stored at 4 °C in the refrigerator. The freshly prepared solution was treated with *t*BuLi and transmetallated with various copper(I) salts (entries 14-16). CuCN which forms higher order cuprates was also tested here. They exert a higher tendency to transfer the carbon-based nucleophilic substituent. Since these also showed no reactivity Gillmann cuprate was finally chosen (entries 17-18) along with activation of the alkynoate by a boron-based Lewis acid. Unfortunately, these conditions did not result in conversion of the starting material. Attempts were also pursued to react the freshly prepared vinyl bromide solution as a Grignard reagent and to transmetallate it to various copper(I) salts which however, did not exert the desired reactivity (entries 19-20). As a last possibility, tin-based methods are also reported where the tin reagent is activated by the addition of phenyllithium to form an ate-complex that transfers the vinyl group to the copper(I) salt. Unfortunately, no conversion was observed in this case either. Based on these results, a different approach was envisaged to access the northern fragment.



232 **296**

Scheme 72: First Approach towards the Northern Fragment.

Table 6: Screening of the conjugate addition approach.

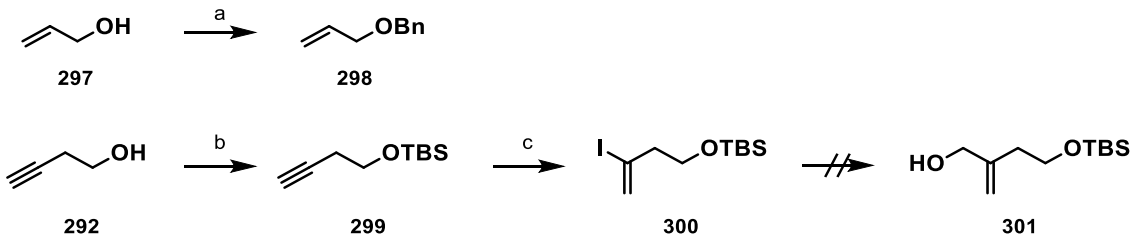
entry	R-Br	metall	Cu-salt	conditions	result
1	$Br(CH_2)_2$	*n*BuLi	CuI	THF, -78 °C, 15 min *then* Cu, THF, -30 °C, 1 h *then* **232**, -78 °C, 2 h	n.c.
2	$TBSO(CH_2)_2$	*n*BuLi	CuI	THF, -78 °C, 15 min *then* Cu, THF, -30 °C, 1 h *then* **232**, -78 °C, 2 h	n.c.

3	$TBSO(CH_2)_2$	*t*BuLi	CuI	THF, -78 °C, 15 min *then* Cu, THF, -30 °C, 1 h *then* **232**, -78 °C, 2 h	n.c.
4	vinylMg (old)	Mg-soln.	CuI	Cu, THF, 0 °C, 0.5 h *then* **232**, -78 °C, 1 h	n.c.
5	vinylMg (old)	Mg-soln.	CuI	Cu, THF, 0 °C, 0.5 h *then* **232**, -78 °C, 1 h	n.c.
6	vinylMg (old)	Mg-soln.	CuI	Cu, THF, 0 °C, 0.5 h *then* **232**, -78 °C, 1 h	n.c.
7	vinylMg (new)	Mg-soln.	CuI	Cu, THF, 0 °C, 0.5 h *then* **232**, -78 °C, 1 h	n.c.
8	vinyl (old)	*t*BuLi	CuBr·DMS	Et_2O, -78 °C, 15 min *then* Cu, Et_2O, -78 °C, 0.5 h *then* **232**, -78 °C *to* rt, 1 h	n.c.
9	vinyl (old)	*t*BuLi	CuBr·DMS	Et_2O, -78 °C, 15 min *then* Cu, DMS, -78 °C, 0.5 h *then* **232**, -78 °C *to* rt, 1 h	n.c.
10	vinyl (old)	*t*BuLi	CuBr·DMS	Et_2O, -78 °C, 15 min *then* Cu, S*i*Pr_2, -78 °C, 0.5 h *then* **232**, -78 °C *to* rt, 1 h	n.c.
11	vinyl (new)	*t*BuLi	CuBr·DMS	Et_2O, -78 °C, 15 min *then* Cu, Et_2O, -78 °C, 0.5 h *then* **232**, -78 °C *to* rt, 1 h	n.c.
12	vinyl (new)	*t*BuLi	CuBr·DMS	Et_2O, -78 °C, 15 min *then* Cu, DMS, -78 °C, 0.5 h *then* **232**, -78 °C *to* rt, 1 h	n.c.
13	vinyl (new)	*t*BuLi	CuBr·DMS	Et_2O, -78 °C, 15 min *then* Cu, S*i*Pr_2, -78 °C, 0.5 h *then* **232**, -78 °C *to* rt, 1 h	n.c.
14	vinyl (selfmade)	*t*BuLi	CuBr·DMS	Et_2O, -78 °C, 15 min *then* Cu, Et_2O, -78 °C, 0.5 h *then* **232**, -78 °C *to* rt, 1 h	n.c.

15	vinyl (selfmade)	*t*BuLi	CuI	Et_2O, -78 °C, 15 min *then* Cu, Et_2O, -78 °C, 0.5 h *then* **232**, -78 °C *to* rt, 1 h	n.c.
16	vinyl (selfmade)	*t*BuLi	CuCN	Et_2O, -78 °C, 15 min *then* Cu, Et_2O, -78 °C, 0.5 h *then* **232**, -78 °C *to* rt, 1 h	n.c.
17	vinyl (selfmade)	*t*BuLi	2-Th-CuCN	Et_2O, -78 °C, 15 min *then* Cu, Et_2O, -78 °C, 1 h *then* **232**, -78 °C *to* rt, 1 h	n.c.
18	vinyl (selfmade)	*t*BuLi	2-Th-CuCN	Et_2O, -78 °C, 15 min *then* Cu, Et_2O, -78 °C, 1 h *then* **232**, $BF_3{\cdot}OEt_2$, -78 °C *to* rt, 1 h	n.c.
19	vinyl (selfmade)	Mg	2-Th-CuCN	I_2 (cat.), THF, rt, 0.5 h, *then* Cu, Et_2O, -78 °C, 1 h *then* **232**, -78 °C *to* rt, 1 h	n.c.
20	vinyl (selfmade)	Mg	CuBr·DMS	I_2 (cat.), THF, rt, 0.5 h, *then* Cu, DMS, -78 °C, 1 h *then* **232**, -78 °C *to* rt, 1 h	n.c.
21	vinyl	Sn	CuI	PhLi, THF, rt, 0.5 h *then* Cu, Et_2O, -78 °C, 0.5 h *then* **232**, Et_2O, -78 °C, 2 h	n.c.

5.3.2.3 Second Approach towards the Northern Fragment

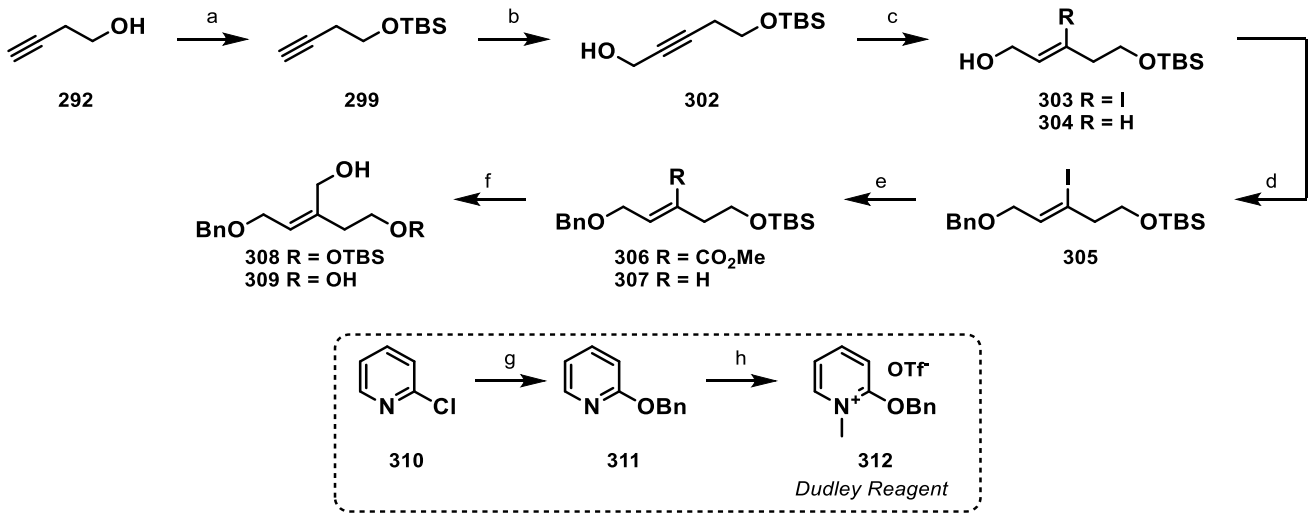
As a next consideration, a (*Z*)-selective cross-metathesis reaction catalyzed by a ruthenium complex was pursued[128] allowing allylbenzyl ether **298** to be synthesized in one step in moderate yields (s. scheme 73). On the other hand, an enal-like system protected as an acetal bearing an exomethylene double bond is required. The synthesis starts with the protection of alcohol **292** as a TBS ether followed by iodination with I-B-BBN which gave vinyl iodide **300** in good yields. Unfortunately, the metallation did not show any reactivity under standard conditions. Probably the quality of the *t*BuLi reagent was not good enough but fresh solutions did not give positive results either. Later, carbonylation was also probed with this molecule but the yields were not good enough to make this sequence viable.



Scheme 73: Tested synthesis *via* a (*Z*)-selective cross metathesis: a) NaH, 0 °C, 1 h, *then* BnBr, 75 °C, 1 h, 47%; b) TBSCl, imid., CH_2Cl_2, 0 °C *to* rt, 1.5 h, 92%; c) I-B-BBN, hex, 0 °C *to* rt, o/n, *then* AcOH, NaOAc, rt, 1 h, 72%.

5.3.2.4 Third Approach towards the Northern Fragment

The next approach is based on the hydroalumination of propargyl alcohols which should give the required *trans*-configured double bond. Therefore, alcohol **292** was first protected again as a TBS ether and then acylated with paraformaldehyde as an electrophile which proceeded in very good yield. Alcohol **299** formed was to be used in the next step a hydroalumination using Red-Al® as the reagent of choice. The intermediate aluminum species should be captured with formate esters or various electrophiles (e.g., $(CH_2O)_n$, $MeCO_2CN$, $MeCO_2Cl$, $EtCO_2Cl$, NBS, DMF followed by $NaBH_4$). Interestingly, only the electrophile iodine showed reactivity towards the metal species. Transmetallation with CuCl or MeLi also did not work and led only to bishydrogenated product **304**. Thus, vinyl iodide **303** was obtained in good yield and protected with the Dudley reagent which was synthesized in two steps starting from pyridine **310** according to the literature procedure.[129] This reagent was chosen because the vinyl moiety is considered too unstable under basic or acidic conditions. With protected vinyl iodide **305** in hand halogen metal exchange procedures were tested in the following.



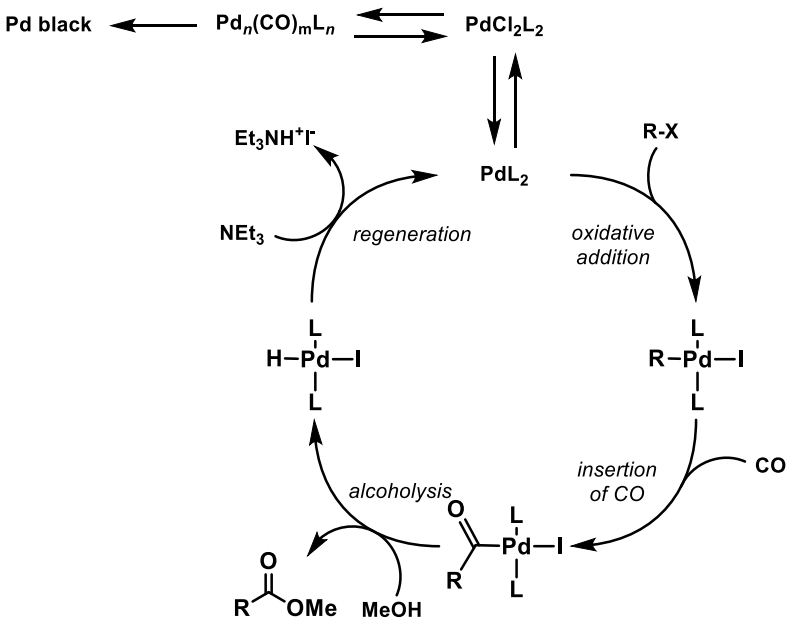
Scheme 74: Failed approach towards the iodide fragment: a) TBSCl, imid., CH_2Cl_2, 0 °C *to* rt, 1.5 h, 92%; b) *n*BuLi, THF, -78 °C, 30 min, *then* $(CH_2O)_n$, -78 °C *to* rt, 30 min, 97%; c) Red-Al®, KO*t*Bu, Et_2O, 0 °C *to* rt, 2 h, *then* EtOAc, 0 °C, 15 min, *then* I_2, THF, -78 °C, 10 min, 75%; d) Dudley Reagent **312**, Proton Sponge®, $PhCF_3$, 83 °C, o/n, 67% (92% brsm); e) $PdCl_2(PPh_3)_2$, NEt_3, PPh_3, CO (1 atm), DMF/MeOH, 70 °C, o/n, 71%; f) DIBAL-H, CH_2Cl_2, -78 °C, 5 min, 75%; g) 18-crown-6, KOH, BnOH, rf, 2 h, 98%; h) MeOTf, PhMe, 0 °C to rt, 1 h, 99%.

Regardless of the metallizing agent chosen, only the hydrogenated product was obtained or the iodide was not reacted at all. The quality of the organometallic reagents was checked by titration and new reagents were ordered if necessary. However, no conversion to the desired product or to similar systems with other electrophiles (e.g. CO_2 or formate esters) was observed.

Table 7: Failed halogen metal exchange procedures to convert vinyliodide **305** into alcohol **308**.

entry	metallating agent	electrophile	temperatures [°C]	result
1	*t*BuLi	$(CH_2O)_n$	-78; -90; -110	**304**; n.c.
2	*n*BuLi	$(CH_2O)_n$	-78 *to* rt	**304**; n.c.
3	*i*PrMgCl·LiCl	$(CH_2O)_n$	0 *to* rt	n.c.
4	MeLi	$(CH_2O)_n$	0; rt	**304**; n.c.
5	*t*BuLi	$EtCO_2Cl$	-78; -90; -110	**304**; n.c.
6	*t*BuLi	CO_2	-78; -90; -110	**304**; n.c.
7	MeLi	$EtCO_2Cl$	0; rt	**304**; n.c.
8	MeLi	CO_2	0; rt	**304**; n.c.

Palladium-catalyzed carbonylation reactions and Heck alkoxycarbonylations, represent another way to convert vinyl iodides into the corresponding enones.[130,131] A very interesting type of carbonylation was described by Mats Larhed, who used metal-bonded carbon monoxide that can be released under microwave irradiating conditions.[132,133] Here, after some test reactions the focus was on transition metal-based carbonylations. The mechanism of the carbonylative cross-coupling reaction has already been studied by several groups and it is depicted in scheme 75.[131,134–137] The mechanism starts with an oxidative addition and insertion into the carbon-halogen bond after formation of the necessary *in situ* formation of the Pd(0) species. Subsequently, carbon monoxide inserts into the palladium-carbon bond to form an acyl-palladium complex. The latter undergoes an alcoholysis by the attack of the nucleophile in this case methanol forming the desired enone and the hydropalladium complex. The latter is regenerated by decomposition into the active Pd(0) species and HI which is neutralized by the base NEt_3. It should be noted that "Pd black" formation is observed initially when the thermally unstable complex $Pd_n(CO)_mL_n$ is formed[138] which as was later found can be prevented by adding an excess of base and ligand at a lower reaction temperature.



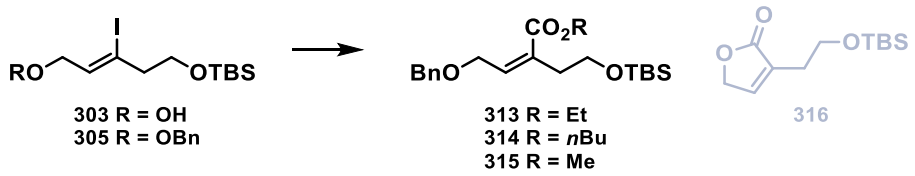
Scheme 75: Mechanism of a Heck alcoxycarbonylation (with L = PPh_3).

Therefore, the first test reactions were conducted as summarized in table 8. Either the conversion of protected iodide **305** to enone **313** or **314** or unprotected iodide **303** to lactone **316** was tested. Following Larhed's protocol, no product could be isolated because the reaction mixture decomposed due to microwave irradiation (entry 1). Using the same conditions without irradiation, traces of the desired product were found as judged by mass spectrometric analysis (entry 2). By slightly changing the conditions, small amounts of the desired products could be isolated: First, the palladium source was changed from a Pd(II) salt to palladium(0) on charcoal, the base was exchanged for DIPEA and DMAP was used as an additive to promote attachment of the alcohol solvent to the palladium complex (s. entry 3). For the unprotected alcohol, 34% of the desired lactone was isolated but unfortunately the lactone could not be opened under either basic or acidic conditions without loss of the TBS group. When these conditions were applied to protected iodide **305**, only traces of the desired product were detected (s. entry 4). Therefore, the alcoholic solvent was replaced by *n*BuOH and finally small amounts of the desired product were isolated (s. entry 5). With these motivating results in hand, both optimizations could be carried out but Heck carbonylations with gaseous carbon monoxide were also tested as these tend to have higher reactivity. Initially, two different standard conditions were chosen (s. entries 6-7) but neither led to conversion of unprotected iodide **303**. Finally, using the conditions of Hirama and co-workers[139] for protected iodide **305** (s. entries 8-9) a good yield of 64% of the desired product was obtained. The only drawback was that 60 mol% of catalyst was required for this reaction. Therefore, improved conditions had to be sought. First, the catalyst loading was reduced to 10 mol% and an additional equivalent of PPh_3 was added as a ligand. The idea was that the ligand might be consumed during the reaction. Therefore, the maximum yield was limited to the amount of

catalyst used. As shown in entry 10, the yield was slightly increased to 71%, and the reaction time was also extended to overnight. Next, the more electron-rich ligand P*n*Bu$_3$ was chosen (s. entry 11), which interestingly did not lead to any conversion. By returning to the previous conditions and increasing the amount of ligand added to two equivalents of PPh$_3$, 96% of desired enone **321** was finally isolated (s. entry 12).

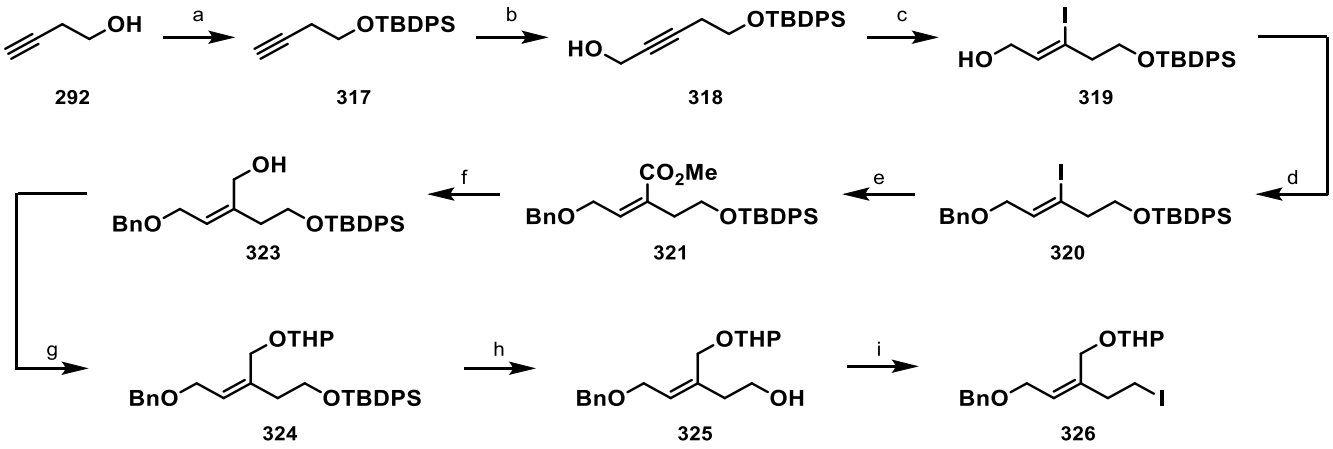
Table 8: Explored and optimized carbonylation reaction towards enone **306**.

entry	starting material	conditions	result
1	**305**	$Mo(CO)_6$, $Pd(OAc)_2$, EtOH, DBU, dioxane, 115 °C, 15 min, µwave	burned
2	**305**	$Mo(CO)_6$, $Pd(OAc)_2$, EtOH, DBU, dioxane, 115 °C, 15 min	traces **313**
3	**303**	$Mo(CO)_6$, Pd/C, EtOH, DIPEA, DMAP, dioxane, 115 °C, 15 min	**313** (34%)
4	**305**	$Mo(CO)_6$, Pd/C, EtOH, DIPEA, DMAP, dioxane, 115 °C, 15 min	traces **313**
5	**305**	$Mo(CO)_6$, Pd/C, EtOH, DIPEA, DMAP, dioxane, 115 °C, 15 min	**313** (21%)
6	**303**	$PdCl_2(PPh_3)_2$, K_2CO_3, H_2NNH_2, THF, rt, 72 h	n.c.
7	**303**	$Pd(OAc)_2$, NaOAc · 3 H_2O, MeOH, rt, o/n	n.c.
8	**305**	$PdCl_2(PPh_3)_2$ (60 mol%), NEt_3, DMF/MeOH,70 °C, 1 h	**306** (64%, 50 mg scale)
9	**305**	$PdCl_2(PPh_3)_2$ (60 mol%), NEt_3, DMF/MeOH, 70 °C, 1 h	**3006** (64%, 500 mg scale)
10	**305**	$PdCl_2(PPh_3)_2$ (10 mol%), PPh_3 (1 eq) NEt_3, DMF/MeOH, 70 °C, o/n	**36** (71%)
11	**305**	$PdCl_2(PPh_3)_2$ (10 mol%), P*n*Bu$_3$ (1 eq) NEt_3, DMF/MeOH, 70 °C, o/n	n.c.
12	**305**	$PdCl_2(PPh_3)_2$ (10 mol%), PPh_3 (2 eq) NEt_3, DMF/MeOH, 70 °C, o/n	**321** (96%)



Scheme 76: Explored and optimized carbonylation reaction towards enone **306**.

With these conditions, further synthesis to the northern fragment could finally be investigated. Unfortunately, the next reaction led to the next hurdle. The reduction with DIBAL-H worked well on a small scale, but on a larger scale the yield dropped dramatically. Diol **309** was found to be a competing byproduct formed. With the small amounts available, alcohol **308** was protected as the THP acetal in the following, but even under the chosen conditions, the TBS group was cleaved. Thus, the more stable TBDPS group had to be incorporated and the whole sequence repeated.

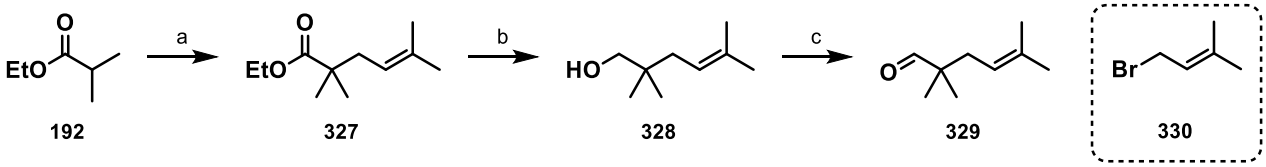


Scheme 77: Final synthesis of the southern fragment **326** with the correct protection groups: a) TBDPSCl, imid., CH_2Cl_2, rt, o/n, *quant.*; b) *n*BuLi, THF, -78 °C, 30 min, *then* $(CH_2O)_n$, -78 °C *to* rt, 30 min, 75% (87% brsm); c) Red-Al®, Et_2O, 0 °C *to* rt, 1 h, *then* EtOAc, 0 °C, 15 min, *then* I_2, THF, -78 °C, 10 min, 95%; d) Dudley Reagent **312**, Proton Sponge®, $PhCF_3$, 83 °C, o/n, 64% (87% brsm); e) $PdCl_2(PPh_3)_2$, NEt_3, PPh_3, CO (1 atm), DMF/MeOH, 70 °C, o/n, 97%; f) DIBAL-H, CH_2Cl_2, -78 °C, 5 min, 90%; g) DHP, *p*TsOH·H_2O, CH_2Cl_2, 0 °C, 10 min, 95%; h) TBAF, THF, 0 °C *to* rt, o/n, 93%; i) imid., I_2, PPh_3, CH_2Cl_2, rt, 2 h, 86%.

Again, alcohol **292** was protected with the TBDPS group and then extended by one carbon atom to give alcohol **318** in very good yield. Hydroalumination could be carried out here in a similar yield that established the vinyl iodide group. Alcohol **319** was protected with the Dudley reagent as benzyl ether and protected vinyl iodide **320** was used in the following to carry out the Heck carbonylation using the optimized protocol. Enone **321** was obtained in excellent yield. The reduction with DIBAL-H now worked smoothly and the alternative silyl protecting group turned out to be stable so that desired alcohol **323** could be accessed. The subsequent introduction of the THP group had to be

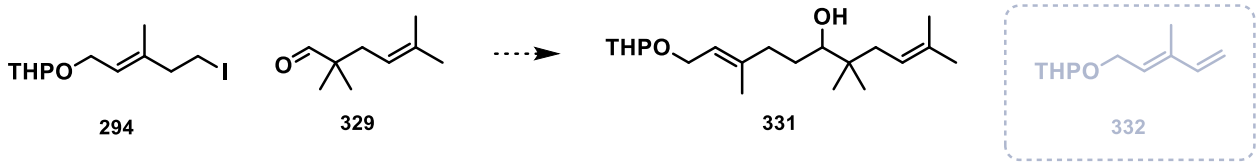
carried out at short reaction times at 0 °C to prevent side reactions and protected triol **324** was obtained in very good yield. Deprotection of the silyl group and conversion of the free alcohol to primary iodide **326** using the conditions for Appel reactions were also achieved out in good yields and the desired northern fragment was obtained in nine steps with an overall yield of 48%. With both fragments in hand, the 1,2-addition could be tested next.

5.3.3 Conjunction of Both Fragments



Scheme 78: Synthesis of test aldehyde **329**: a) *n*BuLi, DIPA, THF, -78 °C, 10 min, *then* **192**, THF, -78 °C, 1 h, *then* **330**, -78 °C *to* rt, o/n, 50%; b) $LiAlH_4$, Et_2O, -78 °C, 30 min, 75%; c) DMSO, $(COCl)_2$, CH_2Cl_2, -78 °C, 10 min, *then* **328**, CH_2Cl_2, -78 °C, 15 min, *then* NEt_3, -78 °C *to* rt, 30 min, 49%.

To explore the merging of the two fragments initial experiments were performed with the previously synthesized test iodide **294** and simpler test aldehyde **329** was also synthesized in three steps from prenyl bromide **330** in good yields (s. scheme 78). First, classical halogen metal exchange conditions at -78 °C were investigated (s. table 9, entry 1). Unfortunately, these showed no consumption of the iodide leading to the conclusion that the quality of the *t*BuLi was insufficient. However, the quality of this reagent is critical for this reaction. An indication concerning its quality is that the solution creates flames when exposed to air. Unfortunately, this was no longer the case with the solution used in experiment 1.



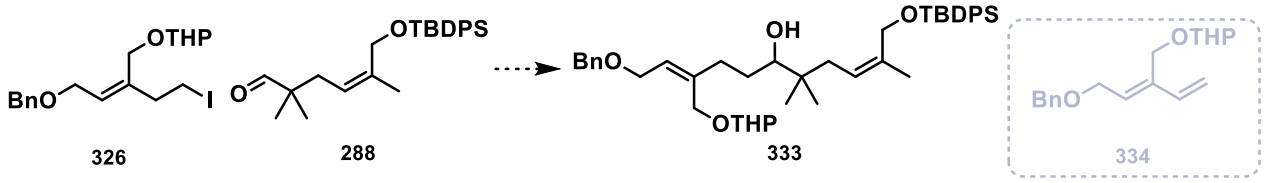
Scheme 79: 1,2-Additon of test substrates **294** and **329**.

Table 9: Tested 1,2-addition of test molecules.

entry	conditions	result
1	*t*BuLi, Et_2O, -78 °C, 0.5 h *then* **329**, Et_2O, -78 °C, 0.5 h	n.c.
2	*t*BuLi, Et_2O/HMPA, -78 °C *to* rt, 0.5 h *then* cool to -78 °C, **329**, Et_2O, -78 °C, 2 h	**332**

3	*t*BuLi, Et_2O, -78 °C, 0.5 h *then* **329**, Et_2O, -78 °C, 2 h	**331** traces
4	*t*BuLi, Et_2O, -78 °C, 2 h *then* **329**, Et_2O, -78 °C *to* rt, o/n	**331** traces
5	*t*BuLi, Et_2O, -40 °C, 0.5 h *then* **329**, Et_2O, -40 °C, 2 h	**331** traces
6	*t*BuLi, THF, -78 °C, 0.5 h *then* $LaCl_3 \cdot 2$ LiCl, THF, -78 °C, 1 h *then* **329**, Et_2O, -78 °C, 1 h	**331** traces

Further experiments were performed with a fresh bottle of the lithium-organic reagent. A mixture of Et_2O and HMPA (s. entry 2) resulted in the consumption of iodide **294** and the formation of a new very UV-active spot that was found to be less polar on TLC than the parent material. The product could not be isolated, presumably being diene **332** formed by β-hydride elimination. Therefore, HMPA was again excluded from the reaction mixture and the original conditions were employed again (entry 3) resulting in a trace of product as judged by thin-layer chromatography. Confirmation of the formation of the product was also obtained by ESI-LCT-HRMS. Increasing the times of transmetallation or changing the temperatures during this step also did not improve the yield (entries 4-5). When the newly formed organolithium speicies was transmetallated into the corresponding lanthanum (entry 6), only traces of the desired product were found to be formed. In studying these reactions TLC analysis was performed prior to the addition of the aldehyde. In all cases, the UV-active spot of iodide **294** disappeared and a non-UV-active spot of similar polarity was formed suggesting that the halogen metal exchange succeeded but that the lithiate was not stable at the chosen temperatures. Since these were only test substrates, it was assumed that the organolithium species of the original substrates might be more stable because it may be stabilized by the neighboring oxygen groups of the protecting groups. However, when the desired substrates were employed the results did not change. In most cases using the same conditions as described in table 9, only traces of desired product **333** were found to have formed, and in most cases TLC analysis again showed a strongly UV-active spot that could be diene **334**. Unfortunately, this could not be isolated either.



Scheme 80: 1,2-Additon of correct substrates **326** and **288**.

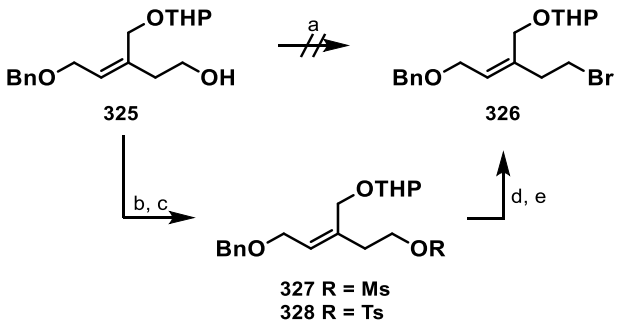
Therefore, a few more test reactions were performed to rule out possible systematic errors. One consideration was that the quality of the solvent was not sufficient to make this type of reaction feasible. Therefore, different sources were chosen (s. table 10, entries 1-3) but they gave similar results throughout. The best yield was obtained with freshly distilled Et_2O over sodium and benzophenone, and the halogen metal exchange for this case was studied in more detail. When the transmetallation reaction time was extended, only the formation of diene **334** was observed, and when it was shortened to about 1 min, only traces of the desired product were found. This means that the time required for complete conversion of iodide **326** must be about 30 min, since after 1 min iodide **326** was still visible according to TLC analysis and after 20-30 min this was no longer present (s. entries 4-5). Entry 6 also shows a lower temperature but no improvement was found.

Table 10: Tested 1,2-addition of correct molecules.

entry	conditions	result
1	*t*BuLi, Et_2O (SPS), -78 °C, 0.5 h *then* **288**, Et_2O, -78 °C, 1 h	**334**
2	*t*BuLi, Et_2O (bottle), -78 °C, 0.5 h *then* **288**, Et_2O, -78 °C, 1 h	**333** (4%)
3	*t*BuLi, Et_2O (freshly distilled), -78 °C, 0.5 h *then* **288**, Et_2O, -78 °C, 1 h	**333** (10%)
4	*t*BuLi, Et_2O (freshly distilled), -78 °C, 2 h *then* **288**, Et_2O, -78 °C, 1 h	**334**
5	*t*BuLi, Et_2O (freshly distilled), -78 °C, 1 min *then* **288**, Et_2O, -78 °C, 1 h	**333** traces
6	*t*BuLi, Et_2O (freshly distilled), -90 °C, 0.5 h *then* **288**, Et_2O, -90 °C, 1 h	**333** traces

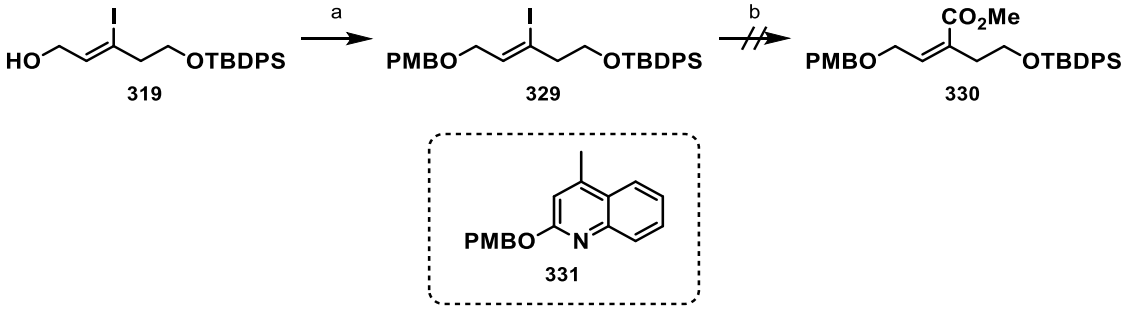
This suggests that the main problem is that the lithiate is either not stable or not reactive enough for 1,2-addition to occur. Rather, β-hydride elimination appears to be preferred. Therefore, perhaps alternatively other organometallic species such as SmI_2, LiDBB or Mg^0 can be used to realize the transformion. When using freshly prepared SmI_2 or LiDBB under similar conditions no transformation of the iodide was observed. When the use of the Grignard reagent was attempted, no conversion was observed either. Therefore, it was assumed that the Grignard reagent generated from the less reactive bromide may exhibit the desired reactivity instead. Starting with alcohol **325**, bromide **326** was synthesized following various routes and these included either a direct Appel reaction or a two-step pro-

cedure with mesylate **327** or tosylate **328** as intermediates. Although bromide **326** was readily available, a Grignard reaction did not lead to the desired product because the same side reactions occurred as described previously.



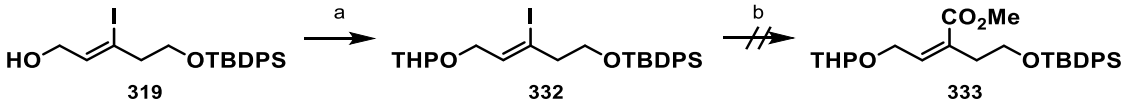
Scheme 81: Synthesis of bromide **326**: a) *decomp.*; b) NEt_3, MsCl, CH_2Cl_2, 0 °C *to* rt, 30 min, 87%; c) NEt_3, TsCl, DMAP, CH_2Cl_2, 0 °C *to* rt, o/n, 85%; d) NaBr, DMF, 50 °C, o/n, 73%; e) NaBr, DMF, 50 °C, o/n, 78%.

Another problem could be associated with the chosen protecting groups, since they can interfere with the desired reactivity. First, the benzyl group was replaced by the more electron-rich PMB group which has the advantage of reducing the possibility of deprotonation in the benzylic position (s. scheme 82). Although protection with the PMB version using Dudley´s reagent was readily achieved, the subsequent Heck carbonylation did not proceed as hoped. No product was obtained despite the fact that the starting material was consumed.



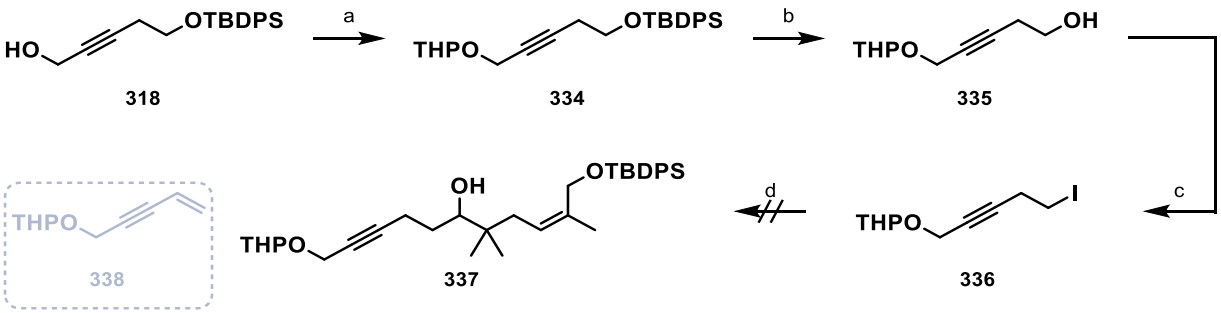
Scheme 82: Failed synthesis of the PMB-derivative: a) MeOTf, MgO, **331**, $PhCF_3$, 0 °C *to* rt, 1 h, 73%; b) $PdCl_2(PPh_3)_2$, NEt_3, PPh_3, CO (1 atm), DMF/MeOH, 70 °C, o/n, *decomp*.

Next, an attempt was pursued to install the THP group (s. scheme 83). Since THP ether **332** was available, lithiation procedures according to the literature[140] were also tried, but failed and did not lead to any conversion. Also, the optimized conditions for Heck carbonylation gave the same results as for the PMB derivative. Subsequently, attempts were also made to protect allyl alcohol **319** as a *t*Bu ether but no conversion was achieved using various standard conditions.[141,142]



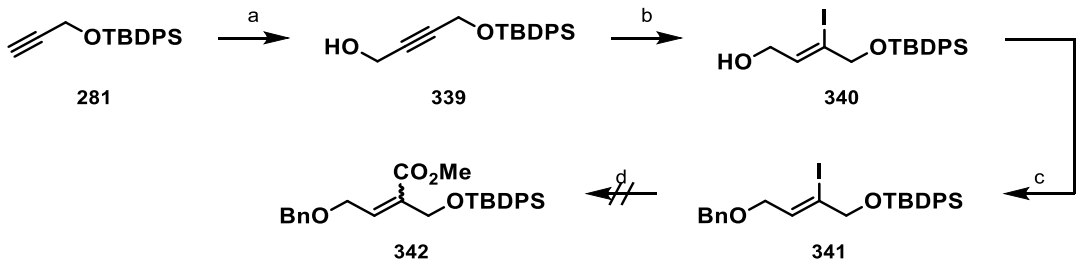
Scheme 83: Failed synthesis of the THP-derivative: a) DHP, *p*TsOH·H_2O, CH_2Cl_2, 0 °C, 30 min, 72%; b) different procedures.

Since all the methods described so far failed, it was speculated that perhaps a molecule functionalized to a lower degree would be the right choice since it should undergo fewer side reactions. Therefore, readily available alcohol **318** was protected as the THP acetal, followed by removal of the TBDPS protecting group and formation of alcohol **335**. The subsequent Appel reaction also succeeded with good yield which finally gave corresponding iodide **336** (s. scheme 84). Unfortunately, after applying the conditions listed in table 10, the TLC analysis again revealed only traces of desired product **337** or non-isolable spot of diene **338**.



Scheme 84: Synthesis of simpler iodide **336** and addition to aldehyde **288**: a) DHP, *p*TsOH·H_2O, CH_2Cl_2, 0 °C *to* rt, 1 h, 91%; b) TBAF, THF, 0 °C *to* rt, o/n, 71%; c) imid., I_2, PPh_3, CH_2Cl_2, rt, 3 h, 86%; d) different procedures.

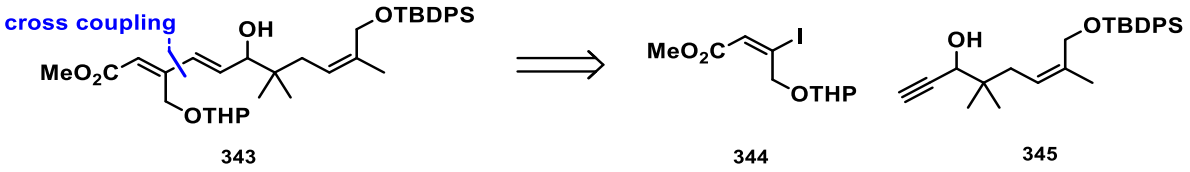
Essentially, what all these approaches have in common is that a diene system can be formed as a product of a side reaction. Therefore, it is assumed that a fragment should be synthesized that is one carbon atom shorter preventing the undesirable β-hydride elimination. On the other hand, the aldehyde was elongated to the epoxide, which could be ring-opened at the less sterically hindered primary position to give the desired product. Synthesis of the truncated northern fragment began with the known TBDPS-protected propargyl alcohol **281** which was acetylated with paraformaldehyde to give alcohol **339**. Hydroalumination using Red-Al® gave vinyl iodide **340** which was then benzyl-protected to give cross-coupling precursor **341** in good yield. Unfortunately, at this stage the success story ended, as an inseparable 1:1 mixture of double bond isomers was formed in poor yield under the known optimized conditions.



Scheme 85: Aborted synthesis of the shortened northern fragment: a) *n*BuLi, THF, -78 °C, 30 min, *then* $(CH_2O)_n$, -78 °C *to* rt, o/n, 83%; b) Red-Al®, Et_2O, 0 °C, 1 h, *then* EtOAc, 0 °C, 20 min, *then* I_2, 0 °C, 10 min, 56%; c) Dudley Reagent, Proton Sponge®, $PhCF_3$, 83 °C, o/n, 56% (65% brsm); d) $PdCl_2(PPh_3)_2$, NEt_3, PPh_3, CO (1 atm), DMF/MeOH, 70 °C, o/n, *decomp*.

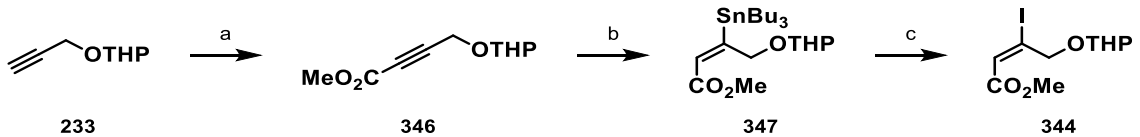
5.3.4 Cross-Coupling Approach

The next concept was to perform a sp^2-sp^2 cross-coupling reaction to combine both fragments by shifting the retrosynthetic cut by two carbon atom positions (s. scheme 86). This resulted in the new northern fragment **344** and the extended southern fragment **345** which were to be synthesized starting from aldehyde **288**. The necessary double bond should be reduced later using Red-Al® which can reduce this type of allylic alcohols to the corresponding alkanes.[143]



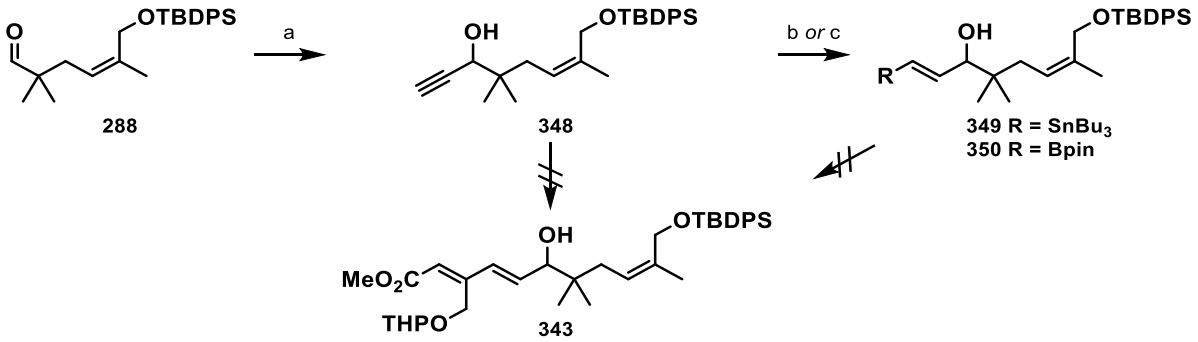
Scheme 86: New retrosynthetic cut using a cross coupling reaction.

Starting with the known THP-protected propargyl alcohol **233** this was converted to alkynoate **346**. This could be subjected to a conjugate addition with copper cyanide and tributyltin hydride to provide required (*E*)-stannane **347** which was readily converted to corresponding vinyl iodide **344** in good yields (s. scheme 87).



Scheme 87: Synthesis of the new northern fragment for the cross coupling approach: a) *n*BuLi, THF, -78 °C, 1 h, *then*, $ClCO_2Me$, -78 °C, *to* rt, o/n, 91%; b) *n*BuLi, CuCN, THF, -78 °C, 15 min, *then*, $SnBu_3H$, -78 °C, 15 min, *then* **346**, MeOH, THF, -78 °C, 30 min, *quant*.; c) I_2, CH_2Cl_2, 0 °C, 2 h, 81%.

On the other hand, aldehyde **288** was converted to propargyl alcohol **348** in good yield by the addition of ethynylmagnesium bromide. This alkyne can then be converted *in situ* to a vinylboron species by a procedure of Fürstner which unfortunately did not provide reasonable results.[144] Therefore, either vinylstannane **349** or vinylboronate **350** were isolated in good yields (s. scheme 88).



Scheme 88: Synthesis of the elongated southern fragment and tried coupling with the northern fragment: a) ethynyl-MgBr, Et_2O, 0 °C, 15 min, 96%; b) $PdCl_2(PPh_3)_2$, $SnBu_3H$, THF, rt, 15 min, 94%; c) CuCl, KO*t*Bu, PPh_3, B_2pin_2, THF, rt, 15 min, *then* **348**, MeOH, THF, 0 °C *to* rt, o/n, 57%.

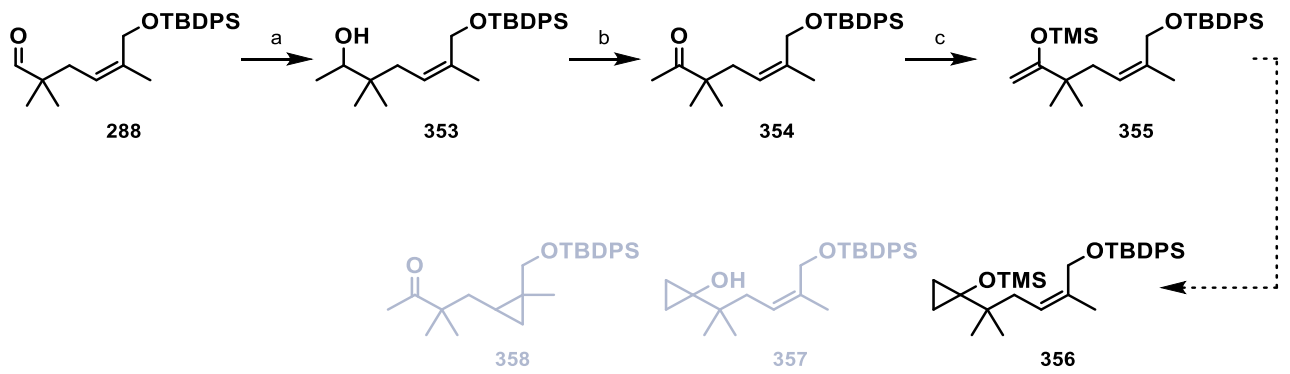
Using the classical conditions for the Stille cross coupling reaction with vinyl stannane **349** or the Suzuki cross coupling reaction with vinylborane **350**, no desired product was obtained.[145,146] The products found could not be identified but also did not contain the important signals in the ^1H NMR spectrum for example the diene system. Therefore, a Heck reaction was attempted to give the ketone instead of the allylic alcohol, since the organic palladium intermediate undergoes a chain migration process to reach the enol which tautomerizes to the more stable ketone **352** (s. scheme 89). New vinyl alcohol **351** was again obtained from aldehyde **288** in good yield and submitted directly to the conditions of the Heck reaction. Unfortunately, using standard conditions[147] along with vinyl iodide **344** only TBDPS-deprotected alcohol of aldehyde **288** was found and no conversion of iodide was encounteres. Therefore, this idea was discarded.

Scheme 89: Heck coupling approach: a) vinylMgBr, Et_2O, 0 °C, 1 h, 75%.

5.3.5 β-Cu$^{(II)}$ Ketone Generation Approach

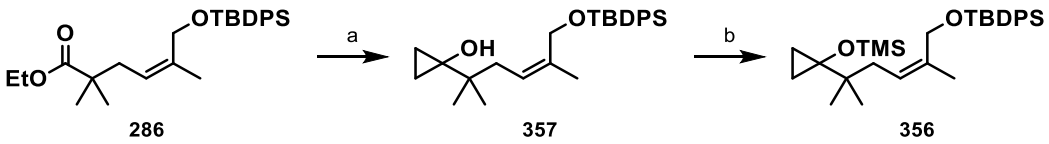
Another route to synthesize ketone coupling product **352** could be by conjugate addition of β-Cu(II) ketones to alkynoates or sulfonates. This method was first published in 1993 by Sonoda and co-workers using similar systems.[148] The principal idea here is that a fluoride of the tetrafluoroborate

anion attacks the TMS-protected cyclopropanol which then opens up to form the ketone and an organocuprate species in the β-position to the ketone. This can then attack the Michael acceptor and form the coupling product.



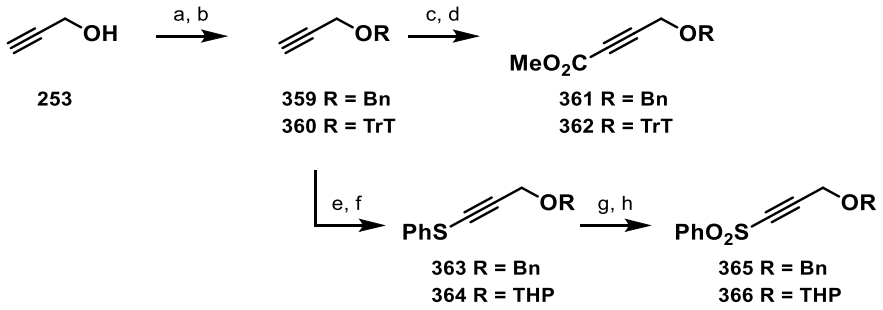
Scheme 90: Failed synthesis of cyclopropanol **356**: a) MeMgBr, Et_2O, 0 °C, 20 min, 81%; b) DMSO, $(COCl)_2$, CH_2Cl_2, -78 °C, 10 min, *then* **353**, CH_2Cl_2, -78 °C, 15 min, *then* NEt_3, -78 °C *to* rt, 30 min, 83%; c) NEt_3, TMSOTf, Et_2O, 0 °C *to* rt, 92%.

In a first attempt, the desired cyclopropanol was synthesized by a protocol similar to the one reported in the original work. Aldehyde **288** was converted into TMS enol ether **355** by addition of a methyl magnesium species followed by Swern oxidation and enolization by silylation using the reagent TMSOTf which shows a higher reactivity than TMSCl. This sequence succeeded in good yield. Next, a Simmons-Smith reaction was performed to favor the more electron-rich double bond of the enol ether.[149] Unfortunately, a mixture composed of the desired product and the non silylated derivative formed as well as a side product in which the other olefinic double bond was converted into the cyclopropane ring (s. scheme 90). Therefore, the strategy was changed and starting from ester **286** a Kulinkovich reaction was carried out to directly lead to cyclopropanol **357**. This transformation succeeded in very good yield, since only one functional group can be converted to the cyclopropane. Again, protection with TMSOTf led to desired precursor **356** required for the new key step.



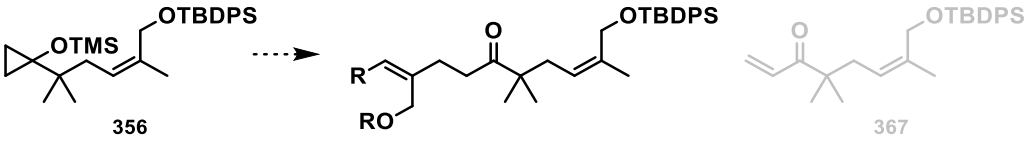
Scheme 91: Synthesis of the key step precursor **356**: a) EtMgBr, $Ti(OiPr)_4$, THF, 0 °C, 30 min, 75%; b) NEt_3, TMSOTf, Et_2O, 0 °C *to* rt, 91%.

On the other hand, various alkynoates and sulfonates were prepared (s. scheme 92) using the known procedure for alkynoates and sulfonates.[150] First, propargyl alcohol **253** was protected with the appropriate protecting group, followed by acylation with methyl chloroformate or a mixture of methyl iodide and diphenyl disulfide to furnish the corresponding thioether. Next, thioethers **363** and **364** were oxidized to the corresponding sulfones in good yields using H_2O_2 and a molybdenum catalyst.



Scheme 92: Synthesis of Michael acceptor systems: a) NaH, DMF, 0 °C, 30 min, *then* BnBr, 0 °C *to* rt, o/n, *quant.*; b) TrtCl, DMAP, pyr., CH_2Cl_2, rt, o/n, 66%; c) *n*BuLi, THF, -78 °C, 1 h, *then*, $ClCO_2Me$, -78 °C, *to* rt, 2 h, 82%; d) *n*BuLi, THF, -78 °C, 1 h, *then*, $ClCO_2Me$, -78 °C, *to* rt, o/n, 92%; e) **359**, *n*BuLi, THF, -78 °C, 1 h, *then* PhSSPh, MeI, THF, premixed rt, 1 h, *to* rt, 1 h, 73%; f) **233**, *n*BuLi, THF, -78 °C, 1 h, *then* PhSSPh, MeI, THF, premixed rt, 1 h, *to* rt, 1 h, 95%; g) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, H_2O_2, EtOH, rt, o/n, 81%; h) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, H_2O_2, EtOH, rt, o/n, 47%.

Now that both fragments were available, some initial test reactions were performed. Unfortunately, in most cases no conversion of the starting materials was observed. Interestingly, only in entries 1 and 2 enone **367** was found to be formed as a by-product. Presumably, the problem lies in the mixing of the reagents. It turned out that the copper salt probably had to be freshly dried each time before it could be used.



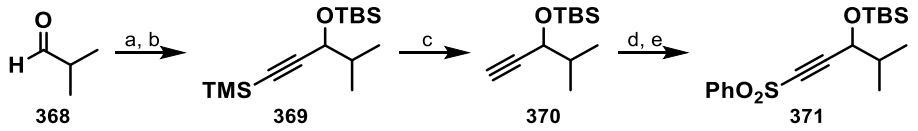
Scheme 93: Tested addition of β-Cu(II) ketones to Michael-acceptors.

Table 11: Different changes in the procedure of the addition of β-Cu ketones onto Michael acceptors.

entry	electrophile	changes in procedure	result
1	R_1 = THP; R_2 = CO_2Me	non	**367** & **356**
2	R_1 = THP; R_2 = CO_2Me	$Cu(BF_4)_2$ freshly dried	**367**
3	R_1 = Bn; R_2 = CO_2Me	non	**356** & **361**
4	R_1 = Bn; R_2 = CO_2Me	water not added	n.c.

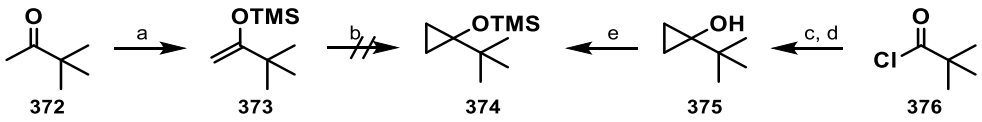
5	R_1 = Bn; R_2 = SO_2Ph	non	**356** & **365**
6	R_1 = THP; R_2 = SO_2Ph	non	**356** & **366**

Since no conversion could be achieved in the initial experiments, two known fragments were resynthesized to study the reaction *per se*. Addition of lithiated TMS alkyne to aldehyde **368** followed by deprotection of the alcohol with the TBS group afforded ether **369** in good yield. Selective deprotection of the carbon-bonded TMS group with K_2CO_3 in MeOH gave alkyne **370** which was converted to corresponding sulfone **371** in good yield.



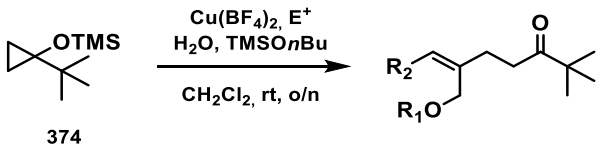
Scheme 94: Synthesis of sulfone **371**: a) TMS-acetylene, *n*BuLi, THF, -78 °C, 30 min, *then* **368**, THF, *to* 0 °C 2 h, 95%; b) 2,6-lutidine, TBSOTf, CH_2Cl_2, 0 °C *to* rt, 2 h, 99%; c) K_2CO_3, MeOH, rt, o/n, *quant*.; d) **370**, *n*BuLi, THF, -78 °C, 1 h, *then* PhSSPh, MeI, THF, premixed rt, 1 h, *to* rt, 1 h, 87%; e) $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, H_2O_2, EtOH, rt, o/n, 76%.

On the other hand, cyclopropanol **374** was to be synthesized by enolization of **372** followed by a Simmons-Smith reaction. Unfortunately, this approach led to decomposition as the TMS enol ether was not stable under the chosen conditions. Therefore, a route *via* a Kulinkovich reaction was explored which eventually led to desired cyclopropanol **374**.



Scheme 95: Synthesis of cyclopropanol **374**: a) NEt_3, TMSOTf, Et_2O, rt, 4 h, *quant.*; b) *decomp*.; c) MeOH, 0 °C *to* rt 1 h, 36%; d) EtMgBr, $Ti(OiPr)_4$, THF, 0 °C, 30 min, 38%; e) NEt_3, TMSOTf, Et_2O, 0 °C *to* rt, 2 h, 80%.

Next, TMS-cyclopropanol **374** was submitted to a first study using different electrophiles. Reactions with the new alkynones and sulfynones gave only traces of the product, which were identified by HRMS (s. table 12). Interestingly, the best yield for the product was found with DMAD (entry 8).

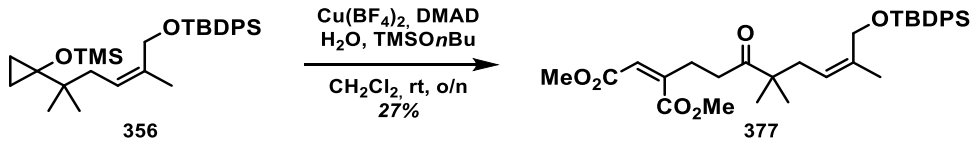


Scheme 96: Conjugate addition with the test cyclopropanol **374**.

Table 12: Tested conjugate additions.

entry	electrophile	result
1	**371**	traces
2	R_1 = THP; R_2 = CO_2Me	traces
3	R_1 = Bn; R_2 = CO_2Me	traces
4	R_1 = Trt; R_2 = CO_2Me	traces
5	R_1 = EE; R_2 = CO_2Me	traces
6	R_1 = Bn; R_2 = SO_2Ph	traces
7	R_1 = THP; R_2 = SO_2Ph	traces
8	DMAD	traces

Therefore, DMAD was used in a reaction with cyclopropanol **356** giving ketone **377** in a yield of 27%. This could serve as a starting point for further synthesis, as the two corresponding alcohols of the enoate could be differentiated in an acetylation with an enzyme, e.g., a lipase[151] and the ketone must be protected as an acetal or reduced into the corresponding alcohol and then protected. Since optimization did not improve the yield, it was decided to finally discontinue the whole project.



Scheme 97: Conjugate addition with DMAD and cyclopropanol **356**.

6 Biotransformation Project

A series of new farnesyl derivatives were synthesized – someof which were part of a bachelor thesis supervised - which were utilized in enzymological transformations.[152] The new feature of this group of derivatives is an oxygen substituent at one of the given methyl groups (s. figure 98).

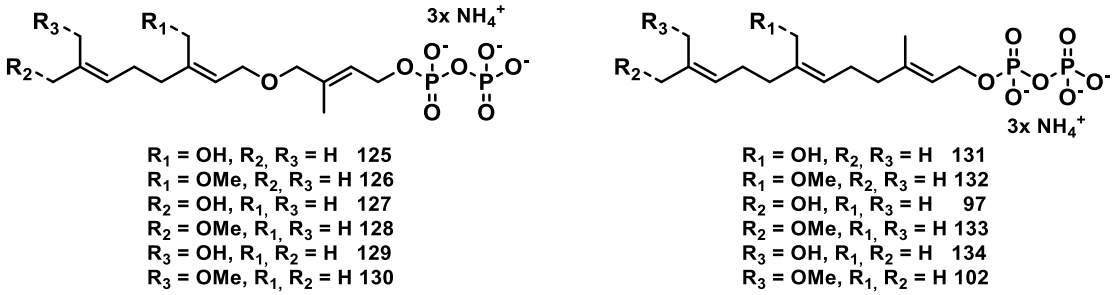


Figure 98: Envisioned farnesyl deriavtives: For each oxidized methyl group two derivatives are envisoned, bearing either an OH or OMe residue.

A general overview over the concept of this project is shown in figure 99. On one side, the necessary STCs were isolated from heterologous production in *E. coli*. On the other hand, the FPP-analogs were synthesized by classic organic synthesis. Then, acceptance of novel substrates was tested on an analytical scale and product evaluation was carried out by GC-MS. Upon a positive hit, the transformation was repeated on a larger scale to allow isolation of the product and elucidation of its structure by NMR-spectroscopy or accompanying methods.

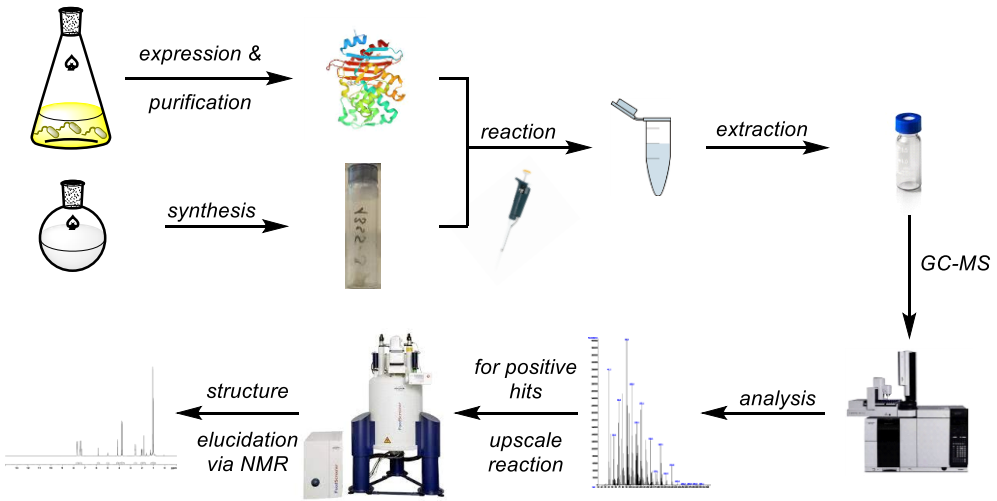
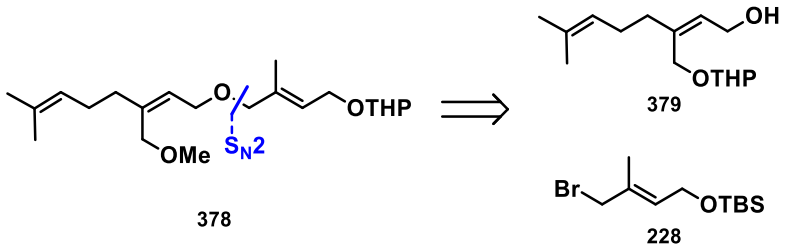


Figure 99: Overview of the overall process within the biotransformation project.

6.1 C-9-oxy Oxa-Farnesyl Derivatives

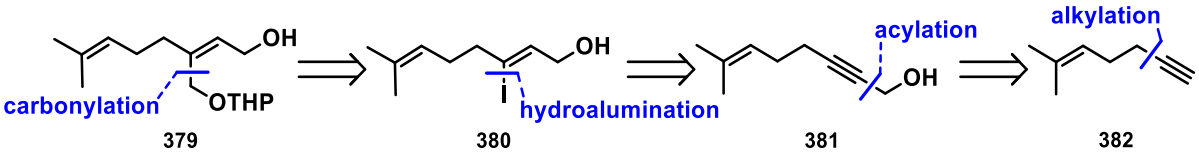
6.1.1 First Generation Retrosynthesis

The main retrosynthetic cut separates the molecule into the known bromide **228** and the new oxy-geraniol fragment **379** and the oxygen had to be suitably protected during the synthesis. Before the final conversion of the alcohol to the corresponding pyrophosphate different derivatives can be specifically targeted.



Scheme 100: Retrosynthesis of the new farnesyl derivative **378**.

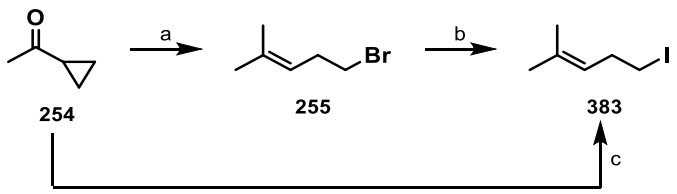
A sequence was pursued, similar to the successful approach towards iodide **326** on tricycle **1**. The possible key intermediate **381** was synthesized by the bachelor student Merlin Hauer.[152]



Scheme 101: New retrosynthesis of oxy-geraniol fragment **379**.

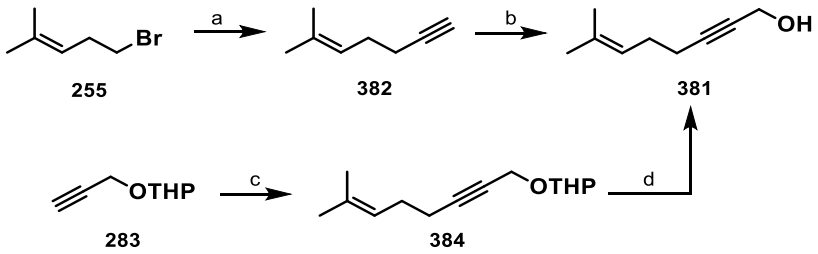
6.1.2 First Genertion Synthesis

The main idea is to introduce the homoprenyl moiety *via* a S_N2 displacement. Therefore, bromide **255** as well as iodide **383** were synthesized. The latter can be accessed by direct transformation of **254** with methylmagnesium iodide or by a two-step sequence first preparing bromide **255** which then is transformed into iodide **383** by means of a Finkelstein reaction. Both routes were performed in good yields.



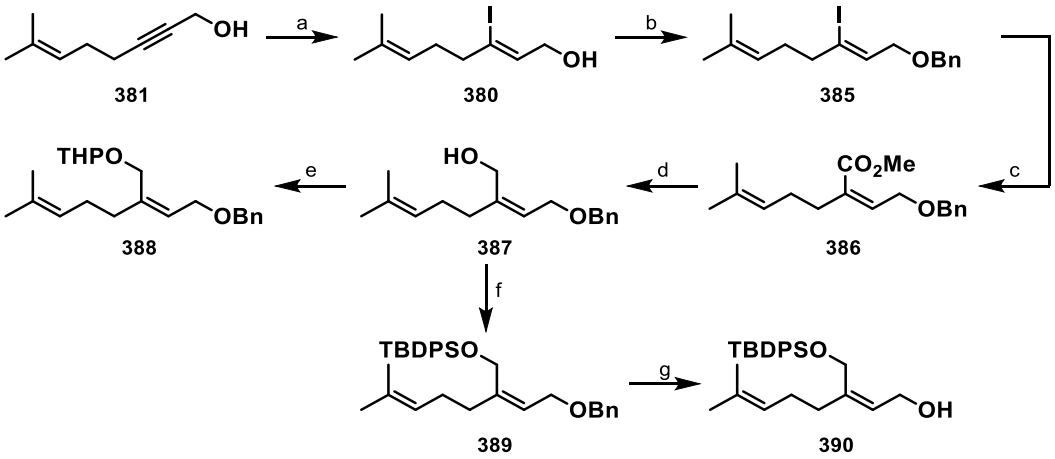
Scheme 102: Synthesis of the homoprenyl fragments: a) MeMgBr, THF, rf, 0.5 h, *then* H_2SO_4/H_2O, 10 °C, 0.5 h, 60%; b) NaI, acetone, rt, o/n, 92%; c) MeMgI, THF, 0 °C *to* rt, 1 h, *then* H_2SO_4/H_2O, 10 °C, 0.5 h, 67%.

To synthesize alcohol **381** either an alkylation using the lithium acetylene-EDA complex followed by an acylation or an alkylation of THP-propargyl alcohol followed by deprotection can be envisaged. As found out, the first sequence proved to be superior when using bromide **255** as the alkylating agent. Using iodide **383** instead of bromide **255** did not lead to any improved yield although normally iodide is the better leaving group. Presumably, the nucleophile is not good enough to increase the yield of this reaction significantly. With around 40% the yield is similar to the literature report. The following acylation can be performed with very good yields leading to the less volatile alcohol **381**. When following the route with the THP group included the volatility of the intermediates is reduced while however the step count is increased and the yields are not considerably better. Therefore, the first route towards alcohol **381** was chosen to be preferred (top, scheme 103).



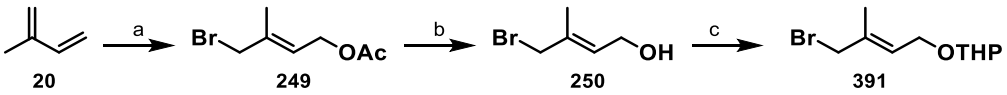
Scheme 103: Two alternative routes towards key alcohol **381**: a) Lithium acetylene-EDA complex, DMSO, 0 °C *to* rt, 2 h, 60%; b) *n*BuLi, THF, -78 °C, 1 h, *then* $(CH_2O)_n$, -78 °C *to* rt, 2 h, 91%; c) *n*BuLi, THF, -20 °C, 2 h, *then* **255**, DMPU, -20 °C *to* rt, o/n, 44%; d) *p*TsOH·H_2O, MeOH, rt, 1 h, *quant*.

Trying different procedures, the best conditions for the hydroalumination were found under refluxing induction and the trapping of the metal species by NIS. Unfortunately, at this point efforts to couple both fragments only resulted in elimination of the iodide and formation of alcohol **381**. Therefore, the alcohol had to be protected using the Dudley reagent followed by the previously described carbonylation procedure which provided access to enone **386**. Here, a small optimization was necessary. It was shown that changing the ratio of the solvents and using a 2:1 excess of methanol leads to doubling of the yield. Ester **386** was easily reduced using DIBAL-H that gave allyl alcohol **387** in very good yield. Unfortunately, THP protection of this alcohol was not a straightforward task. Even after short reaction times and low temperatures, only small amounts of the product were obtained although the conversion was complete as judged by TLC. Thus, allyl alcohol **387** was TBDPS protected under standard conditions yielding protected alcohol **389** in satisfying amounts. In the next step, the deprotection of the benzyl group was examined. The best results were found when chosing a SET-type removal using LiDBB. It should be noted, however that also a small amount of the double bond isomer was found besides the desired alcohol **390**.



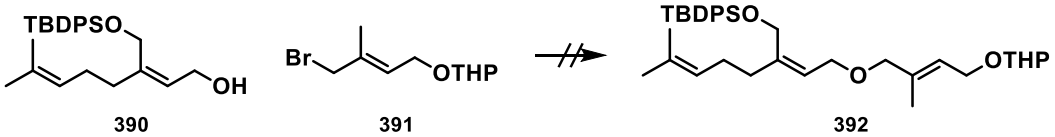
Scheme 104: Synthesis of oxy-geraniol fragment **390**: a) Red-Al®, THF, rf, 2 h, *then* NIS, THF, rt, 1.5 h, 73%; b) Dudley Reagent, Proton Sponge®, $PhCF_3$, 83 °C, o/n, 66%; c) $PdCl_2(PPh_3)_2$, NEt_3, PPh_3, CO (1 atm), DMF/MeOH, 70 °C, o/n, 71%; d) DIBAL-H, CH_2Cl_2, -78 °C, 5 min, 94%; e) DHP, *p*TsOH·H_2O, CH_2Cl_2, 0 °C, 10 min, 20%; f) TBDPSCl, imid., CH_2Cl_2, 0 °C, 5 min, *quant.*; g) LiDBB, THF, -78 °C, 78% 4:1 *E/Z*.

As the protection group strategy was changed for this fragment, it had consequently to be changed for the isoprene fragment. Therefore, a THP-derivative was synthesized in good yields, as shown in scheme 105.



Scheme 105: Synthesis of isoprene derivative **391**: a) NBS, AcOH, 0 °C to rt, o/n; b) K_2CO_3, MeOH/H_2O, rt, 1 h, 25% *o2s*; c) DHP, *p*TsOH·H_2O, CH_2Cl_2, 0 °C, 10 min, 49% 5:1 *E/Z*.

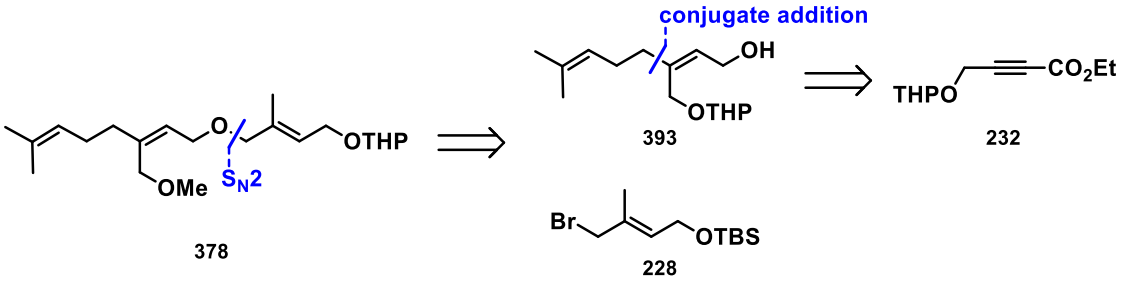
With this in hand, first test reactions were performed in order to couple both fragments (scheme 106). With our known conditions, no productformation was encountered. Therefore, more time has to be invested here by exploring different conditions. Principally the route had to be changed in order to prevent formation of *E/Z*-mixtures as pure isomers are critical for interpreting the results of biotransformation experiments.



Scheme 106: First test reaction towards the combined molecule.

6.1.3 Second Generation Retrosynthesis

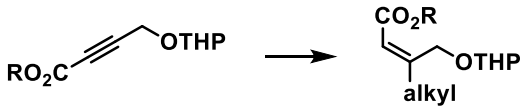
Following the new retrosynthetic idea for accessing substrate **378**, the same retrosynthetic bond cleavage were pursued. The oxy-geraniol fragment is thought to be synthesized according to a literature procedure by conjugate addition of homoprenyl bromide **255** to known alkynoate **232** (scheme 107).



Scheme 107: Retrosynthesis of the new farnesyl derivative **378**.

6.1.4 Second Generation Synthesis

With both fragments already from previous syntheses in hand, the described conditions were tested (s. table 13).[116,153,154] In a few first test runs (s. entries 1-3) either 1,2-addition product or an inseparable mixture of *E*/*Z*-isomers were obtained. As the Grignard reagent was prepared *in situ* and completely consumed, a few different mistakes should be excluded: Next, the magnesium was stirred with diluted HCl, washed successively with an excess of acetone and diethylether and then dried under high vacuum directly before use and only absolute THF was used. The Grignard reagent was also titrated using phenantrolene and menthol.[155] It showed that the concentration on these small scales was always lower then calculated and therefore not enough Grignard reagent was prepared. In order not to waste too much of the precious bromide, *n*butyl-bromide was used as a test reagent and the Grignard reagent was produced on a larger scale that allowed to determine its concentration by titration as the same as the theoretical one. Also, to exclude problems of the transmetallation procedure, the CuBr·DMS complex was freshly produced.[156] With this set of new reagents in hand, the original as well as a few alternative procedures were tested (s. entries 4-8). Unfortunately, whatever conditions were chosen or which additives were used, no conversion was observed. Finally, a similar approach as reported by Carreira[157] was probed in which a homoallyl bromide was transmetalated using *t*BuLi. However, this only led again to the 1,2-addition product (s. entry 9).



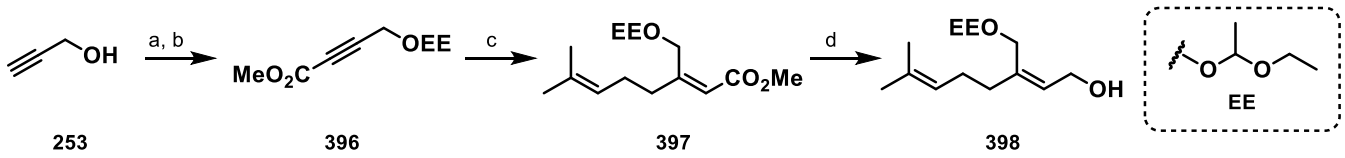
Scheme 108: Overview of the screening proess of the conjugate addition approach.

Table 13: Screening table of conjugate addition approach.

entry	R	Grignard	Cu-salt	sol-vent	addi-tives	procedure	result
1	Et	homo-prenyl (1.5 eq)	CuBr·DMS (1.5 eq)	THF	-	Mg, **255**, 2 h, rt *then* -50 °C, Cu, 0.5 h *then* -78 °C, **233**, 1 h	1,2-add
2	Et	homo-prenyl (1.5 eq)	CuBr·DMS (1.5 eq)	THF	-	Mg, **255**, 2 h, rt *then* -50 °C, Cu, 0.5 h *then* -78 °C, **233**, 1 h	75% 2:1 for de-sired
3	Me	homo-prenyl (1.5 eq)	CuBr·DMS (1.5 eq)	THF	-	Mg, **255**, 2 h, rt *then* -50 °C, Cu, 0.5 h *then* -78 °C, **346**, 1 h	71% 2:1 for de-sired
4	Me	*n*butyl (1.5 eq)	CuBr·DMS (1.5 eq)	THF	-	Mg, **255**, 2 h, rf *then* 0 °C, Cu, 1 h *then* -78 °C, **346**, 1 h	n.c.
5	Me	*n*butyl (1.1 eq)	CuI (2.0 eq)	Et_2O	TMEDA (3 eq)	Mg, **255**, 2 h, rf *then* -78 °C, Cu, 2 h *then* -78 °C, **346**, 1 h	28% only desired
6	Me	*n*butyl (2.2 eq)	CuI (1.1 eq)	Et_2O	TMEDA (3 eq)	Mg, **255**, 2 h, rf *then* -78 °C, Cu, 2 h *then* -78 °C, **346**, 1 h	n.c.
7	Me	*n*butyl (1.05 eq)	CuI (1.1 eq)	Et_2O	TMEDA (3 eq)	Mg, **255**, 2 h, rf *then* -78 °C, Cu, 2 h *then* -78 °C, **346**, 1 h	n.c.
8	Me	*n*butyl (1.5 eq)	CuBr·DMS (1.5 eq)	Et_2O	-	Mg, **255**, 2 h, rf *then* -78 °C, Cu, 2 h *then* -78 °C, **346**, o/n	decomp.
9	Me	*n*butyl (1.5 eq)	Cu(thienyl) CNCLi	Et_2O	$BF_3{\cdot}Et_2O$ (1.1 eq)	*t*BuLi, **255**, -78 °C, 0.5 h *then* -78 °C, Cu, 1 h *then* -78 °C, **346**, o/n	decomp.

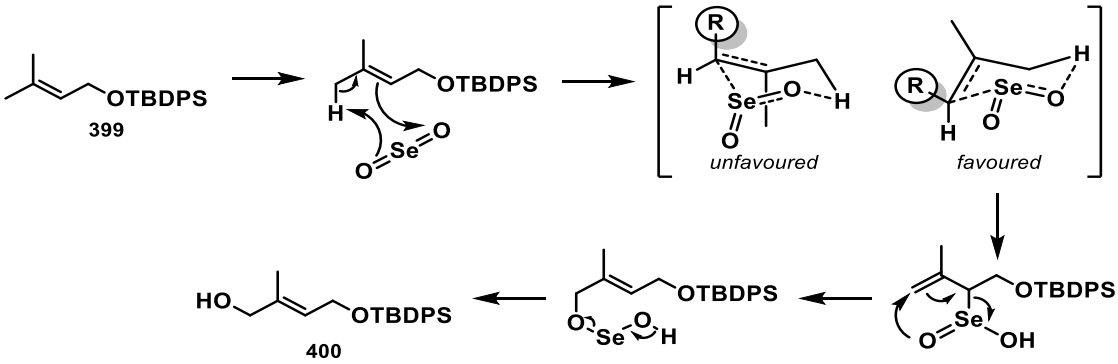
Since these conditions did not work, the original molecule was synthesized in two steps and the Grignard reagent was produced on a gram scale to reproduce the published chemistry following Li's procedure.[154,158] Finally, this approach showed a positive result yielding enoate **397** in good yield as

a single double bond isomer. The synthesis of the oxy-geraniol fragment **398** was terminated by reducing the ester in very good yield using DIBAL-H.

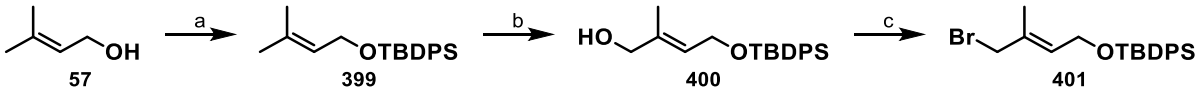


Scheme 109: Reproduced published sequence with working conjugate addition towards final oxy-geraniol fragment: a) vinylethylether, PPTS, CH_2Cl_2, 0 °C *to* rt, 1 h, 95%; b) *n*BuLi, THF, -78 °C, 1 h, *then*, $ClCO_2Me$, -78 °C, *to* rt, 2 h, 84%; c) **255**, Mg, I_2 (cat.), Et_2O, rf, 1.5 h, *then* CuBr·DMS, THF, -40 °C, 2 h, *then* **396**, THF, -78 °C, 2 h, 72%; d) DIBAL-H, CH_2Cl_2, -78 °C, 5 min, 98%.

Bromide **401** was synthesized *via* a new approach applying a Riley oxidation which gives the necessary double bond geometry with complete selectivity. The rational of the Riley oxidation is shown in scheme 110. It starts with an ene-reaction that is geometrically restricted to a proton on the methyl group located in the *cis*-position to the vinylic proton as in the transitition state the large residue is oriented in a pseudoequatorial position. If the other methyl group will be attacked, the large residue would be in the pseudoaxially oriented which is less favoured. After that, a [2,3]-rearrangement takes place giving the seleniol-intermediate which is finally cleaved to give the desired alcohol or alternatively undergoes oxidation to the corresponding aldehyde.[159]

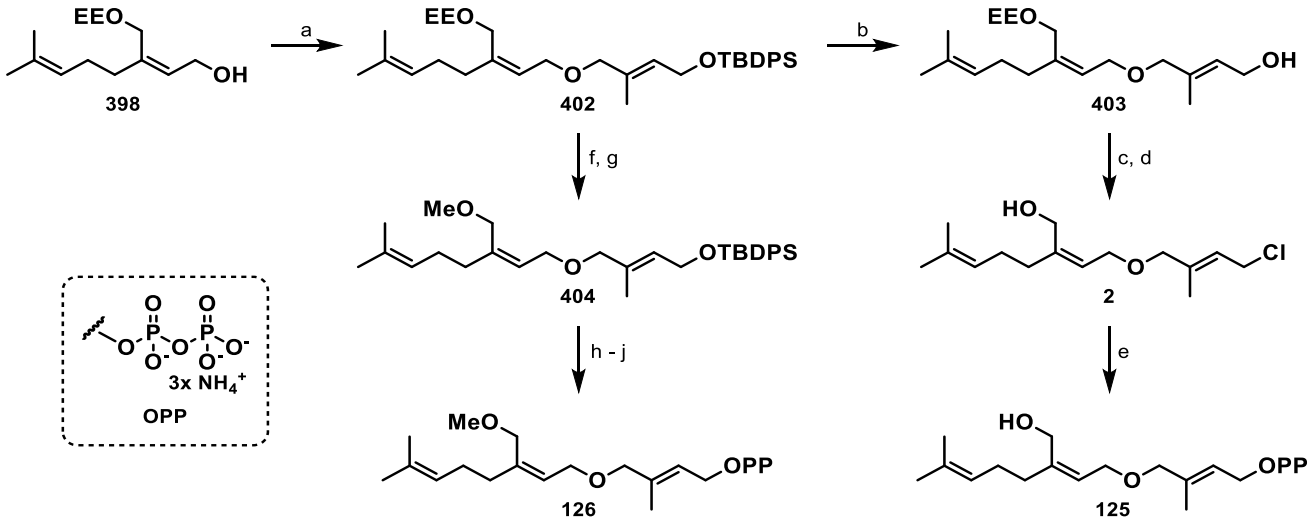


Scheme 110: Mechanism of the Riley oxidation explained on the example of alkene **399**.



Scheme 111: Synthesis of bromide **401** *via* the Riley oxidation pathway: a) imid., TBDPSCl, CH_2Cl_2, rt, o/n, *quant.*; b) i. SeO_2, *t*BuOOH, salicyl acid, CH_2Cl_2, rt, 2 d, ii. $NaBH_4$, MeOH, 0 °C, 30 min, 62%; c) NBS, PPh_3, CH_2Cl_2, 0 °C, 2 h, 83%.

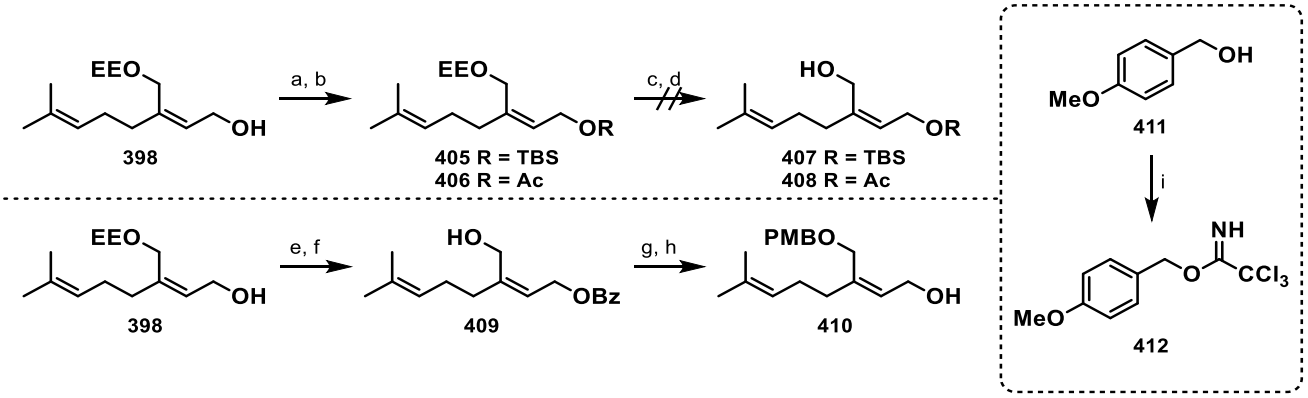
Starting from prenol (**57**) which was TBDPS protected and Riley oxidation provided alcohol **400** which was followed by an Appel reaction that gave a straight forward access to bromide **401**. Combination of both fragments turnred out to wotk perfectly. Only, a small optimization was necessary to trigger the reactivity of alcohol **398** for which its steric hinderance can be made responsible. Here, addition of TBAI and refluxing conditions allowed the Williamson ether synthesis to proceed with full conversion. In order to finalize the syntheses of both derivatives, the synthesis diverged at this point into two different pathways. For the methylether-derivative, at first the acetale protection protected alcohol was liberated and the resulting alcohol was O-methylated applying harsh conditions using an access of methyliodide in the presence of a base. Then the TBDPS group was removed under standard conditions and the alcohol was transformed into pyrophosphate **126** *via* the corresponding chloride in good yields.



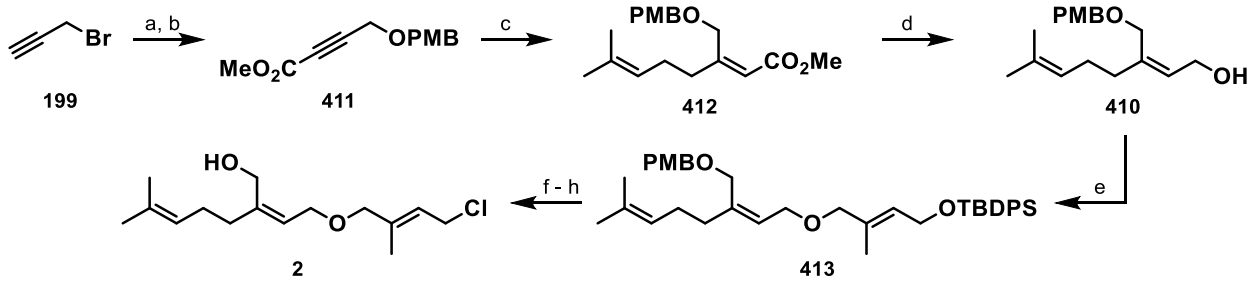
Scheme 112: Synthesis of both derivatives: a) NaH, THF, rf, 2 h, *then* TBAI, **398**, THF, rf, o/n, 99%; b) TBAF, THF, 0 °C *to* rt, o/n, 89%; c) DMS, NCS, CH_2Cl_2, -30 °C *to* 0 °C, 10 min, *then* **403**, CH_2Cl_2, -30 °C *to* 0 °C, 2 h, 22%; d) *p*TsOH·H_2O, MeOH, 0 °C *to* rt, 1 h, 97%; e) (nBu$_4$N)$_3$P$_2$O$_7$H, 3Å-sieves, MeCN, 0 °C *to* rt, 2 h, 75%; f) *p*TsOH·H_2O, MeOH, 0 °C *to* rt, 1 h, 71%; g) NaH, MeI, THF/DMF (3:1), 0 °C, 1 h, *to* rt, 1 h, 84%; h) TBAF, THF, 0 °C *to* rt, 89%; i) DMS, NCS, CH_2Cl_2, -30 °C *to* 0 °C, 10 min, *then alc.*, CH_2Cl_2, -30 °C *to* 0 °C, o/n, 85% (96% brsm); j) (nBu$_4$N)$_3$P$_2$O$_7$H, 3Å-sieves, MeCN, 0 °C *to* rt, o/n, *quant.*

The other route to the other derivative that bears a free hydroxy group commenced with removal of the TBDPS group and the free alcohol was converted to the corresponding chloride. Unfortunately, at this point the liability of the EE group became a problem despite different chlorination procedures were employed. Next to several products originating from side reactions also the deprotected product and a double chlorinated product were found leading to a very low yield for the desried chloride. Nevertheless, alcohol **2** was obtained after deprotection under standard conditions and the chemoselective transformation to pyrophosphate **125** which worked in high yield. Thus, both FPP-derivatives

were ready for semi-quantitative biotransformatiions and analysis. The synthesis of **125** was repeated on a larger scale using a different protection group strategy. At first, it was tested, if alcohol **398** could be protected by a TBS group or alternatively as an acetate ester which however appeared to be instable under aqueous workup condition or the following deprotection. The benzoate group which forms more stable esters was the first choice for protection group. The resulting benzoate was deprotected under standard conditions and EE group could thus be exchanged with the PMB group under mild conditions and good yield. Deprotection of the benzoate liberated the alcohol by using NaOMe along with TBAI. Since the overall yield of this whole sequence was not high, it was tested, if the conjugate addition would work using the PMB group right from the very beginning.



Scheme 113: Reprotection strategy for new alcohol fragment **410**: a) Ac_2O, NEt_3, DMAP, CH_2Cl_2, rt, 2 h, 91%; b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 81%; c) *decomp.*; d) *decomp.*; e) BzCl, NEt_3, DMAP, CH_2Cl_2, rt, 1 h, *quant.*; f) *p*TsOH·H_2O, MeOH, 0 °C *to* rt, 40 min, 96%; g) **412**, CSA, CH_2Cl_2, rt, 2 d, 91%; h) NaOMe, TBAI, MeOH, rt, 3 h, 91%; i) NaH, Et_2O, rt, 1 h, *then* Cl_3CCN, 0 °C, 1 h, 81%.



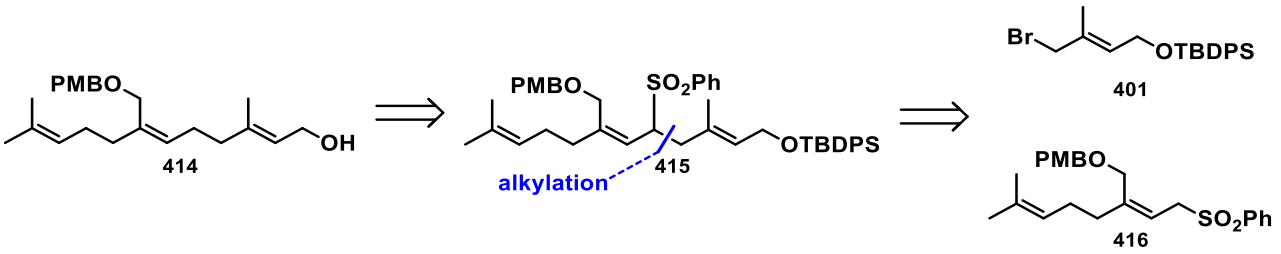
Scheme 114: Repeated synthesis with new protection group: a) NaH, PMB-OH, THF, rt, o/n, *quant.*; b) *n*BuLi, THF, -78 °C, 1 h, *then*, $ClCO_2Me$, -78 °C, *to* rt, o/n, 87%; c) **255**, Mg, I_2 (cat.), Et_2O, rf, 1.5 h, *then* CuBr·DMS, THF, -40 °C, 2 h, *then* **411**, THF, -78 °C, 2 h, 89%; e) DIBAL-H, CH_2Cl_2, -78 °C, 5 min, *quant.*; f) NaH, THF, rf, 2 h, *then* TBAI, **410**, THF, rf, o/n, 94%; b) TBAF, THF, 0 °C *to* rt, o/n, 84%; g) DMS, NCS, CH_2Cl_2, -30 °C *to* 0 °C, 10 min, *then alc.*, CH_2Cl_2, -30 °C *to* 0 °C, 2 h, 85%; h) $AlCl_3$, EtSH, CH_2Cl_2, rt, 2 h, 68%.

Therefore, the whole synthesis was repeated and satisfingly the conjugate addition as the key step proceeded even better when using the PMB group. The sequence was completed in similar yields and final deprotection using a catalytic system of $AlCl_3$ and ethanethiol led to alcohol **2** in good yields.[160]

6.2 C-9 oxy Farnesyl Derivatives

6.2.1 First Generation Retrosynthesis

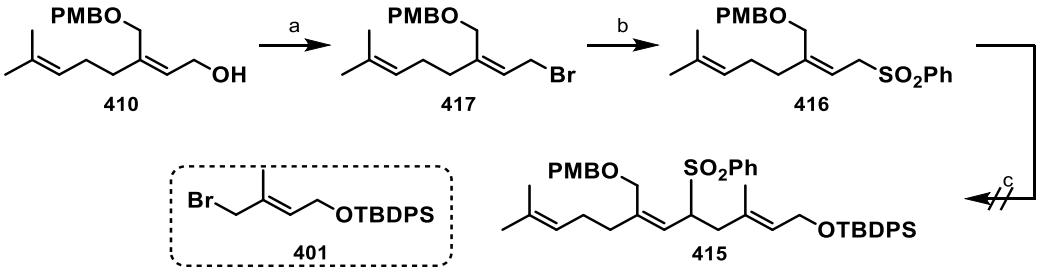
In order to synthesize the corresponding farnesyl derivatives **131** and **132** a retrosynthesis using an alkylation approach with sulfones was applied.[78] The necessary fragments were basically in hand, only small functional group manipulations were necessary so that bromide **401** and sulfone **416** served as starting materials.



Scheme 115: Retrosynthesis using an alkylation approach towards derivatives **131** and **132**.

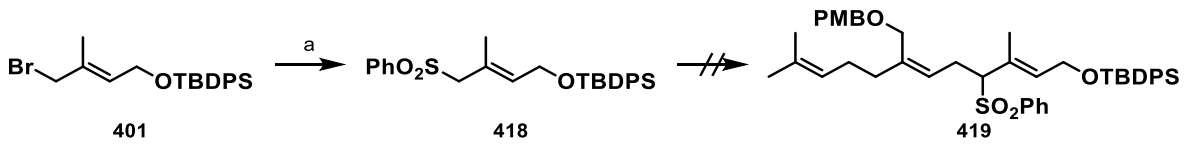
6.2.2 First Generation Synthesis

Interestingly, alcohol **410** was easily transformed into sulfone **416** *via* bromide **417**. When it was treated with a base, a yellowish color occured indicating the formation of the anion but upon addition of the electrophile no conversion was observed but full recovery of both materials instead had to be isolated. When the temperature was raised the anion turned out to be instable and again both starting materials were recovered. It can be concluded that sp^3-based chemistry to introduce the sulfone moiety is principally possible at this carbon atom but due to steric hindrance caused by the adjacent PMB group at various temperatures a nucleophilic attack of this carbon atom is too hindered.



Scheme 116: First approach to **415** using an alkylation with sulfones: a) PBr_3, Et_2O, 0 °C, 30 min, 94%; b) PPh_3, NBS, DMF, 0 °C *to* rt, 30 min, *then* $NaSO_2Ph$, TBAI, rt, 1.5 h, 76%; c) *n.c.*

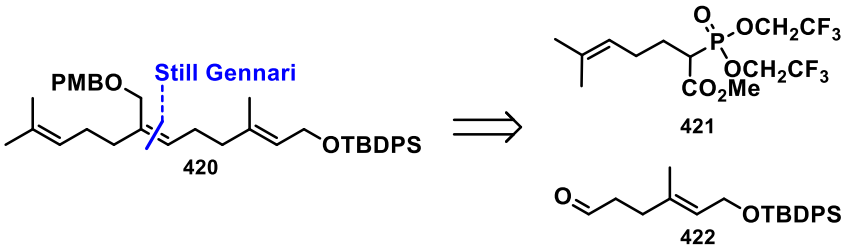
Therefore, the functional groups necessary for coupling both fragments were exchanged to bypass this problem. Then, the corresponding sulfone **418** was synthesized. When it was treated with a base only decomposition was observed, as the yellow color of the generated anion immediately changed to black. Even lower temperatures such as -110 °C or Barbier type conditions only provided traces of the desired product, as the decomposition seemed to be faster than the reaction itself.



Scheme 117: Second approach with exchanged terminal functional groups: a) $NaSO_2Ph$, TBAI, rt, 1.5 h, *quant.*

6.2.3 Second Generation Retrosynthesis

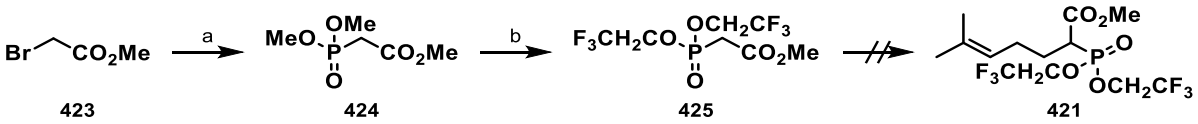
Next a Wittig approach was pursued applying the Still-Gennari variant leading to aldehyde **422** and reagent **421** as starting point. The Still-Gennari version of the HWE reaction is a standard procedure to build (*Z*)-configured α,β-unsaturated esters.[161] While aldehyde **422** should be easily accessed starting from geraniol, the more challenging modified Still-Gennari phosphonate reagent was synthesized first.



Scheme 118: Retrosynthesis using a Still-Genarri Wittig type reaction towards derivatives **131** and **132**.

6.2.4 Second Generation Synthesis

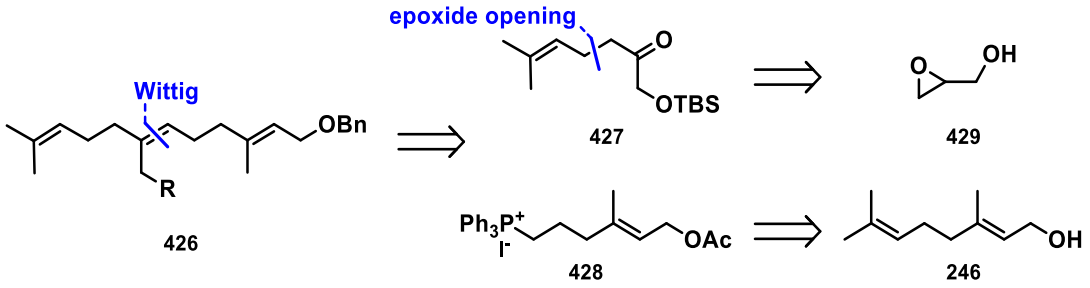
While the aldehyde could easily be synthesized according to a literature procedure,[162] the reagent was planned to be synthesized in three steps. The original Still-Gennari reagent (**425**) was straight forwardless prepared in very good yields. Unfortunately, alkylation of **425** was not as facile as thought. No conversion was observed when only one equivalent or slight excess of base was used. When up to two equivalents of base were used, a complex mixture of products was obtained. By using the commercially reagent instead, no product could be obtained as well.



Scheme 119: Synthesis of the substituted Still-Genarri reagent **421**: a) $P(OMe)_3$, 160 °C, 2 h, 67%; b) TMSBr, CH_2Cl_2, rt, 4 h, *then* solvent switch to $CHCl_3$, PPh_3, I_2, rt, 15 min, *then* imid., *to* 50 °C, 30 min, *to* 60 °C, CF_3CH_2OH, o/n, 77%.

6.2.5 Third Generation Retrosynthesis

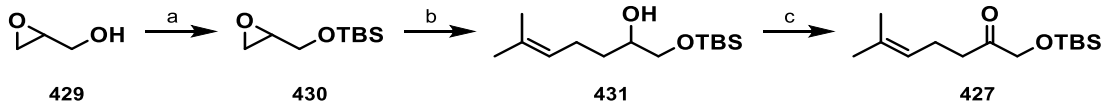
In order to synthesize the corresponding farnesyl derivatives **131** and **132**, the next retrosynthetic approach relies on a Wittig reaction as key step following a procedure similar by Sato.[163] This led to ketone precursor **427** which can be accessed *via* a copper-catalyzed regioselective ring opening of glycidol (**429**). On the other hand, Wittig salt **428** can be synthesized from geraniol **246**.



Scheme 120: Retrosynthesis of C-9 oxy farnesyl derivatives.

6.2.6 Third Generation Synthesis

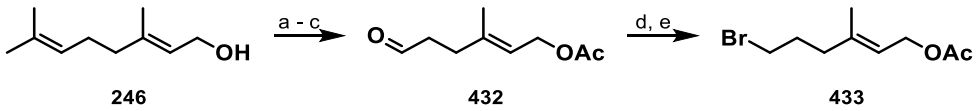
Ketone **427** was synthesized in three steps according to a literature procedure.[164] TBS protection followed by copper-catalyzed regioselective ring opening of epoxide **430** at the sterically less hindered site worked in very good yields. The sequence was finalized by oxidation to the ketone applying standard Swern conditions.



Scheme 121: Synthesis of ketone **427**: a) imid., TBSCl, THF, rt, o/n, 81%; b) prenylchloride, Mg, I_2 (cat.), THF, 0 °C, 30 min, *then* **430**, CuI, THF, -60 °C *to* -20 °C, o/n, 81%; c) DMSO, $(COCl)_2$, CH_2Cl_2, -78 °C, 10 min, *then* **431**, CH_2Cl_2, -78 °C, 15 min, *then* NEt_3, -78 °C *to* rt, 30 min, 85%.

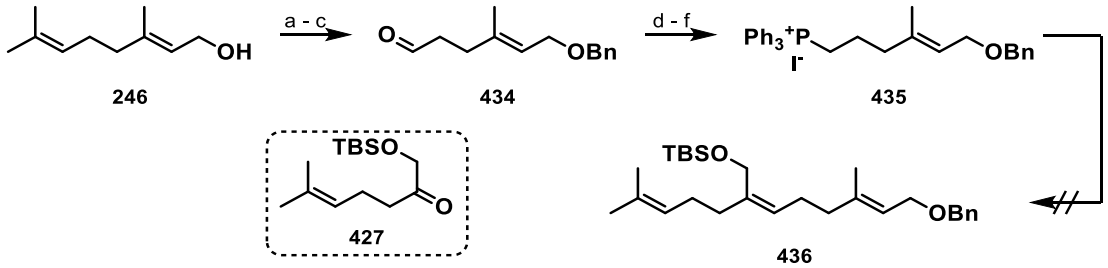
Next, the Wittig salt was synthesized the standard condition developed in the group en route to bromide **433**. Protection, epoxidation followed by periodate cleavage gave rise to aldehyde **432**. Reduction and Appel halogenation yielded bromide **433** in good yield. Unfortunately, conversion to the

corresponding Wittig salt failed due to cleavage of the acetate group in the presence of PPh_3. Other less reactive phosphines were insufficient to achieve a conversion.



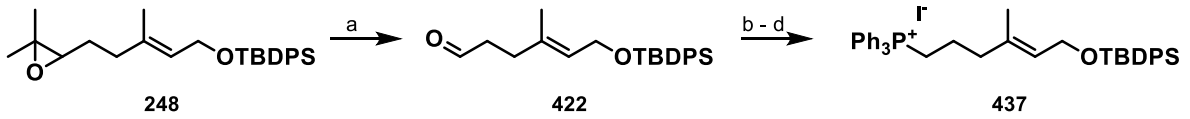
Scheme 122: Failed synthesis of Wittig Salt **428** using the acetate protecting group: a) Ac_2O, pyr., NEt_3, CH_2Cl_2, rt, o/n, 95%; b) *m*CPBA, CH_2Cl_2, -20 °C, 1.5 h, 98%; c) $HIO_4 \cdot 2H_2O$, 0 °C, 2 h, 78%; d) $NaBH_4$, EtOH, 0 °C, 1 h, 71%; e) CBr_4, PPh_3, CH_2Cl_2, 0 °C *to* rt, 2 h, 91%.

Therefore, the synthesis was repeated this time with a benzyl protection group. Benzyl protection followed by epoxidation and periodate cleavage led to aldehyde **434** which was submitted to a reduction followed by an Appel reaction to give the corresponding iodide in good yield. Final conversion to the corresponding Wittig salt turned out to be tricky, as the excess of PPh_3 could not be removed by recrystallization. But column chromatography yielded the pure Wittig salt in good yield which was submitted to the Wittig reaction. The first test runs did not lead to any conversion even though the right bright color of the anion was observed and both starting materials were reisolated. Therefore, a small optimization programme was pursued by changing deprotonation times and the reaction temperatures. As an indicator, the deprotonated Wittig salt was treated with deuterated methanol to prove the formation of the anion. Interestingly, the red bright color was obtained at all times, but a deuteration of **435** could not be identified by NMR-spectroscopy. Therefore, it was thought that the problem is associated with the chosen protection group on the ketone and thus, the protection groups on both fragments were exchanged.



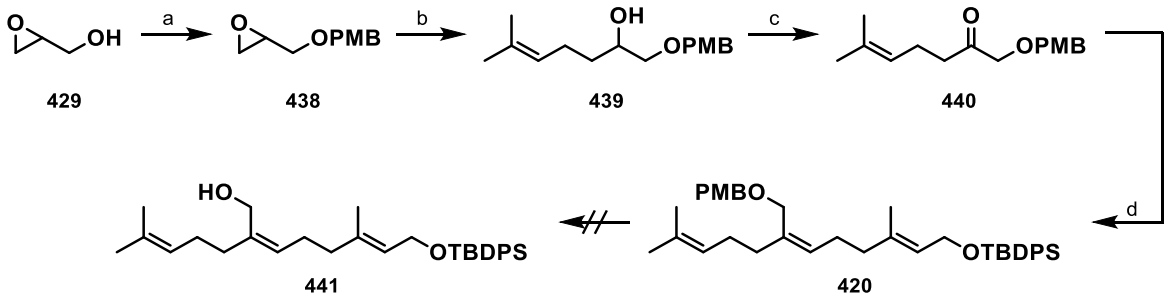
Scheme 123: Synthesis of Wittig Salt **437** using the benzyl protecting group: a) NaH, DMF, 0 °C, 30 min, *then* BnBr, *to* rt, o/n, *quant*.; b) *m*CPBA, CH_2Cl_2, -20 °C, 1.5 h, 70%; c) $HIO_4 \cdot 2H_2O$, 0 °C, 2 h, 75%; d) $NaBH_4$, EtOH, 0 °C, 1 h, 90%; e) imid., PPh_3, I_2, CH_2Cl_2, rt, 45 min, 91%; f) PPh_3, neat, 110 °C, 89%.

At first, the new Wittig salt was synthesized starting from the epoxide **248** reported before. Similar conditions as for the other both Wittig salts were applied leading to **437** in good yield.



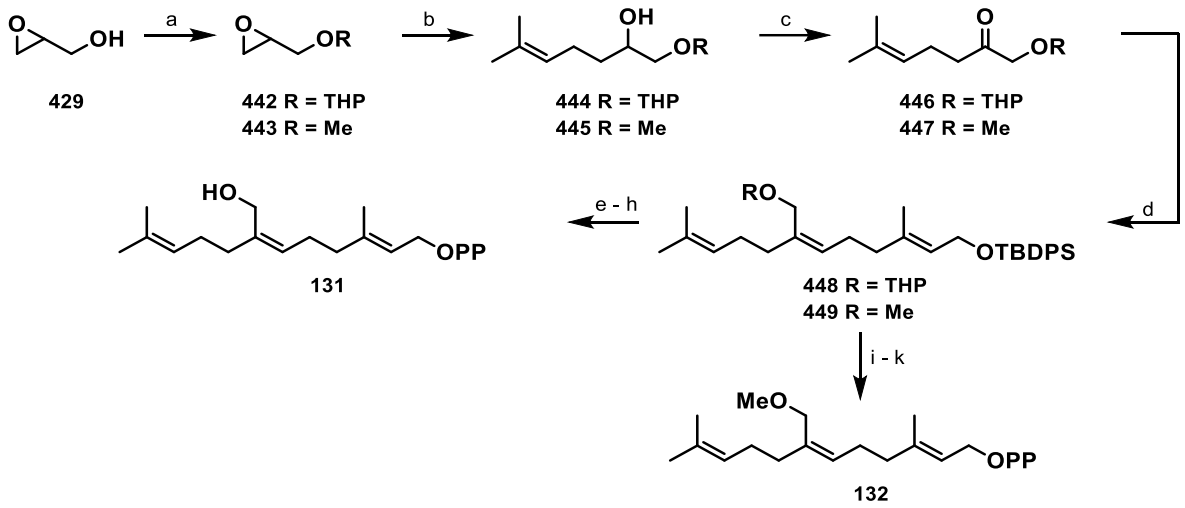
Scheme 124: Synthesis of new Wittig salt bearing the silyl protecting group: a) $HIO_4 \cdot 2H_2O$, THF, 0 °C, 40 min, *quant.*; b) $NaBH_4$, EtOH, 0 °C, 20 min, 63%; c) *i.* MsCl, NEt_3, CH_2Cl_2, 0 °C, 2 h: *ii.* NaI, acetone, 50 °C, o/n, 84%; d) PPh_3, PhMe, rf, *quant*.

On the other hand, pursuing the same strategy as before, new ketone **440** was synthesiszed in three steps in overall good yield, this time replacing the TBS group by the PMB group which was thought to be cleaved more easyly than the benzyl group. Now, the Wittig reaction was finally possible. Here, a slight excess of base was necessary to push the reaction to full conversion based on the ylide. Also only a single double bond isomer was formed, giving rise of the desired (*Z*)-product which was proven by NOE-measurements.[163,165]



Scheme 125: Synthesis of new PMB-protected ketone **440** and combination of both fragments by Wittig olefination: a) NaH, DMF, 0 °C, 2 h, *then* TBAI, PMBCl, *to* rt, o/n, 74%; b) prenylchloride, Mg, I_2 (cat.), THF, 0 °C, 30 min, *then* **438**, CuI, THF, -60 °C *to* -20 °C, o/n, *quant.*; c) DMSO, $(COCl)_2$, CH_2Cl_2, -78 °C, 10 min, *then* **439**, CH_2Cl_2, -78 °C, 15 min, *then* NEt_3, -78 °C *to* rt, 30 min, 75%; d) *n*BuLi, THF/HMPA (16:1), -78 °C, 1 h, *then* **440**, THF, -78 °C, *to* rt, o/n, 60% (only *Z*).

Unfortunately, the selective deprotection of the PMB group in presence of the TBDPS group was not possible though a variety of tested methods covered single electron donators up to Lewis acids. These led to loss of both protection groups. Therefore, two new ketones were synthesized, one for each derivative. For the derivative with the free hydroxy group, the THP protecting group was chosen and for the derivative with the methylether the necessary methyl group was directly introduced right at the beginning. Here, the volatility of the intermediates turned out to be tricky, leading to decreased yields. Nevertheless, both ketones were obtained in good yield using the described chemistry before. The Wittig olefination was performed leading to a single double bond isomer again, this was proven by conducting NOE-experiments. The syntheses were finally finished using the established chemistry to give rise to both pyrophosphates **131** and **132** in good yields.

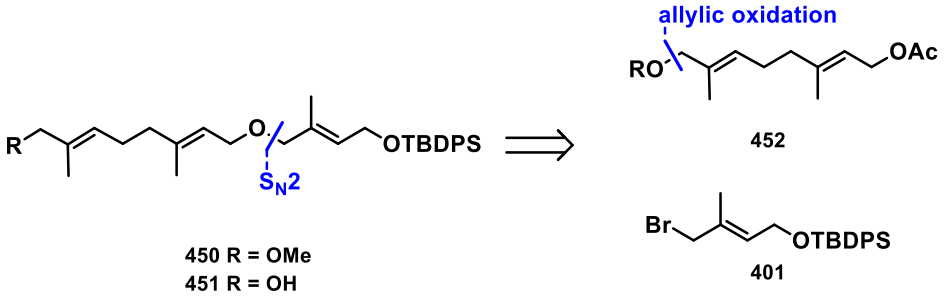


Scheme 126: Final synthesis of both derivatives with optimized protecting groups: a) DHP, *p*TsOH·H_2O, CH_2Cl_2, 0 °C, 30 min, 80% or MeI, Ag_2O, 3Å-sieves, CH_2Cl_2, rf, o/n, *quant.*; b) prenylchloride, Mg, I_2 (cat.), THF, 0 °C, 30 min, *then* **442-443**, CuI, THF, -60 °C *to* -20 °C, o/n, 88% (for OTHP) or 73% (for OMe); c) DMSO, $(COCl)_2$, CH_2Cl_2, -78 °C, 10 min, *then* **444-445**, CH_2Cl_2, -78 °C, 15 min, *then* NEt_3, -78 °C *to* rt, 30 min, 67% (for OTHP) or 87% (for OMe); d) *n*BuLi, THF/HMPA (16:1), -78 °C, 1 h, *then* **446** or **447**, THF, -78 °C, *to* rt, o/n, 71% (only *Z*) (for OTHP) or 40% (for OMe); e) TBAF, THF, 0 °C *to* rt, 93%; f) DMS, NCS, CH_2Cl_2, -30 °C *to* 0 °C, 10 min, *then alc.*, CH_2Cl_2, -30 °C *to* 0 °C, 1 h, 87%; g) *p*TsOH·H_2O, MeOH, 0 °C *to* rt, 1 h, 48%; h) $(n Bu_4N)_3P_2O_7H$, 3Å-sieves, MeCN, 0 °C *to* rt, o/n, 92%; i) TBAF, THF, 0 °C *to* rt, 95%; j) MsCl, collidine, DMF, 0 °C, 20 min, *then* LiCl, *to* rt, 2 h, 76%; k) $(n Bu_4N)_3P_2O_7H$, 3Å-sieves, MeCN, 0 °C *to* rt, o/n, 77%.

6.3 C-1 oxy Oxa-Farnesyl Derivatives

6.3.1 Retrosynthesis

In order to synthesize derivatives **127** and **128**, a similar strategy as described above was pursued. The targeted fragments would be bromide **401** and acetate **452** whereas the necessary alcohol moiety is introduced *via* an allylic oxidation reaction. Acetate **452** can be synthesized from geraniol.

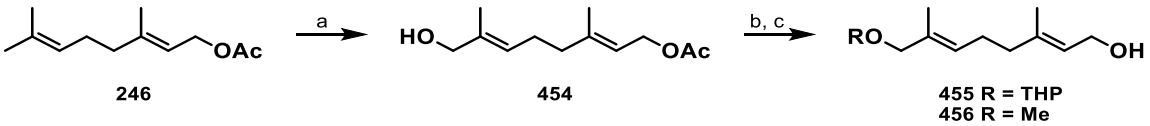


Scheme 127: Retrosynthesis of C-1-oxy oxa-farnesyl derivatives.

6.3.2 Synthesis

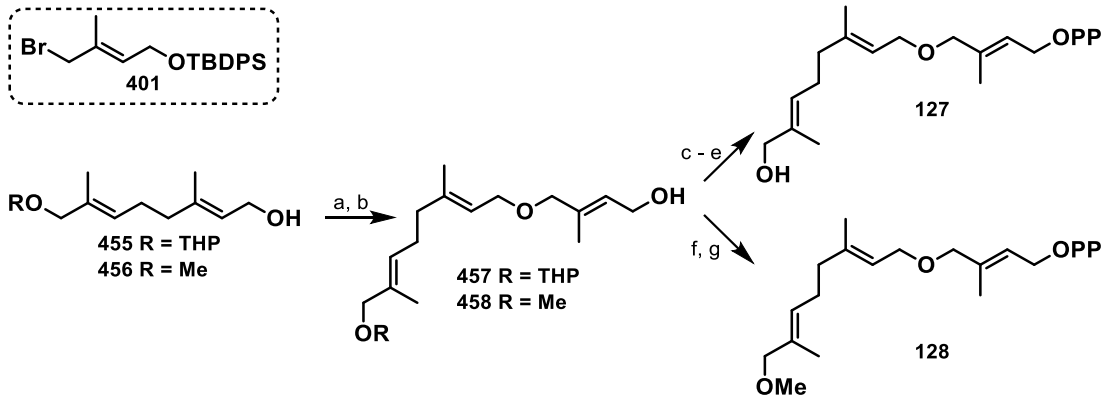
The sequence starts with the allylic oxidation which yielded alcohol **454** in only moderate yield. A problem in this case is a second oxidation at the other possible carbon atom and alternatively cleavage

of the acetate group. Protection of the newly generated alcohol followed by saponification yielded alcohols **455** & **456** in good yield.



Scheme 128: Synthesis of alcohol fragment **455** & **456**: a) SeO_2, *t*BuOOH, salicylic acid, CH_2Cl_2, rt, o/n, 41%; b) DHP, *p*TsOH·H_2O, CH_2Cl_2, 0 °C, 30 min, 97% or MeI, Ag_2O, MeCN, 45 °C, o/n, 49% (78% brsm); c) 1 M NaOH, MeOH, rt, 1 h, 90% (for OTHP) or K_2CO_3, MeOH, rt, 2 h, 80% (for OMe).

With both fragments in hand, the coupling was pursued. Applying the previously developed conditions for the Williamson ether synthesis, it was found that heating the mixture under refluxing conditions was unnecessary and indeed the reaction can be performed at room temperature to give the ether in good yield. The silyl protecting group was removed under standard conditions to liberate alcohols **457** & **458**. For the derivative with the free alcohol group, a consisting sequence of chlorination, THP-deprotection anda S_N2 reaction to introduce the diphosphate moiety was performed to give rise to derivative **127** in excellent yield. To finish the synthesis of the methyl derivative **128**, only the transformation into the pyrophosphate moiety was necessary.

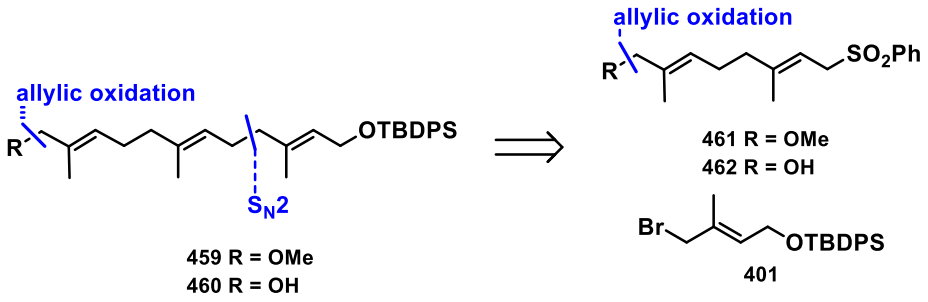


Scheme 129: Synthesis of novel C-1-oxy oxa farnesol derivatives: a) NaH, THF, 1 h, *then* TBAI, **455**-**456**, THF, o/n, 92% (for THP) or 56% (for OMe); b) TBAF, THF, 0 °C *to* rt, o/n, 85% (for OTHP) or 90% (for OMe); c) DMS, NCS, CH_2Cl_2, -30 °C *to* 0 °C, 10 min, *then* **457**, CH_2Cl_2, -30 °C *to* 0 °C, 2 h, 87%; d) *p*TsOH·H_2O, MeOH, 0 °C *to* rt, 1 h, *quant.*; e) $(n Bu_4N)_3P_2O_7H$, 3Å-sieves, MeCN, 0 °C *to* rt, o/n, 81%; f) DMS, NCS, CH_2Cl_2, -30 °C *to* 0 °C, 10 min, *then* **458**, CH_2Cl_2, -30 °C *to* 0 °C, 2 h, 87% (*quant.* brsm); g) $(n Bu_4N)_3P_2O_7H$, 3Å-sieves, MeCN, 0 °C *to* rt, o/n, 81%.

6.4 C-1 oxy Farnesyl Derivatives

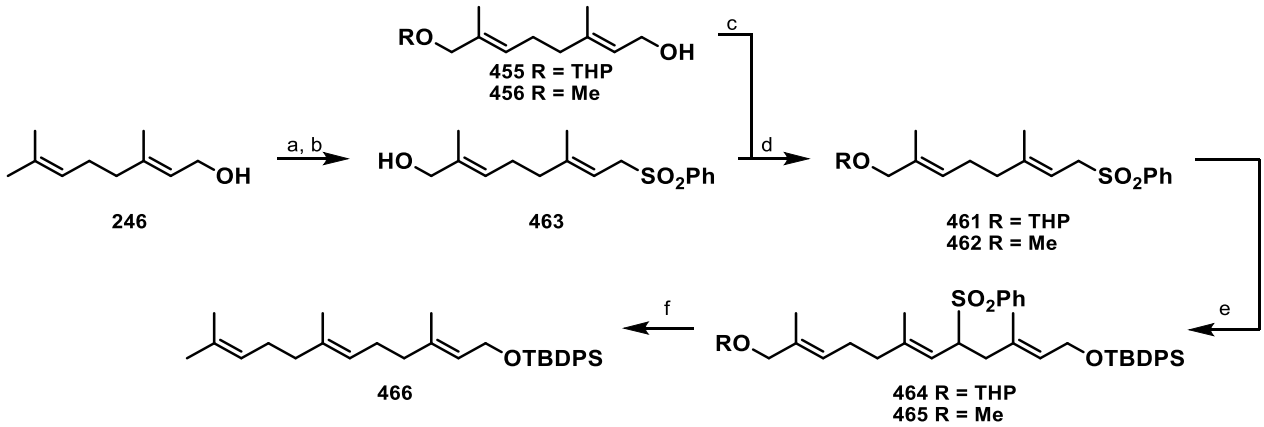
6.4.1 Retrosynthesis

In this retrosynthetic approach, the farnesyl derivative was devided into two fragments namely a sulfone and a bromide which were planned to be coupled in a typical S_N2-type reaction.[78] Sulfone **461-462** can be synthesized from geraniol **246** and bromide **401** as was already described before. Alternatively, a direct allylic oxidation of farensol could be performed which is less favoured as formation of several side products can occur.[166]



Scheme 130: Retrosynthesis of C-1-oxy farnesyl derivatives.

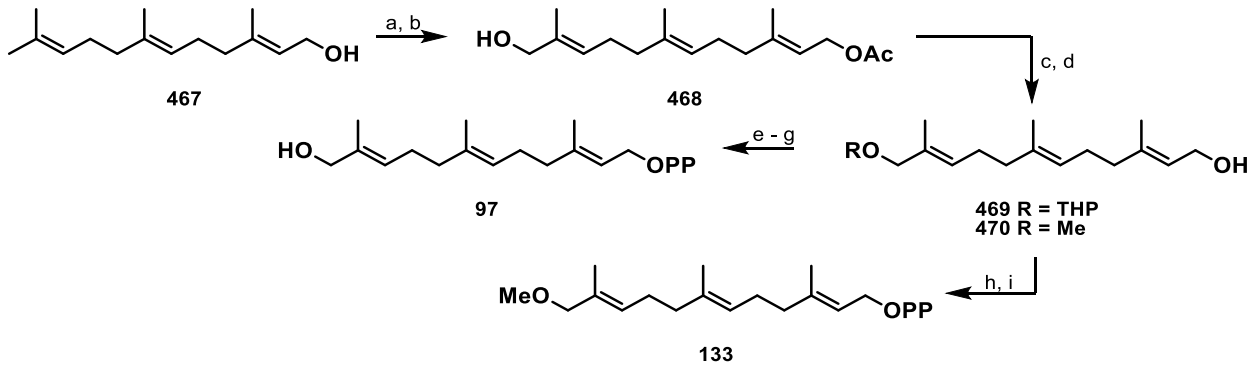
6.4.2 Synthesis



Scheme 131: Failed approach towards C-1-oxy farnesol derivatives *via* the alkylation route: a) NBS, PPh_3, DMF, 0 °C *to* rt, 30 min, *then* TBAI, $NaSO_2Ph$, rt, 2 h, 72%; b) *i.* SeO_2, *t*BuOOH, salicylic acid, CH_2Cl_2, rt, 2 d, 41%, *ii.* $NaBH_4$, MeOH, 0 °C, 1 h, 65%; c) NBS, PPh_3, DMF, 0 °C *to* rt, 30 min, *then* TBAI, $NaSO_2Ph$, rt, 2 h, 74% (for OTHP), 57% (for OMe); d) DHP, *p*TsOH·H_2O, CH_2Cl_2, 0 °C, 30 min, 92% or MeI, Ag_2O, CH_2Cl_2, rt, o/n, 9%; e) *n*BuLi, THF/HMPA (4:1), -78 °C, 1.5 h, *then* **461-462**, -78 °C, 2 h, 77% (for OTHP) or 77% (for OMe); f) diverse procedures.

Starting from geraniol it was transformed into the corresponding sulfone which underwent an allylic oxidation to give alcohol **463** as the only product. The alcohol moiety was protected with THP or alternatively transformed into the corresponding methylether in good yield. Next, sulfones **461** and **462** were alkylated using KHMDS and DME to give rise to the coupling products **464** and **465** in

good yield. An improvement was achieved when *n*BuLi and a mixture of THF/HMPA were used instead. Unfortunately, several conditions to remove the phenylsulfonyl group led to a completely reduced farnesol derivative **466** which also had lost the alcohol group that was introduced by allylic oxidation. Due to this side reaction, the synthesis was reevaluated and the less favored allylic oxidation of farnesol was pursued. Several procedures were published so far and most rely by repeatedly performing this reaction in cycles to increase the yield.[166] The major problem here is the generation of the secondary alcohol as a side product which cannot be completely prevented. Therefore, a tedious purification protocol became necessary. As a protecting group acetate was chosen with which best results were obtrained. After acetylation and allylic oxidation alcohol **468** was formed as the major product in acceptable yield. The alcohol moiety was THP protected and the acetate was cleaved by hydrolysis under standard conditions to yield alcohol **469** & **470** in good yields. This can be either submitted to a three step chlorination protocol composed of deprotection and substitution to yield the final pyrophosphate **97** in good yield. On the other hand, to introduce the methylether, a reprotection strategy was pursued and the methylether was introduced in moderate yields. It would have been beneficial to repeat the synthesis again with a different protecting group. The synthesis was finished by transforming alcohol **470** into pyrophosphate **133** in good yields using standard conditions. With both derivatives in hand, first biotransformations on an analytical scale were started.



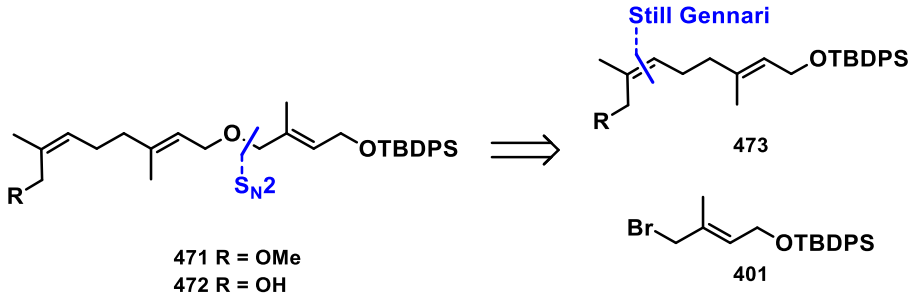
Scheme 132: Synthesis of C-1-oxy farnesol derivatives: a) NEt_3, Ac_2O, DMAP, CH_2Cl_2, 0 °C, 10 min, *quant.*; b) SeO_2, *t*BuOOH, salicylic acid, CH_2Cl_2, rt, o/n, 31% (40% brsm); c) DHP, *p*TsOH·H_2O, CH_2Cl_2. 0 °C, 5 min, 99% or MeI, Ag_2O, MeCN, 45 °C, o/n, 72%; d) 1 M NaOH, rt, 1 h, 86% (for OTHP), 97% (for OMe); e) MsCl, collidine, DMF, 0 °C, 20 min, *then* LiCl, *to* rt, 2 h, 80%; f) *p*TsOH·H_2O, MeOH, 0 °C *to* rt, 1 h, *quant.*; g) $(n Bu_4N)_3P_2O_7H$, 3Å-sieves, MeCN, 0 °C *to* rt, o/n, 62%; h) MsCl, collidine, DMF, 0 °C, 20 min, *then* LiCl, *to* rt, 2 h, 78%; i) $(n Bu_4N)_3P_2O_7H$, 3Å-sieves, MeCN, 0 °C *to* rt, o/n, 79%.

6.5 C-6 oxy Oxa-Farnesyl Derivatives

6.5.1 Retrosynthesis

In order to synthesize this couple of derivatives, the first retrosynthetic cleavage was linked to a Williamson ether synthesis which led requires **473** and **401** as starting materials. While bromide **401** is

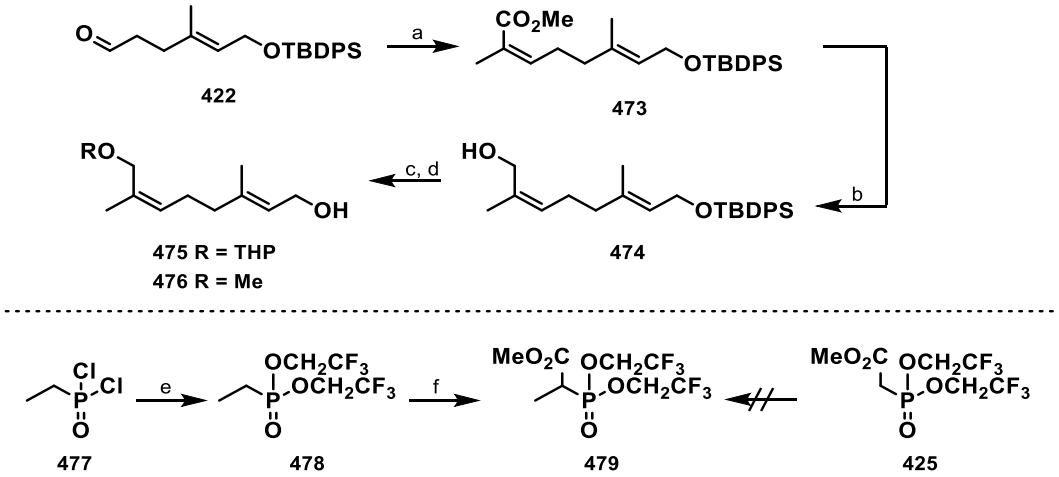
known, the challenge of **473** was found to be associated with the generation of the (*Z*)-configured olefinic double bond. This challenge can be solved by the Still-Gennari variant of the HWE olefination. The corresponding aldehyde can be accessed from geraniol **246**.



Scheme 133: Retrosynthesis of C-6-oxy oxa-farnesyl derivatives.

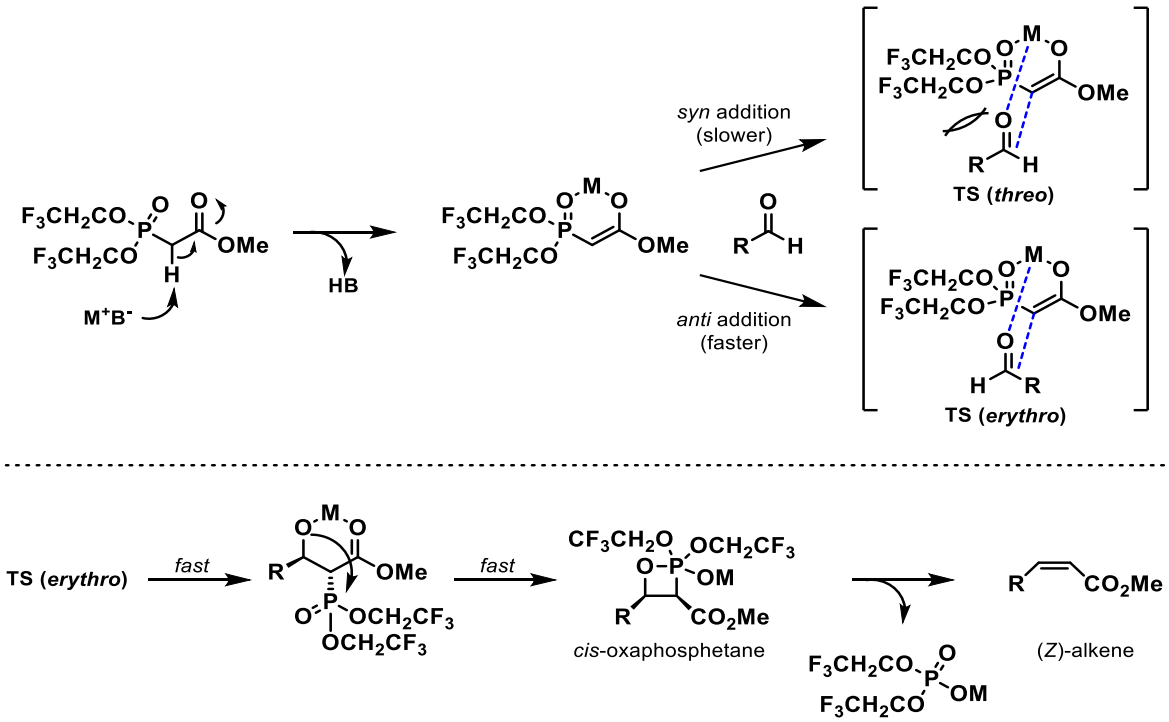
6.5.2 Synthesis

The Still-Gennari reagent was synthesized starting from ethylphosphonate **477**, as a methylation of **425** was not applicable here. The required ester moiety was introduced by simultaneous addition of the orthoformiate and phosphonate **478** to the base to prevent decomposition of the unstable lithiated phosphonate.[167] Applying standard Still-Gennari conditions, the desired double bond configuration and the (*Z*)-alkene was obtained as the single product in very good yield. This was confirmed by conducting NOE-experiments. The synthesis was terminated by reduction of ester **473**, protection of the alcohol and liberation of the other alcohol which provided access to **475** and **476** in very good yield.



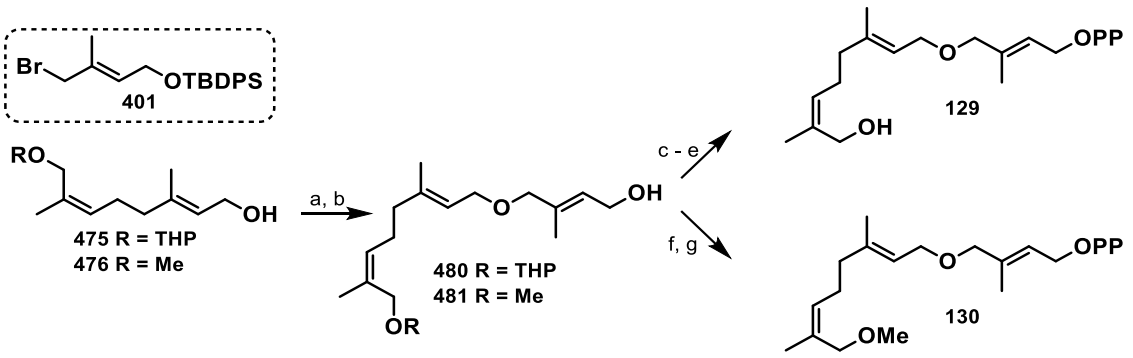
Scheme 134: Synthesis of alcohol **475** & **476** *via* the Still-Gennari-HWE approach: a) 18-crown-6, KHMDS, **479**, THF, -78 °C, 20 min, *then* **422**, THF, -78 °C, 30 min, *quant*. (only *Z*); b) DIBAL-H, CH_2Cl_2, -78 °C, 5 min, 97%; c) DHP, *p*TsOH·H_2O, CH_2Cl_2, 0 °C, 30 min, 94% or NaH, MeI, THF/DMF (3:1), 0 °C, 1 h, *to* rt, 4 h, 81% (94% brsm); d) TBAF, THF, 0 °C *to* rt, o/n, 90% (for OTHP) or 65% (for OMe); e) CF_3CH_2OH, NEt_3, THF, 0 °C *to* rt, 2 h, 87%; f) *n*BuLi, HMDS, THF, -78 °C *to* 0 °C, 1 h, *then* $MeCO_2Cl$, **478**, THF, -78 °C, 15 min, *to* 0 °C, 30 min, 76%.

A stereochemical rational for the Still-Gennari variant of the Horner-Wadsworth-Emmons reaction is shown in scheme 135. The mechanism of HWE reactions is well studied: The initial addition of the phosphonate stabilized carbanion to an aldehyde (or ketone) is reversible and followed by subsequent formation of the oxaphosphetane. The next irreversible step is the elimination of the phosphate ester. Depending on the residues on the phosphonate, either the thermodynamically favored *trans*-oxaphosphetane is formed during equilibration of the intermediates.[168] Here, due to the strong electronwithdrawing effect of the trifluoroethanol groups, the formation of the *cis*-oxaphosphetane is favoured as a result of the more stabilized *erythro* transition state resulting from the *anti* addition of the anion to the aldehyde. These kind of substituents inhibit the decomposition of the adduct to the starting materials, thus producing the kinetically favoured (*Z*)-product.[161] Another reason may be the steric hinderance of larger groups attached to the phosphor which e.g. was observed for aryloxy-subsitituents.[169] It was also found that addition of crown ether is necessary to prevent chelation of the oxyanion which would allow for a faster ring closure of the desired oxaphosphetane.[161,170]



Scheme 135: Stereochemically rational of the Still-Gennari olefination.[168]

The synthesis was wrapped up by applying the previously described Williamson ether synthesis conditions, followed by deprotection. In the end, in case of the methylether derivative **130** the pyrophosphates were prepared under standard conditions and in case of the free hydroxyl group alcohol **480** was transformed into pyrophosphate **129** in good yield by a standard three step protocol. With both derivatives in hand, first qualitative biotransformation assays on a analytical scale were performed.

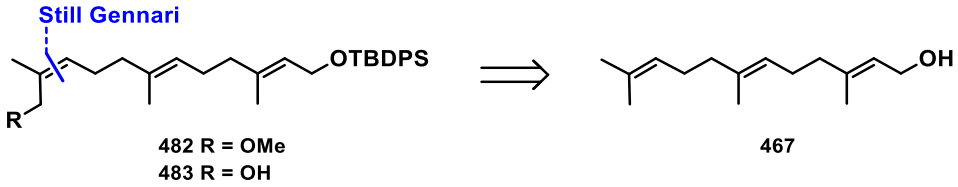


Scheme 136: Endgame synthesis of derivatives **129** and **130**: a) NaH, THF, 1 h, *then* TBAI, **475** & **476**, THF, o/n, 85% (for THP) or 92% (for OMe); b) TBAF, THF, 0 °C *to* rt, o/n, 88% (for OTHP) or 77% (for OMe); c) DMS, NCS, CH_2Cl_2, -30 °C *to* 0 °C, 10 min, *then* **480**, CH_2Cl_2, -30 °C *to* 0 °C, 2 h, 89%; d) *p*TsOH·H_2O, MeOH, 0 °C *to* rt, 2 h, *quant.*; e) $(n Bu_4N)_3P_2O_7H$, 3Å-sieves, MeCN, 0 °C *to* rt, o/n, 50%; f) DMS, NCS, CH_2Cl_2, -30 °C *to* 0 °C, 10 min, *then* **481**, CH_2Cl_2, -30 °C *to* 0 °C, 2 h, 48%; g) $(n Bu_4N)_3P_2O_7H$, 3Å-sieves, MeCN, 0 °C *to* rt, o/n, 46%.

6.6 C-6 oxy Farnesyl Derivatives

6.6.1 Retrosynthesis

In order to synthesize this couple of derivatives, again a Still-Gennari-variant of the HWE olefination was considered to build up the (*Z*)-configured olefinic double bond. The corresponding aldehyde can be obtained from farnesol **467**.

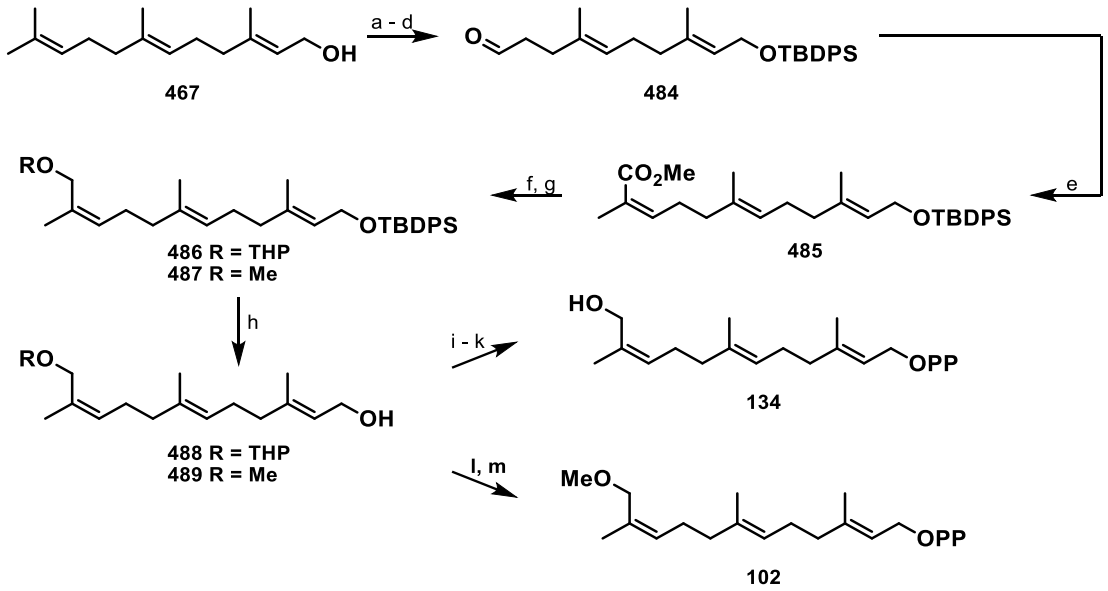


Scheme 137: Retrosynthesis of C-6-oxy farnesyl derivatives.

6.6.2 Synthesis

The synthesis was performed in a similar fashion to the corresponding oxa-derivatives. TBDPS-protection of farnesol followed by selective epoxidation *via* a two step protocoll using NBS followed by elimination using K_2CO_3 in MeOH and finally oxidative cleavage was performed in good yield. Due to the extra double bond, yields are lower than for the corresponding geraniol derivative but the side products could be commonly removed. Applying previously described Still-Gennari conditions led to enone **485** in very good yields and the configuration of the (*Z*)-alkene which was obtained as the only product was confirmed by conducting NOE-experiments. The synthesis was finished by reduction of the ester to the corresponding alcohol followed by protection with the required reagent systems allowing to access either the THP-protected alcohol **488** or the methyl ether **489** in very good yields. Deprotection of the alcohol group and transformation into the corresponding pyrophosphates led to

the final products in good yields. With both derivatives in hand, first qualitative biotransformation on an analytical scale were performed.



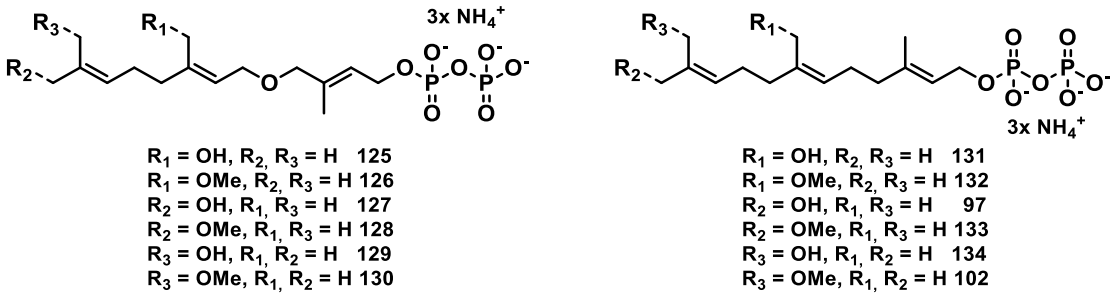
Scheme 138: Synthesis of C-6-oxy farnesol derivatives: a) TBDPSCl, imid., CH_2Cl_2, 0 °C *to* rt, 1 h; b) NBS, THF/H_2O (3:1), 0 °C *to* rt, 1 h; c) K_2CO_3, MeOH, rt, 1 h; d) H_5IO_6, $NaIO_4$, THF/H_2O (4:1), 0 °C *to* rt, 1.5 h, 38% *o4s*; e) 18-crown-6, KHMDS, **479**, THF, -78 °C, 20 min, *then* **484**, THF, -78 °C, 30 min, 96% (only *Z*); f) DIBAL-H, CH_2Cl_2, -78 °C, 5 min, 98%; g) DHP, *p*TsOH·H_2O, CH_2Cl_2, 0 °C, 30 min, 91% or NaH, MeI, THF/DMF (3:1), 0 °C, 1 h, *to* rt, 3 h, 61% (88% brsm); h) TBAF, THF, 0 °C *to* rt, o/n, 93% (for OTHP) or 90% (for OMe); i) DMS, NCS, CH_2Cl_2, -30 °C *to* 0 °C, 10 min, *then* **488**, CH_2Cl_2, -30 °C *to* 0 °C, 2 h, 89%; j) *p*TsOH·H_2O, MeOH, 0 °C *to* rt, 2 h, 34%; k) (nBu$_4$)$N_3P_2O_7H$, 3Å-sieves, MeCN, 0 °C *to* rt, o/n, *quant.*; l) MsCl, collidine, DMF, 0 °C, 20 min, *then* LiCl, *to* rt, 2 h, *quant.*; m) (nBu$_4$N)$_3P_2O_7H$, 3Å-sieves, MeCN, 0 °C *to* rt, o/n, 91%.

6.7 Analytical Enzymological Assays

With all desired farnesyl analogs on hand, the *in vitro* acceptance for eight selected STCs (Bot2, PenA, Cop4, GcoA, Tps32, Cyc1, Tri5 and Hvs1) was investigated. The used assay and its analysis using GC-MS are based on the work by Oberhauser and Harms.[171,172] Tests were performed on an analytical scale to determine the substrate acceptance. In order to identify novel products, a preparative scale of the enzymological reactions was performed to isolate products. Extracts from these reactions were purified using SiO_2 column chromatography and the structure analysis was performed by NMR measurements. General procedures for assays and reactions on preparative scale are reported in the experimental part. The assays were performed at 37 °C to achieve higher acceptance of the derivatives due to higher flexibility of the substrates and enzymes.[171] Enzymes were purified according to the previously reported procedures.[86,171,172]

Table 14: Expected *m/z* of possible novel products.

analog	125	126	131	132	127	128	97	133	129	130	134	102
***m/z* (-H)**	236	250	220	234	236	250	220	234	236	250	220	234
***m/z* (+H_2O)**	254	268	238	252	254	268	238	252	254	268	238	252



R_1 = OH, R_2, R_3 = H 125
R_1 = OMe, R_2, R_3 = H 126
R_2 = OH, R_1, R_3 = H 127
R_2 = OMe, R_1, R_3 = H 128
R_3 = OH, R_1, R_2 = H 129
R_3 = OMe, R_1, R_2 = H 130

R_1 = OH, R_2, R_3 = H 131
R_1 = OMe, R_2, R_3 = H 132
R_2 = OH, R_1, R_3 = H 97
R_2 = OMe, R_1, R_3 = H 133
R_3 = OH, R_1, R_2 = H 134
R_3 = OMe, R_1, R_2 = H 102

Figure 139: Overview of synthesized derivatives.

Assays were analyzed using GC-MS based methods. Signals with the corresponding mass-to-charge ratio (*m/z*), which were not detected in a negative control for each analog, were defined as a novel product. Negative controls were run in a similar fashion as the assay itself, only in absence of any STC. Furthermore, retention times of novel products were brought into comparison by determining retention indices based on a hydrocarbon grid. Products with the same retention indices and fragmentation pattern were defined as the same products. Based on the peak height in the FID chromatogram it is possible to estimate whether an isolation of the product should be pursued on a scale using 10-20 mg of the pyrophosphate in the preparative assay. The cut off value amounts to around 500.000. As the cyclization cascade are either terminated by addition of a molecule of water or elimination of a hydrogen, two different *m/z* were searched for each analog and are shown in table 14.

6.7.1 Analytical Enzymological Assays of C-9 Oxy-Derivatives

At first derivatives **125** and **126** were tested. As shown in figures 140 and 141, both derivatives were hardly accepted by all enzymes. Only a slight preference for the derivative with the free hydroxyl group was observed. Tps32 and Hvs1 revealed the highest potency for accepting this derivative, producing the same product with a *m/z* of 236. This result shows that the cyclization cascade was terminated by the elimination of a proton. On the other hand, the derivative that also contains the methylether moiety was not transformed into substantial amounts of new products by any of the chosen STCs. Therefore, no further investigations were pursued, as the amounts of products were lower than the defined cut-off value for large scale biotransformations.

Table 15: Novel terpenoids produced by STCs from derivative **131**: Highlighted in grey are products that are formed in an amount suitable for large scale production, the relative amount of products are categorized into three groups: *main* producer of product among all STCs, *major* product of a single STC, *minor* product of a single STC which is in part also produced by other STCs.

STC	terpenoid	t_r [min]	RI	*m/z*	classification
Bot2	pdt1	9,897	1591	220	main
PenA	pdt1	10,083	1623	220	major
	pdt2	10,257	1653	220	minor
	pdt3	10,365	1672	220	main
	pdt4	11,305	1845	220/238	major
Cop4	pdt1	9,464	1520	220	minor
	pdt2	9,844	1582	220	main
	pdt3	10,043	1616	220	minor
GcoA	pdt1	9,783	1572	220	minor
Tps32	pdt1	9,894	1554	220	minor
	pdt2	10,258	1654	220	main
Cyc1	pdt1	10,084	1623	220	minor
	pdt2	10,360	1671	220	minor
Tri5	pdt1	9,787	1573	220	main
	pdt2	10,360	1671	220	minor
Hvs1	pdt1	10,257	1653	220	major

Derivatives **131** and **132** that lack the presence of an ether group in the backbone were tested (s. figures 142 and 143). These substrates were better accepted by the same set of STCs. Also, derivative **131** showed a broader degree of acceptance than its methylether analog. **131** was accepted by all STCs, only GcoA produces novel terpenoids in a smaller amount but the same products were also produced by Tri5. The comparison of the products is shown in tables 15 and 16. In total 18 new products were formed, 15 having a *m/z* of 220, or 234, respectively for the methylether derivative, when a proton is eliminated at the end of the cyclization cascade. Interestingly, also three prodcuts were formed showing a *m/z* of 238, or 252, respectively for the methylether derivative, when the cyclization cascade is terminated by addition of water. For methylether derivative **132** Bot2 showed the broadest range of acceptance for this new functionality. Here, the isolation of products can be pursued. Similar results were found for Cop4 and PenA. Cyc1 and Tri5 also produced novel terpenoids however in lower amounts while Tps32, Hvs1 and GcoA do not shown any substantial formation of novel terpenoids.

Table 16: Novel terpenoids produced by STCs from derivative **132**: Highlighted in grey are products that are formed in an amount suitable for large scale production, the relative amount of products are categorized into three groups: *main* producer of product among all STCs, *major* product of a single STC, *minor* product of a single STC which is in part also produced by other STCs.

STC	terpenoid	t_r [min]	RI	*m/z*	classification
Bot2	pdt1	9,966	1602	234	main
	pdt2	10,060	1619	234	minor
	pdt3	10,177	1639	234	major
	pdt4	11,237	1832	234/252	main
	pdt5	11,402	1864	234/252	main
PenA	pdt1	9,790	1574	234	main
	pdt2	10,086	1623	234	main
Cop4	pdt1	10,063	1619	234	main
	pdt2	10,438	1685	234/252	major
	pdt3	11,397	1863	234/252	minor
Cyc1	pdt1	9,788	1573	234	minor
	pdt2	10,184	1641	234	minor
Tri5	pdt1	9,789	1573	234	minor
	pdt2	10,061	1619	234	minor
	pdt3	10,114	1628	234	main
	pdt4	10,189	1642	234	minor

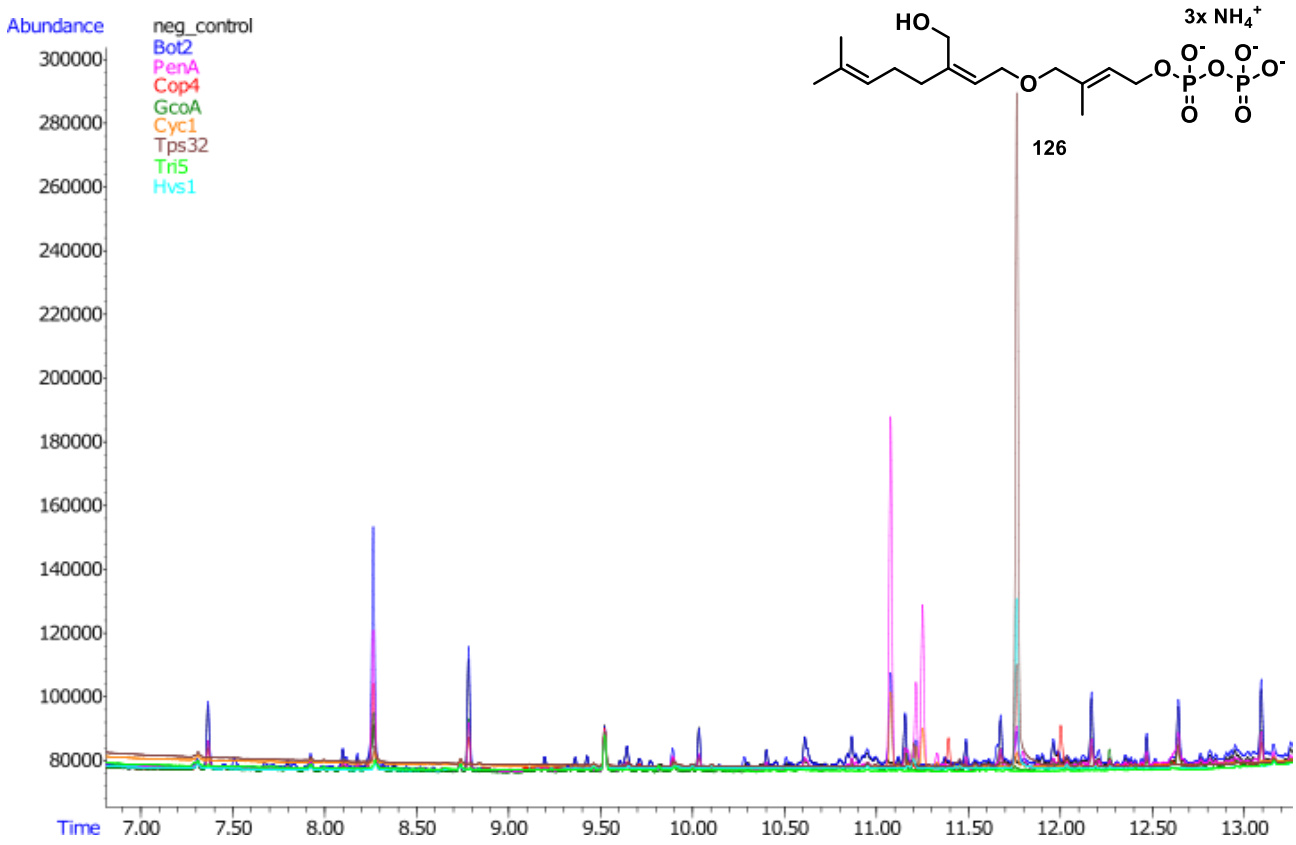


Figure 140: Overlay of FID-chromatograms of product mixtures resulting from enzymological assays for C-9-oxy oxa farnesyl derivative **125** (C-9 oxy oxa with OH).

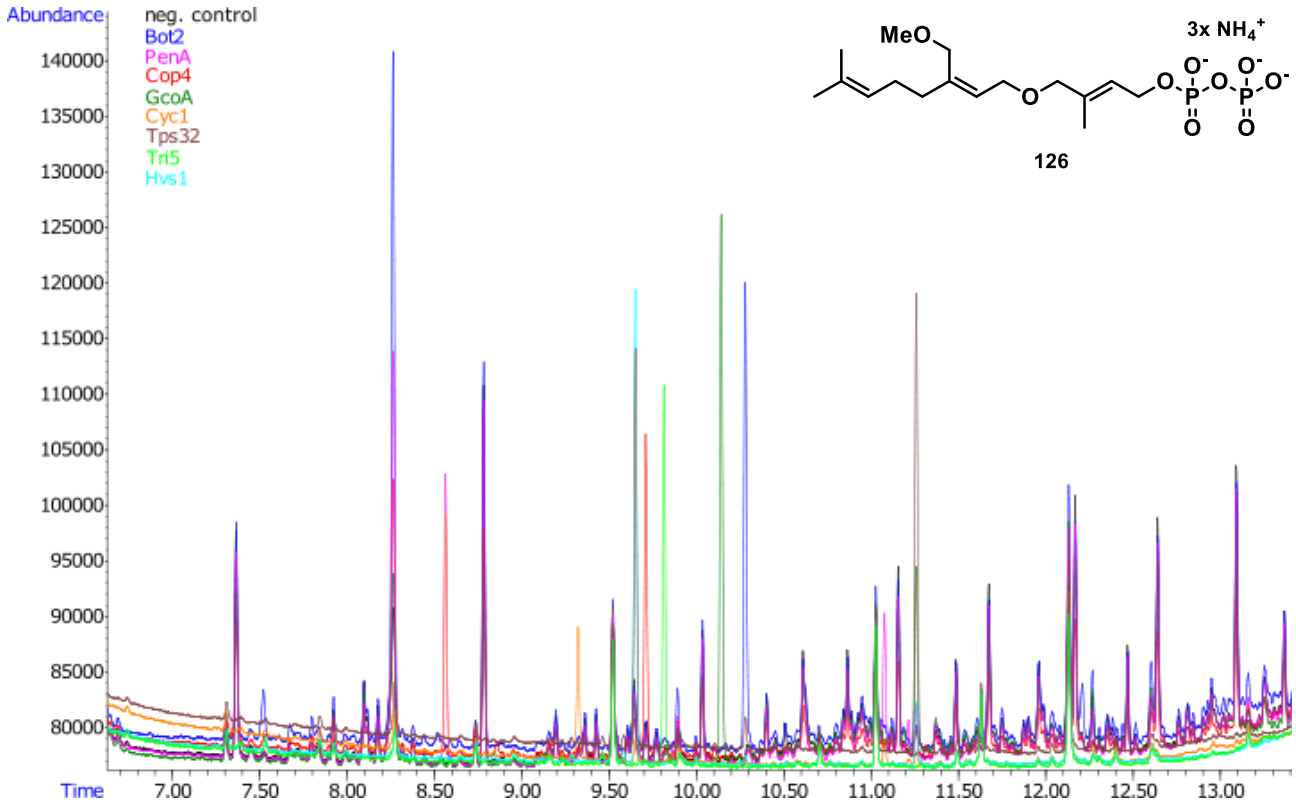


Figure 141: Overlay of FID-chromatograms of product mixtures resulting from enzymological assays for C-9-oxy oxa farnesyl derivative **126** (C-9 oxy oxa with OMe).

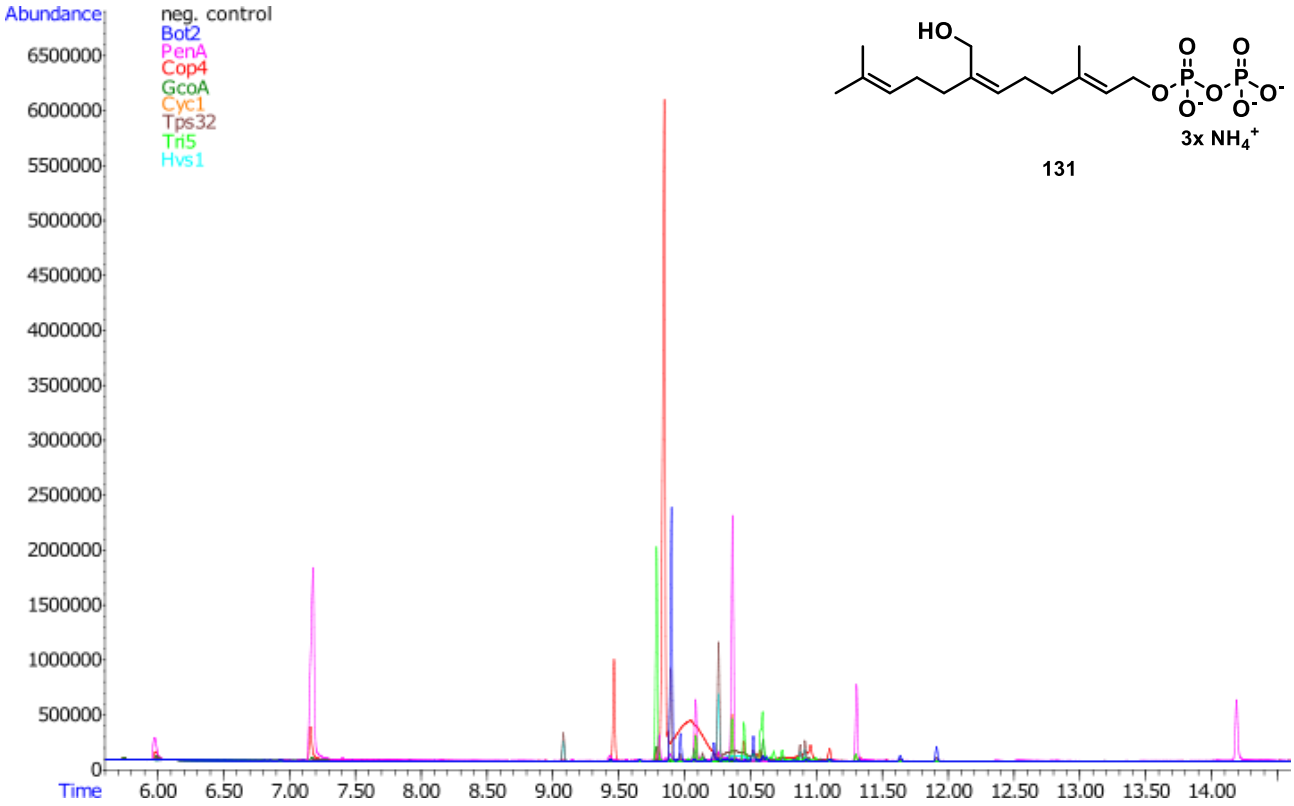


Figure 142: Overlay of FID-chromatograms of product mixtures resulting from enzymological assays for C-9-oxy farnesyl derivative **131** (C-9 oxy with OH).

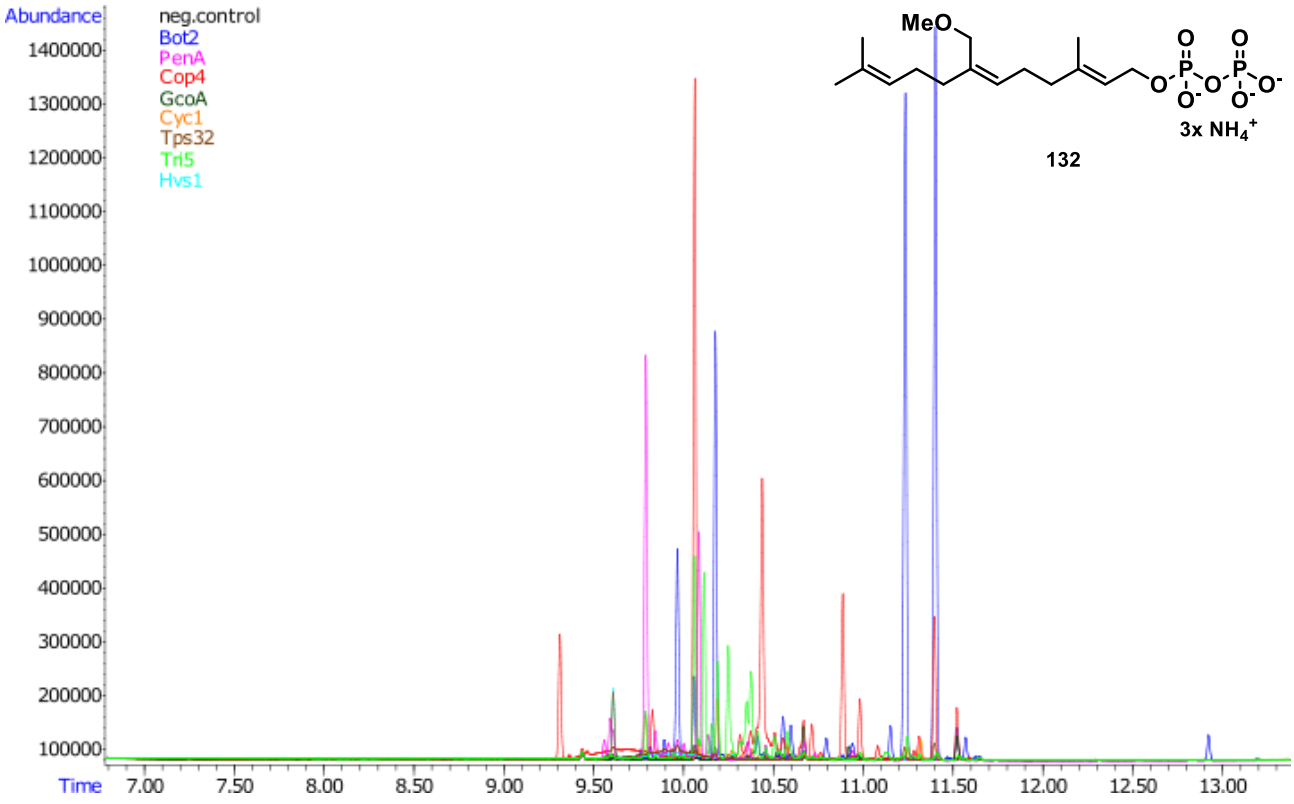


Figure 143: Overlay of FID-chromatograms of product mixtures resulting from enzymological assays for C-9-oxy farnesyl derivative **132** (C-9 oxy with OMe).

6.7.2 Analytical Enzymological Assays of C-1 Oxy-Derivatives

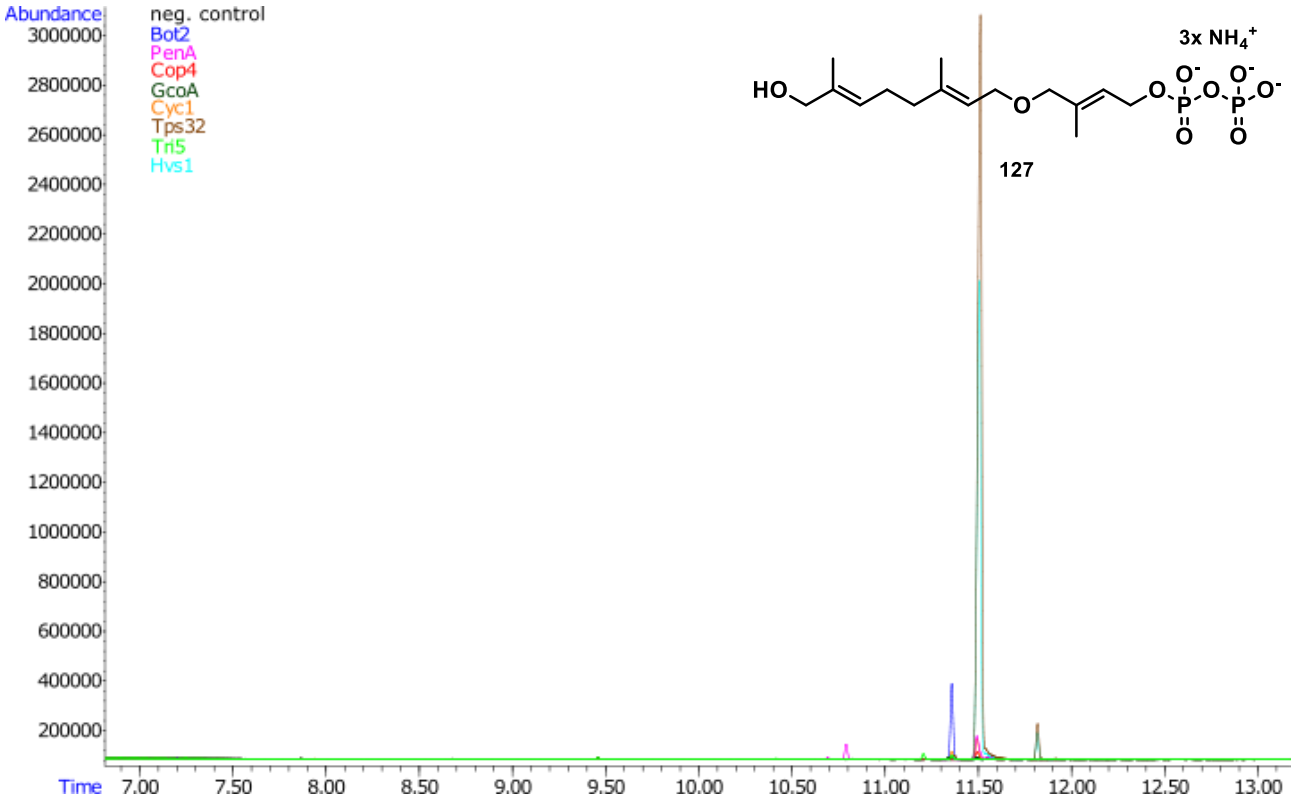


Figure 144: Overlay of FID-chromatograms of product mixtures resulting from enzymological assays for C-1-oxy oxa farnesyl derivative **127** (C-1 oxy oxa with OH).

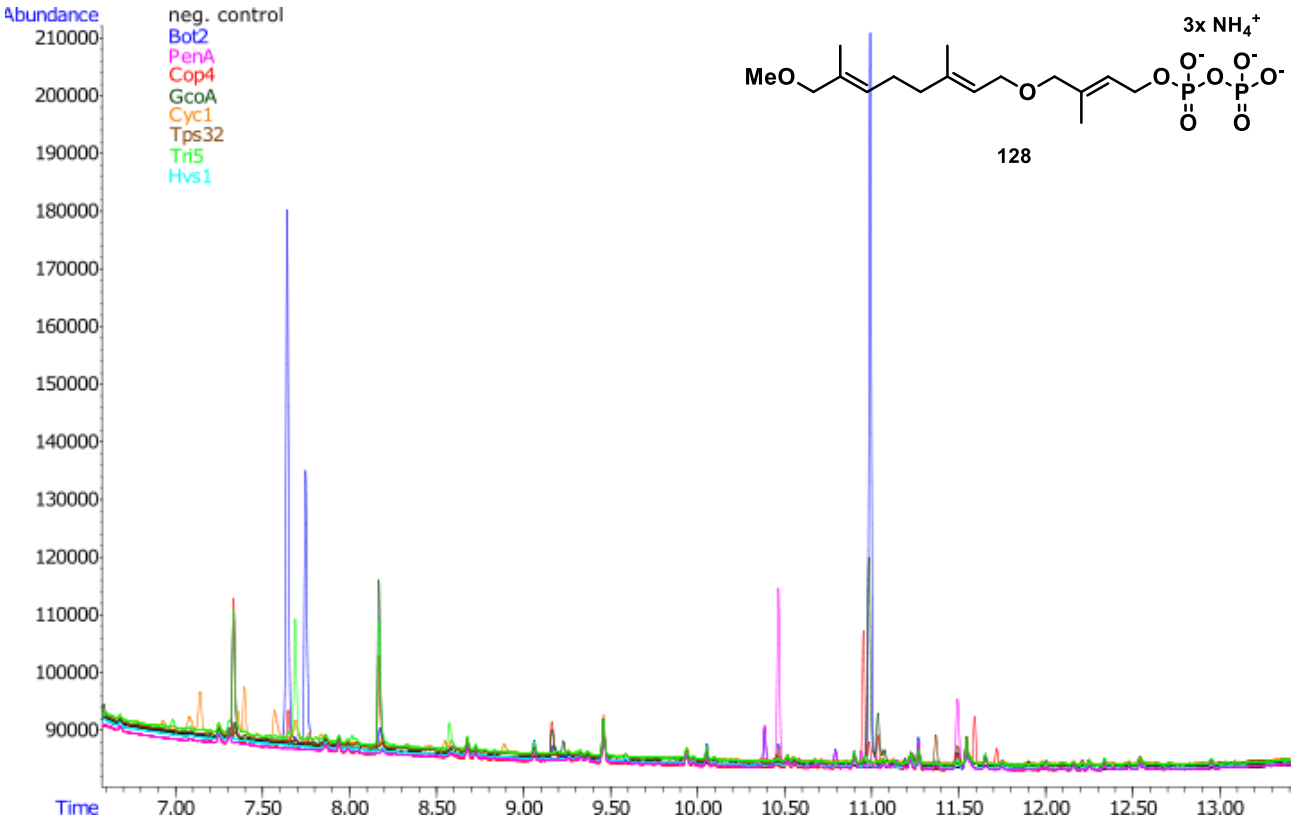


Figure 145: Overlay of FID-chromatograms of product mixtures resulting from enzymological assays for C-1-oxy oxa farnesyl derivative **128** (C-1 oxy oxa with OMe).

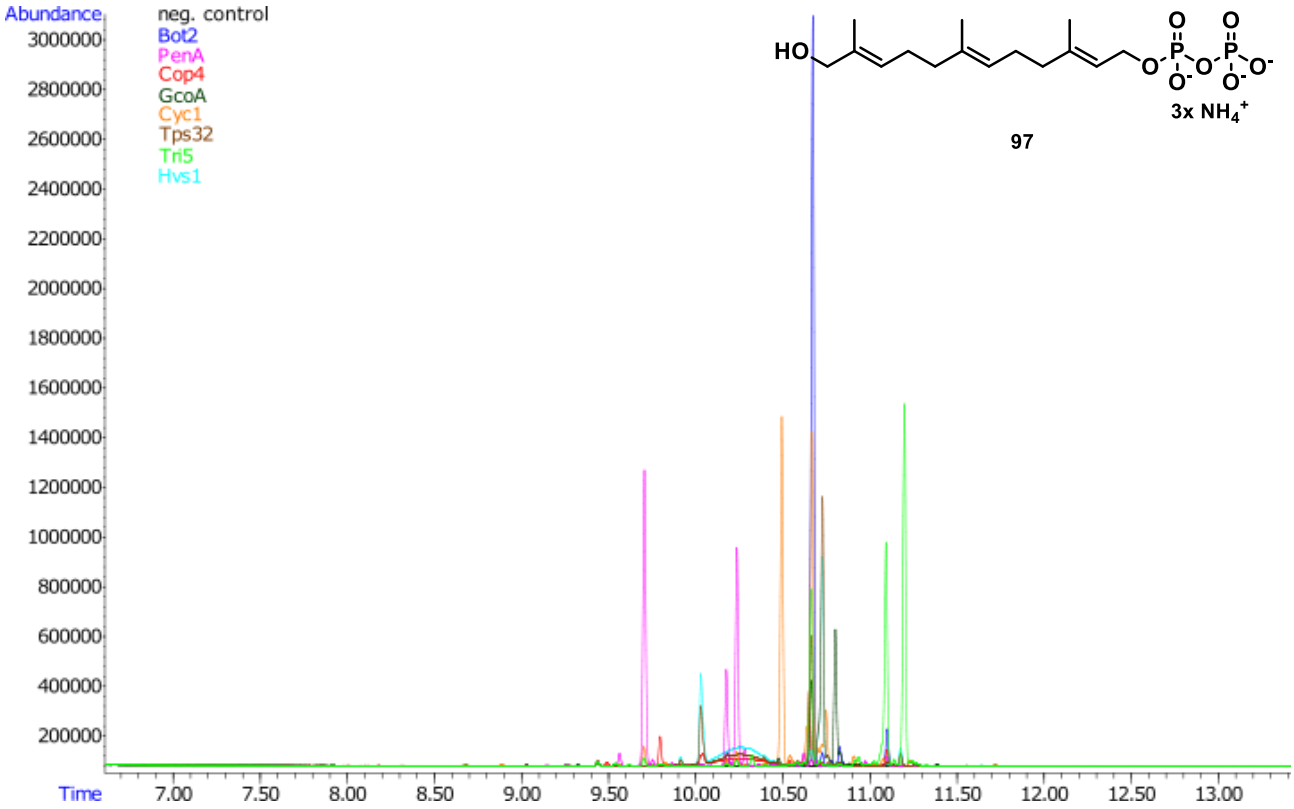


Figure 146: Overlay of FID-chromatograms of product mixtures resulting from enzymological assays for C-1-oxy farnesyl derivative **97** (C-1 oxy with OH).

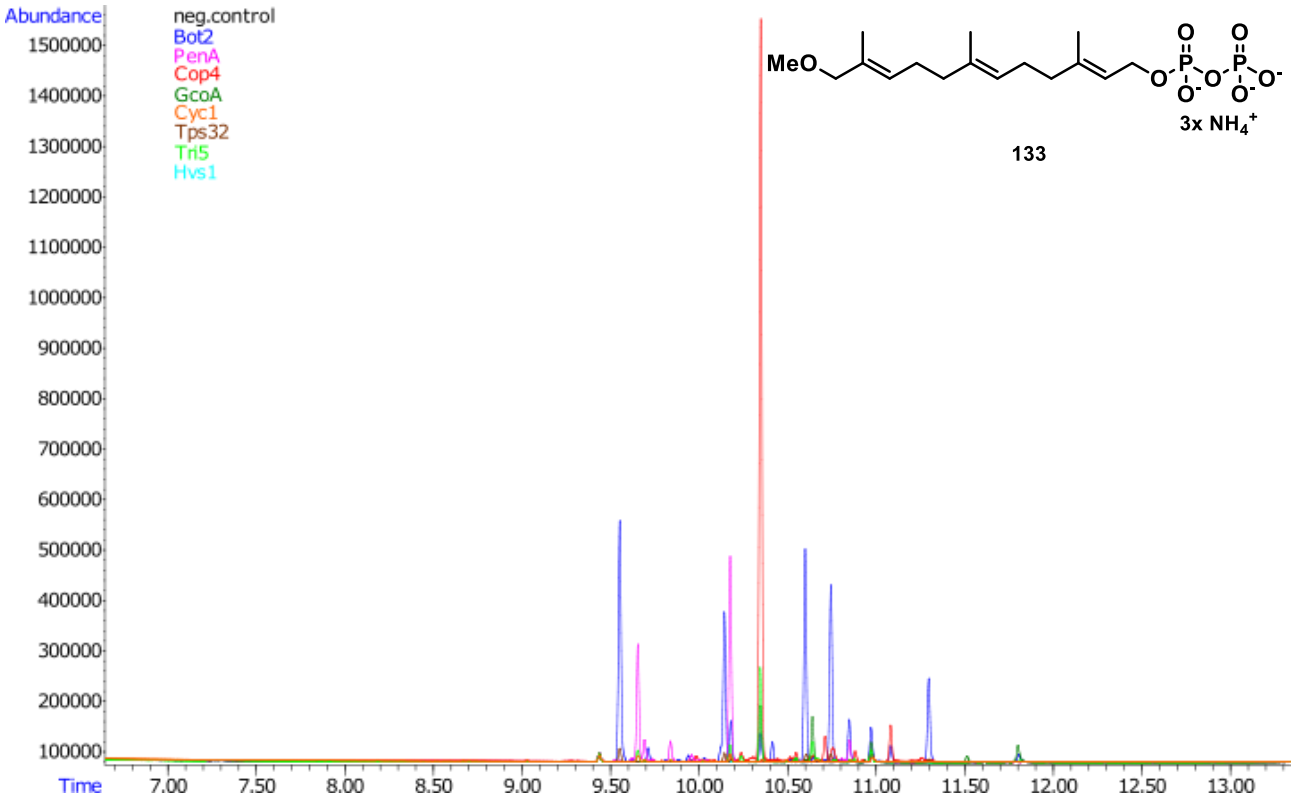


Figure 147: Overlay of FID-chromatograms of product mixtures resulting from enzymological assays for C-1-oxy farnesyl derivative **133** (C-1 oxy with OMe).

Derivatives **127** and **128** were submitted for biotransformation studies. Here, the terminal methyl group was oxidized and an oxygen atom was inserted into the backbone. The results, summarized in figure 144 and 145, show that derivative **127** with the free hydroxyl group was accepted by Tps32 and Hvs1 producing the same product in amounts that its isolation can be striven for. Also Bot2 produced only one product in a larger amount but it is still below the set threshold value. The other STCs only produced traces of novel terpenoids which were not further pursued. For derivative **128** with the additional methylether a different result was observed. Here, the analog was barely accepted by any STC, only Bot2 produced three terpenoids in traces amount. The other STCs did not accept or produced any novel terpenoid. The results from this set of biotransformations are summarized in table 17. The product generated by Tps32 and Hvs1 shows a *m/z* of 236 which corresponds to a cyclization cascade that was terminated by the elimination of a proton. The isolation of the product should be pursued using Tps32 rather than Hvs1 since the product is relatively formed in smaller amount by the latter STC.

Table 17: Novel terpenoids produced by STCs from derivative **127**: Highlighted in grey are products that are formed in an amount suitable for large scale production, the relative amount of products are categorized into two groups: *main* producer of product among all STCs, *major* product of a single STC.

STC	terpenoid	t_r [min]	RI	*m/z*	classification
Tps32	pdt1	11,510	1878	236	main
Hvs1	Pdt1	11,503	1876	236	major

For the derivatives devoid of an oxygen atom in the backbone similar results as before were observed: In total both derivatives were accepted by several STCs, derivative **97** with the free hydroxyl group was transformed by all STCs except by Cop4. Each of the biotransformations conducted with Bot2, PenA, GcoA, Cyc1, Tps32 and Tri5 gave at least one unique product which was not produced by any other STC. Only, Hvs1 produced terpenoids that were also covered in biotransformations by other STCs. Interestingly, all detected terpenoids show a *m/z* of 220 indicating that the cyclization cascade is terminated by the elimination of a proton. The results are summarized in figure 146 as well as in table 18. On the other hand, derivative **133** bearing the methylether group again was not well accepted, Bot2 and PenA produced novel terpenoids in amounts around the chosen treshold level. Only Cop4 showed a higher degree of acceptance and thus formation of a larger amunt of a single product. The remaining STCs did not accept this derivative or form novel terpenoids other than in trace amounts. Most products have a *m/z* of 234 showing that the cyclization cascade was terminated by the elimination of a proton. Only, two products formed by Bot2 have a *m/z* of 252 for the methylether

derivative indicating that the cyclization cascade was terminated by addition of water (s. figure 147 and table 19).

Table 18: Novel terpenoids produced by STCs from derivative **97**: Highlighted in grey are products that are formed in an amount suitable for large scale production, the relative amount of products are categorized into three groups: *main* producer of product among all STCs, *major* product of a single STC, *minor* product of a single STC which is in part also produced by other STCs.

STC	terpenoid	t_r [min]	RI	*m/z*	classification
Bot2	pdt1	10,672	1727	220	main
PenA	pdt1	9,705	1560	220	main
	pdt2	10,176	1639	220	main
	pdt3	10,236	1650	220	main
GcoA	pdt1	10,663	1725	220	minor
	pdt2	10,802	1751	220	main
Tps32	pdt1	10,664	1725	220	minor
	pdt2	10,727	1737	220	main
Cyc1	pdt1	10,494	1694	220	main
	pdt2	10,667	1726	220	major
Tri5	pdt1	10,663	1725	220	major
	pdt2	11,092	1804	220	main
	pdt3	11,197	1824	220	main
Hvs1	pdt1	10,731	1738	220	major

Table 19: Novel terpenoids produced by STCs from derivative **133**: Highlighted in grey are products that are formed in an amount suitable for large scale production, the relative amount of products are categorized into three groups: *main* producer of product among all STCs, *major* product of a single STC, *minor* product of a single STC which is in part also produced by other STCs.

STC	terpenoid	t_r [min]	RI	*m/z*	classification
Bot2	pdt1	9,552	1534	234	main
	pdt2	10,143	1633	234	main
	pdt3	10,599	1713	234	main
	pdt4	10,745	1740	234/252	main
	pdt5	11,297	1844	252	main
PenA	pdt1	9,654	1551	234	main
	pdt2	10,176	1615	234	main

Cop4	pdt1	10,348	1669	234	main
Tri5	pdt1	10,345	1669	234	minor
GcoA	pdt1	10,346	1669	234	minor

6.7.3 Analytical Enzymological Assays of C-6 Oxy-Derivatives

Derivatives **129** and **130** were submitted to the biotransformation studies. Here, the other terminal methyl group was oxidized and an oxygen atom was inserted into the backbone. Unfortunately, here similar results as for derivatives **125** and **126** were observed. For the derivative with the free hydroxyl group only Bot2, PenA and Tps32 revealed formation of smaller amounts of new terpenoids below the threshold set for isolation. Other STCs like Cop4 and Hvs1 produced new products in trace amounts while Cyc1, GcoA and Tri5 did not accept this derivative (s. figure 148). The products produced by Bot2 and PenA have a *m/z* of 236 showing that the cyclization cascade was terminated by the elimination of a proton. If the structures of these products have to be elucidated, larger amounts of STCs and pyrophosphates have to be prepared. In essence, the methylether derivative **130** were not well accepted by any STC. Only the production of trace amounts of new products was observed. Therefore, no further investigations on this analog were pursued (s. figure 149).

Table 20: Novel terpenoids produced by STCs from derivative **134**: Highlighted in grey are products that are formed in an amount suitable for large scale production, the relative amount of products are categorized into three groups: *main* producer of product among all STCs, *major* product of a single STC, *minor* product of a single STC which is in part also produced by other STCs.

STC	**terpenoid**	**t_r [min]**	**RI**	***m/z***	**classification**
Bot2	pdt1	10,494	1701	220	major
	pdt2	10,635	1727	220	major
	pdt3	10,758	1750	220	main
PenA	pdt1	10,277	1664	220	main
	pdt2	10,648	1730	220	main
	pdt3	10,995	1793	220	main
GcoA	pdt1	10,504	1703	220	main
Tsp32	pdt1	10,491	1700	220	major
	pdt2	10,634	1727	220	minor
	pdt3	10,743	1747	220	major
Cyc1	pdt1	10,635	1727	220	major
	pdt2	10,987	1791	220	minor

Tri5	pdt1	9,557	1542	220	main
	pdt2	11,015	1796	220	main
	pdt3	11,085	1810	220	main
Hvs1	pdt1	10,740	1747	220	major

Next, derivatives **134** and **102** that lack the ether group were tested. Again, these analogs showed a broader acceptance with a preference for that analog that has the free hydroxyl group in comparison to the methylether. For **134** several new products were detected, mostly produced by Bot2, PenA, GcoA and Tri5. Tps32, Cyc1 and Hvs1 produced a similar range of new terpenoids but in smaller amounts. Only Cop4 did not accept this derivative. The products generated have a *m/z* of 220 showing that the cyclization cascade is terminated by the elimination of a proton. Meanwhile, methylether derivative **102** only Tri5 produced terpenoids in substantial amounts that is also produced by other STCs (Cop4, GcoA, Bot2) but to a smaller degree. Bot2 and GcoA also produce other terpenoids but these are formed in amounts around the area of the set threshold value. Therfore, the isolation of these might be tedious. Interestingly, Bot2 as well as GcoA produced a new terpenoid that has a *m/z* of 252 showing that the cyclization cascade is terminated by addition of water in each case (s. figure 150 & 151 and table 20 & 21).

Table 21: Novel terpenoids produced by STCs from derivative **102**: Highlighted in grey are products that are formed in an amount suitable for large scale production, the relative amount of products are categorized into three groups: *main* producer of product among all STCs, *major* product of a single STC, *minor* product of a single STC which is in part also produced by other STCs.

STC	**terpenoid**	**t_r [min]**	**RI**	***m/z***	**classification**
Bot2	pdt1	10,253	1660	234	main
	pdt2	10,464	1695	234	minor
	pdt3	11,222	1836	234/252	minor
GcoA	pdt1	10,253	1660	234	minor
	pdt2	10,545	1710	234	major
	pdt3	11,714	1933	252	major
Tri5	pdt1	10,257	1660	234	main
	pdt2	10,641	1728	234	minor
	pdt3	10,767	1752	234	minor
Cop4	pdt1	10,253	1660	234	minor

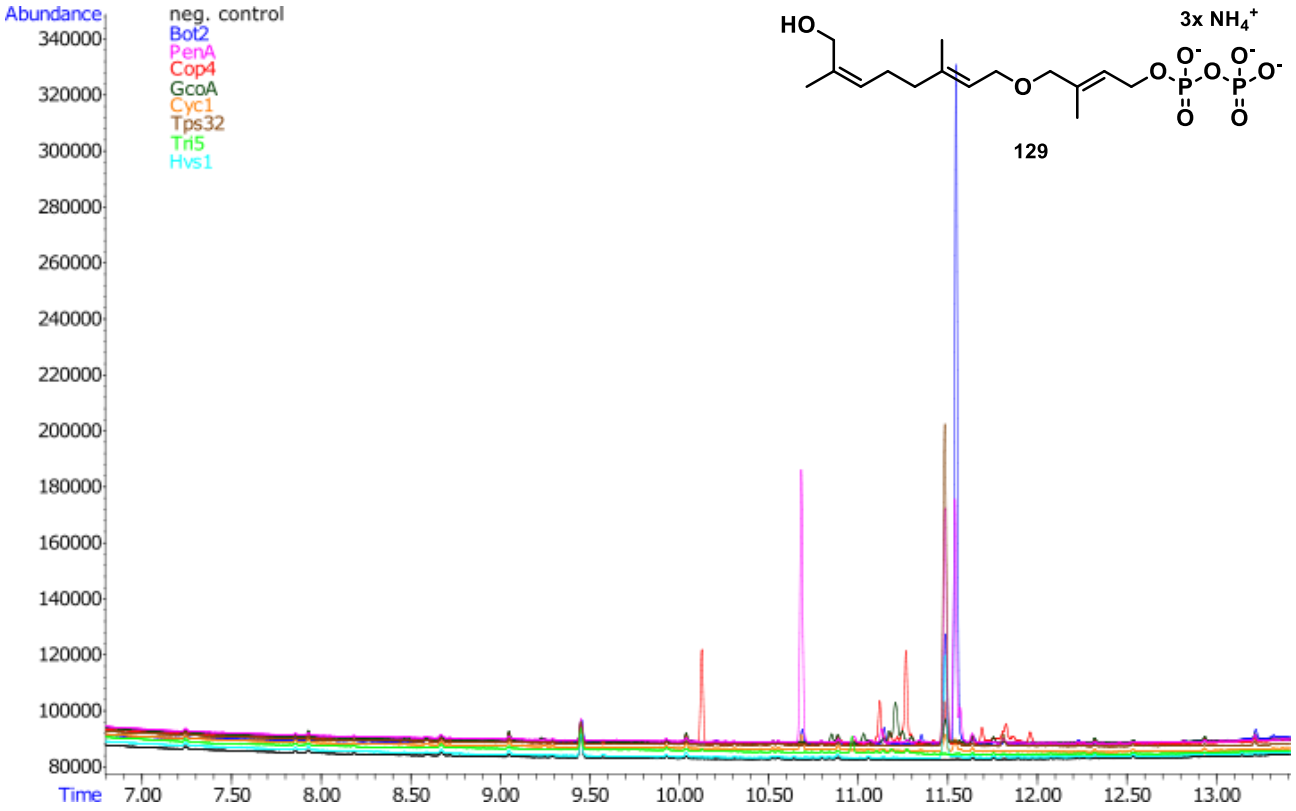


Figure 148: Overlay of FID-chromatograms of product mixtures resulting from enzymological assays for C-6-oxy oxa farnesyl derivative **129** (C-6 oxy oxa with OH).

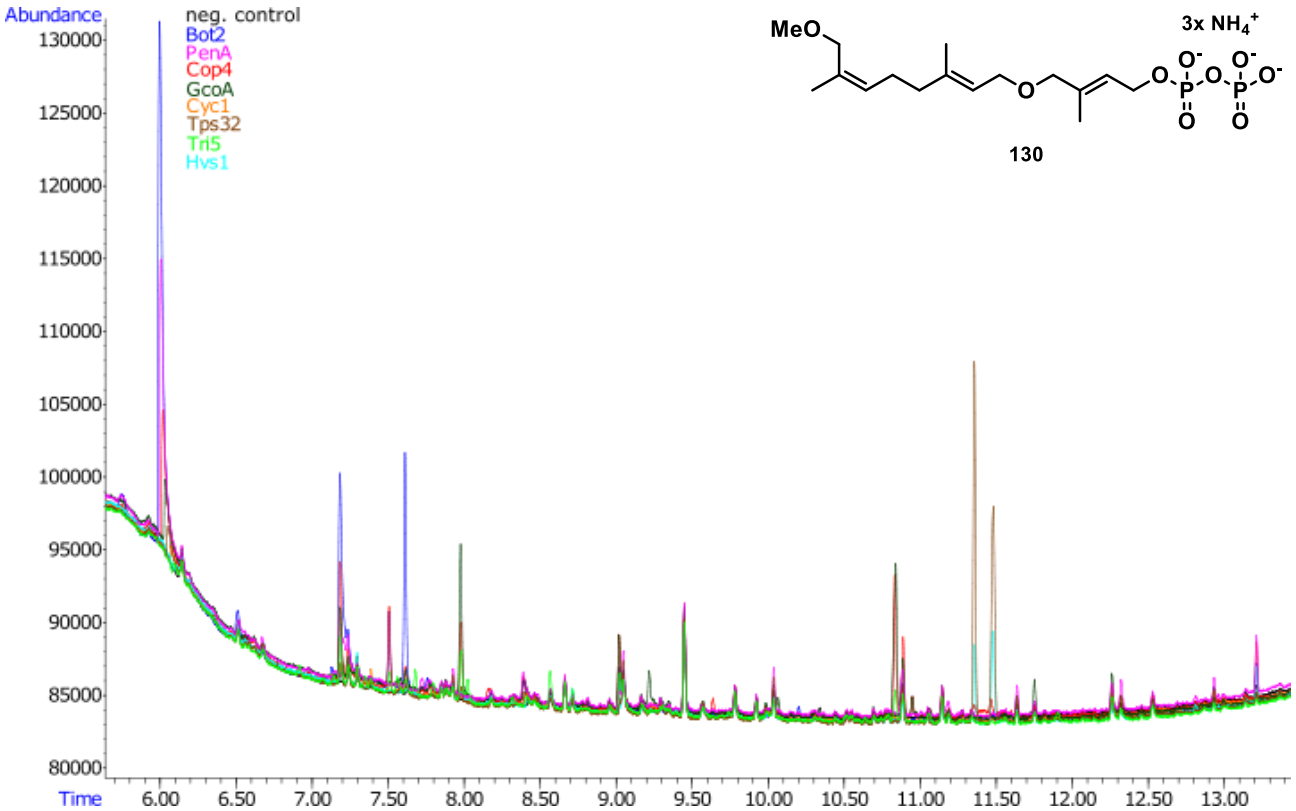


Figure 149: Overlay of FID-chromatograms of product mixtures resulting from enzymological assays for C-6-oxy oxa farnesyl derivative **130** (C-6 oxy oxa with OMe).

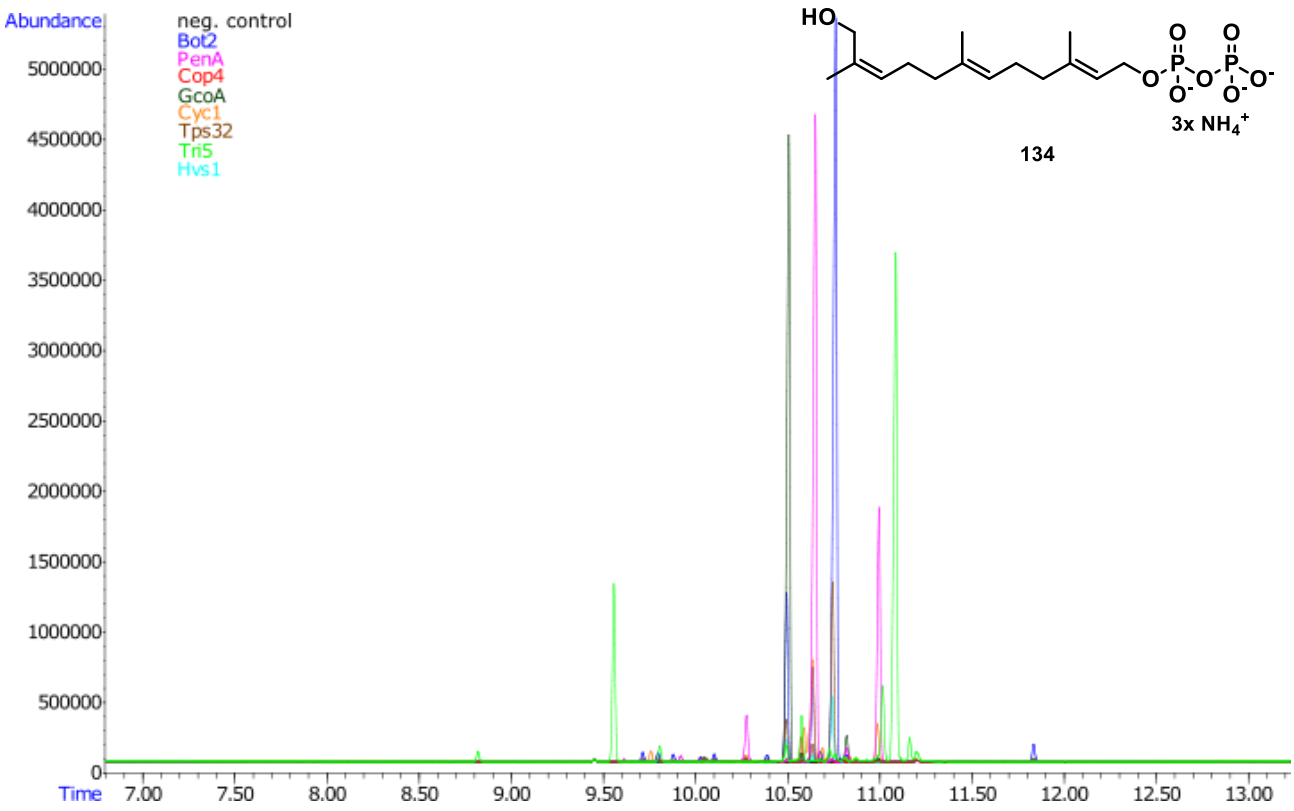


Figure 150: Overlay of FID-chromatograms of product mixtures resulting from enzymological assays for C-6-oxy farnesyl derivative **133** (C-6 oxy with OH).

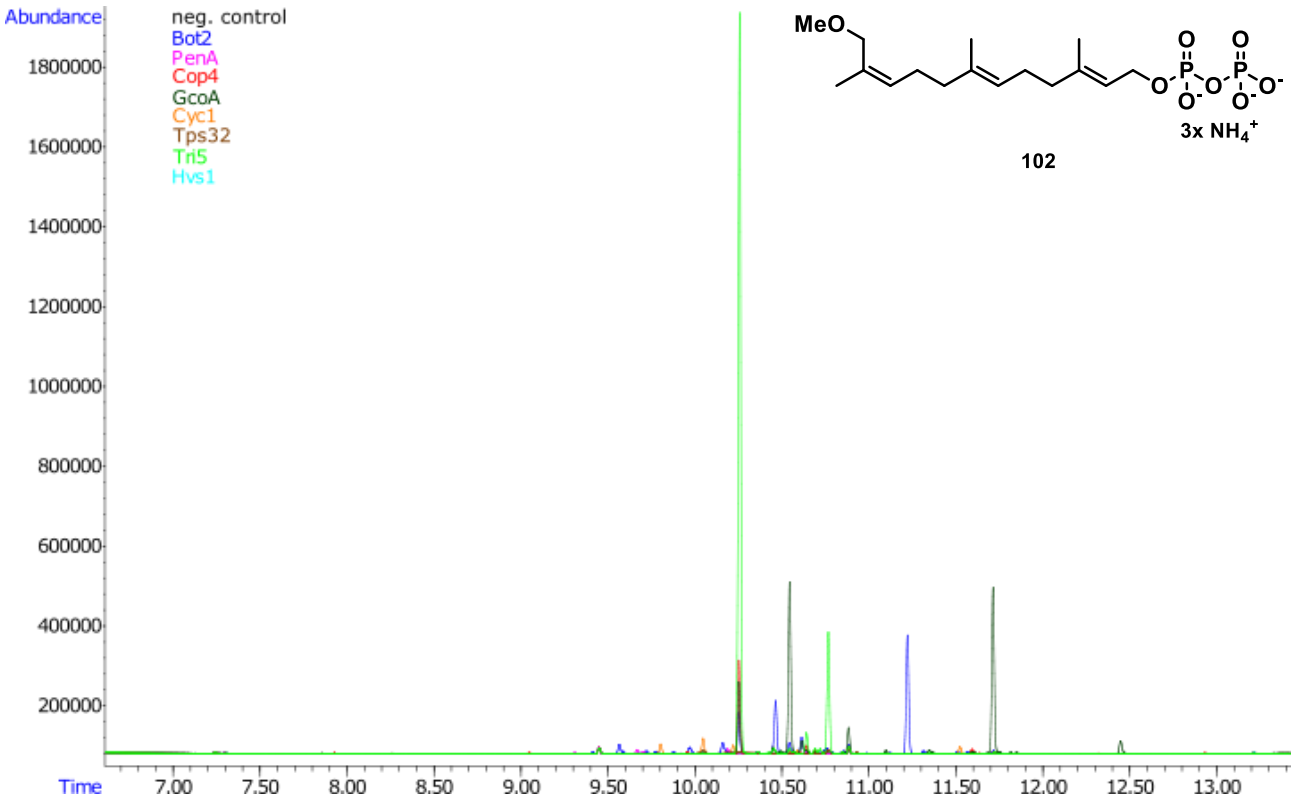


Figure 151: Overlay of FID-chromatograms of product mixtures resulting from enzymological assays for C-6-oxy farnesyl derivative **102** (C-6 oxy with OMe).

With all these results collected so far, a matrix was developed that shows the combinations of substrate analogs and STCs and which should be used for transformations on a larger scale allowing to isolate and structurally elucidate new terpenoids (s. table 22). Since most of the derivatives that contain the oxygen atom in the backbone were much less accepted, these FPP derivatives except for **127** can be abandoned for large scale preparation. One reason for the lack of acceptance might be that due to the extra oxygen atom in the linear chain their constitution is folded in a way that hampers proper fitting in the active center of the STCs. On the other hand, derivatives without this additional oxygen were susceptible of being accepted by STCs irrespective of the position of where the oxygen functionality is attached to. Also, here it is apparent that derivatives with the free hydroxyl group were better accepted than those that have a methylether instead. Here, the steric hinderance of an extra methyl group may lead to unfavourable interactions in the active site compared to the hydroxyl group. Another cause might also be the polarity of the residue. Since the OH residue can form hydrogen bonds that can be beneficial of being accepted and thus would fit better into the active site of selected STCs. This could be explored by molecular modeling, e.g. using alpha fold, or co-crystallization experiments of the corresponding STC and the substrate analog.

Table 22: Summary of analytical enzymological transformations: Highlighted in grey are products that are formed in an amount suitable for large scale production, the relative amount of products are categorized into three groups: + = produces major amount of one or several terpenoids, *o* = produces minor amount of one or several terpenoids, - = produces trace amount of one or several terpenoids or analog was not accepted.

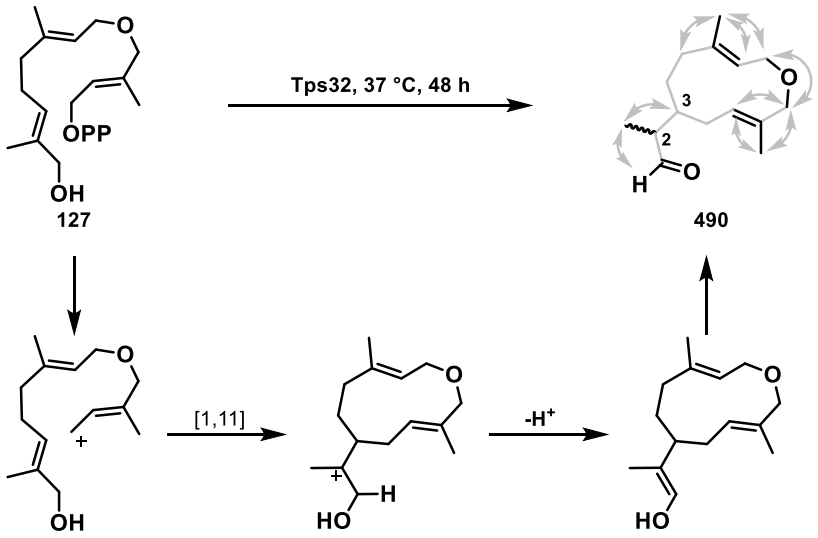
analog	Bot2	PenA	Cop4	GcoA	Cyc1	Tps32	Tri5	Hvs1
C-9-oxy oxa w/ OH	o	o	-	-	-	o	-	o
C-9-oxy oxa w/ OMe	o	-	-	-	-	-	-	-
C-9-oxy w/ OH	+	+	+	o	o	+	+	+
C-9-oxy w/ OMe	+	+	+	o	-	-	o	o
C-1-oxy oxa w/ OH	o	o	o	o	-	+	-	+
C-1-oxy oxa w/ OMe	o	o	-	o	-	-	o	-
C-1-oxy w/ OH	+	+	-	+	+	+	+	o
C-1-oxy w/ OMe	+	+	+	o	-	-	o	-
C-6-oxy oxa w/ OH	o	o	o	-	-	o	-	o
C-6-oxy oxa w/ OMe	o	o	-	-	-	-	-	-
C-6-oxy w/ OH	+	+	-	+	o	o	+	o
C-6-oxy w/ OMe	o	-	o	o	-	-	+	-

These findings are in line with Allemann's work who used derivatives **97** – **99** with the STC ADS to form arteminisin analogs.[81,83] They could show that these derivatives were transformed to different sesquiterpenes with interesting structural motives. Therefore, selected examples of the two known and ten new oxygenated derivatives were submitted for biotransforamtions on a larger scale to identify novel terpenoids and elucidate their structure.

6.7.4 Structure Elucidation of Novel Terpenoids

In order to elucidate the structures of newly formed terpenoids, selected biotransformations were performed on a larger scale. A general procedure is shown in the experimental part of this thesis. Due to the volatility of the products careful evaporation was essential. Residual signals of impurities comonly referred as pentanes. Therefore, 2D-NMR spectra were recorded followed by additional NMR-experiments such as the measurements of NOE correlations were used to elucidate their structures.

Starting with the transformation of **127** with Tps32, the ^{1}H-NMR spectrum revealed a set of signals indicating the presence of two diastereoisomers. This was obvious, as the doublets at around δ = 9.0 ppm which refer to an aldehyde give integrals in a ratio of 1.1:1. In addition, two doublets of a methyl group located in the neighborhood were found. Furthermore, two multipletts, each integrating to one proton at δ = 5.2 ppm indicated that two olefinic double bonds were still present. Next, there a total of four protons next to a heteroatom around δ = 4.0 ppm were present leading to the conclusion that those are located next to the ether moiety of the starting material. Based on HMBC and COSY correlations, the following structure was suggested (s. scheme 152). As the GC-MS analysis showed a *m/z* of 236 that is in line with the terminal elimination of a proton to form the aldehyde. Also, experimental observations support the formation of an aldehyde, as the vanillin stain gave a blue colored spot on the TLC plate and a R_f-value of 0.37 in PE/EtOAc 10:1 and UV-activity when excerted irridating at 254 nm were observed. Interstingly, the product excerted a strong odor of hazelnut. The proposed mechanism starts with cleavage of the pyrophosphate moiety, followed by a 1,11-cyclization which is typical for the STC Tps32.[173] Then, an elimination of a proton takes place to form an enolether that tautomerizes to the final aldehyde. As the last step is a uncatalyzed chemical process a mixture of almost 1:1 of both diastereoisomers sensibly formed. Those findings are in accordance with Allemann's work who used a similar substrate to achieve the synthesis of artemisinin (s. figure 153).[81]



Scheme 152: Proposed mechanism of the cyclization of **127** to aldeyhde **490** in the presence of Tps32: COSY-correlations are shown by grey bonds, important HMBC-correlations are represented by grey arrows.

In order to determine the stereochemistry of the new products different approaches were pursued. At first a comparsion with literature data was applied. Viridiflorene (**491**) is the natural product formed from FPP by Tps32 (s. figure 153). Here, the stereocenter at C-3 is (*R*)-configured. This stereocenter is considered to be set, as the enzyme provides a chiral catalytic prodcut commonly generating the same absolute stereocenter at this position. Therefore, the proton at C-3 of **490a** & **490b** should be pointing upwards. Next, in NOE-experiments it was shown that the protons at C-2 and C-3 of the minor diastereoisomer interact with each other, showing that they are oriented *syn* to another. This results in the stereochemistry for both diastereoisomers shown in figure 153. A comparison with Allemann's finding is difficult, as in his work a different enzyme that follows another cyclization mechanism was used. Nevertheless, also here formation of a (*R*)-configured stereocenter was reported.[81] In order to further determine the stereochemistry aldehyde **490** was planned to be transformed into its corresponding tosylhydrazone. Most of these are easily cristallized, allowing to perform X-ray crystallographic measurements which allows to determine the absolute configuration. Unfortunately, applying standard conditions the desired product could not be obtained.

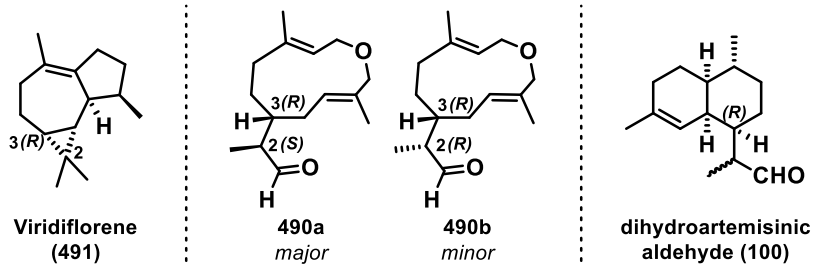
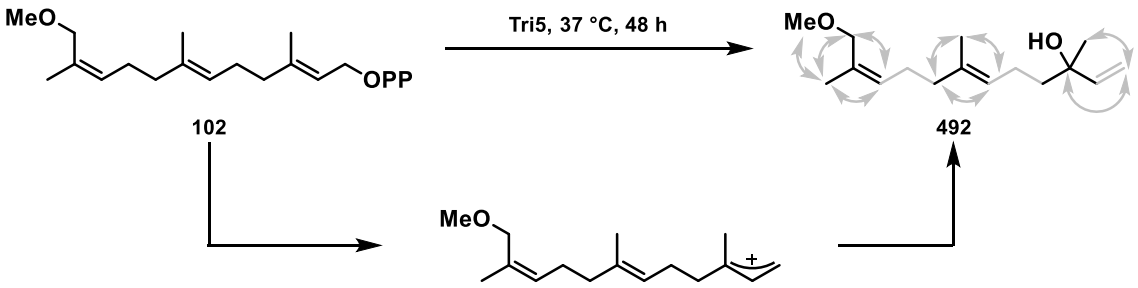


Figure 153: Proposed absolute stereochemistry based on comparison of produced aldehydes **490a** & **490b** with other terpenpoid natural products and NOE-experiments.

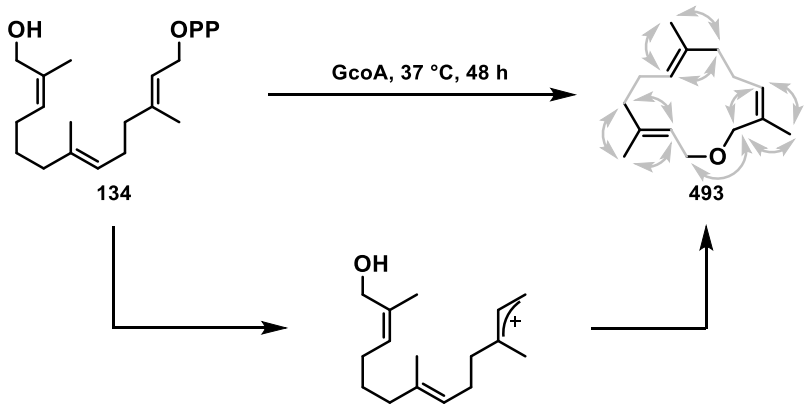
Next, transformation of methylether derivative **102** was carried out with the STC Tri5 yielding two products but only one of these could structurally be elucidated. The second product was not available in sufficient amount. Nevertheless a strong scent of freshly caramelized popcorn was apparent. A first glance at the ^{1}H-NMR showed four protons in the area δ = 5 ppm and one characteristic doublet of doublets at δ = 6.5 ppm. This is a typical signal for a proton at a terminal double bond as its coupling partners were also found in the mentioned δ = 5 ppm area. Furthermore, two singulets integrating to two and three in the area between δ = 4 and 3 ppm indicating the methyl ether and the corresponding CH_2-group. In the aliphatic area of the spectrum a similar set of signals was obtained as in the synthesis of pyrophosphate precursos leading to the idea that the initially formed allylic cation was quenched with water leading to the isomerized alcohol as shown in scheme 154. The proposed structure was verified by measurements of 2D-NMR spectra. The GC-MS data showed a *m/z* of 234 which speaks for an elimination product. Since those measurements are performed by heat induction elimination of tertiary alcohols often occurs leading to a false positive result for an elimination product.



Scheme 154: Proposed mechanism of the transformation of **102** to terminal alkene **492** by Tri5: COSY-correlations are marked in form of grey bonds, important HMBC-correlations are shown as grey arrows.

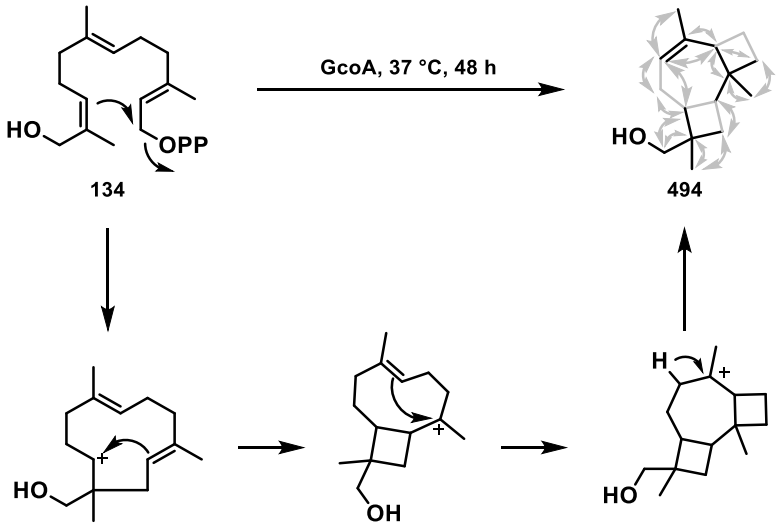
Furthermore, the corresponding derivative **134** with the free hydroxyl group was transformed with GcoA resulting in three new products. These were separated by column chromatography and their structures were elucidated. Unfortunately, the second product (based on their polarity on TLC) was lost during a second purification and its structure could not be elucidated. Starting with the structure of elucidation of the first product one finds three tripletts in the area δ = 5 ppm. Also, one doublet and one singulet in the area δ = 4 ppm each integrating to two protons. This led to the hypothesis that a macrocycle without any further cyclizations was formed. Furthermore, in the aliphatic area the set of ^{1}H-NMR signals shows similarity to spectra of molecules during the synthesis of pyrophosphate **134**. In the HMBC-spectrum a correlation between both CH_2-groups next to a heteroatom is clearly visible, supporting the initial hypothesis. This macrocycle is formed by attack of the free hydroxyl group onto the initially formed allylic cation after cleavage of the pyrophosphate moiety. Lastly, experimental

data such as a blue stain in vanillin on a TLC plate and a high R_f-value (0.63 in 3:1 PE/EtOAc) and a *m/z* of 220 further support the suggested structure. A proposed mechanism is shown in scheme 155.



Scheme 155: Proposed mechanism of the GcoA-catalyzed cyclization of **134** to macrocycle **493**: COSY-correlations are presented as grey bonds, important HMBC-correlations are presented as grey arrows.

The third product was found to be the most interesting one. As only one signal in the area of δ = 5 ppm was apparent, possibly a tricycle was formed in this cascade. Furthermore, analysis of the HSQC spectrum showed that three quaternary C-atoms are formed in the product which is in line with this hypothesis. Next, a broad signal representing a free hydroxyl group and two doublets of doublets at δ = 3.5 ppm are formed leading to the conclusion that a primary alcohol functionality must be located next to a stereocenter as both protons have different chemical shifts. Following different HMBC-correlations a carbon backbone composed of a tricyclic 7-4-4 ring system was supposedly present. In order to achieve a better understanding of the large number of HMBC cross peaks a H2BC-experiment was carried out which revealed only ^{2}J-couplings. In order to determine the geometry of the double bond a comparison of coupling constants was pursued. Both methyl groups appeared as a doublet at δ = 0.86 ppm with a coupling constant of J = 6.5 Hz and the doublet of triplets at δ = 5.40 ppm with a coupling constant of J = 6.6 Hz. Usually, allylic coupling constants appear to be not larger than J = 3 Hz, however it may be increased here due to the rigid ring system. Therefore, a first proposed mechanism was developed that is shown in scheme 156. Important COSY and HMBC correlations are also shown. These findings are also in line with experimental data as a *m/z* of 220 and a lower R_f-value (0.35 in 3:1 PE/EtOAc) that is typical for multicyclic compounds.



Scheme 156: Proposed mechanism of the GcoA-catalyzed cyclization of **134** to alcohol **494**: COSY-correlations are presented in form of grey bonds, important HMBC-correlations are visualized as grey arrows.

In order to obtain an idea about the stereochemistry a series of NOE experiments were performed giving rise to suggest the relative stereochemistry. Interesting correlations are those next to the stereocenters. Starting from the methyl group at position 14, the proton at C-3 and the CH_2-group next to C-2 were identified as correlation partners. Thus, both cyclobutane rings have to be *trans* annulated. This was confirmed by interactions between the proton at C-15 with the proton at C-8 and the methyl group at C-2. These findings are in line with the proposed cyclization mechanism of GcoA which produces β-caryolanol which also has a *trans* annulated ring system.[174]

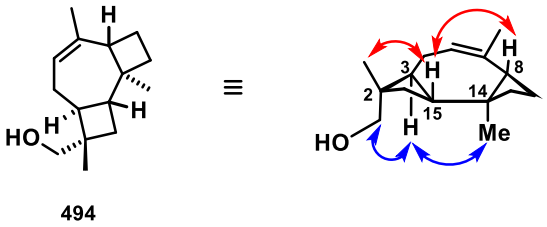
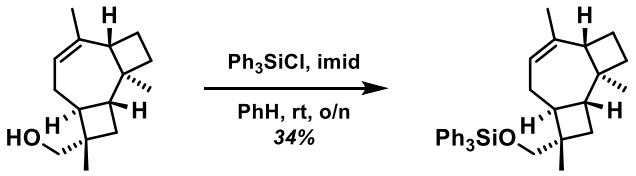


Figure 157: Proposed relative stereochemistry of **494**: Red arrows display NOE-correlations on the top face, blue arrows represent NOE-correlations on the bottom face.

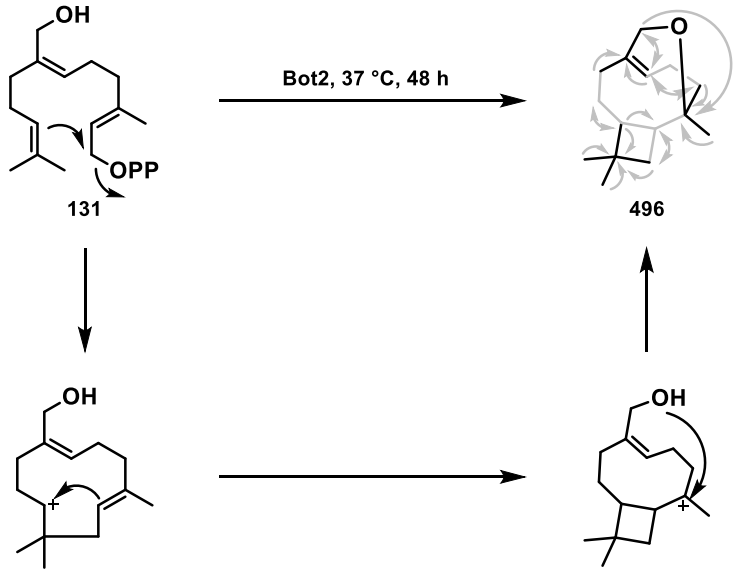
To gain information on the absolute stereochemistry it was thought to prepare silylether **495** from **494** which are prone to form crystalline compounds. Thus, absolute configuration would be resolved by X-ray crystallographic analysis. However, even **495** was obtained as a solid compound, it was not possible to obtain a clean crystal which could be analyzed.



494 495

Scheme 158: Synthesis of crystalline derivative **495** of the biotransformation prodcut of **494** with GcoA.

Furthermore, also derivative **131** was exposed to the STC Bot2 which provided new terpenoids. Here, a first glance at the recorded NMR-spectra showed that only one double bond remained in the product. Together with experimental data showing a *m/z* of 220 and a higher R_f-value (0.60 in 5:1 PE/EtOAc), the spot staining blue on TLC with the vanillin stain, led to a hypothesis that a macrocyclic ether must have formed. Further investigation of the ^{1}H-NMR spectrum showed that only two signals were clearly located in the area of δ = 4 ppm meaning that the alcohol moiety must be closing an ether macrocycle now by forming a quaternary carbon center. Analysis of HSQC and HMBC data verified this hypothesis. Also, here it was clear that the product contains three CH-, in total six CH_2-groups and three methyl residues. Combination of different correlations colledted from HMBC, COSY and HSQC experiments leads to the final hypothesis that the product consisted of a 9-4-annulated ring system with an additional bridged ether group. This is shown in scheme 159. This mechanism is also in line with the one known for FPP and Bot2.[175] Starting with the formation of the cyclobutane ring by two consecutive cyclization steps the tertiary cation was trapped by addition of the free alcohol, thus preventing further cyclizations.



Scheme 159: Proposed mechanism of the Bot2-catalyzed cyclization of **131** to cyclic ether **496**: COSY-correlations are presented as grey bonds, important HMBC-correlations are visualized as grey arrows.

In order to obtain an idea about the relative stereochemistry a series of NOE-experiments were performed. Here, an interaction between the proton at C-15 with the methyl group C-16 was detected, suggesting a *syn* orientation. Based on this result, the ether bridge had to be located on top of the macrocycle. On the other hand, no interaction between the proton at C-3 and C-15 was detected, suggesting an *anti* annulation of the cyclobutane ring. Comparison with the stereocenters found in the natural product, the proton at C-3 should point upwards, as this center was initially formed during the first cyclization step. This center therefore should have the same absolute configuration as found in the natural product, as the enzyme provides a chiral active pocket leading to the same absolute configuration of the stereocenter. Combination with the results collected from the NOE-experiments allows to propose the absolute stereochemistry as shown in figure 160.

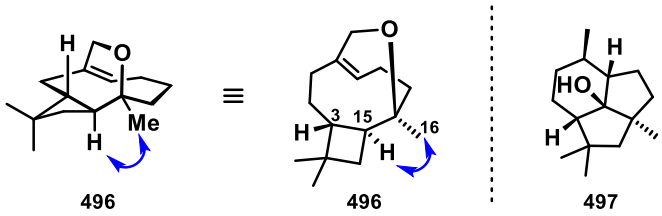
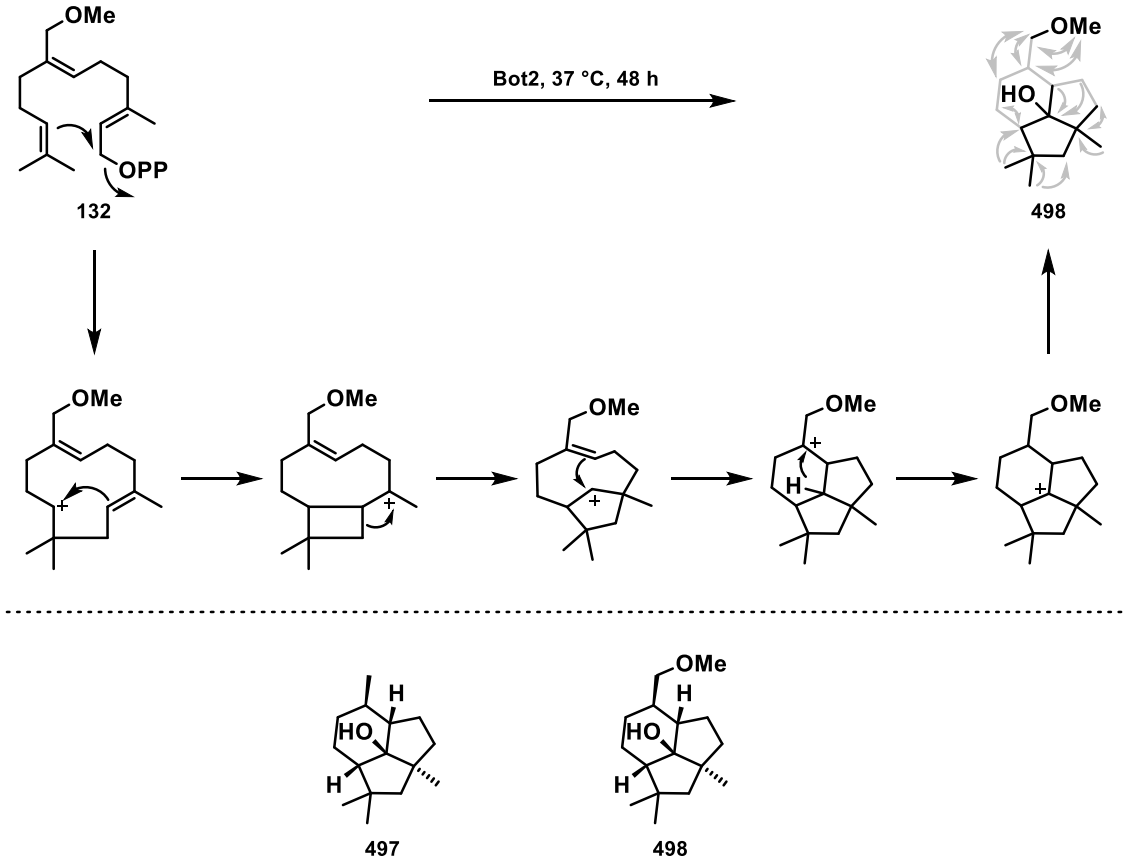


Figure 160: Proposed stereochemistry of **496** based on comparison with similar natural products and NOE-experiments (blue arrows represent NOE-correlations on the bottom face).

On the other hand, also methylether derivative **132** was transformed by the STC Bot2. Here the formation of four products was detected by GC-MS analysis but only two of them could be isolated and structure elucidation could be performed. For the first product, an initial interpretation of the ^{1}H-NMR spectra showed that no signals in the area which is typical for double bonds was present. This led to the hypothesis that a tricyclic product was formed. Furthermore, a singluett at δ = 3.15 ppm that integrated to three protons, suggests that the methylether was still present in the new product. In the neighborhood of this signal two doublets of doublets are found each representing one proton. Thus, there has to be a stereocenter next to the CH_2-group which is adjacent to the methylether. Further analysis of the HSQC experiments showed that three tertiary and three quaternary carbon centers are part of the product next to four methyl groups and six CH_2-groups. Together with HMBC and COSY-experiments as well as experimental data showing a *m/z* of 220 and a lower R_f-value (0.33 in 5:1 PE/EtOAc), a tricyclic product with a tertiary alcohol can be proposed, that is shown in scheme 161. Even though the detected *m/z* value advocated an elimination a product. Since those MS-measurements are performed by heat induction elimination of the tertiary alcohols often occurs pretending the presence of an elimination product. Interestingly, the proposed structure has the same constitution as the natural produced presilphiperfolan-8-β-ol (**497**) usually formed by Bot2. Comparison of re-

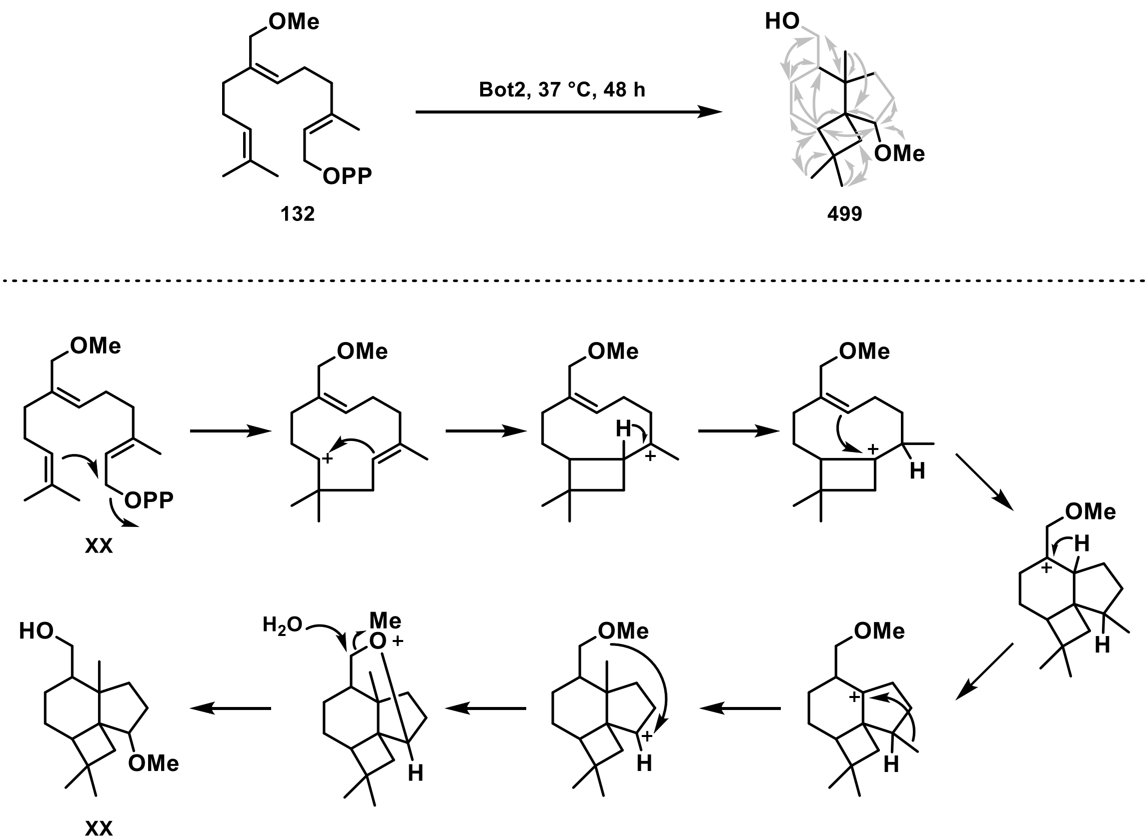
ported NMR data revealed that several signals match in chemical shift and splitting that further supports the proposed structure.[172] Based on these similarities, a mechanism can be formulated that includes the configuration of the formed stereocenters to be identical as found in the natural product.[175–177]



Scheme 161: Proposed mechanism of the Bot2-catalyzed cyclization of **132** to tertiary alcohol **498**: COSY-correlations are presented as grey bonds, important HMBC-correlations are visualized as grey arrows; below comparison of **498** with presilpheiperfolan-8-β-ol (**497**) with matching relative stereochemistry.

The second product that could be isolated in sufficient amount creates particular attention as no olefinic double bond could be found by NMR-spectroscopic analysis. In addition, a broad signal dedicated to an OH proton was found at δ = 2.70 ppm. This result is in line with experimental data collected by GC-MS measurements showing a *m/z* of 254 and a smaller R_f-value (0.12 in 5:1 PE/EtOAc) leading to the proposal that a multicyclic product that bears a primary alcohol group was formed. As the ^{1}H-NMR-spectrum turned out to be very complex, specifically in the area between δ = 1.8 and 1.4 ppm, the HSQC spectrum was used first to determine the multiplicity and number of carbon atoms. As a result, three quaternary, three tertiary, six secondary and four primary carbon atoms were encountered. By following this line of analysis, the HMBC and COSY data sets were analyzed to identify several smaller fragments which had to be brought together to finalize a structure proposal.

One interesting observation was that the methylether moiety must have shifted, as it is not attached to the carbon atom but is linked to a secondary carbon atom. In addition, this position shows a neighboring quaternary center. On the other hand, the alcohol moiety appeared to be a primary one and this also neighbored by a second quaternary center. This quaternary center also bears one methyl substituent which was assigned using again an H2BC experiment. A third fragment was unfolded starting from the *gem*-dimethyl group that incorporated the remaining quaternary center. Here, in the neighborhood a CH_2-group at around δ = 1.5 ppm was detected with an accountable coupling constant.



Scheme 162: Proposed mechanism of the cyclization of **132** to yield the tricyclic terpenoide **499** in the presence of Bot2: COSY-correlations are shown for bonds marked in grey, important HMBC-correlations marked as grey arrows.

In this neighborhood the interesting tertiary carbon atom is bound to which a proton in the area of δ = 1.6 ppm. This signal associated with important correlations in the HMBC and COSY spectra, allowing to combine this fragment with the fragment that contains the primary alcohol. The fragment of the methyl ether was assigned based on the HMBC correlations with the chemical shift (δ) for the CH-group at 1.6 ppm. This leads to the conclusion that the methylether had to be located on the face of the cyclobutane. Finally, a hypothesis was drafted that's us based on a 4-6-5 membered tricyclic ring system that may have formed *via* an interesting mechanism, as shown in scheme 162. The mechanism starts as usual with the formation of the cyclobuatne. But now, a 1,2-hydride shift takes place

to for another tertiary cation. Thus, the Wagner Meerwein rearrangement did not occur. This resulting cation is attacked by the remaining olefinic double bond to form the desired tricyclic backbone along with a new tertiary cation β-positioned to the methylether. At this stage, a second 1,2-hydride shift takes place that yields another tertiary cation. At this point, a 1,3-methyl shift takes place to form a secondary cation which is located at the position as already in the beginning of this cascade. From previous experiments, it is known that this position can be attacked by the free hydroxy group (s. scheme 159). Now, the methylether bridges across to the cation and the resulting bridged oxonium ion opens up by nucleophilic attack of water. Noteworthy, this bridge should be similarly positioned as the cation formed for the proposed mechanism when FPP serves as substrate for Bot2. Mechanistically, this is remarkable route through still closely related to the natural mechanism allowing to from the primary alcohol and the seconday methylether in one cascade sequence.

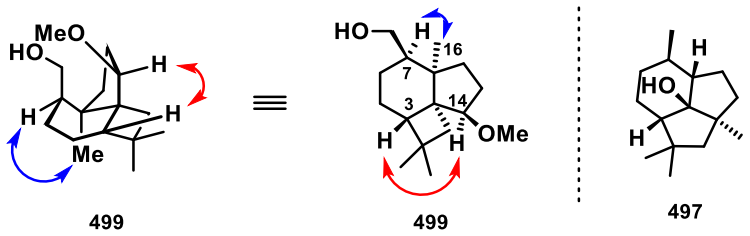


Figure 163: Proposed relative stereochemistry of **499**: red arrows are NOE-correlations found for the top face, blue arrows are NOE-correlations located t the bottom face; comparison of **499** with presilpheiperfolan-8-β-ol (**497**) and absolute as well as relative stereochemistry related to the new terpenoid **499**.

In order to decipher the stereochemistry of **499** a series of NOE experiments were performed, that provided through space correlations between protons at C-3 and C-14 and between protons at C-7 and those of the methyl group of C-16. From these results, a hypothesis was developed that suggests that the cyclohexane and cyclopentane rings are *syn*-annulated while the cyclobutene and the cyclohexane rings are *trans* annulated. This would provide a rationale for the observed NOE-correlations. Thus, the methyl group of C-16 has to point into the opposite direction to the proton at C-3. Therefore, the proton at C-7 and the methylgroup of C-16 have to face the bottom face of the ring system. The upwards pointing primary alcohol is also in line with the proposed mechanism, as it is oriented on the same side as the methylether at C-14. Comparison with the natural product formed by Bot 2 with FPP **497** allows to determine the absolute configuration at C-3. Since this stereocenter was formed in the first step of the cyclization cascade and did not change as the cationic cascade proceeds, it can be assumed that the same absolute stereochemistry can be assigned here, too.[175–177] This allows to suggest the absolute stereochemical for **499** as shown in figure 163.

7 Summary and Outlook

7.1 Total Synthesis of Tricycle 1

In the course of this thesis different retrosynthetic approaches of tricycle **1** were pursued.

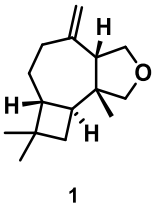
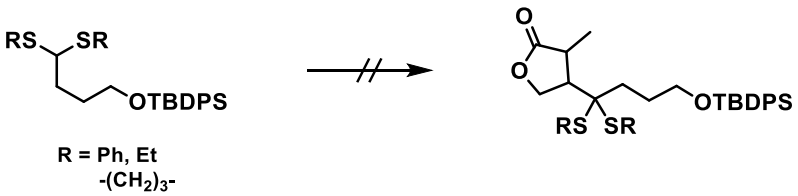


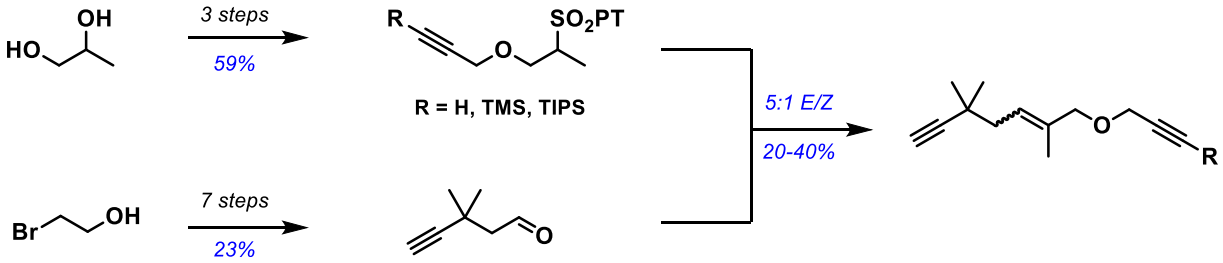
Figure 164: Total Synthesis goal: tricyclic terpenoid **1**.

The first one inludes a conjugate addition of a dithiane or its acetal-analogs. As this reaction failed at an early stage of this synthesis, this approach was dismissed (s. scheme 165).



Scheme 165: Failed synthesis of conjugate addition with dithianes.

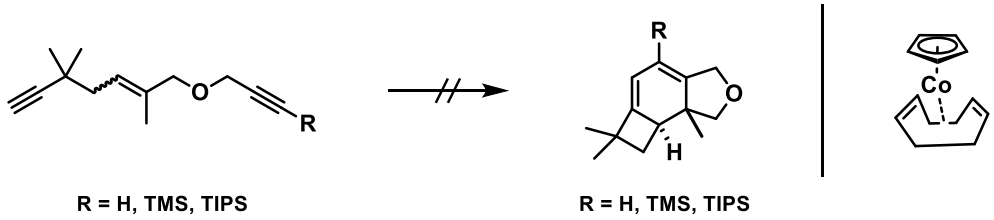
Therefore, a new strategy was pursued in which a [2+2+2]-cycloaddition plays a central role that allows to built up of the [4.6.5]-tricycle. Following this strategy, the first milestone was the synthesis of both fragments which were thought to be combined later through a Julia-Kocienski olefination.



Scheme 166: Achieved synthesis following the retrosynthetic approach using a [2+2+2]-cycloaddition as a key step.

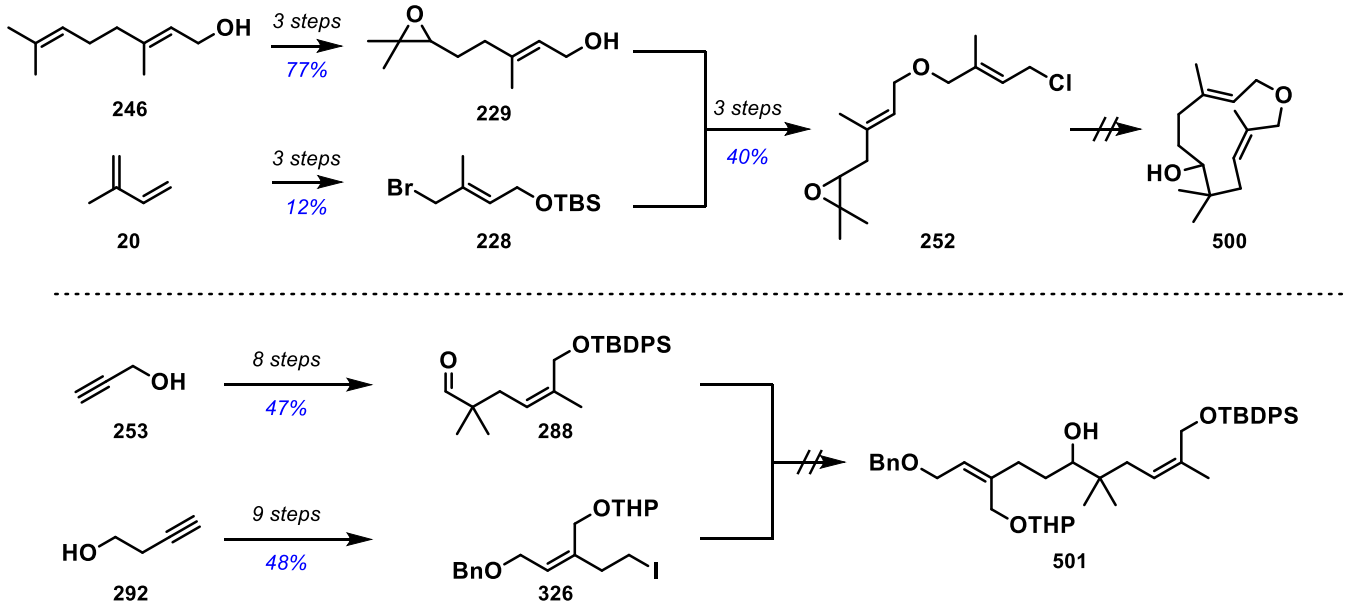
Different approaches towards both fragments were pursued, finally giving access to sulfone **164** by selective propargylation of propane diol (**179**) followed by functional group manipulations. In parallel aldehyde **165** was prepared starting from bromoethanol. Here, the breakthrough was to transform an aldehyde into the corresponding alkyne using the Colvin's modification of the Corey Fuchs reaction. **164** was synthesized in three steps with an overall yield of 59% on a gram scale and **165** in seven

steps in an overall yield of 23%. Both fragments were combined in the envisioned olefination. Barbier conditions were necessary to prevent decomposition of sulfone **164**. Here, a ~4:1 E/Z-mixture was obtained using unoptimized conditions. Before optimization was started, the key step was tested.



Scheme 167: Unsuccessfull [2+2+2]-cycloaddition and envisioned novel cobalt-catalyst.

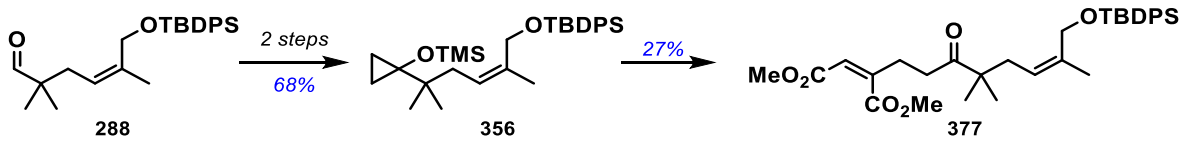
Unfortunately, [2+2+2]-cycloadditon was not successful although various conditions were tested only leading to recovered starting material. The gem-dimethyl group was spotted to be a problem, as it is located in the neighborhood of the terminal alkyne. Thus, similar systems were synthesized to explore the reactivity of this system either lacking methyl groups or silyl residues at the terminal alkynes. None of these approaches showed intentions to undergo a [2+2+2]-cycloaddition. This led to the idea that also the catalyst might not be reactive enough. This might be explored in the future, as the synthesis of a catalyst with different ligands was started but could not be finished in the framework of this thesis. If a cyclization is possible, the Julia-Kocienski might have to be optimized also.



Scheme 168: Achieved synthesis following both accesses towards the precursor for different cyclizations.

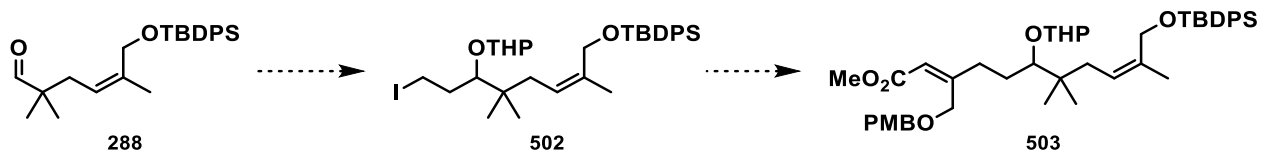
The next retrosynthetic approach was based by dividing it into two routes: The first one included the macrocyclization via opening of an epoxide with an internal nucleophile, the second one envisoned

the coupling of two fragments followed by macrocyclization employing an intramolecular Williamson ether synthesis. Therefore, at first simplified precursors were synthesized to explore which route is more promising. For pursuing the first idea, the necessary precursor **252** was synthesized in a few steps starting from isoprene and geraniol. However, epoxide opening turned out to be not successful. Thus, the second strategy was pursued. Here, various approaches towards both fragments were explored. The final routes include a (*Z*)-selective conjugate addition of a cupurate to an alkynoate which gave aldehyde **288** in eight steps with an overall yield of 47%. On the other hand, iodide **326** was synthesized in nine steps in an overall yield of 48%. Here, a sequence of a *trans*-hydroalumination using Red-Al followed by a Heck carbonylation was the solution to form the necessary triol moiety. As the coupling of both fragments was not successful, various related ideas were pursued, from which an approach *via* a conjugate addition of a β-Cu^{II}-ketone to an alkynoate crystallized as the main idea. Here, at first aldehyde **288** was easily transformed into cyclopropanol **356** applying a Kulinkovich reaction. On the other hand, various alkynoate or sulphonate systems were synthesized but only DMAD showed the desired reactivity, hence it still gave only low yields.



Scheme 169: Achieved synthesis using the β-Cu^{II} ketone procedure.

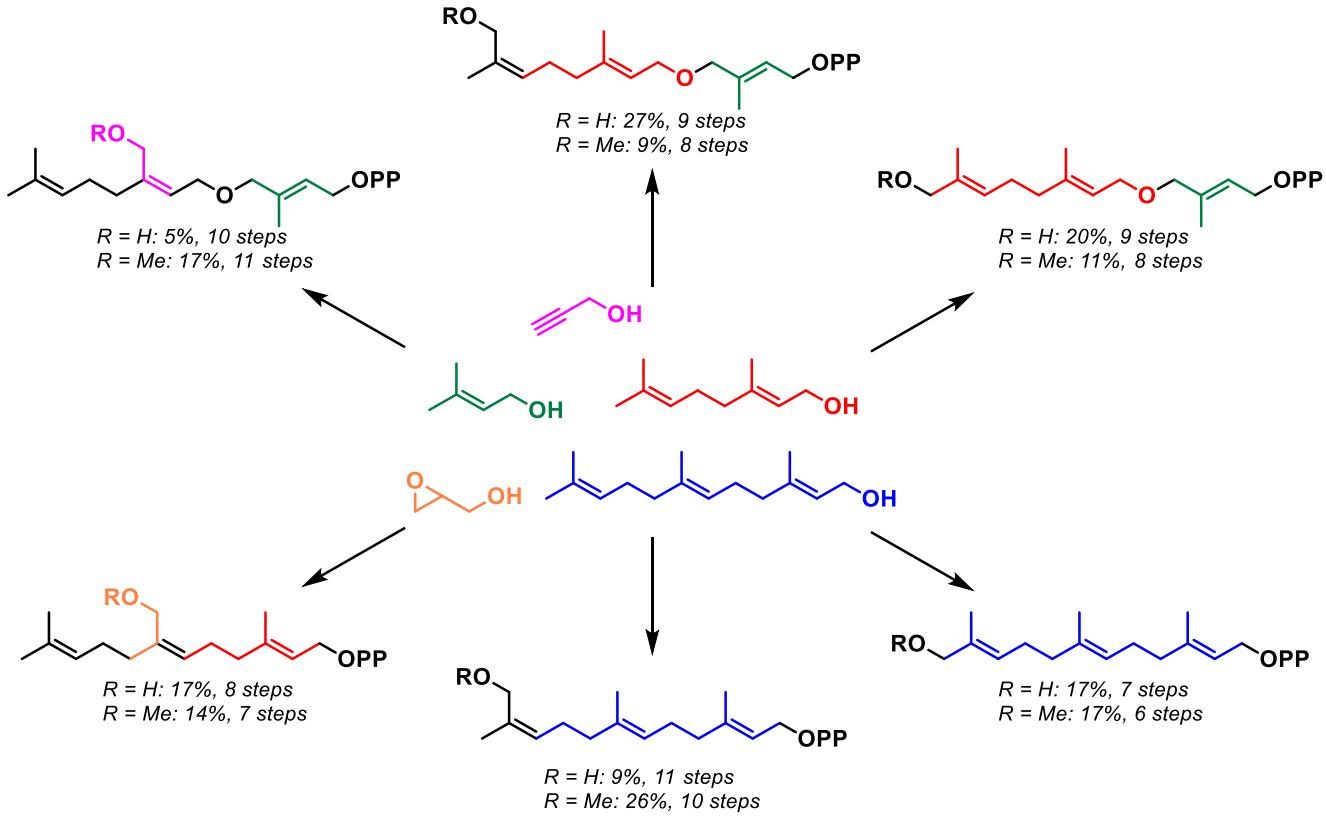
At this point, the total synthesis project was stopped, as this detour included many more steps which were necessary to finish the synthesis. Also, only low yields were achieved leading to a tedious endgame with presumable problems in gaining enough material. In the future, this reaction can be optimized allowing to explore the endgame of this synthesis with differentiation of both esters followed by the macrocyclization and the radical cascade sequence to form tricyclic terpenoid **1**. Another idea, would be to transform aldehyde **288** into iodide **502** which might be used for a conjugate addition chemistry similar as described in the synthesis of the aldehyde itself. This would prevent hampering differentiation chemistry of both esters, as noted in the previous idea.



Scheme 170: Envisioned alternative route to achieve the combination of both fragments.

7.2 Biotransformation Project

This topic is divided in three parts: Firstly, the necessary STCs were overexpressed and isolated by following standard procedures developed in our group. Secondly, the novel pyrophosphates had to be synthesized. Here, a wide range of chemistry centered around double and triple bonds was pursued, finally giving rise to all desired farnesol analogs. Mostly, the same starting building blocks were used as shown in scheme 171. For C-9 derivatives either an (*Z*)-selective conjugate addition or a Wittig reaction was performed. For C-6 derivatives the Still-Gennari Wittig reaction was used to achieve the desired stereochemistry of the terminal double bond. For C-1 derivatives an allylic oxidation was used to introduce the oxygen at the terminal position. Also, a new protocol was developed for the Williamson ether synthesis of the more hindered alcohols for the deriavtives with the oxygen inserted into the linear backbone. Thus all 12 desired pyrophosphates were synthesized in 6-11 steps with an overall yield of 5-27%.



Scheme 171: Achieved synthesis of farnesyl analogs with their basic building blocks marked in different colors, atoms and bonds in black derive from key step reactions or reagents introduced to building blocks.

With all pyrophosphates in hand, the third part of this subproject was initiated. At first, all derivatives were submitted to biotransformation protocols on an analytical scale to explore the spectrum of acceptance of the STCs for the new pyrophosphate deriavtives. GC-MS analysis of these reactions clearly showed a trend. Acceptance for those deriavtives that lack an ether group in the backbone

irrespertective of the residue on and the position of the oxygen at the terminal methyl groups was broader. Only one of the STCs selected showed a sudden acceptance of a single derivative. Also, it was found that within the group of “carbon-only“ backbone derivatives, those were accepted with the free hydroxygroup. These were transformed by more STCs and a greater turnover was detected. In total 52 novel sesquiterpenes were detected in amounts that they might be collected in amounts to isolate and structurally characterize them. Selected examples of deriavtives were used for the isolation and structure elucidation. The characterized products are shown in figure 172.

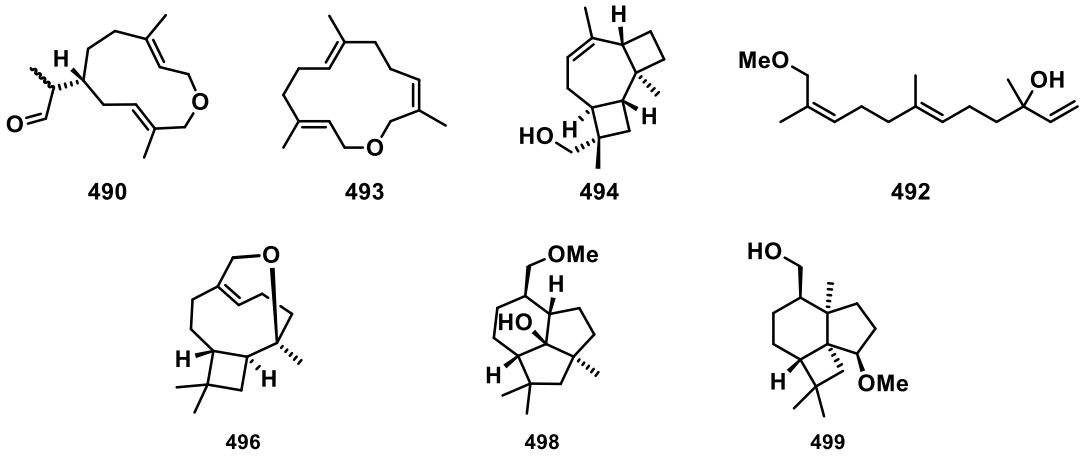


Figure 172: Isolated structures of novel terpenoids produced by different STCs: **490** by Tps32, **493** & **494** by GcoA, **492** by Tri5, **496**, **498** & **499** by Bot2; yields were not determined.

In the future, the structures of the remaining novel terpenoids will have to be elucidated. Also, an optimization of selected biotransformation experiments should be conducted to increase the yield of new terpenes that are formed in lower amount. Furthermore, also these derivatives can be submitted for transformations with an enzyme cocktail which includes terpene synthases that allows the elongation by addition of an extra IPP unit followed by cyclization of a diterpene cyclase. Since these substrates with heteroatoms were accepted, it is also interesting to oxidize the methyl group which is in very close proximity to the pyrophosphate or introduce other functional groups as -SH, -SMe or mixtures with oxygen-based moieties which were readily accepted by our STCs when sulfur was inserted into the linear backbone. Furthermore, also multioxidized derivatives can be of interest, as the insertion of any extra oxygen atoms changes the molecular properties, for example volatility and possible olfactometric properties. Possible synthetic targets are shown in figure 173.

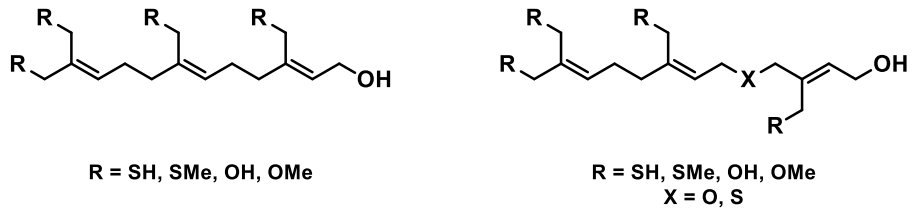


Figure 173: Envisioned structures for future farnesyl analogs.

Another very interesting approach is to include modeling of active sites of the eight STCs and thus rationally predict spaces within the active pocket which allow to add additional residues to the FPP-analogs. This procedure might increase the acceptance of substrates as fitting analogs can be synthesized for individual enzymes. Alternatively, enzymes could be modified by site-directed mutagenesis to allow more space within the active site to accept the previously synthesized unnatural FPP-analogs.

8 Experimental

8.1 General

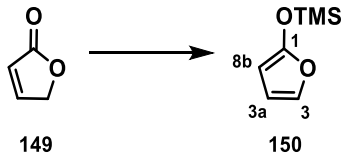
Unless stated otherwise, all reactions with an aqueous phase being absent were performed in flame-dried glassware under an atmosphere of argon. Dry DMF, Et_2O and CH_2Cl_2 were obtained by passing these solvents through activated columns on a solvent purification system. THF was distilled over sodium and benzophenone. NEt_3 and DIPA were distilled over KOH. Purchased reagents and chemicals were used as received, unless stated otherwise. Reactions were monitored by TLC on aluminum plates coated with silica gel, type 60 F254 by Merck and visualized by UV irradiation or development with a potassium permanganate, cerium, anisaldehyde or vanilline stain. Volatile solvents were removed under reduced pressure with a rotary evaporator. All column chromatography was performed using Machery-Nagel Silica 60 M (40 - 63 μm). ^{1}H NMR, ^{13}C NMR and ^{31}P-NMR spectra were recorded with Bruker AVS or DRX spectrometers operating at 400, 500 or 600 MHz for ^{1}H, 100, 125 or 150 MHz for ^{13}C, or 162 MHz for ^{31}P in various deuterized solvents. Chemical shifts are reported relative to the residual solvent signal (^{1}H-NMR: δ = 7.26 ppm ($CDCl_3$), 3.58 ppm (d_8-THF), 4.79 ppm (D_2O) 7.16 ppm (C_6D_6);^{13}C-NMR: δ = 77.2 ppm ($CDCl_3$), 128.06 (C_6D_6)). NMR data are reported as follows: chemical shift (multiplicity, coupling constants where applicable, number of hydrogens, assigned hydrogen). Splitting for ^{1}H-NMR is reported with the following symbols: bs = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, qi = quintet, se = sextet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, tt = triplet of triplets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, o = octet, m = multiplet. For ^{13}C-NMR the degree of substitution degree is reported as: p = primary C-atom, s = secondary C-atom, t = tertiary C-atom and q = quaternary C-atom. If necessary, COSY, HMBC, HSQC and NOE experiments were conducted for full characterization. High resolution mass spectra (HRMS) were obtained at 70 eV with a type VG Autospec spectrometer (Micromass), with a type LCT (ESI) (Micromass), with a type Q-TOF (Micromass) spectrometer in combination with a Waters Aquity Ultraperformance LC (UPLC) system, with a UPLC/Q-TOF-MS combination (Dionex Ultimate 3000/BrukerMaxis HD) or as a gas chromatography with a HP6890.

Ion exchange chromatography was performed using the Amberchrom® 50WX8 (H^+-form, 100-200 mesh) which can be reused up to ten times. 100 g of the material were taken up in water and washed with an excess of 6% aq. NH_3 (1/4 concentrated). The residue was then washed with an excess of water and transferred into a column where it was stored in an upright position. The column was stored in its H^+-form, therefore the material was washed with an excess of 3 M HCl until pH = 1 was reached. After that, it was washed with an excess of water until pH = 7 was reached. Prior to use, the column was washed with 6% aq. NH_3 (~50 mL) until the material changed its color from brown to light orange. Then the column was washed with an excess of water (~200 mL) until pH = 7 was reached.

Then it was equilibrated with IEB (aq. 25 mM NH_4HCO_3 with 2% *i*PrOH, ~100 mL). At this point, the reaction mixture was dissolved in IEB and loaded onto the column which was performed using gravity-powered flow. When the purification was finished the material was transformed back to its H^+-form by washing it with 3 M HCl (~50 mL) until pH = 1 was reached (the color changes from light orange back to brown). Then it was washed with an excess of water (~200 mL) until pH = 7 was reached. The eluent was concentrated *in vacuo* and the residue was lyophilized overnight. The residue was dissolved in 0.05 M NH_4HCO_3 (2 mL) and transferred into a 15 mL Falcon-tube. Then a 1:1 mixture of *i*PrOH/MeCN (9 mL) was added and the mixture was thoroughly mixed using a vortex. The suspension was centrifuged at 5000 g for 10 min and the supernatant was collected. The solid was redissolved in 0.05 M NH_4HCO_3 (2 mL) and a 1:1 mixture of *i*PrOH/MeCN (9 mL) was added and the mixture was thoroughly mixed using a vortex. The suspension was centrifuged at 5000 rpm for 10 min and the supernatant was collected. The comb. supernatants were concentrated *in vacuo* and lyophilized overnight to give the desired pyrophosphates.

8.2 First Synthetic Approach

(Furan-2-yloxy)trimethylsilane 150

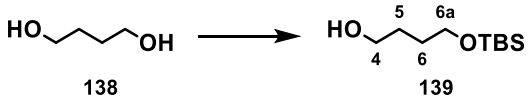


149 150

NEt_3 (6.0 mL, 42.82 mmol, 1.20 eq) and TMSOTf (6.8 mL, 37.46 mmol, 1.05 eq) were sequentially added dropwise to a stirred solution of enone **149** (2.5 mL, 35.68 mmol, 1.00 eq) in CH_2Cl_2 (25.5 mL) at 0 °C. The resulting mixture was allowed to warm to rt overnight and diluted with pentanes (20 mL). The layers were separated, the org. layer was washed with pH 7 buffer (50 mL), 0.5 M $CuSO_4$-solution (2x 50 mL), brine (2x 50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* at 200 mbar. High vacuum distillation yielded silanol **150** (bp.: 62 °C, 1 mbar, 3.30 g, 21.05 mmol, 59 %) as a colorless liquid which has to be stored at -20 °C. The analytical data match those reported in the literature.[178]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.82 (dd, *J* = 2.19, 1.10 Hz, 1H, H-3), 6.21 (dd, *J* = 3.12, 2.26 Hz, 1H, H-8b), 5.10 (dd, *J* = 3.16, 1.07 Hz, 1H, H-3a), 0.30 (s, 9H, TMS) ppm; **bp.:** 62 °C (1 mbar).

4-((*tert*-Butyldimethylsilyl)oxy)butan-1-ol 139

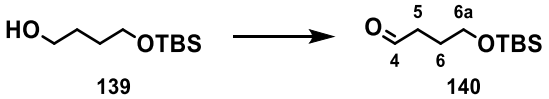


138 139

NaH (60 % on mineral oil, 310.7 mg, 7.77 mmol, 0.70 eq) was added in small portions to a stirred solution of 1,4-butanediol (**138**) (1.00 g, 11.10 mmol, 1.00 eq) in THF (1.2 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min, then TBSCl (1.17 g, 7.77 mmol, 0.70 eq) was added at 0 °C in small portions. The mixture was allowed to warm to rt and stirred at rt for 1 h. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (3.0 mL), the layers were separated, the aq. layers were extracted with EtOAc (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* Column chromatography (PE/EtOAc 3:1) yielded alcohol **139** (1.17 g, 5.70 mmol, 52 %) as a colorless oil. The analytical data match those reported in the literature.[179]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.67-3.62 (m, 4H, H-6a, H-4), 2.62 (bs, 1H, O*H*), 1.66-1.60 (m, 4H, H-5, H-6), 0.89 (s, 9H, TBS), 0.06 (s, 6H, TBS) ppm; $\mathbf{R_f}$ (5:1 PE/EtOAc): 0.24.

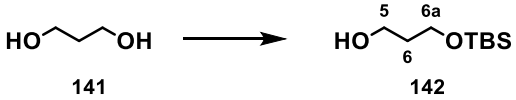
4-((*tert*-Butyldimethylsilyl)oxy)butanal 140



DMSO (110 µL, 1.47 mmol, 3.00 eq) was added dropwise to a stirred solution of oxalylchloride (70 µL, 0.73 mmol, 1.50 eq) in CH_2Cl_2 (1.3 mL) at -78 °C. The mixture was stirred at -78 °C for 10 min, then alcohol **139** (100.0 mg, 0.49 mmol, 1.00 eq) in CH_2Cl_2 (1.8 mL) was added dropwise at -78 °C. The mixture was stirred at -78 °C for 15 min, then NEt_3 (200 µL, 1.47 mmol, 3.00 eq) was added dropwise at -78 °C, then the mixture was allowed to warm to rt and stirred at rt for 30 min. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (5.0 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 10 mL), the comb. org. layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* at 30 °C and 200 mbar. Column chromatography (pentanes/Et_2O 10:1) yielded aldehyde **140** (99.0 mg, 0.49 mmol, *quant.*) as a colorless oil. The analytical data match those reported in the literature.[180]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.78 (t, *J* = 1.71 Hz, 1H, H-4), 3.64 (t, *J* = 6.00 Hz, 2H, H-6a), 2.50 (dt, *J* = 7.10, 1.69 Hz, 2H, H-5), 1.88-1.82 (m, 2H, H-6), 0.88 (s, 9H, TBS), 0.03 (s, 6H, TBS) ppm; $\mathbf{R_f}$ (10:1 pentanes/Et_2O): 0.57.

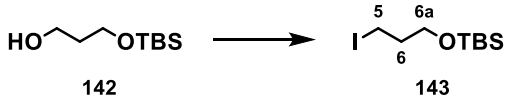
3-((*tert*-Butyldimethylsilyl)oxy)propan-1-ol 142



1,3-Propanediol (**141**) (470 µL, 6.57 mmol, 1.00 eq) in THF (3.3 mL) was added dropwise to a stirred solution of NaH (60 % on mineral oil, 262.8 mg, 6.57 mmol, 1.00 eq) in THF (6.6 mL) at 0 °C and the resulting mixture was allowed to warm to rt and stirred at rt for 45 min. TBSCl (990.3 mg, 6.57 mmol, 1.00 eq) in THF (3.3 mL) was added dropwise at rt and the mixture was stirred at rt for 1 h. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (20 mL), the layers were separated and the aq. layer was extracted with Et_2O (3x 30 mL), the comb. org. layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1) yielded alcohol **142**(1.05 g, 3.94 mmol, 60 %) as a colorless oil. The analytical data match those reported in the literature.[181]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.83 (t, *J* = 5.63 Hz, 2H, H-6a), 3.80 (t, *J* = 5.54 Hz, 2H, H-5), 2.61 (bs, 1H, O*H*), 1.77 (q, *J* = 5.59 Hz, 2H, H-6), 0.90 (s, 9H, TBS), 0.07 (s, 6H, TBS) ppm; $\mathbf{R_f}$ (5:1 PE/EtOAc): 0.30.

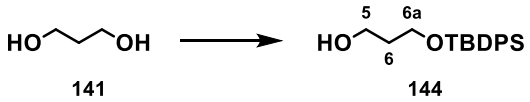
tert-Butyl(3-iodopropoxy)dimethylsilane 143



Imidazole (375.5 mg, 5.52 mmol, 1.50 eq) and iodine (1.27 g, 5.00 mmol, 1.36 eq) were sequently added in one portion to a stirred solution of PPh_3 (1.16 g, 4.41 mmol, 1.20 eq) in CH_2Cl_2 (11.0 mL) at rt. Then alcohol **142** (700.0 mg, 3.68 mmol, 1.00 eq) in CH_2Cl_2 (4.6 mL) was slowly added and the resulting mixture was stirred at rt for 4 h under exclusion of light. The reaction was terminated by addition of a 10% aq. $Na_2S_2O_3$-solution (20 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* at 30 °C and 200 mbar. Column chromatography (100% pentanes) yielded iodide **143** (760.6 mg, 3.68 mmol, *quant.*) as a colorless oil. The analytical data match those reported in the literature.[181]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.67 (t, J = 5.70 Hz, 2H, H-6a), 3.28 (t, J = 6.70 Hz, H-5), 2.02-1.96 (m, 2H, H-6), 0.90 (s, 9H, TBS), 0.07 (s, 6H, TBS) ppm; $\mathbf{R_f}$ (pentanes): 0.31.

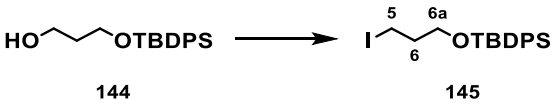
3-((*tert*-Butyldiphenylsilyl)oxy)propan-1-ol 144



*n*BuLi (1.6 M in hexanes, 8.2 mL, 13.14 mmol, 1.00 eq) and TBDPSCl (3.4 mL, 13.14 mmol, 1.00 eq) were sequently added dropwise to a stirred solution of 1,3-propanediol (**141**) in THF (21.9 mL) at -78 °C. The mixture was stirred at -78 °C for 15 min, then it was allowed to warm to rt, stirred at rt for 30 min and then heated under refluxing conditions for 3 h. After completion of the reaction, the mixture was concentrated *in vacuo* and dry loaded on silica. Column chromatography (PE/Et_2O 1:1) yielded alcohol **144** (4.37 g, 13.14 mmol, *quant.*) as a yellow oil. The analytical data match those reported in the literature.[182]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.71-7.68 (m, 4H, TBDPS), 7.47-7.38 (m, 6H, TBDPS), 3.86 (t, J = 5.58 Hz, 4H, H-6a, H-5), 2.42 (t, J = 5.16 Hz, 1H, O*H*), 1.82 (s, 9H, TBDPS) ppm; $\mathbf{R_f}$ (1:1 PE/Et_2O): 0.50.

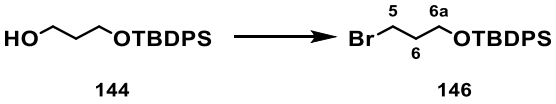
tert-Butyl(3-iodopropoxy)diphenylsilane 145



Imidazole (324.7 mg, 4.77 mmol, 1.50 eq) and iodine (1.10 g, 4.32 mmol, 1.36 eq) were sequentially added in one portion to a stirred solution of PPh_3 (1.00 g, 3.82 mmol, 1.20 eq) in CH_2Cl_2 (9.5 mL) at rt. Then alcohol **144** (1.00 g, 3.18 mmol, 1.00 eq) in CH_2Cl_2 (4.0 mL) was slowly added and the resulting mixture was stirred at rt for 4 h under exclusion of light. The reaction was terminated by addition of a 10% aq. $Na_2S_2O_3$-solution (20 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (100% pentanes) yielded iodide **145** (1.35 g, 3.18 mmol, *quant.*) as a colorless oil. The analytical data match those reported in the literature.[183]

^{1}H-NMR (400 MHz, $CDCl_3$): δ =7.68-7.66 (m, 4H, TBDPS), 7.44-7.37 (m, 6H, TBDPS), 3.71 (t, J = 5.66 Hz, 2H, H-6a), 3.35 (t, J = 6.80 Hz, 2H, H-5), 2.03 (qi, J = 6.27 Hz, 2H, H-6), 1.05 (s, 9H, TBDPS) ppm; $\mathbf{R_f}$ (PE): 0.41.

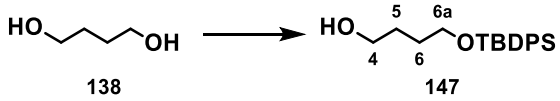
(3-Bromopropoxy)(*tert*-butyl)diphenylsilane 146



Imidazole (129.9 mg, 1.91 mmol, 1.50 eq) and bromine (90 µL, 1.73 mmol, 1.36 eq) were sequently added to a stirred solution of PPh_3 (400.3 mg, 1.53 mmol, 1.20 eq) in CH_2Cl_2 (3.8 mL) at rt. Then alcohol **144** (400.0 mg, 1.28 mmol, 1.00 eq) in CH_2Cl_2 (1.6 mL) was slowly added and the resulting mixture was stirred at rt for 4 h under exclusion of light. The reaction was terminated by addition of a 10% aq. $Na_2S_2O_3$-solution (20 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (100% pentanes) yielded bromide **146** (350.5 mg, 0.93 mmol, 73 %) as a colorless oil. The analytical data match those reported in the literature.[184]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.68-7.66 (m, 4H, TBDPS), 7.44-7.37 (m, 6H, TBDPS), 3.78 (t, J = 5.68 Hz, 2H, H-6a), 3.59 (t, J = 6.63 Hz, H-5), 2.08 (qi, J = 6.08 Hz, 2H, H-6), 1.06 (s, 9H, TBDPS) ppm; $\mathbf{R_f}$ (PE): 0.25.

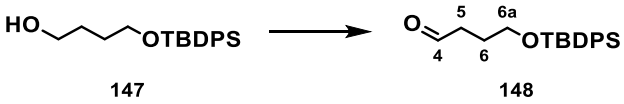
4-((*tert*-Butyldiphenylsilyl)oxy)butan-1-ol 147



*n*BuLi (1.6 M in hexanes, 6.9 mL, 11.10 mmol, 1.00 eq) and TBDPSCl (2.9 mL, 11.10 mmol, 1.00 eq) were sequently added dropwise to a stirred solution of 1,4-butanediol (**138**) in THF (15.9 mL) at -78 °C. The mixture was allowed to warm to rt and relfuxed for 4 h. After completion of the reaction, the mixture was concentrated *in vacuo* and dry loaded on silica. Column chromatography (PE/Et_2O 1:1) yielded alcohol **147** (3.26 g, 9.92 mmol, 89 %) as a slightly yellow oil. The analytical data match those reported in the literature.[185]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.69 (m, 4H, TBDPS), 7.43-7.37 (m, 6H, TBDPS), 3.72-3.65 (m, 4H, H-4, H-6a), 1.71-1.63 (m, 4H, H-5, H-6), 1.06 (s, 9H, TBDPS) ppm; **R_f** (1:1 PE/Et_2O): 0.50.

4-((*tert*-Butyldiphenylsilyl)oxy)butanal 148

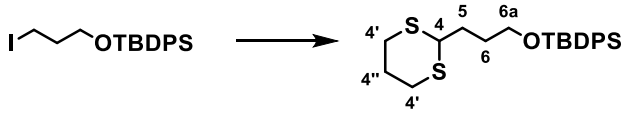


DMSO (650 µL, 9.13 mmol, 3.00 eq) was added dropwise to a stirred solution of oxalylchloride (400 µL, 4.57 mmol, 1.50 eq) in CH_2Cl_2 (7.6 mL) at -78 °C. The mixture was stirred at -78 °C for 10 min, then alcohol **147** (1.00 g, 3.04 mmol, 1.00 eq) in CH_2Cl_2 (11.4 mL) was added dropwise at -78 °C. The mixture was stirred at -78 °C for 15 min, then NEt_3 (1.3 mL, 9.13 mmol, 3.00 eq) was added dropwise at -78 °C, then the mixture was allowed to warm to rt and stirred at rt for 30 min. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (20 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 20 mL), the comb. org. layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 50:1) yielded aldehyde **148** (892.8 mg, 2.74 mmol, 90 %) as a colorless oil. The analytical data match those reported in the literature.[186]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.80 (t, J = 1.66 Hz, 1H, H-4), 7.66-7.64 (m, 4H, TBDPS), 7.43-7.37 (m, 6H, TBDPS), 3.69 (t, J = 5.99 Hz, 2H, H-6a), 2.55 (dt, J = 10.85, 1.51 Hz, 2H, H-5), 1.89 (qi, J = 6.57 Hz, 2H, H-6), 1.05 (s, 9H, TBDPS) ppm.

R_f (50:1 PE/EtOAc): 0.41.

(3-(1,3-Dithian-2-yl)propoxy)(*tert*-butyl)diphenylsilane A'

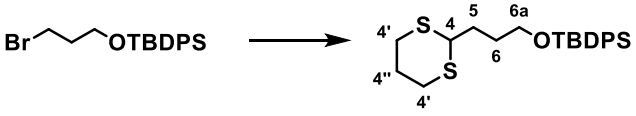


145 **A'**

*n*BuLi (2.5 M in hex, 2.4 mL, 5.89 mmol, 5.00 eq) was added dropwise to a stirred solution of 1,3-dithiane (0.71 g, 5.89 mmol, 5.00 eq) in Et_2O (19.6 mL) and HMPA (4.1 mL) at -30 °C. The mixture was stirred at -20 °C for 1.5 h, then iodide **145** (0.50 g, 1.18 mmol, 1.00 eq) in Et_2O (11.2 mL) was added dropwise at -20 °C. The mixture was allowed to warm to rt and stirred for 0.5 h at rt. The reaction was terminated by diluting with Et_2O (20 mL) and subsequent addition of a sat. aq. NH_4Cl-solution (30 mL). The layers were separated, the aq. layer was extracted with Et_2O (3x 30 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 100:0 – 100:1 – 50:1) yielded dithiane **A'** (491.2 mg, 1.18 mmol, *quant.*) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.68-7.66 (m, 4H, TBDPS), 7.45-7.36 (m, 6H, TBDPS), 4.03 (t, *J* = 6.84 Hz, 1H, H-4), 3.68 (t, *J* = 5.98 Hz, 2H, H-6a), 2.85-2.82 (m, 4H, H-4'), 1.91-1.74 (m, 6H, H-4'', H-5, H-6), 1.06 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 135.7 (t, TBDPS), 134.0 (q, TBDPS), 129.7 (t, TBDPS), 127.8 (t, TBDPS), 63.3 (s, C-6a), 47.5 (t, C-4), 32.1 (s, C-5), 30.5 (s, C-4'), 29.6 (C-4''), 27.0 (p, TBDPS), 26.1 (s, C-6), 19.3 (q, TBDPS) ppm; **HRMS (EI-GCT):** *m/z calc.* for $C_{19}H_{23}S_2OSi$ $[M\text{-}t\text{Bu}]^+$: 359.0960; *found*: 359.0960; $\mathbf{R_f}$ (50:1 PE/EtOAc): 0.30.

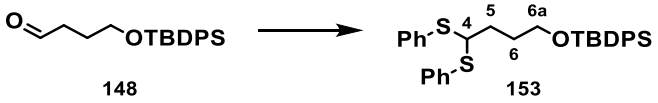
(3-(1,3-Dithian-2-yl)propoxy)(*tert*-butyl)diphenylsilane A'



146 **A'**

*n*BuLi (2.5 M in hex, 2.6 mL, 6.62 mmol, 5.00 eq) was added dropwise to a stirred solution of 1,3-dithiane (0.80 g, 6.62 mmol, 5.00 eq) in Et_2O (22.1 mL) and HMPA (4.6 mL) at -30 °C. The mixture was stirred at -20 °C for 1.5 h, then bromide **146** (0.50 g, 1.32 mmol, 1.00 eq) in Et_2O (13.2 mL) was added dropwise at -20 °C. The mixture was allowed to warm to rt and stirred for 0.5 h at rt. The reaction was terminated by diluting with Et_2O (20 mL) and subsequent addition of a sat. aq. NH_4Cl-solution (30 mL). The layers were separated, the aq. layer was extracted with Et_2O (3x 30 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 100:0 – 100:1 – 50:1) yielded dithiane **A'** (551.8 mg, 1.32 mmol, *quant.*) as a yellow oil. The analytical data match those reported above.

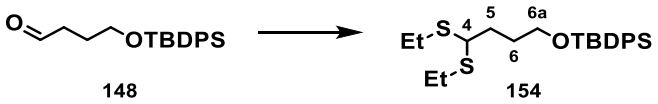
(4,4-Bis(phenylthio)butoxy)(*tert*-butyl)diphenylsilane 153



$BF_3 \cdot OEt_2$ (50 µL, 0.37 mmol, 2.40 eq) was added dropwise to a solution of aldehyde **148** (50.0 mg, 0.15 mmol, 1.00 eq) and thiophenol (40 µL, 0.34 mmol, 2.20 eq) in chloroform (190 µL) at 0 °C. The mixture was stirred at 0 °C for 1 h. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (10 mL), the layers were separated, the aq. layer was extracted with PE (3x 10 mL), the comb. org. layers were washed with an aq. 5% NaOH-solution (30 mL) and water (30 mL), dried over $MgSO_4$, filtered and *in vacuo* concentrated. Column chromatography (100:1 – 50:1 – 20:1) yielded thioacetal **153** (73.0 mg, 0.14 mmol, 90 %) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.72-7.70 (m, 4H, TBDPS), 7.45-7.38 (m, 6H, TBDPS), 7.30-7.26 (m, 10H, SPh), 4.38 (t, *J* = 6.14 Hz, 1H, H-4), 2.89 (t, *J* = 6.62 Hz, 2H, H-6a), 1.97-1.96 (m, 4H, H-5, H-6), 1.10 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 137.1 (SPh or TBDPS), 134.6 (SPh or TBDPS), 134.6 (SPh or TBDPS), 133.0 (SPh or TBDPS), 130.4 (SPh or TBDPS), 130.4 (SPh or TBDPS), 129.5 (SPh or TBDPS), 129.1 (SPh or TBDPS), 129.0 (SPh or TBDPS), 1280. (SPh or TBDPS), 128.0 (SPh or TBDPS), 126.2 (SPh or TBDPS), 58.1 (t, C-4), 34.8 (s, C-5), 33.4 (s, C-6a), 26.6 (s, C-6), 26.1 (p, TBDPS), 19.3 (q, TBDPS) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{32}H_{36}S_2OSiNa$ $[M+Na]^+$: 551.1875; *found*: 551.1881; $\mathbf{R}_f$ (20:1 PE/EtOAc): 0.56.

(4,4-Bis(ethylthio)butoxy)(*tert*-butyl)diphenylsilane 154

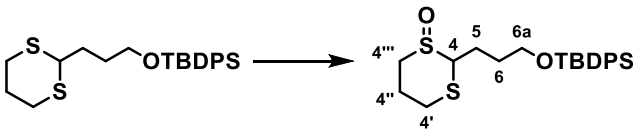


$AlCl_3$ (6.9 mg, 0.05 mmol, 0.34 eq) was added in small portions to a solution of aldehyde **148** (50.0 mg, 0.15 mmol, 1.00 eq) and ethanethiol (30 µL, 0.38 mmol, 2.50 eq) in DCE (260 µL) at rt. The mixture was stirred at rt for 15 min. The reaction was terminated by addition of water (10 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 10 mL), the comb. org. layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography yielded thioacetal **154** (67.0 mg, 0.15 mmol, *quant.*) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.67-7.65 (m, 4H, TBDPS), 7.42-7.36 (m, 6H, TBDPS), 3.79 (t, *J* = 6.94 Hz, 1H, H-4), 3.68 (t, *J* = 6.00 Hz, 2H, H-6a), 2.71-2.53 (m, 4H, SEt), 1.94-1.89 (m, 2H, H-6), 1.83-1.76 (m, 2H, H-5), 1.24 (t, *J* = 7.44 Hz, 6H, SEt), 1.05 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 135.7 (t, TBDPS), 134.0 (q, TBDPS), 129.7 (t, TBDPS), 127.8 (t, TBDPS), 63.4 (s, C-6a), 51.3 (t, C-4), 32.5 (s, C-6), 30.5 (s, C-5), 27.0 (p, TBDPS), 24.2 (s, Et), 19.4 (q,

TBDPS), 14.7 (p, Et) ppm; **HRMS (EI-GCT):** *m/z calc.* for $C_{20}H_{27}S_2OSi$ $[M\text{-}t\text{Bu}]^+$: 375.1273; *found*: 375.1265; $\mathbf{R}_f$ (20:1 PE/EtOAc): 0.59.

2-(3-((*tert*-Butyldiphenylsilyl)oxy)propyl)-1,3-dithiane 1-oxide 155

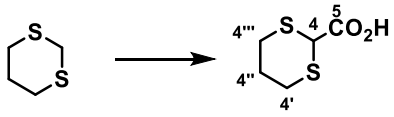


A' 155

$NaIO_4$ (477.7 mg, 2.23 mmol, 1.10 eq) in water (5.0 mL) was added dropwise to a stirred solution of dithiane **A'** (846.2 mg, 2.03 mmol, 1.00 eq) in MeOH (29.0 mL) at 0 °C. The mixture was stirred at 0 °C for 16 h, then was allowed to warm to rt. The white participate was filtered off, washed with an excess of CH_2Cl_2. The filtrate was concentrated *in vacuo*, the remaining oil was portioned between water (10 mL) and CH_2Cl_2 (10 mL), the aq. layer was extracted with CH_2Cl_2 (2x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 0:1) yielded sulfoxide **155** (383.9 mg, 0.89 mmol, 44%) as a yellow oil.[1]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.67-7.65 (m, 4H, TBDPS), 7.44-7.36 (m, 6H, TBDPS), 3.70 (t, *J* = 5.98 Hz, 2H, H-6a), 3.62 (dd, *J* = 9.00, 3.68 Hz, 1H, H-4), 3.43-3.40 (m, 1H), 2.69-2.55 (m, 3H), 2.47-2.40 (m, 2H), 2.32-2.25 (m, 1H), 1.95-1.81 (m, 2H), 1.76-1.66 (m, 1H), 1.05 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 135.6 (t, TBDPS), 133.7 (q, TBDPS), 129.6 (t, TBDPS), 127.7 (t, TBDPS), 65.9 (t, C-4), 63.2 (s, C-6a), 53.8, 30.0, 29.4, 28.8, 26.9 (p, TBDPS), 25.6, 19.2 (q, TBDPS) ppm; **HRMS (EI-LCT):** *m/z calc.* for $C_{19}H_{23}S_2O_2Si$ $[M\text{-}t\text{Bu}]^+$: 375.0909; *found*: 375.0909; $\mathbf{R}_f$ (0:1 PE/EtOAc): 0.24.

1,3-Dithiane-2-carboxylic acid 156



504 156

*n*BuLi (1.6 M in hex, 5.5 mL, 8.73 mmol, 1.05 eq) was added dropwise to a stirred solution of 1,3-dithiane (**504**) (1.00 g, 8.32 mmol, 1.00 eq) in THF (41.6 mL) at -20 °C. The mixture was stirred at -20 °C for 1.5 h, then small pieces of solid CO_2 (1.83 g, 41.58 mmol, 5.00 eq) were added at once at -20 °C. The mixture was stirred at -20 °C for one hour, then it was allowed to warm to rt and stirred at rt for 2 h. The reaction was terminated by addition of 2 M HCl (20 mL), the biphasic mixture was concentrated *in vacuo* until the aq. layer was left which was acidified to pH = 3 with 1 M HCl, then

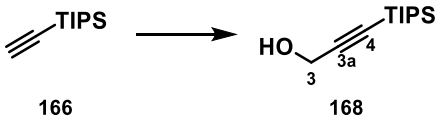
[1] A precise assignment of all protons and carbons was not possible due to strong overlap in the 2D-spectra as the product is a mix of diastereoisomers which could not be separated.

extracted with EtOAc (3x 40 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. Column chromato-graphy (PE/EtOAc 4:1) yielded acid **156** (800.3 mg, 4.87 mmol, 59%) as a white solid. The analytical data match those reported in the literature.[187]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.81 (bs, 1H, CO_2H), 4.16 (s, 1H, H-4), 3.45-3.38 (m, 2H, H-4' or H-4'''), 2.60 (dq, J = 14.0 Hz, 2.7 Hz, 2H, H-4''), 2.18-2.15 (m, 1H, H-4' or H-4'''), 2.09-1.98 (m, 1H, H-4' or H-4''') ppm; **R_f** (2:1 PE/EtOAc): 0.25; **mp.:** 113 °C.

8.3 Second Synthetic Approach

3-(Tri*iso*propylsilyl)prop-2-yn-1-ol 168

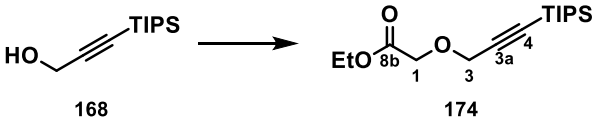


166 168

*t*BuLi (1.9 M in pentanes, 3.6 mL, 6.84 mmol, 1.24 eq) was added dropwise to a stirred solution of alkyne **166** (1.2 mL, 5.51 mmol, 1.00 eq) in THF (11.5 mL) at -40 °C, the resulting mixture was stirred at -40 °C for 30 min, then paraformaldehyde (248.3 mg, 8.27 mmol, 1.50 eq) was added in one portion and the mixture was stirred at -40 °C for further 20 min. The reaction was terminated by pouring it into an aq. sat. NH_4Cl-solution (15 mL) and stirred for 15 min. The layers were separated, the aq. layer was extracted with Et_2O (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. High vacuum distillation (1 mbar, 100 °C) yielded alcohol **168** (920.0 mg, 4.33 mmol, 77%) as a colorless oil. The analytical data match those reported in the literature.[188]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.30 (d, J = 6.24 HZ, 2H, H-3), 1.59 (m, 1H, OH), 1.07 (s, 21H, TIPS) ppm; **R_f** (10:1 PE/EtOAc): 0.36; **bp.:** 100 °C, 1 mbar.

Ethyl 2-((3-(tri*iso*propylsilyl)prop-2-yn-1-yl)oxy)acetate 174



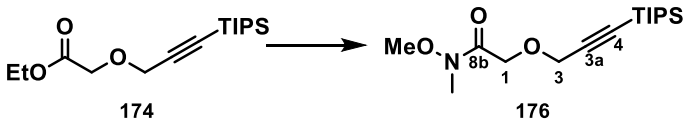
168 174

Alcohol **168** (934.9 mg, 4.40 mmol, 1.05 eq) was added dropwise to a stirred solution of NaH (60% on mineral oil, 201.2 mg, 5.03 mmol, 1.20 eq) in THF (5.6 mL) at 0 °C. The mixture was allowed to warm to rt and stirred at rt for 1 h, then α-bromo ethylacetate (470.0 µL, 4.19 mmol, 1.00 eq) was added dropwise at rt and the resulting mixture was stirred at rt for 3 h. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (5 mL), the aq. layer was extracted with EtOAc (3x 10 mL), the comb. org. layer were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated

in vacuo. Column chromatography (PE/EtOAc 50:1 – 20:1) yielded ester **174** (626.0 mg, 2.10 mmol, 50%, 62% brsm) as a colorless oil. The analytical data match those reported in the literature.[189]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.36 (s, 2H, H-1), 4.23 (m, 4H, H-3, Et), 1.29 (t, J = 7.14 Hz, 3H, Et), 1.07 (s, 21H, TIPS) ppm; **R_f** (10:1 PE/EtOAc): 0.60.

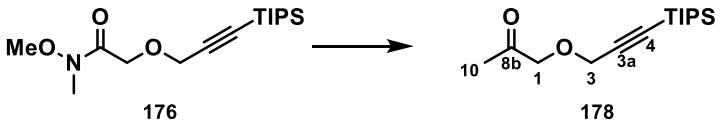
N-Methoxy-*N*-methyl-2-((3-(tri*iso*propylsilyl)prop-2-yn-1-yl)oxy)acetamide 176



*i*PrMgCl (2.0 M in THF, 2.3 mL, 4.52 mmol, 4.50 eq) was added dropwise to a stirred solution of ester **174** (300.00 mg, 1.01 mmol, 1.00 eq) and Weinreb amine-HCl salt (147.1 mg, 1.51 mmol, 1.50 eq) in THF (2.9 mL) at -20 °C. The resulting mixture was allowed to warm to rt overnight. The reaction as terminated by addition of a sat. aq. NH_4Cl-solution (5 mL), the layers were separated, the aq. layer was extracted with EtOAc (3x 10 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1 – 3:1) yielded amine **176** (51.0 mg, 0.16 mmol, 16%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.43 (s, 2H, H-1), 4.38 (s, 2H, H-3), 3.68 (s, 3H, OMe), 3.19 (s, 3H, NMe), 1.07 (s, 21H, TIPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 172.6 (q, C-8b), 102.5 (q, C-4), 88.8 (q, C-3a), 65.8 (s, C-1), 61.5 (p, OMe), 59.1 (s, C-3), 32.4 (p, NMe), 18.7 (p, TIPS), 11.5 (t, TIPS) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{16}H_{31}NO_3SiNa$ $[M+Na]^+$: 336.1971; *found*: 336.1972; **R_f** (3:1 PE/EtOAc): 0.26.

1-((3-(Tri*iso*propylsilyl)prop-2-yn-1-yl)oxy)propan-2-one 178

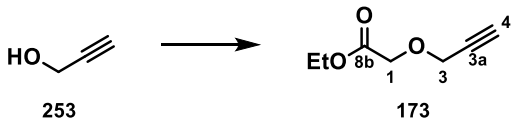


MeMgBr (3.0 M in Et_2O, 90.0 µL, 0.27 mmol, 1.50 eq) was added dropwise to a stirred solution of Weinreb amide **176** (56.0 mg, 0.18 mmol, 1.00 eq) in THF (410.0 µL) at 0 °C, then the mixture was stirred at 0 °C for 1 h. The reaction was terminated by addition of 2 M aq. HCl (1 mL), the layers were separated, the aq. layer was extracted with Et_2O (3x 2 mL), the comb. org. layers were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (pentanes/Et_2O 2:1) yielded ketone **178** (40.0 mg, 0.15 mmol, 83%) as a brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.30 (s, 2H, H-1), 4.17 (s, 2H, H-3), 2.17 (s, 3H, H-10), 1.06 (s, 21H, TIPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 206.5 (q, C-8b), 102.0 (q, C-4), 89.3 (q, C-3a),

74.3 (s, C-1), 59.3 (s, C-3), 26.6 (p, C-10), 18.7 (p, TIPS), 11.7 (t, TIPS) ppm; **HRMS (EI-GCT):** *m/z calc.* for $C_{12}H_{21}O_2Si$ [M-*i*Pr]$^+$: 225.1311; *found*: 225.1312; $\mathbf{R_f}$ (10:1 PE/EtOAc): 0.50.

Ethyl 2-(prop-2-yn-1-yloxy)acetate 173

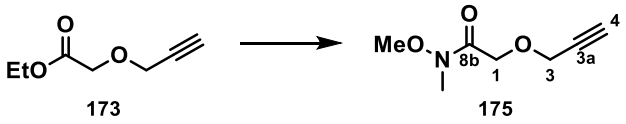


253 173

Propargyl alcohol was freshly distilled over CaH_2 under high vacuum and stored for weeks under Argon at -20 °C. Alcohol **253** (3.2 mL, 53.51 mmol, 1.00 eq) was added dropwise to a stirred solution of NaH (60% on mineral oil, 2.57 g, 64.22 mmol, 1.20 eq) in THF (31.5 mL) at 0 °C. The mixture was allowed to warm to rt and stirred at rt for 1 h. Then α-bromo ethylacetate (7.1 mL, 64.22 mmol, 1.20 eq) was added dropwise at rt and the resulting mixture was stirred at rt for 3 h. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (40 mL), the aq. layer was extracted with EtOAc (3x 50 mL), the comb. org. layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. High vacuum distillation (1 mbar, bp.: 53 °C) yielded ester **173** (5.41 g, 38.04 mmol, 71%) as a colorless oil. The analytical data match those reported in the literature.[92]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.31 (d, *J* = 2.20 Hz, 2H, H-3), 4.23 (q, *J* = 7.20 Hz, 2H, Et), 4.19 (s, 2H, H-1), 2.47 (t, *J* = 2.26 Hz, 1H, H-4), 1.29 (t, *J* = 7.20 Hz, 3H, Et) ppm; $\mathbf{R_f}$ (10:1 PE/EtOAc): 0.36; **bp.:** 53 °C, 1 mbar.

***N*-Methoxy-*N*-methyl-2-(prop-2-yn-1-yl)oxy)acetamide 175**



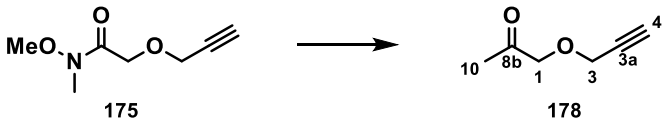
173 175

*i*PrMgCl (2.0 M in THF, 35.2 mL, 70.35 mmol, 4.50 eq) was added dropwise to a stirred solution of ester **173** (1.00 g, 7.03 mmol, 1.00 eq) and Weinreb amine-HCl salt (3.43 g, 35.17 mmol, 1.50 eq) in THF (20.1 mL) at -20 °C. The resulting mixture was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (20 mL), the layers were separated, the aq. layer was extracted with EtOAc (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 2:1 – 1:1) yielded amine **175** (568.6 mg, 3.62 mmol, 52%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.38 (s, 2H, H-1), 4.33 (d, *J* = 2.3 Hz, 2H, H-3), 3.69 (s, 3H, OMe), 3.18 (s, 3H, NMe), 2.45 (t, *J* = 2.76 Hz, 1H, H-4) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 170.5 (q, C-8b), 79.1 (q, C-3a), 75.4 (t, C-4), 66.1 (s, C-1), 61.6 (p, OMe), 58.3 (s, C-3), 32.4 (p, NMe) ppm;

HRMS (ESI-LCT): *m/z calc.* for $C_7H_{11}NO_3Na$ $[M+Na]^+$: 180.0637; *found*: 180.0632; $\mathbf{R_f}$ (3:1 PE/EtOAc): 0.12.

1-(Prop-2-yn-1-yl)oxy)propan-2-one 177

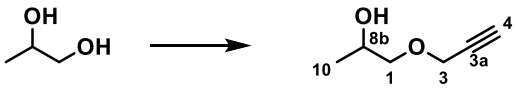


175 178

MeMgBr (3.0 M in Et_2O, 1.2 mL, 3.74 mmol, 1.50 eq) was added dropwise to a stirred solution of Weinreb amide **175** (392.1 mg, 2.49 mmol, 1.00 eq) in THF (5.7 mL) at 0 °C, then the mixture was stirred at 0 °C for 1 h. The reaction was terminated by addition of 2 M aq. HCl (6 mL), the layers were separated, the aq. layer was extracted with Et_2O (3x 10 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (pentanes/Et_2O 10:1) yielded ketone **178** (256.0 mg, 2.28 mmol, 92%) as a brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.26 (d, *J* = 2.28 Hz, 2H, H-3), 4.16 (s, 2H, H-1), 2.47 (t, *J* = 2.35 Hz, 1H, H-4), 2.17 (s, 3H, H-10) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 206.0 (q, C-8b), 78.7 (t, C-4), 75.7 (q, C-3a), 74.5 (s, C-1), 58.5 (s, C-3), 26.6 (p, C-10) ppm; **HRMS (EI-GCT):** *m/z calc.* for $C_6H_8O_2$ [M]: 112.0524; *found*: 112.0526; $\mathbf{R_f}$ (10:1 PE/EtOAc): 0.16.

1-(Prop-2-yn-1-yloxy)propan-2-ol 180

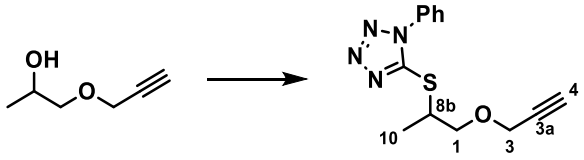


179 180

1,2-Propanediol (**179**) (13.5 mL, 184.92 mmol, 4.40 eq) in THF (110 mL) was added slowly to a stirred solution of NaH (60% on mineral oil, 1.85 g, 46.23 mmol, 1.10 eq) in THF (95 mL) at 0 °C. The mixture was stirred at rt for 2 h, then propargylbromide (80% in PhMe, 6.3 mL, 42.03 mmol, 1.00 eq) was added dropwise at 0 °C and the resulting brown mixture was heated under refluxing conditions for 3 h. The reaction was terminated by addition of water (100 mL) and concentrated *in vacuo* until the aq. layer was left. The aq. layer was extracted with EtOAc (4x 100 mL), the comb. org. layers were washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 3:1) yielded alcohol **180** (3.62 g, 31.72 mmol, 75%, 6:1 ratio of regioisomers for the desired isomer) as a yellow oil. The analytical data math those reported in the literature.[190]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.20 (d, *J* = 2.07 Hz, 2H, H-3), 4.00 (t, *J* = 7.56 Hz, 1H, H-8b), 3.55 (dd, *J* = 9.38, 2.98 Hz, 1H, H-1), 3.32 (dd, *J* = 9.18, 8.18 Hz, 1H, H-1), 2.45 (d, *J* = 2.38 Hz, 1H H-4), 2.30 (bs, 1H, O*H*), 1.16 (d, *J* = 6.36 Hz, 3H, H-10) ppm; $\mathbf{R_f}$ (3:1 PE/EtOAc): 0.29.

1-Phenyl-5-((1-(prop-2-yn-1-yloxy)propan-2-yl)thio)-1*H*-tetrazole 181

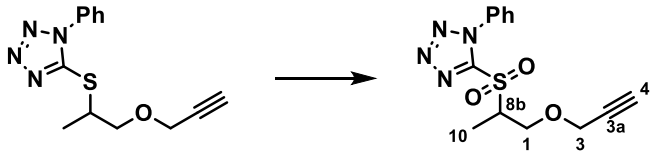


180 181

DIAD (7.8 mL, 39.98 mmol, 1.10 eq) was added dropwise to a stirred solution of alcohol **180** (4.15 g, 36.47 mmol, 1.00 eq), PPh_3 (10.49 g, 39.98 mmol, 1.10 eq) and HS-PT (7.13 g, 39.98 mmol, 1.10 eq) in THF (120 mL) at rt and the resulting mixture was stirred at rt overnight. The reaction mixture was dry loaded on silica and column chromatography (PE/EtOAc 20:1 – 10:1 – 5:1) yielded thioether **181** (9.48 g, 34.54 mmol, 95%) as a yellowish oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.59-7.53 (m, 5H, PT), 4.27 (dq, *J* = 6.38, 1.79 Hz, 1H, H-8b), 4.19 (d, *J* = 2.42 Hz, 2H, H-3), 3.81 (dd, *J* = 5.31, 1.07 Hz, 2H, H-1), 2.42 (d, *J* = 2.32 Hz, 1H, H-4), 1.55 (d, *J* = 7.02 Hz, 3H, H-10) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 153.9 (q, PT), 130.3 (t, PT), 130.0 (t, PT), 129.9 (t, PT), 124.2 (t, PT), 124.0 (q, PT), 79.3 (q, C-3a), 75.1 (t, C-4), 72.8 (s, C-1), 58.6 (s, C-3), 43.9 (t, C-8b), 18.4 (p, C-10) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{13}H_{14}N_4OSNa$ $[M+Na]^+$: 297.0786; *found*: 297.0785; $\mathbf{R}_f$ (2:1 PE/EtOAc): 0.63.

1-Phenyl-5-((1-(prop-2-yn-1-yloxy)propan-2-yl) sulfonyl)-1*H*-tetrazole 164

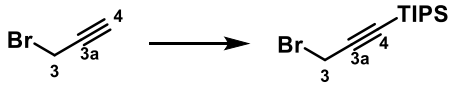


181 164

$(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (2.13 g, 1.72 mmol, 0.05 eq) in H_2O_2 (30% wt in H_2O, 43.0 mL, 414.49 mmol, 12.00 eq) was added slowly to a stirred solution of thioether **181** (9.48 g, 34.54 mmol, 1.00 eq) in wet EtOH (140 mL) at rt and the resulting mixture was stirred at rt overnight. The reaction mixture was diluted with CH_2Cl_2 (100 mL), the layers were separated and the aq. layer was extracted with CH_2Cl_2 (3x 100 mL), the comb. org. layers were washed with water (200 mL) and brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1 – 3:1) yielded sulfone **164** (8.78 g, 28.67 mmol, 83%) as a white amorphous solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.65-7.57 (m, 5H, PT), 4.03-3.99 (m, 3H H-3, H-8b), 3.91 (dd, *J* = 10.38, 6.98 Hz, 1H, H-1), 3.83 (dd, *J* = 10.04, 4.80 Hz, 1H, H-1), 2.45 (t, *J* = 2.32 Hz, 1H, H-4), 1.51 (d, *J* = 7.08 Hz, 3H, H-10) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 153.8 (q, PT), 131.6 (q, PT), 129.6 (t, PT); 126.0 (t, PT), 78.2 (q, C-3a), 75.9 (t, C-4), 68.2 (s, C-1), 61.3 (t, C-8b), 58.7 (s, C-3), 10.0 (p, C-10) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{13}H_{14}N_4O_3SNa$ $[M+Na]^+$: 329.0684; *found*: 329.0683;$\mathbf{R}_f$ (3:1 PE/EtOAc): 0.40; **mp.:** 108 °C.

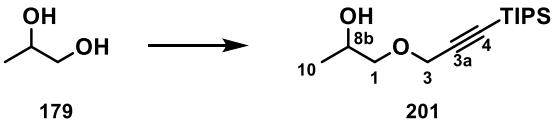
(3-Bromoprop-1-yn-1-yl)tri*iso*propylsilane 200



*n*BuLi (1.6 M in hex, 6.3 mL, 10.09 mmol, 1.20 eq) was added dropwise to a stirred solution of propargyl bromide (**199**) (80% wt in PhMe, 1.3 mL, 8.41 mmol, 1.00 eq) in THF (28.0 mL) at -78 °C, the mixture was stirred at -78 °C for 10 min, then TIPSCl (2.2 mL, 10.09 mmol, 1.20 eq) was added dropwise at -78 °C, the mixture was allowed to warm to rt and stirred for 2 h. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (20 mL), the layers were separated and the aq. layer was extracted with CH_2Cl_2 (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. High vacuum distillation (1 mbar, 91 °C) yielded bromide **200** (2.27 g, 8.23 mmol, 98%) as a colorless liquid. The analytical data match those reported in the literature.[191]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.94 (s, 2H, H-3), 1.07 (s, 21H, TIPS) ppm; **R_f** (10:1 PE/EtOAc): 0.90; **bp.:** 91 °C, 1 mbar.

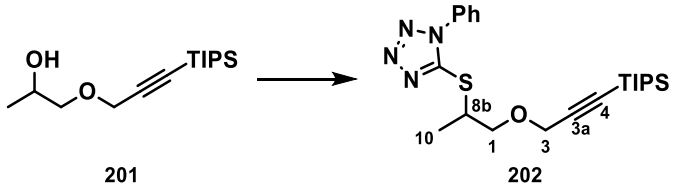
1-((3-(Tri*iso*propylsilyl)prop-2-yn-1-yl)oxy)propan-2-ol 201



1,2-Propanediol (**179**) (0.58 mL, 7.99 mmol, 4.40 eq) in THF (4.8 mL) was added slowly to a stirred solution of NaH (60% on mineral oil, 79.9 mg, 2.00 mmol, 1.10 eq) in THF (4.0 mL) at 0 °C. The mixture was stirred at rt for 2 h, then bromide **200** (0.50 g, 1.82 mmol, 1.00 eq) was added dropwise at 0 °C and the resulting brown mixture was heated under refluxing conditions for 3 h. The reaction was terminated by addition of water (10 mL) and concentrated *in vacuo* until the aq. layer was left. The aq. layer was extracted with EtOAc (4x 10 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 3:1) yielded alcohol **201** (439.1 mg, 1.62 mmol, 89%, 3:1 ratio of regioisomers for the desired isomer) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.23 (d, J = 3.32 Hz, 2H, H-3), 4.02-3.98 (m, H-8b), 3.57 (dd, J = 9.42, 3.01 Hz, 1H, H-1), 3.34 (dd, J = 9.54, 7.89 Hz, 1H, H-1), 2.28 (d, J = 3.06 Hz, 1H, OH), 1.16 (d, J = 6.43 Hz, 3H, H-10), 1.07 (s, 21H, TIPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 103.2 (q, C-4), 88.2 (q, C-3a), 75.3 (s, C-1), 66.5 (t, C-8b), 59.4 (s, C-3), 18.8 (p, C-10), 18.7 (p, TIPS), 11.3 (t, TIPS) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{15}H_{30}O_2SiNa$ $[M+Na]^+$: 293.1913; *found*: 293.1914; **R_f** (3:1 PE/EtOAc): 0.57.

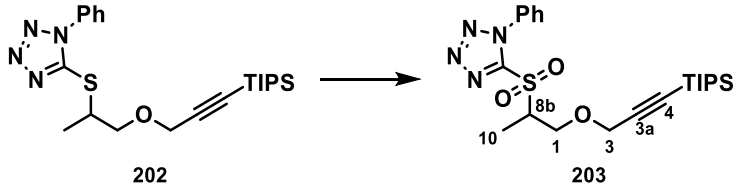
1-Phenyl-5-((1-((3-(tri*iso*propylsilyl)prop-2-yn-1-yl)oxy)propan-2-yl)thio)-1*H*-tetrazole 202



DIAD (350.0 µL, 1.79 mmol, 1.10 eq) was added dropwise to a stirred solution of alcohol **201** (439.0 mg, 1.62 mmol, 1.00 eq), PPh_3 (468.2 mg, 1.798 mmol, 1.10 eq) and HS-PT (318.2 mg, 1.79 mmol, 1.10 eq) in THF (17.0 mL) at rt and the resulting mixture was stirred overnight. The reaction mixture was dry loaded on silica and column chromatography (PE/EtOAc 50:1 - 20:1) yielded thioether **202** (398.1 mg, 0.92 mmol, 57%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.57-7.51 (m, 5H, PT), 4.33-4.27 (m, 1H, H-8b), 4.22 (s, 2H, H-3), 3.81 (dq, *J* = 14.40, 4.89 Hz, 2H, H-1), 1.54 (d, *J* = 7.01 Hz, 3H, H-10), 1.04-1.03 (m, 21H, TIPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 154.0 (q, PT), 133.8 (q, PT), 130.2 (t, PT), 129.8 (t, PT), 124.1 (t, PT), 102.7 (q, C-4) 88.5 (q, C-3a), 72.3 (s, C-1), 59.3 (s, C-3), 44.1 (t, C-8b), 18.6 (p, TIPS), 17.8 (p, C-10), 11.2 (t, TIPS) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{22}H_{34}N_4OSiSNa$ $[M+Na]^+$: 453.2120; *found*: 453.2117; $\mathbf{R}_f$ (2:1 PE/EtOAc): 0.81.

1-Phenyl-5-((1-((3-(tri*iso*propylsilyl)prop-2-yn-1-yl)oxy)propan-2-yl)sulfonyl)-1*H*-tetrazole 203

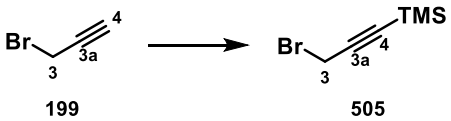


$(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (57.1 mg, 0.05 mmol, 0.05 eq) in H_2O_2 (30% wt in H_2O, 1.2 mL, 11.09 mmol, 12.00 eq) was added slowly to a stirred solution of thioether **202** (398.1 mg, 0.92 mmol, 1.00 eq) in wet EtOH (3.7 mL) at rt and the resulting mixture was stirred at rt overnight. The reaction mixture was diluted with CH_2Cl_2 (10 mL), the layers were separated and the aq. layer was extracted with CH_2Cl_2 (3x 10 mL), the comb. org. layers were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1 – 5:1) yielded sulfone **203** (330.7 mg, 0.72 mmol, 77%) as a colorless syrup.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.67-7.56 (m, 5H, PT), 4.15-4.09 (m, 1H, H-8b), 4.04 (s, 2H, H-3), 3.93-3.85 (m, 2H, H-1), 1.51 (d, *J* = 7.05 Hz, 3H, H-10), 1.05-1.04 (m, 21H, TIPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 153.7 (q, PT), 133.3 (q, PT), 131.6 (t, PT), 129.6 (t, PT), 126.0 (t, PT), 125.8 (t, PT), 101.5 (q, C-4), 89.5 (q, C-3a), 67.8 (s, C-1), 61.3 (t, C-8b), 59.5 (s, C-3), 18.7

(p, TIPS), 11.2 (t, TIPS), 10.0 (p, C-10) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{22}H_{34}N_4O_3SiSNa$ $[M+Na]^+$: 485.2019; *found*: 485.2018; $\mathbf{R}_f$ (5:1 PE/EtOAc): 0.50.

(3-Bromoprop-1-yn-1-yl)tri*iso*propylsilane 505

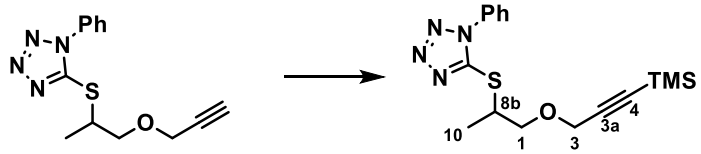


199 505

*n*BuLi (1.6 M in hex, 6.3 mL, 10.09 mmol, 1.20 eq) was added dropwise to a stirred solution of propargyl bromide (**199**) (80% wt in PhMe, 1.3 mL, 8.41 mmol, 1.00 eq) in THF (28.0 mL) at -78 °C, the mixture was stirred at -78 °C for 10 min, then TMSCl (1.3 mL, 10.09 mmol, 1.20 eq) was added dropwise at -78 °C, the mixture was allowed to warm to rt and stirred at rt for 2 h. The reaction was terminated by addition of sat. aq. NH_4Cl-solution (20 mL), the layers were separated and the aq. layer was extracted with CH_2Cl_2 (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. High vacuum distillation (1 mbar, 70-90 °C) yielded bromide **505** (0.95 g, 4.99 mmol, 59%) as a colorless liquid. The analytical data match those reported in the literature. [192]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.91 (s, 2H, H-3), 0.18 (s, 9H, TMS) ppm; $\mathbf{R}_f$ (10:1 PE/EtOAc): 0.90; **bp.:** 70-90 °C, 1 mabr.

1-Phenyl-5-((1-((3-(trimethylsilyl)prop-2-yn-1-yl)oxy)propan-2-yl)thio)-1*H*-tetrazole 204



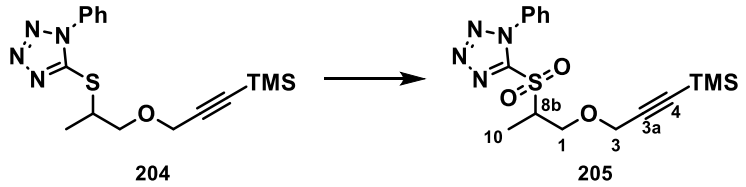
181 204

LiHMDS (1.0 M in THF, 4.3 mL, 4.27 mmol, 1.00 eq) was added dropwise to a stirred solution of alkyne **181** (1.17 g, 4.27 mmol, 1.00 eq) in THF (14.2 mL) at -78 °C, then the mixture was stirred at -78 °C for 1 h and TMSCl (540.0 µL, 4.27 mmol, 1.00 eq) was added dropwise at -78 °C. The resulting mixture was stirred at -78 °C for 1 h, then allowed to warm to rt and the reaction was terminated by addition of a sat. aq. NH_4Cl-solution (10 mL). The layers were separated, the aq. layer was extracted with Et_2O (3x 20 mL), the comb. org. layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1 – 5:1) yielded thioether **204** (1.21 g, 3.50 mmol, 82%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.59-7.54 (m, 5H, PT), 4.27 (dq, *J* = 10.42, 1.45 Hz, 1H, H-8b), 4.19 (s, 2H, H-3), 3.80 (d, *J* = 5.67 Hz, 2H, H-1), 1.55 (d, *J* = 7.01 Hz, 3H, H-10), 0.16 (s, 9H, TMS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 154.0 (q, PT), 133.8 (q, PT), 130.2 (t, PT), 130.0 (t,

PT), 129.9 (t, PT), 124.2 (t, PT), 101.0 (q, C-3a), 92.2 (q, C-4), 72.7 (s, C-1), 59.4 (s, C-3), 44.0 (t, C-8b), 18.4 (p, C-10), -0.1 (p, TMS) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{16}H_{22}N_4OSiSNa$ $[M+Na]^+$: 369.1181; *found*: 369.1179; $\mathbf{R_f}$ (10:1 PE/EtOAc): 0.33.

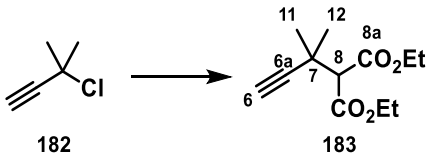
1-Phenyl-5-((1-((3-(trimethylsilyl)prop-2-yn-1-yl)oxy)propan-2-yl)sulfonyl)-1*H*-tetrazole 205



$(NH_4)_6Mo_7O_{24}\cdot4H_2O$ (0.85 g, 0.69 mmol, 0.05 eq) in H_2O_2 (30% wt in H_2O, 17.1 mL, 165.90 mmol, 12.00 eq) was added slowly to a stirred solution of thioether **204** (4.79 g, 13.82 mmol, 1.00 eq) in wet EtOH (55 mL) at rt and the resulting mixture was stirred at rt overnight. The reaction mixture was diluted with CH_2Cl_2 (50 mL), the layers were separated and the aq. layer was extracted with CH_2Cl_2 (3x 50 mL), the comb. org. layers were washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1 – 5:1) yielded sulfone **205** (4.95 g, 13.07 mmol, 95%) as a white amorphous solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.67-7.57 (m, 5H, PT), 4.10-3.98 (m, 1H, H-8b), 3.97 (s, 2H, H-3), 3.87 (dd, *J* = 10.18, 7.30 Hz, 1H, H-1), 3.79 (dd, *J* = 10.32, 5.00 Hz, 1H, H-1), 1.54 (s, 2H, H-1), 1.50 (d, *J* = 7.12 Hz, 3H, H-10), 0.17 (s, 9H, TMS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 155.7 (q, PT), 133.4 (q, PT), 131.6 (t, PT), 129.6 (t, PT), 126.1 (t, PT), 110.9 (q, C-3a), 99.7 (q, C-4), 68.2 (s, C-1), 61.3 (s, C-3), 59.5 (t, C-8b), 9.8 (p, C-10), -0.16 (p, TMS) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{16}H_{22}N_4O_3SiSNa[M+Na]^+$: 401.1080; *found*: 401.1086; $\mathbf{R_f}$ (5:1 PE/EtOAc): 0.47; **mp.:** 102 °C.

Diethyl 2-(2-methylbut-3-yn-2-yl)malonate 183

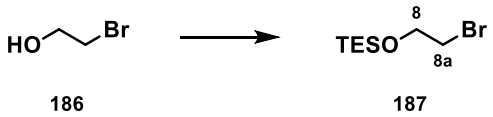


EtOH (24.1 mL) was added slowly under stirring to small pieces of sodium (475.2 mg, 20.67 mmol, 1.06 eq) keeping the temperature below 10 °C. The resulting mixture was stirred at rt for 10 min, then diethylmalonate (3.2 mL, 20.67 mmol, 1.06 eq) was added dropwise at rt and stirred at rt for 30 min. Chloride **182** (2.0 g, 19.50 mmol, 1.00 eq) was added dropwise at rt and the resulting mixture was heated to 60 °C for 4 h. Upon completion analyzed by TLC, the mixture was poured into ice water (40 mL), the layers were separated and the aq. layer was extracted with MTBE (4x 50 mL), the comb.

org. layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Vacuum distillation (12 mbar, 78 °C) yielded malonate **183** (730.0 mg, 3.22 mmol, 17%) as a colorless oil. The analytical data match those reported in the literature.[95]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.21 (q, *J* = 7.13 Hz, 4H, Et), 3.45 (s, 1H, H-8), 2.20 (s, 1H, H-6), 1.46 (s, 6H, H-11, H-12), 1.27 (t, *J* = 7.15 Hz, Et) ppm; **R_f** (5:1 PE/EtOAc): 0.68; **bp.:** 78 °C, 12 mbar.

(2-Bromoethoxy)triethylsilane 187

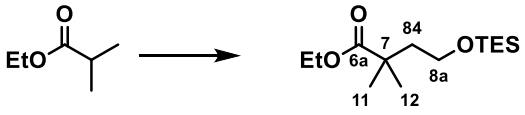


186 187

TESOTf (5.4 mL, 24.01 mmol, 1.00 eq) was added dropwise to a stirred solution of 2-bromoethanol (**186**) (1.7 mL, 24.01 mmol, 1.00 eq) and NEt_3 (8.4 mL, 60.01 mmol, 2.50 eq) in CH_2Cl_2 (55 mL) at 0 °C. The mixture was warmed to rt and stirred at rt for 1 h. The reaction was terminated by addition of water (50 mL), the layers were separated, the aq. layer was extracted with Et_2O (3x 50 mL), the comb. org. layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/Et_2O 40:1) yielded bromide **187** (6.04 g, 24.01 mmol, *quant.*) as a colorless oil. The analytical data match those reported in the literature.[96]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.89 (t, *J* = 6.66 Hz, 2H, H-8a), 3.40 (t, *J* = 7.37 Hz, 2H, H-8), 0.97 (t, *J* = 7.92 Hz, 9H, TES), 0.62 (q, *J* = 7.94 Hz, 6H, TES) ppm; **R_f** (40:1 PE/Et_2O): 0.71.

Ethyl 2,2-dimethyl-4-((triethylsilyl)oxy)butanoate 188



192 188

LDA (1.0 M in THF, 5.2 mL, 10.33 mmol, 1.20 eq) was added dropwise to ethyl *iso*butyrate (**192**) (1.2 mL, 8.61 mmol, 1.00 eq) in THF (21.5 mL) at -78 °C, the resulting mixture was stirred at -78 °C for 1 h, then bromide **187** (2.7 g, 11.19 mmol, 1.30 eq) was added dropwise at -78 °C. The mixture was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (20 mL), the layers were separated, the aq. layer was extracted with EtOAc (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1) yielded ester **188** (2.46 g, 8.61 mmol, *quant.*) as a colorless oil. The analytical data match those reported in the literature.[96]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.10 (q, *J* = 7.12 Hz, 2H, Et), 3.61 (t, *J* = 7.38 Hz, 2H, H-8a), 1.82 (t, *J* = 7.37 Hz, 2H, H-8), 1.25 (t, *J* = 7.15 Hz, 3H, Et), 1.18 (s, 6H, H-11, H-12), 0.95 (t, *J* = 7.94 Hz, 9H, TES), 0.58 (q, *J* = 7.96 Hz, 6H, TES) ppm; **R_f** (10:1 PE/EtOAc): 0.38.

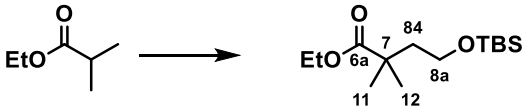
(2-Bromoethoxy)(*tert*-butyl)dimethylsilane 193

186 193

NEt_3 (36.8 mL, 264.07 mmol, 1.10 eq) in CH_2Cl_2 (120 mL) was added slowly to a stirred solution of 2-bromoethanol (**186**) (17.1 mL, 240.07 mmol, 1.00 eq) and TBSCl (39.8 g, 264.07 mmol, 1.10 eq) in CH_2Cl_2 (75 mL) at rt. Then 4-DMAP (146.7 mg, 1.20 mmol, 0.01 eq) was added in one portion and the resulting mixture was stirred at rt overnight. The reaction was terminated by addition of water (100 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (2x 100 mL), the comb. org. layers were washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/Et_2O 20:1) yielded bromide **193** (48.4 g, 202.38 mmol, 85%) as a colorless oil. The analytical data match those reported in the literature.[193]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.89 (t, *J* = 6.56 Hz, 2H, H-8a), 3.40 (t, *J* = 6.73 Hz, 2H, H-8), 0.90 (s, 9H, TBS), 0.09 (s, 6H, TBS) ppm; **R_f** (20:1 PE/Et_2O): 0.86.

Ethyl 4-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethylbutanoate 194

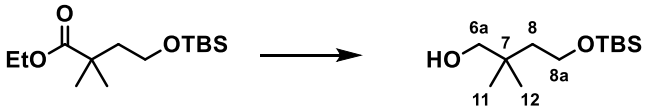


192 194

*n*BuLi (1.6 M in hex, 77.0 mL, 123.11 mmol, 1.10 eq) was added dropwise to DIPA (19.0 mL, 134.30 mmol, 1.20 eq) in THF (135 mL) at -78 °C and the mixture was stirred at -78 °C for 10 min, then ethyl *iso*butyrate (**192**) (15.0 mL, 111.91 mmol, 1.00 eq) in THF (225 mL) was added dropwise at -78 °C. The resulting mixture was stirred at -78 °C for 1 h, then bromide **193** (34.8 g, 145.49 mmol, 1.30 eq) was added dropwise at -78 °C. The mixture was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (150 mL), the layers were separated, the aq. layer was extracted with EtOAc (3x 150 mL), the comb. org. layers were washed with brine (500 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 100:1 – 50:1 – 20:1) yielded ester **194** (35.02 g, 111.91 mmol, *quant.*) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.10 (q, *J* = 7.12 Hz, 2H, Et), 3.62 (t, *J* = 7.25 Hz, 2H, H-8a), 1.80 (t, *J* = 7.23 Hz, 2H, H-8), 1.24 (t, *J* = 7.10 Hz, 3H, Et). 1.18 (s, 6H, H-11, H-12), 0.88 (s, 9H, TBS), 0.03 (s, 6H, TBS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 177.8 (q, C-6a), 60.4 (s, Et), 60.2 (s, C-8a), 43.0 (s, C-8), 40.8 (q, C-7), 26.1 (p, TBS), 25.6 (p, C-11, C-12), 18.5 (q, TBS), 14.3 (p, Et), -5.2 (p, TBS) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{14}H_{30}O_3SiNa$ $[M+Na]^+$: 297.1862; *found*: 297.1861; **R_f** (20:1 PE/EtOAc): 0.57.

4-((*tert*-Butyldimethylsilyl)oxy)-2,2-dimethylbutan-1-ol 195

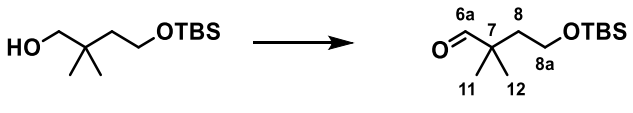


194 195

$LiAlH_4$ (691.3 mg, 18.22 mmol, 1.00 eq) was added in one portion to a stirred solution of ester **194** (5.00 g, 18.22 mmol, 1.00 eq) in Et_2O (61.0 mL) at -78 °C. The mixture was stirred at -78 °C for 30 min, the reaction was terminated by slow addition of MeOH (10 mL) at -78 °C, then diluted with a sat. aq. Rochelle salt-solution (50 mL) and EtOAc (50 mL) and stirred at rt for 3 h. The layers were separated, the aq. layer was extracted with EtOAc (3x 50 mL), the comb. org. layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded alcohol **195** (4.34 g, 18.22 mmol, *quant.*) as a colorless oil. The analytical ^{1}H-NMR data match those reported in the literature.[194]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.70 (t, J = 5.90 Hz, 2H, H-8a), 3.55 (t, J = 7.00 Hz, 1H, OH), 3.28 (d, J = 6.96 Hz, 2H, H-6), 1.50 (t, J = 5.34 Hz, 2H, H-8), 0.91-0.90 (m, 15H, TBS, H-11, H-12), 0.09 (s, 6H, TBS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 71.6 (s, C-6a), 60.1 (s, C-8a), 42.7 (s, C-8), 35.3 (q, C-7), 26.0 (p, TBS), 25.3 (p, C-11, C-12), 18.3 (q, TBS), 5.4 (p, TBS) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{12}H_{28}O_2SiNa$ $[M+Na]^+$: 255.1756; *found*: 255.1754; **R_f** (20:1 PE/EtOAc): 0.31.

4-((*tert*-Butyldimethylsilyl)oxy)-2,2-dimethylbutanal 196



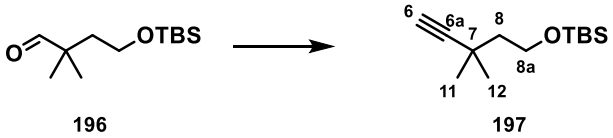
195 196

DMSO (4.4 mL, 61.68 mmol, 3.00 eq) was added dropwise to a stirred solution of oxalylchloride (2.8 mL, 30.84 mmol, 1.50 eq) in CH_2Cl_2 (77.0 mL) at -78 °C, the resulting mixture was stirred at -78 °C for 10 min, then alcohol **195** (4.78 g, 20.56 mmol, 1.00 eq) in CH_2Cl_2 (52.0 mL) was added dropwise at -78 °C and the mixture was stirred at -78 °C for 15 min. Then NEt_3 (8.6 mL, 61.68 mmol, 3.00 eq) was added dropwise at -78 °C and the mixture was allowed to warm to rt and stirred at rt for 30 min. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (100 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 100 mL), the comb. org. layers were washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1 – 10:1) yielded aldehyde **196** (4.43 g, 19.21 mmol, 93%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.46 (s, 1H, H-6a), 3.62 (t, J = 6.08 Hz, 2H, H-8a), 1.75 (t, J = 6.08 Hz, 2H, H-8), 1.06 (s, 6H, H-11, H-12), 0.86 (s, 9H, TBS), 0.02 (s, 6H, TBS) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 205.6 (t, C-6a), 59.3 (s, C-8a), 41.1s, C-8), 37.0 (q, C-7), 26.0 (p, TBS), 21.6 (p, C-11, C-12), 18.4 (q, TBS), -5.4 (p, TBS) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{12}H_{26}O_2SiNa$ $[M+Na]^+$: 253.1600; *found*: 253.1601; $\mathbf{R_f}$ (10:1 PE/EtOAc): 0.83.

tert-Butyl((3,3-dimethylpent-4-yn-1-yl)oxy)dimethylsilane 197

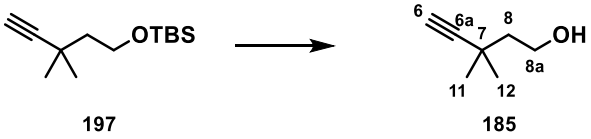


196 197

*n*BuLi (2.5 M in hex, 60.0 mL, 149.73 mmol, 3.00 eq) was added dropwise to a stirred solution of TMS-diazomethane (2.0 M in Et_2O, 37.8 mL, 74.86 mmol, 1.50 eq) in THF (150 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 10 min, then aldehyde **196** (11.50 g, 49.91 mmol, 1.00 eq) in THF (125 mL) was added dropwise at -78 °C. The resulting mixture was allowed to warm to rt overnight. The reaction was terminated by addition of water (100 mL), the layers were separated, the aq. layer was extracted with Et_2O (3x 100 mL), the comb. org. layers were washed with brine (300 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 50:1 – 20:1 – 10:1) yielded alkyne **197** (6.09 g, 26.91 mmol, 54%) as a yellow oil. The NMR data match those reported in the literature.[195]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.82 (t, J = 7.38 Hz, 2H, H-8a), 2.09 (s, 1H, H-6), 1.68 (t, J = 7.74 Hz, 2H, H-8), 1.23 (s, 6H, H-11, H-12), 0.90 (s, 9H, TBS), 0.06 (s, 6H, TBS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 91.4 (q, C-6a), 68.1 (t, C-6), 60.8 (s, C-8a), 45.4 (s, C-8), 29.8 (q, C-7), 29.8 (p, C-11, C-12), 26.1 (p, TBS), 18.4 (q, TBS), -5.1 (p, TBS) ppm; **HRMS (EI-GCT):** *m/z calc.* for $C_9H_{17}OSiNa$ $[M-t\text{Bu}]^+$: 169.1049; *found*: 169.1051; $\mathbf{R_f}$ (20:1 PE/EtOAc): 0.83.

3,3-Dimethylpent-4-yn-1-ol 185

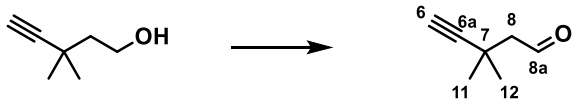


197 185

TBAF (1.0 M in THF, 81.0 mL, 80.71 mmol, 3.00 eq) was added dropwise to a stirred solution of alkyne **197** (6.09 g, 26.90 mmol, 1.00 eq) in THF (90 mL) at 0 °C. The resulting mixture was allowed to warm overnight. The reaction mixture was terminated by addition of a sat. aq. NH_4Cl-solution (100 mL), the layers were separated, the aq. layer was extracted with EtOAc (3x 100 mL), the comb. org. layers were washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded alcohol **185** (1.58 g, 14.12 mmol, 52%) as a colorless oil. The analytical data match those reported in the literature.[96]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.86 (q, J = 5.81 Hz, 2H, H-8a), 2.16 (s, 1H, H-6), 1.80 (t, J = 3.50 Hz, 1H, OH), 1.73 (t, J = 6.63 Hz, 2H, H-8), 1.26 (s, 6H, H-11, H-12), ppm; **R_f** (10:1 PE/EtOAc): 0.18.

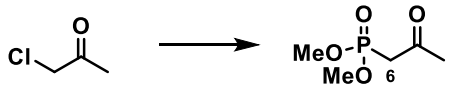
3,3-Dimethylpent-4-yn-1-al 165



185 165

DMSO (3.4 mL, 48.08 mmol, 3.00 eq) was added dropwise to a stirred solution of oxalylchloride (2.1 mL, 24.04 mmol, 1.50 eq) in CH_2Cl_2 (60.0 mL) at -78 °C, the resulting mixture was stirred at -78 °C for 10 min, then alcohol **185** (1.80 g, 16.03 mmol, 1.00 eq) in CH_2Cl_2 (40.0 mL) was added dropwise at -78 °C and the mixture was stirred at -78 °C for 15 min. Then NEt_3 (6.7 mL, 48.08 mmol, 3.00 eq) was added dropwise at -78 °C and the mixture was allowed to warm to rt and stirred at rt for 30 min. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (50 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 50 mL), the comb. org. layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield crude aldehyde **165** as brown oil which was used without further purification for the next step.

Dimethyl (2-oxopropyl)phosphonate 506

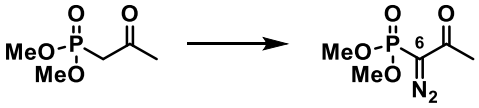


171 506

KI (49.34 g, 297.23 mmol, 1.00 eq) was added to a stirred solution of α-chloro acetone (**171**) (24.0 mL, 297.23 mmol, 1.00 eq) in acetonitrile (100 mL) and acetone (50 mL) at rt and the mixture was stirred at rt for 2 h, then trimethyl phosphite (35.2 mL, 297.23 mmol, 1.00 eq) was added in one portion and the mixture was heated to 50 °C for 24 h. The mixture was cooled to rt, filtered and concentrated *in vacuo*. High vacuum distillation (1 mbar, 70 °C) yielded phosphonate **506** (33.00 g, 198.66 mmol, 67%) as a brown oil. The analytical data match those reported in the literature.[196]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.79 (d, J = 11.21 Hz, 6H, OMe), 3.10 (d, J = 22.82 Hz, 2H, H-6), 2.32 (s, 3H, CH_3) ppm; **R_f** (1:1 PE/EtOAc): 0.05; **bp.:** 70 °C; 1 mbar.

