Towards the Total Synthesis of Meridamycins

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„Life is nothing but an electron looking for a place to rest.”

Albert Szent-Györgyi, The Nobel Prize in Physiology or Medicine 1937

Abstract

This thesis aims towards establishing a route for the synthesis of meridamycins with special focus on 3-normeridamycin.

Meridamycins are non-immunosuppressive pipecolic acid natural products that have shown neuroprotective activity. The first member of the family was isolated in 1994 but, up to this day, there is no total synthesis reported. The structure of meridamycin has been published in several instances but recent analysis of the biosynthetic gene cluster has called into question the absolute configuration of its fourteen stereocentres. The aim of this project is the total synthesis of meridamycin firstly, to confirm the configuration of the stereocentres in this natural product and through that validate the method used to predict those stereocentres based only on gene cluster analysis and, secondly to explore the neuroprotective activity of meridamycin and its derivatives.

The southern fragment of 3-normeridamycin was synthesized in the longest linear sequence of 16 steps in 3.1% overall yield from commercially available starting materials. The synthesis features a highly convergent assembly of the central region containing four asymmetric centres by performing two subsequent stereoselective boron-mediated aldol reactions on either side of the ethyl methyl ketone. The remaining keto group is then reduced by using Evans-Tischenko's method and the proline-containing amino acid fragment is installed using a diazoamide Roskamp reaction, which, to our knowledge, is the first use of this type of reaction in the natural product synthesis. The synthesis of southern fragment was then finished by installing the "tricarbonyl" moiety and closing the lactol ring.

Previously, synthesis of the *C1-C9* part of the northern fragment was achieved by Dominik Göppert MSc. This work further elaborated the synthesis until *C14*. The highlights of the sequence are three boron-mediated transformations – firstly alkylating the terminal alkyne using Zweifel olefination, then performing a directed boron insertion to the distal position of the homopropargylic alcohol and finally attaching the *C10-C14* fragment by lithiation-borylation methodology. Overall, the *C1-C14* section of the northern fragment of meridamycin was prepared in a four-step sequence from *C1-C9* fragment in 14.9% yield.

In the course of the work, the synthesis of the sourthern fragment of 3-normeridamycin was achieved and a significant progress was made towards completing the northern fragment.

Keywords: total synthesis, natural products, meridamycin

Kurzfassunng

Die vorliegende Arbeit befasst sich damit, einen Weg für die Synthese von Meridamycinen mit besonderem Fokus auf 3-Normeridamycin zu etablieren.

Meridamycine sind nicht-immunsuppressive Pipecolinsäure-Naturstoffe, die eine neuroprotektive Aktivität zeigen. Das erste Mitglied dieser Familie wurde 1994 isoliert, jedoch ist bis heute keine Totalsynthese bekannt. Die Struktur von Meridamycin wurde in mehreren Fällen publiziert, aber die jüngste Analyse des Biosynthesegenclusters hat die absolute Konfiguration seiner vierzehn Stereozentren in Frage gestellt. Ziel dieses Projekts ist die Totalsynthese von Meridamycin, um einerseits die Konfiguration der Stereozentren in diesem Naturstoff zu bestätigen und dadurch die Methode zu validieren, mit der diese Stereozentren nur auf der Grundlage der Genclusteranalyse vorhergesagt werden können. Andererseits, soll die neuroprotektive Aktivität von Meridamycin und seiner Derivate untersucht werden.

Das Südfragment von 3-Normeridamycin wurde in einer längsten linearen Sequenz von 16 Stufen mit einer Gesamtausbeute von 3,1% aus kommerziell erhältlichen Ausgangsverbindungen synthetisiert. Die Synthese zeichnet sich durch eine stark konvergente Anordnung des zentralen Abschnitts aus vier asymmetrischen Zentren aus, indem zwei aufeinanderfolgende stereoselektive Bor-vermittelte Aldolreaktionen auf beiden Seiten des Ethylmethylketons durchgeführt werden. Die verbleibende Ketogruppe wird anschließend unter Verwendung des Evans-Tischenko-Protokolls reduziert. Das Prolin-enthaltende Aminosäurefragment wird unter Verwendung einer Diazoamid-Roskamp-Reaktion installiert, dessen Einsatz unseres Wissens nach die erste Verwendung dieser Art von Reaktion in der Naturstoffsynthese ist. Die Synthese des südlichen Fragments wird dann beendet, indem die "Tricarbonyl"-Einheit installiert und das Lactol geschlossen wird.

Bisher wurde die Synthese des C1-C9-Abschnitts des Nordfragments von Dominik Göppert MSc durchgeführt. Diese Arbeit hat die Synthese bis C14 weiterentwickelt. Die Highlights der Sequenz sind drei Bor-vermittelte Transformationen: Zu Beginn wird das terminale Alkin mit Hilfe der Zweifel-Olefinierung alkyliert, anschließend die distale Position des Homopropargylalkohols dirigierend boryliert und das C10-C14-Fragment wird anschließend durch eine Lithiierungs-Borylierungsmethode installiert. Insgesamt wird der C1-C14-Abschnitt des Meridamycin-Nordragments in einer vierstufigen Sequenz aus dem C1-C9-Fragment in einer Ausbeute von 14,9% hergestellt.

Im Laufe der Arbeit wurde die Synthese des Nebenfragments von 3-Normeridamycin erfolgreich abgeschlossen und bedeutende Fortschritte bei der Vollendung des Nordfragments erzielt.

Schlüsselwörter: Totalsynthese, Naturstoffe, Meridamycin

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Table of Contents

Abbreviations

°C – degrees Celsius

2,2-DMP – 2,2-dimethoxypropane

α – optical rotation

Å – angstrom

δ – chemical shift

μL – microlitre

μW – microwave

μmol – micromole

ABSA – acetamidobenzenesulfonyl azide

Ac – acyl

aq. – aqueous

Ar – aryl

AT – acyl transferase

BINAP – 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl

Bn – benzyl

Boc – *tert*-butyloxycarbonyl

BSA – bis(trimethylsilyl)acetamide

CAM – ceric ammonium molybdate

CAN – ceric ammonium nitrate

Cb – diisopropylcarbamoyl

Cp – cyclopentyl

CSA – camphorsulfonic acid

Cy – cyclohexyl

D – aspartate

DCC – *N*,*N'*-dicyclohexylcarbodiimide

DDQ – 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DEIPS – diethylisopropylsilyl

DIAD – diisopropyl azodicarboxylate

DIBAL – diisobutylaluminium hydride

DIPCl – *B*-chlorodiisopinocampheyl borane

D*i*PEA – *N*,*N*-diisopropylethylamine

DMAP – 4-dimethylaminopyridine

DMDO – dimethyldioxirane

DMF – *N*,*N*-dimethylformamide

DMP – Dess-Martin periodinane

DMSO – dimethylsulfoxide

DNA – deoxyribonucleic acid

DNPH – dinitrophenylhydrazine

dr – diastereomeric ratio

EC_{50} – half maximal effective concentration

ECD – electronic circular dichroism

EDCI – *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride

ee – enantiomeric excess

eq – equivalent

ER – enoyl reductase

Et – ethyl

FID – flame ionization detector

FKBP – FK506 binding protein

GC – gas chromatography

HMDS – hexamethyldisilazane

HMPA – hexamethylphosphoramide

HOMO – highest occupied molecular orbital

HPLC – high performance liquid chromatography

i – *iso*

IC_{50} – half maximal inhibitory concentration

Ipc – *iso*pinocampheyl

KHMDS – potassium hexamethyldisilazid

KR – ketoreductase

KS – ketosynthase

L – leucine

LA – Lewis acid

LDA – lithium diisopropylamide

LiHMDS – lithium hexamethydisilazid

M – molar

*m*CPBA – *meta*-chloroperbenzoic acid

Me – methyl

MeCN – acetonitrile

Mip – macrophage infectivity potentiator

mL – milliliter

MPP^+ – 1-methyl-4-phenylpyridinium

MS – molecular sieves

mTOR – mammalian target of rapamycin

NBO – natural bond orbital

NBS – *N*-bromosuccinimide

ng – nanogram

NHC – *N*-heterocyclic carbene

NHK – Nozaki-Hiyama-Kishi

nM – nanomolar

NMO – *N*-morpholine oxide

NMR – nuclear magnetic resonance

NOESY – nuclear Overhauser effect spectroscopy

NRPS – non-ribosomal peptide synthetase

Ns – nosyl

ORF – open reading frame

P – proline

PEPPSI – pyridine-enhanced precatalyst preparation stabilization and initiation

Ph – phenyl

PIDA – (diacetoxyiodo)benzene

pin – pinacol

PKS – polyketide synthase

PMA – phosphomolybdic acid

PMB – 4-methoxybenzyl

Pr – propyl

py – pyridine

R – alkyl

R_f – retention factor

s – *sec*

sat. – saturated

t – *tert*

TBAF – tetrabutylammonium fluoride

TBDPS – *tert*-butyldiphenylsilyl

TBS – *tert*-butyldimethylsilyl

TES – triethylsilyl

Tf – triflyl

TFA – trifluoroacetic acid

THF – tetrahydrofuran

TIB – 2,4,6-triisopropyl benzoate

TIPS – triisopropylsilyl

TLC – thin-layer chromatography

TMEDA – tetramethylethylenediamine

TMS – trimethylsilyl

TRIP – 3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate

UV-Vis – ultraviolet-visible

VMAR – vinylogous Mukaiyama aldol reaction

W – tryptophan

1. Introduction

1.1 Chemistry as a Tool for Making Life Better

Life is chemistry. Chemistry explores the interactions of living and non-living matter on its most basic level. While the public's appreciation of chemists might not be as high as that of engineers, physicists or biologists, none of their work would be possible without our help – be it the materials used by engineers and physicists or the knowledge and methods biologists apply for researching the underlaying interactions between living organisms. Paraphrasing George Whitesides: "We (the chemists) change the way you live and die."[1] Not on an abstract level but very directly by being responsible for preparing almost any material you use in everyday life, protecting the food you eat from pests and preserving it until you get hungry, and even keeping you alive against any kind of disease you might contact during your life. It can be even said that no other field of science has more direct effect and greater impact on your everyday life compared to chemistry.

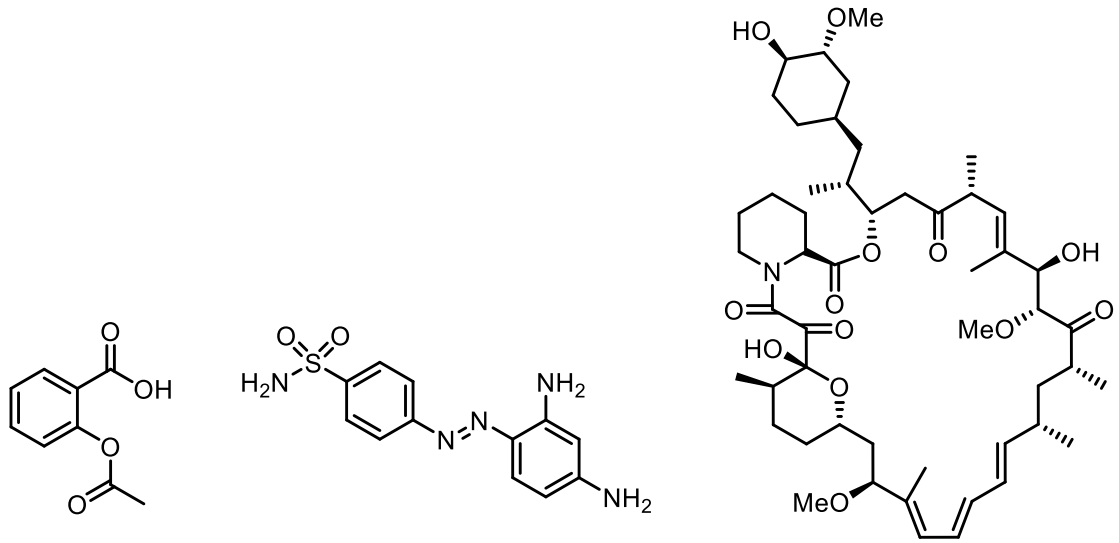


Figure 1: Structures of aspirin (**1**), prontosil (**2**) and rapamycin (**3**).

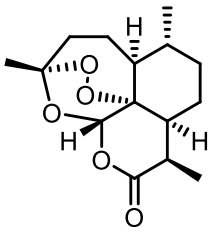
Introduction of synthetic drugs had one of the greatest impacts on overall improvement of life quality during the 20th century, preceded only by improvements in sanitation and availability of clean drinking water. Not to mention the first, even the last two are closely related to

advancements in chemical science – either in the form of chemical water purification systems or materials used for construction of the sanitation networks. As for the first, then preparing new drugs and other bioactive compounds is the centerpiece of synthetic organic chemistry. The role of synthetic drugs in the development of medical science cannot be over-emphasized. Be it introduction of common use pain killers (e.g. aspirin (**1**)), antibiotics (e.g. sulfonamide **2**), immunosuppressants (e.g. rapamycin (**3**)) or other drugs, they have been paramount for saving more and more human lives (Figure 1).

While many of the previously untreatable diseases can nowadays be cured with a few pills, there remains a number of afflictions which we are still defenseless against. For example, with the increase in life-expectancy, neurodegenerative disorders like Alzheimer's[2] and Parkinson's[3] disease have emerged as an increasingly important field of research. The loss in quality of life and high costs related to managing these diseases, have prompted many large pharmaceutical companies to invest heavily into researching for a cure. Unfortunately, the complexity of neurodegenerative diseases and difficulties in identifying the underlying mechanism, have made finding one unsuccessful. While a cure for those diseases has thus far eluded the medical community, then treatment of symptoms is still possible. Some of the drugs viable for symptomatic treatment of Parkinson's disease is rapamycin and related pipecolic acid natural products.

New drugs cannot be discovered and made without the help of chemists. The methods for finding new drugs can be divided into two categories: 1) target-based discovery, where the molecular target for the drug is known and the structure of the drug can be optimized using computational methods and 2) phenotypic discovery, where compounds are tested directly on diseased samples and after positive response the drug and the target can be elucidated. Interestingly, even though target-based discovery enables modeling of drugs that are highly specific for a particular disease and have minimal amount of side-effects, then most of the first-in-class drugs still come from phenotypic discovery.[4] One recent success story of phenotypic screening is artemisin (**4**), an anti-malarial drug discovered from Chinese herbal medicine which was the object of 2015 Nobel Prize in Medicine (Figure 2).[a]

[a] The Nobel Prize was awarded in 2015 even though the drug itself was discovered already in 1972.



Artemisin
(4)

Figure 2: Structure of artemisin (**4**).

Isolation of potential drugs from phenotypic screening of herbal medicines or bacterial extracts necessitates a determination of their structure. There are numerous analytical methods available to determine the structure of isolated compounds and with advances in our understanding of biosynthesis of those compounds, the computational methods predicting the structure based on the genetic sequence are providing a complementary method to traditional analytical techniques. Nevertheless, those methods are not infallible and the final proof for the proposed structure would be laboratory preparation of the compound of interest.

All aforementioned reasons illustrate the importance of synthetic organic chemistry and research into preparation of natural products. Maybe one day chemical and biological science will evolve to the level where the structures of compounds can be completely predicted based on the amino acid sequence of the genes, and those genes can be modified to produce every kind of molecule one can think of, but this day is not here yet. Until then, synthetic preparation of the compounds remains a fundamental part of chemical science and cornerstone of drug discovery.

1.2 Meridamycins

1.2.1 Meridamycins and Other Pipecolic Acid Natural Products

The first entry into the class of pipecolic acid natural products was rapamycin (**3**), isolated in 1975 from an Eastern Island soil sample and determined to be synthesized by *Streptomyces hygroscopicus.*[5] It did not attract much attention from the synthetic community until 1987, when FK506 (**5**) was isolated and its immunosuppressive activity, which was greater than then commonly used cyclosporins, was discovered.[6] The next ten years saw intense synthetic interest towards preparation of those two compounds as well as towards the chemistry of related structural motifs. That work culminated with total syntheses of FK506 by scientist at Merck,[7] and groups of Schreiber[8] and Ireland;[9] and rapamycin by groups of Nicolaou,[10] Schreiber,[11] Danishefsky,[12] Smith[13] and Ley[14].

In 1994, a new pipecolic acid natural product, meridamycin (**6**), was isolated from two different strains of *Streptomyces* independently by scientists at Sandoz[15] and Merck[16]. The new compound shared with rapamycin and FK506 the same FKBP-binding pipecoline–tricarbonyl-lactol motif but lacked the immunosuppressive activity. Probably because of that, there was not much synthetic interest towards the molecule and up to this day there is no total synthesis reported.

Structurally, meridamycin is a 27-membered macrolactone containing 14 stereogenic centres. The western part of the molecule harbors the highly characteristic FKBP-binding pipecoline-tricarbonyl-lactol motif, which was one of the central elements in the rapamycin and FK506 syntheses. The pipecolinic acid is joined with the polyketide part through an amide bond, which is directly followed by a carbonyl group and a lactol. That means that in the open-chain form, there would be three carbonyl groups next to each other, hence the term “tricarbonyl”. The polyketide part of the molecule consists of a 30-carbon backbone containing three *E* double bonds, which is adorned with eight hydroxy, six methyl and one ethyl group, all synthesized directly on the PKS. As opposed to rapamycin and FK506, meridamycin lacks the cyclohexyl moiety at the beginning of the polyketide fragment (Figure 3).

In 2006, two analogues of meridamycin – 36-keto-meridamycin[17] and 3-nomeridamycin (**11**)[18] were isolated from mutated *Streptomyces sp*. NRRL 30748 and fermentation extracts of

the soil actinomycete *Streptomyces sp*. LL-C31037, respectively. In 3-normeridamycin, the pipecolic acid moiety is substituted with L-proline and it showed promising results in neuroprotective assays. Four more analogues, meridamycins A, B, C and D, were isolated in 2016 from SR107 mutant strain of *Streptomyces sp*. LZ35.[19] Meridamycins A (**7**) and B (**8**) are uncyclized analogues of meridamycin, where the acid moiety of pipecoline is either free or methylated, respectively. Meridamycins C (**9**) and D (**10**) are truncated analogues, in which the polyketide chain is two carbons shorter and the pipecolinic acid moiety is not present. Additionally, the carbon corresponding to *C14* in meridamycin is in both compounds fully reduced. The terminal carbon is oxidized to the carboxylic acid and meridamycins C (**9**) and D (**10**) correspond to the free acid and the methyl ester, respectively.

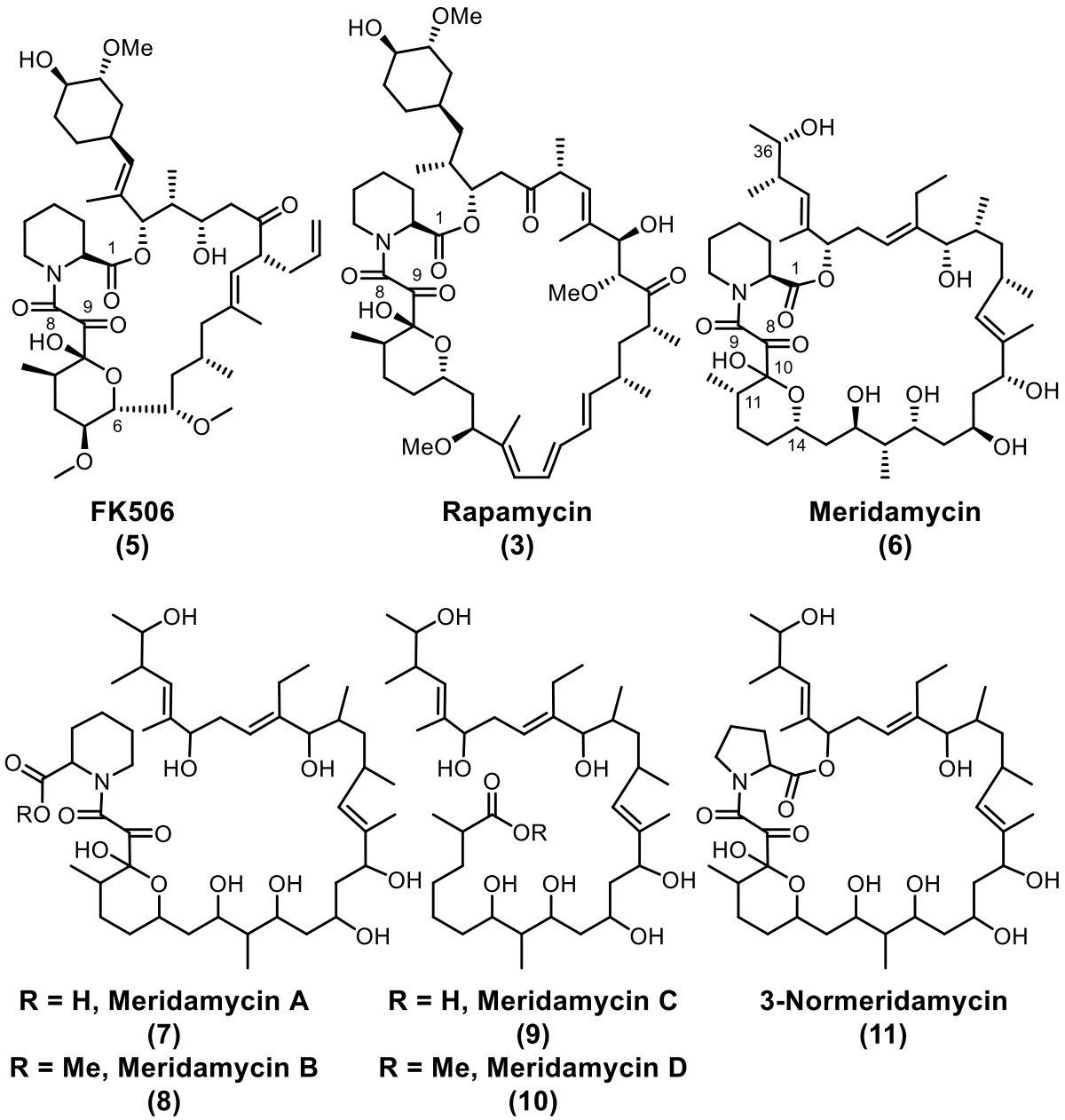


Figure 3: Pipecolic acid natural products FK506 (**5**), rapamycin (**3**), meridamycin (**6**), meridamycin analogues (**7**-**10**) and 3-normeridamycin (**11**).

1.2.2 Bioactivity of Meridamycins and Pipecolic Acid Natural Products

The pipecolic acid natural products rapamycin (**3**) (Sirolimus, Rapamune®) and FK506 (**5**) (Tacrolimus, Prograf®) are approved drugs that are used to suppress the immunoresponse after organ transplants. They bind to FK506-binding proteins (e.g. FKBP12), which mechanistically are peptidylpropyl *cis-trans* isomerases, form drug-target ternary complexes and suppress the immune response by inhibiting the signal-transduction pathways required for T-cell proliferation. The protein binding region of both of these molecules comprises of the pipecolate and hemiketal moieties, and the *C8* and *C9* carbonyl groups (Figure 3) have been demonstrated to play the critical role in forming the FK506 complex with FKBP12.[20] Meridamycin containing the same region as aforementioned immunosuppressants, also binds to the FKBP12 but it does not induce the immunosuppressive effect. The latter has been shown to be caused by the cyclohexyl moiety present in rapamycin (**3**) and FK506 (**5**) but absent in meridamycins.

In fact, meridamycin (**6**) binds with FKBP12 with an IC_{50} of 10 ng/mL in competitive binding assay, which is more strongly than either FK506 or rapamycin and can therefore reverse the immunosuppressive effect of rapamycin and FK506. Additionally, meridamycin has reported to be a Mip (macrophage infectivity potentiator) inhibitor, which means it could be used to treat some viral infections caused by organisms of the genera Chlamidia, Neisseria and Legionella. In addition to immunosuppressive and proliferative activity, rapamycin and FK506 have been shown to promote nerve growth regeneration in animal models in both peripheral and central nervous system and have been proposed for treatment of spinal cord injuries[21] Alzheimer's and Parkinson's diseases.[22] Meridamycins, which bind FKBPs but do not act with calcineurin or mTOR effector proteins, are non-immunosuppressive but retain their neuroregenerative ability,[23] therefore being more suitable for treatment of neurological diseases. For example, 3-normeridamycin (**11**) restored dopamine uptake with an EC_{50} of 110nM in dopaminergic receptors challenged with neurotoxin MPP^+.[18] Meridamycin and meridamycin analogues have been patented for treatment of neurodegenerative disorders.[24,25]

1.2.3 Biosynthesis of Meridamycins

Meridamycin consists of a polyketide region and an amino acid region, therefore the biosynthesis is governed by a type I polyketide synthase (PKS) and a non-ribosomal peptide synthetase (NRPS). He et al.[17] and Haydock et al.[26] have separated the biosynthetic gene cluster from *Streptomyces* sp. NRRL 30748 and *Streptomyces* sp. DSM 4137, respectively.

The group of He determined the DNA sequence and identified six genes responsible for the biosynthesis of meridamycin (**6**) – one NRPS gene (*merP*), four PKS genes (*merA, B, C, D*), and a cytochrome P450 monooxygenase gene (*merE*). The merP gene exhibits similarity with RapP and FkbP, which are genes responsible for installing the pipecolic acid moiety in rapamycin and FK506, respectively. Similarily to RapP and FkbP, merP has the C-A-T-C domain organization. The A domain is supposedly responsible for recognizing and activating the L-pipecolic acid, while the last C domain is responsible for polyketide-peptide chain termination and macrocyclization. The four PKS genes *merA*, *merB*, *merC* and *merD* encode a large PKS complex consisting of four polypeptides containing 65 enzymatic domains including one loading module and 14 extender modules. The 14 modules extend the carbon chain by 28 carbons, exactly matching with the polyketide structure of meridamycin and not containing any silent modules (as was the case for the biosynthetic gene clusters of FK506 and rapamycin). The predicted substrate specificities of acyltransferase (AT) domains agree with the determined structure of meridamycin: AT3, 8, 9, 11, 12 and 14 are specific for malonate extenders; AT1, 2, 5, 6, 7, 10 and 13 are specific for methylmalonate; and AT4 is specific for ethylmalonate. Downstream of *merD* is the *merE* gene, which encodes a cytochrome P450 monooxygenase presumably responsible for oxidation at the *C9* of the macrolactone ring.[17]

The group of Haydock determined that the polyketide backbone of meridamycin in DSM 4137 was encoded by three large ORFs – *merA, merB* and *merC.* Analysis of the amino acid sequence of encoded AT domains conformed to the structure of meridamycin consisting of acetate starter unit and 14 PKS extension modules. The organization of the PKS showed close similarity with the related cluster from *Streptomyces* sp. NRRL 30748 with 95% identity at the protein level. Haydock also proposed that there was a single base error in the sequence reported by He et al. resulting in dividing the last gene into two, while actually it should be a contiguous sequence encoding a single ORF.[26] Immediately downstream from *merC* lies a cytochrome P450 hydroxylase denoted *merD* (corresponding to *merE* for He et al.), which

surprisingly, did not show particular similarity to the genes from NRRL 30746. Upstream of *merA* is the *merP* which exhibits very high end-to-end sequence similarity with the corresponding gene from NRRL 30748 and high degree of identity to other NRPS proteins incorporating pipecolate (Figure 4).

Both biosynthetic gene clusters agree that the complete polyketide backbone is synthesized by PKS without any silent modules present and without any post-PKS modifications with the exception of oxidation of the "tricarbonyl" region by cytochrome P450 monooxygenase. The pipecolate unit is installed by an upstream NRPS, which is also responsible for the macrocyclization giving directly the structure of meridamycin. One can assume that the biosynthesis of different meridamycin analogues follows the same principal pathway with differences only in isolated biosynthetic modules. Therefore, one could also assume that the stereochemistry in meridamycin and its analogues should be self-consistent.

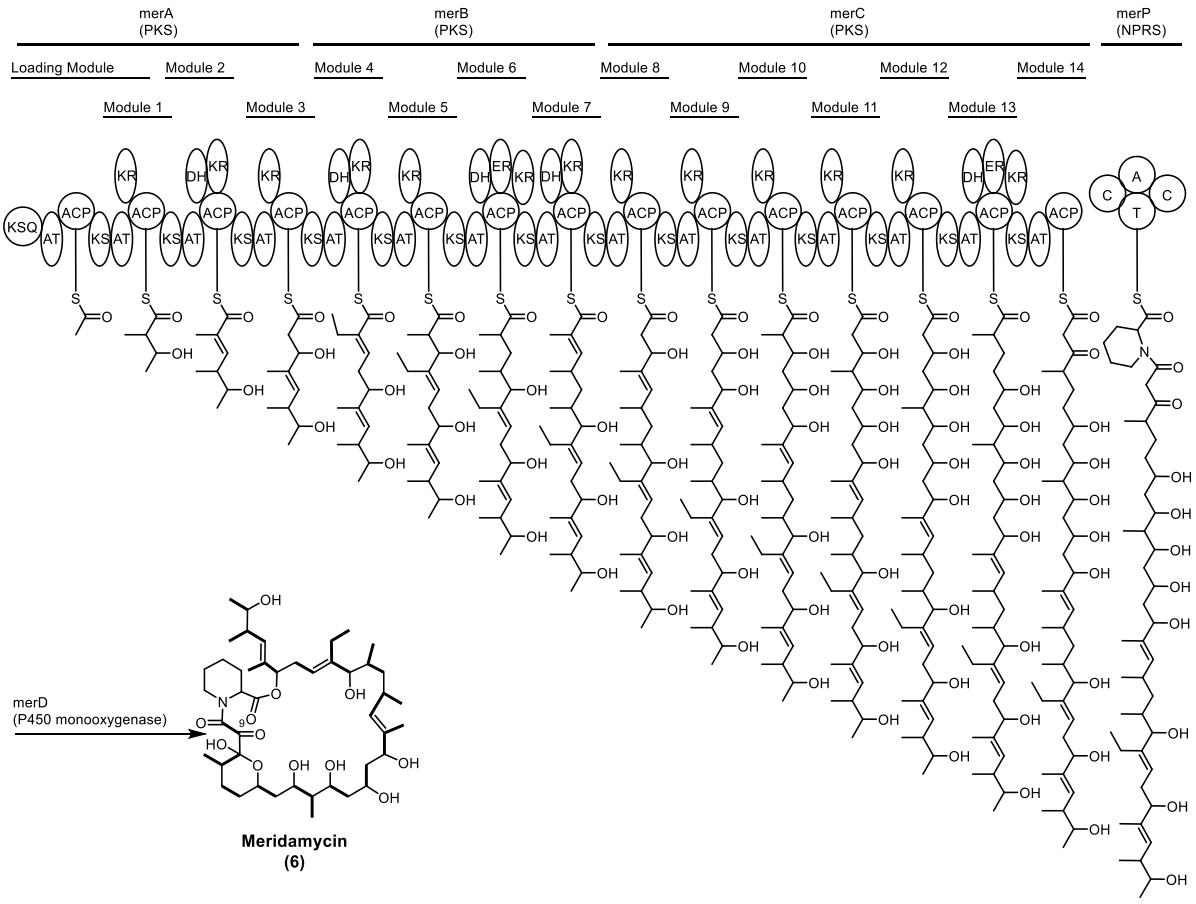


Figure 4: Proposed biosynthesis of meridamycin (**6**) according to He[17] and modified by Haydock.[26]

1.3 Methods for Determination of Stereochemistry in Natural Products

Isolation of new natural compounds always requires the identification of the isolated structure. While the molecular formula and connectivity between atoms is relatively easy to determine, then assigning relative and absolute configuration to stereogenic centres can be a more difficult endeavor.

The most reliable method for determining the absolute configuration of stereocentres in natural products is the X-ray crystallography – when the molecule give well-defined crystals, the structure determination is an easy task. In cases, when the crystals are not obtainable, some other methods have to be applied. The most convenient and widely applied structural analysis method, NMR spectroscopy, does not offer direct information about absolute configuration but using chiral derivatization (e.g. Mosher esters[27]) or chiral shift reagents[28] provides the absolute configuration in a more roundabout way. Recently, ECD (electronic circular dichroism) has evolved into a viable tool for absolute configuration determination – the better is a match between calculated ECD spectrum and the measured one, the higher is the chance of assigned configuration being correct.[29]

In addition to methods for determining the absolute configuration, NMR provides a number of options for obtaining information about the relative configuration of atoms in the molecule. The NOESY experiments show which atoms are close to each other in three-dimensional space, the Ryschnovski acetonide method gives the relationship between 1,3-diols[30], and comparing proton-proton and proton-carbon coupling constants according to the Murata method[31] can give information about two adjacent stereocentres. Therefore, if configuration of one of the carbons in the molecule is known, then NMR is a powerful tool for assigning stereocentres in the vicinity. NMR as a method is well suited for compounds with well-defined three-dimensional structures, but less useful for compounds which have many low energy conformations.

For polyketides, absolute stereochemistry can also be assigned based on biosynthetic gene cluster analysis. Namely, as the amino acid sequence of the biosynthetic domain determines its structure and function, then patterns in the amino acid sequence can indicate the stereochemical outcome of the reaction catalyzed by that domain. For example, for isolated methyl groups, Leadley et al. determined that presence of tyrosine in the catalytic domain of

ER (enoyl reductase) gives the L-configured methyl branches, whereas its absence results in the D configuration.[32] The configuration of hydroxy groups and the α-centres is determined by the KR (ketoreductase) domain (the α-centres are generated in the KS (ketosynthase) step but as the 1,3-dicarbonyl compounds are easily enolized, the final stereochemical outcome is determined by the KR region). In the simplest cases, one amino acid at a certain position (D95 and W141 for L-configured alcohols, and P144 and R148 for D-configured alcohols; Caffrey numbering[33]) is indicative of the alcohol configuration. Keatinge-Clay and Stroud determined that for L-configured alcohols, a histidine residue in particular position suggests that α-centre is L-configured and its absence implies to D-configuration. For D-configured alcohols, a proline 13 residues C-terminal to the LDD motif differentiates between the L and D configuration of the α-centre.[34] On the other hand, natural products that are exception to that observation have been reported, which means that the situation is more complicated than previous observations suggest.

Recently, Kalesse and Kitsche used the profile hidden Markov model to analyze the KR regions and to predict the configuration of stereocentres.[35] They found that while, in most cases, previously used single point analysis offers a good indication of the stereochemical outcome, there exists a number of exceptions which would be misclassified using that approach. Their statistical method determined six relevant positions for discriminating between the L- and D-configured alcohols. It gave superior results to the previously used single point method and also offered a quantitative indicator to assess the quality of the prediction. Namely, if the absolute value of the ScoreDiff parameter in their method was greater than 15, then the stereocentre could be assigned with confidence. Comparing their predictions with literature known compounds using leave-one-out cross-validation method, gave a confident prediction to 74 out of 78 compounds. The last four were assigned correctly but with low confidence level.

Using the same method for the α-methyl branches determined four relevant amino acid positions for the set of L-configured alcohols and three relevant positions for D-configured alcohols. They could confidently assign the methyl groups following L-configured alcohols, but due to limited number available sequences with D-configured alcohols, the predictions for D-L and D-D combinations were more likely to give incorrect results. The quality of statistical methods depends on the quality of the input data and as there were less known KR sequences for D-configured secondary alcohols, especially the ones that would be followed by a D-methyl branch, then it reflected in the confidence level of the prediction. That also means that

as more and more PKS sequences are described, the precision of this method can be further increased.

Overall, gene cluster analysis offers a powerful and fast method for predicting the stereochemistry in natural polyketides and recent advances in the field have made it a reliable tool which can be used with confidence.

1.3.1 Stereochemistry of Meridamycins

The overall structure of meridamycin has been reported in three distinct cases[15,16,19] and it has been confirmed by analyses of biosynthetic gene clusters.[17,26] The absolute stereochemistry of its fourteen stereocentres, though, is up to some controversy (Figure 5).[35] Scientists from Sandoz[15] were the first to report the structure of the meridamycin (**6**) as well as the configuration of thirteen out of the fourteen stereocentres, unfortunately they did not provide the basis on which the absolute stereochemistry was determined and they only provided minimal analytic data to support their assignment (Figure 6). In the following publication by Merck,[16] the stereochemistry was left undetermined but they did propose an opposite configuration for the *C23* double bond. More recently, Kalesse and Kitsche analyzed the meridamycin biosynthetic gene cluster by computational methods and found that nine of the thirteen reported stereocentres should have an opposite configuration.[35] They also proposed absolute stereochemistry to the previously unassigned *C27* methyl substituted carbon.

It is difficult to assess the reliability of the stereochemical assignment by scientists at Sandoz based on their publication. It is maybe meaningful to note that the relative stereochemistry of different regions in meridamycin closely matches between assignments by Sandoz and by that of Kalesse and Kitsche. One could then propose that Sandoz determined the relative stereochemistry in the molecule and assigned the absolute stereochemistry according to one stereocentre they were confident about, for example the stereocentre at *C11*, which is consistently L-configured in rapamycin (**3**) and FK506 (**5**), and part of the FKBP12 binding region but D-configured in meridamycins according to the method by Leadley.

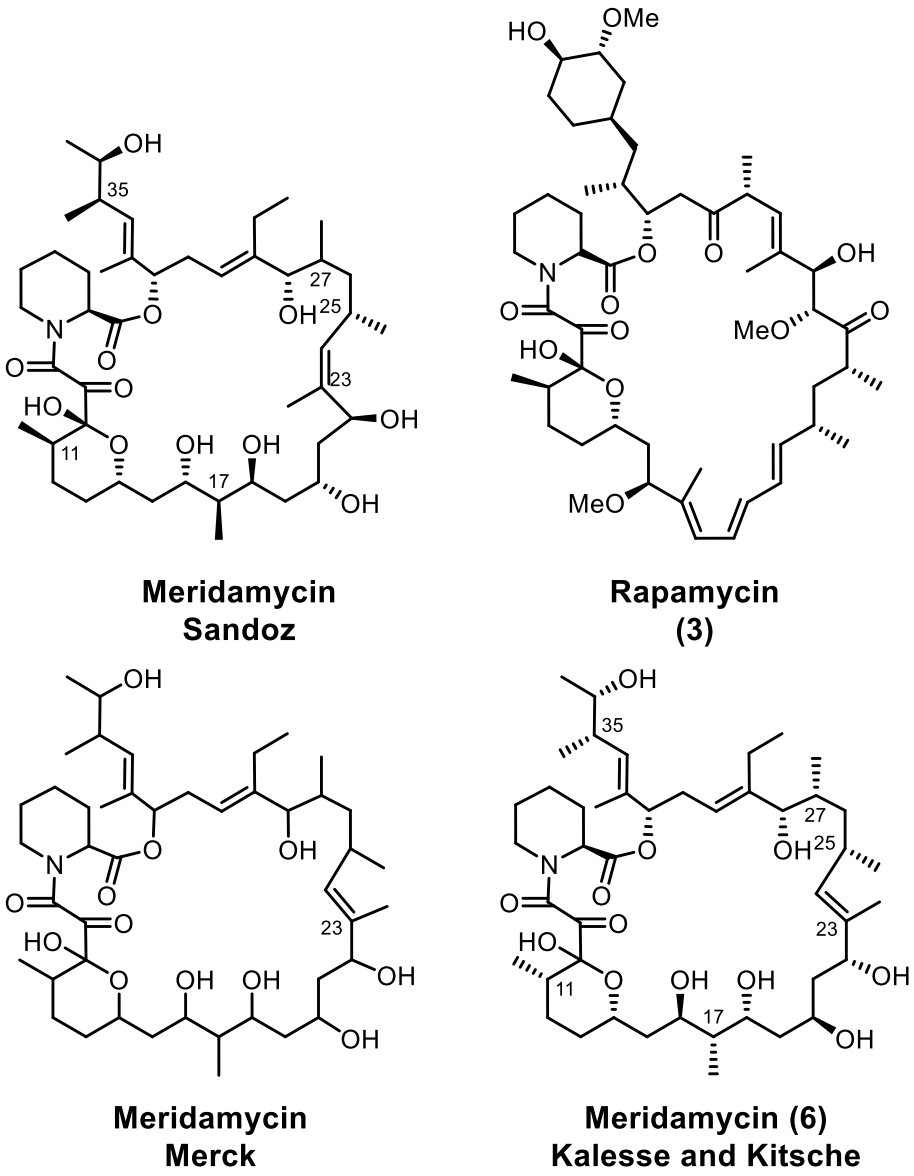


Figure 5: Structures proposed for meridamycin (**6**) and comparison with rapamycin (**3**).

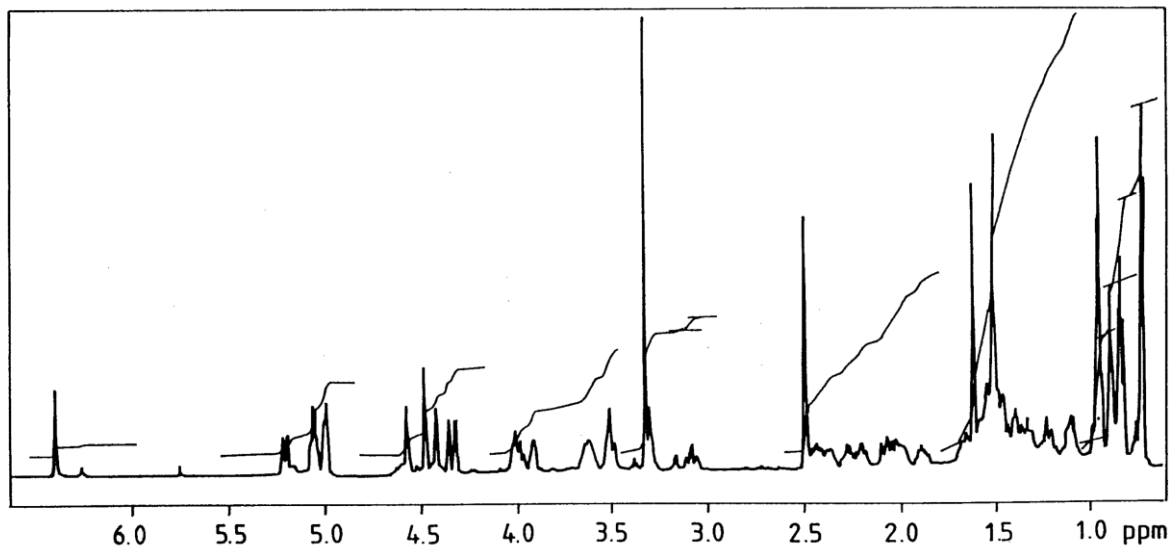


Figure 6: ^{1}H NMR of meridamycin (**6**) by Sandoz GmbH.[15]

Kalesse and Kitsche analyzed the meridamycin synthesizing gene cluster using the hidden Markov model and could predict with high confidence that three hydroxy groups belong to the L-series and five to the D-series (Table 1). The methyl group at *C35* followed an L-configured alcohol and could be confidently assigned as D-configured. The last two methyl groups, which were following D-configured alcohols and had ScoreDiff values under 15, were tentatively assigned as L-configured. The relative configuration around *C17* well matches with the relative configuration assigned by Sandoz, which indirectly supports the assignment. The methyl group at *C27*, which coincidentally was also the only stereocentre left unassigned by Sandoz, had a ScoreDiff value of −8.44 and is the first one that should be re-evaluated if the data of the synthetic meridamycin sample will not be matching the natural.

The two isolated methyl groups at *C11* and *C25* can be analyzed according to the method by Leadly et al. and both assigned as L-configured.[32]

This work relies on the gene cluster analysis for assignment of the stereocentres in meridamycins.

Table 1: Configuration of stereocentres in meridamycin (**6**) based on gene cluster analysis by Kalesse and Kitsche.[35]

Ketoreductase	Predicted alcohol configuration[a]	Score difference	Predicted methyl configuration[a]	Score difference
KR1	L	−32.19	D	21.41
KR3	D	32.95		
KR5	D	56.91	L	−8.44
KR8	L	−51.76		
KR9	D	32.66		
KR10	D	66.45	L	−5.22
KR11	L	−57.63		
KR12	D	32.50		

[a] L- *and* D-*configuration in polyketide synthesis follows the Fischer notation – the PKS bound carboxylate end of the polyketide points upwards and the free end downwards, if the alcohol or the methyl group points to the right, it is the* D *isomer, and if to the left, it is the* L *isomer.*

1.4 Synthesis of Polyketide Natural Products

In the next sections, a short overview is provided of methods and strategies used in the practical part of the work. The theoretical basis is followed by a few relevant examples from the literature when applicable. When possible, lessons learned from total syntheses of related pipecolic acid natural products are disclosed.

1.4.1 Synthesis of Pipecolic Acid Natural Products

During the late 80s, when the immunosuppressive activity of the FK506 (**5**) and related pipecolic acid natural products (Figure 7) was discovered, they immediately draw great interest from the synthetic community. The research program by Merck Co. quickly finished the first total synthesis of FK506 (**5**) in 1989.[7] The first report was followed by a total synthesis by Schreiber in 1990[8] but it took five more years for the next, and thus far the last, to be completed by the group of Ireland[9]. In addition to total syntheses, groups of Sih,[36] Dansihefsky[37] and Smith[38] have reported partial syntheses of FK506. The main difficulties associated with the syntheses were the instability of the tricarbonyl unit, especially to base mediated benzilic acid rearrangement, and the lability of the pipecolic acid stereocentre towards epimerization. Additionally, the double bond at *C19* could easily isomerize into conjugation with the carbonyl group at *C22*.

The total synthesis of rapamycin (**3**) was further complicated by larger size and the *C17-C22* triene unit. The first total synthesis was completed in 1993 by Nicolaou,[10] whose achievement was quickly repeated by Schreiber[11] and Danishefsky[12] later the same year. Two years later, Smith completed the synthesis of rapamycin and its *C27* demethoxy analogue,[13] while it took more than 12 more years until Ley published his work towards preparation of the molecule in 2007.[14]

In addition to FK506 (**5**) and rapamycin (**3**), there are two synthetic studies of related non-immunosuppressive pipecolic acid natural products antascomicins A (**12**) and B (**13**). In 2005, Ley reported a total synthesis of antascomicin B[39] and in 2006 Chakrabarty reported his work toward the synthesis of antascomicin A[40].

Until this day, there is no reported synthesis of meridamycin or its analogues.

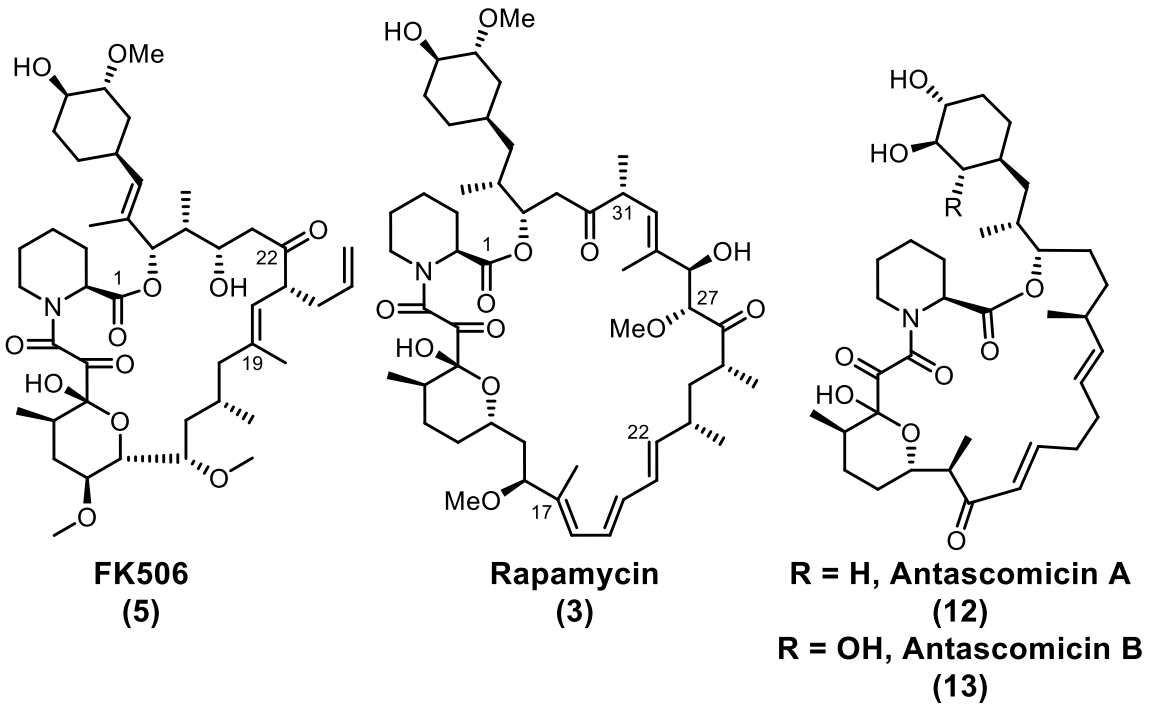


Figure 7: Structures of FK506 (**5**), rapamycin (**3**), antascomicins A (**12**) and B (**13**).

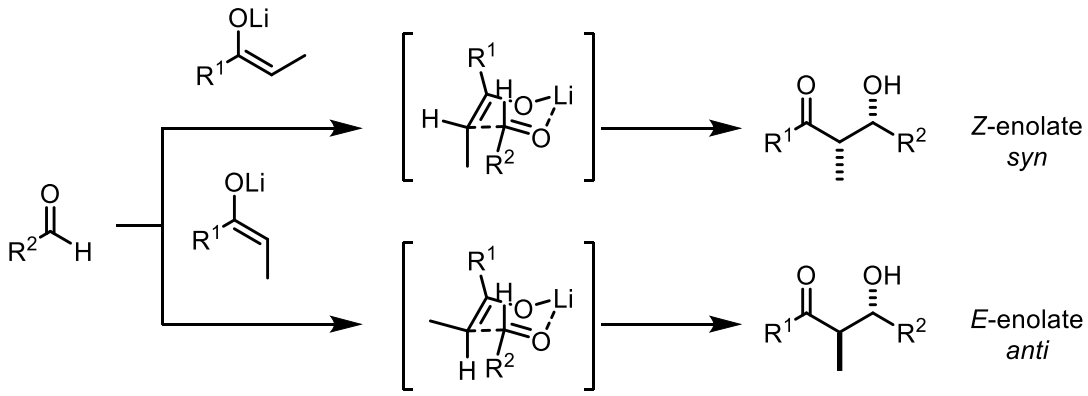
1.4.2 Aldol Reactions

Aldol reactions are the nature's preferred method for connecting two carbons with each other. In a reaction between two carbonyl compounds, one acts as a nucleophile through the α-carbon and the other as an electrophile at the carbonyl group. One or two new stereogenic centres are created giving rise up to four possible isomers as the carbon chains are connected. In all the reactions of biologically relevant compounds, the stereochemistry can and should be controlled, so that only one possible isomer is produced. The stereochemical control can be achieved by either substrate control or by catalyst control. Nature easily assembles complex molecules relying on enzymatic catalysts but for chemists, it is often easier to control the stereochemistry by relying on inherent selectivity of the substrates. The latter could be divided into three distinct cases: 1) unmodified substrates lead to one desired isomer (either through closed or open transition state; 2) one of the substrates is truncated and a chiral group is installed, which then controls the stereochemistry but has to be removed later (chiral auxiliary method); 3) one of the substrates is modified with a transient chiral group (installed at the beginning of the reaction and removed during the work-up) that controls the stereochemistry (chiral ligand).

Use of chiral catalysts in aldol reactions will not be covered.

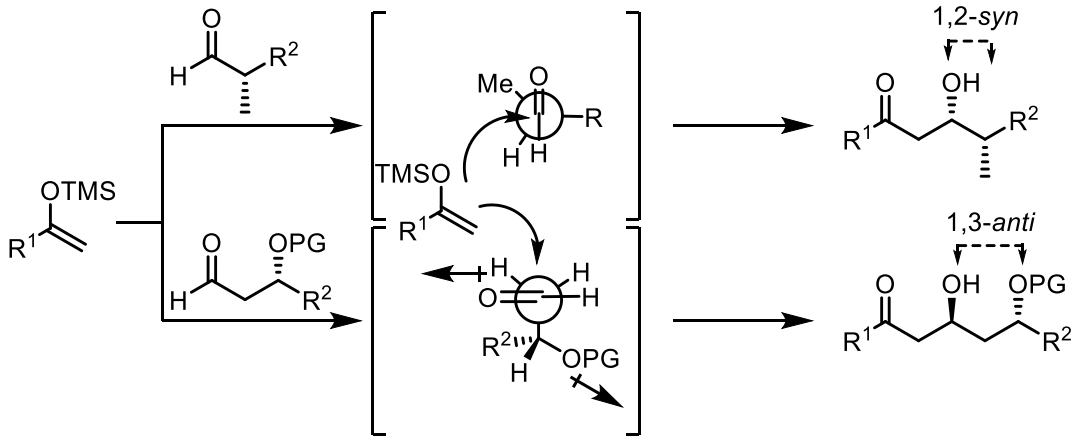
1.4.2.1 Substrate Induced Stereocontrol

Relative stereochemistry between two new stereocentres is generally controlled by the enolate geometry. That especially applies to enolates bearing a coordinating heteroatom on the oxygen that can interact with aldehyde and form a closed transition state. That closed transition state usually adopts the *chair* conformation with minimal diaxial relationships (the Zimmermann-Traxler model,[41] Scheme 1), therefore dictating the relative orientation of the enolate and the aldehyde. According to the model, *Z*-enolates give the *syn*-products, and the *E*-enolates the *anti*-products.



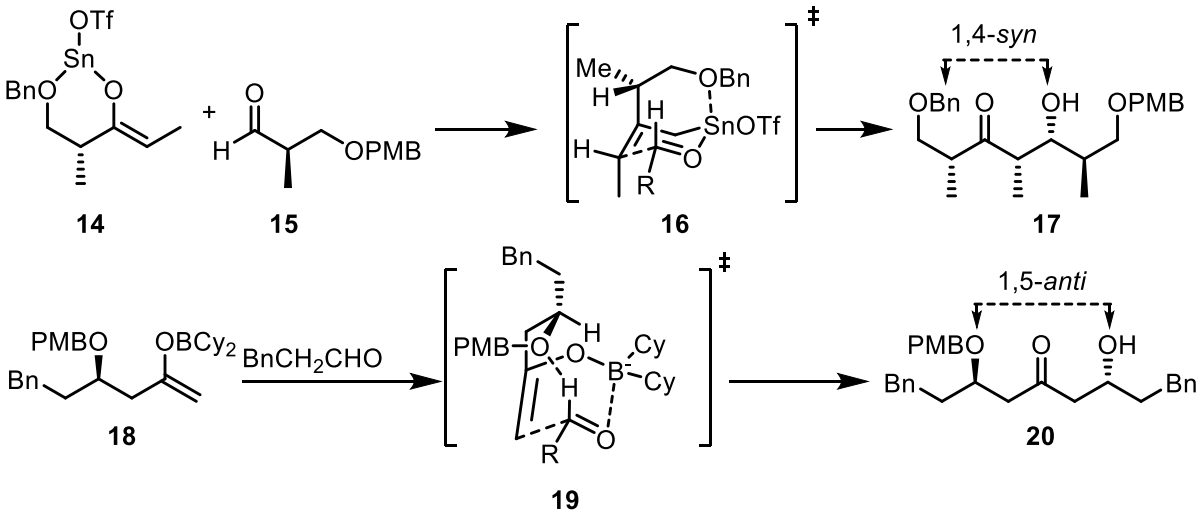
Scheme 1: Zimmermann-Traxler model for relative stereocontrol in aldol reaction.

Substrate based asymmetric induction can be caused by either the aldehyde or the ketone component. Generally, it is easier to predict the effect of the aldehyde on the stereochemical outcome. For α-branched aldehydes, the Felkin-Anh[42,43] model applies, which predicts that α-methyl aldehydes would prefer the *syn* configuration between the methyl and hydroxy group (upper row Scheme 2). Naturally there can be other than purely steric effects affecting the transition state of the addition and correspondingly suitable transition state model should be applied (modified Cornforth model[44] for α-oxygenated aldehydes, chelation control in case of polar groups and chelating agent etc.). For β-alkoxy aldehydes, either polar model minimizing the dipole moment in transition state (lower, Scheme 2) or chelation controlled model applies. The 1,2- and 1,3-inductive effects can be either reinforcing or opposing and depending on the desired stereochemical outcome, suitable reaction conditions and protecting group strategies should be applied.



Scheme 2: Aldehyde asymmetric induction.

Predicting the asymmetric induction caused by the ketone component is generally more complicated. For example, for α-substituted *E*-enolates the transition state with minimized 1,3-allylic strain is preferred in case of alkyl substituents and minimization of dipole moment in case of alkoxy substituents,[45] whereas for β-alkoxy substituents the coordination with a chelating Lewis acid (Scheme 3, upper) or hydrogen bonding with the formyl hydrogen (Scheme 3, lower) is relevant. For example, the tin enolate **14** forms an chelated transition state **16** in it reaction with aldehyde **15** giving 1,4-*syn* product **17**.[46] On the other hand, for compound **18**, the transition state **19** is stabilized by formyl hydrogen bonding with the OPMB group and the transition state is changed from *chair* to *boat*, and 1,5-*anti* product **20** is obtained.[47]

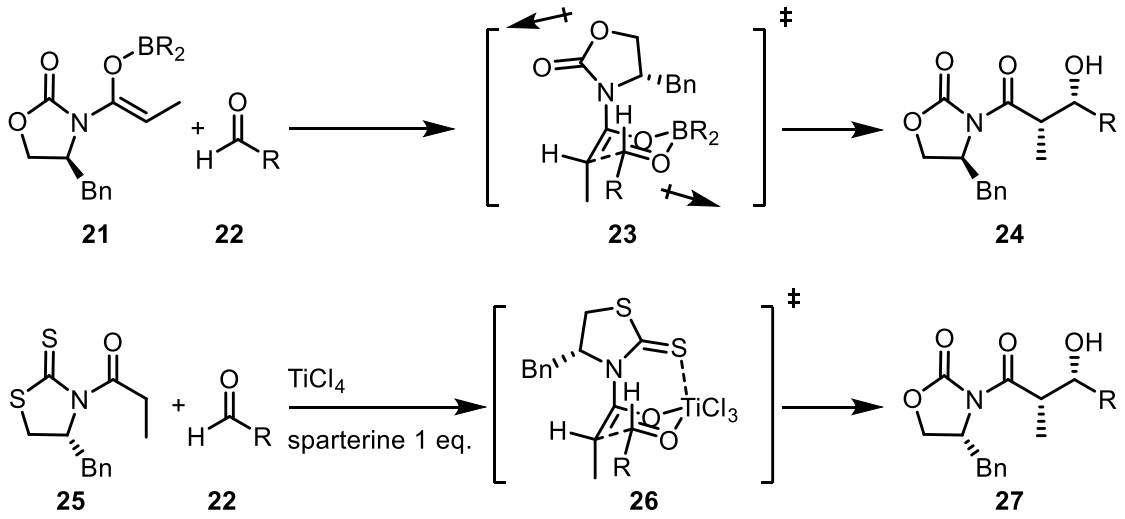


Scheme 3: Enolate asymmetric induction by β-alkoxy substituents.

While the plethora of different effects and interactions that has to be considered when designing a suitable aldol reaction greatly complicates the analysis, it also offers chemists a variety of possibilities to tailor the reaction to his specific needs, therefore making the methodology applicable to almost any substituent pattern. In cases where the substrate control will not provide the desired stereochemical outcome, chiral auxiliaries or chiral ligands can be used.

Chiral auxiliaries were the first method that really enabled laboratory synthesis of any kind of polyketide framework. Some of the most commonly used chiral auxiliaries are derived from natural amino acids (phenylalanine and valine), which are turned, for example, into oxazolidinones (Evans auxiliary[48]) or thiazolidinones (Nagao auxiliary[49], Crimmins aldol[50]). The auxiliary adopts a preferred conformation during a reaction with aldehyde **22** either

through electrostatic interactions (as is the case for Evans auxiliary derived reagent **21** in transition state **23**) or chelation (as is the case for Nagao auxiliary **25** in transition state **26**) and blocks one enantioface of the enolate therefore giving rise to only one product - **24** or **27** for Evans and Crimmins aldols, respectively (Scheme 4).



Scheme 4: Evans (**21**) and Nagao (**25**) auxiliaries in aldol reactions with general aldehyde **22**.

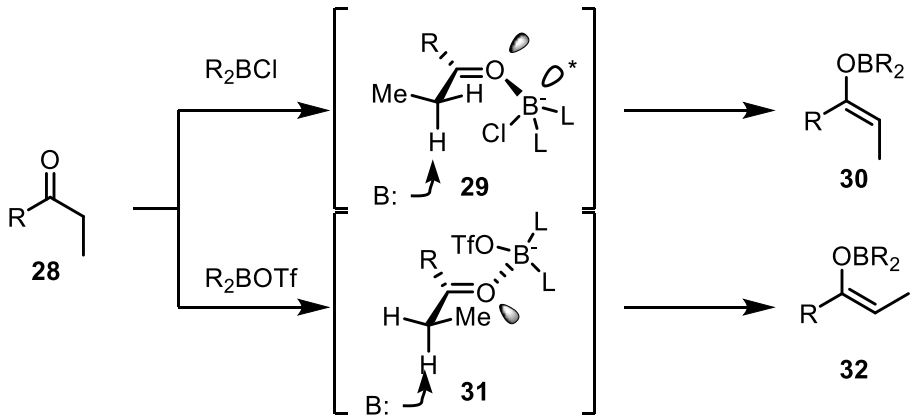
While chiral auxiliaries were a tremendous step forward in the field of stereospecific synthesis, they also add several additional steps into the synthetic sequence and are therefore not very economical. Using chiral ligands instead of auxiliaries offers perhaps the most versatile method for controlling stereochemical outcome of aldol reactions. It avoids the cumbersome installation and removal of the chiral auxiliaries but retains the ability to control stereochemical outcome and is sometimes even able to override the inherent selectivities of the substrates. The use of chiral ligands on boron enolates was pioneered and developed by Paterson et al. who showed that isopinocampheyl ligand on boron gives high stereoselectivities in reactions between simple ketones and aldehydes.[51]

1.4.2.2 Chiral Ligands and Boron Aldols

Enolization of ketones with boranes takes place in the presence of a tertiary amine in a non-polar solvent. Usually, R_2BCl[52] or R_2BOTf[53] together with a sterically hindered tertiary amine are used, as non-hindered amines tend to complex strongly with the boron reagent and give poor enolization.[52] For dialkylboron chlorides, triethylamine is generally used because it

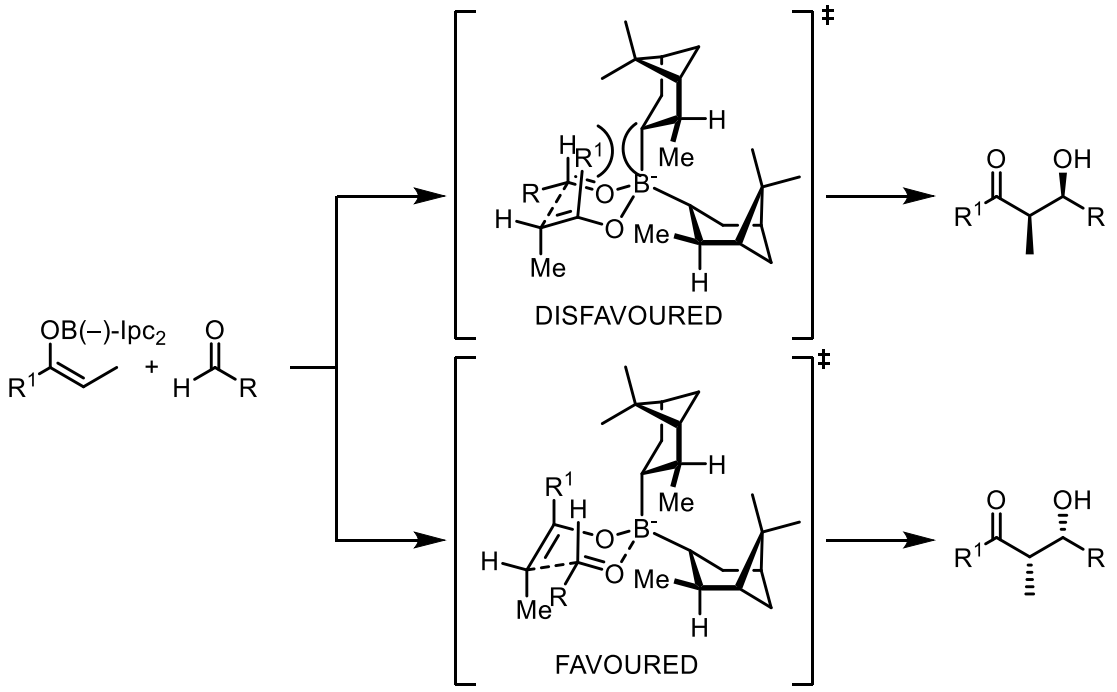
forms a solid salt that precipitates out of the solution, therefore facilitating reaction monitoring. In case of methyl ketones, both reagents selectively enolize on the methyl side at low temperatures but thermodynamic enolization with Ipc_2BOTf prefers the more substituted end of the ketone.[54] At the same time, in case of ethyl ketones, the dialkylboron chlorides selectively give the *E*-enol borinates, whereas the dialkylboron triflates give the *Z* isomer, therefore enabling access to both diastereomers of the aldol reaction just by changing the counter-ion of the boron reagent.[55] This selective enolization is caused by subtle electronic- and steric effects of the counter-ions to the borinate complex (Scheme 5).

The strong anomeric effect from the oxygen lone pair forces the B-X bond to eclipse with the C-O double bond, an effect which is further reinforced by the bulky ligands on the boron. In reactions with general ethyl ketone **28**, the L_2BCl prefers the sterically less hindered side giving complex **29**, where the chlorine atom is directed towards one of the hydrogens of the α-methyl group therefore giving the α-carbon a partial negative charge and activating it towards deprotonation by non-bulky bases. When Et_3N is used as a base, the *E*-enolate **30** is obtained. For L_2BOTf, the steric bulk of the triflate group increases the dihedral angle between the carbonyl group and the B-X bond, therefore decreasing the electronic preference for the boron to adopt a single low-energy conformation. That means that both complexes are available for deprotonation and with bulky bases, the base prefers to approach from the less hindered side, therefore the transition state **31** is preferred and *Z*-enolate **32** can be obtained (Scheme 5).[56]



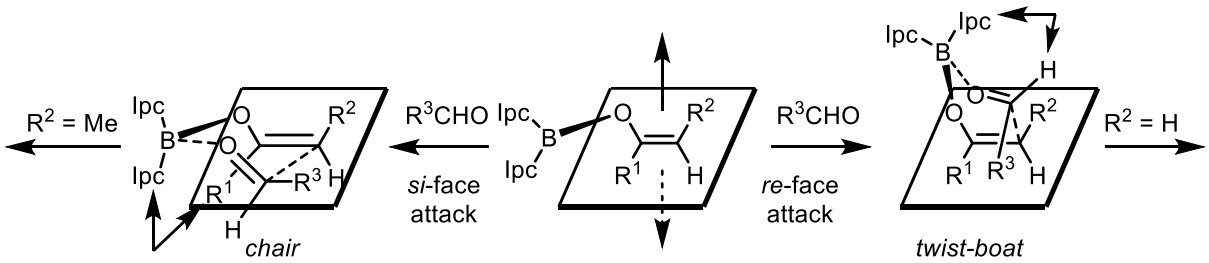
Scheme 5: Counter-ion effect on the enolization of general ethyl ketone **28** with boron reagents.

Paterson et al. demonstrated that reactions of boron enolates proceed in high stereoselectivity in case of isopinocampheyl substituents on boron.[51] In reactions with ethyl ketones, the diastereofacial selectivity is believed to be caused by the steric interactions between the R^1 group of the ketone and the methyl group from the isopinocampheyl ligand in the DISFAVOURED transition state (Scheme 6).[57] Interestingly, while the *Z*-enolates give high yields and stereoselectivities, the *E*-enolates perform poorly.[58]



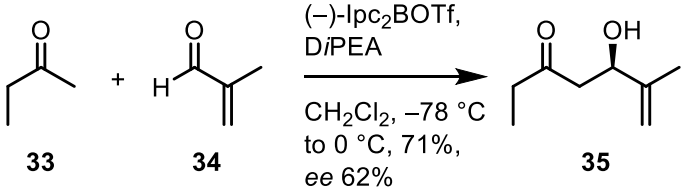
Scheme 6: (−)-Ipc borane in reactions of ethyl ketones.

Performing aldol reactions with diisopinocampheylborinates prepared from methyl ketones, leads to a reversal of aldehyde enantiofacial selectivity compared to the enolates prepared from ethyl ketones. Those surprising results were rationalized by a change in transition state from standard *chair*-like transition state in case of ethyl ketones (TR *chair* on Scheme 7) to *twist-boat* in case of methyl ketones (TR *twist-boat* on Scheme 7), which in turns leads to the opposite stereochemical outcome. The rationale for preferring the *twist-boat* transition state in case of methyl ketones is the steric repulsion between the Ipc ligand on boron and the R^1 end of the ketone in the *chair* transition state, and small steric repulsion between the Ipc ligand and the hydrogen (R^2 on Scheme 7) in the *twist-boat* transition state.[59] That reasoning was further supported by ab initio calculations by Houk et al.[54]



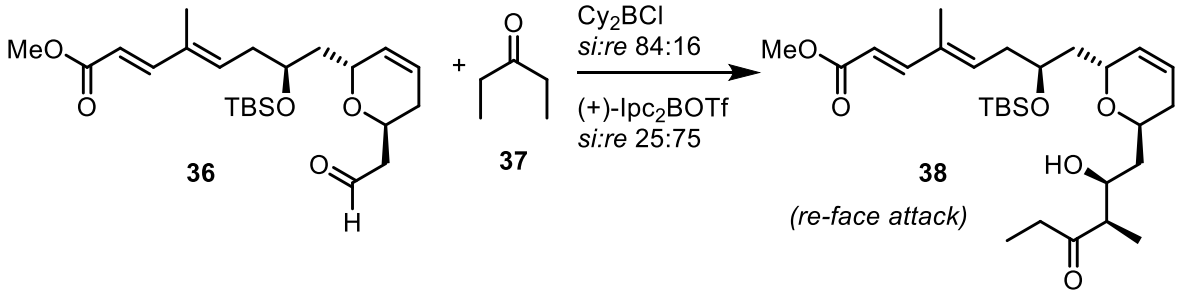
Scheme 7: Change from chair-like transition state, in case of ethyl ketones, to twist-boat in case of methyl ketones. [59]

For methyl ketones, the enantioselectivities are good in case of a large substituent on the other side of the ketone but can decrease down to 3:2 in case of a simple ethyl substituent.[58] For example, reaction between butanone (**33**) and methacrolein (**34**) took place with good regiocontrol but gave only about 4:1 ratio for stereoisomer **35** (Scheme 8).



Scheme 8: Paterson's aldol reaction with butanone (**33**) and methacrolein (**34**).

Paterson elegantly demonstrated the feasibility of Ipc-mediated boron aldol reactions in his synthesis of swinholide A,[60] where, in the preparation of ketone **38**, the stereoselectivity of substrate directed aldol reaction of aldehyde **36** with diethyl ketone (**37**) was completely overruled by the (+)-Ipc$_2$BOTf reagent (Scheme 9).

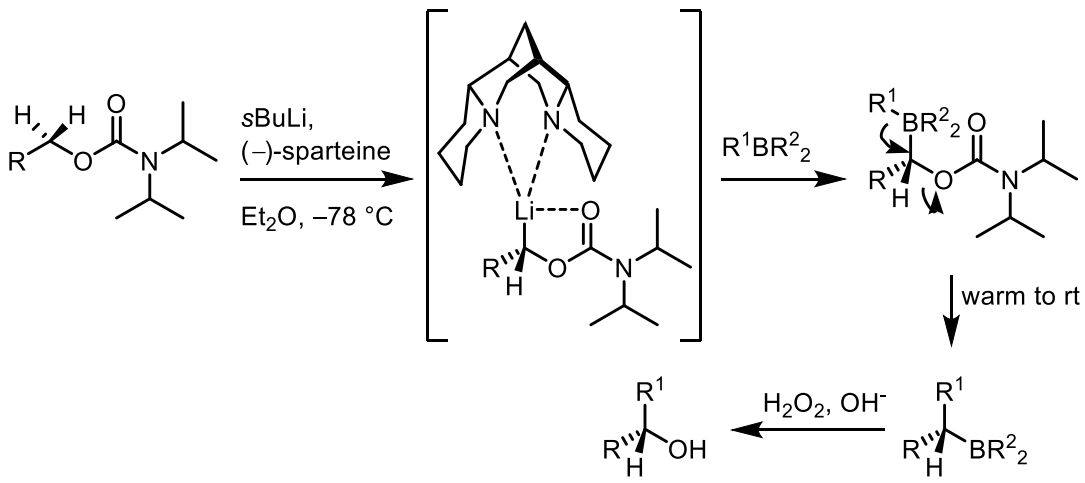


Scheme 9: Paterson's synthesis of Swinholide A.

Merck used boron Evans aldol with nBu$_2$BOTf in the late stage of FK506 synthesis,[61] which shows that boron-mediated aldol reactions are compatible with pipecolic acid moieties and are applicable for the fragment coupling reaction in meridamycin synthesis.

1.4.3 Lithiation-Borylation Methodology

A lithiation-borylation technique for forming carbon-carbon bonds was pioneered by Kocienski[62] and Aggarwal[63], who combined Hoppe's chiral anion[64] formation with 1,2-metallate rearrangement (Matteson rearrangement)[65] of boronates creating a versatile and effective methodology for assembling carbon backbones of natural products.[66] First, a chiral anion is formed which then adds to the boron species; upon warming, 1,2-metallate rearrangement takes place forming a new carbon-carbon bond in stereospecific manner. Resulting new boron compound can then be used in following reactions or oxidized to the corresponding alcohol (Scheme 10).

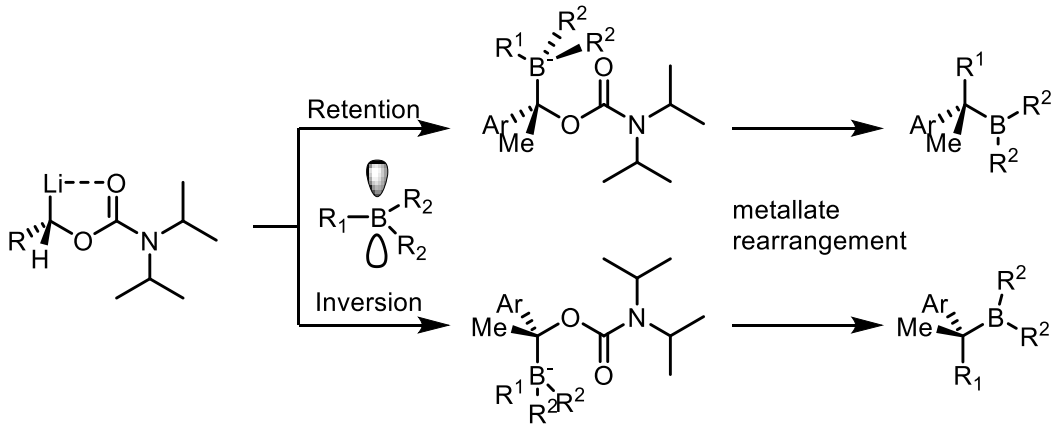


Scheme 10: General mechanism of lithiation-borylation methodology.

Chiral anions may be formed by substrate dependent stereospecific deprotonation, stereospecific tin-lithium exchange or by asymmetric deprotonation. The most commonly used and the most versatile method in lithiation-borylation chemistry is asymmetric deprotonation developed by Hoppe et al.[64] When deprotonating a carbamate at low temperatures in the presence of sparteine, a configurationally stable organolithium species is formed which can then act as a nucleophile towards boron or other electrophiles. The method was later extended to 2,4,6-triisopropyl benzoates, which also cleanly form a stable anion but sometimes perform better in the following Matteson rearrangement step.[67] The formation of chiral organolithium compound works well for simple primary carbamates and benzoates, but organolithiums derived from allylic or benzylic primary alcohols are configurationally less stable and require more complex ligands on boron.[68] On the other hand, organolithiums derived from benzylic or allylic secondary alcohols are configurationally stable and can be

used. Simple secondary carbamates are generally not acidic enough for deprotonation to take place, though deprotonation is possible for secondary alkyl benzoates.[69]

The borylation of the chiral anion can take place either with inversion or retention of stereochemistry. In general, the borylation takes place with retention of stereochemistry but invertive pathways have been observed in case of organolithiums derived from benzylic secondary carbamates. Aggarwal et al. rationalized it by proposing a coordination between the lithium atom and the oxygens of the boronic ester directing the retentive substitution, whereas for boranes the coordination cannot take place and substitution happens with inversion.[70] For organolithiums derived from primary carbamates, the reactions occur with complete retention of configuration, presumably due to having very little electron density opposite to the metal (Scheme 11).



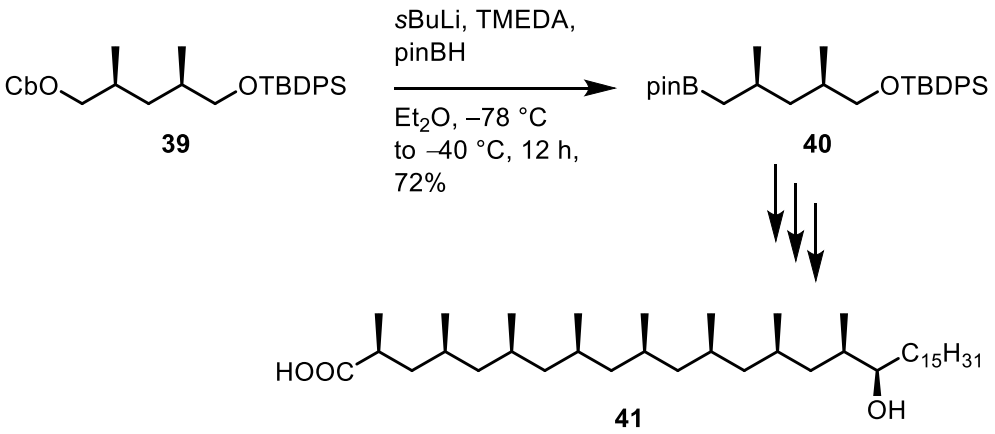
Scheme 11: Borylation and Matteson rearrangement of secondary carbamates.