Ohira-Bestman reagent 507

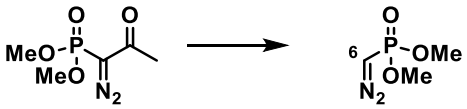


506 507

NaH (60% on mineral oil, 577.9 mg, 14.45 mmol, 1.20 eq) was added in small portions to a stirred solution of phosphonate **506** (2.00 g, 12.04 mmol, 1.00 eq) in PhMe (24.0 mL) at 0 °C The mixture was stirred at 0 °C for 1 h, then *p*-ABSA (2.60 g, 10.84 mmol, 0.90 eq) in THF (10.0 mL) was added dropwise at 0 °C, then the mixture was allowed to warm to rt and stir at rt overnight. The reaction was terminated by addition of PE (30 mL), the participate was filtered off and washed with Et_2O (3x 50 mL). The filtrate was concentrated *in vacuo*. Column chromatography (PE/EtOAc 2:1 – 1:2) yielded the Ohira-Bestman reagent **507** (1.63 g, 8.46 mmol, 71%) as a yellow oil. The analytical data match those reported in the literature.[196]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.84 (d, *J* = 12.10 Hz, 6H, OMe), 2.27 (s, 3H, Me) ppm; **R_f** (1:1 PE/EtOAc): 0.15.

Gilbert-Seyferth reagent 508

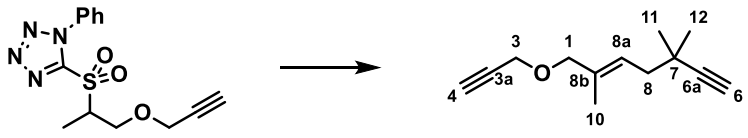


507 508

K_2CO_3 (14.3 mg, 0.10 mmol, 0.20 eq) was added to the Ohira-Bestman reagent **507** (100.0 mg, 0.52 mmol, 1.00 eq) in MeOH (520 µL) at rt and the mixture was stirred at rt for 15 min. After completion indicated by TLC analysis the participate is filtered of and the filtrate is concentrated *in vacuo*. Column chromatography (CH_2Cl_2/acetone 9:1) yielded the Gilbert-Seyferth reagent **508** (56.6 mg, 0.38 mmol, 73%) as a yellow oil. The analytical data match those reported in the literature.[97]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.78 (d, *J* = 11.80 Hz, 6H, OMe) ppm; **R_f** (1:1 PE/EtOAc): 0.16.

(*E*)-3,3,6-Trimethyl-7-(prop-2-yn-1-yloxy)hept-5-en-1-yne 163



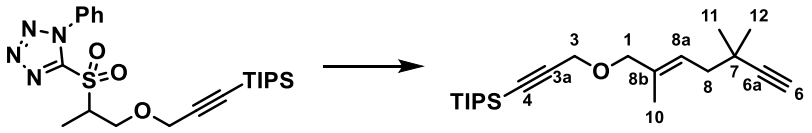
164 163

LiHMDS (1.0 M in THF, 3.9 mL, 3.92 mmol, 1.20 eq) was added dropwise to a stirred solution of aldehyde **165** (395.6 mg, 3.59 mmol, 1.10 eq) and sulfone **164** (1.00 g, 3.26 mmol, 1.00 eq) in THF (8.2 mL) at -78 °C. The mixture was allowed to warm to rt overnight. The reaction was terminated

by addition of water (10 mL), diluted with Et_2O (10 mL), the layers were separated, the aq. layer was extracted with Et_2O (3x 10 mL), the comb. org. layers were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated under exclusion of light at 30 °C *in vacuo*. Column chromatography (pentanes/Et_2O 100:0 – 100:1) yielded enediyne **163** (277.7 mg, 1.46 mmol, 45% 4:1 *E*/*Z*) as a yellow oil.

HRMS (ESI-LCT): *m/z calc.* for $C_{13}H_{18}ONa$ $[M+Na]^+$: 213.1255; *found*: 213.1257; $\mathbf{R_f}$ (20:1 PE/EtOAc): 0.58.

(*E*)-Tri*iso*propyl(3-((2,5,5-trimethylhept-2-en-6-yn-1-yl)oxy)prop-1-yn-1-yl)silane 206

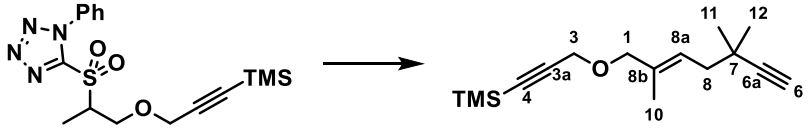


203 **206**

LiHMDS (1.0 M in THF, 0.86 mL, 0.86 mmol, 1.20 eq) was added dropwise to a stirred solution of aldehyde **165** (86.7 mg, 0.79 mmol, 1.10 eq) and sulfone **203** (331.0 mg, 0.72 mmol, 1.00 eq) in THF (1.8 mL) at -78 °C. The mixture was allowed to warm to rt overnight. The reaction was terminated by addition of water (2 mL), diluted with Et_2O (5 mL), the layers were separated, the aq. layer was extracted with Et_2O (3x 5 mL), the comb. org. layers were washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated under exclusion of light *in vacuo*. Column chromatography (pentanes/Et_2O 100:0 – 100:1) yielded enediyne **206** (112.4 mg, 0.32 mmol, 45% 3:1 *E*/*Z*) as a yellow oil.

HRMS (ESI-LCT): *m/z calc.* for $C_{22}H_{38}OSiNa$ $[M+Na]^+$: 369.2590; *found*: 369.2592; $\mathbf{R_f}$ (20:1 PE/EtOAc): 0.68.

(*E*)-Trimethyl(3-((2,5,5-trimethylhept-2-en-6-yn-1-yl)oxy)prop-1-yn-1-yl)silane 207



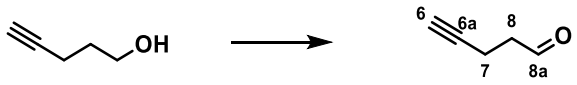
205 **207**

LiHMDS (1.0 M in THF, 1.6 mL, 1.59 mmol, 1.20 eq) was added dropwise to a stirred solution of aldehyde **165** (160.1 mg, 0.79 mmol, 1.10 eq) and sulfone **205** (500.0 mg, 1.32 mmol, 1.00 eq) in THF (3.3 mL) at -78 °C. The mixture was allowed to warm to rt overnight. The reaction was terminated by addition of water (5 mL), diluted with Et_2O (10 mL), the layers were separated, the aq. layer was extracted with Et_2O (3x 10 mL), the comb. org. layers were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated under exclusion of light *in vacuo*. Column

chromatography (pentanes/Et_2O 100:0 – 100:1) yielded enediyne **207** (145.0 mg, 0.55 mmol, 42% 5:1 *E*/*Z*) as a yellow oil.

HRMS (ESI-LCT): *m/z calc.* for $C_{16}H_{25}OSiNa$ $[M+Na]^+$: 285.1651; *found*: 285.1648; $\mathbf{R_f}$ (20:1 PE/EtOAc): 0.86.

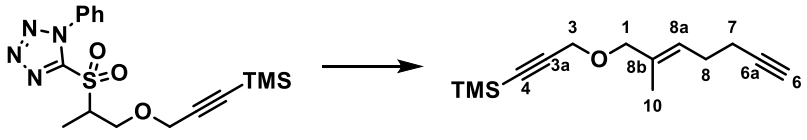
Pent-4-ynal 211



210 **211**

DMSO (1.8 mL, 24.96 mmol, 3.00 eq) was added dropwise to a stirred solution of oxalylchloride (1.1 mL, 12.48 mmol, 1.50 eq) in CH_2Cl_2 (31.0 mL) at -78 °C, the resulting mixture was stirred at -78 °C for 10 min, then pent-4-ynol **210** (0.77 mL, 8.32 mmol, 1.00 eq) in CH_2Cl_2 (21.0 mL) was added dropwise at -78 °C and the mixture was stirred at -78 °C for 15 min. Then NEt_3 (3.5 mL, 24.96 mmol, 3.00 eq) was added dropwise at -78 °C and the mixture was allowed to warm to rt and stirred at rt for 30 min. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (40 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 50 mL), the comb. org. layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield crude aldehyde **211** as brown oil which was used without further purification for the next step.

(*E*)-Trimethyl(3-((2-methylhept-2-en-6-yn-1-yl)oxy)prop-1-yn-1-yl)silane 212

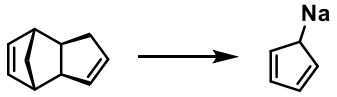


205 **212**

LiHMDS (1.0 M in THF, 7.8 mL, 7.83 mmol, 1.20 eq) was added dropwise to a stirred solution of aldehyde **211** (589.6 mg, 7.18 mmol, 1.10 eq) and sulfone **205** (2.00 g, 6.53 mmol, 1.00 eq) in THF (16.0 mL) at -78 °C. The mixture was allowed to warm to rt overnight. The reaction was terminated by addition of water (15 mL), diluted with Et_2O (20 mL), the layers were separated, the aq. layer was extracted with Et_2O (3x 20 mL), the comb. org. layers were washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated under exclusion of light *in vacuo*. Column chromatography (pentanes/Et_2O 100:0 – 100:1) yielded enediyne **212** (196.1 mg, 1.21 mmol, 19% 3:1 *E*/*Z*) as a yellow oil.

HRMS (ESI-LCT): *m/z calc.* for $C_{14}H_{22}OSiNa$ $[M+Na]^+$: 257.1338; *found*: 257.1338; $\mathbf{R_f}$ (50:1 PE/EtOAc): 0.48.

Cyclopenta-2,4-dien-1-yl sodium 215

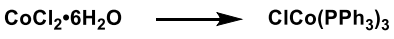


214 **215**

Small pieces of sodium (0.50 g, 21.74 mmol, 1.00 eq) were added in one portion to a degassed solution of decyclopentadien (**214**) (22.0 mL) and the resulting mixture was heated to reflux for 4 h until the evolution of H_2 gas stopped and a white participate was formed. The mixture was cooled to rt, then filtered through a glass frit under a stream of argon, washed with degassed pentanes (3x 100 mL). Drying under high vacuum yielded sodium cyclopentadienyl **215** (1.91 g, 21.74 mmol, *quant.*) as light brown solid which has to be stored under argon in the glove box. The analytical data match those reported in the literature.[197]

^{1}H-NMR (400 MHz, d_8-THF): δ = 5.72 (s, 5H, Cp) ppm.

$CoCl(PPh_3)_3$ 217



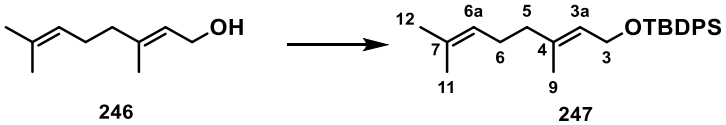
216 **217**

$CoCl_2 \cdot 6H_2O$ (1.00 g, 4.20 mmol, 1.00 eq) and PPh_3 (3.36 g, 12.82 mmol, 3.05 eq) were dissolved in EtOH (70.0 mL) and the resulting mixture was degassed by bubbling argon through under ultra-sonication for 10 min. Then the mixture was heated to 65 °C for 30 min until a fine light blue powder crushes out. Then, the mixture is cooled to 30 °C and $NaBH_4$ (159.0 mg, 4.20 mmol, 1.00 eq) was added in small portions until the color changes to green-brown. The residue is filtered of under a stream of argon, the residue is washed with degassed EtOH (2x 50 mL) until no blue color is observed, then with degassed water (50 mL) and an excess of degassed hexanes. Drying under high vacuum yielded $CoCl(PPh_3)_3$ **217** (3.10 g, 3.51 mmol, 84%) as a brown solid. The analytical data and color changes match those reported in the literature.[198]

mp.: 177 °C.

8.4 Third Synthetic Approach

(*E*)-*tert*-Butyl((3,7-dimethylocta-2,6-dien-1-yl)oxy)diphenylsilane 247



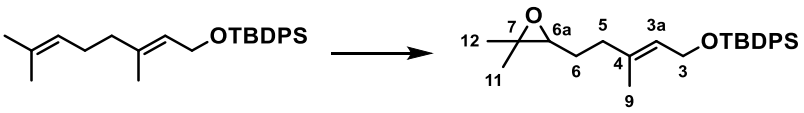
246 **247**

TBDPSCl (3.7 mL, 14.26 mmol, 1.10 eq) was added dropwise to a stirred solution of geraniol (**246**) (2.3 mL, 12.97 mmol, 1.00 eq) and imidazole (1.94 g, 28.53 mmol, 2.20 eq) in DMF (13.0 mL) at 0 °C. Then the mixture was stirred at 0 °C for 10 min and then allowed to warm to rt and stirred at rt

for 2.5 h. The reaction was terminated by addition of water (20 mL), the layers were separated, the aq. layer was extracted with Et_2O (3x 20 mL), the comb. org. layers were washed with a sat. aq. $NaHCO_3$-solution (50 mL), brine (2x 50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1) yielded silyl ether **247** (5.74 g, 12.97 mmol, *quant*.) as a colorless oil. The analytical data match those reported in the literature.[86]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.73-7.69 (m, 4H, TBDPS), 7.44-7.36 (m, 6H, TBDPS), 5.38 (t, *J* = 5.78 Hz, 1H, H-3a), 5.10 (t, *J* = 6.80 Hz, 1H, H-6a), 4.23 (d, *J* = 6.24 Hz, 2H, H-3), 2.10-1.96 (m, 4H, H-6, H-5), 1.69 (s, 3H, H-9), 1.61 (s, 3H, H-11 or H-12), 1.44 (s, 3H, H-11 or H-12), 1.05 (s, 9H, TBDPS) ppm; **R_f** (5:1 PE/EtOAc): 0.76.

(*E*)-*tert*-Butyl((5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-en-1-yl)oxy)diphenylsilane 248

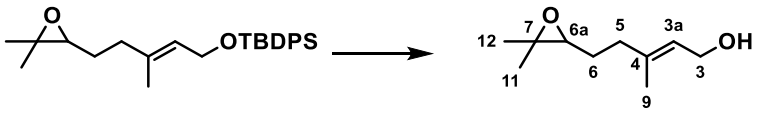


247 248

*m*CPBA (7.99 g, 35.66 mmol, 1.10 eq) was added in one portion to a stirred solution of silyl ether **247** (12.73 g, 32.42 mmol, 1.00 eq) in CH_2Cl_2 (90.0 mL) at 0 °C. The mixture was stirred at 0 °C for 1.5 h. The reaction was terminated by dilution with CH_2Cl_2 (100 mL), the mixture was washed with water (2x 100 mL), a sat. aq. $NaHCO_3$-solution (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1) yielded epoxide **248** (9.29 g, 22.71 mmol, 70%) as a colorless oil. The analytical data match those reported in the literature.[86]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.73-7.67 (m, 4H, TBDPS), 7.44-7.35 (m, 6H, TBDPS), 5.41 (t, *J* = 6.30 Hz, 1H, H-3a), 4.22 (d, *J* = 6.20 Hz, 2H, H-3), 2.70 (t, *J* = 6.26 Hz, 1H, H-6a), 2.17-2.07 (m, 2H, H-5), 1.68-1.59 (m, 2H, H-6), 1.46 (s, 3H, H-9), 1.30 (s, 3H, H-11 or H-12), 1.26 (s, 3H, H-11 or H-12), 1.04 (s, 9H, TBDPS) ppm; **R_f** (100:10 PE/EtOAc): 0.10.

(*E*)-5-(3,3-Dimethyloxiran-2-yl)-3-methylpent-2-en-1-ol 229



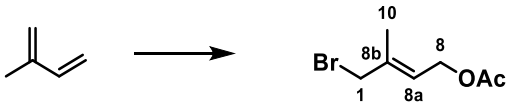
248 229

TBAF (1.0 M in THF, 7.8 mL, 7.79 mmol, 1.50 eq) was added drowise to a stirred solution of silyl ether **248** (2.12 g, 5.19 mmol, 1.00 eq) in THF (22.6 mL) at 0 °C. The mixture was allowed to warm to rt and stirred at rt for 3 h. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (20 mL), the layers were separated, the aq. layer was extracted with EtOAc (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in*

vacuo. Column chromatography (PE/EtOAc 1:3) yielded alcohol **229** (679.4 mg, 3.99 mmol, 77%) as a colorless oil. The analytical data match those reported in the literature.[199]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.46 (dt, *J* = 6.95, 1.27 Hz, 1H, H-3a), 4.17 (s, 2H, H-3), 2.71 (t, *J* = 6.62 Hz, 1H, H-6a), 2.25-2.12 (m, 2H, H-5), 1.70 (s, 3H, H-9), 1.69-1.63 (m, 2H, H-6), 1.31 (s, 3H, H-11 or H-12), 1.26 (s, 3H, H-11 or H-12) ppm; **R_f** (1:3 PE/EtOAc): 0.65.

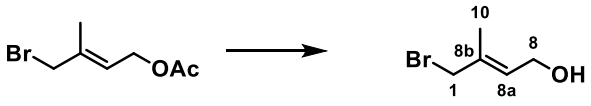
(*E*)-4-Bromo-3-methylbut-2-en-1-yl acetate 249



20 249

NBS (12.54 g, 70.46 mmol, 0.80 eq) was added in one portion to a stirred solution of isoprene (**20**) (8.8 mL, 88.08 mmol, 1.00 eq) in acetic acid (37.0 mL) at 0 °C. The resulting mixture was allowed to warm to rt overnight. The reaction was terminated by addition of water (50 mL). The layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 50 mL), the comb. org. layers were washed with water (100 mL), a sat. aq. $NaHCO_3$-solution (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give crude acetate **249** as a yellow oil which was used without further purification for the next step.

(*E*)-4-Bromo-3-methylbut-2-en-1-ol 250

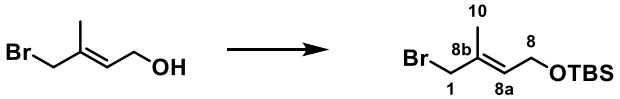


249 250

A solution of K_2CO_3 (8.63 g, 62.46 mmol, 1.00 eq) in water (25.6 mL) was added slowly to a stirred solution of crude acetate **249** (12.93 g, 62.46 mmol, 1.00 eq) in MeOH (104 mL) at rt. The mixture was stirred at rt for 1 h. The reaction was terminated by addition of water (100 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 100 mL), the comb. org. layers were washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* under exclusion of light at 30 °C. Column chromatography (PE/EtOAc 7:1 – 5:1 – 3:1) yielded alcohol **250** (2.60 g, 15.77 mmol, 25% as a 5:1 *E*/*Z* mixture) as a colorless oil which has to be stored in darkness. The analytical data match those reported in the literature.[200]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.79 (t, *J* = 6.36 Hz, 1H, H-8a), 4.20 (d, *J* = 6.24 Hz, 2H, H-8), 3.96 (s, 2H, H-1), 1.81 (s, 3H, H-10), 1.41 (bs, 1H, OH) ppm; **R_f** (3:1 PE/EtOAc): 0.20.

(*E*)-((4-Bromo-3-methylbut-2-en-1-yl)oxy)(*tert*-butyl)dimethylsilane 228

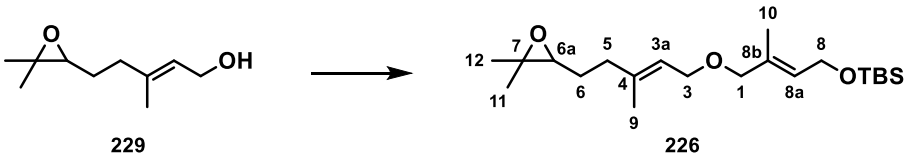


250 228

Imidazole (2.15 g, 31.54 mmol, 2.00 eq) and TBSCl (3.57 g, 23.65 mmol, 1.50 eq) were added to a stirred solution of alcohol **250** (2.60 g, 15.77 mmol, 1.00 eq) in DMF (40.0 mL) at rt. The resulting mixture was stirred at rt for 20 min. The reaction was terminated by addition of water (40 mL) and the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 50 mL), the comb. org. layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* at 30 °C under exclusion light. Column chromatography (PE/EtOAc 50:1) yielded bromide **228** (2.12 g, 7.61 mmol, 48%) as a colorless oil which has to be stored in darkness at -20 °C. The analytical data match those reported in the literature.[201]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.66 (t, *J* = 5.72 Hz, 1H, H-8a), 4.23 (d, *J* = 5.88 Hz, 2H, H-8), 4.01 (s, 2H, H-1), 1.75 (s, 3H, H-10), 0.90 (s, 9H, TBS), 0.07 (s, 6H, TBS) ppm; **R_f** (20:1 PE/EtOAc): 0.83.

tert-Butyl (((*E*)-4-(((*E*)-5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-en-1-yl)oxy)-3-methylbut-2-en-1-yl)oxy)dimethylsilane 226



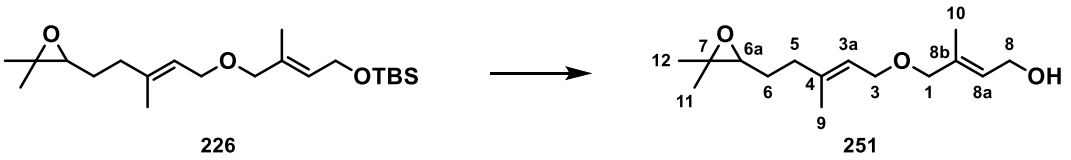
229 226

Alcohol **229** (250.0 mg, 1.47 mmol, 1.00 eq) in DMF (770 µL) was added dropwise to a stirred solution of NaH (60% on mineral oil, 88.1 mg, 2.20 mmol, 1.50 eq) in DMF (4.0 mL) at 0 °C. The mixture was allowed to warm to rt and stirred at rt for 30 min, then bromide **228** (410.1 mg, 1.47 mmol, 1.00 eq) was added dropwise at rt and the mixture was stirred at rt overnight. The reaction was terminated by addition of water (5 mL) and concentrated *in vacuo* until the aq. layer was left. The aq. layer was extracted with EtOAc (3x 10 mL), the comb. org. layers were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 50:1) yielded silyl ether **226** (379.4 mg, 1.03 mmol, 70%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.56 (t, *J* = 6.20 Hz, 1H, H-8a), 5.39 (t, *J* = 6.86 Hz, 1H, H-3a), 4.24 (d, *J* = 5.88 Hz, 2H, H-8), 3.93 (d, *J* = 6.64 Hz, 2H, H-3), 3.85 (s, 2H, H-1), 2.71 (t, *J* = 6.22 Hz, 1H, H-6a), 2.23-2.09 (m, 2H, H-5), 1.68-1.66 (m, 8H, H-6, H-11, H-12), 1.30 (s, 3H, H-9 or H-10), 1.26 (s, 3H, H-9 or H-10), 0.90 (s, 9H, TBS), 0.07 (s, 6H, TBS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 139.2 (q, C-4), 133.6 (q, C-8b), 127.8 (t, C-8a), 121.7 (t, C-3a), 75.8 (s, C-1), 68.7 (q, C-7), 66.2

(s, C-3), 64.2 (t, C-6a), 60.1 (s, C-8), 36.3 (s, C-5), 27.3 (p, C-9), 26.1 (p, TBS), 25.0 (p, C-11, C-12), 18.9 (s, C-6), 16.7 (q, TBS), 14.2 (p, C-10), -5.0 (p, TBS) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{21}H_{40}O_3SiNa$ $[M+Na]^+$: 391.2644; *found*: 391.2644; $\mathbf{R_f}$ (10:1 PE/EtOAc): 0.49.

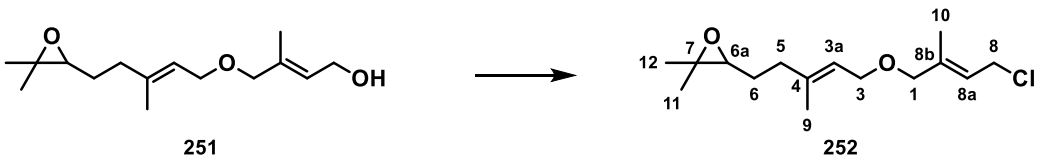
(*E*)-4-(((*E*)-5-(3,3-Dimethyloxiran-2-yl)-3-methylpent-2-en-1-yl)oxy)-3-methylbut-2-en-1-ol 251



226 251

TBAF (1.0 M in THF, 3.2 mL, 3.09 mmol, 3.00 eq) was added dropwise to a stirred solution of silyl ether **226** (379.4 mg, 1.03 mmol, 1.00 eq) in THF (3.4 mL) at 0 °C. The mixture was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (5 mL), the layers were separated, the aq. layer was extracted with EtOac (3x 10 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 2:1) yielded alcohol **251** (227.9 mg, 0.90 mmol, 87%) as a colorless oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 5.66 (t, *J* = 6.68 Hz, 1H, H-8a), 5.40 (t, *J* = 6.26 Hz, 1H, H-3a), 4.21 (d, *J* = 6.20 Hz, 2H, H-8), 4.14 (d, *J* = 5.88 Hz, 1H, OH), 3.96 (d, *J* = 6.30 Hz, 2H, H-3), 3.86 (s, 2H, H-1), 2.71 (t, *J* = 6.20 Hz, 1H, H-6a), 2.25-2.10 (m, 2H, H-5), 1.70-1.65(m, 8H, H-6, H-11, H-12), 1.30 (s, 3H, H-9), 1.26 (s, 3H, H-10) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 139.4 (q, C-4), 136.1 (q, C-8b), 126.1 (t, C-8a), 121.5 (t, C-3a), 75.5 (s, C-1), 68.9 (q, C-7), 66.5 (s, C-3), 64.2 (t, C-6a), 59.3 (s, C-8), 36.4 (s, C-5), 27.3 (p, C-9), 25.0 (p, C-11, C-12), 18.9 (s, C-6), 14.2 (p, C-10) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{15}H_{26}O_3Na$ $[M+Na]^+$: 277.1780; *found*: 277.1780; $\mathbf{R_f}$ (1:3 PE/EtOAc): 0.50.

3-((*E*)-5-(((*E*)-4-Chloro-2-methylbut-2-en-1-yl)oxy)-3-methylpent-3-en-1-yl)-2,2-dimethyloxirane 252



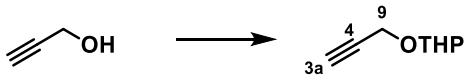
251 252

Dimethylsulfide (11 µL, 0.14 mmol, 1.20 eq) wad added dropwise to NCS (17.3 mg, 0.13 mmol, 1.10 eq) in CH_2Cl_2 (260.0 µL) at 0 °C and the resulting mixture was stirred at 0 °C for 5 min. Then a solution of alcohol **251** (30.0 mg, 0.12 mmol, 1.00 eq) in CH_2Cl_2 (190.0 µL) was added dropwise at 0 °C. The resulting mixture was allowed to warm to rt over a period of 4 h. The reaction was terminated by addition of brine (1 mL) and diluted with Et_2O (10 mL) and water (10 mL). The layers were

separated and the aq. layer was extracted with Et_2O (3x 10 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1) yielded chloride **252** (20.8 mg, 0.08 mmol, 65%) as a colorless oil.[2]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.71 (dt, *J* = 7.92, 1.58 Hz, 1H, H-8a), 5.39 (dt, *J* = 6.75, 0.97 Hz, 1H, H-3a), 4.12 (d, *J* = 7.72 Hz, 2H, H-8), 3.96 (d, *J* = 6.68 Hz, 2H, H-3), 3.88 (s, 2H, H-1), 2.71 (t, *J* = 6.22 Hz, 1H, H-6a), 2.26-2.10 (m, 2H, H-5), 1.74 (s, 3H, H-11 or H-12), 1.68-1.63 (m, 5H, H-6, H-11 or H-12), 1.31 (s, 3H, H-9), 1.26 (s, 3H, H-10) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 139.6 (q, C-4),139.1 (q, C-8b), 122.4 (t, C-8a), 121.4 (t, C-3a), 74.9 (s, C-1), 66.6 (q, C-7), 64.2 (s, C-3), 58.5 (t, C-6a), 40.3 (s, C-8), 36.4 (s, C-5), 27.3 (p, C-9), 25.0 (p, C-11, C-12), 18.9 (s, C-6), 13.9 (p, C-10) ppm; $\mathbf{R_f}$ (3:1 PE/EtOAc): 0.71.

2-(Prop-2-yn-1-yloxy)tetrahydro-2*H*-pyran 233

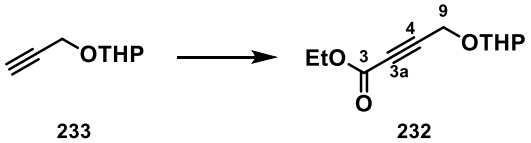


253 233

DHP (1.8 mL, 18.73 mmol, 1.05 eq) was added to a stirred solution of propargyl alcohol **253** (1.2 mL, 17.84 mmol, 1.00 eq) and *p*TsOH·H_2O (307.2 mg, 1.78 mmol, 0.10 eq) in CH_2Cl_2 (36.0 mL) at 0 °C. The resulting mixture was warmed to rt and stirred at rt for 1 h. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (30 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 30 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1) yielded ether **233** (2.12 g, 15.15 mmol, 85%) as a yellow oil. The analytical data match those reported in the literature.[202]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.82 (t, *J* = 3.29 Hz, 1H, THP), 4.32-4.20 (m, 2H, H-9), 3.87-3.81 (m, 1H, THP), 3.56-3.51 (m, 1H, THP), 2.41 (t, *J* = 2.39 Hz, 1H, H-3a), 1.87-1.70 (m, 2H, THP), 1.65-1.52 (m, 4H, THP) ppm; $\mathbf{R_f}$ (10:1 PE/EtOAc): 0.71.

Ethyl 4-((tetrahydro-2*H*-pyran-2-yl)oxy)but-2-ynoate 232



233 232

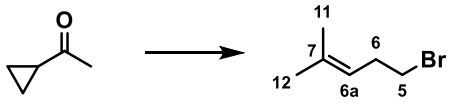
*n*BuLi (1.6 M in hexanes, 2.6 mL, 3.92 mmol, 1.10 eq) was added dropwise to a stirred solution of alkyne **233** (0.50 g, 3.57 mmol, 1.00 eq) in THF (10.0 mL) at -78 °C. The resulting mixture was

[2] Only the mass of fragments in all available mass spectrometric experiments (ESI-LCMS, EI-GCMS, ACP, GC-MS) were found not the one of the complete molecule.

stirred at -78 °C for 1 h. Then ethylchloroformiate (0.68 mL, 7.13 mmol, 2.00 eq) was added dropwise and the mixture was allowed to warm to -10 °C over a period of 2 h. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (10 mL) and the mixture was warmed to rt and then concentrated *in vacuo*. The resulting aq. layer was diluted with Et_2O (10 mL), the layers were separated and the org. layer was washed with 10% HCl (10 mL), a sat. aq. $NaHCO_3$-solution (10 mL), brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded ester **232** (0.70 g, 3.30 mmol, 92%) as a yellow oil. The analytical data match those reported in the literature.[203]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.84 (t, *J* = 2.98 Hz, 1H, THP), 4.41 (s, 2H, H-9), 4.26 (q, *J* = 7.13 Hz, 2H, Et), 3.87-3.81 (m, 1H, THP), 3.59-3.56 (m, 1H, THP), 1.87-1.73 (m, 2H, THP), 1.68-1.56 (m, 4H, THP), 1.34 (t, *J* = 7.18 Hz, 3H, Et) ppm; **R_f** (10:1 PE/EtOAc): 0.43.

5-Bromo-2-methylpent-2-ene 255

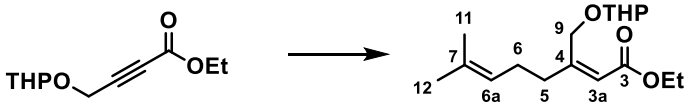


254 255

Cyclopropylmethylketone **254** (4.7 mL, 47.55 mmol, 1.00 eq) in THF (7.2 mL) was added dropwise to a solution of MeMgBr (3.0 M in Et_2O, 19.0 mL, 57.06 mmol, 1.20 eq) in THF (19.0 mL) at rt, then the mixture was heated under refluxing conditions for 30 min. The resulting mixture was cooled to rt and transferred slowly onto an ice cold mixture of conc. H_2SO_4/H_2O (1:2, 50 mL) keeping the temperature below 10 °C. The resulting mixture was stirred at 0 °C for 30 min. The layers were separated, the aq. layer was extracted with Et_2O (3x 50 mL), the comb. org. layers were washed with a sat. aq. $NaHCO_3$-solution (2x 100 mL), brine (100 mL), dried over $MgSO_4$, conctrated *in vacuo*. Distillation (60-65 °C, 22 mbar) yielded bromide **255** (4.82 g, 24.33 mmol, 51%) as a colorless oil. The analytical data match those reported in the literature.[204]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.13 (tt, *J* = 7.14, 1.37 Hz, 1H, H-6a), 3.34 (t, *J* = 7.34 Hz, 2H, H-5), 2.56 (q, *J* = 7.58 Hz, 2H, H-6), 1.72 (s, 3H, H-11 or H-12), 1.63 (s, 3H, H-11 or H-12) ppm; **R_f** (50:1 PE/EtOAc): 0.83; **bp.:** 60-65 °C, 22 mbar.

Ethyl (*Z*)-7-methyl-3-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)octa-2,6-dienoate 231



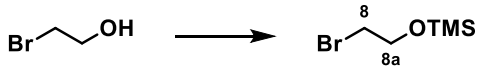
232 231

Bromide **255** (230.5 mg, 1.41 mmol, 1.50 eq) was added dropwise to magnesium turnings (38.9 mg, 1.60 mmol, 1.70 eq) in THF (0.81 mL) at rt. The reaction was started by addition of a catalytic amount

of iodine and careful heating. Once the exothermic reaction was complete the mixture was stirred at rt for 2 h, then it was cooled to -50 °C. In another flask, CuBr·DMS (290.6 mg, 1.41 mmol, 1.50 eq) was dissolved in THF (1.3 mL) and added dropwise to the mixture. The mixture was stirred at -50 °C for 30 min, then it was cooled to -78 °C and ester **232** (200.0 mg, 0.94 mmol, 1.00 eq) was added dropwise. The mixture was stirred at -78 °C for 1 h, then the reaction was terminated by addition of a sat. aq. NH_4Cl-solution (5 mL) and allowed to warm to rt. The layers were separated and the aq. layer was extracted with hexanes (3x 5 mL), the comb. org. layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 50:1) yielded enone **231** (201.3 mg, 0.68 mmol, 72%, 5:1 mixture *E*/*Z*) as a colorless oil. The analytical data match those reported in the literature.[116]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.72 (s, 1H, THP), 5.11 (tt, *J* = 7.00, 1.30 Hz, 1H, H-3a), 4.72 (s, 2H, H-9), 4.63 (t, *J* = 3.42 Hz, 1H, H-6a), 4.14 (q, *J* = 7.12 Hz, 2H, Et), 3.89-3.84 (m, 1H, THP), 3.56-3.50 (m, 1H, THP), 2.36-2.32 (m, 2H, H-5 or H-6), 2.22-2.19 (m, 2H, H-5 or H-6), 1.86-1.51 (m, 12H, H-11, H-12, THP), 1.27 (t, *J* = 7.00 Hz, 3H, Et) ppm; **R_f** (20:1 PE/EtOAc): 0.55.

(2-Bromoethoxy)trimethylsilane 256



186 256

HMDS (8.0 mL, 38.41 mmol, 1.60 eq) was added slowly to 2-bromoethanol **186** (1.7 mL, 24.01 mmol, 1.00 eq) at 0 °C, the resulting mixture was allowed to warm to rt overnight to give crude silyl ether **256** which was directly submitted for the next reaction.

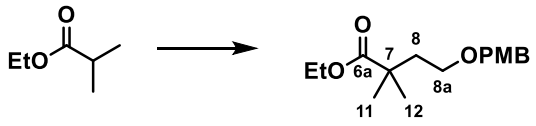
1-((2-Bromoethoxy)methyl)-4-methoxybenzene 257

186 257

PMB-trichloroacetimidate (2.26 g, 8.00 mmol, 1.00 eq) was added dropwise to a stirred solution of 2-bromoethanol **186** (0.57 mL, 8.00 mmol, 1.00 eq) and CSA (185.9 mg, 0.80 mmol, 0.10 eq) in CH_2Cl_2 (16.0 mL) at 0 °C. The resulting mixture was allowed to warm to rt overnight. The mixture was filtered, washed with an excess of CH_2Cl_2, the filtrated was washed with a sat. aq. $NaHCO_3$-solution (100 mL), water (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded bromide **257** (1.39 g, 5.66 mmol, 71%) as a colorless oil. The analytical data match those reported in the literature.[205]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 8.60 Hz, 2H, PMB), 6.89 (d, *J* = 8.60 Hz, 2H, PMB), 4.52 (s, 2H, PMB), 3.81 (s, 3H, PMB), 3.76 (t, *J* = 6.22 Hz, 2H, H-8), 3.47 (t, *J* = 6.22 Hz, 2H, H-8a) ppm; **R_f** (5:1 PE/EtOAc): 0.74.

Ethyl 4-((4-methoxybenzyl)oxy)-2,2-dimethylbutanoate 258

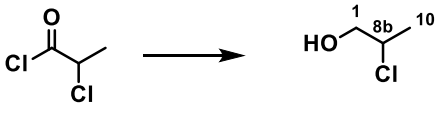


192 258

*n*BuLi (1.6 M in hex, 3.0 mL, 4.73 mmol, 1.10 eq) was added dropwise to a stirred solution of DIPA (0.73 mL, 5.17 mmol, 1.20 eq) in THF (5.2 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 10 min, then ester **192** (0.58 mL, 4.30 mmol, 1.00 eq) in THF (8.6 mL) was added dropwise and the resulting mixture was stirred at -78 °C for 1 h. Then bromide **257** (1.37 g, 5.60 mmol, 1.30 eq) was added dropwise at -78 °C and then the mixture was allowed to warm to rt overnight. The reaction was terminated by addition of aq. 1 M HCl (20 mL), the layers were separated, the aq. layer was extracted with EtOAc (3x 20 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1 – 10:1) yielded ester **258** (0.85 g, 3.03 mmol, 70%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.60 Hz, 2H, PMB), 6.86 (d, *J* = 8.64 Hz, 2H, PMB), 4.39 (s, 2H, PMB), 4.06 (q, *J* = 7.20 Hz, 2H, Et), 3.80 (s, 3H, PMB), 3.46 (t, *J* = 6.96 Hz, 2H, H-8a), 1.88 (t, *J* = 7.18 Hz, 2H, H-8), 1.22-1.18 (m, 8H, H-11, H-12, Et) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 177.8 (q, C-6a), 159.2 (q, PMB), 130.7 (q, PMB), 129.4 (t, PMB), 113.8 (t, PMB), 72.8 (s, PMB), 67.0 (s, C-8a), 60.4 (s, Et), 55.4 (p, PMB), 40.8 (s, C-8), 40.0 (q, C-7), 25.6 (p, Et), 14.3 (p, C-11, C-12) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{16}H_{24}O_4Na$ $[M+Na]^+$: 303.1573; *found*: 303.1572; **R_f** (10:1 PE/EtOAc): 0.47.

2-Chloropropan-1-ol 262



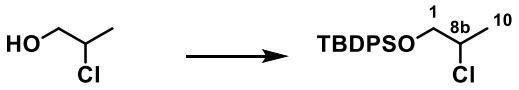
261 262

$LiAlH_4$ (1.79 g, 47.25 mmol, 1.20 eq) was added to Et_2O (68 mL) and heated under refluxing conditions for 3 h and then cooled to 0 °C. Acid chloride **261** (3.9 mL, 39.38 mmol, 1.00 eq) was added dropwise to the stirred gray slurry at 0 °C and the resulting mixture was stirred at 0 °C for 15 min. The reaction was carefully terminated by addition of water (50 mL) and a 10% aq. H_2SO_4 (20 mL) and the layers were separated. The aq. layer was extracted with Et_2O (3x 50 mL), the comb. org.

layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Distillation (100 mbar, 70 °C) yielded alcohol **262** (2.59 g, 27.39 mmol, 70%) as a colorless oil. The analytical data match those reported in the literature.[206,207]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.21-4.14 (m, 1H, H-8b), 3.77 (dd, *J* = 11.96, 3.92 Hz, 1H, H-1), 3.64 (dd, *J* = 11.96, 7.16 Hz, 1H, H-1), 2.08 (bs, 1H, O*H*), 1.53 (d, *J* = 6.68 Hz, 3H, H-10) ppm; **R_f** (5:1 PE/EtOAc): 0.33; **bp.:** 70 °C, 100 mbar.

tert-Butyl(2-chloropropoxy)diphenylsilane 263

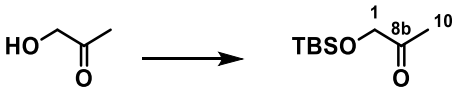


262 **263**

TBDPSCl (5.5 mL, 21.02 mmol, 1.10 eq) was added dropwise to a stirred solution of alcohol **262** (1.81 g, 19.11 mmol, 1.00 eq) and imidazole (2.86 g, 42.05 mmol, 2.20 eq) in DMF (20 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 10 min and then allowed to warm to rt over 2 h. The reaction was terminated by addition of water (20 mL), the layers were separated, the aq. layer was extracted with Et_2O (3x 20 mL), the comb. org. layers were washed with a sat. aq. $NaHCO_3$-solution (50 mL), brine (2x 50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give crude silyl ether **263** (6.36 g, 19.11 mmol, *quant.*) as a colorless oil which was used directly for the next step. The analytical data match those reported in the literature.[208]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.73-7.66 (m, 4H, TBDPS), 7.46-7.37 (m, 6H, TBDPS), 4.04 (6.38 Hz, 1H, H-8b), 3.79 (dd, *J* = 10.42, 5.56 Hz, 1H, H-1), 3.66 (dd, *J* = 10.44, 6.59 Hz, 1H, H-1), 1.52 (d, *J* = 6.60 Hz, 3H, H-10), 1.07 (s, 9H, TBDPS) ppm; **R_f** (5:1 PE/EtOAc): 0.80.

1-((*tert*-Butyldimethylsilyl)oxy)propan-2-one 245

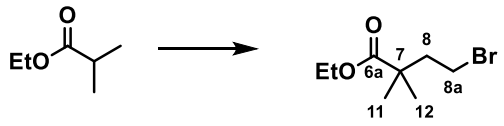


265 **245**

Imidazole (2.02 g, 29.70 mmol, 2.20 eq) was added in one portion to a stirred solution of hydroxyacetone **265** (0.94 mL, 13.50 mmol, 1.00 eq) and TBSCl (3.05 g, 20.25 mmol, 1.50 eq) in CH_2Cl_2 (45 mL) at 0 °C. The resulting mixture was allowed to warm to rt and stirred at rt for 2.5 h. The reaction was terminated by addition of brine (50 mL), the layers were separated and the aq. layer was extracted with Et_2O (3x 50 mL), the comb. org. layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded ketone **245** (2.29 g, 12.15 mmol, 90%) as a colorless oil. The analytical data match those reported in the literature.[209]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.15 (s, 2H, H-1), 2.17 (s, 3H, H-10), 0.92 (s, 9H, TBS), 0.09 (s, 6H, TBS) ppm; $\mathbf{R_f}$ (10:1 PE/EtOAc): 0.70.

Ethyl 4-bromo-2,2-dimethylbutanoate 266

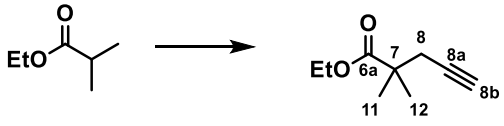


192 266

*n*BuLi (1.6 M in hex, 11.8 mL, 18.94 mmol, 1.10 eq) was added dropwise to a stirred solution of DIPA (2.9 mL, 20.66 mmol, 1.20 eq) in THF (21 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 10 min, then ester **192** (2.3 mL, 17.22 mmol, 1.00 eq) in THF (35 mL) was added dropwise at -78 °C. The resulting mixture was stirred at -78 °C and then dibromomethane (2.0 mL, 22.38 mmol, 1.30 eq) was added dropwise at -78 °C. The resulting mixture was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (60 mL), the layers were separated, the aq. layer was extracted with EtOAc (3x 50 mL), the comb. org. layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1 – 10:1) yielded ester **266** (2.22 g, 9.93 mmol, 58%) as a yellow oil. The analytical data match those reported in the literature.[210]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.13 (q, J = 7.12 Hz, 2H, Et), 3.36-3.32 (m, 2H, H-8a), 2.16-2.12 (m, 2H, H-8), 1.26 (t, J = 7.00 Hz, 3H, Et), 1.20 (s, 6H, H-11, H-12) ppm; $\mathbf{R_f}$ (10:1 PE/EtOAc): 0.75.

Ethyl 2,2-dimethylpent-4-ynoate 267

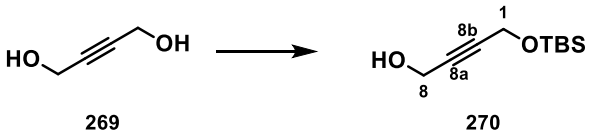


192 267

*n*BuLi (1.6 M in hex, 8.88 mL, 14.20 mmol, 1.10 eq) was added dropwise to a stirred solution of DIPA (2.2 mL, 15.50 mmol, 1.20 eq) in THF (15.5 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 10 min, then ester **192** (1.7 mL, 12.91 mmol, 1.00 eq) in THF (26 mL) was added dropwise at -78 °C. The resulting mixture was stirred at -78 °C and then propargyl bromide (80% wt in PhMe, 2.4 mL, 12.91 mmol, 1.00 eq) was added dropwise at -78 °C. The resulting mixture was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (50 mL), the layers were separated, the aq. layer was extracted with EtOAc (3x 50 mL), the comb. org. layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1 – 10:1) yielded ester **267** (1.44 g, 9.34 mmol, 72%) as a colorless oil. The analytical data match those reported in the literature.[211]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.15 (q, *J* = 7.12 Hz, 2H, Et), 2.44 (d, *J* = 2.56 Hz, 2H, H-8), 2.00 (t, *J* = 2.58 Hz, 1H, H-8b), 1.27-1.24 (m, 9H, Et, H-11, H-12) ppm; **R_f** (10:1 PE/EtOAc): 0.56.

4-((*tert*-Butyldimethylsilyl)oxy)but-2-yn-1-ol 270

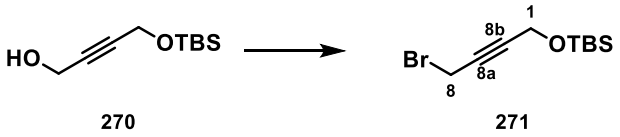


269 270

Imidazole (2.97 g, 43.56 mmol, 0.75 eq) and TBSCl (5.25 g, 34.85 mmol, 0.60 eq) were added in one portion to a stirred solution of diole **269** (5.00 g, 58.08 mmol, 1.00 eq) in DMF (65 mL) at rt. The resulting mixture was stirred at rt overnight. The reaction was terminated by addition of water (50 mL), the layers were separated, the aq. layer was extracted with EtOAc (3x 50 mL), the comb. org. layers were washed with a sat. aq. $NaHCO_3$-solution (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded alcohol **270** (3.33 g, 16.62 mmol, 29%) as a colorless oil. The analytical data match those reported in the literature.[212]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.35 (t, *J* = 1.77 Hz, 2H, H-8), 4.30 (bs, 2H, H-1), 0.91 (s, 9H, TBS), 0.12 (s, 6H, TBS) ppm; **R_f** (2:1 PE/EtOAc): 0.71.

((4-Bromobut-2-yn-1-yl)oxy)(*tert*-butyl)dimethylsilane 271

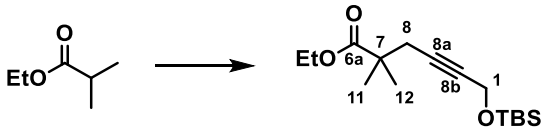


270 271

NEt_3 (0.64 mL, 4.62 mmol, 1.85 eq) and MsCl (0.29 mL, 3.74 mmol, 1.50 eq) were added dropwise to a stirred solution of alcohol **270** (0.50 g, 2.50 mmol, 1.00 eq) in THF (9.6 mL) at 0 °C. The resulting mixture was allowed to warm to rt and stirred at rt for 30 min. The suspension was filtered through a glass frit into a flask charged with LiBr (1.08 g, 12.48 mmol, 5.00 eq) in THF (7.8 mL). The mixture was stirred at rt for 30 min. The reaction was terminated by diluting with Et_2O (30 mL), the solid was filtered off again and washed with an excess of Et_2O. The org. layer was washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded bromide **271** (353.9 mg, 1.34 mmol, 54%) as a colorless oil. The analytical data match those reported in the literature.[213]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.37 (t, *J* = 2.01 Hz, 2J, H-1), 3.94 (t, *J* = 2.14 Hz, 2H, H-8), 0.91 (s, 9H, TBS), 0.12 (s, 6H, TBS) ppm; **R_f** (10:1 PE/EtOAc): 0.88.

Ethyl 4-((4-methoxybenzyl)oxy)-2,2-dimethylbutanoate 272

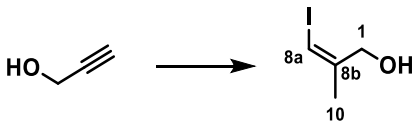


192 272

*n*BuLi (2.5 M in hex, 0.57 mL, 1.42 mmol, 1.10 eq) was added dropwise to a stirred solution of DIPA (0.22 mL, 1.55 mmol, 1.20 eq) in THF (1.5 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 10 min, then ester **192** (0.18 mL, 1.29 mmol, 1.00 eq) in THF (2.6 mL) was added dropwise and the resulting mixture was stirred at -78 °C for 1 h. Then bromide **271** (339.9 mg, 1.29 mmol, 1.00 eq) was added dropwise at -78 °C and then the mixture was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (10 mL), the layers were separated, the aq. layer was extracted with EtOAc (3x 10 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 50:1) yielded ester **272** (329.8 mg, 1.11 mmol, 86%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.29 (t, *J* = 2.04 Hz, 2H, H-1), 4.13 (q, *J* = 7.11 Hz, 2H, Et), 2.46 (t, *J* = 2.04 Hz, H-8), 1.25 (m. 9H, Et, H-11, H-12), 0.90 (s, 9H, TBS), 0.11 (s, 6H, TBS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 176.9 (q, C-6a), 81.9 (q, C-8a), 81.0 (q, C-8b), 60.8 (s, Et), 52.0 (s, C-8), 42.2 (s, C-1), 30.1 (q, C-7), 26.0 (p, TBS), 24.7 (p, C-11, C-12), 18.4 (q, TBS), 14.3 (p, Et), -5.0 (p, TBS) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{16}H_{30}O_3SiNa$ $[M+Na]^+$: 321.1862; *found*: 321.1861; $\mathbf{R_f}$ (10:1 PE/EtOAc): 0.70.

(*Z*)-3-Iodo-2-methylprop-2-en-1-ol 274

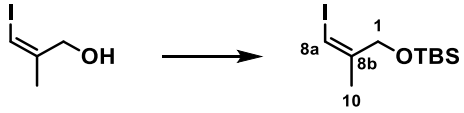


253 274

Propargyl alcohol **253** (2.6 mL, 45.49 mmol, 1.00 eq) was added to CuI (0.87 g, 4.54 mmol, 0.10 eq) in THF (46 mL) at -20 °C, then MeMgBr (3.0 M in Et_2O, 34.0 mL, 100.07 mmol, 2.20 eq) was added dropwise at -20 °C. The mixture was allowed to warm to -10 °C over 30 min and then iodine (11.55 g, 45.49 mmol, 1.00 eq) in THF (10.1 mL) and Et_2O (10.1 mL) was added dropwise at -10 °C. The resulting mixture was allowed to warm to rt and stirred at rt for 30 min. The reaction was terminated by addition of a 1:1 mixture of brine and a sat. aq. NH_4Cl-solution (100 mL), the layers were separated, the aq. layer was extracted with Et_2O (3x 100 mL), the comb. org. layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give crude alcohol **274** (6.29 g, 31.79 mmol, 70%) as a yellow oil which was directly submitted for the next reaction without further purification. The analytical data match those reported in the literature.[214]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.98 (t, J = 0.74 Hz, 1H, H-8b), 4.25 (s, 2H, H-1), 1.98 (d, J = 1.40 Hz, 3H, H-10), 1.53 (bs, 1H, OH) ppm; **R_f** (10:1 PE/EtOAc): 0.19.

(*Z*)-*tert*-Butyl((3-iodo-2-methylallyl)oxy)dimethylsilane 275

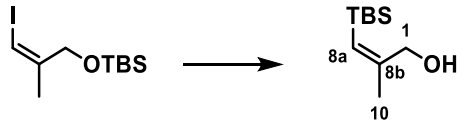


274 275

Imidazole (2.38 g, 35.00 mmol, 1.00 eq) and TBSCl (5.28 g, 35.00 mmol, 1.10 eq) were added to a solution of alcohol **274** (6.3 g, 31.82 mmol, 1.00 eq) in THF (64 mL) at 0 °C. The resulting mixture was allowed to warm to rt and stirred at rt overnight. The mixture was filtered over a glass frit and washed with THF (50 mL) and the filtrate was concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1 – 10:1) yielded iodide **275** (8.32 g, 26.65 mmol, 84%) as a yellow oil. The analytical data match those reported in the literature.[214]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.86 (d, J = 1.57 Hz, 1H, H-8a), 4.24 (s, 2H, H-1), 1.91 (s, 3H, H-10), 0.91 (s, 9H, TBS), 0.10 (s, 6H, TBS) ppm; **R_f** (10:1 PE/EtOAc): 0.86.

(*Z*)-3-(*tert*-Butyldimethylsilyl)-2-methylprop-2-en-1-ol 276



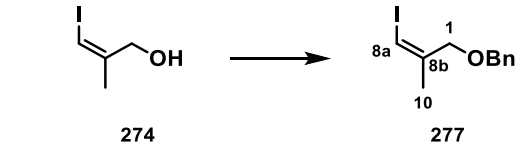
275 276

*n*BuLi (2.5 M in hex, 0.71 mL, 1.76 mmol, 1.10 eq) was added dropwise to a stirred solution of iodide **275** (0.50 g, 1.60 mmol, 1.00 eq) in THF (0.4 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 1 h, then paraformaldehyde (96.2 mg, 3.20 mmol, 2.00 eq) was added in one portion at -78 °C. The resulting mixture was allowed to warm to rt and stirred at rt for 20 min. The reaction was terminated by addition of water (2 mL), the layers were separated and the aq. layer was extracted with CH_2Cl_2 (3x 5 mL), the comb. org. layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded alcohol **276** (227.4 mg, 1.22 mmol, 76%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.43 (d, J = 1.52 Hz, 1H, H-8a), 4.12 (s, 2H, H-1), 1.96 (d, J = 1.60 Hz, 3H, H-10), 1.25 (bs, 1H, OH), 0.88 8s, 9H, TBS), 0.09 (s, 6H, TBS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 205.1 (t, C-8a), 42.7 (s, C-1), 26.5 (p, TBS), 16.6 (p, C-10), 13.3 (q, TBS),

-4.8 (p, TBS), -5.7 (p, TBS) ppm;[3] **GC-MS:** *m/z calc.* for $C_6H_{13}OSiNa$ $[M\text{-}t\text{Bu}]^+$: 129.0736; *found*: 129.0736; $\mathbf{R_f}$ (10:1 PE/EtOAc): 0.31.

(*Z*)-(((3-Iodo-2-methylallyl)oxy)methyl)benzene 277

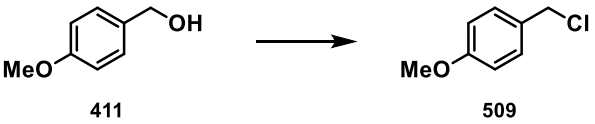


274 277

NaH (60% on mineral oil, 202.0 mg, 5.05 mmol, 2.00 eq) was added in one portion to a stirred solution of alcohol **274** (0.50 g, 2.52 mmol, 1.00 eq) in THF (12.6 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 1 h. BnBr (330.0 µL, 2.78 mmol, 1.10 eq) at 0 °C and the mixture was allowed to warm to rt and stirred at rt for 1 h. The reaction was terminated by addition of aq. 2 M HCl (2 mL), diluted with water (10 mL) and the aq. layer was extracted with Et_2O (3x 10 mL), the comb. org. layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1) yielded iodide **277** (0.66 g, 2.31 mmol, 91%) as a colorless oil. The analytical data match those reported in the literature.[215]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.41-7.30 (m, 5H, Bn), 6.08 (s, 1H, H-8a), 4.51-4.50 (m, 2H, Bn), 4.18 (s, 2H, H-1), 1.98 (d, *J* = 1.17 Hz, 3H, H-10) ppm; $\mathbf{R_f}$ (50:1 PE/EtOAc): 0.41.

1-(Chloromethyl)-4-methoxybenzene 509



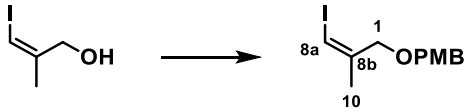
411 509

Alcohol **411** (9.1 mL, 72.37 mmol, 1.00 eq) was added slowly to stirred conc. HCl (18 mL) at rt and the resulting mixture was stirred at rt for 15 min. The reaction was terminated by dilution with PE (50 mL), the layers were separated and the org. layer was washed with a sat. aq. $NaHCO_3$-solution (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give crude chloride **509** (10.46 g, 66.77 mmol, 92%) as a colorless oil. The analytical data match those reported in the literature.[216]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.32 (d, *J* = 8.64 Hz, 2H, Ar), 6.88 (d, *J* = 8.64 Hz, 2H, Ar), 4.57 (s, 2H, CH_2), 3.81 (s, 3H, OMe) ppm.

[3] A signal for C-8b was not found, presumably due to relaxation properties of this molecule. The assignment is tentative and was done based on literature precedence for similar vinylsilanes.

(*Z*)-1-(((3-Iodo-2-methylallyl)oxy)methyl)-4-methoxybenzene 278

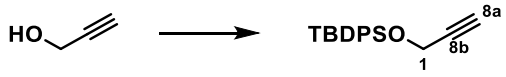


274 278

NaH (60% on mineral oil, 0.53 g, 13.37 mmol, 2.00 eq) was added in one portion to a stirred solution of alcohol **274** (1.32 g, 6.69 mmol, 1.00 eq) in THF (34.0 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min, then PMBCl (1.15 g, 7.35 mmol, 1.00 eq) was added dropwise at 0 °C. The mixture was allowed to warm to rt and stirred at rt overnight. The reaction was terminated by addition of aq. 2 M HCl (10 mL), diluted with water (20 mL), the layers were separated, the aq. layer was extracted with Et_2O (3x 30 mL), the comb. org. layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 50:1 – 20:1) yielded iodide **278** (1.19 g, 3.73 mmol, 56%) as a yellow oil. The analytical data match those reported in the literature.[217]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.56 Hz, 2H, PMB), 6.89 (d, *J* = 8.60 Hz, 2H, PMB), 6.06 (s, 1H, H-8a), 4.42 (s, 2H, PMB), 4.14 (s, 2H, H-a), 3.81 (s, 3H, PMB), 1.95 (d, *J* = 1.36 Hz, 3H, H-10) ppm; **R_f** (20:1 PE/EtOAc): 0.30.

***tert*-Butyldiphenyl(prop-2-yn-1-yloxy)silane 281**



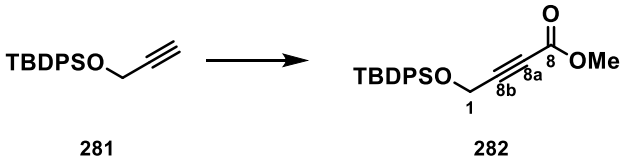
253 281

TBDPSCl (7.7 mL, 29.43 mmol, 1.10 eq) and imidazole (2.00 g, 29.43 mmol, 1.10 eq) were added to a stirred solution of propargyl alcohol **253** (1.6 mL, 26.76 mmol, 1.00 eq) in CH_2Cl_2 (54 mL) at 0 °C. The resulting mixture was allowed to warm to rt overnight. The reaction was terminated by addition of water (50 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 50 mL), the comb. org. layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1) yielded alkyne **281** (7.84 g, 26.63 mmol, *quant.*) as a white amorphous solid. The analytical data match those reported in the literature.[218]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.72-7.70 (m, 4H, TBDPS), 7.46-7.38 (m, 6H, TBDPS), 4.31 (d, *J* = 2.32 Hz, 2H, H-1), 2.39 (t, *J* = 2.38 Hz, 1H, H-8a), 1.07 (s, 9H, TBDPS) ppm.

R_f (20:1 PE/EtOAc): 0.72; **mp.:** 59 °C.

Methyl 4-((*tert*-butyldiphenylsilyl)oxy)but-2-ynoate 282

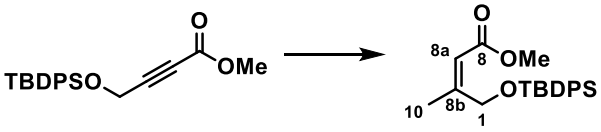


281 282

*n*BuLi (2.5 M in hex, 10.2 mL, 25.55 mmol, 1.10 eq) was added dropwise to a stirred solution of alkyne **281** (6.84 g, 23.23 mmol, 1.00 eq) in THF (100 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 1 h, then methylchloroformiate (2.0 mL, 25.55 mmol, 1.10 eq) was added dropwise at -78 °C and the mixture was allowed to warm to rt and stirred at rt for 2 h. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (100 mL), the layers were separated, the aq. layer was extracted with EtOAc (3x 100 mL), the comb. org. layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1) yielded ester **282** (7.47 g, 21.15 mmol, 91%) as a white amorphous solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.70-7.68 (m, 4H, TBDPS), 7.47-7.38 (m, 6H, TBDPS), 4.40 (s, 2H, H-1), 3.78 (s, 3H, OMe), 1.06 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 153.9 (q, C-8), 135.7 (t, TBDPS), 132.5 (q, TBDPS), 130.2 (t, TBDPS), 128.0 (t, TBDPS), 86.0 (q, C-8b), 76.6 (q, C-8a), 52.9 (s, C-1), 52.4 (p, OMe), 26.8 (p, TBDPS), 19.3 (q, TBDPS) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{21}H_{24}O_3SiNa$ $[M+Na]^+$: 375.1392; *found*: 375.1394; **R_f** (20:1 PE/EtOAc): 0.47; **mp.:** 52 °C.

Methyl (*Z*)-4-((*tert*-butyldiphenylsilyl)oxy)-3-methylbut-2-enoate 283



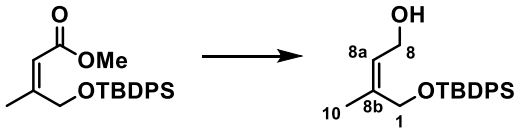
282 283

MeLi (1.6 M in Et_2O, 11.8 mL, 18.72 mmol, 2.20 eq) was added dropwise to a stirred solution of CuI (1.78 g, 9.36 mmol, 1.10 eq) in THF (31 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min, then it was cooled to -78 °C and ester **282** (3.00 g, 8.51 mmol, 1.00 eq) in THF (17.0 mL) was added dropwise at -78 °C. The resulting mixture was stirred at -78 °C for 2 h. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (30 mL) at -78 °C, then it was warmed to rt. The layers were separated, the aq. layer was extracted with Et_2O (3x 30 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1) yielded enone **283** (2.93 g, 7.96 mmol, 93%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.67-7.64 (m, 4H, TBDPS), 7.42-7.35 (m, 6H, TBDPS), 5.65 (d, *J* = 1.32 Hz, 1H, H-8a), 4.86 (s, 2H, H-1), 3.57 (s, 3H, OMe), 2.08 (s, 3H, H-10), 1.08 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 166.3 (q, C-8), 160.5 (q, C-8b), 135.7 (t, TBDPS),

133.6 (q, TBDPS), 129.8 (t, TBDPS), 127.8 (t, TBDPS), 114.8 (t, C-8a), 63.8 (p, OMe), 51.0 (s, C-1), 27.0 (p, TBDPS), 21.8 (p, C-10), 19.5 (q, TBDPS) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{22}H_{28}O_3SiNa$ $[M+Na]^+$: 391.1705; *found*: 391.1707; $\mathbf{R_f}$ (20:1 PE/EtOAc): 0.47.

(*Z*)-4-((*tert*-Butyldiphenylsilyl)oxy)-3-methylbut-2-en-1-ol 284

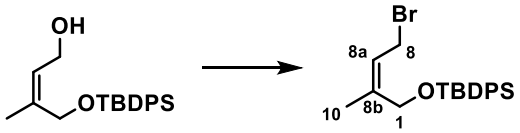


283 284

DIBAL-H (1.0 M in hex, 24.0 mL, 23.85 mmol, 3.00 eq) was quickly added to a stirred solution of enone **283** (2.93 g, 7.95 mmol, 1.00 eq) at -78 °C and the resulting mixture was stirred at -78 °C for 5 min. The reaction was terminated by addition of MeOH (10 mL) at -78 °C and the mixture was diluted with CH_2Cl_2 (100 mL) and an aq. 10% Rochelle salt-solution (100 mL), warmed to rt and stirred at rt for 1 h. The layers were separated and the aq. layer was extracted with CH_2Cl_2 (3x 100 mL), the comb. org. layers were washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1 – 5:1) yielded allyl alcohol **284** (2.66 g, 7.83 mmol, 98%) as a colorless oil. The analytical data match those reported in the literature.[219]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.69-7.67 (m, 4H, TBDPS), 7.44-7.37 (m, 6H, TBDPS), 5.46 (t, *J* = 6.96 Hz, 1H, H-8a), 4.19 (s, 2H, H-1), 3.92 (bs, 2H, H-8), 1.83 (s, 3H, H-10), 1.22 (bs, 1H, OH), 1.05 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 138.6 (q, C-8b), 135.8 (t, TBDPS), 133.5 (q, TBDPS), 129.9 (t, TBDPS), 127.9 (t, TBDPS), 125.8 (t, C-8a), 62.9 (s, C-1), 58.7 (s, C-8), 26.9 (p, TBDPS), 21.5 (p, C-10), 19.3 (q, TBDPS) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{22}H_{28}O_3SiNa$ $[M+Na]^+$: 363.1756; *found*: 363.1757; $\mathbf{R_f}$ (10:1 PE/EtOAc): 0.23.

(*Z*)-((4-Bromo-2-methylbut-2-en-1-yl)oxy)(*tert*-butyl)diphenylsilane 285

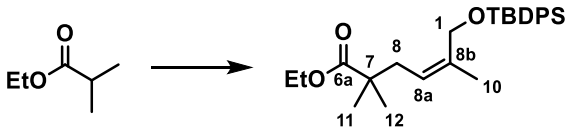


284 285

PBr_3 (140.0 µL, 1.47 mmol, 0.50 eq) was added dropwise to a stirred solution of allyl alcohol **284** (1.00 g, 2.94 mmol, 1.00 eq) in Et_2O (15.0 mL) at 0 °C. The resulting mixture was allowed to warm to rt and stirred at rt for 30 min, then the reaction was terminated by addition of brine (20 mL). The layers were separated, the aq. layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give crude bromide **285** (1.10 g, 2.72 mmol, 93%) as a colorless oil which was directly submitted for the next reaction.

HRMS (EI-GCT): *m/z calc.* for $C_{17}H_{18}OSiBrNa$ $[M\text{-}tBu]^+$: 345.0310; *found*: 345.0310; $\mathbf{R_f}$ (20:1 PE/EtOAc): 0.71.

Ethyl (*Z*)-6-((*tert*-butyldiphenylsilyl)oxy)-2,2,5-trimethylhex-4-enoate 286

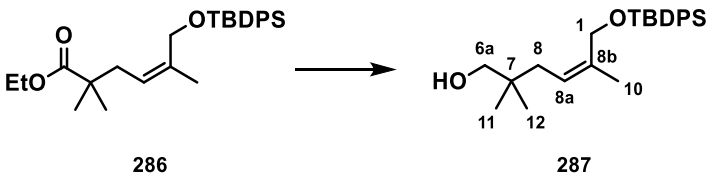


192 286

*n*BuLi (2.5 M in hex, 1.2 mL, 2.94 mmol, 1.10 eq) was added dropwise to a stirred solution of DIPA (0.45 mL, 3.20 mmol, 1.20 eq) in THF (3.2 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 10 min, then ester **192** (0.36 mL, 2.67 mmol, 1.00 eq) in THF (5.4 mL) was added dropwise at -78 °C. The resulting mixture was stirred at -78 °C for 1 h, then bromide **285** (1.08 g, 2.67 mmol, 1.00 eq) was added dropwise at -78 °C. The mixture was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (10 mL), the layers were separated, the aq. layer was extracted with EtOAc (3x 10 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 50:1 – 20:1) yielded ester **286** (0.76 g, 1.73 mmol, 65% *o2s*) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.70-7.67 (m, 4H, TBDPS), 7.45-7.37 (m, 6H, TBDPS), 5.12 (t, *J* = 8.30 Hz, 1H, H-8a), 4.15 (s, 2H, H-a), 4.05 (q, *J* = 7.12 Hz, 2H, Et), 2.03 (d, *J* = 8.48 Hz, 2H, H-8), 1.83 (s, 3H, H-10), 1.18 (t, *J* = 7.15 Hz, 3H, Et), 1.05-1.04 (m, 15H, TBDPS, H-11, H-12) ppm;
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 177.7 (q, C-6a), 137.2 (q, C-8b), 135.8 (t, TBDPS), 133.9 (q, TBDPS), 129.7 (t, TBDPS), 127.8 (t, TBDPS), 122.0 (t, C-8a), 62.6 (s, C-1), 60.4 (s, Et), 42.5 (q, C-7), 38.1 (s, C-8), 27.0 (p, TBDPS), 24.9 (p, C-11, C-12), 19.4 (p, C-10), 14.3 (q, TBDPS) ppm;
HRMS (ESI-LCT): *m/z calc.* for $C_{27}H_{38}O_3SiNa$ $[M+Na]^+$: 461.2488; *found*: 461.2487; $\mathbf{R_f}$ (10:1 PE/EtOAc): 0.58.

(*Z*)-6-((*tert*-Butyldiphenylsilyl)oxy)-2,2,5-trimethylhex-4-en-1-ol 287



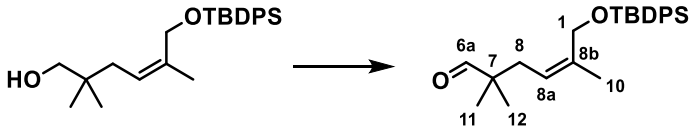
286 287

DIBAL-H (1.0 M in hex, 8.4 mL, 8.34 mmol, 3.00 eq) was quickly added to a stirred solution of ester **286** (1.22 g, 2.78 mmol, 1.00 eq) in CH_2Cl_2 (8.4 mL) at -78 °C. The mixture was stirred at -78 °C for 5 min. The reaction was terminated by addition of MeOH (3 mL) at -78 °C, then the mixture was diluted with CH_2Cl_2 (30 mL) and an aq. 10% Rochelle salt-solution (30 mL) and the mixture

was allowed to warm to rt and stirred at rt for 1 h. The layers were separated and the aq. layer was extracted with CH_2Cl_2 (3x 30 mL), the comb. org. layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1 – 5:1) yielded alcohol **287** (1.07 g, 2.69 mmol, 97%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.71-7.68 (m, 4H, TBDPS), 7.45-7.37 (m, 6H, TBDPS), 5.30 (t, *J* = 7.76 Hz, 1H, H-8a), 4.16 (s, 2H, H-1), 3.23 (d, *J* = 6.52 Hz, 2H, H-6a), 1.83 (d, *J* = 8.12 Hz, 2H, H-8), 1.78 (s, 3H, H-10), 1.26 (t, *J* = 7.17 Hz, 1H, OH), 1.06 (s, 9H, TBDPS), 0.82 (s, 6H, H-11, H-12) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 136.2 (q, C-8b), 135.9 (t, TBDPS), 133.7 (q, TBDPS), 129.8 (t, TBDPS), 127.8 (t, TBDPS), 123.9 (t, C-8a), 71.3 (s, C-6a), 62.6 (s, C-1), 36.3 (s, C-8), 36.2 (q, C-7), 27.0 (p, TBDPS), 24.2 (p, C-11, C-12), 22.0 (p, C-10), 19.4 (q, TBDPS) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{25}H_{36}O_2SiNa$ $[M+Na]^+$: 419.2382; *found*: 419.2383; **R_f** (10:1 PE/EtOAc): 0.26.

(*Z*)-6-((*tert*-Butyldiphenylsilyl)oxy)-2,2,5-trimethylhex-4-enal 288

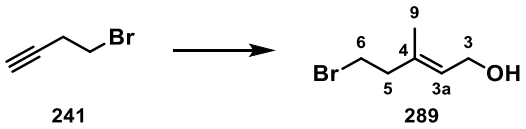


287 288

DMSO (0.58 mL, 8.07 mmol, 3.00 eq) was added dropwise to a stirred solution of oxalylchloride (0.35 mL, 4.04 mmol, 1.50 eq) in CH_2Cl_2 (10.2 mL) at -78 °C. The mixture was stirred at -78 °C for 10 min, then alcohol **287** (1.07 g, 2.69 mmol, 1.00 eq) in CH_2Cl_2 (6.8 mL) was added dropwise at -78 °C, the resulting mixture was stirred at -78 °C for 15 min, then NEt_3 (1.2 mL, 8.07 mmol, 3.00 eq) was added dropwise at -78 °C. The resulting mixture was allowed to warm to rt and stirred at rt for 30 min. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (20 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1) yielded aldehyde **288** (0.96 g, 2.44 mmol, 91%) as a colorless oil

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.35 (s, 1H, H-6a), 7.69-7.67 (m, 4H, TBDPS), 7.44-7.37 (m, 6H, TBDPS), 5.09 (t, *J* = 7.19 Hz, 1H, H-8a), 4.15 (s, 2H, H-1), 1.95 (d, *J* = 7.60 Hz, 2H, H-8), 1.83 (s, 3H, H-10), 1.05 (s, 9H, TBDPS), 0.94 (s, 6H, H-11, H-12) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 206.2 (t, C-6a), 137.9 (q, C-8b), 135.8 (t, TBDPS), 133.8 (q, TBDPS), 129.8 (t, TBDPS), 127.8 (t, TBDPS), 120.7 (t, C-8a), 62.5 (s, C-1), 46.3 (q, C-7), 34.8 (s, C-8), 26.9 (p, TBDPS), 21.6 (p, C-10), 21.2 (p, C-11, C-12), 19.4 (q, TBDPS) ppm; **GC-MS:** *m/z calc.* for $C_{21}H_{25}O_2SiNa$ $[M-tBu]^+$: 337.1624; *found*: 337.1621; **R_f** (50:1 PE/EtOAc): 0.32.

(*E*)-5-Bromo-3-methylpent-2-en-1-ol 289

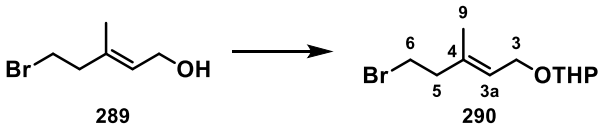


241 289

$AlMe_3$ (2.0 M in hex, 2.8 mL, 5.64 mmol, 2.50 eq) was added dropwise to a stirred solution of Cp_2ZrCl_2 (164.9 mg, 0.56 mmol, 0.25 eq) in CH_2Cl_2 (2.3 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min, then alkyne **241** (0.22 mL, 2.26 mmol, 1.00 eq) in CH_2Cl_2 (1.2 mL) was added dropwise at 0 °C. The resulting mixture was allowed to warm to rt overnight. Then it was cooled to 0 °C and paraformaldehyde (0.34 g, 11.28 mmol, 5.00 eq) was added in small portions at 0 °C. The resulting mixture was stirred at 0 °C for 3 h. Then it was slowly transferred onto an ice cooled solution of a aq. 10% HCl (10 mL, carefully, violent exothermic reaction!). The mixture was filtered through a pad of Celite^{TM}, washed with CH_2Cl_2 (30 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1) yielded alcohol **289** (276.3 mg, 1.54 mmol, 68%) as a colorless oil. The analytical data match those reported in the literature.[220]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.49 (dt, *J* = 6.76, 1.00 Hz, 1H, H-3a), 4.18 (d, *J* = 6.76 Hz, 2H, H-3), 3.46 (t, *J* = 7.34 Hz, 2H, H-6), 2.58 (t, *J* = 7.18 Hz, 2H, H-5), 1.70 (s, 3H, H-9), 1.26 (bs, 1H, OH) ppm; $\mathbf{R_f}$ (5:1 PE/EtOAc): 0.19.

(*E*)-2-((5-Bromo-3-methylpent-2-en-1-yl)oxy)tetrahydro-2*H*-pyran 290

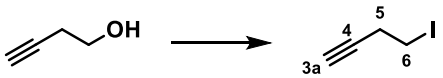


289 290

DHP (170 µL, 1.85 mmol, 1.20 eq) and *p*TsOH·H_2O (5.3 mg, 0.03 mmol, 0.02 eq) were added to a stirred solution of alcohol **289** (276.0 mg, 1.54 mmol, 1.00 eq) in CH_2Cl_2 (5.2 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 0.5 h. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (5 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 10 mL), the comb. org. layers were washed with water (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1) yielded bromide **290** (328.5 mg, 1.25 mmol, 81%) as a colorless oil. The analytical data match those reported in the literature.[220]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.46-5.42 (m, 1H, H-3a), 4.64-4.62 (m, 1H, THP), 4.24 (ddd, *J* = 12.20, 6.25, 0.81 Hz, 1H, H-3), 4.05 (ddd, *J* = 12.18, 7.29, 0.53 Hz, 1H, H-3), 3.91-3.86 (m, 1H, THP), 3.54-3.49 (m, 1H, THP), 3.46 (t, *J* = 7.46 Hz, 2H, H-6), 2.59 (t, *J* = 8.14 Hz, 2H, H-5), 1.85-1.71 (m, 1H, THP), 1.70 (s, 3H, H-9), 1.62-1.50 (m, 5H, THP) ppm; $\mathbf{R_f}$ (20:1 PE/EtOAc): 0.32.

4-Iodobut-1-yne 293

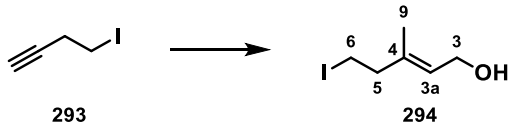


292 293

Mesylchloride (4.8 mL, 59.92 mmol, 1.40 eq) was added dropwise to a stirred solution of alcohol **292** (3.4 mL, 42.80 mmol, 1.00 eq) and NEt_3 (7.8 mL, 55.64 mmol, 1.30 eq) in CH_2Cl_2 (86 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h. The reaction was terminated by addition of aq. 1 M HCl (50 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 50 mL), the comb. org. layers were washed with a sat. aq. $NaHCO_3$-solution (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give crude mesylate which was used directly for the next step. NaI (7.70 g, 51.36 mmol, 1.20 eq) was added in one portion to a stirred solution of the crude mesylate in acetone (110 mL) at rt and the resulting mixture was heated under refluxing conditions for 4 h. The mixture was cooled to rt, the white participate was filtered off and washed with an excess of acetone. The filtrate was concentrated *in vacuo* at 30 °C and 200 mbar, then portioned between Et_2O (50 mL) and an aq. 10% $Na_2S_2O_3$-solution (50 mL), the aq. layer was extracted with Et_2O (2x 50 mL), the comb. org. layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* at 30 °C and 200 mbar. Distillation (65 °C, 80 mbar) yielded iodide **293** (2.35 g, 13.06 mmol, 31%) as a colorless oil. The analytical data match those reported in the literature.[221]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.24 (t, J = 7.26 Hz, 2H, H-6), 2.79 (dt, J = 7.28, 2.40 Hz, 2H, H-5), 2.16 (t, J = 2.57 Hz, 1H, H-3a) ppm; **R_f** (PE): 0.50.

(*E*)-5-Iodo-3-methylpent-2-en-1-ol 294



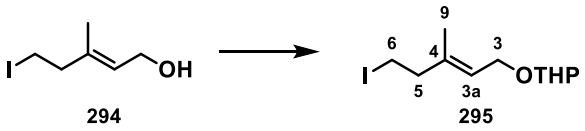
293 294

$AlMe_3$ (2.0 M in hex, 17.0 mL, 32.65 mmol, 2.50 eq) was added dropwise to a stirred solution of Cp_2ZrCl_2 (0.95 g, 3.27 mmol, 0.25 eq) in CH_2Cl_2 (53 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min, then alkyne **293** (2.35 g, 13.06 mmol, 1.00 eq) in CH_2Cl_2 (6.6 mL) was added dropwise at 0 °C. The resulting mixture was allowed to warm to rt overnight. Then it was cooled to 0 °C and paraformaldehyde (1.96 g, 65.31 mmol, 5.00 eq) was added in small portions at 0 °C. The resulting mixture was stirred at 0 °C for 3 h. Then it was slowly transferred onto an ice cooled solution of a aq. 10% HCl (50 mL, carefully, violent exothermic reaction!). The mixture was filtered through a pad of Celite^{TM}, washed with CH_2Cl_2 (30 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 50 mL), the comb. org. layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1) yielded alcohol **294**

(1.24 g, 5.47 mmol, 42%) as a colorless oil. The analytical data match those reported in the literature.[222]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.47 (dt, *J* = 6.77, 1.13 Hz, 1H, H-3a), 4.17 (d, *J* = 6.45 Hz, 2H, H-3), 3.25 (t, *J* = 7.50 Hz, 2H, H-6), 2.57 (t, *J* = 7.52 Hz, 2H, H-5), 1.68 (s, 3H, H-9), 1.26 (bs, 1H, OH) ppm; **R_f** (5:1 PE/EtOAc): 0.33.

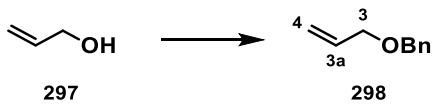
(*E*)-2-((5-Iodo-3-methylpent-2-en-1-yl)oxy)tetrahydro-2*H*-pyran 295



DHP (0.60 mL, 6.56 mmol, 1.20 eq) and *p*TsOH·H_2O (18.8 mg, 0.11 mmol, 0.02 eq) were added to a stirred solution of alcohol **294** (1.24 g, 5.46 mmol, 1.00 eq) in CH_2Cl_2 (19 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 0.5 h. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (20 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 20 mL), the comb. org. layers were washed with water (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1) yielded iodide **295** (1.45 g, 4.67 mmol, 85%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.42 (t, *J* = 6.76 Hz, 1H, H-3a), 4.65-4.63 (m, 1H, THP), 4.23 (dd, *J* = 12.14, 6.26 Hz, 1H, H-3), 4.05 (dd, *J* = 12.18 Hz, 7.30 Hz, 1H, H-3), 3.91-3.86 (m, 1H, THP), 3.54-3.49 (m, 1H, THP), 3.24 (t, *J* = 7.60 Hz, 2H, H-6), 2.59 (t, *J* = 7.58 Hz, 2H, H-5), 1.86-1.71 (m, 1H, THP), 1.68 (s, 3H, H-9), 1.62-1.51 (m, 5H, THP) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 138.3 (q, C-4), 123.6 (t, C-3a), 98.0 (t, THP), 63.5 (s, C-3), 62.5 (s, THP), 43.7 (s, C-5), 30.8 (s, THP), 25.9 (s, THP), 19.8 (s, THP), 15.9 (p, C-9), 3.9 (s, C-6) ppm; **HRMS (EI-GCT):** *m/z calc.* for $C_{11}H_{19}O_2INa$ [M]: 310.0430; *found*: 310.0428; **R_f** (20:1 PE/EtOAc): 0.38.

((Allyloxy)methyl)benzene 298

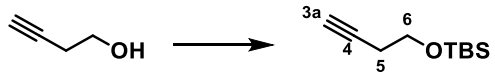


NaH (60% on mineral oil, 1.35 g, 33.57 mmol, 0.65 eq) was added portionwise to a stirred solution of allyl alcohol **297** (3.5 mL, 51.65 mmol, 1.00 eq) in THF (13.0 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 1 h. Then benzylbromide (3.1 mL, 25.83 mmol, 0.50 eq) was added dropwise and the mixture was heated at 75 °C for 1 h. The mixture was cooled to rt and the reaction was terminated by addition of a sat. aq. NH_4Cl-solution (10 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 10 mL), the comb. org. layers were dried over $MgSO_4$, filtered and

concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1) yielded ether **298** (3.63 g, 24.50 mmol, 47%) as a colorless oil. The analytical data match those reported in the literature.[223]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 4.37 Hz, 4H, Bn), 7.31-7.28 (m, 1H, Bn), 6.01-5.92 (m, 1H, H-3a), 5.32 (dd, *J* = 17.24, 1.57 Hz, 1H, H-4 *trans*), 5.21 (d, *J* = 10.36 Hz, 1H, H-4 *cis*), 4.53 (s, 2H, Bn), 4.04 (d, *J* = 5.60 Hz, 2H, H-3) ppm; $\mathbf{R_f}$ (10:1 PE/EtOAc): 0.72.

(But-3-yn-1-yloxy)(*tert*-butyl)dimethylsilane 292

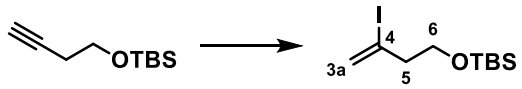


292 299

TBSCl (7.45 g, 49.44 mmol, 1.10 eq) in CH_2Cl_2 (13.5 mL) was added slowly to a stirred solution of alcohol **292** (3.4 mL, 44.94 mmol, 1.00 eq) and imidazole (6.12 g, 89.88 mmol, 2.00 eq) in CH_2Cl_2 (25.0 mL) at 0 °C. The resulting mixture was allowed to warm to rt and stirred at rt for 1.5 h. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (30 mL), the layers were separated and the aq. layer was extracted with CH_2Cl_2 (3x 20 mL), the comb. org. layers were washed with a sat. aq. $NaHCO_3$-solution (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded silyl ether **299** (7.60 g, 41.24 mmol, 92%) as a colorless oil. The analytical data match those reported in the literature.[224]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.74 (t, *J* = 7.15 Hz, 2H, H-6), 2.40 (dt, *J* = 7.21, 2.54 Hz, 2H, H-5), 1.96 (t, *J* = 2.6 Hz, 1H, H-3a), 0.90 (s, 9H, TBS), 0.08 (s, 6H, TBS) ppm; $\mathbf{R_f}$ (10:1 PE/EtOAc): 0.86.

tert-Butyl((3-iodobut-3-en-1-yl)oxy)dimethylsilane 300

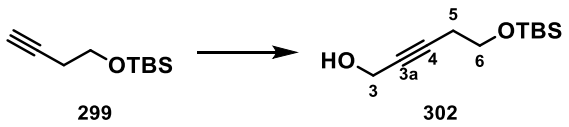


299 300

B-I-9-BBN (1.0 M in hex, 3.3 mL, 3.25 mmol, 1.20 eq) was added dropwise to a stirred solution of alkyne **299** (0.50 g, 2.71 mmol, 1.00 eq) in hexanes (20.0 mL) at 0 °C. The resulting mixture was allowed to warm to rt overnight. Then AcOH (0.54 mL, 9.49 mmol, 3.50 eq) and NaOAc (267.0 mg, 3.25 mmol, 1.20 eq) were added at rt and the mixture was stirred at rt for 1 h. The reaction was terminated by dilution with hexanes (10 mL) and water (10 mL), the layers were separated and the org. layer was successively washed with a sat. aq. $NaHCO_3$-solution (20 mL), water (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (pentanes/Et_2O 20:1) yielded vinyliodide **300** (0.61 g, 1.95 mmol, 72%) as a colorless oil. The analytical data match those reported in the literature.[225]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.08 (d, *J* = 1.22 Hz, 1H, H-3a *trans*), 5.76 (s, 1H, H-3a *cis*), 3.73 (t, *J* = 6.31 Hz, 2H, H-6), 2.59 (t, *J* = 6.27 Hz, 2H, H-5), 0.89 (s, 9H, TBS), 0.07 (s, 6H, TBS) ppm; **R_f** (20:1 PE/EtOAc): 0.85.

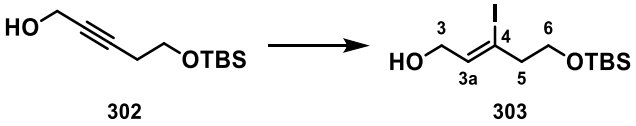
5-((*tert*-Butyldimethylsilyl)oxy)pent-2-yn-1-ol 302



*n*BuLi (2.5 M in hex, 4.8 mL, 11.93 mmol, 1.10 eq) was added dropwise to a stirred solution of alkyne **299** (2.00 g, 10.85 mmol, 1.00 eq) in THF (55 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 30 min, then paraformaldehyde (0.65 g, 21.70 mmol, 2.00 eq) was added in one portion at -78 °C and the mixture was allowed to warm to rt and stirred at rt for further 30 min. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (50 mL), the layers were separated and the aq. layer was extracted with EtOAc (3x 30 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1) yielded alcohol **302** (2.26 g, 10.53 mmol, 97%) as a colorless oil. The analytical data match those reported in the literature.[226]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.24 (dt, *J* = 5.93, 2.07 Hz, 2H, H-3), 3.72 (t, *J* = 7.14 Hz, 2H, H-6), 2.44 (t, *J* = 7.15, 2.07 Hz, 2H, H-5), 0.90 (s, 9H, TBS), 0.07 (s, 6H, TBS) ppm; **R_f** (3:1 PE/EtOAc): 0.72.

(*Z*)-5-((*tert*-Butyldimethylsilyl)oxy)-3-iodopent-2-en-1-ol 303

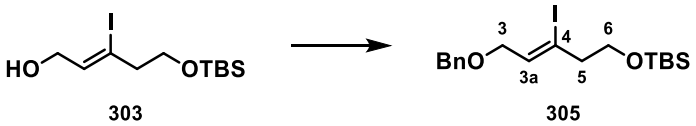


Alcohol **302** (9.85 g, 45.96 mmol, 1.00 eq) in Et_2O (100 mL) was added dropwise to a stirred solution of Red-Al® (3.5 M in PhMe, 40.0 mL, 137.88 mmol, 3.00 eq) and KO*t*Bu (0.52 g, 4.60 mmol, 0.10 eq) in Et_2O (275 mL) at 0 °C. The mixture was allowed to warm to rt and stirred at rt for 2 h. The mixture was cooled to 0 °C and EtOAc (11.5 mL, 114.90 mmol, 2.50 eq) was added dropwise at 0 °C and the resulting mixture was stirred at 0 °C for 15 min before being cooled to -78 °C. Then a solution of iodine (17.50 g, 68.94 mmol, 1.50 eq) in THF (24 mL) was added dropwise at -78 °C and the resulting mixture was stirred at -78 °C for further 10 min. The reaction was terminated by addition of a 1:1 mixture of an aq. 10% $Na_2S_2O_3$-solution and a sat. aq. Rochelle salt-solution (300 mL). The layers were separated, the aq. layer was extracted with Et_2O (3x 200 mL), the comb. org. layers were

washed with brine (400 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1) yielded alcohol **303** (11.72 g, 34.25 mmol, 75%) as a yellow oil. The analytical data match those reported in the literature.[227]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.91 (tt, *J* = 5.89, 1.11 Hz, 1H, H-3a), 4.19 (t, *J* = 5.82 Hz, 2H, H-3), 3.74 (t, *J* = 6.35 Hz, 2H, H-6), 2.71 (dt, *J* = 6.46, 0.77 Hz, 2H, H-5), 1.48 (t, *J* = 5.96 Hz, 1H, OH), 0.88 (s, 9H, TBS), 0.06 (s, 6H, TBS) ppm; $\mathbf{R_f}$ (5:1 PE/EtOAc): 0.50.

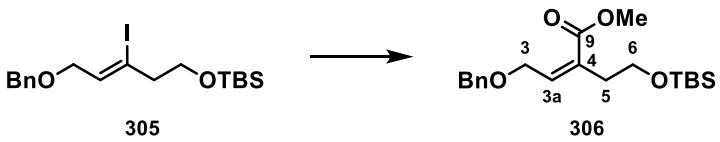
(*Z*)-((5-(Benzyloxy)-3-iodopent-3-en-1-yl)oxy)(*tert*-butyl)dimethylsilane 305



A mixture of alcohol **303** (1.51 g, 4.41 mmol, 1.00 eq), Dudley reagent **312** (3.08 g, 8.82 mmol, 2.00 eq) and proton sponge® (1.89 g, 8.82 mmol, 2.00 eq) in $PhCF_3$ (30 mL) was heated to 83 °C overnight. The reaction mixture was filtered over Celite™ and washed with an excess of CH_2Cl_2, concentrated *in vacuo* and dry loaded on silica. Column chromatography (PE/EtAOc 20:1 – 10:1) yielded benzylether **305** (1.28 g, 2.97 mmol, 67%, 92% brsm) as a brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.37-7.28 (m, 5H, Bn), 5.91 (t, *J* = 5.50 Hz, 1H, H-3a), 4.52 (s, 2H, Bn), 4.09 (d, *J* = 5.51 Hz, 2H, H-3), 3.74 (t, *J* = 6.37 Hz, 2H, H-6), 2.72 (t, *J* = 6.08 Hz, 2H, H-5), 0.88 (s, 9H, TBS), 0.06 (s, 6H, TBS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 138.2 (q, Bn), 134.1 (t, C-3a), 128.5 (t, Bn), 127.9 (t, Bn), 127.8 (t, Bn), 105.6 (q, C-4), 74.7 (s, C-3), 72.6 (s, Bn), 61.9 (s, C-6), 48.5 (s, C-5), 26.0 (p, TBS), 18.4 (q, TBS), -5.1 (p, TBS) ppm; **HRMS (EI-GCT):** *m/z calc.* for $C_{14}H_{22}IO_2Si$ $[M\text{-}t\text{Bu}]^+$: 375.0277; *found*: 375.0270; $\mathbf{R_f}$ (10:1 PE/EtOAc): 0.61.

Methyl (*Z*)-4-(benzyloxy)-2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)but-2-enoate 306

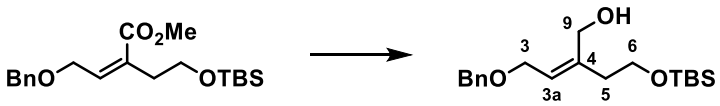


$PdCl_2(PPh_3)_2$ (16.2 mg, 0.02 mmol, 0.10 eq) was added to a by bubbling argon with a balloon under ultra-sonication through degassed solution of vinyliodide **305** (100.0 mg, 0.23 mmol, 1.00 eq), NEt_3 (320 µL, 2.31 mmol, 10.00 eq), PPh_3 (60.7 mg, 0.23 mmol, 1.00 eq) in DMF (2.3 mL) and MeOH (2.3 mL). The atmosphere was exchanged with CO by bubbling it from a balloon through the solution while stirring for 5 min. Then the mixture was heated to 70 °C overnight under an atmosphere of CO in a balloon. The mixture was cooled to 0 °C and the reaction was terminated by addition of a sat. aq. NH_4Cl-solution (5 mL). The mixture was diluted by addition of EtOAc (5 mL), the layers were separated and the aq. layer was extracted with EtOAc (3x 10 mL), the comb. org. layers were washed

with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1) yielded enone **306** (59.5 mg, 0.16 mmol, 71%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.37-7.28 (m, 5H, Bn), 6.23 (t, *J* = 4.90 Hz, 1H, H-3a), 4.54 (s, 2H, Bn), 4.48 (d, *J* = 4.87 Hz, 2H, H-3), 3.72 (s, 3H, CO_2Me), 3.69 (t, *J* = 6.77 Hz, 2H, H-6), 2.50 (t, *J* = 6.48 Hz, 2H, H-5), 0.88 (s, 9H, TBS), 0.02 (s, 6H, TBS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 167.5 (q, C-9), 144.2 (t, C-3a), 138.2 (q, Bn), 128.5 (t, Bn), 127.92 (q, C-4), 127.88 (t, Bn), 127.8 (t, Bn), 72.9 (s, Bn), 69.2 (s, C-3), 62.4 (s, C-6), 51.6 (p, CO_2Me), 37.2 (s, C-5), 26.0 (p, TBS), 18.5 (q, TBS), -5.2 (p, TBS) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{20}H_{32}O_4SiNa$ $[M+Na]^+$: 387.1968; *found*: 387.1964; **R_f** (10:1 PE/EtOAc): 0.68.

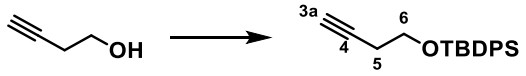
(*Z*)-4-(Benzyloxy)-2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)but-2-en-1-ol 308



DIBAL-H (1.0 M in hex, 1.8 mL, 1.77 mmol, 3.00 eq) was quickly added to a stirred solution of enone **306** (215.1 mg, 0.59 mmol, 1.00 eq) in CH_2Cl_2 (2.0 mL) at -78 °C. The mixture was stirred at -78 °C for 5 min. The reaction was terminated by addition of MeOH (0.2 mL) at -78 °C, then the mixture was diluted with a 1:1 mixture of EtOAc and a sat. aq. Rochelle salt-solution (20 mL) and allowed to warm to rt and stirred at rt for 1 h. The layers were separated, the aq. layer was extracted with EtAOc (3x 10 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1 – 5:1) yielded allyl alcohol **308** (148.0 mg, 0.44 mmol, 75%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.35-7.27 (m, 5H, Bn), 5.57 (t, *J* = 6.64 Hz, 1H, H-3a), 4.51 (s, 2H, Bn), 4.10 (dd, *J* = 12.86, 6.29 Hz, 4H, H-3, H-9), 3.76 (t, *J* = 5.74 Hz, 2H, H-6), 3.43 (t, *J* = 6.09 Hz, 1H, OH), 2.39 (t, *J* = 5.71 Hz, H-5), 0.90 (s, 9H, TBS), 0.08 (s, 6H, TBS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 142.5 (q, C-4), 138.3 (q, Bn), 128.6 (t, Bn), 128.0 (t, Bn), 127.8 (t, Bn), 125.6 (t, C-3a), 72.5 (s, Bn), 66.0 (s, C-3), 64.2 (s, C-9), 60.8 (s, C-6), 39.1 (s, C-5), 26.0 (p, TBS), 18.4 (q, TBS), -5.4 (p, TBS) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{19}H_{32}O_3SiNa$ $[M+Na]^+$: 359.2019; *found*: 359.2021; **R_f** (10:1 PE/EtOAc): 0.24.

(But-3-yn-1-yloxy)(*tert*-butyl)diphenylsilane 317

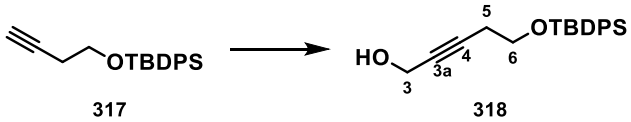


292 317

TBDPSCl (12.5 mL, 47.08 mmol, 1.10 eq) and imidazole (5.83 g, 85.60 mmol, 2.00 eq) were subsequently added to a stirred solution of alcohol **292** (3.3 mL, 42.80 mmol, 1.00 eq) in DMF (43 mL) at rt and stirred overnight at rt. The reaction was terminated by addition of water (20 mL), the layers were separated, the aq. layer was extracted with EtOAc (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded silylether **317** (13.69 g, 42.8 mmol, *quant.*) as a colorless oil. The analytical data match those reported in the literature.[228]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.69-7.67 (m, 4H, TBDPS), 7.45-7.36 (m, 6H, TBDPS), 3.79 (t, *J* = 7.04 Hz, 2H, H-6), 2.45 (dd, *J* = 7.02, 2.96 Hz, 2H, H-5), 1.95 (t, *J* = 2.68 Hz, 1H, H-3a), 1.06 (s, 9H, TBDPS) ppm; $\mathbf{R_f}$ (10:1 PE/EtOAc): 0.73.

5-((*tert*-Butyldiphenylsilyl)oxy)pent-2-yn-1-ol 318

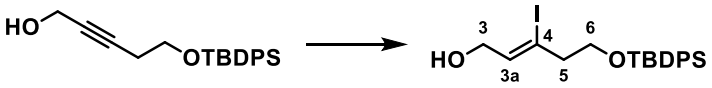


317 318

*n*BuLi (1.6 M in hex, 19.5 mL, 30.84 mmol, 1.10 eq) was added dropwise to a stirred solution of alkyne **317** (8.65 g, 28.04 mmol, 1.00 eq) in THF (140 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 30 min, then paraformaldehyde (1.68 g, 56.07 mmol, 2.00 eq) was added in one portion at -78 °C and the mixture was allowed to warm to rt and stirred at rt for further 30 min. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (100 mL), the layers were separated and the aq. layer was extracted with EtOAc (3x 100 mL), the comb. org. layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1) yielded alcohol **318** (7.08 g, 20.91 mmol, 75%, 87% brsm) as a colorless oil. The analytical data match those reported in the literature.[229]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.69-7.67 (m, 4H, TBDPS), 7.45-7.36 (m, 6H, TBDPS), 4.20 (dt, *J* = 5.99, 2.14 Hz, 2H, H-3), 3.77 (t, *J* = 7.04 Hz, 2H, H-6), 2.48 (tt, *J* = 7.00, 3.32 Hz, H-5), 1.37 (t, *J* = 6.08 Hz, 1H, OH), 1.06 (s, 9H, TBDPS) ppm; $\mathbf{R_f}$ (5:1 PE/EtOAc): 0.43.

(*Z*)-5-((*tert*-Butyldiphenylsilyl)oxy)-3-iodopent-2-en-1-ol 319

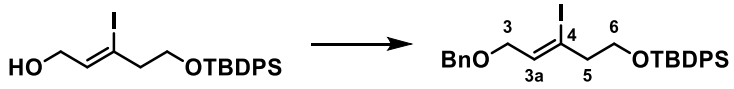


318 319

Red-Al® (3.5 M in PhMe, 4.5 mL, 15.86 mmol, 2.00 eq) was added dropwise to a stirred solution of alcohol **318** (2.68 g, 7.93 mmol, 1.00 eq) in Et_2O (28.0 mL) at 0 °C. The mixture was allowed to warm to rt and stirred at rt for 1 h. Then, the mixture was cooled to 0 °C and EtOAc (0.78 mL, 7.93 mmol, 1.00 eq) was added dropwise at 0 °C and the resulting mixture was stirred at 0 °C for 10 min before being cooled to -78 °C. Then iodine (3.02 g, 11.89 mmol, 1.50 eq) was added portionwise at -78 °C and the resulting mixture was allowed to warm to rt in a water bath over 30 min. The reaction was terminated by addition of a 1:1 mixture of an aq. 10% $Na_2S_2O_3$-solution and a sat. aq. Rochelle salt-solution (50 mL). The layers were separated, the aq. layer was extracted with Et_2O (3x 50 mL), the comb. org. layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1) yielded alcohol **319** (3.52g, 7.55 mmol, 95%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.67-7.65 (m, 4H, TBDPS), 7.46-7.37 (m, 6H, TBDPS), 5.91 (tt, *J* = 5.89, 1.55 Hz, 1H, H-3a), 4.18 (t, *J* = 5.91 Hz, 2H, H-3), 3.80 (t, *J* = 6.18 Hz, 2H, H-6), 2.74 (t, *J* = 6.08 Hz, 2H, H-5), 1.42 (t, *J* = 6.03 Hz, 1H, OH), 1.04 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 136.0 (q, TBDPS), 135.8 (t, TBDPS), 133.7 (t, C-3a), 129.8 (t, TBDPS), 127.8 (t, TBDPS), 105.7 (q, C-4), 67.5 (s, C-3), 62.4 (s, C-6), 48.2 (s, C-5), 27.0 (p, TBDPS), 19.4 (q, TBDPS) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{21}H_{27}IO_2SiNa$ $[M+Na]^+$: 489.0723; *found*: 489.0732; $\mathbf{R_f}$ (5:1 PE/EtOAc): 0.35.

(*Z*)-((5-(benzyloxy)-3-iodopent-3-en-1-yl)oxy)(*tert*-butyl)diphenylsilane 320



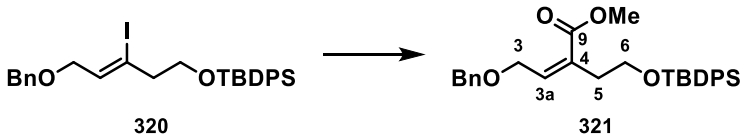
319 320

A mixture of alcohol **319** (2.10 g, 4.50 mmol, 1.00 eq), Dudley reagent **312** (3.14 g, 9.00 mmol, 2.00 eq) and proton sponge® (1.93 g, 9.00 mmol, 2.00 eq) in $PhCF_3$ (30 mL) was heated to 83 °C overnight. The reaction mixture was filtered over Celite™ and washed with an excess of CH_2Cl_2, concentrated *in vacuo* and dry loaded on silica. Column chromatography (PE/EtAOc 20:1 – 10:1) yielded benzylether **320** (1.59 g, 2.86 mmol, 64%, 87% brsm) as a light brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.67-7.65 (m, 4H, TBDPS), 7.44-7.28 (m, 11H, TBDPS, Bn), 5.93 (tt, *J* = 5.40, 1.13 Hz, 1H, H-3a), 4.52 (s, 2H, Bn), 4.10 (d, *J* = 5.51 Hz, 2H, H-3), 3.79 (t, *J* = 6.24 Hz, 2H, H-6), 2.74 (dt, *J* = 6.15, 0.64 Hz, 2H, H-5), 1.04 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz,**

$CDCl_3$): δ = 138.2 (q, TBDPS), 135.7 (t, TBDPS), 134.3 (t, C-3a), 133.8 (q, Bn), 129.8 (t, Bn), 128.55 (t, TBDPS), 128.53 (t, Bn), 127.9 (t, Bn), 127.8 (t, TBDPS), 105.6 (q, C-4), 74.7 (s, C-3), 72.6 (s, Bn), 62.4 (s, C-6), 48.3 (s, C-5), 27.0 (p, TBDPS), 19.4 (q, TBDPS) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{28}H_{33}IO_2Si$ $[M+Na]^+$: 579.1192; *found*: 579.1217; $\mathbf{R_f}$ (10:1 PE/EtOAc): 0.74.

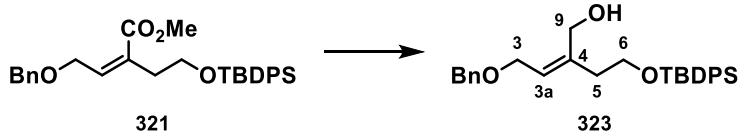
Methyl (*Z*)-4-(benzyloxy)-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)but-2-enoate 321



$PdCl_2(PPh_3)_2$ (119.9 mg, 0.17 mmol, 0.10 eq) was added to a by bubbling argon with a balloon under ultra-sonication through degassed solution of vinyl iodide **320** (0.95 g, 1.71 mmol, 1.00 eq), NEt_3 (2.4 mL, 17.09 mmol, 10.00 eq), PPh_3 (0.90 g, 3.42 mmol, 2.00 eq) in DMF (17 mL) and MeOH (17 mL). The atmosphere was exchanged with CO by bubbling it from a balloon through the solution while stirring for 5 min. Then the mixture was heated to 70 °C overnight under an atmosphere of CO in a balloon. The mixture was cooled to 0 °C and the reaction was terminated by addition of a sat. aq. NH_4Cl-solution (10 mL). The mixture was diluted by addition of EtOAc (10 mL), the layers were separated and the aq. layer was extracted with EtOAc (3x 20 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1) yielded enone **321** (0.81 g, 1.65 mmol, 97%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.65-7.63 (m, 4H, TBDPS), 7.43-7.28 (m, 11H, TBDPS, Bn), 6.24 (t, *J* = 4.83 Hz, 1H, H-3a), 4.53 (s, 2H, Bn), 4.49 (d, *J* = 4.88 Hz, 2H, H-3), 3.74 (t, *J* = 6.45 Hz, 2H, H-6), 3.62 (s, 3H, CO_2Me), 2.54 (dt, *J* = 6.60, 0.80 Hz, 2H, H-5), 1.04 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 167.4 (q, C-9), 144.5 (t, C-3a), 138.2 (q, Bn), 135.7 (t, TBDPS), 133.9 (q, TBDPS), 129.7 (t, TBDPS), 128.5 (t, Bn), 128.4 (q, C-4), 127.9 (t, Bn), 127.8 (t, Bn), 127.7 (t, TBDPS), 72.9 (s, Bn), 69.2 (s, C-3), 63.0 (s, C-6), 51.5 (p, CO_2Me), 36.9 (s, C-5), 27.0 (p, TBDPS), 19.3 (q, TBDPS) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{30}H_{36}O_4SiNa$ $[M+Na]^+$: 511.2281; *found*: 511.2278; $\mathbf{R_f}$ (10:1 PE/EtOAc): 0.50.

(*Z*)-4-(Benzyloxy)-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)but-2-en-1-ol 323

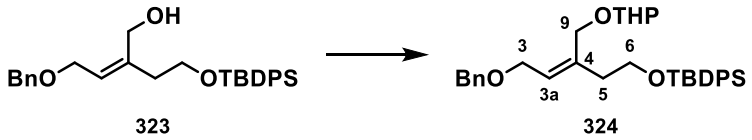


DIBAL-H (1.0 M in hex, 10.0 mL, 9.87 mmol, 3.00 eq) was quickly added to a stirred solution of enone **321** (1.61 g, 3.29 mmol, 1.00 eq) in CH_2Cl_2 (11.0 mL) at -78 °C. The mixture was stirred at -78 °C for 5 min. The reaction was terminated by addition of MeOH (5 mL) at -78 °C, then the

mixture was diluted with a 1:1 mixture of EtOAc and a sat. aq. Rochelle salt-solution (100 mL) and allowed to warm to rt and stirred at rt for 1 h. The layers were separated, the aq. layer was extracted with EtAOc (3x 50 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1 – 5:1) yielded allyl alcohol **323** (1.36 g, 2.96 mmol, 90%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.67-7.65 (m, 4H, TBDPS), 7.45-7.27 (m, 11H, TBDPS, Bn), 5.57 (t, *J* = 6.66 Hz, 1H, H-3a), 4.52 (s, 2H, Bn), 4.14 (d, *J* = 5.92 Hz, 2H, H-3), 4.09 (d, *J* = 6.64 Hz, 2H, H-9), 3.77 (t, *J* = 5.88 Hz, 2H, H-6), 3.01 (t, *J* = 6.26 Hz, 1H, OH), 2.41 (t, *J* = 5.88 Hz, 2H, H-5), 1.05 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 142.1 (q, C-4), 138.2 (q, Bn), 135.7 (t, TBDPS), 133.1 (q, TBDPS), 130.0 (t, Bn), 128.6 (t, TBDPS), 128.0 (t, Bn), 127.9 (t, TBDPS), 127.8 (t, Bn), 126.0 (t, C-3a), 72.5 (s, Bn), 65.9 (s, C-9), 64.5 (s, C-6), 61.0 (s, C-3), 38.7 (s, C-5), 26.9 (p, TBDPS), 19.2 (q, TBDPS) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{29}H_{36}O_3SiNa$ $[M+Na]^+$: 483.2331; *found*: 483.2334; **R_f** (5:1 PE/EtOAc): 0.33.

(*Z*)-((5-(Benzyloxy)-3-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)pent-3-en-1-yl)oxy)(*tert*-butyl)diphenylsilane 324

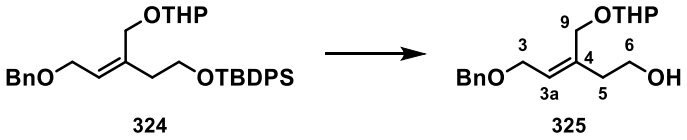


DHP (0.14 mL, 1.55 mmol, 1.20 eq) and *p*TsOH·H_2O (4.4 mg, 0.03 mmol, 0.02 eq) were added to a stirred solution of allyl alcohol **323** (0.59 g, 1.29 mmol, 1.00 eq) in CH_2Cl_2 (4.3 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 10 min. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (5 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 5 mL), the comb. org. layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded protected triol **324** (0.67 g, 1.22 mmol, 95%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.67-7.65 (m, 4H, TBDPS), 7.43-7.24 (m, 11H, TBDPS, Bn), 5.62 (t, *J* = 6.56 Hz, 1H, H-3a), 4.49 (s, 3H, Bn, THP), 4.13-4.09 (m, 3H, H-9, H-3), 3.95-3.93 (m, 1H, H-9), 3.79 (t, *J* = 6.92 Hz, 2H, H-6), 3.76-3.72 (m, 1H, THP), 3.45-3.40 (m, 1H, THP), 2.42 (t, *J* = 6.94 Hz, 2H, H-5), 1.79-1.69 (m, 1H, THP), 1.65-1.45 (m, 5H, THP), 1.04 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 138.5 (q, Bn), 137.0 (q, C-4), 135.7 (t, TBDPS), 134.1 (q, TBDPS), 129.7 (t, TBDPS), 128.5 (t, TBDPS), 127.9 (t, Bn), 127.7 (t, Bn), 127.6 (t, Bn), 127.6 (t, C-3a), 97.7 (t, THP), 72.3 (s, Bn), 66.2 (s, C-3) 64.5 (s, C-9), 63.0 (s, C-6), 62.2 (s, THP), 38.5 (s, C-5), 30.6 (s, THP), 27.0 (p, TBDPS), 25.6 (s, THP), 19.5 (q, TBDPS), 19.3 (s, THP) ppm; **HRMS**

(ESI-LCT): *m/z calc.* for $C_{34}H_{44}O_4SiNa$ $[M+Na]^+$: 567.2907; *found*: 567.2904; $\mathbf{R_f}$ (10:1 PE/EtOAc): 0.34.

(*Z*)-5-(Benzyloxy)-3-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)pent-3-en-1-ol 325

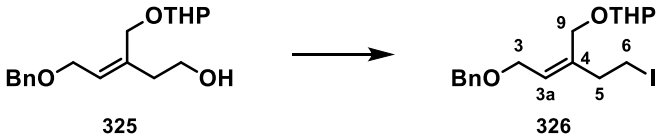


324 325

TBAF (1.0 M in THF, 8.2 mL, 8.20 mmol, 3.00 eq) was added dropwise to a stirred solution of protected triol **324** (1.49 g, 2.73 mmol, 1.00 eq) in THF (28.0 mL) at 0 °C. The resulting mixture was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (20 mL), the layers were separated, the aq. layer was extracted with EtOAc (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 3:1) yielded alcohol **325** (0.78 g, 2.55 mmol, 93%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.35-7.27 (m, 5H, Bn), 5.71 (t, *J* = 6.61 Hz, 1H, H-3a), 4.61 (t, *J* = 3.32 Hz, 1H, THP), 4.51 (s, 2H, Bn), 4.24 (d, *J* = 11.49 Hz, 1H, H-9), 4,12 (d, *J* = 6.65 Hz, 2H, H-3), 4.01 (d, *J* = 11.48 Hz, 1H, H-9), 3.84-3.78 (m, 1H, THP), 3.74 (t, *J* = 5.90 Hz, 2H, H-6), 3.52-3.47 (m, 1H, THP), 2.42 (t, *J* = 5.90 Hz, 2H, H-5), 1.81-1.68 (m, 2H, THP), 1.59-1.51 (m, 4H, THP) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 138.3 (q, Bn), 137.3 (q, C-4), 129.0 (t, C-3a), 128.6 (t, Bn), 128.0 (t, Bn), 127.8 (t, Bn), 98.3 (t, THP), 72.6 (s, Bn), 66.1 (s, C-3), 64.8 (s, C-9), 62.4 (s, THP), 61.9 (s, C-6), 39.8 (s, C-5), 30.5 (s, THP), 25.4 (s, THP), 19.4 (s, THP) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{18}H_{26}O_4Na$ $[M+Na]^+$: 329.1729; *found*: 329.1725; $\mathbf{R_f}$ (1:1 PE/EtOAc): 0.50.

(*Z*)-2-((4-(Benzyloxy)-2-(2-iodoethyl)but-2-en-1-yl)oxy)tetrahydro-2*H*-pyran 326



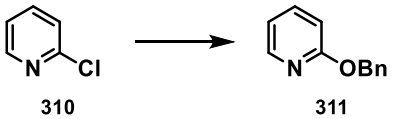
325 326

Imidazole (61.1 mg, 0.90 mmol, 1.10 eq) and iodine (248.5 mg, 0.98 mmol, 1.20 eq) were added to a stirred solution of PPh_3 (256.8 mg, 0.98 mmol, 1.20 eq) in CH_2Cl_2 (2.5 mL). Then a solution of alcohol **325** (250.0 mg, 0.82 mmol, 1.00 eq) in CH_2Cl_2 (1.1 mL) was added dropwise at rt. The resulting mixture was excluded from light and stirred at rt for 2 h. The reaction was terminated by addition of an aq. 10% $Na_2S_2O_3$-solution (2 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 5 mL), the comb. org. layers were washed with brine (5 mL), dried over

$MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1 – 10:1) yielded iodide **326** (290.9 mg, 0.70 mmol, 86%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.35-7.27 (m, 5H, Bn), 5.65 (t, *J* = 6.53 Hz, 1H, H-3a), 4.56 (t, *J* = 3.87 Hz, 1H, THP), 4.52 (s, 2H, Bn), 4.18 (d, *J* = 12.14 Hz, 1H, H-9), 4.11 (d, *J* = 6.53 Hz, 2H, H-3), 4.04 (d, *J* = 12.14 Hz, 1H, H-9), 3.83-3.77 (m, 1H, THP), 3.50-3.48 (m, 1H, THP), 3.31 (t, *J* = 7.37 Hz, 2H, H-6), 2.72 (o, *J* = 7.25 Hz, 2H, H-5), 1.82-1.65 (m, 2H, THP), 1.62-1.56 (m, 4H, THP) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 138.5 (q, C-4), 138.4 (q, Bn), 128.6 (t, Bn), 128.1 (t, C-3a), 128.0 (t, Bn), 127.9 (t, Bn), 97.7 (t, THP), 72.5 (s, Bn), 66.0 (s, C-3), 63.9 (s, C-9), 62.4 (s, THP), 39.9 (s, C-5), 30.7 (s, THP), 25.6 (s, THP), 19.6 (s, THP), 4.5 (s, C-6) ppm; **HRMS (ESI-LCT):** *m/z calc*. for $C_{18}H_{25}O_3Na^{127}I$ $[M+Na]^+$: 439.0746; *found*: 439.0743; $\mathbf{R_f}$ (10:1 PE/EtOAc): 0.37.

2-(Benzyloxy)pyridine 311

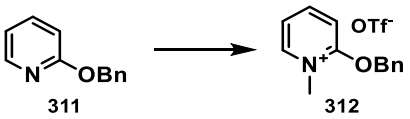


310 311

A mixture of 2-chloropyridine **310** (8.4 mL, 88.07 mmol, 1.00 eq), benzyl alcohol (10.2 mL, 96.88 mmol, 1.10 eq), 18-crown-6 (0.93 g, 3.52 mmol, 0.04 eq) and KOH (9.88 g, 176.15 mmol, 2.00 eq) in PhMe (110 mL) were heated under refluxing conditions for 2 h separating the accumulating water *via* a Dean-Stark trap. The mixture was cooled to rt and the reaction was terminated by addition of ice-cold water (100 mL). The layers were separated, the aq. layer was extracted with EtOAc (3x 50 mL), the comb. org. layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded ether **311** (15.98 g, 86.27 mmol, 98%) as a colorless oil. The analytical data match those reported in the literature.[230]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.19-8.18 (m, 1H, Pyr), 7.61-7.57 (m, 1H, Pyr), 7.48-7.46 (m, 2H, Bn), 7.40-7.36 (m, 2H, Bn), 7.34-7.32 (m, 1H, Bn), 6.90 -6.87 (m, 1H, Pyr), 6.83-6.80 (m, 1H, Pyr), 5.39 (s, 2H, Bn) ppm; $\mathbf{R_f}$ (10:1 PE/EtOAc): 0.50.

2-(Benzyloxy)-1-methylpyridin-1-iumtriflate (Dudley Reagent) 312



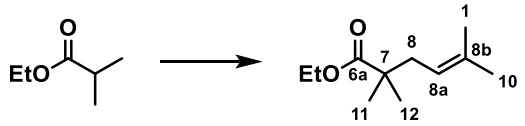
311 312

MeOTf (1.3 mL, 11.34 mmol, 1.05 eq) was added dropwise to a stirred solution of pyridine **311** (2.00 g, 10.80 mmol, 1.00 eq) in PhMe (11.0 mL) at 0 °C. The resulting mixture was allowed to warm to rt over 1 h. The reaction mixture was concentrated *in vacuo* and dried under high vacuum to yield

pure Dudley reagent **312** (3.75 g, 10.73 mmol, 99%) as a white solid which can be used without further purification and was stored at -20 °C until use. The analytical data match those reported in the literature.[129]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.49-8.48 (m, 1H, Pyr), 8.36-8.31 (m, 1H, Pyr), 7.61-7.59 (m, 1H, Pyr), 7.52-7.41 (m, 6H, Bn, Pyr), 5.57 (s, 2H, Bn), 4.11 (s, 3H, Me) ppm; **mp.:** 84 °C.

Ethyl 2,2,5-trimethylhex-4-enoate 327

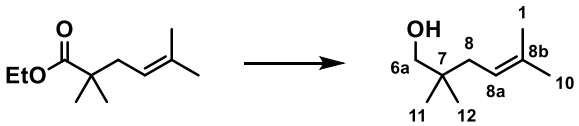


192 327

*n*BuLi (1.6 M in hex, 4.2 mL, 6.63 mmol, 1.10 eq) was added dropwise to a stirred solution of DIPA (1.02 mL, 7.23 mmol, 1.20 eq) in THF (7.2 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 10 min, then ester **192** (0.81 mL, 6.03 mmol, 1.00 eq) in THF (12.2 mL) was added dropwise and the resulting mixture was stirred at -78 °C for 1 h. Then prenylbromide (0.84 mL, 7.23 mmol, 1.20 eq) was added dropwise at -78 °C and the mixture was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (10 mL), the layers were separated, the aq. layer was extracted with EtOAc (3x 10 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1) yielded ester **327** (0.56 g, 0.85 mmol, 50%) as a colorless oil. The analytical data match those reported in the literature.[231]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.07 (tt, J = 7.55, 2.09 Hz, 1H, H-8a), 4.10 (q, J = 7.29 Hz, 2H, Et), 2.21 (d, J = 7.74 Hz, 2H, H-8), 1.69 (d, J = 0.63 Hz, 3H, H-10), 1.60 (s, 3H, H-1), 1.24 (t, J = 7.14 Hz, 3H, Et), 1.15 (s, 6H, H-11, H-12) ppm; **R_f** (20:1 PE/EtOAc): 0.54.

2,2,5-Trimethylhex-4-en-1-ol 328



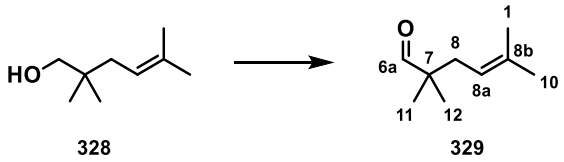
327 328

$LiAlH_4$ (113.4 mg, 2.99 mmol, 1.00 eq) was added in small portions to a stirred solution of ester **327** (550.8 mg, 2.98 mmol, 1.00 eq) in Et_2O (10.0 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 30 min and then the reaction was terminated by addition of MeOH (2 mL) at -78 °C. The mixture was allowed to warm to rt and diluted with a 1:1 mixture of EtOAc and a sat. aq. Rochelle salt-solution (50 mL) and stirred at rt for 1 h. The layers were separated, the aq. layer was extracted with EtAOc (3x 20 mL), the comb. org. layers were washed with brine, dried over $MgSO_4$, filtered

and concentrated *in vacuo*. Crude alcohol **328** (320.1 mg, 2.25 mmol, 75%), an oil, was directly used for the next step without any further purification.

R_f (20:1 PE/EtOAc): 0.23.

2,2,5-Trimethylhex-4-enal 329



328 329

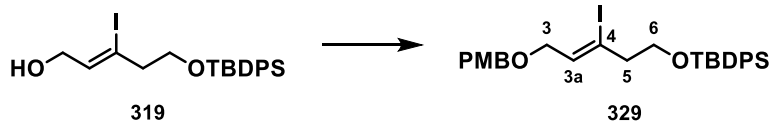
DMSO (0.48 mL, 6.75 mmol, 3.00 eq) was added dropwise to a stirred solution of oxalylchloride (290 µL, 3.38 mmol, 1.50 eq) in CH_2Cl_2 (8.4 mL) at -78 °C, the resulting mixture was stirred at -78 °C for 10 min, then alcohol **328** (320.1 mg, 2.25 mmol, 1.00 eq) in CH_2Cl_2 (5.6 mL) was added dropwise at -78 °C and the mixture was stirred at -78 °C for 15 min. Then NEt_3 (0.94 mL, 6.75 mmol, 3.00 eq) was added dropwise at -78 °C and the mixture was allowed to warm to rt and stirred at rt for 30 min. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (20 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1) yielded aldehyde **329** (154.3 mg, 1.10 mmol, 49%) as a colorless oil. The analytical data match those reported in the literature.[231]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.47 (s, 1H, H-6a), 5.05 (tt, J = 7.65, 2.07 Hz, 1H, H-8a), 2.15 (d, J = 7.60 Hz, 2H, H-8), 1.70 (d, J = 0.66 Hz, 3H, H-10), 1.60 (s, 3H, H-1), 1.04 (s, 6H, H-11, H-12) ppm; **R_f** (20:1 PE/EtOAc): 0.64.

Samarium(II) iodide

The following procedure was performed according to Procter's procedure starting from inactive samarium metal.[232] Samarium (0.50 g, 3.33 mmol, 1.00 eq) was added to a previously flame-dried Schlenk flask and the flask was backfilled with argon three times. After stirring at high speed for 24 h under argon, THF (13.9 mL) and then iodine (422.0 mg, 1.66 mmol, 0.50 eq) in THF (3.0 mL) were added and the resulting brown mixture was heated to 60 °C for 24 h. After a few hours the solution turned blue and the color was consistent. Then heating was stopped and the solution was settled for 2 h prior to being used. The solution was used as a 0.1 M solutiom as being prepared but without further titration.

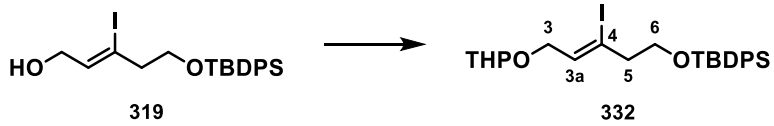
(*Z*)-*tert*-Butyl((3-iodo-5-((4-methoxybenzyl)oxy)pent-3-en-1-yl)oxy)diphenylsilane 329



MeOTf (0.80 mL, 7.29 mmol, 2.00 eq) was added dropwise to a stirred solution of alcohol **319** (1.70 g, 3.64 mmol, 1.00 eq), MgO (293.9 mg, 7.29 mmol, 2.00 eq) and the PMB-Dudley reagent[4] (2.04 g, 7.29 mmol, 2.00 eq) in $PhCF_3$ (37.0 mL) at 0 °C and the mixture was allowed to warm to rt over 1 h. Then reaction mixture was diluted with EtOAc (20 mL), subsequently washed with water (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 50:1 – 20:1 – 10:1) yielded vinyl iodide **329** (1.57 g, 2.68 mmol, 73%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.67-7.65 (m, 4H, TBDPS), 7.44-7.35 (m, 6H, TBDPS), 7.27-7.25 (m, 2H, PMB), 6.88-6.86 (m, 2H, PMB), 5.91 (t, *J* = 5.50 Hz, 1H, H-3a), 4.45 (s, 2H, PMB), 4.07 (d, *J* = 5.52 Hz, 2H, H-3), 3.80-3.77 (m, 5H, PMB, H-6), 2.74 (t, *J* = 6.82 Hz, 2H, H-5), 1.04 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 159.4 (q, PMB), 135.8 (t, TBDPS), 134.4 (t, C-3a), 133.8 (q, TBDPS), 130.3 (q, PMB), 129.8 (t, TBDPS), 129.6 (t, PMB), 127.9 (t, TBDPS), 114.0 (t, PMB), 105.5 (q, C-4), 74.4 (s, C-3), 72.3 (s, PMB), 62.5 (s, C-6), 55.5 (p, PMB), 48.3 (s, C-5), 27.0 (p, TBDPS), 19.4 (q, TBDPS) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{29}H_{35}O_3SiNa^{127}I$ $[M+Na]^+$: 609.1298; *found*: 609.1298; $\mathbf{R}_f$ (5:1 PE/EtOAc): 0.71.

(*Z*)-*tert*-Butyl((3-iodo-5-((tetrahydro-2*H*-pyran-2-yl)oxy)pent-3-en-1-yl)oxy)diphenylsilane 332

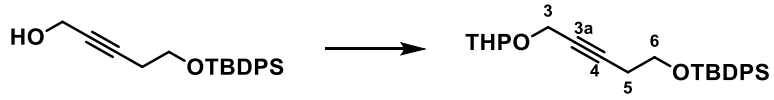


DHP (0.86 mL, 9.51 mmol, 1.20 eq) and *p*TsOH·H_2O (27.3 mg, 0.16 mmol, 0.02 eq) were subsequently added to a stirred solution of allyl alcohol **319** (3.70 g, 7.93 mmol, 1.00 eq) in CH_2Cl_2 (27.0 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (20 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 50:1 – 20:1) yielded vinyl iodide **332** (3.13 g, 5.69 mmol, 72%) as a colorless oil.[5] The analytical data match those reported in the literature.[140]

[4] It was synthesized by students as part of their OCII teaching laboratory training according to literature procedure.[277]
[5] The product was obtained as a mixture of isomers. Only shifts (δ) and coupling constants (J) of the major isomer are reported here.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.68-7.65 (m, 4H, TBDPS), 7.45-7.37 (m, 6H, TBDPS), 5.91 (t, *J* = 5.65 Hz, 1H, H-3a), 4.65 (t, *J* = 3.39 Hz, 1H, THP), 4.30-4.04 (m, 2H, H-3), 3.90-3.85 (m, 1H, THP), 3.79 (t, *J* = 6.45 Hz, 2H, H-6), 3.54 (m, 1H, THP), 2.75 (t, *J* = 5.90 Hz, 2H, H-5), 1.85-1.68 (m, 2H, THP), 1.60-1.50 (m, 4H, THP), 1.04 (s, 9H, TBDPS) ppm; **R_f** (10:1 PE/EtOAc): 0.50.

tert-Butyldiphenyl((5-((tetrahydro-2*H*-pyran-2-yl)oxy)pent-3-yn-1-yl)oxy)silane 334

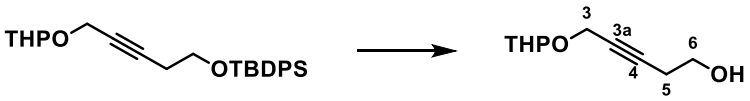


318 334

DHP (1.5 mL, 16.01 mmol, 1.20 eq) and *p*TsOH·H_2O (250.7 mg, 1.46 mmol, 0.02 eq) were added to a stirred solution of propargyl alcohol **318** (4.93 g, 14.56 mmol, 1.00 eq) in CH_2Cl_2 (29.0 mL) at 0 °C. The resulting mixture was allowed to warm to rt over 1 h. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (20 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1) yielded ether **334** (5.58 g, 13.20 mmol, 91%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.69-7.67 (m, 4H, TBDPS), 7.45-7.37 (m, 6H, TBDPS), 4.79 (t, *J* = 3.24 Hz, 1H, THP), 4.22 (ddt, *J* = 36.94, 15.32, 3.16 Hz, 2H, H-3), 3.85-3.79 (m, 1H, THP), 3.77 (t, *J* = 7.13 Hz, 2H, H-6), 3.51-3.49 (m, 1H, THP), 2.49 (tt, *J* = 7.14, 3.13 Hz, 2H, H-5), 1.85-1.67 (m, 2H, THP), 1.63-1.50 (m, 4H, THP), 1.06 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 135.7 (t, TBDPS), 133.8 (q, TBDPS), 129.8 (t, TBDPS), 127.9 (t, TBDPS), 96.9 (t, THP), 83.6 (q, C-4), 77.2 (q, C-3a), 62.6 (s, C-6), 54.7 (s, C-3), 30.4 (s, THP), 27.0 (p, TBDPS), 25.5 (s, C-5), 23.2 (s, THP), 19.4 (q, TBDPS), 19.2 (s, THP) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{26}H_{34}O_3SiNa$ $[M+Na]^+$: 445.2175; *found*: 445.2165; **R_f** (10:1 PE/EtOAc): 0.53.

5-((Tetrahydro-2*H*-pyran-2-yl)oxy)pent-3-yn-1-ol 335



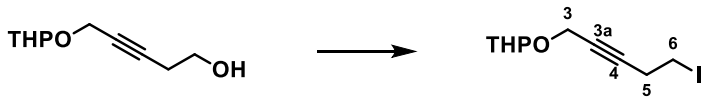
334 335

TBAF (1.0 M in THF, 50.0 mL, 49.36 mmol, 3.00 eq) was added dropwise to a stirred solution of protected diol **334** (5.57 g, 16.45 mmol, 1.00 eq) in THF (55.0 mL) at 0 °C. The resulting mixture was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (50 mL), the layers were separated, the aq. layer was extracted with EtOAc (3x 50 mL), the comb. org. layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in*

vacuo. Column chromatography (PE/EtOAc 3:1 – 1:1) yielded alcohol **335** (2.16 g, 11.72 mmol, 71%) as a colorless oil. The analytical data match those reported in the literature.[233]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.80 (t, *J* = 3.25 Hz, 1H, THP), 4.26 (ddt, *J* = 36.64, 15.30, 2.07 Hz, 2H, H-3), 3.87-3.82 (m, 1H, THP), 3.72 (t, *J* = 6.16 Hz, 2H, H-6), 3.54-3.52 (m, 1H, THP), 2.50 (tt, *J* = 6.22, 2.22 Hz, 2H, H-5), 1.86-1.70 (m, 2H, THP), 1.65-1.53 (m, 4H, THP) ppm; **R_f** (5:1 PE/EtOAc): 0.12.

2-((5-Iodopent-2-yn-1-yl)oxy)tetrahydro-2*H*-pyran 336

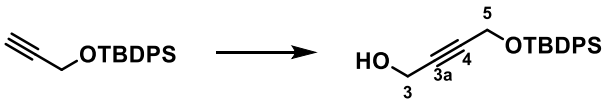


335 336

Imidazole (1.20 g, 17.58 mmol, 1.50 eq) and iodine (4.16 g, 16.41 mmol, 1.40 eq) were subsequently added to a stirred solution of PPh_3 (3.69 g, 14.06 mmol, 1.20 eq) in CH_2Cl_2 (35.0 mL). Then a solution of alcohol **335** (2.16 g, 11.72 mmol, 1.00 eq) in CH_2Cl_2 (15.0 mL) was added dropwise at rt. The resulting mixture was excluded from light and stirred at rt for 3 h. The reaction was terminated by addition of an aq. 10% $Na_2S_2O_3$-solution (20 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1) yielded iodide **336** (3.06 g, 10.39 mmol, 89%) as a colorless oil. The analytical data match those reported in the literature.[234]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.83 (t, *J* = 3.26 Hz, 1H, THP), 4.24 (ddt, *J* = 36.54, 15.35, 1.81 Hz, 2H, H-3), 3.87-3.81 (m, 1H, THP), 3.55-3.52 (m, 1H, THP), 3.22 (t, *J* = 7.34 Hz, 2H, H-6), 2.82 (tt, *J* = 7.28, 1.79 Hz, 2H, H-5), 1.86-1.71 (m, 2H, THP), 1.65-1.54 (m, 4H, THP) ppm; **R_f** (5:1 PE/EtOAc): 0.68.

4-((*tert*-Butyldiphenylsilyl)oxy)but-2-yn-1-ol 339



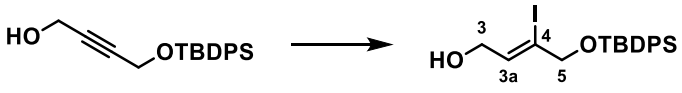
281 339

*n*BuLi (2.5 M in hex, 4.5 mL, 11.21 mmol, 1.10 eq) was added dropwise to a stirred solution of alkyne **281** (3.00 g, 10.19 mmol, 1.00 eq) in THF (51.0 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 30 min, then paraformaldehyde (0.92 g, 30.56 mmol, 3.00 eq) was added in one portion at -78 °C and the mixture was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (20 mL), the layers were separated and the aq. layer was extracted

with EtOAc (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 4:1) yielded alcohol **339** (2.73 g, 8.41 mmol, 83%) as a colorless oil. The analytical data match those reported in the literature.[235]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.72-7.70 (m, 4H, TBDPS), 7.46-7.38 (m, 6H, TBDPS), 4.37 (t, *J* = 1.69 Hz, 2H, H-5), 4.20 (dt, *J* = 6.25, 1.67 Hz, 2H, H-3), 1.28 (t, *J* = 6.21 Hz, 1H, OH), 1.06 (s, 9H, TBDPS) ppm; $\mathbf{R_f}$ (5:1 PE/EtOAc): 0.29.

(*Z*)-4-((*tert*-Butyldiphenylsilyl)oxy)-3-iodobut-2-en-1-ol 340

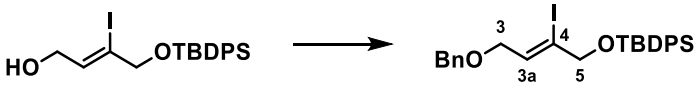


339 340

Alcohol **339** (2.15 g, 6.64 mmol, 1.00 eq) in Et_2O (4.3 mL) was added dropwise to a stirred solution of Red-Al® (3.5 M in PhMe, 4.0 mL, 13.94 mmol, 2.10 eq) in Et_2O (24.0 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 1 h. Then EtOAc (0.62 mL, 6.31 mmol, 0.95 eq) was added dropwise at 0 °C and the resulting mixture was stirred at 0 °C for 20 min, then iodine (2.53 g, 9.96 mmol, 1.50 eq) was added in small portions at 0 °C and the resulting mixture was stirred at 0 °C for 10 min. The reaction was terminated by addition of a 1:1 mixture of an aq. 10% $Na_2S_2O_3$-solution and a sat. aq. Rochelle salt-solution (30 mL). The layers were separated, the aq. layer was extracted with Et_2O (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1) yielded alcohol **340** (1.68 g, 3.72 mmol, 56%) as white long needles. The analytical data match those reported in the literature.[236]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.68-7.66 (m, 4H, TBDPS), 7.47-7.38 (m, 6H, TBDPS), 6.31 (t, *J* = 5.75 Hz, 1H, H-3a), 4.28-4.25 (m, 4H, H-3, H-5), 1.47 (bt, *J* = 5.16 Hz, 1H, OH), 1.09 (s, 9H, TBDPS) ppm; $\mathbf{R_f}$ (5:1 PE/EtOAc): 0.36; **mp.:** 49 °C.

(*Z*)-((4-(Benzyloxy)-2-iodobut-2-en-1-yl)oxy)(*tert*-butyl)diphenylsilane 341

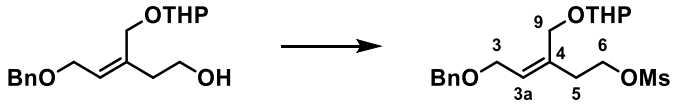


340 341

A mixture of alcohol **340** (1.79 g, 5.52 mmol, 1.00 eq), Dudley reagent **312** (3.85 g, 11.03 mmol, 2.00 eq) and proton sponge® (2.37 g, 11.03 mmol, 2.00 eq) in $PhCF_3$ (37 mL) was heated to 83 °C overnight. The reaction mixture was filtered over Celite™ and washed with an excess of CH_2Cl_2, concentrated *in vacuo* and dry loaded on silica. Column chromatography (PE/EtAOc 10:1) yielded benzylether **341** (1.67 g, 3.09 mmol, 56%, 65% brsm) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.69-7.66 (m, 4H, TBDPS), 7.46-7.29 (m, 11H, TBDPS, Bn), 6.35 (t, *J* = 5.64 Hz, 1H, H-3a), 4.53 (s, 2H, Bn), 4.29 (d, *J* = 1.33 Hz, 2H, H-5), 4.18 (d, *J* = 5.70 Hz, 2H, H-3), 1.09 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 138.2 (q, TBDPS), 135.7 (t, TBDPS), 133.2 (t, Bn), 130.8 (t, C-3a), 130.1 (t, TBDPS), 128.6 (t, Bn), 128.1 (t, Bn), 128.0 (t, TBDPS), 127.9 (q, Bn), 107.7 (q, C-4), 73.8 (s, C-3), 72.6 (s, Bn), 71.7 (s, C-5), 27.0 (p, TBDPS), 19.5 (q, TBDPS) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{27}H_{31}IO_2SiNa$ $[M+Na]^+$: 565.1036; *found*: 565.1036; **R_f** (10:1 PE/EtOAc): 0.71.

(*Z*)-5-(Benzyloxy)-3-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)pent-3-en-1-yl methanesulfonate 327

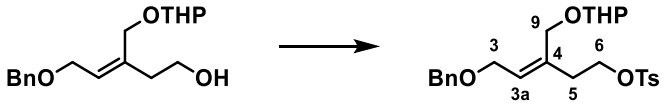


325 **327**

NEt_3 (1.4 mL, 9.79 mmol, 3.00 eq) and MsCl (0.28 mL, 3.59 mmol, 1.10 eq) were successively added to a stirred solution of alcohol **325** (1.00 g, 3.26 mmol, 1.00 eq) in CH_2Cl_2 (13.0 mL) at 0 °C. The mixture was allowed to warm to rt over 30 min, then diluted with CH_2Cl_2 (20 mL). The org. layer was successively washed with 1 M HCl (10 mL), water (2x 20 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 2:1 – 1:1) yielded mesylate **327** (1.09 g, 2.84 mmol, 87%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.35-7.27 (m, 5H, Bn), 5.70 (t, *J* = 6.58 Hz, 1H, H-3a), 4.56 (t, *J* = 3.50 Hz, 1H, THP), 4.50 (s, 2H, Bn), 4.34 (t, *J* = 7.06 Hz, 2H, H-6), 4.23 (d, *J* = 12.29 Hz, 1H, H-9), 4.10 (d, *J* = 6.56 Hz, 2H, H-3), 4.04 (d, *J* = 12.29 Hz, 1H, H-9), 3.83-3.78 (m, 1H, THP), 3.52-3.47 (m, 1H, THP), 2.99 (s, 3H, Ms), 2.60 (t, *J* = 6.94 Hz, 2H, H-5), 1.80-1.67 (m, 2H, THP), 1.60-1.50 (m, 4H, THP) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 138.2 (q, C-4), 134.8 (q, Bn), 129.0 (t, C-3a), 128.6 (t, Bn), 128.0 (t, Bn), 127.9 (t, Bn), 98.2 (t, THP), 72.6 (s, Bn), 68.6 (s, C-6), 65.9 (s, C-9), 64.5 (s, C-3), 62.4 (s, THP), 37.7 (p, Ms), 35.3 (s, C-5), 30.7 (s, THP), 25.5 (s, THP), 19.6 (s, THP) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{19}H_{28}O_6SNa$ $[M+Na]^+$: 407.1504; *found*: 407.1498; **R_f** (2:1 PE/EtOAc): 0.11.

(*Z*)-5-(Benzyloxy)-3-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)pent-3-en-1-yl 4-methylbenzene-sulfonate 328

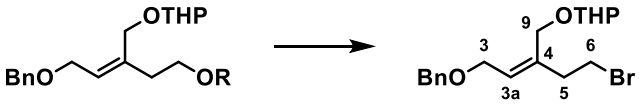


325 328

TsCl was freshly recrystallized from PE and stored under an atmosphere of Argon in a brown glass bottle at rt. NEt_3 (1.3 mL, 8.08 mmol, 3.00 eq), DMAP (3.6 mg, 0.03 mmol, 0.01 eq) and TsCl (0.62 g, 3.23 mmol, 1.10 eq) were successively added to a stirred solution of alcohol **325** (0.90 g, 2.93 mmol, 1.00 eq) in CH_2Cl_2 (12 mL) at 0 °C. The mixture was allowed to warm to rt overnight, then diluted with CH_2Cl_2 (20 mL). The org. layer was successively washed with 1 M HCl (10 mL), water (2x 20 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 2:1 – 1:1) yielded mesylate **328** (1.53 g, 2.50 mmol, 85%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.79-7.77 (m, 2H, Ts), 7.36-7.27 (m, 7H, Ts, Bn), 5.57 (t, *J* = 6.50 Hz, 1H, H-3a), 4.49-4.47 (m, 3H, THP, Bn), 4.16 (t, *J* = 7.04 Hz, 2H, H-6), 4.10 (d, *J* = 10.92 Hz, 1H, H-9), 4.04 (d, *J* = 6.51 Hz, 2H, H-3), 3.93 (d, *J* = 12.17 Hz, 1H, H-9), 3.77-3.71 (m, 1H, THP), 3.47-3.43 (m, 1H, THP), 2.49 (t, *J* = 7.04 Hz, 2H, H-5), 2.43 (s, 3H, Ts), 1.74-1.47 (m, 6H, THP) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 144.8 (q, Ts), 138.3 (q, C-4), 134.8 (q, Bn), 133.3 (t, Ts), 129.9 (t, Bn), 128.6 (q, C-3a), 128.6 (t, Ts), 128.1 (t, Bn), 128.0 (t, Bn), 127.8 (q, Ts), 98.0 (t, THP), 72.5 (s, Bn), 69.1 (s, C-6), 65.9 (s, C-9), 64.3 (s, C-3), 62.3 (s, THP), 34.8 (s, C-5), 30.6 (s, THP), 25.5 (s, THP), 21.8 (p, Ts), 19.5 (s, THP) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{25}H_{32}O_6SNa$ $[M+Na]^+$: 483.1817; *found*: 483.1808; $\mathbf{R_f}$ (2:1 PE/EtOAc): 0.11.

(*Z*)-2-((4-(Benzyloxy)-2-(2-bromoethyl)but-2-en-1-yl)oxy)tetrahydro-2*H*-pyran 326



327 R = Ms
328 R = Ts

326

Method A:

Mesylate **327** (56.3 mg, 0.15 mmol, 1.00 eq) and NaBr (45.2 mg, 0.44 mmol, 3.00 eq) were dissolved in DMF (3.0 mL) and heat to 50 °C in a sealed tube overnight. The reaction was terminated by addition of water (5 mL), the layers were separarted, the aq. layer was extracted with Et_2O (3x 10 mL), the comb. org. layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated

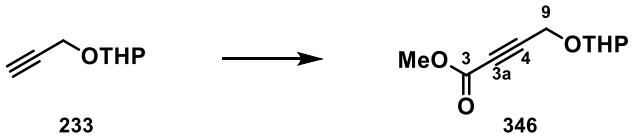
in vacuo. Colum chromatography (PE/EtOAc 10:1) yielded bromide **326** (39.5 mg, 0.11 mmol, 73%) as a colorless oil.

Methode B:

Tosylate **328** (56.1 mg, 0.14 mmol, 1.00 eq) and NaBr (42.6 mg, 0.41 mmol, 3.00 eq) were dissolved in DMF (2.8 mL) and heat to 50 °C in a sealed tube overnight. The reaction was terminated by addition of water (5 mL), the layers were separarted, extracted with Et_2O (3x 10 mL), washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Colum chromatography (PE/EtOAc 10:1) yielded bromide **326** (39.6 mg, 0.11 mmol, 78%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.35-7.27 (m, 5H, Bn), 5.67 (t, *J* = 6.54 Hz, 1H, H-3a), 4.56 (t, *J* = 3.64 Hz, 1H, THP), 4.51 (s, 2H, Bn), 4.19 (d, *J* = 12.13 Hz, 1H, THP), 4.11 (d, *J* = 6.49 Hz, 1H, H-3), 4.05 (d, *J* = 12.09 Hz, 1H, THP), 3.83-3.78 (m, 1H, THP), 3.54-3.46 (m, 3H, THP, H-6), 2.71 (o, *J* = 7.07 Hz, 2H, H-5), 1.82-1.65 (m, 2H, THP), 1.60-1.51 (m, 4H, THP) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 138.3 (q, C-4), 137.0 (q, Bn), 128.5 (t, Bn), 128-5 (t, C-3a), 128.0 (t, Bn), 127.8 (t, Bn), 97.9 (t, THP), 72.4 (s, Bn), 65.9 (s, C-3), 64.1 (s, C-9), 62.4 (s, THP), 38.9 (s, C-5), 31.5 (s, THP), 30.7 (s, C-6), 25.5 (s, THP), 19.5 (s, THP) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{18}H_{25}O_3BrNa$ $[M+Na]^+$: 391.0885; *found*: 391.0881; **R_f** (2:1 PE/EtOAc): 0.40.

Methyl 4-((tetrahydro-2*H*-pyran-2-yl)oxy)but-2-ynoate 346

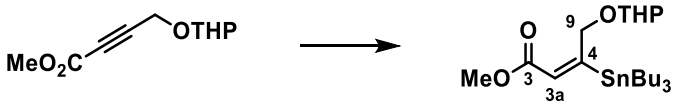


233 346

*n*BuLi (1.6 M in hex, 11.0 mL, 17.51 mmol, 1.10 eq) was added dropwise to a stirred solution of ether **233** (2.23 g, 15.92 mmol, 1.00 eq) in THF (80 mL) at -78 °C and the resulting mixture was stirred at -78 °C for 1 h. Then methylchloroformiate (1.4 mL, 17.52 mmol, 1.10 eq) was added dropwise at -78 °C and the resulting mixture was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (50 mL), the layers were separated, the aq. layer was extracted with EtOAc (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography yielded alkynoate **346** (2.88 g, 14.51 mmol, 91%) as a colorless oil. The analytical data match those reported in the literature.[237]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.81 (t, *J* = 2.96 Hz, 1H, THP), 4.38 (s, 2H, H-9), 3.85-3.78 (m, 1H, THP, CO_2Me), 3.57-3.53 (m, 1H, THP), 1.82-1.54 (m, 6H, THP) ppm; **R_f** (10:1 PE/EtOAc): 0.53.

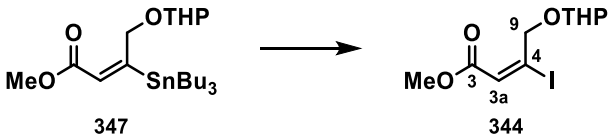
Methyl (*E*)-3-iodo-4-((tetrahydro-2*H*-pyran-2-yl)oxy)but-2-enoate 347



*n*BuLi (1.6 M in hex, 14.0 mL, 22.20 mmol, 2.20 eq) was added dropwise to a stirred slurry of CuCN (0.91 g, 10.09 mmol, 1.00 eq) in THF (34.0 mL) at -78 °C and the resulting mixture was stirred at -78 °C for 15 min. Then tributyltinhydride (6.0 mL, 22.20 mmol, 2.20 eq) was added dropwise at -78 °C and the resulting mixture was stirred at -78 °C for 15 min. Then a solution of alkynoate **346** (2.00 g, 10.09 mmol, 1.00 eq) and MeOH (2.1 mL, 50.45 mmol, 5.00 eq) in THF (21.0 mL) was added dropwise at -78 °C and the resulting mixture was stirred at -78 °C for 30 min. The reaction was terminated by addition of an aq. 10:1 NH_4Cl/NH_4OH solution (30 mL), the layers were separated, the aq. layer was extracted with EtOAc (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1 – 10:1) yielded vinyl stannane **347** (4.94 g, 10.09 mmol, *quant.*) as a colorless oil. The analytical data match those reported in the literature.[237]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.93 (t, *J* = 2.65 Hz, 1H, H-3a), 5.05 (dd, *J* = 17.35, 2.66 Hz, 1H, H-9), 4.68 (t, *J* = 3.16 Hz, 1H, THP), 4.55 (dd, *J* = 17.35, 2.78 Hz, 1H, H-9), 3.85-3.80 (m, 1H, THP), 3.70 (s, 3H, CO_2*Me*), 3.53-3.50 (m, 1H, THP), 1.85-1.26 (m, 18H, THP, Sn*Bu*$_3$), 1.06-0.87 (m, 15H, Sn*Bu*$_3$) ppm; **R_f** (10:1 PE/EtOAc): 0.63.

Methyl (*E*)-3-iodo-4-((tetrahydro-2*H*-pyran-2-yl)oxy)but-2-enoate 344

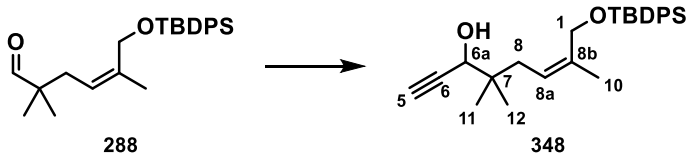


A solution of iodine (352.0 mg, 1.39 mmol, 1.50 eq) in CH_2Cl_2 (4.6 mL) was added dropwise to a stirred solution of vinyl stannane **347** (452.4 mg, 0.92 mmol, 1.00 eq) in CH_2Cl_2 (9.5 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 2 h under exclusion of light. The reaction was terminated by addition of an aq. 10% $Na_2S_2O_3$-solution (10 mL), the layers were separated and the aq. layer was extracted with CH_2Cl_2 (3x 5 mL), the comb. org. layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography under exclusion of light (PE/EtOAc 20:1 – 10:1) yielded vinyl iodide **344** (243.9 mg, 0.75 mmol, 81%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.80 (t, *J* = 1.47 Hz, 1H, H-3a), 4.81 (dd, *J* = 14.22, 1.17 Hz, 1H, H-9), 4.73 (t, *J* = 3.08 Hz, 1H, THP), 4.63 (dd, *J* = 14.25, 1.47 Hz, 1H, H-9), 3.93-3.87 (m, 1H, THP), 3.71 (s, 3H, CO_2Me), 3.56-3.52 (m, 1H, THP), 1.91-1.52 (m, 6H, THP) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 164.4 (q, C-3), 132.4 (t, C-3a), 126.6 (q, C-4), 97.9 (t, THP), 67.9 (s, C-9), 62.2 (s, THP),

52.0 (p, CO_2Me), 30.5 (s, THP), 25.6 (s, THP), 19.0 (s, THP) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{10}H_{15}IO_4SiNa$ $[M+Na]^+$: 348.9913; *found*: 348.9907; $\mathbf{R_f}$ (10:1 PE/EtOAc): 0.31.

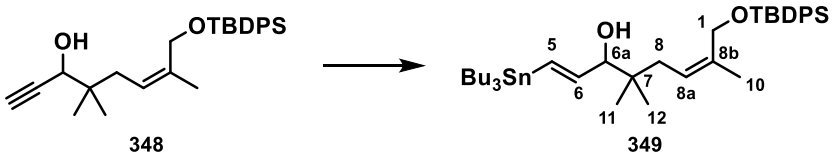
(*Z*)-8-((*tert*-Butyldiphenylsilyl)oxy)-4,4,7-trimethyloct-6-en-1-yn-3-ol 348



Ethynylmagnesium bromide (0.5 M in THF, 7.2 mL, 3.54 mmol, 1.40 eq) was added dropwise to a stirred solution of aldehyde **288** (1.00 g, 2.53 mmol, 1.00 eq) in Et_2O (18.0 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 15 min. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (10 mL), the layers were separated, the aq. layer was extracted with Et_2O (3x 10 mL), the comb. org. layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded propargyl alcohol **348** (1.02 g, 2.42 mmol, 96%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.70-7.67 (m, 4H, TBDPS), 7.45-7.36 (m, 6H, TBDPS), 5.29 (t, *J* = 8.66 Hz, 1H, H-8a), 4.25 (d, *J* = 11.76 Hz, 1H, H-1), 4.12 (d, *J* = 11.80 Hz, 1H, H-1), 4.01 (dd, *J* = 6.42, 2.18 Hz, 1H, H-6a), 2.32 (d, *J* = 2.20 Hz, 1H, H-5), 2.05 (s, 2H, H-8), 1.81 (s, 3H, H-10), 1.06 (s, 9H, TBDPS), 0.91 (d, *J* = 6.56 Hz, 6H, H-11, H-12) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 137.1 (q, C-8b), 135.9 (t, TBDPS), 135.8 (t, TBDPS), 133.9 (q, TBDPS), 133.8 (q, TBDPS), 129.8 (t, TBDPS), 129.7 (t, TBDPS), 122.9 (t, C-8a), 83.6 (q, C-6), 74.1 (t, C-5), 69.6 (t, C-6a), 62.7 (s, C-1), 39.2 (q, C-7), 36.0 (s, C-8), 27.0 (p, TBDPS), 22.9 (p, C-11), 22.6 (p, C-12), 21.9 (p, C-10), 19.5 (q, TBDPS) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{27}H_{36}O_2SiNa$ $[M+Na]^+$: 443.2382; *found*: 443.2380; $\mathbf{R_f}$ (10:1 PE/EtOAc): 0.34.

(1*E*,6*Z*)-8-((*tert*-Butyldiphenylsilyl)oxy)-4,4,7-trimethyl-1-(tributylstannyl)octa-1,6-dien-3-ol 349

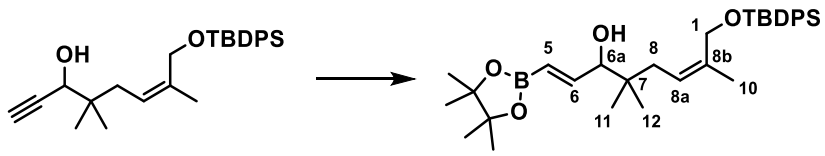


$PdCl_2(PPh_3)_2$ (1.8 mg, 0.003 mmol, 0.02 eq) was added to a by bubbling argon with a balloon with ultra-sonication through degassed solution of alcohol **348** (53.0 mg, 0.13 mmol, 1.00 eq) and tributyltin hydride (40 µL, 0.15 mmol, 1.20 eq) in THF (0.36 mL) at rt and the resulting mixture was stirred at rt for 15 min. Complete conversion was judged by TLC analysis after which, the mixture was concentrated *in vacuo* and dry loaded onto silica. Short plug column chromatography (PE/EtOAc

50:1) yielded crude vinyl stannane **349** (84.3 mg, 0.12 mmol, 94%) as a colorless oil which was directly used for the next step without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.70-7.68 (m, 4H, TBDPS), 7.44-7.36 (m, 6H, TBDPS), 6.09 (d, *J* = 19.16 Hz, 1H, H-5), 5.99 (dd, *J* = 19.14, 5.61 Hz, 1H, H-6), 5.31 (t, *J* = 7.67 Hz, 1H, H-8a), 4.19 (dd, *J* = 36.97, 11.58 Hz, 2H, H-1), 3.71 (t, *J* = 5.10 Hz, 1H, H-6a), 1.82 (s, 3H, H-10), 1.53-1.44 (m, 9H, $SnBu_3$, H-8), 1.35-1.24 (m, 12H, $SnBu_3$), 1.05 (s, 9H, TBDPS), 0.98-0.94 (m, 5H, $SnBu_3$), 0.91-0.78 (m, 21H, $SnBu_3$), 0.77 (d, *J* = 6.52 Hz, 6H, H-11, H-12) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{39}H_{64}O_2SiSnNa$ $[M+Na]^+$: 735.3596; *found*: 735.3594; $\mathbf{R}_f$ (5:1 PE/EtOAc): 0.40.

(1*E*,6*Z*)-8-((*tert*-Butyldiphenylsilyl)oxy)-4,4,7-trimethyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octa-1,6-dien-3-ol 350



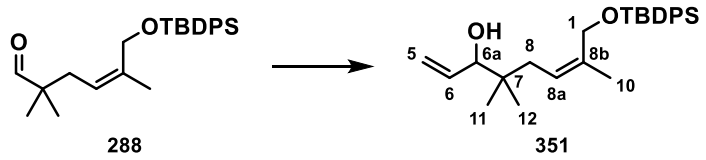
348 350

PPh_3 was freshly recrystallized from EtOH dried under high vacuum prior to use. 1/10 of a mixture of CuCl (10.6 mg, 0.11 mmol, 0.50 eq), KO*t*Bu (48.1 mg, 0.43 mmol, 2.00 eq) and PPh_3 (33.7 mg, 0.13 mmol, 0.60 eq) in THF (1.1 mL) was added dropwise to a stirred solution of B_2pin_2 (59.8 mg, 0.24 mmol, 1.10 eq) in THF (140.0 µL) at rt and the resulting mixture was stirred at rt for 15 min. Then it was cooled to 0 °C and a mixture of alcohol **348** (90.0 mg, 0.21 mmol, 1.00 eq) and MeOH (18 µL, 0.43 mmol, 2.00 eq) in THF (0.72 mL) was added dropwise at 0 °C. The mixture was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (1 mL), the layers were separated, the aq. layer was extracted with Et_2O (3x 1 mL), the comb. org. layers were washed with brine (1 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1 – 5:1) yielded vinyl boronate **350** (66.9 mg, 0.12 mmol, 57%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.69-7.67 (m, 4H, TBDPS), 7.44-7.36 (m, 6H, TBDPS), 6.63 (dd, *J* = 18.06, 5.57 Hz, 1H, H-6), 5.61 (dd, *J* = 18.04, 1.29 Hz, 1H, H-5), 5.29 (t, *J* = 7.57 Hz, 1H, H-8a), 4.17 (dd, *J* = 38.15, 11.61 Hz, 2H, H-1), 3.79 (t, *J* = 4.52 Hz, 1H, H-6a), 1.98 (dd, *J* = 14.37, 8.48 Hz, 1H, H-8), 1.82 (s, 3H, H-10), 1.72 (dd, *J* = 14.19, 7.33 Hz, 1H, H-8), 1.66 (d, *J* = 4.76 Hz, 1H, OH), 1.26 (s, 12H, Bpin), 1.05 (s, 9H, TBDPS), 0.79 (d, *J* = 2.28 Hz, 6H, H-11, H-12) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 152.5 (t, C-6), 136.6 (q, C-8b), 135.9 (t, TBDPS), 135.8 (t, TBDPS), 134.0 (q, TBDPS), 133.9 (q, TBDPS), 129.8 (t, TBDPS), 127.8 (t, TBDPS), 127.8 (t, C-5), 123.2 (t, C-8a), 83.4 (q, Bpin), 79.9 (t, C-6a), 62.7 (s, C-1), 38.6 (q, C-7), 36.9 (s, C-8), 27.0 (p, TBDPS), 25.0 (p, Bpin), 24.9 (p, Bpin), 23.5 (p, C-11), 22.5 (p, C-12), 21.9 (p, C-10), 19.5 (q, TBDPS) ppm; **HRMS**

(ESI-LCT): *m/z calc.* for $C_{33}H_{49}O_4SiBNa$ $[M+Na]^+$: 571.3391; *found*: 571.3391; $\mathbf{R_f}$ (5:1 PE/EtOAc): 0.40.

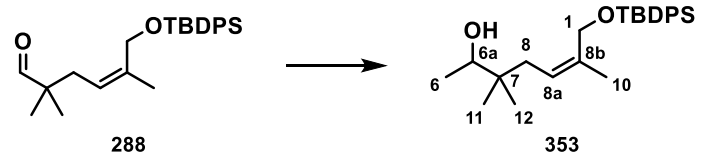
(*Z*)-8-((*tert*-Butyldiphenylsilyl)oxy)-4,4,7-trimethylocta-1,6-dien-3-ol 351



Vinylmagnesium bromide (0.7 M in THF, 3.2 mL, 2.21 mmol, 1.40 eq) was added dropwise to a stirred solution of aldehyde **288** (0.62 g, 1.58 mmol, 1.00 eq) in Et_2O (12.0 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 1 h. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (10 mL), the layers were separated, the aq. layer was extracted with Et_2O (3x 10 mL), the comb. org. layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded allyl alcohol **351** (0.51 g, 1.19 mmol, 75%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.70-7.68 (m, 4H, TBDPS), 7.45-7.37 (m, 6H, TBDPS), 5.88-5.80 (m, 1H, H-6), 5.31 (t, *J* = 7.70 Hz, 1H, H-8a), 5.18 (d, *J* = 17.2 Hz, 1H, H-5 *trans*), 5.12 (d, *J* = 10.20 Hz, 1H, H-5 *cis*), 4.17 (dd, *J* = 40.47, 11.66 Hz, 2H, H-1), 3.74 (t, *J* = 5.46 Hz, 1H, H-6a), 1.99 (dd, *J* = 14.38, 8.84 Hz, 1H, H-8), 1.82 (s, 3H, H-10), 1.71 (dd, *J* = 14.04, 7.32 Hz, 1H, H-8), 1.65 (d, *J* = 4.60 Hz, 1H, OH), 1.05 (s, 9H, TBDPS), 0.79 (d, *J* = 8.62 Hz, 6H, H-11, H-12) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 138.0 (t, C-6), 136.6 (q, C-8b), 135.9 (t, TBDPS), 135.8 (t, TBDPS), 134.0 (q, TBDPS), 133.9 (q, TBDPS), 129.8 (t, TBDPS), 127.8 (t, TBDPS), 123.3 (t, C-8a), 116.4 (s, C-5), 79.3 (t, C-6a), 62.7 (s, C-1), 38.3 (q, C-7), 36.8 (s, C-8), 27.0 (p, TBDPS), 23.3 (p, C-11), 22.5 (p, C-12), 21.9 (p, C-10), 19.5 (q, TBDPS) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{27}H_{38}O_2SiNa$ $[M+Na]^+$: 445.2539; *found*: 445.2536; $\mathbf{R_f}$ (10:1 PE/EtOAc): 0.43.

(*Z*)-7-((*tert*-Butyldiphenylsilyl)oxy)-3,3,6-trimethylhept-5-en-2-ol 353

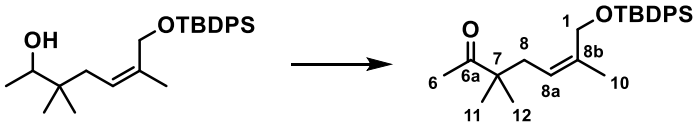


MeMgBr (3.0 M in Et_2O, 1.3 mL, 3.68 mmol, 1.40 eq) was added dropwise to a stirred solution of aldehyde **288** (1.04 g, 2.63 mmol, 1.00 eq) in Et_2O (19.0 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 20 min. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (10 mL), the layers were separated, the aq. layer was extracted with Et_2O (3x 10 mL), the comb. org.

layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded alcohol **353** (0.88 g, 2.13 mmol, 81%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.70-7.68 (m, 4H, TBDPS), 7.44-7.37 (m, 6H, TBDPS), 5.30 (t, *J* = 7.62 Hz, 1H, H-8a), 4.17 (dd, *J* = 45.49, 11.84 Hz, 2H, H-1), 3.46 (q, *J* = 6.48 Hz, 1H, H-6a), 1.95 (dd, *J* = 14.19, 8.41 Hz, 1H, H-8), 1.81 (s, 3H, H-10), 1.70 (dd, *J* = 14.22, 7.17 Hz, 1H, H-8), 1.58 (bs, 1H, OH), 1.05-1.03 (m, 12H, TBDPS, H-6), 0.78 (d, *J* = 12.24 Hz, 6H, H-11, H-12) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 136.3 (q, C-8b), 135.9 (t, TBDPS), 135.8 (t, TBDPS), 133.9 (q, TBDPS), 133.8 (q, TBDPS), 129.8 (t, TBDPS), 129.7 (t, TBDPS), 127.8 (t, TBDPS), 127.8 (t, TBDPS), 123.6 (t, C-8a), 73.8 (t, C-6a), 62.7 (s, C-1), 38.5 (q, C-7), 36.9 (s, C-8), 27.0 (p, TBDPS), 23.3 (p, C-10), 22.0 (p, C-11), 22.0 (p, C-12), 19.4 (q, TBDPS), 17.8 (p, C-6) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{26}H_{38}O_2SiNa$ $[M+Na]^+$: 433.2539; *found*: 433.2548; **R_f** (10:1 PE/EtOAc): 0.31.

(*Z*)-7-((*tert*-Butyldiphenylsilyl)oxy)-3,3,6-trimethylhept-5-en-2-one 354

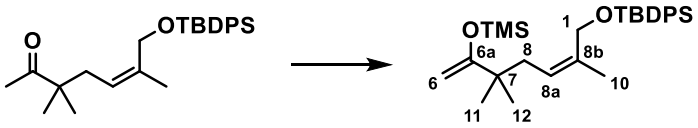


353 354

DMSO (0.46 mL, 6.36 mmol, 3.00 eq) was added dropwise to a stirred solution of oxalylchloride (280 µL, 3.18 mmol, 1.50 eq) in CH_2Cl_2 (16.0 mL) at -78 °C, the resulting mixture was stirred at -78 °C for 10 min, then alcohol **353** (0.87 g, 2.12 mmol, 1.00 eq) in CH_2Cl_2 (5.3 mL) was added dropwise at -78 °C and the mixture was stirred at -78 °C for 15 min. Then NEt_3 (0.89 mL, 6.36 mmol, 3.00 eq) was added dropwise at -78 °C and the mixture was allowed to warm to rt and stirred at rt for 30 min. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (20 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1) yielded ketone **354** (0.72 g, 1.75 mmol, 83%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.69-7.67 (m, 4H, TBDPS), 7.45-7.37 (m, 6H, TBDPS), 5.04 (t, *J* = 7.03 Hz, 1H, H-8a), 4.15 (s, 2H, H-1), 2.02-1.99 (m, 5H, H-6, H-8), 1.82 (d, *J* = 0.68 Hz, 3H, H-10), 1.05 (s, 9H, TBDPS), 0.99 (s, 6H, H-11, H-12) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 213.9 (q, C-6a), 137.5 (q, C-8b), 135.8 (t, TBDPS), 133.9 (q, TBDPS), 129.8 (t, TBDPS), 127.8 (t, TBDPS), 121.7 (t, C-8a), 62.6 (s, C-1), 48.1 (q, C-7), 37.3 (s, C-8), 27.0 (p, TBDPS), 25.3 (p, C-10), 24.2 (p, C-11, C-12), 21.6 (p, C-6), 19.5 (q, TBDPS) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{26}H_{36}O_2SiNa$ $[M+Na]^+$: 431.2382; *found*: 431.2379; **R_f** (20:1 PE/EtOAc): 0.40.

(*Z*)-2,2,5,5,8,12,12-heptamethyl-4-methylene-11,11-diphenyl-3,10-dioxa-2,11-disilatridec-7-ene 355

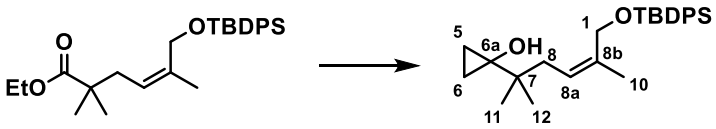


354 355

NEt_3 (0.74 mL, 5.29 mmol, 3.00 eq) and TMSOTf (0.48 mL, 2.64 mmol, 1.50 eq) were subsequently added to a stirred solution of ketone **354** (0.72 g, 1.76 mmol, 1.00 eq) in Et_2O (8.8 mL) at 0 °C. The mixture was allowed to warm to rt overnight. The reaction was terminated by dilution with pentanes (10 mL), the org. layer was washed with a sat. aq. $NaHCO_3$-solution (2x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield crude enol ether **355** (0.78 g, 1.62 mmol, 92%) as a yellow oil which was directly used for the next step without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.70-7.68 (m, 4H, TBDPS), 7.44-7.35 (m, 6H, TBDPS), 5.16 (t, *J* = 6.90 Hz, 1H, H-8a), 4.17 (s, 2H, H-1), 3.95 (dd, *J* = 19.41, 1.08 Hz, 2H, H-6), 1.88 (d, *J* = 7.28 Hz, 2H, H-8), 1.84 (s, 3H, H-10), 1.04 (s, 9H, TBDPS), 0.89 (s, 6H, H-11, H-12), 0.14 (s, 9H, TMS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 165.5 (q, C-6a), 135.8 (t, TBDPS), 135.7 (q, TBDPS), 134.1 (q, C-8b), 129.7 (t, TBDPS), 127.8 (t, TBDPS), 123.7 (t, C-8a), 87.2 (s, C-6), 62.8 (s, C-1), 39.9 (s, C-8), 37.5 (q, C-7), 27.0 (p, TBDPS), 25.9 (p, C-11, C-12), 21.6 (p, C-10), 19.5 (q, TBDPS), 0.3 (p, TMS) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{29}H_{44}O_2Si_2Na$ $[M+Na]^+$: 503.2778; *found*: 503.2783. **R_f** (20:1 PE/EtOAc): 0.70.

(*Z*)-1-(6-((*tert*-Butyldiphenylsilyl)oxy)-2,5-dimethylhex-4-en-2-yl)cyclopropan-1-ol 357



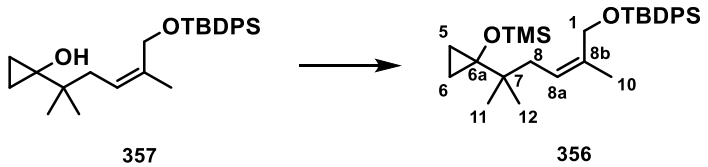
286 357

EtMgBr (3.0 M in Et_2O, 1.3 mL, 3.93 mmol, 5.00 eq) was added dropwise (0.13 mL/min) to a stirred solution of Ti(O*i*Pr)$_4$ (240 µL, 0.79 mmol, 1.00 eq) and ester **286** (345.0 mg, 0.79 mmol, 1.00 eq) in THF (4.0 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min. The reaction was terminated by addition of aq. 10% HCl (5 mL), the layers were separated, the aq. layer was extracted with EtOAc (3x 5 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1 – 10:1) yielded cyclopropanol **357** (249.5 mg, 0.59 mmol, 75%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.70-7.68 (m, 4H, TBDPS), 7.45-7.37 (m, 6H, TBDPS), 5.42 (t, *J* = 9.02 Hz, 1H, H-8a), 4.17 (s, 2H, H-1), 2.42 (s, 1H, OH), 2.01 (d, *J* = 7.92 Hz, 2H, H-8), 1.79 (s, 3H, H-10), 1.05 (s, 9H, TBDPS), 0.81 (s, 6H, H-11, H-12), 0.53 (d, *J* = 2.58 Hz, 4H, H-5, H-6) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 135.9 (t, TBDPS), 135.0 (q, C-8b), 133.8 (q, TBDPS), 129.8 (t, TBDPS), 127.8 (t, TBDPS), 124.8 (t, C-8a), 62.7 (s, C-1), 61.1 (q, C-6a), 37.5 (s, C-8), 27.0 (p, TBDPS), 24.3 (p, C-11, C-12), 22.1 (p, C-10), 19.4 (q, TBDPS), 10.6 (s, C-5, C-6) ppm[6]; **HRMS (ESI-LCT):** *m/z calc.* for $C_{27}H_{38}O_2SiNa$ $[M+Na]^+$: 445.2539; *found*: 445.2541; **R_f** (10:1 PE/EtOAc): 0.13.

(*Z*)-*tert*-Butyl((2,5-dimethyl-5-(1-((trimethylsilyl)oxy)cyclopropyl)hex-2-en-1-yl)oxy)diphenylsilane 356



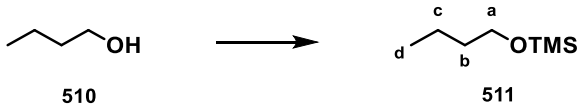
357 356

NEt_3 (250 µL, 1.76 mmol, 3.00 eq) and TMSOTf (160 µL, 0.88 mmol, 1.50 eq) were added to a stirred solution of alcohol **357** (248.0 mg, 0.59 mmol, 1.00 eq) in Et_2O (3.0 mL) at 0 °C. The mixture was allowed to warm to rt overnight. The reaction was terminated by dilution with pentanes (10 mL), the org. layer was washed with a sat. aq. $NaHCO_3$-solution (2x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1 – 5:1) yielded TMS-ether **356** (263.2 mg, 0.53 mmol, 91%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.69-7.68 (m, 4H, TBDPS), 7.42-7.36 (m, 6H, TBDPS), 5.34 (t, *J* = 8.48 Hz, 1H, H-8a), 4.19 (s, 2H, H-1), 1.92 (d, *J* = 7.87 Hz, 2H, H-8), 1.86 (s, 3H, H-10), 1.05 (s, 9H, TBDPS), 0.68 (s, 6H, H-11, H-12), 0.53 (d, *J* = 2.52 Hz, 4H, H-5, H-6), 0.01 (s, 9H, TMS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 135.8 (t, TBDPS), 135.1 (q, TBDPS), 134.1 (q, C-8b), 129.7 (t, TBDPS), 127.8 (t, TBDPS), 123.9 (t, C-8a), 65.6 (q, C-6a), 62.7 (s, C-1), 37.9 (q, C-7), 36.6 (s, C-8), 27.0 (p, TBDPS), 23.7 (p, C-11, C-12), 21.7 (p, C-10), 16.5 (q, TBDPS), 9.5 (s, C-5, C-6), 2.3 (p, TMS), 1.7 (p, TMS) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{30}H_{46}O_2Si_2Na$ $[M+Na]^+$: 517.2934; *found*: 517.2924; **R_f** (5:1 PE/EtOAc): 0.70.

[6] A signal for the quaternary C-atom 7 is missing in the ^{13}C-NMR spectrum, presumably due to relaxation properties of the molecule.

Butoxytrimethylsilane 511

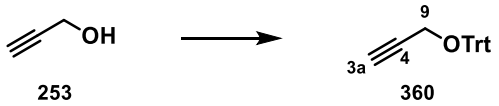


510 511

NBS (360.2 mg, 2.02 mmol, 0.05 eq) was added in one portion to a stirred solution of HMDS (5.9 mL, 28.33 mmol, 0.70 eq) and 1-butanol **510** (3.7 mL, 40.47 mmol, 1.00 eq) at rt and the resulting mixture was heated to 50 °C for 2 h. The reaction was terminated by dilution with pentanes (50 mL), the mixture was filtered through a short pad of silica and washed with an excess of pentanes. Careful concentration (200 mbar, 40 °C) *in vacuo* yielded crude TMS-ether **511** (5.51 g, 37.67 mmol, 93%) as a colorless liquid which was directly used for the next reaction. The analytical data match those reported in the literature.[238]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.58 (t, *J* = 6.65 Hz, 2H, H-a), 1.56-1.48 (m, 2H, H-b), 1.39-1.26 (m, 2H, H-c), 0.91 (t, *J* = 7.37 Hz, 3H, H-d), 0.11 (s, 9H, TMS) ppm; **R_f** (100:1 PE/EtOAc): 0.71.

((Prop-2-yn-1-yloxy)methanetriyl)tribenzene 360

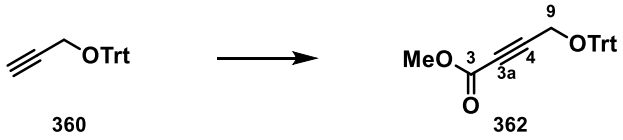


253 360

Propargyl alcohol was freshly distilled from CaH_2. TrtCl (1.09 g, 3.92 mmol, 1.10 eq), DMAP (8.7 mg, 0.07 mmol, 0.02 eq) and pyridine (300 µL, 3.60 mmol, 1.01 eq) were added to a stirred solution of propargyl alcohol **253** (210 µL, 3.57 mmol, 1.00 eq) in CH_2Cl_2 (1.8 mL) at rt and the resulting mixture was stirred at rt overnight. The reaction was terminated by addition of an aq. 1 M $KHSO_4$-solution (5 mL), the aq. layer was extracted with Et_2O (3x 5 mL), the comb. org. layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 50:1) yielded alkyne **360** (07.1 g, 2.37 mmol, 66%) as a white solid. The analytical data match those reported in the literature.[239]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.48-7.46 (m, 6H, Trt), 7.33-7.29 (m, 7H, Trt), 7-26-7-23 (m, 2H, Trt), 3.75 (d, *J* = 2.33 Hz, 2H, H-9), 2.39 (t, *J* = 2.58 Hz, 1H, H-3a) ppm; **R_f** (50:1 PE/EtOAc): 0.50; **mp.:** 113 °C.

Methyl 4-(trityloxy)but-2-ynoate 362



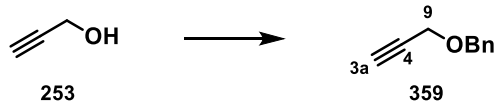
360 362

*n*BuLi (1.6 M in hex, 1.7 mL, 2.58 mmol, 1.10 eq) was added dropwise to a stirred solution of ether **360** (0.70 g, 2.35 mmol, 1.00 eq) in THF (12.0 mL) at -78 °C and the resulting mixture was

stirred at -78 °C for 1 h. Then methylchloroformiate (200 µL, 2.58 mmol, 1.10 eq) was added dropwise at -78 °C and the resulting mixture was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (10 mL), the layers were separated, the aq. layer was extracted with EtOAc (3x 20 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography yielded alkynoate **362** (0.77 g, 2.16 mmol, 92%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.49-7.44 (m, 6H, Trt), 7.34-7.30 (m, 6H, Trt), 7.27-7.24 (m, 3H, Trt), 3.91 (s, 2H, H-9), 3.78 (s, 3H, CO_2Me) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 153.9 (q, C-3), 143.1 (q, Trt), 128.7 (t, Trt), 128.2 (t, Trt), 127.6 (t, Trt), 88.1 (q, C-4), 84.6 (q, C-3a), 52.9 (p, CO_2Me), 52.8 (s, C-9) ppm[7]; **HRMS (ESI-LCT):** *m/z calc.* for $C_{24}H_{20}O_3Na$ $[M+Na]^+$: 379.1310; *found*: 379.1307; **R_f** (10:1 PE/EtOAc): 0.48; **mp.:** 82-84 °C.

((Prop-2-yn-1-yloxy)methyl)benzene 359



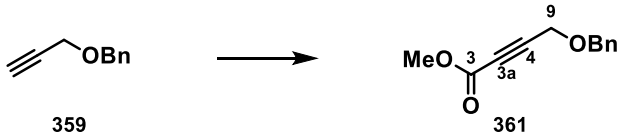
253 359

Propargyl alcohol was freshly distilled from CaH_2. Propargyl alcohol **253** (1.1 mL, 17.84 mmol, 1.00 eq) was slowly added to a stirred solution of NaH (60% on mineral oil, 0.78 g, 19.62 mmol, 1.10 eq) in DMF (18.0 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min, then benzyl bromide (2.4 mL, 19.62 mmol, 1.10 eq) was added dropwise at 0 °C and the mixture was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (10 mL), the layers were separated, the aq. layer was extracted with EtOAc (3x 10 mL), the comb. org. layers were subsequently washed with aq. 10% HCl (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 50:1) yielded ether **359** (2.61 g, 17.84 mmol, *quant.*) as a colorless oil. The analytical data match those reported in the literature.[240]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.37-7.29 (m, 5H, Bn), 1.62 (s, 2H, Bn), 4.18 (d, J = 2.30 Hz, 2H, H-9), 2.47 (t, J = 2.37 Hz, 1H, H-3a) ppm; **R_f** (50:1 PE/EtOAc): 0.66.

[7] A signal for the aliphatic quaternary carbon atom is missing in the ^{13}C-NMR spectrum due to its poor relaxation.

Methyl 4-(benzyloxy)but-2-ynoate 361

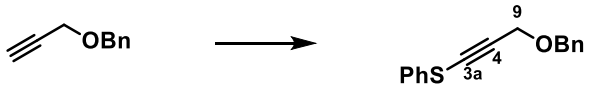


359 361

*n*BuLi (2.5 M in hex, 3.1 mL, 7.52 mmol, 1.10 eq) was added dropwise to a stirred solution of ether **359** (1.00 g, 6.84 mmol, 1.00 eq) in THF (23.0 mL) at -78 °C and the resulting mixture was stirred at -78 °C for 1 h. Then methylchloroformiate (0.69 mL, 8.89 mmol, 1.10 eq) was added dropwise at -78 °C and the resulting mixture was allowed to warm to rt over 2 h. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (20 mL), the layers were separated, the aq. layer was extracted with EtOAc (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography yielded alkynoate **361** (1.14 g, 5.60 mmol, 82%) as a colorless oil. The analytical data match those reported in the literature.[241]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.37-7.31 (m, 5H, Bn), 4.62 (s, 2H, Bn), 4.30 (s, 2H, H-9), 3.80 (s, 3H, CO_2Me) ppm; **R_f** (10:1 PE/EtOAc): 0.40.

(3-(Benzyloxy)prop-1-yn-1-yl)(phenyl)sulfane 363

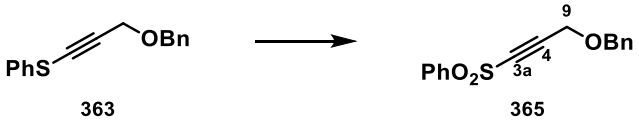


359 363

*n*BuLi (2.5 M in hex, 4.6 mL, 11.36 mmol, 1.10 eq) was added dropwise to a stirred solution of ether **359** (1.51 g, 10.33 mmol, 1.00 eq) in THF (23.0 mL) at -78 °C and the resulting mixture was stirred at -78 °C for 1 h. In a second flask MeI (0.71 mL, 11.36 mmol, 1.10 eq) was added dropwise to a stirred solution of Ph_2S_2 (2.48 g, 11.36 mmol, 1.10 eq) in THF (41.0 mL) at rt and the resulting mixture was stirred at rt for 1 h. Then, the latter was added dropwise to the first mixture at -78 °C and the resulting mixture was allowed to warm to rt and stirred at rt for 1 h. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (30 mL), the layers were separated, the aq. layer was extracted with Et_2O (3x 30 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 50:1) yielded thioether **363** (1.93 g, 7.59 mmol, 73%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.46-7.45 (m, 1H, SPh), 7.44-7.43 (m, 1H, SPh), 7.39-7.29 (m, 7H, Bn, SPh), 7.24-7.22 (m, 1H, SPh), 4.66 (s, 2H, Bn), 4.42 (s, 2H, H-9) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 137.5 (q, Bn), 132.6 (q, SPh), 129.4 (t, Bn), 128.7 (t, Bn), 128.4 (t, SPh), 128.1 (t, Bn), 126.9 (t, SPh), 126.6 (t, SPh), 95.5 (q, C-4), 73.9 (q, C-3a), 71.7 (s, Bn), 58.4 (s, C-9) ppm; **GC-MS:** *m/z calc.* for $C_{16}H_{14}OS$ $[M]^+$: 254.0765; *found*: 254.0775; **R_f** (20:1 PE/EtOAc): 0.42.

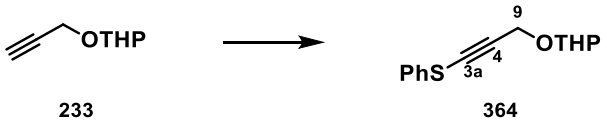
((3-(Benzyloxy)prop-1-yn-1-yl)sulfonyl)benzene 365



$(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (468.9 mg, 0.38 mmol, 0.05 eq) in H_2O_2 (30% wt in H_2O, 9.4 mL, 91.06 mmol, 12.00 eq) was added slowly to a stirred solution of thioether **363** (1.93 g, 7.59 mmol, 1.00 eq) in wet EtOH (31.0 mL) at rt and the resulting mixture was stirred at rt overnight. The reaction mixture was diluted with CH_2Cl_2 (50 mL), the layers were separated and the aq. layer was extracted with CH_2Cl_2 (3x 10 mL), the comb. org. layers were washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1) yielded sulfone **365** (1.76 g, 6.14 mmol, 81%) as a white amorphous solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.04 (m, 2H, SO_2Ph), 7.73 (m, 1H, SO_2Ph), 7.62-7.58 (m, 2H, SO_2Ph), 7.37-7.31 (m, 3H, Bn), 7.28-7.26 (m, 2H, Bn), 4.45 (s, 2H, Bn), 4.28 (s, 2H, H-9) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 141.4 (q, Bn), 136.3 (q, SO_2Ph), 134.6 (t, Bn), 129.6 (t, Bn), 128.8 (t, Bn), 128.5 (t, SO_2Ph), 128.4 (t, SO_2Ph), 127.7 (t, SO_2Ph), 90.8 (q, C-4), 83.3 (q, C-3a), 72.7 (s, Bn), 56.8 (s, C-9) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{16}H_{14}O_3SNa$ $[M+Na]^+$: 309.0561; *found*: 309.0567; **R_f** (10:1 PE/EtOAc): 0.16; **mp.:** 61 °C.

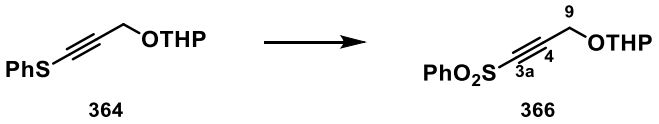
2-((3-(Phenylthio)prop-2-yn-1-yl)oxy)tetrahydro-2*H*-pyran 364



*n*BuLi (2.5 M in hex, 2.6 mL, 6.28 mmol, 1.10 eq) was added dropwise to a stirred solution of ether **233** (0.80 g, 5.71 mmol, 1.00 eq) in THF (13.0 mL) at -78 °C and the resulting mixture was stirred at -78 °C for 1 h. In a second flask MeI (0.40 mL, 6.28 mmol, 1.10 eq) was added dropwise to a stirred solution of Ph_2S_2 (1.37 g, 6.28 mmol, 1.10 eq) in THF (23.0 mL) at rt and the resulting mixture was stirred at rt for 1 h. Then, the latter was added dropwise to the first mixture at -78 °C and the resulting mixture was allowed to warm to rt and stirred at rt for 1 h. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (20 mL), the layers were separated, the aq. layer was extracted with Et_2O (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 50:1 – 20:1) yielded thioether **364** (1.35 g, 5.42 mmol, 95%) as a colorless oil. The analytical data match those reported in the literature.[150]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.44 (m, 2H, SPh), 7.35-7.32 (m, 2H, SPh), 7.24-7.20 (m, 1H, SPh), 4.88 (t, *J* = 3.25 Hz, 1H, THP), 4.51 (d, 3.12 Hz, 2H, H-9), 3.90-3.84 (m, 1H, THP), 3.57-3.54 (m, 1H, THP), 1.85-1.72 (m, 2H, THP), 1.66-1.55 (m, 4H, THP) ppm; **R_f** (20:1 PE/EtOAc): 0.37.

2-((3-(Phenylsulfonyl)prop-2-yn-1-yl)oxy)tetrahydro-2*H*-pyran 366



$(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (49.8 mg, 0.04 mmol, 0.05 eq) in H_2O_2 (30% wt in H_2O, 1.0 mL, 9.66 mmol, 12.00 eq) was added slowly to a stirred solution of thioether **364** (200.0 mg, 0.81 mmol, 1.00 eq) in wet EtOH (3.2 mL) at rt and the resulting mixture was stirred at rt overnight. The reaction mixture was diluted with CH_2Cl_2 (10 mL), the layers were separated and the aq. layer was extracted with CH_2Cl_2 (3x 50 mL), the comb. org. layers were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded sulfone **366** (106.2 mg, 0.38 mmol, 47%) as a colorless syrup. The analytical data match those reported in the literature.[150]

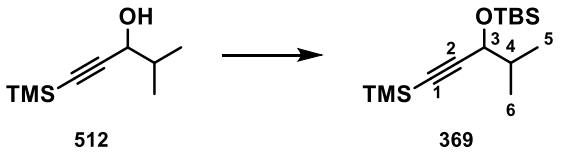
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.03-8.01 (m, 2H, SO_2Ph), 7.71-7.67 (m, 1H, SO_2Ph), 7.61-7.57 (m, 2H, SO_2Ph), 4.70 (t, *J* = 4.04 Hz, 1H, THP), 4.34 (d, *J* = 4.44 Hz, 2H, H-9), 3.77-3.72 (m, 1H, THP), 3.49-3.47 (m, 1H, THP), 1.81-1.66 (m, 2H, THP), 1.64-1.52 (m, 4H, THP) ppm; **R_f** (10:1 PE/EtOAc): 0.16.

4-Methyl-1-(trimethylsilyl)pent-1-yn-3-ol 512

*n*BuLi (1.6 M in hex, 5.2 mL, 8.32 mmol, 1.20 eq) was added dropwise to a stirred solution of TMS-acetylene (1.2 mL, 8.32 mmol, 1.20 eq) in THF (42 mL) at -78 °C. The mixture was stirred at -78 °C for 30 min, then aldehyde **368** (0.64 mL, 6.94 mmol, 1.00 eq) was added dropwise at -78 °C. The mixture was allowed to warm to 0 °C over 2 h. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (20 mL), the layers were separated, the aq. layer was extracted with EtOAc (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded alcohol **512** (1.12 g, 6.57 mmol, 95%) as a colorless oil. The analytical data match those reported in the literature.[242]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.15 (t, *J* = 5.70 Hz, 1H, H-3), 1.86 (se, *J* = 6.56 Hz, 1H, H-4), 1.73 (d, *J* = 5.76 Hz, 1H, OH), 0.99 (t, *J* = 6.63 Hz, 6H, H-5, H-6), 0.17 (s, 9H, TMS) ppm; $\mathbf{R_f}$ (10:1 PE/EtOAc): 0.39.

tert-Butyldimethyl((4-methyl-1-(trimethylsilyl)pent-1-yn-3-yl)oxy)silane 369

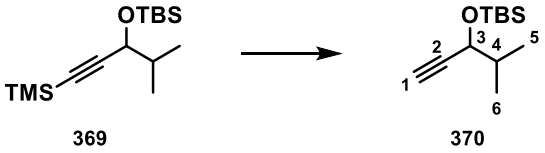


512 369

2,6-Lutidine (1.7 mL, 14.45 mmol, 2.20 eq) and TBSOTf (2.0 mL, 8.54 mmol, 1.30 eq) were successively added to a stirred solution of alcohol **512** (1.12 g, 6.57 mmol, 1.00 eq) in CH_2Cl_2 (42 mL) at 0 °C. The mixture was allowed to warm to rt and stirred for 2 h at rt. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (40 mL), the aq. layer was extracted with Et_2O (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 50:1) yielded TBS ether **369** (1.86 g, 6.53 mmol, 99%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ =4.07 (d, *J* = 6.12 Hz, 1H, H-3), 1.79 (se, *J* = 6.56 Hz, 1H, H-4), 0.95 (dd, *J* = 6.58, 5.68 Hz, 6H, H-5, H-6), 0.90 (s, 9H, TBS), 0.15 (s, 9H, TMS), 0.13 (s, 3H, TBS), 0.10 (s, 3H, TBS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 107.1 (q, C-2), 89.2 (q, C-1), 69.0 (t, C-3), 35.3 (t, C-4), 26.0 (p, TBS), 25.8 (q, TBS), 18.1 (p, C-5), 18.1 (p, C-6), 0.1 (p, TMS), -4.3 (p, TBS), -4.9 (p, TBS) ppm; $\mathbf{R_f}$ (50:1 PE/EtOAc): 0.83.

tert-Butyldimethyl((4-methylpent-1-yn-3-yl)oxy)silane 370

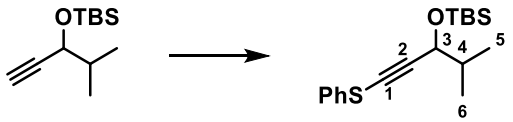


369 370

K_2CO_3 (1.08 g, 7.80 mmol, 1.20 eq) was added to a stirred solution of TMS-alkyne **369** (1.85 g, 6.50 mmol, 1.00 eq) in MeOH (22.0 mL) at rt and the resulting mixture was stirred at rt overnight. The reaction was diluted with pentanes and water (1:1, 50 mL), the aq. layer was extracted with penatnes (4x, 20 mL), the comb. org. layer was washed with water (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (pentanes 100%) yielded alkyne **370** (1.38 g, 6.50 mmol, *quant.*) as a colorless oil. The analytical data match those reported in the literature.[243]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.11 (dd, *J* = 5.68, 2.08 Hz, 1H, H-3), 2.35 (d, *J* = 2.04 Hz, 1H, H-1), 1.82 (se, *J* = 6.46 Hz, 1H, H-4), 0.97 (dd, *J* = 8.06, 6.66 Hz, 6H, H-5, H-6), 0.91 (s, 9H, TBS), 0.13 (s, 3H, TBS), 0.10 (s, 3H, TBS) ppm; $\mathbf{R_f}$ (100:1 PE/EtOAc): 0.63.

tert-Butyldimethyl((4-methyl-1-(phenylthio)pent-1-yn-3-yl)oxy)silane 513

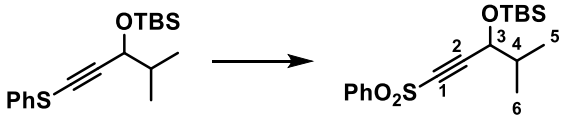


370 513

MeI (480.0 µL, 7.61 mmol, 1.10 eq) was added dropwise to a stirred solution of Ph_2S_2 (1.66 g, 7.61 mmol, 1.10eq) in THF (28.0 mL) at rt and the resulting mixture was stirred at rt for 1 h. In a second flask, *n*BuLi (2.5 M in hex, 3.1 mL, 7.61 mmol, 1.10 mmol) was added dropwise to a stirred solution of alkyne **370** (1.47 g, 6.92 mmol, 1.00 eq) in THF (16.0 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 1 h, then the mixture of the first flask was added dropwise at -78 °C and the resulting mixture was allowed to warm to rt and stirred at rt for 1 h. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (50 mL), the aq. layer was extracted with Et_2O (3x 50 mL), the comb. org. layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE 100%) yielded sulfide **513** (1.92 g, 6.00 mmol, 87%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.44-7.41 (m, 2H, PhS), 7.35-7.31 (m, 2H, PhS), 7.23-7.19 (m, 1H, PhS), 4.34 (d, *J* = 5.64 Hz, 1H, H-3), 1.91 (se, *J* = 6.52 Hz, 1H, H-4), 1.01 (dd, *J* = 7.30, 6.90 Hz, 6H, H-5, H-6), 0.92 (s, 9H, TBS), 0.14 (s, 3H, TBS), 0.11 (s, 3H, TBS) ppm; **R_f** (100:1 PE/EtOAc): 0.72.

tert-Butyldimethyl((4-methyl-1-(phenylsulfonyl)pent-1-yn-3-yl)oxy)silane 371



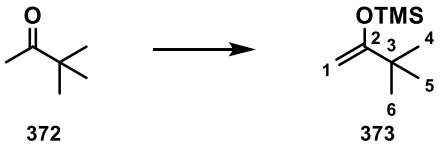
513 371

$(NH_4)_6Mo_7O_{24}{\cdot}4\ H_2O$ (370.1 mg, 0.30 mmol, 0.05 eq) in H_2O_2 (30% wt, 7.5 mL, 71.87 mmol, 12.00 eq) was added dropwise to sulfide **513** (1.92 g, 5.99 mmol, 1.00 eq) in wet EtOH (24.0 mL) at rt and the resulting mixture was stirred at rt overnight. The reaction was diluted with CH_2Cl_2 (30 mL), the aq. layer was extracted with CH_2Cl_2 (3x 20 mL), the comb. org. layers were washwed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 50:1 – 20:1) yielded sulfone **371** (1.60 g, 4.53 mmol, 76%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.01-7.99 (m, 2H, SO_2Ph), 7.69-7.66 (m, 1H, SO_2Ph), 7.60-7.56 (m, 2H, SO_2Ph), 4.19 (d, *J* = 5.73 Hz, 1H, H-3), 1.86 (se, *J* = 6.56 Hz, 1H, H-4), 0.91 (d, *J* = 6.63, 3.32 Hz, 6H, H-5, H-6), 0.82 (s, 9H, TBS), 0.01 (s, 3H. TBS), -0.02 (s, 3H, TBS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 141.9 (q, SO_2Ph), 134.3 (t, SO_2Ph), 129.4 (t, SO_2Ph), 127.5 (t, SO_2Ph), 95.9 (q, C-2), 81.7 (q, C-1), 68.2 (t, C-3), 35.0 (q, C-4), 25.7 (p, TBS), 18.2 (q, TBS), 17.9 (p, C-5), 17.8

(p, C-6), -4.8 (p, TBS), -5.2 (p, TBS) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{18}H_{28}O_3SiSNa$ $[M+Na]^+$: 375.1426; *found*: 375.1427; $\mathbf{R_f}$ (50:1 PE/EtOAc): 0.27.

((3,3-Dimethylbut-1-en-2-yl)oxy)trimethylsilane 373

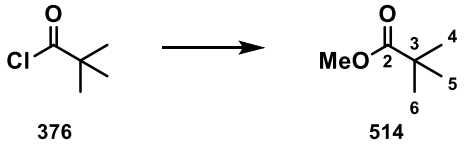


372 373

NEt_3 (4.2 mL, 29.95 mmol, 3.00 eq) and TMSOTf (2.7 mL, 14.98 mmol, 1.50 eq) were successively added to a stirred solution of ketone **372** (1.3 mL, 9.98 mmol, 1.00 eq) in Et_2O (50 mL) at rt. The resulting mixture was allowed to warm to rt and stirred at rt for 4 h. The mixture was diluted with pentanes (50 mL), washed with a sat. aq. $NaHCO_3$-solution (2x 50 mL), dried over $MgSO_4$ and concentrated *vacuo* to yield crude TMS-enolether **373** (1.72 g, 9.98 mmol, *quant.*) as a yellow oil. The analytical data match those reported in the literature.[244]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.08 (d, J = 1.01 Hz, 1H, H-1), 3.93 (d, J = 0.61 Hz, 1H, H-1), 1.04 (s, 9H, H-4, H-5, H-6), 0.21 (s, 9H, TMS) ppm; $\mathbf{R_f}$ (20:1 PE/EtOAc): 0.86.

Methyl pivalate 514

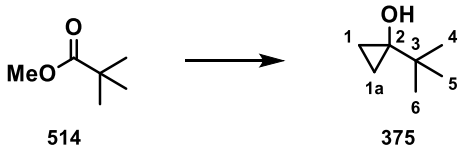


376 514

Acid chloride **376** (4.1 mL, 33.17 mmol, 1.00 eq) was added to MeOH (28.0 mL) at 0 °C and the resulting mixture was allowed to warm to rt and stirred at rt for 1 h. The reaction was terminated by addition of water (20 mL) and diluted with Et_2O (50 mL). The layers were separated and the org. layer was washed with water (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* (45 °C, 100 mbar) to yield ester **514** (1.40 g, 12.05 mmol, 36%) as colorless oil. The analytical data match those reported in the literature.[245]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.66 (s, 3H, OMe), 1.20 (s, 9H, H-4, H-5, H-6) ppm.

1-(*tert*-Butyl)cyclopropan-1-ol 375



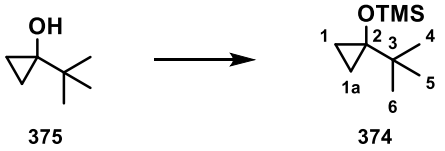
514 375

EtMgBr (3 M in Et_2O, 10.5 mL, 30.13 mmol, 5.00 eq) was added slowly (0.13 mL/min) to a stirred solution of $Ti(OiPr)_4$ (1.8 mL, 6.03 mmol, 1.00 eq) and ester **514** (0.70 g, 6.03 mmol, 1.00 eq) THF

(30.0 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min. The reaction was terminated by addition of 10% HCl (10 mL), the layers were separated, the aq. layer was extracted with EtOAc (3x 10 mL), the comb. org. layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded cyclopropanol **375** (264.1 mg, 2.31 mmol, 38%) as a colorless oil. The analytical data match those reported in the literature.[246]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.83 (bs, 1H, OH), 0.94 (s, 9H, H-4, H-5, H-6), 0.63-0.59 (m, 4H, H-1, H-1a) ppm; **R_f** (10:1 PE/EtOAc): 0.25.

(1-(*tert*-Butyl)cyclopropoxy)trimethylsilane 374

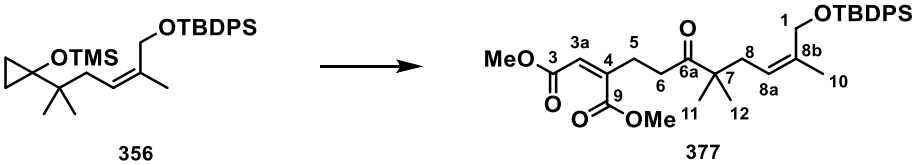


375 374

NEt_3 (0.97 mL, 6.94 mmol, 3.00 eq) and TMSOTf (0.63 mL, 3.47 mmol, 1.50 eq) were successively added to a stirred solution of alcohol **375** (264.0 mg, 2.31 mmol, 1.00 eq) in Et_2O (12.0 mL) at 0 °C. The reaction was allowed to warm to rt and stirred at rt for 2 h. The reaction was diluted with pentanes (20 mL), washed with a sat. aq. $NaHCO_3$-solution (2x 10 mL), brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give crude TMS-ether **374** (342.9 mg, 1.84 mmol, 80%) as a yellow oil which was directly used for the next step. The analytical data match those reported in the literature.[247]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.88 (s, 9H, H-4, H-5, H-6), 0.64-0.60 (m, 4H, H-1, H-1a), 0.10 (s, 9H, TMS) ppm; **R_f** (10:1 PE/EtOAc): 0.68.

Dimethyl 2-((*Z*)-8-((*tert*-butyldiphenylsilyl)oxy)-4,4,7-trimethyl-3-oxooct-6-en-1-yl)maleate 377



356 377

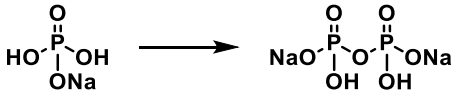
$Cu(BF_4)_2$ was dried under high vacuum at 100 °C for 1 h directly prior to use. TMS-cyclopropanol **356** (50.0 mg, 0.10 mmol, 1.00 eq) was added to a stirred solution of $Cu(BF_4)_2$ (28.8 mg, 0.12 mmol, 1.20 eq) and DMAD (15.0 µL, 0.12 mmol, 1.20 eq) in CH_2Cl_2 (250 µL), TMSO*n*Bu (17.0 µL) and water (3.0 µL) at rt. The resulting mixture was stirred at rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (2 mL) and the aq. layer was extracted with Et_2O (3x 5 mL), the comb. org. layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and

concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1 – 5:1 – 3:1 – 1:1) yielded ketone **377** (15.6 mg, 0.03 mmol, 27%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.68-7.67 (m, 4H, TBDPS), 7.45-7.37 (m, 6H, TBDPS), 5.83 (s, 1H, H-3a), 4.99 (t, *J* = 7.22 Hz, 1H, H-8a), 4.14 (s, 2H, H-1), 3.80 (s, 3H, CO_2Me), 3.71 (s, 3H, CO_2Me), 2.60-2.54 (m, 4H, H-5, H-6), 1.99 (d, *J* = 7.36 Hz, 2H, H-8), 1.81 (s, 3H, H-10), 1.04 (s, 9H, TBDPS), 0.99 (s, 6H, H-11. H-12) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 213.0 (q, C-6a), 169.0 (q. C-9), 165.4 (q, C-3), 149.2 (q, C-4), 137.7 (q, C-8b), 135.8 (t, TBDPS), 133.8 (q, TBDPS), 129.8 (t, TBDPS), 127.8 (t, TBDPS), 121.4 (t, C-8a), 120.5 (t, C-3a), 62.6 (s, C-1), 52.5 (p, CO_2Me), 52.0 (q, CO_2Me), 47.8 (s, C-6), 37.2 (s, C-8), 34.7 (s, C-5), 28.4 (q. TBDPS), 26.9 (p, TBDPS), 24.2 (p, C-11, C-12), 21.6 (p, C-10), 19.4 (q, C-7), ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{33}H_{44}O_6SiNa$ $[M+Na]^+$: 587.2805; *found*: 587.2794; **R_f** (10:1 PE/EtOAc): 0.20.

8.5 Biotransformation Project

Sodium dihydrogen diphosphate 516

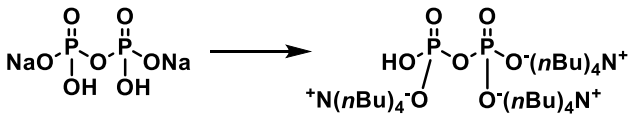


515 516

$NaPO_4H_2$ was freshly recrystallized from a 1:1 mixture of dest. H_2O and abs. EtOH in an ice bath. The obtained needles were filtered off and washed with an excess of abs. EtOH and Et_2O. The crystals were dried under high vacuum at 70 °C for 5 h and then stored under Argon at rt until used. $NaPO_4H_2$ (20.00 g, 166.69 mmol, 1.00 eq) was grinded with a mortar and pestle and the obtained powder was heated in an open flask using a metal heating block to 210 °C overnight. The newly formed powder (18.43 g, 83.04 mmol, *quant.*) was transferred into a new flask and stored in the glove box until further use. The analytical data match those reported in the literature.[248]

^{31}P-NMR (162 MHz, D_2O): δ = -10.18 (s) ppm.

Tri (tetra-*n*-butly)ammonium hydrogen diphosphate 517



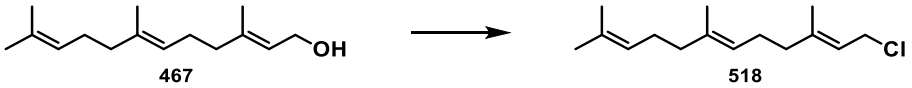
516 517

$Na_2P_2O_7H_2$ (4.32 g, 19.45 mmol, 1.00 eq) was dissolved in water (32.5 mL) and conc. NH_3 (aq. 25%, 1.4 mL) was added. The mixture was loaded onto a column of Dowex AG 50W-X8 cation exchange resin (100–200 mesh, H^+) and eluted with 150 mL of water. The eluent was titrated with (nBu)$_4$OH (40% in water) until a pH of 7.3 is reached. The mixture is concentrated *in vacuo* and the residue was dissolved in water, freezed in liquid nitrogen and lyophilized overnight to yield pyrophosphate **517**

(17.56 g, 19.45 mmol, *quant.*) as a white solid which is stored at 4 °C in the glove. The analytical data match those reported in the literature.[86]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.19-3.15 (m, 24H), 1.66-1.58 (m, 24H), 1.33 (se, 7.34 Hz, 24H), 0.92 (t, 7.36 Hz, 36H).

(2*E*,6*E*)-1-Chloro-3,7,11-trimethyldodeca-2,6,10-triene 518

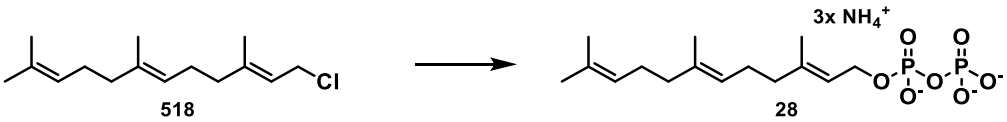


467 518

DMS (40 µL, 0.54 mmol, 1.20 eq) was added dropwise to a stirred solution of NCS (66.1 mg, 0.49 mmol, 1.10 eq) in CH_2Cl_2 (1.0 mL) at -30 °C. The resulting mixture was allowed to warm to 0 °C over 10 min, then it was cooled to -30 °C. Alcohol **467** (100.0 mg, 0.45 mmol, 1.00 eq) in CH_2Cl_2 (0.75 mL) was added dropwise at -30 °C and the resulting mixture was allowed to warm to 0 °C over 2 h. The reaction was terminated by addition of brine (10 mL), the aq. layer was extracted with pentanes (3x 10 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1) yielded chloride **518** (108.0 mg, 0.45 mmol, *quant.*) as a colorless oil. The analytical data match those reported in the literature.[86]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.45 (t, J = 7.96 Hz, 1H), 5.09 (t, J = 6.27 Hz, 1H), 4.10 (d, J = 8.02 Hz, 2H), 2.13-1.96 (m, 8H), 1.73 (s, 3H), 1.68 (s, 3H), 1.60 (s, 6H) ppm; **R_f** (20:1 PE/EtOAc): 0.78.

(2*E*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trien-1-yl trihydrogen triammonium diphosphate 28

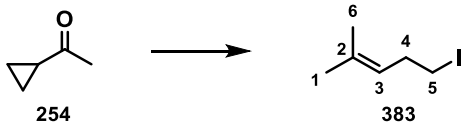


518 28

3Å-sieves were activated by heating to 160 °C overnight under high vacuum. Pieces of preactivated 3Å-sieves were added to a stirred solution of $(n\text{Bu}_4\text{N})_3\text{P}_2\text{O}_7\text{H}$ (487.0 mg, 0.54 mmol, 1.20 eq) in MeCN (5.4 mL) at 0 °C. Then, chloride **518** (108.0 mg, 0.45 mmol, 1.00 eq) in MeCN (4.5 mL) was added dropwise at 0 °C and the resulting mixture was allowed to warm to rt and stirred at rt overnight. The mixture was concentrated *in vacuo* and standard work up using an ion exchange column was applied to yield pyrophosphate **28** (163.2 mg, 0.38 mmol, 84%) as a white gummy which was stored under Argon at -80 °C. The analytical data match those reported in the literature.[86]

^{1}H-NMR (400 MHz, D_2O): δ = 5.45 (t, 1H), 5.22-5.15 (m, 2H), 4.47 (t, 2H), 2.16-2.08 (m, 6H), 2.03-1.99 (m. 2H), 1.71 (s, 3H), 1.67 (s, 3H), 1.61 (s, 6H) ppm.

5-Iodo-2-methylpent-2-ene 383

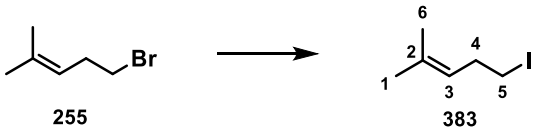


254 383

A solution of cyclopropylmethylketone **254** (3.6 mL, 35.66 mmol, 1.00 eq) in Et_2O (18.0 mL) was added dropwise to a stirred solution of MeMgI (3.0 M in Et_2O, 12.0 mL, 35.66 mmol, 1.00 eq) at 0 °C and the resulting mixture was allowed to warm to rt and stirred at rt for 1 h. The reaction was terminated by transferring the mixture onto a 1:2 mixture of H_2SO_4/H_2O (75 mL) keeping the temperature below 10 °C. The resulting mixture was stirred at rt for 1 h. The layers were separated, the aq. layer was extracted with Et_2O (3x 30 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Distillation (70 °C, 10 mbar) yielded iodide **383** (5.02 g, 23.89 mmol, 67%) as a colorless liquid. The analytical data match those reported in the literature.[249]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.09 (tt, J = 7.38, 0.98 Hz, 1H, H-3), 3.11 (t, J = 7.44 Hz, 2H, H-5), 2.57 (q, J = 7.32 Hz, 2H, H-4), 1.70 (s, 3H, H-1), 1.61 (s, 3H, H-6) ppm; **R_f** (50:1 PE/EtOAc): 0.86; **bp.:** 70 °C (10 mbar).

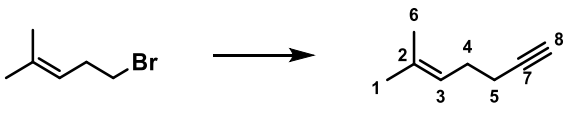
5-Iodo-2-methylpent-2-ene 383



255 383

Bromide **255** (2.00 g, 12.27 mmol, 1.00 eq) was added dropwise to a stirred solution of NaI (4.78 g, 31.89 mmol, 2.60 eq) in acetone (18.5 mL) at rt under exclusion of light. The resulting mixture was stirred overnight and then concentrated *in vacuo*. The residue was diluted in H_2O (30 mL) and extracted with Et_2O (3x 20 mL). The comb. org. layers were washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield crude iodide **383** (2.37 g, 11.27 mmol, 92%) which was used without further purification in the next step. The analytical data match those reported above.

6-Methylhept-5-en-1-yne 382



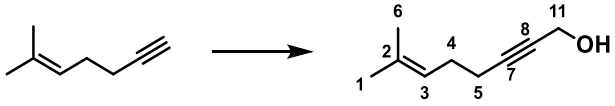
255 382

Bromide **255** (6.47 g, 39.71 mmol, 1.00 eq) was added dropwise to vigorously stirred mixture of lithiumacetylide ethylenediamine complex (4.27 g, 41.70 mmol, 1.05 eq) in DMSO (21 mL) at 0 °C

over 10 min. The mixture was allowed to warm to rt and stirred at rt for 2 h. The reaction was terminated by addition of H_2O (25 mL) keeping the temperature below 15 °C. The layers were separated and the aq. layer was extracted with pentanes (4x 25 mL) and the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Distillation (115-125 °C) yielded alkyne **382** (2.55 g, 23.57mmol, 60%) as a yellow oil. The analytical data match those reported in the literature.[250]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.17-5.15 (m, 1H, H-3), 2.23-2.19 (m, 4H, H-4, H-5), 1.94 (t, J = 2.36 Hz, 1H, H-8), 1.71 (s, 3H, H-6), 1.63 (s, 3H, H-1) ppm; **R_f** (100:1 PE/EtOAc): 0.65.

7-Methyloct-6-en-2-yn-1-ol 381

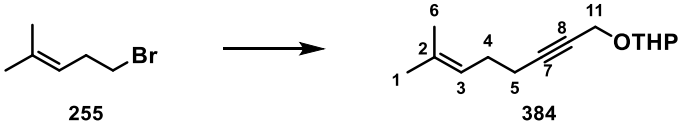


382 381

*n*BuLi (2.5 M in hex, 12.5 mL, 30.85 mmol, 1.10 eq) was added dropwise to a stirred solution of alkyne **382** (3.03 g, 28.01 mmol, 1.00 eq) in THF (70 mL) at −78 °C. The resulting mixture was stirred for 1 h and then paraformaldehyde (1.26 g, 42.00 mmol, 1.50 eq) was added in one portion. The mixture was allowed to warm to rt and was stirred for additional 2 h. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (80 mL) and the layers were separated. The aq. layer was extracted with Et_2O (3x 50 mL) and the comb. org. layers were washed with a sat. aq. $NaHCO_3$-solution (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (pentane/Et_2O 7:3) yielded propargyl alcohol **381** (3.51 g, 25.37mmol, 91%) as a yellow oil. The analytical data match those reported in the literature.[251]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.17-5.14 (m, 1H, H-3), 4.25 (d, J = 5.77 Hz, 2H, H-11), 2.23-2.19 (m, 4H, H-4, H-5), 1.70 (s, 3H, H-6), 1.62 (s, 3H, H-1), 1.53 (bs, 1H, OH) ppm; **R_f** (3:1 PE/EtOAc): 0.52.

2-((7-Methyloct-6-en-2-yn-1-yl)oxy)tetrahydro-2*H*-pyran 384



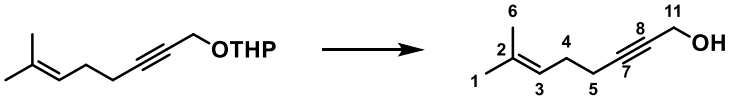
255 384

*n*BuLi (2.5 M in hex, 1.4 mL, 3.50 mmol, 1.90 eq) was added dropwise to a stirred solution of ether **233** (368.4 mg, 2.63 mmol, 1.43 eq) in THF (1.8 mL) at −20 °C and the resulting mixture was stirred for 2 h. Then a solution of bromide **255** (300.0 mg, 1.84 mmol, 1.00 eq) in DMPU (2.6 mL) was added at dropwise at −20 °C. The mixture was allowed to warm to rt overnight. The reaction was

terminated by addition of a sat. aq. NH_4Cl-solution (10 mL). The layers were separated and the aq. layer was extracted with EtOAc (3x 15 mL). The comb. org. layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 25:1) yielded ether **384** (180.4 mg, 0.81 mmol, 44%) as a colorless oil which was directly used for the next step without further purification. The analytical data match those reported in the literature.[251]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.17-5.14 (m, 1H, H-3), 4.82 (q, *J* = 3.67 Hz, 1H, THP), 4.32-4.17 (m, 2H, H-11), 3.87-3.81 (m, 1H, THP), 3.57-3.50 (m, 1H, THP), 2.24-2.17 (m, 4H, H-4, H-5), 1.85-1.73 (m, 1H, THP), 1.70 (s, 3H, H-6), 1.61 (s, 3H, H-1), 1.60-1.52 (m, 5H, THP) ppm; **R_f** (10:1 PE/EtOAc): 0.35.

7-Methyloct-6-en-2-yn-1-ol 381

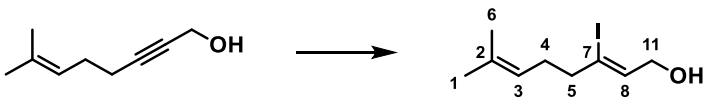


384 **381**

*p*TsOH·H_2O (30.0 mg, 0.17 mmol, 0.10 eq) was added to a stirred solution of ether **384** (377.2 mg, 1.70 mmol, 1.00 eq) in MeOH (23 mL) at rt and the resulting mixture was stirred for 1 h. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (20 mL). The layers were separated and the aq. layer was extracted with CH_2Cl_2 (3x 30 mL). The comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 25:1) yielded alcohol **381** (238.0 mg, 1.71 mmol, *quant.*) as a colorless oil. The analytical data match those reported in the literature.[251]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.17-5.14 (m, 1H, H-3), 4.25 (d, *J* = 5.77 Hz, 2H, H-11), 2.23-2.19 (m, 4H, H-4, H-5), 1.70 (s, 3H, H-6), 1.62 (s, 3H, H-1), 1.53 (bs, 1H, OH) ppm; **R_f** (3:1 PE/EtOAc): 0.52.

(*Z*)-3-Iodo-7-methylocta-2,6-dien-1-ol 380



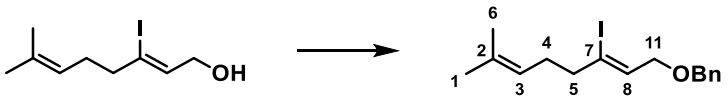
381 **380**

Red-Al® (0.7 mL, 2.43 mmol, 1.68 eq) was added slowly to propargyl alcohol **381** (200.0 mg, 1.45 mmol, 1.00 eq) in THF (2.3 mL) at 0 °C. The resulting mixture was heated under refluxing conditions for 2 h after which it was cooled to rt. A solution of NIS (0.60 g, 2.66 mmol, 1.84 eq) in THF (4.6 mL) was added slowly to the mixture keeping the temperature below 15 °C. The resulting mixture was stirred at rt for 1.5 h and the reaction was terminated by addition of a sat. aq. $Na_2S_2O_3$-

solution (10 mL) and a sat. aq. $NaHCO_3$-solution (10 mL). The layers were separated and the aq. layer was extracted with hexane/ether 1:1 (3x 20 mL). The comb. org. layers were subsequently washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (pentane/Et_2O 10:1) yielded iodide **380** (278.2 mg, 1.05 mmol, 73%) as a yellow oil. The analytical data match those reported in the literature.[252]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.84 (tt, *J* = 5.87, 1.02 Hz, 1H, H-8), 5.07 (tt, *J* = 7.08, 1.34 Hz, 1H, H-3), 4.20 (t, *J* = 5.78 Hz, 2H, H-11), 2.52 (t, *J* = 7.19 Hz, 2H, H-5), 2.22 (q, *J* = 7.19 Hz, 2H, H-4), 1.69 (d, *J* = 0.74 Hz, 3H, H-6), 1.63 (s, 3H, H-1), 1.52 (t, *J* = 5.72 Hz, 1H, OH) ppm; **R_f** (1:1 PE/EtOAc): 0.64.

(*Z*)-(((3-Iodo-7-methylocta-2,6-dien-1-yl)oxy)methyl)benzene 385

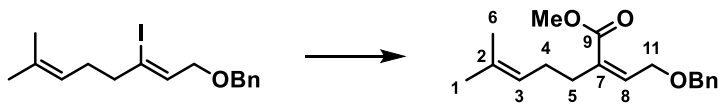


380 385

A mixture of alcohol **380** (404.3 mg, 1.52 mmol, 1.00 eq), Dudley reagent **312** (1.06 g, 3.04 mmol, 2.00 eq) and proton sponge® (1.09 g, 3.04 mmol, 2.00 eq) in $PhCF_3$ (10.2 mL) was heated to 83 °C overnight. The reaction mixture was filtered over Celite™ and washed with an excess of CH_2Cl_2, concentrated *in vacuo* and dry loaded on silica. Column chromatography (PE/EtAOc 20:1) yielded benzylether **385** (355.8 mg, 1.00 mmol, 66%) as an orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.36-7.28 (m, 5H, Bn), 5.82 (t, *J* = 5.56 Hz, 1H, H-8), 5.08 (t, *J* = 7.37 Hz, 1H, H-3), 4.52 (s, 2H, Bn), 4.11 (d, *J* = 5.55 Hz, 2H, H-11), 2.53 (t, *J* = 7.37 Hz, 2H, H-5), 2.22 (q, *J* = 7.21 Hz, 2H, H-4), 1.69 (s, 3H, H-6), 1.63 (s, 3H, H-1) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 138.2 (q, Bn), 133.2 (t, C-8), 132.0 (q, C-2), 128.6 (t, Bn), 128.1 (t, Bn), 127.9 (t, Bn), 122.3 (t, C-3), 110.4 (q, C-7), 74.7 (s, C-11), 72.6 (s, Bn), 45.7 (s, C-5), 28.2 (s, C-4), 25.9 (p, C-6), 18.1 (p, C-1) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{16}H_{21}OINa$ $[M+Na]^+$: 379.0535; *found*: 379.0531; **R_f** (10:1 PE/EtOAc): 0.57.

Methyl (*Z*)-2-(2-(benzyloxy)ethylidene)-6-methylhept-5-enoate 386



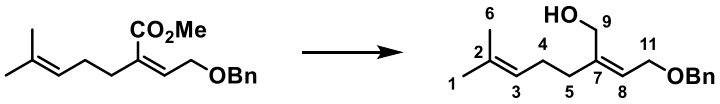
385 386

$PdCl_2(PPh_3)_2$ (0.86 g, 0.83 mmol, 0.10 eq) was added to a by bubbling argon with a balloon with ultra-sonication through degassed solution of vinyl iodide **385** (2.97 g, 8.34 mmol, 1.00 eq), NEt_3 (5.8 mL, 41.72 mmol, 5.00 eq), PPh_3 (4.38 g, 16.69 mmol, 2.00 eq) in DMF (42 mL) and MeOH

(84 mL). The atmosphere was exchanged with CO by bubbling using a balloon through the solution under stirring for 5 min. Then the mixture was heated to 70 °C overnight under an atmosphere of CO stored in a balloon. The mixture was cooled to 0 °C and the reaction was terminated by addition of a sat. aq. NH_4Cl-solution (80 mL). The mixture was diluted by addition of EtOAc (18 mL), the layers were separated and the aq. layer was extracted with EtOAc (3x 100 mL), the comb. org. layers were washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 50:1) yielded enone **386** (1.70 g, 5.85 mmol, 71%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.36-7.27 (m, 5H, Bn), 6.13 (t, *J* = 4.97 Hz, 1H, H-8), 5.10 (t, *J* = 7.00 Hz, 1H, H-3), 4.53 (s, 2H, Bn), 4.47 (d, *J* = 4.94 Hz, 2H, H-11), 3.72 (s, 3H, CO_2Me), 2.29 (t, *J* = 7.37 Hz, 2H, H-5), 2.12 (q, *J* = 7.46 Hz, 2H, H-4), 1.68 (s, 3H, H-6), 1.58 (s, 3H, H-1) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 167.9 (q, C-9), 141.5 (t, C-8), 138.3 (q, Bn), 132.6 (q, C-2), 131.9 (q, C-7), 128.6 (t, Bn), 128.0 (t, Bn), 127.9 (t, Bn), 123.4 (t, C-3), 72.9 (s, Bn), 69.2 (s, C-11), 51.6 (p, CO_2Me), 33.9 (s, C-5), 27.7 (s, C-4), 25.9, (p, C-6), 17.8 (p, C-1) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{18}H_{24}O_3Na$ $[M+Na]^+$: 311.1623; *found*: 311.1627; **R_f** (10:1 PE/EtOAc): 0.20.

(*Z*)-2-(2-(Benzyloxy)ethylidene)-6-methylhept-5-en-1-ol 387

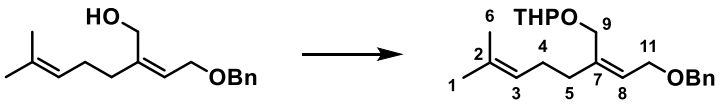


386 387

DIBAL-H (1.0 M in hex, 20.0 mL, 19.80 mmol, 3.00 eq) was rapidly added to a stirred solution of enone **386** (1.90 g, 6.60 mmol, 1.00 eq) in CH_2Cl_2 (20.0 mL) at -78 °C. The mixture was stirred at -78 °C for 5 min. The reaction was terminated by addition of MeOH (10 mL) at -78 °C, then the mixture was diluted with a 1:1 mixture of EtOAc and a sat. aq. Rochelle salt-solution (100 mL) and allowed to warm to rt and stirred at rt for 1 h. The layers were separated, the aq. layer was extracted with EtAOc (3x 50 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded allyl alcohol **387** (1.61 g, 6.17 mmol, 94%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.35-7.28 (m, 5H, Bn), 5.59 (t, *J* = 6.66 Hz, 1H, H-8), 5.11 (bs, 1H, H-3), 4.53 (s, 2H, Bn), 4.10 (t, *J* = 6.76 Hz, 4H, H-9, H-11), 2.17-2.15 (m, 4H, H-4, H-5), 1.92 (t, *J* = 5.89 Hz, 1H, OH), 1.68 (s, 3H, H-6), 1.61 (s, 3H, H-1) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 145.1 (q, C-7), 138.1 (q, Bn), 132.3 (q, C-2), 128.7 (t, Bn), 128.1 (t, Bn), 128.0 (t, Bn), 124.0 (t, C-8), 123.9 (t, C-3), 72.6 (s, Bn), 66.0 (s, C-11), 61.2 (s, C-9), 35.9 (s, C-5), 26. (s, C-4), 25.9 (s, C-6), 17.9 (p C-1) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{17}H_{24}O_2Na$ $[M+Na]^+$: 283.1674; *found*: 283.1668; **R_f** (10:1 PE/EtOAc): 0.20.

(*Z*)-2-((2-(2-(Benzyloxy)ethylidene)-6-methylhept-5-en-1-yl)oxy)tetrahydro-2*H*-pyran 388

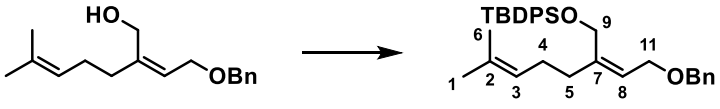


387 388

DHP (89 µL, 0.92 mmol, 1.20 eq) and *p*TsOH·H_2O (2.7 mg, 0.03 mmol, 0.02 eq) were added to a stirred solution of allyl alcohol **387** (200.0 mg, 0.77 mmol, 1.00 eq) in CH_2Cl_2 (1.5 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 10 min. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (2 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 5 mL), the comb. org. layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1) yielded protected diol **388** (51.0 mg, 0.15 mmol, 20%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.35-7.27 (m, 5H, Bn), 5.60 (t, *J* = 6.61 Hz, 1H, H-8), 5.14-5.10 (m, 1H, H-3), 4.56 (t, *J* = 3.33 Hz, 1H, THP), 4.50 (s, 2H, Bn), 4.17 (d, *J* = 11.82 Hz, 1H, H-9), 4.12 (d, *J* = 6.64 Hz, 2H, H-11), 4.02 (d, *J* = 11.80 Hz, 1H, H-9), 3.85-3.80 (m, 1H, THP), 3.55-3.46 (m, 1H, THP), 2.17-2.14 (m, 4H, H-4, H-5), 1.68 (s, 3H, H-6), 1.60-1.49 (m, 9H, H-1, THP) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 140.2 (q, C-7), 138.6 (q, Bn), 132.0 (q, C-2), 128.6 (t, Bn), 128.0 (t, Bn), 128.8 (t, Bn), 125.6 (t, C-8), 124.2 (t, C-3), 97.9 (t, THP), 72.3 (s, Bn), 66.3 (s, C-11), 64.6 (s, C-9), 62.3 (s, THP), 35.5 (s, C-5), 30.7 (s, THP), 26.8 (s, C-4), 25.9 (s, THP), 25.6 (p, C-6), 19.6 (s, THP), 17.9 (p, C-1) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{22}H_{32}O_2Na$ $[M+Na]^+$: 367.2249; *found*: 367.2246; **R_f** (5:1 PE/EtOAc): 0.75.

(*Z*)-((2-(2-(Benzyloxy)ethylidene)-6-methylhept-5-en-1-yl)oxy)(*tert*-butyl)diphenylsilane 389



387 389

TBDPSCl (0.5 mL, 2.02 mmol, 1.05 eq) was added dropwise to a stirred solution of alcohol **387** (0.50 g, 1.92 mmol, 1.00 eq) and imidazole (392.2 mg, 5.76 mmol, 3.00 eq) in CH_2Cl_2 (20.0 mL) at 0 °C. The mixture was stirred at 0 °C for 5 min. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (20 mL). The layers were separated and the aq. layer was extracted with CH_2Cl_2 (3x 20 mL). The comb. org. layers were washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 50:1) yielded ether **389** (0.97 g, 1.96 mmol, *quant.*) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.67-7.65 (m, 4H, TBDPS), 7.45-7.24 (m, 11H, TBDPS, Bn), 5.44 (t, *J* = 6.59 Hz, 1H, H-8), 5.13 (tt, *J* = 6.86, 1.38 Hz, 1H, H-3), 4.35 (s, 2H, Bn), 4.17 (s, 2H, H-9),

3.86 (d, *J* = 6.56 Hz, 2H, H-11), 2.26-2.22 (m, 2H, H-5), 2.17-2.12 (m, 2H, H-4), 1.68 (d, *J* = 0.99 Hz, 3H, H-6), 1.59 (s, 3H, H-1), 1.04 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 142.7 (q, C-7), 138.5 (q, Bn), 135.8 (t, TBDPS), 133.8 (q, TBDPS), 131.8 (q, C-2), 129.8 (t, TBDPS), 128.5 (t, Bn), 128.0 (t, Bn), 127.9 (t, TBDPS), 127.7 (t, Bn), 124.4 (t, C-3), 123.1 (t, C-8), 72.2 (s, Bn), 66.2 (s, C-11), 61.7 (s, C-9), 34.8 (s, C-5), 27.0 (p, TBDPS), 26.9 (s, C-4), 25.9 (p, C-6), 19.4 (q, TBDPS), 17.9 (p, C-1) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{33}H_{42}O_2SiNa$ $[M+Na]^+$: 521.2852; *found*: 521.2838; **R_f** (10:1 PE/EtOAc): 0.46.

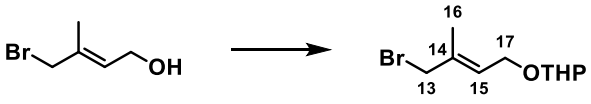
(*Z*)-3-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-7-methylocta-2,6-dien-1-ol 390

389 390

A 1 M solution of LiDBB was added dropwise to a stirred solution of ether **389** (93.4 mg, 0.19 mmol, 1.00 eq) in THF (0.6 mL) at −78 °C until the green color was persistent. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (10 mL). The layers were separated and the aq. layer was extracted with CH_2Cl_2 (3x 5 mL). The comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1) yielded alcohol **390** (59.3 mg, 0.15 mmol, 78%, 4:1 mix at C-8 for desired) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.69-7.67 (m, 4H, TBDPS), 7.47-7.37 (m, 6H, TBDPS), 5.48 (t, *J* = 6.86 Hz, 1H, H-8), 5.09 (t, *J* = 6.72 Hz, 1H, H-3), 4.19 (s, 2H, C-9), 3.96 (d, *J* = 6.78 Hz, 2H, H-11), 2.19-2.05 (m, 4H, H-4, H-5), 1.68 (s, 3H, H-6), 1.58 (s, 3H, H-1), 1.05 (s, 9H, TBDPS) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{26}H_{36}O_2Na$ $[M+Na]^+$: 431.2382; *found*: 431.2382; **R_f** (5:1 PE/EtOAc): 0.33.

(*E*)-2-((4-Bromo-3-methylbut-2-en-1-yl)oxy)tetrahydro-2*H*-pyran 391



250 391

DHP (1.3 mL, 13.77 mmol, 1.20 eq) and *p*TsOH·H_2O (39.6 mg, .023 mmol, 0.02 eq) were added to a stirred solution of allyl alcohol **250** (1.89 g, 11.48 mmol, 1.00 eq) in CH_2Cl_2 (41 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 10 min. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (20 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x

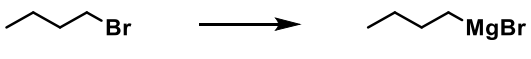
20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 50:1) yielded ether **391** (1.38 g, 5.53 mmol, 49%, *E*/*Z* 5:1) as a colorless oil. The analytical data match those reported in the literature.[86]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.77 (t, *J* = 6.31 Hz, 1H, H-15), 4.62 (t, *J* = 3.34 Hz, 1H, THP), 4.26 (dd, *J* = 12.72, 6.08 Hz, 1H, H-17), 4.04 (dd, *J* = 12.79, 6.94 Hz, 1H, H-17), 3.97 (s, 2H, H-13), 3.89-3.84 (m, 1H, THP), 3.54-3.49 (m, 1H, THP), 1.82 (s, 3H, H-16), 1.75-1.51 (m, 6H, THP) ppm; **R_f** (20:1 PE/EtOAc): 0.72.

Copper bromide dimethyl sulfide complex

CuBr (5.00 g, 34.86 mmol, 1.00 eq) was washed with an excess of MeOH in a fritted column until the filtrate was colorless. It was then dissolved in in an excess of SMe_2 and eluted from the column. Addition of hexanes led to precipation of the $CuBr{\cdot}SMe_2$ complex (5.98 g, 29.08 mmol, 84%) as a white solid which was dried under high vacuum and stored in the glove box at rt.

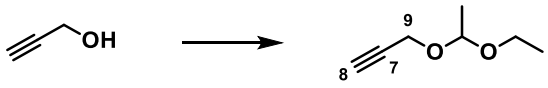
Butylmagnesium bromide 131



519 520

The Grignard reagent was prepared as followed and stored in a flame dried flask under argon at 0 °C. A three neck flask was charged with Mg turnings (0.59 g, 24.08 mmol, 1.10 eq) and Et_2O (6.0 mL) was added. Then, one crystal of iodine was added. A small amount of bromide **519** was added to initiate the reaction. Then a solution of bromide **519** (2.4 mL, 21.89 mmol, 1.00 eq) in Et_2O (55.0 mL) was added dropwise under gentle reflux. The resulting solution was heated under refluxing conditions for 2 h. Then it was cooled to rt and titrated using menthol and phenantrolin as an indicator.[155] The molarity was determined to be 0.30 M.

3-(1-Ethoxyethoxy)prop-1-yne 521



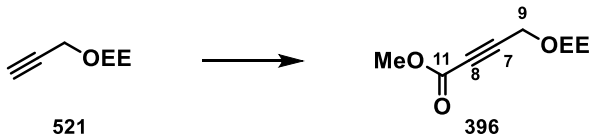
253 521

Propargyl alcohol was freshly distilled from CaH_2. Vinylethylether (5.7 mL, 58.87 mmol, 1.10 eq) was added dropwise to a stirred solution of propargyl alcohol (**253**) (3.1 mL, 53.51 mmol, 1.00 eq) and PPTS (0.67 g, 2.68 mmol, 0.05 eq) in CH_2Cl_2 (15.0 mL) at 0 °C. The resulting mixture was allowed to warm to rt and stirred at rt for 1 h. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (20 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x

20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield crude ether **521** (6.50 g, 50.72 mmol, 95%) as a colorless liquid which was directly used for the next step without further purification. The analytical data match those reported in the literature.[253]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.86 (q, *J* = 5.35 Hz, 1H, EE), 4.21 (d, *J* = 2.60 Hz, 2H, H-9), 3.66 (dq, *J* = 8.66, 7.32 Hz, 1H, EE) 3.52 (dq, *J* = 9.28, 7.10 Hz, 1H, EE), 2.40 (t, *J* = 2.36 Hz, 1H, H-8), 1.34 (d, *J* = 5.52 Hz, 3H, EE), 1.21 (t, *J* = 7.08 Hz, 3H, EE) ppm; **R_f** (50:1 PE/EtOAc): 0.28.

Methyl 4-(1-ethoxyethoxy)but-2-ynoate 396

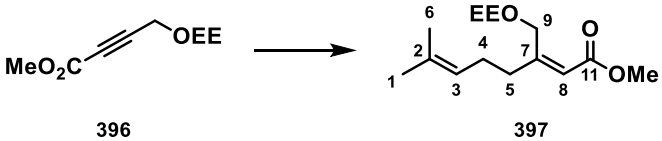


521 396

*n*BuLi (2.5 M in hex, 10.5 mL, 25.75 mmol, 1.10 eq) was added dropwise to a stirred solution of ether **521** (3.00 g, 23.41 mmol, 1.00 eq) in THF (120 mL) at -78 °C and the resulting mixture was stirred at -78 °C for 1 h. Then methylchloroformiate (2.00 mL, 25.75 mmol, 1.10 eq) was added dropwise at -78 °C and the resulting mixture was allowed to warm to rt over 2 h. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (50 mL), the layers were separated, the aq. layer was extracted with EtOAc (3x 50 mL), the comb. org. layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography yielded alkynoate **396** (3.66 g, 19.68 mmol, 84%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.85 (q, *J* = 5.35 Hz, 2H, EE), 4.33 (d, *J* = 2.70 Hz, 2H, H-9), 3.78 (s, 3H, CO_2Me), 3.65 (dq, *J* = 8.85, 7.25 Hz, 1H, EE), 3.51 (dq, *J* = 9.11, 7.16 Hz, 1H, EE), 1.34 (d, *J* = 5.41 Hz, 3H, EE), 1.21 (t, *J* = 7.03 Hz, 3H, EE) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 153.8 (q, C-11), 99.1 (t, EE), 84.4 (q, C-7), 77.2 (q, C-8), 61.1 (s, EE), 53.0 (p, CO_2Me), 52.1 (s, C-9), 19.7 (p, EE), 15.4 (p, EE) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_9H_{14}O_4Na$ $[M+Na]^+$: 209.0790; *found*: 209.0793; **R_f** (10:1 PE/EtOAc): 0.37.

Methyl (*Z*)-3-((1-ethoxyethoxy)methyl)-7-methylocta-2,6-dienoate 397



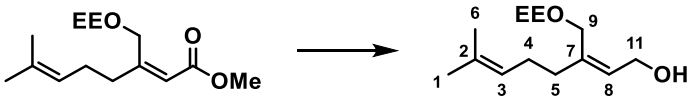
396 397

A two-neck flask equipped with a reflux condenser was charged with Mg turnings (208.8 mg, 8.59 mmol, 1.60 eq) in Et_2O (2.7 mL) and a single crystal of iodine was added. Then a few drops of bromide **255** (1.31 g, 8.06 mmol, 1.50 eq) were added to initiate the reaction and the remaining bromide **255** was carefully added dropwise as a solution in Et_2O (5.4 mL) maintaining a gentle reflux.

Then the solution was heated under refluxing conditions for 1.5 h and then it was cooled to rt and added to a stirred slurry of CuBr·DMS (1.32 g, 6.44 mmol, 1.20 eq) in THF (13.0 mL) at -40 °C. The resulting black mixture was stirred at -40 °C for 2 h and then the mixture was cooled to -78 °C and alkynoate **396** (1.00 g, 5.37 mmol, 1.00 eq) in THF (5.4 mL) was added dropwise at -78 °C. The resulting mixture was stirred at -78 °C for 2 h. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (20 mL) at -78 °C and the mixture was allowed to warm to rt. The layers were separated, the aq. layer was extracted with EtOAc (3x 20 mL), the comb. org. layers were washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography yielded enoate **397** (1.05 g, 3.87 mmol, 72%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.72 (s, 1H, H-8), 5.10 (t, *J* = 7.03 Hz, 1H, H-3), 4.73-4.62 (m, 3H, EE, H-9), 3.71-3.63 (m, 1H, EE), 3.69 (s, CO_2Me), 3.54-3.46 (m, 1H, EE), 2.35-2.31 (m, 2H, H-5), 2.20-2.15 (m, 2H, H-4), 1.68 (s, 3H, H-6), 1.61 (s, 3H, H-1), 1.33 (d, *J* = 5.53 Hz, 3H, EE), 1.21 (t, *J* = 7.05 Hz, 3H, EE) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 166.7 (q, C-11), 160.6 (q, C-7), 132.7 (q, C-2), 123.4 (t, C-3), 116.1 (t, C-8), 100.3 (t, EE), 63.9 (s, C-9), 61.6 (s, EE), 51.3 (p, CO_2Me), 35.3 (s, C-5), 26.6 (s, C-4), 25.9 (p, C-6), 20.2 (p, EE), 17.9 (p, C-1), 15.5 (p, EE) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{15}H_{26}O_4Na$ $[M+Na]^+$: 293.1729; *found*: 293.1717; **R_f** (10:1 PE/EtOAc): 0.57.

(*Z*)-3-((1-Ethoxyethoxy)methyl)-7-methylocta-2,6-dien-1-ol 398



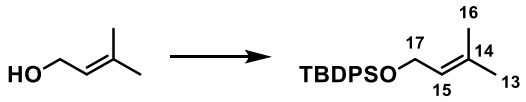
397 **398**

DIBAL-H (1.0 M in hex, 11.1 mL, 11.1 mmol, 3.00 eq) was quickly added to a stirred solution of enoate **397** (1.00 g, 3.70 mmol, 1.00 eq) in CH_2Cl_2 (11.2 mL) at -78 °C. The mixture was stirred at -78 °C for 5 min. The reaction was terminated by addition of MeOH (5 mL) at -78 °C, then the mixture was diluted with a 1:1 mixture of EtOAc and a sat. aq. Rochelle salt-solution (100 mL) and allowed to warm to rt and stirred at rt for 1 h. The layers were separated, the aq. layer was extracted with EtAOc (3x 30 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1 – 2.5) yielded allyl alcohol **398** (0.88 g, 3.61 mmol, 98%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.70 (t, *J* = 7.11 Hz, 1H, H-8), 5.10 (m, 1H, H-3), 4.74 (q, *J* = 5.26 Hz, 1H, EE), 4.23-4.05 (m, 2H, H-11), 4.08 (d, *J* = 2.40 Hz, 2H, H-9), 3.66-3.59 (m, 1H, EE), 3.55-3.47 (m, 1H, EE), 2.13 (s, 4H, H-4, H-5), 1.99 (t, *J* = 5.64 Hz, 1H, OH), 1.68 (s, 3H, H-6), 1.60 (s, 3H, H-1), 1.33 (d, *J* = 5.42 Hz, 3H, EE), 1.22 (t, *J* = 7.08 Hz, 3H, EE) ppm; **^{13}C-NMR**

(100 MHz, $CDCl_3$): δ = 140.2 (q, C-8), 132.1 (q, C-2), 128.2 (t, C-8), 123.9 (t, C-3), 98.7 (t, EE), 62.9 (s, H-9), 60.0 (s, EE), 58.7 (s, C-9), 35.9 (s, C-5), 26.7 (s, C-4), 25.9 (p, C-6), 19.7 (p, EE), 17.9 (p, C-1), 15.4 (p, EE) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{14}H_{26}O_3Na$ $[M+Na]^+$: 265.1780; *found*: 265.1769; $\mathbf{R_f}$ (10:1 PE/EtOAc): 0.14.

tert-Butyl((3-methylbut-2-en-1-yl)oxy)diphenylsilane 399

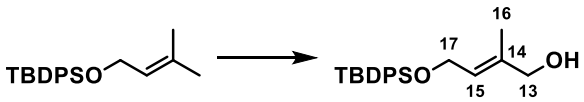


57 399

Imidazole (5.93 g, 87.08 mmol, 2.50 eq) and TBDPSCl (10.0 mL, 38.31 mmol, 1.10 eq) were added to a stirred solution of prenol **57** (3.6 mL, 34.83 mmol, 1.00 eq) in CH_2Cl_2 (35.0 mL) at rt. The resulting mixture was stirred at rt overnight. The mixture was diluted with pentanes (100 mL) and stirred at rt for 30 min. The solid was filtered off and washed with an excess of pentanes. The filtrate was washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield crude TBDPS-ether **399** (11.30 g, 34.83 mmol, *quant.*) as a colorless oil which was directly used for the next step. The analytical data match those reported in the literature.[86]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.71-7.69 (m, 4H, TBDPS), 7.44-7.36 (m, 6H, TBDPS), 5.38 (tt, *J* = 6.42, 1.33 Hz, 1H, H-15), 4.20 (d, *J* = 6.39 Hz, 2H, H-17), 1.69 (s, 3H, H-16), 1.46 (s, 3H, H-13), 1.04 (s. 9H, TBDPS) ppm; $\mathbf{R_f}$ (10:1 PE/EtOAc): 0.50.

(*E*)-4-((*tert*-Butyldiphenylsilyl)oxy)-2-methylbut-2-en-1-ol 400



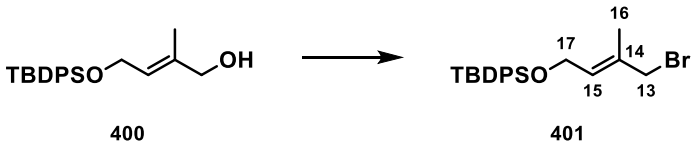
399 400

*t*BuOOH (70% in H_2O, 16.0 mL, 121.91 mmol, 3.50 eq) was added dropwise to a stirred solution of salicylic acid (481.1 mg, 3,48 mmol, 0.10 eq) and SeO_2 (386.5 mg, 3.48 mmol, 0.10 eq) in CH_2Cl_2 (70 mL) at rt. The resulting mixture was stirred at rt for 10 min, then alkene **399** (11.30 g, 34.83 mmol, 1.00 eq) was addd at rt and the resulting mixture was stirred at rt for 2 d. The reaction was terminated by addition of an aq. 10% $NaHCO_3$-solution (100 mL), the layers were separated and the aq. layer was extracted with Et_2O (3x 100 mL), the comb. org. layers were washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was dissolved in MeOH (39.0 mL) and cooled to 0 °C. Then, $NaBH_4$ (1.32 g, 34.83 mmol, 1.00 eq) was added in small portions. The resulting mixture was stirred at 0 °C for 30 min. The reaction was terminated by addition of an Et_2O/water-mixture (1:1, 50 mL), the layers were separated, the aq. layer was extracted with Et_2O (3x 50 mL),

the comb. org. layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded alcohol **400** (7.34 g, 21.55 mmol, 62%) as a colorless oil. The analytical data match those reported in the literature.[86]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.70-7.68 (m, 4H, TBDPS), 7.45-7.36 (m, 6H, TBDPS), 5.62 (dt, *J* = 6.49, 0.56 Hz, 1H, H-15), 4.28 (d, *J* = 6.21 Hz, 2H, H-17), 3.96 (d, *J* = 3.35 Hz, 2H, H-13), 1.48 (s, 3H, H-16), 1.05 (s, 9H, TBDPS) ppm; **R_f** (5:1 PE/EtOAc): 0.45.

(*E*)-4-((*tert*-Butyldiphenylsilyl)oxy)-2-methylbut-2-en-1-ol 401

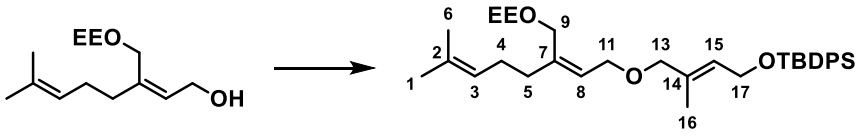


400 401

NBS (2.48 g, 13.91 mmol, 1.10 eq) was added in small portions to a stirred solution of alcohol **400** (4.31 g, 12.64 mmol, 1.00 eq) and PPh_3 (3.98 g, 15.17 mmol, 1.20 eq) in CH_2Cl_2 (80 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 2 h. The mixture was diluted with Et_2O (100 mL) and stirred at rt for 10 min. The solids were filtered off and washed with an excess of Et_2O. The org. layer was concentrated *in vacuo*. Column chromatography (PE/EtOAc 100:1) yielded bromide **401** (4.22 g, 10.46 mmol, 83%) as a colorless oil. The analytical data match those reported in the literature.[86]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.69-7.66 (m, 4H, TBDPS), 7.45-7.37 (m, 6H, TBDPS), 5.79 (t, *J* = 5.78 Hz, 1H, H-15), 4.23 (d, *J* = 5.92 Hz, 2H, H-17), 3.93 (s, 2H, H-13), 1.57 (d, *J* = 0.68 Hz, 3H, H-16), 1.04 (s, 9H, TBDPS) ppm; **R_f** (50:1 PE/EtOAc): 0.64.

(6*E*,11*Z*)-2,2,7,15-Tetramethyl-12-(4-methylpent-3-en-1-yl)-3,3-diphenyl-4,9,14,16-tetraoxa-3-silaoctadeca-6,11-diene 402

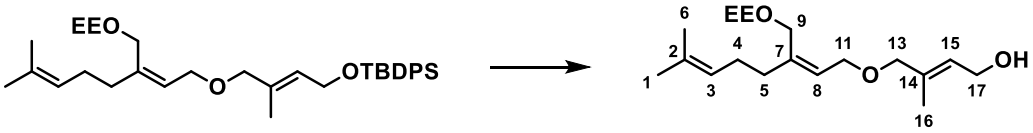


398 402

Alcohol **398** (0.70 g, 2.89 mmol, 1.00 eq) in THF (2.7 mL) was added dropwise to a stirred solution of NaH (60% on mineral oil, 231.1 mg, 5.78 mmol, 2.00 eq) in THF (2.9 mL) at rt. The resulting mixture was heated under refluxing conditions for 2 h, then TBAI (32.1 mg, 0.09 mmol, 0.03 eq) and bromide **401** (1.52 g, 3.75 mmol, 1.30 eq) in THF (1.3 mL) was added dropwise to the refluxing solution and heating was continued overnight. The reaction was terminated by addition of 1 M HCl (5 mL), the aq. layer was extracted with Et_2O (3x 5 mL), the comb. org. layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1 – 10:1) yielded ether **402** (1.62 g, 2.87 mmol, 99%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.69-7.67 (m, 4H, TBDPS), 7.44-7.35 (m, 6H, TBDPS), 5.64 (t, *J* = 5.62 Hz, 1H, H-15), 5.54 (t, *J* = 6.62 Hz, 1H, H-8), 5.11 (m, 1H, H-3), 4.68 (q, 1H, EE), 4.28-4.23 (m, 2H, H-17), 4.09-3.96 (m, 4H, H-9, H-11), 3.83 (s, 2H, H-13), 3.66-3.58 (m, 1H, EE), 3.52-3.44 (m, 1H, EE), 2.15 (m, 4H, H-4, H-5), 1.68 (s, 3H, H-6), 1.61 (s, 3H, H-1), 1.48 (s, 3H, H-16), 1.31 (d, *J* = 5.35 Hz, 3H, EE), 1.20 (t, *J* = 7.03 Hz, 3H, EE), 1.04 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 140.1 (q. C-7, C-14), 135.7 (q, C-2), 135.7 (t, TBDPS), 133.9 (q, C-2), 133.7 (q, TBDPS), 131.9 (q, TBDPS), 129.7 (t, TBDPS), 127.8 (t, TBDPS), 127.4 (t, C-15), 125.4 (t, C-8), 124.1 (t, C-3), 99.1 (t, EE), 75.8 (s, C-13), 68.4 (s, EE), 65.8 (s, C-11), 62.3 (s, C-9), 60.9 (s, C-17), 35.4 (s, C-4), 26.9 (p, TBDPS), 26.7 (s, C-5), 25.9 (p, C-6), 19.9 (p, EE), 19.3 (q, TBDPS), 17.9 (p, C-1), 15.5 (p, EE), 14.2 (p, C-16) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{35}H_{52}O_4SiNa$ $[M+Na]^+$: 587.3533; *found*: 587.3536; **R_f** (10:1 PE/EtOAc): 0.39.

(*E*)-4-(((*Z*)-3-((1-Ethoxyethoxy)methyl)-7-methylocta-2,6-dien-1-yl)oxy)-3-methylbut-2-en-1-ol 403

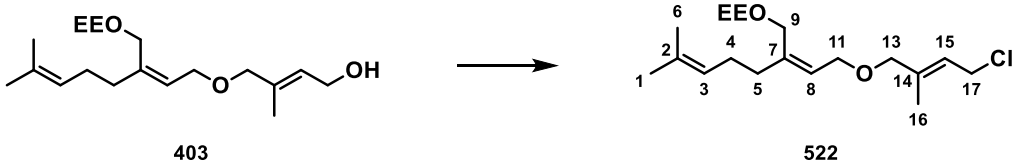


402 403

TBAF (1 M in THF, 3.4 mL, 3.31 mmol, 3.00 eq) was added dropwise to a stirred solution of TBDPS-ether **402** (624.0 mg, 1.10 mmol, 1.00 eq) in THF (12.0 mL) at 0 °C and the resulting mixture was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (20 mL), the aq. layer was extracted with EtOAc (3x 10 mL), the comb. org. layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 3:1 – 1:1) yielded alcohol **403** (322.6 mg, 0.99 mmol, 89%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.66 (tt, *J* = 7.01, 0.64 Hz, 1H, H-15), 5.53 (t, *J* = 6.63 Hz, 1H, H-8), 5.10 (m, 1H, H-3), 4.69 (q, *J* = 5.36 Hz, 1H, EE), 4.20 (d, *J* = 6.63 Hz, 2H, H-17), 4.08 (d, *J* = 11.43 Hz, 1H, H-9), 4.03 (d, *J* = 6.67 Hz, 2H, H-11), 3.99 (d, *J* = 11.37 Hz, 1H, H-9), 3.86 (s, 2H, H-13), 3.66-3.58 (m, 1H, EE), 3.53-3.45 (m, 1H, EE), 2.14 (m, 4H, H-4, H-5), 1.70 (s, 3H, H-6), 1.68 (s, 3H, H-1), 1.60 (s, 3H, H-16), 1.31 (d, *J* = 5.32 Hz, 3H, EE), 1.21 (t, *J* = 7.06 Hz, 3H, EE) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 140.2 (q, C-7), 135.7 (q, C-14), 131.9 (q, C-2), 126.5 (t, C-15), 125.3 (t, C-8), 124.1 (t, C-3), 99.1 (t, EE), 75.3 (s, C-13), 65.7 (s, C-11), 62.6 (s, C-9), 60.4 (s, EE), 59.2 (s, C-17), 35.4 (s, C-4), 26.7 (s, C-5), 25.8 (p C-6), 19.8 (p, EE), 17.8 (p, C-1), 15.5 (p, EE), 14.2 (p, C-16) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{19}H_{34}O_4Na$ $[M+Na]^+$: 349.2355; *found*: 349.2344; **R_f** (5:1 PE/EtOAc): 0.10.

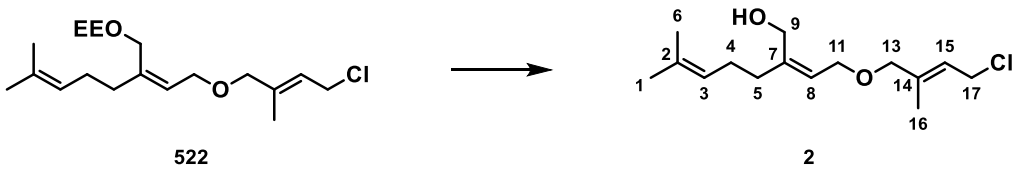
(*Z*)-1-(((*E*)-4-Chloro-2-methylbut-2-en-1-yl)oxy)-3-((1-ethoxyethoxy)methyl)-7-methylocta-2,6-diene 522



DMS (90 µL, 1.21 mmol, 1.20 eq) was added dropwise to a stirred solution of NCS (148.5 mg, 1.11 mmol, 1.10 eq) in CH_2Cl_2 (2.3 mL) at -30 °C. The resulting mixture was allowed to warm to 0 °C over 10 min, then it was cooled to -30 °C. Alcohol **403** (300.0 mg, 1.01 mmol, 1.00 eq) in CH_2Cl_2 (1.7 mL) was added dropwise at -30 °C and the resulting mixture was allowed to warm to 0 °C over 2 h. The reaction was terminated by addition of brine (10 mL), the aq. layer was extracted with Et_2O (3x 10 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 50:1 – 20:1 – 10:1) yielded chloride **522** (75.1 mg, 0.22 mmol, 22%) as a colorless oil. Also 44.4 mg of an inseparable mixture with alcohol **2** was obtained.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.70 (dt, *J* = 7.92, 1.39 Hz, 1H, H-15), 5.53 (t, *J* = 6.64 Hz, 1H, H-8), 5.12-5.09 (m, 1H, H-3), 4.69 (q, *J* = 5.48 Hz, 1H, EE), 4.11 (dd, *J* = 7.91, 0.30 Hz, 2H, H-17), 4.08 (d, *J* = 11.42Hz, 1H, H-9), 4.03 (d, *J* = 6.68 Hz, 2H, H-11), 4.00 (d, *J* = 11.40 Hz, 1H, H-9), 3.88 (s, 2H, H-13), 3.67-3.59 (m, 1H, EE), 3.53-3.45 (m, 1H, EE), 2.17-2.13 (m, 4H, H-4, H-5), 1.74 (d, *J* = 1.34 Hz, 3H, H-6), 1.68 (s, 3H, H-1), 1.60 (d, *J* = 0.76 Hz, 3H, H-16), 1.31 (d, *J* = 5.36 Hz, 3H, EE), 1.21 (t, *J* = 7.10 Hz, 3H, EE) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 140.4 (q, C-7), 139.0 (q, C-14), 132.0 (q, C-2), 125.1 (t, C-8), 124.1 (t, C-3), 122.5 (t, C-15), 99.2 (t, EE), 74.8 (s, C-13), 66.1 (s, C-11), 62.6 (s, C-9), 60.5 (s, EE), 40.3 (s, C-17), 35.4 (s, C-5), 26.7 (s, C-4), 25.8 (p, C-1), 19.9 (p, EE), 17.9 (p, C-6), 15.5 (p, EE), 13.9 (p, C-16) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{19}H_{33}O_3ClNa$ $[M+Na]^+$: 367.2016; *found*: 367.2001; **R_f** (10:1 PE/EtOAc): 0.25.

(*Z*)-2-(2-(((*E*)-4-Chloro-2-methylbut-2-en-1-yl)oxy)ethylidene)-6-methylhept-5-en-1-ol 2

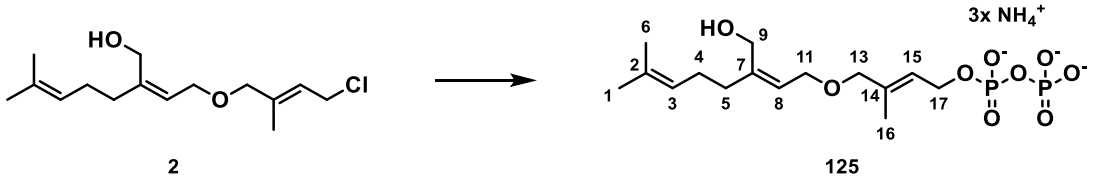


*p*TsOH·H_2O (1.5 mg, 0.01 mmol, 0.10 eq) was added to a stirred solution of ether **522** (29.0 mg, 0.08 mmol, 1.00 eq) in MeOH (1.1 mL) at 0 °C. The resulting mixture was allowed to warm to rt over 1 h. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (5 mL). The aq. layer was extracted with CH_2Cl_2 (3x 10 mL), the comb. org. layers were washed with brine (10 mL),

dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1 – 3:1 – 1:1) yielded alcohol **2** (22.3 mg, 0.08 mmol, 97%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.70 (qt, *J* = 7.91, 2.24 Hz, 1H, H-15), 5.54 (t, *J* = 6.69 Hz, 1H, H-8), 5.12-5.09 (m, 1H, H-3), 4.12-4.10 (m, 4H, H-9, H-17), 4.01 (d, *J* = 6.60 Hz, 2H, H-11), 3.90 (s, 2H, H-13), 2.19-2.15 (m, 4H, H-4, H-5), 1.74 (d, *J* = 0.92 Hz, 3H, H-1), 1.68 (s, 3H, H-6), 1.60 (s, 3H, H-16) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 144.7 (q, C-7), 138.5 (q, C-14), 132.1 (q, C-2), 123.7 (t, C-3, C-8), 122.7 (t, C-15), 74.9 (s, C-13), 65.7 (s, C-11), 60.9 (s, C-9), 40.1 (s, H-17) 35.6 (s, C-5), 26.6 (s, C-4), 25.7 (p, C-6), 17.7 (p, C-16), 13.8 (p, C-1) ppm; **HRMS (ESI-LCT):** *m/z calc*. for $C_{15}H_{25}O_2ClNa$ $[M+Na]^+$: 295.1441; *found*: 295.1432; **R_f** (1:1 PE/EtOAc): 0.66.

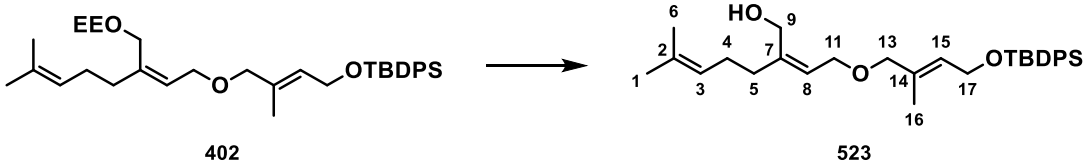
(*E*)-4-(((*Z*)-3-(hydroxymethyl)-7-methylocta-2,6-dien-1-yl)oxy)-3-methylbut-2-en-1-yl triammonium diphosphate 125



Pieces of preactivated 3Å-sieves were added to a stirred solution of $(n\text{Bu}_4\text{N})_3P_2O_7H$ (110.6 mg, 0.13 mmol, 1.50 eq) in MeCN (1.3 mL) at 0 °C. Then, chloride **2** (22.3 mg, 0.08 mmol, 1.00 eq) in MeCN (0.82 mL) was added dropwise at 0 °C and the resulting mixture was allowed to warm to rt and stirred at rt for 2 h. The mixture was concentrated *in vacuo* and standard work up using an ion exchange column was applied to yield pyrophosphate **125** (28.5 mg, 0.06 mmol, 75%) as a white gum which was stored under an atmosphere of Argon at -80 °C.

^{1}H-NMR (400 MHz, D_2O): δ = 5.68 (t, *J* = 6.56 Hz, 1H, H-15), 5.54 (t, *J* = 7.20 Hz, 1H, H-8), 5.22-5.19 (m, 1H, H-3), 4.54 (t, *J* = 6.60 Hz, 2H, H-17), 4.14 (s, 2H, H-9), 4.09 (d, *J* = 7.19 Hz, 2H, H-11), 3.97 (s, 2H, H-13), 2.21-2.17 (m, 4H, H-4, H-5), 1.72 (s, 3H, H-6), 1.69 (s, 3H, H-16), 1.63 (s, 3H, H-1) ppm; **^{13}C-NMR (100 MHz, D_2O):** δ = 143.3 (q, C-7), 136.9 (q, C-14), 133.7 (q, C-2), 123.9 (t, C-8), 123.9, (d, *J* = 7.76 Hz, t, C-15), 123.6 (t, C-3), 74.5 (s, C-13), 65.7 (s, C-11), 62.5 (d, *J* = 5.23 Hz, s, C-17), 58.5 (s, C-9), 34.0 (s, C-5), 25.7 (s, C-4), 24.8 (p, C-1), 16.9 (p, C-6), 13.7 (p, C-16) ppm; **^{31}P-NMR (162 MHz, D_2O):** δ = -9.48 - -10.00 (m, 1P), -10.10 - -10.61 (m, 1P) ppm; **HRMS (ESI-LCT):** *m/z calc*. for $C_{15}H_{27}O_9P_2$ $[M-H]^-$: 413.1130; *found*: 413.1129.

(*Z*)-2-(2-(((*E*)-4-((*tert*-Butyldiphenylsilyl)oxy)-2-methylbut-2-en-1-yl)oxy)ethylidene)-6-methylhept-5-en-1-ol 523

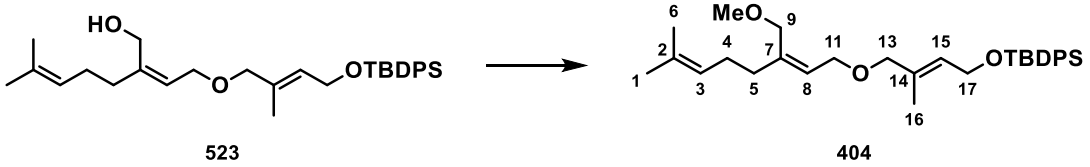


402 523

*p*TsOH·H_2O (19.1 mg, 0.11 mmol, 0.10 eq) was added to a stirred solution of ether **402** (624.0 mg, 1.10 mmol, 1.00 eq) in MeOH (14.0 mL) at 0 °C. The resulting mixture was allowed to warm to rt over 1 h. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (20 mL). The aq. layer was extracted with CH_2Cl_2 (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1 – 3:1) yielded alcohol **523** (387.9 mg, 0.79 mmol, 71%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.69-7.67 (m, 4H, TBDPS), 7.44-7.36 (m, 6H, TBDPS), 5.64 (dt, *J* = 6.09, 1.10 Hz, 1H, H-15), 5.54 (t, *J* = 6.67 Hz, 1H, H-8), 5.13-5.10 (m, 1H, H-3), 4.26 (d, *J* = 5.90 Hz, 2H, C-9), 4.11 (d, *J* = 5.55 Hz, 2H, H-17), 3.96 (d, *J* = 6.68 Hz, 2H, H-11), 3.85 (s, 2H, H-13), 2.20-2.13 (m, 4H, H-4, H-5), 1.97 (t, *J* = 5.90 Hz, 1H, OH), 1.69 (s, 3H, H-6), 1.61 (s, 3H, H-16), 1.48 (s, 3H, H-1), 1.04 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 144.8 (q, C-7), 135.7 (q, TBDPS), 133.9 (t, TBDPS), 133.4 (q, C-14), 132.2 (q, C-2), 129.7 (t, TBDPS), 127.9 (t, TBDPS), 127.8 (t, TBDPS), 127.7 (t, C-8), 124.0 (t, C-15), 124.0 (t, C-3), 75.9 (s, C-13), 65.4 (s, C-11), 61.1 (s, C-17), 60.9 (s, C-9), 35.9 (s, C-5), 27.0 (p, TBDPS), 26.8 (s, C-4), 25.9 (p, C-6), 19.3 (q, TBDPS), 17.9 (p, C-16), 14.2 (p, C-1) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{31}H_{44}O_3SiNa$ $[M+Na]^+$: 515.2957; *found*: 515.2961; **R_f** (5:1 PE/EtOAc): 0.33.

(4*Z*,9*E*)-9,14,14-Trimethyl-4-(4-methylpent-3-en-1-yl)-13,13-diphenyl-2,7,12-trioxa-13-si-lapentadeca-4,9-diene 404

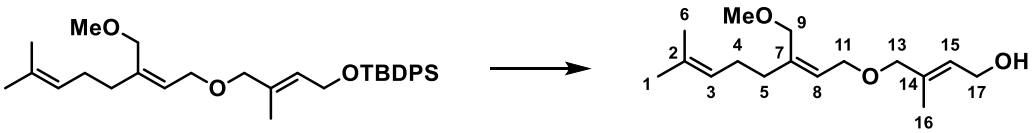


523 404

NaH (95%, 42.55 mg, 1.68 mmol, 2.50 eq) was added to a stirred solution of alcohol **523** (332.0 mg, 0.67 mmol, 1.00 eq) and MeI (0.46 mL, 7.41 mmol, 11.00 eq) in THF/DMF (3:1, 4.5 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 1 h and then allowed to warm to rt and stirred at rt for 1 h. The reaction was terminated by addition of water (10 mL), the aq. layer was extracted with Et_2O (3x 10 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1) yielded ether **404** (288.2 mg, 0.57 mmol, 84%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.70-7.67 (m, 4H, TBDPS), 7.44-7.36 (m, 6H, TBDPS), 5.64 (dt, *J* = 6.13, 1.27 Hz, 1H, H-15), 5.56 (t, *J* = 6.65 Hz, 1H, H-8), 5.14-5.10 (m, 1H, H-3), 4.27 (dd, *J* = 6.19, 0.75 Hz, 2H, H-17), 3.99 (d, *J* = 6.66 Hz, 2H, H-11), 3.93 (s, 2H, H-9), 3.83 (s, 2H, H-13), 3.27 (s, 3H, OMe), 2.14-2.13 (m, 4H, H-4, H-5), 1.68 (s, 3H, H-6), 1.61 (s, 3H, H-16), 1.49 (s, 3H, H-1), 1.04 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 140.1 (q, C-7), 135.7 (t, TBDPS), 134.0 (q, TBDPS), 133.7 (q, C-14), 131.9 (q, C-2), 129.7 (t, TBDPS), 127.8 (t, TBDPS), 127.4 (t, C-15), 125.6 (t, C-8), 124.1 (t, C-3), 75.7 (s, C-13), 70.0 (s, C-9), 65.6 (s, C-11), 60.9 (s, C-17), 58.0 (p, OMe), 35.2 (s, C-5), 27.0 (p, TBDPS), 26.7 (s, C-4), 25.9 (p, C-6), 19.3 (q, TBDPS), 17.9 (p, C-16), 14.2 (p, C-1) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{32}H_{46}O_3SiNa$ $[M+Na]^+$: 529.3114; *found*: 529.3119; **R_f** (10:1 PE/EtOAc): 0.38.

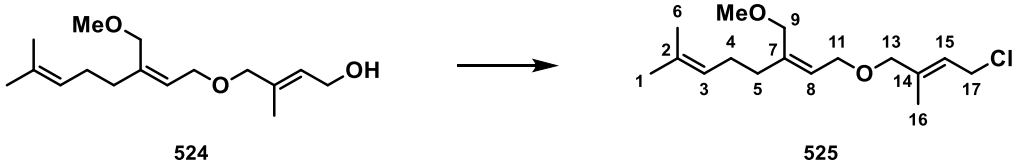
(*E*)-4-(((*Z*)-3-(Methoxymethyl)-7-methylocta-2,6-dien-1-yl)oxy)-3-methylbut-2-en-1-ol 524



TBAF (1 M in THF, 1.8 mL, 1.81 mmol, 3.00 eq) was added dropwise to a stirred solution of TBDPS-ether **404** (306.5 mg, 0.60 mmol, 1.00 eq) in THF (6.2 mL) at 0 °C and the resulting mixture was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (10 mL), the aq. layer was extracted with EtOAc (3x 10 mL), the comb. org. layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 3:1 – 1:1) yielded alcohol **524** (145.2 mg, 0.54 mmol, 89%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.66 (dt, *J* = 7.03, 0.60 Hz, 1H, H-15), 5.56 (t, *J* = 6.60 Hz, 1H, H-8), 5.12-5.08 (m, 1H, H-3), 4.21 (d, *J* = 6.63 Hz, 2H, H-17), 4.03 (d, *J* = 6.63 Hz, 2H, H-11), 3.92 (s, 2H, H-9), 3.87 (s, 2H, H-13), 3.29 (s, 3H, OMe), 2.13-2.12 (m, 4H, H-4, H-5), 1.70 (s, 3H, H-6), 1.68 (s, 3H, H-16), 1.60 (s, 3H, H-1) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 140.1 (q, C-7), 135.9 (q, C-14), 131.9 (q, C-2), 126.2 (t, C-15), 125.5 (t, C-8), 124.1 (t, C-3), 75.5 (s, C-13), 70.0 (s, C-9), 65.9 (s, C-11), 59.3 (s, C-17), 58.1 (p, OMe), 35.3 (s, C-5), 26.6 (s, C-4), 25.8 (p, C-6), 17.8 (p, C-16), 14.2 (p, C-1) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{16}H_{28}O_3Na$ $[M+Na]^+$: 291.1936; *found*: 291.1940; **R_f** (5:1 PE/EtOAc): 0.05.

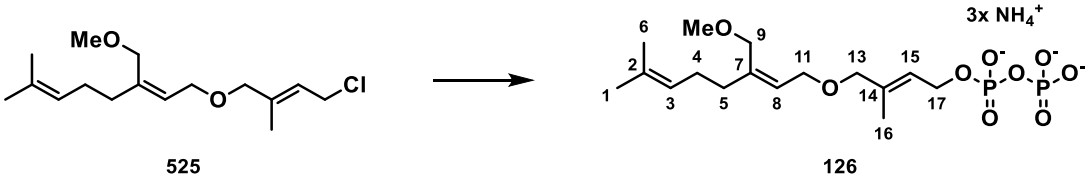
(*Z*)-1-(((*E*)-4-Chloro-2-methylbut-2-en-1-yl)oxy)-3-(methoxymethyl)-7-methylocta-2,6-diene 525



DMS (50 µL, 0.65 mmol, 1.20 eq) was added dropwise to a stirred solution of NCS (79.5 mg, 0.60 mmol, 1.10 eq) in CH_2Cl_2 (1.2 mL) at -30 °C. The resulting mixture was allowed to warm to 0 °C over 10 min, then it was cooled to -30 °C. Alcohol **524** (145.2 mg, 0.54 mmol, 1.00 eq) in CH_2Cl_2 (0.9 mL) was added dropwise at -30 °C and the resulting mixture was allowed to warm to 0 °C overnight. The reaction was terminated by addition of brine (5 mL), the aq. layer was extracted with Et_2O (3x 5 mL), the comb. org. layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1 -1:1) yielded chloride **525** (132.0 mg, 0.46 mmol, 85%, 96% brsm) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.71 (dt, *J* = 8.22, 0.64 Hz, 1H, H-15), 5.55 (t, *J* = 6.62 Hz, 1H, H-8), 5.13-5.08 (m, 1H, H-3), 4.12 (d, *J* = 8.08 Hz, 2H, H-17), 4.02 (d, *J* = 6.64 Hz, 2H, H-11), 3.92 (s, 2H, H-9), 3.88 (s, 2H, H-13), 3.29 (s, 3H, OMe), 2.13-2.12 (m, 4H, H-4, H-5), 1.74 (s, 3H, H-6), 1.68 (s, 3H, H-16), 1.60 (s, 3H, H-1) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 140.4 (q, C-7), 138.9 (q, C-14), 132.0 (q, C-2), 125.3 (t, C-15), 124.0 (t, C-8), 122.5 (t, C-3), 74.8 (s, C-13), 70.0 (s, C-9), 65.9 (s, C-11), 58.1 (p, OMe), 40.3 (s, C-17), 35.3 (s, C-5), 26.6 (s, C-4), 25.8 (p, C-6), 17.9 (p, C-16), 13.9 (p, C-1) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{16}H_{27}O_2ClNa$ $[M+Na]^+$: 309.1597; *found*: 309.1596; **R_f** (10:1 PE/EtOAc): 0.29.

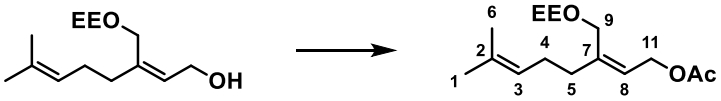
(*E*)-4-(((*Z*)-3-(Methoxymethyl)-7-methylocta-2,6-dien-1-yl)oxy)-3-methylbut-2-en-1-yl triammonium diphosphate 126



Pieces of preactivated 3Å-sieves were added to a stirred solution of $(n\text{Bu}_4\text{N})_3P_2O_7H$ (72.7 mg, 0.13 mmol, 1.05 eq) in MeCN (0.81 mL) at 0 °C. Then, chloride **525** (22.0 mg, 0.08 mmol, 1.00 eq) in MeCN (0.77 mL) was added dropwise at 0 °C and the resulting mixture was allowed to warm to rt overnight. The mixture was concentrated *in vacuo* and standard work up using an ion exchange column was applied to yield pyrophosphate **126** (36.8 mg, 0.08 mmol, *quant.*) as a white gum which was stored under an atmosphere of Argon at -80 °C.

^{1}H-NMR (400 MHz, D_2O): δ = 5.67 (t, *J* = 6.72 Hz, 1H, H-15), 5.62 (t, *J* = 7.24 Hz, 1H, H-8), 5.20-5.15 (m, 1H, H-3), 4.56-4.50 (m, 2H, H-17), 4.08 (d, *J* = 7.00 Hz, 2H, H-11), 4.02 (s, 2H, H-9), 3.95 (s, 2H, H-13), 3.30 (s, 3H, OMe), 2.17-2.13 (m, 4H, H-4, H-5), 1.71 (s, 3H, H-6), 1.68 (s, 3H, H-16), 1.61 (s, 3H, H1) ppm; **^{13}C-NMR (100 MHz, D_2O):** δ = 140.6 (q, C-7), 136.8 (q, C-14), 133.7 (q, C-2), 125.5 (t, C-8), 124.0 (d, *J* = 8.12 Hz, t, C-15), 123.9 (t, C-3), 74.7 (s, C-13), 68.9 (s, H-9), 64.9 (s, H-11), 62.3 (d, *J* = 5.24 Hz, s, C-17), 57.1 (p, OMe), 34.3 (s, C-5), 25.7 (s, C-4), 24.8 (p, C-1), 16.9 (p, C-6), 13.4 (p, C-16) ppm; **^{31}P-NMR (162 MHz, D_2O):** δ = -8.80 - -9.48 (m, 1P), -9.99 - -10.62 (m, 1P) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{16}H_{29}O_9P_2$ $[M-H]^-$: 427.1287; *found*: 427.1279.

(*Z*)-3-((1-Ethoxyethoxy)methyl)-7-methylocta-2,6-dien-1-yl acetate 406

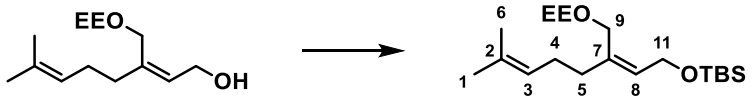


398 **406**

Ac_2O (220 µL, 2.23 mmol, 2.70 eq) was added dropwise to a stirred solution of alcohol **398** (200.0 mg, 0.83 mmol, 1.00 eq), NEt_3 (370 µL, 2.64 mmol, 3.20 eq) and DMAP (10.1 mg, 0.08 mmol, 0.10 eq) in CH_2Cl_2 (1.7 mL) at rt and the resulting mixture was stirred at rt for 2 h. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (5 mL), the aq. layer was extracted with CH_2Cl_2 (3x 5 mL), the comb. org. layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded acetate **406** (212.5 mg, 0.75 mmol, 91%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.51 (t, *J* = 6.90 Hz, 1H, H-8), 5.12-5.07 (m, 1H, H-3), 4.70 (q, *J* = 5.38 Hz, 1H, EE), 4.66 (d, *J* = 7.04 Hz, 2H, H-11), 4.07 (dd, *J* = 34.13, 11.52 Hz, 2H, H-9), 3.67-3.60 (m, 1H, EE), 3.53-3.46 (m, 1H, EE), 2.17-2.10 (m, 4H, H-4, H-5), 2.05 (s, 3H, Ac), 1.68 (s, 3H, H-6), 1.60 (s, 3H, H-1), 1.32 (d, *J* = 5.36 Hz, 3H, EE), 1.21 (t, *J* = 7.04 Hz, 3H, EE) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 171.1 (q, Ac), 142.0 (q, C-7), 132.1 (q, C-2), 123.8 (t, C-8), 122.4 (t, C-3), 99.3 (t, EE), 62.5 (t, C-9), 60.8 (s, EE), 60.6 (s, C-11), 35.4 (s, C-5), 26.6 (s, C-4), 25.8 (p, C-6), 21.2 (p, Ac), 19.8 (p, EE), 17.8 (p, C-1), 15.5 (p, EE) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{16}H_{28}O_4Na$ $[M+Na]^+$: 307.1885; *found*: 307.1882; **R_f** (3:1 PE/EtOAc): 0.50.

((*Z*)-2,2,3,3,10-Pentamethyl-7-(4-methylpent-3-en-1-yl)-4,9,11-trioxa-3-silatridec-6-ene 405

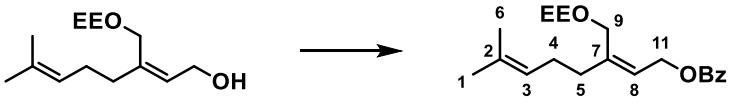


398 405

TBSOTf (150 µL, 0.65 mmol, 1.50 eq) was added dropwise to a stirred solution of alcohol **398** (105.0 mg, 0.43 mmol, 1.00 eq) and 2,6-lutidine (100 µL, 0.87 mmol, 2.00 eq) in CH_2Cl_2 (2.2 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 2 h. The mixture was diluted with CH_2Cl_2 (20 mL), the org. layer was washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded TBS-ether **405** (125.6 mg, 0.35 mmol, 81%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.50 (t, *J* = 6.22 Hz, 1H, H-8), 5.15-5.07 (m, 1H, H-3), 4.69 (q, *J* = 5.30 Hz, 1H, EE), 4.26 (se, *J* = 6.24 Hz, 2H, H-11), 4.02 (dd, *J* = 32.71, 11.30 Hz, 2H, H-9), 3.67-3.59 (m, 1H, EE), 3.53-3.45 (m, 1H, EE), 2.15-2.10 (m, 4H, H-4, H-5), 1.68 (s, 3H, H-6), 1.60 (s, 3H, H-1), 1.31 (d, *J* = 5.36 Hz, 3H, EE), 1.21 (t, *J* = 7.06 Hz, 3H, EE), 0.90 (s, 9H, TBS), 0.07 (s, 6H, TBS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 137.3 (q, C-7), 131.8 (q, C-2), 128.9 (t, C-8), 124.2 (t, C-3), 99.1 (t, EE), 62.8 (t, C-9), 60.4 (s, EE), 59.9 (s, C-11), 35.4 (s, C-5), 26.7 (s, C-4), 26.1 (p, TBS), 25.8 (p, C-6), 19.9 (p, EE), 18.5 (q, TBS), 17.9 (p, C-1), 15.5 (p, EE), -4.9 (p, TBS) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{20}H_{40}O_3SiNa$ $[M+Na]^+$: 379.2644; *found*: 379.2643; $\mathbf{R_f}$ (10:1 PE/EtOAc): 0.50.

(*Z*)-3-((1-Ethoxyethoxy)methyl)-7-methylocta-2,6-dien-1-yl benzoate 526

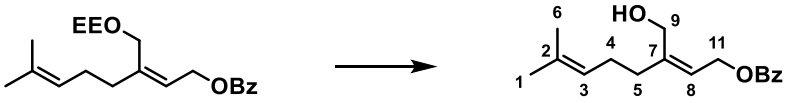


398 526

BzCl (1.6 mL, 13.32 mmol, 3.00 eq) was added dropwise to a stirred solution of alcohol **398** (1.08 g, 4.44 mmol, 1.00 eq), NEt_3 (3.0 mL, 20.87 mmol, 4.70 eq) and DMAP (108.5 mg, 0.89 mmol, 0.10 eq) in CH_2Cl_2 (90 mL) at rt and the resulting mixture was stirred at rt for 1 h. The reaction was terminated by addition of a water (50 mL), the aq. layer was extracted with CH_2Cl_2 (3x 50 mL), the comb. org. layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield crude benzoate **526** (1.54 g, 4.44 mmol, *quant.*) as a colorless oil which was directly used for the next step.

$\mathbf{R_f}$ (3:1 PE/EtOAc): 0.57.

(*Z*)-3-(Hydroxymethyl)-7-methylocta-2,6-dien-1-yl benzoate 409

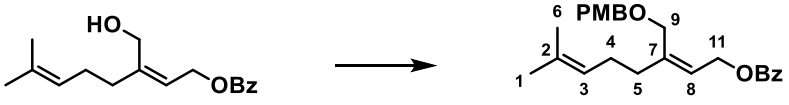


526 409

*p*TsOH·H_2O (76.5 mg, 0.44 mmol, 0.10 eq) was added to a stirred solution of ether **526** (1.54 g, 4.44 mmol, 1.00 eq) in MeOH (45.0 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 40 min. The reaction was terminated by addition of a water (50 mL). The aq. layer was extracted with CH_2Cl_2 (3x 50 mL), the comb. org. layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1 – 3:1) yielded alcohol **409** (1.17 g, 4.28 mmol, 96%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 7.27 Hz, 2H, Bz), 7.56 (t, *J* = 7.39 Hz, 1H, Bz), 7.43 (t, *J* = 7.63 Hz, 2H, Bz), 5.53 (t, *J* = 7.33 Hz, 1H, H-8), 5.09 (t, *J* = 6.35 Hz, 1H, H-3), 4.94 (d, *J* = 7.36 Hz, 2H, H-11), 4.26 (s, 2H, H-9), 2.45 (bs, 1H, OH), 2.25-2.12 (m, 4H, H-4, H-5), 1.65 (s, 3H, H-6), 1.59 (s, 3H, H-1) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 167.0 (q, Bz), 145.4 (q, C-7), 133.2 (t, Bz), 132.3 (q, C-2), 130.3 (q, Bz), 129.8 (t, Bz), 128.5 (t, Bz), 123.7 (t, C-8), 121.5 (t, C-3), 61.4 (s, C-9), 60.6 (s, C-11), 35.6 (s, C-5), 26.7 (s, C-4), 25.8 (p, C-6), 17.9 (p, C-1) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{17}H_{22}O_3Na$ $[M+Na]^+$: 297.1467; *found*: 297.1466; $\mathbf{R_f}$ (3:1 PE/EtOAc): 0.39.

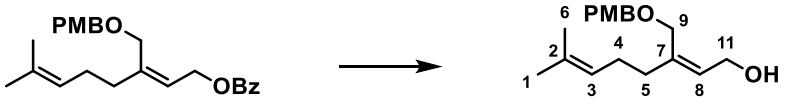
(*Z*)-3-(((4-Methoxybenzyl)oxy)methyl)-7-methylocta-2,6-dien-1-yl benzoate 527



409 527

PMB-trichloroacetimidate (316.7 mg, 1.12 mmol, 1.50 eq) and CSA (8.7 mg, 0.04 mmol, 0.05 eq) were added to a stirred solution of alcohol **409** (205.0 mg, 0.75 mmol, 1.00 eq) in CH_2Cl_2 (2.5 mL) at rt and the resulting mixture was stirred at rt for 2 d. The reaction was terminated by addition of water (5 mL), the aq. layer was extracted with CH_2Cl_2 (3x 5 mL), the comb. org. layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Short plug column chromatography (PE/EtOAc 10:1) yielded crude ether **527** (269.1 mg, 0.68 mmol, 91%) as a colorless oil. **HRMS (ESI-LCT):** *m/z calc.* for $C_{25}H_{30}O_4Na$ $[M+Na]^+$: 417.2042; *found*: 417.2047; $\mathbf{R_f}$ (5:1 PE/EtOAc): 0.33.

(*Z*)-3-(((4-Methoxybenzyl)oxy)methyl)-7-methylocta-2,6-dien-1-ol 410

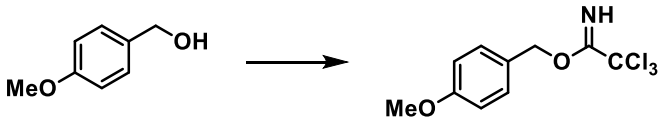


527 410

NaOMe (340.1 mg, 6.30 mmol, 12.00 eq) and TBAI (445.8 mg, 1.21 mmol, 2.30 eq) were added to a stirred solution of ester **527** (207.0 mg, 0.53 mmol, 1.00 eq) in MeOH (8.8 mL) art and the resulting mixture was stirred at rt for 3 h. The reaction was terminated by addition of 1 M HCl (20 mL), diluted with EtOAc (50 mL), the aq. layer was extracted with EtOAc (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 3:1) yielded alcohol **410** (138.5 mg, 0.48 mmol, 91%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.54 Hz, 2H, PMB), 6.88 (d, *J* = 8.61 Hz, 2H, PMB), 5.67 (t, *J* = 6.96 Hz, 1H, H-8), 5.12-5.07 (m, 1H, H-3), 4.42 (s, 2H, PMB), 4.12 (bs, 2H, H-11), 3.99 (s, 2H, C-9), 3.80 (s, 3H, PMB), 2.15-2.08 (m, 4H, H-4, H-5), 1.78 (bs, 1H, OH), 1.68 (s, 3H, H-6), 1.59 (s, 3H, H-1) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 159.4 (q, PMB), 140.4 (q, C-7), 132.1 (q, PMB), 130.2 (q, C-2), 129.6 (t, PMB), 128.2 (t, C-8), 123.9 (t, C-3), 114.0 (t, PMB), 72.3 (s, PMB), 67.7 (s, C-11), 58.9 (s, C-9), 55.4 (p, PMB), 36.1 (s, C-5), 26.7 (s, C-4), 25.8 (p, C-6), 17.9 (p, C-1) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{18}H_{26}O_3Na$ $[M+Na]^+$: 3113.1780; *found*: 313.1772; $\mathbf{R_f}$ (3:1 PE/EtOAc): 0.20.

4-Methoxybenzyl 2,2,2-trichloroacetimidate 412

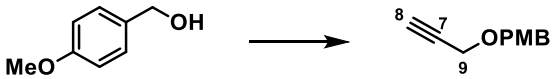


411 412

Alcohol **411** (4.5 mL, 36.19 mmol, 1.00 eq) was added dropwise to a stirred solution of NaH (60%, 289.5 mg, 7.24 mmol, 0.20 eq) in Et_2O (100 mL) at rt and the resulting mixture was stirred at rt for 30 min, then the mixture was cooled to 0 °C and trichloroacetonitrile (4.0 mL, 39.81 mmol, 1.10 eq) was added dropwise at 0 °C and the resulting mixture was stirred at 0 °C for 1 h. The mixture was warmed to rt and concentrated *in vacuo*. The residue was dissolved in pentanes/MeOH (275:1, 30 mL) and stirred for 30 min at rt. The mixture was filtered over Celite^{TM} and concentrated *in vacuo* to yield crude acetimidate **412** (8.32 g, 29.44 mmol, 81%) as a yellow oil which was directly used. The analytical data match those reported in the literature.[254]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.35 (bs, 1H, NH), 7.37 (d, *J* = 8.64 Hz, 2H, Ar), 6.91 (d, *J* = 8.66 Hz, 2H, Ar), 5.27 (s, 2H, CH_2), 3.82 (s, 3H, OMe) ppm; $\mathbf{R_f}$ (3:1 PE/EtOAc): 0.43.

1-Methoxy-4-((prop-2-yn-1-yloxy)methyl)benzene 528

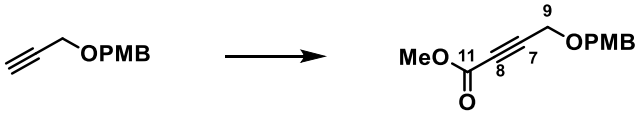


411 528

NaH (60%, 8.68 g, 217.12 mmol, 5.00 eq) and propargylbromide (80% wt in PhMe, 12.91 g, 86.85 mmol, 2.00 eq) were added to a stirred solution of alcohol **411** (5.3 mL, 43.42 mmol, 1.00 eq) in THF (31.0 mL) at rt and the resulting mixture was stirred at rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (20 mL), the aq. layer was extracted with EtOAc (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded alkyne **528** (7.68 g, 43.42 mmol, *quant.*) as a colorless oil. The analytical data match those reported in the literature.[255]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.54 Hz, 2H, PMB), 6.89 (d, *J* = 5.87 Hz, 2H, PMB), 4.55 (s, 2H, PMB), 4.14 (d, *J* = 2.34 Hz, 2H, H-9), 3.81 (s, 3H, PMB), 2.46 (t, *J* = 2.31 Hz, 1H, H-8) ppm; $\mathbf{R_f}$ (5:1 PE/EtOAc): 0.43.

Methyl 4-((4-methoxybenzyl)oxy)but-2-ynoate 411

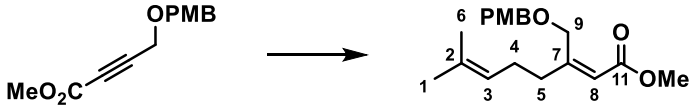


528 411

*n*BuLi (2.5 M in hex, 19.5 mL, 47.92 mmol, 1.10 eq) was added dropwise to a stirred solution of alkyne **528** (7.68 g, 43.56 mmol, 1.00 eq) in THF (150 mL) at -78 °C and the resulting mixture was stirred at -78 °C for 1 h. Then methylchloroformiate (4.4 mL, 56.63 mmol, 1.10 eq) was added dropwise at -78 °C and the resulting mixture was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (50 mL), the layers were separated, the aq. layer was extracted with EtOAc (3x 50 mL), the comb. org. layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography yielded alkynoate **411** (8.88 g, 37.92 mmol, 87%) as a colorless oil. The analytical data match those reported in the literature.[256]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 8.53 Hz, 2H, PMB), 6.89 (d, *J* = 8.55 Hz, 2H, PMB), 4.55 (s, 2H, PMB), 4.26 (s, C-9), 3.81 (s, 3H, PMB), 3.80 (s, 3H, CO_2Me) ppm; $\mathbf{R_f}$ (10:1 PE/EtOAc): 0.20.

Methyl (*Z*)-3-(((4-methoxybenzyl)oxy)methyl)-7-methylocta-2,6-dienoate 412

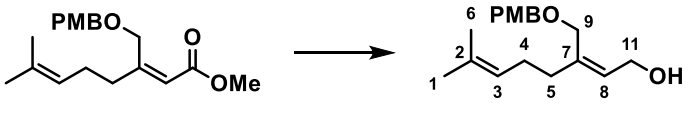


411 412

A two-neck flask equipped with a reflux condenser was charged with Mg turnings (383.7 mg, 15.79 mmol, 3.00 eq) in Et_2O (5.0 mL) and a single crystal of iodine was added. Then a few drops of bromide **255** (1.29 g, 7.89 mmol, 1.50 eq) were added to initiate the reaction and the remaining bromide **255** was carefully added dropwise as a solution in Et_2O (5.3 mL) maintaining a gentle reflux. Then the solution was heated under refluxing conditions for 1.5 h and then it was cooled to rt and added to a stirred slurry of CuBr·DMS (1.30 g, 6.31 mmol, 1.20 eq) in THF (13.0 mL) at -40 °C. The resulting black mixture was stirred at -40 °C for 2 h and then the mixture was cooled to -78 °C and alkynoate **411** (1.23 g, 5.26 mmol, 1.00 eq) in THF (5.4 mL) was added dropwise at -78 °C. The resulting mixture was stirred at -78 °C for 2 h. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (20 mL) at -78 °C and the mixture was allowed to warm to rt. The layers were separated, the aq. layer was extracted with EtOAc (3x 20 mL), the comb. org. layers were washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography yielded enoate **412** (1.48 g, 4.66 mmol, 89%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 7.00 Hz, 2H, PMB), 6.87 (d, *J* = 8.78 Hz, 2H, PMB), 5.74 (s, 1H, H-8), 5.09 (t, *J* = 6.50 Hz, 1H, H-3), 4.63 (s, 2H, PMB), 4.44 (s, 2H, H-9), 3.80 (s, 3H, PMB), 3.68 (s, 3H, CO_2Me), 2.36-2.33 (m, 2H, H-5), 2.20-2.14 (m, 2H, H-4), 1.68 (s, 3H, H-6), 1.58 (s, 3H, H-1) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 166.7 (q, C-11), 160.7 (q, C-8), 159.3 (q, PMB), 132.6 (q, C-2), 130.5 (q, PMB), 129.5 (t, PMB), 123.3 (t, C-3), 116.4 (t, C-8), 113.9 (t, PMB), 72.6 (s, PMB), 68.1 (s, C-9), 55.4 (p, PMB), 51.2 (p, CO_2Me), 35.1 (p, C-5), 26.6 (p, C-4), 25.8 (p, C-6), 17.8 (p, C-1) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{19}H_{26}O_4Na$ $[M+Na]^+$: 341.1729; *found*: 341.1729; $\mathbf{R}_f$ (10:1 PE/EtOAc): 0.33.

(*Z*)-3-(((4-Methoxybenzyl)oxy)methyl)-7-methylocta-2,6-dien-1-ol 410



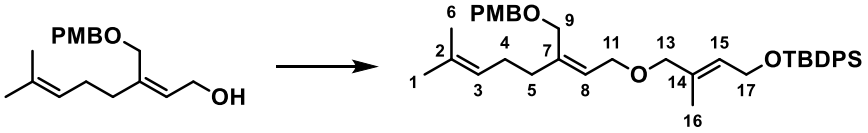
412 410

DIBAL-H (1.0 M in hex, 13.2 mL, 13.19 mmol, 3.00 eq) was quickly added to a stirred solution of enoate **412** (1.40 g, 4.40 mmol, 1.00 eq) in CH_2Cl_2 (13.5 mL) at -78 °C. The mixture was stirred at -78 °C for 5 min. The reaction was terminated by addition of MeOH (5 mL) at -78 °C, then the mixture was diluted with a 1:1 mixture of EtOAc and a sat. aq. Rochelle salt-solution (100 mL) and

allowed to warm to rt and stirred at rt for 1 h. The layers were separated, the aq. layer was extracted with EtAOc (3x 30 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 3:1) yielded allyl alcohol **410** (1.28 g, 4.40 mmol, *quant.*) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.54 Hz, 2H, PMB), 6.88 (d, *J* = 8.61 Hz, 2H, PMB), 5.67 (t, *J* = 6.96 Hz, 1H, H-8), 5.12-5.07 (m, 1H, H-3), 4.42 (s, 2H, PMB), 4.12 (bs, 2H, H-11), 3.99 (s, 2H, C-9), 3.80 (s, 3H, OMe), 2.15-2.08 (m, 4H, H-4, H-5), 1.78 (bs, 1H, OH), 1.68 (s, 3H, H-6), 1.59 (s, 3H, H-1) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 159.4 (q, PMB), 140.4 (q, C-7), 132.1 (q, PMB), 130.2 (q, C-2), 129.6 (t, PMB), 128.2 (t, C-8), 123.9 (t, C-3), 114.0 (t, PMB), 72.3 (s, PMB), 67.7 (s, C-11), 58.9 (s, C-9), 55.4 (p, PMB), 36.1 (s, C-5), 26.7 (s, C-4), 25.8 (p, C-6), 17.9 (p, C-1) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{18}H_{26}O_3Na$ $[M+Na]^+$: 3113.1780; *found*: 313.1772; **R_f** (3:1 PE/EtOAc): 0.20.

(4*Z*,9*E*)-1-(4-Methoxyphenyl)-9,14,14-trimethyl-4-(4-methylpent-3-en-1-yl)-13,13-diphenyl-2,7,12-trioxa-13-silapentadeca-4,9-diene 413



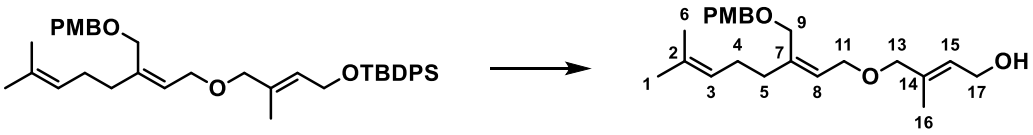
410 413

Alcohol **410** (370.0 mg, 1.27 mmol, 1.00 eq) in THF (1.2 mL) was added dropwise to a stirred solution of NaH (60% on mineral oil, 101.9 mg, 2.55 mmol, 2.00 eq) in THF (1.3 mL) at rt. The resulting mixture was heated under refluxing conditions for 2 h, then TBAI (14.1 mg, 0.04 mmol, 0.03 eq) and bromide **401** (668.2 mg, 1.66 mmol, 1.30 eq) in THF (0.6 mL) was added dropwise to the refluxing solution and heating was continued overnight. The reaction was terminated by addition of 1 M HCl (5 mL), the aq. layer was extracted with Et_2O (3x 5 mL), the comb. org. layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1 – 10:1) yielded ether **413** (0.73 g, 1.19 mmol, 94%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.69-7.67 (m, 4H, TBDPS), 7.44-7.35 (m, 6H, TBDPS), 7.24 (d, *J* = 8.78 Hz, 2H, PMB), 6.86 (d, *J* = 8.63 Hz, 2H, PMB), 5.63 (t, *J* = 5.58 Hz, 1H, H-15), 5.56 (t, *J* = 6.67 Hz, 1H, H-8), 5.12-5.09 (m, 1H, H-3), 4.37 (s, 2H, PMB), 4.26 (d, *J* = 5.94 Hz, 2H, H-17), 3.98 (s, 2H, H-9), 3.94 (d, *J* = 6.67 Hz, 2H, H-11), 3.80-3.79 (m, 5H, PMB, C-13), 2.18-2.11 (m, 4H, H-4, H-5), 1.68 (s, 3H, H-6), 1.59 (s, 3H, H-16), 1.47 (s, 3H, H-1), 1.04 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 159.3 (q. PMB), 140.2 (q, C-7), 135.7 (t, TBDPS), 134.0 (q, TBDPS), 133.7 (q, C-14), 131.9 (q, C-2), 130.6 (q, PMB), 129.7 (t, TBDPS), 129.5 (t, PMB), 127.8 (t, TBDPS), 127.4 (t, C-15), 125.7 (t, C-8), 124.2 (t, C-2), 113.9 (t, PMB), 75.7 (s, C-13), 71.8 (s,

PMB), 67.2 (s, C-9), 65.7 (s, C-11), 60.9 (s, C-17), 55.4 (p, PMB), 35.4 (s, C-5), 27.0 (p, TBDPS), 26.7 (s, C-4), 25.9 (p, C-6), 19.3, (q, TBDPS), 17.9 (p, C-16), 14.2 (p, C-1) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{39}H_{52}O_4SiNa$ $[M+Na]^+$: 635.3533; *found*: 635.3531; $\mathbf{R}_f$ (5:1 PE/EtOAc): 0.38.

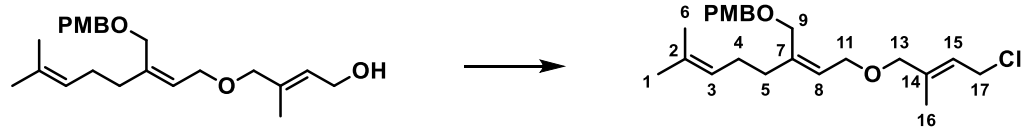
(*E*)-4-(((*Z*)-3-(((4-Methoxybenzyl)oxy)methyl)-7-methylocta-2,6-dien-1-yl)oxy)-3-methylbut-2-en-1-ol 529



TBAF (1 M in THF, 3.6 mL, 3.55 mmol, 3.00 eq) was added dropwise to a stirred solution of TBDPS-ether **413** (0.73 g, 1.18 mmol, 1.00 eq) in THF (12.0 mL) at 0 °C and the resulting mixture was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (20 mL), the aq. layer was extracted with EtOAc (3x 10 mL), the comb. org. layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 1:1) yielded alcohol **529** (374.0 mg, 1.00 mmol, 84%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.44 Hz, 2H, PMB), 6.88 (d, *J* = 8.56 Hz, 2H, PMB), 5.64 (t, *J* = 6.08 Hz, 1H, H-15), 5.56 (t, *J* = 6.68 Hz, 1H, H-8), 5.12-5.09 (m, 1H, H-3), 4.39 (s, 2H, PMB), 4.20 (d, *J* = 6.64 Hz, 2H, H-11), 3.99-3.97 (m, 4H, H-9, H-13), 3.83 (s, 2H, H-17), 3.81 (s, 3H, PMB), 2.19-2.11 (m, 4H, H-4, H-5), 1.68 (s, 6H, H-6, H-16), 1.59 (s, 3H, H-1) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 159.3 (q, PMB), 140.3 (q, C-7), 136.0 (q, C-14), 131.9 (q, C-2), 130.5 (q, PMB), 129.5 (t, PMB), 126.2 (t, C-7), 125.5 (t, C-15), 124.1 (t, C-3), 113.9 (t, PMB), 75.5 (s, C-13), 71.9 (s, PMB), 67.2 (s, C-9), 66.0 (s, C-11), 59.3 (C-17), 55.4 (p, PMB), 35.4 (s, C-5), 26.7 (s, C-4), 25.8 (p, C-6), 17.86 (p, C-16), 14.2 (p, C-1) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{23}H_{34}O_4Na$ $[M+Na]^+$: 397.2355; *found*: 397.2360; $\mathbf{R}_f$ (1:1 PE/EtOAc): 0.23.

1-((((*Z*)-2-(2-(((*E*)-4-Chloro-2-methylbut-2-en-1-yl)oxy)ethylidene)-6-methylhept-5-en-1-yl)oxy)methyl)-4-methoxybenzene 530

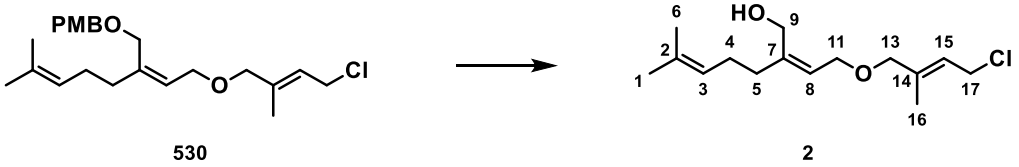


DMS (24 µL, 0.32 mmol, 1.20 eq) was added dropwise to a stirred solution of NCS (39.2 mg, 0.29 mmol, 1.10 eq) in CH_2Cl_2 (0.60 mL) at -30 °C. The resulting mixture was allowed to warm to 0 °C over 10 min, then it was cooled to -30 °C. Alcohol **529** (100.0 mg, 0.27 mmol, 1.00 eq) in CH_2Cl_2 (0.45 mL) was added dropwise at -30 °C and the resulting mixture was allowed to warm to

0 °C over 3 h. The reaction was terminated by addition of brine (5 mL), the aq. layer was extracted with Et_2O (3x 5 mL), the comb. org. layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1) yielded chloride **530** (89.4 mg, 0.23 mmol, 85%) as a colorless oil.

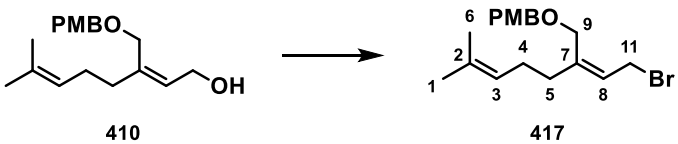
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 7.83 Hz, 2H, PMB), 6.88 (d, *J* = 8.61 Hz, 2H, PMB), 5.69 (dt, *J* = 7.72, 0.60 Hz, 1H, H-8), 5.55 (t, *J* = 6.52 Hz, 1H, H-15), 5.11-5.08 (m, 1H, H-3), 4.39 (s, 2H, PMB), 4.11 (d, *J* = 7.93 Hz, 2H, H-11), 3.98-3.97 (m, 4H, H-9, H-13), 3.84 (s, 2H, H-17), 3.81 (s, 3H, PMB), 2.18-2.11 (m, 4H, H-4, H-5), 1.72 (s, 3H, H-6), 1.68 (s, 3H, H-16), 1.59 (s, 3H, H-1) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 159.3 (q, PMB), 140.6 (q, C-7), 139.0 (q, C-14), 131.9 (q, C-2), 130.5 (q, PMB), 129.5 (t, PMB), 125.3 (t, C-8), 124.1 (t, C-15), 122.5 (t, C-3), 113.9 (t, PMB), 74.8 (s, C-13), 71.9 (s, PMB), 67.2 (s, C-9), 66.0 (s, C-11), 55.4 (p, PMB), 40.3 (s, C-17), 35.4 (s, C-5), 26.7 (s, C-4), 25.8 (p, C-6), 17.9 (p, C-16), 13.9 (p, C-1) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{23}H_{33}O_3ClNa$ $[M+Na]^+$: 415.2016; *found*: 415.2012; **R_f** (5:1 PE/EtOAc): 0.55.

(*Z*)-2-(2-(((*E*)-4-Chloro-2-methylbut-2-en-1-yl)oxy)ethylidene)-6-methylhept-5-en-1-ol 2



$AlCl_3$ (1.0 mg, 0.01 mmol, 0.2 eq) and EtSH (10.5 µL, 0.14 mmol. 4.00 eq) were added to a stirred solution of PMB ether **530** (14.0 mg, 0.04 mmol, 1.00 eq) in CH_2Cl_2 (0.36 mL) at rt and the resulting mixture was stirred for 2 h at rt. The reaction was terminated by addition of water (1 mL) and the aq. layer was extract with EtOAc (3x 1 mL), the comb. org. layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 2:1) yielded alcohol **2** (6.8 mg, 0.03 mmol, 70%) as a colorless oil. The analytical data match those reported before.

(*Z*)-1-(((2-(2-Bromoethylidene)-6-methylhept-5-en-1-yl)oxy)methyl)-4-methoxybenzene 417

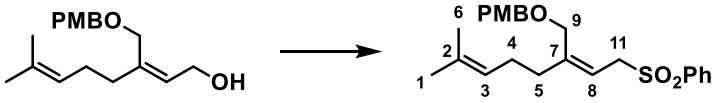


PBr_3 (11 µL, 0.11 mmol, 0.33 eq) was added dropwise to a stirred solution of allyl alcohol **410** (100.0 mg, 0.34 mmol, 1.00 eq) in Et_2O (3.5 mL) at 0 °C and the resulting mixture was stirred at 0 °C. The reaction was terminated by addition of brine (5 mL), the aq. layer was extracted with Et_2O (3x

5 mL), the comb. org. layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield crude bromide **417** (114.7 mg, 0.33 mmol, 94%) as a colorless oil which was directly used for the next step.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 8.76 Hz, 2H, PMB), 6.89 (d, *J* = 8.68 Hz, 2H, PMB), 5.71 (t, *J* = 8.52 Hz, 1H, H-8), 5.08 (t, *J* = 6.80 Hz, 1H, H-3), 4.42 (s, 2H, PMB), 4.04-4.01 (m, 4H, H-9, H-11), 3.81 (s, 3H, PMB), 2.19-2.10 (m, 4H, H-4, H-5), 1.68 (s, 3H, H-6), 1.58 (s, 3H, H-1) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 159.4 (q, PMB), 142.8 (q, C-7), 132.3 (q, PMB), 130.6 (q, C-2), 129.6 (t, PMB), 124.7 (t, C-8), 123.6 (t, C-3), 114.0 (t. PMB), 72.2 (s, PMB), 66.5 (s, C-9), 55.4 (p, PMB), 35.5 (s, C-5), 28.2 (s, C-11), 26.5 (s, C-4), 25.8 (p, C-6), 17.9 (p, C-1) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{18}H_{25}O_2BrNa$ $[M+Na]^+$: 375.0936; *found*: 375.0932; **R_f** (10:1 PE/EtOAc): 0.54.

(*Z*)-1-Methoxy-4-(((6-methyl-2-(2-(phenylsulfonyl)ethylidene)hept-5-en-1-yl)oxy)methyl)benzene 416

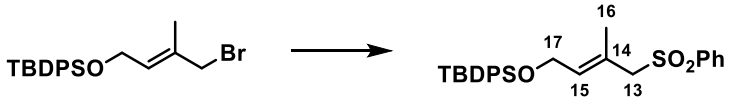


417 416

PPh_3 (144.5 mg, 0.55 mmol, 1.60 eq) and NBS (91.9 mg, 0.52 mmol, 1.50 eq) were added in small portions to a stirred solution of alcohol **417** (100.0 mg, 0.34 mmol, 1.00 eq) in DMF (1.8 mL) at 0 °C and the resulting mixture was allowed to warm to rt over 30 min. Then $NaSO_2Ph$ (113.1 mg, 0.69 mmol, 2.00 eq) and TBAI (12.7 mg, 0.03 mmol, 0.10 eq) were added at rt and the resulting mixture was stirred for 1.5 h. The reaction was diluted with EtOAc and a 10% aq. $Na_2S_2O_3$-solution (1:1, 10 mL). The aq. layer was extracted with EtOAc (3x 10 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1 – 2:1) yielded sulfone **416** (109.2 mg, 0.26 mmol, 76%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 7.32 Hz, 2H, SO_2Ph), 7.61 (t, *J* = 7.44 Hz, 1H, SO_2Ph), 7.50 (t, *J* = 7.64 Hz, 2H, SO_2Ph), 7.17 (d, *J* = 8.58 Hz, 2H, PMB), 6.87 (d, *J*= 8.63 Hz, 2H, PMB), 5.37 (t, *J* = 7.88 Hz, 1H, H-8), 5.04 (t, *J* = 6.31 Hz, 1H, H-3), 4.24 (s, 2H, PMB), 3.90 (d, *J* = 7.93 Hz, 2H, H-11), 3.82 (s, 3H, PMB), 3.63 (s, 2H, H-9), 2.12-2.02 (m, 4H, H-4, H-5), 1.69 (s, 3H, H-6), 1.58 (s, 3H, H-1) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 159.5 (q, PMB), 146.7 (q, C-7), 138.7 (q, SO_2Ph), 133.7 (t, SO_2Ph), 132.4 (q, C-2), 130.0 (q, PMB), 129.6 (t, PMB), 129.1 (t, SO_2Ph), 128,6 (t, SO_2Ph), 123.6 (t, C-8), 114.1 (t, C-3), 114.0 (t, PMB), 72.2 (s, PMB), 67.0 (s, C-9), 55.6 (s, C-11), 55.4 (p, PMB), 35.9 (s, C-5), 26.6 (s, C-4), 25.8 (p, C-6), 17.9 (p, C-1) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{24}H_{30}O_4SNa$ $[M+Na]^+$: 437.1763; *found*: 437.1759; **R_f** (1:1 PE/EtOAc): 0.30.

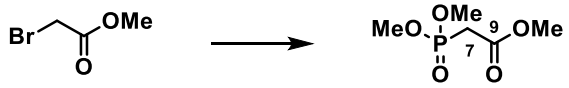
(*E*)-*tert*-Butyl((3-methyl-4-(phenylsulfonyl)but-2-en-1-yl)oxy)diphenylsilane 418



$NaSO_2Ph$ (669.3 mg, 4.08 mmol, 2.00 eq) and TBAI (75.3 mg, 0.20 mmol, 0.10 eq) were added to a stirred solution of bromide **401** (0.82 g, 2.04 mmol, 1.00 eq) in DMF (10.5 mL) at rt and the resulting mixture was stirred for 1.5 h. The reaction was diluted with EtOAc and 10% aq. $Na_2S_2O_3$-solution (1:1, 20 mL). The aq. layer was extracted with EtOAc (3x 10 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 2:1) yielded sulfone **418** (0.95 g, 2.10 mmol, *quant.*) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, J = 7.60 Hz, 2H, SO_2Ph), 7.61-7.59 (m, 5H, TBDPS, SO_2Ph), 7.51 (t, J = 7.63 Hz, 2H, SO_2Ph), 7.45-7.36 (m, 6H, TBDPS), 5.28 (t, J = 5.81 Hz, 1H, H-15), 4.11 (d, J = 5.82 Hz, 2H, H-17), 3.72 (s, 2H, H-13), 1.62 (s, 3H, H-16), 1.00 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 138.3 (q, SO_2Ph), 135.5 (t, TBDPS), 135.2 (q, TBDPS), 133.6 (t, TBDPS), 133.4 (q, C-14), 129.7 (t, SO_2Ph), 129.0 (t, SO_2Ph), 128.5 (t, SO_2Ph), 127.7 (t, TBDPS), 124.8 (t, C-15), 65.9 (C-17), 60.7 (s, C-13), 26.7 (p, TBDPS), 19.1 (q, TBDPS), 17.1 (p, C-16) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{27}H_{32}O_3SNa$ $[M+Na]^+$: 487.1739; *found*: 487.1735; **R_f** (3:1 PE/EtOAc): 0.14.

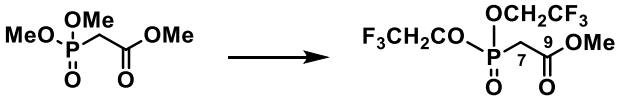
Methyl 2-(dimethoxyphosphoryl)acetate 424



A mixture of ester **423** (10.0 mL, 98.05 mmol, 1.00 eq) and $P(OMe)_3$ (16.5 mL, 137.27 mmol, 1.40 eq) was heated to 80 °C. At this temperature MeBr was removed by distillation. Then, the mixture was heated to 160 °C for 2 h with constant distillation of the crude product. A second distillation (86 °C, 1 mbar) yielded phosphonate **424** (11.92 g, 65.47 mmol, 67%) as a colorless liquid. The analytical data match those reported in the literature.[257]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.81 (d, J = 11.21 Hz, 6H, OMe), 3.75 (s, 3H, CO_2Me), 2.99 (d, J = 22.05 Hz, 2H, H-7) ppm; **bp.**: 86 °C (1 mbar).

Methyl 2-(bis(2,2,2-trifluoroethoxy)phosphoryl)acetate 425

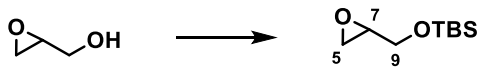


424 425

TMSBr (3.6 mL, 27.46 mmol, 2.50 eq) was added to a stirred solution of phosphonate **424** (2.00 g, 10.98 mmol, 1.00 eq) in CH_2Cl_2 (22.0 mL) at rt and the resulting mixture was stired at rt for 4 h. Then, the solvent was removed under high vacuum and the residue was dissolved in $CHCl_3$ (74 mL) and PPh_3 (7.20 g, 27.46 mmol, 2.50 eq) and iodine (6.97 g, 27.46 mmol, 2.50 eq) were added. The resulting mixture was stirred at rt for 15 min, then imidazole (7.58 g, 109.82 mmol, 10.00 eq) was added and the resulting mixture was heated to 50 °C for 30 min. Then triflouroethanol (3.2 mL, 43.93 mmol, 4.00 eq) was added dropwise and the resulting mixture was heated to 60 °C overnight. The mixture was cooled to rt and filtered and dry loaded on silica. Column chromatography (PE/EtOAc 2:1 - 1:1) yielded phosphonate **425** (2.68 g, 8.41 mmol, 77%) as a colorless oil. The analytical data match those reported in the literature.[258]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.46 (qi, J = 8.17 Hz, 4H, CH_2CF_3), 3.78 (s, 3H, CO_2Me), 3.17 (d, J = 21.13 Hz, 2H, H-7) ppm; **R_f** (2:1 PE/EtOAc): 0.45.

***tert*-Butyldimethyl(oxiran-2-ylmethoxy)silane 430**

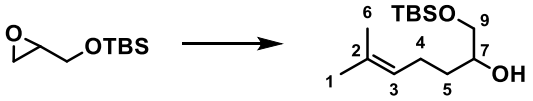


429 430

Glycidol (**429**) was distilled over K_2CO_3 and stored at -20 °C until used. TBSCl (3.05 g, 20.25 mmol, 1.50 eq) and imidazole (1.38 g, 20.25 mmol, 1.50 eq) were added to a stirred solution of alcohol **429** (0.90 mL, 13.50 mmol, 1.00 eq) in THF (20.0 mL) at rt and the resulting mixture was stirred at overnight. The mixture was filtered over Celite^{TM} and washed with an excess of THF and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded epoxide **430** (2.06 g, 10.93 mmol, 81%) as a colorless oil. The analytical data match those reported in the literature.[164]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.85 (dd, J = 12.16, 3.36 Hz, 1H, H-9), 3.66 (dd, J = 11.92, 4.76 Hz, 1H, H-9), 3.10-3.07 (m, 1H, H-7), 2.77 (t, J = 4.60 Hz, 1H, H-5), 2.64 (dd, J = 5.12, 2.68 Hz, 1H, H-5), 0.90 (s, 9H, TBS), 0.08 (s, 6H, TBS) ppm; **R_f** (5:1 PE/EtOAc): 0.55.

1-((*tert*-Butyldimethylsilyl)oxy)-6-methylhept-5-en-2-ol 431

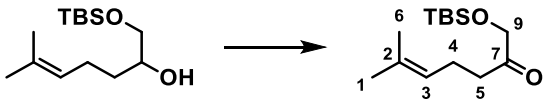


430 **431**

In a two-neck flask equipped with a reflux-condenser Mg turnings (2.82 g, 115.86 mmol, 12.00 eq) and a single crystal of I_2 in THF (7.8 mL) were placed. A solution of prenylchloride (3.3 mL, 28.96 mmol, 3.00 eq) in THF (50.0 mL) was added at 0 °C slowly (0.33 mL/min. The resulting mixture was stirred at 0 °C for 1 h and then transferred to a new flask. The Grignard reagent was titrated three times using menthol and phenantrolin, determining its concentration as 0.6 M. In a new flask, the prepared Grignard reagent (19.3 mL, 11.59 mmol, 1.20 eq) was added dropwise to a stirred solution of CuI (183.9 mg, 0.97 mmol, 0.10 eq) and epoxide **430** (1.82 g, 9.65 mmol, 1.00 eq) in THF (44.0 mL) at -60 °C and the resulting mixture was allowed to warm to -20 °C o/n using a cryo reactor. The reaction was terminated by addition of ice (20 g) and allowed to warm to rt. Then, a sat. aq. NH_4Cl-solution (20 mL) was added and the aq. layer was extracted with EtOAc (4x 20 mL), the comb. org. layers were washed with a sat. aq. $NaHCO_3$-solution, brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded alcohol **431** (2.01 g, 7.80 mmol, 81%) as a colorless oil. The analytical data match those reported in the literature.[164]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.12 (t, J = 7.16 Hz, 1H, H-3), 3.65-3.60 (m, 2H, H-9), 3.40 (dd, J = 10.82, 8.26 Hz, 1H, H-7), 2.40 (bs, 1H, OH), 2.16-2.04 (m, 2H, H-5), 1.69 (s, 3H, H-6), 1.62 (s, 3H, H-1), 1.50-1.39 (m, 2H, H-4), 0.90 (s, 9H, TBS), 0.07 (s, 6H, TBS) ppm; **R_f** (5:1 PE/EtOAc): 0.53.

1-((*tert*-Butyldimethylsilyl)oxy)-6-methylhept-5-en-2-one 427



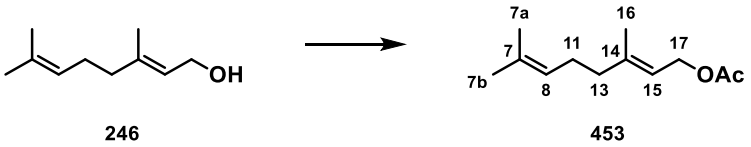
431 **427**

DMSO (1.7 mL, 23.38 mmol, 3.00 eq) was added dropwise to a stirred solution of oxalylchloride (1.0 mL, 11.69 mmol, 1.50 eq) in CH_2Cl_2 (30.0 mL) at -78 °C, the resulting mixture was stirred at -78 °C for 10 min, then alcohol **431** (2.01 g, 7.79 mmol, 1.00 eq) in CH_2Cl_2 (20.0 mL) was added dropwise at -78 °C and the mixture was stirred at -78 °C for 15 min. Then NEt_3 (3.3 mL, 23.38 mmol, 3.00 eq) was added dropwise at -78 °C and the mixture was allowed to warm to rt and stirred at rt for 30 min. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (50 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 50 mL), the comb. org. layers were

washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 50:1 - 20:1) yielded ketone **427** (1.69 g, 6.59 mmol, 85%) as a colorless oil. The analytical data match those reported in the literature.[164]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.07 (t, J = 7.16 Hz, 1H, H-5), 4.16 (s, 2H, H-9), 2.51 (t, J = 7.42 Hz, 2H, H-5), 2.26 (q, J = 7.22 Hz, 2H, H-4), 1.67 (s, 3H, H-6), 1.61 (s, 3H, H-1), 0.92 (s, 9H, TBS), 0.08 (s, 6H, TBS) ppm; **R_f** (10:1 PE/EtOAc): 0.69.

(*E*)-3,7-Dimethylocta-2,6-dien-1-yl acetate 453

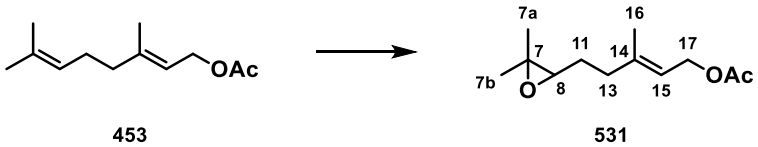


246 453

Ac_2O (2.8 mL, 29.82 mmol, 2.30 eq), pyridine (0.95 mL, 11.67 mmol, 0.90 eq) and NEt_3 (2.8 mL, 19.45 mmol, 1.50 eq) were added to a stirred solution of geraniol (**246**) (2.3 mL, 12.97 mmol, 1.00 eq) in CH_2Cl_2 (13.0 mL) at rt and the mixture was stirred at rt overnight. The reaction was terminated by addition of water (10 mL) and the mixture was stirred at rt for 30 min. The aq. layer was extracted with Et_2O (3x 10 mL), the comb. org. layers were washed with 1 M HCl (10 mL), a sat. aq. $NaHCO_3$-solution (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1) yielded acetate **453** (2.41 g, 12.29 mmol, 95%) as a colorless oil. The analytical data match those reported in the literature.[259]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.34 (t, J = 7.04 Hz, 1H, H-15), 5.08 (t, J = 6.80 Hz, 1H, H-8), 4.59 (d, J = 7.08 Hz, 2H, H-17), 2.11-2.05 (m, 7H, H-11, H-13, Ac), 1.70 (s, 3H, H-16), 1.68 (s, 3H, H-7a), 1.60 (s, 3H, H-7b) ppm; **R_f** (5:1 PE/EtOAc): 0.50.

(*E*)-5-(3,3-Dimethyloxiran-2-yl)-3-methylpent-2-en-1-yl acetate 531

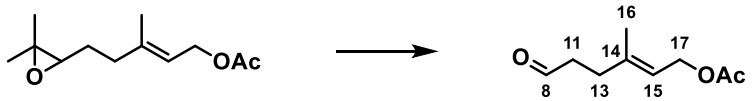


453 531

*m*CPBA (77%, 2.76 g, 12.33 mmol, 1.10 eq) in CH_2Cl_2 (22.5 mL) was added to a stirred solution of acetate **453** (2.20 g, 11.21 mmol, 1.00 eq) in CH_2Cl_2 (22.5 mL) at -20 °C and the resulting mixture was stirred at -20 °C for 1.5 h. The reaction was terminated by addition of 3 M NaOH (20 mL), the aq. layer was extracted with CH_2Cl_2 (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield crude epoxide **531** (2.34 g, 11.00 mmol, 98%) as an colorless oil which was directly used for the next step. The analytical data match those reported in the literature.[260]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.38 (t, *J* = 7.05 Hz, 1H, H-15), 4.59 (d, *J* = 2H, H-17), 2.70 (t, *J* = 6.20 Hz, 1H, H-8), 2.27-2.11 (m, 2H, H-11), 2.05 (s, 3H, Ac), 1.72 (s, 3H. H-16), 1.66 (q, *J* = 7.17 Hz, 2H, H-13), 1.30 (s, 3H, H-7a), 1.26 (s, 3H, H-7b) ppm; **R_f** (5:1 PE/EtOAc): 0.25.

(*E*)-3-Methyl-6-oxohex-2-en-1-yl acetate 432

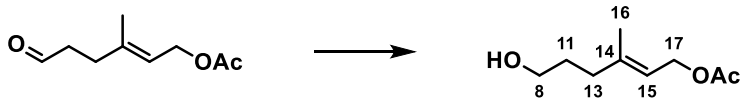


531 432

$HIO_4 \cdot 2H_2O$ (3.01 g, 13.20 mmol, 1.20 eq) was added to a stirred solution of epoxide **531** (2.34 g, 11.00 mmol, 1.00 eq) in THF (55 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 2 h. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (30 mL) and the resulting mixture was allowed to warm to rt and stirred for 15 min. The mixture was filtered over Celite^{TM} and washed with an excess of Et_2O, the aq. layer was extracted with Et_2O (3x 20 mL), the comb. org. layers were washed with a sat. aq. $NaHCO_3$-solution (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield crude aldehyde **432** (1.46 g, 8.55 mmol, 78%) as a yellow oil which was directly used for the next step. The analytical data match those reported in the literature.[260]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.77 (t, *J* = 1.61 Hz, 1H, H-8), 5.35 (qt, *J* = 10.52, 1.33 Hz, 1H, H-15), 4.57 (d, *J* = 6.99 Hz, 2H, H-17), 2.57 (dt, *J* = 7.29, 1.50 Hz, 2H, H-11), 2.37 (t, *J* = 7.51 Hz, 2H, H-13), 2.04 (s, 3H, Ac), 1.72 (s, 3H, H-16) ppm; **R_f** (5:1 PE/EtOAc): 0.13.

(*E*)-6-Hydroxy-3-methylhex-2-en-1-yl acetate 532

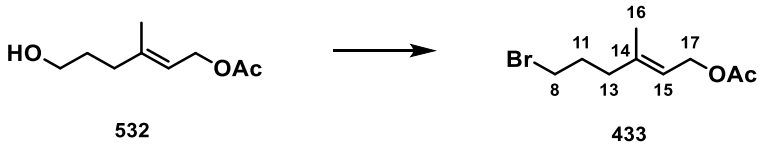


432 532

$NaBH_4$ (354.5 mg, 9.37 mmol, 1.10 eq) was slowly added to a stirred solution of aldehyde **432** (1.45 g, 8.52 mmol, 1.00 eq) in EtOH (26.0 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 1 h. The reaction was terminated by addition of 1 M HCl (10 mL), the aq. layer was extracted with EtOAc (3x 10 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* Column chromatography (PE/EtOAc 3:1 – 1:1) yielded alcohol **532** (1.05 g, 6.09 mmol, 71%) as a yellow oil. The analytical data match those reported in the literature.[260]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.38 (t, *J* = 7.06 Hz, 1H, H-15), 4.58 (d, *J* = 7.04 Hz, 2H, H-17), 3.64 (t, *J* = 6.43 Hz, 2H, H-8), 2.12 (t, *J* = 7.63 Hz, 2H, H-13), 2.05 (s, 3H, Ac), 1.72 (m, 5H, H-11, H-16), 1.40 (bs, 1H, OH) ppm; $\mathbf{R_f}$ (1:1 PE/EtOAc): 0.31.

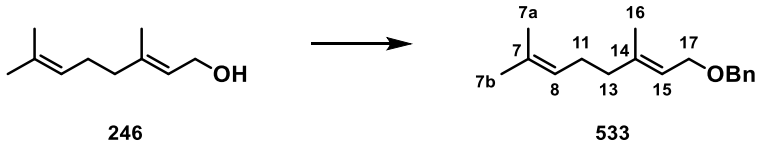
(*E*)-6-Bromo-3-methylhex-2-en-1-yl acetate 433



CBr_4 (2.09 g, 6.32 mmol, 1.10 eq) was added to a stirred solution of PPh_3 (1.66 g, 6.32 mmol, 1.10 eq) and alcohol **532** (0.99 g, 5.74 mmol, 1.00 eq) in CH_2Cl_2 (15.0 mL) at 0 °C and the resulting mixture was allowed to warm to rt over 2 h. The mixture was dry loaded onto silica. Column chromatography (PE/EtOAc 50:1 – 20:1) yielded bromide **433** (1.23 g, 5.25 mmol, 91%) as a colorless oil. The analytical data match those reported in the literature.[261]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.39 (dt, *J* = 7.13, 1.12 Hz, 1H, H-15), 4.59 (d, *J* = 7.56 Hz, 2H, H-17), 3.38 (t, *J* = 6.68 Hz, 2H, H-8), 2.19 (t, *J* = 7.37 Hz, 2H, H-13), 2.06 (s, 3H, Ac), 1.99 (qi, *J* = 7.04 Hz, 2H, H-11), 1.71 (s, 3H, H-16) ppm; $\mathbf{R_f}$ (3:1 PE/EtOAc): 0.56.