The 1,2-metallate rearrangement requires an *anti*-periplanar arrangement between the C-O bond and the rearranging R_1-B bond, which means that the reaction takes place in stereospecific manner. The borylation easily takes place already at −78 °C but the 1,2-metallate rearrangement starts at −40 °C for boranes and needs higher temperatures for boronic esters.[71] The 1,2-metallate rearrangement of boronate complexes derived from secondary alcohols readily occurs already at 0 °C, whereas derivatives of primary alcohols require 35 °C and sometimes an additional Lewis acid ($MgBr_2$) for the rearrangement to take place.[63] That means that there is no free organolithium present when the Matteson rearrangement takes place and reactions generally proceed with high steric fidelity. The racemization may take place in case of sterically hindered boronic esters or carbamates/benzoates, in which rearrangement is slow and dissociation of the boronate complex back to the parent organolithium species can take place. The latter racemizes at

reaction temperatures and the stereoselectivity of reaction decreases. The dissociation-racemization can be suppressed when MeOH or $MgBr_2$ are used as additives or if less hindered neopentyl boronic esters are used instead of pinacol esters.[69] The extent of rearrangement can be readily monitored by ^{11}B NMR, where the signals for ate-complexes are in the range of 0-10 ppm and the product boronic esters should appear around 30 ppm.[72]

Formed new boron compound can then be used further in the same lithiation-borylation strategy[73,74] or oxidized to the alcohol. Oxidation to the alcohol readily takes place with complete retention of configuration when treated with basic hydrogen peroxide,[75] or with sodium perborate[76] if milder conditions are required.

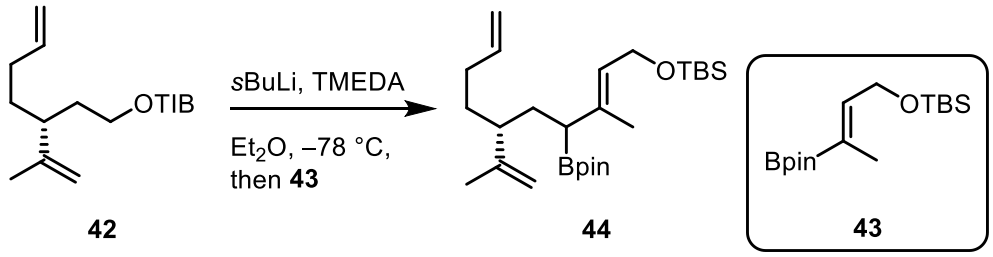
The carbamate **39**, similar to the one planned to use in the syntheses of meridamycins, was used by Aggarwal et al. in their synthesis of hydroxyphthioceranic acid (**41**). Carbamate **39** first undergoes lithiation, then readily adds to pinacolborane and finally 1,2-hydride shift provides the boronate **40**.[77] Further lithiation-borylation steps followed by deprotection and oxidation, gave the acid **41** (Scheme 12).



Scheme 12: Aggarwals's synthesis of hydroxyphthioceranic acid (**41**).

Aggarwal et al. used their lithiation borylation methodology with vinylic boronic ester **43** in the synthesis of California red scale beetle sex pheromone.[72] Asymmetric deprotonation of TIB-ester **42**, followed by addition of boronic ester **43** gave compound **44** (Scheme 13). In this case, the deprotonation step is not performed in asymmetric fashion, therefore giving mixture of diastereomers for **44** but, if needed, then stereocontrol can be easily achieved by using sparteine as a base in deprotonation step. This example provides also one of a few examples where trisubstituted vinylic boronic esters are used in the lithiation-borylation

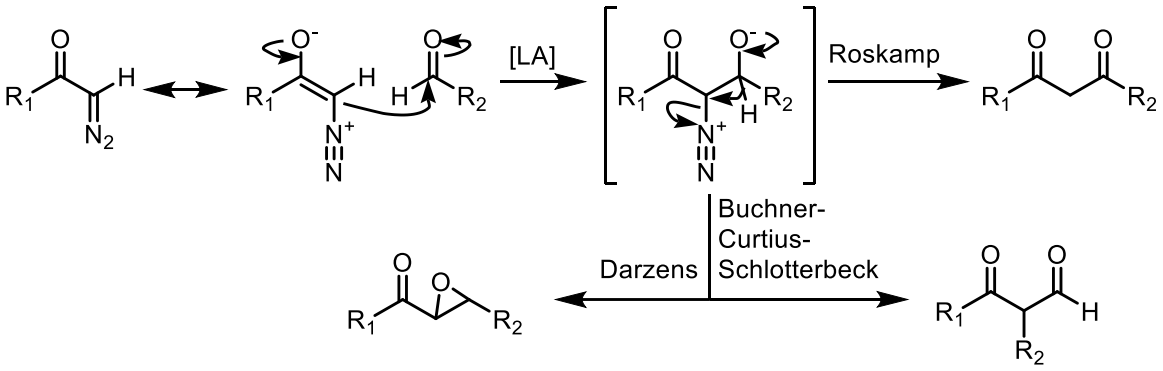
chemistry and is the closest found analogue to the substrates used in the synthesis of meridamycins.



Scheme 13: Lithiation-borylation methodology using vinylic boronic esters in the synthesis of sex pheromone of California red scale beetle.

1.4.4 Roskamp Reaction

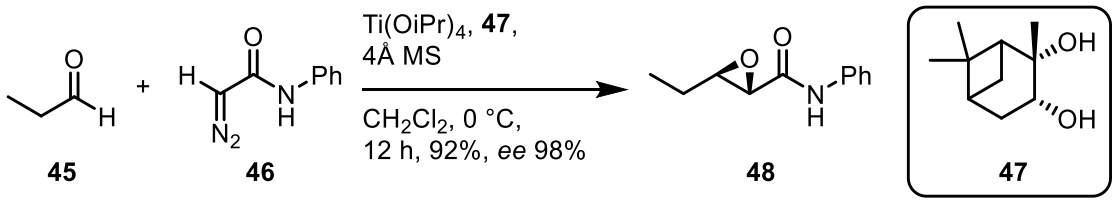
Roskamp reaction[78] takes place between an α-diazo carbonyl compound and an aldehyde. The nucleophilic α-carbon attacks the aldehyde, re-formation of the C-O double bond is accompanied by a 1,2-H shift and expulsion of nitrogen forming a β-keto carbonyl compound. The reaction takes place in the presence of a Lewis acid (usually $SnCl_2$) and does not include a formation of a carbenoid species as Lewis acid supposedly only activates the carbonyl group of the aldehyde. The reaction is highly dependent on the nature of the Lewis acid and several other reactions may take place. If instead of 1,2-H shift, an 1,2-alky shift takes place (common in ketones but rare for aldehydes), it is called Buchner-Curtius-Schlotterbeck reaction,[79,80] or if the oxygen of the aldehyde acts as a nucleophile and expulses nitrogen, it could be called a Darzens reaction (Scheme 14).[81]



Scheme 14: Reactions of diazocarbonyl compounds with aldehydes.

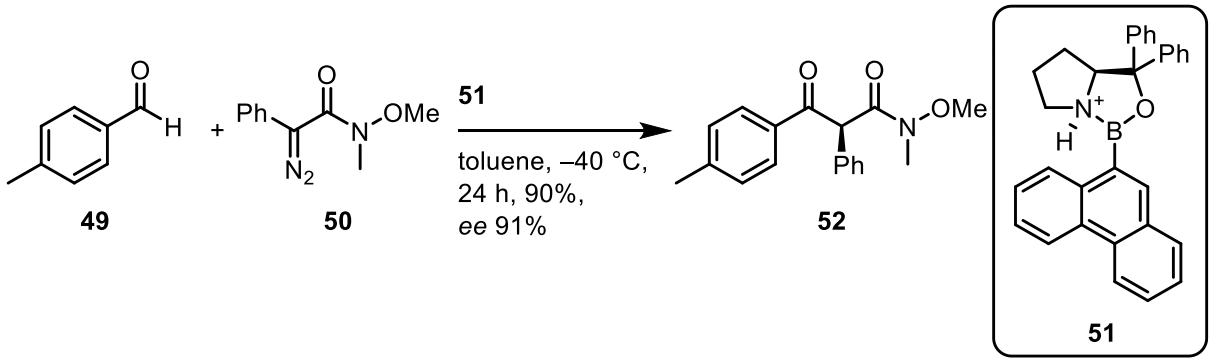
While reactions between diazo compounds and ketones have enjoyed much more interest,[82] reactions with aldehydes have found their own place in total synthesis. Most commonly, commercially available ethyl diazoacetate is used to add two-carbon fragment to the end of the chain obtaining the corresponding β-keto ester. As a few choice examples, Roskamp reaction with ethyl diazoacetate was used in the total syntheses of (+)-himgaline,[83] callipeltoside A,[84] clavonoline[85] and (−)-jiadifenolide[86]. Though $SnCl_2$ is, by far, the most common Lewis acid used in the reaction, some others like $ZrCl_4$,[87] $TiCl_4$,[87] $NbCl_5$,[88] $BF_3{\cdot}Et_2O$,[89] $GeCl_2$,[78] MoO_2Cl_2,[90] activated alumina[91] or zeolites[92] have also been reported. It is worth to mention that in the case of aromatic aldehydes, $NbCl_5$ has been reported to give superior results compared to $SnCl_2$[88,93] and in case of sterically hindered aldehydes, $ZrCl_4$ or $TiCl_4$ are more effective.[87]

Information about the Roskamp reaction with diazoamides is scarce but there are a few relevant examples in the literature. Sun et al. reported that diazoamide **46** reacts with propanal (**45**) in the presence of Ti(O*i*Pr)$_4$ and a chiral diol **47** ligand giving the Darzens reaction product **48** in excellent enantioselectivity (Scheme 15).[94] While these results point to a potential problem in conducting Roskamp reactions with diazoamides, they also provide proof that the initial addition to the aldehyde takes place without issues.



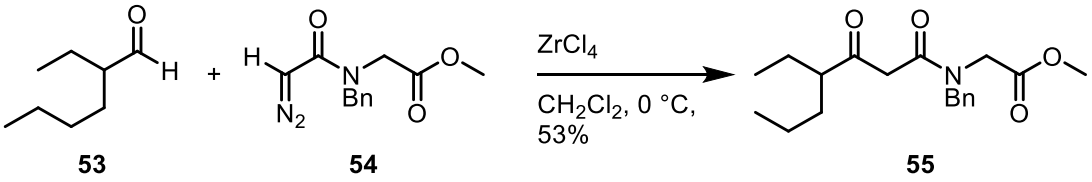
Scheme 15: Darzens condensation between diazoamide **46** and propanal (**45**).

Ryu et al. have reported a reaction between diazo Weinreb amide **50** and aldehyde **49** in the presence of an oxazoborolidinone **51** giving the Roskamp product **52** in high yield and selectivity (Scheme 16).[95] The electronic character of Weinreb amides differs slightly from dialkyl amides, therefore it is difficult to assess if the reactions behave in the same manner. This work also serves as one of the rare examples of using non-metal-based Lewis acids in the Roskamp reaction.



Scheme 16: Enantioselective Roskamp reaction between diazo Weinreb amide **50** and aldehyde **49**.

The only example found from the literature on performing Roskamp reaction with diazoamides bearing alkyl substituents on the nitrogen was work by Yoshii et al. who reported $ZrCl_4$ mediated Roskamp reaction between diazo benzylamide **54** and aldehyde **53** gave the Roskamp product **55** (Scheme 17).[96] That serves as a proof for the feasibility of planned Roskamp reaction for the synthesis of meridamycins.



53 **54** **55**

Scheme 17: Roskamp reaction between diazoamide **54** and aldehyde **53** by Yoshii et al.[96]

1.4.5 Hydrometallation of Internal Alkynes

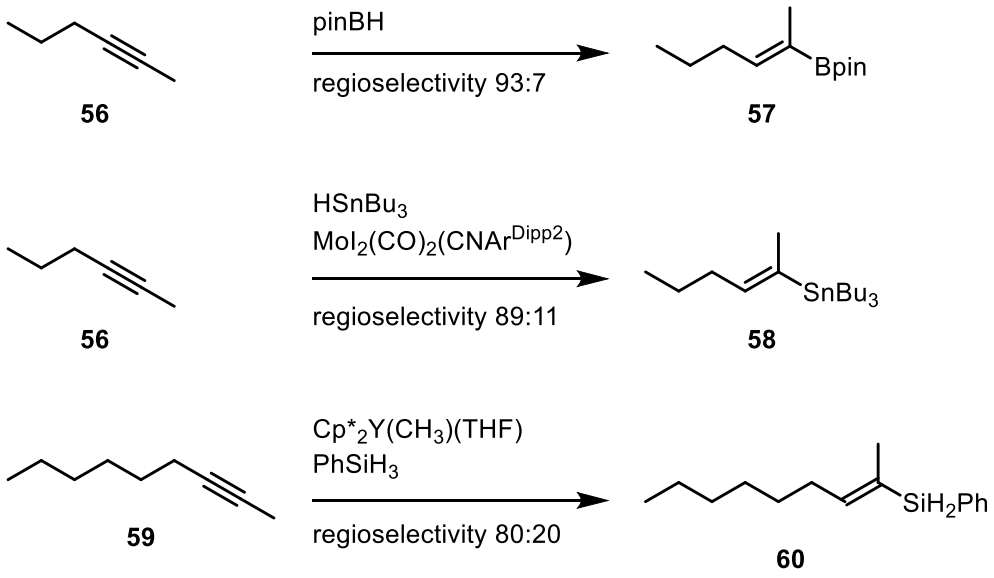
Hydrometallation of alkynes offers an easy access to carbon-chain functionalization. While hydrometallation of terminal alkynes has enjoyed intense synthetic interest, then research with internal alkynes is less developed.[97] This may be partially caused by difficulties in achieving the regioselectivity for the reaction. While regio-differentiaton for internal alkynes is definitely more difficult to achieve, there still remain a number of possibilities like steric differentiation, coordination with a neighboring group, electronic differentiation, or internal hydride delivery. Metal wise, hydrometallations are most often performed with zirconium,[98] tin,[99] boron[100] or silicon.[101]

In the context of this work, the hydrometallation has to differentiate between an ethyl group and α-methylene homopropargylic alcohol. The homopropargylic alcohol side is β-branched and therefore might exhibit some steric differentiation compared to the ethyl group. On the other hand, the hydroxy group of the homopropargylic alcohol also offers an opportunity for coordination or some other orbital interactions. Therefore both options should be considered.

1.4.5.1 Hydrometallations Based on Steric Differentiation

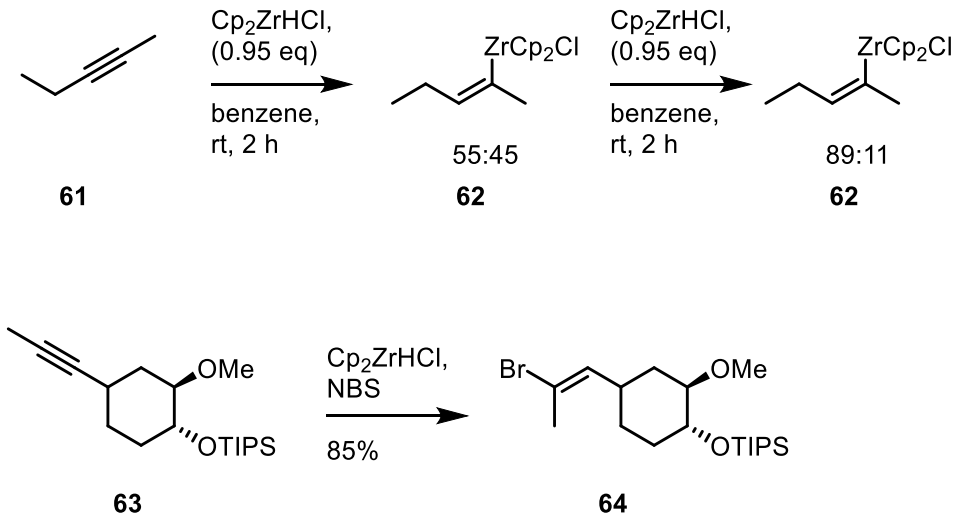
Regioselective hydrometallation based on steric differentiation is highly substrate specific and works best in cases where one of the substituents is methyl and the other one is α-branched. When the other side of the alkyne is not α-branched, then the results vary and the reaction may give low selectivities even with simple methyl groups.

Hydroboration of unbranched alkyne **56** with pinacolborane gave the desired regioisomer **57** in 93:7 ratio,[102] whereas hydrostannation of the same alkyne **56** in the presence of molybdinum catalyst gave **58** in 9:1 regioselectivity.[103] A hydrosilation with a similar substrate **59** using sterically discriminating yttrium catalyst,[104] gave the desired regioisomer **60** in 4:1 ratio with its isomer (Scheme 18).



Scheme 18: Hydrometallations with methyl alkynes using boron, silicon and tin.

Treating a simple alkyne **61** with Schwartz reagent initially forms 55:45 mixture of regioisomers of **62** but in the excess of the reagent it slowly changes to 89:11 mixture. The Schwartz reagent conveniently provides the sterically less hindered product upon equilibration and therefore is the method of choice for hydrometallation reactions that rely on steric differentiation.[105] In Schreiber's synthesis of FK506, internal alkyne **63** was treated with Schwartz reagent,[106] followed by an electrophilic bromine source to get the vinylic bromide **64**.[8] The steric differentiation between a methyl and cyclohexyl group was sufficiently large to provide almost exclusively the desired product (Scheme 19).

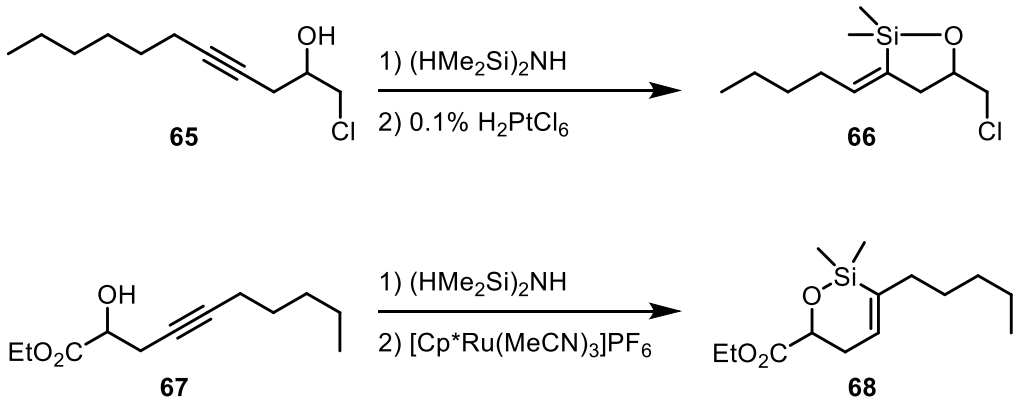


Scheme 19: Hydrozirconation of methyl alkynes.

1.4.5.2 Hydrometallations Directed by Neighboring Groups

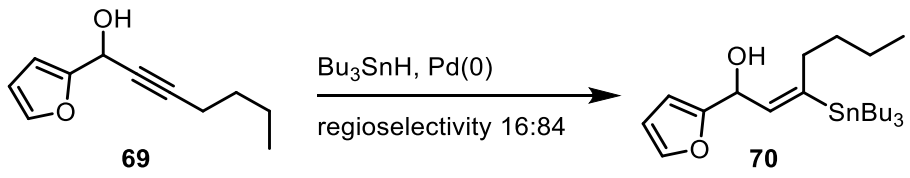
The propargylic and homopropargylic alcohols may give different results with regards to directing effect but as homopropargylic alcohols are generally not well covered in literature, then those two will be discussed together.

Directed hydrosilation of homopropargylic alcohols has been reported to give selective addition to the proximal position of the triple bond like in case of **65** to **66**.[107] The silicon forms first the hydridodimethylsilyl ether and the step is followed by platinum catalyzed intramolecular hydrosilation. Interestingly, changing the catalyst from platinum to cationic ruthenium would favor the 6-endo-dig cyclization and give addition to the distal position like in **67** to **68**, though unfortunately in the undesired *Z*-configuration (Scheme 20).



Scheme 20: Hydrosilation of internal homopropargylic alcohols.

Directed hydrozirconation of propargylic alcohols usually prefers the α-addition,[108] though if there is strong steric differentiation then sterically less hindered product can be obtained when the hydroxy group is not deprotonated. On the other hand, directed hydrostannation of propargylic alcohols has been reported to prefer the β-addition. For example, treating alcohol **69** with tributyltinhydride in the presence of palladium catalyst led to preferential formation of product **70** (Scheme 21).[109]

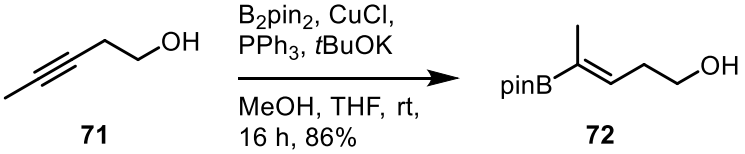


Scheme 21: Hydrostannation of internal propargylic alcohol **69**.

Directed hydroboration of propargylic[110] and homopropargylic[72] alcohols in the presence of Cu(I) catalyst has been reported to give high selectivities towards the distal addition product.

Ito et al. were the first to use the copper(I) salts in reactions between double bonds and diboron reagents.[111] They also determined the importance of the ratio between the Cu(I) species and the phosphine ligand. The copper catalyzed hydroborations have been applied to alkenes,[112] α,β-unsaturated esters,[113] aldehydes,[114] allylic carbonates,[115] and internal alkynes.[116] In case of silylacetylenes, even double borylation has been reported.[117] In most cases, the regioselectivity is determined by the electronic effects, but reversal of regioselectivity depending on the ligands on the copper atom has also been observed.[118]

Carretero et al. were the first to report directed borylation of propargyl-functionalized internal alkynes using copper,[119] though the group by Aggarwal et al. discovered it independently for homopropargylic alcohols during their work towards stereodivergent preparation of trisubstituted alkenes.[72] According to Carretero et al., the directed borylation with bis(pinacolato)diboron in the presence of Cu(I) salts and an alcoholate proceeded with a number of polar coordinating functional groups like sulfides, sulfones, alcohols, ethers etc. Using ligand was not necessary for high regioselectivity but electron-rich monodentate phosphine ligands significantly increased the conversion (from 15% to 98%). Interestingly, Aggarwal et al. reported obtaining higher regioselectivities for homopropargylic alcohols with free hydroxy group, like conversion of **71** to **72** (Scheme 22), as compared to silyl protected alcohols, whereas for Carretero et al., the regioselectivities were not significantly affected by the character of the polar group. At the same time, Park et al. used NHC-copper complexes on internal propargylic alcohols and found that regioselectivity can be completely reversed by using different protecting groups on oxygen – free hydroxy group led to complete β-addition, whereas 4-nitrophenyl ethers gave selectively α-addition.[110] While it cannot be directly assumed that observed similar selectivities in propargylic- and homopropargylic alcohols mean that reactions proceed through the same mechanism, this possibility should not be excluded.



Scheme 22: Directed formal hydroboration of internal homopropargylic alkyne **71**.

Carretero et al. calculated the energy profile for two possible mechanisms of boryl cupration leading to either of the two regioisomers (Figure 8). They found that, the ground state energies of the two possible starting materials and products are very similar but there is a significant difference in the transition state energies preferring the pathway leading to the distal product.[119] NBO analysis suggested that in the **TS**β, oxygen atom orbitals participate in the HOMO, which consists mainly of strong donor-acceptor interactions between boron and the π*(C-C) alkyne orbital. Therefore, the observed regioselectivity seems to be mostly controlled by orbital interactions and not by direct coordination of metal with the polar functional group or steric effects.

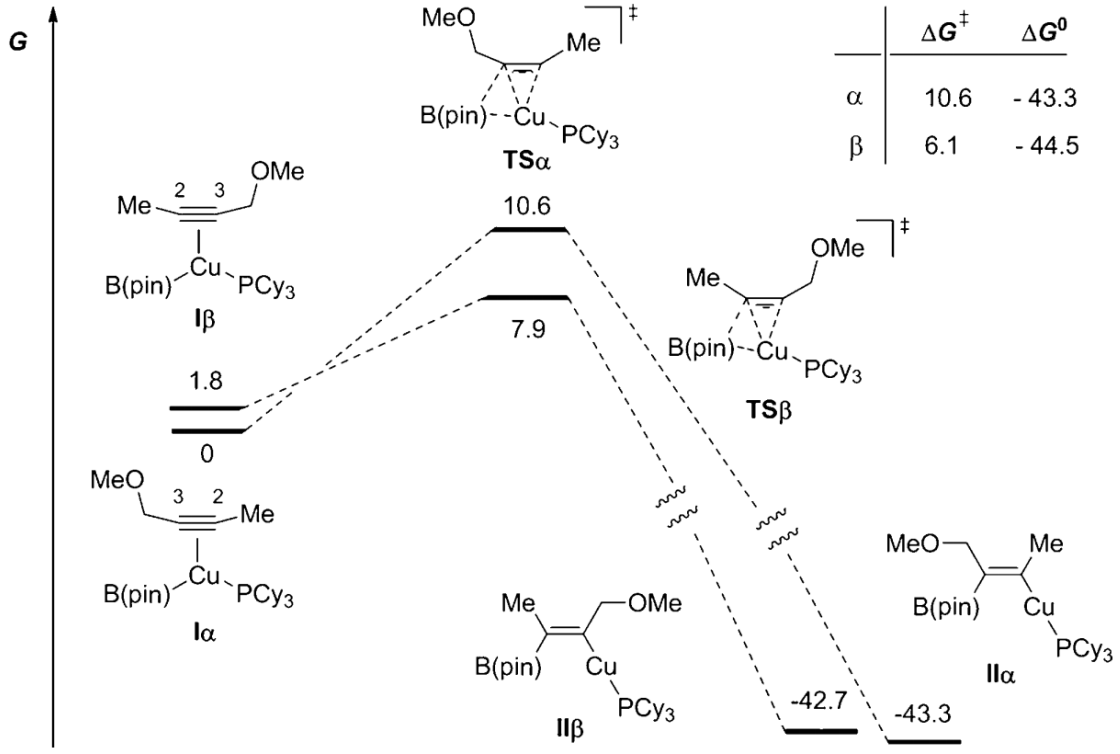
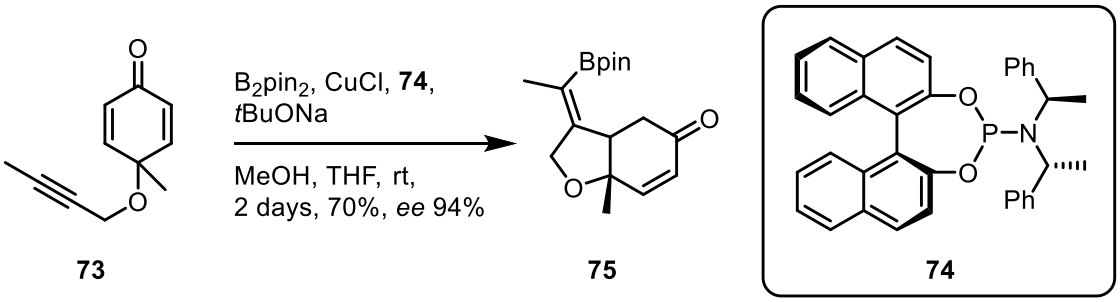


Figure 8: Energy profile for the two possible boryl cuprations of the coordinated alkyne.[119]

Lin et al. used borocupration on internal homopropargylic either to effect concurrent borylation and cyclization of **73** to compound **75** in the presence of chiral catalyst **74** in good yields and selectivities, which demonstrates the feasibility of the method in a more complex setting (Scheme 23).[120]



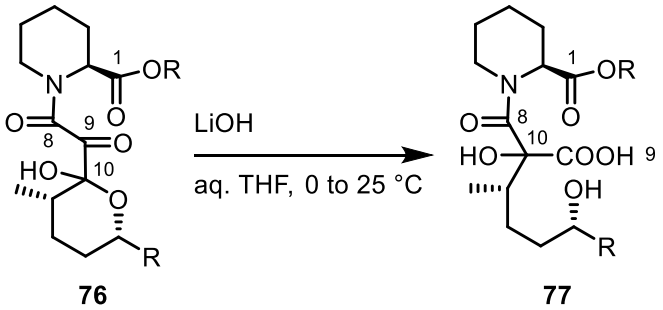
73 **75** **74**

Scheme 23: Borocupration of propargylic ether **73** followed by cyclization to **75**.

1.4.6 α,β-Dicarbonyl Amides and Esters

The chemistry of vicinal polyketones has been reviewed by Rubin in 1975[121] and again in 2000.[122] The tricarbonyl compounds were first discovered already in 1890[123] but did not attract much interest among synthetic chemists before isolation of FK506 in 1987.[6] In the next ten years, the chemistry and preparation of α,β-diketo esters and amides garnered much attention as it was one of the key structural motifs responsible for observed biological activity of FK506, rapamycin and ascomicin.[20]

Chemically, the middle carbonyl group is the most electrophilic of the three and reversibly binds water to form a hydrate. For some time, it was even believed that the binding to the FKBP12 involves covalent bonding through that carbonyl group, until experiments by Schreiber disproved that hypothesis.[124] This, as well as the fact that most amides exist as a mixture of rotamers, should be kept in mind when analyzing the spectra. In the context of pipecolic acid natural products, there is an important side-reaction that has to be considered – the benzilic acid rearrangement of α,β-diketo esters and amides (Scheme 24). For example, in the synthesis of FK506, it was discovered that in compound **76**, benzilic acid rearrangement can easily take place under alkaline conditions forming acid **77**, if hemiacetal at *C10* is not protected.[125,126] Danishefsky et al. found that in FK506 the benzilic acid rearrangement can already take place in refluxing methanol without any additional base.[127] On the other hand, determining whether this transformation has taken place is straightforward using NMR as the carbon chemical shift value for α-keto group at *C9* should be in the range of 192-198 ppm, whereas for the acids and esters, it is around 165-175 ppm.[125]

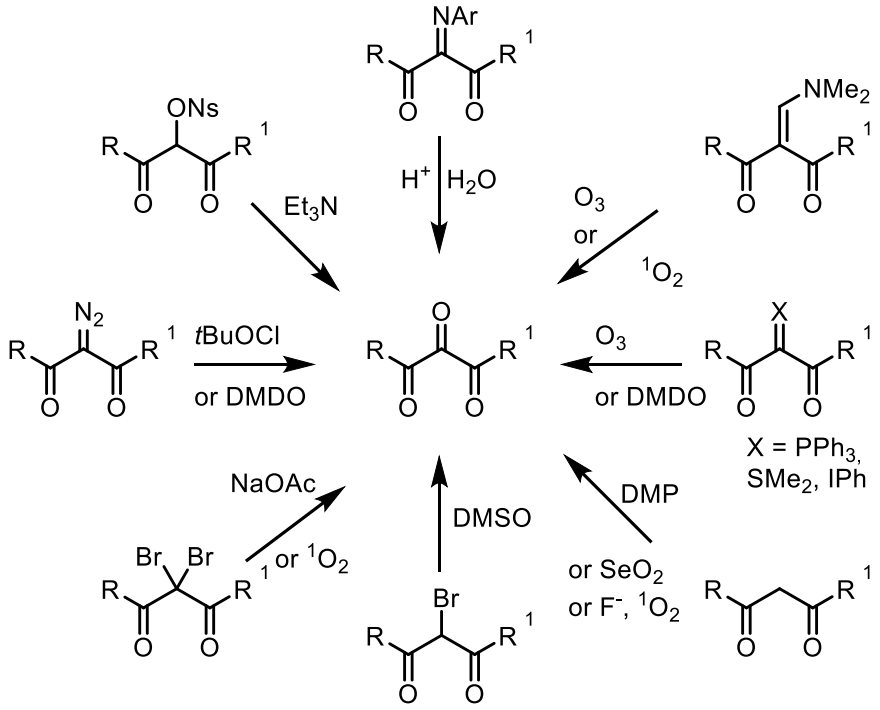


76 **77**

Scheme 24: Benzilic acid rearrangement of tricarbonyl moiety in compound **76**.

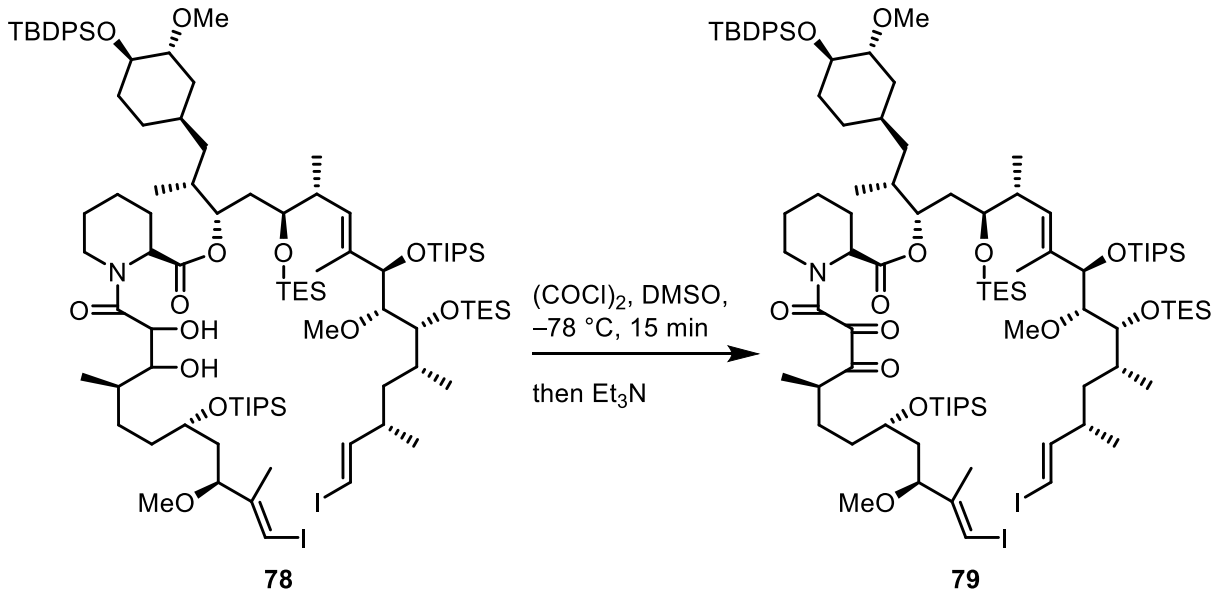
Most of the synthetically useful methods for preparing α,β-diketo esters and amides rely directly or indirectly on derivatives of the corresponding β-keto amides or esters (Scheme 25).

The α-carbon can be either vinylic (imine, alkene, diazo, phosphonium ylide), substituted with heteroatom (bromide, dibromide, nosylate) or just a methylene group. Some methods can also generate the β-carbonyl group in situ from an alcohol.[128] Another relevant method would be a simple oxidation of corresponding α,β-dihydroxy amides or esters. Several different approaches have been applied for preparation of this moiety in the context of pipecolic acid natural products.



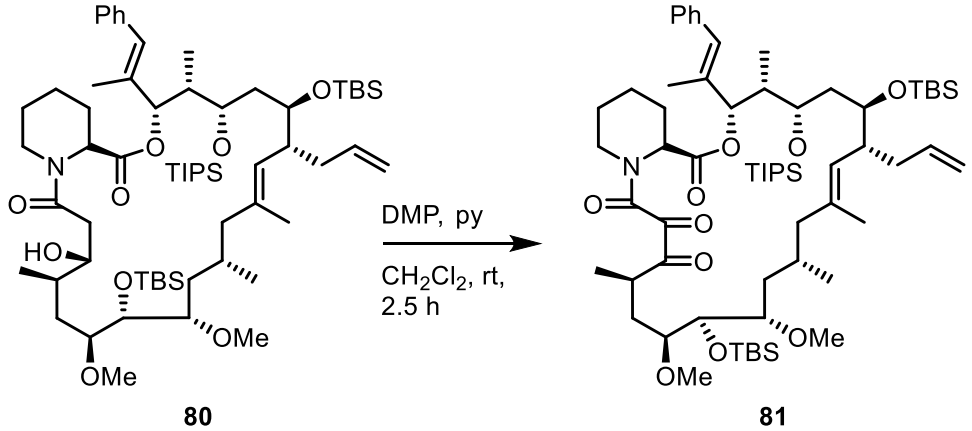
Scheme 25: Preparation of tricarbonyl compounds.

Tricarbonyl formation through oxidizing the α,β-dihydroxy amide can take place under Swern conditions[61] or with DMP[8]. For example, in his total synthesis of rapamycin, Nicolaou used a simple Swern oxidation on advanced intermediate **78** to oxidize two hydroxy groups to the tricarbonyl system in **79** (Scheme 26).[10]



Scheme 26: Oxidation of diol in Nicolaou's synthesis of rapamycin.

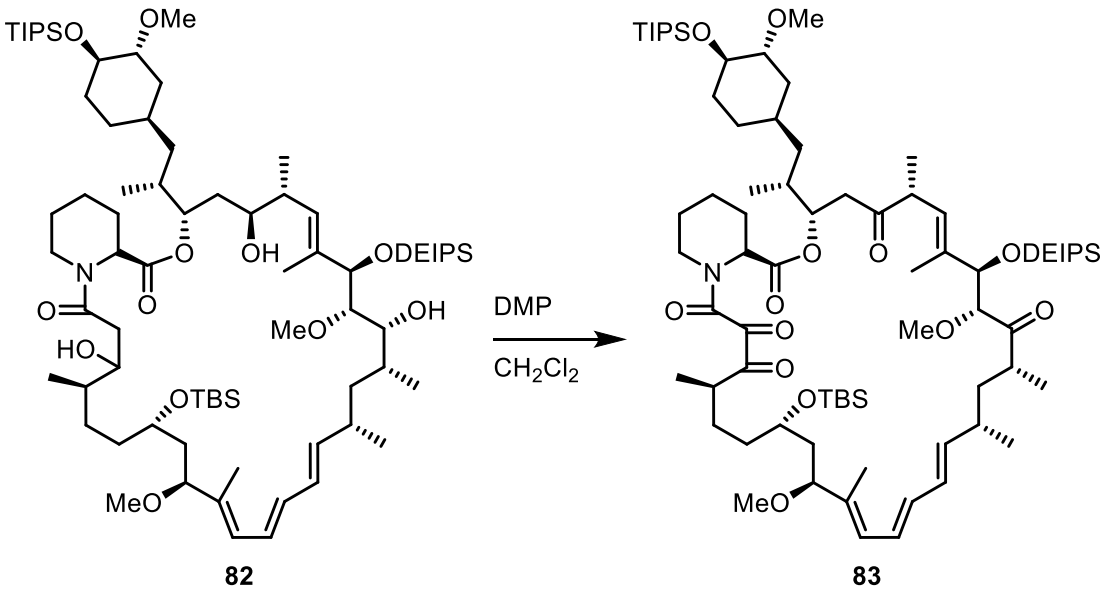
Golec et al. discovered that when β-hydroxy amides or esters are treated with DMP, the oxidation proceeds directly to the diketo amide even when α-hydroxy group is not present.[128] The usefulness of the methodology was proved in the context of preparing FK506 analogues – treating compound **80** with 3-4 equivalents of DMP in the presence of pyridine gave directly tricarbonyl compound **81** (Scheme 27). Similar transformation could also be performed with SeO_2[129] but that reagent would not be compatible with sensitive functional groups present in the later stages of the synthesis.



Scheme 27: Oxidation of β-hydroxy amide **80** with DMP by Golec.

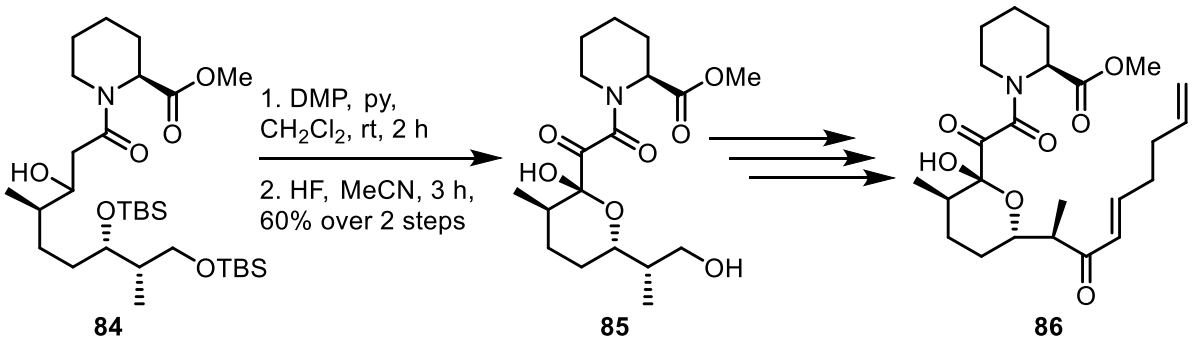
Dess-Martin periodinane was later used in several synthetic sequences for pipecolic acid natural product preparations. Schreiber used the DMP oxidation to install four carbonyl

groups simultaneously in the penultimate step of the rapamycin synthesis on fragment **82** and obtained the desired tetraketone **83** (Scheme 28).[11] Smith et al. used very similar conditions for oxidizing β-hydroxy amide to tricarbonyl in their synthesis of rapamycin.[130]



Scheme 28: Late-stage oxidation of β-hydroxy amide **82** in Schreiber's synthesis of rapamycin.

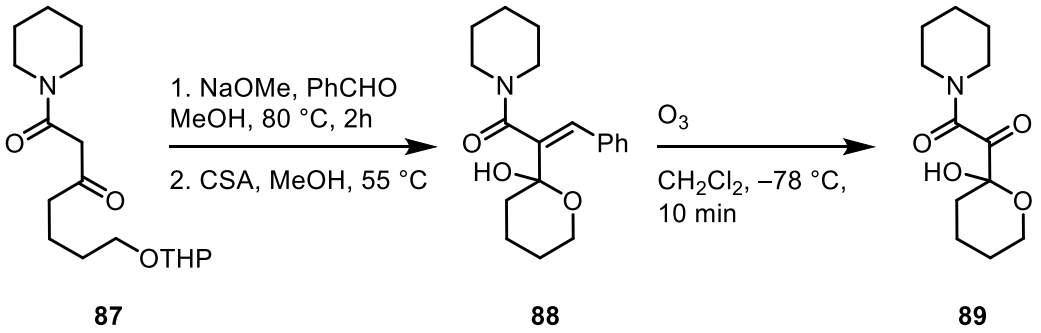
DMP has also been used in preparing the tricarbonyl segment independently in fragment synthesis. Chakrabarty et al. synthesized a tricarbonyl compound **85** in their synthesis of southern fragment **86** of antascomicin A. They treated β-hydroxy amide **84** with DMP to get the corresponding tricarbonyl compound and directly formed the lactol by removing the TBS-protecting groups with HF in MeCN (Scheme 29).[40]



Scheme 29: Oxidation of β-hydroxy amide **84** in Chakrabarty's fragment synthesis of antascomicin A.

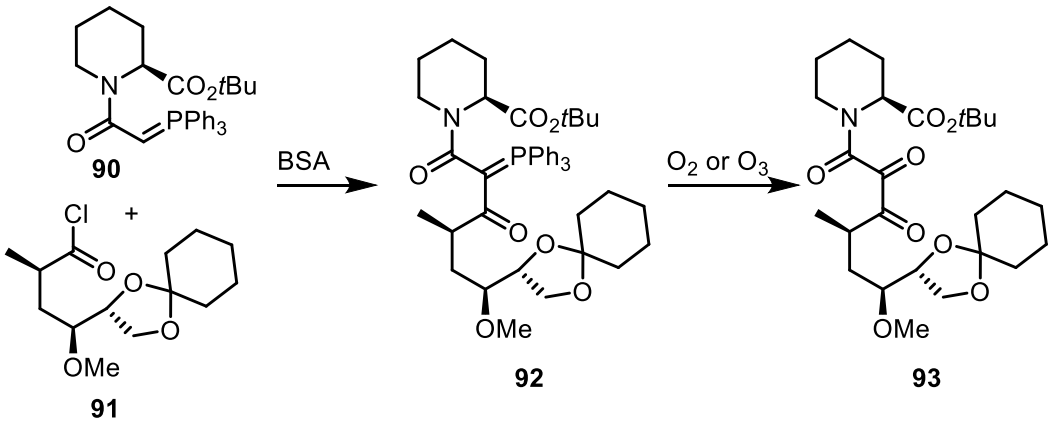
Oxidation of suitable α,β-dihydroxy and β-hydroxy carbonyl compounds are probably the most straightforward and mildest methods for installing the tricarbonyl functionality but they

are certainly not the only options. Rao et al. solution for making this motif was to perform an aldol condensation with the β-keto amide **87** and benzaldehyde giving **88**, and subsequently oxidatively cleave the double bond using ozonolysis, thus forming the tricabonyl compound **89** (Scheme 30).[131]



Scheme 30: Oxidation of β-keto amide **87** by Rao.

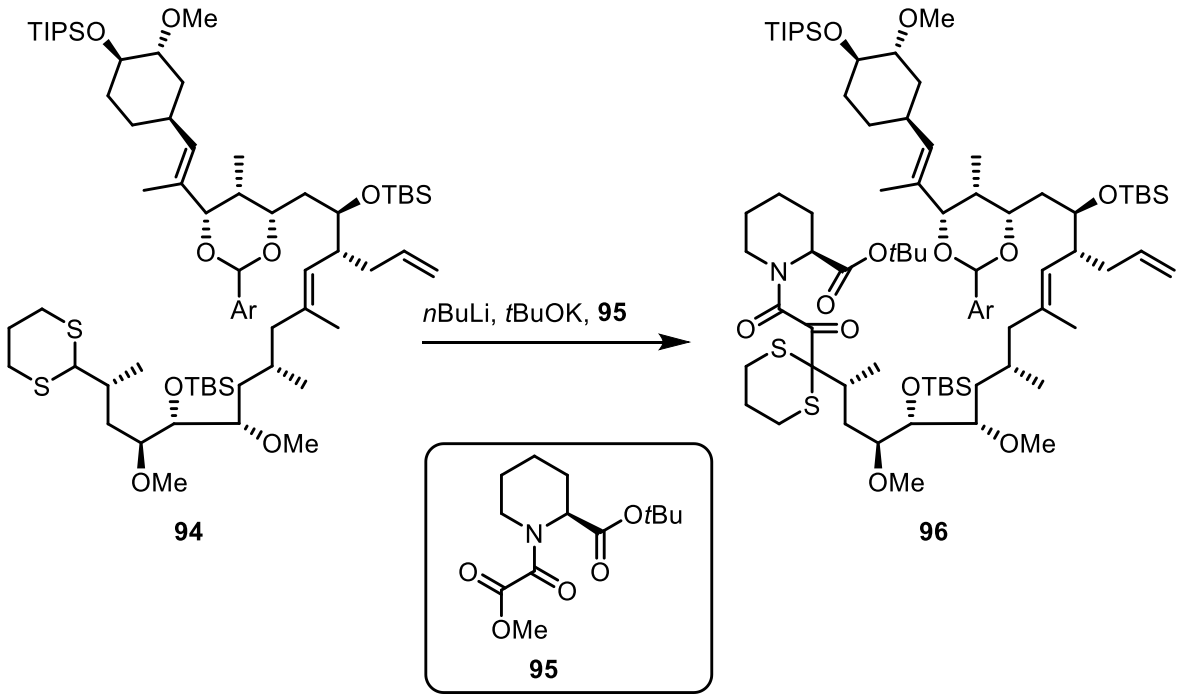
Wassermann et al. reacted an activated acid **91** with a acylphosphoranylidene **90** in the presence of bis(trimethylsilyl)acetamide (BSA) giving the keto ylide carboxylate **92**,[132] which was then oxidatively cleaved to get the tricarbonyl compound **93** (Scheme 31). One of the limitations of this and the previous method is that both ozone and singlet oxygen, which are used to oxidize the ylide or the alkene, respectively, react also with olefins therefore making it unusable in the later stages of the synthesis.



Scheme 31: Preparation of the tricarbonyl moiety by Wassermann.

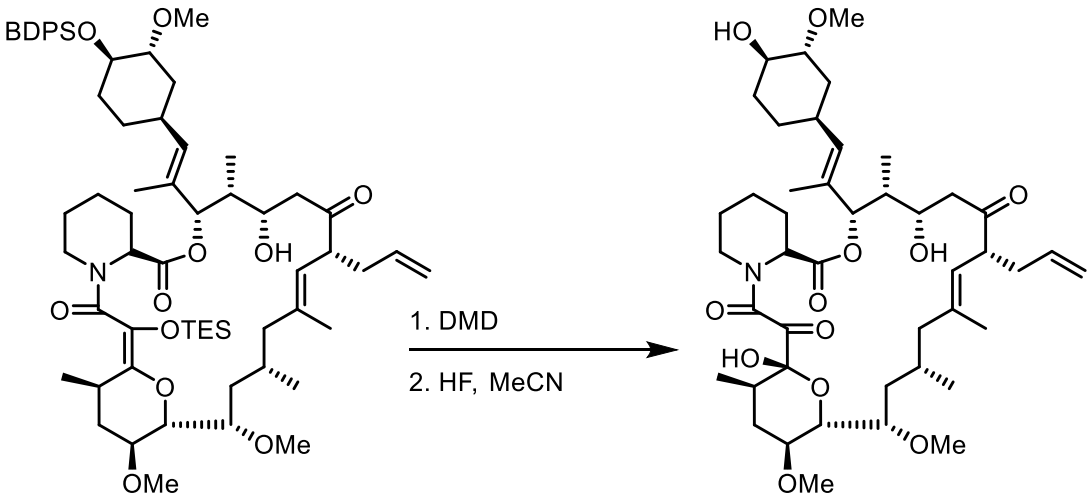
Danishefsky, similarly to Wassermann, directly installed all three carbons of the tricarbonyl moiety in the correct oxidation state. Instead of ylides, they used the 1,3-dithiane **94** and the α-amidoester **95**. Treating them with Shlosser's superbase system LICKOR,[133] which generated a reactive potassiated 1,3-dithiane, directly gave compound **96** (Scheme 32).[37]

Unfortunately later on, they were not able to bring about the macrocyclization and this synthetic approach was eventually abandoned.



Scheme 32: Preparation of the tricarbonyl moiety by Danishefsky.

Ireland has a rather unique solution for the tricarbonyl "problem" – he first prepared the corresponding α-keto amide bordering a tetrahydropyrane ring. Treating it with KHMDS and TESCl at −78 °C gave the corresponding silyl enol ether **97**. It is worth mentioning that KHMDS at −78 °C without polar additives does not enolize esters[134] and therefore did not cause epimerization of the pipecolate ester. Silyl enol ether **97** was then exposed to dimethyldioxirane, which reacted slowly giving a diastereomeric mixture of TES-protected hemiacetals. Global deprotection with HF in MeCN gave FK506 (**5**) in 25% yield and in natural configuration (Scheme 33).[9] It is interesting to note, that deprotection with HF·pyridine complex gave a somewhat cleaner reaction but produced a byproduct highly similar to FK506 and was therefore not applied.



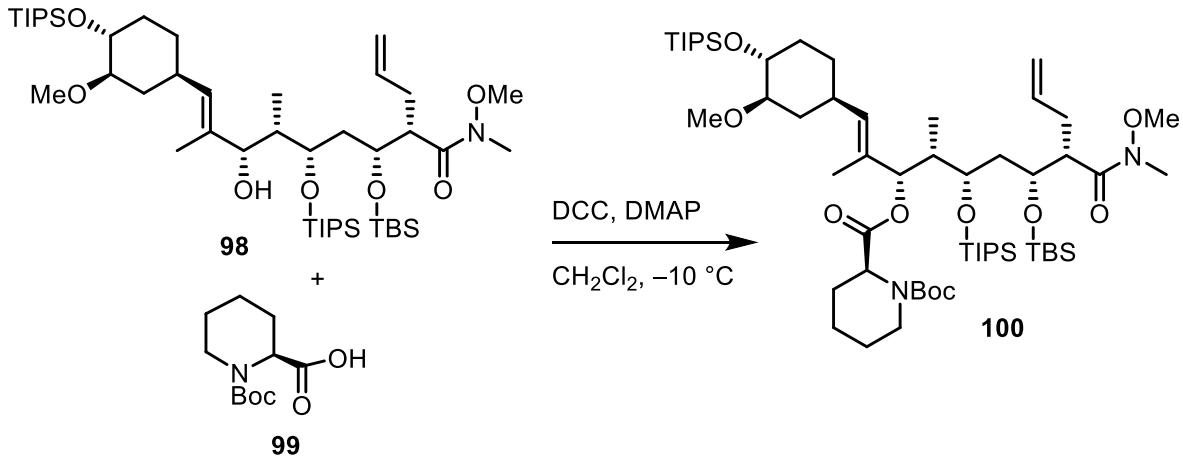
97 **FK506 (5)**

Scheme 33: Preparation of the tricarbonyl moiety in last stages of FK506 (**5**) synthesis by Ireland.

1.4.7 Macrocyclizations in Pipecolic Acid Natural Product Syntheses

The most common method for macrocyclizations in macrolide natural product synthesis generates a bond between a carbon and a heteroatom, usually an amide or ester bond. In macrocylization of compounds containing both of these groups, the question arises which one should be used for closing the macrocycle.

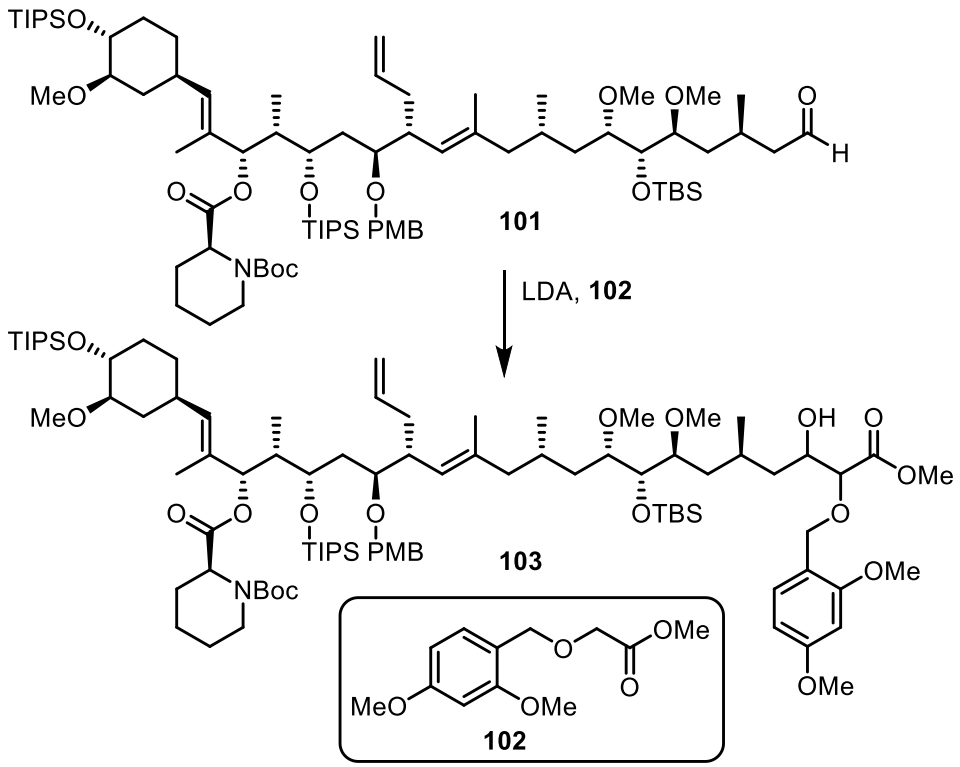
In the first published total synthesis of FK506 by Merck Co. esterification of Boc-protected (*S*)-pipecolic acid **99** with their northern fragment **98** lead to 6-7% of the epimer at 25 °C.[7,61] The amount of epimer in compound **100** decreased to 3-4% at 0 °C and further down to 1-2% at −15 °C, in the end, the optimal conditions was found to be to conduct the experiment at −10 °C (Scheme 34). Those results were confirmed in Schreiber's and Ireland's syntheses, where esterification using compound **99**, DCC and DMAP at −20 °C caused no observable epimerization at pipecolic acid stereocentre.[8,9] Epimerization was also suspected when an advanced intermediate containing the pipecolate ester in the synthesis of FK506 by Ireland was treated with NaOH in aqueous dioxane at elevated temperatures.[135] Namely, they could not directly confirm formation of epimers in the ^{1}H NMR spectrum due to presence of rotamers but they did observe suppression of broad signals previously assigned to pipecolate proton when treating with NaOD in D_2O. For aforementioned reasons, macrolactamization was generally the method of choice in synthesis of pipecolic acid natural products.



Scheme 34: Esterification with pipecolic acid **99** in FK506 synthesis by Merck Co.

On the other hand, Schreiber et al. did not encounter issues with epimerization when performing aldol reaction using a lithium enolate on an advanced intermediate in FK506 and

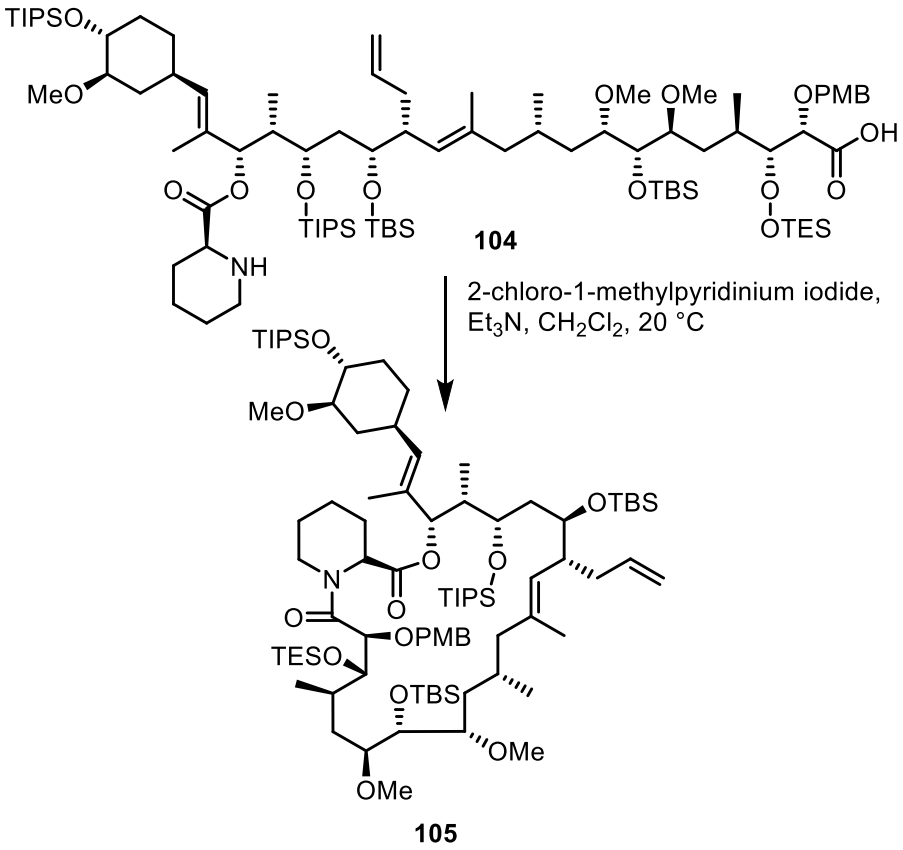
rapamycin syntheses.[8,11] Treatment of **102** with glycolic acid derivative **103** gave the product **104** as an irrelevant mixture of four diastereomers with no significant degree of epimerization at pipecolic acid stereocentre (Scheme 35).



Scheme 35: Aldol reaction with substrate containing the pipecolic acid moiety in Schreiber's synthesis of FK506.

1.4.7.1 Macrolactamization

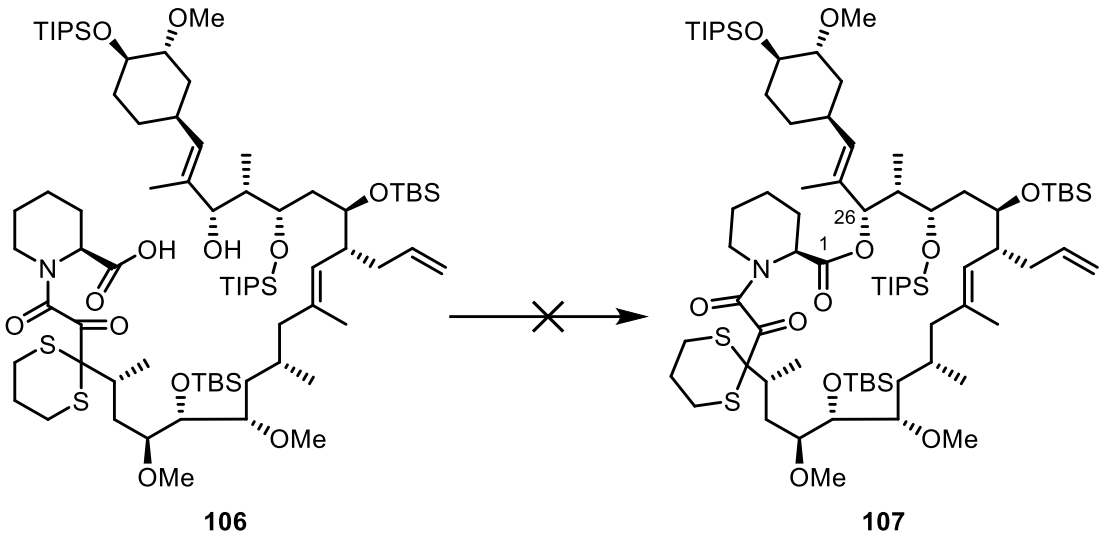
Results discussed in the previous section were Merck Co.'s grounds for choosing macrolactamization strategy for closing the macrocycle. Treatment of **104** with Mukaiyama reagent[136] gave **105**, which was then elaborated to FK506 in eight more steps (only protecting group manipulations and oxidations).[7] A strategy relying on the macrolactamization and Mukaiyama reagent was also used in Schreiber's[8] and Ireland's[9] syntheses of FK506, as well as Schreiber's[11] synthesis of rapamycin.



Scheme 36: Macrolactamization in Merck Co.'s synthesis of FK506.

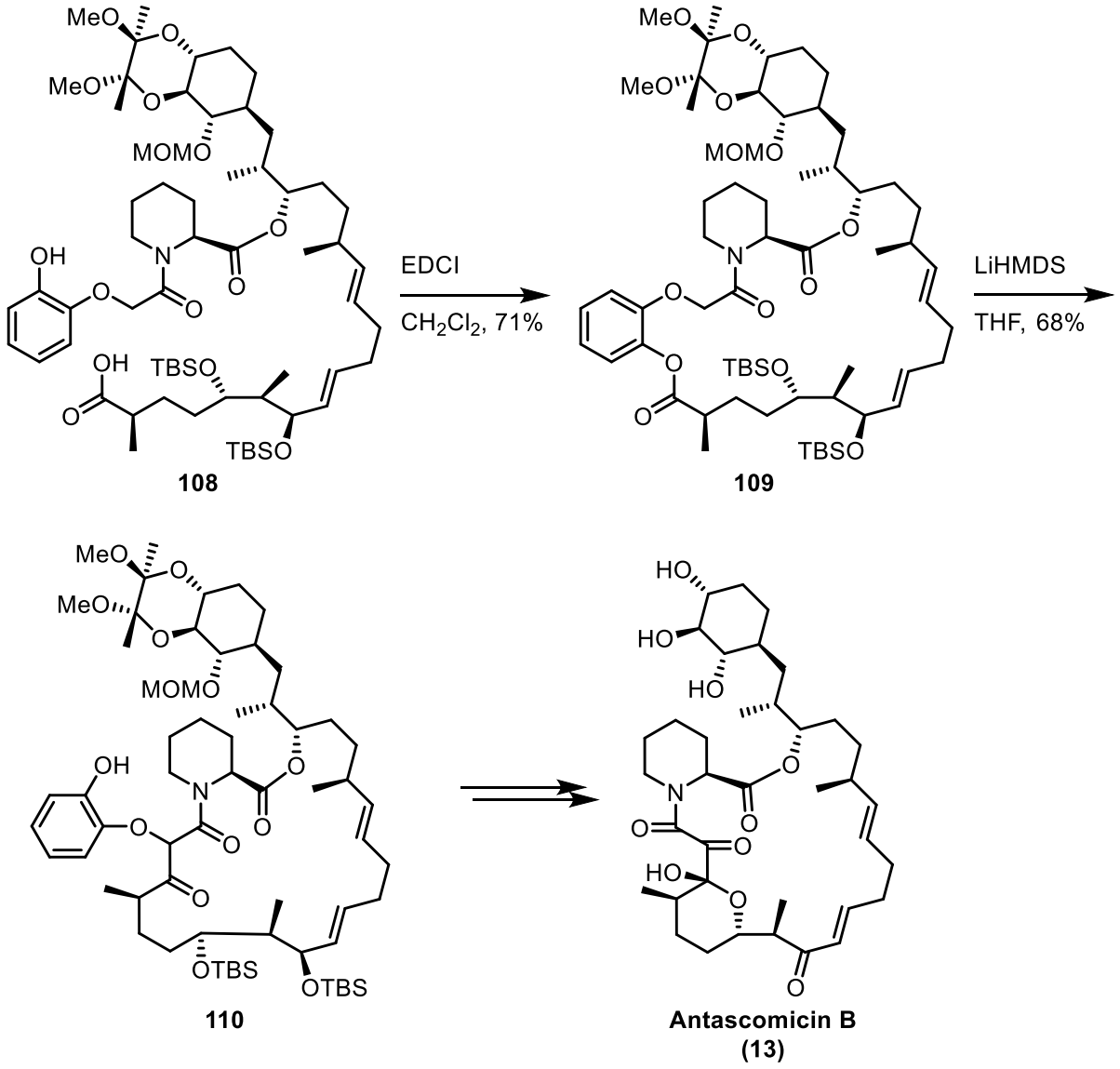
1.4.7.2 Macrolactonization

Danishefsky tried many various conditions (including DCC-DMAP, pyridinium salts and mixed anhydrides) for effecting the macrolactonization of compound **106** to **107** but ^{1}H NMR spectra never showed acylation of *C26* hydroxy group nor esterification of *C1*.[37] They did not conclude, though, that macrocyclization for similar compounds is not possible but proposed that in this particular case the α-keto or β-dithiane moieties next to the amide bond may be detrimental (Scheme 37).



Scheme 37: Failed macrolactonization of **106** in Danishefsky's work towards FK506.

Ley et al.'s use of macrolactonization is actually the only example in the synthesis of related pipecolic natural products.[14,39] Even they did not construct the ester bond between the pipecoline acid moiety and hydroxy group at *C34* but rather used the catechol tether as a setup for transannular aldol reaction and Dieckmann condensation in their syntheses of antascomicin and rapamycin, respectively (Scheme 38). Namely, they used a catechol tether to initially connect the two ends of the advanced intermediate **108** forming the first macrocycle **109**. When treating compound **109** with LiHMDS, deprotonation at *C9* took place, which was followed by transannular Dieckmann condensation, forming the C-C bond between *C9* and *C10* giving the desired macrocycle **110**. After some protecting group removal and oxidation state manipulation steps, antascomicin B (**13**) was obtained.[39]

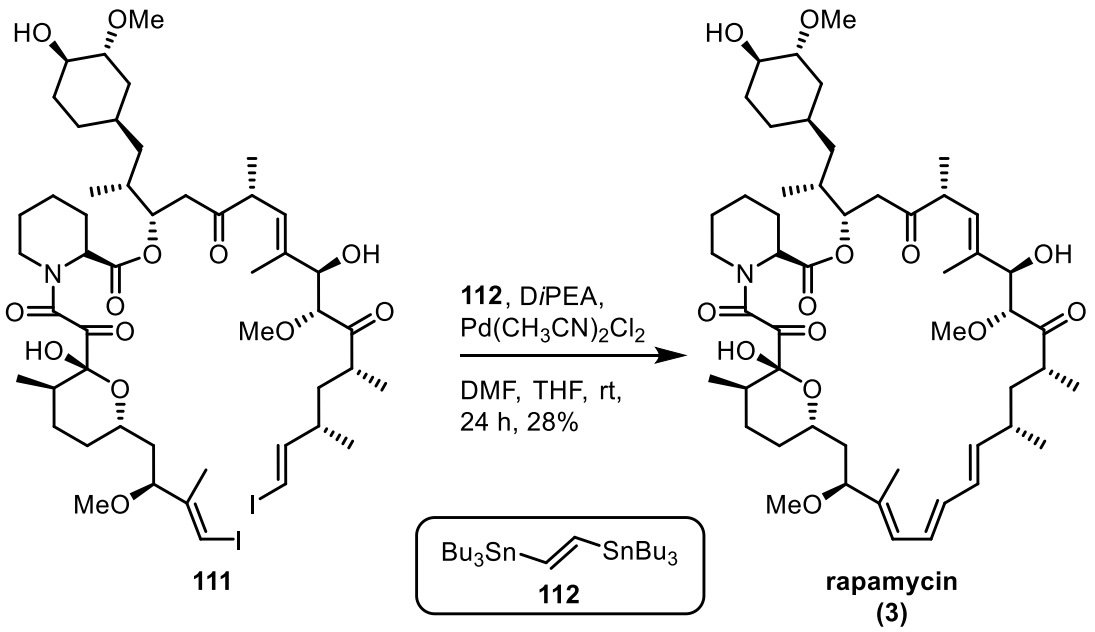


Scheme 38: Macrolactonization and intramolecular Dieckmann condensation in Ley's synthesis of antascomicin B (**13**).

1.4.7.3 Other Macrocyclizations

Though macrolactamization and macrolactonization are, by far, the most used methods in the synthesis of pipecolic acid natural products, there are some noteworthy exceptions. Firstly, Nicolaou applied a bold Stille coupling[137] based "stitching" method in the last step of his synthesis of rapamycin (**3**) by attaching two ends of the bis-vinyliodide **111** with enedistannane **112** (Scheme 39).[10] Even though the reaction was low-yielding, it does not diminish the impressiveness of showcasing the usefulness of Stille coupling in the context of

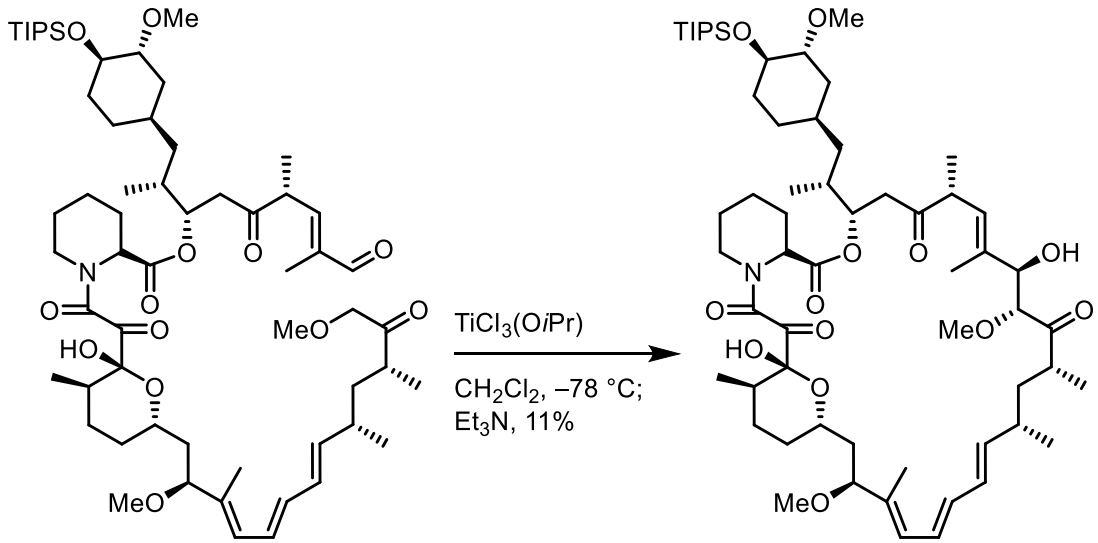
complex natural products. Similar Stille type coupling with an intermediate containing both a vinyl iodide and vinyl stannane was used for macrocyclization in Smith's synthesis of rapamycin.[13]



Scheme 39: Macrocyclization by double Stille coupling in Nicolaou's synthesis of rapamycin (**3**).

Danishefsky had even bolder idea of performing a macroaldolization reaction for closing the 31-membered cycle. They hoped that making a metalloenolate from **113** would lead to macrocyclization. The reaction turned out to be unsurprisingly difficult as most reagents did not lead to desired conversion. Finally, the found that treating compound **113** with $TiCl_3(OiPr)$ gave an isolable amount of desired cyclized product **114** (Scheme 40).[12] Danishefsky's synthesis is also one of the rare examples where tricarbonyl moiety was installed before macrocyclization and proves that this motif is significantly more stable than previously thought.

Using an aldol reaction for macrocyclization is a rather rare strategy[138,139] due to chemoselectivity issues arising from having two enolizable groups in the same molecule, from which the aldehyde is usually more easily enolizable.



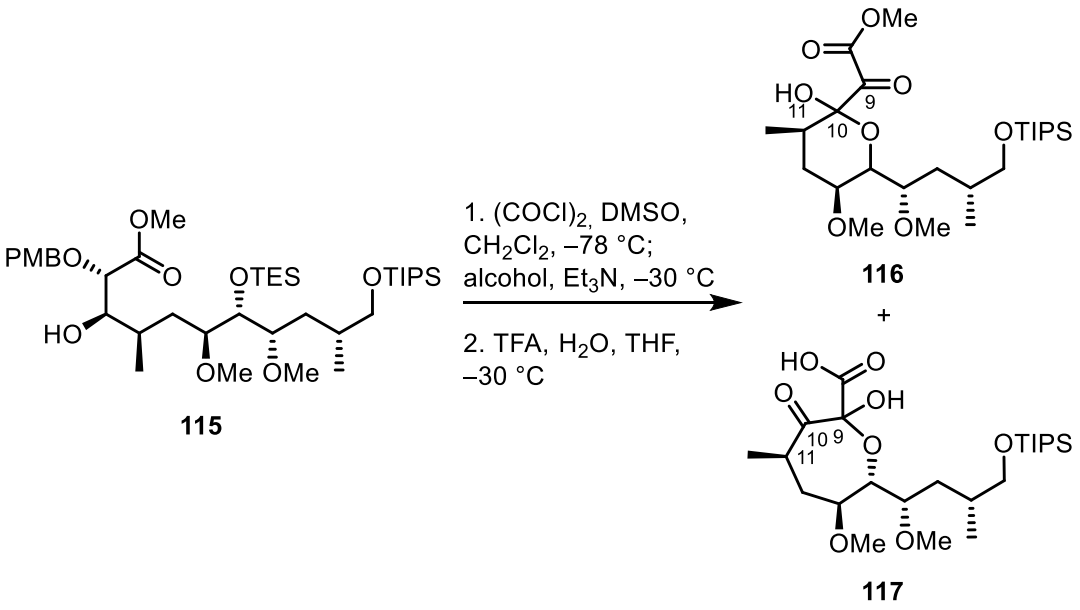
113 **114**

Scheme 40: Late stage macroaldolization of compound **113** in Danishefsky's synthesis of rapamycin.

1.4.8 Hemiketal Formation in Pipecolic Acid Natural Product Syntheses

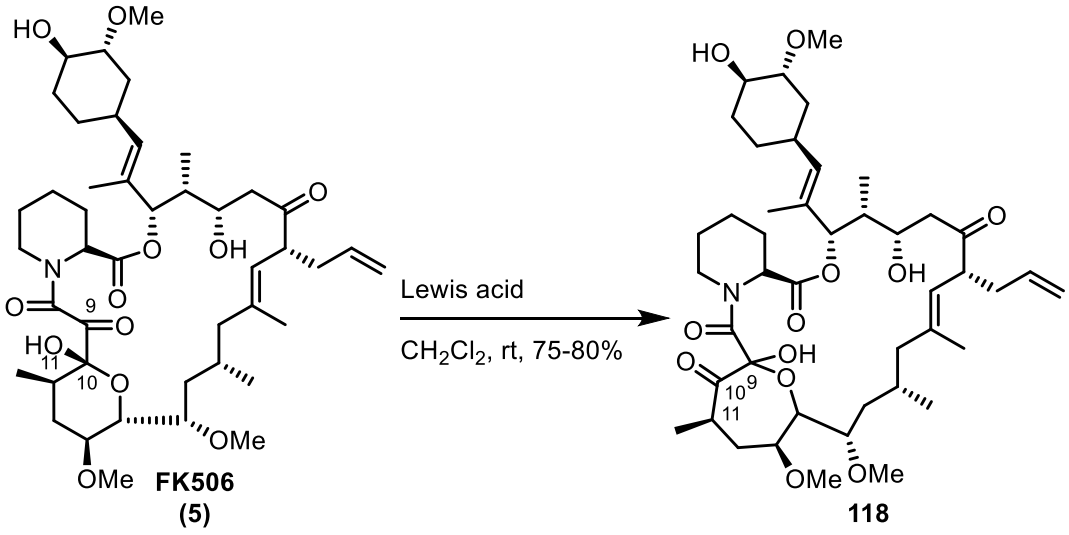
In the macrocyclic pipecolic acid natural product, the hemiketal forms preferentially the six-membered ring with natural stereochemistry,[8,11,61] whereas in smaller fragments the results may vary. Hemiketal formation at the last step of the Ireland's synthesis, **97** successfully gave the desired stereochemistry for FK506 (Scheme 33).[135] In Nicolaou's rapamycin synthesis (Scheme 39), the hemiketal was formed before macrocyclization but they still reported obtaining the product that was identical to the natural sample.[140] This may indicate that the configuration at the hemiketal centre is actually inconsequential as in the natural product it automatically adopts the natural configuration.

In addition to the question of stereoselectivity of the hemiketal formation, there also is a possibility of forming either the six- or seven-membered lactol. While generally six-membered lactols should be preferred, then in case of tricarbonyl compounds, the α-carbonyl group is more electrophilic and might therefore favor a seven-membered form. Merck Co. reported that with simple ester **115**, the six-membered **116** and seven-membered **117** ring form in 1:1 to 4:1 ratio (Scheme 41).[61] They also found that trapping the hemilactol with TMSOTf gives a 2:1 mixture of desired product with an open-chain form, where secondary alcohol is silylated. While differentiating the six- and seven-membered lactol may not be apparent at the first glance, then in depth analysis of the NMR can reveal the differences. For FK506 (**5**), the proton signal at *C11* had a large downfield shift from 2.04 ppm to 3.02 ppm in compound **118** (Scheme 42).[141] This is caused by the neighboring group changing from hemiacetal to a carbonyl group. Also the ^{13}C signal for *C9* alpha to an amide is characteristic - it appears around 192–198 ppm for compound **5** while carbonyl group corresponding to *C10* in **118** should have a chemical shift value around 208-209 ppm.