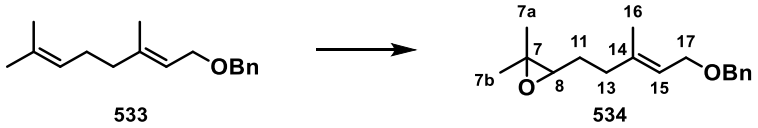
(*E*)-(((3,7-Dimethylocta-2,6-dien-1-yl)oxy)methyl)benzene 533



Geraniol (**246**) (4.5 mL, 25.93 mmol, 1.00 eq) was added dropwise to a stirred solution of NaH (60%, 1.56 g, 38.90 mmol, 1.50 eq) in DMF (44.0 mL) at 0 °C, the mixture was stirred at 0 °C for 30 min, then BnBr (3.7 mL, 31.12 mmol, 1.20 eq) was added dropwise at 0 °C and the resulting mixture was allowed to warm to rt overnight. The reaction was terminated by addition of water (50 mL), the aq. layer was extracted with EtOAc (3x 30 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography yielded ether **533** (6.34 g, 25.94 mmol, *quant.*) as a colorless oil. The analytical data match those reported in the literature.[262]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.37-7.28 (m, 5H, Bn), 5.41 (t, *J* = 6.70 Hz, 1H, H-15), 5.10 (t, *J* = 6.70 Hz, 1H, H-8), 4.50 (s, 2H, Bn), 4.03 (d, *J* = 6.76 Hz, 2H, H-17), 2.12-2.03 (m, 4H, H-11, H-13), 1.68 (s, 3H, H-16), 1.65 (s, 3H, H-7a), 1.61 (s, 3H, H-7b) ppm; $\mathbf{R_f}$ (5:1 PE/EtOAc): 0.60.

(*E*)-3-(5-(Benzyloxy)-3-methylpent-3-en-1-yl)-2,2-dimethyloxirane 534

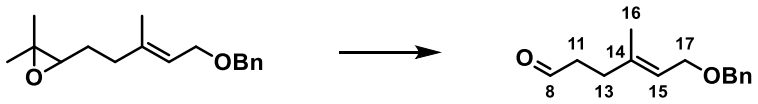


533 534

*m*CPBA (77%, 3.86 g, 17.22 mmol, 1.10 eq) in CH_2Cl_2 (32.0 mL) was added to a stirred solution of benzyl ether **533** (3.83 g, 15.66 mmol, 1.00 eq) in CH_2Cl_2 (32.0 mL) at -20 °C and the resulting mixture was stirred at -20 °C for 1.5 h. The reaction was terminated by addition of 3 M NaOH (20 mL), the aq. layer was extracted with CH_2Cl_2 (3x 30 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1) yielded epoxide **534** (2.85 g, 10.93 mmol, 70%) as a colorless oil The analytical data match those reported in the literature.[263]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.35-7.27 (m, 5H, Bn), 4.51 (s, 2H, Bn), 4.03 (d, *J* = 6.71 Hz, 2H, H-17), 2.71 (t, *J* = 6.22 Hz, 1H, H-8), 2.26-2.11 (m, 2H, H-11), 1.70-1.63 (m, 5H, H-13, H-16), 1.30 (s, 3H, H-7a), 1.26 (s, 3H, H-7b) ppm; **R_f** (5:1 PE/EtOAc): 0.38.

(*E*)-6-(Benzyloxy)-4-methylhex-4-enal 434



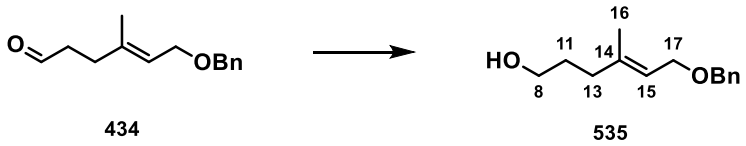
534 434

$HIO_4 \cdot 2H_2O$ (2.99 g, 13.12 mmol, 1.20 eq) was added to a stirred solution of epoxide **534** (2.85 g, 10.93 mmol, 1.00 eq) in THF (55 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 2 h. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (30 mL) and the resulting mixture was allowed to warm to rt and stirred for 15 min. The mixture was filtered over Celite^{TM} and washed with an excess of Et_2O, the aq. layer was extracted with Et_2O (3x 20 mL), the comb. org. layers were washed with a sat. aq. $NaHCO_3$-solution (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1) yielded aldehyde **434** (1.78 g, 8.17 mmol, 75%) as a colorless oil. The analytical data match those reported in the literature.[264]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.78 (t, *J* = 1.58 Hz, 1H, H-8), 7.35-7.27 (m, 5H, Bn), 5.42 (dt, *J* = 6.95, 0.62 Hz, 1H, H-15), 4.50 (s, 2H, Bn), 4.02 (d, *J* = 6.64 Hz, 2H, H-17), 2.57 (dd, *J* = 9.00,

7.32 Hz, 2H, H-11), 2.37 (t, *J* = 7.50 Hz, 2H, H-13), 1.66 (s, 3H, H-16) ppm; $\mathbf{R_f}$ (5:1 PE/EtOAc): 0.25.

(*E*)-6-(Benzyloxy)-4-methylhex-4-en-1-ol 535

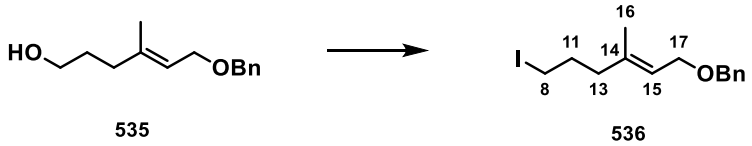


434 535

$NaBH_4$ (198.3 mg, 5.24 mmol, 1.10 eq) was slowly added to a stirred solution of aldehyde **434** (1.04 g, 4.77 mmol, 1.00 eq) in EtOH (14.5 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 1 h. The reaction was terminated by addition of 1 M HCl (10 mL), the aq. layer was extracted with EtOAc (3x 10 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 3:1) yielded alcohol **535** (0.95 g, 4.31 mmol, 90%) as a colorless oil. The analytical data match those reported in the literature.[163]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.35-7.28 (m, 5H, Bn), 5.44 (t, *J* = 6.96 Hz, 1H, H-15), 4.50 (s, 2H, Bn), 4.03 (d, *J* = 6.64 Hz, 2H, H-17), 3.67 (t, *J* = 7.46 Hz, 2H, H-8), 2.12 (t, *J* = 7.46 Hz, 2H, H-13), 1.77-1.68 (m, 2H, H-11), 1.67 (s, 3H, H-16), 1.33 (bs, 1H, OH) ppm; $\mathbf{R_f}$ (2:1 PE/EtOAc): 0.40.

(*E*)-(((6-Iodo-3-methylhex-2-en-1-yl)oxy)methyl)benzene 536

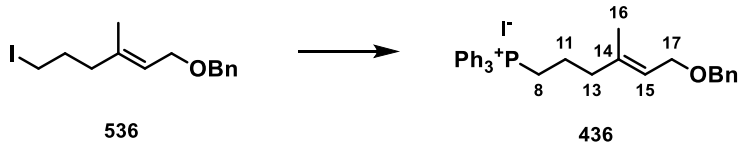


535 536

Imidazole (0.53 g, 7.76 mmol, 1.80 eq), PPh_3 (1.47 g, 5.61 mmol, 1.30 eq) and iodine (1.31 g, 5.17 mmol, 1.20 eq) were added to a stirred solution of alcohol **535** (0.95 g, 4.31 mmol, 1.00 eq) in CH_2Cl_2 (22.0 mL) at rt for 45 min in darkness. The reaction was terminated with a 10% aq. $Na_2S_2O_3$-solution (10 mL), the aq. layer was extracted with Et_2O (3x 10 mL), the comb. org. layer was washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* in darkness at 40 °C. Column chromatography (PE/EtOAc 20:1 – 10:1) yielded iodide **536** (1.29 g, 3.91 mmol, 91%) as a colorless oil. The analytical data match those reported in the literature.[163]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.35-7.27 (m, 5H, Bn), 5.45 (dt, *J* = 6.71, 1.24 Hz, 1H, H-15), 4.51 (s, 2H, Bn), 4.03 (d, *J* = 6.67 Hz, 2H, H-17), 3.16 (t, *J* = 6.92 Hz, 2H, H-8), 2.14 (t, *J* = 7.32 Hz, 2H, H-13), 1.95 (qi, *J* = 7.13 Hz, 2H, H-11), 1.64 (s, 3H, H-16) ppm; **R_f** (10:1 PE/EtOAc): 0.55.

(*E*)-(6-(Benzyloxy)-4-methylhex-4-en-1-yl)triphenylphosphonium iodide 436

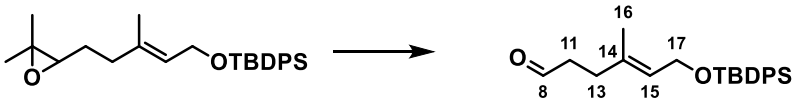


536 436

A mixture of iodide **536** (1.90 g, 5.75 mmol, 1.00 eq) and PPh_3 (2.11 g, 8.06 mmol, 1.40 eq) was heated to 110 °C in a sealed tube overnight. The residue was suspended in CH_2Cl_2 (50 mL) and dry loaded on silica. Column chromatography ($CHCl_3$/MeOH 100:0 - 10:1) yielded Wittig salt **436** (3.06 g, 5.15 mmol, 89%) as a white solid. The analytical data match those reported in the literature.[163]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.85-7.59 (m, 12H, PPh_3), 7.33-7.28 (m, 8H, Bn, PPh_3), 5.34 (t, *J* = 6.10 Hz, 1H, H-15), 4.47 (s, 2H, Bn), 3.98 (d, *J* = 6.60 Hz, 2H, H-17), 3.81-3.74 (m, 2H, H-8), 2.41 (t, *J* = 7.27 Hz, 2H, H-13); 1.85-1.76 (m, 2H, H-11), 1.56 (s, 3H, H-16) ppm; **R_f** (10:1 $CHCl_3$/MeOH): 0.53; **mp.**: 163 °C.

(*E*)-6-((*tert*-Butyldiphenylsilyl)oxy)-4-methylhex-4-enal 422

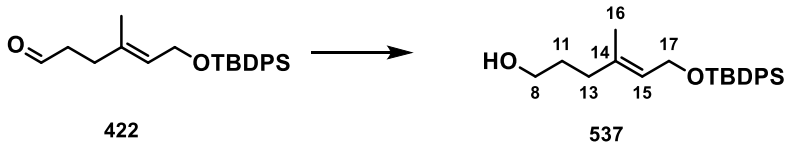


248 422

$HIO_4 \cdot 2H_2O$ (5.28 g, 23.17 mmol, 1.40 eq) was added to a stirred solution of epoxide **428** (6.76 g, 16.55 mmol, 1.00 eq) in THF (85 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 40 min. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (50 mL) and the resulting mixture was allowed to warm to rt and stirred for 15 min. The mixture was filtered over Celite™ and washed with an excess of Et_2O, the aq. layer was extracted with Et_2O (3x 30 mL), the comb. org. layers were washed with a sat. aq. $NaHCO_3$-solution (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield crude aldehyde **422** (6.07 g, 16.55 mmol, *quant.*) as a yellow oil which was directly used for the next step. The analytical data match those reported in the literature.[162]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.75 (t, *J* = 1.72 Hz, 1H, H-8), 7.69-7.66 (m, 4H, TBDPS), 7.44-7.36 (m, 6H, TBDPS), 5.38 (dt, *J* = 6.53, 0.62 Hz, 1H, H-15), 4.21 (dd, *J* = 6.27 Hz, 0.72 Hz, 2H, H-17), 2.50 (dt, *J* = 7.18, 0.56 Hz, 2H, H-11), 2.29 (t, *J* = 7.63 Hz, 2H, H-13), 1.44 (s, 3H, H-16), 1.04 (s, 9H, TBDPS) ppm; **R_f** (5:1 PE/EtOAc): 0.40.

(*E*)-6-((*tert*-Butyldiphenylsilyl)oxy)-4-methylhex-4-en-1-ol 537

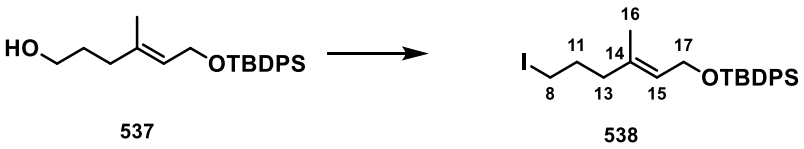


422 537

$NaBH_4$ (1.25 g, 33.10 mmol, 2.00 eq) was slowly added to a stirred solution of aldehyde **422** (6.07 g, 16.55 mmol, 1.00 eq) in EtOH (330 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 20 min. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (100 mL), the aq. layer was extracted with EtOAc (3x 300 mL), the comb. org. layers were washed with brine (300 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1) yielded alcohol **537** (3.87 g, 10.49 mmol, 63%) as a yellow oil. The analytical data match those reported in the literature.[162]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.70-7.68 (m, 4H, TBDPS), 7.42-7.36 (m, 6H, TBDPS), 5.41 (dt, *J* = 6.25, 1.25 Hz, 1H, H-15), 4.21 (d, *J* = 5.84 Hz, 2H, H-8), 3.62 (t, *J* = 6.36 Hz, 2H, H-17), 2.05 (t, *J* = 7.97 Hz, 2H, H-13), 1.66 (qi, *J* = 7.03 Hz, 2H, H-11), 1.46 (s, 3H, H-16), 1.26 (t, *J* = 7.14 Hz, 1H, OH), 1.04 (s, 9H, TBDPS) ppm; **R_f** (5:1 PE/EtOAc): 0.55.

(*E*)-*tert*-Butyl((6-iodo-3-methylhex-2-en-1-yl)oxy)diphenylsilane 538



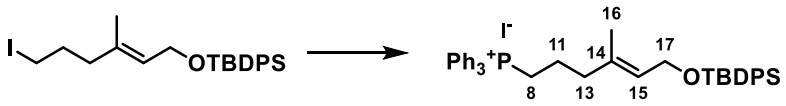
537 538

MsCl (0.97 mL, 12.57 mmol, 1.20 eq) and NEt_3 (3.0 mL, 20.94 mmol, 2.00 eq) were added to a stirred solution of alcohol **537** (3.86 g, 10.47 mmol, 1.00 eq) in CH_2Cl_2 (55 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 2 h. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (20 mL), the aq. layer was extracted with CH_2Cl_2 (3x 20 mL), the comb. org. layers were washed with 1 M HCl (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was dissolved in acetone (100 mL) and NaI (2.04 g, 13.61 mmol, 1.30 eq) was added and the resulting mixture was heated to 50 °C overnight. The mixture was concentrated *in*

vacuo and the resiue was dissolved in 1:1 mixture of an aq. 10% $Na_2S_2O_3$-solution and a sat. aq. $NaHCO_3$-solution (50 mL), the aq. layer was extracted with Et_2O (3x 30 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 50:1) yielded iodide **538** (4.23 g, 8.83 mmol, 84%) as a colorless oil. The analytical data match those reported in the literature.[162]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.70-7.67 (m, 4H, TBDPS), 7.44-7.36 (m, 6H, TBDPS), 5.42 (dt, *J* = 6.24, 1.18 Hz, 1H, H-15), 4.22 (d, *J* = 5.76 Hz, 2H, H-17), 3.13 (t, *J* = 7.00 Hz, 2H, H-8), 2.07-2.04 (m, 2H, H-13), 1.93-1.86 (m, 2H, H-11), 1.42 (s, 3H, H-16), 1.04 (s, 9H, TBDPS) ppm; **R_f** (10:1 PE/EtOAc): 0.65.

(*E*)-(6-((*tert*-Butyldiphenylsilyl)oxy)-4-methylhex-4-en-1-yl)triphenylphosphonium iodide 437

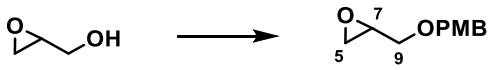


538 437

A mixture of iodide **538** (4.22 g, 8.81 mmol, 1.00 eq) and PPh_3 (2.77 g, 10.57 mmol, 1.20 eq) in PhMe (45 mL) was heated in a sealed tube under refluxing conditions overnight. The mixture was concentrated *in vacuo* and loaded onto a silica column. Column chromatography (DCM/MeOH 20:1 – 10:1) yielded Wittig salt **437** (6.55 g, 8.81 mmol, *quant*.) as a white solid. The analytical data match those reported in the literature.[265]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.85-7.78 (m, 9H, PPh_3), 7.71-7.66 (m, 6H, PPh_3), 7.63-7.61 (m, 4H, TBDPS), 7.410-7.31 (m, 6H, TBDPS), 5.32 (t, *J* = 6.09 Hz, 1H, H-15), 4.15 (d, *J* = 6.08 Hz, 2H, H-17), 3.78-3.71 (m, 2H, H-8), 2.33 (t, *J* = 7.10 Hz, 2H, H-13), 1.77 (se, *J* = 7.86 Hz, 2H, H-11), 1.34 (s, 3H, H-16), 0.98 (s, 9H, TBDPS) ppm; **m.p.:** 63 °C.

2-(((4-Methoxybenzyl)oxy)methyl)oxirane 438



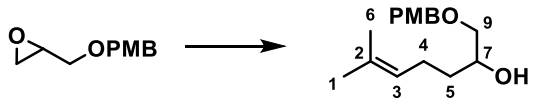
429 438

Glycidol **429** (0.90 mL, 13.50 mmol, 1.00 eq) in DMF (5.0 mL) was added dropwise to a stirred solution of NaH (60% on mineral oil, 0.81 g, 20.25 mmol, 1.50 eq) in DMF (13.0 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 30 min. Then TBAI (149.6 mg, 0.41 mmol, 0.03 eq) and PMBCl (2.96 g, 18.90 mmol, 1.40 eq) were added and the resulting mixture was allowed to warm to rt overnight. The reaction was terminated by addition of water (20 mL), the aq. layer was extracted with Et_2O (3x 20 mL), the comb. org. layers were washed with water (2x 30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1)

yielded epoxide **438** (1.95 g, 10.15 mmol, 74%) as a colorless oil. The analytical data match those reported in the literature.[266]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 8.71 Hz, 2H, PMB), 6.88 (d, *J* = 8.66 Hz, 2H, PMB), 4.52 (q, *J* = 11.64 Hz, 2H, PMB), 3.81 (s, 3H, PMB), 3.73 (dd, *J* = 11.43, 3.06 Hz, 1H, H-9), 3.41 (dd, *J* = 11.41, 5.83 Hz, 1H, H-9), 3.19-3.15 (m, 1H, H-7), 2.80 (dd, *J* = 4.89, 4.27 Hz, 1H, H-5), 2.61 (dd, *J* = 5.01, 2.69 Hz, 1H, H-5) ppm; $\mathbf{R_f}$ (2:1 PE/EtOAc): 0.49.

1-((4-Methoxybenzyl)oxy)-6-methylhept-5-en-2-ol 439

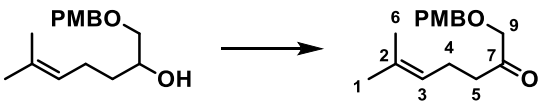


438 **439**

In a two-neck flask equipped with a reflux-condenser Mg turnings (2.98 g, 122.54 mmol, 10.00 eq) and a single crystal of I_2 in THF (8.2 mL) were placed. A solution of prenylchloride (3.5 mL, 30.63 mmol, 2.50 eq) in THF (50.0 mL) was added at 0 °C slowly (0.33 mL/min). The resulting mixture was stirred at 0 °C for 1 h and then transferred to a new flask. The Grignard reagent was titrated three times using menthol and phenantrolin, determining its concentration as 0.56 M. In a new flask, the prepared Grignard reagent (16.4 mL, 14.70 mmol, 1.20 eq) was added dropwise to a stirred solution of CuI (233.4 mg, 1.23 mmol, 0.10 eq) and epoxide **438** (2.38 g, 12.26 mmol, 1.00 eq) in THF (50 mL) at -60 °C and the resulting mixture was allowed to warm to -20 °C o/n using a cryo reactor. The reaction was terminated by addition of ice (20 g) and allowed to warm to rt. Then a sat. aq. NH_4Cl-solution (20 mL) was added and the aq. layer was extracted with EtOAc (4x 20 mL), the comb. org. layers were washed with a sat. aq. $NaHCO_3$-solution, brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield crude alcohol **439** (3.27 g, 12.25 mmol, *quant.*) as a yellow oil which was directly used for the next step without further purification.

HRMS (ESI-LCT): *m/z calc.* for $C_{16}H_{24}O_3Na$ $[M+Na]^+$: 287.1623; *found*: 287.1628; $\mathbf{R_f}$ (2:1 PE/EtOAc): 0.40.

1-((4-Methoxybenzyl)oxy)-6-methylhept-5-en-2-one 440

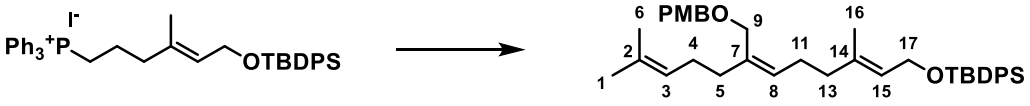


439 **440**

DMSO (2.7 mL, 37.11 mmol, 3.00 eq) was added dropwise to a stirred solution of oxalylchloride (1.6 mL, 18.55 mmol, 1.50 eq) in CH_2Cl_2 (46.0 mL) at -78 °C, the resulting mixture was stirred at -78 °C for 10 min, then alcohol **439** (3.27 g, 12.37 mmol, 1.00 eq) in CH_2Cl_2 (31.0 mL) was added

dropwise at -78 °C and the mixture was stirred at -78 °C for 15 min. Then NEt_3 (5.2 mL, 37.11 mmol, 3.00 eq) was added dropwise at -78 °C and the mixture was allowed to warm to rt and stirred at rt for 30 min. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (50 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 50 mL), the comb. org. layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1 - 5:1) yielded ketone **440** (2.42 g, 9.24 mmol, 75%) as a yellow oil.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 8.64 Hz, 2H, PMB), 6.89 (d, *J* = 9.28 Hz, 2H, PMB), 5.05 (t, *J* = 7.18 Hz, 1H, H-3), 4.51 (s, 2H, PMB), 4.02 (s, 2H, H-9), 3.81 (s, 3H, PMB), 2.47 (t, *J* = 7.40 Hz, 2H, H-5), 2.26 (q, *J* = 7.18 Hz, 2H, H-4), 1.66 (s, 3H, H-6), 1.60 (s, 3H, H-1) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 208.9 (q, C-7), 159.6 (q, PMB), 133.1 (q, C-2), 129.8 (s, PMB), 129.4 (q, PMB), 122.7 (s, C-3), 114.0 (s, PMB), 74.9 (s, C-9), 73.1 (s, PMB), 55.4 (p, PMB), 39.2 (s, C-5), 25.8 (p, C-1), 22.2 (s, C-4), 17.8 (p, C-6) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{16}H_{22}O_3Na$ $[M+Na]^+$: 285.1467; *found*: 285.1472; **R_f** (2:1 PE/EtOAc): 0.52.

tert-Butyl(((2*E*,6*Z*)-7-(((4-methoxybenzyl)oxy)methyl)-3,11-dimethyldodeca-2,6,10-trien-1-yl)oxy)diphenylsilane 420



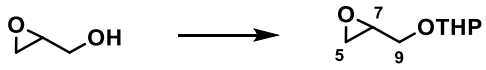
437 420

*n*BuLi (2.5 M in hex, 0.87 mL, 2.16 mmol, 1.60 eq) was added dropwise to a stirred solution of Wittig salt **437** (1.00 g, 1.35 mmol, 1.00 eq) in a mixture of THF (22.5 mL) and HMPA (1.4 mL) at -78 °C and the resulting mixture was stirred at -78 °C for 1 h. Then ketone **440** (0.42 g, 1.62 mmol, 1.20 eq) in THF (3.3 mL) was added dropwise at -78 °C. The resulting mixture was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (20 mL), the aq. layer was extracted with Et_2O (3x, 20 mL), the comb. org. layers were washed with water (2x 20 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 50:1 – 20:1) yielded olefine **420** (0.48 g, 0.80 mmol, 60%) as a colorless oil.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.70-7.68 (m, 4H, TBDPS), 7.43-7.35 (m, 6H, TBDPS), 7.27-7.25 (m, 4H, PMB)[8], 6.86 (d, *J* = 8.63 Hz, 2H, PMB), 5.38-5.35 (m, 2H, H-8, H-15), 5.12-5.08 (m, 1H, H-3), 4.39 (s, 2H, PMB), 4.21 (d, *J* = 6.17 Hz, 2H, H-17), 3.98 (s, 2H, H-9), 3.79 (s, 3H, PMB), 2.15-2.07 (m, 6H, H-11, H-13, H-5), 2.01-1.97 (m, 2H, H-4), 1.67 (s, 3H, H-6), 1.58 (s, 3H, H-16), 1.42 (s, 3H, H-1), 1.04 (s, 9H, TBDPS) ppm; **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 159.3 (q, PMB), 136.8

[8] This signal in the ^{1}H-NMR spectrum integrates to four instead of the expected two protons as the residue signal of $CHCl_3$ is overlapping.

(q, C-14), 136.2 (q, C-7), 135.8 (t, TBDPS), 134.2 (q, C-2), 131.5 (q, TBDPS), 130.9 (q, PMB), 129.6 (t, PMB), 129.5 (t, TBDPS), 129.1 (t, C-8), 127.7 (t, TBDPS), 124.5 (t, C-3), 124.5 (t, C-15), 113.9 (t, PMB), 71.7 (s, PMB), 67.1 (s, C-9), 61.3 (C-17), 55.4 (p, PMB), 39.8 (s, C-4), 35.5 (s, C-5), 27.0 (s, C-11 or C-13), 27.0 (p, TBDPS), 26.2 (s, C-11 or C-13), 25.8 (p, C-6), 19.3 (q, TBDPS), 17.9 (p, C-16), 16.5 (p, C-1) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{39}H_{52}O_3SiNa$ $[M+Na]^+$: 619.3583; *found*: 619.3602; $\mathbf{R}_f$ (10:1 PE/EtOAc): 0.53.

2-(Oxiran-2-ylmethoxy)tetrahydro-2*H*-pyran 442

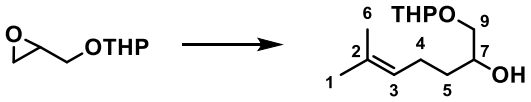


429 442

DHP (1.65 mL, 18.22 mmol, 1.35 eq) and *p*TsOH·H_2O (69.7 mg, 0.41 mmol, 0.03 eq) were added to a stirred solution of alcohol **429** (0.90 mL, 13.50 mmol, 1.00 eq) in CH_2Cl_2 (13.5 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min. The reaction was terminated by addition of NEt_3 (0.12 mL, 0.81 mmol, 0.06 eq) and the mixture was concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1) yielded ether **442** as a 1:1 mixture of diastereoisomers (1.70 g, 10.74 mmol, 80%) as a colorless oil. The analytical data match those reported in the literature.[267]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.76 (t, *J* = 3.92 Hz, 1H, THP), 4.65 (t, *J* = 3.56 Hz, 1H, THP), 3.95 (dd, *J* = 11.58, 3.18 Hz, 1H, H-9), 3.90-2.84 (m, 2H, THP), 3.74 (dd, *J* = 11.70, 5.06 Hz, 1H, H-9), 3.69 (dd, *J* = 11.68, 3.40 Hz, 1H, H-9), 3.53-3.49 (m, 2H, THP), 3.40 (dd, *J* = 11.76, 6.32 Hz, 1H, H-9), 3.22-3.17 (m, 2H, H-7), 2.83-2.80 (m, 2H, H-5), 2.69 (dd, *J* = 5.13, 2.64 Hz, 1H, H-5), 2.60 (4.86, 2.58 Hz, 1H, H-5), 1.85-1.52 (m, 12H, THP) ppm; $\mathbf{R}_f$ (5:1 PE/EtOAc): 0.31.

6-Methyl-1-((tetrahydro-2*H*-pyran-2-yl)oxy)hept-5-en-2-ol 444



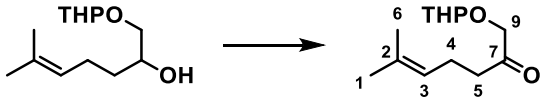
442 444

In a two-neck flask equipped with a reflux-condenser Mg turnings (3.12 g, 128.19 mmol, 12.00 eq) and a single crystal of I_2 in THF (8.5 mL) were placed. A solution of prenylchloride (3.6 mL, 32.05 mmol, 3.00 eq) in THF (55.0 mL) was added at 0 °C slowly (0.33 mL/min). The resulting mixture was stirred at 0 °C for 1 h and then transferred to a new flask. The Grignard reagent was titrated three times using menthol and phenantrolin, determining its concentration to be 0.52 M. In a new flask, the prepared Grignard reagent (24.7 mL, 12.82 mmol, 1.20 eq) was added dropwise to a stirred solution of CuI (203.4 mg, 1.07 mmol, 0.10 eq) and epoxide **442** (1.69 g, 10.68 mmol, 1.00 eq) in THF (50 mL) at -60 °C and the resulting mixture was allowed to warm to -20 °C o/n using a cryo reactor. The reaction was terminated by addition of ice (20 g) and allowed to warm to rt. Then a sat.

aq. NH_4Cl-solution (20 mL) was added and the aq. layer was extracted with EtOAc (4x 20 mL), the comb. org. layers were washed with a sat. aq. $NaHCO_3$-solution, brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield crude alcohol **444** (2.15 g, 9.40 mmol, 88%) as a yellow oil which was directly used for the next step without further purification.

HRMS (ESI-LCT): *m/z calc.* for $C_{13}H_{24}O_3Na$ $[M+Na]^+$: 251.1623; *found*: 251.1626; $\mathbf{R_f}$ (2:1 PE/EtOAc): 0.29.

6-Methyl-1-((tetrahydro-2*H*-pyran-2-yl)oxy)hept-5-en-2-one 446

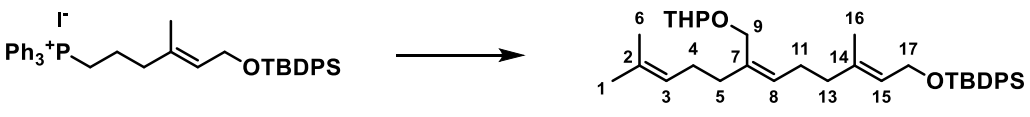


444 446

DMSO (2.0 mL, 28.12 mmol, 3.00 eq) was added dropwise to a stirred solution of oxalylchloride (1.2 mL, 14.06 mmol, 1.50 eq) in CH_2Cl_2 (35.0 mL) at -78 °C, the resulting mixture was stirred at -78 °C for 10 min, then alcohol **444** (2.14 g, 9.37 mmol, 1.00 eq) in CH_2Cl_2 (23.5 mL) was added dropwise at -78 °C and the mixture was stirred at -78 °C for 15 min. Then NEt_3 (4.0 mL, 28.12 mmol, 3.00 eq) was added dropwise at -78 °C and the mixture was allowed to warm to rt and stirred at rt for 30 min. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (50 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 50 mL), the comb. org. layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1) yielded ketone **446** (1.43 g, 6.31 mmol, 67%) as a yellow oil. The analytical data match those reported in the literature.[268]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.08 (t, *J* = 6.48 Hz, 1H, H-3), 4.64 (t, *J* = 3.45 Hz, 1H, THP), 4.25 (d, *J* = 16.51 Hz, 1H, H-9), 4.13 (d, *J* = 17.25 Hz, 1H, H-9), 3.86-3.850 (m, 1H, THP), 3.52-3.50 (m, 1H, THP), 2.50 (dt, *J* = 7.42, 1.83 Hz, 2H, H-5), 2.28 (q, *J* = 7.35 Hz, 2H, H-4), 1.89-1.70 (m, 3H, THP), 1.67 (s, 3H, H-6), 1.62 (s, 3H, H-1), 1.60-1.54 (m, 3H, THP) ppm; $\mathbf{R_f}$ (5:1 PE/EtOAc): 0.47.

***tert*-Butyl(((2*E*,6*Z*)-3,11-dimethyl-7-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)dodeca-2,6,10-trien-1-yl)oxy)diphenylsilane 448**



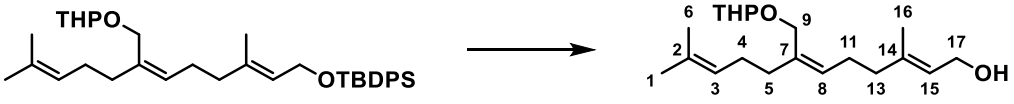
437 448

*n*BuLi (1.6 M in hex, 1.4 mL, 2.16 mmol, 1.60 eq) was added dropwise to a stirred solution of Wittig salt **437** (1.00 g, 1.35 mmol, 1.00 eq) in a mixture of THF (22.5 mL) and HMPA (1.4 mL) at -78 °C and the resulting mixture was stirred at -78 °C for 1 h. Then ketone **446** (0.37 g, 1.62 mmol, 1.20 eq)

in THF (3.3 mL) was added dropwise at -78 °C. The resulting mixture was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (20 mL), the aq. layer was extracted with Et_2O (3x 20 mL), the comb. org. layers were washed with water (2x 20 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 50:1) yielded olefine **448** (0.54 g, 0.96 mmol, 71%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.71-7.67 (m, 4H, TBDPS), 7.44-7.35 (m, 6H, TBDPS), 5.41-5.35 (m, 2H, H-8, H-15), 5.13-5.09 (m, 1H, H-3), 4.59 (t, *J* = 3.52 Hz, 1H, THP), 4.22 (dd, *J* = 6.28, 0.51 Hz, 2H, H-17), 4.18 (d, *J* = 11.48 Hz, 1H, H-9), 4.04 (d, *J* = 11.42 Hz, 1H, H-9), 3.91-3.86 (m, 1H, THP), 3.54-3.49 (m, 1H, THP), 2.21-1.99 (m, 8H, H-4, H-5, H-11, H-13), 1.88-1.79 (m, 1H, THP), 1.74-1.70 (m, 1H, THP), 1.68 (s, 3H, H-1), 1.63-1.49 (m, 7H, THP, H-16), 1.44 (s, 3H, H-6) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 136.8 (q, C-7), 135.9 (q, C-14), 135.7 (t, TBDPS), 134.2 (q, C-2), 131.5 (q, TBDPS), 129.6 (t, TBDPS), 129.1 (t, C-8), 127.7 (t, TBDPS), 124.5 (t, C-15), 124.4 (t, H-3), 97.8 (t, THP), 64.4 (s, C-9), 62.3 (s, THP), 61.3 (s, C-17), 39.9 (s, C-13), 35.6 (s, C-5), 30.8 (s, THP), 27.1 (s, C-11), 27.0 (p, TBDPS), 26.1 (s, C-4), 25.8 (p, C-1), 25.7 (s, THP), 19.7 (s, THP), 19.3 (p, C-16), 17.9 (q, TBDPS), 16.4 (p, C-6) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{36}H_{52}O_3SiNa$ $[M+Na]^+$: 583.3583; *found*: 583.3581; **R_f** (10:1 PE/EtOAc): 0.58.

(2*E*,6*Z*)-3,11-Dimethyl-7-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)dodeca-2,6,10-trien-1-ol 539



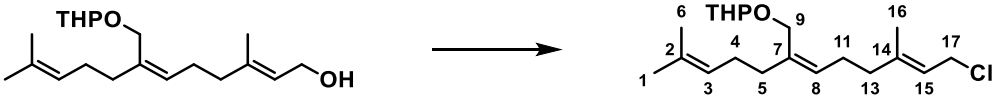
448 539

TBAF (1 M in THF, 2.9 mL, 2.86 mmol, 3.00 eq) was added dropwise to a stirred solution of TBDPS-ether **448** (0.54 g, 0.95 mmol, 1.00 eq) in THF (16.0 mL) at 0 °C and the resulting mixture was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (20 mL), the aq. layer was extracted with EtOAc (3x 20 mL), the comb. org. layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 3:1) yielded alcohol **539** (0.28 g, 0.88 mmol, 93%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.41 (tq, *J* = 7.01, 1.24 Hz, 1H, H-8), 5.34 (t, *J* = 7.29 Hz, 1H, H-15), 5.13-5.09 (m, 1H, H-3), 4.59 (t, *J* = 3.41 Hz, 1H, THP), 4.18 (d, *J* = 11.44 Hz, 1H, H-9), 4.14 (d, *J* = 7.00 Hz, 2H, H-17), 4.02 (d, *J* = 11.43 Hz, 1H, H-9), 3.91-3.85 (m, 1H, THP), 3.55-3.49 (m, 1H, THP), 2.24-2.19 (m, 2H, H-13), 2.15-2.04 (m, 6H, H-4, H-5, H-11), 1.87-1.69 (m, 2H, THP), 1.68 (s, 6H, H-1, H-16), 1.63-1.51 (m, 7H, H-6, THP) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 139.3 (q, C-7), 136.1 (q, C-14), 131.6 (q, C-2), 128.9 (t, C-7), 124.4 (t, C-15), 124.0 (t, C-3), 97.9 (t, THP),

64.4 (s, C-9), 62.3 (s, THP), 59.5 (s, C-17), 39.7 (s, C-13), 35.5 (s, C-5), 30.8 (s, THP), 27.1 (s, C-11), 26.1 (s, C-4), 25.8 (p, C-1), 25.7 (s, THP), 19.6 (s, THP), 17.9 (p, C-16), 16.5 (p, C-6) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{20}H_{34}O_3Na$ $[M+Na]^+$: 345.2406; *found*: 345.2411; $\mathbf{R_f}$ (3:1 PE/EtOAc): 0.38.

2-(((2*Z*,6*E*)-8-Chloro-6-methyl-2-(4-methylpent-3-en-1-yl)octa-2,6-dien-1-yl)oxy)tetrahydro-2*H*-pyran 540

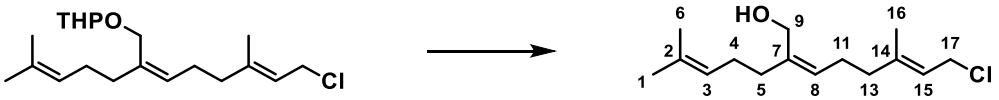


539 **540**

DMS (0.96 mL, 1.30 mmol, 1.50 eq) was added dropwise to a stirred solution of NCS (150.7 mg, 1.13 mmol, 1.30 eq) in CH_2Cl_2 (2.3 mL) at -30 °C. The resulting mixture was allowed to warm to 0 °C over 10 min, then it was cooled to -30 °C. Alcohol **539** (0.28 g, 0.87 mmol, 1.00 eq) in CH_2Cl_2 (1.5 mL) was added dropwise at -30 °C and the resulting mixture was allowed to warm to 0 °C over 1 h. The reaction was terminated by addition of brine (10 mL), the aq. layer was extracted with Et_2O (3x 10 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded chloride **540** (0.26 g, 0.76 mmol, 87%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.44 (tq, *J* = 11.99, 1.30 Hz, 1H, H-8), 5.34 (t, *J* = 7.16 Hz, 1H, H-15), 5.13-5.09 (m, 1H, H-3), 4.59 (t, *J* = 3.41 Hz, 1H, THP), 4.17 (d, *J* = 11.33 Hz, 1H, H-9), 4.09 (d, *J* = 7.92 Hz, 2H, H-17), 4.02 (d, *J* = 11.55 Hz, 1H, H-9), 3.91-3.85 (m, 1H, THP), 3.55-3.49 (m, 1H, THP), 2.25-2.19 (m, 2H, H-13), 2.14-2.06 (m, 5H, H-4, H-5, H-11), 1.87-1.77 (m, 1H, THP), 1.74-1.66 (m, 7H, THP, H-1, H-16), 1.63-1.50 (m, 7H, THP, H-6) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 142.5 (q, C-7), 136.3 (q, C-14), 131.6 (q, C-2), 128.6 (t, C-8), 124.4 (t, C-15), 120.7 (t, C-3), 97.8 (t, THP), 64.4 (s, C-9), 62.3 (s, THP), 41.2 (s, C-17), 39.8 (s, C-13), 35.5 (s, C-5), 30.8 (s, THP), 27.1 (s, C-11), 25.9 (s, C-4), 25.9 (p, C-1), 25.7 (s, THP), 19.6 (s, THP), 17.9 (p, C-16), 16.2 (p, C-6) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{20}H_{33}O_2ClNa$ $[M+Na]^+$: 363.2067; *found*: 363.2071; $\mathbf{R_f}$ (2:1 PE/EtOAc): 0.69.

(2*Z*,6*E*)-8-Chloro-6-methyl-2-(4-methylpent-3-en-1-yl)octa-2,6-dien-1-ol 541

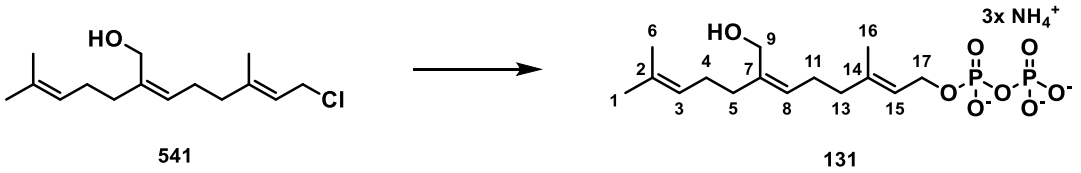


540 **541**

*p*TsOH·H_2O (7.7 mg, 0.05 mmol, 0.10 eq) was added to a stirred solution of ether **540** (152.0 mg, 0.45 mmol, 1.00 eq) in wet MeOH (5.6 mL) at 0 °C. The resulting mixture was allowed to warm to rt over 1 h. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (20 mL). The aq. layer was extracted with CH_2Cl_2 (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography yielded alcohol **541** (54.5 mg, 0.21 mmol, 48%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.45 (dt, *J* = 7.83, 0.78 Hz, 1H, H-8), 5.28 (t, *J* = 7.27 Hz, 1H, H-15), 5.13-5.09 (m, 1H, H-3), 4.12 (s, 2H, H-9), 4.09 (d, *J* = 8.02 Hz, 2H, H-17), 2.25-2.20 (m, 2H, H-13), 2.15-2.07 (m, 6H, H-4, H-5, H-11), 1.73 (s, 3H, H-1), 1.69 (s, 3H, H-16), 1.61 (s, 3H, H-6) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 142.3 (q, C-7), 139.0 (q, C-14), 132.0 (q, C-2), 127.9 (t, C-8), 124.2 (t, C-15), 121.0 (t, C-3), 60.5 (s, C-9), 41.2 (s, C-17), 39.7 (s, C-13), 35.3 (s, C-5), 27.2 (s, C-11), 25.8 (s, C-4, C-1), 17.9 (p, C-16), 16.3 (p, C-6) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{15}H_{25}OClNa$ $[M+Na]^+$: 279.1492; *found*: 279.1492; **R_f** (3:1 PE/EtOAc): 0.38.

(2*E*,6*Z*)-7-(Hydroxymethyl)-3,11-dimethyldodeca-2,6,10-trien-1-yl triammonium diphosphate 131

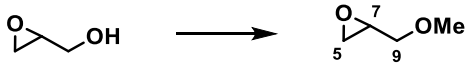


541 131

Preactivated pieces of 3Å-sieves were added to a stirred solution of ($n$$Bu_4N)_3P_2O_7H$ (351.4 mg, 0.39 mmol, 2.00 eq) in MeCN (3.9 mL) at 0 °C. Then chloride **541** (50.0 mg, 0.19 mmol, 1.00 eq) in MeCN (2.0 mL) was added dropwise at 0 °C and the resulting mixture was allowed to warm to rt and stirred at rt overnight. The mixture was concentrated *in vacuo* and standard work up using an ion exchange column was applied to yield pyrophosphate **131** (80.6 mg, 0.18 mmol, 92%) as a white gum which was stored under an atmosphere of Argon at -80 °C.

^{1}H-NMR (600 MHz, D_2O): δ = 5.47 (dt, *J* = 7.13, 1.03 Hz, 1H, H-8), 5.42 (t, *J* = 7.36 Hz, 1H, H-15), 5.22-5.19 (m, 1H, H-3), 4.49 (t, *J* = 6.35 Hz, 2H, H-17), 4.13 (s, 2H, H-9), 2.27-2.23 (m, 2H, H-13), 2.16-2.11 (m, 6H, H-4, H-5, H-11), 1.73 (s, 3H, H-1), 1.70 (s, 3H, H-16), 1.62 (s, 3H, H-6) ppm; **^{13}C-NMR (150 MHz, D_2O):** δ = 142.7 (q, C-7), 137.4 (q, C-14), 133.6 (q, C-2), 129.0 (t, C-8), 124.3 (t, C-3), 119.6 (d, *J* = 8.01 Hz, t, C-15), 62.9 (d, *J* = 5.59 Hz, s, C-17), 58.6 (s, C-9), 39.0 (s, C-13), 34.1 (s, C-5), 26.0 (s, C-11), 25.2 (s, C-4), 24.8 (p, C-1), 17.0 (p, C-16), 15.6 (p, C-6) ppm; **^{31}P-NMR (162 MHz, D_2O):** δ = -9.93 - -10.69 (m, 2P) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{15}H_{27}O_8P_2$ $[M-H]^-$: 397.1181; *found*: 397.1176.

2-(Methoxymethyl)oxirane 443

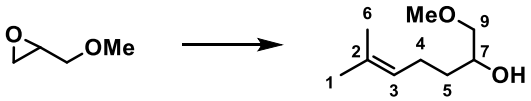


429 443

A mixture of glycidol (**429**) (1.8 mL, 27.00 mmol, 1.00 eq), Ag_2O (6.26 g, 27.00 mmol, 1.00 eq), MeI (16.8 mL), 269.98 mmol, 10.00 eq) and 3Å-sieves in CH_2Cl_2 (16.0 mL) were heated under refluxing conditions overnight. The mixture was cooled to rt and filtered through a pad of Celite^{TM} and washed with CH_2Cl_2 (30 mL). CH_2Cl_2 and remaining MeI were distilled off at 80 °C (1 atm) yielding epoxide **443** (2.38 g, 26.99 mmol, *quant.*) as a colorless liquid. The analytical data match those reported in the literature.[269]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.70 (dd, *J* = 11.39, 2.94 Hz, 1H, H-9), 3.41 (s, 3H, OMe), 3.33 (dd, *J* = 11.38, 5.87 Hz, 1H, H-9), 3.17-3.13 (m, 1H, H-7), 2.80 (dd, *J* = 4.93, 4.25 Hz, 1H, H-5), 2.62 (dd, *J* = 4.99, 2.70 Hz, 1H, H-5) ppm; **R_f** (5:1 PE/EtOAc): 0.31.

1-Methoxy-6-methylhept-5-en-2-ol 445

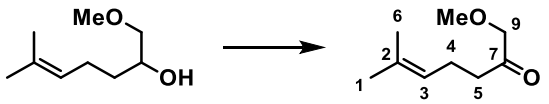


443 445

In a two-neck flask equipped with a reflux-condenser Mg turnings (3.59 g, 147.54 mmol, 10.00 eq) and a single crystal of I_2 in THF (10.0 mL) were placed. A solution of prenylchloride (4.2 mL, 69.89 mmol, 2.50 eq) in THF (62 mL) was added at 0 °C slowly (0.33 mL/min). The resulting mixture was stirred at 0 °C for 1 h and then transferred to a new flask. The Grignard reagent was titrated three times using menthol and phenantrolin, determining its concentration to be 0.56 M. In a new flask, the prepared Grignard reagent (31.6 mL, 17.71 mmol, 1.20 eq) was added dropwise to a stirred solution of CuI (281.0 mg, 1.48 mmol, 0.10 eq) and epoxide **443** (1.30 g, 14.75 mmol, 1.00 eq) in THF (67 mL) at -60 °C and the resulting mixture was allowed to warm to -20 °C overnight using a cryo reactor. The reaction was terminated by addition of ice (20 g) and allowed to warm to rt. Then a sat. aq. NH_4Cl-solution (20 mL) was added and the aq. layer was extracted with EtOAc (4x 20 mL), the comb. org. layers were washed with a sat. aq. $NaHCO_3$-solution, brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield crude alcohol **445** (1.70 g, 10.77 mmol, 73%) as a yellow oil which was directly used for the next step without further purification.

HRMS (GC-MS): *m/z calc.* for $C_9H_{18}O_2$ [M]: 158.1307; *found*: 158.1308; **R_f** (3:1 PE/EtOAc): 0.33.

1-Methoxy-6-methylhept-5-en-2-one 447

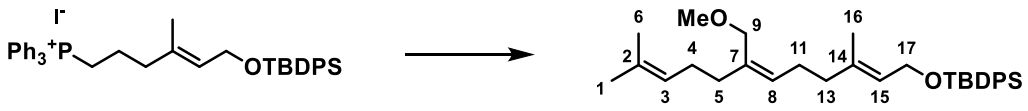


445 447

DMSO (1.3 mL, 17.96 mmol, 3.00 eq) was added dropwise to a stirred solution of oxalylchloride (0.77 mL, 8.98 mmol, 1.50 eq) in CH_2Cl_2 (22.5 mL) at -78 °C, the resulting mixture was stirred at -78 °C for 10 min, then alcohol **445** (0.95 g, 5.99 mmol, 1.00 eq) in CH_2Cl_2 (15.0 mL) was added dropwise at -78 °C and the mixture was stirred at -78 °C for 15 min. Then NEt_3 (2.5 mL, 17.96 mmol, 3.00 eq) was added dropwise at -78 °C and the mixture was allowed to warm to rt and stirred at rt for 30 min. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (50 mL), the layers were separated, the aq. layer was extracted with CH_2Cl_2 (3x 30 mL), the comb. org. layers were washed with brine (80 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* at 200 mbar and 35 °C. Column chromatography (pentanes/Et_2O 1:1) yielded ketone **447** (0.81 g, 5.19 mmol, 87%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.06 (t, *J* = 7.19 Hz, 1H, H-3), 4.00 (s, 2H, H-9), 3.41 (s, 3H, OMe), 2.45 (t, *J* = 7.38 Hz, 2H, H-5), 2.27 (q, *J* = 7.40 Hz, 2H, H-4), 1.67 (s, 3H, H-1), 1.61 (s, 3H, H-6) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 208.6 (q, C-7), 133.2 (q, C-2), 122.6 (t, C-3), 78.8 (s, C-9), 59.4 (p, OMe), 39.0 (s, C-5), 25.8 (p, C-1), 22.2 (s, C-4), 17.8 (p, C-6) ppm; **HRMS (GC-MS):** *m/z calc.* for $C_9H_{16}O_2$ [M]: 156.1150; *found*: 156.1150; **R_f** (3:1 PE/EtOAc): 0.43.

tert-Butyl(((2*E*,6*Z*)-7-(methoxymethyl)-3,11-dimethyldodeca-2,6,10-trien-1-yl)oxy)diphenylsilane 449



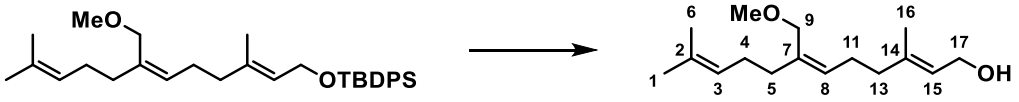
437 449

*n*BuLi (1.6 M in hex, 0.87 mL, 1.38 mmol, 1.60 eq) was added dropwise to a stirred solution of Wittig salt **437** (0.64 g, 0.86 mmol, 1.00 eq) in a mixture of THF (14.5 mL) and HMPA (0.87 mL) at -78 °C and the resulting mixture was stirred at -78 °C for 1 h. Then ketone **447** (162.0 mg, 1.04 mmol, 1.20 eq) in THF (2.1 mL) was added dropwise at -78 °C. The resulting mixture was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (10 mL), the aq. layer was extracted with Et_2O (3x, 10 mL), the comb. org. layers were washed with water (2x 20 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromato-graphy (PE/EtOAc 50:1 – 20:1) yielded olefine **449** (174.8 mg, 0.36 mmol, 40%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.71-7.68 (m, 4H, TBDPS), 7.44-7.35 (m, 6H, TBDPS), 5.40-5.35 (m, 2H, H-8, H-15), 5.12-5.08 (m, 1H, H-3), 4.22 (dd, *J* = 6.29, 0.53 Hz, 2H, H-17), 3.92 (s, 2H,

H-9), 3.30 (s, 3H, OMe), 2.19-1.98 (m, 8H, H-4, H-5, H-11, H-13), 1.68 (s, 3H, H-6), 1.60 (s, 3H, H-16), 1.44 (s, 3H, H-1), 1.04 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 136.8 (q, C-7), 136.0 (q, C-14), 125.8 (t, TBDPS), 134.2 (q, TBDPS), 131.6 (q, C-2), 129.6 (t, TBDPS), 129.1 (t, C-8), 127.7 (t, TBDPS), 124.5 (t, C-15), 124.4 (t, C-2), 69.8 (s, C-9), 61.3 (s, C-17), 57.9 (p, OMe), 39.8 (s, C-13), 35.4 (s, C-5), 27.0 (p, TBDPS, C-13), 26.2 (s, C-11), 25.8 (p, C-6), 19.3 (q, TBDPS), 17.9 (p, C-16), 16.5 (p, C-1) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{32}H_{46}O_2SiNa$ $[M+Na]^+$: 513.3165; *found*: 513.3162; **R_f** (10:1 PE/EtOAc): 0.55.

(2*E*,6*Z*)-7-(Methoxymethyl)-3,11-dimethyldodeca-2,6,10-trien-1-ol 542

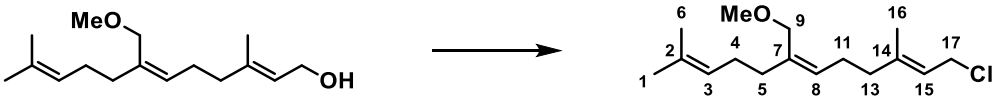


449 542

TBAF (1 M in THF, 0.86 mL, 0.86 mmol, 3.00 eq) was added dropwise to a stirred solution of TBDPS-ether **449** (140.0 mg, 0.29 mmol, 1.00 eq) in THF (4.8 mL) at 0 °C and the resulting mixture was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (10 mL), the aq. layer was extracted with EtOAc (3x 10 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 3:1) yielded alcohol **542** (68.6 mg, 0.27 mmol, 95%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.40 (dt, *J* = 6.89, 0.87 Hz, 1H, H-8), 5.34 (t, *J* = 7.26 Hz, 1H, H-15), 5.12-5.08 (m, 1H, H-2), 4.13 (d, *J* = 7.19 Hz, 2H, H-15), 3.89 (s, 2H, H-9), 3.30 (s, 3H, OMe), 2.23-2.17 (m, 2H, H-13), 2.09-2.03 (m, 6H, H-4, H-5, H-11), 1.68 (s, 6H, H-6, H-16), 1.60 (s, 3H, H-1), 1.38 (bs, 1H, OH) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 139.2 (q, C-7), 136.4 (q, C-14), 131.6 (q, C-2), 128.7 (t, C-8), 124.4 (t, C-15), 124.2 (t, C-3), 69.8 (s, C-9), 59.4 (s, C-17), 58.1 (p, OMe), 39.5 (s, C-13), 35.4 (s, C-5), 26.9 (s, C-4), 26.1 (s, C-11), 25.8 (p, C-1), 17.9 (p, C-6), 16.4 (p, C-16) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{16}H_{28}O_2Na$ $[M+Na]^+$: 275.1987; *found*: 275.1976; **R_f** (2:1 PE/EtOAc): 0.32.

(2*E*,6*Z*)-1-Chloro-7-(methoxymethyl)-3,11-dimethyldodeca-2,6,10-triene 543



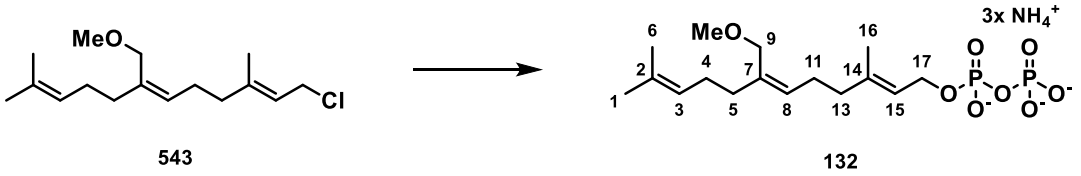
542 543

MsCl (0.04 mL, 0.50 mmol, 2.00 eq) was added dropwise to a stirred solution of alcohol **542** (63.4 mg, 0.25 mmol, 1.00 eq) and collidine (0.21 mL, 1.51 mmol, 6.00 eq) in DMF (8.4 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 20 min. Then LiCl (42.6 mg, 1.00 mmol, 4.00 eq)

was added at 0 °C and the mixture was allowed to warm to rt over 2 h. The reaction was terminated by addition of brine (10 mL) and diluted with a 1:1 mixture of Et_2O and water (10 mL). The aq. layer was extracted with Et_2O (3x 10 mL), the comb. org. layers were washed with an aq. 10% $CuSO_4$-solution (20 mL), sat. aq. $NaHCO_3$-solution (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded chloride **543** (51.8 mg, 0.19 mmol, 76%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.45 (dt, *J* = 7.96, 1.28 Hz, 1H, H-8), 5.34 (t, *J* = 7.20 Hz, 1H, H-15), 5.13-5.08 (m, 1H, H-3), 4.09 (d, *J* = 7.92 Hz, 2H, H-17), 3.91 (s, 2H, H-9), 3.29 (s, 3H, OMe), 2.24-2.18 (m, 2H, H-13), 2.10-2.06 (m, 6H, H-4, H-5, H-11), 1.73 (d, *J* = 0.65 Hz, 3H, H-6), 1.68 (s, H-16), 1.60 (s, 3H, H-1) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 142.4 (q, C-7), 136.5 (q, C-14), 131.6 (q, C-2), 128.5 (t, C-8), 124.4 (t, C-15), 120.8 (t, C-3), 69.8 (s, C-9), 58.0 (p, OMe), 41.2 (s, C-17), 39.7 (s, C-13), 35.4 (s, C-5), 26.9 (s, C-4), 25.9 (s, C-11), 25.8 (p, C-1), 17.9 (p, C-6), 16.3 (p, C-16) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{16}H_{27}OClNa$ $[M+Na]^+$: 293.1648; *found*: 293.1639; **R_f** (2:1 PE/EtOAc): 0.66.

(2*E*,6*Z*)-7-(Methoxymethyl)-3,11-dimethyldodeca-2,6,10-trien-1-yl triammonium diphosphate 132

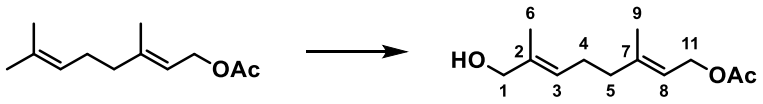


543 132

Preactivated pieces of 3Å-sieves were added to a stirred solution of $(n\text{Bu}_4\text{N})_3P_2O_7H$ (333.2 mg, 0.37 mmol, 2.00 eq) in MeCN (3.7 mL) at 0 °C. Then chloride **543** (50.0 mg, 0.18 mmol, 1.00 eq) in MeCN (1.9 mL) was added dropwise at 0 °C and the resulting mixture was allowed to warm to rt and stirred at rt overnight. The mixture was concentrated *in vacuo* and standard work up using an ion exchange column was applied to yield pyrophosphate **132** (65.7 mg, 0.14 mmol, 77%) as a white gum which was stored under an atmosphere of Argon at -80 °C.

^{1}H-NMR (600 MHz, D_2O): δ = 5.52 (t, *J* = 7.36 Hz, 1H, H-8), 5.47 (dt, *J* = 7.10, 0.96 Hz, 1H, H-15), 5.20 (tt, *J* = 6.81, 1.34 Hz, 1H, H-3), 4.50-4.48 (m, 2H, H-17), 4.03 (s, 2H, H-9), 3.33 (s, 3H, OMe), 2.28-2.24 (s, 2H, H-13), 2.16-2.08 (s, 6H, H-4, H-5, H-11), 1.73 (s, 3H, H-6), 1.70 (s, 3H, H-16), 1.63 (s, 3H, H-1) ppm; **^{13}C-NMR (150 MHz, D_2O):** δ = 142.7 (q, C-7), 134.8 (q, C-14), 133.6 (q, C-2), 130.9 (t, C-8). 124.2 (t, C-15), 119.7 (d, *J* = 7.88 Hz, t, C-15), 69.2 (s, C-9), 62.9 (d, *J* = 5.26 Hz, s, C-17), 57.0 (p, OMe), 38.9 (s, C-13), 34.5 (s, C-5), 26.0 (s, C-4), 25.5 (s, C-11), 24.8 (p, C-1), 17.0 (p, C-6), 15.6 (p, C-16) ppm; **^{31}P-NMR (162 MHz, D_2O):** δ = -9.98 - -10.48 (m, 2P) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{16}H_{29}O_8P_2$ $[M-H]^-$: 411.1338; *found*: 411.1335.

(2*E*,6*E*)-8-Hydroxy-3,7-dimethylocta-2,6-dien-1-yl acetate 454

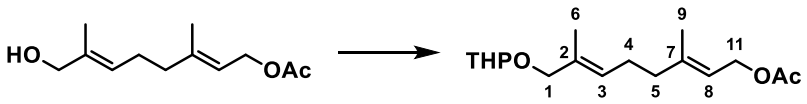


453 454

*t*BuOOH (70% in H_2O, 0.66 mL, 5.09 mmol, 2.50 eq) was added dropwise to a stirred solution of SeO_2 (6.8 mg, 0.06 mmol, 0.03 eq) and salicylic acid (28.2 mg, 0.20 mmol, 0.10 eq) in CH_2Cl_2 (3.4 mL) at rt and the resulting mixture was stirred at rt for 15 min. Then acetate **453** (400.0 mg, 2.04 mg, 1.00 eq) was added dropwise and the resulting mixture was stirred at rt overnight. The reaction was terminated with a mixture of water and 10% aq. $NaHCO_3$-solution (10 mL), the aq. layer was extracted with Et_2O (3x 10 mL), the comb. org. layer was washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1 – 2:1) yielded alcohol **454** (176.1 mg, 0.83 mmol, 41%) as a colorless oil. The analytical data match those reported in the literature.[166]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.39-5.32 (m, 2H, H-3, H-8), 4.58 (d, *J* = 7.06 Hz, 2H, H-11), 3.99 (s, 2H, H-1), 2.20-2.07 (m, 4H, H-4, H-5), 2.06 (s, 3H, Ac), 1.71 (s, 3H, H-9), 1.67 (s, 3H, H-6), 1.36 (bs, OH) ppm; $\mathbf{R_f}$ (5:1 PE/EtOAc): 0.20.

(2*E*,6*E*)-3,7-Dimethyl-8-((tetrahydro-2*H*-pyran-2-yl)oxy)octa-2,6-dien-1-yl acetate 544



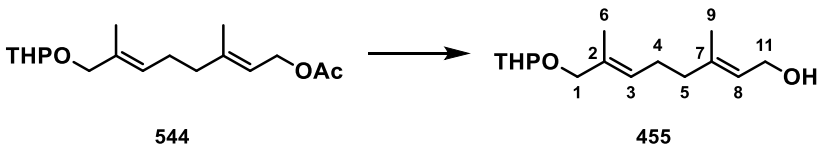
454 544

DHP (0.64 mL, 7.07 mmol, 2.00 eq) and *p*TsOH·H_2O (6.1 mg, 0.04 mmol, 0.01 eq) were added to a stirred solution of allyl alcohol **454** (0.75 g, 3.53 mmol, 1.00 eq) in CH_2Cl_2 (7.0 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min. The reaction was terminated by addition of water (10 mL), the layers were separated, the aq. layer was extracted with EtOAc (3x 10 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1) yielded acetate **544** (1.02 g, 3.42 mmol, 97%) as a colorless oil. The analytical data match those reported in the literature.[166]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.41 (dt, *J* = 6.89, 1.18 Hz, 1H, H-8), 5.35 (dt, *J* = 7.11, 1.22 Hz, 1H, H-3), 4.61-4.58 (m, 3H, THP, H-11), 4.10 (d, *J* = 11.16 Hz, 1H, H-1), 3.91-3.85 (m, 1H, THP),

3.84 (d, *J* = 11.96 Hz, 1H, H-1), 3.53-3.48 (m, 1H, THP), 2.20-2.15 (m, 2H, H-5), 2.10-2.08 (m, 2H, H-4), 2.06 (s, 3H, Ac), 1.87-1.74 (m, 2H, THP), 1.70 (s, 3H, H-9), 1.66 (s, 3H, H-6), 1.62-1.51 (m, 4H, THP) ppm; $\mathbf{R_f}$ (5:1 PE/EtOAc): 0.44.

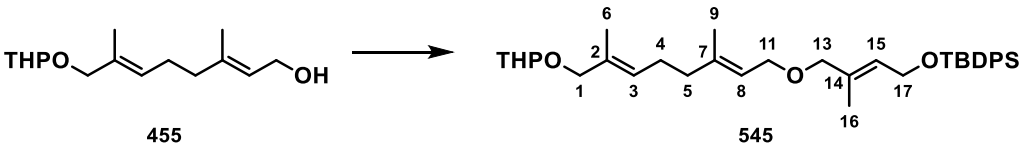
(2*E*,6*E*)-3,7-Dimethyl-8-((tetrahydro-2*H*-pyran-2-yl)oxy)octa-2,6-dien-1-ol 455



1 M NaOH was added to a stirred solution of acetate **544** (0.25 g, 0.83 mmol, 1.00 eq) in MeOH (4.2 mL) at rt until pH = 11 was reached. The resulting mixture was stirred at rt for 1 h. The reaction was terminated by addition of water (10 mL), the aq. layer was extracted with EtOAc (3x 10 mL), the comb. org. layer was washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1 – 2:1) yielded alcohol **455** (165.3 mg, 0.65 mmol, 78%) as a colorless oil. The analytical data match those reported in the literature.[166]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.43-5.39 (m, 2H, H-3, H-8), 4.61 (t, *J* = 3.48 Hz, 1H, THP), 4.14 (d, *J* = 7.40 Hz, 2H, H-11), 4.09 (d, *J* = 11.64 Hz, 1H, H-1), 3.90-3.85 (m, 2H, H-9, THP), 3.54-3.48 (m, 1H, THP), 2.23-2.15 (m, 2H, H-5), 2.10-2.06 (m, 2H, H-4). 1.88-1.70 (m, 2H, THP), 1.67 (s, 3H, H-9), 1.67 (s, 3H, H-6), 1.63-1.51 (m, 4H, THP) ppm; $\mathbf{R_f}$ (5:1 PE/EtOAc): 0.18.

***tert*-Butyl(((*E*)-4-(((2*E*,6*E*)-3,7-dimethyl-8-((tetrahydro-2*H*-pyran-2-yl)oxy)octa-2,6-dien-1-yl)oxy)-3-methylbut-2-en-1-yl)oxy)diphenylsilane 545**

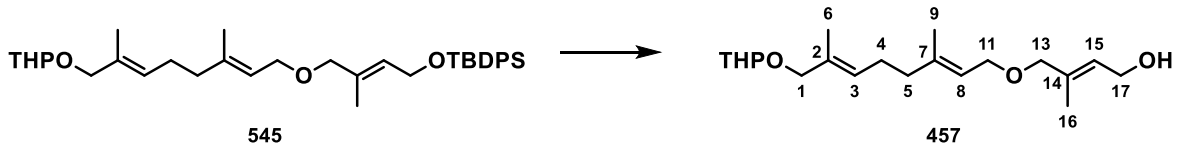


Alcohol **455** (0.72 g, 2.83 mmol, 1.00 eq) in THF (2.6 mL) was added dropwise to a stirred solution of NaH (95%, 151.0 mg, 5.66 mmol, 2.00 eq) in THF (2.8 mL) at rt and the resulting mixture was stirred at rt for 1 h. Then TBAI (31.4 mg, 0.08 mmol, 0.03 eq) and bromide **401** (1.48 g, 3.68 mmol, 1.30 eq) were added at rt. The resulting mixture was stirred at rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (10 mL), the aq. layer was extracted with Et_2O (3x 10 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1 -10:1) yielded ether **545** (1.51 g, 2.62 mmol, 92%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.70-7.67 (m, 4H, TBDPS), 7.44-7.35 (m, 6H, TBDPS), 5.64 (dt, *J* = 6.08, 1.22 Hz, 1H, H-15), 5.42 (dt, *J* = 6.91, 1.10 Hz, 1H, H-3), 5.35 (dt, *J* = 6.83, 1.20 Hz, 1H,

H-8), 4.60 (t, *J* = 3.57 Hz, 1H, THP), 4.26 (dd, *J* = 6.17, 0.55 Hz, 2H, H-17), 4.10 (d, *J* = 11.52 Hz, 1H, H-1), 3.91 (d, *J* = 6.65 Hz, 2H, H-11), 3.89-3.85 (m, 2H, H-1, THP), 3.83 (s, 2H, H-13), 3.53-3.47 (m, 1H, THP), 2.21-2.15 (m, 2H, H-4), 2.09-2.05 (m, 2H, H-5), 1.87-1.80 (m, 1H, THP), 1.76-1.68 (m, 1H, THP), 1.66 (s, 6H, H-6, H-16), 1.63-1.50 (m, 4H, THP), 1.49 (s, 3H, H-9), 1.04 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 140.0 (q, C-7), 135.7 (t, TBDPS), 134.0 (q, TBDPS), 133.8 (q, C-14), 132.3 (q, C-2), 129.7 (t, TBDPS), 127.8 (t, TBDPS), 127.6 (t, C-3), 127.3 (t, C-15), 121.2 (t, C-8), 97.6 (t, THP), 75.6 (s, H-13), 73.0 (s, C-1), 66.1 (s, C-11), 62.3 (s, THP), 60.9 (s, C-17), 39.3 (s, C-5), 30.8 (s, THP), 26.9 (p, TBDPS), 26.2 (s, C-4), 25.7 (s, THP), 19.7 (q, TBDPS), 19.3 (s, THP), 16.6 (p, C-9), 14.2 (p, C-6), 14.2 (p, C-16) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{36}H_{52}O_4SiNa$ $[M+Na]^+$: 599.3533; *found*: 599.3551; **R_f** (10:1 PE/EtOAc): 0.41.

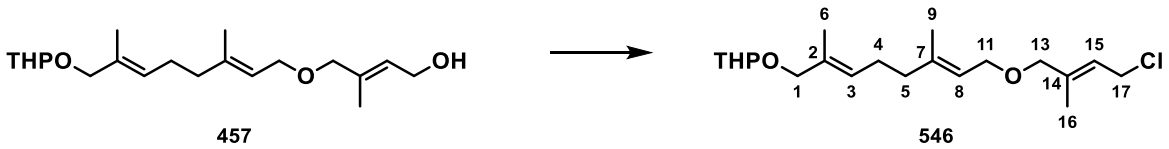
(*E*)-4-(((2*E*,6*E*)-3,7-Dimethyl-8-((tetrahydro-2*H*-pyran-2-yl)oxy)octa-2,6-dien-1-yl)oxy)-3-methylbut-2-en-1-ol 457



TBAF (1 M in THF, 8.3 mL, 8.32 mmol, 3.00 eq) was added dropwise to a stirred solution of TBDPS-ether **545** (1.6 g, 2.77 mmol, 1.00 eq) in THF (28 mL) at 0 °C and the resulting mixture was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (20 mL), the aq. layer was extracted with EtOAc (3x 20 mL), the comb. org. layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 3:1 – 1:1) yielded alcohol **457** (0.80 g, 2.36 mmol, 85%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.66 (tq, *J* = 6.68, 1.28 Hz, 1H, H-15), 5.41 (dt, *J* = 6.85, 1.17 Hz, 1H, H-3), 5.36 (dt, *J* = 6.76, 1.25 Hz, 1H, H-8), 4.60 (t, *J* = 3.53 Hz, 1H, THP), 4.21 (dd, *J* = 6.68, 0.69 Hz, 2H, H-17), 4.10 (d, *J* = 11.67 Hz, 1H, H-1), 3.95 (d, *J* = 6.63 Hz, 2H, H-11), 3.90-3.82 (m, 4H, THP, H-1, H-13), 3.53-3.48 (m, 1H, THP), 2.20-2.15 (m, 2H, H-4), 2.09-2.06 (m, 2H, H-5), 1.87-1.70 (m, 5H, THP, H-9), 1.66 (s, 6H, H-6, H-16), 1.64-1.50 (m, 4H, THP) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 140.1 (q, C-7), 136.1 (q, C-14), 132.3 (q, C-2), 127.5 (t, C-3), 126.1 (t, C-15), 121.2 (t, C-8), 97.6 (t, THP), 75.3 (s, C-13), 73.0 (s, C-1), 66.6 (s, C-11), 62.3 (s, THP), 59.3 (s, C-17), 39.3 (s, C-5), 30.8 (s, THP), 26.1 (s, C-4), 25.6 (s, THP), 19.7 (s, THP), 16.6 (p, C-9), 14.2 (p, C-6, C-16) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{20}H_{34}O_4Na$ $[M+Na]^+$: 361.2355; *found*: 361.2353; **R_f** (2:1 PE/EtOAc): 0.20.

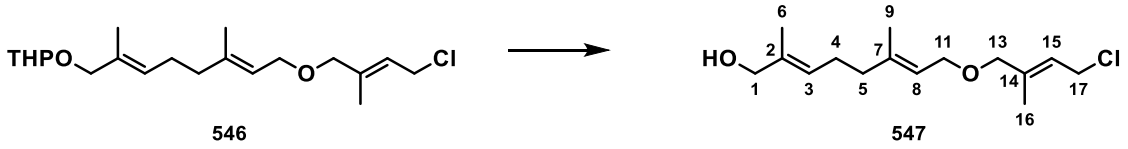
2-(((2*E*,6*E*)-8-(((*E*)-4-Chloro-2-methylbut-2-en-1-yl)oxy)-2,6-dimethylocta-2,6-dien-1-yl)oxy)tetrahydro-2*H*-pyran 546



DMS (26 µL, 0.36 mmol, 1.20 eq) was added dropwise to a stirred solution of NCS (43.4 mg, 0.33 mmol, 1.10 eq) in CH_2Cl_2 (0.65 mL) at -30 °C. The resulting mixture was allowed to warm to 0 °C over 10 min, then it was cooled to -30 °C. Alcohol **457** (100.0 mg, 0.30 mmol, 1.00 eq) in CH_2Cl_2 (0.50 mL) was added dropwise at -30 °C and the resulting mixture was allowed to warm to 0 °C over 2 h. The reaction was terminated by addition of brine (5 mL), the aq. layer was extracted with Et_2O (3x 10 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded chloride **546** (91.3 mg, 0.26 mmol, 87%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.71 (tq, *J* = 7.98, 1.34 Hz, 1H, H-15), 5.42 (dt, *J* = 6.86, 1.17 Hz, 1H, H-3), 5.35 (dt, *J* = 6.78, 1.24 Hz, 1H, H-8), 4.60 (t, *J* = 3.38 Hz, 1H, THP), 4.13-4.08 (m, 3H, H-1, H-17), 3.95 (d, *J* = 9.73 Hz, 2H, H-11), 3.88-3.83 (m, 4H, THP, H-1, H-13), 3.53-3.48 (m, 1H, THP), 2.21-2.15 (m, 2H, H-4), 2.09-2.06 (m, 2H, H-5), 1.87-1.80 (m, 1H, THP), 1.75 (d, *J* = 0.80 Hz, 3H, H-9), 1.66 (s, 6H, H-6, H-16), 1.64-1.51 (m, 5H, THP) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 140.3 (q, C-7), 139.1 (q, C-14), 132.4 (q, C-2), 127.5 (t, C-3), 122.4 (t, C-15), 121.0 (t, C-8), 97.6 (t, THP), 74.7 (s, C-13), 73.0 (s, C-1), 66.6 (s, C-11), 62.3 (s, THP), 40.3 (s, C-17), 39.3 (s, C-5), 30.8 (s, THP), 26.2 (s, C-4), 25.7 (s, THP), 19.7 (s, THP), 16.6 (p, C-9), 14.2 (p, C-6), 13.9 (p, C-16) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{20}H_{33}O_3ClNa$ $[M+Na]^+$: 379.2016; *found*: 379.2014; **R_f** (2:1 PE/EtOAc): 0.69.

(2*E*,6*E*)-8-(((*E*)-4-Chloro-2-methylbut-2-en-1-yl)oxy)-2,6-dimethylocta-2,6-dien-1-ol 547

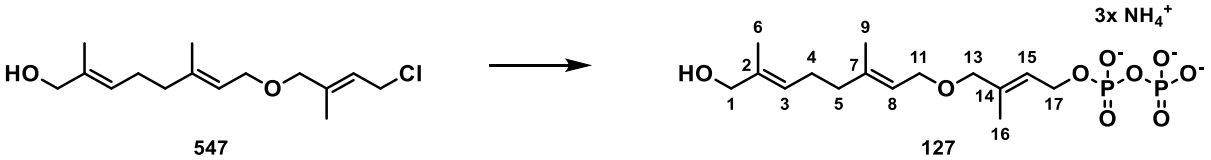


*p*TsOH·H_2O (2.9 mg, 0.02 mmol, 0.10 eq) was added to a stirred solution of ether **546** (59.0 mg, 0.17 mmol, 1.00 eq) in wet MeOH (2.1 mL) at 0 °C. The resulting mixture was allowed to warm to rt over 2 h. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (20 mL). The aq.

layer was extracted with CH_2Cl_2 (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield crude alcohol **547** (46.1 mg, 0.02 mmol, *quant.*) as a colorless oil which was directly used for the next step without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.70 (tq, *J* = 7.92, 1.35 Hz, 1H, H-15), 5.40-5.33 (m, 2H, H-3, H-8), 4.12 (d, *J* = 7.94 Hz, 2H, H-17), 3.99 (s, 2H, H-1), 3.95 (d, *J* = 9.78 Hz, 2H, H-11), 3.88 (s, 2H, H-13), 2.20-2.15 (m, 2H, H-4), 2.40-2.06 (m, 2H, H-5), 1.75 (s, 3H, H-9), 1.66 (s, 6H, H-6, H-16), 1.49 (bs, 1H, OH) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 140.1 (q, C-7), 139.1 (q, C-14), 135.3 (q, C-2), 125.8 (t, C-3), 122.5 (t, C-15), 121.1 (t, C-8), 74.8 (s, C-13), 69.1 (s, C-1), 66.6 (s, C-11), 40.3 (s, C-17), 39.3 (s, C-5), 25.9 (s, C-4), 16.6 (p, C-9), 13.9 (p, C-6), 13.9 (p, C-16) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{15}H_{25}O_2ClNa$ $[M+Na]^+$: 295.1441; *found*: 295.1449; **R_f** (5:1 PE/EtOAc): 0.20.

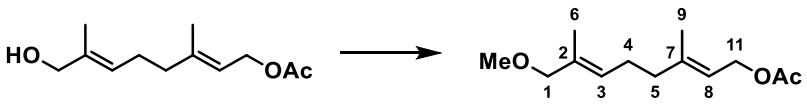
(*E*)-4-(((2*E*,6*E*)-8-Hydroxy-3,7-dimethylocta-2,6-dien-1-yl)oxy)-3-methylbut-2-en-1-yl triammonium diphosphate 127



Preactivated pieces of 3Å-sieves were added to a stirred solution of $(n\text{Bu}_4\text{N})_3P_2O_7H$ (182.6 mg, 0.20 mmol, 1.20 eq) in MeCN (2.1 mL) at 0 °C. Then chloride **547** (46.0 mg, 0.17 mmol, 1.00 eq) in MeCN (1.7 mL) was added dropwise at 0 °C and the resulting mixture was allowed to warm to rt and stirred at rt overnight. The mixture was concentrated *in vacuo* and standard work up using an ion exchange column was applied to yield pyrophosphate **127** (56.7 mg, 0.14 mmol, 81%) as a white gum which was stored under an atmosphere of Argon at -80 °C.

^{1}H-NMR (400 MHz, D_2O): δ = 5.72-5.67 (m, 1H, H-17), 5.43 (dt, *J* = 7.09, 1.30 Hz, 1H, H-3), 5.38 (dt, *J* = 7.37, 1.20 Hz, 1H, H-8), 4.58-4.53 (m, 2H, H-17), 4.03 (d, *J* = 7.20 Hz, 2H, H-1), 3.96-3.96 (m, 4H, H-11, H-13), 2.24-2.19 (m, 2H, H-4), 2.15-2.11 (m, 2H, H-5), 1.73 (s, 3H, H-9), 1.70 (s, 3H, H-16), 1.65 (s, 3H, H-6) ppm; **^{13}C-NMR (100 MHz, D_2O):** δ = 143.1 (q, C-7), 137.0 (q, C-14), 134.5 (q, C-2), 126.5 (t, C-3), 123.8 (t, C-15), 119.3 (t, C-8), 74.6 (s, C-13), 67.6 (s, C-1), 65.7 (s, C-11), 62.4 (s, C-17), 38.4 (s, C-5), 25.1 (s, C-4), 15.5 (p, C-9), 13.4 (p, C-6), 13.0 (p, C-16) ppm; **^{31}P-NMR (162 MHz, D_2O):** δ = -4.52 - -12.27 (m, 2P) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{15}H_{28}O_9P_2Na$ $[M+Na]^+$: 437.1106; *found*: 437.1108.

(2*E*,6*E*)-3,7-Dimethyl-8-((tetrahydro-2*H*-pyran-2-yl)oxy)octa-2,6-dien-1-yl acetate 548

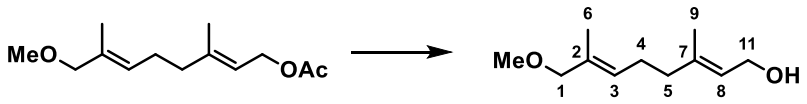


454 548

A mixture of alcohol **454** (3.51 g, 16.52 mmol, 1.00 eq), Ag_2O (7.66 g, 33.06 mmol, 2.00 eq) and MeI (2.1 mL, 33.06 mmol, 2.00 eq) in MeCN (28 mL) was heated in sealed tube to 45 °C overnight. The mixture was diluted with EtOAc (50 mL), filtered over Celite™ and washed with an excess of EtOAc. The filtrate was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1) yielded methylether **548** (1.81 g, 8.03 mmol, 49%, 78% brsm) as a colorless oil. The analytical data match those reported in the literature.[270]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.39-5.33 (m, 2H, H-3, H-8), 4.58 (d, *J* = 7.09 Hz, 2H, H-11), 3.78 (s, 2H, H-1), 3.27 (s, 3H, OMe), 2.21-2.15 (m, 2H, H-4), 2.11-2.09 (m, 2H, H-5), 2.05 (s, 3H Ac), 1.71 (s, 3H, H-9), 1.64 (s, 3H, H-6) ppm; **R_f** (5:1 PE/EtOAc): 0.40.

(2*E*,6*E*)-8-Methoxy-3,7-dimethylocta-2,6-dien-1-ol 456

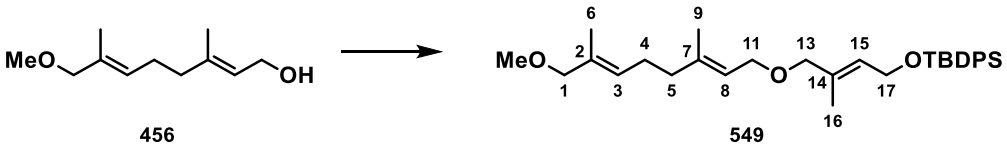


548 456

K_2CO_3 (2.20 g, 15.91 mmol, 2.00 eq) was added to a stirred solution of acetate **548** (1.80 g, 7.95 mmol, 1.00 eq) in wet MeOH (27 mL) at rt and the resulting mixture was stirred at rt for 2 h. The mixture was diluted with a 1:1 mixture of EtOAc/H_2O (50 mL) and the aq. layer was extracted with EtOAc (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 1:1) yielded alcohol **456** (1.18 g, 6.39 mmol, 80%) as a colorless oil. The analytical data match those reported in the literature.[270]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.44-5.36 (m, 2H, H-3, H-8), 4.15 (d, *J* = 6.68 Hz, 2H, H-11), 3.78 (s, 2H, H-1), 3.27 (s, 3H, OMe), 2.21-2.15 (m, 2H, H-4), 2.09-2.06 (m, 2H, H-5), 1.68 (s, 3H, H-9), 1.64 (s, 3H, H-6), 1.24 (bs, 1H, OH) ppm; **R_f** (1:1 PE/EtOAc): 0.37.

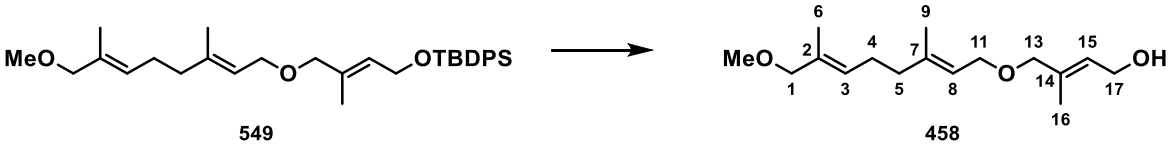
(4*E*,8*E*,13*E*)-4,8,13,18,18-Pentamethyl-17,17-diphenyl-2,11,16-trioxa-17-silanonadeca-4,8,13-triene 549



Alcohol **456** (0.60 g, 3.26 mmol, 1.00 eq) in THF (3.0 mL) was added dropwise to a stirred solution of NaH (95%, 164.5 mg, 6.51 mmol, 2.00 eq) in THF (3.3 mL) at rt and the resulting mixture was stirred at rt for 1 h. Then TBAI (36.1 mg, 0.10 mmol, 0.03 eq) and bromide **401** (1.71 g, 4.23 mmol, 1.30 eq) were added at rt. The resulting mixture was stirred at rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (10 mL), the aq. layer was extracted with Et_2O (3x 10 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1 -10:1) yielded ether **549** (0.93 g, 1.82 mmol, 56%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.70-7.67 (m, 4H, TBDPS), 7.44-7.35 (m, 6H, TBDPS), 5.64 (dt, *J* = 6.10, 1.05 Hz, 1H, H-15), 5.41-5.34 (m, 2H, H-3, H-8), 4.26 (dd, *J* = 7.37, 0.72 Hz, 2H, H-17), 3.91 (d, *J* = 6.73 Hz, 2H, H-11), 3.83 (s, 2H, H-13), 3.78 (s, 2H, H-1), 3.27 (s, 3H, OMe), 2.21-2.16 (m, 2H, H-4), 2.10-2.06 (s, 2H, H-5), 1.66 (s, 3H, H-9), 1.64 (s, 3H, H-6), 1.49 (s, 3H, H-16), 1.04 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 139.9 (q, C-7), 135.7 (t, TBDPS), 134.0 (q, TBDPS), 133.8 (q, C-14), 132.4 (q, C-2), 129.7 (t, TBDPS), 127.9 (t, C-3), 127.8 (t, TBDPS), 127.3 (t, C-15), 121.3 (t, C-8), 78.8 (s, C-11), 75.6 (s, C-1), 66.1 (s, C-13), 60.9 (s, C-17), 57.5 (p, OMe), 39.3 (s, C-5), 26.9 (p, TBDPS), 26.1 (s, C-4), 19.3 (q, TBDPS), 16.6 (p, C-9), 14.2 (p, C-6), 13.9 (p, C-16) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{32}H_{46}O_3SiNa$ $[M+Na]^+$: 529.3114; *found*: 529.3112; **R_f** (10:1 PE/EtOAc): 0.33.

(*E*)-4-(((2*E*,6*E*)-8-Methoxy-3,7-dimethylocta-2,6-dien-1-yl)oxy)-3-methylbut-2-en-1-ol 458

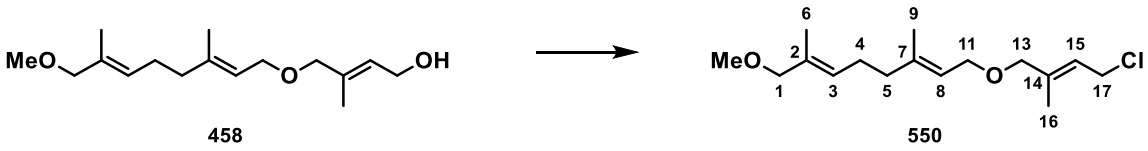


TBAF (1 M in THF, 5.5 mL, 5.45 mmol, 3.00 eq) was added dropwise to a stirred solution of TBDPS-ether **549** (0.92 g, 1.82 mmol, 1.00 eq) in THF (18 mL) at 0 °C and the resulting mixture was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (10 mL), the aq. layer was extracted with EtOAc (3x 20 mL), the comb. org. layers were washed with brine

(30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 3:1 – 1:1) yielded alcohol **458** (0.44 g, 1.64 mmol, 90%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.66 (tq, *J* = 6.70, 1.30 Hz, 1H, H-15), 5.40-5.34 (m, 2H, H-3, H-8), 4.22 (d, *J* = 6.66 Hz, 2H, H-17), 3.95 (d, *J* = 6.26 Hz, 2H, H-11), 3.86 (s, 2H, H-13), 3.78 (s, 2H, H-1), 3.27 (s, 3H, OMe), 2.21-2.15 (m, 2H, H-4), 2.10-2.06 (m, 2H, H-5), 1.70 (s, 3H, H-16), 1.66 (s, 3H, H-9), 1.64 (s, 3H, H-6) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 140.0 (q, C-7), 136.2 (q, C-14), 132.5 (q, C-2), 127.8 (t, C-3), 126.1 (t, C-15), 121.2 (t, C-8), 78.8 (s, C-11), 75.4 (s, C-1), 66.6 (s, C-13), 59.3 (s, C-17), 57.5 (p, OMe), 39.3 (s, C-5), 26.1 (s, C-4), 16.6 (p, C-9), 14.2 (p, C-6), 13.9 (p, C-16) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{16}H_{28}O_3Na$ $[M+Na]^+$: 291.1936; *found*: 291.1934; **R_f** (2:1 PE/EtOAc): 0.21.

(2*E*,6*E*)-8-(((*E*)-4-Chloro-2-methylbut-2-en-1-yl)oxy)-1-methoxy-2,6-dimethylocta-2,6-diene 550



DMS (33 µL, 0.45 mmol, 1.20 eq) was added dropwise to a stirred solution of NCS (54.8 mg, 0.41 mmol, 1.10 eq) in CH_2Cl_2 (0.82 mL) at -30 °C. The resulting mixture was allowed to warm to 0 °C over 10 min, then it was cooled to -30 °C. Alcohol **458** (100.0 mg, 0.37 mmol, 1.00 eq) in CH_2Cl_2 (0.62 mL) was added dropwise at -30 °C and the resulting mixture was allowed to warm to 0 °C over 2 h. The reaction was terminated by addition of brine (5 mL), the aq. layer was extracted with Et_2O (3x 10 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded chloride **550** (92.4 mg, 0.32 mmol, 87%, *quant.* brsm) as a colorless oil.

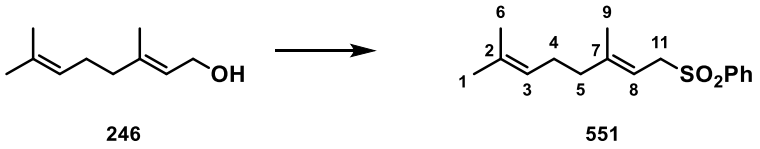
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.69 (tq, *J* = 11.86, 1.35 Hz, 1H, H-15), 5.40-5.34 (m, 2H, H-3, H-8), 4.12 (d, *J* = 8.30 Hz, 2H, H-17), 3.95 (d, *J* = 6.70 Hz, 2H, H-11), 3.88 (s, 2H, H-1), 3.78 (s, 2H, H-13), 3.27 (s, 3H, OMe), 2.21-2,15 (m, 2H, H-4), 2.10-2.06 (m, 2H, H-5), 1.75 (d, *J* = 0.53 Hz, 3H, H-16), 1.67 (s, 3H, H-9), 1.64 (s, 3H, H-6) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 140.2 (q, C-7), 139.1 (q, C-14), 132.5 (q, C-2), 127.7 (t, C-3), 122.4 (t, C-15), 121.0 (t, C-8), 78.8 (s, C-11), 74.8 (s, C-1), 66.6 (s, C-13), 57.5 (p, OMe), 40.3 (s, C-17), 39.3 (s, C-5), 26.1 (s, C-4), 16.6 (p, C-9), 13.9 (p, C-6), 13.9 (p, C-16) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{16}H_{27}O_2ClNa$ $[M+Na]^+$: 309.1597; *found*: 309.1599; **R_f** (2:1 PE/EtOAc): 0.50.

(*E*)-4-(((2*E*,6*E*)-8-Methoxy-3,7-dimethylocta-2,6-dien-1-yl)oxy)-3-methylbut-2-en-1- triammonium diphosphate 128

Preactivated pieces of 3Å-sieves was added to a stirred solution of (nBu$_4$N)$_3$P$_2$O$_7$H (347.3 mg, 0.38 mmol, 1.20 eq) in MeCN (3.9 mL) at 0 °C. Then chloride **550** (92.0 mg, 0.32 mmol, 1.00 eq) in MeCN (3.2 mL) was added dropwise at 0 °C and the resulting mixture was allowed to warm to rt and stirred at rt overnight. The mixture was concentrated *in vacuo* and standard work up using an ion exchange column was applied to yield pyrophosphate **128** (129.7 mg, 0.30 mmol, 94%) as a white gum which was stored under an atmosphere of Argon at -80 °C.

^{1}H-NMR (400 MHz, D$_2$O): δ = 5.69 (t, J = 6.34 Hz, 1H, H-15), 5.48 (dt, J = 7.02, 1.08 Hz, 1H, H-3), 5.38 (dt, J = 7.20, 1.16 Hz, 1H, H-8), 4.55 (t, J = 6.49 Hz, 2H, H-17), 4.03 (d, J = 6.93 Hz, 2H, H-11), 3.96 (s, 2H, H-1), 3.87 (s, 2H, H-13), 3.28 (s, 3H, OMe), 2.27-2.21 (m, 2H, H-4), 2.17-2.13 (m, 2H, H-5), 1.72 (s, 3H, H-9), 1.70 (d, J = 0.95 Hz, 3H, H-16), 1.64 (s, 3H, H-6) ppm; **^{13}C-NMR (100 MHz, D$_2$O):** δ = 142.9 (q, C-7), 137.0 (q, C-14), 131.6 (q, C-2), 129.6 (t, C-3), 123.8 (d, J = 7.77 Hz, t, C-15), 119.4, (t, C-8), 78.3 (s, C-11), 74.6 (s, C-1), 65.7 (s, C-13), 62.4, (d, J = 4.93 Hz, s, C-17), 56.4 (p, OMe), 38.3 (s, C-5), 25.2 (s, C-4), 15.5 (p, C-9), 13.5 (p, C-6), 13.1 (p, C-16) ppm; **^{31}P-NMR (162 MHz, D$_2$O):** δ = -8.27 - -9.66 (m, 1P), -9.86 - -10.60 (m, 1P) ppm; **HRMS (ESI-LCT):** *m/z calc.* for C$_{16}$H$_{29}$O$_9$P$_2$ [M-H]$^-$: 427.1287; *found*: 427.1280.

(*E*)-((3,7-Dimethylocta-2,6-dien-1-yl)sulfonyl)benzene 551

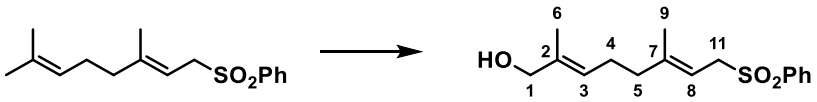


NBS (5.19 g, 29.17 mmol, 1.50 eq) was added in small portions to a stirred solution of PPh$_3$ (8.16 g, 31.12 mmol, 1.60 eq) and geraniol **246** (3.4 mL, 19.45 mmol, 1.00 eq) in DMF (100 mL) at 0 °C. The resulting mixture was allowed to warm to rt over 30 minutes. Then TBAI (0.72 g, 1.95 mmol, 0.10 eq) and NaSO$_2$Ph (6.39 g, 38.90 mmol, 2.00 eq) were added at rt and the resulting mixture was stirred at rt for 3 h. The reaction was terminated by addition of a 1:1 mixture of EtOAc and a 10% Na$_2$S$_2$O$_3$-solution (100 mL), the aq. layer was extracted with EtOAc (3x 50 mL), the comb. org. layers were washed with brine (150 mL), dried over MgSO$_4$, filtered and concentrated *in vacuo*. Column

chromatography (PE/EtOAc 4:1) yielded sulfone **551** (3.88 g, 13.92 mmol, 72%) as a colorless oil. The analytical data match those reported in the literature.[78]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.88-7.86 (m, 2H, SO_2Ph), 7.66-7.61 (m, 1H, SO_2Ph), 7.55-7.51 (m, 2H, SO_2Ph), 5.19 (dt, *J* = 7.92, 1.11 Hz, 1H, H-8), 5.05-5.01 (m, 1H, H-3), 3.81 (d, *J* = 7.97 Hz, 2H, H-11), 2.02-1.99 (m, 4H, H-4, H-5), 1.68 (s, 3H, H-6), 1.59 (s, 3H, H-1), 1.31 (d, *J* = 1.20 Hz, 3H, H-9) ppm; $\mathbf{R_f}$ (2:1 PE/EtOAc): 0.50.

(2*E*,6*E*)-2,6-Dimethyl-8-(phenylsulfonyl)octa-2,6-dien-1-ol 463

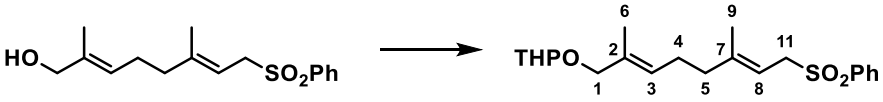


551 463

*t*BuOOH (70% in H_2O, 6.5 mL, 48.65 mmol, 3.50 eq) was added dropwise to a stirred solution of salicylic acid (192.0 mg, 1.39 mmol, 0.10 eq) and SeO_2 (154.2 mg, 1.39 mmol, 0.10 eq) in CH_2Cl_2 (14 mL) at rt. The resulting mixture was stirred at rt for 10 min, then alkene **551** (3.87 g, 13.90 mmol, 1.00 eq) was added at rt and the resulting mixture was stirred at rt for 2 d. The reaction was terminated by addition of an aq. 10% $NaHCO_3$-solution (20 mL), the layers were separated and the aq. layer was extracted with Et_2O (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was dissolved in MeOH (14 mL) and cooled to 0 °C. Then, $NaBH_4$ (262.9 mg, 6.95 mmol, 0.50 eq) was added in small portions. The resulting mixture was stirred at 0 °C for 1 h. The reaction was terminated by addition of a 1:1 mixture of Et_2O and water-mixture (20 mL), the layers were separated, the aq. layer was extracted with Et_2O (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 2:1 – 1:1) yielded alcohol **463** (2.66 g, 9.02 mmol, 65%) as a yellow oil. The analytical data match those reported in the literature.[78]

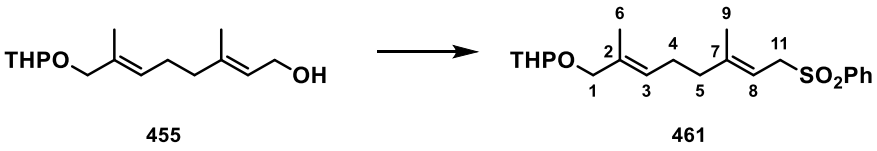
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.89-7.87 (m, 2H, SO_2Ph), 7.67-7.62 (m, 2H, SO_2Ph), 7.57-7.53 (m, 2H, SO_2Ph), 5.34 (dt, *J* = 6.51, 0.61 Hz, 1H, H-8), 5.20 (dt, *J* = 8.29, 0.60 Hz, 1H, H-3), 4.00 (s, 2H, H-1), 3.80 (d, *J* = 7.94 Hz, 2H, H-11), 2-16-2.05 (m, 4H, H-4, H-5), 1.66 (s, 3H, H-6), 1.58 (bs, 1H, OH), 1.39 (d, *J* = 1.01 Hz, 3H, H-9) ppm; $\mathbf{R_f}$ (1:1 PE/EtOAc): 0.29.

2-(((2*E*,6*E*)-2,6-Dimethyl-8-(phenylsulfonyl)octa-2,6-dien-1-yl)oxy)tetrahydro-2*H*-pyran 461



463 461

DHP (1.6 mL, 17.02 mmol, 2.00 eq) and *p*TsOH·H_2O (14.7 mg, 0.09 mmol, 0.01 eq) were added to a stirred solution of alcohol **463** (2.51 g, 8.51 mmol, 1.00 eq) in CH_2Cl_2 (25 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 30 min. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (10 mL), the aq. layer was extracted with Et_2O (3x 10 mL), the comb. org. layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 3:1) yielded sulfone **461** (2.96 g, 7.83 mmol, 92%) as a colorless oil. The analytical data match those reported in the literature.[271]

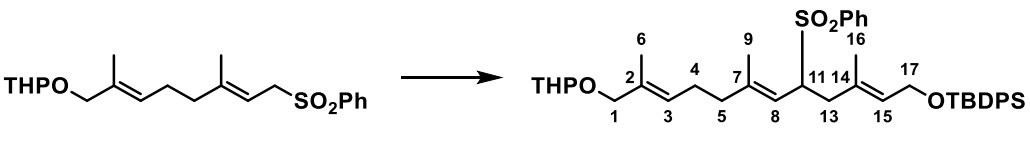


455 461

Alternatively, NBS (173.5 mg, 0.98 mmol, 1.50 eq) was added to a stirred solution of alcohol **455** (165.3 mg, 0.65 mmol, 1.00 eq) and PPh_3 (272.7 mg, 1.04 mmol, 1.50 eq) in DMF (3.3 mL) at 0 °C and the resulting mixture was allowed to warm to rt 30 min. Then TBAI (24.0 mg, 0.07 mmol, 0.10 eq) and $NaSO_2Ph$ (213.4 mg, 1.30 mmol, 2.00 eq) were added at rt and the resulting mixture was stirred at rt for 2 h. The reaction was terminated by dilution of 1:1 mixture of EtOAc and an aq. 10% solution of $Na_2S_2O_3$ (10 mL), the aq. layer was extracted with EtOAc (3x 10 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 2:1 – 1:1) yielded sulfone **461** (183.2 mg, 0.48 mmol, 74%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.88-7.85 (m, 2H, SO_2Ph), 7.66-7.62 (m, 1H, SO_2Ph), 7.56-7.52 (m, 2H, SO_2Ph), 5.36 (t, *J* = 6.13 Hz, 1H, H-8), 5.19 (dt, *J* = 8.26, 0.58 Hz, 1H, H-3), 4.59 (t, *J* = 3.56 Hz, 1H, THP), 4.10 (d, *J* = 10.41 Hz, 1H, H-1), 3.90-3.85 (m, 1H, THP), 3.85-3.79 (m, 3H, H-1, H-11), 3.53-3.48 (m, 1H, THP), 2.11-2.00 (m, 4H, H-4, H-5), 1.88-1.79 (m, 1H, THP), 1.77-1.68 (m, 1H, THP), 1.64 (s, 3H, H-6), 1.62-1.50 (m, 4H, THP), 1.31 (d, *J* = 1.13 Hz, 3H, H-9) ppm; **R_f** (5:1 PE/EtOAc): 0.10.

tert-Butyldiphenyl (((2*E*,6*E*,10*E*)-3,7,11-trimethyl-5-(phenylsulfonyl)-12-((tetrahydro-2*H*-pyran-2-yl)oxy)dodeca-2,6,10-trien-1-yl)oxy)silane 464



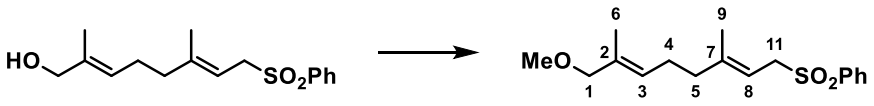
461 464

*n*BuLi (1.6 M in hex, 1.8 mL, 2.91 mmol, 1.10 eq) was added dropwise to a stirred solution of sulfone **461** (1.00 g, 2.64 mmol, 1.00 eq) in a mixture of THF (8.0 mL) and HMPA (2.2 mL) at -78 °C

and the resulting mixture was stirred at -78 °C for 1.5 h. Then bromide **401** (1.12 g, 2.77 mmol, 1.05 eq) in THF (5.6 mL) was added dropwise at -78 °C and the resulting mixture was stirred at -78 °C for 2 h. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (10 mL), the aq. layer was extracted with EtOAc (3x 10 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1 - 3:1) yielded sulfone **464** (1.43 g, 2.04 mmol, 77%) as a colorless oil.

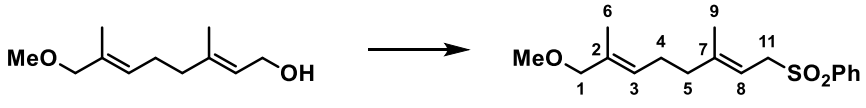
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.85-7.83 (m, 2H, SO_2Ph), 7.64-7.60 (m, 5H, TBDPS, SO_2Ph, 7.54-7.50 (m, 2H, SO_2Ph), 7.42-7.34 (m, 6H, TBDPS), 5.40-5.32 (m, 2H, H-3, H-15), 4.93-4.91 (m, 1H, H-8), 4.15-4.07 (m, 3H, H-1, H-17), 3.91-3.80 (m, 3H, H-1, H-11, THP), 3.51-3.47 (m, 1H, THP), 2.88 (d, *J* = 13.17 Hz, 1H, H-13), 2.29 (dd, *J* = 13.45, 11.52 Hz, 1H, H-13), 2.00-1.66 (m, 8H, H-4, H-5, THP), 1.62 (s, 3H, H-16), 1.61-1.50 (m, 4H, THP), 1.38 (s, 3H, H-6), 1.16 (s, 3H, H-16), 1.01 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 138.0 (q, TBDPS), 135.7 (t, TBDPS), 135.7 (t, SO_2Ph), 133.9 (q, C-14), 133.6 (q, C-2), 132.0 (q, C-7), 129.7 (t, TBDPS), 129.4 (t, SO_2Ph), 129.4 (t, C-3), 129.0 (q, SO_2Ph), 12.9 (t, SO_2Ph), 127.8 (t, TBDPS), 127.0 (t, C-15), 117.3 (t, C-15), 97.7 (t, THP), 72.9 (s, C-1), 63.5 (t, C-13), 62.4 (s, THP), 60.9 (s, C-17), 39.5 (s, C-5), 35.4 (s, C-11), 30.8 (s, THP), 26.9 (p, TBDPS), 26.2 (s, THP), 25.6 (s, C-4), 19.7 (q, TBDPS), 19.3 (s, THP), 16.6 (p, C-16), 16.6 (p, C-6), 14.2 (p, C-9) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{42}H_{56}O_5SSiNa$ $[M+Na]^+$: 723.3515; *found*: 723.3515; $\mathbf{R}_f$ (2:1 PE/EtOAc): 0.52.

(((2*E*,6*E*)-8-Methoxy-3,7-dimethylocta-2,6-dien-1-yl)sulfonyl)benzene 462



463 462

A mixture of MeI (0.08 mL, 1.15 mmol, 3.30 eq), Ag_2O (81.1 mg, 0.35 mmol, 1.00 eq) and alcohol **463** (103.0 mg, 0.35 mmol, 1.00 eq) in CH_2Cl_2 (1.8 mL) were stirred at rt overnight. The reaction mixture was filtered over Celite^{TM}, washed with an excess of CH_2Cl_2 and concentrated *in vacuo*. Column chromatography (PE/EtOAc 2:1) yielded sulfone **462** (9.5 mg, 0.03 mmol, 9%) as a colorless oil.



456 462

Alternatively, NBS (0.83 g, 4.69 mmol, 1.50 eq) was added to a stirred solution of alcohol **456** (0.58 g, 3.13 mmol, 1.00 eq) and PPh_3 (1.31 g, 5.00 mmol, 1.50 eq) in DMF (16.0 mL) at 0 °C and

the resulting mixture was allowed to warm to rt 30 min. Then TBAI (115.5 mg, 0.31 mmol, 0.10 eq) and $NaSO_2Ph$ (1.03 g, 6.25 mmol, 2.00 eq) were added at rt and the resulting mixture was stirred overnight. The reaction was terminated by dilution of 1:1 mixture of EtOAc and an aq. 10% solution of $Na_2S_2O_3$ (20 mL), the aq. layer was extracted with EtOAc (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 2:1 – 1:1) yielded sulfone **462** (0.55 g, 1.79 mmol, 57%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.88-7.76 (m, 2H, SO_2Ph), 7.66-7.62 (m, 1H, SO_2Ph), 7.56-7.51 (m, 2H, SO_2Ph), 5.33 (t, *J* = 6.11 Hz, 1H, H-3), 5.20 (t, *J* = 7.55 Hz, 1H, H-8), 3.81 (d, *J* = 7.92 Hz, 2H, H-11), 3.78 (s, 2H, H-1), 3.28 (s, 3H, OMe), 2.09-2.03 (m, 4H, H-4, H-5), 1.62 (s, 3H, H-9), 1.32 (s, 3H, H-6) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 146.2 (q, SO_2Ph), 138.8 (q, C-7), 133.7 (t, SO_2Ph), 132.9 (q, C-2), 129.1 (t, SO_2Ph), 128.7 (t, SO_2Ph), 126.9 (t, C-3), 110.6 (t, C-8), 78.6 (s, C-1), 57.7 (p, OMe), 56.2 (s, C-11), 39.4 (s, C-5), 25.9 (s, C-4), 16.3 (p, C-6), 14.0 (p, C-9) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{17}H_{24}O_3SNa$ $[M+Na]^+$: 331.1344; *found*: 331.1352; **R_f** (2:1 PE/EtOAc): 0.36.

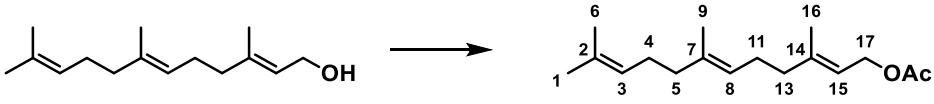
tert-Butyl (((2*E*,6*E*,10*E*)-12-methoxy-3,7,11-trimethyl-5-(phenylsulfonyl)dodeca-2,6,10-trien-1-yl)oxy)diphenylsilane 465

*n*BuLi (1.6 M in hex, 1.3 mL, 1.97 mmol, 1.10 eq) was added dropwise to a stirred solution of sulfone **462** (0.55 g, 1.79 mmol, 1.00 eq) in a mixture of THF (5.5 mL) and HMPA (1.5 mL) at -78 °C and the resulting mixture was stirred at -78 °C for 1.5 h. Then bromide **401** (0.76 g, 1.88 mmol, 1.05 eq) in THF (3.8 mL) was added dropwise at -78 °C and the resulting mixture was stirred at -78 °C for 2 h. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (10 mL), the aq. layer was extracted with EtOAc (3x 10 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1 - 3:1) yielded sulfone **465** (0.87 g, 1.39 mmol, 77%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.85-7.83 (m, 2H, SO_2Ph), 7.64-7.61 (m, 5H, TBDPS, SO_2Ph), 7.54-7.50 (m, 2H, SO_2Ph), 7.43-7.34 (m, 6H, TBDPS), 5.38 (t, *J* = 6.20 Hz, 1H, H-15), 5.30 (t, *J* = 6.11 Hz, 1H, H-3), 4.92 (d, *J* = 10.22 Hz, 1H, H-8), 4.15-4.09 (m, 2H, H-17), 3.91-3.85 (m, 1H, H-11), 3.75 (s, 2H, H-1), 3.26 (s, 3H, OMe), 2.87 (d, *J* = 13.42 Hz, 1H, H-13), 2.29 (dd, *J* = 13.53, 12.08 Hz, 1H, H-13), 2.01-1.89 (m, 4H, H-4, H-5), 1.60 (s, 3H, H-16), 1.38 (s, 3H, H-6), 1.17 (d, *J* = 1.13 Hz, 3H, H-9), 1.00 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 145.2 (q, SO_2Ph),

138.0 (q, C-7), 135.7 (t, TBDPS), 133.9 (q, C-2), 133.6 (q, TBDPS), 132.8 (t, C-3), 129.7 (t, SO_2Ph), 129.4 (t, SO_2Ph), 128.9 (t, C-8), 127.8 (t, SO_2Ph), 127.8 (t, TBDPS), 127.1 (t, TBDPS), 117.4 (t, C-15), 78.6 (s, C-1), 63.5 (s, C-11), 60.9 (s, C-17), 57.7 (p, OMe), 39.5 (s, C-5), 37.3 (s, C-13), 26.9 (p, TBDPS), 26.1 (s, C-4), 19.3 (q, TBDPS), 16.6 (p, C-16), 16.5 (p, C-6), 13.9 (p, C-9) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{38}H_{50}O_4SSiNa$ $[M+Na]^+$: 653.3097; *found*: 653.3092; $\mathbf{R_f}$ (3:1 PE/EtOAc): 0.39.

(2*E*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trien-1-yl acetate 552

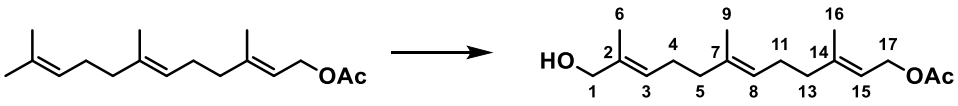


467 **552**

NEt_3 (1.9 mL, 13.49 mmol, 1.50 eq), DMAP (10.1 mg, 0.09 mmol, 0.01 eq) and Ac_2O (1.1 mL, 10.79 mmol, 1.20 eq) were added to a stirred solution of farnesol **467** (2.3 mL, 8.99 mmol, 1.00 eq) in CH_2Cl_2 (30.0 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 10 min. The reaction was terminated by addition of water (30 mL), the aq. layer was extracted with CH_2Cl_2 (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1) yielded acetate **552** (2.38 g, 8.99 mmol, *quant.*) as a colorless oil. The analytical data match those reported in the literature.[272]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.34 (dt, *J* = 7.12, 1.19 Hz, 1H, H-15), 5.11-5.07 (m, 2H, H-3, H-8), 4.59 (d, *J* = 7.12 Hz, 2H, H-17), 2.14-1.95 (m, 11H, H-4, H-5, H-11, H-13, Ac), 1.70 (s, 3H, H-1), 1.68 (s, 3H, H-6), 1.60 (s, 6H, H-9, H-16) ppm; $\mathbf{R_f}$ (5:1 PE/EtOAc): 0.64.

(2*E*,6*E*,10*E*)-12-Hydroxy-3,7,11-trimethyldodeca-2,6,10-trien-1-yl acetate 468



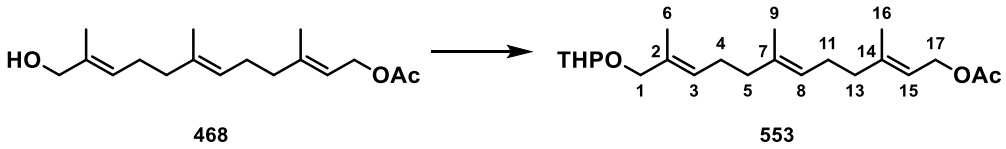
552 **468**

*t*BuOOH (70% in H_2O, 3.5 mL, 27.02 mmol, 3.00 eq) was added dropwise to a stirred solution of salicylic acid (124.4 mg, 0.90 mmol, 0.10 eq) and SeO_2 (99.9 mg, 0.90 mmol, 0.10 eq) in CH_2Cl_2 (18.0 mL) at rt. The resulting mixture was stirred at rt for 10 min, then alkene **552** (2.38 g, 9.01 mmol, 1.00 eq) in CH_2Cl_2 (7.0 mL) was added at rt and the resulting mixture was stirred at rt overnight. The reaction was terminated by addition of an aq. 10% $NaHCO_3$-solution (20 mL), the layers were separated and the aq. layer was extracted with Et_2O (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography

(PE/EtOAc 10:1) yielded alcohol **468** (0.79 g, 2.82 mmol, 31%, 40% brsm) as a colorless oil. The analytical data match those reported in the literature.[166]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.40-5.32 (m, 2H, H-3, H-15), 5.10 (t, *J* = 6.28 Hz, 1H, H-8), 4.59 (d, *J* = 7.10 Hz, 2H, H-17), 3.99 (s, 2H, H-1), 2.18-1.99 (m, 11H, H-3, H-4, H-11, H-13, Ac), 1.70 (s, 3H, H-6), 1.67 (s, 3H, H-6), 1.60 (s, 3H, H-16) ppm; **R_f** (5:1 PE/EtOAc): 0.18.

(2*E*,6*E*,10*E*)-3,7,11-Trimethyl-12-((tetrahydro-2*H*-pyran-2-yl)oxy)dodeca-2,6,10-trien-1-yl acetate 553

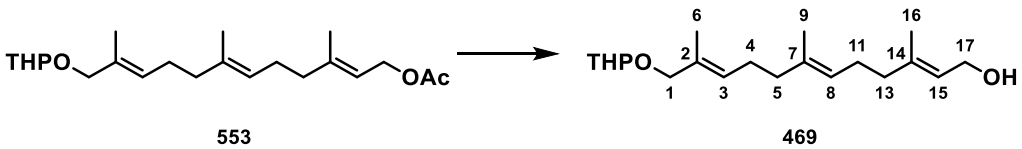


468 553

DHP (0.51 mL, 5.63 mmol, 2.00 eq) and *p*TsOH·H_2O (4.9 mg, 0.03 mmol, 0.01 eq) were added to a stirred solution of alcohol **468** (0.79 g, 2.82 mmol, 1.00 eq) in CH_2Cl_2 (5.8 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 5 min. The reaction was terminated by addition of water (10 mL), the aq. layer was extracted with EtOAc (3x 10 mL), the comb. org. layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded acetate **553** (1.02 g, 2.80 mmol, 99%) as a colorless oil. The analytical data match those reported in the literature.[166]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.41 (t, *J* = 6.79 Hz, 1H, H-3), 5.34 (dt, *J* = 7.05, 1.11 Hz, 1H, H-15), 5.10 (t, *J* = 6.07 Hz, 1H, H-8), 4.59 (m, 3H, H-17, THP), 4.10 (d, *J* = 11.82 Hz, 1H, H-1), 3.91-3.83 (m, 2H, H-1, THP), 3.55-3.48 (m, 1H, THP), 2.18-2.00 (m, 11H, H-4, H-5, H-11, H-13, Ac), 1.89-1.73 (2H, THP), 1.70 (s, 3H, H-6), 1.66 (s, 3H, H-9), 1.60-1.51 (m, 7H, H-16, THP) ppm; **R_f** (5:1 PE/EtOAc): 0.38.

(2*E*,6*E*,10*E*)-3,7,11-trimethyl-12-((tetrahydro-2*H*-pyran-2-yl)oxy)dodeca-2,6,10-trien-1-ol 469



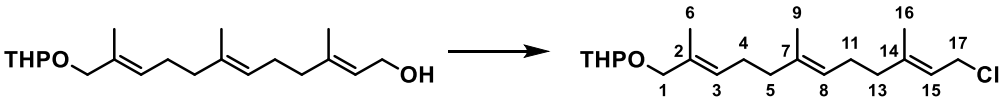
553 469

1 M NaOH was added dropwise to a stirred solution of acetate **553** (1.00 g, 2.74 mmol, 1.00 eq) in MeOH (14.0 mL) at rt until pH of 11-12 was reached. The resulting mixture was stirred at rt for 1 h. The reaction was terminated by addition of water (20 mL), the aq. layer was extracted with EtOAc (3x 20 mL), the comb. org. layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and

concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1 – 1:1) yielded alcohol **469** (0.76 g, 2.37 mmol, 86%) as a colorless oil. The analytical data match those reported in the literature.[166]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.41 (t, *J* = 6.83 Hz, 2H, H-3, H-15), 5.11 (t, *J* = 6.18 Hz, 1H, H-8), 4.60 (t, *J* = 3.50 Hz, 1H, THP), 4.15 (d, *J* = 6.82 Hz, 2H, H-17), 4.10 (d, *J* = 11.57 Hz, 1H, H-1), 3.91-3.83 (m, 2H, H-1, THP), 3.53-3.48 (m, 1H, THP), 2.16-2.00 (m, 8H, H-4, H-5, H-11, H-13), 1.89-1.50 (m, 15H, THP, H-6, H-9, H-16) ppm; **R_f** (5:1 PE/EtOAc): 0.25.

2-(((2*E*,6*E*,10*E*)-12-Chloro-2,6,10-trimethyldodeca-2,6,10-trien-1-yl)oxy)tetrahydro-2*H*-pyran 554

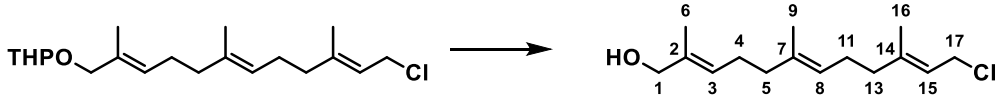


469 554

MsCl (0.05 mL, 0.65 mmol, 2.00 eq) was added dropwise to a stirred solution of alcohol **469** (105.0 mg, 0.33 mmol, 1.00 eq) and collidine (0.26 mL, 1.95 mmol, 6.00 eq) in DMF (11.0 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 20 min. Then LiCl (55.2 mg, 1.30 mmol, 4.00 eq) was added at 0 °C and the mixture was allowed to warm to rt over 2 h. The reaction was terminated by addition of brine (10 mL) and diluted with a 1:1 mixture of Et_2O and water (10 mL). The aq. layer was extracted with Et_2O (3x 10 mL), the comb. org. layers were washed with an aq. 10% $CuSO_4$-solution (20 mL), sat. aq. $NaHCO_3$-solution (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded chloride **554** (88.8 mg, 0.26 mmol, 80%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.47 (m, 2H, H-3, H-15), 5.10 (t, *J* = 6.15 Hz, 1H, H-8), 4.60 (t, *J* = 3.48 Hz, 1H, THP), 4.11-4.09 (m, 3H, H-17, H-1), 3.91-3.83 (m, 2H, H-1, THP), 3.53-3.48 (m, 1H, THP), 2.22-2.00 (m, 8H, H-4, H-5, H-11, H-13), 1.88-1.51 (m, 15H, THP, H-6, H-9, H-16) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 142.9 (q, C-14), 135.5 (q, C-8), 132.0 (q, C-2), 128.0 (t, C-3), 123.8 (t, C-8), 120.5 (t, C-15), 97.5 (t, THP), 73.1 (s, C-1), 62.3 (s, THP), 41.3 (s, C-17), 39.6 (s, C-5), 39.4 (s, C-13), 30.8 (s, THP), 26.5 (s, C-4), 26.2 (s, C-11), 25.7 (s, THP), 19.7 (s, THP), 16.3 (p, C-16), 16.2 (p, C-9), 14.2 (p, C-6) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{20}H_{33}O_2ClNa$ $[M+Na]^+$: 363.2067; *found*: 363.2071; **R_f** (2:1 PE/EtOAc): 0.57.

(2*E*,6*E*,10*E*)-12-Chloro-2,6,10-trimethyldodeca-2,6,10-trien-1-ol 555

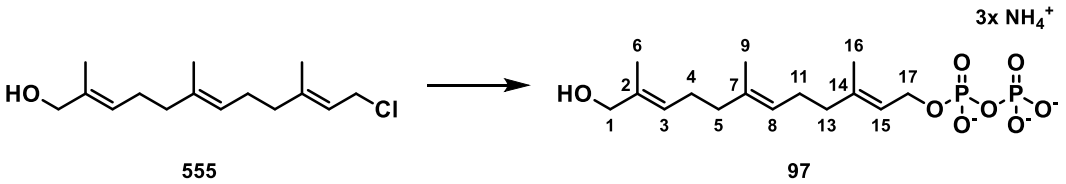


554 555

*p*TsOH·H_2O (4.0 mg, 0.02 mmol, 0.10 eq) was added to a stirred solution of ether **554** (80.0 mg, 0.23 mmol, 1.00 eq) in wet MeOH (2.9 mL) at 0 °C. The resulting mixture was allowed to warm to rt over 1 h. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (20 mL). The aq. layer was extracted with CH_2Cl_2 (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield crude alcohol **555** (60.3 mg, 0.23 mmol, *quant.*) as a colorless oil which was directly used for the next step without further purification. The analytical data match those reported in the literature.[81]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.45 (dt, *J* = 7.99, 1.25 Hz, 1H, H-15), 5.39 (dt, *J* = 6.96, 1.27 Hz, 1H, H-3), 5.10 (t, *J* = 6.29 Hz, 1H, H-8), 4.10 (d, *J* = 8.02 Hz, 2H, H-17), 4.00 (s, 2H, H-1), 2.18-2.00 (m, 8H, H-4, H-5, H-11, H-13), 1.73 (d, *J* = 0.98 Hz, 3H, H-6), 1,67 (s, 3H, H-16), 1.61 (s, 3H, H-9) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{15}H_{25}OClNa$ $[M+Na]^+$: 279.1492; *found*: 279.1484; **R_f** (2:1 PE/EtOAc): 0.44.

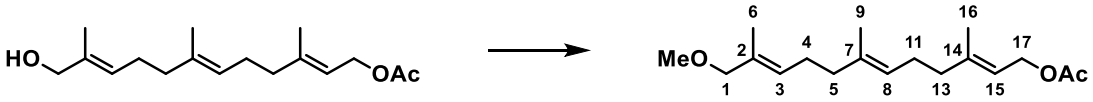
(2*E*,6*E*,10*E*)-12-Hydroxy-3,7,11-trimethyldodeca-2,6,10-trien-1-yl triammonium diphosphate 97



Preactivated pieces of 3Å-sieves was added to a stirred solution of (nBu$_4$N)$_3$$P_2O_7$H (386.5 mg, 0.43 mmol, 2.00 eq) in MeCN (4.3 mL) at 0 °C. Then chloride **555** (55.0 mg, 0.21 mmol, 1.00 eq) in MeCN (2.1 mL) was added dropwise at 0 °C and the resulting mixture was allowed to warm to rt and stirred at rt overnight. The mixture was concentrated *in vacuo* and standard work up using an ion exchange column was applied to yield pyrophosphate **97** (60.0 mg, 0.13 mmol, 62%) as a white gum which was stored under an atmosphere of Argon at -80 °C. The analytical data math those reported in the literature.[81]

^{1}H-NMR (400 MHz, D_2O): δ = 5.49-5.42 (m, 2H, H-1, H-15), 5.23 (t, *J* = 6.37 Hz, 1H, H-8), 4.51-4.49 (m, 2H, H-17), 3.97 (s, 2H, H-1), 2.21-2.05 (8H, H-4, H-5, H-11, H-13), 1.74 (s, 3H, H-6), 1.65 (s, 3H, H-16), 1.64 (s, 3H, H-9) ppm; **^{13}C-NMR (100 MHz, D_2O):** δ = 143.1 (q, C-14), 136.5 (q, C-2), 134.3 (q, C-7), 127.0 (t, C-3), 124.3 (t, C-8), 119.5 (t, C-15), 67.7 (s, C-1), 62.9 (s, C-17), 38.7 (s, C-13), 38.4 (s, C-5), 25.5 (s, C-11), 25.4 (s, C-4), 15.6 (p, C-6), 15.2 (p, C-16), 12.9 (p, C-9) ppm; **^{31}P-NMR (162 MHz, D_2O):** δ = -8.45 - -11.55 (m, 2P) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{15}H_{27}O_8P_2$ $[M-H]^-$: 397.1181; *found*: 397.1169.

(2*E*,6*E*,10*E*)-12-Methoxy-3,7,11-trimethyldodeca-2,6,10-trien-1-yl acetate 556

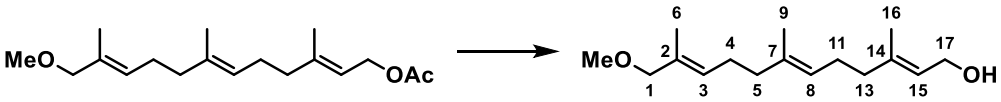


468 556

A mixture of alcohol **468** (0.32 g, 1.14 mmol, 1.00 eq), Ag_2O (0.53 g, 2.28 mmol, 2.00 eq) and MeI (0.14 mL, 2.28 mmol, 2.00 eq) in MeCN (2.0 mL) was heated in sealed tube to 45 °C overnight. The mixture was diluted with EtOAc (10 mL), filtered over Celite™ and washed with an excess of EtOAc. The filtrate was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1) yielded methylether **556** (0.24 g, 0.82 mmol, 72%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.40-5.32 (m, 2H, H-3, H-15), 5.10 (t, *J* = 6.13 Hz, 1H, H-8), 4.59 (d, *J* = 7.15 Hz, 2H, H-17), 3.78 (s, 2H, H-1), 3.27 (s, 3H, OMe), 2.21-2.00 (m, 11H, H-4, H-5, H-11, H-13), 1.70 (s, 3H, H-6), 1.64 (s, 3H, H-16), 1.60 (s, 3H, H-9) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 171.3 (q, Ac), 142.4 (q, C-14), 135.3 (q, C-2), 132.1 (q, C-7), 128.2 (t, C-3), 124.0 (t, C-8), 118.4 (t, C-15), 78.8 (s, C-1), 61.5 (s, C-17), 57.4 (p, OMe), 39.6 (s, C-13), 39.4 (s, C-5), 26.4 (s, C-11), 26.3 (s, C-4), 21.2 (p, Ac), 16.6 (p, C-6), 16.2 (p, C-16), 13.9 (p, C-9) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{18}H_{30}O_3Na$ $[M+Na]^+$: 317.2093; *found*: 317.2087; **R_f** (5:1 PE/EtOAc): 0.43.

(2*E*,6*E*,10*E*)-12-Methoxy-3,7,11-trimethyldodeca-2,6,10-trien-1-ol 470

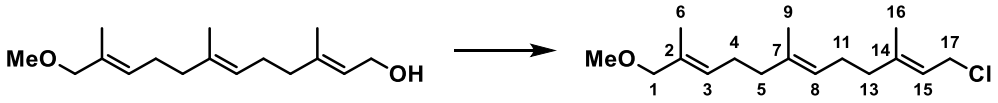


556 470

1 M NaOH was added dropwise to a stirred solution of acetate **556** (0.23 g, 0.78 mmol, 1.00 eq) in MeOH (4.0 mL) at rt until pH of 11-12 was reached. The resulting mixture was stirred at rt for 30 min. The reaction was terminated by addition of water (20 mL), the aq. layer was extracted with EtOAc (3x 20 mL), the comb. org. layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 5:1 – 1:1) yielded alcohol **470** (0.19 g, 0.76 mmol, 97%) as a colorless oil. The analytical data match those reported in the literature.[83]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.43-5.36 (m, 2H, H-3, H-15), 5.11 (t, *J* = 6.27 Hz, 1H, H-8), 4.15 (d, *J* = 6.82 Hz, 2H, H-17), 3.78 (s, 2H, H-1), 3.27 (s, 3H, OMe), 2.20-2.00 (m, 8H, H-4, H-5, H-11, H-13), 1.68 (s, 3H, H-6), 1.63 (s, 3H, H-16), 1.60 (s, H-9), 1.30 (bs, 1H, OH) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{16}H_{28}O_2Na$ $[M+Na]^+$: 275.1987; *found*: 275.1985; **R_f** (2:1 PE/EtOAc): 0.25.

(2*E*,6*E*,10*E*)-12-Chloro-1-methoxy-2,6,10-trimethyldodeca-2,6,10-triene 557

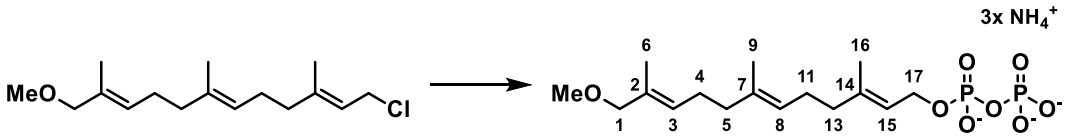


470 557

MsCl (0.06 mL, 0.66 mmol, 2.00 eq) was added dropwise to a stirred solution of alcohol **470** (83.0 mg, 0.33 mmol, 1.00 eq) and collidine (0.27 mL, 1.97 mmol, 6.00 eq) in DMF (11.0 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 20 min. Then LiCl (55.8 mg, 1.32 mmol, 4.00 eq) was added at 0 °C and the mixture was allowed to warm to rt over 2 h. The reaction was terminated by addition of brine (10 mL) and diluted with a 1:1 mixture of Et_2O and water (10 mL). The aq. layer was extracted with Et_2O (3x 10 mL), the comb. org. layers were washed with an aq. 10% $CuSO_4$-solution (20 mL), sat. aq. $NaHCO_3$-solution (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded chloride **557** (69.6 mg, 0.26 mmol, 78%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.44 (dt, *J* = 7.98, 1.18 Hz, 1H, H-15), 5.38 (t, *J* = 6.92 Hz, 1H, H-3), 5.10 (t, *J* = 6.23 Hz, 1H, H-8), 4.10 (d, *J* = 7.99 Hz, 2H, H-17), 3.78 (s, 2H, H-1), 3.27 (s, 3H, OMe), 2.16-2.00 (m, 8H, H-4, H-5, H-11, H-13), 1.73 (s, 3H, H-6), 1.64 (s, 3H, H-16), 1.60 (s, 3H, H-9) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 142.9 (q, C-14), 135.4 (q, C-7), 132.1 (q, C-2), 128.2 (t, C-3), 123.8 (t, C-8), 120.5 (t, C-15), 78.8 (s, C-1), 57.5 (p, OMe), 41.3 (s, C-17), 39.6 (s, C-13), 39.4 (s, C-5), 26.4 (s, C-11), 26.2 (s, C-4), 16.3 (p, C-6), 16.2 (p, C-16), 13.9 (p, C-9) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{16}H_{27}OClNa$ $[M+Na]^+$: 293.1648; *found*: 293.1652; **R_f** (2:1 PE/EtOAc): 0.60.

(2*E*,6*E*,10*E*)-12-Methoxy-3,7,11-trimethyldodeca-2,6,10-trien-1-yl triammonium diphosphate 133



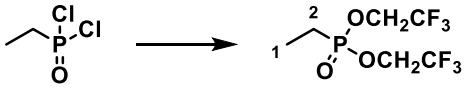
557 133

Preactivated pieces of 3Å-sieves was added to a stirred solution of $(n\text{Bu}_4\text{N})_3P_2O_7H$ (419.8 mg, 0.47 mmol, 2.00 eq) in MeCN (4.7 mL) at 0 °C. Then chloride **557** (63.0 mg, 0.23 mmol, 1.00 eq) in MeCN (2.4 mL) was added dropwise at 0 °C and the resulting mixture was allowed to warm to rt and stirred at rt overnight. The mixture was concentrated *in vacuo* and standard work up using an ion exchange column was applied to yield pyrophosphate **133** (85.5 mg, 0.18 mmol, 79%) as a white gum

which was stored under an atmosphere of Argon at -80 °C. The analytical data match those reported in the literature.[83]

^{1}H-NMR (400 MHz, D_2O): δ = 5.50-5.44 (m, 2H, H-3, H-15), 5.23 (t, *J* = 6.30 Hz, 1H, H-8), 4.51-4.47 (m, 2H, H-17), 3.88 (s, 2H, H-1), 3.28 (s, 3H, OMe), 2.23-2.07 (m, 8H, H-4, H-5, H-11, H-13), 1.73 (s, 3H, H-6), 1.64 (s, 6H, H-9, H-16) ppm; **^{13}C-NMR (100 MHz, D_2O):** δ = 143.1 (q, C-14), 136.4 (q, C-7), 131.3 (q, C-2), 130.1 (t, C-3), 124.4 (t, C-8), 119.5 (d, *J* = 7.59 Hz, t, C-15), 78.4 (s, C-1), 62.9 (d, *J* = 4.30 Hz, s, C-17), 56.3 (p, OMe), 38.8 (s, C-13), 38.3 (s, C-5), 25.6 (s, C-11), 25.4 (s, C-4), 15.6 (p, C-6), 15.1 (p, C-16), 13.1 (p, C-9) ppm; **^{31}P-NMR (162 MHz, D_2O):** δ = -9.06 - -10.64 (m, 2P) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{16}H_{29}O_8P_2Na$ $[M-H]^-$: 411.1338; *found*: 411.1334.

Bis(2,2,2-trifluoroethyl) ethylphosphonate 478

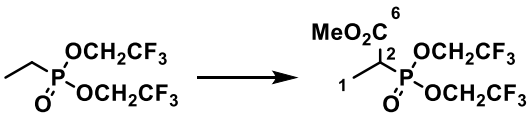


477 478

Phosphonate **477** (3.7 mL, 34.71 mmol, 1.00 eq) was added dropwise to a stirred solution of trifluoroethanol (5.5 mL, 76.36 mmol, 2.00 eq) and NEt_3 (10.6 mL, 76.36 mmol, 2.20 eq) in THF (110 mL) at 0 °C. The resulting mixture was allowed to warm to rt and stirred at rt for 2 h. The reaction was terminated by filtration and the residue was washed with an excess of THF and the filtrate was concentrated *in vacuo*. Vacuum distillation (100 °C, 4 mbar) yielded phosphonate **478** (8.26 g, 30.13 mmol, 87%) as a colorless liquid. The analytical data match those reported in the literature.[273]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.44-4.32 (m, 4H, CH_2CF_3), 1.93 (dq, *J* = 17.74, 7.69, 2H, H-2), 1.22 (dt, *J* = 21.62, 7.68 Hz, 3H, H-1) ppm; **bp.:** 100 °C, 4 mbar.

Methyl 2-(*bis*(2,2,2-trifluoroethoxy)phosphoryl)propanoate (Still-Genarri Reagent) 479



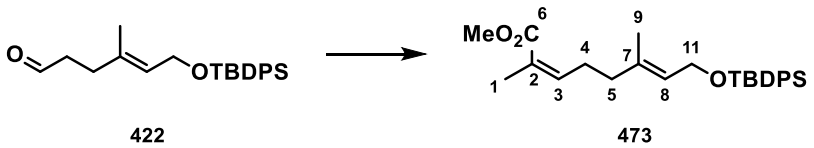
478 479

*n*BuLi (1.6 M in hex, 5.3 mL, 8.39 mmol, 2.30 eq) was added to a solution of freshly distilled HMDS (1.8 mL, 8.39 mmol, 2.30 eq) in THF (10.5 mL) at -78 °C and the resulting mixture was allowed to warm to 0 °C and stirred at 0 °C for 1 h. Then the mixture was cooled to -78 °C and a solution of phosphonate **478** (1.00 g, 3.65 mmol, 1.00 eq) and methylchloroformiate (0.34 mL, 4.38 mmol, 1.20 eq) in THF (10.5 mL) was added dropwise at -78 °C. The resulting mixture was stirred at -78 °C for 15 min before ist was allowed to warm to 0 °C over 30 min. The reaction was terminated by

addition of 1 M HCl until a pH of 1 was reached. The aq. layer was extracted with CH_2Cl_2 (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 2:1) yielded phosphonate **479** (0.93 g, 2.79 mmol, 76%) as a colorless oil. The analytical data match those reported in the literature.[273]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.49-4.38 (m, 4H, CH_2CF_3), 3.78 (s, 3H, CO_2Me), 3.21 (dq, *J* = 22.49, 7.50 Hz, 1H, H-2), 1.52 (dd, *J* = 19.31, 7.39 Hz, 3H, H-1) ppm; **R_f** (1:1 PE/EtOAc): 0.33.

Methyl (2*Z*,6*E*)-8-((*tert*-butyldiphenylsilyl)oxy)-2,6-dimethylocta-2,6-dienoate 473

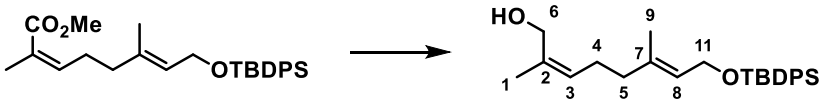


422 473

18-crown-6 was freshly recrystallized and stored at -20 °C under an atmosphere of Argon until used according to literature procedure.[274] KHMDS (0.5 M in PhMe, 4.5 mL, 2.23 mmol, 1.20 eq) was added dropwise to a stirred solution of phosphonate **479** (0.93 g, 2.78 mmol, 1.50 eq) and 18-crown-6 (2.94 g, 11.13 mmol, 6.00 eq) in THF (55 mL) at -78 °C and the resulting mixture was stirred at -78 °C for 20 min. Then aldehyde **422** (0.68 g, 1.86 mmol, 1.00 eq) in THF (6.2 mL) was added dropwise at -78 °C and the resuting mixture was stirred at -78 °C for 30 min. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (50 mL), the aq. layer was extracted with Et_2O (3x 30 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded ester **473** (0.81 g, 1.86 mmol, *quant*.) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.70-7.67 (m, 4H, TBDPS), 7.44-7.35 (m, 6H, TBDPS), 5.92 (dt, *J* = 7.25, 1.29 Hz, 1H, H-3), 5.40 (dt, *J* = 6.30, 1.32 Hz, 1H, H-8), 4.21 (d, *J* = 6.28 Hz, 2H, H-11), 3.73 (s, 3H, CO_2Me), 2.57 (q, *J* = 7.43 Hz, 2H, H-4), 2.07 (t, *J* = 7.43 Hz, 2H, H-5), 1.88 (d, *J* = 1.33 Hz, 3H, H-1), 1.43 (d, *J* = 1.38 Hz, 3H, H-9), 1.04 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 168.6 (q, C-6), 143.0 (t, C-2), 136.4 (q, C-7), 135.7 (t, TBDPS), 134.2 (q, TBDPS), 129.6 (t, TBDPS), 127.7 (t, TBDPS), 127.1 (q, C-2), 124.9 (t, C-8), 61.2 (s, C-11), 51.4 (p, CO_2Me), 39.1 (s, C-5), 27.8 (s, C-4), 27.0 (p, TBDPS), 20.8 (q, TBDPS), 19.3 (p, C-1), 16.3 (p, C-9) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{27}H_{36}O_3SiNa$ $[M+Na]^+$: 459.2331; *found*: 459.2331; **R_f** (5:1 PE/EtOAc): 0.66.

(2*Z*,6*E*)-8-((*tert*-Butyldiphenylsilyl)oxy)-2,6-dimethylocta-2,6-dien-1-ol 474

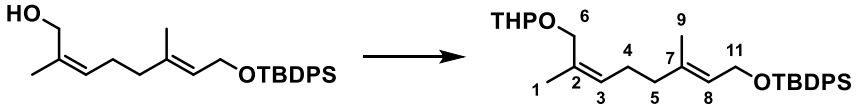


473 474

DIBAL-H (1.0 M in hex, 6.2 mL, 6.18 mmol, 3.00 eq) was quickly added to a stirred solution of enone **473** (0.90 g, 2.06 mmol, 1.00 eq) in CH_2Cl_2 (6.4 mL) at -78 °C. The mixture was stirred at -78 °C for 5 min. The reaction was terminated by addition of MeOH (5 mL) at -78 °C, then the mixture was diluted with a 1:1 mixture of EtOAc and a sat. aq. Rochelle salt-solution (100 mL) and allowed to warm to rt and stirred at rt for 1 h. The layers were separated, the aq. layer was extracted with EtAOc (3x 50 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 3:1) yielded allyl alcohol **474** (0.82 g, 2.01 mmol, 97%) as a colorless oil. The analytical data match those reported in the literature.[275]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.70-7.68 (m, 4H, TBDPS), 7.44-7.36 (m, 6H, TBDPS), 5.36 (dt, *J* = 6.36, 1.00 Hz, 1H, H-8), 5.27 (t, *J* = 7.36 Hz, 1H, H-3), 4.20 (d, *J* = 6.27 Hz, 2H, H-17), 4.11 (s, 2H, H-6), 2.14 (q, *J* = 7.28 Hz, 2H, H-4), 1.99 (t, *J* = 7.46 Hz, 2H, H-5), 1.80 (d, *J* = 1.29 Hz, 3H, H-1), 1.46 (s, 3H, H-9), 1.04 (s, 9H, TBDPS) ppm; **R_f** (10:1 PE/EtOAc): 0.31.

***tert*-Butyl (((2*E*,6*Z*)-3,7-dimethyl-8-((tetrahydro-2*H*-pyran-2-yl)oxy)octa-2,6-dien-1-yl)oxy)diphenylsilane 558**



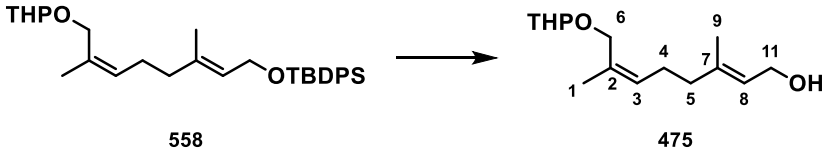
474 558

DHP (0.18 mL, 1.96 mmol, 2.00 eq) and *p*TsOH·H_2O (1.7 mg, 0.01 mmol, 0.01 eq) were added to a stirred solution of alcohol **474** (0.40 g, 0.98 mmol, 1.00 eq) in CH_2Cl_2 (2.0 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 30 min. The reaction was terminated by addition of water (10 mL), the aq. layer was extracted with EtOAc (3x 10 mL), the comb. org. layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded ether **558** (0.45 g, 0.92 mmol, 94%) as a colorless oil. The analytical data match those reported in the literature.[275]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.70-7.68 (m, 4H, TBDPS), 7.43-7.35 (m, 6H, TBDPS), 5.39-5.33 (m, 2H, H-3, H-8), 4.59 (t, *J* = 3.48 Hz, 1H, THP), 4.21 (d, *J* = 5.90 Hz, 2H, H-17), 4.12 (d, *J* =

11.43 Hz, 1H, H-6), 4.07 (d, *J* = 11.40 Hz, 1H, H-6), 3.92-3.86 (m, 1H, THP), 3.54-3.48 (m, 1H, THP), 2.18-2.13 (m, 2H, H-4), 2.01-1.97 (m, 2H, H-5), 1.87-1.68 (m, 5H, THP, H-1), 1.63-1.50 (m, 4H, THP), 1.43 (s, 3H, H-9), 1.04 (s, 9H, TBDPS) ppm; $\mathbf{R_f}$ (3:1 PE/EtOAc): 0.72.

(2*E*,6*Z*)-3,7-Dimethyl-8-((tetrahydro-2*H*-pyran-2-yl)oxy)octa-2,6-dien-1-ol 475

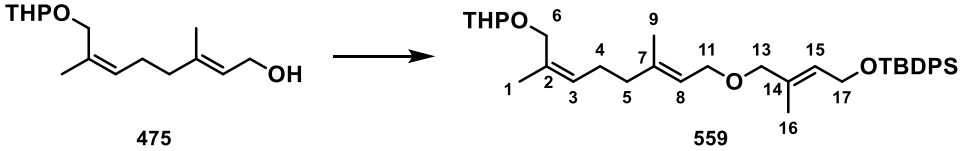


558 475

TBAF (1 M in THF, 2.8 mL, 2.76 mmol, 3.00 eq) was added dropwise to a stirred solution of TBDPS-ether **558** (0.45 g, 0.92 mmol, 1.00 eq) in THF (9.5 mL) at 0 °C and the resulting mixture was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (10 mL), the aq. layer was extracted with EtOAc (3x 20 mL), the comb. org. layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 2:1 – 1:1) yielded alcohol **475** (0.21 g, 0.82 mmol, 90%) as a colorless oil. The analytical data match those reported in the literature.[275]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.41 (dq, *J* = 6.97, 1.28 Hz, 1H, H-3), 5.33 (t, *J* = 6.71 Hz, 1H, H-8), 4.58 (t, *J* = 3.53 Hz, 1H, THP), 4.14-4.11 (m, 3H, H-17, H-6), 4.05 (dd, *J* = 11.36, 0.52 Hz, 1H, H-6), 3.91-3.86 (m, 1H, THP), 3.55-3.49 (m, 1H, THP), 2.22-2.17 (m, 2H, H-4), 2.07 (m, 2H, H-5), 1.87-1.80 (m, 1H, THP), 1.77 (d, *J* = 1.22 Hz, 3H, H-1), 1.75-1.69 (m, 1H, THP), 1.67 (s, 3H, H-9), 1.64-1.50 (m, 4H, THP) ppm; $\mathbf{R_f}$ (3:1 PE/EtOAc): 0.19.

***tert*-Butyl(((*E*)-4-(((2*E*,6*Z*)-3,7-dimethyl-8-((tetrahydro-2*H*-pyran-2-yl)oxy)octa-2,6-dien-1-yl)oxy)-3-methylbut-2-en-1-yl)oxy)diphenylsilane 559**

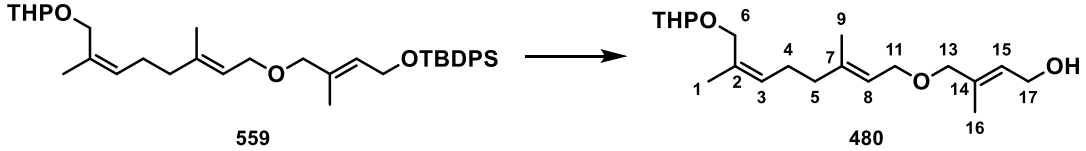


475 559

Alcohol **475** (0.21 g, 0.81 mmol, 1.00 eq) in THF (0.73 mL) was added dropwise to a stirred solution of NaH (90%, 43.0 mg, 1.61 mmol, 2.00 eq) in THF (0.81 mL) at rt and the resulting mixture was stirred at rt for 1 h. Then TBAI (8.9 mg, 0.02 mmol, 0.03 eq) and bromide **401** (0.43 g, 1.05 mmol, 1.30 eq) were added at rt. The resulting mixture was stirred at rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (5 mL), the aq. layer was extracted with Et_2O (3x 5 mL), the comb. org. layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1 -10:1) yielded ether **559** (0.39 g, 0.68 mmol, 85%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.70-7.67 (m, 4H, TBDPS), 7.44-7.35 (m, 6H, TBDPS), 5.64 (dt, *J* = 6.13, 1.26 Hz, 1H, H-15), 5.37-5.33 (m, 2H, H-3, H-8), 4.58 (dd, *J* = 3.97, 3.08 Hz, 1H, THP), 4.26 (dd, *J* = 6.12, 0.72 Hz, 2H, H-17), 4.12 (d, *J* = 11.37 Hz, 1H, H-6), 4.07 (d, *J* = 11.37 Hz, 1H, H-6), 3.91 (d, *J* = 6.70 Hz, 2H, H-11), 3.89-3.86 (m, 1H, THP), 3.82 (s, 2H, H-13), 3.54-3.48 (m, 1H, THP), 2.23-2.17 (m, 2H, H-4), 2.07-2.04 (m, 2H, H-5), 1.87-1.79 (m, 1H, THP), 1.77 (d, *J* = 1.32 Hz, 3H, H-1), 1.75-1.68 (m, 1H, THP), 1.65 (s, 3H, H-16), 1.63-1.50 (m, 4H, THP), 1.49 (s, 3H, H-9), 1.05 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 139.8 (q, C-2), 135.7 (t, TBDPS), 134.0 (q, TBDPS), 133.9 (q, C-14), 132.3 (q, C-7), 129.7 (t, TBDPS), 129.1 (t, C-3), 127.3 (t, TBDPS), 127.3 (t, C-15), 121.4 (t, C-8), 97.7 (t, THP), 75.6 (s, C-13), 66.1 (s, C-11), 65.5 (s, C-6), 62.3 (s, THP), 60.9 (s, C-17), 39.9 (s, C-5), 30.8 (s, THP), 27.0 (p, TBDPS), 26.1 (s, C-4), 25.7 (s, THP), 21.9 (p, C-1), 19.7 (s, THP), 19.3 (q, TBDPS), 16.6 (p, C-16), 14.2 (p, C-9) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{36}H_{52}O_4SiNa$ $[M+Na]^+$: 599.3533; *found*: 599.3527; **R_f** (10:1 PE/EtOAc): 0.29.

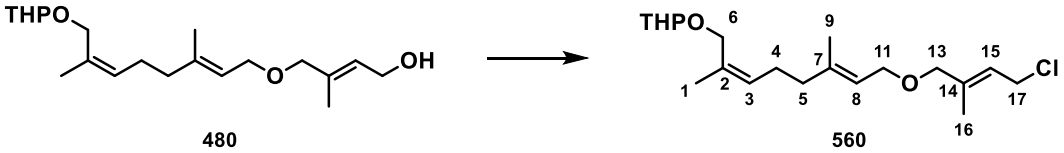
(*E*)-4-(((2*E*,6*Z*)-3,7-Dimethyl-8-((tetrahydro-2*H*-pyran-2-yl)oxy)octa-2,6-dien-1-yl)oxy)-3-methylbut-2-en-1-ol 480



TBAF (1 M in THF, 2.1 mL, 2.03 mmol, 3.00 eq) was added dropwise to a stirred solution of TBDPS-ether **559** (0.39 g, 0.68 mmol, 1.00 eq) in THF (6.8 mL) at 0 °C and the resulting mixture was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (10 mL), the aq. layer was extracted with EtOAc (3x 20 mL), the comb. org. layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 2:1 – 1:1) yielded alcohol **480** (0.20 g, 0.59 mmol, 88%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.66 (dt, *J* = 6.70, 1.26 Hz, 1H, H-15), 5.35 (t, *J* = 6.79 Hz, 2H, H-3, H-8), 4.58 (t, *J* = 3.36 Hz, 1H, THP), 6.63 (d, *J* = 4.22 (d, *J* = 6.63 Hz, 2H, H-17), 4.12 (d, *J* = 11.24 Hz, 1H, H-6), 4.06 (d, *J* = 11.39 Hz, 1H, H-6), 3.95 (d, *J* = 6.72 Hz, 1H, H-11), 3.91-3.86 (m, 3H, THP, H-13), 3.54-3.49 (m, 1H, THP), 2.22-2.17 (m. 2H, H-4), 2.07-2.03 (m, 2H, H-5), 1.87-1.51 (m, 15H, THP, H-1, H-9, H-16) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 139.9 (q, C-2), 136.2 (q, C-7), 132.3 (q, C-14), 129.0 (t, C-3), 126.1 (t, C-15), 121.2 (t, C-8), 97.7 (t, THP), 75.3 (s, C-13), 66.6 (s, C-11), 65.5 (s, C-6), 62.3 (s, THP), 59.3 (s, C-17), 39.9 (s, C-5), 30.8 (s, THP), 26.1 (s, C-4), 25.6 (s, THP), 21.9 (p, C-1), 19.6 (s, THP), 16.6 (p, C-16), 14.2 (p, C-9) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{20}H_{34}O_4Na$ $[M+Na]^+$: 361.2355; *found*: 361.2351; **R_f** (2:1 PE/EtOAc): 0.24.

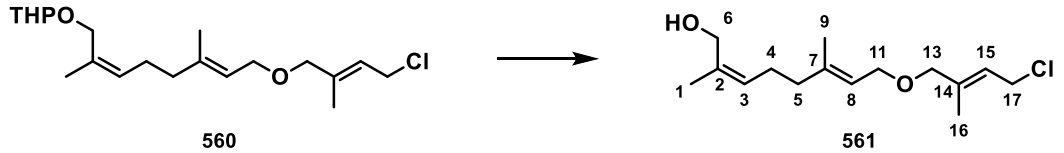
2-(((2*Z*,6*E*)-8-(((*E*)-4-Chloro-2-methylbut-2-en-1-yl)oxy)-2,6-dimethylocta-2,6-dien-1-yl)oxy)tetrahydro-2*H*-pyran 560



DMS (64 µL, 0.86 mmol, 1.50 eq) was added dropwise to a stirred solution of NCS (100.0 mg, 0.75 mmol, 1.30 eq) in CH_2Cl_2 (1.5 mL) at -30 °C. The resulting mixture was allowed to warm to 0 °C over 10 min, then it was cooled to -30 °C. Alcohol **480** (195.0 mg, 0.58 mmol, 1.00 eq) in CH_2Cl_2 (0.96 mL) was added dropwise at -30 °C and the resulting mixture was allowed to warm to 0 °C over 2 h. The reaction was terminated by addition of brine (10 mL), the aq. layer was extracted with Et_2O (3x 10 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded chloride **560** (183.4 mg, 0.51 mmol, 89%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.71 (dt, *J* = 7.88, 1.37 Hz, 1H, H-15), 5.35 (t, *J* = 6.68 Hz, 2H, H-3, H-8), 4.58 (t, *J* = 3.50 Hz, 1H, THP), 4.13-4.05 (m, 4H, H-17, H-6), 3.95 (d, *J* = 6.63 Hz, 2H, H-11), 3.92-3.86 (m, 3H, THP, H-13), 3.54-3.49 (m, 1H, THP), 2.23-2.17 (m, 2H, H-4), 2.07-2.04 (m, 2H, H-5), 1.87-1.79 (m, 1H, THP), 1.76 (d, *J* = 0.92 Hz, 3H, H-1), 1.75 (s, 3H, H-16), 1.73-1.67 (m, 1H, THP), 1.65 (s, 3H, H-9), 1.63-1.51 (m, 4H, THP) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 140.1 (q, C-2), 139.1 (q, C-14), 132.3 (q, C-7), 129.0 (t, C-3), 122.4 (t, C-15), 121.1 (t, C-8), 97.7 (t, THP), 74.7 (s, C-13), 66.6 (s, C-11), 65.5 (s, C-6), 62.3 (s, THP), 40.3 (s, C-17), 39.9 (s, C-5), 30.8 (s, THP), 26.1 (s, C-4), 25.6 (s, THP), 21.9 (p, C-1), 19.7 (s, THP), 13.9 (p, C-16), 11.3 (p, C-9) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{20}H_{33}O_3ClNa$ $[M+Na]^+$: 379.2016; *found*: 379.2008; **R_f** (2:1 PE/EtOAc): 0.54.

(2*Z*,6*E*)-8-(((*E*)-4-Chloro-2-methylbut-2-en-1-yl)oxy)-2,6-dimethylocta-2,6-dien-1-ol 561



*p*TsOH·H_2O (8.4 mg, 0.05 mmol, 0.10 eq) was added to a stirred solution of ether **560** (175.0 mg, 0.49 mmol, 1.00 eq) in wet MeOH (6.5 mL) at 0 °C. The resulting mixture was allowed to warm to rt over 2 h. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (20 mL). The aq. layer was extracted with EtOAc (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield crude alcohol **561** (136.7 mg,

0.49 mmol, *quant.*) as a colorless oil which was directly used for the next step without further purification.

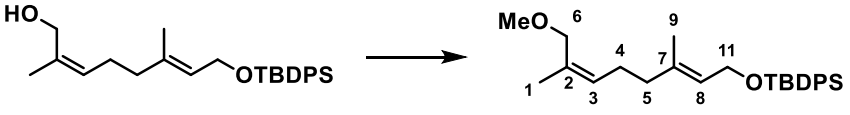
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.70 (dt, *J* = 8.04, 1.24 Hz, 1H, H-15), 5.33 (t, *J* = 6.31 Hz, 1H, H-3), 5.25 (t, *J* = 7.45 Hz, 1H, H-8), 4.12 (d, *J* = 7.90 Hz, 2H, H-17), 4.08 (s, 2H, H-6), 3.92 (d, *J* = 6.88 Hz, 2H, H-11), 3.88 (s, 2H, H-13), 2.21-2.15 (m, 2H, H-4), 2.07-2.03 (m, 2H, H-5), 1.79 (s, 3H, H-1), 1.75 (s, 3H, H-16), 1.67 (s, 3H, H-9), 1.53 (bs, 1H, OH) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 140.2 (q, C-2), 139.0 (q, C-14), 135.3 (q, C-7), 127.5 (t, C-3), 122.6 (t, C-15), 121.4 (t, C-8), 75.0 (s, C-13), 66.4 (s, C-11), 61.6 (s. C-6), 40.3 (s, C-17), 39.6 (s, C-5), 25.9 (s, C-4), 21.4 (p, C-1), 16.7 (p, C-16), 13.9 (p, C-9) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{15}H_{25}O_2ClNa$ $[M+Na]^+$: 295.1441; *found*: 295.1437; **R_f** (3:1 PE/EtOAc): 0.33.

(*E*)-4-(((2*E*,6*Z*)-8-Hydroxy-3,7-dimethylocta-2,6-dien-1-yl)oxy)-3-methylbut-2-en-1-yl triammonium diphosphate 129

Preactivated pieces of 3Å-sieves was added to a stirred solution of $(n\text{Bu}_4\text{N})_3\text{P}_2\text{O}_7\text{H}$ (165.4 mg, 0.18mmol, 2.50 eq) in MeCN (1.8 mL) at 0 °C. Then chloride **561** (20.0 mg, 0.08 mmol, 1.00 eq) in MeCN (0.74 mL) was added dropwise at 0 °C and the resulting mixture was allowed to warm to rt and stirred at rt overnight. The mixture was concentrated *in vacuo* and standard work up using an ion exchange column was applied to yield pyrophosphate **129** (17.0 mg, 0.04 mmol, 50%) as a white gum which was stored under an atmosphere of Argon at -80 °C.

^{1}H-NMR (500 MHz, D_2O): δ = 5.70 (t, *J* = 6.77 Hz, 1H, H-15), 5.41-5.36 (m, 2H, H-3, H-8), 4.55 (t, *J* = 7.00 Hz, 2H, H-17), 4.11 (s, 2H, H-6), 4.03 (d, *J* = 7.27 Hz, 2H, H-11), 3.97 (s, 2H, H-13), 2.25-2.21 (m, 2H, H-4), 2.13-2.10 (m, 2H, H-5), 1.75 (d, *J* = 1.04 Hz, 3H, H-1), 1.73 (s, 3H, H-16), 1.69 (s, 3H, H-9) ppm; **^{13}C-NMR (125 MHz, D_2O):** δ = 142.9 (q, C-2), 136.9 (q, C-14), 134.0 (q, C-7), 128.5 (t, C-3), 123.9 (d, *J* = 8.03 Hz, t, C-15), 119.5 (t, C-8), 75.6 (s, C-13), 65.6 (s, C-11), 62.4 (d, *J* = 5.24 Hz, s, C-17), 60.1 (s, C-6), 38.9 (s, C-5), 25.1 (s, C-4), 20.5 (p, C-1), 15.5 (p, C-16), 13.4 (p, C-9) ppm; **^{31}P-NMR (162 MHz, D_2O):** δ = -9.51 - -9.62 (m, 1P), -10.33 - -10.44 (m, 1P) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{15}H_{27}O_9P_2$ $[M-H]^-$: 413.1130; *found*: 413.1125.

tert-Butyl(((2*E*,6*Z*)-8-methoxy-3,7-dimethylocta-2,6-dien-1-yl)oxy)diphenylsilane 562

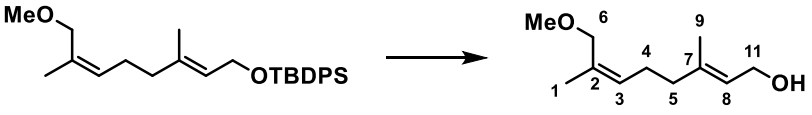


474 562

NaH (90%, 64.0 mg, 2.40 mmol, 2.50 eq) was added to a stirred solution of alcohol **474** (0.39 g, 0.96 mmol, 1.00 eq) and MeI (0.18 mL, 2.88 mmol, 5.00 eq) in THF/DMF (3:1, 6.5 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 1 h before it was allowed to warm to rt and stirred for 4 h. The reaction was terminated by addition of water (10 mL), the aq. layer was extracted with Et_2O (3x 10 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1) yielded ether **562** (0.33 g, 0.78 mmol, 81%, 94% brsm) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.70-7.68 (m, 4H, TBDPS), 7.44-7.35 (m, 6H, TBDPS), 5.39-5.33 (m, 2H, H-3, H-8), 4.22 (d, *J* = 6.06 Hz, 2H, H-11), 3.91 (s, 2H, C-6), 3.29 (s, 3H, OMe), 2.17-2.11 (m, 2H, H-4), 2.01-1.97 (m, 2H, H-5), 1.73 (d, *J* = 1.11 Hz, 3H, H-1), 1.44 (s, 3H, H-9), 1.04 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 136.5 (q, C-7), 135.6 (t, TBDPS), 134.1 (q, TBDPS), 132.1 (q, C-2), 129.5 (t, TBDPS), 129.0 (t, C-8), 124.4 (t, C-3), 70.9 (s, C-6), 61.1 (s, C-11), 57.6 (p, OMe), 39.6 (s, C-5), 26.9 (p, TBDPS), 25.9 (s, C-4), 21.5 (p, C-1), 19.2 (q, TBDPS), 16.3 (p, C-9) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{27}H_{38}O_2SiNa$ $[M+Na]^+$: 445.2539; *found*: 445.2539; **R_f** (3:1 PE/EtOAc): 0.68.

(2*E*,6*Z*)-8-Methoxy-3,7-dimethylocta-2,6-dien-1-ol 476



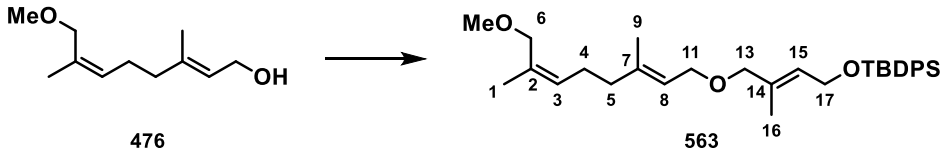
562 476

TBAF (1 M in THF, 2.4 mL, 2.32 mmol, 3.00 eq) was added dropwise to a stirred solution of TBDPS-ether **562** (0.33 g, 0.78 mmol, 1.00 eq) in THF (8.0 mL) at 0 °C and the resulting mixture was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (10 mL), the aq. layer was extracted with EtOAc (3x 20 mL), the comb. org. layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 2:1 – 1:1) yielded alcohol **476** (0.13 g, 0.51 mmol, 65%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.39 (dq, *J* = 10.49, 1.26 Hz, 1H, H-3), 5.33 (dt, *J* = 7.20, 0.91 Hz, 1H, H-8), 4.13 (dd, *J* = 6.93, 0.40 Hz, 2H, H-11), 3.89 (s, 2H, H-6), 3.30 (s, 3H, OMe), 2.21-2.15 (m, 2H, H-4), 2.06-2.02 (m, 2H, H-5), 1.74 (d, *J* = 1.24 Hz, 3H, H-1), 1.68 (d, *J* = 0.97 Hz, 3H, H-9), 1.46 (bs, 1H, OH) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 139.1 (q, C-7), 132.6 (q, C-2), 128.8 (t,

C-8), 124.2 (t, C-3), 71.1 (s, C-6), 59.4 (s, C-11), 58.0 (p, OMe), 39.6 (s, C-5), 26.1 (s, C-4), 21.7 (p, C-1), 16.4 (p, C-9) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{11}H_{20}O_2Na$ $[M+Na]^+$: 207.1361; *found*: 207.1358; $\mathbf{R_f}$ (3:1 PE/EtOAc): 0.16.

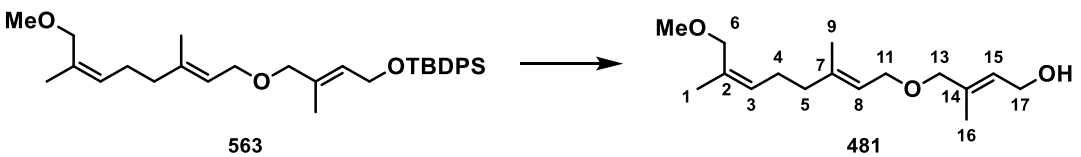
(4*Z*,8*E*,13*E*)-4,8,13,18,18-Pentamethyl-17,17-diphenyl-2,11,16-trioxa-17-silanonadeca-4,8,13-triene 563



Alcohol **476** (0.12 g, 0.65 mmol, 1.00 eq) in THF (0.60 mL) was added dropwise to a stirred solution of NaH (90%, 34.7 mg, 1.30 mmol, 2.00 eq) in THF (0.66 mL) at rt and the resulting mixture was stirred at rt for 1 h. Then TBAI (7.3 mg, 0.02 mmol, 0.03 eq) and bromide **401** (0.34 g, 0.85 mmol, 1.30 eq) were added at rt. The resulting mixture was stirred at rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (5 mL), the aq. layer was extracted with Et_2O (3x 5 mL), the comb. org. layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1 -10:1) yielded ether **563** (0.31 g, 0.60 mmol, 92%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.70-7.67 (m, 4H, TBDPS), 7.44-7.36 (m, 6H, TBDPS), 5.64 (dt, *J* = 6.11, 1.24 Hz, 1H, H-15), 5.38-5.33 (m, 2H, H-3, H-8), 4.27 (dd, *J* = 6.12, 0.76 Hz, 2H, H-17), 3.92-3.90 (m, 4H, H-6, H-11), 3.83 (s, 2H, H-13), 3.28 (s, 3H, OMe), 2.20-2.16 (m, 2H, H-4), 2.07-2.03 (m, 2H, H-5), 1.74 (d, *J* = 1.28 Hz, 3H, H-1), 1.65 (s, 3H, H-16), 1.49 (s, 3H, H-9) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 139.7 (q, C-2), 135.7 (t, TBDPS), 134.0 (q, TBDPS), 133.8 (q, C-14), 132.4 (q, C-7), 129.7 (t, TBDPS), 129.0 (t, C-3), 127.8 (t, TBDPS), 127.3 (t, C-15), 121.4 (t, C-8), 75.6 (s, C-13), 71.0 (s, C-6), 66.1 (s, C-11), 60.9 (s, C-17), 57.8 (p, OMe), 39.9 (s, C-5), 27.0 (p, TBDPS), 26.1 (s, C-4), 21.6 (p, C-1), 19.3 (q, TBDPS), 16.6 (p, C-16), 14.2 (p, C-9) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{32}H_{46}O_3SiNa$ $[M+Na]^+$: 529.3114; *found*: 529.3116; $\mathbf{R_f}$ (10:1 PE/EtOAc): 0.35.

(*E*)-4-(((2*E*,6*Z*)-8-Methoxy-3,7-dimethylocta-2,6-dien-1-yl)oxy)-3-methylbut-2-en-1-ol 481

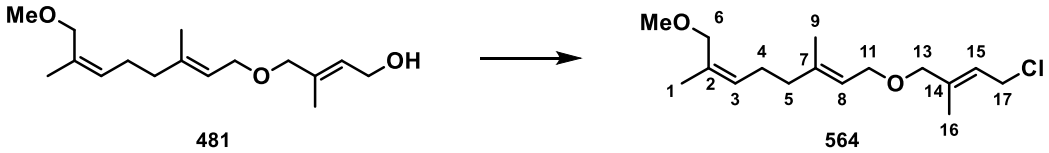


TBAF (1 M in THF, 1.8 mL, 1.78 mmol, 3.00 eq) was added dropwise to a stirred solution of TBDPS-ether **563** (0.30 g, 0.59 mmol, 1.00 eq) in THF (6.0 mL) at 0 °C and the resulting mixture was allowed

to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (10 mL), the aq. layer was extracted with EtOAc (3x 20 mL), the comb. org. layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 2:1 – 1:1) yielded alcohol **481** (0.12 g, 0.46 mmol, 77%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.66 (dt, *J* = 6.71, 1.26 Hz, 1H, H-15), 5.37-5.34 (m, 2H, H-3, H-8), 4.22 (d, *J* = 6.67 Hz, 2H, H-17), 3.95 (d, *J* = 6.59 Hz, 2H, H-11), 3.91 (s, 2H, H-6), 3.86 (s, 2H, H-13), 3.28 (s, 3H, OMe), 2.22-2.16 (m, 2H, H-4), 2.07-2.03 (m, 2H, H-5), 1.73 (d, *J* = 1.38 Hz, 3H, H-1), 1.71 (s, 3H, H-16), 1.66 (s, 3H, H-9) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 138.9 (q, C-2), 136.1 (q, C-14), 132.4 (q, C-7), 129.0 (t, C-3), 126.1 (t, C-15), 121.3 (t, C-8), 75.4 (s, C-13), 71.0 (s, C-6), 66.5 (s, C-11), 59.3 (s, C-17), 57.8 (p, OMe), 39.8 (s, C-5), 26.1 (s, C-4), 21.6 (p, C-1), 16.6 (p, C-16), 14.2 (p, C-9) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{16}H_{28}O_3Na$ $[M+Na]^+$: 291.1936; *found*: 291.1934; **R_f** (2:1 PE/EtOAc): 0.18.

(2*Z*,6*E*)-8-(((*E*)-4-Chloro-2-methylbut-2-en-1-yl)oxy)-1-methoxy-2,6-dimethylocta-2,6-diene 564



DMS (18 µL, 0.22 mmol, 1.50 eq) was added dropwise to a stirred solution of NCS (25.9 mg, 0.19 mmol, 1.30 eq) in CH_2Cl_2 (0.39 mL) at -30 °C. The resulting mixture was allowed to warm to 0 °C over 10 min, then it was cooled to -30 °C. Alcohol **481** (40.0 mg, 0.15 mmol, 1.00 eq) in CH_2Cl_2 (0.25 mL) was added dropwise at -30 °C and the resulting mixture was allowed to warm to 0 °C over 2 h. The reaction was terminated by addition of brine (10 mL), the aq. layer was extracted with Et_2O (3x 10 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded chloride **564** (20.3 mg, 0.07 mmol, 48%) as a colorless oil.

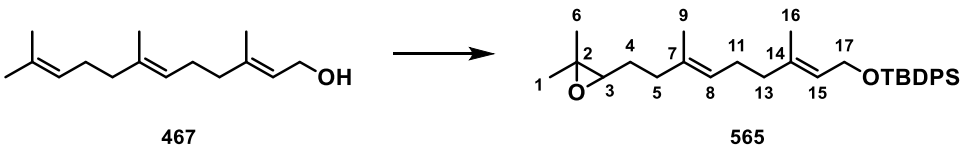
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.71 (dt, *J* = 7.92, 1.17 Hz, 1H, H-15), 5.35 (t, *J* = 6.70 Hz, 2H, H-3, H-8), 4.12 (d, *J* = 7.92 Hz, 2H, H-17), 3.95 (d, *J* = 7.70 Hz, 2H, H-11), 3.91 (s, 2H, H-6), 3.88 (s, 2H, H-13), 3.29 (s, 3H, OMe), 2.22-2.16 (m, 2H, H-4), 2.07-2.03 (m, 2H, H-5), 1.75 (s, 3H, H-16), 1.73 (d, *J* = 0.95 Hz, 3H, H-1), 1.66 (s, 3H, H-9) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 140.1 (q, C-2), 139.1 (q, C-14), 132.4 (q, C-7), 128.9 (t, C-3), 122.4 (t, C-15), 121.1 (t, C-8), 74.8 (s, C-13), 71.0 (s, C-6), 66.6 (s, C-11), 57.8 (p, OMe), 40.3 (s, C-17), 39.8 (s, C-5), 26.1 (s, C-4), 21.6 (p, C-1), 16.6 (p, C-16), 13.9 (s, C-9) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{16}H_{27}O_2ClNa$ $[M+Na]^+$: 309.1597; *found*: 309.1596; **R_f** (2:1 PE/EtOAc): 0.56.

(*E*)-4-(((2*E*,6*Z*)-8-Methoxy-3,7-dimethylocta-2,6-dien-1-yl)oxy)-3-methylbut-2-en-1-yl triammonium diphosphate 130

Preactivated pieces of 3Å-sieves were added to a stirred solution of $(n\text{Bu}_4\text{N})_3\text{P}_2\text{O}_7\text{H}$ (141.6 mg, 0.16 mmol, 2.50 eq) in MeCN (1.6 mL) at 0 °C. Then chloride **564** (18.0 mg, 0.06 mmol, 1.00 eq) in MeCN (0.63 mL) was added dropwise at 0 °C and the resulting mixture was allowed to warm to rt and stirred at rt overnight. The mixture was concentrated *in vacuo* and standard work up using an ion exchange column was applied to yield pyrophosphate **130** (13.7 mg, 0.03 mmol, 46%) as a white gum which was stored under an atmosphere of Argon at -80 °C.

^{1}H-NMR (500 MHz, D_2O): δ = 5.70 (dt, *J* = 6.78, 1.10 Hz, 1H, H-15), 5.50 (t, *J* = 6.82 Hz, 1H, H-3), 5.38 (dt, *J* = 7.25, 1.20 Hz, 1H, H-8), 4.55 (t, *J* = 6.88 Hz, 2H, H-17), 4.04-4.02 (m, 4H, H-6, H-11), 3.97 (s, 2H, H-13), 3.33 (s, 3H, OMe), 2.26-2.22 (m, 2H, H-4), 2.14-2.11 (m, 2H, H-5), 1.73 (s, 3H, H-16), 1.72 (d, *J* = 1.04 Hz, 3H, H-1), 1.69 (d, *J* = 0.78 Hz, 3H, H-9) ppm; **^{13}C-NMR (125 MHz, D_2O):** δ = 142.8 (q, C-2), 136.9 (q, C-14), 131.3 (q, C-7), 130.6 (t, C-3), 123.0 (d, *J* = 8.06 Hz, t, C-15), 119.5 (t, C-8), 74.6 (s, C-13), 70.6 (s, C-6), 65.6 (s, C-11), 62.5 (d, *J* = 5.74 Hz, s, C-17), 56.9 (p, OMe), 38.8 (s, C-5), 25.3 (s, C-4), 20.7 (p, C-1), 15.5 (p, C-16), 13.4 (p, C-9) ppm; **^{31}P-NMR (162 MHz, D_2O):** δ = -9.79 - -9.94 (m, 1P), -10.37 - -10.49 (m, 1P) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{16}H_{29}O_9P_2$ $[M\text{-}H]^-$: 427.1287; *found*: 427.1291.

***tert*-Butyl(((2*E*,6*E*)-9-(3,3-dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dien-1-yl)oxy)diphenylsilane 565**

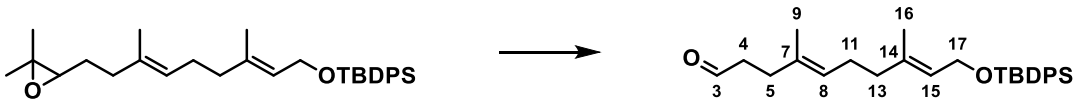


TBDPSCl (4.7 mL, 17.99 mmol, 2.00 eq) and imid. (2.02 g, 29.68 mmol, 3.30 eq) were added to a stirred solution of farnesol **467** (2.3 mL, 8.99 mmol, 1.00 eq) in CH_2Cl_2 (20.0 mL) at 0 °C and the resulting mixture was allowed to warm to rt and stirred at rt for 1 h. The reaction was terminated by dilution with CH_2Cl_2 (50 mL), the org. layer was washed with water (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield crude ether which was dissolved in a 3:1 mixture of THF/H_2O (120 mL) and NBS (2.24 g, 12.59 mmol, 1.40 eq) was added in small portions at 0 °C and the resulting mixture was allowed to warm to rt and stirred at rt for 1 h. The reaction was terminated by addition of water (500 mL), the aq. layer was extracted with PE (4x 100 mL), the comb. org. layers

were washed with brine (300 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield crude bromide which was dissolved in wet MeOH (50 mL). K_2CO_3 (2.49 g, 17.99 mmol, 2.00 eq) was added at rt and the resulting mixture was stirred at rt for 1 h. The reaction was terminated by concentration *in vacuo*. The residue was taken up in a 1:1 mixture of PE/water (100 mL), the aq. layer was extracted with PE (3x 40 mL), the comb. org. layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Short plug column chromatography (PE/EtOAc 50:1 – 10:1) yielded crude epoxide **565** which was directly employed in the next reaction without further purification.

R_f (5:1 PE/EtOAc): 0.50.

(4*E*,8*E*)-10-((*tert*-Butyldiphenylsilyl)oxy)-4,8-dimethyldeca-4,8-dienal 484



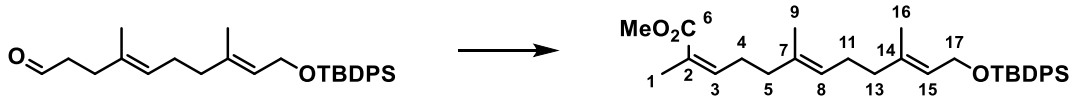
565 484

H_5IO_6 (2.21 g, 9.69 mmol, 1.10 eq) and $NaIO_4$ (1.24 g, 5.81 mmol, 0.66 eq) were added to a stirred solution of crude epoxide **565** (4.20 g, 8.81 mmol, 1.00 eq) in a 4:1 mixture of THF/water (65 mL) at 0 °C and the resulting mixture was allowed to warm to rt and stirred for 1.5 h. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (60 mL) and the resulting mixture was stirred for 15 min. The mixture was diluted with EtOAc (20 mL) and the aq. layer was extracted with EtOAc (3x 50 mL), the comb. org. layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 100:1 – 50:1 – 20:1) yielded aldehyde **484** (1.44 g, 3.31 mmol, 38%) as a colorless oil. The analytical data match those reported in the literature.[276]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.73 (t, *J* = 1.86 Hz, 1H, H-3), 7.70-7.68 (m, 4H, TBDPS), 7.44-7.36 (m, 6H, TBDPS), 5.37 (dt, *J* = 6.33, 1.24 Hz, 1H, H-15), 5.14 (dt, *J* = 6.96, 0.92 Hz, 1H, H-8), 4.22 (d, *J* = 6.08 Hz, 2H, H-17), 2.52-2.48 (m, 2H, H-4), 2.32 (m, 2H, H-5), 2.10-2.06 (m, 2H, H-11), 1.99-1.96 (m, 2H, H-13), 1.61 (s, 3H, H-16), 1.43 (s, 3H, H-9), 1.04 (s, 9H, TBDPS) ppm;

R_f (50:1 PE/EtOAc): 0.34.

Methyl (2*Z*,6*E*,10*E*)-12-((*tert*-butyldiphenylsilyl)oxy)-2,6,10-trimethyldodeca-2,6,10-trieno-ate 485

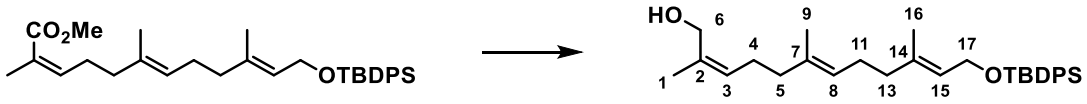


484 **485**

KHMDS (0.5 M in PhMe, 3.9 mL, 1.93 mmol, 1.20 eq) was added dropwise to a stirred solution of phosphonate **479** (0.81 g, 2.42 mmol, 1.50 eq) and 18-crown-6 (2.56 g, 9.66 mmol, 6.00 eq) in THF (50 mL) at -78 °C and the resulting mixture was stirred at -78 °C for 20 min. Then aldehyde **484** (0.70 g, 1.61 mmol, 1.00 eq) in THF (5.4 mL) was added dropwise at -78 °C and the resulting mixture was stirred at -78 °C for 30 min. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (50 mL), the aq. layer was extracted with Et_2O (3x 30 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1) yielded ester **485** (0.78 g, 1.55 mmol, 96%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.71-7.68 (m, 4H, TBDPS), 7.44-7.35 (m, 6H, TBDPS), 5.91 (dq, *J* = 7.32, 1.27 Hz, 1H, H-3), 5.38 (dt, *J* = 6.34, 1.37 Hz, 1H, H-15), 5.13 (dt, *J* = 6.83, 1.17 Hz, 1H, H-8), 4.22 (dd, *J* = 6.34, 0.49 Hz, 2H, H-17), 3.73 (s, 3H, CO_2Me), 2.58-2.52 (m, 2H, H-4), 2.10-2.04 (m, 4H, H-5, H-11), 2.00-1.96 (m, 2H, H-13), 1.88 (q, *J* = 1.38 Hz, 3H, H-1), 1.60 (s, 3H, H-16), 1.43 (s, 3H, H-9), 1.04 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 168.6 (q, C-6), 143.4 (t, C-3), 137.2 (q, C-8), 135.8 (t, TBDPS), 134.5 (q, C-14), 134.2 (q, TBDPS), 129.6 (t, TBDPS), 127.7 (t, TBDPS), 126.9 (q, C-2), 124.9 (t, C-8), 124.2 (t, C-15), 61.3 (s, C-17), 51.3 (p, CO_2Me), 39.6 (s, C-5), 39.3 (s, C-13), 28.1 (s, C-4), 27.0 (p, TBDPS), 26.5 (s, C-11), 20.8 (p, C-1), 19.3 (q, TBDPS), 16.5 (p, C-16), 16.0 (p, C-9) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{32}H_{44}O_3SiNa$ $[M+Na]^+$: 527.2597; *found*: 527.2960; **R_f** (20:1 PE/EtOAc): 0.31.

(2*Z*,6*E*,10*E*)-12-((*tert*-Butyldiphenylsilyl)oxy)-2,6,10-trimethyldodeca-2,6,10-trien-1-ol 566



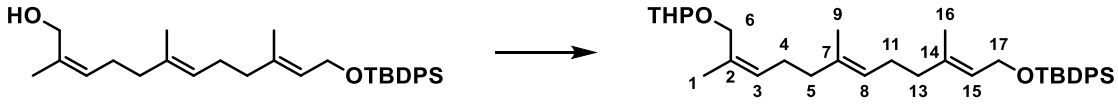
485 **566**

DIBAL-H (1.0 M in hex, 4.6 mL, 4.53 mmol, 3.00 eq) was quickly added to a stirred solution of enone **485** (0.76 g, 1.51 mmol, 1.00 eq) in CH_2Cl_2 (4.6 mL) at -78 °C. The mixture was stirred at -78 °C for 5 min. The reaction was terminated by addition of MeOH (5 mL) at -78 °C, then the mixture was diluted with a 1:1 mixture of EtOAc and a sat. aq. Rochelle salt-solution (100 mL) and allowed to warm to rt and stirred at rt for 1 h. The layers were separated, the aq. layer was extracted with EtAOc (3x 50 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$,

filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 3:1) yielded allyl alcohol **566** (0.71 g, 1.48 mmol, 98%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.70-7.68 (m, 4H, TBDPS), 7.44-7.35 (m, 6H, TBDPS), 5.38 (dt, *J* = 6.30, 1.19 Hz, 1H, H-15), 5.28 (t, *J* = 7.04 Hz, 1H, H-3), 5.11 (dt, *J* = 6.87, 1.21 Hz, 1H, H-8), 4.22 (d, *J* = 5.82 Hz, 2H, H-17), 4.10 (s, 2H, H-6), 2.17-2.06 (m, 4H, H-4, H-11), 2.01-1.96 (m, 4H, H-5, H-13), 1.79 (d, *J* = 1.32 Hz, 3H, H-1), 1.60 (s, 3H, H-16), 1.44 (s, 3H, H-9), 1.04 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 137.1 (q, C-14), 135.8 (t, TBDPS), 134.8 (q, C-2), 134.5 (q, C-8), 134.2 (q, TBDPS), 129.6 (t, TBDPS), 128.4 (t, C-3), 127.7 (t, TBDPS), 124.7 (t, C-8), 124.2 (t, C-15), 61.8 (s, C-6), 61.3 (s, C-17), 40.0 (s, C-13), 39.6 (s, C-5), 27.0 (p, TBDPS), 26.4 (s, C-11), 26.4 (s, C-4), 21.4 (p, C-1), 19.3 (q, TBDPS), 16.5 (p, C-16), 16.2 (p, C-9) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{31}H_{44}O_2SiNa$ $[M+Na]^+$: 499.3008; *found*: 499.3008; **R_f** (3:1 PE/EtOAc): 0.50.

tert-Butyldiphenyl(((2*E*,6*E*,10*Z*)-3,7,11-trimethyl-12-((tetrahydro-2*H*-pyran-2-yl)oxy)dodeca-2,6,10-trien-1-yl)oxy)silane 486



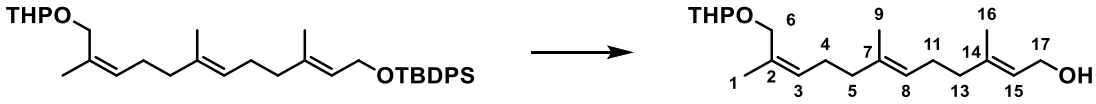
566 486

DHP (0.27 mL, 2.96 mmol, 2.00 eq) and *p*TsOH·H_2O (2.6 mg, 0.02 mmol, 0.01 eq) were added to a stirred solution of allyl alcohol **566** (0.71 g, 1.48 mmol, 1.00 eq) in CH_2Cl_2 (3.0 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min. The reaction was terminated by addition of water (10 mL), the layers were separated, the aq. layer was extracted with EtOAc (3x 10 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded ether **486** (0.76 g, 1.35 mmol, 91%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.70-7.68 (m, 4H, TBDPS), 7.43-7.35 (m, 6H, TBDPS), 5.39-5.33 (m, 2H, H-3, H-15), 5.11 (t, *J* = 6.33 Hz, 1H, H-8), 4.58 (t, *J* = 3.46 Hz, 1H, THP), 4.22 (d, *J* = 6.08 Hz, 2H, H-17), 4.12 (d, *J* = 11.43 Hz, 1H, H-6), 4.07 (d, *J* = 11.35 Hz, 1H, H-6), 3.92-3.86 (m, 1H, THP), 3.54-3.49 (m, 1H, THP), 2.18-2.12 (m, 2H, H-11), 2.09-2.04 (m, 2H, H-4), 2.01-1.96 (m, 4H, H-5, H-13), 1.88 (m, 1H, THP), 1.76 (d, *J* = 0.85 Hz, 3H, H-1), 1.74-1.66 (m, 1H, THP), 1.63-1.49 (m, 7H, THP, H-16), 1.44 (s, 3H, H-9), 1.04 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 137.2 (q, C-14), 135.8 (t, TBDPS), 134.9 (q, C-2), 134.2 (q, TBDPS), 131.9 (q, C-7), 129.6 (t, TBDPS), 129.5 (t, C-3), 127.7 (t, TBDPS), 124.5 (t, C-8), 124.1 (t, C-15), 97.7 (t, THP), 65.6 (s, C-6), 62.3 (s, THP), 61.3 (s, C-17), 40.0 (s, C-13), 39.6 (s, C-5), 30.8 (s, THP), 27.0 (p,

TBDPS), 26.5 (s, C-11), 26.4 (s, C-4), 25.7 (s, THP), 21.9 (p, C-1), 19.7 (s, THP), 19.3 (q, TBDPS), 16.5 (p, C-16), 16.1 (p, C-9) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{36}H_{52}O_3SiNa$ $[M+Na]^+$: 583.3583; *found*: 583.3586; $\mathbf{R_f}$ (3:1 PE/EtOAc): 0.60.

(2*E*,6*E*,10*Z*)-3,7,11-Trimethyl-12-((tetrahydro-2*H*-pyran-2-yl)oxy)dodeca-2,6,10-trien-1-ol 488

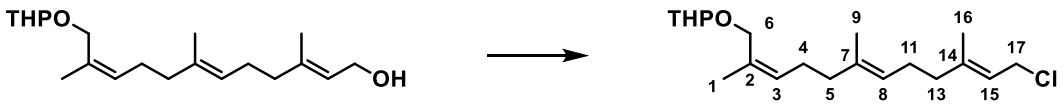


486 488

TBAF (1 M in THF, 2.3 mL, 2.25 mmol, 3.00 eq) was added dropwise to a stirred solution of TBDPS-ether **486** (0.42 g, 0.75 mmol, 1.00 eq) in THF (7.5 mL) at 0 °C and the resulting mixture was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (10 mL), the aq. layer was extracted with EtOAc (3x 20 mL), the comb. org. layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 2:1) yielded alcohol **488** (0.23 g, 0.70 mmol, 93%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.41 (tq, *J* = 6.90, 1.26 Hz, 1H, H-15), 5.34 (t, *J* = 7.03 Hz, 1H, H-3), 5.11 (t, *J* = 6.79, 1.10 Hz, 1H, H-8), 4.59 (t, *J* = 3.53 Hz, 1H, THP), 4.15 (d, *J* = 6.85 Hz, 2H, H-17), 4.12 (d, *J* = 11.41 Hz, 1H, H-6), 4.08 (d, *J* = 11.23 Hz, 1H, H-6), 3.92-3.86 (m, 1H, THP), 3.54-3.49 (m, 1H, THP), 2.18-2.09 (m, 4H, H-4, H-11), 2.06-1.97 (m, 4H, H-5, H-13), 1.89-1.79 (m, 1H, THP), 1.76 (d, *J* = 1.17 Hz, 3H, H-1), 1.74-1.70 (m, 1H, THP), 1.68 (s, 3H, H-16), 1.62-1.50 (m, 7H, THP, H-9) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 139.8 (q, C-14), 135.1 (q, C-2), 131.9 (q, C-7), 129.4 (t, C-3), 124.2 (t, C-8), 123.7 (t, C-15), 97.7 (t, THP), 65.6 (s, C-6), 62.3 (s, THP), 59.6 (s, C-17), 40.0 (s, C-13), 39.6 (s, C-5), 30.8 (s, THP), 26.5 (s, C-11), 26.3 (s, C-4), 25.7 (s, THP), 21.8 (p, C-1), 19.7 (s, THP), 16.4 (p, C-16), 16.2 (p, C-9) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{20}H_{34}O_3Na$ $[M+Na]^+$: 345.2406; *found*: 345.2406; $\mathbf{R_f}$ (2:1 PE/EtOAc): 0.35.

2-(((2*Z*,6*E*,10*E*)-12-Chloro-2,6,10-trimethyldodeca-2,6,10-trien-1-yl)oxy)tetrahydro-2*H*-pyran 567



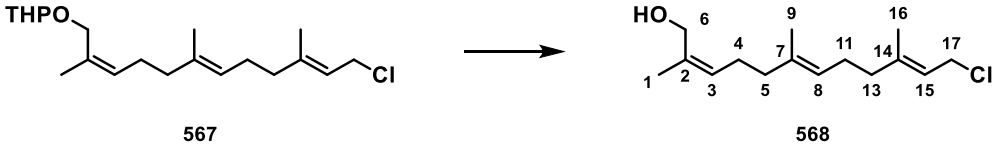
488 567

DMS (75 µL, 1.02 mmol, 1.50 eq) was added dropwise to a stirred solution of NCS (118.4 mg, 0.89 mmol, 1.30 eq) in CH_2Cl_2 (1.8 mL) at -30 °C. The resulting mixture was allowed to warm to 0 °C over 10 min, then it was cooled to -30 °C. Alcohol **488** (0.22 g, 0.68 mmol, 1.00 eq) in CH_2Cl_2

(1.2 mL) was added dropwise at -30 °C and the resulting mixture was allowed to warm to 0 °C over 2 h. The reaction was terminated by addition of brine (10 mL), the aq. layer was extracted with Et_2O (3x 10 mL), the comb. org. layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded chloride **567** (0.21 g, 0.61 mmol, 89%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.44 (dt, *J* = 8.00, 1.26 Hz, 1H, H-15), 5.34 (t, *J* = 6.90 Hz, 1H, H-3), 5.09 (dt, *J* = 6.71, 1.10 Hz, 1H, H-8), 4.58 (t, *J* = 3.54 Hz, 1H, THP), 4.13-4.05 (m, 4H, H-6, H-17), 3.92-3.86 (m, 1H, THP), 3.54-3.49 (m, 1H, THP), 2.18-1.97 (m, 8H, H-4, H-5, H-11, H-13), 1.88-1.80 (m, 1H, THP), 1.76 (d, *J* = 1.17 Hz, 3H, H-1), 1.75-1.66 (m, 4H, THP, H-16), 1.63-1.51 (m, 7H, THP, H-9) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 142.9 (q, C-14), 135.3 (q, C-2), 132.0 (q, C-7), 129.4 (t, C-3), 123.9 (t, C-8), 120.5 (t, C-15), 97.7 (t, THP), 65.6 (s, C-6), 62.3 (s, THP), 41.3 (s, C-17), 40.0 (s, C-13), 39.6 (s, C-5), 30.8 (s, THP), 26.4 (s, C-11), 26.2 (s, C-4), 25.7 (s, THP), 21.9 (p, C-1), 19.7 (s, THP), 16.3 (p, C-16), 16.2 (p, C-9) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{20}H_{33}O_2ClNa$ $[M+Na]^+$: 363.2067; *found*: 363.2062; **R_f** (2:1 PE/EtOAc): 0.66.

(2*Z*,6*E*,10*E*)-12-Chloro-2,6,10-trimethyldodeca-2,6,10-trien-1-ol 568



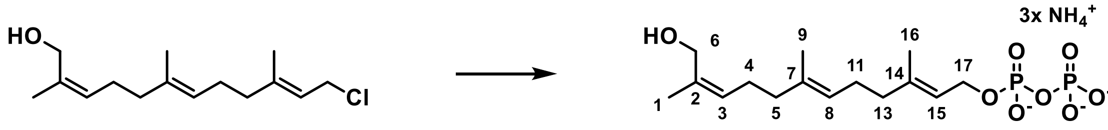
567 **568**

*p*TsOH·H_2O (10.1 mg, 0.06 mmol, 0.10 eq) was added to a stirred solution of ether **567** (200.0 mg, 0.59 mmol, 1.00 eq) in wet MeOH (7.5 mL) at 0 °C. The resulting mixture was allowed to warm to rt over 2 h. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (20 mL). The aq. layer was extracted with CH_2Cl_2 (3x 20 mL), the comb. org. layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* Column chromatography (PE/EtOAc 10:1 – 5:1) yielded alcohol **568** (50.9 mg, 0.20 mmol, 34%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.44 (dt, *J* = 7.96, 1.12 Hz, 1H, H-15), 5.28 (t, *J* = 7.11 Hz, 1H, H-3), 5.09 (t, *J* = 6.23 Hz, 1H, H-8), 4.11-4.09 (m, 4H, H-6, H-17), 2.17-1.98 (m, 8H, H-4, H-5, H-11, H-13), 1.79 (d, *J* = 1.09 Hz, 3H, H-1), 1.73 (s, 3H, H-16), 1.60 (s, 3H, H-9), 1.13 (bs, 1H, OH) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 142.8 (q, C-14), 135.3 (q, C-2), 134.5 (q, C-7), 128.4 (t, C-3), 124.2 (t, C-8), 120.5 (t, C-15), 61.8 (s, C-6), 41.3 (s, C-17), 39.9 (s, C-13), 39.5 (s, C-5), 26.3 (s, C-11), 26.2 (s, C-4), 21.4 (p, C-1), 16.3 (p, C-16), 16.2 (p, C-9) ppm; **R_f** (2:1 PE/EtOAc): 0.50.[9]

[9] Using different MS-ionisation and spectrocopic methods only allowed to detect fragments of the product but not the molecule ion could be found.

(2*E*,6*E*,10*Z*)-12-Hydroxy-3,7,11-trimethyldodeca-2,6,10-trien-1-yl triammonium diphosphate 134

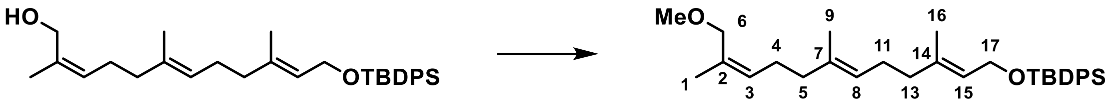


568 134

Preactivated pieces of 3Å-sieves were added to a stirred solution of (nBu$_4$N)$_3$P$_2$O$_7$H (188.9 mg, 0.21 mmol, 2.50 eq) in MeCN (2.1 mL) at 0 °C. Then chloride **568** (21.5 mg, 0.08 mmol, 1.00 eq) in MeCN (0.84 mL) was added dropwise at 0 °C and the resulting mixture was allowed to warm to rt and stirred at rt overnight. The mixture was concentrated *in vacuo* and standard work up using an ion exchange column was applied to yield pyrophosphate **134** (33.4 mg, 0.09 mmol, *quant.*) as a white gum which was stored under an atmosphere of Argon at -80 °C.

^{1}H-NMR (400 MHz, D$_2$O): δ = 5.47 (t, J = 6.68 Hz, 1H, H-15), 5.39 (t, J = 7.37 Hz, 1H, H-3), 5.22 (t, J = 6.26 Hz, 1H, H-8), 4.51-4.48 (m, 2H, H-17), 4.11 (s, 2H, H-6), 2.21-2.02 (m, 8H, H-4, H-5, H-11, H-13), 1.75 (d, J = 1.20 Hz, 3H, H-1), 1.73 (s, 3H, H-16), 1.63 (s, 3H, H-9) ppm; **^{13}C-NMR (100 MHz, D$_2$O):** δ = 143.0 (q, C-14), 136.3 (q, C-2), 133.8 (q, C-7), 128.9 (t, C-3), 124.5 (t, C-8), 119.5 (d, J = 7.42 Hz, t, C-15), 62.9-62.8 (m, s, C-17), 60.1 (s, C-6), 39.0 (s, C-13), 38.7 (s, C-5), 25.5 (s, C-11), 25.4 (s, C-4), 20.5 (p, C-1), 15.6 (p, C-16), 15.2 (p, C-9) ppm; **^{31}P-NMR (162 MHz, D$_2$O):** δ = -9.59 - -10.89 (m, 2P) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{15}H_{27}O_8P_2$ [M-H]$^-$: 397.1181; *found*: 397.1184.

***tert*-Butyl(((2*E*,6*E*,10*Z*)-12-methoxy-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)oxy)diphenylsilane 487**



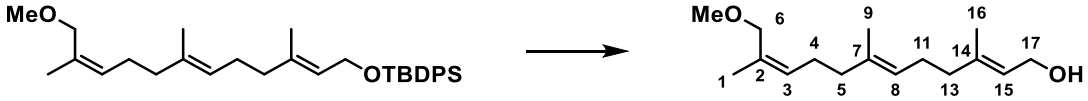
566 487

NaH (90%, 38.5 mg, 1.44 mmol, 2.50 eq) was added to a stirred solution of alcohol **566** (0.28 g, 0.58 mmol, 1.00 eq) and MeI (0.18 mL, 2.88 mmol, 5.00 eq) in THF/DMF (3:1, 3.8 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 1 h before it was allowed to warm to rt and stirred for 3 h. The reaction was terminated by addition of water (10 mL), the aq. layer was extracted with Et$_2$O (3x 10 mL), the comb. org. layers were washed with brine (20 mL), dried over MgSO$_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 20:1) yielded ether 4**87** (0.17 g, 0.35 mmol, 61%, 88% brsm) as a colorless oil.

^{1}H-NMR (400 MHz, CDCl$_3$): δ = 7.70-7.68 (m, 4H, TBDPS), 7.44-7.35 (m, 6H, TBDPS), 5.40-5.33 (m, 2H, H-3, H-15), 5.11 (t, J = 6.26 Hz, 1H, H-8), 4.22 (d, J = 6.21 Hz, 2H, H-15), 3.91 (s, 2H,

H-6), 3.28 (s, 3H, OMe), 2.17-1.97 (m, 8H, H-4, H-5, H-11, H-13), 1.73 (d, *J* = 1.01 Hz, 3H, H-1), 1.60 (s, 3H, H-16), 1.44 (s, 3H, H-9), 1.04 (s, 9H, TBDPS) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 137.2 (q, C-14), 135.7 (t, TBDPS), 134.8 (q, C-2), 134.2 (q, TBDPS), 132.0 (q, C-7), 129.6 (t, TBDPS), 129.4 (t, C-3), 127.7 (t, TBDPS), 124.5 (t, C-8), 124.2 (t, C-15), 71.0 (s, C-6), 61.2 (s, C-17), 57.7 (p, OMe), 40.0 (s, C-13), 39.6 (s, C-5), 27.0 (p, TBDPS), 26.5 (s, C-11), 26.4 (s, C-4), 21.6 (p, C-1), 19.3 (q, TBDPS), 16.5 (p, C-16), 16.2 (p, C-9) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{32}H_{46}O_2SiNa$ $[M+Na]^+$: 513.3165; *found*: 513.3167; **R_f** (3:1 PE/EtOAc): 0.69.

(2*E*,6*E*,10*Z*)-12-Methoxy-3,7,11-trimethyldodeca-2,6,10-trien-1-ol 489

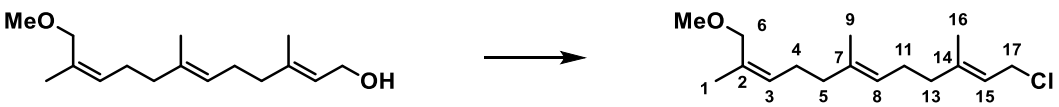


487 489

TBAF (1 M in THF, 1.1 mL, 1.01 mmol, 3.00 eq) was added dropwise to a stirred solution of TBDPS-ether **487** (0.17 g, 0.34 mmol, 1.00 eq) in THF (3.4 mL) at 0 °C and the resulting mixture was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. aq. NH_4Cl-solution (10 mL), the aq. layer was extracted with EtOAc (3x 20 mL), the comb. org. layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 2:1) yielded alcohol **489** (76.5 mg, 0.30 mmol, 90%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.42 (tq, *J* = 6.92, 1.25 Hz, 1H, H-15), 5.34 (t, J = 6.85 Hz, 1H, H-3), 5.11 (dt, *J* = 6.78, 1.17 Hz, 1H, H-8), 4.15 (d, *J* = 6.93 Hz, 2H, H-17), 3.91 (s, 2H, H-6), 3.29 (s, 3H, OMe), 2.17-1.98 (m, 8H, H-4, H-5, H-11, H-13), 1.73 (d, *J* = 1.29 Hz, 3H, H-1), 1.68 (d, *J* = 0.52 Hz, 3H, H-16), 1.60 (s, 3H, H-9) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 139.9 (q, C-14), 135.0 (q, C-7), 132.1 (q, C-2), 129.4 (t, C-3), 124.3 (t, C-8), 123.6 (t, C-15), 71.0 (s, C-6), 59.6 (s, C-17), 57.7 (p, OMe), 39.9 (s, C-13), 39.6 (s, C-5), 26.4 (s, C-11), 26.4 (s, C-4), 21.6 (p, C-1), 16.4 (p, C-16), 16.2 (p, C-9) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{16}H_{28}O_2Na$ $[M+Na]^+$: 275.1987; *found*: 275.1984; **R_f** (2:1 PE/EtOAc): 0.29.

(2*Z*,6*E*,10*E*)-12-Chloro-1-methoxy-2,6,10-trimethyldodeca-2,6,10-triene 569



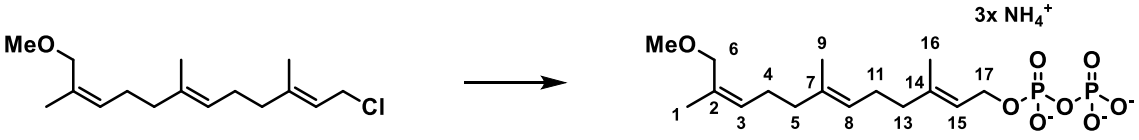
489 567

MsCl (0.05 mL, 0.55 mmol, 2.00 eq) was added dropwise to a stirred solution of alcohol **489** (70.0 mg, 0.28 mmol, 1.00 eq) and collidine (0.22 mL, 1.66 mmol, 6.00 eq) in DMF (9.5 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 20 min. Then LiCl (47.1 mg, 1.11 mmol, 4.00 eq)

was added at 0 °C and the mixture was allowed to warm to rt over 2 h. The reaction was terminated by addition of brine (10 mL) and diluted with a 1:1 mixture of Et_2O and water (10 mL). The aq. layer was extracted with Et_2O (3x 10 mL), the comb. org. layers were washed with an aq. 10% $CuSO_4$-solution (20 mL), sat. aq. $NaHCO_3$-solution (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc 10:1) yielded chloride **567** (74.9 mg, 0.28 mmol, *quant.*) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.44 (tq, *J* = 7.95, 1.26 Hz, 1H, H-15), 5.34 (dt, *J* = 7.24, 1.26 Hz, 1H, H-3), 5.09 (dt, *J* = 6.77, 1.21 Hz, 1H, H-8), 4.10 (d, *J* = 7.95 Hz, 2H, H-17), 3.91 (s, 2H, H-6), 3.28 (s, 3H, OMe), 2.17-1.97 (m, 8H, H-4, H-5, H-11, H-13), 1.74-1.73 (m, 6H, H-1, H-16), 1.60 (s, 3H, H-9) ppm; **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 142.8 (q, C-14), 135.3 (q, C-2), 132.1 (q, C-7), 129.3 (t, C-3), 124.0 (t, C-8), 120.5 (t, C-15), 71.0 (s, C-6), 57.7 (p, OMe), 41.3 (s, C-17), 39.9 (s, C-13), 39.5 (s, C-5), 26.4 (s, C-11), 26.2 (s, C-4), 21.6 (p, C-1), 16.3 (p, C-16), 16.2 (p, C-9) ppm; **R_f** (2:1 PE/EtOAc): 0.29.[10]

(2*E*,6*E*,10*Z*)-12-Methoxy-3,7,11-trimethyldodeca-2,6,10-trien-1-yl triammonium diphosphate 102



567 **102**

Preactivated pieces of 3Å-sieves were added to a stirred solution of $(n\text{Bu}_4\text{N})_3\text{P}_2\text{O}_7\text{H}$ (166.6 mg, 0.18 mmol, 2.50 eq) in MeCN (1.9 mL) at 0 °C. Then chloride **567** (20.0 mg, 0.07 mmol, 1.00 eq) in MeCN (0.74 mL) was added dropwise at 0 °C and the resulting mixture was allowed to warm to rt and stirred at rt overnight. The mixture was concentrated *in vacuo* and standard work up using an ion exchange column was applied to yield pyrophosphate **102** (31.3 mg, 0.07 mmol, 91%) as a white gum which was stored under an atmosphere of Argon at -80 °C.

^{1}H-NMR (400 MHz, D_2O): δ = 5.50-5.45 (m, 2H, H-15, H-3), 5.22 (t, *J* = 6.22 Hz, 1H, H-8), 4.50 (t, *J* = 5.95 Hz, 2H, H-17), 4.01 (s, 2H, H-6), 3.32 (s, 3H, OMe), 2.22-2.03 (m, 8H, H-4, H-5, H-11, H-13), 1.73 (d, *J* = 1.01 Hz, 3H, H-16), 1.72 (d, *J* = 1.26 Hz, 3H, H-1), 1.63 (s, 3H, H-9) ppm; **^{13}C-NMR (100 MHz, D_2O):** δ = 143.1 (q, C-14), 136.2 (q, C-2), 131.1 (q, C-7), 130.9 (t, C-3), 124.6 (t, C-8), 119.5 (d, *J* = 7.96 Hz, t, C-15), 70.6 (s, C-6), 62.9 (d, *J* = 4.94 Hz, s, C-17), 56.8 (p, OMe), 38.9 (s, C-13), 38.8 (s, C-5), 25.6 (s, C-11), 25.6 (s, C-4), 20.7 (p, C-1), 15.6 (p, C-16), 15.2 (p, C-9) ppm; **^{31}P-NMR (162 MHz, D_2O):** δ = -9.48 - -10.03 (m, 1P), -10.12 – 10.59 (m, 1P) ppm; **HRMS (ESI-LCT):** *m/z calc.* for $C_{16}H_{29}O_8P_2$ $[M\text{-}H]^-$: 411.1338; *found*: 411.1342.

[10] Using different ionisation and spectrocopic methods only fragments but not the molecule ion could be found.

8.6 Enzymological Work

8.6.1 Enzyme Overexpression and Purification

For the enzyme overexpression, stock cultures of *E. coli* BL21(DE3) containing the pET-28a(+) plasmid, harboring the corresponding gene of each sesquiterpene cyclase (Tps32, Cop4, GcoA, Cyc1, Bot2, PenA, Tri5, Hvs1) were kindly received from Catherine Victoria.

A seed culture was grown in LB-medium (4 mL) with 50 µg/mL kanamycin and 50 µL of the stock culture in a 15 mL Falcon tube at 30 °C, 120 rpm overnight. The main culture was grown in 2TY-medium (100 mL) with 50 µg/mL kanamycin and 1 mL of the seed culture in a 250 mL Erlenmeyer flask at 37 °C and 180 rpm until OD_{600} of the culture reached a value between 0.4 and 0.7. The heterologous expression was induced by adding 0.5 M IPTG into the culture and the overexpression was carried out at 16 °C and 180 rpm overnight.

The medium was removed by centrifugation (5800 rpm, 10 min, 4 °C). The cell pellets could be either used directly or stored at -20 °C until use. The pellet was suspended in 30 mL of lysis buffer + 10 mM imid. and the cells were disrupted using ultrasonfication (20 min, 4 s on, 6 s off, 37% amplitude, 4 °C). The supernatant was collected after centrifugation (7000 rpm, 20 min, 4 °C) and filtered through a sterile filter (0.45 µM). The filtrate was subjected to an affinity chromatography, the filtrate was loaded twice. Impurities were washed with lysis buffer + 25 mM imid. and the desired protein was eluted with lysis buffer + 250 mM imid (6 mL) which was directly collected in a diaphragm tube. Concentration was performed in a centrifuge at 4500 rpm for 15 min at 4 °C. The concentrate was taken up in lysis buffer and loaded onto a desalting column. The protein was eluted with 3 mL of lysis buffer and collected in a diaphragm tube. The final concentrate was taken up in the same amount of preservation buffer and the protein concentration was determined using photometry. The protein was stored at -80 °C until use.

The purity of the produced enzymes was controlled performing a SDS-PAGE with a 5% collection gel and a 15% separation gel. The SDS-PAGE was run applying 100 V for 30 min and then 150 V for 1.5 h. The samples were prepared by mixing 0.8 mL of the Laemmli mix with 0.1 mL of a 10% SDS-solution and 0.1 mL 1 M DTT and 10 µL of the protein and then heated for 10 min in a thermoblock at 95 °C. The final gel was developed using the Coomassie stain overnight on a shaker. Then it was washed with water (3x) and excess color was removed by washing with acetic acid overnight on a shaker.

New stock cultures were made by using the pellet of 1 mL seed culture (centrifuge at 9000 rpm, 1 min) which is redissolved in 25% glycerol/water in a 2 mL cryoculture vial which is then stored at -80 °C.

8.6.2 Enzyme Assays

For a qualitative and semi-quantitative biotransformation the desired pyrophosphate (150 µM) was incubated with 0.1 g/L of the corresponding STC together with an 50 mM HEPES-buffer (pH = 7,5), 5 mM DTT and 5 mM $MgCl_2$ in a final volume of 0.5 mL in a small glass vial. The mixture was incubated at 37 °C and 200 rpm for 30 min and then extracted with 100 µL of GCMS-grade hexanes. The layers were separated using centrifugation at 2000 rpm for 4 min at 4 °C. Then 60 µL of the org. layer was collected and submitted for GC-MS analysis. If a semi-quantitative analysis was performed, 3 µL of an internal standard was added. For the analysis of the enzymatic transformations, GC-MS and GC-FID measurements based on an equipment and method as shown in table 23 & 24 was used.

Table 23: Equipment data for the used GC-MS and details to the used methods.

manufacturer	Hewlett Packard, Inc.
device	GC System 6890 Series HP 5973 Quadrupole Mass Selective Detector
column	Optima 5 (Poly(5%-phenyl-95%-methylsiloxane), length: 30 m, inner diameter: 0.32 mm, film thickness: 0.25 µm Macherey-Nagel GmbH & Co. KG
carriergas	Helium
split	splitless & split to 1:40
injection volume	1–5 µL
injection temperature	60 °C → 12 °C/min to 300 °C
purge flow	2 min
flow rate	15 mL/min
temperature program	iso 50 °C for 1 min → 20 °C/min to 300 °C → iso 300 °C for 6 min
total run time	20 min
ionization source	EI (70 eV)
detector	flame ionization detector (FID) and MS
MS	ion trap
mass range	40-500u

For biotransformations on a large scale to isolate novel products, the desired pyrophosphate (1 mM) was incubated with 0.1 g/L of the corresponding STC together in a 50 mM HEPES-buffer (pH = 7.5),

5 mM DTT, 50 mM NaCl, 10 mM $MgCl_2$, 1 U PPase and 0.2% (v/v) Tween20 in a final volume of 25 or 50 mL in a Erlenmeyerflask. The mixture was incubated at 37 °C and 100 rpm for 12-24 h and then the same amount of STC was added again to the reaction mixture. Then, incubation was continued and after further 12 h, the mixture was cooled to 15 °C and overlayed with 25 mL of GCMS-ultra grade pentanes and shaked for further 12 h. Then the mixture was transferred into a separation funnel and the layers were separated. The aq. layer was extracted with GCMS-ultra grade pentanes (3x 25 mL) and the comb. org. layers were washed with brine until no foam forming interphase was present. The org. extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* (30 °C, 850 mbar). Final residues of solvent were evaporated in a stream of Argon to yield crude products which were purified using standard column chromatography.

8.6.3 Media and Devices

device	definition
pipetts	Pipetman P2, P10, P20, P100, P200, P1000 (Gilson)
shaker	Innova 44, Excella E24 (New Brunswick Scientific Co.)
centrifuge	Heraeus Megafuge 16R (Thermo Fisher Scientific, Inc.)
pH-meter	pHenomenal 1000L (VWR international)
ultrasonificator	Sonopuls HD3100 + KE76 Sonotrode (Bandelin electronic GmbH & Co. KG)
vortex	Vortex Genie 2 (Scientific Industries, Inc.)
photometer	FoodALYT Photometer (Omnilab-Laborzentrum GmbH & Co. KG)
photometer 2	DS-11+ Spectrophotometer (DeNovix, Inc.)
affinity column	Protino® Ni-NTA-Agarose (Machery-Nagel)
desalting column	PD10 (GE Healthcare)
diaphragm tube	Amicon Ultra-15 Centrifugal Filter Units 30 kDA (Merck)
electrophoresis	PerfectBlue Gel System Midi S (Peqlab Biotechnologie GmbH)
	gel chamber system ComPhor Mini (Biozym Scientific GmbH)
	gel chamber system Mini-PROTEAN® Tetra Cell (Bio-Rad Laboratories, Inc.)
	Consort Electrophoresis Power Supply E833 (Sigma Aldrich Co.)
	Consort Electrophoresis Power Supply E835 (Sigma Aldrich Co.)
	Gel Doc™ XR+ System (Bio-Rad Laboratories, Inc.)
water purifier	Ultra-Clear (SG Wasseraufbereitungs- und Regenerierstation GmbH)
autoclave	2100 Classic (Prestige Medical Co.)
autoclave 2	VX-95 (Systec GmbH)

LB-medium	
0.50%	yeast extract
1%	Tryptone
0.05%	NaCl

2TY-medium	
1%	yeast extract
1.60%	Tryptone
0.50%	NaCl

lysis buffer	
40 mM	TRIS-HCl
100 mM	NaCl
pH	8

2x preservation buffer	
20 mM	TRIS-HCl
100 mM	NaCl
1 mM	DTT
20% (v/v)	glycerine
pH	8

Laemmli mix	
150mM	TRIS-HCl (pH 6.8)
6% (m/v)	SDS
30% (v/v)	glycerine
0.02% (m/v)	bromophenol blue

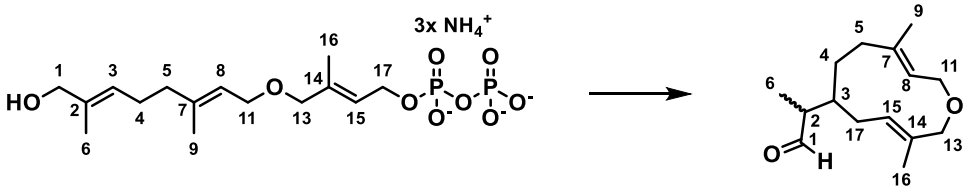
10x SDS buffer	
0.25 M	TRIS base
1% (m/v)	SDS

Coomassie Stain	
25% (v/v)	*i*PrOH
10% (v/v)	AcOH
0.1% (m/v)	Coomassie brilliant blue P250

HEPES assay buffer	
50 mM	HEPES
5 mM	DTT
pH	7.5

8.7 Structure Elucidation

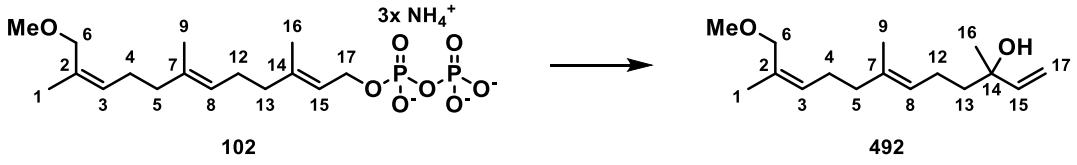
2-((3*E*,9*E*)-3,9-Dimethyloxacycloundeca-3,9-dien-6-yl)propanal 490



Pyrophosphate **127** (23 mg, 0.05 mmol) was transformed with Tps32 following the general procedure above. The crude product was purified using column chromatography (pentanes/Et_2O 1:0 – 1:1) to yield aldehyde **490** (7.0 mg, 0.03 mmol, 60%) as a yellow liquid with a strong odor of hazelnut.

^{1}H-NMR (600 MHz, C_6D_6): δ = 9.42 (d, *J* = 1.14 Hz, 0.5 H, H-1-maj), 9.39 (d, *J* = 1.32 Hz, 0.5 H, H-1-min), 5.23-5.19 (m, 1H, H-15), 5.18-5.13 (m, 1H, H-8), 4.18-4.11 (m, 2H, H-13), 4.04-4.02 (m, 1H, H-11), 3.79-3.75 (m, 1H, H-11), 1.91-1.81 (m, 2H, H-2, H-17), 1.76-1.72 (m, 1H, H-17), 1.62 (s, 3H, H-9), 1.52-1.45 (m, 3H, H-3, H-4-maj, H-5-maj), 1.40 (dd, *J* = 9.40, 0.69 Hz, 3H, H-16), 1.36-1.31 (m, 1H, H-5-maj), 1.28-1.23 (m, 2x 0.5H, H-4-min, H-5-min), 1.06-0.90 (m, 2x 0.5H, H-4-min, H-5-min), 0.84-0.83 (m, 3H, H-6) ppm; **^{13}C-NMR (150 MHz, C_6D_6):** δ = 203.1 (t, C-1-maj), 203.0 (t, C-1-min), 136.8/136.6 (q, C-14), 136.4 (q, C-7), 126.2/126.1 (t, C-8). 125.7 (t, C-15), 79.8 (s, C-11), 69.3/69.2 (s, C-13), 53.5 (t, C-2-min), 53.2 (t, C-2-maj), 40.9 (t, C-3-maj), 39.9/39.8 (s, C-17), 32.8 (s, C-5-maj), 31.6 (s, C-5-min), 30.9 (s, C-4-maj), 29.8 (s, C-4-min), 17.6 (p, C-16), 14.7 (p, C-9), 9.8/9.5 (p, C-6) ppm; **HRMS (CI-GC):** *m/z calc.* for $C_{15}H_{24}O_2$ [M]: 236.1776; *found*: 236.1774; **R_f** (10:1 PE/EtOAc): 0.37.

(6*E*,10*Z*)-12-Methoxy-3,7,11-trimethyldodeca-1,6,10-trien-3-ol 492



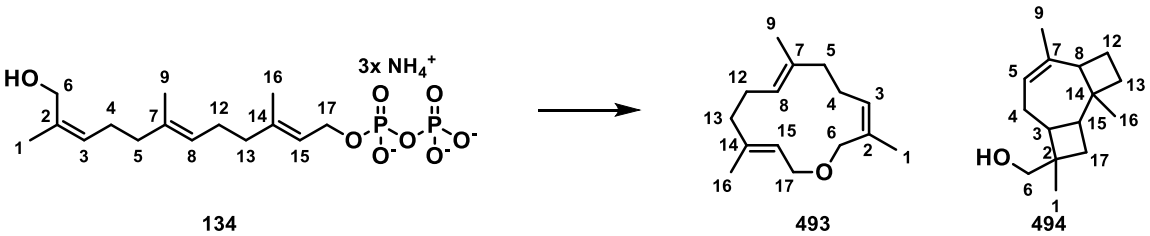
Pyrophosphate **102** (11.5 mg, 0.02 mmol) was transformed by Tri5 following the general procedure mentioned above. The crude product was purified using column chromatography (pentanes/Et_2O 10:1 – 5:1 – 3:1) to yield alcohol **492** (2.9 mg) as a colorless liquid. A second fraction was obtained with a strong odor of popcorn but it was not enough material for a structure elucidation. The fraction still contained pentane impurities not allowing to precisely determine the exact yield.

^{1}H-NMR (600 MHz, C_6D_6): δ = 6.37 (dd, *J* = 17.62, 11.08 Hz, 1H, H-15), 5.34 (dt, *J* = 7.25, 1.11 Hz, 1H, H-3), 5.24-5.22 (m, 1H, H-8), 5.21 (d, *J* = 17.17 Hz, 1H, H-17-trans), 4.98 (d, *J* = 10.21 Hz, 1H, H-17-cis), 3.86 (s, 2H, H-6), 3.12 (s, 3H, OMe), 2.27-2.26 (m, 4H, H-12, H-13), 2.18-2.11 (m, 2H, H-4), 2.03-2.01 (m, 2H, H-5), 1.83 (d, *J*= 1.20 Hz, 3H, H-1), 1.53 (s, 3H, H-9), 1.29 (s, 3H,

H-16) ppm; **^{13}C-NMR (150 MHz, C_6D_6):** δ = 146.4 (q, C-14), 139.4 (t, C-15), 135.0 (q, C-7), 132.9 (q, C-2), 128.7 (t, C-3), 124.9 (t, C-8), 113.2 (s, C-17), 71.1 (s, C-6), 57.4 (p, OMe), 40.3 (s, C-5), 31.9 (s, C-13), 31.8 (p, C-16), 27.0 (s, C-12), 26.6 (s, C-4), 21.8 (p, C-1), 16.1 (p, C-9) ppm; **HRMS (CI-GC):** *m/z calc.* for $C_{16}H_{26}O$ $[M-H_2O]^+$: 234.1984; *found*: 234.1983; **R_f** (3:1 PE/EtOAc): 0.53.

(3*Z*,7*E*,11*E*)-3,7,11-Trimethyloxacyclotrideca-3,7,11-triene 493

(1,4,8-Trimethyltricyclo[7.2.0.0^{2,5}]undec-7-en-4-yl)methanol 494



Pyrophosphate **134** (11.2 mg, 0.03 mmol) was transformed by GcoA following the general procedure mentioned above. The crude product was purified using column chromatography (pentanes/Et_2O 10:1 – 5:1 – 3:1) to yield ether **493** (3.0 mg) as a colorless liquid as the first fraction. A second fraction was obtained with a strong odor of popcorn but it was not enough material for a structure elucidation. As a third fraction alcohol **494** (6.7 mg) was obtained as a colorless liquid. All fractions still contained pentane impurities not allowing to precisely determine the exact yield.

493:

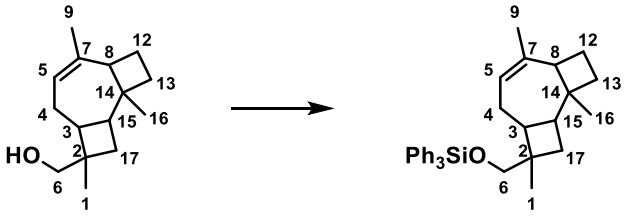
^{1}H-NMR (600 MHz, C_6D_6): δ = 5.31 (dq, *J* = 6.23, 1.17 Hz, 1H, H-15), 5.12 (dt, *J* = 7.86, 1.26 Hz, 1H, H-3), 4.97 (dt, *J* = 7.53, 1.09 Hz, 1H, H-8), 4.03 (dd, *J* = 6.24, 0.66 Hz, 2H, H-17), 3.98 (s, 2H, H-6), 2.08-2.05 (m, 4H, H-4, H-5, H-12, H-13), 1.98-1.63 (m, 2H, H-4, H-5), 1.94-1.92 (m, 2H, H-12, H-13), 1.91 (d, *J* = 0.96 Hz, 3H, H-1), 1.54 (s, 3H, H-9), 1.45 (s, 3H, H-16) ppm; **^{13}C-NMR (150 MHz, C_6D_6):** δ = 137.7 (q, C-14), 136.9 (q, C-7), 134.5 (q, C-2), 127.6 (t, C-3), 124.4 (t, C-8), 124.0 (t, C-15), 66.9 (s, C-6), 66.3 (s, C-17), 39.3 (s, C-5), 39.0 (s, C-13), 29.3 (s, C-4), 25.5 (s, C-12), 21.6 (p, C-1), 18.4 (p, C-9), 16.2 (p, C-16) ppm; **HRMS (CI-GC):** *m/z calc.* for $C_{15}H_{25}O$ $[M+H]^+$: 221.1905; *found*: 221.1904; **R_f** (3:1 PE/EtOAc): 0.63.

494:

^{1}H-NMR (600 MHz, C_6D_6): δ = 5.40 (dt, *J* = 6.57, 1.20 Hz, 1H, H-5), 3.54 (dd, *J* = 10.36, 2.85 Hz, 1H, H-6), 3.42 (dd, *J* = 10.39, 2.16 Hz, 1H, H-6), 2.52 (dt, *J* = 9.18, 2.16 Hz, 1H, H-8), 2.21 (dt, *J* = 13.81, 8.40 Hz, 1H, H-12), 1.91-1.84 (m, 2H, H-12, H-4), 1.70 (ddt, *J* = 15.89, 11.00, 2.39 Hz, 1H, H-4), 1.56 (d, *J* = 12.01 Hz, 1H, H-17), 1.46 (dd, *J* = 10.96, 6.87 Hz, 1H, H-13), 1.42-1.38 (m, 1H, H-15), 1.31-1.24 (m, 3H, H-3, H-13, H-17), 1.23 (s, 3H, H-1), 0.85 (d, *J* = 6.48 Hz, 3H, H-9), 0.79 (bs, 1H, OH), 0.75 (s, 3H, H-16) ppm; **^{13}C-NMR (150 MHz, C_6D_6):** δ = 146.0 (q, C-7), 112.7 (t,

C-5), 70.0 (s, C-6), 60.0 (t, C-8), 51.6 (q, C-2), 48.4 (q, C-14), 47.4 (s, C-17), 37.4 (t, C-15), 37.1 (s, C-13), 35.3 (s, C-4), 35.1 (s, C-12), 32.9 (t, C-3), 27.1 (p, C-1), 23.6 (p, C-16), 20.4 (p, C-9) ppm; **HRMS (CI-GC):** *m/z calc.* for $C_{15}H_{24}O$ [M]: 220.1827; *found*: 220.1827; $\mathbf{R_f}$ (3:1 PE/EtOAc): 0.35.

Triphenyl((1,4,8-trimethyltricyclo[7.2.0.0^{2,5}]undec-7-en-4-yl)methoxy)silane 495

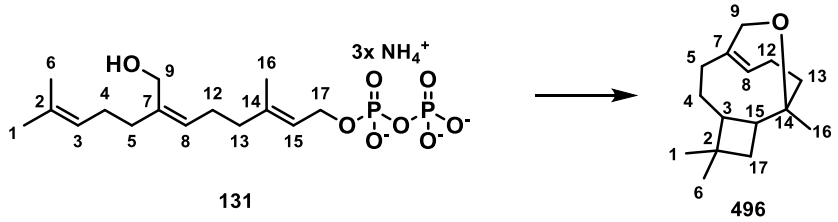


Imidiazol (6.5 mg, 0.10 mmol, 3.00 eq) and Ph_3SiCl (13.1 mg, 0.05 mmol, 1.40 eq) were added to a stirred solution of alcohol **494** (7.0 mg, 0.04 mmol, 1.00 eq) in benzene (0.8 mL) at rt and the resulting mixture was stirred at rt overnight. The reaction was terminated by addition of a sat. aq. $NaHCO_3$-solution (5 mL), the aq. layer was extracted with Et_2O (3x 5 mL), the comb. org. layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Consecutive purification using column chromatography (PE/EtOAc 50:1 – 20:1 – 10:1) and preparative TLC (PE/CH_2Cl_2 50:1) yielded silyl ether **495** (5.2 mg, 0.01 mmol, 34%) as a white crystalline solid.

^{1}H-NMR (500 MHz, C_6D_6): δ = 7.83-7.81(m, 5H, $SiPh_3$), 7.53-7.51 (m, 2H, $SiPh_3$), 7.22-7.19 (m, 8H, $SiPh_3$), 5.39 (dt, *J* = 6.55, 1.95 Hz, 1H, H-5), 4.08 (d, *J* = 9.55 Hz, 1H, H-6), 3.91 (d, *J* = 9.65 Hz, 1H, H-6), 2.53 (d, *J* = 9.92 Hz, 1H, H-8), 2.18 (dt, *J* = 13.85, 8.40 Hz, 1H, H-12), 1.87-1.78 (m, 2H, H-4, H-12), 1.76 (d, *J* = 12.13 Hz, 1H, H-17), 1.69-1.63 (m, 1H, H-4), 1.46 (s, 3H, H-1), 1.44-1.16 (m, 17H, H-3, H-13, H-15, H-17),[11] 0.82 (d, *J* = 6.40 Hz, 3H, H-9), 0.60 (s, 3H, H-16) ppm; **^{13}C-NMR (125 MHz, C_6D_6):** δ = 145.7 (q, C-7), 136.0 (t, $SiPh_3$), 135.0 (q, $SiPh_3$), 130.3 (t, $SiPh_3$), 129.1 (t, $SiPh_3$), 127.4 (t, $SiPh_3$), 113.0 (t, C-5), 71.0 (s, C-6), 60.1 (t, C-8), 51.9 (q, C-2), 48.4 (q, C-14), 47.4 (s, C-17), 37.4 (t, C-3), 37.0 (s, C-13), 35.2 (s, C-4), 35.1 (s, C-12), 32.8 (t, C-15), 27.9 (p, C-1), 23.4 (p, C-16), 20.3 (p, C-9) ppm; **HRMS (EI-LCT):** *m/z calc.* for $C_{33}H_{38}O$ Si[M]: 478.2692; *found*: 478.2703; $\mathbf{R_f}$ (5:1 PE/EtOAc): 0.65.

[11] The integral is higher than the 5 protons which appear in this area due to impurties of pentanes and grease.

(1R)-1,4,4-Trimethyl-12-oxatricyclo[6.3.2.0^{2,5}]tridec-8-ene 496

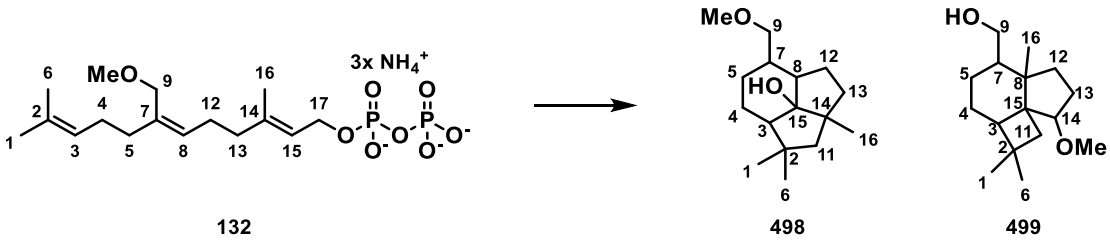


Pyrophosphate **131** (11.2 mg, 0.03 mmol) was transformed by Bot2 following the general procedure mentioned above. The crude product was purified using column chromatography (pentanes/Et_2O 1:0 – 1:1) to yield ether **496** (2.7 mg) as a colorless liquid as the first fraction. The fraction still contained pentane impurities not allowing to precisely determine the exact yield.

^{1}H-NMR (500 MHz, C_6D_6): δ = 5.48 (dt, *J* = 8.03 Hz, 1H, H-8), 4.58 (dd, *J* = 14.58, 1.08 Hz, 1H, H-9), 3.92 (d, *J* = 14.60 Hz, 1H, H-9), 3.06-2.98 (m, 1H, H-12), 2.02 (dt, *J* = 10.12, 8.95 Hz, 1H, H-15), 1.97-1.89 (m, 2H, H-13, H-5), 1.74-1.69 (m, 1H, H-12), 1.68-1.61 (m, 2H, H-3, H-5), 1.49-1.45 (m, 1H, H-17), 1.38-1.32 (m, 3H, H-4, H-13), 1.17-1.15 (m, 1H, H-17), 1.06 (s, 3H, H-16), 0.95 (s, 3H, H-1 or H-6), 0.91 (s, 3H, H-1 or H-6) ppm; **^{13}C-NMR (125 MHz, C_6D_6):** δ = 136.3 (q, C-7), 129.0 (t, C-8), 77.7 (q, C-14), 66.4 (s, C-9), 50.3 (t, C-15), 47.8 (t, C-3), 36.6 (s, C-17), 33.8 (s, C-5), 33.7 (s, C-13), 33.3 (q, C-2), 31.3 (p, C-16), 30.1 (p, C-1 or C-6), 36.3 (s, C-4), 23.7 (s, C-12), 22.1 (p, C-1 or C-6) ppm; **HRMS (CI-GC):** *m/z calc.* for $C_{15}H_{25}O$ $[M+H]^+$: 221.1905; *found*: 221.1895; **R_f** (5:1 PE/EtOAc): 0.60.

5-(Methoxymethyl)-1,1,2a-trimethyldecahydro-2a^1*H*-cyclopenta[*cd*]inden-2a^1-ol 498

(8-Methoxy-2,2,5a-trimethyldecahydrocyclobuta[*d*]inden-5-yl)methanol 499



Pyrophosphate **132** (23.3 mg, 0.06 mmol) was transformed by Bot2 following the general procedure mentioned above. The crude product was purified using column chromatography (pentanes/Et_2O 1:0 – 10:1 – 5:1 – 3:1 - 1:1) to yield tertiary alcohol 4**98** (2.7 mg) as a colorless liquid as the first fraction. The second fraction **499** (2.3 mg) provided a colorless liquid. All fractions still contained pentane impurities not allowing to precisely determine the exact yield.

498:

^{1}H-NMR (600 MHz, C_6D_6): δ = 3.17-3.15 (m, 4H, HH-9, OMe), 2.96 (dd, *J* = 8.83, 7.26 Hz, 1H, H-9), 2.31 (dt, *J* = 13.56, 8.85 Hz, 1H, H-12), 2.10 (d, *J* = 11.36 Hz, 1H, H-17), 2.06 (q, *J* = 9.62 Hz,

1H, H-13), 1.94-1.88 (m, 2H, H-5, H-12), 1.62-1.57 (m, 1H, H-7), 1.51-1.44 (m, 1H, H-4), 1.34 (s, 3H, H-1 or H-6), 1.30-1.26 (m, 1H, H-H-4), 1.26-1.19 (m, 1H, H-8), 1.16 (d, J = 11.03 Hz, 1H, H-17), 1.13 (s, 3H, H-1 or H-6), 1.10 (s, 3H, H-16), 1.00-0.93 (m, 1H, H-5) ppm; **^{13}C-NMR (150 MHz, C_6D_6):** δ = 96.2 (q, C-15), 78.0 (s, C-9), 58.8 (p, OMe), 56.6 (q, C-14), 52.5 (t, C-3), 49.2 (s, C-17), 48.0 (q, C-2), 44.5 (t, C-8), 43.3 (t, C-7), 36.5 (p, C-1 or C-6), 34.1 (s, C-13), 33.8 (s, C-12), 29.6 (s, C-5), 28.0 (p, C-16 or C-1 or C-6), 28.0 (p, C-16 or C-1 or C-6), 26.6 (s, C-4) ppm; **HRMS (CI-GC):** *m/z calc.* for $C_{16}H_{26}O$ $[M\text{-}H_2O]^+$: 234.1984; *found*: 234.1987; **R_f** (5:1 PE/EtOAc): 0.33.

499:

^{1}H-NMR (500 MHz, C_6D_6): δ = 3.84 (d, J = 5.55 Hz, 2H, H-9), 3.18-3.16 (m, 1H, H-14), 2.83 (s, 3H, OMe), 2.73 (bs, 1H, OH), 2.26-2.21 (m, 1H, H-7), 1.98-1.91 (m, 1H, H-5), 1.72-1.40 (m, 13H, H-3, H-4, H-5, H-11, H-12, H-13),[12] 1.30 (s, 3H, H-16), 0.88 (s, 3H, H-1 or H-6), 0.87 (s, 3H, H-1 or H-6) ppm; **^{13}C-NMR (125 MHz, C_6D_6):** δ = 90.4 (t, C14), 71.2 (q, C-8), 65.9 (t, C-3), 64.8 (s, C-9), 59.9 (s, C-11), 55.7 (p, OMe), 49.5 (q, C-15), 47.8 (t, C-7), 40.5 (s, C-13), 40.1 (q, C-2), 32.2 (p, C-1 or C-6), 32.0 (s, C-5), 27.8 (p, C-16), 26.9 (p, C-1 or C-6), 26.5 (s, C-12), 23.7 (s, C-4) ppm; **HRMS (CI-GC):** *m/z calc.* for $C_{16}H_{27}O$ $[M\text{-}H_2O+H^+]^+$: 235.2062; *found*: 235.2064; **R_f** (5:1 PE/EtOAc): 0.12.

[12] The integral is higher than the 10 protons which appear in this area due to impurties of pentanes and grease.

9 References

[1] W. C. Liao, Y. H. Lin, T. M. Chang, W. Y. Huang, *Food Chem.* **2012**, *132*, 2188–2193.

[2] J. A. Molhuysen, J. Gerbrandy, L. A. De Vries, J. C. De Jong, J. B. Lenstra, K. P. Turner, J. G. G. Borst, *Lancet* **1950**, *256*, 381–386.

[3] R. S. H. Finney, G. F. Somers, *J. Pharm. Pharmacol.* **1958**, *10*, 613–620.

[4] K. C. Nicolaou, D. Vourloumis, N. Winssinger, P. S. Baran, *Angew. Chem. Int. Ed.* **2000**, *39*, 44–122.

[5] F. Wöhler, *Ann. Phys. Chem.* **1828**, *87*, 253–256.

[6] H. Kolbe, *Ann. Chem. Pharm.* **1845**, *54*, 145–188.

[7] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 799–805.

[8] G. Komppa, S. V. Hintikka, *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 898–899.

[9] J. Bredt, W. H. Perkin jun., *J. Prakt. Chemie* **1914**, *89*, 209–257.

[10] R. Willstätter, *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 129–144.

[11] R. Robinson, *J. Chem. Soc., Trans.* **1917**, *111*, 762–768.

[12] H. Fischer, K. Zeile, *Justus Liebigs Ann. Chem.* **1929**, *468*, 98–116.

[13] W. E. Bachmann, W. Cole, A. L. Wilds, *J. Am. Chem. Soc.* **1939**, *61*, 974–975.

[14] The Royal Swedish Academy of Sciences, "Noble Prize," can be found under https://www.nobelprize.org/prizes/lists/all-nobel-prizes/, **n.d.**

[15] R. B. Woodward, R. Hoffmann, *Angew. Chem. Int. Ed.* **1969**, *8*, 781–853.

[16] R. B. Woodward, R. Hoffmann, *J. Am. Chem. Soc.* **1965**, *87*, 2511–2513.

[17] R. B. Woodward, R. Hoffmann, *J. Am. Chem. Soc.* **1965**, *87*, 2046–2048.

[18] R. B. Woodward, R. Hoffmann, *J. Am. Chem. Soc.* **1965**, *87*, 395–397.

[19] R. B. Woodward, W. E. Doering, *J. Am. Chem. Soc.* **1944**, *66*, 849–850.

[20] E. C. Kornfeld, E. J. Fornefeld, G. B. Kline, M. J. Mann, R. G. Jones, R. B. Woodward, *J. Am. Chem. Soc.* **1954**, *76*, 5257–5258.

[21] R. B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, H. Vorbrüggen, *J. Am. Chem. Soc.* **1966**, *88*, 852–853.

[22] R. B. Woodward, *Science* **1966**, *153*, 487–493.

[23] R. B. Woodward, W. J. Greenlee, *J. Am. Chem. Soc.* **1976**, *98*, 6075–6076.

[24] W. J. Greenlee, R. B. Woodward, *Tetrahedron* **1980**, *36*, 3361–3366.

[25] W. J. Greenlee, R. B. Woodward, *Tetrahedron* **1980**, *36*, 3367–3375.

[26] R. B. Woodward, E. Logusch, K. P. Nambiar, K. Sakan, D. E. Ward, B. W. Au-Yeung, P. Balaram, L. J. Browne, P. J. Card, C. H. Chen, *J. Am. Chem. Soc.* **1981**, *103*, 3210–3213.

[27] R. B. Woodward, B. W. Au-Yeung, P. Balaram, L. J. Browne, D. E. Ward, B. W. Au-Yeung, P. Balaram, L. J. Browne, P. J. Card, C. H. Chen, *J. Am. Chem. Soc.* **1981**, *103*, 3213–3215.

[28] R. B. Woodward, E. Logusch, K. P. Nambiar, K. Sakan, D. E. Ward, B. W. Au-Yeung, P. Balaram, L. J. Browne, P. J. Card, C. H. Chen, *J. Am. Chem. Soc.* **1981**, *103*, 3215–3217.

[29] E. J. Corey, *The Logic of Chemical Synthesis*, WILEY-VCH Verlag, New York, **1990**.

[30] E. J. Corey, "Compiled Works of E.J. Corey," can be found under http://ejcorey.org/corey/methods/methods.php, **n.d.**

[31] E. J. Corey, M. Ohno, P. A. Vatakencherry, R. B. Mitra, *J. Am. Chem. Soc.* **1961**, *83*, 1251–1253.

[32] E. J. Corey, G. E. Keck, I. Szekely, *J. Am. Chem. Soc.* **1977**, *99*, 2006–2008.

[33] E. J. Corey, B. E. Roberts, B. R. Dixon, *J. Am. Chem. Soc.* **1995**, *117*, 193–196.

[34] R. A. Holton, C. Somoza, H. Kim, F. Liang, R. J. Biediger, P. D. Boatman, M. Shindo, C. C. Smith, S. Kim, H. Nadizadeh, et al., *J. Am. Chem. Soc.* **1994**, *116*, 1597–1598.

[35] R. A. Holton, H. Kim, C. Somoza, F. Liang, R. J. Biediger, P. D. Boatman, M. Shindo, C. C. Smith, S. Kim, H. Nadizadeh, et al., *J. Am. Chem. Soc.* **1994**, *116*, 1599–1600.

[36] Z. G. Brill, H. K. Grover, T. J. Maimone, *Science* **2016**, *352*, 1078–1082.

[37] A. Kössel, "Ueber die chemische Zusammensetzung der Zelle," **1879**.

[38] D. J. Kliebenstein, *Plant, Cell Environ.* **2004**, *27*, 675–684.

[39] G. Habermehl, P. Hammann, H. C. Krebs, W. Ternes, *Naturstoffchemie*, Springer Verlag, Berlin Heidelberg, **2008**.

[40] IUPAC, "IUPAC Definitions," can be found under https://www.qmul.ac.uk/sbcs/iupac/medchem/ix.html#p7, **1998**.

[41] A. G. Atanasov, S. B. Zotchev, V. M. Dirsch, I. E. Orhan, M. Banach, J. M. Rollinger, D. Barreca, W. Weckwerth, R. Bauer, E. A. Bayer, et al., *Nat. Rev. Drug Discov.* **2021**, *20*, 200–216.

[42] S. Bernardini, A. Tiezzi, V. Laghezza Masci, E. Ovidi, *Nat. Prod. Res.* **2018**, *32*, 1926–1950.

[43] D. J. Newman, G. M. Cragg, *J. Nat. Prod.* **2007**, *70*, 461–477.

[44] D. D. Baker, M. Chu, U. Oza, V. Rajgarhia, *Nat. Prod. Rep.* **2007**, *24*, 1225–1244.

[45] T. J. Maimone, P. S. Baran, *Nat. Chem. Biol.* **2007**, *3*, 396–407.

[46] A. Kekulé, *Lehrbuch Der Organischen Chemie*, Ferdinand Enke, Erlangen, **1866**.

[47] E. Breitmaier, *Terpenes*, Wiley-VCH Verlag GmbH, Weinheim, **2006**.

[48] S. Krishna, L. Bustamante, R. K. Haynes, H. M. Staines, *Trends Pharmacol. Sci.* **2008**, *29*, 520–527.

[49] O. Wallach, *Terpene und Camphor: Zusammenfassung eigener Untersuchungen auf dem Gebiet der alicyclischen Kohlenstoffverbindungen*, Veit, Leipzig, **1909**.

[50] L. Ruzicka, *Experientia* **1953**, *9*, 357–368.

[51] D. W. Christianson, *Chem. Rev.* **2017**, *117*, 11570–11648.

[52] H. K. Lichtenthaler, M. Rohmer, J. Schwender, *Physiol. Plant.* **1997**, *101*, 643–652.

[53] J. M. Vinokur, T. P. Korman, Z. Cao, J. U. Bowie, *Biochemistry* **2014**, *53*, 4161–4168.

[54] W. Eisenreich, A. Bacher, D. Arigoni, F. Rohdich, *Cell. Mol. Life Sci.* **2004**, *61*, 1401–1426.

[55] W. Eisenreich, F. Rohdich, A. Bacher, W. Eisenreich, *Trends Plant Sci.* **2001**, *6*, 78–84.

[56] E. Cordoba, M. Salmi, P. León, *J. Exp. Bot.* **2009**, *60*, 2933–2943.

[57] C. D. Poulter, H. C. Rilling, *Acc. Chem. Res.* **1978**, *11*, 307–313.

[58] B. A. Kellogg, C. D. Poulter, *Curr. Opin. Chem. Biol.* **1997**, *1*, 570–578.

[59] J. S. Yu, T. S. Kleckley, D. F. Wiemer, *Org. Lett.* **2005**, *7*, 4803–4806.

[60] Y. Shao, J. T. Eummer, R. A. Gibbs, *Org. Lett.* **1999**, *1*, 627–630.

[61] T. J. Zahn, J. Whitney, C. Weinbaum, R. A. Gibbs, *Bioorganic Med. Chem. Lett.* **2001**, *11*, 1605–1608.

[62] K. Naruta, Y.; Maruyama, *Chem. Lett.* **1987**, *16*, 963–966.

[63] H. Pommer, A. Nürrenbach, *Pure Appl. Chem.* **1975**, *43*, 527–551.

[64] J. Nowicki, *Molecules* **2000**, *5*, 1033–1050.

[65] La Roche, *Procedere Pour La Preparation de Composes Carbonyles Non Satures*, **1961**, 634738A.

[66] Hoffman-La Roche, *A Process for the Manufacture of Unsaturated Ketones*, **1961**, 865478.

[67] BASF, *Verfahren Zur Herstellung von Citral*, **1980**, 021074.

[68] W. Reif, H. Grassner, *Chemie Ing. Tech.* **1973**, *45*, 646–652.

[69] M. F. Carroll, *J. Chem. Soc.* **1940**, 704–706.

[70] H. Pommer, *Angew. Chem.* **1960**, *72*, 811–819.

[71] B. T. Ueberbacher, M. Hall, K. Faber, *Nat. Prod. Rep.* **2012**, *29*, 337–350.

[72] D. J. Miller, R. K. Allemann, *Nat. Prod. Rep.* **2012**, *29*, 60–71.

[73] J. Degenhardt, T. G. Köllner, J. Gershenzon, *Phytochemistry* **2009**, *70*, 1621–1637.

[74] R. K. Allemann, *Pure Appl. Chem.* **2008**, *80*, 1791–1798.

[75] P. Baer, P. Rabe, K. Fischer, C. A. Citron, T. A. Klapschinski, M. Groll, J. S. Dickschat, *Angew. Chem. Int. Ed.* **2014**, *53*, 7652–7656.

[76] V. Harms, A. Kirschning, J. S. Dickschat, *Nat. Prod. Rep.* **2020**, *37*, 1080–1097.

[77] A. Hou, L. Lauterbach, J. S. Dickschat, *Chem. Eur. J.* **2020**, *26*, 2178–2182.

[78] V. Harms, B. Schröder, C. Oberhauser, C. D. Tran, S. Winkler, G. Dräger, A. Kirschning, *Org. Lett.* **2020**, *22*, 4360–4365.

[79] S. Touchet, K. Chamberlain, C. M. Woodcock, D. J. Miller, M. A. Birkett, J. A. Pickett, R. K. Allemann, *Chem. Commun.* **2015**, *51*, 7550–7553.

[80] O. Cascón, S. Touchet, D. J. Miller, V. Gonzalez, J. A. Faraldos, R. K. Allemann, *Chem. Commun.* **2012**, *48*, 9702–9704.

[81] M. Demiray, X. Tang, T. Wirth, J. A. Faraldos, R. K. Allemann, *Angew. Chem. Int. Ed.* **2017**, *56*, 4347–4350.

[82] X. Tang, M. Demiray, T. Wirth, R. K. Allemann, *Bioorganic Med. Chem.* **2018**, *26*, 1314–1319.

[83] M. Demiray, D. J. Miller, R. K. Allemann, *Beilstein J. Org. Chem.* **2019**, *15*, 2184–2190.

[84] F. Huynh, D. J. Grundy, R. L. Jenkins, D. J. Miller, R. K. Allemann, *ChemBioChem* **2018**, *19*, 1834–1838.

[85] R. Lauchli, K. S. Rabe, K. Z. Kalbarczyk, A. Tata, T. Heel, R. Z. Kitto, F. H. Arnold, *Angew. Chem. Int. Ed.* **2013**, *52*, 5571–5574.

[86] C. Oberhauser, V. Harms, K. Seidel, B. Schröder, K. Ekramzadeh, S. Beutel, S. Winkler, L. Lauterbach, J. S. Dickschat, A. Kirschning, *Angew. Chem. Int. Ed.* **2018**, *57*, 11802–11806.

[87] M. Woyciechowska, G. Forcher, S. Buda, J. Mlynarski, *Chem. Commun.* **2012**, *48*, 11029–11031.

[88] B. T. Gröbel, S. D., *Synthesis* **1977**, *6*, 357–402.

[89] M. Medarde, A. C. Ramos, R. P. De Clairac, E. Caballero, *J. Chem. Soc. Perkin Trans* **1994**, *2*, 45–47.

[90] D. R. St Laurent, L. A. Paquette, *J. Org. Chem.* **1986**, *51*, 3861–3864.

[91] E. J. Corey, D. Seebach, *Angew. Chem. Int. Ed.* **1965**, *4*, 1075–1077.

[92] W. Fu, M. Nie, A. Wang, Z. Cao, W. Tang, *Angew. Chem. Int. Ed.* **2015**, *54*, 2520–2524.

[93] T. Shimizu, K. Osako, T. Nakata, *Tetrahedron Lett.* **1997**, *38*, 2685–2688.

[94] P. R. Blakemore, W. J. Cole, P. J. Kocieński, A. Morley, *Synlett* **1998**, 26–28.

[95] E. Rank, R. Brückner, *European J. Org. Chem.* **1998**, *1998*, 1045–1053.

[96] Y. Li, R. Zhang, A. Ali, J. Zhang, X. Bi, J. Fu, *Org. Lett.* **2017**, *19*, 3087–3090.

[97] D. G. Brown, E. J. Velthuisen, J. R. Commerford, R. G. Brisbois, T. R. Hoye, *J. Org. Chem.* **1996**, *61*, 2540–2541.

[98] A. G. Myers, P. S. Dragovich, E. Y. Kuo, *J. Am. Chem. Soc.* **1992**, *114*, 9369–9386.

[99] N. Saito, Y. Sugimura, Y. Sato, *Synlett* **2014**, 736–740.

[100] E. W. Colvin, B. J. Hamill, *J. Chem. Soc. Perkin Trans. 1* **1977**, 869–873.

[101] E. D. Sternberg, K. Peter, C. Vollhardt, *J. Am. Chem. Soc.* **1980**, *102*, 4839–4841.

[102] J. C. Clinet, E. Dufiach, K. Peter, C. Vollhardt, *J. Am. Chem. Soc.* **1983**, *105*, 6710–6712.

[103] E. D. Sternberg, K. P. C. Vollhardt, *J. Org. Chem.* **1984**, *49*, 1564–1573.

[104] E. P. Johnson, K. C. Peter Vollhardt, *J. Am. Chem. Soc.* **1991**, *113*, 381–382.

[105] K. P. C. Vollhardt, *Angew. Chem. Int. Ed.* **1984**, *23*, 539–556.

[106] M. J. Eichberg, R. L. Dorta, K. Lamottke, K. P. C. Vollhardt, *Org. Lett.* **2000**, *2*, 2479–2481.

[107] F. Slowinski, C. Aubert, M. Malacria, *J. Org. Chem.* **2003**, *68*, 378–386.

[108] M. Kögl, L. Brecker, R. Warrass, J. Mulzer, *European J. Org. Chem.* **2008**, 2714–2730.

[109] T. Gadek, K. P. C. Vollhardt, *Angew. Chem. Int. Ed.* **1981**, *20*, 802–803.

[110] V. Gandon, N. Agenet, K. P. C. Vollhardt, M. Malacria, C. Aubert, *J. Am. Chem. Soc.* **2006**, *128*, 8509–8520.

[111] H. G. Schuster-Woldan, F. Basolo, *J. Am. Chem. Soc.* **1966**, *88*, 1657–1663.

[112] K. Jonas, C. Krüger, *Angew. Chem.* **1980**, *92*, 513–531.

[113] K. Jonas, E. Deffense, D. Habermann, *Angew. Chem. Int. Ed.* **1983**, *22*, 716–717.

[114] R. B. King, P. M. Treichel, F. G. A. Stone, *J. Am. Chem. Soc.* **1961**, *83*, 3593–3597.

[115] T. Takahashi, H. Nemoto, Y. Kanda, J. Tsuji, Y. Fukazawa, T. Okajima, Y. Fujise, *Tetrahedron* **1987**, *43*, 5499–5520.

[116] C. Dale Poulter, P. L. Wiggins, T. L. Plummer, *J. Org. Chem.* **1981**, *46*, 1532–1538.

[117] E. Brenna, F. Distante, F. G. Gatti, G. Gatti, *Catal. Sci. Technol.* **2017**, 1497–1507.

[118] E. I. Negishi, D. Y. Kondakov, D. Choueiry, K. Kasai, T. Takahashi, *J. Am. Chem. Soc.* **1996**, *118*, 9577–9588.

[119] P. G. Bulger, M. G. Moloney, P. C. Trippier, *Synlett* **2003**, 1871–1873.

[120] Y. Hatanaka, T. Hiyama, *Tetrahedron Lett.* **1988**, *29*, 97–98.

[121] H. F. Sore, D. T. Blackwell, S. J. F. MacDonald, D. R. Spring, *Org. Lett.* **2010**, *12*, 2806–2809.

[122] Z. Gan, Y. Wu, L. Gao, X. Sun, J. Lei, Z. Song, L. Li, *Tetrahedron* **2012**, *68*, 6928–6934.

[123] C. K. G. Gerlinger, S. Krüger, T. Gaich, *Chem. Eur. J.* **2018**, *24*, 3994–3997.

[124] M. W. Tjepkema, T. Wong, P. D. Wilson, A. G. Fallis, *Can. J. Chem.* **1997**, 1542–1551.

[125] S. Woodward, *Chem. Soc. Rev.* **2000**, *29*, 393–401.

[126] X. X. Peng, Y. J. Deng, X. L. Yang, L. Zhang, W. Yu, B. Han, *Org. Lett.* **2014**, *16*, 4650–4653.

[127] H. Helmboldt, M. Hiersemann, *J. Org. Chem.* **2009**, *74*, 1698–1708.

[128] B. L. Quigley, R. H. Grubbs, *Chem. Sci.* **2014**, *5*, 501–506.

[129] K. W. C. Poon, S. E. House, G. B. Dudley, *Synlett* **2005**, 3142–3144.

[130] A. Brennführer, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2009**, *48*, 4114–4133.

[131] A. Schoenberg, I. Bartoletti, R. F. Heck, *J. Org. Chem.* **1974**, *39*, 3318–3326.

[132] N. F. K. Kaiser, A. Hallberg, M. Larhed, *J. Comb. Chem.* **2002**, *4*, 109–111.

[133] X. Wu, R. Rönn, T. Gossas, M. Larhed, *J. Org. Chem.* **2005**, *70*, 3094–3098.

[134] J. Albaneze-Walker, C. Bazaral, T. Leavey, P. G. Dormer, J. A. Murry, *Org. Lett.* **2004**, *6*, 2097–2100.

[135] J. K. Stille, P. K. Wong, *J. Org. Chem.* **1975**, *40*, 532–534.

[136] P. E. Garrou, R. F. Heck, *J. Am. Chem. Soc.* **1976**, *98*, 4115–4127.

[137] W. R. Moser, A. W. Wang, N. K. Kildahl, *J. Am. Chem. Soc.* **1988**, *110*, 2816–2820.

[138] A. G. Sergeev, A. Spannenberg, M. Beller, *J. Am. Chem. Soc.* **2008**, *130*, 15549–15563.

[139] K. Yamada, M. J. Lear, T. Yamaguchi, S. Yamashita, I. D. Gridnev, Y. Hayashi, M. Hirama, *Angew. Chem. Int. Ed.* **2014**, *53*, 13902–13906.

[140] M. Aoki, H. Kato, M. Sudoh, T. Tsukuda, M. Masubuchi, K. Kawasaki, *REMEDY FOR VIRAL DISEASE*, **2005**, EP 1 593 378 B1.

[141] A. Alexakis, M. Gardette, S. Colin, *Tetrahedron Lett.* **1988**, *29*, 2951–2954.

[142] N. Mallesha, S. Prahlada Rao, R. Suhas, D. Channe Gowda, *Tetrahedron Lett.* **2012**, *53*, 641–645.

[143] V. Bažant, M. Čapka, M. Černý, V. Chvalovský, K. Kochloefl, M. Kraus, J. Málek, *Tetrahedron Lett.* **1968**, *9*, 3303–3306.

[144] M. Besev, C. Brehm, A. Fürstner, *Collect. Czechoslov. Chem. Commun.* **2005**, *70*, 1696–1708.

[145] J. Frackenpohl, G. Bojack, R. Baltz, U. Bickers, M. Busch, J. Dittgen, J. Franke, J. Freigang, E. Grill, S. Gonzalez, et al., *European J. Org. Chem.* **2018**, 1416–1425.

[146] N. Miyaura, A. Suzuki, *J. Chem. Soc. Chem. Commun.* **1979**, 866–867.

[147] M. Saravanan, B. Satyanarayana, P. P. Reddy, *Synth. Commun.* **2013**, *43*, 2050–2056.

[148] I. Ryu, K. Matsumoto, Y. Kameyama, M. Ando, N. Kusumoto, A. Ogawa, N. Kambe, S. Murai, N. Sonoda, *J. Am. Chem. Soc.* **1993**, *115*, 12330–12339.

[149] I. Ryu, T. Aya, S. Otani, S. Murai, N. Sonoda, *J. Organomet. Chem.* **1987**, *321*, 279–290.

[150] S. T. Kabanyane, D. J. MacGee, *Can. J. Chem.* **1992**, *70*, 2758–2763.

[151] T. Ezawa, Y. Kawashima, T. Noguchi, S. Jung, N. Imai, *Tetrahedron Asym.* **2017**, *28*, 266–281.

[152] M. Hauer, Synthetic Studies towards Oxa-Farnesol Derivatives, Leibniz University of Hanover, **2021**.

[153] R. J. Anderson, V. L. Corbin, G. Cotterrell, G. R. Cox, C. A. Henrick, F. Schaub, J. B. Siddall, *J. Am. Chem. Soc.* **1975**, *97*, 1197–1204.

[154] T. Ohashi, Y. Miyazawa, S. Ishizaki, Y. Kurobayashi, T. Saito, *J. Agric. Food Chem.* **2019**, *67*, 7410–7415.

[155] H. S. Lin, L. A. Paquette, *Synth. Commun.* **1994**, *24*, 2503–2506.

[156] P. G. M. Wuts, *Synth. Commun.* **1981**, *11*, 139–140.

[157] C. M. Gampe, E. M. Carreira, *Chem. Eur. J.* **2012**, *18*, 15761–15771.

[158] C. C. Wang, W. D. Z. Li, *J. Org. Chem.* **2012**, *77*, 4217–4225.

[159] W.-D. Woggon, F. Ruther, H. Egli, *J. Chem. Soc., Chem. Commun.* **1980**, *346*, 706–708.

[160] A. Bouzide, G. Sauvé, *Synlett* **1997**, 1153–1154.

[161] W. C. Still, C. Gennari, *Tetrahedron Lett.* **1983**, *24*, 4405–4408.

[162] N. S. George, K. E. Anderson, A. G. M. Barrett, *European J. Org. Chem.* **2013**, 7604–7610.

[163] S. Inoue, K. Honda, N. Iwase, K. Sato, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1629–1635.

[164] F. Löbermann, L. Weisheit, D. Trauner, *Org. Lett.* **2013**, *15*, 4324–4326.

[165] S. Kikumasa, M. Osamu, I. Seiichi, K. Toru, F. Fumio, *Chem. Lett.* **1981**, *10*, 1711–1714.

[166] Y. Suhara, Y. Hirota, K. Nakagawa, M. Kamao, N. Tsugawa, T. Okano, *Bioorganic Med. Chem.* **2008**, *16*, 3108–3117.

[167] C. Patois, P. Savignac, E. About-Jaudet, N. Collignon, *Synth. Commun.* **1991**, *21*, 2391–2396.

[168] I. Janicki, P. Kiełbasiński, *Adv. Synth. Catal.* **2020**, *362*, 2552–2596.

[169] K. Ando, *J. Org. Chem.* **1997**, *62*, 1934–1939.

[170] J. Motoyoshiya, T. Kusaura, K. Kokin, S. I. Yokoya, Y. Takaguchi, S. Narita, H. Aoyama, *Tetrahedron* **2001**, *57*, 1715–1721.

[171] C. M. Oberhauser, Biotransformation von Farnesylpyrophosphat-Analoga durch Sesquiterpencyclasen, Gottfried Wilhelm Leibniz Universität Hannover, **2018**.

[172] V. Harms, Biotransformationen natürlicher und unnatürlicher Substrate zur Bildung von Terpenoiden mit olfaktorischen Eigenschaften, Gottfried Wilhelm Leibniz Universität Hannover, **2021**.

[173] W. K. W. Chou, I. Fanizza, T. Uchiyama, M. Komatsu, H. Ikeda, D. E. Cane, *J. Am. Chem. Soc.* **2010**, *132*, 8850–8851.

[174] C. Nakano, S. Horinouchi, Y. Ohnishi, *J. Biol. Chem.* **2011**, *286*, 27980–27987.

[175] X. Lin, D. E. Cane, *J. Am. Chem. Soc.* **2009**, *131*, 6332–6333.

[176] S. C. Wang, D. J. Tantillo, *Org. Lett.* **2008**, *10*, 4827–4830.

[177] D. J. Tantillo, *Chem. Soc. Rev.* **2010**, *39*, 2847–2854.

[178] Y. H. Shi, Z. Wang, Y. Shi, W. P. Deng, *Tetrahedron* **2012**, *68*, 3649–3653.

[179] J. Emsermann, T. Opatz, *European J. Org. Chem.* **2017**, *2017*, 3362–3372.

[180] R. K. Boeckman, J. M. Niziol, K. F. Biegasiewicz, *Org. Lett.* **2018**, *20*, 5062–5065.

[181] S. Nagasawa, Y. Sasano, Y. Iwabuchi, *Angew. Chem. Int. Ed.* **2016**, *55*, 13189–13194.

[182] K. Nacro, M. Baltas, L. Gorrichon, *Tetrahedron* **1999**, *55*, 14013–14030.

[183] F. Zhou, J. Zhu, Y. Zhang, S. Zhu, *Angew. Chem. Int. Ed.* **2018**, *57*, 4058–4062.

[184] N. Yoneda, Y. Fukata, K. Asano, S. Matsubara, *Angew. Chem. Int. Ed.* **2015**, *54*, 15497–15500.

[185] A. Erkkilä, P. M. Pihko, *J. Org. Chem.* **2006**, *71*, 2538–2541.

[186] N. M. Friedemann, A. Härter, S. Brandes, S. Groß, D. Gerlach, W. Münch, D. Schollmeyer, U. Nubbemeyer, *Euro. J. Org. Chem.* **2012**, 2346–2358.

[187] E. Capitò, L. Bernardi, M. Comes-Franchini, F. Fini, M. Fochi, S. Pollicino, A. Ricci, *Tetrahedron Asym.* **2005**, *16*, 3232–3240.

[188] B. Vaz, L. Otero, R. Álvarez, Á. R. de Lera, *Chem. Eur. J.* **2013**, *19*, 13065–13074.

[189] F. Kurosawa, T. Nakano, T. Soeta, K. Endo, Y. Ukaji, *J. Org. Chem.* **2015**, *80*, 5696–5703.

[190] T. Harada, K. Muramatsu, K. Mizunashi, C. Kitano, D. Imaoka, T. Fujiwara, H. Kataoka, *J. Org. Chem.* **2008**, *73*, 249–258.

[191] J. F. Rodríguez, K. I. Burton, I. Franzoni, D. A. Petrone, I. Scheipers, M. Lautens, *Org. Lett.* **2018**, *20*, 6915–6919.

[192] J. Gala de Pablo, D. R. Chisholm, A. Steffen, A. K. Nelson, C. Mahler, T. B. Marder, S. A. Peyman, J. M. Girkin, C. A. Ambler, A. Whiting, et al., *Analyst* **2018**, *143*, 6113–6120.

[193] J. Vader, H. Sengers, A. de Groot, *Tetrahedron* **1989**, *45*, 2131–2142.

[194] E. J. Miller, E. Jecs, V. M. Truax, B. M. Katzman, Y. A. Tahirovic, R. J. Wilson, K. M. Kuo, M. B. Kim, H. H. Nguyen, M. T. Saindane, et al., *J. Med. Chem.* **2018**, *61*, 946–979.

[195] P. H. S. Paioti, J. M. Ketcham, A. Aponick, *Org. Lett.* **2014**, *16*, 5320–5323.

[196] J. Pietruszka, A. Witt, *Syntehsis* **2006**, 4266–4268.

[197] T. K. Panda, M. T. Gamer, P. W. Roesky, *Organometallics* **2003**, *22*, 877–878.

[198] S. K. Bagal, R. M. Adlington, J. E. Baldwin, R. Marquez, *J. Org. Chem.* **2004**, *69*, 9100–9108.

[199] T. Isaka, M. Hasegawa, H. Toshima, *Biosci. Biotechnol. Biochem.* **2011**, *75*, 2213–2222.

[200] T. N. Van, N. De Kimpe, *Tetrahedron* **2000**, *56*, 7969–7973.

[201] C. Infante-Rodriguez, L. Domon, P. Breuilles, D. Uguen, *Bull. Chem. Soc. Jpn.* **2015**, *88*, 308–326.

[202] P. A. Allegretti, E. M. Ferreira, *Org. Lett.* **2011**, *13*, 5924–5927.

[203] G. Cai, W. Zhu, D. Ma, *Tetrahedron* **2006**, *62*, 5697–5708.

[204] F. Salvaggio, J. T. Hodgkinson, L. Carro, S. M. Geddis, W. R. J. D. Galloway, M. Welch, D. R. Spring, *Eur. J. Org. Chem.* **2016**, 434–437.

[205] H. Fujita, H. Terasaki, S. Kakuyama, K. Hioki, M. Kunishima, *Org. Lett.* **2019**, *21*, 3093–3097.

[206] A. El-Qisairi, P. M. Henry, *J. Organomet. Chem.* **2000**, *603*, 50–60.

[207] W. Fickett, H. K. Garner, H. J. Lucas, *J. Am. Chem. Soc.* **1951**, *73*, 5063–5067.

[208] B. Gaspar, E. M. Carreira, *Angew. Chem. Int. Ed.* **2008**, *47*, 5758–5760.

[209] M. S. Davey, R. Malde, R. C. Mykura, A. T. Baker, T. E. Taher, C. S. Le Duff, B. E. Willcox, Y. Mehellou, *J. Med. Chem.* **2018**, *61*, 2111–2117.

[210] D. Butler, N. Iwamoto, I. Zlatev, G. L. Verdine, M. Meena, N. Svrzikapa, *Preparation of Chiral Controlled Oligonucleotide via Sulfurization and Condensation Reactions*, **2014**,

WO2014/012081A2.

[211] W. J. Ramsay, N. A. W. Bell, Y. Qing, H. Bayley, *J. Am. Chem. Soc.* **2018**, *140*, 17538–17546.

[212] Y. T. Ma, Y. Yang, P. Cai, D. Y. Sun, P. A. Sánchez-Murcia, X. Y. Zhang, W. Q. Jia, L. Lei, M. Guo, F. Gago, et al., *J. Nat. Prod.* **2018**, *81*, 524–533.

[213] S. Levin, R. R. Nanl, S. E. Reisman, *Org. Lett.* **2010**, *12*, 780–783.

[214] D. J. Del Valle, M. J. Krische, *J. Am. Chem. Soc.* **2013**, *135*, 10986–10989.

[215] M. Kunishima, K. Hioki, K. Kono, A. Kato, S. Tani, *J. Org. Chem.* **1997**, *62*, 7542–7543.

[216] S. Amin, S. S. Hecht, D. Hoffmann, *J. Org. Chem.* **1981**, *46*, 2394–2398.

[217] D. R. Williams, P. K. Mondal, S. A. Bawel, P. P. Nag, *Org. Lett.* **2014**, *16*, 1956–1959.

[218] I. Larrosa, M. I. Da Silva, P. M. Gómez, P. Hannen, E. Ko, S. R. Lenger, S. R. Linke, A. J. P. White, D. Wilton, A. G. M. Barrett, *J. Am. Chem. Soc.* **2006**, *128*, 14042–14043.

[219] Y. Nagashima, K. Sasaki, T. Suto, T. Sato, N. Chida, *Chem. Asian J.* **2018**, *13*, 1024–1028.

[220] K. J. Temple, E. N. Wright, C. A. Fierke, R. A. Gibbs, *Bioorganic Med. Chem. Lett.* **2016**, *26*, 3499–3502.

[221] W. Tang, E. V. Prusov, *Angew. Chem. Int. Ed.* **2012**, *51*, 3401–3404.

[222] J. A. Bergman, K. Hahne, J. Song, C. A. Hrycyna, R. A. Gibbs, *ACS Med. Chem. Lett.* **2012**, *3*, 15–19.

[223] A. Pollex, M. Hiersemann, *Org. Lett.* **2005**, *7*, 5705–5708.

[224] B. Göricke, M. F. Bieber, K. E. Mohr, D. Menche, *Angew. Chem. Int. Ed.* **2019**, *58*, 13019–13023.

[225] H. Hassan, V. Pirenne, M. Wissing, C. Khiar, A. Hussain, F. Robert, Y. Landais, *Chem. Eur. J.* **2017**, *23*, 4651–4658.

[226] K. Matsumoto, M. Suyama, S. Fujita, T. Moriwaki, Y. Sato, Y. Aso, S. Muroshita, H. Matsuo, K. Monda, K. Okuda, et al., *Chem. Eur. J.* **2015**, *21*, 11590–11602.

[227] F. Glaus, K. H. Altmann, *Angew. Chem. Int. Ed.* **2012**, *51*, 3405–3409.

[228] T. O. Ronson, M. J. Burns, M. H. H. Voelkel, K. J. Evans, J. M. Lynam, R. J. K. Taylor, I. J. S. Fairlamb, *Chem. Eur. J.* **2015**, *21*, 18905–18909.

[229] K. Ohtsuki, K. Matsuo, T. Yoshikawa, C. Moriya, K. Tomita-Yokotani, K. Shishido, M. Shindo, *Org. Lett.* **2008**, *10*, 1247–1250.

[230] A. J. Serio-Duggan, E. J. J. Grabwoski, W. K. Russ, *Synthesis* **1980**, 573–575.

[231] D. M. Hodgson, K. C. Ying, I. Nuzzo, G. Freixas, K. K. Kulikiewicz, E. Cleator, J. M. Paris, *J. Am. Chem. Soc.* **2007**, *129*, 4456–4462.

[232] M. Szostak, M. Spain, D. J. Procter, *J. Org. Chem.* **2012**, *77*, 3049–3059.

[233] D. Brillon, P. Deslongchamps, *Can. J. Chem.* **1987**, *65*, 56–68.

[234] J. Vat, H. D. Doan, J. Chardigny, J. L. Sébédio, A. Grandgirard, *Chem. Phys. Lipids* **1994**, *74*, 185–193.

[235] L. K. C. De La Cruz, S. L. Benoit, Z. Pan, B. Yu, R. J. Maier, X. Ji, B. Wang, *Org. Lett.* **2018**, *20*, 897–900.

[236] L. E. Overman, M. D. Rosen, *Tetrahedron* **2010**, *66*, 6514–6525.

[237] G. Reginato, A. Capperucci, A. Degl'Innocenti, A. Mordini, S. Pecchi, *Tetrahedron* **1995**, *51*, 2129–2136.

[238] R. Mello, J. Martínez-Ferrer, A. Alcalde-Aragonés, T. Varea, R. Acerete, M. E. González-Núñez, G. Asensio, *J. Org. Chem.* **2011**, *76*, 10129–10139.

[239] V. Druais, M. J. Hall, C. Corsi, S. V. Wendeborn, C. Meyer, J. Cossy, *Org. Lett.* **2009**, *11*, 935–938.

[240] T. Ishikawa, T. Mizuta, K. Hagiwara, T. Aikawa, T. Kudo, S. Saito, *J. Org. Chem.* **2003**, *68*, 3702–3705.

[241] S. M. Sparks, A. J. Gutierrez, K. J. Shea, *J. Org. Chem.* **2003**, *68*, 5274–5285.

[242] G. Malik, R. A. Swyka, V. K. Tiwari, X. Fei, G. A. Applegate, D. B. Berkowitz, *Chem. Sci.* **2017**, *8*, 8050–8060.

[243] R. E. Maleczka, B. Ghosh, W. P. Gallagher, A. J. Baker, J. A. Muchnij, A. L. Szymanski, *Tetrahedron* **2013**, *69*, 4000–4008.

[244] N. Esumi, K. Suzuki, Y. Nishimoto, M. Yasuda, *Org. Lett.* **2016**, *18*, 5704–5707.

[245] S. T. Heller, R. Sarpong, *Org. Lett.* **2010**, *12*, 4572–4575.

[246] A. Fadel, J. Salaun, *Tetrahedron* **1985**, *41*, 1267–1275.

[247] A. B. Charette, A. Beauchemin, in *Org. React.*, Wiley-VCH, **2001**, pp. 1–415.

[248] R. N. Bell, in *Inorg. Synth.*, Audrieth, Ludwig, F., **1950**, pp. 98–101.

[249] M. Michalak, K. Michalak, Z. Urbanczyk-Lipkowska, J. Wicha, *J. Org. Chem.* **2011**, *76*, 7497–7509.

[250] O. Zhurakovskyi, R. M. P. Dias, A. Noble, V. K. Aggarwal, *Org. Lett.* **2018**, *20*, 3136–3139.

[251] A. Vattekkatte, N. Gatto, E. Schulze, W. Brandt, W. Boland, *Org. Biomol. Chem.* **2015**, *13*, 4776–4784.

[252] P. V. Fish, *Synth. Commun.* **1996**, *26*, 433–444.

[253] A. J. Poss, R. K. Belter, *J. Org. Chem.* **1987**, *52*, 4810–4812.

[254] J. C. Meyer, Synthese und Konformationsanalysen und biologische Bewertung von neuen desmethylierten Carolacton-Derivaten, Leibniz Universität Hannover, **2020**.

[255] J. Schießl, J. Schulmeister, A. Doppiu, E. Wörner, M. Rudolph, R. Karch, A. S. K. Hashmi, *Adv. Synth. Catal.* **2018**, *360*, 2493–2502.

[256] T. Fukuzaki, S. Kobayashi, T. Hibi, Y. Ikuma, J. Ishihara, N. Kanoh, A. Murai, *Org. Lett.*

2002, *4*, 2877–2880.

[257] S. Sano, E. Kujime, Y. Takemoto, M. Shiro, Y. Nagao, *Chem. Pharm. Bull.* **2005**, *53*, 131–134.

[258] S. Sano, T. Matsumoto, M. Toguchi, M. Nakao, *Synlett* **2018**, 1461–1464.

[259] J. M. Álvarez-Calero, Z. D. Jorge, G. M. Massanet, *Org. Lett.* **2016**, *18*, 6344–6347.

[260] M. Uyanik, K. Ishihara, H. Yamamoto, *Org. Lett.* **2006**, *8*, 5649–5652.

[261] K. Mori, Y. Nakazono, *Liebigs Ann. Chem.* **1988**, 167–174.

[262] S. Zhu, N. Niljianskul, S. L. Buchwald, *Nat. Chem.* **2016**, *8*, 144–150.

[263] F. L. Wu, B. P. Ross, R. P. McGeary, *European J. Org. Chem.* **2010**, 1989–1998.

[264] J. F. Zhao, T. P. Loh, *Angew. Chem. Int. Ed.* **2009**, *48*, 7232–7235.

[265] J. Rinkel, P. Rabe, P. Garbeva, J. S. Dickschat, *Angew. Chem. Int. Ed.* **2016**, *55*, 13593–13596.

[266] K. S. Kumar, C. S. Reddy, *Org. Biomol. Chem.* **2012**, *10*, 2647–2655.

[267] S. Sommer, M. Kühn, H. Waldmann, *Adv. Synth. Catal.* **2008**, *350*, 1736–1750.

[268] D. J. Miller, F. Yu, D. W. Knight, R. K. Allemann, *Org. Biomol. Chem.* **2009**, *7*, 962–975.

[269] A. Gromov, Studies towards the Total Synthesis of Branimycin, Universität Wien, **2009**.

[270] M. B. Reardon, M. Xu, Q. Tan, P. G. Baumgartel, D. J. Augur, S. Huo, C. E. Jakobsche, *J. Org. Chem.* **2016**, *81*, 10964–10974.

[271] I. J. S. Fairlamb, J. M. Dickinson, R. O'Connor, L. H. Cohen, C. F. Van Thiel, *Bioorg. Chem.* **2003**, *31*, 80–97.

[272] S. A. Snyder, E. J. Corey, *J. Am. Chem. Soc.* **2006**, *128*, 740–742.

[273] S. Rivière, C. Vielmuth, C. Ennenbach, A. Abdelrahman, C. Lemke, M. Gütschow, C. E. Müller, D. Menche, *ChemMedChem* **2020**, *15*, 1348–1363.

[274] G. W. Gokel, D. J. Cram, C. L. Liotta, H. P. Harris, F. L. Cook, *Org. Synth.* **1977**, *57*, 30.

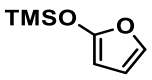
[275] J. P. Malerich, D. Trauner, *J. Am. Chem. Soc.* **2003**, *125*, 9554–9555.

[276] W. Dai, J. Zheng, X. Yan, W. Tang, L. Hu, Y. Zhang, *Synlett* **2021**, 1469–1472.

[277] E. O. Nwoye, G. B. Dudley, *Chem. Commun.* **2007**, 1436–1437.

10 Supplement

10.1 Total Synthesis NMR-Spectra



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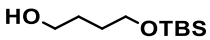

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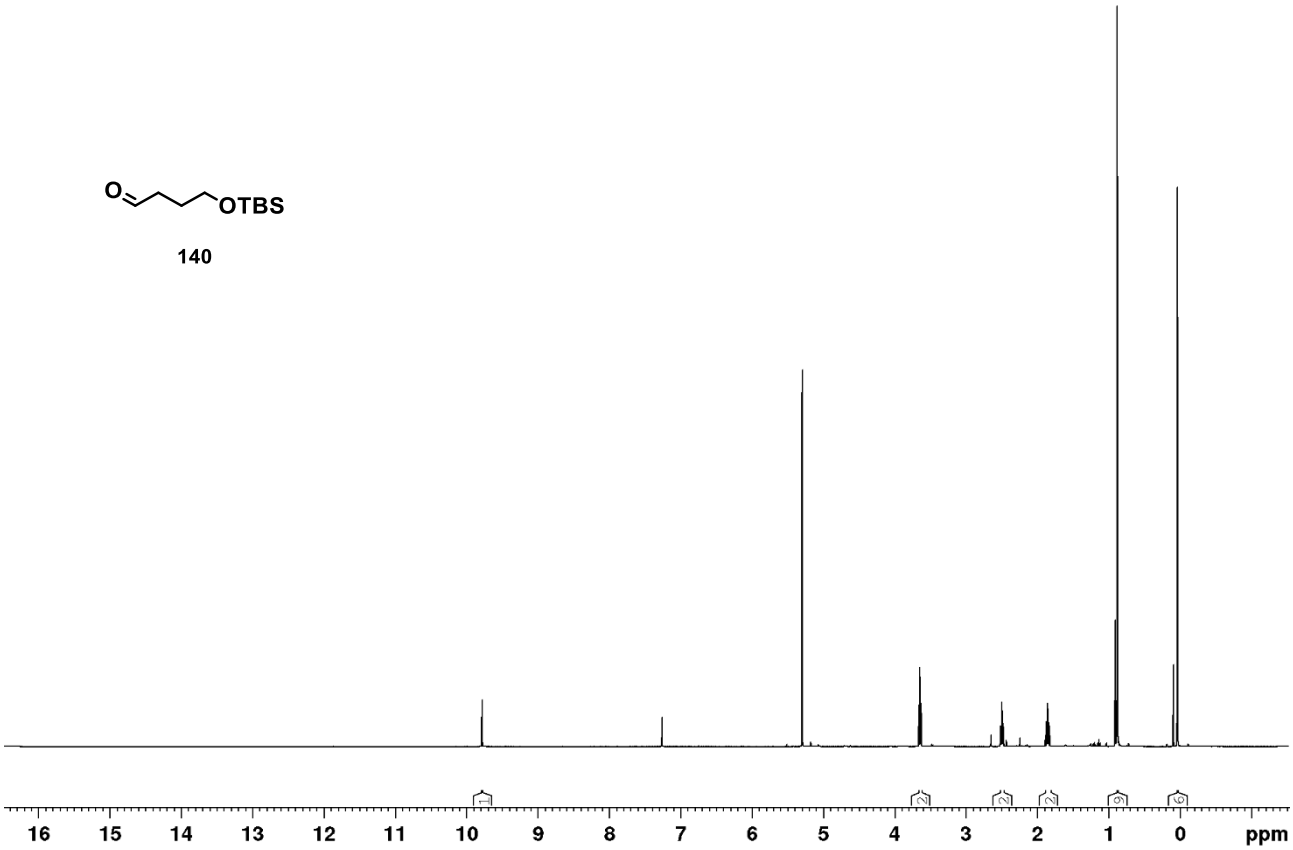
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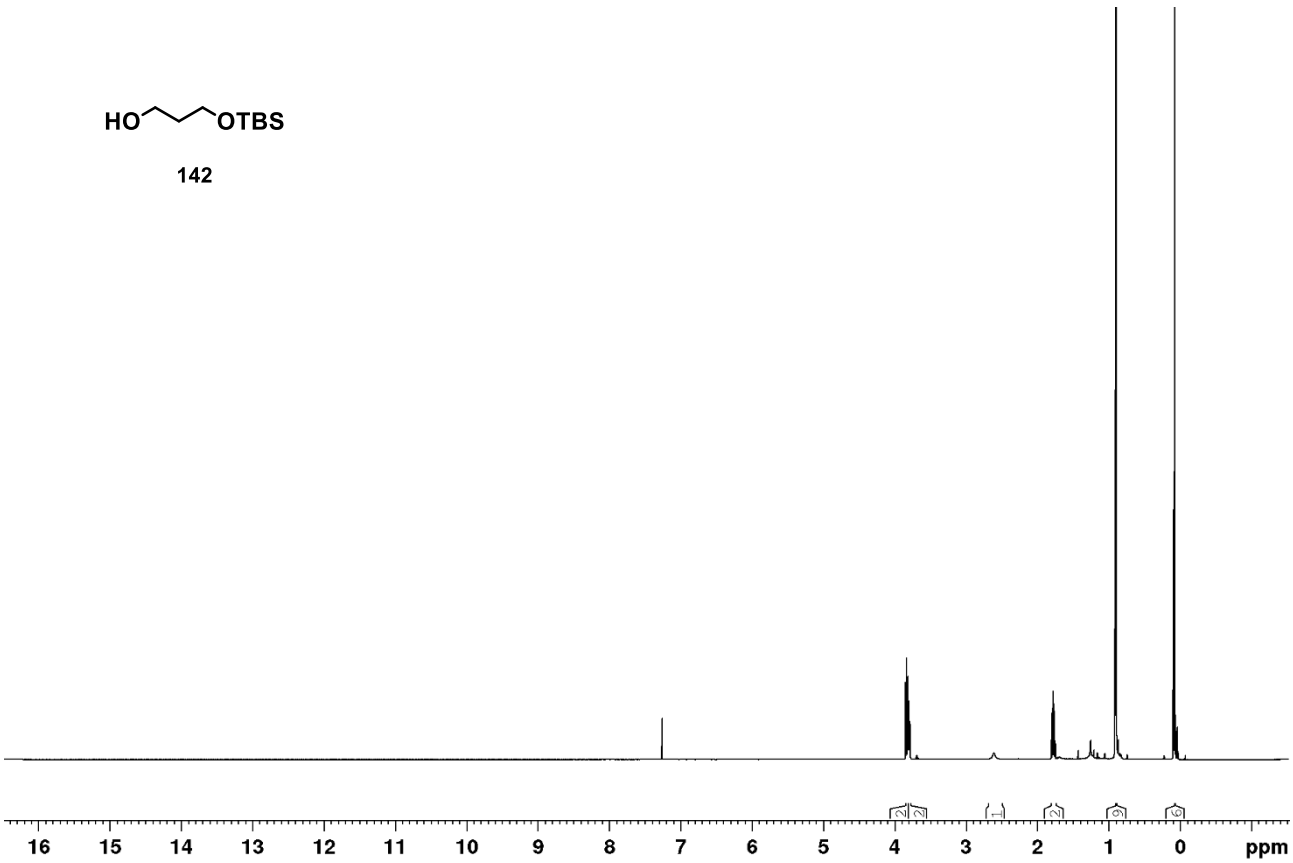
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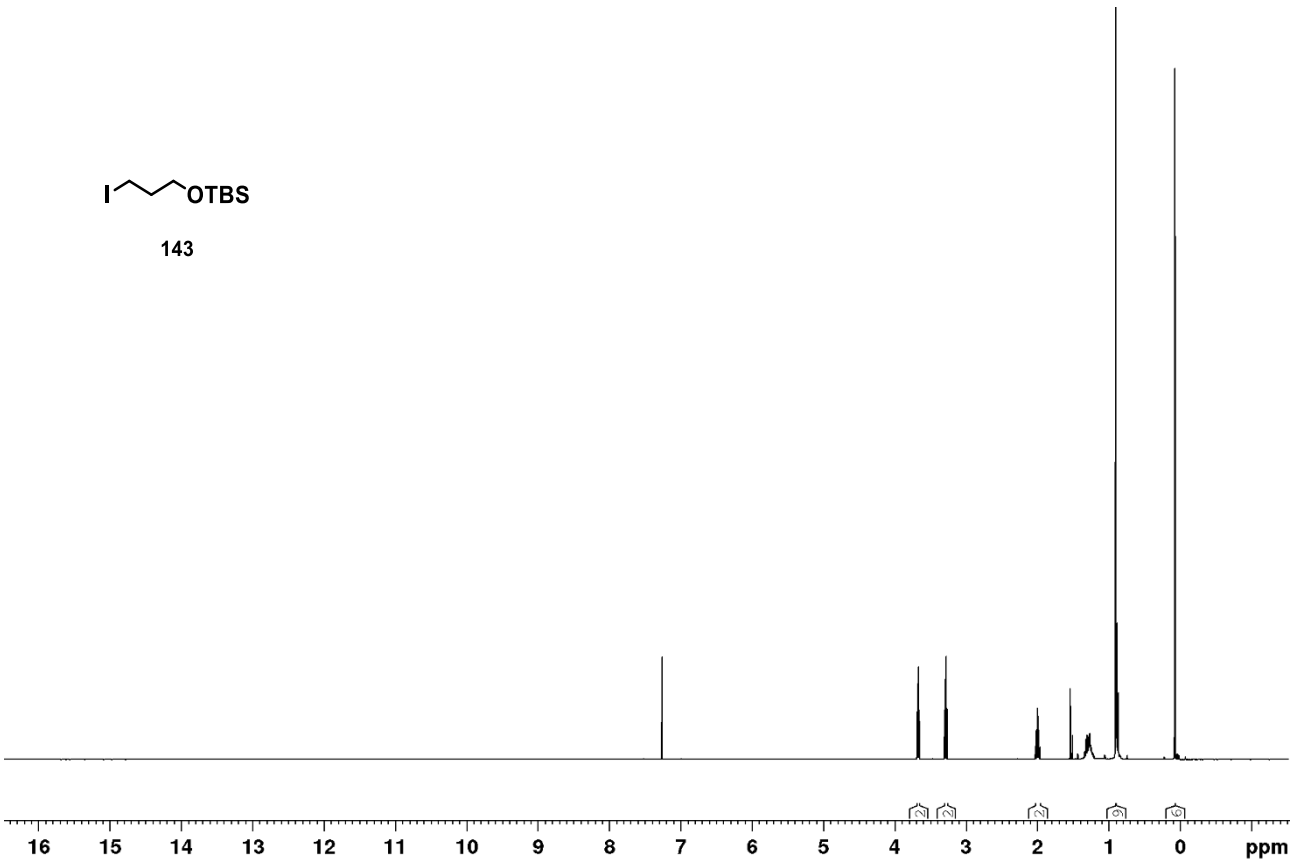
I
OTBS
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13
12
11
10
9
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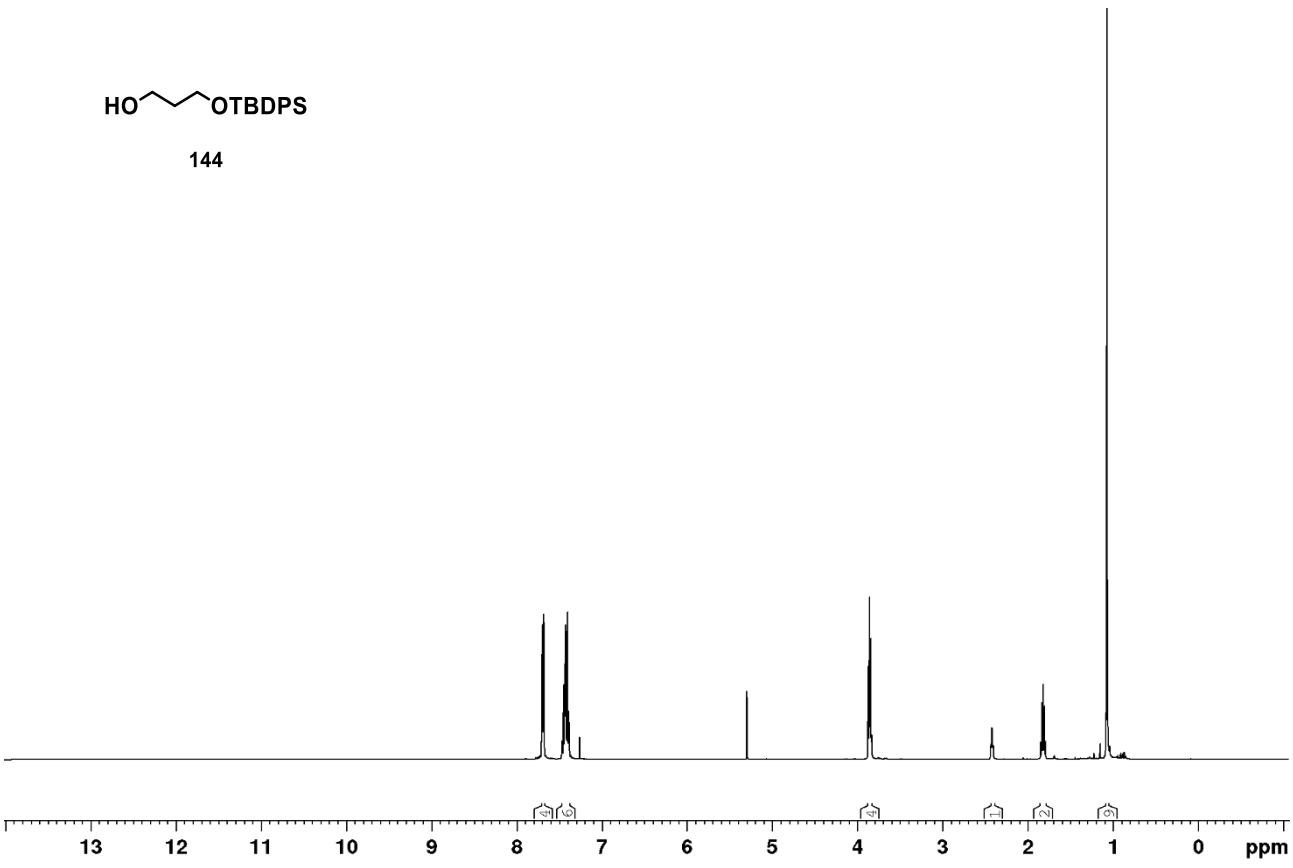
6
5
4
3
2
1
0
ppm

143


HO
OTBDPS
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12
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8
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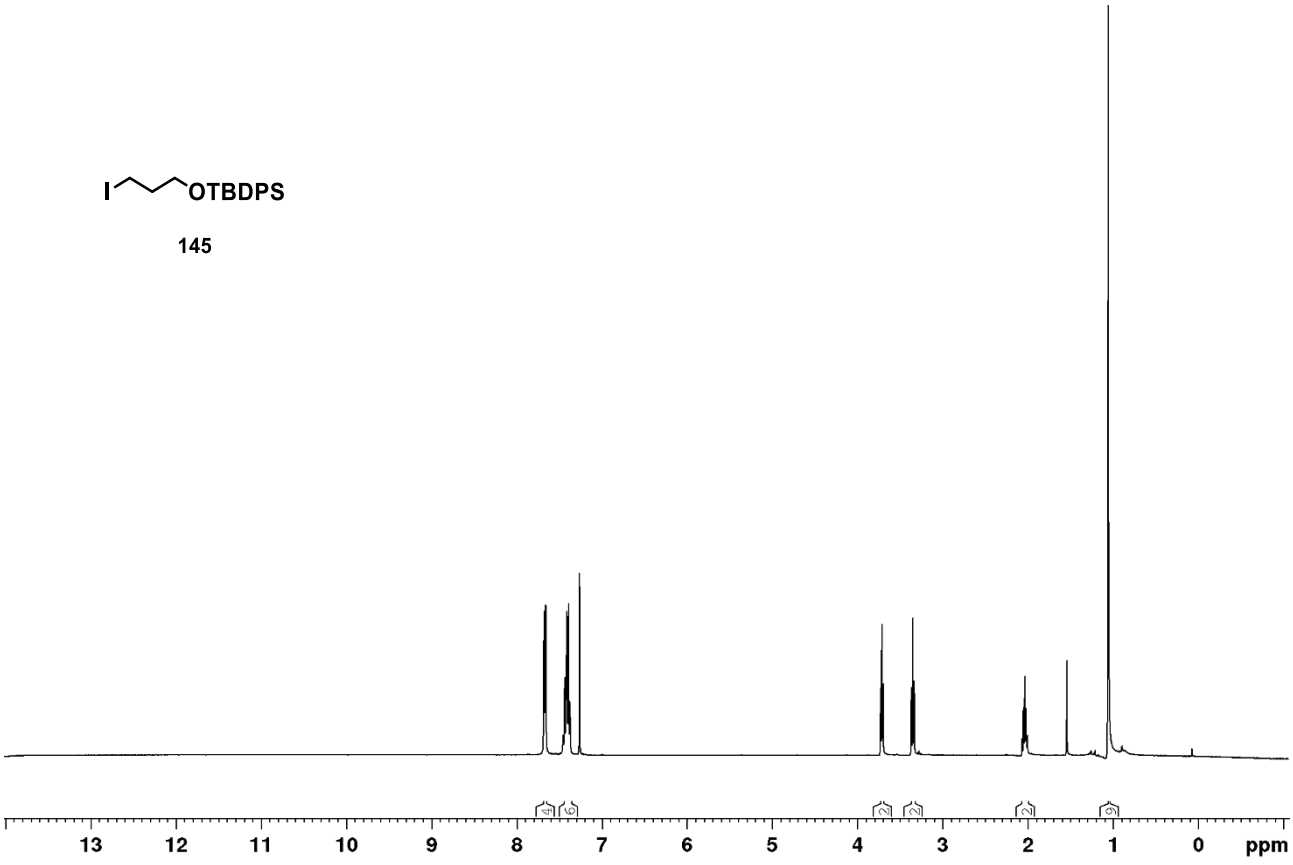
6
5
4
3
2
1
0
ppm

144


I
OTBDPS
145
13
12
11
10
9
8
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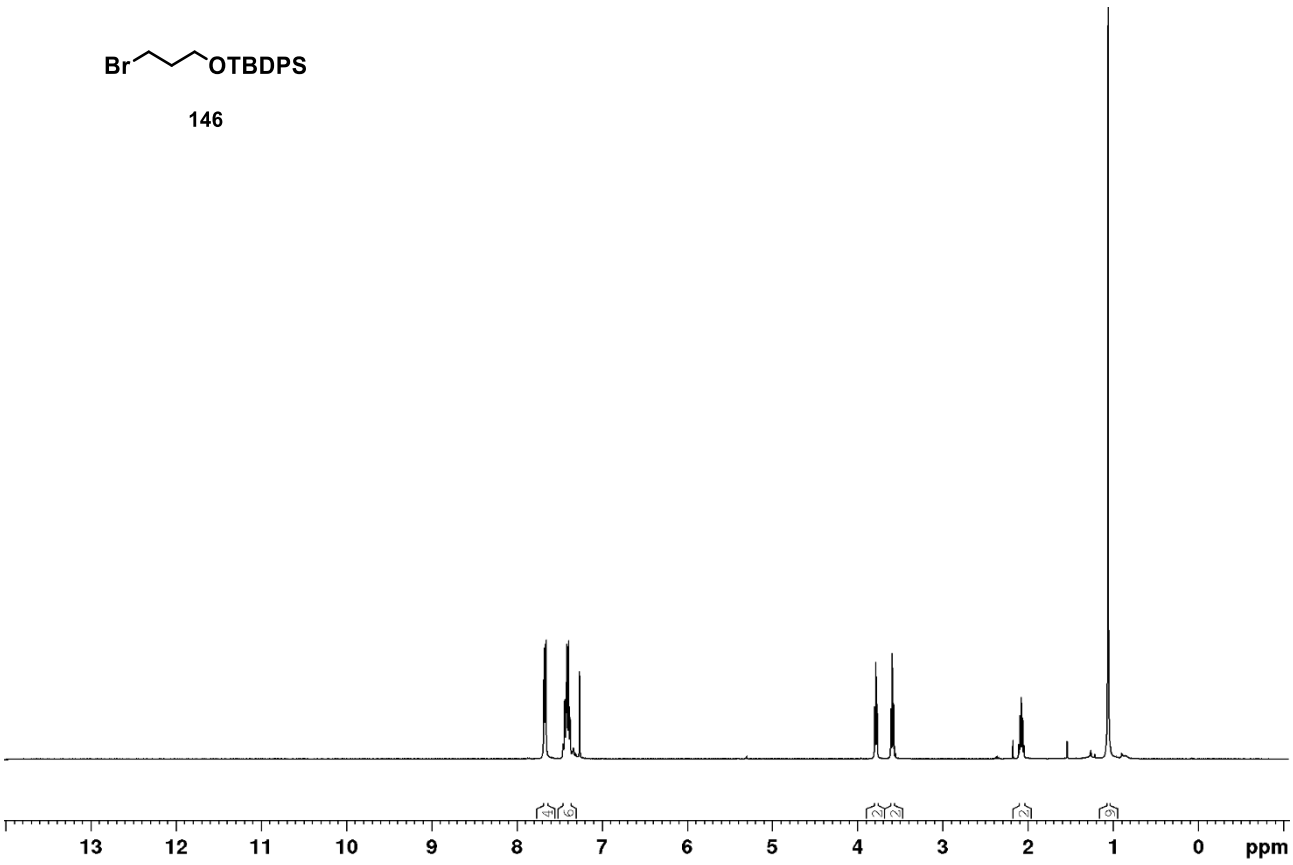
6
5
4
3
2
1
0
ppm


Br
OTBDPS
146
13
12
11
10
9
8
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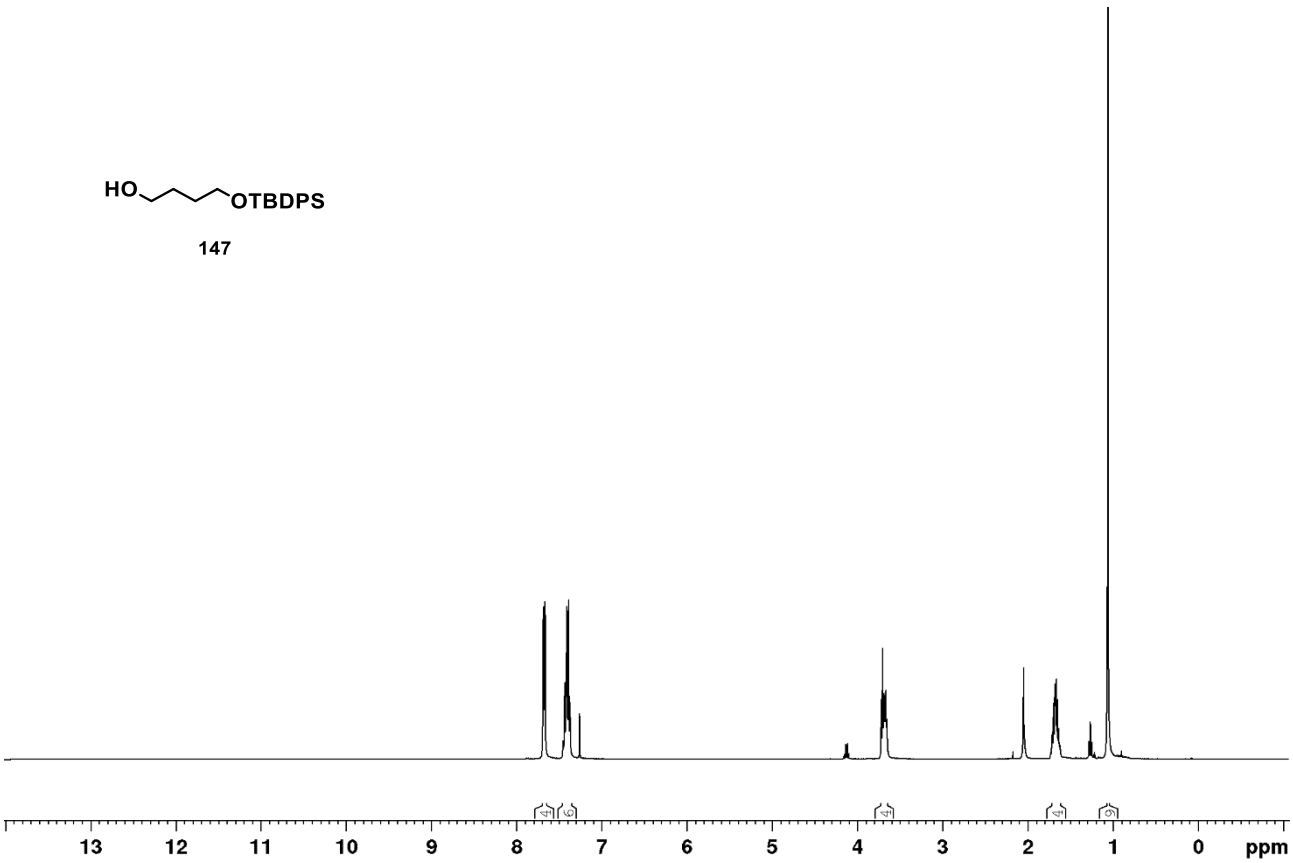
6
5
4
3
2
1
0
ppm


HO
OTBDPS
147
13
12
11
10
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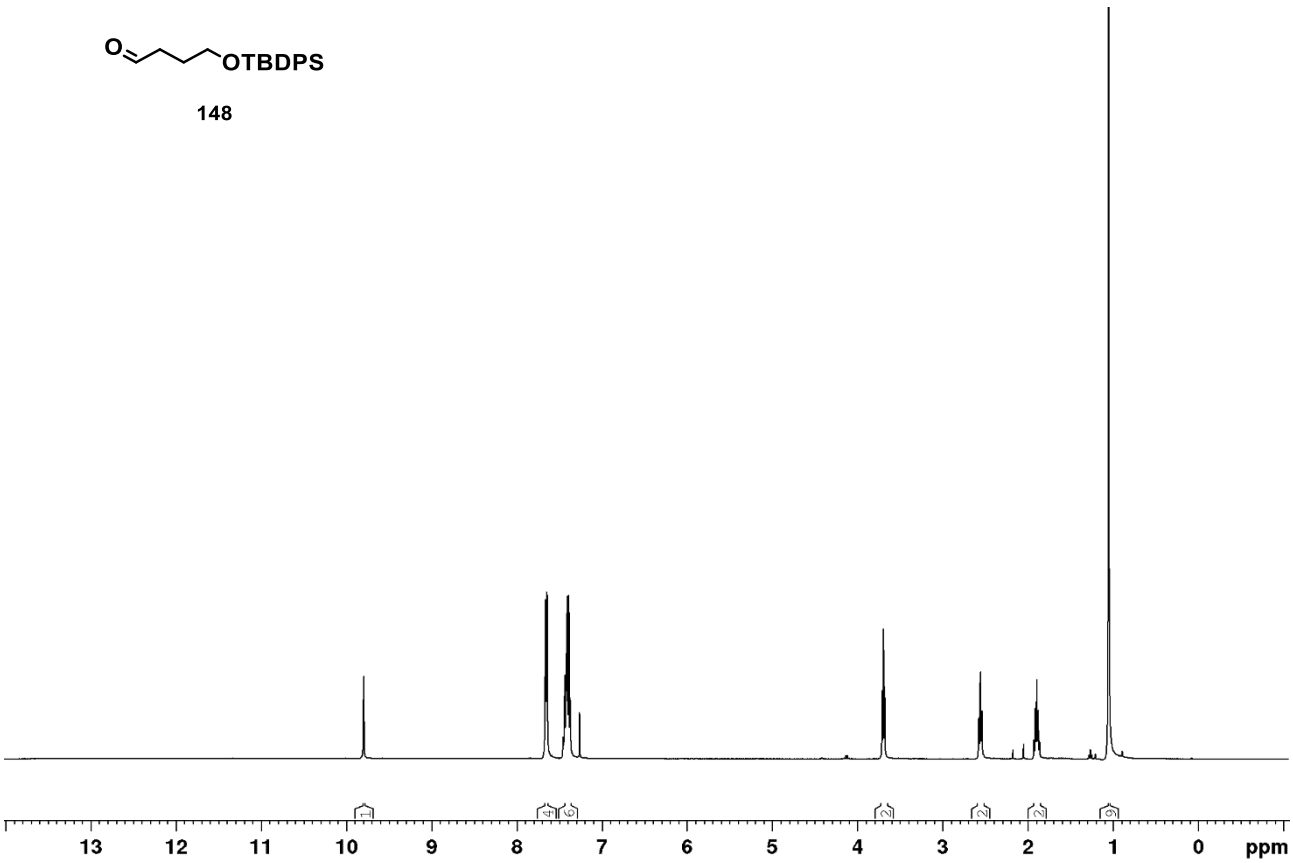
7
6
5
4
3
2
1
0
ppm


O
OTBDPS
148
13
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6
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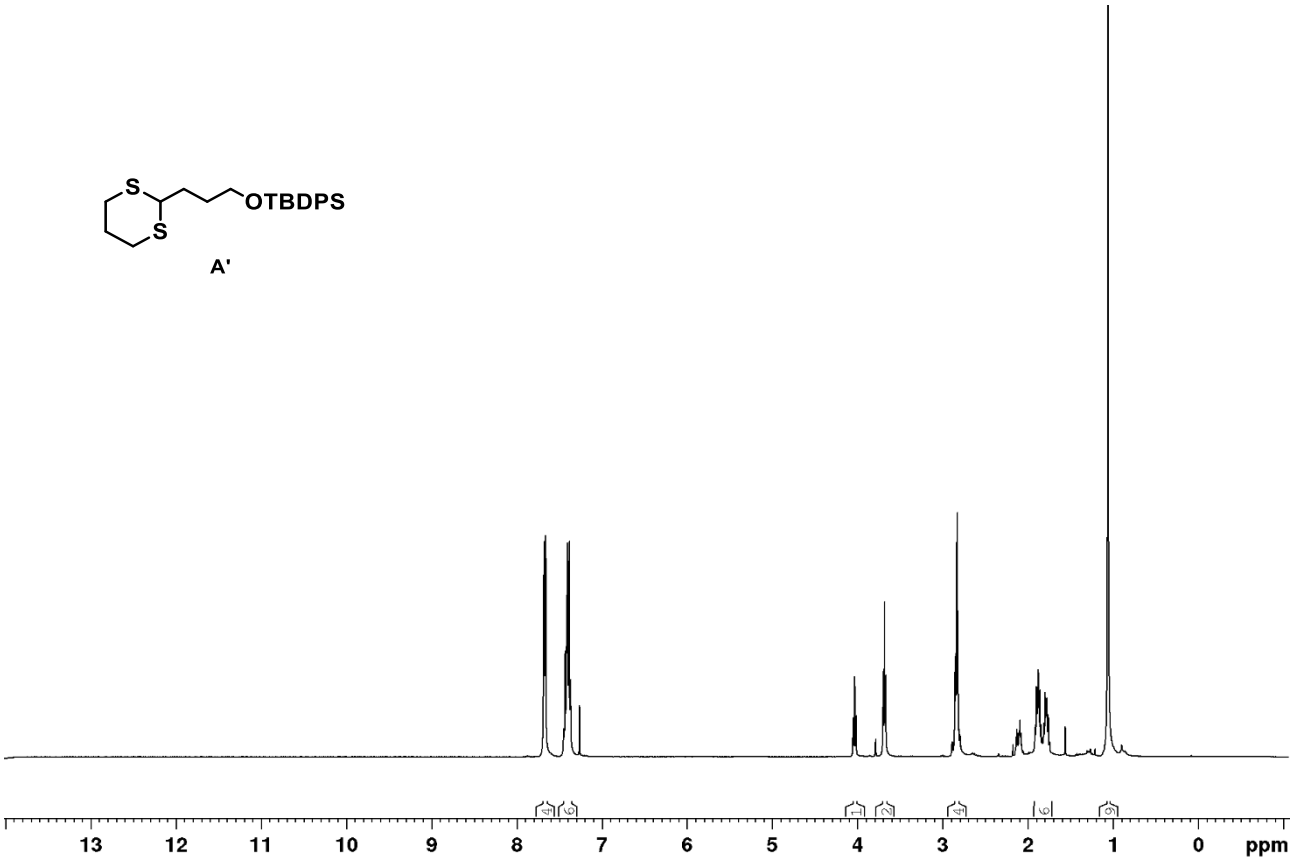
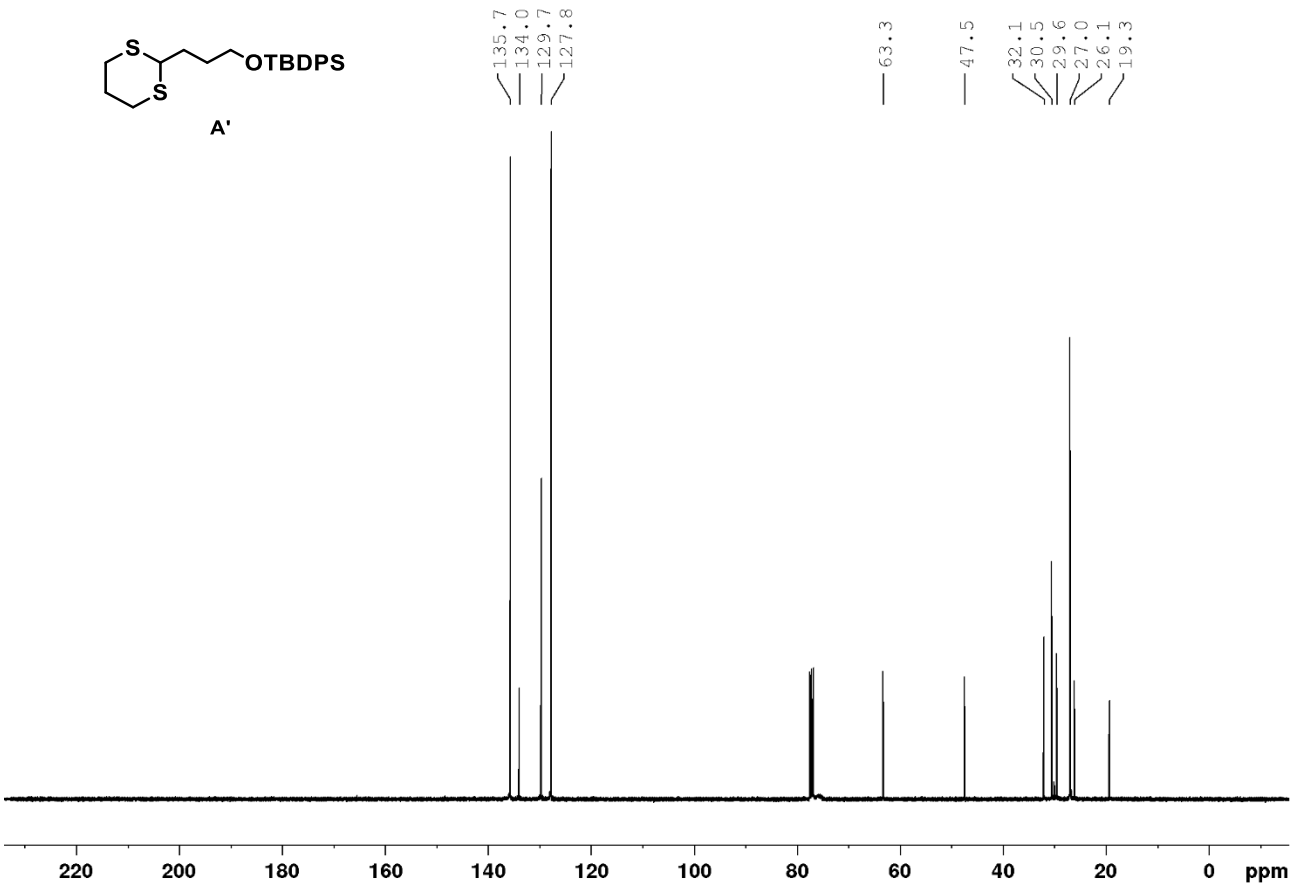
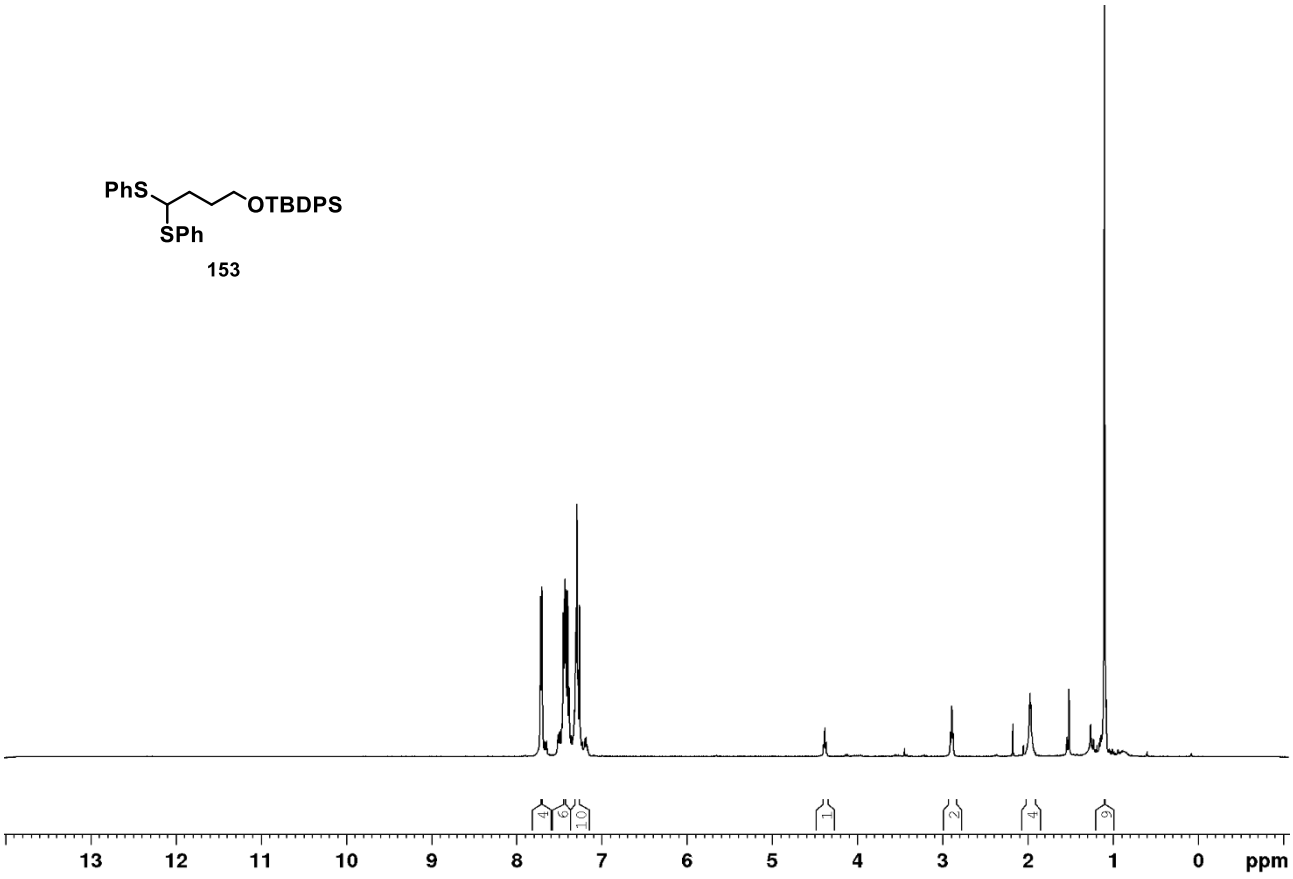
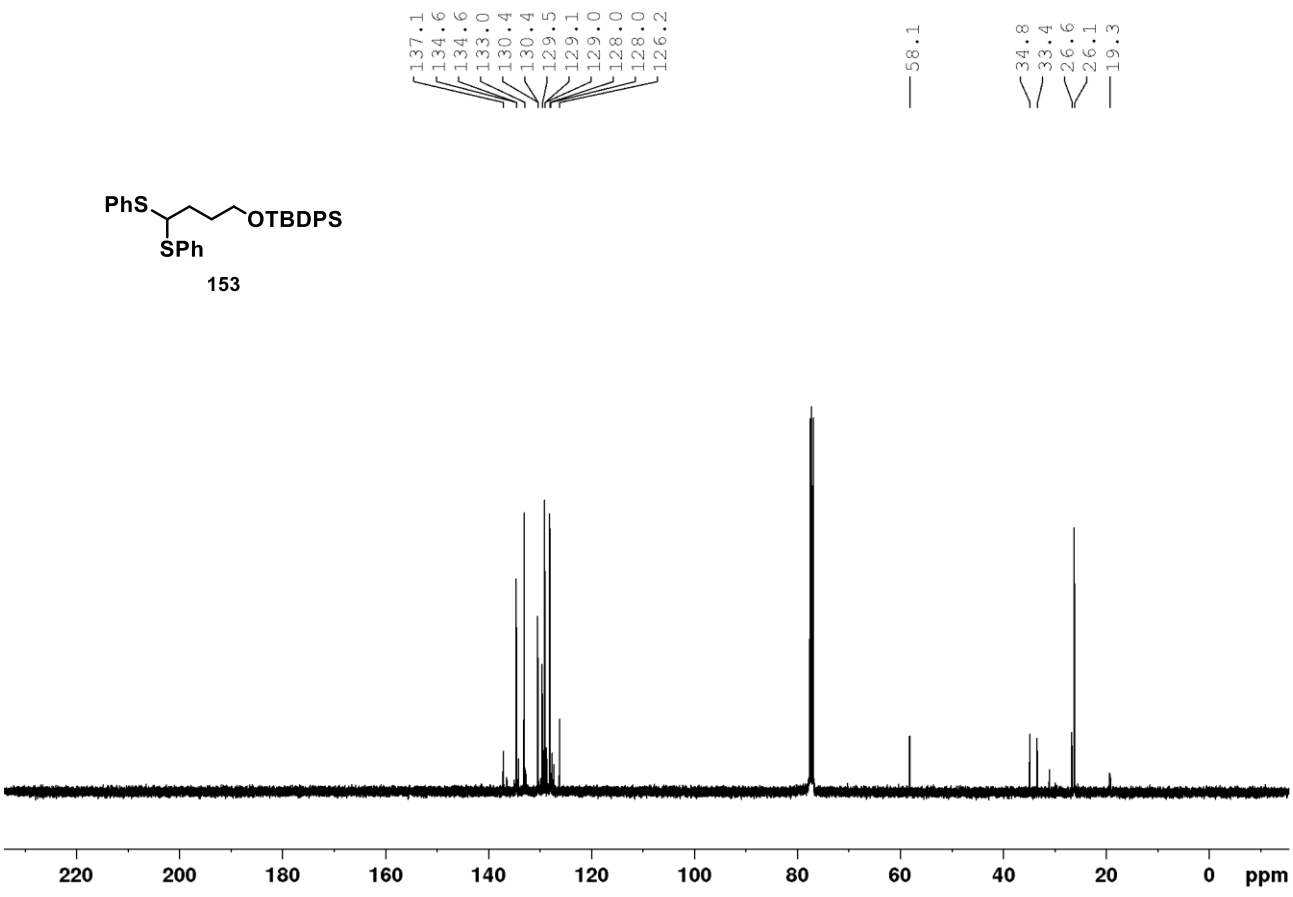
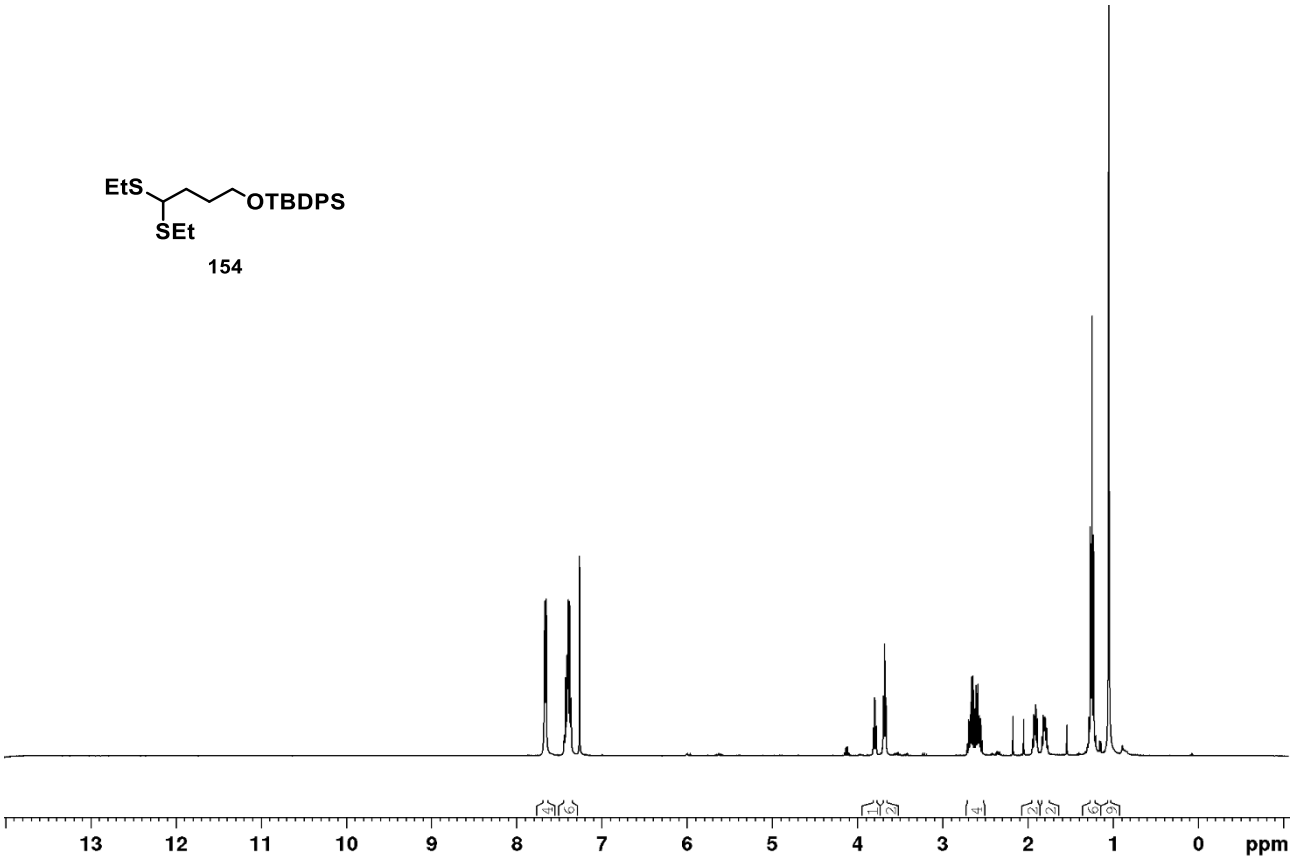
4
3
2
1
0
ppm

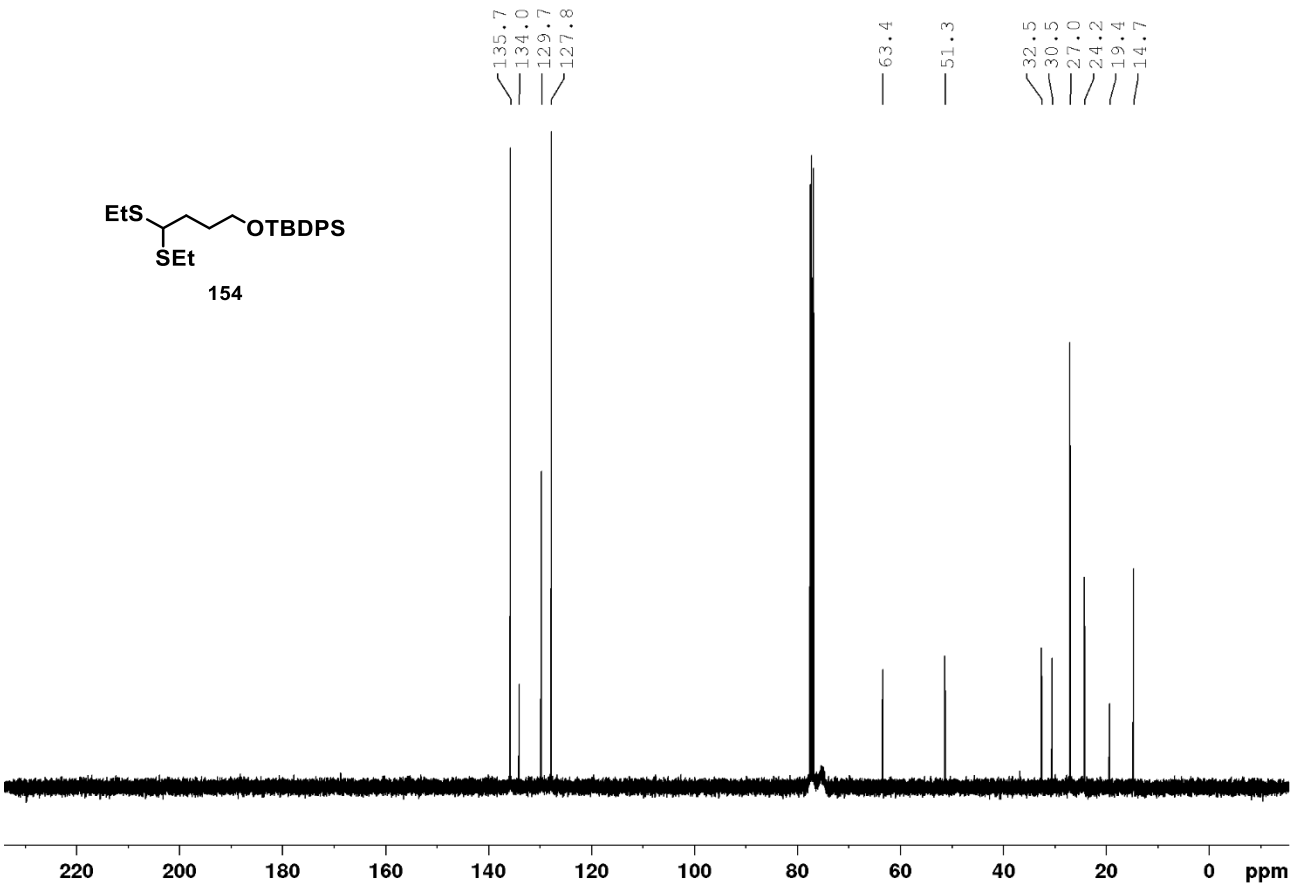

S
S
OTBDPS
A'
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

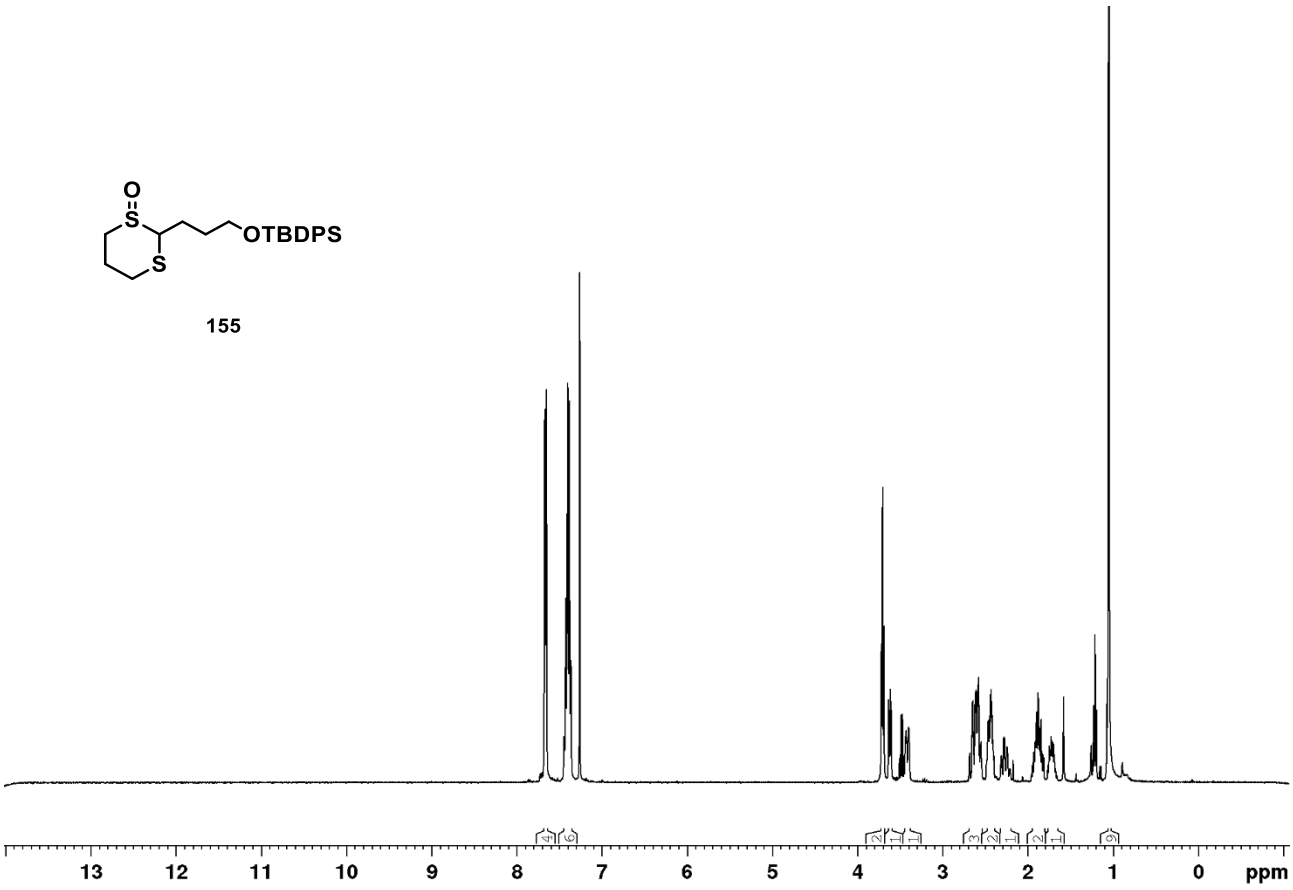

S
S
OTBDPS
A'
135.7
134.0
129.7
127.8
63.3
47.5
32.1
30.5
29.6
27.0
26.1
19.3
220
200
180
160
140
120
100
80
60
40
20
0
ppm

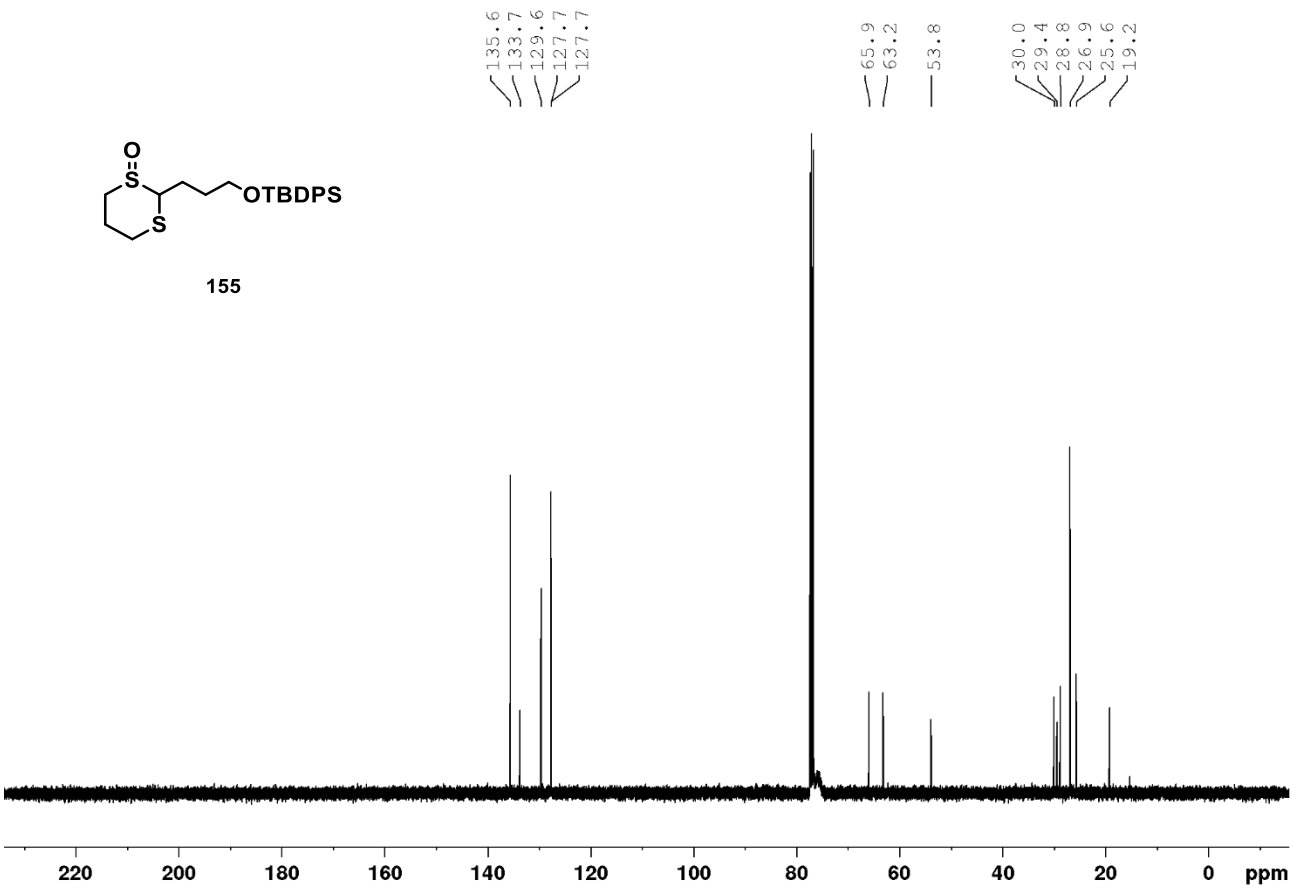

PhS
OTBDPS
SPh
153
4
6
10
1
2
4
9
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

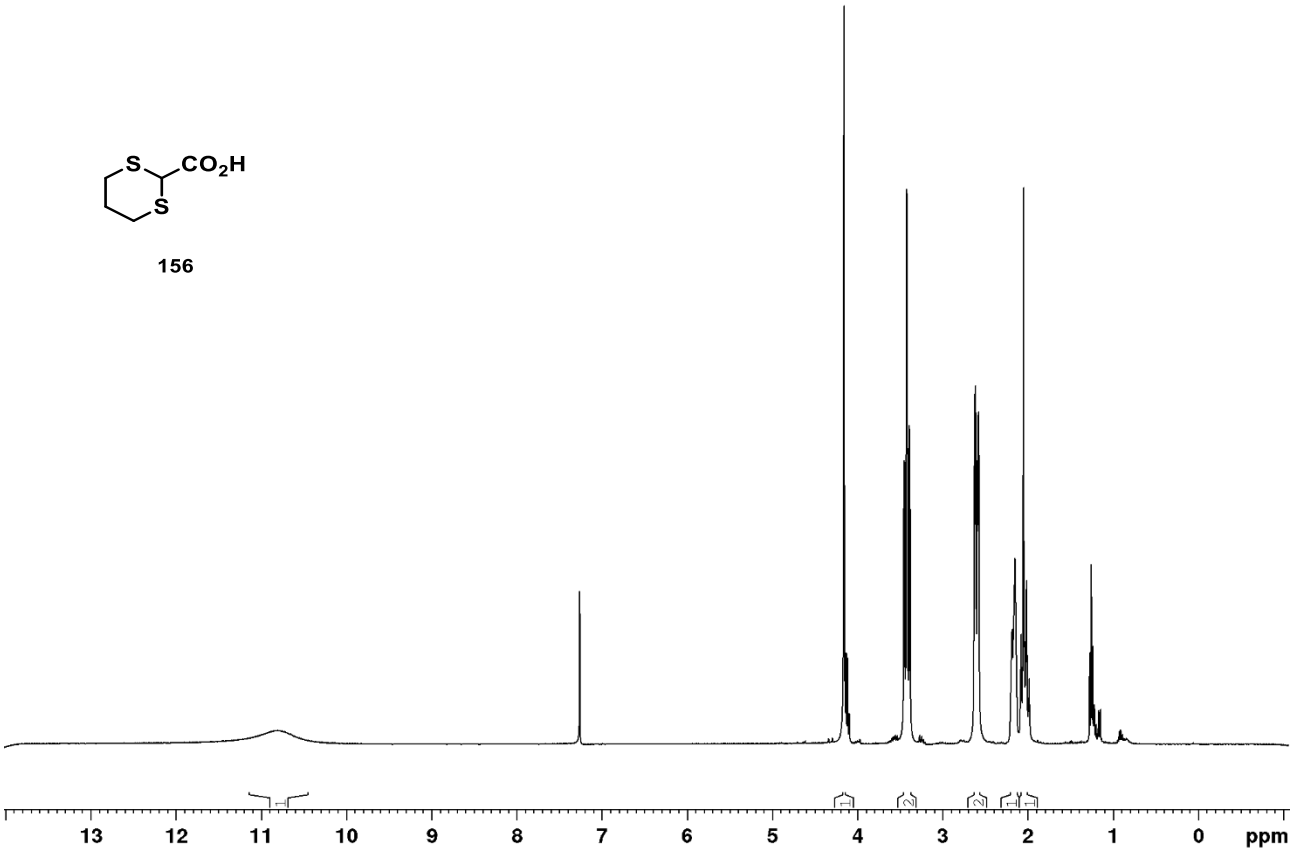

137.1
134.6
134.6
133.0
130.4
130.4
129.5
129.1
129.0
128.0
128.0
126.2
58.1
34.8
33.4
26.6
26.1
19.3
PhS
OTBDPS
SPh
153
220
200
180
160
140
120
100
80
60
40
20
0
ppm

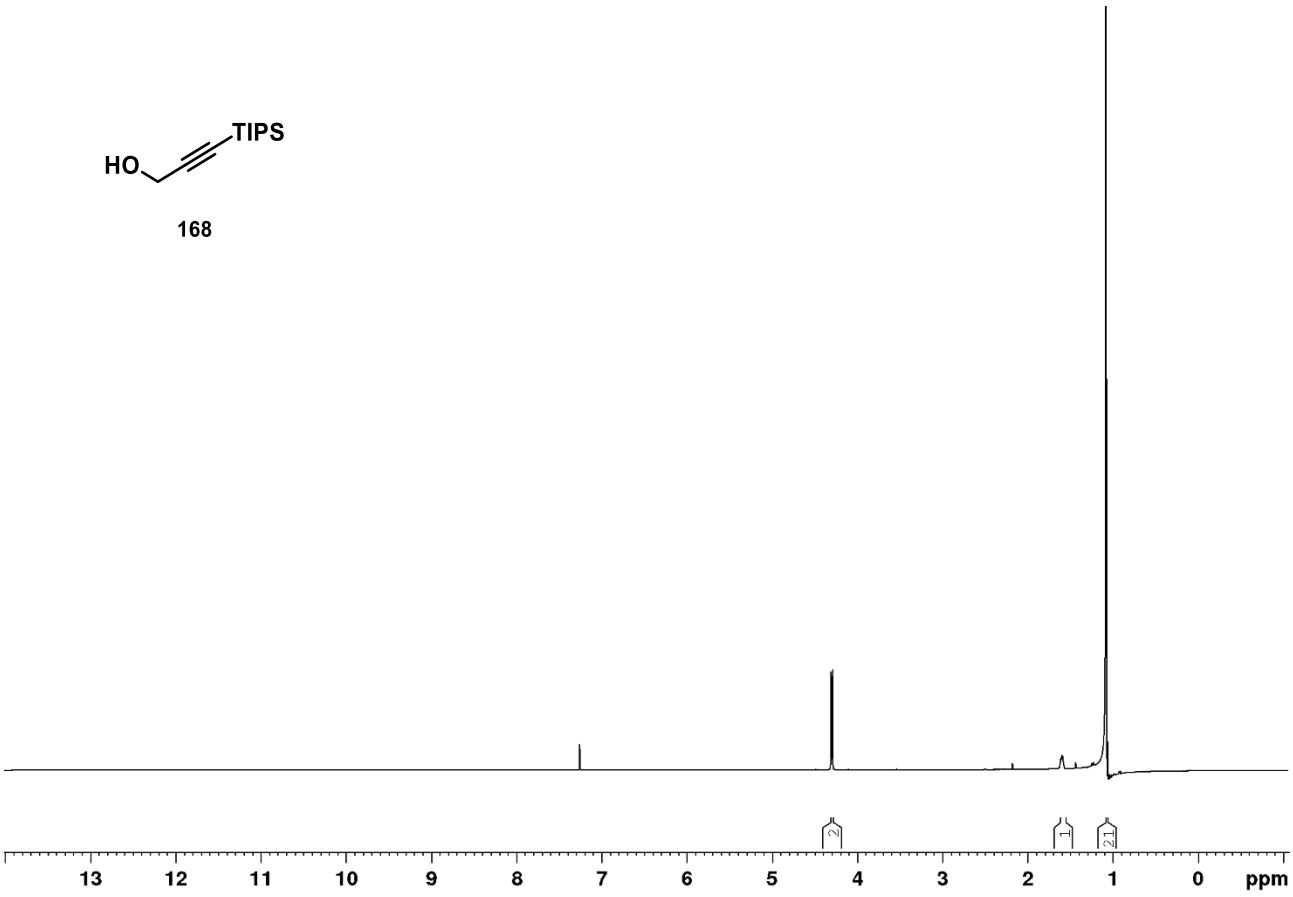

EtS
OTBDPS
SEt
154
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

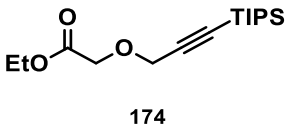

135.7
134.0
129.7
127.8
63.4
51.3
32.5
30.5
27.0
24.2
19.4
14.7
EtS
OTBDPS
SEt
154
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
S
S
OTBDPS
155
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


135.6
133.7
129.6
127.7
127.7
65.9
63.2
53.8
30.0
29.4
28.8
26.9
25.6
19.2
O
S
S
OTBDPS
155
220
200
180
160
140
120
100
80
60
40
20
0
ppm

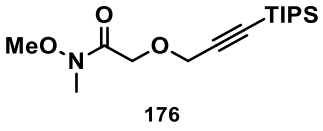

S
CO2H
S
156
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


TIPS
HO
168
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


O
EtO
O
TIPS

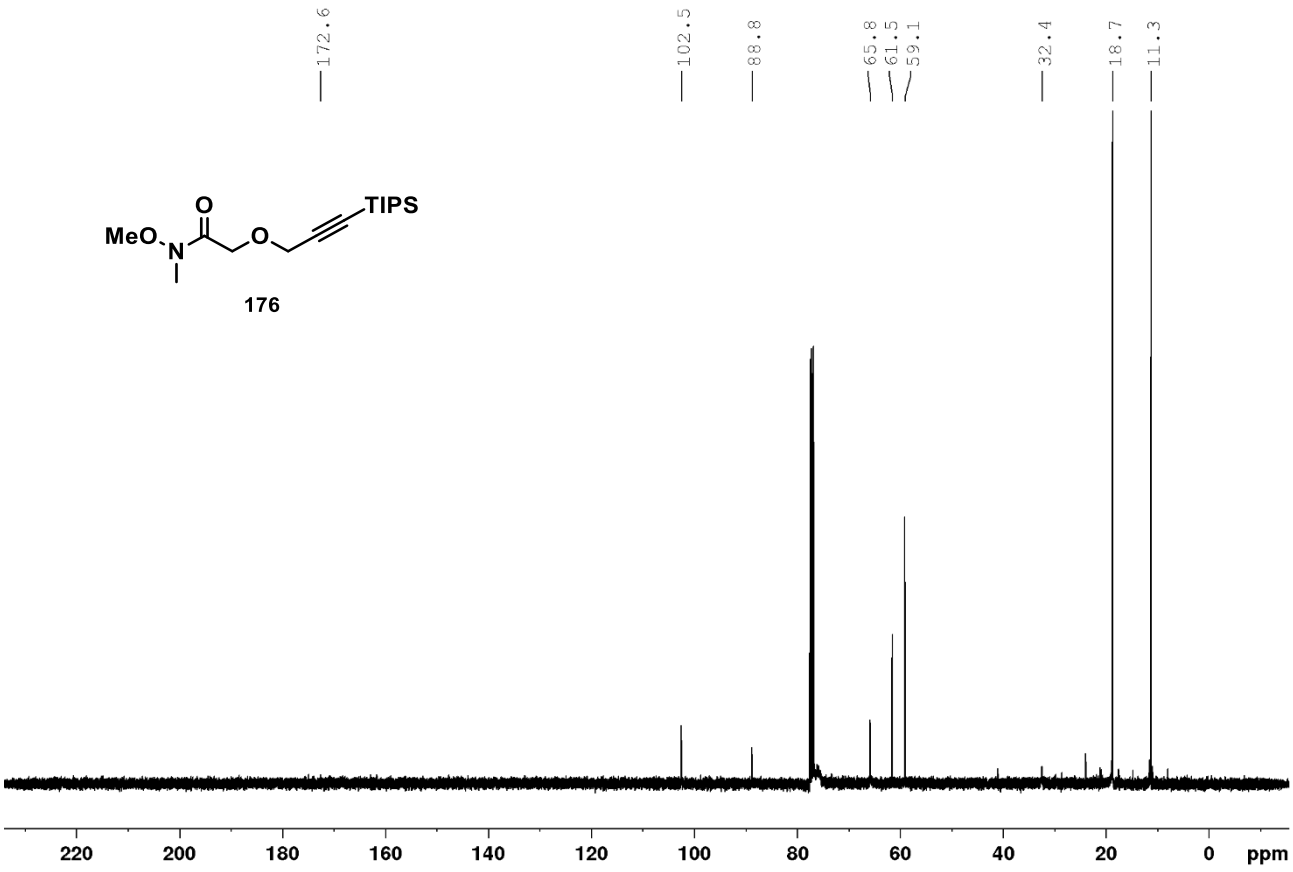
174

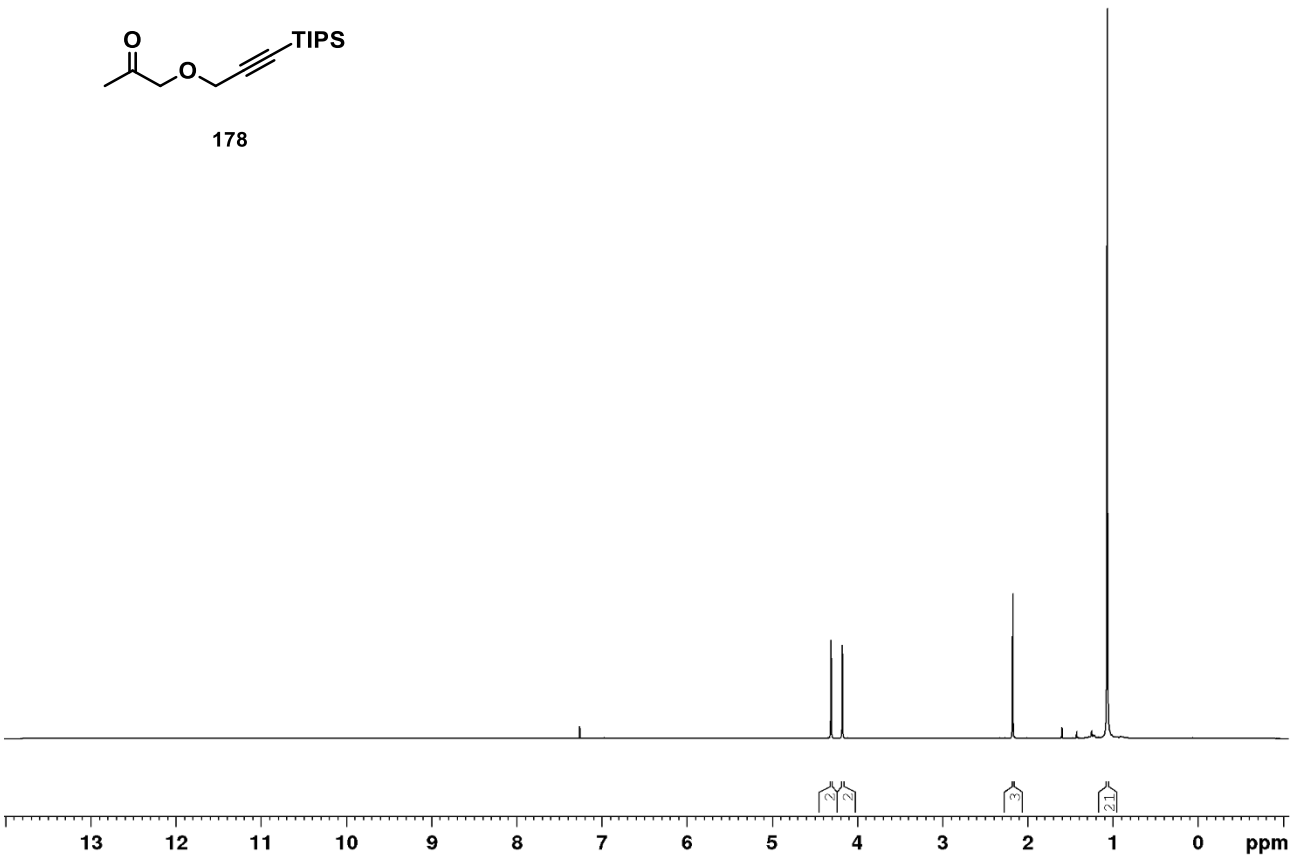
2
4
3
21
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

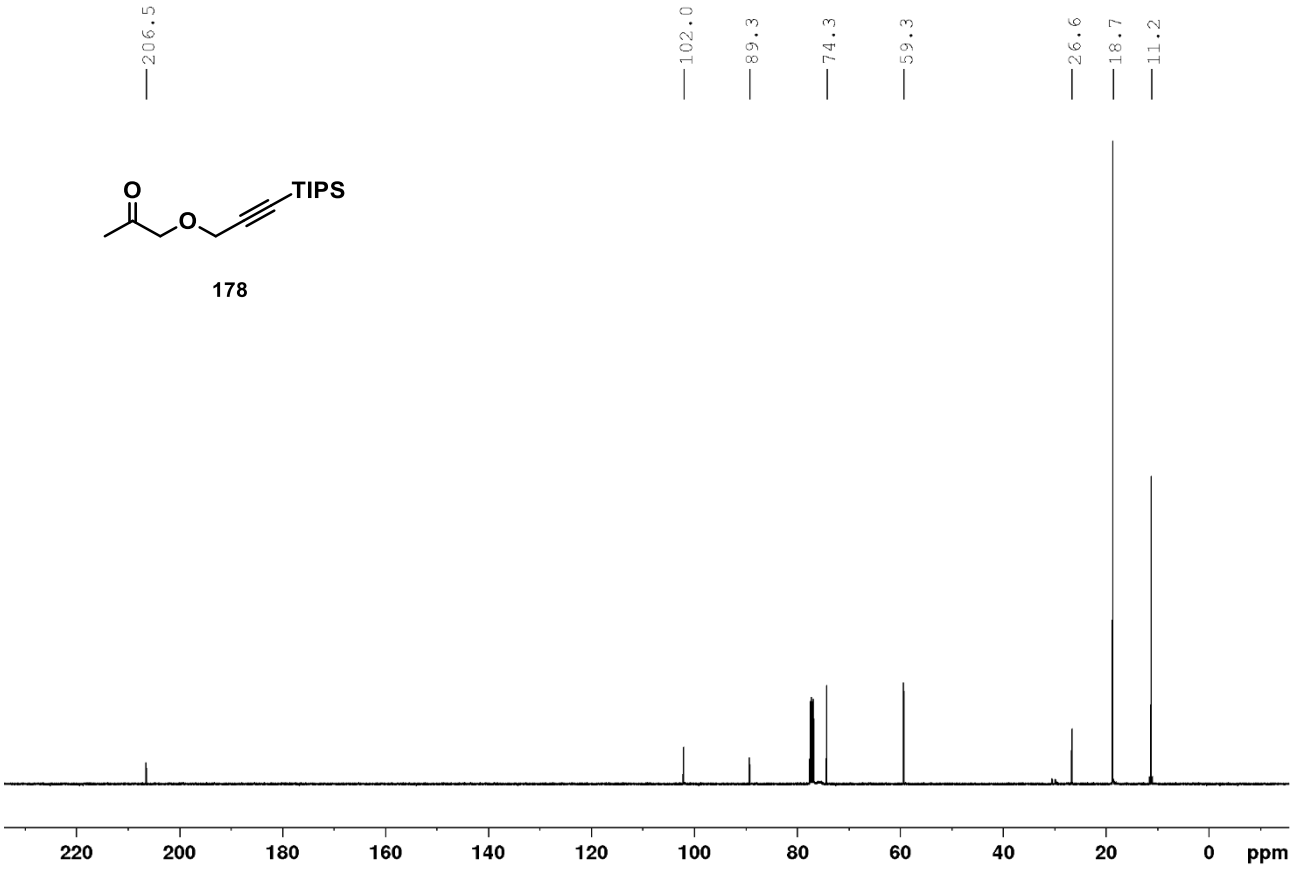

MeO
N
O
O
TIPS

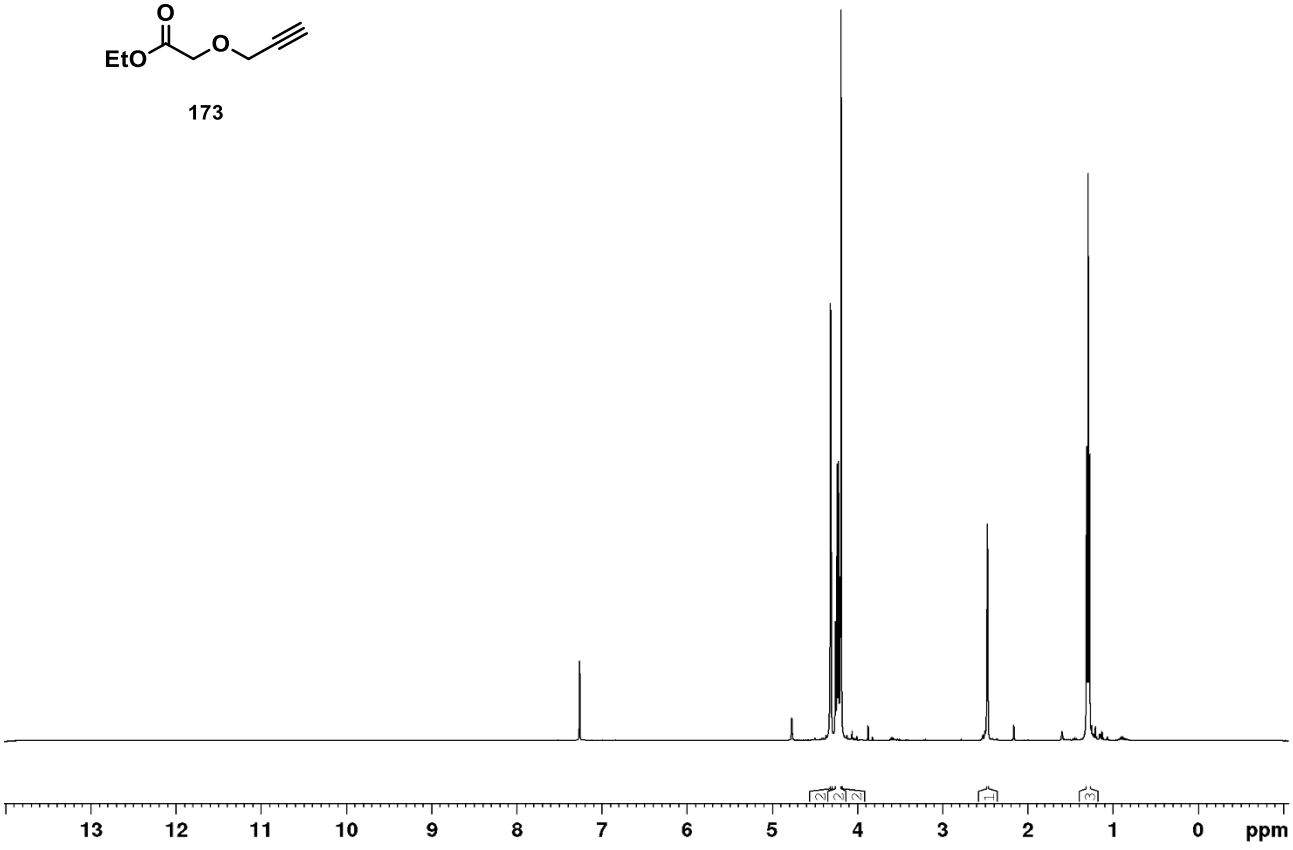
176

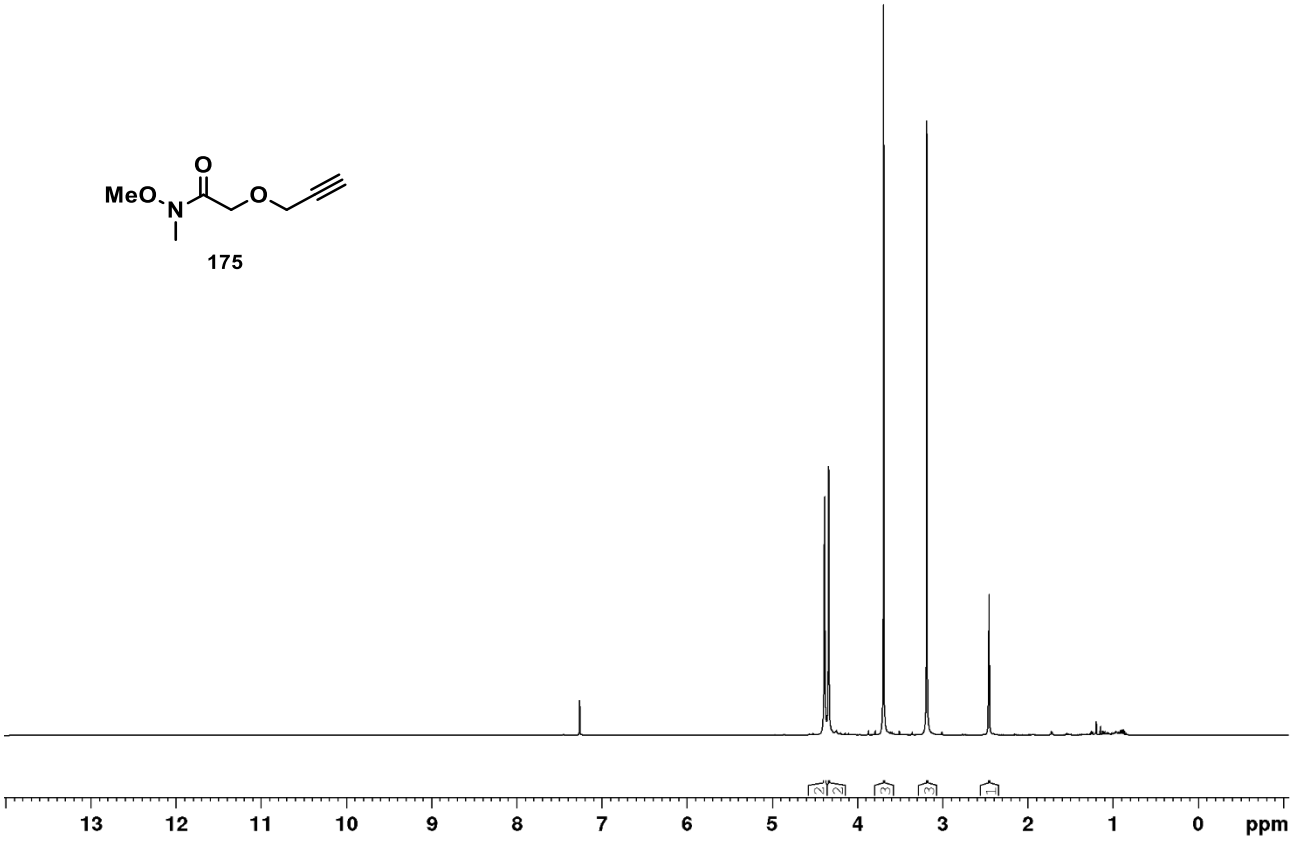
2
2
3
3
21
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

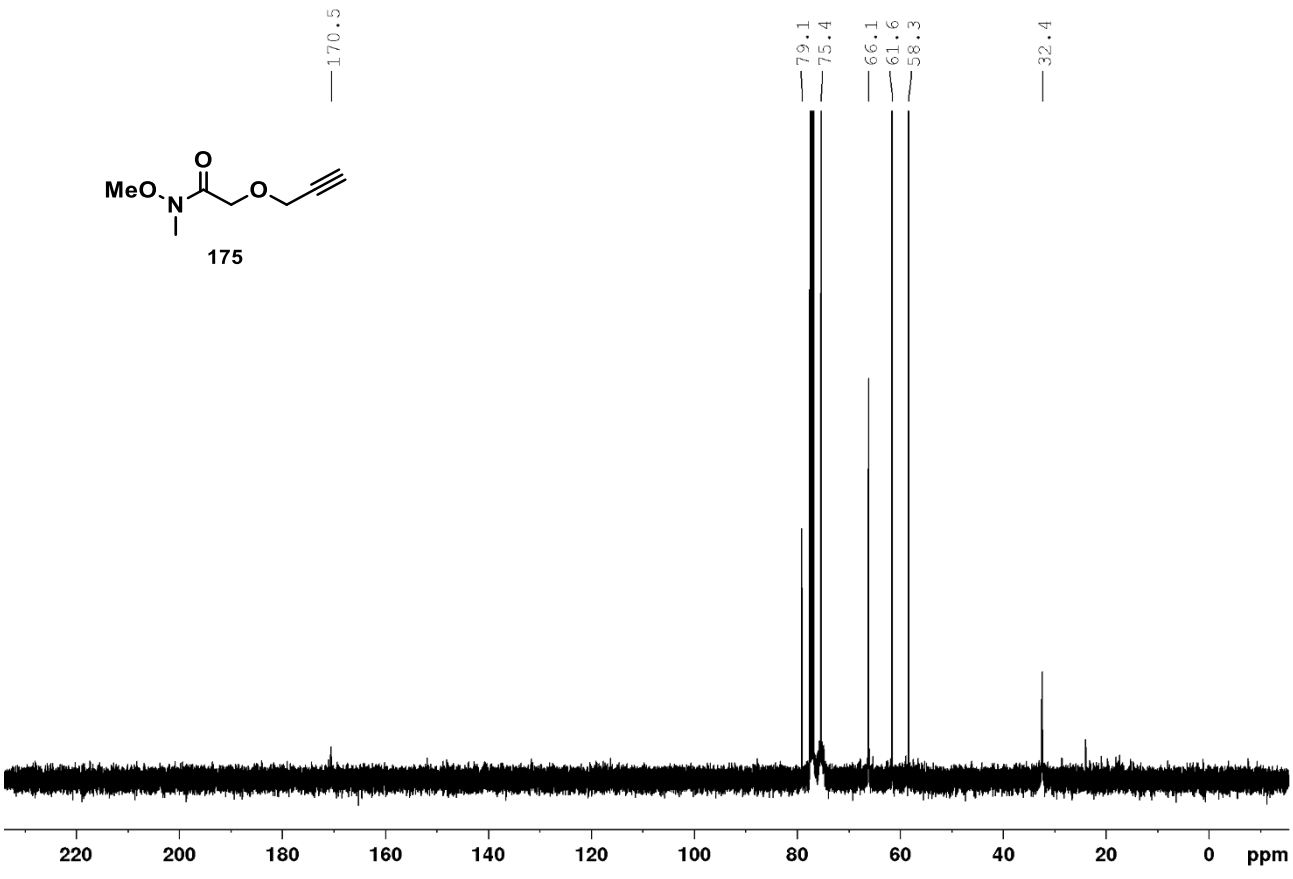

172.6
102.5
88.8
65.8
61.5
59.1
32.4
18.7
11.3
MeO
N
O
O
TIPS
176
220
200
180
160
140
120
100
80
60
40
20
0
ppm

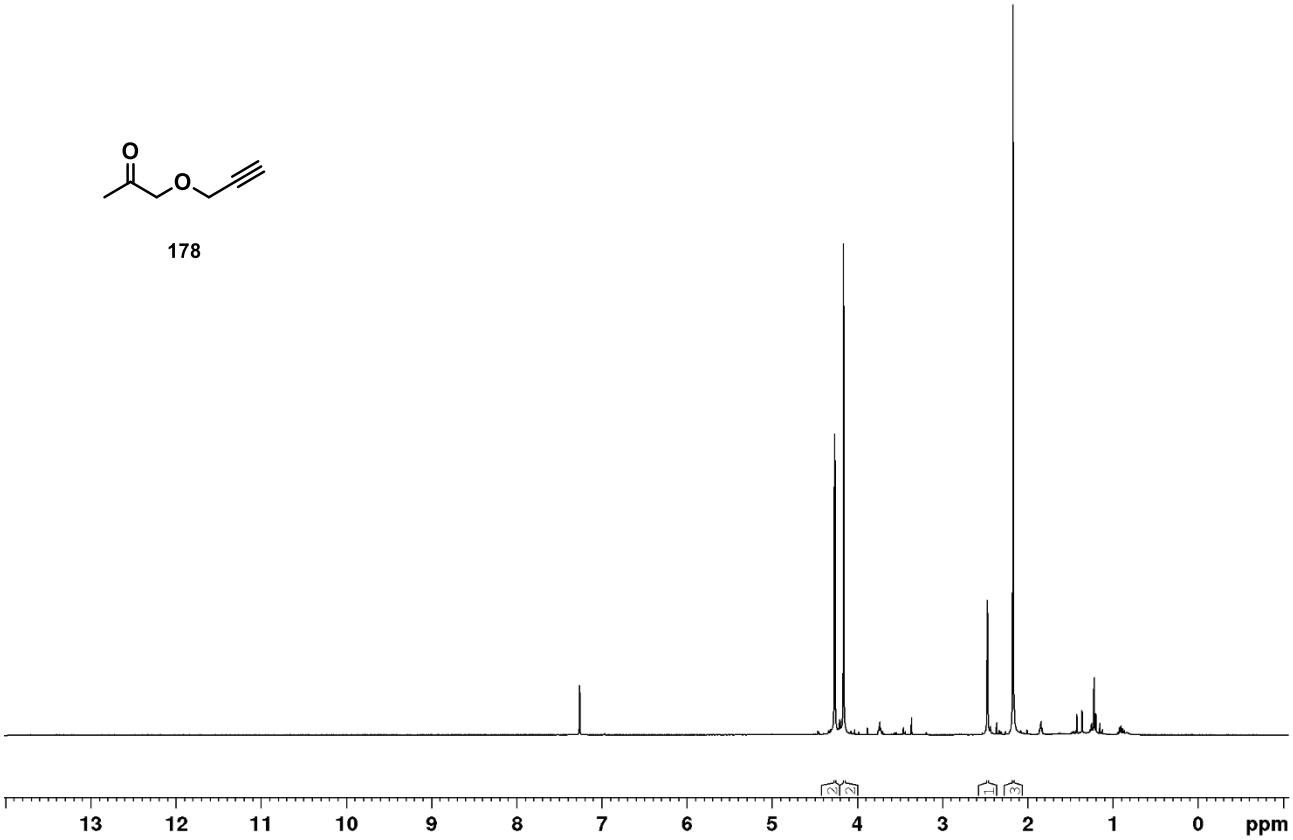

O
O
TIPS
178
2
2
3
21
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

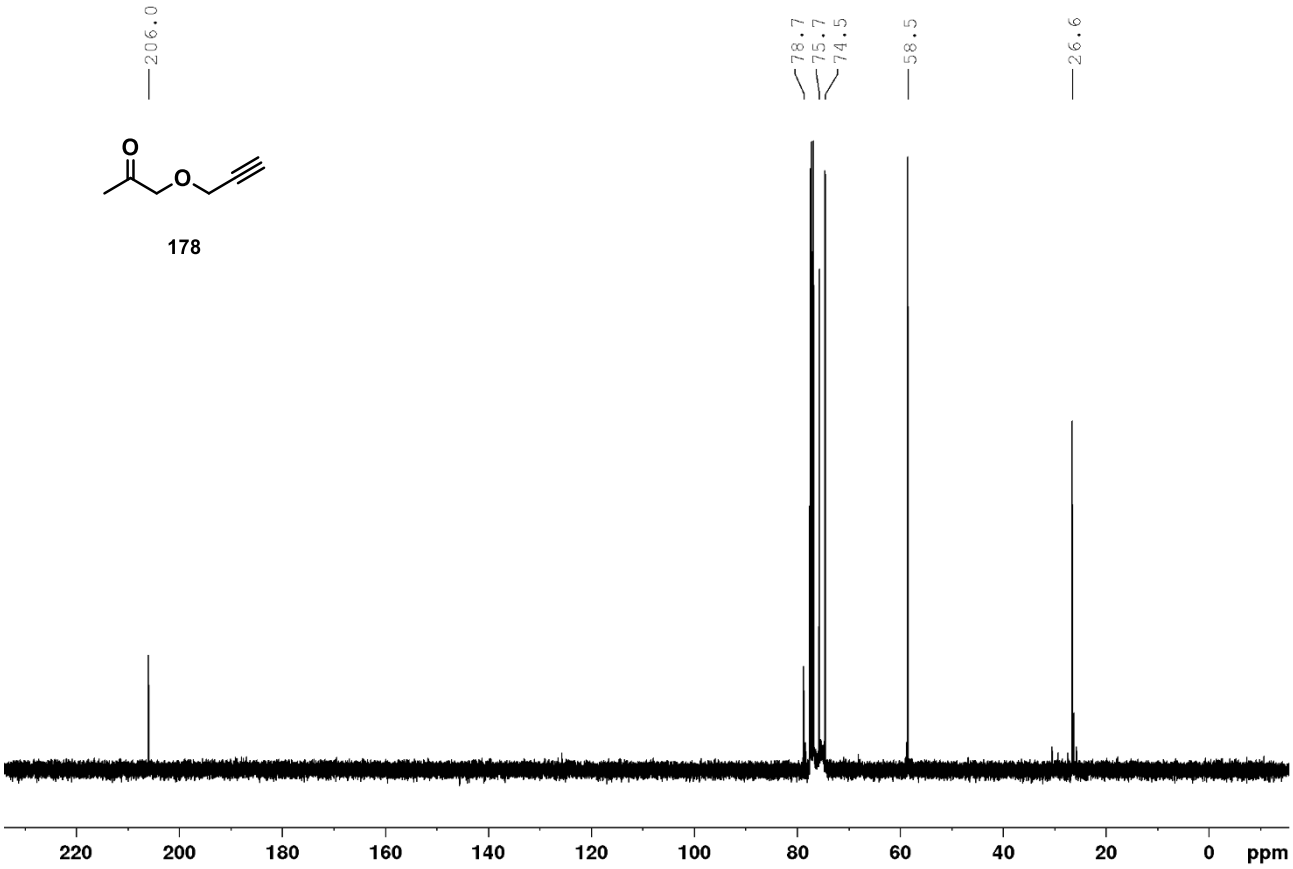

206.5
102.0
89.3
74.3
59.3
26.6
18.7
11.2
O
O
TIPS
178
220
200
180
160
140
120
100
80
60
40
20
0
ppm

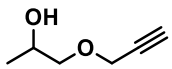

O
EtO
O
173
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


MeO
N
O
O
175
2
2
3
3
1
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


170.5
79.1
75.4
66.1
61.6
58.3
32.4
MeO
N
O
O
175
220
200
180
160
140
120
100
80
60
40
20
0
ppm

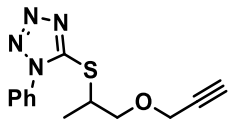

178
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


206.0
78.7
75.7
74.5
58.5
26.6
178
220
200
180
160
140
120
100
80
60
40
20
0
ppm


OH
O

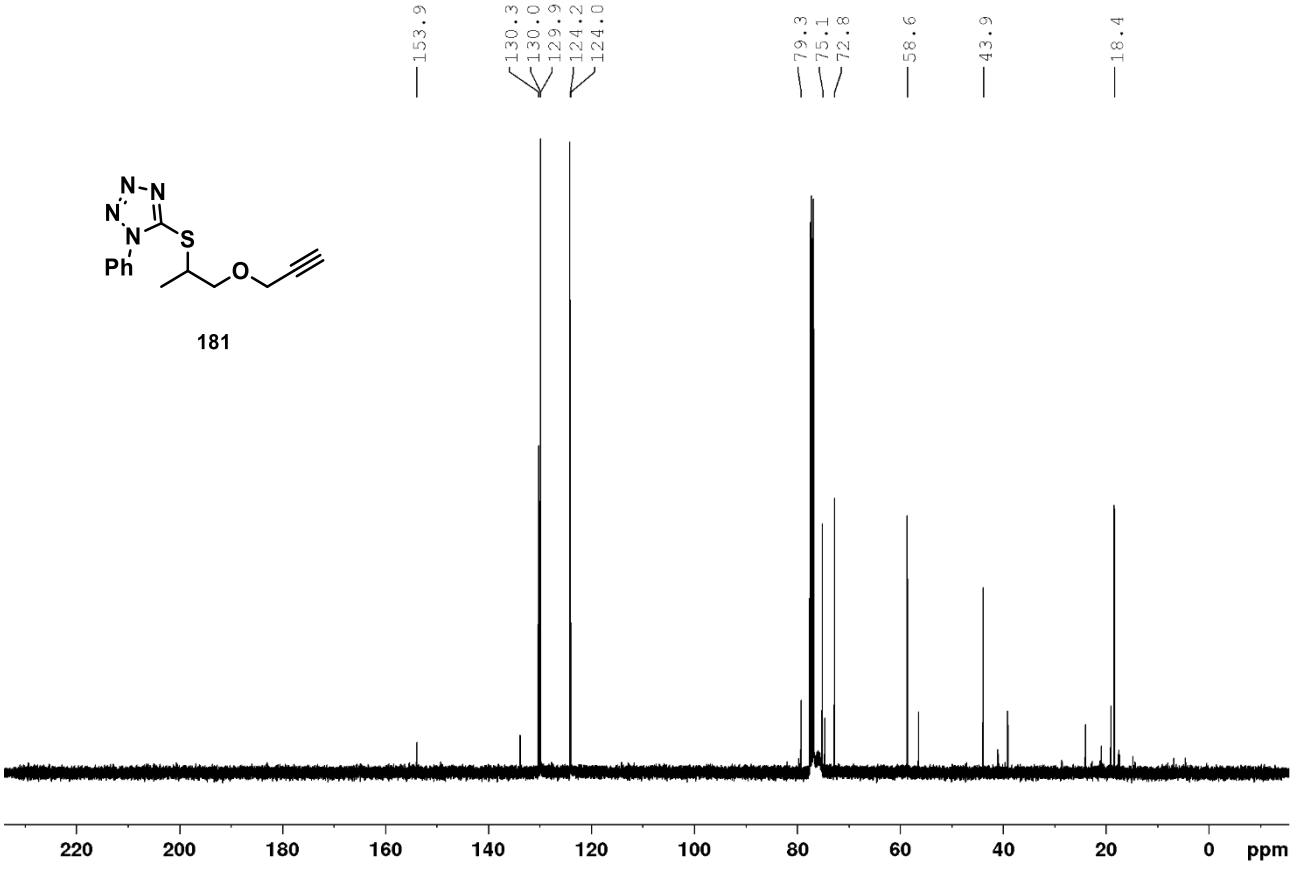
180

13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

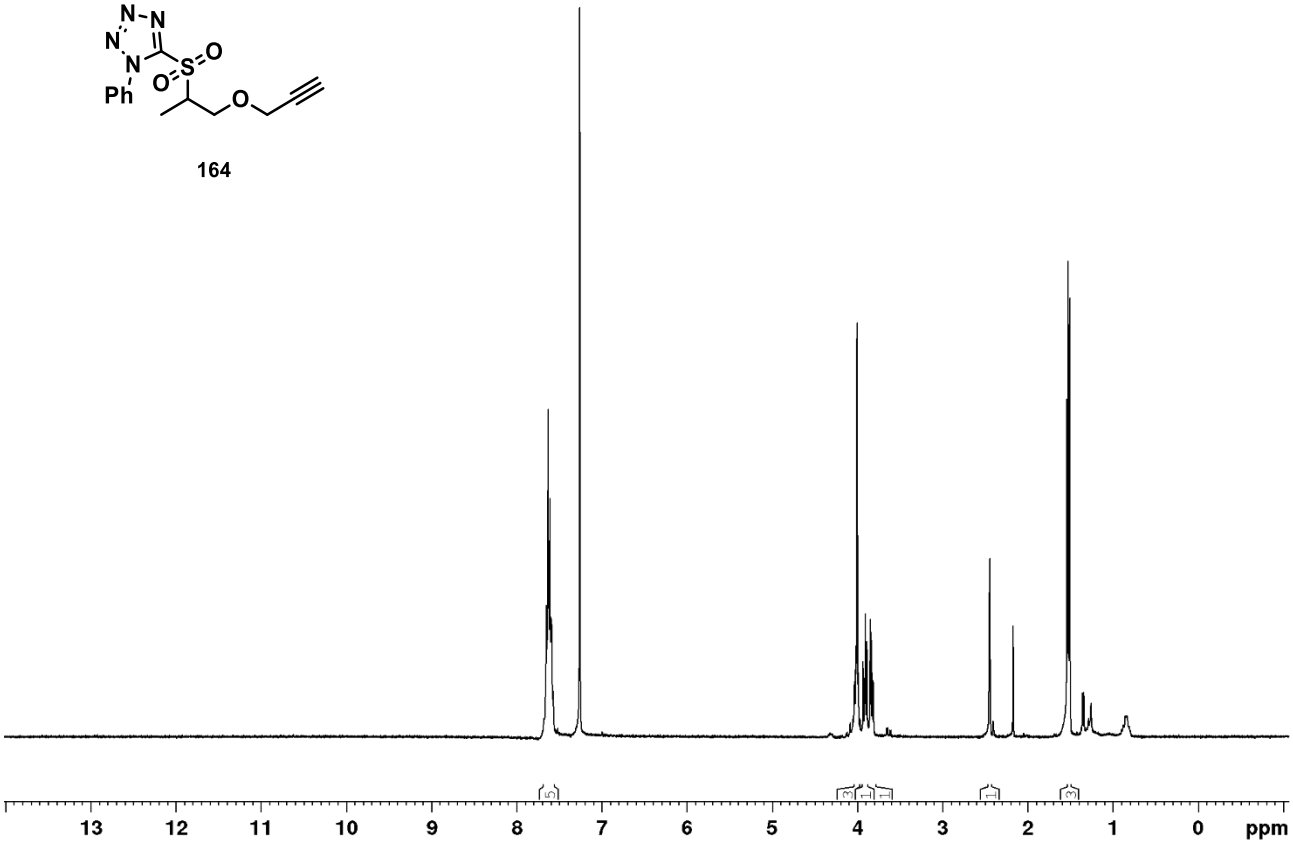

N
N
N
N
S
Ph
O

181

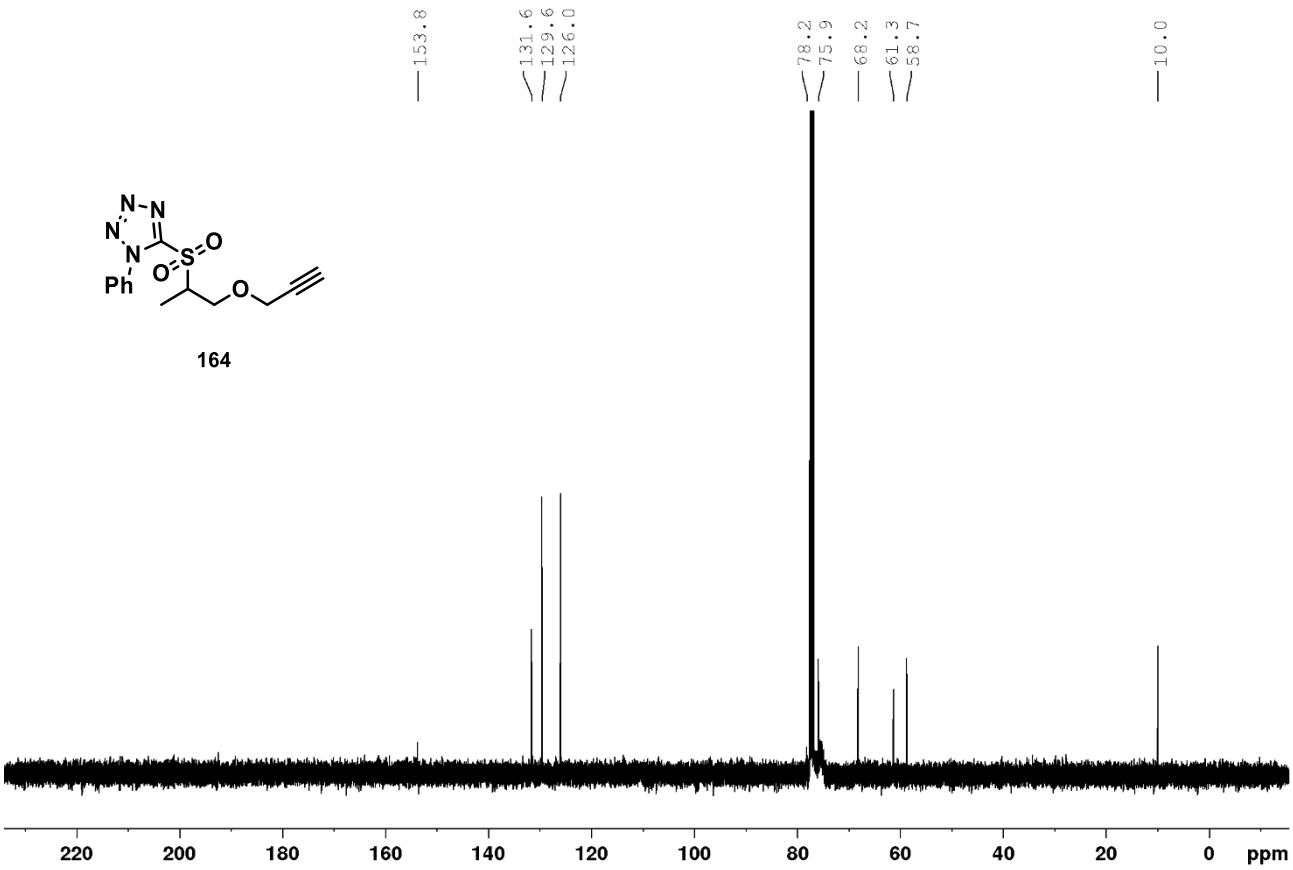
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


153.9
130.3
130.0
129.9
124.2
124.0
79.3
75.1
72.8
58.6
43.9
18.4
N
N
N
S
Ph
O
220
200
180
160
140
120
100
80
60
40
20
0
ppm

181


N
N
N
S
O
O
Ph
O
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

164

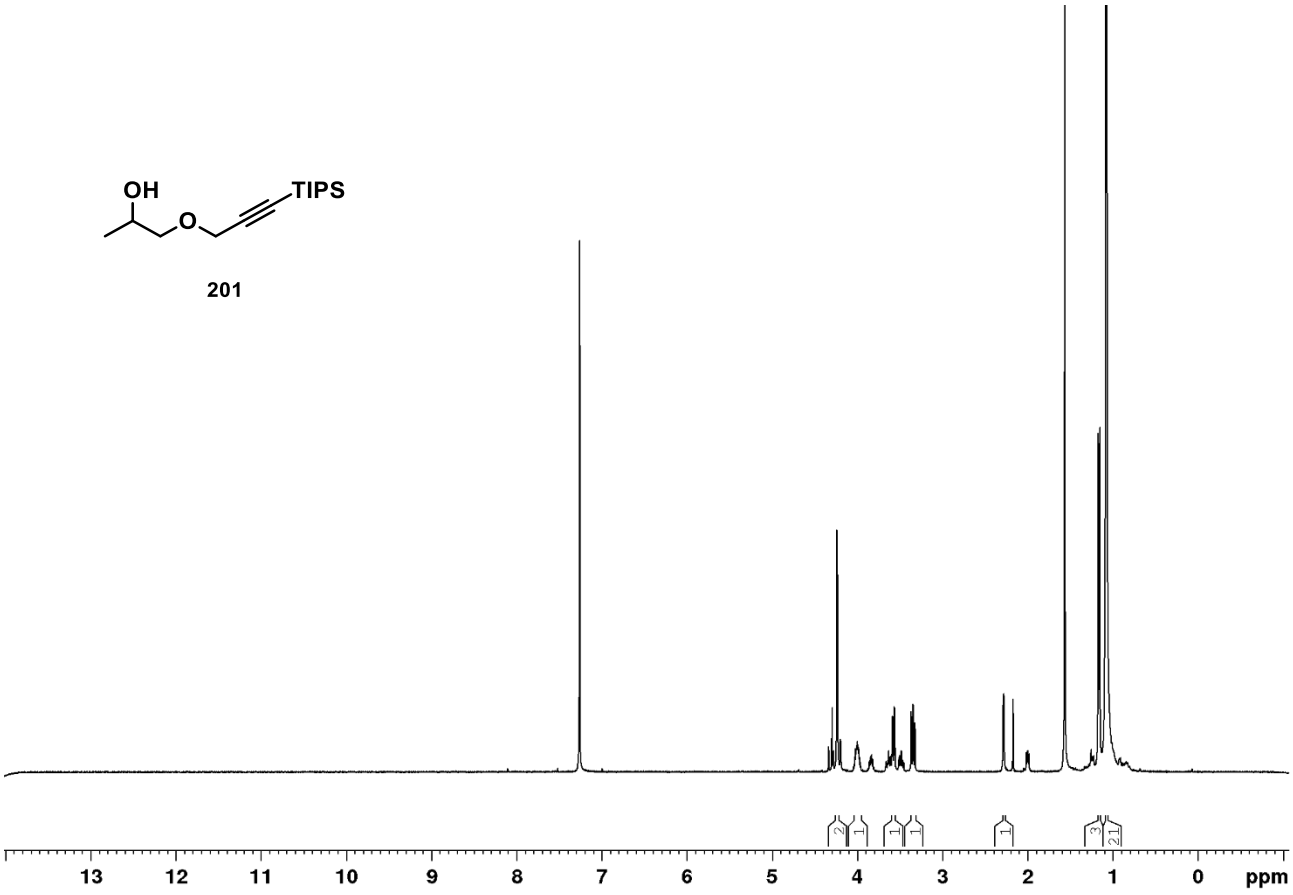

153.8
131.6
129.6
126.0
78.2
75.9
68.2
61.3
58.7
10.0
N
N
N
N
Ph
S
O
O
O
220
200
180
160
140
120
100
80
60
40
20
0
ppm

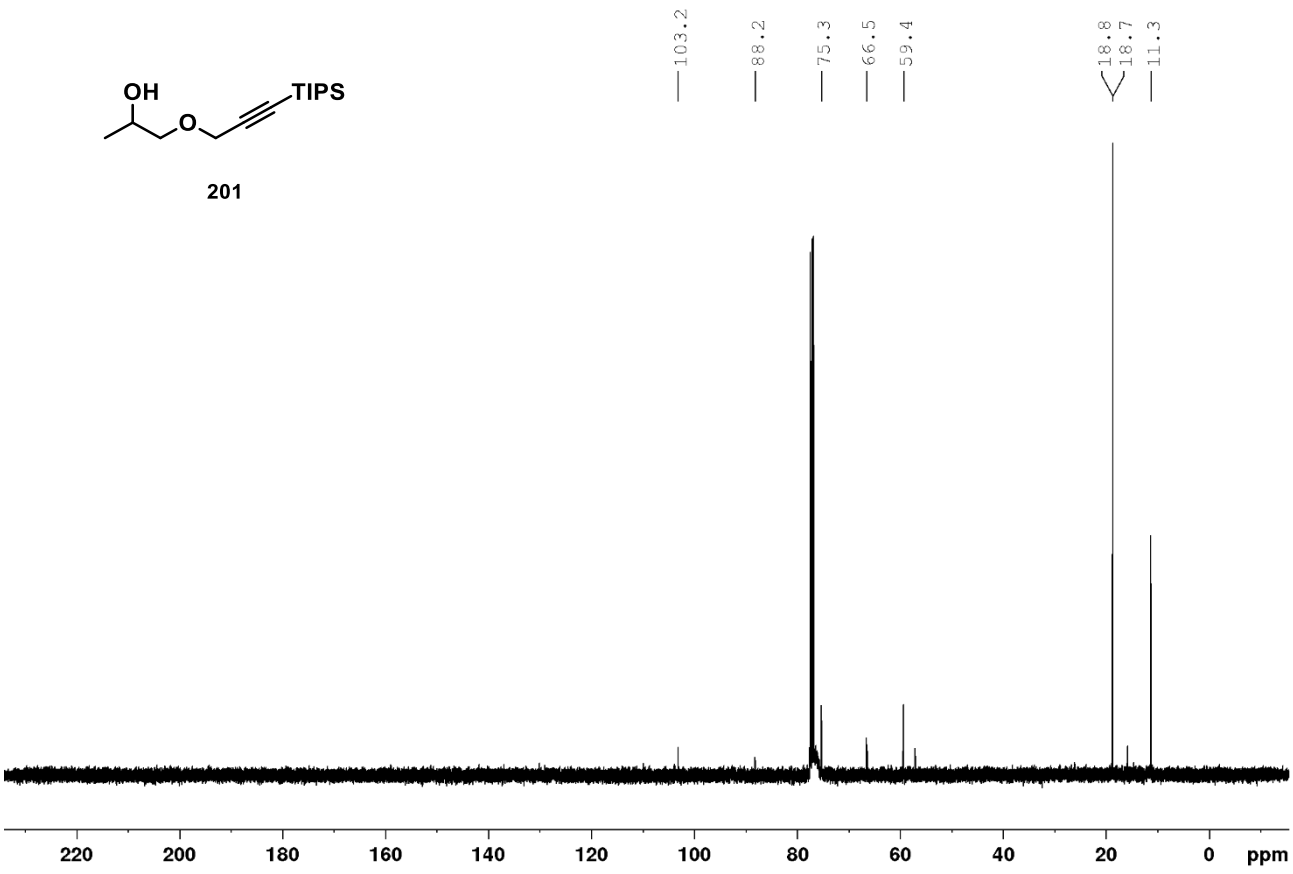
164

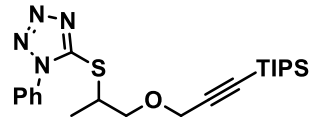

TIPS
Br

200

2
21
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

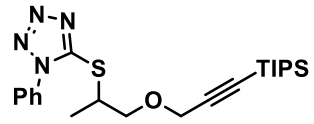

OH
TIPS
O
201
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


OH
TIPS
O
201
103.2
88.2
75.3
66.5
59.4
18.8
18.7
11.3
220
200
180
160
140
120
100
80
60
40
20
0
ppm


N
N
N
N
S
Ph
O
TIPS

202

5
1
2
2
3
21
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


N
N
N
N
S
Ph
O
TIPS

202

154.0
133.8
130.2
129.8
124.1
102.7
88.5
72.3
59.3
44.1
18.6
17.8
11.2
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200
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120
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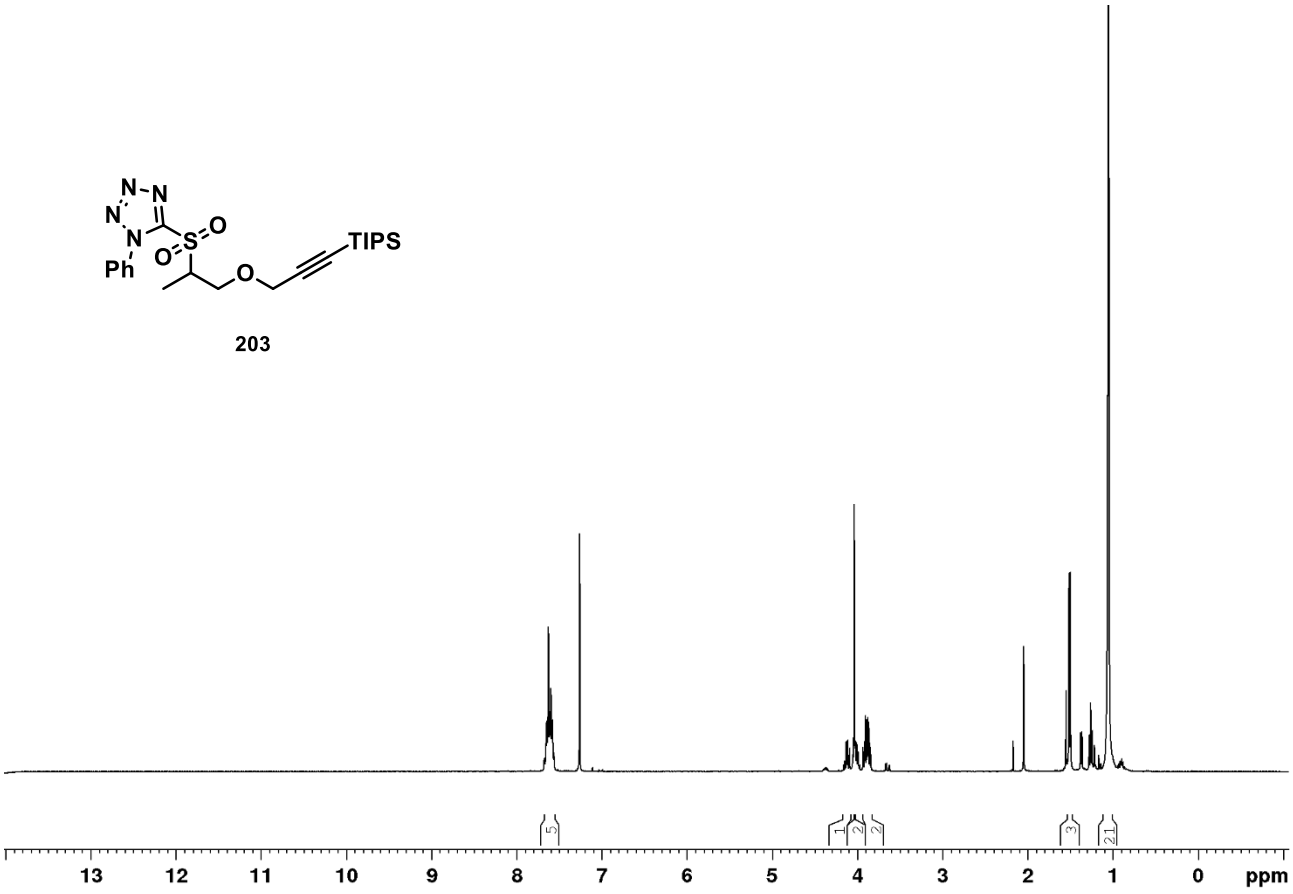
TIPS
Ph
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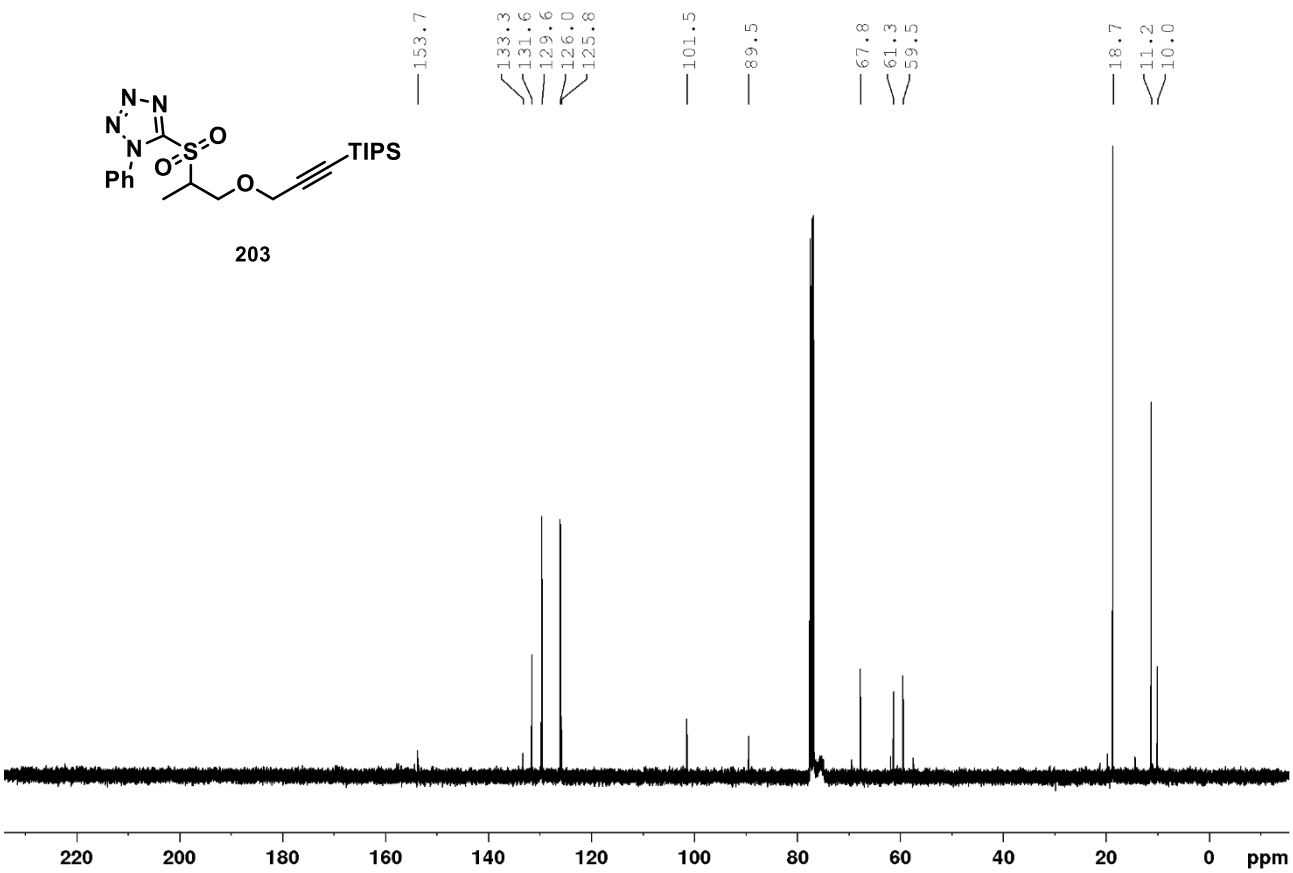
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133.3
131.6
129.6
126.0
125.8
101.5
89.5
67.8
61.3
59.5
18.7
11.2
10.0
TIPS
Ph
203
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200
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120
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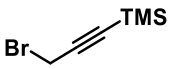
TMS
Br

505

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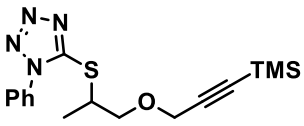
ppm


N
N
N
N
S
Ph
O
TMS

204

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12
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6
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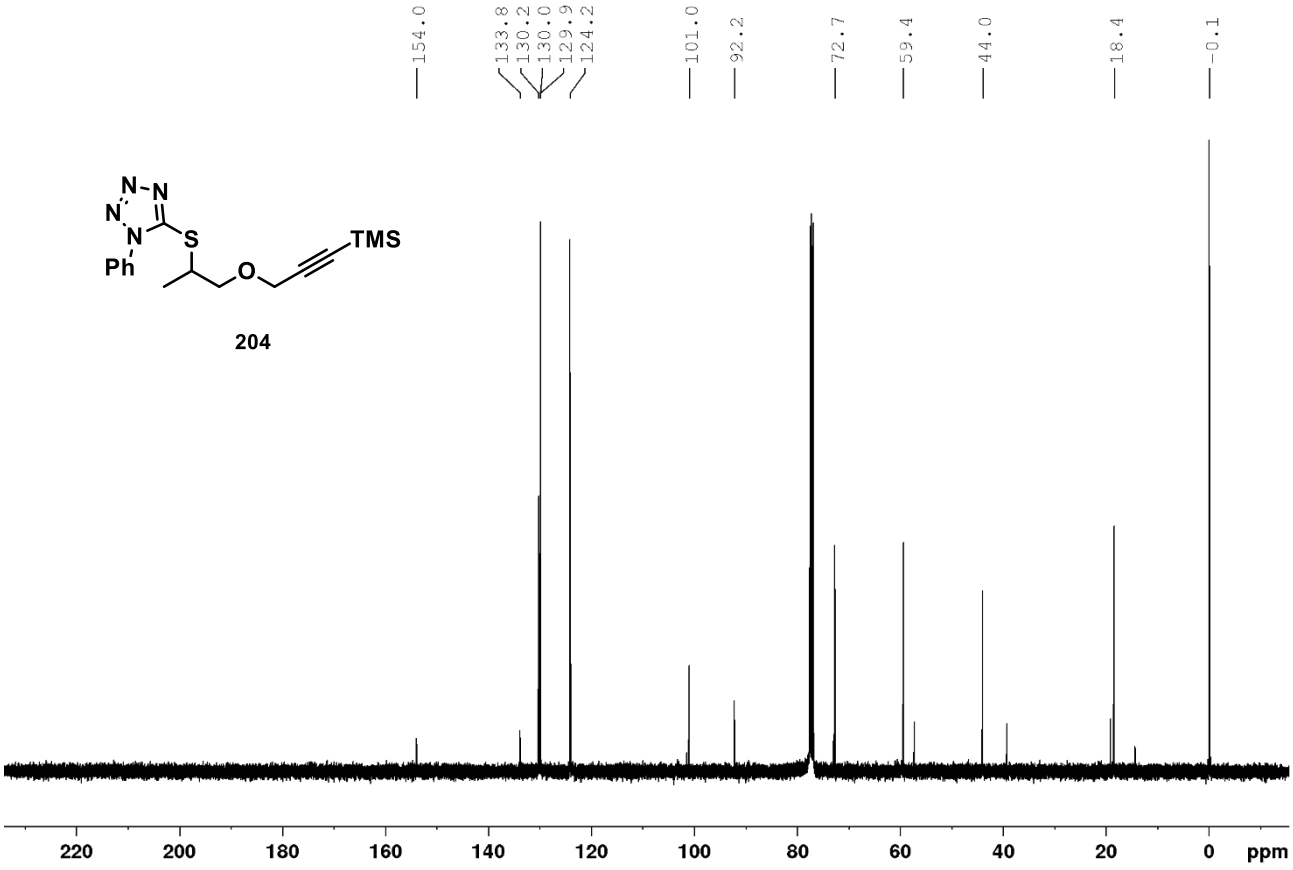
0
ppm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129.9
124.2
101.0
92.2
72.7
59.4
44.0
18.4
-0.1
N
N
N
N
S
Ph
O
TMS
220
200
180
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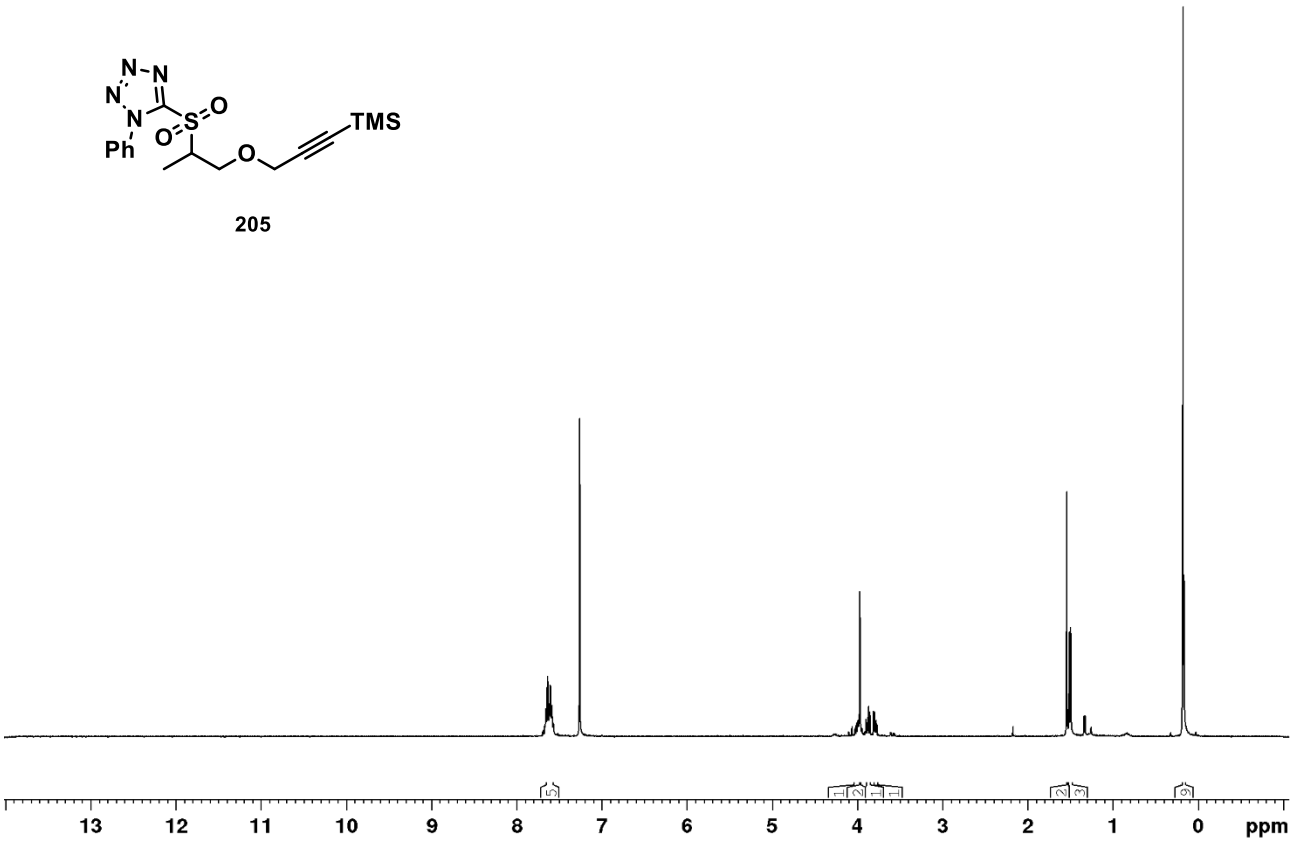
100
80
60
40
20
0
ppm

204


N
N
N
N
S
O
O
Ph
O
TMS
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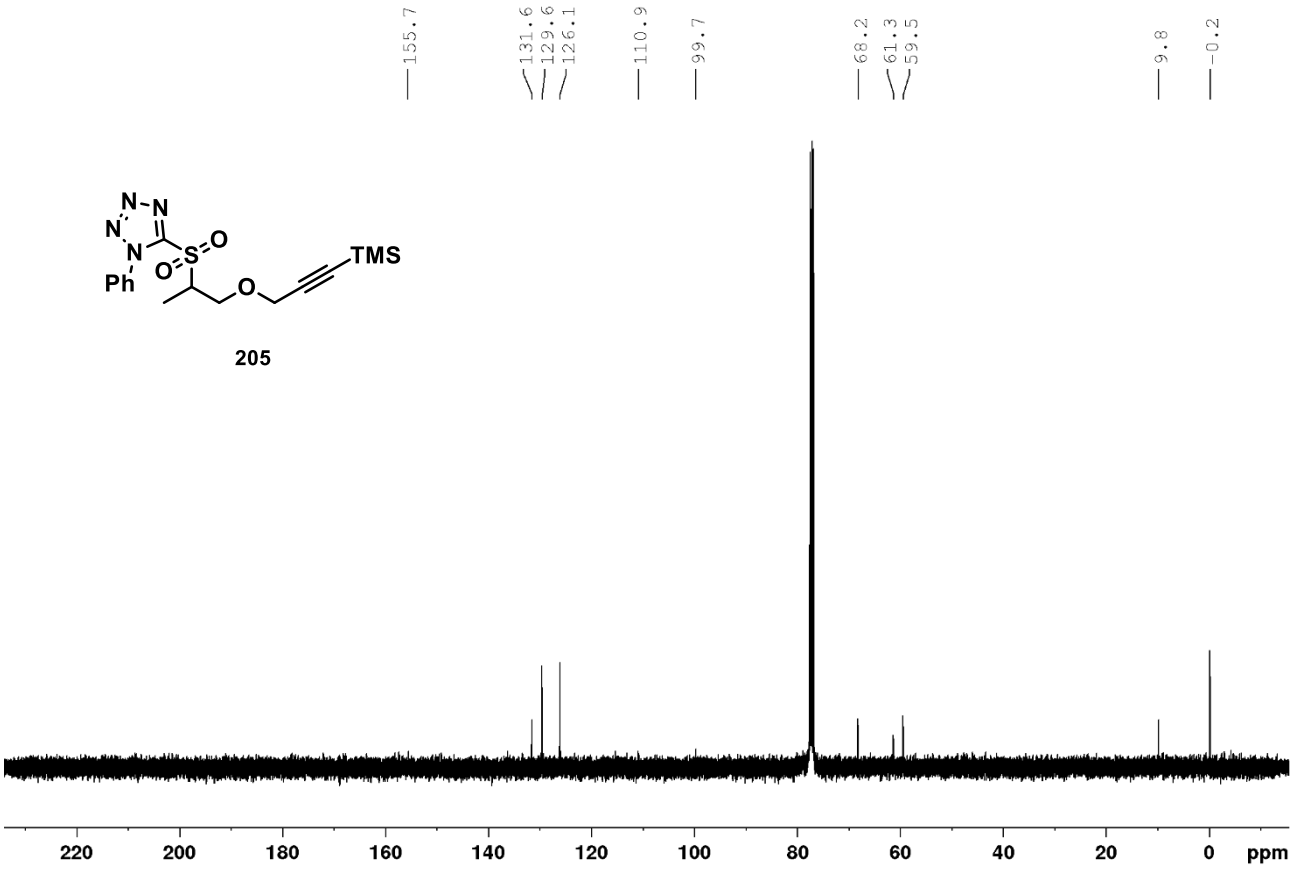
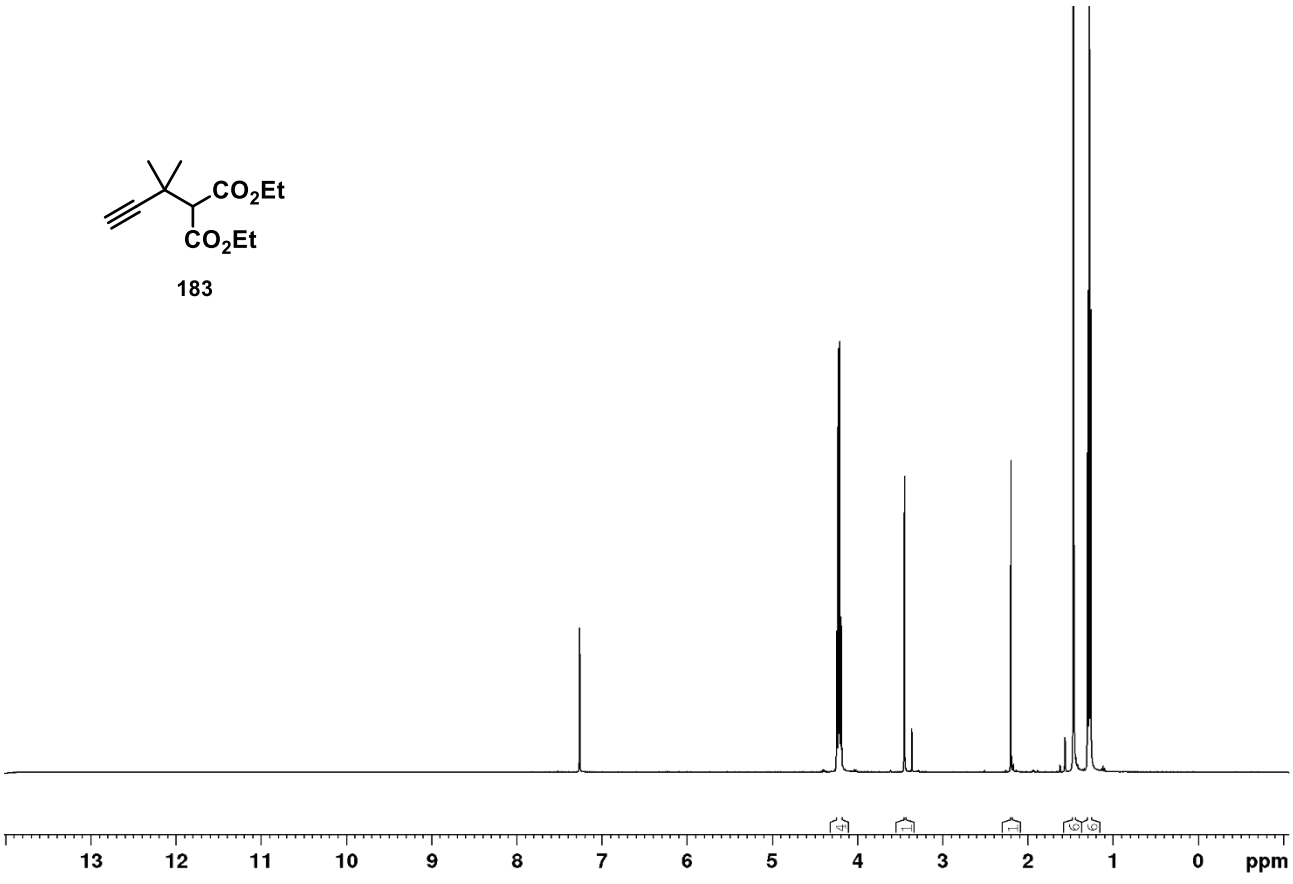
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

205


155.7
131.6
129.6
126.1
110.9
99.7
68.2
61.3
59.5
9.8
-0.2
N
N
N
N
Ph
S
O
O
O
TMS
220
200
180
160
140
120
100
80
60
40
20
0
ppm

205


CO2Et
CO2Et
13
12
11
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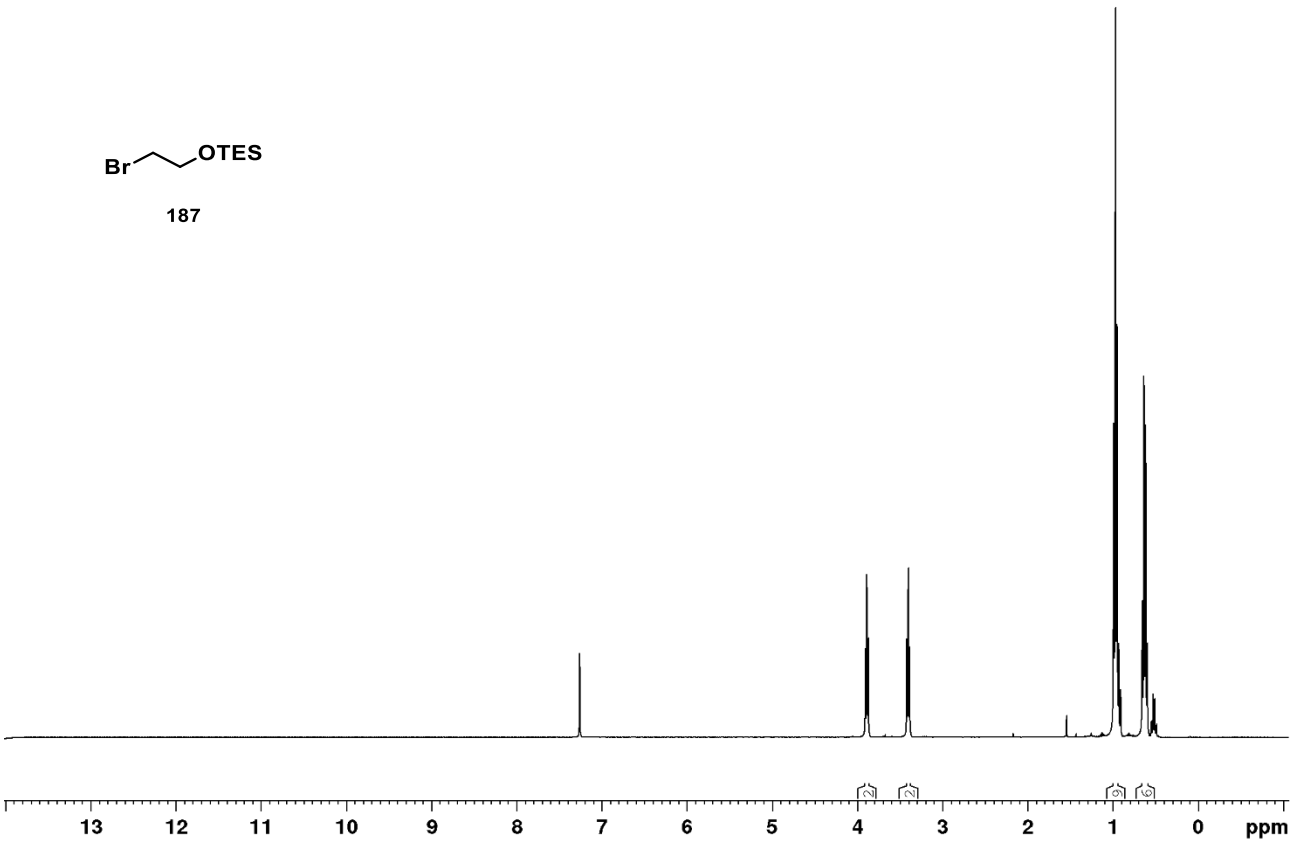
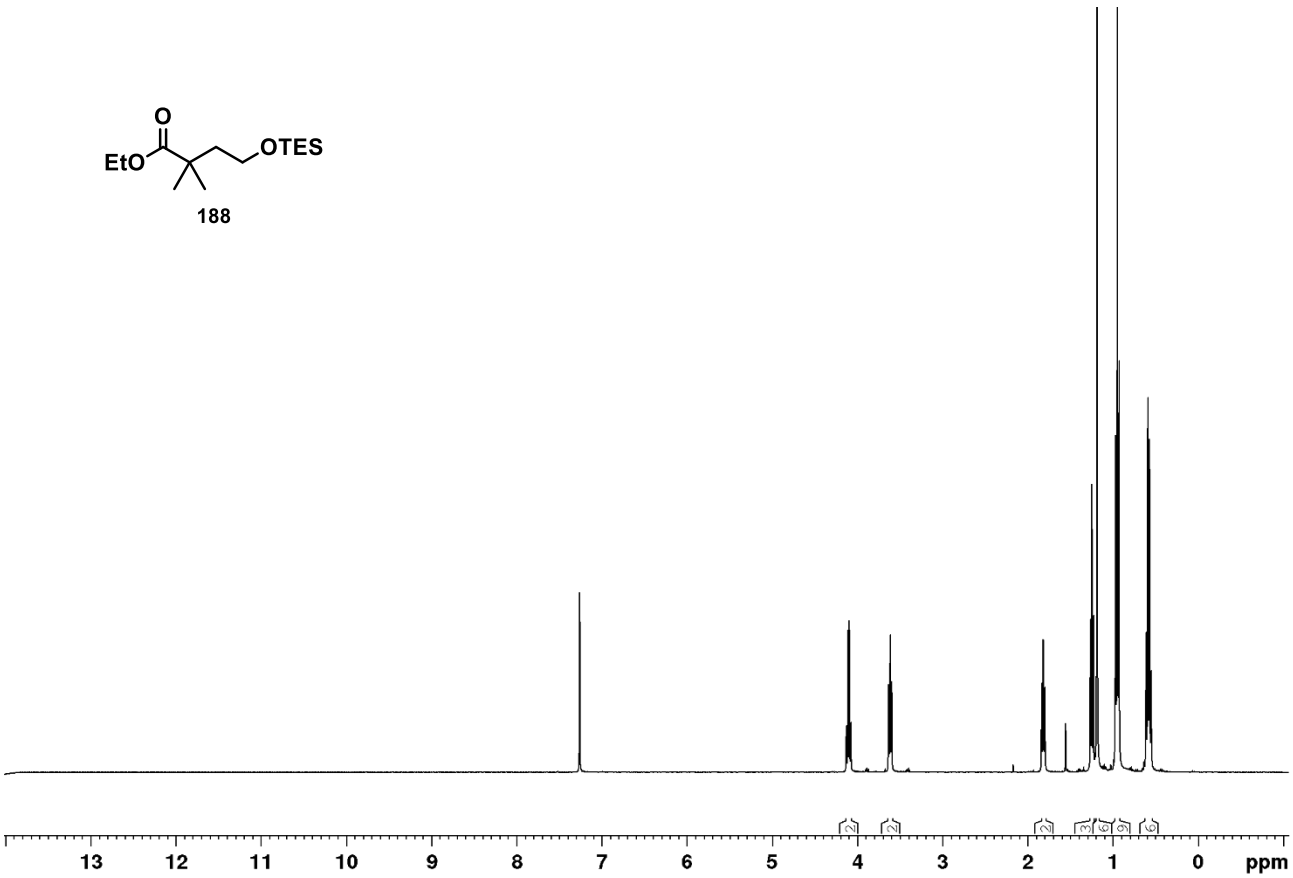
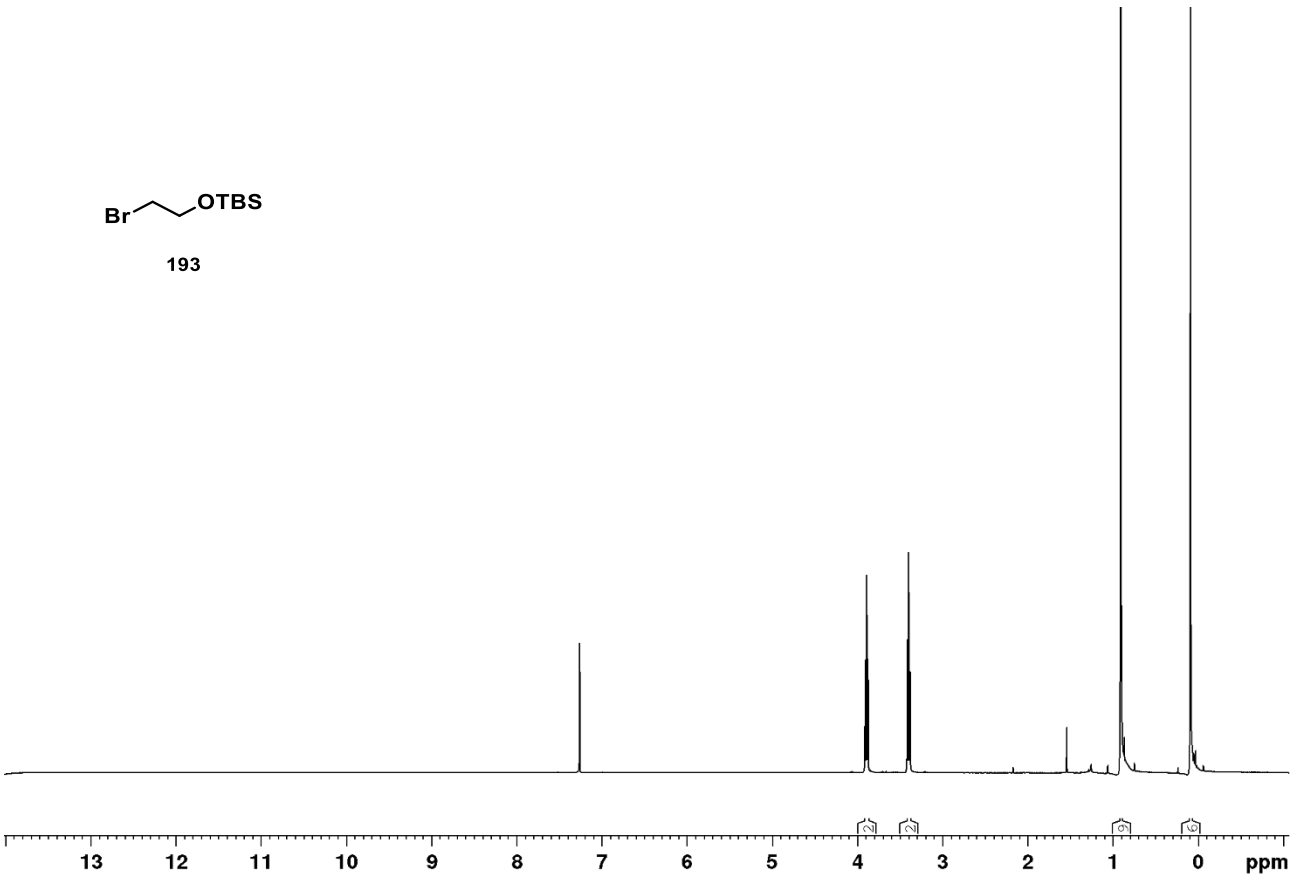
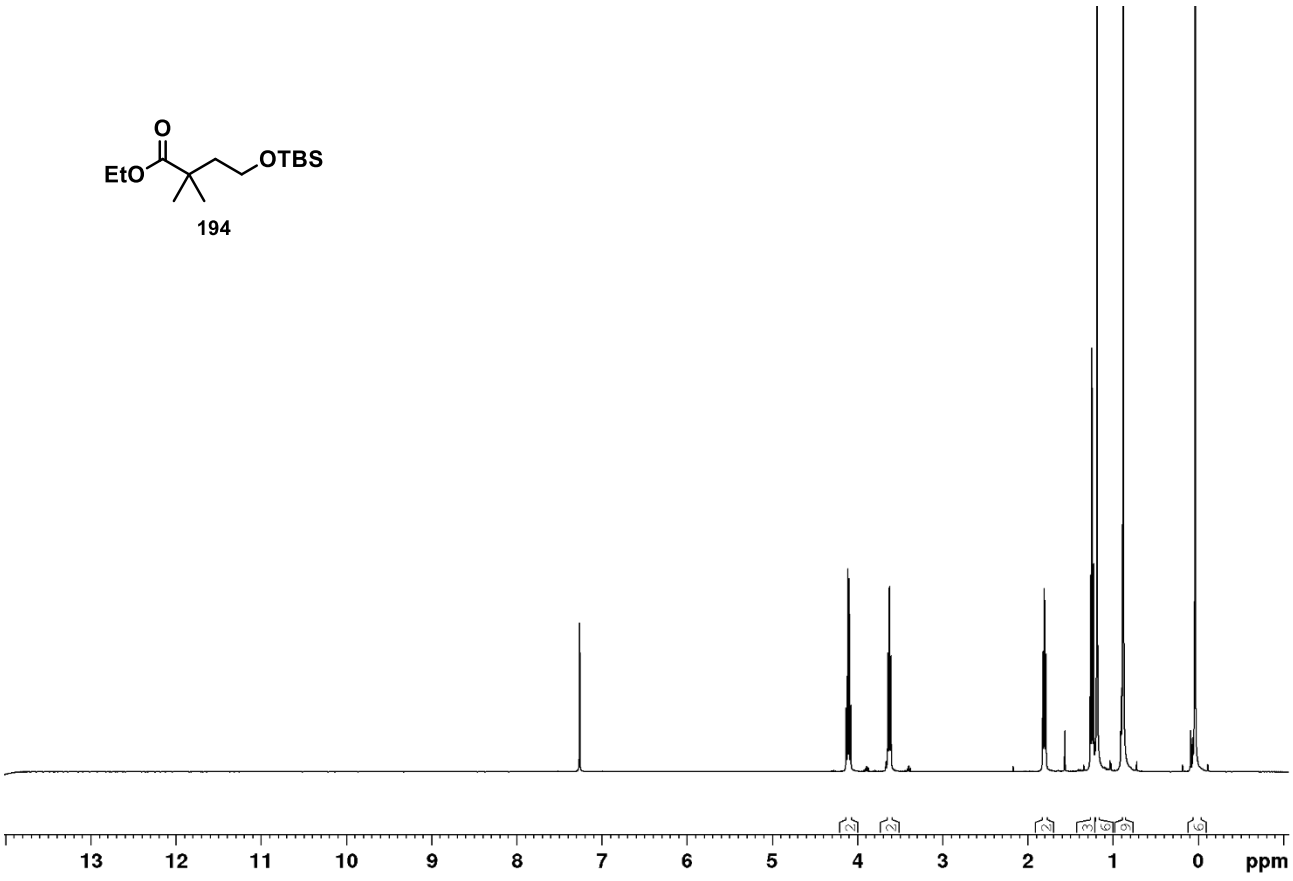
8
7
6
5
4
3
2
1
0
ppm

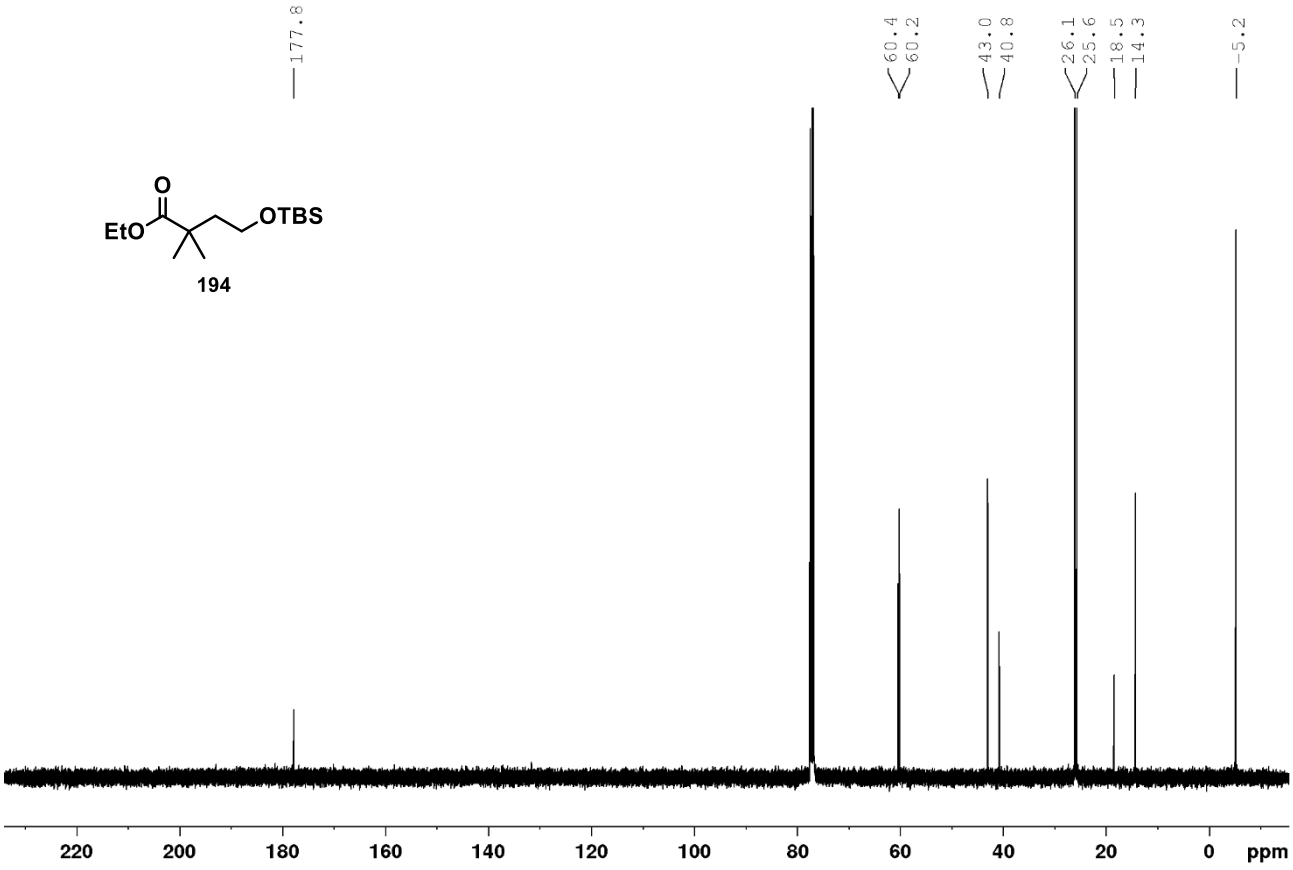
183

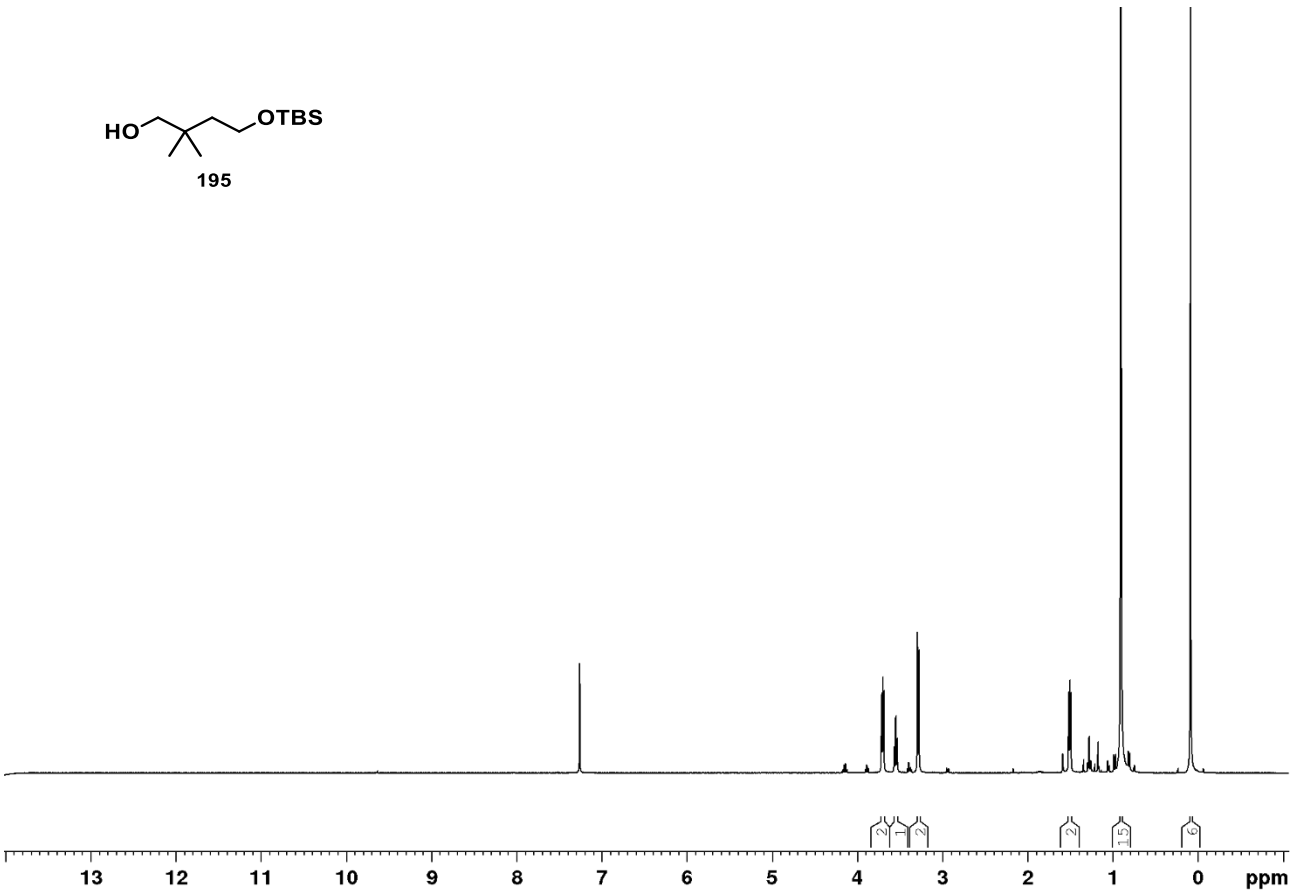

Br
OTES
187
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

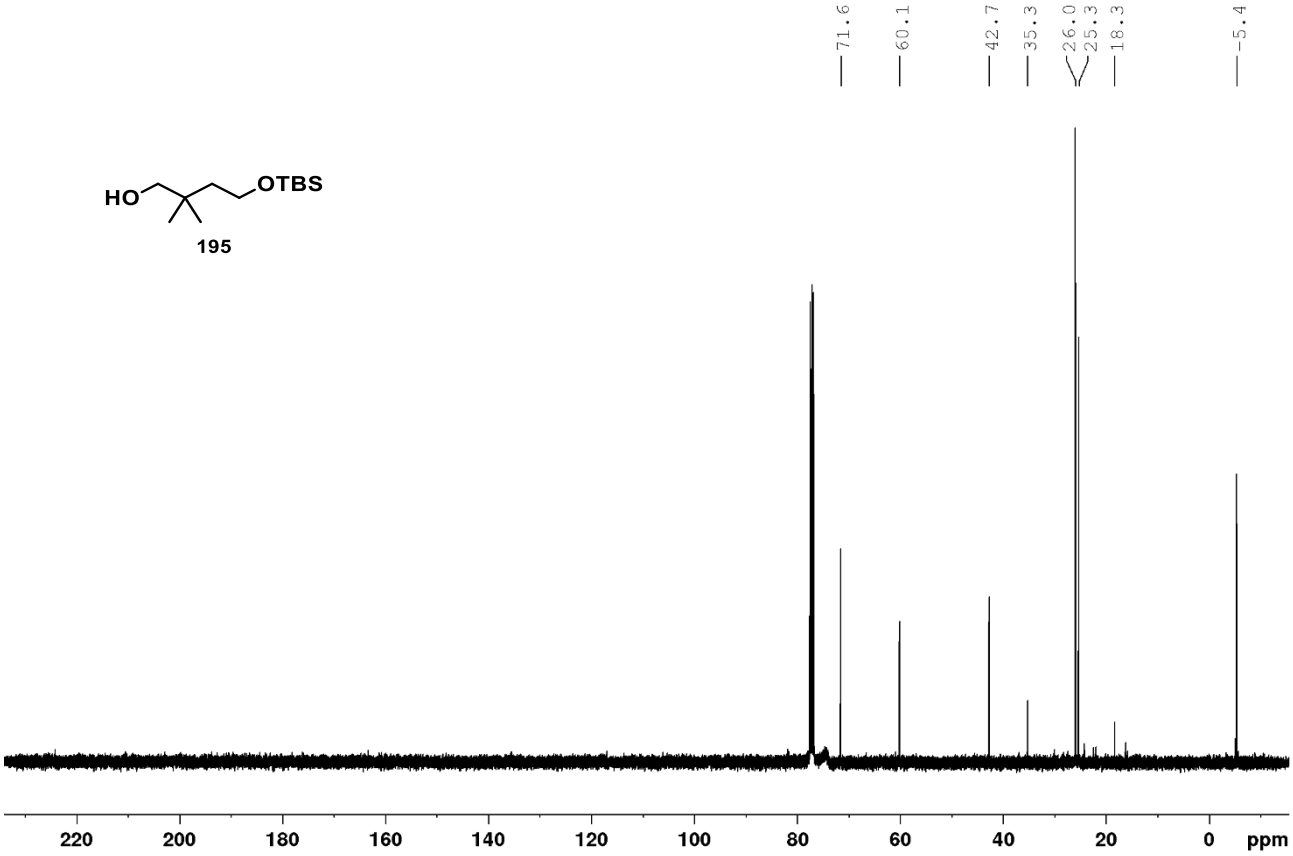

O
EtO
OTES
188
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

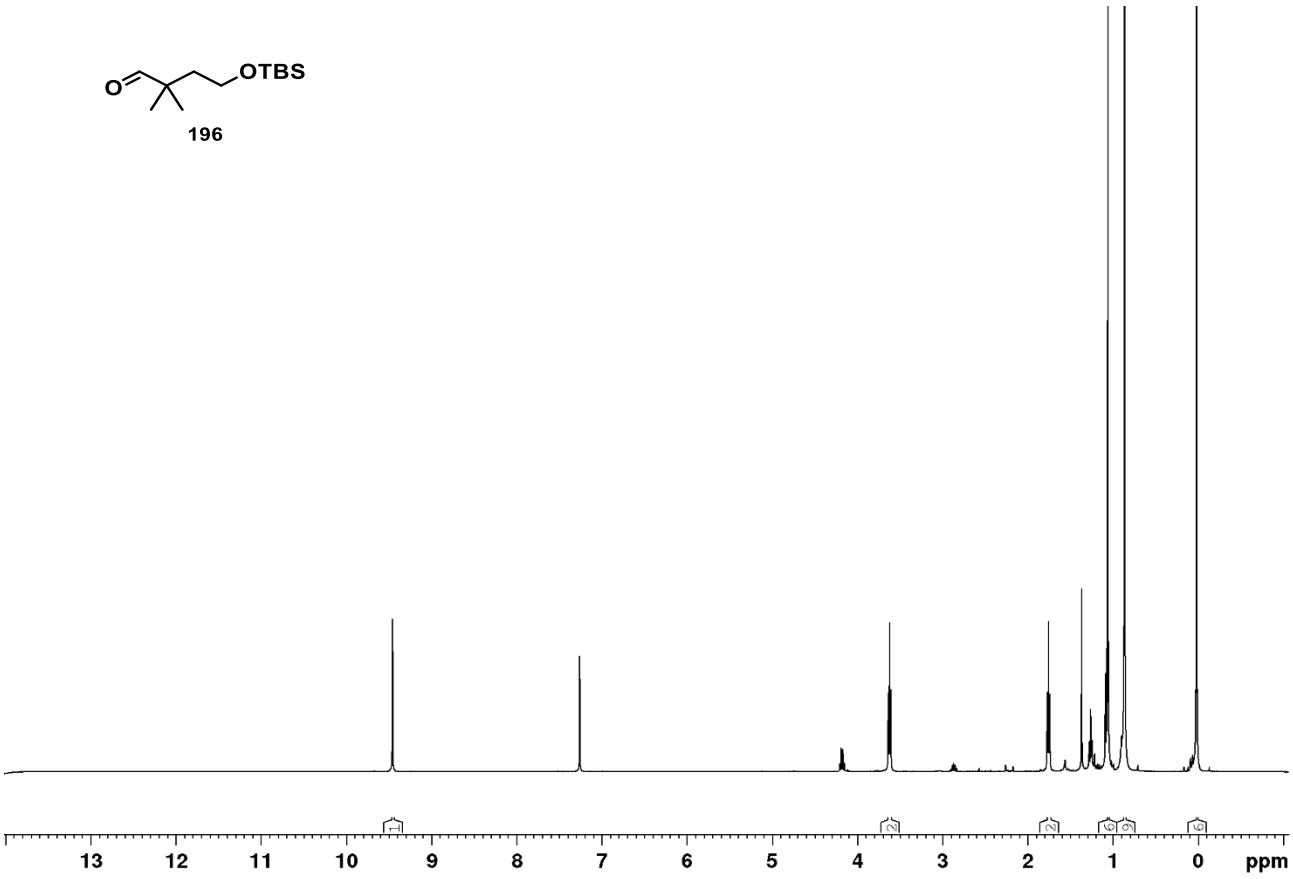

Br
OTBS
193
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

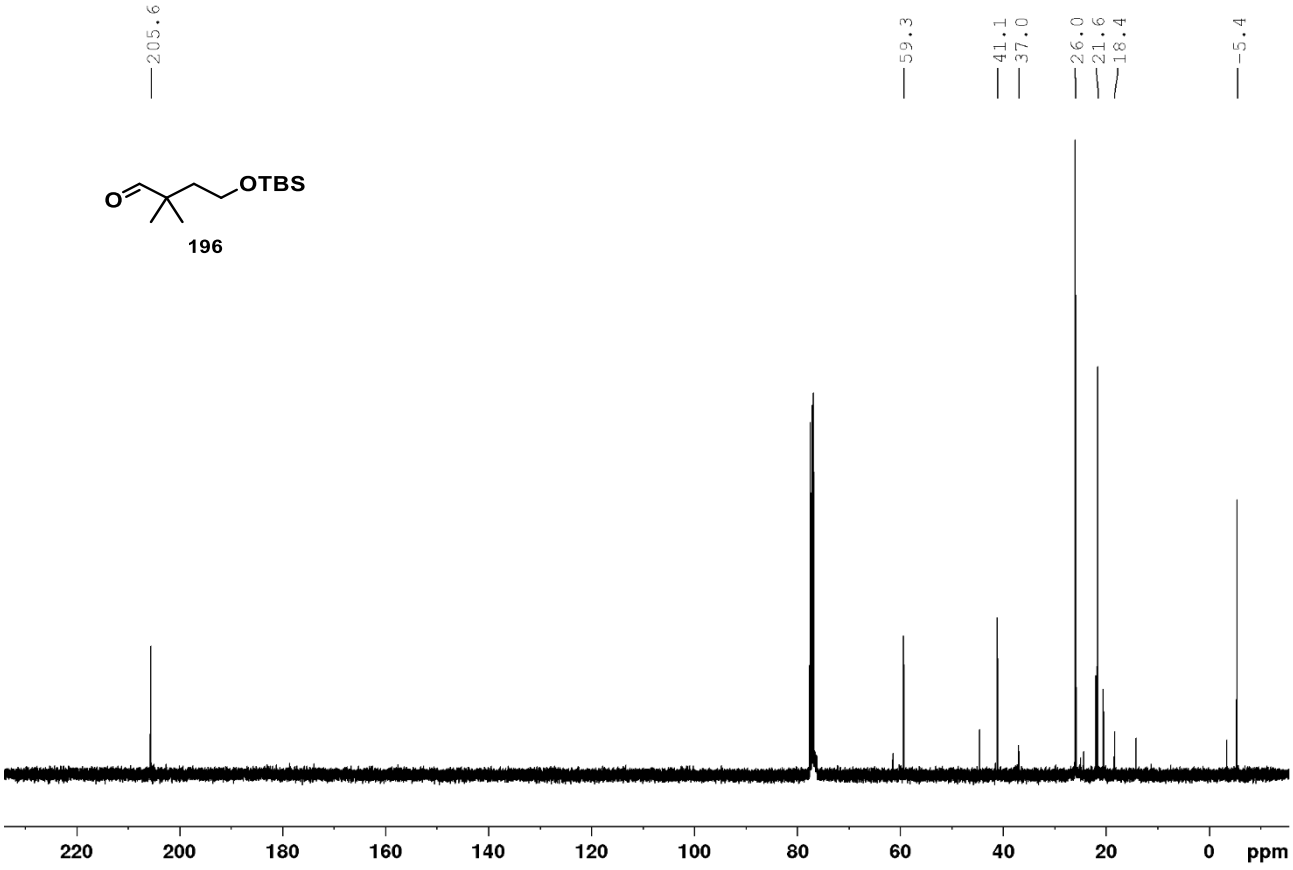

O
EtO
OTBS
194
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


177.8
60.4
60.2
43.0
40.8
26.1
25.6
18.5
14.3
-5.2
O
EtO
OTBS
194
220
200
180
160
140
120
100
80
60
40
20
0
ppm


HO
OTBS
195
2
1
2
2
15
6
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


71.6
60.1
42.7
35.3
26.0
25.3
18.3
-5.4
HO
OTBS
195
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
OTBS
196
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


205.6
59.3
41.1
37.0
26.0
21.6
18.4
-5.4
O
OTBS
196
220
200
180
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120
100
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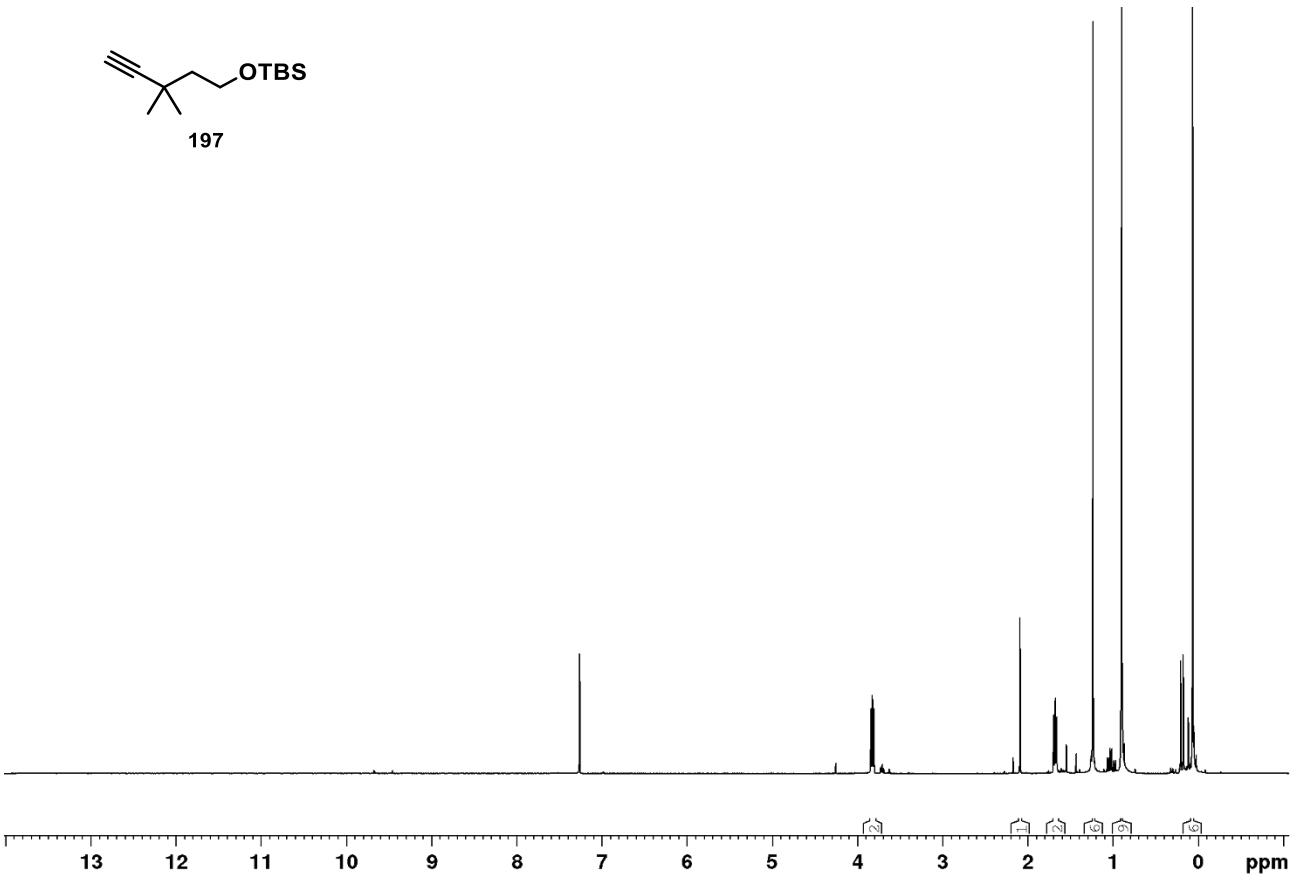
40
20
0
ppm


OTBS
197
13
12
11
10
9
8
7
6
5
4
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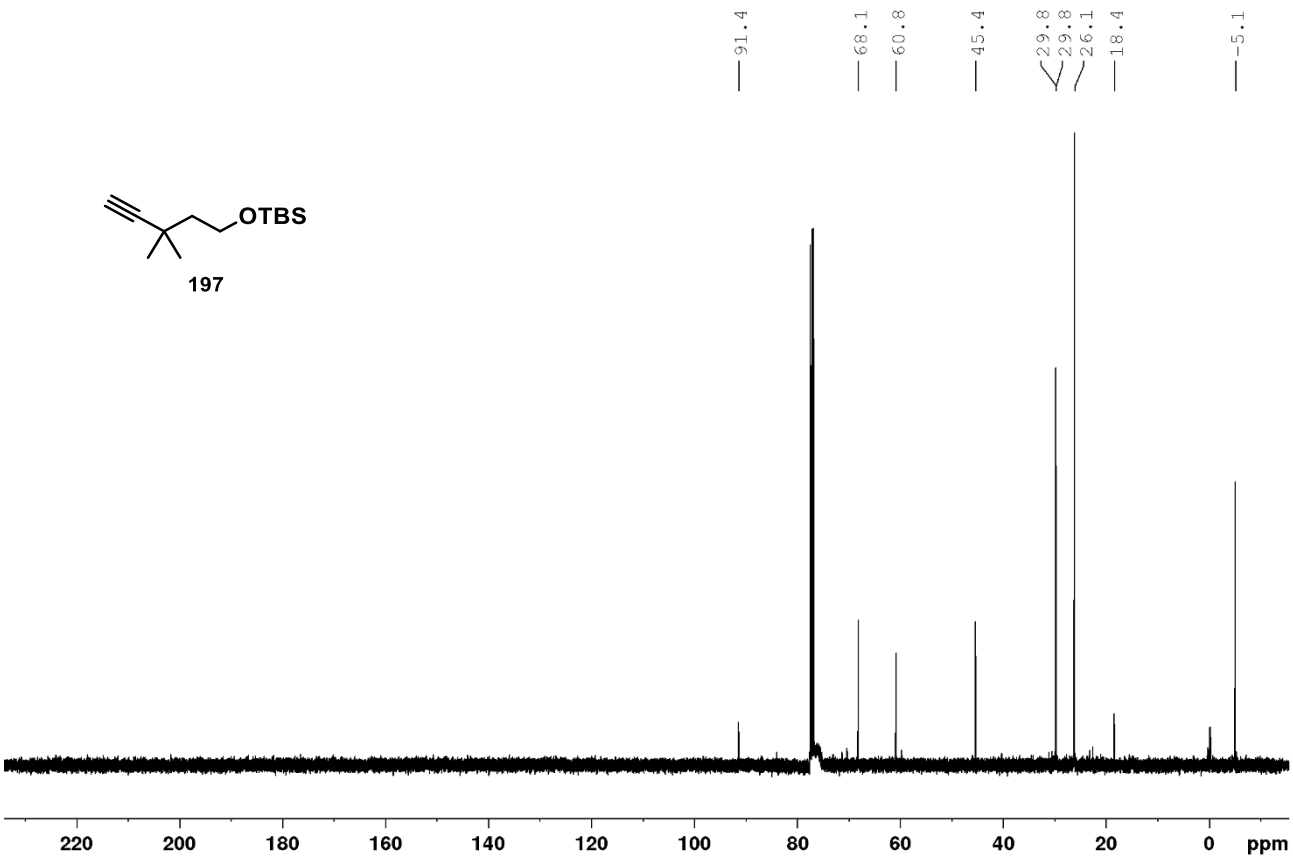
2
1
0
ppm


91.4
68.1
60.8
45.4
29.8
29.8
26.1
18.4
-5.1
OTBS
197
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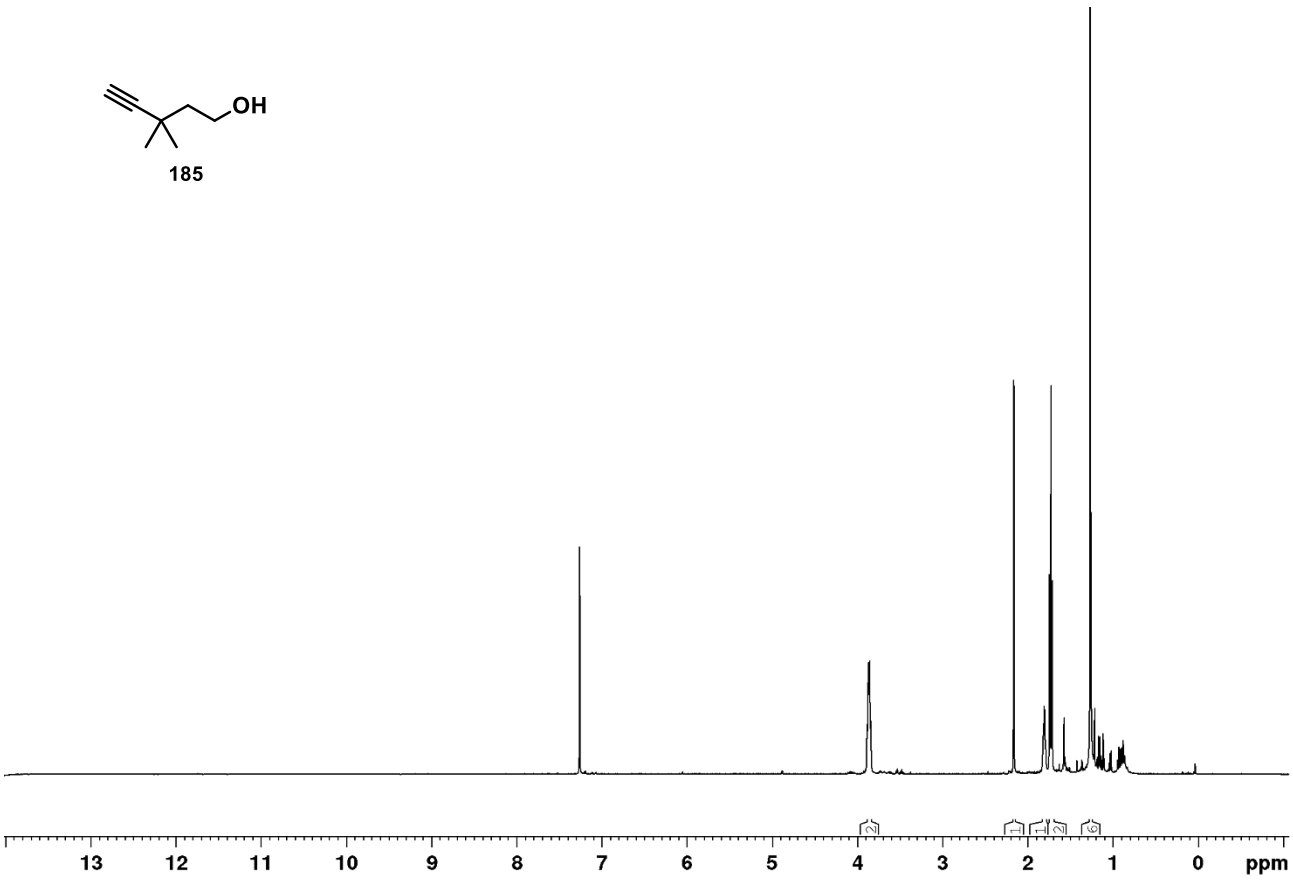
200
180
160
140
120
100
80
60
40
20
0
ppm


OH
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6
5
4
3
2
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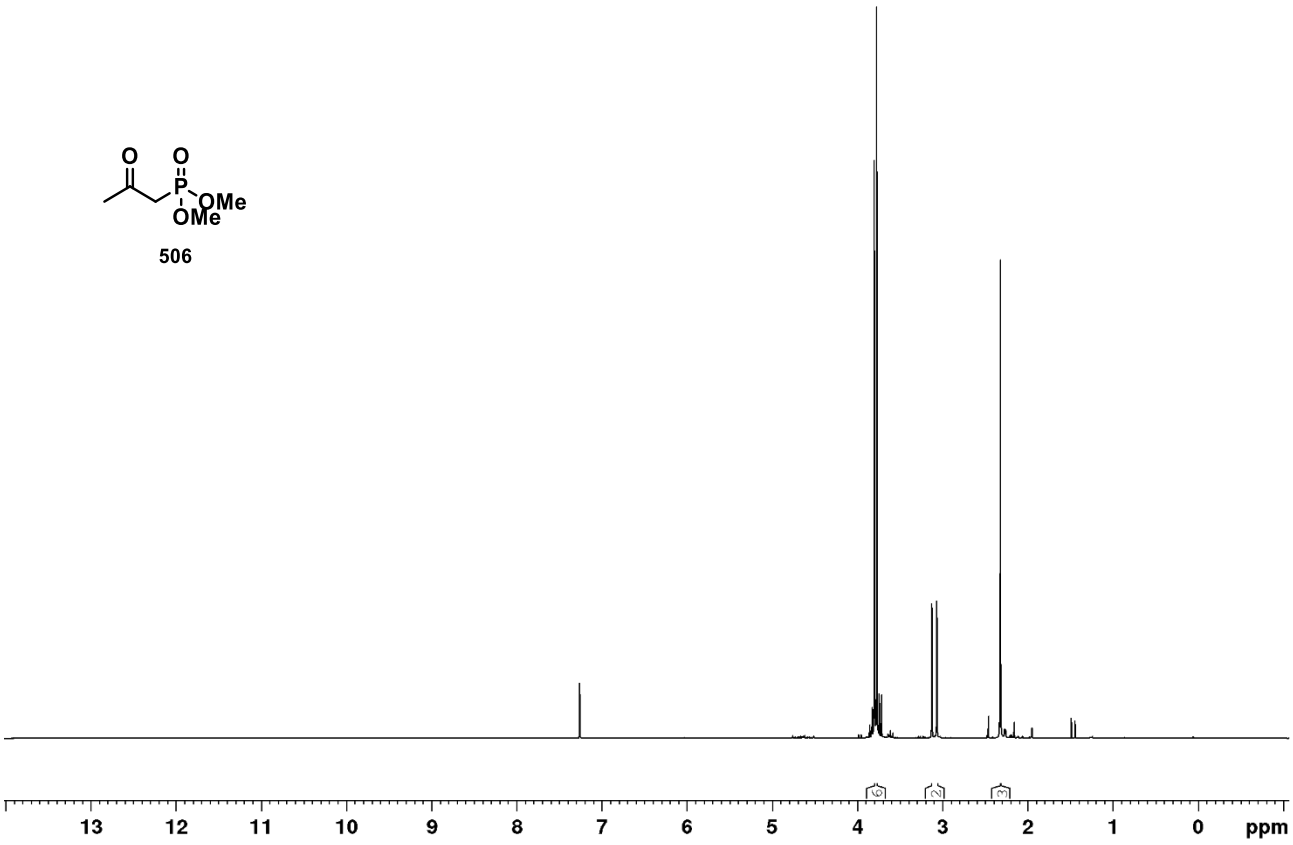
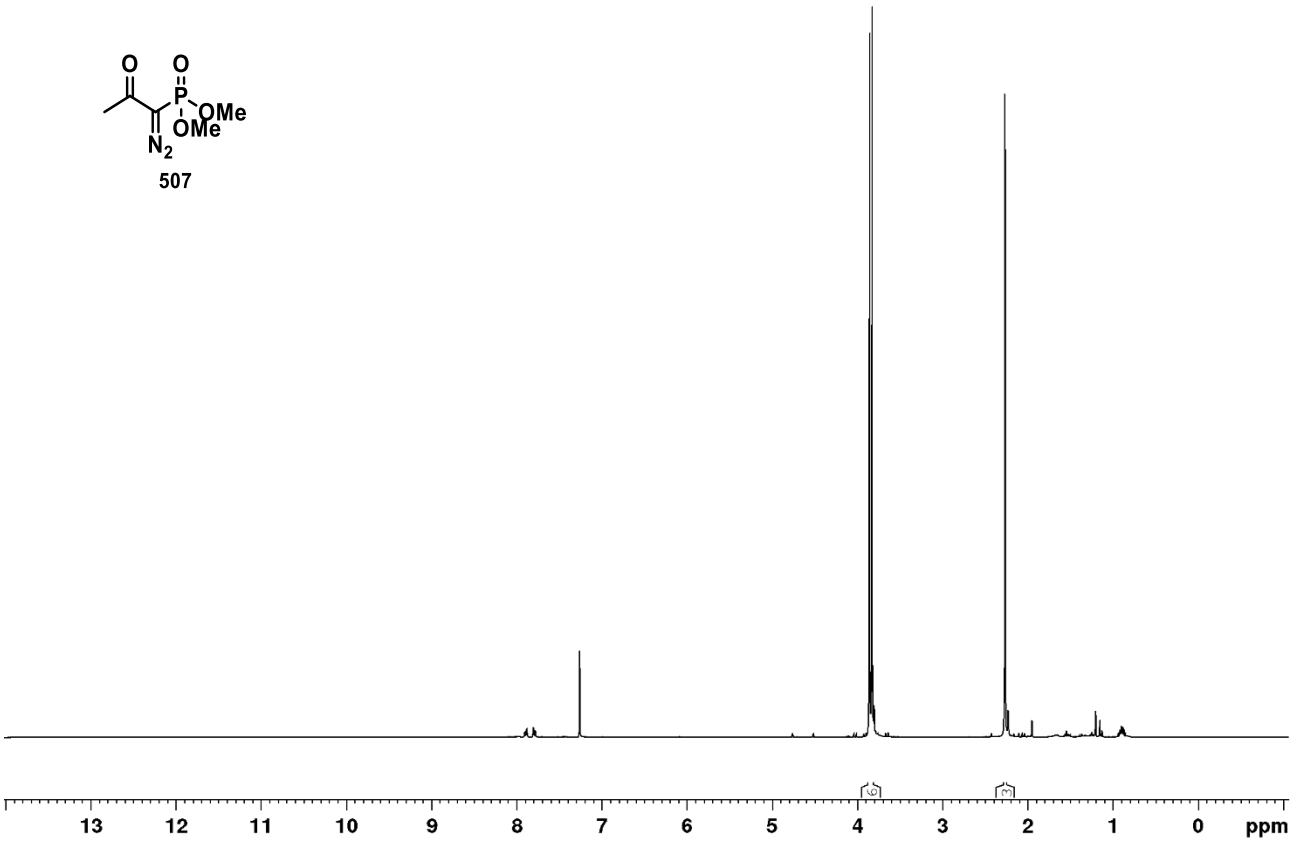
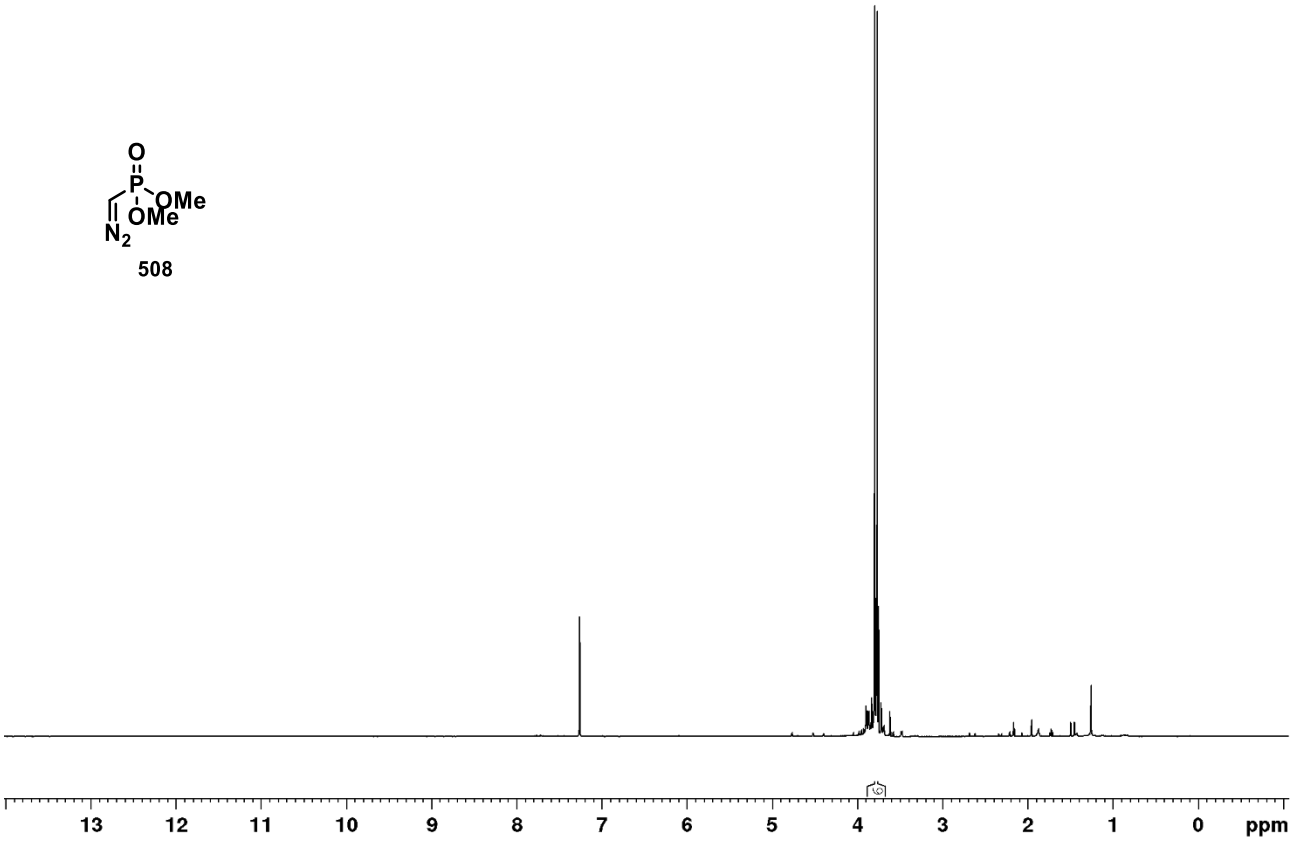
0
ppm

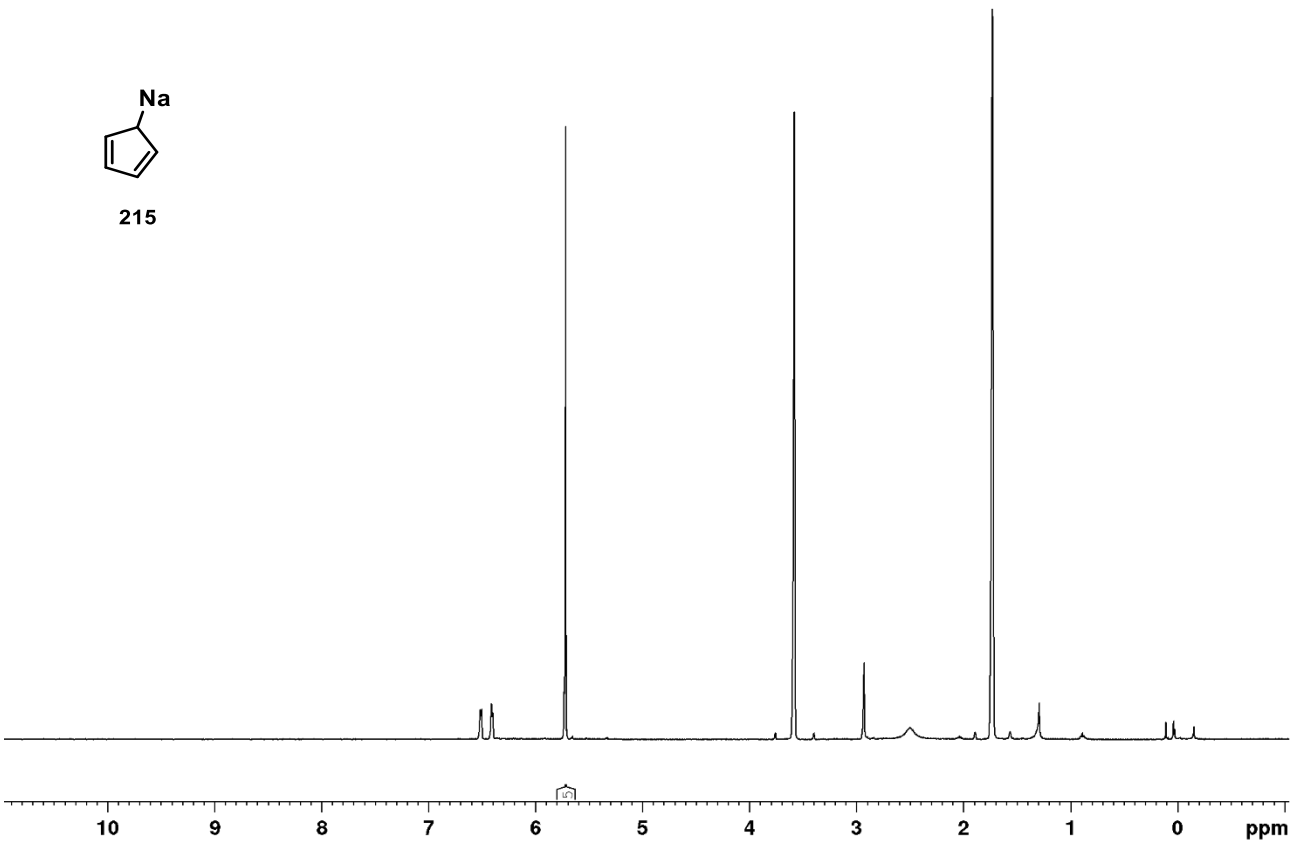

O
O
P
OMe
OMe
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

506


O
O
P
OMe
OMe
N2
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

507


O
P
OMe
OMe
N2
508
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


Na
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2
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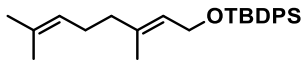
0
ppm


OTBDPS

247

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12
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10
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8
7
6
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4
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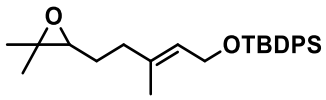
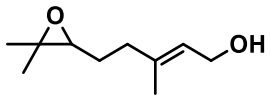
2
1
0
ppm

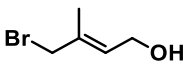

O
OTBDPS

248

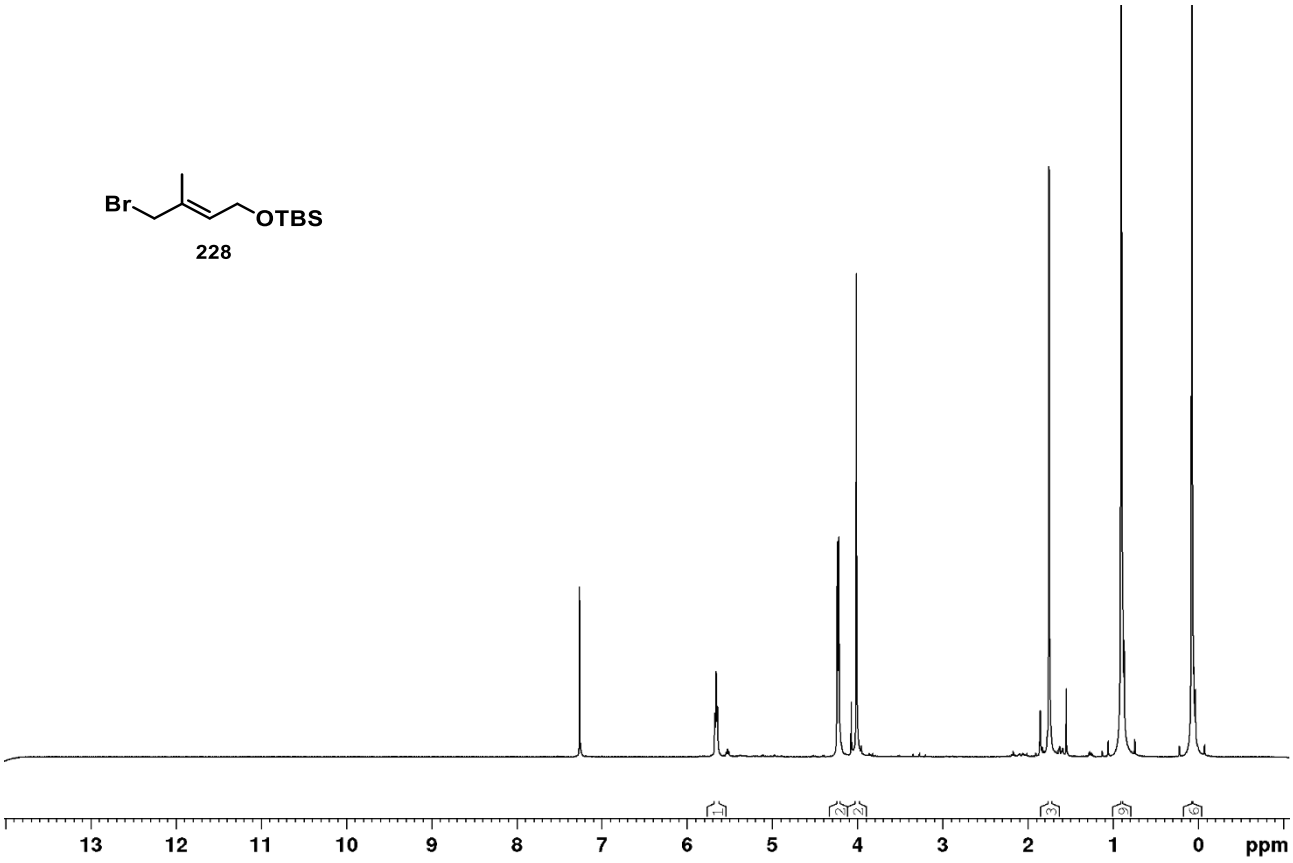
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm



229



250


Br
OTBS
228
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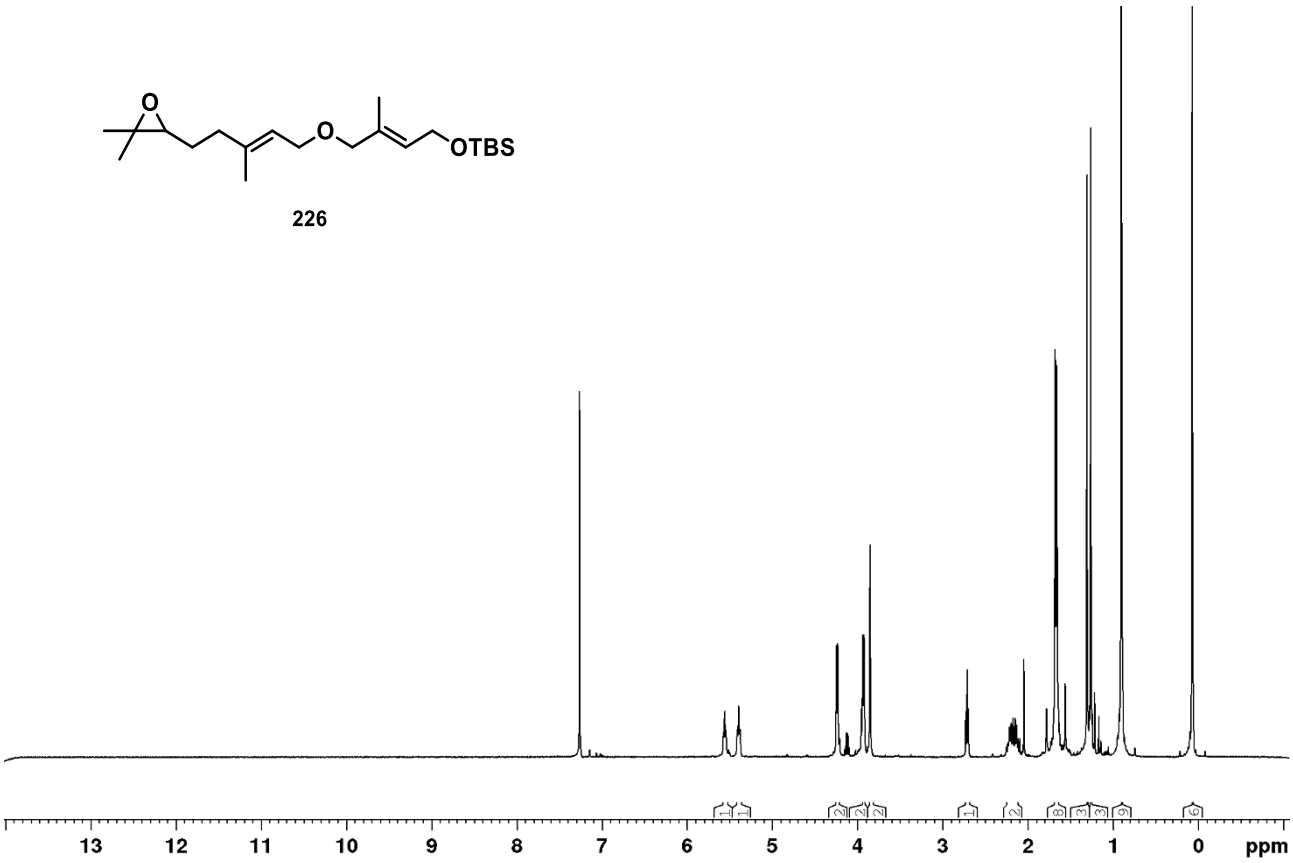
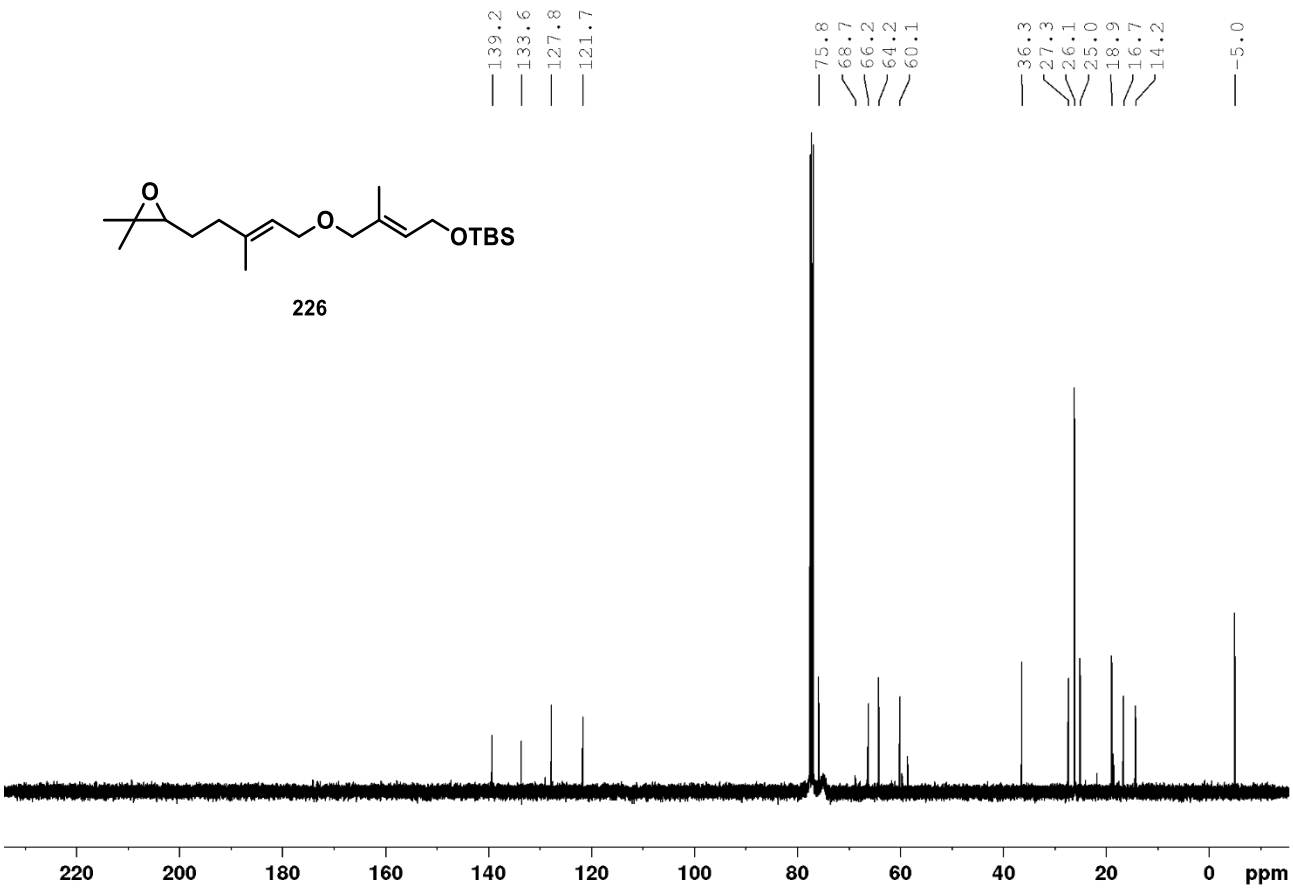
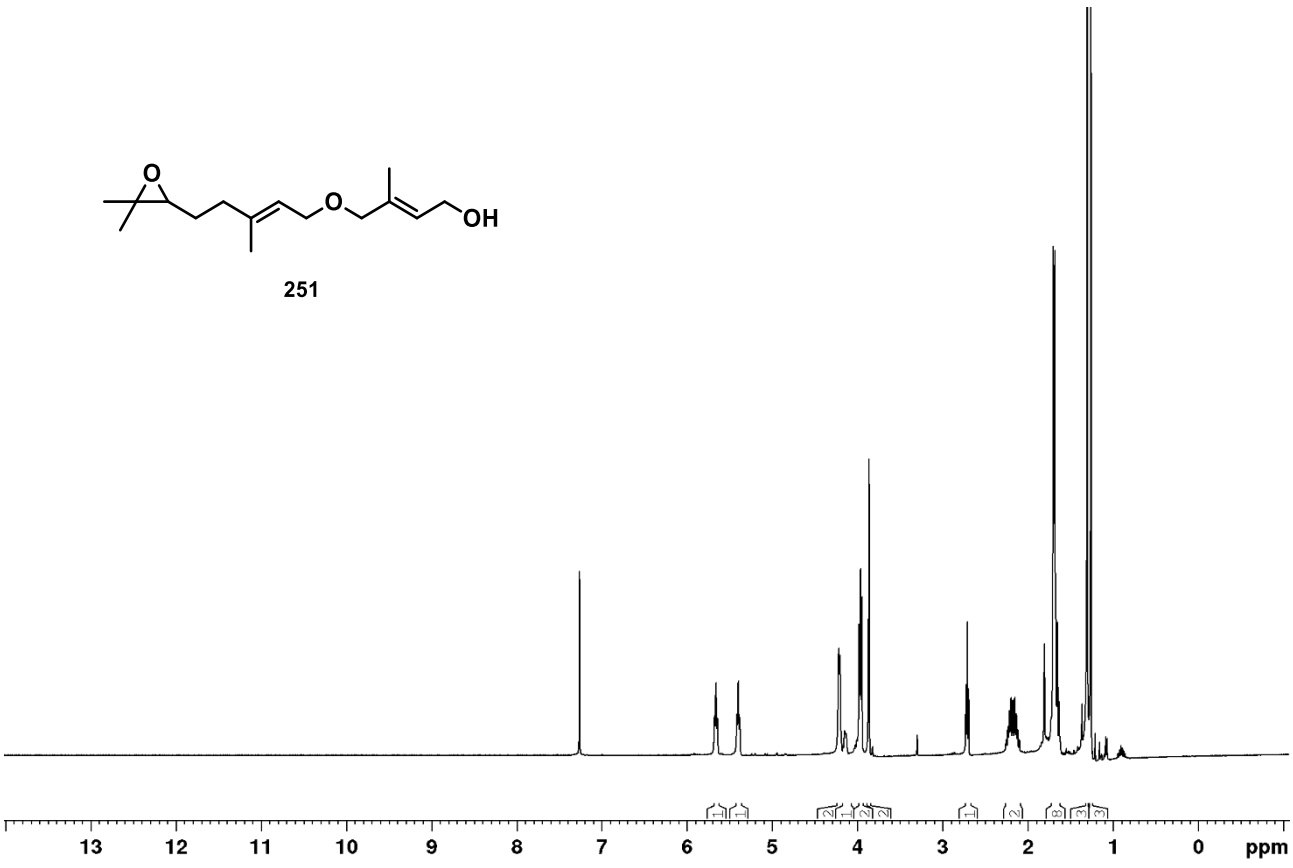
11
10
9
8
7
6
5
4
3
2
1
0
ppm

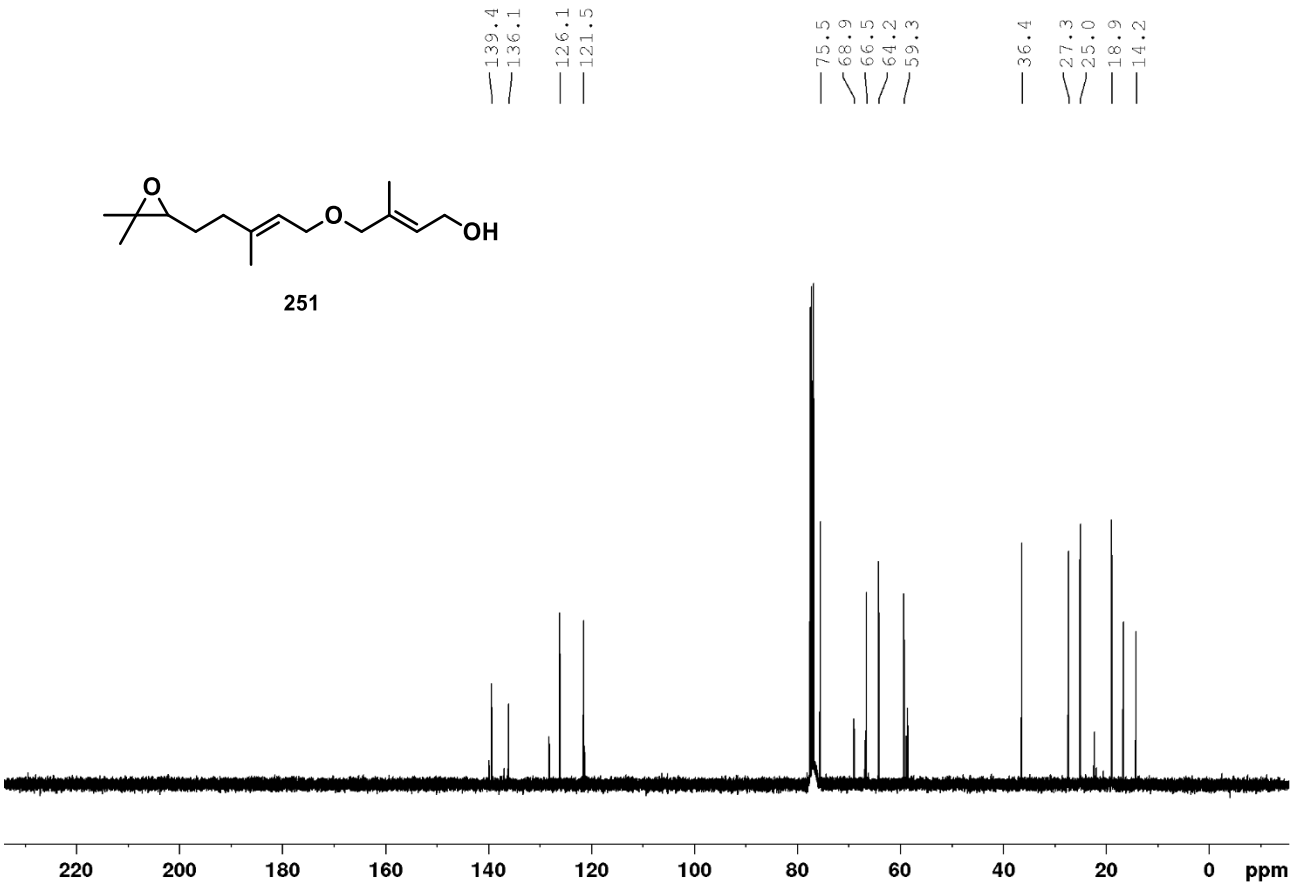

O
O
OTBS
226
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


139.2
133.6
127.8
121.7
75.8
68.7
66.2
64.2
60.1
36.3
27.3
26.1
25.0
18.9
16.7
14.2
-5.0
O
O
OTBS
220
200
180
160
140
120
100
80
60
40
20
0
ppm

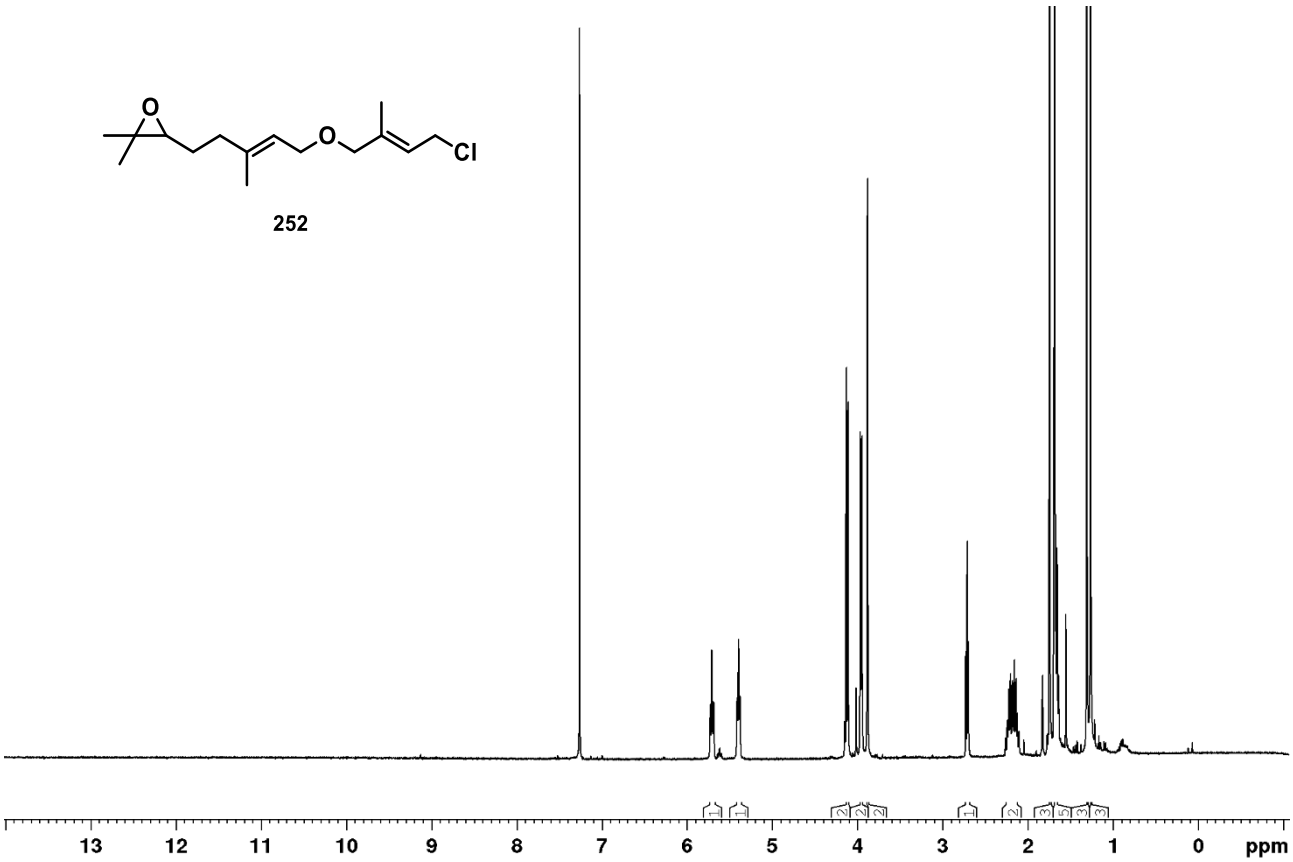
226


O
O
OH
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

251


139.4
136.1
126.1
121.5
75.5
68.9
66.5
64.2
59.3
36.4
27.3
25.0
18.9
14.2
O
O
OH
220
200
180
160
140
120
100
80
60
40
20
0
ppm

251


O
O
Cl
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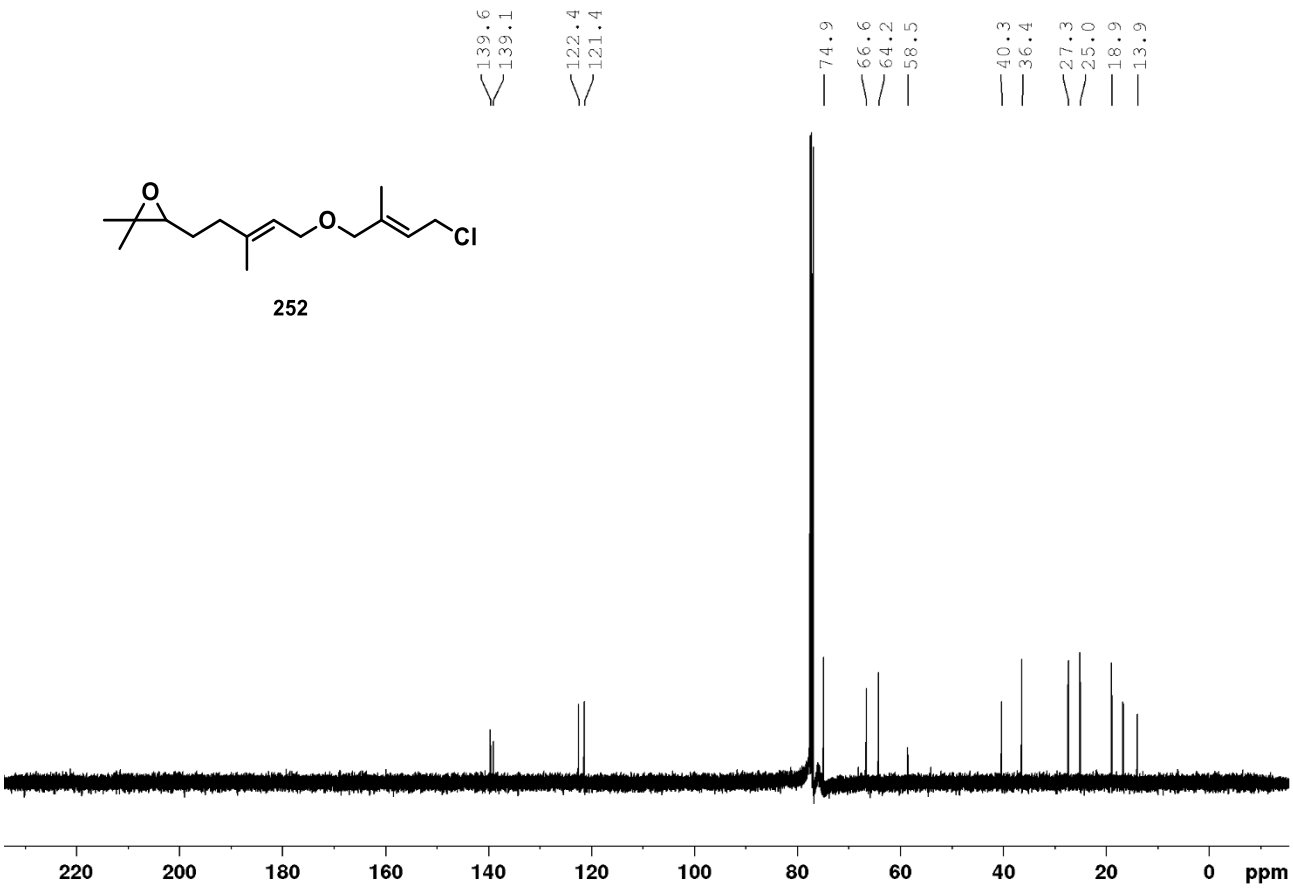
8
7
6
5
4
3
2
1
0
ppm

252


139.6
139.1
122.4
121.4
74.9
66.6
64.2
58.5
40.3
36.4
27.3
25.0
18.9
13.9
O
O
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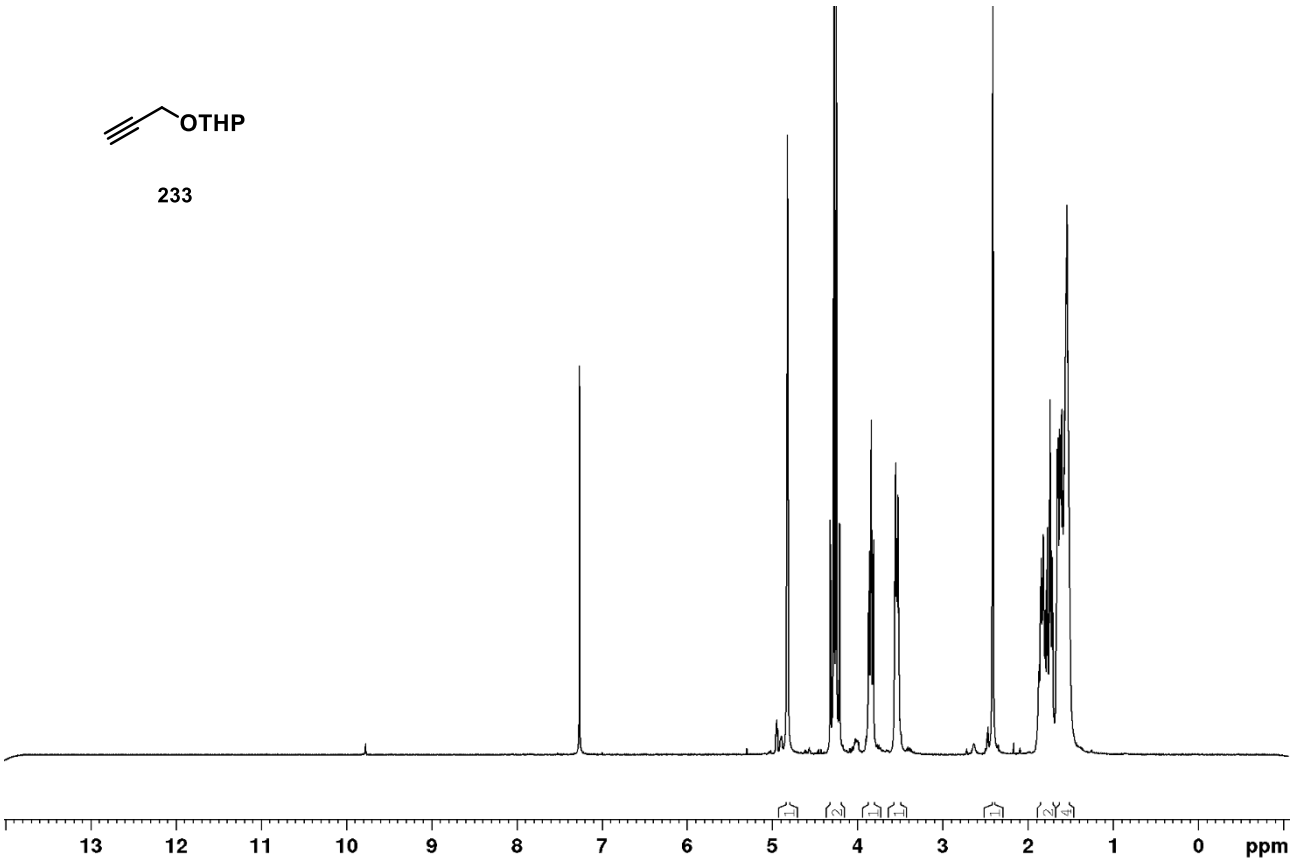
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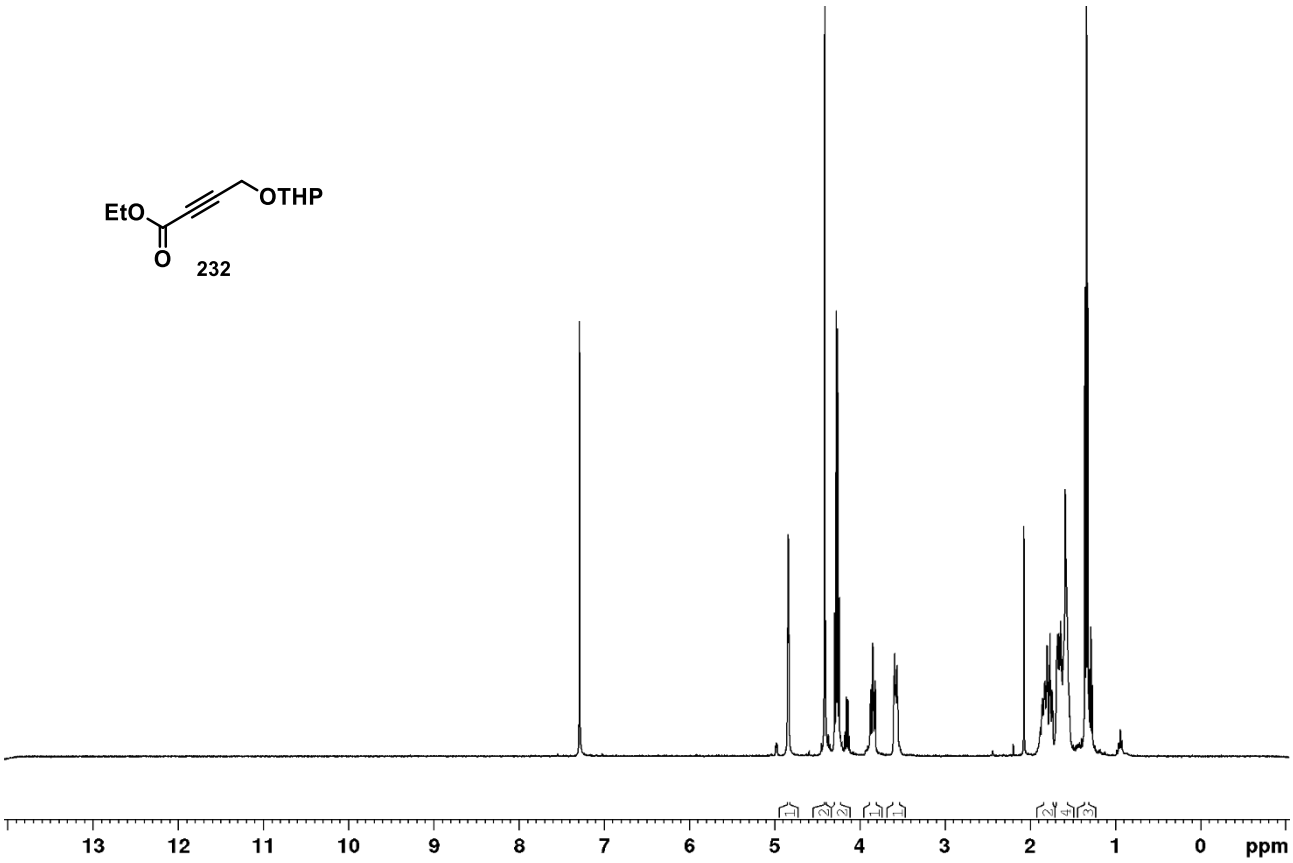
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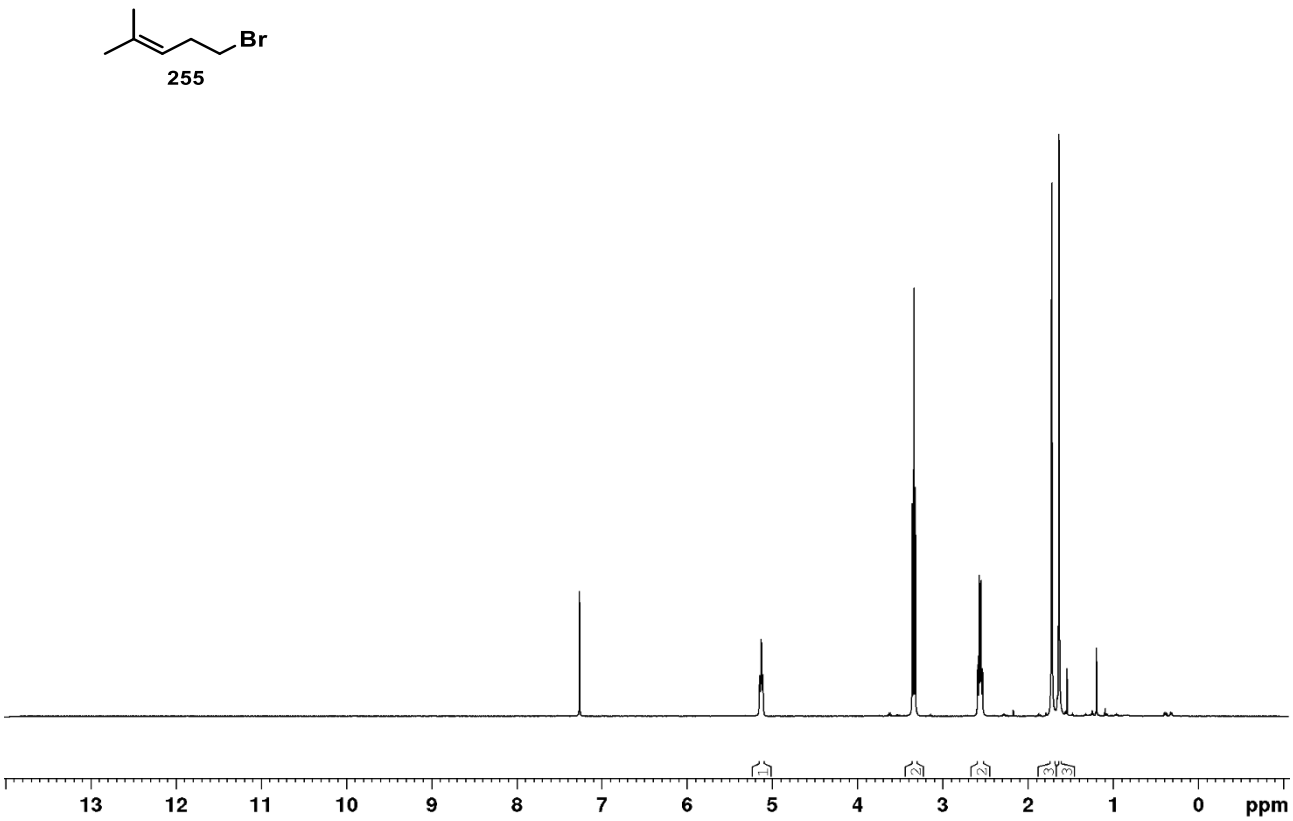
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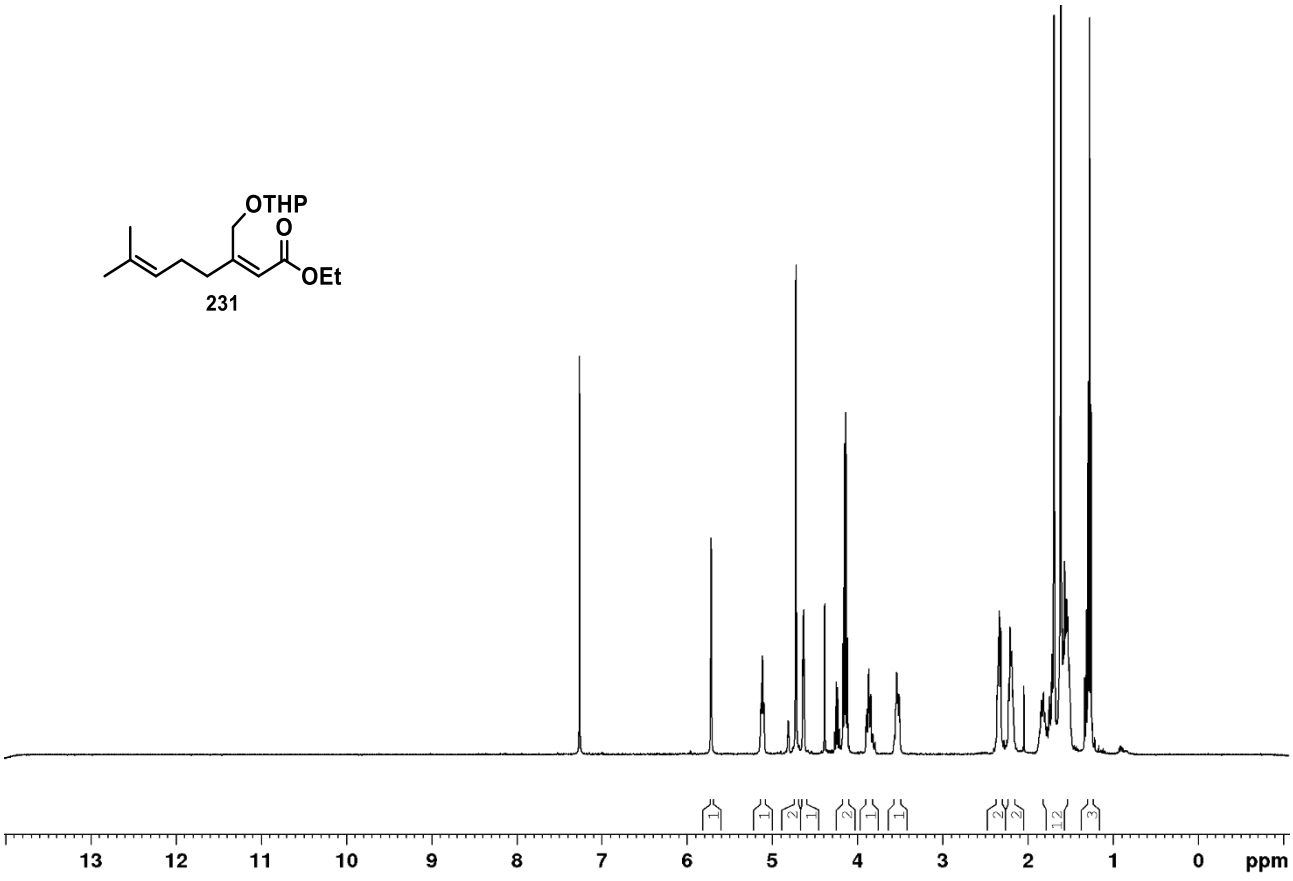
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OEt
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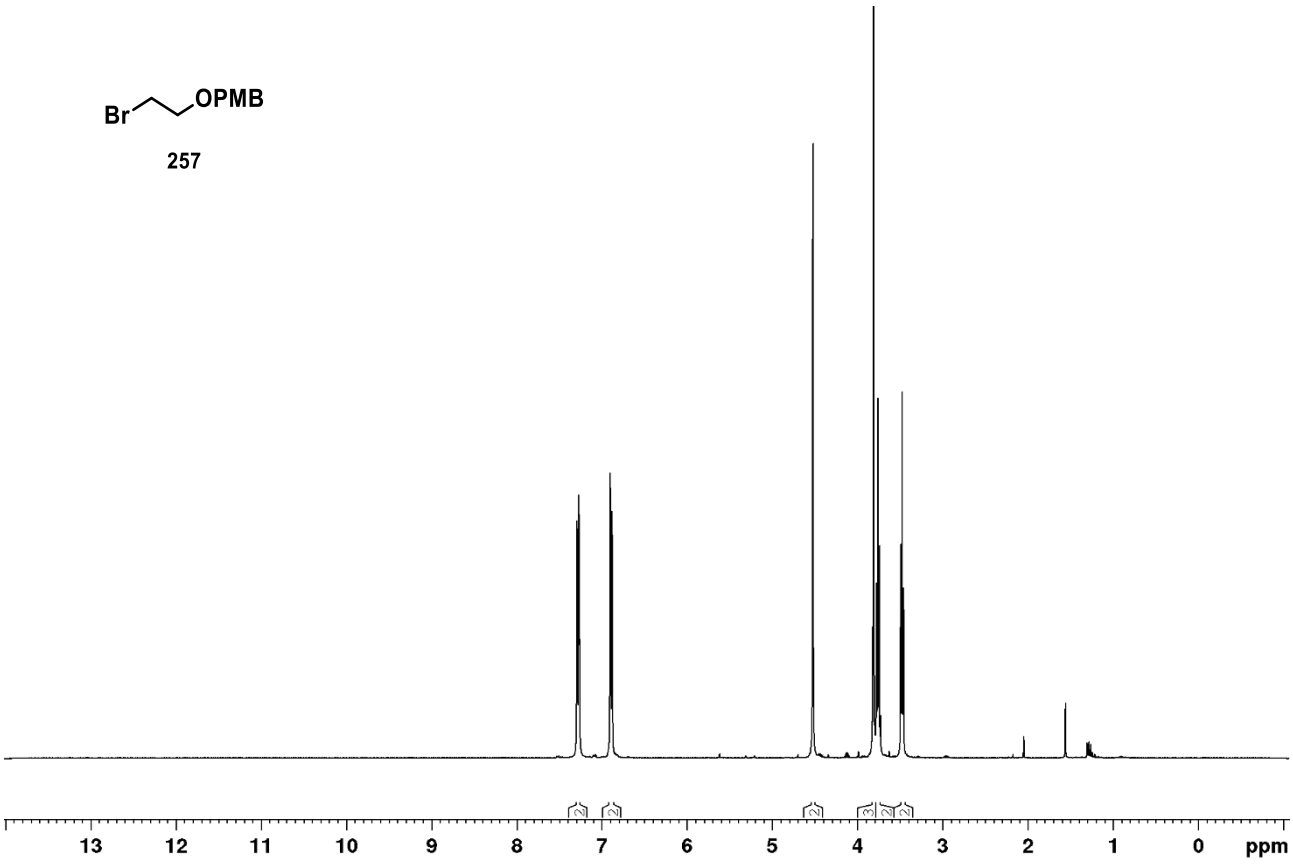
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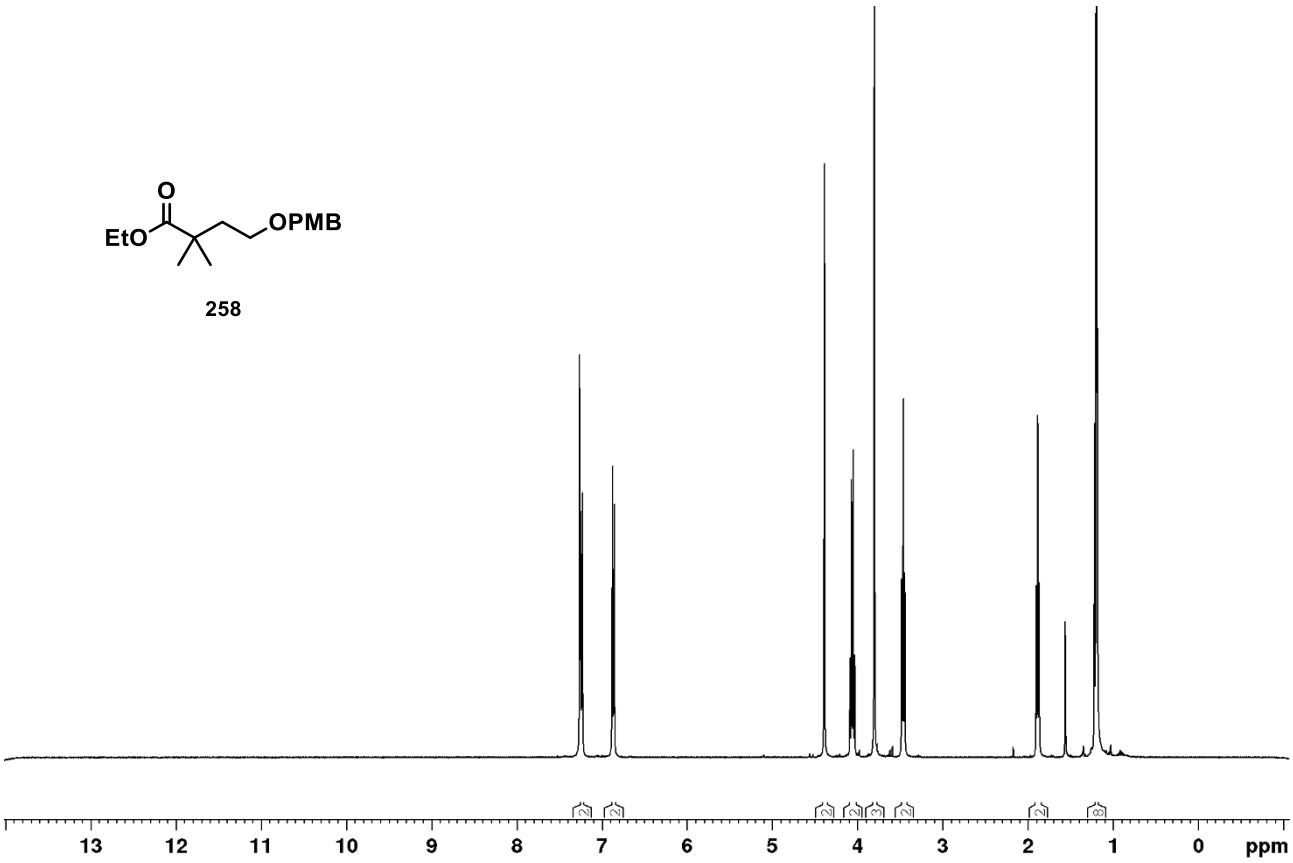
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OPMB
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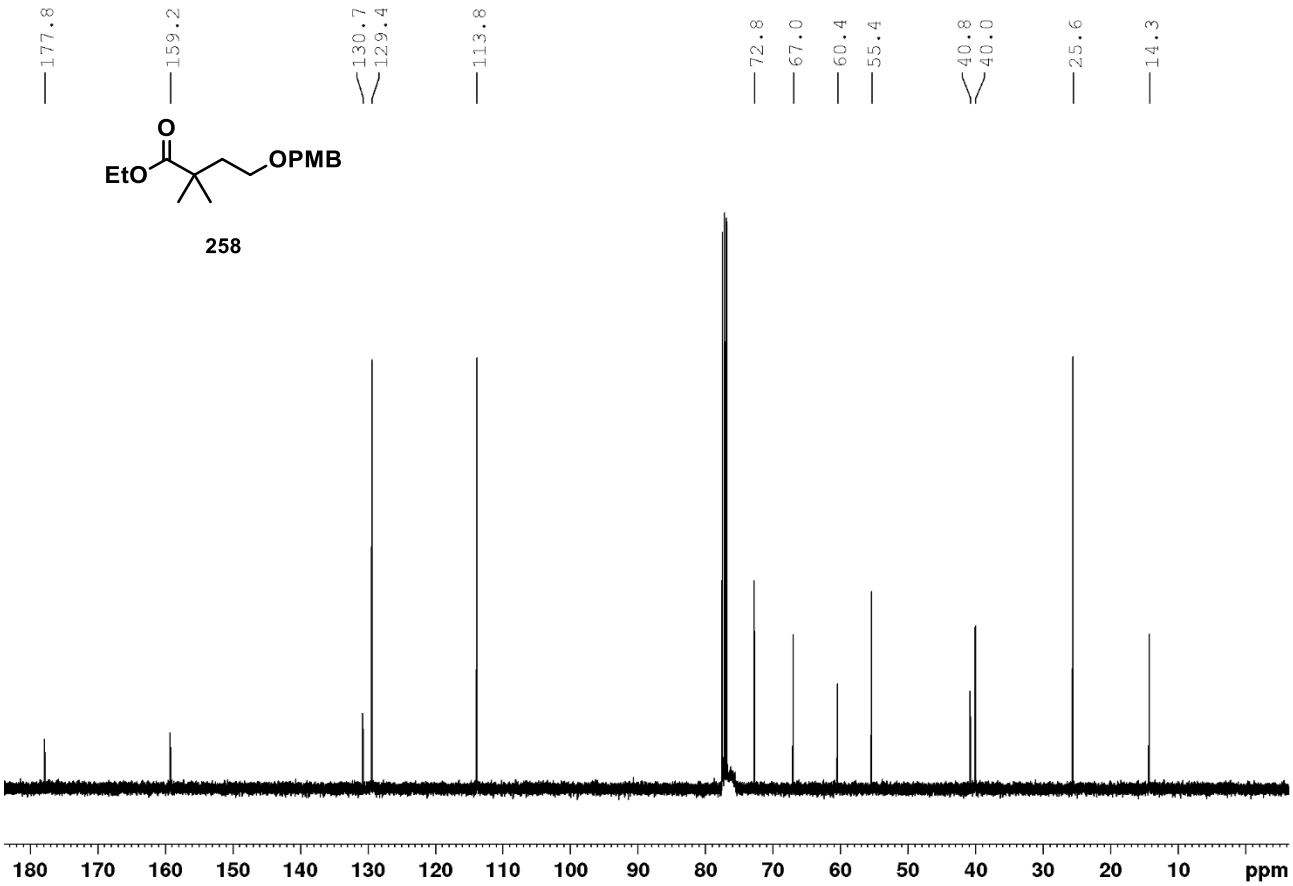
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72.8
67.0
60.4
55.4
40.8
40.0
25.6
14.3
O
EtO
OPMB
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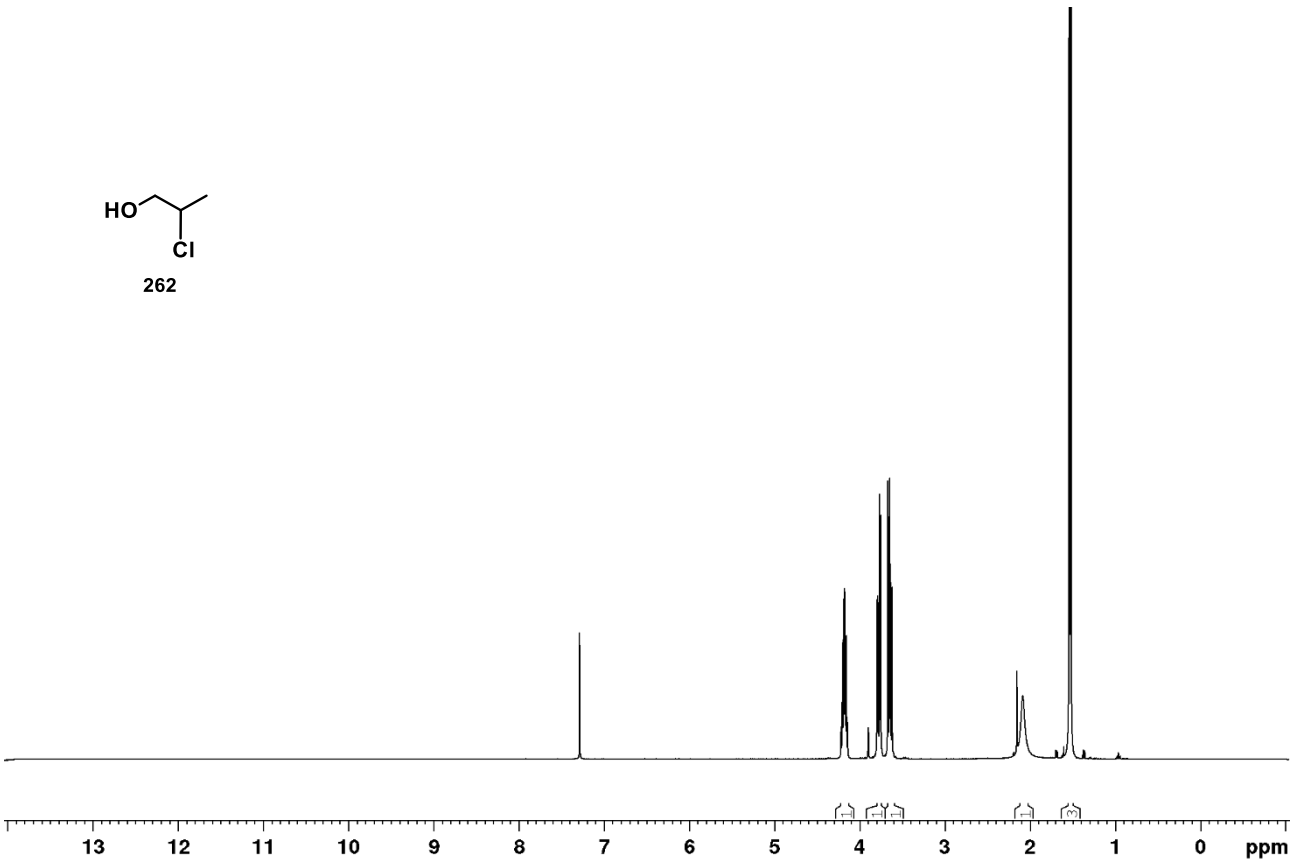
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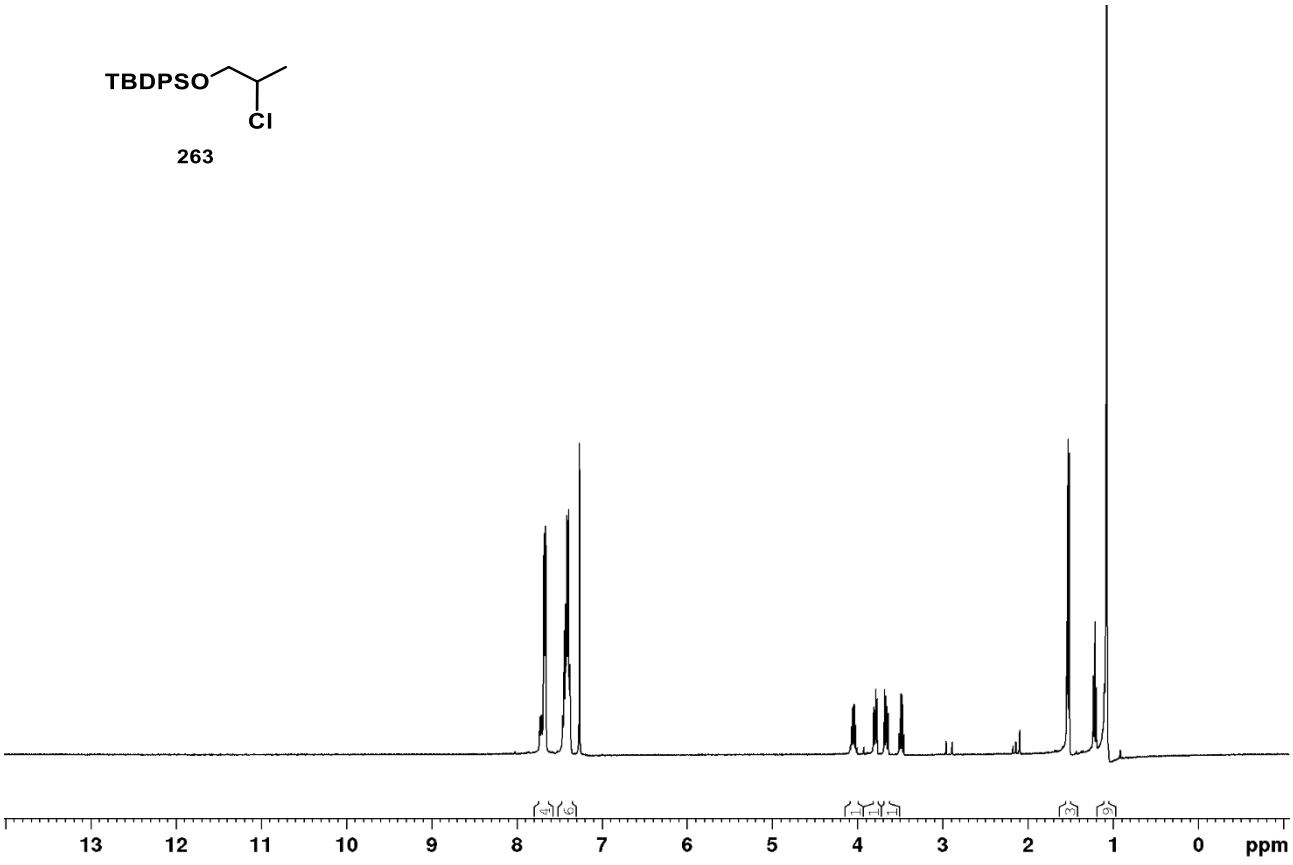
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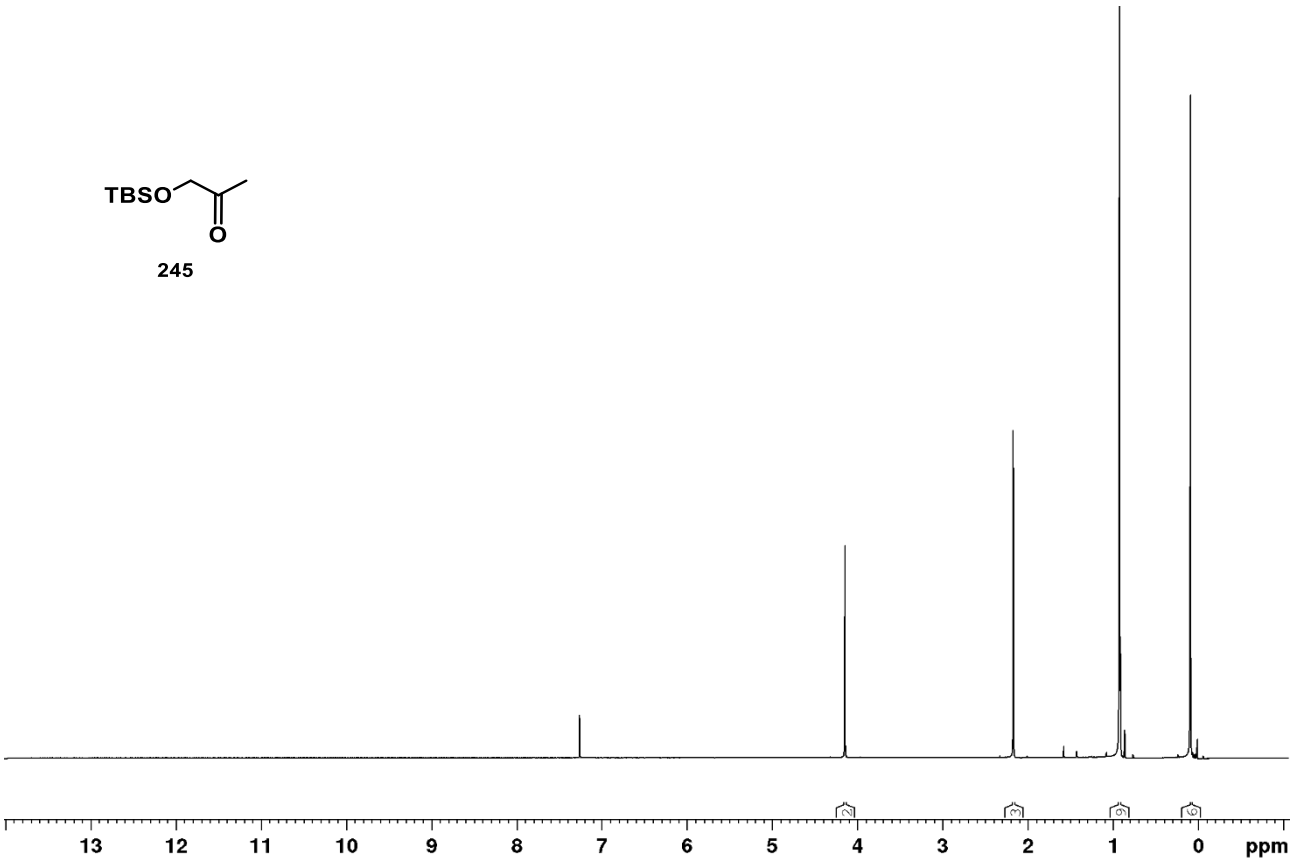
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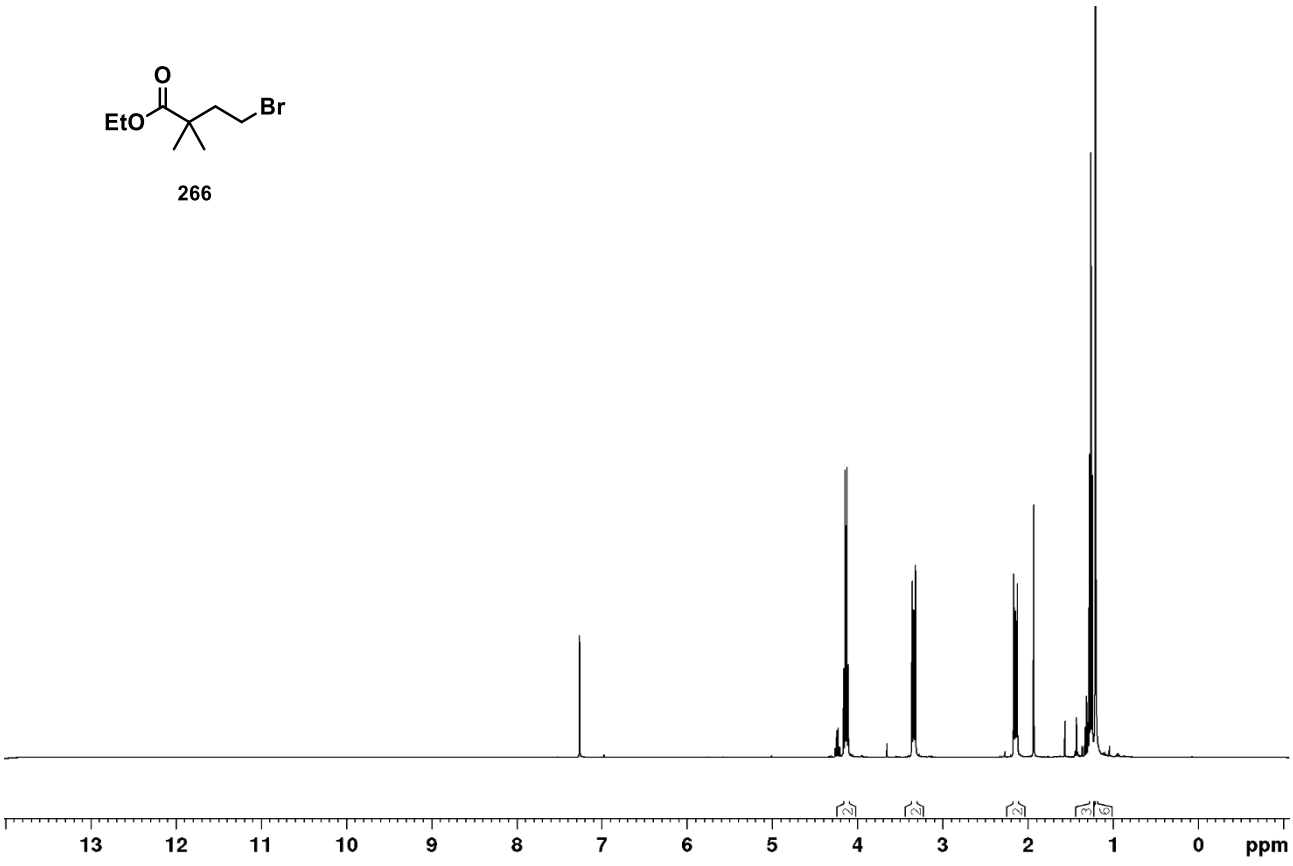
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EtO
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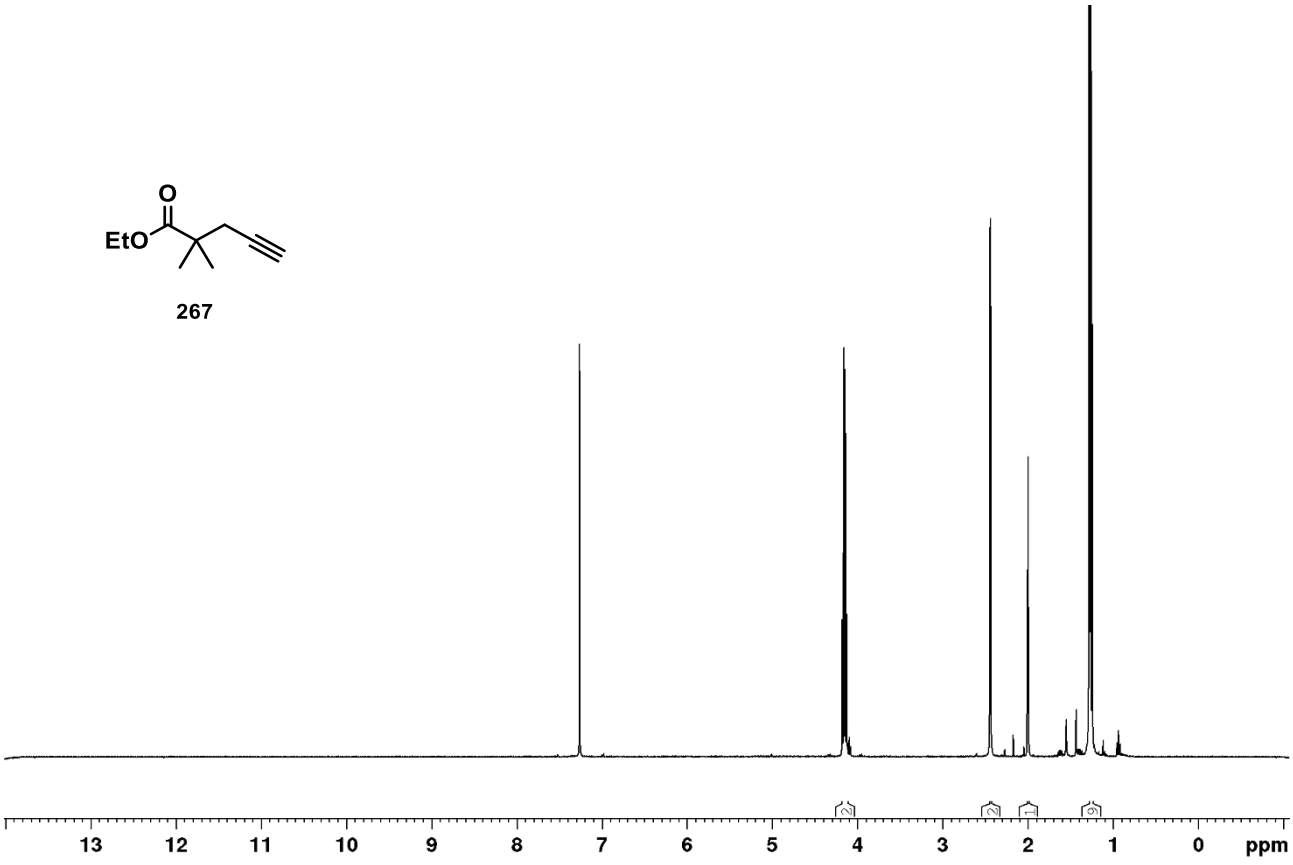
ppm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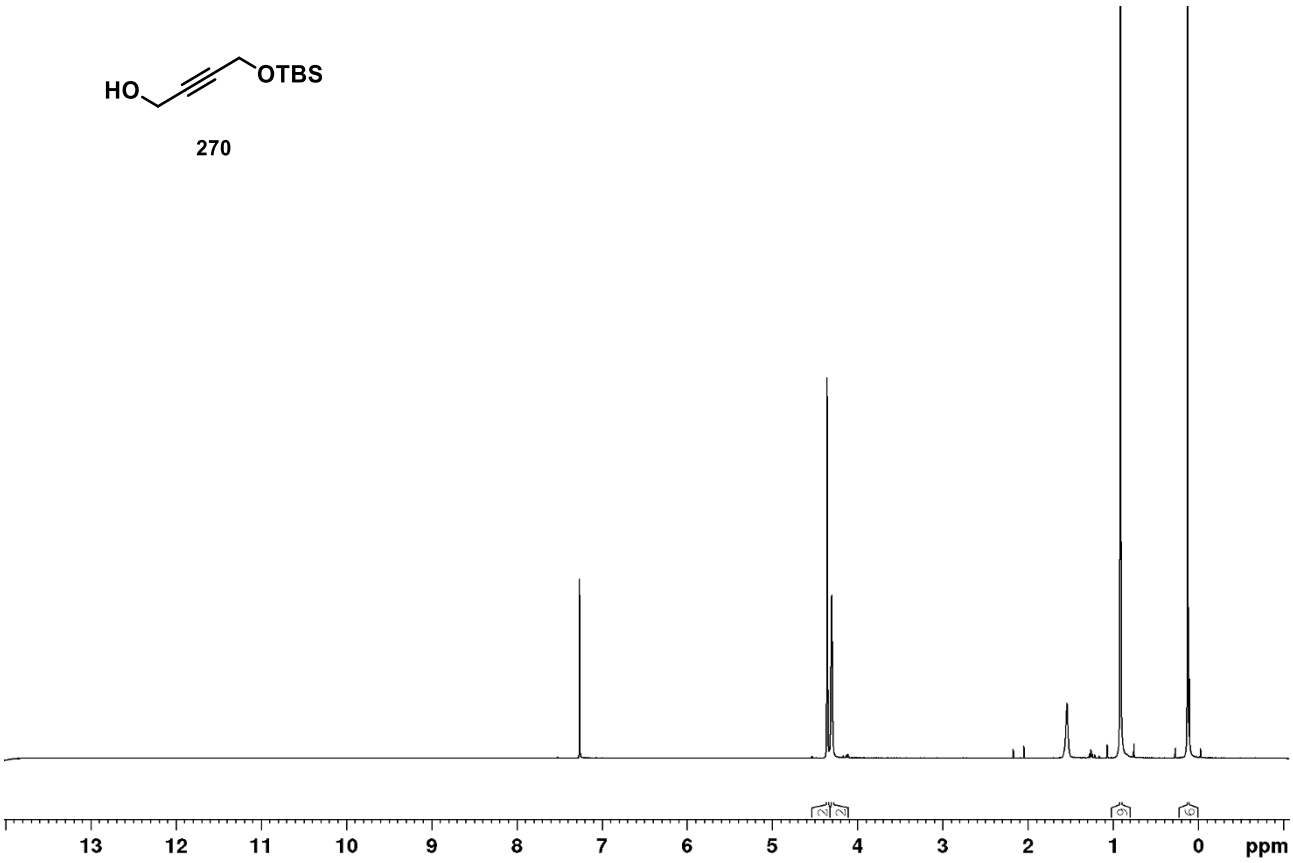
ppm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OTBS
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4
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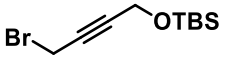
2
1
0
ppm


Br
OTBS

271

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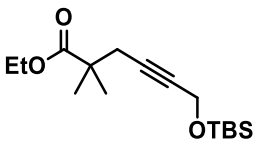
O
EtO
OTBS

272

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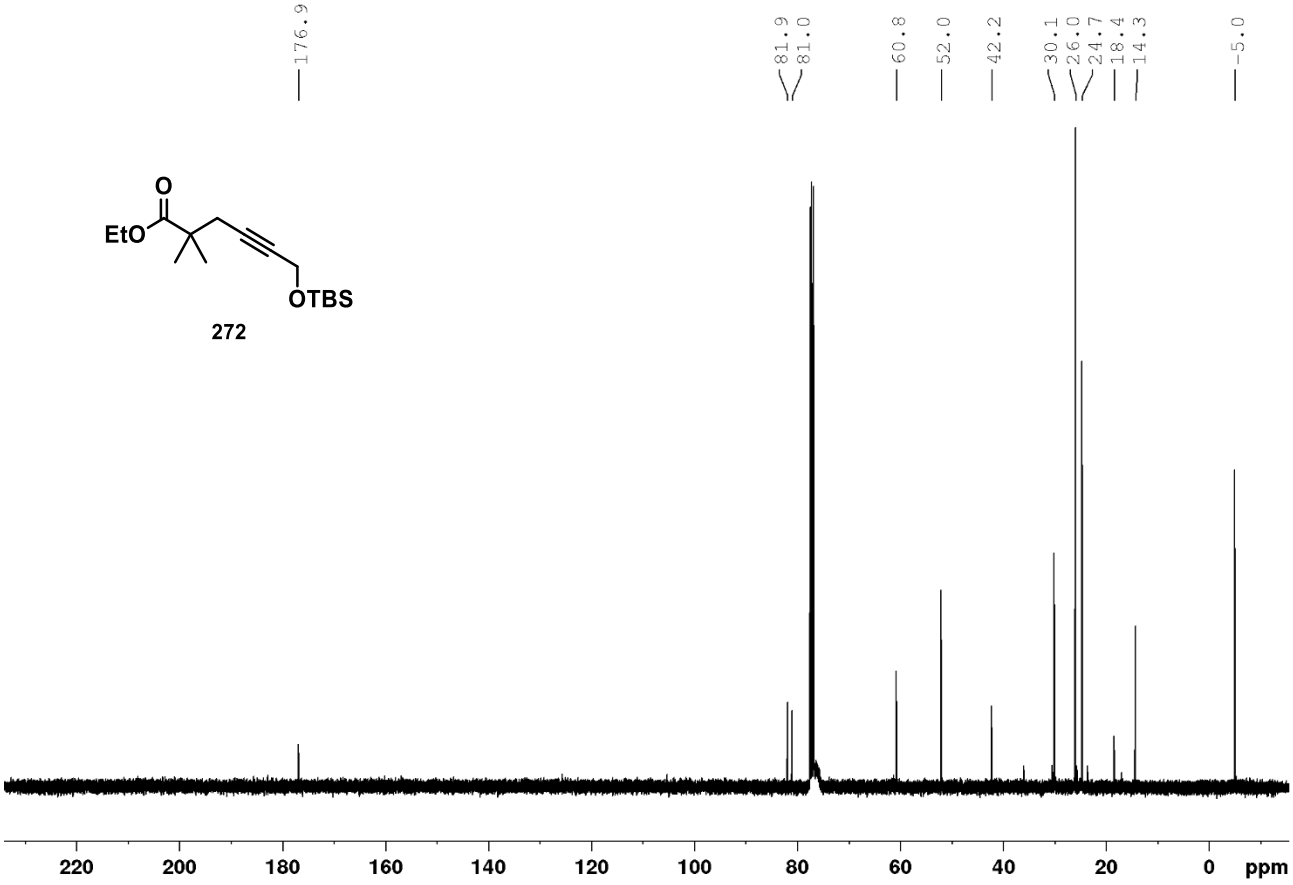
ppm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81.9
81.0
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52.0
42.2
30.1
26.0
24.7
18.4
14.3
-5.0
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OTBS
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100
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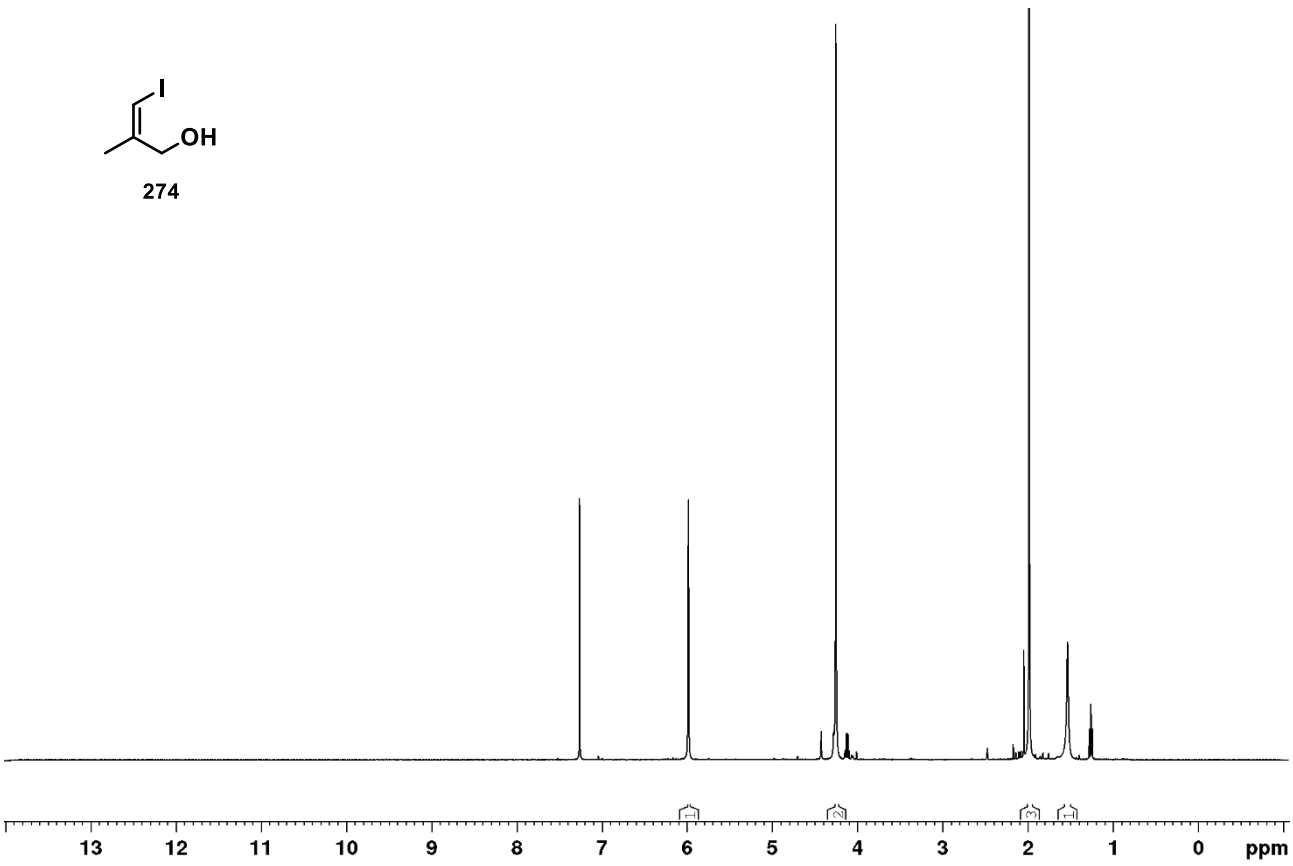
60
40
20
0
ppm

272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ppm

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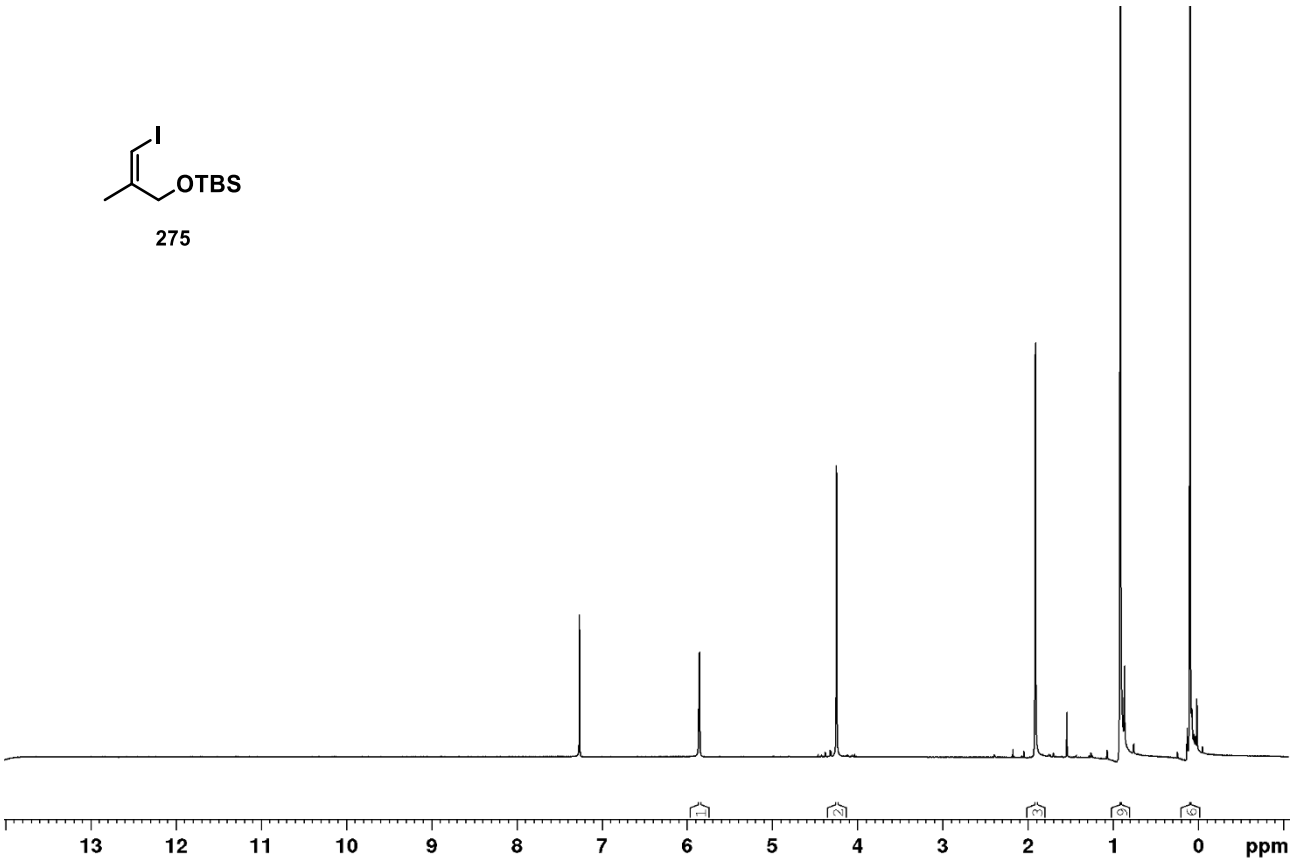
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ppm

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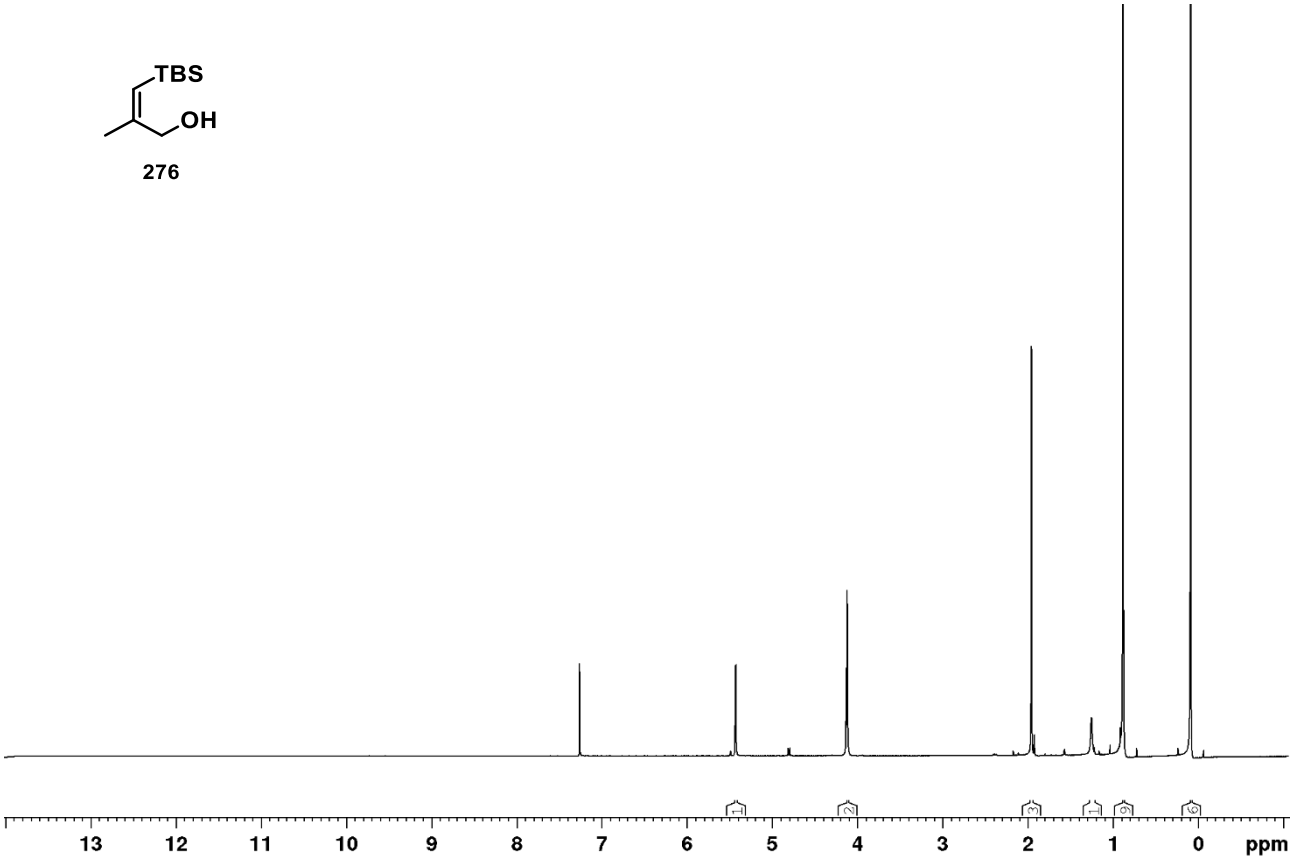
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3
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ppm

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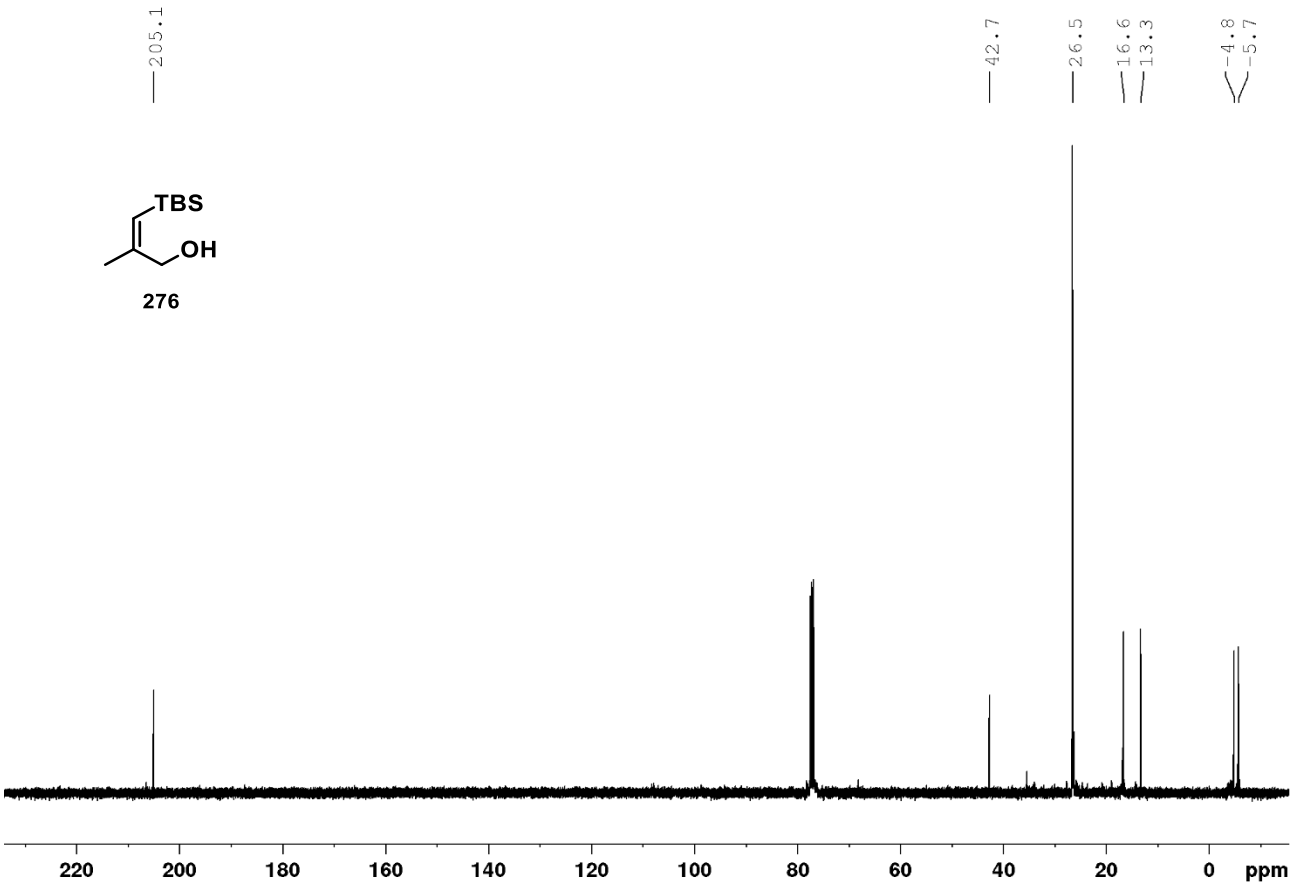
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42.7
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16.6
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-5.7
TBS
OH
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180
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140
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100
80
60
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20
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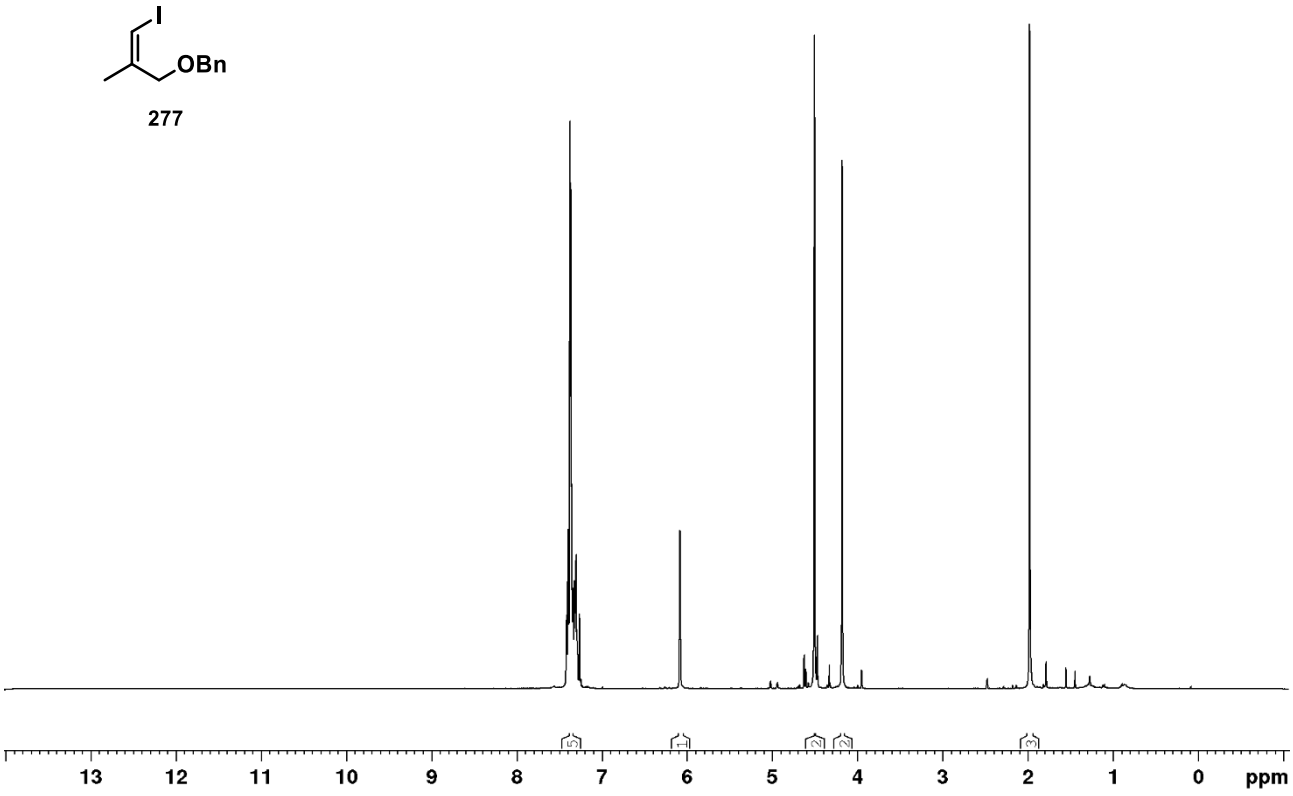
ppm

276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ppm

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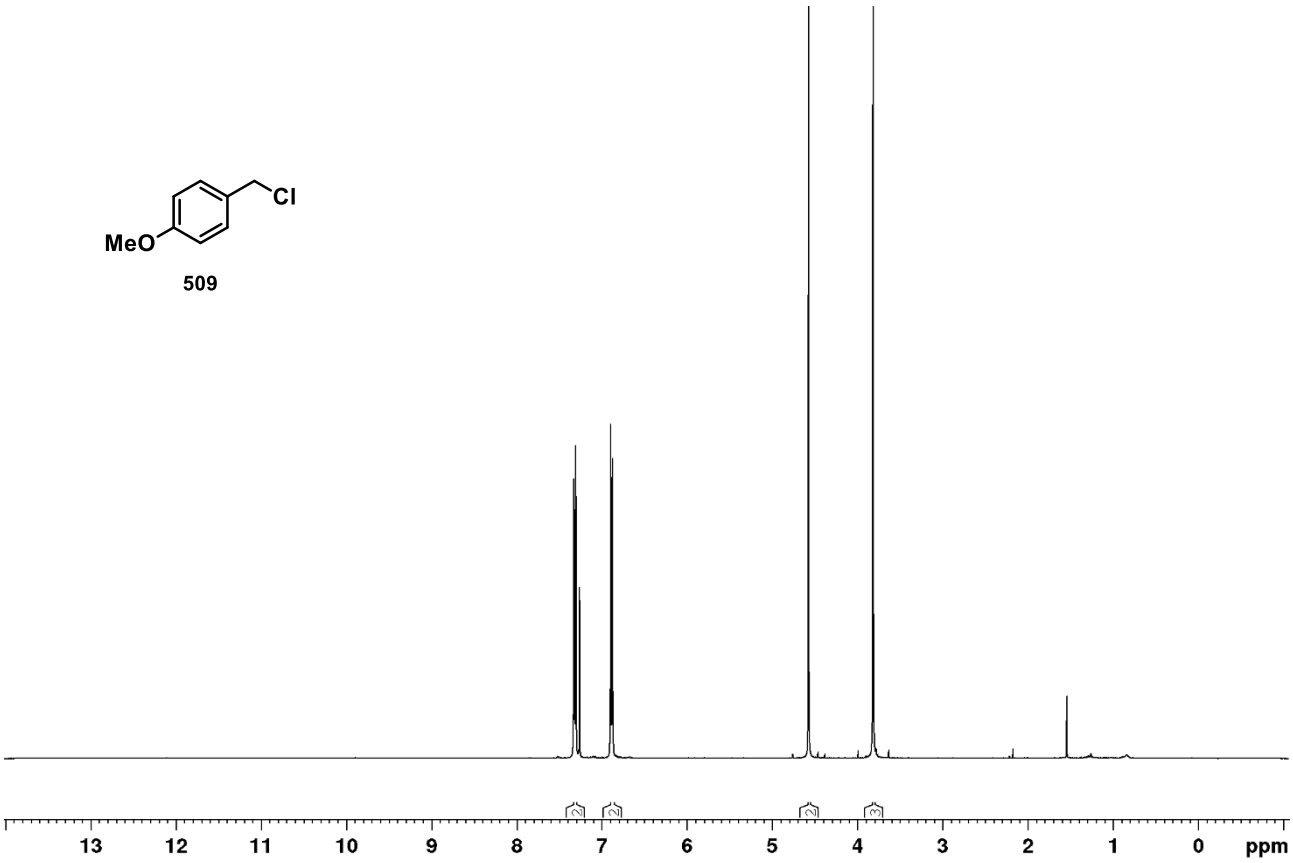
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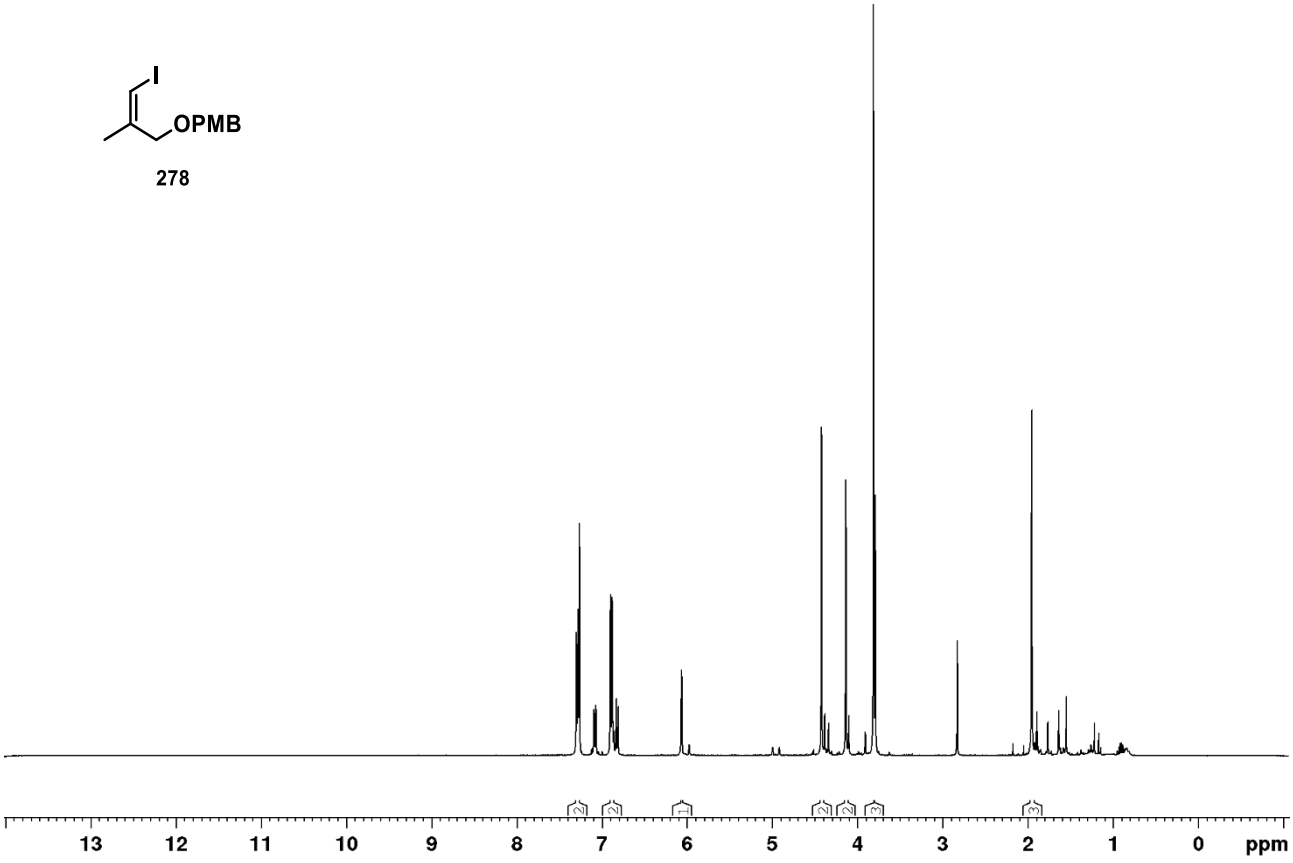
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OPMB
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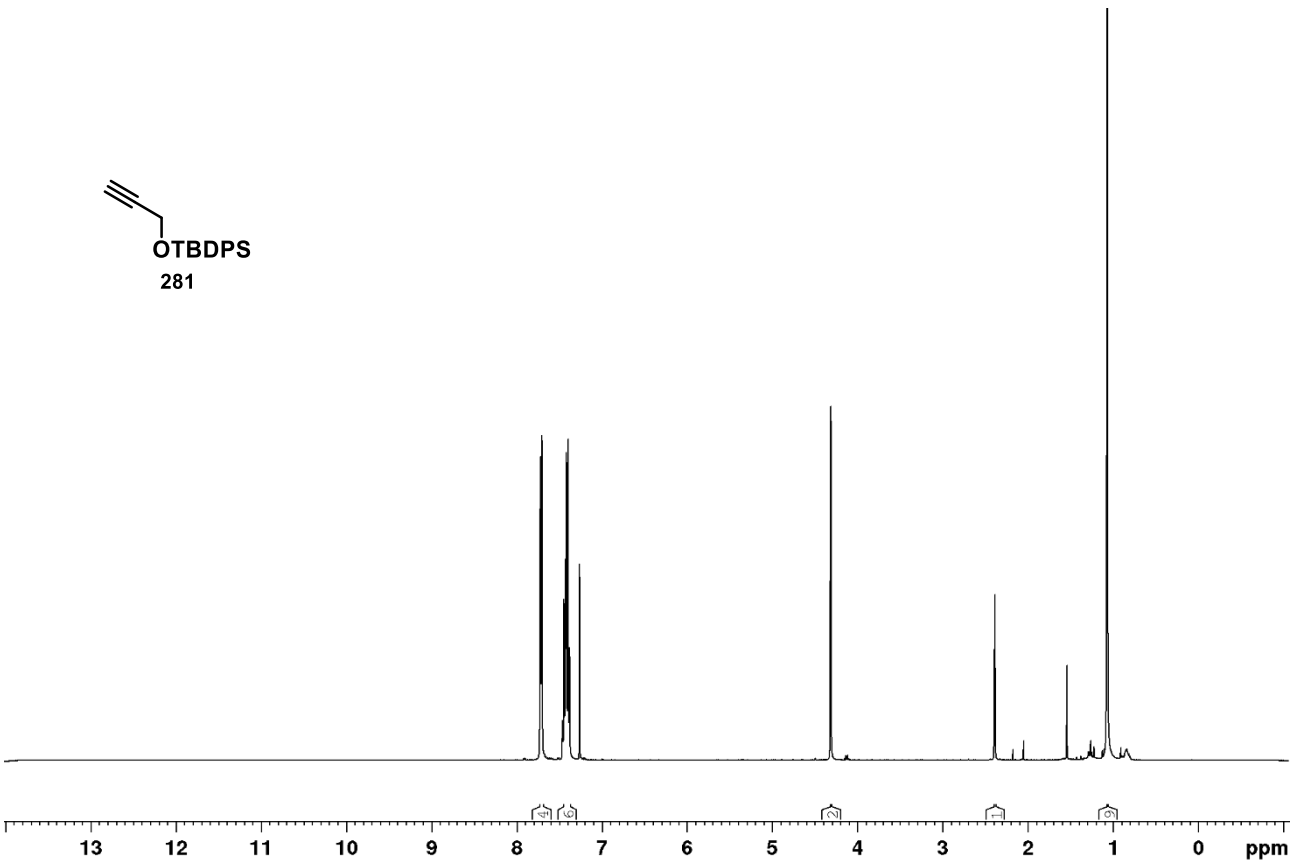
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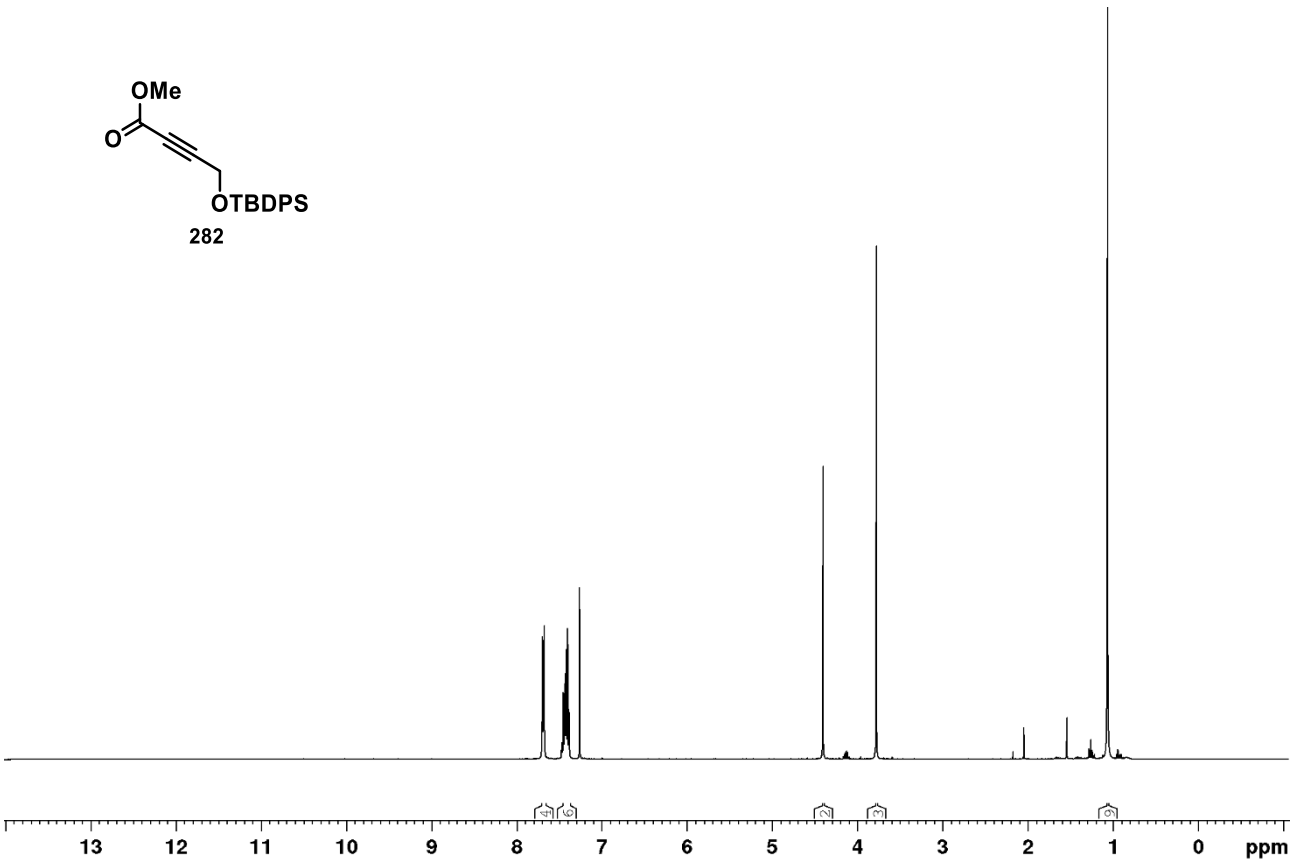
0
ppm


OMe
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OTBDPS
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2
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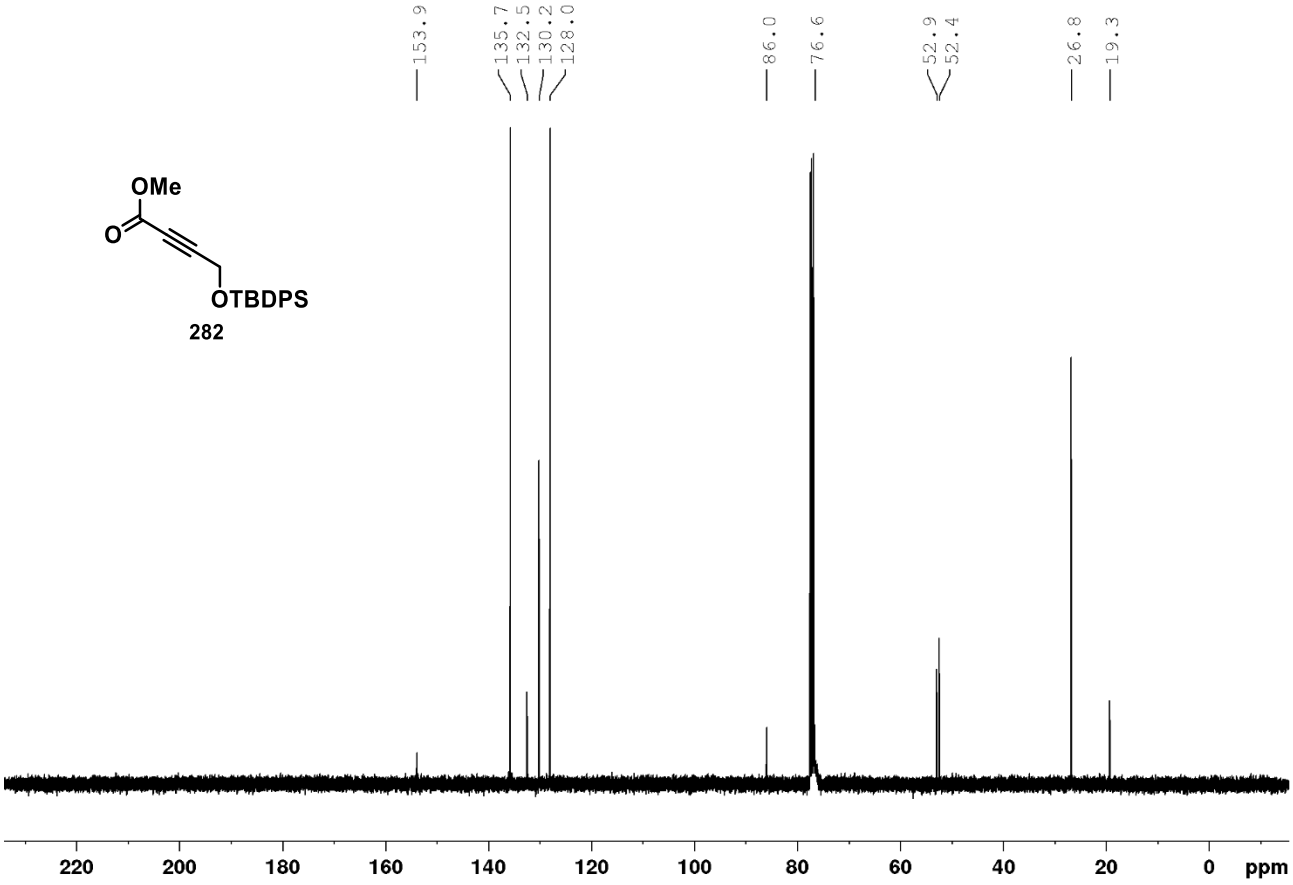
0
ppm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132.5
130.2
128.0
86.0
76.6
52.9
52.4
26.8
19.3
OMe
O
OTBDPS
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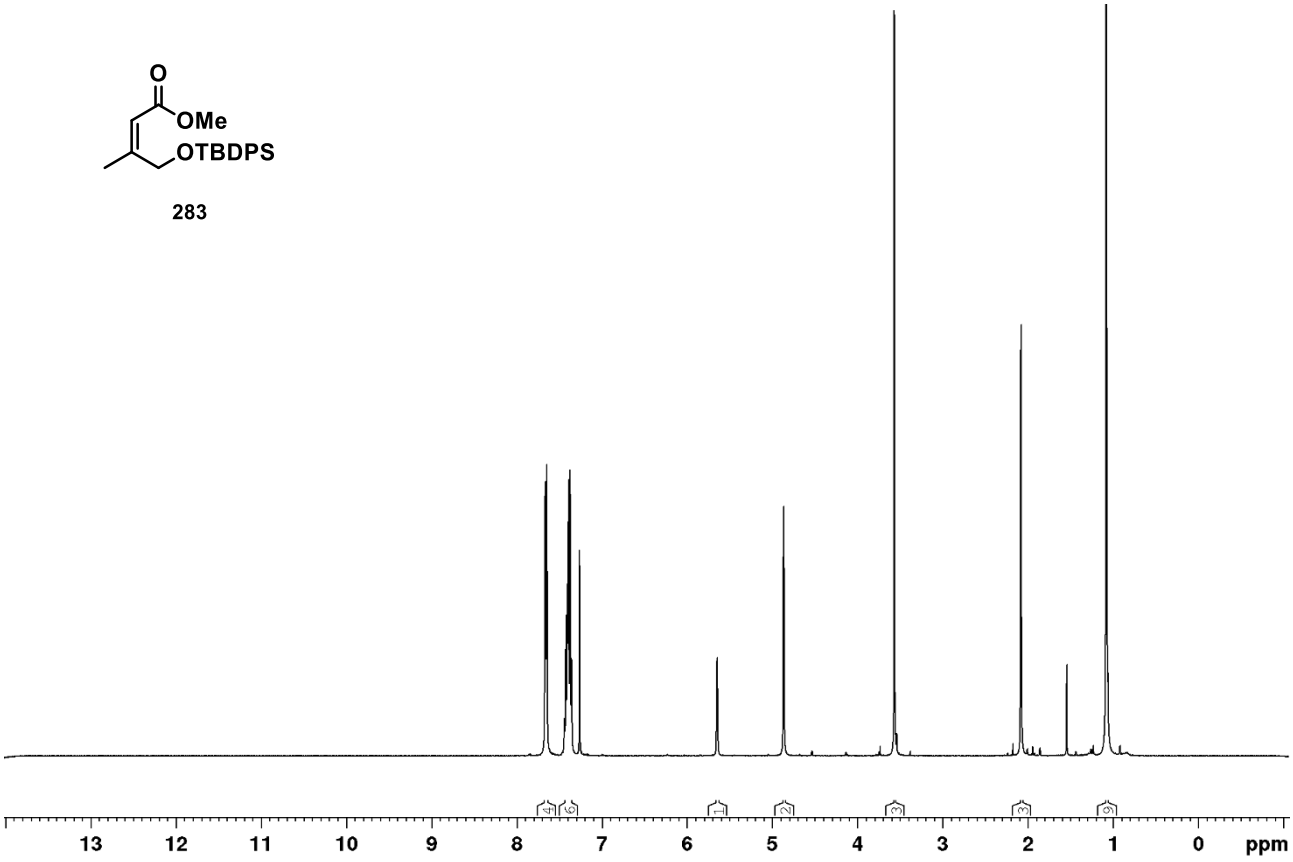
100
80
60
40
20
0
ppm

282


O
OMe
OTBDPS
13
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11
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9
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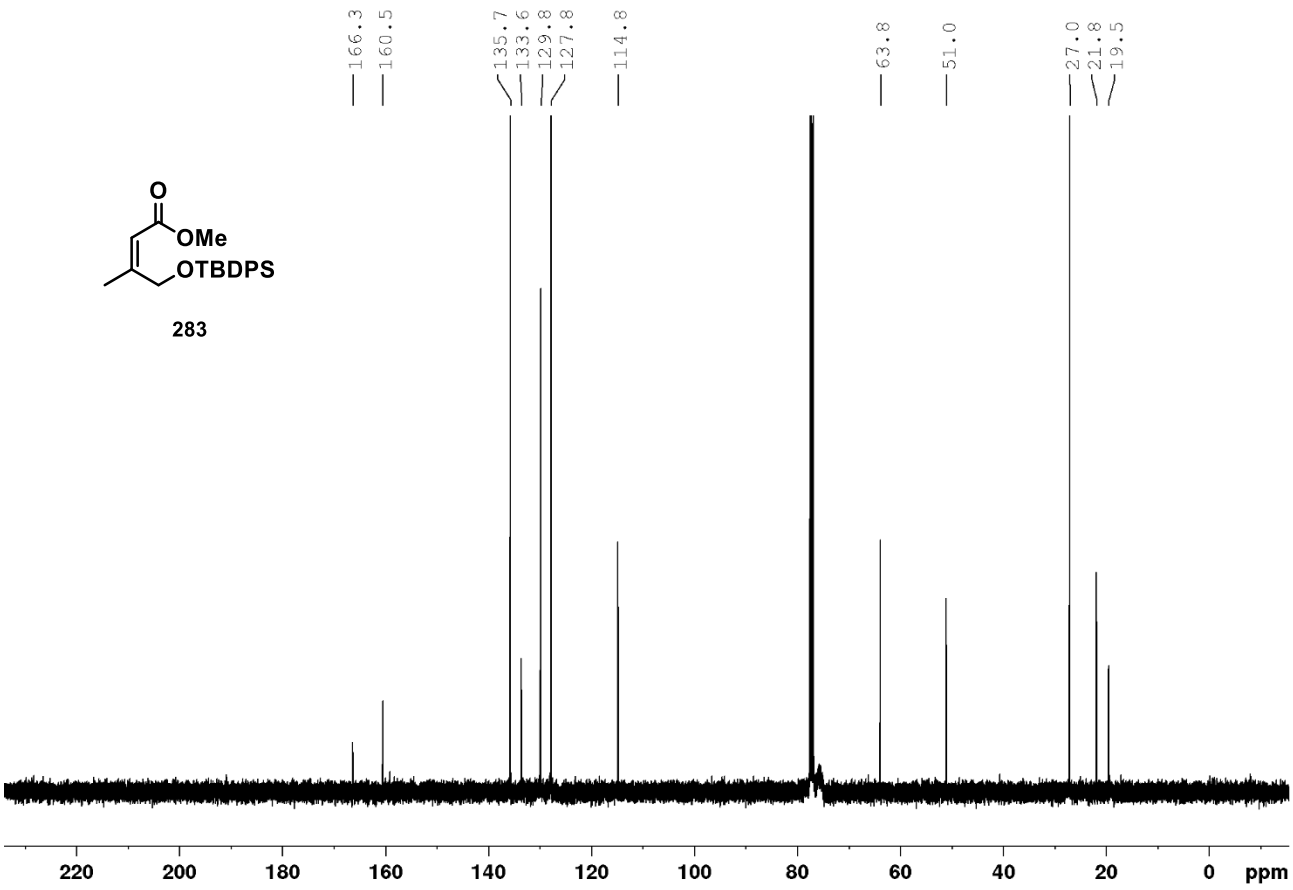
7
6
5
4
3
2
1
0
ppm

283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133.6
129.8
127.8
114.8
63.8
51.0
27.0
21.8
19.5
O
OMe
OTBDPS
283
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160
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120
100
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60
40
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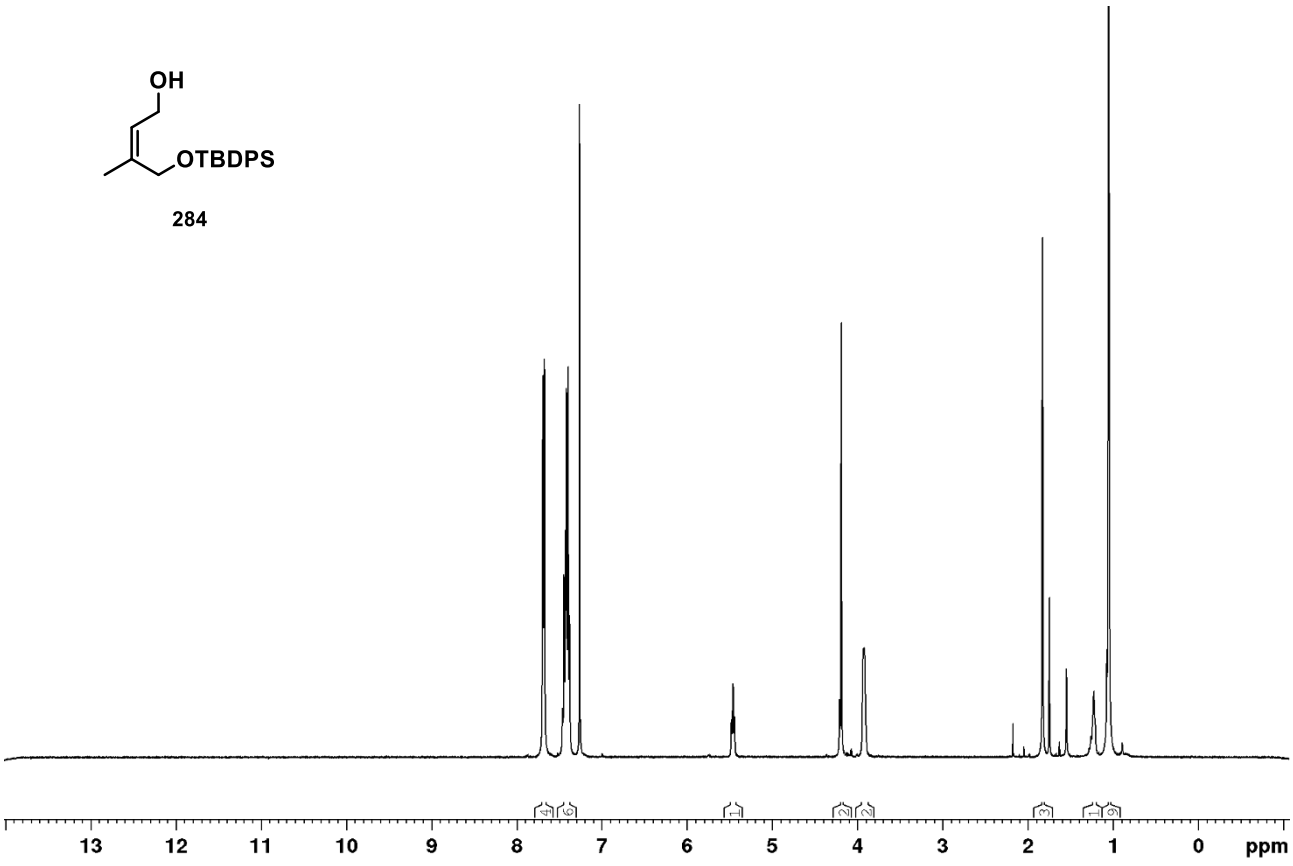
0
ppm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2
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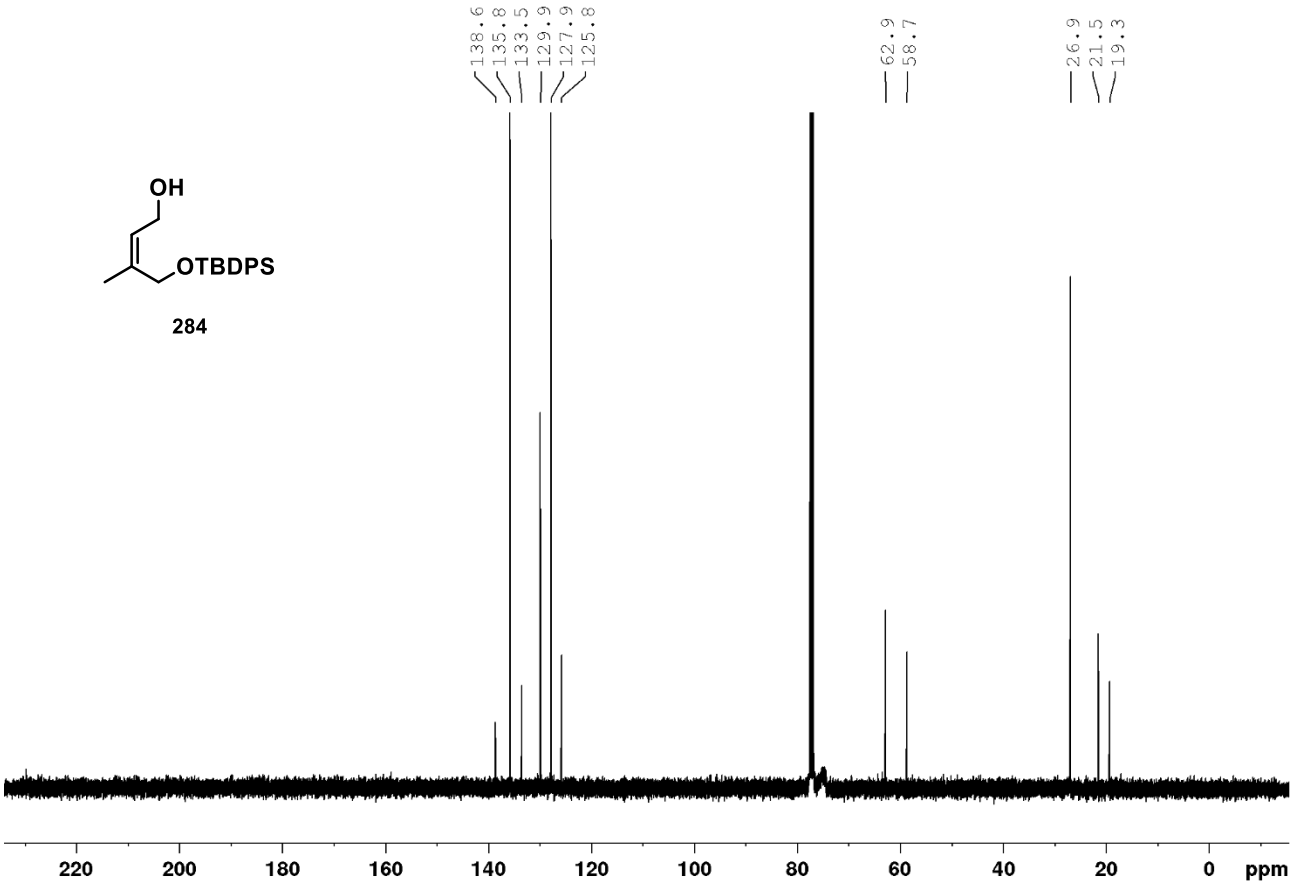
0
ppm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127.9
125.8
62.9
58.7
26.9
21.5
19.3
OH
OTBDPS
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160
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100
80
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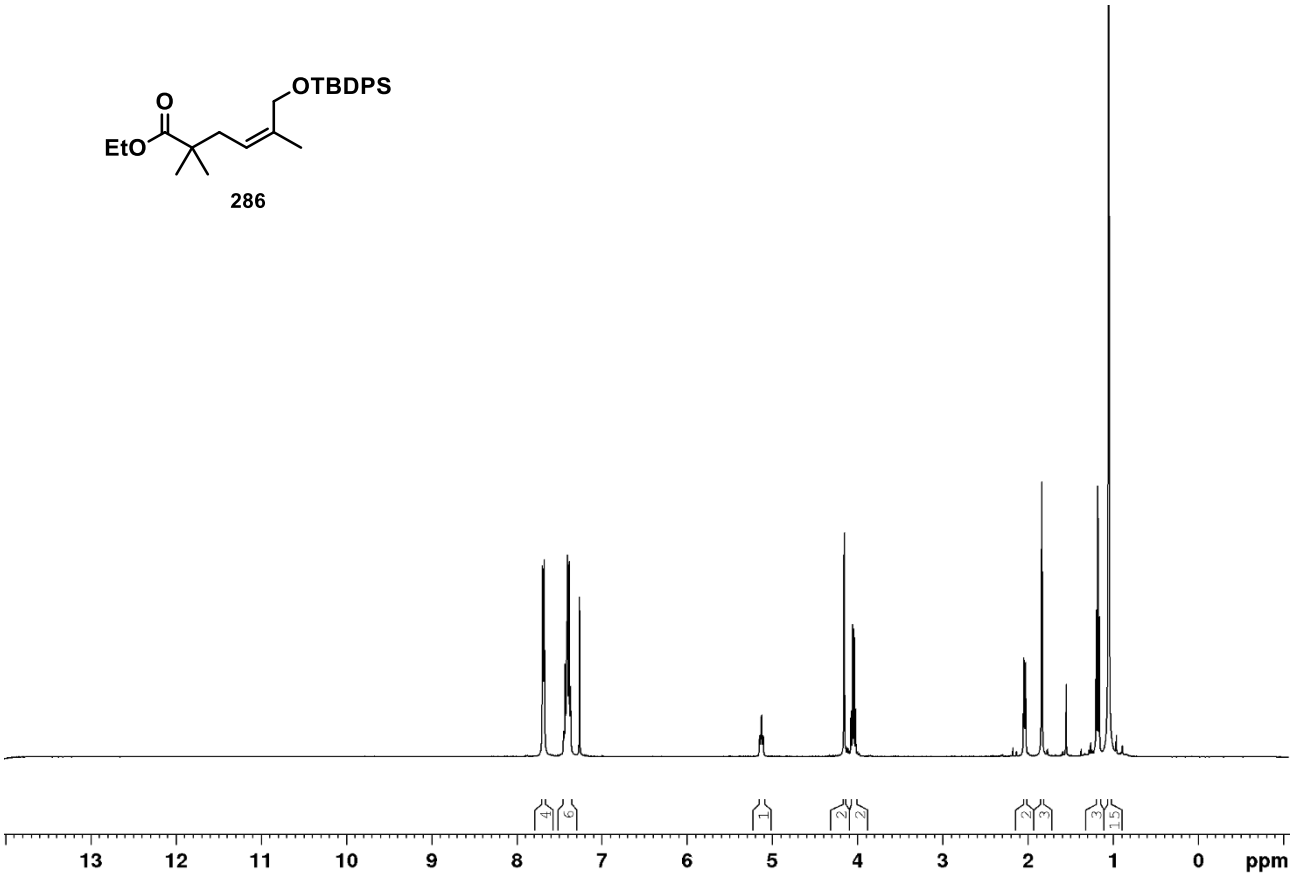
0
ppm

284


OTBDPS
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EtO
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9
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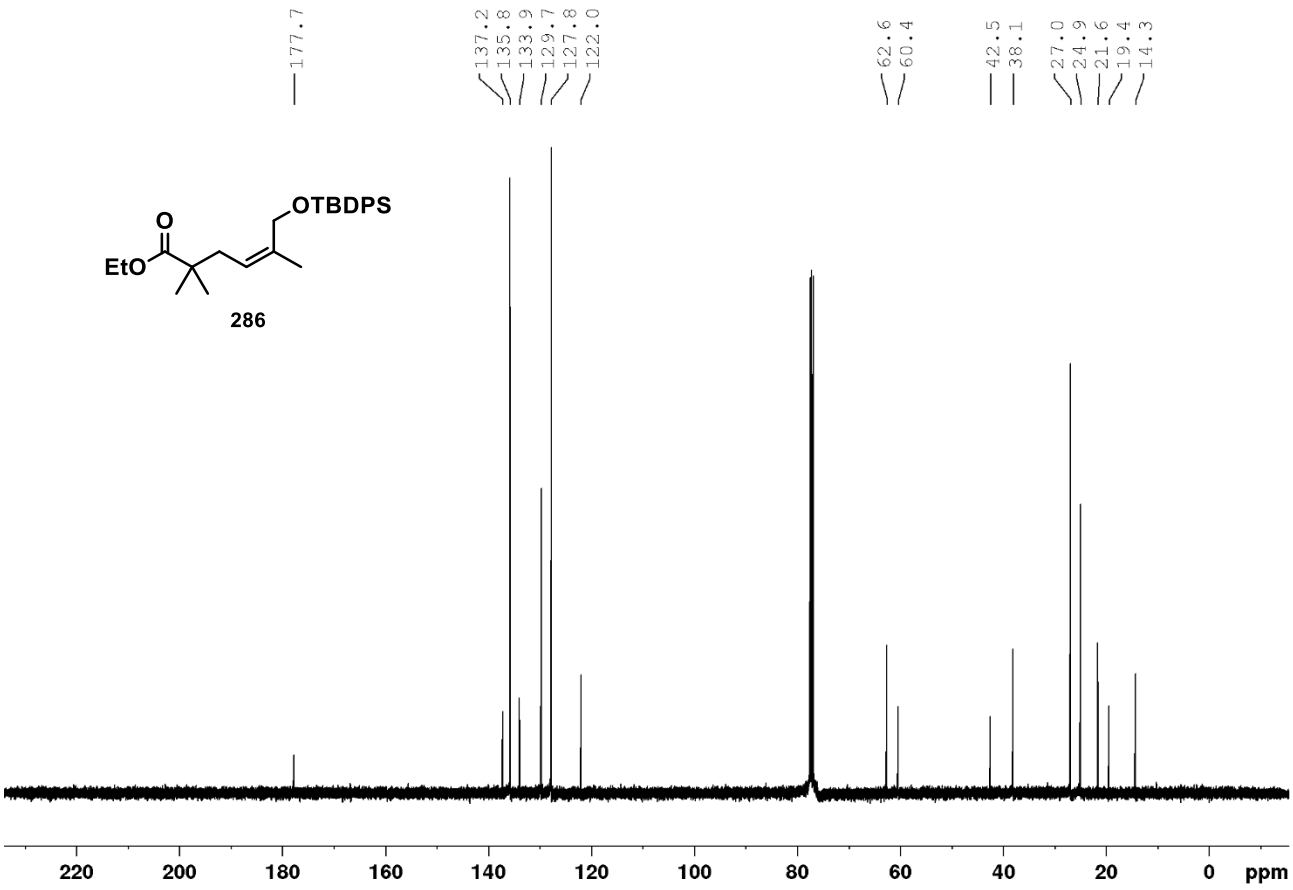
5
4
3
2
1
0
ppm

286


177.7
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135.8
133.9
129.7
127.8
122.0
62.6
60.4
42.5
38.1
27.0
24.9
21.6
19.4
14.3
OTBDPS
O
EtO
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200
180
160
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100
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20
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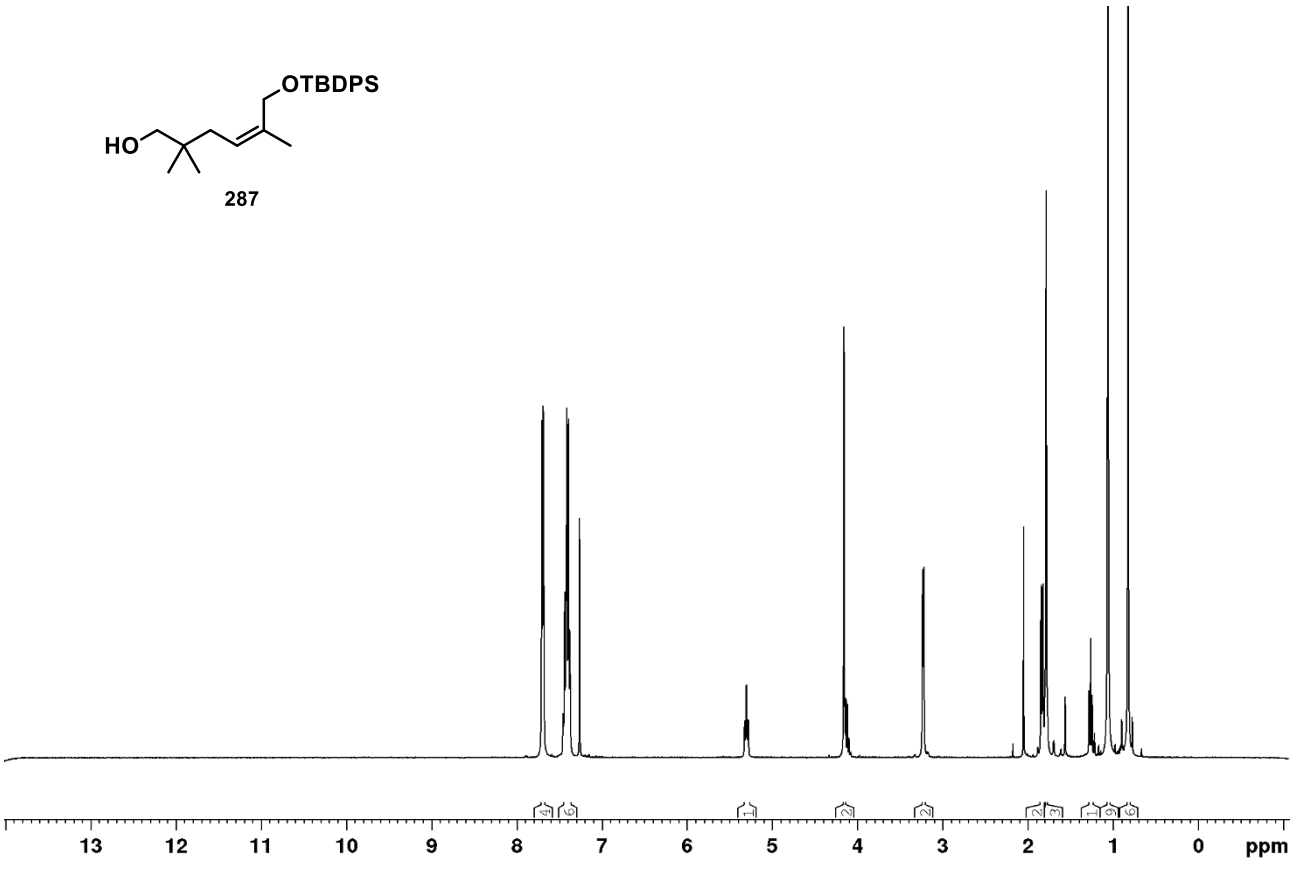
ppm

286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6
5
4
3
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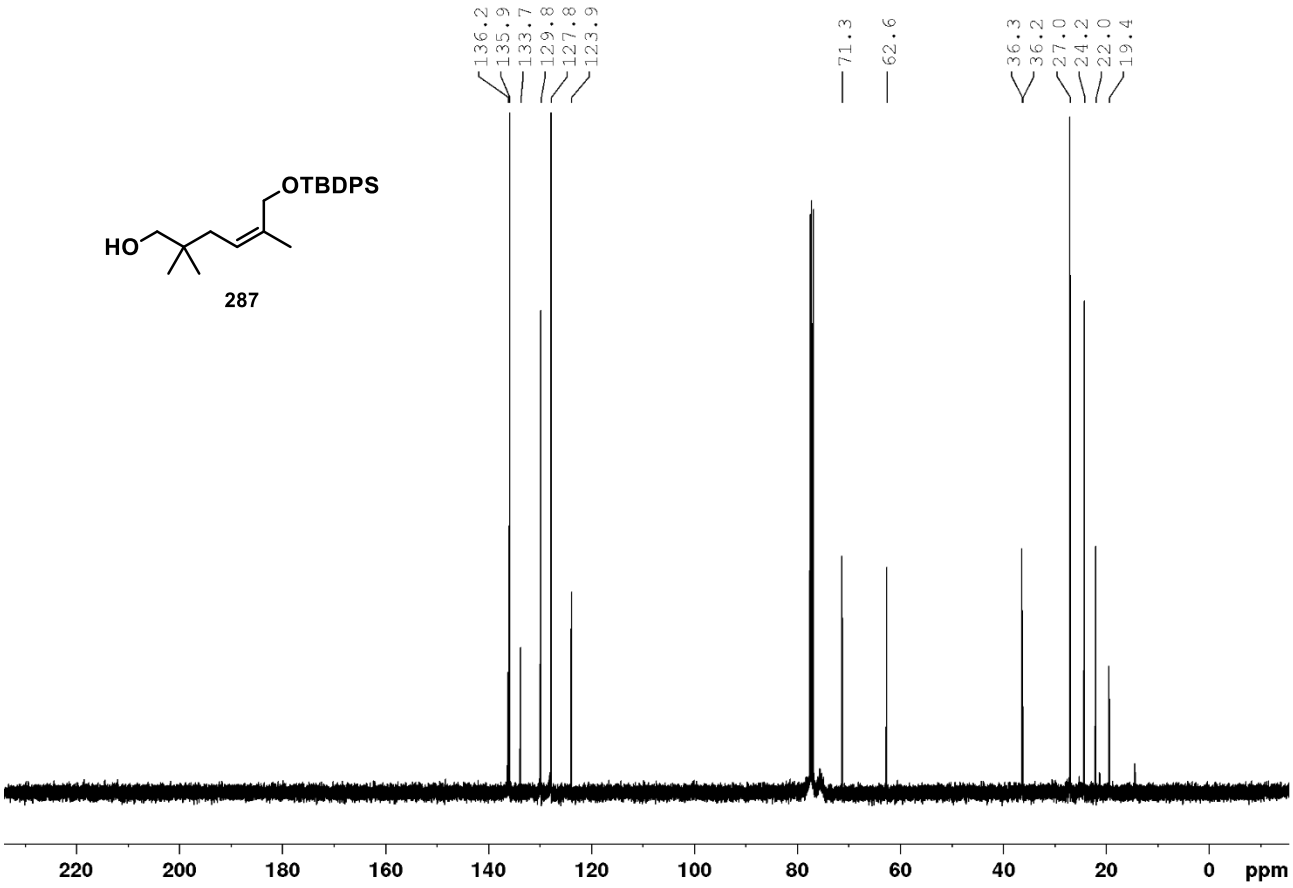
1
0
ppm

287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133.7
129.8
127.8
123.9
71.3
62.6
36.3
36.2
27.0
24.2
22.0
19.4
OTBDPS
HO
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200
180
160
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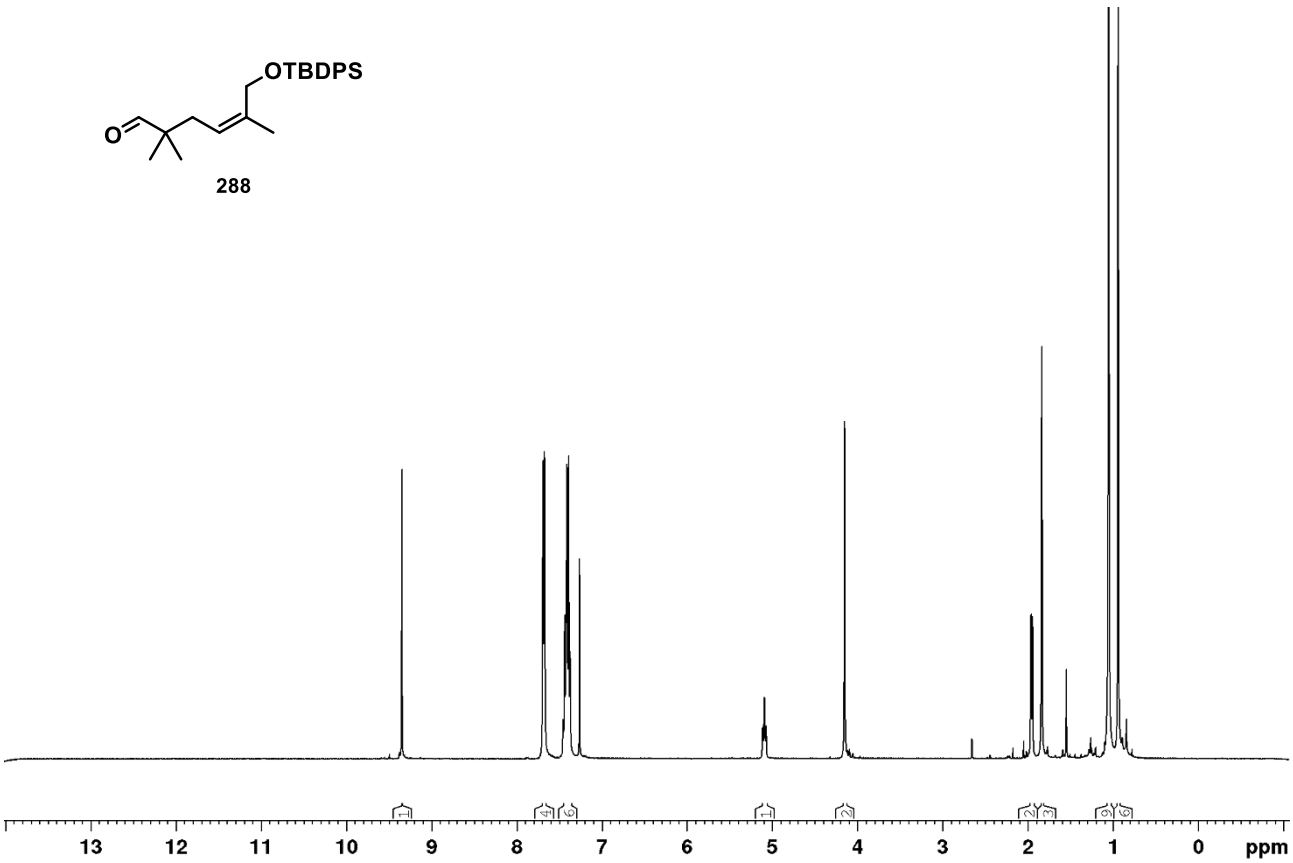
120
100
80
60
40
20
0
ppm


OTBDPS
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288
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4
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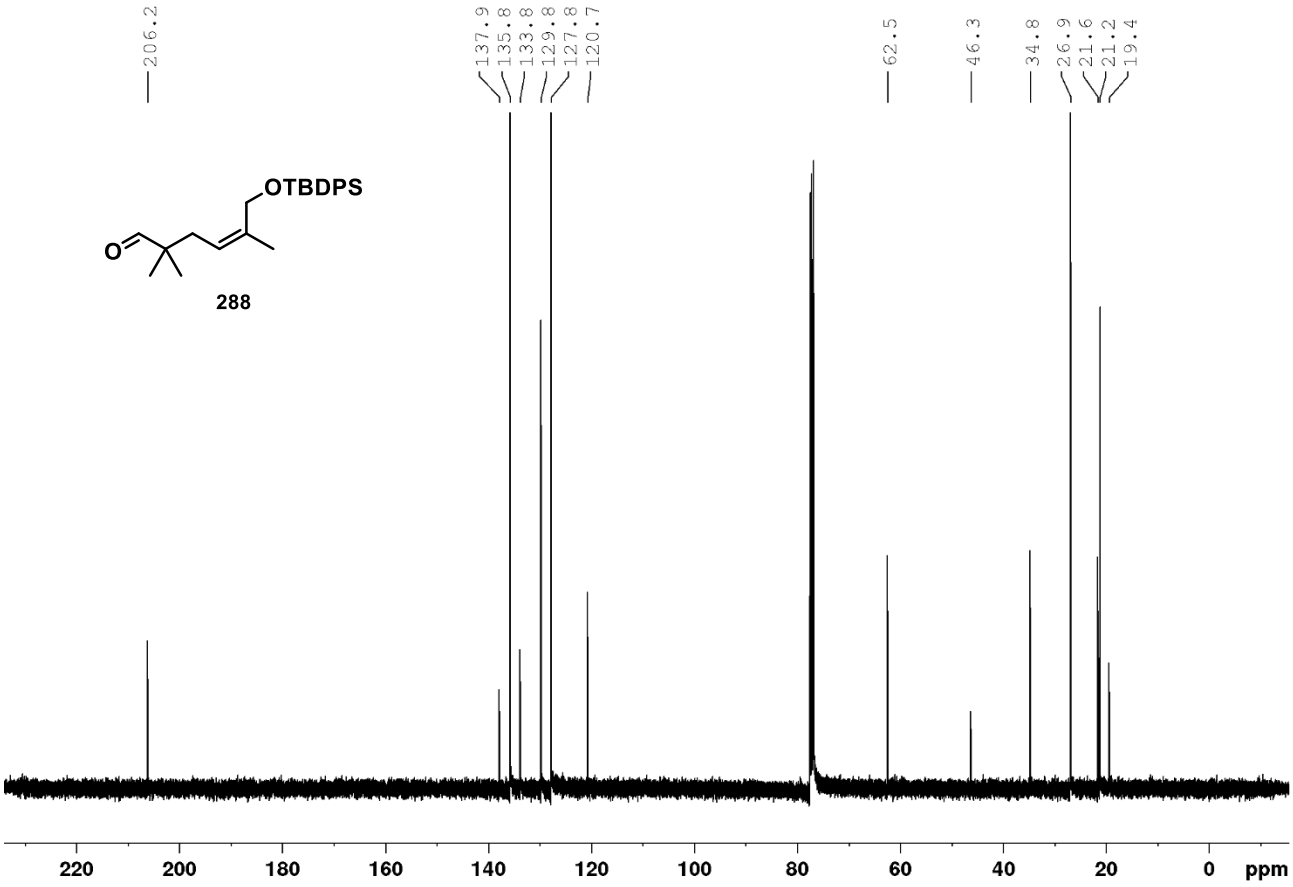
2
1
0
ppm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133.8
129.8
127.8
120.7
62.5
46.3
34.8
26.9
21.6
21.2
19.4
OTBDPS
O
288
220
200
180
160
140
120
100
80
60
40
20
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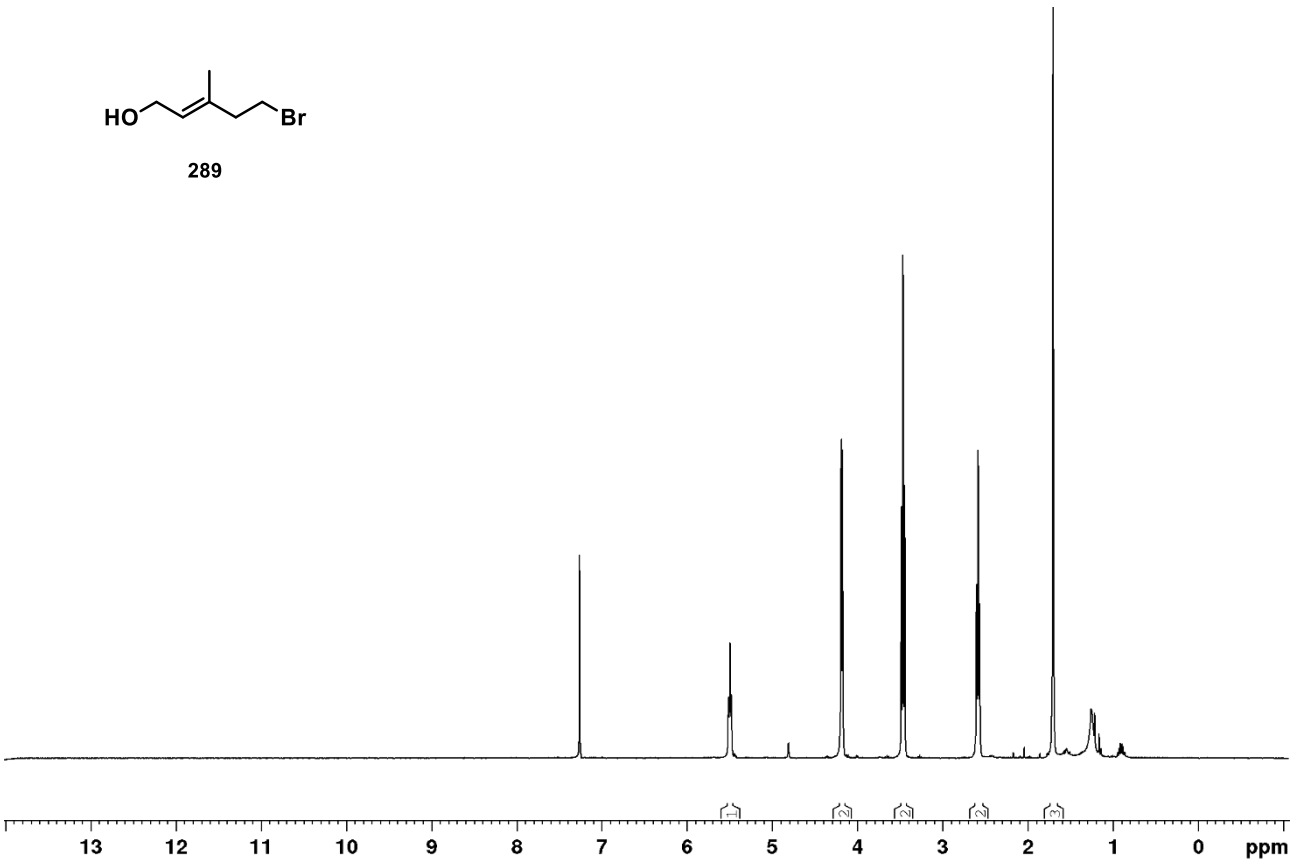
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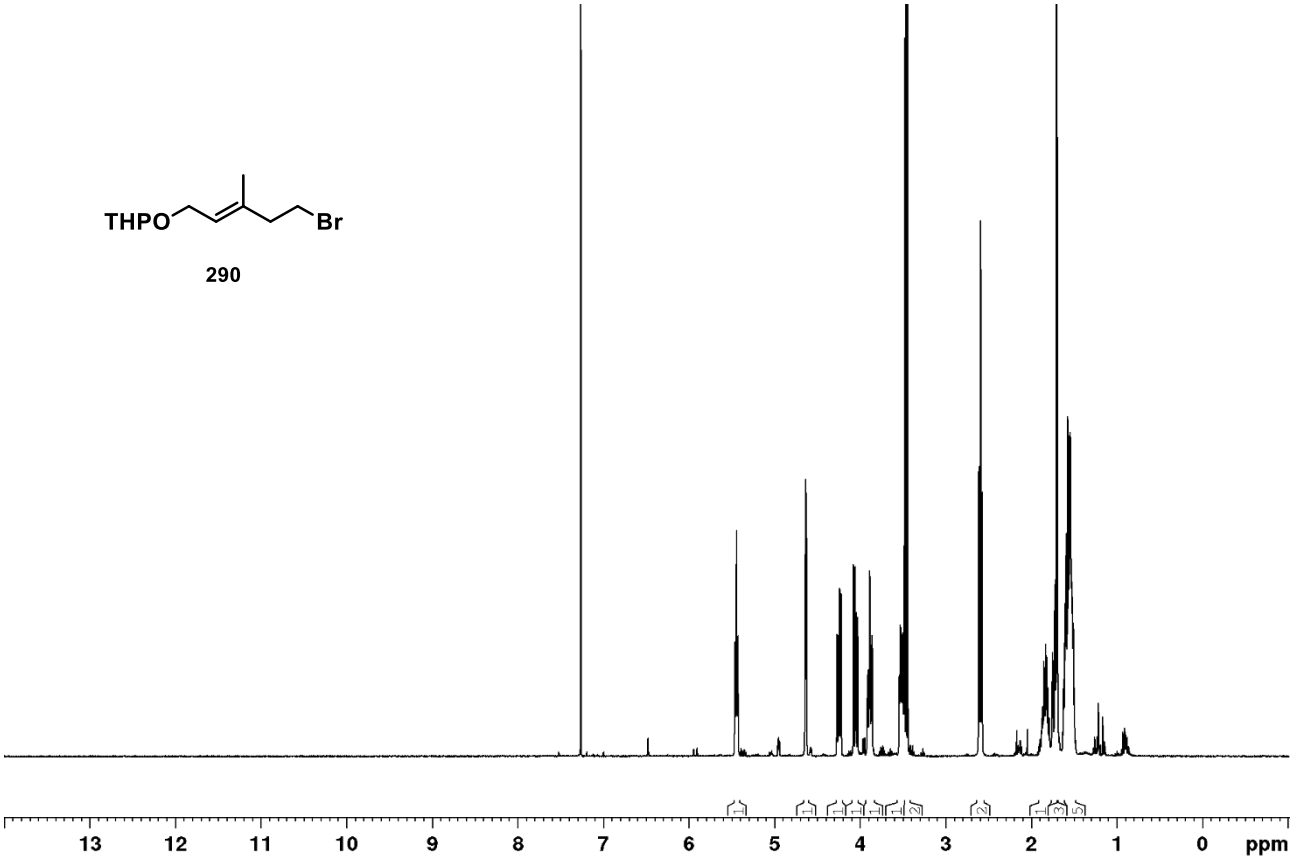

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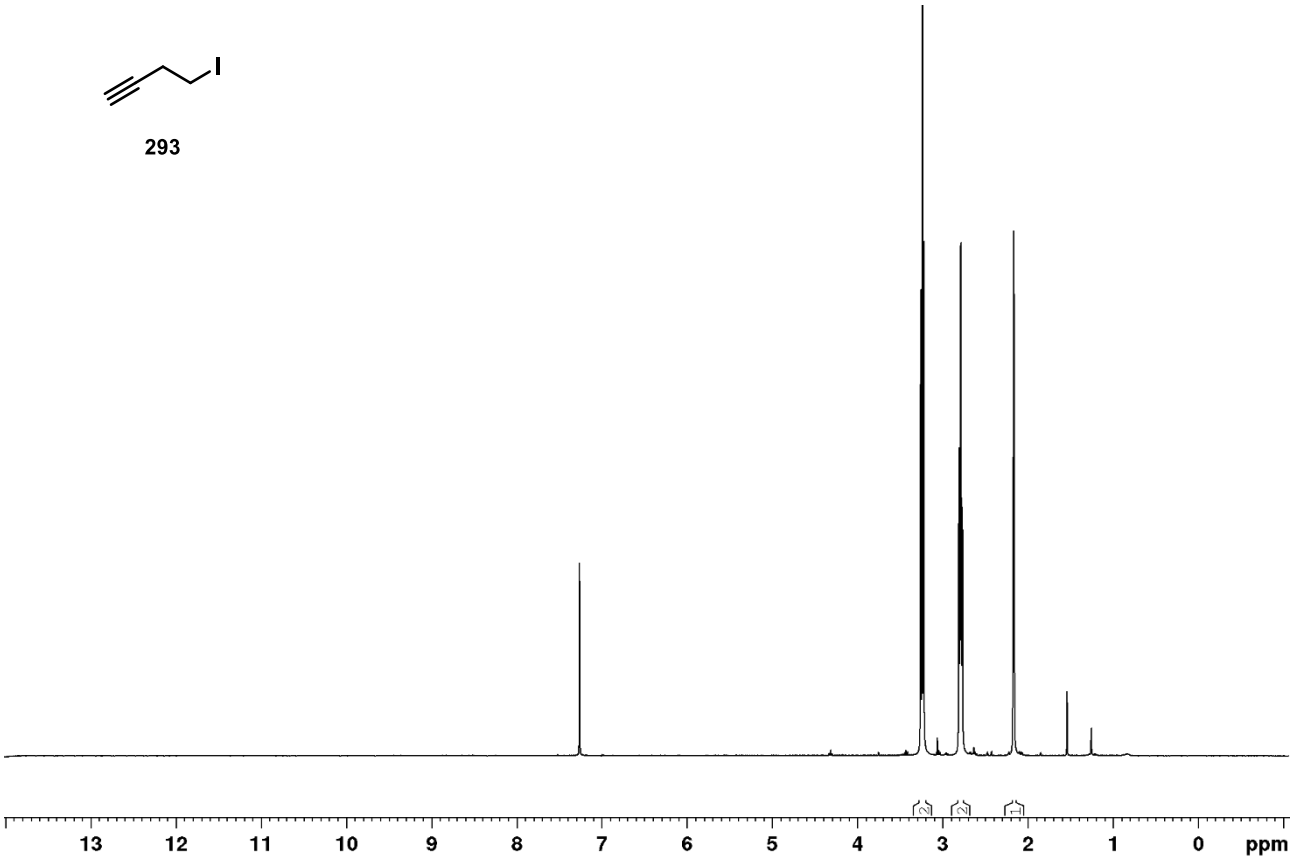

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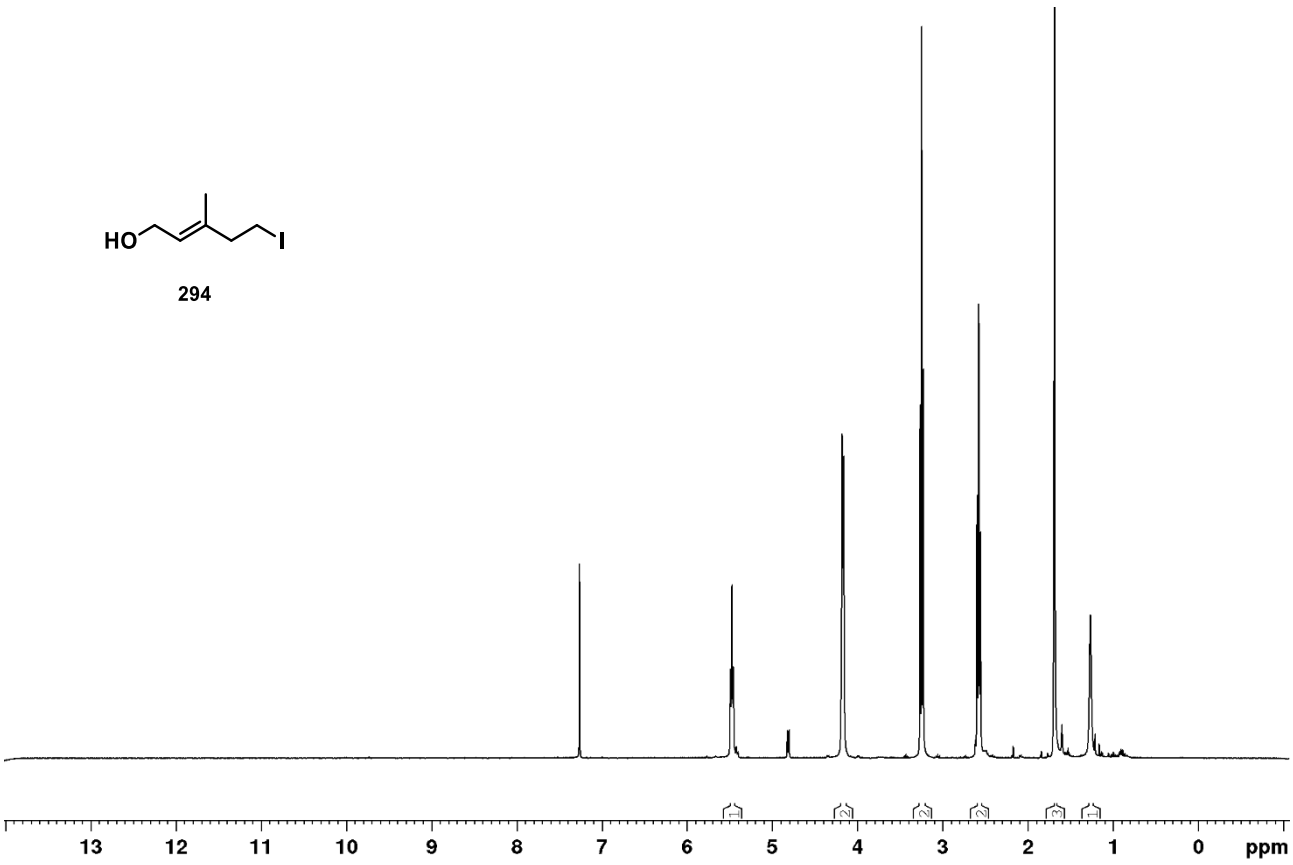
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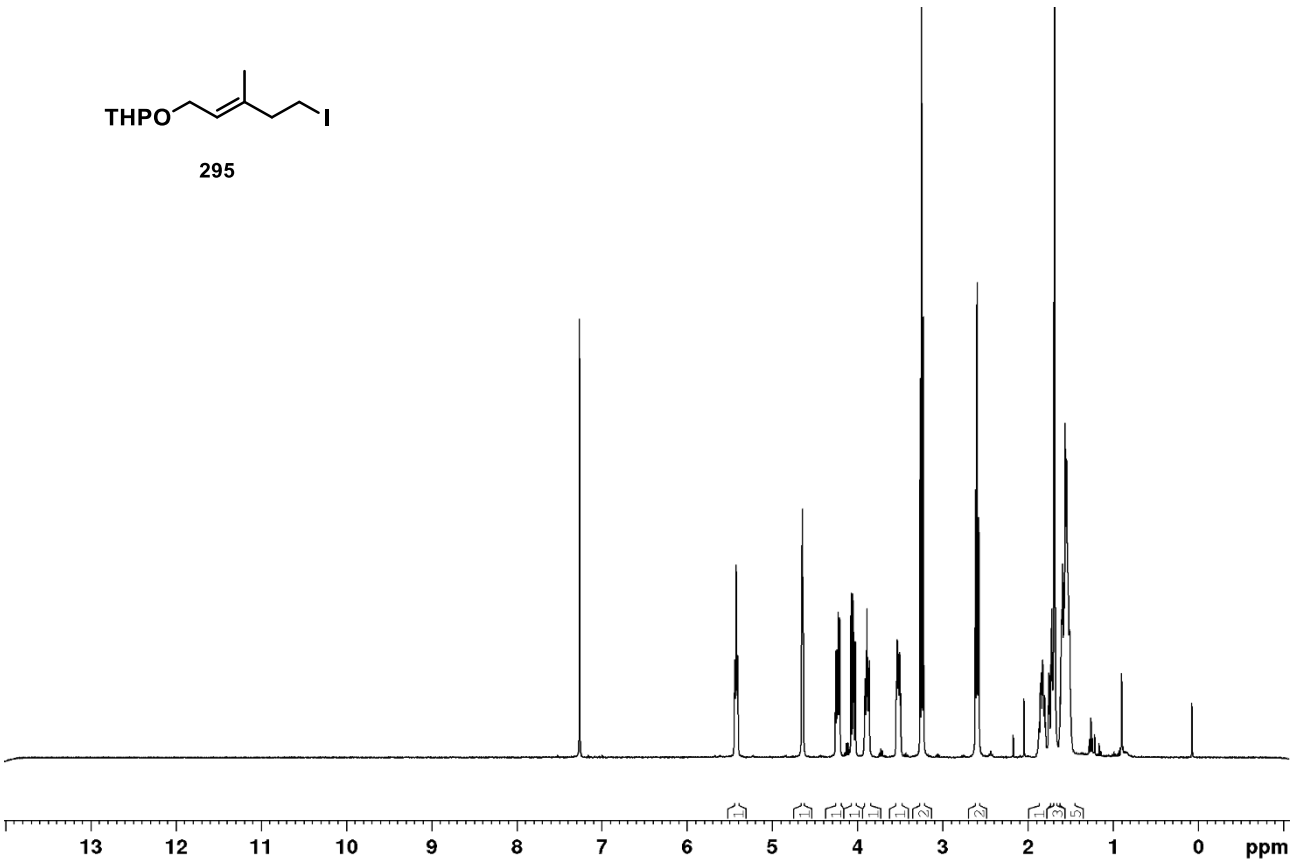
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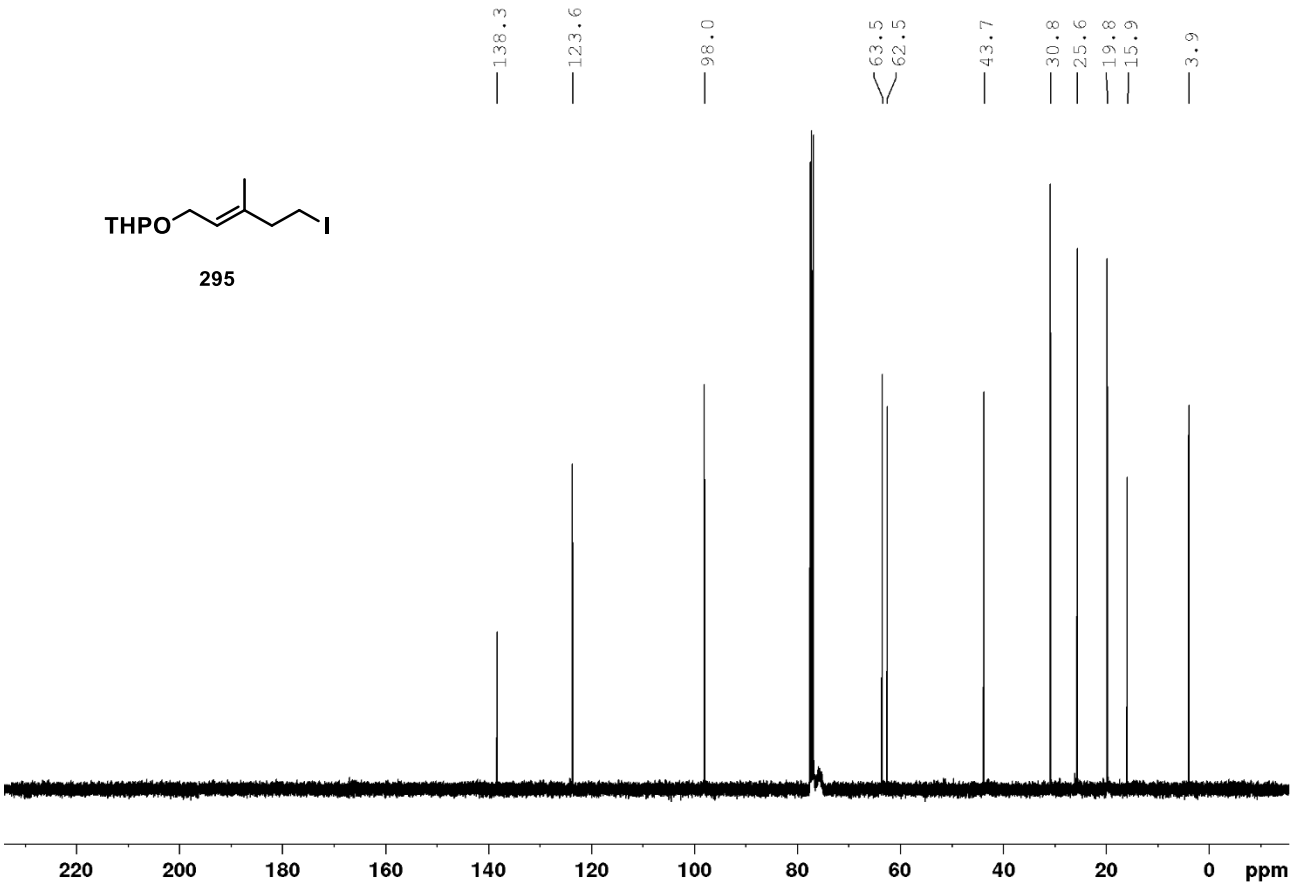
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62.5
43.7
30.8
25.6
19.8
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THPO
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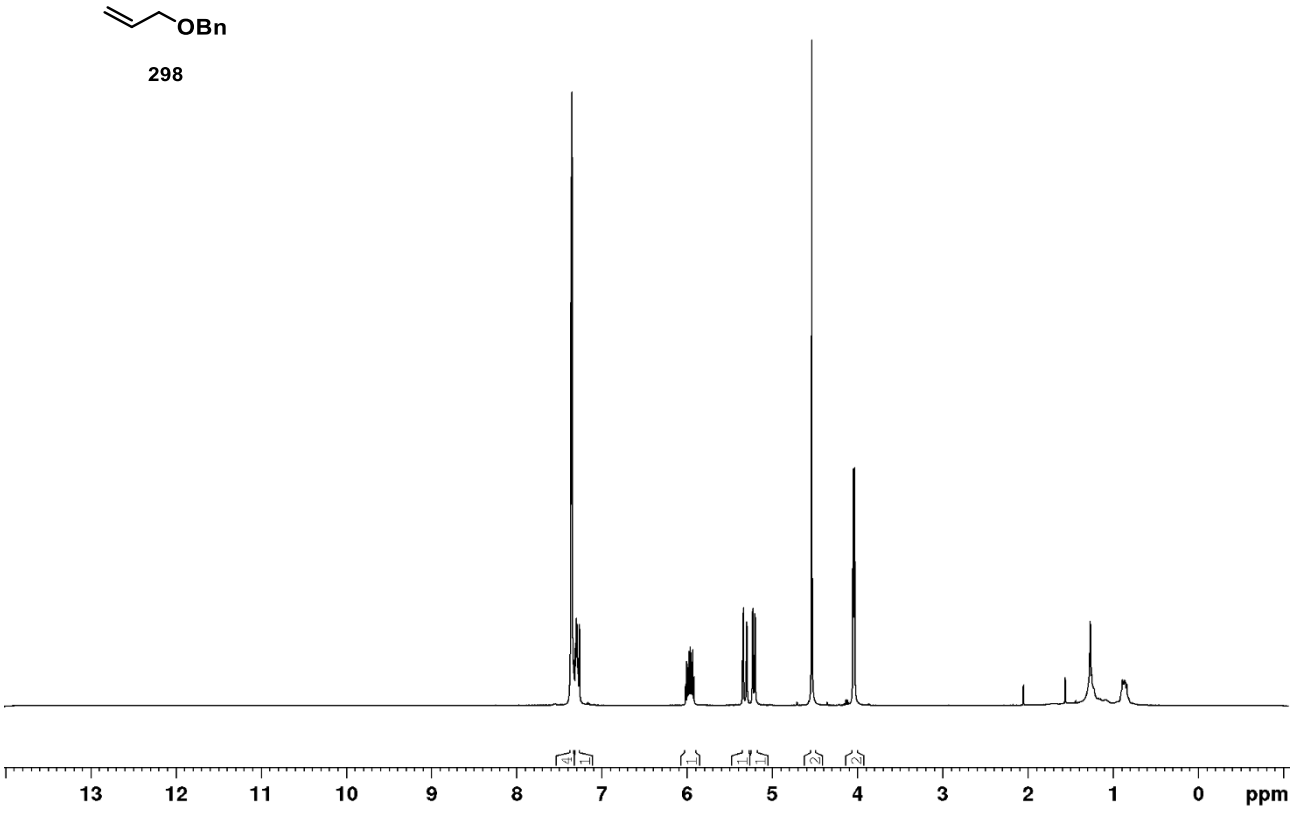
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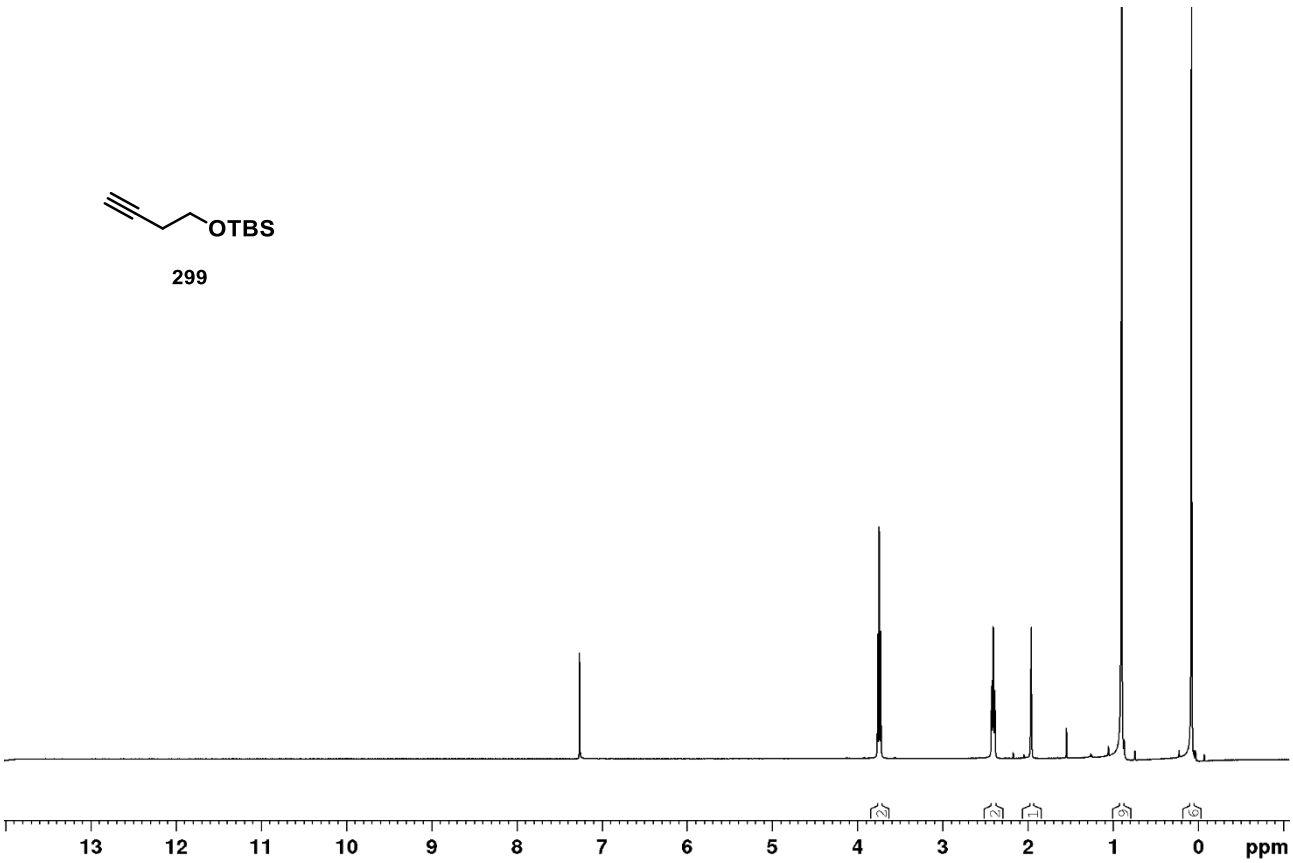
298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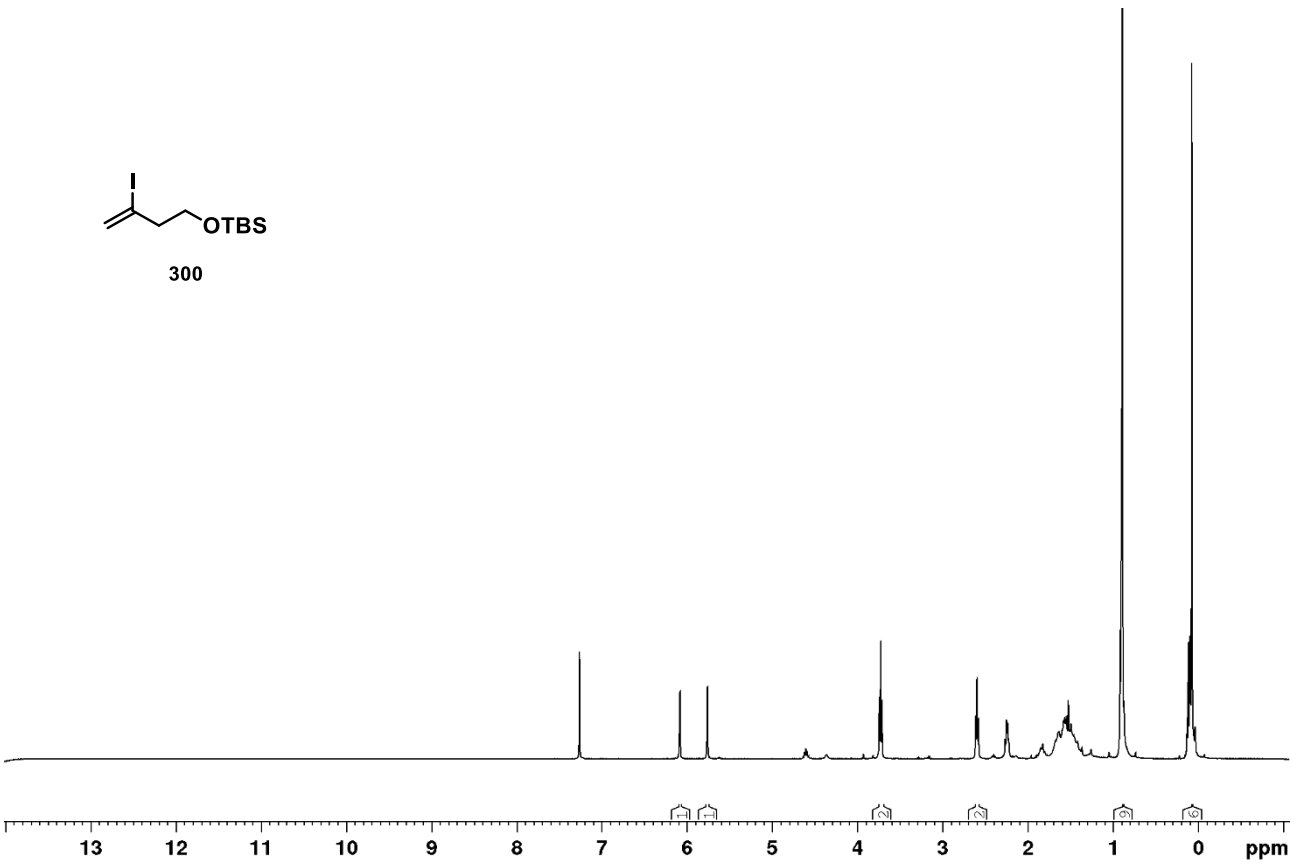
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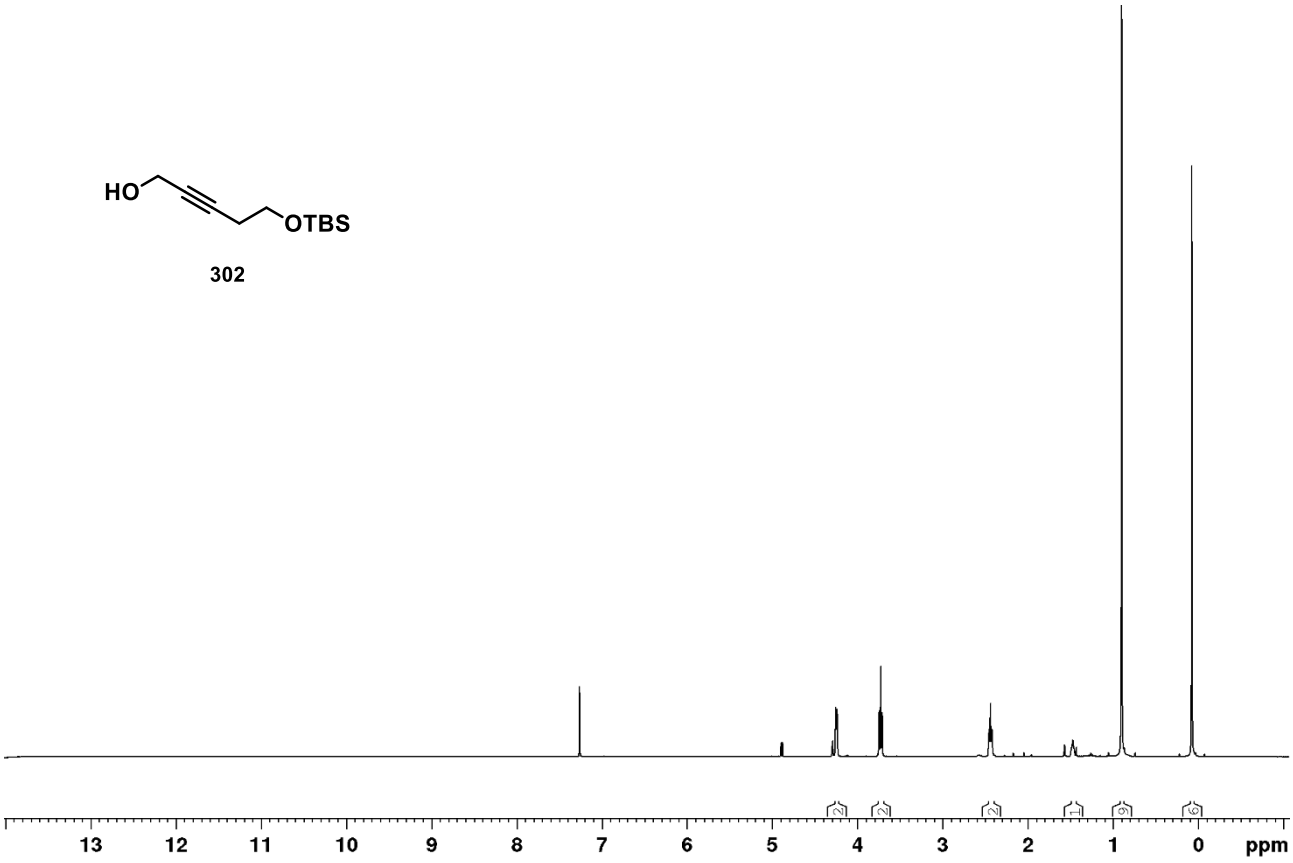
ppm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OTBS
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5
4
3
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1
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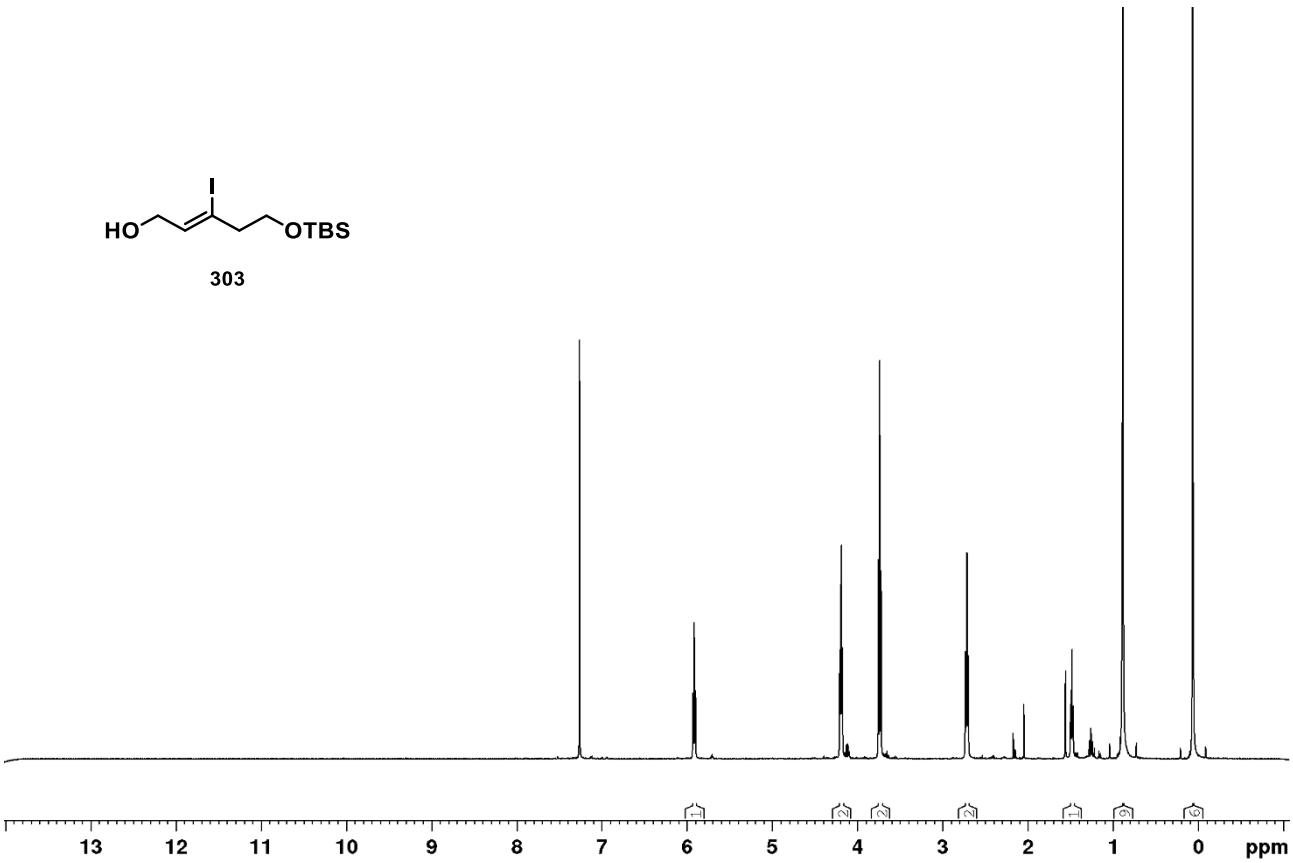
ppm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HO
OTBS
303
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8
7
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5
4
3
2
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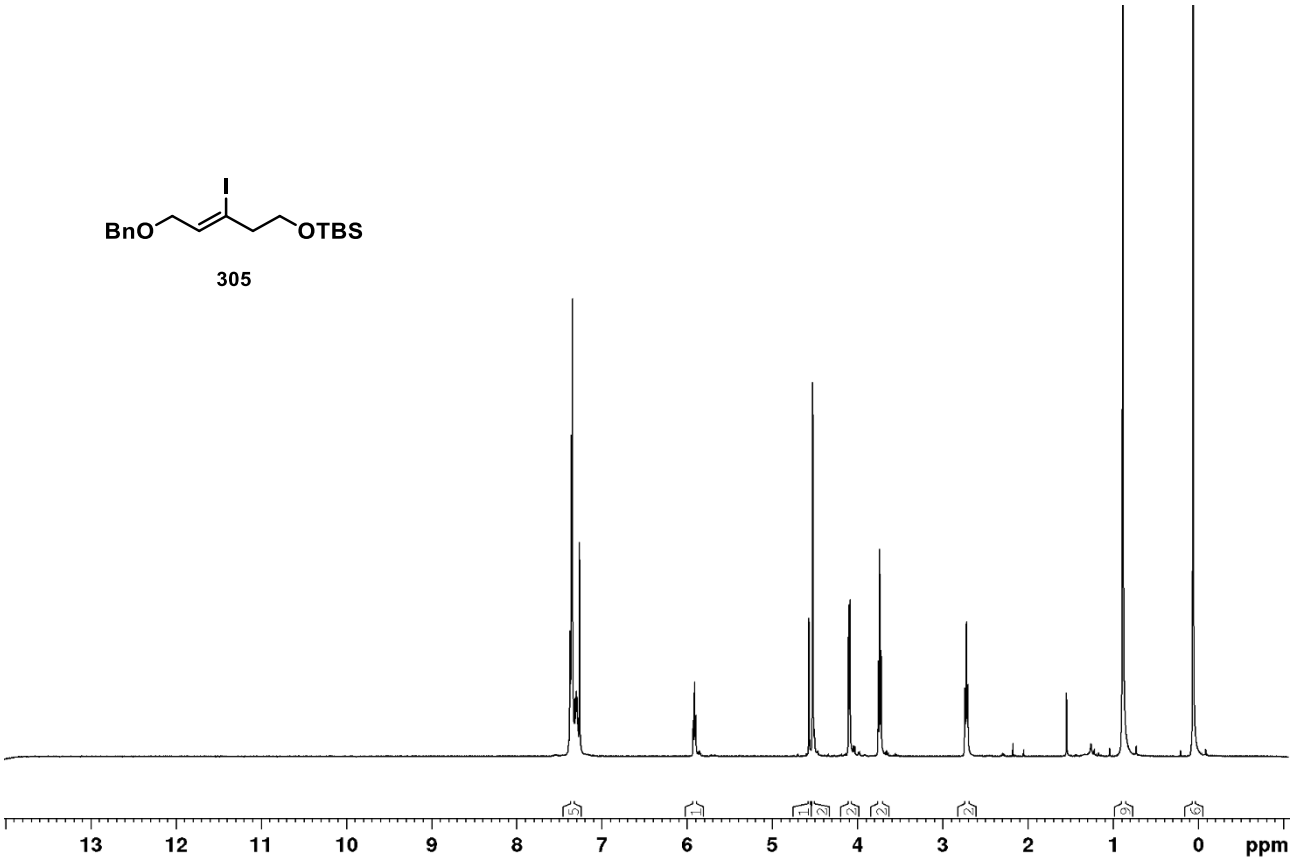
0
ppm


BnO
OTBS
305
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10
9
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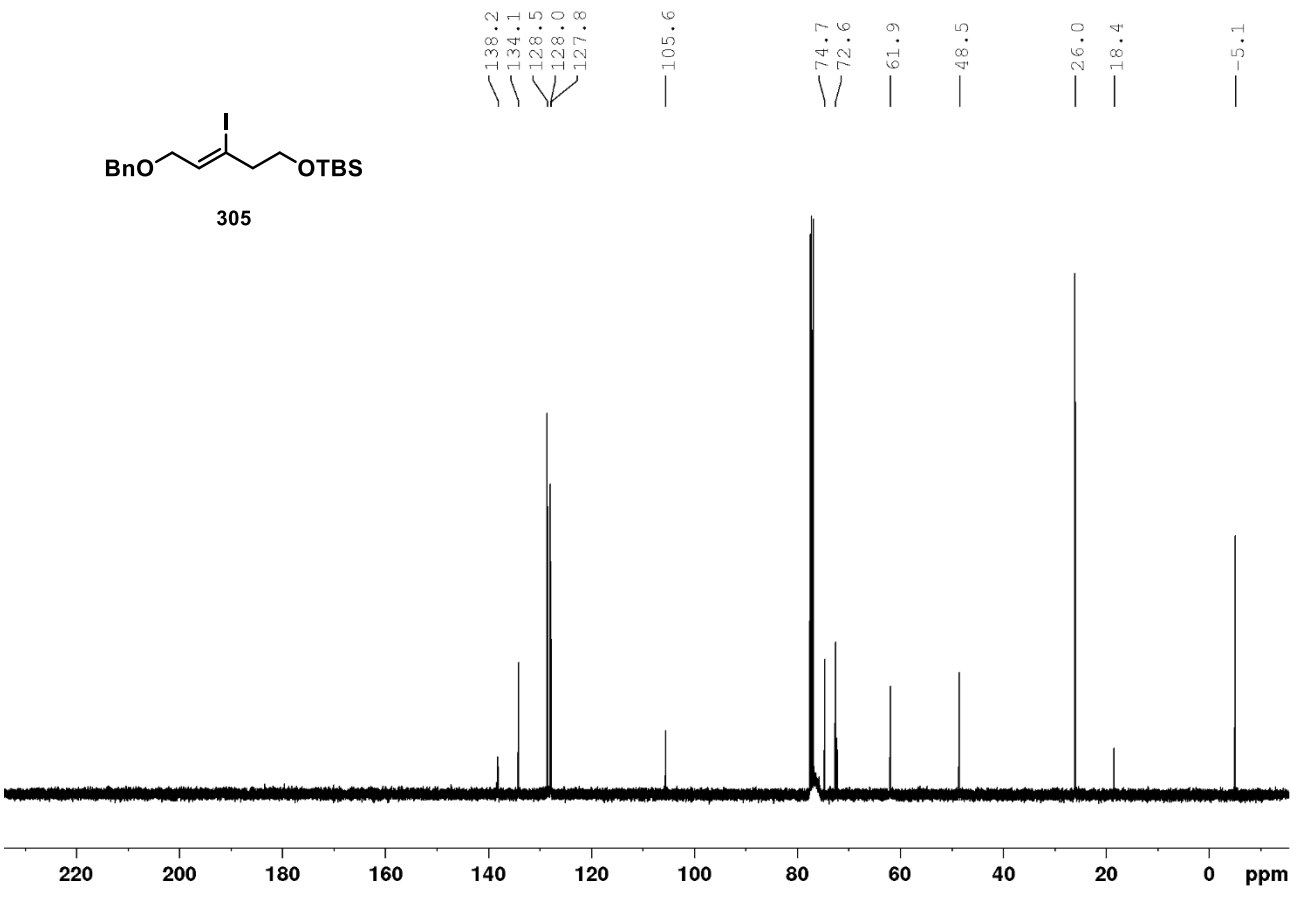
7
6
5
4
3
2
1
0
ppm