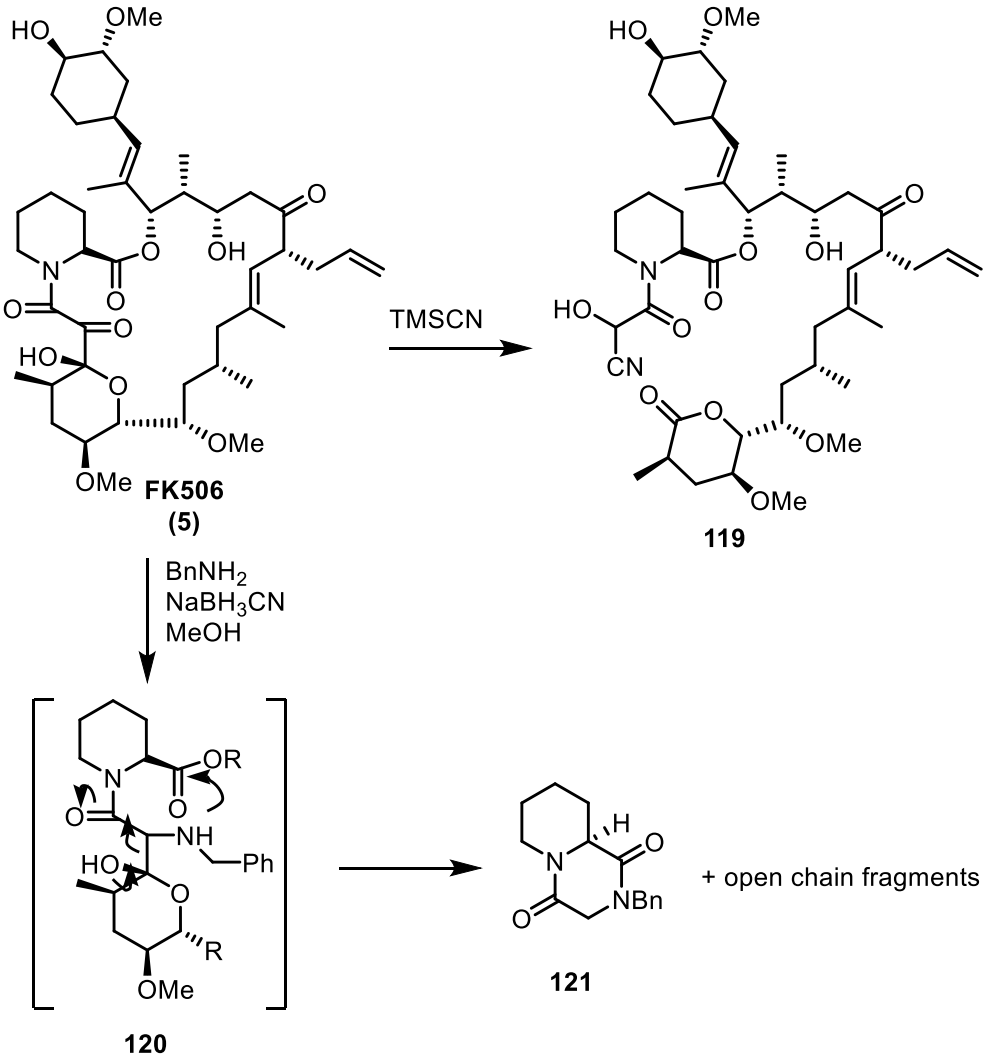
Scheme 41: Six- versus seven-membered lactol formation.

While selectively forming the six-membered lactol is definitely important in the fragment synthesis, this may not be relevant in the natural product. When analyzing the natural sample of rapamycin, Hughes et al. found that it contained a small amount of the seven-membered analogue, which slowly converts back to natural rapamycin.[141] Therefore, one can assume that in the natural product the six- and seven-membered forms exist in equilibrium strongly favoring the natural six-membered lactol. In case of FK506 (**5**) and ascomycin (*C21* ethyl analogue of FK506) it was demonstrated that this equilibrium may be reversed and in the presence of Lewis acids ($ZnCl_2$, $ZnBr_2$, ZnI_2 or $Ti(OiPr)_4$) the seven-membered lactol **118** can be obtained (Scheme 42).[142]



Scheme 42: Isomerization of FK506 (**5**) to the seven-membered lactol **118** in the presence of Lewis acids.

As mentioned previously, the unprotected hemiketal is unstable and easily undergoes benzilic acid rearrangement.[125,126] Danishefsky et al. also found that the group is in general unstable towards different nucleophiles. Upon treating the natural FK506 (**5**) with TMSCN to form a cyanohydrin at the central *C9* carbonyl group and see if this group could be used as a masked carbonyl functionality in the total synthesis, they found that C-C bond cleavage takes place instead, forming the open-chain compound **119**, which contains a lactone and an acyl cyanohydrin (Scheme 43). Also, treating **5** with benzylamine in the presence of a sodium cyanoborohydrine led to formation of diketopiperazine **121** probably through intermediate **120**.



Scheme 43: Instability of the free tricarbonyl moiety towards nucleophiles.

Aforementioned reasons necessitate the use of protecting group for the hemiacetalic oxygen. When the oxygen is protected, the benzilic acid rearrangement cannot take place anymore and a bulky protecting group would also shield the α-carbonyl group against nucleophilic attacks. Another aspect to keep in mind is that removing TBS protecting group from tertiary alcohol may be complicated and one should consider more easily removable TES or TMS groups. Smith et al. found that even installing the protecting group might be problematic and highly dependent on the conditions.[130]

2 Results and Discussion

2.1 Retrosynthesis

3-normeridamycin (**11**) was chosen as a primary synthetic target in this study towards preparation of meridamycins. Dividing the molecule into the northern and southern fragment with late amino acid motif introduction offers an easy access to all known meridamycins from common intermediates and minimal amount of changes in the synthetic sequence.

The most distinct features of 3-normeridamycin (**11**) could be said to be 14 stereogenic centres, 27-membered macrolactone and a highly characteristic 1,2,3-tricarbonyl functionality starting with a 6-membered hemiketal and ending with a cyclic amino acid. The last motif is the binding site with the FK506 binding protein and a common feature in several similar natural products.[143] Previous work on related natural products revealed, that in case of pipecolic acid, the α-carbon of the amino acid moiety, *C2* is highly labile and easily epimerizes under macrolactonization conditions.[7] It was also discovered that *C8* and *C9* can be oxidized after macrocyclization and in situ formed hemiketal adopts the natural configuration.[8,11,61] It should also be kept in mind, that if a tricarbonyl motif is installed earlier in the synthetic sequence, then after oxidation of *C8*, benzilic acid rearrangement can easily take place under alkaline conditions if hemiacetal at *C9* is not protected.[125,126] Keeping aforementioned points in mind, it was decided to centre the first retrosynthesis around fully decorated southern fragment, which would be the most step-economic approach having the least amount of oxidation state and protecting group manipulations. On the other hand, there should remain a possibility to easily change the route in case the issues arising from the tricabonyl motif turn out to be insurmountable.

The most common disconnection of macrocyclic natural products containing N and O atoms cleave the bond between the heteroatom and a carbonyl group. 3-normeridamycin (**11**) contains both amide and ester functionalities; the syntheses of related natural products FK506 and rapamycin feature macrocyclizations mainly through macrolactamization.[7–9,11] Macrolactonization strategy has been generally ignored due to possibility of epimerizing the pipecolate stereocentre. On the other hand, in case of proline, the stereocentre should be more stable towards epimerization and macrolactonization remains a viable strategy. It was decided that in the retrosynthetic strategy towards meridamycins, there should remain a possibility to

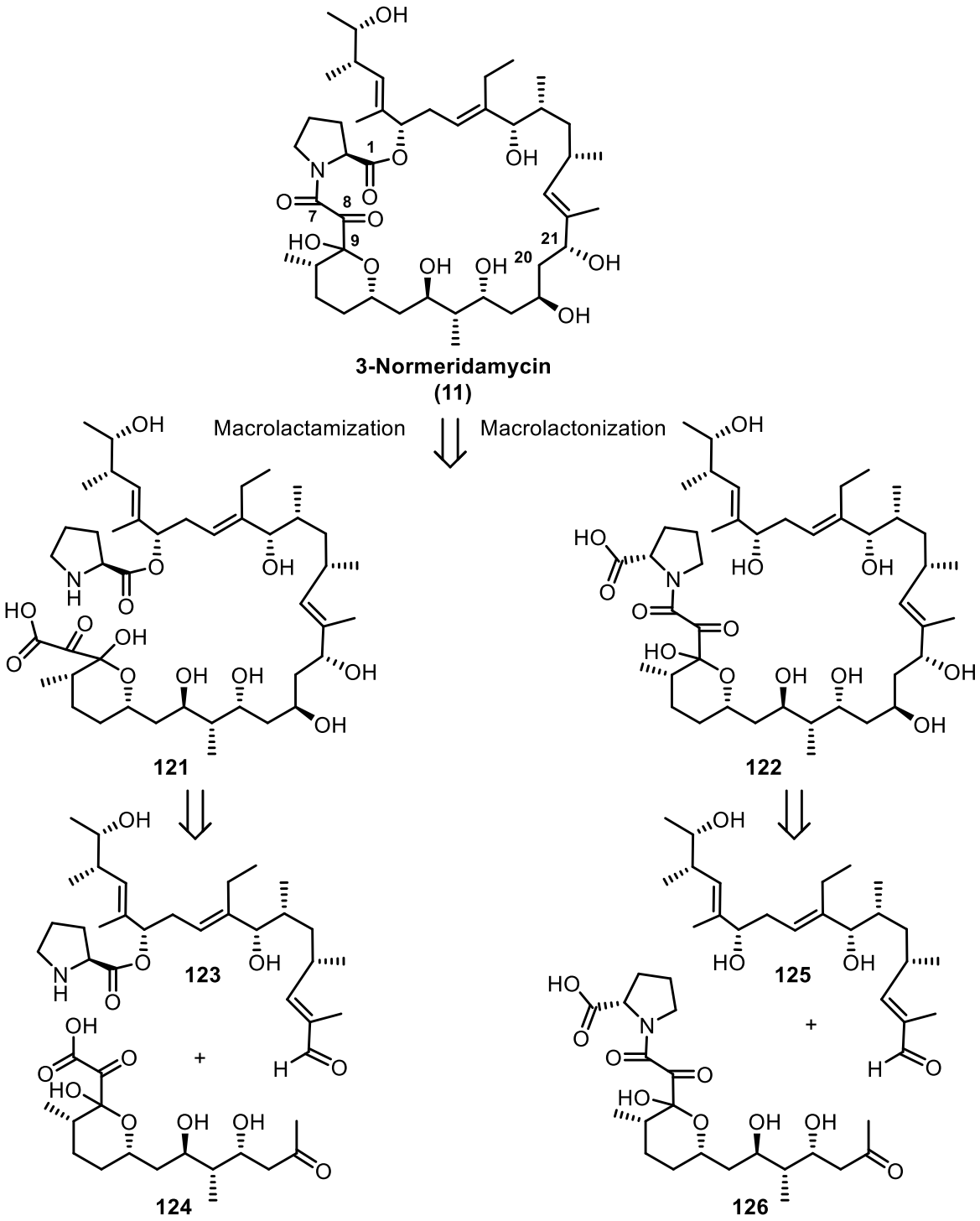
perform macrocyclization with either of the precursors **121** and **122**, and therefore the amino acid moiety should be attached in a later stage of the fragment synthesis.

It was decided to perform the second major disconnection between *C20* and *C21* which have two hydroxy groups in 1,3-relationship and correspond to an aldol disconnection. That would give either fragments **123** and **124**, or **125** and **126** as primary targets for the synthesis (scheme 44). Due to more cumbersome synthesis of the carbon framework of fragments **123** and **125**, the synthesis featuring macrolactonization for ring-closing was chosen as the primary approach. Therefore, compounds **127** and **128** were chosen as the key intermediates in the current venture towards total synthesis of meridamycins (Scheme 45). The fragment **127** is common in all known meridamycins.

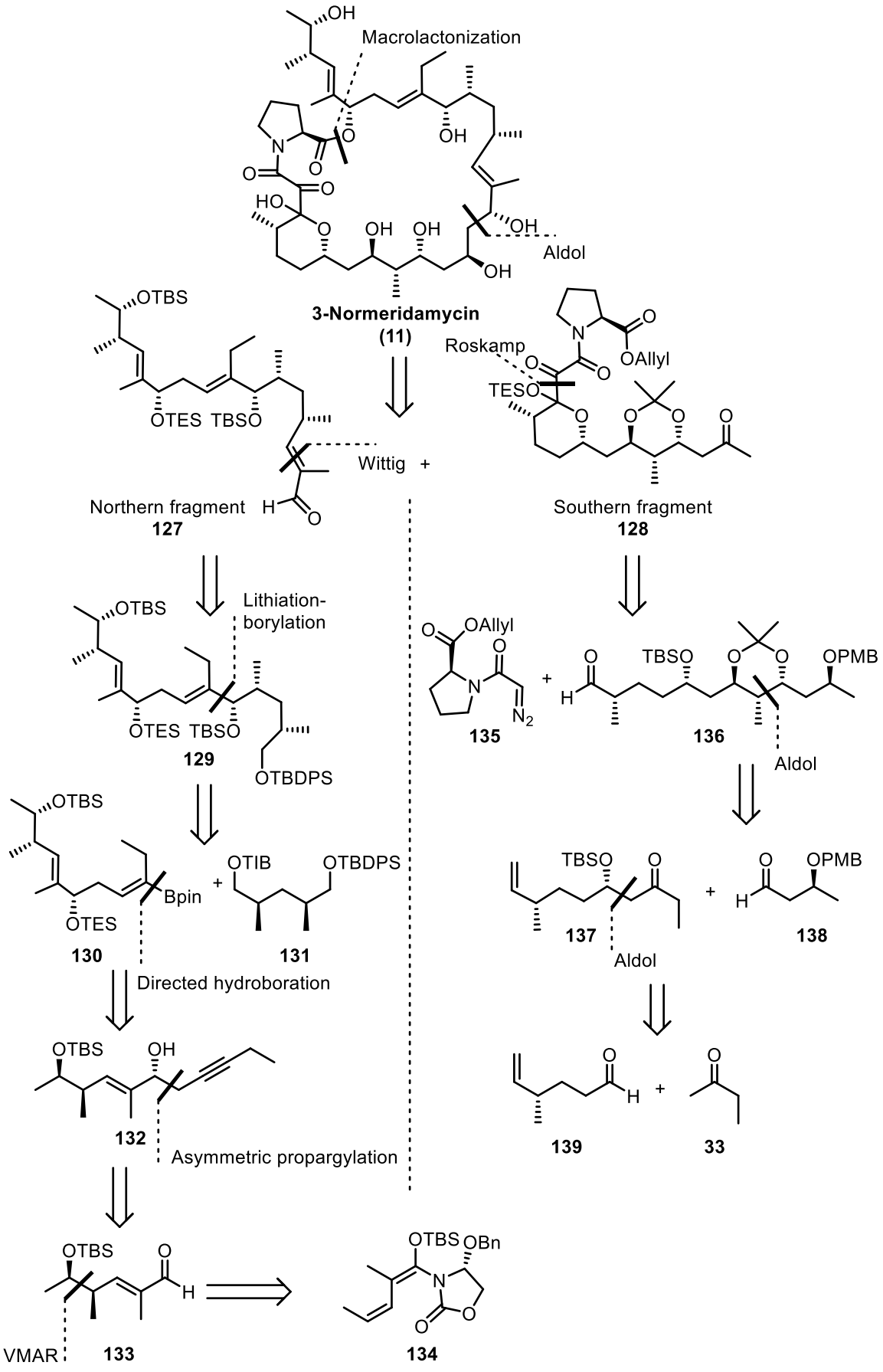
Chosen retrosynthesis divides 3-normeridamycin (**11**) into two fragments of roughly equal size by disconnecting the ester bond of the macrolactone and the carbon-carbon bond between *C20* and *C21*. Those disconnections lead to the northern fragment **127** and the southern fragment **128** providing a convergent approach for assembling the carbon framework of the 3-normeridamycin (**11**).

The northern fragment **127** would be derived from compound **129** by using a Wittig reaction and some functional group manipulations. A lithiation-borylation strategy, promoted by Aggarwal's group,[73,74] would lead to compound **131** and to boronic ester **130**. The vinylic boronic ester **130** would be prepared from internal alkyne **132**, which in turn would be formed by asymmetric propargylation of aldehyde **133**. The aldehyde **133** can be easily accessed through using *N*,*O*-keteneacetal **134** in *syn*-selective Kobayashi aldol reaction that was recently established in our group.[144]

The fully decorated southern fragment **128** would be derived from aldehyde **136** by coupling the amino acid fragment **135** using a Roskamp reaction.[78] It was realized that precursor of the aldehyde **136** could be rapidly accessed by performing two subsequent aldol reaction on either side of the central four-carbon fragment. An aldol disconnection on the ethyl side would lead to ketone **137** and literature known aldehyde **138**,[145] and subsequent aldol disconnection on the methyl side would lead to (*S*)-citronellene derived aldehyde **139** and butanone (**33**) as initial building blocks (Scheme 45).



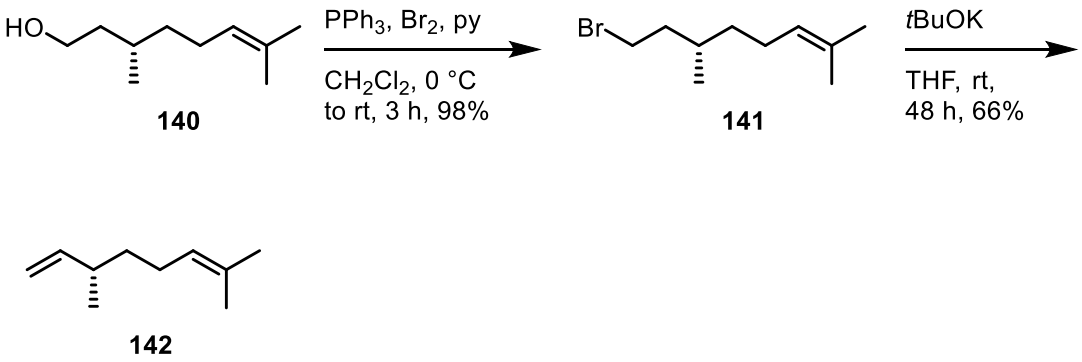
Scheme 44: Retrosynthesis of 3-normeridamycin (**11**) using macrolactamization and macrolactonization strategies.



Scheme 45: Retrosynthesis of 3-normeridamycin (**11**) using macrolactonization strategy.

2.2 The Synthesis of the Southern Fragment 128

The synthesis of the southern fragment **128** started from (*S*)-citronellol (**140**) according to known procedures.[146] Under Mitsunobu conditions,[147,148] the alcohol was first turned into the bromide **141** and then eliminated with *t*BuOK giving the (*S*)-citronellene (**142**). The bromination proceeded smoothly in high yields; the elimination had a high conversion but moderate yield due to side-reaction and polymerization taking place during the purification by distillation. Distillation under reduced pressure could be tried in the future to improve the purity and yield. Alternatively, preparing (*S*)-citronellene (**142**) over the tosylate was also tested but the elimination was more problematic and full conversion to diene was not achieved (Scheme 46).

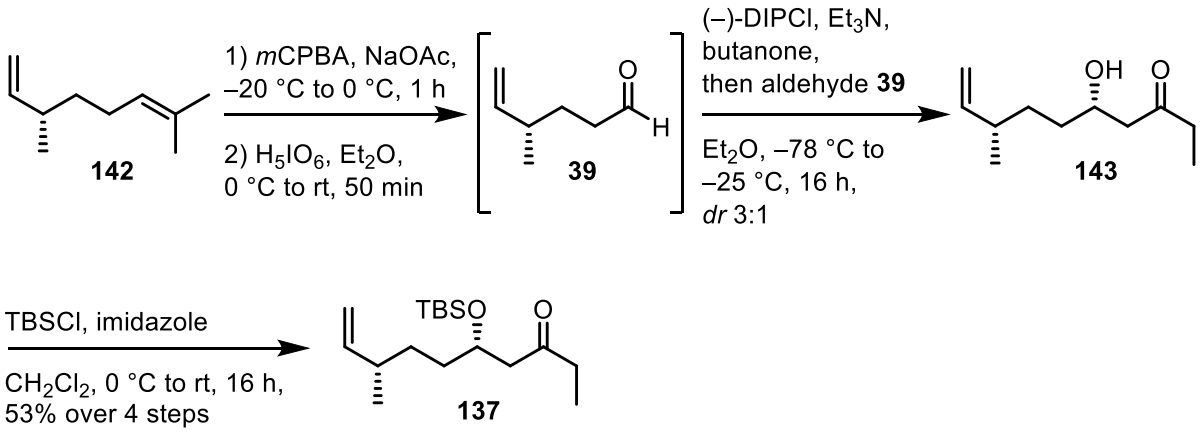


Scheme 46: Synthesis of (*S*)-citronellene (**142**).

In the next step, the more electron rich double bond of the diene **142** was epoxidised with *m*CPBA and then cleaved with periodic acid giving aldehyde **139**.[149] The epoxidation and aldehyde formations were monitored with GC FID, which indicated that both reactions took place with full conversion and minimal amount of side-products. Unfortunately isolation of the aldehyde **139** in acceptable purity was not possible. It was discovered, that compound **39** was highly volatile and decomposed rapidly at elevated temperatures, and therefore it was decided to use the crude aldehyde directly in the next reaction.

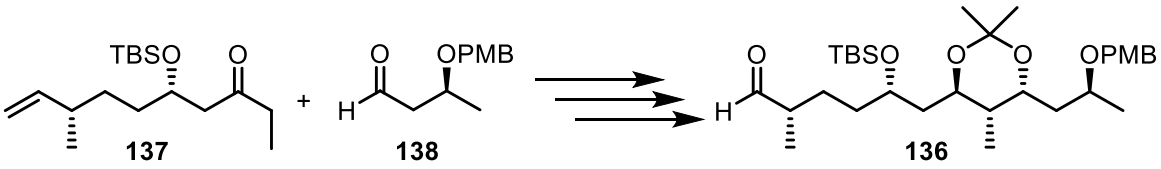
The boron-mediated aldol reaction was performed according to the procedures by Paterson et al. who discovered that reactions of boron enolates proceed in high stereoselectivity in case of isocpinocampheyl substituents on boron.[59] In this work, the reaction of aldehyde **139** with methyl ethyl ketone (**33**) in the presence of (−)-Ipc_2BCl ((−)-DIPCl) proceeded in 2:1 to 3:1 stereoselectivity with high conversion, which agrees with the previous work. As opposed to

Paterson et al., enolization at the ethyl side of the ketone was not observed.[58] Unfortunately, the obtained aldol product was inseparable from the isopinocamphol side-product using column chromatography or other purification methods. In larger scales, most of the isocpinoamphol could be removed by cooling the columned mixture to 0 °C and decanting the liquid alcohol **143** from crystallized isopinocamphol. The latter is still partially soluble in the former and fully soluble in all tested solvents rendering that purification method only partially effective. Therefore, the mixture was directly treated with TBSCl to protect the free alcohol giving ketone **137**, which was separated in high purity and in 53% yield over previous four steps (Scheme 47).



Scheme 47: Synthesis of ketone **137** using the (−)-DIPCl mediated aldol reaction.

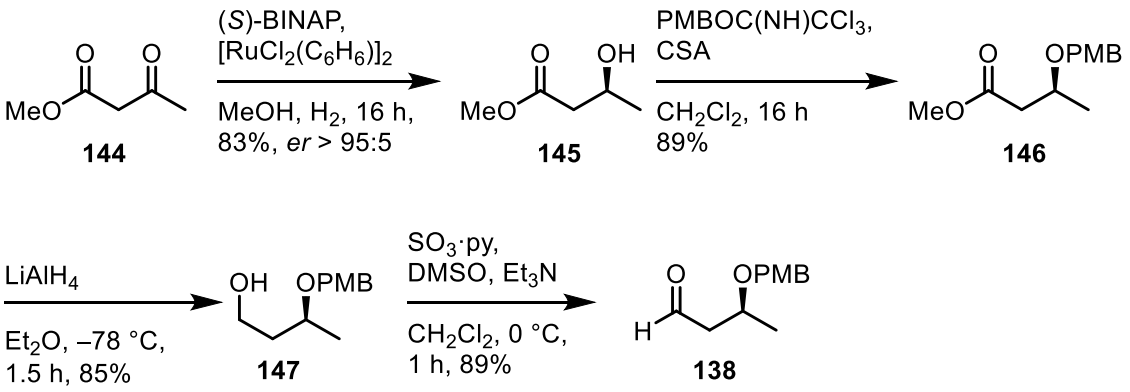
With the first key intermediate, ketone **137** in hand, the next four-carbon fragment needed to be added to the ethyl side of the ketone. The absolute stereochemistry of the α- and β-position is determined by the chiral substituent on the boron (in current case the (−)-isopinocampheyl), while the relative stereochemistry of those positions is determined by the geometrical isomers of the boron enolate. For compound **137**, (−)-Ipc_2BOTf has to be used to arrive at desired stereochemical outcome. According to the 1,3-induction model, the stereoselectivity could be further reinforced by using *S*-stereoisomer of the β-alkoxy aldehyde **138**. After the aldol reaction, an *anti*-reduction, acetonide protection and oxidative cleavage of the double bond would then lead to the compound **136** (Scheme 48).



Scheme 48: Preparation of aldehyde **136**.

A literature known aldehyde **138**[145] was chosen as a suitable coupling partner for the ketone **137**. The hydroxy group of the aldehyde **138** needed a protecting group orthogonal to acetonide- and silicon based protecting groups which could be removed before coupling of the southern fragment **128** and northern fragment **127**. Even though the stereochemistry of the hydroxy group in aldehyde **136** is inconsequential due to being oxidized to the ketone for the fragment coupling, it was decided to prepare it selectively in *S*-configuration in order to firstly, enhance the stereoselectivity of the aldol reaction; and secondly to simplify the analysis of the intermediary compounds. In the end, PMB-group was deemed as a suitable protecting group.

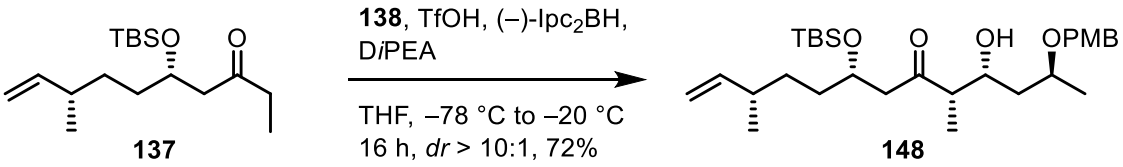
Synthesis of the aldehyde **138** started from methyl acetoacetate (**144**) using Noyori reduction[150] which gave alcohol **145**. The alcohol was protected using 4-methoxybenzyl-2,2,2-trichloroacetimidate ($PMBOC(NH)CCl_3$) under acidic conditions giving ester **146**. In this case, simpler protecting group reagents like PMB-bromide or -chloride are not suitable due to possibility of retro-aldol reaction taking place with compound **145** under basic conditions. The ester **146** was reduced with $LiAlH_4$ to primary alcohol **147**, which was then oxidized to desired aldehyde **138** under Parikh-Doering[151] conditions (Scheme 49).



Scheme 49: Synthesis of aldehyde **138** from methyl acetoacetate (**144**).

The aldol reaction between ketone **137** and aldehyde **138** proceeded in good selectivities and acceptable yields giving ketone **148** (Scheme 50). The (−)-Ipc_2BOTf for the reaction was

prepared directly before reaction as a solution in hexane by reacting freshly opened triflic acid (TfOH) with (−)-Ipc_2BH according to procedure by Paterson and co-workers.[152,153] The quality of (−)-Ipc_2BOTf can be assessed by the color of the solution – there should be a strongly colored bottom layer containing the TfOH and a colorless upper layer containing approximately 1.2 M solution of (−)-Ipc_2BOTf in hexane. In cases where there was no phase separation or upper layer was strongly colored, the reaction was performed again with fresh triflic acid and/or freshly prepared borane. The initial reaction between the borane and the acid can be very fast, therefore suitably sized vessel and cooling should be applied; at the same time, the last phases of the reaction can proceed very slowly due to small reaction surface, therefore it is recommended to grind the borane into fine powder before performing the reaction. (−)-Ipc_2BH was prepared according to a modified procedure by Brown and Joshi[154] and stored at −25 °C in a glove-box. The borane should be white crystalline solid, in cases where it had turned into a waxy solid, the borane was discarded and prepared fresh.

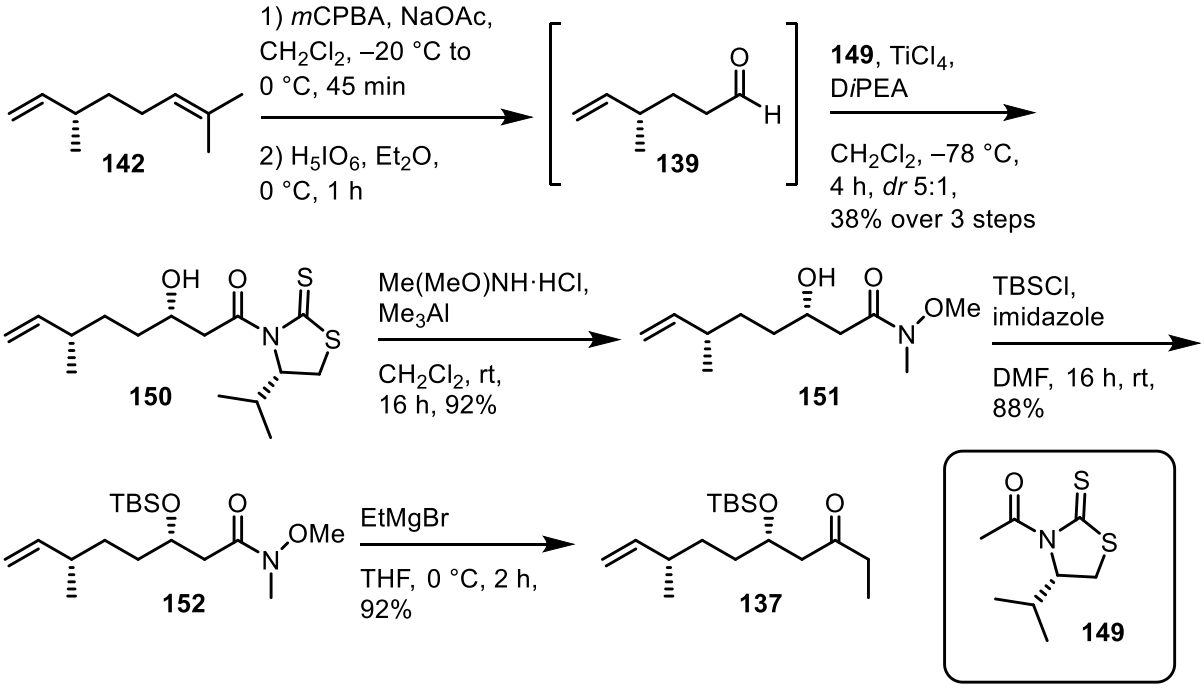


Scheme 50: (−)-IpcBOTf mediated aldol reaction between ethyl ketone **137** and aldehyde **138**.

Due to the previous aldol reaction giving a 3:1 mixture of diastereomers, the selectivities for the second aldol reaction and the following reactions were difficult to determine. To facilitate the analysis, it was decided to establish the route and to assess the stereoselectivity of the following reactions using stereochemically pure ketone **137**. To that end, an alternative route using the Crimmins aldol[49,50] strategy for preparation of compound **137** was developed (Scheme 51).

The Crimmins aldol route started also from (*S*)-citronellene (**142**), which was similarly turned into aldehyde **139** and crude aldehyde was reacted with Nagao auxiliary **149** (prepared according to the procedure by Urpi et al.[155]). The reaction between aldehyde **139** and thiazolidinethione **149** gave the product **150** in moderate but sufficient yields. The reaction also gave 20% of the undesired diastereomer, which was easily removed by column chromatography giving compound **150** in high stereochemical purity. The Nagao auxiliary was removed with *N*,*O*-dimethylhydroxylamine[156] in the presence of Me_3Al forming Weinreb amide **151**. The free hydroxy group was protected as a TBS-ether giving compound **152**,

which was then reduced with ethyl Grignard reagent directly giving ketone **137**. The advantage of using Weinreb amides can here be fully demonstrated as the nucleophilic attack on the carbonyl group forms a stable magnesium coordinated complex, which only breaks down during the workup and avoids over-reduction to the tertiary alcohol.



Scheme 51: Synthesis of ketone **137** using the Crimmins aldol approach.

The Nagao auxiliary derived ketone **137** was used to determine the stereoselectivity of the Ipc_2BOTf mediated aldol reaction. Figure 18 shows the difference in the proton signals around 5.65 ppm for the reactions performed with the boron enolate (Figure 18, left) and the Nagao auxiliary (Figure 18, right) derived ketone **137**, respectively. It can be seen that in case of the stereochemically pure **137** the reaction proceeds with very high stereoselectivities (*dr* > 20:1) but in case of 3:1 mixture, the amount of structurally similar impurities was increased. Those impurities were inseparable at this stage but could be removed by column chromatography after installing the cyclic acetonide three steps later.

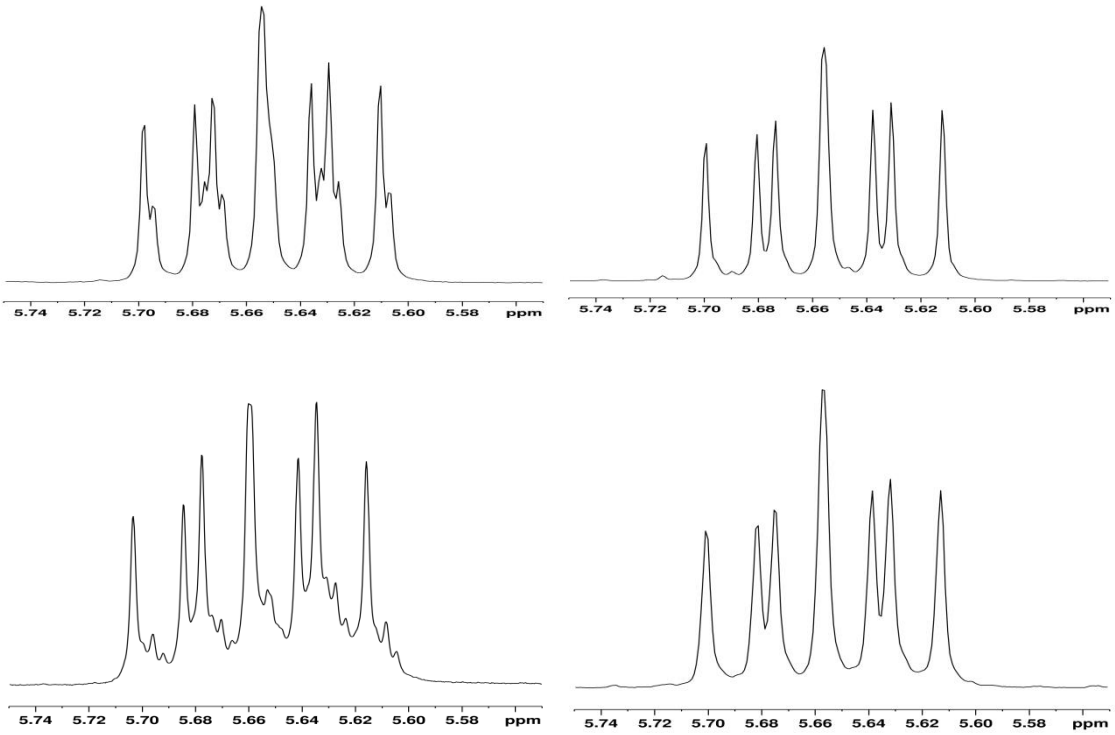
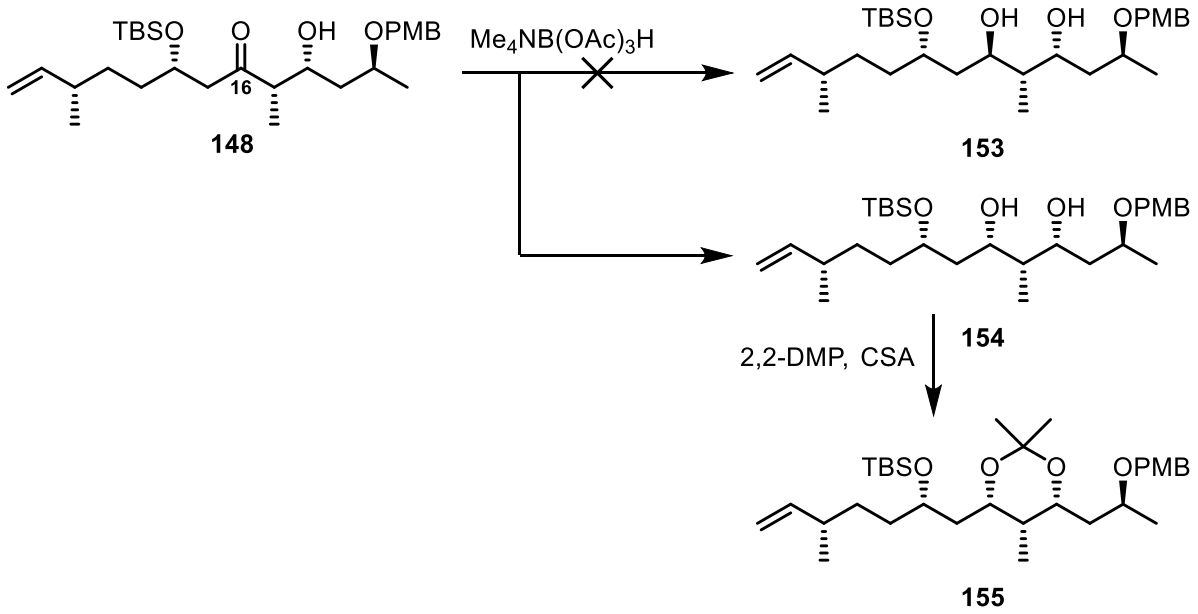


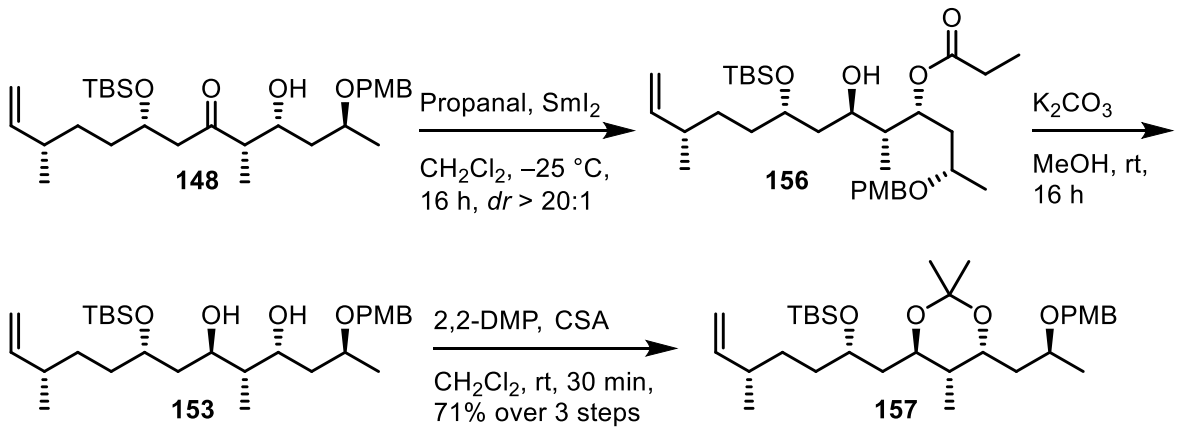
Figure 9: ^{1}H NMR proton signals around 5.65 ppm belonging to ketone **137** prepared by (−)-DIPCl route (upper, left) or Crimmins aldol approach (upper, right), and to aldol product **148** prepared from 3:1 mixture (lower, left) and > 95:5 mixture (lower, right) of ketone **137**.

After successful assembly of the carbon framework, the oxidation state at *C16* still had to be adjusted. Stereoselective reduction of β-hydroxy ketones is well established in synthetic chemistry.[157] The stereoselective *anti*-reduction of β-hydroxy ketones can be done by using reductant that coordinates with both oxygens and delivers a hydride internally. The most common reagent for that use is the $Me_4NBH(OAc)_3$, the Evans-Saksena reagent,[158,159] which has found extensive use in natural product synthesis.[160–162] In current case, reduction of **148** with this reagent gave a mixture of diastereomers preferring the usually unfavoured *syn*-isomer **154** and not the desired *anti*-isomer **153**. It was not determined whether the reason for observed undesired diastereomer formation was coordination of boron with the δ-OPMB group, which could lead to a transition state favouring the *syn*-diol formation, or a competing external hydride delivery which would also lead to the *syn*-diol formation. The stereochemistry of the diol was determined by Ryschnovsky's acetonide method[30,163] (Figure 19) on compound **155** (Scheme 52).



Scheme 52: Reduction of ketone **148** using Evans-Saksena reagent.

Having obtained negative results from the more straightforward Evans-Saksena reduction, another well-known method for *anti*-reduction of β-hydroxy ketones – the Evans-Tischenko reduction was considered.[164] In the presence of an aldehyde, the hydroxy ketone forms a hemiacetal, which is bi-coordinated to the samarium metal. An intramolecular hydride delivery simultaneously reduces the keto group to an alcohol and oxidizes the hemiacetal to an ester. Indeed, treating hydroxy ketone **148** with SmI_2 in the presence of propanal led to formation of propionate **156** (Scheme 53). It has been reported that only catalytic amount of SmI_2 is required for the reaction[164] but in current case, using sub-stoichiometric amounts of SmI_2 only gave partial conversion. The SmI_2 solution was prepared freshly before use according to method by Kagan et al.[165] and not stored longer than four weeks in dark at room temperature. Interestingly, the reaction seemed to proceed faster when a 1-2-week-old solution was used as compared to the SmI_2 solution prepared on the same day. One possible reason for that observation could be that there was initially a partial over-oxidation of the Sm^{II} to Sm^{III} and the latter was reduced to the former by metallic samarium upon longer storage.[166]



Scheme 53: Reduction of hydroxyketone **148** using the Evans-Tischenko protocol.

The propionate group in alcohol **156** was hydrolyzed in aqueous methanol giving the diol **153**, which was then protected as acetonide with 2,2-dimethoxypropane (2,2-DMP) giving compound **157**. Forming the acetonide offered a convenient method to determine the relative stereochemistry of the 1,3-dihydroxy groups and therefore also the diastereoselectivity of the reduction reaction. Namely, Ryschnovsky et al.[30] determined that *syn*-diols exist predominantly in chair conformation whereas the *anti*-diols adopt the twist-boat conformation. That leads to significant difference in the chemical shift values of the carbons of the methyl groups of the acetonide in case of *syn*-diols (upper part of Figure 10, signals at 20.0 and 30.5 ppm), while the same signals have very similar values for the *anti*-diols (lower part of Figure 10, signals around 25 ppm). Thus, it was confirmed that the Evans-Saksena reduction had given the *syn*-product, whereas with Evans-Tischenko method the *anti*-product was obtained.

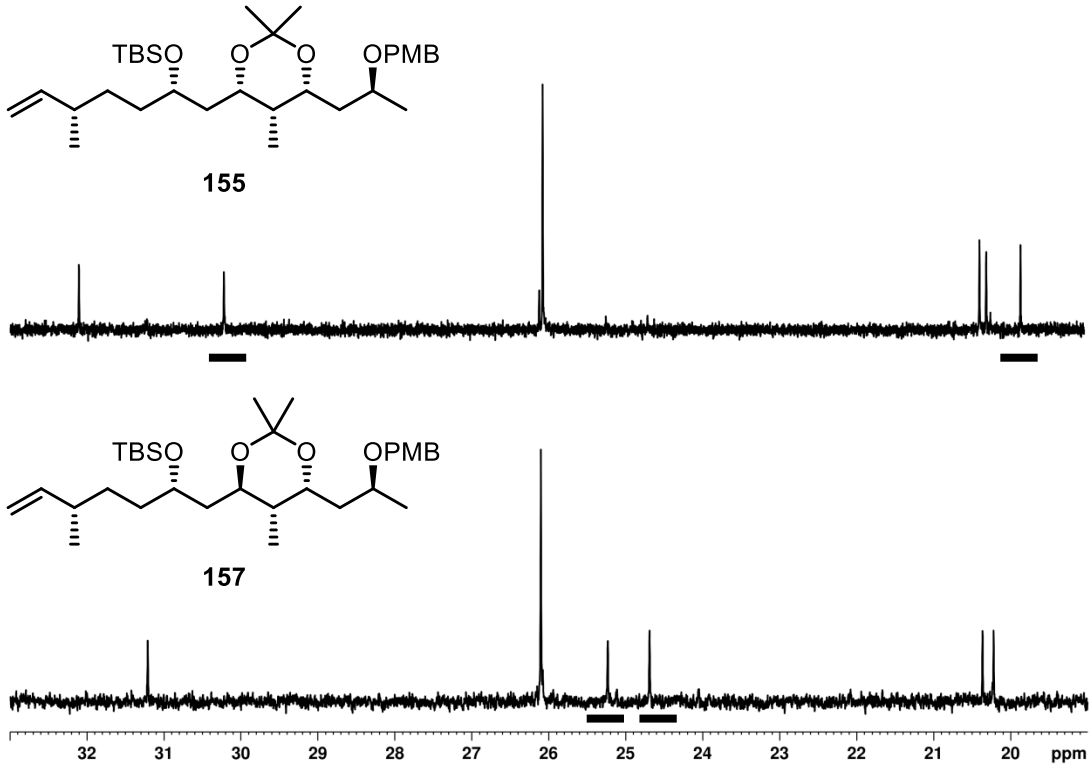
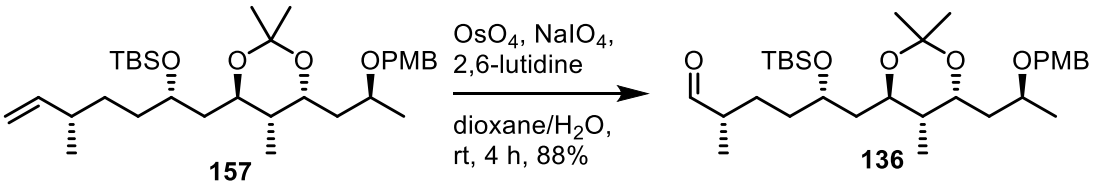


Figure 10: ^{13}C NMR data of acetal **157** prepared using the Evans-Saksena (upper) and Evans-Tischenko (lower) methods.

The two most common methods for oxidative cleavage of double bonds are ozonolysis and Johnson-Lemieux oxidation.[167] In case of compound **157**, ozonolysis led to a complex mixture without one main product. That may have been caused by co-oxidation of the aromatic ring of the oxidation sensitive 4-methoxybenzyl group. Dihydroxylation with OsO_4 in the presence of 2,6-lutidine, on the other hand, proceeded smoothly leading to the terminal glycol, which was cleaved in situ with sodium periodate giving the desired aldehyde **136** (Scheme 54).[168] The aldehyde **136** was initially used in following reactions but at one point in time, it was realized that a mixture of isomers had formed and preceding intermediates were reanalyzed. When examining the proton spectra signals belonging to the methyl group in α-position to the aldehyde (Figure 11), it was realized that epimerization had probably taken place under oxidative cleavage conditions and instead of sodium periodate, (diacetoxyiodo)benzene should be used.



Scheme 54: Oxidative cleavage of the alkene **157** using $NaIO_4$.

Oxidation of the double bond of the alkene **157** took place in the presence of OsO_4, with *N*-morpholine oxide (NMO) as a stoichiometric oxidant and (diacetoxyiodo)benzene (PIDA) was used for glycol cleavage in the mixture of acetone and water.[169] That provided aldehyde **136** in good yields and high purity (Scheme 55).

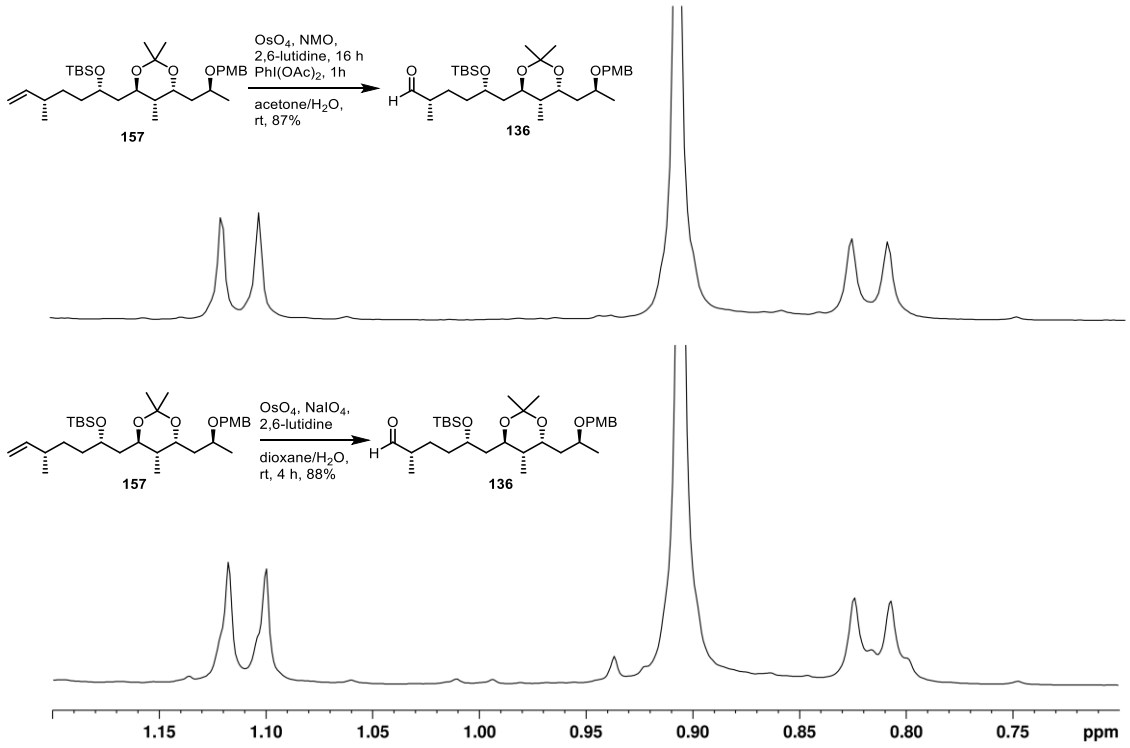
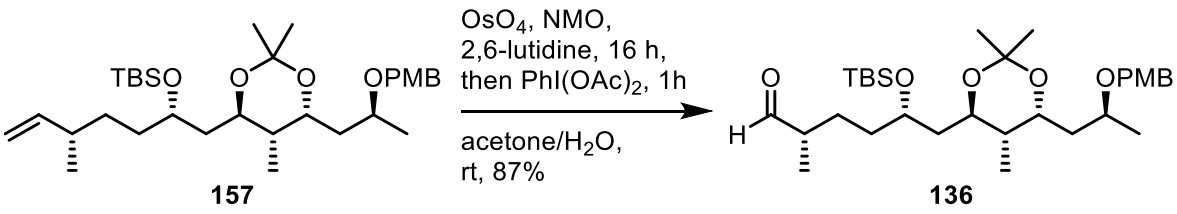
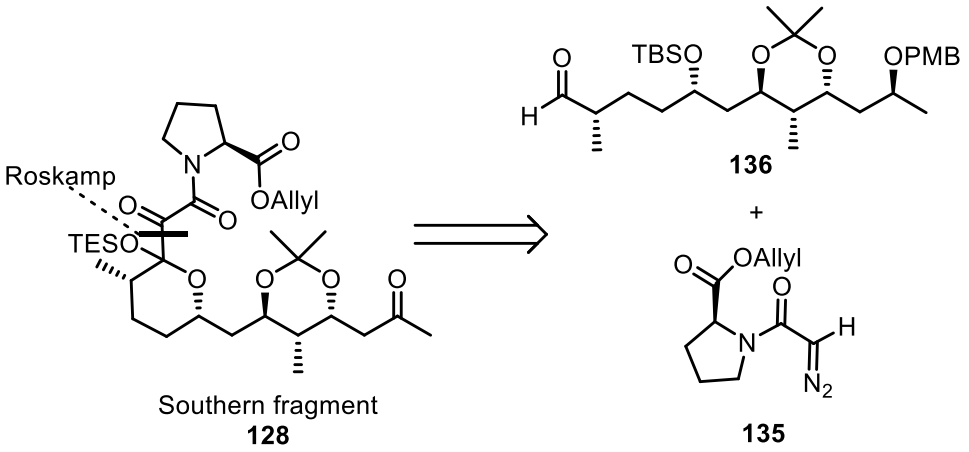


Figure 11: ^{1}H NMR of the aliphatic region of aldehyde **136** prepared using $NaIO_4$ (lower) and $PhI(OAc)_2$ (upper) for glycol cleavage.



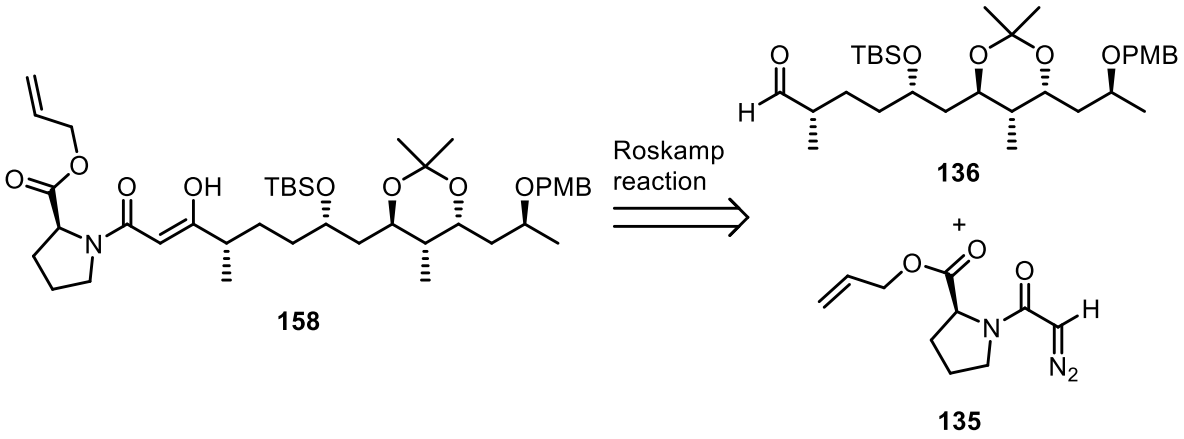
Scheme 55: Oxidative cleavage of the alkene **157** using $PhI(OAc)_2$.

Looking back at the retrosynthesis of the southern fragment **128** (Scheme 56), one can see that there are only two carbons and the amino acid moiety **135** missing from aldehyde **136**. One option to install the final fragment would be an aldol reaction with N-acylated amino acid. The downside of that method is that under basic conditions, the α-chiral carbonyl compounds may epimerize and that has also been reported as one of the problems in previous syntheses of similar compounds.[7,61] Therefore, a Roskamp reaction was chosen as a mild method to install the amino acid fragment. A Roskamp reaction[78] between aldehydes and ethyl diazoacetate has found extensive use in natural product synthesis[84,86,170] for two-carbon chain elongation forming β-keto esters. On the other hand, no previous precedence for using α-diazo amides instead of ethyl diazoacetate in natural product synthesis could be found. Thus, it was interesting to explore if this mild method could be extended to α-diazo amides.



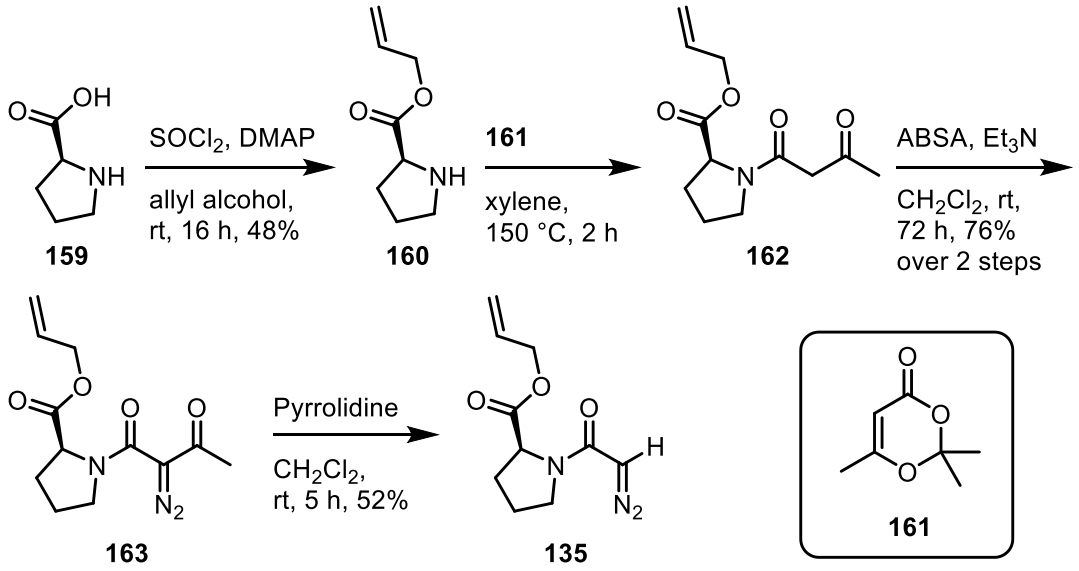
Scheme 56: Retrosynthesis of the southern fragment **128**.

In addition to the aldehyde **136**, the Roskamp reaction required a previously unknown α-diazo amide **135** (Scheme 57). There are a number of methods used for preparing α-diazo carbonyl compounds.[170–172] One of the milder and therefore more often used methods is the Regitz diazotransfer,[173] where a 1,3-dicarbonyl compounds reacts with an organic azide giving a 2-diazo-1,3-dicarbonyl intermediate. The extra acyl group is usually easily removed with basic workup.



Scheme 57: Retrosynthesis of the β-keto amide **158**.

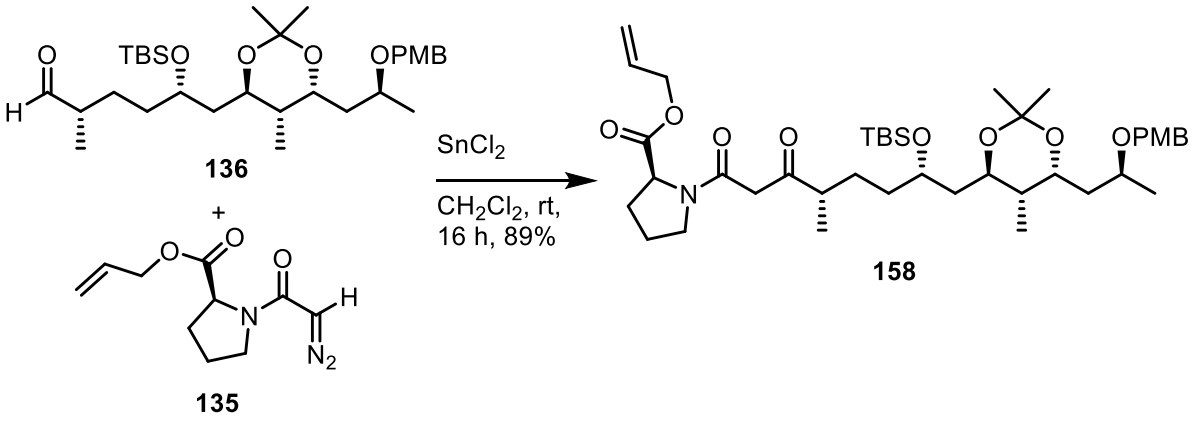
The O-allylation of (*S*)-proline (**159**) was performed according to a known procedure[174] over the acylchloride with $SOCl_2$ and 4-*N*,*N*-dimethylaminopyridine (DMAP) giving the product **160**. Due to allyl ester **160** polymerizing easily, it should be stored at −25 °C and used shortly after preparation. To form the β-keto amide, the secondary amine **160** was treated with dioxinone **161**. At elevated temperature, the latter goes through a retro Diels-Alder reaction forming a ketene intermediate, which rapidly reacts with the amino group giving desired product **162**. The crude β-keto amide **162** was directly dissolved in dichloromethane and treated with 4-azetamidobenzenesulfonyl azide (ABSA) giving diazo compound **163** through the Regitz diazotransfer reaction.[175] In case of similar intermediates having an ester group at one end, the deacylation takes easily place upon extracting with weakly alkaline solution.[176] Unfortunately, treating compound **163** with any aqueous base led to rapid decomposition and it was not possible to obtain desired product. Treatment with different non-aqueous bases (diethylamine, piperidine, BnOLi, methanolic K_2CO_3) gave variable results leading to either small amount of desired product or to direct decomposition. Freshly distilled pyrrolidine was the only base discovered that led to acceptable yields of desired α-diazo amide **135**. Shorter reaction times (4-6 h) gave a partial deacylation with significant amount of unreacted starting material; longer reaction times (14-20 h) led to full conversion but also gave significant amount of decomposition and overall separated yields of the product **135** were not better than for the shorter reaction times (Scheme 58).



Scheme 58: Synthesis of the diazoamide **135**.

With both coupling partners in hand, the stage was set to study the Roskamp reaction. The initial experiments on the Roskamp reaction (Scheme 59) were always deemed unsuccessful. Further investigation using aldehyde **136** and ethyl diazoacetate, or diazo compound **135** with a simpler aldehyde indicated that both starting materials are compatible with the reaction conditions. Deeper look into the reaction revealed that analysis by the standard methods is complicated for this particular reaction. The product **158** exists as a mixture of the keto and enol form and does not react well with standard laboratory stains, therefore giving rise to very light streaking spot on a TLC which can practically not be observed in diluted solutions.

Initially the yields for the reaction were in the range of 30-40%, therefore a variety of different Lewis acids ($BF_3{\cdot}Et_2O$, $NbCl_5$, $Sc(OTf)_3$, $ZrCl_4$, $Ti(O\mathit{i}Pr)_4$ were tested but non gave superior results to $SnCl_2$. It was discovered that the yield of the reaction is highly dependent on how freshly the aldehyde and the diazo compound were prepared. Using substrates that were less than 24 h old, the yields were increased to the range of 80-90% but decreased rapidly to 30-50% when reactants were stored for 2-3 days. In literature, it is mentioned that the role of $SnCl_2$ in the Roskamp reaction is purely Lewis acidic and nitrogen evolution should begin after addition of an aldehyde. In our case, we observed gas evolution directly after adding the diazoamide to the $SnCl_2$, seems to indicate that there is either an initial reaction between those two reagents or a side-reaction taking place. On the other hand, as the reaction outcome was not adversely affected by those observations then that topic was not further pursued.



Scheme 59: Roskamp reaction between diazoamide **135** and aldehyde **136**.

Another complication arose when analyzing the formed Roskamp product **158** – the NMR spectrum for the compound is highly complex (Figure 12). The compound exists as a mixture of keto and enol form, as well as gives rise to two distinct rotamers around the amide bond. Therefore, it was difficult to determine whether observed signals were caused by conformational or configurational changes in the molecule. For example, the signals around 14.4 ppm belong to the OH proton of the enol and if the product **158** exists as two rotamers, we would expect to see two distinct signals. In the proton spectrum for the product, two distinct signals appear at 14.27 and 14.48 ppm. A closer look on those signal reveals that there are also smaller overlapping signals under both of them, which could belong either to diastereomers or some other conformers of the compound. Variable temperature measurements revealed coalescence of signals at 14.27 and 14.48 ppm but we were not able to determine if the smaller signals at 14.29 and 14.46 are coalescing as well or not. An alternative method for determining whether the signals arise from configurational or conformational changes is to perform a chemical-exchange experiment – if the protons behave spectroscopically as if they are under chemical exchange, the signals do not belong to diastereomers.[177] One method to conduct a 1D-selective chemical-exchange NMR experiment is to use a gradient 1D NOE pulse sequence, if the targeted signal at the site of irradiation corresponds to a proton under significant chemical exchange with another proton on the saturation time scale, the signals corresponding to the second proton will also appear diminished due to a saturation transfer, resulting in a second negative signal in the difference spectrum. Irradiating the signal at 14.27 ppm led to negative signal at 14.48 ppm, which confirms the variable temperature measurement results that these signals belong to amide bond rotamers (Figure 12, upper zoom in). At the same time, irradiating the signal at 14.48 ppm led to negative of signals at 14.27 and 14.46 ppm (Figure 12, lower zoom in), which

indicates that both signals arise from proton under chemical exchange and therefore also the small signal at 14.46 ppm does not belong to a diastereomer.

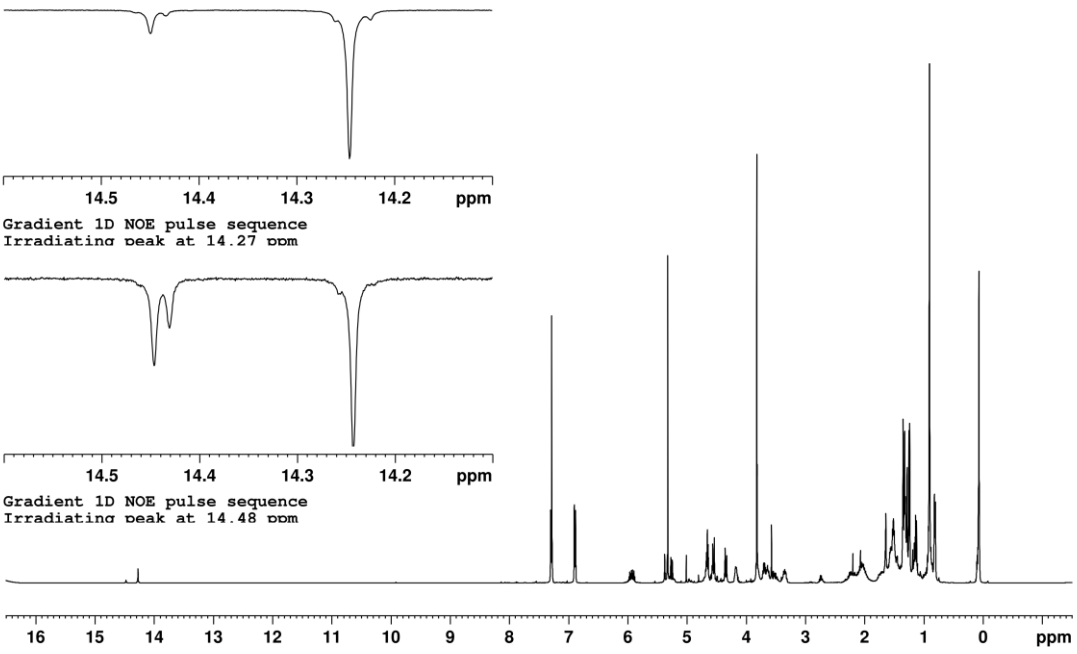
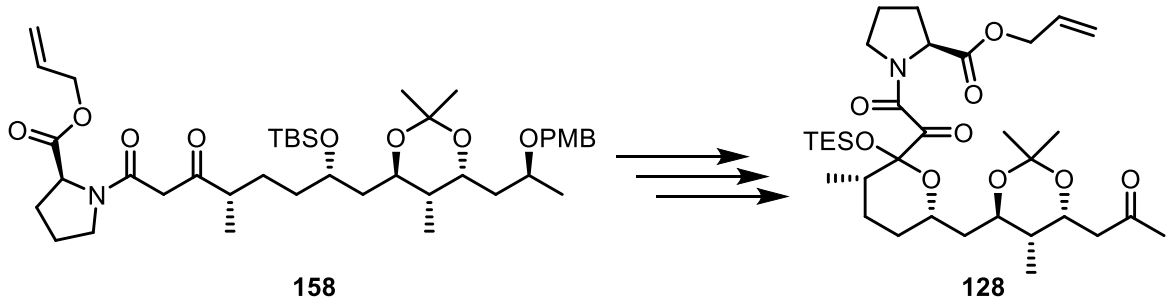


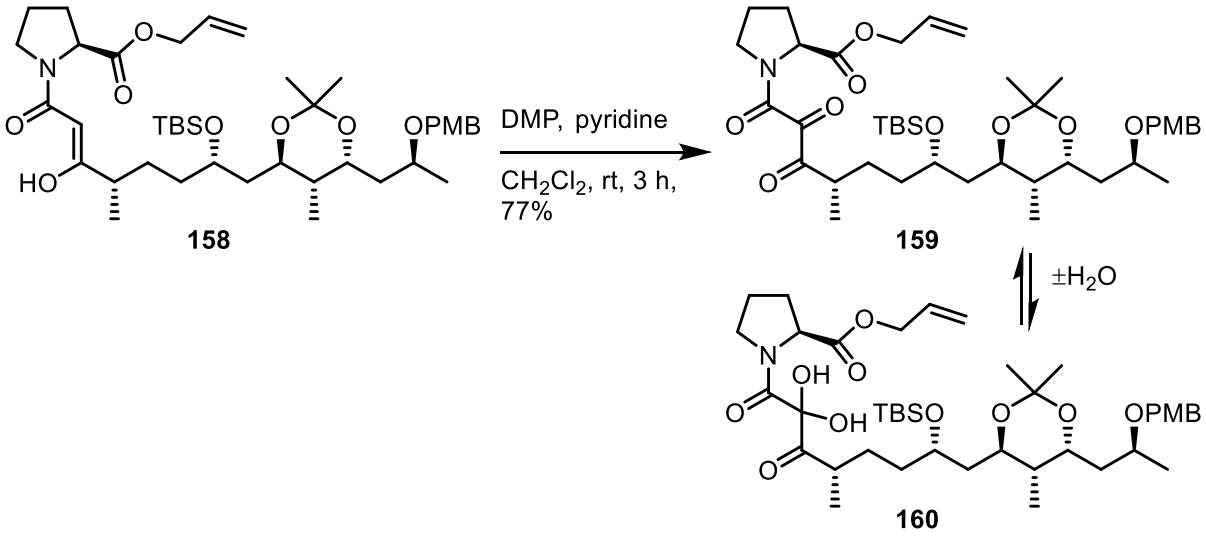
Figure 12: Chemical-exchange experiment for the signals at 14.27 and 14.46 ppm for Roskamp product **158**.

The compound **158** contained the full carbon skeleton for the southern fragment **128** (Scheme 60). What was still remaining, were the oxidation of the α-methylene group to form the 1,2,3-tricarbonyl motif, lactol formation and protection, PMB-deprotection and oxidation to the methyl ketone. The 1,2,3-tricarbonyl motif was extensively studied during the synthesis of rapamycin and FK506.[127–129,131,132,178] Under neutral conditions, the group is relatively stable but rapidly decomposes under acidic or basic conditions. The easiest method for preparation would probably be oxidation of β-hydroxy or β-keto carbonyl compounds with Dess-Martin periodinane.[128] The lactol formation has previously been performed when macrocycle is already closed and then it adopts the natural configuration as was in the case of FK506 and rapamycin syntheses.[8,10–14,135] In this case, the lactol formation would probably led to a mixture of diastereomers but it was believed that once the macrocycle would be installed, the lactol would equilibrate to the thermodynamically more stable natural isomer.



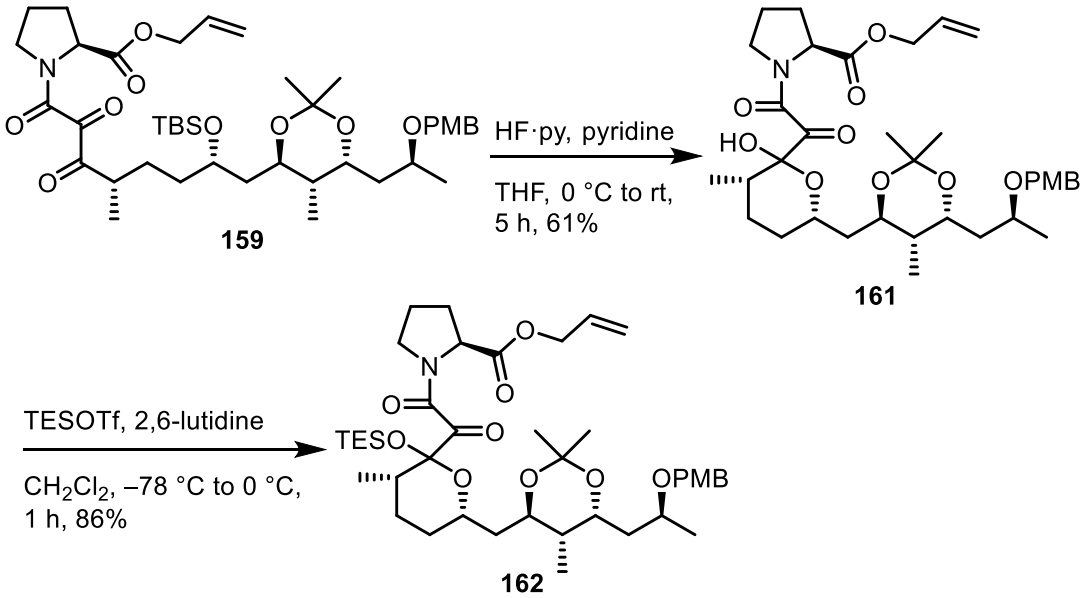
Scheme 60: Preparation of the southern fragment **128** from β-keto amide **158**.

The initial oxidation reactions of compound **158** to **159** with the DMP were unsuccessful. While testing the quality of the DMP, it was discovered that even though oxidation of simple alcohols took readily place, oxidation of α-methylene group on simpler β-keto esters and amides did not proceed. More thorough search through the literature revealed that more complicated oxidations with DMP can be capricious and strongly influenced by minor details as well as highly dependent on the quality of DMP.[179] Treatment of **158** with freshly prepared DMP in the presence of dry pyridine led to formation of the desired tricarbonyl compound **159** which could be easily confirmed by bright yellow color of the reaction mixture. Disappearance of the signals around 14.4 ppm in the proton spectrum confirmed that the α-methylene group was successfully oxidized. On the other hand, the spectrum remained highly complex as the tricarbonyl compound **159** forms very easily hydrate **160** and still contains the amide bond giving rise to rotamers. It is interesting to note that the solved crystal structure of FK506[180] showed that carbonyl groups adopt a dihedral angle of 95°, which could in turn signify another set of low energy conformers, which may have long interconversion on NMR timescale and therefore give another set of signals. On the other hand, compared to the Roskamp product **158**, the analysis by TLC was conveniently simple and enabled facile and rapid reaction monitoring (Scheme 61).



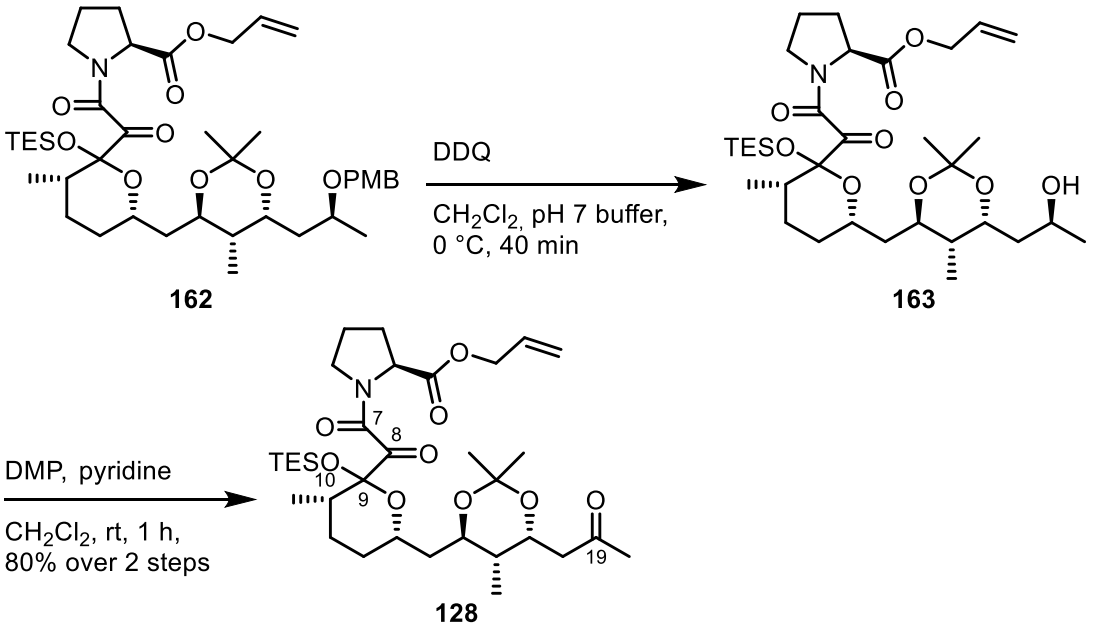
Scheme 61: Oxidation of the β-keto amide **158** to the tricarbonyl compound **159** and its hydrate **160**.

The tricarbonyl compounds are not exceedingly stable, therefore the next planned step was the lactol formation by deprotection of the TBS-group. Then, the formed lactol should be directly trapped with another protecting group to stabilize the tricarbonyl motif towards future reaction conditions. It was anticipated that a set of epimers would form which differ in the configuration of the hemiacetal centre and therefore complicate the analysis of future intermediates. What was not anticipated, was that the compounds **161** and **162** are insensitive towards most staining agents and do not absorb light in the UV-Vis region therefore complicating the reaction monitoring by TLC or HPLC and all the reaction monitoring had to be done by NMR. Treatment of TBS-ether **159** with TBAF, HF·Et_3N or aqueous HF led to either no reaction or to direct decomposition. The desired lactol **161** was only obtained using a freshly opened bottle of HF·pyridine complex. The formed lactol **161** was unstable, decomposed on overnight storage and was therefore directly protected with TESOTf giving the protected lactol **162** in 52% yield over two steps (Scheme 62).



Scheme 62: Synthesis of lactol **162**.

Treatment of protected lactol **162** with DDQ liberated the secondary alcohol giving **163**, which was then directly oxidized to the ketone **128** (Scheme 63). While all those reactions can be confirmed by NMR, the spectra remained too complex for signal assignment. The last reaction gave two spots on TLC, which were inseparable by column chromatography. Purification by HPLC revealed four different peaks on the chromatogram; two of which belonged to the two epimers at the acetalic *C9*, one which looked very similar to desired compound **128** (it could belong to the corresponding seven-membered lactol, which is known to exist in equilibrium with the six-membered lactol in the natural products)[141] and one which we were not able to identify.



Scheme 63: Synthesis of southern fragment **128**.

Analysis of the NMR spectrum of southern fragment **128** confirmed the existence of α-keto amide group and that no benzilic acid rearrangement had taken place under reaction conditions. Previous literature suggests that the α-keto group carbon *C29* should come at 192-198 ppm for pipecolic acid natural products whereas for the benzilic acid rearranged product the value would be in the range of 167-173 ppm.[125] The compound **128** has signals at 209.7 and 201.2 ppm, which would correspond to the keto groups at *C19* and *C8*, respectively. The analysis is further confirmed by the existence of two acetalic carbons at 102.0 and 101.5 ppm, belonging to acetonide protecting group and *C9*, respectively. The formation of the seven-membered lactol was ruled out based on the chemical shift value of the proton at *C10* – it had a value of 2.16 ppm, while for rapamycin, it is reported that for six-membered lactols, the value would be 2.04 ppm, whereas for seven-membered lactol, it would significantly increase due to being next to a carbonyl group and would appear around 3.02 ppm.[141]

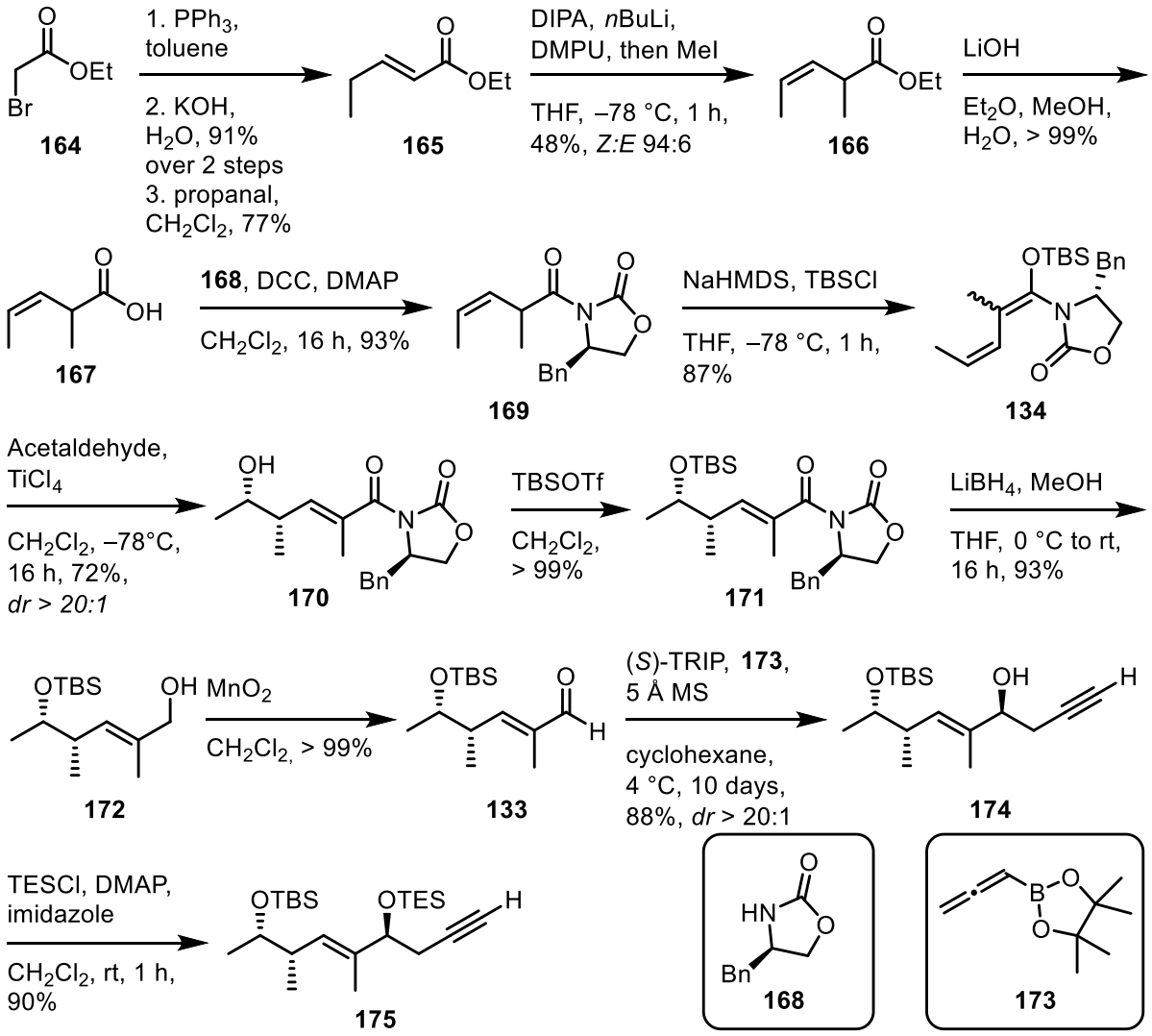
This concluded the synthesis of the southern fragment **128** of the 3-normeridamycin. The synthesis proceeded in the longest linear sequence 16 steps from (*S*)-citronellol (**140**) and in overall yield of 3.1%. The main features of the synthesis include two subsequent stereoselective boron enolate mediated aldol reactions on either side of the butanone and a Roskamp reaction for attaching the acetylated (*S*)-proline fragment. It was realized, that even though installing the amino acid fragment, forming the tricarbonyl moiety and the

6-membered lactol is possible for this substrate, they cause difficulties in analysis, reaction monitoring and stability, and should probably be installed later in the synthesis.

2.3 Towards the Synthesis of the Northern Fragment 127

Large part of the work on the northern fragment was done by Dominik Göppert, a fellow PhD student in our group. He established the synthesis until compound **175** and his procedures were adopted with minimal changes (Scheme 64).

The synthesis of the northern fragment **127** started from ethyl bromoacetate **164**, which was transformed into a Wittig reagent and reacted with propanal giving pentenoate **165**. Deprotonation with LDA at the γ-position and methylation of corresponding enolate according to the procedure by Kende and Toder[181] giving the α-methylation and β,γ-*Z*-double bond. The reason for *Z*-selectivity in the methylation reaction is not clear, though allylic strain and aromaticity of crotyl anion species were proposed as plausible explanations. The ester **166** was hydrolyzed to acid **167** which was then coupled with Evans auxiliary **168** under standard peptide coupling conditions. The oxazolidinone **169** was deprotonated and trapped with TBSCl giving the *N*,*O*-ketene acetal **134**. The VMAR with acetaldehyde takes place through the γ-position and selectively installed two required stereocentres giving the oxazolidinone **170**.[144] Configuration of the α,β-double bond is inconsequential with regards to the outcome of the reaction, while the configuration of the γ,δ-double bond controls the diastereoselectivity. The reactions generally proceeded with good stereoselectivity but the yields seemed to be highly dependent on the quality of $TiCl_4$, acetaldehyde and the *N*,*O*-ketene acetal **134**. The following TBS-protection took place in quantitative yield giving **171**, which was then reduced with $LiBH_4$ to the allylic alcohol **172**. The allylic alcohol **172** was oxidized to the corresponding aldehyde **133** with MnO_2. After extensive screening, Dominik Göppert determined the procedure by Houk et al.[182] using the boronic ester **173** as a nucleophile and chiral (*S*)-TRIP phosphoric acid for chiral induction to be optimal for obtaining the alcohol **174** in good yields and selectivities. The free alcohol was protected using TESCl giving the terminal alkyne **175** in good yields.

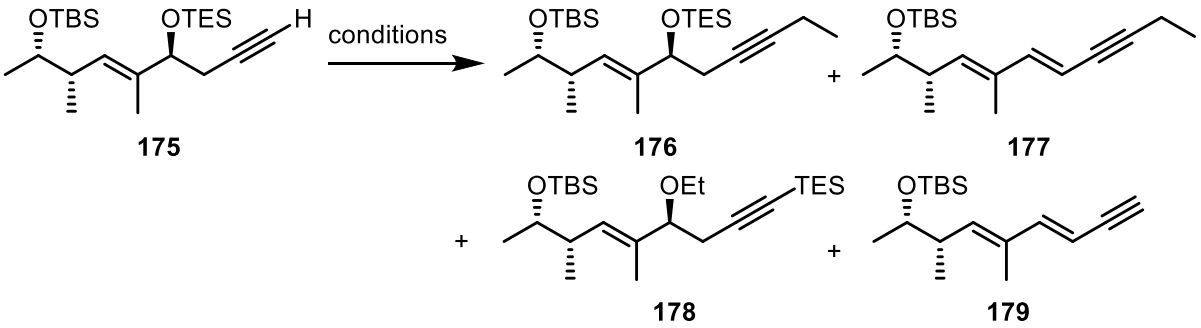


Scheme 64: Synthesis of terminal alkyne **175**, developed by Dominik Göppert.

The first step needing a more thorough investigation was an alkylation of the terminal alkyne **175**. Preliminary tests had shown that the reaction proceeds with moderate conversion giving a number of inseparable side products. After analyzing the reaction mixtures, compounds **176-179** were identified as the main components, though several additional side-products could be observed (Scheme 65).

A selection of ethylation conditions is given in Table 2. It was realized that in the presence of polar additives like HMPA, the retro-Brook rearrangement took place, which led to product **178** (entry 3). Polar additives and increased reaction temperature also increased the amount of elimination leading to compounds **177** and **179** (entry 4). Without HMPA, the reaction was sluggish and only led to partial conversion with rest of the starting material staying intact (entry 5). Quenching the alkyne anion with deuterated water confirmed that the deprotonation

takes place rapidly even at low temperatures and the complications rise from the inefficient alkylation step (entries 1 and 2). Screening of different bases and electrophiles revealed that the lithium anion is the most reactive one and other electrophiles besides the iodide are not sufficiently active for reaction to take place (entries 6-12). Addition of TMEDA as an additive and running the reaction in diethyl ether did not lead elimination nor retro-Brook rearrangement but gave lower conversion than previous results (entry 13). In addition to simple alkylation, Sonogashira cross-coupling conditions were tried but they did not lead to isolation of the desired product (entry 14).



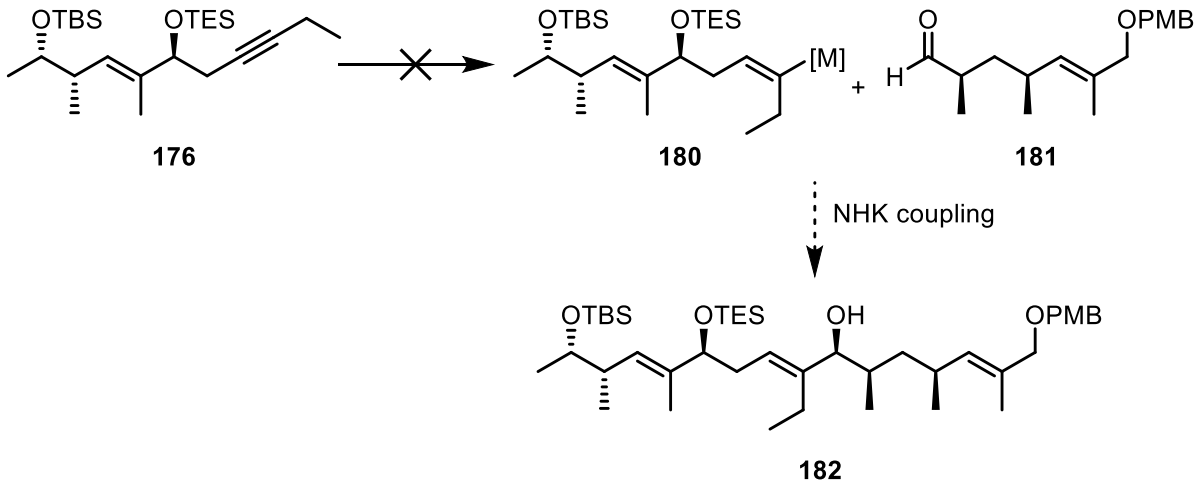
Scheme 65: Ethylation of terminal alkyne **175**.

Table 2: Ethylation of the terminal alkyne **175**

	Conditions	**Result**
1	*n*BuLi, THF -78 °C 1 h; D_2O, 0 °C, 5 min	90% deuterium incorporation
2	*n*BuLi, HMPA, THF -78 °C 1 h; D_2O, 0 °C, 5 min	partial deuterium incorporation, retro-Brook rearrangement
3	*n*BuLi, HMPA, THF -78 °C 1 h; EtI, 0 °C, 1 h	complex mixture
4	*n*BuLi, HMPA, THF -78 °C 1 h; EtI, -78 °C, 1 h	**175**:**176**:**178**:other 24:12:15:50
5	*n*BuLi, , THF -78 °C 1 h; EtI, -78 °C to 0 °C, 1 h	**175**:**176** 67:33
6	*n*BuLi, , THF -78 °C 1 h; EtBr, -78 °C to 0 °C, 1 h	no reaction
7	*n*BuLi, , THF -78 °C 1 h; EtOMs, -78 °C to 0 °C, 1 h	no reaction
8	*n*BuLi, , THF -78 °C 1 h; EtOTs, -78 °C to 0 °C, 1 h	no reaction
9	*n*BuLi, , THF -78 °C 1 h; EtOTf, -78 °C to 0 °C, 1 h	complex mixture
10	*n*BuLi, , Et_2O, -78 °C 1 h; EtI, -78 °C to 0 °C, 1 h	no reaction
11	EtMgBr, , THF -78 °C 1 h; EtI, -78 °C to 0 °C, 1 h	no reaction
12	KH, THF -78 °C 1 h; EtI, -78 °C to 0 °C, 1 h	no reaction
13	*n*BuLi, TMEDA, Et_2O, -78 °C 1 h; EtI, -78 °C to 0 °C, 1 h	**175**:**176** 75:25
14	PEPPSI-*i*Pr, CuI, Cs_2CO_3, EtI, DMF, DME,	no reaction

Ethyl iodide as the electrophile gave a clean conversion to the desired product **176** in 30-40% yield with rest of the starting material intact. Quenching the reaction with deuterated water showed that rest of the starting material had already been protonated during the reaction. That led us to hypotize that alkylidyne lithium species also acts as a base towards ethyl iodide, therefore giving back the starting material **175** and releasing ethene gas. Finally, adding three equivalents of base and electrophile in four portions over 4 hours led to 76% conversion to the desired product **176.**

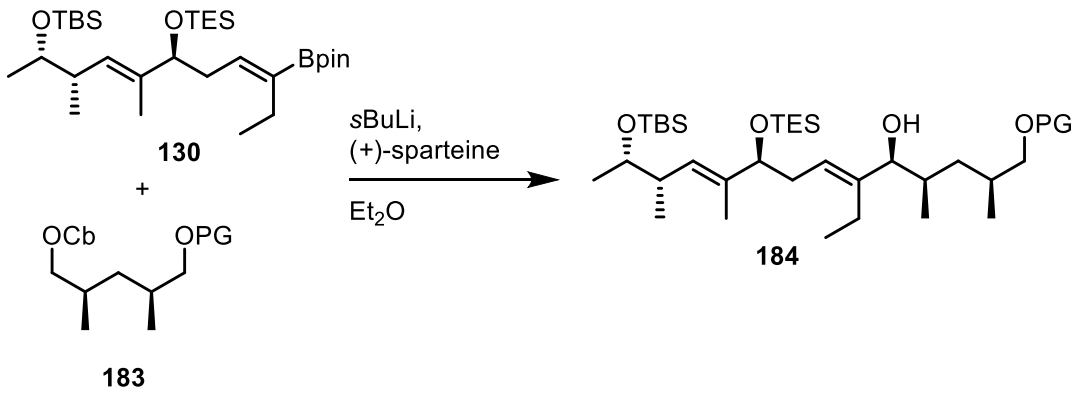
The initial plans involved a regioselective hydrometallation of the internal alkyne **176** with plans to follow the reaction with Nozaki-Hiyama-Kishi (NHK) coupling[183,184] with suitable aldehyde to build up the carbon skeleton of the northern fragment. Unfortunately, all tries to hydrometallate the alkyne **176** led to nearly equal mixture of regioisomers under both, hydrozirconation and hydrostannylation conditions, which indicates that as opposed to the methyl group, the ethyl group is too large to offer large enough steric differentiation between the sides of the internal alkyne (Scheme 66). At this stage, it was thought that it might be possible to use the homopropargylic hydroxy group to direct the hydrometallation or hydroboration to the desired distal position. While there is literature precedence that propargylic and homopropargylic alcohols can direct the hydrometallation to the proximal position[185,186] through coordination between the oxygen and metal atom, then selectively metallating the distal position is not known.



Scheme 66: Desired hydrometallation of alkyne **176**.

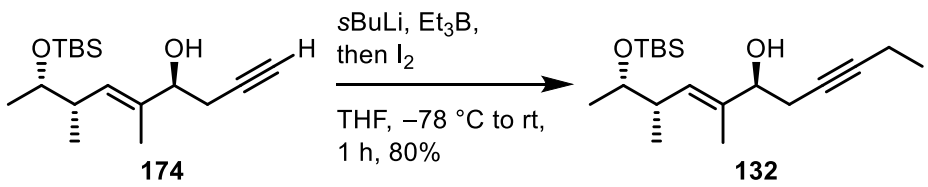
At the same time, recent publications by Aggarwal et al.[72] and Carretero et al.[119] reported a formal hydroboration using a similar system. They realized that directed borocupration reaction of the homopropargylic alcohols would lead to a vinylic boronic ester, where copper

is attached to the proximal position and boron to the distal position of the formed alkene. The copper atom could be easily removed during the work-up. The formal hydroboration could be then followed by protection of the free alcohol giving a vinylic boronic ester **130** suitable for lithiation-borylation methodology with coupling partner **183**. That offered an alternative retrosynthetic approach to fragment **127** through compound **184** involving the chemistry promoted by Aggarwal et al.[73,74] using Hoppe's chiral anions[64] followed by borylation and 1,2-metallate rearrangement (Scheme 67).



Scheme 67: Fragment coupling using the lihtiation-borylation methodology.

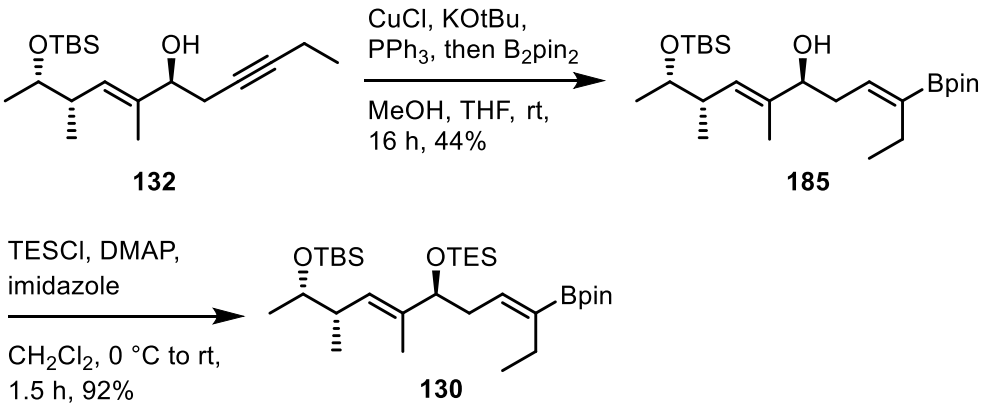
This new approach required an internal alkyne with a free hydroxy group **132**, which would have required deprotecting the recently installed TES group because all direct alkylation trials on compound **174** had been unsuccessful. Armed with the knowledge that deprotonation of the terminal alkyne proceeds rapidly but subsequent alkylation with alkyl halides is troublesome, it was decided to try running the reaction according to Zweifel olefination conditions.[187] Boron, having a free orbital, should be easily accessible for the alkylidyne-lithium species and addition of the free hydroxy group to the boron would inconsequential due to it being hydrolyzed during the work-up. This approach, indeed, gave the product **132** in clean manner and in good yield (Scheme 68).



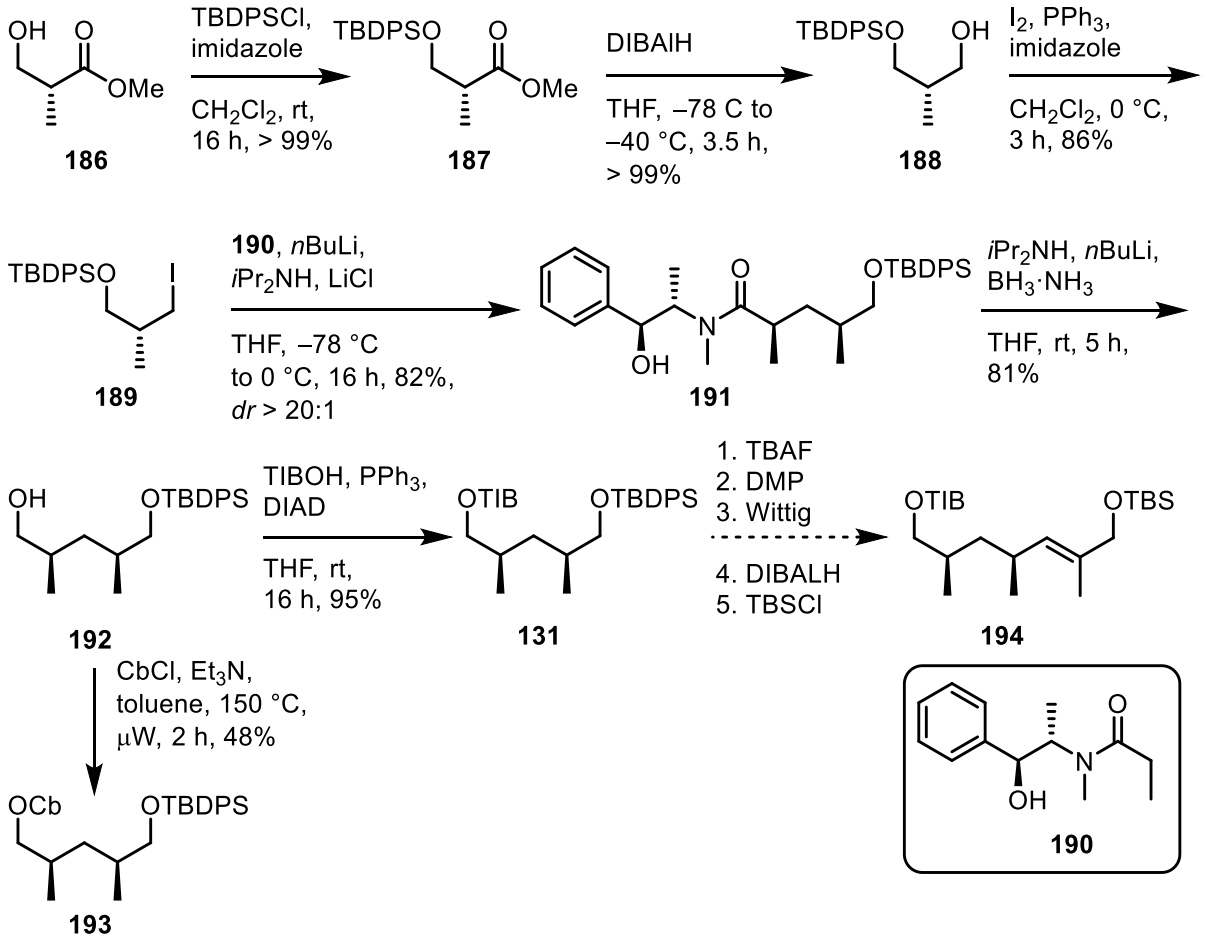
Scheme 68: Synthesis of internal alkyne **132** using Zweifel olefination.

Aforementioned directed borocupration reaction has previously been tested on rather simple substrates, therefore it was delightful to find that conversion of **132** to the boronic ester **185**

proceeded smoothly without major side-products, albeit in only partial conversion. Due to time constraints, this reaction was not further optimized. The protection of the free hydroxy group of **185** was successfully performed using standard conditions giving boronic ester **130** in good yields (Scheme 69). With that, the western part of the northern fragment **127** was successfully prepared and ready for coupling to the eastern part **183**.



Scheme 69: Synthesis of vinyl boronic ester **130** using formal directed hydroboration.



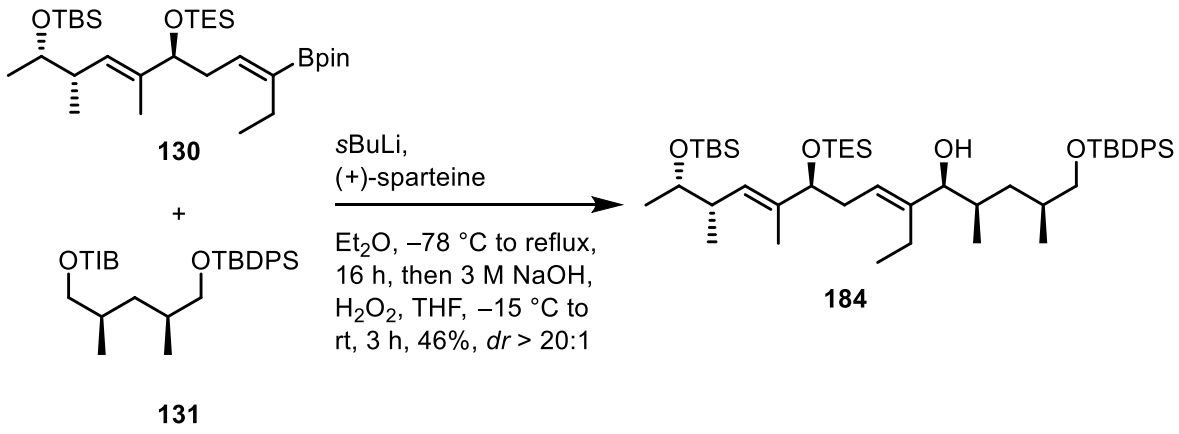
Scheme 70: Synthesis of Cb- and TIB-esters **190** and **131**.

The carbamate **193** has been previously used in lithiation-borylation strategy,[77] which is why this particular fragment and protecting group strategy was initially chosen for the eastern part of the northern fragment **127**. After some test coupling reactions, it was discovered that the TIB-ester analogue **131** is more suitable for coupling with vinylic boronic esters and was chosen as the directing group for chiral anion formation. Ideally, the TIB-ester **194** would be optimal for the coupling but it was suspected that the more acidic allylic position might compete for the deprotonation during Hoppe's chiral anion formation, which is why the shorter fragment **131** was chosen as the coupling partner and the coupling would have to be followed by subsequent carbon chain elongation by two additional units. In longer term, the TBDPS group should also be substituted with a TBS or some other more easily removable protecting group to avoid side-reaction during the deprotection step but that was not in the scope of this thesis.

The reaction sequence started with the Roche ester **186**, which was protected using TBDPS-group giving ester **187**, which was then reduced to alcohol **188**. The following Apple

reaction gave the iodide **189**, which was substituted according to procedure by Myers et al.[188] yielding the amide **191**. Reduction with borane-ammonia complex gave alcohol **192**, which was esterificated under Mitsunobu conditions giving TIB ester **131**. Alternatively, carbamate **193** was easily available when alcohol **192** was treated with *N*,*N*-diisopropylcarbamoyl chloride in a microwave reactor (Scheme 70).

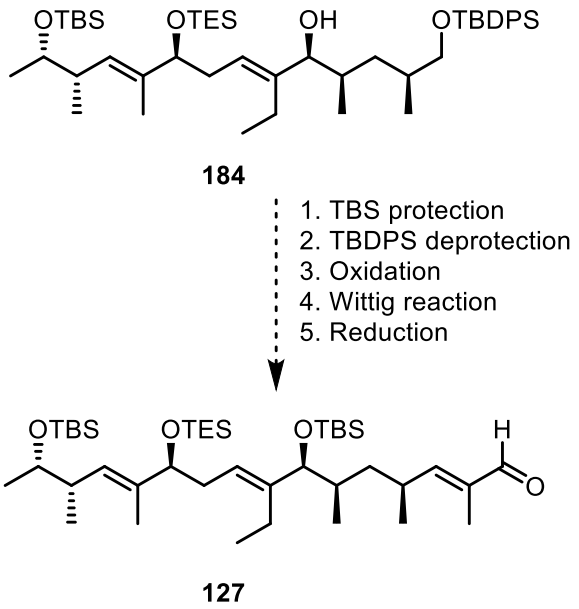
With boronic ester **130** and TIB ester **131** in hand, the fragment coupling by 1,2-metallate rearrangement was tested. Initial studies on compound **131** had shown that chiral anion formation takes place without issues, but literature mentioned that the 1,2-metallate rearrangement may be difficult with vinylic boronic esters. Therefore, it was gratifying to find that the desired product **184** was obtained (Scheme 71), though in modest yields. At this stage, continuation of this work in the context of current thesis was discontinued due to time constraints and the project will be continued by co-workers.



Scheme 71: Lithiation-borylation method for preparation of alcohol **184**.

Overall, the synthetic sequence for the preparation of the northern fragment **127** was extended by four steps including the coupling of the northeastern fragment **131** and the northwestern fragment **130**, therefore only missing two carbons from the complete carbon skeleton of fragment **127**.

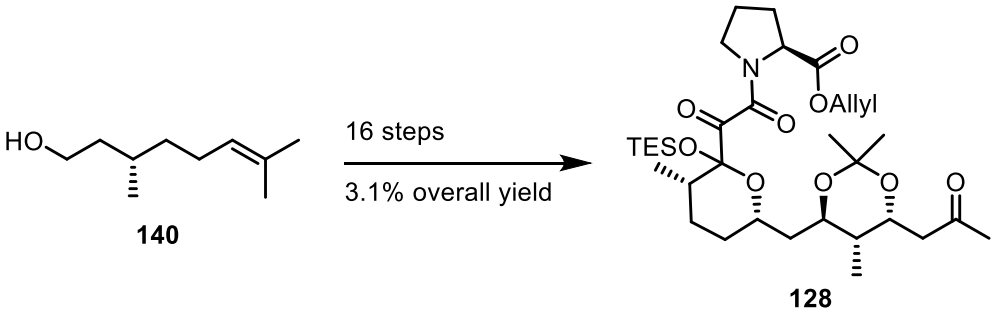
To finish the synthesis of the northern fragment **127**, the alcohol **184** has to be protected and the TBDPS protecting group removed. The primary alcohol has to be oxidized to the aldehyde, which would then be reacted with a stabilized Wittig reagent installing the last two carbon atoms and giving the *E*-configured double bond. The ester would then be reduced to the aldehyde, which would give the desired northern fragment **127** (Scheme 72) ready to be coupled with the southern fragment **128**.



Scheme 72: Finishing the synthesis of the northern fragment **127**.

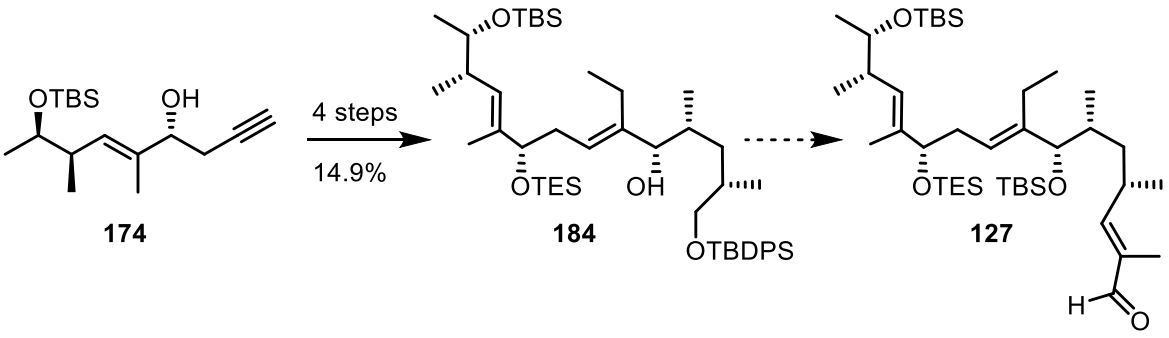
3 Summary and Outlook

The synthesis of the southern fragment **128** was established in the longest linear sequence 16 steps from (*S*)-citronellol **140** and in overall yield of 3.1% (Scheme 73). The main features of the synthesis include two subsequent stereoselective boron enolate mediated aldol reactions on either side of the butanone and a Roskamp reaction adding the acetylated L-proline fragment. It was realized, that even though installing the amino acid fragment, forming the tricarbonyl moiety and the six-membered lactol is possible for this substrate, they cause difficulties in analysis, reaction monitoring and stability, and should probably be installed later in the synthesis.



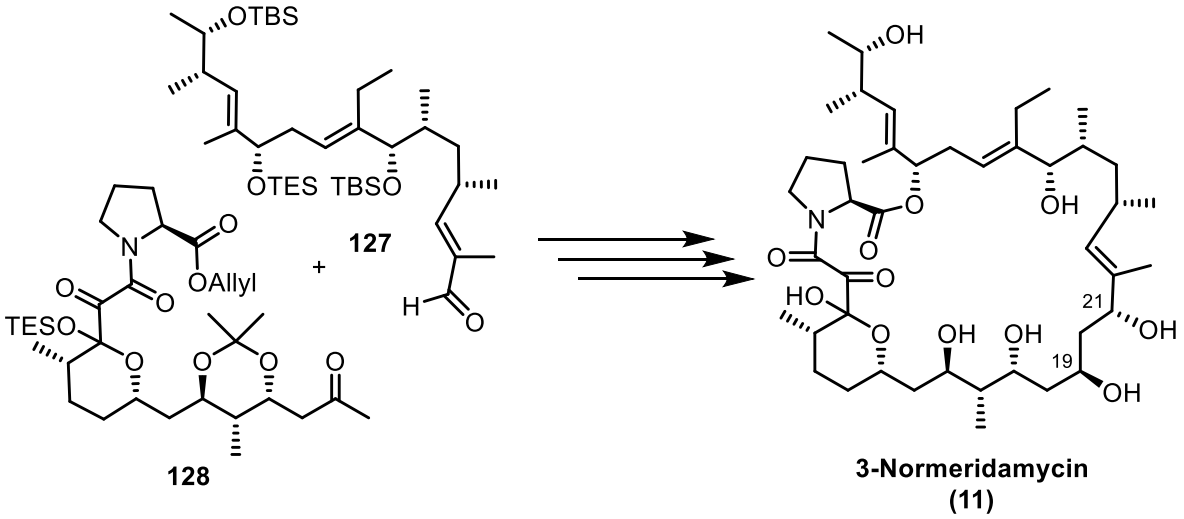
Scheme 73: Preparation of the southern fragment **128**.

The synthesis of the northern fragment **127** has been previously established by Dominik Göppert until compound **174**. In the course of this work, the sequence was extended until compound **184** by a combination of Zweifel olefination, directed borocupration and Aggarwal's lithiation-borylation strategy. To obtain the complete northern fragment **127**, the carbon skeleton should be extended by two more carbons through, for example, a Wittig olefination reaction (Scheme 74).



Scheme 74: Towards the northern fragment **127**.

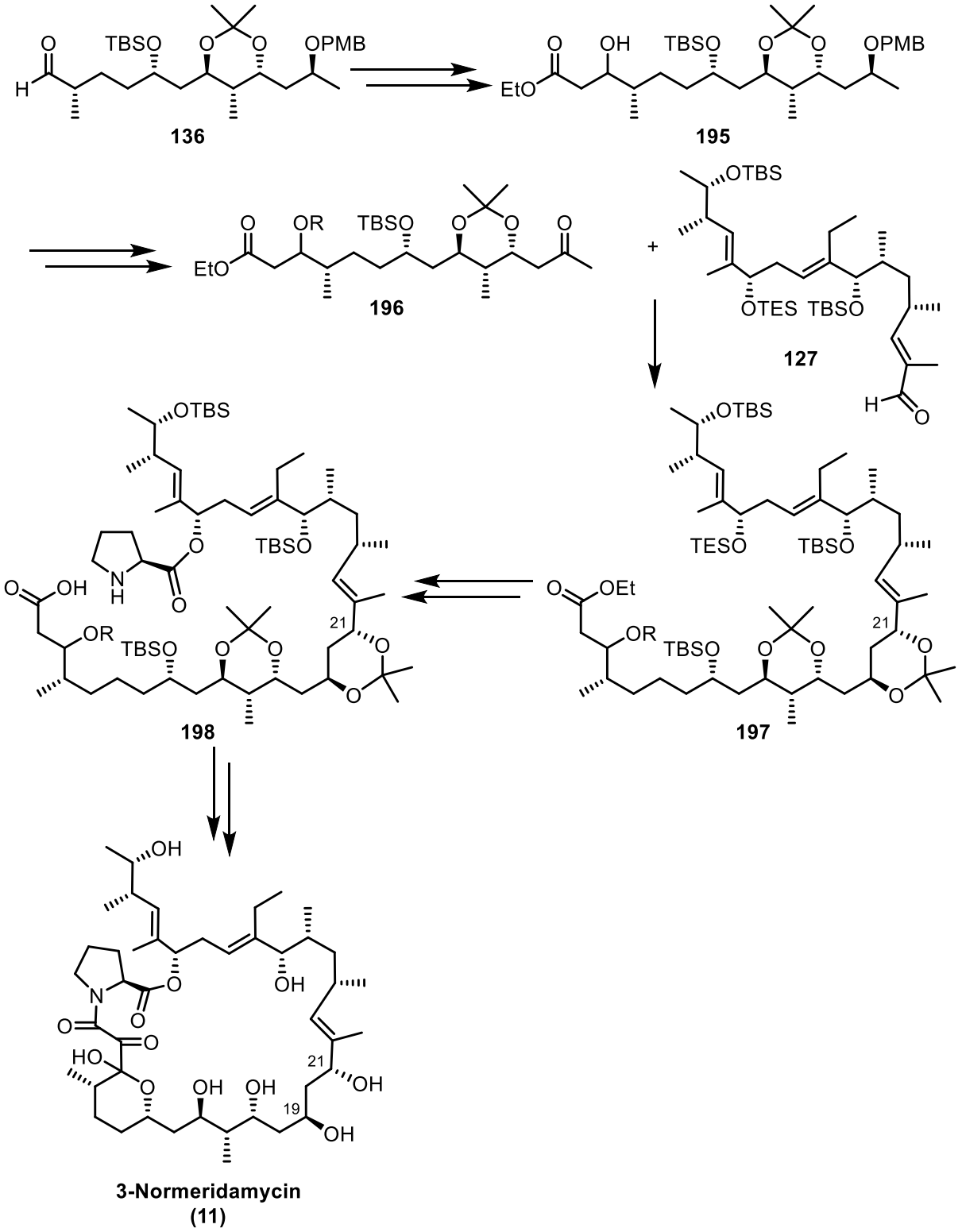
The reaction sequence could be continued in two different ways. The first option would be to continue working with the southern fragment **128** – coupling to the northern fragment **127** by a stereoselective boron enolate aldol reaction should be followed by *anti*-reduction of the hydroxy groups at carbons *C19* and *C21*, which would then be protected as an acetonide. The TES and allyl protecting groups should then be removed and the 27-membered ring should be closed by a macrolactonization reaction. Global deprotection would then give the 3-normeridamycin (**11**) (Scheme 75).



Scheme 75: Preparation of 3-normeridamycin (**11**) from fragments **127** and **128**.

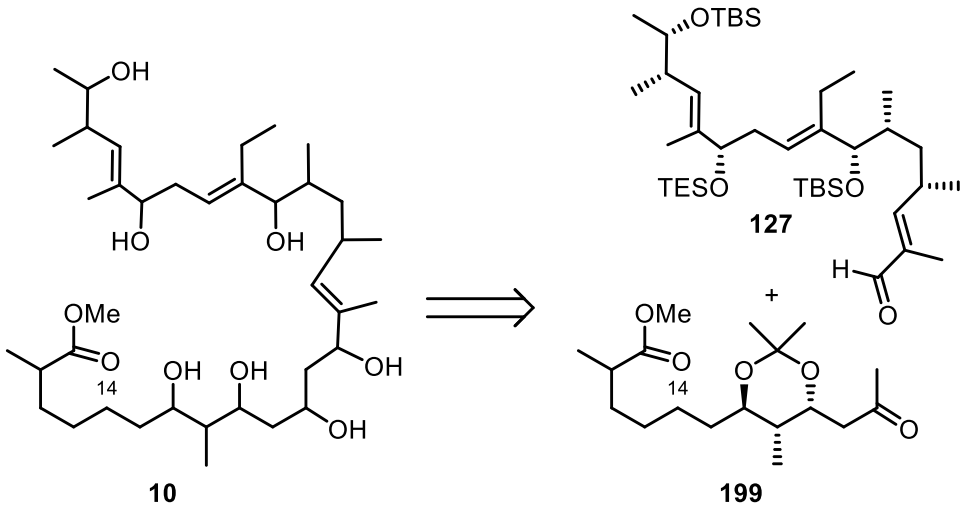
An alternative option would be to install the amino acid fragment and tricarbonyl moiety later in the synthesis. Then one could add an acetate group to aldehyde **136** either by performing and acetate aldol reaction or by using ethyldiazo acetate as a substrate in Roskamp reaction and then reducing the β-keto group to an alcohol **195**. The alcohol **195** must be protected orthogonally to the other protecting groups in the molecule (for example with o-nitrobenzyl group[189]) so it would be possible to remove it separately in the end to install the tricarbonyl motif. Then, fragment **196** could be connected to northern fragment **127** through stereoselective boron enolate aldol reaction. Once the fragments are coupled, an *anti*-reduction has to be performed at carbon *C19* using Evans-Saksena[159] or Evans Tischenko[164] methods and the diol then protected as an acetonide arriving at compound **197**. After removing the TES-group, the fragment could be coupled to N-protected L-proline and unmasking carboxylic acid and amine functionalities would lead to compound **198**. Macrolactamization would close the 27-membered macrocycle, then previously protected

alcohol at *C9* should be deprotected and treatment with Dess-Martin periodinane would install the tricarbonyl moiety. Global deprotection would then give the 3-normeridamycin (**11**) (Scheme 76).



Scheme 76: Alternative method for macrocycle formation through macrolactamization.

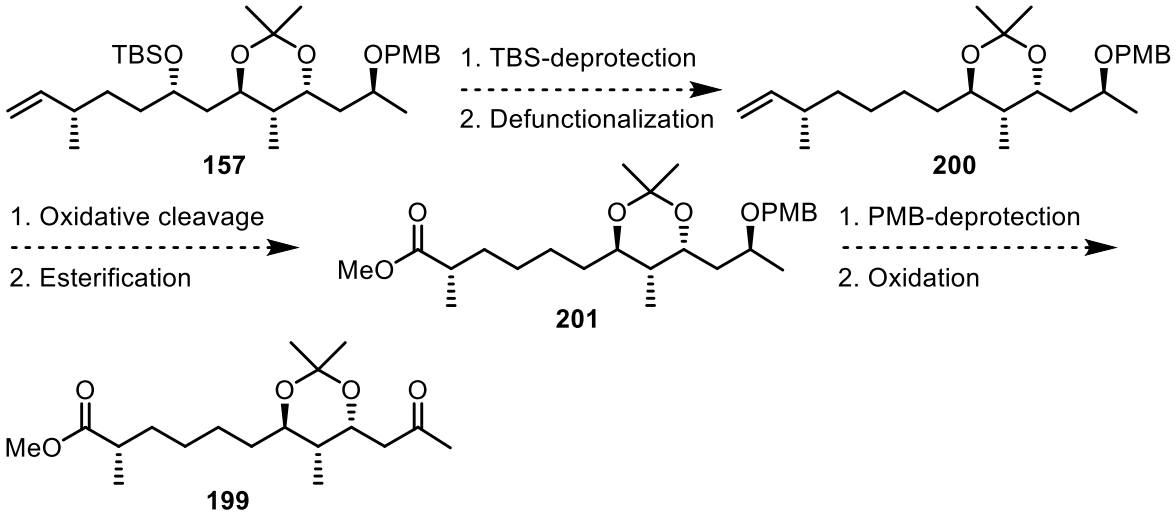
In the last stages of current work, a number of new natural products belonging to the meridamycin family were isolated.[19] One of them, meridamycin D (**10**), is a truncated analogue which is missing the FKBP12 binding region – the amino acid, tricarbonyl region and the 6-membered lactol – but retaining the PKS synthesized carbon skeleton, with an exception of a hydroxy group at *C14* (Scheme 77, meridamycin numbering). Biosynthetically, it is logical to assume the configuration of stereocenters in 3-normeridamycin (**11**) and meridamycin D (**10**) is identical. Therefore, this unique entry could be a valuable resource for ascertaining the validity of stereochemical assignment of meridamycins proposed through computational methods.



Scheme 77: Preparation of meridamycin D (**10**).

Meridamycin D (**10**) could be easily accessed through compounds **127** and **199** through aldol reaction, *anti*-reduction and global deprotection. Compound **127** is an unmodified northern fragment from the 3-normeridamycin (**11**) synthesis and could be directly used for meridamycin D (**10**). Compound **199** could be easily accessed from southern fragment intermediate **157**. The main task would be removing the functionality at *C14*. To do that, the TBS-protecting group should first be removed giving the free alcohol. There are a number of methods to defunctionalize alcohols – the most straightforward method would be to activate the alcohol with a Lewis acid and then treat it with a reducing agent[190]; most of the methods, though, go over an activated intermediate which is then reduced through a radical process (Barton-McCombie,[191] halide-Bu_3SnH[192] etc) or eliminated and the formed alkene then hydrogenated. Neither of the last two methods is well compatible with the terminal double bond in compound **200** and would probably require it to be first transformed into the methyl ester. Turning the terminal alkene into a methyl ester could be achieved by oxidative cleavage

of the double bond to an aldehyde[168], Pinnick oxidation[193] to the carboxylic acid and subsequent methylation. That would give the compound **201**, where PMB-deprotection and oxidation of the alcohol to the ketone would lead to fragment **199** (Scheme 78).



Scheme 78: Preparation of ketone **199** for the synthesis of meridamycin D (**10**).

4 Experimental Part

4.1 General Information

All reactions were carried out in dried glassware using standard Schlenk techniques. Glassware was dried by heating under *vacuo* and cooled to room temperature under a flow of argon. Reactions were performed in septum sealed flasks under positive pressure of argon, unless stated otherwise (*open flask*). Various temperature were obtained as follows: elevated temperatures – Heidolph MR HEI-TEC magnetic stirring plates, RT (room temperature, corresponds to 17-28 °C depending on the time of the year); 4 °C - SAMSUNG RL34LCMG refrigerator; 0 °C - ice-water bath; −18 °C - NaCl-ice bath; −28 °C - SAMSUNG RL34LCMG refrigerator; −78 °C - dry ice acetone bath, all other negative temperatures were obtained by using Julabo FT902 thermostat. All reagents were purchased from commercial sources and used without further purification, unless stated otherwise. Anhydrous THF was distilled from sodium-benzophenone, CH_2Cl_2 and all amine bases were distilled from CaH_2, other anhydrous solvents were purchased from Acros Organics over molecular sieves and under inert atmosphere.

The reactions were stirred magnetically unless otherwise stated and monitored using thin layer chromatography (TLC) by Merck® 60-F254 or Machery-Nagel GmbH & Co. ALUGRAM® Xtra SIL G/UV_{254} plates and visualized by ultraviolet light or by staining with aqueous potassium permanganate ($KMnO_4$), ceric ammonium nitrate (CAN), ceric ammonium molybdate (CAM), dinitrophenylhydrazine (DNPH), phosphomolybdic acid (PMA) or vanilline. Preparative flash chromatography was performed on Kieselgel 60 M (0.04 – 0.063 mm) under compressed air.

^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance III HD (400 MHz) using solvent residual signals as internal reference: $CDCl_3$ δ_H = 7.26 ppm, δ_C = 77.16 ppm; CD_3OD δ_H = 3.31 ppm, δ_C = 49.00 ppm. Chemical shifts (δ) are given as parts per million (ppm), coupling constants are reported in hertz (Hz) and multiplicity is indicated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal.

The high-resolution mass spectra (HRMS) were recorded on a Waters Micromass LCT Premier spectrometer using electrospray ionization.

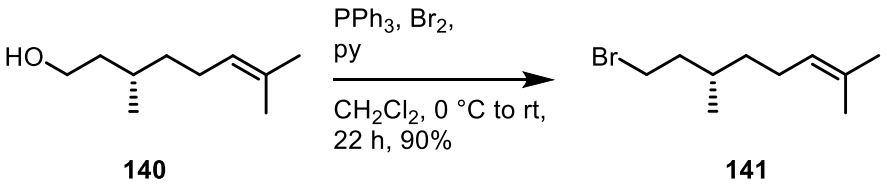
Gas chromatography (GC) was performed on Hewlett-Packard machine using OPTIMA – 5 – 0.25 μm, 30 m * 0.32mm column with following method: 50 °C hold 1 min, 25 °/min to 300 °C, 300 °C hold 9 min; FID detector.

Preparative high-performance liquid chromatography was performed on Agilent Prostar machine using Reprospher 100 C18-DE, 10 μm; 250 x 20 mm column and gradient elution with mixture of deionized water and MeCN.

Compound names were generated using ChemDraw®.

4.2 Experimental Procedures

(*S*)-Citronellylbromide (141):



PPh_3 (40.3 g, 154 mmol) was dissolved in 200 mL of CH_2Cl_2 and cooled on ice-water bath to internal temperature of 3 °C. Br_2 (7.25 mL, 141 mmol) was added dropwise keeping internal temperature under 8 °C. After 15 minutes, a mixture of (*S*)-citronellol (**140**) (20.0 g, 128 mmol) and pyridine (11.3 mL, 141 mmol) in 50 mL of CH_2Cl_2 was added over 30 minutes keeping the internal temperature below 8 °C. The reaction mixture was stirred at room temperature for 22 hours. Then, the reaction mixture was filtered, concentrated and filtered through plug of silica. Silica was washed 3 times with 50 mL of hexane. Solvents were removed under reduced pressure, which resulted in product (**141**) (25.1 g, 115 mmol) as a colorless transparent liquid in 90% yield.

GC purity: 99%, 6.87 min.

R_f: 0.86 (PE:EtOAc 9:1, $KMnO_4$).

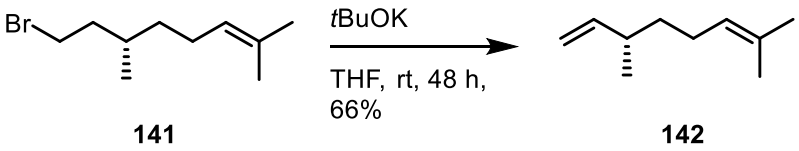
$[\alpha]_D^{20}$: +6.8 (1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.13 – 5.04 (m, 1H), 3.54 – 3.32 (m, 2H), 2.09 – 1.79 (m, 3H), 1.74 – 1.62 (m, 5H), 1.61 (s, 3H), 1.34 (m, 1H), 1.18 (m, 1H), 0.90 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 131.6, 124.5, 40.1, 36.7, 32.2, 31.5, 25.9, 25.5, 19.0, 17.8.

^{1}H NMR data and optical rotation matched literature values.[194]

(*S*)-Citronellene (142):



141 **142**

Citronellyl bromide **141** (20.2 g, 92.3 mmol) was dissolved in 120 mL of THF and *t*BuOK (15.5 g, 138 mmol) was added in one portion. Mixture was stirred at room temperature for 48 hours. To reaction mixture 350 mL of H_2O was added and it was extracted with 3 x 75 mL pentane. Organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Obtained crude product was purified by distillation at 80 °C, 40 mbar, which gave (*S*)-citronellene (**142**) (8.36 g, 60.5 mmol) as colorless transparent liquid in 66% yield.

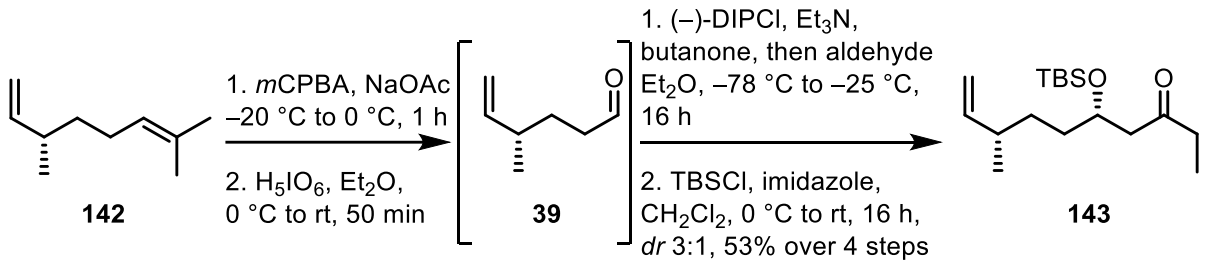
GC purity: 86-96%, 4.25 min.

$[\alpha]_D^{20}$: +9.0 (1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.66 – 5.74 (m, 1H), 5.08 – 5.12 (m, 1H), 4.90 – 4.98 (m, 2H), 2.09 – 2.16 (m, 1H), 1.93 – 1.99 (m, 2H), 1.68 (d, *J* =1.0 Hz, 3H), 1.60 (s, 3H), 1.28 – 1.34 (m, 2H), 0.98 (d, *J* = 6.8 Hz, 3H).

^{1}H NMR data and optical rotation matched literature values.[195]

(5*S*,8*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-8-methyldec-9-en-3-one (137):



A solution of (*S*)-citronellene (**142**) (6.57 g, 47 mmol) *[1]* and NaOAc (4.09 g, 50 mmol) in 120 mL CH_2Cl_2 was cooled to −15 to −20 °C on NaCl-ice bath. *m*CPBA (11.2 g, 50 mmol; ≤77 % stabilized with water) was added in small portions over 40 minutes. The reaction mixture was stirred at 0 °C for 1 hour. Then, the reaction was quenched with 40 mL sat. aq. $NaHCO_3$ solution at 0 °C and stirred until mixture became clear. Layers were separated and aqueous layer was extracted 3 x 50 mL CH_2Cl_2. Combined organic layers were washed with 80 mL of 1 M NaOH solution and dried over $MgSO_4$. The solvent was removed under reduced pressure and mixture was concentrated twice with 20 mL Et_2O. To thus obtained crude epoxide, 130 mL of Et_2O was added and cooled to 0 °C. H_5IO_6 (16.2 g, 71 mmol) was added at that temperature over 10 minutes. The reaction mixture was stirred 15 minutes at 0 °C, after which the ice-water bath was removed and stirring continued for additional 40 minutes *[2]*. The reaction mixture was filtered through a plug of celite®, washed with 100 mL sat. aq. $NaHCO_3$ and dried over $MgSO_4$. Volatiles were removed at 35 °C, 600 mbar. The crude aldehyde was immediately used in the following aldol reaction *[3]*.

(−)-DIPCl *[4]* (21.2 g, 66.1 mmol) in 240 mL dry Et_2O was cooled to −78 °C and freshly distilled Et_3N (11.3 mL, 80.8 mmol) was added. Butanone (4.3 mL, 48 mmol) in 15 mL of dry Et_2O was dried over CaH_2 *[5]* and added in 5 minutes to the reaction mixture. The mixture was stirred 1 hour at −78 °C and freshly prepared aldehyde (**39**) in 10 mL Et_2O was dried over CaH_2 and added dropwise to the reaction. The reaction mixture was stirred 1 hour at −78 °C and 15 hours at −25 °C. Then, the reaction mixture was warmed to 0 °C and 140 mL of 30% H_2O_2/MeOH/pH 7 buffer (3:3:1) was added over 10 minutes. It was stirred additional 10 minutes at 0 °C and 1.5 h without external cooling. Layers were separated and aqueous layer was extracted 3 x 50 mL Et_2O. Combined organic layers were washed with 100 mL sat. aq. $NaHCO_3$, 100 mL of brine and dried over Na_2SO_4. The product was purified by flash column chromatography (CH_2Cl_2:Et_2O 4:1) *[6]*.

6.06 g of the once-columned aldol reaction product was dissolved in 130 mL CH_2Cl_2 and imidazole (6.72 g, 99 mmol), followed by TBSCl (7.44 g, 49 mmol) were added. The reaction mixture was stirred 16 hours at room temperature, after which it was washed with 100 mL H_2O. Aqueous layer was extracted 4 x 20 mL CH_2Cl_2, combined organics were washed once more with 50 mL H_2O and dried over $MgSO_4$. Volatiles were removed under reduced pressure and crude product purified by flash column chromatography (PE:EtOAc 50:1 to 10:1). Ketone **137** (4.42 g, 15 mmol) was obtained as colorless oil in 53% yield from (*S*)-citronellene (**142**) and as 3:1 mixture with its diastereomer *[7]*.

GC purity: epoxide: 95%, 5.11 min; aldehyde: 86%, 3.42 min.

R_f: 0.92 (PE:EtOAc 3:1, $KMnO_4$); 0.40 (PE:EtOAc 20:1).

$[\alpha]_D^{20}$: +15.3 (1.0, $CHCl_3$), +47.2° (1.0, $CHCl_3$) for major diastereomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.61 – 5.70 (m, 1H), 4.89 – 4.97 (m, 2H), 4.12 – 4.18 (m, 1H), 2.56 – 2.62 (m, 1H), 2.37 – 2.47 (m, 2H), 2.03 – 2.10 (m, 2H), 1.37 – 1.47 (m, 2H), 1.25 – 1.33 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.85 (s, 9H), 0.05 (s, 3H), 0.00 (s, 3H). For major diastereomer.

^{13}C NMR (100 MHz, $CDCl_3$): δ 210.7, 144.6, 112.9, 69.4, 49.8, 38.0, 37.9, 35.4, 31.9, 26.0, 20.4, 18.1, 7.6, −4.4, −4.6. For major diastereomer.

HRMS (ESI): calcd for $C_{17}H_{34}O_2SiNa$ $[M+Na]^+$ 321.2226; found, 321.2221.

[1] GC purity between 86 - 93%.

[2] Longer reaction times led to decomposition of the aldehyde.

[3] Aldehyde is unstable towards storage and turns yellow upon contact with air. It decomposes at temperatures above 65 °C and evaporates at reduced pressures. Therefore, crude material was used in the aldol reaction.

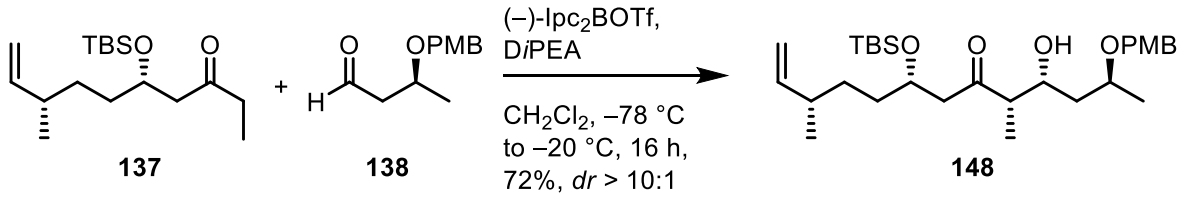
[4] Both, solution of (−)-DIPCl and solid worked well. The solid was stored in the glovebox freezer and had a longer shelf-life compared to the solution stored in a fridge.

[5] Drying with CaH_2 in this and following steps means that solution of reagent (ketone or aldehyde) was treated with a spatula tip of CaH_2 powder, it was left to stand for 10-20 minutes at room temperature under argon, then the solution was collected using syringe and directly added to the reaction.

[6] Separation of the aldol product from the isopinocamphol side-product was not possible. Therefore, the mixture of aldol product and isopinocamphol was used directly in the next step.

[7] Analytical sample of desired diastereomer was prepared using Nagao aldol approach.

(2*S*,4*R*,5*S*,8*S*,11*S*)-8-((*tert*-Butyldimethylsilyl)oxy)-4-hydroxy-2-((4-methoxybenzyl)oxy)-5,11-dimethyltridec-12-en-6-one (148):



Stock solution of (−)-Ipc$_2$BOTf was prepared by suspending (−)-Ipc$_2$BH *[1]* (7.3 g, 25.5 mmol) in 12 mL dry *n*-hexane, cooling it to 0 °C and adding TfOH (2.25 mL, 25.5 mmol) *[2]*. After addition, bubbling could be observed from the surface of the white solid, the cooling bath was removed. After slowly stirring for 2 hours *[3]*, no more white solid was present. It resulted in upper colorless hexane layer, which contained (−)-Ipc$_2$BOTf and was assumed to be 1.2 M, and lower strongly colored layer, which was discarded. If the upper layer was colored yellow, it was assumed that one of the reagents was of dissatisfying quality and reaction was repeated with fresh reagents.

Ketone **137** and aldehyde **138** were both dried by three cycles of adding and evaporating toluene, subsequently dissolved in CH_2Cl_2 and stored 20 min over few milligrams of CaH_2 *[4]*. (−)-Ipc$_2$BOTf (~1.2 M in hexane) (8.38 mL, 10.1 mmol) was added to 12 mL of CH_2Cl_2 and cooled to −78 °C. Freshly distilled D*i*PEA *[5]* (3.5 mL, 20.2 mmol) was added over 2 minutes, followed by ketone **137** (2.00 g, 6.70 mmol) in 18 mL CH_2Cl_2. Reaction mixture was stirred 2.5 hours at that temperature. Aldehyde **138** (4.19 g, 20.2 mmol) in 18 mL CH_2Cl_2 was added over 10 minutes. Reaction mixture was stirred additional 30 minutes at −78 °C and kept at −25 °C (no stirring) for 18 h. Then, it was warmed to 0 °C and 50 mL mixture of 30% H_2O_2/MeOH/pH 7 buffer (1:2:2) was added. Reaction mixture was stirred 2.5 h at room temperature, extracted 4 x 40 mL CH_2Cl_2, combined organics were washed with 100 mL sat. aq. $NaHCO_3$, dried over $MgSO_4$ and concentrated. Crude product was purified by flash column chromatography (PE:EtOAc 3:1) resulting in ketone **148** (2.45 g, 4.83 mmol) as a colorless oil in 72% yield.

R_f: 0.25 **(**PE:EtOAc 9:1, PMA).

$[\alpha]_D^{20}$ = +16.6(1.0, $CHCl_3$); +62° (1.0, $CHCl_3$) for major diastereomer.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.27 (m, 2H), 6.85 – 6.88 (m, 2H), 5.61 – 5.71 (m, 1H), 4.89 – 4.97 (m, 2H), 4.54 (d, *J* = 11.9 Hz, 1H), 4.37 (d, *J* = 11.9 Hz, 1H), 4.16 – 4.24 (m, 2H),

3.79 (s, 3H), 3.78 – 3.84 (m, 1H), 3.12 (d, *J* = 2.9 Hz, 1H), 2.68 – 2.74 (m, 1H), 2.41 – 2.54 (m, 2H), 2.03 – 2.10 (m, 1H), 1.59 – 1.64 (m, 1H), 1.25 – 1.48 (m, 5H), 1.23 (d, *J* = 6.2 Hz, 3H), 1.10 (d, *J* = 7.4 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.85 (s, 9H), 0.05 (s, 3H), 0.00 (s, 3H). For major diastereomer.

^{13}C NMR (101 MHz, $CDCl_3$) δ 214.0, 159.3, 144.6, 130.8, 129.5, 114.0, 112.9, 72.2, 70.6, 68.5, 68.0, 55.4, 51.9, 49.3, 40.8, 37.9, 35.3, 31.9, 31.8, 26.0, 20.4, 19.6, 18.1, 10.1, −4.4, −4.5. For major diastereomer.

HRMS (ESI): calcd for $C_{29}H_{51}O_5Si$ $[M+H]^+$ 507.3506, found 507.3505.

[1] Should be white hard solid, not waxy. Prepared from (+)-α-pinene according to procedure by Ian Paterson.[196,196,197]

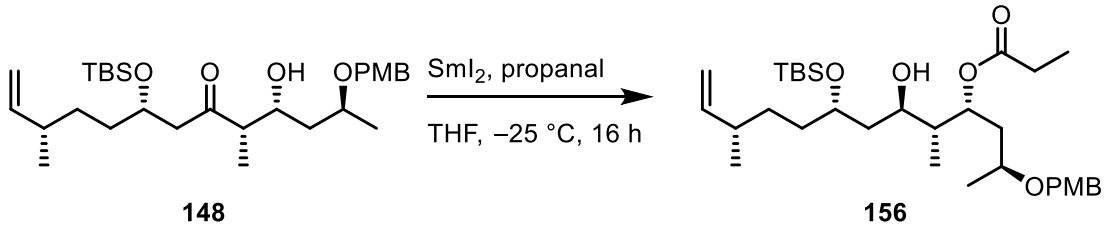
[2] Stirring should be slow, not mixing the layers. Hexane layer should be basically colourless, if it's completely yellow-red it can be discarded. For clean reaction, fresh TfOH is imperative, generally TfOH bottle should not be older than 2 weeks. Careful, TfOH corrodes through the plastic of syringes, addition should be completed in less than 1 minute after transferring TfOH into the syringe.

[3] If pieces of borane are bigger it could take somewhat longer, usually no more than 3 h.

[4] Drying with CaH_2 in this and following steps means that solution of reagent (ketone or aldehyde) was treated with a spatula tip of CaH_2 powder, it was left to stand for 10-20 minutes at room temperature under argon, then the solution was removed using syringe and directly added to the reaction.

[5] Usually no more than 3 weeks old. Distilled from CaH_2 and stored over 3 Å molecular sieves.

(2*S*,4*R*,5*R*,6*R*,8*S*,11*S*)-8-((*tert*-Butyldimethylsilyl)oxy)-6-hydroxy-2-((4-methoxybenzyl)oxy)-5,11-dimethyltridec-12-en-4-yl propionate (156):



148 **156**

Samarium metal (1.0 g, 6.65 mmol) was transferred into 50 mL flask and evacuated-backfilled 3 times with argon. Pieces of solid samarium metal were stirred with magnetic stirring bar for 30 min, after that freshly purified 1,2-diiodoethane (940 mg, 3.32 mmol) was added. Evacuation and backfilling with argon was repeated 3 more times. Then, 33 mL dry THF were added. Gas evolution could be observed and after 2-3 minutes, reaction flask was once more evacuated and backfilled 3 times with Argon. After 5-15 minutes the solution turned dark blue and was stirred overnight under argon. The solution was assumed to be ~0.1 M and was used after settling for 30 minutes *[1]*.

Solution of freshly distilled propanal (2.12 mL, 29.6 mmol) in 25 mL THF was cooled to 0 °C and SmI_2 (26 mL, 2.6 mmol) *[2]* as an about 0.1 M solution in THF was added. Reaction mixture was stirred 5 min at 0 °C and then cooled to −25 °C. Solution of hydroxyketone **148** (1.00 g, 1.97 mmol) in 5 mL THF was added dropwise over 30 minutes. Mixture was stirred at that temperature for 16 hours, quenched by adding 20 mL sat. aq. $NaHCO_3$, warmed to room temperature and extracted 4 x 30 mL $CHCl_3$ *[3]*, dried over Na_2SO_4 and concentrated under reduced pressure. Crude alcohol **156** was used in the next reaction without further purification.

R_f: 0.69 **(**PE:EtOAc 5:1, PMA).

$[\alpha]_D^{20}$ = +58.1 (1.0, $CHCl_3$) for major stereoisomer.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.27 (m, 2H), 6.85 – 6.87 (m, 2H), 5.62 – 5.71 (m, 1H), 5.57 (td, *J* = 9.5, 2.1 Hz, 1H), 4.89 – 4.97 (m, 2H), 4.47 (d, *J* = 10.7 Hz, 1H), 4.28 (d, *J* = 10.7 Hz, 1H), 3.97 – 4.02 (m, 1H), 3.88 (d, *J* = 2.1 Hz, 1H), 3.79 (s, 3H), 3.42 – 3.49 (m, 1H), 3.28 – 3.36 (m, 1H), 2.25 – 2.33 (m, 2H), 2.02 – 2.09 (m, 1H), 1.78 – 1.85 (m, 1H), 1.55 – 1.66 (m, 2H), 1.42 – 1.50 (m, 2H), 1.24 – 1.39 (m, 4H), 1.20 (d, *J* = 6.2 Hz, 3H), 1.12 (t, *J* = 7.4 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.86 (s, 9H), 0.83 (d, 6.9 Hz, 3H), 0.04 (s, 3H), 0.03 (s, 3H). For major diastereomer.

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.7, 159.2, 144.7, 130.7, 129.7, 113.9, 112.8, 71.3, 71.0, 70.6, 69.5, 68.8, 55.4, 44.3, 40.9, 40.7, 38.1, 35.6, 31.9, 27.8, 26.1, 20.5, 19.9, 18.2, 10.1, 9.3, −4.1, −4.7. For major diastereomer.

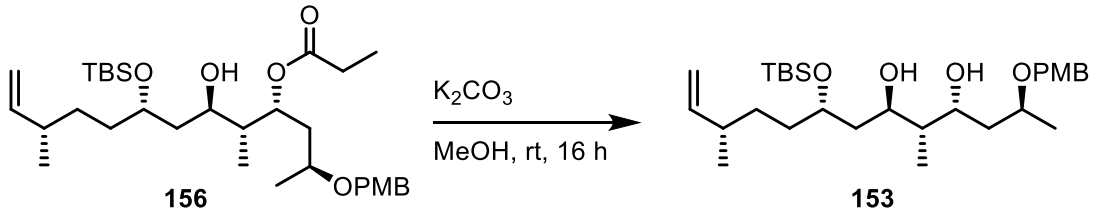
HRMS (ESI): calcd for $C_{32}H_{56}O_6SiNa$ $[M+Na]^+$ 587.3744; found, 587.3742.

[1] Obtained solution of SmI_2 could be stored for up to 3 weeks by letting it stand in dark at room temperature in septum capped flask. Before using the stored solution was stirred 1 hour at room temperature and then let to settle for 30 minutes before use. The pure solution of SmI_2 and suspension with metallic Sm can have different reactivities.[198]

[2] In theory, only catalytic amounts of SmI_2 are needed for the reaction. In practice, the reaction was faster and more likely to go to completion when larger amounts of SmI_2 were used. 1.3 eq. took it to completion in 1 h, at the same time with 0.7 eq. in most cases it took 5 hours and in some cases the complete consumption was not observed at all.

[3] Phase separation is not very good when more than 0.5 eq. SmI_2 are used. Phase separation with CH_2Cl_2 is horrendous.

(2*S*,4*R*,5*S*,6*R*,8*S*,11*S*)-8-((*tert*-Butyldimethylsilyl)oxy)-2-((4-methoxybenzyl)oxy)-5,11-dimethyltridec-12-ene-4,6-diol (153):



Crude alcohol **156** (1.11 g, 1.97 mmol) was dissolved in 10 mL MeOH and dry K_2CO_3 (600 mg, 4.34 mmol) was added. Mixture was stirred at room temperature for 24 h, after which 10 mL H_2O and 10 mL CH_2Cl_2 were added. Layers were separated, aqueous layer extracted 4 x 10 mL CH_2Cl_2 *[1]* and combined organics were dried over Na_2SO_4. Volatiles were removed under reduced pressure and crude diol **153** (1.0 g, 1.97 mmol) was generally *[2]* used in the following reaction without further purification.

R_f: 0.31 **(**PE:EtOAc, 5:1, PMA).

$[\alpha]_D^{20}$ = +25.5 (1.0, $CHCl_3$) for major stereoisomer.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.29 (m, 2H), 6.84 – 6.88 (m, 2H), 5.61 – 5.71 (m, 1H), 4.42 – 4.55 (m, 2H), 4.55 (d, *J* = 11.2 Hz, 1H), 4.42 (d, *J* = 11.2 Hz, 1H), 4.18 – 4.25 (m, 2H), 3.94 – 4.03 (m, 2H), 3.83 – 3.89 (m, 1H), 3.79 (s, 3H), 3.63 – 3.64 (m, 1H), 2.05 – 2.13 (m, 2H), 1.70 – 1.80 (m, 2H), 1.46 – 1.60 (m, 5H), 1.18 – 1.35 (m, 2H), 1.24 (d, *J* = 6.3 Hz, 3H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 144.3, 131.2, 129.4, 113.9, 113.1, 72.7, 72.6, 72.2, 70.7, 69.6, 55.4, 43.0, 40.8, 39.5, 37.9, 33.7, 32.9, 26.0, 20.5, 20.1, 18.1, 12.2, −4.4, −4.6.

HRMS (ESI) calcd for $C_{29}H_{52}O_5SiNa$ $[M+Na]^+$ 531.3482; found, 531.3484.

[1] After 4 washes, no more product in organic phase.

[2] In cases where many side-products were observed, crude material was purified by column chromatography (PE:EtOAc, 4:1).

***tert*-Butyl(((2*S*,5*S*)-1-((4*R*,5*S*,6*R*)-6-((*S*)-2-((4-methoxybenzyl)oxy)propyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-5-methylhept-6-en-2-yl)oxy)dimethylsilane (157):**

Crude diol **153** (1.0 g, 1.97 mmol) was dissolved in 10 mL dry CH_2Cl_2 and 2,2-DMP (10 mL, 113 mmol) followed by CSA (20 mg, 0.09 mmol) were added. Mixture was stirred at room temperature for 30 minutes. 20 mL of saturated aqueous $NaHCO_3$ was added and the aqueous phase was extracted 4 times with CH_2Cl_2 *[1]*. Combined organic layers were dried over Na_2SO_4 and volatiles removed under reduced pressure. Crude product was purified by flash column chromatography (PE:EtOAc 20:1) *[2]* giving the acetal **157** (815 mg, 1.48 mmol) as a colorless oil in 71% yield from the hydroxyketone **148**.

R_f: 0.88 **(**PE:EtOAc, 5:1, $KMnO_4$); 0.33 (PE:EtOAc, 15:1).

$[\alpha]_D^{20}$ = +49.8 (1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.28 (m, 2H), 6.86 – 6.89 (m, 2H), 5.63 – 5.72 (m, 1H), 4.89 – 4.97 (m, 2H), 4.53 (d, *J* = 11.2 Hz, 1H), 4.32 (d, *J* = 11.2 Hz, 1H), 4.11 – 4.18 (m, 1H), 3.75 – 3.81 (m, 1H), 3.80 (s, 3H), 3.65 – 3.70 (m, 1H), 3.31 – 3.36 (m, 1H), 2.02 – 2.09 (m, 1H), 1.40 – 1.61 (m, 7H), 1.33 (s, 3H), 1.31 (s, 3H), 1.26 – 1.36 (m, 2H), 1.22 (d, *J* = 5.9 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 0.79 (d, *J* = 6.8 Hz, 3H), 0.04 (s, 3H), 0.04 (s, 3H).

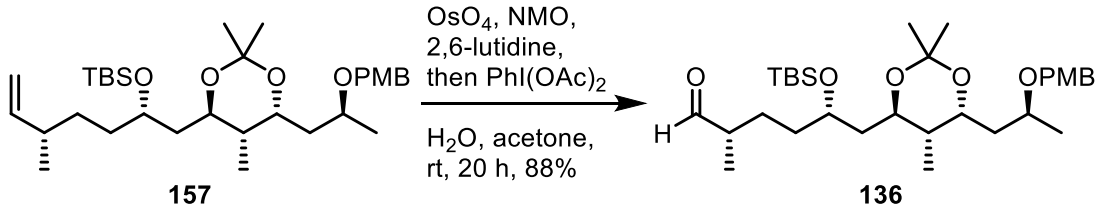
^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 144.9, 131.1, 129.6, 114.0, 112.7, 100.5, 72.3, 71.8, 70.6, 69.8, 65.4, 55.4, 43.1, 40.6, 39.0, 38.1, 35.8, 31.2, 26.1, 25.2, 24.7, 20.4, 20.2, 18.2, 11.6, −3.5, −4.4.

HRMS (ESI): calcd for $C_{32}H_{56}O_5SiNa$ $[M+Na]^+$ 571.3795; found, 571.3792.

[1] The organic phase still contains the product (according to TLC) after 4 extractions but the mass of product in the 5th extraction was under 0.5%.

[2] At this stage, it is possible to separate the C13 isomeric product from the first aldol reaction and obtain stereoisomerically pure acetal.

(2*S*,5*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-6-((4*R*,5*S*,6*R*)-6-((*S*)-2-((4-methoxybenzyl) oxy)propyl) -2,2,5-trimethyl-1,3-dioxan-4-yl)-2-methylhexanal (136):



157 **136**

The alkene **157** (200 mg, 0.36 mmol) *[1]* was dissolved in 5.5 mL 10/1 mixture of acetone/water and 2,6-lutidine (84 µL, 0.73 mmol), then *N*-methylmorpholine *N*-oxide (64 mg, 0.55 mmol) and OsO_4 (74 µL, 7.30 µmol mmol; 2.5% solution in *t*BuOH) were added. The reaction mixture was stirred 20 h at room temperature, after which phenyliodine(III)diacetate (176 mg, 0.55 mmol) *[2]* was added and the reaction mixture was stirred for additional 2 hours at that temperature *[3]*. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ solution, extracted 3 x 5 mL EtOAc. The combined organic layers were washed once with 1M aq. $CuSO_4$ solution and dried over Na_2SO_4. The crude material was purified by flash column chromatography (PE:EtOAc 10:1 to 5:1) and the aldehyde **136** (176 mg, 0.32 mmol) was obtained as colorless oil in 88% yield *[4]*.

R_f: 0.39 **(**PE:EtOAc, 10:1, PMA).

$[\alpha]_D^{20}$ = +43.0 (1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (d, *J* = 2.0 Hz, 1H), 7.25 – 7.28 (m, 2H), 6.85 – 6.88 (m, 2H), 4.53 (d, *J* = 10.4, 1H), 4.31 (d, *J* = 10.4 Hz, 1H), 4.13 – 4.18 (m, 1H), 3.80 (s, 3H), 3.78 – 3.83 (m, 1H), 3.64 – 3.70 (m, 1H), 3.31 (td, *J* = 8.0, 3.7 Hz, 1H), 2.26 – 3.32 (m, 1H), 1.68 – 1.83 (m, 1H), 1.39 – 1.62 (m, 8H), 1.33 (s, 3H), 1.30 (s, 3H), 1.22 (d, *J* = 6.2 Hz, 3H), 1.09 (d, *J* = 7.2 Hz, 3H), 0.88 (s, 9H), 0.79 (d, *J* = 7.0 Hz, 3H), 0.05 (s, 6H).

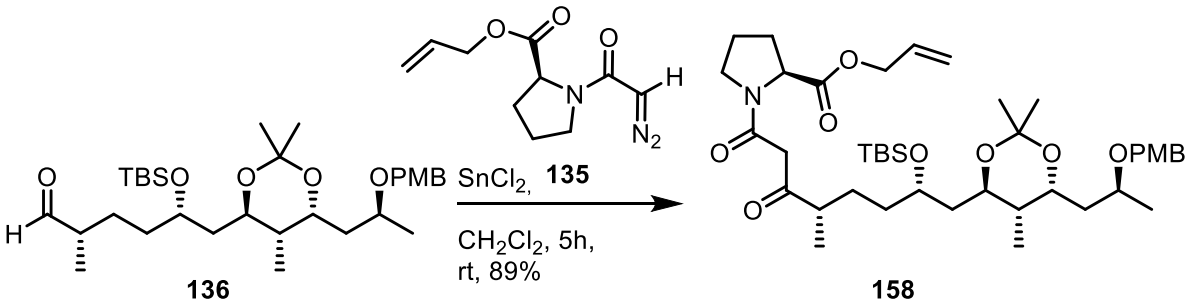
^{13}C NMR (101 MHz, $CDCl_3$) δ 205.2, 159.3, 131.2, 129.6, 114.0, 100.6, 72.3, 71.7, 70.6, 69.7, 65.4, 55.4, 46.6, 40.7, 39.0, 35.3, 26.0, 26.0, 25.2, 25.1, 24.6, 20.2, 18.2, 13.5, 11.6, −3.7, −4.4.