138.2
134.1
128.5
128.0
127.8
105.6
74.7
72.6
61.9
48.5
26.0
18.4
-5.1
BnO
OTBS
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200
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120
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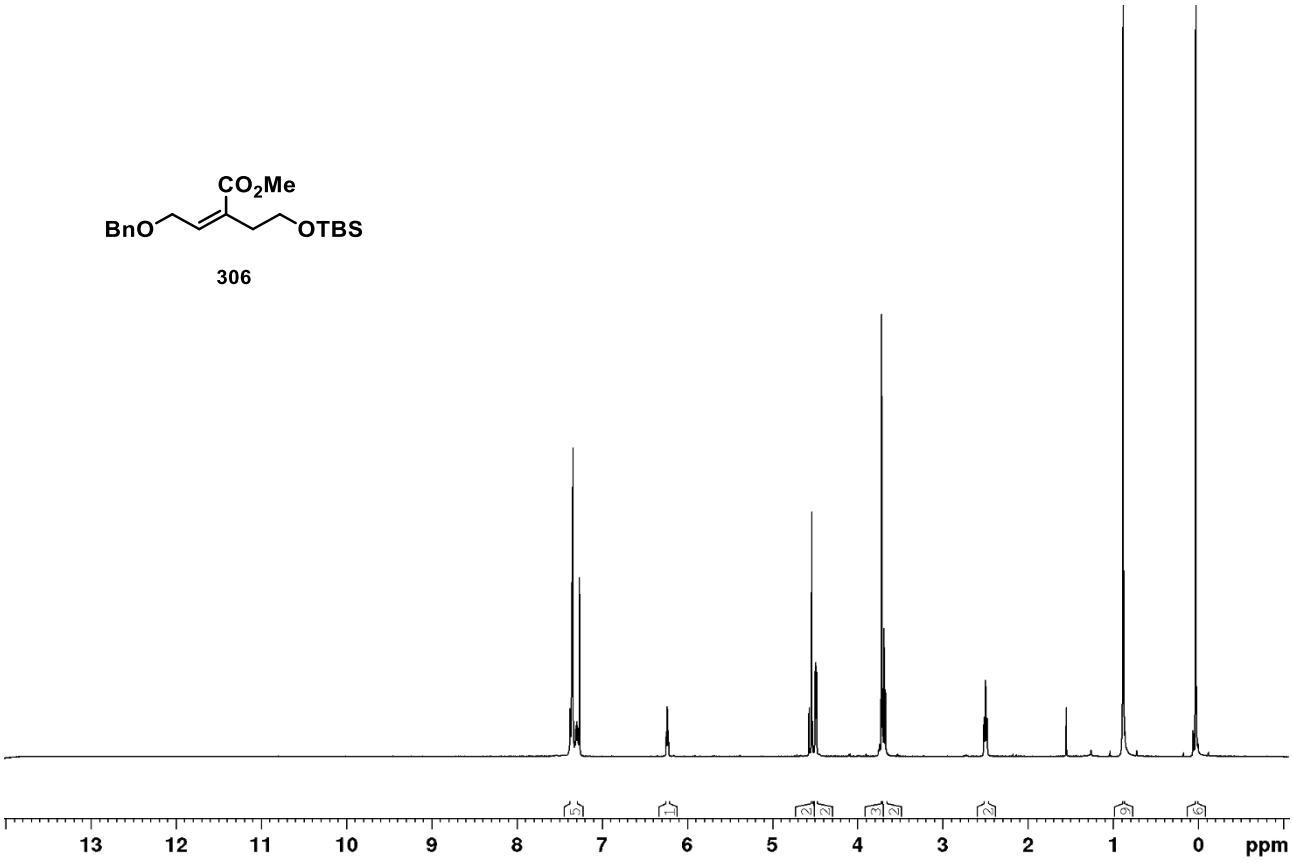
60
40
20
0
ppm


CO2Me
BnO
OTBS
306
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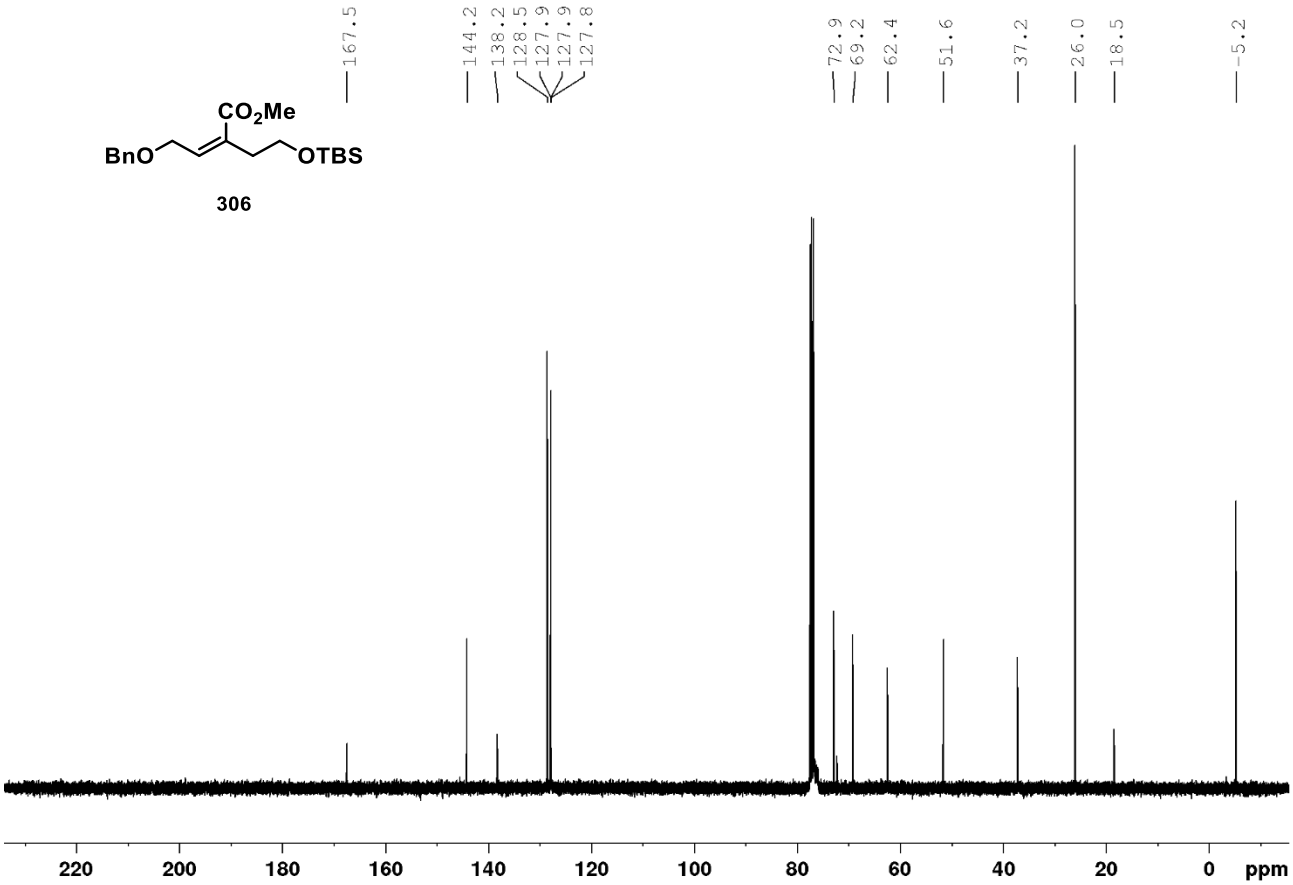
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm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144.2
138.2
128.5
127.9
127.9
127.8
72.9
69.2
62.4
51.6
37.2
26.0
18.5
-5.2
CO2Me
BnO
OTBS
306
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200
180
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60
40
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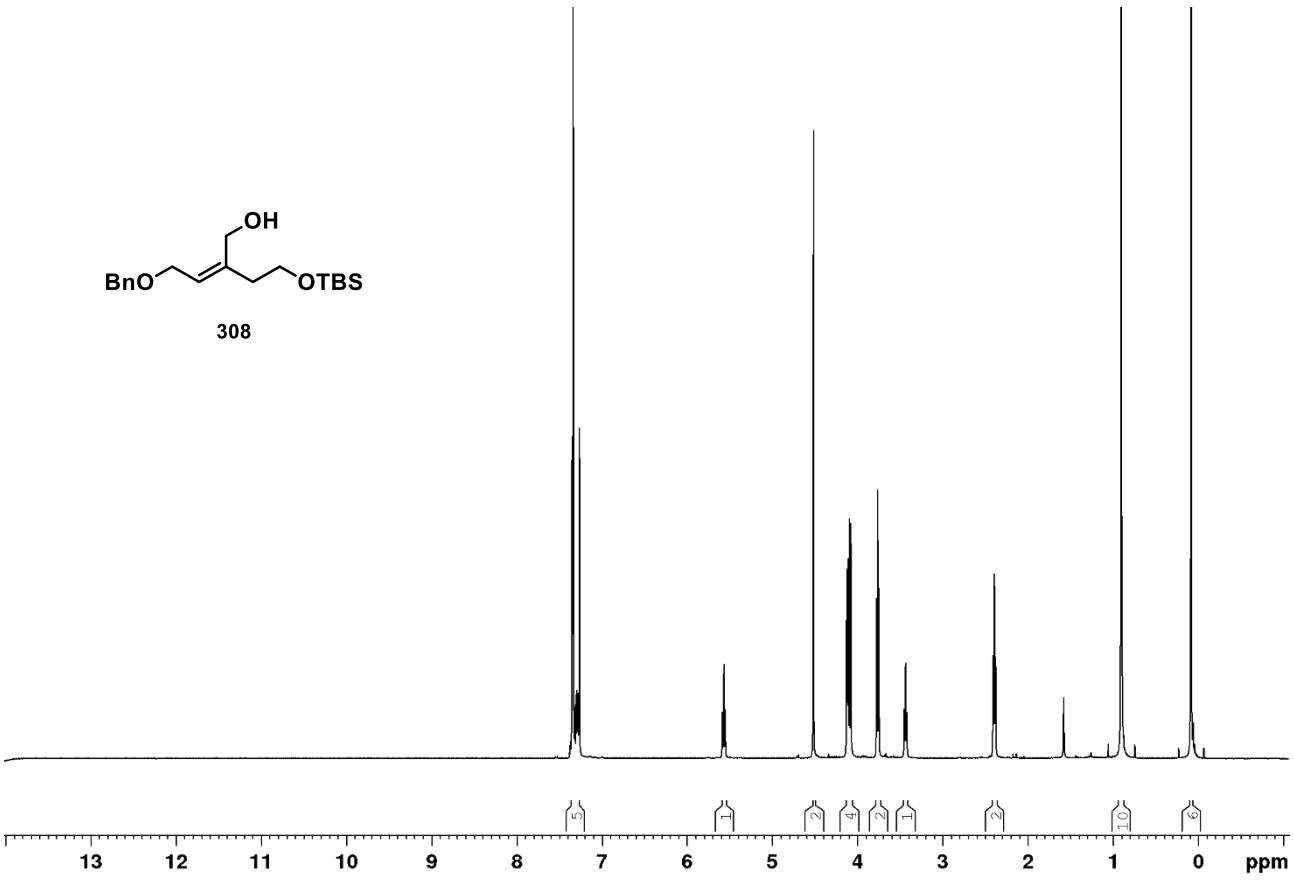
ppm


OH
BnO
OTBS
308
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1
2
10
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11
10
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6
5
4
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2
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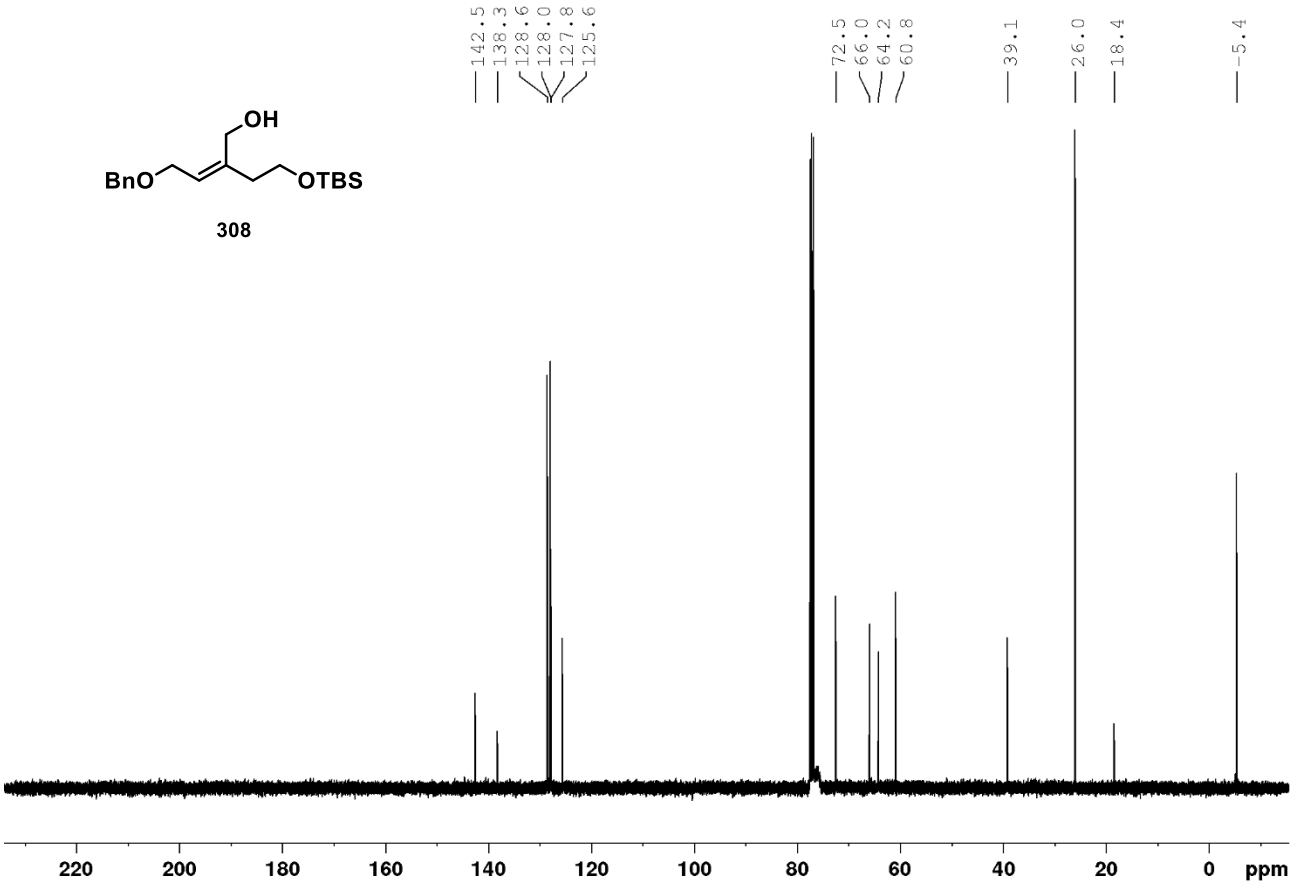
0
ppm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138.3
128.6
128.0
127.8
125.6
72.5
66.0
64.2
60.8
39.1
26.0
18.4
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OH
BnO
OTBS
308
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200
180
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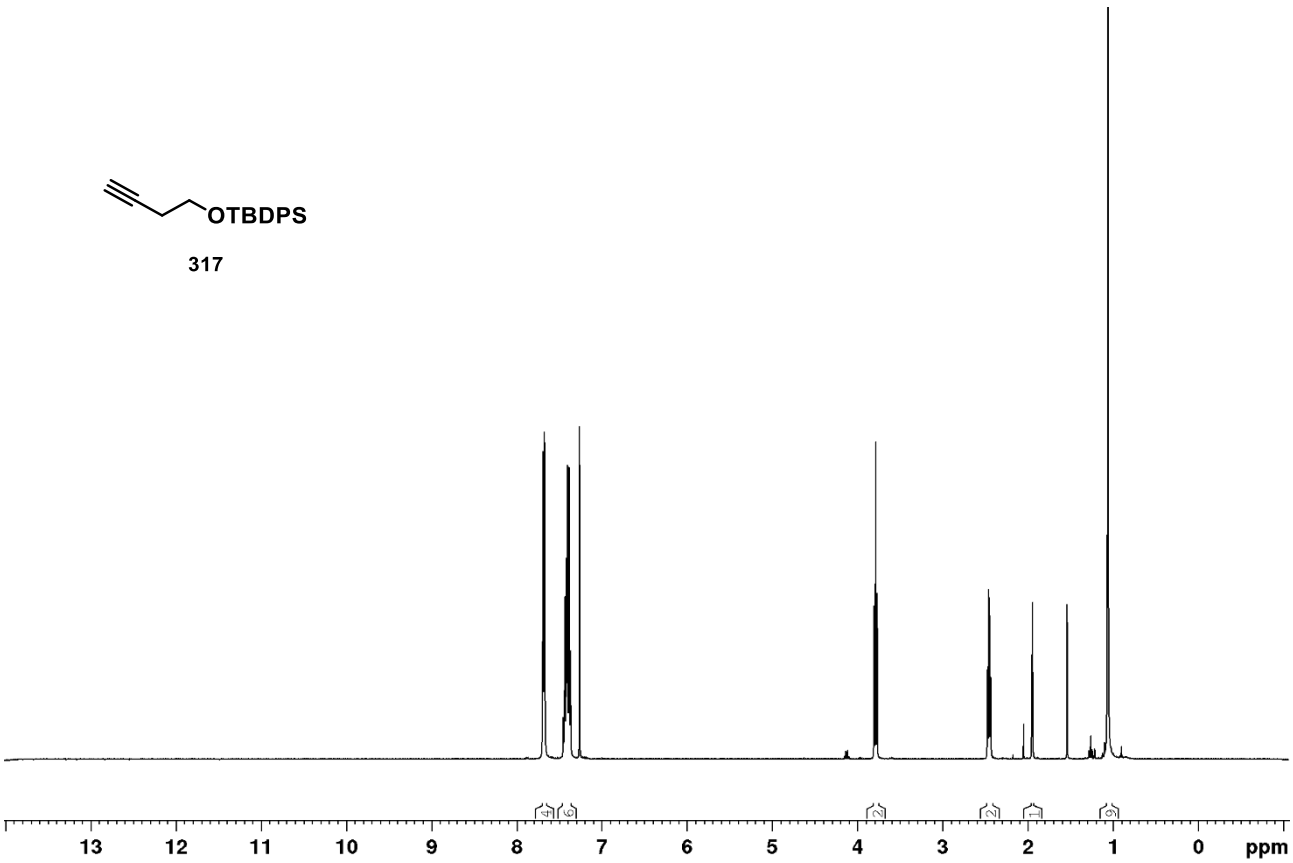
40
20
0
ppm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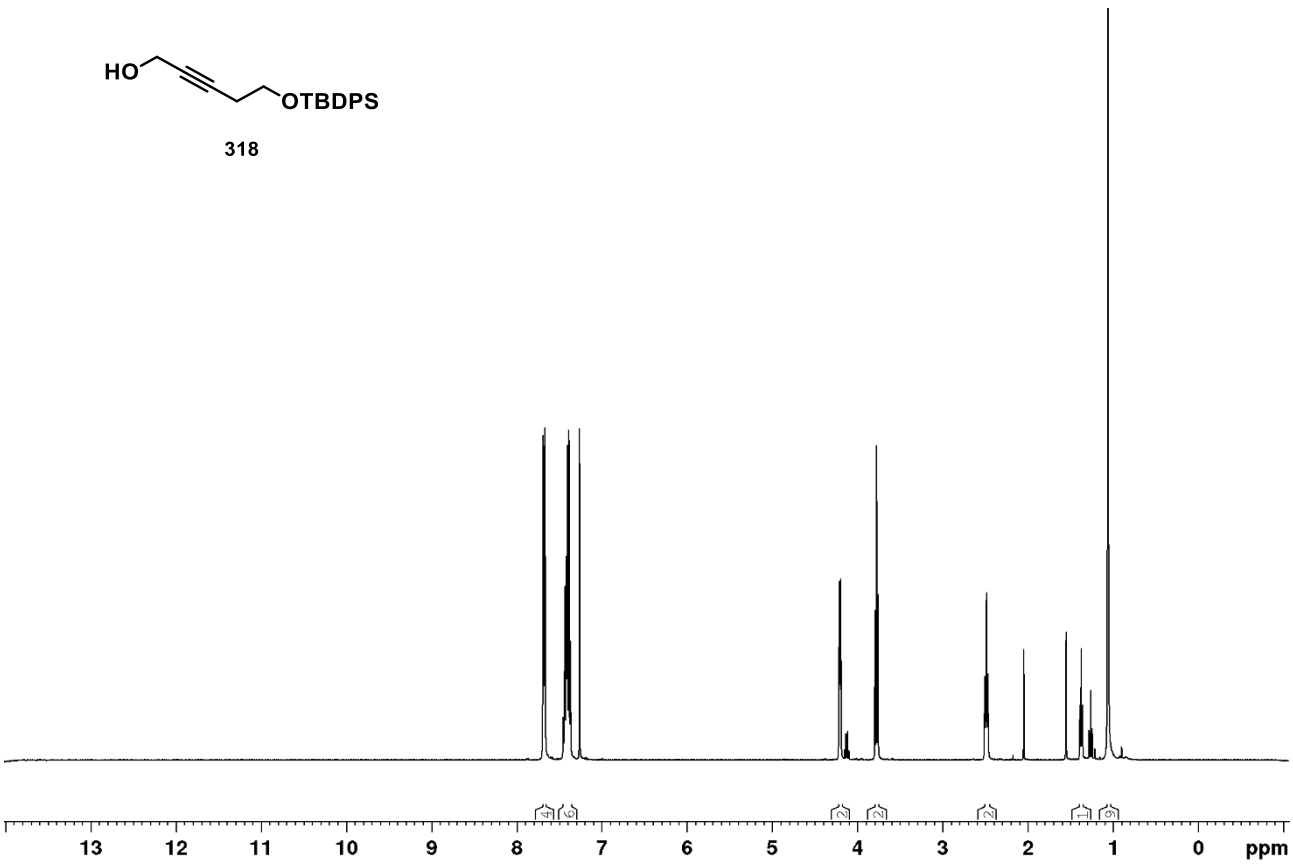
HO
OTBDPS
318
13
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11
10
9
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5
4
3
2
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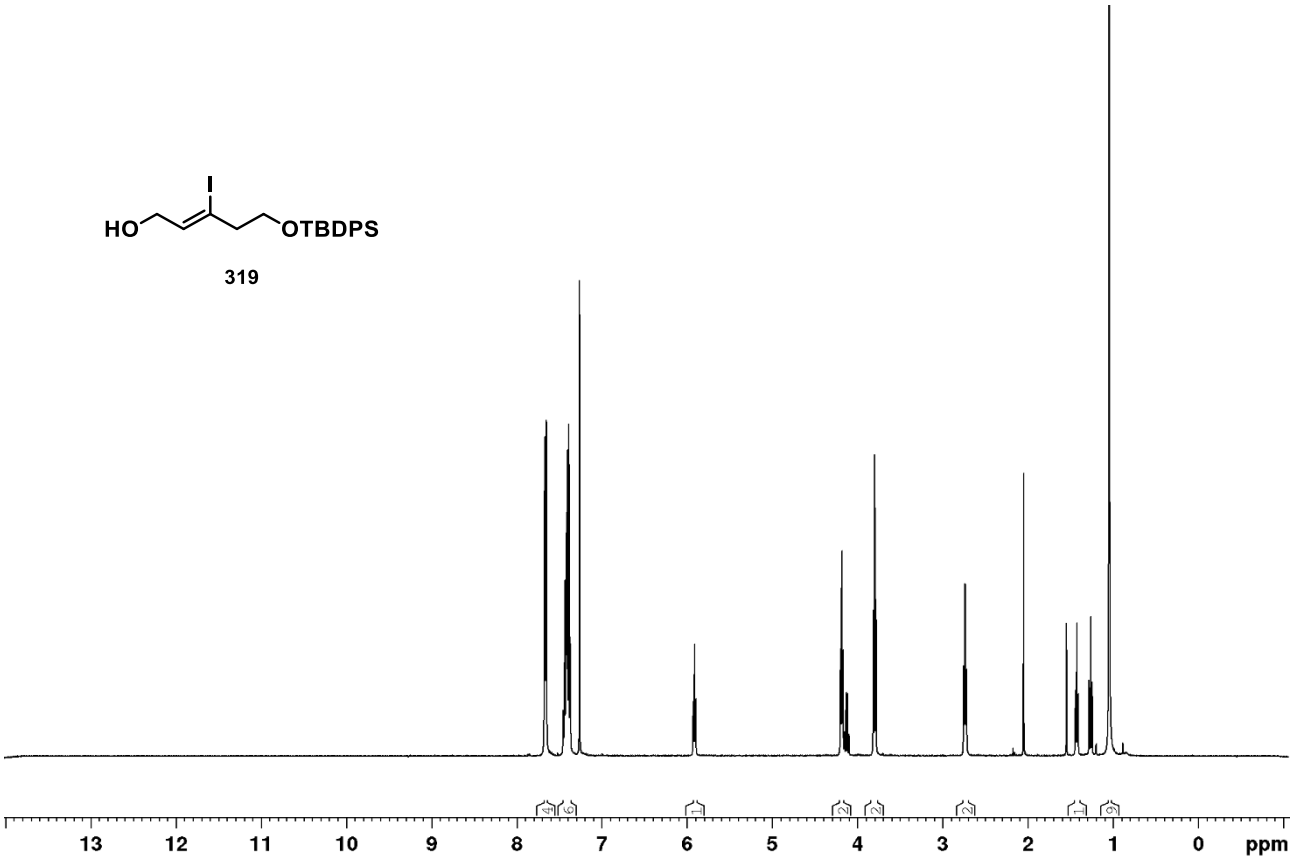
0
ppm


HO
OTBDPS
319
13
12
11
10
9
8
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6
5
4
3
2
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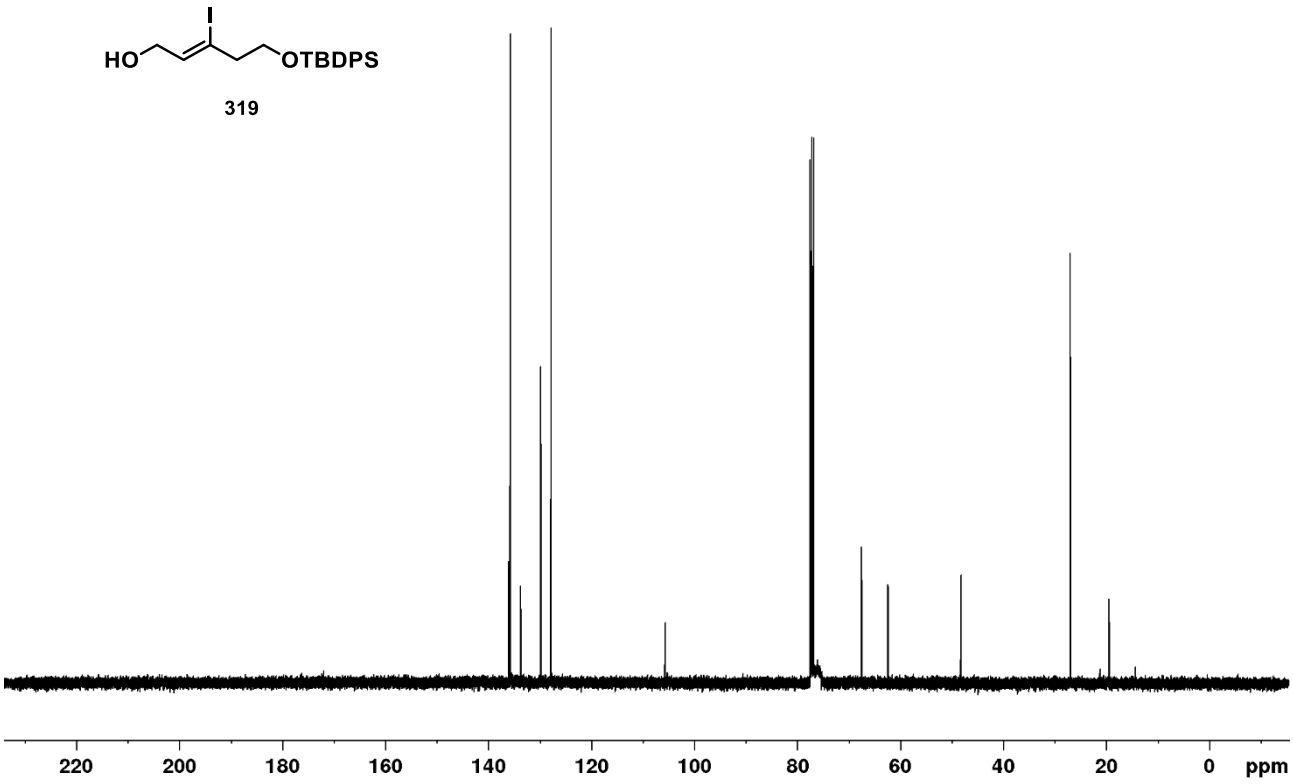
0
ppm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OTBDPS
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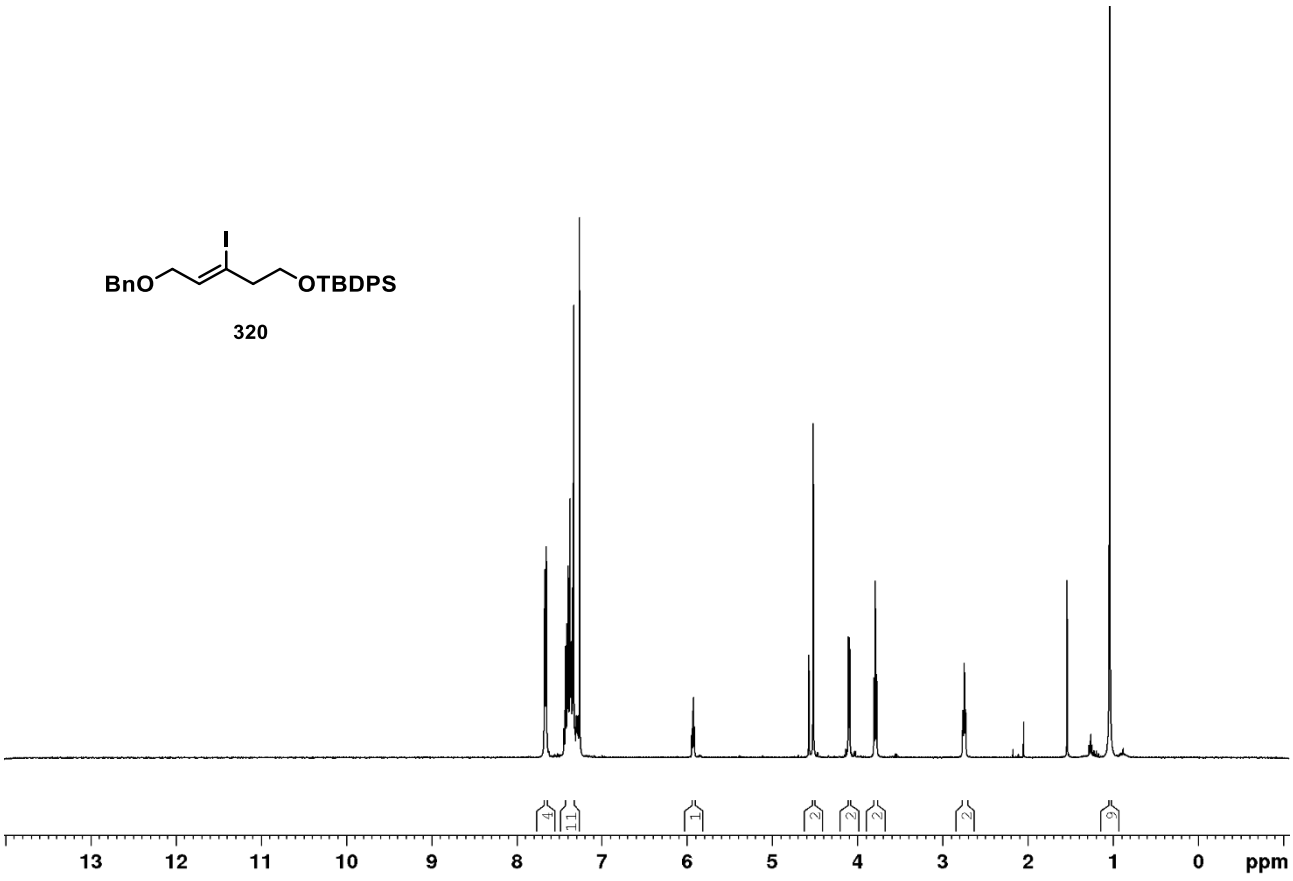
40
20
0
ppm


BnO
OTBDPS
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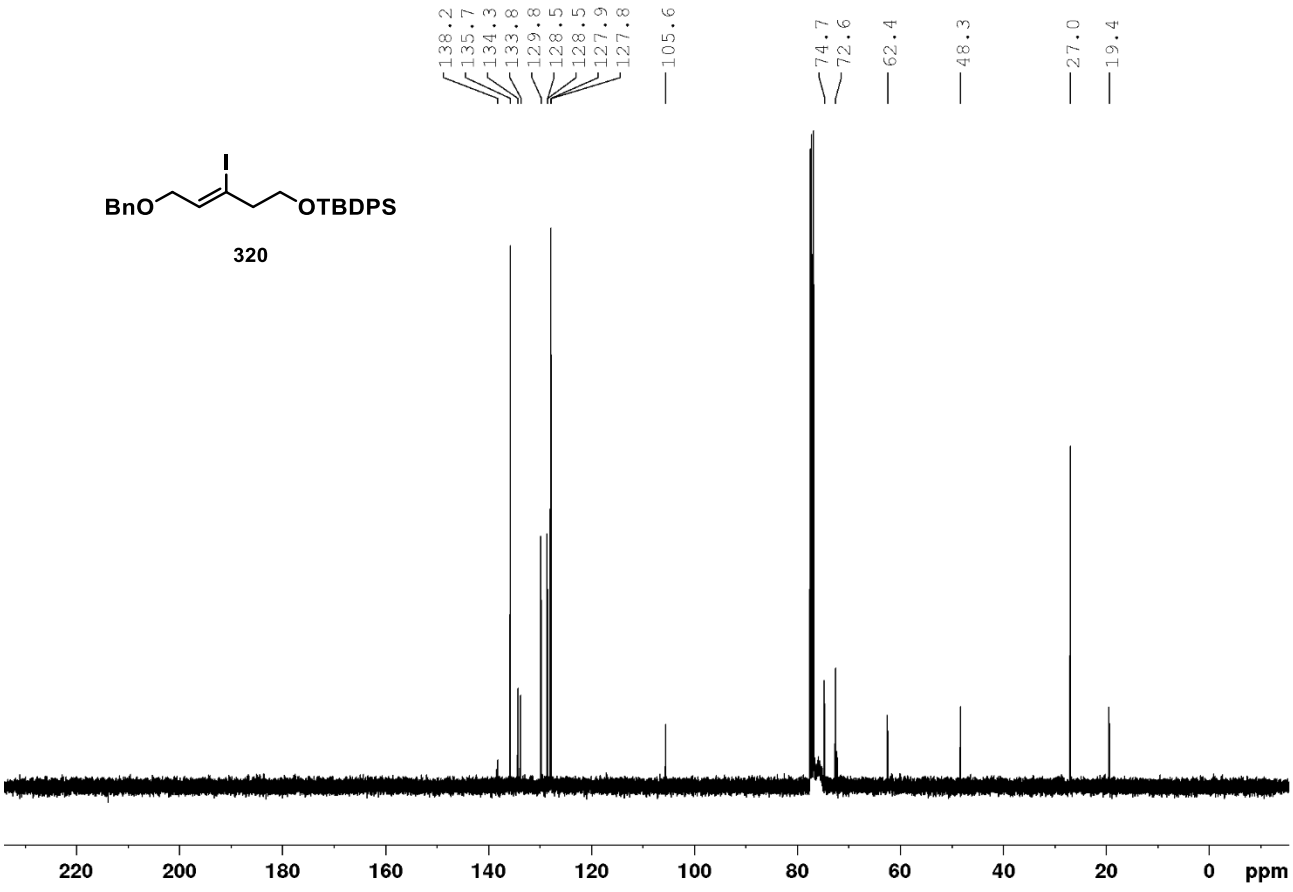
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134.3
133.8
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128.5
127.9
127.8
105.6
74.7
72.6
62.4
48.3
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19.4
BnO
OTBDPS
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200
180
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100
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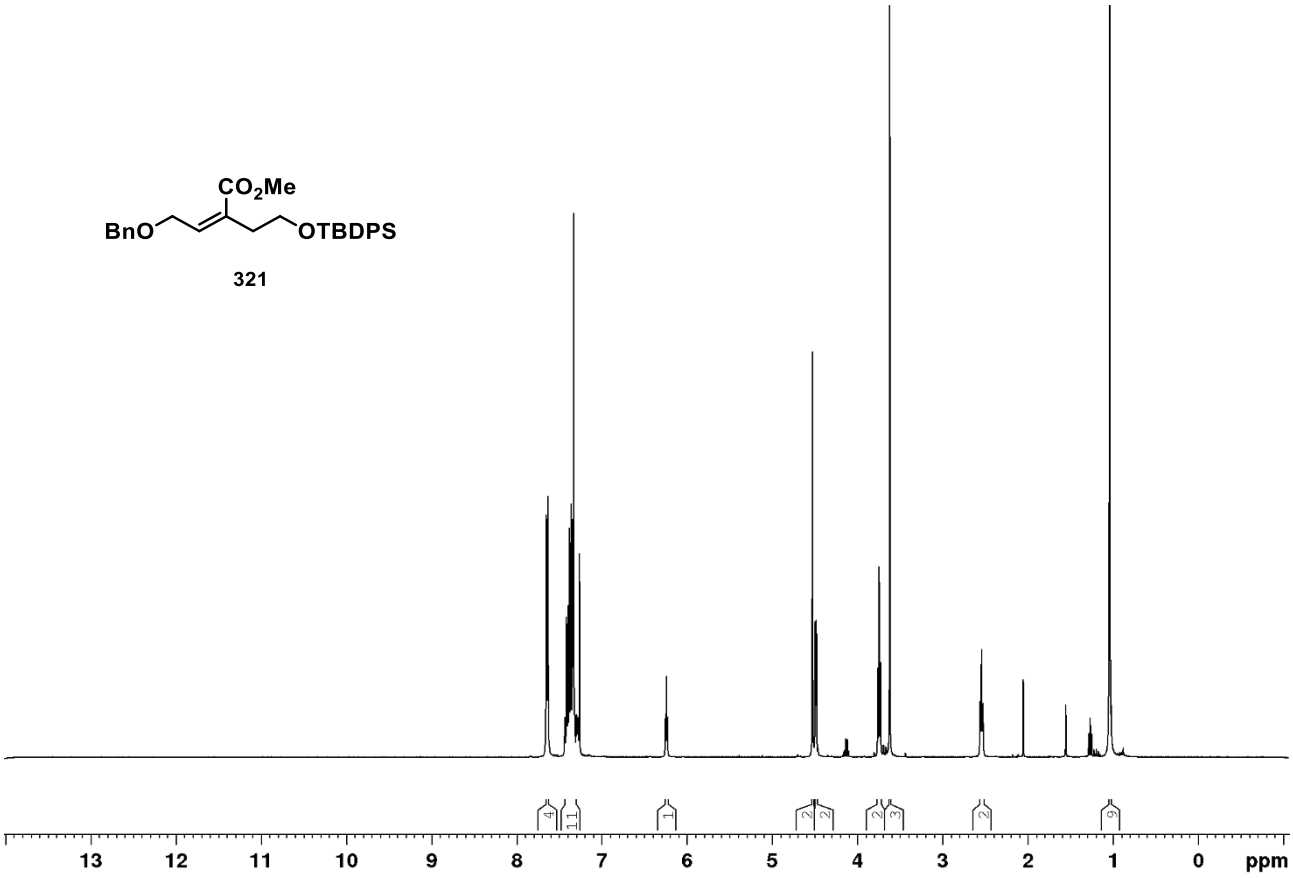
20
0
ppm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BnO
OTBDPS
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6
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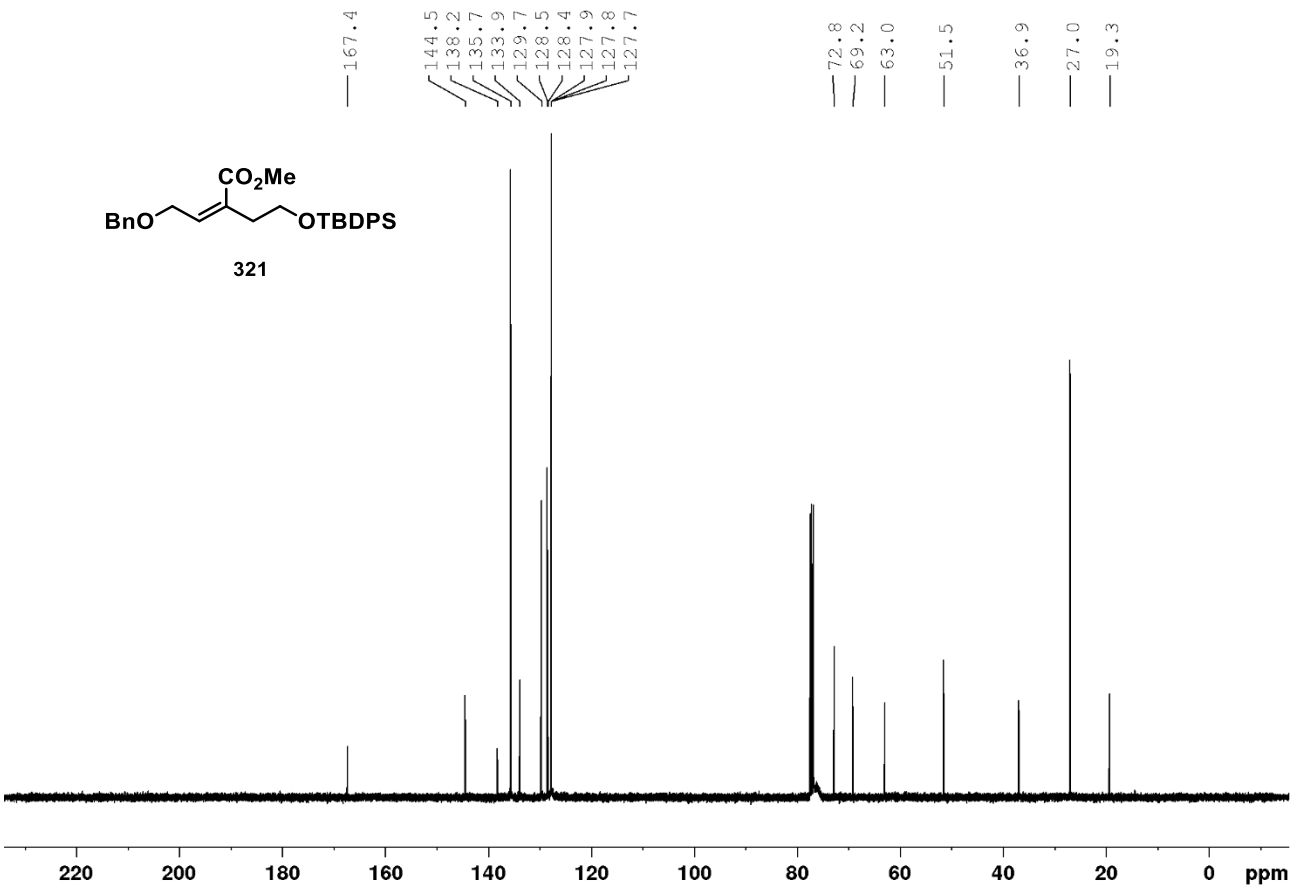
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127.7
72.8
69.2
63.0
51.5
36.9
27.0
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CO2Me
BnO
OTBDPS
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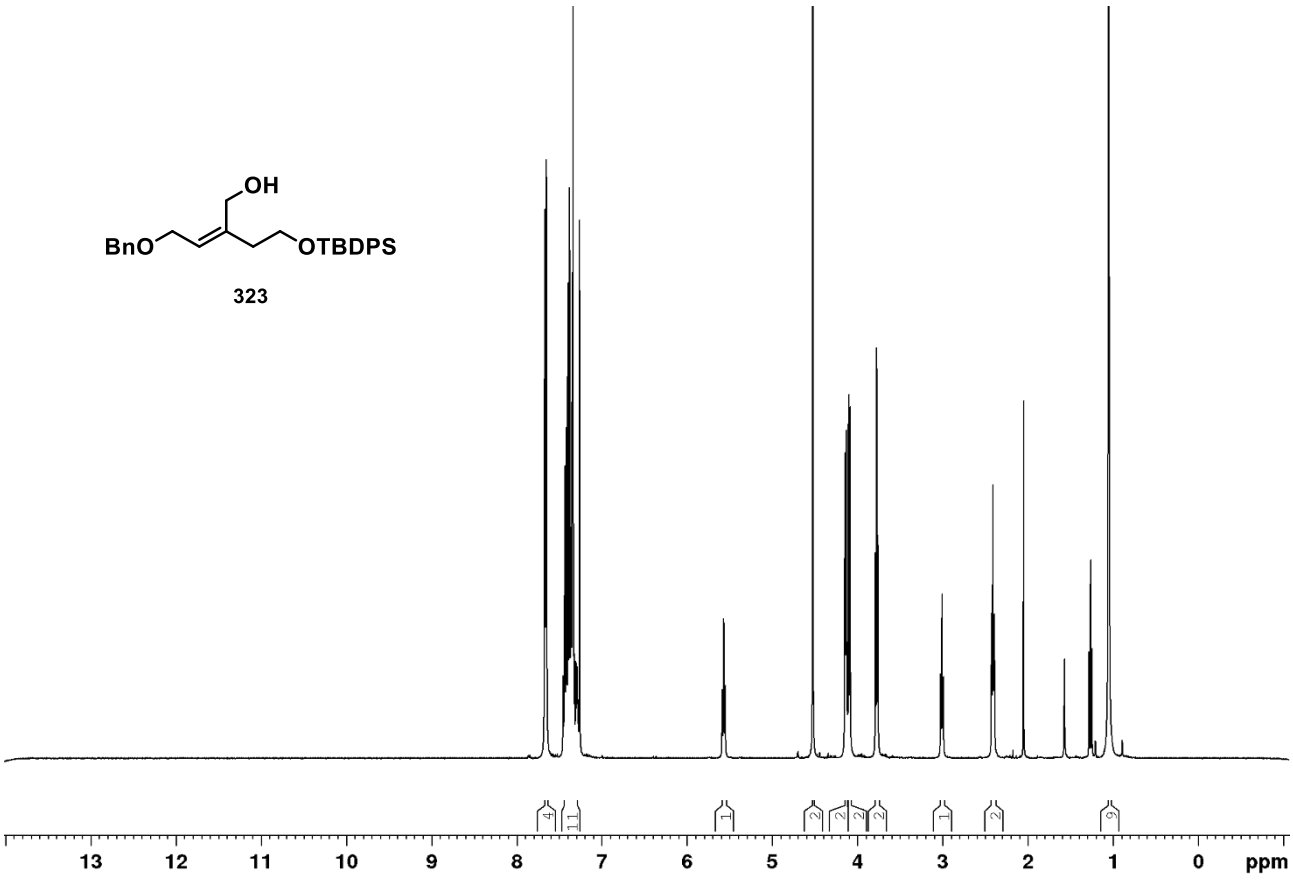
ppm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OTBDPS
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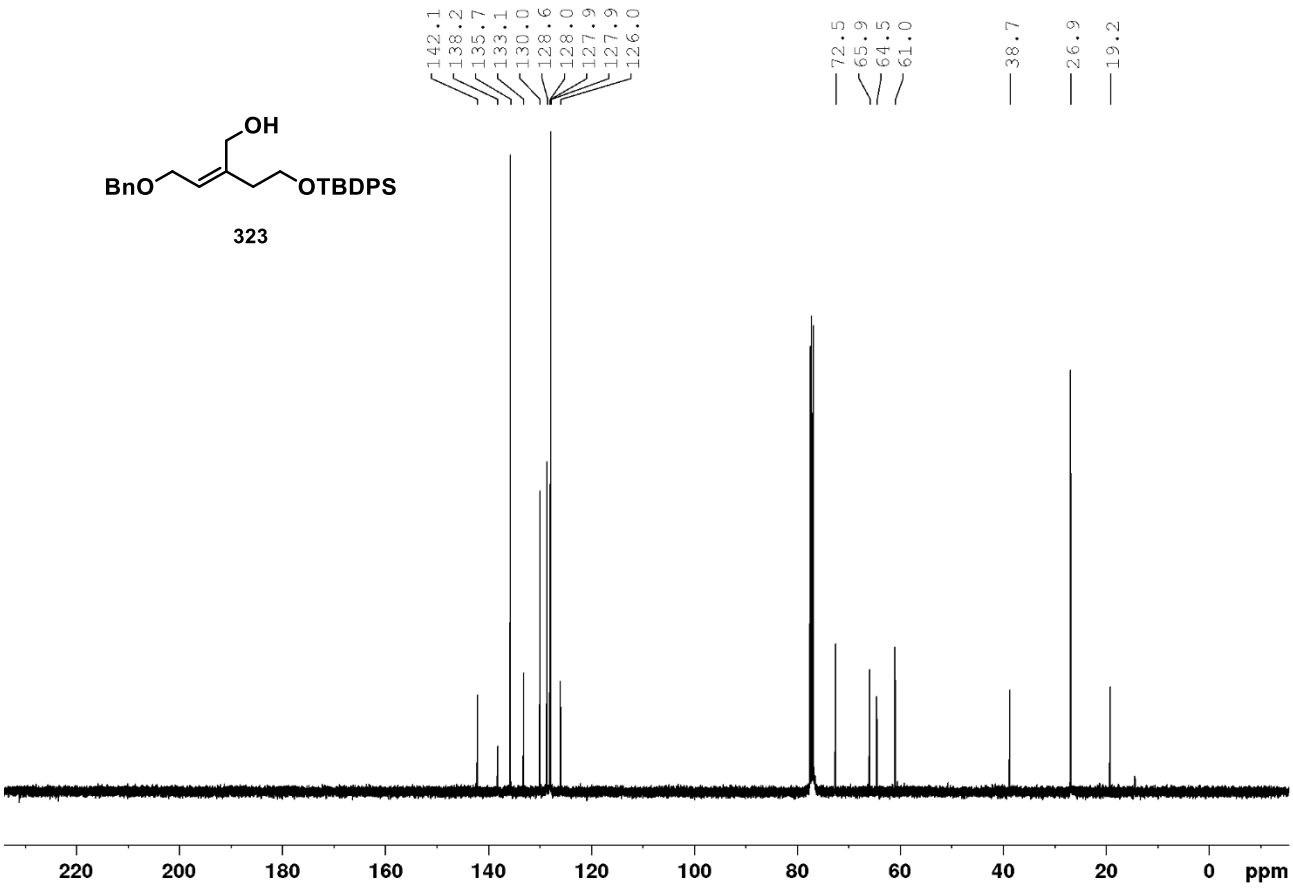
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65.9
64.5
61.0
38.7
26.9
19.2
OH
BnO
OTBDPS
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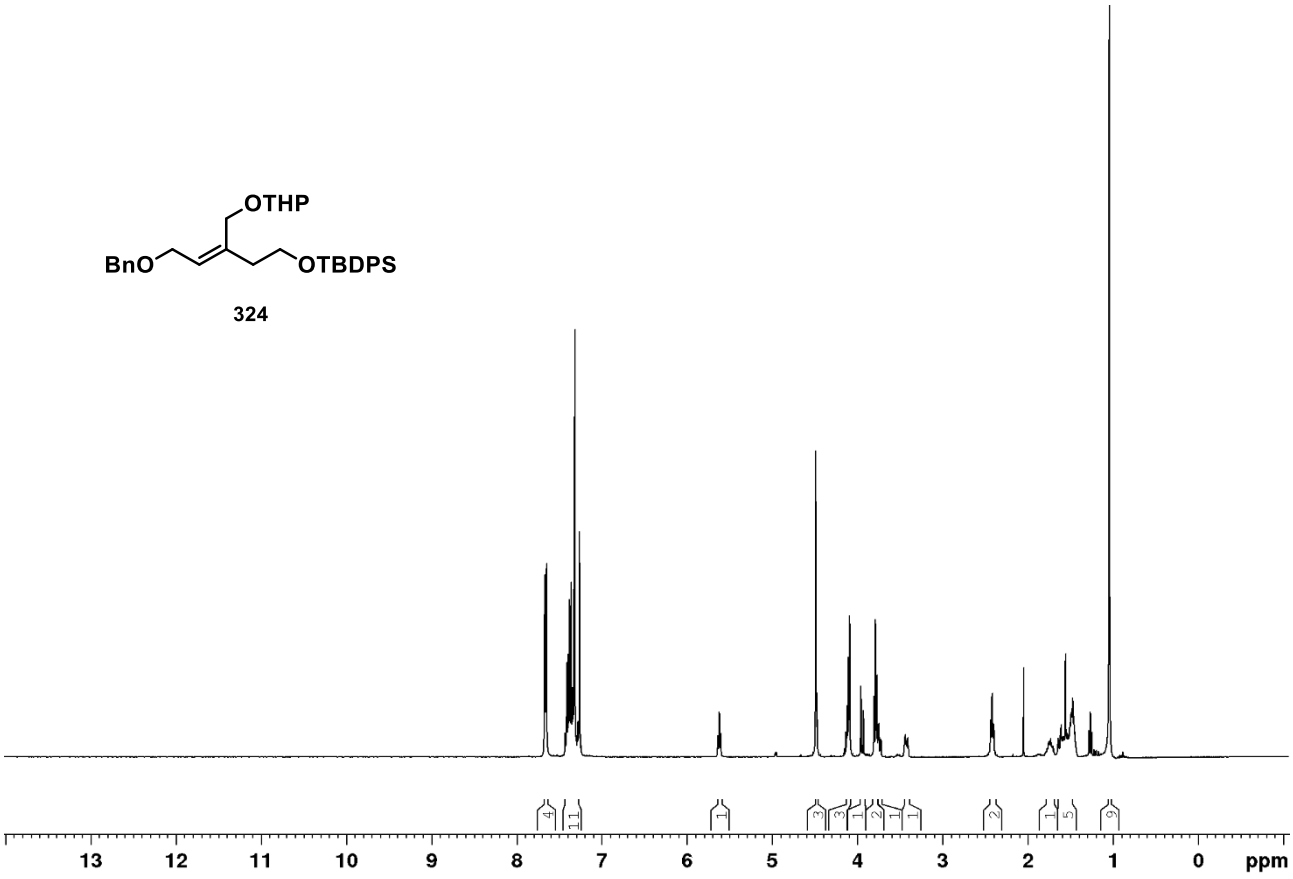
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BnO
OTBDPS
324
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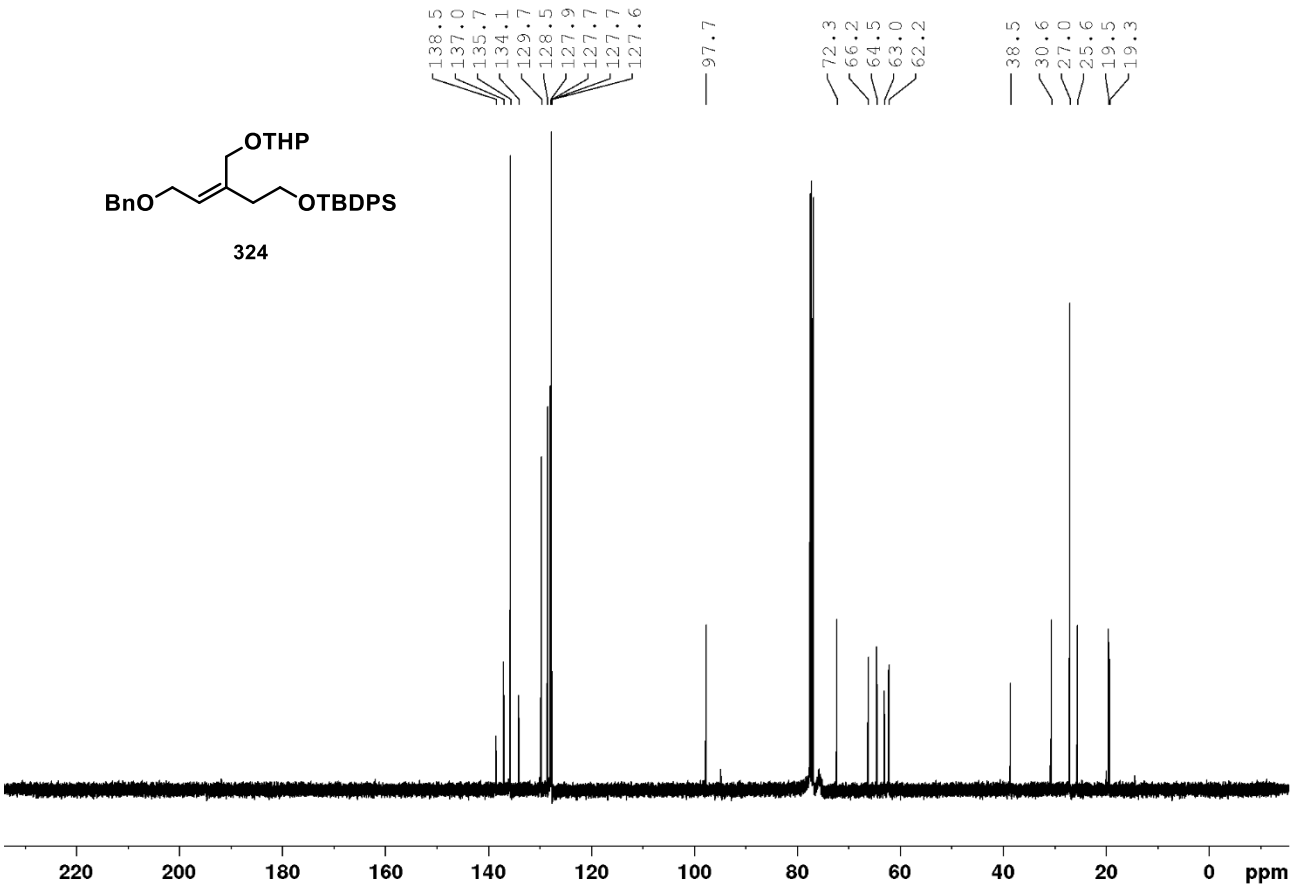
ppm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127.6
97.7
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66.2
64.5
63.0
62.2
38.5
30.6
27.0
25.6
19.5
19.3
OTHP
BnO
OTBDPS
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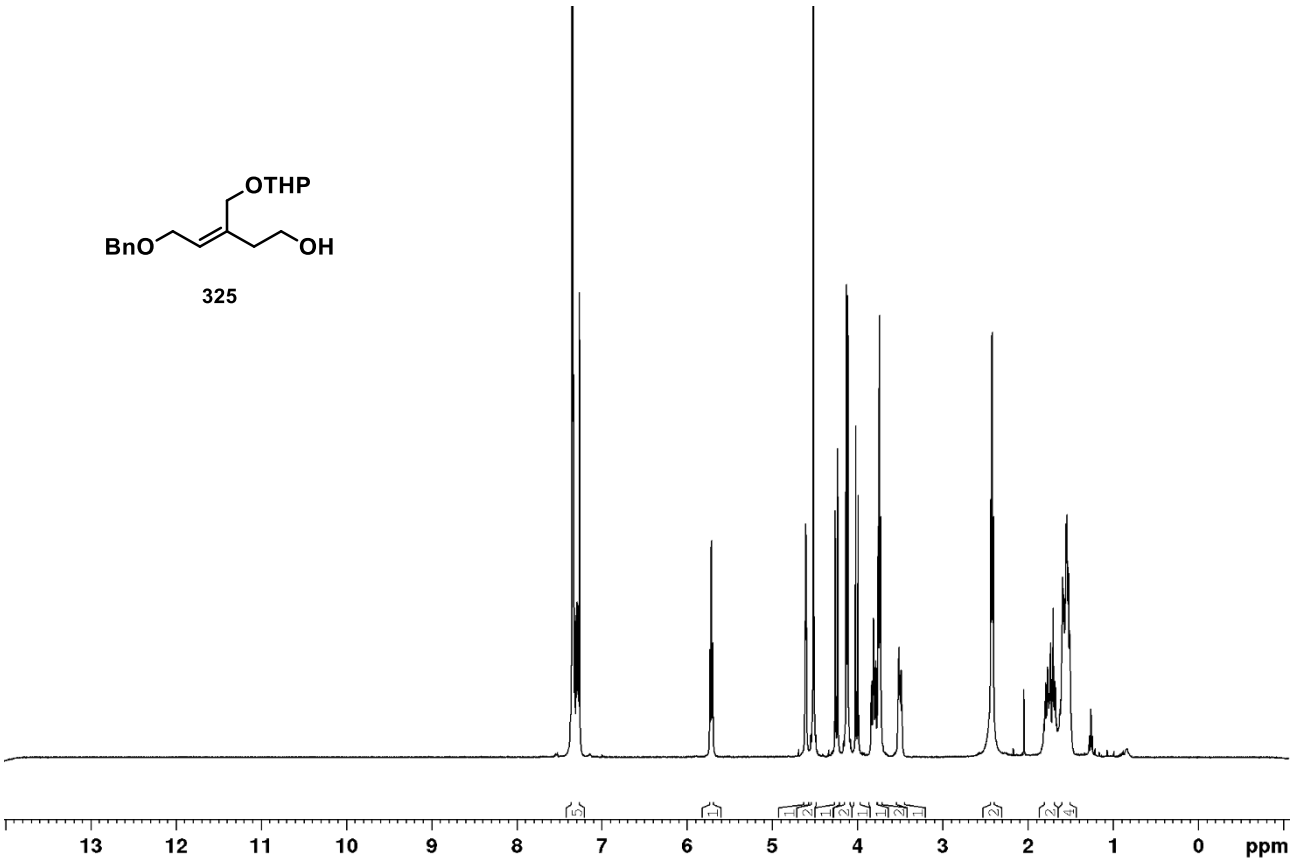
ppm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BnO
OH
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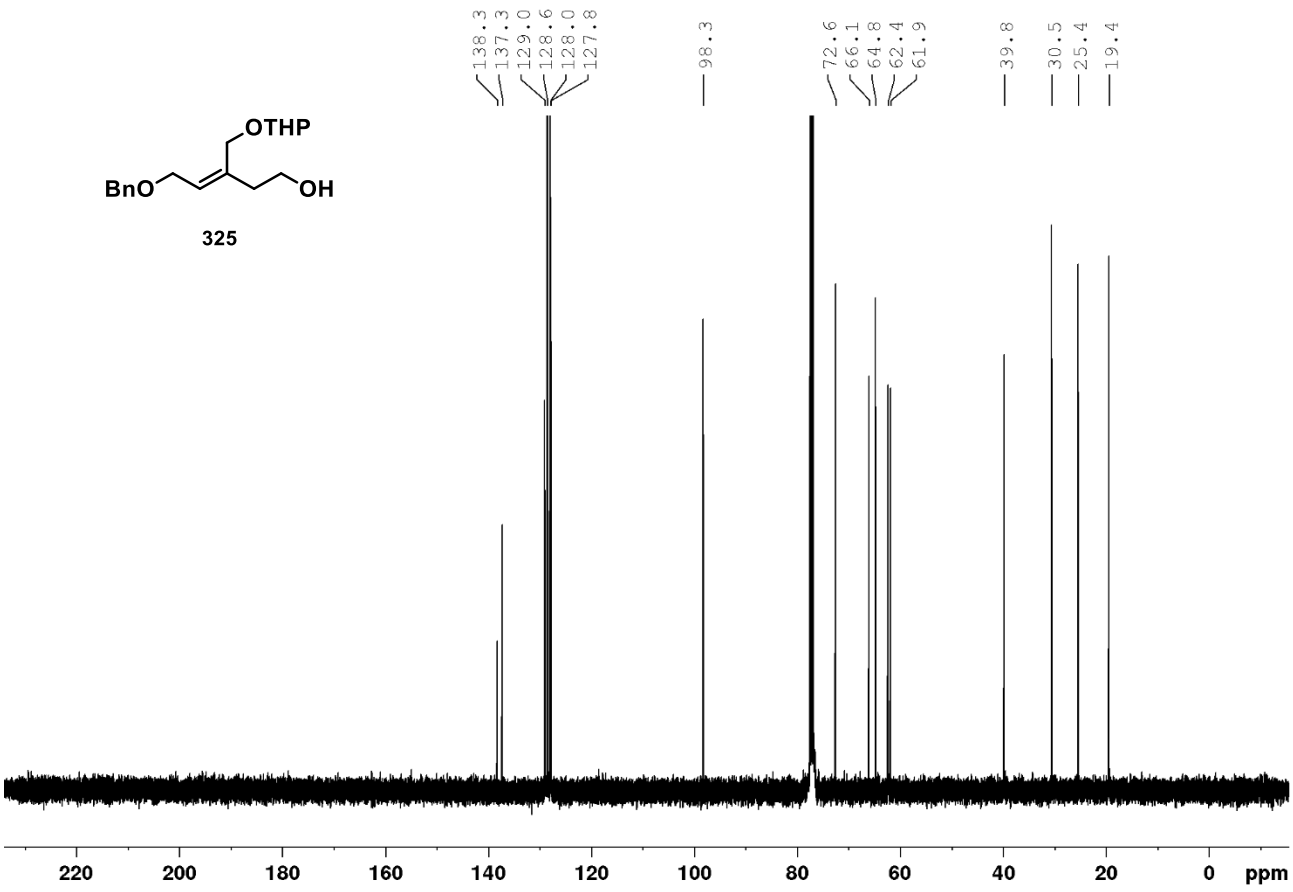
ppm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129.0
128.6
128.0
127.8
98.3
72.6
66.1
64.8
62.4
61.9
39.8
30.5
25.4
19.4
OTHP
BnO
OH
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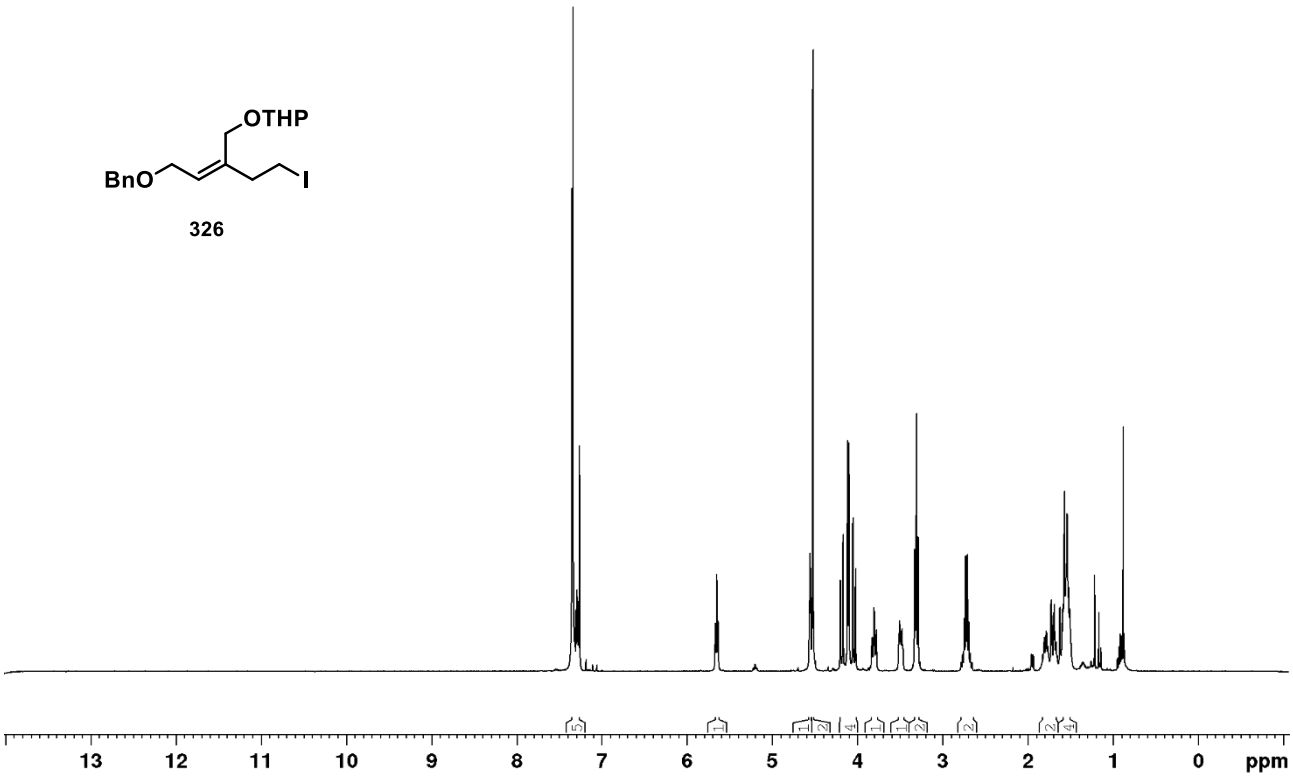
ppm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BnO
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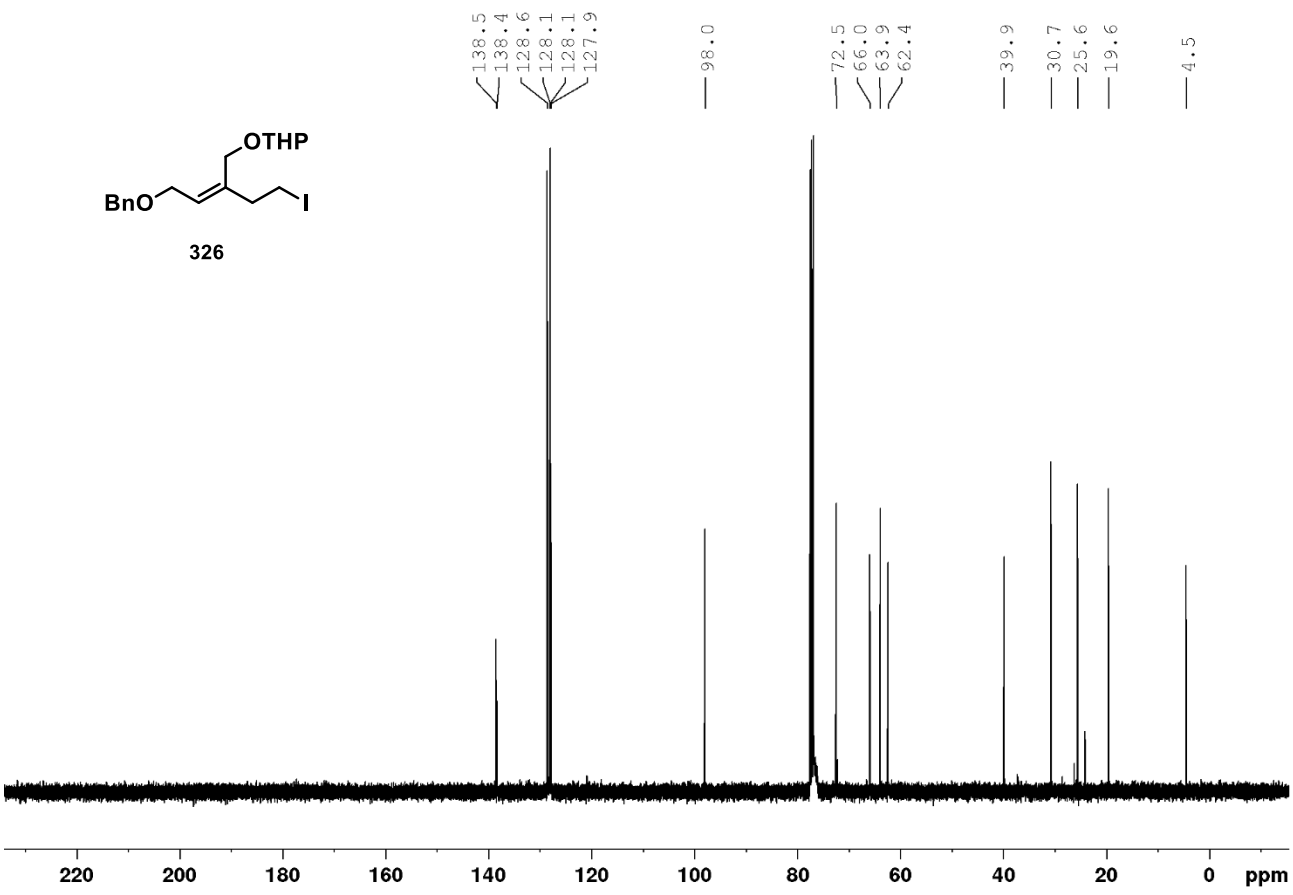
ppm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138.4
128.6
128.1
128.1
127.9
98.0
72.5
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63.9
62.4
39.9
30.7
25.6
19.6
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BnO
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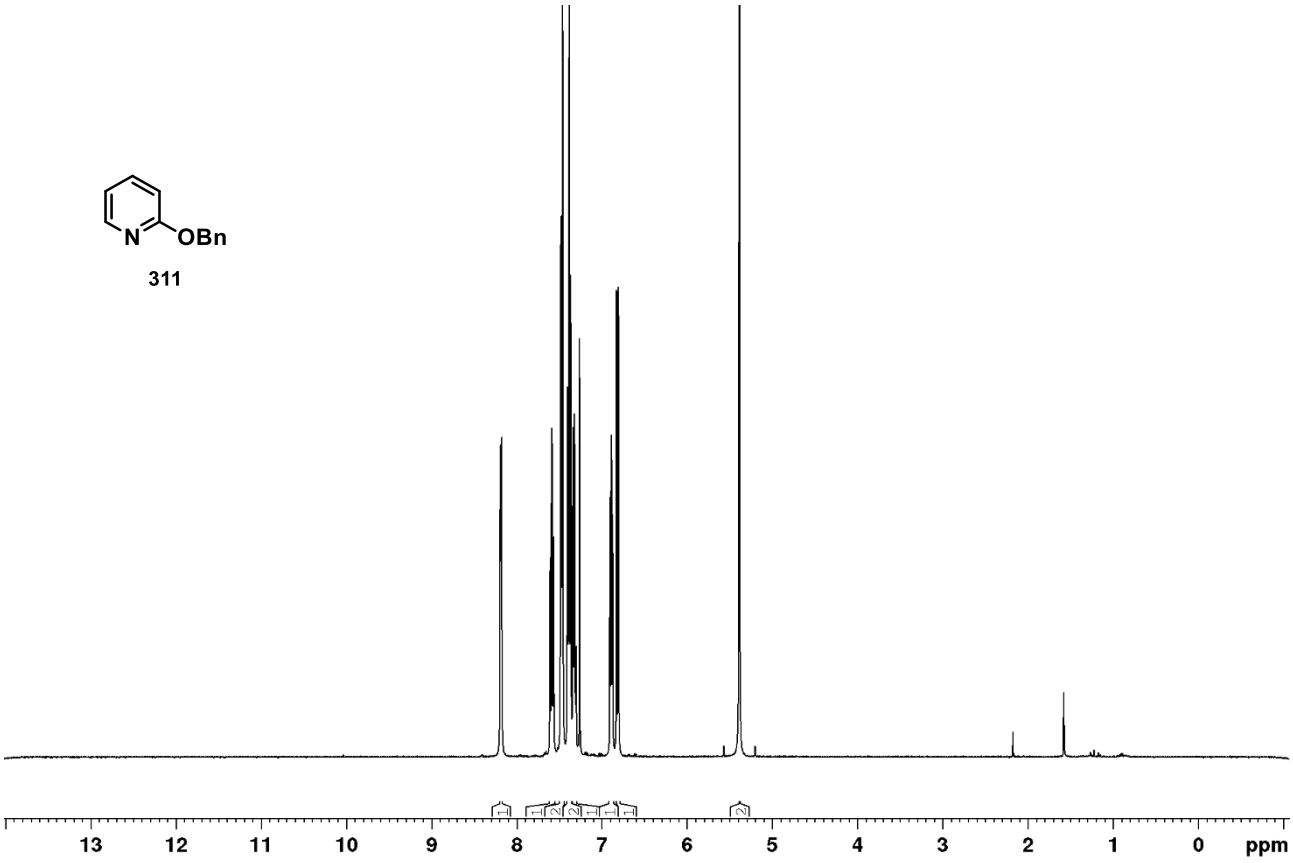
ppm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1
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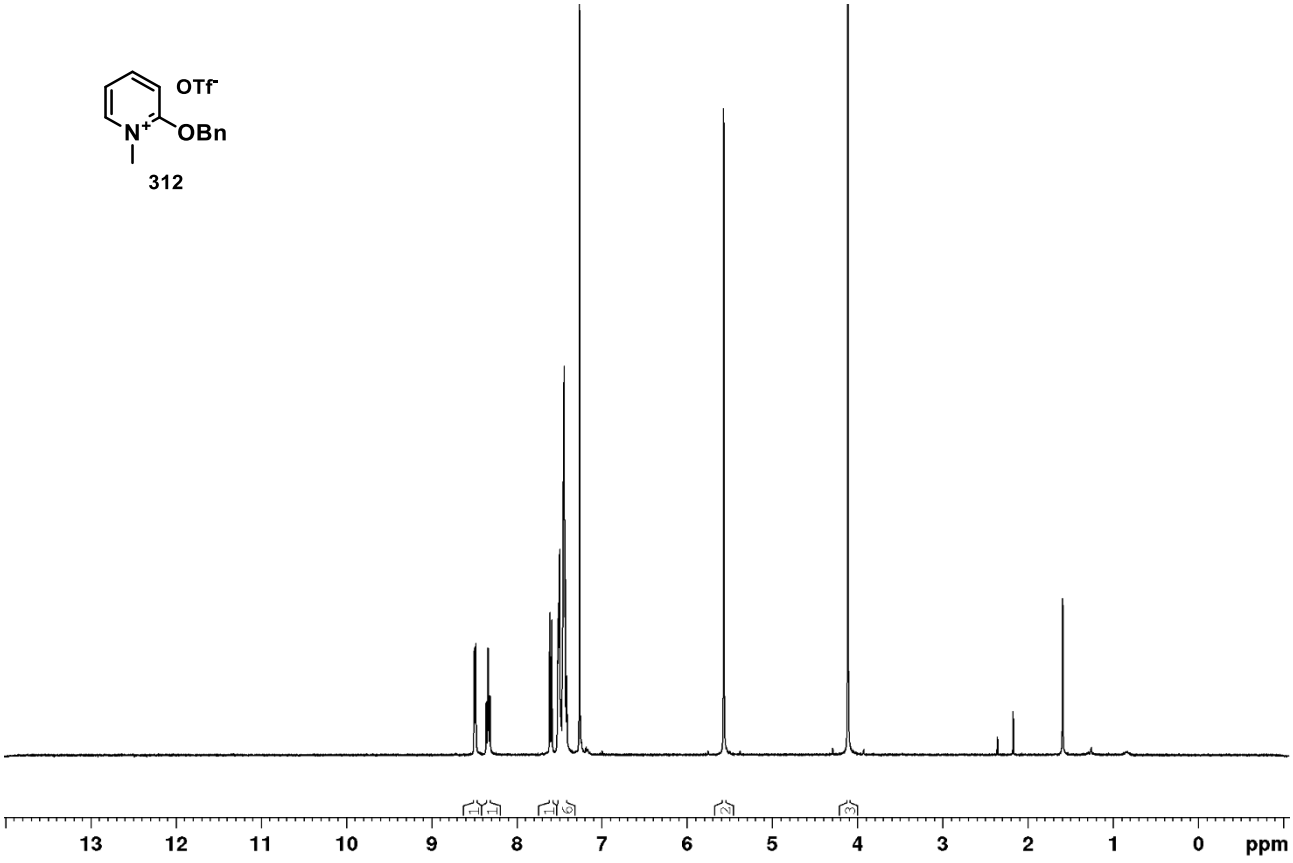
ppm


OTf⁻
N⁺
OBn
312
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3
2
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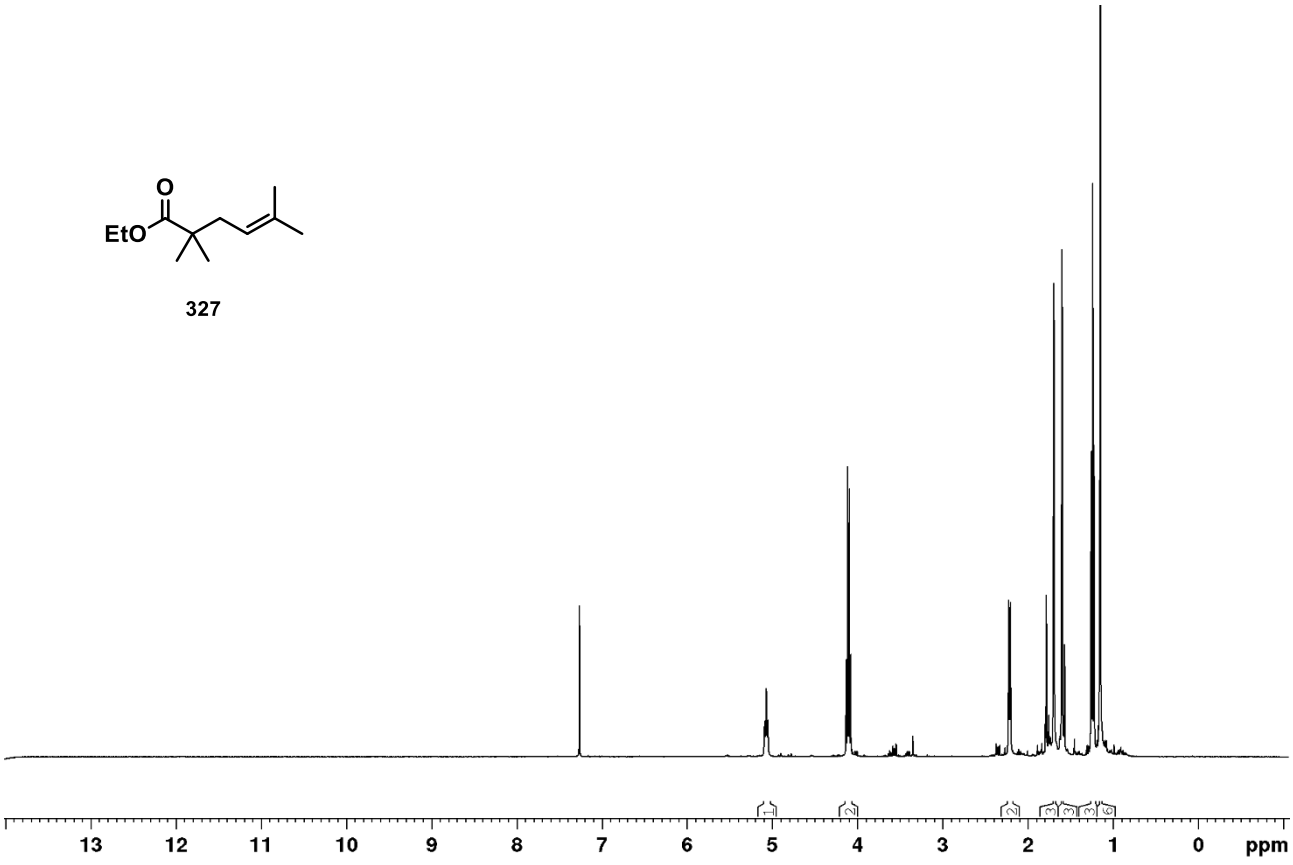
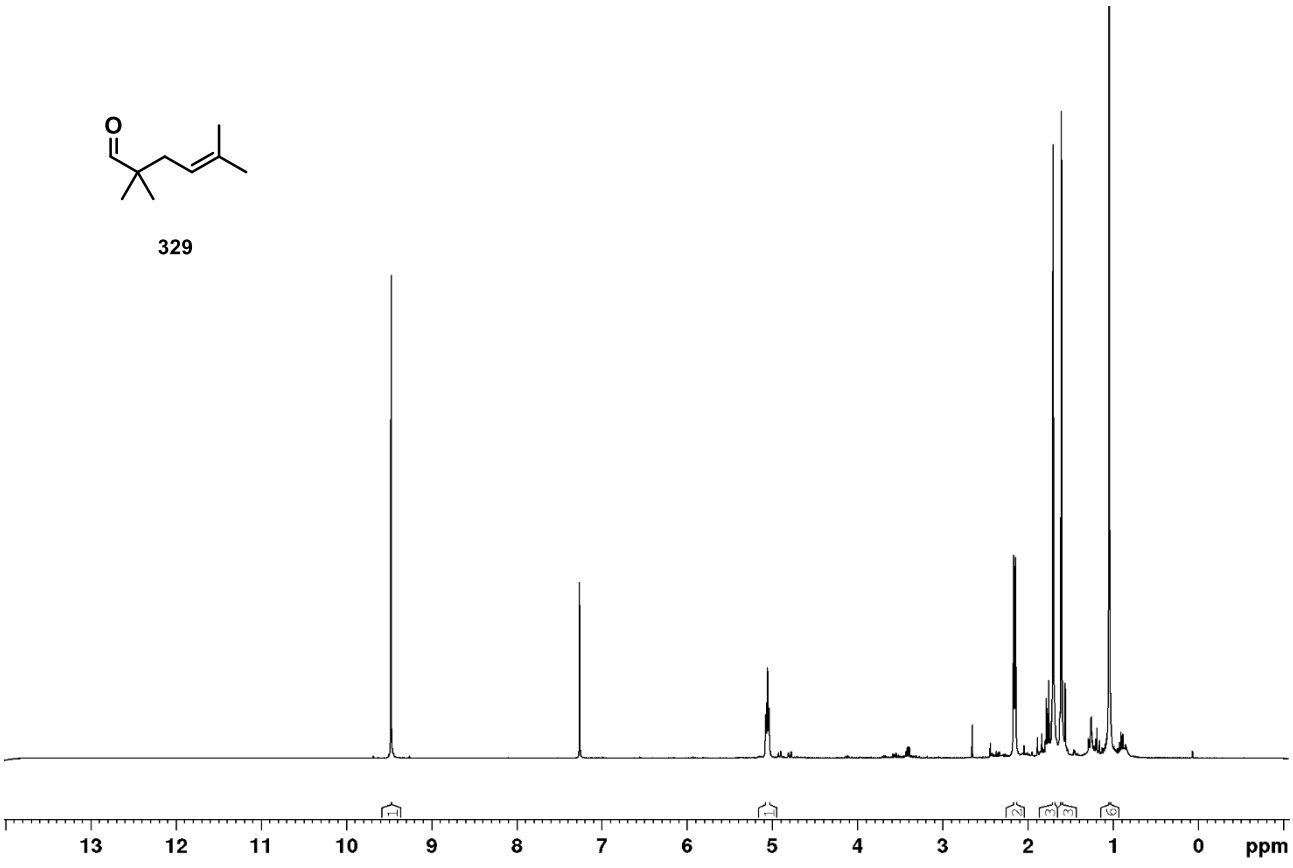
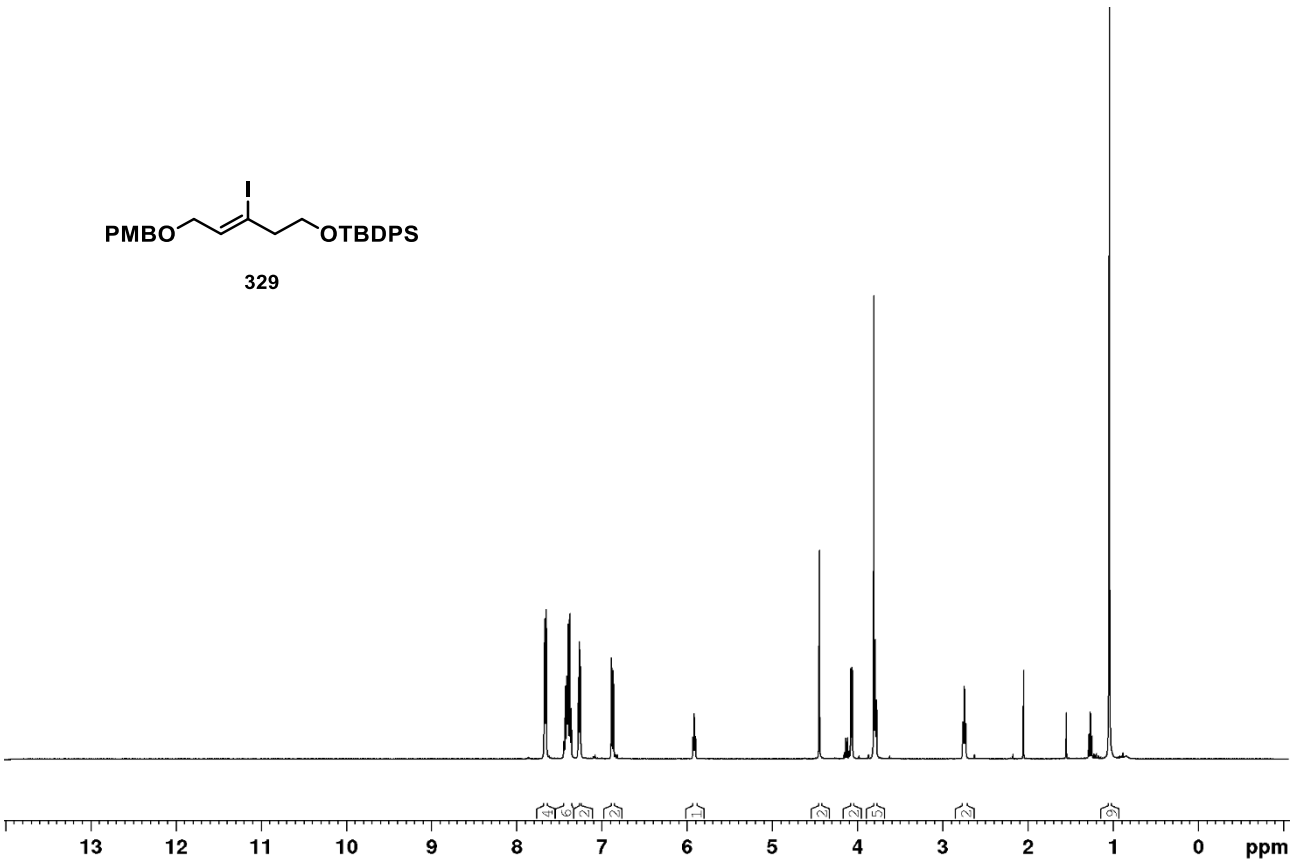
0
ppm



327



329


PMBO
OTBDPS
329
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7
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5
4
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2
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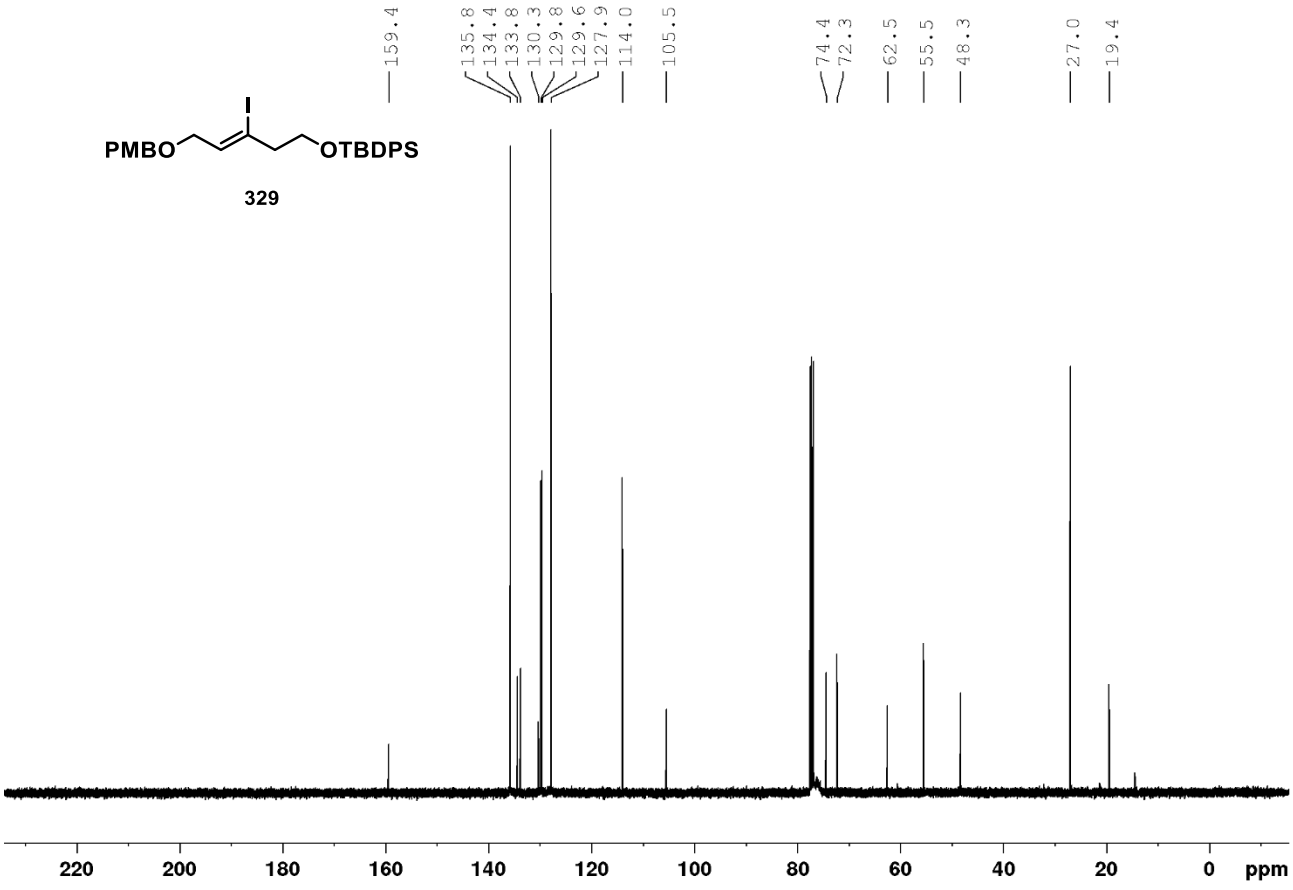
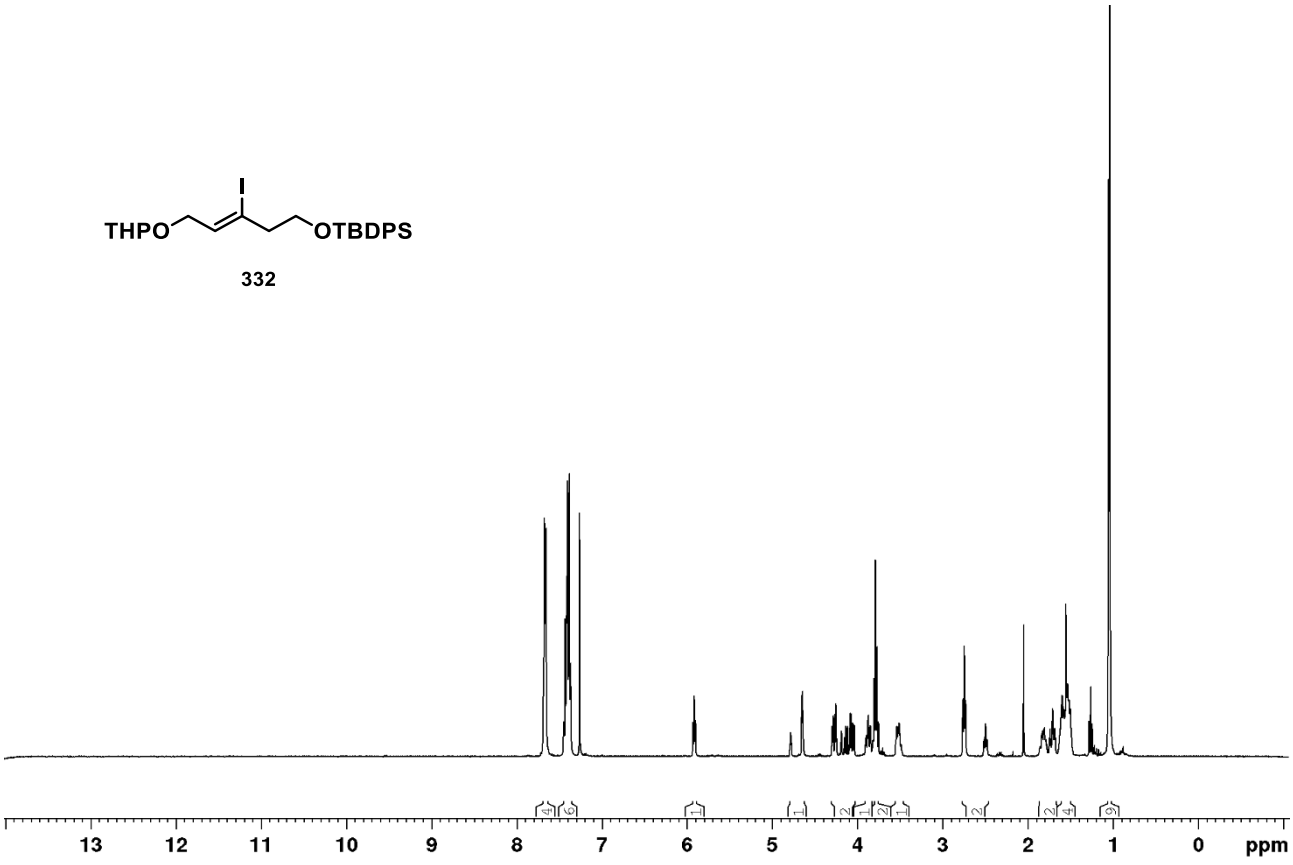
0
ppm


159.4
135.8
134.4
133.8
130.3
129.8
129.6
127.9
114.0
105.5
74.4
72.3
62.5
55.5
48.3
27.0
19.4
PMBO
OTBDPS
329
220
200
180
160
140
120
100
80
60
40
20
0
ppm


THPO
OTBDPS
13
12
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10
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8
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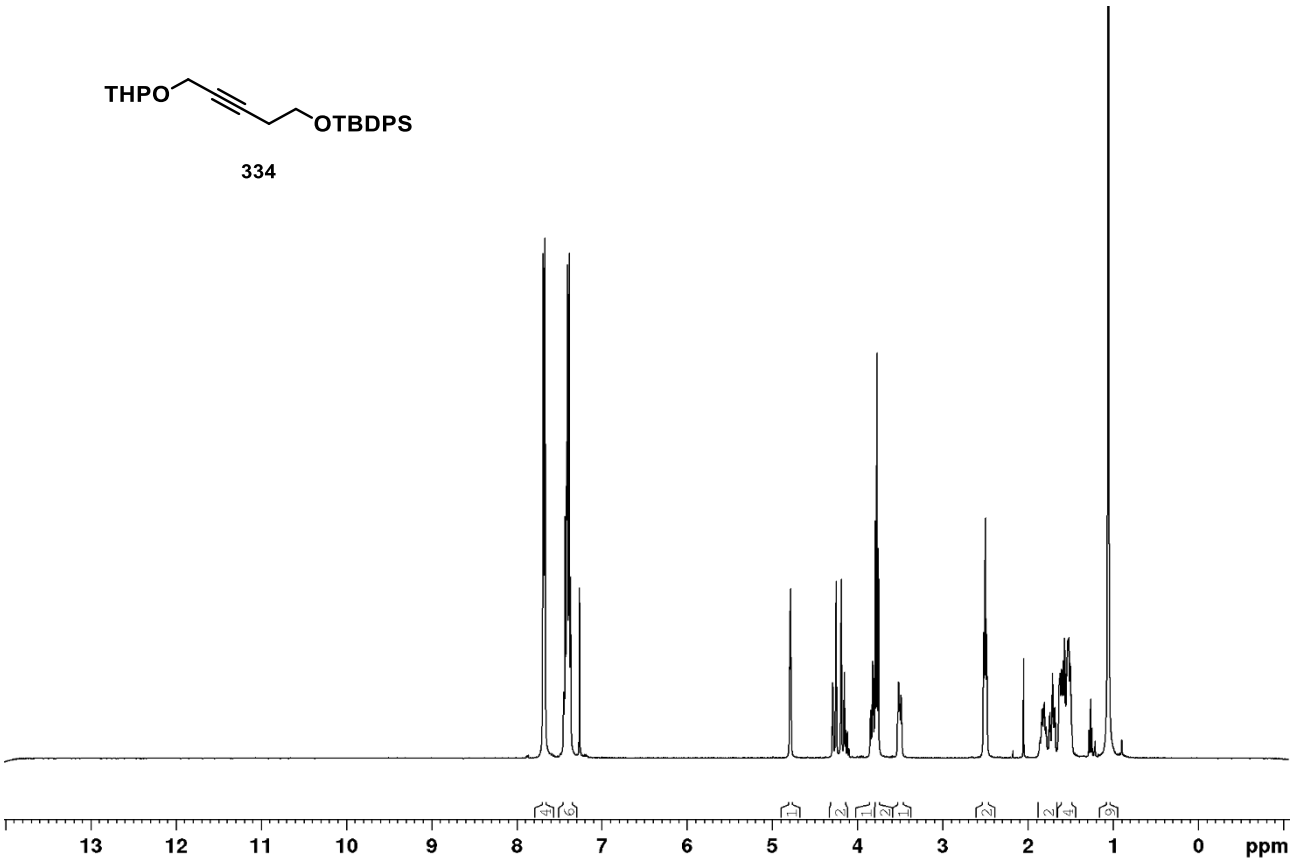
6
5
4
3
2
1
0
ppm

332


THPO
OTBDPS
13
12
11
10
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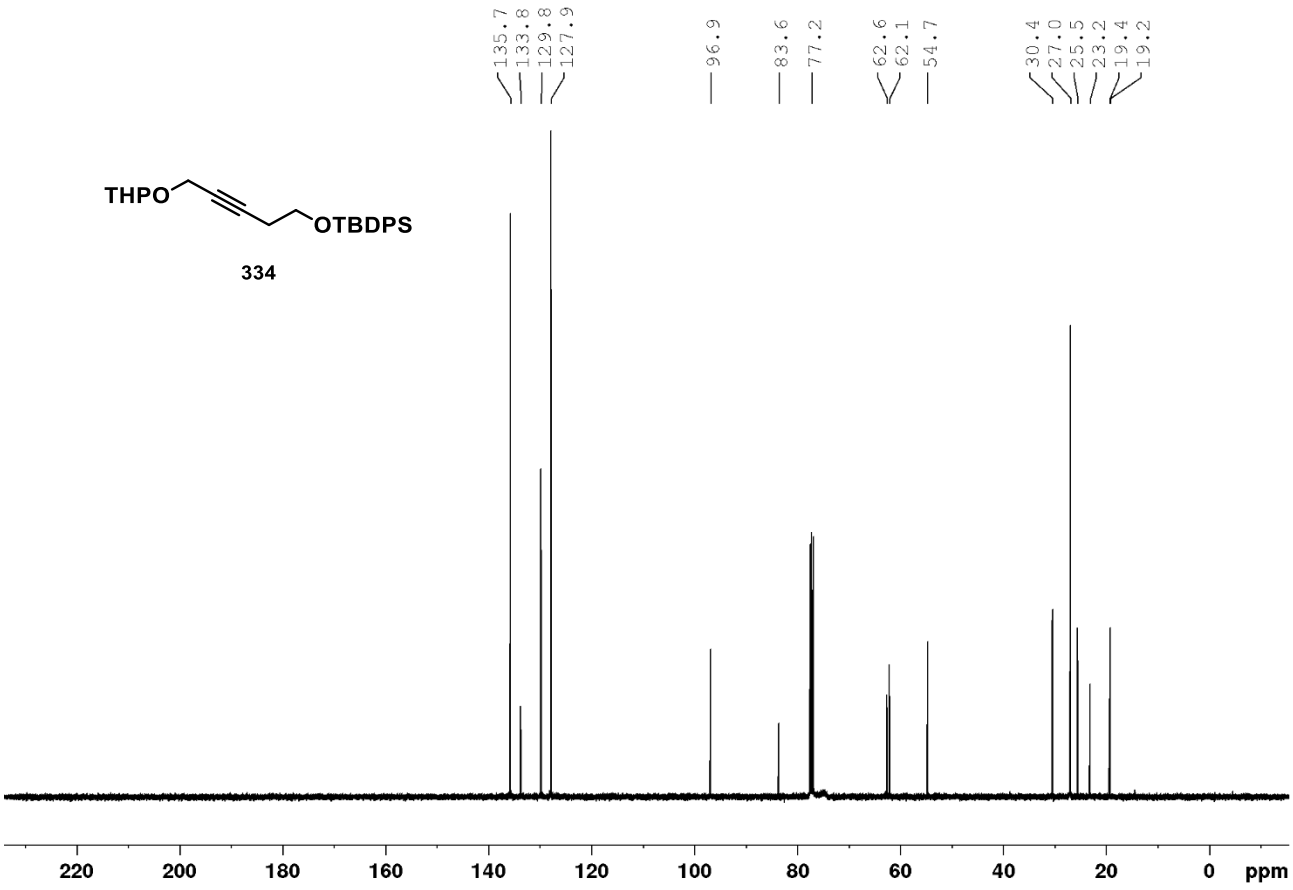
8
7
6
5
4
3
2
1
0
ppm

334


135.7
133.8
129.8
127.9
96.9
83.6
77.2
62.6
62.1
54.7
30.4
27.0
25.5
23.2
19.4
19.2
THPO
OTBDPS
334
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200
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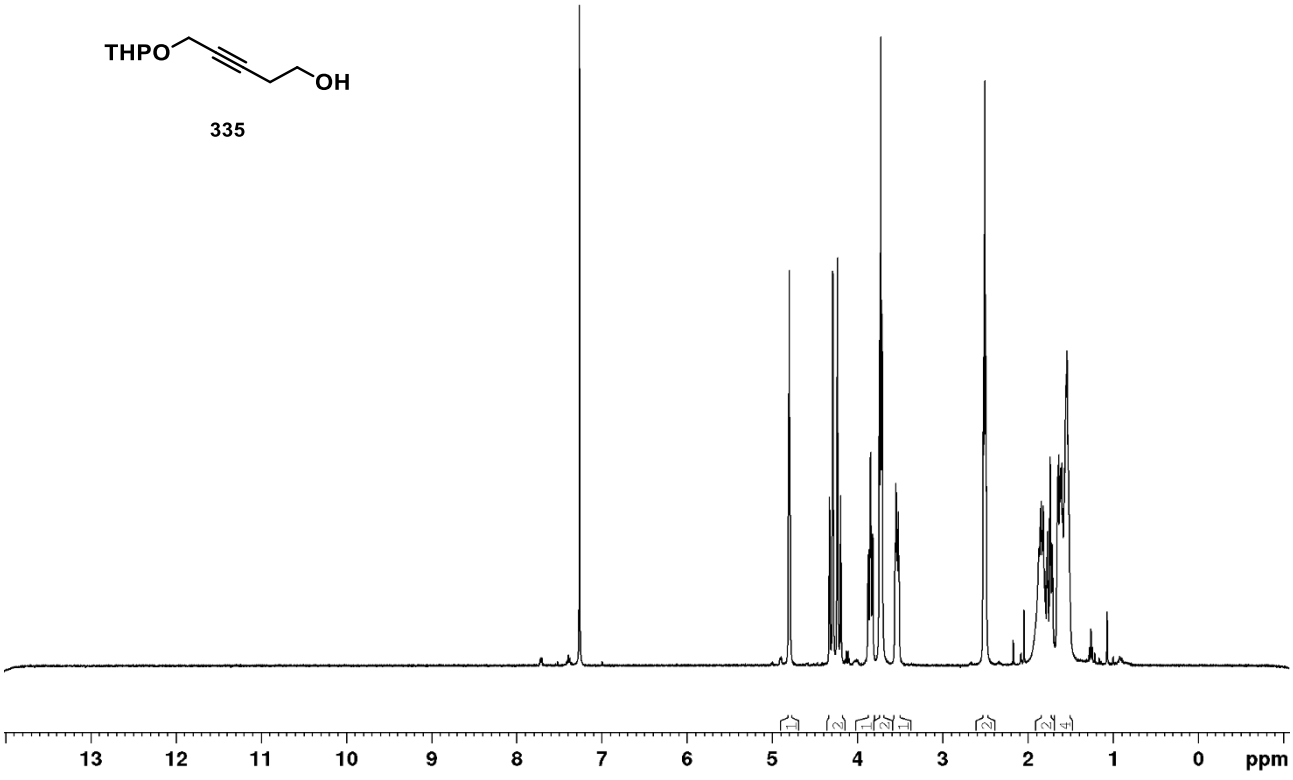
120
100
80
60
40
20
0
ppm


THPO
OH
335
13
12
11
10
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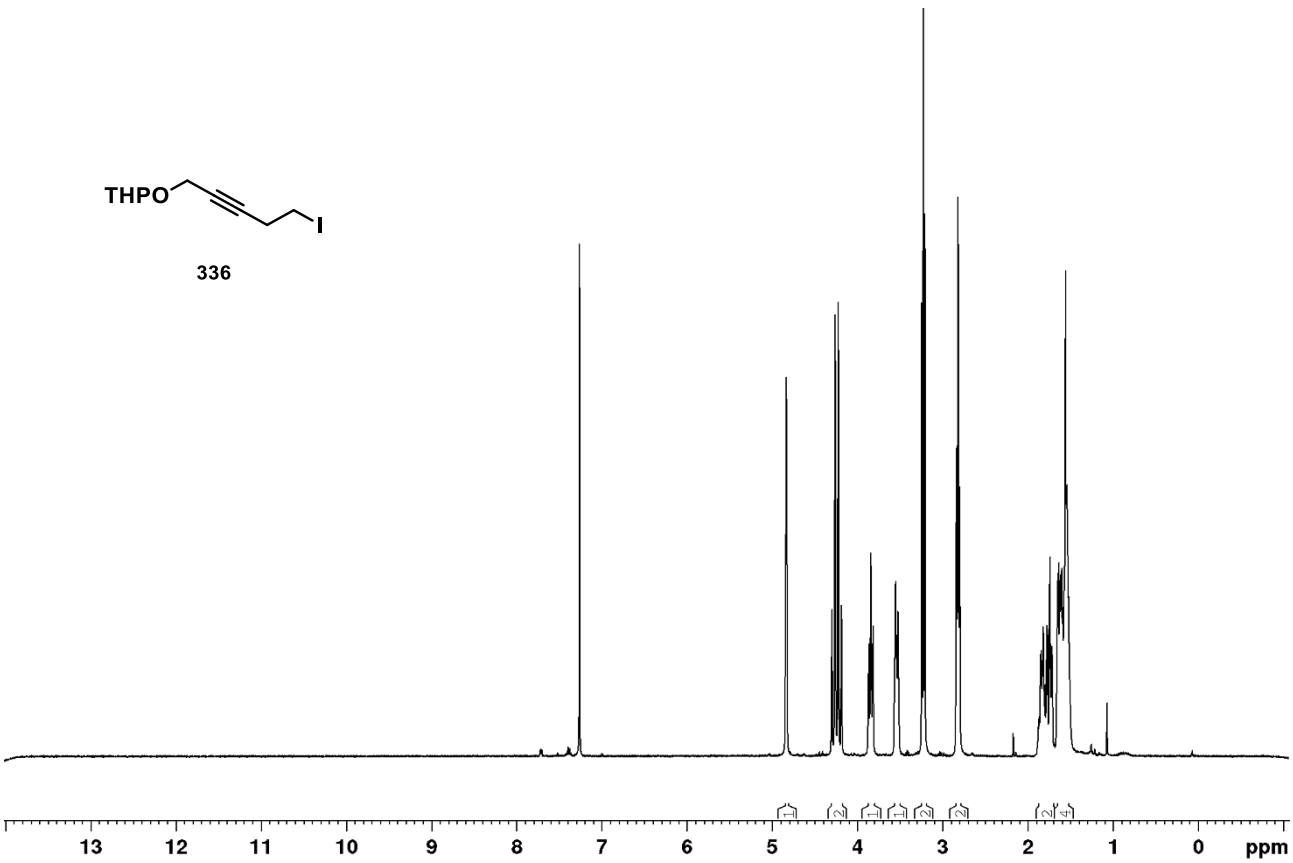
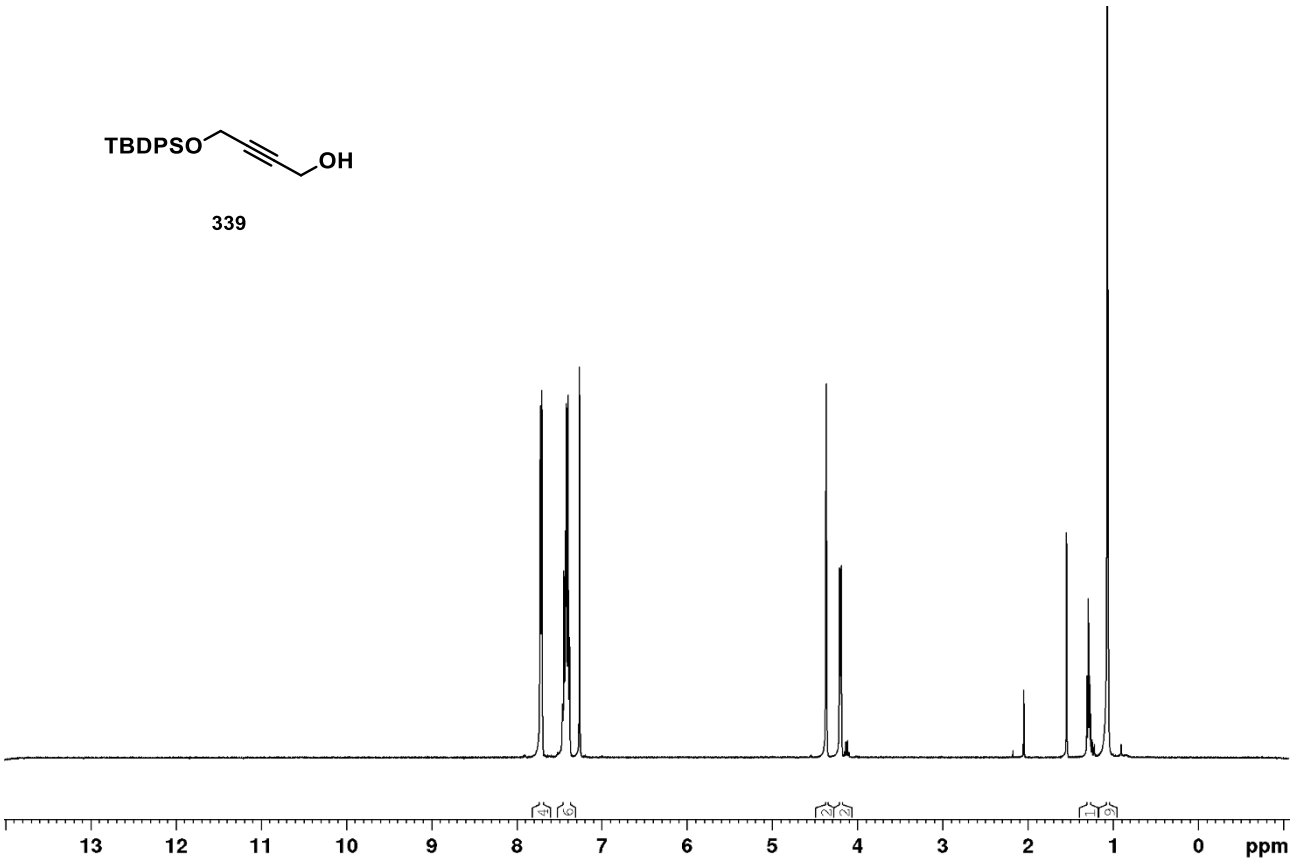
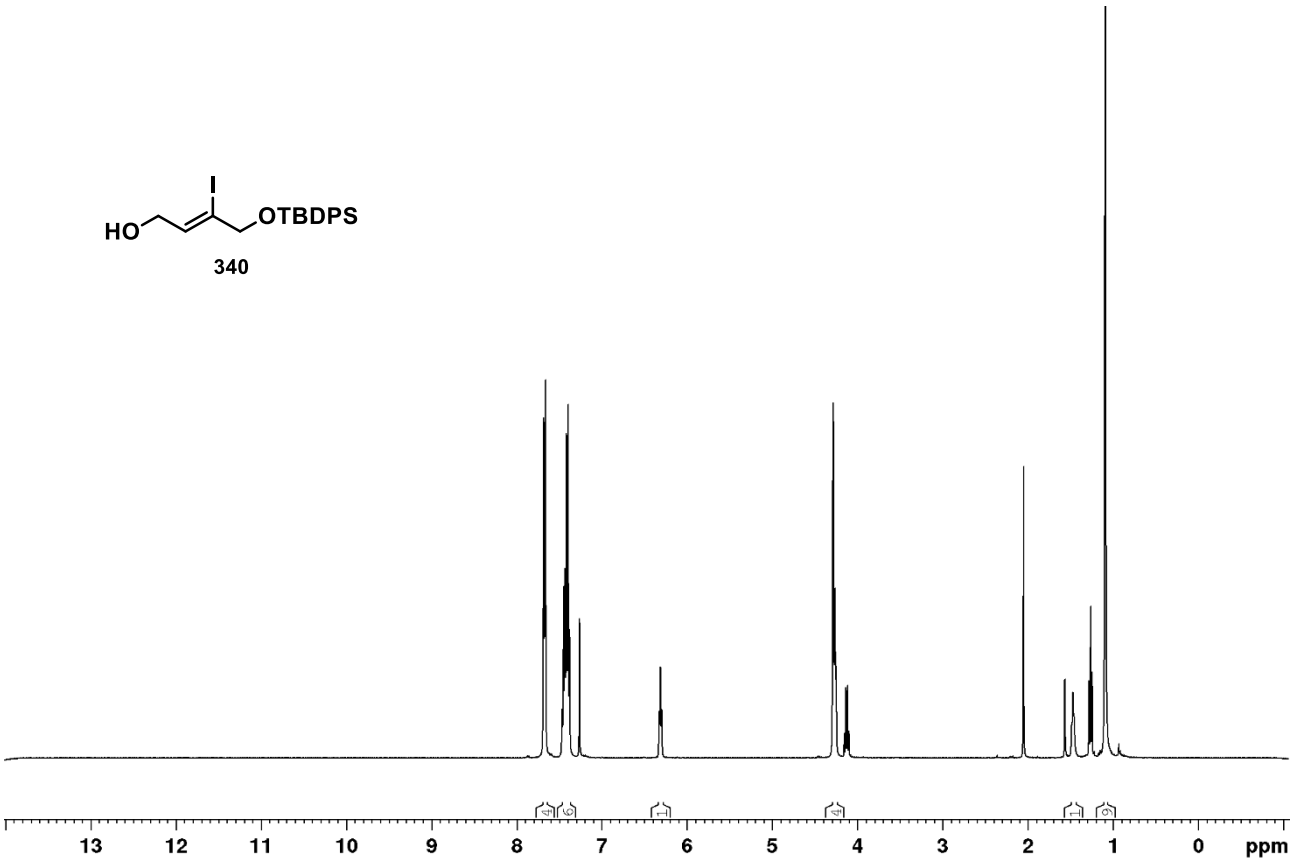
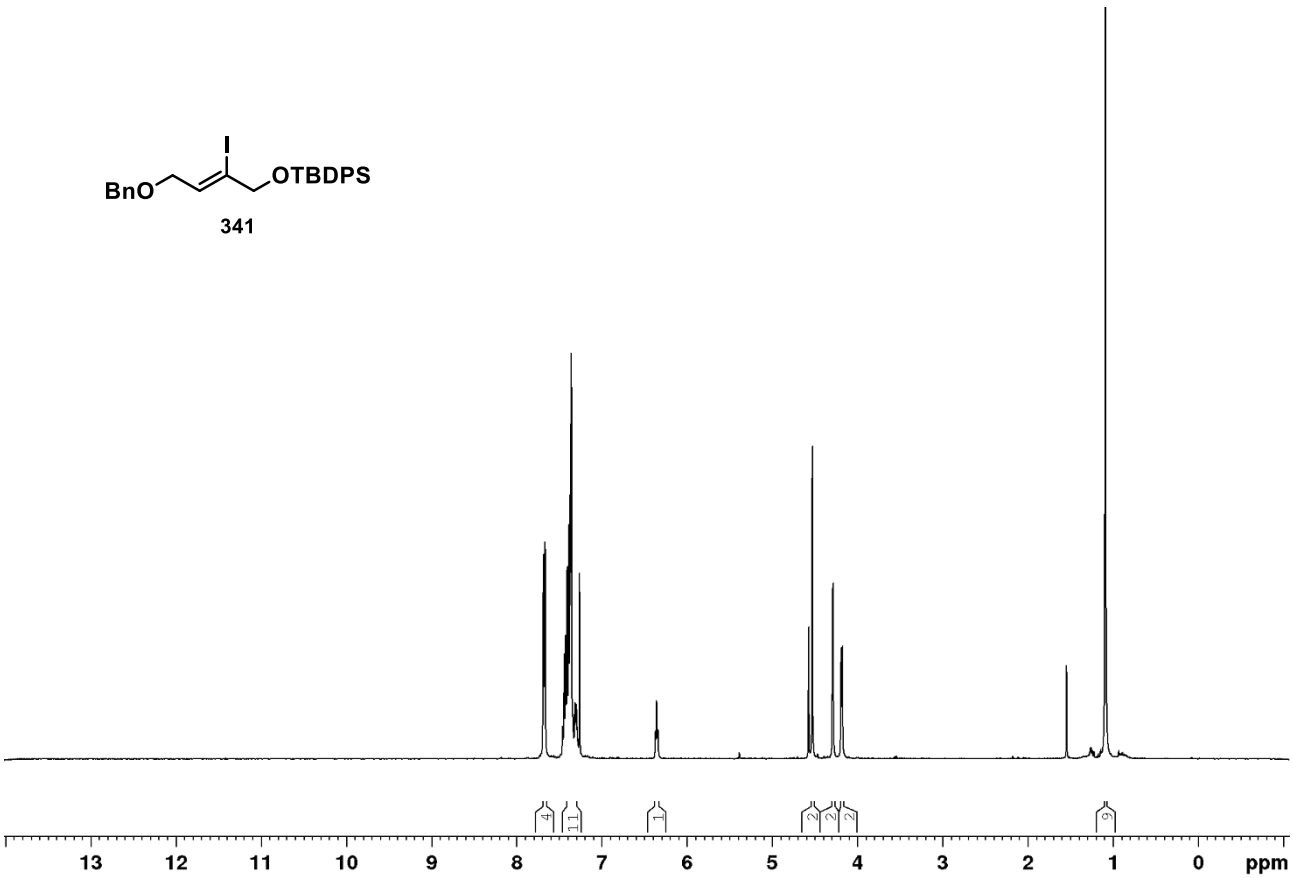
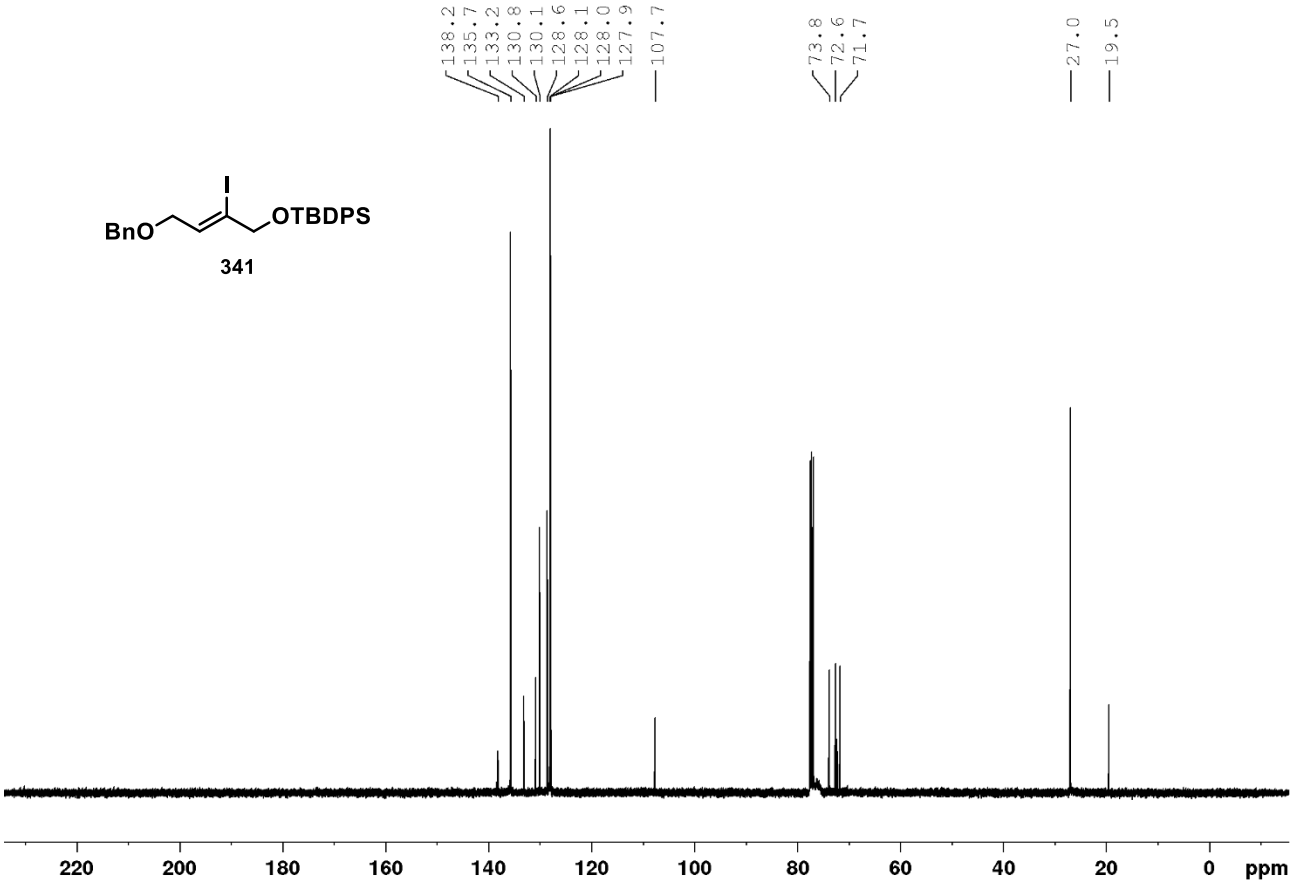
8
7
6
5
4
3
2
1
0
ppm

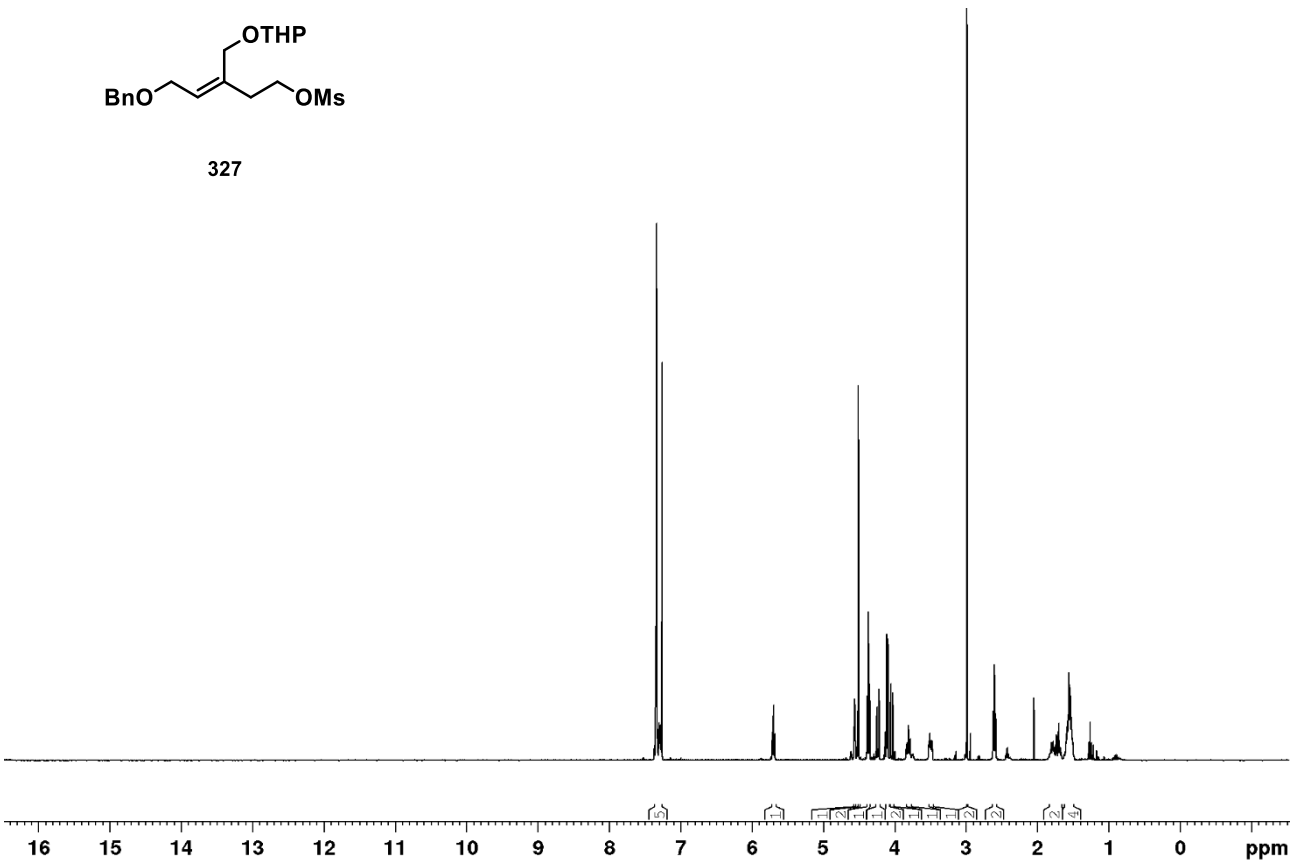

THPO
I
336
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

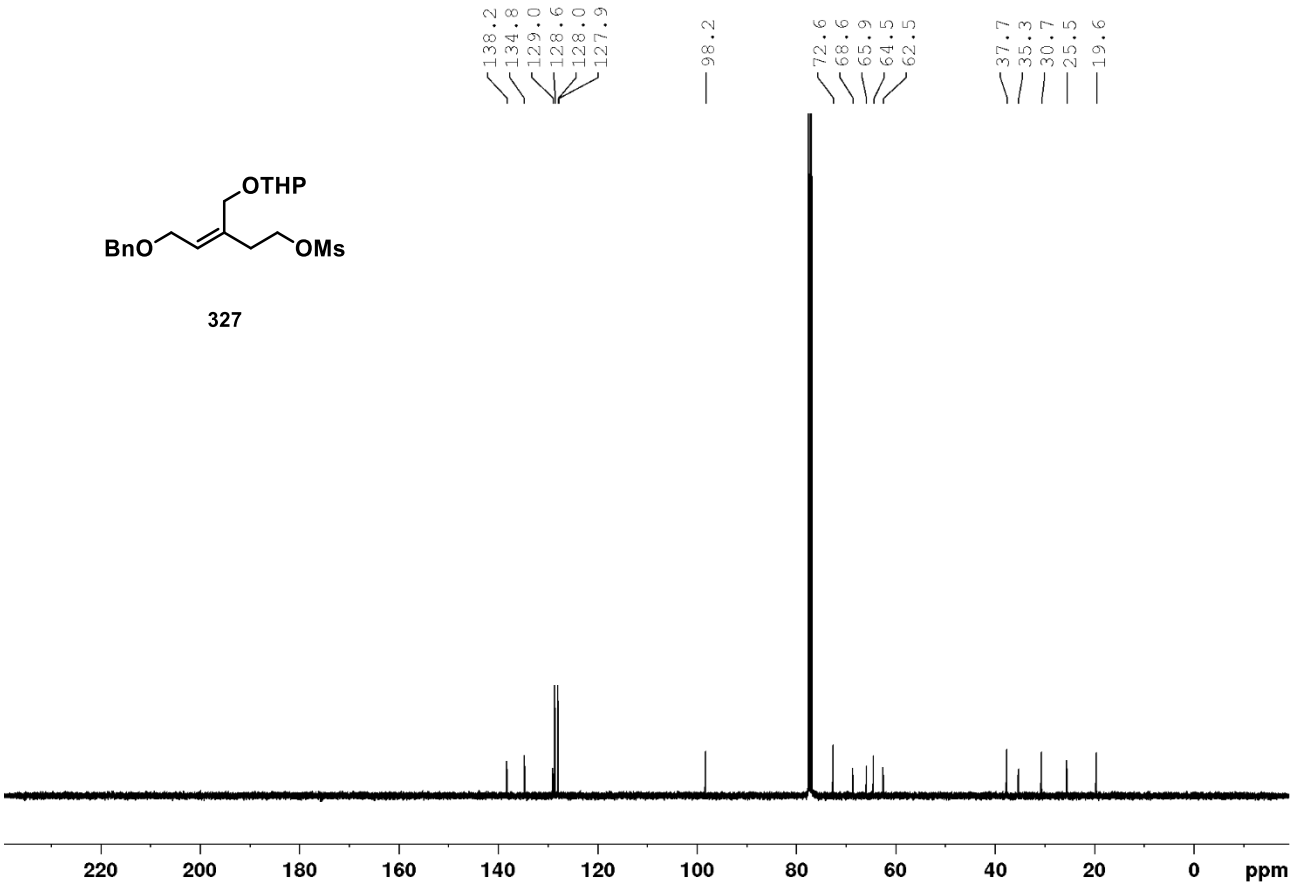

TBDPSO
OH
339
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


HO
OTBDPS
340
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

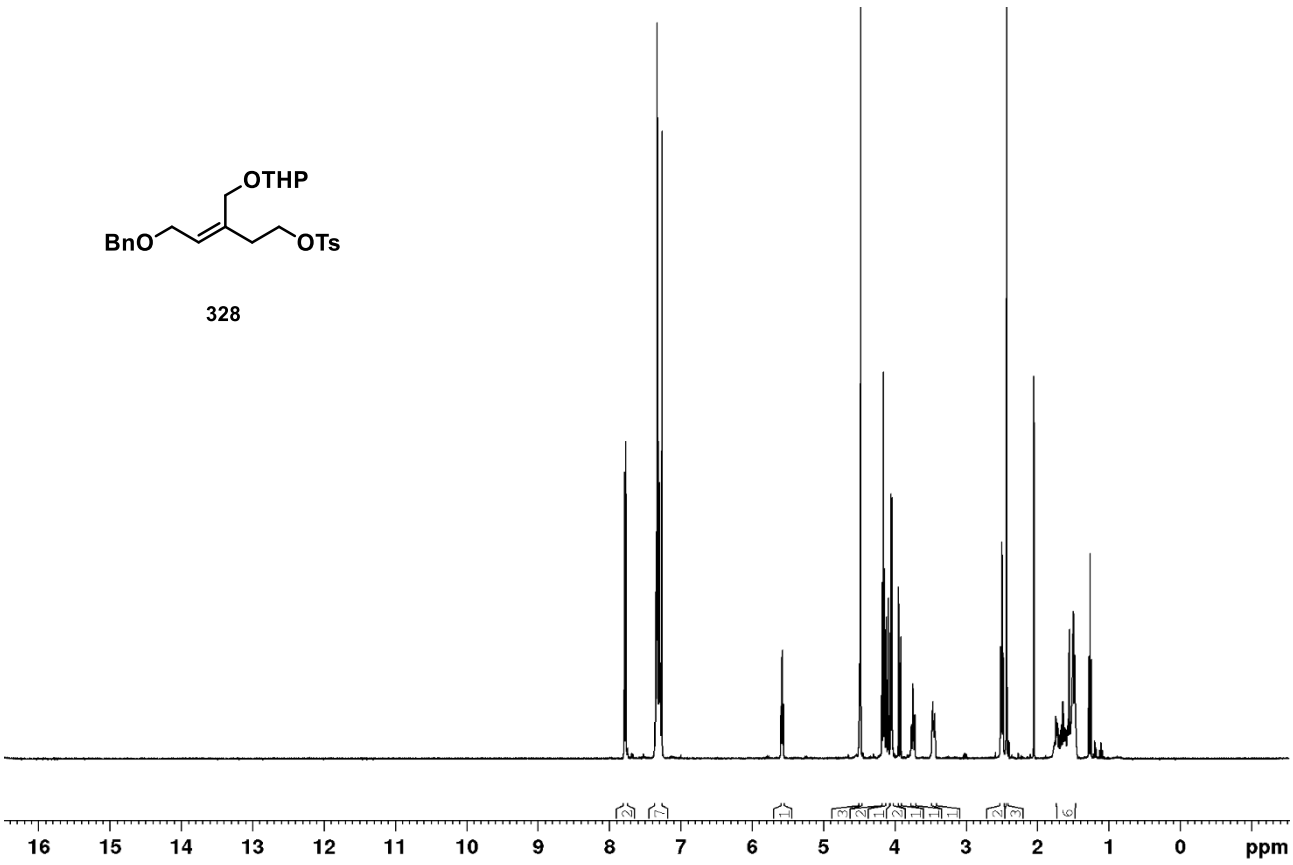

BnO
OTBDPS
341
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


138.2
135.7
133.2
130.8
130.1
128.6
128.1
128.0
127.9
107.7
73.8
72.6
71.7
27.0
19.5
BnO
OTBDPS
341
220
200
180
160
140
120
100
80
60
40
20
0
ppm

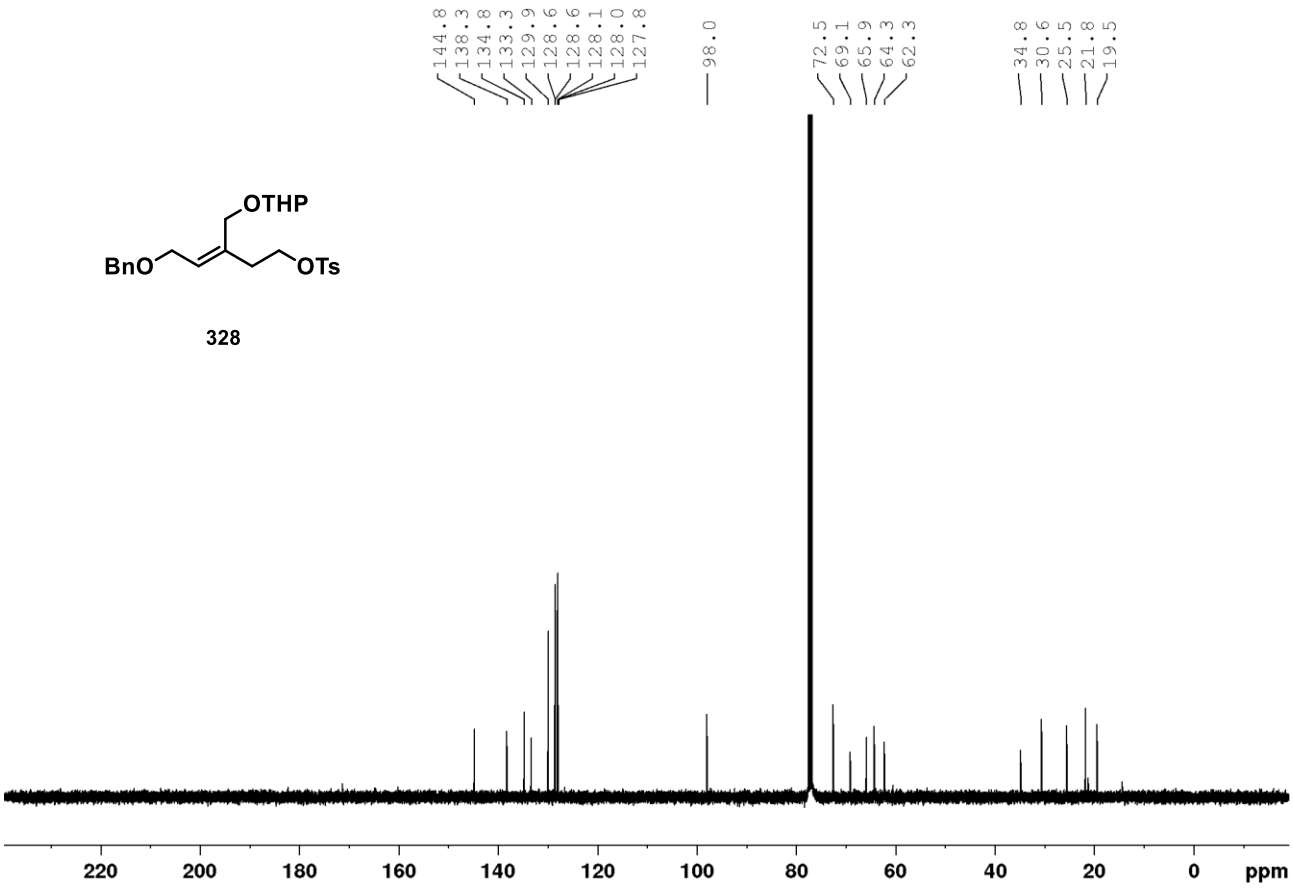

OTHP
BnO
OMs
327
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


138.2
134.8
129.0
128.6
128.0
127.9
98.2
72.6
68.6
65.9
64.5
62.5
37.7
35.3
30.7
25.5
19.6
OTHP
BnO
OMs
220
200
180
160
140
120
100
80
60
40
20
0
ppm

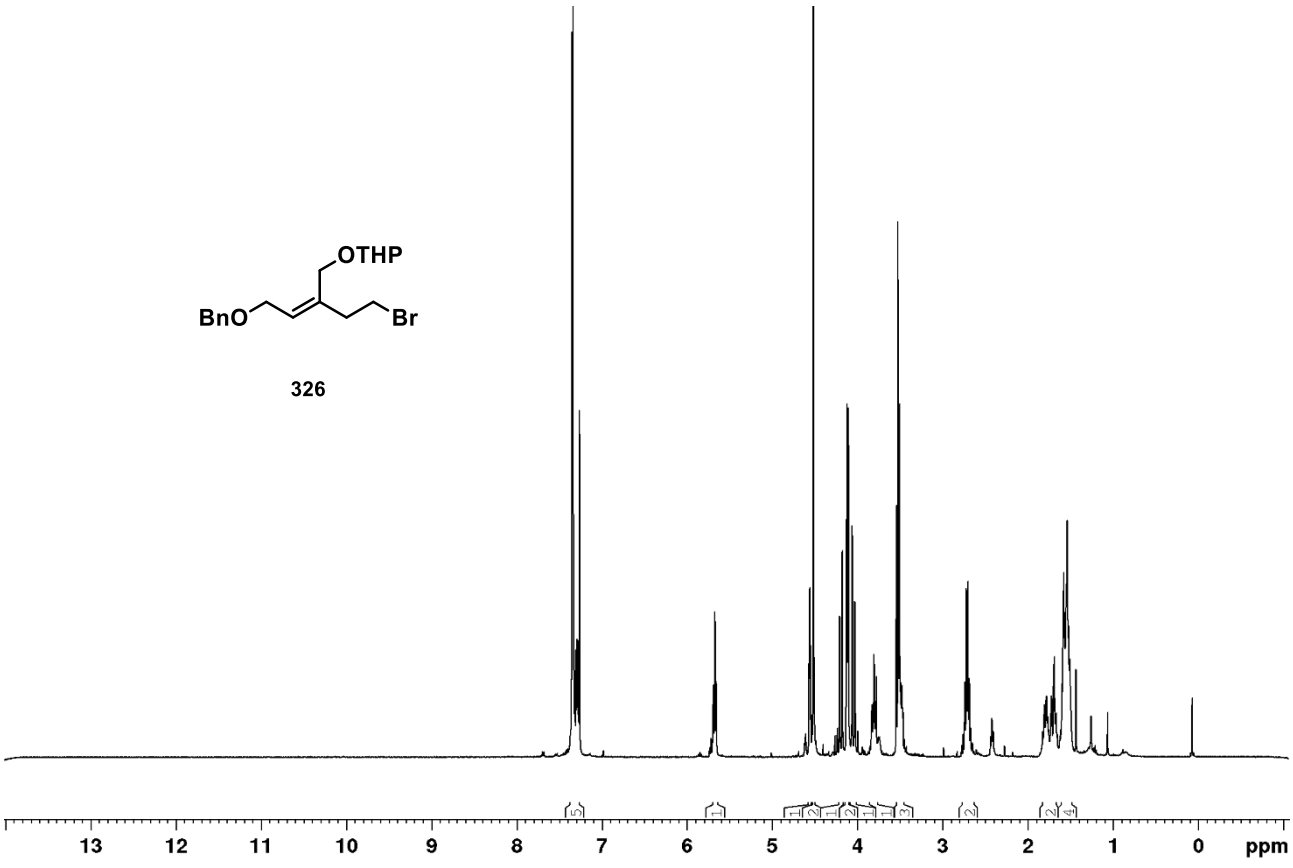
327


OTHP
BnO
OTs
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

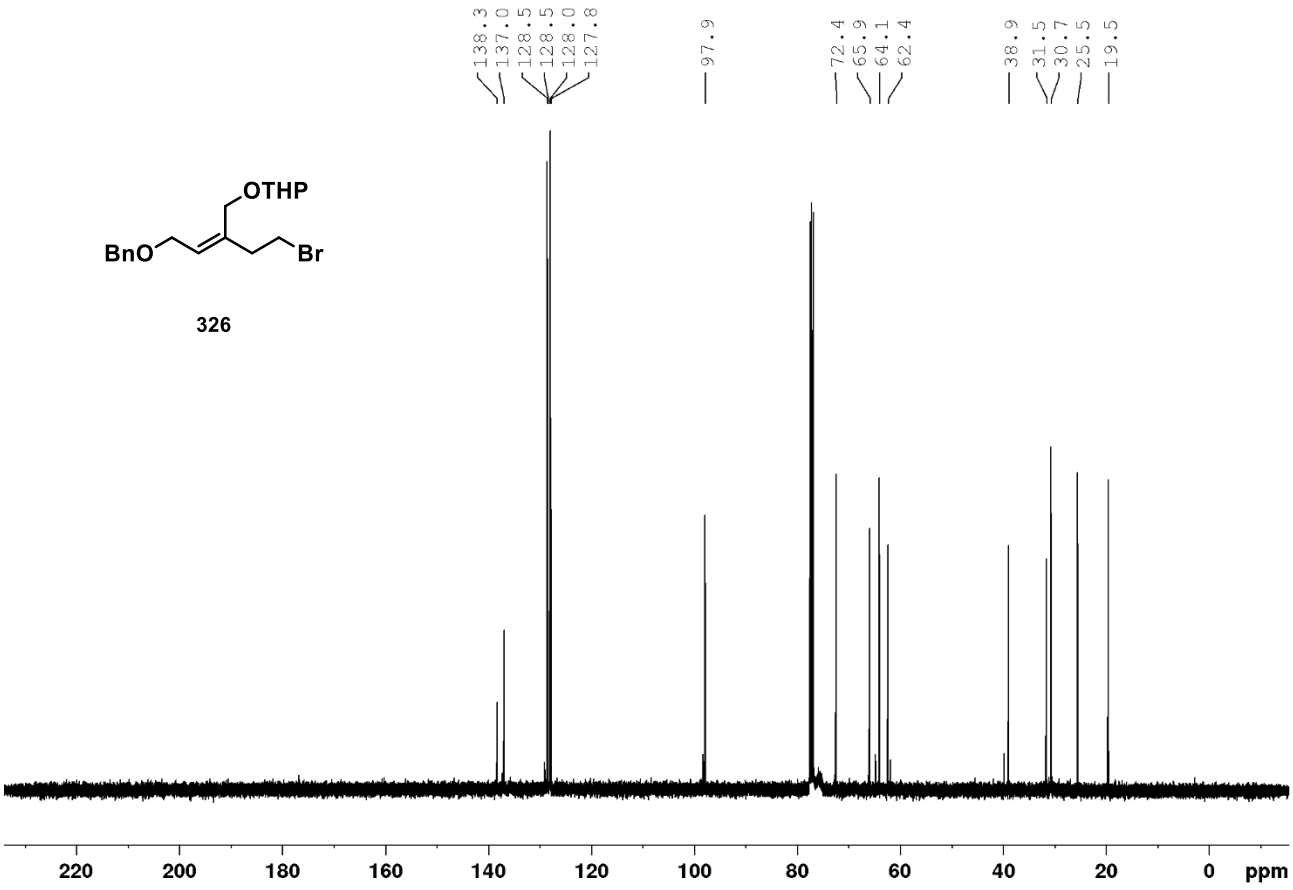
328


144.8
138.3
134.8
133.3
129.9
128.6
128.6
128.1
128.0
127.8
98.0
72.5
69.1
65.9
64.3
62.3
34.8
30.6
25.5
21.8
19.5
OTHP
BnO
OTs
220
200
180
160
140
120
100
80
60
40
20
0
ppm

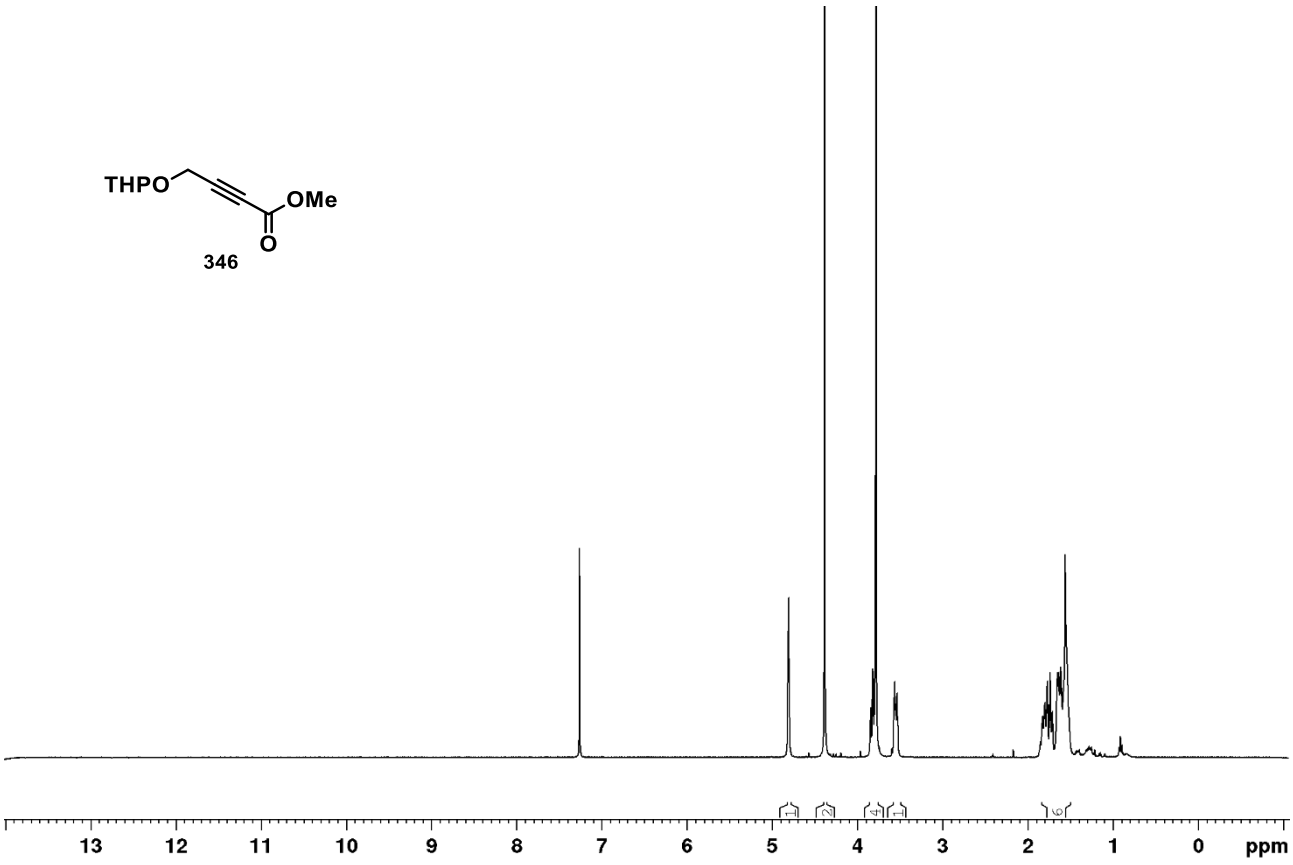
328


OTHP
BnO
Br
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

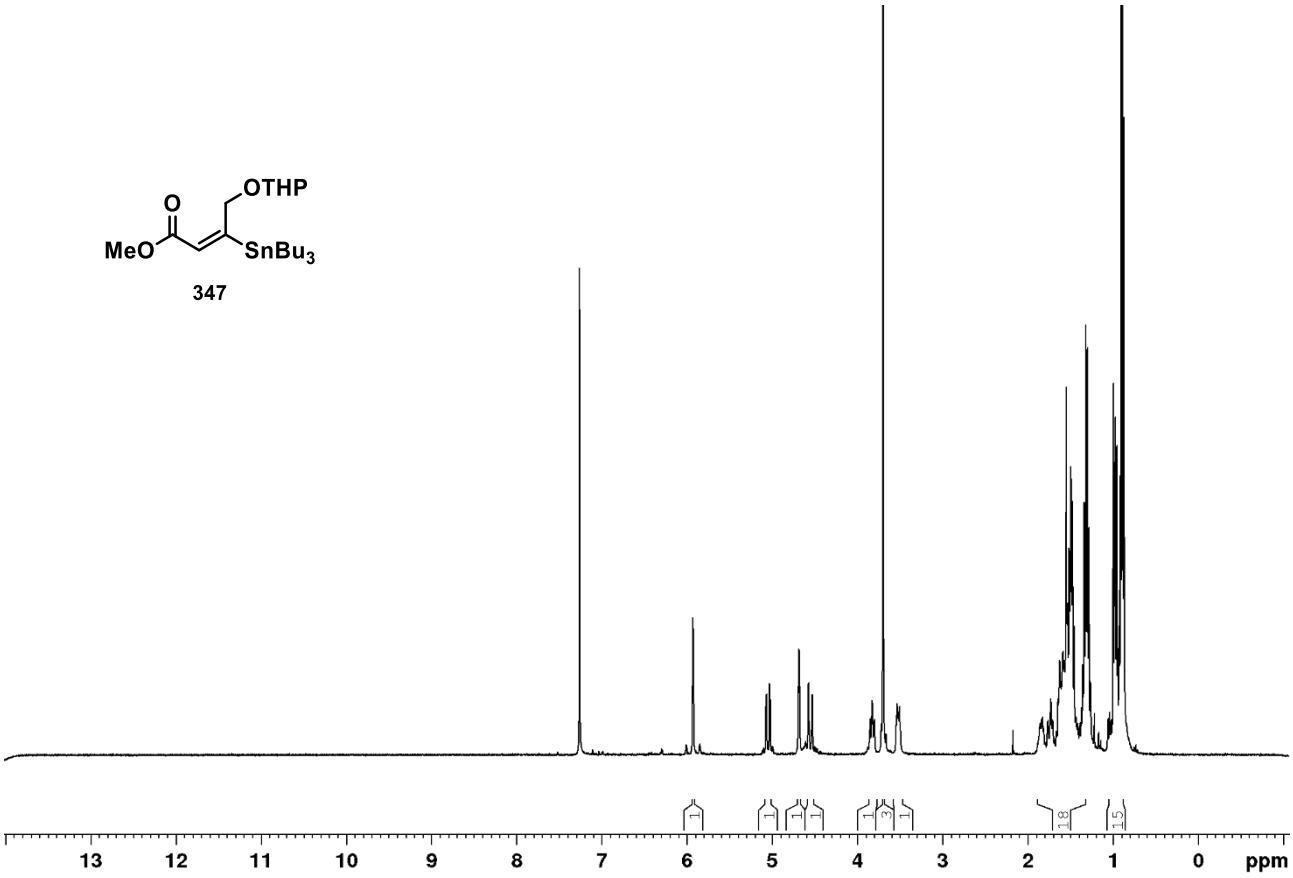
326

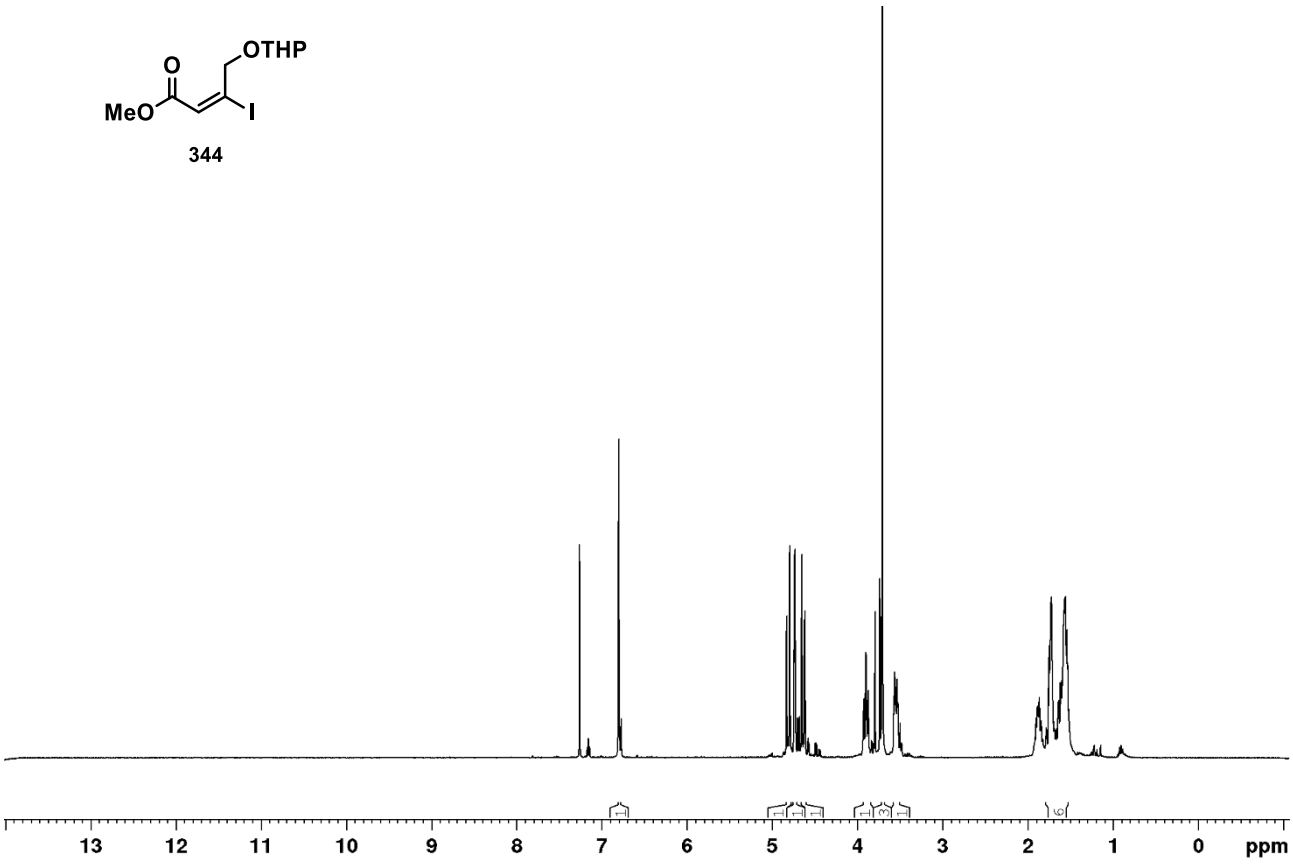

138.3
137.0
128.5
128.5
128.0
127.8
97.9
72.4
65.9
64.1
62.4
38.9
31.5
30.7
25.5
19.5
OTHP
BnO
Br
220
200
180
160
140
120
100
80
60
40
20
0
ppm

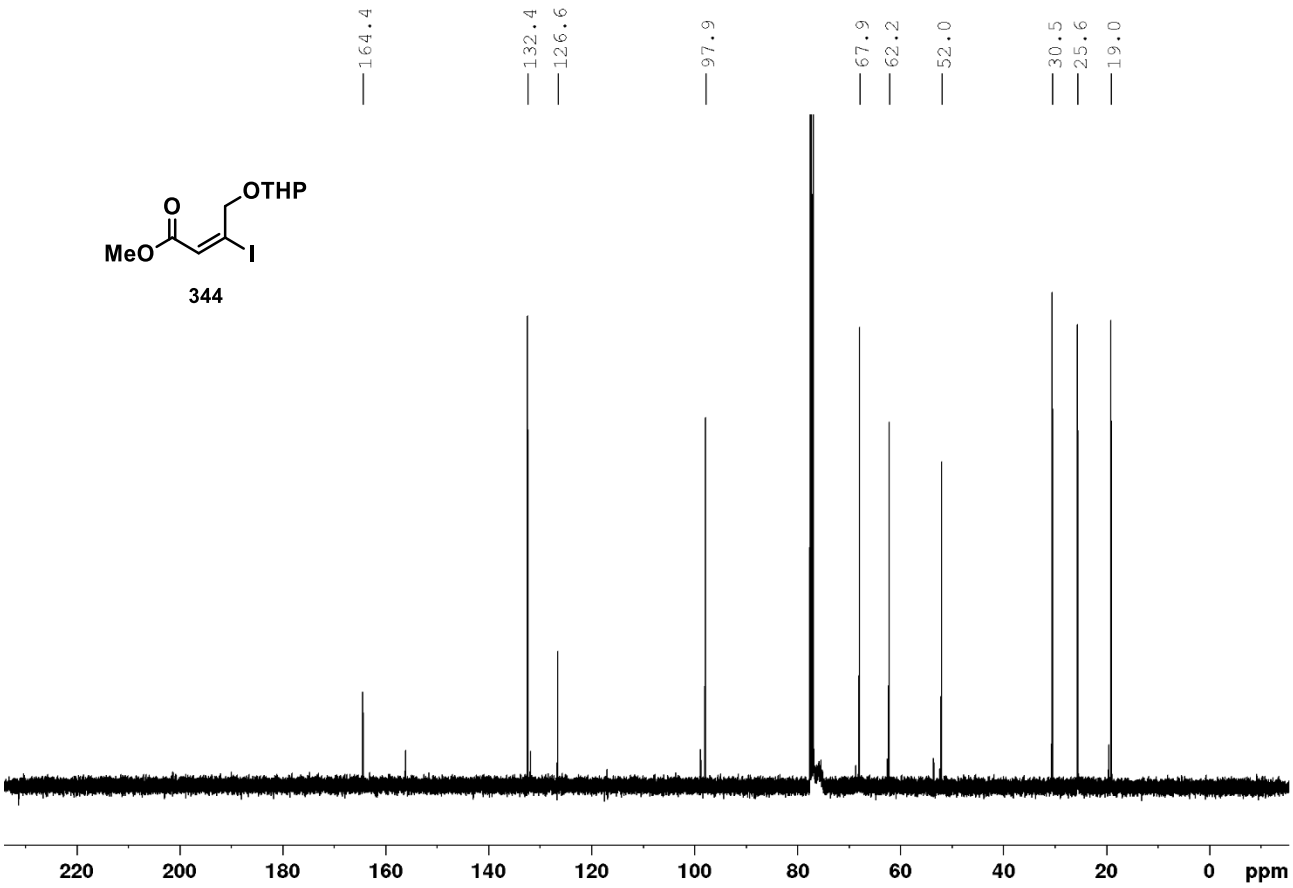
326


THPO
OMe
O
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

346


OTHP
O
MeO
SnBu3
347
1
1
1
1
1
3
1
18
15
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


OTHP
O
MeO
I
344
1
1
1
1
1
3
1
6
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


164.4
132.4
126.6
97.9
67.9
62.2
52.0
30.5
25.6
19.0
OTHP
O
MeO
I
344
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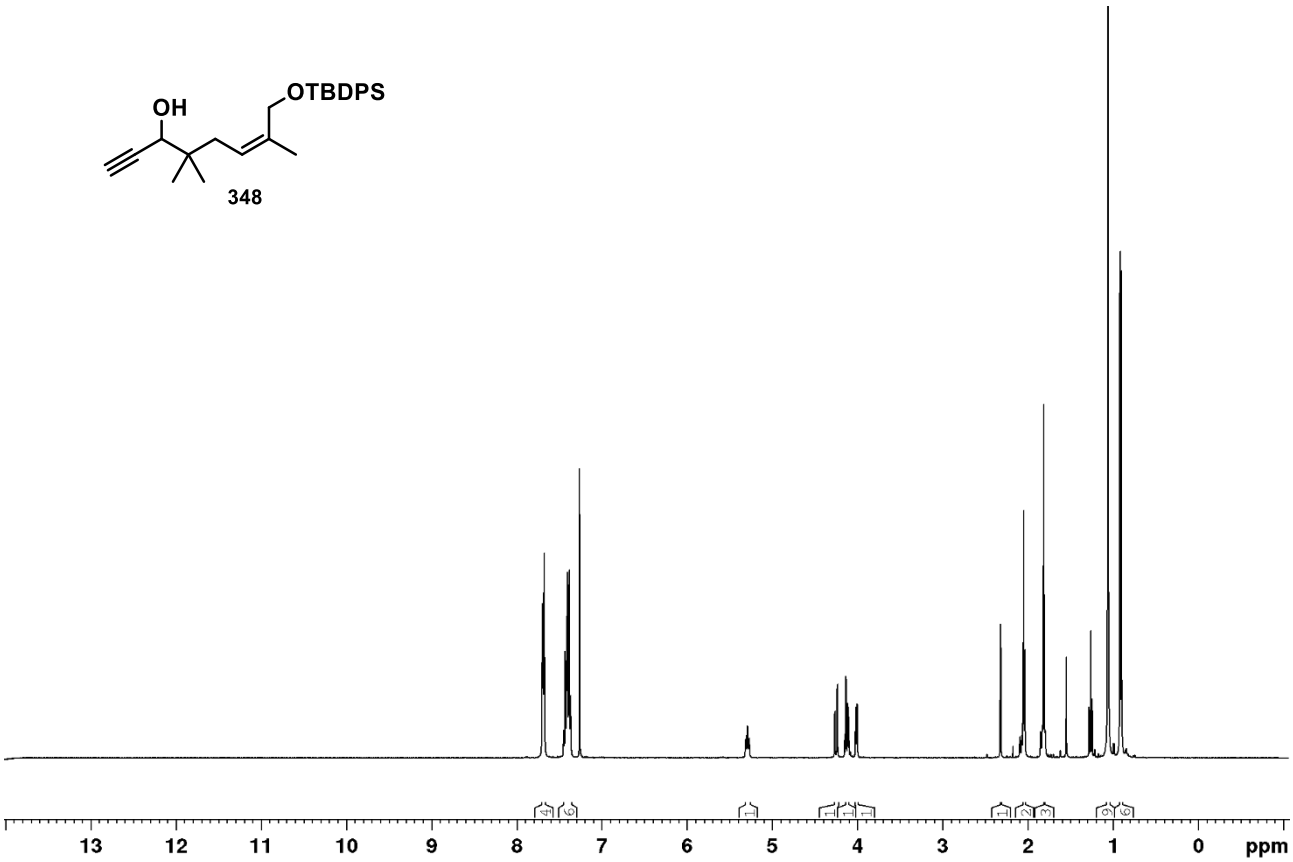
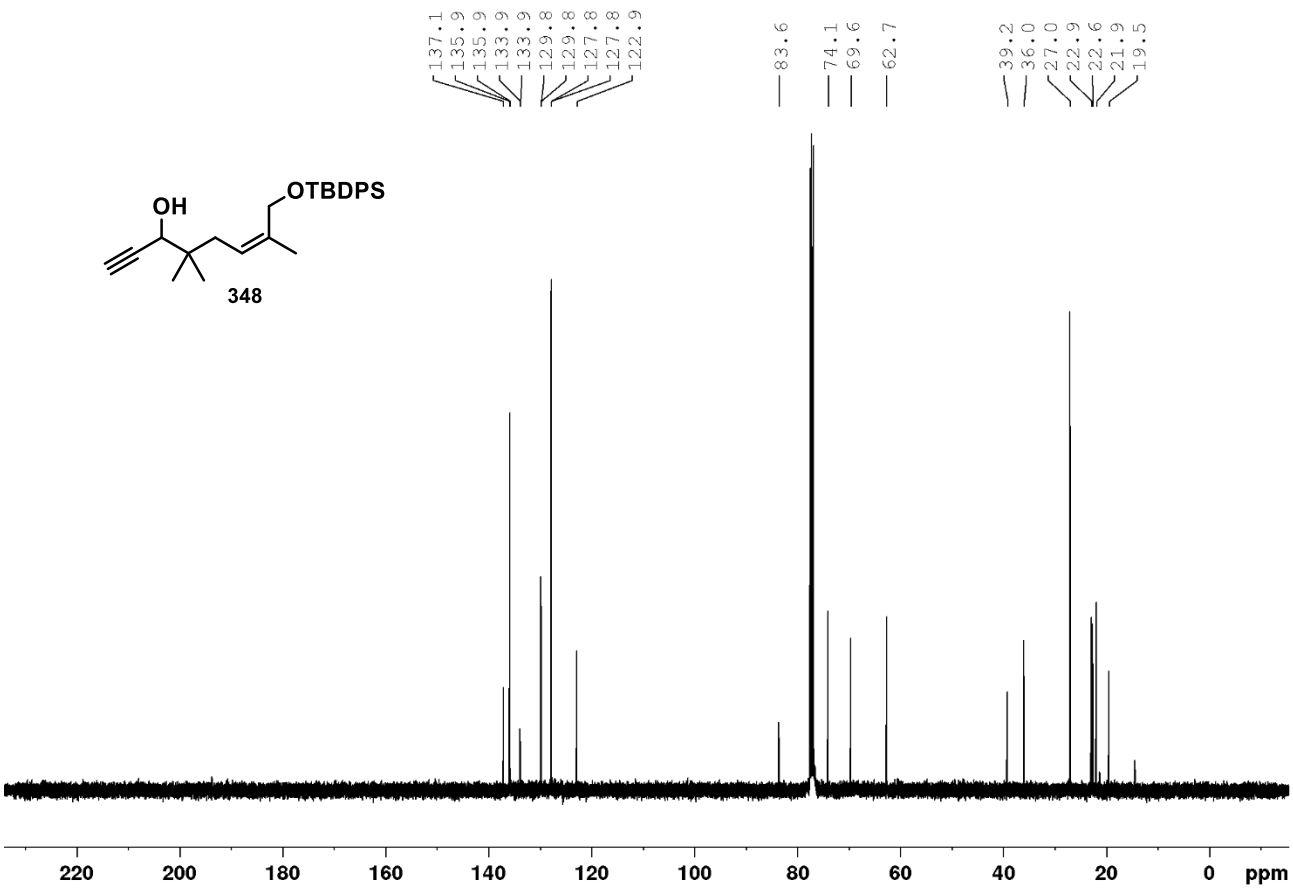
200
180
160
140
120
100
80
60
40
20
0
ppm


OH
OTBDPS
348
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


137.1
135.9
135.9
133.9
133.9
129.8
129.8
127.8
127.8
122.9
83.6
74.1
69.6
62.7
39.2
36.0
27.0
22.9
22.6
21.9
19.5
OH
OTBDPS
348
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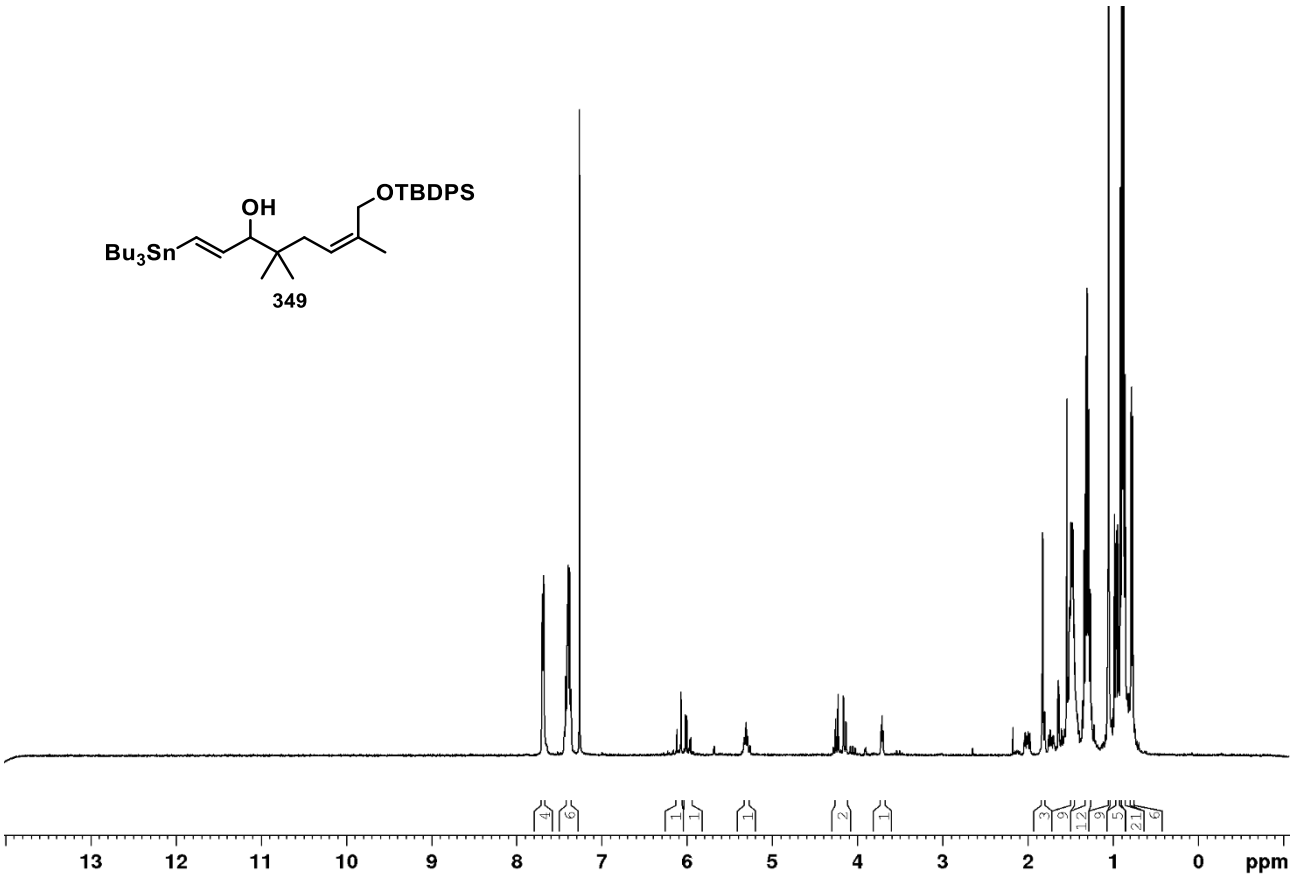
200
180
160
140
120
100
80
60
40
20
0
ppm


OH
OTBDPS
Bu3Sn
349
4
6
1
1
1
2
1
3
9
12
3
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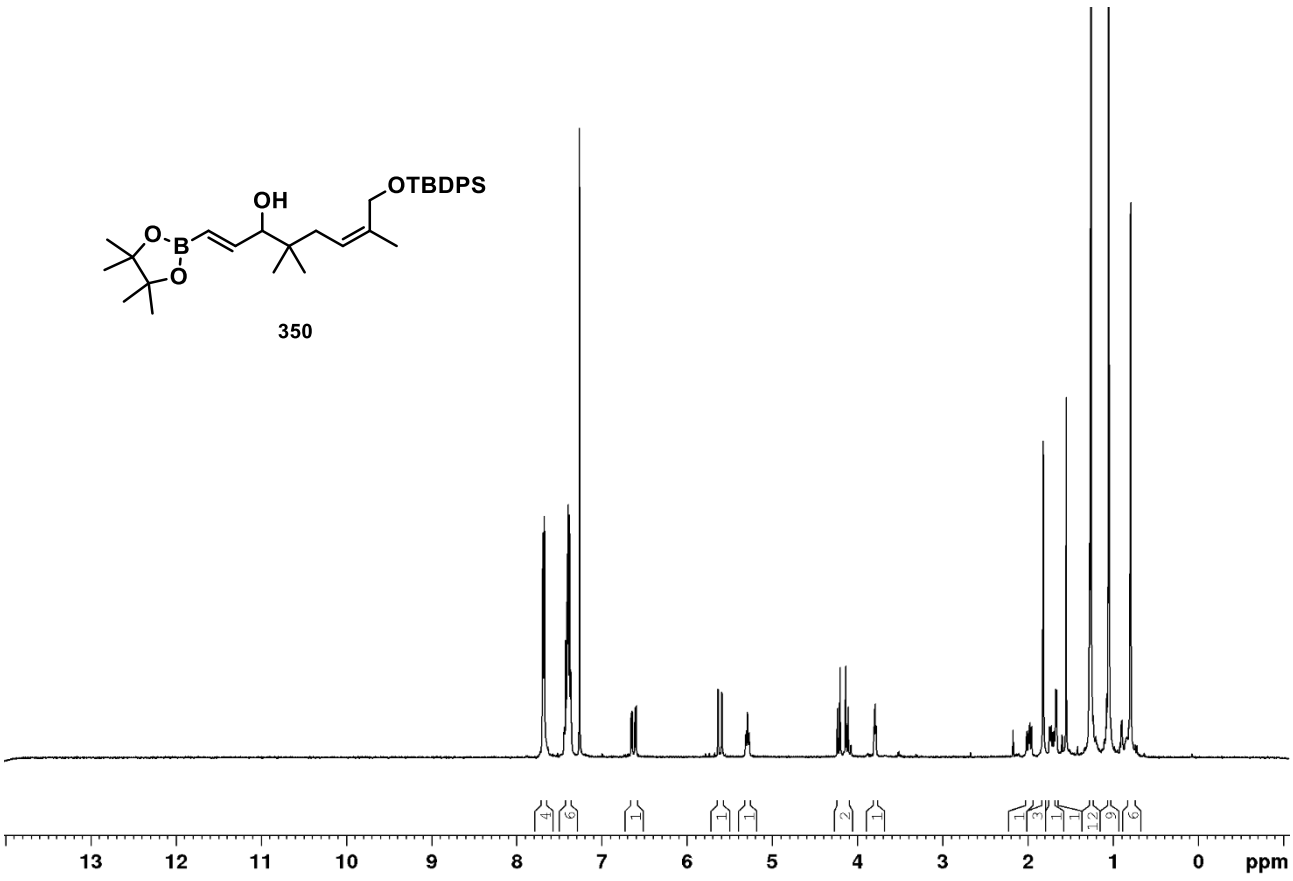
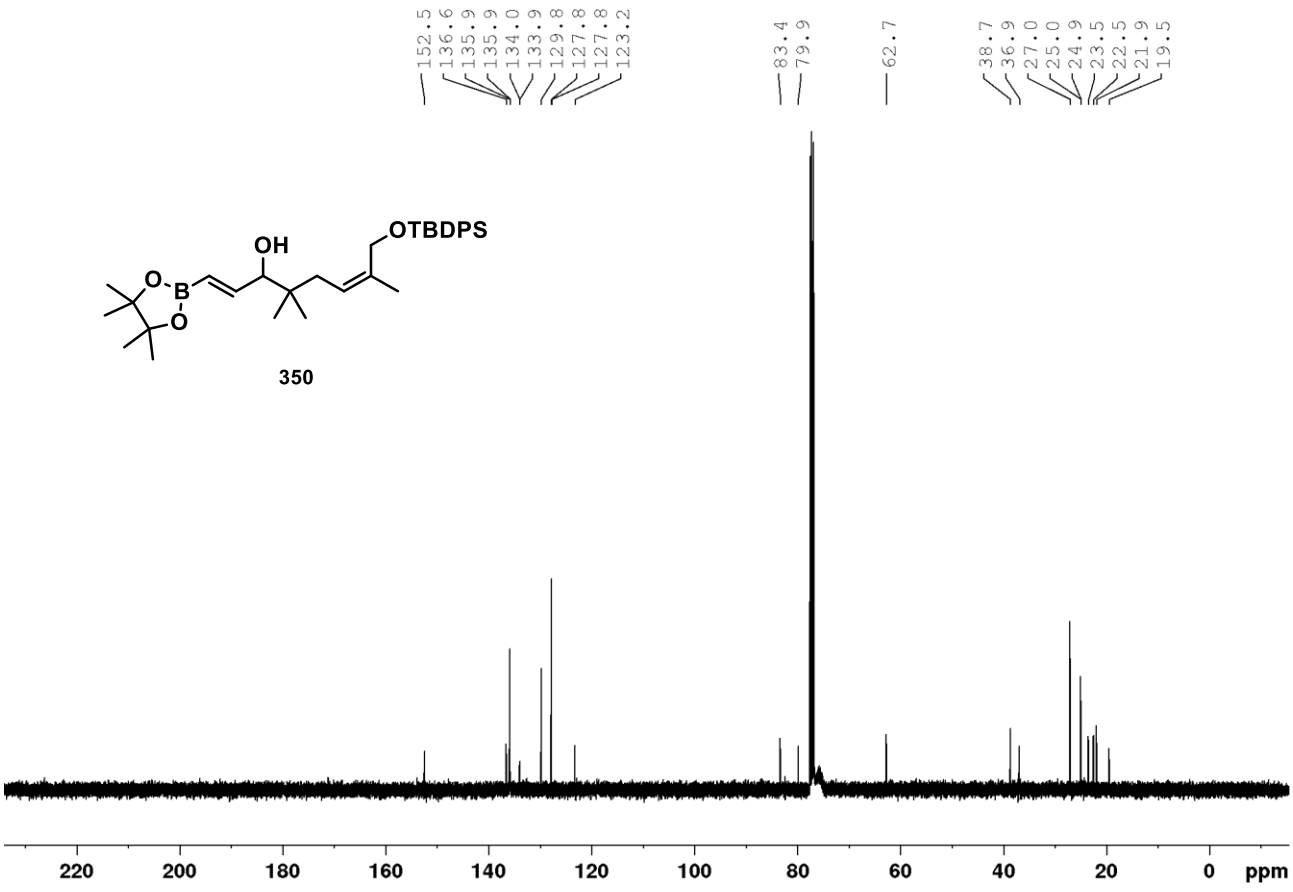
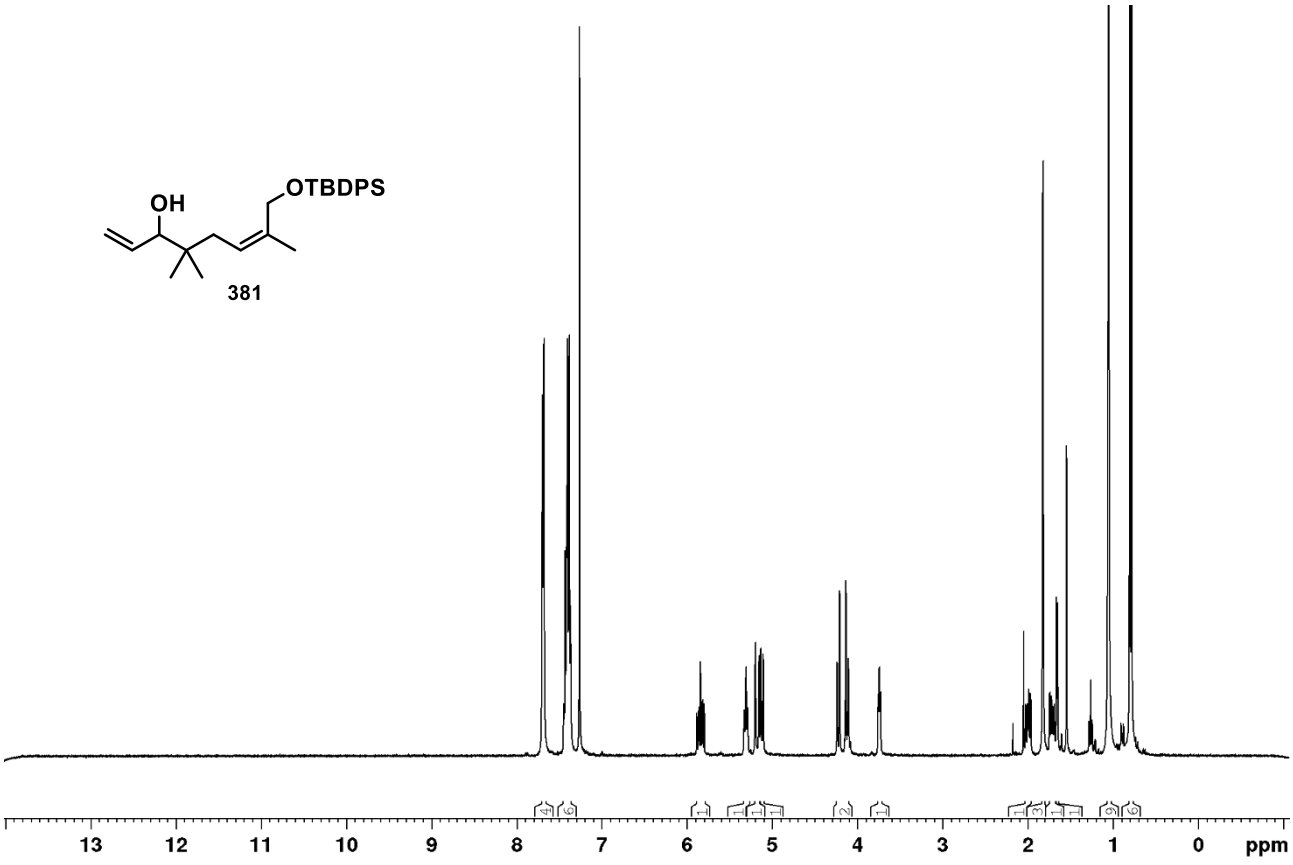
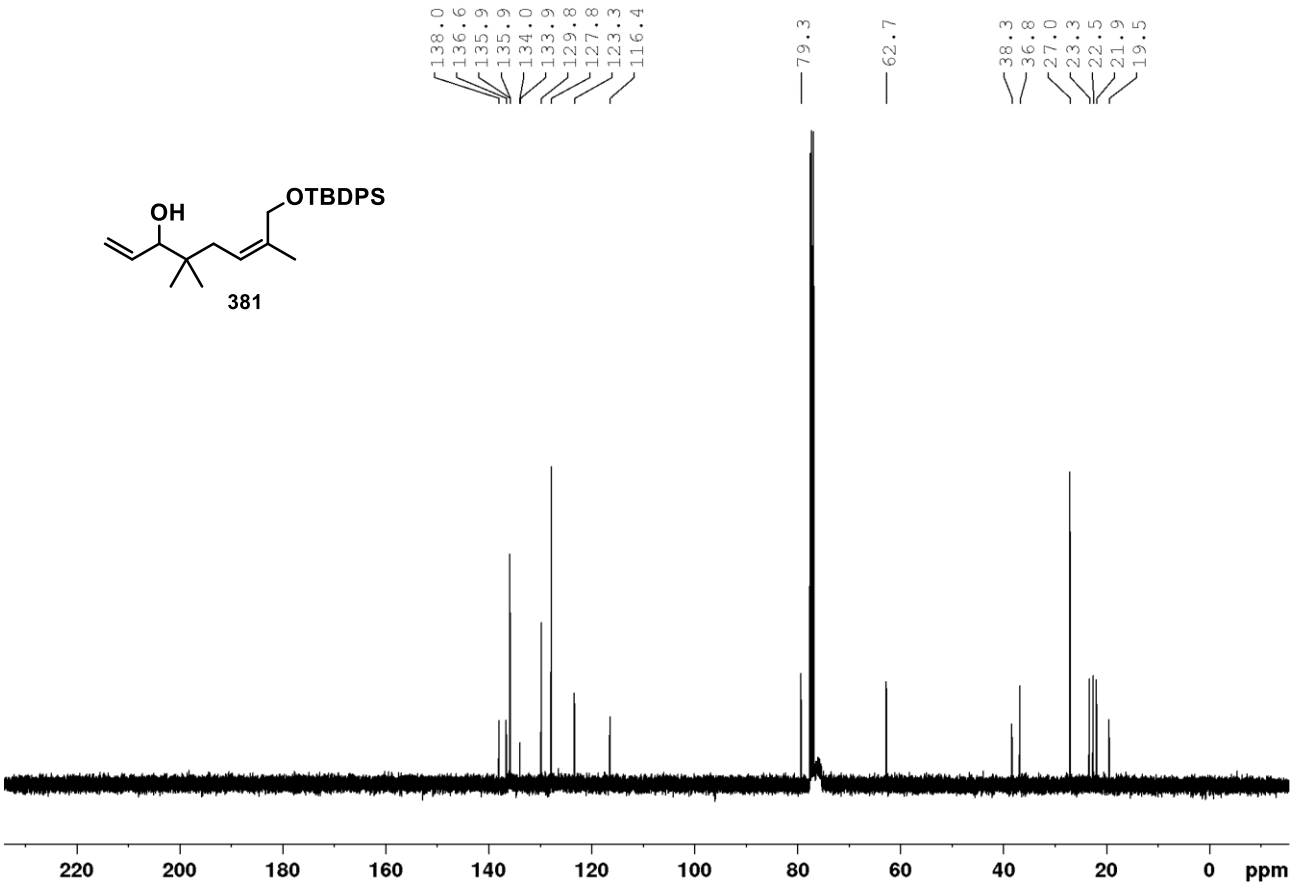
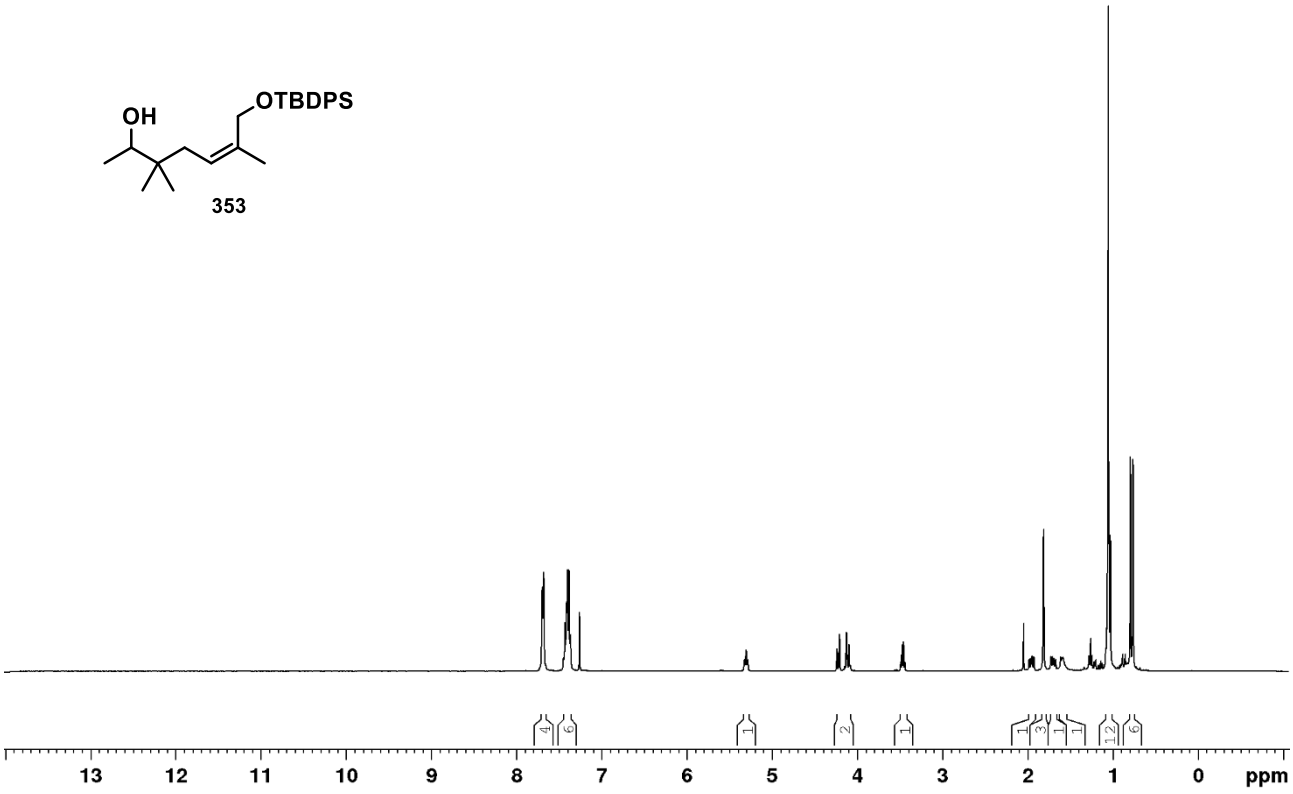
21
6
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

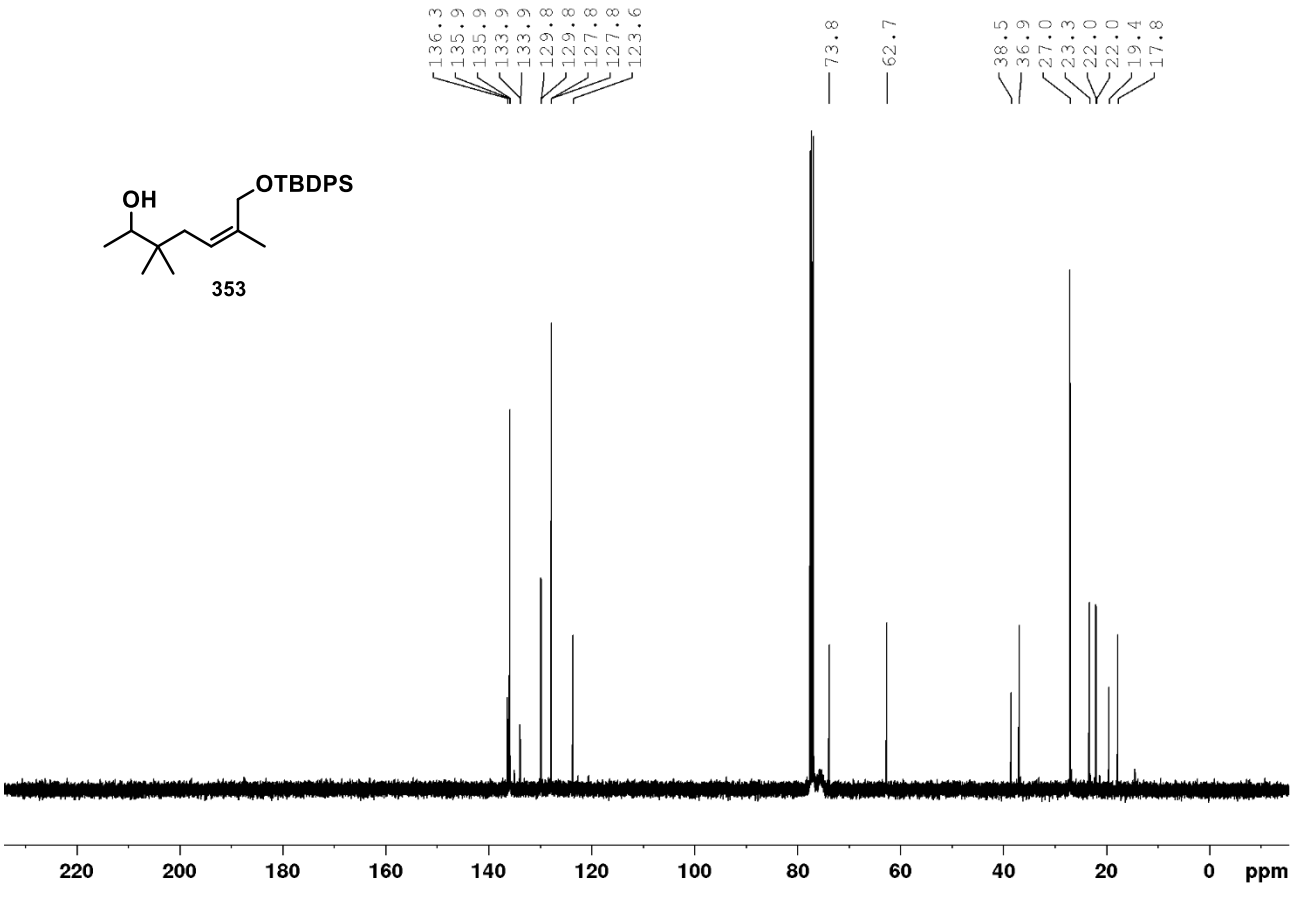

OH
OTBDPS
O
B
O
350
4
6
1
1
1
2
1
1
3
1
1
12
9
6
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

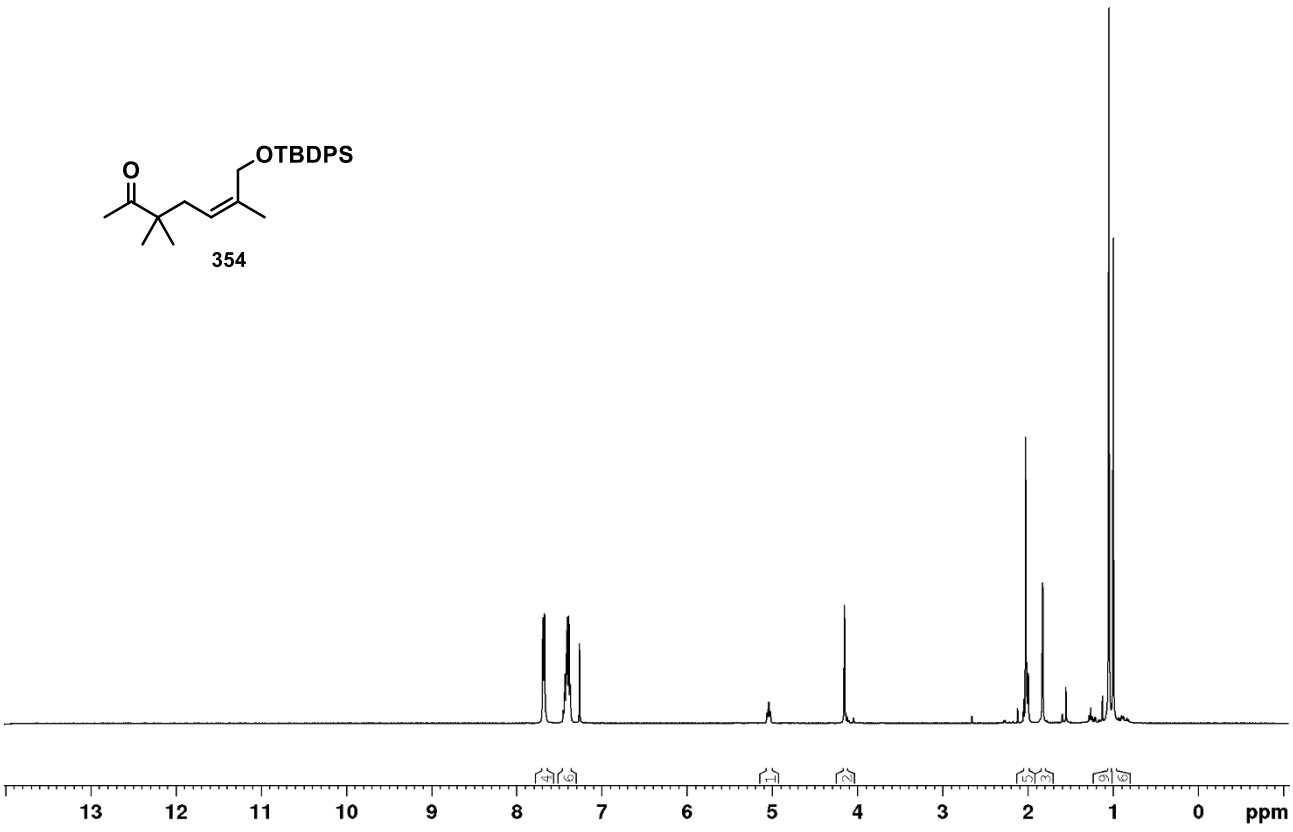

152.5
136.6
135.9
135.9
134.0
133.9
129.8
127.8
127.8
123.2
83.4
79.9
62.7
38.7
36.9
27.0
25.0
24.9
23.5
22.5
21.9
19.5
OH
OTBDPS
O
B
O
350
220
200
180
160
140
120
100
80
60
40
20
0
ppm

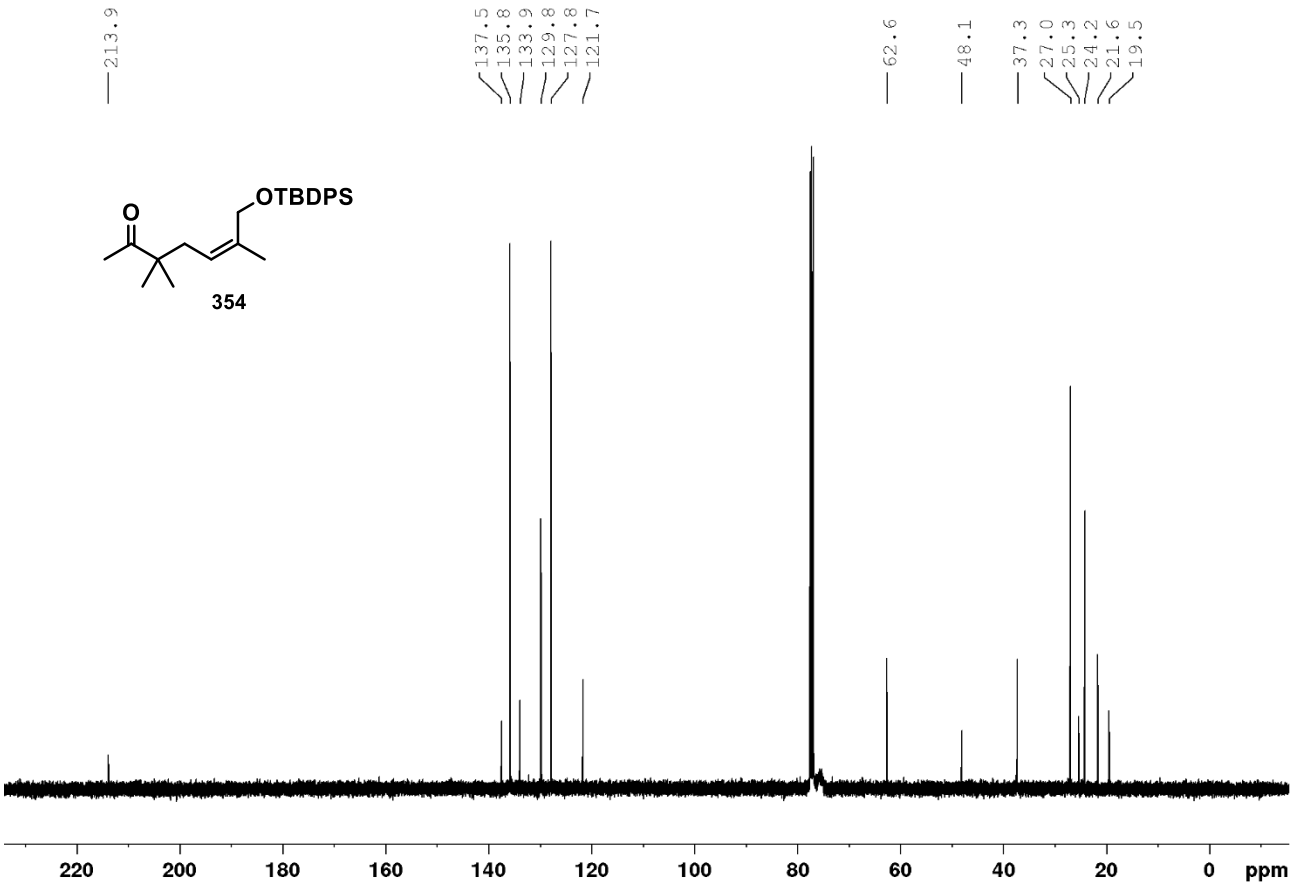

OH
OTBDPS
381
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

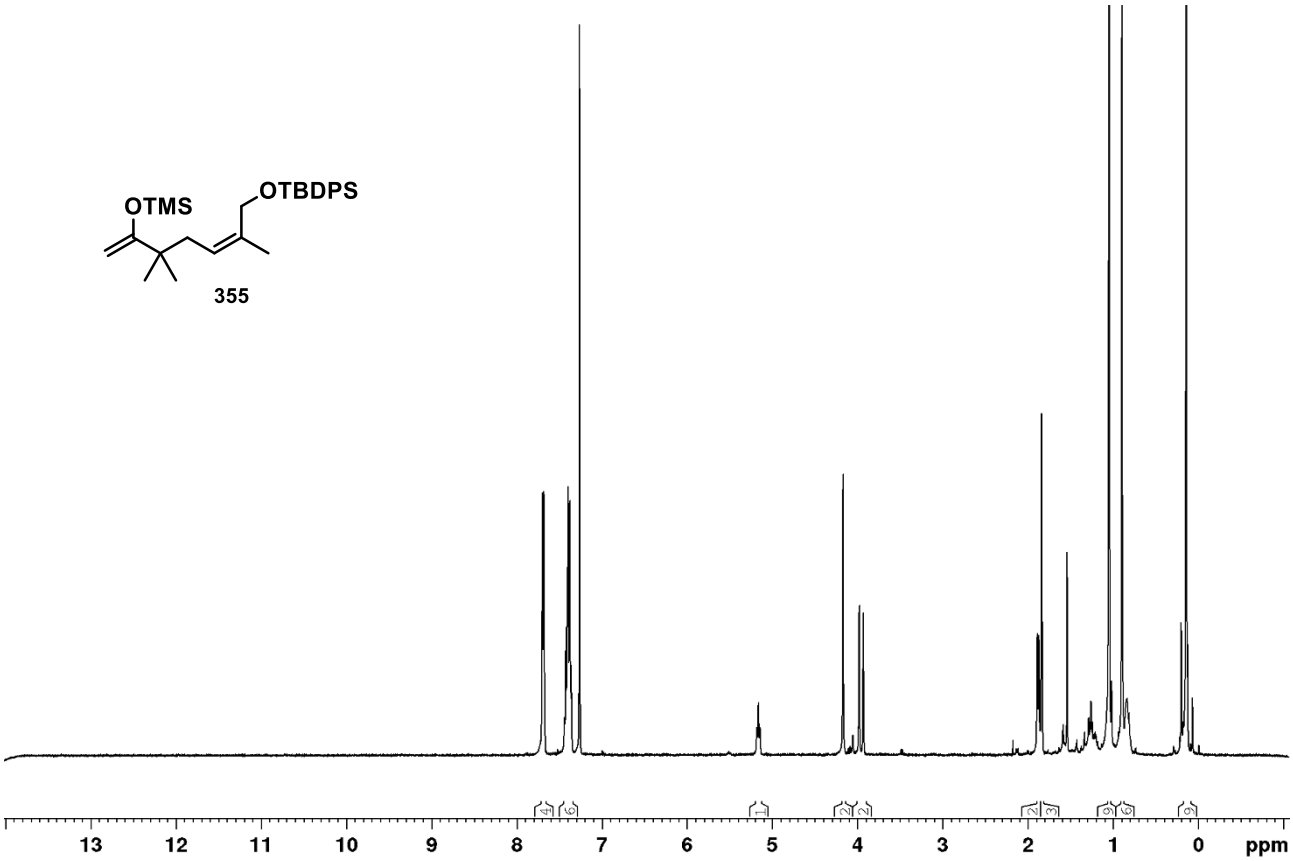

138.0
136.6
135.9
135.9
134.0
133.9
129.8
127.8
123.3
116.4
79.3
62.7
38.3
36.8
27.0
23.3
22.5
21.9
19.5
OH
OTBDPS
381
220
200
180
160
140
120
100
80
60
40
20
0
ppm

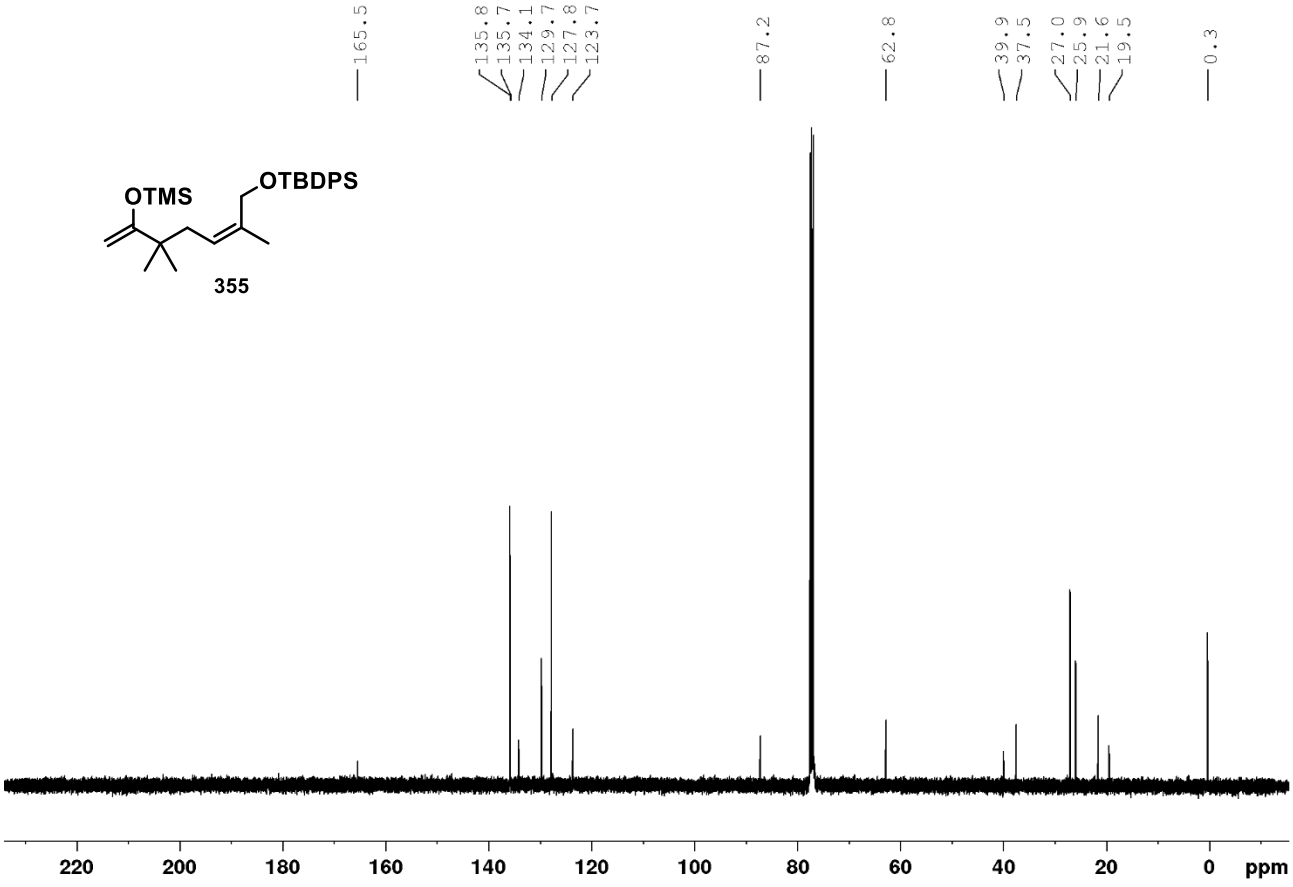

OH
OTBDPS
353
4
6
1
2
1
1
3
1
1
12
6
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

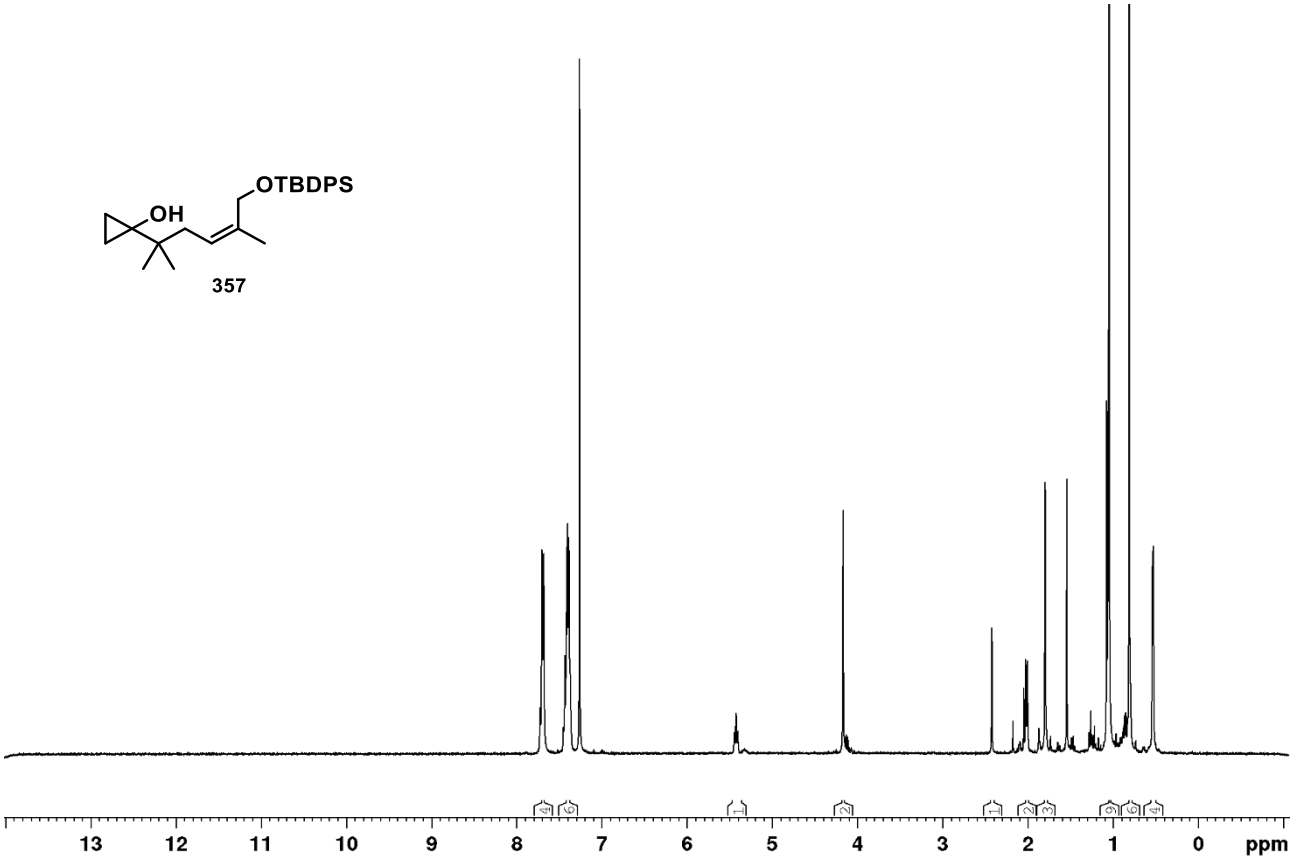

136.3
135.9
135.9
133.9
133.9
129.8
129.8
127.8
127.8
123.6
73.8
62.7
38.5
36.9
27.0
23.3
22.0
22.0
19.4
17.8
OH
OTBDPS
353
220
200
180
160
140
120
100
80
60
40
20
0
ppm


OTBDPS
O
354
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


213.9
137.5
135.8
133.9
129.8
127.8
121.7
62.6
48.1
37.3
27.0
25.3
24.2
21.6
19.5
OTBDPS
O
354
220
200
180
160
140
120
100
80
60
40
20
0
ppm


OTMS
OTBDPS
355
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


165.5
135.8
135.7
134.1
129.7
127.8
123.7
87.2
62.8
39.9
37.5
27.0
25.9
21.6
19.5
0.3
OTMS
OTBDPS
355
220
200
180
160
140
120
100
80
60
40
20
0
ppm


OTBDPS
OH
357
13
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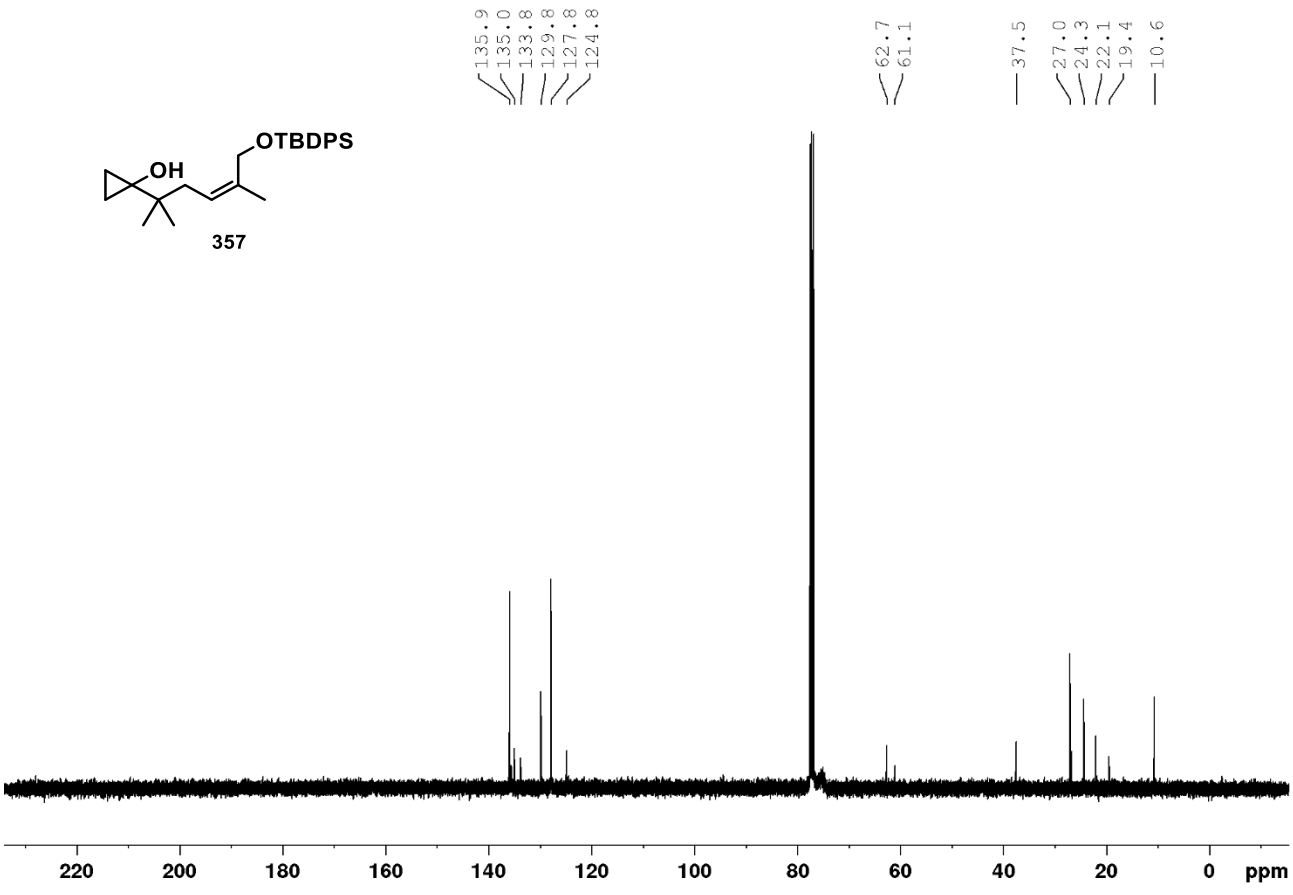
11
10
9
8
7
6
5
4
3
2
1
0
ppm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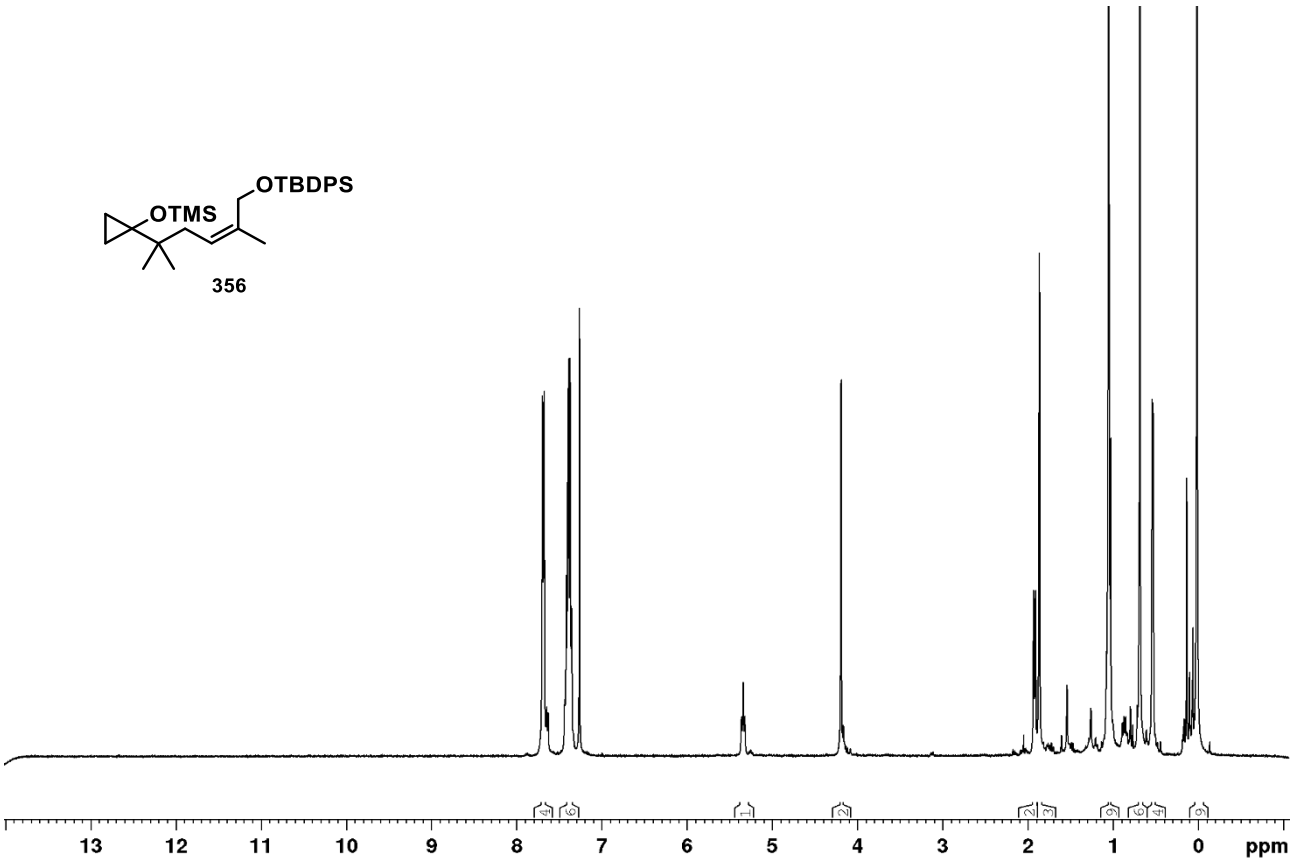
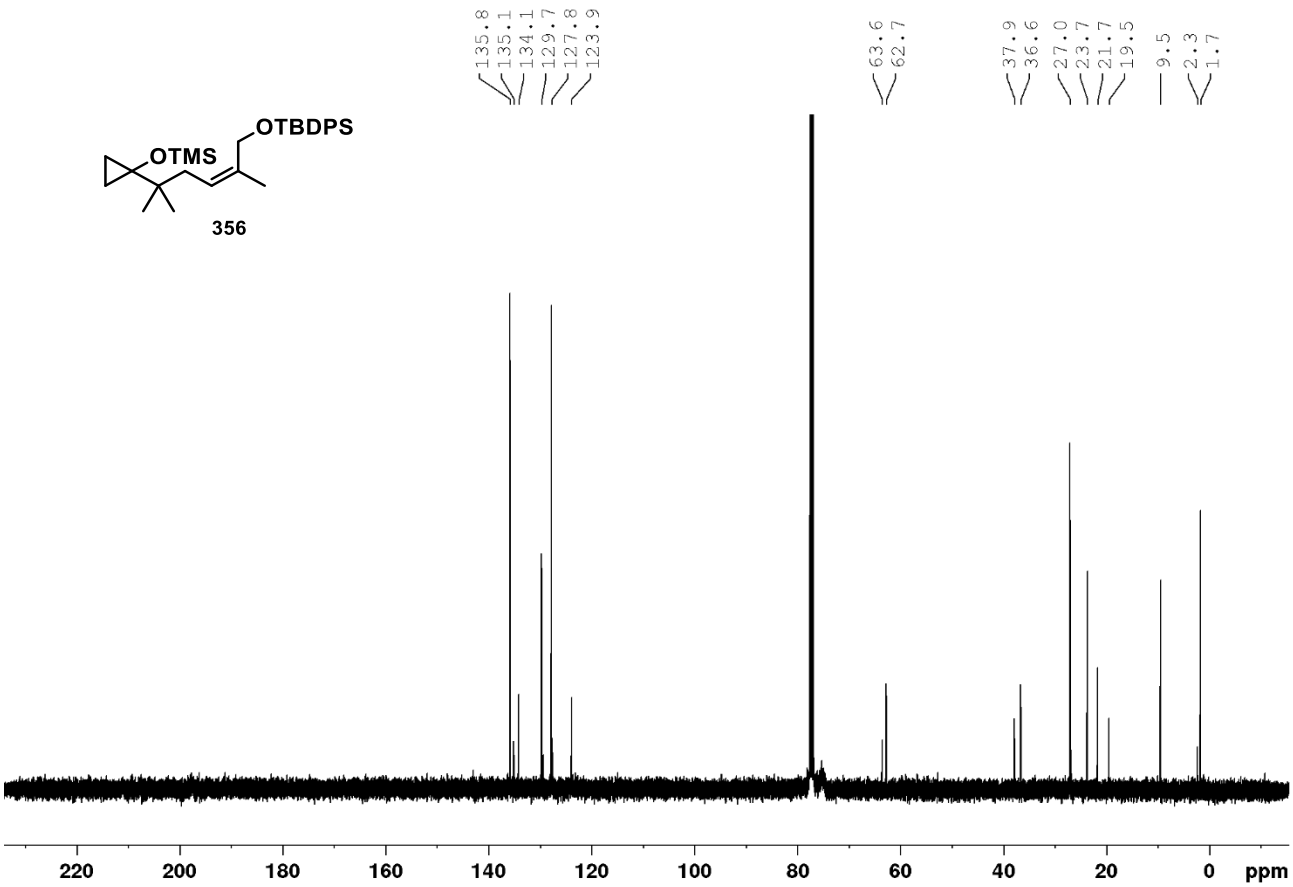
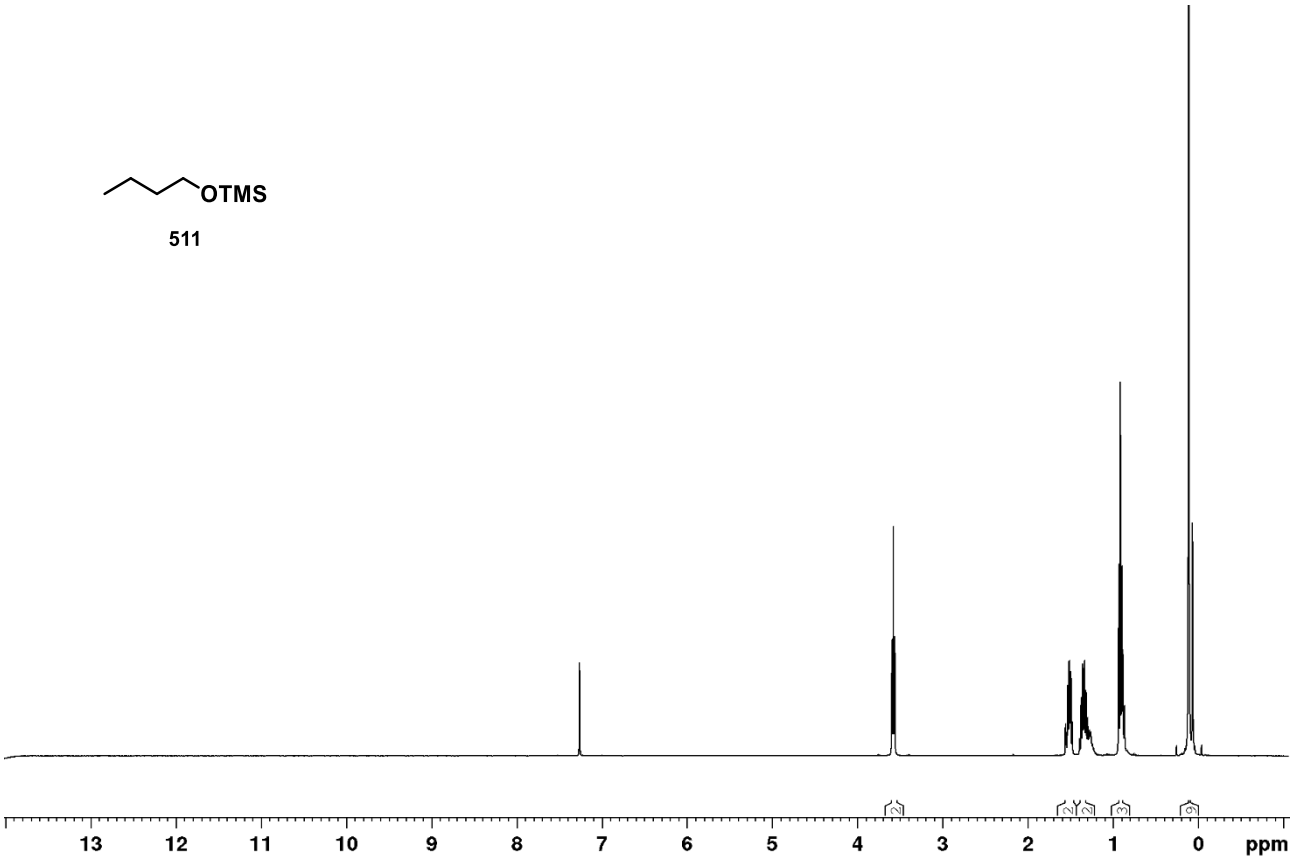
135.0
133.8
129.8
127.8
124.8
62.7
61.1
37.5
27.0
24.3
22.1
19.4
10.6
OTBDPS
OH
357
220
200
180
160
140
120
100
80
60
40
20
0
ppm


OTBDPS
OTMS
356
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


135.8
135.1
134.1
129.7
127.8
123.9
63.6
62.7
37.9
36.6
27.0
23.7
21.7
19.5
9.5
2.3
1.7
OTBDPS
OTMS
356
220
200
180
160
140
120
100
80
60
40
20
0
ppm


OTMS
511
13
12
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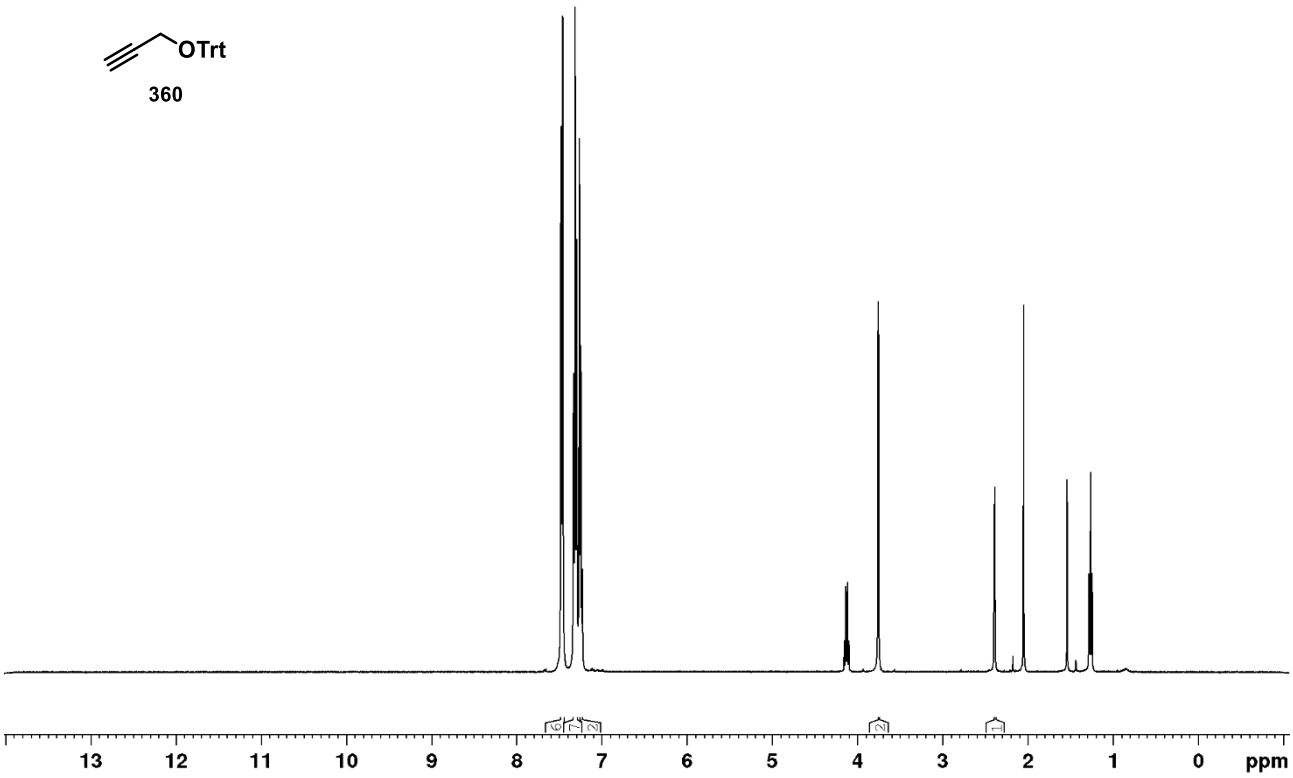
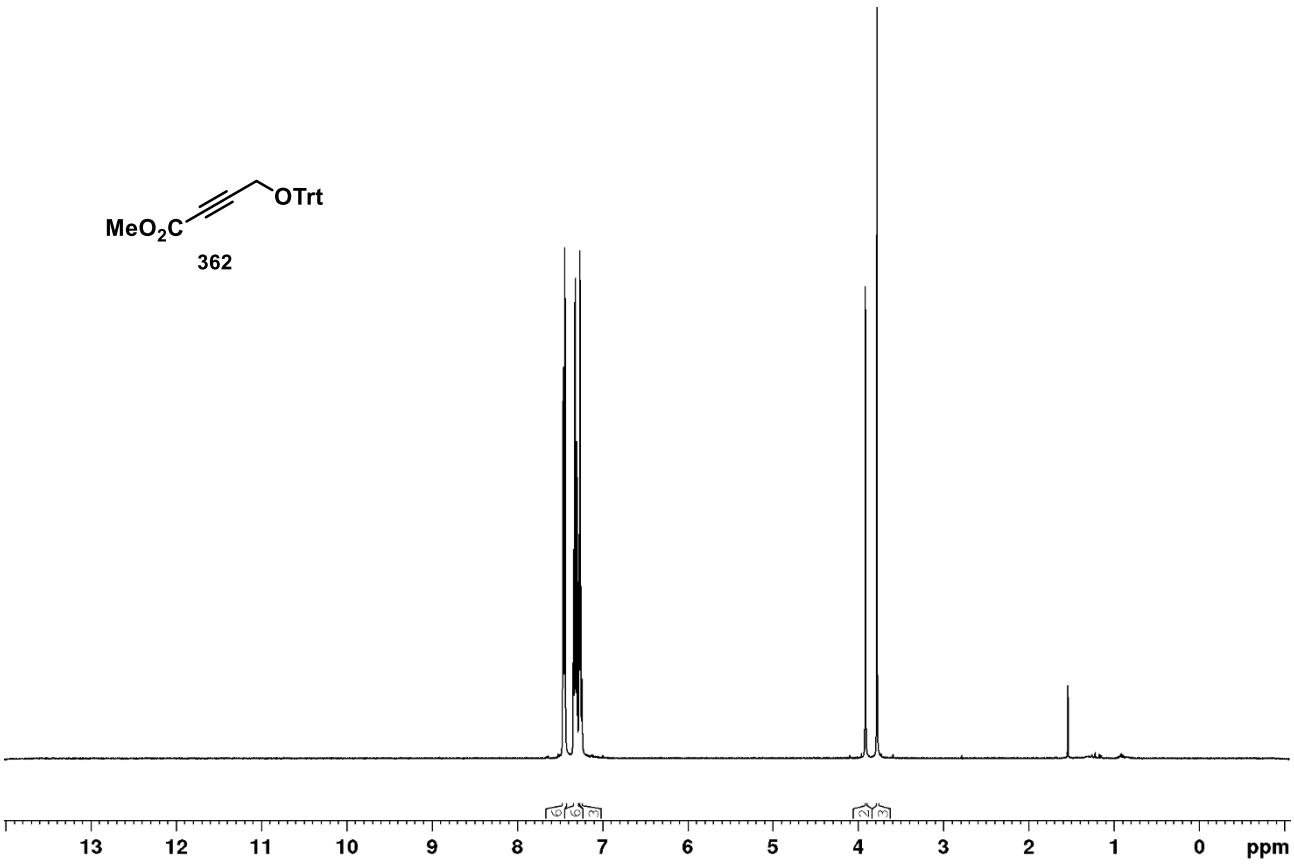
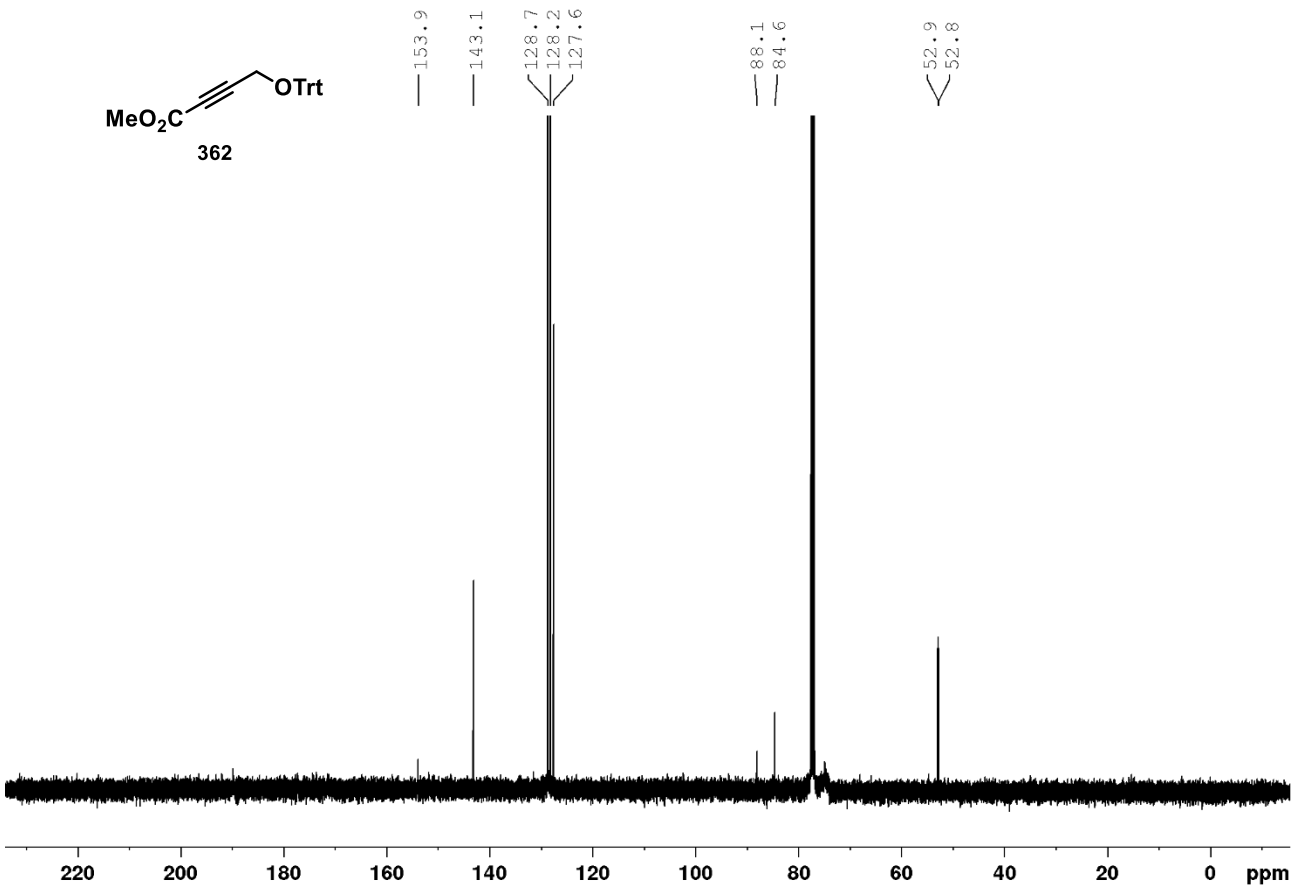
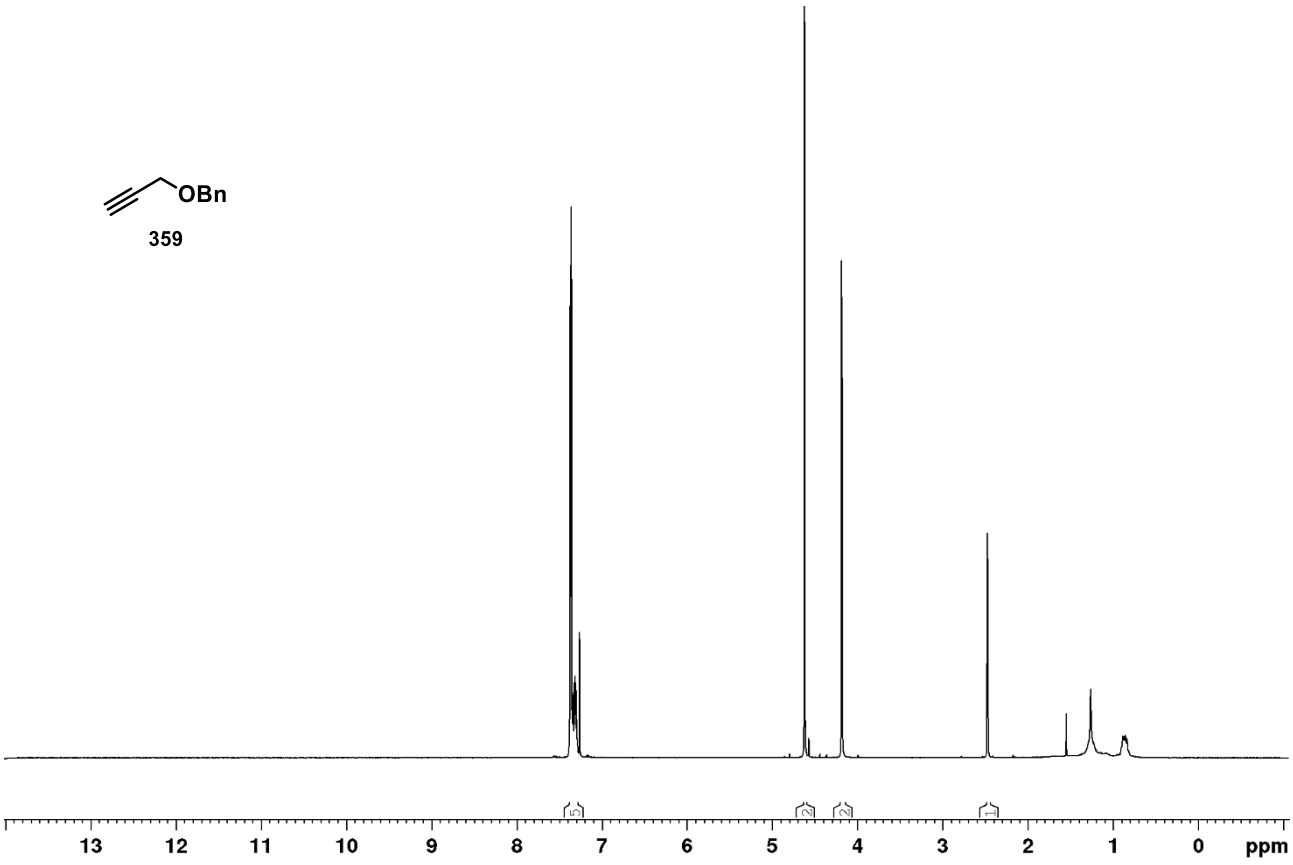
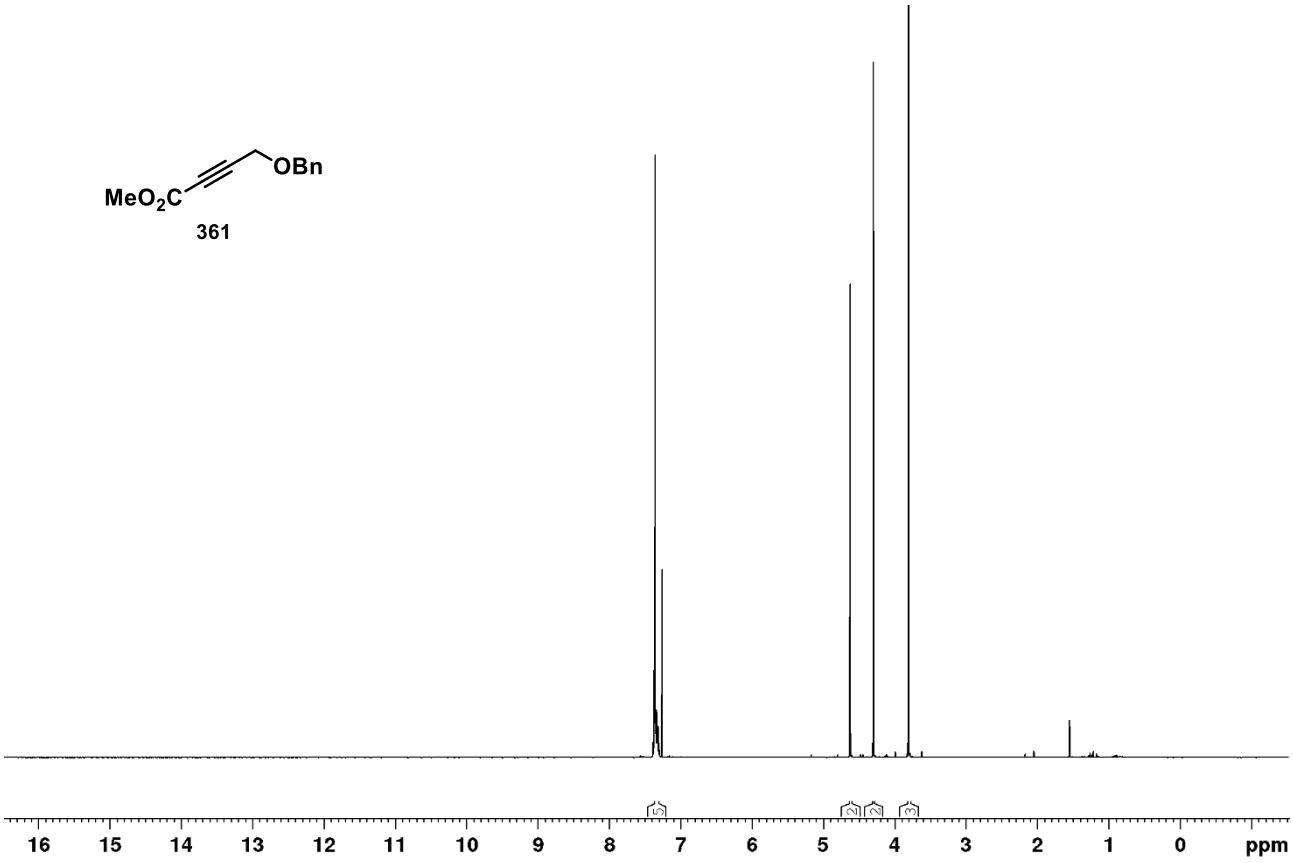
10
9
8
7
6
5
4
3
2
1
0
ppm

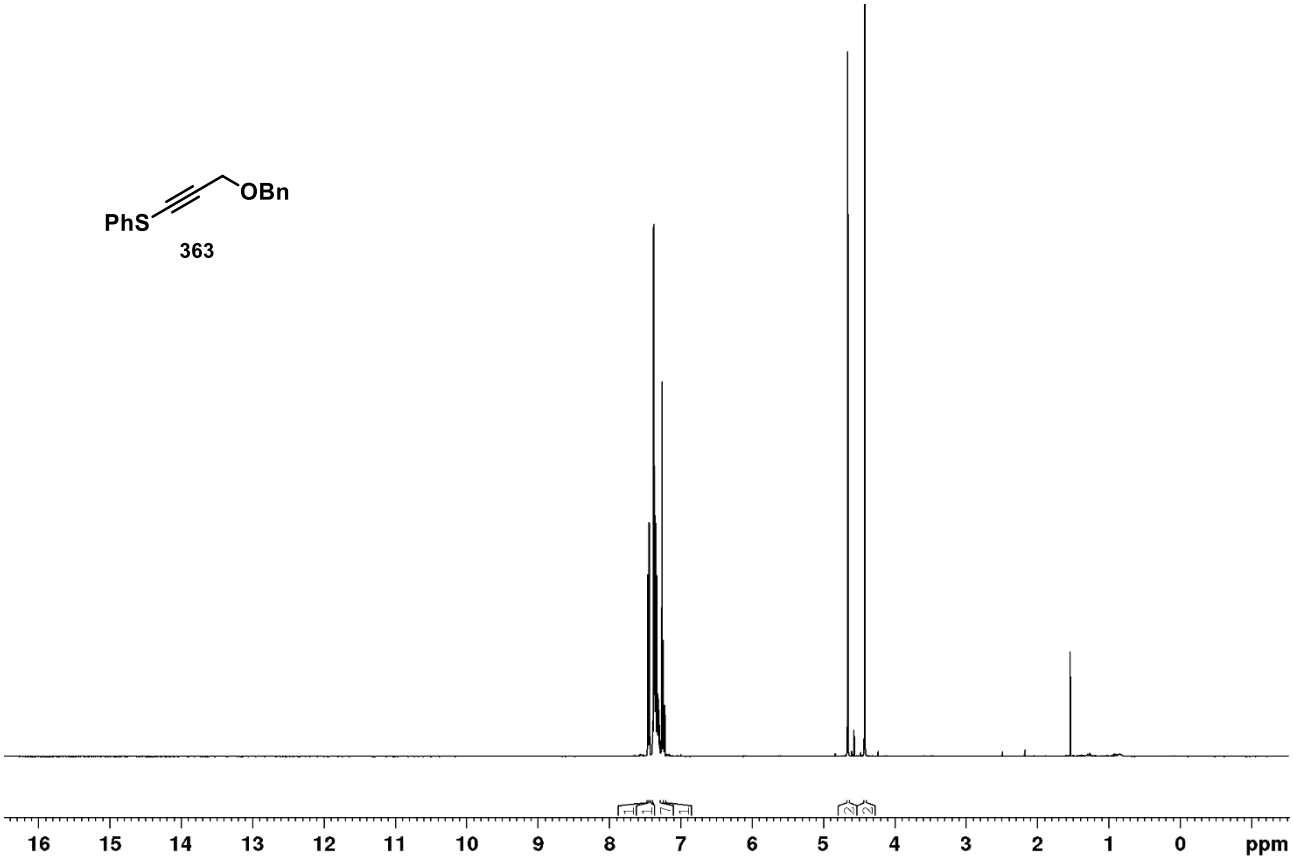

OTrt
360
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

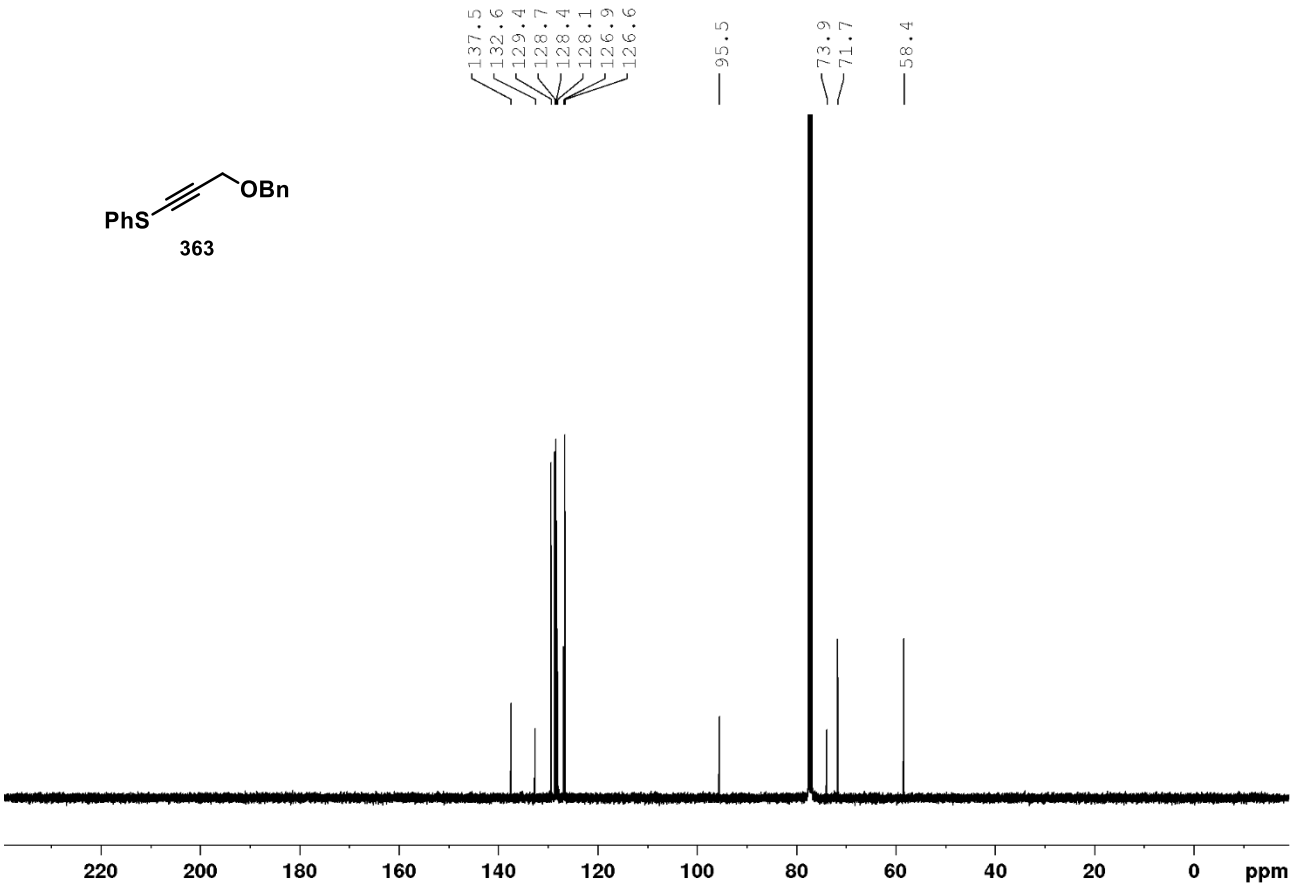

MeO2C
OTrt
362
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

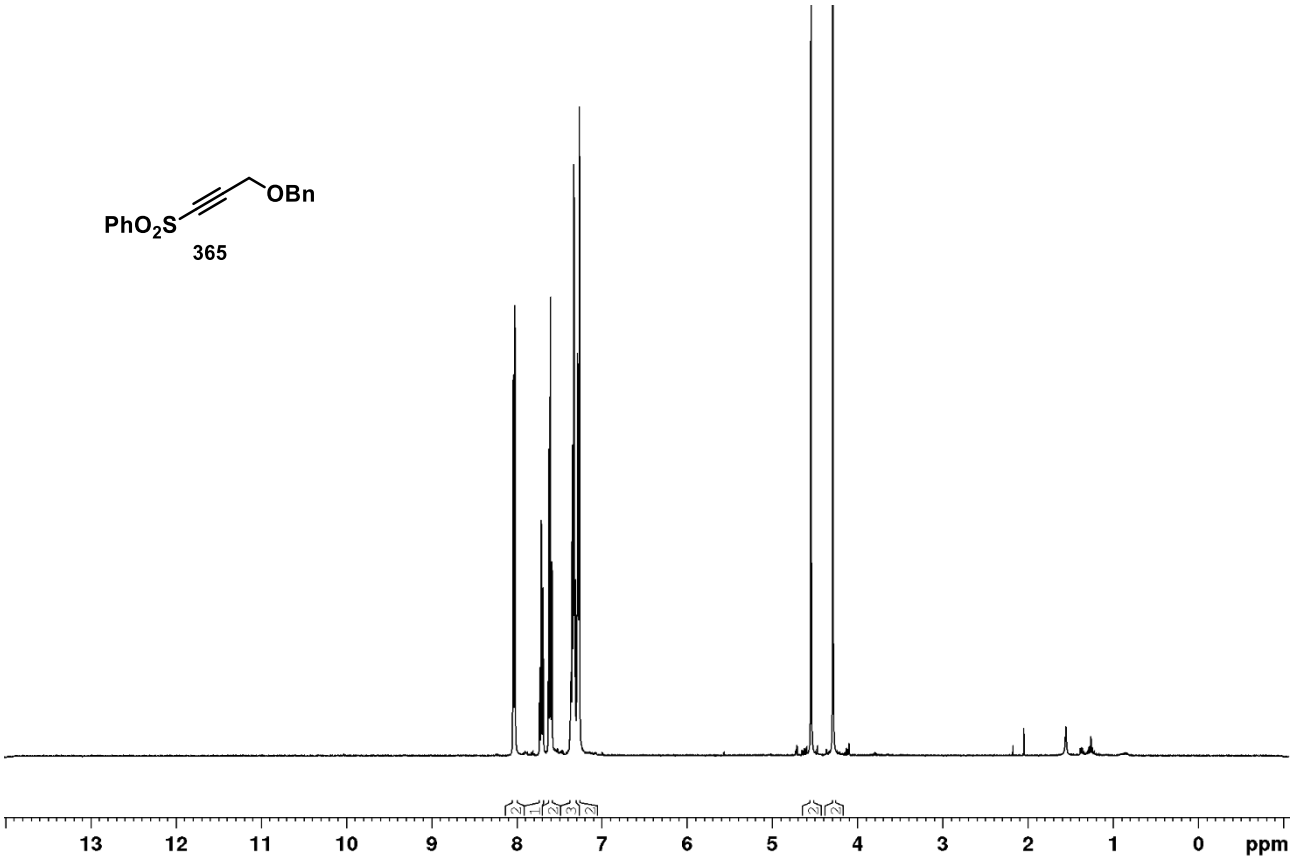

MeO2C
OTrt
362
153.9
143.1
128.7
128.2
127.6
88.1
84.6
52.9
52.8
220
200
180
160
140
120
100
80
60
40
20
0
ppm

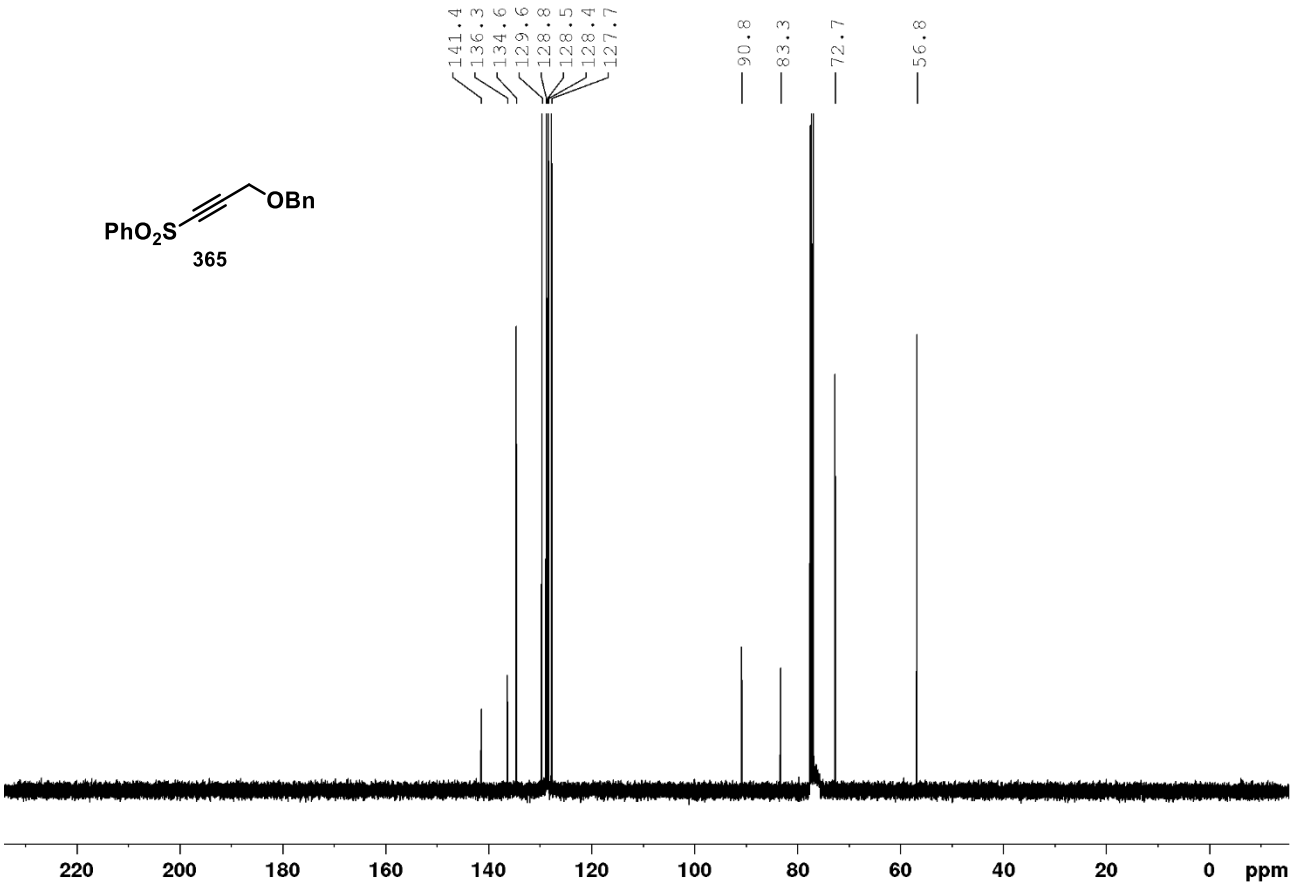

OBn
359
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

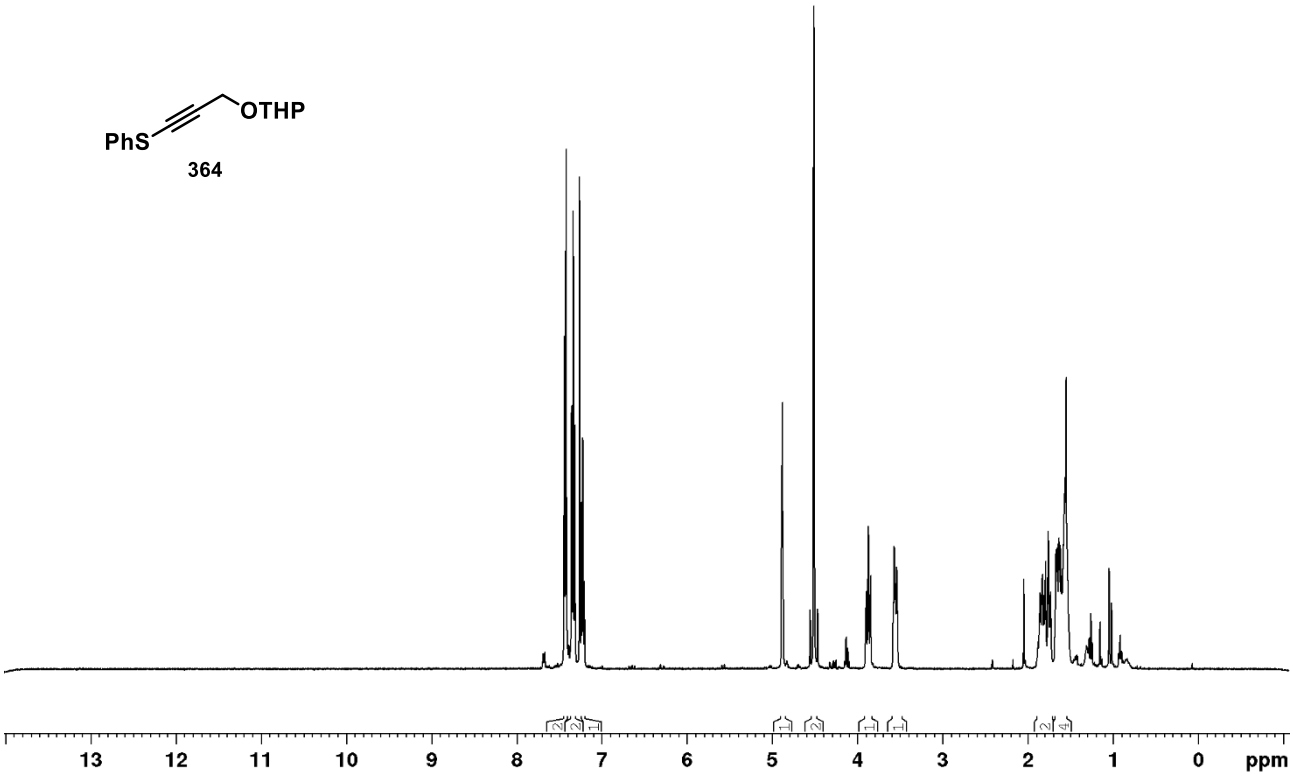

OBn
MeO2C
361
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

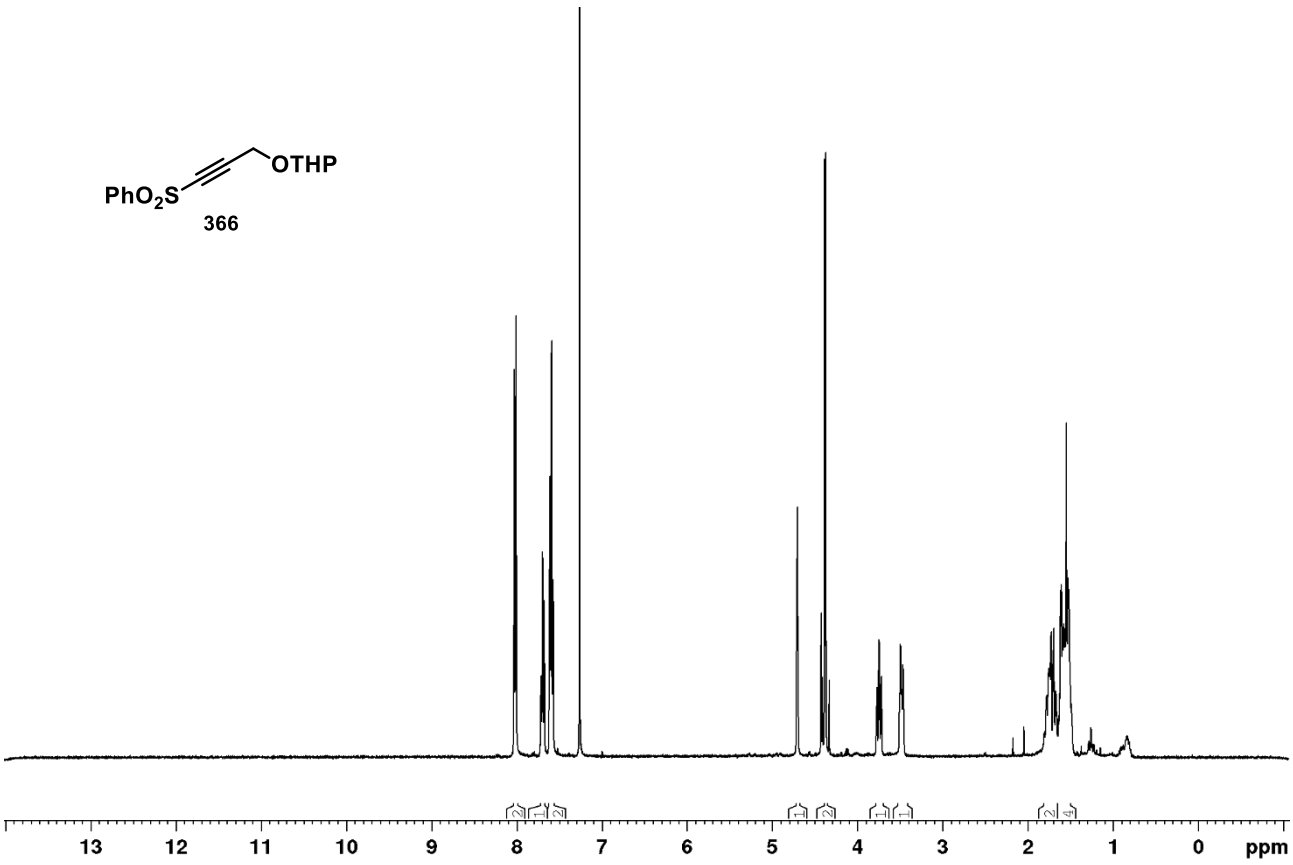

OBn
PhS
363
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

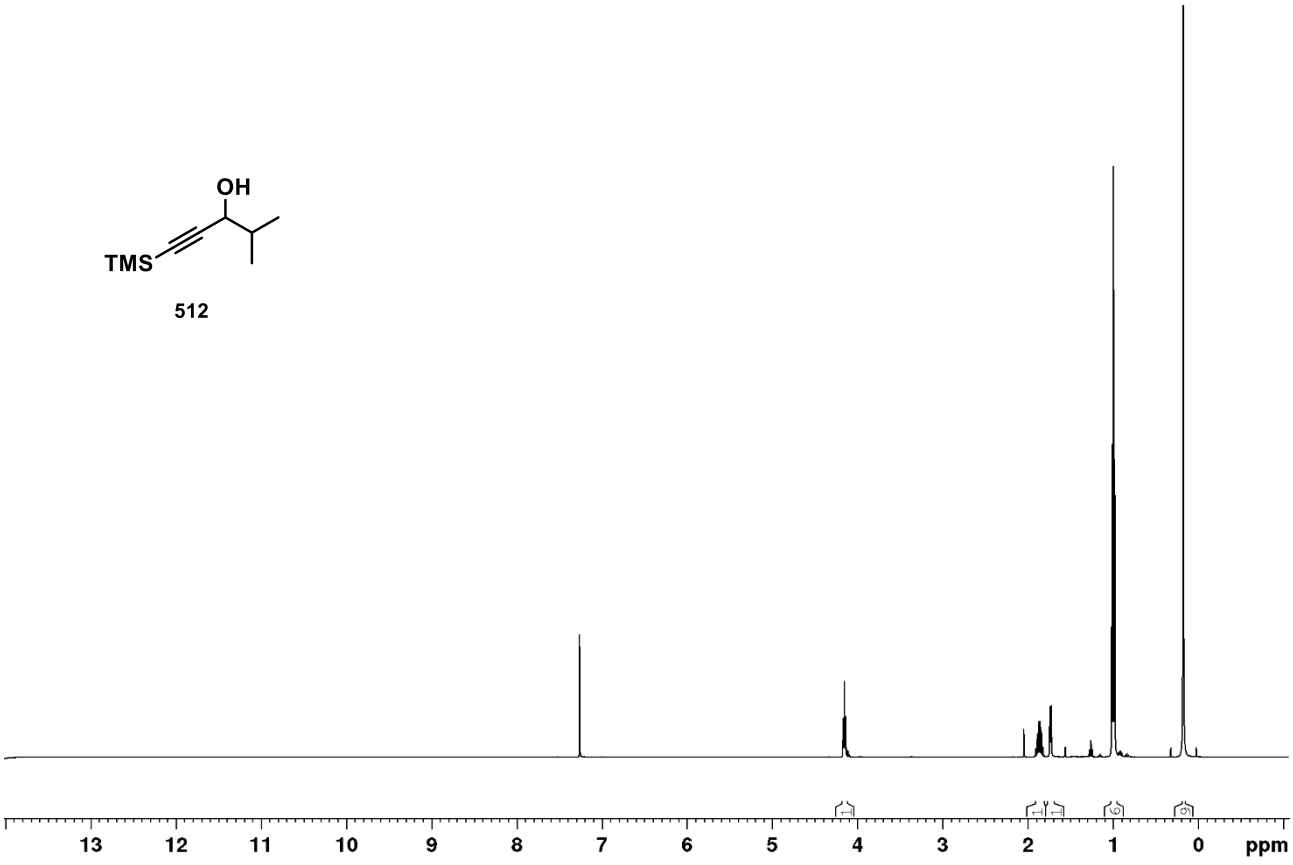

137.5
132.6
129.4
128.7
128.4
128.1
126.9
126.6
95.5
73.9
71.7
58.4
OBn
PhS
363
220
200
180
160
140
120
100
80
60
40
20
0
ppm

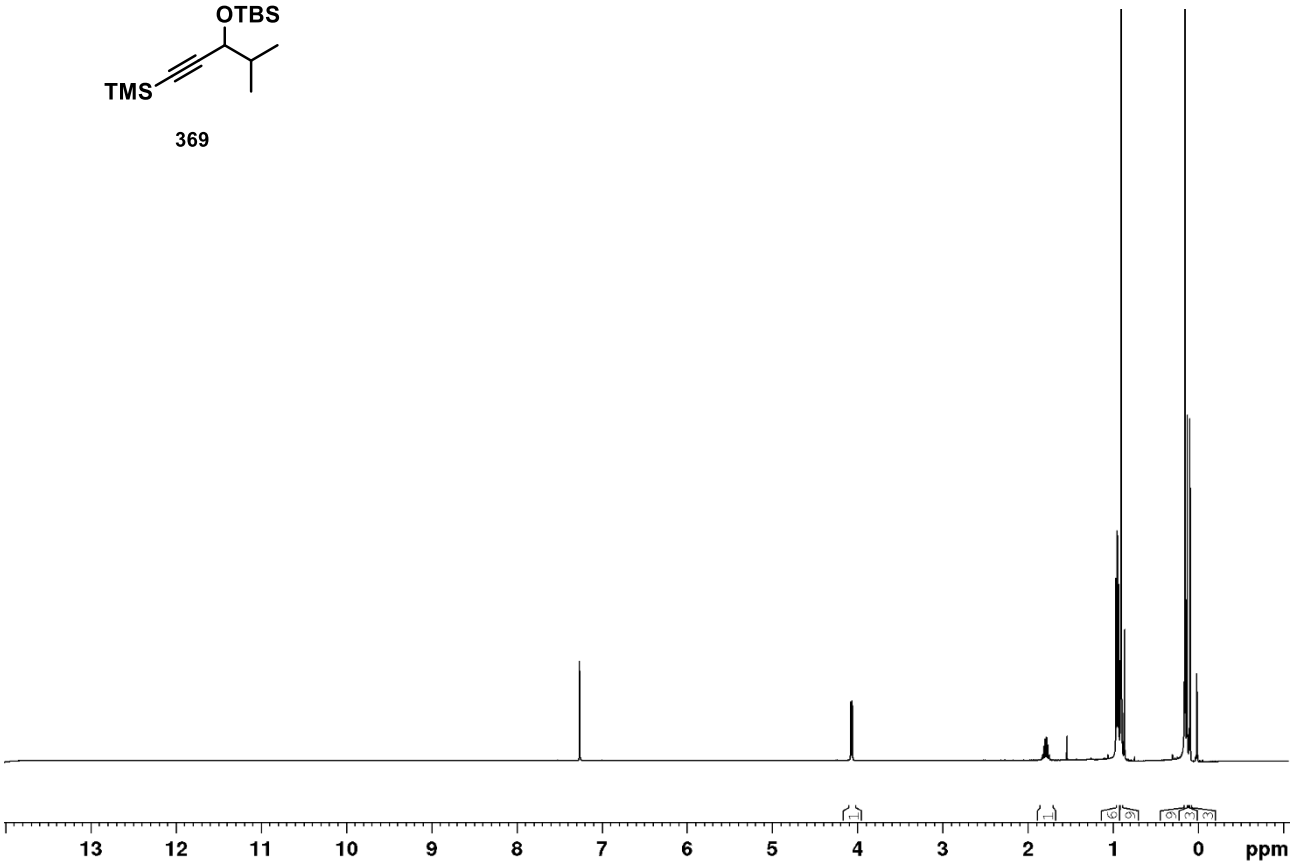

OBn
PhO2S
365
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

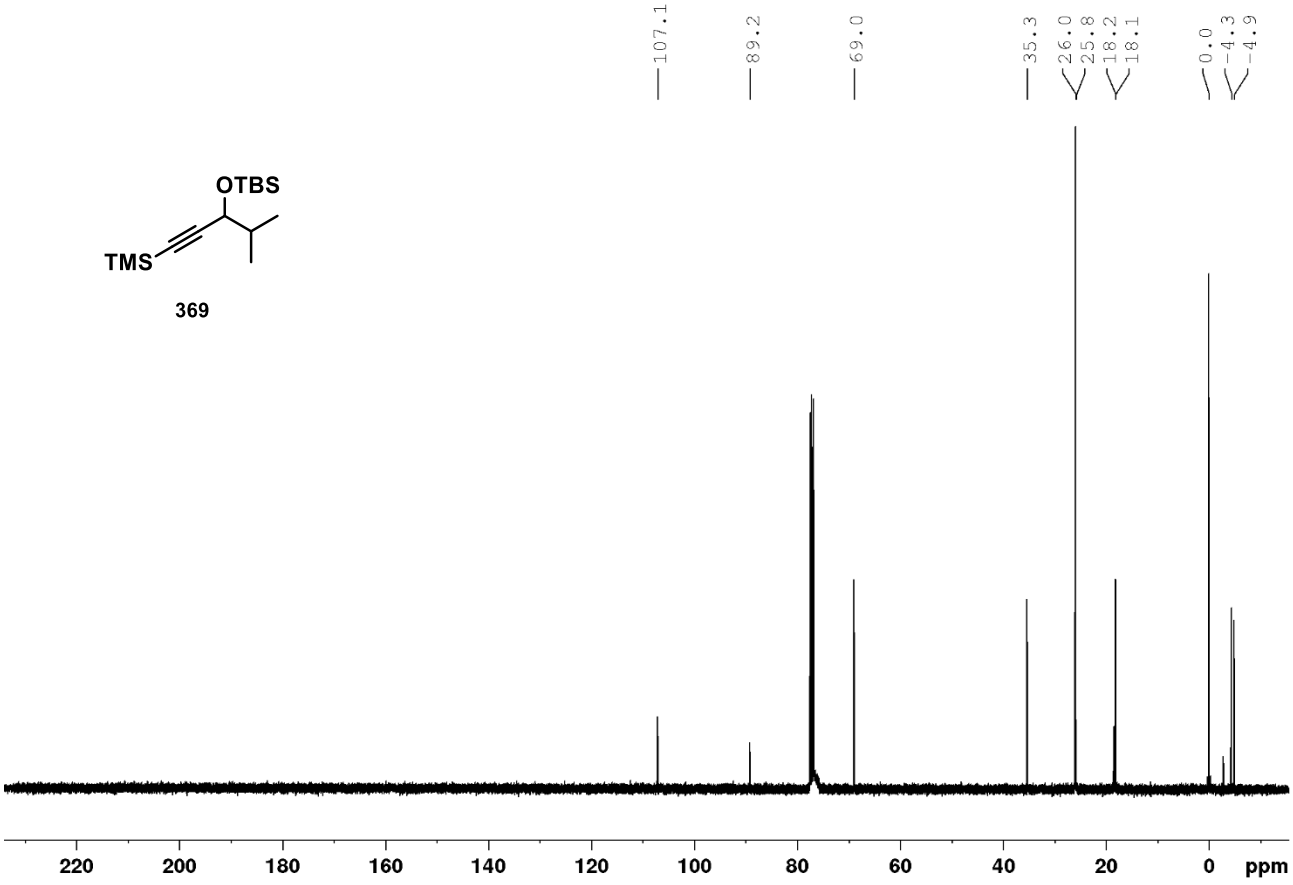

141.4
136.3
134.6
129.6
128.8
128.5
128.4
127.7
90.8
83.3
72.7
56.8
OBn
PhO2S
365
220
200
180
160
140
120
100
80
60
40
20
0
ppm


PhS
OTHP
364
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

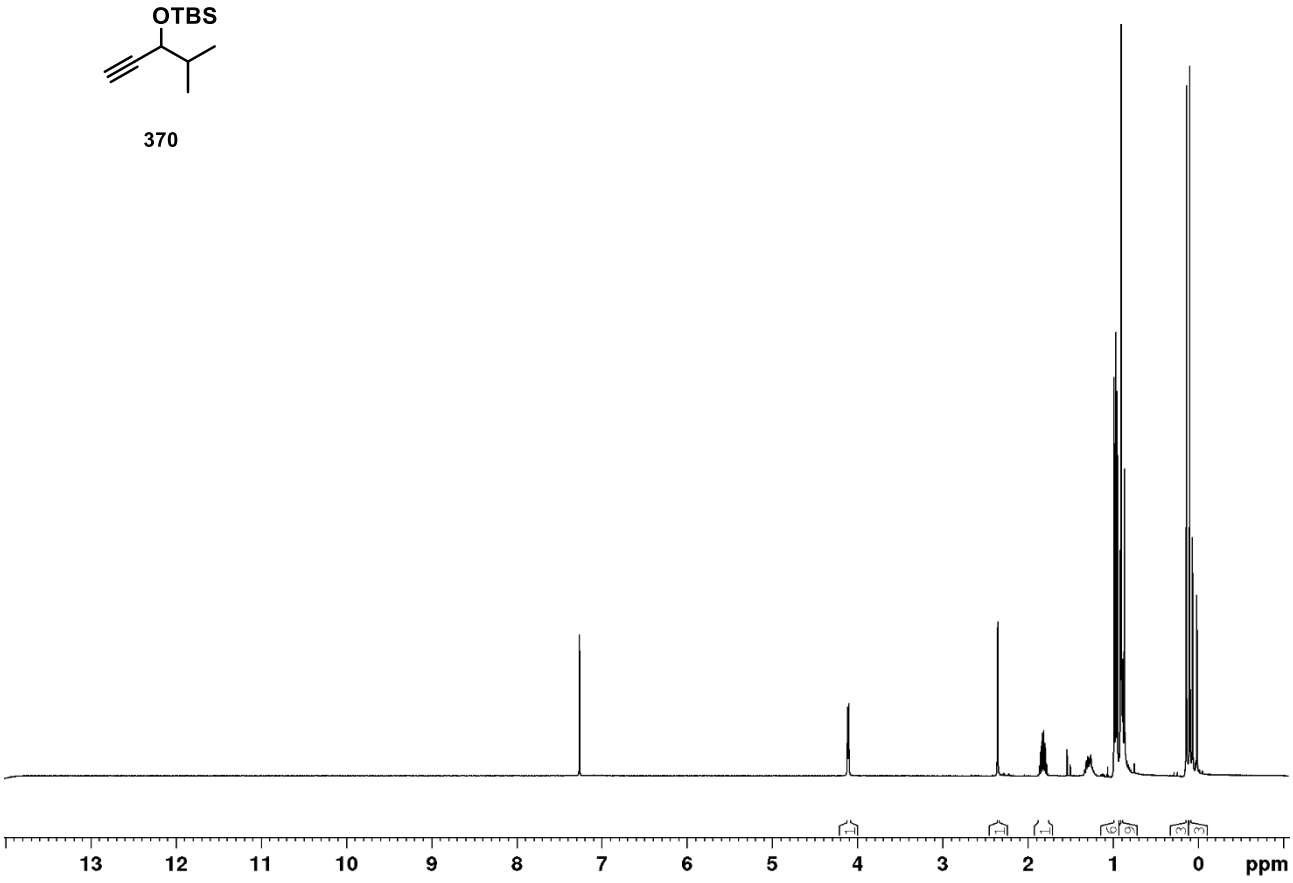

PhO2S
OTHP
366
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


OH
TMS
512
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

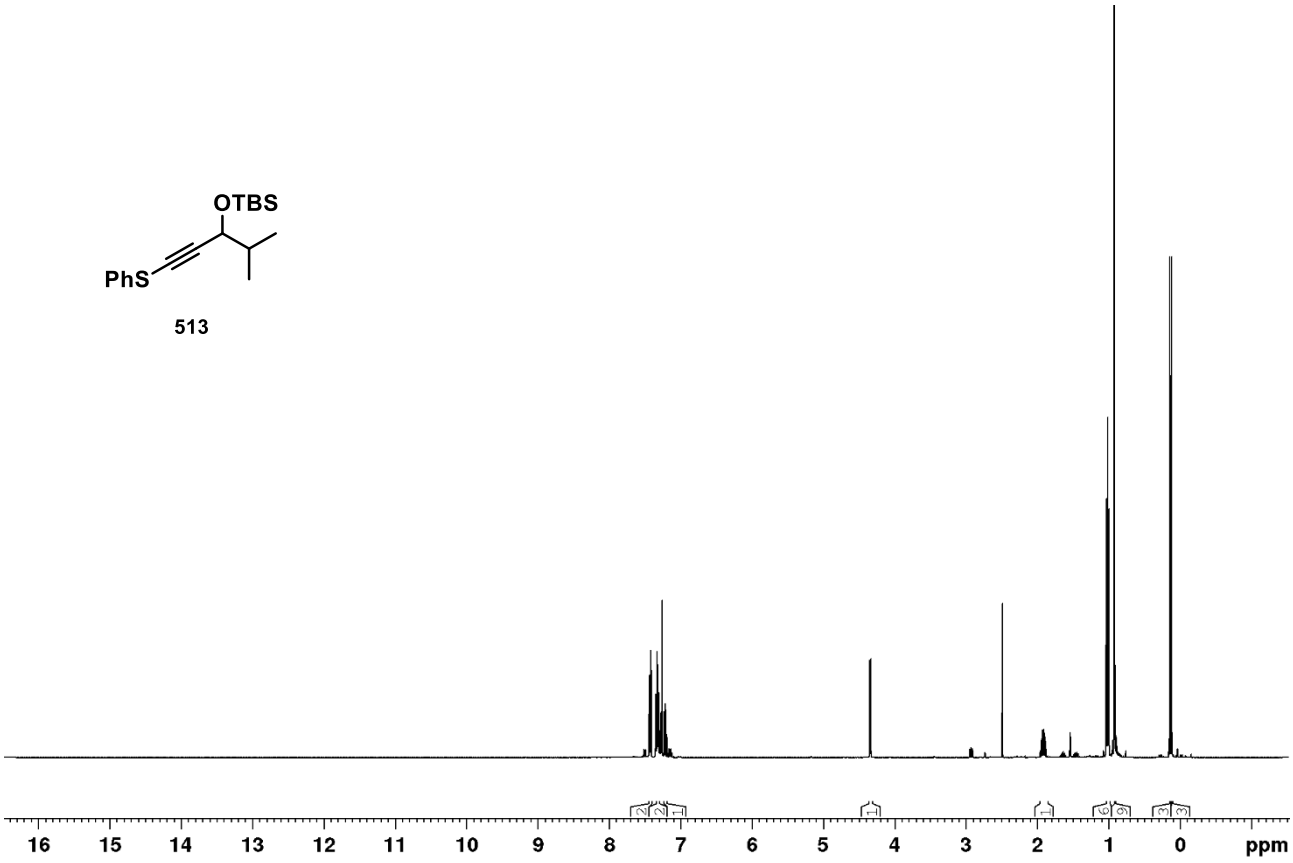

OTBS
TMS
369
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

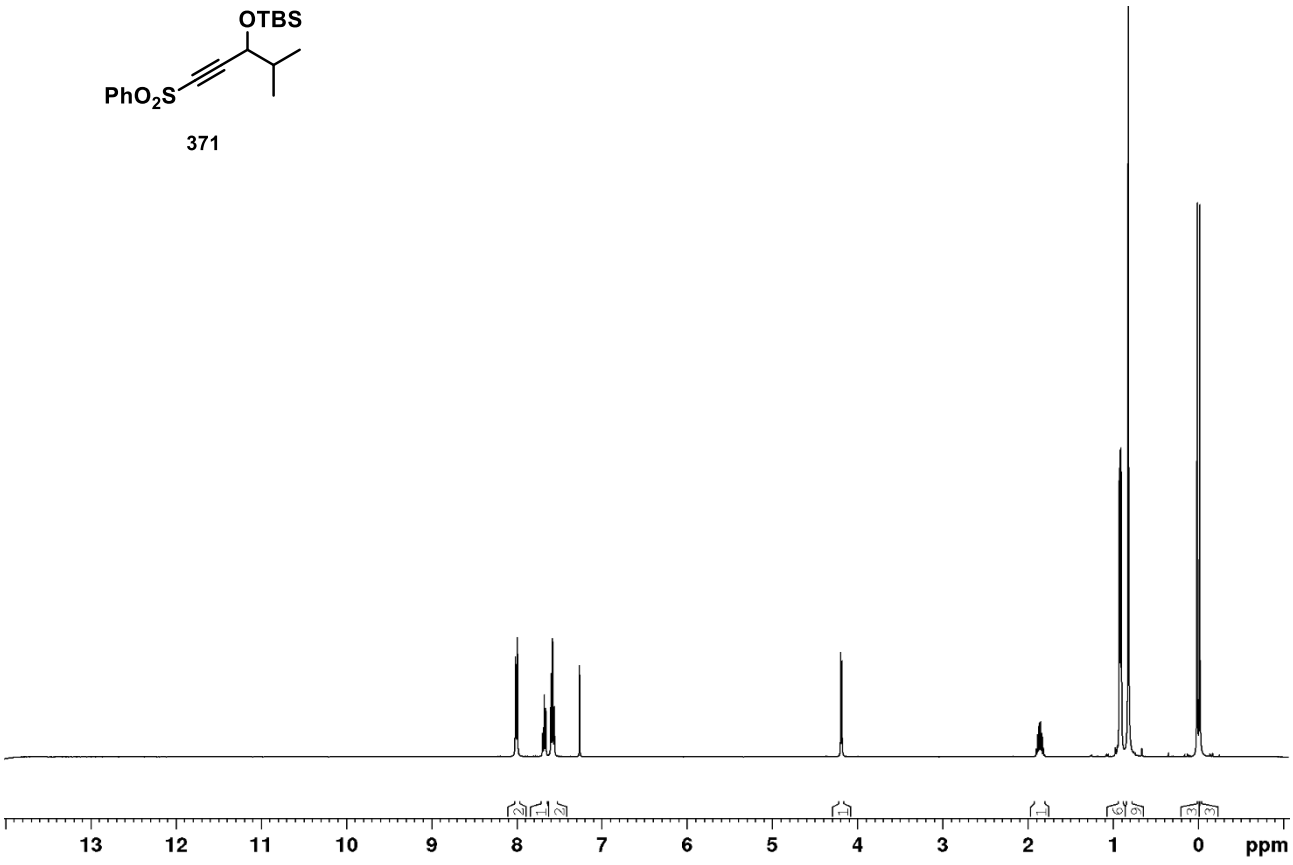

107.1
89.2
69.0
35.3
26.0
25.8
18.2
18.1
0.0
-4.3
-4.9
OTBS
TMS
220
200
180
160
140
120
100
80
60
40
20
0
ppm

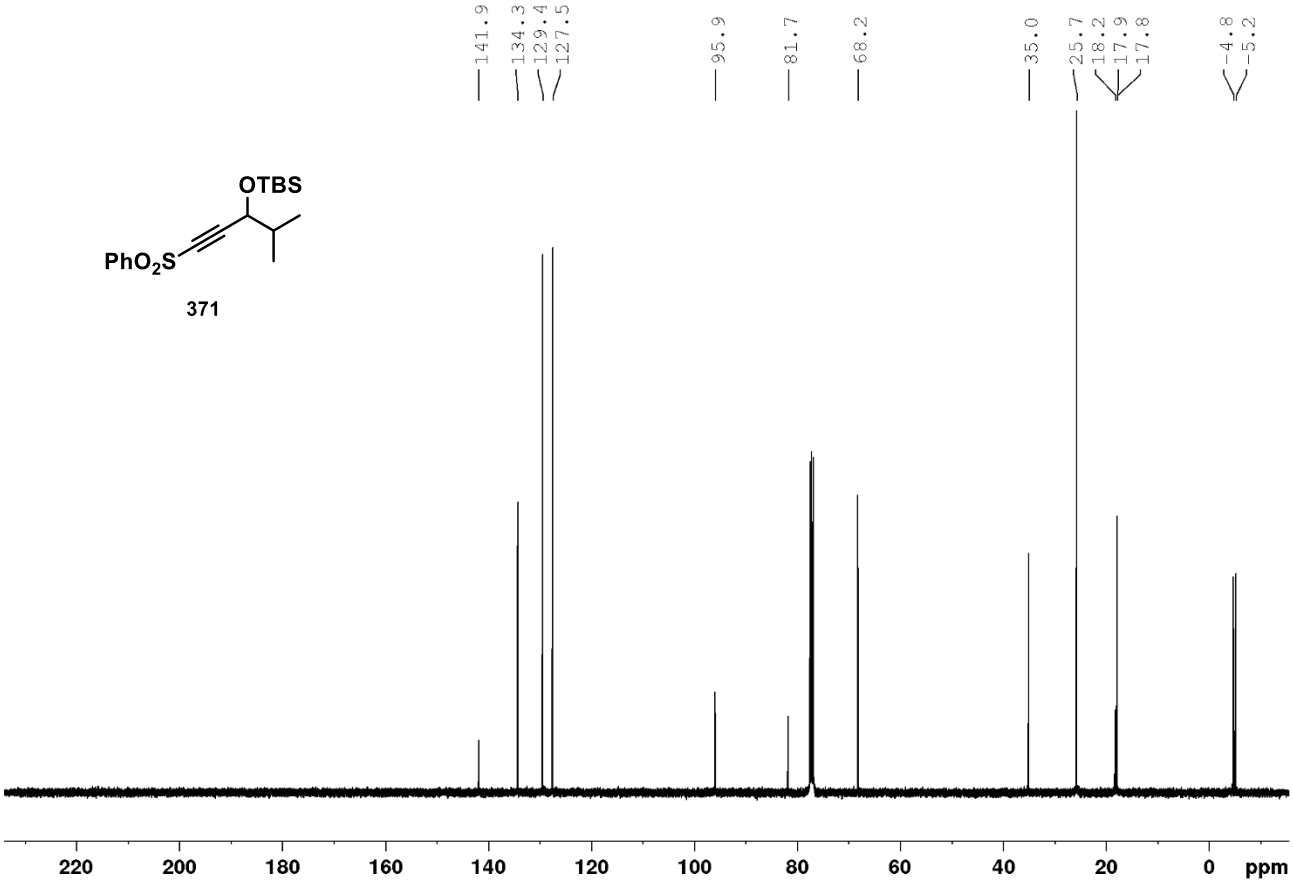
369


OTBS
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

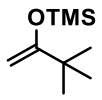
370


OTBS
PhS
513
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm


OTBS
PhO2S
371
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm

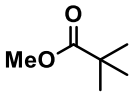

141.9
134.3
129.4
127.5
95.9
81.7
68.2
35.0
25.7
18.2
17.9
17.8
-4.8
-5.2
OTBS
PhO2S
220
200
180
160
140
120
100
80
60
40
20
0
ppm

371


OTMS

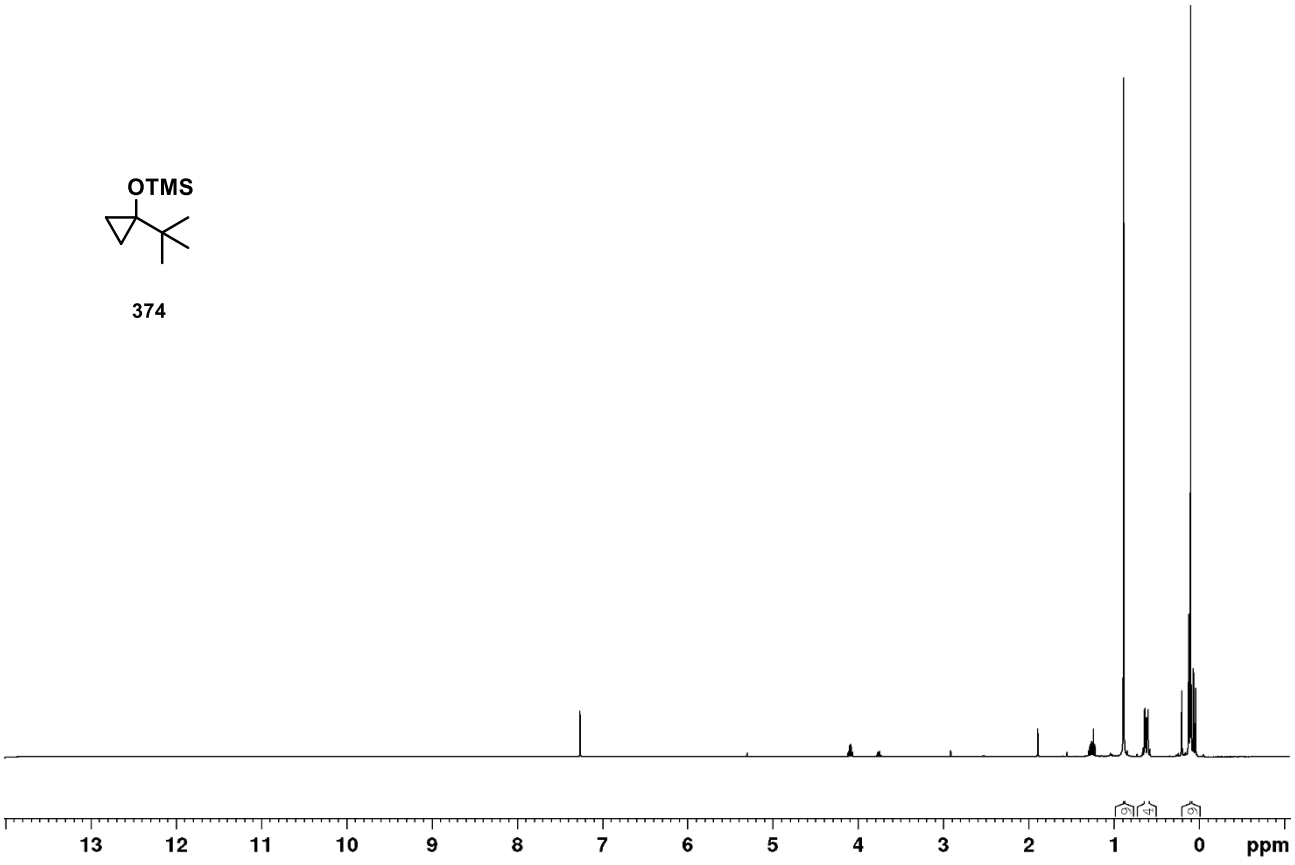
373

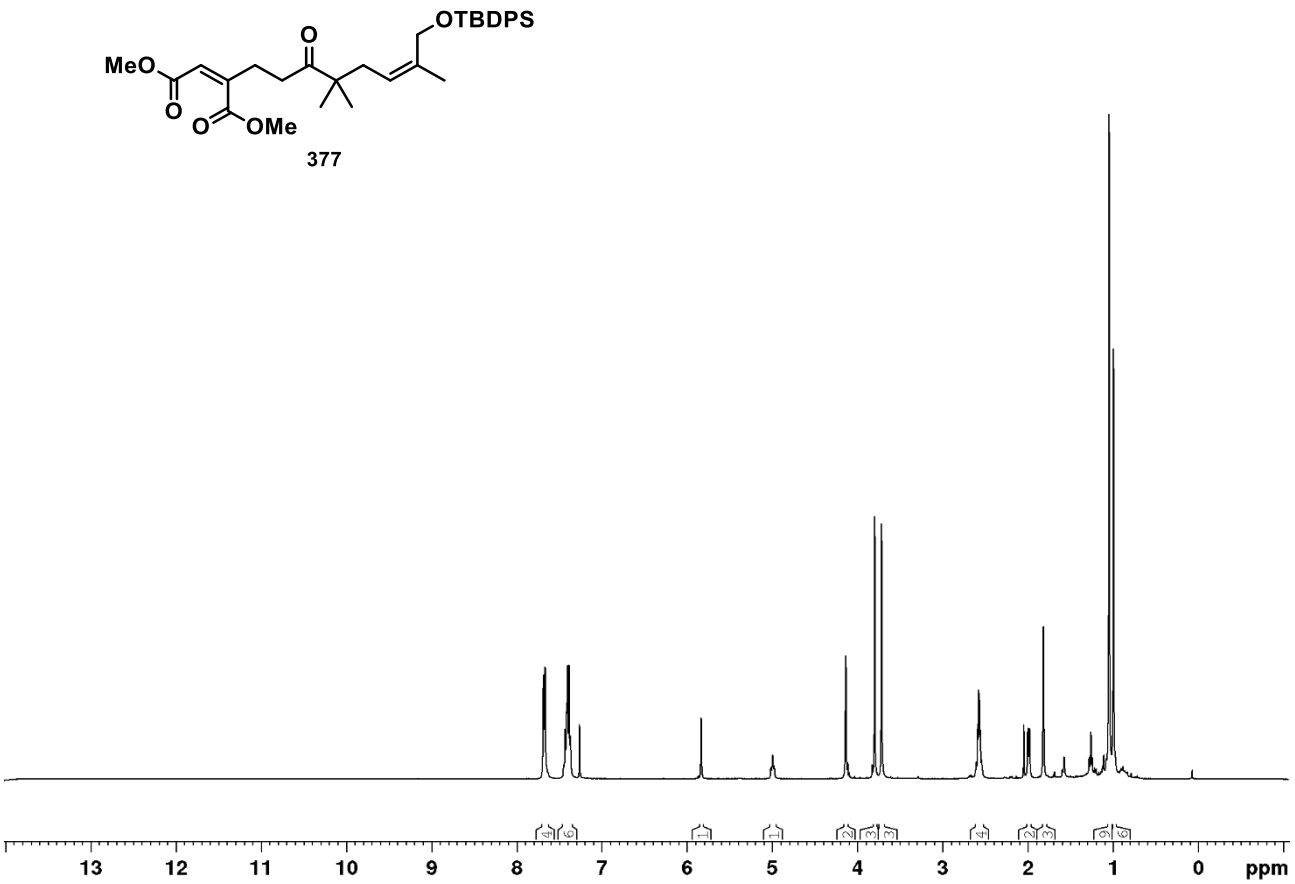
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

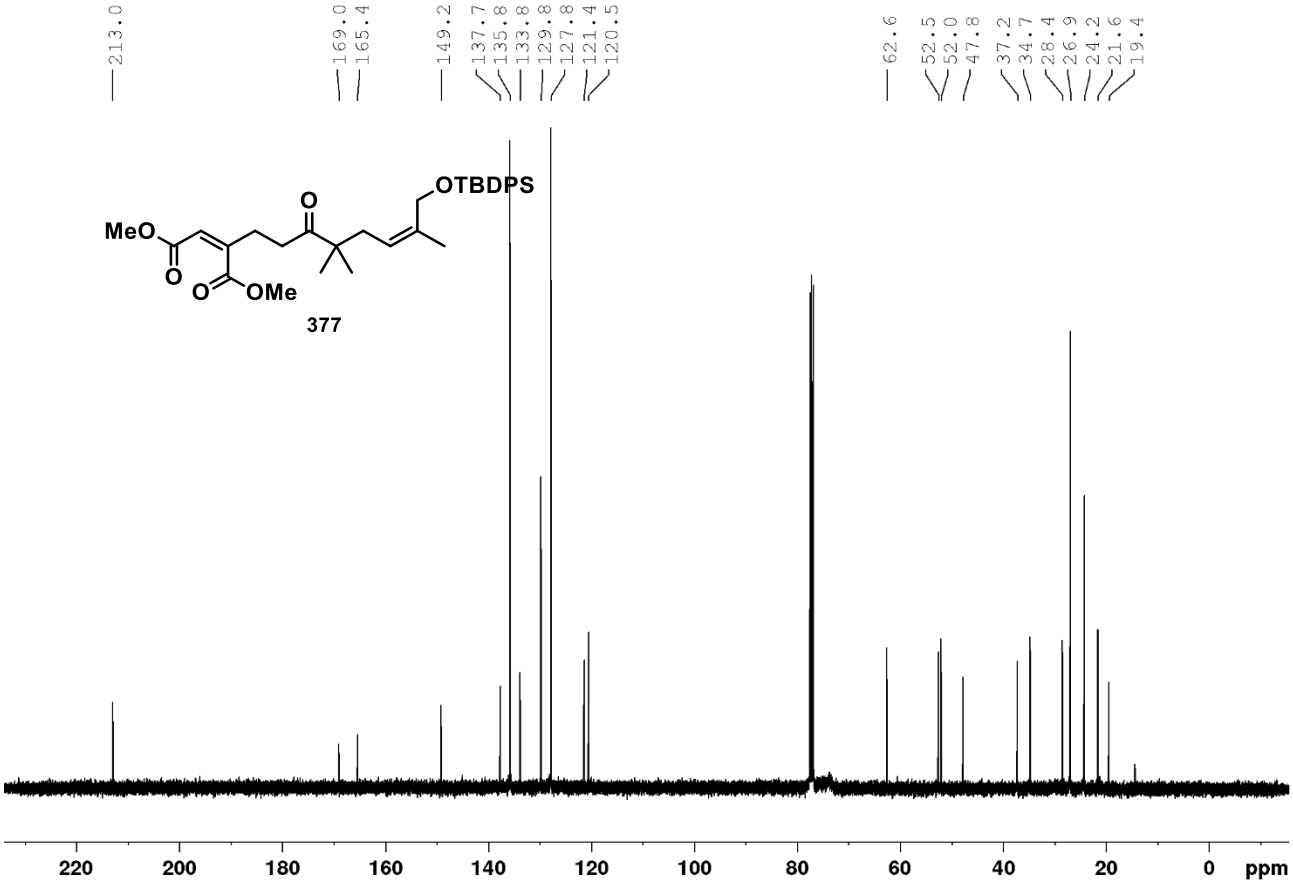


514

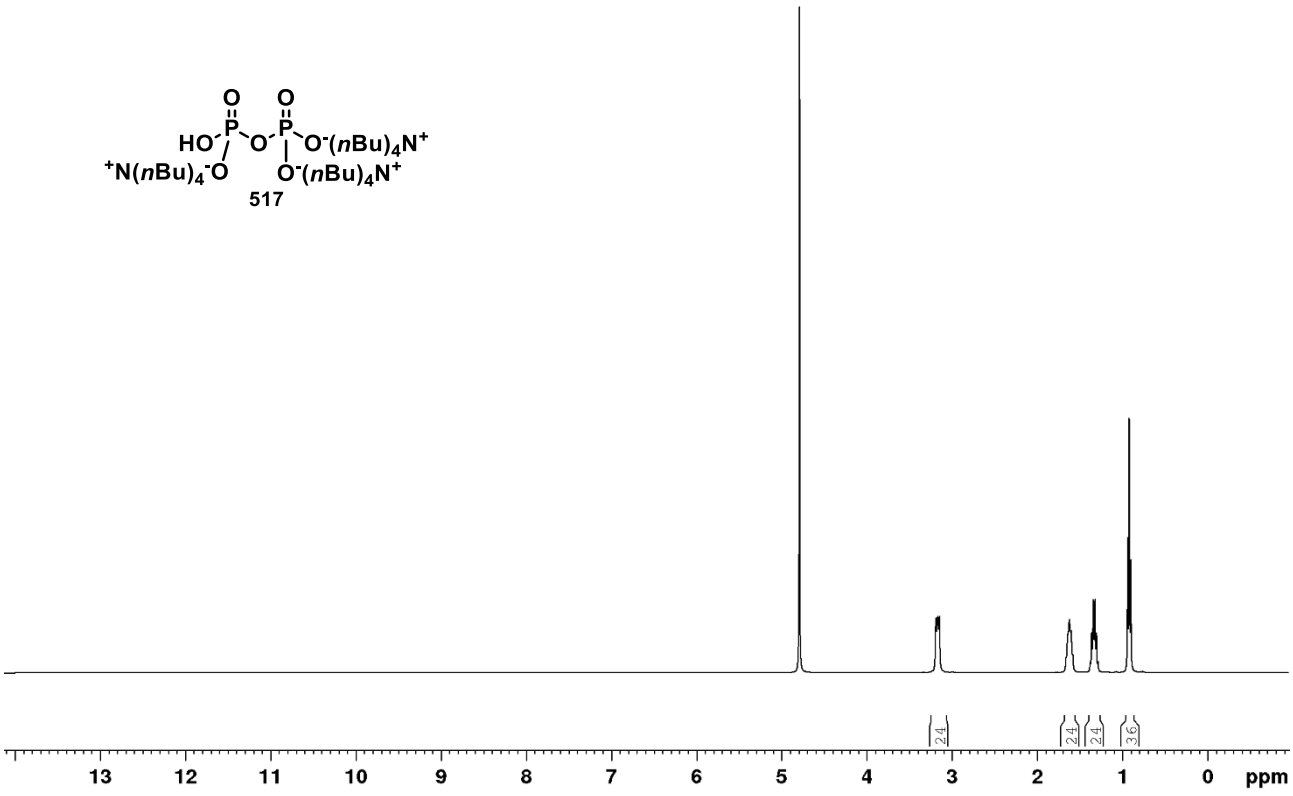
375

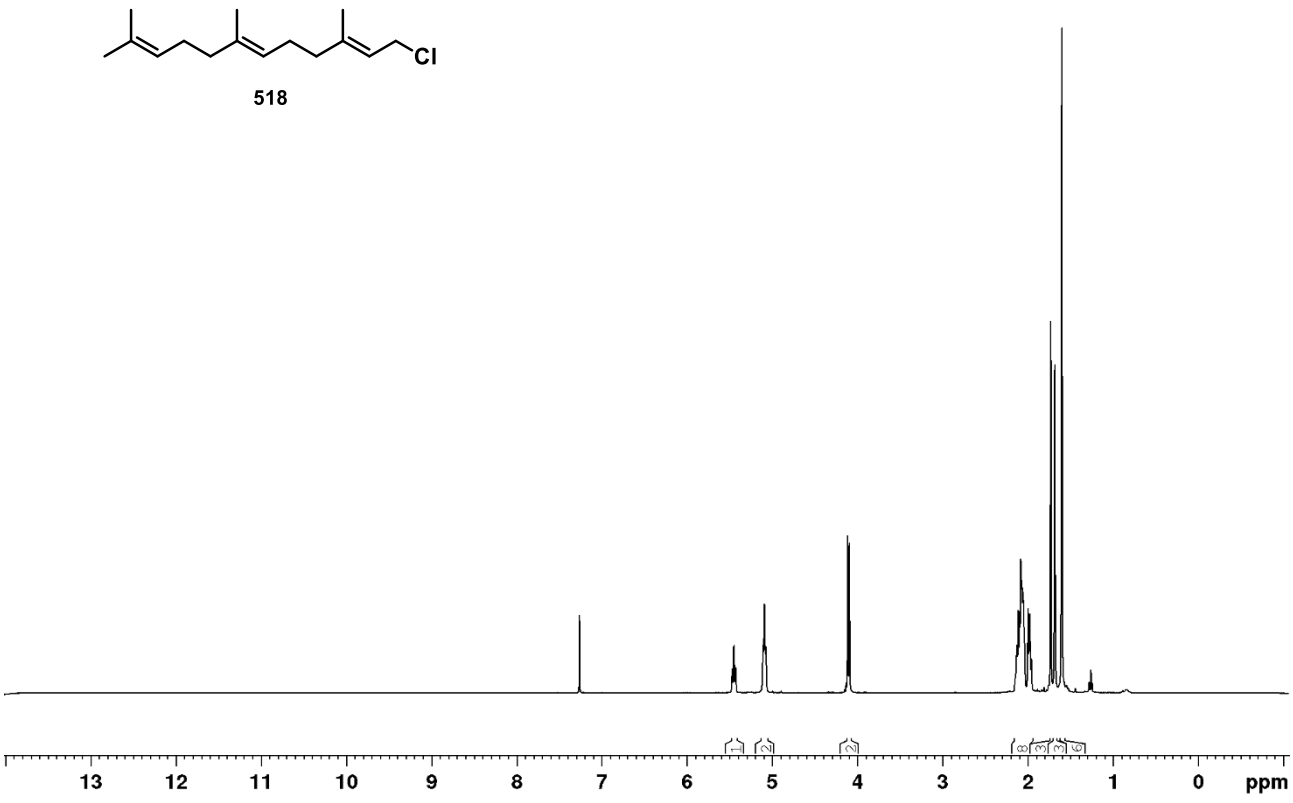

OTMS
374
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

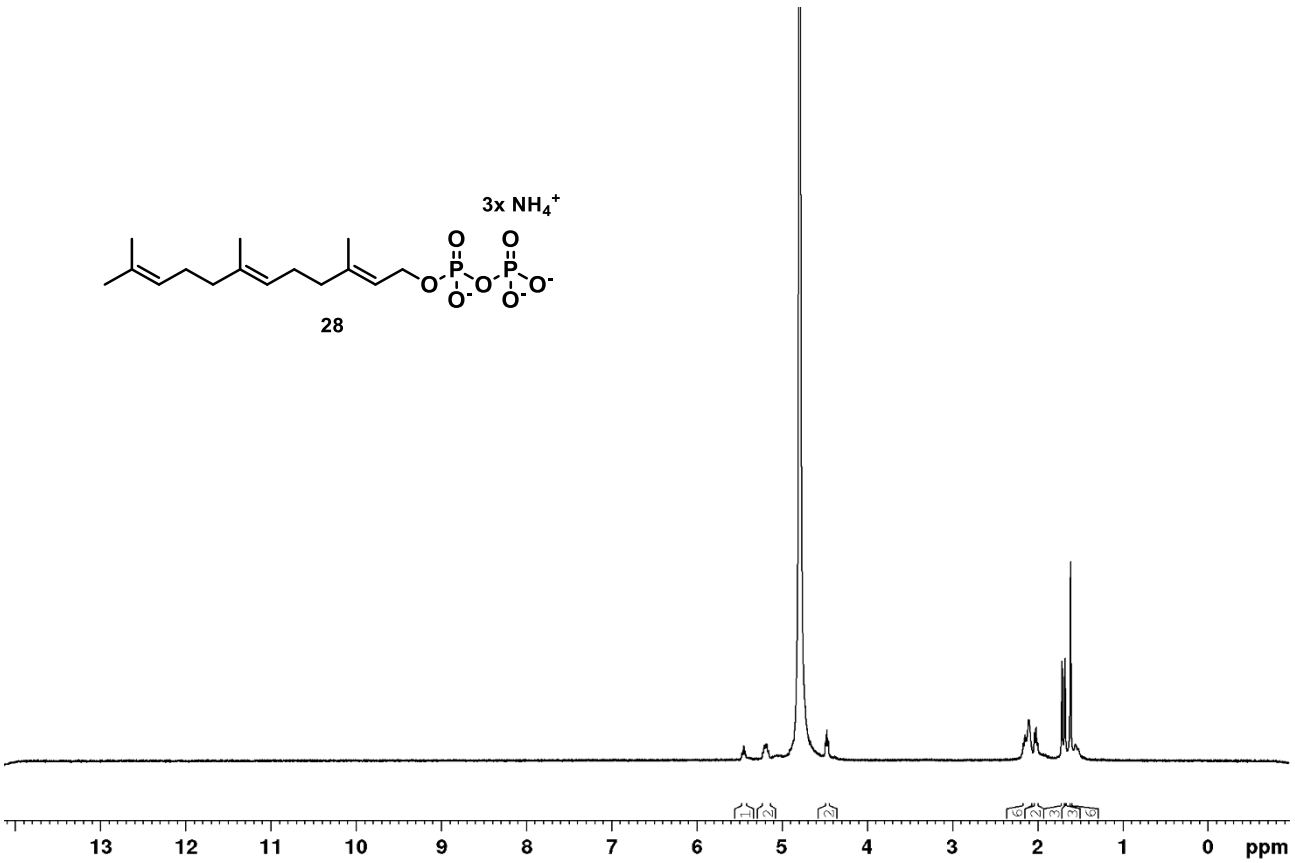

OTBDPS
MeO
O
O
O
OMe
377
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

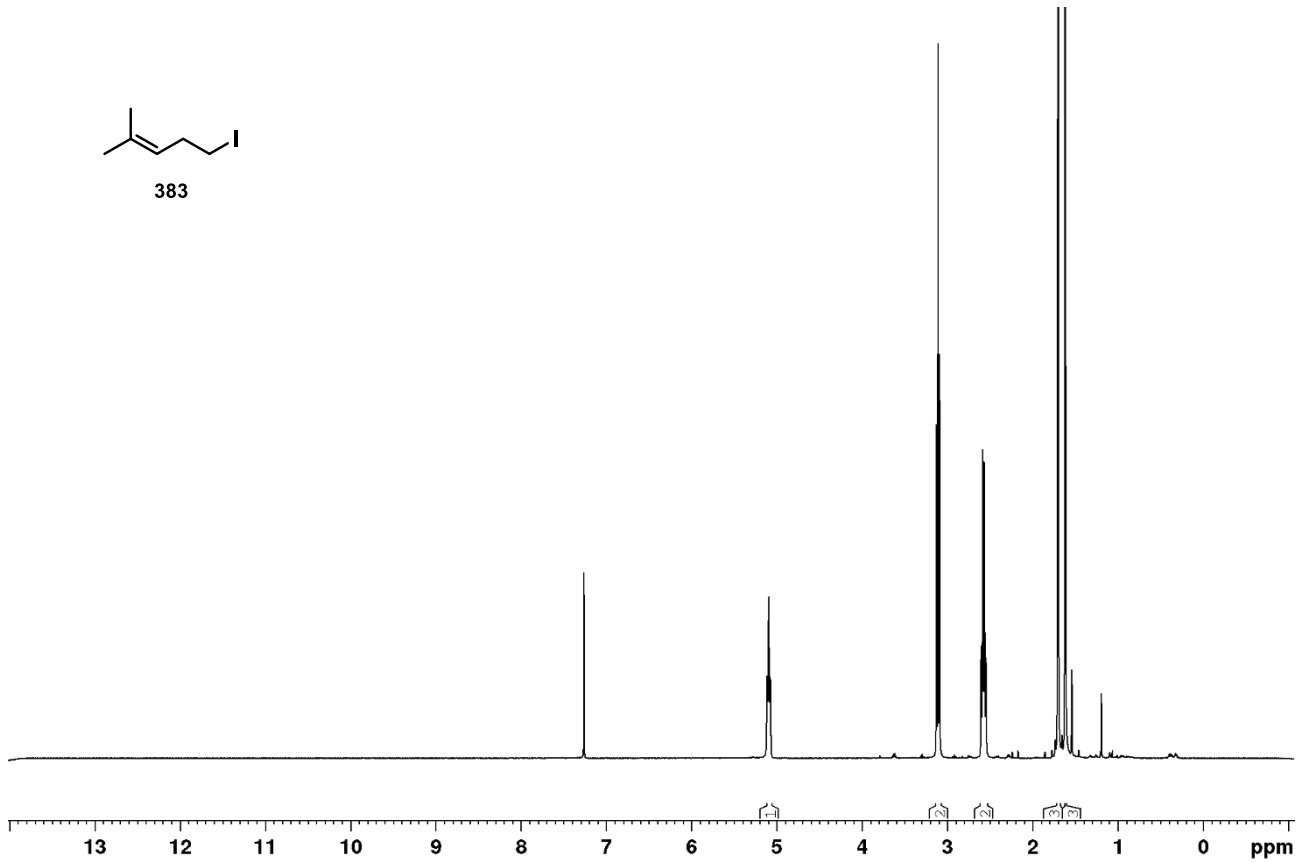

213.0
169.0
165.4
149.2
137.7
135.8
133.8
129.8
127.8
121.4
120.5
62.6
52.5
52.0
47.8
37.2
34.7
28.4
26.9
24.2
21.6
19.4
OTBDPS
MeO
O
O
O
OMe
377
220
200
180
160
140
120
100
80
60
40
20
0
ppm

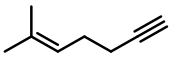
10.2 Biotransformations-Synthesis NMR-Spectra






3x NH_4^+
28
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm


383
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm



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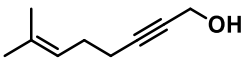

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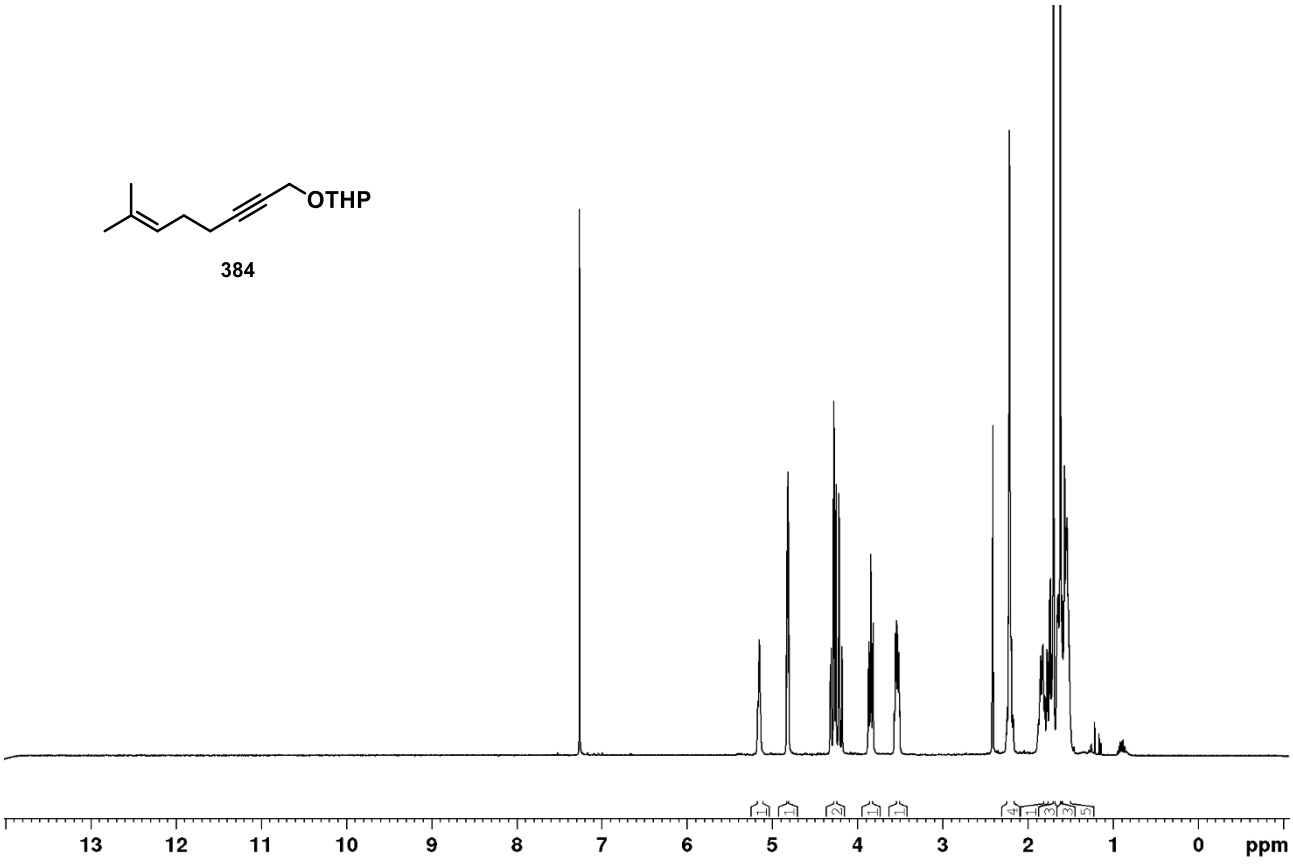
OTHP
384
13
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9
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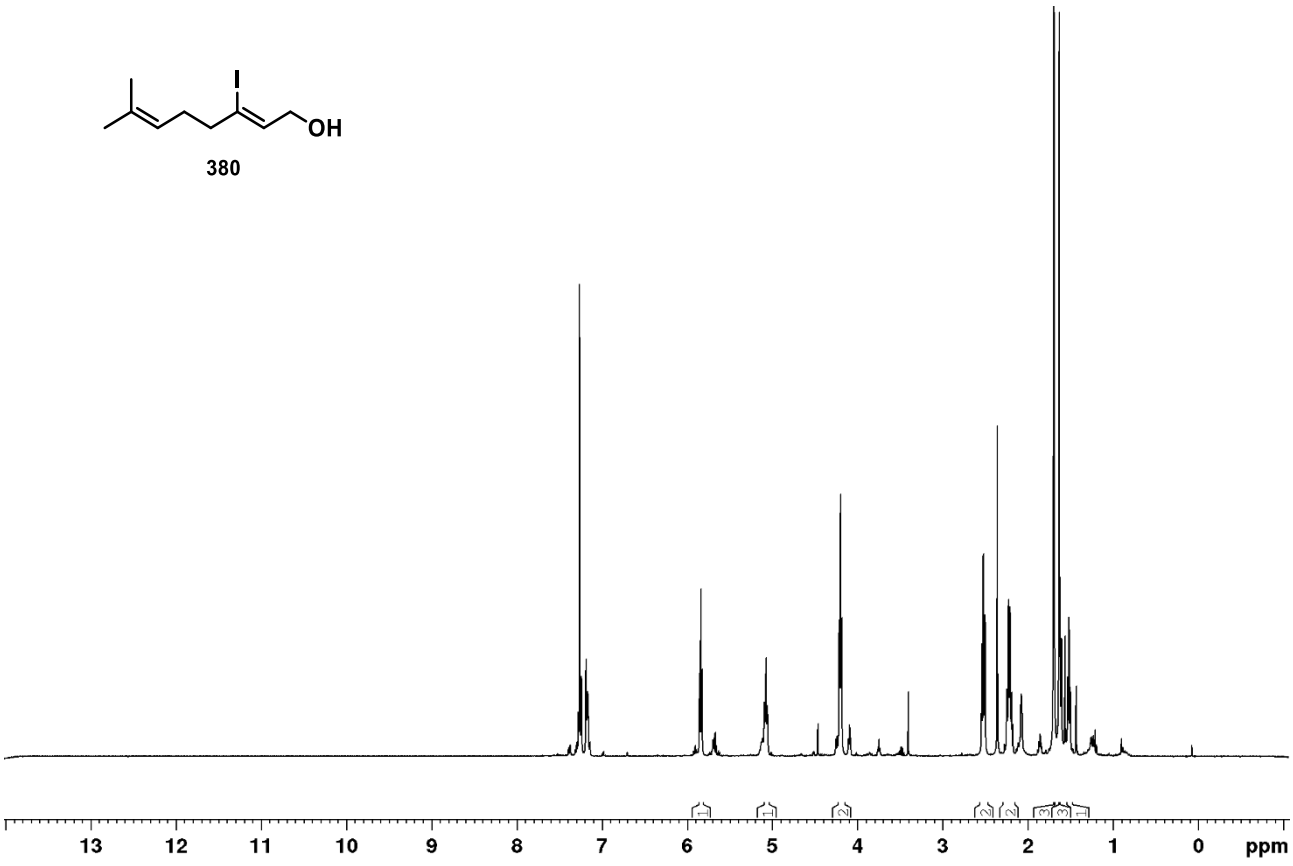
6
5
4
3
2
1
0
ppm


I
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6
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4
3
2
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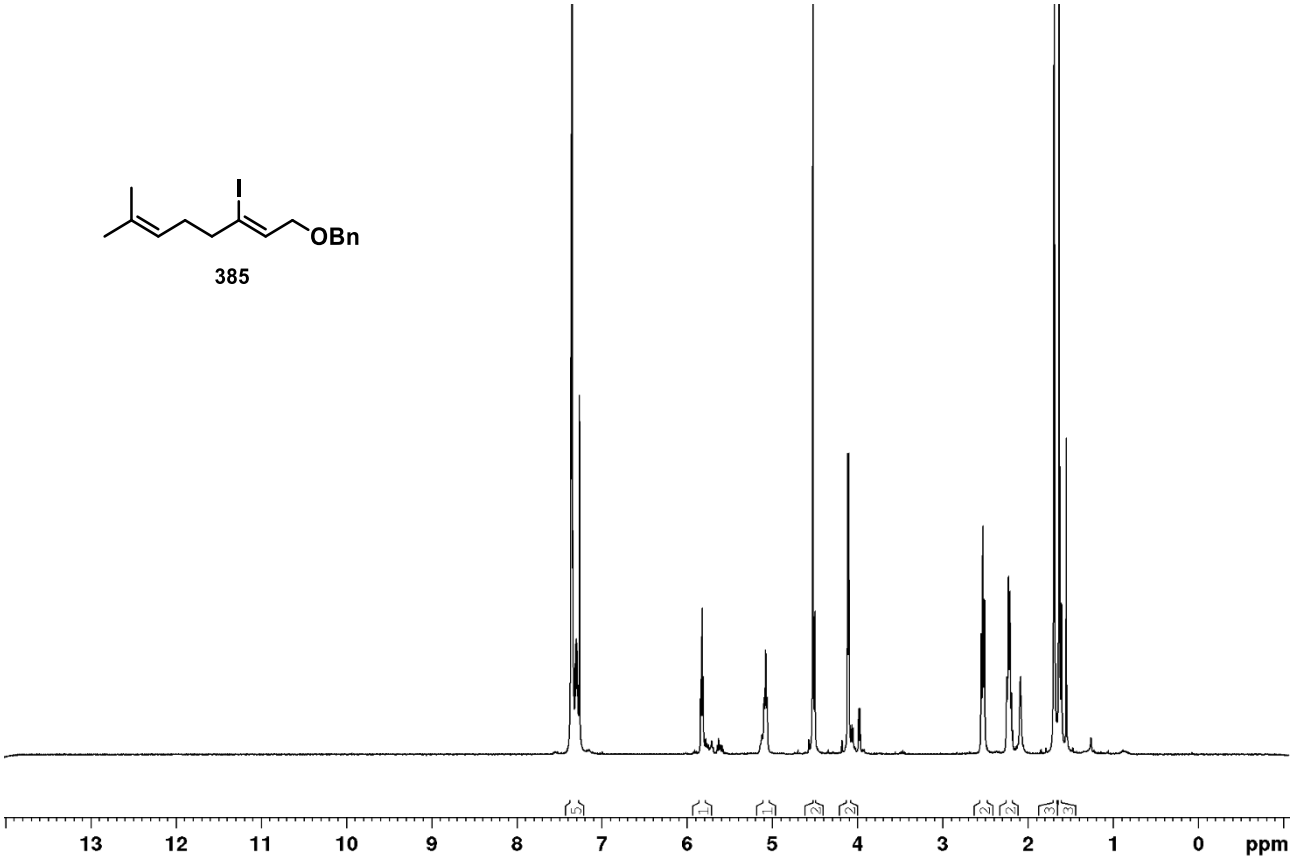
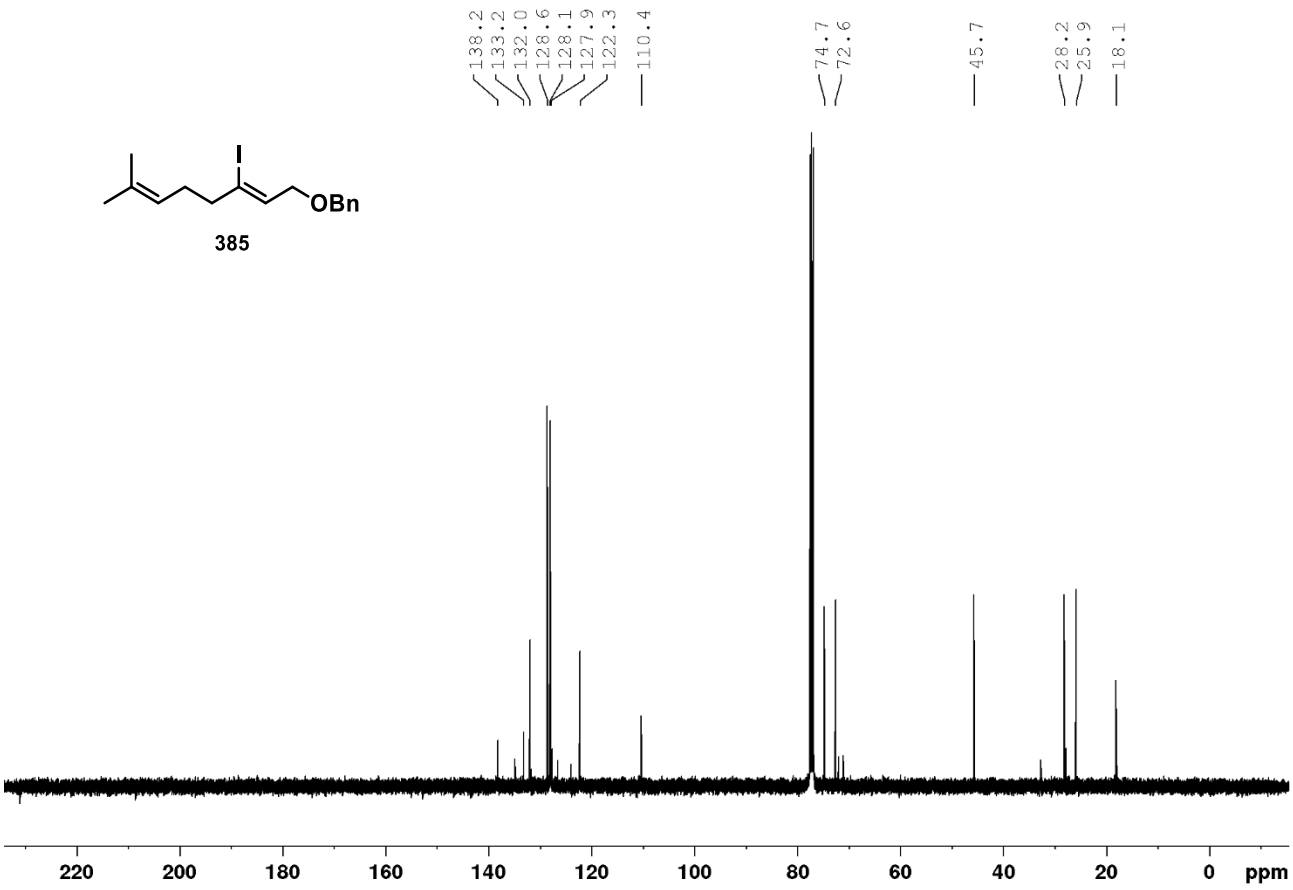
0
ppm


OBn
385
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm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133.2
132.0
128.6
128.1
127.9
122.3
110.4
74.7
72.6
45.7
28.2
25.9
18.1
OBn
385
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200
180
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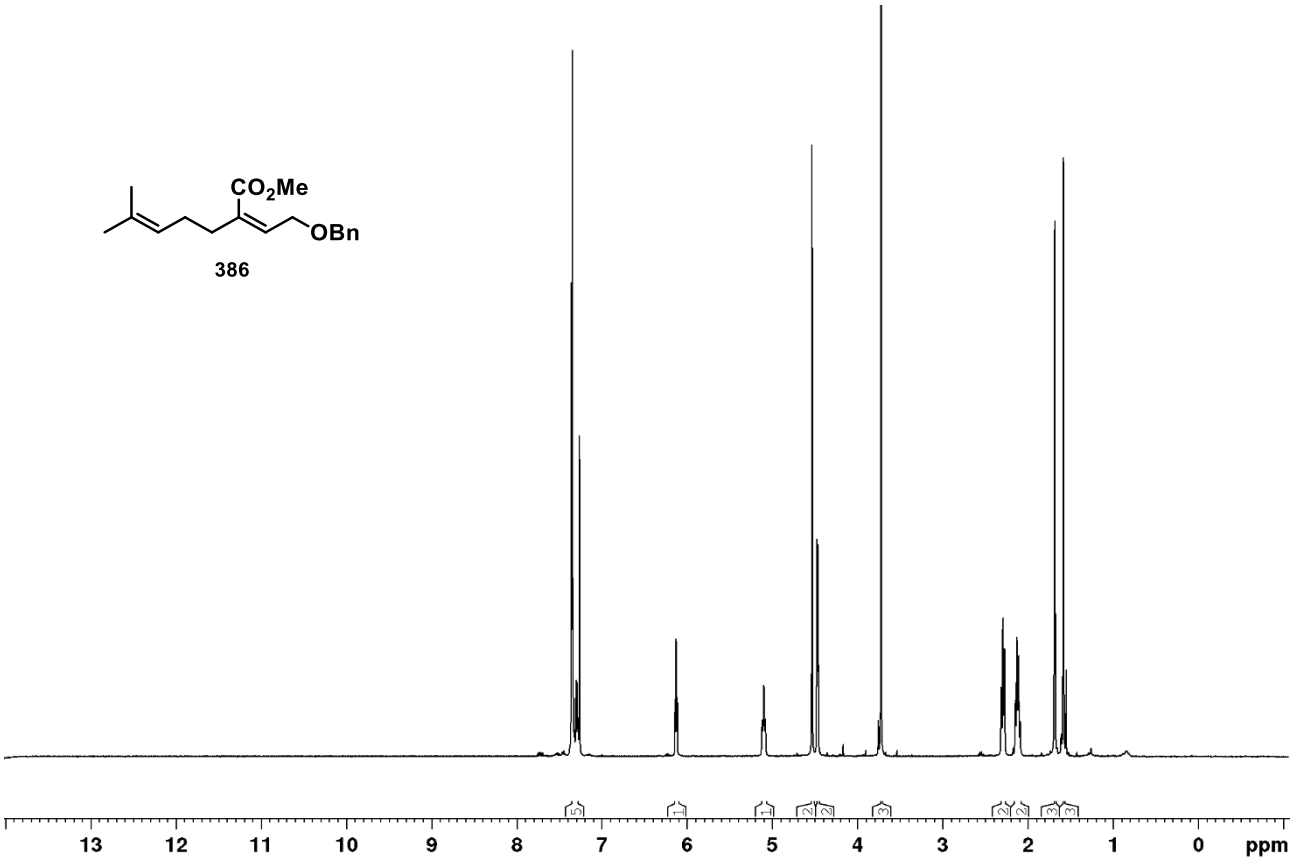
140
120
100
80
60
40
20
0
ppm


CO2Me
OBn
386
13
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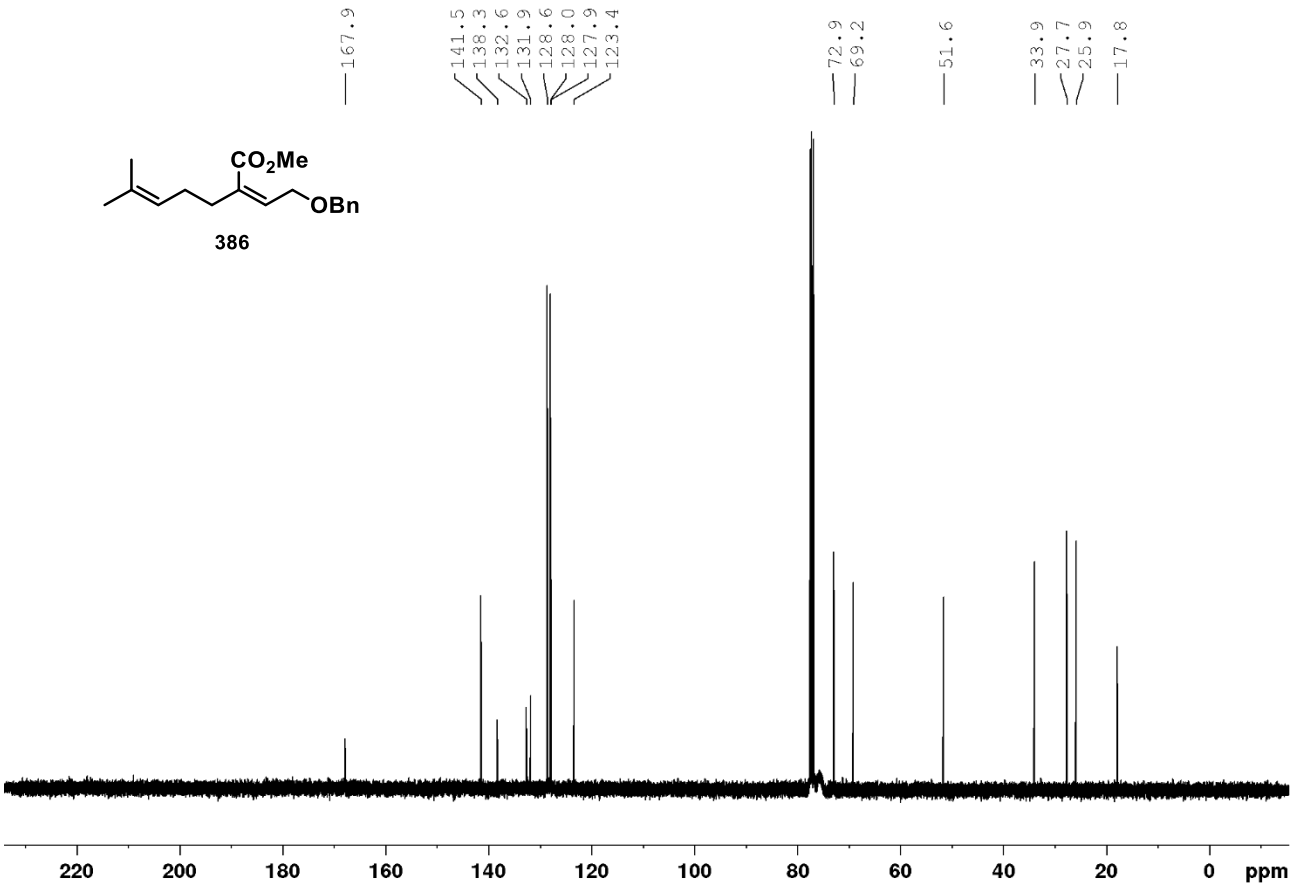
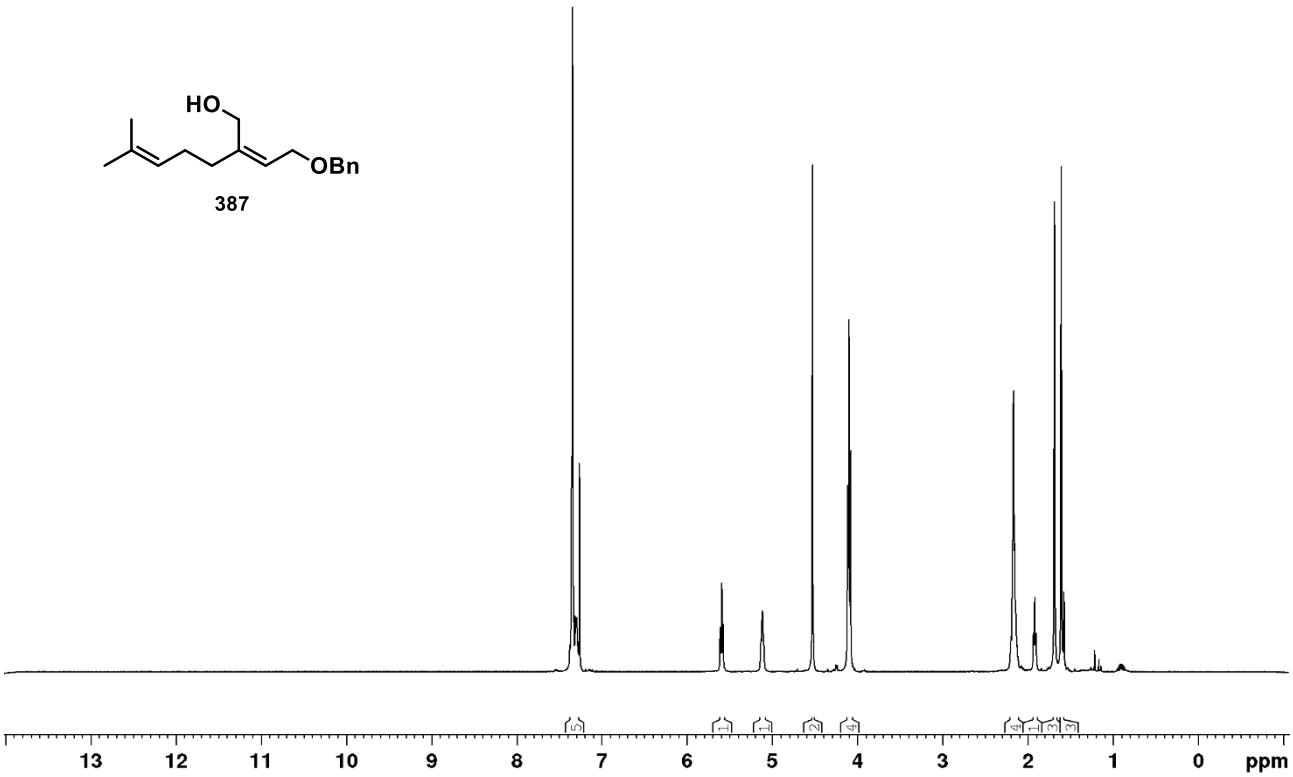
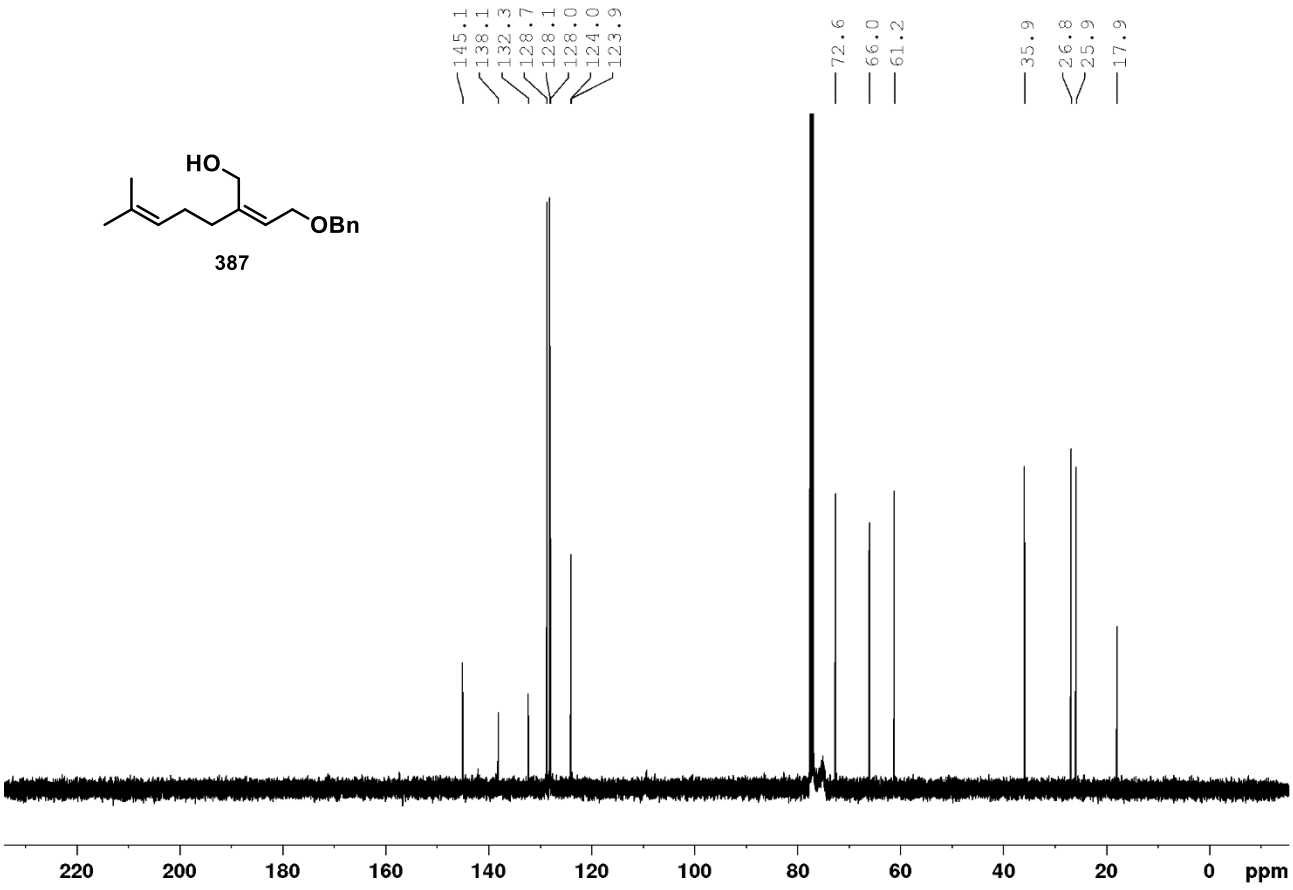
7
6
5
4
3
2
1
0
ppm


167.9
141.5
138.3
132.6
131.9
128.6
128.0
127.9
123.4
72.9
69.2
51.6
33.9
27.7
25.9
17.8
CO2Me
OBn
386
220
200
180
160
140
120
100
80
60
40
20
0
ppm


HO
OBn
387
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm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138.1
132.3
128.7
128.1
128.0
124.0
123.9
72.6
66.0
61.2
35.9
26.8
25.9
17.9
HO
OBn
387
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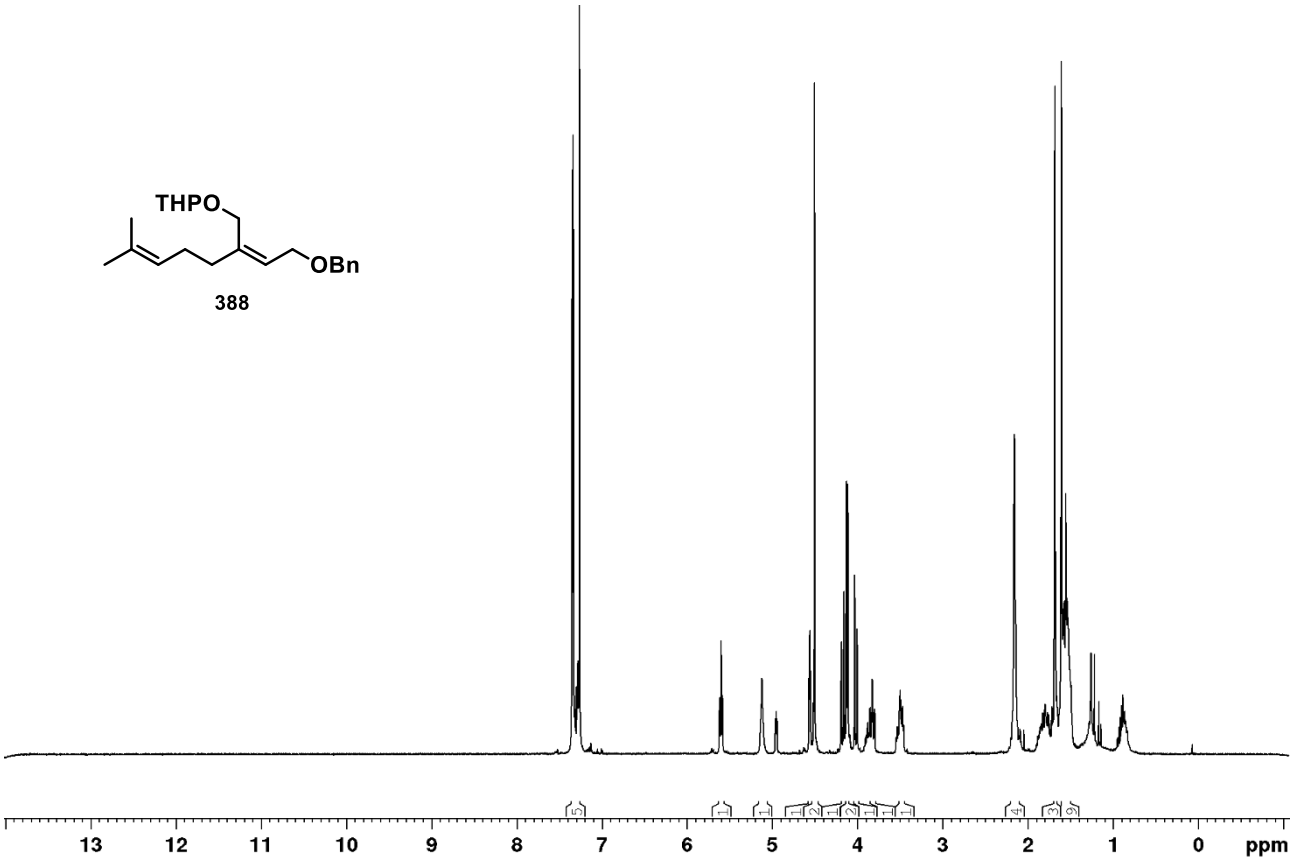
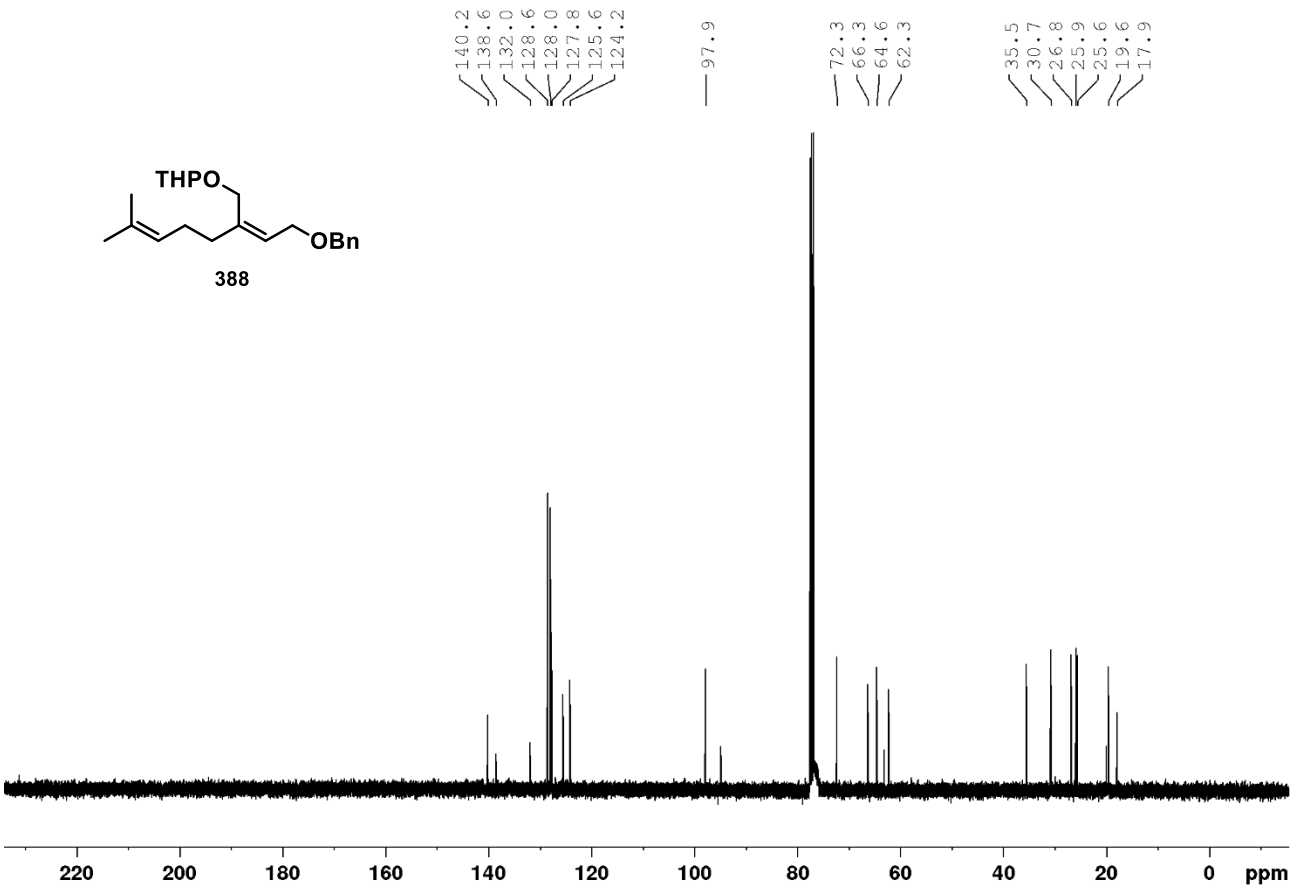
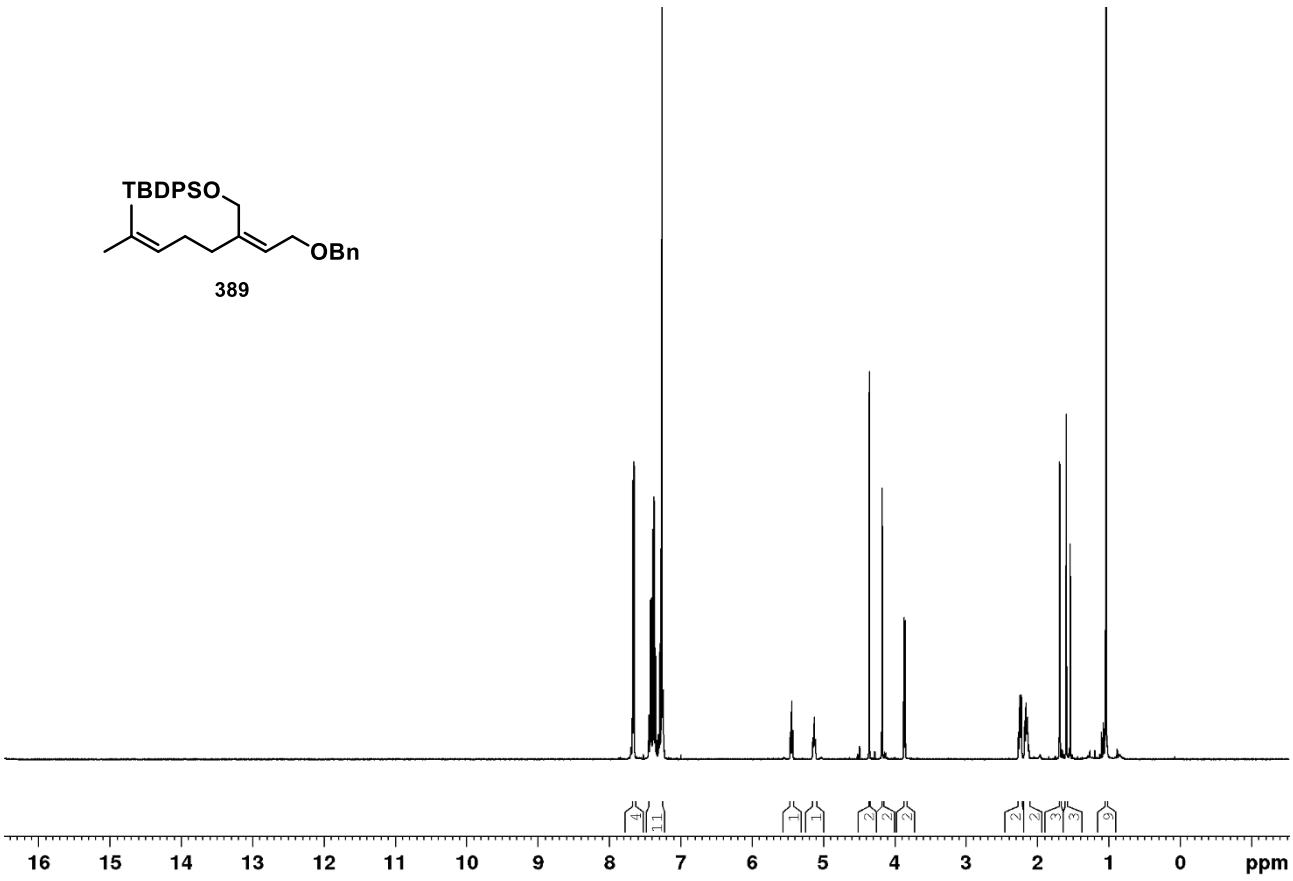
200
180
160
140
120
100
80
60
40
20
0
ppm


THPO
OBn
388
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


140.2
138.6
132.0
128.6
128.0
127.8
125.6
124.2
97.9
72.3
66.3
64.6
62.3
35.5
30.7
26.8
25.9
25.6
19.6
17.9
THPO
OBn
388
220
200
180
160
140
120
100
80
60
40
20
0
ppm


TBDPSO
OBn
389
4
11
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2
2
2
2
2
3
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14
13
12
11
10
9
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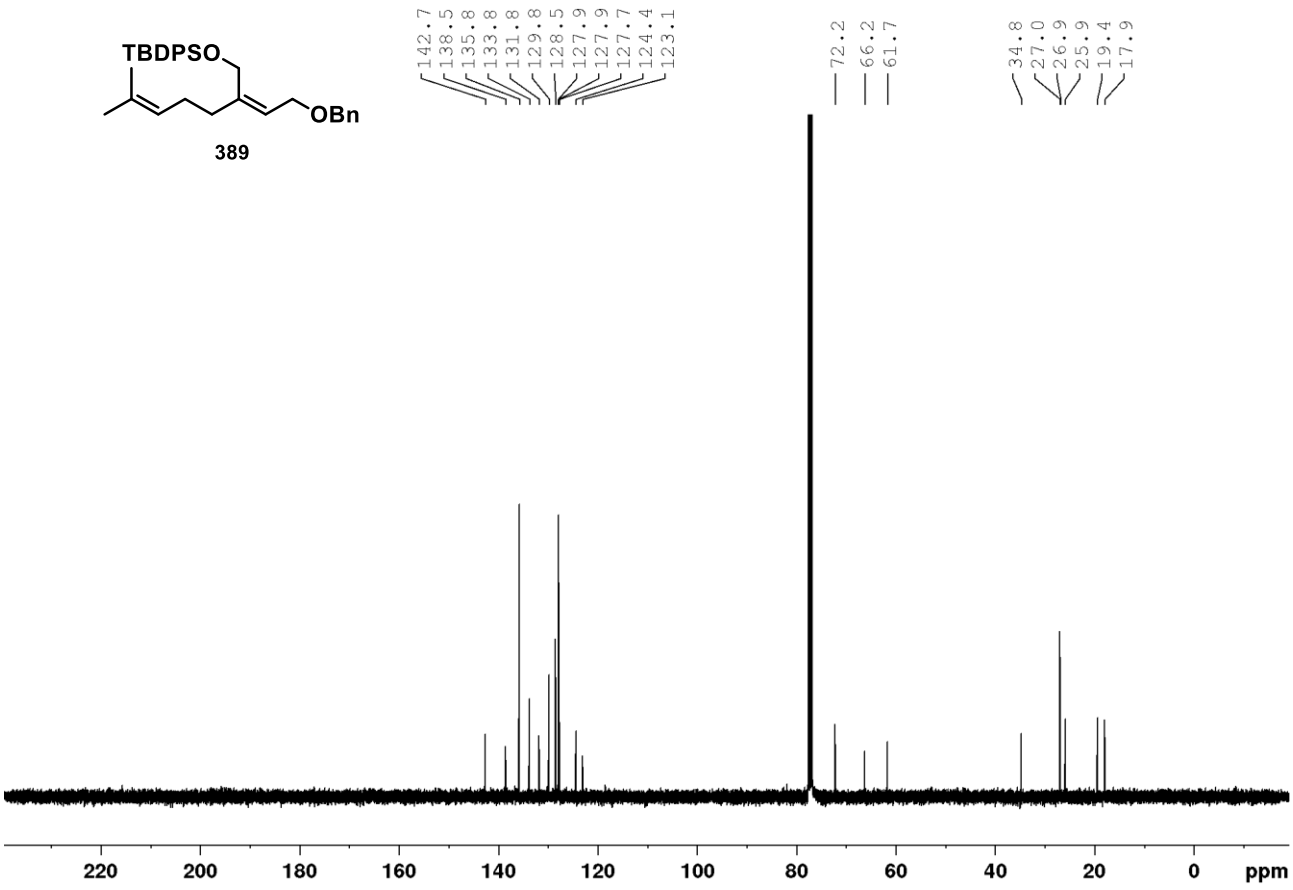
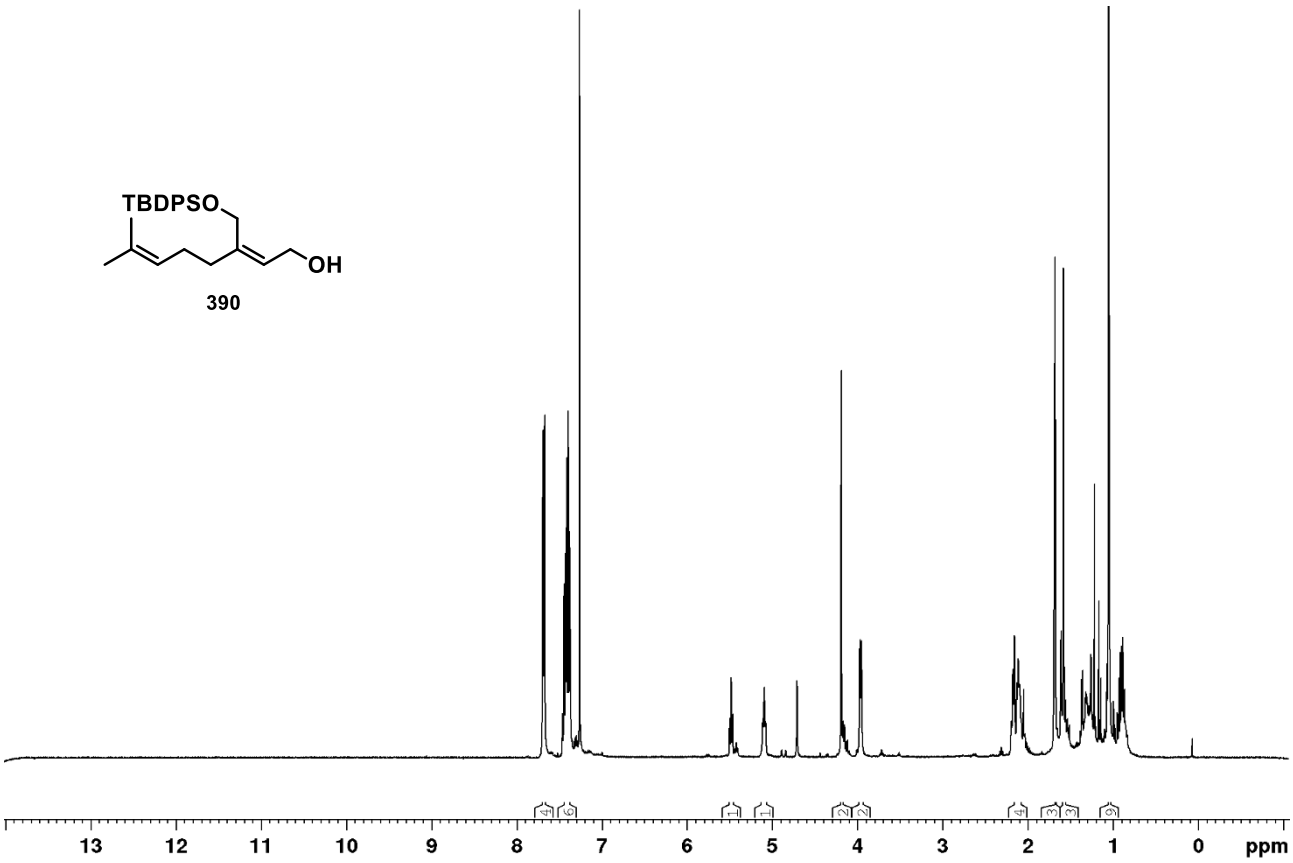
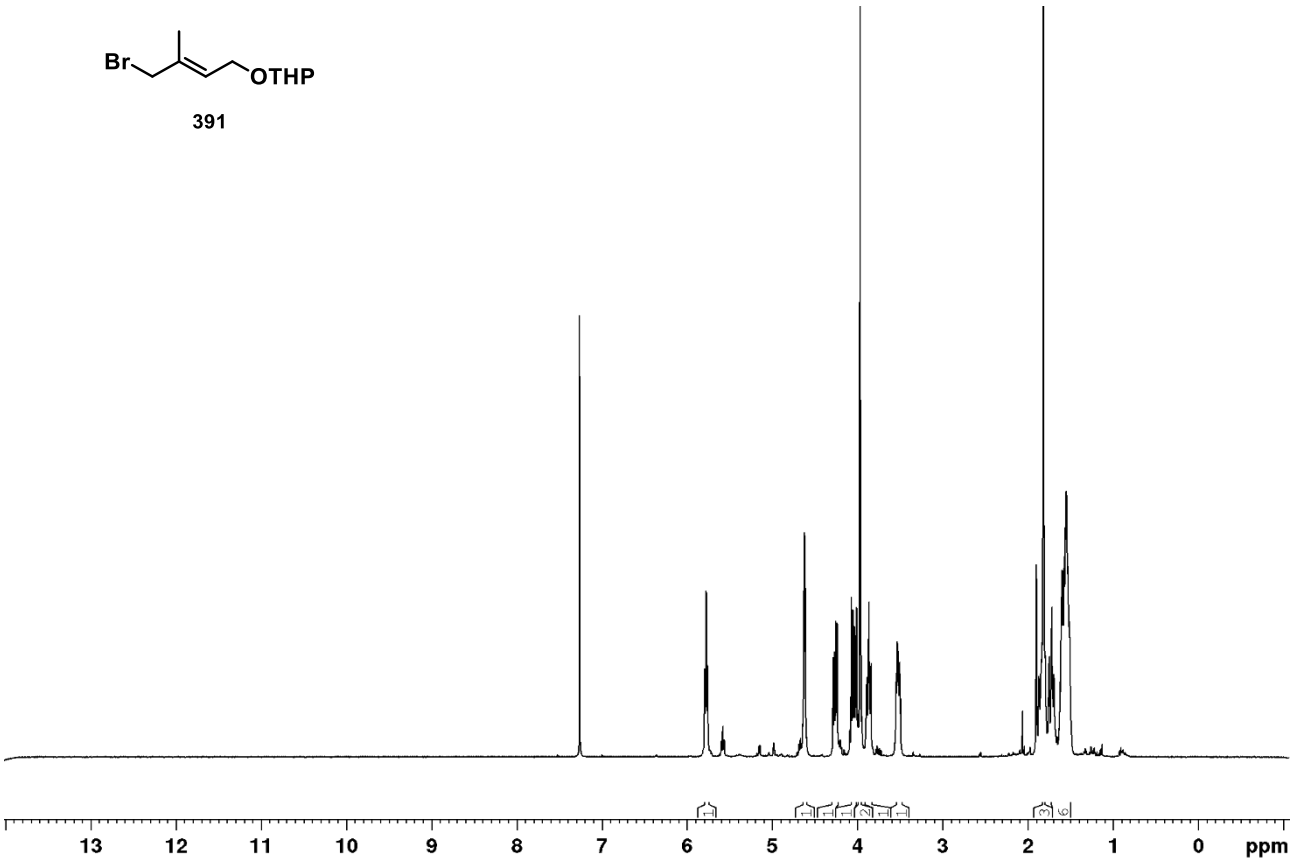
6
5
4
3
2
1
0
ppm


TBDPSO
OBn
389
142.7
138.5
135.8
133.8
131.8
129.8
128.5
127.9
127.9
127.7
124.4
123.1
72.2
66.2
61.7
34.8
27.0
26.9
25.9
19.4
17.9
220
200
180
160
140
120
100
80
60
40
20
0
ppm


TBDPSO
OH
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

390


Br
OTHP
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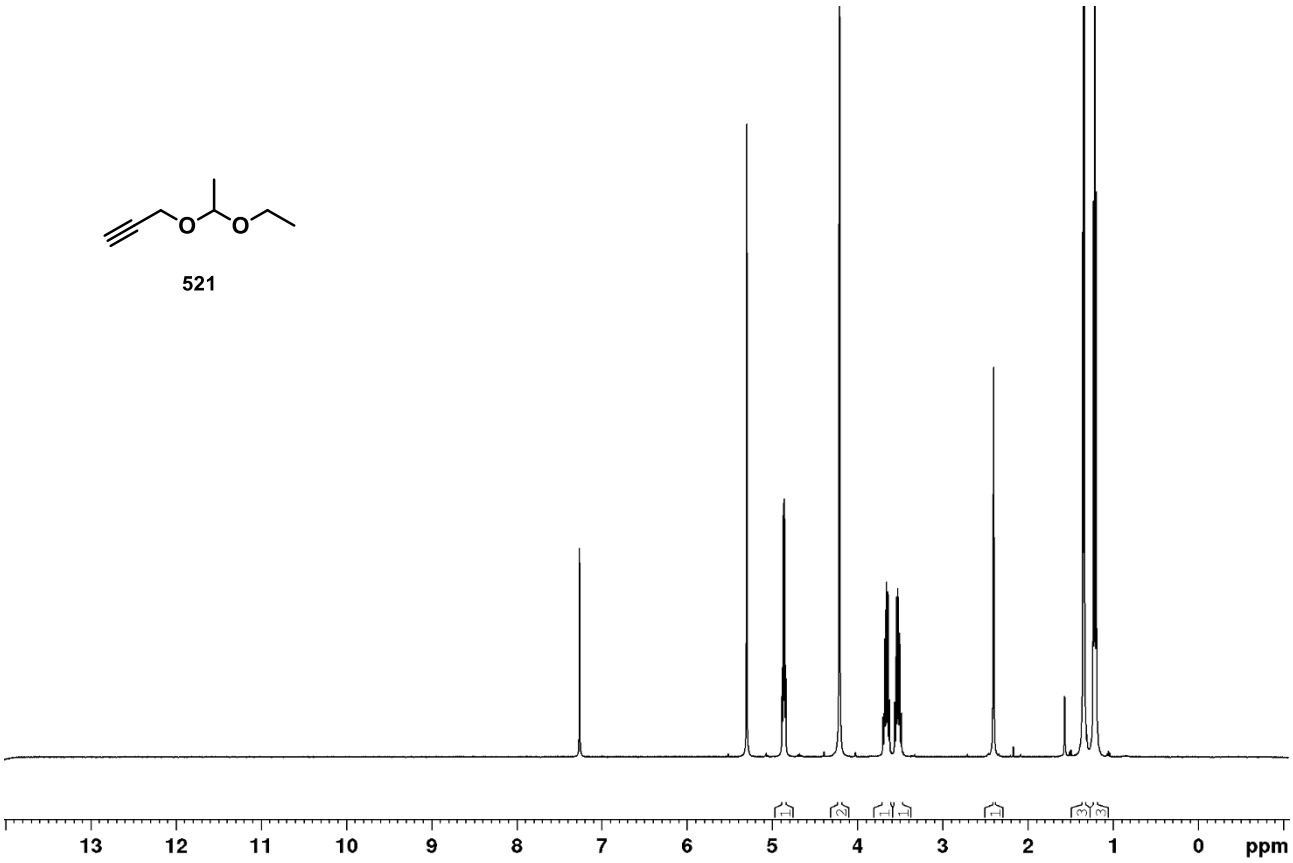
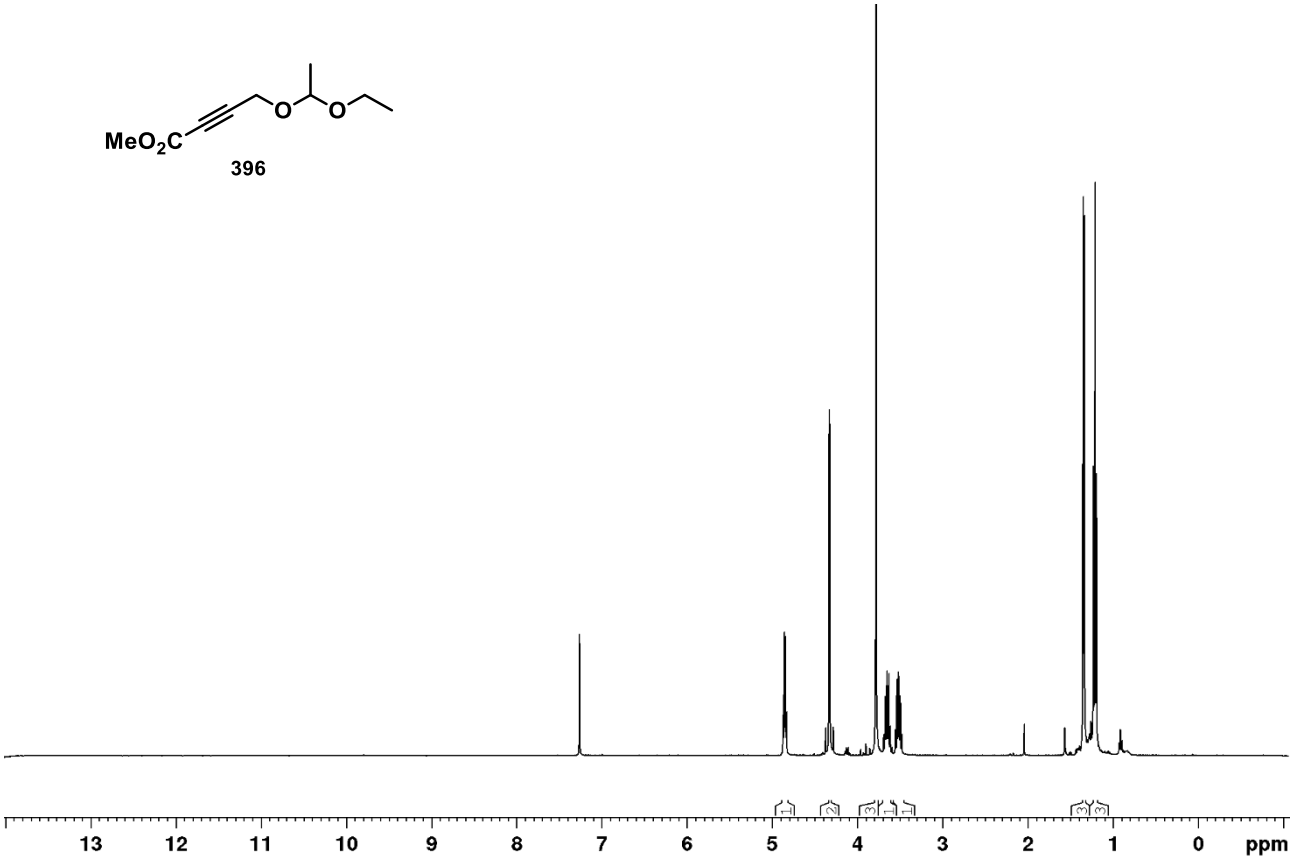
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

391


O
O
521
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


MeO2C
O
O
396
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12
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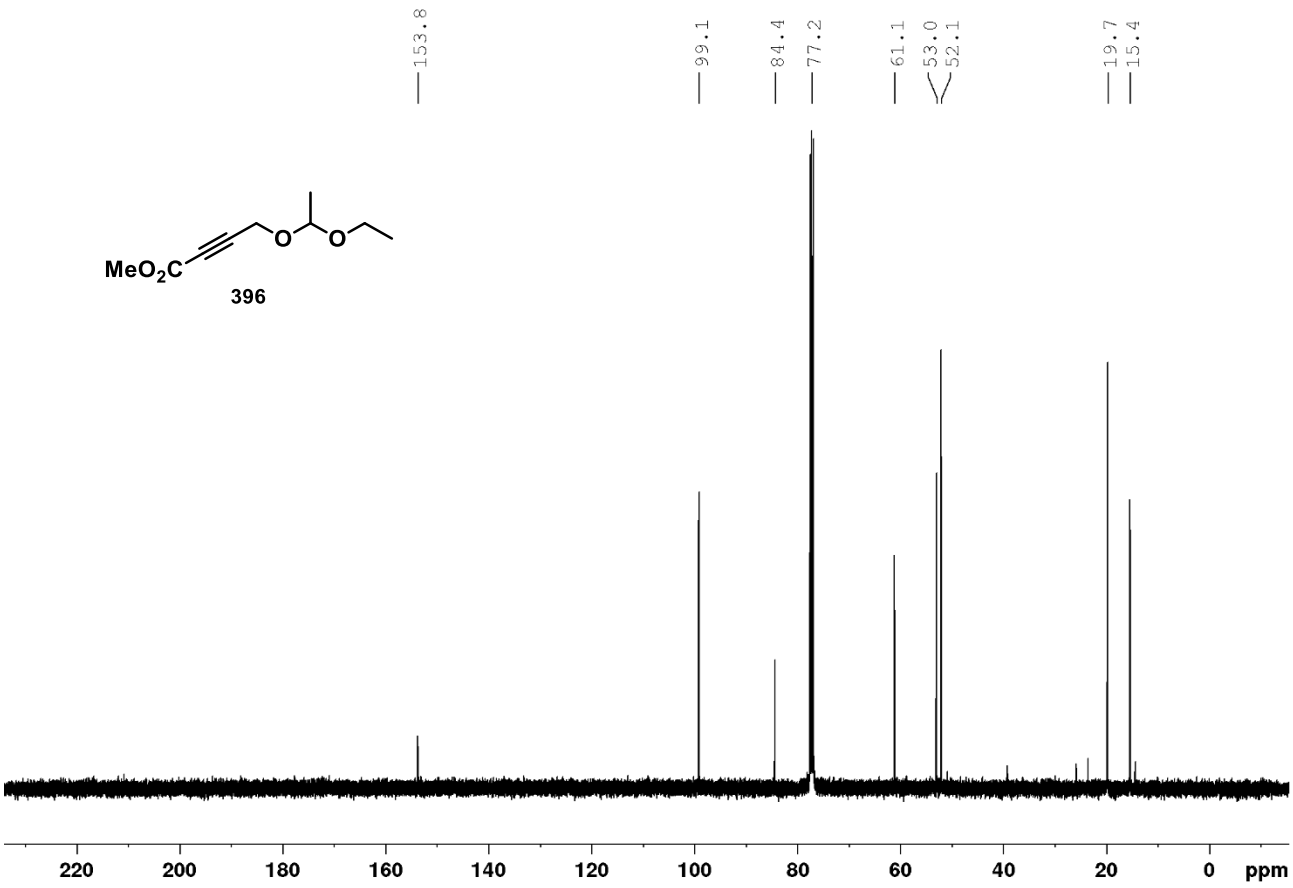
9
8
7
6
5
4
3
2
1
0
ppm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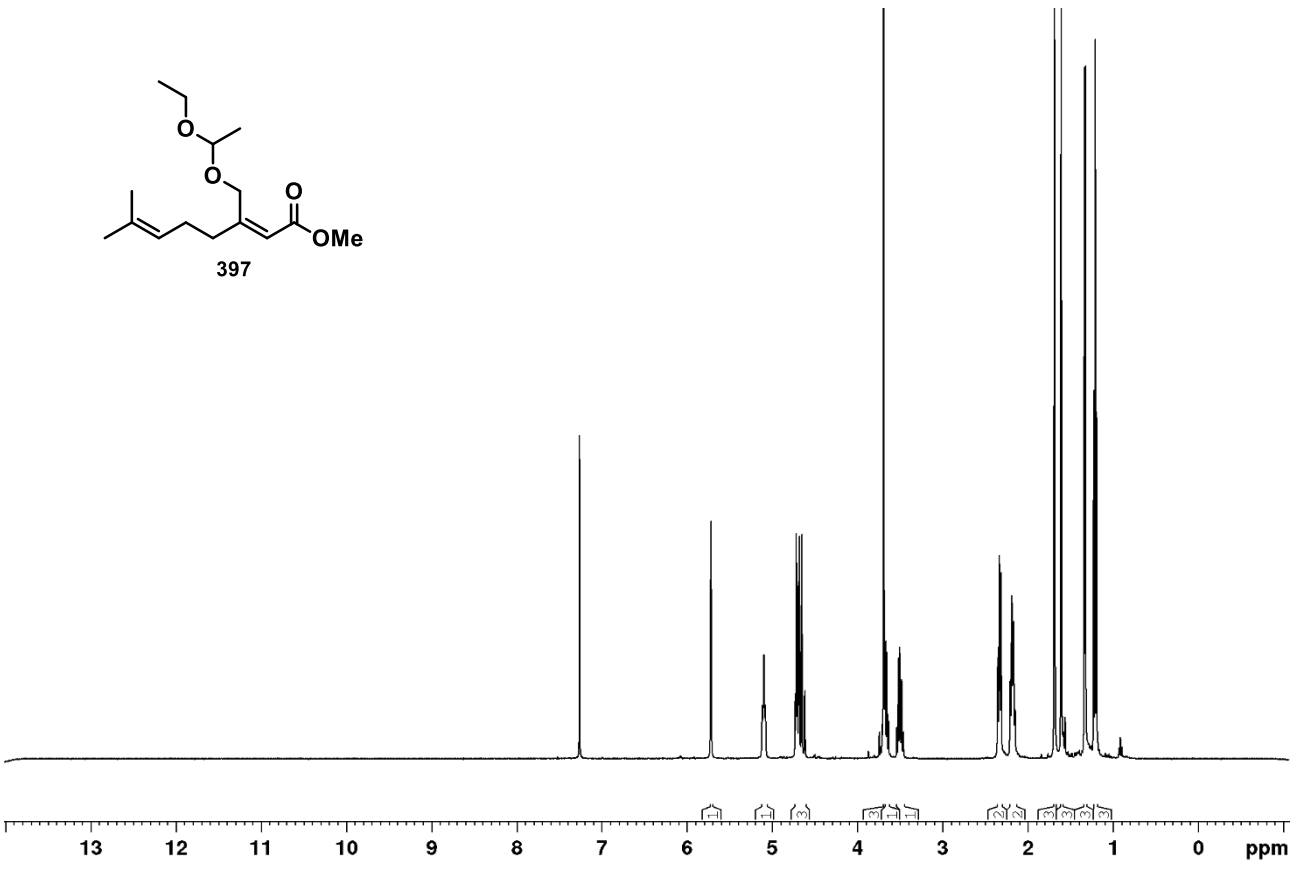
99.1
84.4
77.2
61.1
53.0
52.1
19.7
15.4
MeO2C
O
O
220
200
180
160
140
120
100
80
60
40
20
0
ppm

396


O
O
O
OMe
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11
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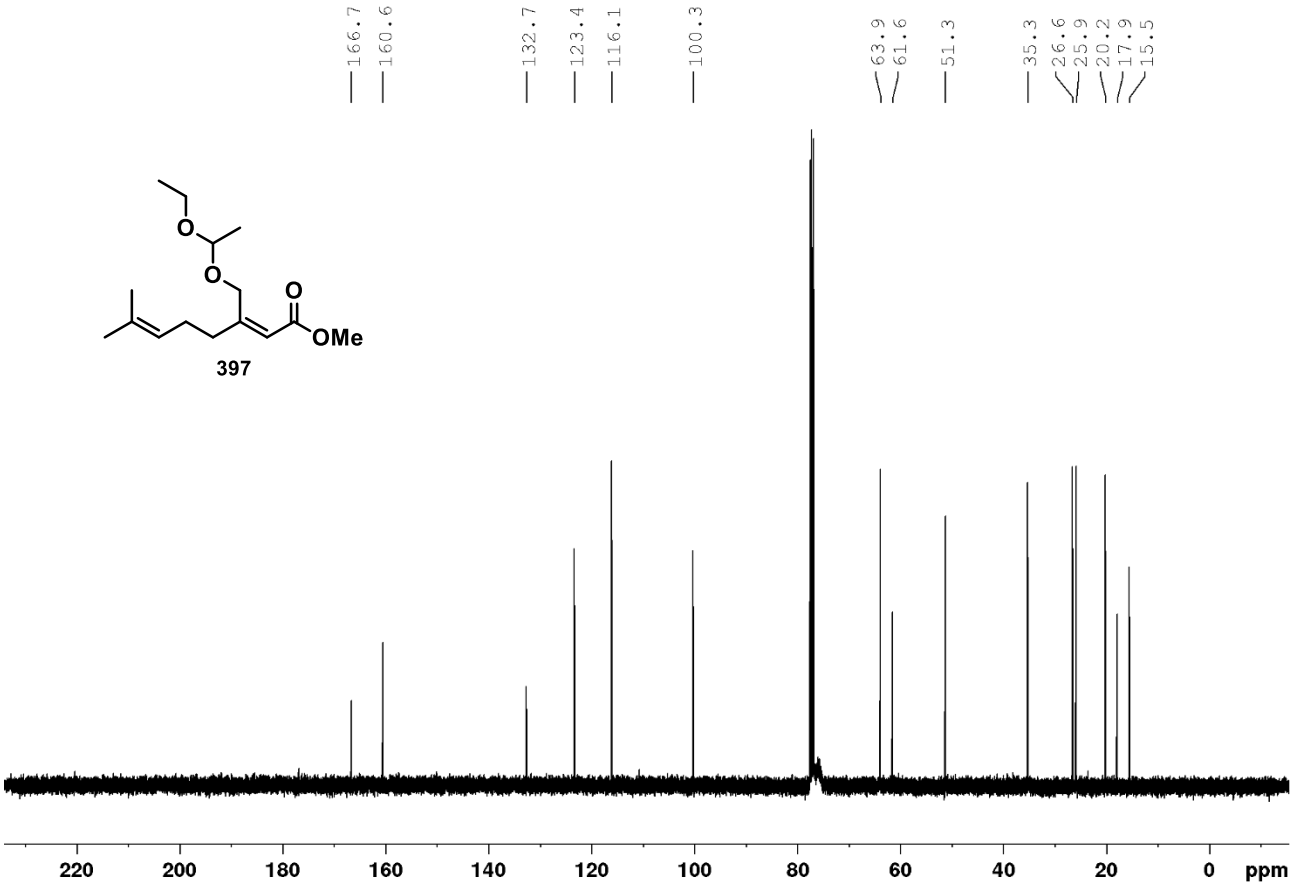
9
8
7
6
5
4
3
2
1
0
ppm

397


166.7
160.6
132.7
123.4
116.1
100.3
63.9
61.6
51.3
35.3
26.6
25.9
20.2
17.9
15.5
O
O
O
OMe
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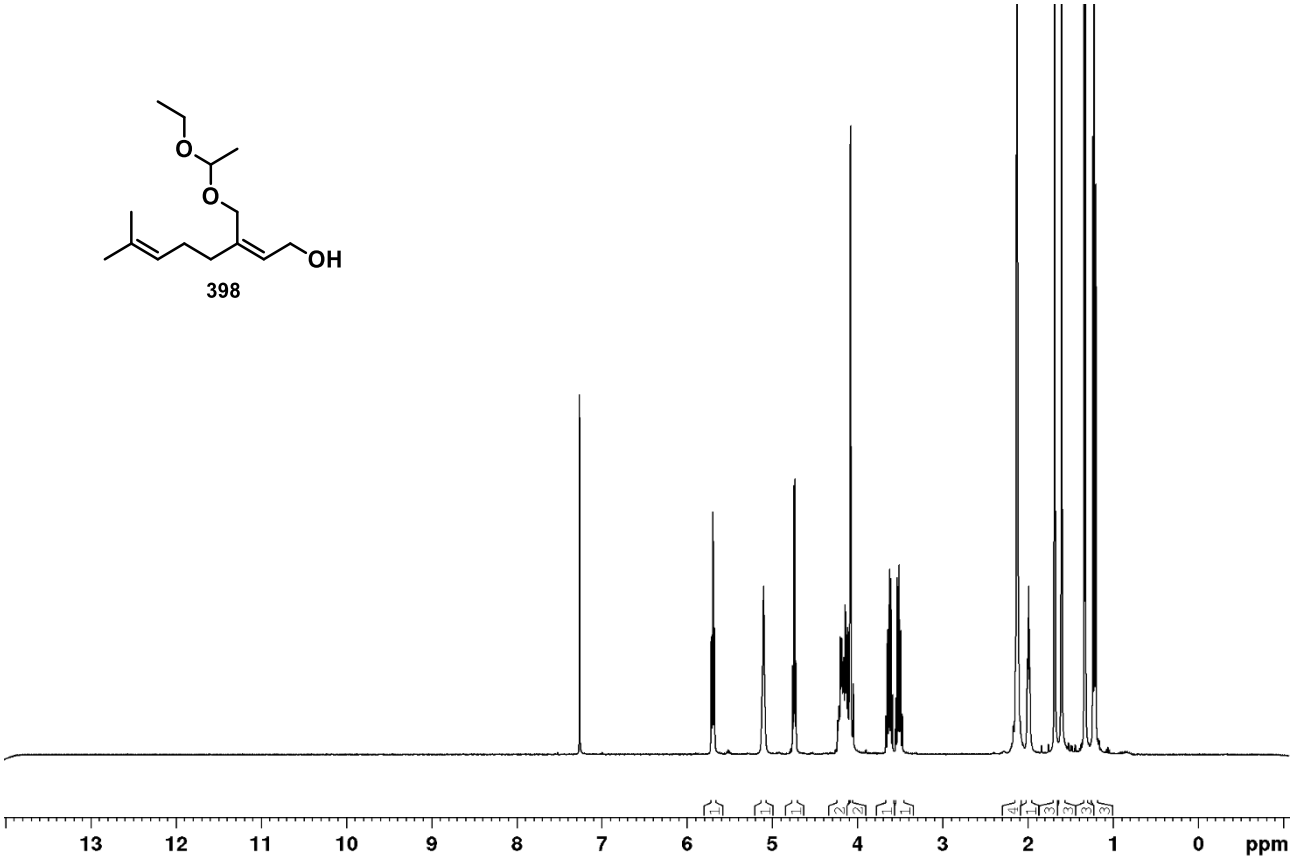
200
180
160
140
120
100
80
60
40
20
0
ppm

397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O
OH
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12
11
10
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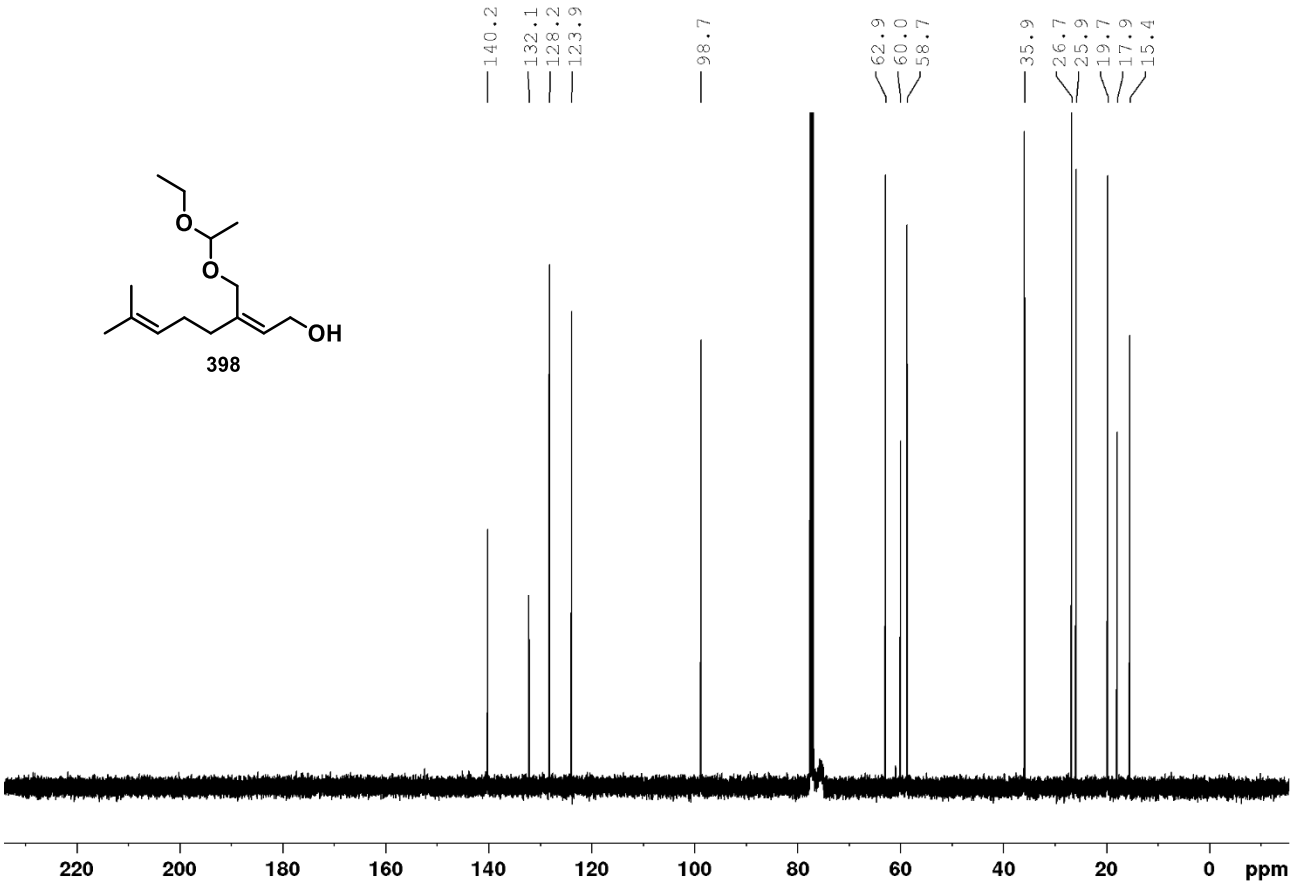
8
7
6
5
4
3
2
1
0
ppm

398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132.1
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123.9
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62.9
60.0
58.7
35.9
26.7
25.9
19.7
17.9
15.4
O
O
OH
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200
180
160
140
120
100
80
60
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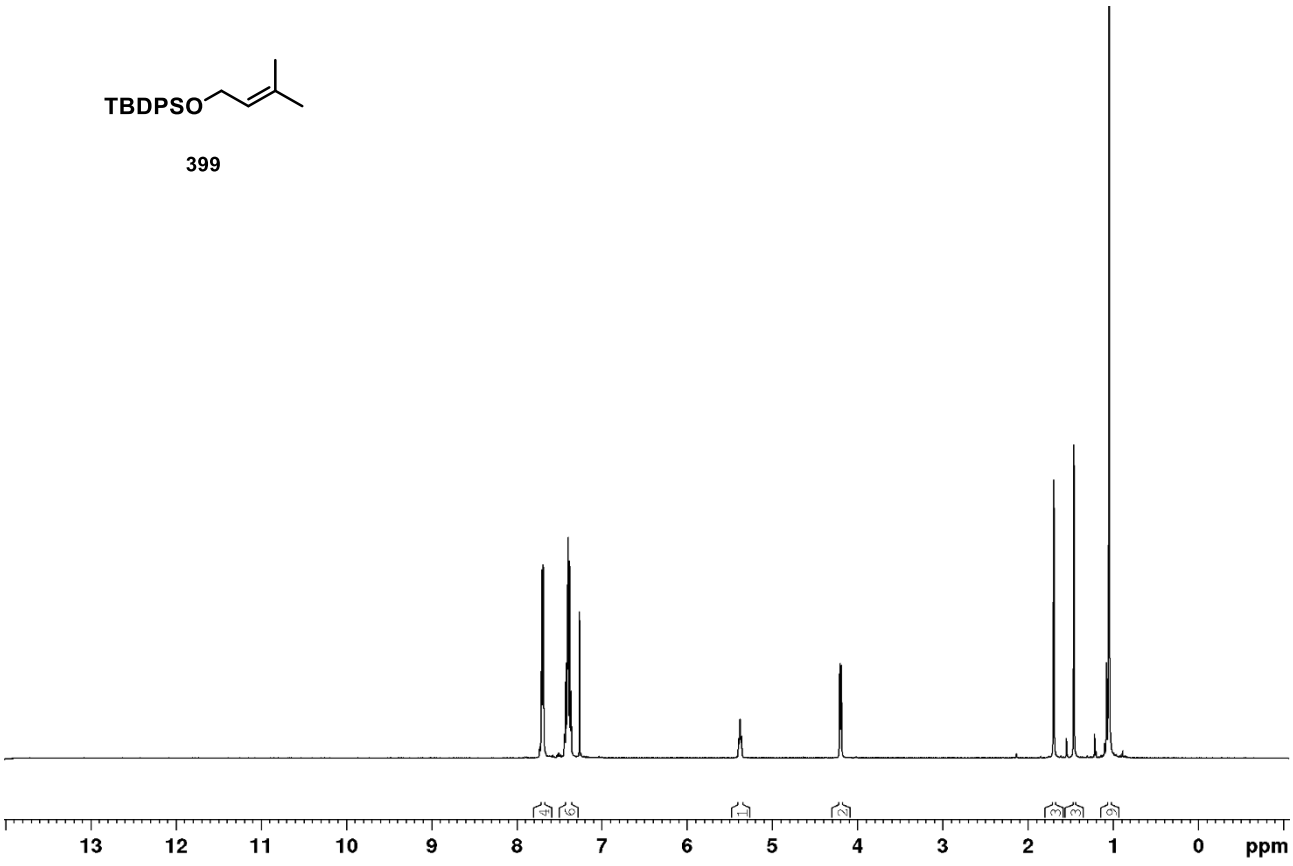
20
0
ppm

398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5
4
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2
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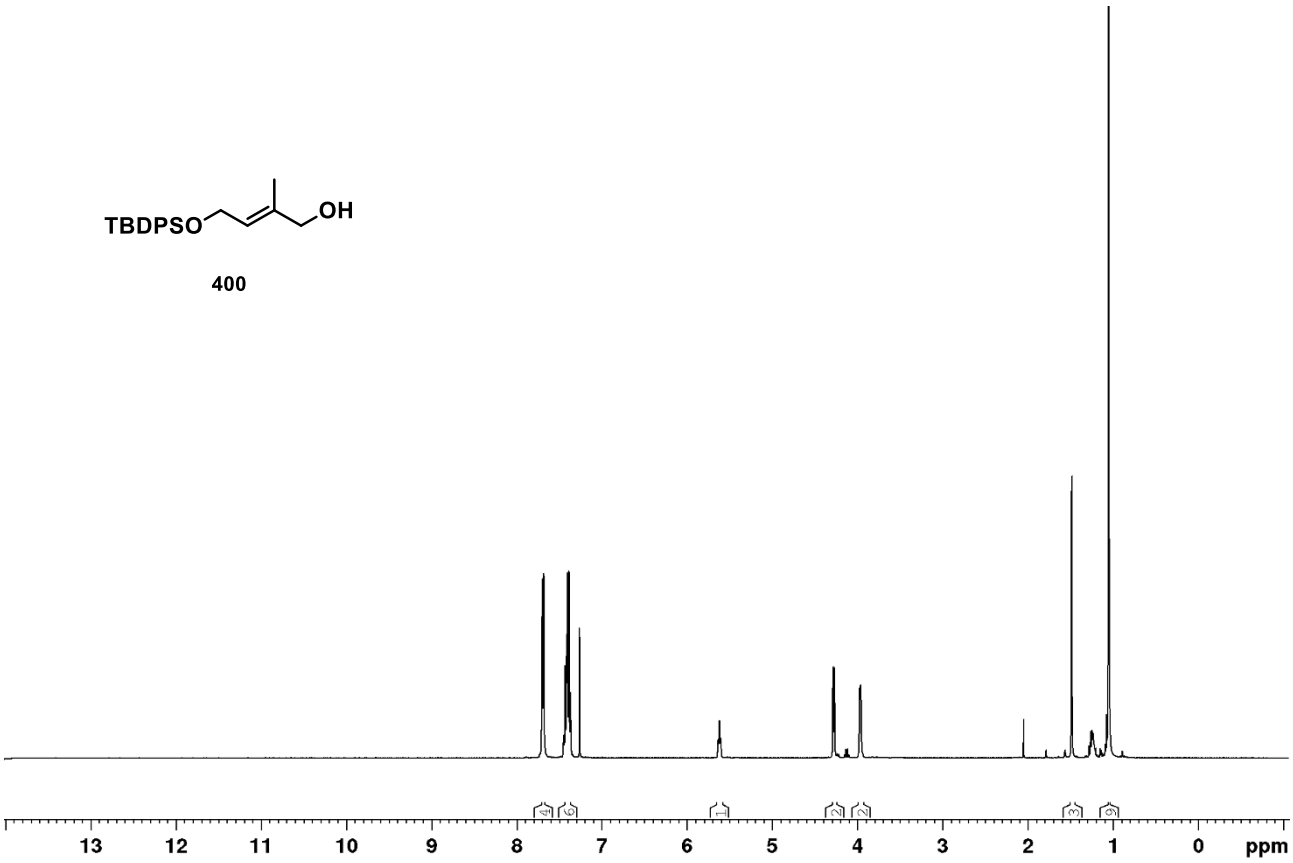
0
ppm

399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OH
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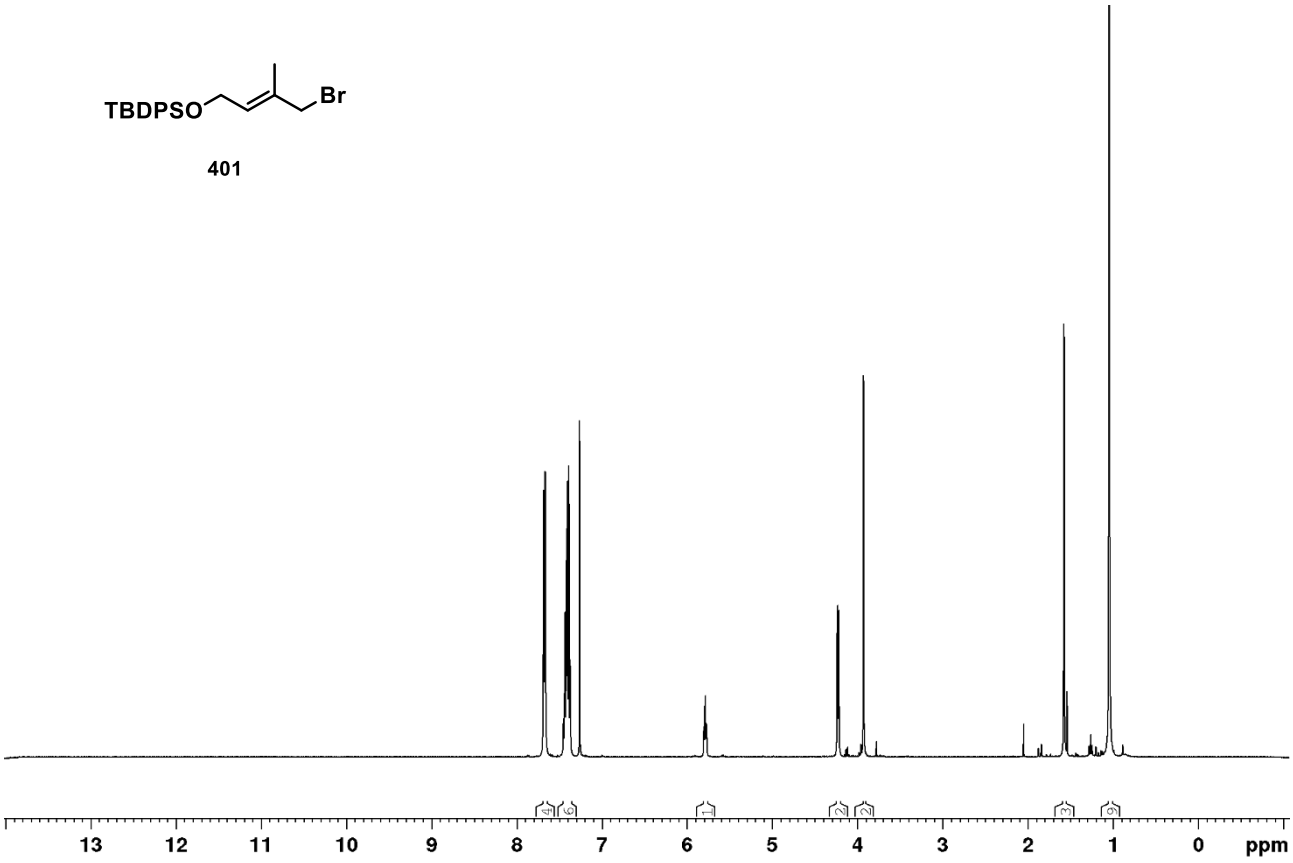
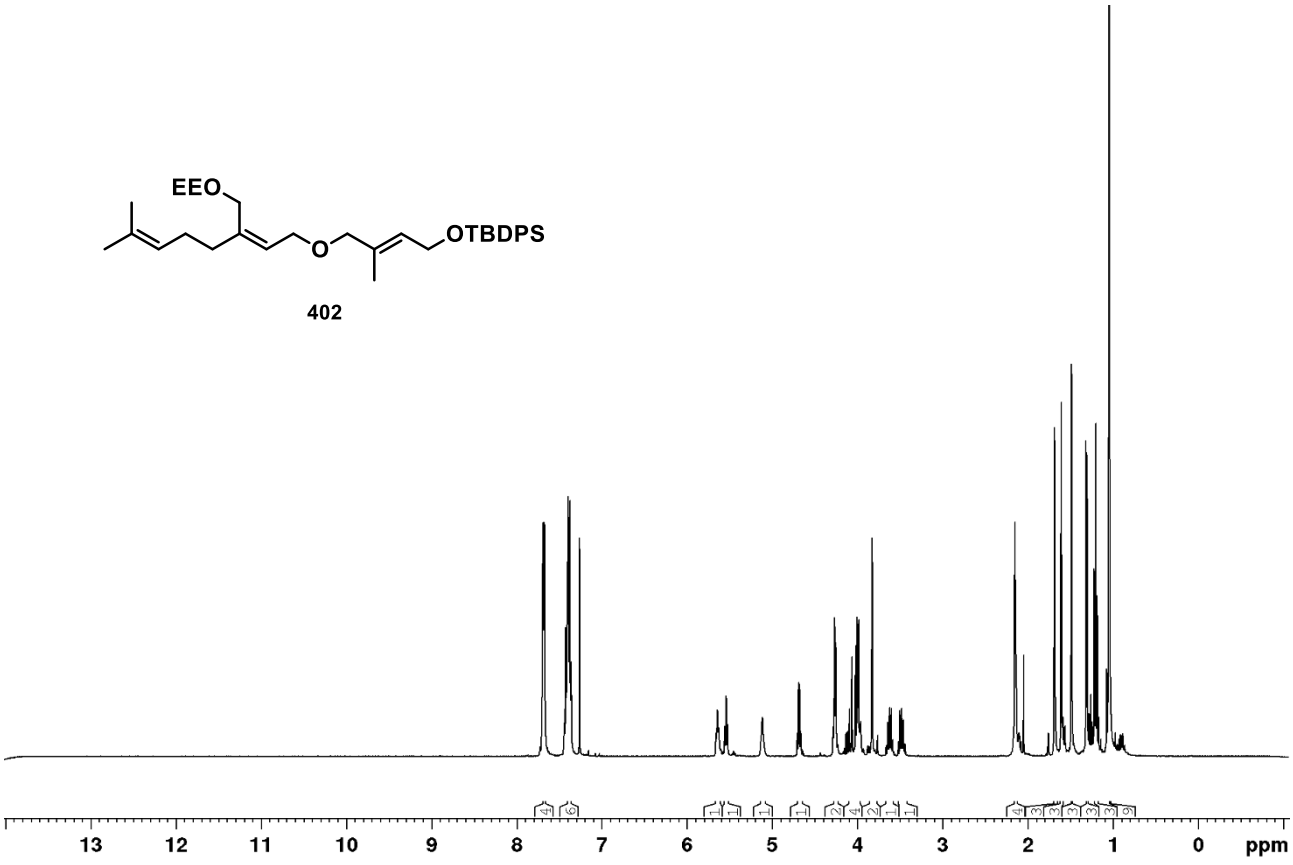
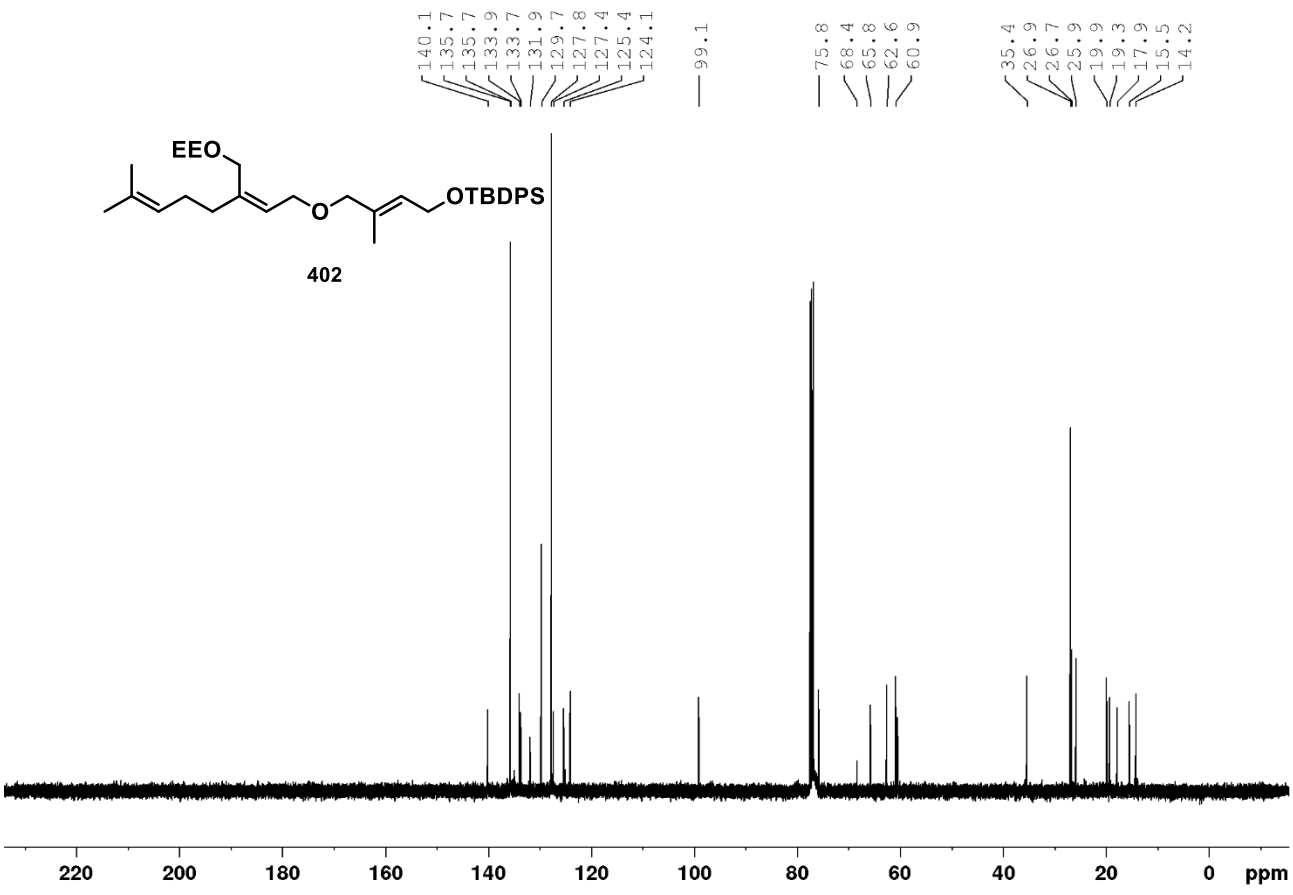
6
5
4
3
2
1
0
ppm


TBDPSO
Br
401
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


EEO
OTBDPS
O
402
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm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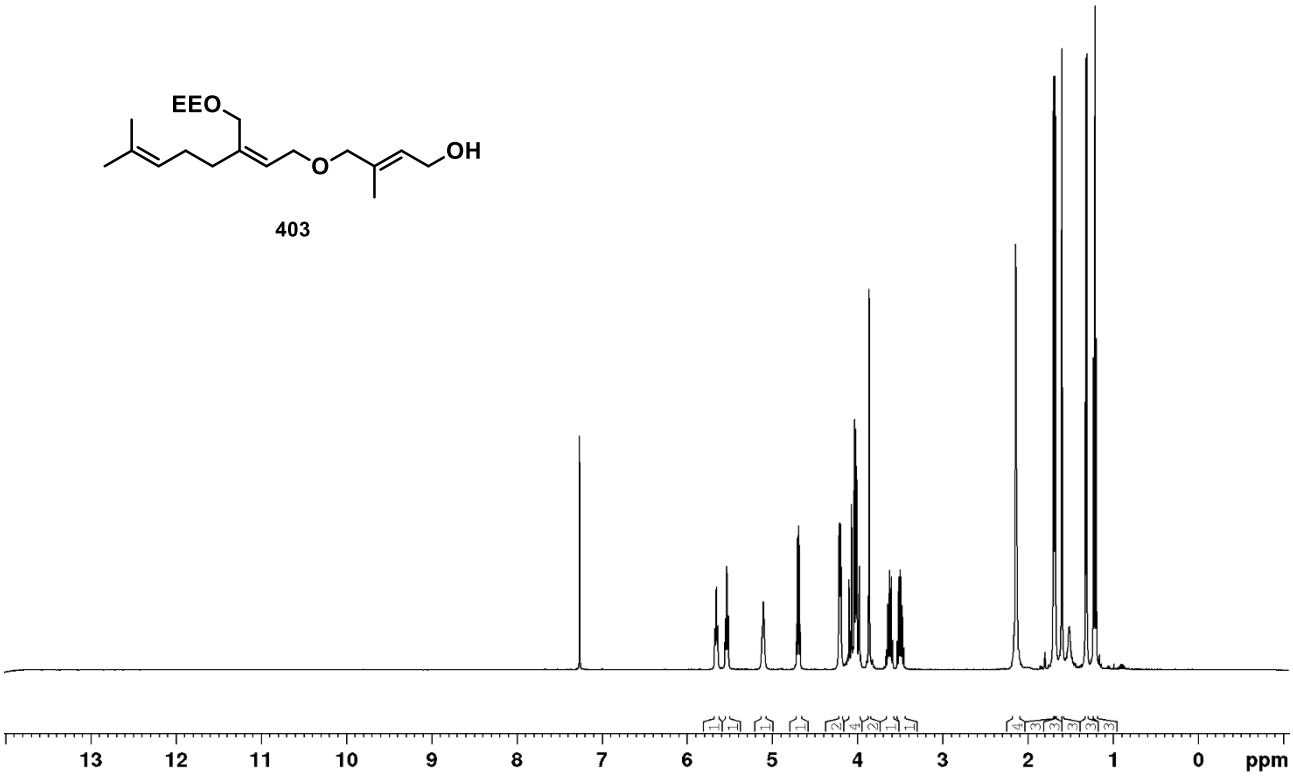
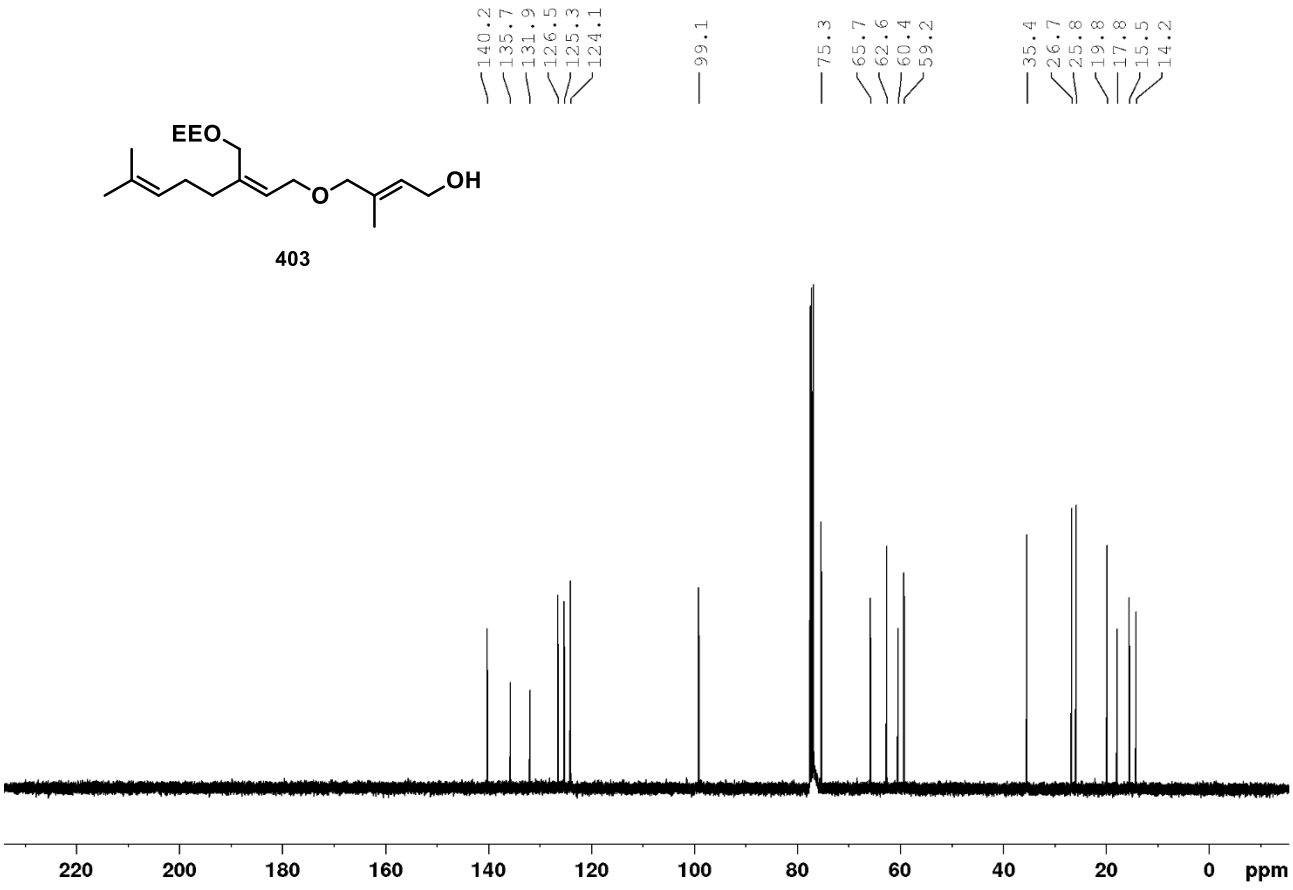
135.7
135.7
133.9
133.7
131.9
129.7
127.8
127.4
125.4
124.1
99.1
75.8
68.4
65.8
62.6
60.9
35.4
26.9
26.7
25.9
19.9
19.3
17.9
15.5
14.2
EEO
OTBDPS
O
402
220
200
180
160
140
120
100
80
60
40
20
0
ppm


EEO
O
OH
403
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm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135.7
131.9
126.5
125.3
124.1
99.1
75.3
65.7
62.6
60.4
59.2
35.4
26.7
25.8
19.8
17.8
15.5
14.2
EEO
O
OH
403
220
200
180
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140
120
100
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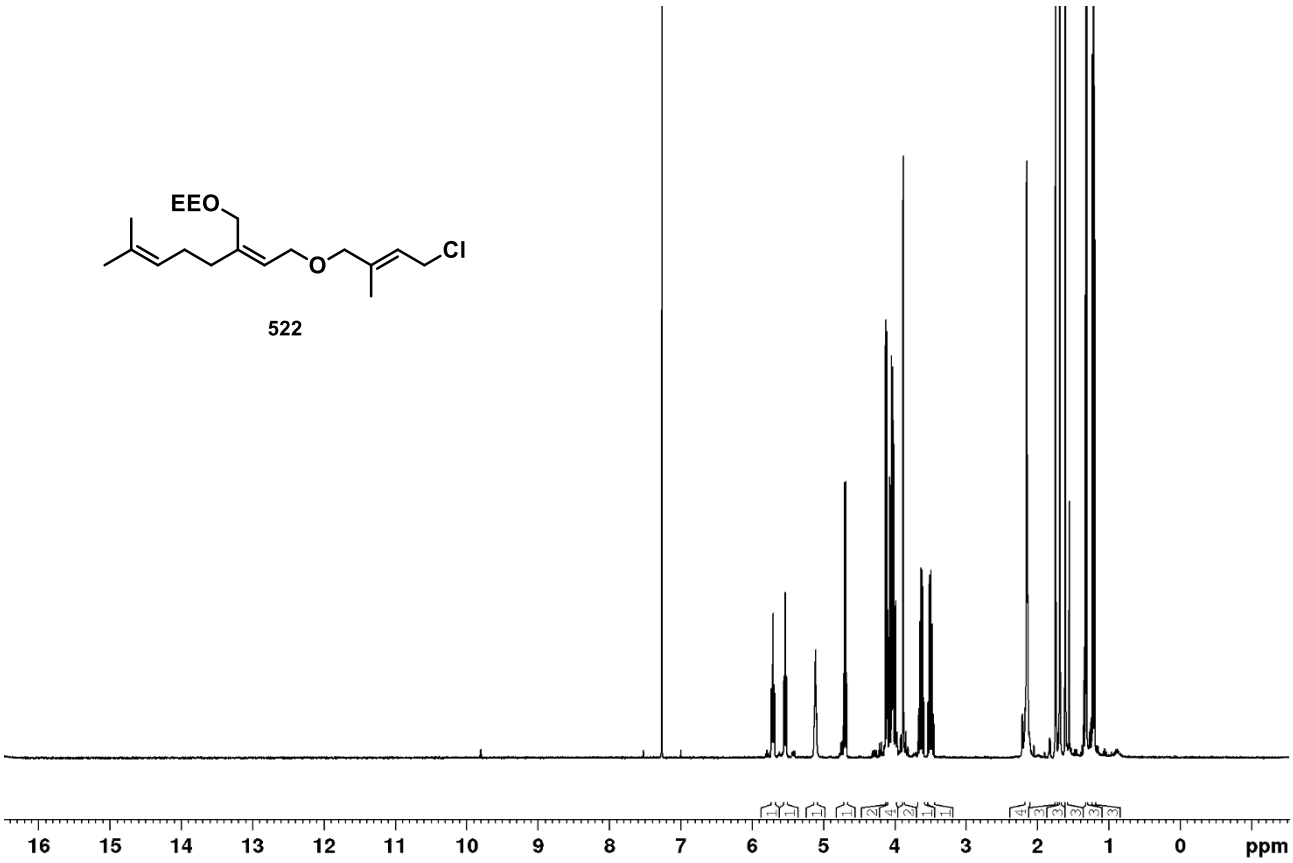
40
20
0
ppm


EEO
O
Cl
522
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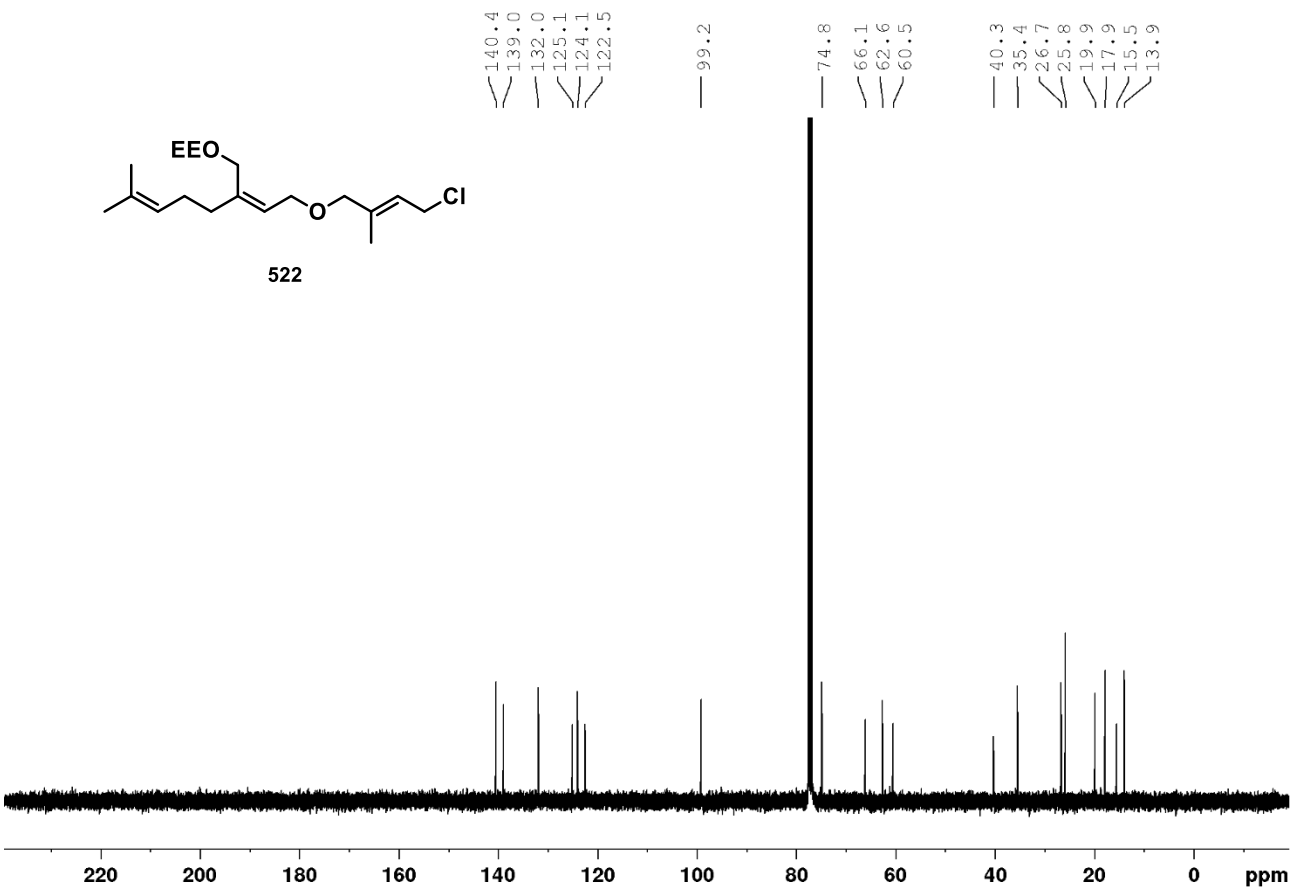
11
10
9
8
7
6
5
4
3
2
1
0
ppm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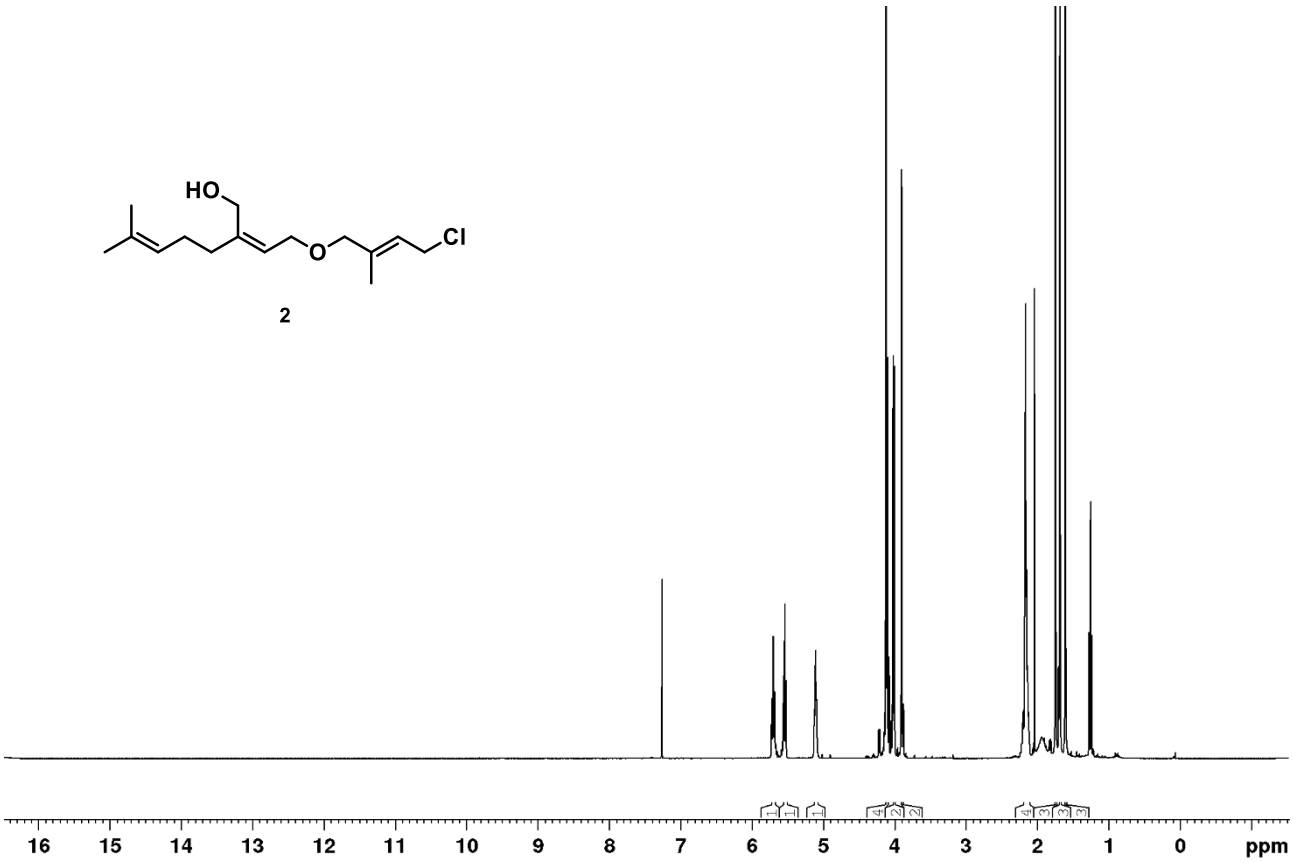
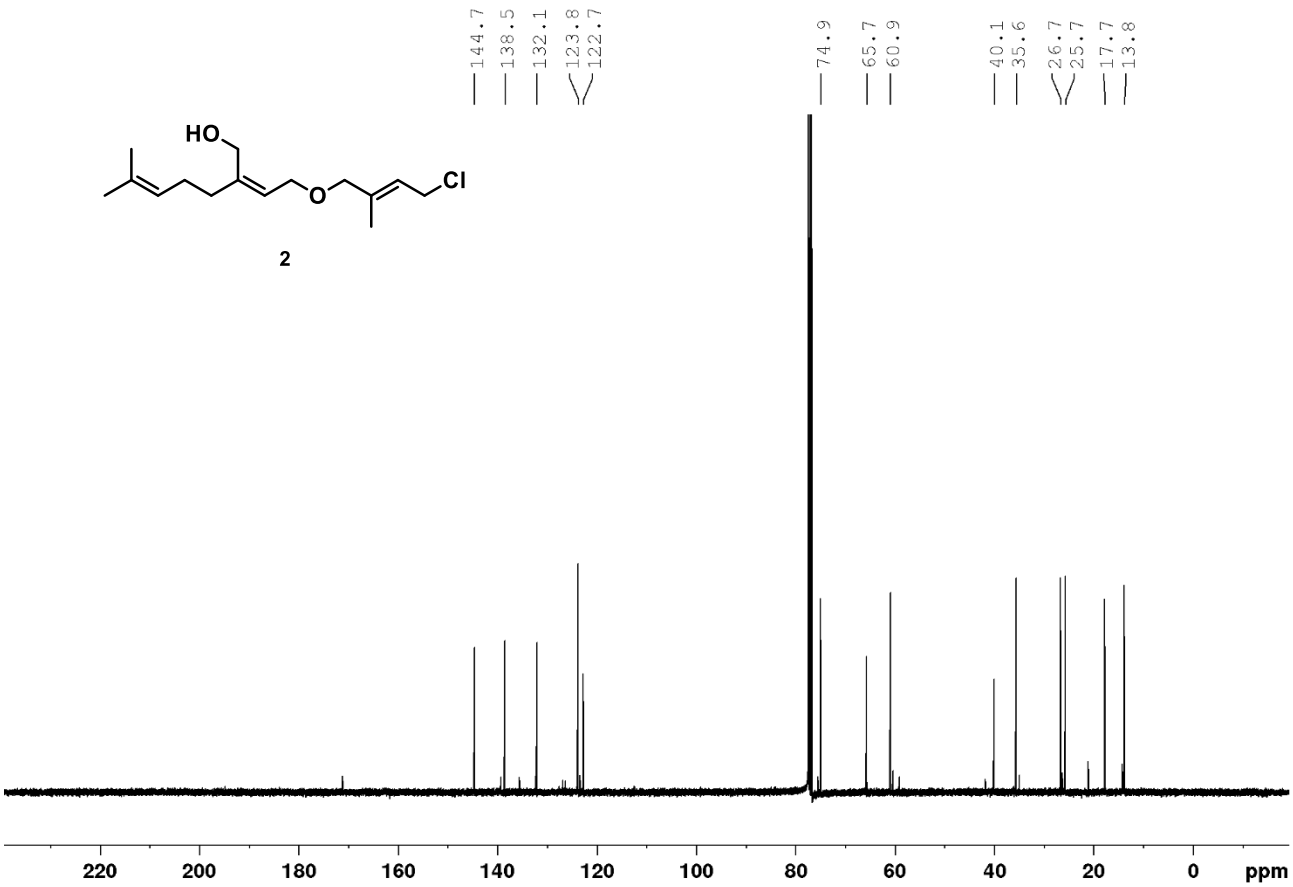
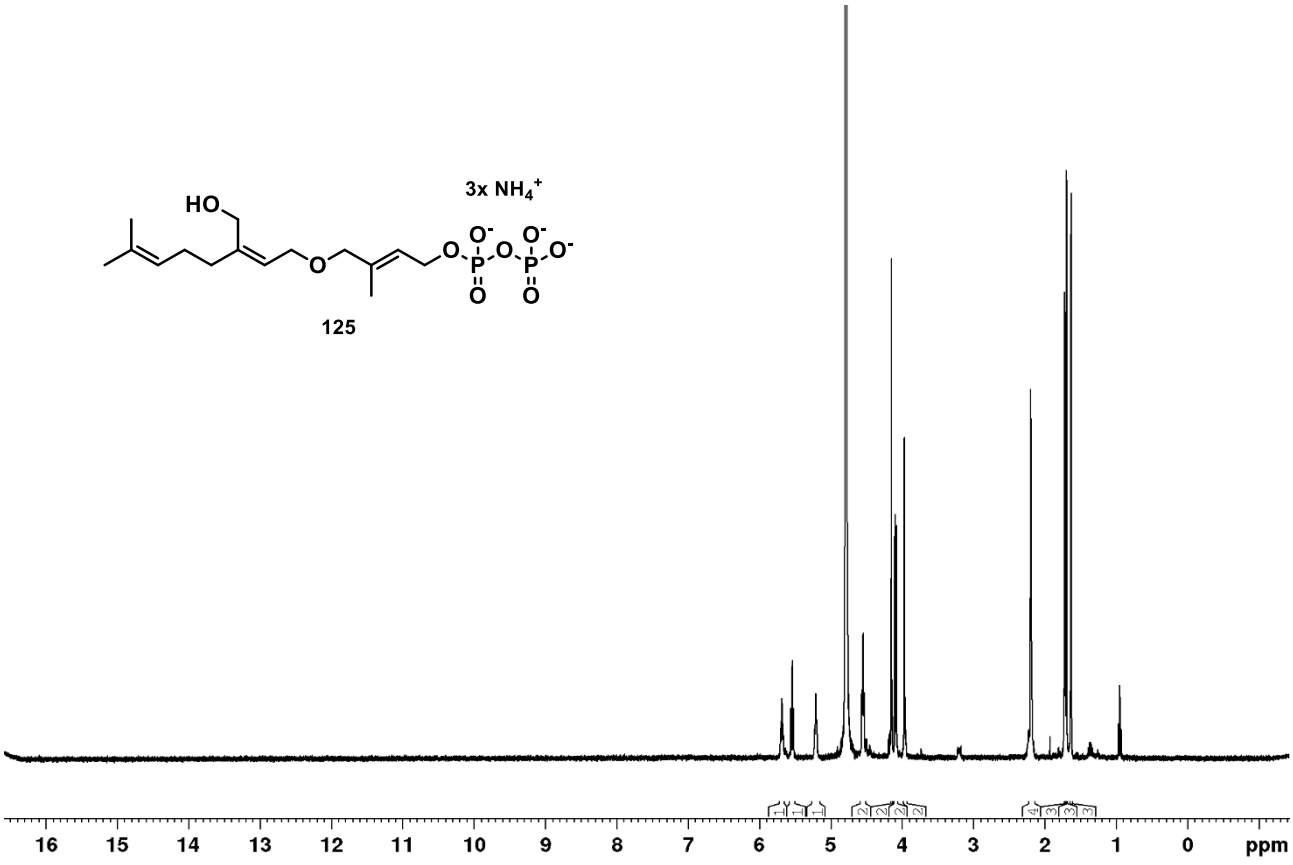
139.0
132.0
125.1
124.1
122.5
99.2
74.8
66.1
62.6
60.5
40.3
35.4
26.7
25.8
19.9
17.9
15.5
13.9
EEO
O
Cl
522
220
200
180
160
140
120
100
80
60
40
20
0
ppm


HO
O
Cl
2
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


144.7
138.5
132.1
123.8
122.7
74.9
65.7
60.9
40.1
35.6
26.7
25.7
17.7
13.8
HO
O
Cl
2
220
200
180
160
140
120
100
80
60
40
20
0
ppm


HO
3x NH4+
O-
O-
O-
O-
O
O
O
P
P
O
O
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14
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10
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6
5
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3
2
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0
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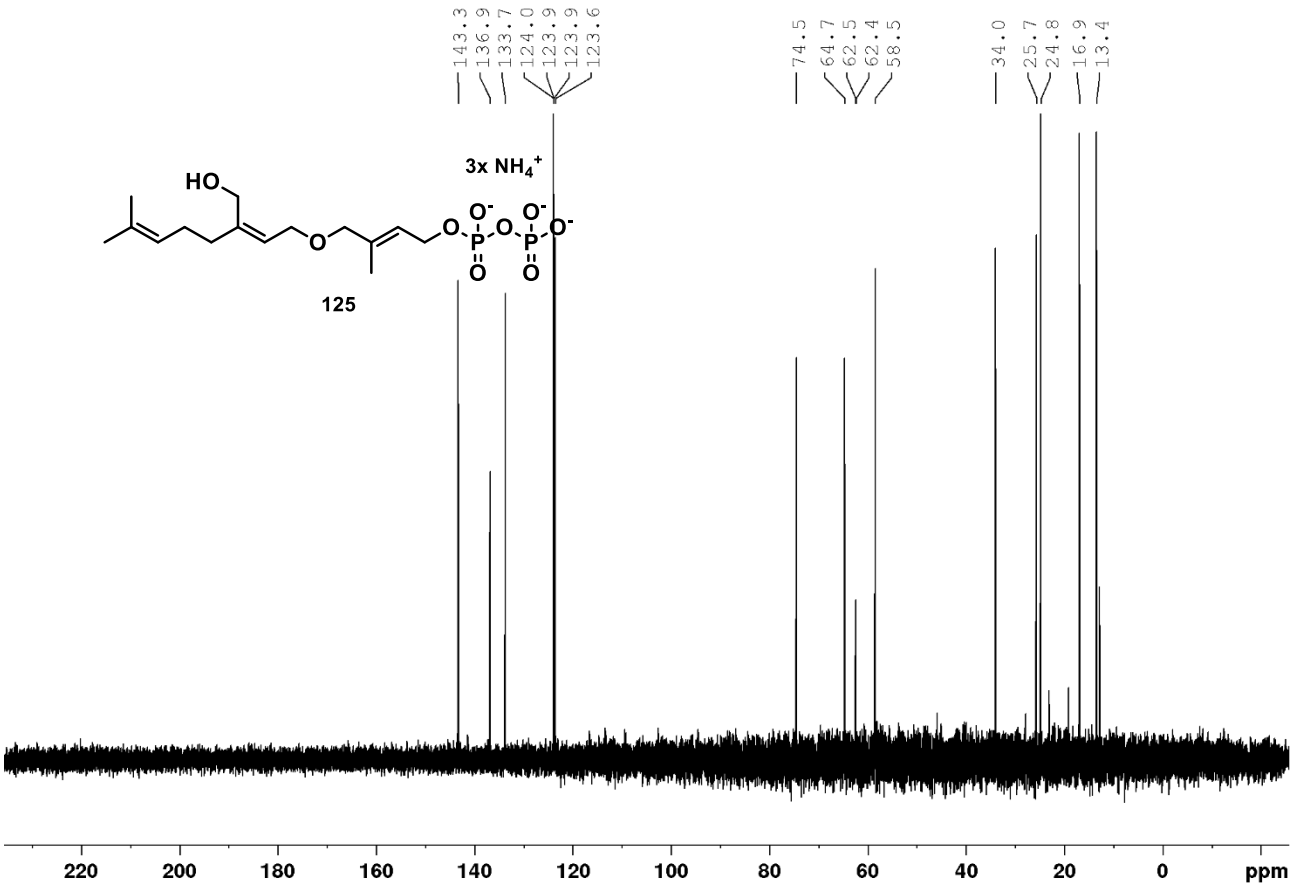
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136.9
133.7
124.0
123.9
123.9
123.6
74.5
64.7
62.5
62.4
58.5
34.0
25.7
24.8
16.9
13.4
HO
3x NH4+
O-
O-
O-
O-
O
O
O
P
P
O
O
125
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200
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120
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0
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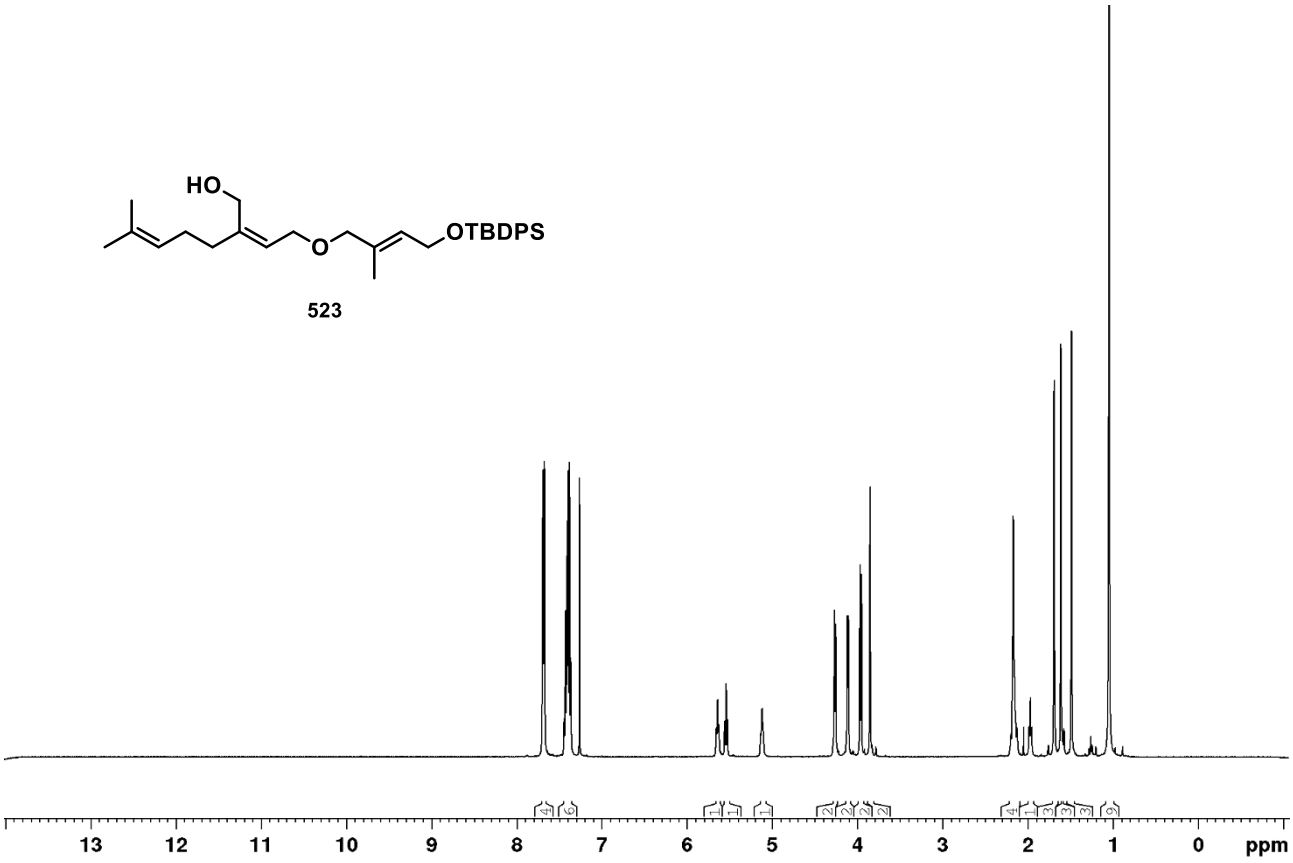
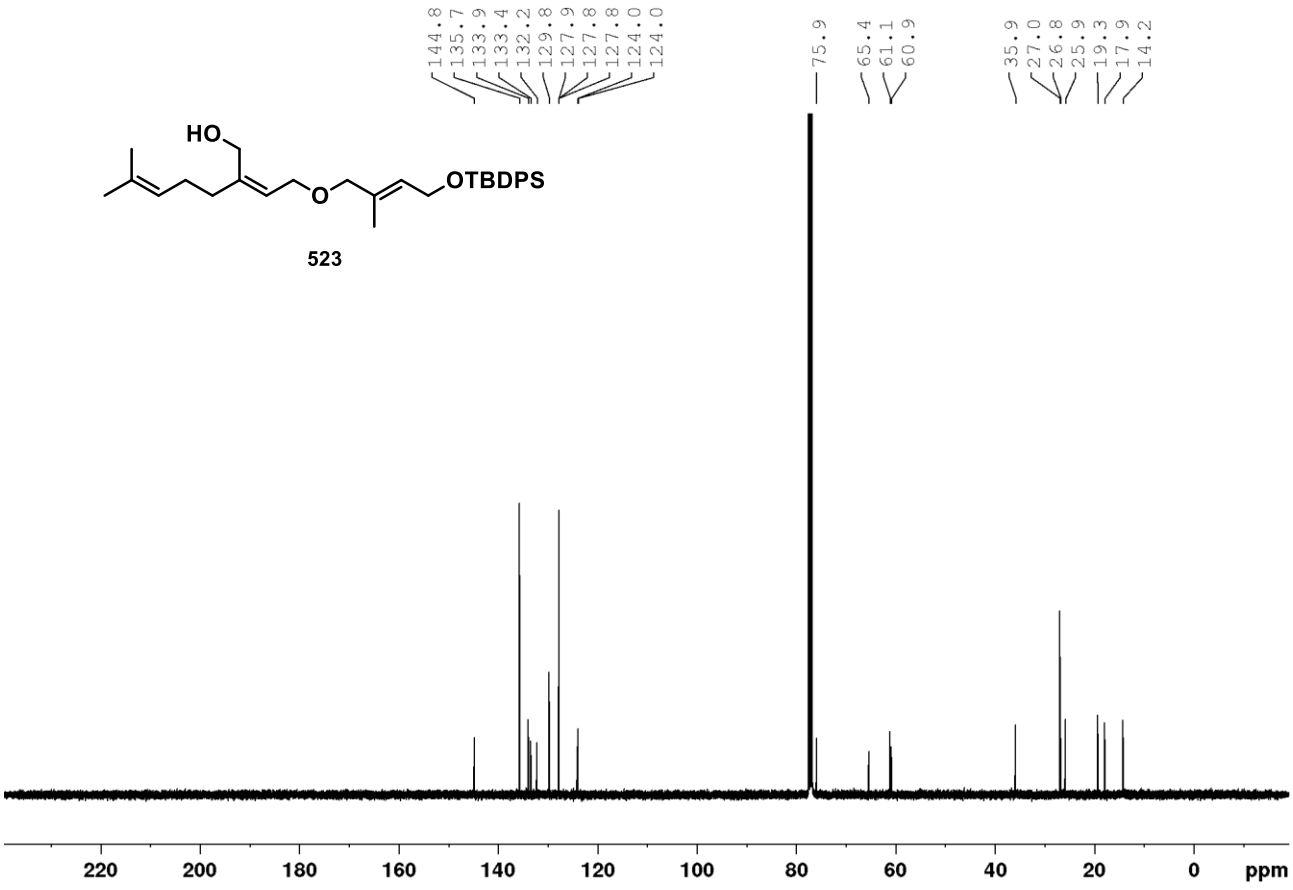

HO
O
OTBDPS
523
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm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133.9
133.4
132.2
129.8
127.9
127.8
127.8
124.0
124.0
75.9
65.4
61.1
60.9
35.9
27.0
26.8
25.9
19.3
17.9
14.2
HO
O
OTBDPS
523
220
200
180
160
140
120
100
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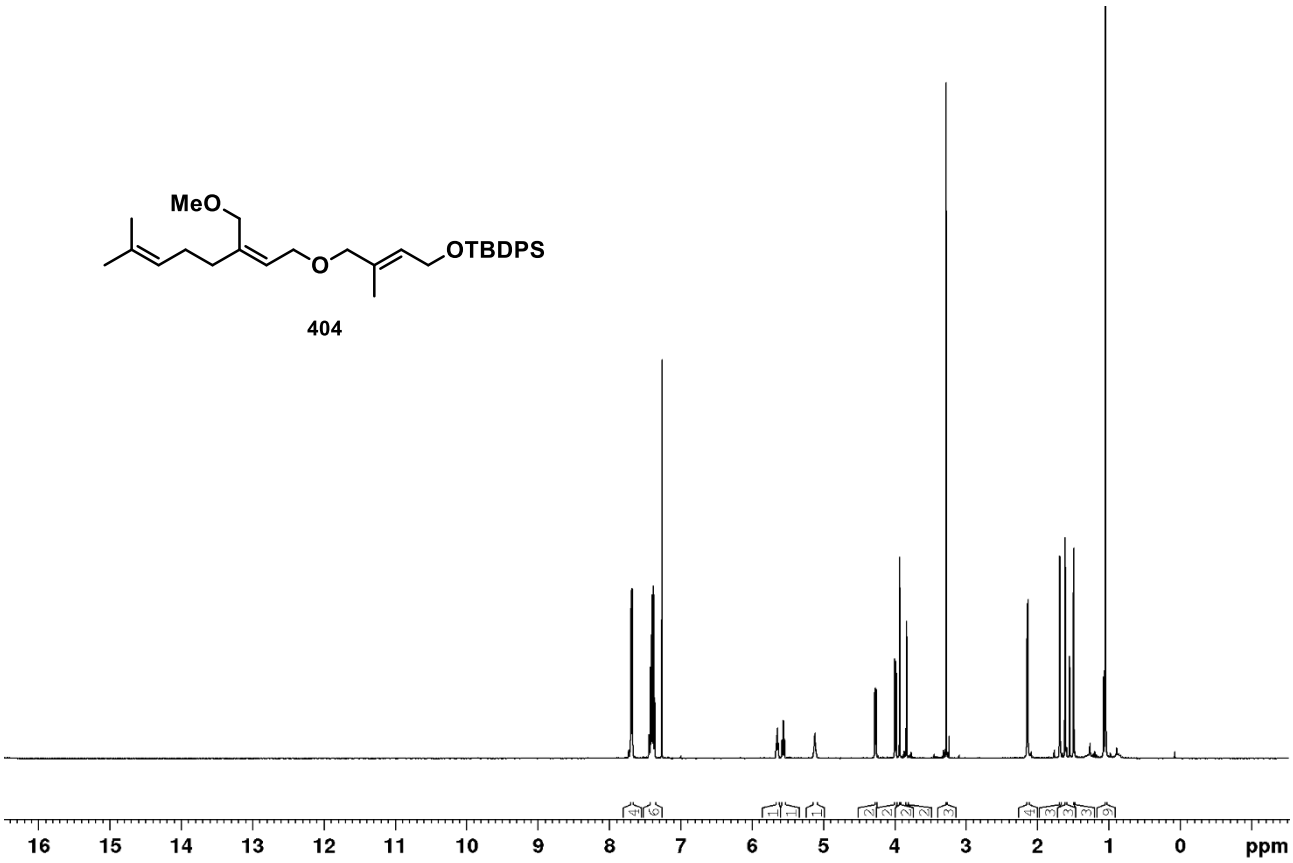
60
40
20
0
ppm


MeO
OTBDPS
O
404
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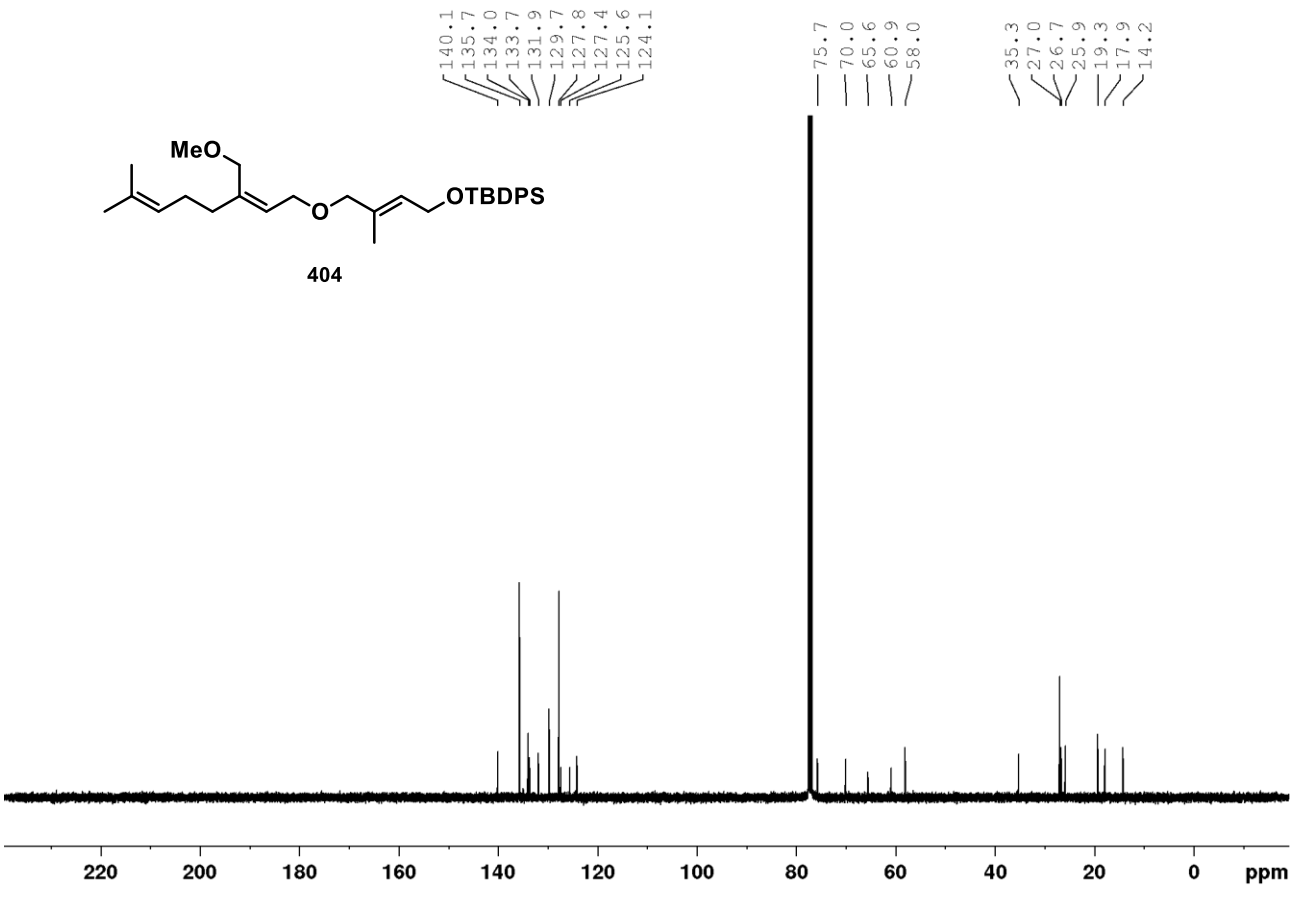
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm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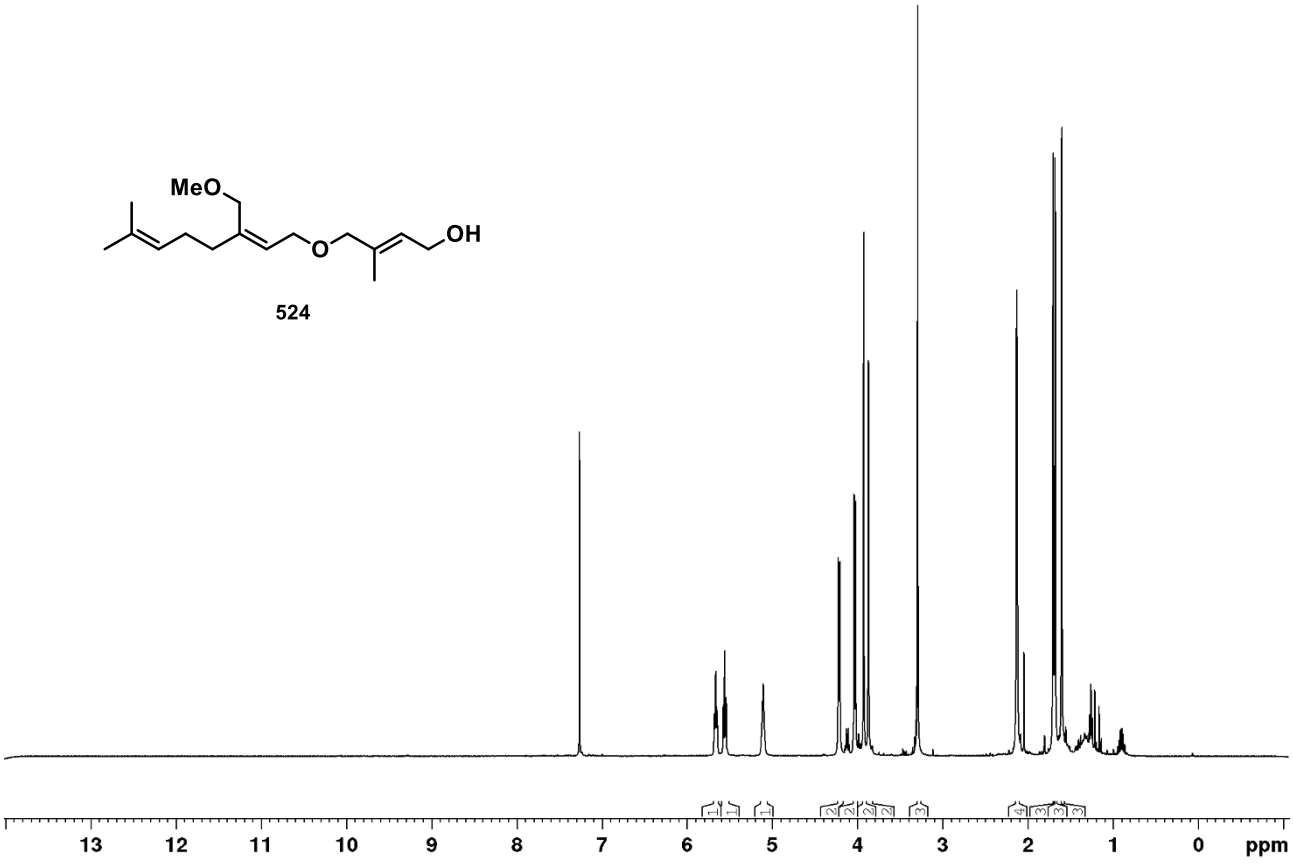
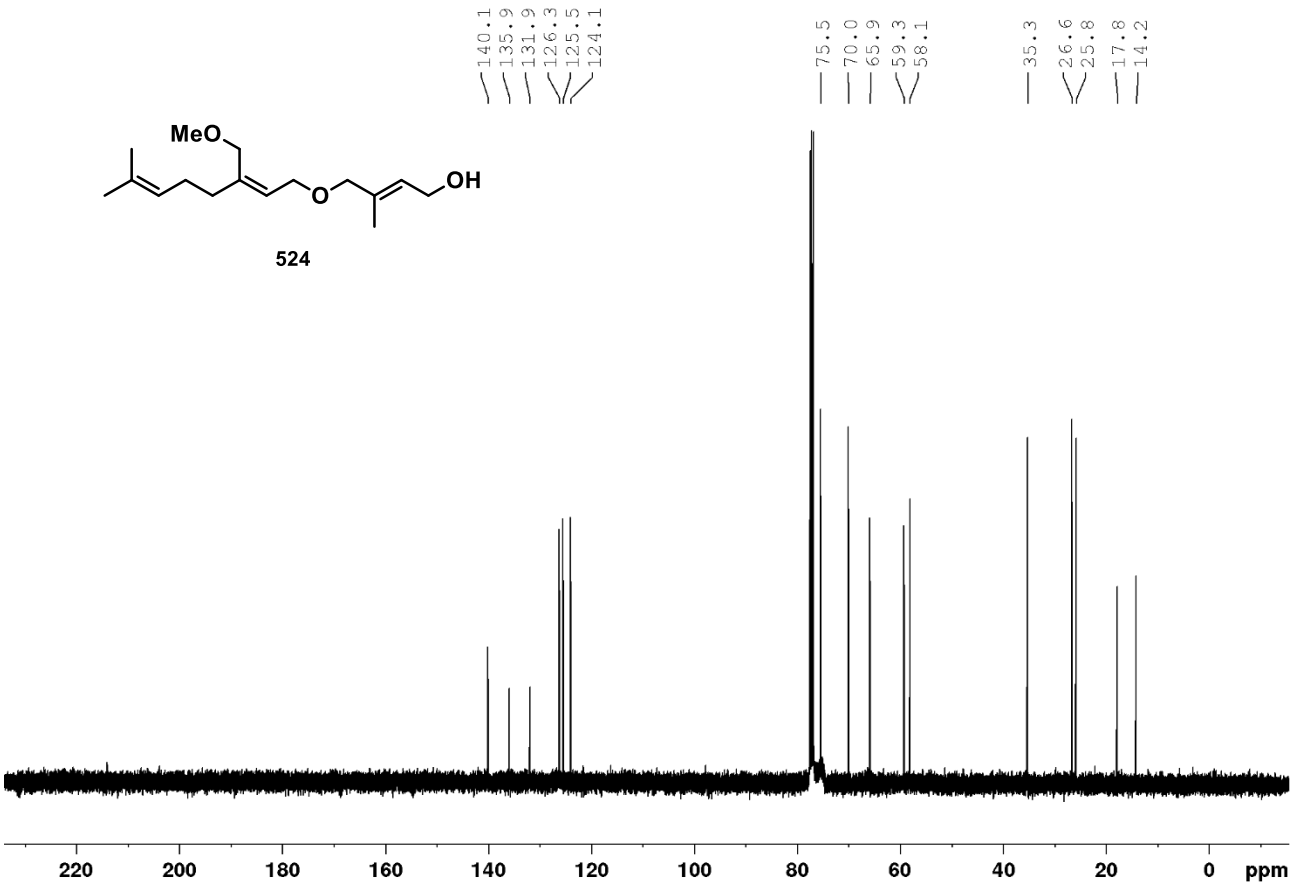
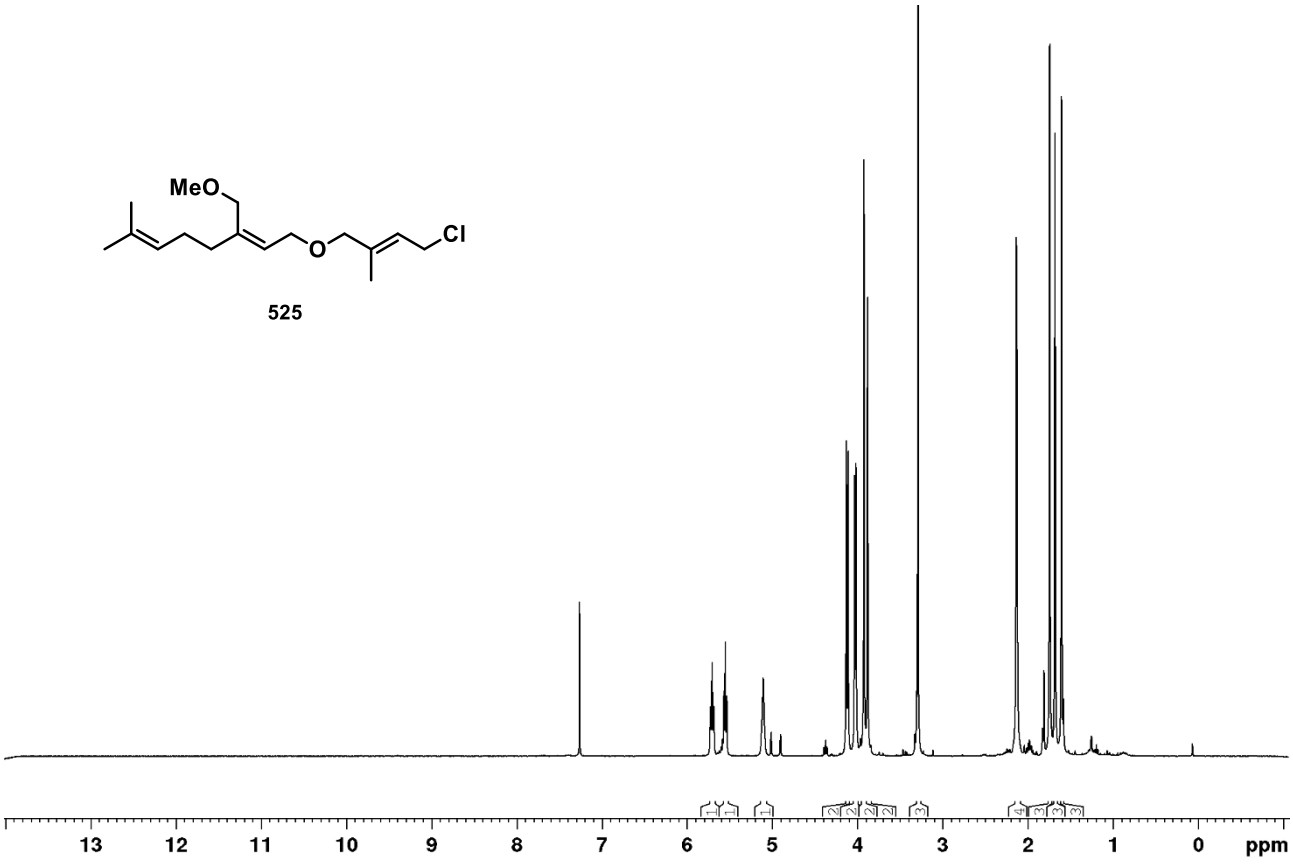
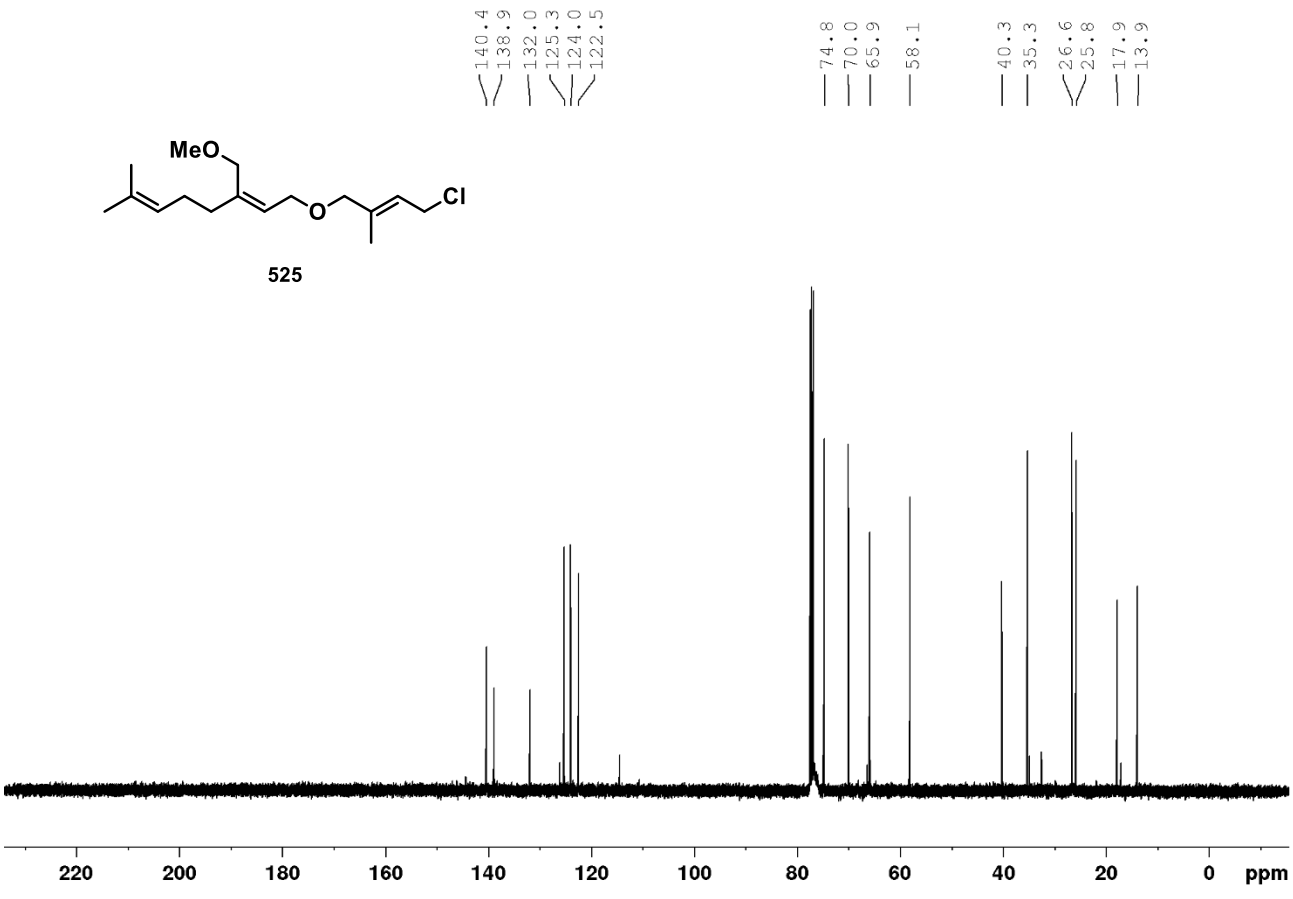
135.7
134.0
133.7
131.9
129.7
127.8
127.4
125.6
124.1
75.7
70.0
65.6
60.9
58.0
35.3
27.0
26.7
25.9
19.3
17.9
14.2
MeO
OTBDPS
O
404
220
200
180
160
140
120
100
80
60
40
20
0
ppm


MeO
OH
O
524
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


140.1
135.9
131.9
126.3
125.5
124.1
75.5
70.0
65.9
59.3
58.1
35.3
26.6
25.8
17.8
14.2
MeO
OH
O
524
220
200
180
160
140
120
100
80
60
40
20
0
ppm


MeO
Cl
O
525
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm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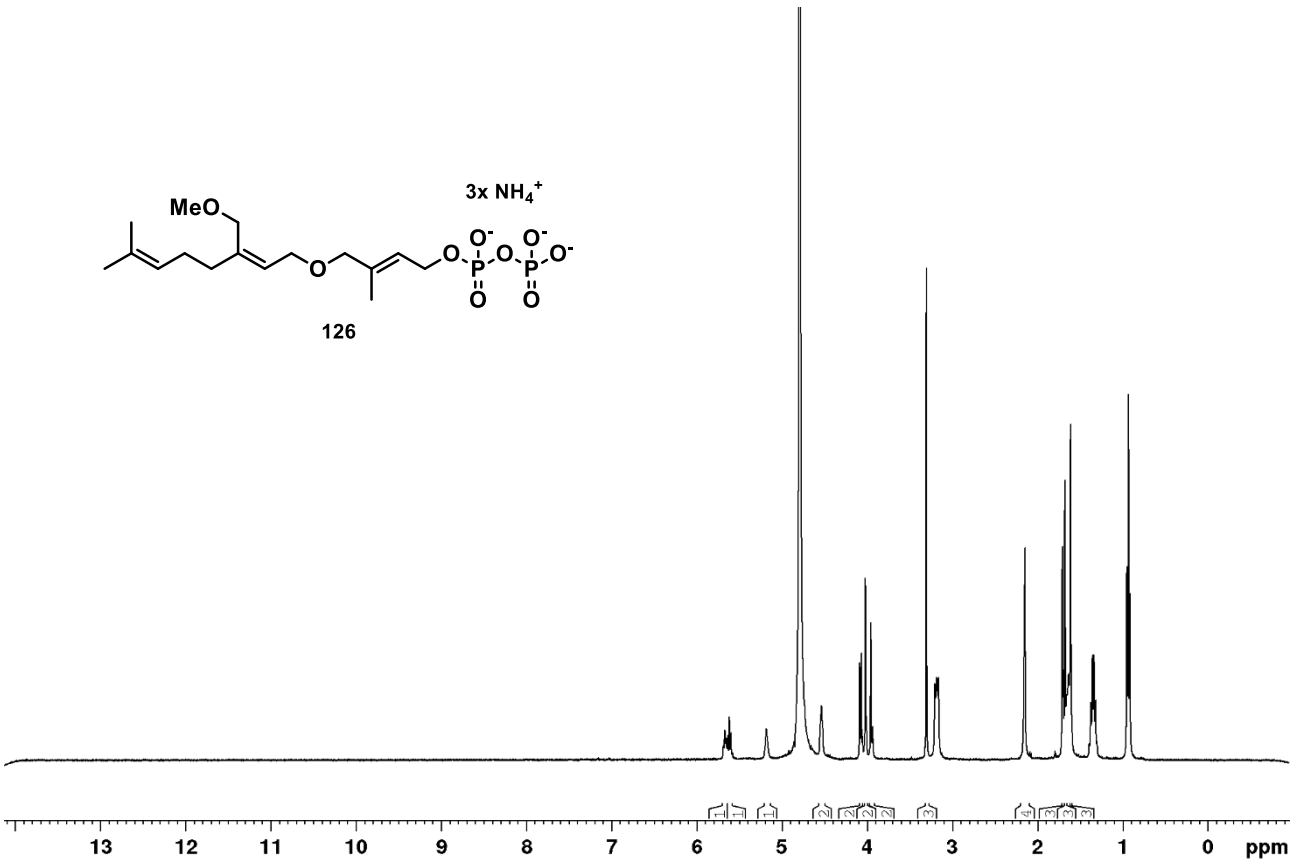
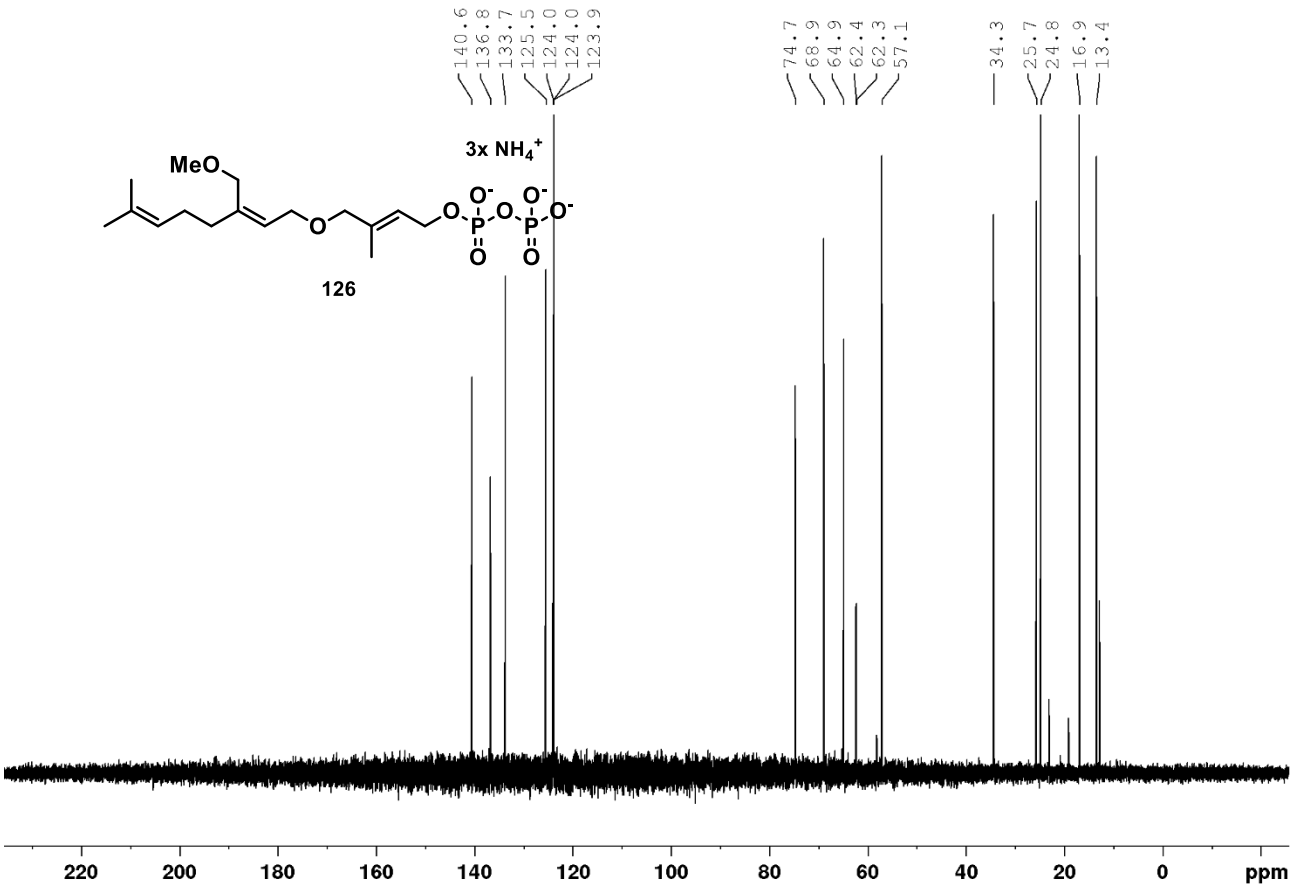
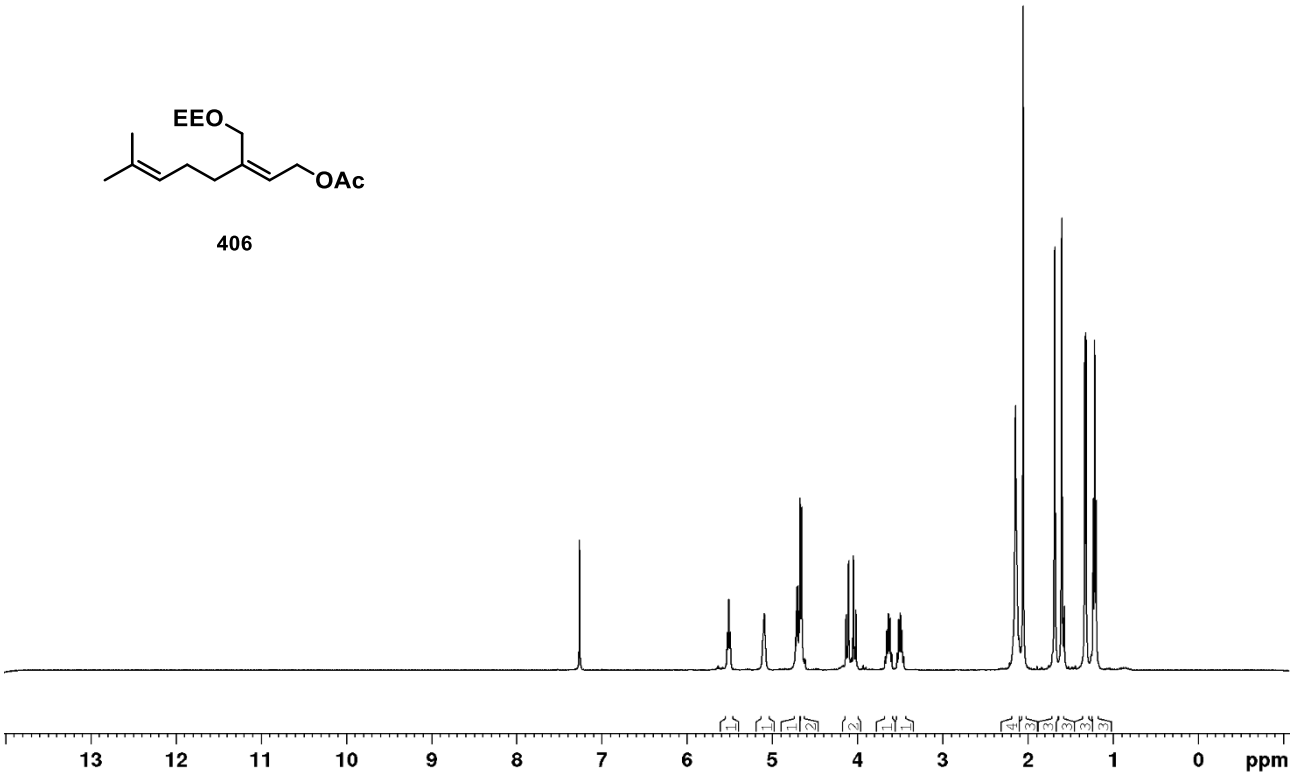
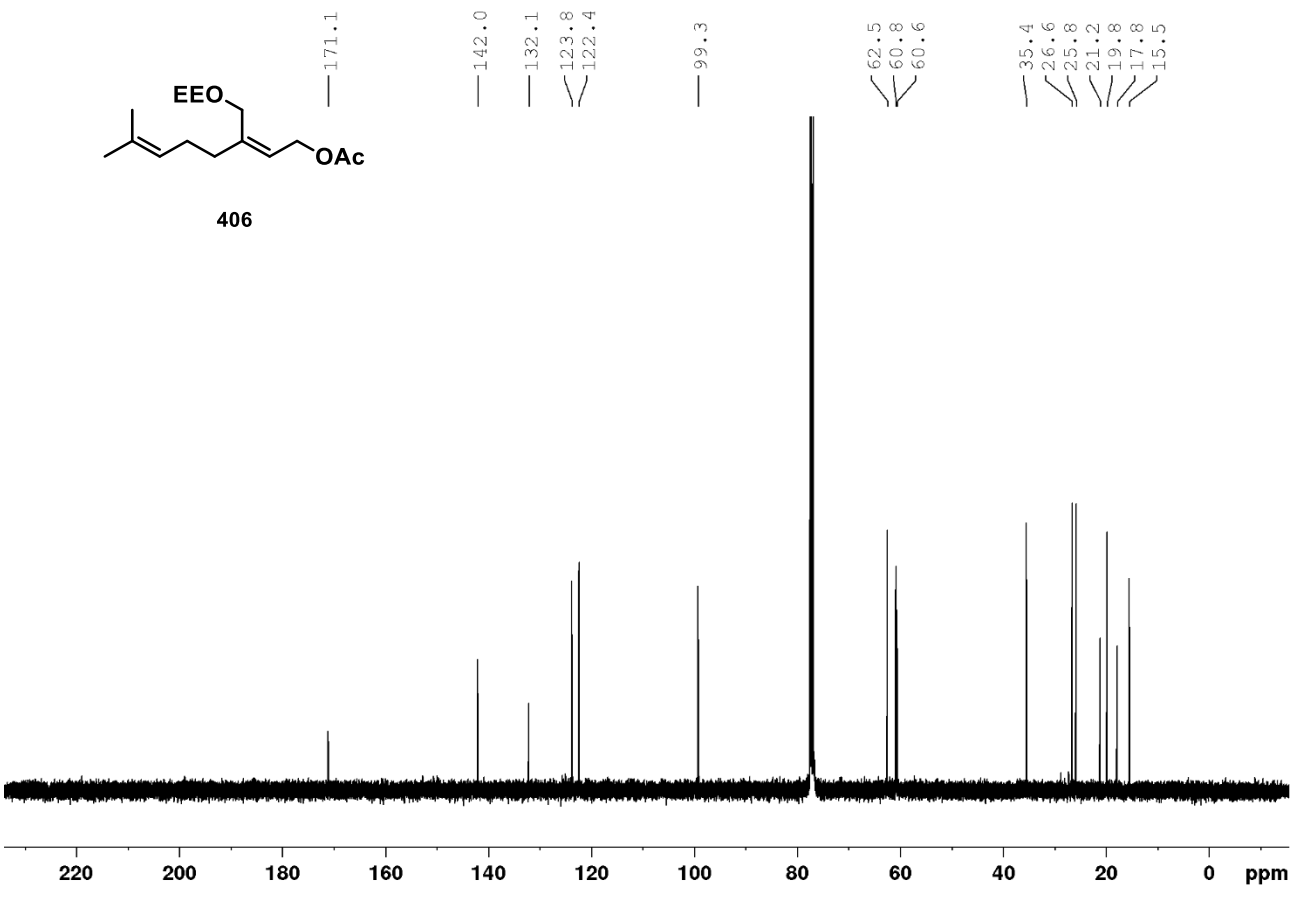
138.9
132.0
125.3
124.0
122.5
74.8
70.0
65.9
58.1
40.3
35.3
26.6
25.8
17.9
13.9
MeO
Cl
O
525
220
200
180
160
140
120
100
80
60
40
20
0
ppm


MeO
3x NH4+
126
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


140.6
136.8
133.7
125.5
124.0
124.0
123.9
74.7
68.9
64.9
62.4
62.3
57.1
34.3
25.7
24.8
16.9
13.4
MeO
3x NH4+
126
220
200
180
160
140
120
100
80
60
40
20
0
ppm


EEO
OAc
406
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm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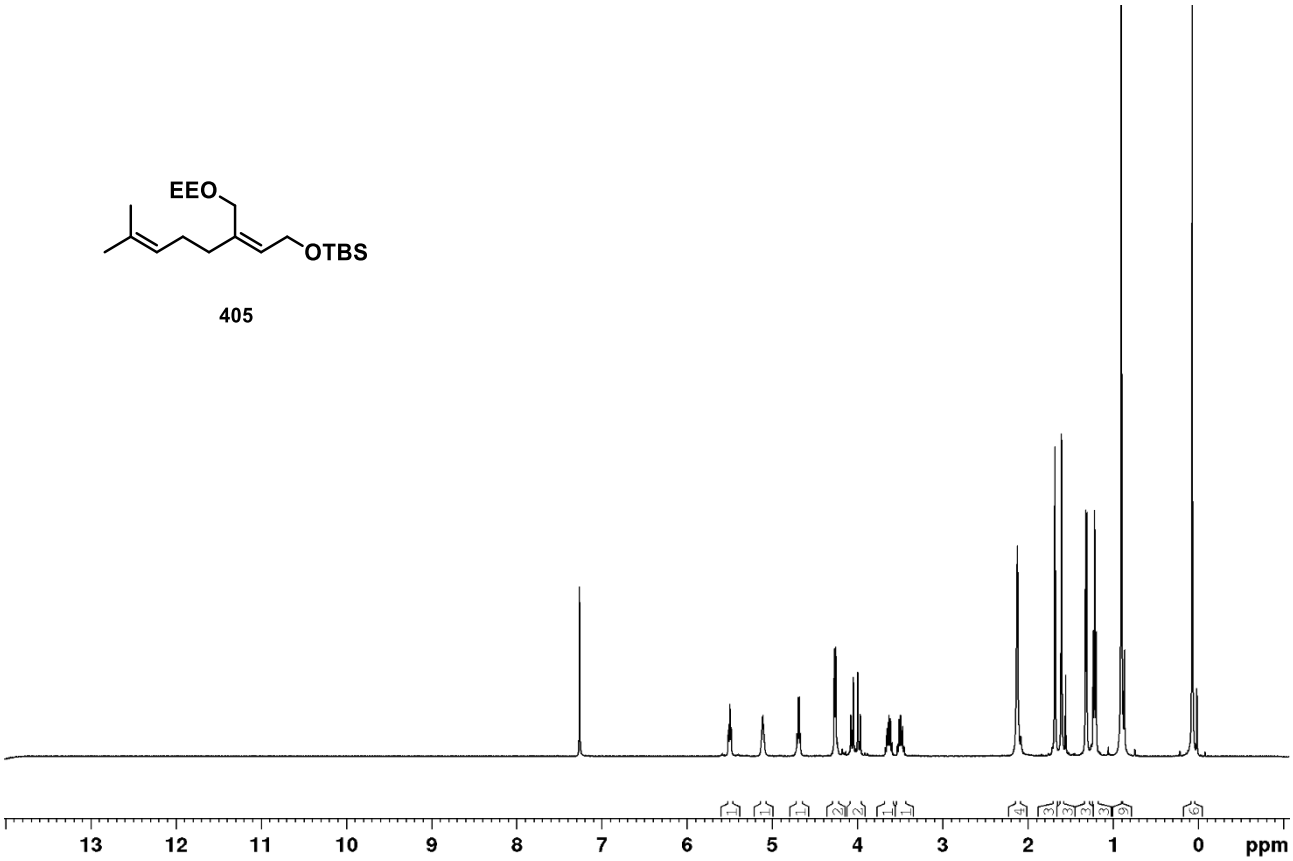
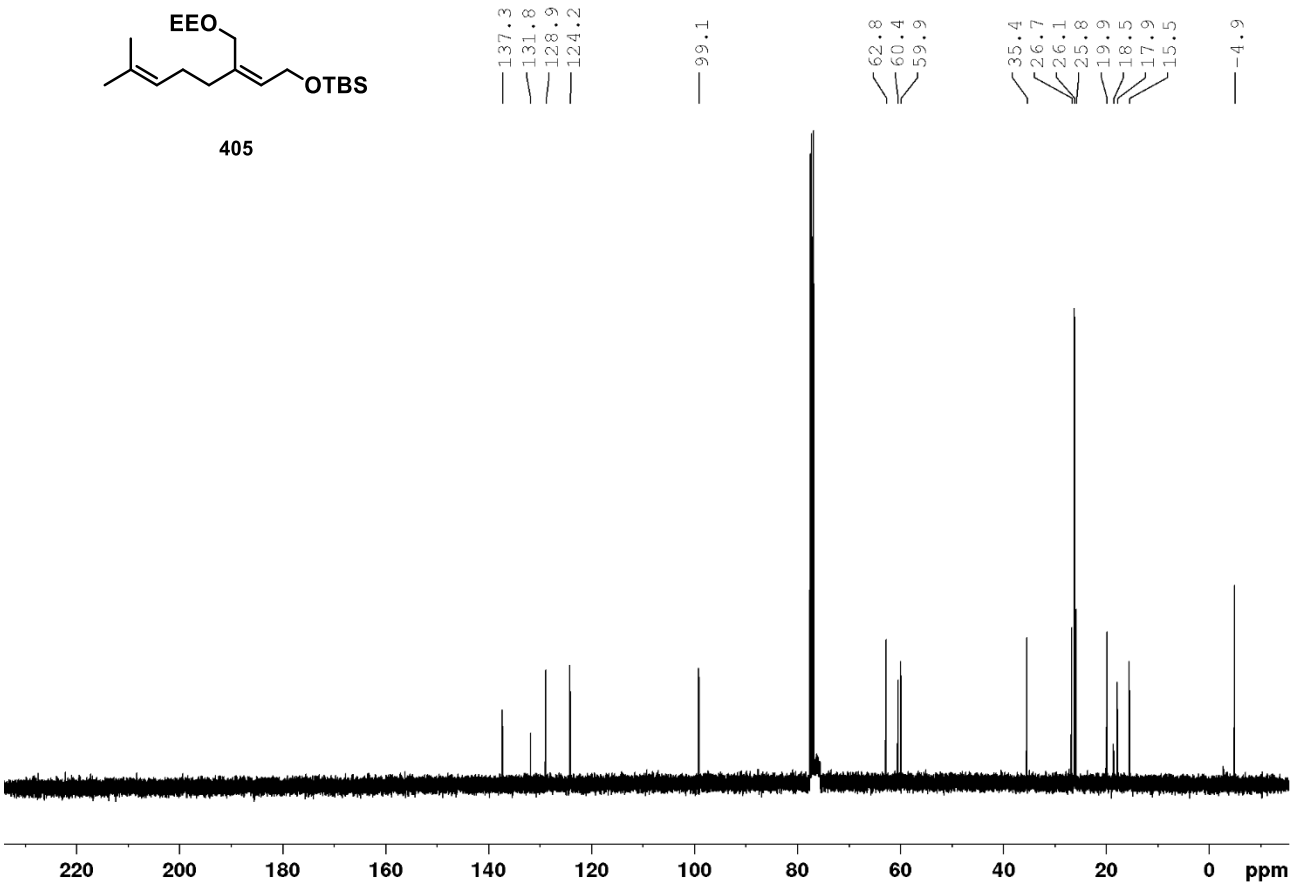
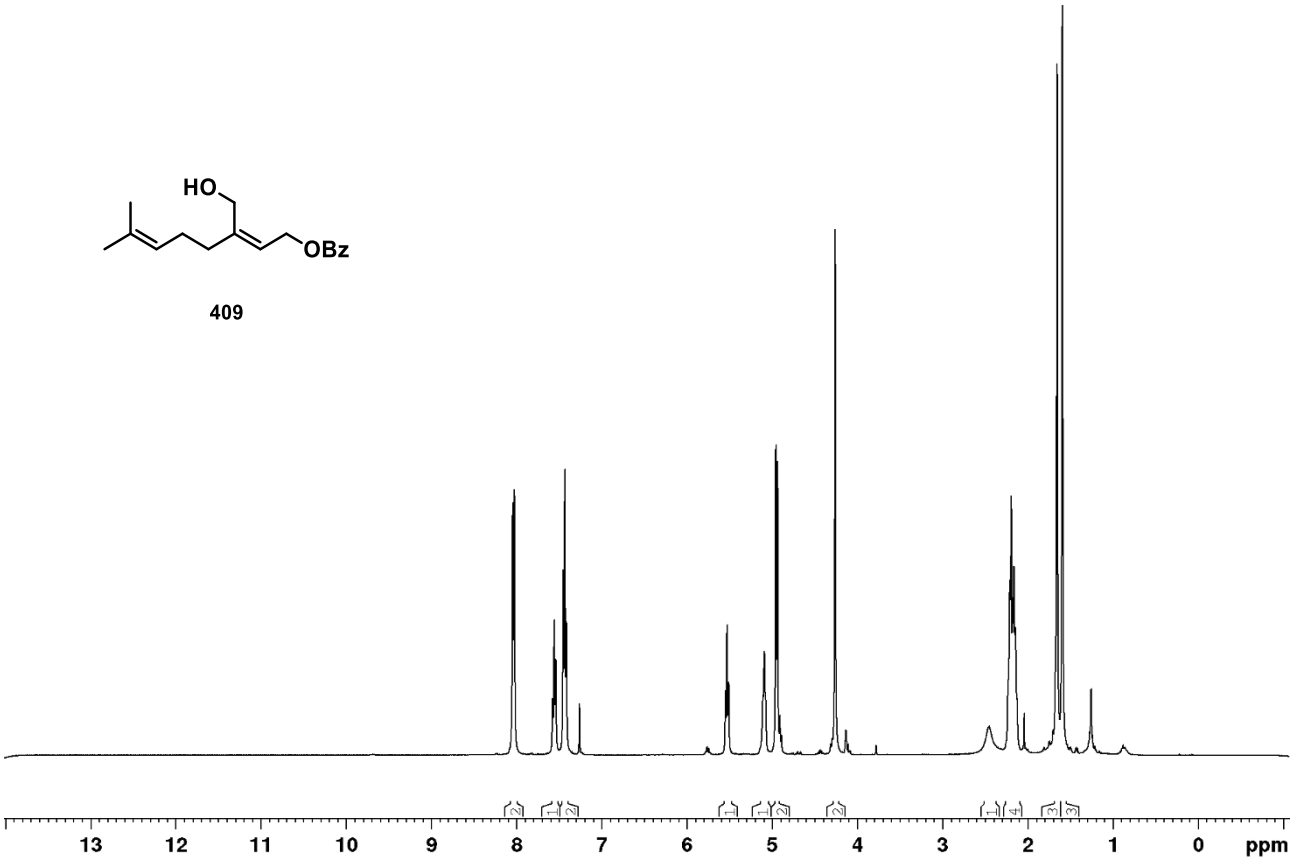
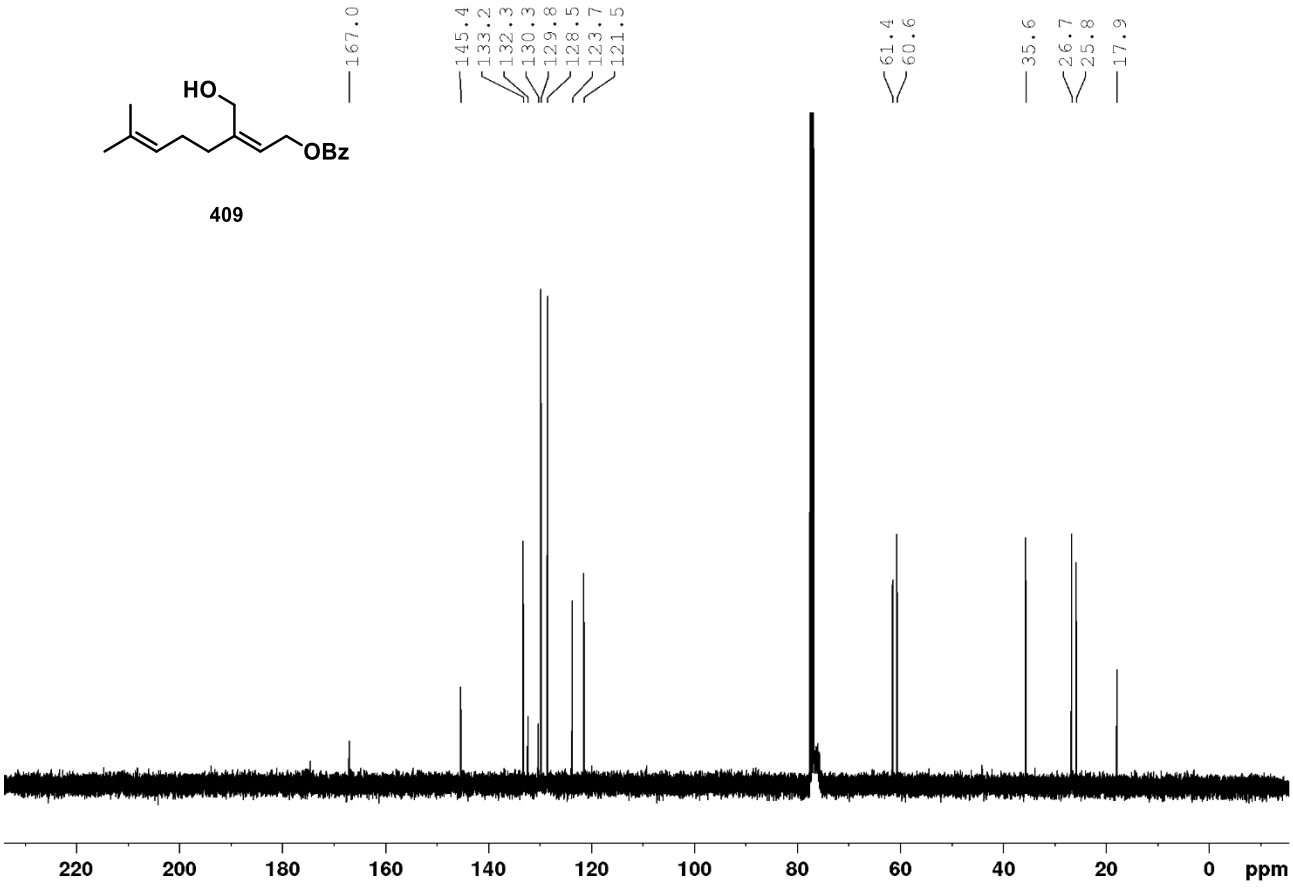
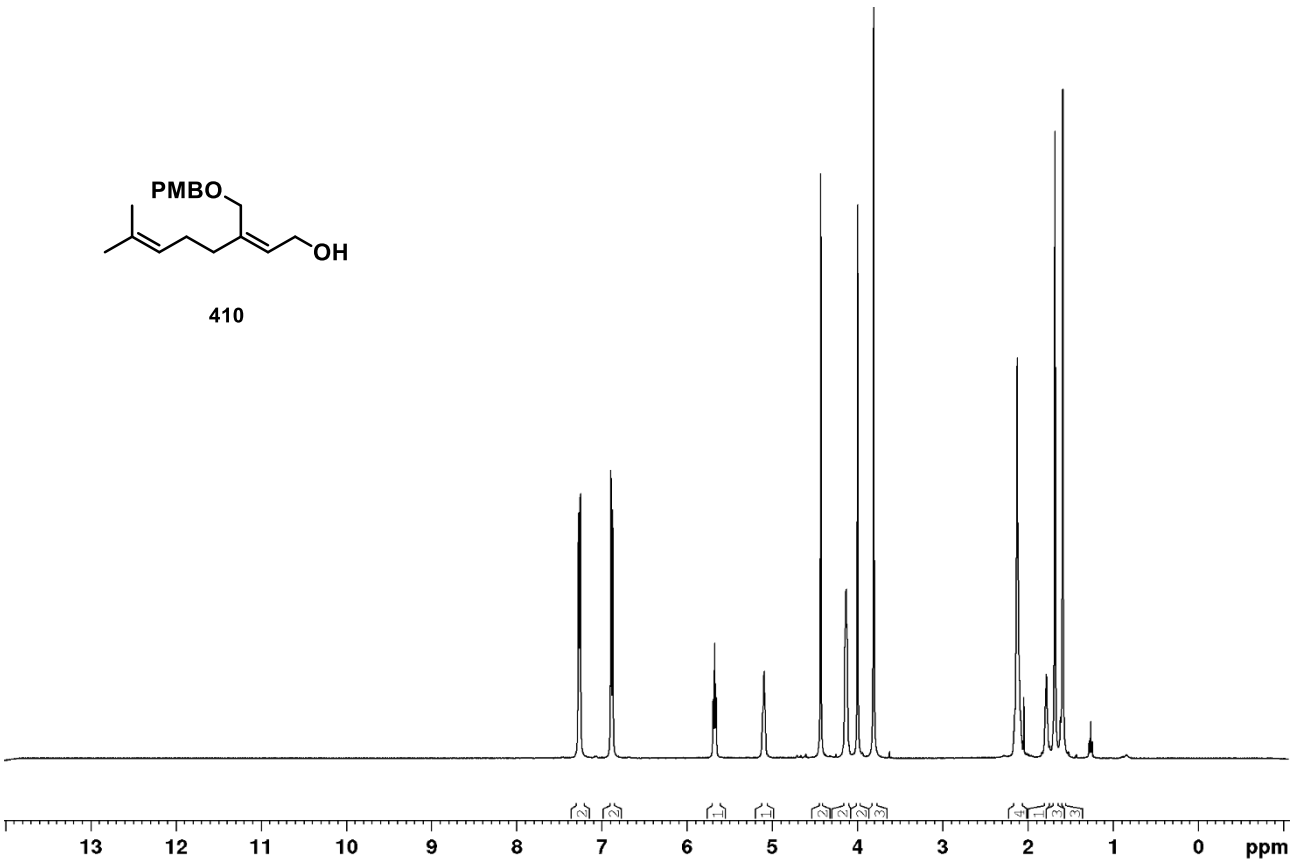
142.0
132.1
123.8
122.4
99.3
62.5
60.8
60.6
35.4
26.6
25.8
21.2
19.8
17.8
15.5
EEO
OAc
406
220
200
180
160
140
120
100
80
60
40
20
0
ppm

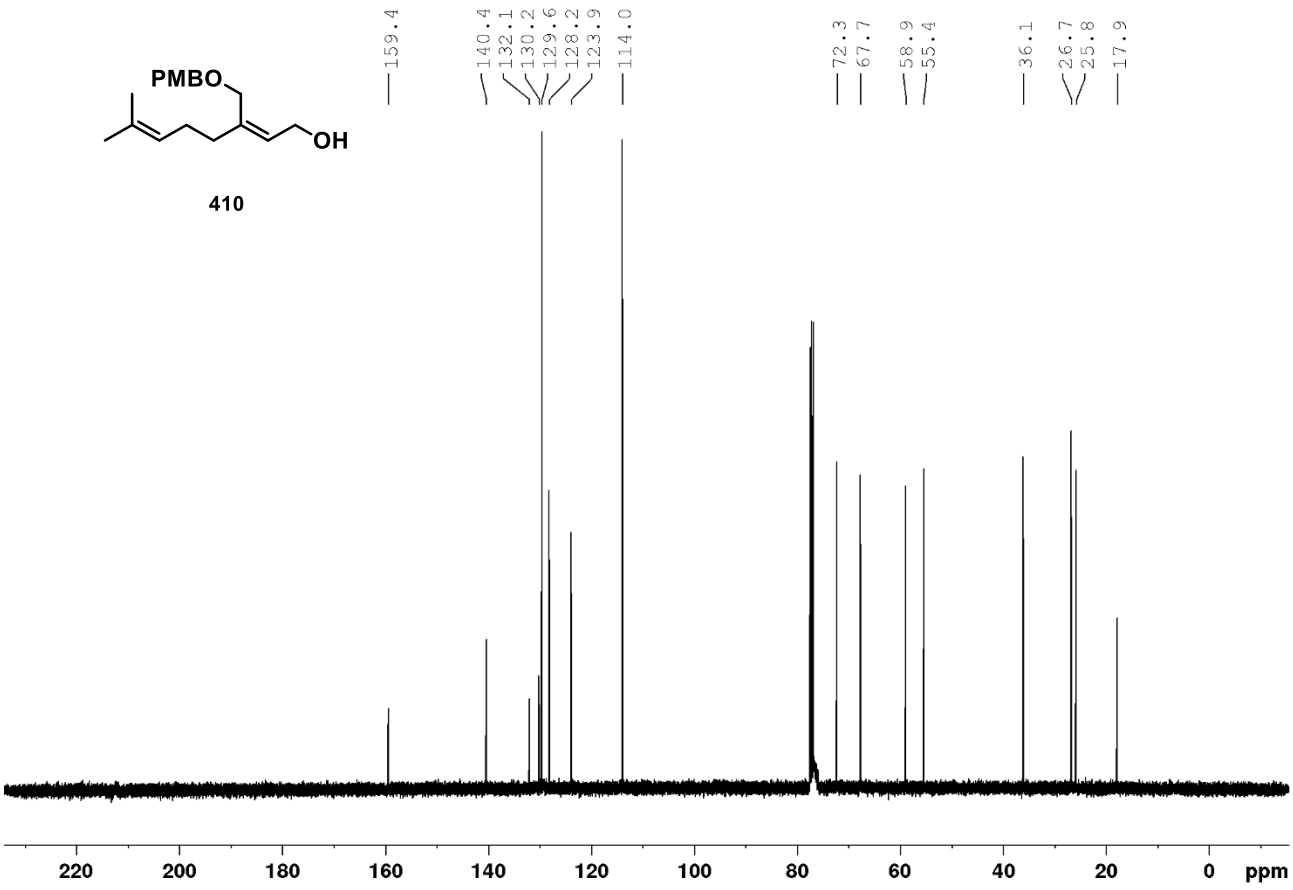

EEO
OTBS
405
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


EEO
OTBS
405
137.3
131.8
128.9
124.2
99.1
62.8
60.4
59.9
35.4
26.7
26.1
25.8
19.9
18.5
17.9
15.5
-4.9
220
200
180
160
140
120
100
80
60
40
20
0
ppm


HO
OBz
409
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


167.0
145.4
133.2
132.3
130.3
129.8
128.5
123.7
121.5
61.4
60.6
35.6
26.7
25.8
17.9
HO
OBz
409
220
200
180
160
140
120
100
80
60
40
20
0
ppm


PMBO
OH
410
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm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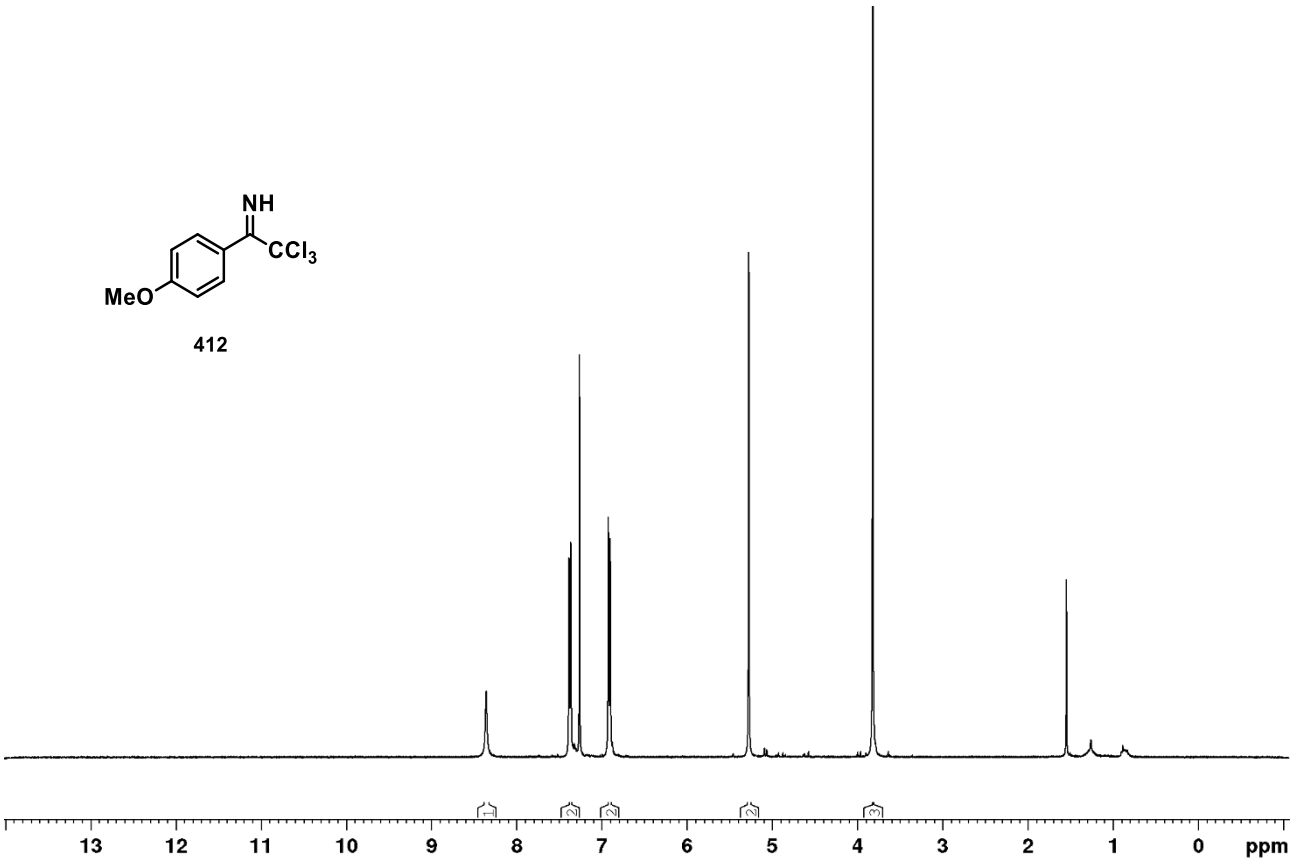
140.4
132.1
130.2
129.6
128.2
123.9
114.0
72.3
67.7
58.9
55.4
36.1
26.7
25.8
17.9
PMBO
OH
410
220
200
180
160
140
120
100
80
60
40
20
0
ppm


NH
CCl3
MeO
412
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12
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10
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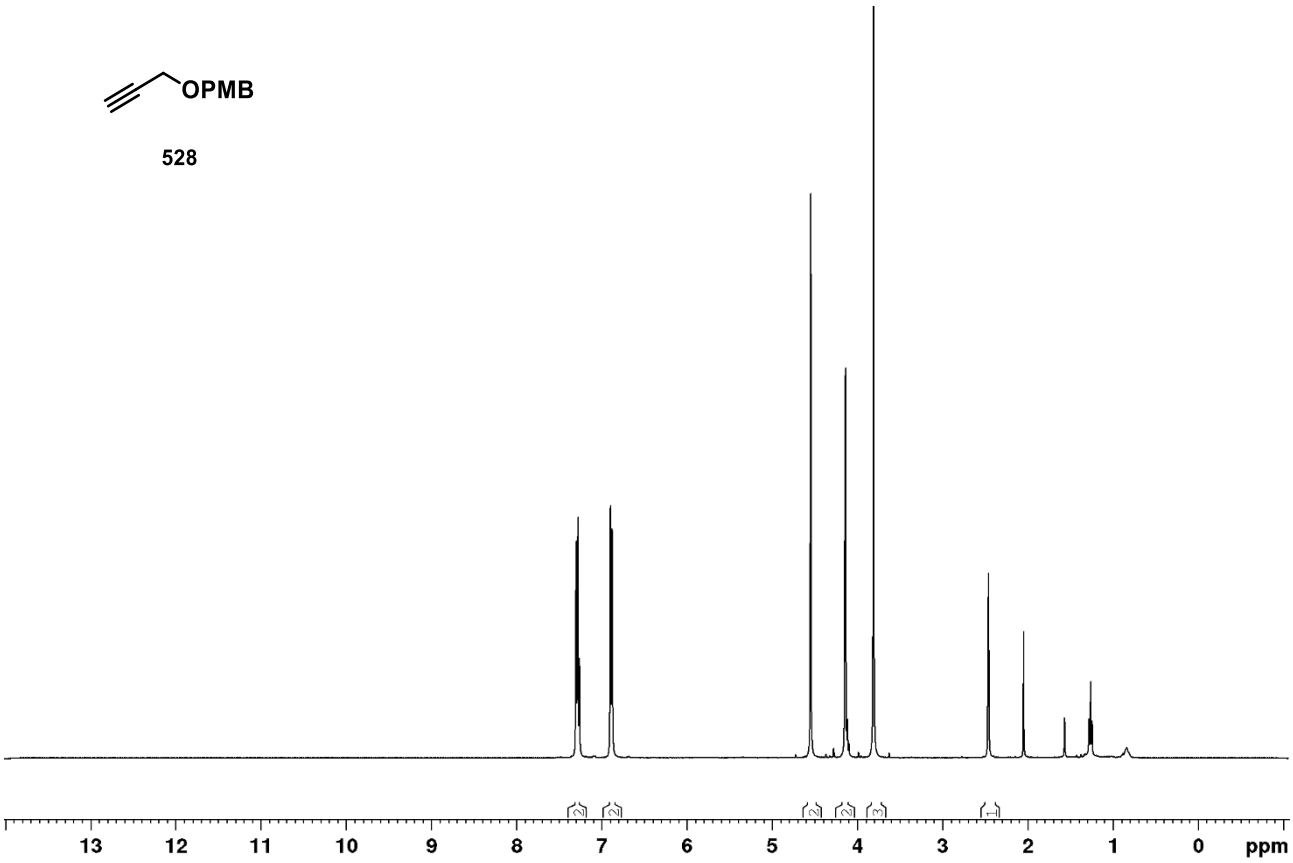
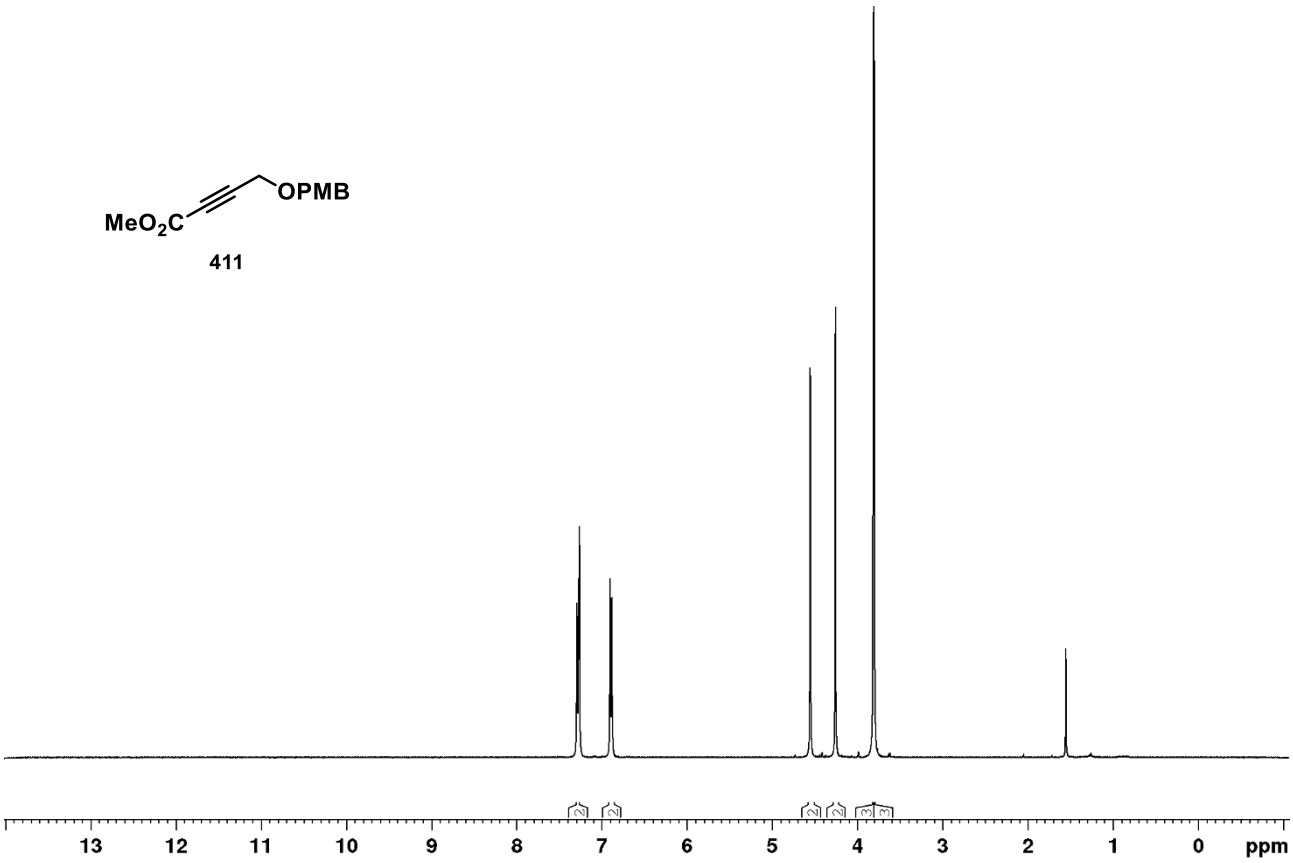
8
7
6
5
4
3
2
1
0
ppm


OPMB
528
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


OPMB
MeO2C
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8
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6
5
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2
1
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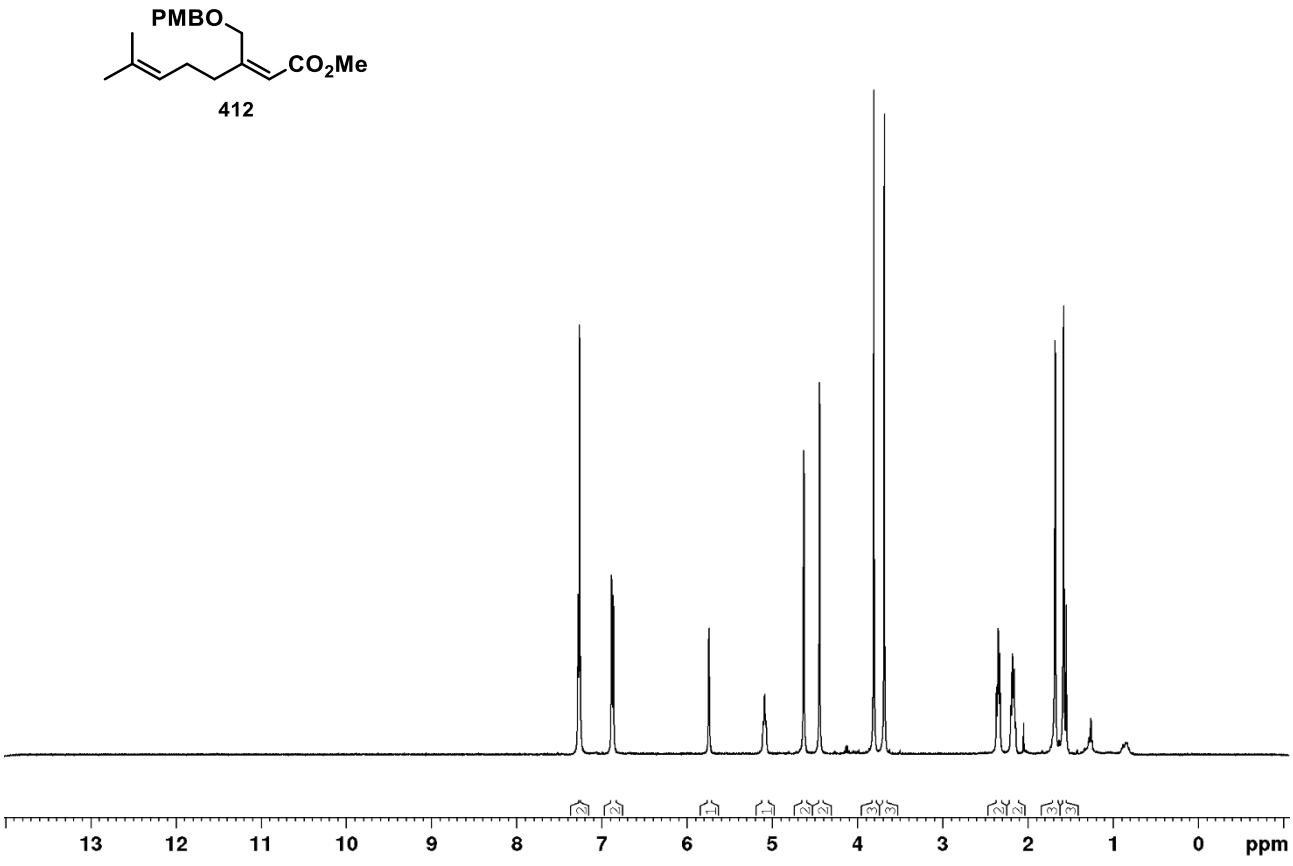
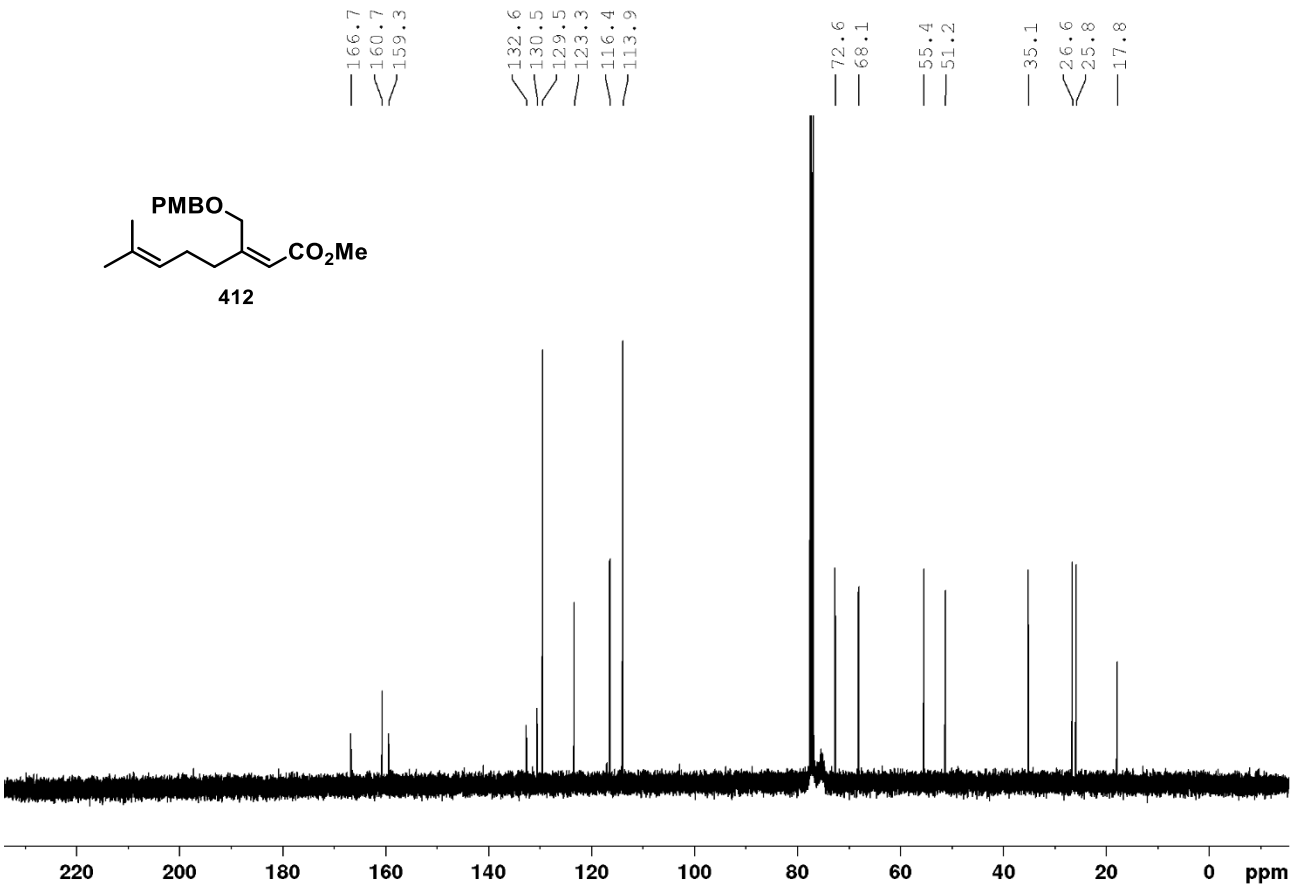
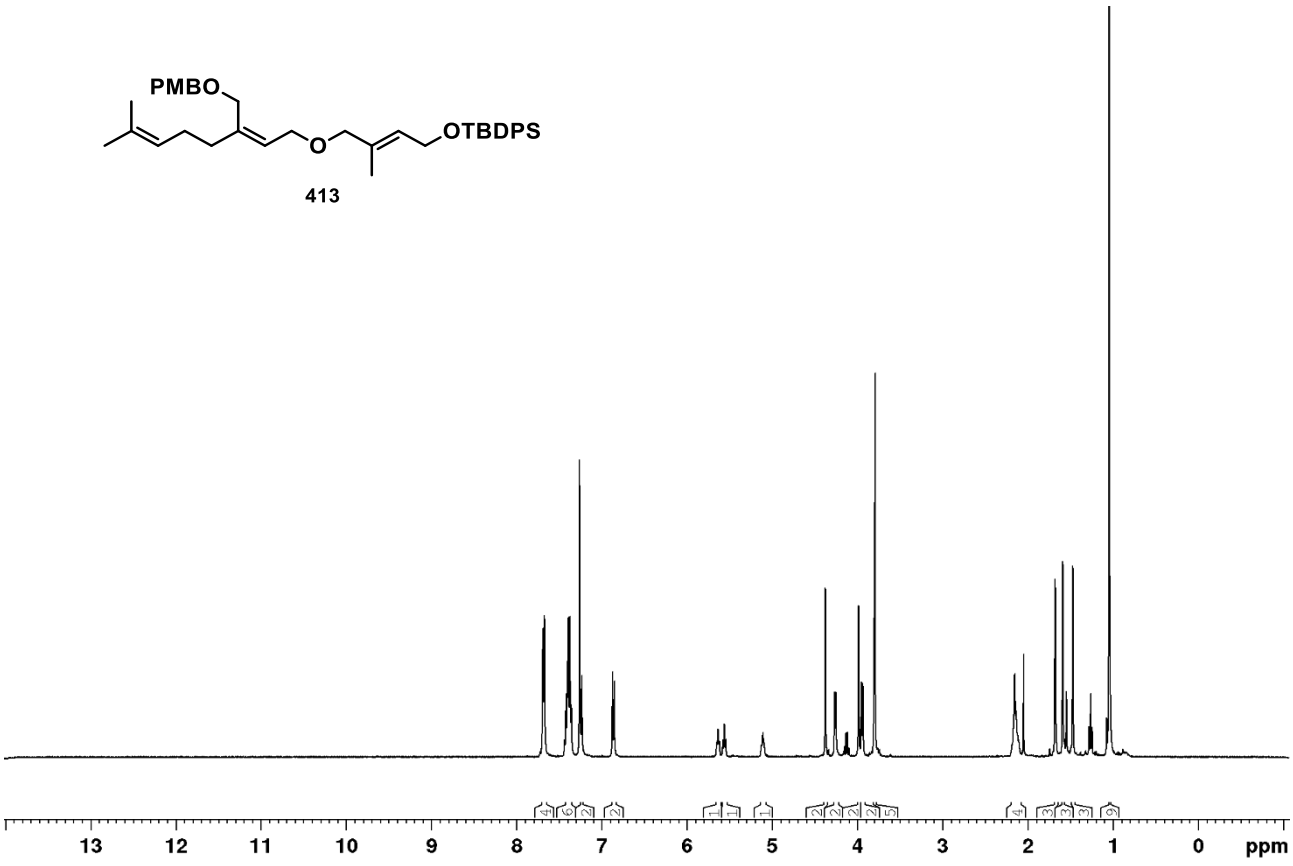
ppm

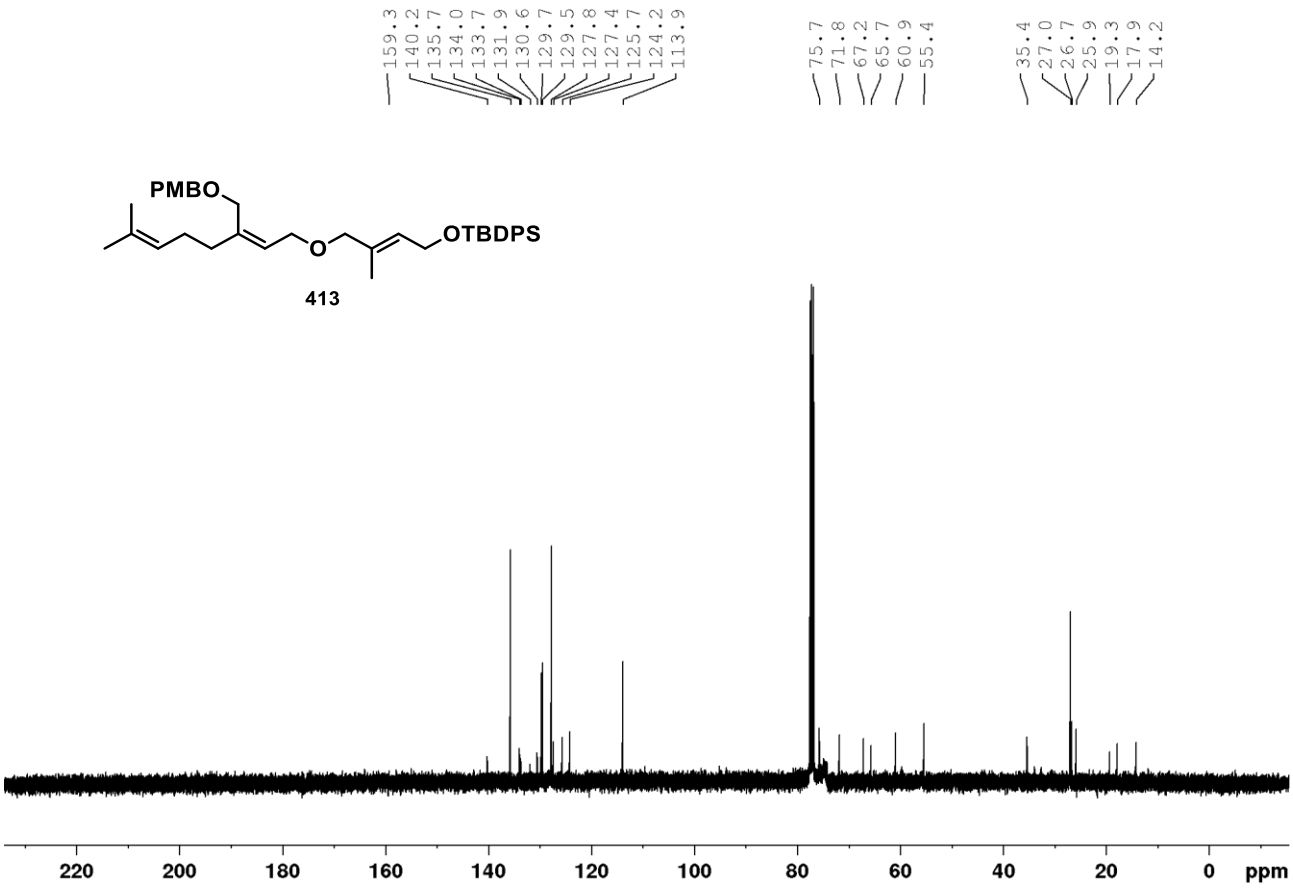

PMBO
CO2Me
412
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


166.7
160.7
159.3
132.6
130.5
129.5
123.3
116.4
113.9
72.6
68.1
55.4
51.2
35.1
26.6
25.8
17.8
PMBO
CO2Me
220
200
180
160
140
120
100
80
60
40
20
0
ppm

412


PMBO
OTBDPS
O
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

413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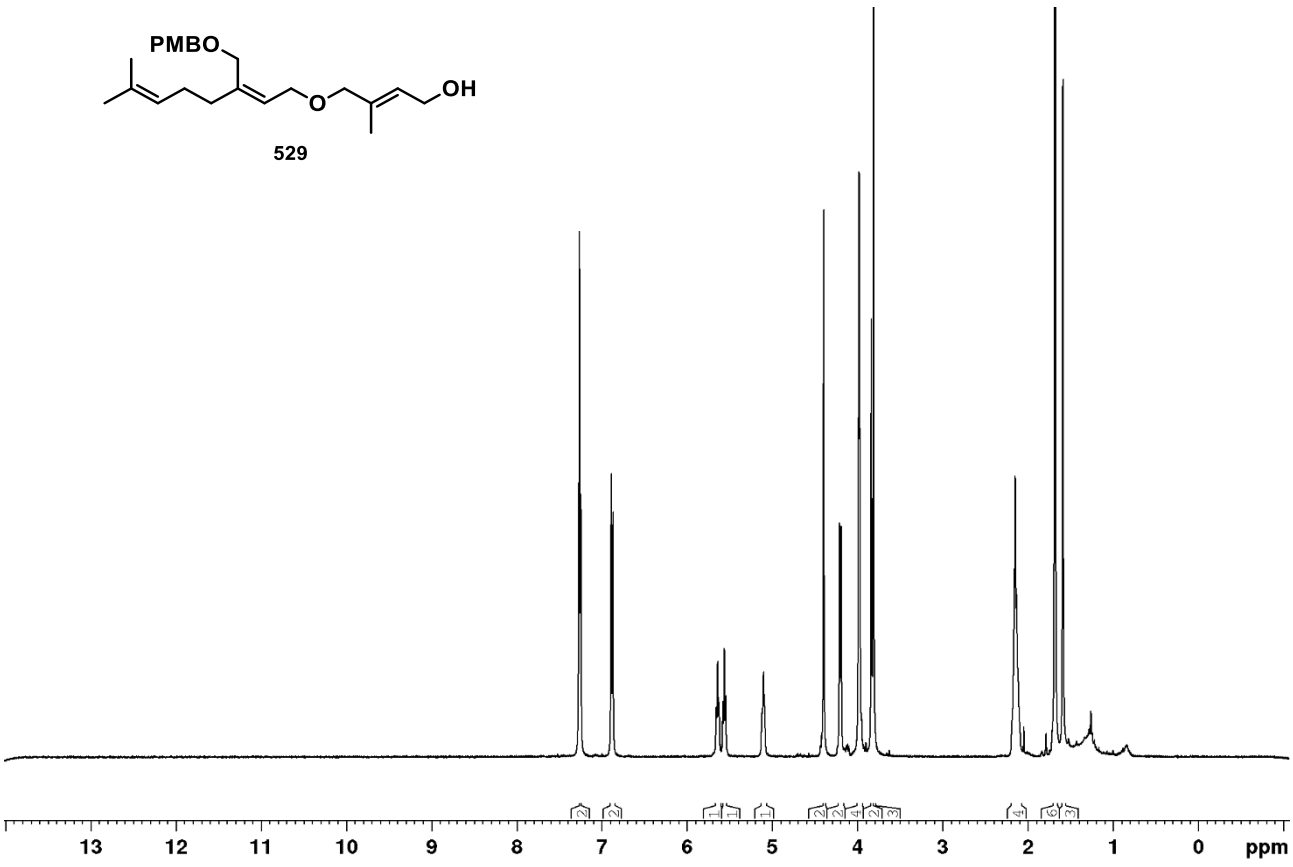
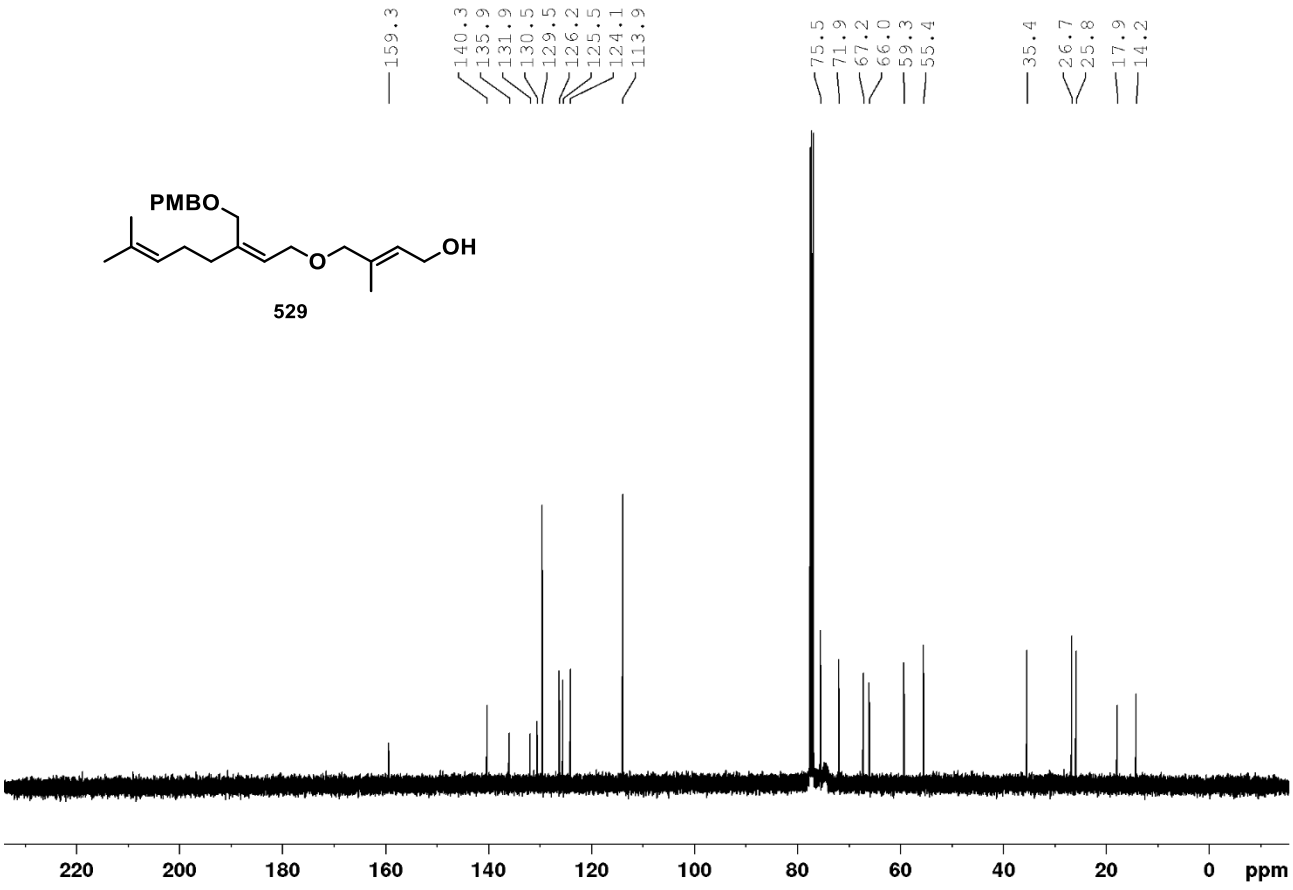
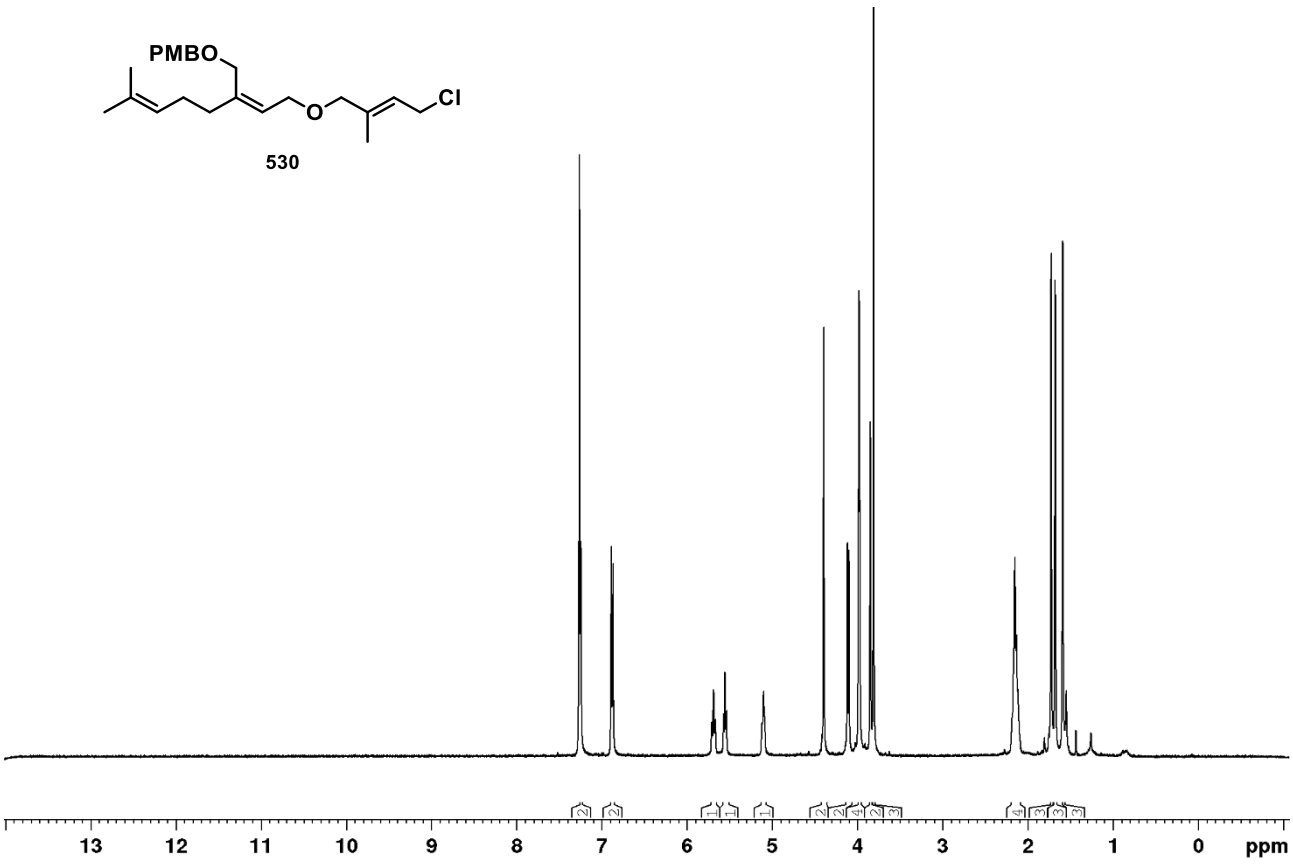
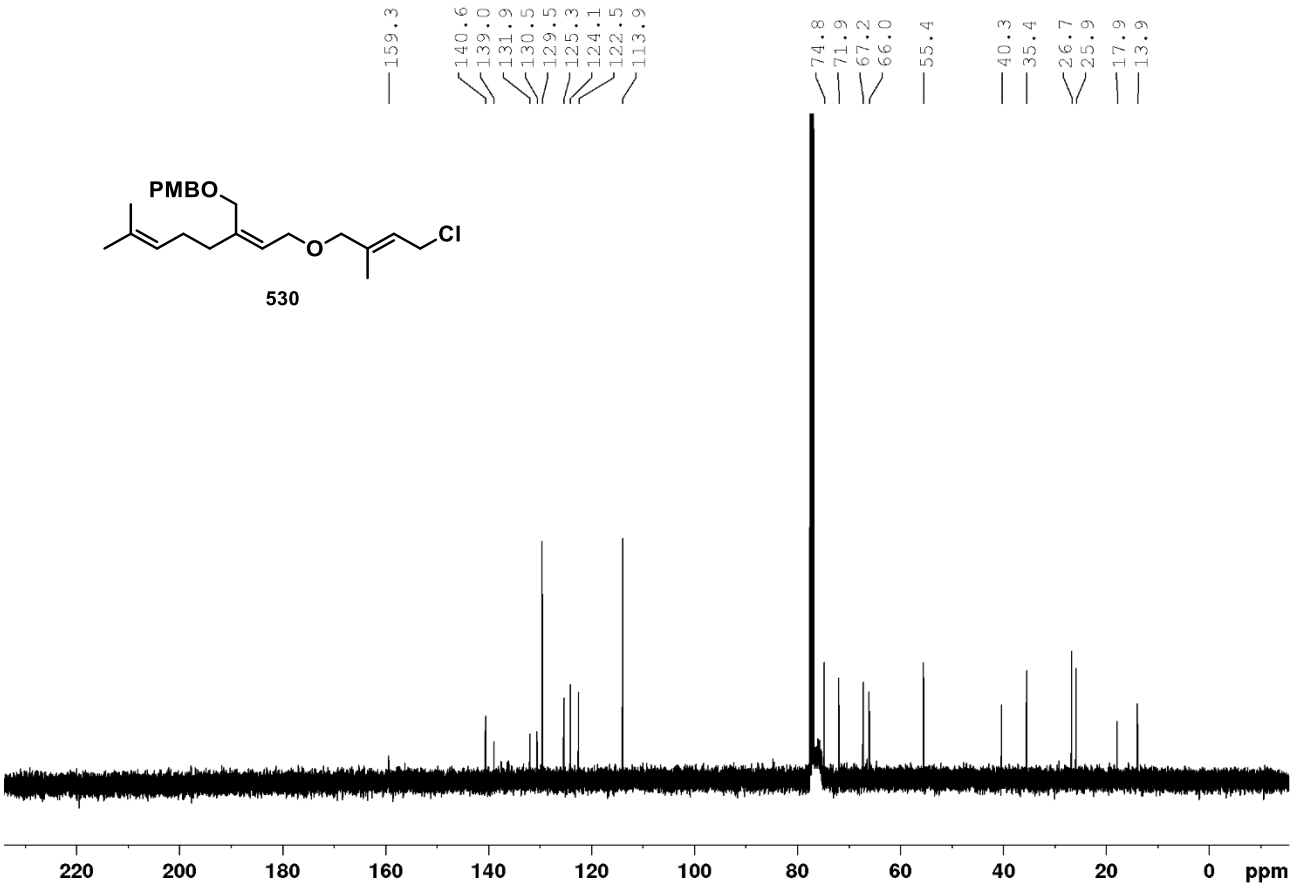
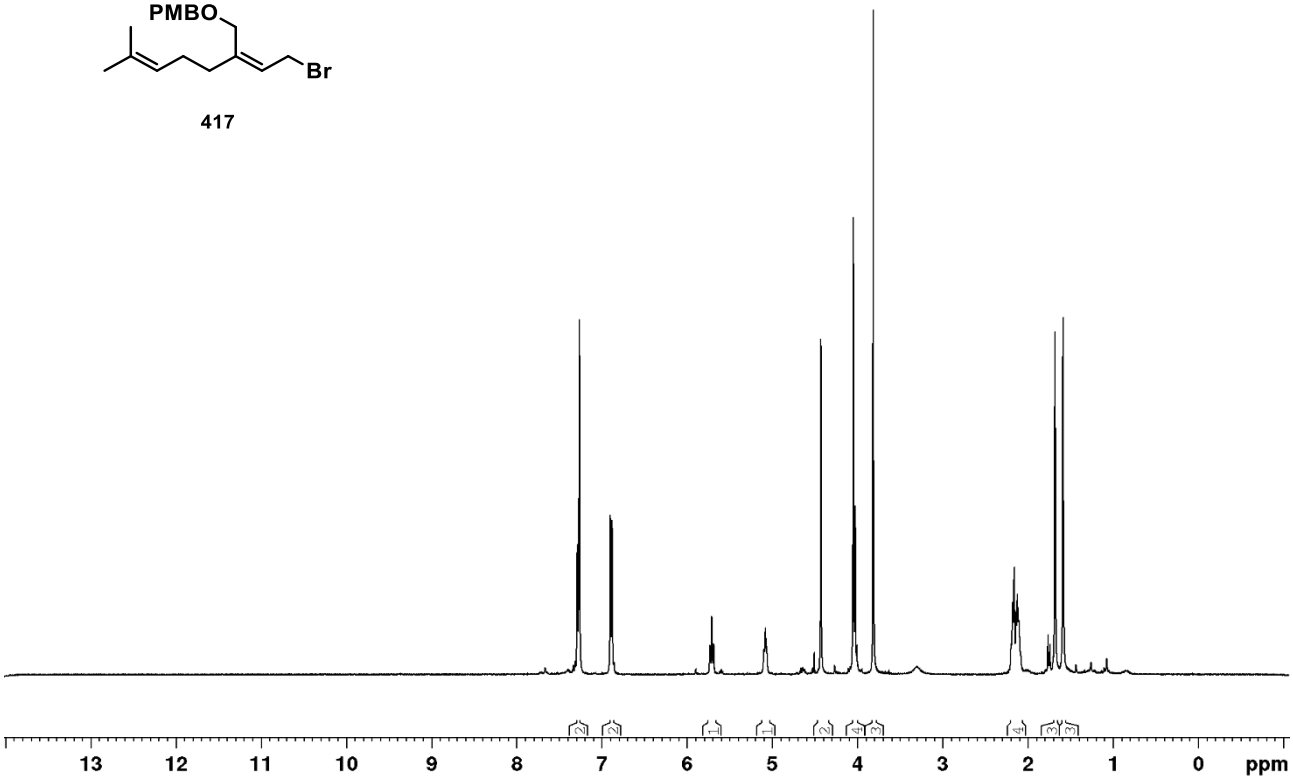
140.2
135.7
134.0
133.7
131.9
130.6
129.7
129.5
127.8
127.4
125.7
124.2
113.9
75.7
71.8
67.2
65.7
60.9
55.4
35.4
27.0
26.7
25.9
19.3
17.9
14.2
PMBO
O
OTBDPS
413
220
200
180
160
140
120
100
80
60
40
20
0
ppm

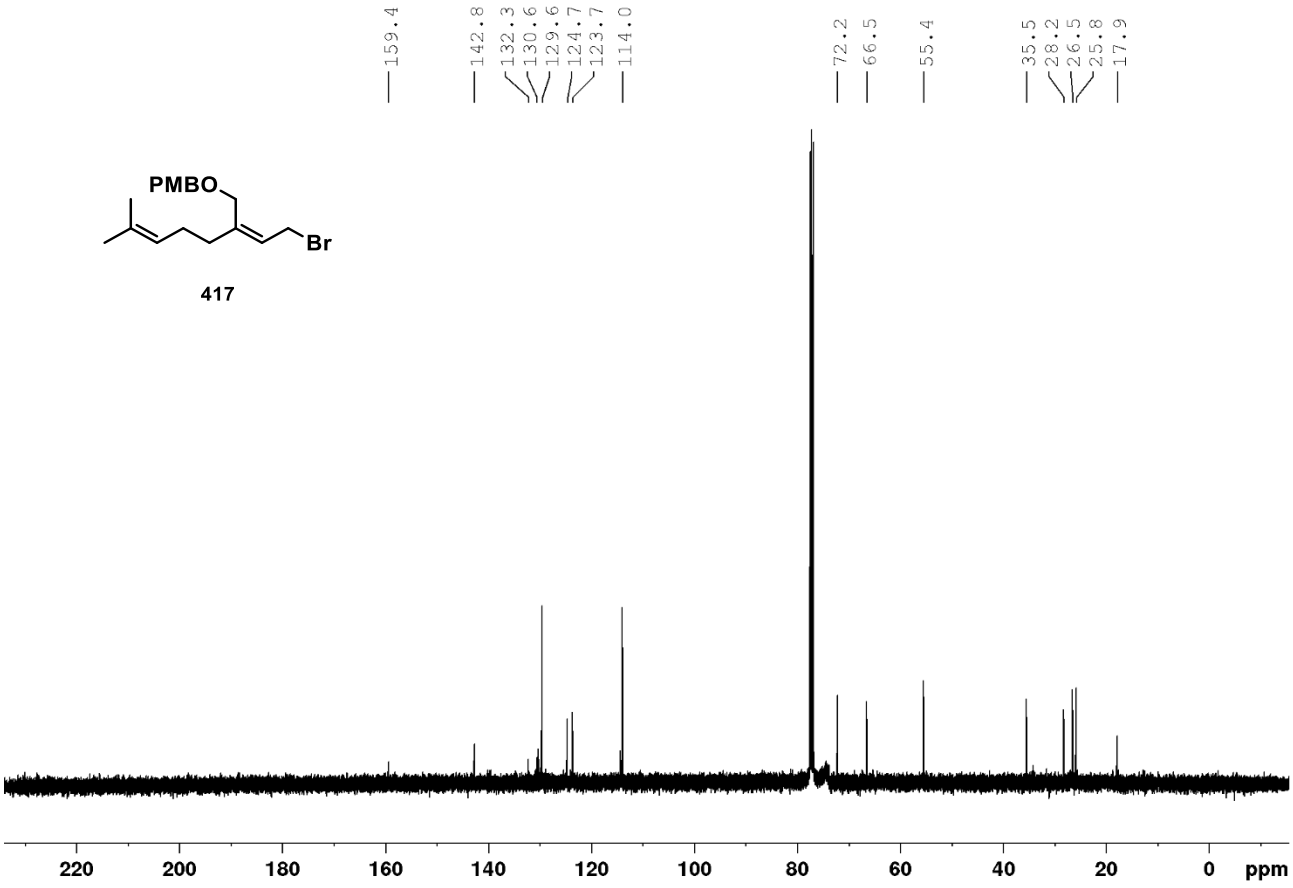

PMBO
O
OH
529
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


159.3
140.3
135.9
131.9
130.5
129.5
126.2
125.5
124.1
113.9
75.5
71.9
67.2
66.0
59.3
55.4
35.4
26.7
25.8
17.9
14.2
PMBO
O
OH
529
220
200
180
160
140
120
100
80
60
40
20
0
ppm

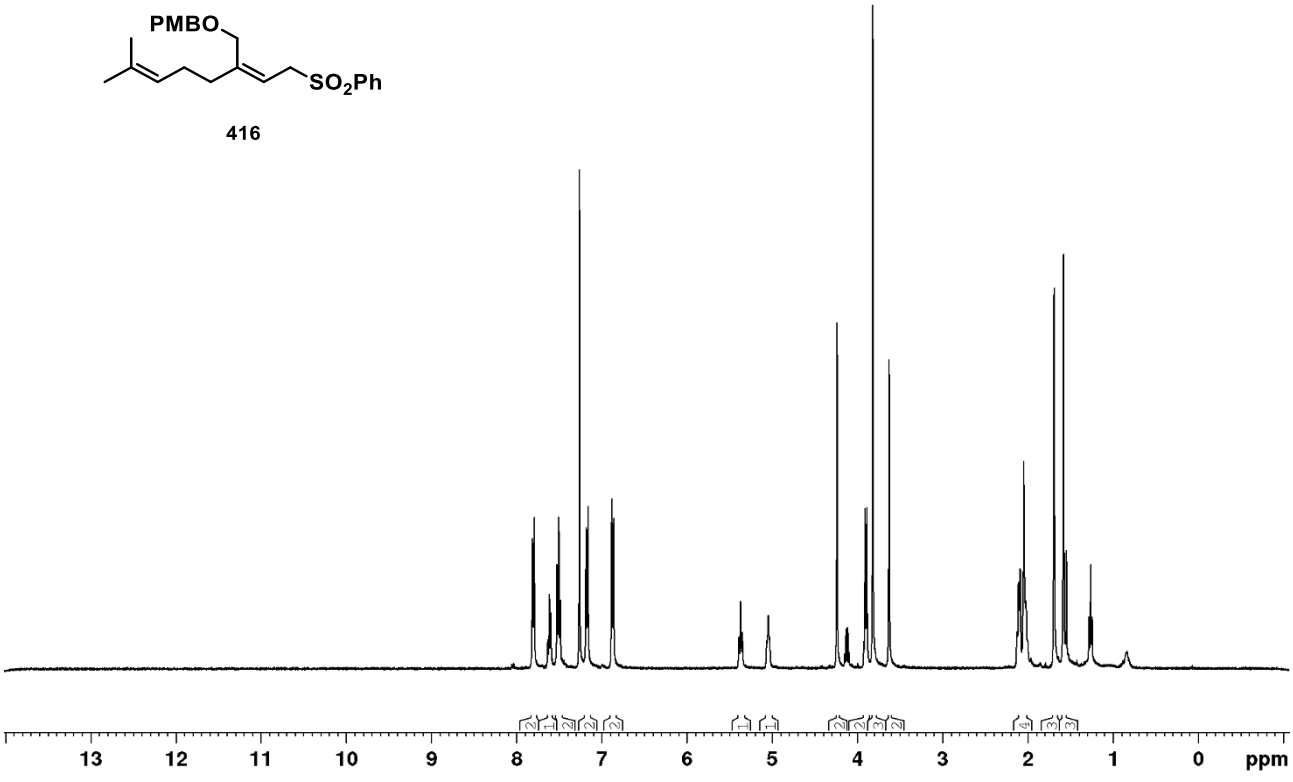

PMBO
O
Cl
530
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


159.3
140.6
139.0
131.9
130.5
129.5
125.3
124.1
122.5
113.9
74.8
71.9
67.2
66.0
55.4
40.3
35.4
26.7
25.9
17.9
13.9
PMBO
O
Cl
530
220
200
180
160
140
120
100
80
60
40
20
0
ppm


PMBO
Br
417
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


159.4
142.8
132.3
130.6
129.6
124.7
123.7
114.0
72.2
66.5
55.4
35.5
28.2
26.5
25.8
17.9
PMBO
Br
220
200
180
160
140
120
100
80
60
40
20
0
ppm

417


PMBO
SO2Ph
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12
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9
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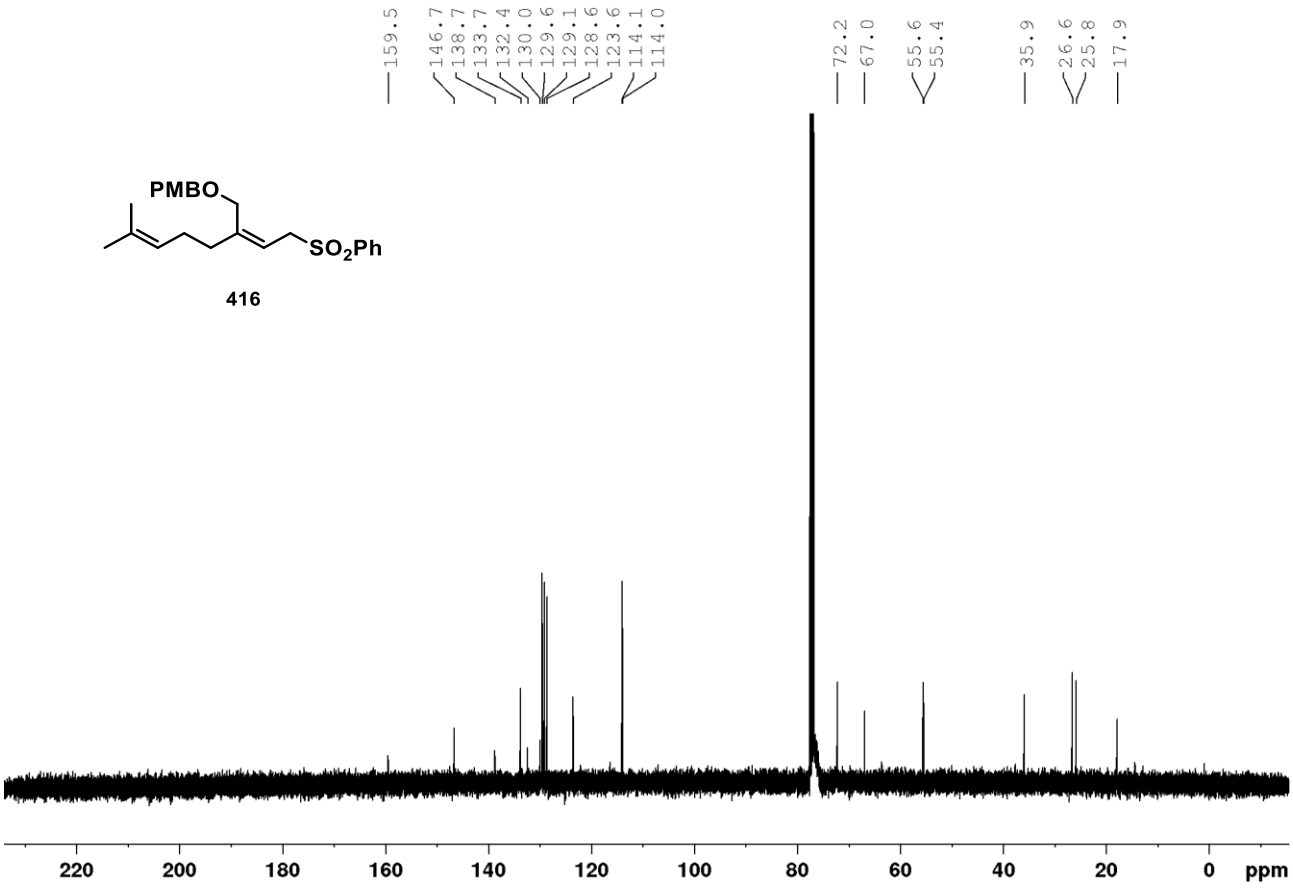
7
6
5
4
3
2
1
0
ppm

416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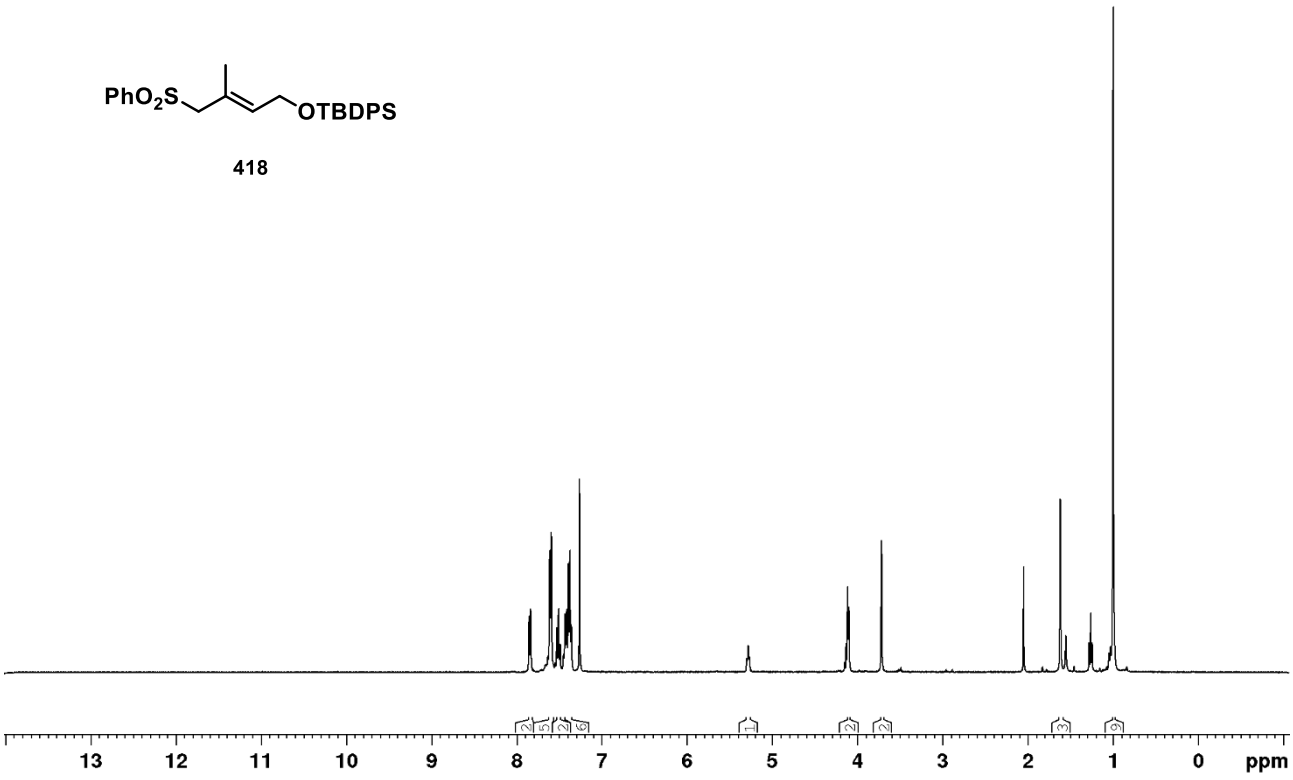
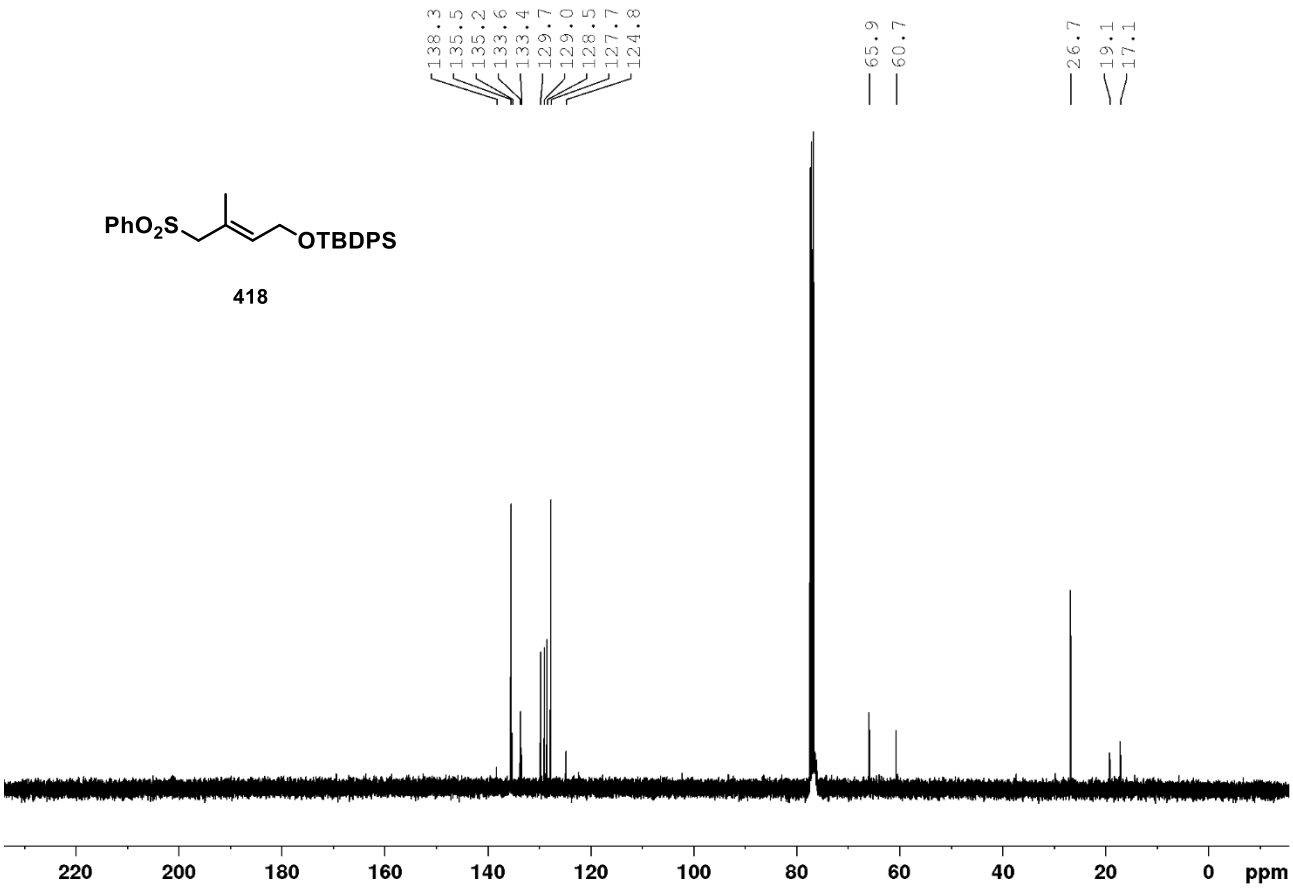
146.7
138.7
133.7
132.4
130.0
129.6
129.1
128.6
123.6
114.1
114.0
72.2
67.0
55.6
55.4
35.9
26.6
25.8
17.9
PMBO
SO2Ph
220
200
180
160
140
120
100
80
60
40
20
0
ppm

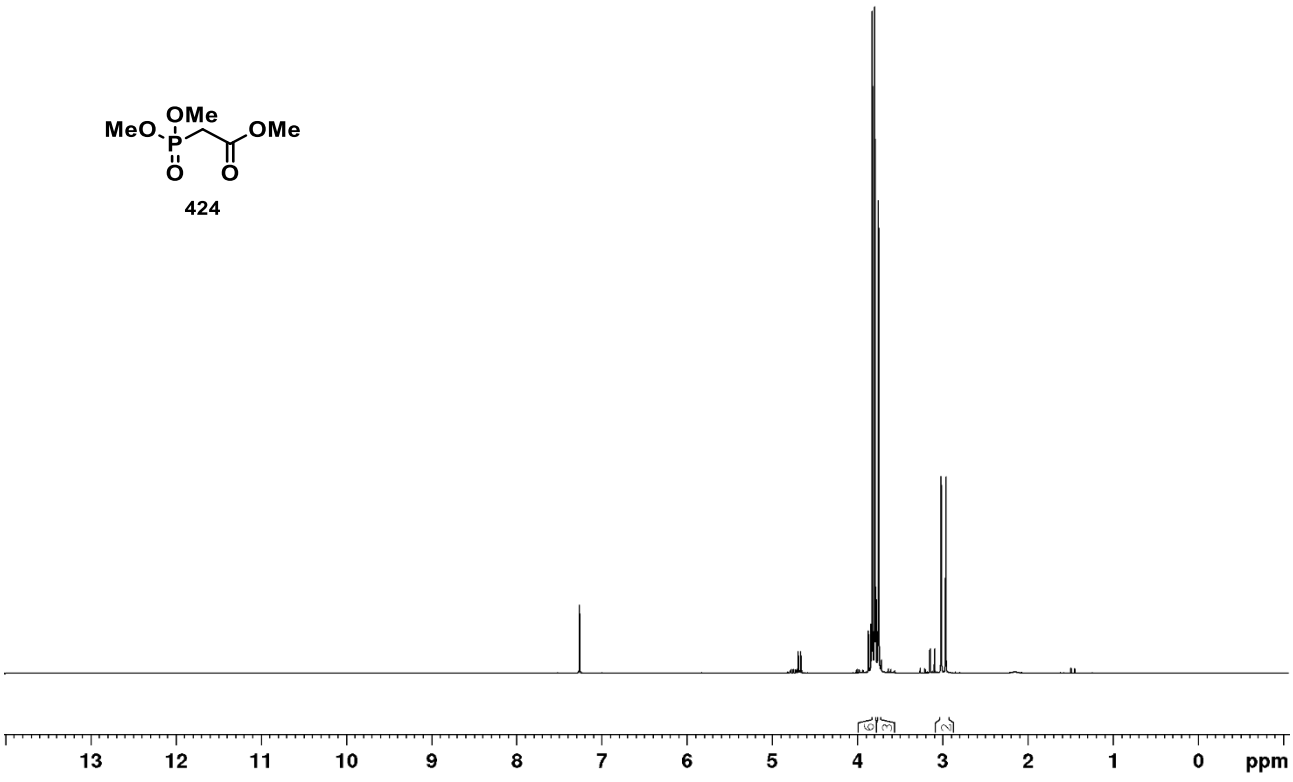
416


PhO2S
OTBDPS
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

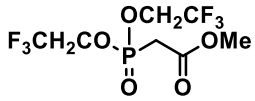
418


138.3
135.5
135.2
133.6
133.4
129.7
129.0
128.5
127.7
124.8
65.9
60.7
26.7
19.1
17.1
PhO2S
OTBDPS
220
200
180
160
140
120
100
80
60
40
20
0
ppm

418


MeO
OMe
P
O
OMe
O
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

424


OCH2CF3
F3CH2CO
P
OMe
O
O

425

13
12
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10
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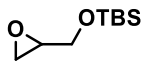
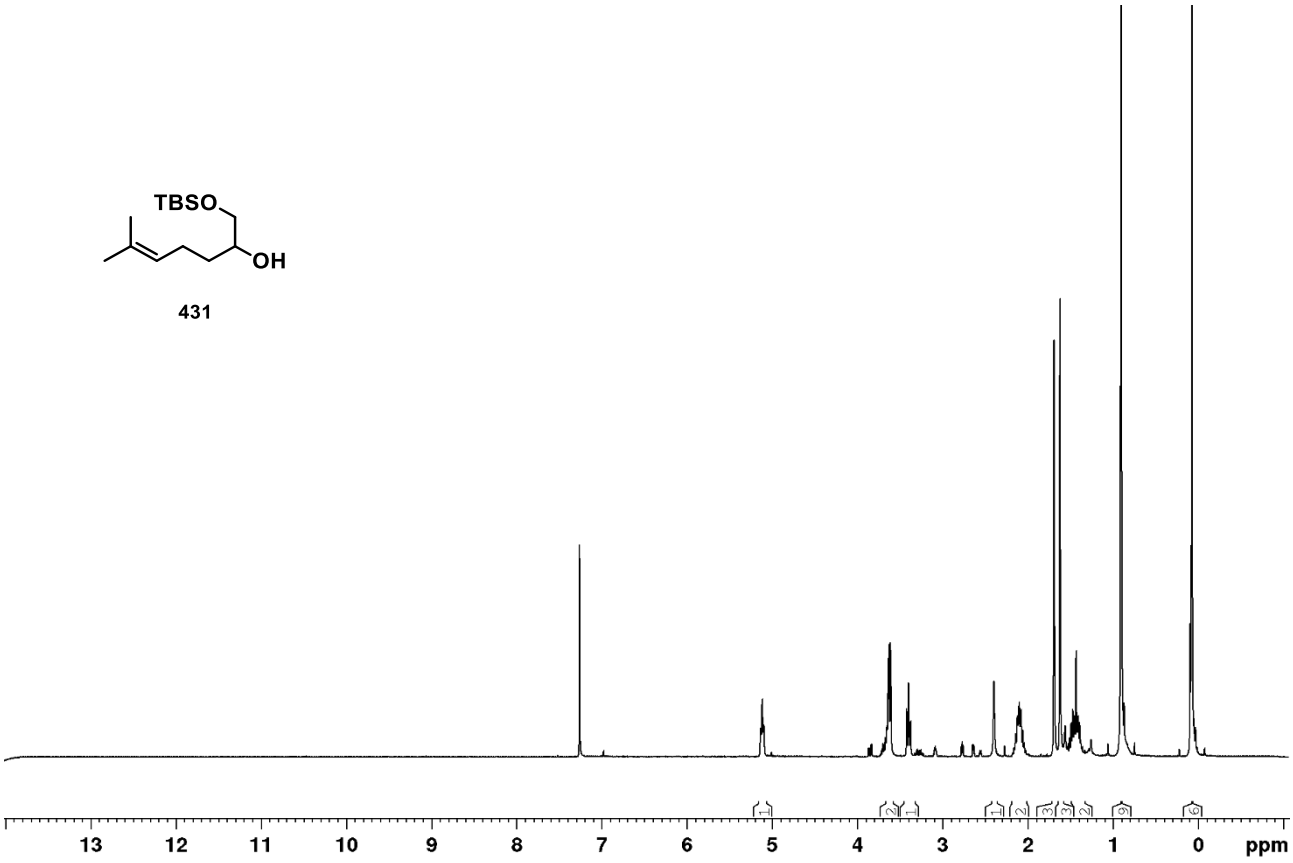
8
7
6
5
4
3
2
1
0
ppm


O
OTBS

430

13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


TBSO
OH
431
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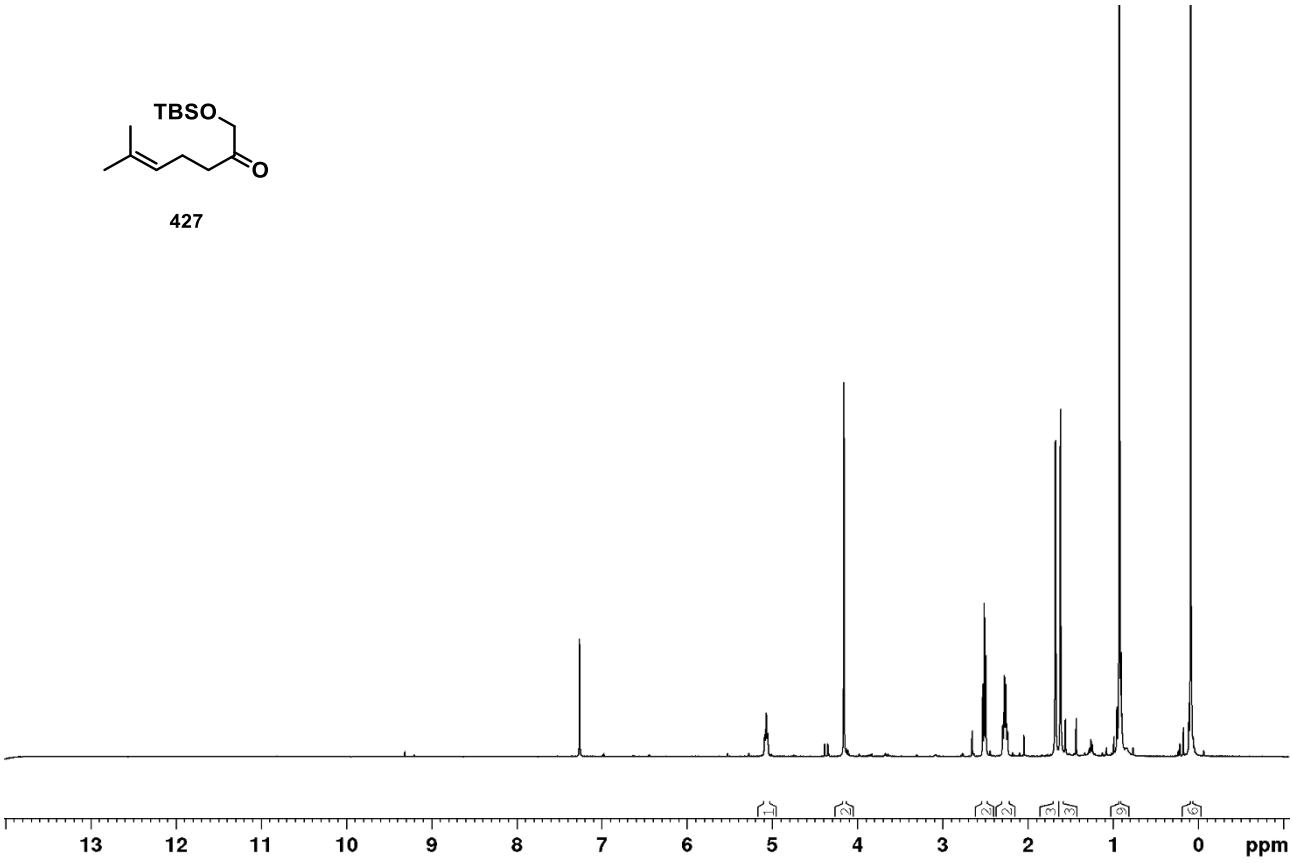
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


TBSO
O
427
13
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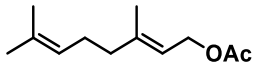
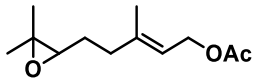
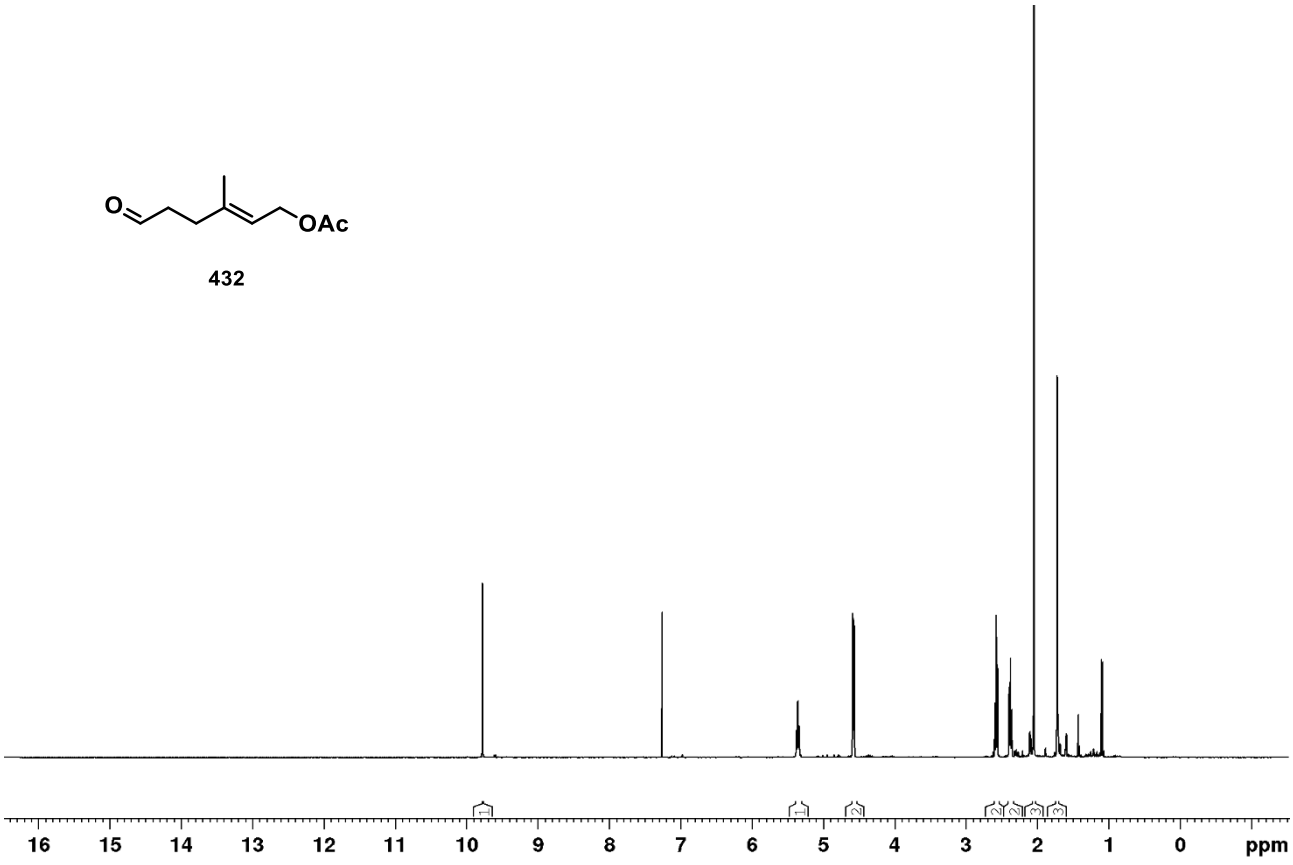
11
10
9
8
7
6
5
4
3
2
1
0
ppm



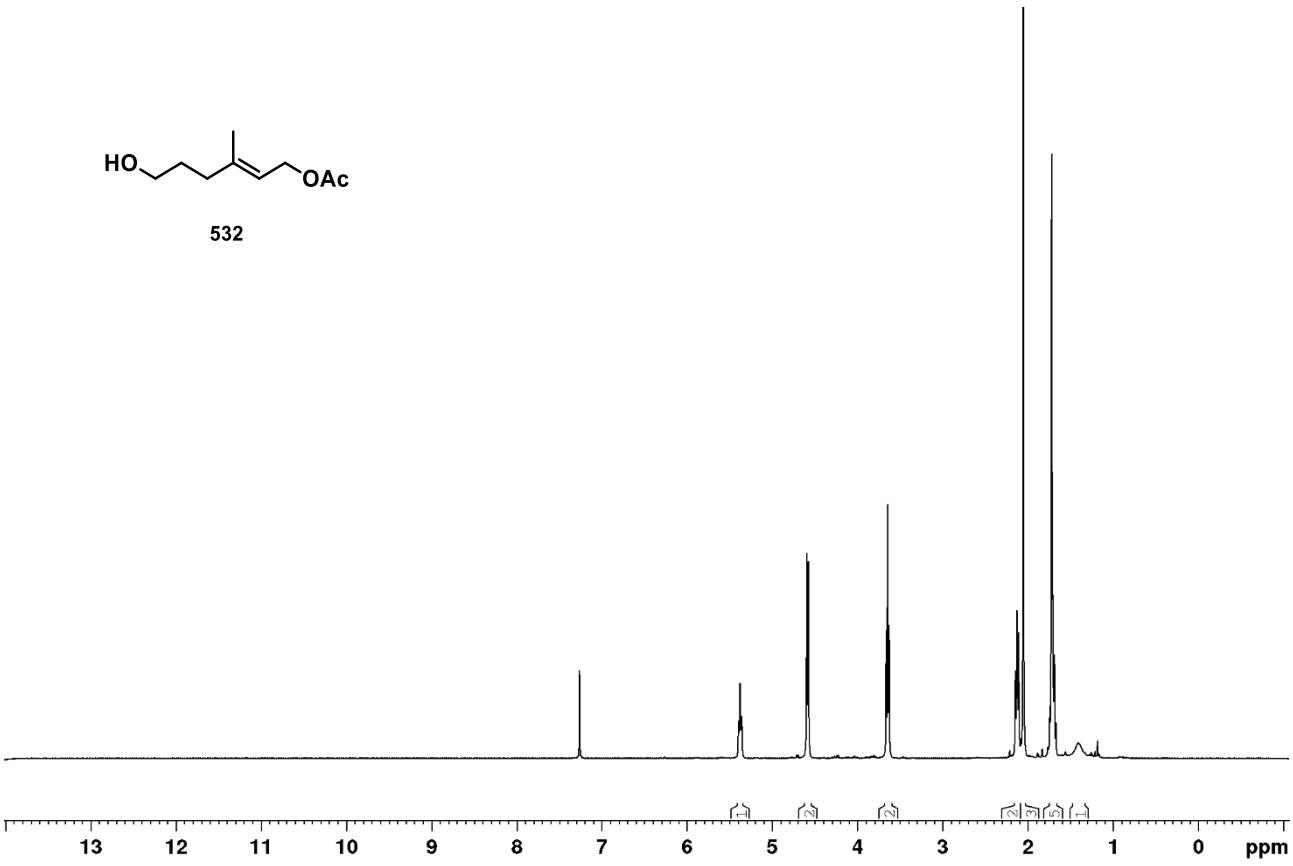
453



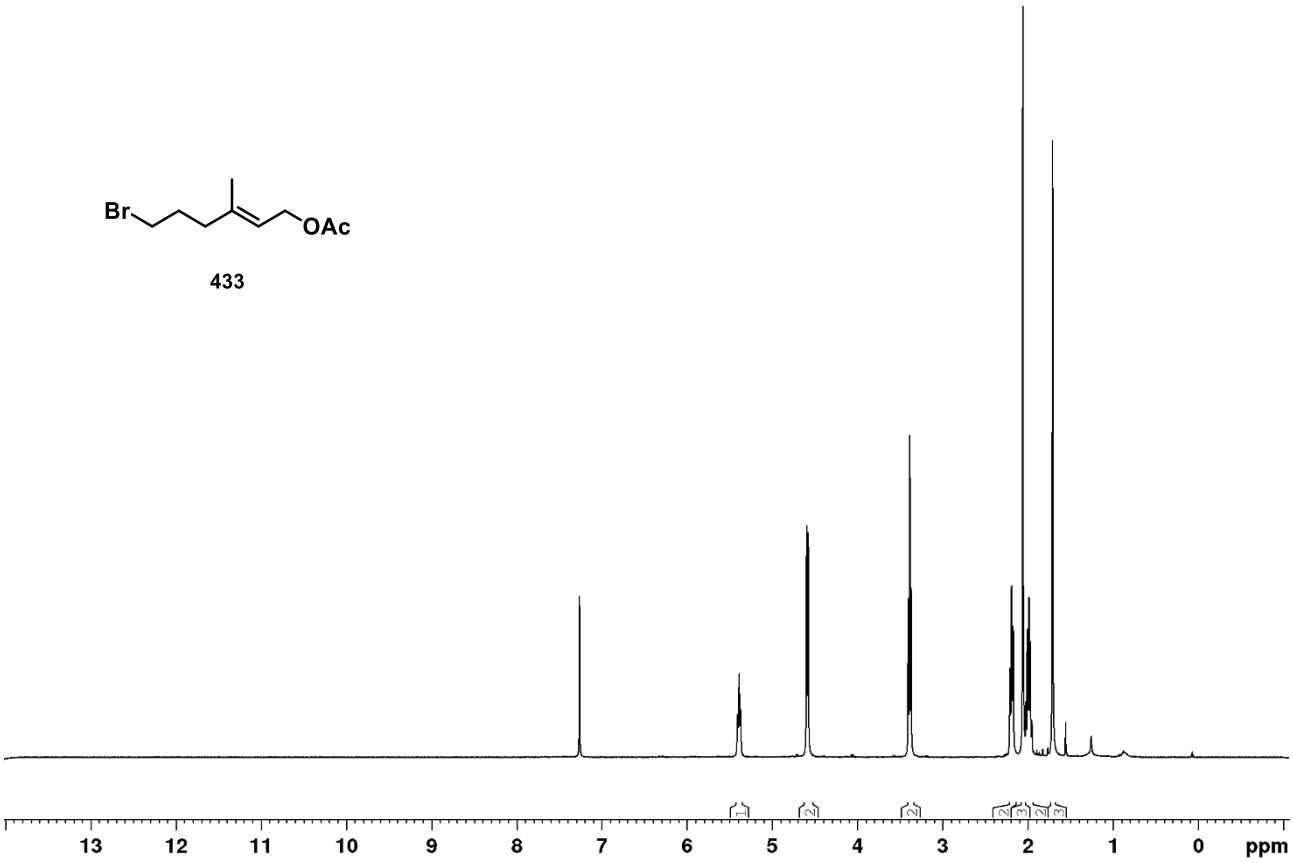
531

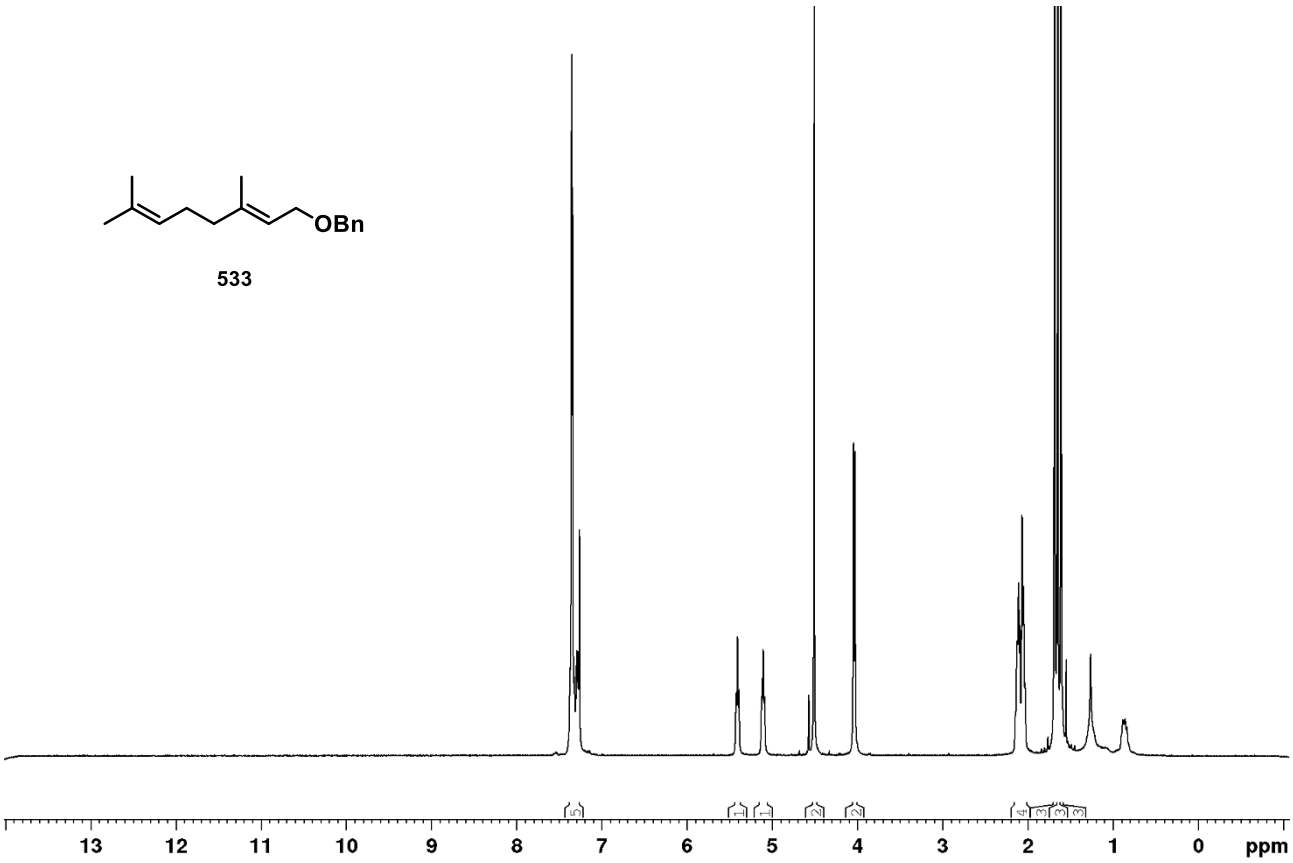

O
OAc
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm

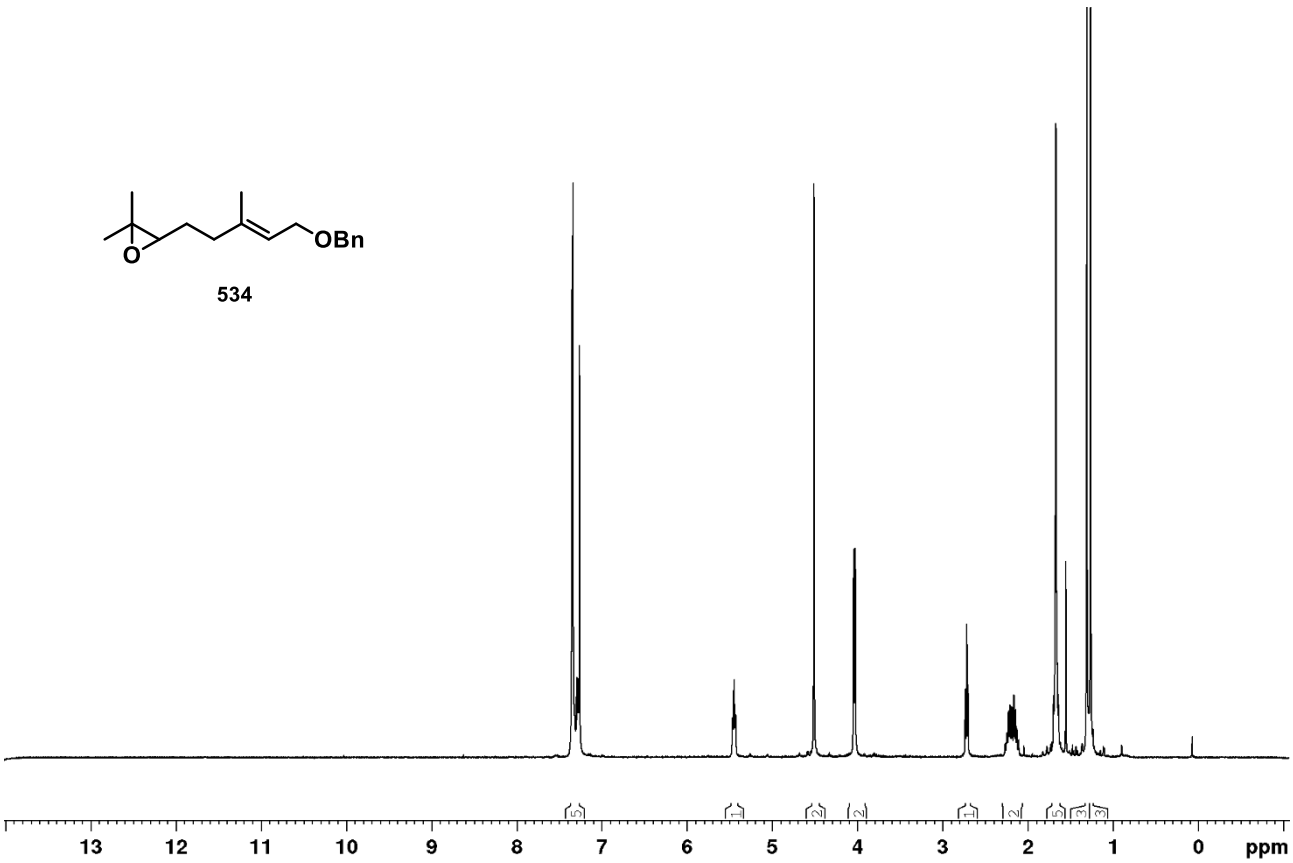
432

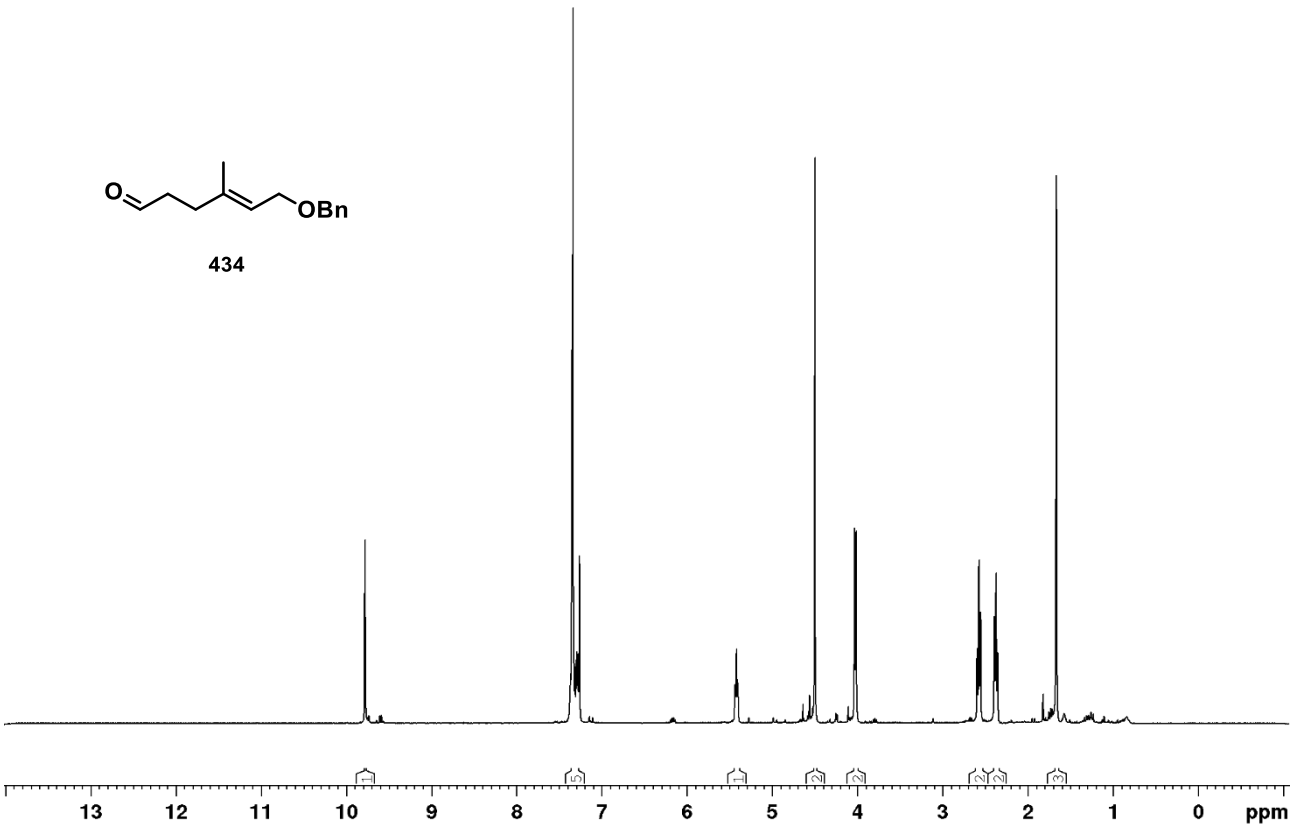

HO
OAc
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm

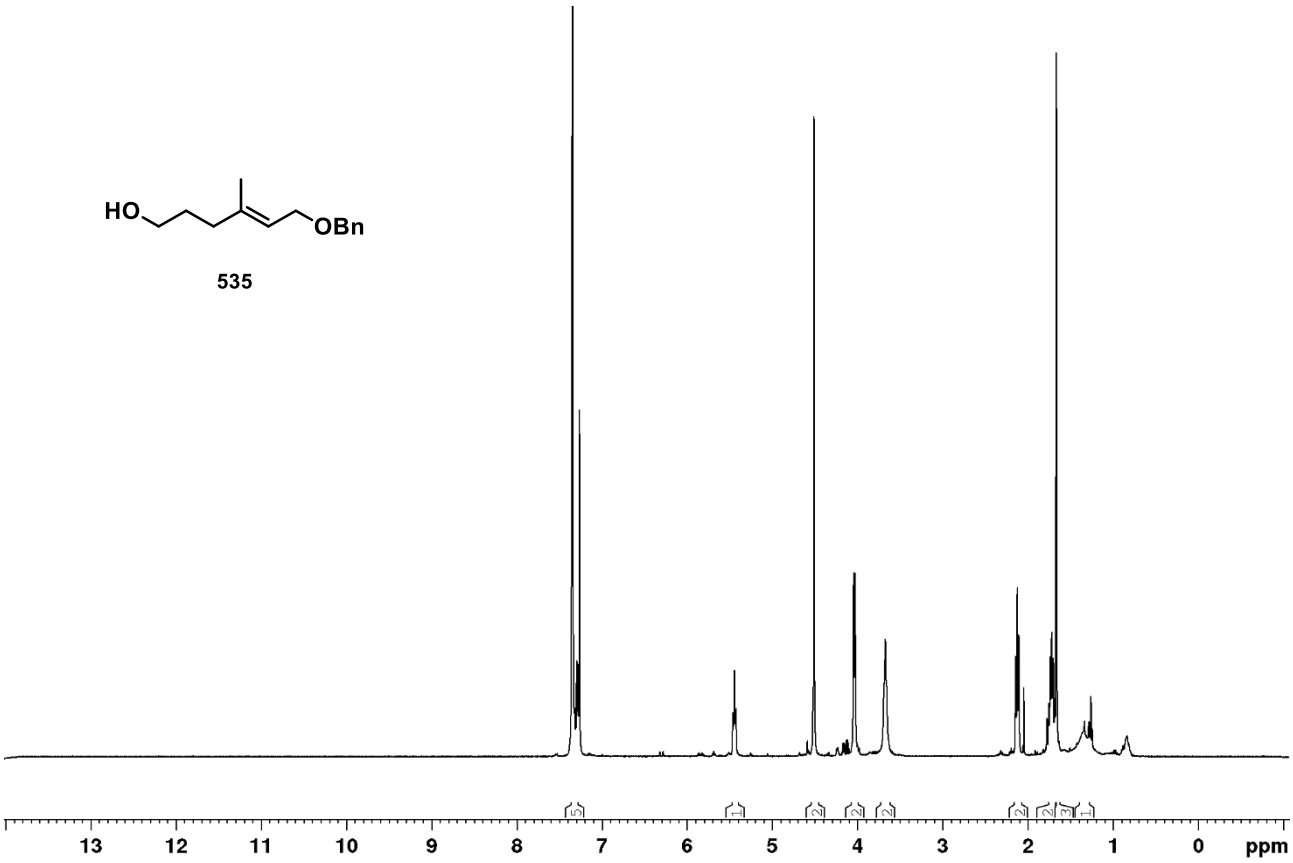
532

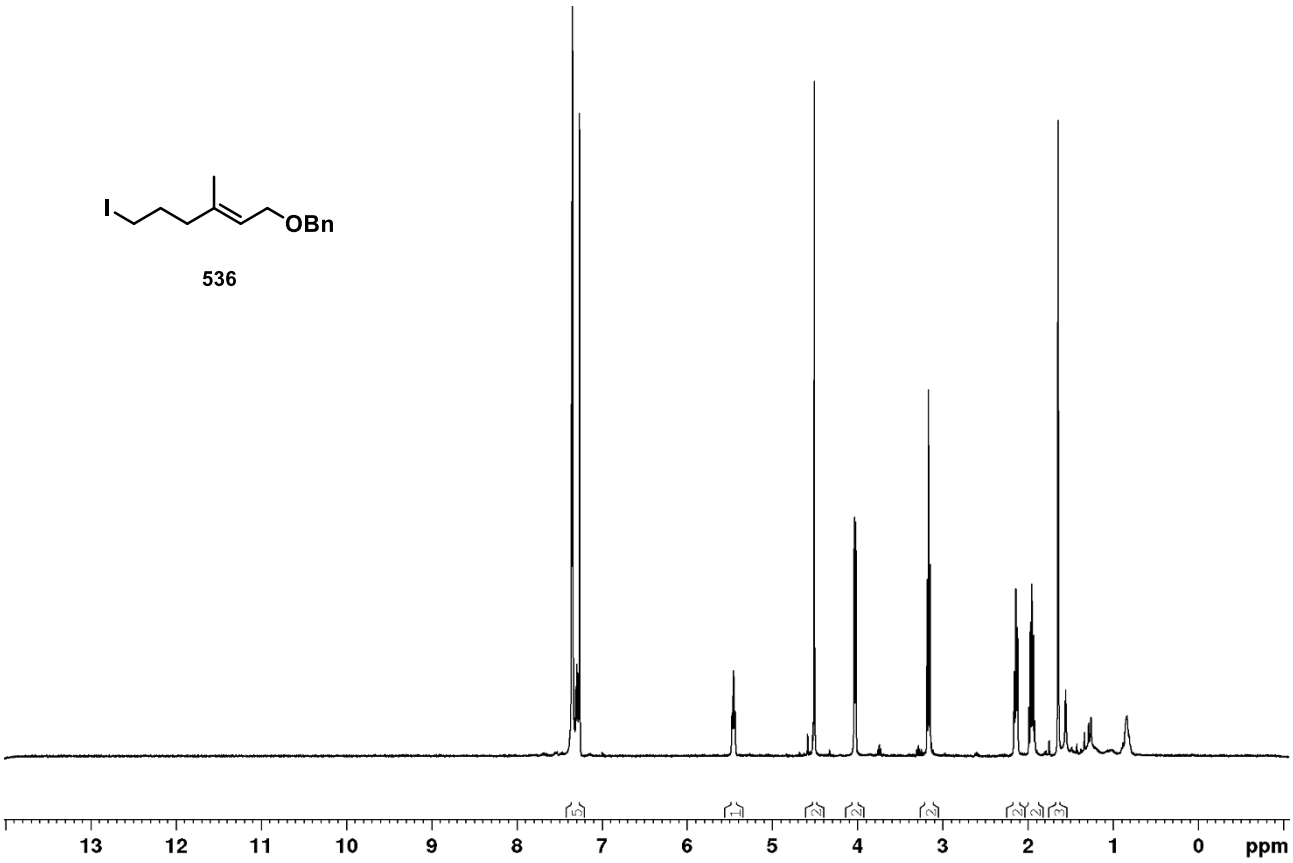

Br
OAc
433
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

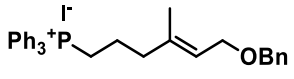

OBn
533
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


OBn
O
534
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


O
OBn
434
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

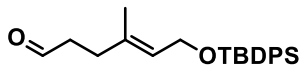

HO
OBn
535
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


I
OBn
536
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


I-
Ph3+P
OBn

436

12
8
1
2
2
2
2
2
3
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


O
OTBDPS

422

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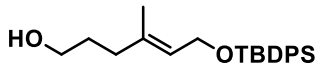
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


HO
OTBDPS

537

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9
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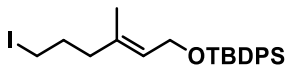
7
6
5
4
3
2
1
0
ppm


I
OTBDPS

538

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7
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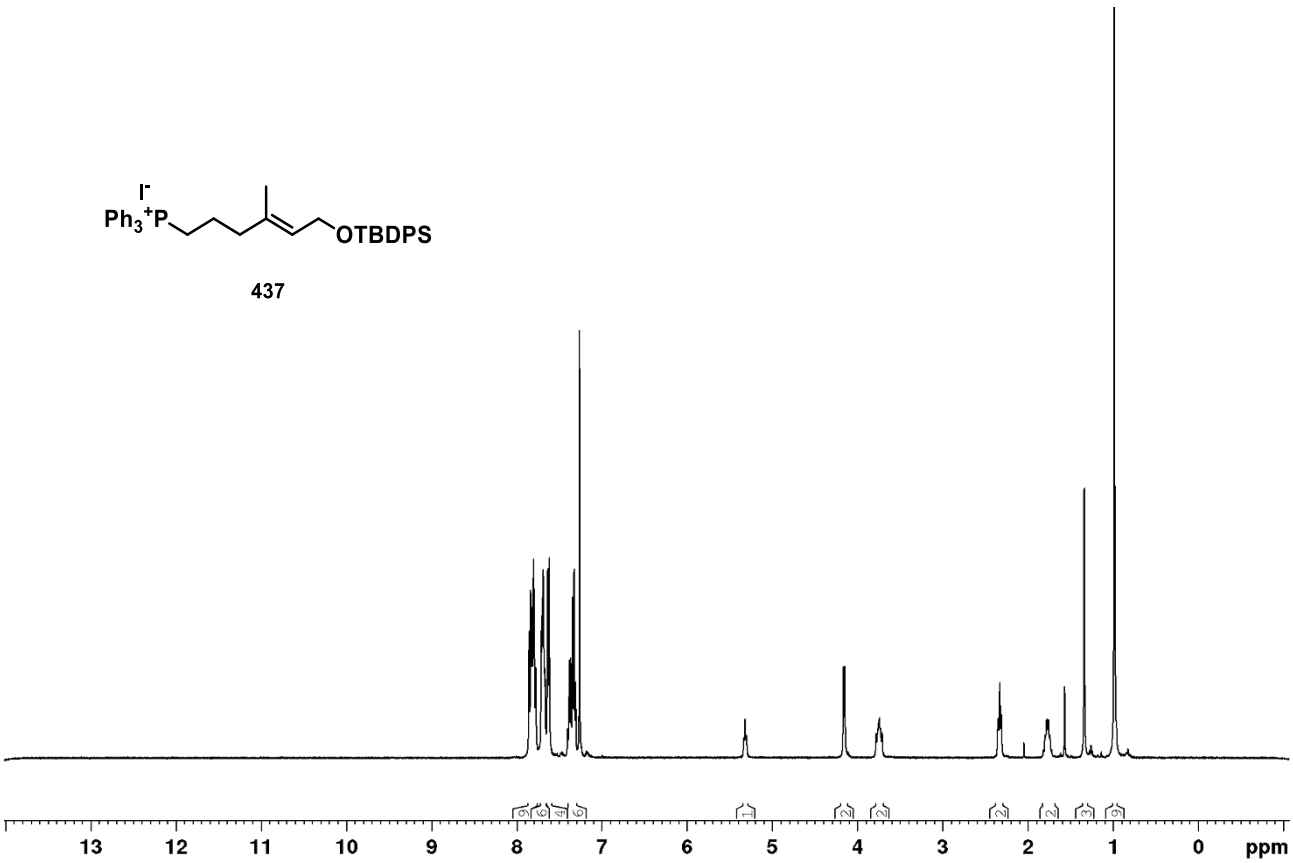
4
3
2
1
0
ppm


I-
Ph3+P
OTBDPS
437
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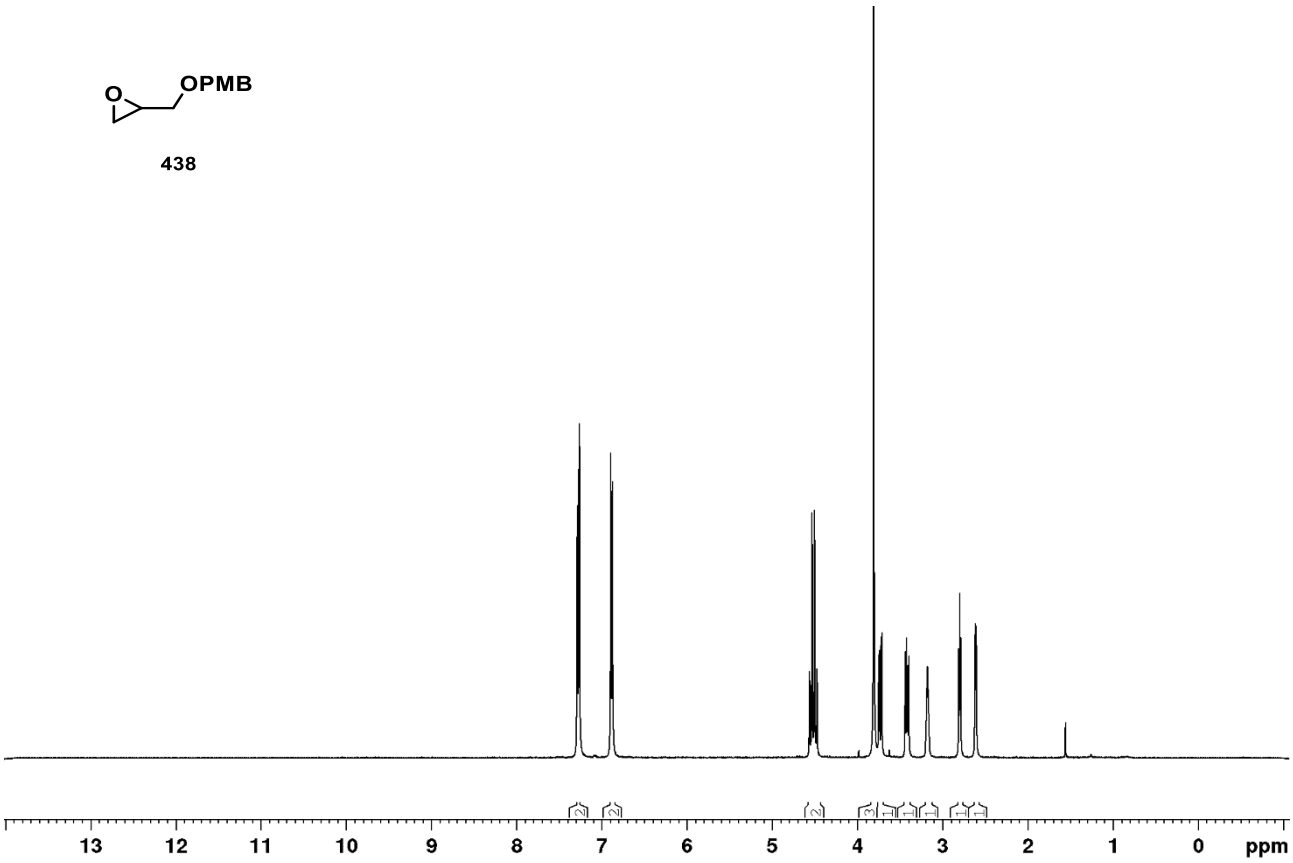
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


O
OPMB
438
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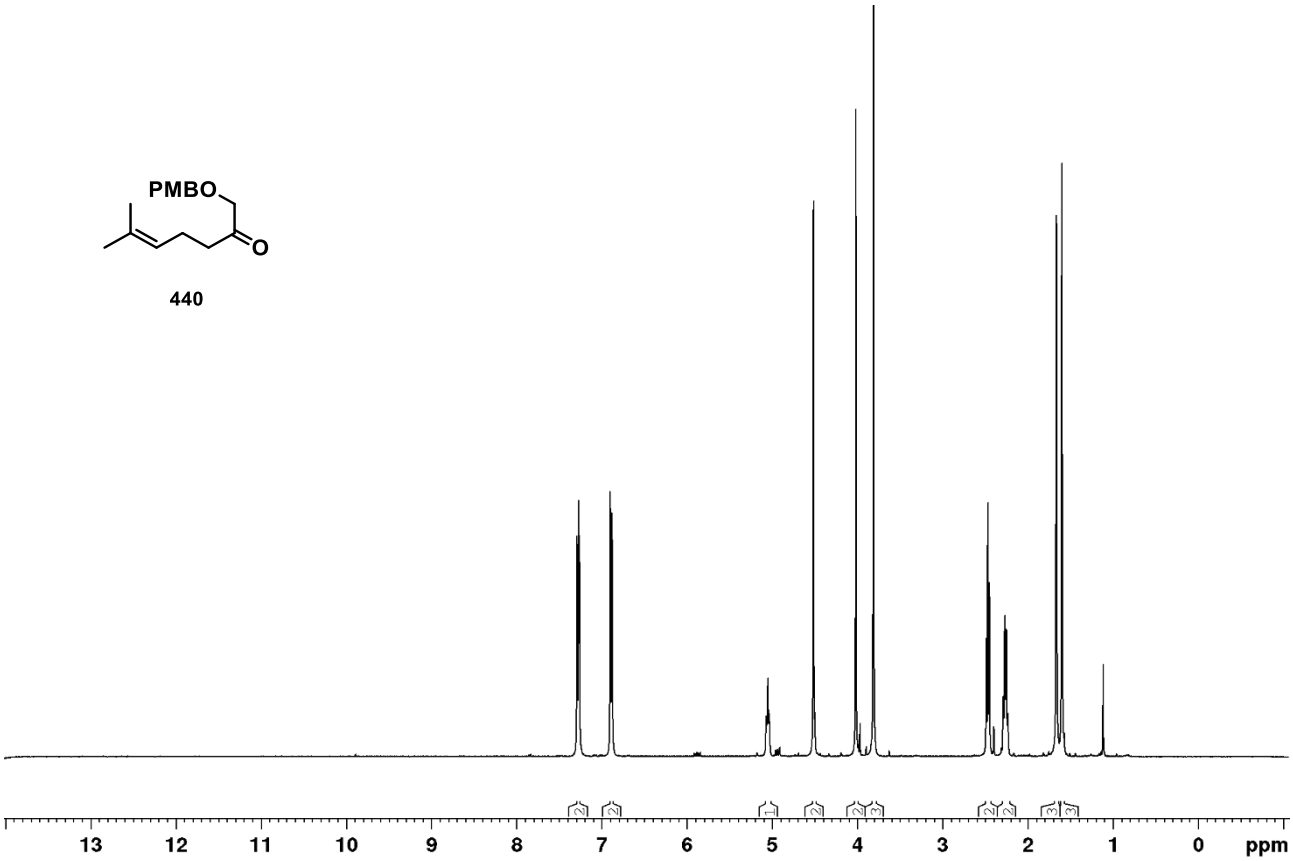
6
5
4
3
2
1
0
ppm


PMBO
O
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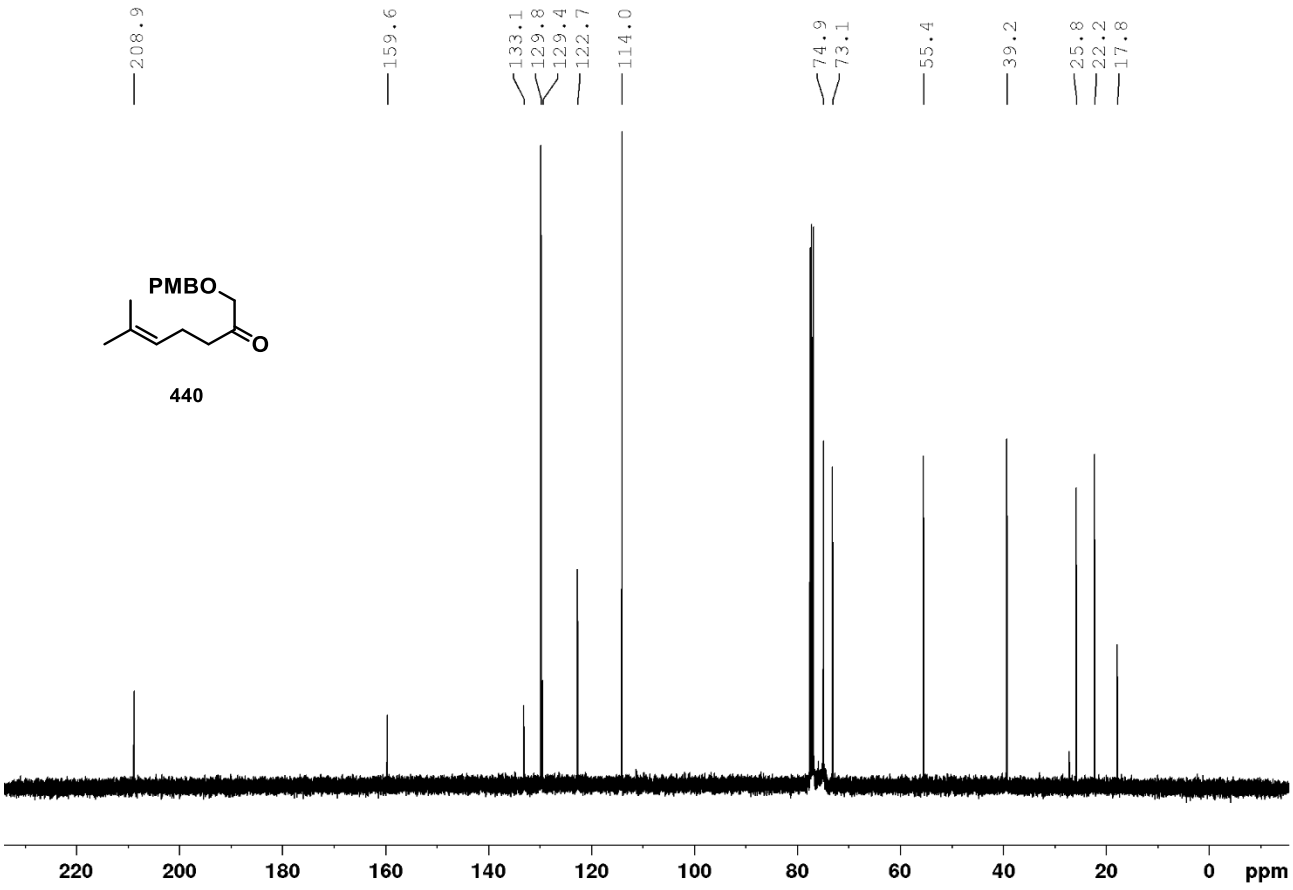
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm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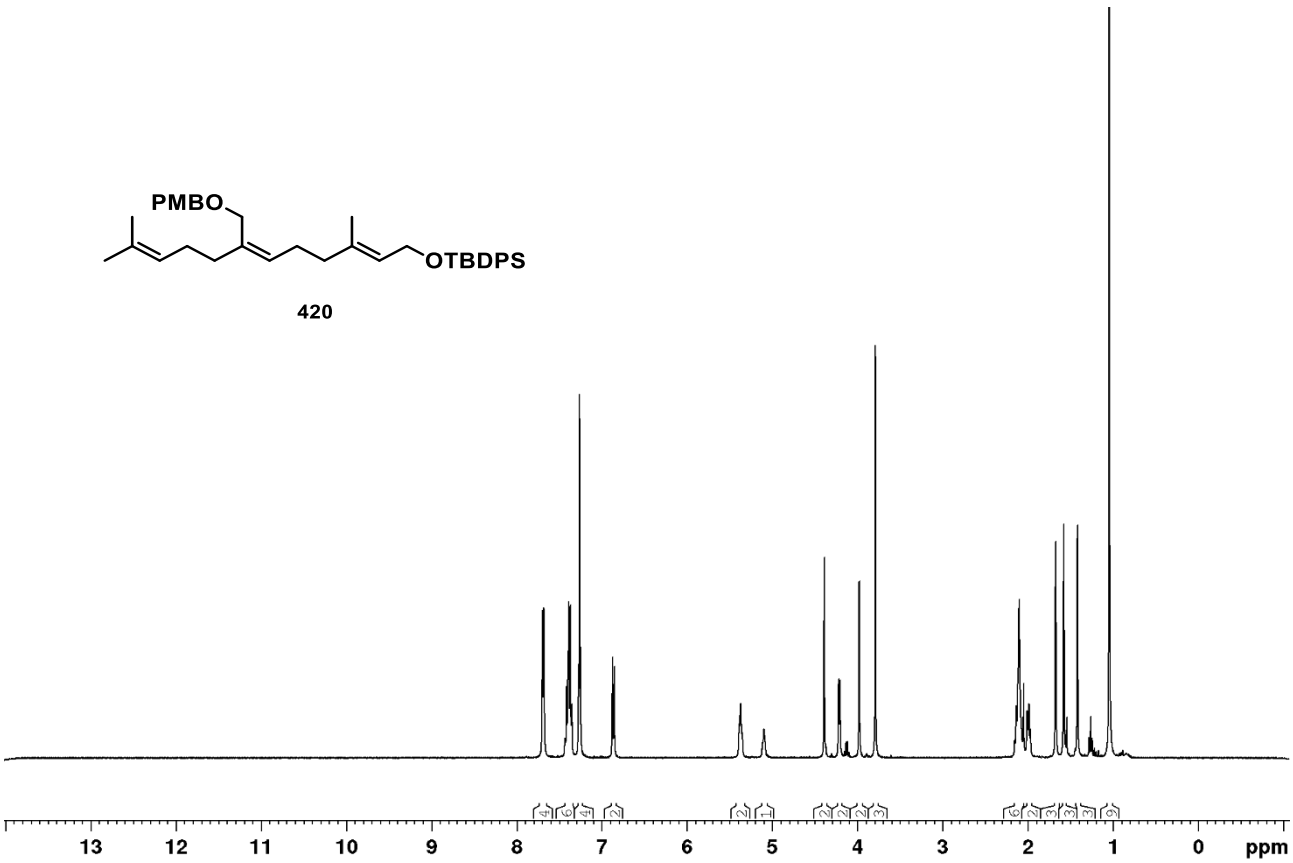
159.6
133.1
129.8
129.4
122.7
114.0
74.9
73.1
55.4
39.2
25.8
22.2
17.8
PMBO
O
440
220
200
180
160
140
120
100
80
60
40
20
0
ppm


PMBO
OTBDPS
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13
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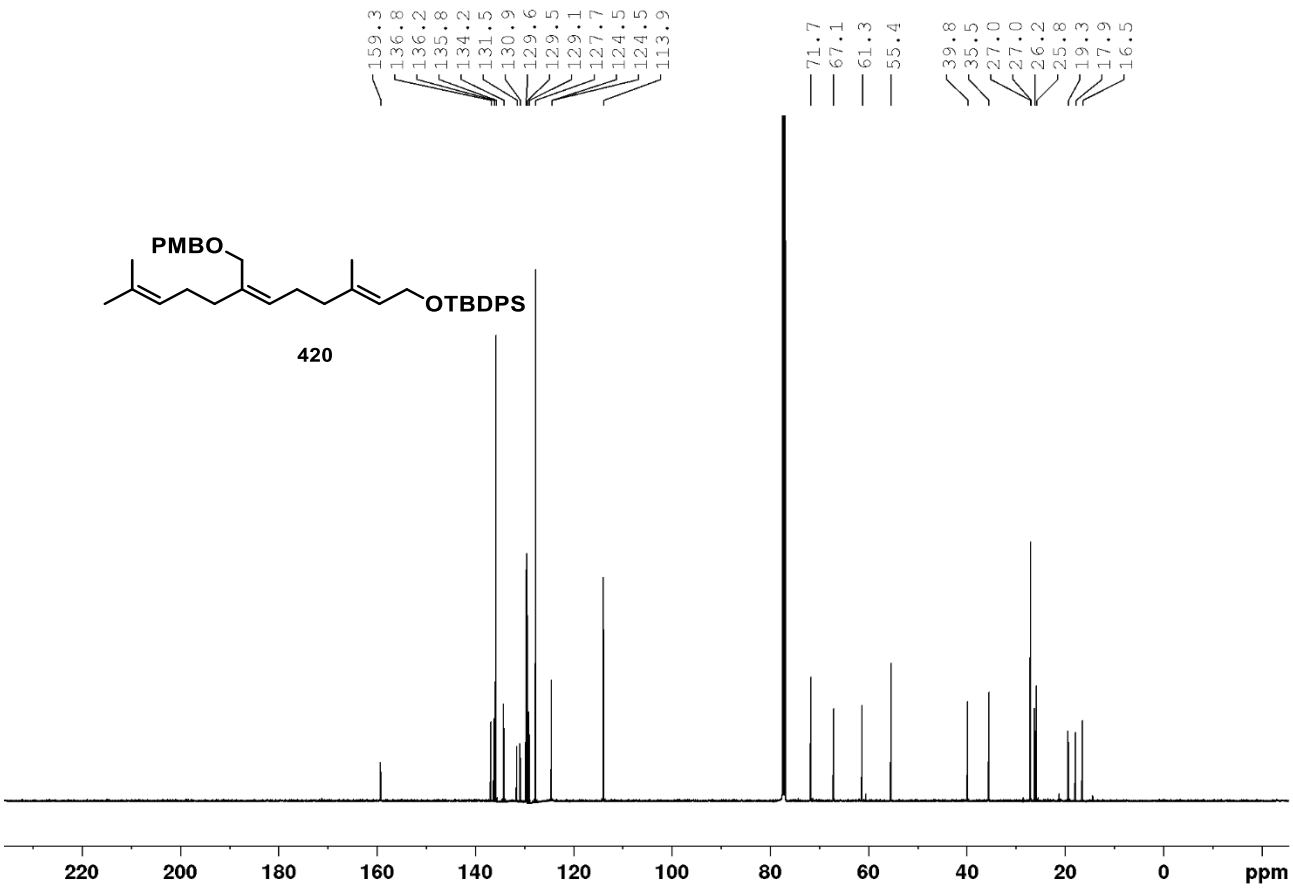
11
10
9
8
7
6
5
4
3
2
1
0
ppm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136.8
136.2
135.8
134.2
131.5
130.9
129.6
129.5
129.1
127.7
124.5
124.5
113.9
71.7
67.1
61.3
55.4
39.8
35.5
27.0
27.0
26.2
25.8
19.3
17.9
16.5
PMBO
OTBDPS
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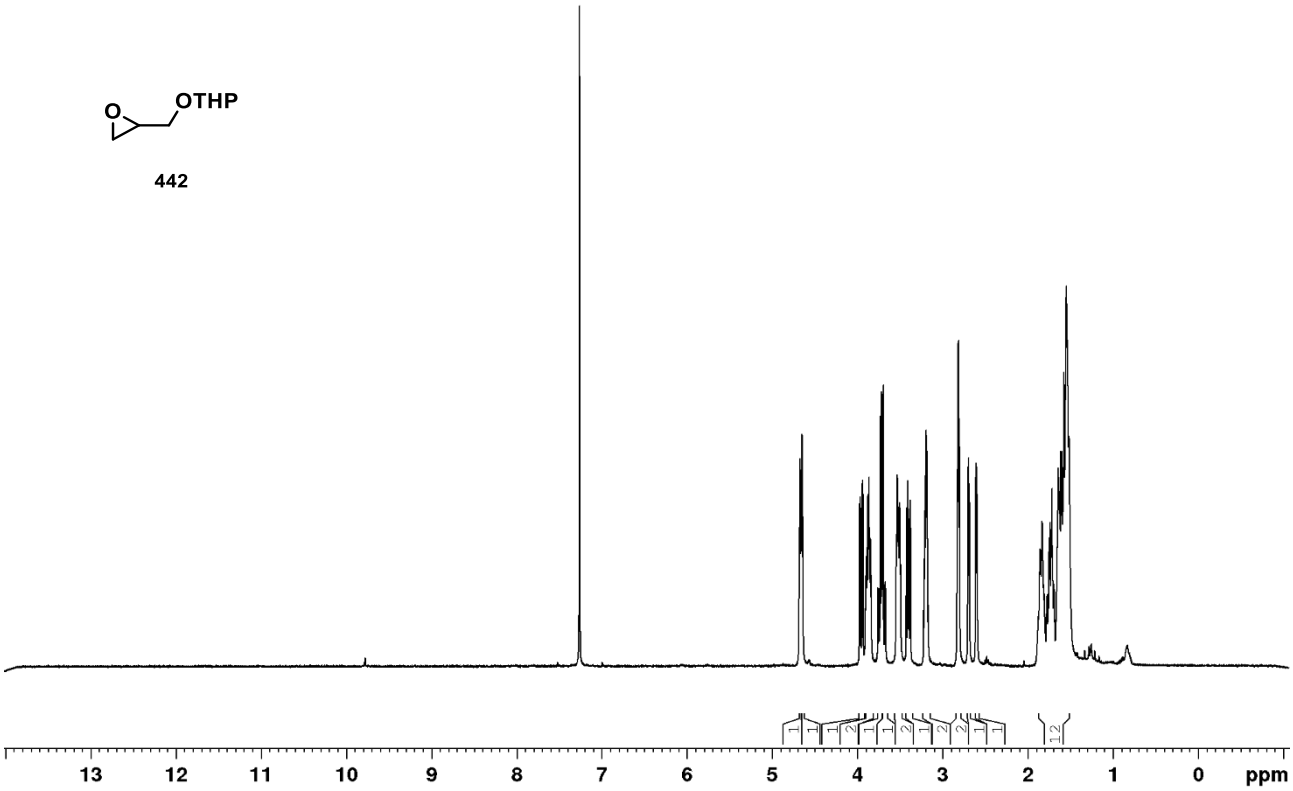
220
200
180
160
140
120
100
80
60
40
20
0
ppm


OTHP
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6
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4
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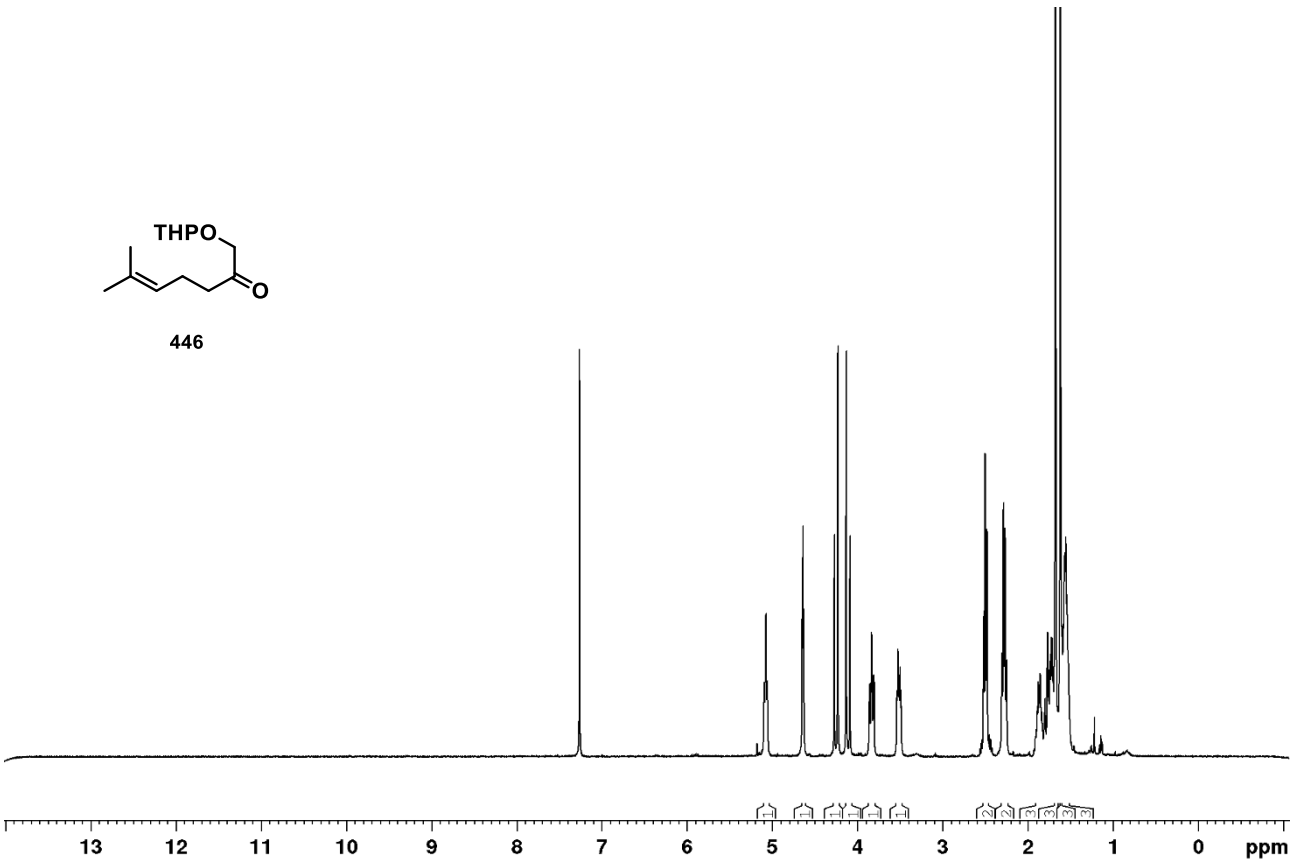
2
1
0
ppm


THPO
O
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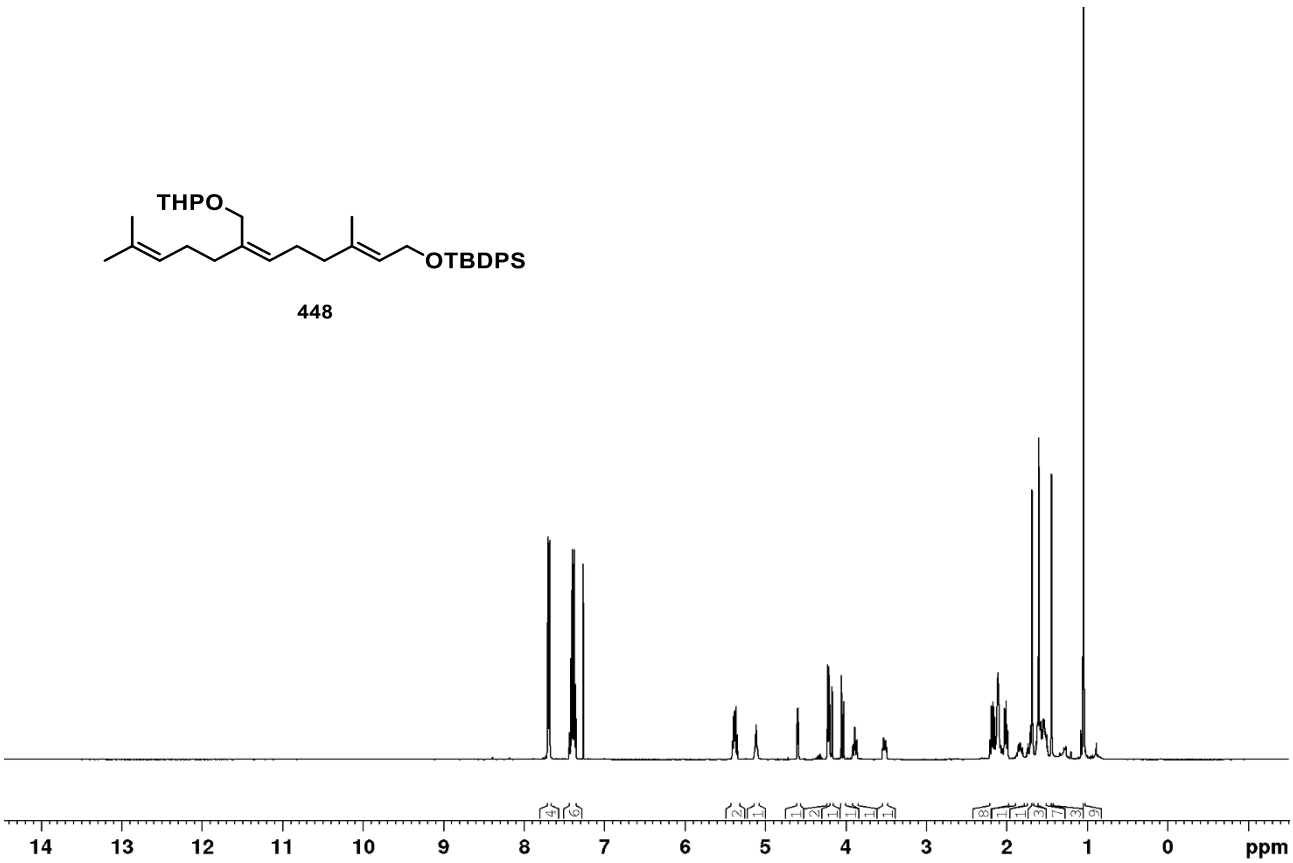
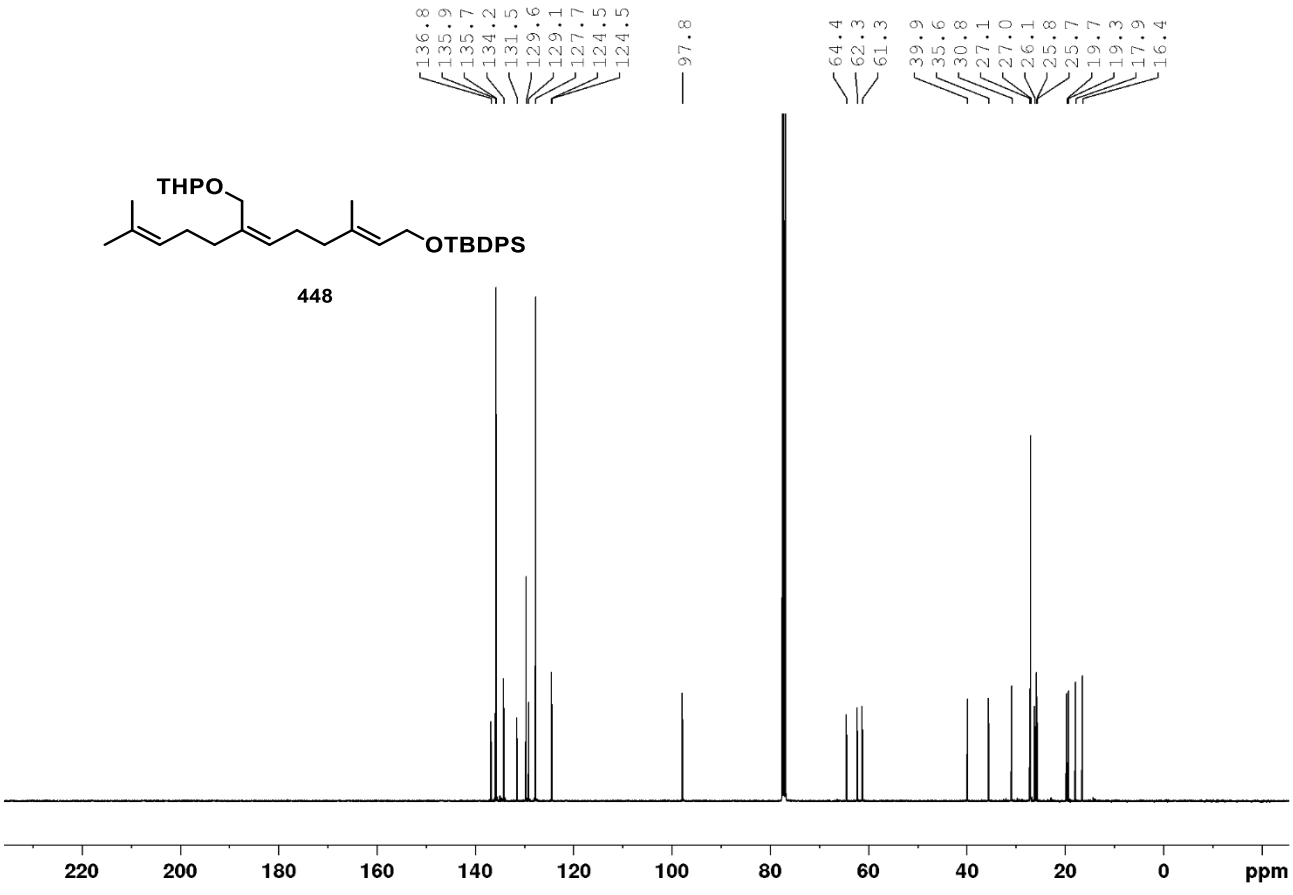
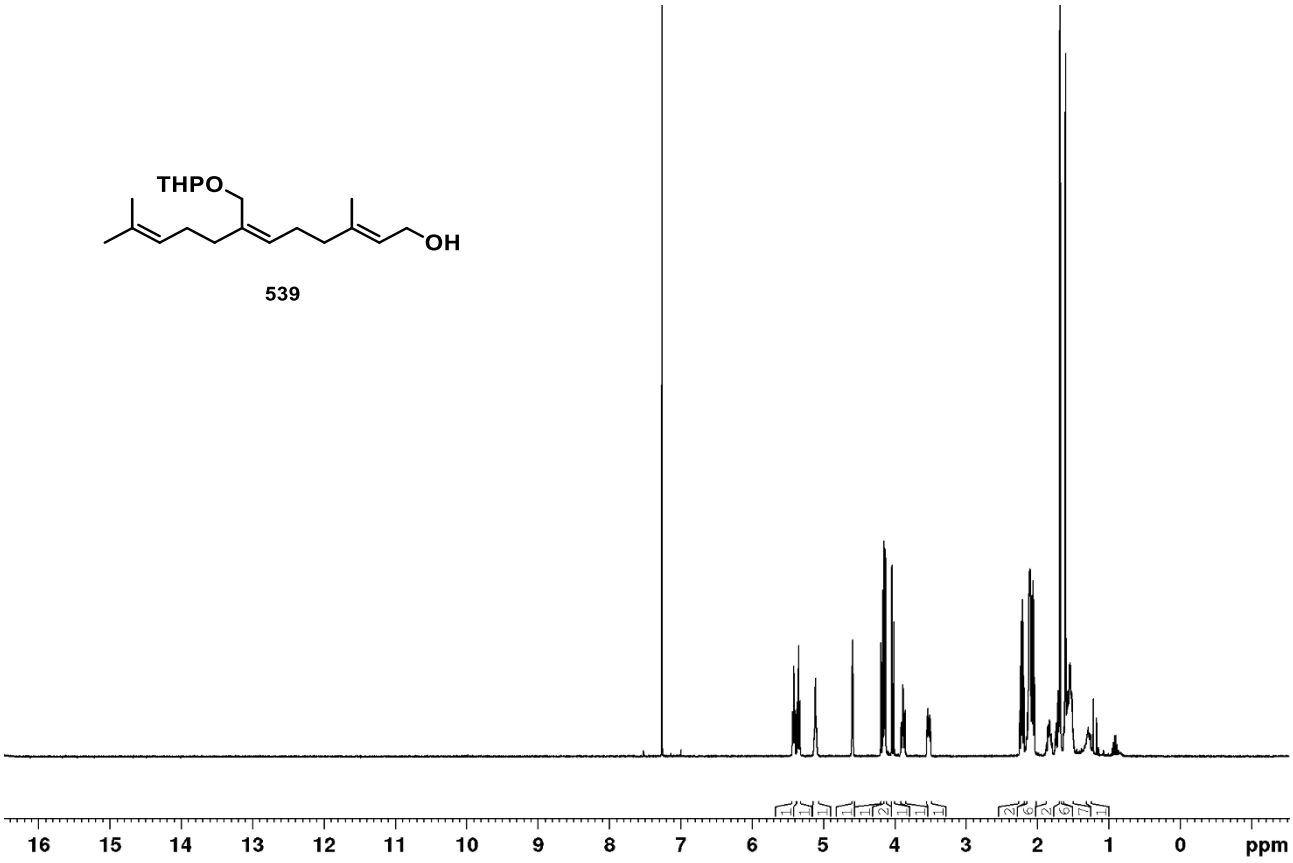
8
7
6
5
4
3
2
1
0
ppm


THPO
OTBDPS
448
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


136.8
135.9
135.7
134.2
131.5
129.6
129.1
127.7
124.5
124.5
97.8
64.4
62.3
61.3
39.9
35.6
30.8
27.1
27.0
26.1
25.8
25.7
19.7
19.3
17.9
16.4
THPO
OTBDPS
448
220
200
180
160
140
120
100
80
60
40
20
0
ppm


THPO
OH
539
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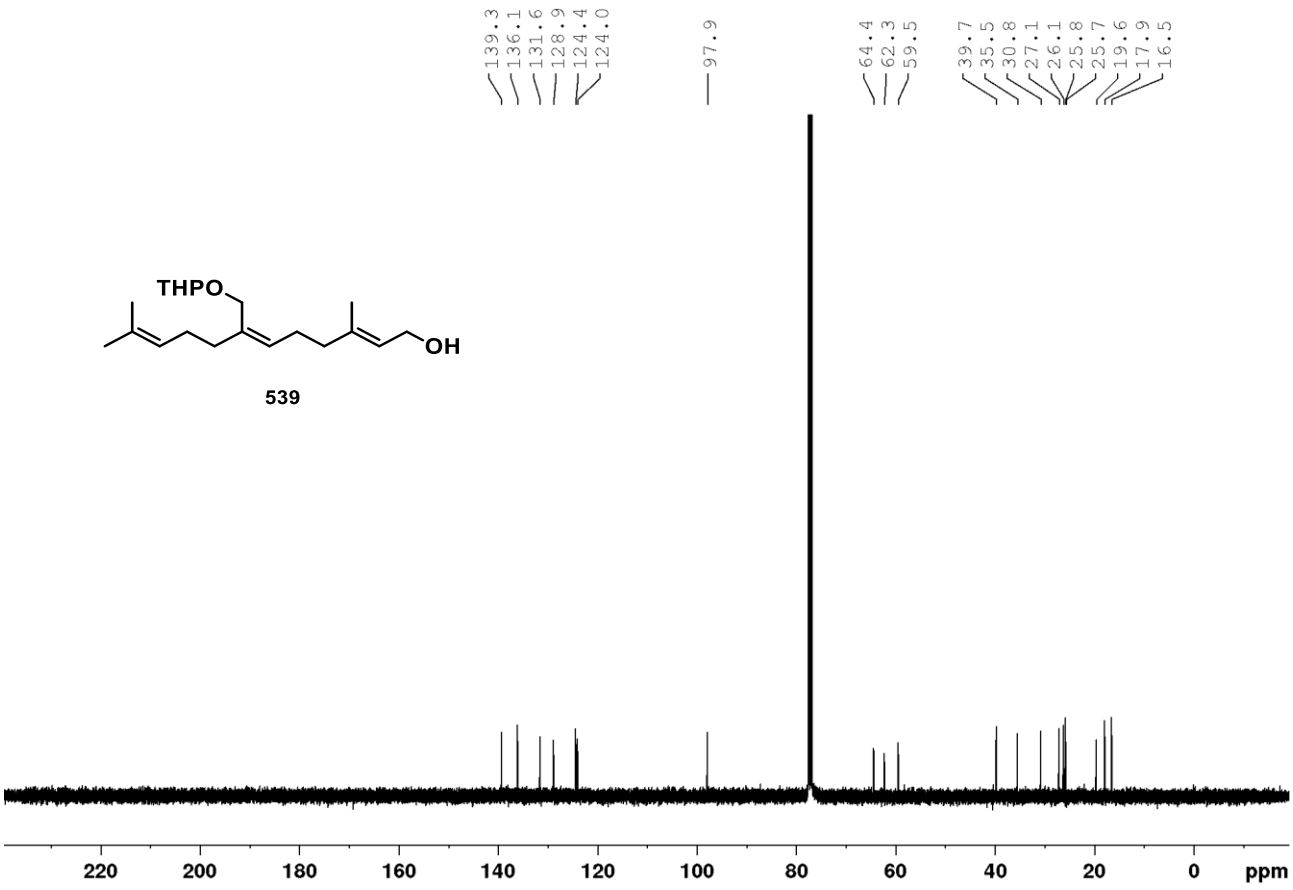
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


139.3
136.1
131.6
128.9
124.4
124.0
97.9
64.4
62.3
59.5
39.7
35.5
30.8
27.1
26.1
25.8
25.7
19.6
17.9
16.5
THPO
OH
539
220
200
180
160
140
120
100
80
60
40
20
0
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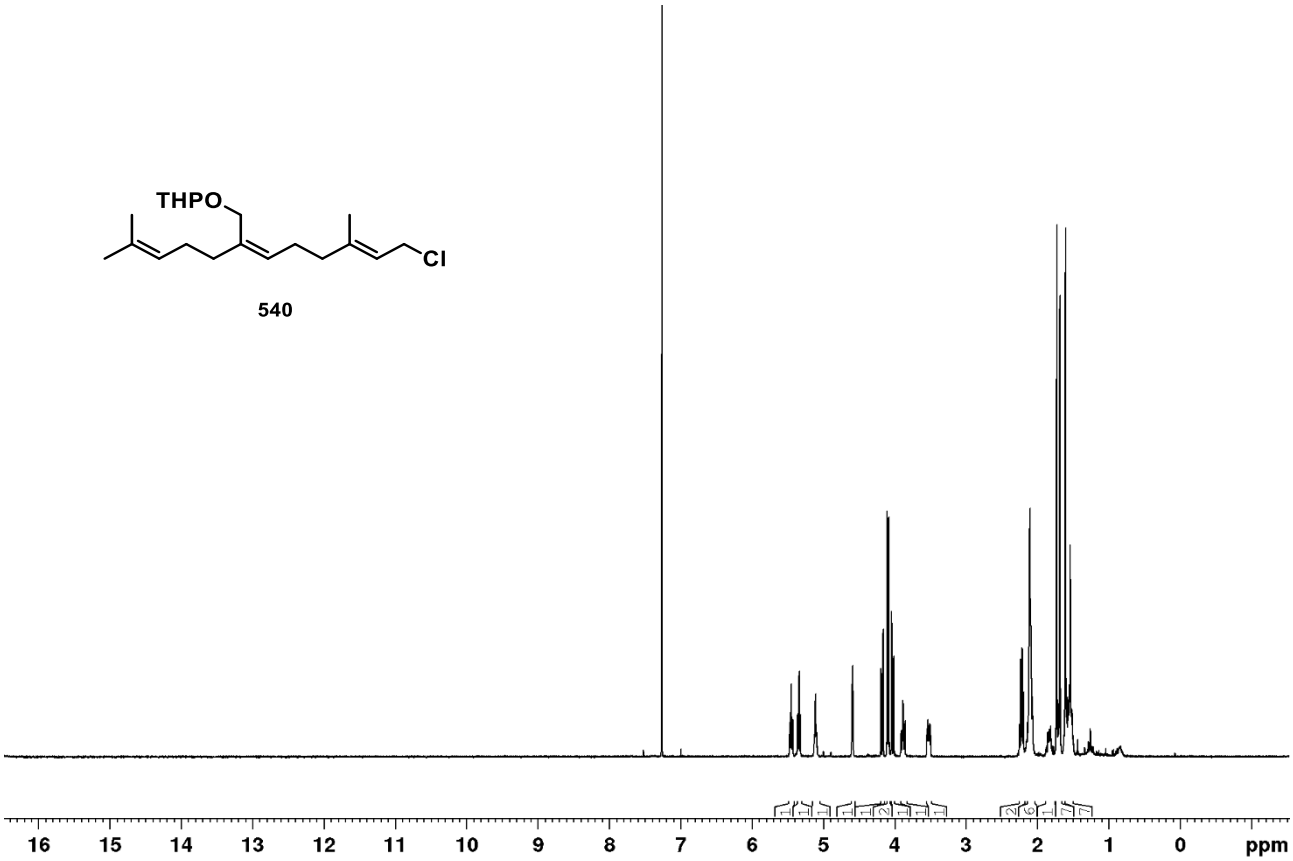
THPO
Cl
540
16
15
14
13
12
11
10
9
8
7
6
5
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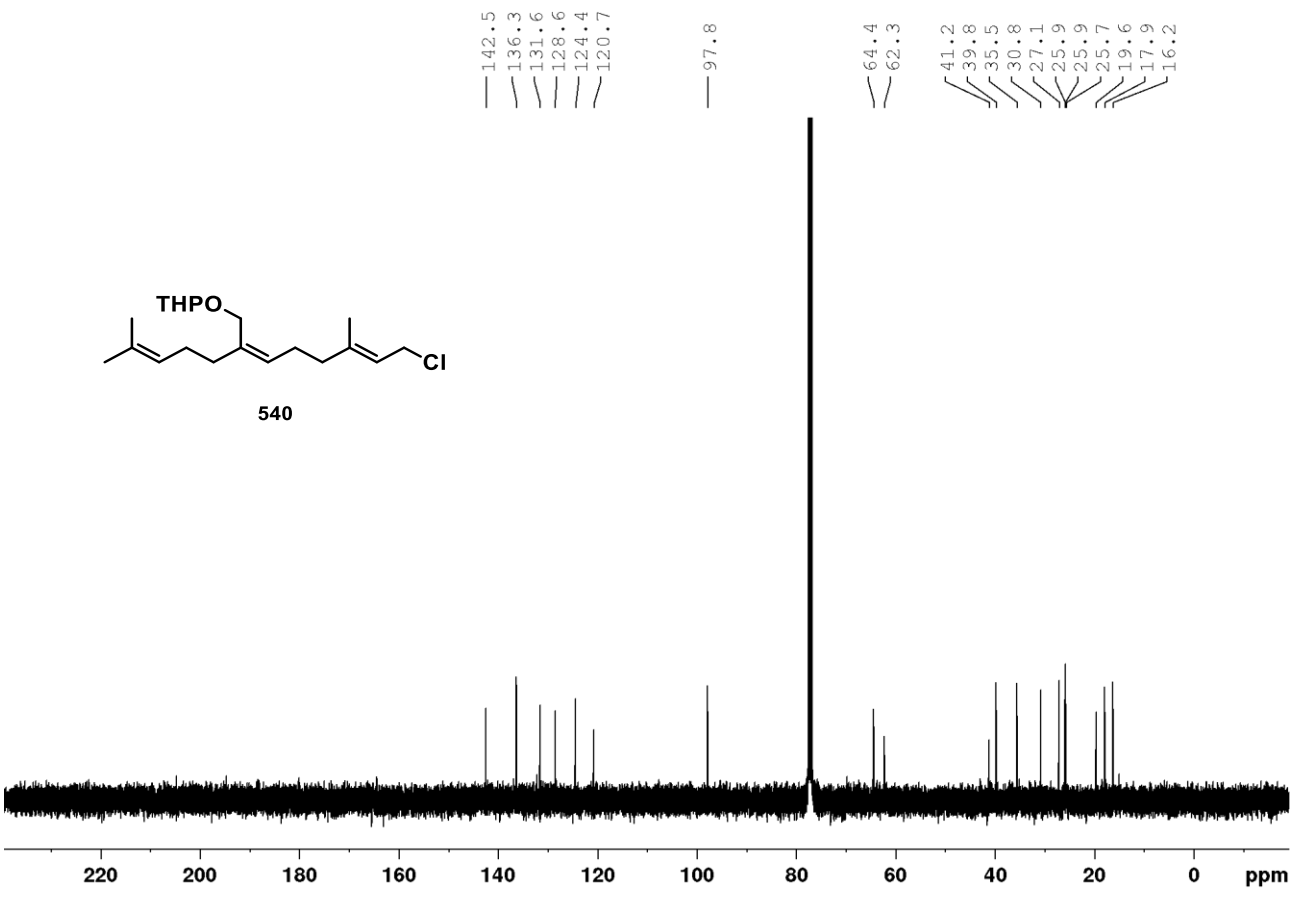
3
2
1
0
ppm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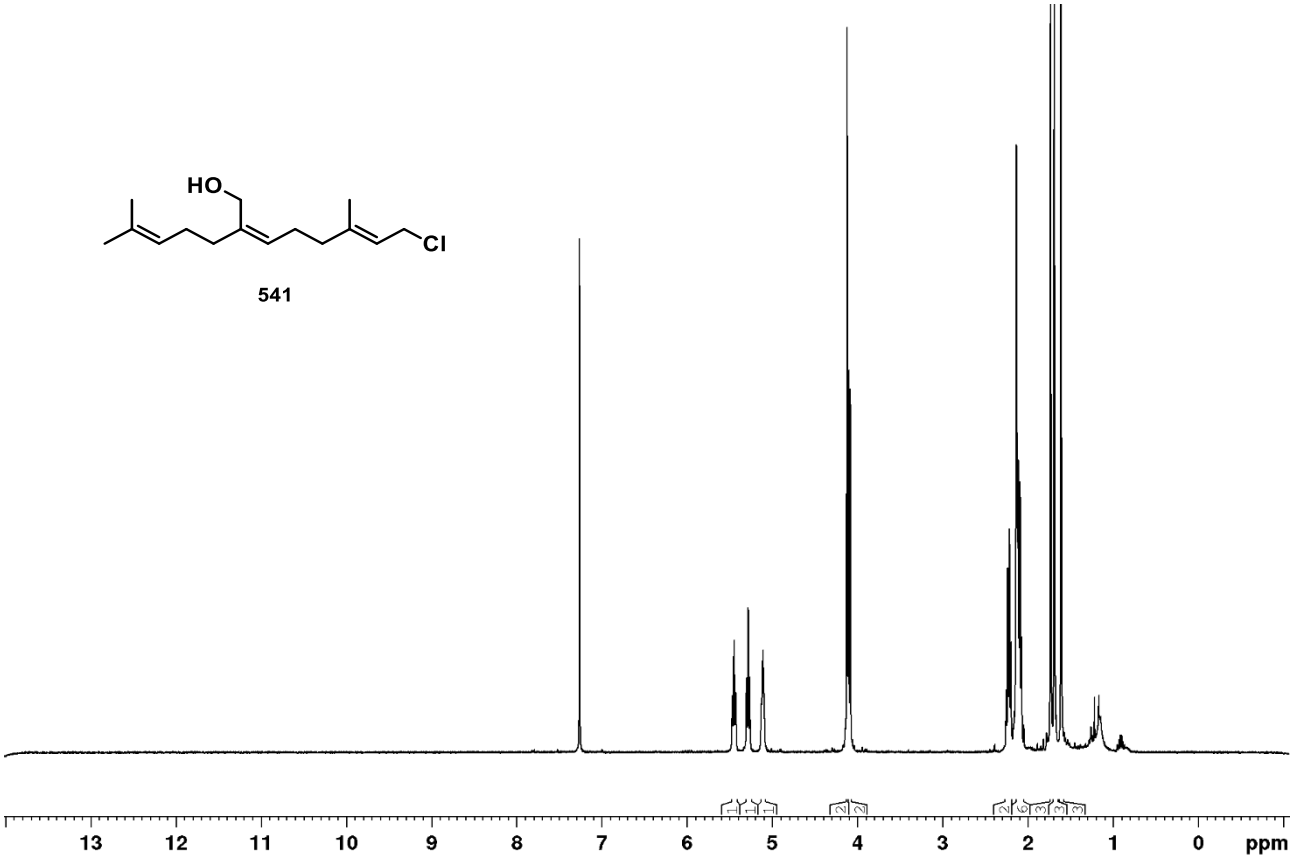
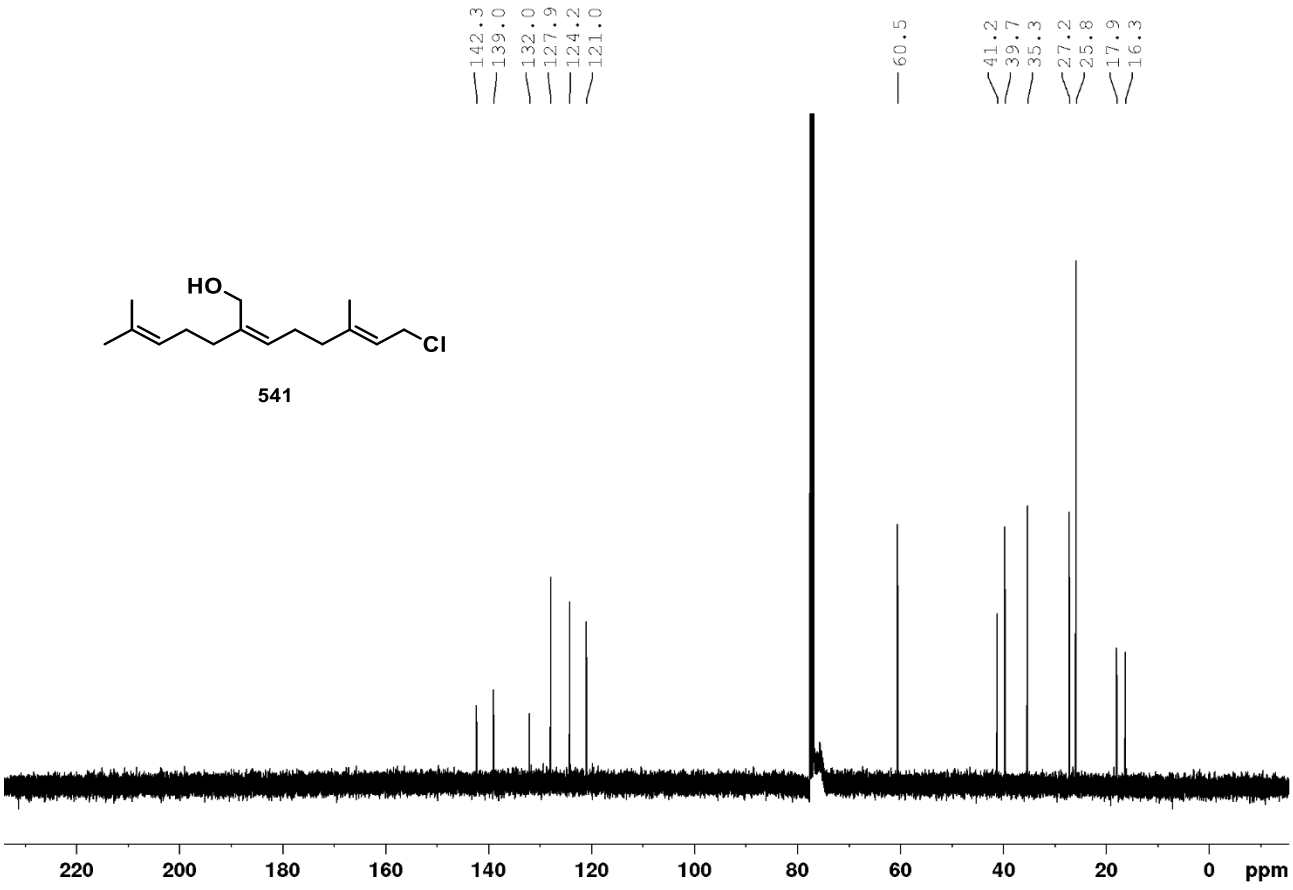
136.3
131.6
128.6
124.4
120.7
97.8
64.4
62.3
41.2
39.8
35.5
30.8
27.1
25.9
25.9
25.7
19.6
17.9
16.2
THPO
Cl
540
220
200
180
160
140
120
100
80
60
40
20
0
ppm