HRMS (ESI) calcd for $C_{31}H_{55}O_6Si$ $[M+H]^+$ 551.3768; found, 551.3766.

[1] Should be freshly purified, otherwise the next reaction (Roskamp) gives much lower yields.

[3] Reaction monitored with PE:EtOAc 1:1.

Allyl ((4*S*,7*S*)-7-((*tert*-butyldimethylsilyl)oxy)-8-((4*R*,5*S*,6*R*)-6-((*S*)-2-((4-methoxybenzyl)oxy)propyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-4-methyl-3-oxooctanoyl)-L-prolinate (158):



The $SnCl_2$ (121 mg, 0.64 mmol) was transferred to the 25 mL round bottomed flask in a glovebox and diazo compound **135** *[1]* (567 mg, 2.54 mmol) in 15 mL CH_2Cl_2 was transferred to the flask using standard Schlenk techniques *[2]*, followed by the aldehyde **136** (175 mg, 0.32 mmol) in 2 mL CH_2Cl_2. The reaction mixture was stirred for 5 hours (or until no more aldehyde was present) in the dark at room temperature. The reaction was then quenched with half-saturated aqueous $NaHCO_3$ solution and aqueous layer was extracted 3 times with $CHCl_3$ *[3]*. The combined organic layers were dried over Na_2SO_4 and crude product was purified by flash column chromatography (PE:EtOAc 2:1 to 1:1) *[4]* giving the β-keto amide **158** (212 mg, 0.28 mmol) as clear colorless oil in 89% yield.

R_f: 0.60 (PE:EtOAc, 1:1, $KMnO_4$) spot is generally 0.5 units long or 0.50 (PE:EtOAc:Et_3N, 3:1:0.1, PMA).

$[\alpha]_D^{20}$ = +21.1 (1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 14.25 (s, 0.4H), 7.27 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.3 Hz, 2H), 5.86 – 5.96 (m, 1H), 5.22 – 5.35 (m, 2H), 4.99 (s, 0.4H), 4.51 – 4.66 (m, 4H), 4.30 – 4.34 (m, 1H), 4.13 – 4.18 (m, 1H), 3.80 (s, 3H), 3.74 – 3.81 (m, 1H), 3.55 (s, 0.7H), 3.44 – 3.71 (m, 4H), 3.28 – 3.36 (m, 1H), 1.91 – 2.28 (m, 5H), 1.40 – 1.67 (m 8H), 1.32 (s, 3H), 1.30 (s, 3H), 1.26 – 1.33 (m, 1H), 1.22 (d, *J* = 5.9 Hz, 3H), 1.08 – 1.13 (m, 3H), 0.88 (s, 9H), 0.79 (d, *J* = 6.8 Hz, 3H), 0.04 (s, 6H). Compound exists as a mixture of enone and keto form, as well as a mixture of rotamers and conformers.[177] *[5]*

^{13}C NMR (101 MHz, $CDCl_3$) δ 207.7, 172.2, 171.8, 170.9, 165.5, 159.2, 132.0, 132.0, 131.1, 131.1, 129.5, 118.5, 118.5, 114.0, 100.5, 100.5, 86.8, 72.3, 71.7, 70.6, 69.8, 69.7, 65.8, 65.8, 65.4, 65.4, 59.0, 58.3, 55.4, 49.2, 47.8, 46.7, 46.3, 43.0, 40.6, 40.4, 38.9, 35.4, 29.5, 27.3,

26.1, 26.1, 25.2, 24.9, 24.6, 24.6, 20.2, 18.3, 18.2, 18.2, 16.0, 11.6, −3.6, −4.4. Compound exists as a mixture of enone and keto form, as well as a mixture of rotamers and conformers.

HRMS (ESI) calcd for $C_{41}H_{67}NO_9NaSi$ $[M+Na]^+$ 768.4483; found, 768.4478.

[1] Diazo compound was not stored for a longer time than 2 weeks and aldehyde was freshly prepared from freshly columned alkene. Aldehyde that was not freshly prepared or not prepared from freshly purified alkene, gave significantly inferior yields.

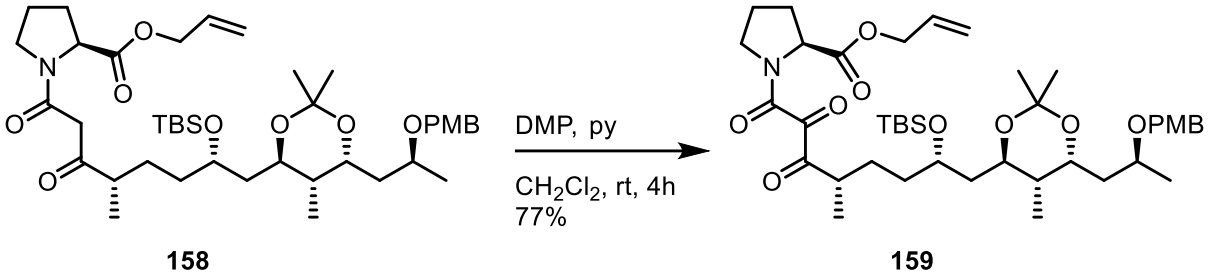
[2] Significant gas evolution.

[3] First 3 extractions usually good, after that starts to give emulsions.

[4] The product is streaking and does not stain well on TLC. Usually all the fractions that did not contain any other impurities were collected, even if there appeared nothing upon staining with $KMnO_4$.

[5]Enone O-H has δ 14.25 and appears as 2 major and 2 minor singlets. Enone C-H has δ 4.99, dicarbonyl CH_2 has δ 3.55.

Allyl ((4*S*,7*S*)-7-((*tert*-butyldimethylsilyl)oxy)-8-((4*R*,5*S*,6*R*)-6-((*S*)-2-((4-methoxybenzyl)oxy)propyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-4-methyl-2,3-dioxooctanoyl)-L-prolinate (159):



158 **159**

The β-keto amide **158** (137 mg, 0.18 mmol) was dissolved in 5 mL CH_2Cl_2 and pyridine (1.32 mL, 102 mmol) was added. Dess-Martin periodinane (397 mg, 0.94 mmol) *[1]* was added under argon flow. The reaction mixture turns yellow during the reaction. The reaction was stirred 4 hours at room temperature, after which the reaction mixture was diluted with CH_2Cl_2 and washed with sat. aq. $NaHCO_3$ solution *[2]*. The aqueous layer was washed 4 x 5 mL $CHCl_3$, combined organic layers were dried over Na_2SO_4 and volatiles removed under reduced pressure. The crude product was purified by flash column chromatography (PE:EtOAc:Et_3N 3:1:0.1 to 2:1:0.1) and the tricarbonyl compound **159** (105 mg, 0.14 mmol) was obtained as colorless oil in 77% yield.

R_f: 0.21(PE:EtOAc:Et_3N, 3:1:0.1, PMA). *[3]*

$[\alpha]_D^{20}$ = +22.9 (1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.28 (m, 2H), 6.85 – 6.89 (m, 2H), 5.81 – 5.96 (m, 1H), 5.23 – 5.36 (m, 2H), 4.59 – 4.76 (m, 3H), 4.52 (d, *J* = 10.7 Hz, 1H), 4.52 (d, *J* = 10.7 Hz, 1H), 4.12 – 4.17 (m, 1H), 3.79 (s, 3H), 3.72 – 3.86 (m, 1H), 3.60 – 3.70 (m, 2H), 3.26 – 3.35 (m, 1H), 2.99 – 3.14 (m, 1H), 2.19 – 2.36 (m, 1H), 1.76 – 2.13 (m, 4H), 1.40 – 1.66 (m, 8H), 1.32 (s, 3H), 1.30 (s, 3H), 1.22 (d, *J* = 6.2 Hz, 3H), 1.16 (d, *J* = 7.0 Hz, 3H), 0.87 (s, 9H), 0.78 (d, *J* = 6.8 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H). Exists as a mixture of tricarbonyl, its hydrate and rotamers.

^{13}C NMR (101 MHz, $CDCl_3$) δ 204.4, 204.2, 186.7, 186.3, 171.2, 170.5, 162.6, 161.5, 159.2, 131.8, 131.5, 131.1, 129.5, 119.2, 118.8, 114.0, 100.5, 72.3, 71.7, 70.6, 69.5, 69.5, 66.4, 66.1, 65.4, 59.5, 59.0, 55.4, 47.2, 47.1, 42.9, 41.6, 41.2, 40.6, 38.9, 35.4, 31.3, 29.0, 26.2, 26.1,

25.2, 24.9, 24.6, 22.2, 20.2, 18.2, 14.7, 11.6, −3.6, −4.4. Exists as a mixture of tricarbonyl, its hydrate and rotamers.

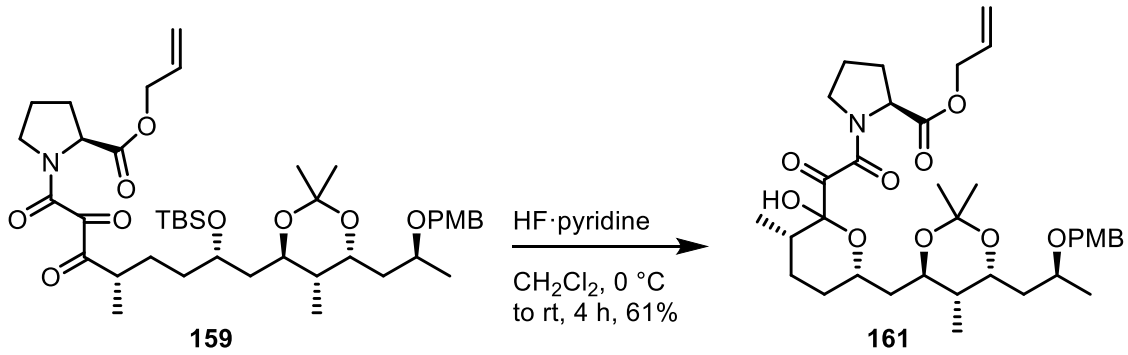
HRMS (ESI) calcd for $C_{41}H_{67}NO_{11}NaSi$ $[M+H_2O+Na]^+$ 800.4381; found, 800.4380.

[1] DMP should be prepared from high quality IBX. The reaction took approximately 12 h with freshly prepared DMP, 4-8 hours with 2-6 week-old DMP and did not work at all if DMP was more than 8 weeks old. Adding 1 equivalent of water to the reaction did not improve the reaction under any conditions.

[2] Washing with aqueous acid solution or $CuSO_4$ to remove excess pyridine make the layer separation extremely difficult.

[3] R_f values are very similar and sometimes it is difficult to determine if reaction took place using only TLC. Also, the R_f values from crude reaction mixture are not representative due to high concentration of pyridine. If checked by NMR, there should be no signals appearing in the 14-15 ppm region.

Allyl (2-((3*S*,6*S*)-2-hydroxy-6-(((4*R*,5*S*,6*R*)-6-((*S*)-2-((4-methoxybenzyl)oxy)propyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)methyl)-3-methyltetrahydro-2H-pyran-2-yl)-2-oxoacetyl)-L-prolinate (161):



159 161

Tricarbonyl compound **159** (70 mg, 0.092 mmol) was dissolved in 10 mL 1:1 mixture of pyridine/THF and cooled to 0 °C. HF pyridine complex (2.5 mL, 96 mmol) was added dropwise. Reaction mixture was gradually warmed to room temperature and stirred for 4 h *[1]*. The reaction mixture was cooled to 0 °C and quenched with sat. aq. $NaHCO_3$ solution, solid $NaHCO_3$ was added until no more gas evolution took place. The aqueous layer was extracted 3 x 5 mL CH_2Cl_2, organic layers were combined and dried over Na_2SO_4. The crude product was purified by flash column chromatography (PE:EtOAc 2:1) giving lactol **161** (36 mg, 0.056 mmol) as slightly yellow oil in 61% yield.

R_f: 0.16 (PE:EtOAc:Et_3N, 3:1:0.1, PMA), 0.53 (PE:EtOAc, 2:1); 0.19 (PE:EtOAc 3:1).

$[\alpha]_D^{20}$ = +17.2 (1.0, $CHCl_3$).

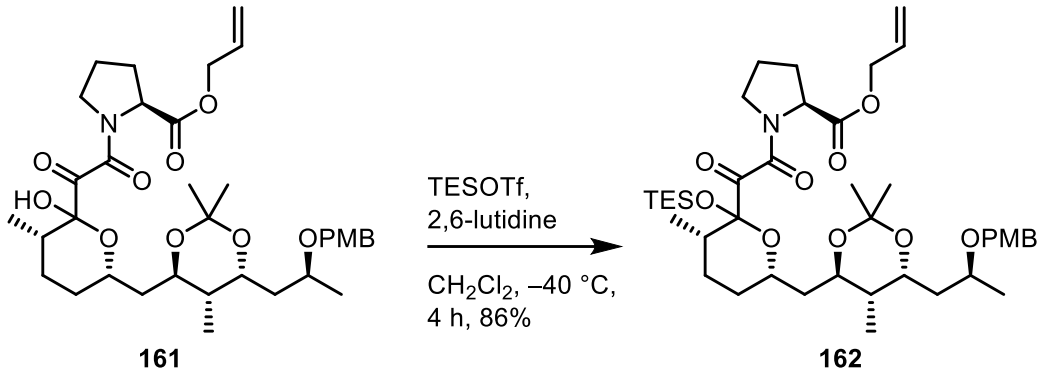
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.27 (m, 2H), 6.85 – 6.87 (m, 2H), 5.83 – 5.98 (m, 1H), 5.22 – 5.36 (m, 2H), 4.51 – 4.69 (m, 4H), 4.27 – 4.33 (m, 1H), 4.01 – 4.24 (m, 2H), 3.79 (s, 3H), 3.31 – 3.73 (m, 4H), 1.40 – 2.41 (m, 16H), 1.19 – 1.36 (m, 12H), 0.73 – 1.05 (m, 7H). Compound exists as a mixture of diastereomers, rotamers and conformers. *[2]*

HRMS (ESI) calcd for $C_{35}H_{51}NO_{10}Na$ $[M+Na]^+$ 668.3411; found, 668.3412.

[1] The starting material and product have very similar R_f values and monitoring the reaction by TLC is complicated. The R_f values of reaction mixture are not representative due to high concetration of pyridine.

[2] Spectrum is too complex for interpretation.

Allyl (2-((3*S*,6*S*)-6-(((4*R*,5*S*,6*R*)-6-((*S*)-2-((4-methoxybenzyl)oxy)propyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)methyl)-3-methyl-2-((triethylsilyl)oxy)tetrahydro-2H-pyran-2-yl)-2-oxoacetyl)-L-prolinate (162):



161 162

Lactol **161** (30 mg, 0.046 mmol) was dissolved in 3 mL CH_2Cl_2 and cooled to -40 °C. 2,6-lutidine (80 µL, 0.69 mmol) was added and reaction mixture stirred for 10 minutes. TESOTf (53 µL, 0.23 mmol) was added dropwise and reaction mixture was stirred at -40 °C for 4 hours. The reaction mixture was quenched with 3 mL sat. aq. $NaHCO_3$ solution and aqueous layer was extracted 3 x 5 mL CH_2Cl_2. Combined organic layers were dried over Na_2SO_4. Crude product was purified by flash column chromatography (PE:EtOAc 4:1 to 3:1) giving protected lactol **162** (30 mg, 0.039 mmol) as colorless oil in 86% yield.

R_f: 0.42 (PE:EtOAc, 3:1, PMA).

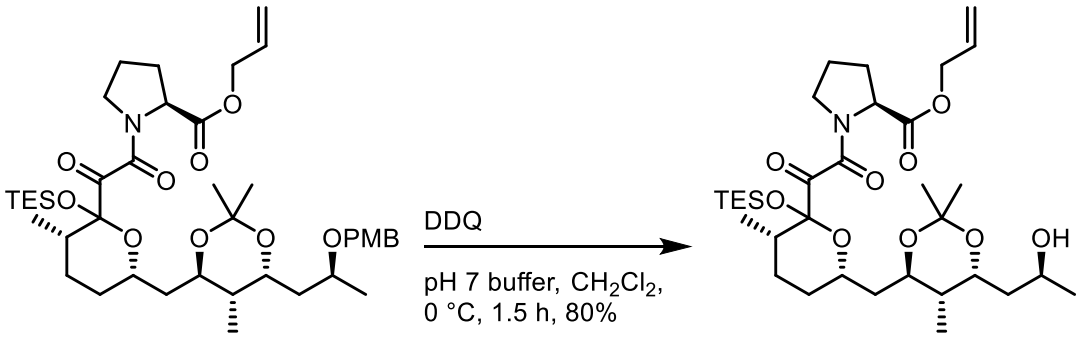
$[\alpha]_D^{20}$ = +14.1 (1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.27 (m, 2H), 6.85 – 6.87 (m, 2H), 5.85 – 5.95 (m, 1H), 5.30 – 5.35 (m, 1H), 5.20 – 5.26 (m, 1H), 4.48 – 4.69 (m, 4H), 4.29 – 4.36 (m, 1H), 4.07 – 4.19 (m, 2H), 3.80 (s, 3H), 3.27 – 3.73 (m, 4H), 1.63 – 2.27 (m, 7H), 1.43 – 1.54 (m, 6H), 1.29 – 1.34 (m, 5H), 1.21 – 1.27 (m, 4H), 0.88 – 1.02 (m, 11H), 0.75 – 0.83 (m, 4H), 0.62 – 0.73 (m, 6H). *[1]*

HRMS (ESI) calcd for $C_{41}H_{65}NO_{10}NaSi$ $[M+Na]^+$ 782.4275; found, 782.4281.

[1] Spectrum is too complex for interpretation.

Allyl (2-((3*S*,6*S*)-6-(((4*R*,5*S*,6*R*)-6-((*S*)-2-hydroxypropyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)methyl)-3-methyl-2-((triethylsilyl)oxy)tetrahydro-2H-pyran-2-yl)-2-oxoacetyl)-L-prolinate (163):



162 **163**

Protected lactol **162** (25 mg, 0.033 mmol) was dissolved in 3 mL CH_2Cl_2, 0.5 mL pH 7 buffer solution was added and mixture was cooled to 0 °C. DDQ (15 mg, 0.66 mmol) was added in one portion and reaction mixture stirred at that temperature for 1.5 hours. The reaction mixture was quenched with 3 mL saturated aqueous $NaHCO_3$ solution and aqueous layer was extracted 3 times with 5 mL CH_2Cl_2. Combined organic layers were dried over Na_2SO_4. Crude product was purified by column chromatography (PE:EtOAc 4:1 to 1:1) giving alcohol **163** (17 mg, 0.026 mmol) as colorless oil in 80% yield.

R_f: 0.17 (PE:EtOAc, 2:1, PMA).

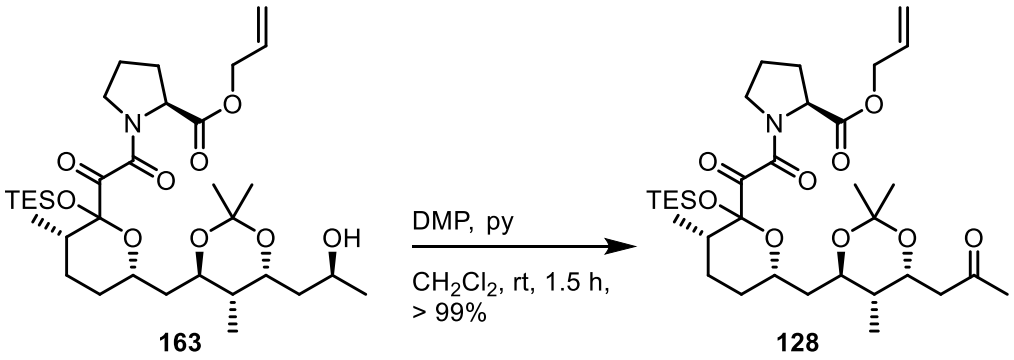
$[\alpha]_D^{20}$ = +18.4 (1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 – 5.94 (m, 1H), 5.30 – 5.36 (m, 1H), 5.20 – 5.26 (m, 1H), 4.51 – 4.71 (m, 3H), 4.10 – 4.24 (m, 1H), 3.97 – 4.04 (m, 2H), 3.34 – 3.75 (m, 3H), 2.13 – 2.29 (m, 2H), 1.98 – 2.09 (m, 2H), 1.84 – 1.98 (m, 2H), 1.62 – 1.84 (m, 3H), 1.45 (s, 1H), 1.33 – 1.38 (m, 7H), 1.22 – 1.26 (m, 7H), 0.81 – 1.03 (m, 16H), 0.65 – 0.72 (m, 6H). *[1]*

HRMS (ESI) calcd for $C_{33}H_{57}NO_9NaSi$ $[M+Na]^+$ 662.3700; found, 662.3703.

[1] Spectrum is too complex for interpretation.

Allyl (2-((3S,6S)-3-methyl-2-((triethylsilyl)oxy)-6-(((4R,5R,6R)-2,2,5-trimethyl-6-(2-oxopropyl)-1,3-dioxan-4-yl)methyl)tetrahydro-2H-pyran-2-yl)-2-oxoacetyl)-L-prolinate (128) – the southern fragment of 3-normeridamycin:



163 128

Alcohol **163** (13 mg, 0.020 mmol) was dissolved in 1.5 mL CH_2Cl_2, pyridine (50 μL, 0.62 mmol) and cooled to 0 °C. DMP (9 mg, 0.02 mmol) was added in one portion and reaction mixture stirred at that temperature for 1.5 hours. The reaction mixture was quenched with 3 mL saturated aqueous $NaHCO_3$ solution and aqueous layer was extracted 3 times with 2 mL CH_2Cl_2. Combined organic layers were dried over Na_2SO_4. Crude product was purified by column chromatography (PE:EtOAc 4:1 to 1:1) giving ketone **128** (13 mg, 0.02 mmol) as colorless oil in quantitative yield. Analytically pure sample was obtained by purification by HPLC.

R_f: 0.60 (PE:EtOAc, 2:1, Vanilline).

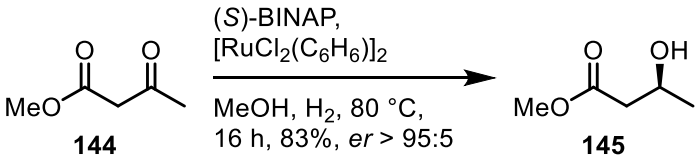
$[\alpha]_D^{20}$ = +13.4 (1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 – 6.02 (m, 1H), 5.39 (dd, *J* = 17.3, 1.5 Hz, 1H), 5.26 (dd, *J* = 10.6, 1.5 Hz, 1H), 4.60 – 4.73 (m, 2H), 4.48 (dd, *J* = 8.8, 3.8 Hz, 1H), 4.37 – 4.41 (m, 1H), 4.22 – 4.28 (m, 1H), 3.57 – 3.69 (m, 1H), 3.44 – 3.54 (m, 2H), 2.68 (dd, *J* = 16.5, 9.7 Hz, 1H), 2.46 (dd, *J* = 16.5, 4.1 Hz, 1H), 2.19 (s, 3H), 2.14 – 2.31 (m, 3H), 1.98 – 2.10 (m, 3H), 1.75 – 1.81 (m, 1H), 1.63 – 1.70 (m, 1H), 1.51 – 1.61 (m, 3H), 1.40 – 1.45 (m, 1H), 1.33 (s, 3H), 1.31 (s, 3H), 1.05 (d, *J* = 7.2 Hz, 3H), 1.01 (t, *J* = 7.9 Hz, 9H), 0.85 (d, *J* = 7.0 Hz, 3H), 0.73 (q, *J* = 7.9 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.7, 201.2, 172.3, 166.6, 133.3, 118.6, 102.0, 101.5, 72.1, 69.0, 66.9, 66.8, 59.8, 48.2, 45.3, 42.3, 41.1, 35.0, 30.7, 30.0, 26.8, 26.6, 25.7, 25.3, 24.7, 15.7, 12.3, 7.5, 6.9.

HRMS (ESI) calcd for $C_{35}H_{55}NO_9NaSi$ $[M+Na]^+$ 660.3544; found, 660.3548.

(*S*)-Methyl-3-hydroxybutanate (145):



Methylacetoacetate was purified by distillation under reduced pressure (40 mbar, 70 °C). Solution of methylacetoacetate and methanol (dry) was degassed prior to reaction by 3-4 freeze-thaw cycles.

Dichloro(benzene)ruthenium(II)dimer (43 mg, 0.086 mmol) and (*S*)-BINAP (107 mg, 0.172 mmol) were weighted under air and transferred to 50 mL Schlenk tube under a flow of argon. Reaction vessel was evacuated and refilled with argon 3 times. 4 mL DMF was added and reaction was stirred 15 minutes in oil bath which was pre-heated to 100 °C. Mixture was cooled to 50 °C and DMF removed by evacuating the mixture for 2 hours. This provided the hydrogenation catalyst as a red solid. Degassed (4 freeze-thaw cycles) mixture of methylacetoacetate (**144**) (18.6 mL, 172 mmol) and 20 mL methanol was added to freshly prepared catalyst and stirred at room temperature until catalyst was mostly dissolved giving dark-red solution. Mixture was transferred to bomb-reactor and flushed 6 times with hydrogen. Hydrogen pressure was set to 30 bar and reaction stirred for 16 hours at 80 °C *[1]*. Methanol was removed under reduced pressure (100 mbar, 40 °C oil bath) and hydroxy ester **145** (16.8 g, 142 mmol) was obtained after distillation (25 mbar, 69-70 °C) as a clear colorless liquid in *er* > 95:5 *[2]* and in 83% yield.

$[\alpha]_D^{20}$ = +47.9 (1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 – 4.11 (m, 1H), 3.66 (d, *J* = 0.6 Hz, 3H), 3.06 (br, 1H), 2.68 – 2.17 (m, 2H), 1.18 (dd, *J* = 6.3, 0.7 Hz, 3H).

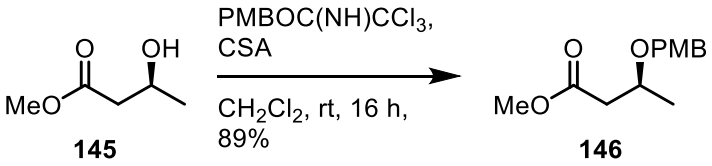
^{13}C NMR (101 MHz, $CDCl_3$) δ 173.29, 64.28, 51.75, 42.73, 22.55.

NMR data and optical rotation matched literature values.[199]

[1] Under 60 °C no reaction takes place.

[2] Enantiomeric ratio was assessed by optical rotation value.

Methyl (*S*)-3-((4-methoxybenzyl)oxy)butanoate (146):



Hydroxyester **145** (1.0 g, 8.5 mmol) was dissolved in 18 mL of CH_2Cl_2 and *p*-methoxybenzyltrichloroacetimidate (3.61 g, 12.8 mmol) was added, followed by CSA (200 mg, 0.85 mmol). Mixture was stirred 16 hours at room temperature, extracted with 40 mL sat. aq. $NaHCO_3$ and aqueous layer was washed 3 x 10 mL CH_2Cl_2. Combined organics were washed with brine and dried over $MgSO_4$. Crude product was purified by flash column chromatography (PE:EtOAc 10:1). Protected alcohol **146** (1.8 g, 7.6 mmol) was obtained as a clear colorless liquid in 89% yield.

R_f: 0.25 (PE:EtOAc 9:1, $KMnO_4$).

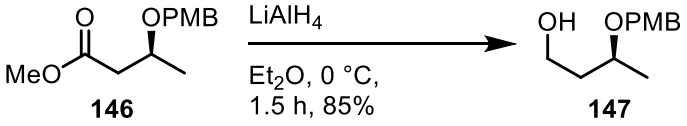
$[\alpha]_D^{20}$ = +23.7 (1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.17 (m, 2H), 6.92 – 6.78 (m, 2H), 4.46 (dd, *J* = 29.7, 11.2 Hz, 2H), 4.05 – 3.92 (m, 1H), 3.79 (s, 3H), 3.67 (s, 3H), 2.64 (dd, *J* = 15.1, 7.3 Hz, 1H), 2.42 (dd, *J* = 15.1, 5.8 Hz, 1H), 1.24 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.07, 159.27, 130.71, 129.36, 113.88, 71.68, 70.64, 55.39, 51.69, 41.98, 19.99.

NMR data and optical rotation matched literature values.[200]

(*S*)-3-((4-Methoxybenzyl)oxy)butan-1-ol (147):



146 **147**

$LiAlH_4$ (4.08 g, 108 mmol) in dry 54 mL Et_2O was cooled to 0 °C and ester **146** (19.2 g, 83 mmol) in 22 mL dry Et_2O was added over 45 minutes. The ice-water bath was removed and reaction mixture stirred for 1.5 h. Then, 100 mL dry Et_2O was added and mixture cooled back to 0 °C. 150 mL Rochelle salt solution was added dropwise and reaction mixture stirred overnight at room temperature. Layers were separated and aqueous layer was washed 3 x 30 mL Et_2O. Combined organic fractions were dried over $MgSO_4$, volatiles removed under reduced pressure and crude product was purified by flash column chromatography (PE:EtOAc 2:1). Alcohol **147** (14.7 g, 70.1 mmol) was obtained in 85% yield as a slightly yellow oil.

R_f: 0.27 (PE:EtOAc 2:1, $KMnO_4$).

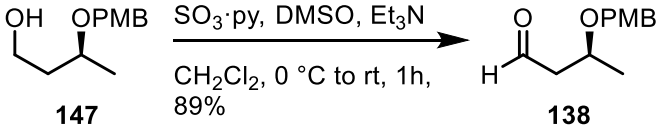
$[\alpha]_D^{20}$ = +61.2 (1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 , 2H), 4.57 (d, *J* = 11.6 Hz, 1H), 4.37 (d, *J* = 11.6 Hz, 1H), 3.80 (s, 3H), 3.69 – 3.81 (m, 3H), 2.57 (s, 1H), 1.71 – 1.79 (m, 2H), 1.24 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.35, 130.61, 129.45, 114.01, 74.51, 70.20, 61.11, 55.40, 38.89, 19.50.

NMR data and optical rotation matched literature values.[200]

(*S*)-3-((4-methoxybenzyl)oxy)butanal (138):



Alcohol **147** (7.4 g, 35.0 mmol) was dissolved in 176 mL CH_2Cl_2 and cooled to 0 °C. Et_3N (24.5 mL, 176 mmol), SO_3·py (16.8 g, 106 mmol) and DMSO (37.5 mL, 530 mmol) were added consecutively. Mixture was stirred 5 minutes at 0 °C and 2 hours at room temperature. 200 mL of H_2O was added and layers separated. Aqueous layer was washed 3 x 30 mL CH_2Cl_2, combined organics dried over Na_2SO_4, filtered and volatiles removed under reduced pressure. Crude product was purified by flash column chromatography (PE:EtOAc 4:1) to yield aldehyde **138** (6.51 g, 31.2 mmol) in 89% yield as slightly yellow oil.

R_f: 0.58 (PE:EtOAc 2:1, $KMnO_4$).

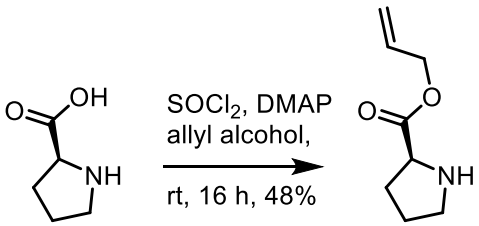
$[\alpha]_D^{20}$ = +33.0 (1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (t, *J* = 2.1 Hz, 1H), 7.22 – 7.26 (m, 2H), 6.84 – 6.89 (m, 2H), 4.53 (d, *J* = 11.3 Hz, 1H), 4.40 (d, *J* = 11.3 Hz, 1H), 4.02 – 4.10 (m, 1H), 3.79 (s, 3H), 2.68 (ddd, *J* = 2.6, 7.5, 16.4 Hz, 1H), 2.50 (ddd, *J* = 1.9, 5.0, 16.4 Hz, 1H), 1.28 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 201.7, 159.3, 130.4, 129.4, 113.9, 70.4, 70.0, 55.4, 50.6, 19.9.

NMR data and optical rotation matched literature values.[201]

Allyl L-prolinate (160):



159 **160**

L-proline (**159**) (20.0 g, 174 mmol) was mixed with allylic alcohol (40.0 mL, 590 mmol) and DMAP (120 mg, 0.98 mmol) was added. To this mixture, $SOCl_2$ (13.9 mmol, 191 mmol) was added dropwise over 1 hour on water bath. Reaction mixture was stirred at room temperature for 20 hours after which, the allylic alcohol was removed under reduced pressure. Resulting oil was dissolved in 80 mL CH_2Cl_2 and Et_3N (24.0 mL, 174 mmol) was added dropwise over 15 minutes on ice-water bath. After complete addition, the cooling bath was removed and mixture was stirred at room temperature for 1 hour. Then, 20 mL Et_2O was added. Resulting solid was filtered and filtrate concentrated under reduced pressure. Resulting crude oil was purified by vacuum distillation (1 mbar, 57 °C). Title compound **160** (13.0 g, 83.7 mmol) was obtained as clear colorless liquid in 48% yield and stored at −25 °C *[1]*.

$[\alpha]_D^{20}$ = −31.0 (1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 – 5.96 (m, 1H), 5.31 (dq, *J* = 1.6, 17.4 Hz, 1H), 5.23 (dq, *J* = 1.6, 10.6 Hz, 1H), 4.61 (d, *J* = 5.8 Hz, 2H), 3.77 (dd, *J* = 5.7, 8.7 Hz, 1H), 3.04 – 3.10 (m, 1H), 2.87 – 2.93 (m, 1H), 2.19 (s, 1H), 2.08 – 2.17 (m, 1H), 1.81 – 1.90 (m, 1H), 1.69 – 1.78 (m, 2H).

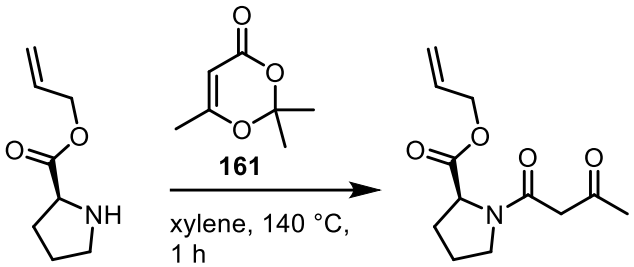
^{13}C NMR (101 MHz, $CDCl_3$) δ175.3, 132.1, 118.6, 65.6, 59.9, 47.2, 30.4, 25.6.

HRMS (ESI) calcd for $C_{10}H_{15}NO_3Na$ $[M+Na]^+$ 220.0950; found, 220.0951.

NMR data and optical rotation matched literature values.[202]

[1] Polymerizes rapidly at 4 °C, stored without significant polymerization up to 2 months at −25 °C.

Allyl (3-oxobutanoyl)-L-prolinate (162):



160 162

Allyl L-prolinate (**160**) (6.67 g, 43 mmol) was dissolved in 107 mL xylene and 2,2,6-trimethyl-4H-1,3-dioxin-4-one (**161**) (6.0 mL, 43 mmol) was added. Sealed flask was heated 1 hour at 140 °C, after which the volatiles were removed under reduced pressure. Resulting black oil (**162**) was used directly in the next reaction.

R_f: 0.40 (EtOAc, $KMnO_4$).

$[\alpha]_D^{20}$ = −34.6 (1.0, $CHCl_3$).

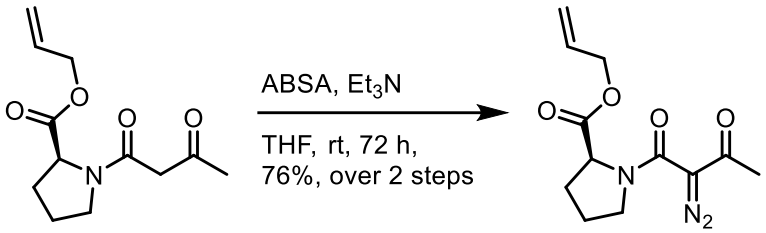
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 – 5.95 (m, 1H), 5.22 – 5.35 (m, 2H), 4.61 – 4.64 (m, 2H), 4.55 – 4.59 (m, 1H), 3.52 – 3.62 (m, 2H), 2.38 (s, 3H), 2.25 – 2.34 (m, 1H), 1.95 – 2.16 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 159.9, 131.8, 118.8, 66.0, 60.1, 48.6, 29.4, 28.0, 24.9. *[1]*

HRMS (ESI) calcd for $C_{12}H_{17}NONa$ $[M+Na]^+$ 262.1055; found, 262.1055.

[1] Signals belonging to the protons and carbons involved in the keto-enol tautomerization of the β-ketoamide do not appear due to long relaxation times.

Allyl (2-diazo-3-oxobutanoyl)-L-prolinate (163):



162 **163**

Acetoacetyl amide **162** (8.18 g, 34.2 mmol), ABSA (8.22 g, 34.2 mmol) and Et_3N (14.3 mL mL, 103 mmol) were dissolved in 100 mL THF. Reaction mixture was stirred at room temperature in absence of light for 72 hours. Crude mixture was filtered through plug of silica and Na_2SO_4 *[1]* (about 5 cm of silica and on top of it about 5 cm of Na_2SO_4). Filtrate was concentrated, suspended in 30 mL of CH_2Cl_2 and filtered once more through plug of silica and Na_2SO_4. After concentrating, the crude solid was purified by flash column chromatography (PE:EtOAc 1:1 to EtOAc, $KMnO_4$) giving diazo compound **163** (6.90 g, 26 mmol) as a yellow oil in 76% yield over previous 2 steps.

Rf: 0.68 (EtOAc, $KMnO_4$)

$[\alpha]_D^{20}$ = −49.5 (1.0, $CHCl_3$).

^{1}H NMR (400 MHz, CD_3CN) δ 5.91 – 6.01 (m, 1H), 5.36 (ddt, *J* = 1.5, 1.6, 17.1 Hz, 1H), 5.25 (ddt, *J* = 1.4, 1.5, 10.5 Hz, 1H), 4.62 (dt, *J* = 1.5, 5.4 Hz, 2H), 4.48 – 4.51 (m, 1H), 3.57 (t, *J* = 6.6 Hz, 2H), 2.32 (s, 3H), 2.27 – 2.35 (m, 1H), 1.92 – 2.07 (m, 3H).

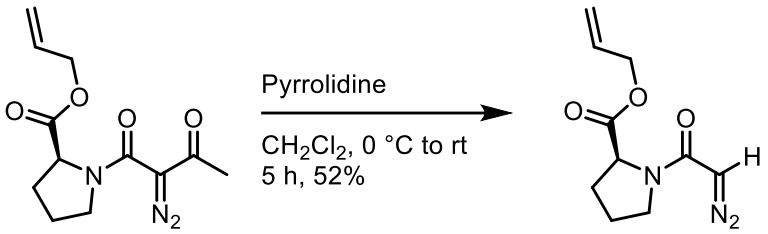
^{13}C NMR (101 MHz, CD_3CN) δ 190.8, 172.5, 160.6, 133.3, 118.0, 74.1, 66.1, 60.9, 49.3, 30.2, 27.9, 25.6. *[2]*

HRMS (ESI) calcd for $C_{12}H_{15}N_3O_4Na$ $[M+Na]^+$ 288.0960; found, 288.0959.

[1] Use a column with wide circumference, column clogs rapidly if no Na_2SO_4 is used.

[2] ^{13}C signals belonging to diazo (74.1 ppm) and β-keto (190.8 ppm) carbons are difficult to observe.

Allyl (2-diazoacetyl)-L-prolinate (135):



163 **135**

Diazo compound **163** (1.02 g, 3.77 mmol) was dissolved in 25 mL CH_2Cl_2 and freshly distilled pyrrolidine *[1]* (3.1 mL, 37.7 mmol) was added at 0 °C. Reaction mixture was stirred for 5 hours *[2]* at room temperature. Then the reaction mixture was washed 4 x 20 mL H_2O. Organic layer was dried over Na_2SO_4, filtered, volatiles removed under reduced pressure and purified by flash column chromatography (PE:EtOAc 1:1 to 1:2). Deacylated diazo compound **135** (437 mg, 1.96 mmol) was obtained in 52% yield as a yellow oil.

R_f: 0.32 (PE:EtOAc 1:1, $KMnO_4$).

$[\alpha]_D^{20}$ = −61.3 (1.0, $CHCl_3$).

^{1}H NMR (400 MHz, CD_3CN) δ 5.88 – 5.99 (m, 1H), 5.33 (ddt, *J* = 1.5, 1.6, 17.2 Hz, 1H), 5.17 – 5.24 (m, 2H), 4.57 – 4.62 (m, 2H), 4.38 – 4.49 (m, 1H), 3.27 – 3.55 (m, 2H), 2.10 – 2.2.9 (m, 2H), 1.89 – 2.01 (m, 2H).

^{13}C NMR (101 MHz, CD_3CN) δ 173.8, 165.8, 134.1, 118.0, 66.8, 66.6, 60.6, 47.9, 30.7, 25.9. *[3]*

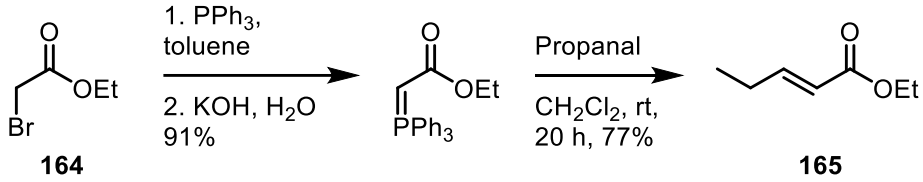
HRMS (ESI) calcd for $C_{10}H_{13}N_3O_3Na$ $[M+Na]^+$ 246.0855; found, 246.0848.

[1] With older pyrrolidine the yields steadily decrease. Any aqueous base leds to decomposition.

[2] Incomplete conversion but longer reaction times did not increase the yield.

[3] One of the double bond signals appears under the solvent signal.

Ethyl (*E*)-pent-2-enoate (165):



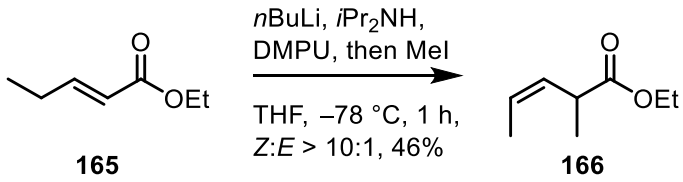
4 L 3-necked flask was equipped with mechanical stirrer. PPh_3 (262 g, 1.00 mol) was dissolved in 1.0 L toluene and ethyl bromoacetate (**164**) (110 mL, 1.00 mol) was added through dropping funnel in a course of 1 hour at room temperature. Mixture was stirred 20 h at room temperature. Formed solid Wittig salt was filtered and dried overnight in air to remove most of the toluene. Then, it was charged into 800 mL water (about 400 mL water for 200 g salt) and put on rotary evaporator auto mode – salt dissolves and some additional amount of toluene is removed (best not to remove all toluene or formed Wittig reagent will be very hard solid). KOH solution was added and kept on rotary evaporator until solution turned clear with solid pieces of Wittig reagent floating on top of the solution. If some product falls out as an oil, then evaporation is continued until it turns solid. Product is filtered, washed once with H_2O, crushed into small pieces with mortar and pestle and dried overnight under high-vacuum (about 0.1-0.2 mbar). Wittig reagent (316 g, 0.91 mol) was obtained as a white solid in 91% yield.

Propanal (33.2 mL, 463 mmol) was mixed with 1.2 L CH_2Cl_2 and Wittig reagent (193 g, 553 mmol) was added in one portion. Reaction mixture was stirred 20 h at room temperature, concentrated under reduced pressure and 100 mL pentane was added to the flask. Mixture was kept 10 min at room temperature, filtered and solid was washed with pentane. Filtrate was concentrated and pentane added once more. This process was repeated 3 times, until no more triphenylphosphine oxide crystallized out. The crude mixture was purified by vacuum distillation (50 mbar, 63 °C) and title compound **165** (45.8 g, 357 mmol) was obtained as clear colorless liquid in 77% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (dt, *J*=15.7, 6.4 Hz, 1H), 5.80 (dt, *J*=15.7, 1.6 Hz, 1H), 4.17 (q, *J* =7.2 Hz, 2H), 2.18 – 2.25 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.06 (t, *J* = 7.4 Hz, 3H).

^{1}H NMR data matched literature values.[203]

Ethyl (*Z*)-2-methylpent-3-enoate (166):



165 **166**

DIPA (59.0 mL, 421 mmol) in 350 mL THF was cooled to −78 °C and *n*BuLi 2.5 M (154 mL, 386 mmol) was added through a dropping funnel in a course of 20 minutes. Mixture was stirred 10 min at −78 °C and then warmed to 0 °C and stirred for additional 35 min. Then, it was cooled to −78 °C and DMPU (46.4 mL, 386 mmol) was added over the course of 40 min through a syringe pump. Mixture was stirred 30 min at that temperature and ester **165** (45.0 g, 351 mmol) in 40 mL THF was added dropwise in the course of 15 min. Reaction mixture was stirred for 30 min and MeI *[1]* (26.1 mL, 421 mmol) was added over the course of 20 min. Mixture was stirred for additional 1 h, then 50 mL H_2O was added and mixture warmed to room temperature. Additional 100 mL H_2O was added and layers separated. Aqueous layer was washed 3 x 50 mL Et_2O, combined organic phases were washed once with H_2O, once with brine, dried over $MgSO_4$, filtered and concentrated. Crude product was purified by vacuum distillation *[2]* (40 mbar, 63-65 °C) to give title compound **166** (23.0 g, 161 mmol) as a clear colorless liquid in 46% yield and with *Z*:*E* ratio 94:6.

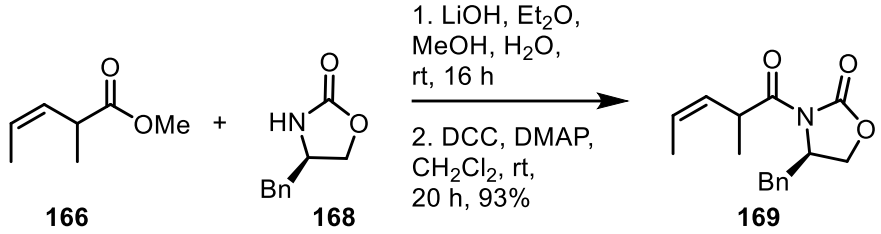
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50 – 5.59 (m, 1H), 5.38 – 5.44 (m, 1H), 4.11 (q, *J* = 7.3 Hz, 1H), 3.38 – 3.46 (m, 1H), 1.65 (dd, *J* = 6.9, 1.7 Hz, 3H). 1.23 (q, *J* = 7.3 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.27, 129.78, 125.94, 60.57, 37.97, 17.93, 14.30, 13.07.

[1] Previous procedures usually recommend using up to 5 equivalents of MeI, reaction monitoring by GC shows that the starting material is completely consumed already after addition of 1 equivalent of MeI.

[2] Distillation should be performed very carefully as compound is prone to bumping (superheating).

(4*R*)-4-Benzyl-3-((*Z*)-2-methylpent-3-enoyl)oxazolidin-2-one (169):



Ester **166** (23.0 g, 162 mmol) was dissolved in a mixture of 120 mL MeOH and 400 mL Et_2O. To this mixture, LiOH (19.0 g, 809 mmol) *[1]* in 200 mL H_2O was added and reaction stirred at room temperature for 20 h, after which TLC showed complete consumption of starting material. Reaction mixture was acidified with 2 M aqueous HCl and extracted 4 x 70 mL Et_2O. Combined organic phases were dried over Na_2SO_4. Volatiles were removed under reduced pressure, and residual MeOH and H_2O were removed by adding EtOAc and toluene, respectively, to the crude product and removing the volatiles under reduced pressure *[2]*. Corresponding acid (18.5 g, 162 mmol) was obtained as colorless liquid in quantitative yield. Crude material was used directly in the next reaction.

Acid derived from ester **166** (9.8 g, 86 mmol), Evans auxiliary **168** (15.3 g, 86 mmol) and DCC (17.7 g, 86 mmol) were dissolved in 120 mL CH_2Cl_2 and cooled on ice-water bath. DMAP (1.5 g, 19 mmol) was added in one portion. Mixture was stirred 1 h at 0 °C and then 19 h at room temperature. The precipitate was filtered, washed twice with CH_2Cl_2 and organic phase washed with H_2O, brine and dried over $MgSO_4$. Crude product was purified by flash column chromatography (PE:EtOAc 5:1), which yielded oxazolidinone **169** (22.0 g, 78 mmol) as viscous liquid in 93% yield as an inconsequential mixture of diastereomers *[3]*.

R_f: 0.43 (PE:EtOAc 4:1, $KMnO_4$).

$[\alpha]_D^{20}$ = -28.0 (1.0, $CHCl_3$) for mixture of diastereomers; -87.0 and +15.6 for pure compounds.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.34 (m, 3H), 7.18 – 7.21 (m, 2H), 5.50 – 5.73 (m, 2H), 4.80 – 4.88 (m, 1H), 4.66 – 4.72 (m, 1H), 4.13 – 3.23 (m, 2H), 3.20 – 3.27 (m, 1H), 2.73 – 2.80 (m, 1H), 1.73 (d, *J* = 6.7 Hz, 3H), 1.27 (d, *J* = 6.8 Hz, 3H). Mixture of diastereomers.

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.0, 175.9, 153.2, 153.1, 135.4, 135.3, 129.6, 129.4, 129.2, 129.1, 129.0, 127.5, 127.4, 127.0, 126.7, 66.2, 66.0, 55.6, 55.3, 38.0, 37.9, 36.4, 36.3, 18.5, 18.3, 13.5, 13.4. Mixture of diastereomers.

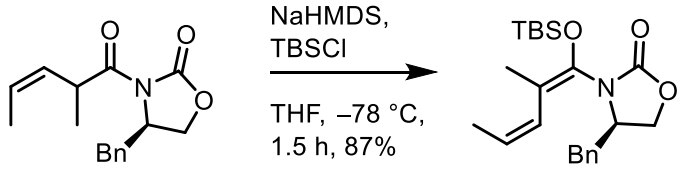
NMR values and optical rotation matched literature values.[144]

[1] Previously, 1 eq. of LiOH has been used. In my hands, that led only to partial conversion.

[2] Care should be taken to remove all residual MeOH and H_2O for the coupling to proceed reliably.

[3] Diastereomers are separable on silica if so desired.

(*R*)-4-Benzyl-3-((1*E*,3*Z*)-1-((*tert*-butyldimethylsilyl)oxy)-2-methylpenta-1,3-dien-1-yl)oxazolidin-2-one (134):



169 **134**

Oxazolidinone **169** (14.2 g, 52.0 mmol) in 150 mL THF was cooled to −78 °C and NaHMDS (39 mL, 77.9 mmol, 2 M in THF) was added over 10 minutes. The mixture was stirred at −78 °C for 90 minutes and then TBSCl (15.7 g, 104 mmol) in 40 mL THF was added through a syringe pump in the course of 40 minutes. The reaction mixture was stirred for additional 1.5 h and then quenched by addition of sat. aq. NH_4Cl solution. The mixture was warmed to room temperature, diluted with H_2O and extracted 3 x EtOAc. Combined organic layers were washed with brine and dried over Na_2SO_4. Volatiles were removed under reduced pressure and crude product purified by flash column chromatography (PE:EtOAc 10:1) yielding product **134** (17.6 g, 45.2 mmol) as colorless oil in 87% yield.

R_f: 0.57 (PE:EtOAc 4:1, $KMnO_4$)

$[\alpha]_D^{20}$ = +63 (1.0, $CHCl_3$).

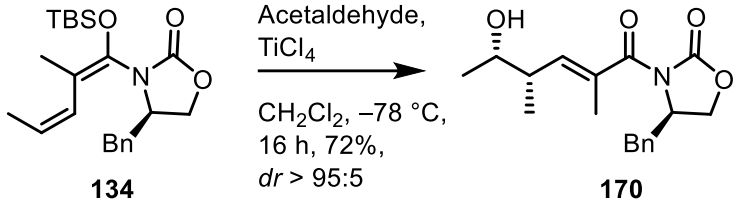
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.35 (m, 3H), 7.15 – 7.17 (m, 2H), 5.99 (d, *J* = 11.5 Hz, 1H), 5.52 (dq, *J* = 11.5 Hz, 6.5 Hz), 4.20 – 4.26 (m, 2H), 4.04 – 4.10 (m, 1H), 3.20 – 3.24 (m, 1H), 2.59 – 2.64 (m, 1H), 1.96 (s, 3H), 1.80 (dd, *J* = 7.3, 1.6 Hz, 3H), 1.02 (s, 9H), 0.26 (s, 3H), 0.20 (s, 3H). Signals for the major rotamer.

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9, 136.0, 135.4, 129.0, 127.2, 126.9, 126.3, 115.7, 68.0, 56.9, 39.1, 25.8, 18.2, 16.4, 15.2, −4.3, −4.5. *[1]*

HRMS (ESI) calcd for $C_{22}H_{34}NO_3Si$ $[M+H]^+$ 388.2308; found, 388.2312.

[1] One of the carbon signals overlaps with the signal at 129.0 ppm. Several others are very wide and low intensity.

(*R*)-4-Benzyl-3-((4*S*,5*S*,*E*)-5-hydroxy-2,4-dimethylhex-2-enoyl)oxazolidin-2-one (170):



Acetaldehyde (1.27 mL, 22.7 mmol) *[1]* was dissolved in 100 mL CH_2Cl_2 and cooled to −78 °C. $TiCl_4$ (11.35 mL, 11.35 mmol, 1 M in CH_2Cl_2) was added dropwise and reaction mixture stirred at −78 °C for 30 minutes. Keteneacetal **134** (4.40 g, 11.35 mmol) in 15 mL CH_2Cl_2 was added in the course of 5 minutes. Reaction was stirred 16 h at −78 °C and was then quenched with 100 mL of half-saturated aqueous $NaHCO_3$ solution. Organic layer was diluted with EtOAc and separated. Aqueous layer extracted 3 x EtOAc. Combined organic layers were dried over Na_2SO_4 and volatiles removed under reduced pressure. Crude product was purified by flash column chromatography (PE:EtOAc 6:1 to 1:1) *[2]* and oxazolidinone **170** (2.58 g, 8.13 mmol) was obtained as white crystalline solid in *dr* > 95:5 and in 72% yield *[3]*.

R_f: 0.57 (PE:EtOAc 4:1, $KMnO_4$).

$[\alpha]_D^{20}$ = -28 (1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.36 (m, 3H), 7.19 – 7.23 (m, 2H), 5.74 (dq, *J* = 10.4, 1.5 Hz, 1H), 4.66-4.72 (m, 1H), 4.25 (d, *J* = 8.5 Hz, 1H), 4.20 (d, *J* = 4.5 Hz, 1H), 3.72 – 3.79 (m, 1H), 3.35 (d, *J* = 3.5 Hz, 1H), 2.87 (d, *J* = 9.3 Hz, 1H), 2.66 – 2.75 (m, 1H), 1.98 (d, *J* = 1.5 Hz, 3H), 1.15 (d, *J* = 6.5 Hz, 3H), 1.05 (d, *J* = 7.0 Hz, 3H). Signals for the major rotamer.

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 153.4, 138.5, 135.2, 132.0, 129.6, 129.1, 127.5, 71.8, 66.5, 55.7, 39.8, 37.6, 19.6, 15.5, 14.4.

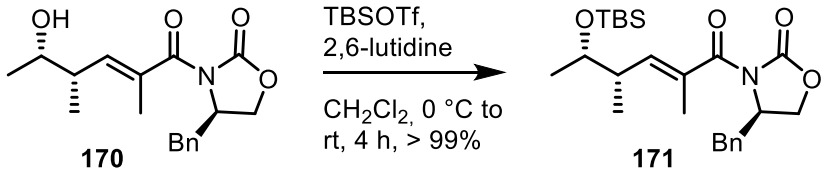
HRMS (ESI) calcd for $C_{18}H_{23}NO_4Na$ $[M+Na]^+$ 340.1525; found, 340.1524.

[1] Boiling point of acetaldehyde is 21 °C, therefore reagent is NOT warmed to room temperature before use. Measuring small quantities (under 200 μL) is complicated.

[2] Generally, unreacted starting material comes at 2:1 ratio and product starts coming at 1:1 ratio.

*[3] Reaction performed on 15 g scale had yield of 50%, probably due to older $TiCl_4$ and/or keteneacetal **134**.*

(*R*)-4-Benzyl-3-((4*S*,5*S*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-2,4-dimethylhex-2-enoyl)oxazolidin-2-one (171):



Oxazolidinone **170** (6.24 g, 19.7 mmol) was dissolved in 180 mL CH_2Cl_2 and 2,6-lutidine (5.03 mL, 43.3 mmol) was added. The mixture was cooled to 0 °C and TBSOTf (5.88 mL, 25.6 mmol) was added. Reaction mixture gradually warmed to room temperature and was stirred for 4 h. The reaction was quenched with 150 mL aq. Sat. $NaHCO_3$ solution, layers separated and aqueous layer extracted 3 times with CH_2Cl_2. Combined organic layers were dried over Na_2SO_4 and volatiles removed under reduced pressure. Crude product was purified by flash column chromatography (PE:EtOAc 10:1 to 5:1) and protected alcohol **171** (8.5 g, 19.7 mmol) was obtained as a clear colorless liquid in quantitative yield.

R_f: 0.31 (PE:EtOAc 9:1, $KMnO_4$).

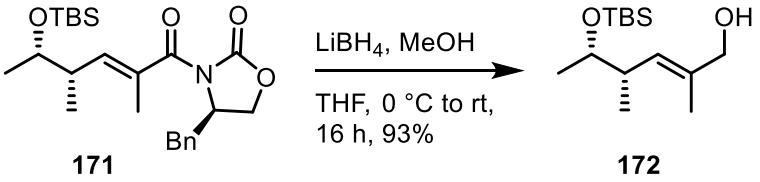
$[\alpha]_D^{20}$ = -31 (1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.35 (m, 3H), 7.19 – 7.21 (m, 2H), 5.90 (dq, *J* = 10.4, 1.5 Hz, 1H), 4.66-4.74 (m, 1H), 4.18 (ddd, *J* = 39.1, 9.2, 8.3 Hz, 2H), 3.59 – 3.66 (m, 1H), 3.36 (dd, *J* = 13.4, 3.3 Hz, 1H), 2.82 (d, *J* = 13.4, 9.2 Hz, 1H), 2.45 – 2.55 (m, 1H), 1.93 (d, *J* = 1.5 Hz, 3H), 1.15 (d, *J* = 6.2 Hz, 3H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H). Signals for the major rotamer.

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 153.2, 142.5, 135.4, 129.9, 129.6, 129.1, 127.5, 71.8, 66.5, 55.7, 41.5, 37.7, 26.0, 22.2, 18.2, 15.5, 13.9, -4.1, -4.7.

HRMS (ESI) calcd for $C_{24}H_{37}NO_4NaSi$ $[M+Na]^+$ 454.2390; found, 454.2395.

(4*S*,5*S*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-2,4-dimethylhex-2-en-1-ol (172):



171 **172**

TBS-protected alcohol **171** (3.55 g, 8.24 mmol) was dissolved in 40 mL THF and MeOH (1.67 mL, 41.2 mmol) was added. Mixture was cooled to 0 °C and $LiBH_4$ (10.3 mL, 41.2 mmol, 4 M in THF) was added dropwise. Mixture was gradually warmed to room temperature and stirred for 16 h. Reaction was quenched by addition of 40 mL 2 M aqueous HCl and extracted 2 times with EtOAc. Combined organic phases were washed with saturated aqueous $NaHCO_3$ and dried over Na_2SO_4. Volatiles were removed under reduced pressure and crude product purified by flash column chromatography (PE:EtOAc 9:1). The alcohol **172** (1.99 g, 7.65 mmol) was obtained as clear colourless liquid in 93% yield.

R_f: 0.27 (PE:EtOAc 9:1, $KMnO_4$). *[1]*

$[\alpha]_D^{20}$ = +7.9 (1.0, $CHCl_3$).

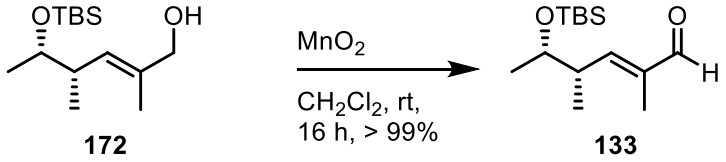
^{1}H NMR (400 MHz, MeOH-d_4) δ 5.25 (dq, *J* = 9.9, 1.3 Hz, 1H), 3.92 (s, 2H), 3.61 (quint, *J* = 6.7 Hz, 1H), 2.34 – 2.43 (m, 1H), 1.66 (d, *J* = 1.3 Hz, 3H), 1.10 (d, *J* = 6.1 Hz, 3H) 0.96 (d, *J* = 6.7 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).

^{13}C NMR (101 MHz, MeOH-d_4) δ 135.5, 130.1, 74.0, 69.0, 41.6, 26.4, 22.3, 19.0, 17.2, 14.2, −4.1, −4.6.

HRMS (ESI) calcd for $C_{14}H_{30}O_2NaSi$ $[M+Na]^+$ 281.1913; found, 281.1911.

[1] Starting material and product spots overlap on TLC but product is not UV active..

(4*S*,5*S*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-2,4-dimethylhex-2-enal (133):



172 **133**

TBS-protected alcohol **172** (1.45 g, 5.61 mmol) was dissolved in 10 mL CH_2Cl_2 and MnO_2 (9.75 g, 112 mmol) was added in one portion *[1]*. The reaction mixture was stirred for 16 h at room temperature. Subsequently, the crude mixture was filtered through plug of celite® and solvent removed under reduced pressure. Crude aldehyde **133** (1.44 g, 5.60 mmol) was used directly in the next reaction without further purification *[2]*.

R_f: 0.62 (PE:EtOAc 9:1, $KMnO_4$).

$[\alpha]_D^{20}$ = +6.7 (1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (s, 1H), 6.36 (dq, *J* = 10.2, 1.4 Hz, 1H), 3.74 (quint, *J* = 6.4 Hz, 1H), 2.64 – 2.73 (m, 1H), 1.76 (d, *J* = 1.3 Hz, 3H), 1.12 (d, *J* = 6.2 Hz, 3H) 1.06 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H).

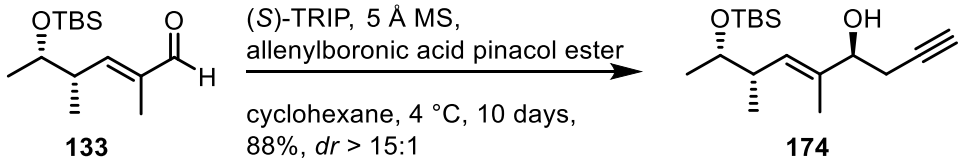
^{13}C NMR (101 MHz, $CDCl_3$) δ 195.7, 157.5, 138.7, 71.5, 41.6, 26.0, 21.7, 18.2, 15.3, 9.7, −4.1, −4.7.

HRMS (ESI) calcd for $C_{14}H_{28}O_2NaSi$ $[M+Na]^+$ 279.1756; found, 279.1755.

[1] Using less than 20 eq. MnO_2 led to slower conversion and additional amount of MnO_2 was added on the next day to drive reaction to completeness.

[2] Aldehyde could be columned with PE:EtOAc 20:1 and purification was critical for the next reaction. Aldehyde should not be stored but freshly prepared.

(4*S*,7*S*,8*S*,*E*)-8-((*tert*-butyldimethylsilyl)oxy)-5,7-dimethylnon-5-en-1-yn-4-ol (174):



133 **174**

Freshly activated 5 Å MS (2.73 g, 0.5 g/mmol) and (*S*)-TRIP catalyst (311 mg, 0.41 mmol) were charged into a 50 mL round-bottomed flask. Flask was evacuated and backfilled with argon. Freshly prepared aldehyde **133** (1.34 g, 5.22 mmol) in 27 mL cyclohexane was transferred to the reaction flask, which was then cooled to 8 °C. Allenylboronic acid pinacol ester (1.96 mL, 10.9 mmol) *[1]* was added dropwise and mixture stirred at 4 °C for 10 days *[2]*. Thereafter, the reaction mixture was diluted with 20 mL EtOAc and filtered through a plug of celite®. Filtrate was washed with 50 mL 1 M aqueous NaOH solution and aqueous layer was extracted 3 times with EtOAc. The combined organic layers were washed once with brine and dried over Na_2SO_4. Crude product was purified by flash column chromatography (PE:EtOAc 10:1) to yield alcohol **174** (1.37 g, 4.62 mmol) as a colorless oil in 88% yield.

R_f: 0.43 (PE:EtOAc 9:1, Vanilline).

$[\alpha]_D^{20}$ = +2.8 (1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.32 (td, *J* = 1.0, 9.9 Hz, 1H), 4.16 (t, *J* = 6.3 Hz, 1H), 3.56 (quint, *J* = 6.5 Hz, 1H), 2.46 (dd, *J* = 2.6, 6.3 Hz, 2H), 2.32 – 2.41 (m, 1H), 2.02 (t, *J* = 2.6 Hz, 1H), 1.83 (br, 1H), 1.64 (d, *J* = 1.3 Hz, 3H), 1.09 (d, *J* = 6.2 Hz, 3H) 0.94 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 134.7, 130.6, 81.1, 75.3, 72.6, 70.7, 40.5, 26.0, 26.0, 22.0, 18.3, 16.9, 12.5, −4.1, −4.6. *[3]*

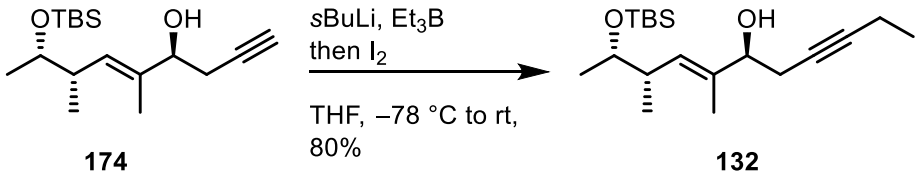
HRMS (ESI) calcd for $C_{17}H_{32}O_2NaSi$ $[M+Na]^+$ 319.2069; found, 319.2072.

[1] The boronic ester was distilled or used from freshly opened bottle.

[2] Reaction rate (but not diastereoselectivity) seems to depend significantly on the purity of (S)-TRIP catalyst. Freshly bought (S)-TRIP led to full consumption of starting material in 20 h but older catalyst required up to 10 days for full conversion.

[3] In some cases, the signals at 26.0 ppm are overlapping and not distinguishable from each other.

(6*S*,9*S*,10*S*,*E*)-10-((*tert*-butyldimethylsilyl)oxy)-7,9-dimethylundec-7-en-3-yn-6-ol (132):



174 **132**

Termianl alkyne **174** (250 mg, 0.84 mmol) was co-evaporated with toluene 3 times and dissolved in 8 mL dry THF. The reaction mixture was cooled to −78 °C and *s*BuLi (1.3 mL, 1.68 mmol, 1.3 M in hexane) was added. Reaction mixture was stirred 1 hour at −78 °C and then warmed to 0 °C. Et_3B (1.7 mL, 1.68 mmol, 1 M in THF) was added, stirred 10 minutes at 0 °C and cooled to −78 °C. Iodine (429 mg, 1.68 mmol) in 1.5 mL dry MeOH was added dropwise. The reaction mixture was stirred for 30 minutes and NaOMe (364 mg, 6.74 mmol) in 2 mL dry MeOH was added *[1]*. The reaction mixture was stirred for additional 50 min at −78 °C and 2 hour at room temperature. The mixture was treated with 20 mL saturated $Na_2S_2O_3$ solution and aqueous layer was extracted 3 times with Et_2O. The combined organic layers were dried over Na_2SO_4. The crude product was purified by flash column chromatography (PE:EtOAc 10:1) giving the alcohol **132** (221 mg, 0.68 mmol) in 80% yield as a colorless oil.

R_f: 0.57 (PE:EtOAc 9:1, $KMnO_4$).

$[\alpha]_D^{20}$ = −2.4 (1.0, $CHCl_3$).

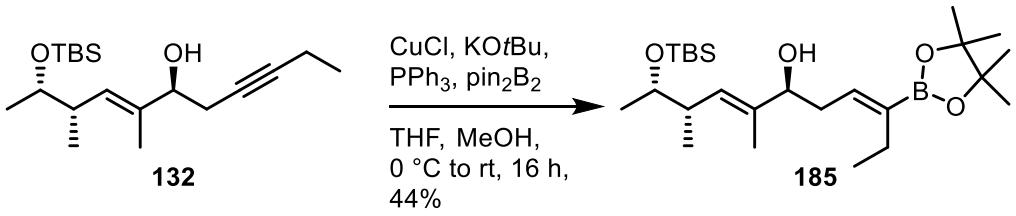
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29 (dt, *J* = 9.9, 1.0 Hz, 1H), 4.07 – 4.11 (m, 1H), 3.51 – 3.58 (m, 1H), 2.40 – 2.43 (m, 2H), 2.31 – 2.38 (m, 1H), 2.16 (qt, *J* = 7.4, 2.4 Hz, 2H), 1.97 (d, *J* = 3.6 Hz, 1H), 1.63 (d, *J* = 1.3 Hz, 3H), 1.11 (t, *J* = 7.6 Hz, 3H), 1.09 (d, *J* = 6.0 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.0, 130.2, 84.7, 75.6, 75.5, 72.7, 40.5, 26.5, 26.1, 22.1, 18.3, 17.0, 14.3, 12.6, 12.6, −4.1, −4.6.

HRMS (ESI) calcd for $C_{14}H_{28}O_2SiNa$ $[M+Na]^+$ 347.2380; found, 347.2382.

[1] Iodine and NaOMe were not easily soluble in MeOH and required sonication.

(3*Z*,6*S*,7*E*,9*S*,10*S*)-10-((*tert*-butyldimethylsilyl)oxy)-7,9-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)undeca-3,7-dien-6-ol (185):



CuCl (1.8 mg, 0.019 mmol), KO*t*Bu (8.3 mg, 0.74 mmol) and PPh_3 (5.8 mg, 0.022 mmol) were dissolved in 100 µL THF and stirred at room temperature for 30 minutes giving a black suspension *[1]*. That solution was added to B_2pin_2 (52 mg, 0.20 mmol) in 1 mL THF and stirred for additional 15 minutes. The solution was cooled to 0 °C and alkyne **132** (60 mg, 0.19 mmol) and MeOH (15 µL, 0.37 mmol) in 500 µL THF were added. The reaction mixture was stirred at room temperature for 16 h and quenched with sat. aq. NH_4Cl solution. The aqueous layer was extracted 3 times with Et_2O, combined organics were dried over Na_2SO_4. Crude product was purified by flash column chromatography (PE:Et_2O 5:1 to 2:1) giving the boronic ester **185** (37 mg, 0.082 mmol) in 44% yield (72% brsm) as colorless oil.

R_f: 0.29 (PE:EtOAc 10:1, $KMnO_4$).

$[\alpha]_D^{20}$ = −4.5 (1.0, $CHCl_3$).

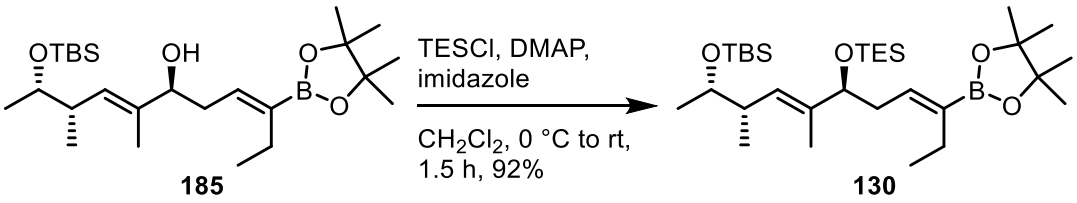
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21 (t, *J* = 6.8 Hz, 1H), 5.24 (dt, *J* = 9.9, 1.2 Hz, 1H), 4.08 (t, *J* = 6.1 Hz, 1H), 3.52 – 3.59 (m, 1H), 2.29 – 2.47 (m, 3H), 2.15 (q, *J* = 7.4 Hz, 2H), 1.63 (d, *J* = 1.3 Hz, 3H), 1.52 (d, *J* = 2.5 Hz, 1H), 1.24 (s, 12H), 1.09 (d, *J* = 6.2 Hz, 3H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.5, 135.9, 129.9, 83.2, 76.9, 72.7, 40.5, 34.3, 26.1, 24.9, 22.2, 22.1, 18.3, 17.0, 14.8, 12.4, −4.1, −4.6.

HRMS (ESI) calcd for $C_{25}H_{49}O_4BSiNa$ $[M+Na]^+$ 475.3391; found, 475.3392.

[1] Stock solution using 10 times larger amounts was prepared and used.

(5*S*,8*S*,9*S*,*E*)-3,3-diethyl-6,8,9,11,11,12,12-heptamethyl-5-((*Z*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-2-en-1-yl)-4,10-dioxa-3,11-disilatridec-6-ene (130):



Alcohol **185** (31 mg, 68 µmol) was dissolved in 2 mL dry CH_2Cl_2. Imidazole (7 mg, 103 µmol) and catalytic amount of DMAP were added. Reaction mixture was cooled to 0 °C and TESCl (14 µL, 83 µmol) was added. The reaction mixture was stirred 30 minutes at that temperature and 60 minutes without external cooling. The reaction mixture was treated with sat. aq. $NaHCO_3$ solution, layers were separated and aqueous layer was extracted 3 times with CH_2Cl_2. Combined organic layers were dried over Na_2SO_4 and volatiles were removed under reduced pressure. The crude product was purified by flash column chromatography (PE:Et_2O 97:3 to 95:5) giving the boronic ester **130** (35 mg, 62 µmol) in 92% yield as a colorless oil.

R_f: 0.82 (PE:EtOAc 10:1, $KMnO_4$).

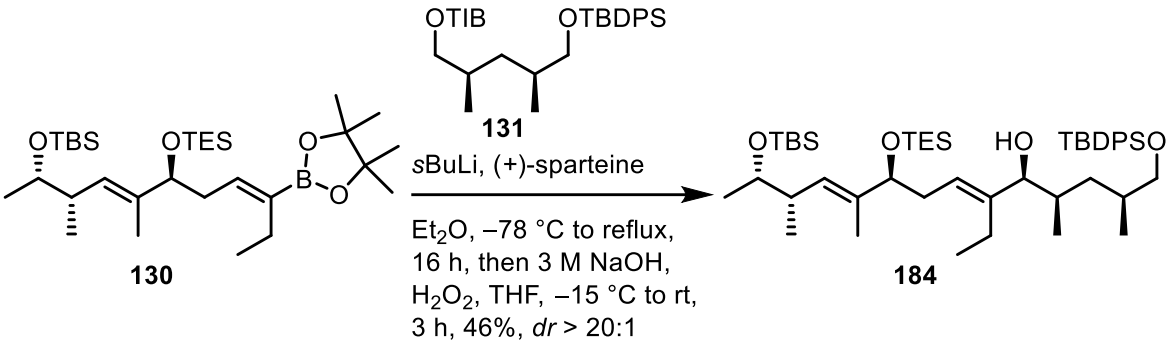
$[\alpha]_D^{20}$ = −1.2 (1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.18 (t, *J* = 7.0 Hz, 1H), 5.12 (d, *J* = 9.9 Hz, 1H), 4.01 (t, *J* = 6.8 Hz, 1H), 3.47 – 3.55 (m, 1H), 2.28 – 2.35 (m, 3H), 2.11 (q, *J* = 7.5 Hz, 2H), 1.58 (d, *J* = 1.1 Hz, 3H), 1.23 (s, 12H), 1.08 (d, *J* = 6.1 Hz, 3H), 0.91 (t, *J* = 8.0 Hz, 9H), 0.90 (s, 9H), 0.89 – 0.94 (m, 6H), 0.56 (q, *J* = 8.0 Hz, 6H), 0.05 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.0, 136.5, 129.0, 83.0, 78.2, 72.9, 40.7, 35.6, 26.1, 24.9, 22.2, 22.0, 18.3, 17.3, 14.9, 11.6, 7.0, 4.9, −4.1, −4.6.

HRMS (ESI) calcd for $C_{31}H_{63}O_4BSi_2Na$ $[M+Na]^+$ 589.4256; found, 589.4257.

(6*S*,8*R*,9*S*,10*E*,13*S*,14*E*,16*S*,17*S*)-10-ethyl-2,2,6,8,14,16,17,19,19,20,20-undecamethyl-3,3-diphenyl-13-((triethylsilyl)oxy)-4,18-dioxa-3,19-disilahenicosa-10,14-dien-9-ol (184):



A solution of TIB ester **131** (44 mg, 0.074 mmol) and (+)-sparteine (19 µL, 0.080 mmol) in 0.62 mL dry Et_2O under argon was cooled to −78 °C. *s*BuLi (60 µL, 0.078 mmol, 1.3 M in cyclohexane) was added dropwise and the reaction mixture was stirred at −78 °C for 4.5 hours. Next, boronic ester **130** (31 mg, 0.055 mmol) dissolved in 0.3 mL Et_2O was added dropwise and the reaction mixture, which turned light brown, was stirred for 1 h before being allowed to warm up to room temperature. The reaction mixture was then heated at reflux for 16 h. The reaction was quenched with the addition of sat. aq. NH_4Cl solution, diluted with water and extracted 3 times with Et_2O. The combined organic extracts were dried over $MgSO_4$, volatiles removed under reduced pressure and crude product was purified by flash column chromatography (PE:Et_2O, 100:1 to 97:3) yielding intermediary boronic ester (32.5 mg, 0.036 mmol) as a colorless oil in 65% yield. The boronic ester (7.0 mg, 0.0076 mmol) was dissolved in 0.5 mL THF and cooled to −15 °C. A freshly prepared solution of 30% H_2O_2 and 3 M NaOH (1:1, 0.15 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature and monitored by TLC until no more boronic ester remained. The solution was cooled to 0 °C and quenched by a dropwise addition of saturated aqueous $Na_2S_2O_3$. Aqueous phase was extracted 3 times with Et_2O and the combined organic extracts were dried over $MgSO_4$, filtered, concentrated under reduced pressure and purified by flash column chromatography (PE:Et_2O 100:1 to 25:1) yielding alcohol **184** as a colorless oil (4 mg, 0.0049 mmol) in 70% yield with no observable amount of epimer, overall yield over 2 steps was 46%.

R_f: 0.15 (PE:Et_2O 25:1, CAM).

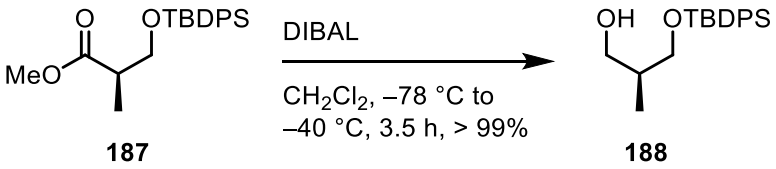
$[\alpha]_D^{20}$ = −2.0 (0.4, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.67 (m, 4H), 7.35 – 7.44 (m, 6H), 5.25 (t, *J* = 7.1 Hz, 1H), 5.11 (d, *J* = 10.2 Hz, 1H), 3.95 (t, *J* = 6.7 Hz, 1H), 3.83 (t, *J* = 4.3 Hz, 1H), 3.49 – 3.56 (m, 2H), 3.38 – 3.43 (m, 1H), 2.23 – 2.36 (m, 3H), 1.96 – 2.05 (m, 1H), 1.85 – 1.92 (m, 1H), 1.63 – 1.78 (m, 2H), 1.59 (d, *J* = 1.2 Hz, 3H), 1.41 – 1.48 (m, 1H), 1.20 – 1.33 (m, 1H), 1.15 (d, *J* = 3.6 Hz, 1H), 1.09 (d, *J* = 6.3 Hz, 3H), 1.05 (s, 9H), 0.89 (s, 9H), 0.89 – 0.97 (m, 26H), 0.78 (d, *J* = 6.9 Hz, 3H), 0.56 (q, *J* = 7.8 Hz, 6H), 0.05 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5, 136.7, 135.8, 135.8, 134.2, 134.1, 129.6, 129.2, 127.7, 122.1, 78.7, 78.7, 72.9, 68.7, 40.6, 38.0, 34.7, 33.3, 33.3, 27.0, 26.1, 22.2, 21.5, 19.5, 18.3, 18.3, 17.5, 14.3, 14.1, 11.6, 7.1, 5.0, −4.1, −4.6.

HRMS (ESI) calcd for $C_{48}H_{84}O_4Si_3Na$ $[M+Na]^+$ 831.5575; found, 831.5579.

(*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-methylpropan-1-ol (188):



187 **188**

Ester **187** (5.70 g, 16.0 mmol) was dissolved in 80 mL dry CH_2Cl_2 and cooled to −78 °C. DIBAL (40 mL, 40 mmol, 1M in THF) was added with a syringe pump over 50 minutes. The reaction mixture was gradually warmed to −40 °C and stirred at that temperature for 3.5 hours. The reaction mixture was quenched by adding 100 mL aqueous solution of sodium potassium tartrate and vigorously stirred for 16 hours. Organic phase was separated and aqueous layer was extracted 4 times with EtOAc. The combined extracts were dried over Na_2SO_4 and volatiles removed under reduced pressure. The crude alcohol **188** (5.25 g, 16.0 mmol) was used in the subsequent reaction without further purification.

R_f: 0.17 (PE:EtOAc 10:1, $KMnO_4$).

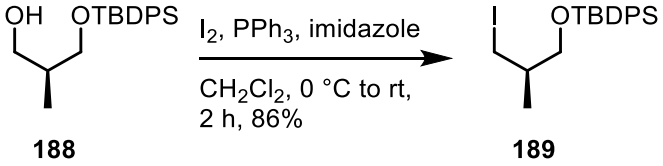
$[\alpha]_D^{20}$ = −4.9 (1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.70 (m, 4H), 7.39 – 7.47 (m, 6H), 3.74 (dd, *J* = 10.1, 4.6 Hz, 1H), 3.68 (d, *J* = 6.2 Hz, 2H), 3.61 (dd, *J* = 10.1, 7.7 Hz, 1H), 2.56 (br, 1H), 2.00 – 2.05 (m, 1H), 1.07 (s, 9H), 0.84 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.7, 135.7, 133.3, 133.3, 129.9, 127.9, 68.9, 67.8, 37.4, 27.0, 19.3, 13.3.

NMR and optical rotation data matched literature values.[204]

(*R*)-*tert*-Butyl(3-iodo-2-methylpropoxy)diphenylsilane (189):



188 **189**

Alcohol **188** (1.5 g, 4.57 mmol) was dissolved in 10 mL dry CH_2Cl_2 and PPh_3 (1.55 g, 5.93 mmol), imidazole (466 mg, 6.85 mmol) were added. Thea reaction mixture was cooled to 0 °C. Iodine (1.56 g, 6.16 mmol) was added in 8 portions over 30 minutes. The reaction mixture was stirred in dark at room temperature for 2 hours. The reaction mixture was quenched by adding 10 mL cold sat. aq. $Na_2S_2O_3$, organic layer was washed 2 times with saturated aqueous $Na_2S_2O_3$ until organic layer became colorless. The combined organic extracts were dried over Na_2SO_4 and volatiles removed under reduced pressure. The crude product was purified by flash column chromatography (PE:Et_2O 95:5) giving iodide **189** (1.73 g, 3.95 mmol) as a slightly yellow oil in 86% yield.

R_f: 0.83 (PE:EtOAc 10:1, $KMnO_4$).

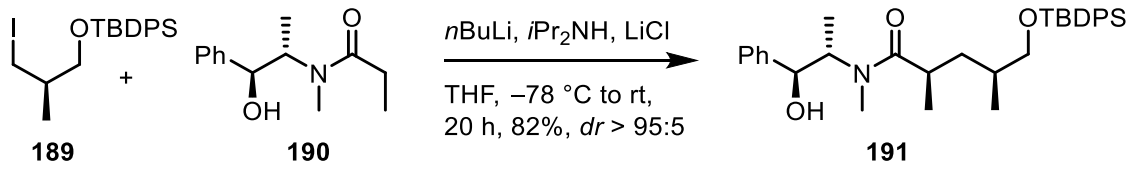
$[\alpha]_D^{20}$ = −3.8 (1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.72 (m, 4H), 7.39 – 7.48 (m, 6H), 3.61 (dd, *J* = 10.2, 5.0 Hz, 1H), 3.49 (dd, *J* = 10.2, 6.9 Hz, 1H), 3.42 (dd, *J* = 9.6, 5.0 Hz, 1H), 3.36 (dd, *J* = 9.6, 5.8 Hz, 1H), 1.17 – 1.79 (m, 1H), 1.09 (s, 9H), 0.98 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.8, 135.7, 133.7, 133.6, 129.8, 129.8, 127.8, 67.5, 37.7, 27.0, 19.4, 17.5, 13.7.

NMR and optical rotation data matched literature values.[205]

(2*R*,4*S*)-5-((*tert*-butyldiphenylsilyl)oxy)-*N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,2,4-trimethylpentanamide (191):



N,*N*-Diisopropylamine (2.06 mL, 14.7 mmol) was dissolved in 15 mL dry THF, dry LiCl (1.89 g, 44.6 mmol) was added in one portion and the mixture cooled to −78 °C. *n*BuLi (5.5 mL, 13.8 mmol, 2.5 M in hexanes) was added, the reaction mixture was stirred 10 minutes at −78 °C, 5 minutes at 0 °C and cooled back to −78 °C. (1*S*,2*S*)-(+)-pseudoephedrine-propionamide (**190**) (1.59 g, 7.18 mmol) in 20 mL THF was added dropwise over 15 minutes. The reaction mixture was stirred 1 hour at −78 °C, 30 minutes at 0 °C, 5 minutes at room temperature and cooled back to 0°C. The iodide **189** (1.60 g, 3.65 mmol) in 4 mL THF was added over 5 minutes. The reaction mixture was stirred in the dark at room temperature for 20 hours. The reaction mixture was cooled to 0 °C and quenched by adding 10 mL half-saturated aqueous NH_4Cl solution. The aqueous phase was extracted 3 times with EtOAc, combined organic extracts were dried over Na_2SO_4. The crude product was purified by flash column chromatography (PE:EtOAc 3:2) giving amide **191** (1.60 g, 3.00 mmol) as a colorless oil in 82% yield and with no observable amount of epimer.

R_f: 0.29 (PE:EtOAc 3:2, $KMnO_4$).

$[\alpha]_D^{20}$ = +34.4 (1.0, $CHCl_3$).

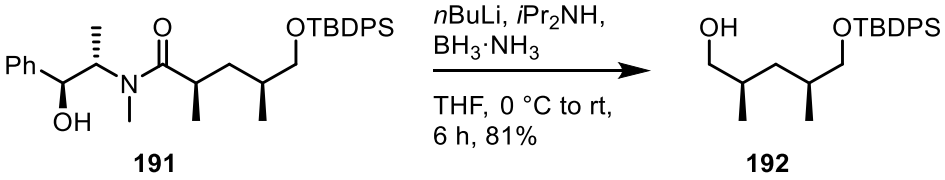
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.70 (m, 4H), 7.23 – 7.44 (m, 11H), 4.61 (t, *J* = 6.9 Hz, 1H), 4.36 (br, 1H), 3.52 (dd, *J* = 9.8, 4.9 Hz, 1H), 3.43 (dd, *J* = 9.8, 6.1 Hz, 1H), 2.78 (s, 3H), 2.65 – 2.73 (m, 1H), 1.61 – 1.77 (m, 2H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.06 (s, 9H), .088 (d, *J* = 6.8 Hz, 3H). *[1]*

^{13}C NMR (101 MHz, $CDCl_3$) δ 179.2, 142.8, 135.7, 135.7, 134.0,, 134.0, 129.7, 129.7, 128.4, 127.7, 126.3, 68.9, 37.2, 34.2, 33.4, 27.0, 19.4, 17.8, 17.5, 14.5.

NMR and optical rotation data matched literature values.[206]

[1] Compound exists as a mixture of amide bond rotamers.

(2*R*,4*S*)-5-((*tert*-Butyldiphenylsilyl)oxy)-2,4-dimethylpentan-1-ol (192):



191 **192**

Diisopropylamine (2.20 mL, 15.7 mmol) was dissolved in 12 mL dry THF and cooled to −78 °C. *n*BuLi (5.7 mL, 14.2 mmol, 2.5 M in hexanes) was added, the reaction mixture was stirred 10 minutes at −78 °C, 10 minutes at 0 °C and $BH_3 \cdot NH_3$ (451 mg, 14.6 mmol) was added under a flow of argon. The reaction mixture was stirred 15 minutes at 0 °C, 15 minutes at room temperature and cooled back to 0 °C. Amide **191** (1.94 g, 3.65 mmol) in 5 mL THF was added dropwise over 5 minutes. The reaction mixture was gradually warmed to room temperature and stirred for 6 hours. After complete consumption of the starting material, the reaction mixture was cooled to 0 °C and quenched by adding 36 mL 3 M aqueous HCl. It was stirred for 30 minutes. 20 mL Et_2O was added, layers separated and aqueous phase was extracted 3 times with Et_2O. Combined organic extracts were washed 3 times with 3 M aqueous HCl, once with brine and dried over anhydrous Na_2SO_4. The crude product was purified by flash column chromatography (PE:EtOAc 4:1) giving alcohol **192** (1.10 g, 2.97 mmol) as a colorless oil in 81% yield.

R_f: 0.54 (PE:EtOAc 4:1, $KMnO_4$).

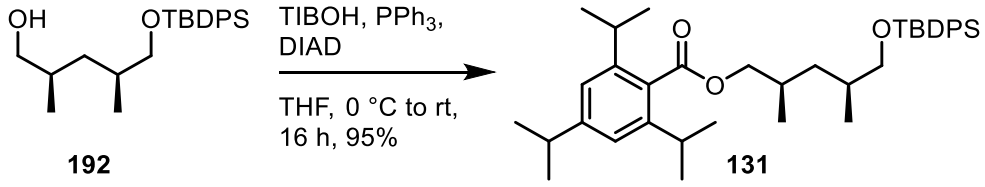
$[\alpha]_D^{20}$ = −0.9 (1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.69 (m, 4H), 7.37 – 7.45 (m, 6H), 3.42 – 3.55 (m, 3H), 3.33 – 3.38 (m, 1H), 1.71 – 1.79 (m, 1H), 1.60 – 1.68 (m, 1H), 1.43 – 1.50 (m, 1H), 1.32 (br, 1H), 1.09 (s, 9H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.8, 135.8, 134.1, 134.1, 129.7, 127.7, 127.7, 68.9, 68.4, 37.3, 33.3, 33.3, 27.0, 19.4, 18.0, 17.6.

NMR and optical rotation data matched literature values.[206]

(2*R*,4*S*)-5-((*tert*-Butyldiphenylsilyl)oxy)-2,4-dimethylpentyl 2,4,6-triisopropylbenzoate (131):



192 131

Alcohol **192** (500 mg, 1.35 mmol) was dissolved in 4 mL dry THF; PPh_3 (354 mg, 1.35 mmol) and 2,4,6-triisopropylbenzoic acid (305 mg, 1.23 mmol) were added and mixture cooled to 0 °C. DIAD (266 µL, 1.35 mmol) was added dropwise and reaction mixture was gradually warmed to room temperature. The reaction was stirred for 16 hours and quenched with sat. aq. $NaHCO_3$ solution. Aqueous phase was extracted 3 times with CH_2Cl_2, combined organic extracts were dried over Na_2SO_4 and volatiles removed under reduced pressure. The crude product was purified by flash column chromatography (PE:Et_2O 50:1) and ester **131** (770 mg, 1.28 mmol) was obtained as a colorless oil in 95% yield.

R_f: 0.54 (PE:Et_2O 50:1, $KMnO_4$)

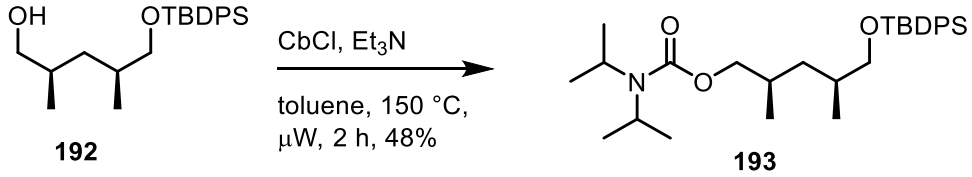
$[\alpha]_D^{20}$ = −4.2 (0.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.65 (m, 4H), 7.33 – 7.43 (m, 6H), 6.99 (s, 2H), 4.18 (dd, *J* = 10.7, 4.9 Hz, 1H), 4.00 (dd, *J* = 10.7, 7.0 Hz, 1H), 3.51 (dd, *J* = 10.0, 5.1 Hz, 1H), 3.39 (dd, *J* = 10.0, 6.6 Hz, 1H), 2.79 – 2.92 (m, 3H), 1.89 – 1.97 (m, 1H), 1.74 – 1.82 (m, 1H), 1.45 – 1.52 (m, 1H), 1.24 (d, *J* = 7.3 Hz, 6H), 1.22 (d, *J* = 2.0 Hz, 6H), 1.21 (d, *J* = 2.1 Hz, 6H), 1.21 – 1.28 (m, 1H), 1.03 (s, 9H), 0.97 (d, *J* = 6.4 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 150.1, 144.8, 135.7, 130.1, 129.7, 127.7, 127.7, 121.0, 68.8, 37.6, 34.6, 33.1, 31.7, 30.1, 27.0, 24.3, 24.1, 19.4, 17.9, 17.8.

HRMS (ESI) calcd for $C_{39}H_{56}O_3SiNa$ $[M+Na]^+$ 623.3896; found, 623.3894.

(2*R*,4*S*)-5-((*tert*-butyldiphenylsilyl)oxy)-2,4-dimethylpentyl diisopropylcarbamate (193):



192 193

Alcohol **192** (100 mg, 0.27 mmol) was dissolved in 4 mL dry toluene and *N*,*N*-diisopropyl carbamoyl chloride (52 mg, 0.32 mmol), followed by Et_3N (49 μL, 0.35 mmol) were added. The reaction mixture was heated at 150 °C in a microwave reactor for 2 hours. Then it was cooled to room temperature, diluted with Et_2O, washed 2 x 5 mL 2 M aqueous HCl, once with brine and dried over $MgSO_4$. Crude product was purified by flash chromatography (PE:EtOAc 10:1) giving carbamate **193** (65 mg, 0.13 mmol) as a colorless oil in 48% yield.

R_f: 0.45 (PE:Et_2O 10:1).

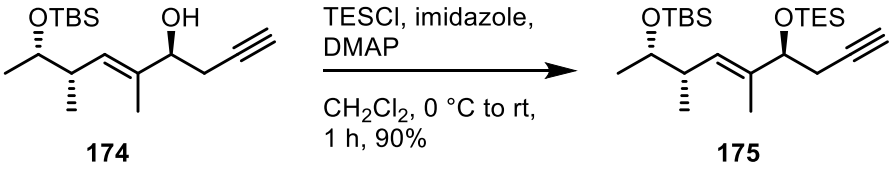
$[\alpha]_D^{20}$ = −4.4 (1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.67 (m, 4H), 7.35 – 7.44 (m, 6H), 3.98 (dd, *J* = 10.5, 5.1 Hz, 1H), 3.9 (br, 2H), 3.80 (dd, *J* = 10.5, 7.2 Hz, 1H), 3.52 (dd, *J* = 9.8, 5.1 Hz, 1H), 3.40 (dd, *J* = 9.8, 6.4 Hz, 1H), 1.75 – 1.90 (m, 2H), 1.42 – 1.49 (m, 1H), 1.19 (d, *J* = 6.8 Hz, 12H), 1.05 (s, 9H), 0.96 (d, *J* = 6.4 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 135.8, 134.1, 129.6, 127.7, 69.9, 69.1, 45.9, 37.9, 33.2, 30.5, 27.0, 21.2, 19.4, 18.3, 17.8.

NMR spectra and optical rotation matched literature values.[207]

(5*S*,8*S*,9*S*,*E*)-3,3-diethyl-6,8,9,11,11,12,12-heptamethyl-5-(prop-2-yn-1-yl)-4,10-dioxa-3,11-disilatridec-6-ene (175):



174 **175**

Alcohol **174** (500 mg, 1.69 mmol), imidazole (345 mg, 5.06 mmol) and catalytic amount of DMAP were dissolved in 17 mL of CH_2Cl_2. The mixture was cooled to 0 °C and TESCl (566 μL, 3.37 mmol) was added dropwise. White suspension formed during the addition. The reaction mixture was slowly warmed to room temperature and stirred for 1 hour, or until all the starting material was consumed. The reaction mixture was diluted with 15 mL CH_2Cl_2 and washed with half-saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted three times with CH_2Cl_2 and combined organic layers were dried over Na_2SO_4. Volatiles were removed under reduced pressure and crude product purified by flash column chromatography (PE:EtOAc 100:1) giving title compound **175** (622 mg, 1.52 mmol) as clear colorless liquid in 90% yield.

R_f: 0.50 (PE:Et_2O 50:1, Vanilline).

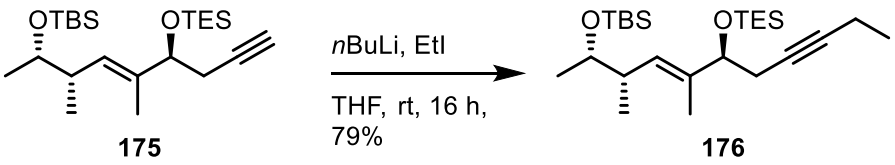
$[\alpha]_D^{20}$ = +3.4 (1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (d, *J* = 10.3 Hz, 1H), 4.13 (t, *J* = 6.4 Hz, 1H), 3.50 – 3.57 (m, 1H), 2.31 – 2.39 (m, 3H), 1.92 (t, *J* = 2.70 Hz, 1H), 1.60 (d, *J* = 1.3 Hz, 3H), 1.54 (s, 3H), 1.09 (d, *J* = 6.2 Hz, 3H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.90 (s, 9H), 0.58 (q, *J* = 8.0 Hz, 6H), 0.05 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.4, 130.1, 82.0, 77.0, 72.9, 69.8, 40.8, 27.2, 26.1, 22.1, 18.3, 17.3, 11.5, 7.0, 4.9, −4.1, −4.6.

HRMS (ESI) calcd for $C_{23}H_{46}O_2NaSi_2$ $[M+Na]^+$ 433.2934; found, 433.2933.

(5*S*,8*S*,9*S*,*E*)-3,3-diethyl-6,8,9,11,11,12,12-heptamethyl-5-(pent-2-yn-1-yl)-4,10-dioxa-3,11-disilatridec-6-ene (176):



175 **176**

Terminal alkyne **175** (120 mg, 0.29 mmol) was dissolved in 5 mL dry THF and cooled to −30 °C. *n*BuLi (130 µL, 0.32 mmol, 2.5 M in hexanes) was added and reaction mixture stirred 1 hour at that temperature. EtI (26 µL, 0.32 mmol) was added dropwise and the reaction mixture was stirred for 16 hours, gradually warming to room temperature. The crude NMR showed 65% conversion *[1]*. The reaction mixture was cooled back to −30 °C and *n*Buli (130 µL, 0.32 mmol, 2.5 M in hexanes) was added and reaction mixture stirred 1 hour at that temperature. EtI (26 µL, 0.32 mmol) was added dropwise and the reaction mixture was stirred for 4 hours, gradually warming to room temperature. That procedure was repeated 2 more times. The crude NMR showed 6% of starting material with around 15% of elimination product. Reaction mixture was quenched with 5 mL H_2O, organic layer was separated, washed once with 5 mL aqueous half-saturated $NaHCO_3$ and dried over Na_2SO_4. Crude product was purified by flash column chromatography (PE:EtOAc 100:1 to 50:1) giving internal alkyne **176** (100 mg, 0.23 mmol) in 79% yield.

R_f: 0.29 (PE:Et_2O 50:1, Vanilline). *[2]*

$[\alpha]_D^{20}$ = +1.0 (1.0, $CHCl_3$).

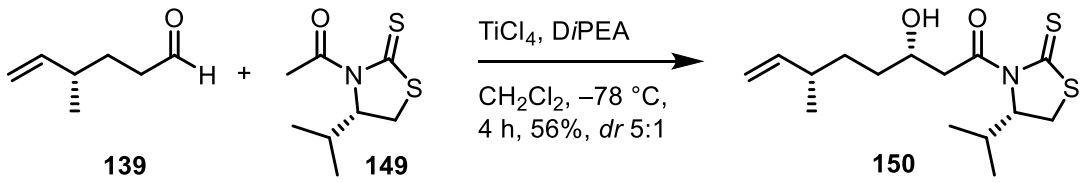
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20 (d, *J* = 10.0 Hz, 1H), 4.07 (t, *J* = 6.7 Hz, 1H), 3.50 – 3.56 (m, 1H), 2.30 – 2.35 (m, 1H), 2.31 (dt, *J* = 6.8, 2.6 Hz, 2H), 2.13 (qt, *J* = 7.6, 2.6 Hz, 2H), 1.59 (d, 1.3 Hz, 3H), 1.09 (d, *J* = 5.6 Hz, 3H), 1.08 (t, *J* = 7.2 Hz, 3H), 0.94 (t, 8.1 Hz, 9H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.58 (q, *J* = 7.2 Hz, 6H), 0.05 (s, 6H).

HRMS (ESI) calcd for $C_{25}H_{50}O_2NaSi_2$ $[M+Na]^+$ 461.3247; found, 461.3246.

[1] Mini quench – 100 µL of reaction aliquot was quenched with 1 drop of H_2O and volatiles were removed in vacuo for 30 minutes. 600 µL $CDCl_3$ was added and sample measured with NMR.

[2] R_f values of the product and starting material are indistinguishable from each other.

(3*S*,6*S*)-3-hydroxy-1-((*S*)-4-isopropyl-2-thioxothiazolidin-3-yl)-6-methyloct-7-en-1-one (150):



The Nagao auxiliary **149** (2.0 g, 9.85 mmol) was dissolved in 50 mL CH_2Cl_2 and cooled to 0 °C. $TiCl_4$ (10.8 mL, 10.8 mmol, 1 M in CH_2Cl_2) was added dropwise and after complete addition, the reaction mixture was cooled to −78 °C. D*i*PEA (1.71 mL, 9.85 mmol) was added over 5 minutes and the mixture was stirred 2 hours at that temperature. Freshly prepared aldehyde **139** (1.10 g, 9.85 mmol) *[1]* was dissolved in 20 mL CH_2Cl_2 and added to the reaction mixture dropwise over 10 minutes. The reaction mixture was stirred 2 hours at −78 °C and quenched by addition of 25 mL aqueous half-saturated NH_4Cl solution. The aqueous phase was extracted 3 times with CH_2Cl_2, combined organic extracts were dried over Na_2SO_4 and crude product was purified by flash chromatography (PE:EtOAc 3:1). Title compound **150** (1.73 g, 5.48 mmol) was obtained as a yellow oil in 56% yield from the crude aldehyde **139** and in 38% yield over three steps from (*S*)-citronellenne (**142**).

R_f: 0.40 (PE:EtOAc 3:1, $KMnO_4$) *[2]*

$[\alpha]_D^{20}$ = +293 (1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.64 – 5.73 (m, 1H), 5.14 – 5.18 (m, 1H), 4.92 – 5.00 (m, 2H), 4.07 – 4.13 (m, 1H), 3.64 (dd, *J* = 17.8, 2.4 Hz, 1H), 3.52 (dd, *J* = 11.6, 8.2 Hz, 1H), 3.11 (dd, *J* = 17.5, 9.0 Hz, 1H), 3.03 (dd, *J* = 11.6, 0.9 Hz, 1H), 2.78 (d, *J* = 3.1 Hz, 1H), 2.32 – 2.41 (m, 1H), 2.09 – 2.16 (m, 1H), 1.47 – 1.56 (m, 3H), 1.26 – 1.37 (m, 2H), 1.07 (d, *J* = 7.6 Hz, 3H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H).

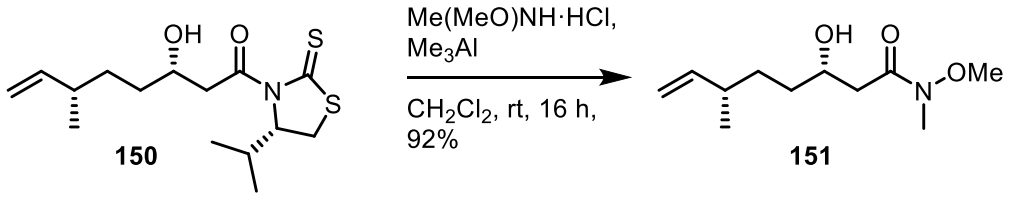
^{13}C NMR (101 MHz, $CDCl_3$) δ 203.2, 173.4, 144.5, 113.0, 71.5, 68.4, 45.7, 38.0, 34.2, 32.6, 31.0, 30.7, 20.4, 19.2, 18.0.

HRMS (ESI) calcd for $C_{15}H_{25}NO_2NaS_2$ $[M+Na]^+$ 338.1224; found, 338.1228.

*[1] For preparation of the aldehyde **139**, please check preparation of compound **137** on page 100.*

[2] The other diastereomer has a slightly higher R_f value.

(3*S*,6*S*)-*N*,3-dihydroxy-*N*,6-dimethyloct-7-enamide (151):



N,*O*-dimethylhydroxylamine hydrochloride (1.07 g, 10.9 mmol) was dissolved in 14 mL CH_2Cl_2 and cooled to 0 °C. Trimethylaluminium (5.47 mL, 10.9 mmol, 2 M in toluene) was added dropwise, the mixture was stirred 30 minutes at 0 °C and cooled to −20 °C. Thiazolidinethione **150** (1.40 g, 4.75 mmol) was dissolved in 5 mL CH_2Cl_2 and added dropwise over 2 minutes. The reaction mixture was gradually warmed to room temperature and stirred for 16 hours. Then, 25 mL of 0.5 M aqueous HCl was added. The aqueous layer was extracted 3 times with CH_2Cl_2 and combined organic extracts were dried over $MgSO_4$. The crude product was purified by flash column chromatography (PE:EtOAc 3:1) and Weinreb amide **151** (940 mg, 4.37 mmol) was obtained in 92% yield.

R_f: 0.11 (PE:EtOAc 3:1, $KMnO_4$).

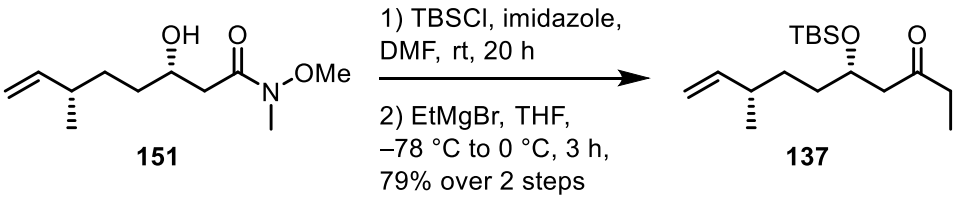
$[\alpha]_D^{20}$ = +46.4 (1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 – 5.74 (m, 1H), 4.90 – 4.99 (m, 2H), 3.96 – 4.01 (m, 1H), 3.78 (d, *J* = 3.0 Hz, 1H), 3.69 (s, 3H), 3.19 (s, 3H), 2.66 (d, *J* = 16.5 Hz, 1H), 2.44 (dd, *J* = 16.5, 10.3 Hz, 1H), 1.44 – 1.55 (m, 3H), 1.28 – 1.36 (m, 1H), 1.01 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 144.7, 112.9, 68.3, 61.4, 38.4, 38.1, 34.5, 32.6, 32.0, 20.4.

HRMS (ESI) calcd for $C_{11}H_{21}NO_3Na$ $[M+Na]^+$ 238.1419; found, 238.1422.

(5*S*,8*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-8-methyldec-9-en-3-one (137):



The Weinreb amide **151** (500 mg, 2.32 mmol) was dissolved in 9 mL dry DMF and cooled to 0 °C. Imidazole (473 mg, 6.97 mmol) and TBSCl (525 mg, 3.48 mmol) were added in one portion. Cooling was removed and the reaction mixture was stirred for 20 hours at room temperature. Then, 10 mL of saturated $NaHCO_3$ solution was added and crude mixture was extracted 3 times with Et_2O. Combined organic extracts were washed once with brine and dried over $MgSO_4$. The crude product was filtered through a plug of silica (PE:EtOAc 3:1) and volatiles were removed under reduced pressure. Thus obtained protected Weinreb amide was dissolved in 10 mL THF and cooled to −78 °C. EtMgBr (1.67 mL, 5.0 mmol, 3 M in THF) was added dropwise over 3 minutes and −78 °C cooling bath was substituted with ice-water bath. The reaction mixture was stirred 3 hours at 0 °C and quenched by addition of 10 mL half-saturated aqueous NH_4Cl solution. The phases were separated and aqueous layer was extracted 4 times with Et_2O. Combined organic extracts were dried over $MgSO_4$ and crude product was purified by flash column chromatography (PE:EtOAc 20:1) giving ketone **137** (548 mg, 1.84 mmol) as a colorless oil in 79% yield from the Weinreb amide **151**.

R_f: 0.69 (PE:EtOAc 20:1, $KMnO_4$).

$[\alpha]_D^{20}$ = +47.0 (1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.61 – 5.70 (m, 1H), 4.89 – 4.97 (m, 2H), 4.12 – 4.18 (m, 1H), 2.56 – 2.62 (m, 1H), 2.37 – 2.47 (m, 2H), 2.03 – 2.10 (m, 2H), 1.37 – 1.47 (m, 2H), 1.25 – 1.33 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.85 (s, 9H), 0.05 (s, 3H), 0.00 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 210.7, 144.6, 112.9, 69.4, 49.8, 38.0, 37.9, 35.4, 31.9, 26.0, 20.4, 18.1, 7.6, -4.4, -4.6.

HRMS (ESI) calcd for $C_{11}H_{21}NO_3Na$ $[M+Na]^+$ 238.1419; found, 238.1422.

5 References

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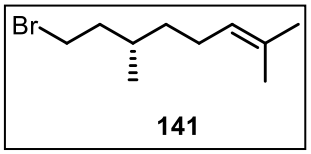
6 Supplementary Materials

6.1 NMR Spectra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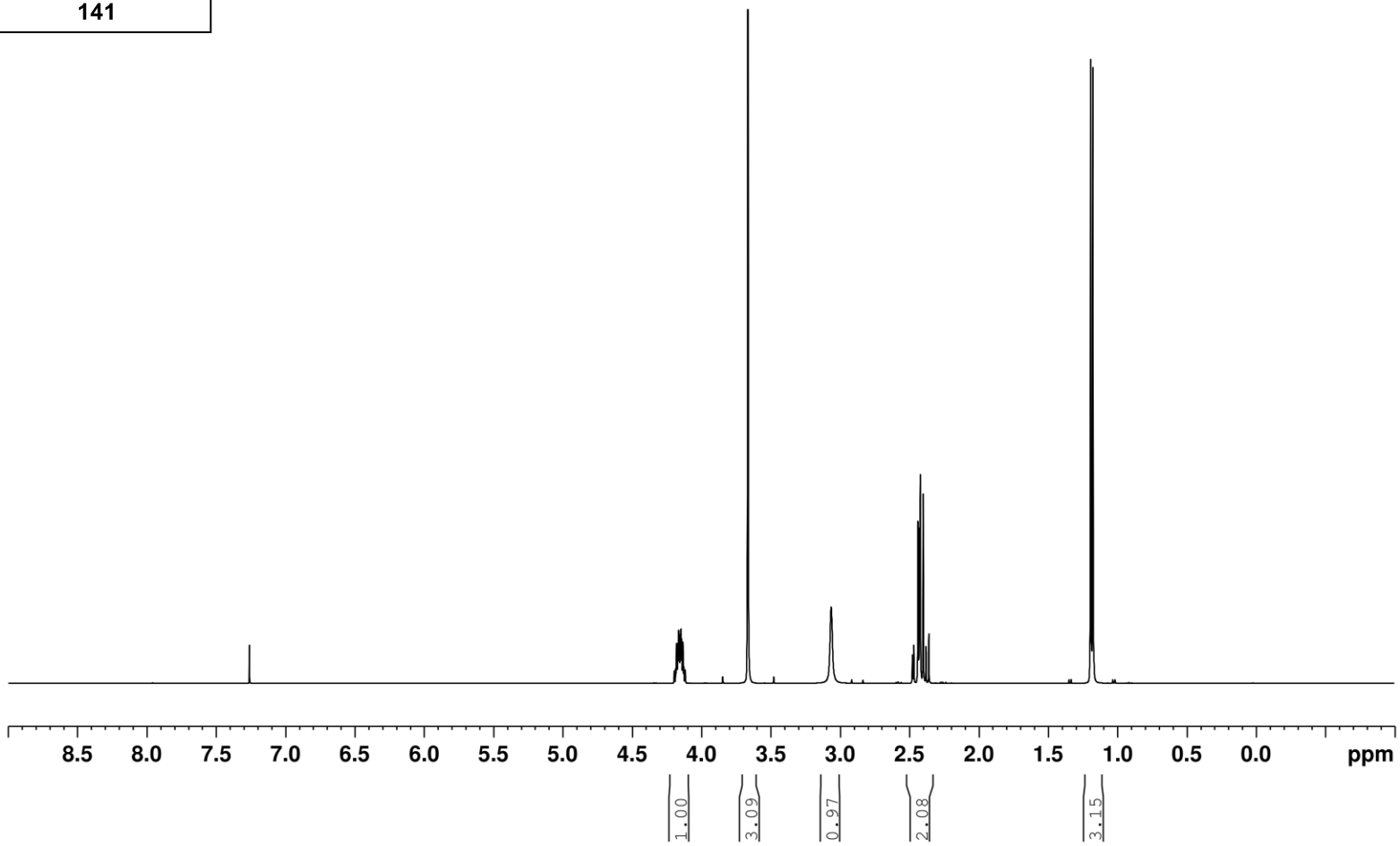
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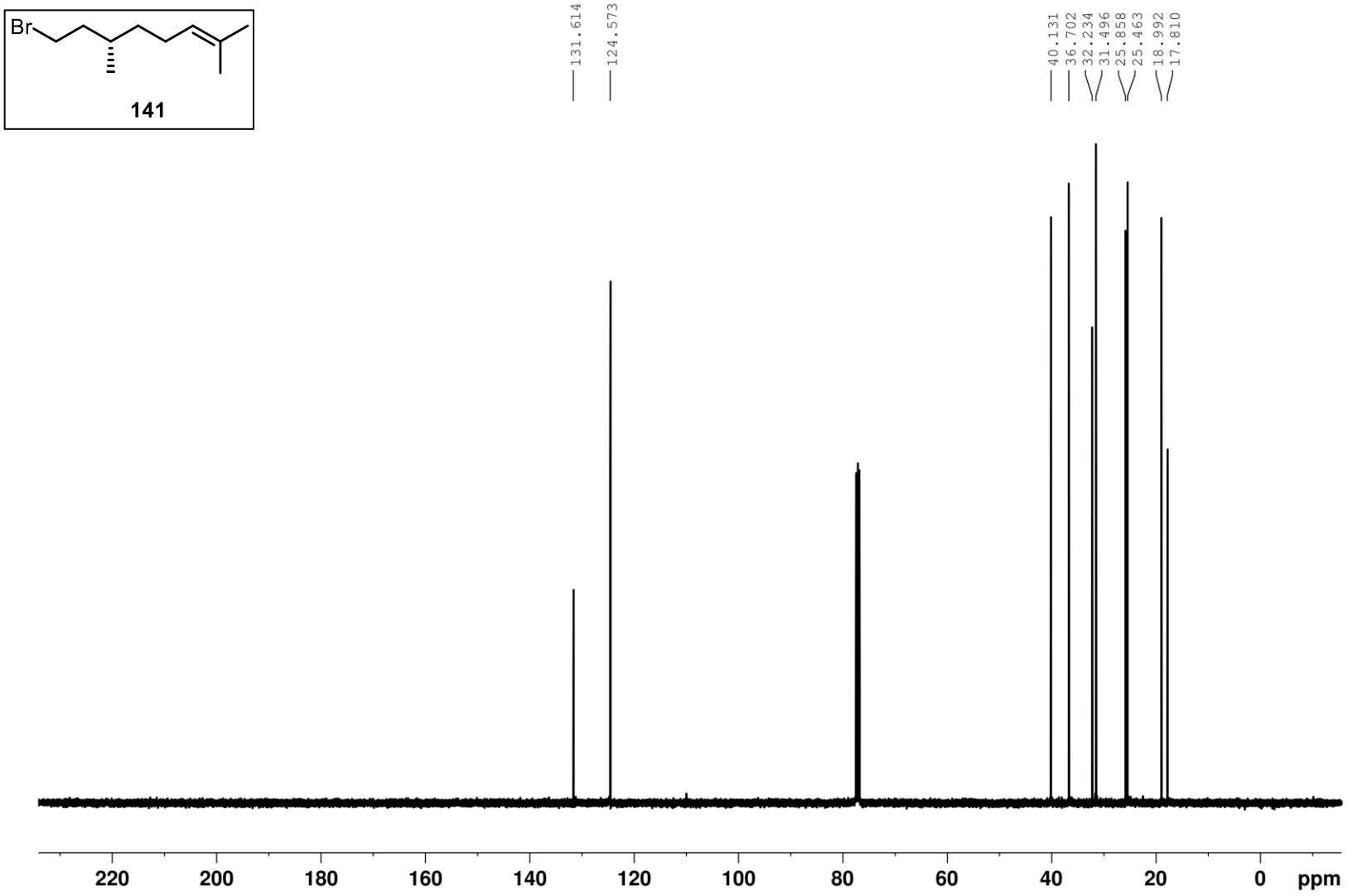
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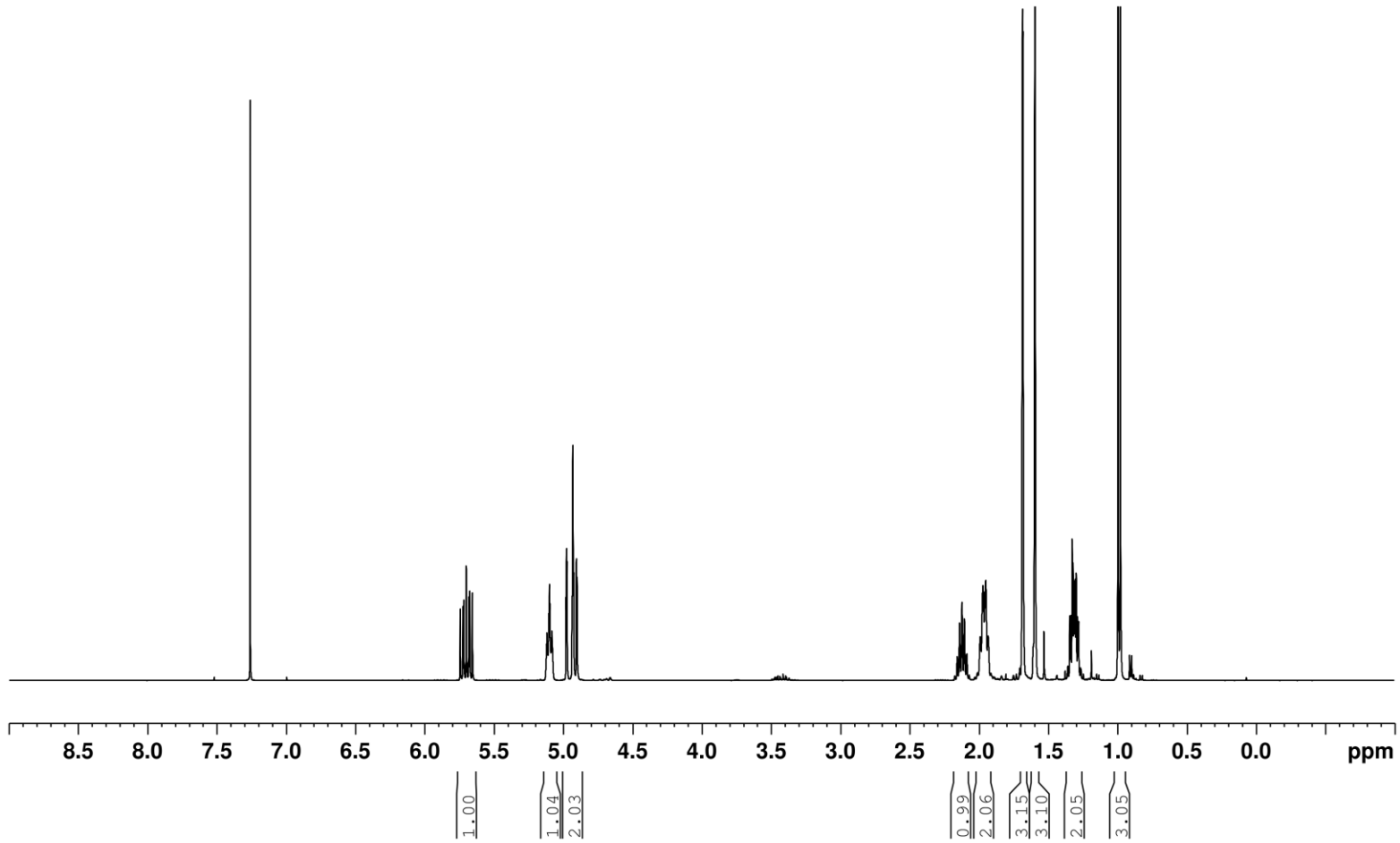
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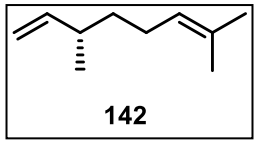
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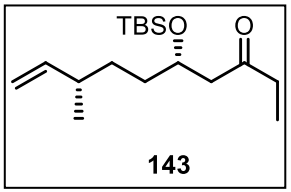
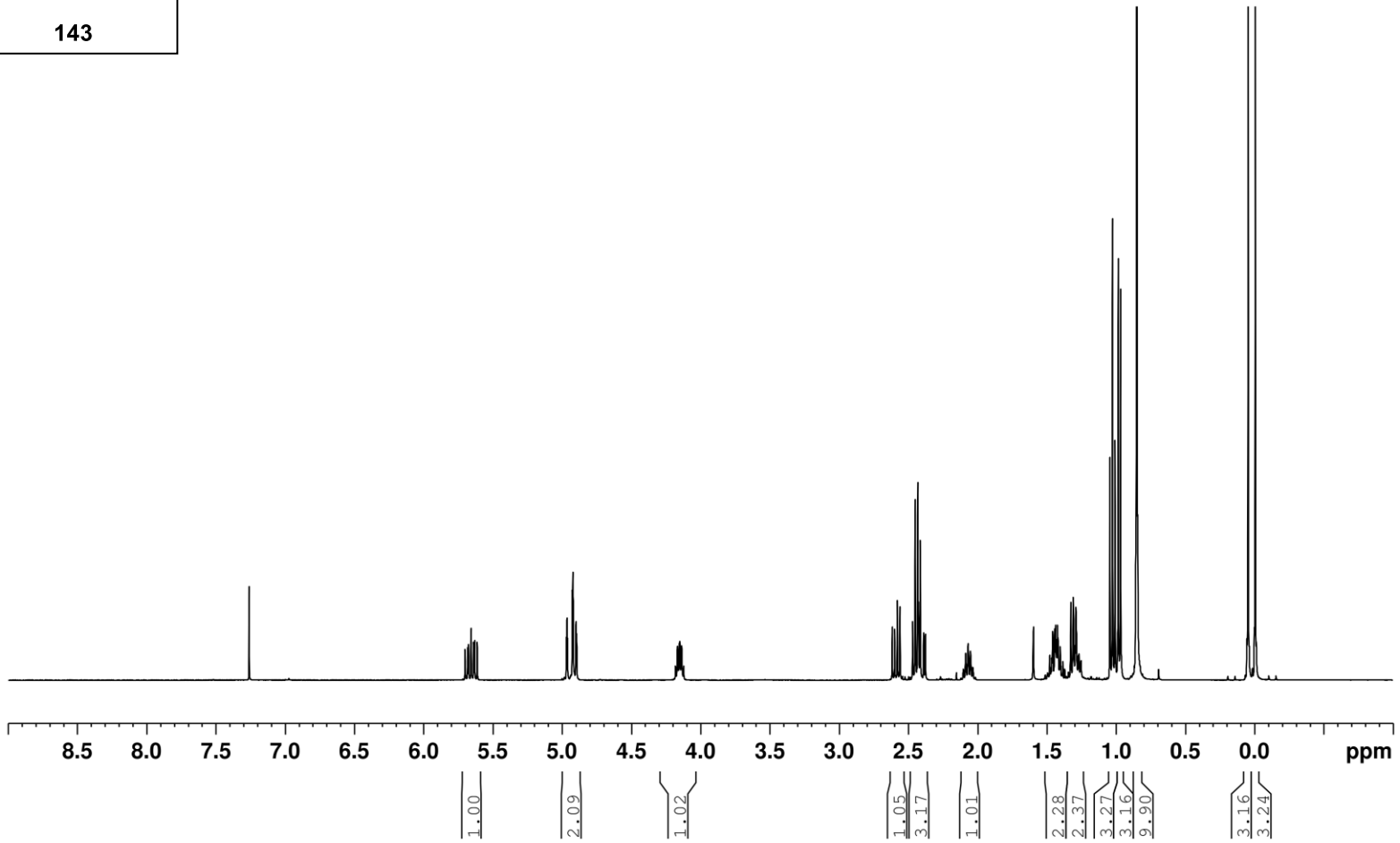
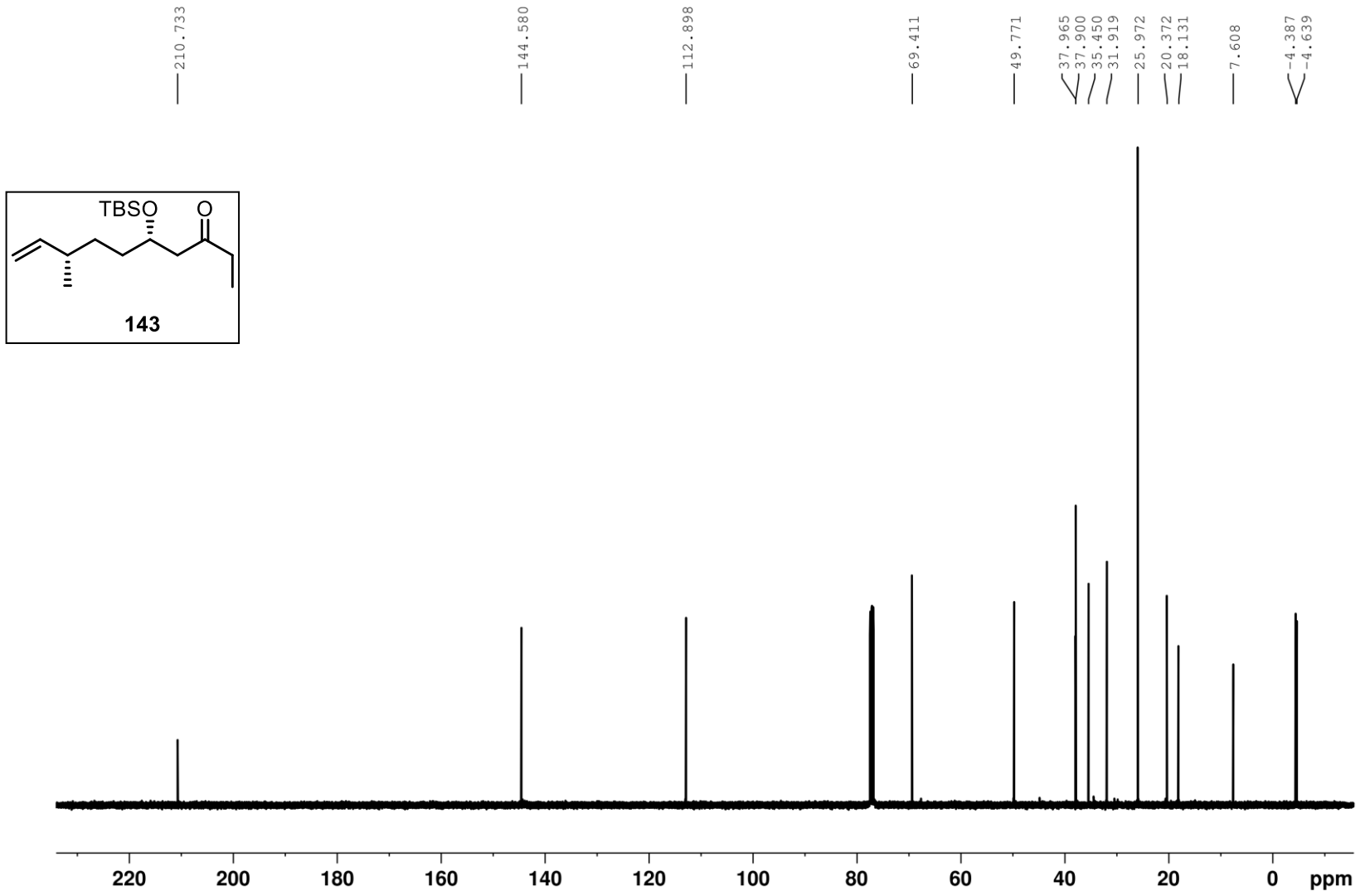
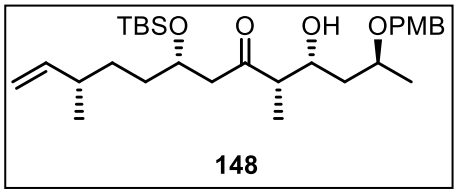
0
ppm

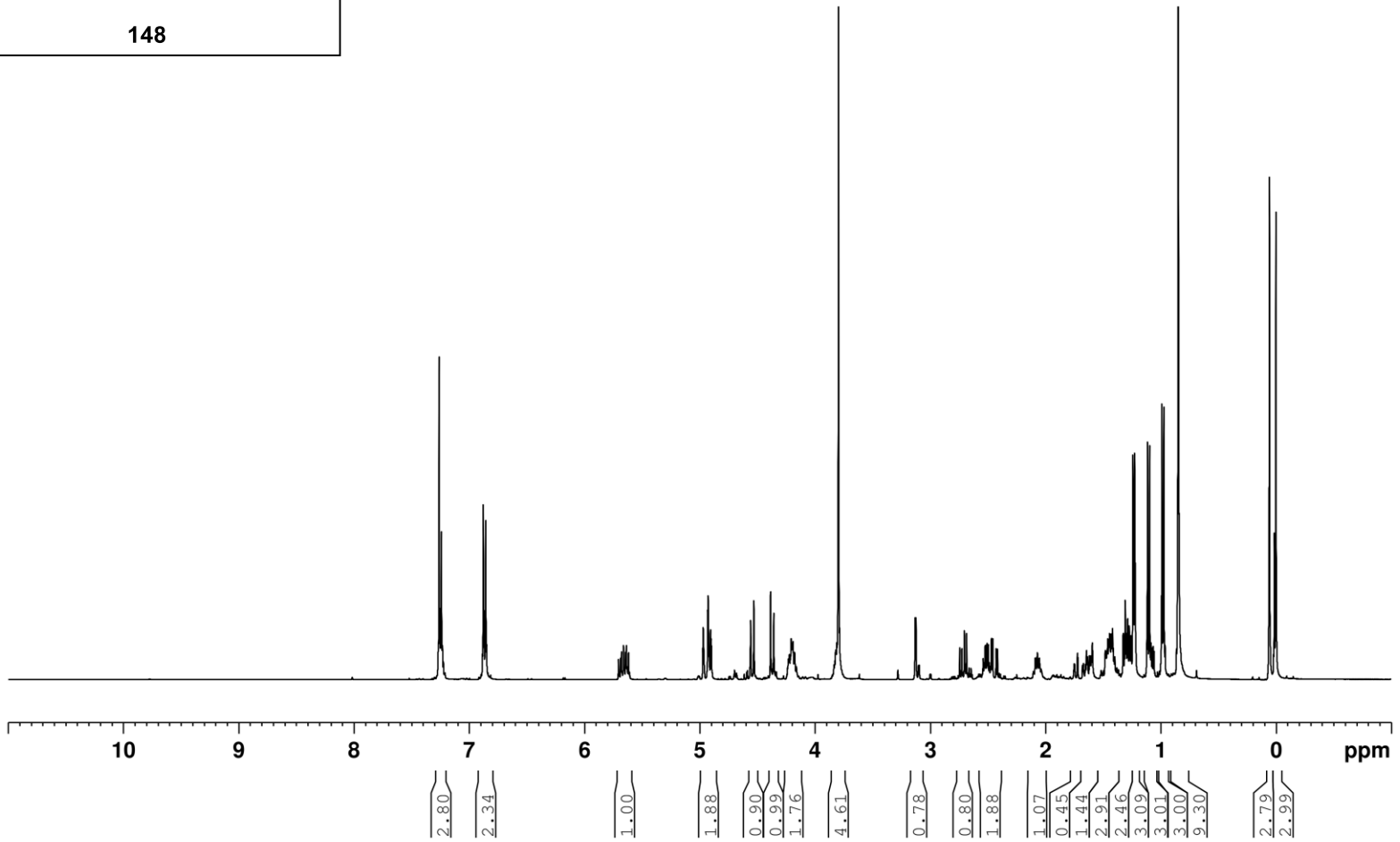

TBSO
O
143


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.00
2.09
1.02
1.05
3.17
1.01
2.28
2.37
3.27
3.16
9.90
3.16
3.24

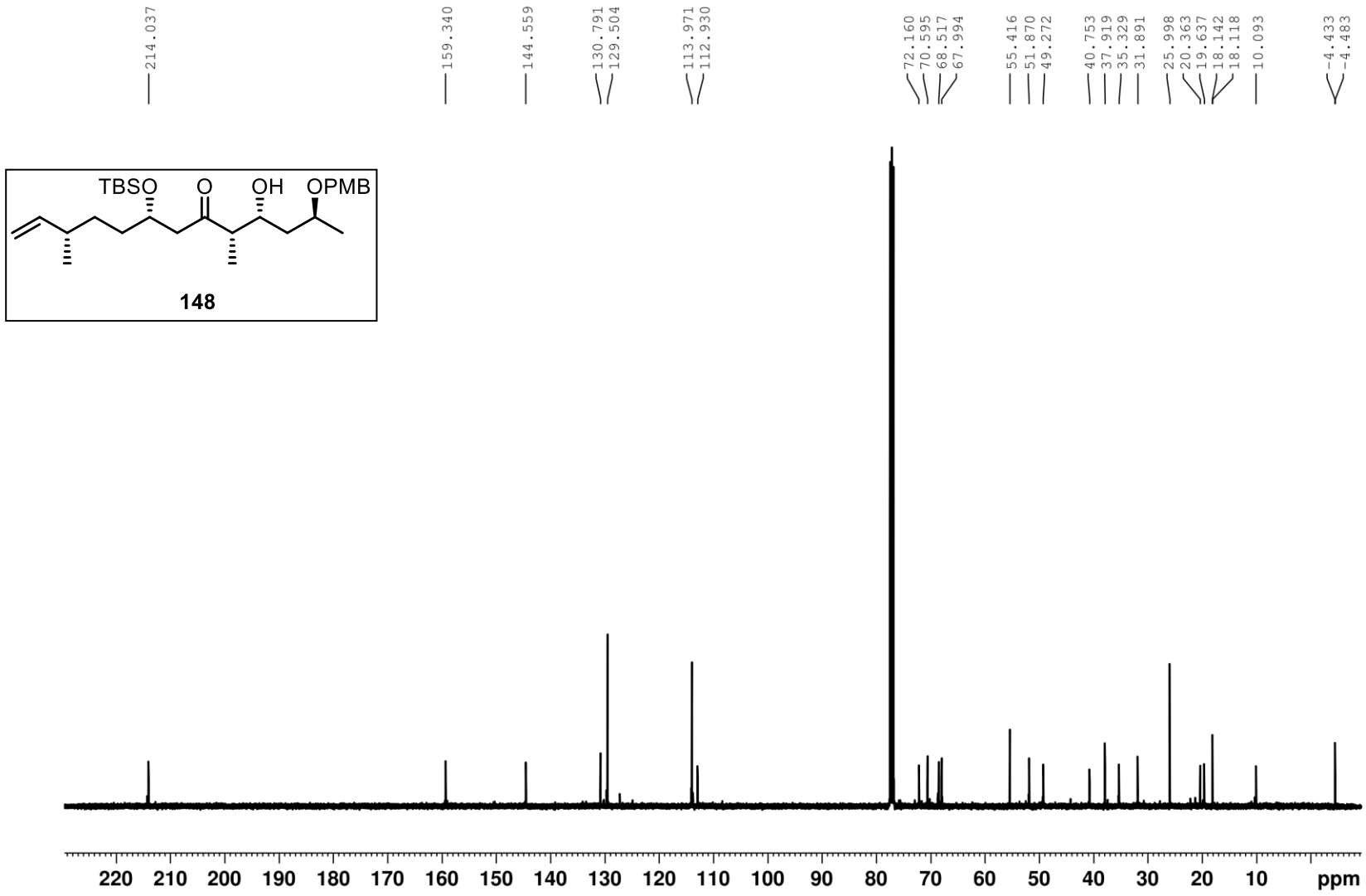

210.733
144.580
112.898
69.411
49.771
37.965
37.900
35.450
31.919
25.972
20.372
18.131
7.608
-4.387
-4.639
TBSO
O
143
220
200
180
160
140
120
100
80
60
40
20
0
ppm

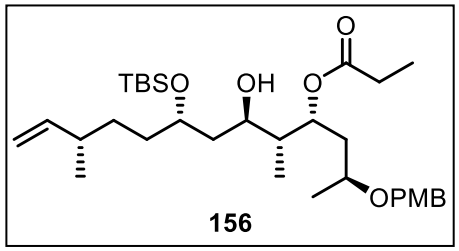

TBSO
O
OH
OPMB

148

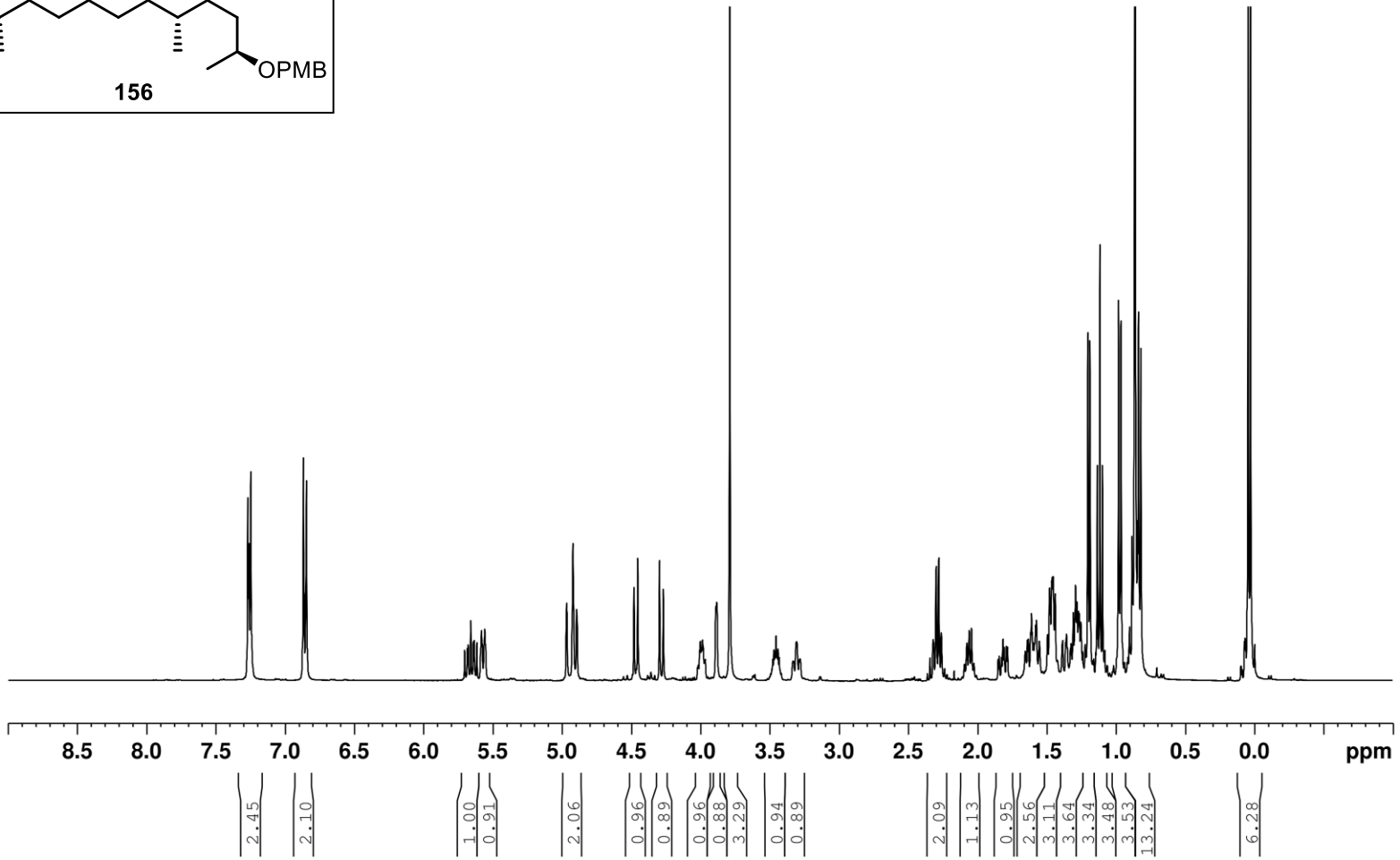

10
9
8
7
6
5
4
3
2
1
0
ppm
2.80
2.34
1.00
1.88
0.90
0.99
1.76
4.61
0.78
0.80
1.88
1.07
0.45
1.44
2.91
2.46
3.09
3.01
3.00
9.30
2.79
2.99

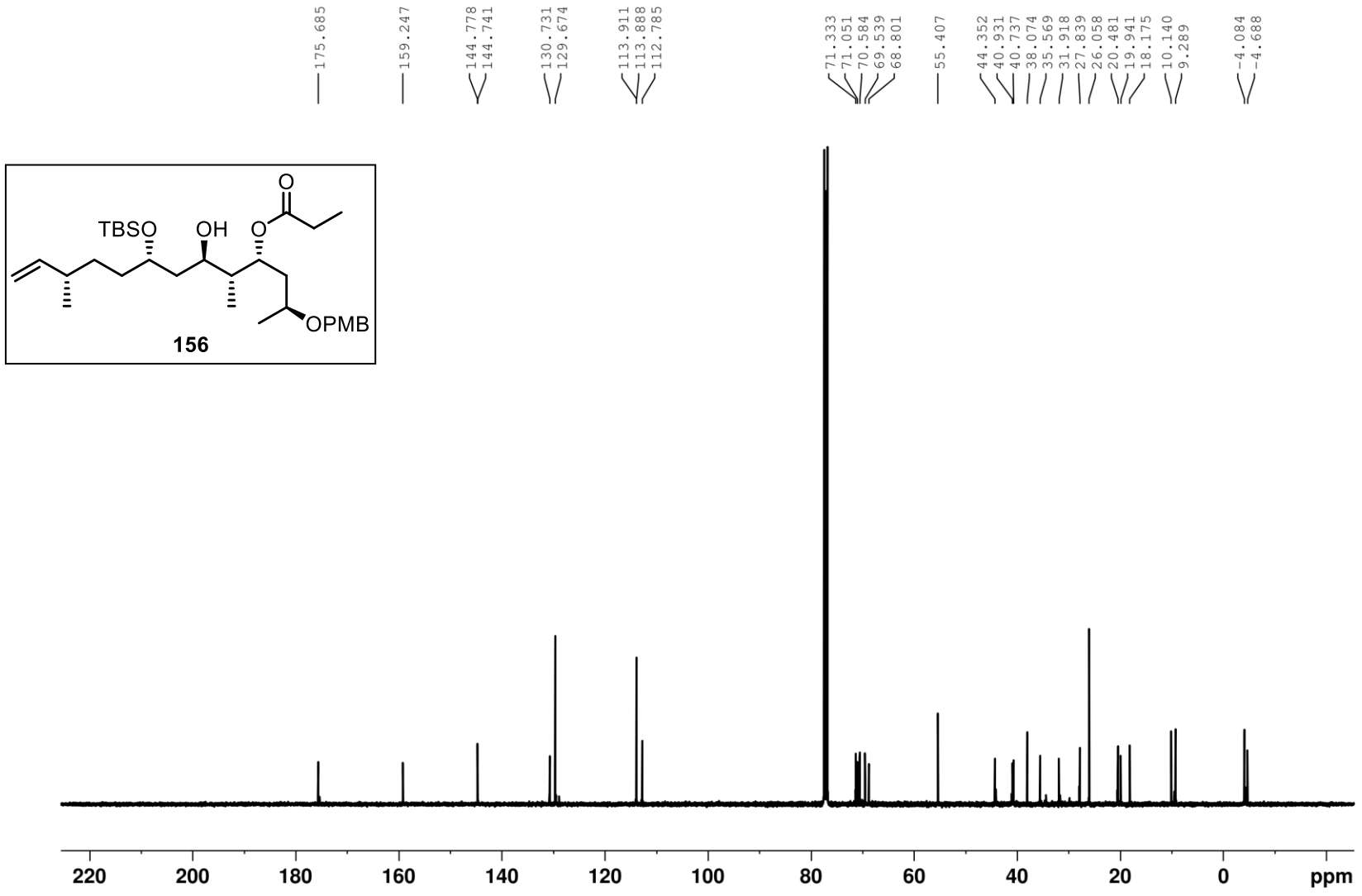
#

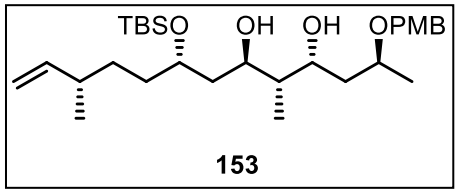

214.037
159.340
144.559
130.791
129.504
113.971
112.930
72.160
70.595
68.517
67.994
55.416
51.870
49.272
40.753
37.919
35.329
31.891
25.998
20.363
19.637
18.142
18.118
10.093
-4.433
-4.483
TBSO
O
OH
OPMB
148
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


TBSO
OH
O
O
OPMB

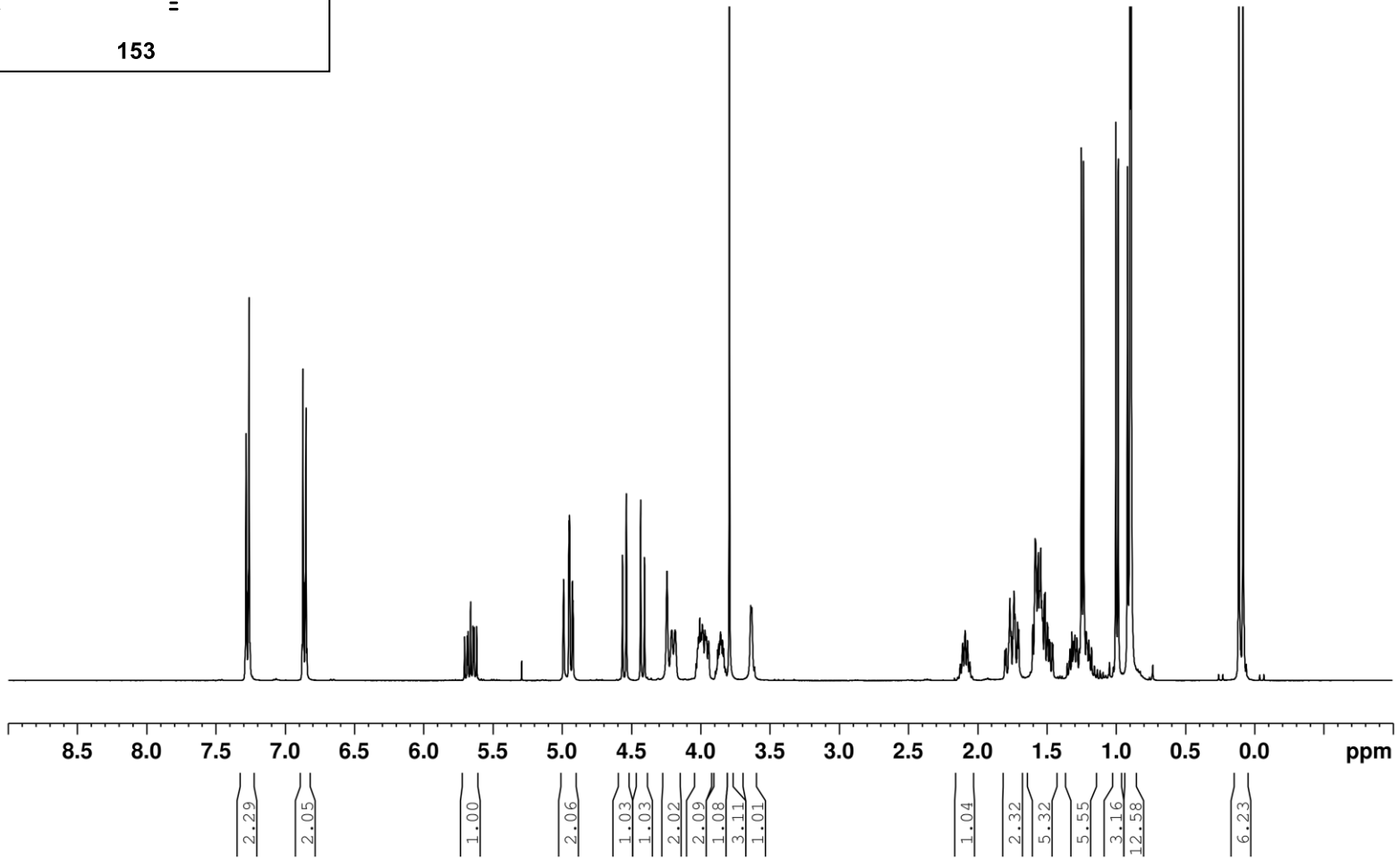
156

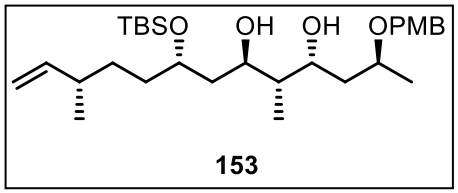

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
2.45
2.10
1.00
0.91
2.06
0.96
0.89
0.96
0.88
3.29
0.94
0.89
2.09
1.13
0.95
2.56
3.11
3.64
3.34
3.48
3.53
13.24
6.28


175.685
159.247
144.778
144.741
130.731
129.674
113.911
113.888
112.785
71.333
71.051
70.584
69.539
68.801
55.407
44.352
40.931
40.737
38.074
35.569
31.918
27.839
26.058
20.481
19.941
18.175
10.140
9.289
-4.084
-4.688
TBSO
OH
O
O
OPMB
156
220
200
180
160
140
120
100
80
60
40
20
0
ppm

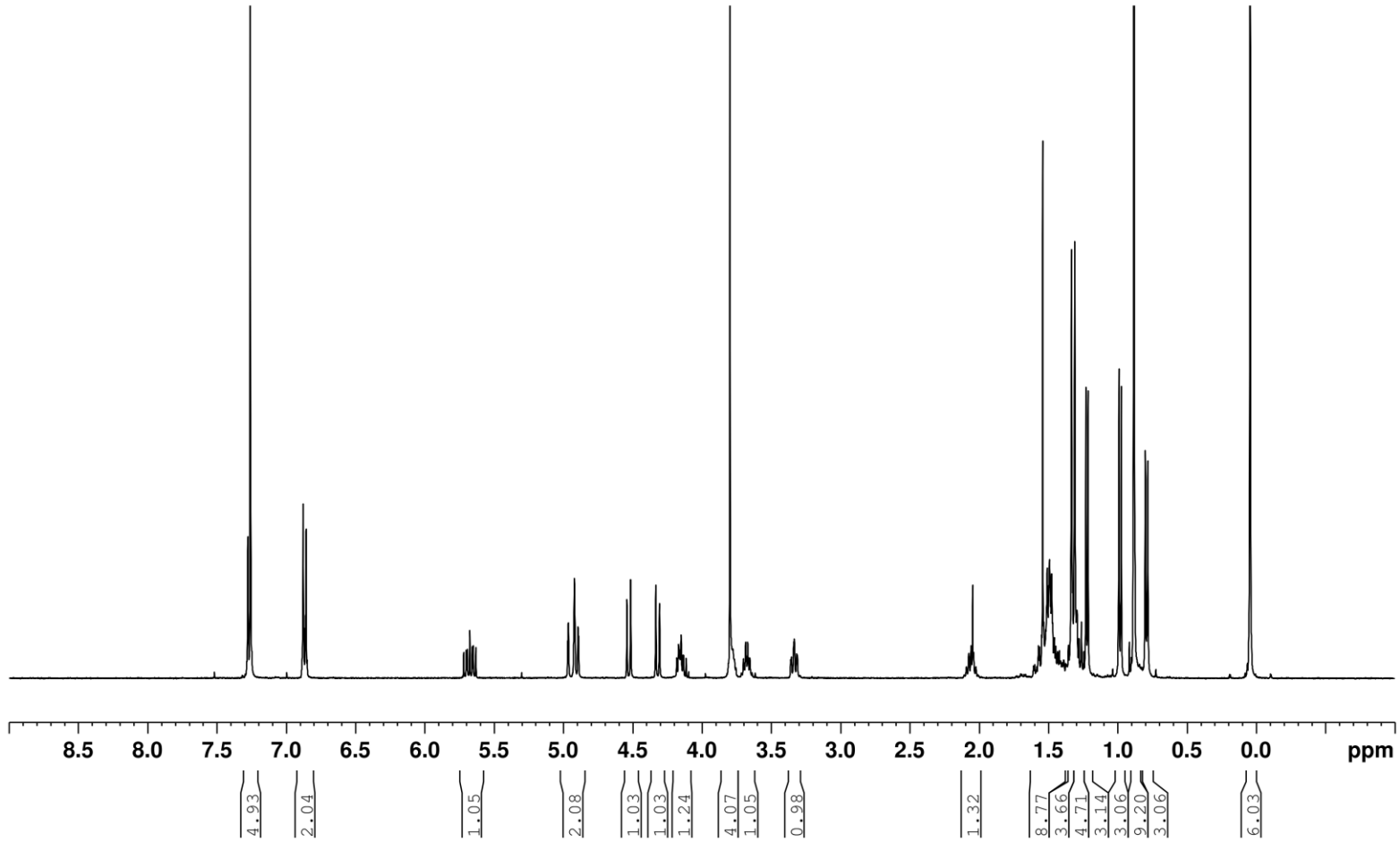

TBSO
OH
OH
OPMB

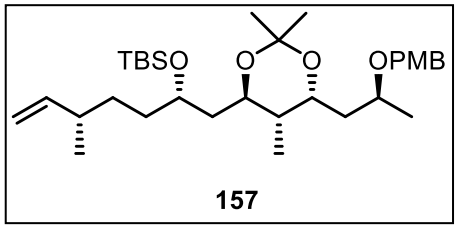
153


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
2.29
2.05
1.00
2.06
1.03
1.03
2.02
2.09
1.08
3.11
1.01
1.04
2.32
5.32
5.55
3.16
12.58
6.23


TBSO
OH
OH
OPMB
153

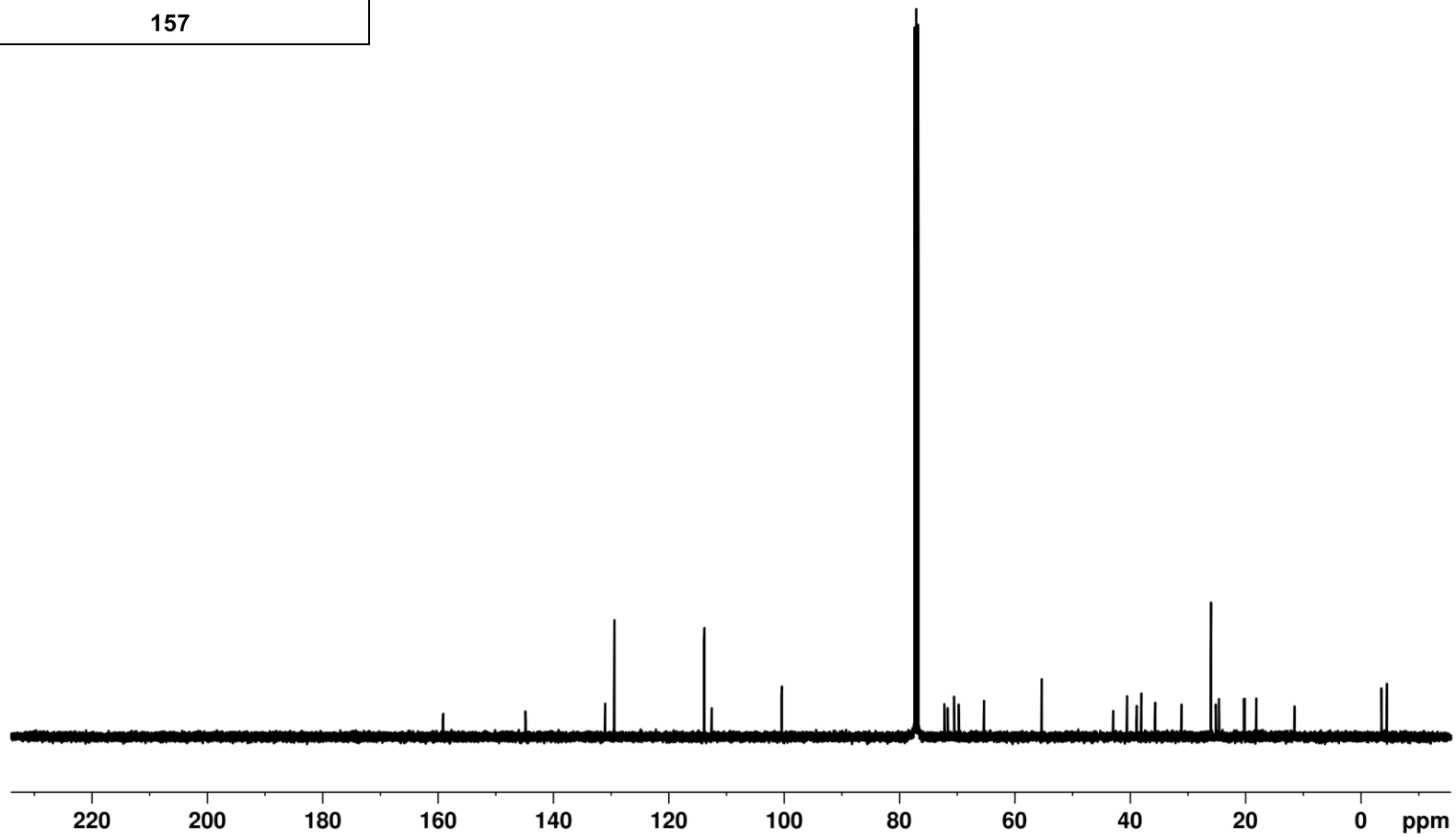
159.196
144.345
131.196
129.393
113.878
113.142
72.662
72.560
72.168
70.743
69.614
55.388
42.967
40.754
39.531
37.924
33.692
32.890
25.955
20.537
20.059
18.075
12.227
-4.409
-4.590
220
200
180
160
140
120
100
80
60
40
20
0
ppm