HO
Cl
541
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm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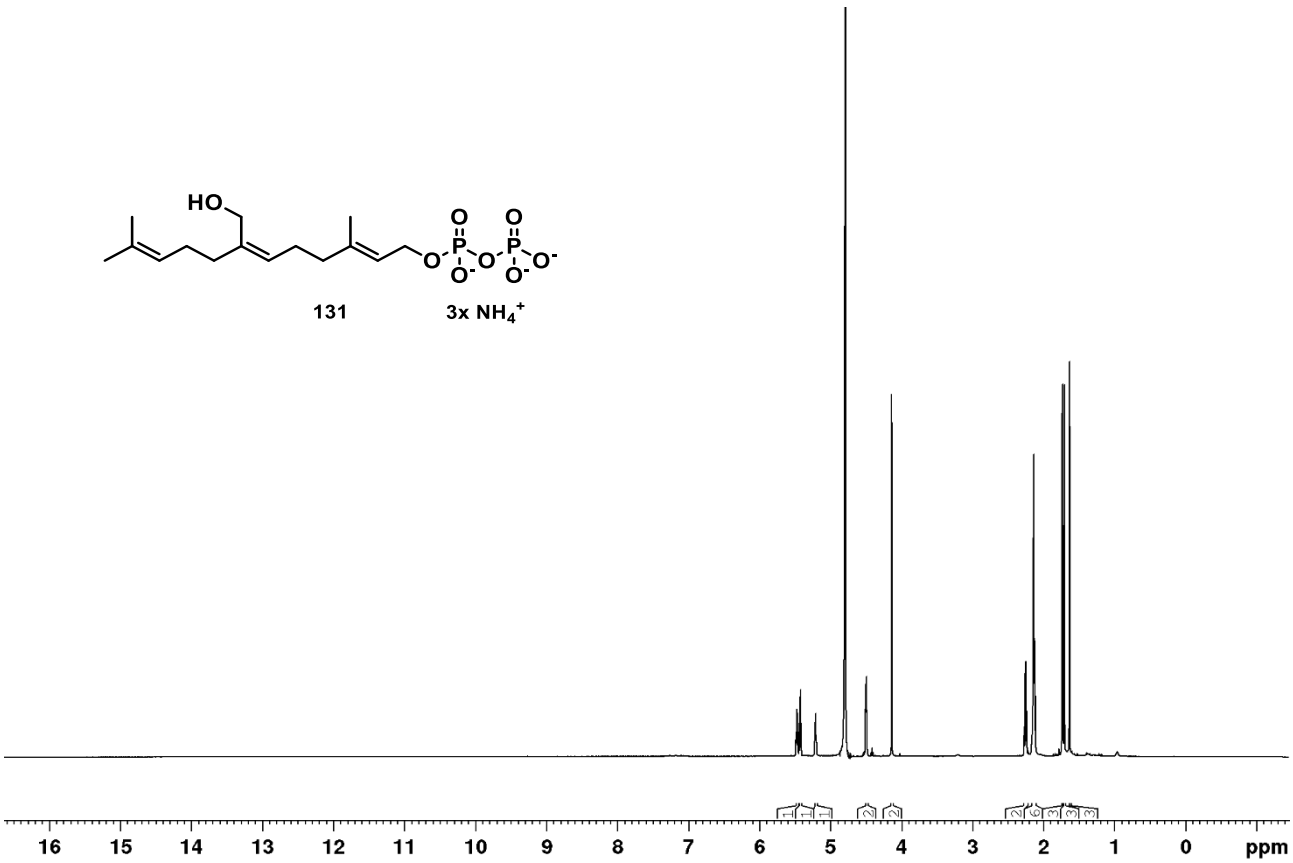
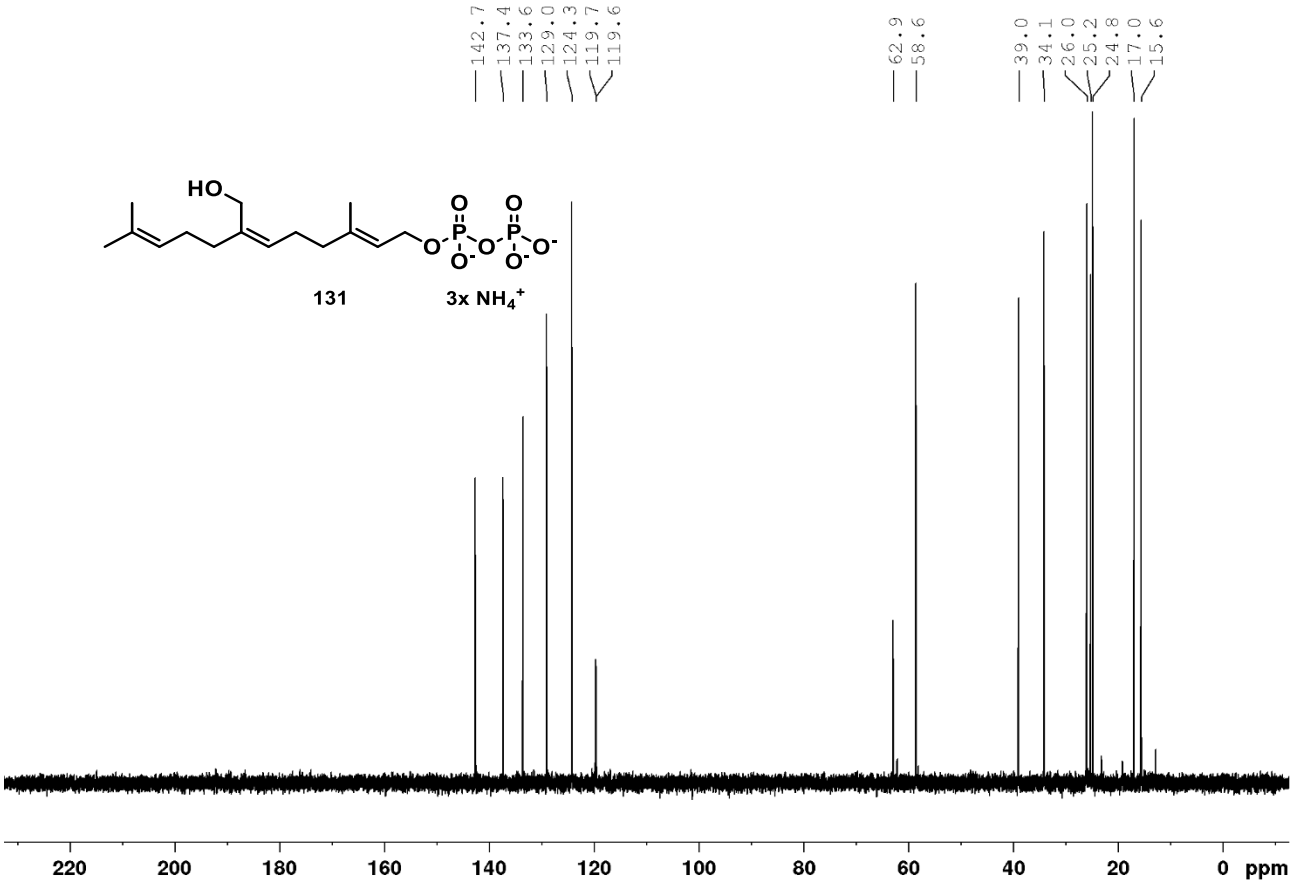
139.0
132.0
127.9
124.2
121.0
60.5
41.2
39.7
35.3
27.2
25.8
17.9
16.3
HO
Cl
541
220
200
180
160
140
120
100
80
60
40
20
0
ppm


HO
O
O
P
O
O
O
P
O
O
O
O
O
O
131
3x NH4+
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm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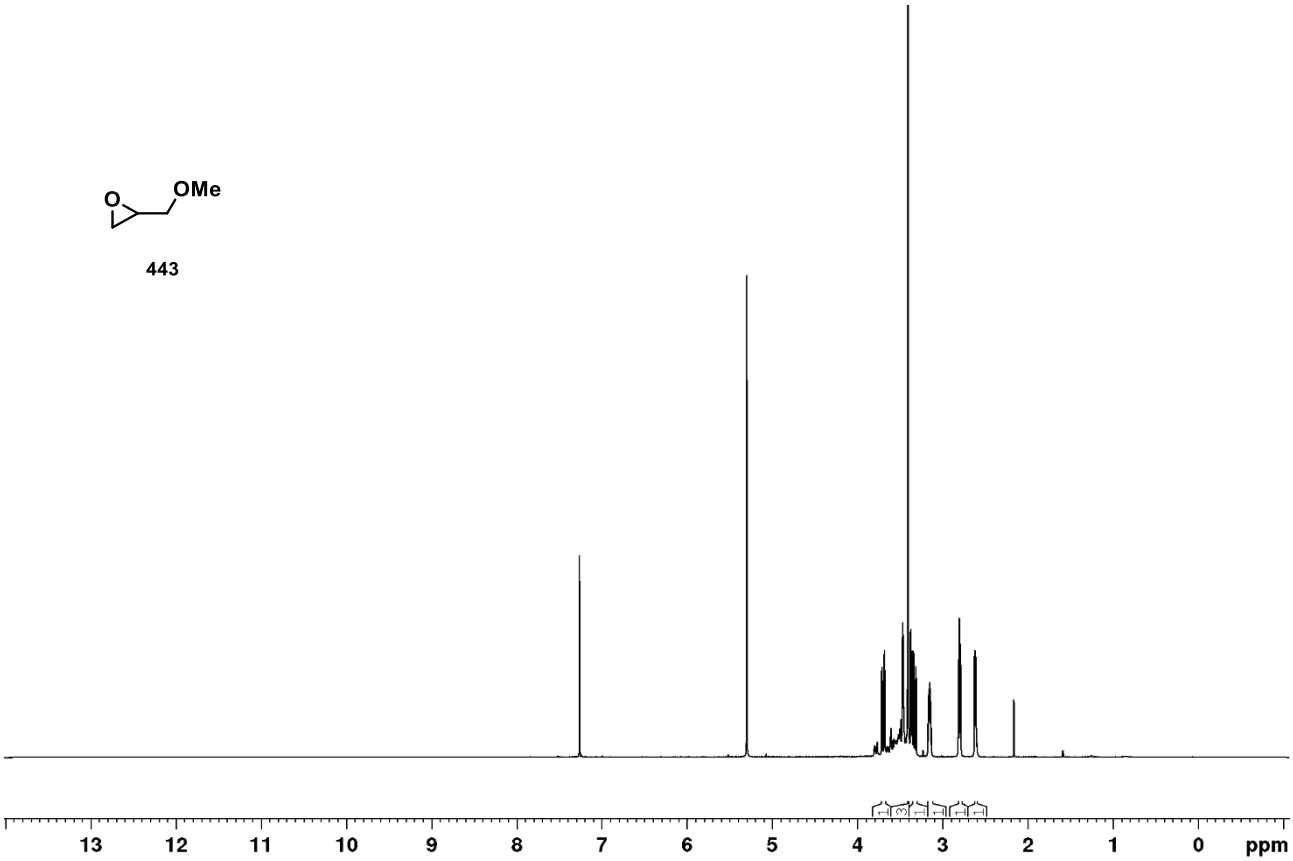
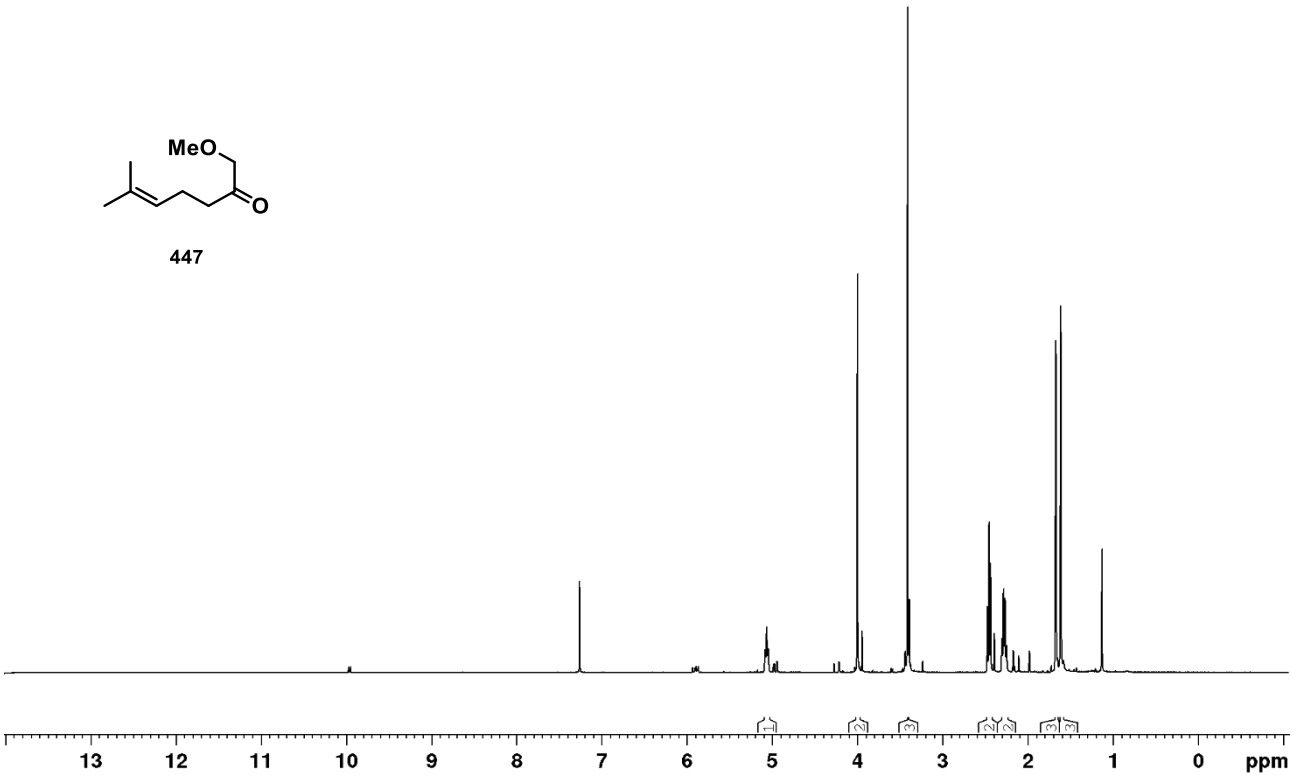
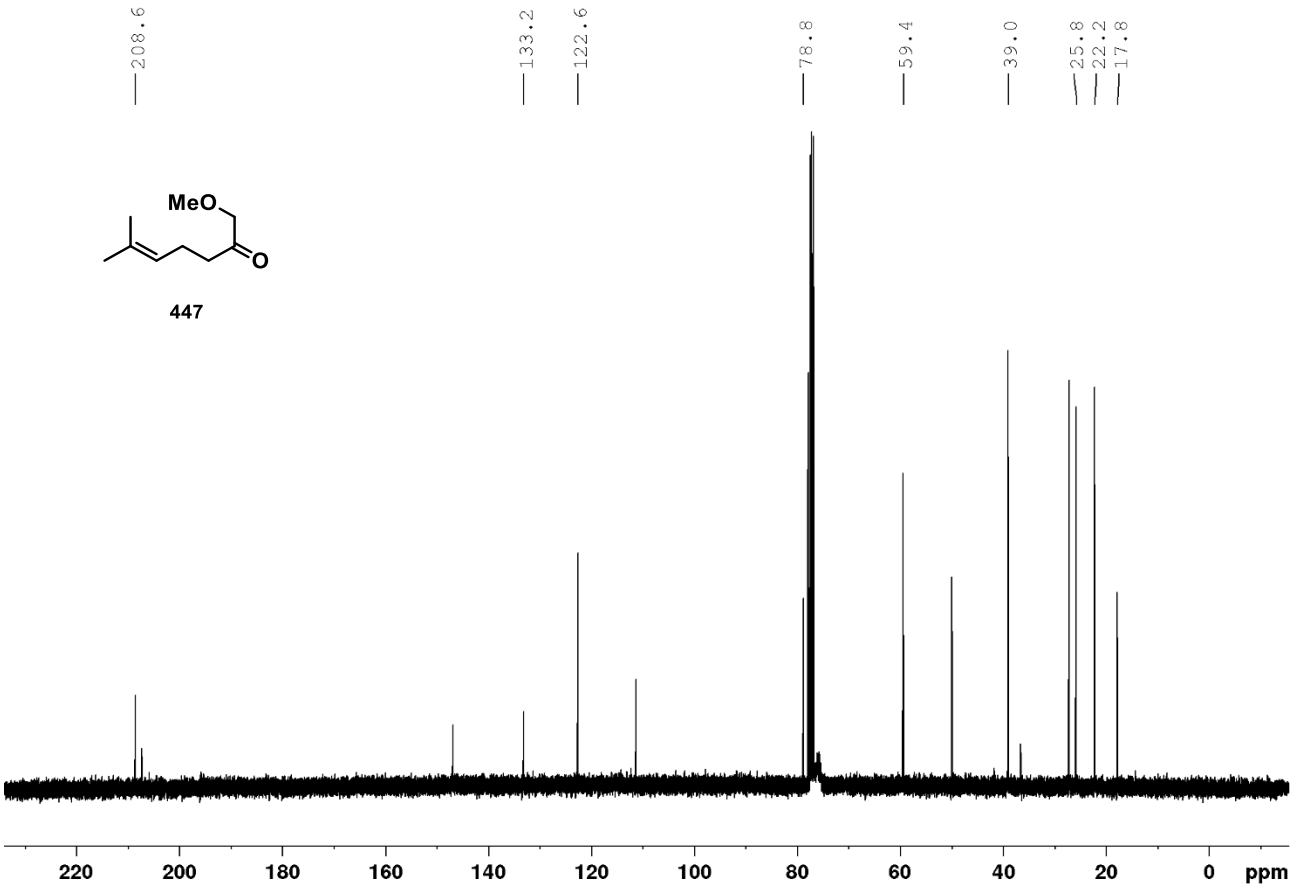
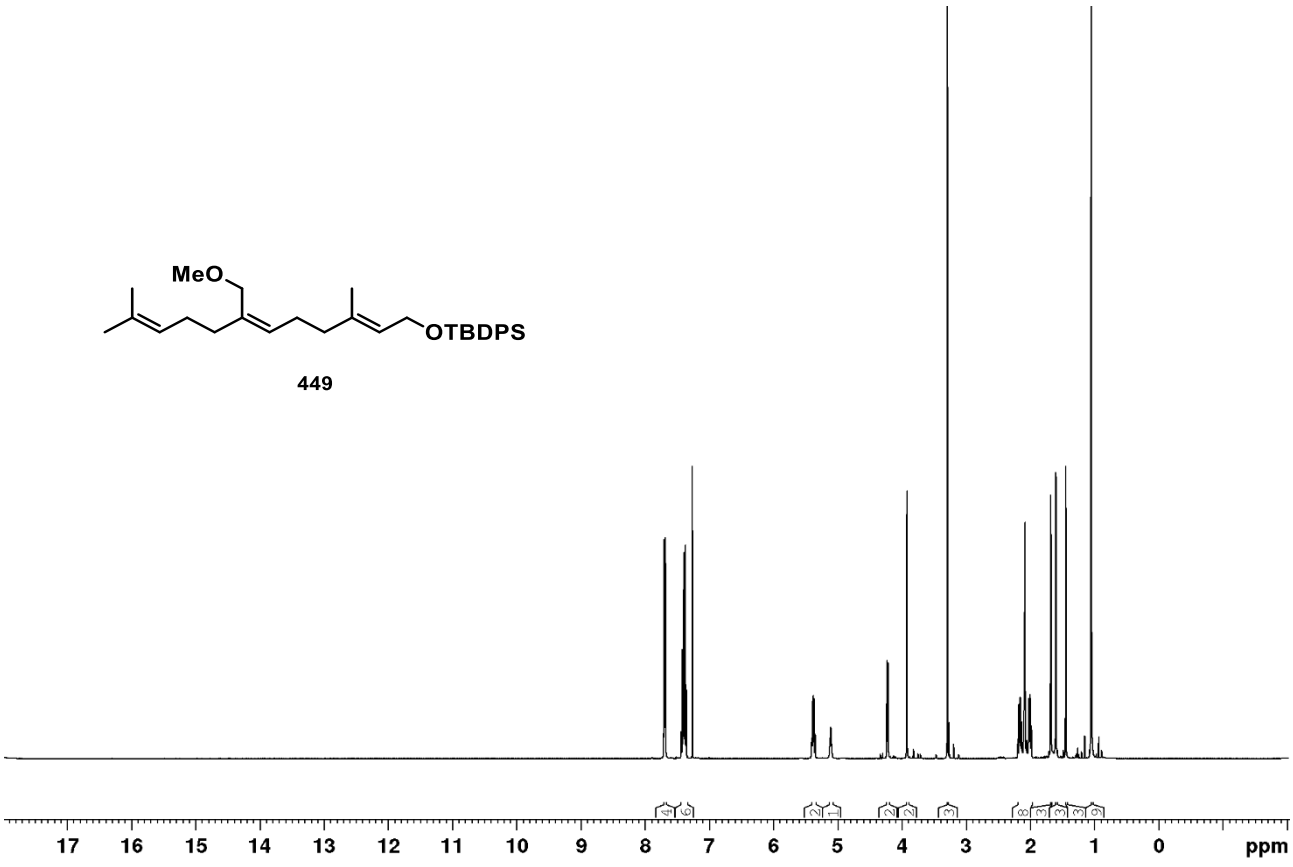
137.4
133.6
129.0
124.3
119.7
119.6
62.9
58.6
39.0
34.1
26.0
25.2
24.8
17.0
15.6
HO
O
O
P
O
O
O
P
O
O
O
O
O
O
131
3x NH4+
220
200
180
160
140
120
100
80
60
40
20
0
ppm


OMe
O
443
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

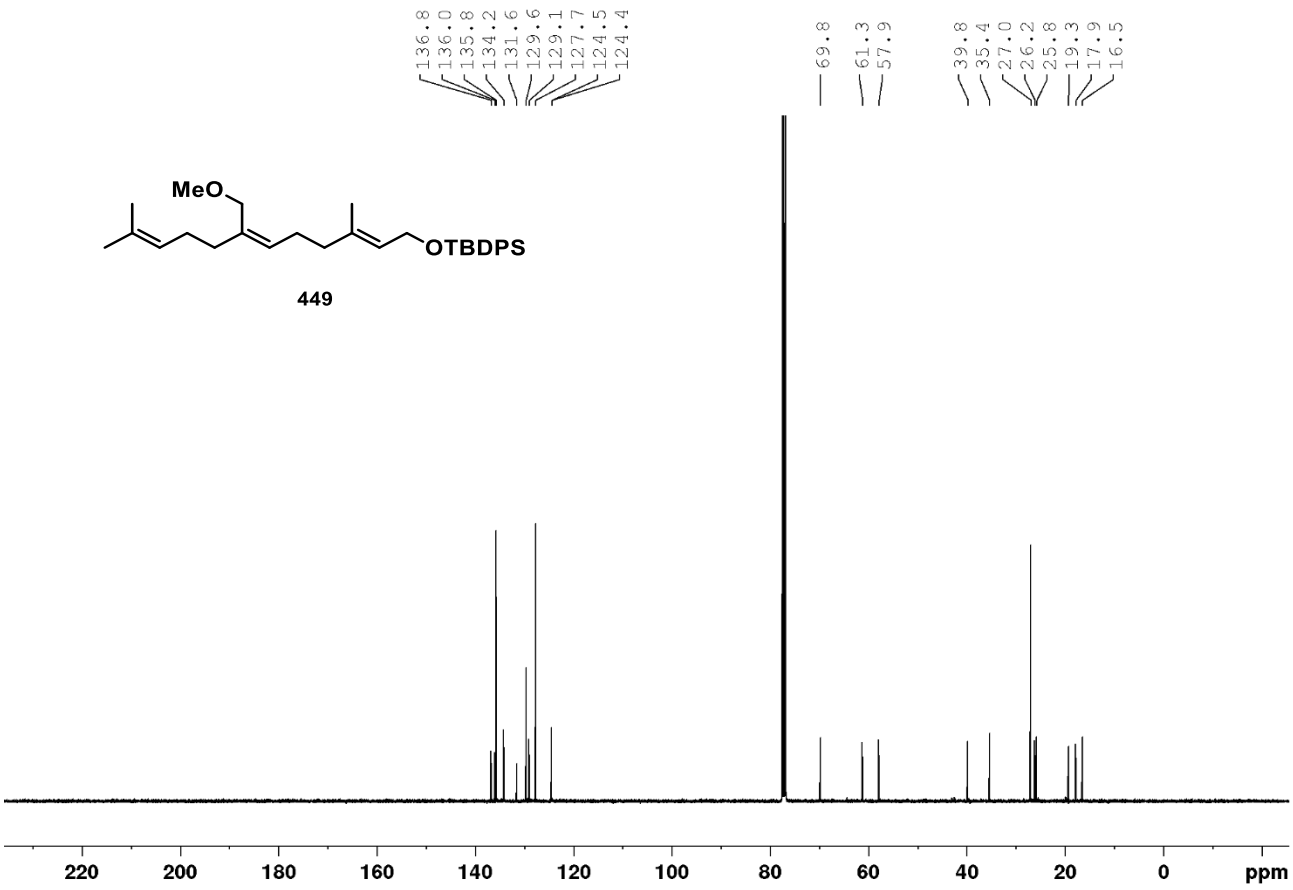

MeO
O
447
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

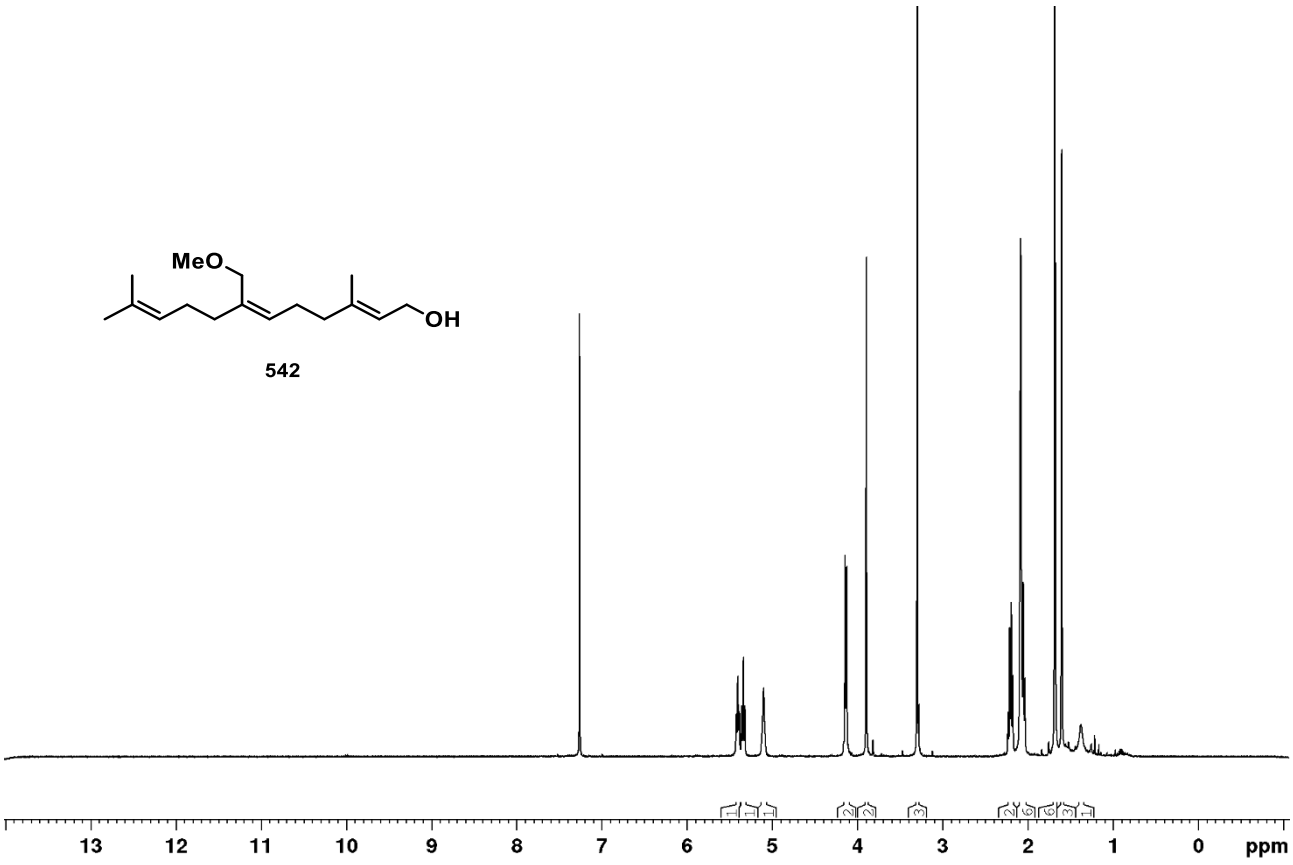

208.6
133.2
122.6
78.8
59.4
39.0
25.8
22.2
17.8
MeO
O
220
200
180
160
140
120
100
80
60
40
20
0
ppm

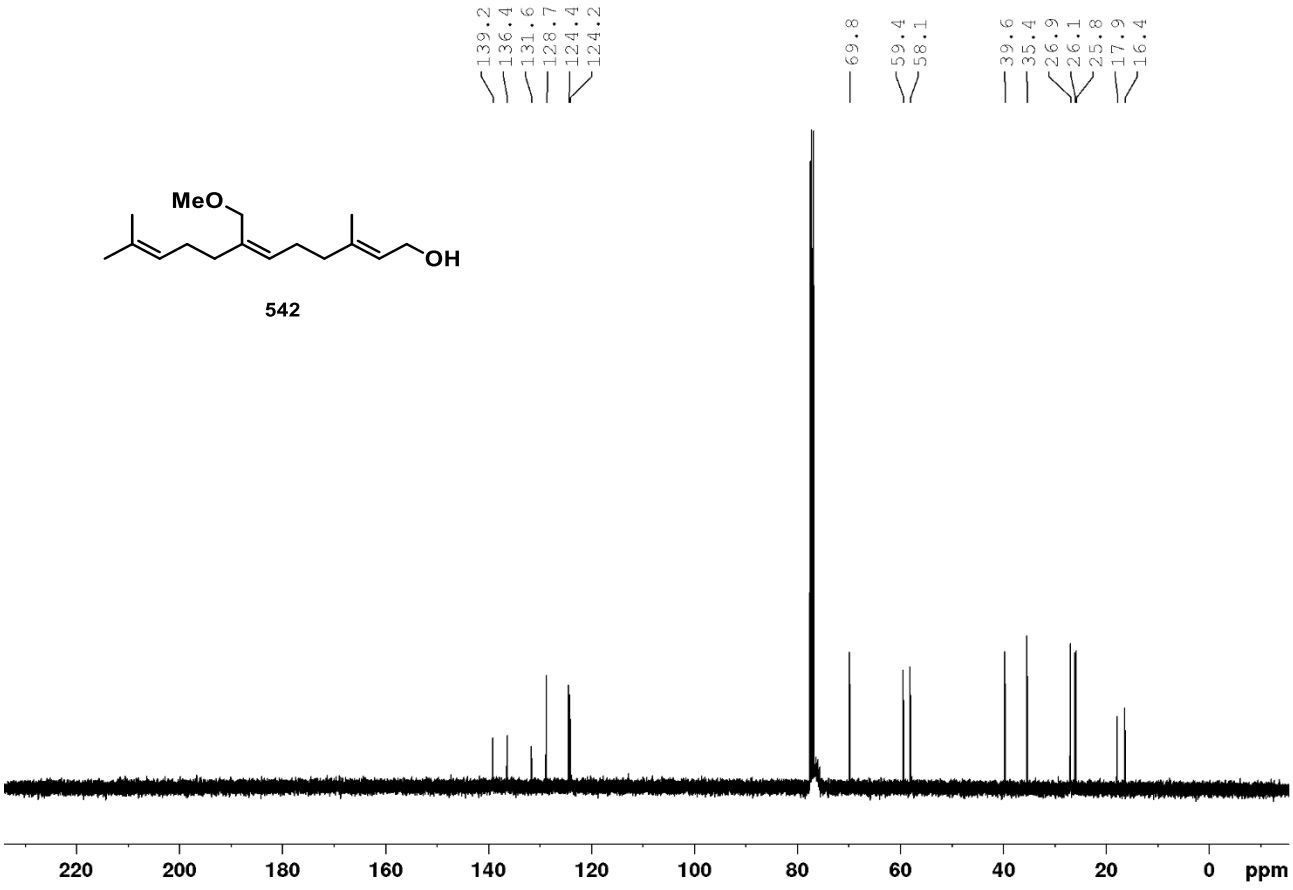
447


MeO
OTBDPS
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

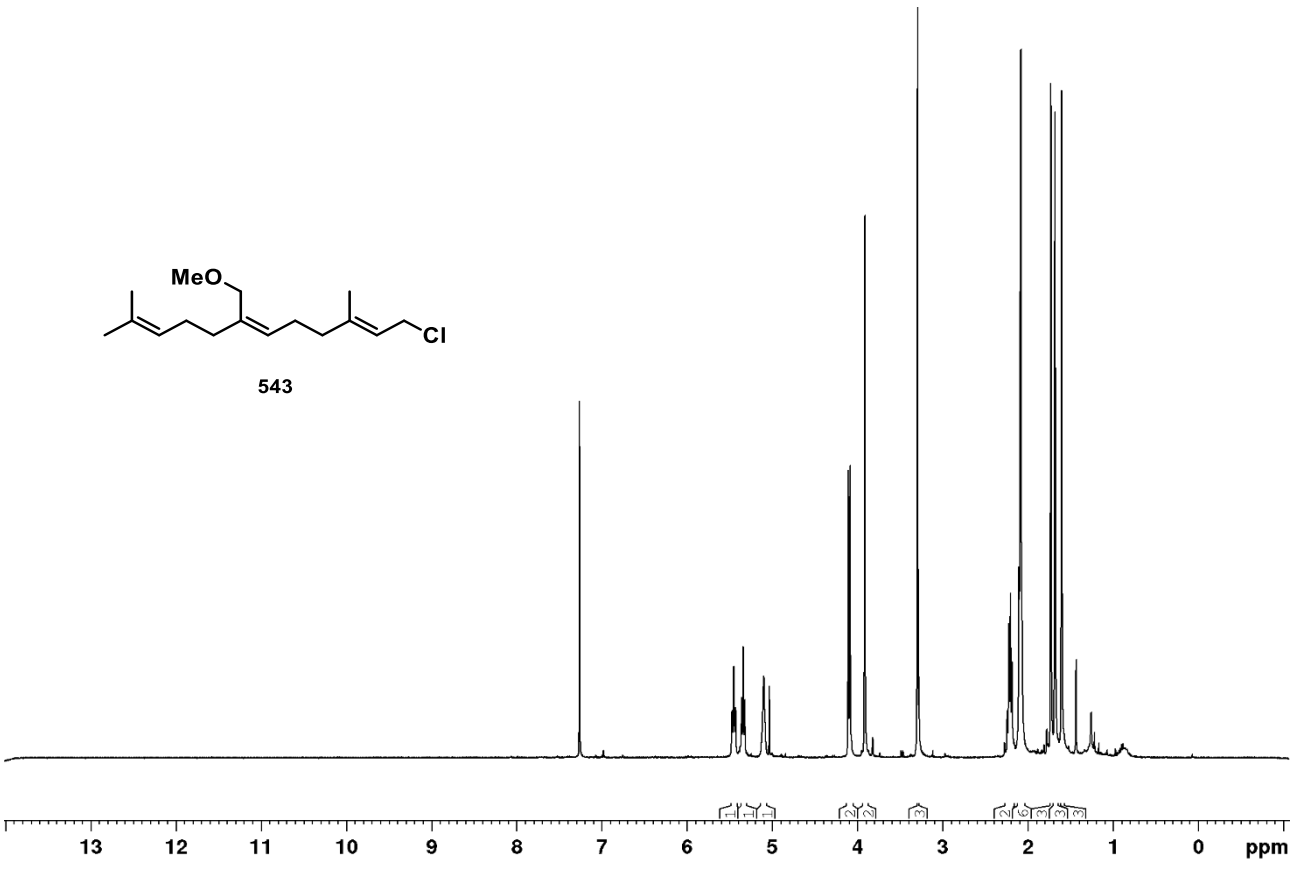
449


136.8
136.0
135.8
134.2
131.6
129.6
129.1
127.7
124.5
124.4
69.8
61.3
57.9
39.8
35.4
27.0
26.2
25.8
19.3
17.9
16.5
MeO
OTBDPS
449
220
200
180
160
140
120
100
80
60
40
20
0
ppm

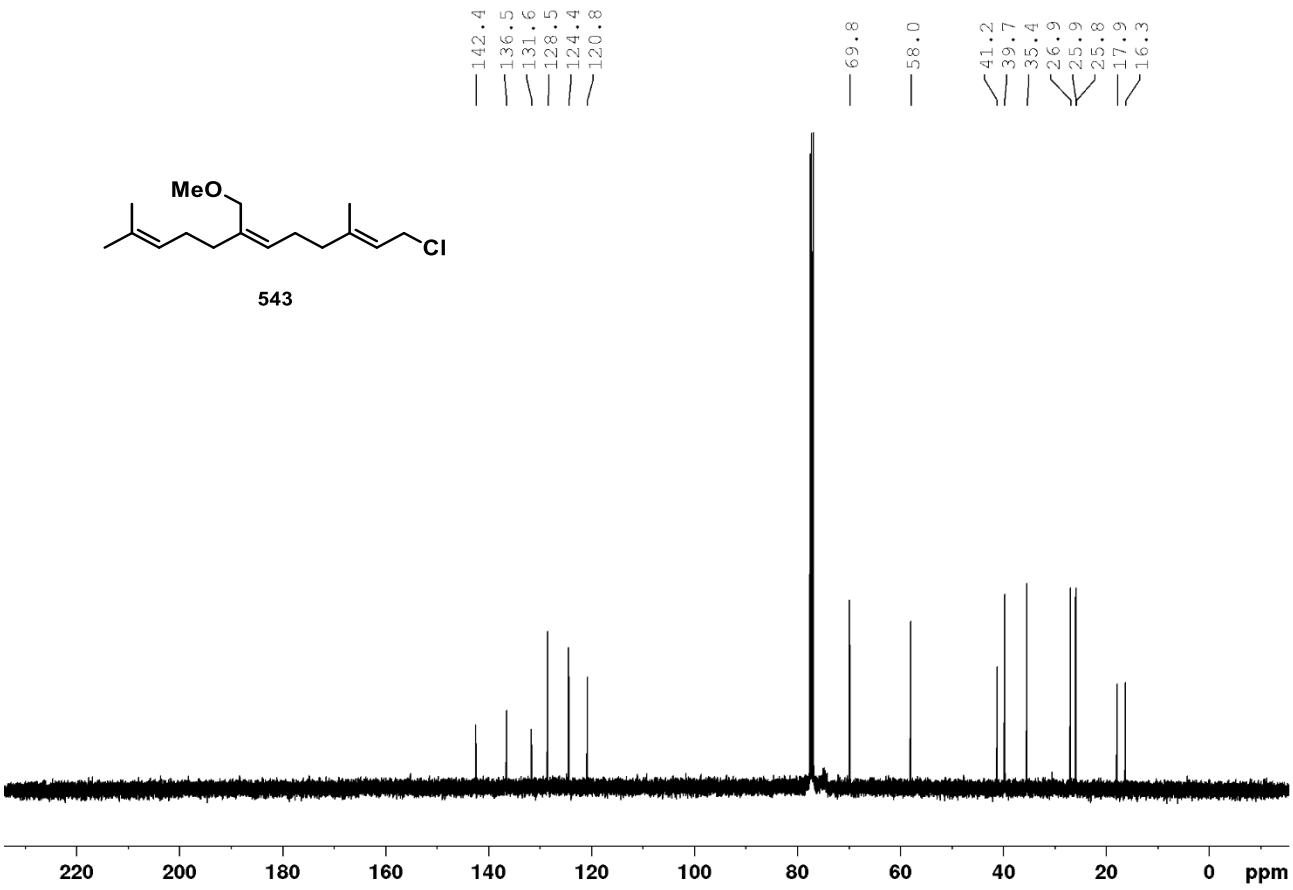

MeO
OH
542
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

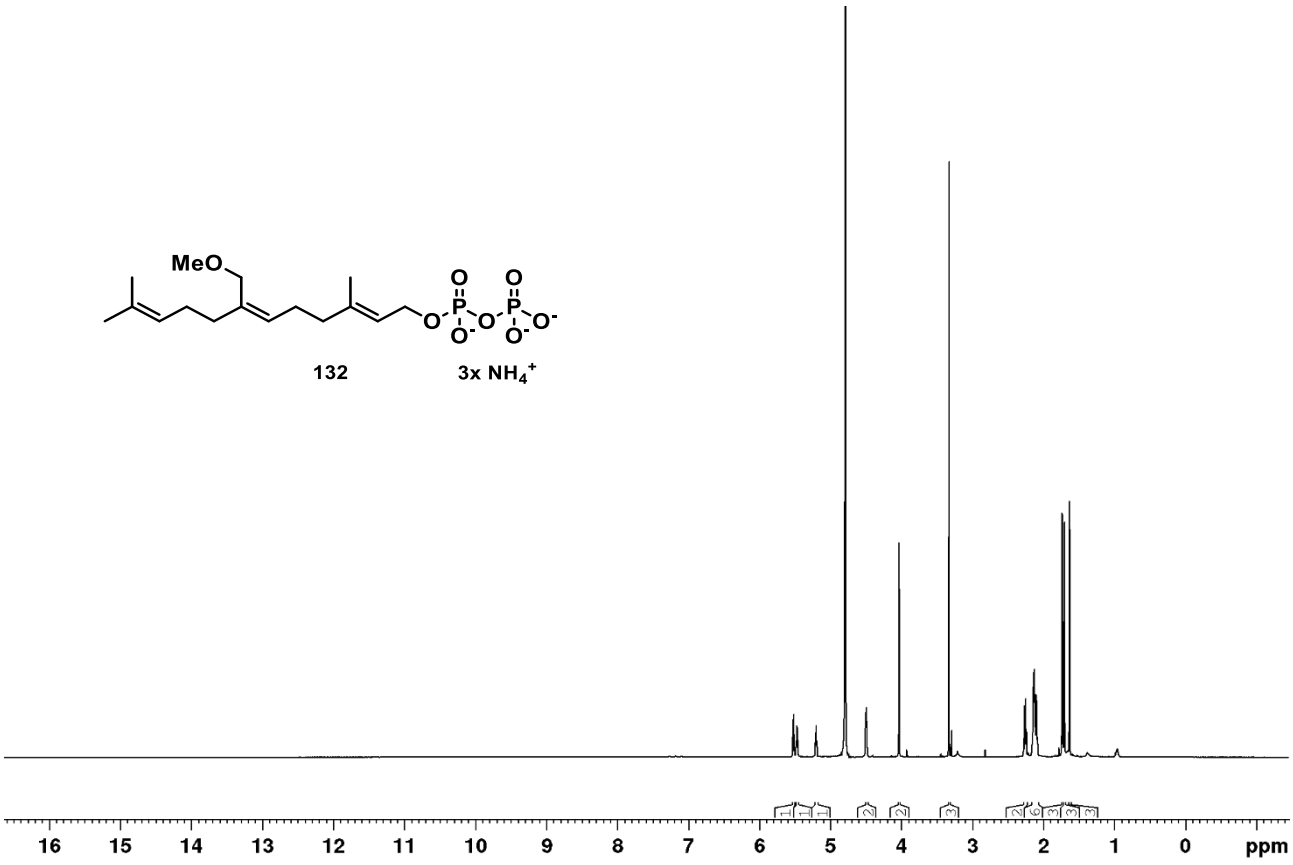

139.2
136.4
131.6
128.7
124.4
124.2
69.8
59.4
58.1
39.6
35.4
26.9
26.1
25.8
17.9
16.4
MeO
OH
220
200
180
160
140
120
100
80
60
40
20
0
ppm

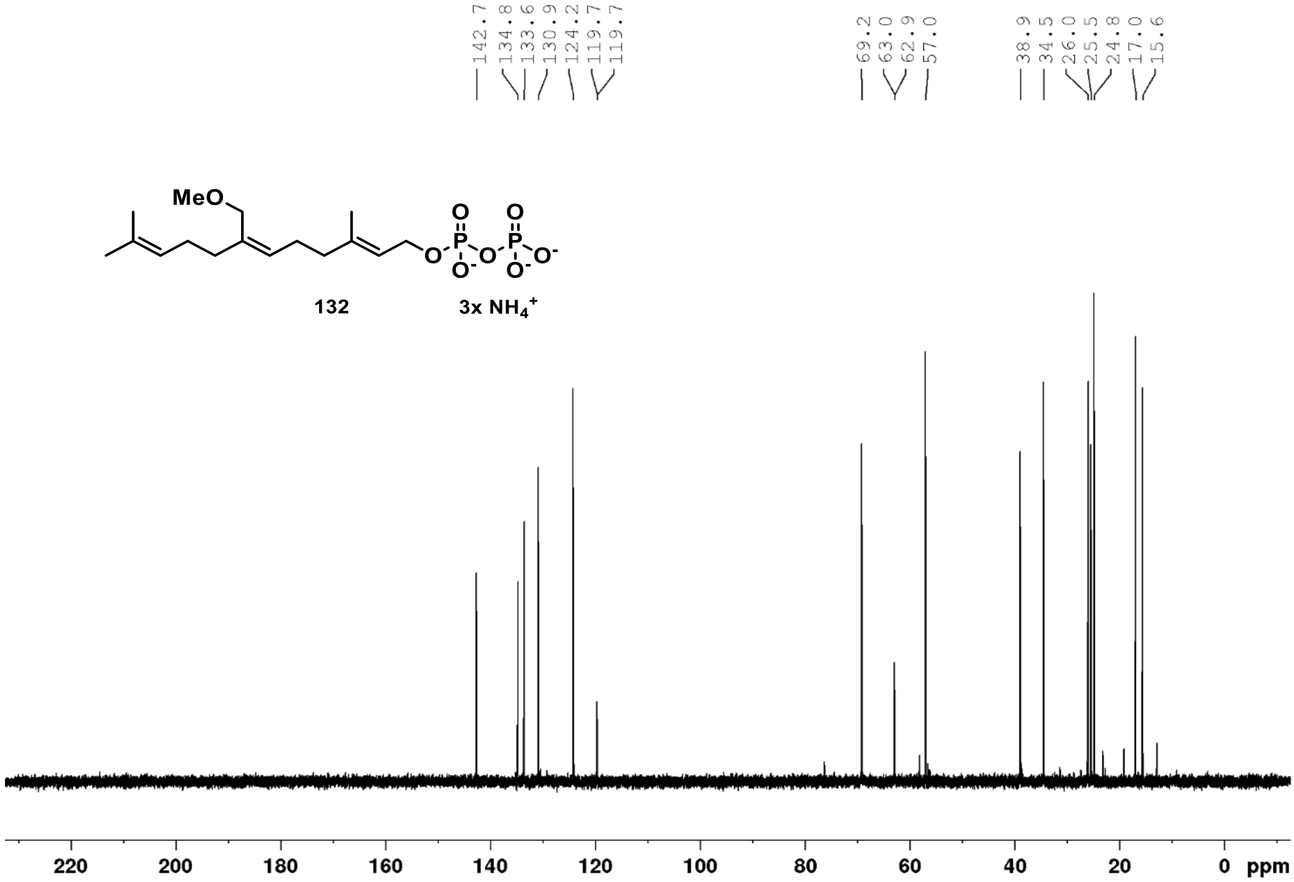
542

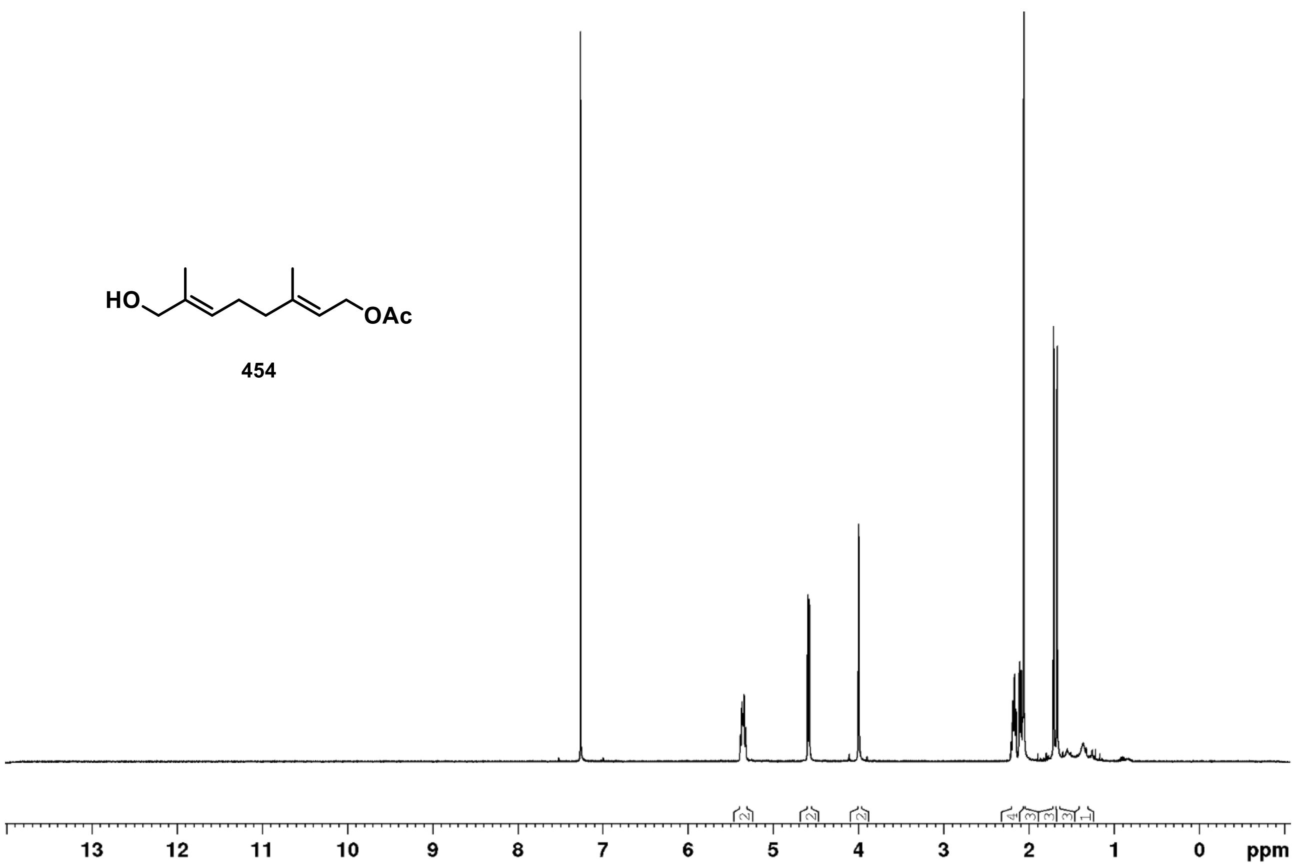

MeO
Cl
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

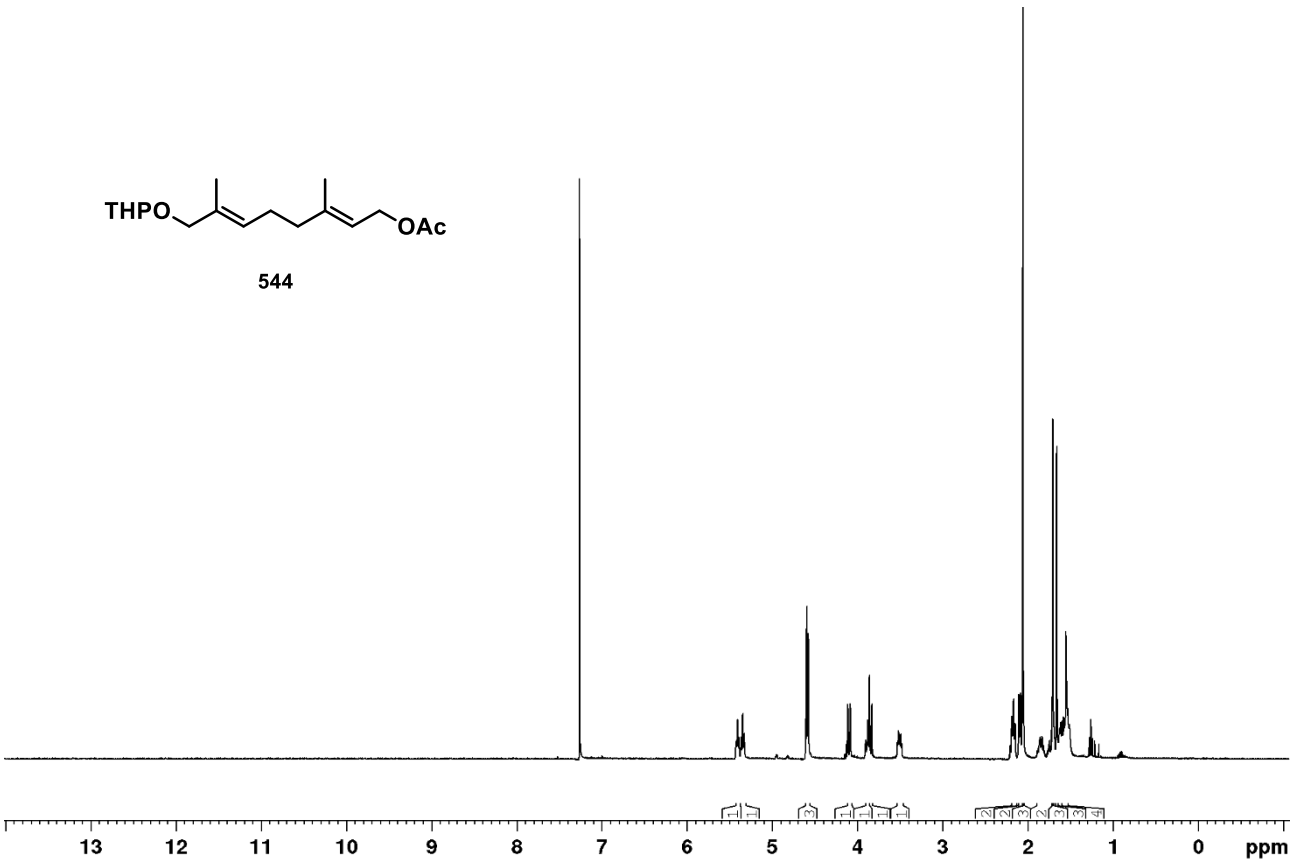
543

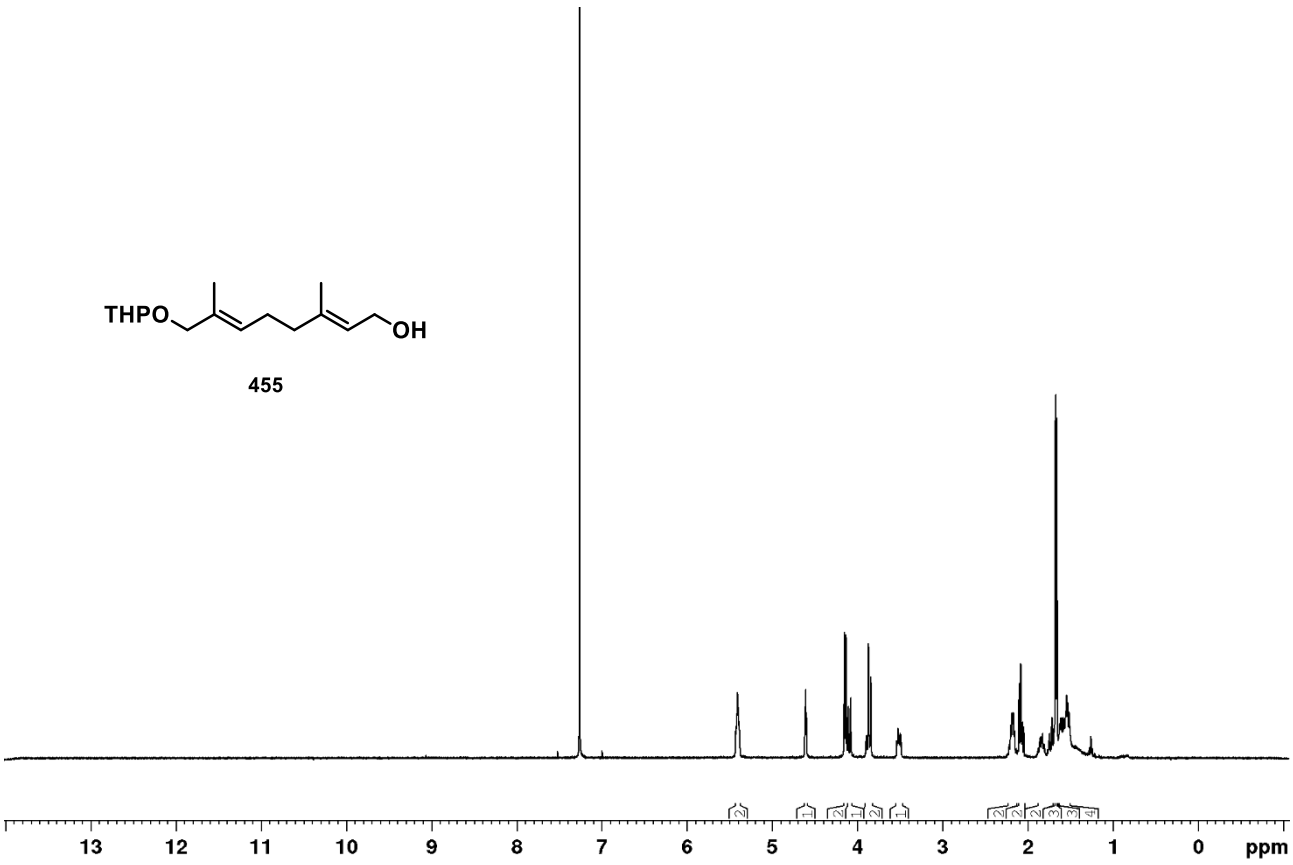

142.4
136.5
131.6
128.5
124.4
120.8
69.8
58.0
41.2
39.7
35.4
26.9
25.9
25.8
17.9
16.3
MeO
Cl
543
220
200
180
160
140
120
100
80
60
40
20
0
ppm

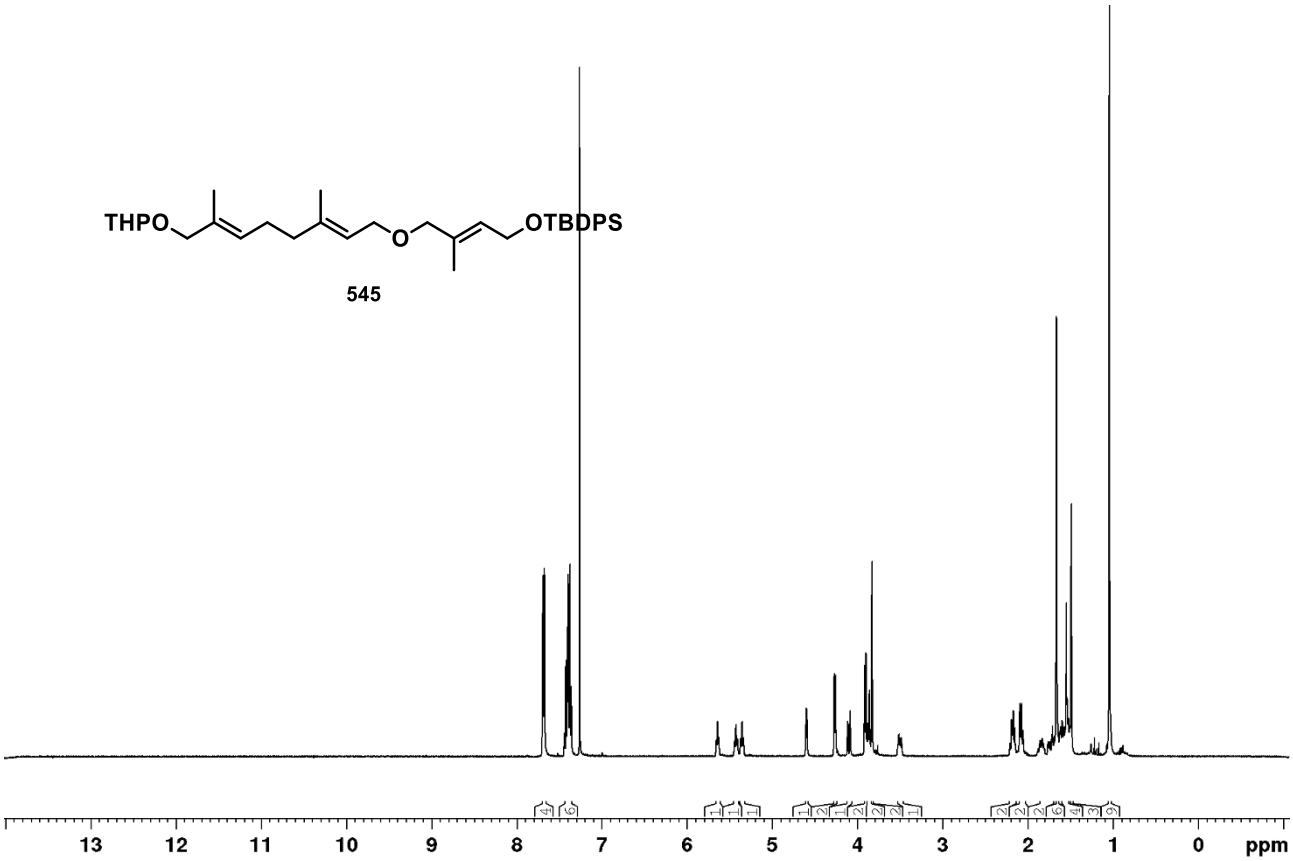

MeO
O
P
O
O
O
O
O
O
O
O
P
O
O
132
3x NH4+
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

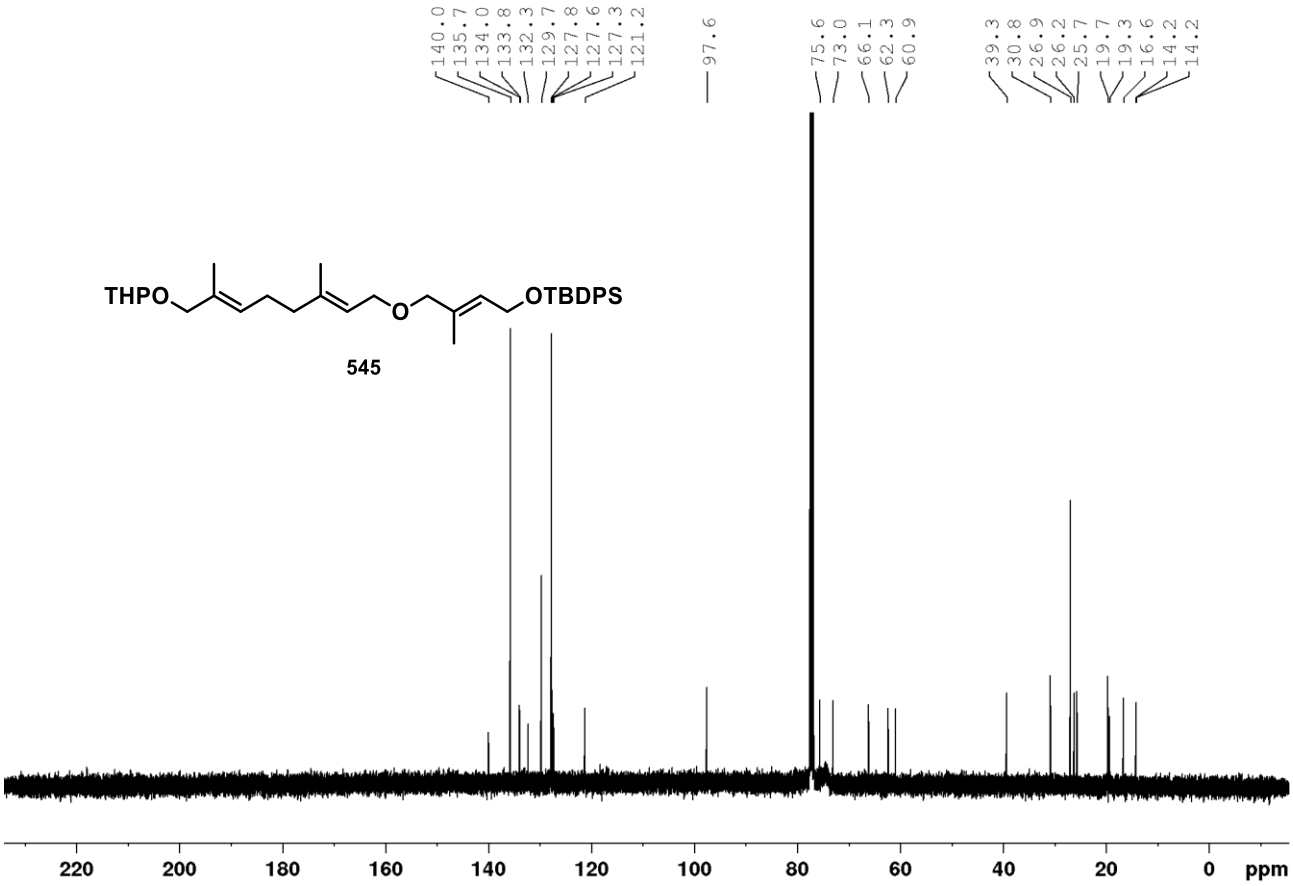

142.7
134.8
133.6
130.9
124.2
119.7
119.7
69.2
63.0
62.9
57.0
38.9
34.5
26.0
25.5
24.8
17.0
15.6
MeO
132
3x NH_4^+
220 200 180 160 140 120 100 80 60 40 20 0 ppm


HO
OAc
454
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm


THPO
OAc
544
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


THPO
OH
455
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


THPO
O
OTBDPS
545
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm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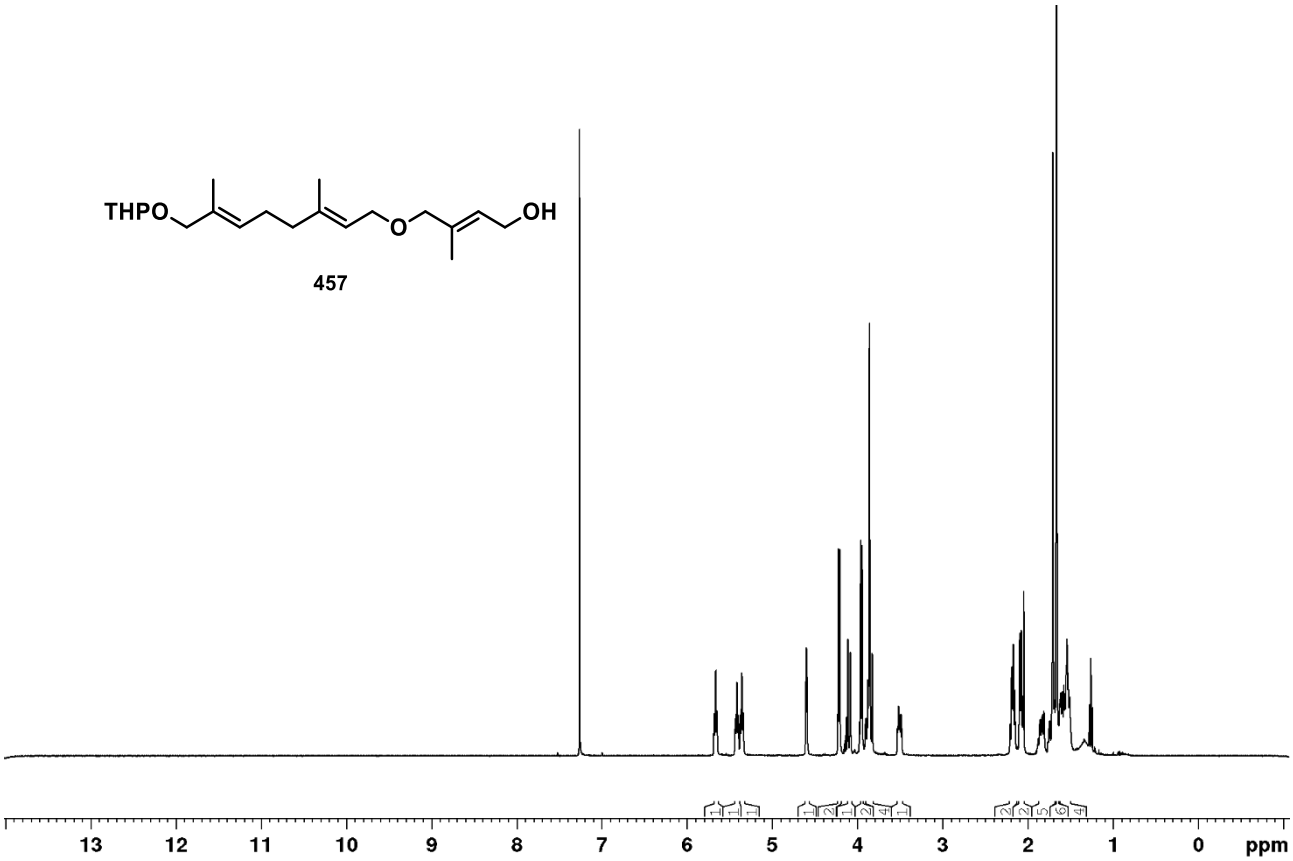
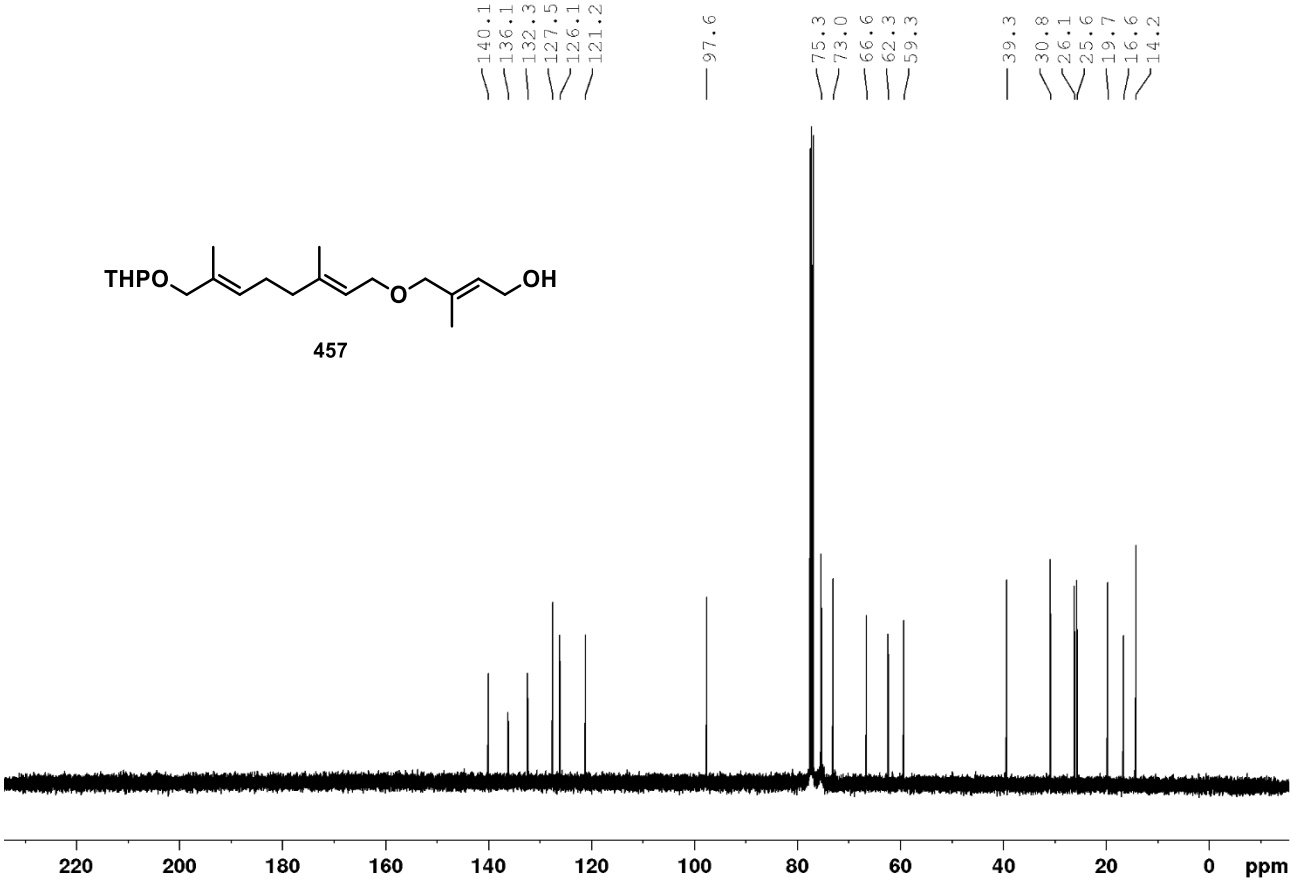
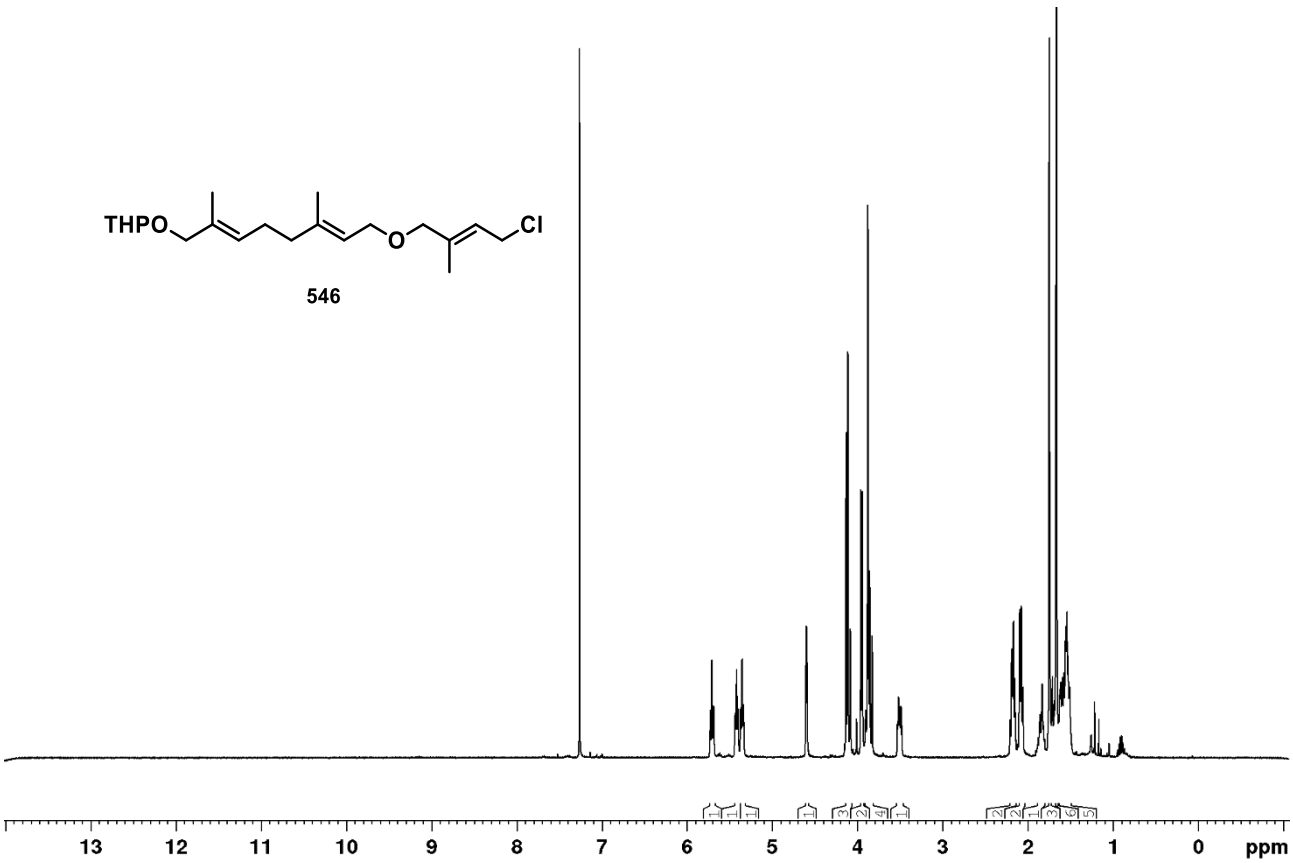
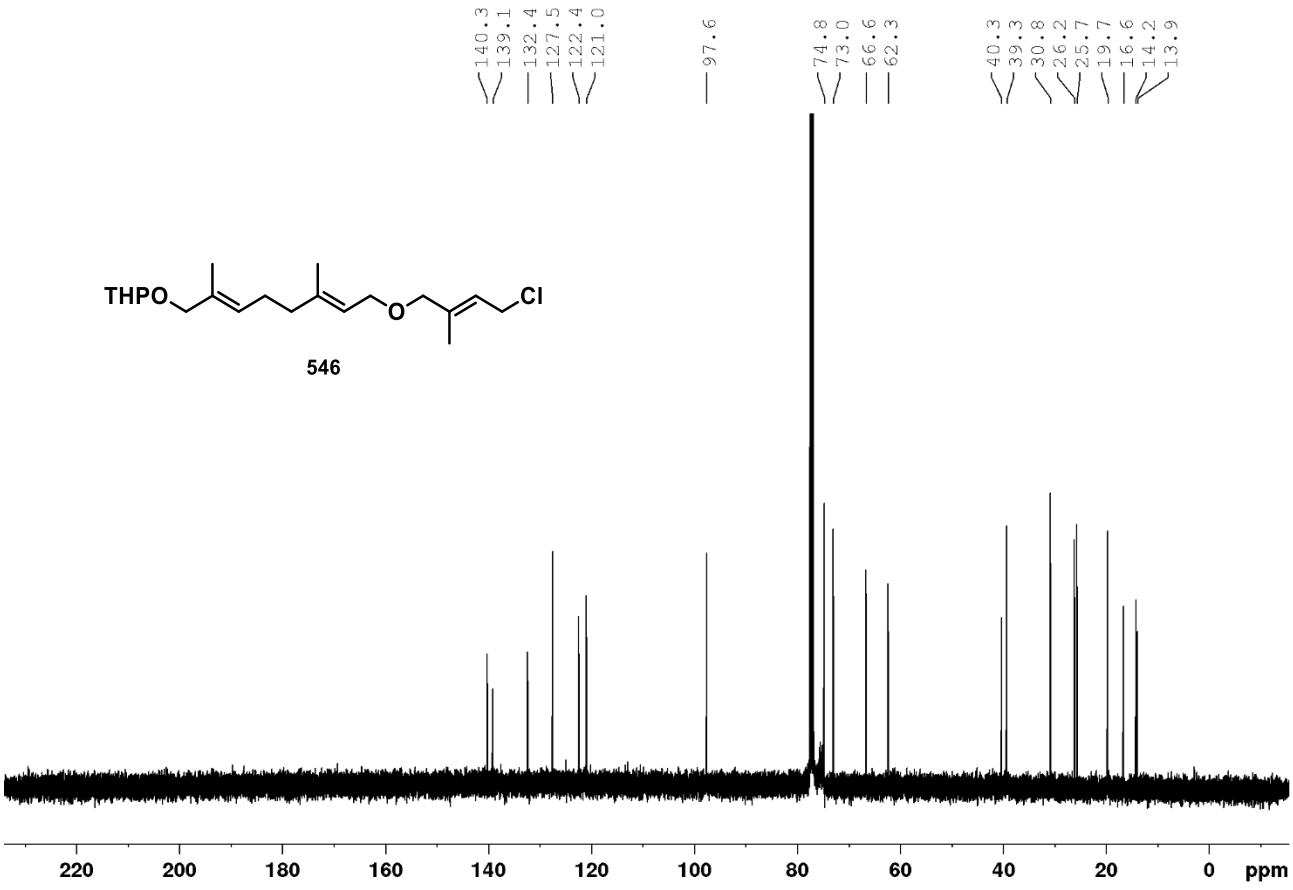
135.7
134.0
133.8
132.3
129.7
127.8
127.6
127.3
121.2
97.6
75.6
73.0
66.1
62.3
60.9
39.3
30.8
26.9
26.2
25.7
19.7
19.3
16.6
14.2
14.2
THPO
O
OTBDPS
545
220
200
180
160
140
120
100
80
60
40
20
0
ppm


THPO
OH
O
457
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


140.1
136.1
132.3
127.5
126.1
121.2
97.6
75.3
73.0
66.6
62.3
59.3
39.3
30.8
26.1
25.6
19.7
16.6
14.2
THPO
OH
O
457
220
200
180
160
140
120
100
80
60
40
20
0
ppm


THPO
O
Cl
546
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm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139.1
132.4
127.5
122.4
121.0
97.6
74.8
73.0
66.6
62.3
40.3
39.3
30.8
26.2
25.7
19.7
16.6
14.2
13.9
THPO
O
Cl
546
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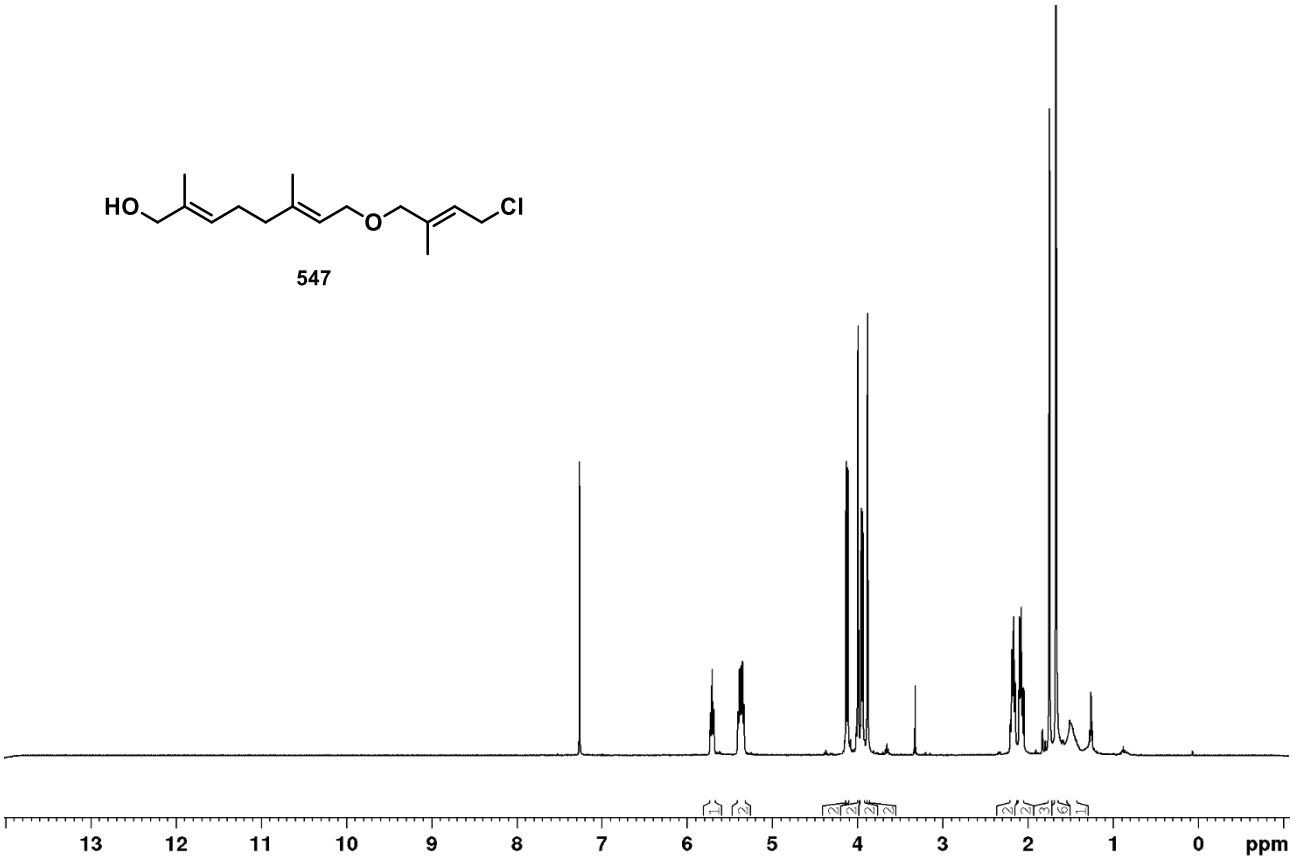
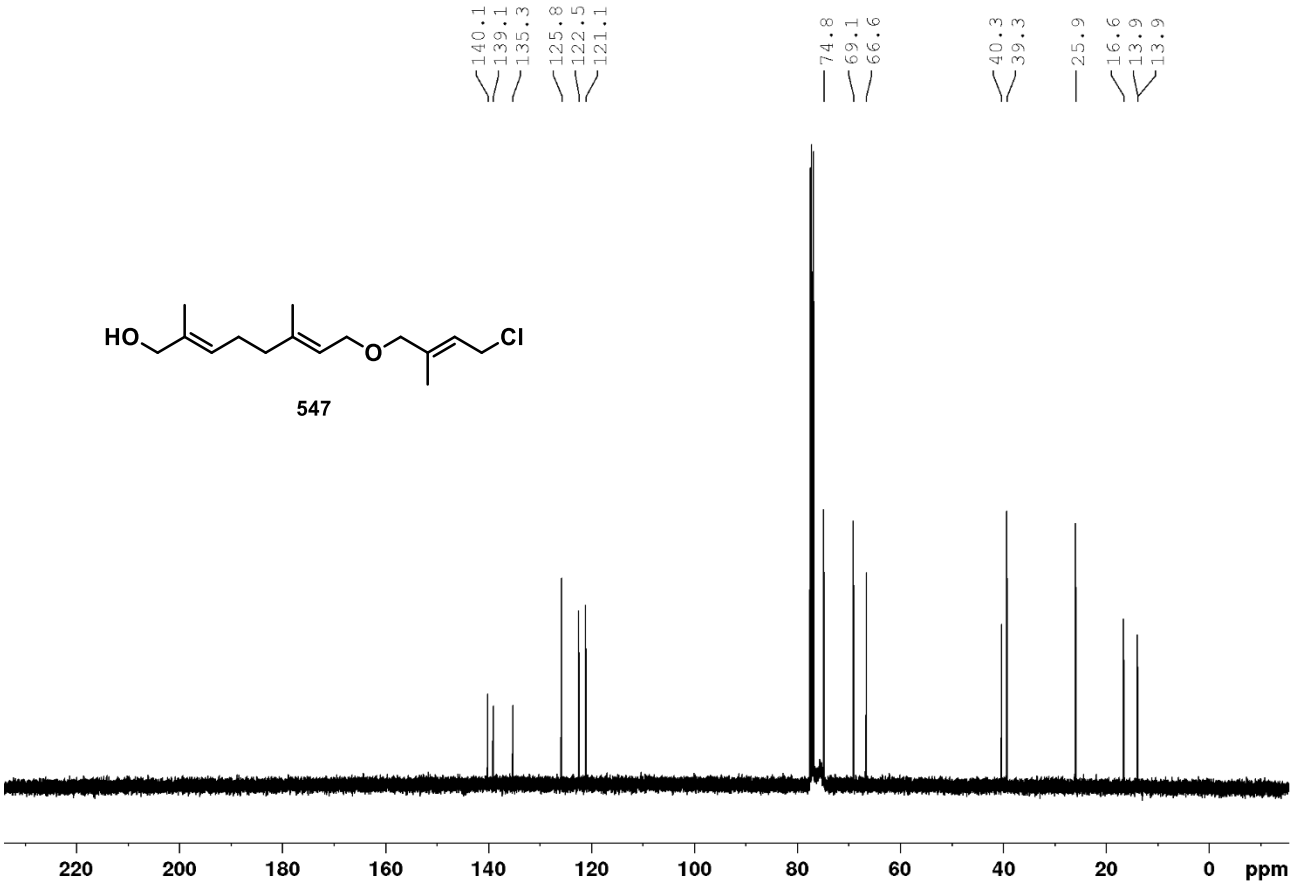
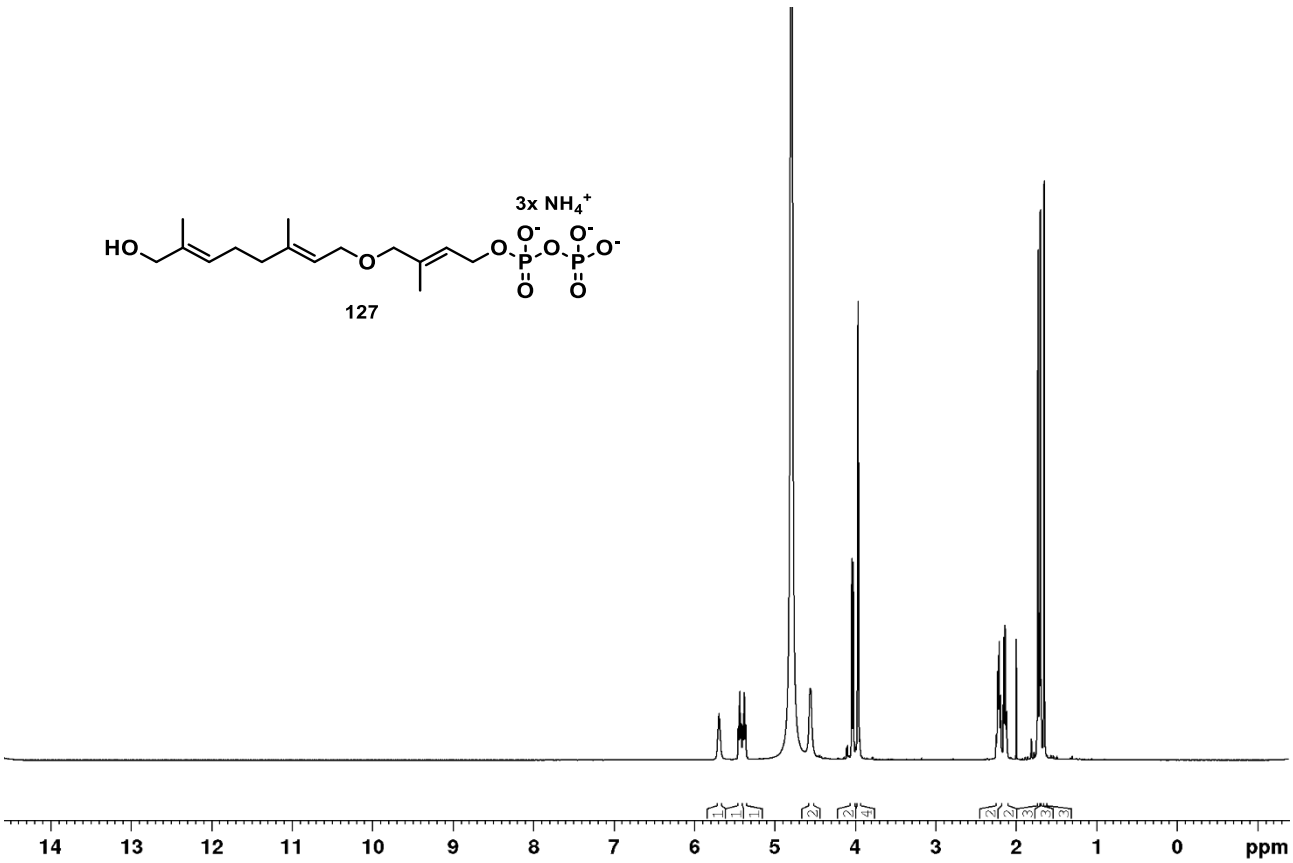
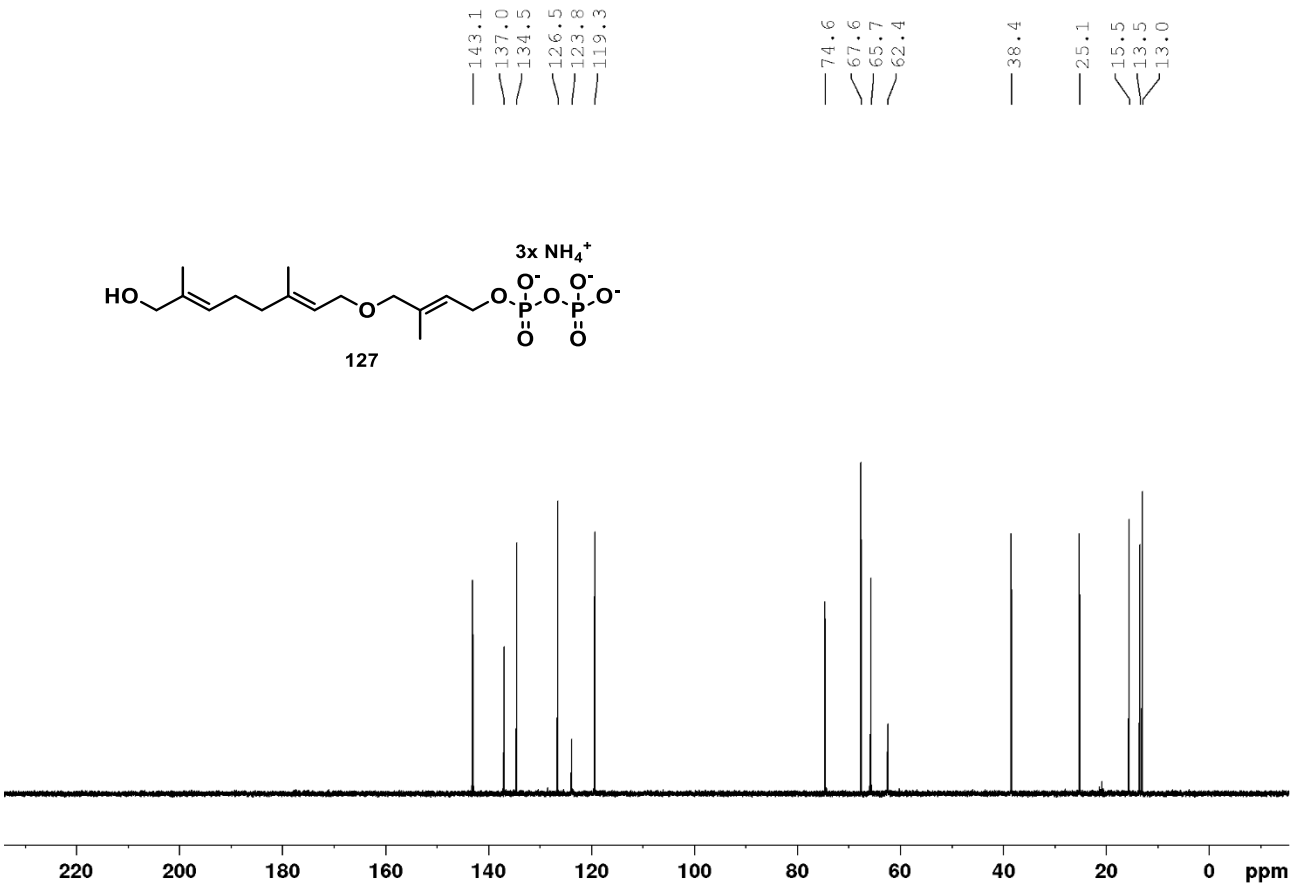
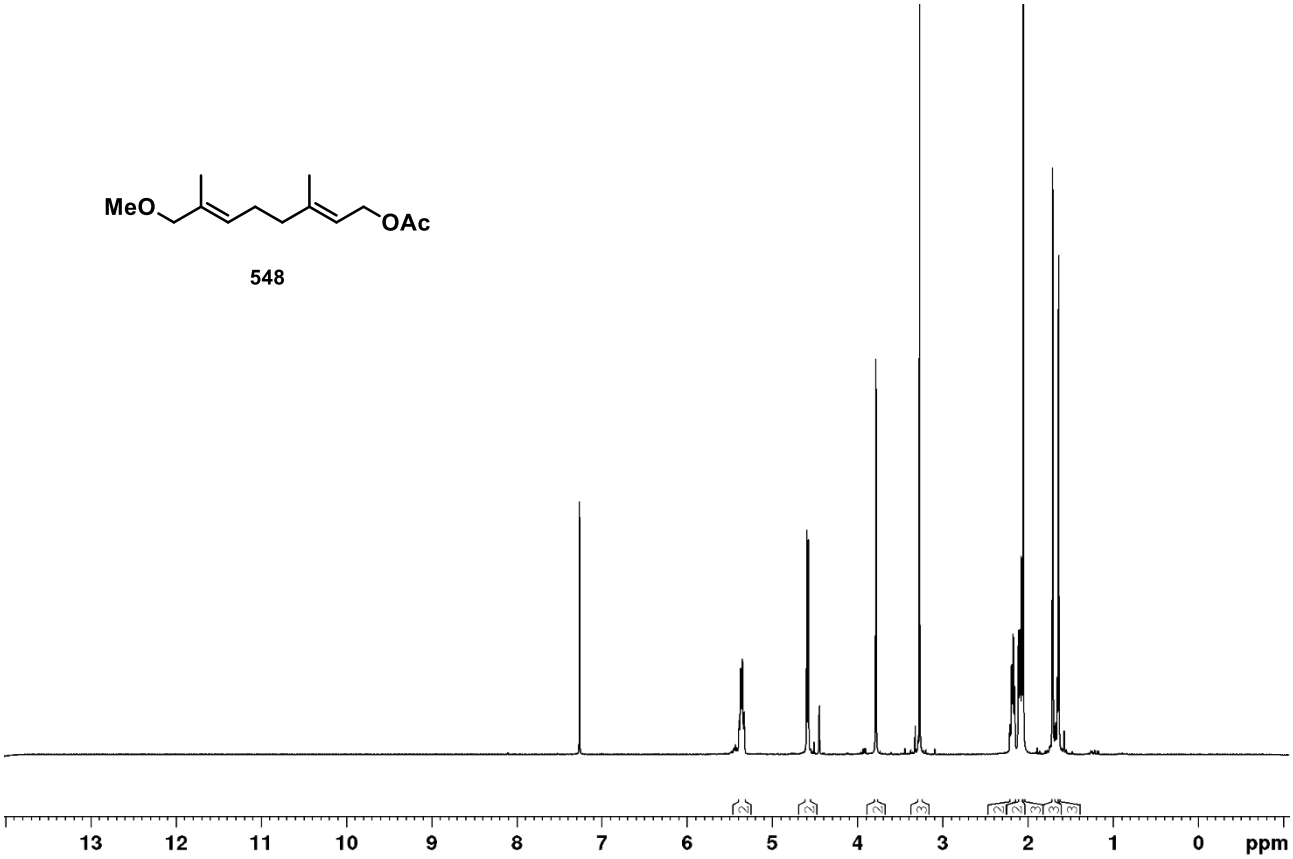
200
180
160
140
120
100
80
60
40
20
0
ppm

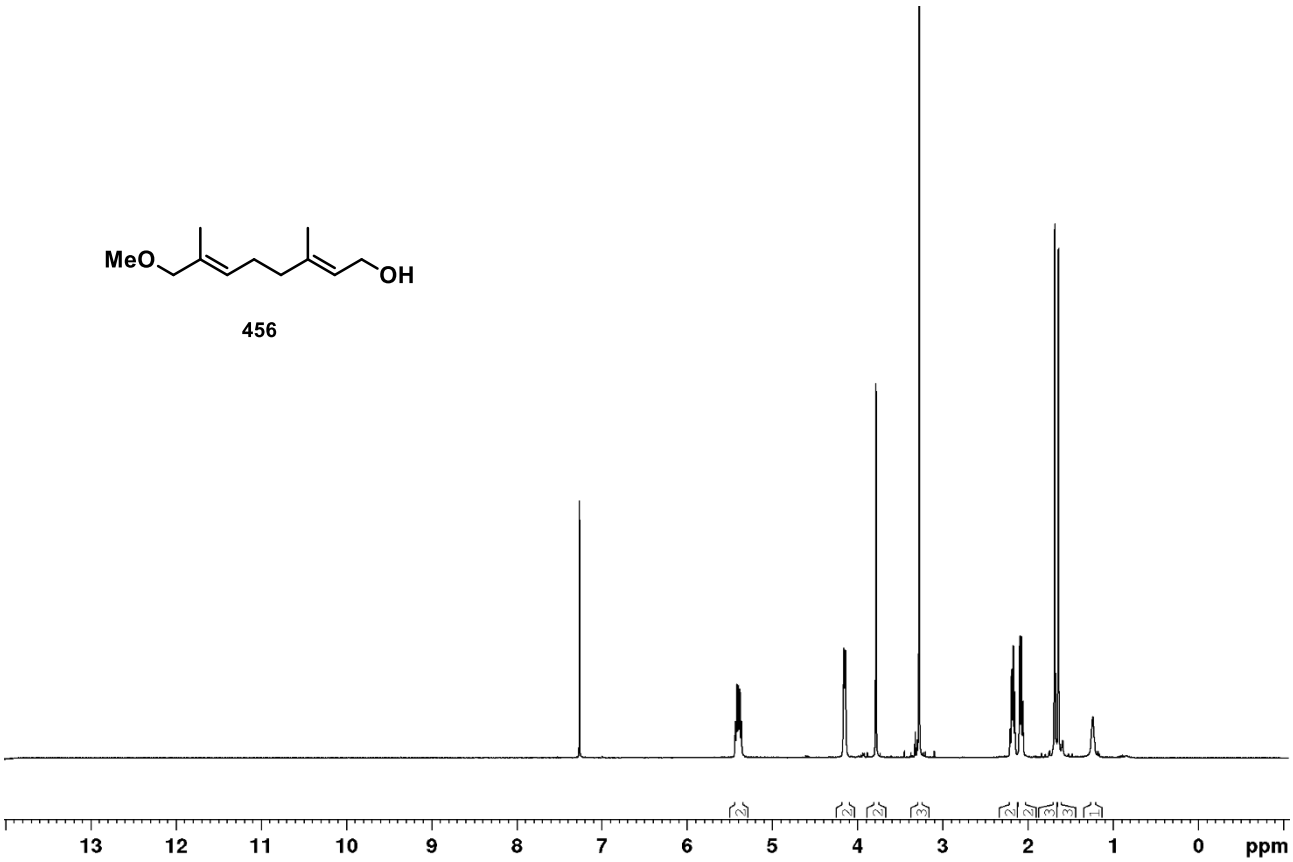

HO
O
Cl
547
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

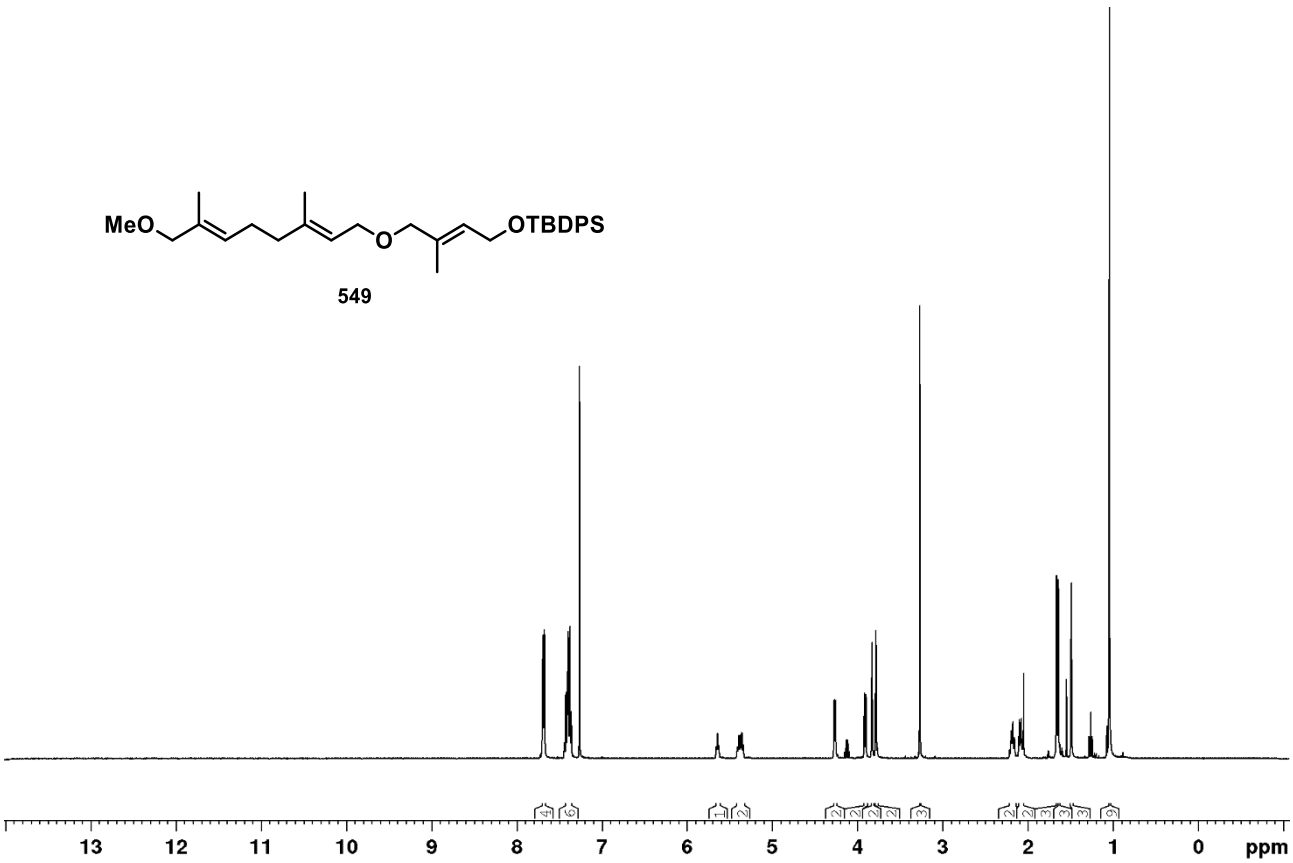

140.1
139.1
135.3
125.8
122.5
121.1
74.8
69.1
66.6
40.3
39.3
25.9
16.6
13.9
13.9
HO
O
Cl
547
220
200
180
160
140
120
100
80
60
40
20
0
ppm

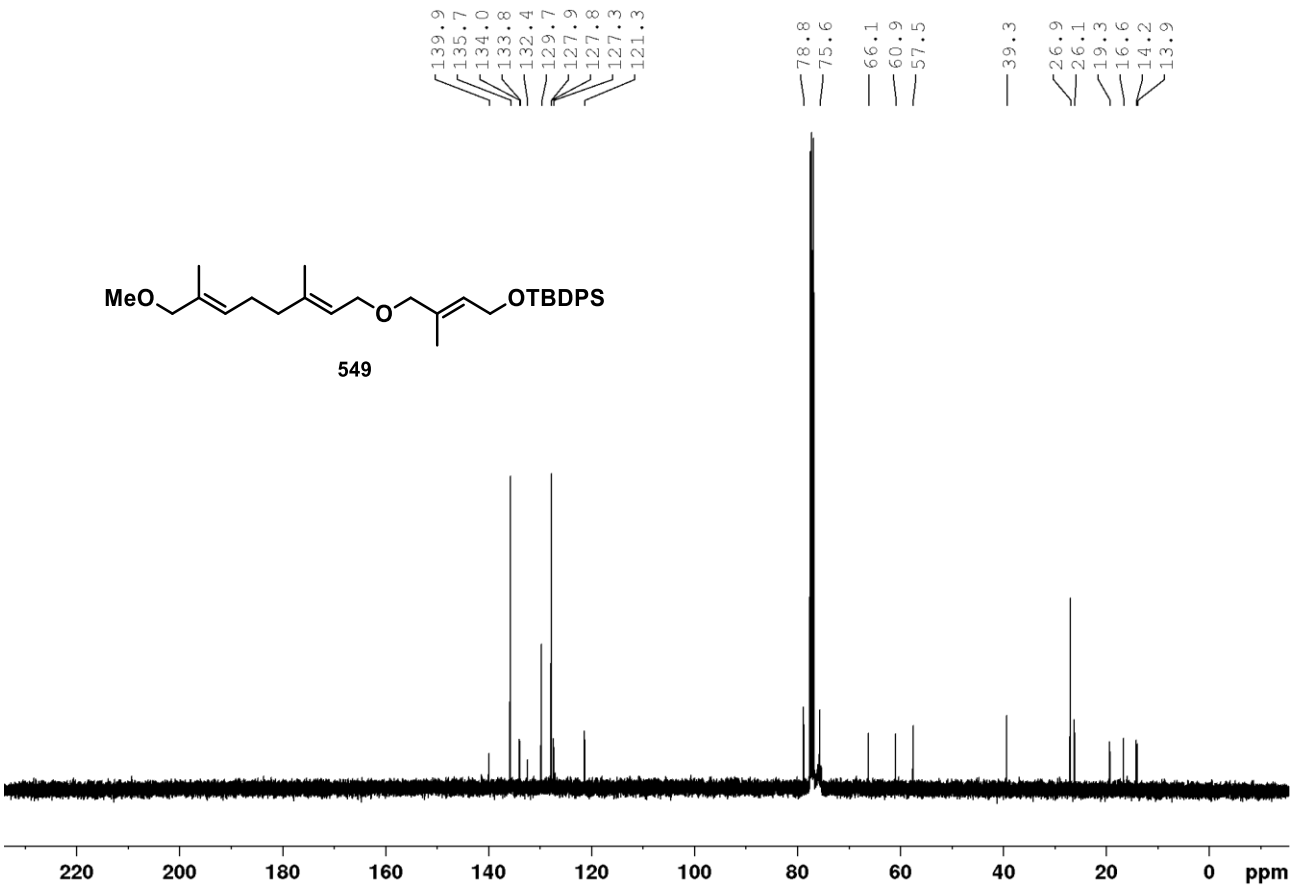

3x NH4+
HO
O
O
O
O-
O-
O-
P
P
O
O
127
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


143.1
137.0
134.5
126.5
123.8
119.3
74.6
67.6
65.7
62.4
38.4
25.1
15.5
13.5
13.0
3x NH4+
HO
O
O
O
O-
O-
O-
P
P
O
O
127
220
200
180
160
140
120
100
80
60
40
20
0
ppm


MeO
OAc
548
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


MeO
OH
456
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


MeO
O
OTBDPS
549
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm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135.7
134.0
133.8
132.4
129.7
127.9
127.8
127.3
121.3
78.8
75.6
66.1
60.9
57.5
39.3
26.9
26.1
19.3
16.6
14.2
13.9
MeO
O
OTBDPS
549
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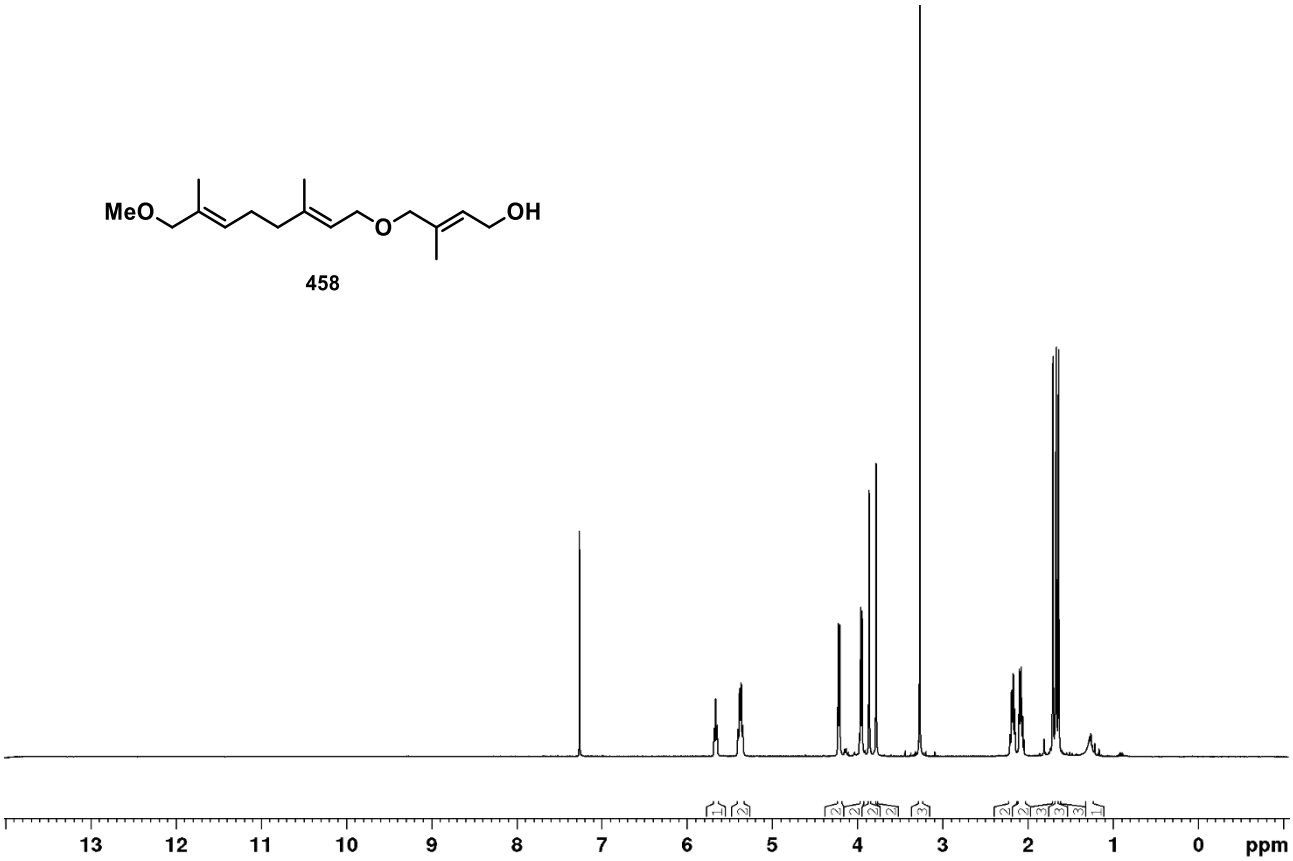
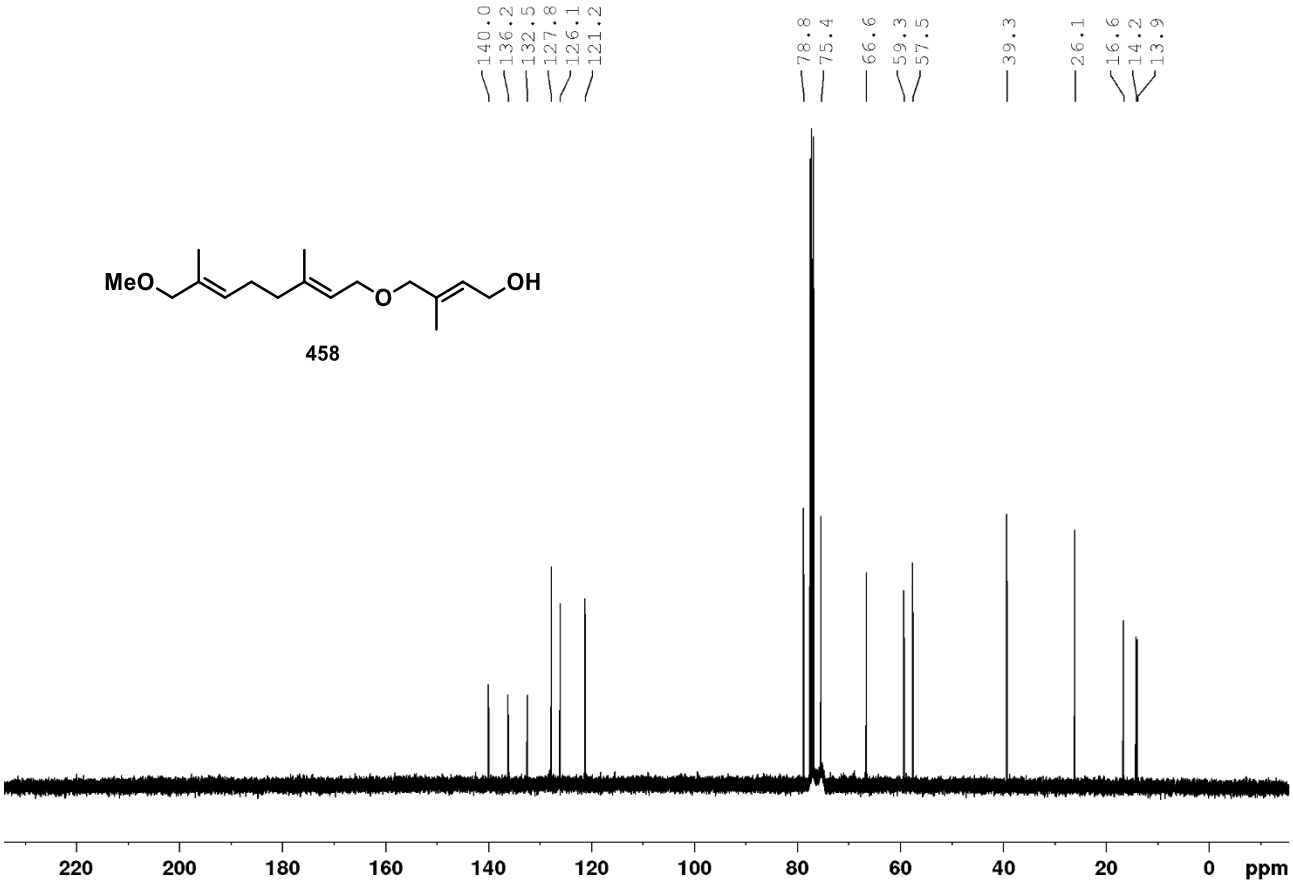
200
180
160
140
120
100
80
60
40
20
0
ppm


MeO
O
OH
458
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm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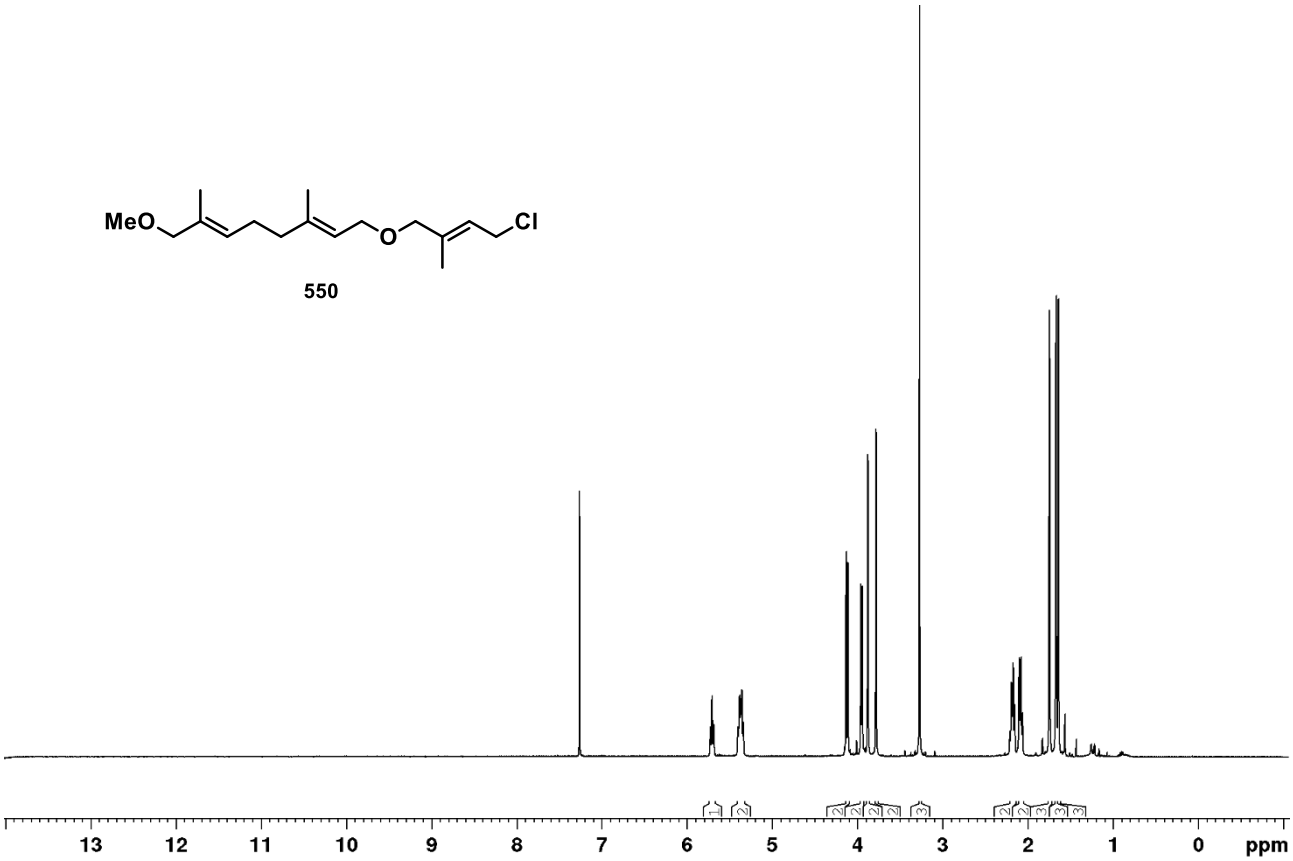
136.2
132.5
127.8
126.1
121.2
78.8
75.4
66.6
59.3
57.5
39.3
26.1
16.6
14.2
13.9
MeO
O
OH
458
220
200
180
160
140
120
100
80
60
40
20
0
ppm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O
Cl
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13
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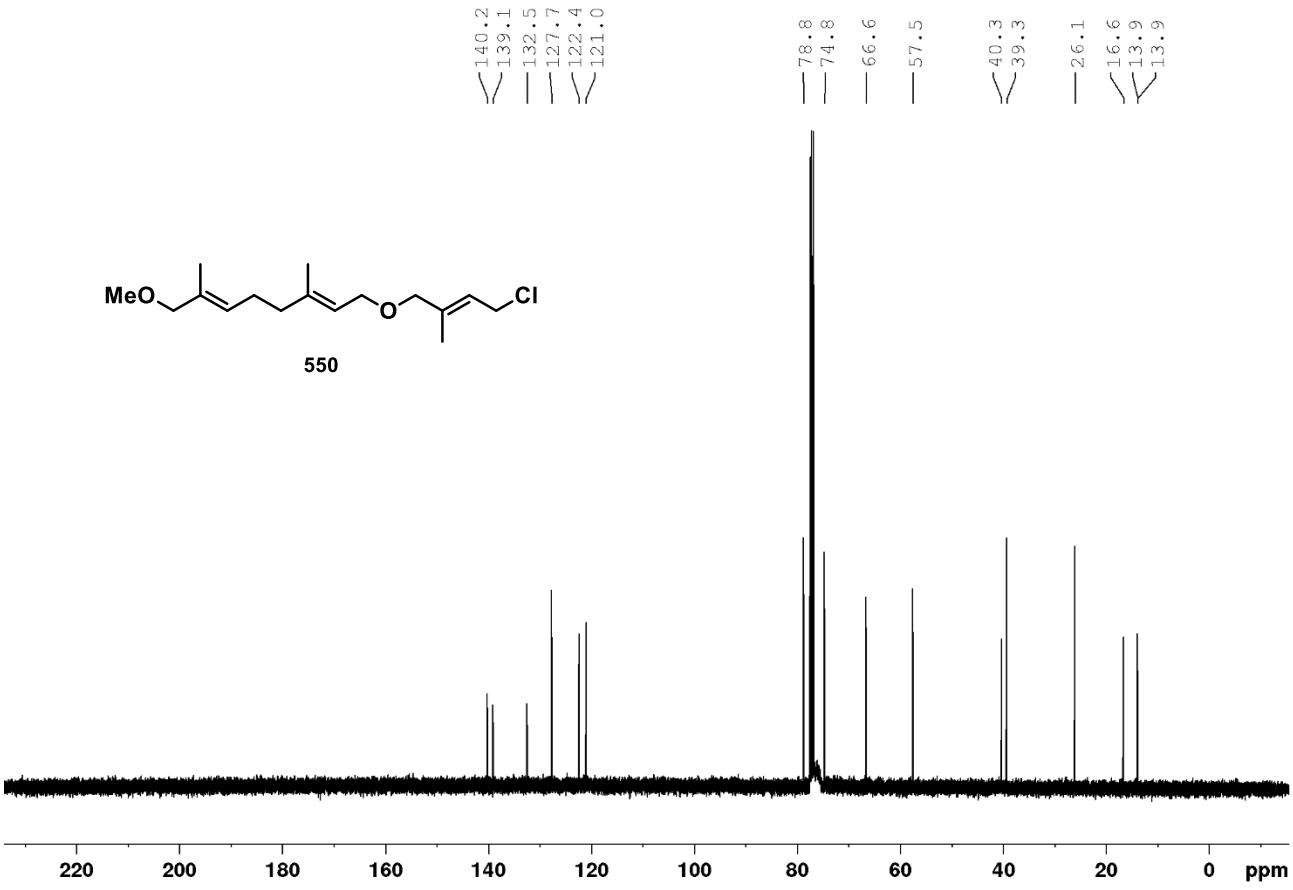
11
10
9
8
7
6
5
4
3
2
1
0
ppm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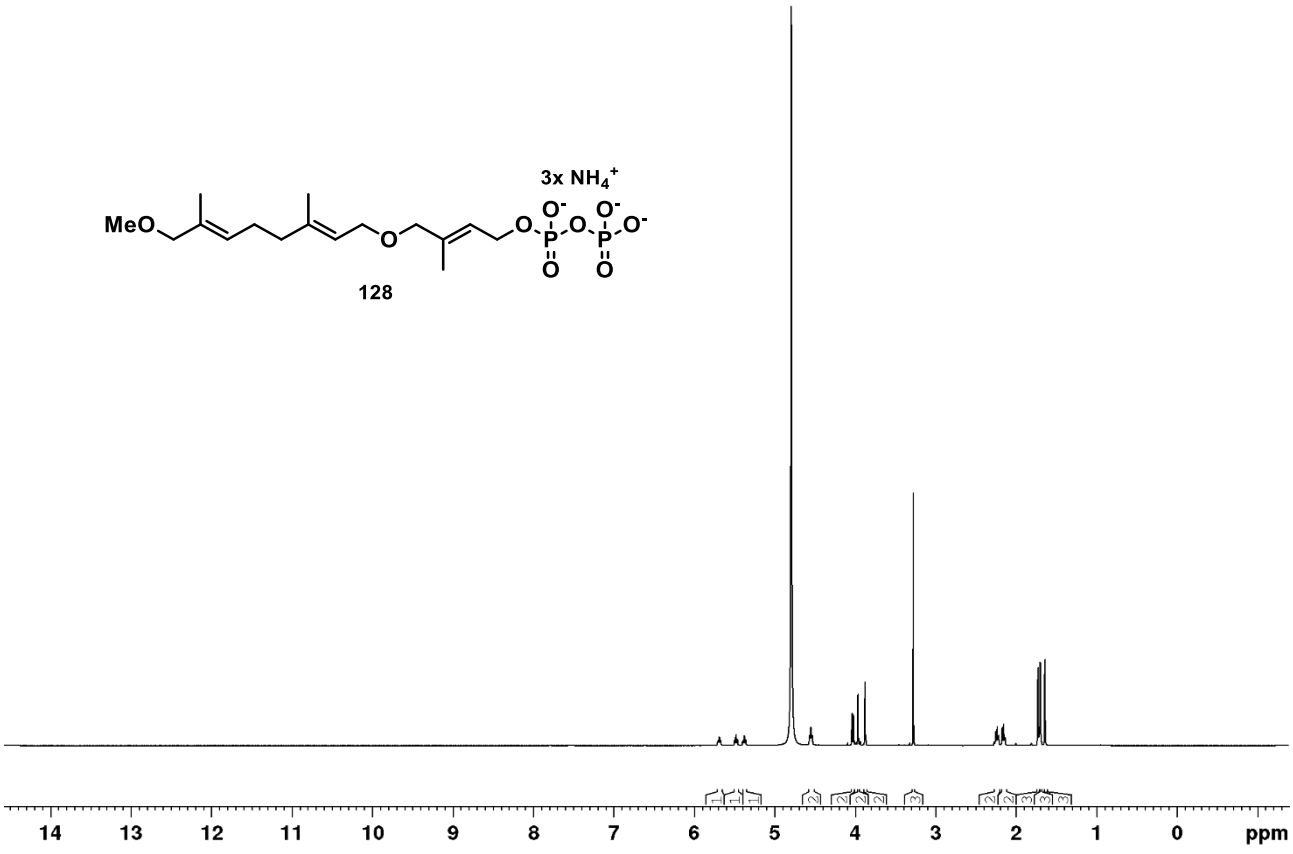
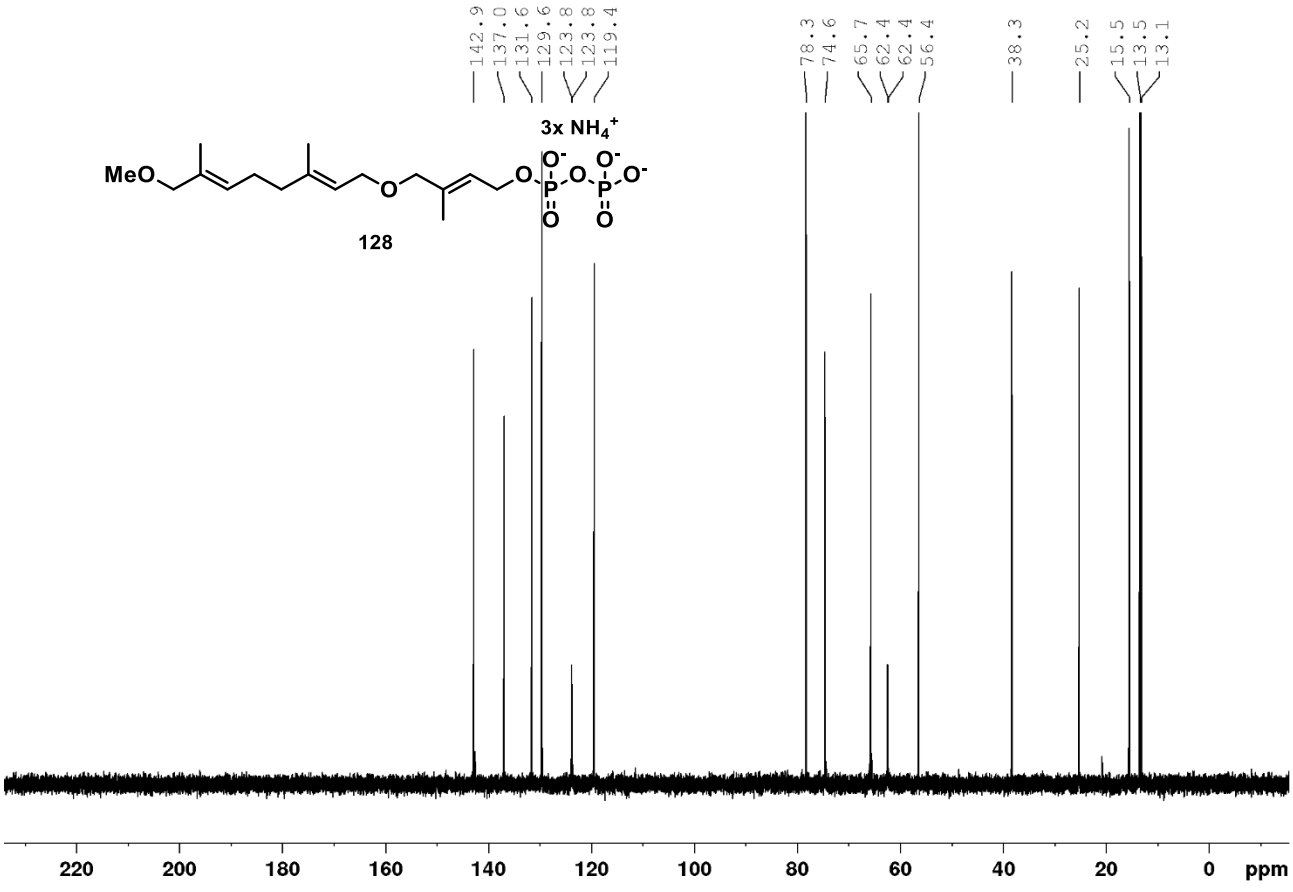
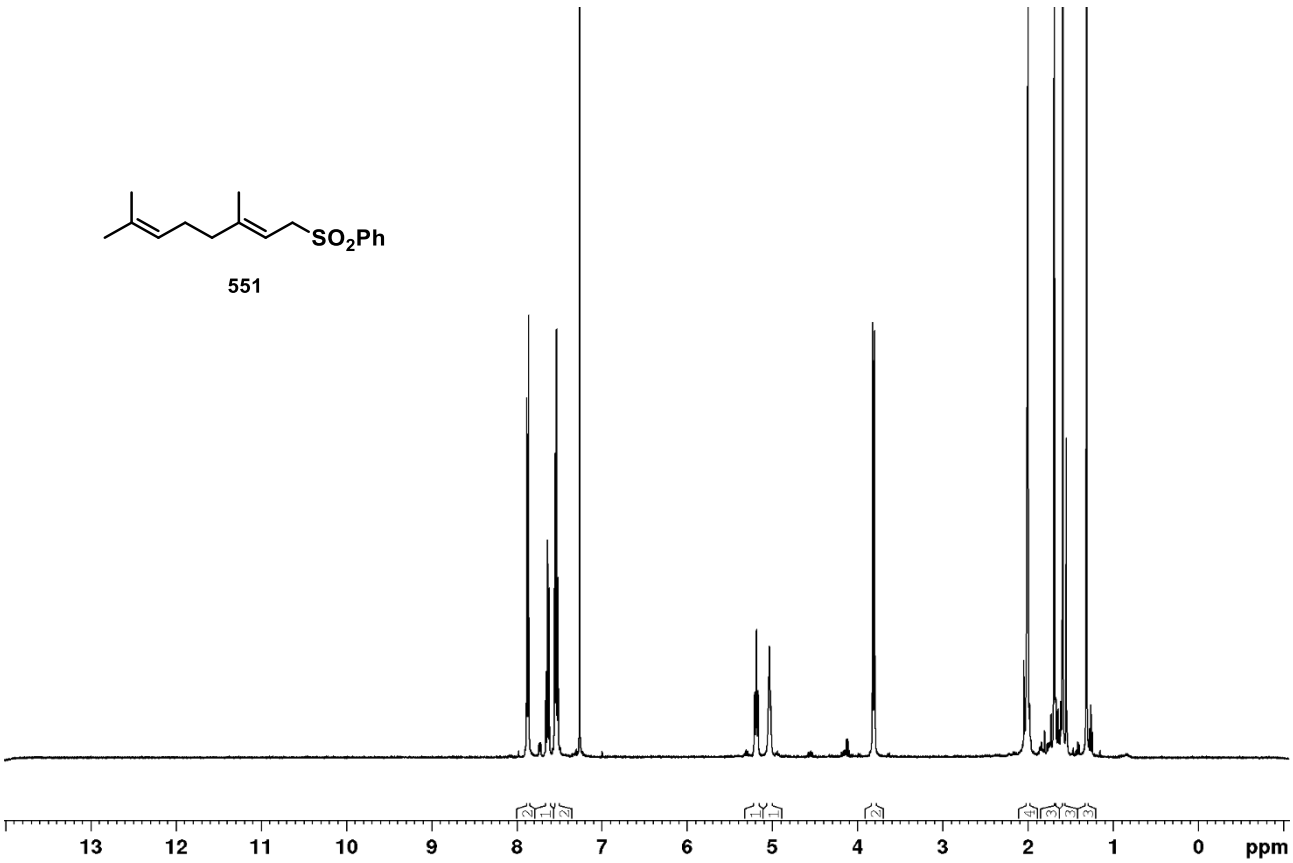
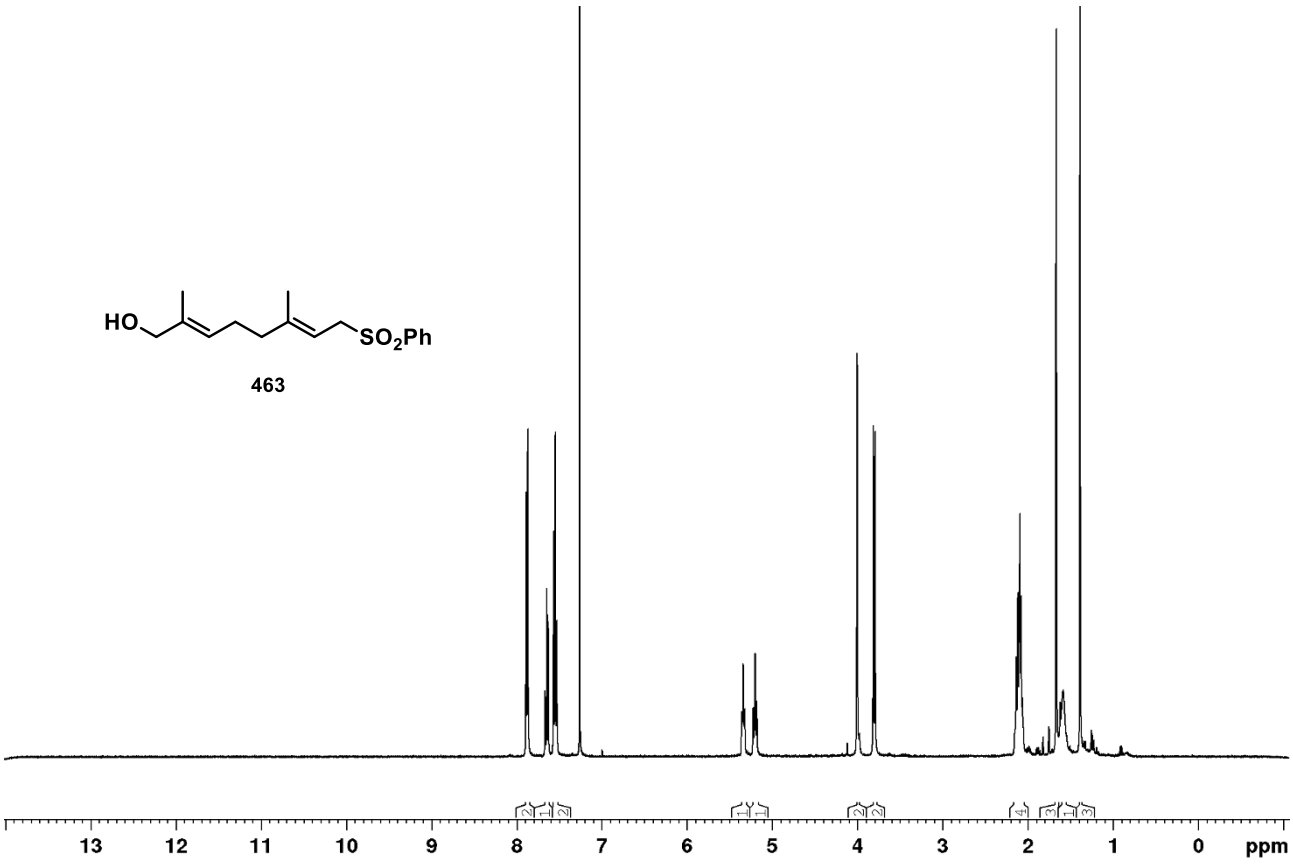
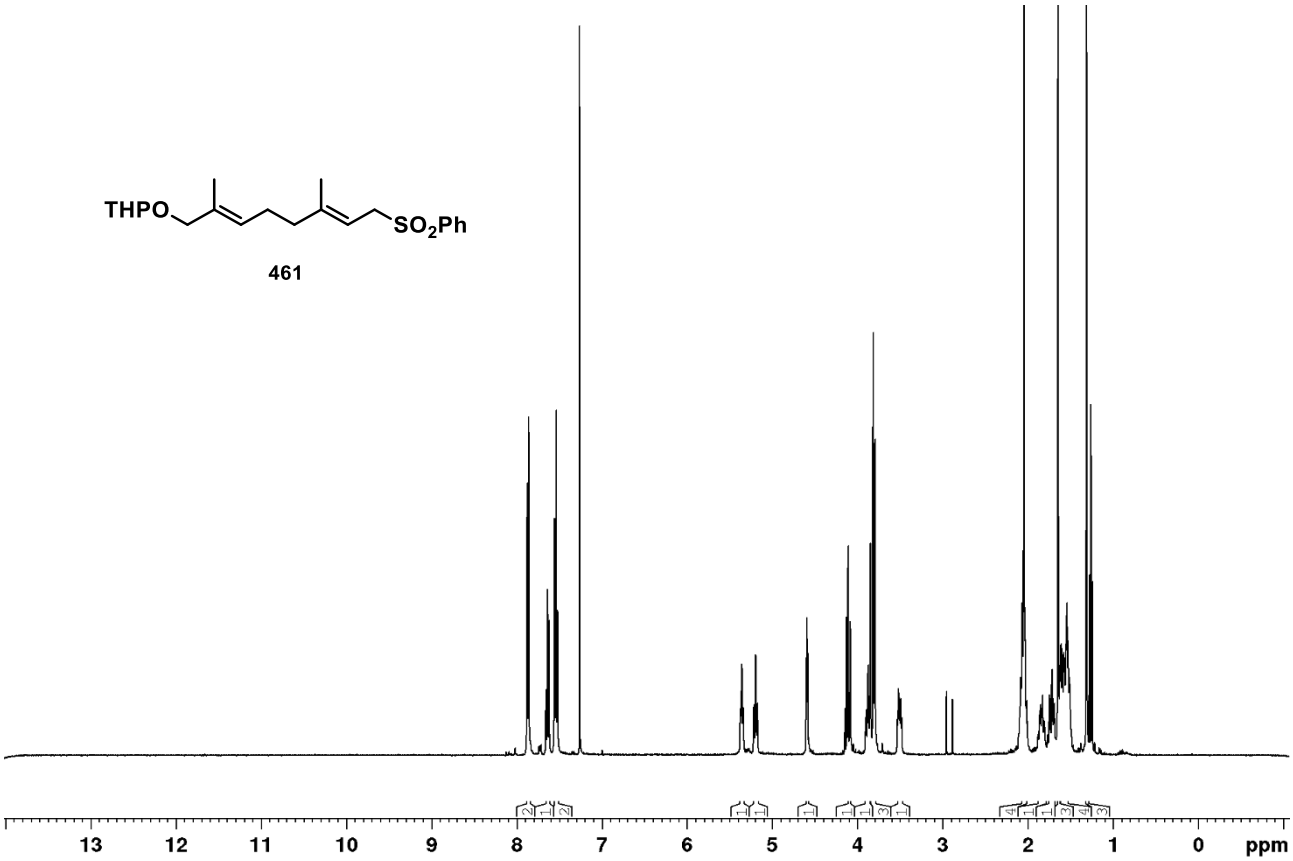
139.1
132.5
127.7
122.4
121.0
78.8
74.8
66.6
57.5
40.3
39.3
26.1
16.6
13.9
13.9
MeO
O
Cl
550
220
200
180
160
140
120
100
80
60
40
20
0
ppm

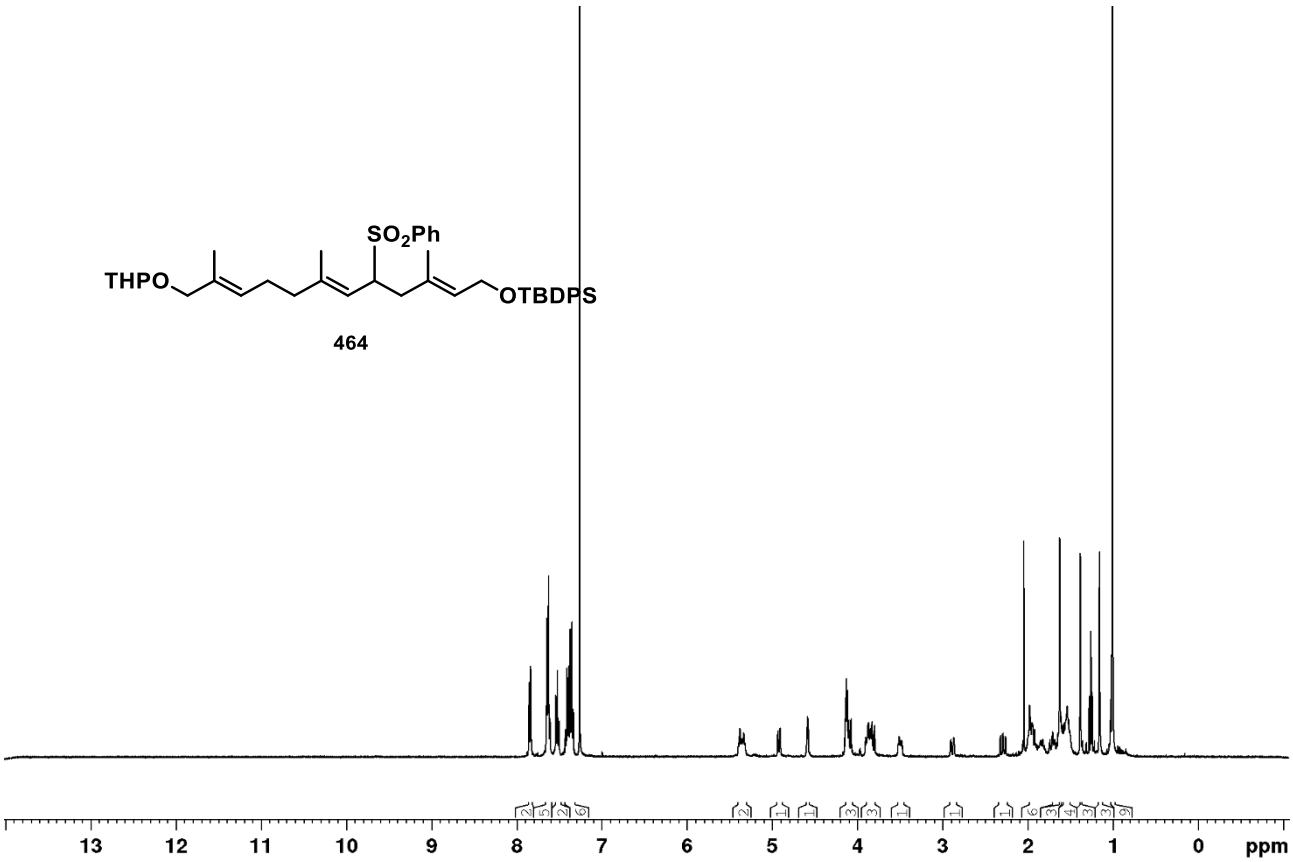

3x NH4+
MeO
O
O
O
O-
O-
O-
P
P
O
O
128
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

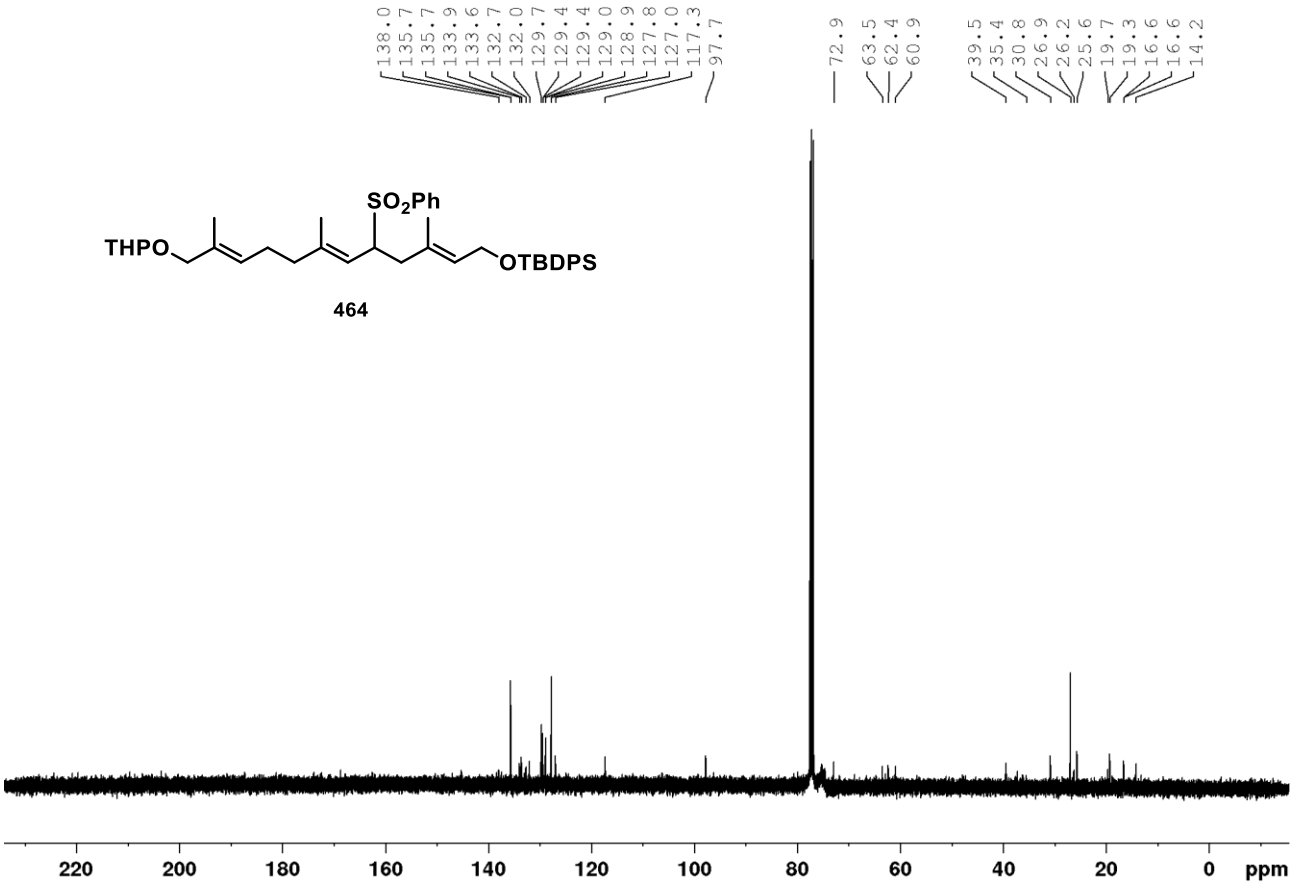

142.9
137.0
131.6
129.6
123.8
123.8
119.4
78.3
74.6
65.7
62.4
62.4
56.4
38.3
25.2
15.5
13.5
13.1
3x NH4+
MeO
O
O
O
O-
O-
O-
P
P
O
O
128
220
200
180
160
140
120
100
80
60
40
20
0
ppm


SO2Ph
551
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


HO
SO2Ph
463
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


THPO
SO2Ph
461
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


SO2Ph
THPO
OTBDPS
464
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm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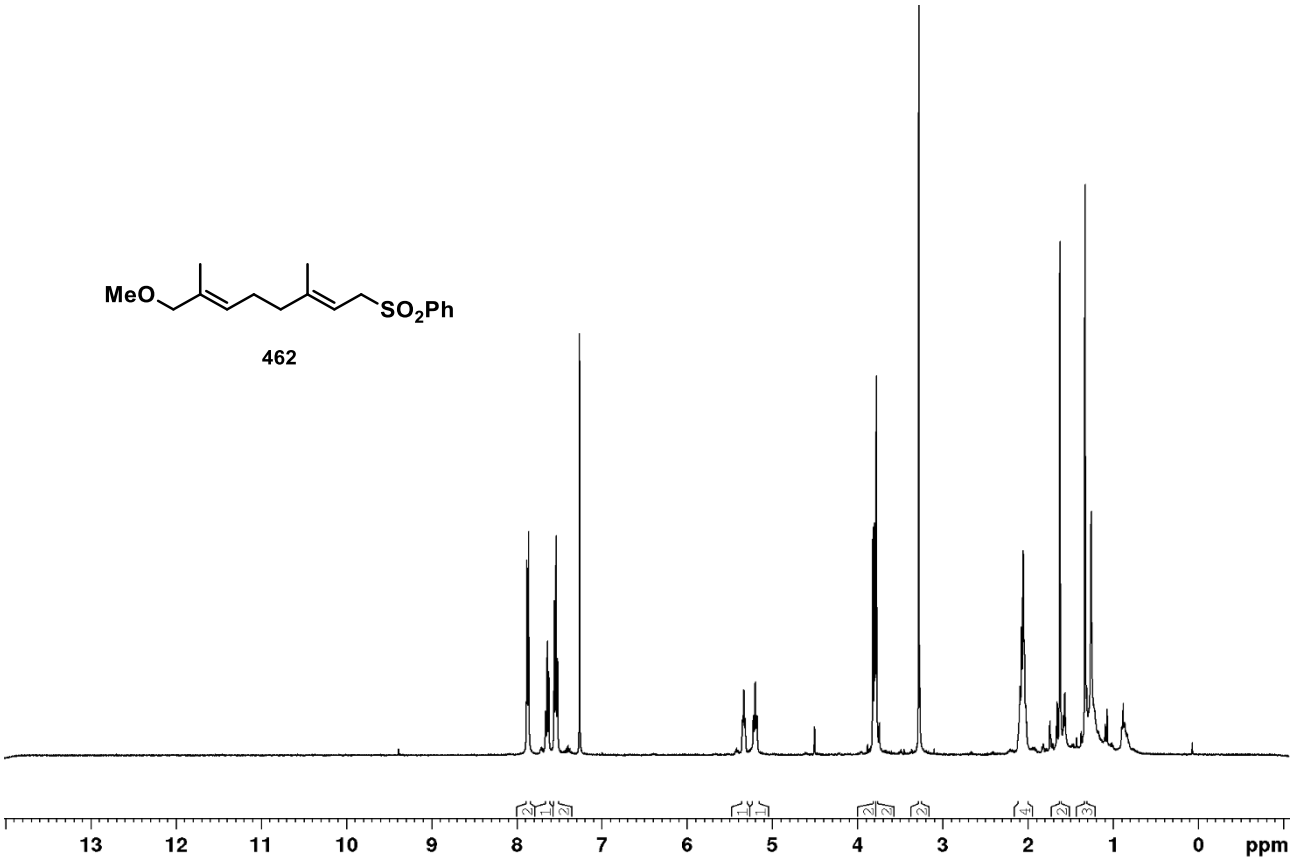
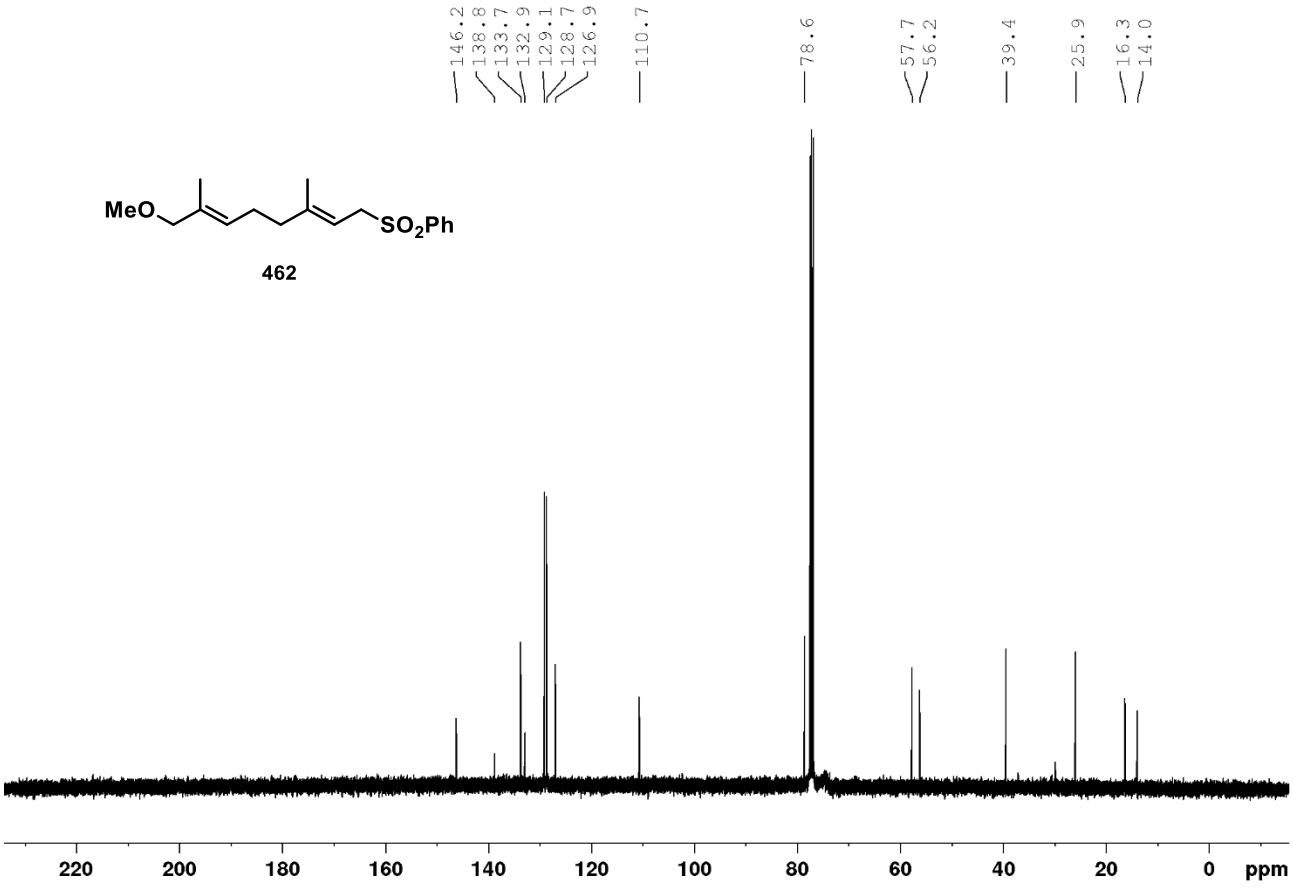
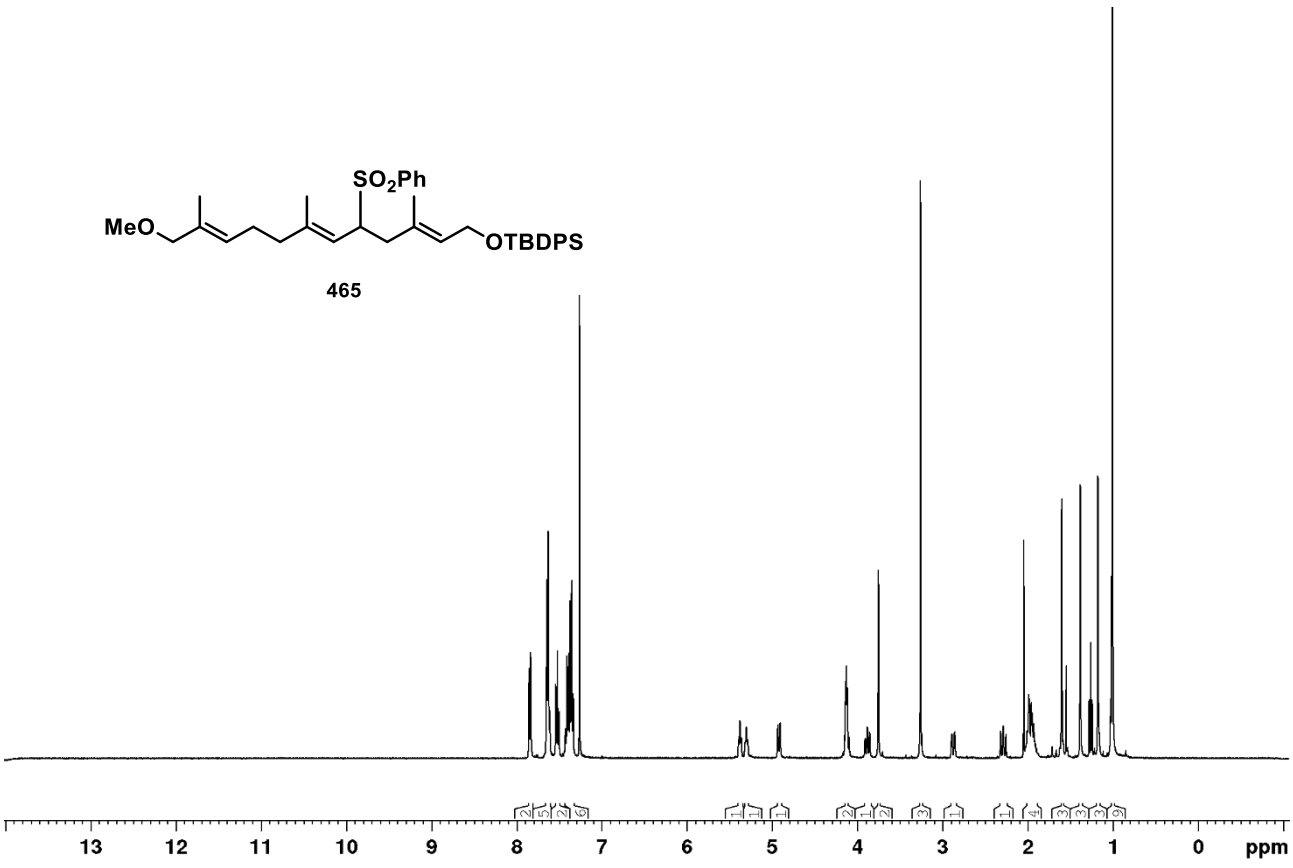
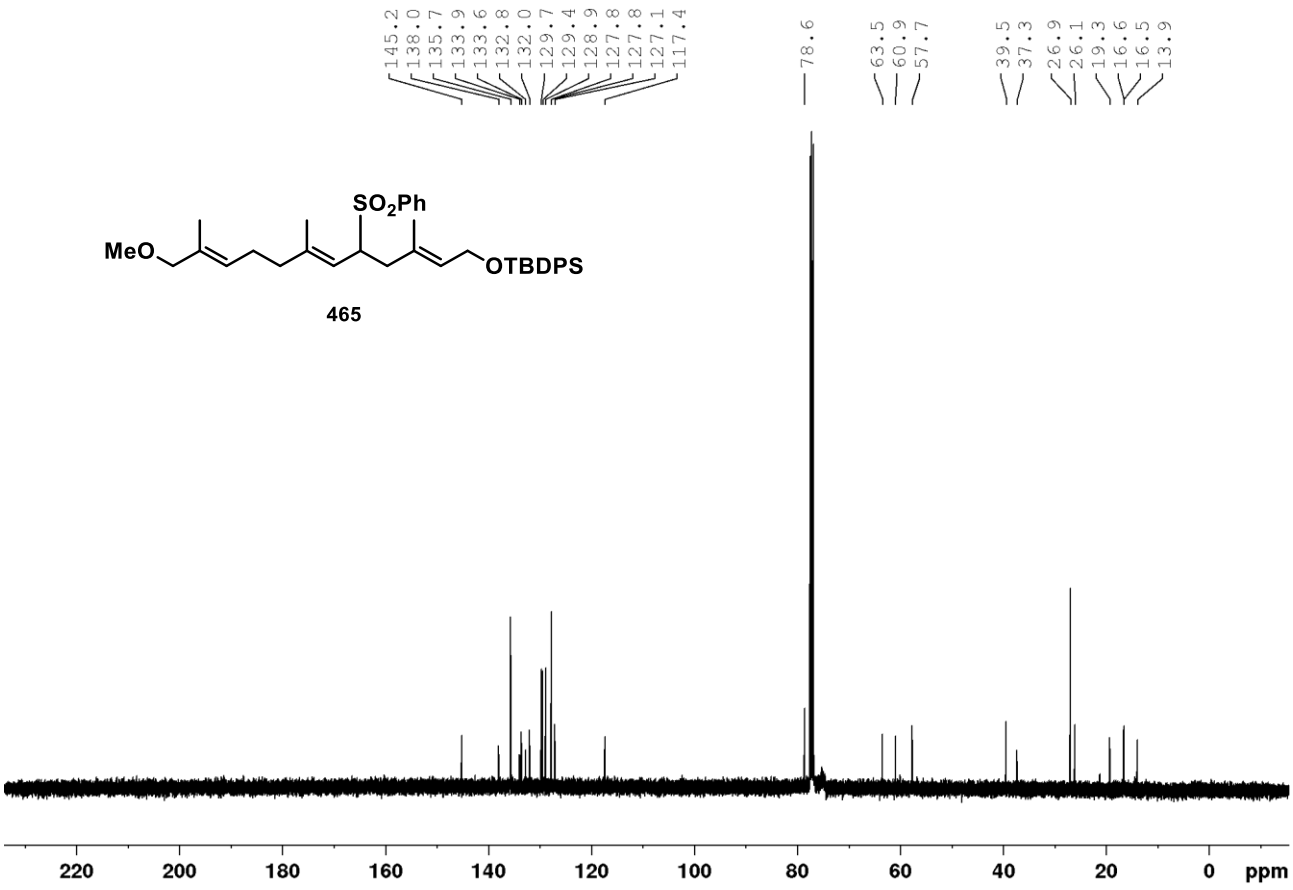
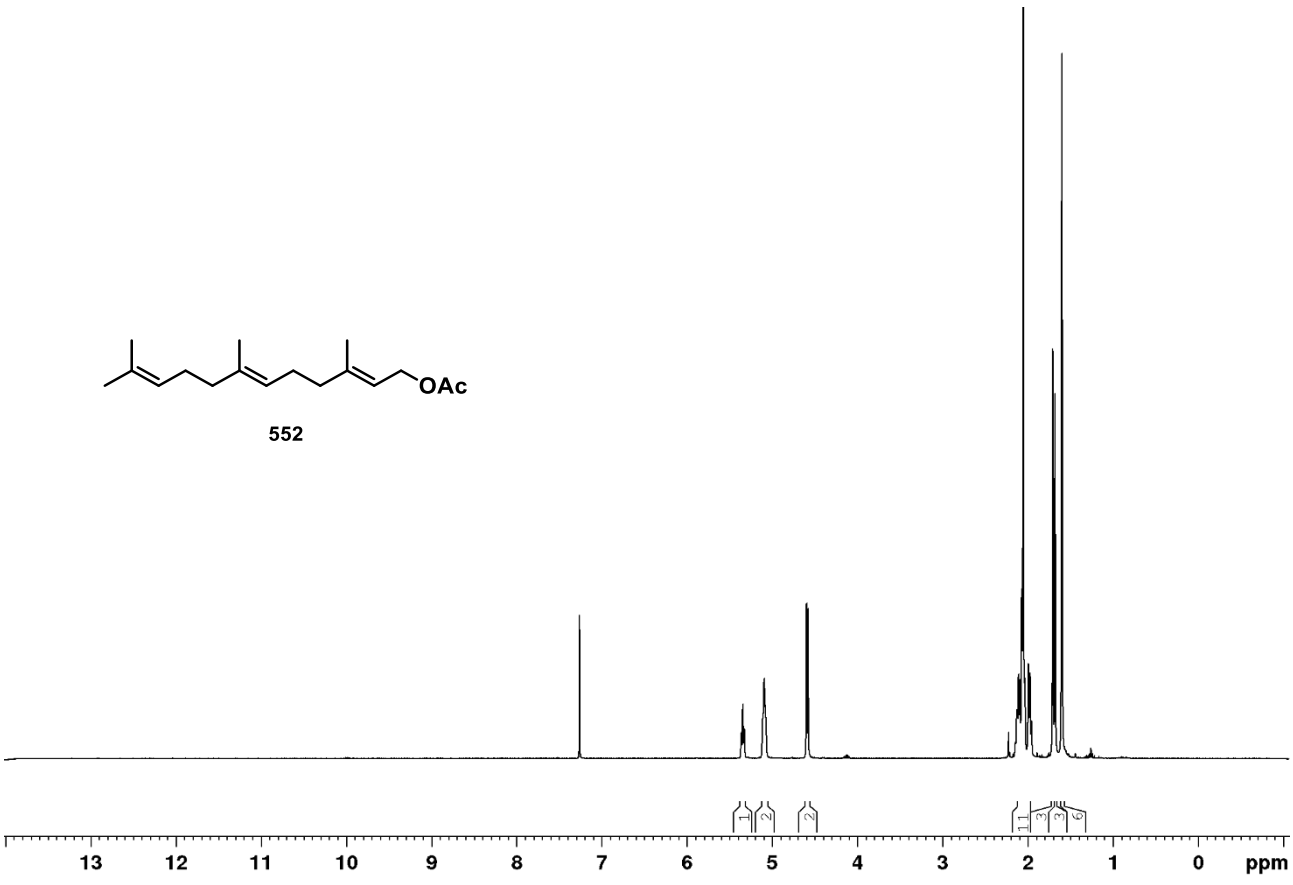
135.7
135.7
133.9
133.6
132.7
132.0
129.7
129.4
129.4
129.0
128.9
127.8
127.0
117.3
97.7
72.9
63.5
62.4
60.9
39.5
35.4
30.8
26.9
26.2
25.6
19.7
19.3
16.6
16.6
14.2
SO2Ph
THPO
OTBDPS
464
220
200
180
160
140
120
100
80
60
40
20
0
ppm

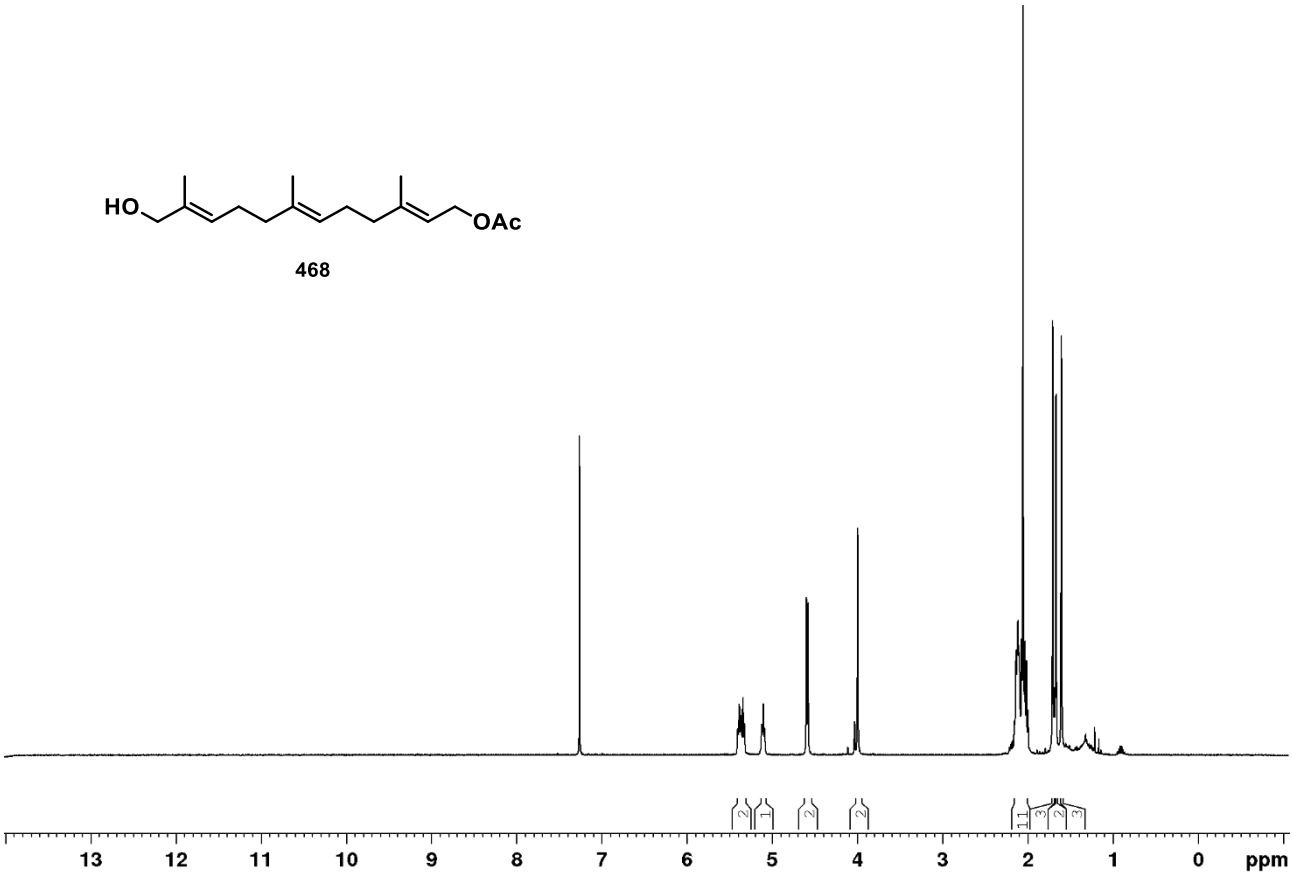

MeO
SO2Ph
462
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


146.2
138.8
133.7
132.9
129.1
128.7
126.9
110.7
78.6
57.7
56.2
39.4
25.9
16.3
14.0
MeO
SO2Ph
462
220
200
180
160
140
120
100
80
60
40
20
0
ppm

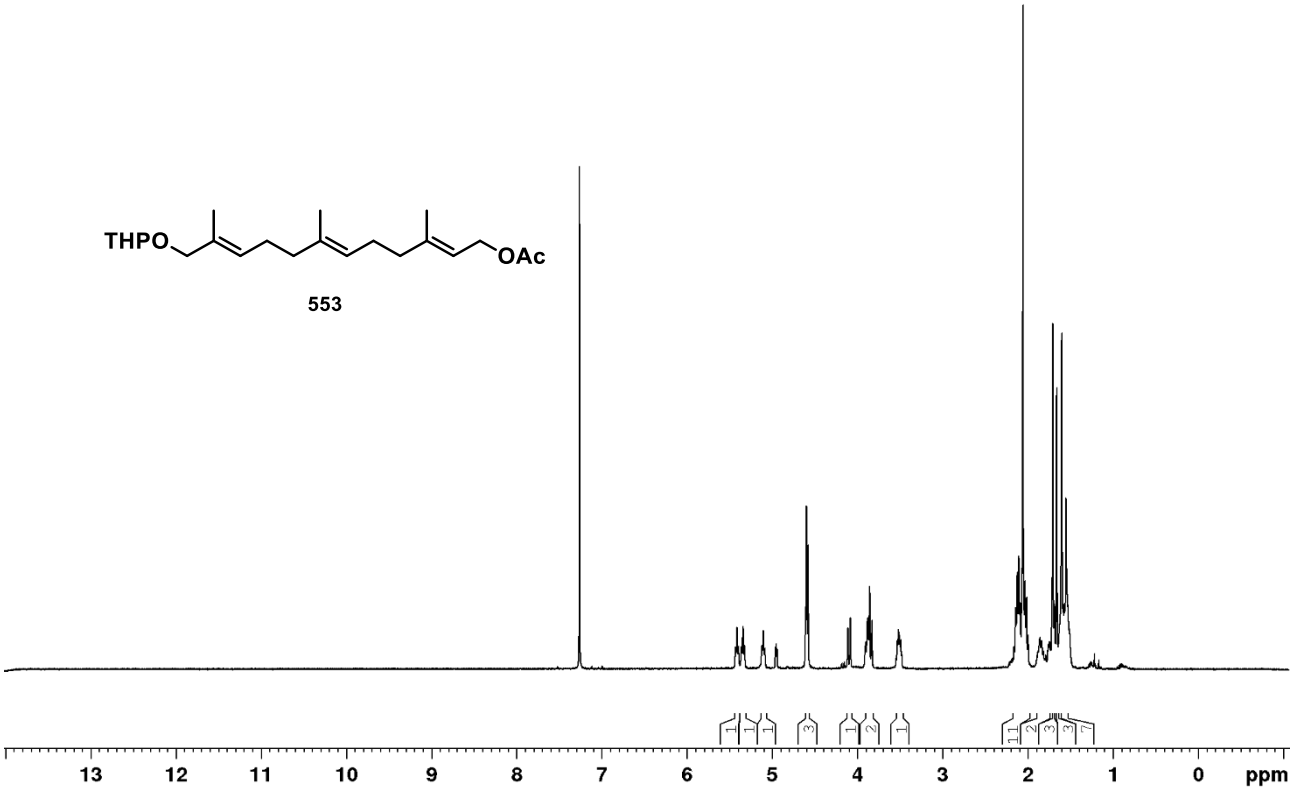

SO2Ph
MeO
OTBDPS
465
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


145.2
138.0
135.7
133.9
133.6
132.8
132.0
129.7
129.4
128.9
127.8
127.8
127.1
117.4
78.6
63.5
60.9
57.7
39.5
37.3
26.9
26.1
19.3
16.6
16.5
13.9
SO2Ph
MeO
OTBDPS
465
220
200
180
160
140
120
100
80
60
40
20
0
ppm

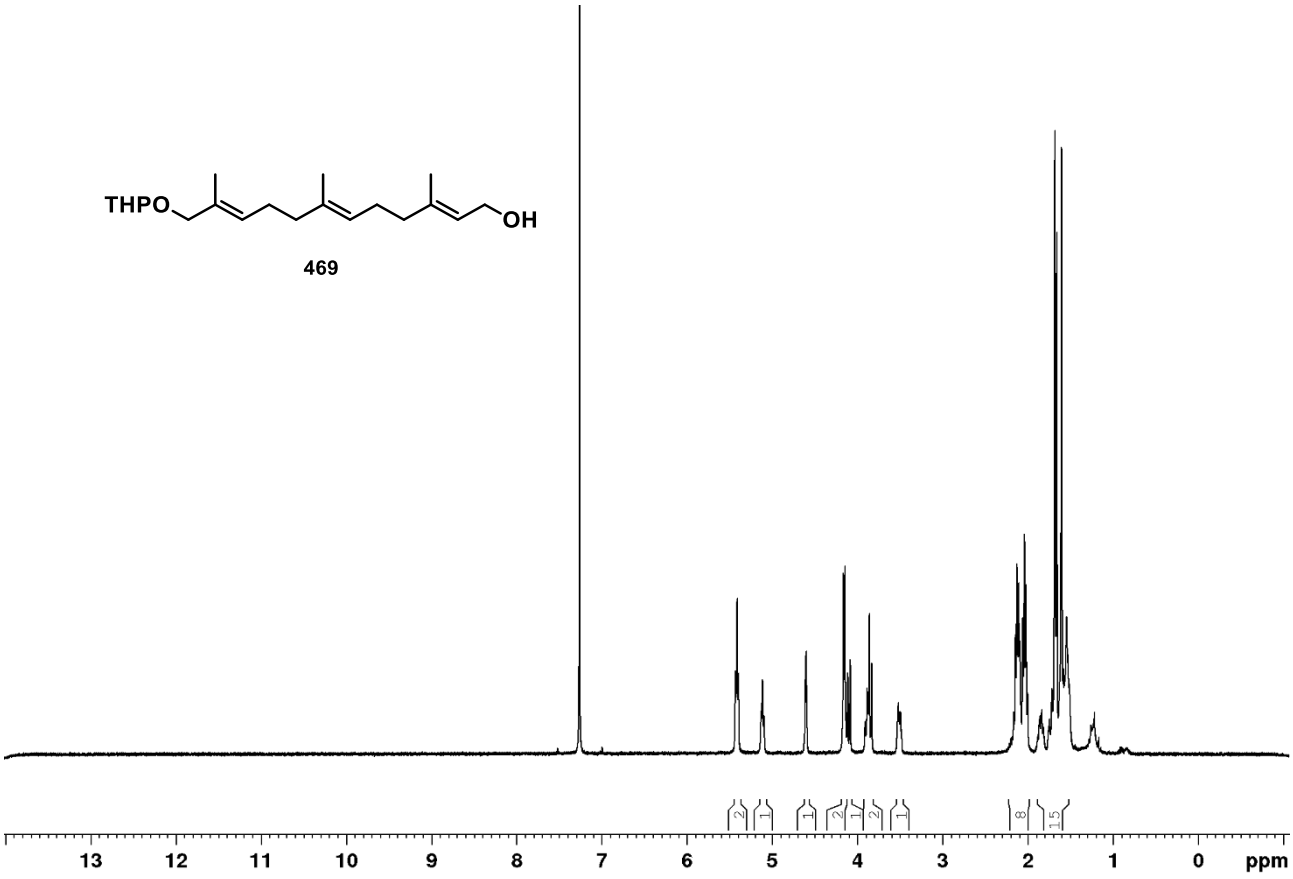

OAc
552
1
2
2
11
3
3
6
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

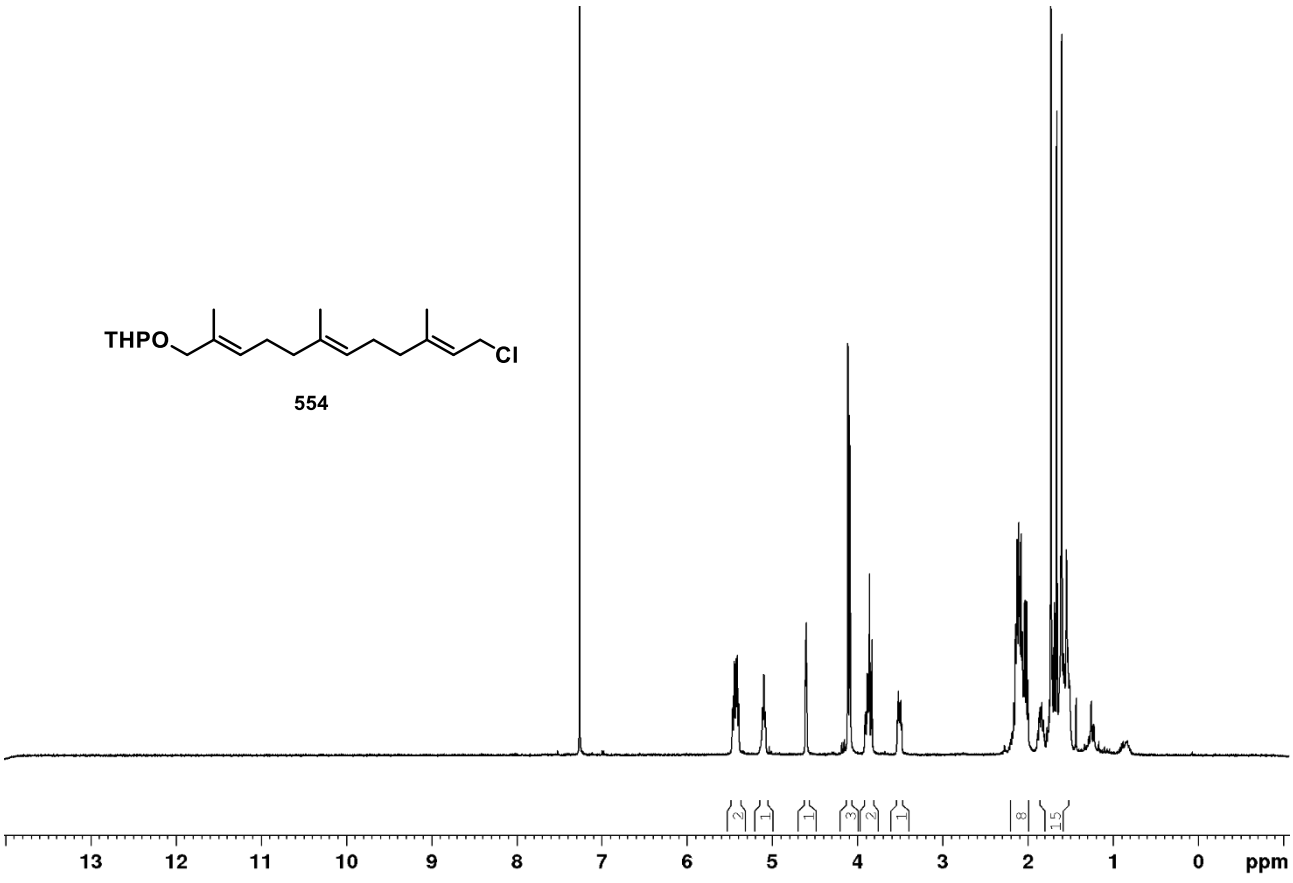

HO
OAc
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

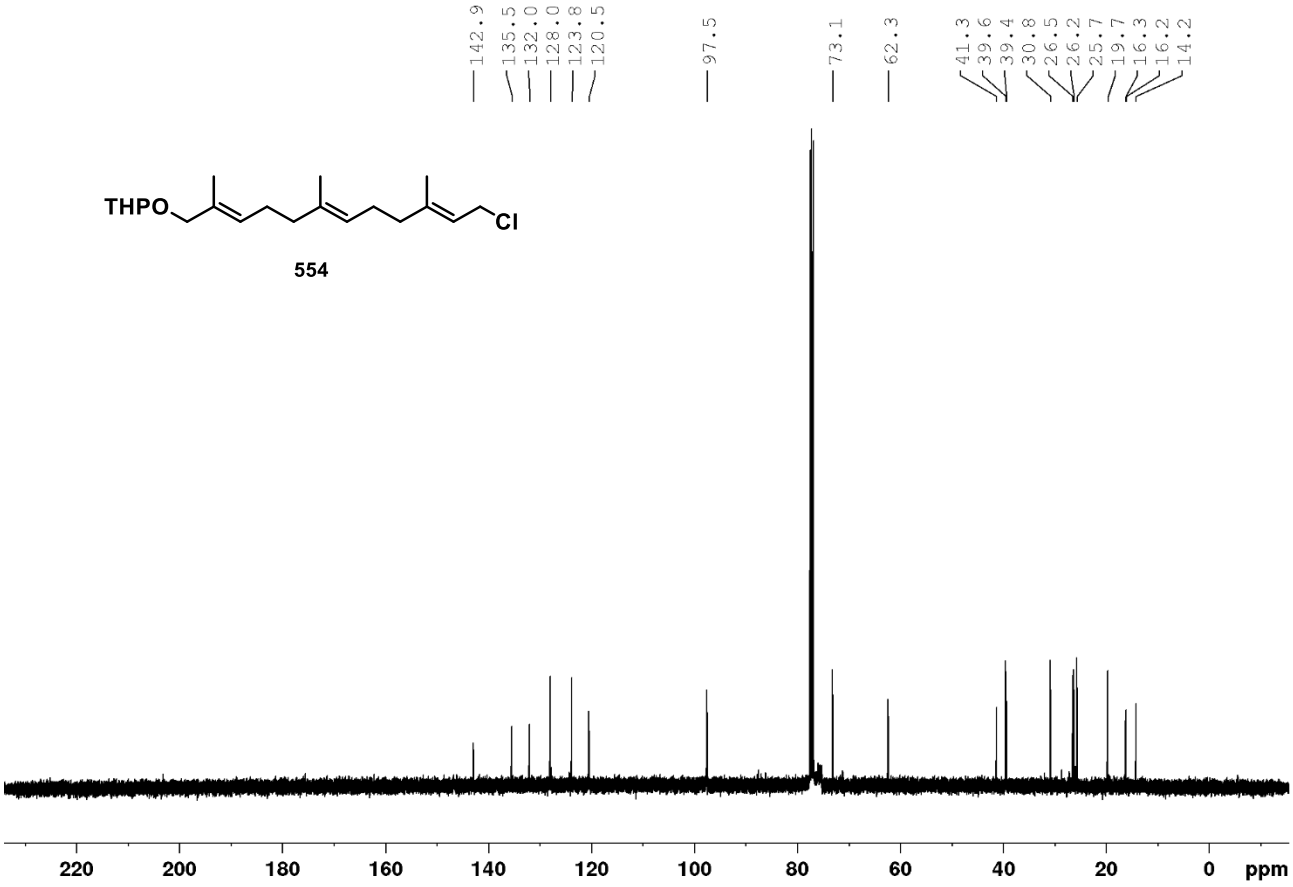
468

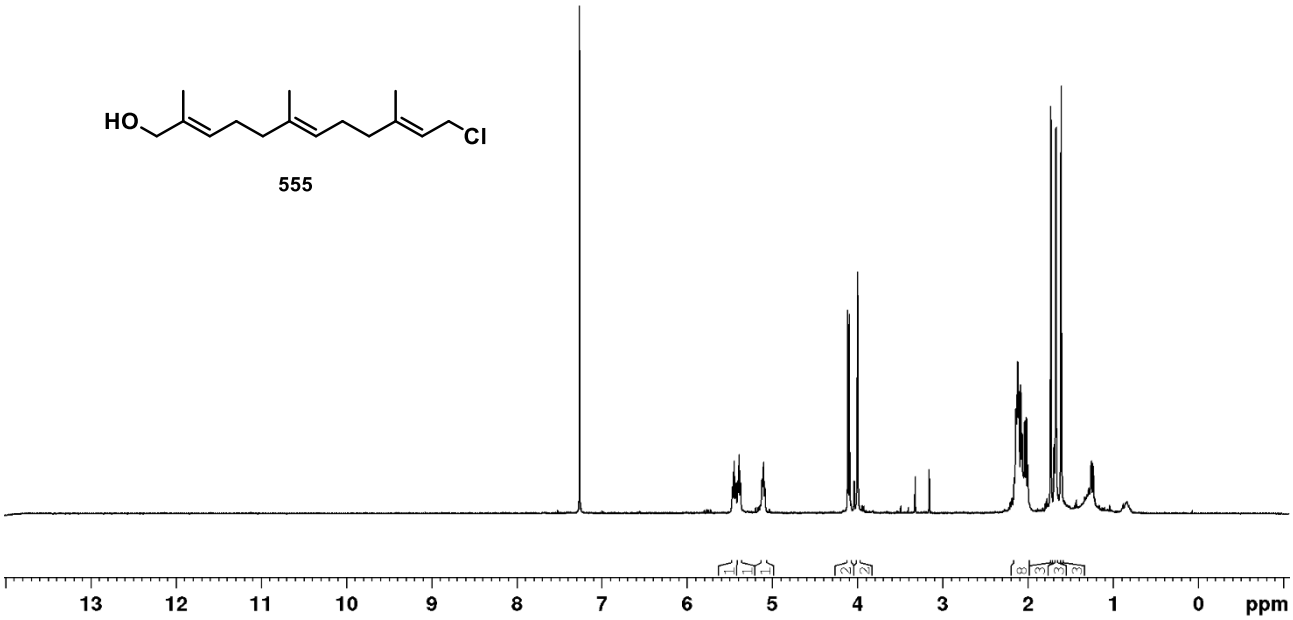

THPO
OAc
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

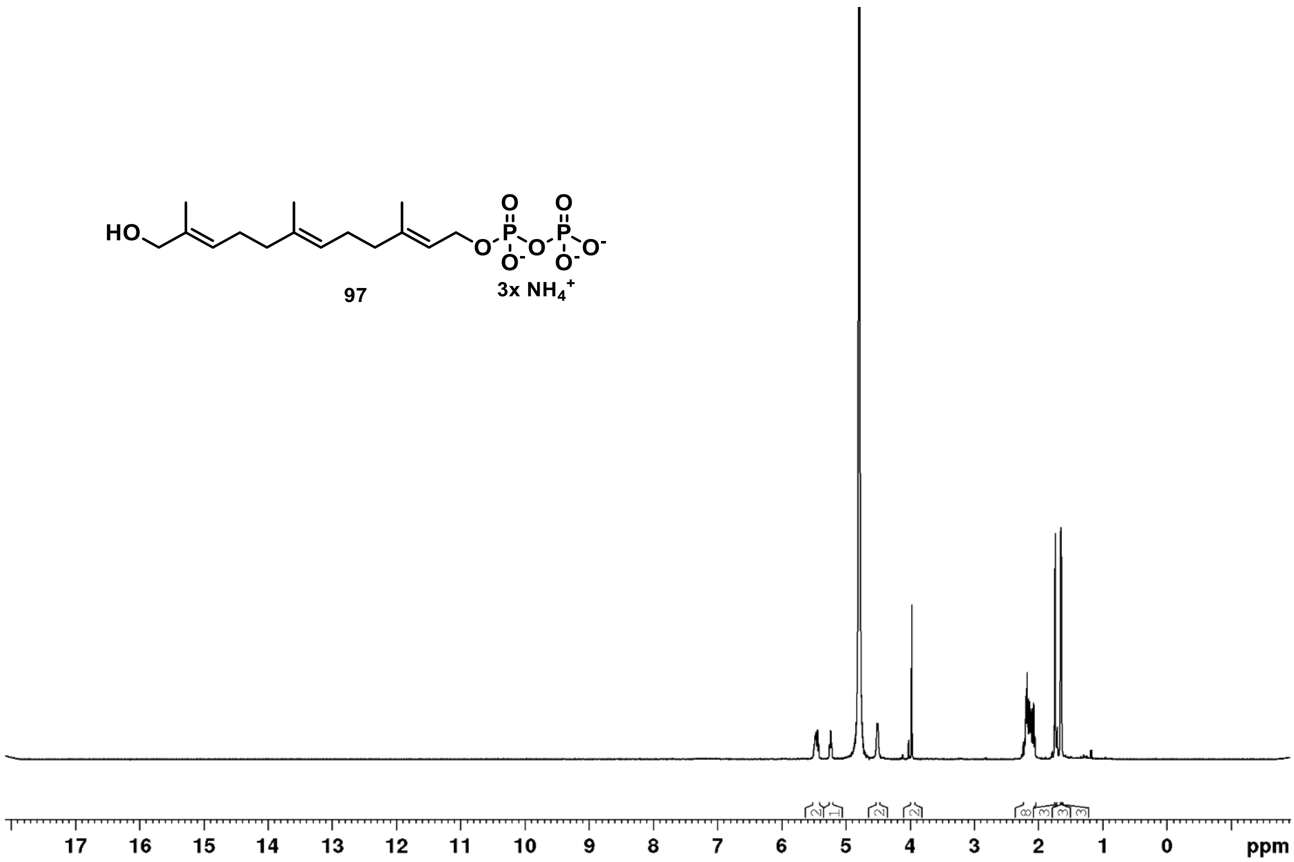
553

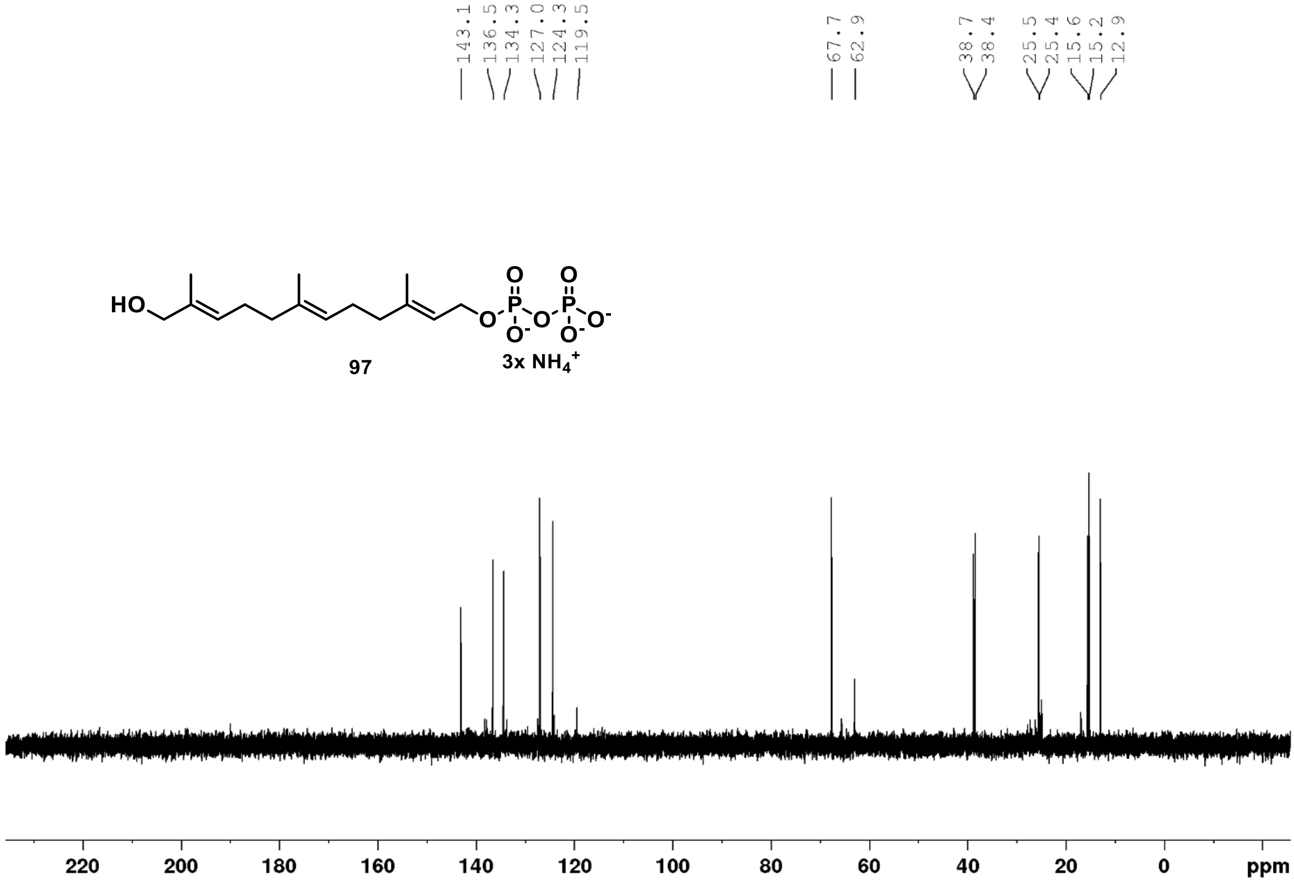

THPO
OH
469
2
1
1
2
1
2
1
8
15
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

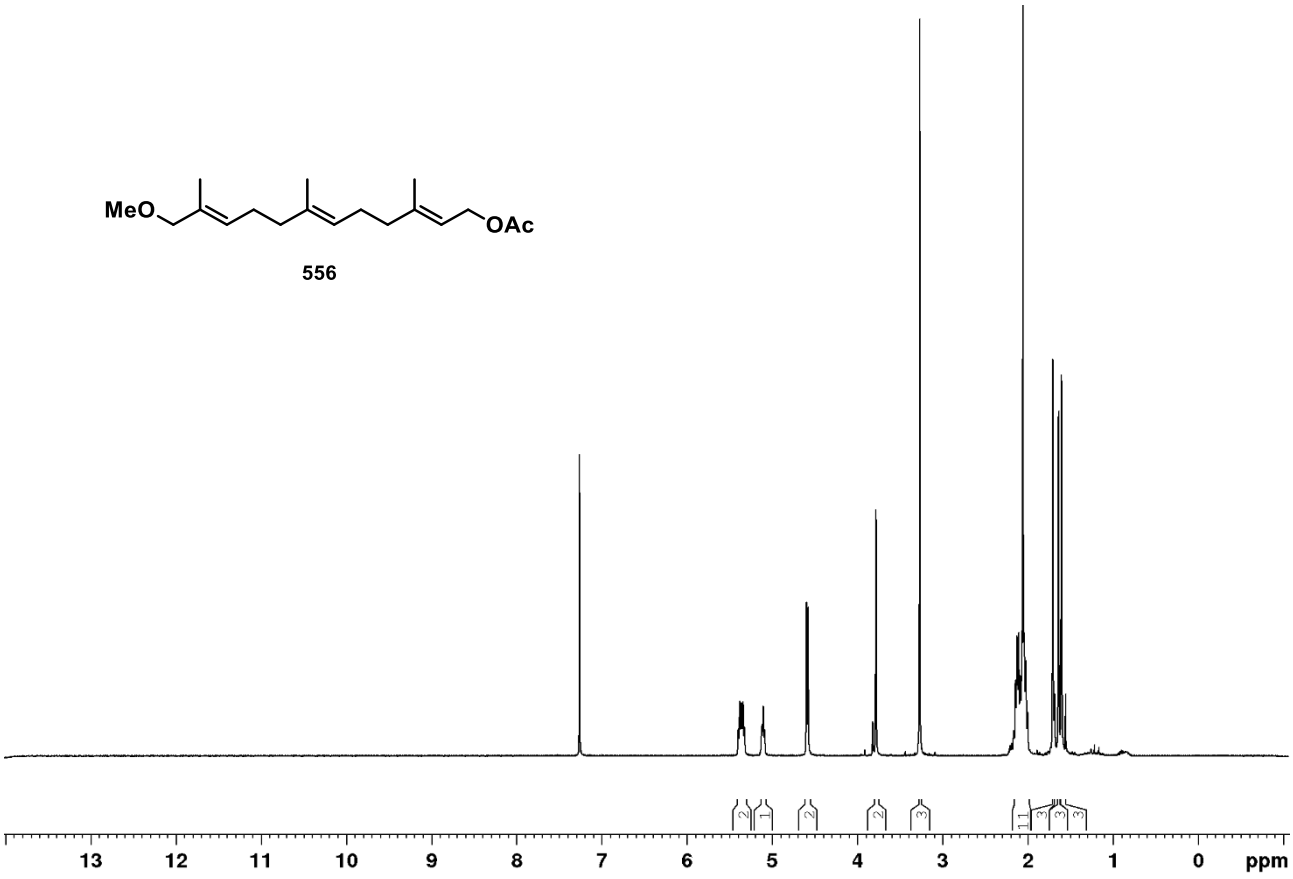

THPO
Cl
554
2
1
1
3
2
1
8
15
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

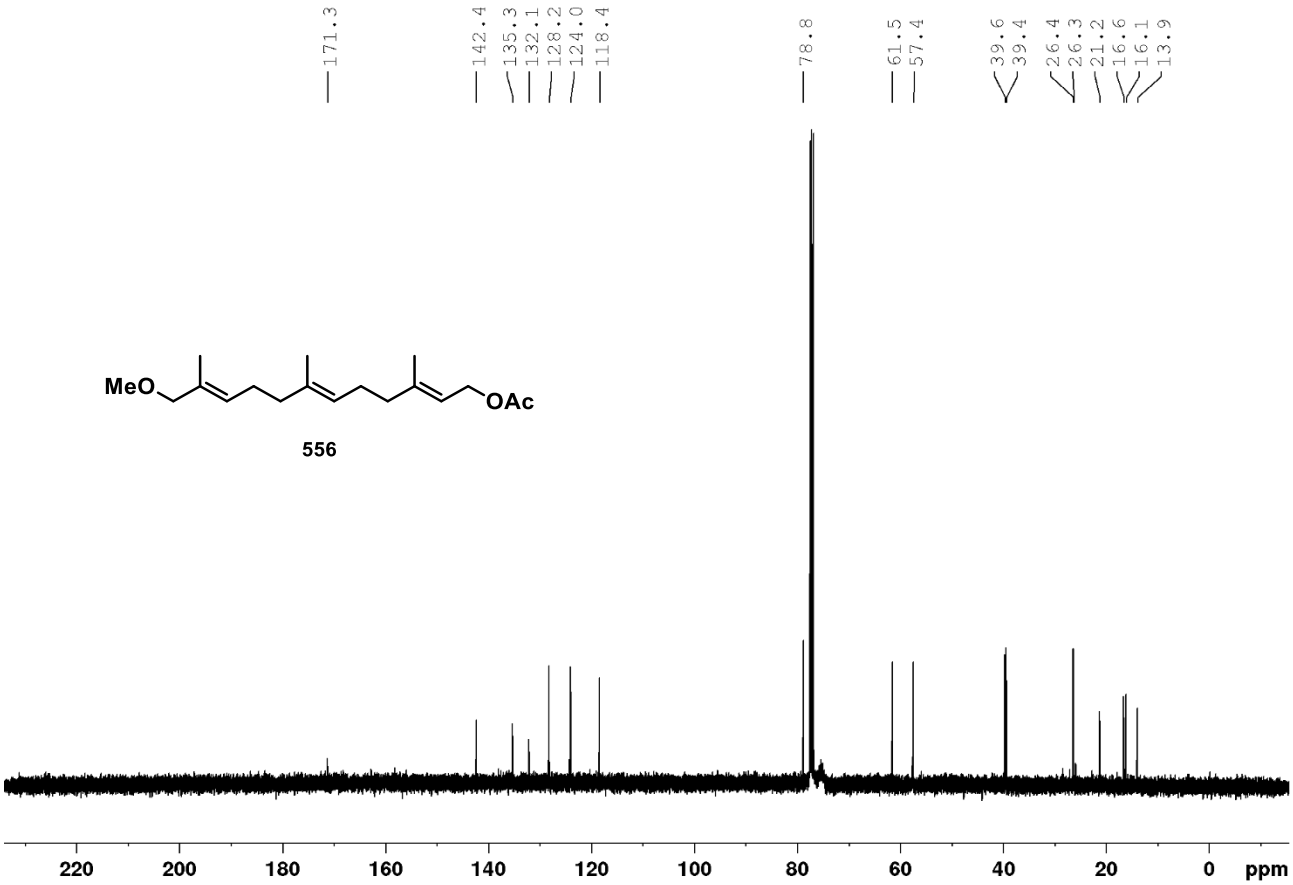

142.9
135.5
132.0
128.0
123.8
120.5
97.5
73.1
62.3
41.3
39.6
39.4
30.8
26.5
26.2
25.7
19.7
16.3
16.2
14.2
THPO
Cl
554
220
200
180
160
140
120
100
80
60
40
20
0
ppm

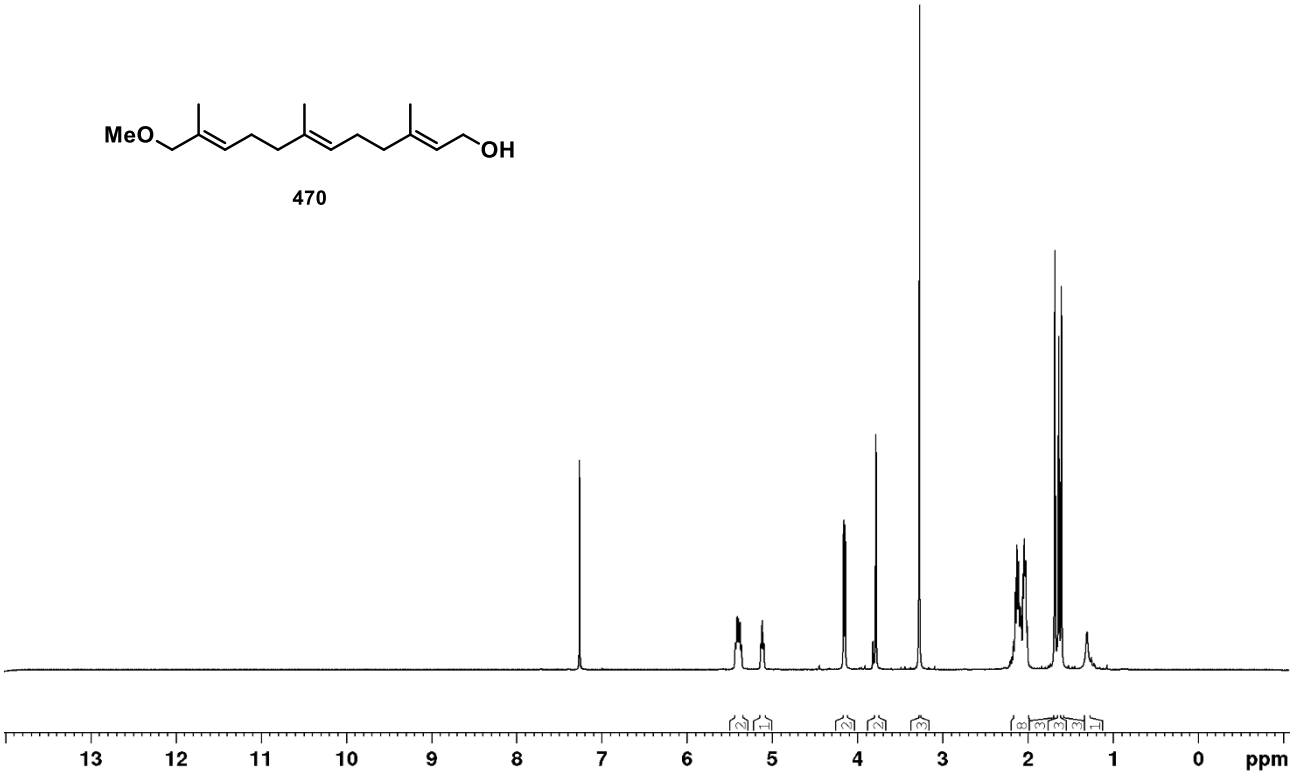

HO
Cl
555
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


HO
O
P
O
P
O⁻
97
3x NH4+
17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm

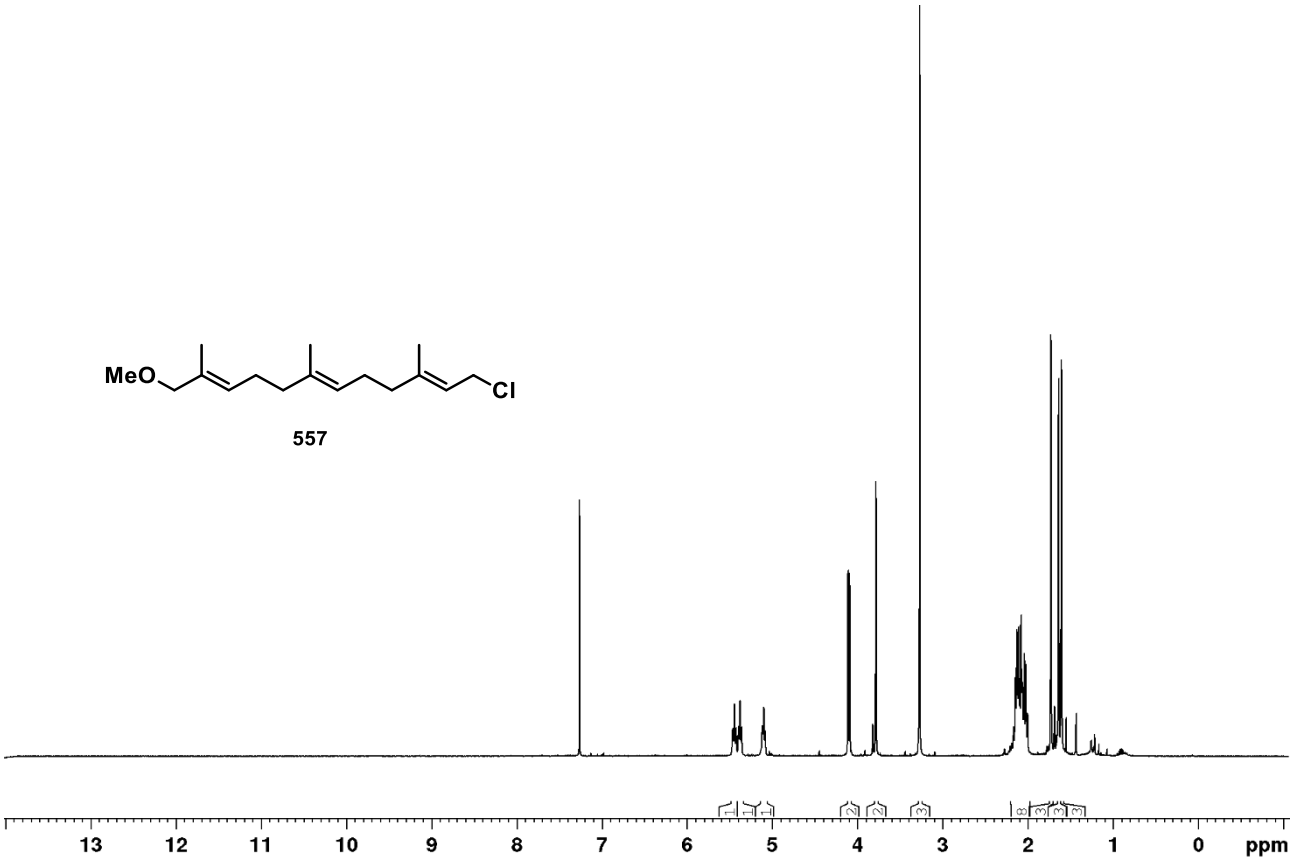

143.1
136.5
134.3
127.0
124.3
119.5
67.7
62.9
38.7
38.4
25.5
25.4
15.6
15.2
12.9
HO
97
3x NH4+
220 200 180 160 140 120 100 80 60 40 20 0 ppm


MeO
OAc
556
2
1
2
2
3
11
3
3
3
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

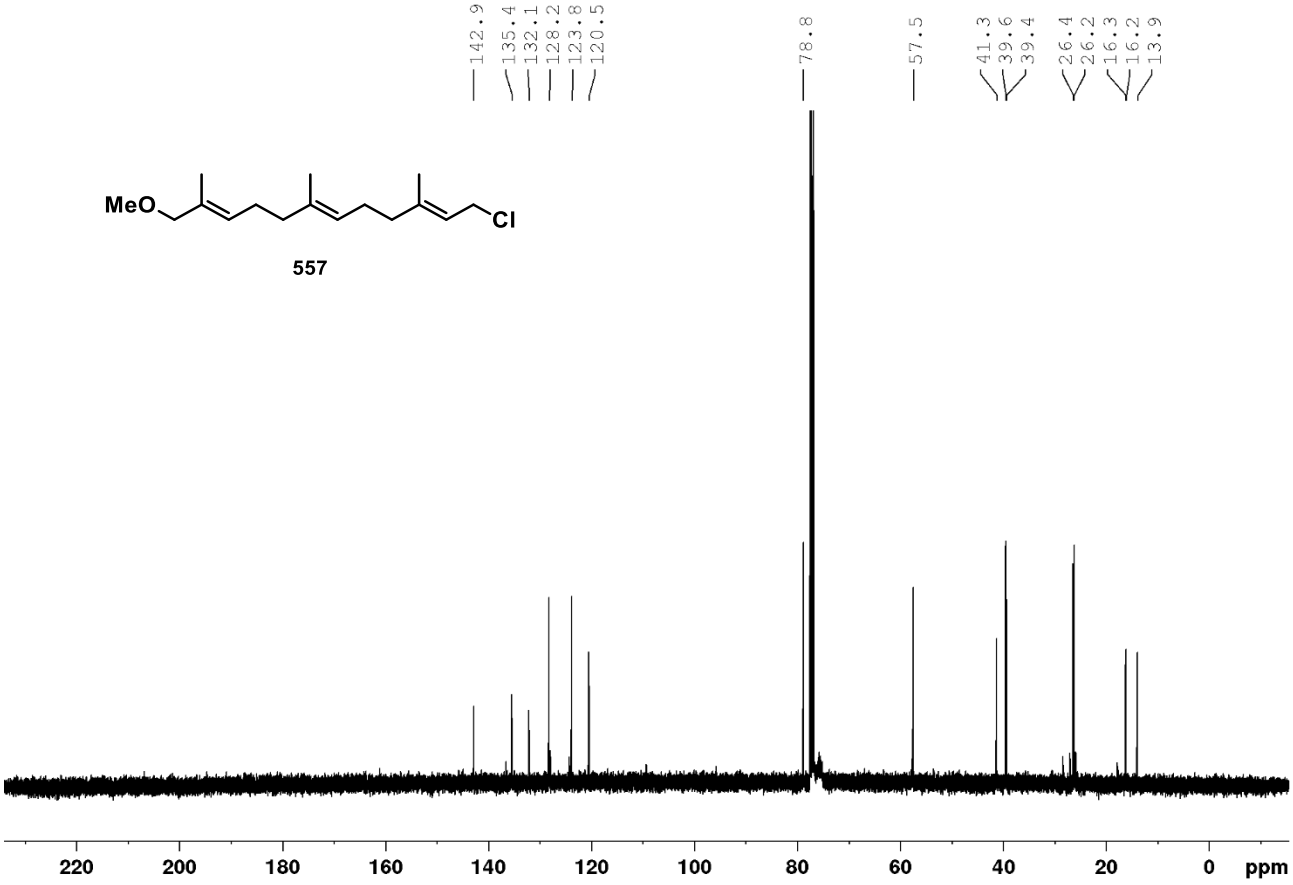

171.3
142.4
135.3
132.1
128.2
124.0
118.4
78.8
61.5
57.4
39.6
39.4
26.4
26.3
21.2
16.6
16.1
13.9
MeO
OAc
556
220
200
180
160
140
120
100
80
60
40
20
0
ppm


MeO
OH
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

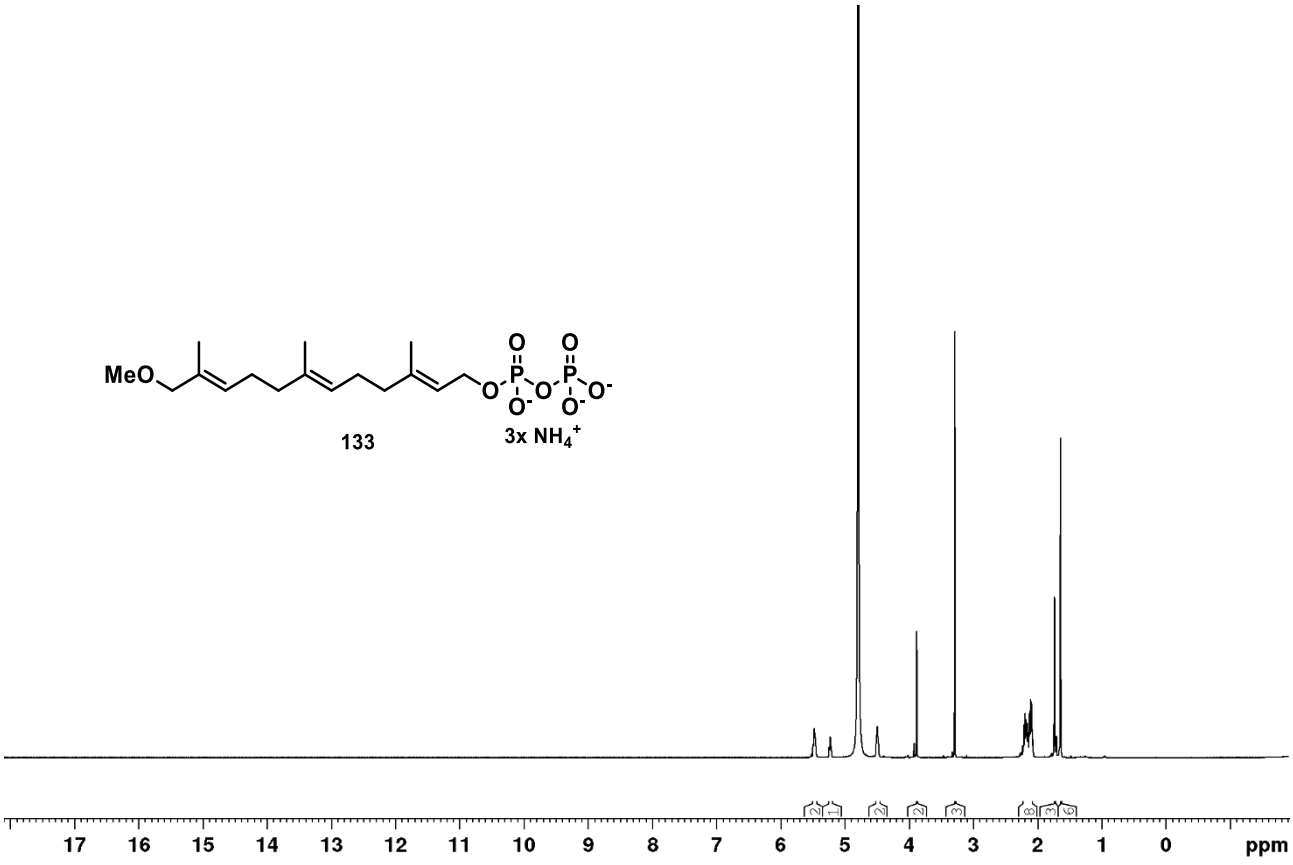
470


MeO
Cl
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

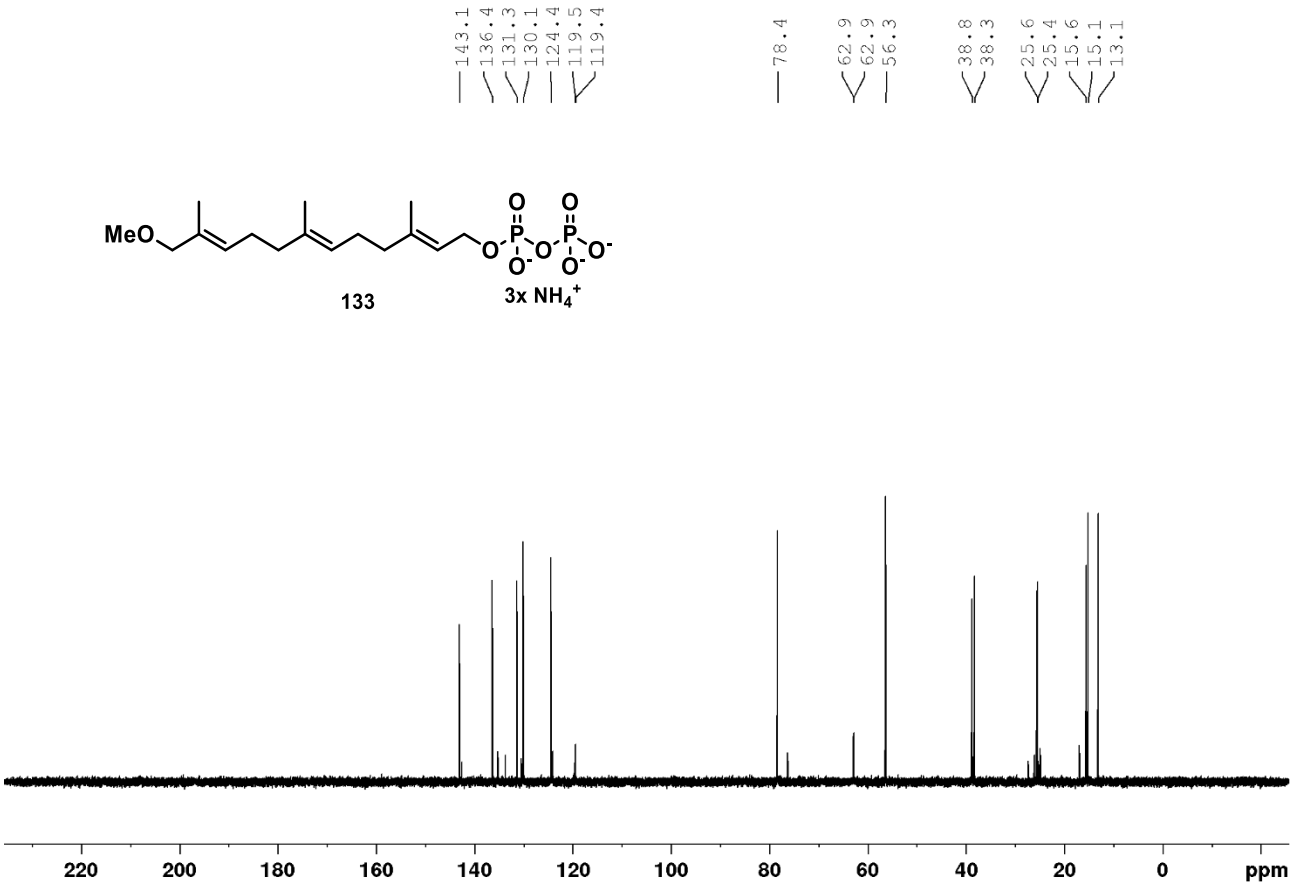
557

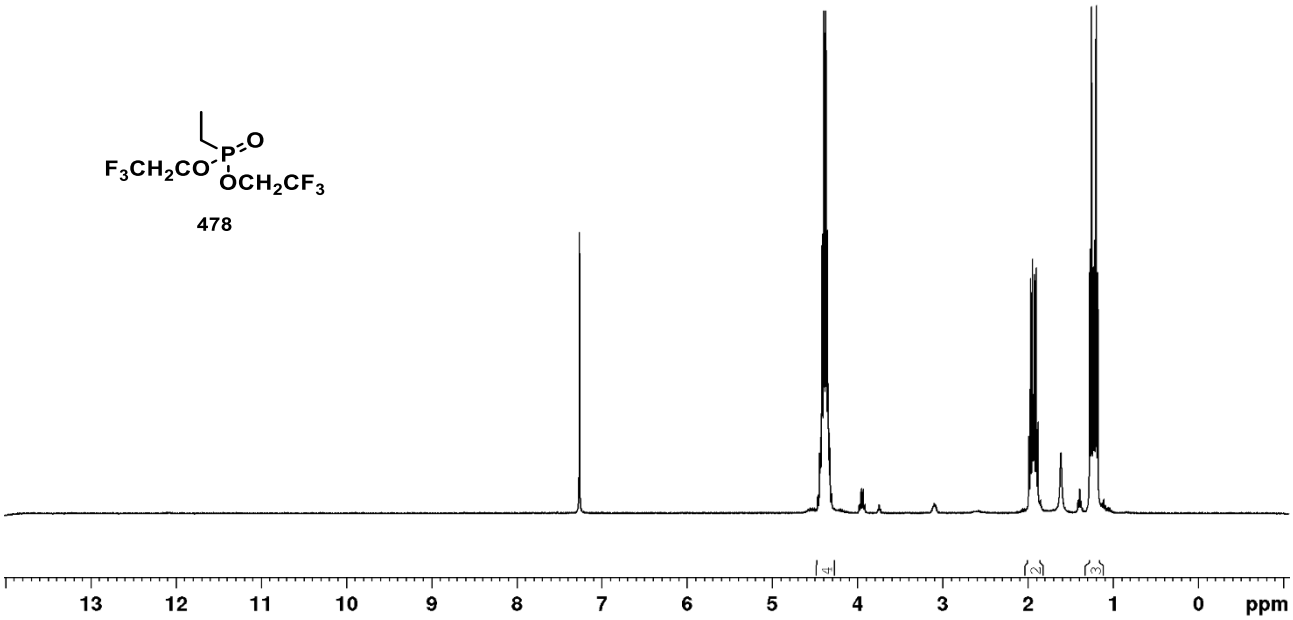

142.9
135.4
132.1
128.2
123.8
120.5
78.8
57.5
41.3
39.6
39.4
26.4
26.2
16.3
16.2
13.9
MeO
Cl
220
200
180
160
140
120
100
80
60
40
20
0
ppm

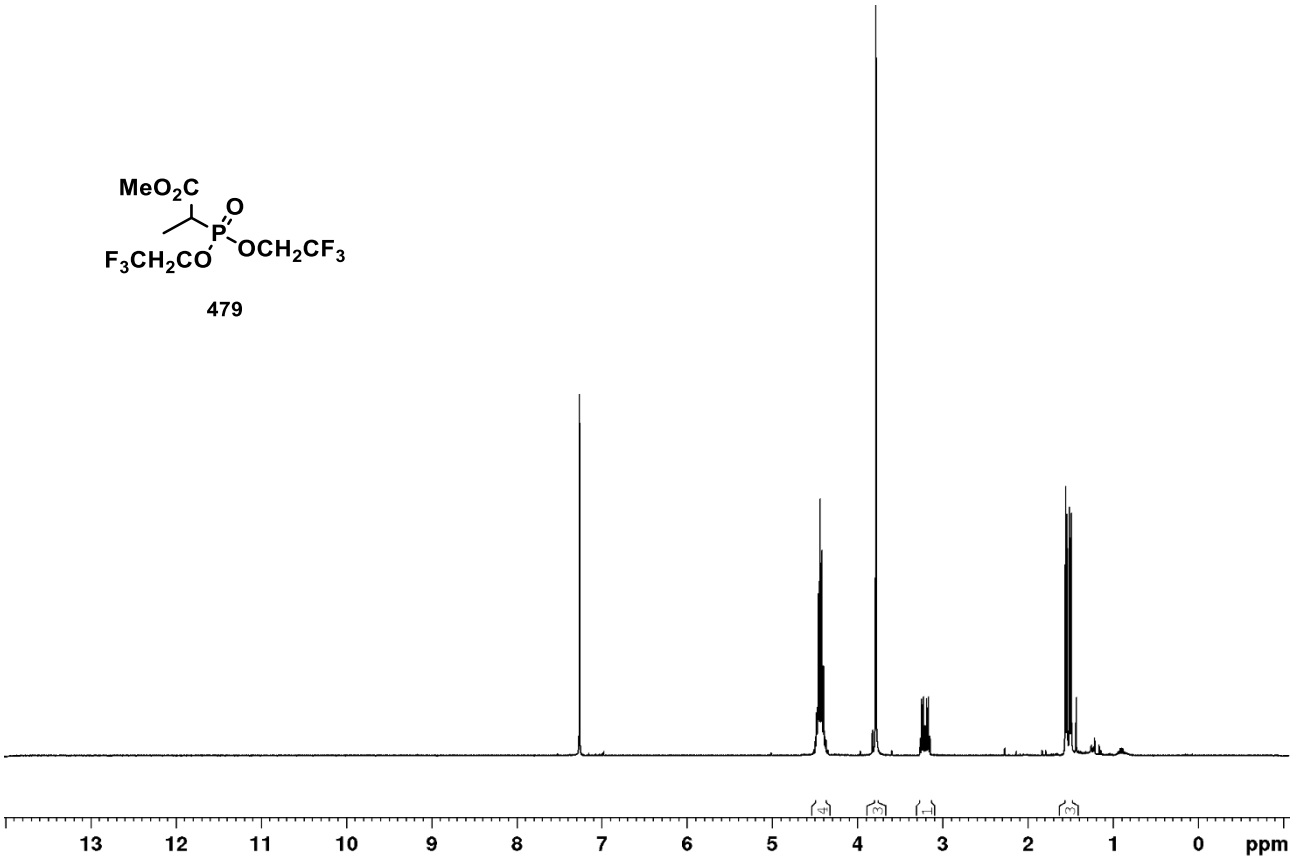
557

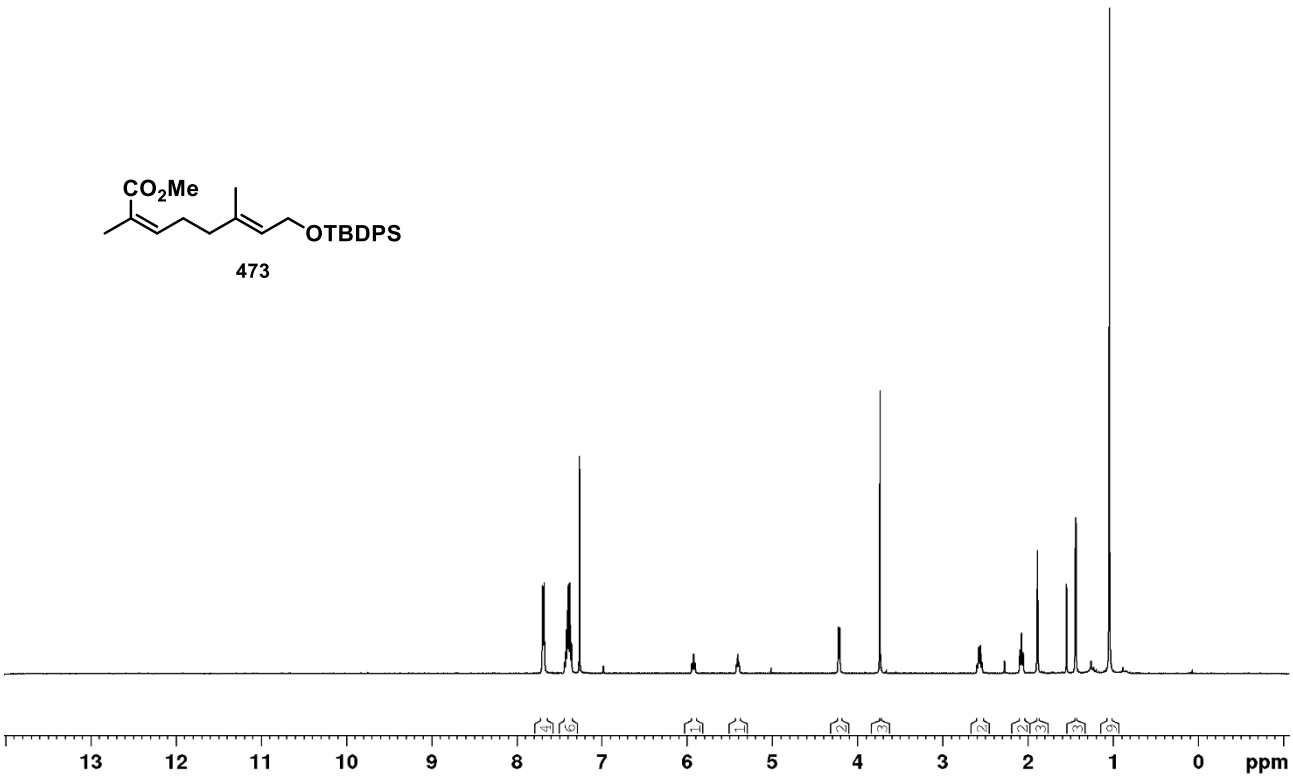

MeO
O
P
O-
3x NH4+
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

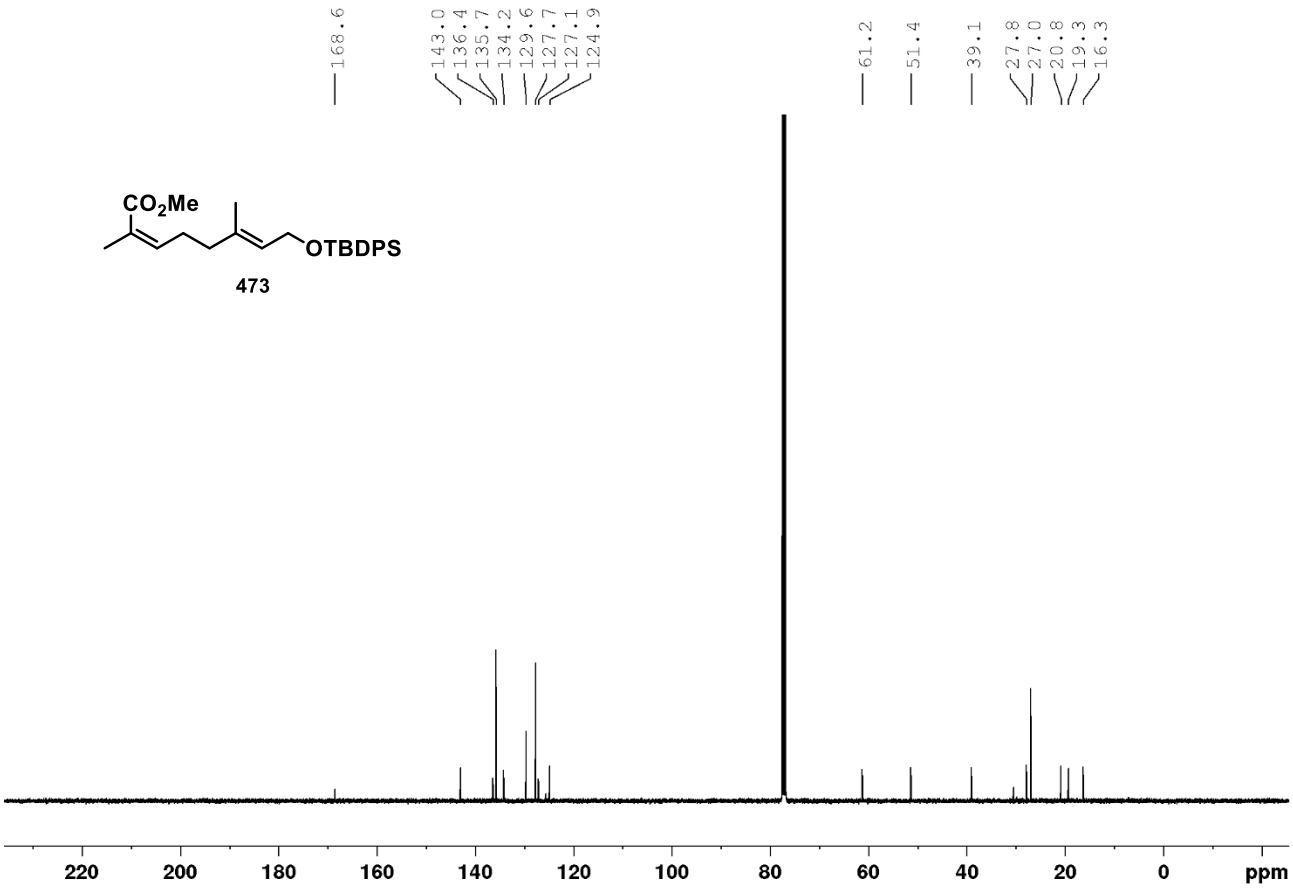
133

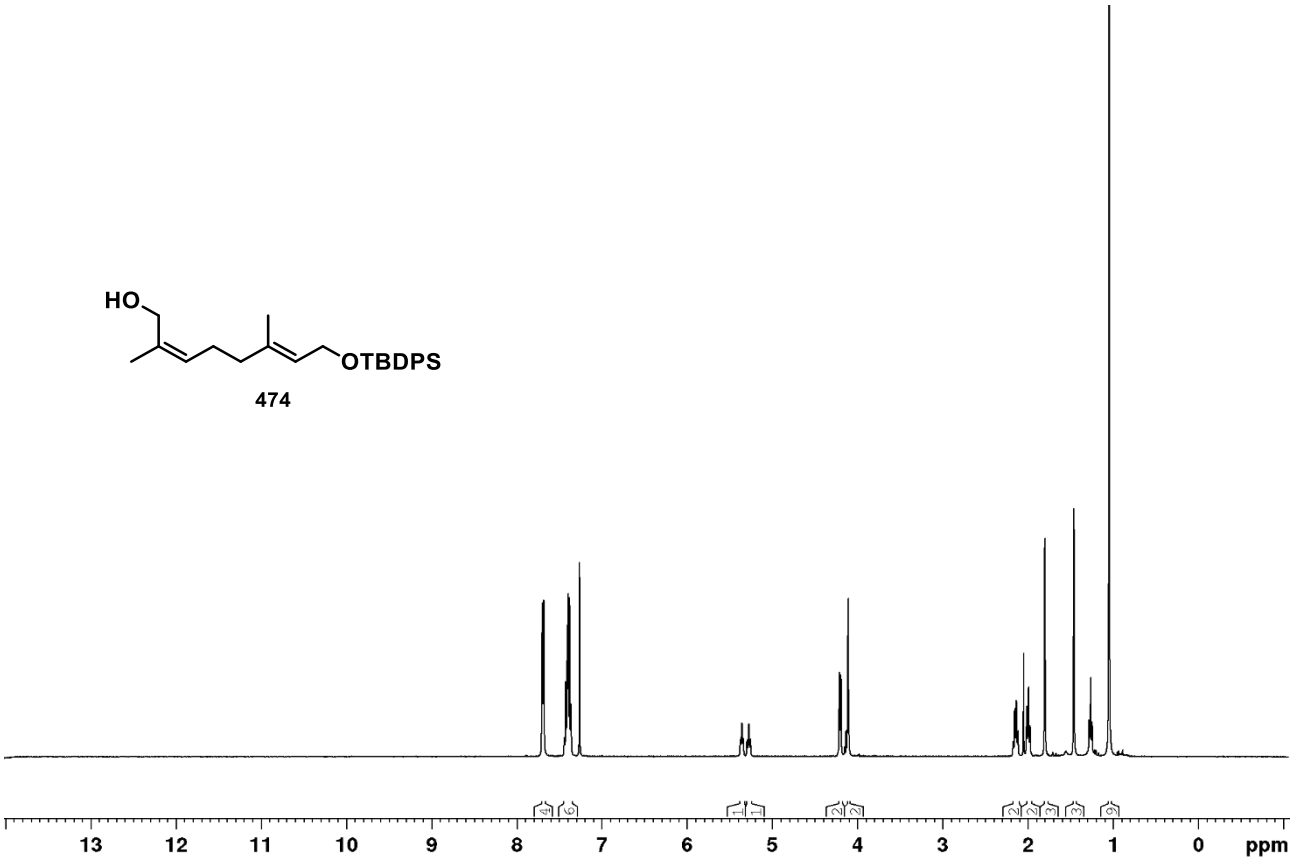

143.1
136.4
131.3
130.1
124.4
119.5
119.4
78.4
62.9
62.9
56.3
38.8
38.3
25.6
25.4
15.6
15.1
13.1
MeO
133
3x NH4+
220
200
180
160
140
120
100
80
60
40
20
0
ppm

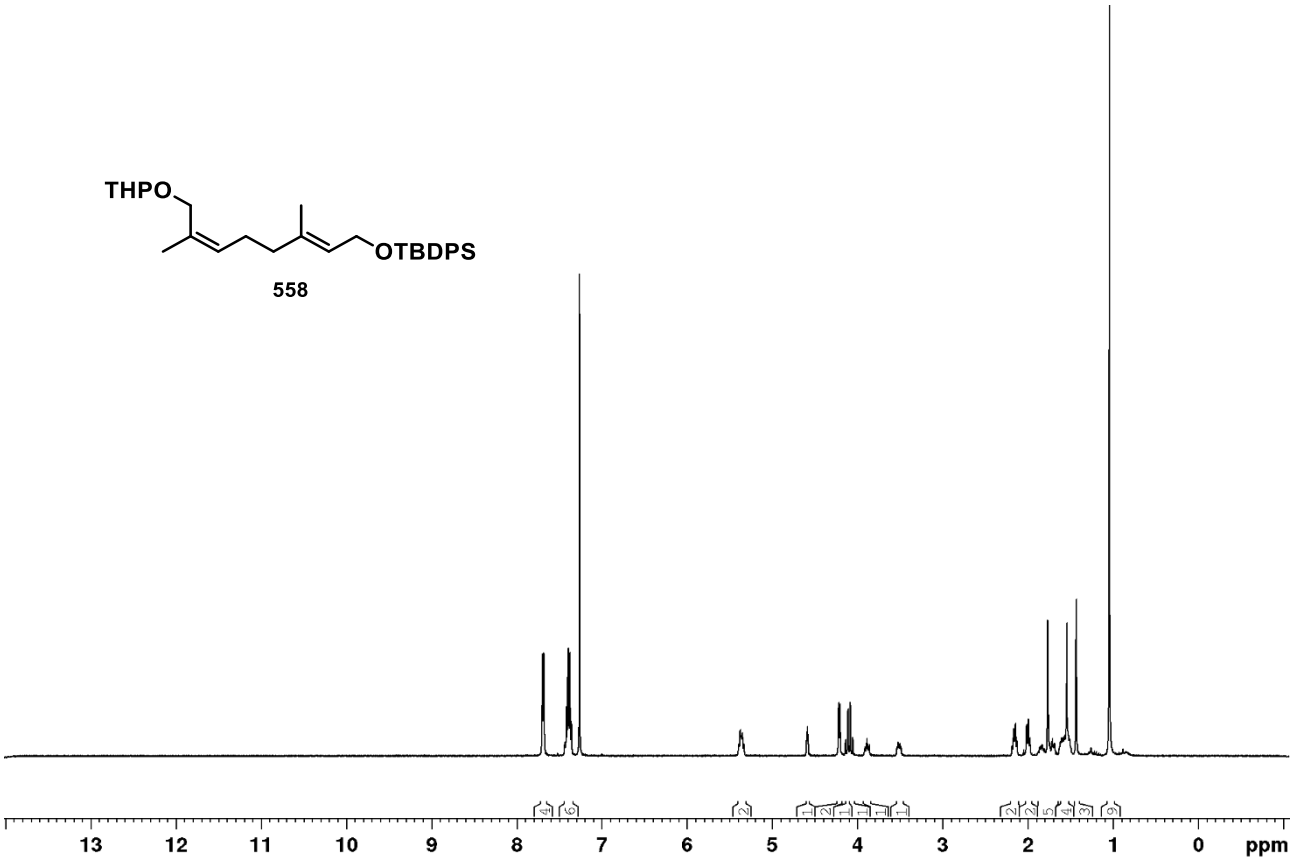

F3CH2CO
OCH2CF3
478
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

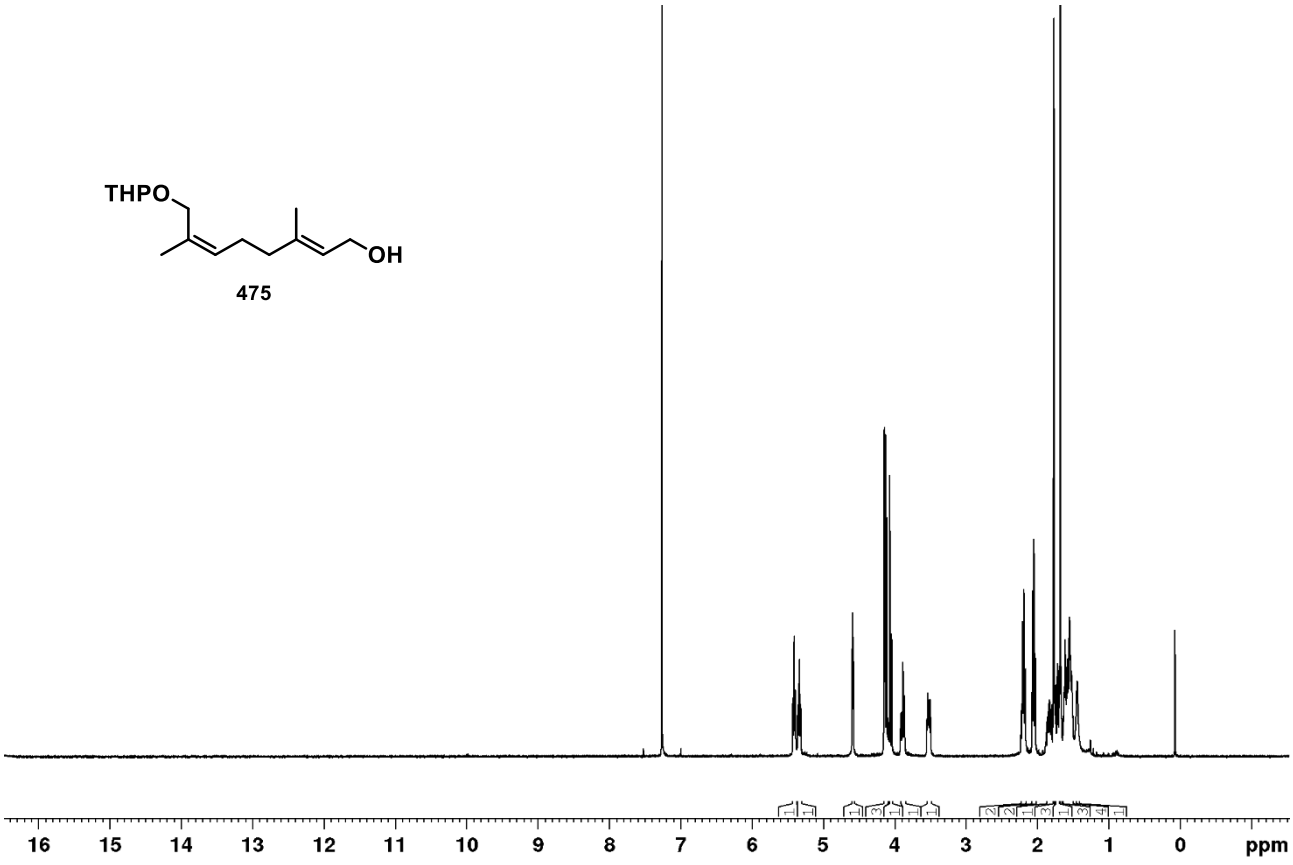

MeO2C
O
P
OCH2CF3
F3CH2CO
479
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm

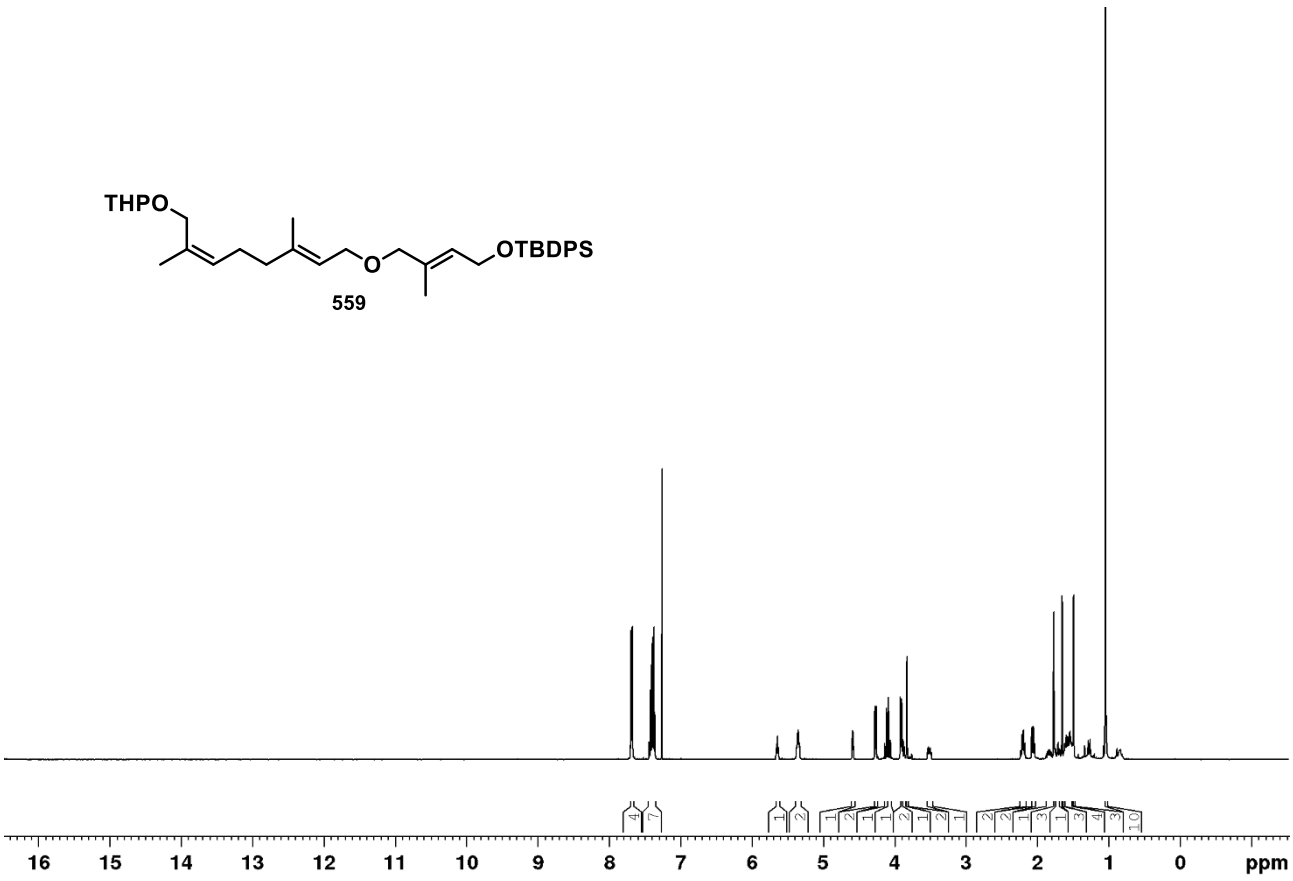

CO2Me
OTBDPS
473
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm

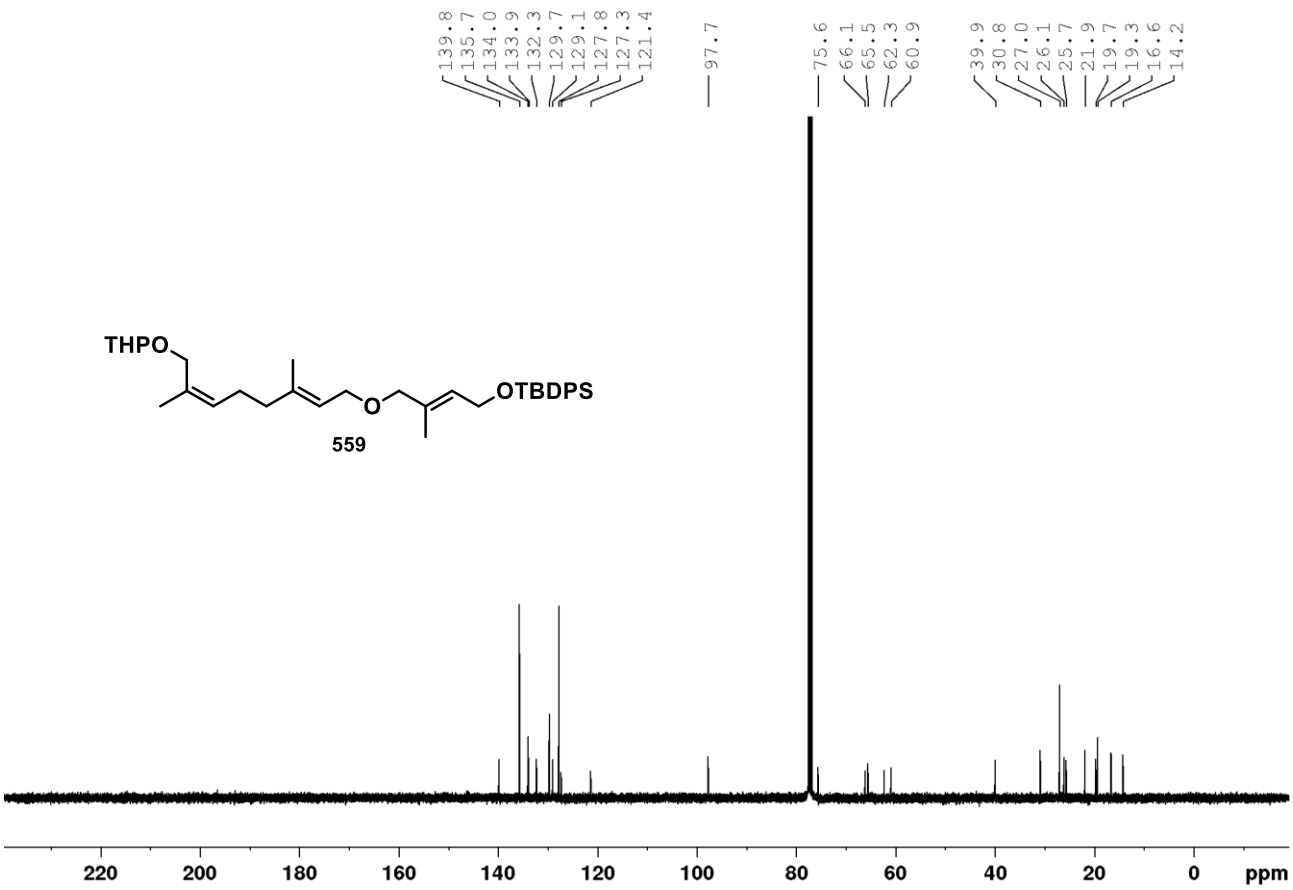

168.6
143.0
136.4
135.7
134.2
129.6
127.7
127.1
124.9
61.2
51.4
39.1
27.8
27.0
20.8
19.3
16.3
CO2Me
OTBDPS
473
220
200
180
160
140
120
100
80
60
40
20
0
ppm

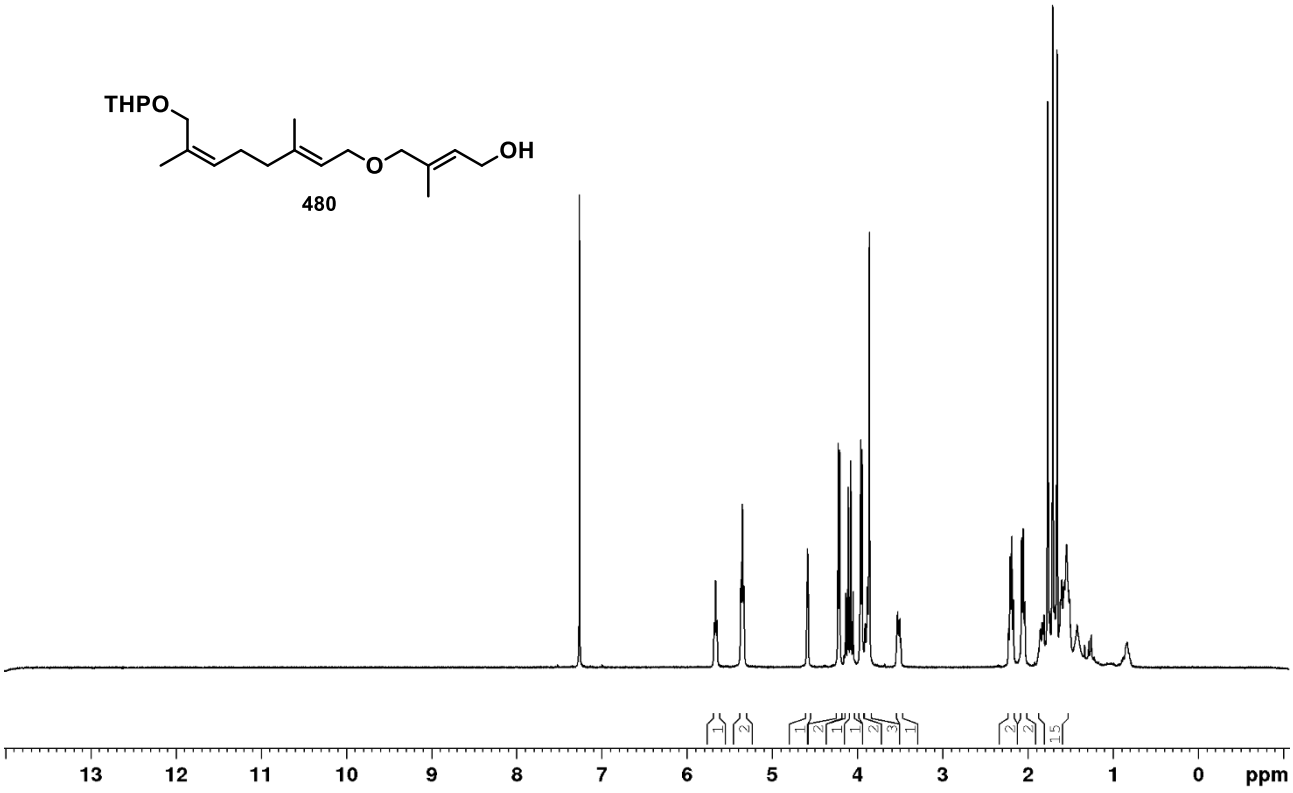

HO
OTBDPS
474
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

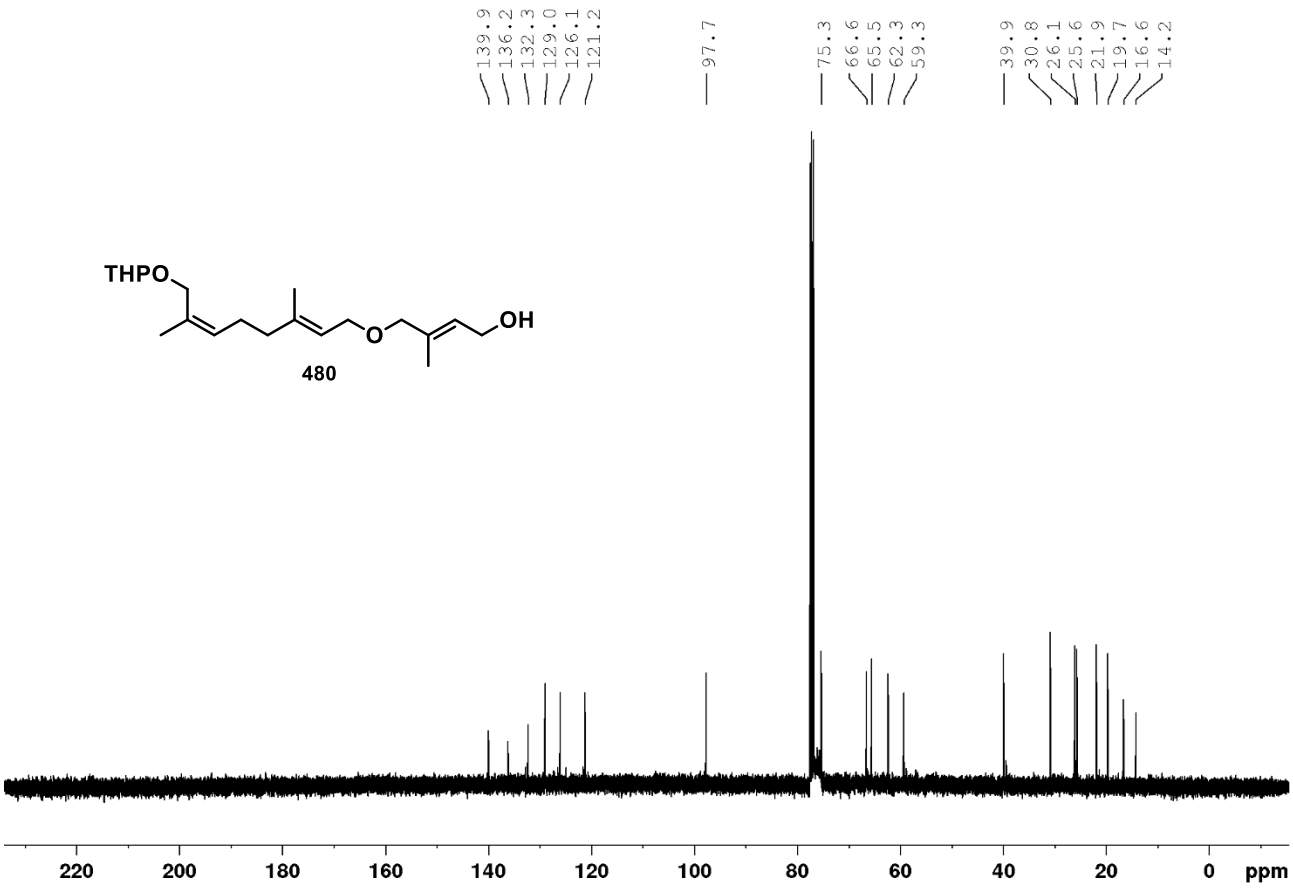

THPO
OTBDPS
558
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm

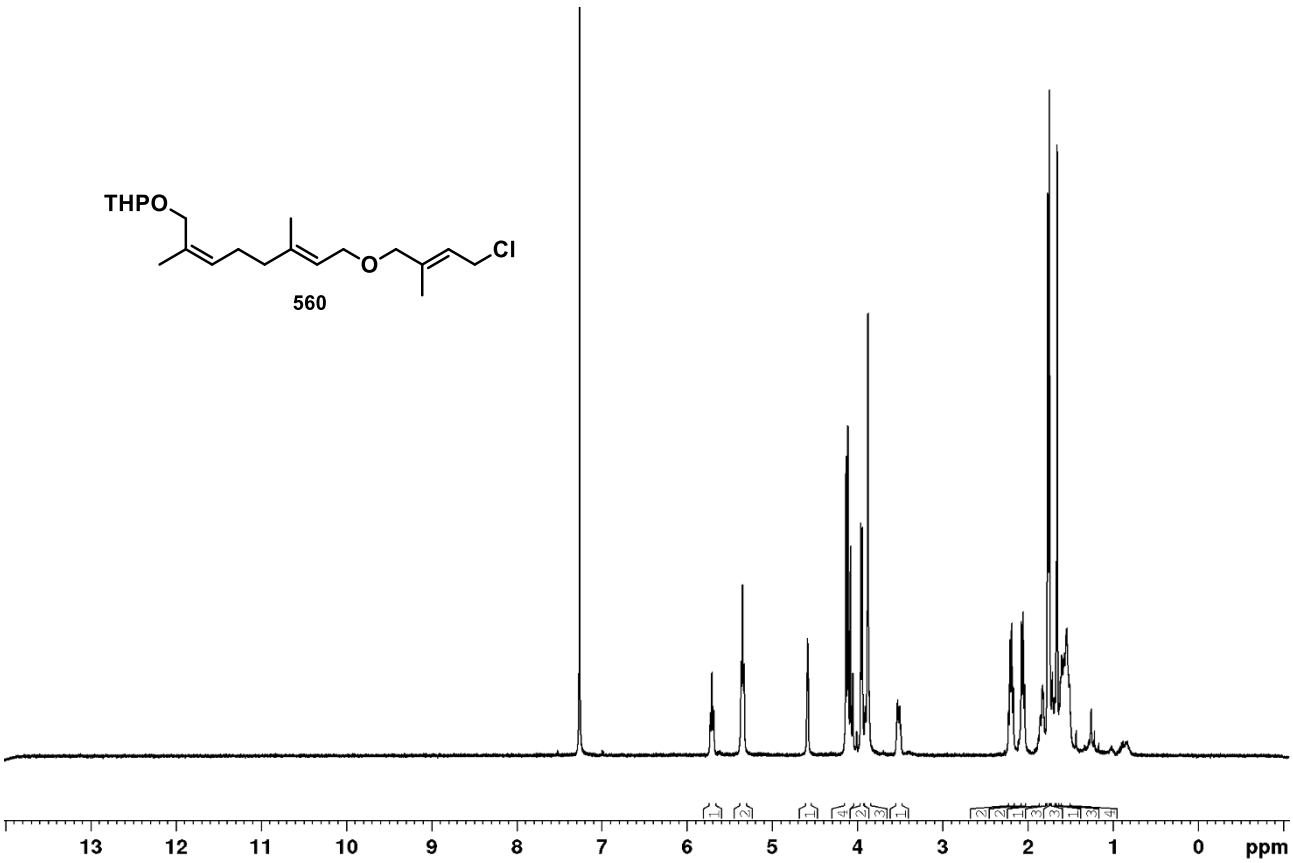

THPO
OH
475
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm

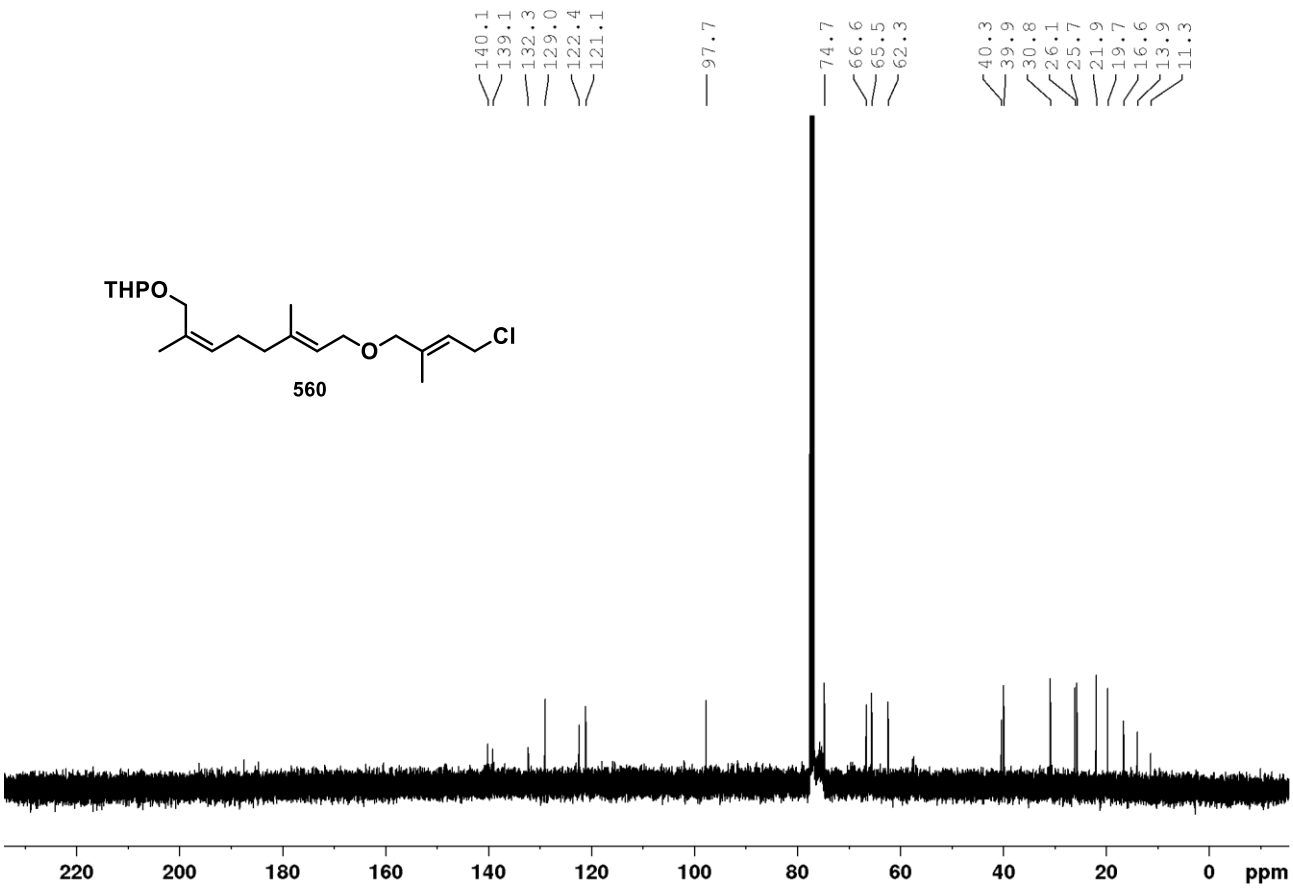

THPO
OTBDPS
O
559
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm

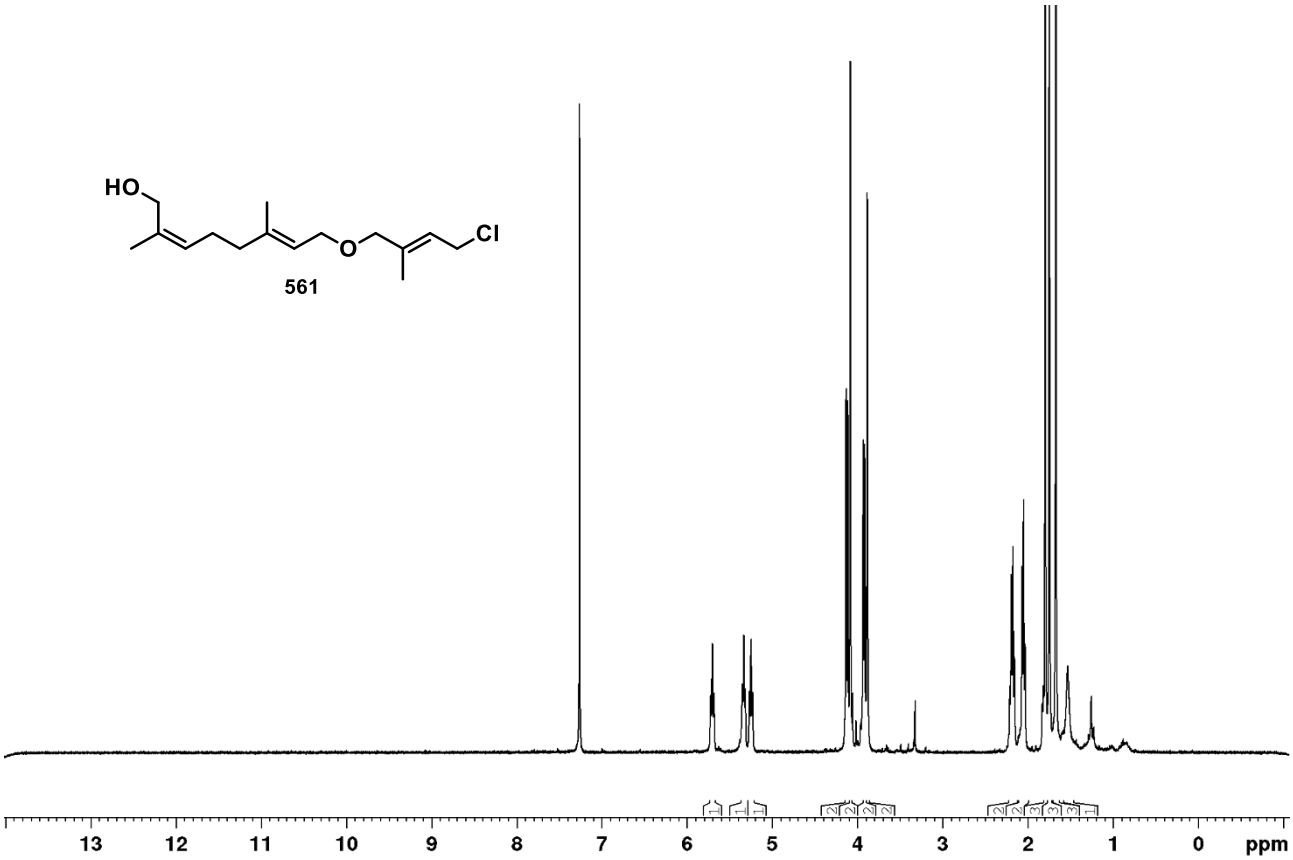

139.8
135.7
134.0
133.9
132.3
129.7
129.1
127.8
127.3
121.4
97.7
75.6
66.1
65.5
62.3
60.9
39.9
30.8
27.0
26.1
25.7
21.9
19.7
19.3
16.6
14.2
THPO
OTBDPS
O
559
220 200 180 160 140 120 100 80 60 40 20 0 ppm

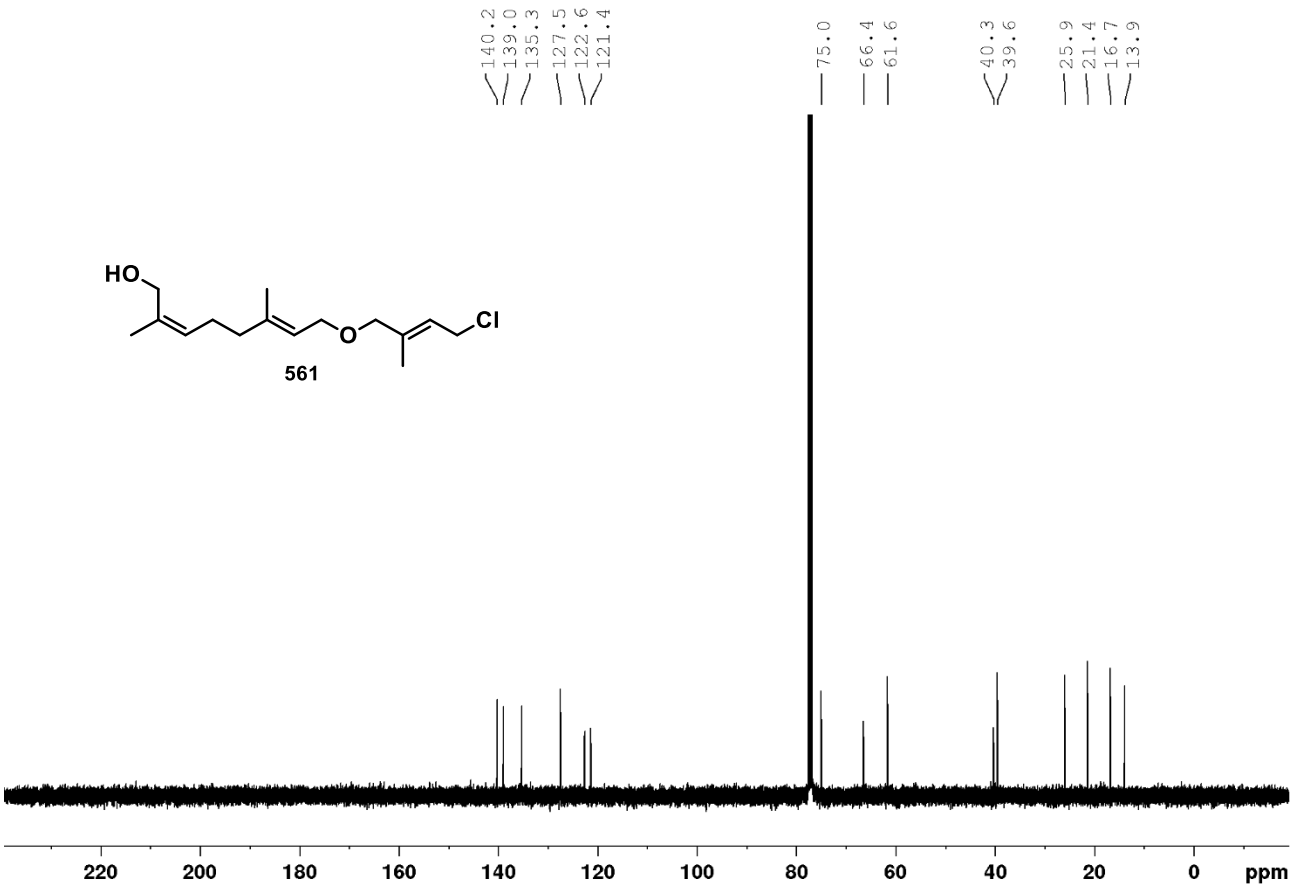

THPO
OH
O
480
1
2
1
2
1
1
2
3
1
2
2
15
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

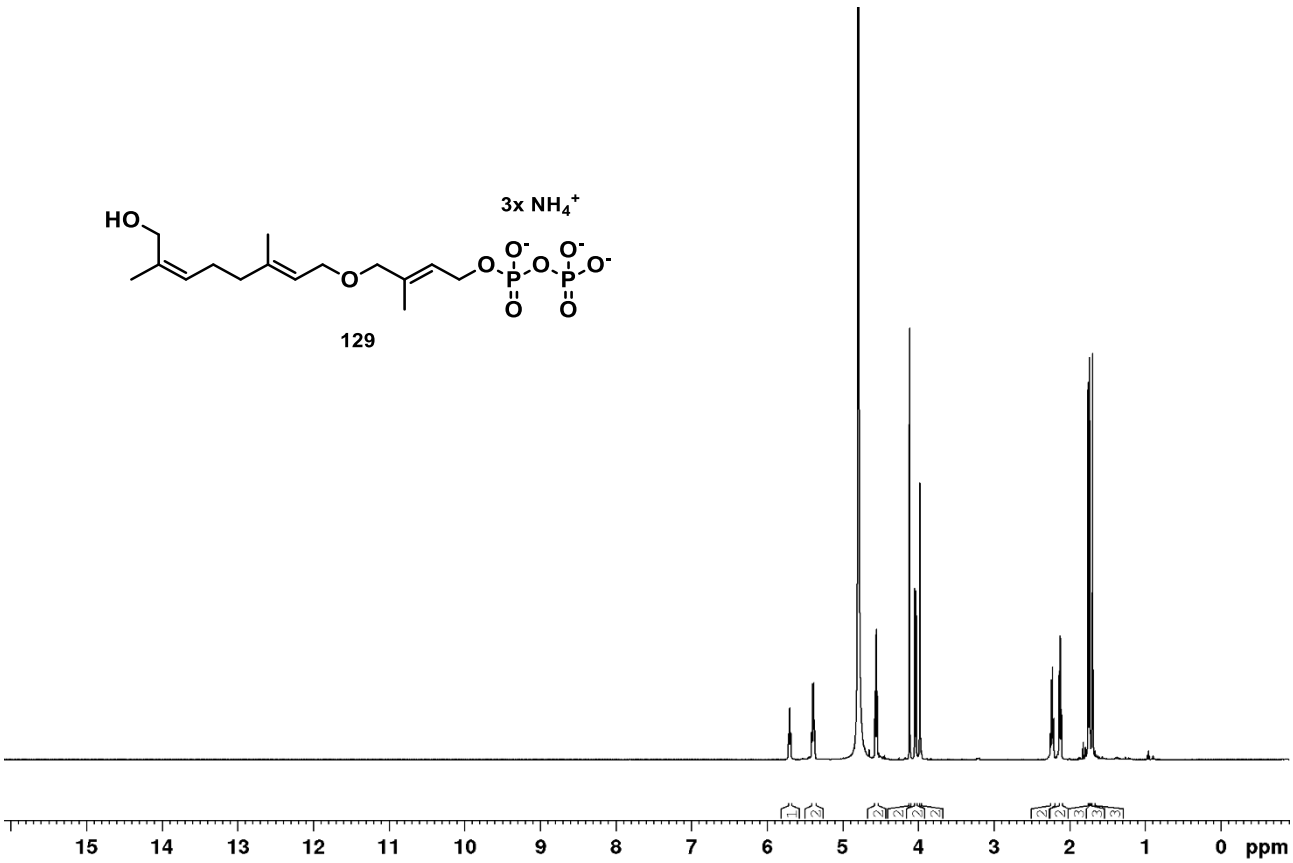

139.9
136.2
132.3
129.0
126.1
121.2
97.7
75.3
66.6
65.5
62.3
59.3
39.9
30.8
26.1
25.6
21.9
19.7
16.6
14.2
THPO
OH
O
480
220
200
180
160
140
120
100
80
60
40
20
0
ppm

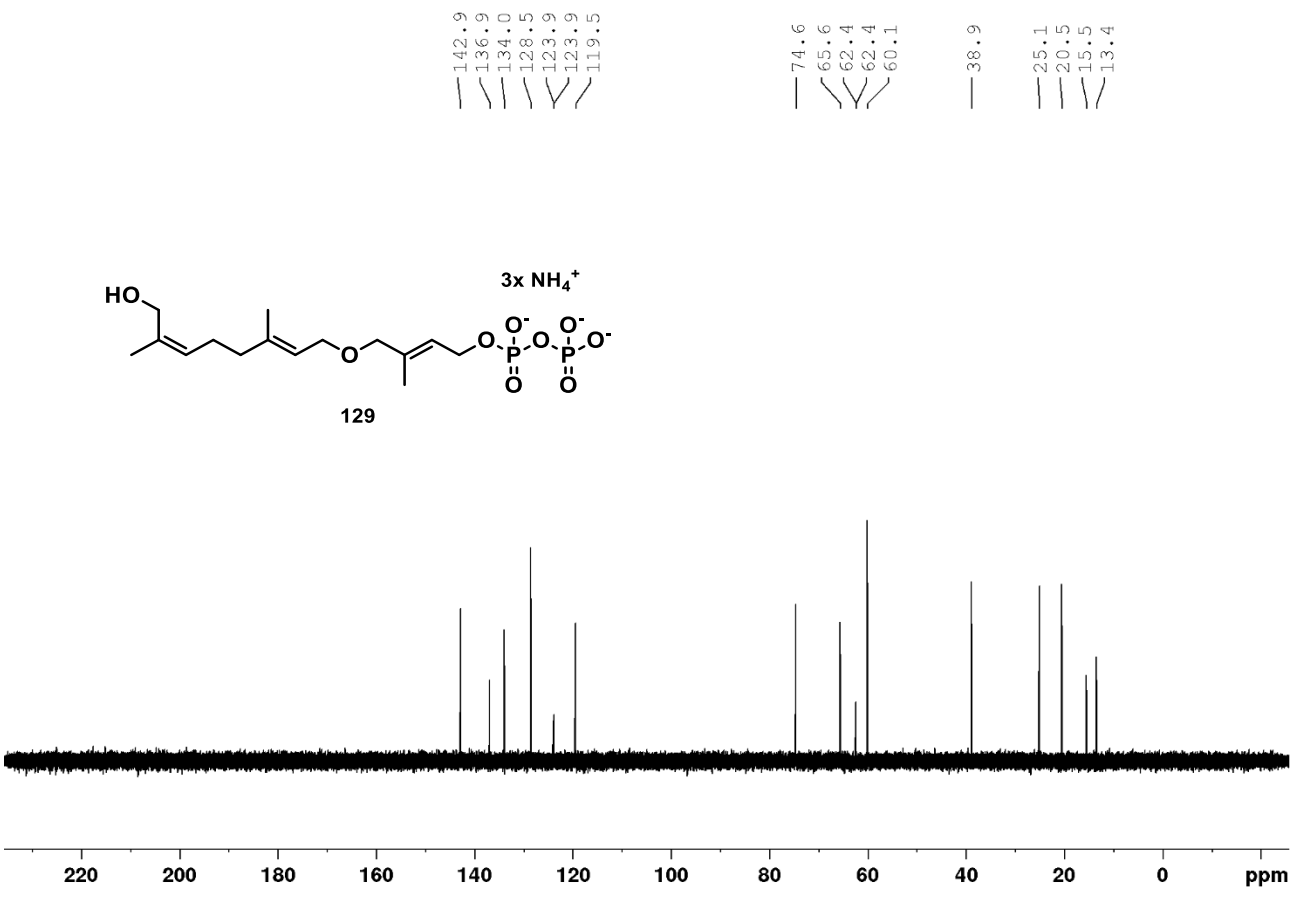

THPO
Cl
O
560
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

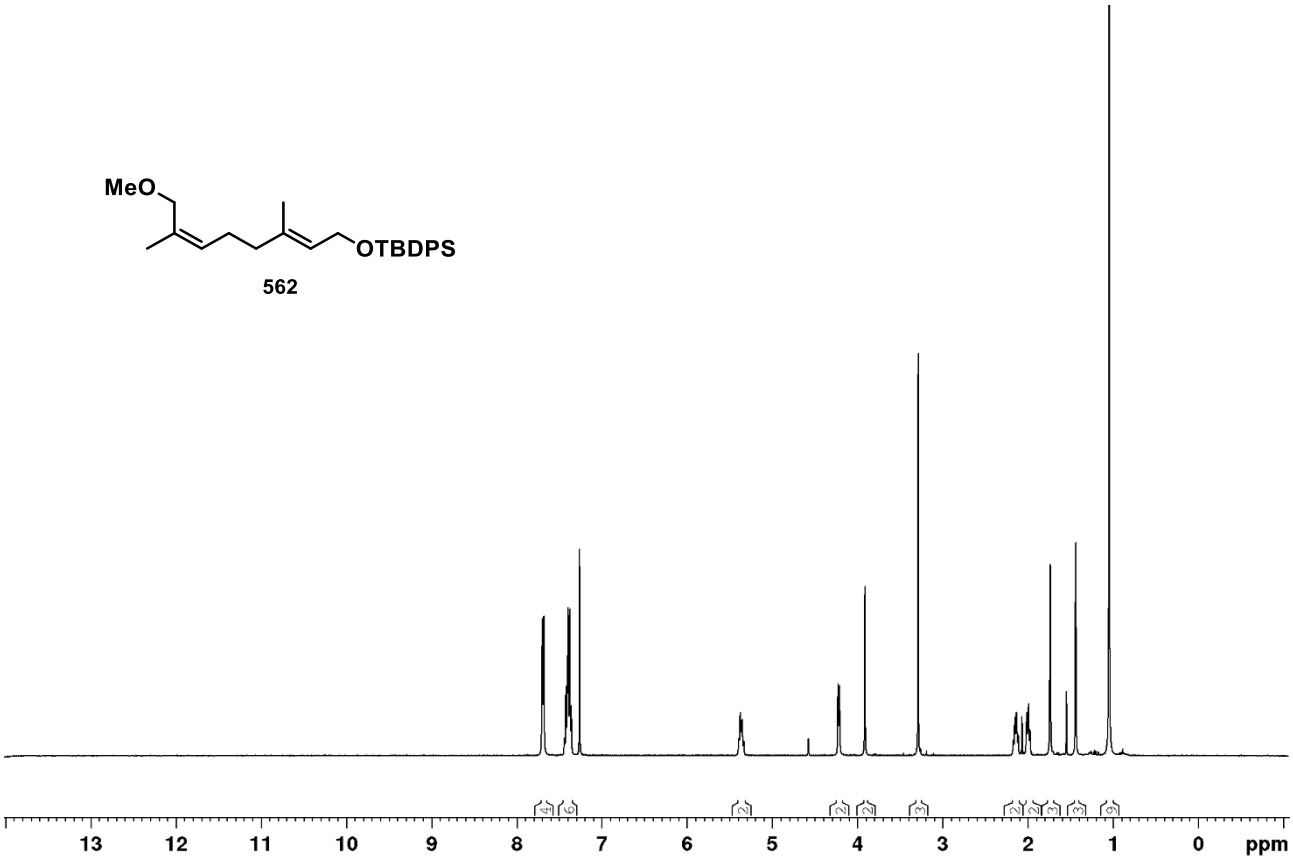

140.1
139.1
132.3
129.0
122.4
121.1
97.7
74.7
66.6
65.5
62.3
40.3
39.9
30.8
26.1
25.7
21.9
19.7
16.6
13.9
11.3
THPO
Cl
O
560
220
200
180
160
140
120
100
80
60
40
20
0
ppm

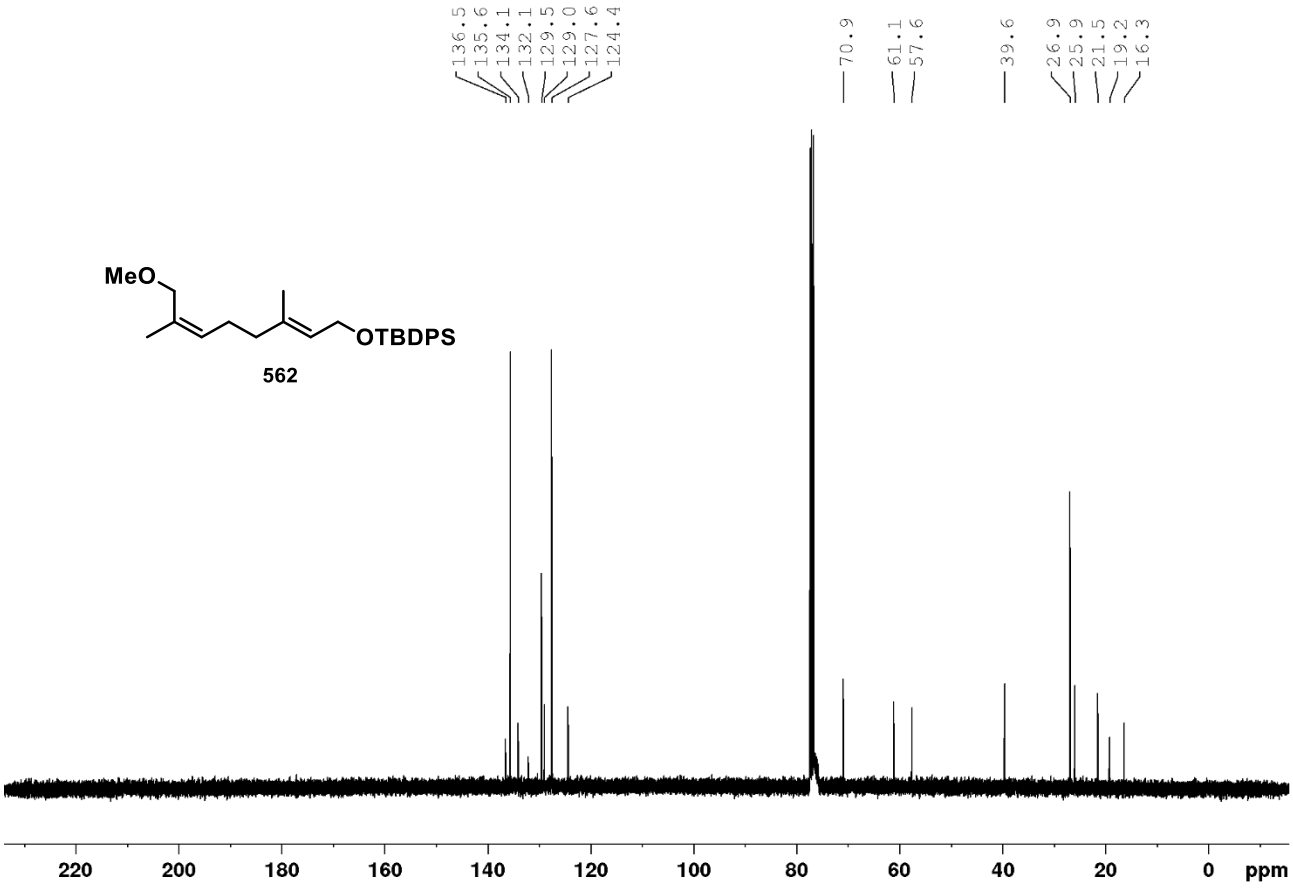

HO
O
Cl
561
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

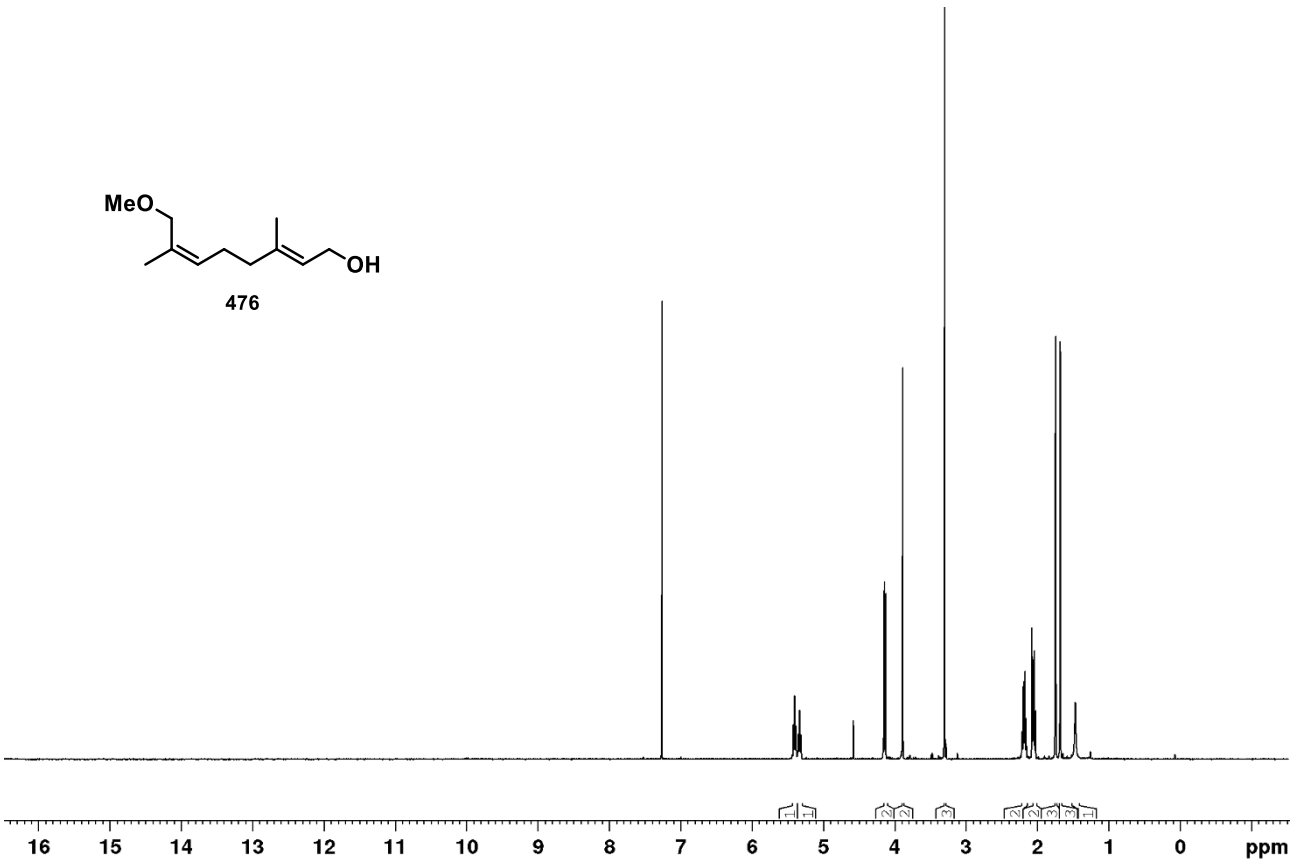

140.2
139.0
135.3
127.5
122.6
121.4
75.0
66.4
61.6
40.3
39.6
25.9
21.4
16.7
13.9
HO
O
Cl
561
220
200
180
160
140
120
100
80
60
40
20
0
ppm

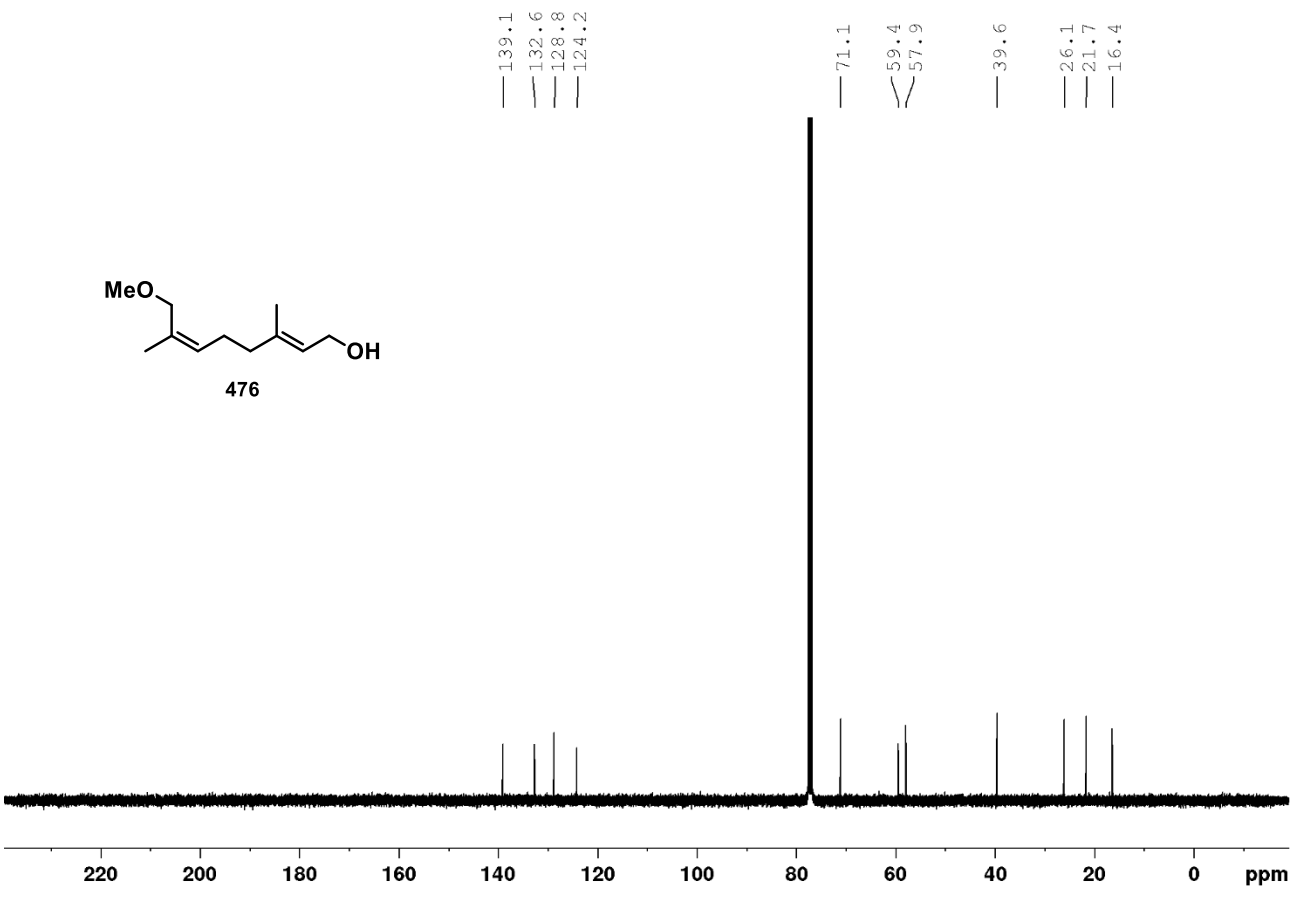

HO
3x NH4+
O-
O-
O-
O-
O
O
P
P
O
O
O
O
129
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

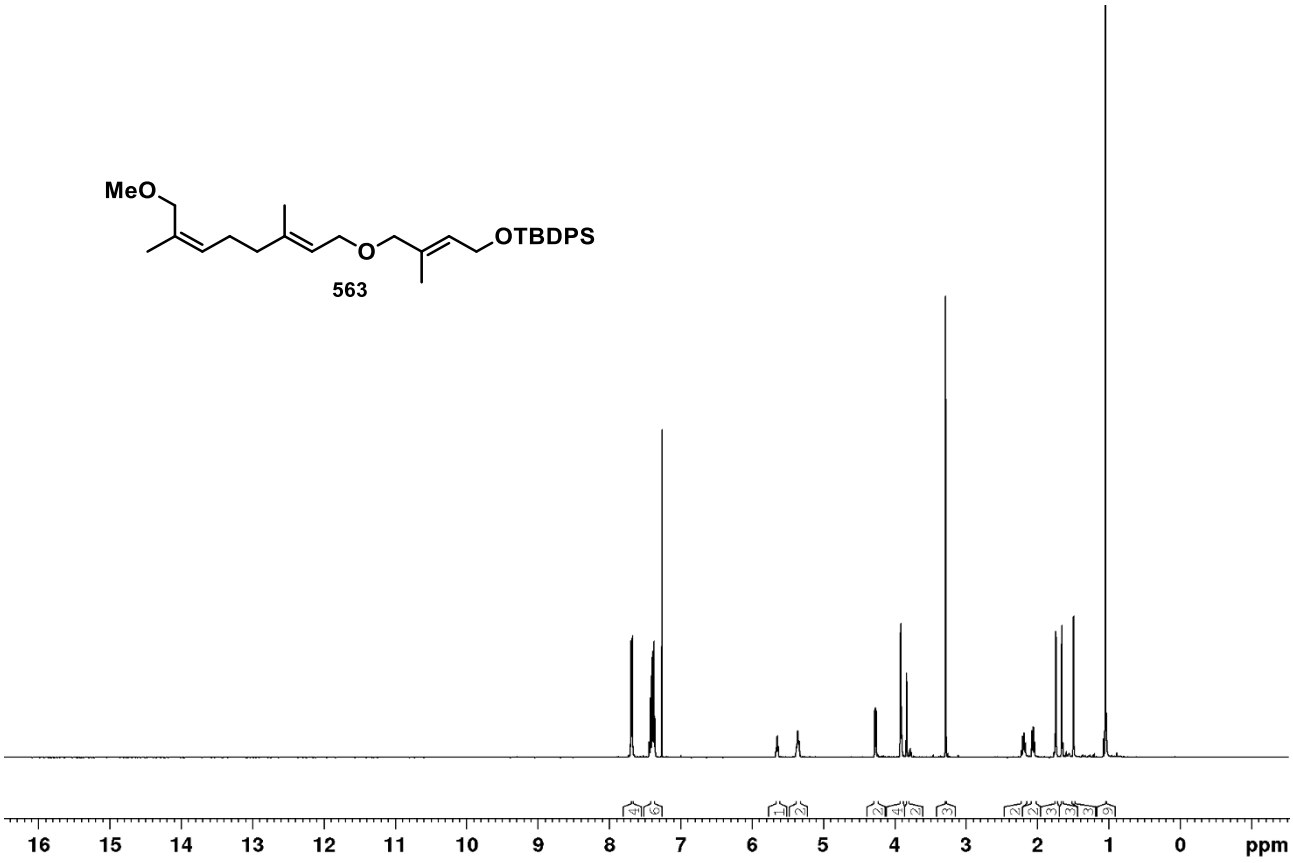

142.9
136.9
134.0
128.5
123.9
123.9
119.5
74.6
65.6
62.4
62.4
60.1
38.9
25.1
20.5
15.5
13.4
HO
3x NH4+
O-
O-
O-
O-
O
O
P
P
O
O
O
O
129
220
200
180
160
140
120
100
80
60
40
20
0
ppm

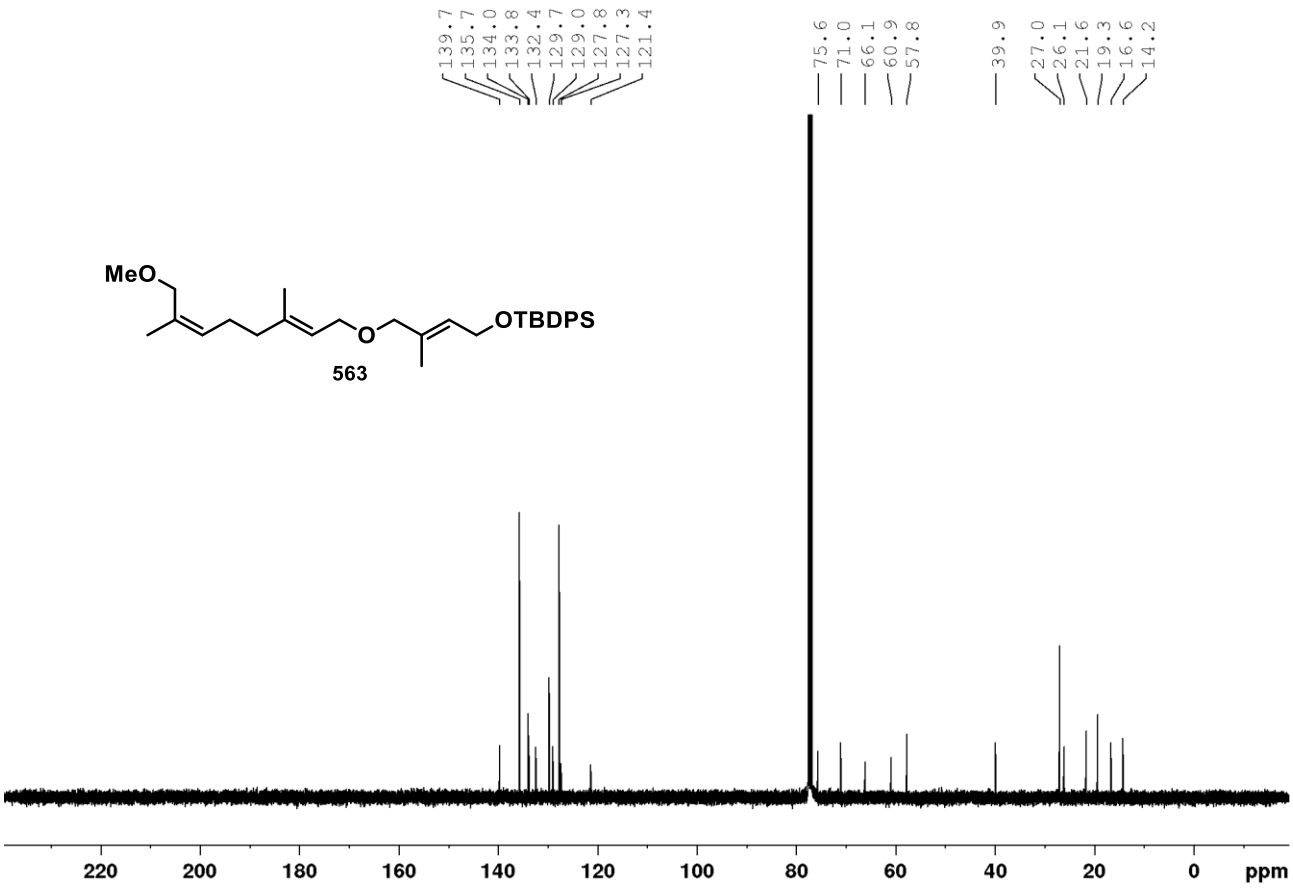

MeO
OTBDPS
562
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


136.5
135.6
134.1
132.1
129.5
129.0
127.6
124.4
70.9
61.1
57.6
39.6
26.9
25.9
21.5
19.2
16.3
MeO
OTBDPS
562
220
200
180
160
140
120
100
80
60
40
20
0
ppm


MeO
OH
476
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


139.1
132.6
128.8
124.2
71.1
59.4
57.9
39.6
26.1
21.7
16.4
MeO
OH
476
220
200
180
160
140
120
100
80
60
40
20
0
ppm


MeO
OTBDPS
O
563
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm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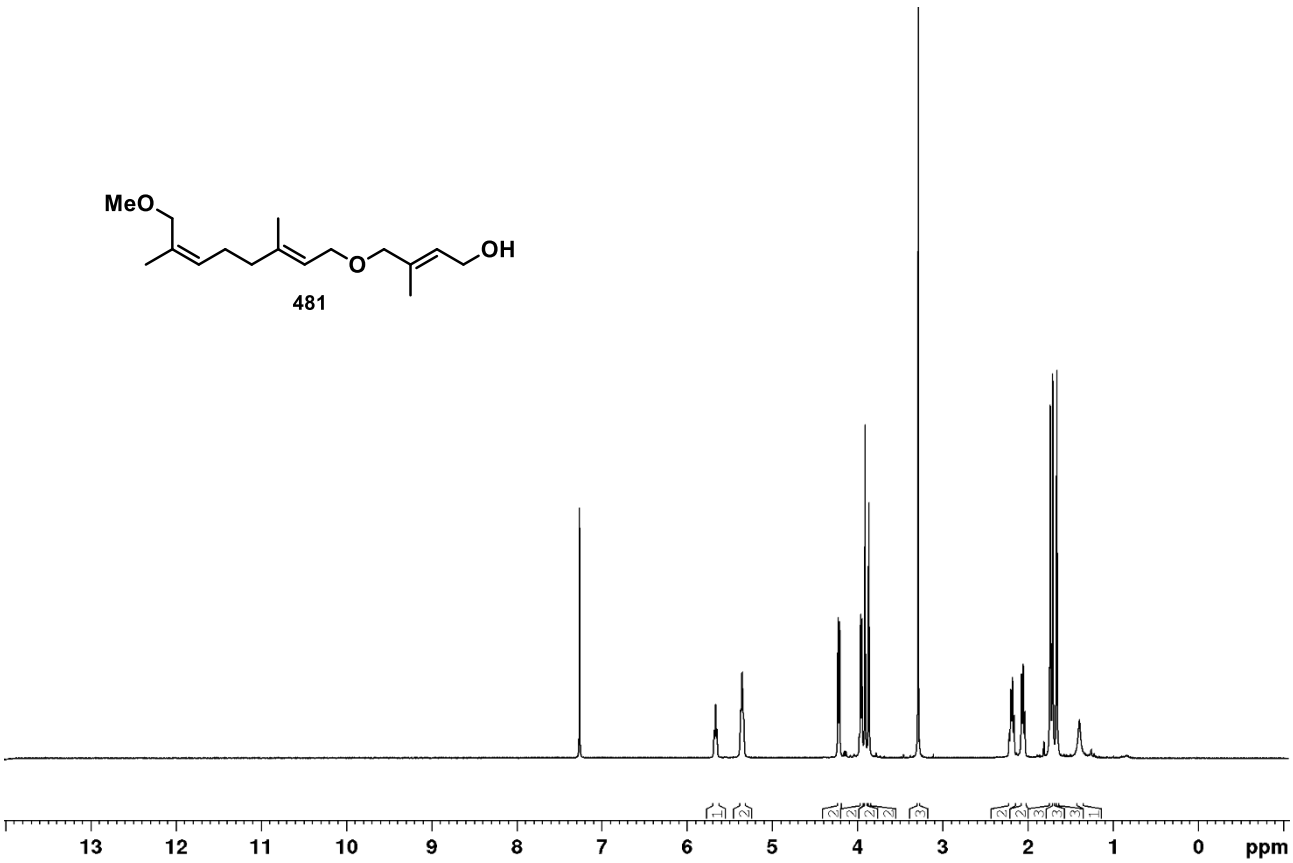
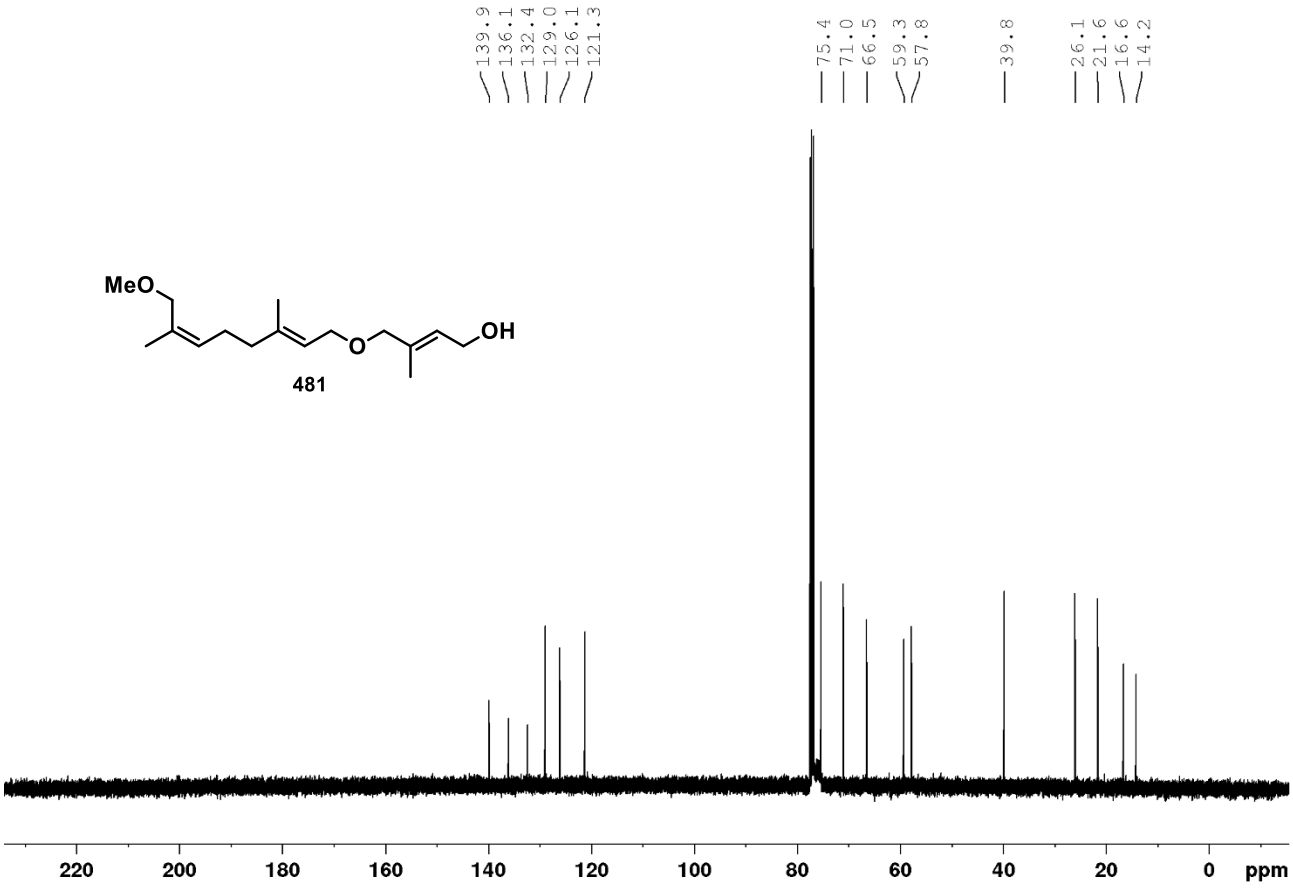
135.7
134.0
133.8
132.4
129.7
129.0
127.8
127.3
121.4
75.6
71.0
66.1
60.9
57.8
39.9
27.0
26.1
21.6
19.3
16.6
14.2
MeO
OTBDPS
O
563
220
200
180
160
140
120
100
80
60
40
20
0
ppm


MeO
OH
O
481
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm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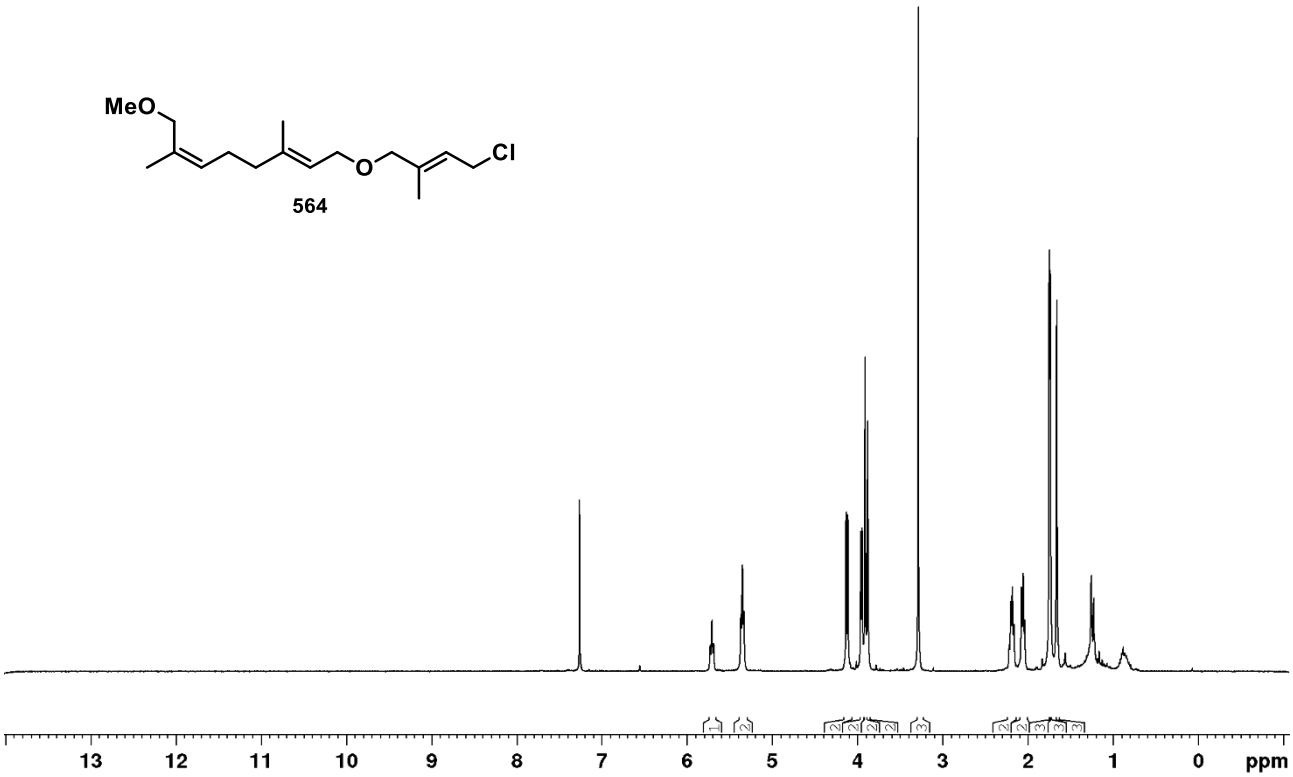
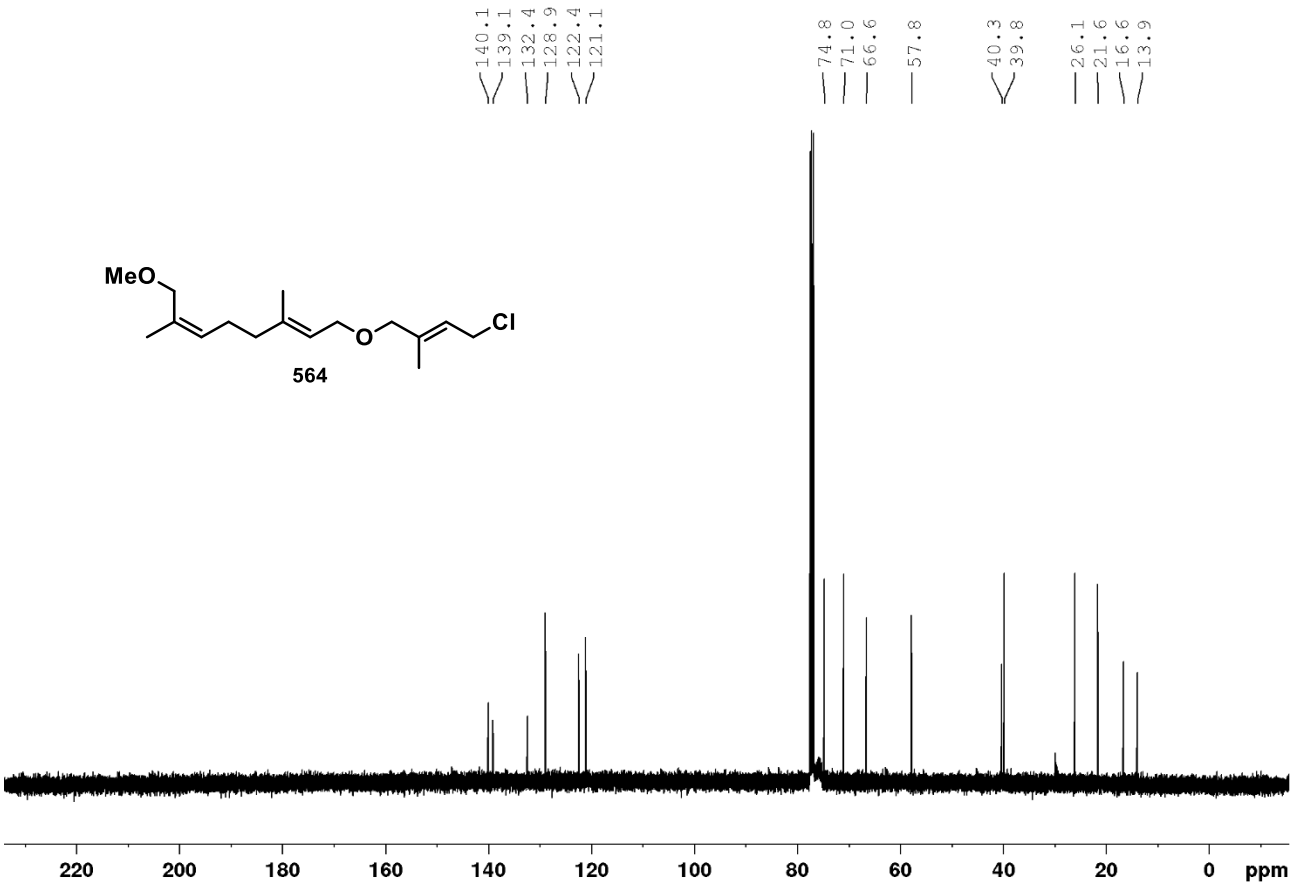
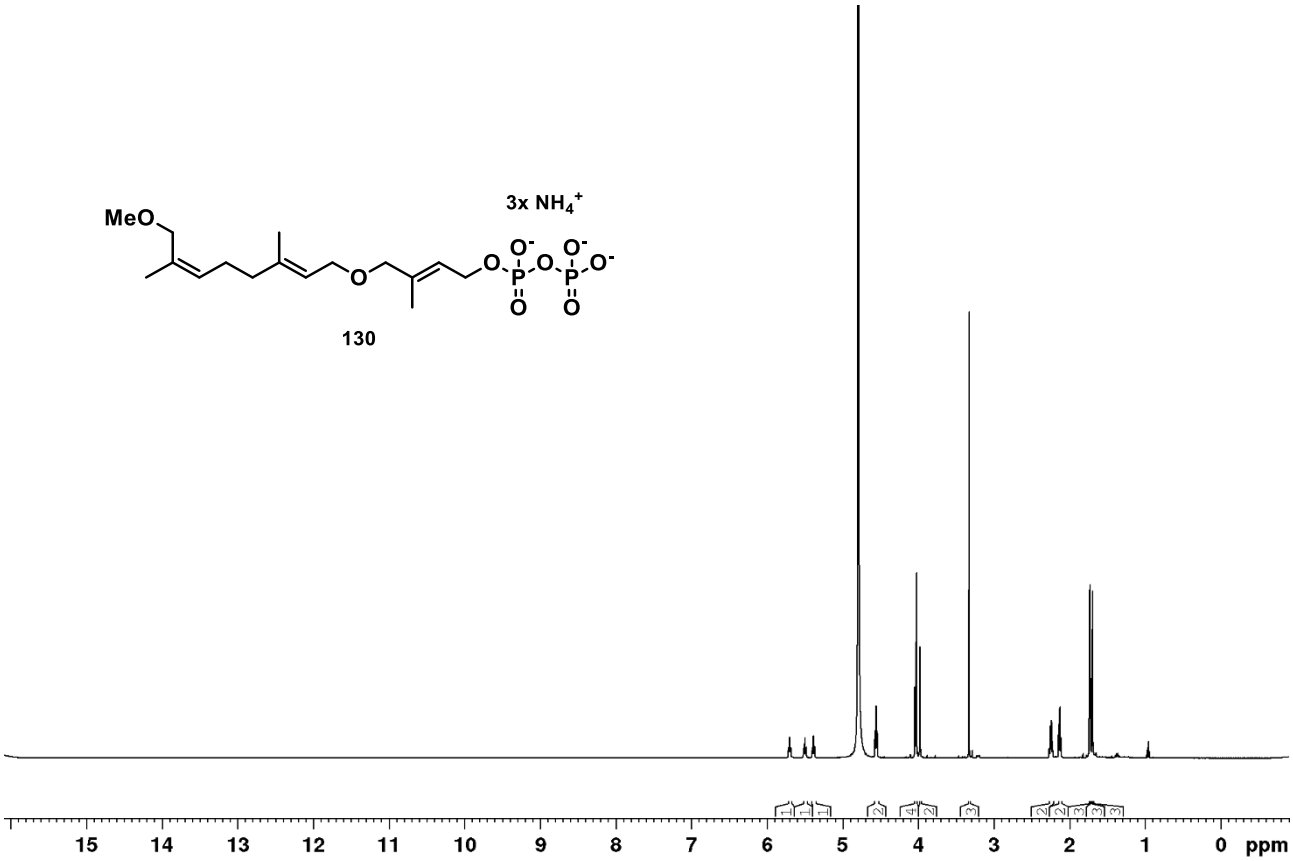
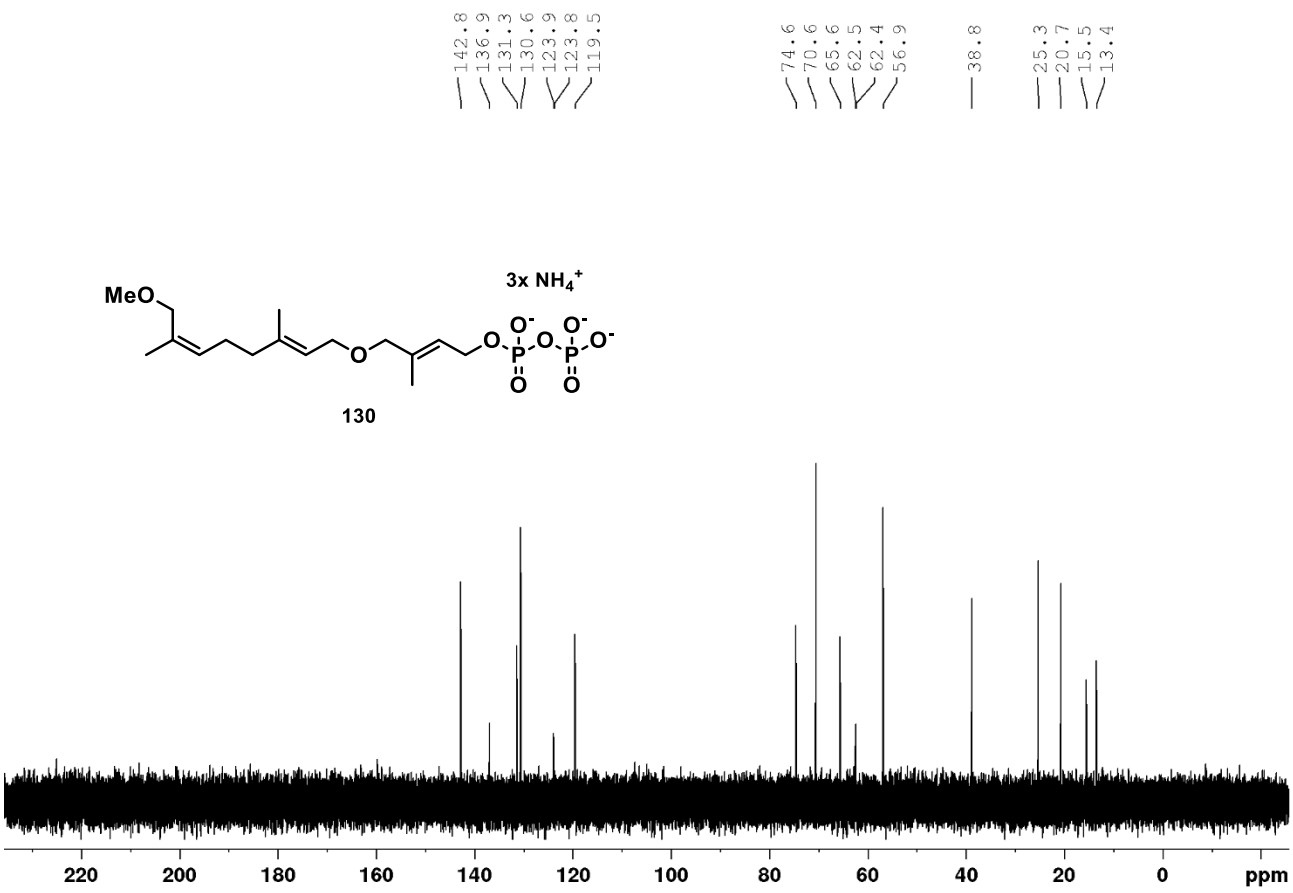
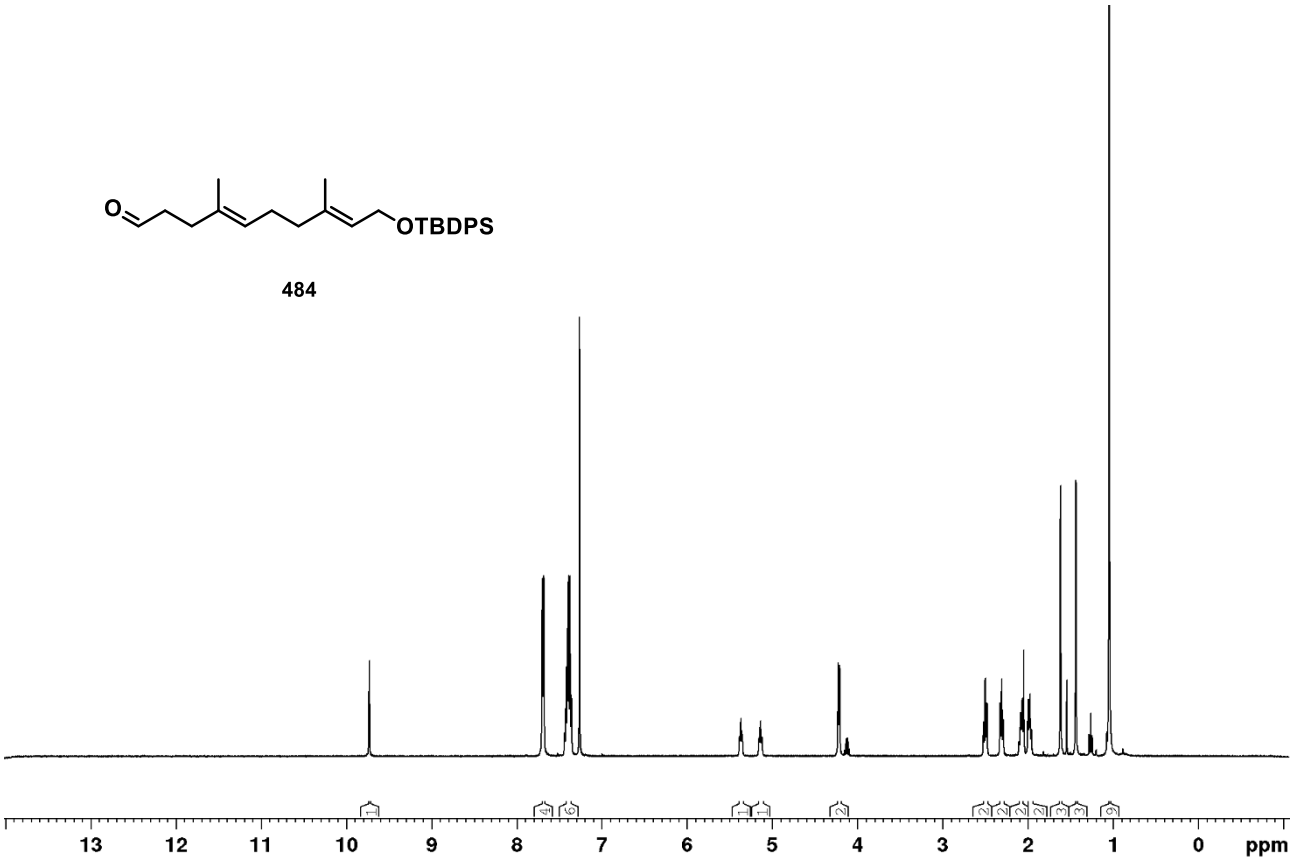
136.1
132.4
129.0
126.1
121.3
75.4
71.0
66.5
59.3
57.8
39.8
26.1
21.6
16.6
14.2
MeO
OH
O
481
220
200
180
160
140
120
100
80
60
40
20
0
ppm


MeO
O
Cl
564
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

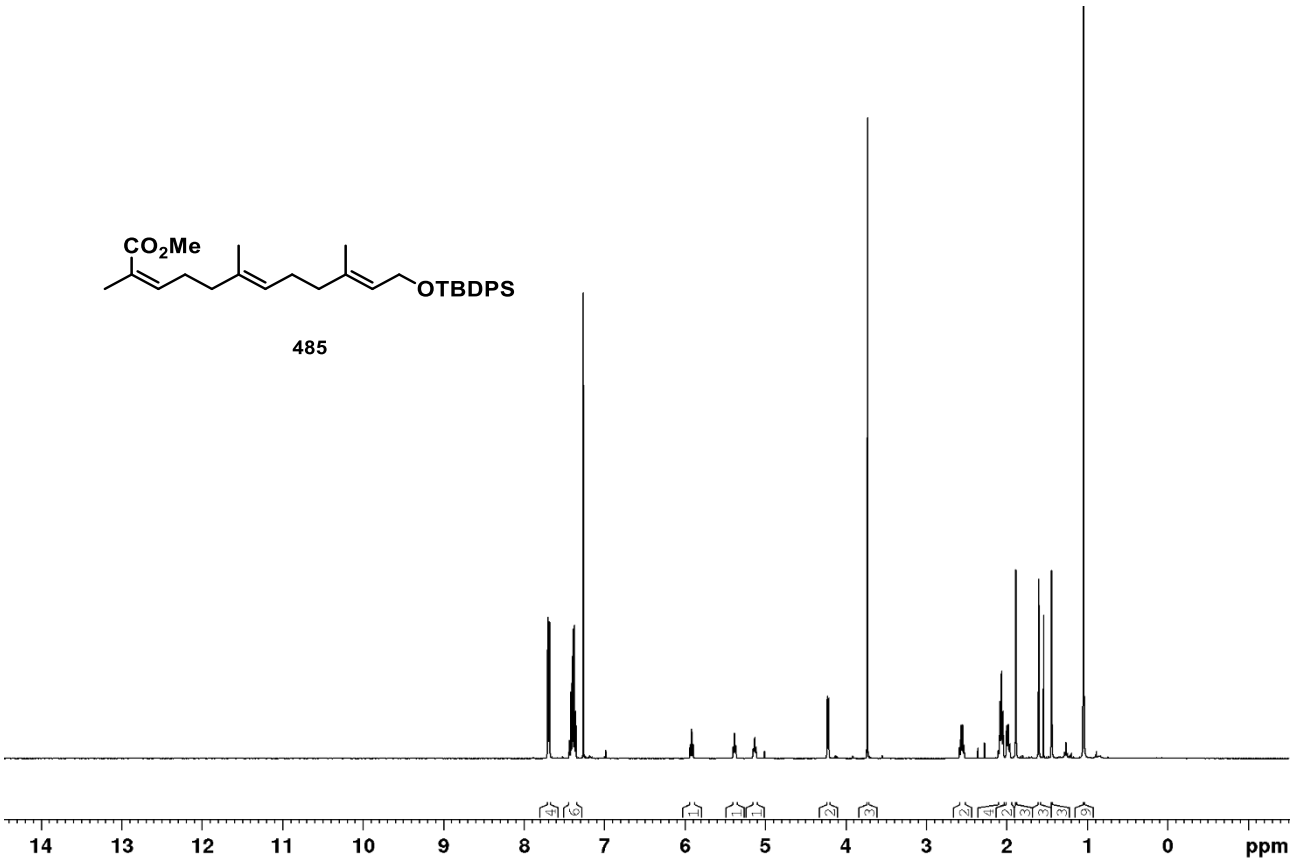

140.1
139.1
132.4
128.9
122.4
121.1
74.8
71.0
66.6
57.8
40.3
39.8
26.1
21.6
16.6
13.9
MeO
O
Cl
564
220
200
180
160
140
120
100
80
60
40
20
0
ppm


MeO
3x NH4+
O-
O-
O-
O
O
O
P
P
O
O
O
O
130
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