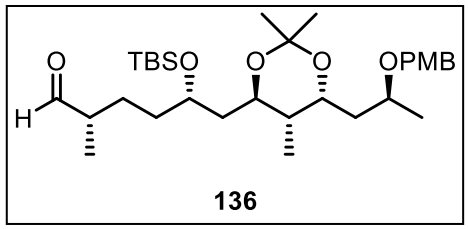

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
4.93
2.04
1.05
2.08
1.03
1.03
1.24
4.07
1.05
0.98
1.32
8.77
3.66
4.71
3.14
3.06
9.20
3.06
6.03



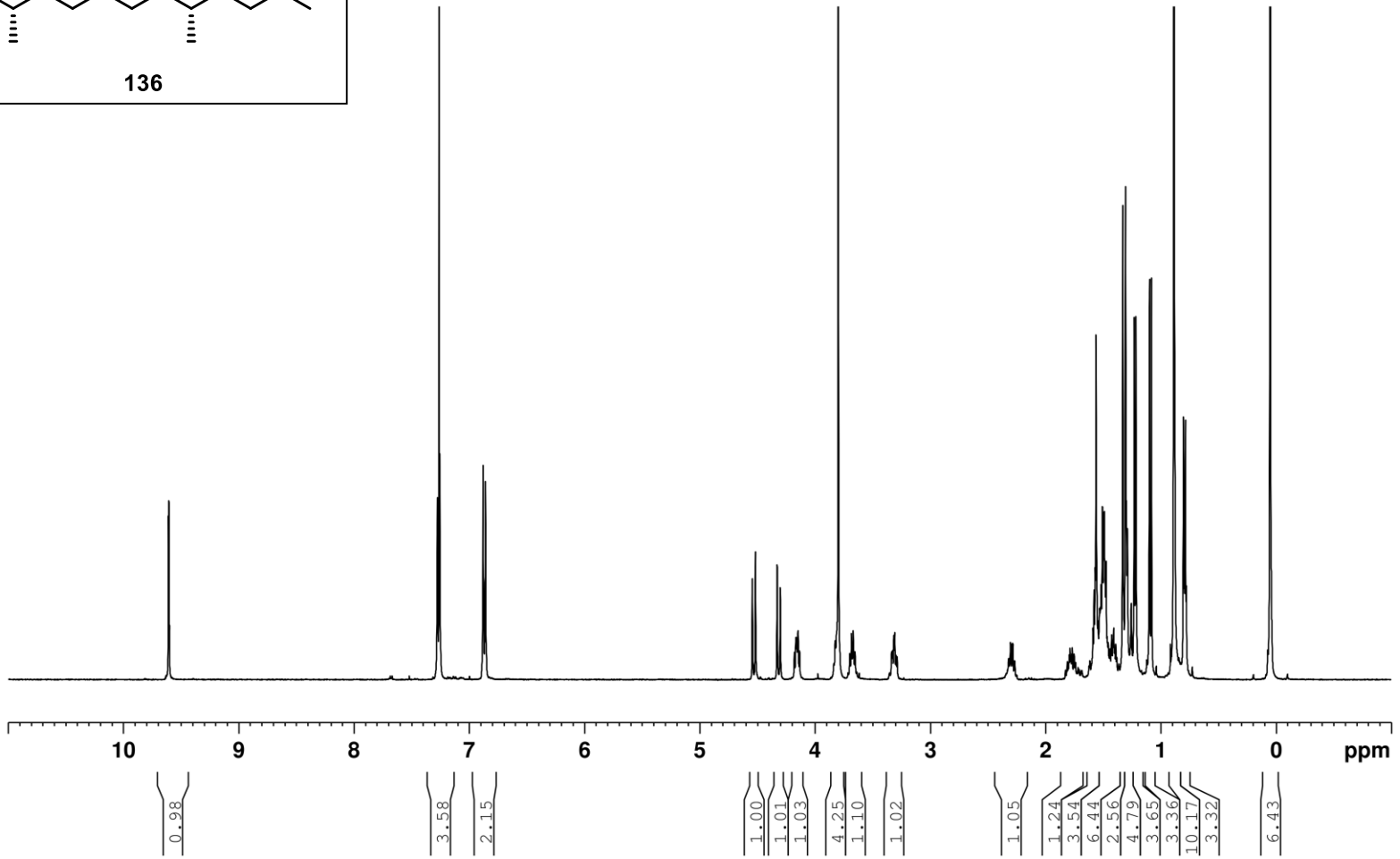
157

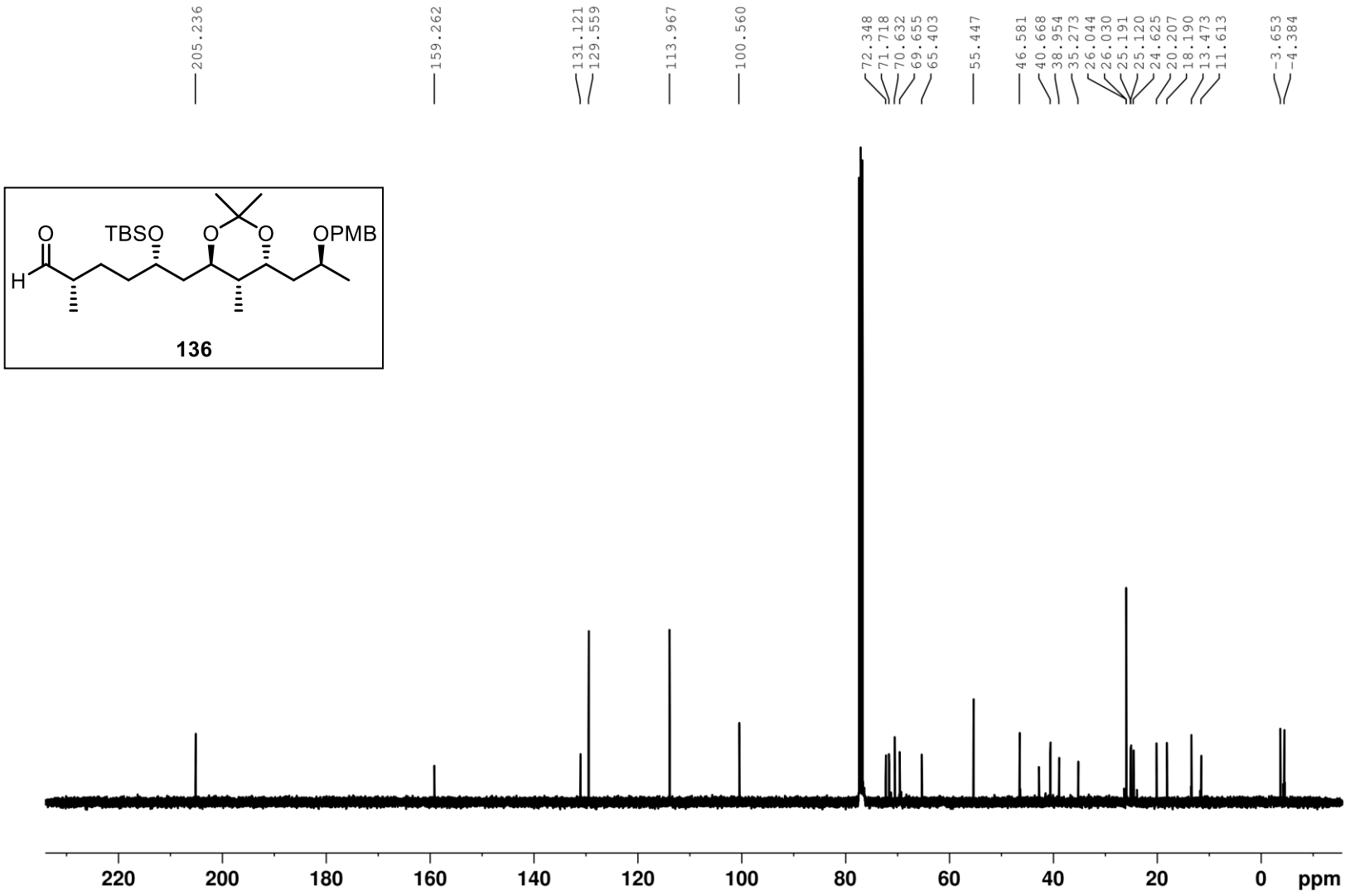
159.250
144.935
131.145
129.560
113.962
112.650
100.519
72.305
71.758
70.637
69.809
65.429
55.447
43.053
40.650
38.982
38.147
35.783
31.210
26.102
25.233
24.691
20.364
20.220
18.224
11.583
-3.492
-4.395

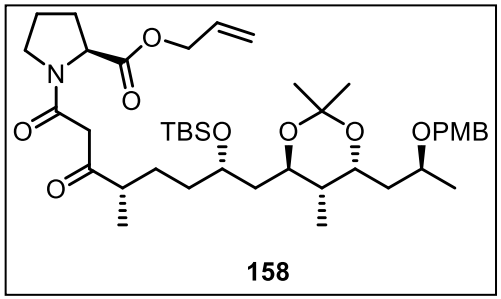



O
TBSO
O
O
OPMB
H

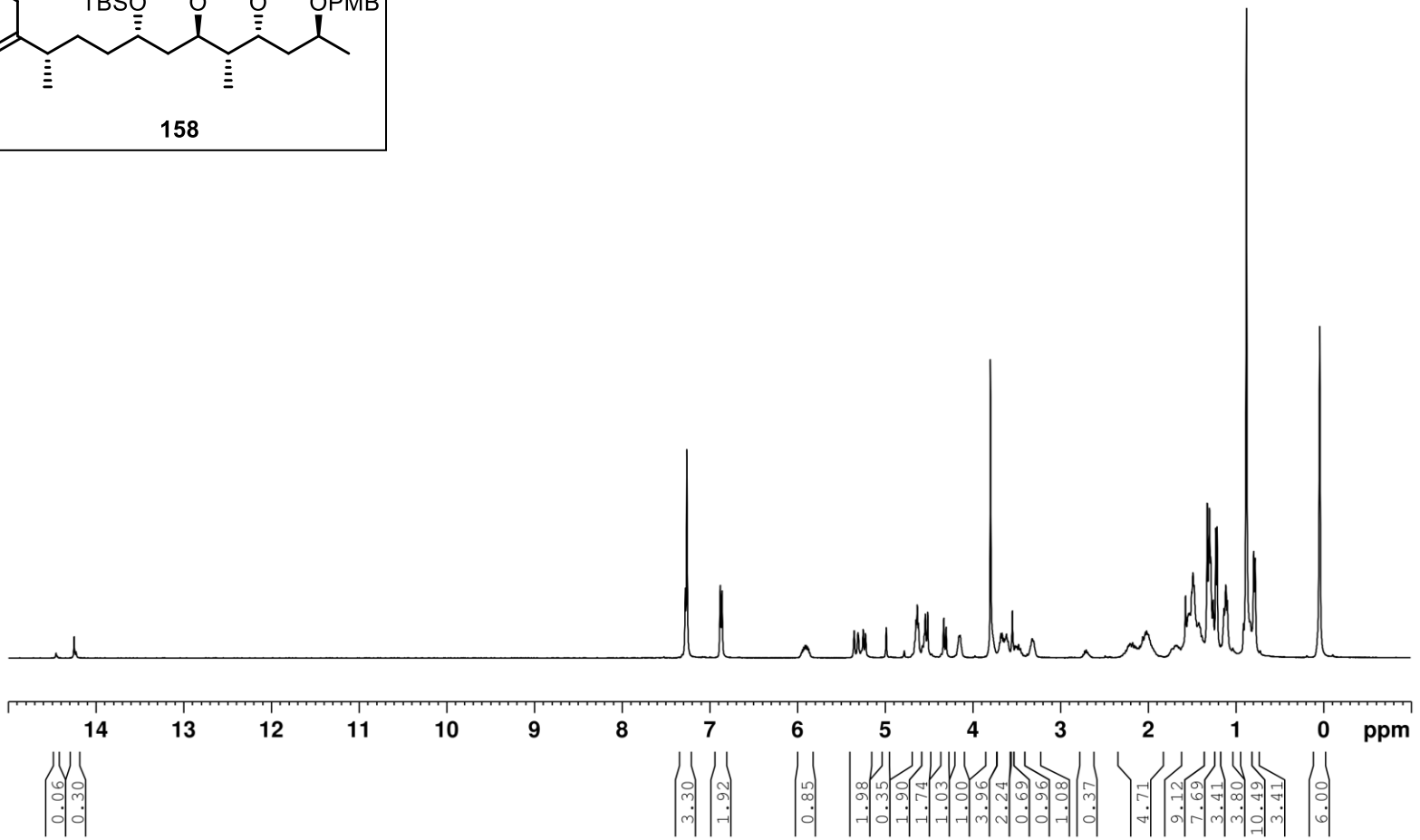
136

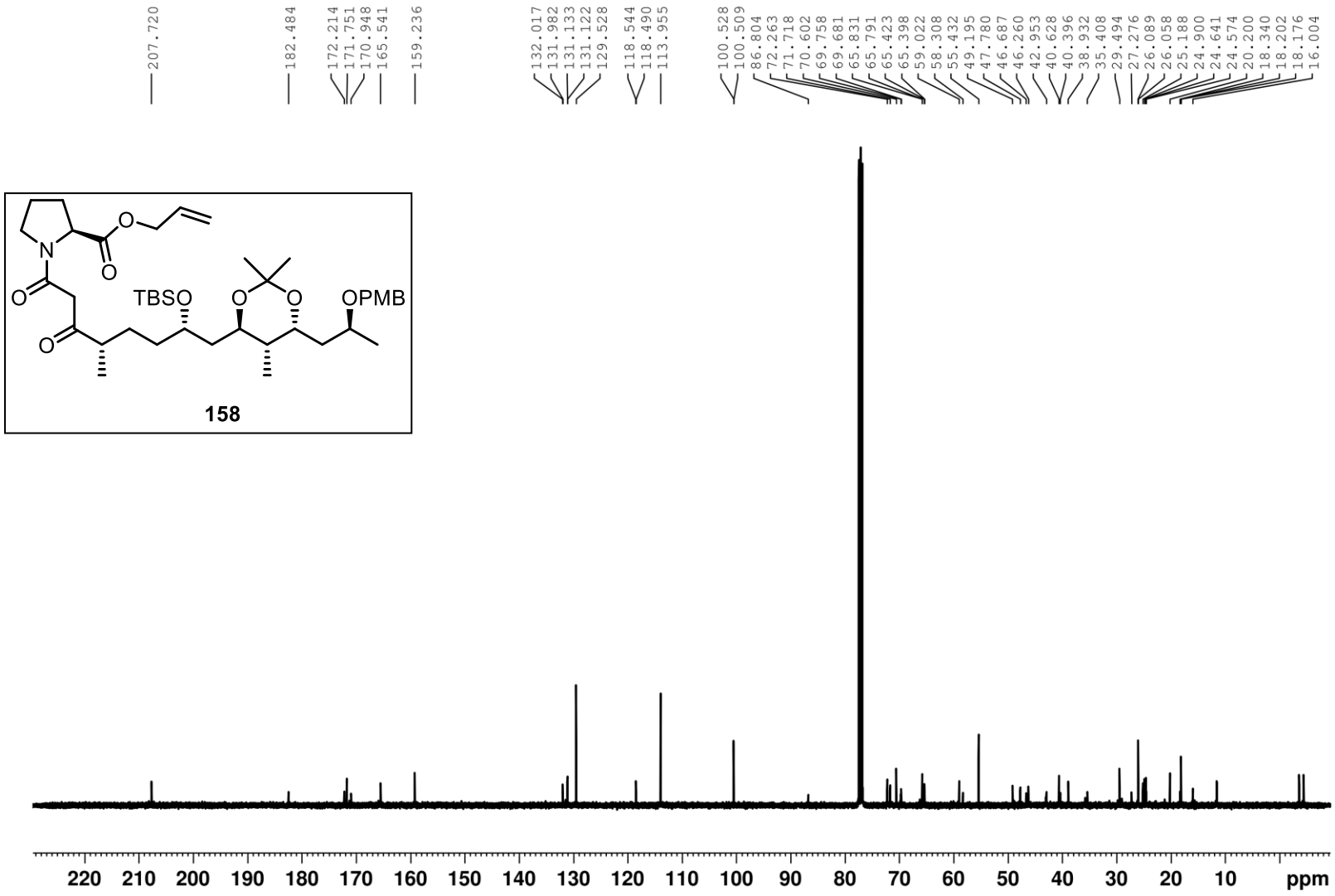

10
9
8
7
6
5
4
3
2
1
0
ppm
0.98
3.58
2.15
1.00
1.01
1.03
4.25
1.10
1.02
1.05
1.24
3.54
6.44
2.56
4.79
3.65
3.36
10.17
3.32
6.43

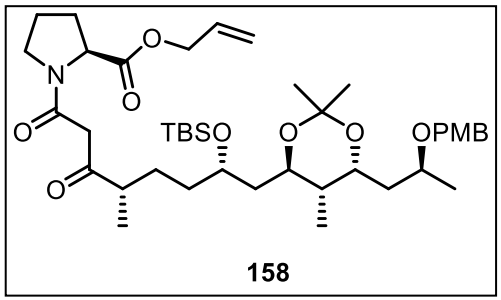

205.236
159.262
131.121
129.559
113.967
100.560
72.348
71.718
70.632
69.655
65.403
55.447
46.581
40.668
38.954
35.273
26.044
26.030
25.191
25.120
24.625
20.207
18.190
13.473
11.613
-3.653
-4.384
O
TBSO
O
O
OPMB
H
136
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
N
O
O
O
TBSO
O
O
OPMB
O

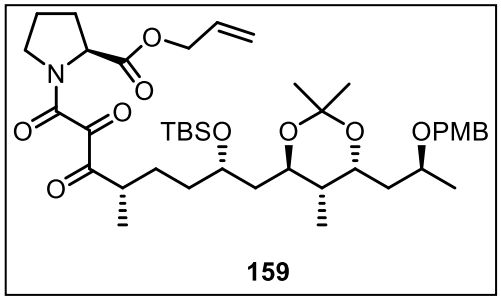
158


14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.06
0.30
3.30
1.92
0.85
1.98
0.35
1.90
1.74
1.03
1.00
3.96
2.24
0.69
0.96
1.08
0.37
4.71
9.12
7.69
3.41
3.80
10.49
3.41
6.00

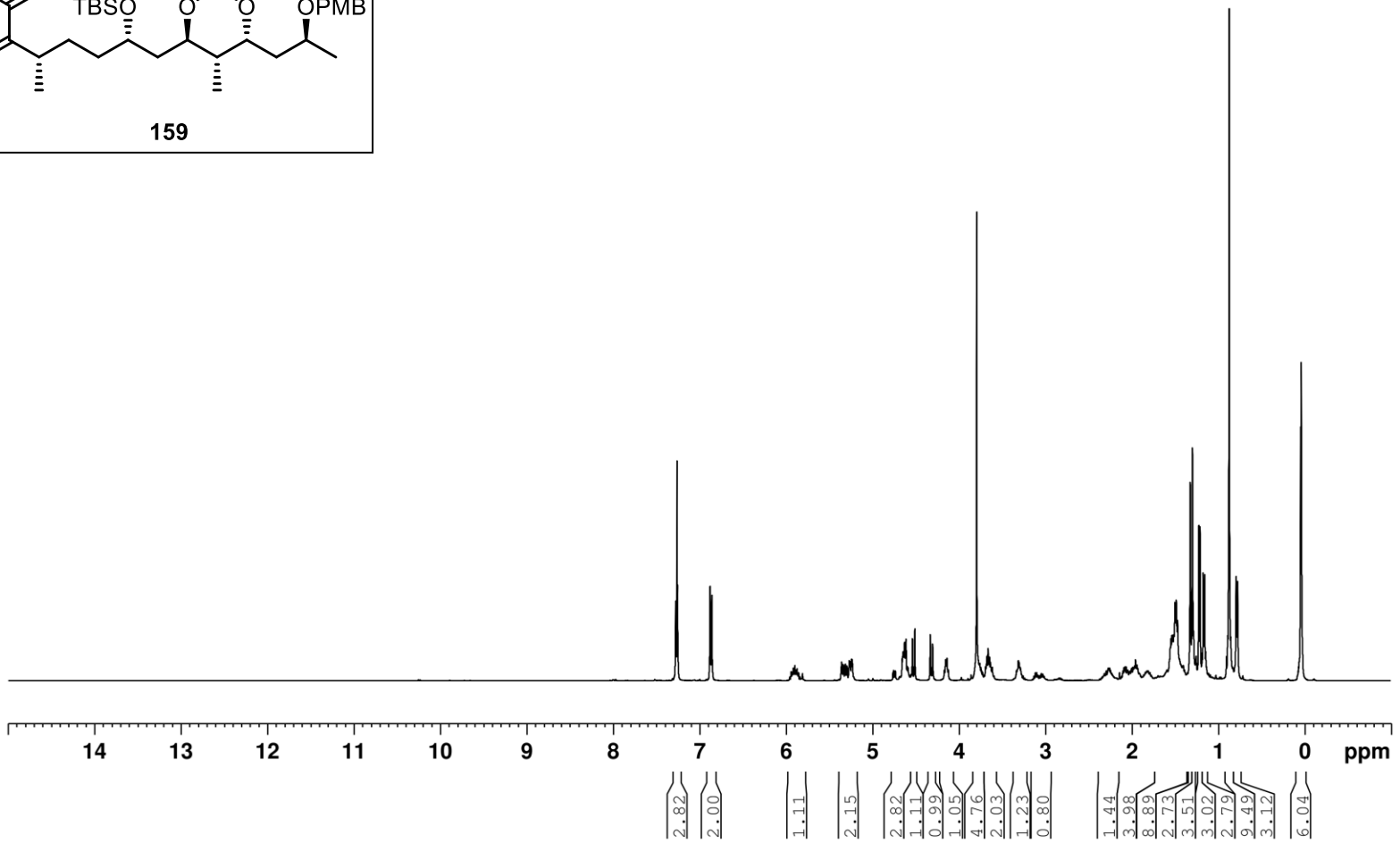

207.720
182.484
172.214
171.751
170.948
165.541
159.236
132.017
131.982
131.133
131.122
129.528
118.544
118.490
113.955
100.528
100.509
86.804
72.263
71.718
70.602
69.758
69.681
65.831
65.791
65.423
65.398
59.022
58.308
55.432
49.195
47.780
46.687
46.260
42.953
40.628
40.396
38.932
35.408
29.494
27.276
26.089
26.058
25.188
24.900
24.641
24.574
20.200
18.340
18.202
18.176
16.004
TBSO
OPMB
158
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

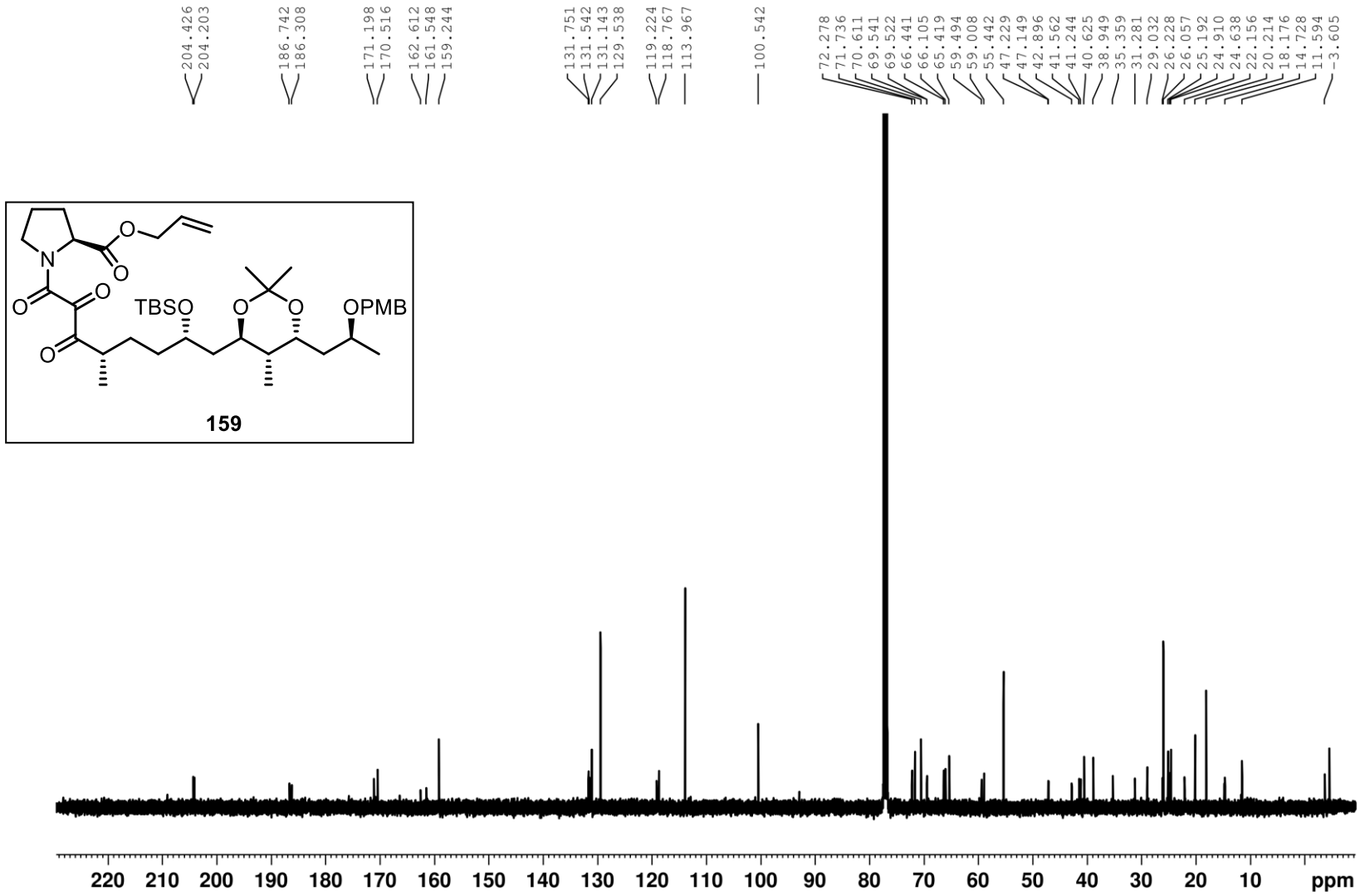

TBSO
OPMB
158

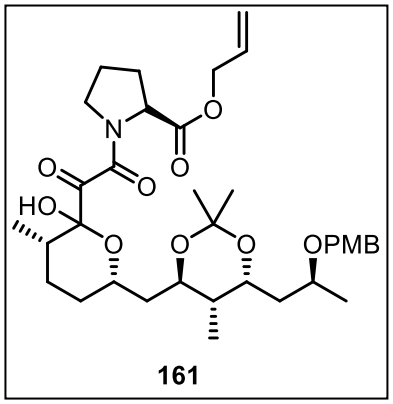
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
1d-NOE steady state, saturation of spins at 14.27 ppm
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
1d-NOE steady state, saturation of spins at 14.47 ppm


O
N
O
O
O
TBSO
O
O
OPMB
O

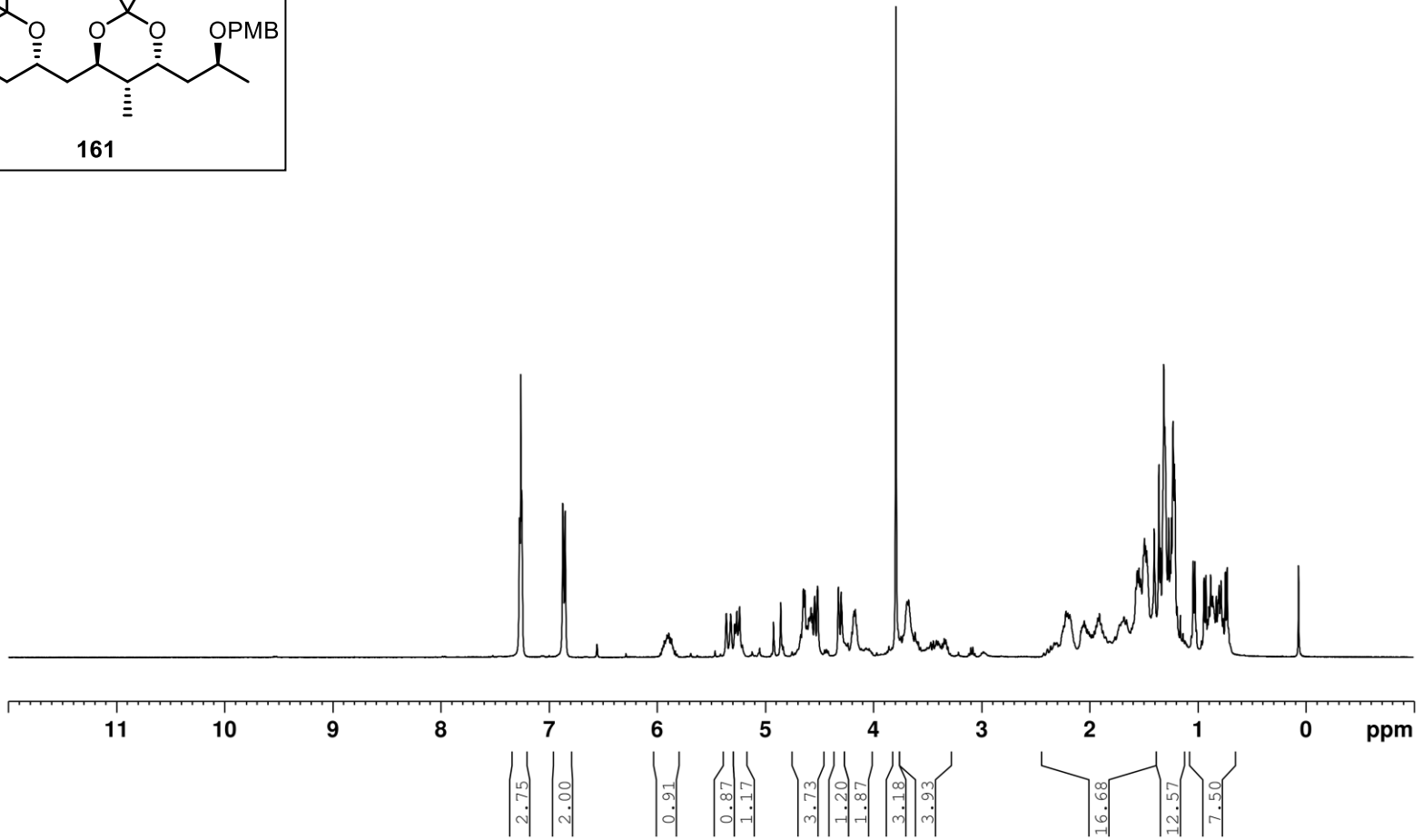
159

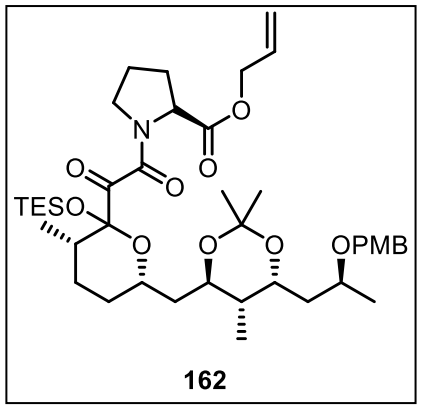

14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
2.82
2.00
1.11
2.15
2.82
1.11
0.99
1.05
4.76
2.03
1.23
0.80
1.44
3.98
8.89
2.73
3.51
3.02
2.79
9.49
3.12
6.04


204.426
204.203
186.742
186.308
171.198
170.516
162.612
161.548
159.244
131.751
131.542
131.143
129.538
119.224
118.767
113.967
100.542
72.278
71.736
70.611
69.541
69.522
66.441
66.105
65.419
59.494
59.008
55.442
47.229
47.149
42.896
41.562
41.244
40.625
38.949
35.359
31.281
29.032
26.228
26.057
25.192
24.910
24.638
22.156
20.214
18.176
14.728
11.594
-3.605
TBSO
OPMB
159
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


HO
O
O
O
O
O
O
O
OPMB

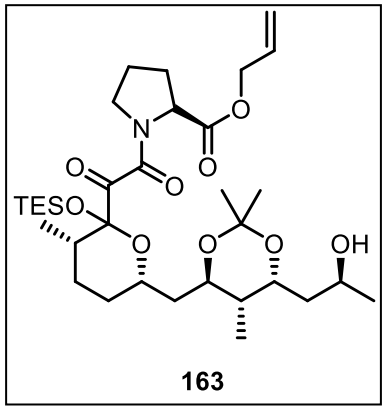
161


11
10
9
8
7
6
5
4
3
2
1
0
ppm
2.75
2.00
0.91
0.87
1.17
3.73
1.20
1.87
3.18
3.93
16.68
12.57
7.50


TESO
O
O
O
O
O
O
O
O
OPMB

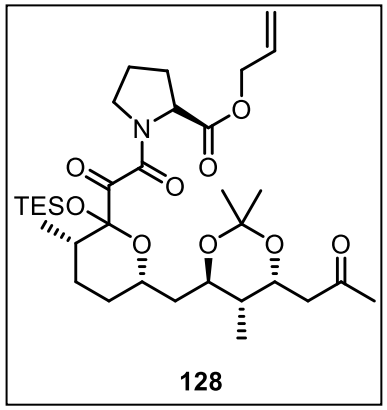
162

11
10
9
8
7
6
5
4
3
2
1
0
ppm
4.91
1.95
1.00
0.98
1.06
3.88
1.19
1.75
3.05
4.17
7.56
5.67
4.99
4.60
10.94
3.96
5.58


TESO
O
N
O
O
O
O
O
O
O
OH

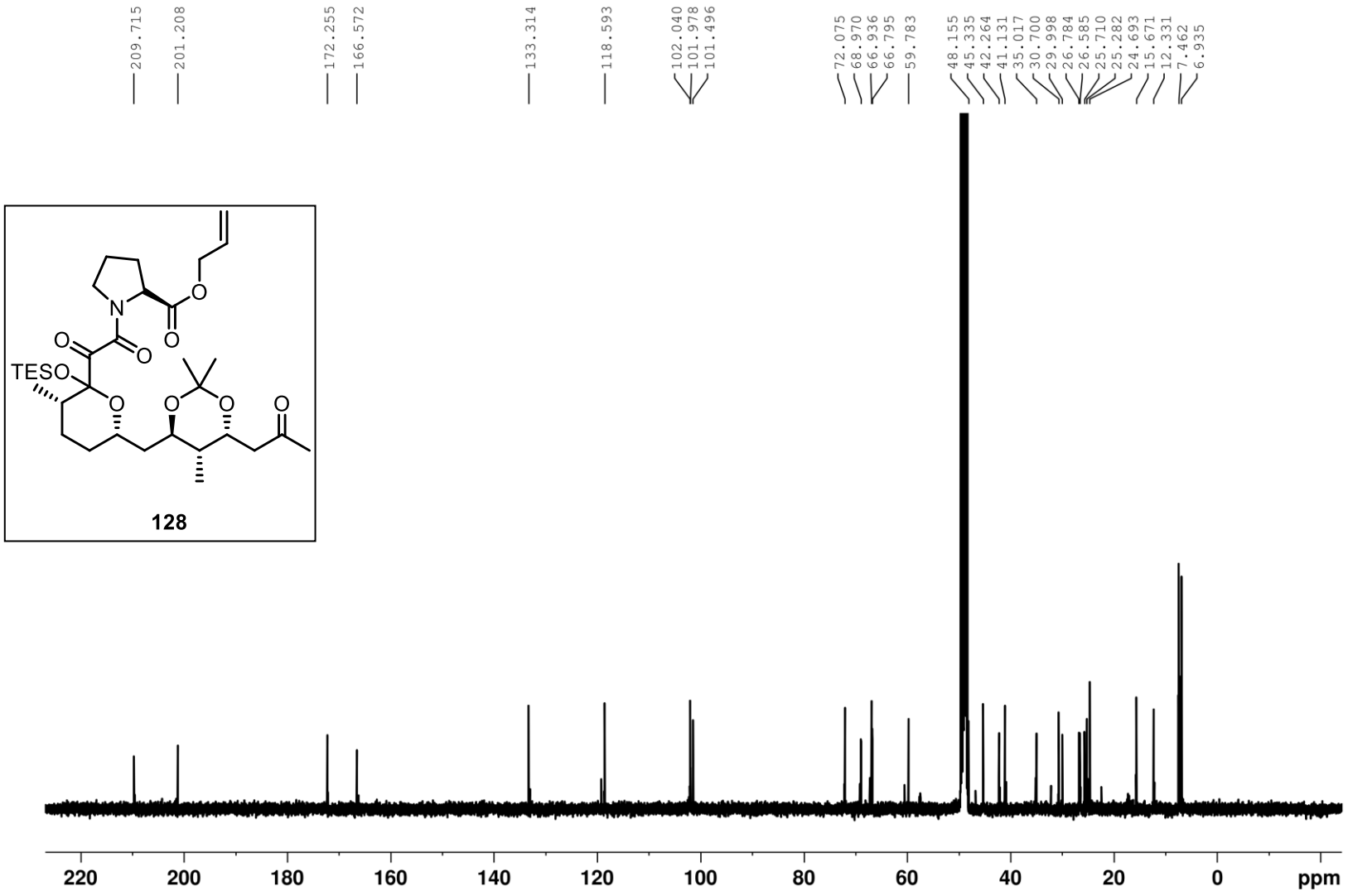
163

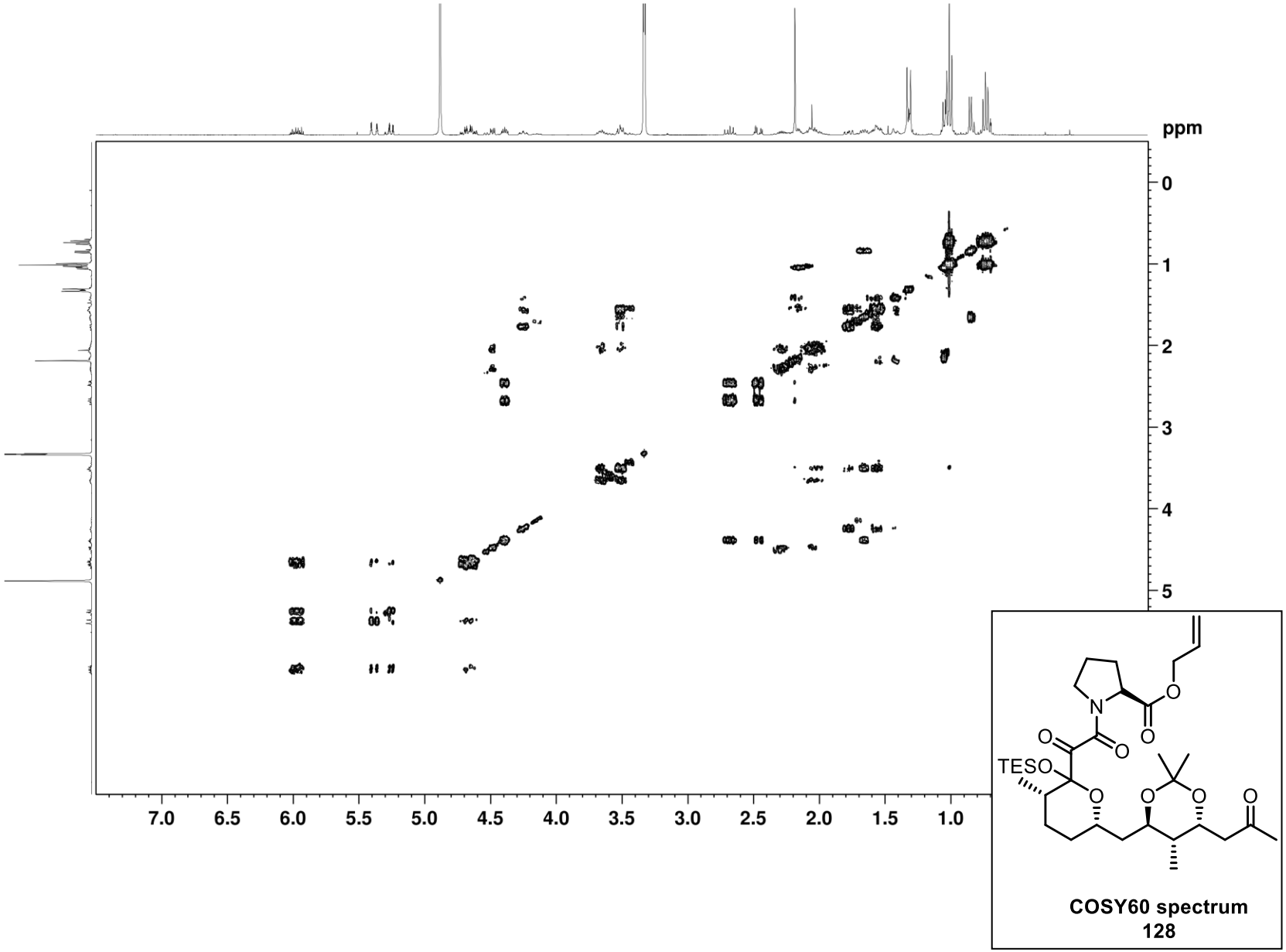
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.93
2.00
2.76
1.39
1.43
1.85
0.97
1.71
2.07
2.17
3.59
4.59
1.79
7.37
6.90
16.49
6.71

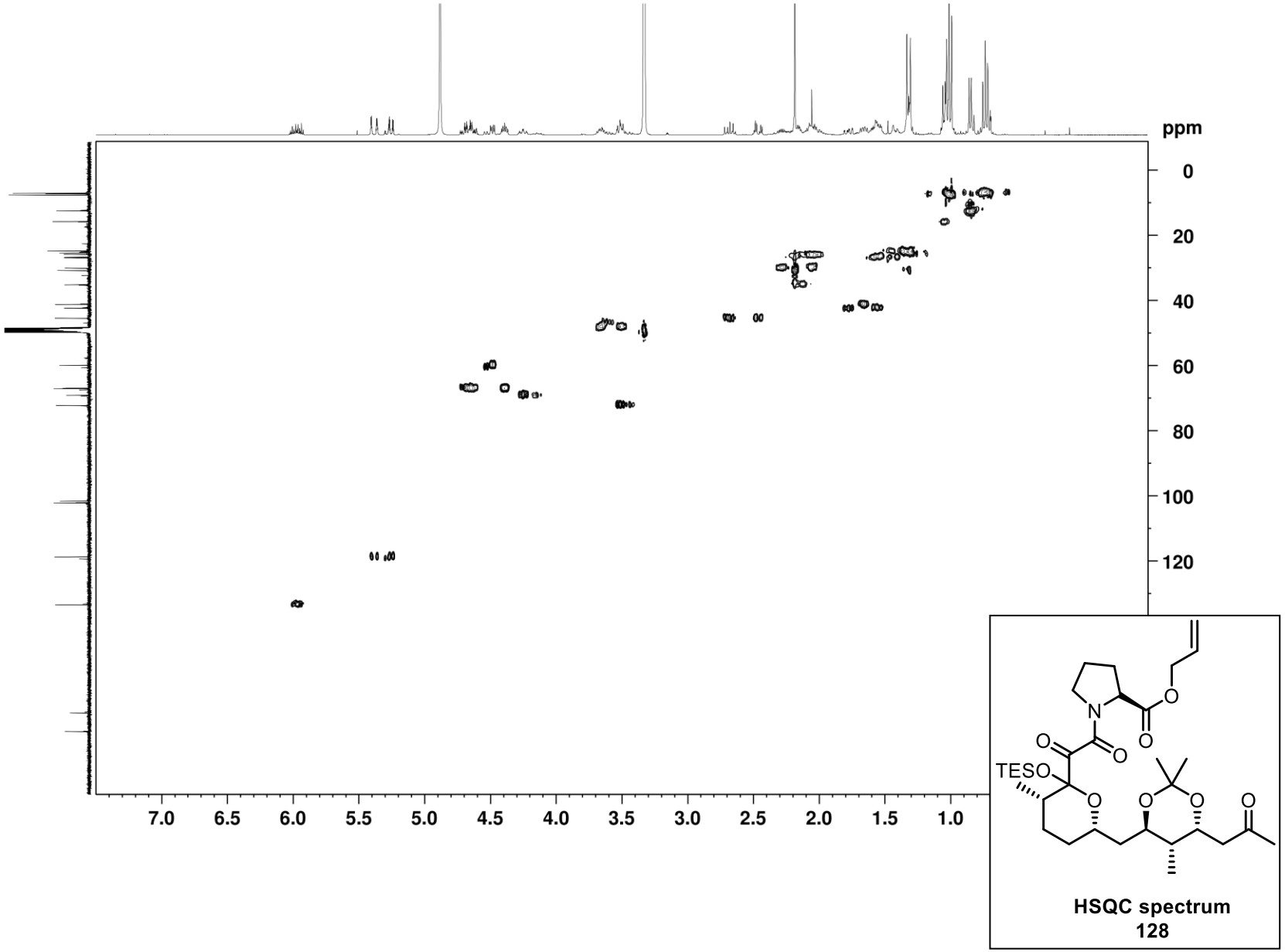

TESO
O
N
O
O
O
O
O
O
O
O

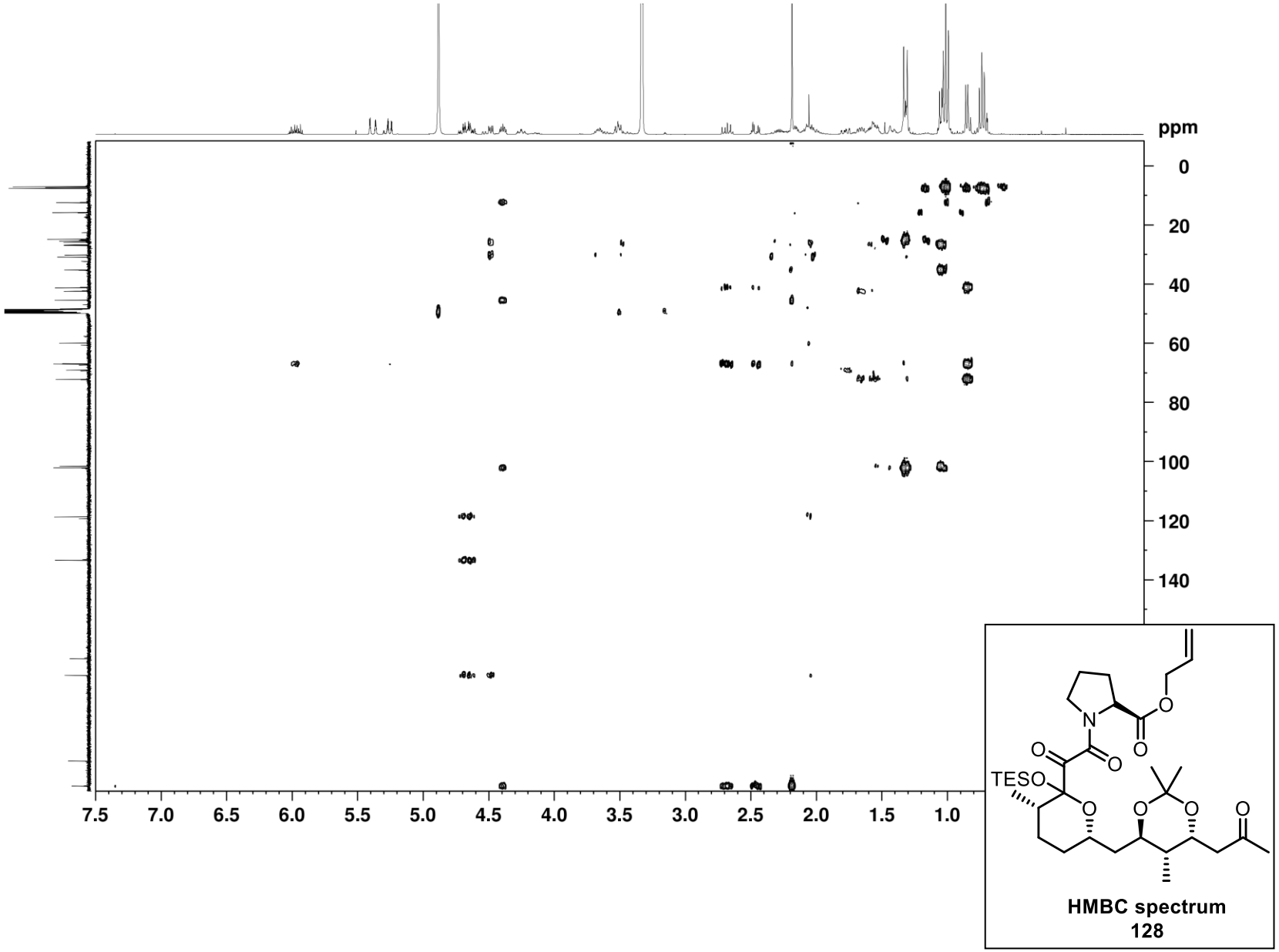
128

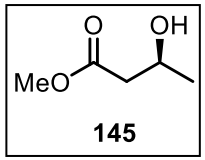
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


209.715
201.208
172.255
166.572
133.314
118.593
102.040
101.978
101.496
72.075
68.970
66.936
66.795
59.783
48.155
45.335
42.264
41.131
35.017
30.700
29.998
26.784
26.585
25.710
25.282
24.693
15.671
12.331
7.462
6.935
TESO
O
N
O
O
O
O
O
O
O
O
128
220
200
180
160
140
120
100
80
60
40
20
0
ppm

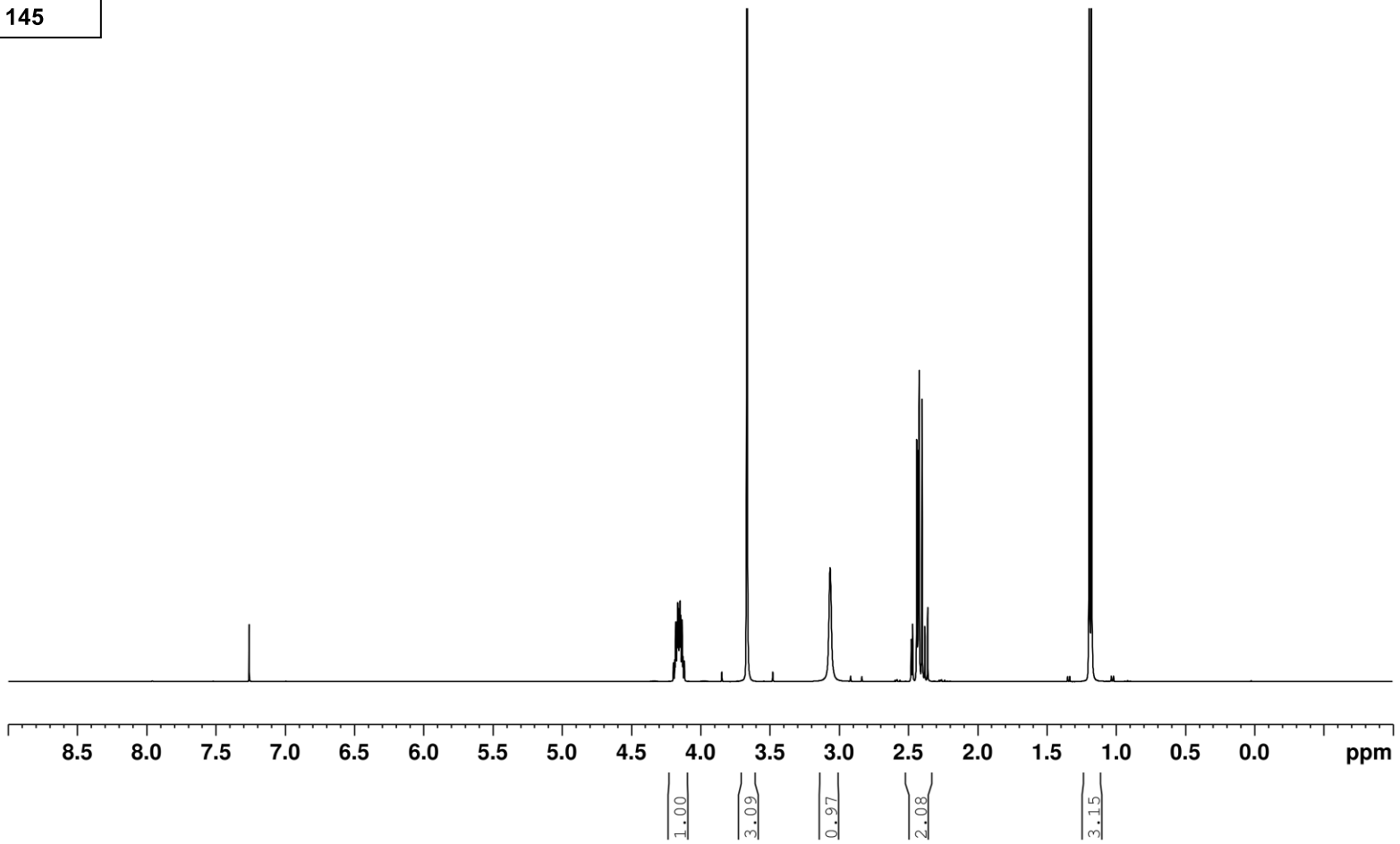

ppm
0
1
2
3
4
5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
TESO
N
O
O
O
O
O
O
O
O
O
COSY60 spectrum
128

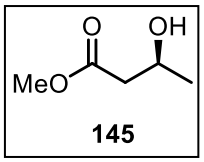

ppm
0
20
40
60
80
100
120
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
TESO
N
O
O
O
O
O
O
O
O
HSQC spectrum
128

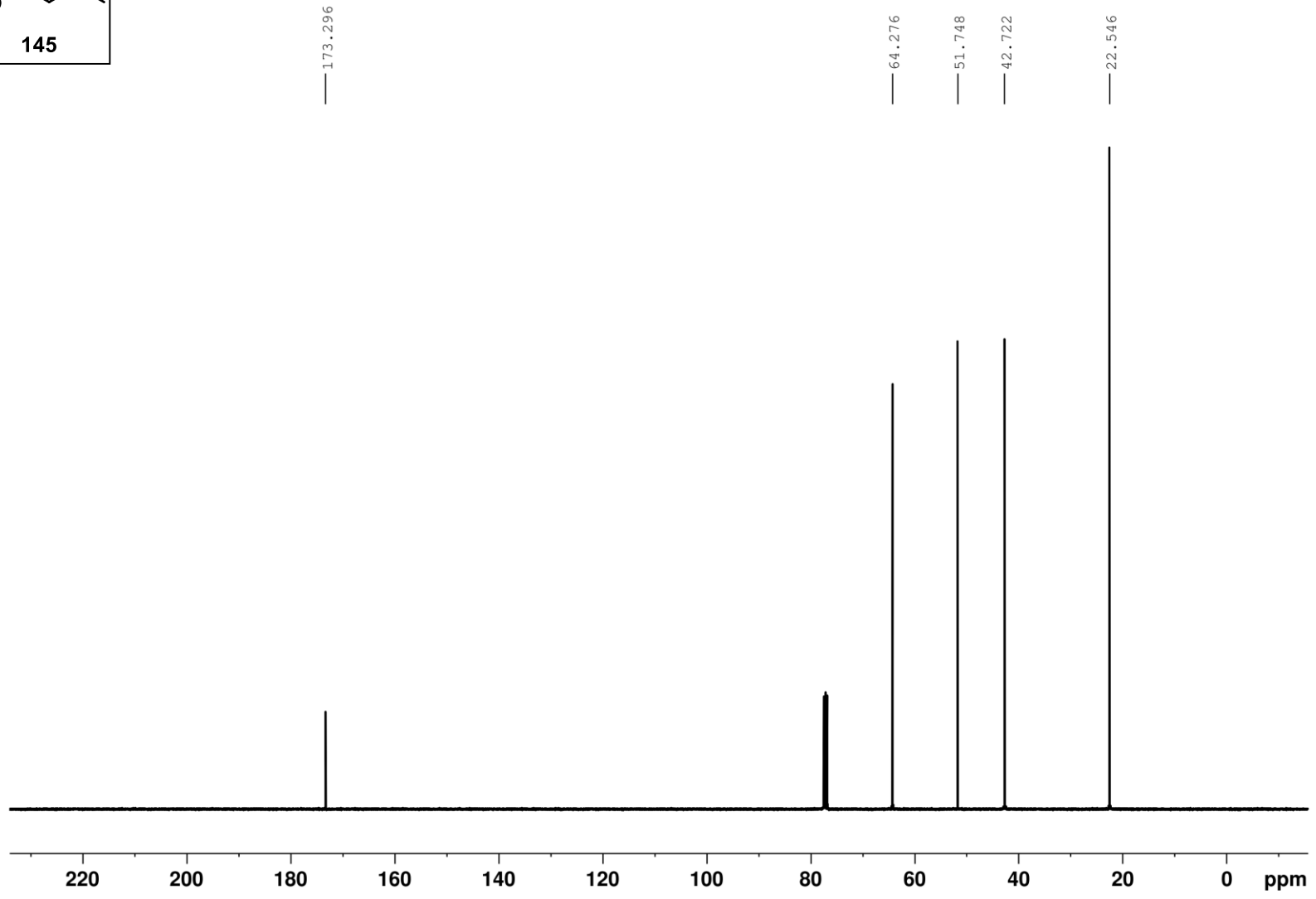

ppm
0
20
40
60
80
100
120
140
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
TESO
N
O
O
O
O
O
O
O
O
HMBC spectrum
128

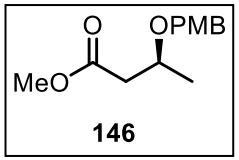

O
OH
MeO

145

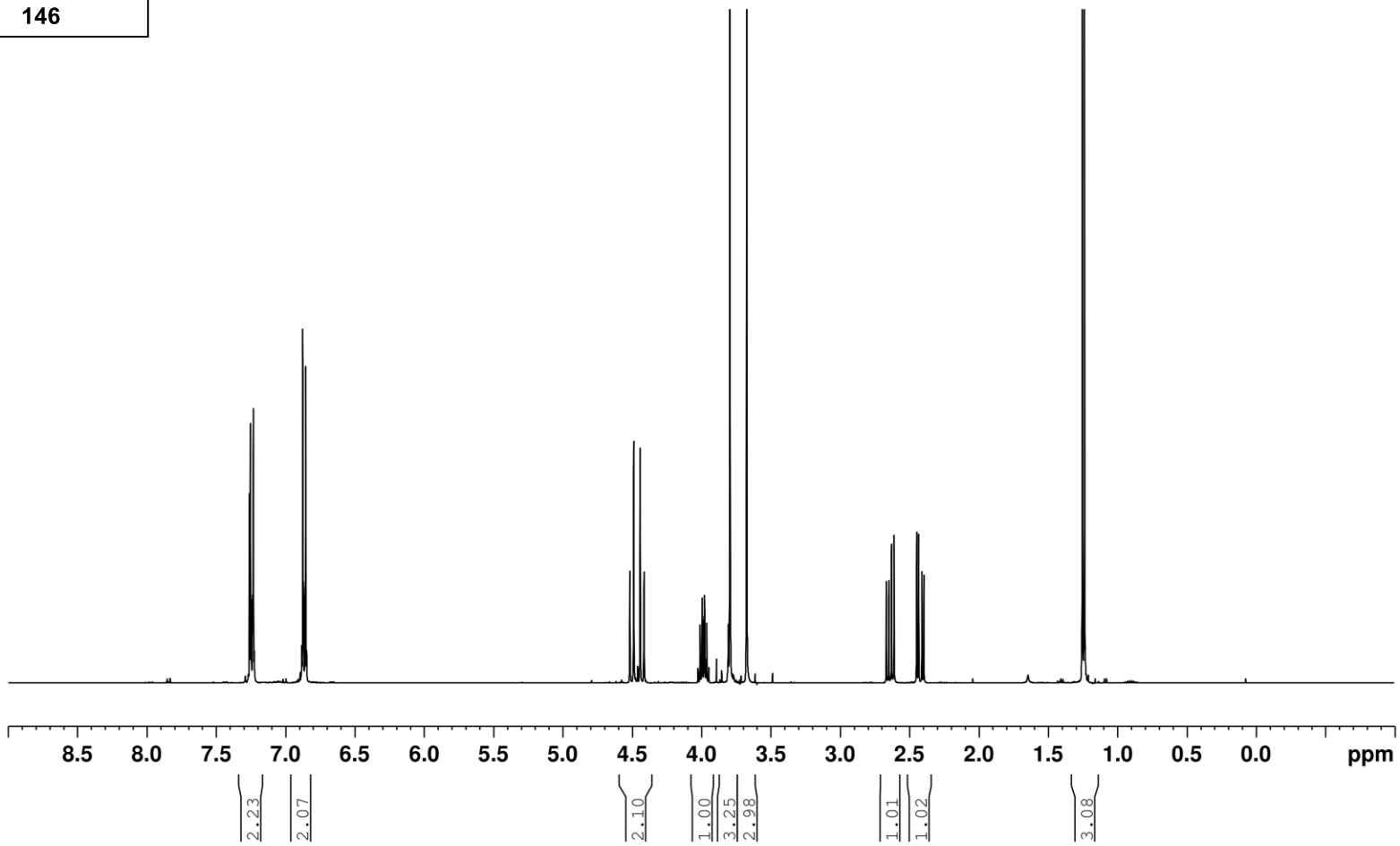

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.00
3.09
0.97
2.08
3.15

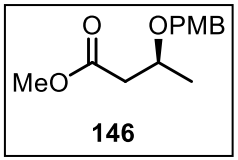

O
OH
MeO
145


173.296
64.276
51.748
42.722
22.546
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
OPMB
MeO

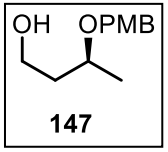
146

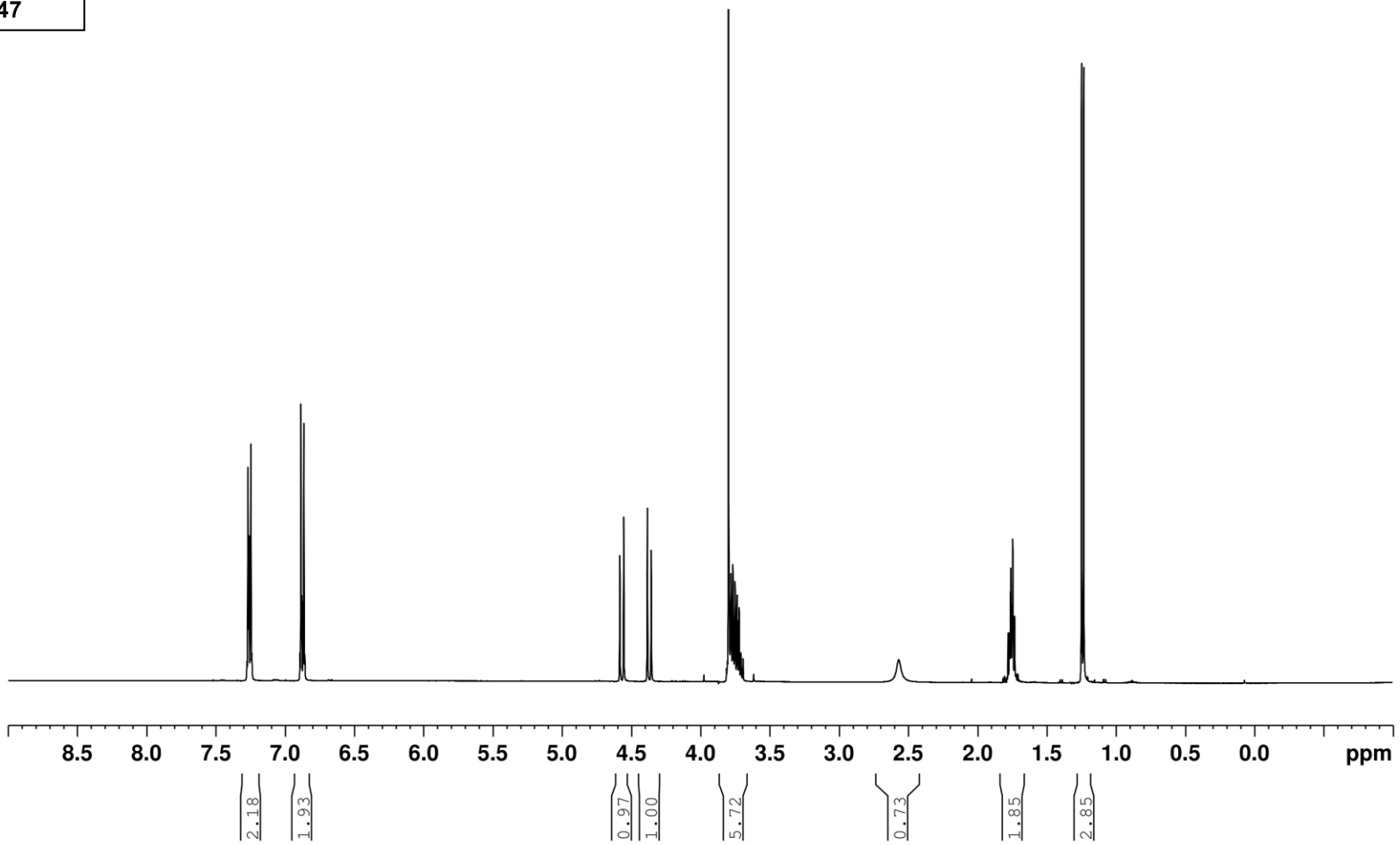

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
2.23
2.07
2.10
1.00
3.25
2.98
1.01
1.02
3.08

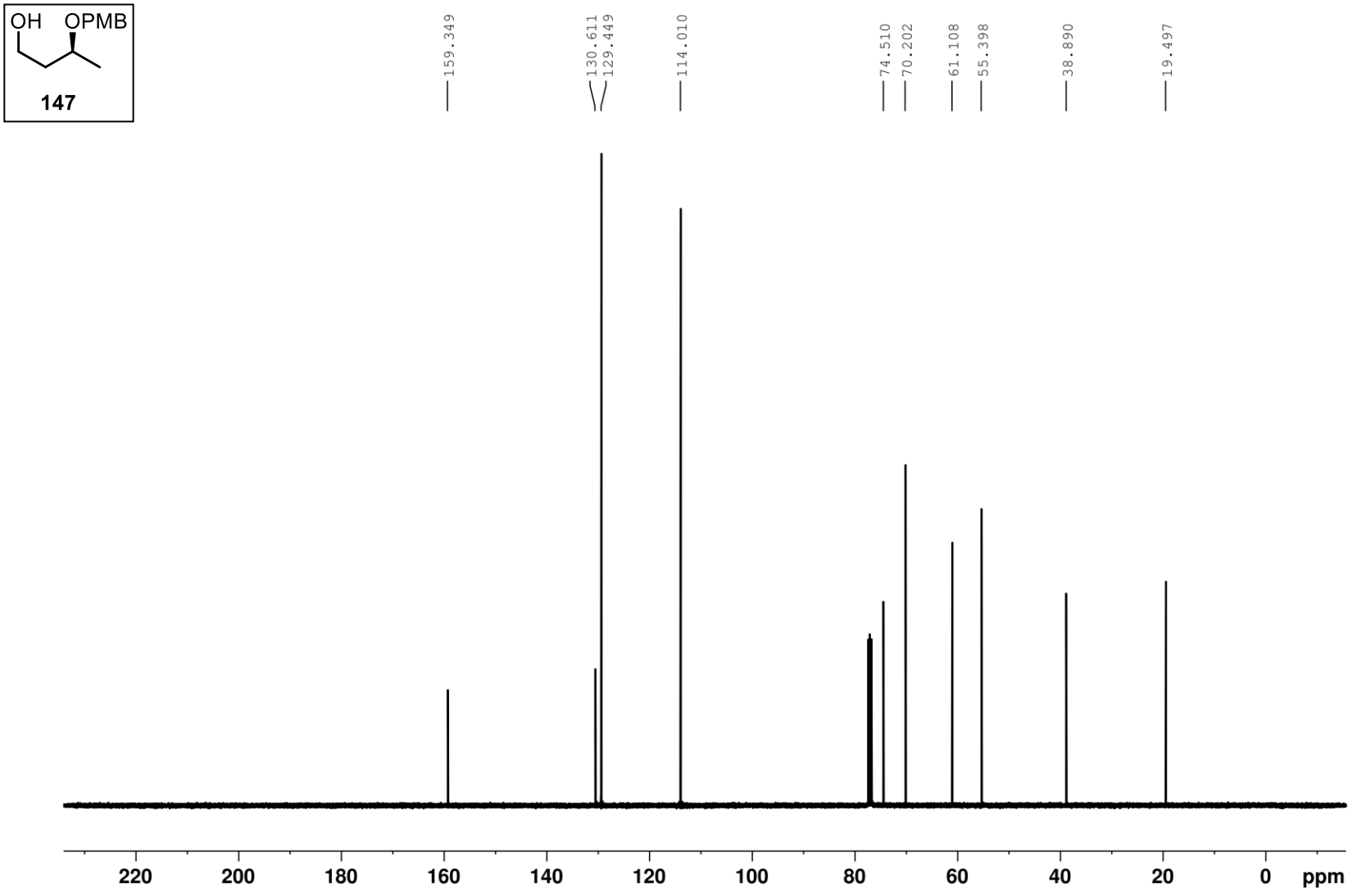

O
OPMB
MeO

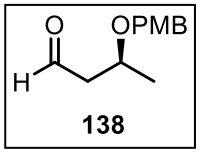
146

172.078
159.274
130.718
129.361
113.880
71.678
70.634
55.388
51.686
41.972
19.983
220
200
180
160
140
120
100
80
60
40
20
0
ppm

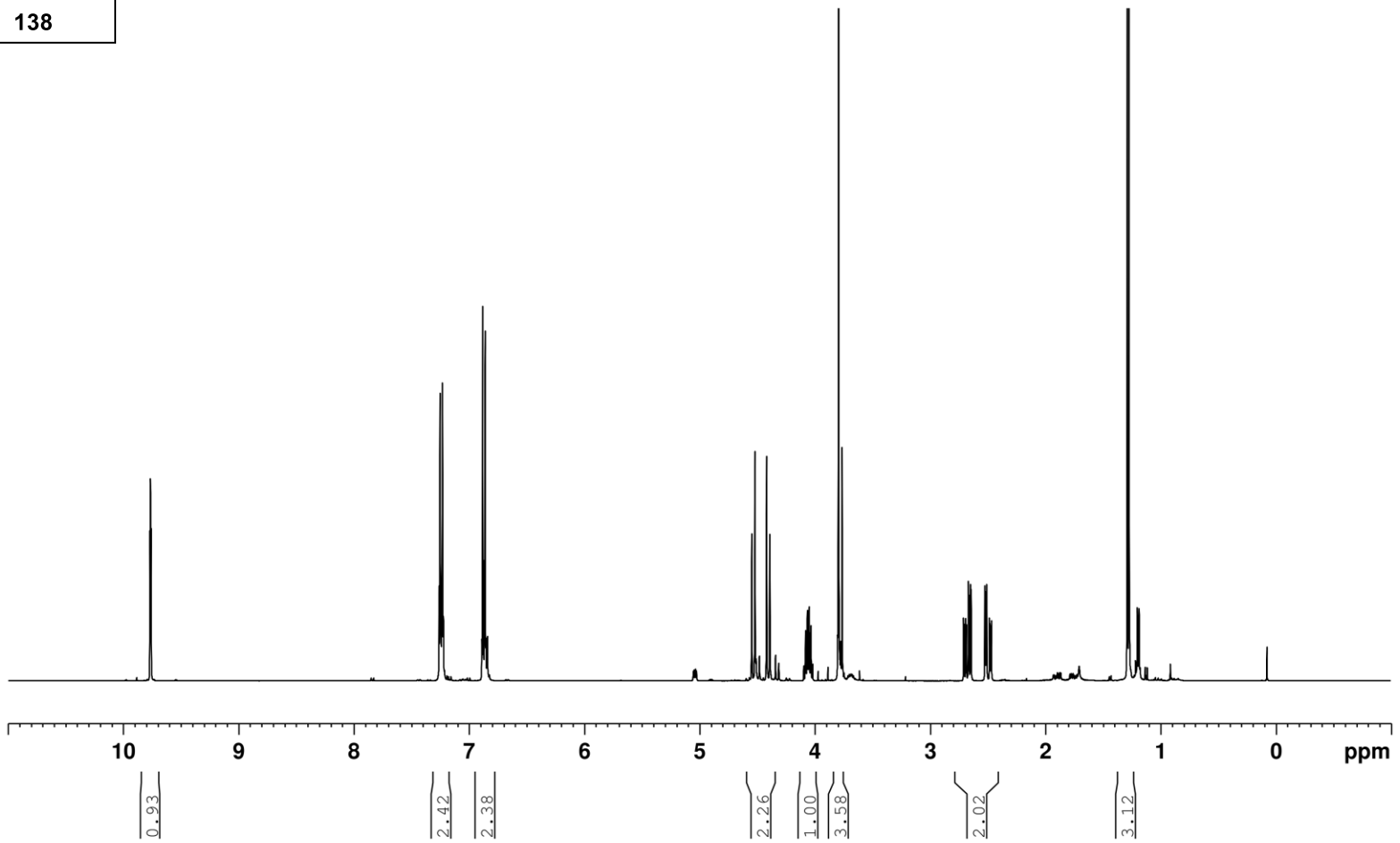

OH
OPMB
147

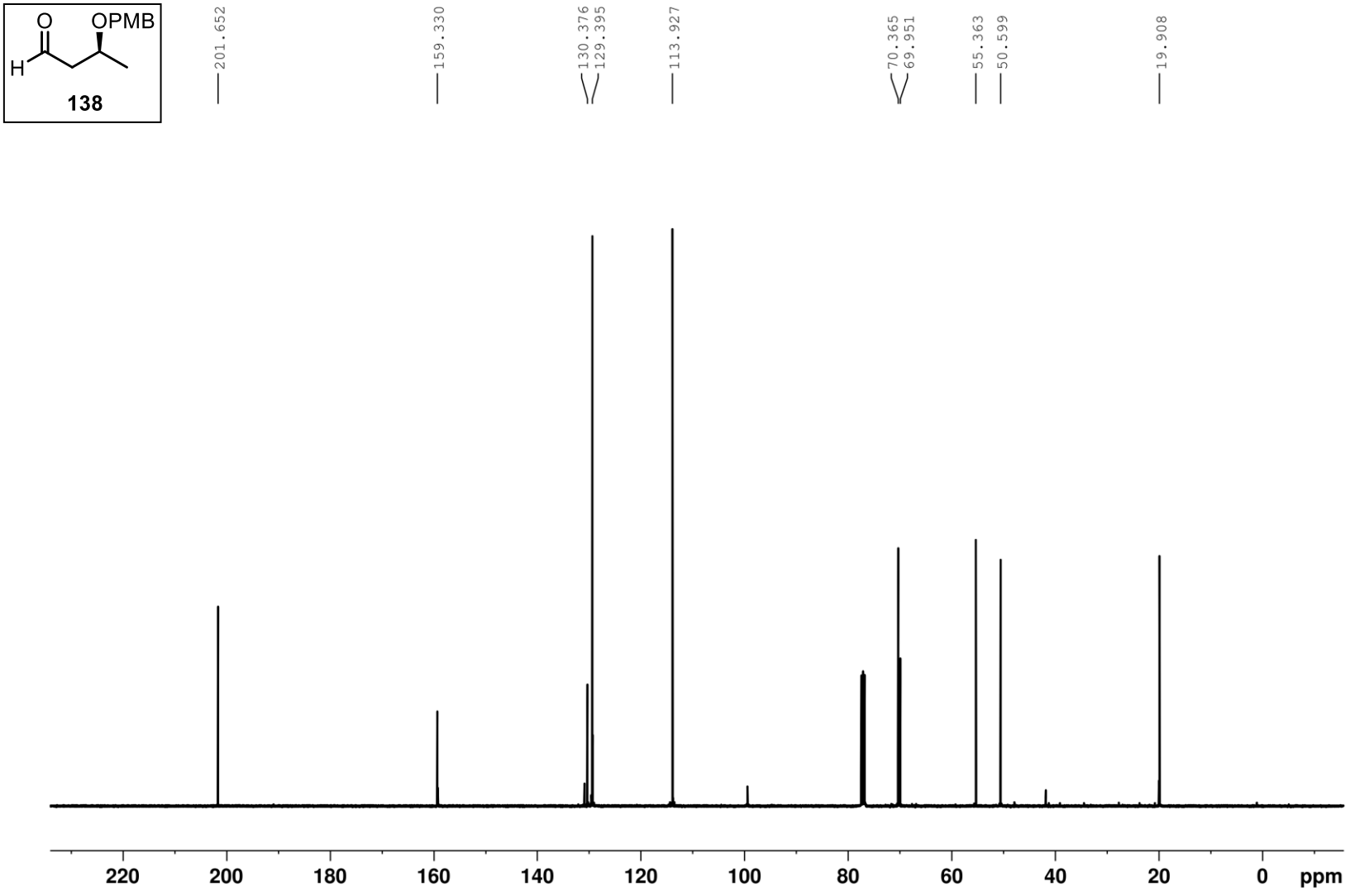

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
2.18
1.93
0.97
1.00
5.72
0.73
1.85
2.85