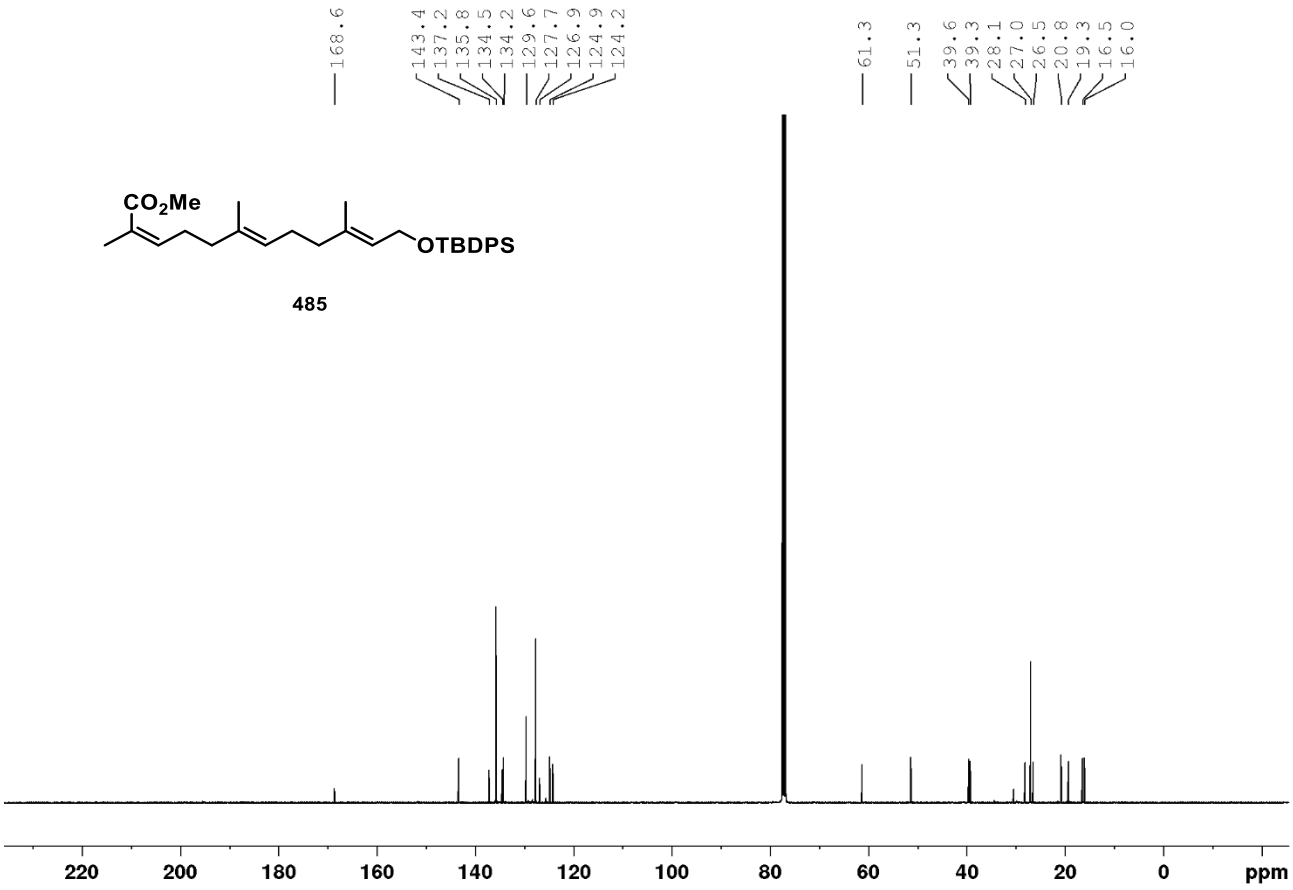

142.8
136.9
131.3
130.6
123.9
123.8
119.5
74.6
70.6
65.6
62.5
62.4
56.9
38.8
25.3
20.7
15.5
13.4
MeO
3x NH4+
O-
O-
O-
O
O
O
P
P
O
O
O
O
130
220
200
180
160
140
120
100
80
60
40
20
0
ppm

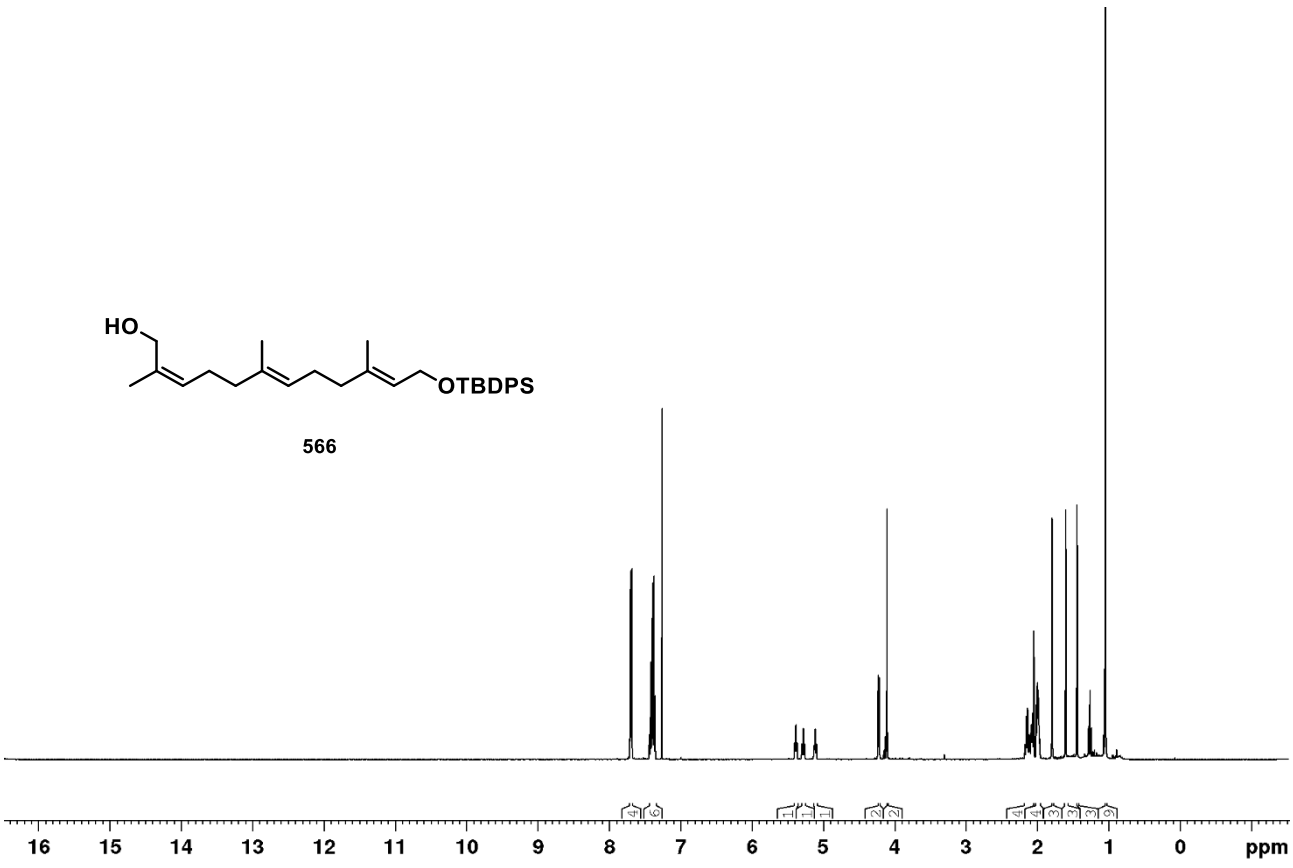

O
OTBDPS
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

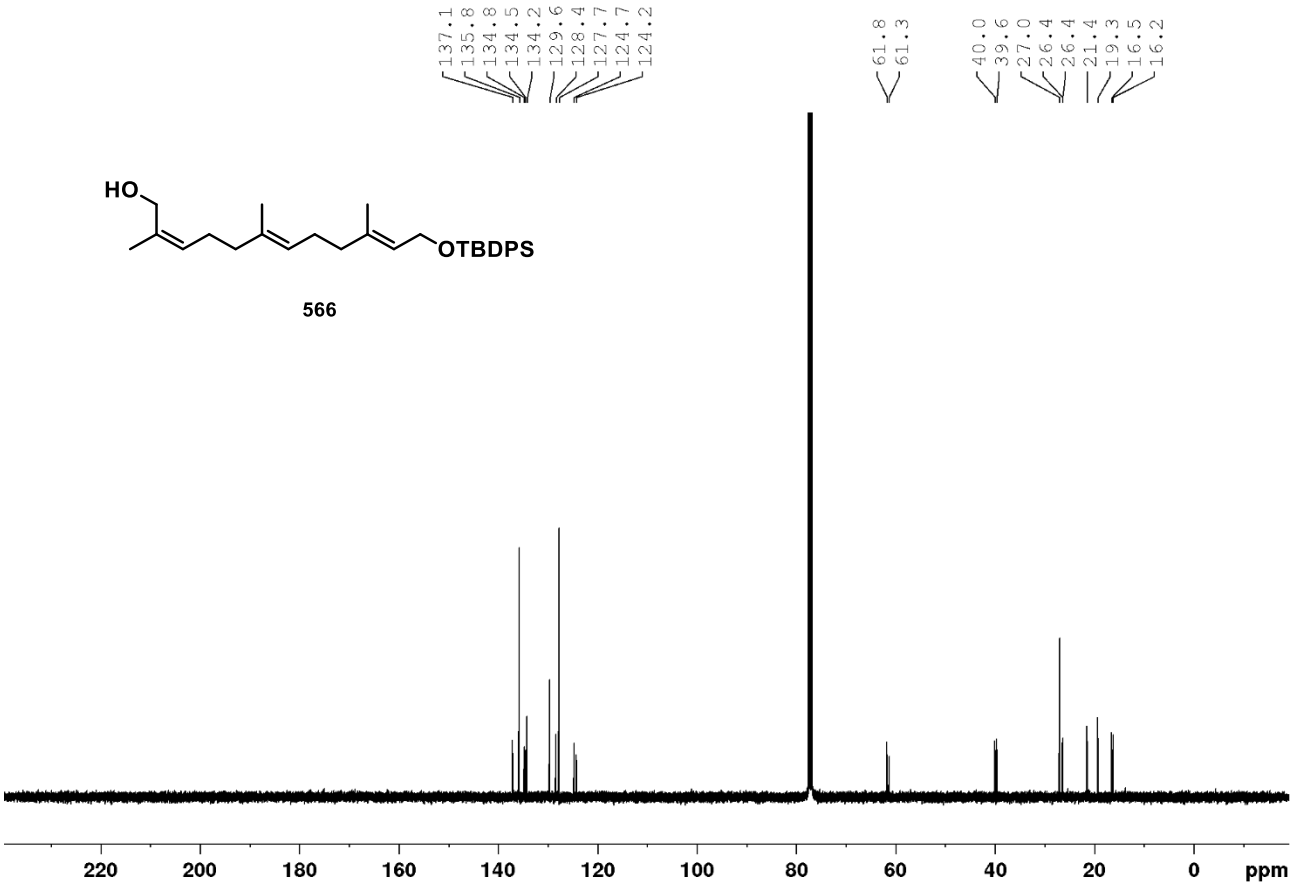
484


CO2Me
OTBDPS
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

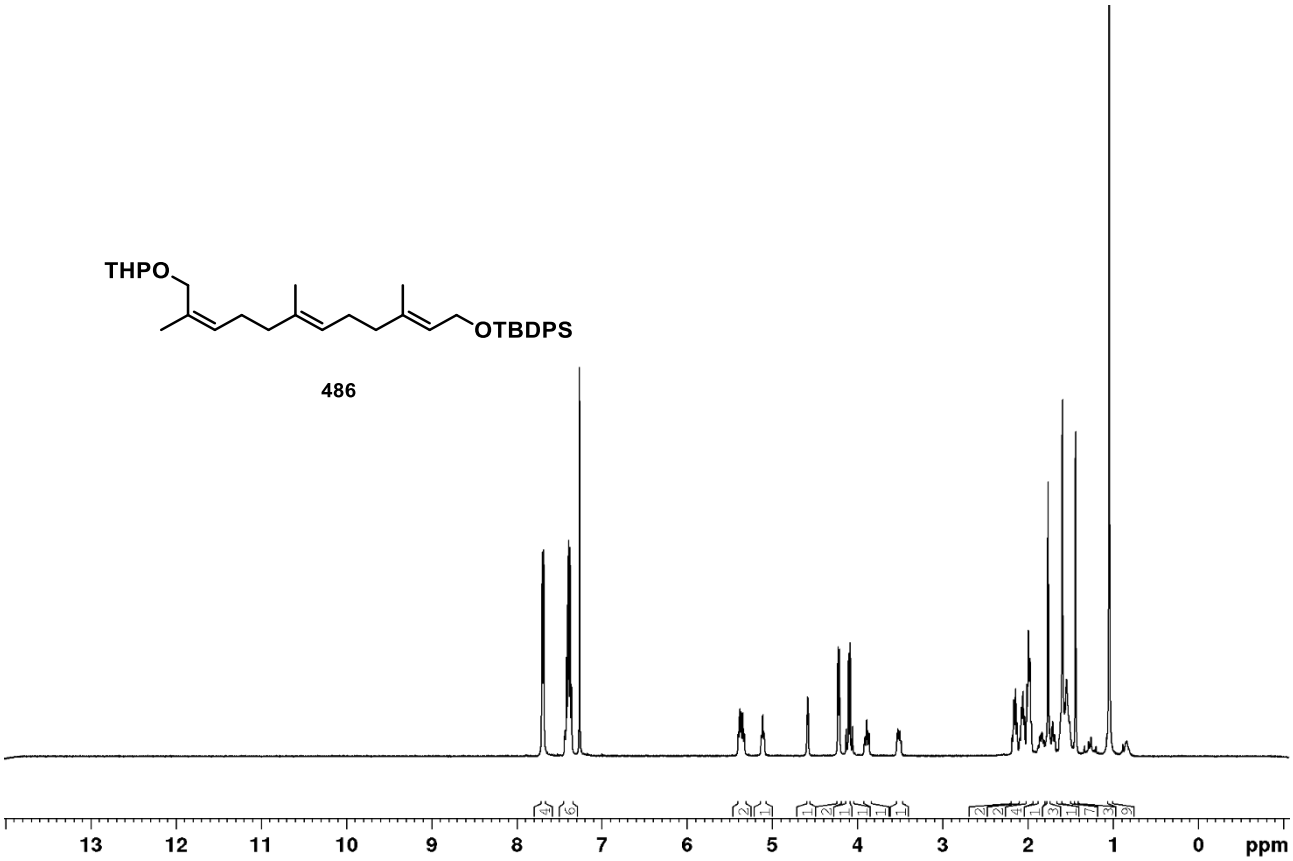
485


168.6
143.4
137.2
135.8
134.5
134.2
129.6
127.7
126.9
124.9
124.2
61.3
51.3
39.6
39.3
28.1
27.0
26.5
20.8
19.3
16.5
16.0
CO2Me
OTBDPS
485
220
200
180
160
140
120
100
80
60
40
20
0
ppm

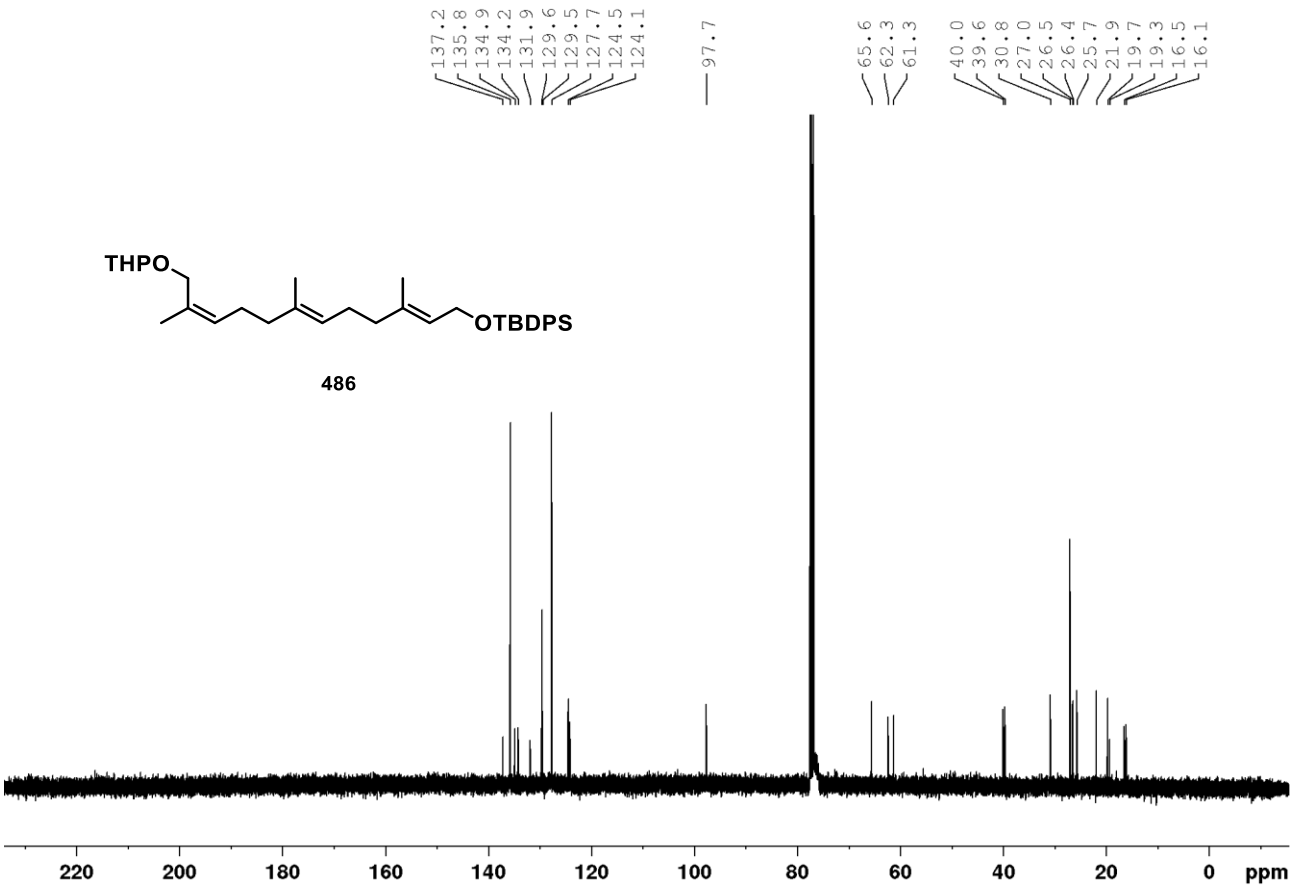

HO
OTBDPS
566
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


137.1
135.8
134.8
134.5
134.2
129.6
128.4
127.7
124.7
124.2
61.8
61.3
40.0
39.6
27.0
26.4
26.4
21.4
19.3
16.5
16.2
HO
OTBDPS
220
200
180
160
140
120
100
80
60
40
20
0
ppm

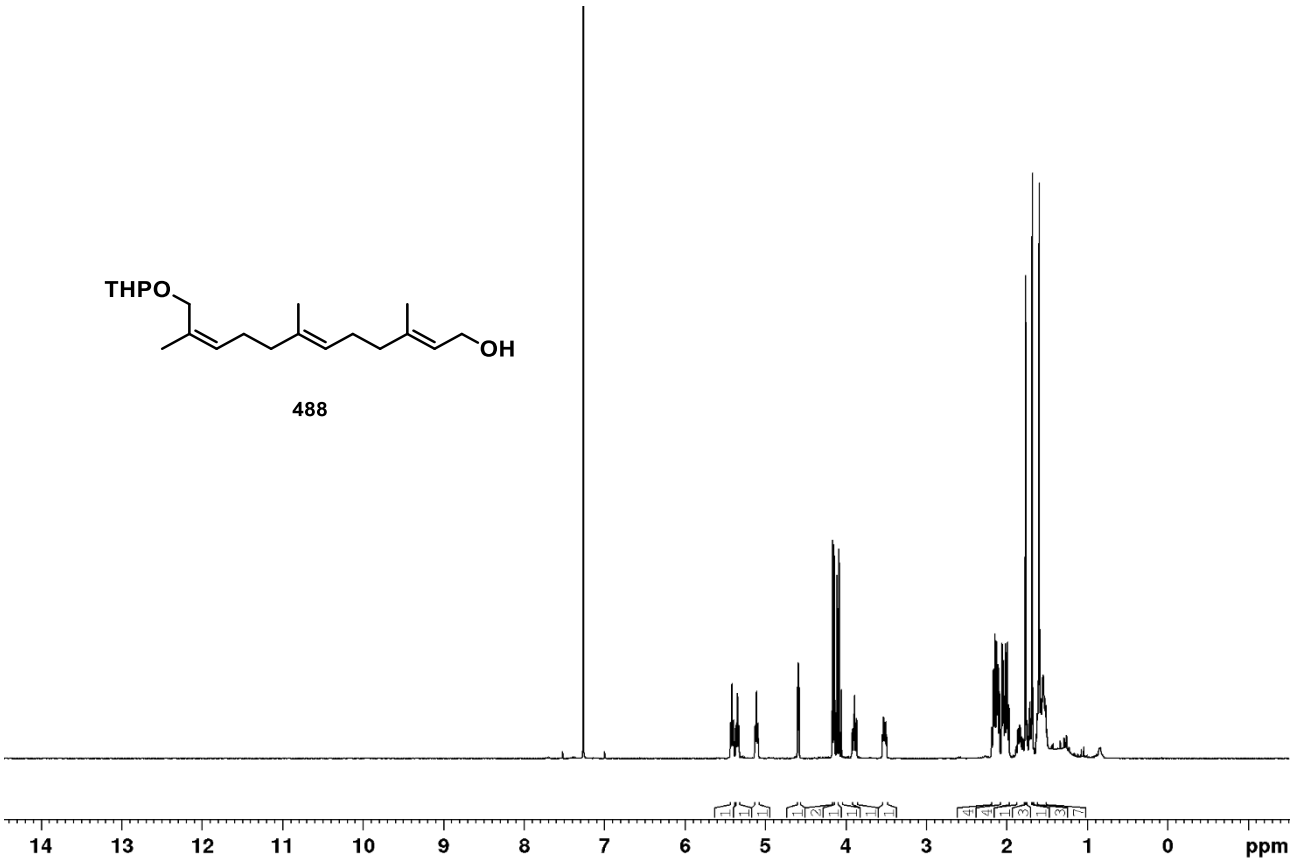
566


THPO
OTBDPS
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

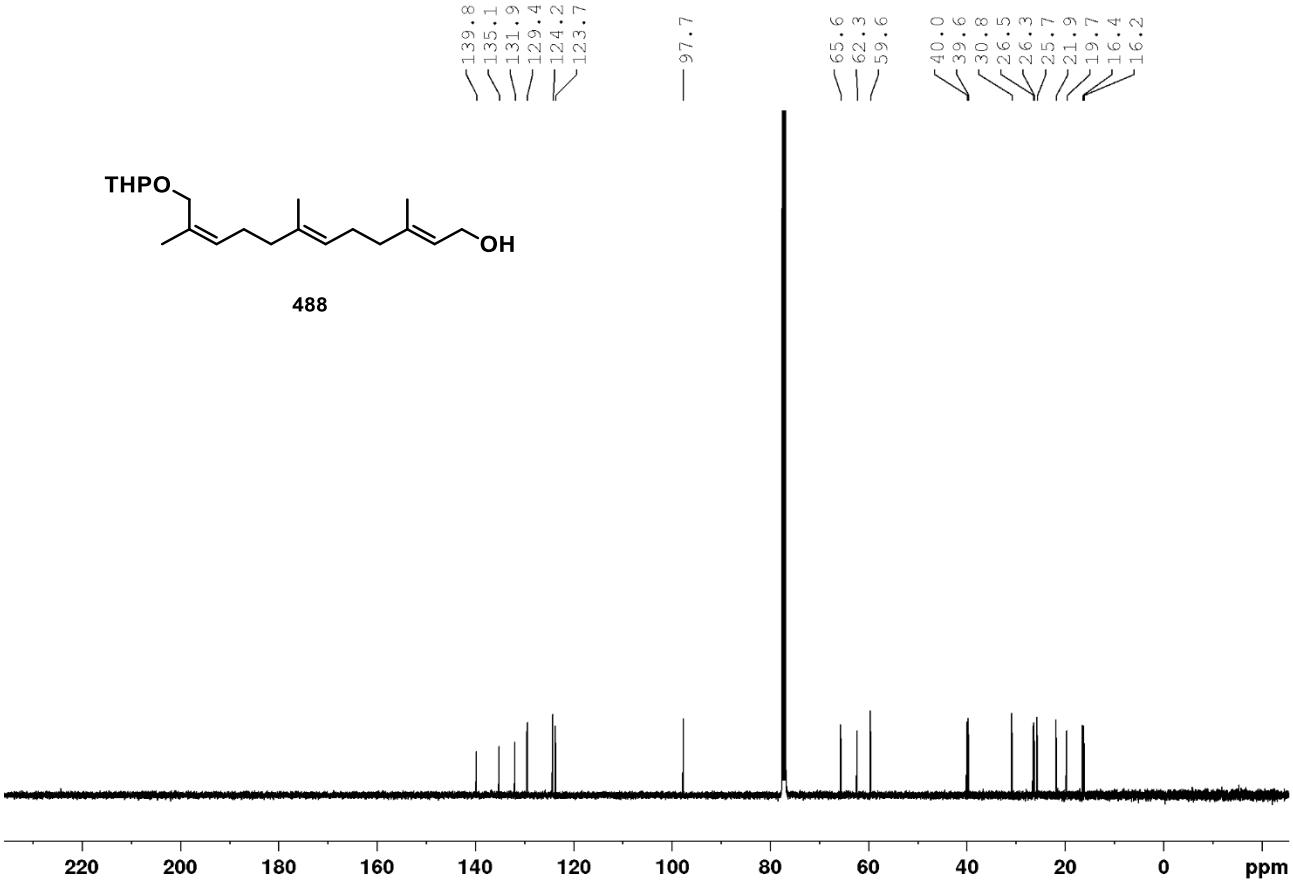
486

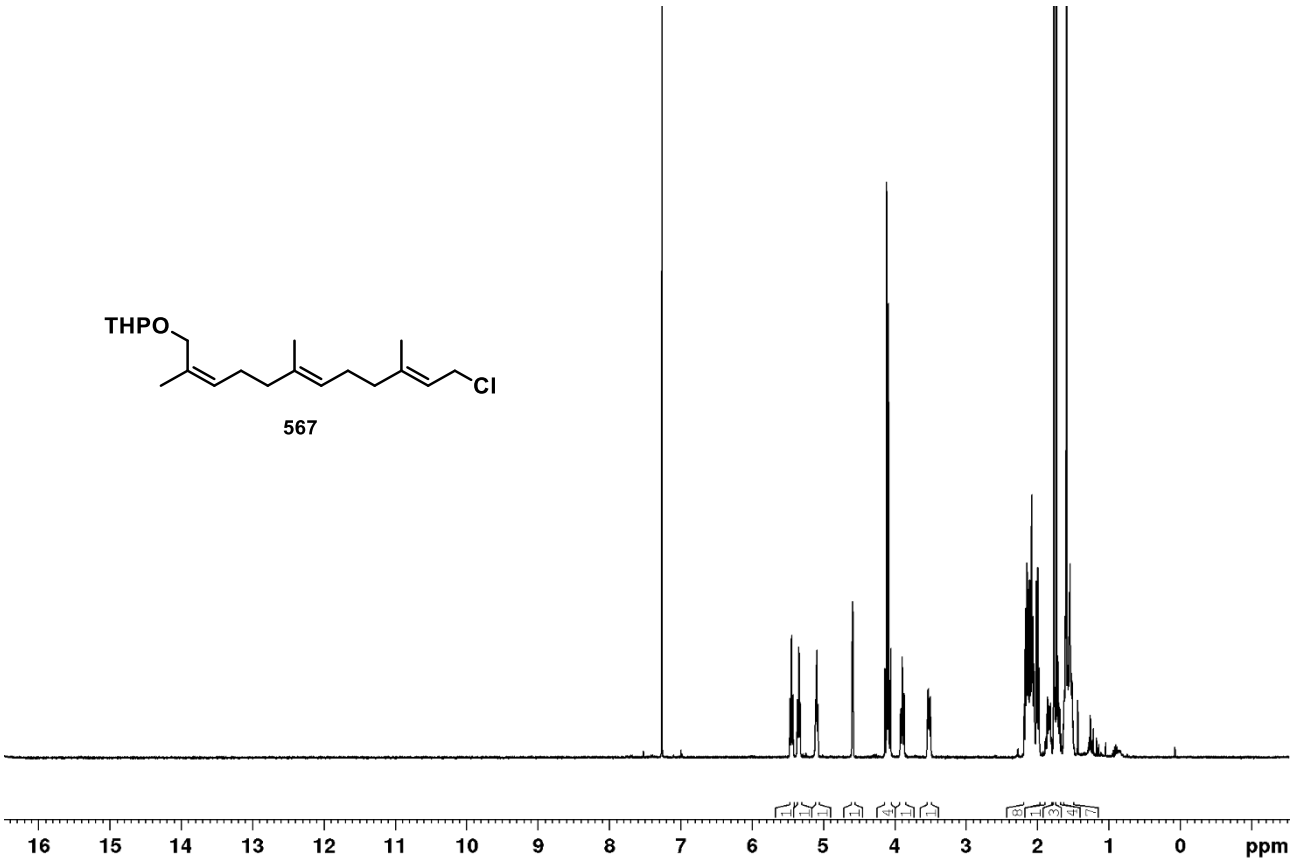

137.2
135.8
134.9
134.2
131.9
129.6
129.5
127.7
124.5
124.1
97.7
65.6
62.3
61.3
40.0
39.6
30.8
27.0
26.5
26.4
25.7
21.9
19.7
19.3
16.5
16.1
THPO
OTBDPS
220
200
180
160
140
120
100
80
60
40
20
0
ppm

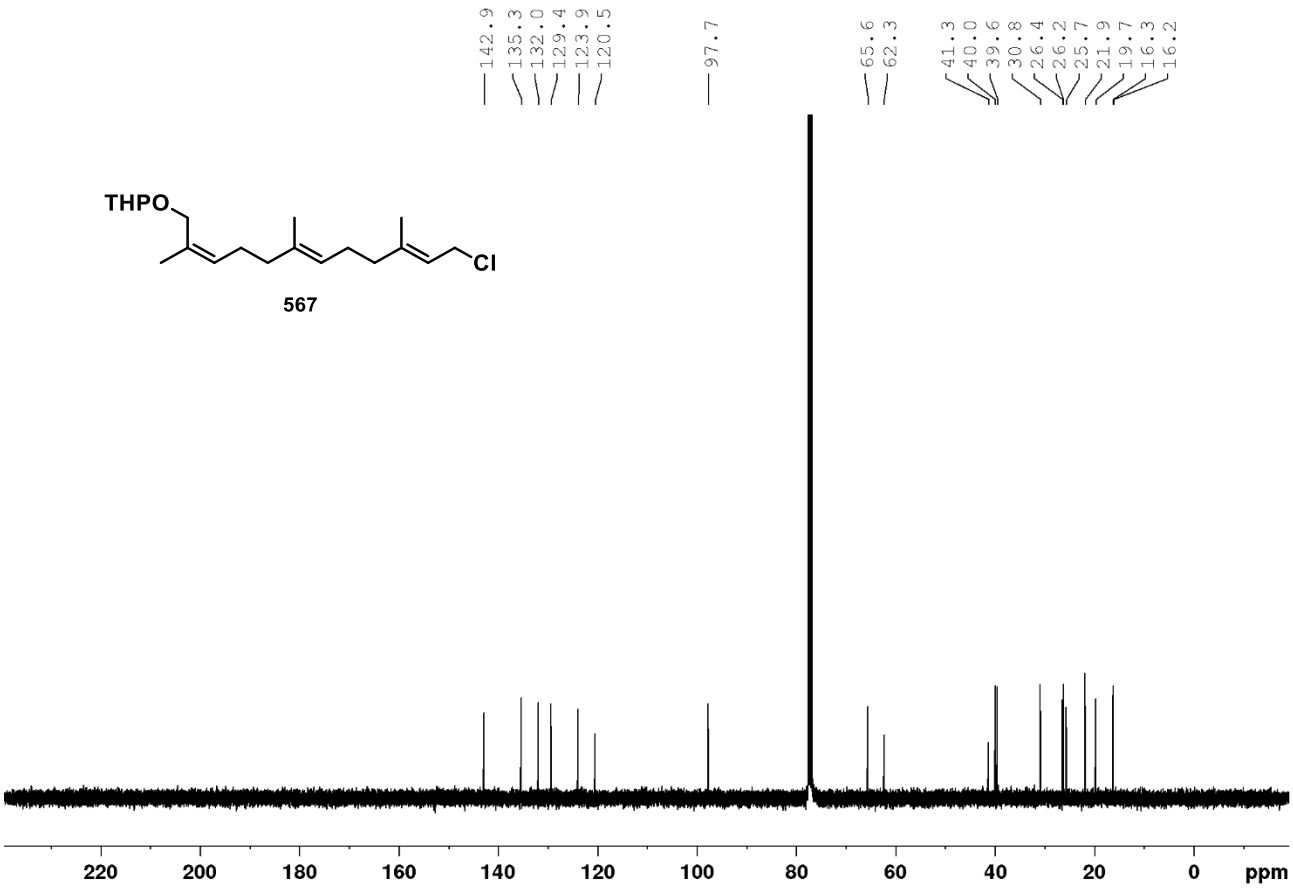
486


THPO
OH
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

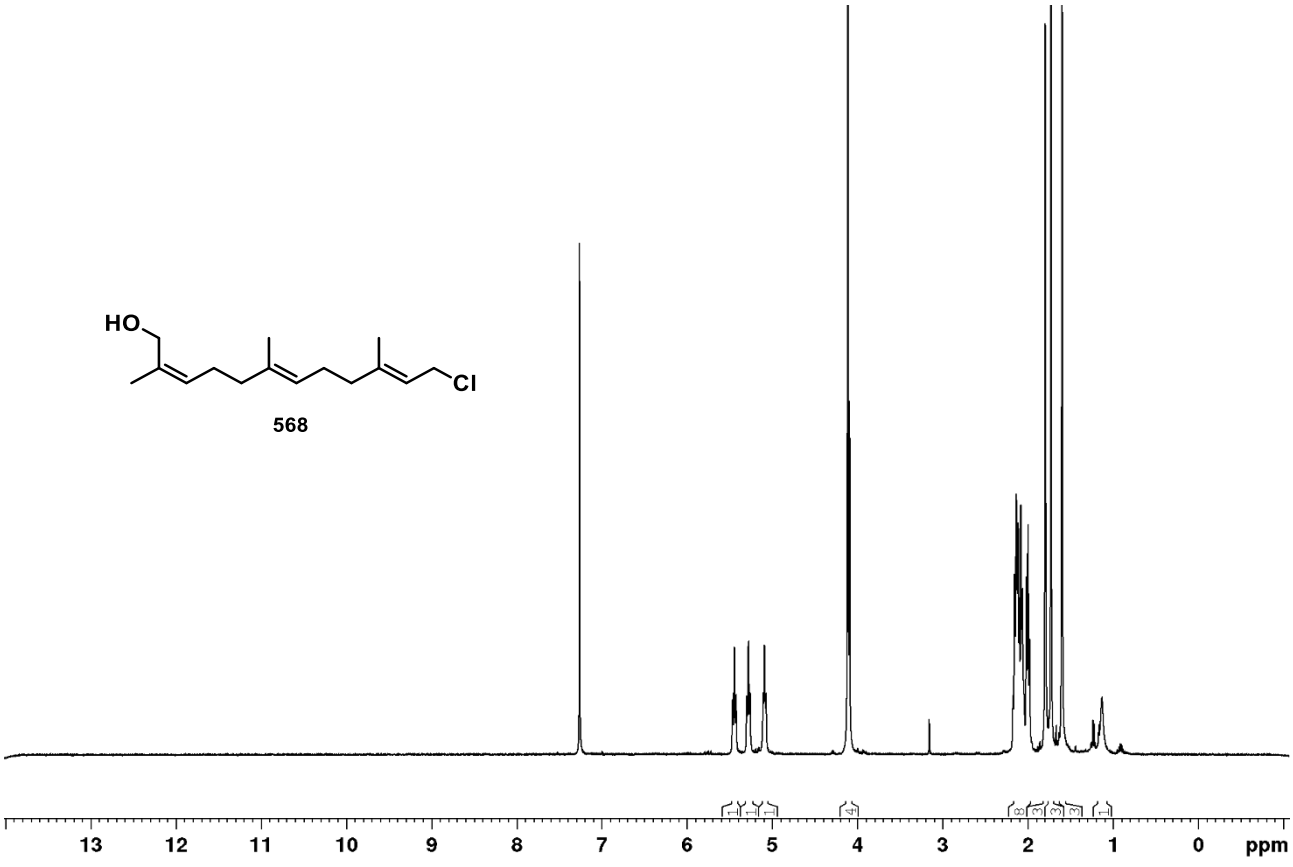
488


139.8
135.1
131.9
129.4
124.2
123.7
97.7
65.6
62.3
59.6
40.0
39.6
30.8
26.5
26.3
25.7
21.9
19.7
16.4
16.2
THPO
OH
488
220
200
180
160
140
120
100
80
60
40
20
0
ppm

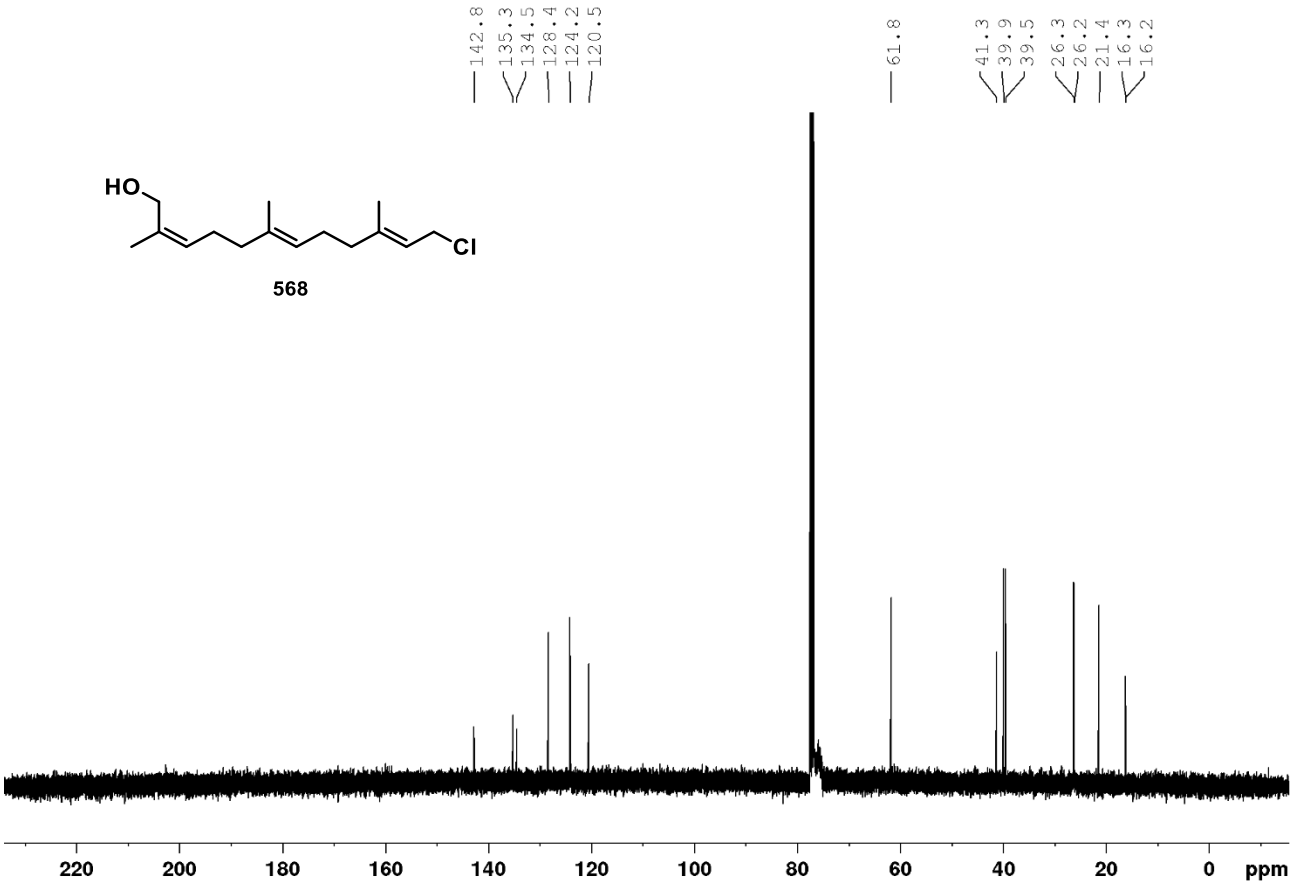

THPO
Cl
567
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

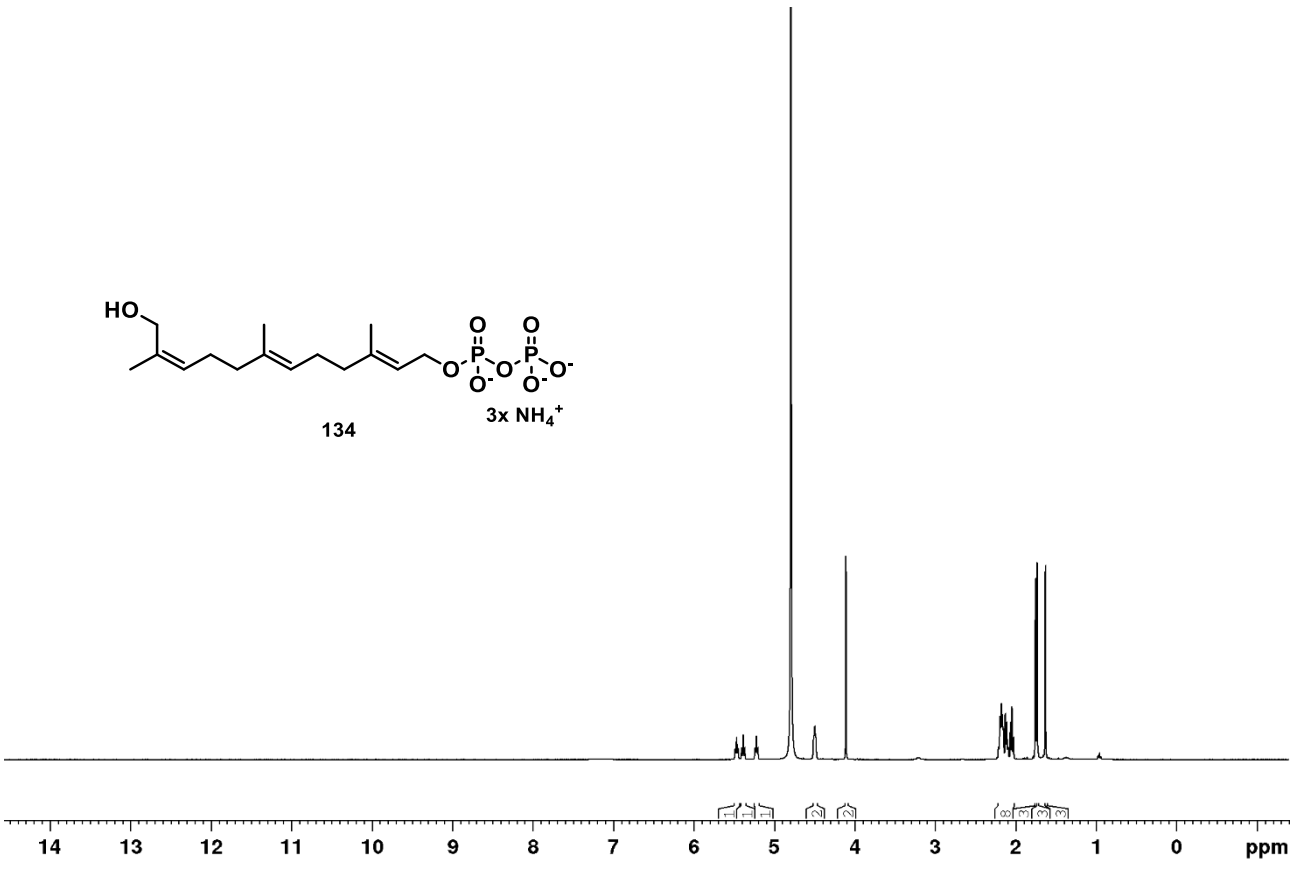

142.9
135.3
132.0
129.4
123.9
120.5
97.7
65.6
62.3
41.3
40.0
39.6
30.8
26.4
26.2
25.7
21.9
19.7
16.3
16.2
THPO
Cl
220
200
180
160
140
120
100
80
60
40
20
0
ppm

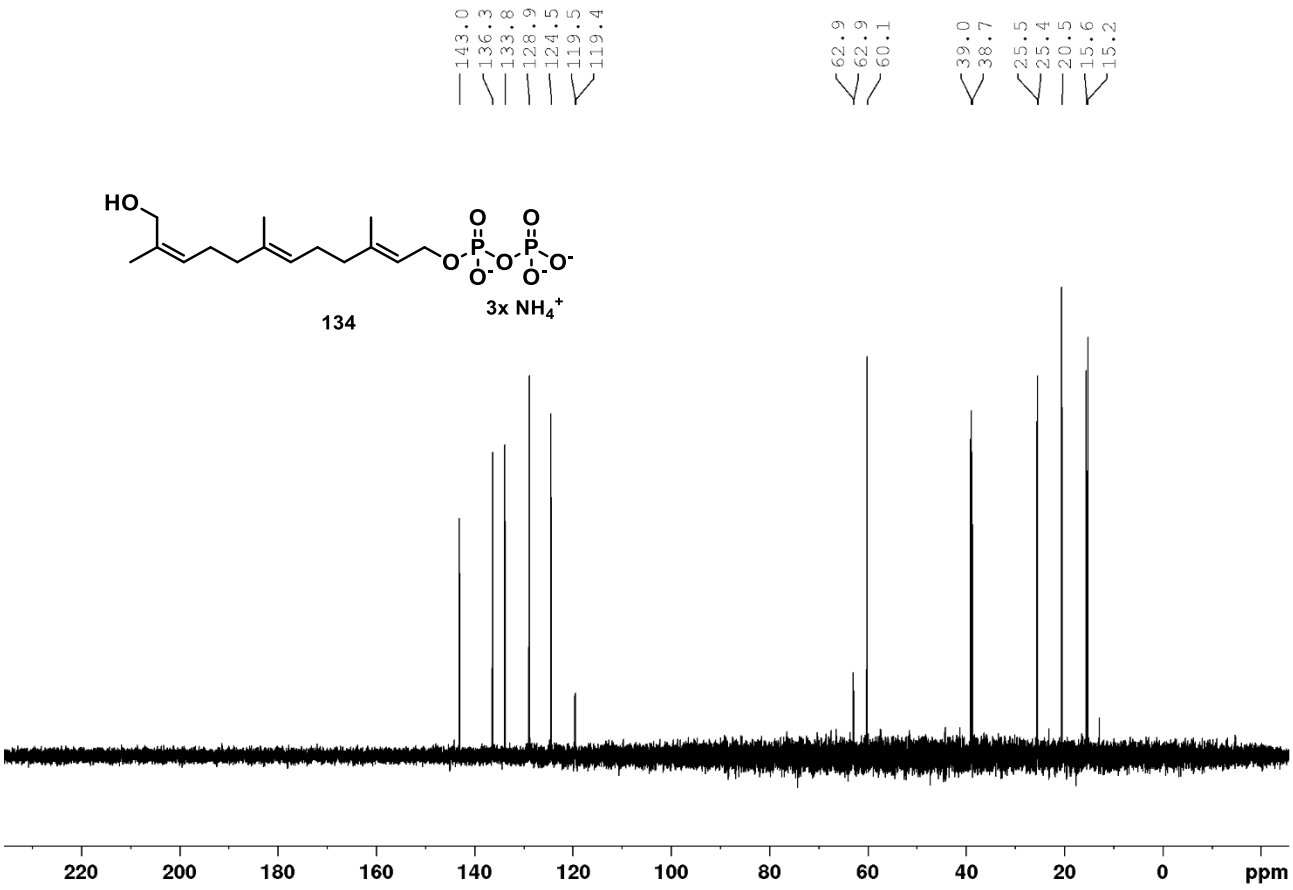
567

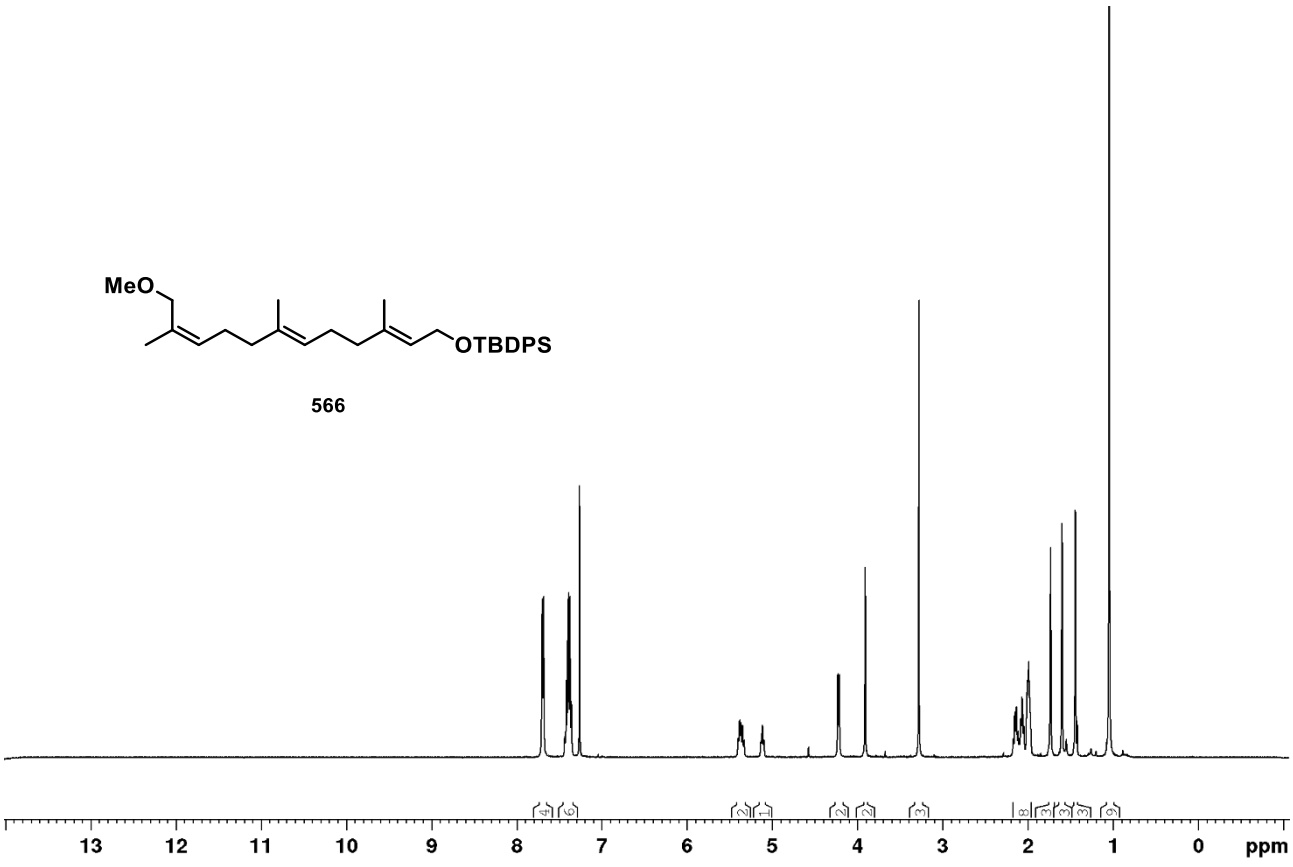

HO
Cl
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

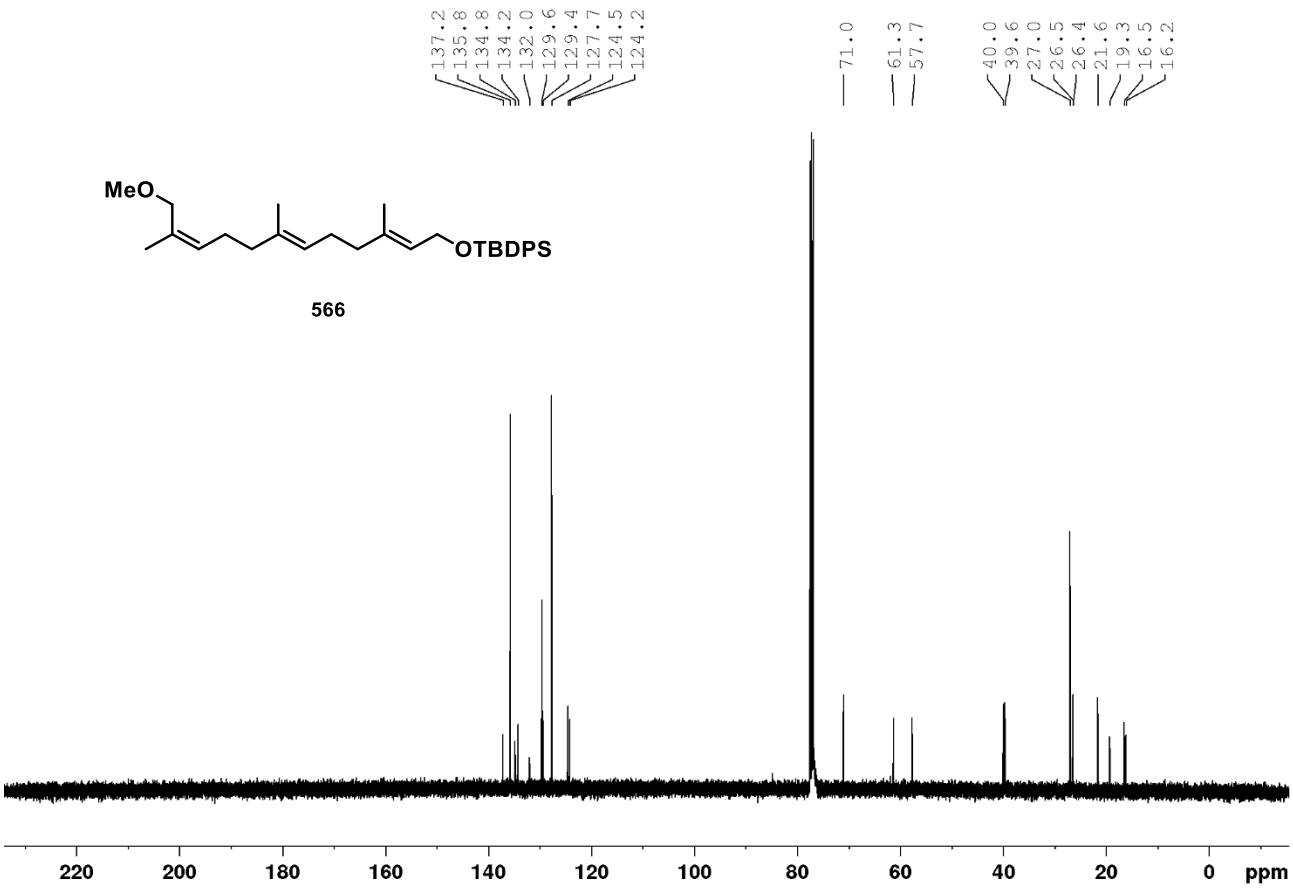
568


142.8
135.3
134.5
128.4
124.2
120.5
61.8
41.3
39.9
39.5
26.3
26.2
21.4
16.3
16.2
HO
Cl
568
220
200
180
160
140
120
100
80
60
40
20
0
ppm

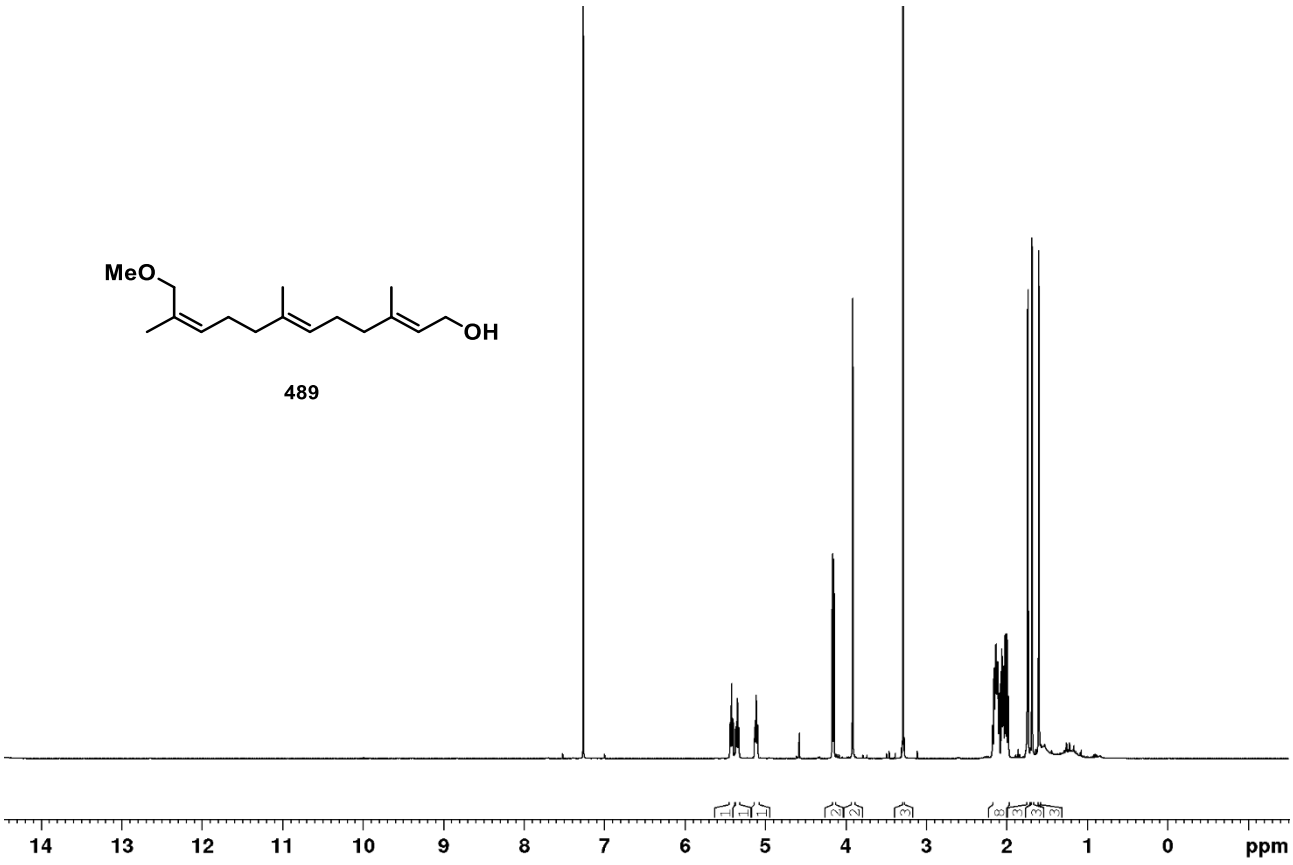

HO
O
P
O
O
O
O
O
O
P
O
O
3x NH4+
134
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


143.0
136.3
133.8
128.9
124.5
119.5
119.4
62.9
62.9
60.1
39.0
38.7
25.5
25.4
20.5
15.6
15.2
HO
O
O
O
O
O
O
O
O
O
3x NH_4^+
134
220
200
180
160
140
120
100
80
60
40
20
0
ppm

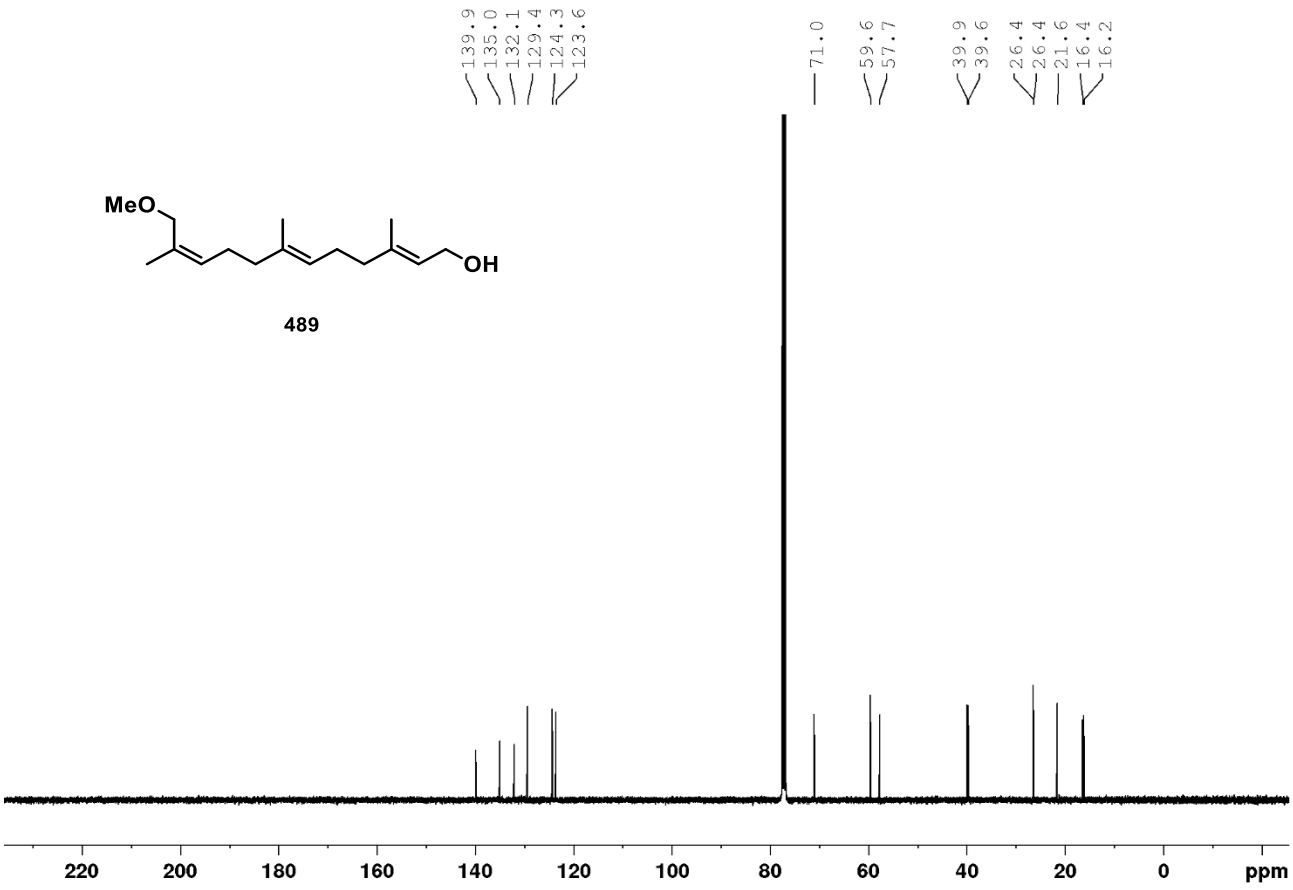

MeO
OTBDPS
566
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


137.2
135.8
134.8
134.2
132.0
129.6
129.4
127.7
124.5
124.2
71.0
61.3
57.7
40.0
39.6
27.0
26.5
26.4
21.6
19.3
16.5
16.2
MeO
OTBDPS
220
200
180
160
140
120
100
80
60
40
20
0
ppm

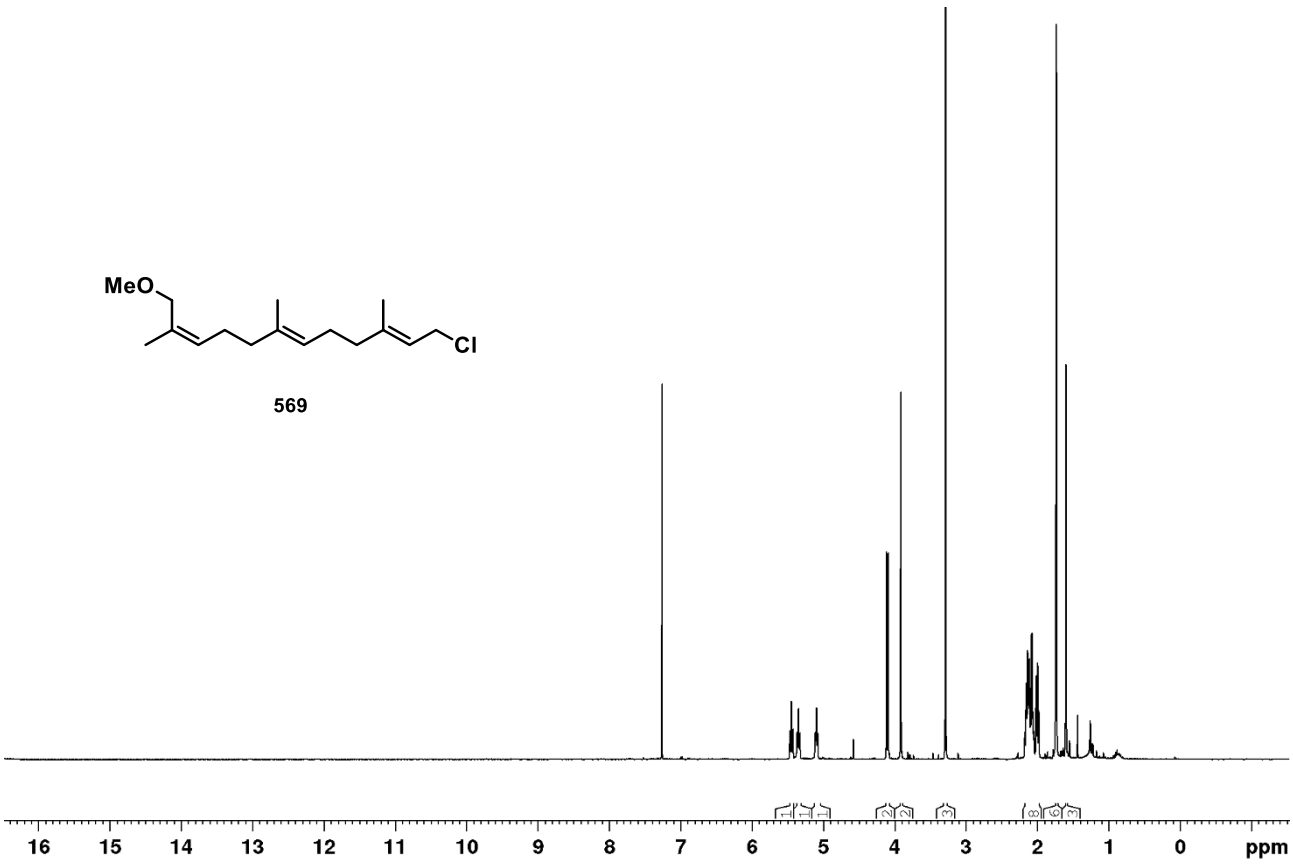
566


MeO
OH
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

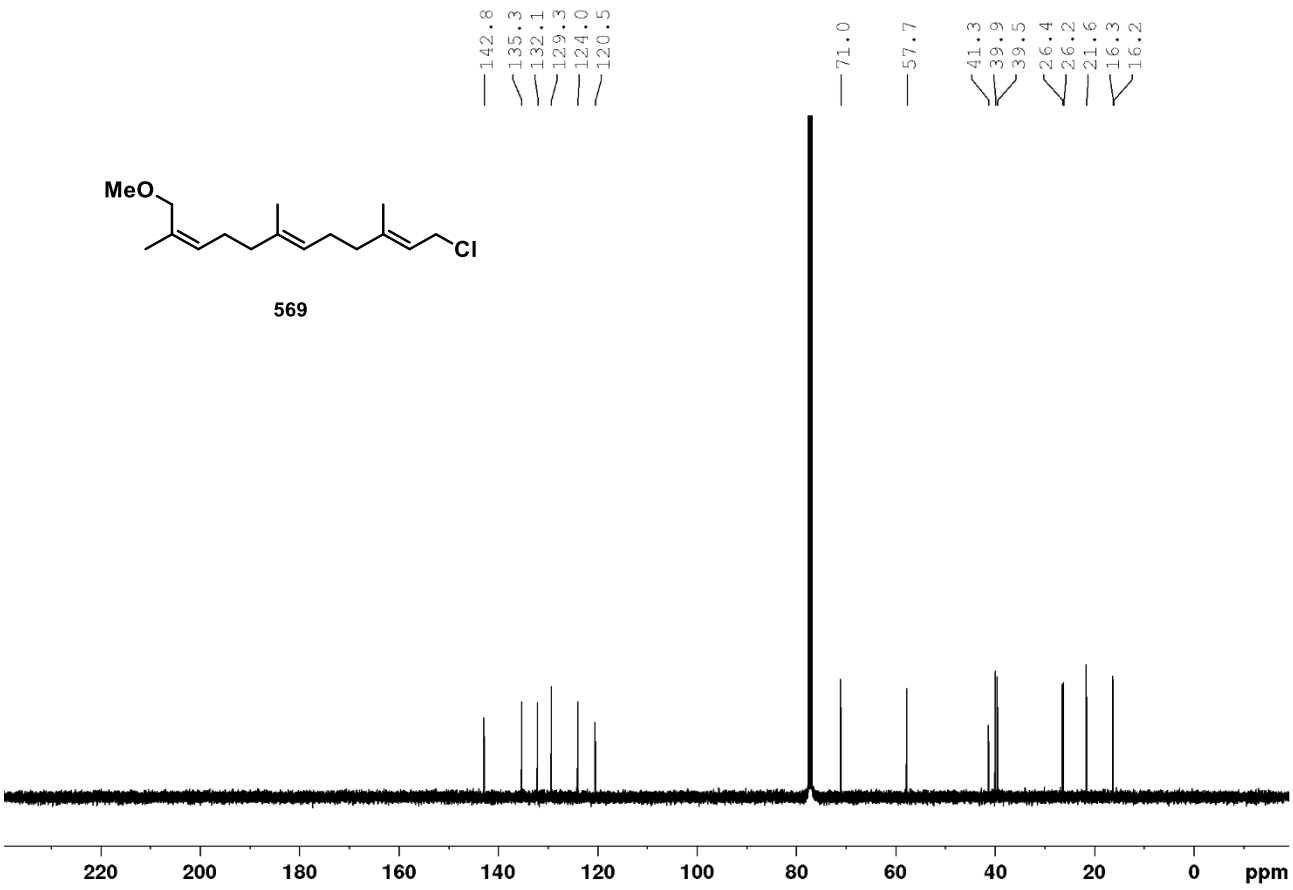
489


139.9
135.0
132.1
129.4
124.3
123.6
71.0
59.6
57.7
39.9
39.6
26.4
26.4
21.6
16.4
16.2
MeO
OH
220
200
180
160
140
120
100
80
60
40
20
0
ppm

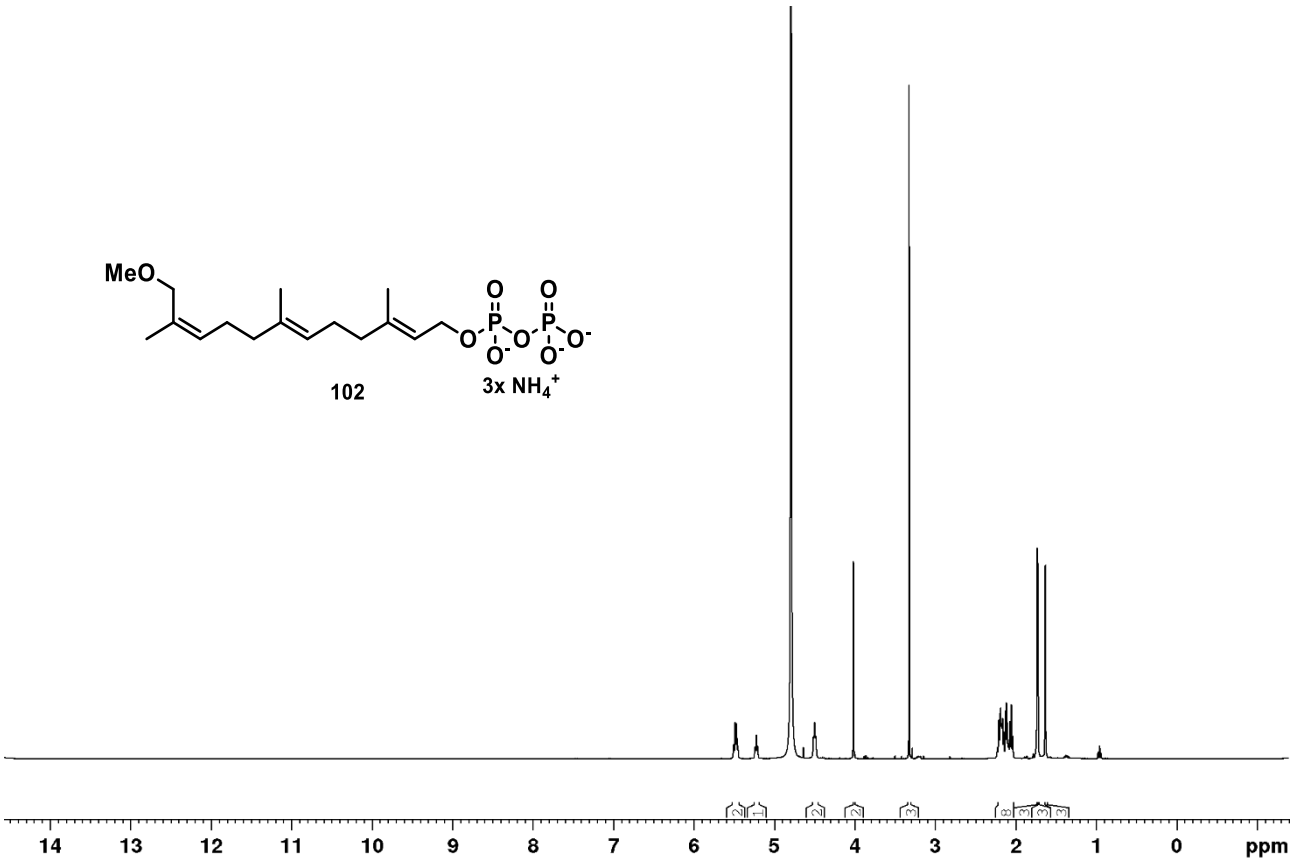
489


MeO
Cl
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

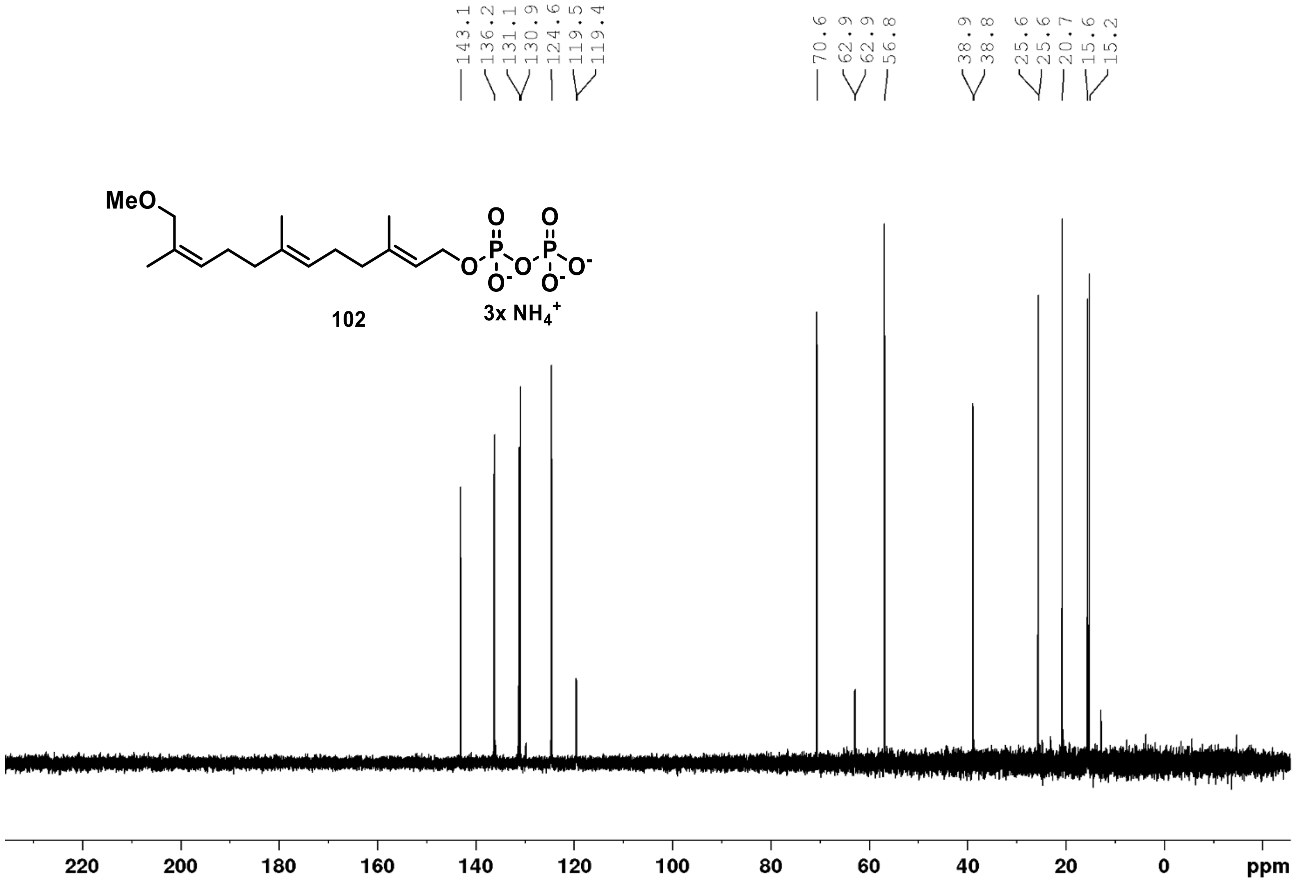
569


142.8
135.3
132.1
129.3
124.0
120.5
71.0
57.7
41.3
39.9
39.5
26.4
26.2
21.6
16.3
16.2
MeO
Cl
220
200
180
160
140
120
100
80
60
40
20
0
ppm

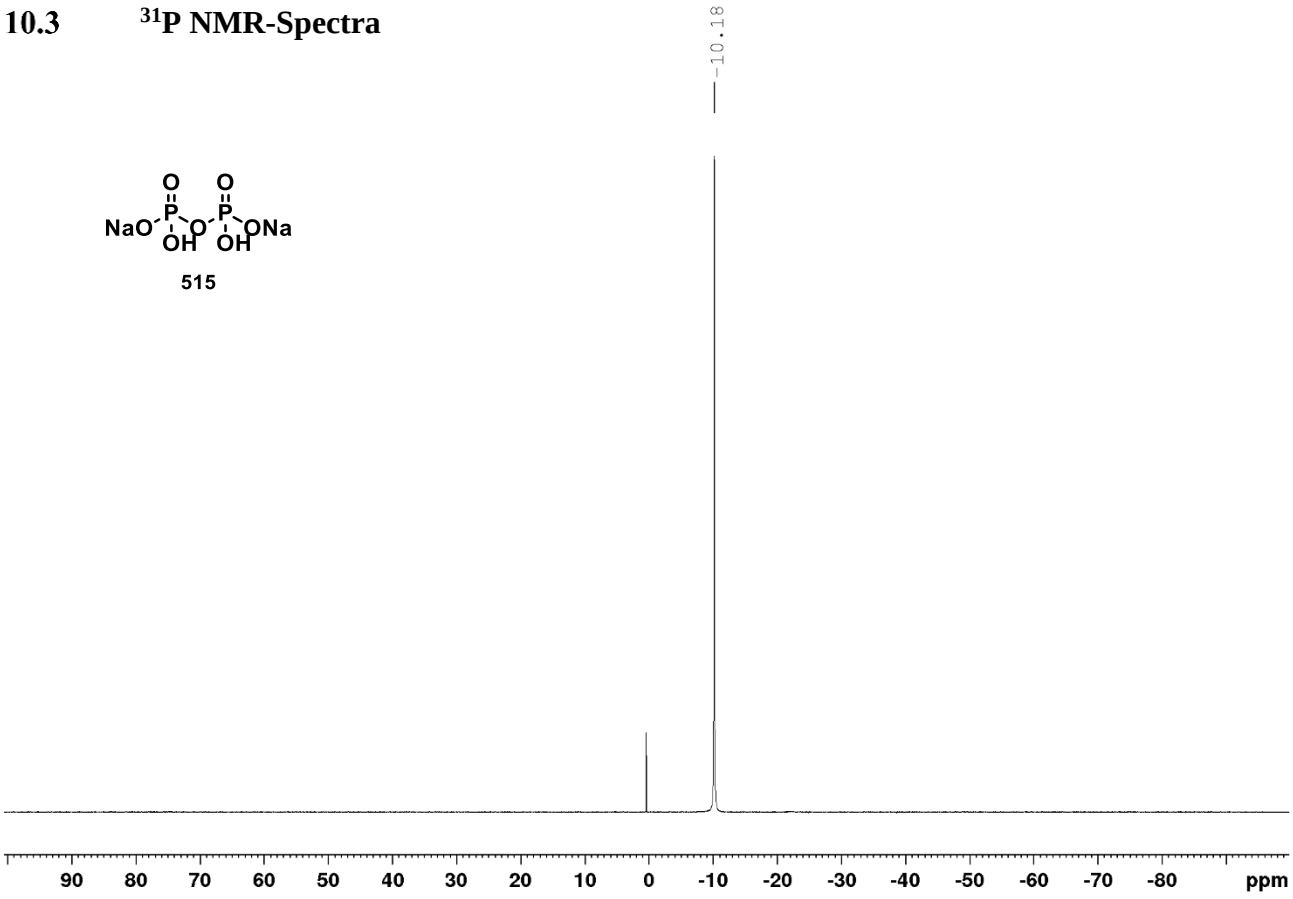
569

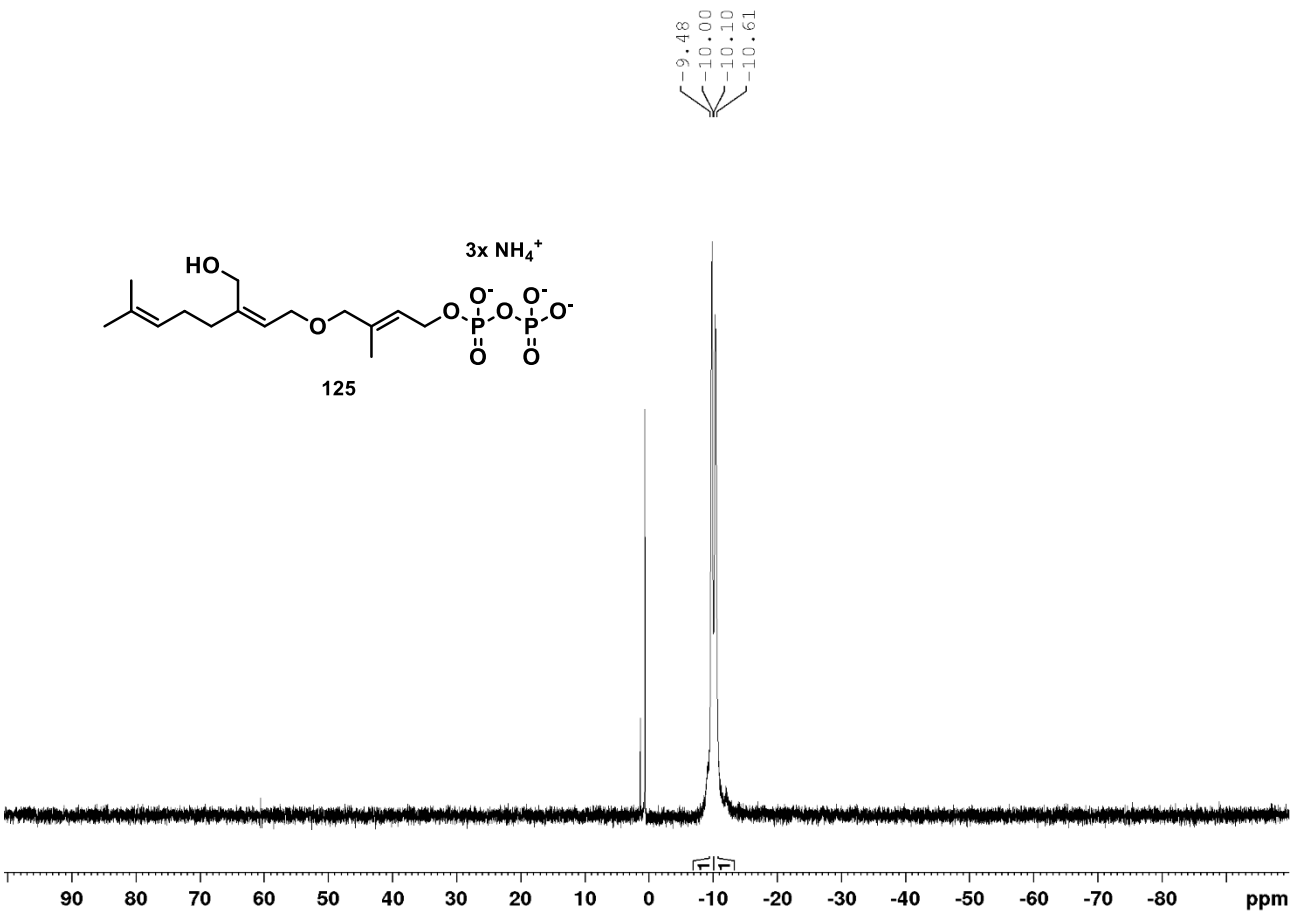

MeO
O
P
O
O
P
O
O
O
O
O
3x NH4+
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

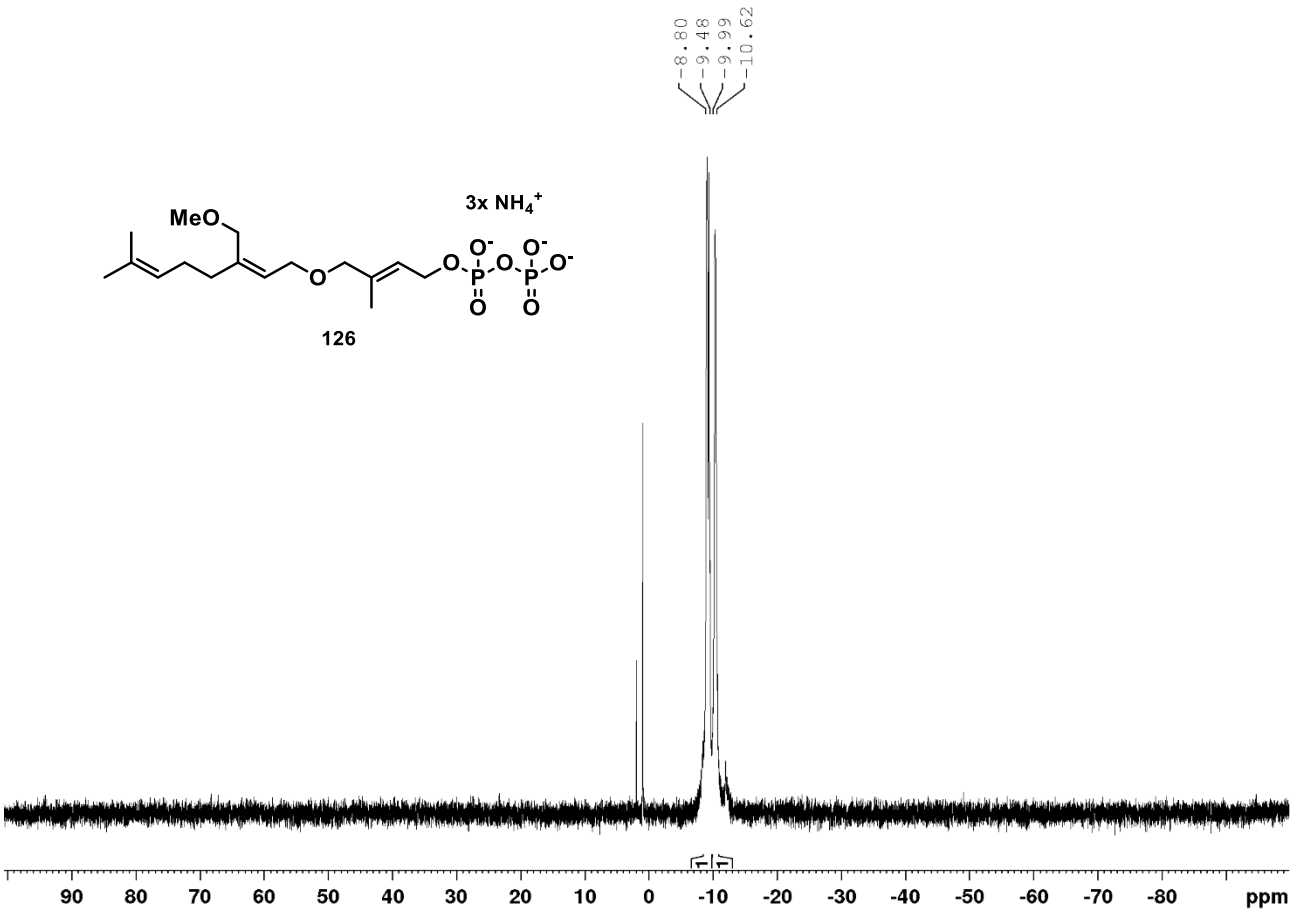
102

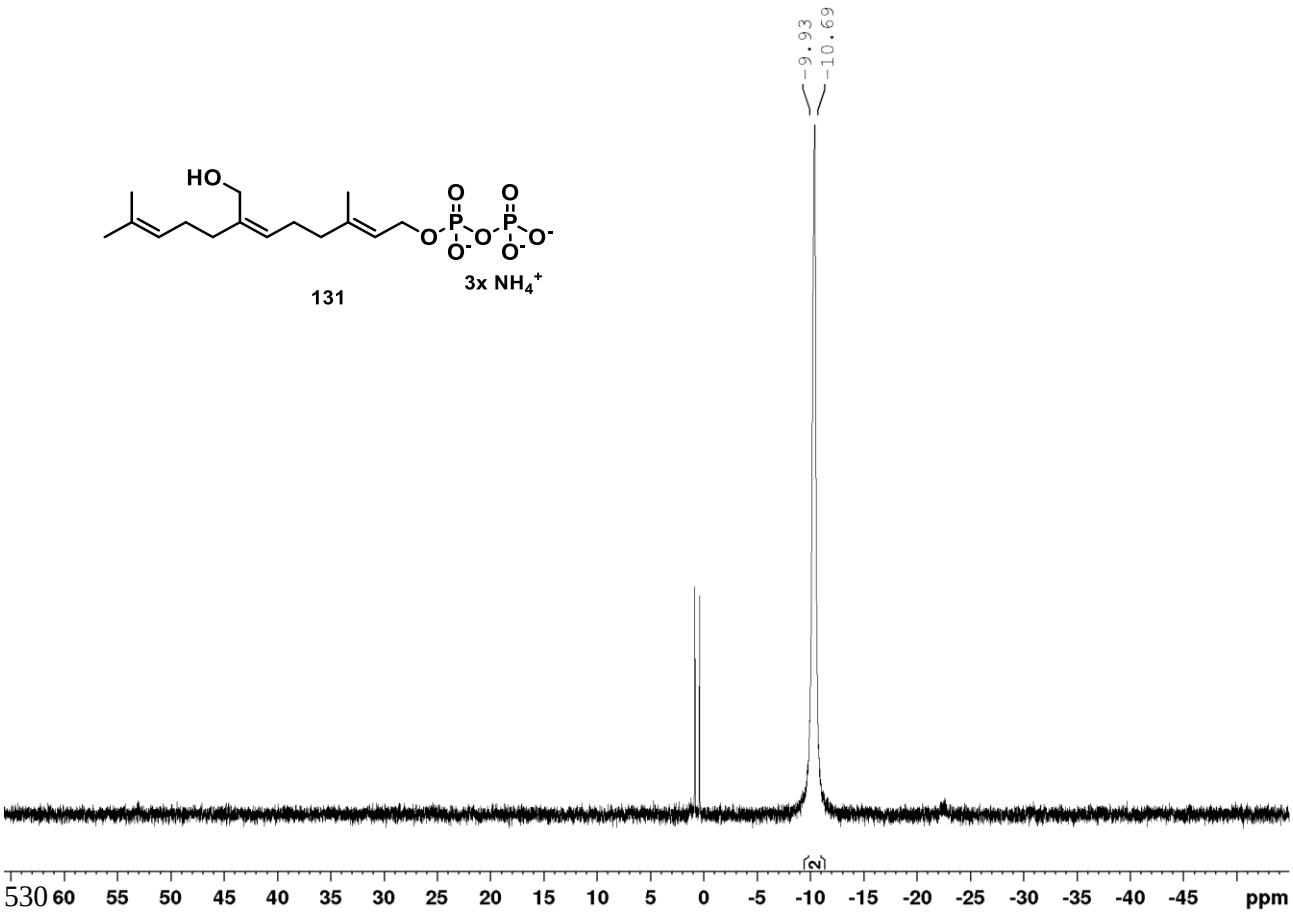

143.1
136.2
131.1
130.9
124.6
119.5
119.4
70.6
62.9
62.9
56.8
38.9
38.8
25.6
25.6
20.7
15.6
15.2
MeO
O
P
O-
3x NH4+
102
220
200
180
160
140
120
100
80
60
40
20
0
ppm

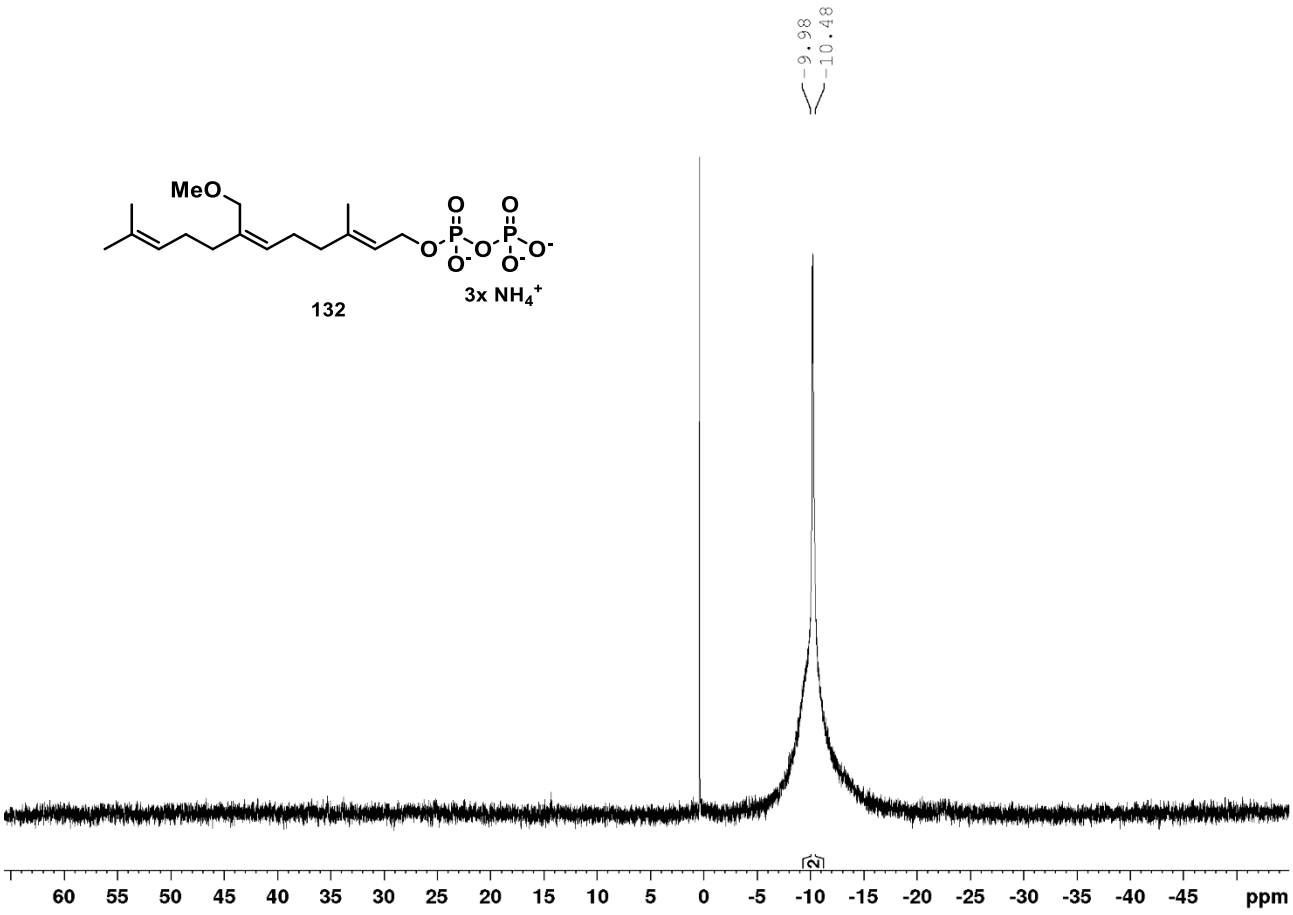
10.3 ^{31}P NMR-Spectra

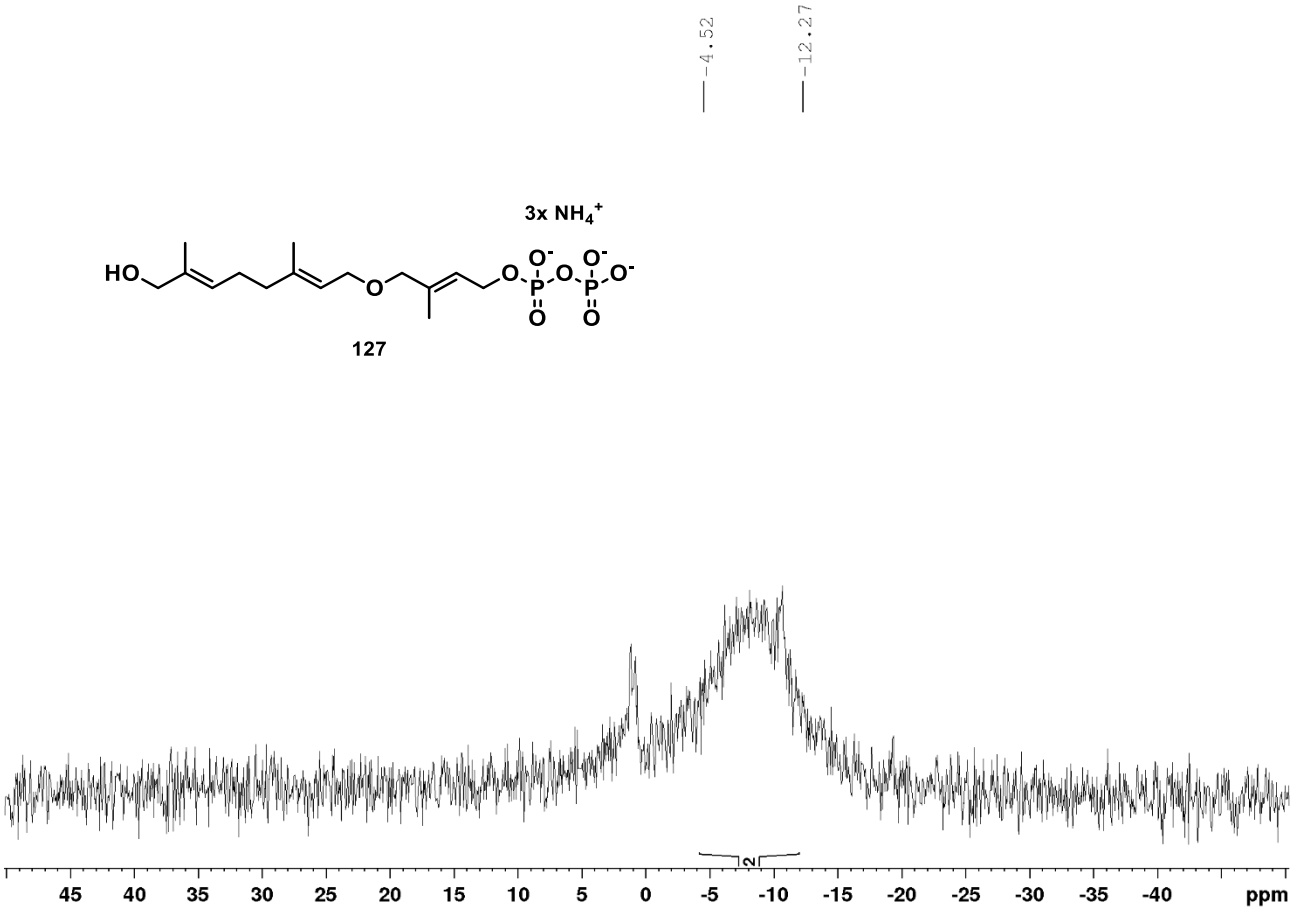


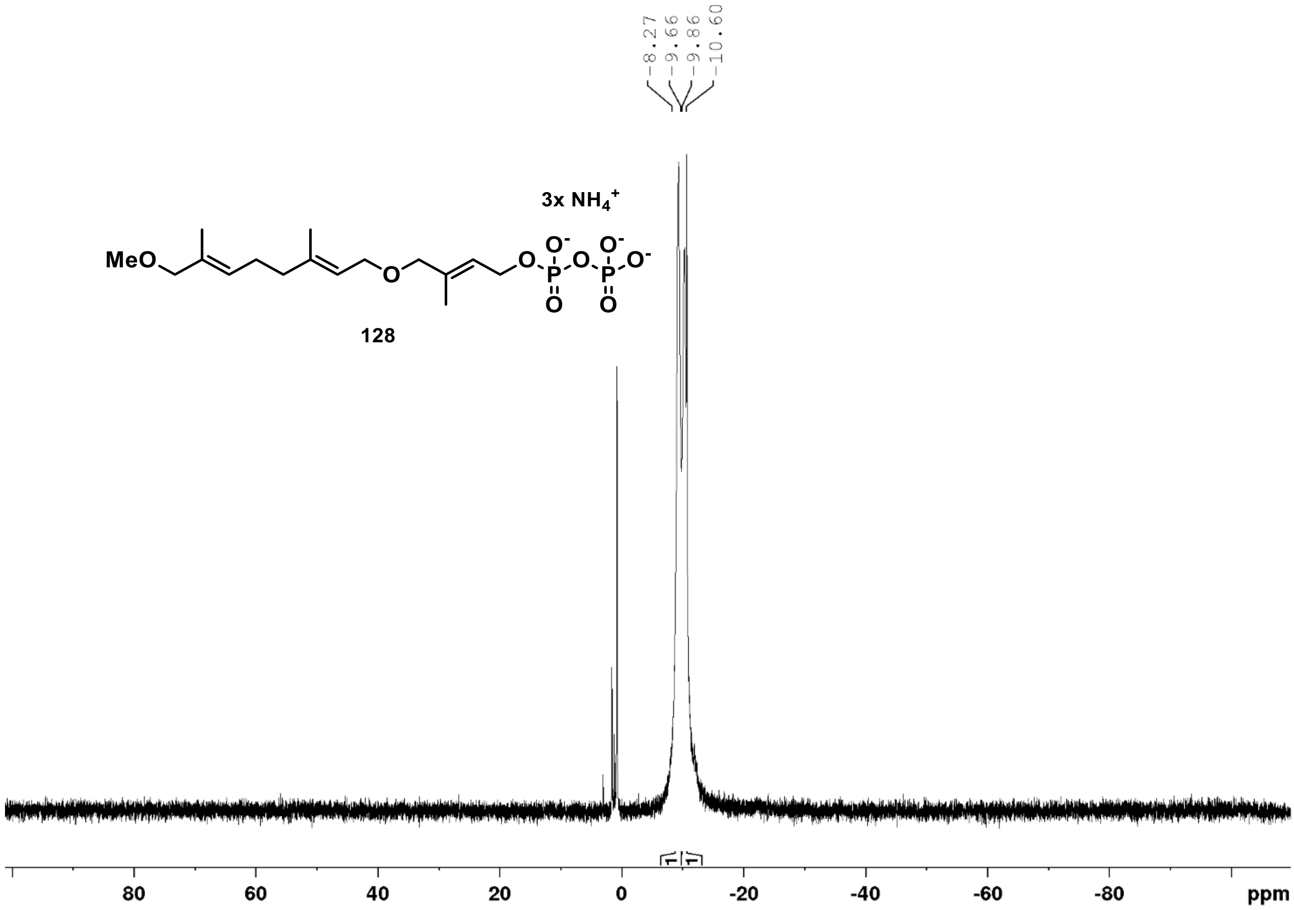


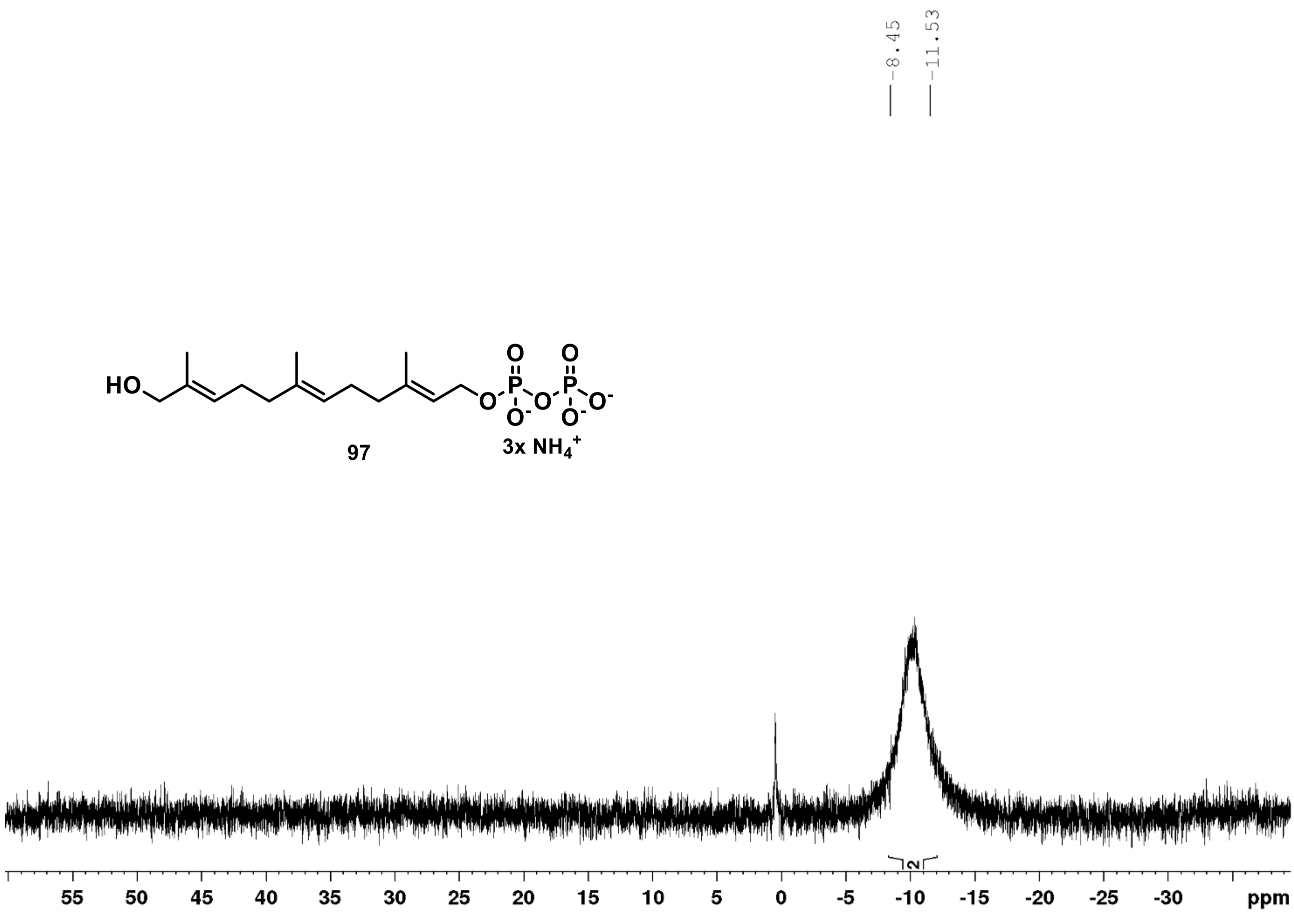

-8.80
-9.48
-9.99
-10.62
MeO
3x NH4+
126
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 ppm

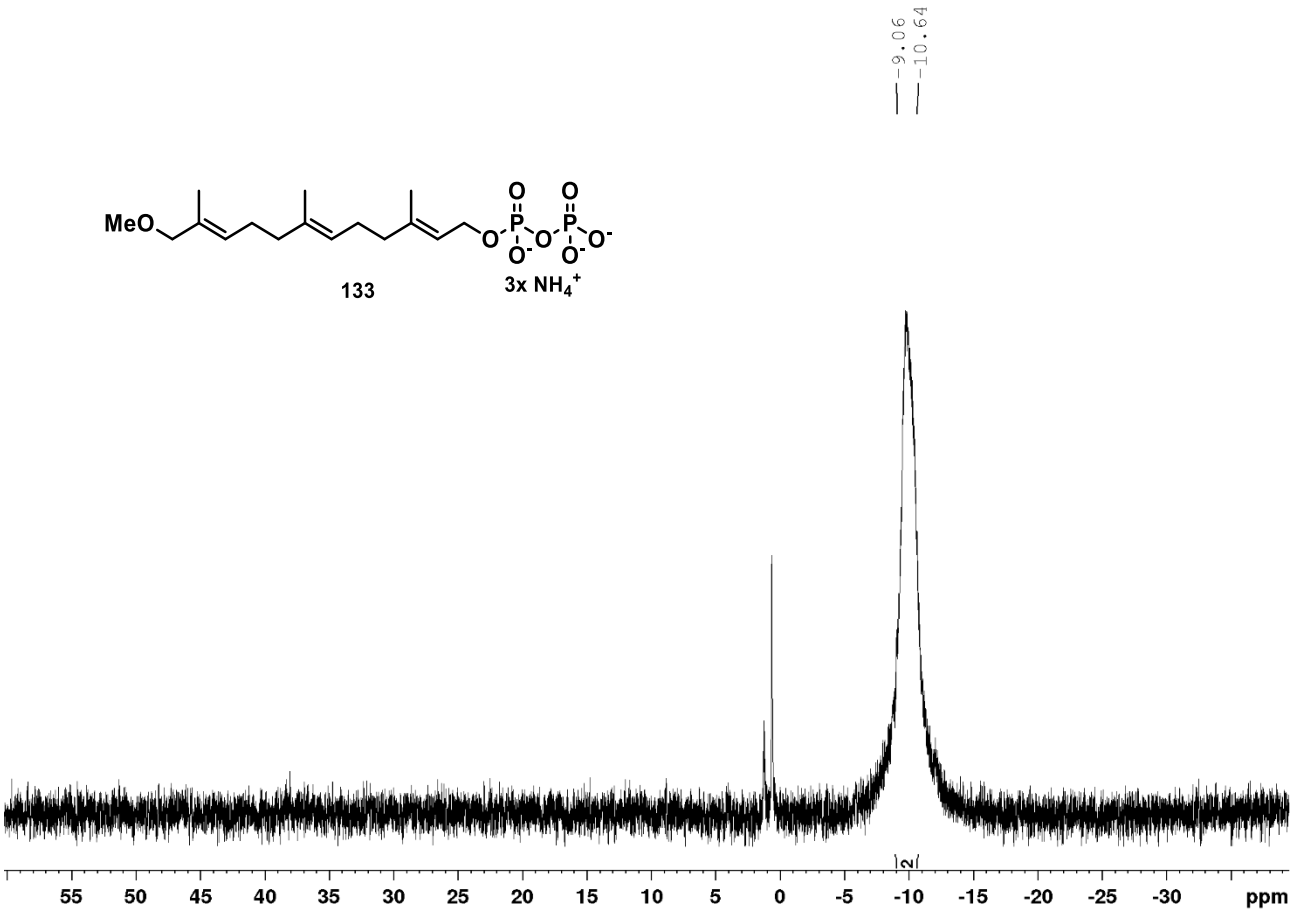

-9.93
-10.69
HO
131
3x NH4+
60 55 50 45 40 35 30 25 20 15 10 5 0 -5 -10 -15 -20 -25 -30 -35 -40 -45 ppm

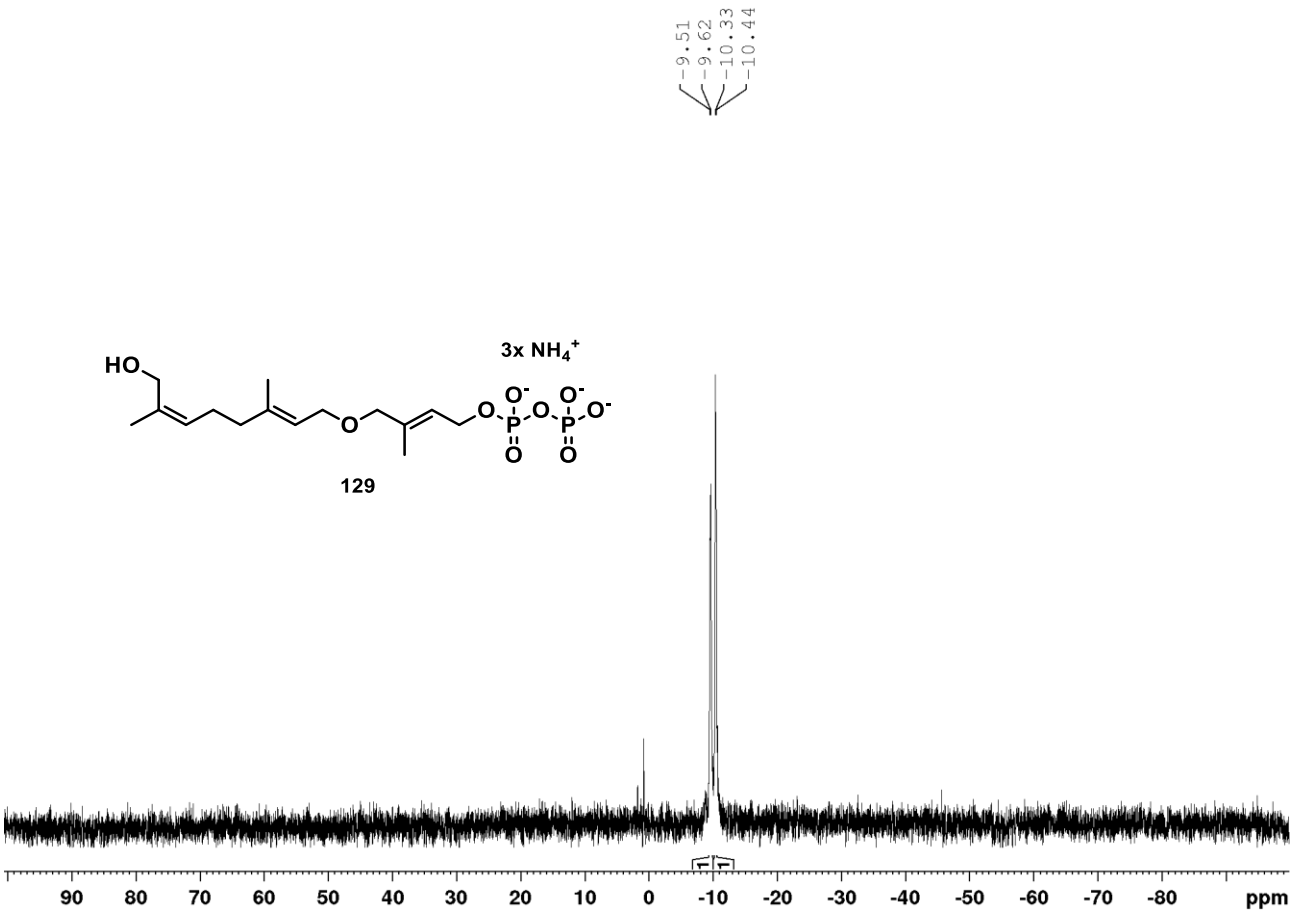

-9.98
-10.48
MeO
O
O
P
O
O
P
O
O
O
O
O
3x NH4+
132
60 55 50 45 40 35 30 25 20 15 10 5 0 -5 -10 -15 -20 -25 -30 -35 -40 -45 ppm

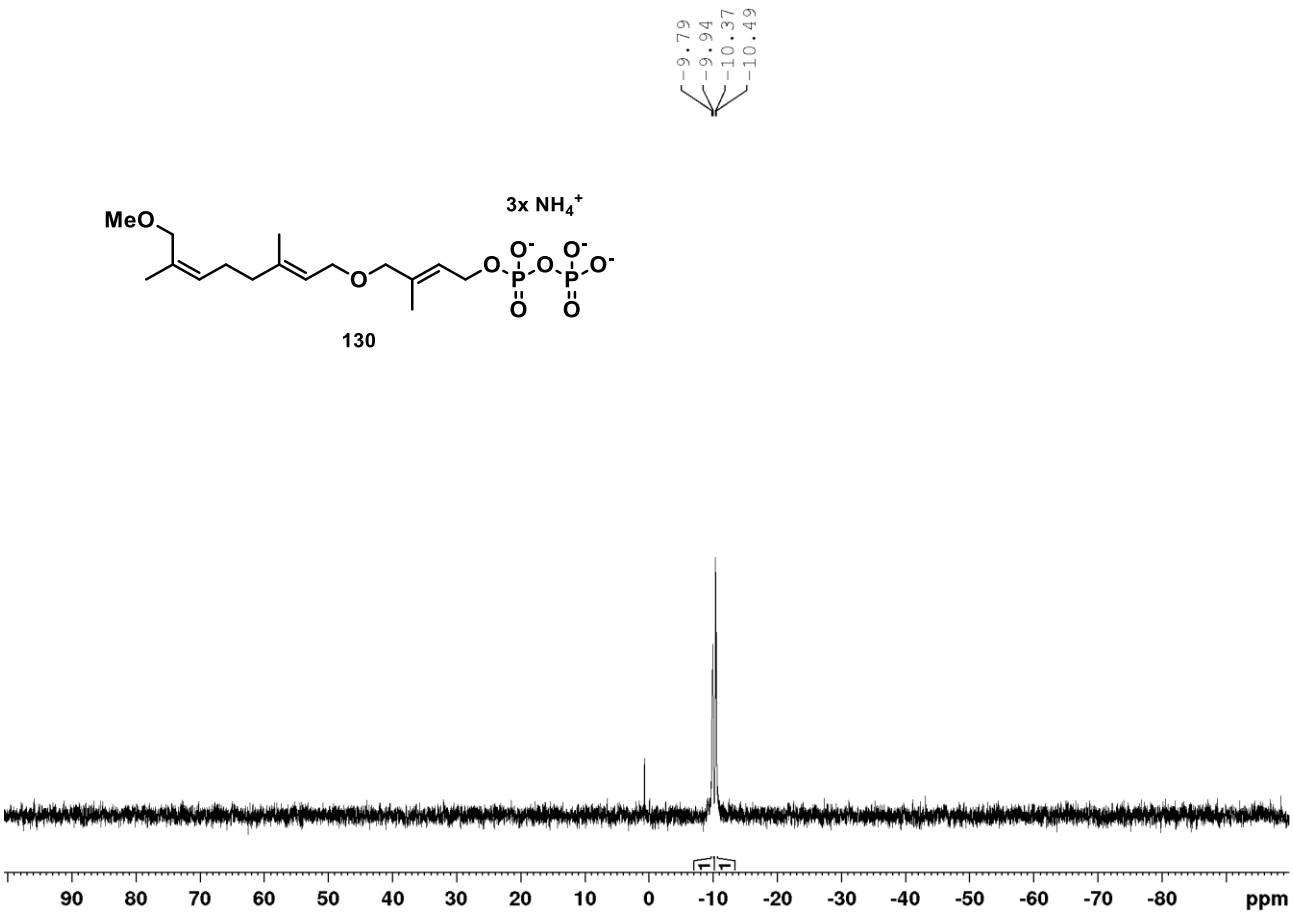

-4.52
-12.27
3x NH4+
HO
O
O
O
O
O
O
O
O
P
P
127
45 40 35 30 25 20 15 10 5 0 -5 -10 -15 -20 -25 -30 -35 -40 ppm

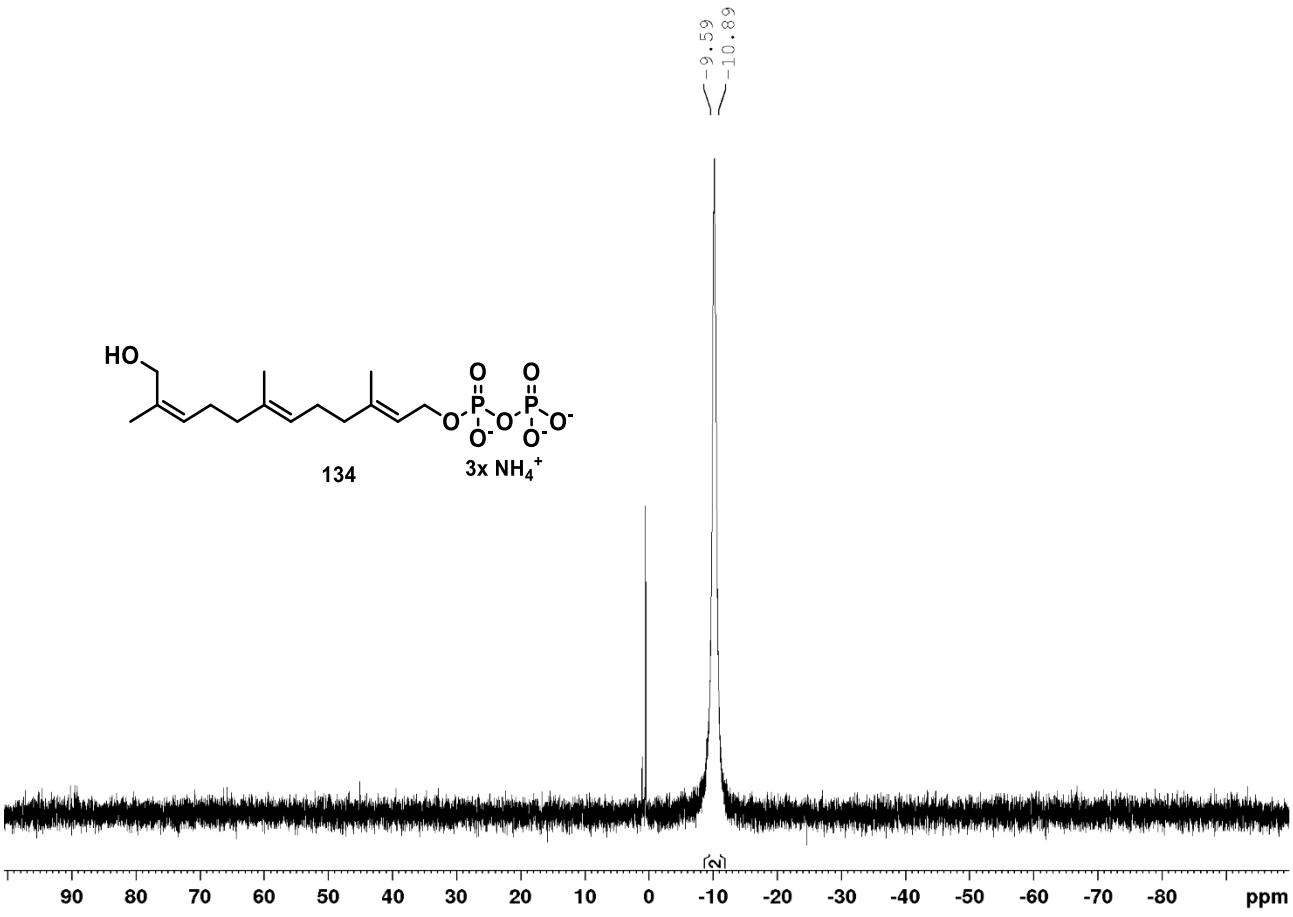

-8.27
-9.66
-9.86
-10.60
3x NH_4^+
MeO
128
1
1
80
60
40
20
0
-20
-40
-60
-80
ppm

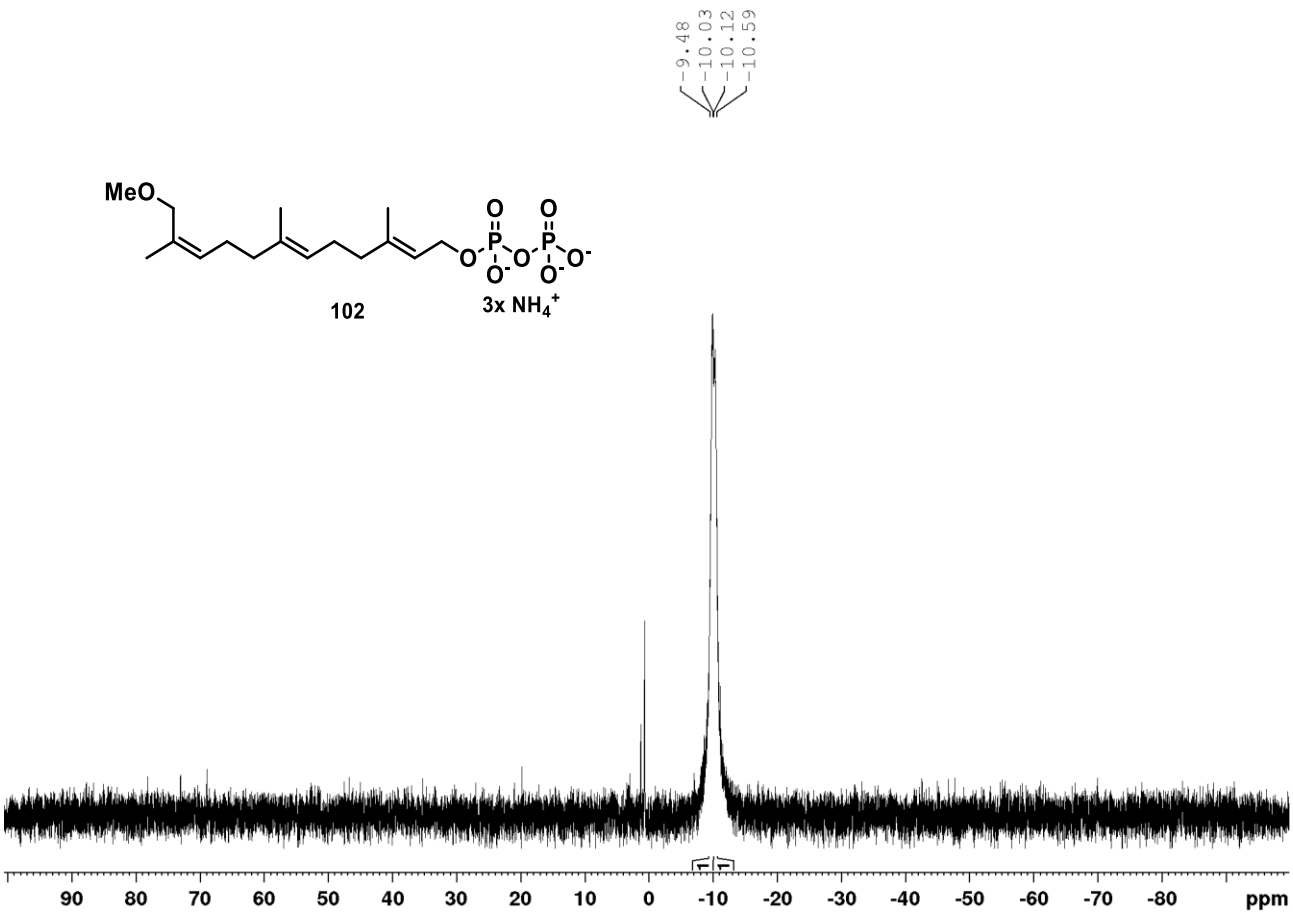

-8.45
-11.53
HO
97
3x NH_4^+
2
55
50
45
40
35
30
25
20
15
10
5
0
-5
-10
-15
-20
-25
-30
ppm


-9.06
-10.64
MeO
133
3x NH4+
55 50 45 40 35 30 25 20 15 10 5 0 -5 -10 -15 -20 -25 -30 ppm

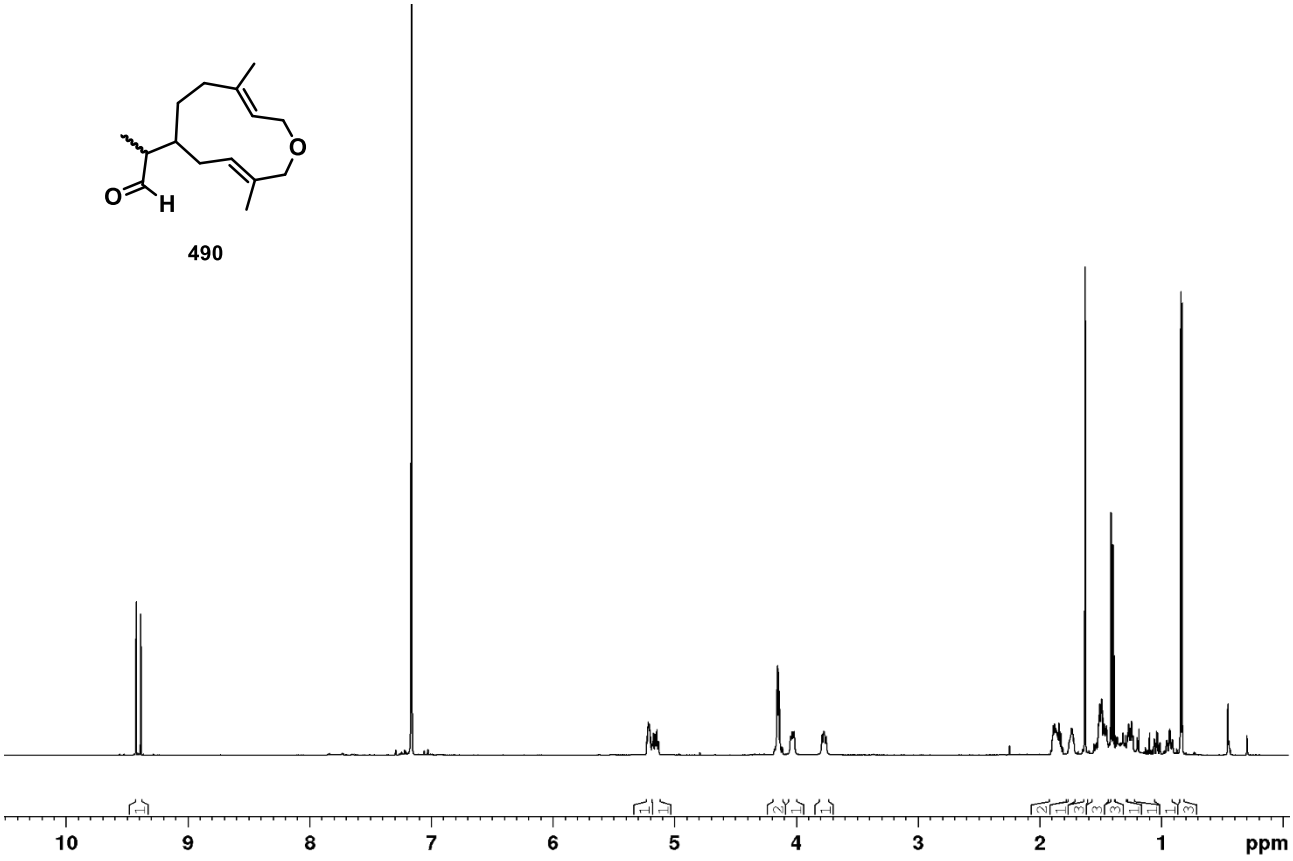

-9.51
-9.62
-10.33
-10.44
HO
3x NH4+
129
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 ppm

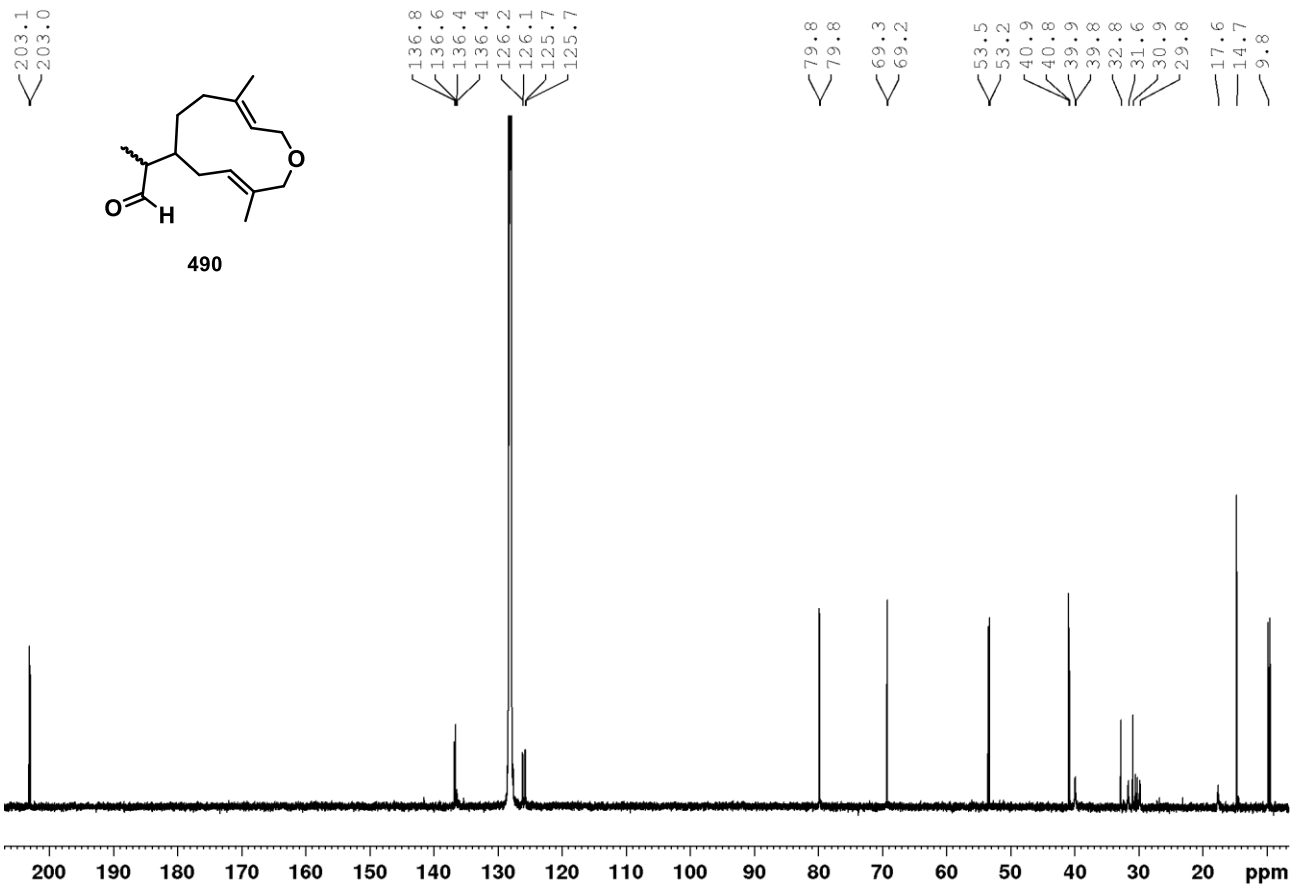

-9.79
-9.94
-10.37
-10.49
MeO
3x NH4+
130
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 ppm


-9.59
-10.89
HO
134
3x NH4+
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 ppm

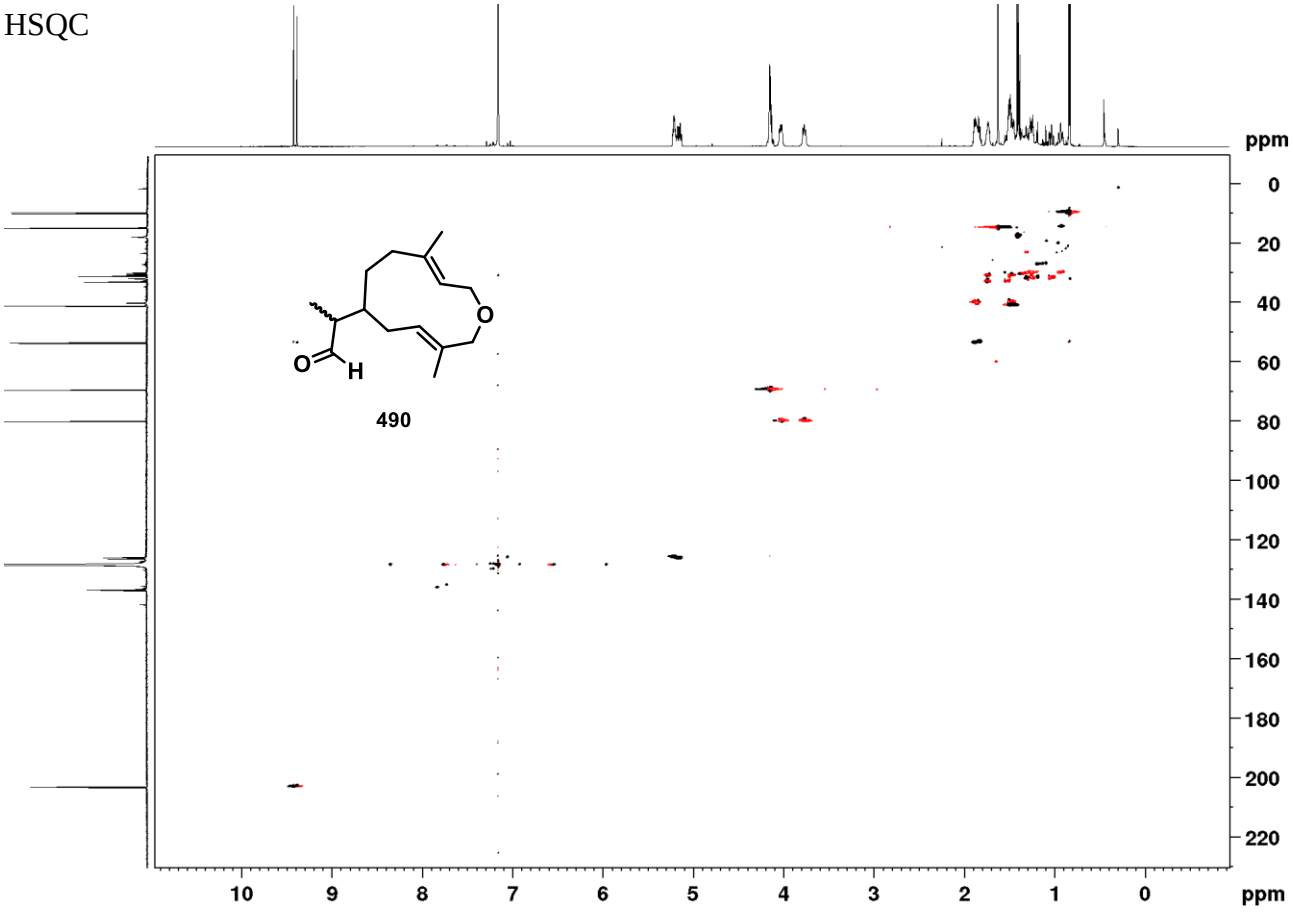

-9.48
-10.03
-10.12
-10.59
MeO
O
O
P
O
O
O
O
P
O
O
O
102
3x NH4+
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
ppm

10.4 Biotransformation Products NMR-Spectra

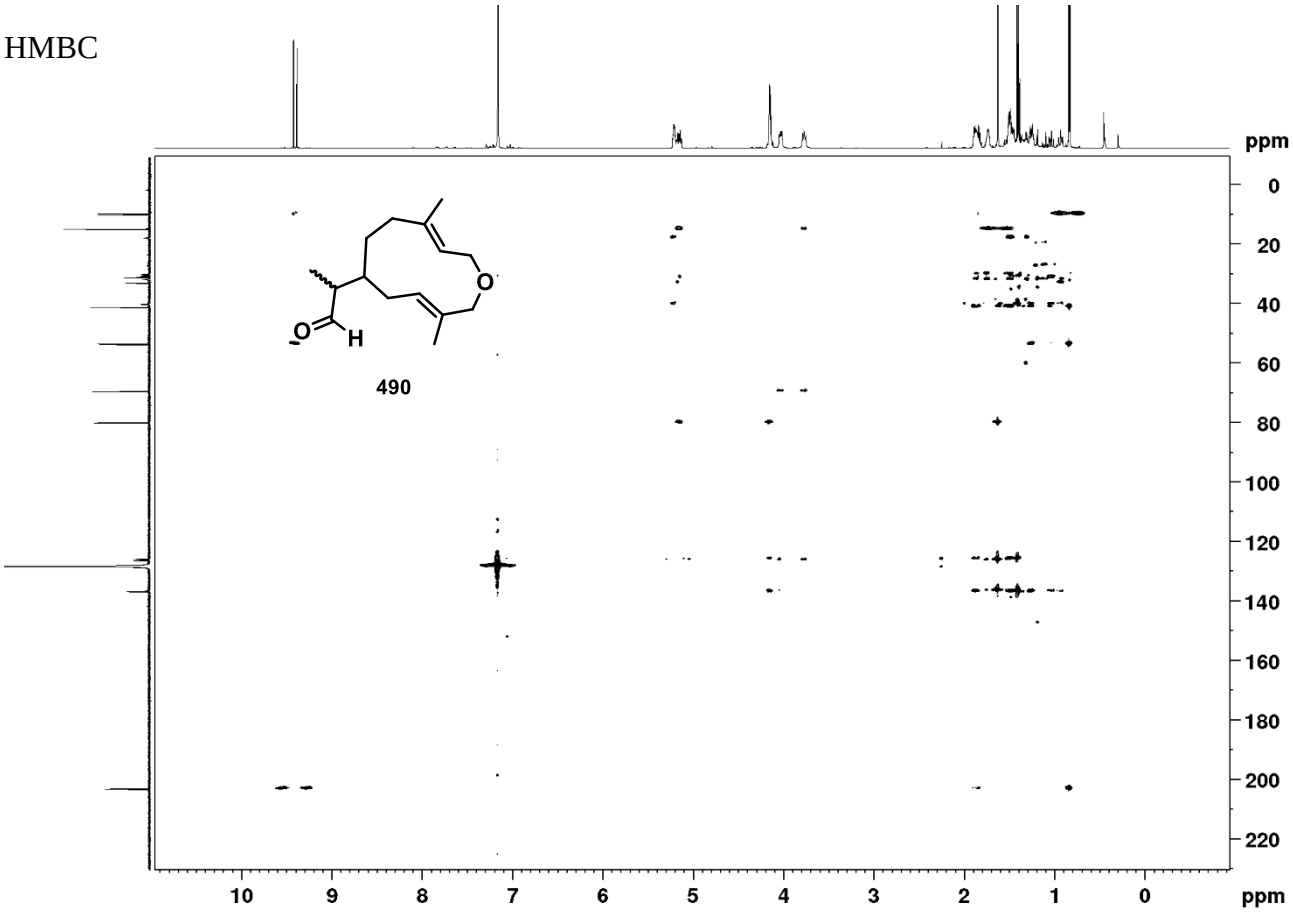




HSQC


ppm
0
20
40
60
80
100
120
140
160
180
200
220
10
9
8
7
6
5
4
3
2
1
0
ppm
O
O
H
490

HMBC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7
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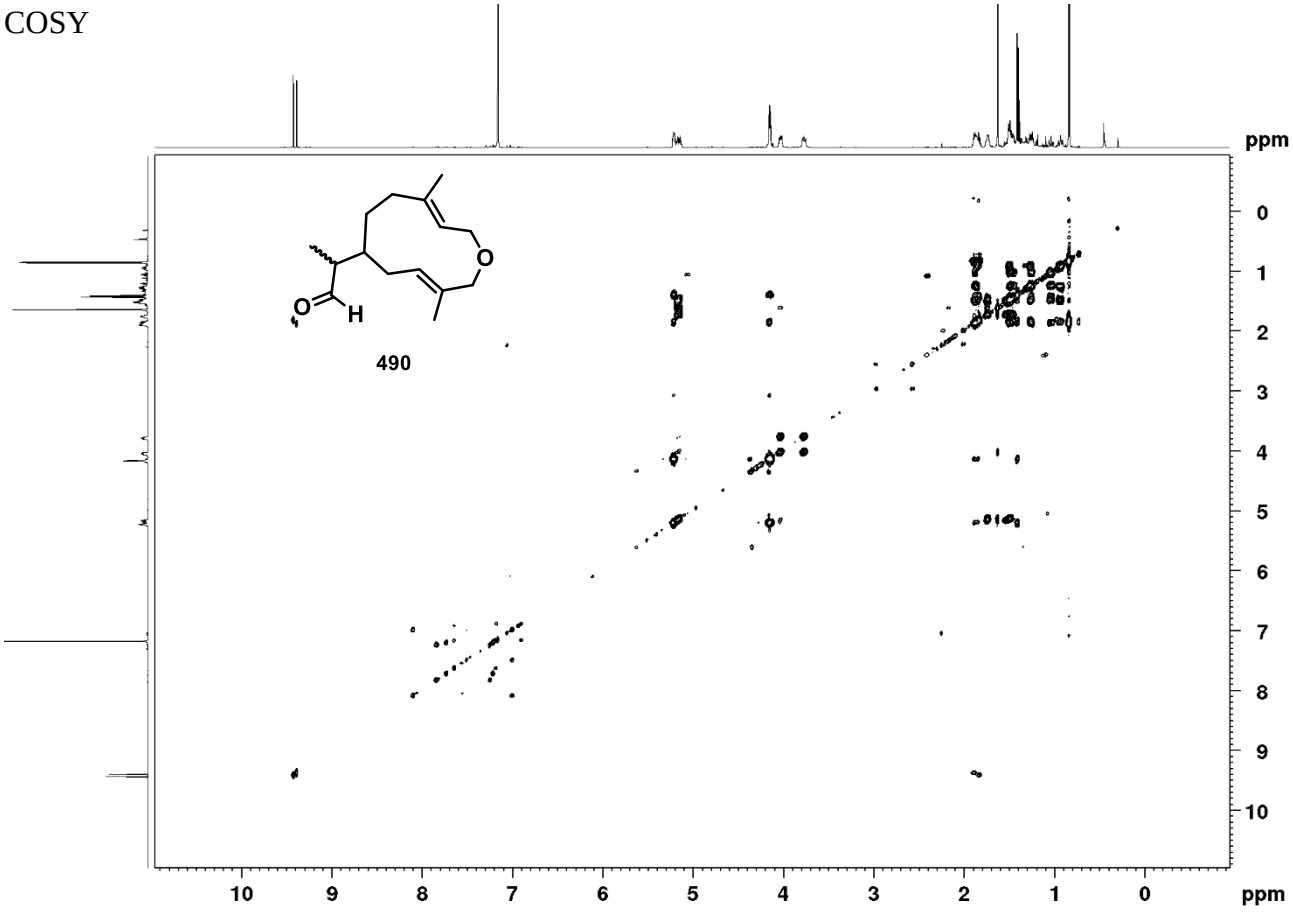
0
ppm
O
O
H
490

COSY


O
O
H
490
ppm
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2
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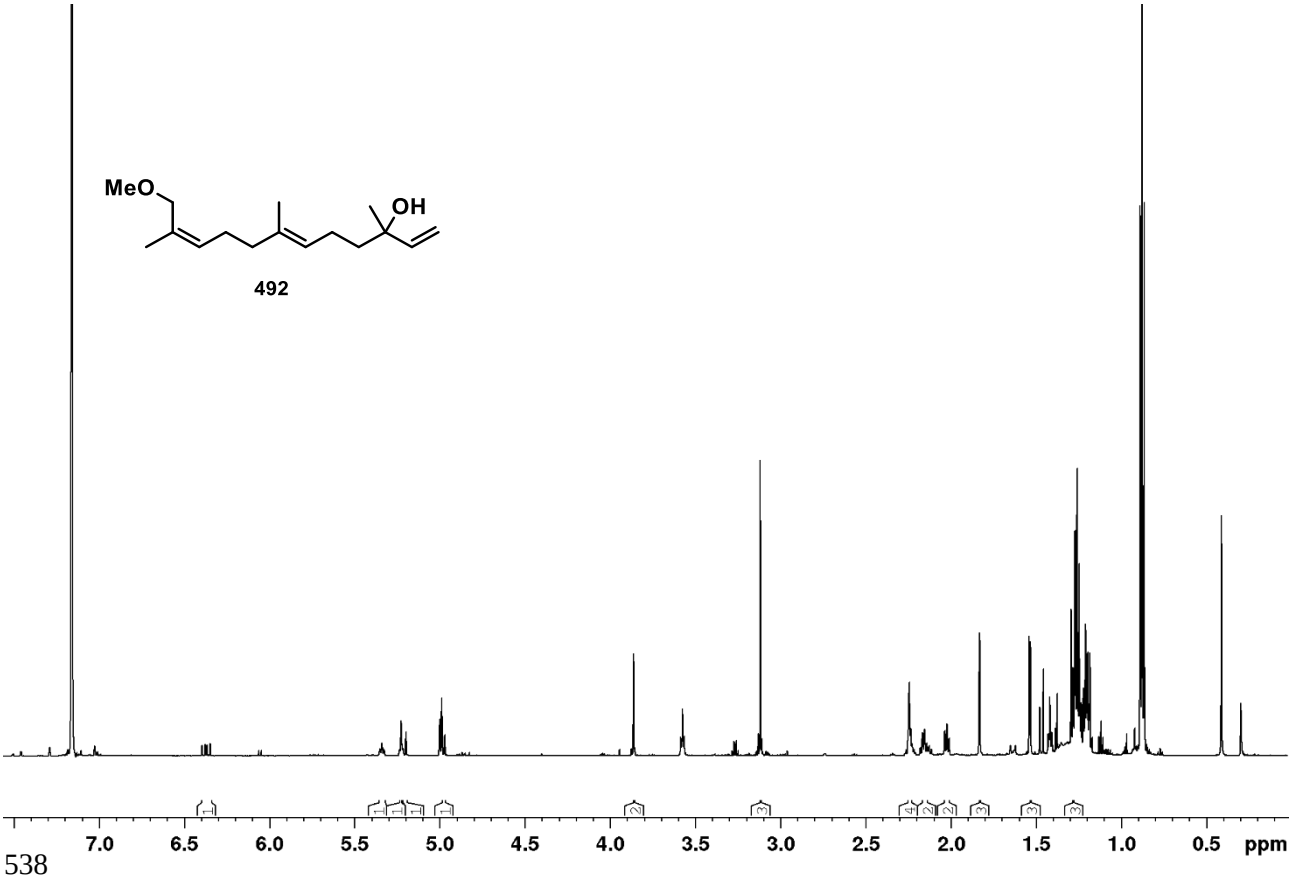
0
ppm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OH
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3.0
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2.0
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1.0
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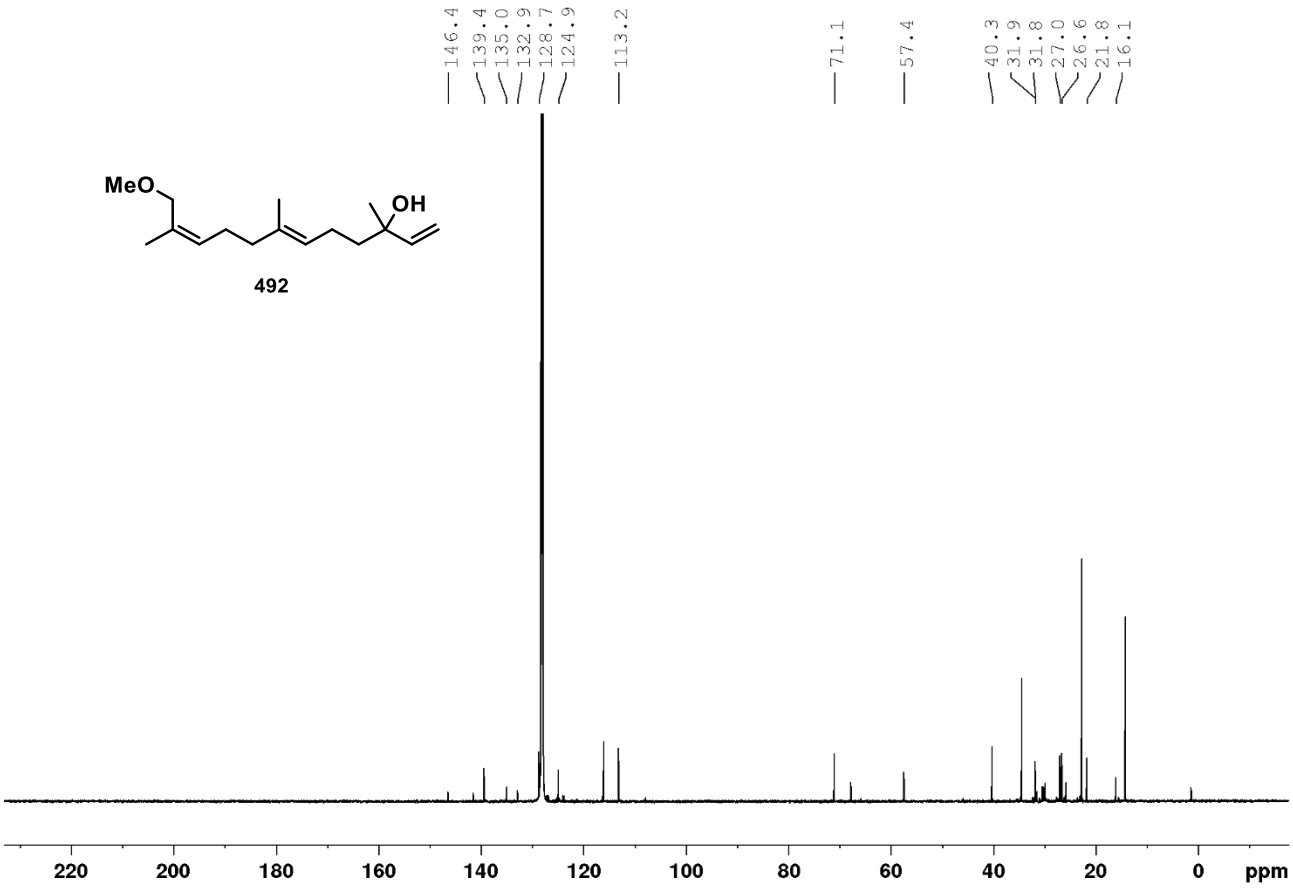
ppm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113.2
71.1
57.4
40.3
31.9
31.8
27.0
26.6
21.8
16.1
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OH
492
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180
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140
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100
80
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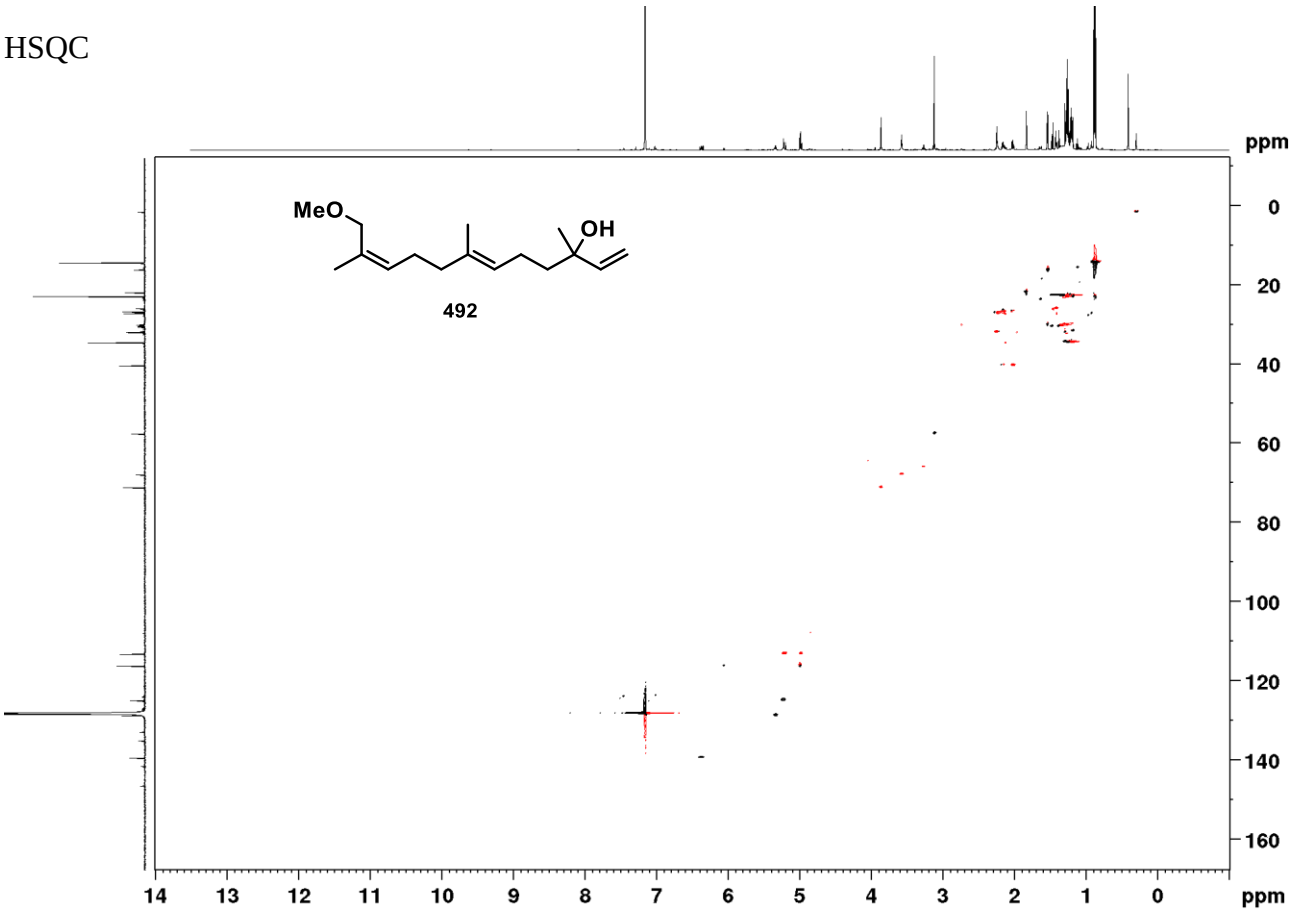
20
0
ppm

HSQC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OH
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1
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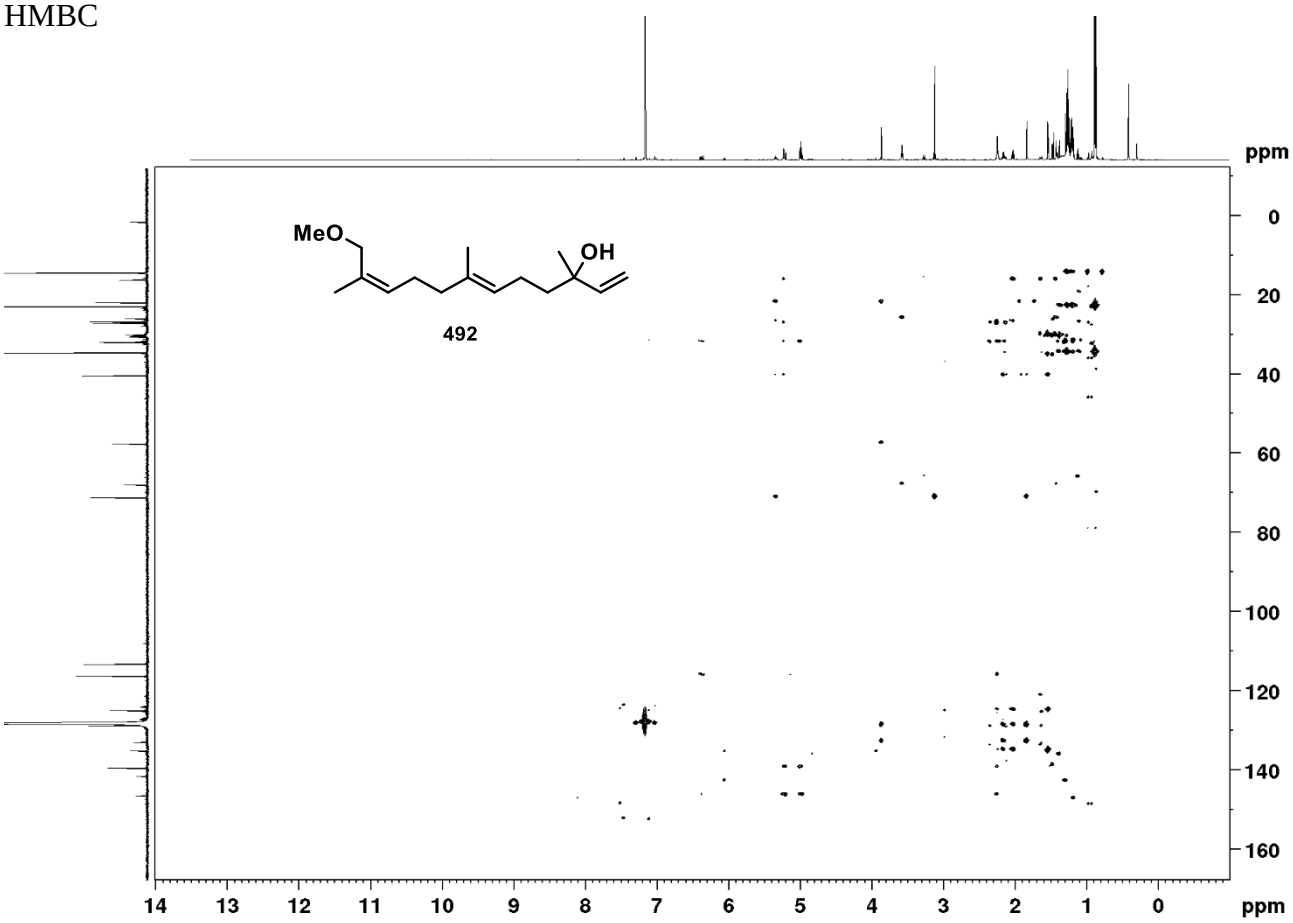
ppm

HMBC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OH
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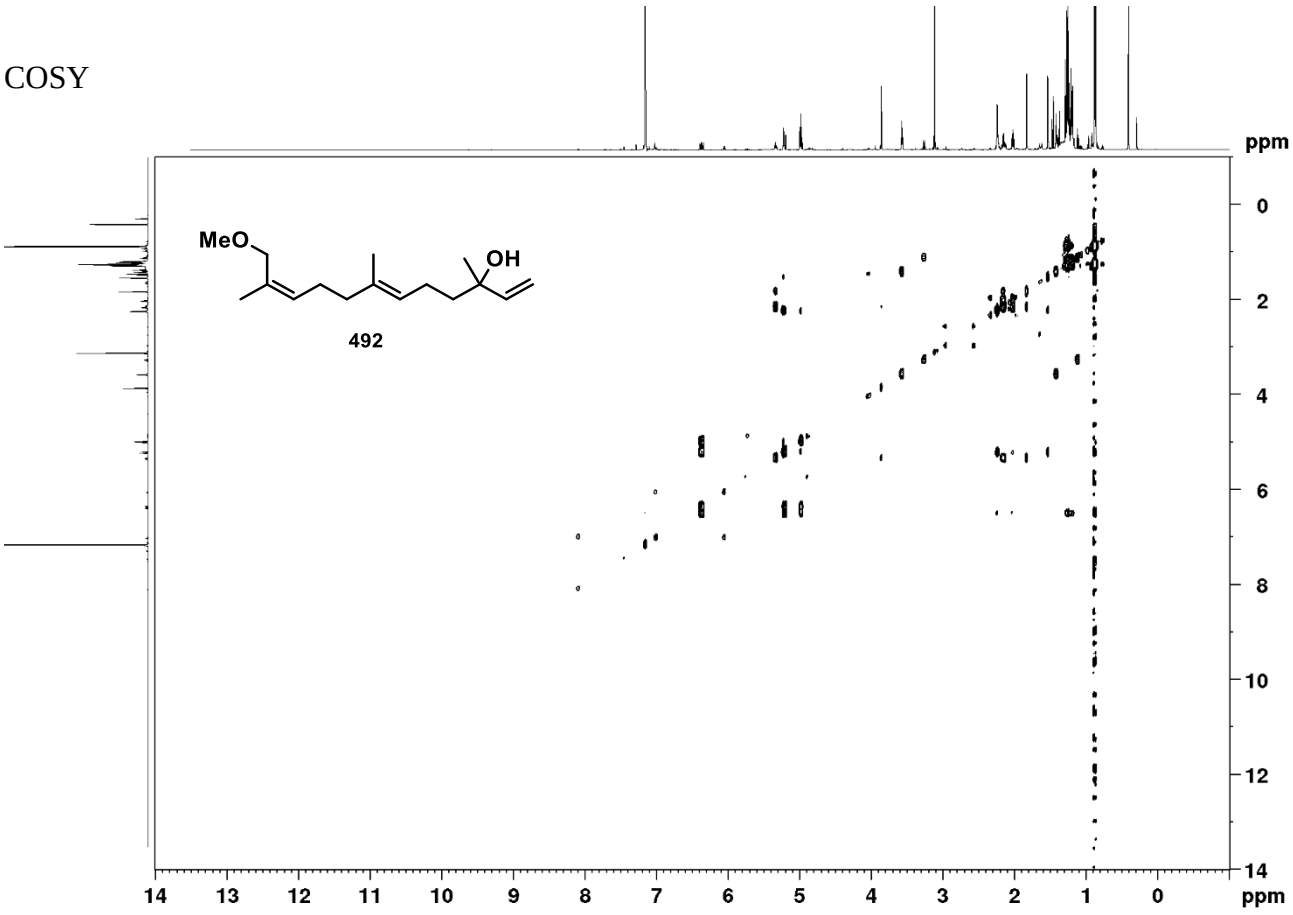
80
100
120
140
160
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0
ppm

COSY


MeO
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14
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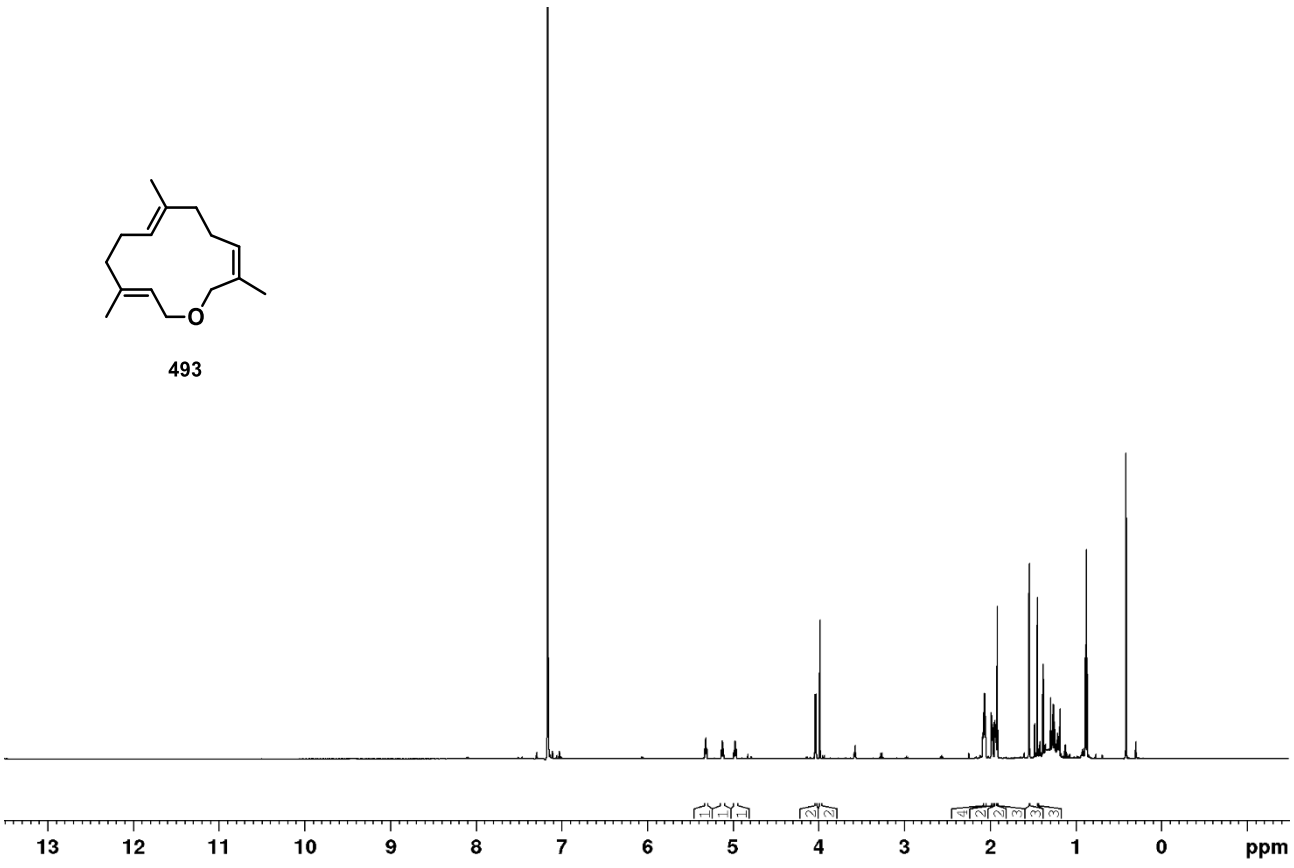
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2
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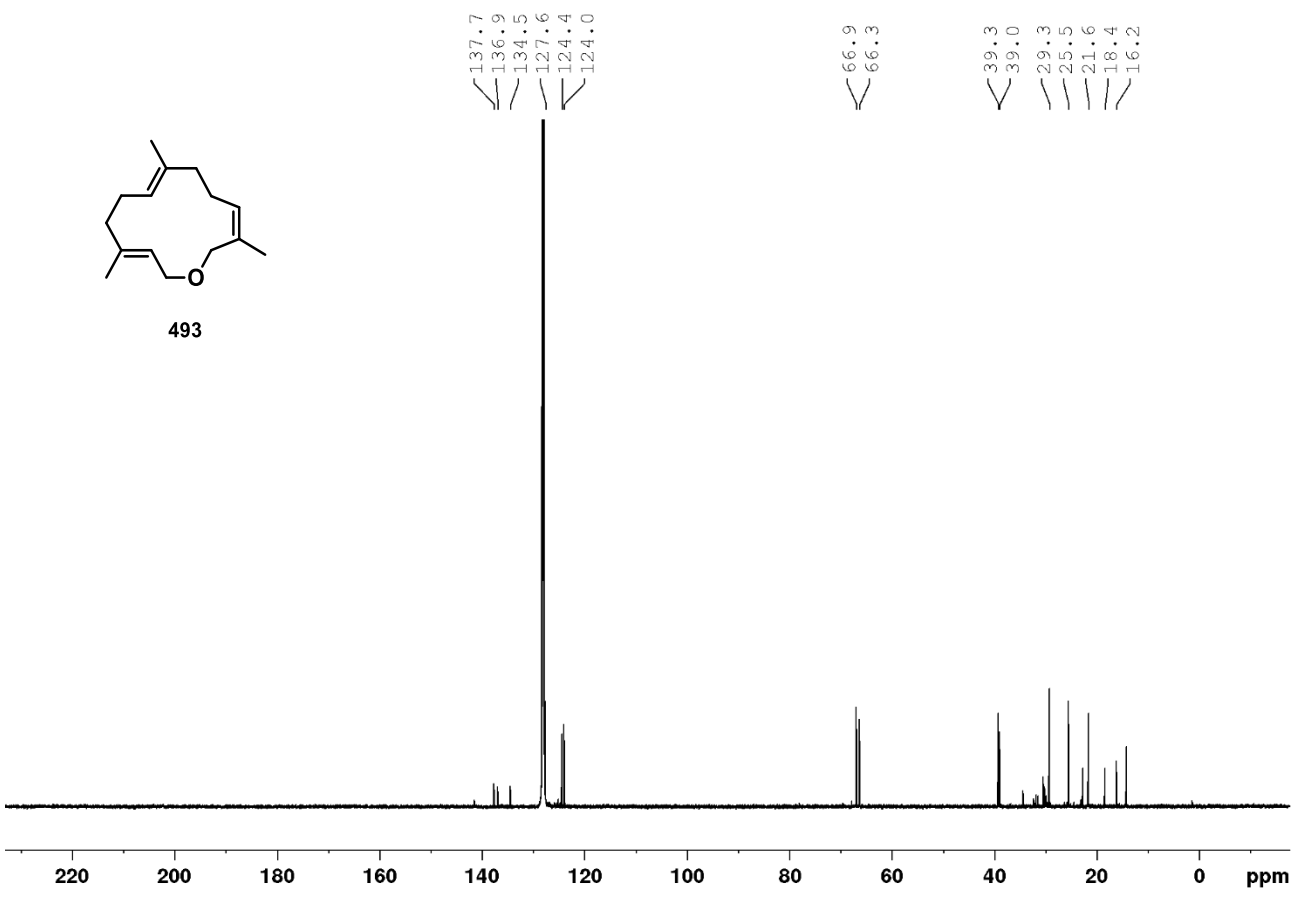
ppm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136.9
134.5
127.6
124.4
124.0
66.9
66.3
39.3
39.0
29.3
25.5
21.6
18.4
16.2
493
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200
180
160
140
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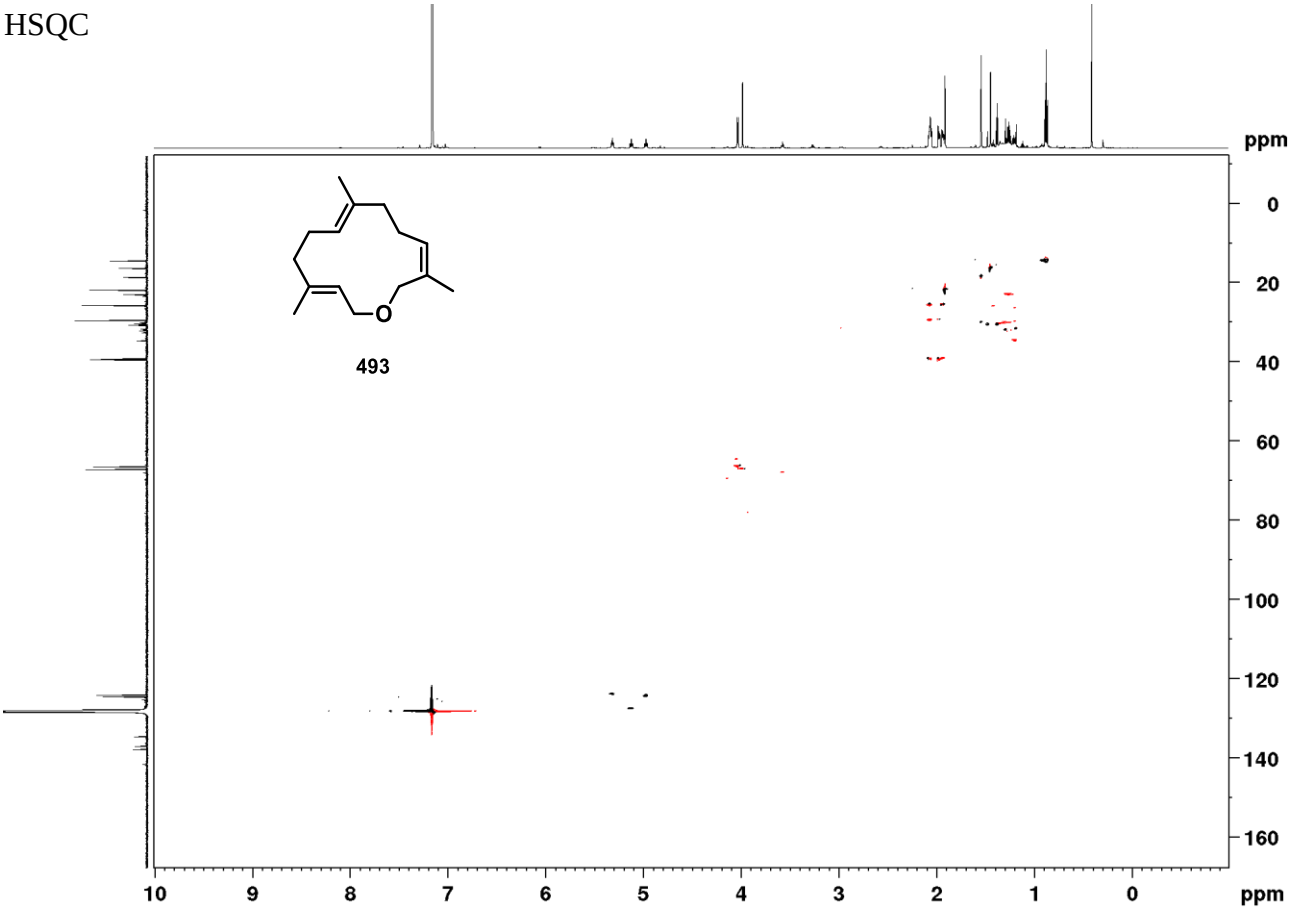
100
80
60
40
20
0
ppm

HSQC


ppm
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100
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140
160
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8
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4
3
2
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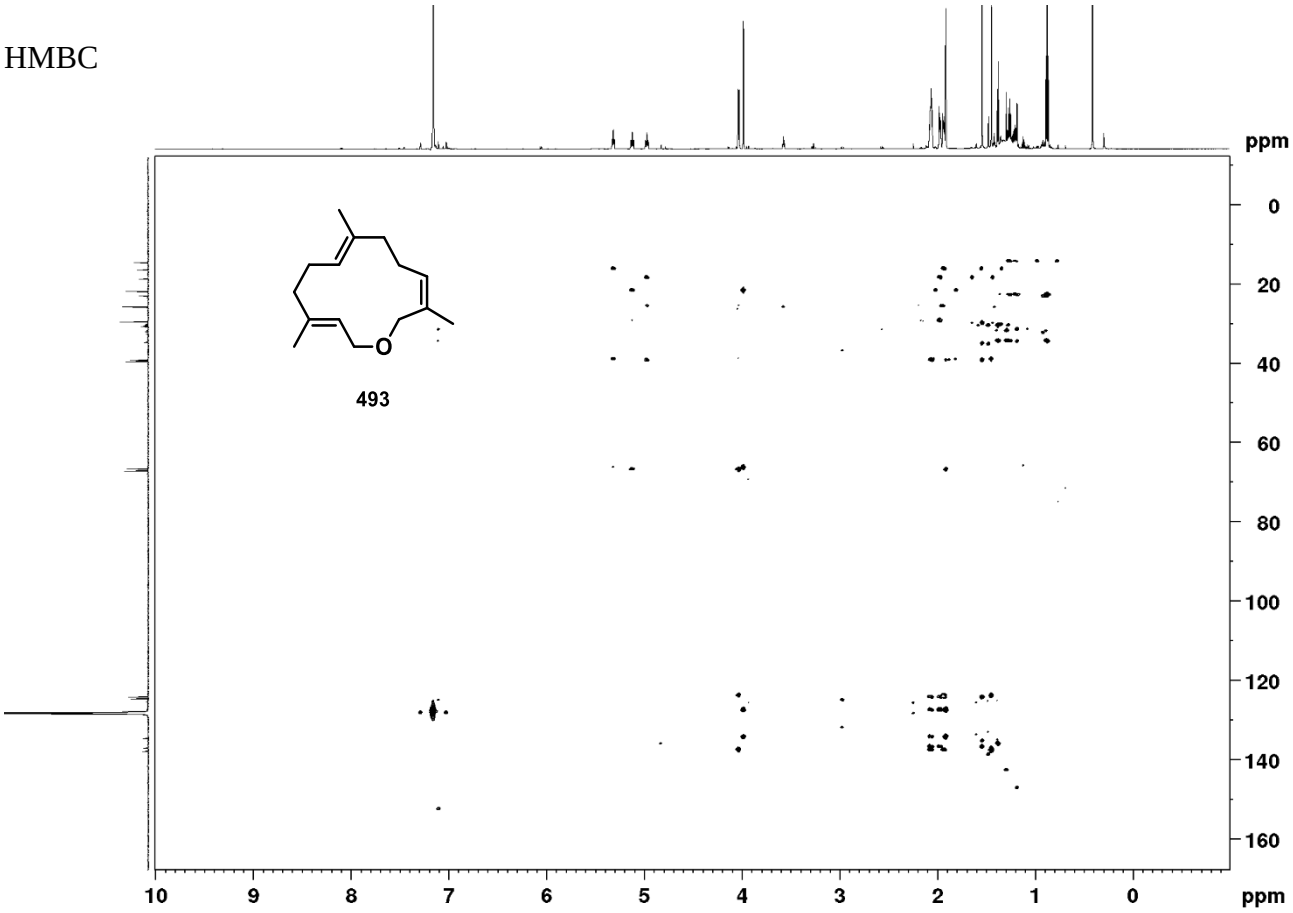
ppm
493

HMBC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100
120
140
160
10
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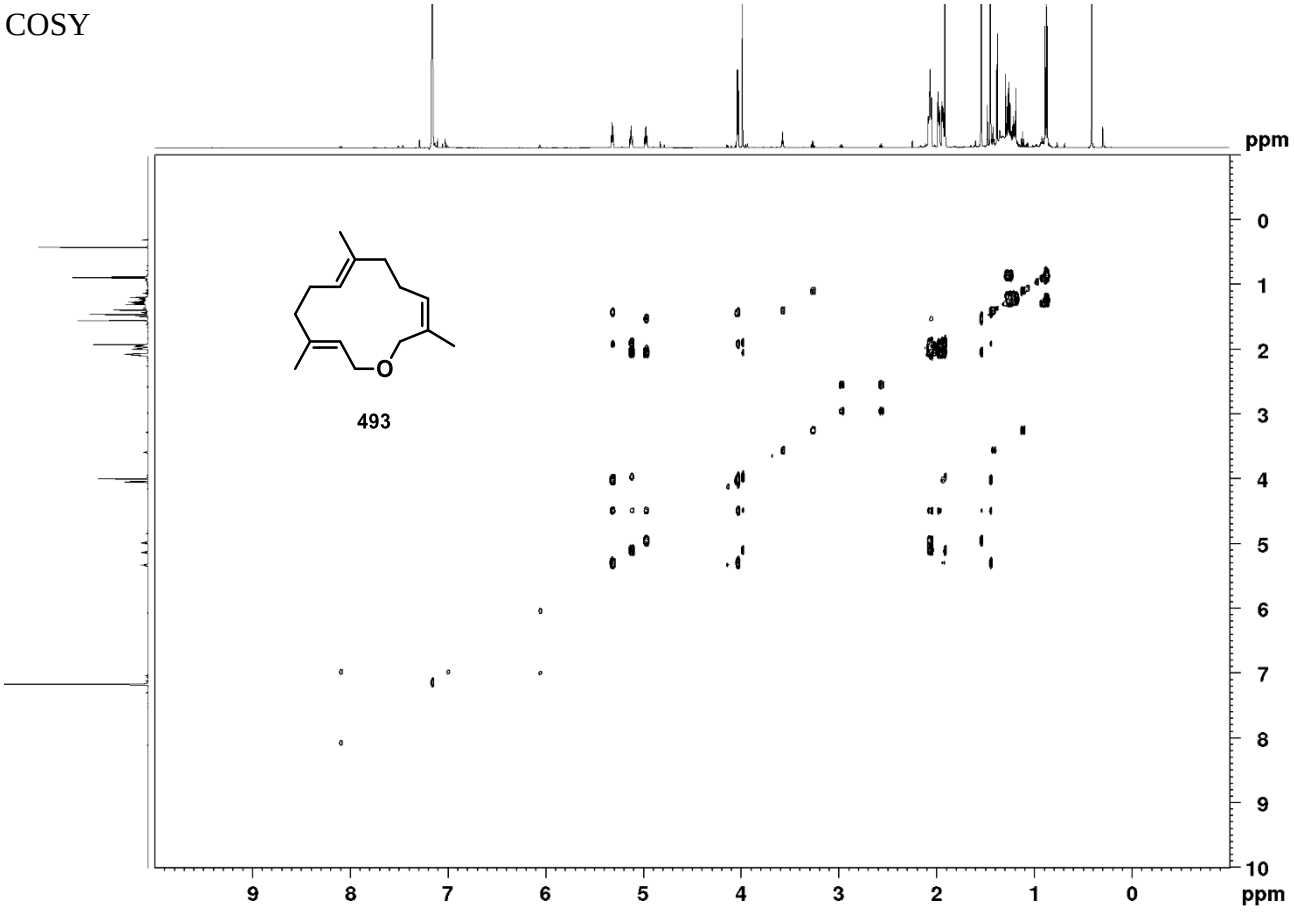
8
7
6
5
4
3
2
1
0
ppm
493

COSY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8
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5
4
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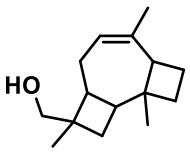
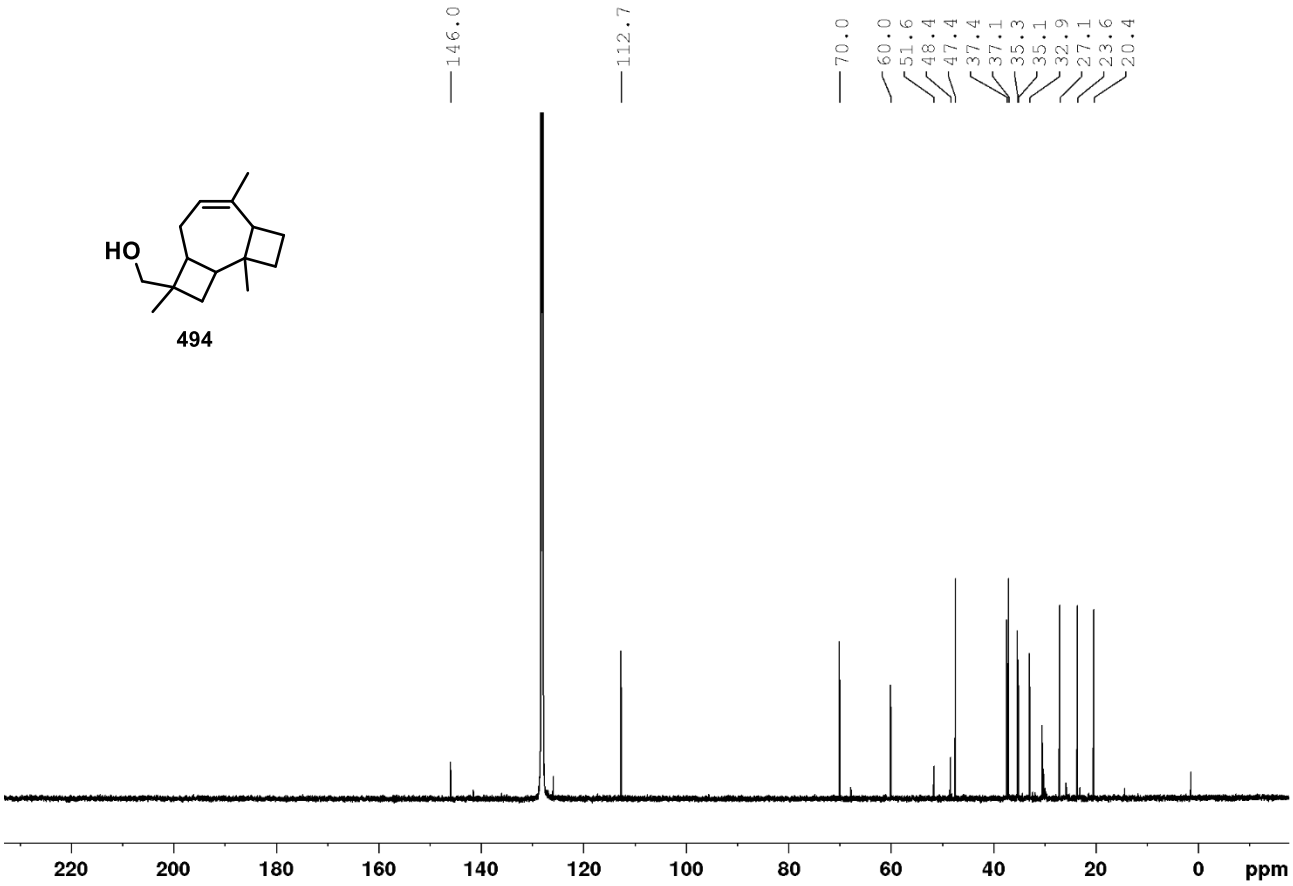
1
0
ppm

493


HO

494

13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm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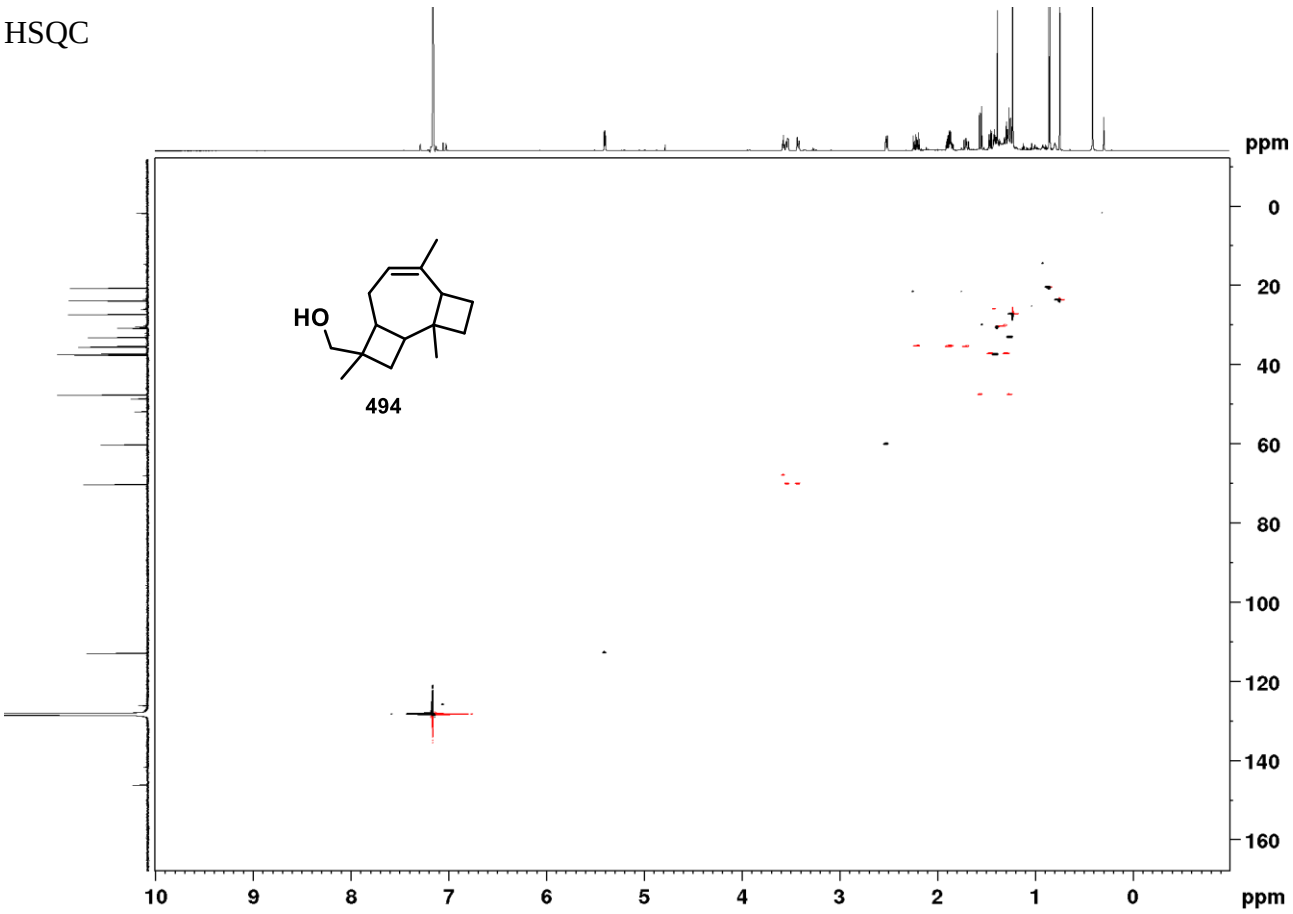
112.7
70.0
60.0
51.6
48.4
47.4
37.4
37.1
35.3
35.1
32.9
27.1
23.6
20.4
HO
494
220
200
180
160
140
120
100
80
60
40
20
0
ppm

HSQC


HO
494
ppm
0
20
40
60
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120
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160
10
9
8
7
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4
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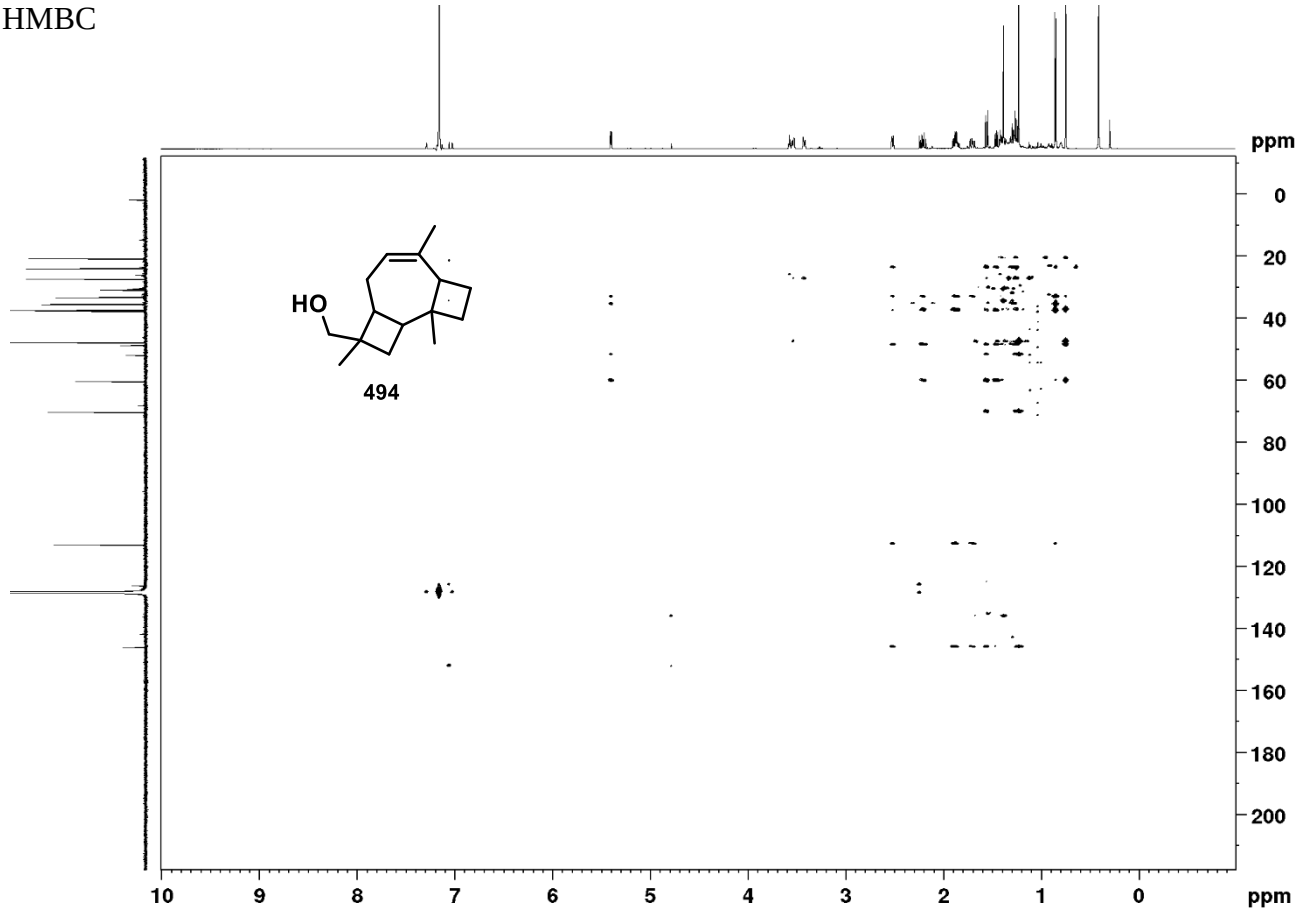
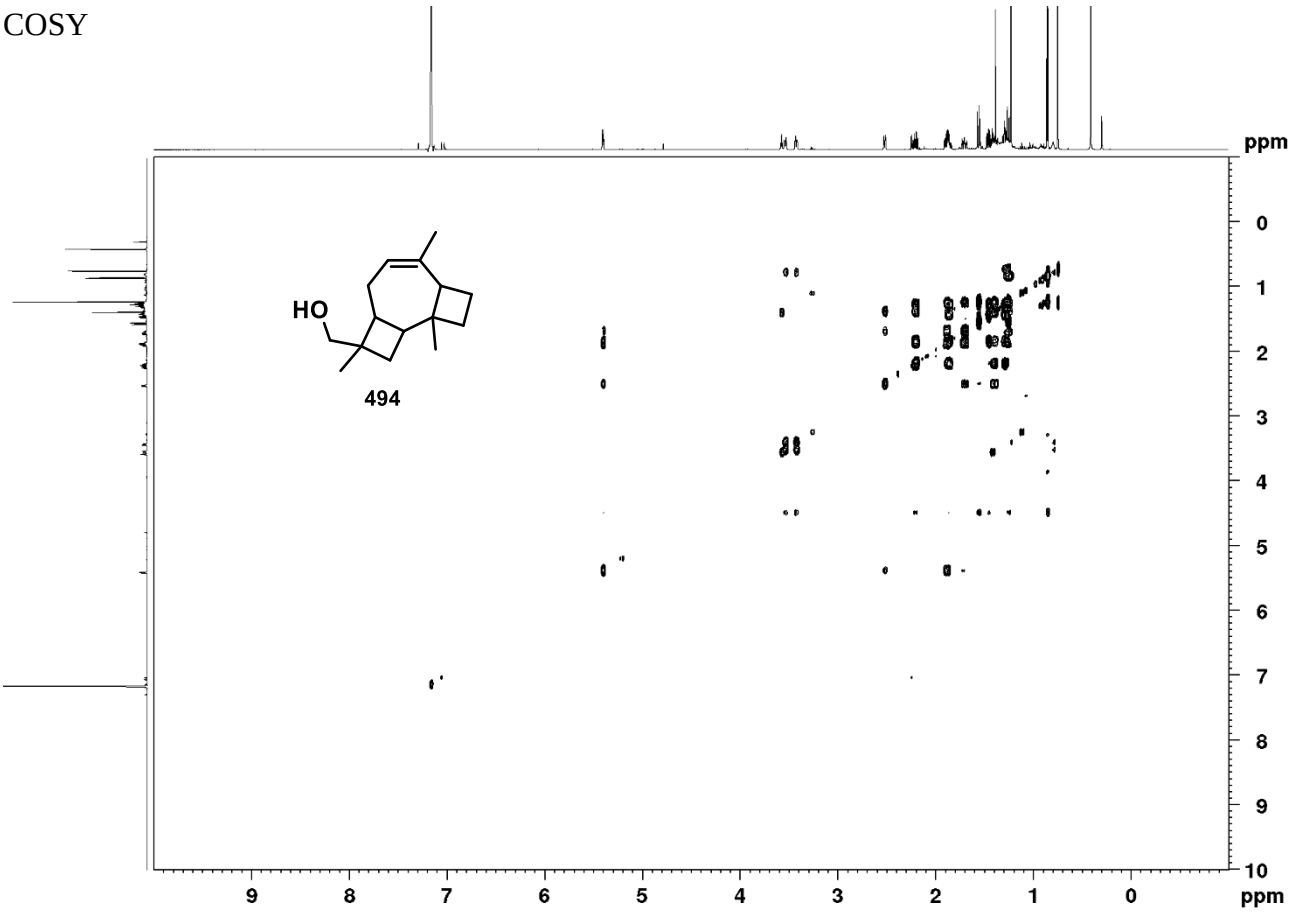
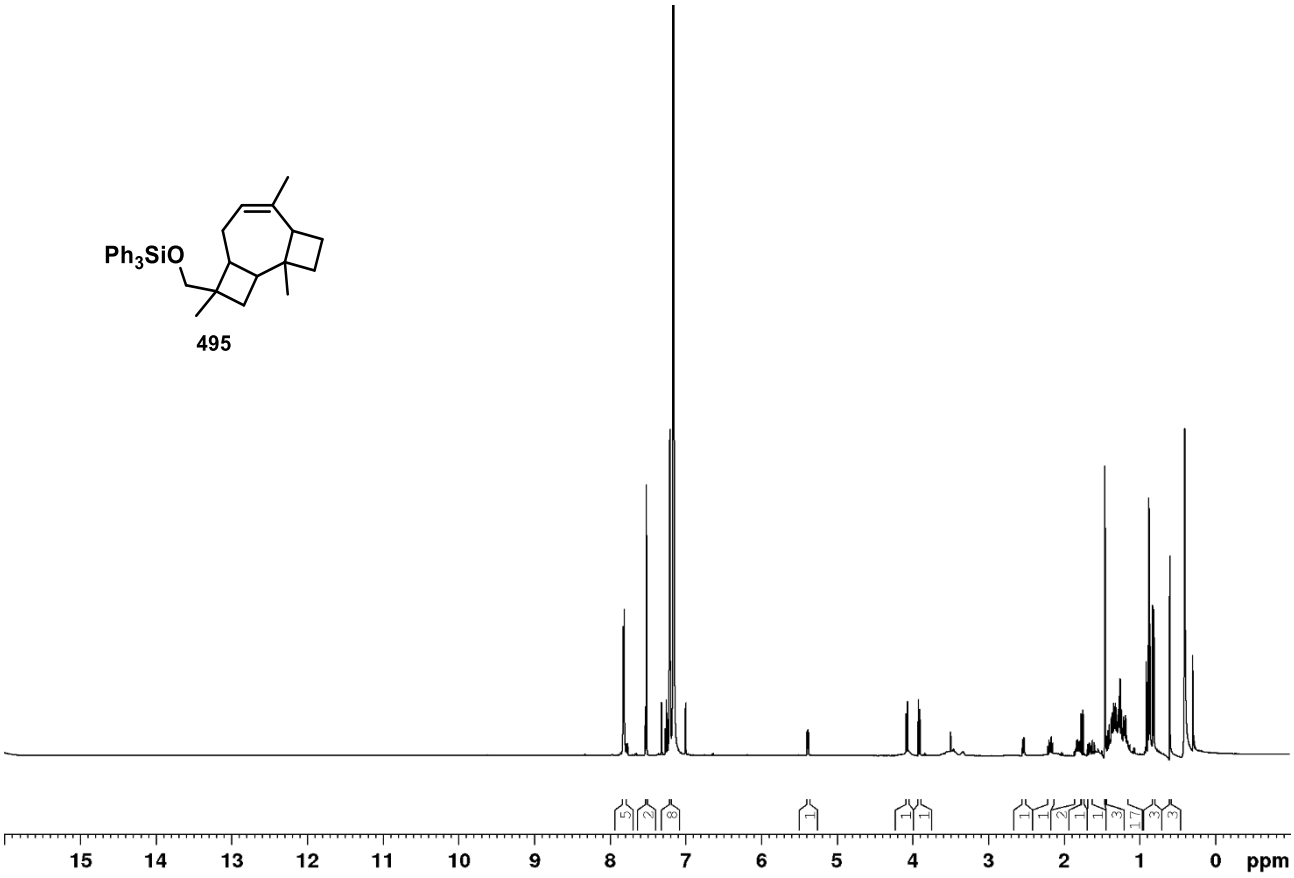
1
0
ppm

HMBC


HO
494
ppm
0
20
40
60
80
100
120
140
160
180
200
10
9
8
7
6
5
4
3
2
1
0
ppm

COSY


HO
494
ppm
0
1
2
3
4
5
6
7
8
9
10
9
8
7
6
5
4
3
2
1
0
ppm


Ph3SiO
495
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2
8
1
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1
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2
1
1
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14
13
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6
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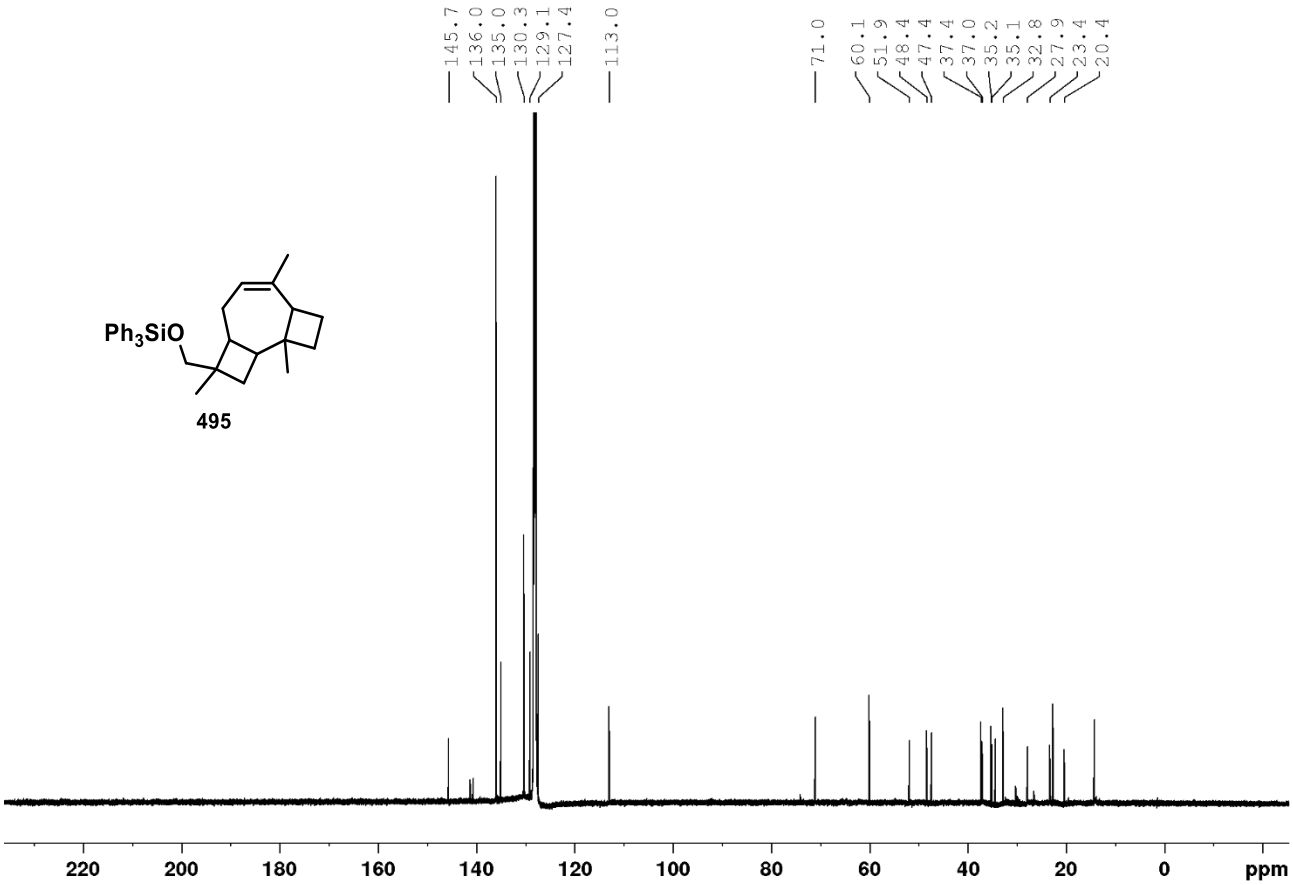
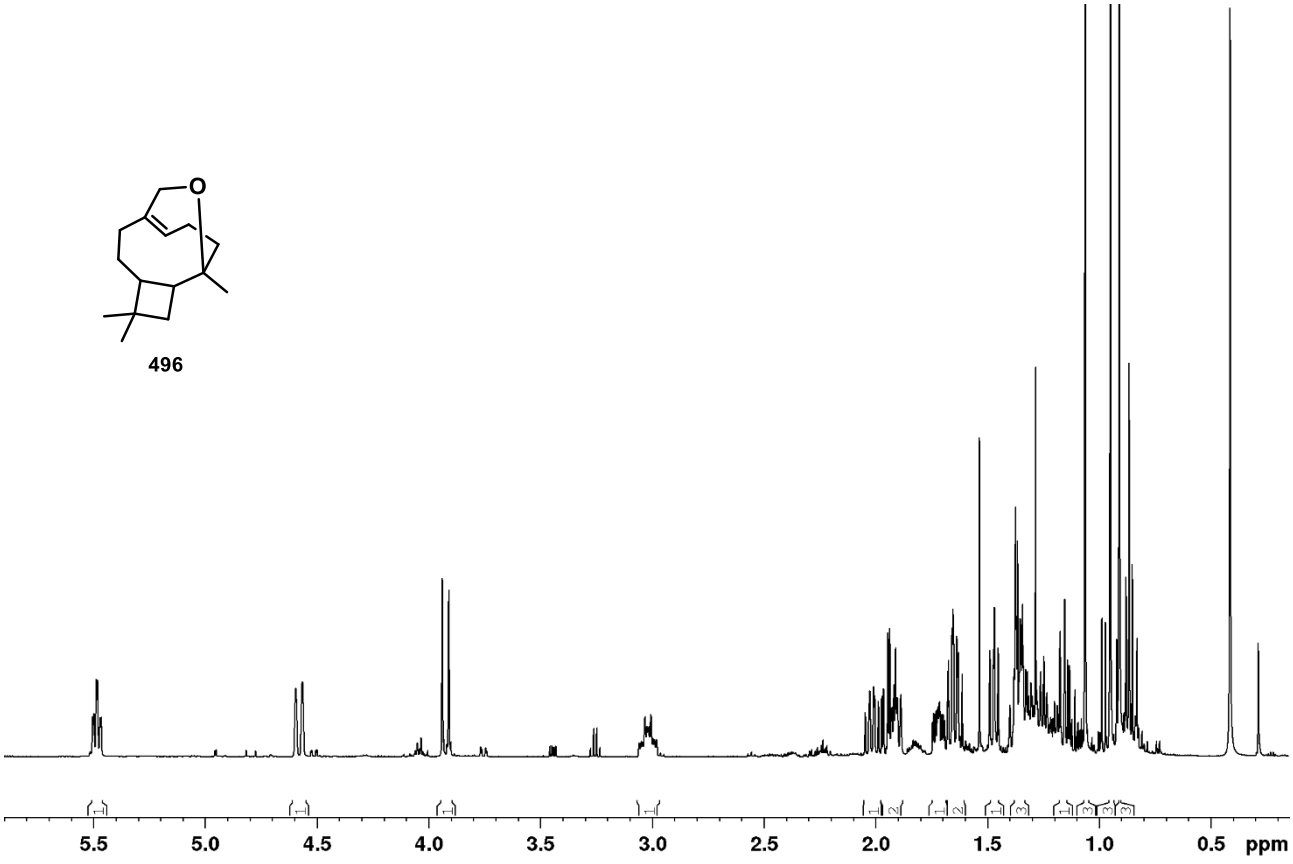

145.7
136.0
135.0
130.3
129.1
127.4
113.0
71.0
60.1
51.9
48.4
47.4
37.4
37.0
35.2
35.1
32.8
27.9
23.4
20.4
Ph3SiO
495
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
496
5.5
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4.5
4.0
3.5
3.0
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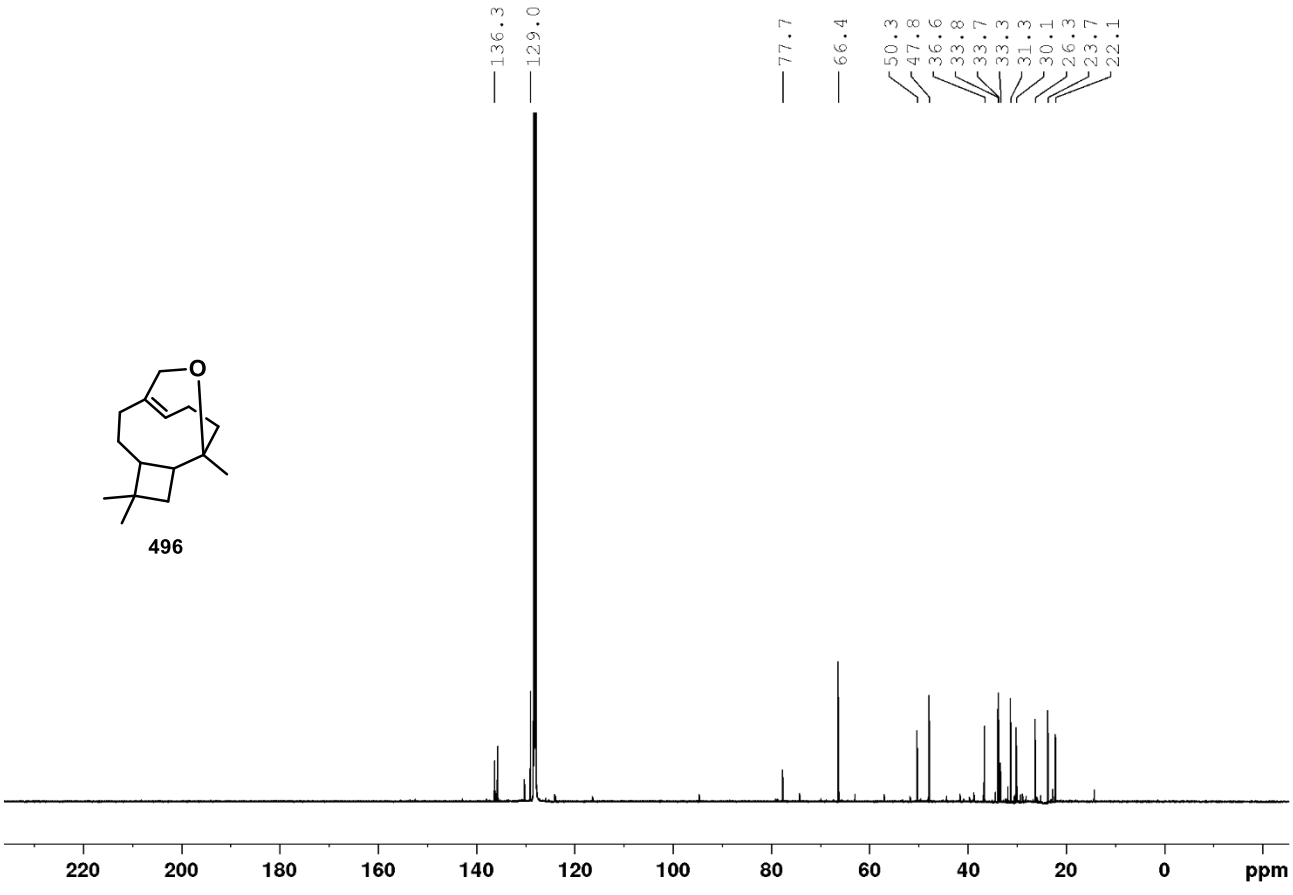
2.0
1.5
1.0
0.5
ppm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129.0
77.7
66.4
50.3
47.8
36.6
33.8
33.7
33.3
31.3
30.1
26.3
23.7
22.1
O
496
220
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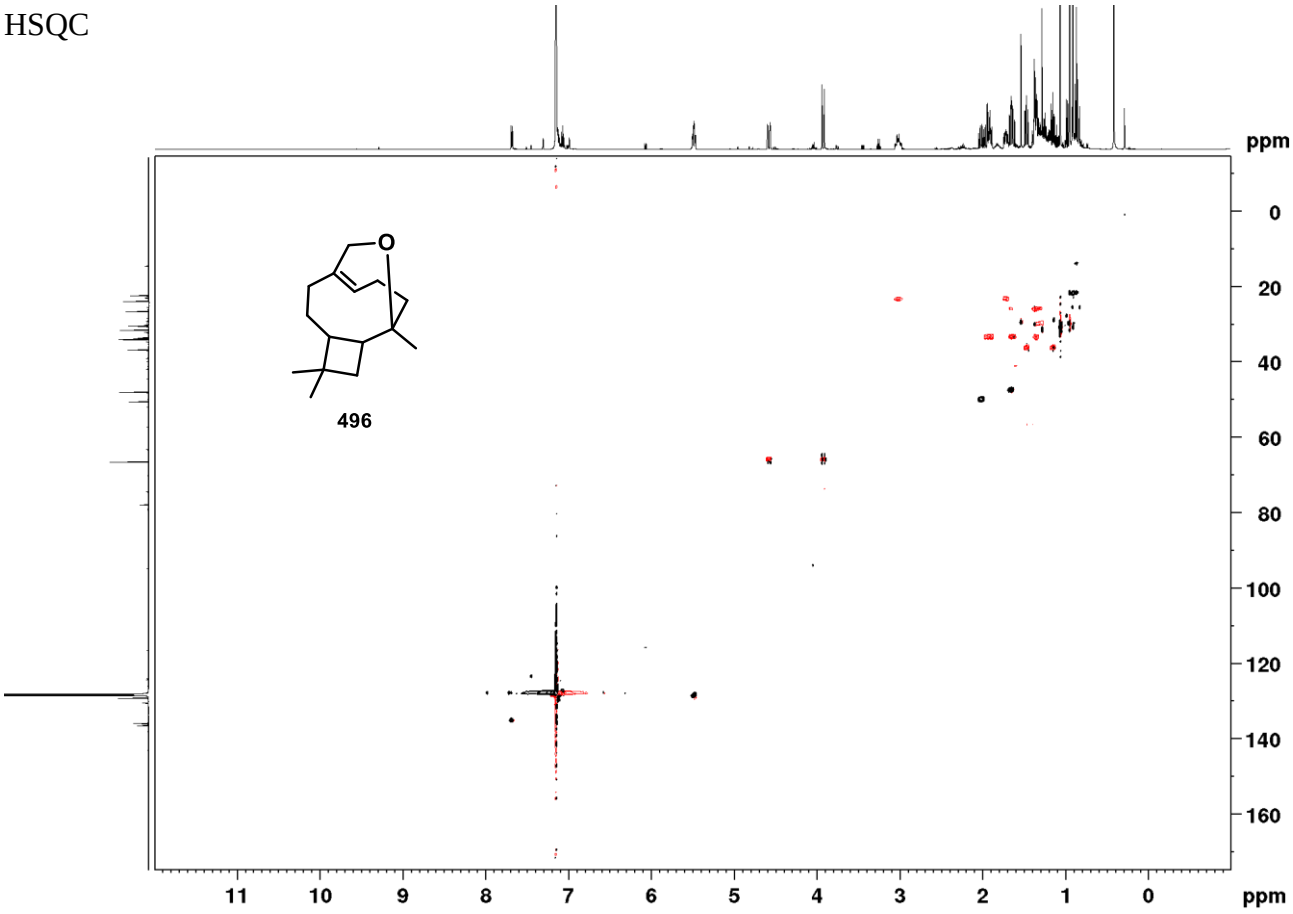
180
160
140
120
100
80
60
40
20
0
ppm

HSQC


O
496
ppm
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100
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140
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9
8
7
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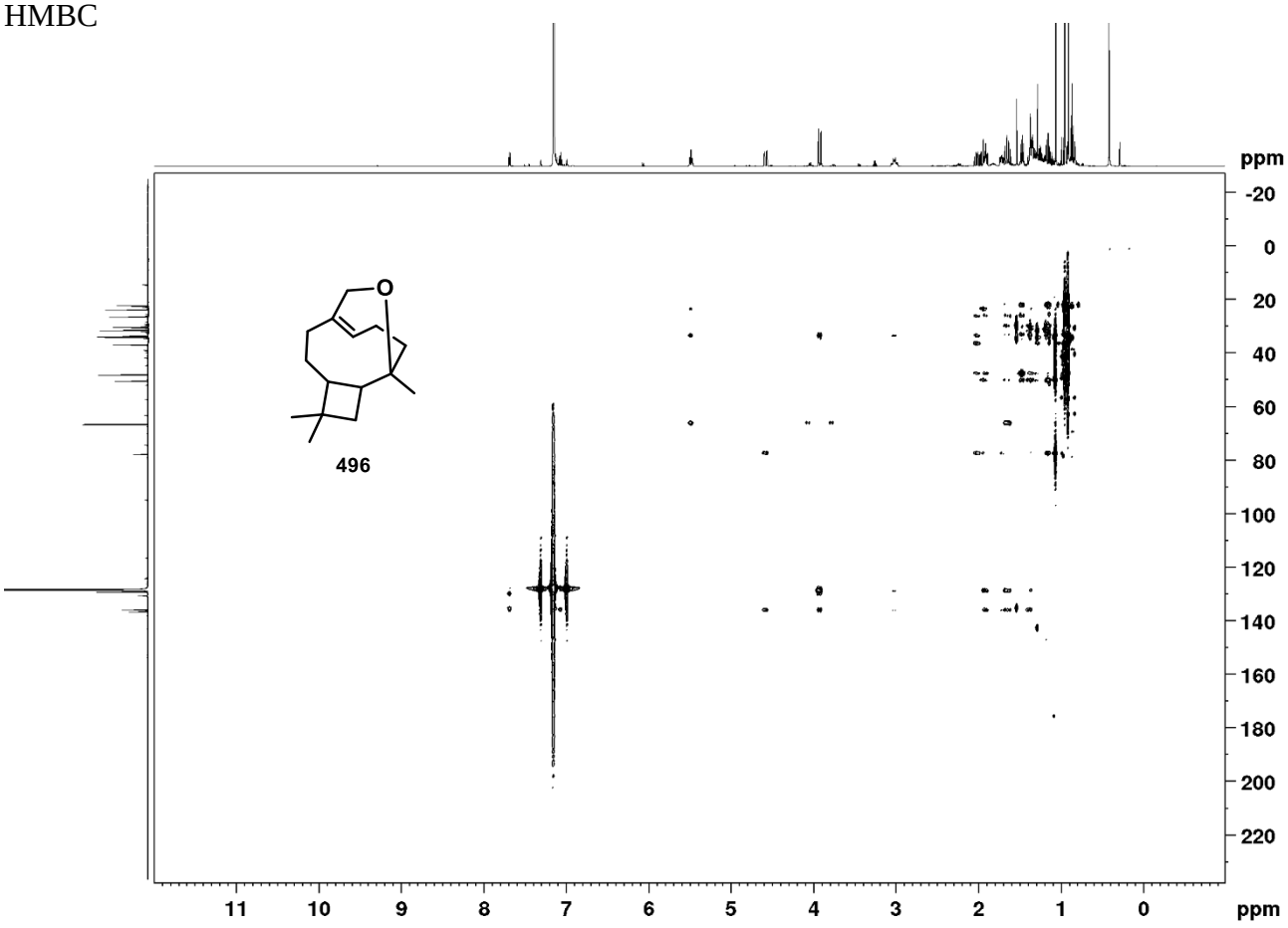
5
4
3
2
1
0
ppm

HMBC


O
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ppm
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4
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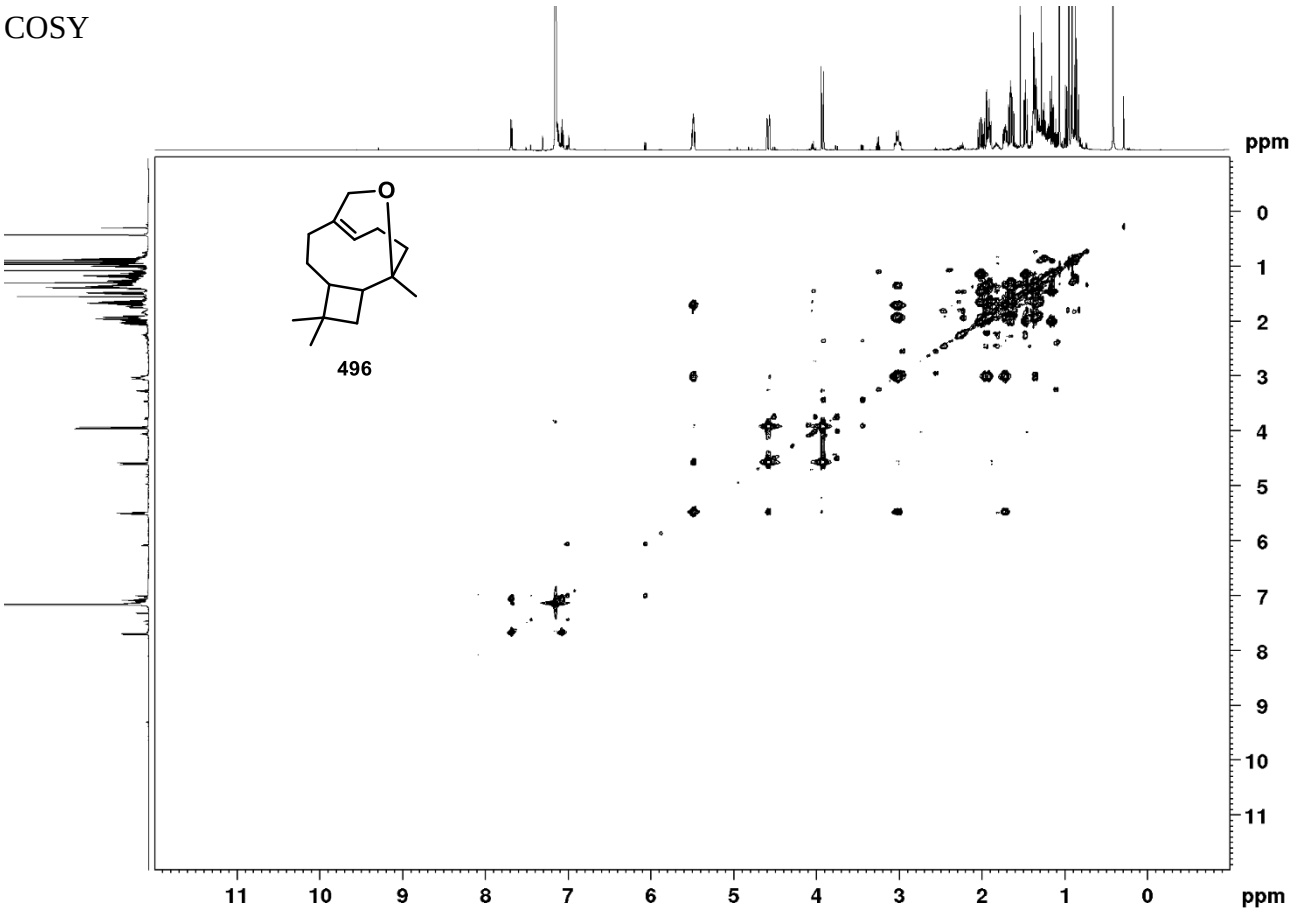
ppm

COSY


O
496
ppm
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11
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10
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6
5
4
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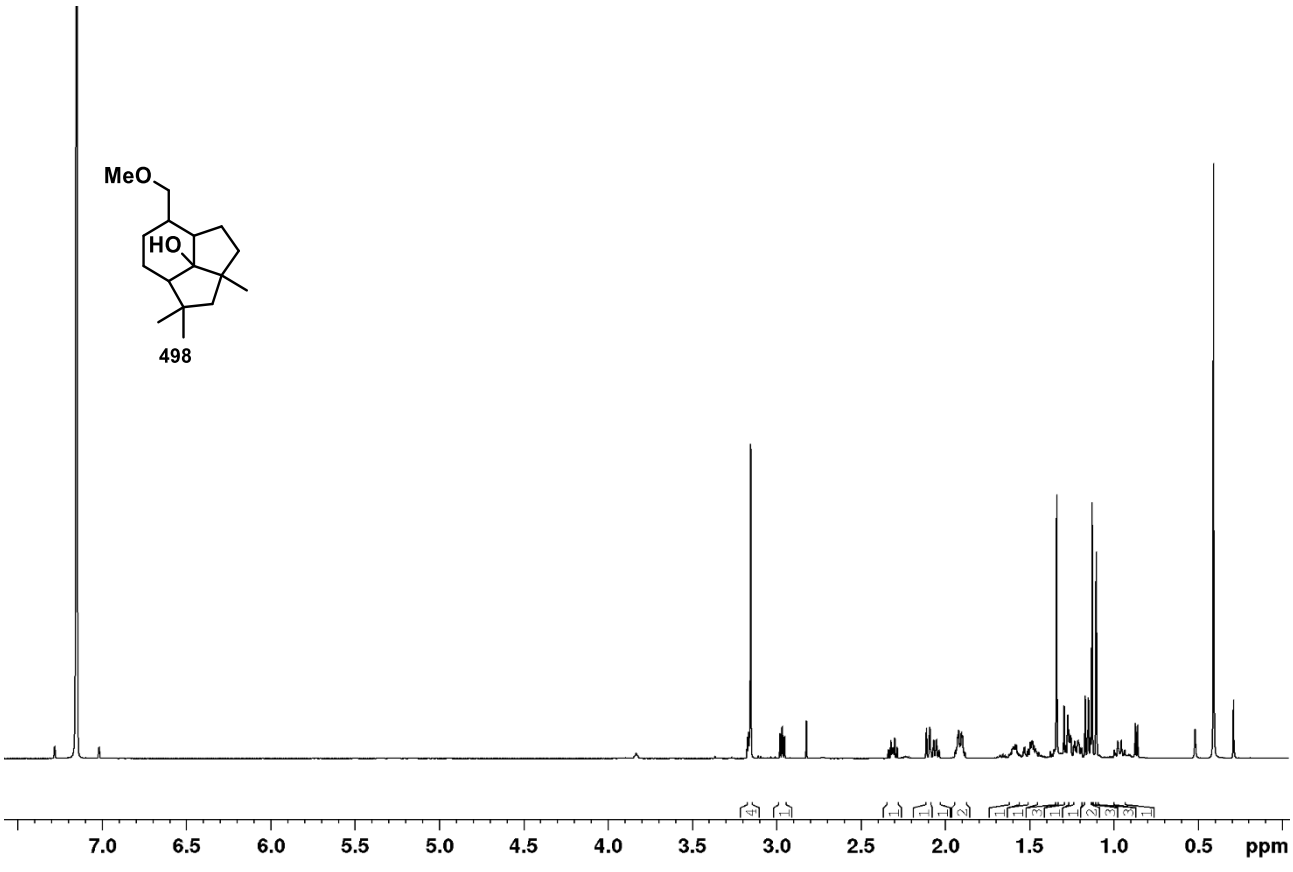
0
ppm


MeO
HO
498
7.0
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6.0
5.5
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4.5
4.0
3.5
3.0
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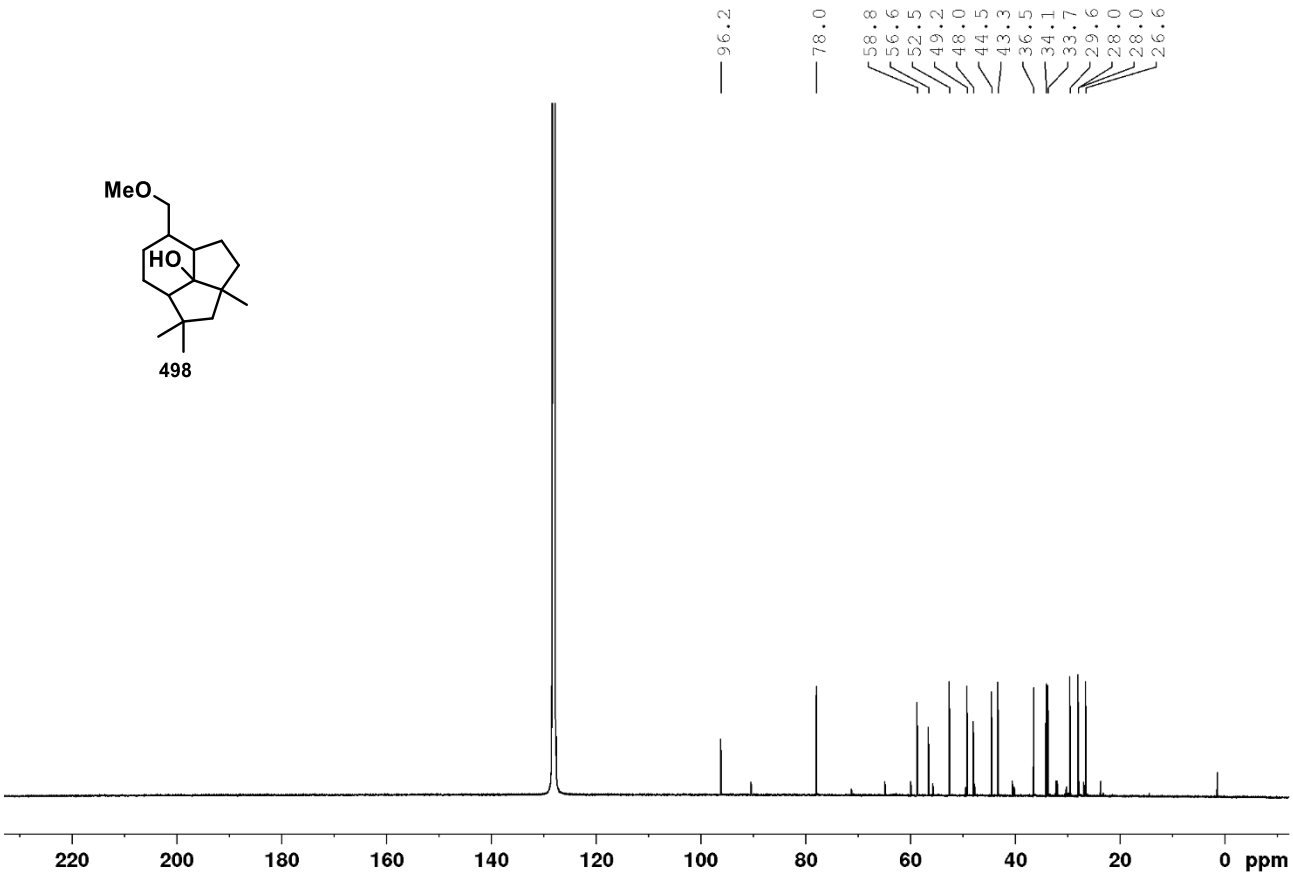
2.0
1.5
1.0
0.5
ppm


96.2
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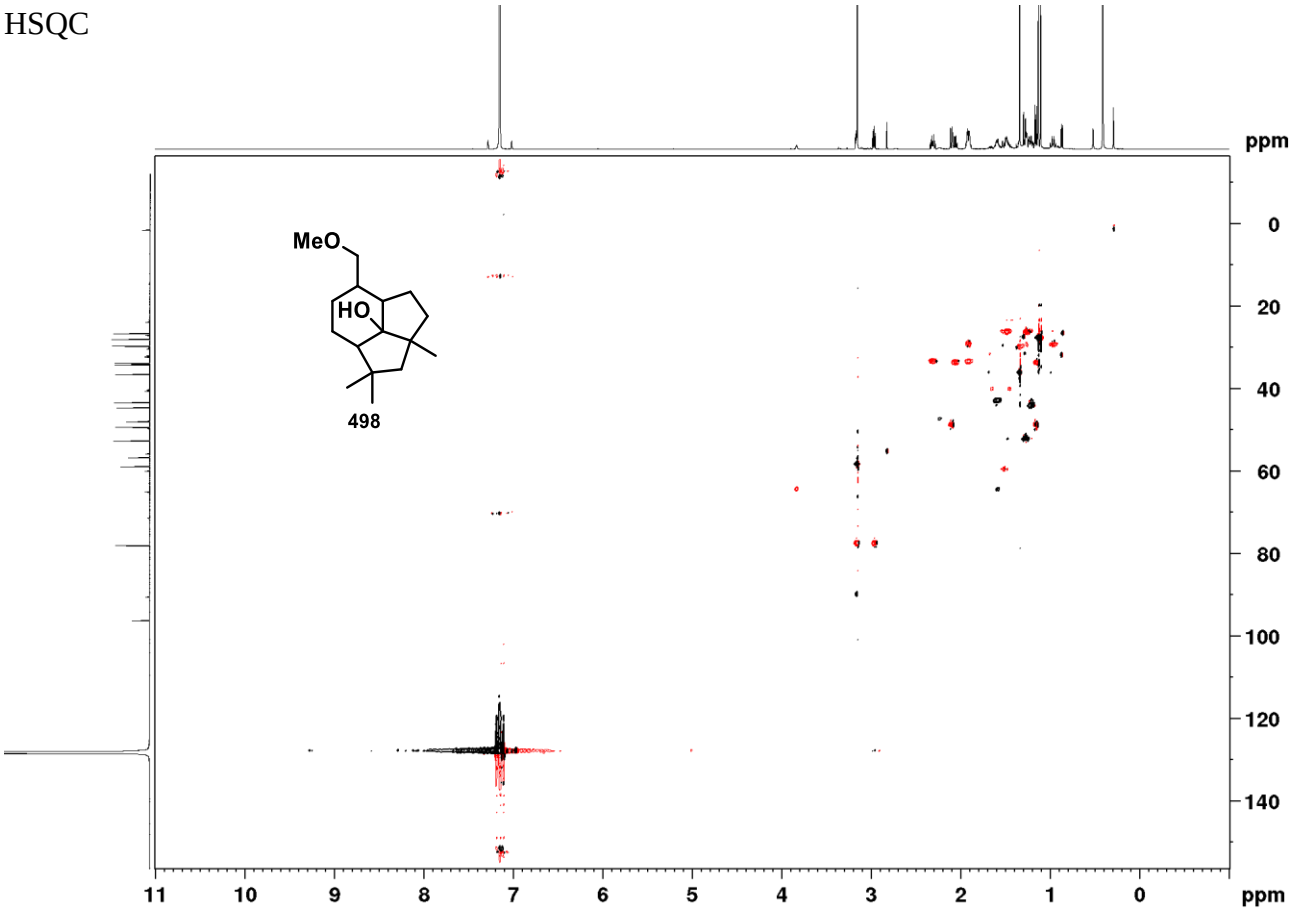
58.8
56.6
52.5
49.2
48.0
44.5
43.3
36.5
34.1
33.7
29.6
28.0
28.0
26.6
MeO
HO
498
220
200
180
160
140
120
100
80
60
40
20
0
ppm

HSQC


ppm
0
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40
60
80
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140
MeO
HO
498
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7
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4
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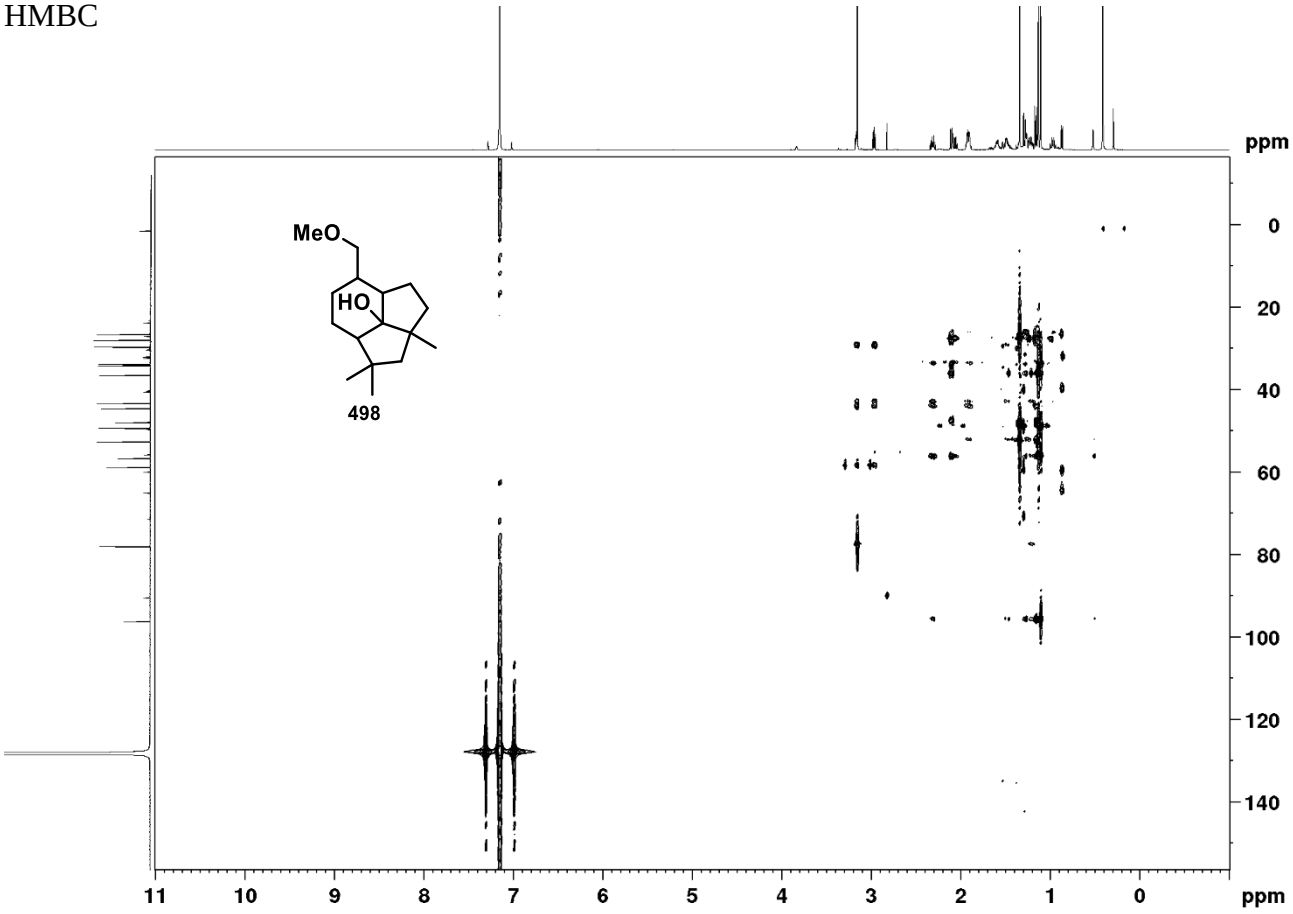
1
0
ppm

HMBC


MeO
HO
498
ppm
0
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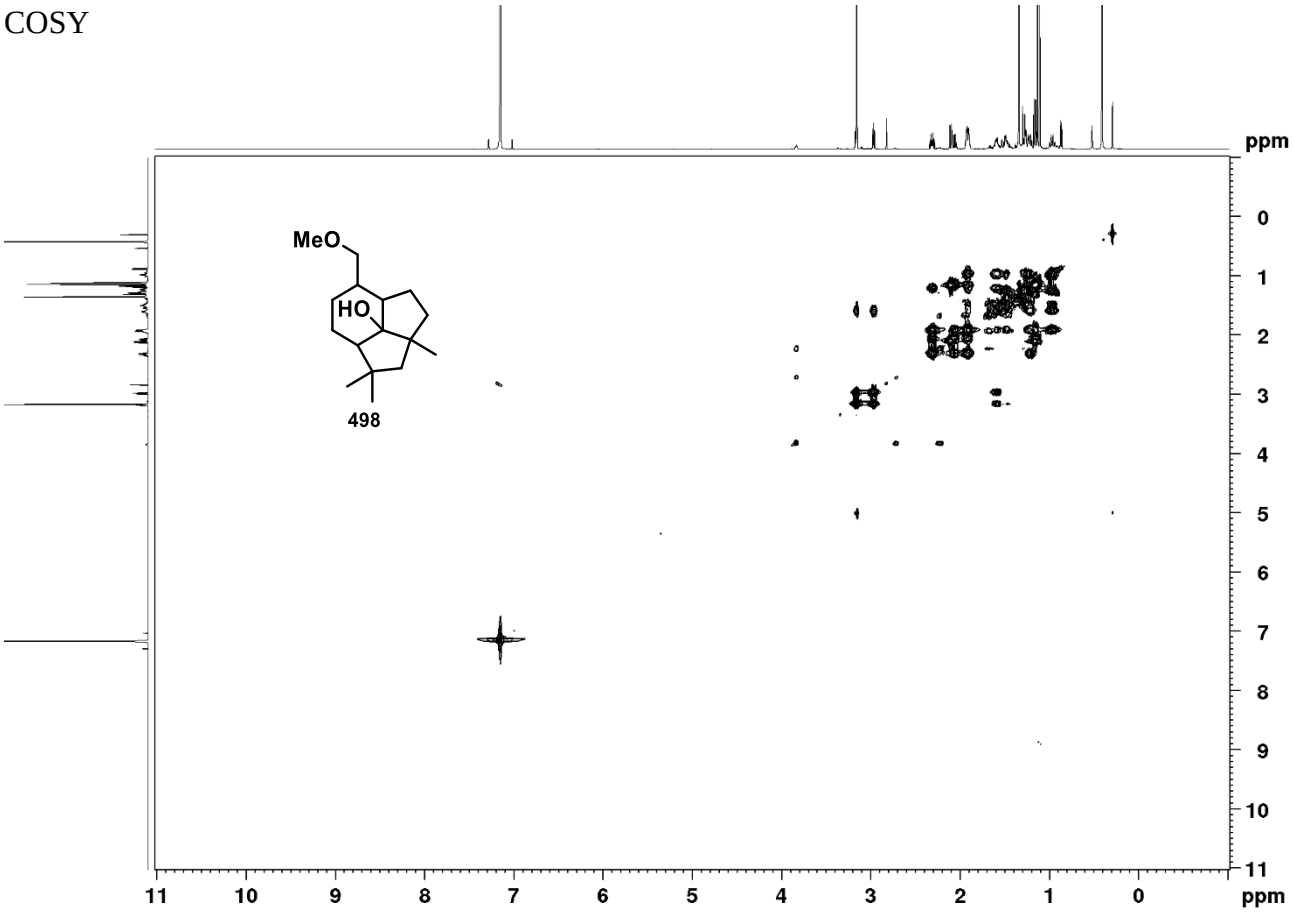
120
140
11
10
9
8
7
6
5
4
3
2
1
0
ppm

COSY


MeO
HO
498
ppm
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11
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6
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4
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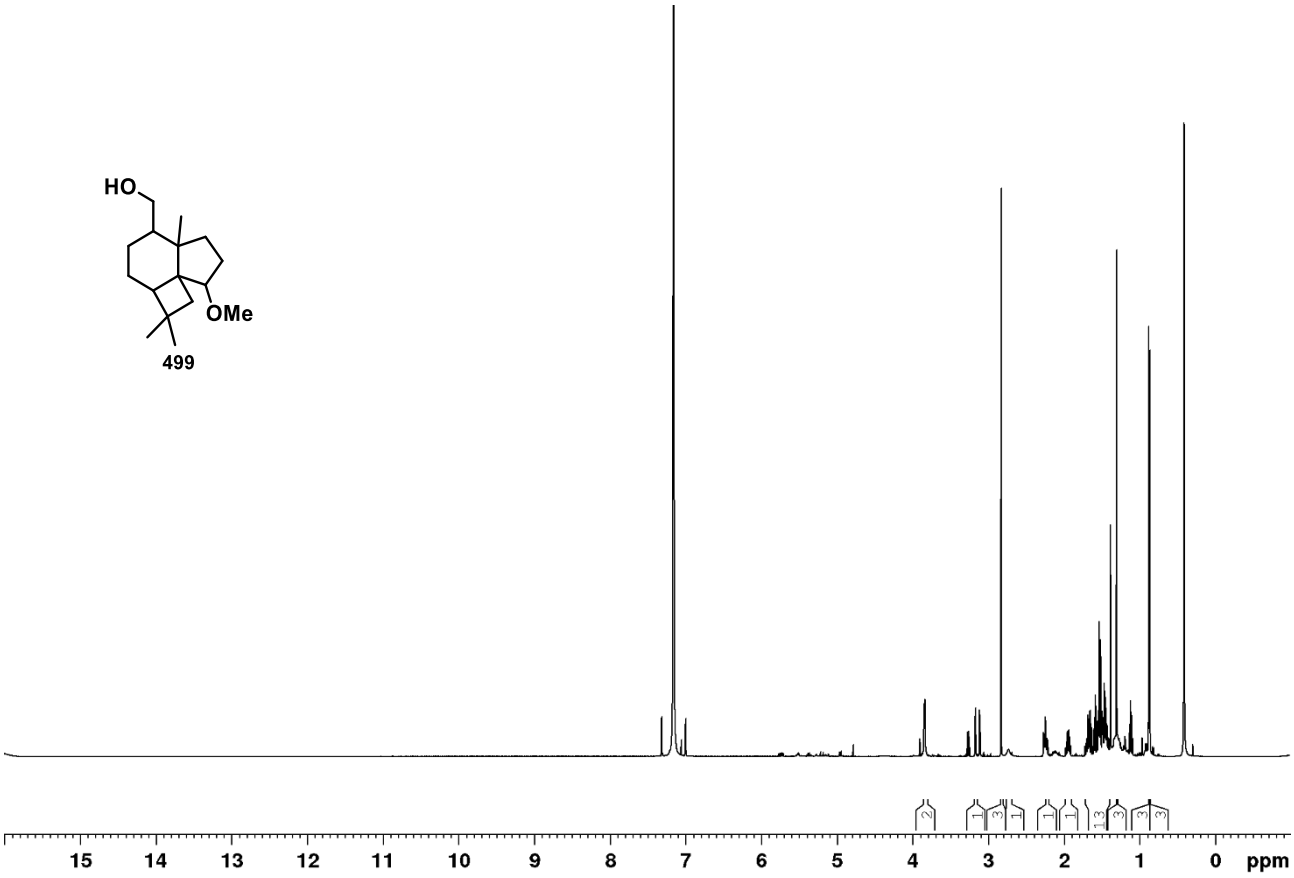
2
1
0
ppm


HO
OMe
499
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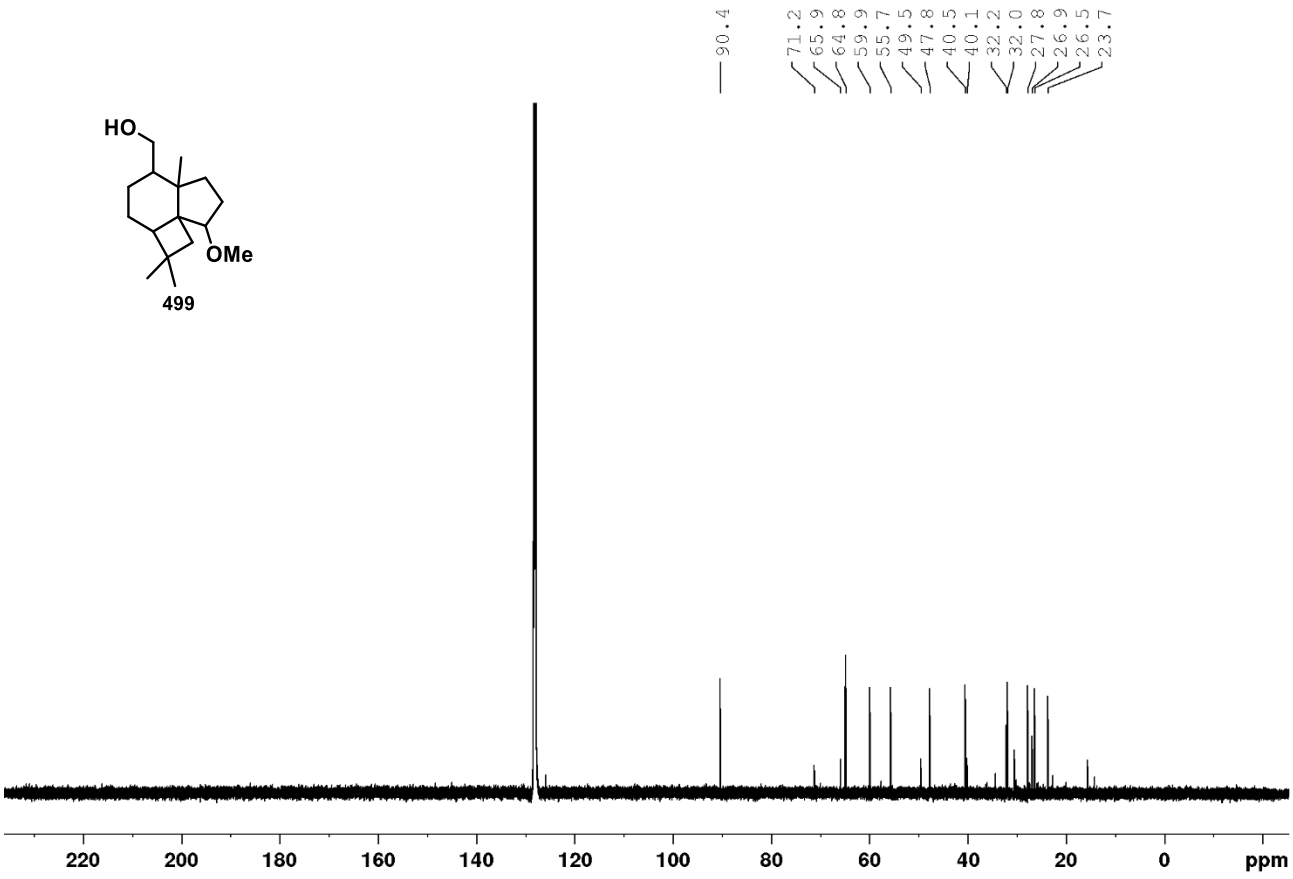
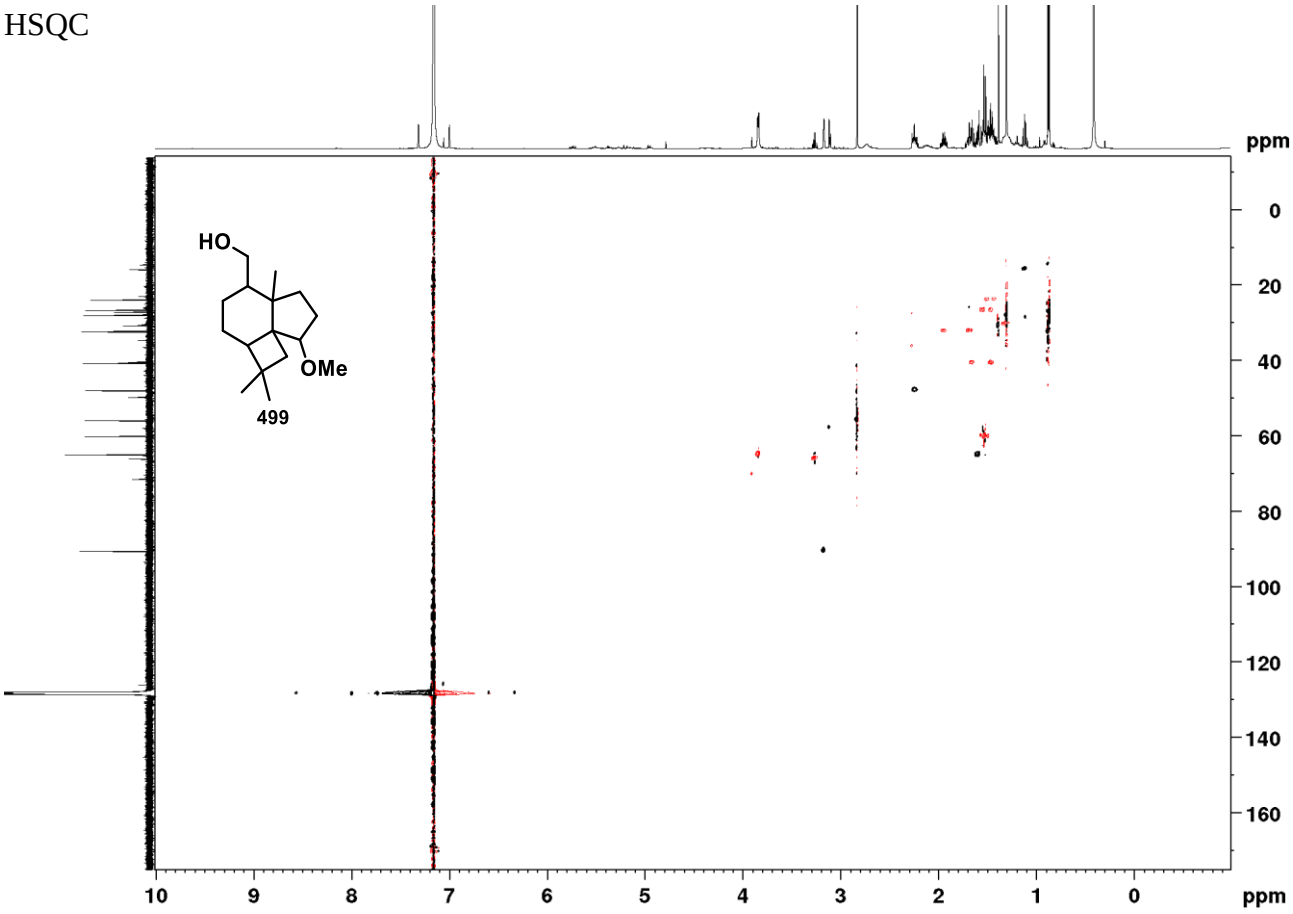
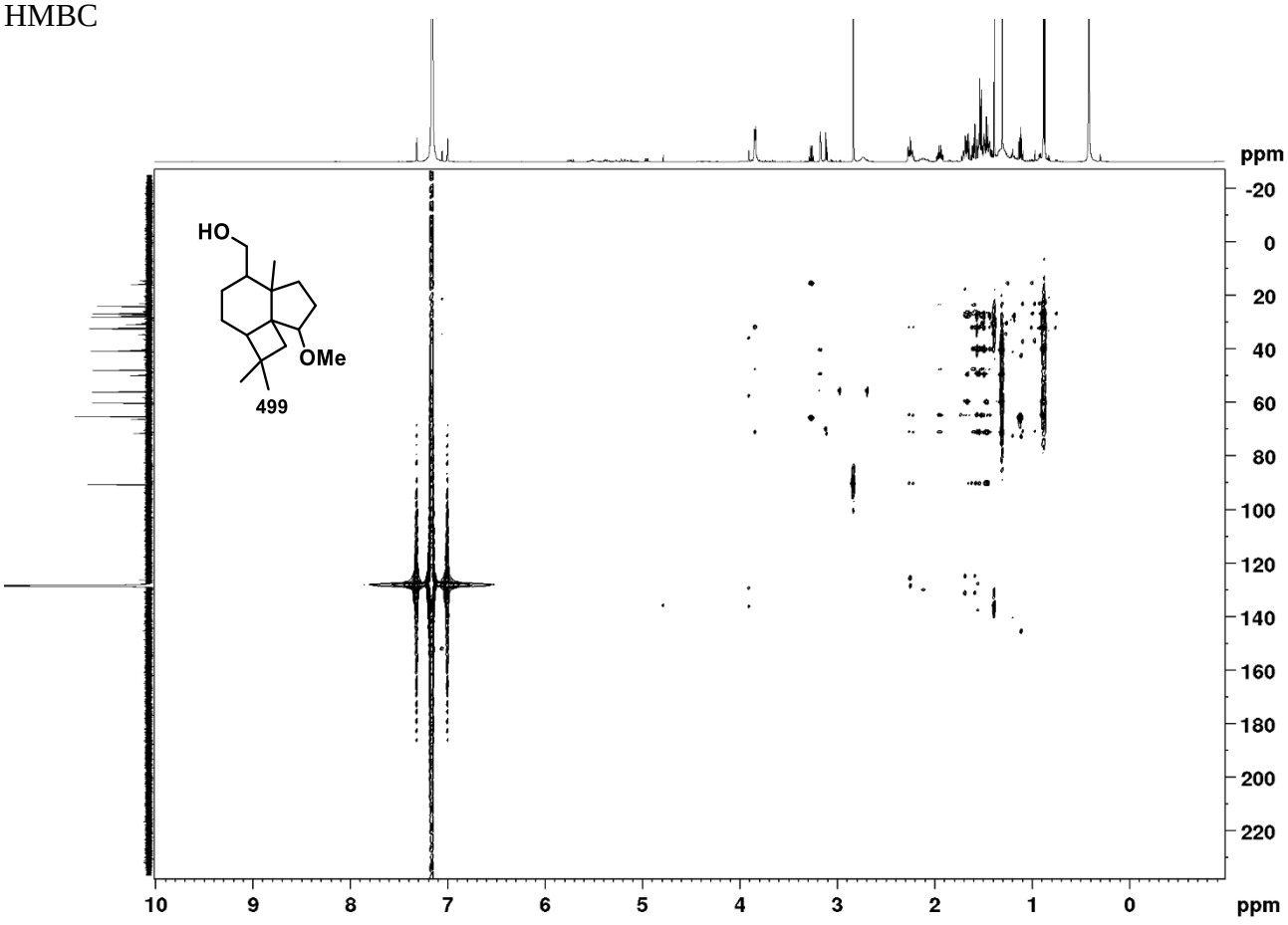
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


90.4
71.2
65.9
64.8
59.9
55.7
49.5
47.8
40.5
40.1
32.2
32.0
27.8
26.9
26.5
23.7
HO
OMe
499
220
200
180
160
140
120
100
80
60
40
20
0
ppm

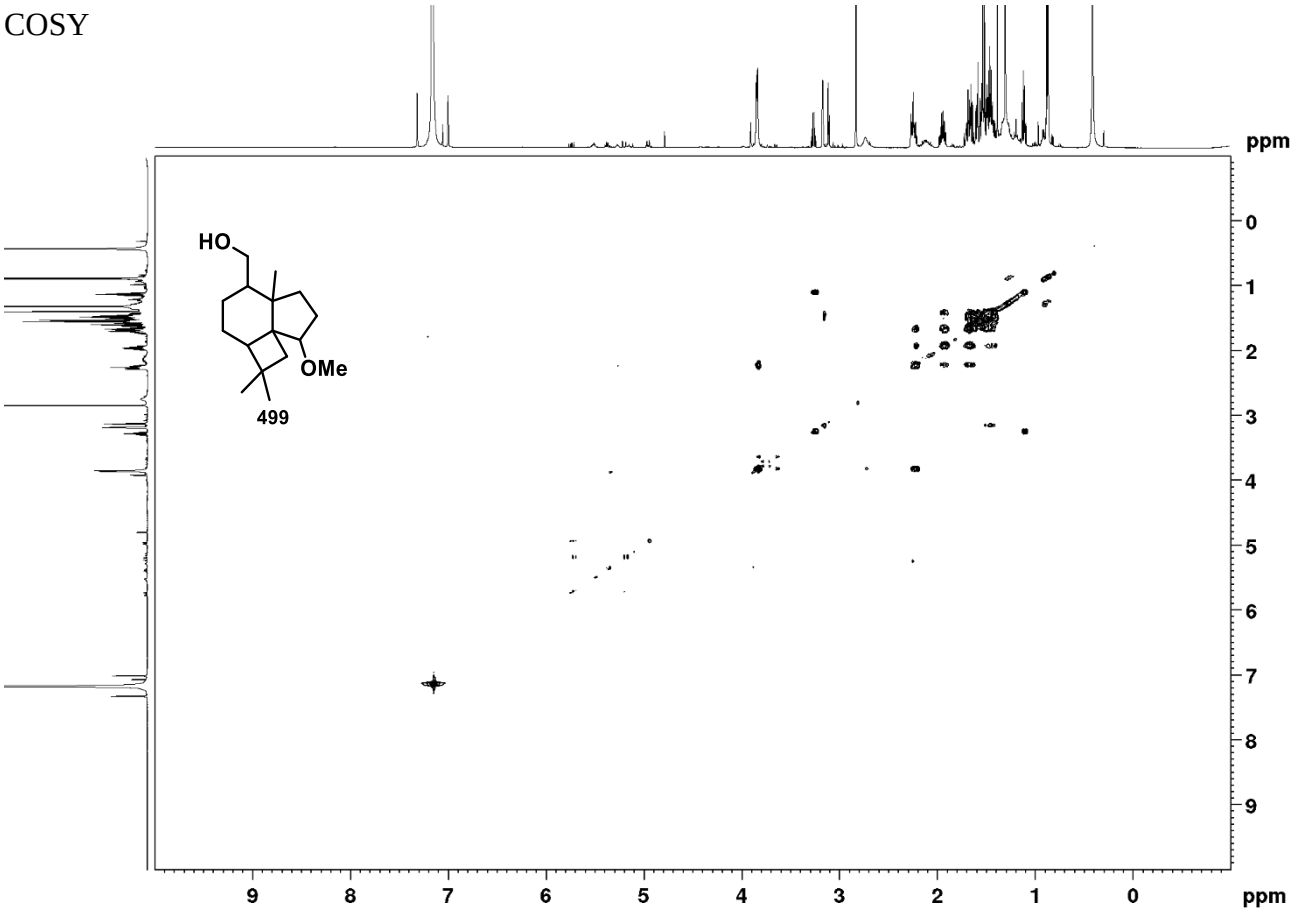
HSQC


HO
OMe
499
ppm
0
20
40
60
80
100
120
140
160
10
9
8
7
6
5
4
3
2
1
0
ppm

HMBC

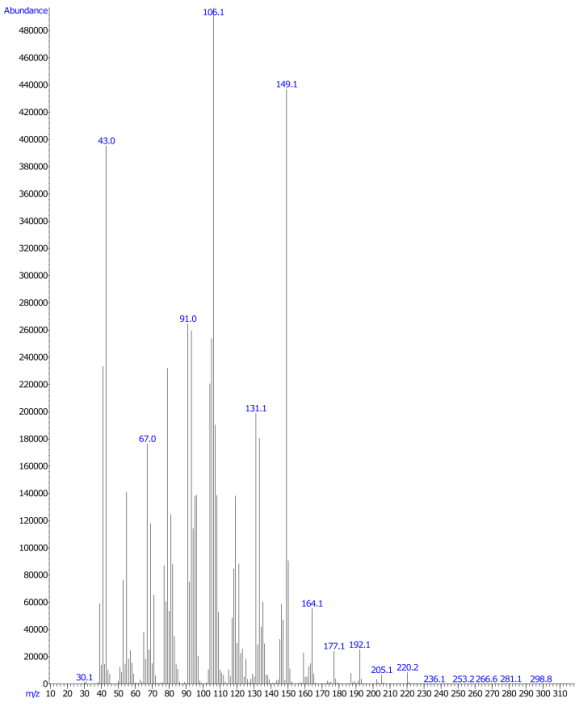

HO
OMe
499
ppm
-20
0
20
40
60
80
100
120
140
160
180
200
220
10
9
8
7
6
5
4
3
2
1
0
ppm

COSY

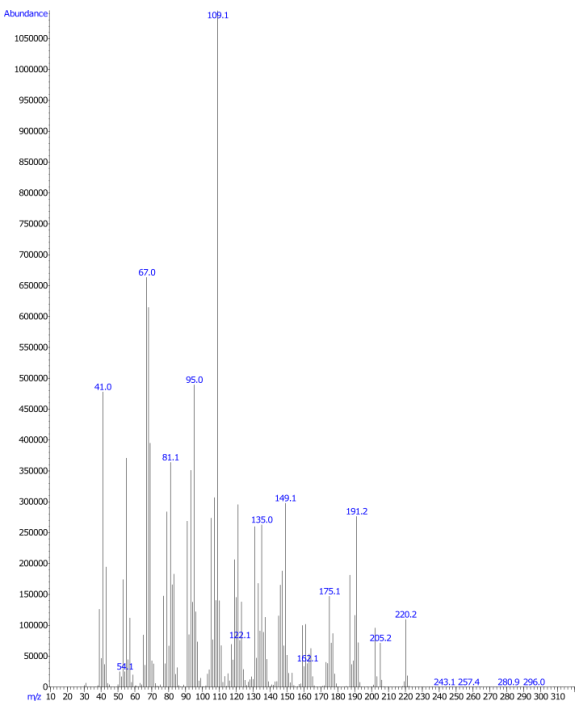


10.5 Mass Spectra

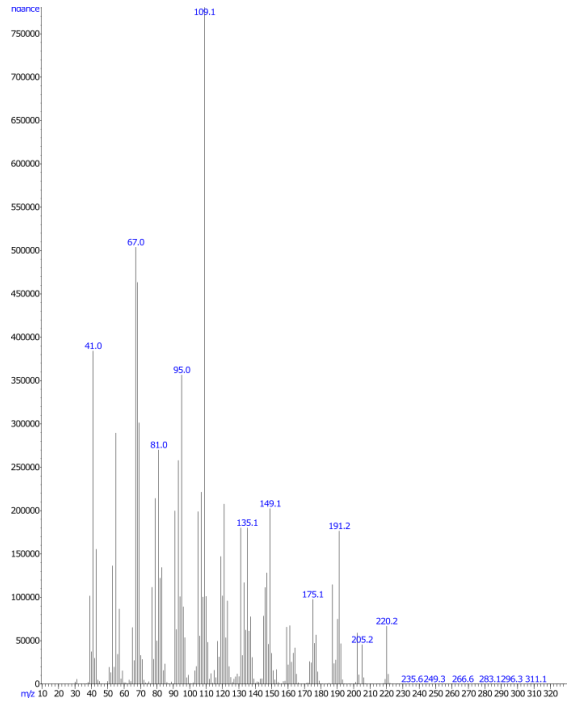
131 + Bot2 pdt1 (t_r = 9,897 min, RI = 1591):



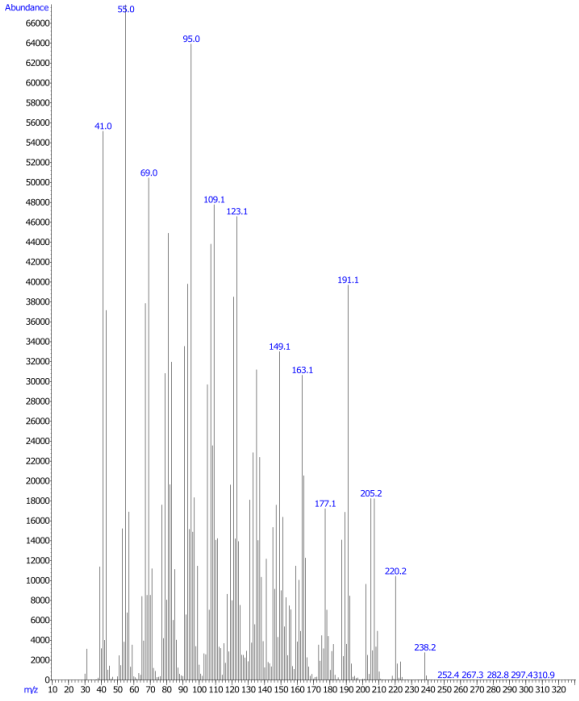
131 + PenA pdt1 (t_r = 10,083 min, RI = 1623):



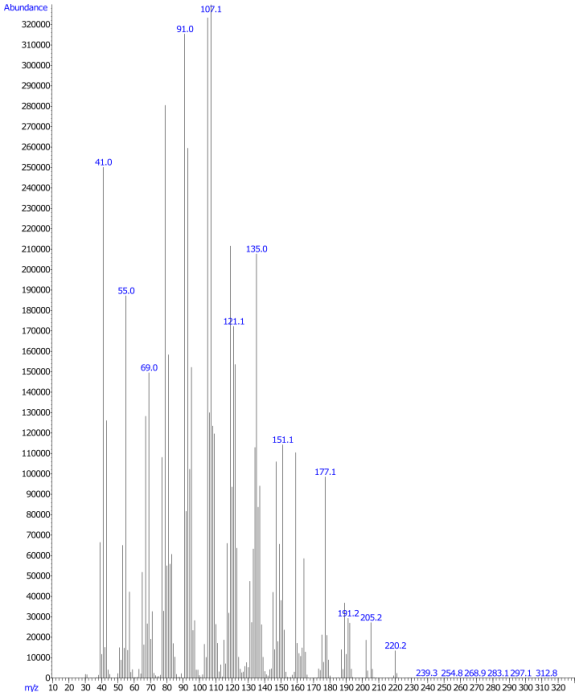
131 + PenA pdt3 (t_r = 10,365 min, RI = 1672):



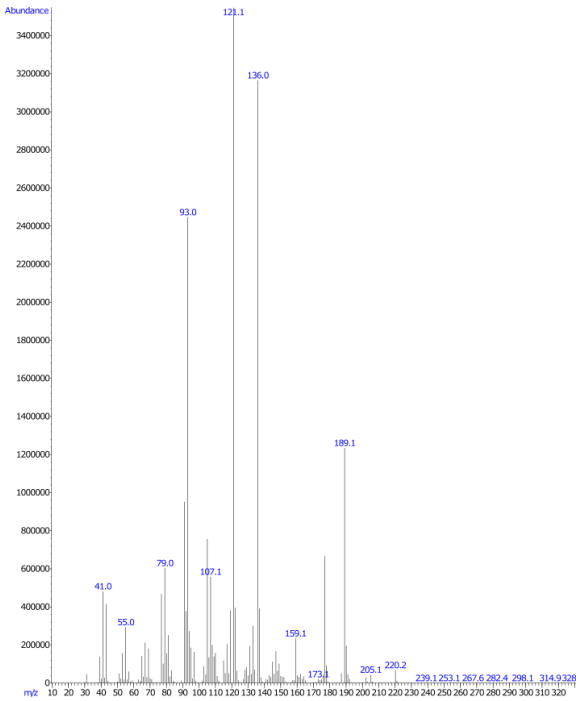
131 + PenA pdt4 (t_r = 11,308 min, RI = 1845):



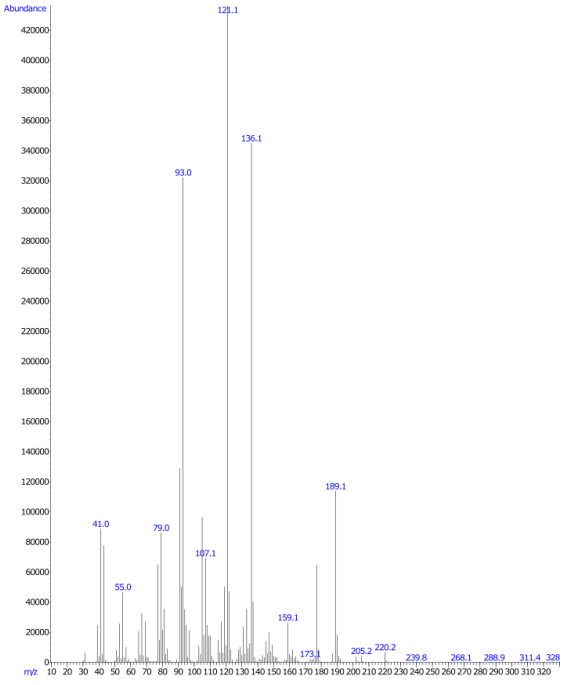
131 + Cop4 pdt1 (t_r = 9,464 min, RI = 1520):



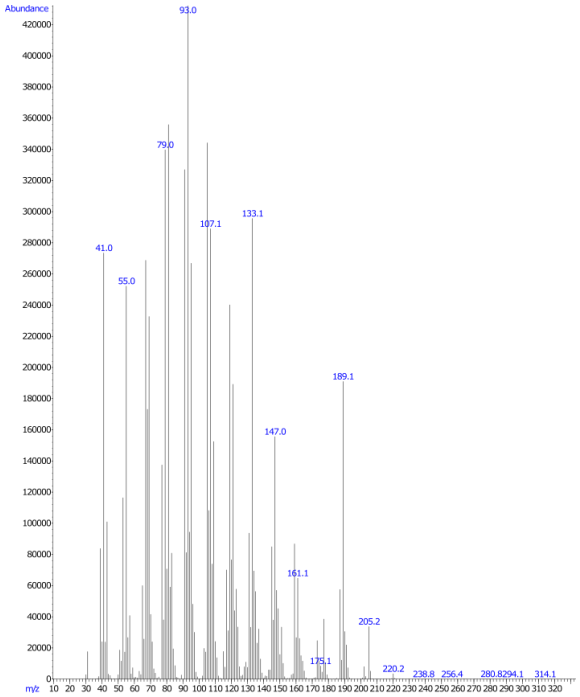
131 + Cop4 pdt2 (t_r = 9,844 min, RI = 1582):



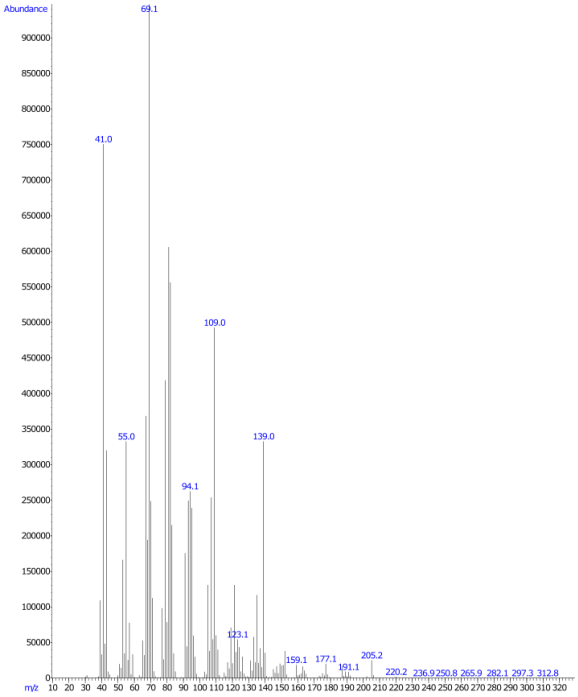
131 + Cop4 pdt3 (t_r = 10,043 min, RI = 1616):



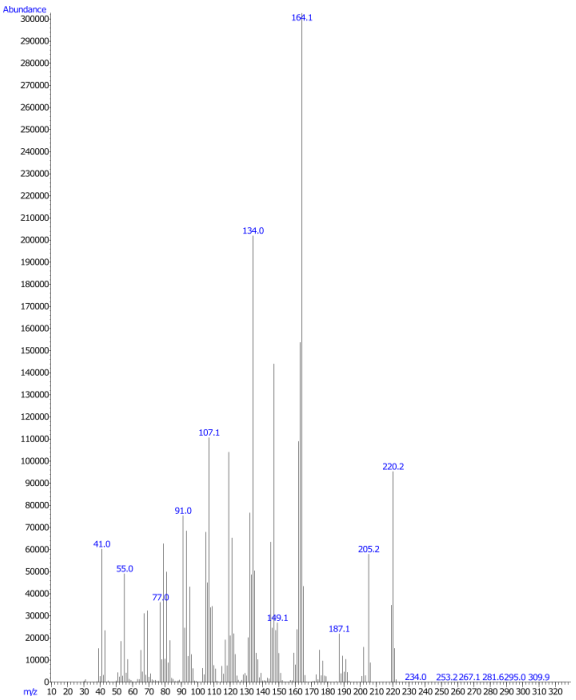
131 + Tps32 pdt2 (t_r = 10,258 min, RI = 1654):



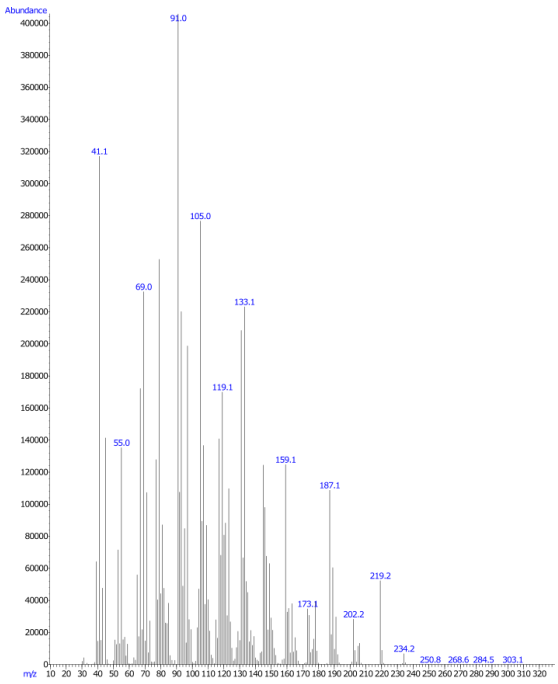
131 + Tri5 pdt1 (t_r = 9,787 min, RI = 1573):



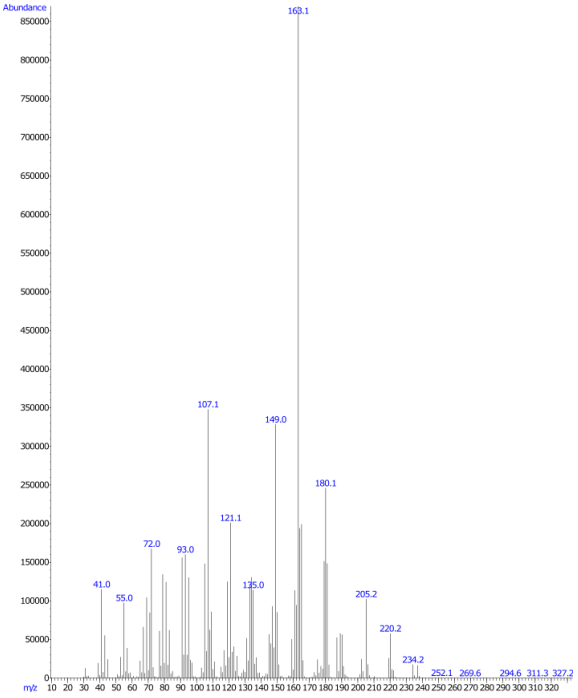
132 + Bot2 pdt1 (t_r = 9,966 min, RI = 1602):



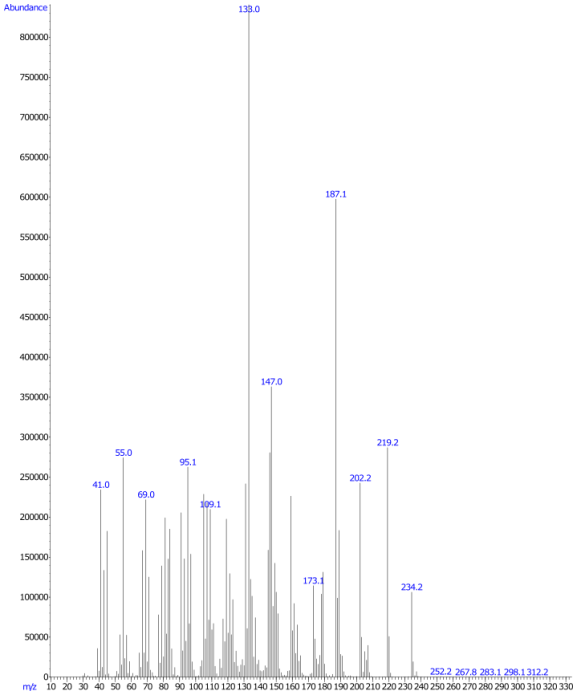
132 + Bot2 pdt3 (t_r = 10,177 min, RI = 1639):



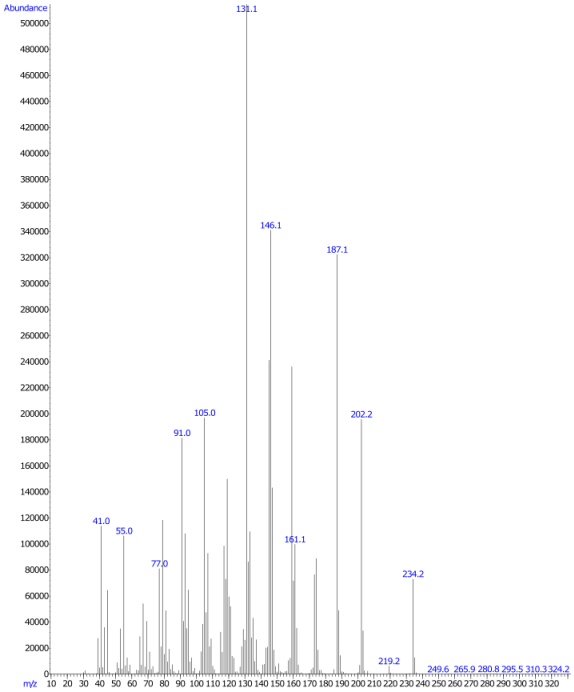
132 + Bot2 pdt4 (t_r = 11,237 min, RI = 1832):



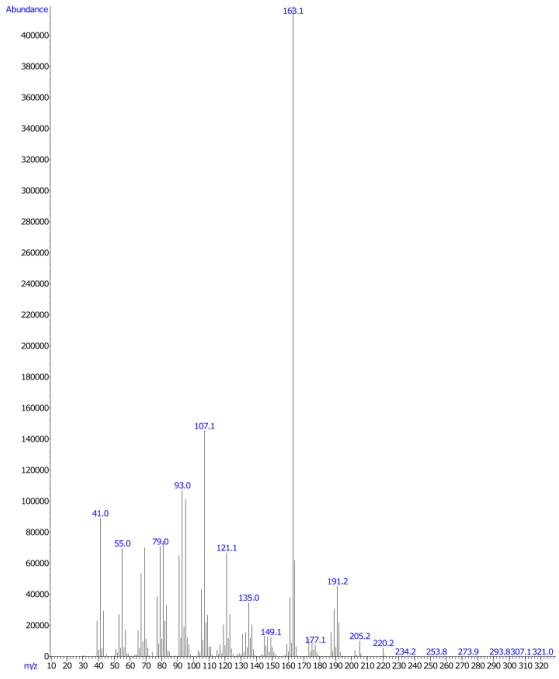
132 + Bot2 pdt5 (t_r = 11,402 min, RI = 1864):



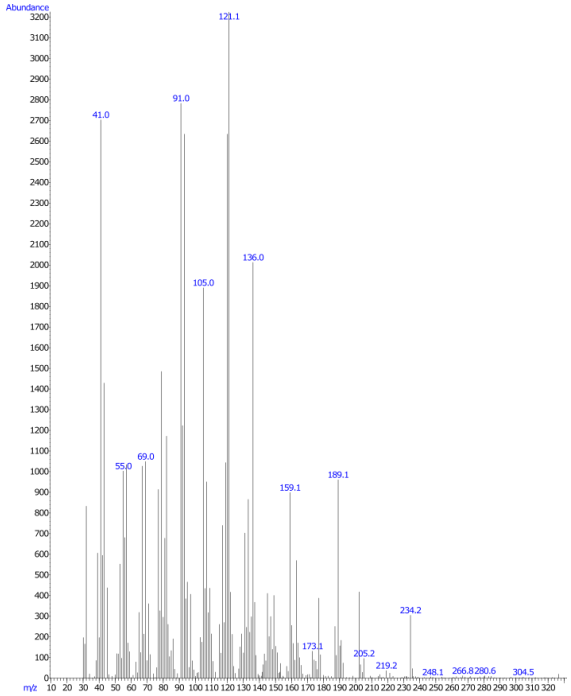
132 + PenA pdt1 (t_r = 9,790 min, RI = 1574):



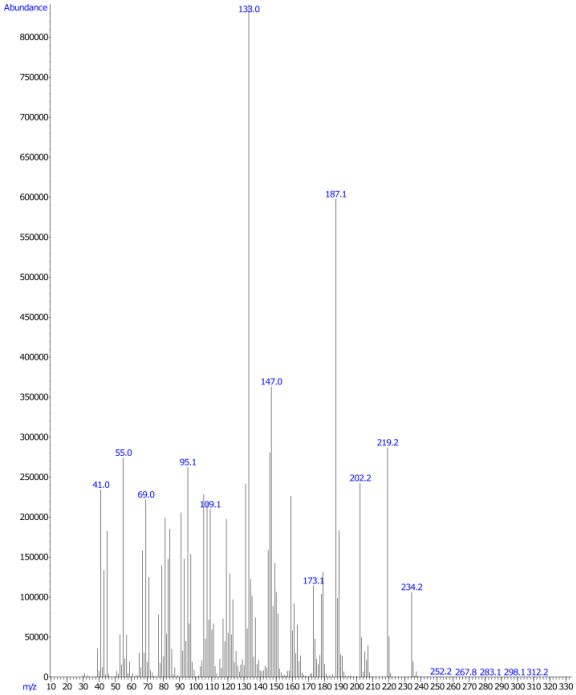
132 + PenA pdt2 (t_r = 10,086 min, RI = 1623):



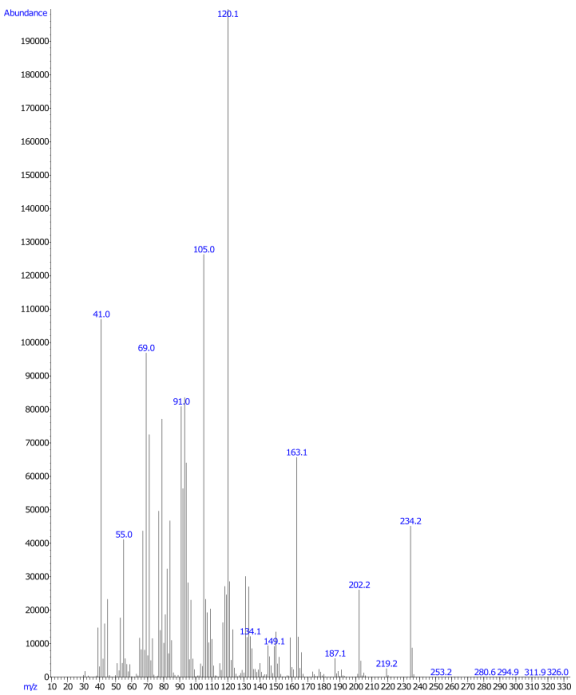
132 + Cop4 pdt1 (t_r = 10,063 min, RI = 1619):



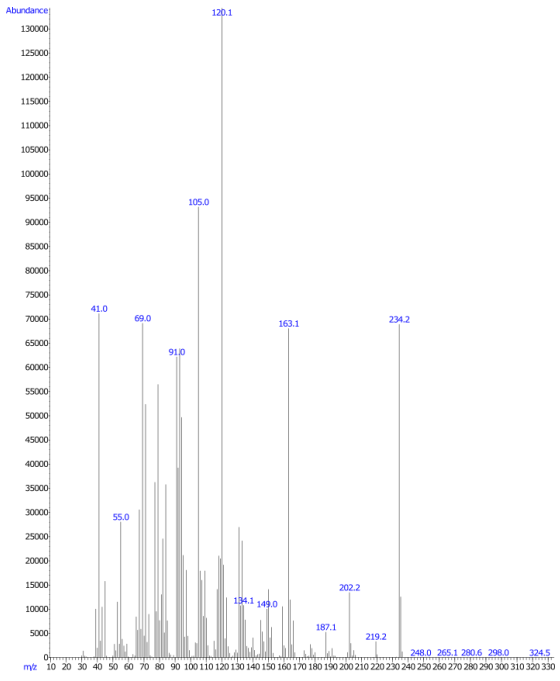
132 + Cop4 pdt2 (t_r = 10,438 min, RI = 1685):



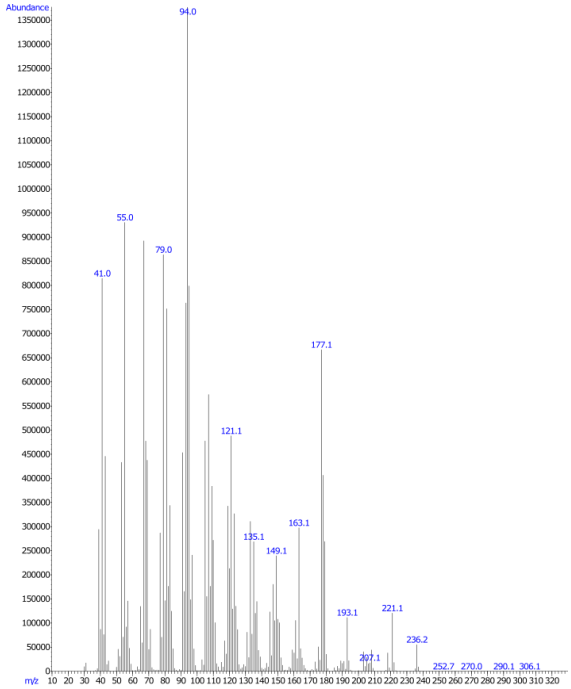
132 + Tri5 pdt3 (t_r = 10,114 min, RI = 1628):



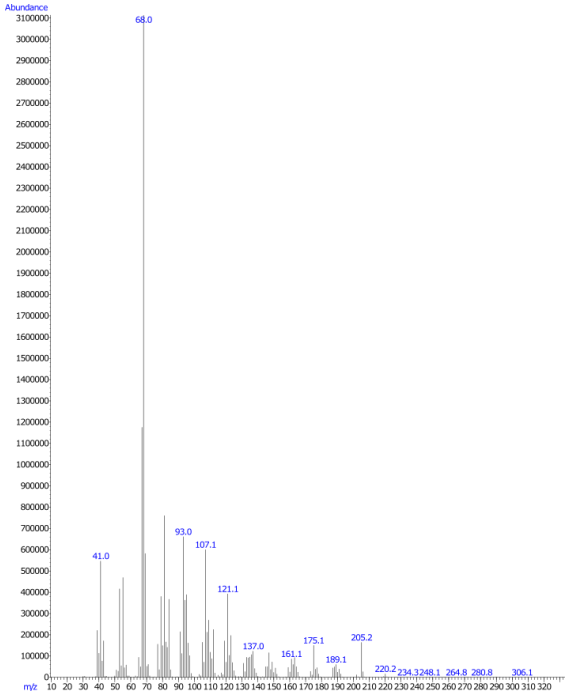
132 + Tri5 pdt4 (t_r = 10,189 min, RI = 1642):



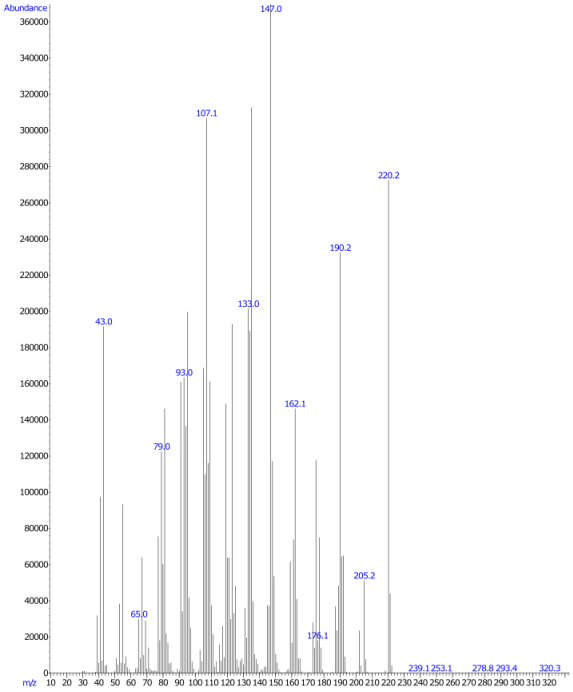
127 + Tps32 pdt1 (t_r = 11,510 min, RI = 1878):



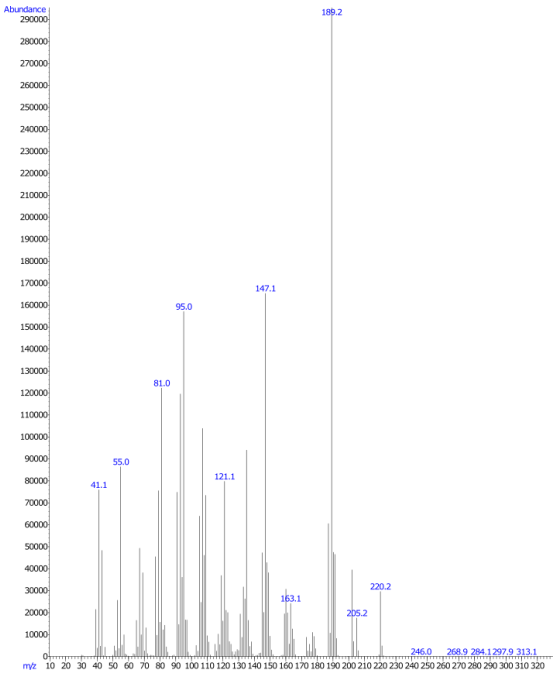
97 + Bot2 pdt1 (t_r = 10,672 min, RI = 1727):



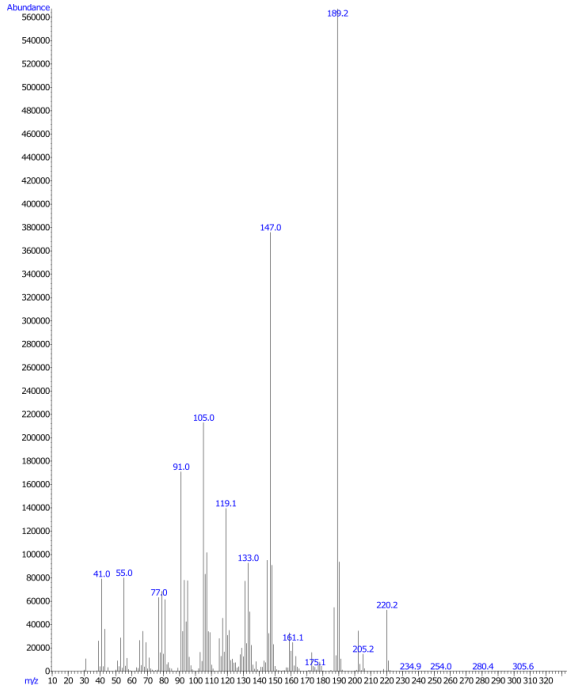
97 + PenA pdt1 (t_r = 9,705 min, RI = 1560):



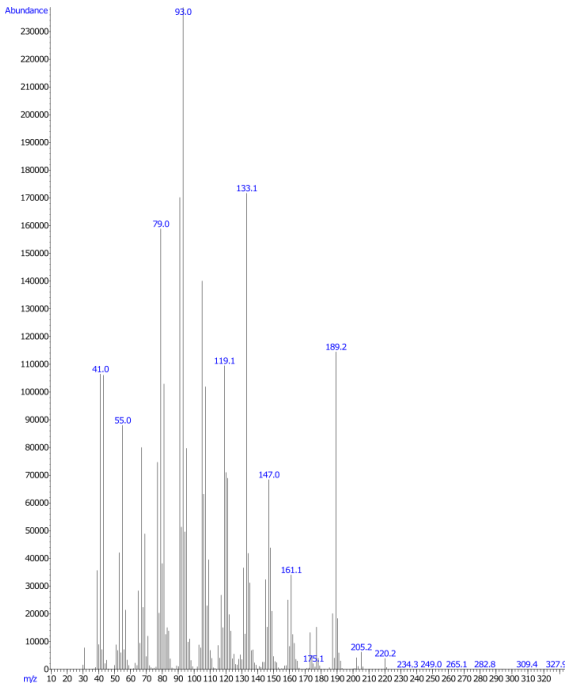
97 + PenA pdt2 (t_r = 10,176 min, RI = 1639):



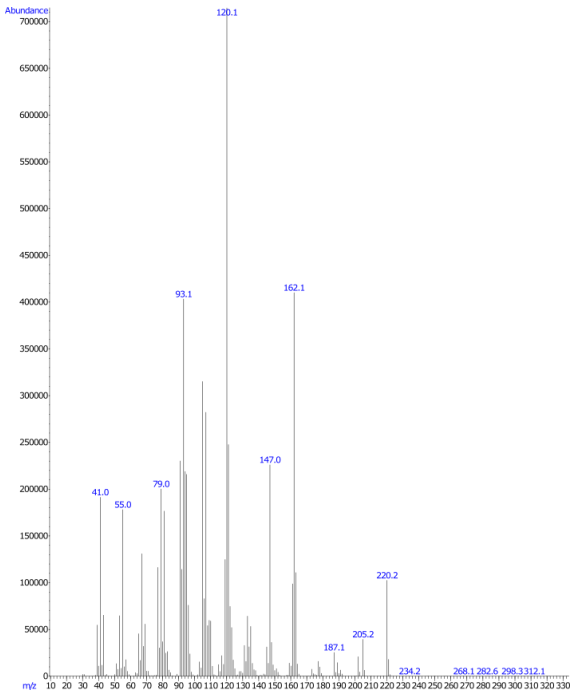
97 + PenA pdt3 (t_r = 10,236 min, RI = 1650):



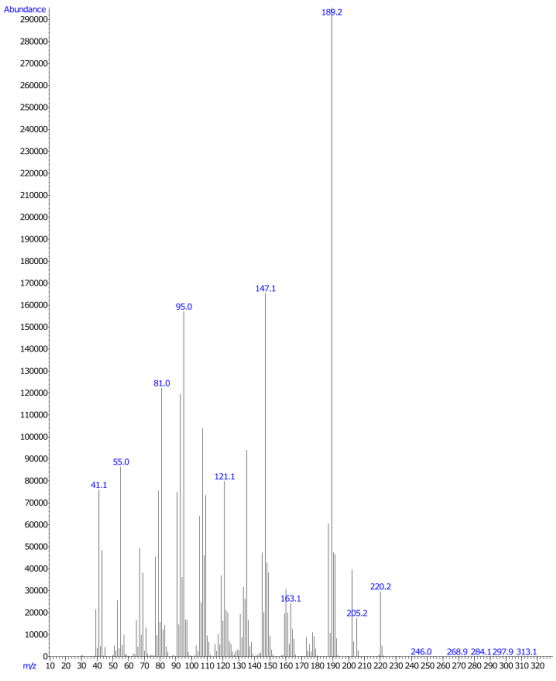
97 + GcoA pdt2 (t_r = 10,802 min, RI = 1751):



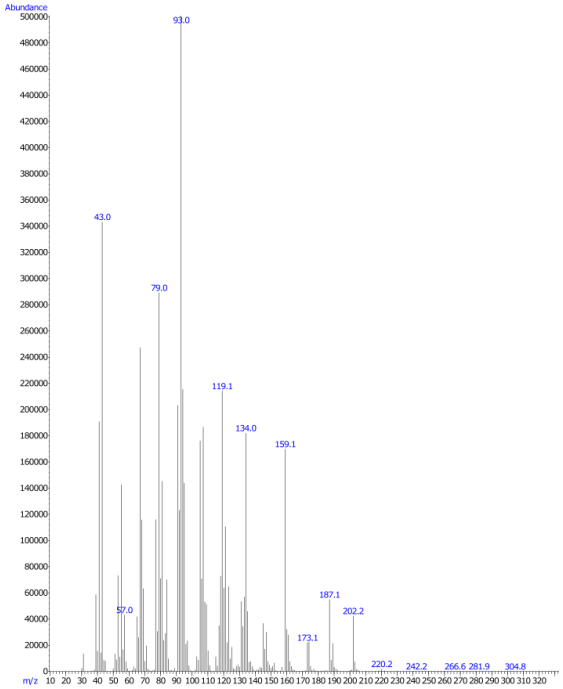
97 + Tps32 pdt2 (t_r = 10,727 min, RI = 1737):



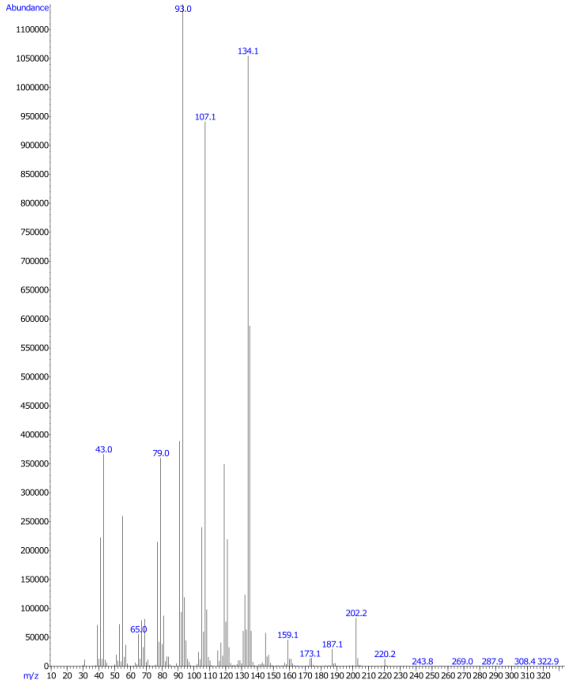
97 + Cyc1 pdt1 (t_r = 10,494 min, RI = 1694):



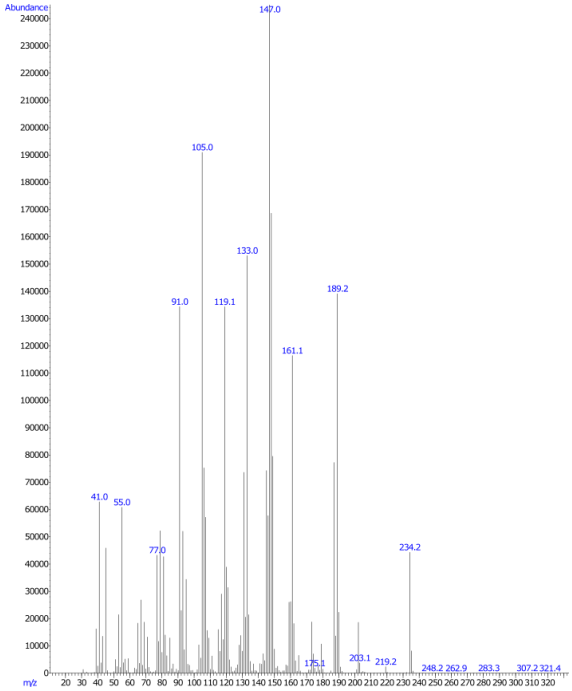
97 + Tri5 pdt2 (t_r = 11,092 min, RI = 1804):



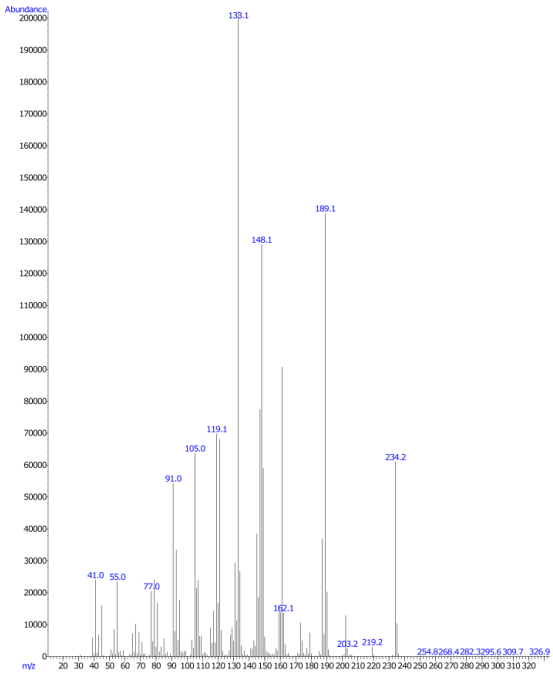
97 + Tri5 pdt3 (t_r = 11,197 min, RI = 1824):



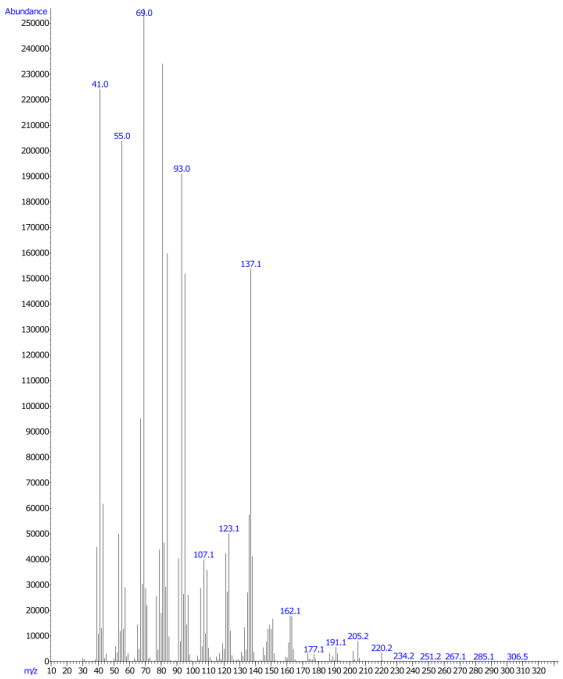
133 + Bot2 pdt1 (t_r = 9,552 min, RI = 1534):



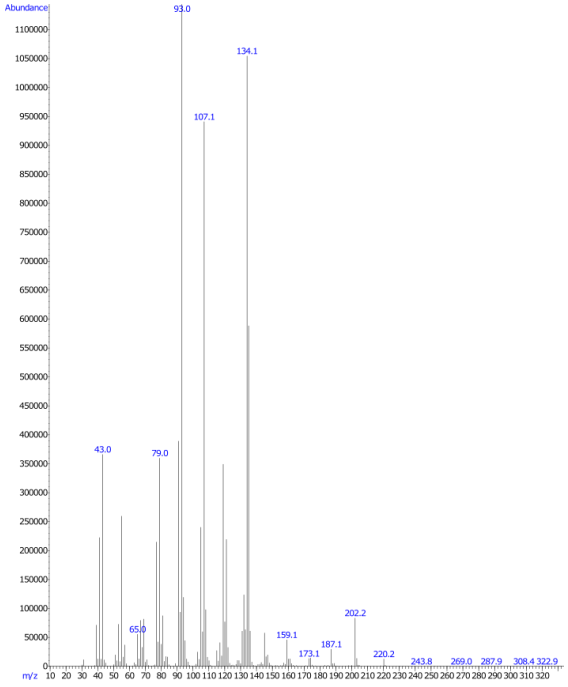
133 + Bot2 pdt2 (t_r = 10,143 min, RI = 1633):



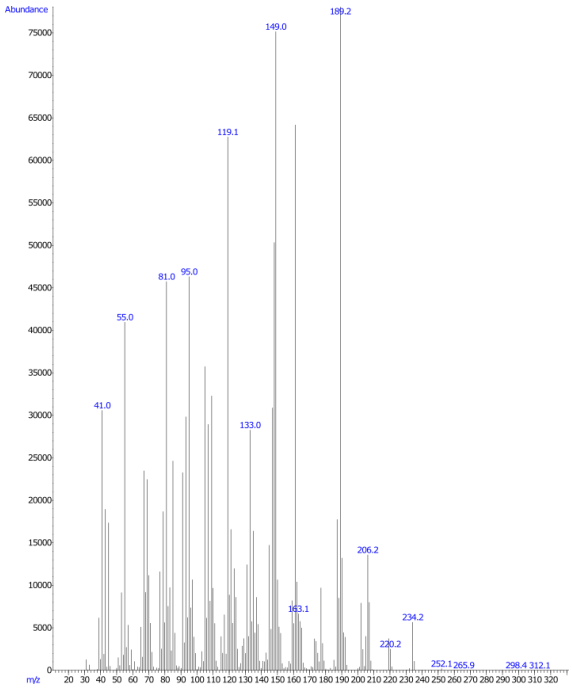
133 + Bot2 pdt3 (t_r = 10,599 min, RI = 1713):



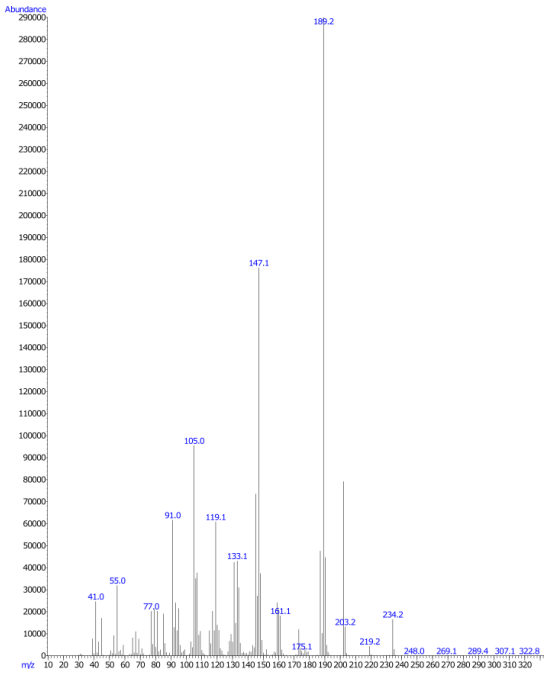
133 + Bot2 pdt4 (t_r = 10,745 min, RI = 1740):



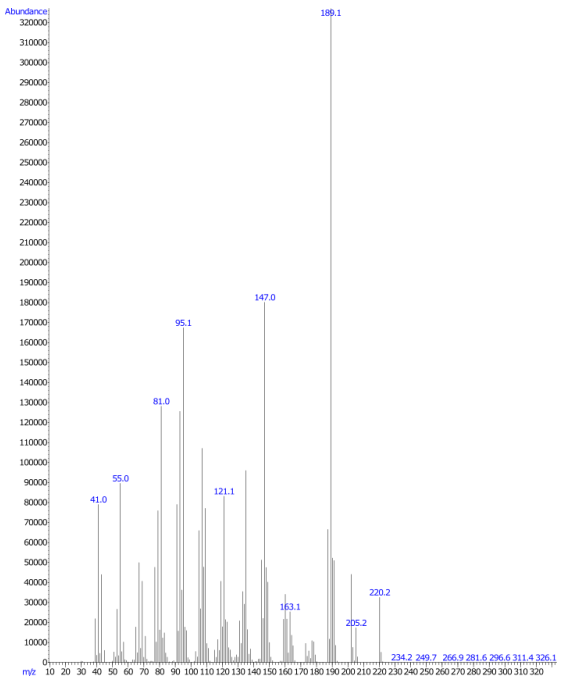
133 + Bot2 pdt5 (t_r = 11,297 min, RI = 1844):



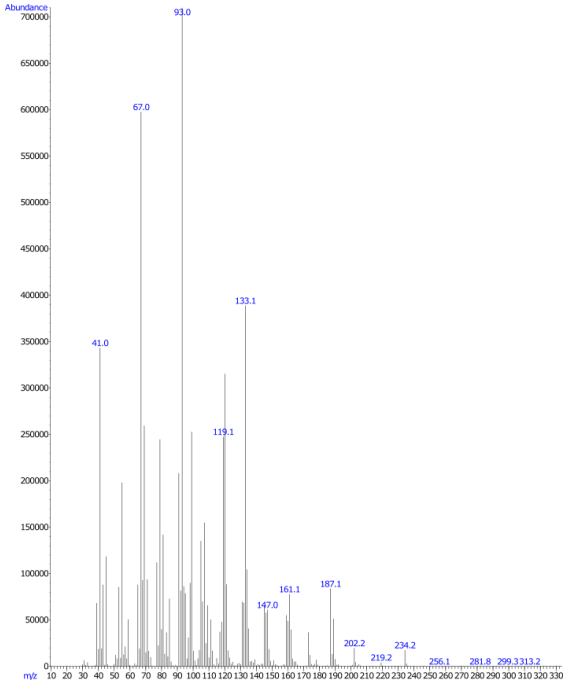
133 + PenA pdt1 (t_r = 9,654 min, RI = 1551):



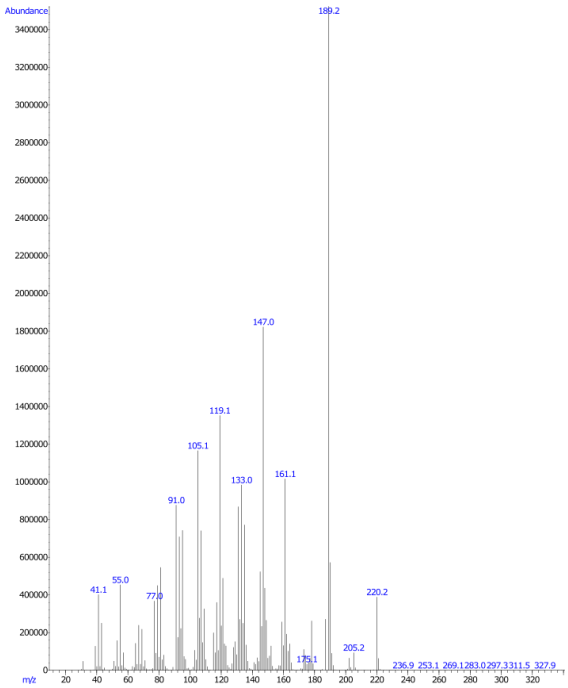
133 + PenA pdt2 (t_r = 10,176 min, RI = 1615):



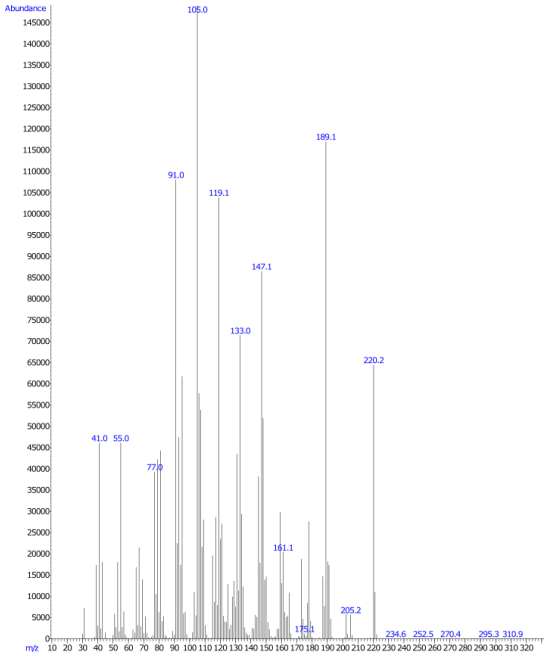
133 + Cop4 pdt1 (t_r = 10,348 min, RI = 1669):



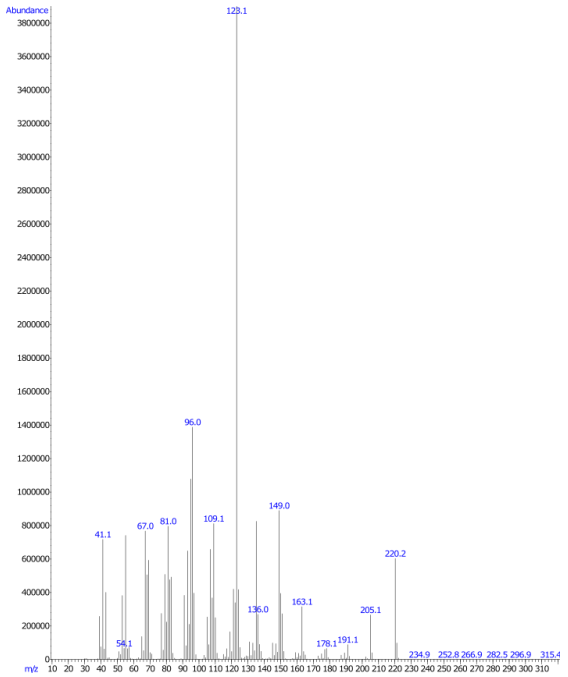
134 + Bot2 pdt3 (t_r = 10,758 min, RI = 1750):



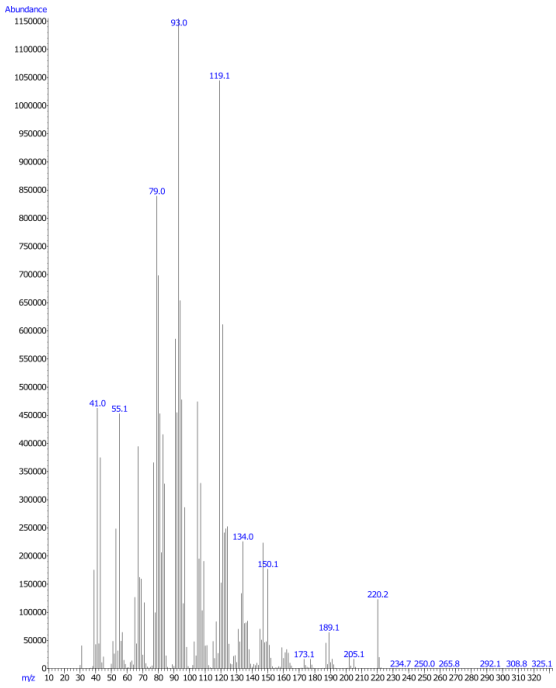
134 + PenA pdt1 (t_r = 10,277 min, RI = 1664):



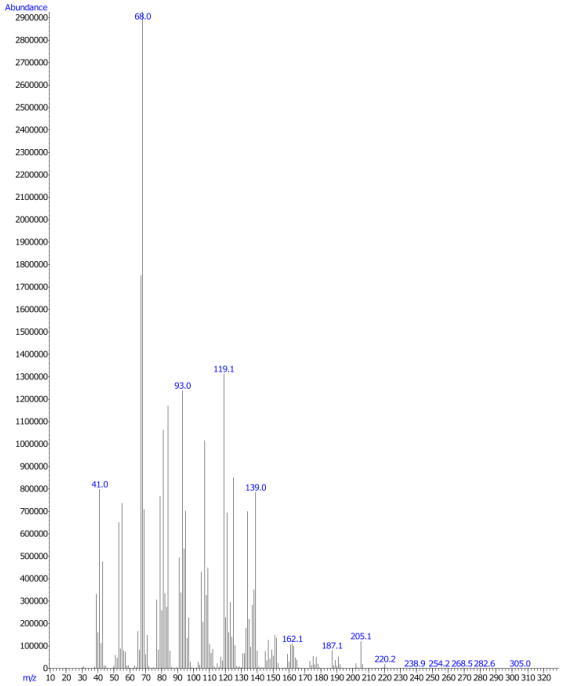
134 + PenA pdt2 (t_r = 10,648 min, RI = 1730):



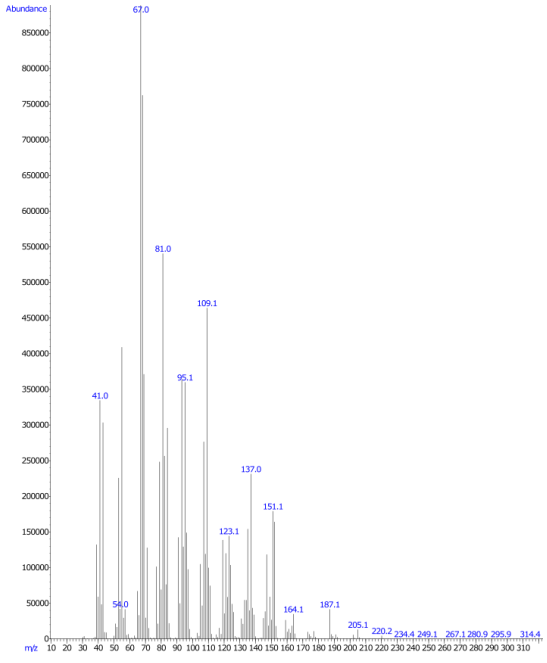
134 + PenA pdt3 (t_r = 10,995 min, RI = 1793):



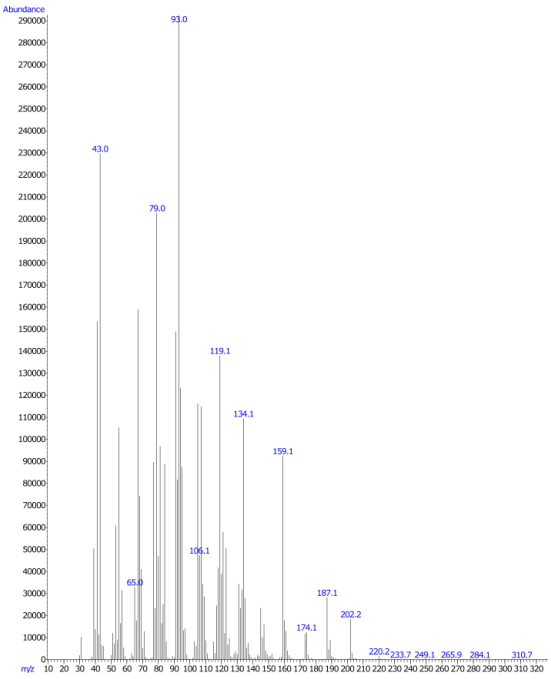
134 + GcoA pdt1 (t_r = 10,504 min, RI = 1703):



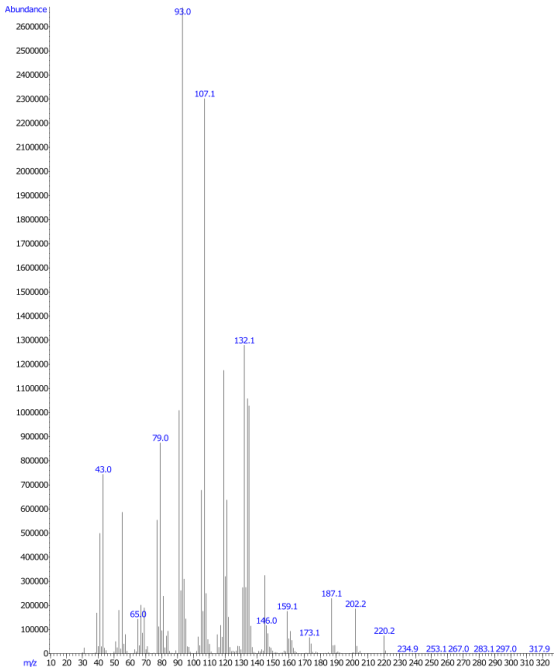
134 + Tri5 pdt1 (t_r = 9,557 min, RI = 1542):



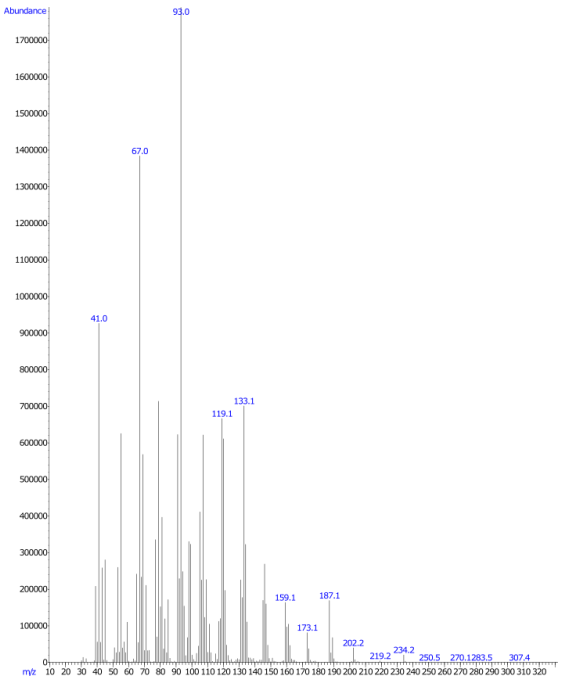
134 + Tri5 pdt2 (t_r = 11,015 min, RI = 1796):



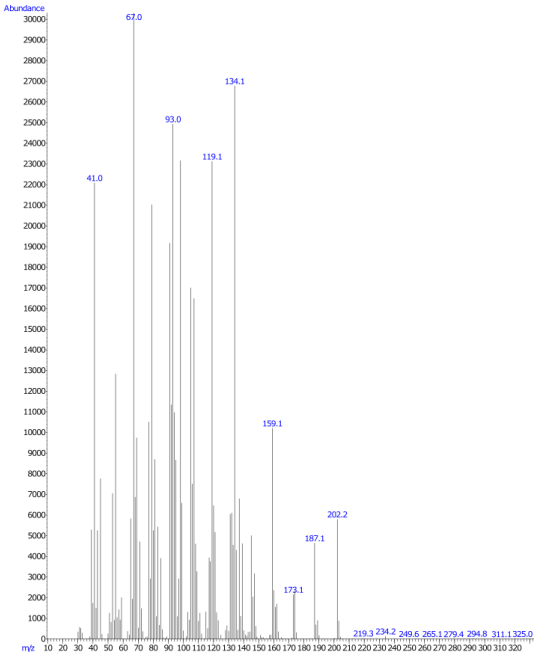
134 + Tri5 pdt3 (t_r = 11,085 min, RI = 1810):



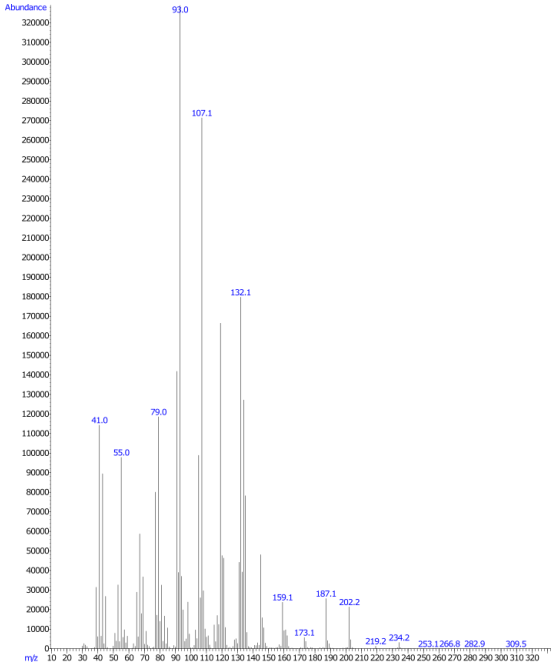
102 + Tri5 pdt1 (t_r = 10,257 min, RI = 1660):



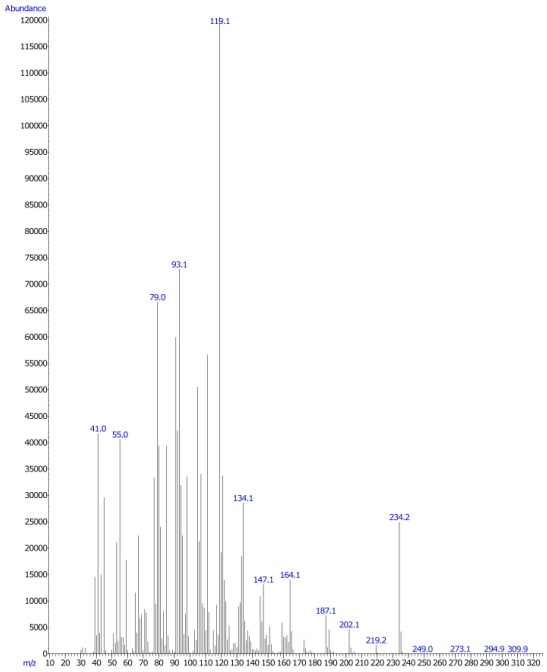
102 + Tri5 pdt2 (t_r = 10,641 min, RI = 1728):



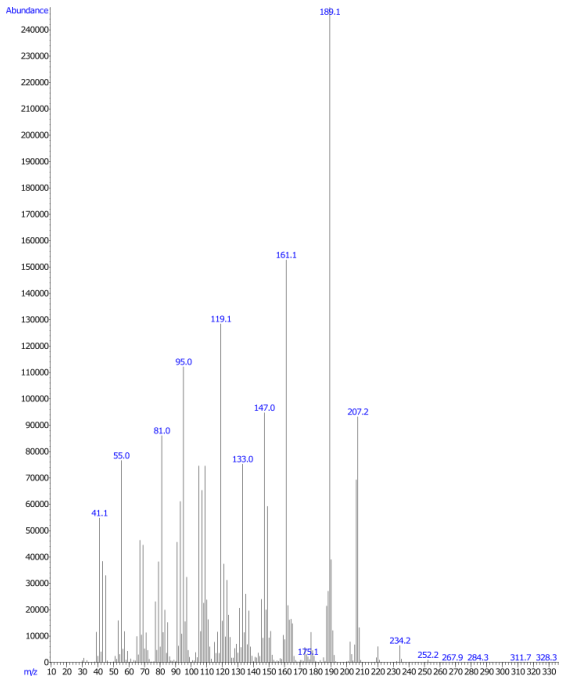
102 + Tri5 pdt3 (t_r = 10,767 min, RI = 1752):



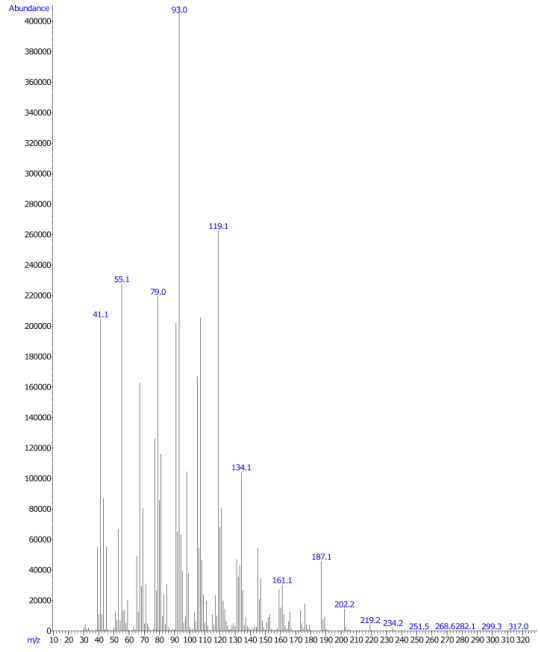
102 + Bot2 pdt2 (t_r = 10,464 min, RI = 1695):



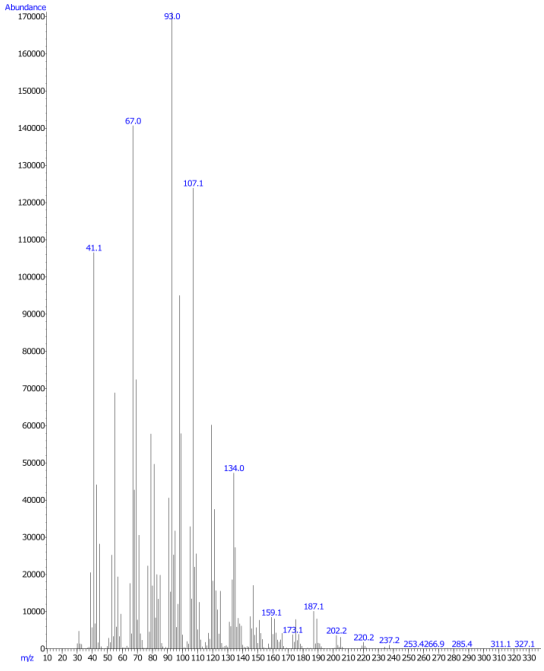
102 + Bot2 pdt3 (t_r = 10,257 min, RI = 1660):



102 + GcoA pdt2 (t_r = 10,545 min, RI = 1710):



102 + GcoA pdt3 (t_r = 11.714 min, RI = 1933):



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12 Lebenslauf und Publikationen

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Name	Malte Moeller
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Akademischer Werdegang

PROMOTIONSSTUDIUM– Leibniz Universität Hannover *seit 01/2019*

Promotion zu dem Thema „Synthese von natürlichen und unnatürlichen terpenoiden Naturstoffen“ im Arbeitskreis von Prof. Dr. Andreas Kirschning am Institut für Organische Chemie

MASTER STUDIUM – Leibniz Universität Hannover *10/2016 - 11/2018*

Studium M.Sc. Wirk- und Naturstoffchemie (Abschlussnote: **1,3**), abschließende Masterarbeit zu dem Thema „Synthese von neuen Cystobactamid-Derivaten“ (Note: **1,0**) im Arbeitskreis von Prof. Dr. Andreas Kirschning am Institut für Organische Chemie

FORSCHUNGSAUFENTHALT – University of California, Berkeley *09/2017 – 03/2018*

Praxissemester bei Prof. Tom Maimone an der University of California at Berkeley

BACHELOR STUDIUM – Medizinische Hochschule Hannover *10/2013 – 09/2016*

Studium B.Sc. Biochemie (Abschlussnote: **1,2** mit Auszeichnung), abschließende Bachelorarbeit zu dem Thema „Rho-GTPase vermittelte Regulation kortikaler Formine von D. discoideum“ (Note: **1,0**) im Arbeitskreis von Prof. Dr. Jan Faix am Institut für Biophysikalische Chemie

ABITUR – Gymnasium Burgdorf *07/2005 – 06/2013*

Erhalt der Hochschulreife am Gymnasium Burgdorf im Naturwissenschaftlichen Profil (Note: **1,4**)

Wissenschaftliche Beiträge und Publikationen

Posterpräsentation bei der ORCHEM 2022 in Münster *09/2022*

Synthesis of Unnatural Terpenoid Natural Products

Posterpräsentation bei dem LUCS 2022 in Hannover *07/2022*

Towards the Total Synthesis of Unnatural Terpenoid Natural Products

Posterpräsentation bei der PACIFICHEM 2021 auf Hawaii *12/2021*

Towards the Total Synthesis of Unnatural Terpenoid Natural Products

A Nimbolide-Based Kinase Degrader Preferentially Degrades Oncogenic BCR-ABL *04/2020*

B. Tong*, J.N. Spradlin*, L.F.T. Novaes, E. Zhang, X. Hu, M. Moeller, S.M. Brittain, L.M. McGregor, J.M. McKenna, J.A. Tallarico, M. Schirle, T.J. Maimone#, D.K. Nomura#, ACS Chem. Biol. 2020, 15, 1788-1794, https://doi.org/10.1021/acschembio.0c00348 [* geteilte Erstautorenschaft, # geteilte Co-Autorenschaft]

Scalable Syntheses of Methoxyaspartate and Preparation of the Antibiotic Cystobactamid 861-2 and Highly Potent Derivatives *10/2019*

M. Moeller*, M.D. Norris*, T. Planke, K. Cirnski, J. Herrmann, R. Müller, A. Kirschning, Organic Letters, 2019, 21, 8369-8372, https://doi.org/10.1021/acs.orglett.9b03143, [* geteilte Erstautorenschaft]

Posterpräsentation bei der ESOC 2019 in Wien *07/2019*

Improved Synthesis of Cystobactamid 861-2 and Analogs