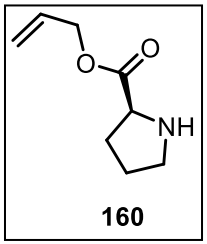

OH
OPMB
147
159.349
130.611
129.449
114.010
74.510
70.202
61.108
55.398
38.890
19.497
220
200
180
160
140
120
100
80
60
40
20
0
ppm



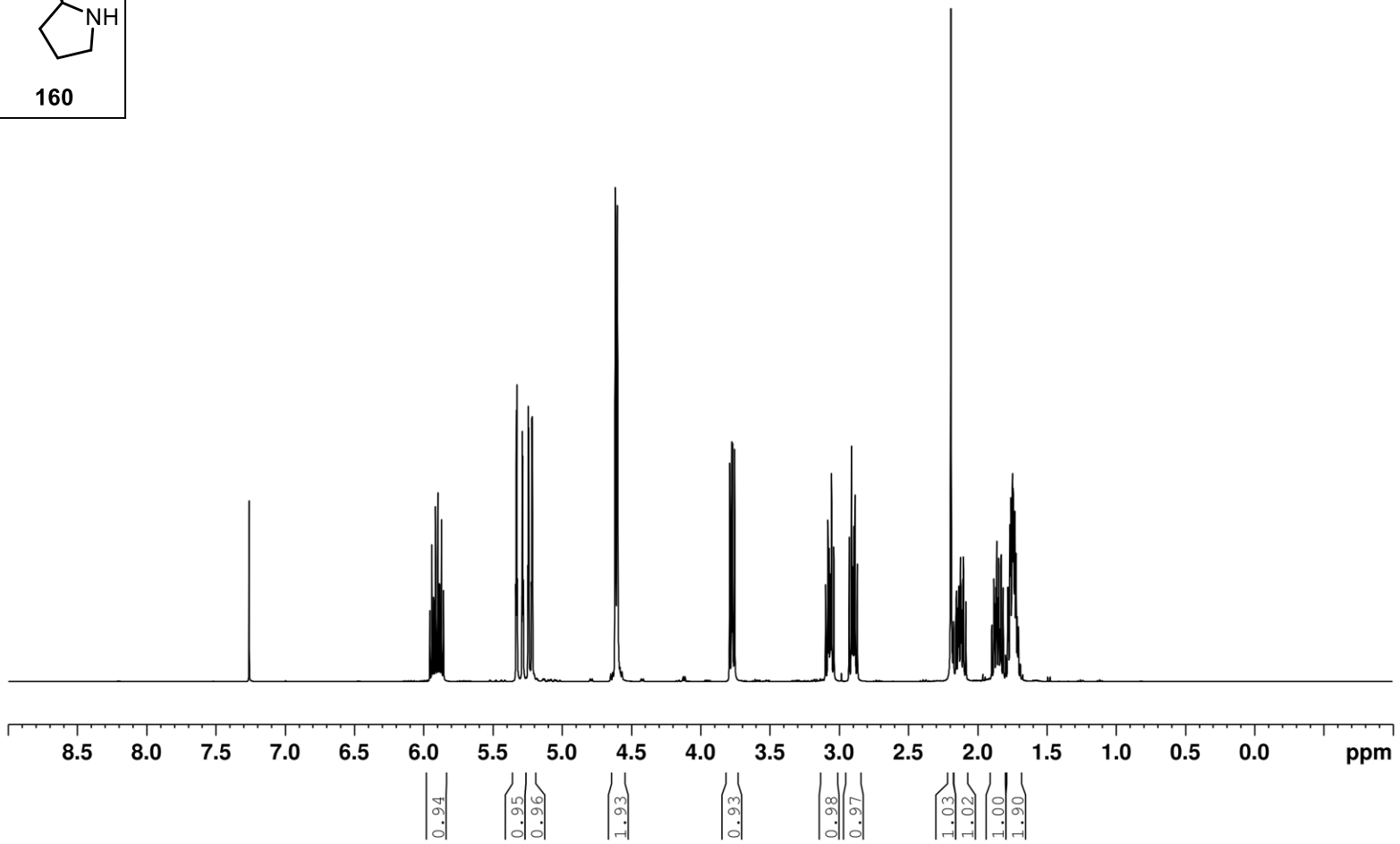
138

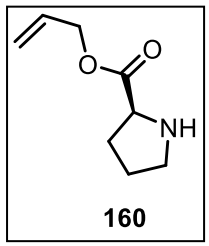



O
OPMB
H
138
201.652
159.330
130.376
129.395
113.927
70.365
69.951
55.363
50.599
19.908
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
O
NH

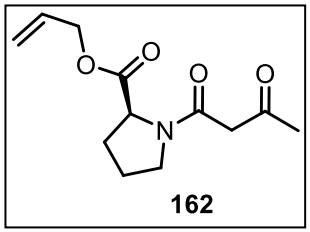
160

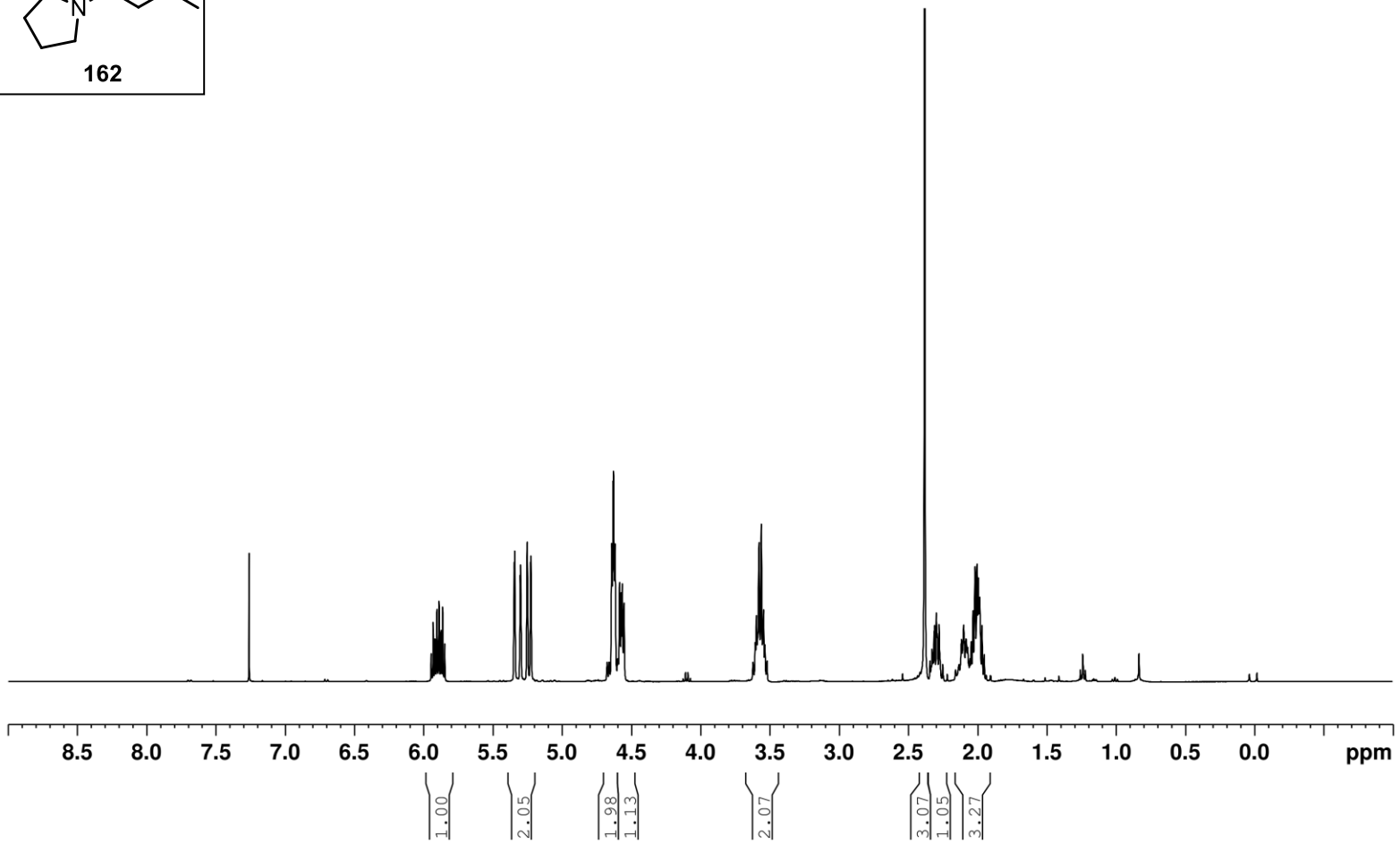

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
0.94
0.95
0.96
1.93
0.93
0.98
0.97
1.03
1.02
1.00
1.90

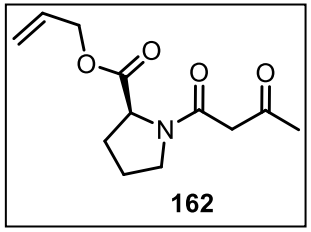

O
O
NH

160

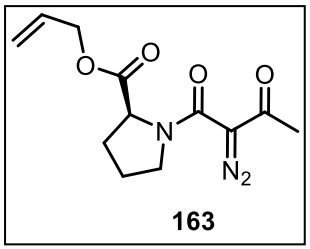
175.323
132.104
118.556
65.598
59.871
47.162
30.385
25.614
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
O
O
O
N
162

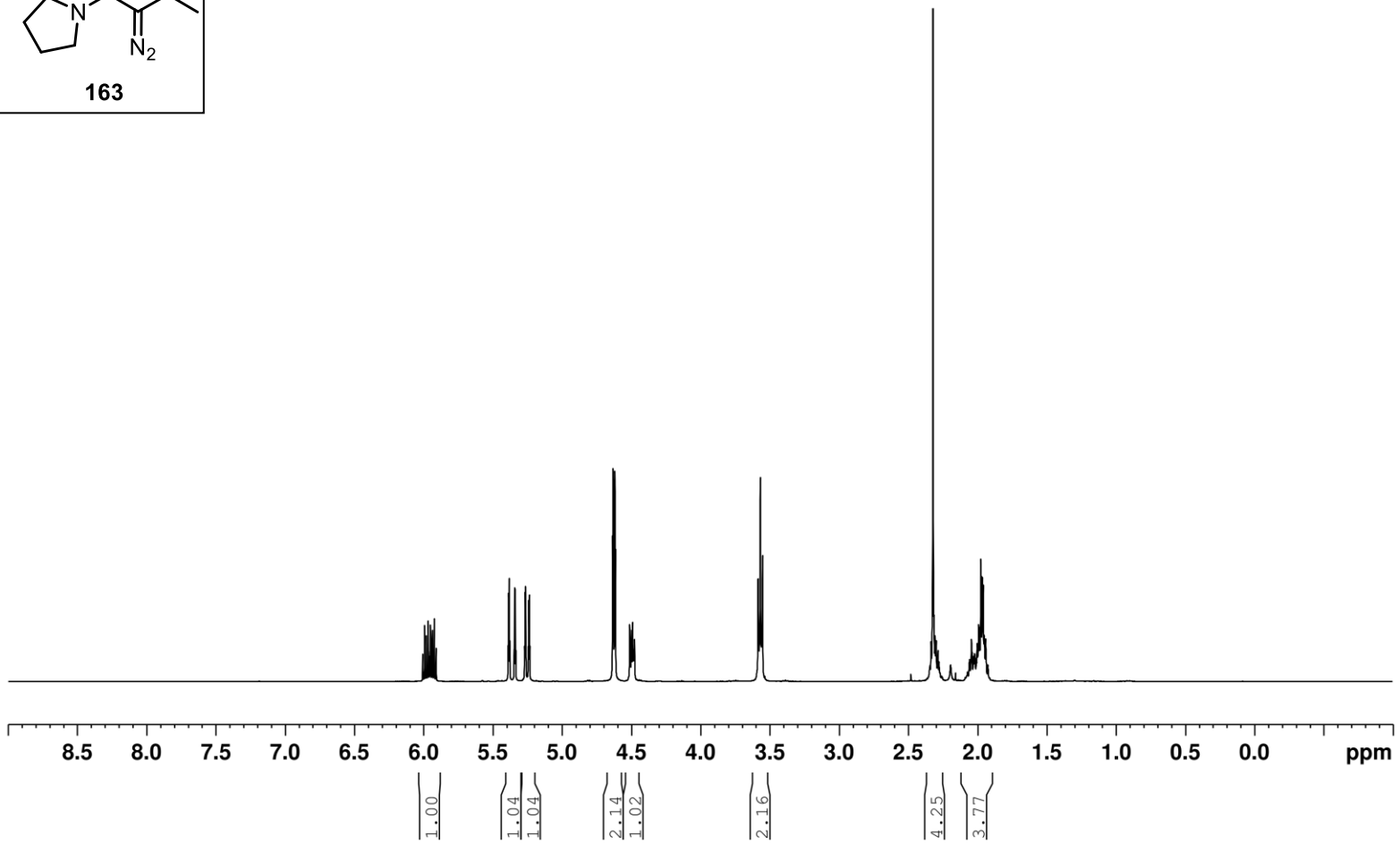

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.00
2.05
1.98
1.13
2.07
3.07
1.05
3.27

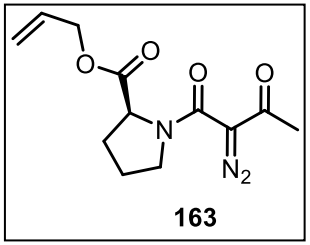

O
O
O
O
N
162

171.457
159.877
131.760
118.824
65.993
60.067
48.560
29.450
27.975
24.938
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
O
O
O
N
N2

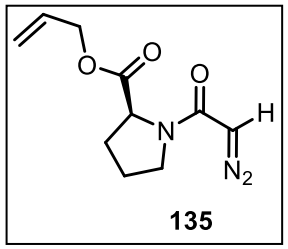
163


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.00
1.04
1.04
2.14
1.02
2.16
4.25
3.77

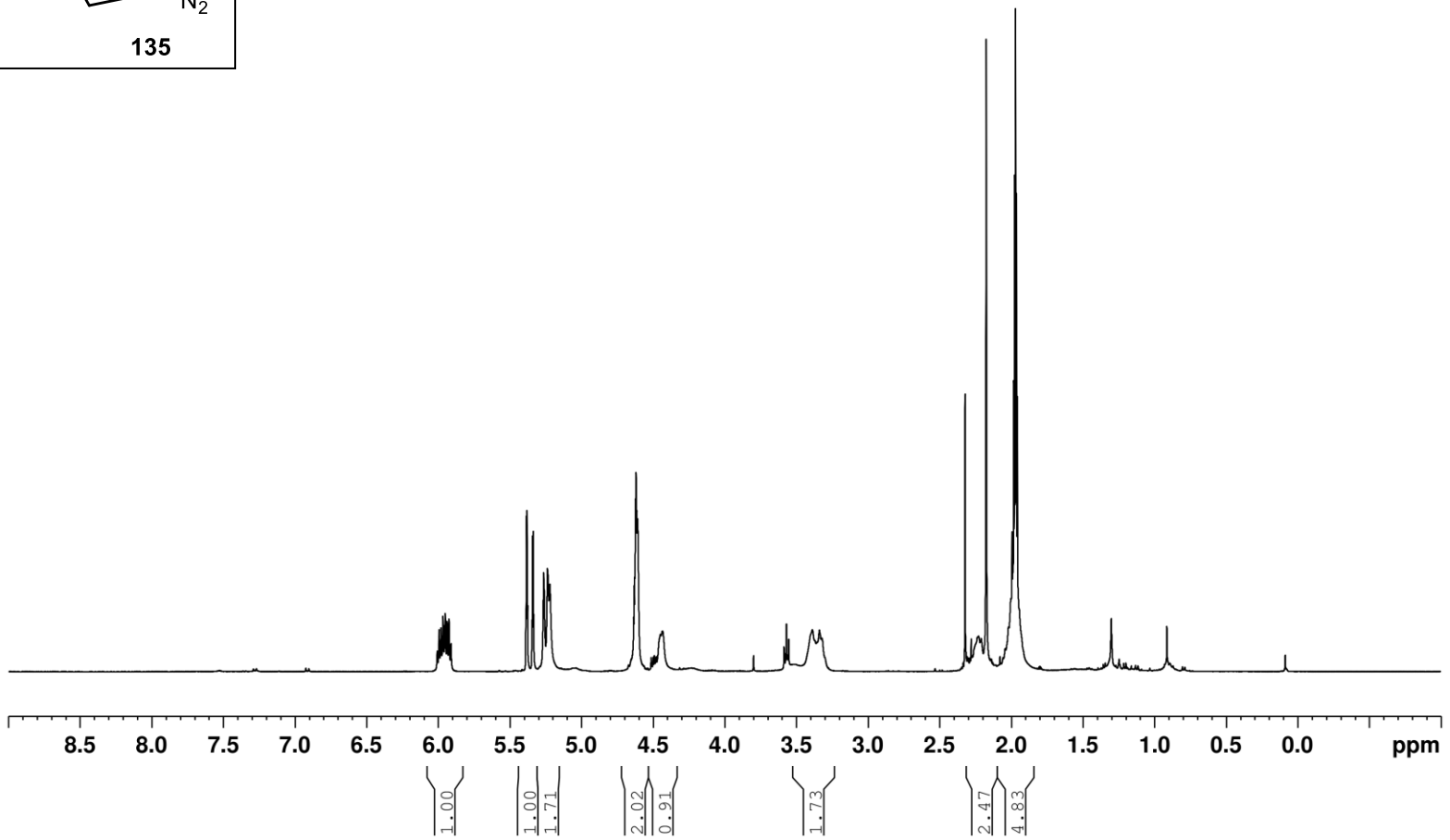

O
O
O
O
N
N_2

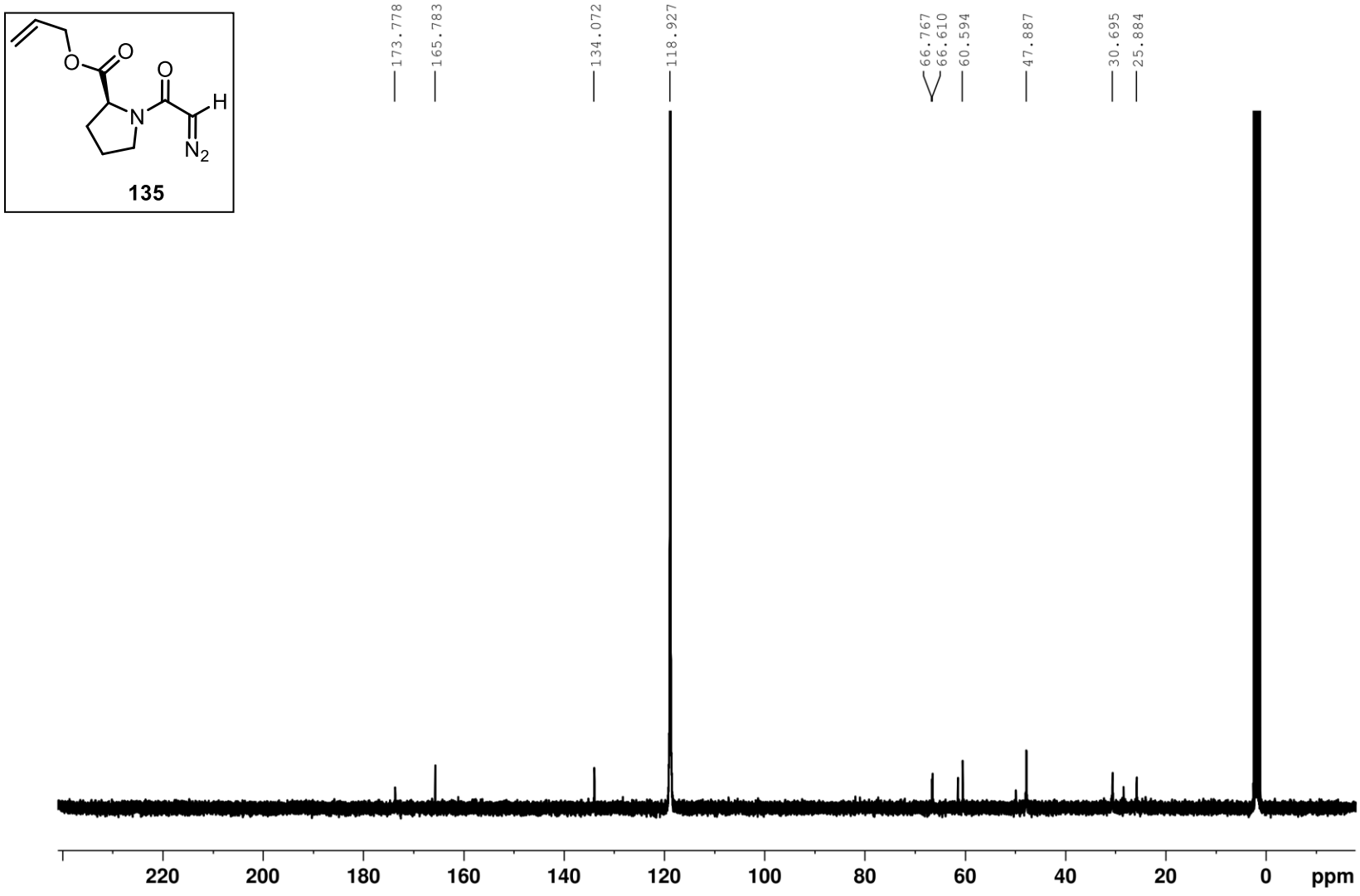
163

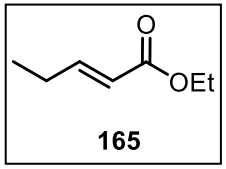
190.830
172.499
160.572
133.341
118.034
74.118
66.120
60.909
49.337
30.174
27.887
25.553
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
O
O
N
H
N_2

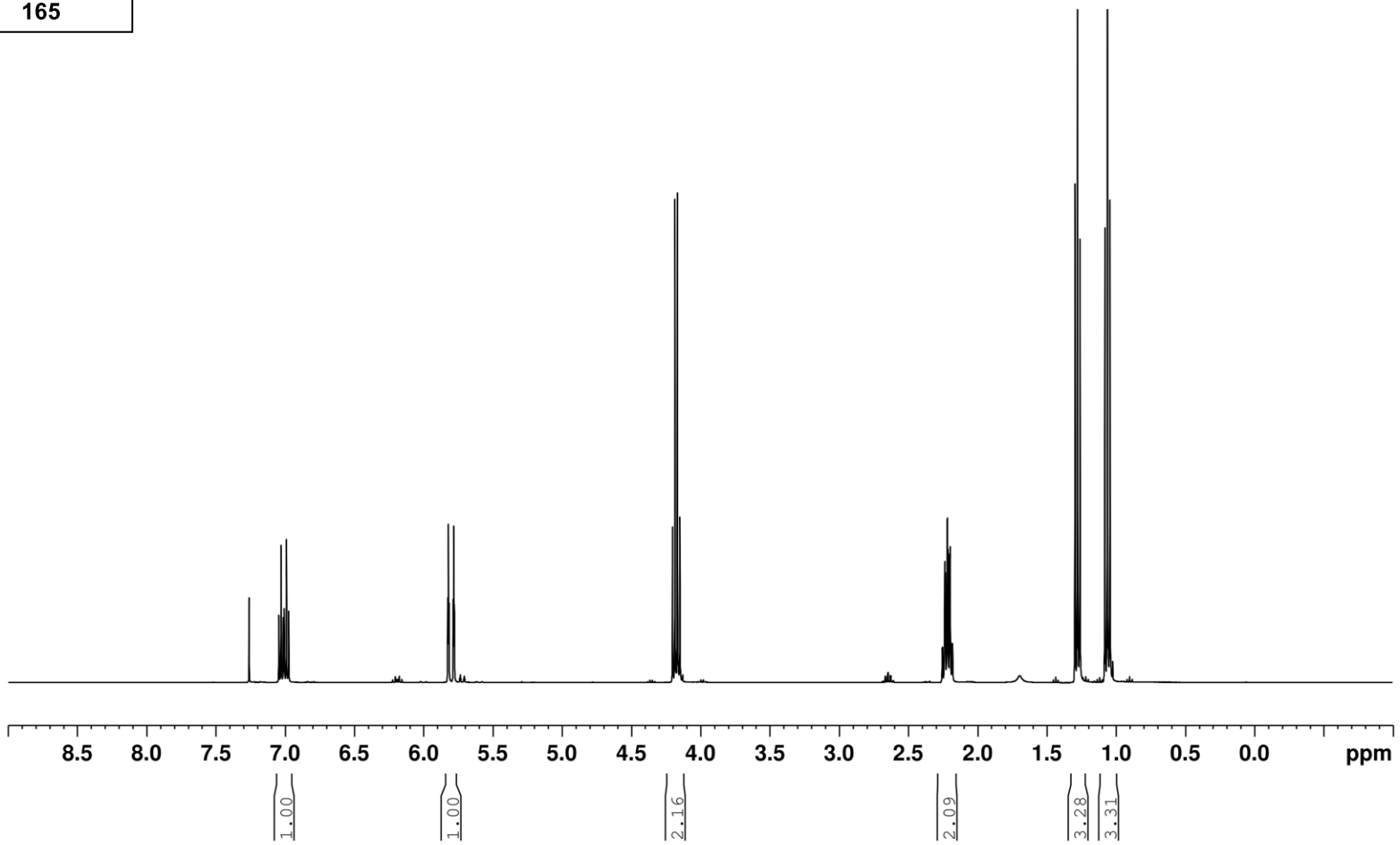
135

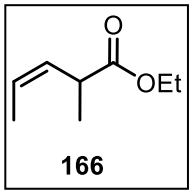

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.00
1.00
1.71
2.02
0.91
1.73
2.47
4.83


173.778
165.783
134.072
118.927
66.767
66.610
60.594
47.887
30.695
25.884
O
O
N
O
H
N2
135
220
200
180
160
140
120
100
80
60
40
20
0
ppm

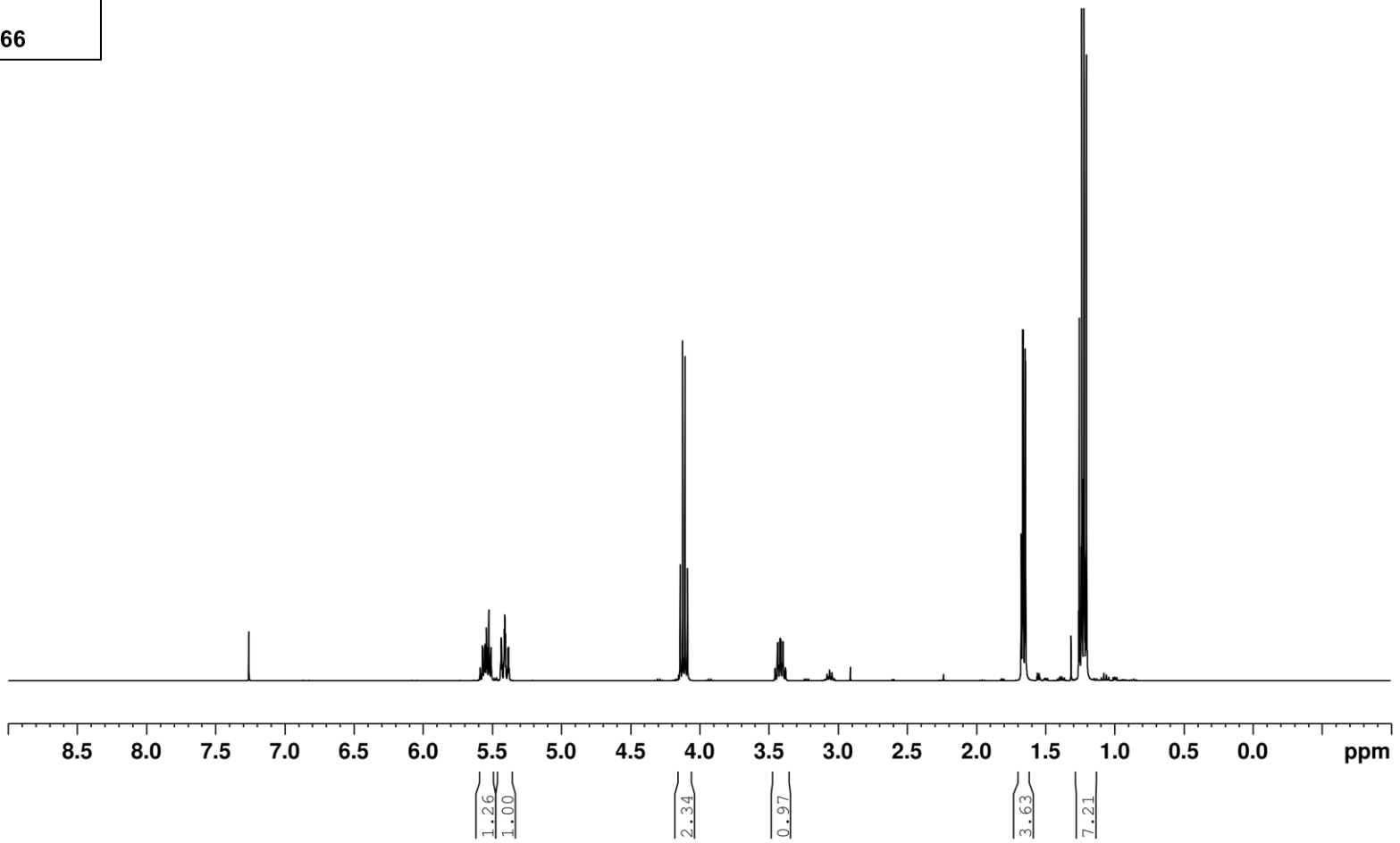

O
OEt

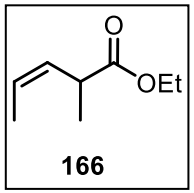
165

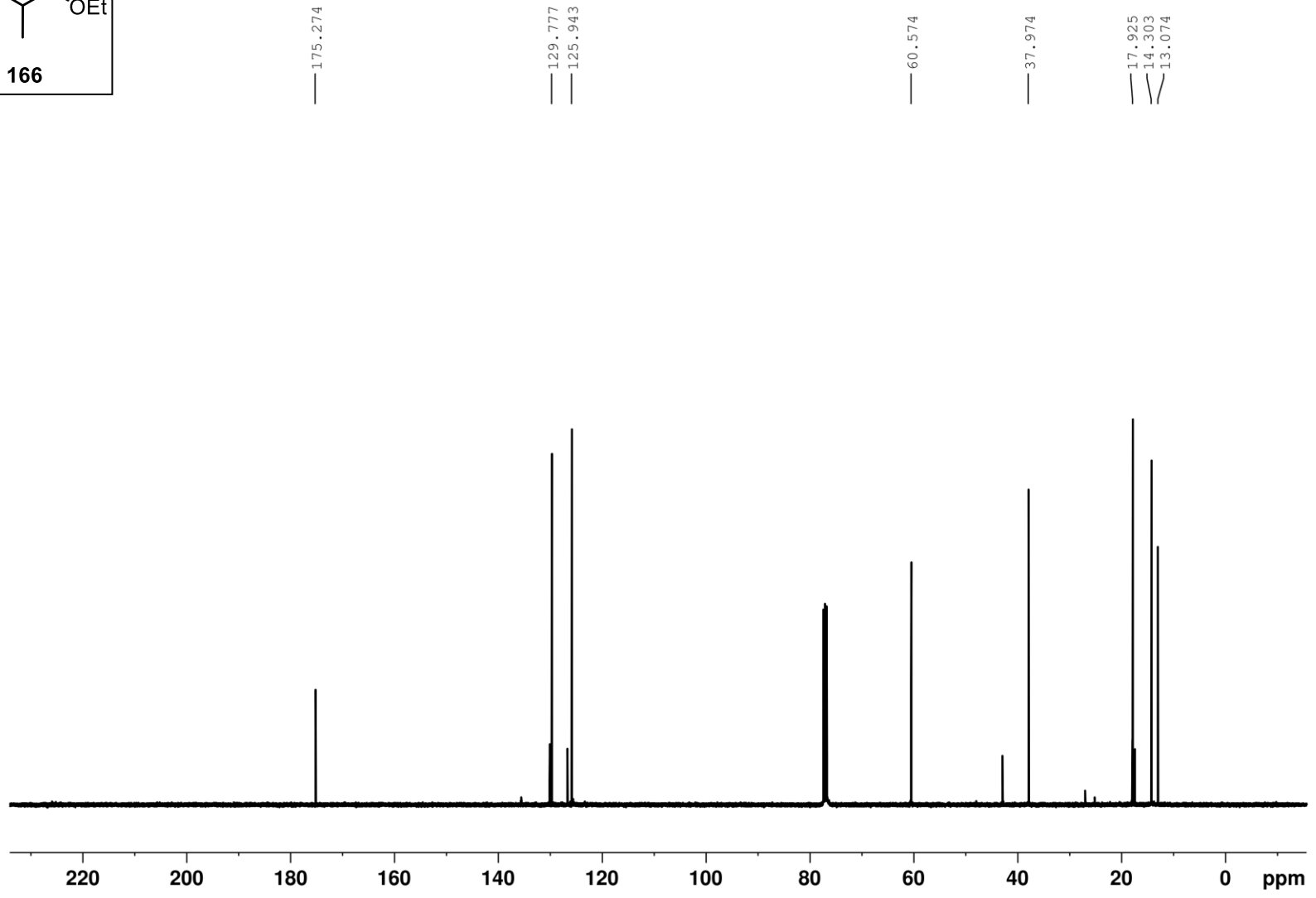

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.00
1.00
2.16
2.09
3.28
3.31

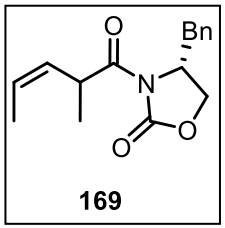

O
OEt

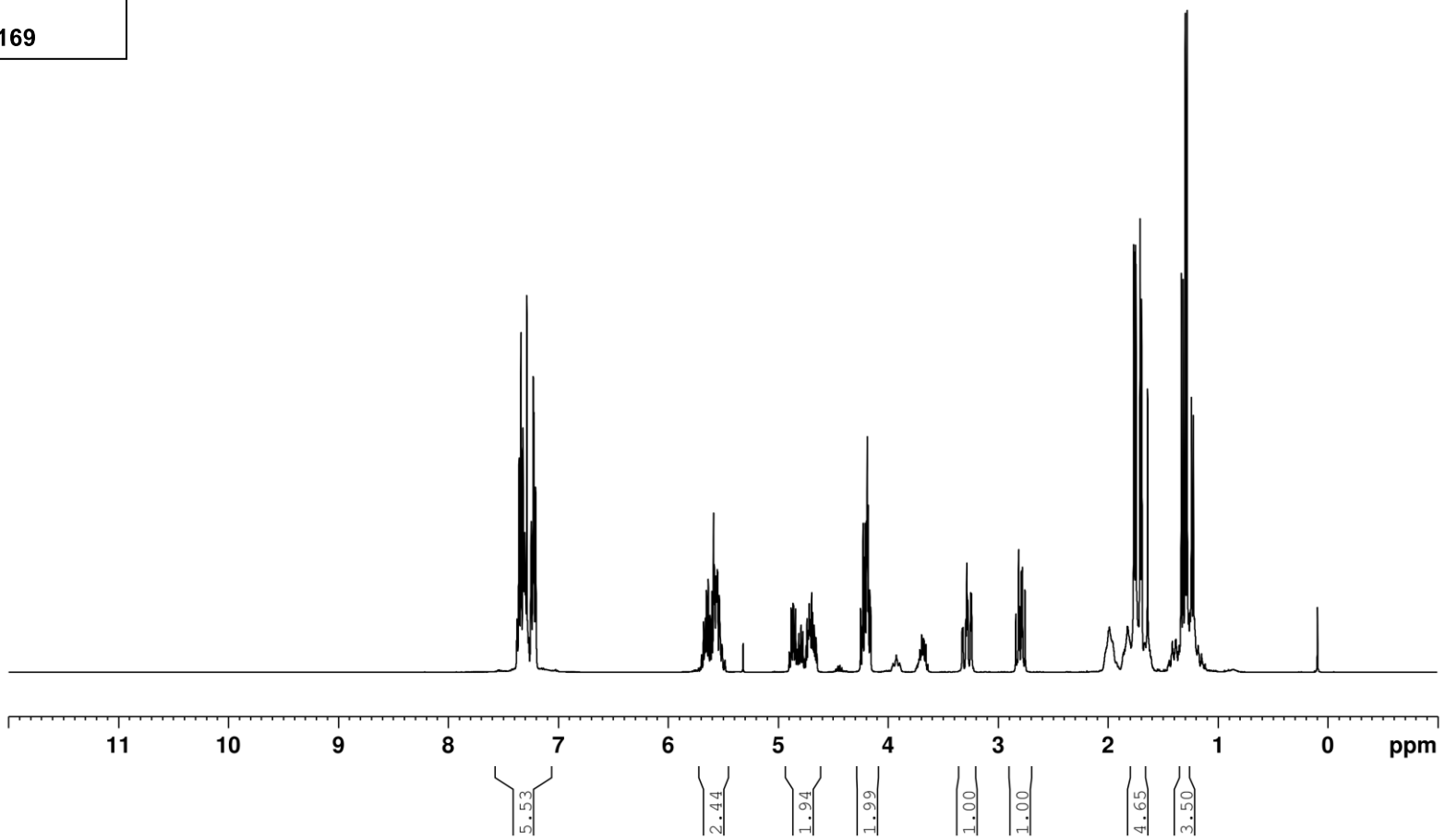
166

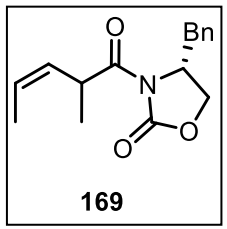

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.26
1.00
2.34
0.97
3.63
7.21


O
OEt
166

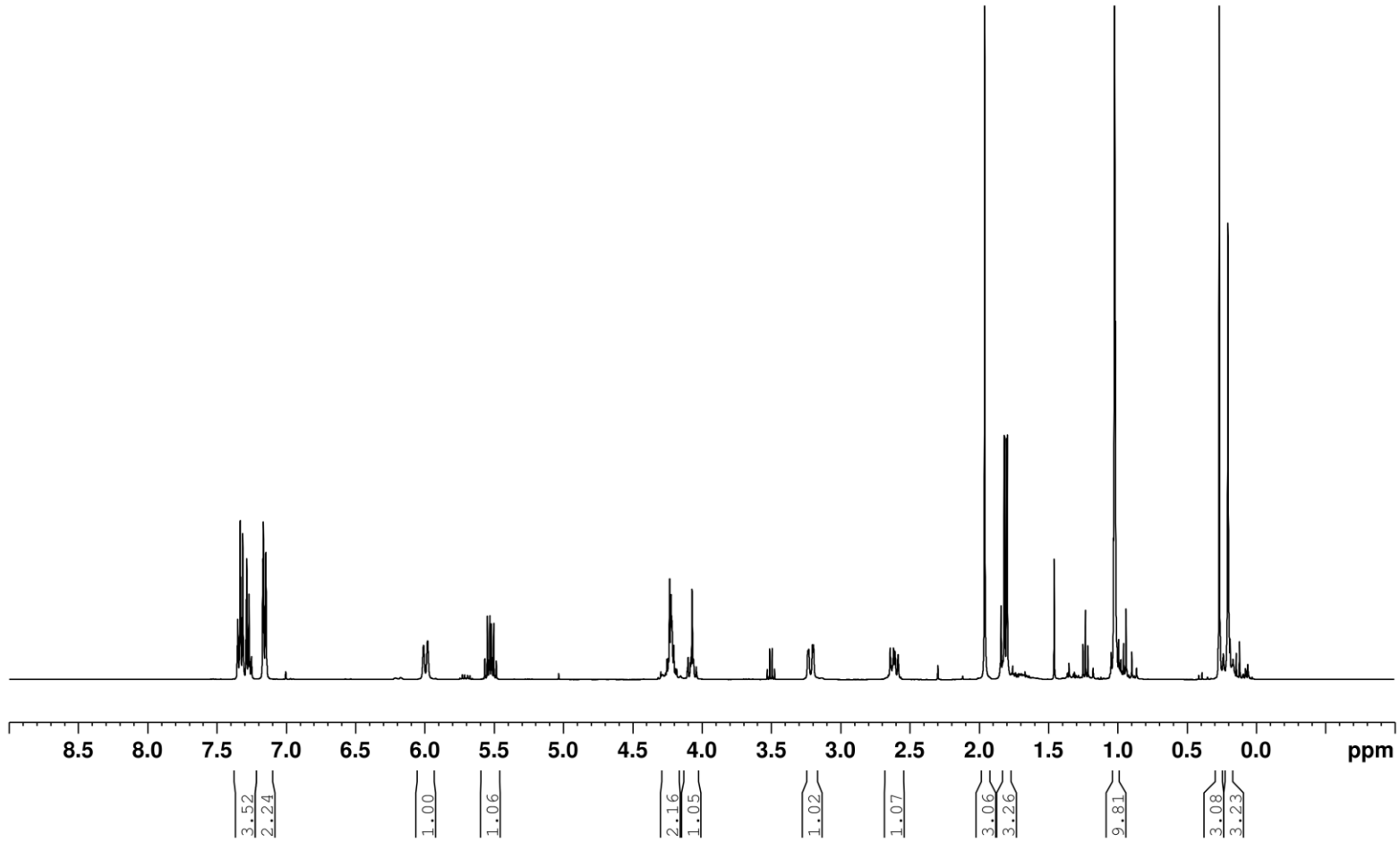

175.274
129.777
125.943
60.574
37.974
17.925
14.303
13.074
220
200
180
160
140
120
100
80
60
40
20
0
ppm

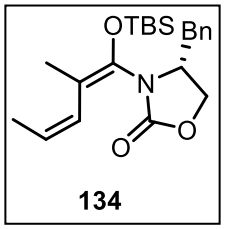

O
Bn
N
O
O
169


11
10
9
8
7
6
5
4
3
2
1
0
ppm
5.53
2.44
1.94
1.99
1.00
1.00
4.65
3.50


O
Bn
N
O
O
169

175.986
175.900
153.165
153.102
135.431
135.348
129.580
129.382
129.222
129.067
129.047
127.475
127.440
126.959
126.665
66.155
66.030
55.636
55.327
38.041
37.874
36.356
36.287
18.527
18.311
13.470
13.371
220
200
180
160
140
120
100
80
60
40
20
0
ppm


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
3.52
2.24
1.00
1.06
2.16
1.05
1.02
1.07
3.06
3.26
9.81
3.08
3.23


OTBS
Bn
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O
O
134

154.881
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135.369
128.986
127.193
126.926
126.259
115.683
67.970
56.852
39.092
25.793
18.184
16.432
15.218
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-4.509
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200
180
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120
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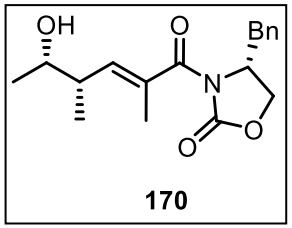
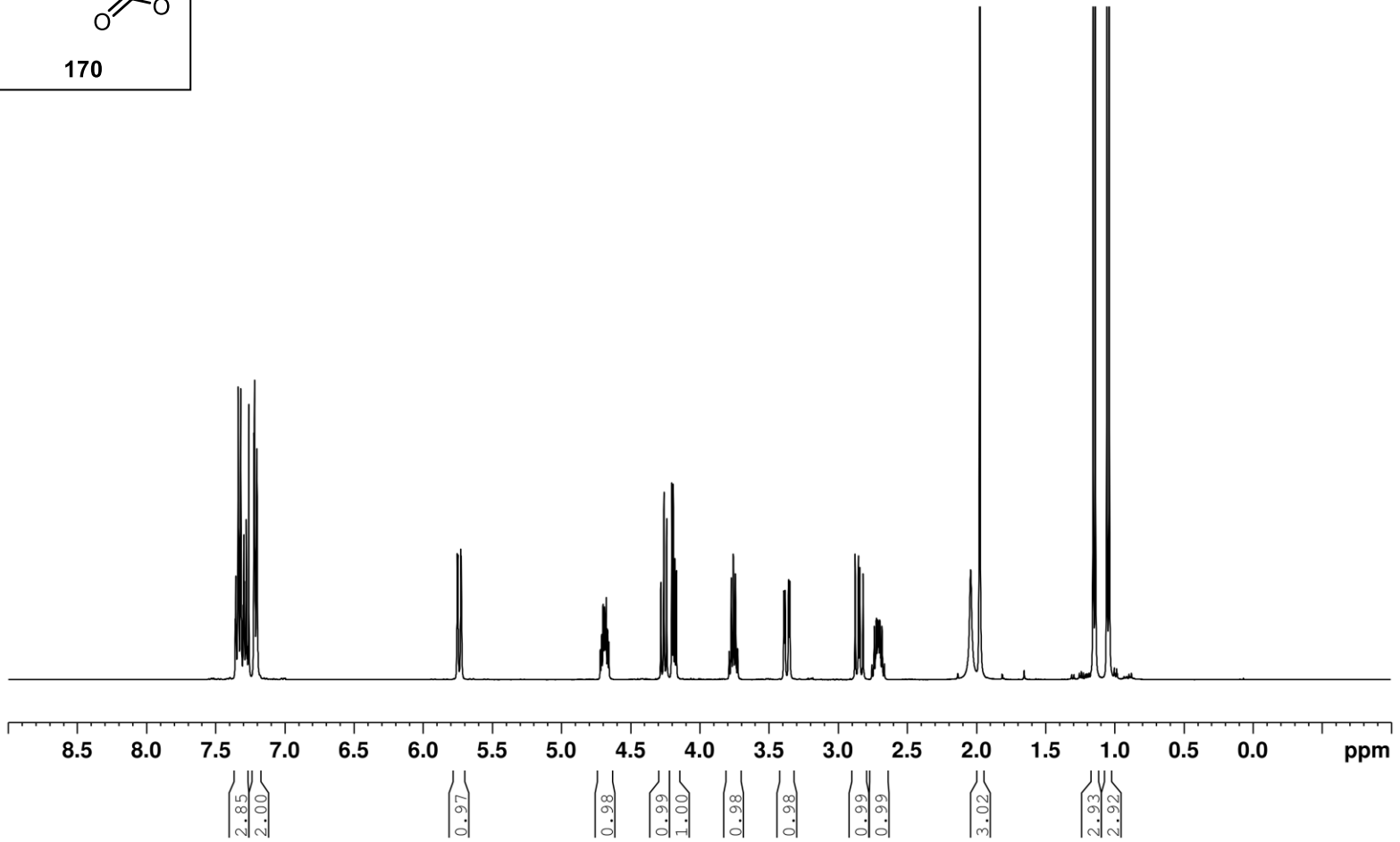
40
20
0
ppm


OH
O
Bn
N
O
O
170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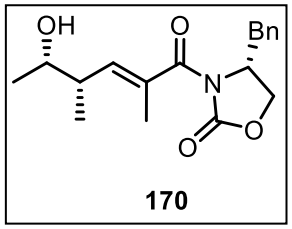
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
2.85
2.00
0.97
0.98
0.99
1.00
0.98
0.98
0.99
0.99
3.02
2.93
2.92


OH
O
Bn
N
O
O
170

171.860
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138.512
135.207
131.991
129.603
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127.543
71.819
66.534
55.704
39.812
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40
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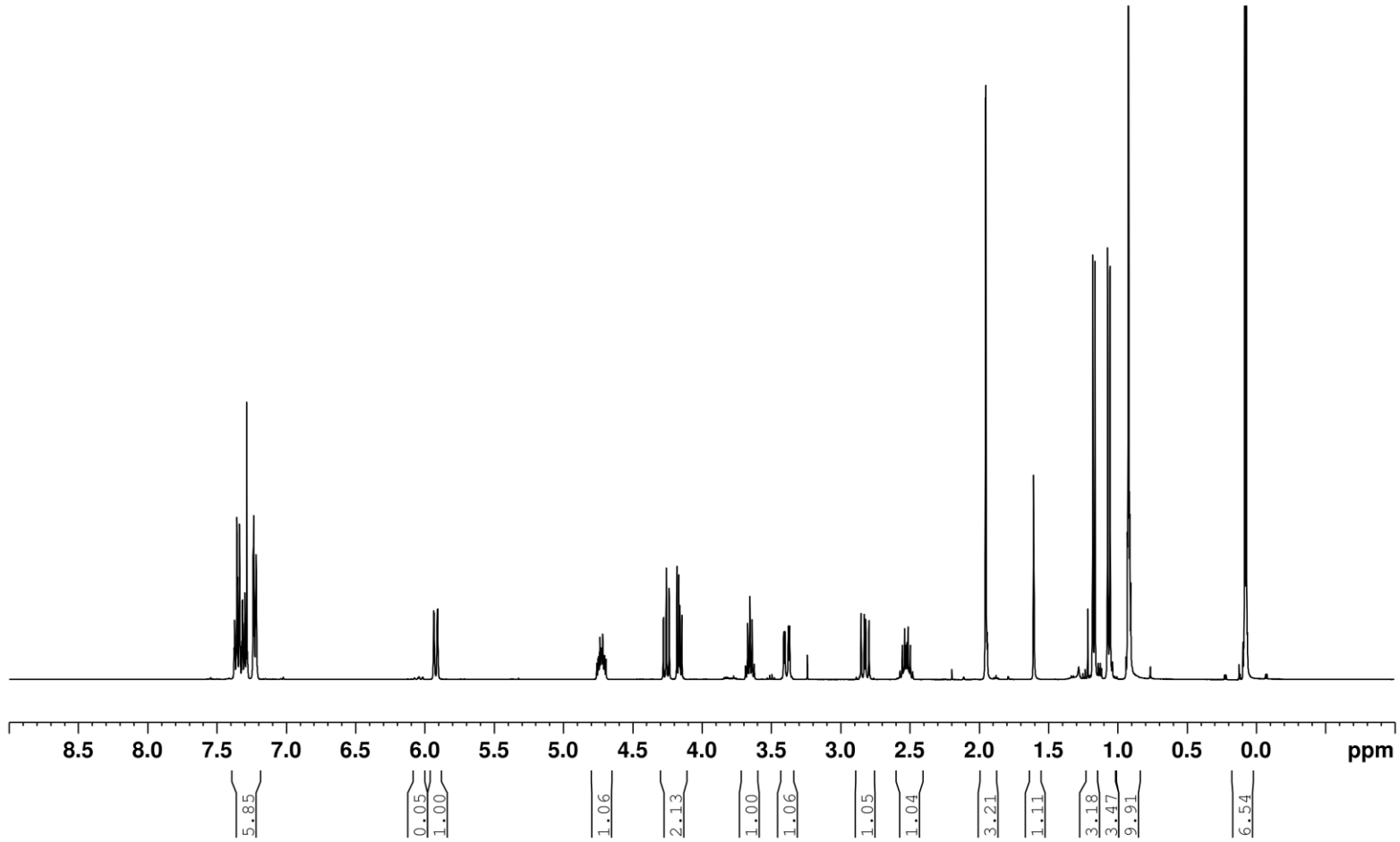
0
ppm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5.0
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4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
5.85
0.05
1.00
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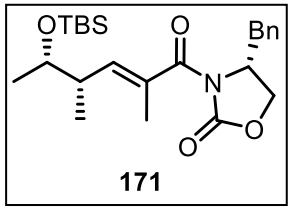
1.00
1.06
1.05
1.04
3.21
1.11
3.18
3.47
9.91
6.54


OTBS
O
Bn
N
O
O
171

172.200
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142.476
135.377
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129.573
129.071
127.473
71.845
66.534
55.657
41.460
37.747
26.018
22.218
18.248
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200
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120
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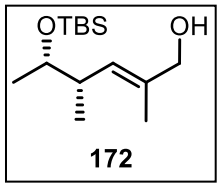
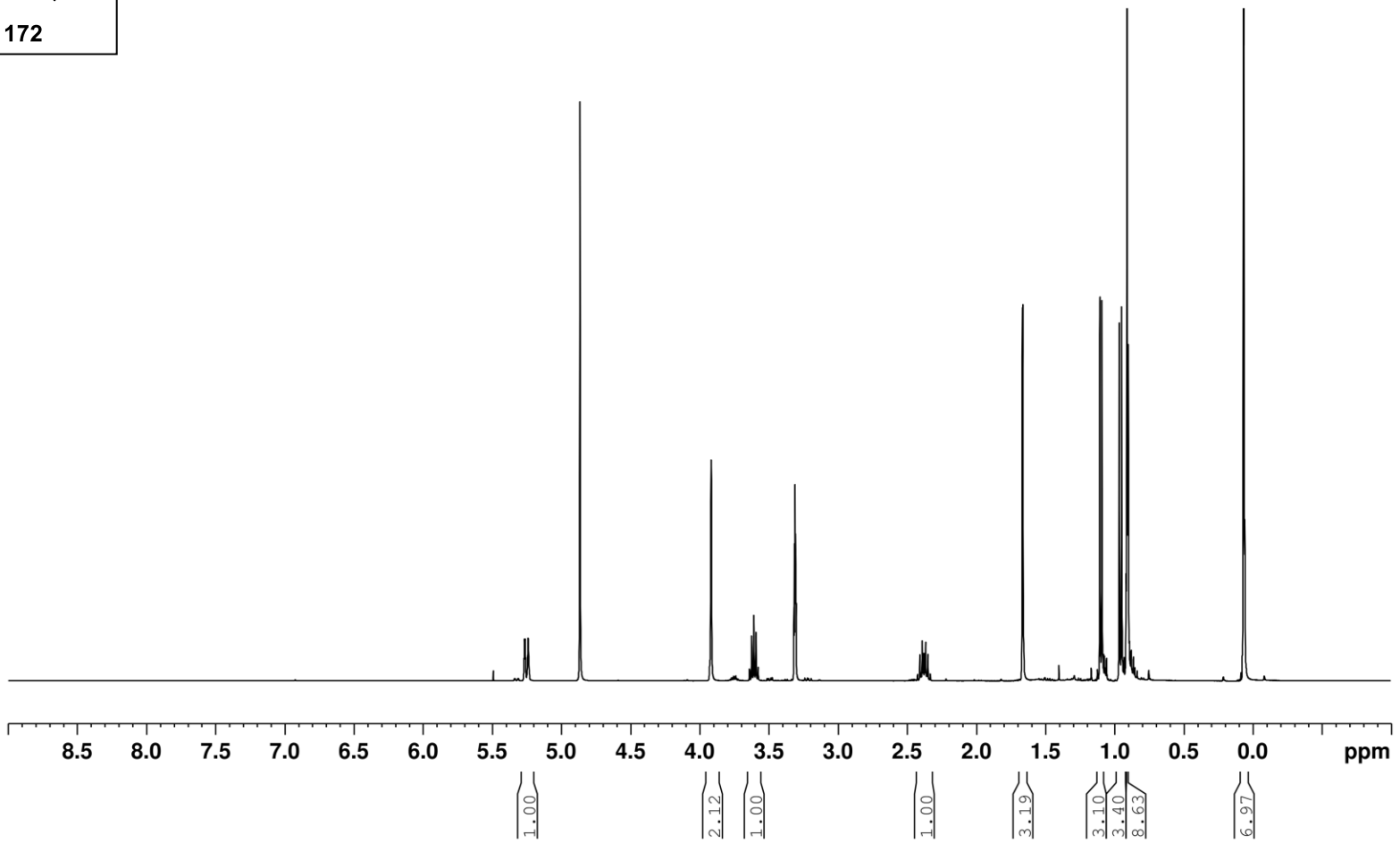
40
20
0
ppm


OTBS
OH
172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6.5
6.0
5.5
5.0
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4.0
3.5
3.0
2.5
2.0
1.5
1.0
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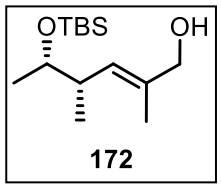
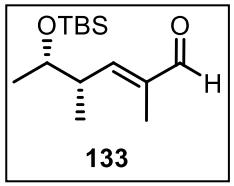
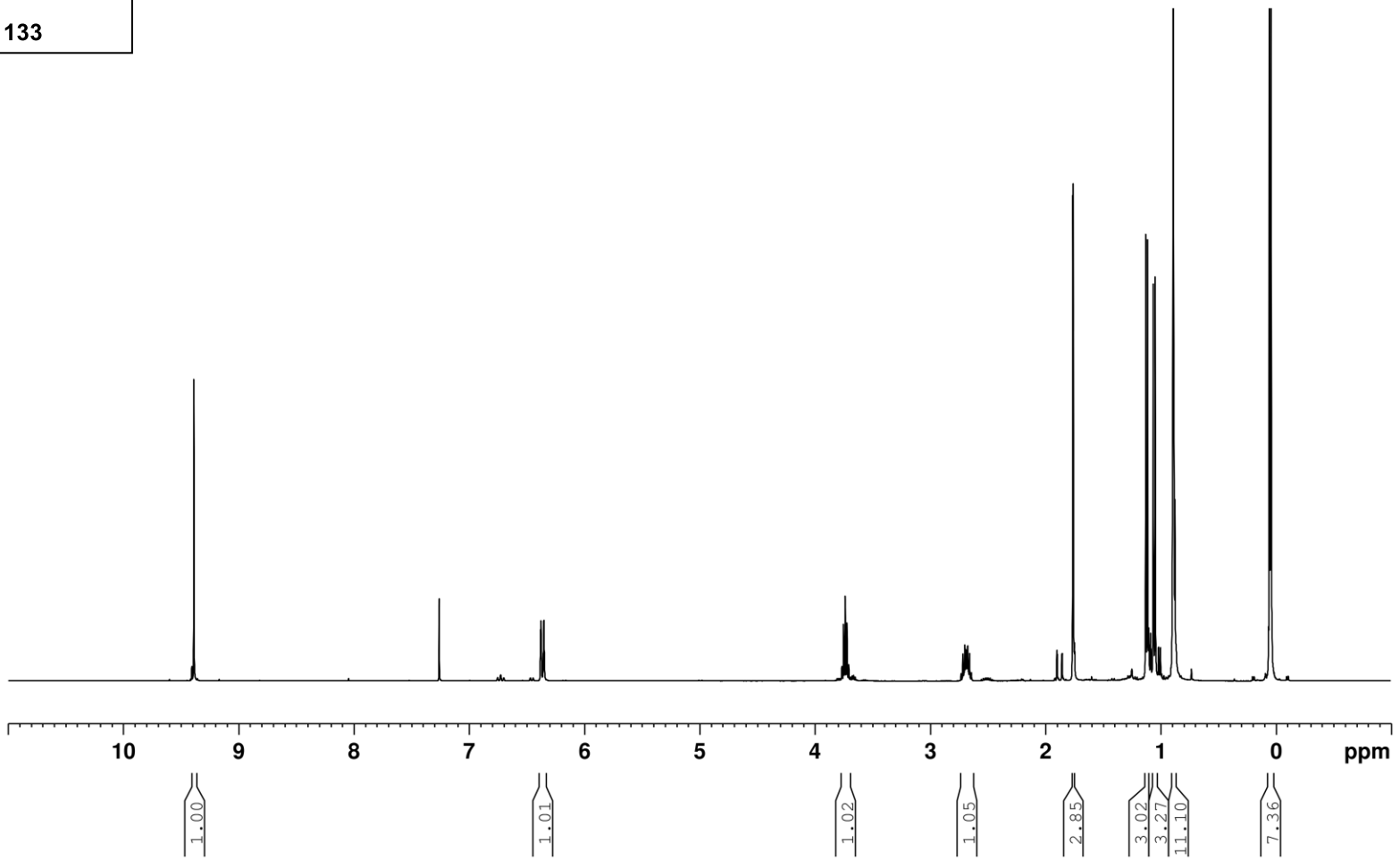
0.0
ppm
1.00
2.12
1.00
1.00
3.19
3.10
3.40
8.63
6.97

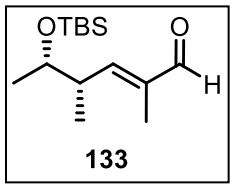

OTBS
OH
172

135.504
130.078
74.022
68.962
41.563
26.397
22.260
18.961
17.235
14.198
-4.085
-4.580
220
200
180
160
140
120
100
80
60
40
20
0
ppm

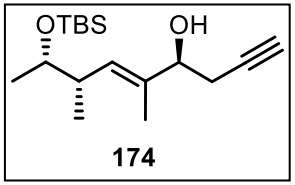


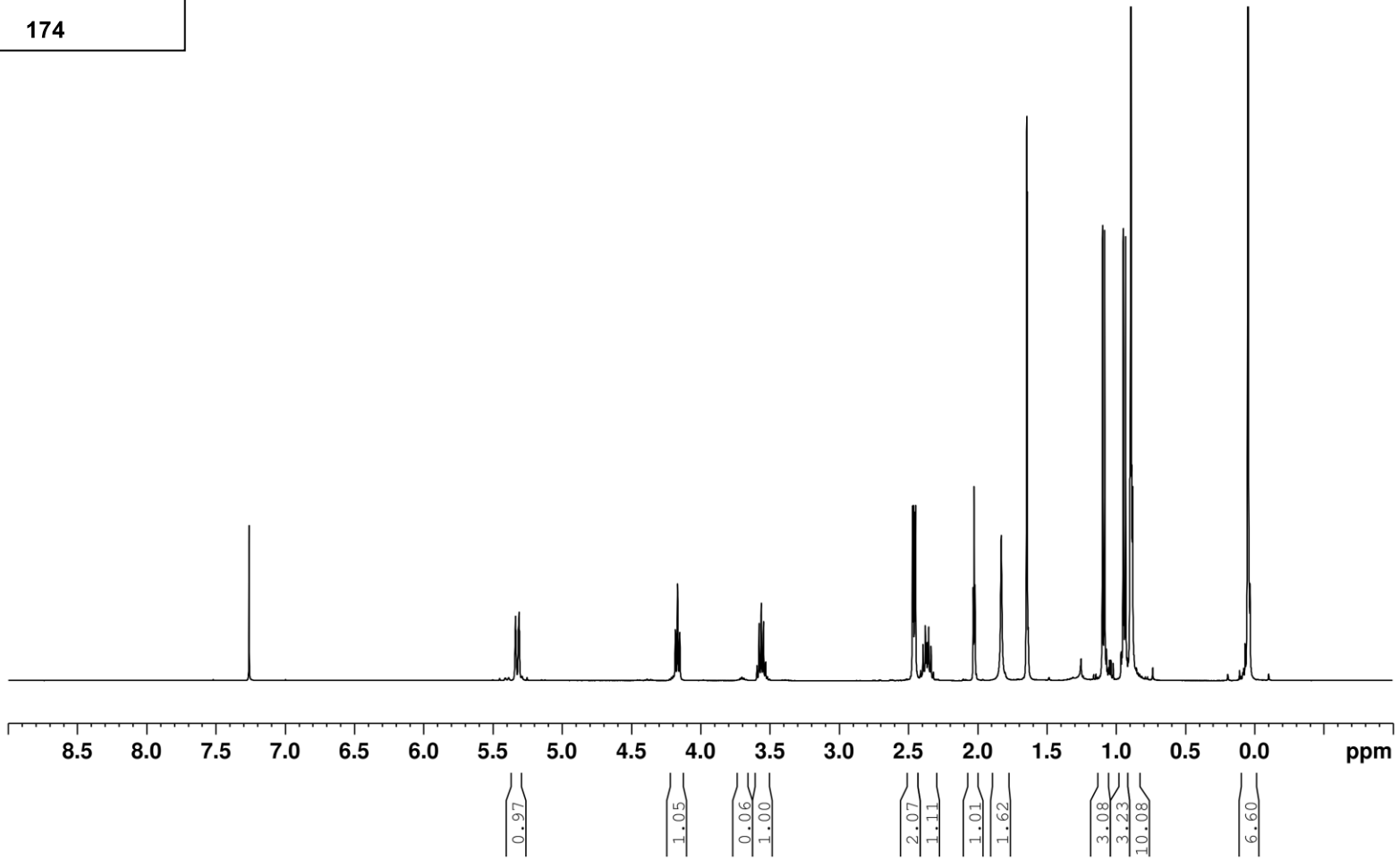
133




OTBS
O
H
133

195.730
157.539
138.696
71.451
41.608
25.958
21.698
18.213
15.321
9.670
-4.139
-4.686
220
200
180
160
140
120
100
80
60
40
20
0
ppm


OTBS
OH
174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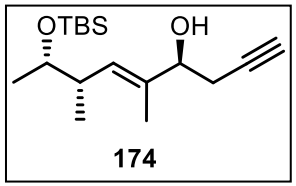
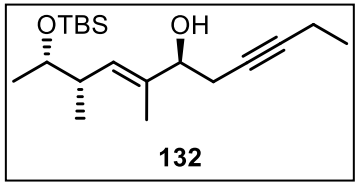
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
0.97
1.05
0.06
1.00
2.07
1.11
1.01
1.62
3.08
3.23
10.08
6.60

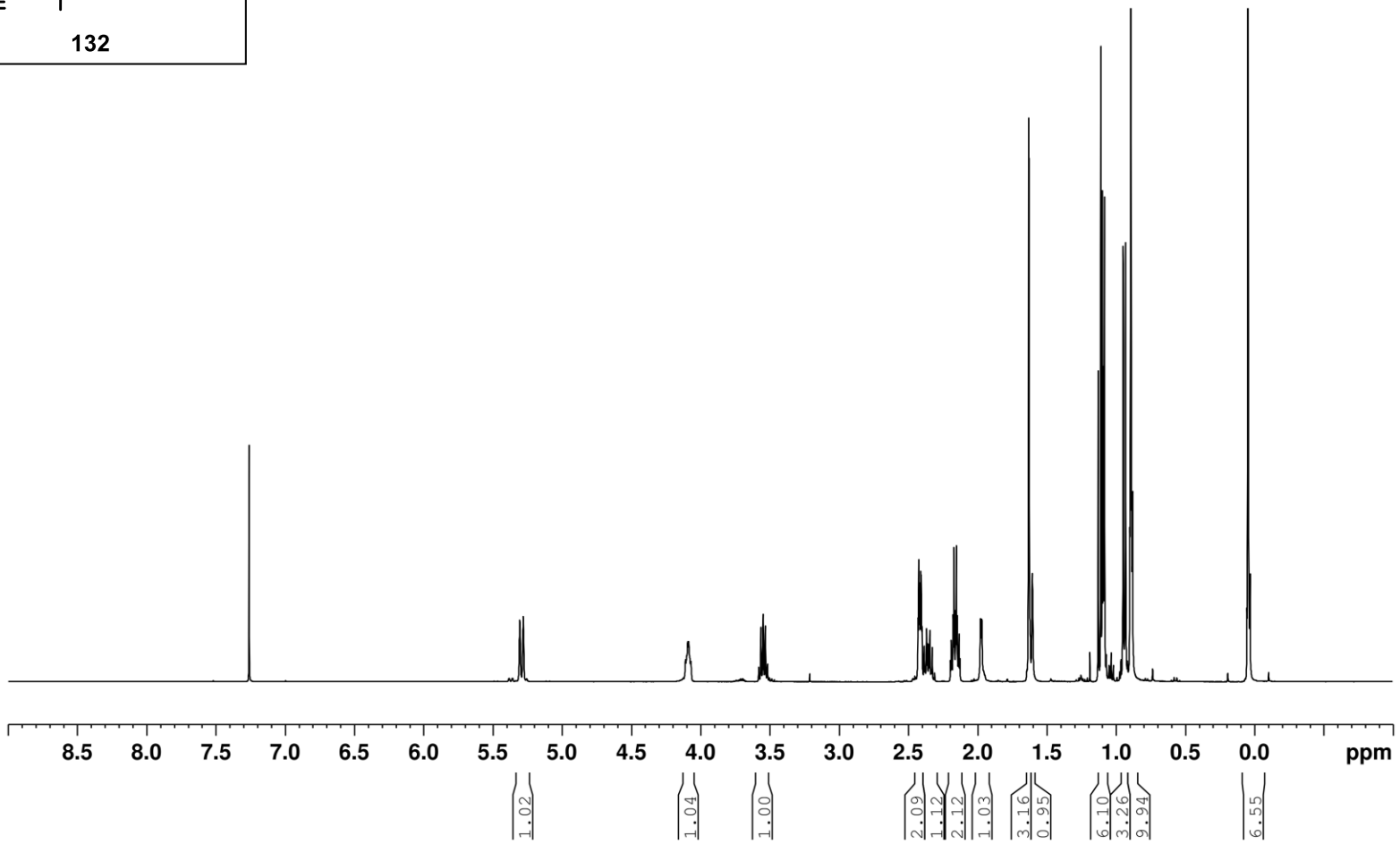

OTBS
OH

174

134.723
130.581
81.086
75.321
72.630
70.749
40.511
26.041
22.014
18.271
16.931
12.456
-4.119
-4.589
220
200
180
160
140
120
100
80
60
40
20
0
ppm


OTBS
OH

132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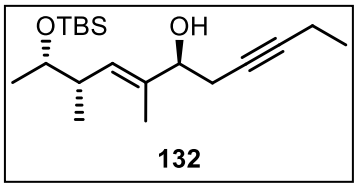
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.02
1.04
1.00
2.09
1.12
2.12
1.03
3.16
0.95
6.10
3.26
9.94
6.55


OTBS
OH
132

135.006
130.159
84.654
75.581
75.520
72.735
40.534
26.493
26.050
22.078
18.277
17.022
14.324
12.571
12.556
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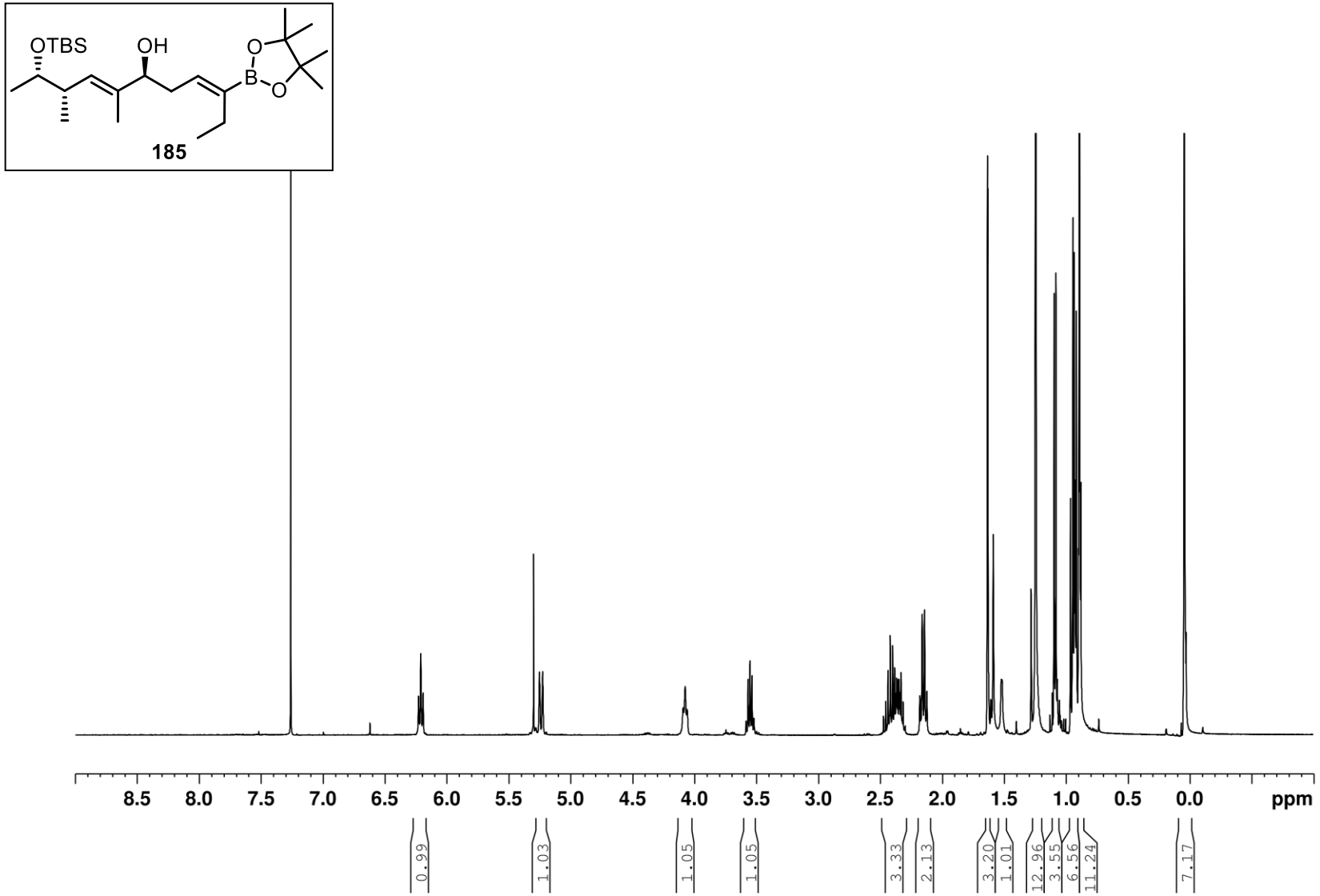
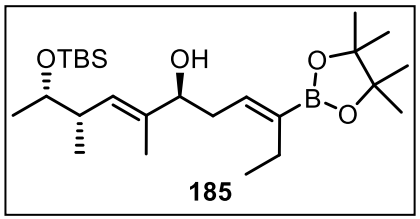
-4.587
220
200
180
160
140
120
100
80
60
40
20
0
ppm


OTBS
OH
O
B
O
185
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
0.99
1.03
1.05
1.05
3.33
2.13
3.20
1.01
12.96
3.55
6.56
11.24
7.17


OTBS
OH
O
B
O
185

140.473
135.927
129.902
83.209
76.944
72.705
40.497
34.287
26.062
24.894
22.175
22.118
18.287
16.958
14.840
12.375
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-4.578
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200
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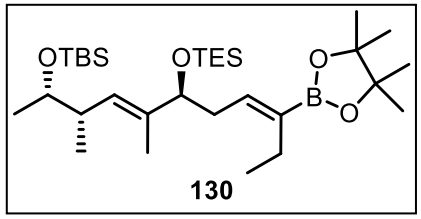
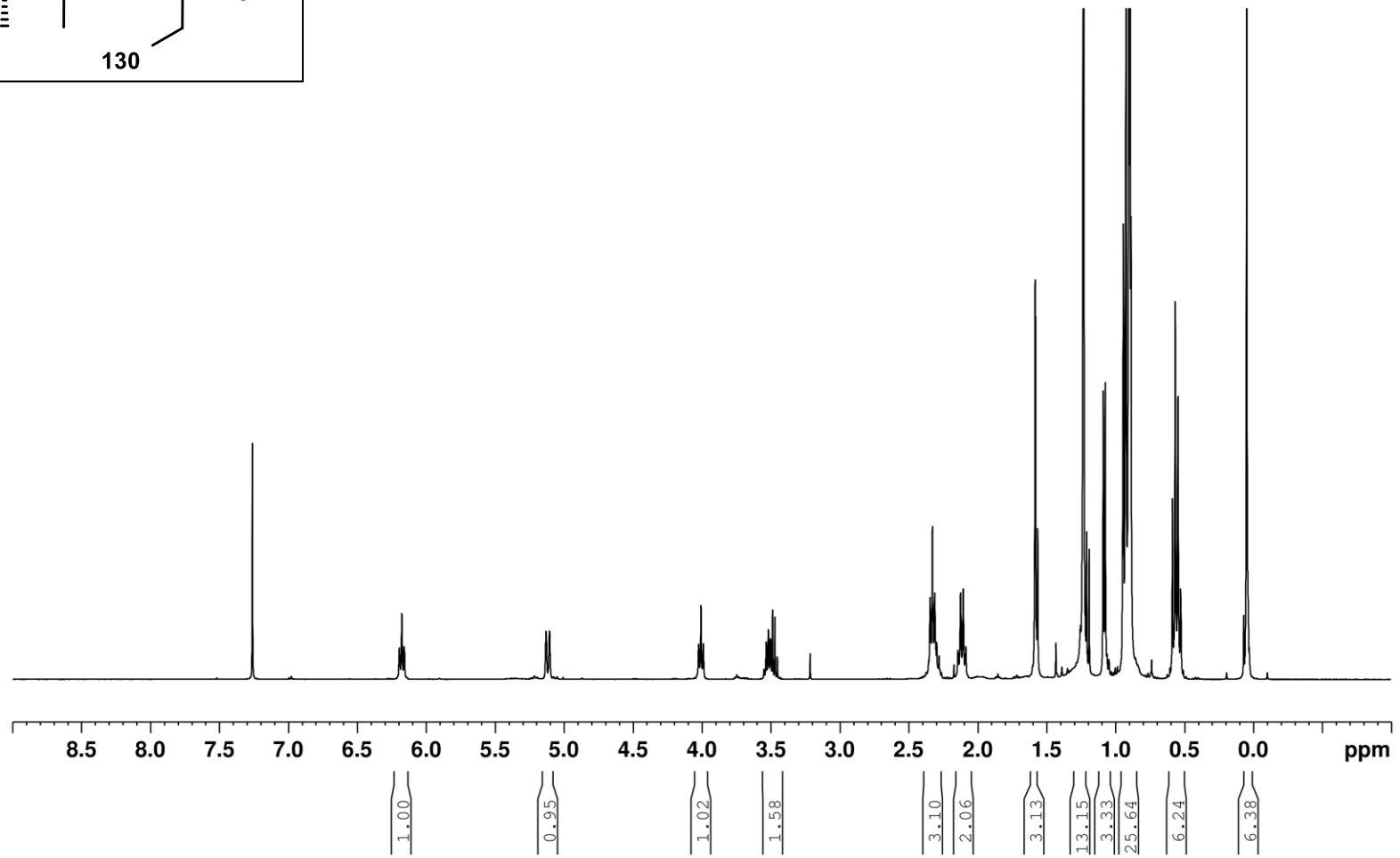
120
100
80
60
40
20
0
ppm


OTBS
OTES
O
B
O
130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6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
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1.02
1.58
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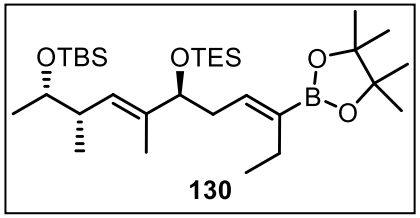
2.06
3.13
13.15
3.33
25.64
6.24
6.38


OTBS
OTES
O
B
O
130

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136.502
129.005
83.034
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72.942
40.682
35.602
26.069
24.867
22.236
22.002
18.286
17.339
14.934
11.637
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-4.630
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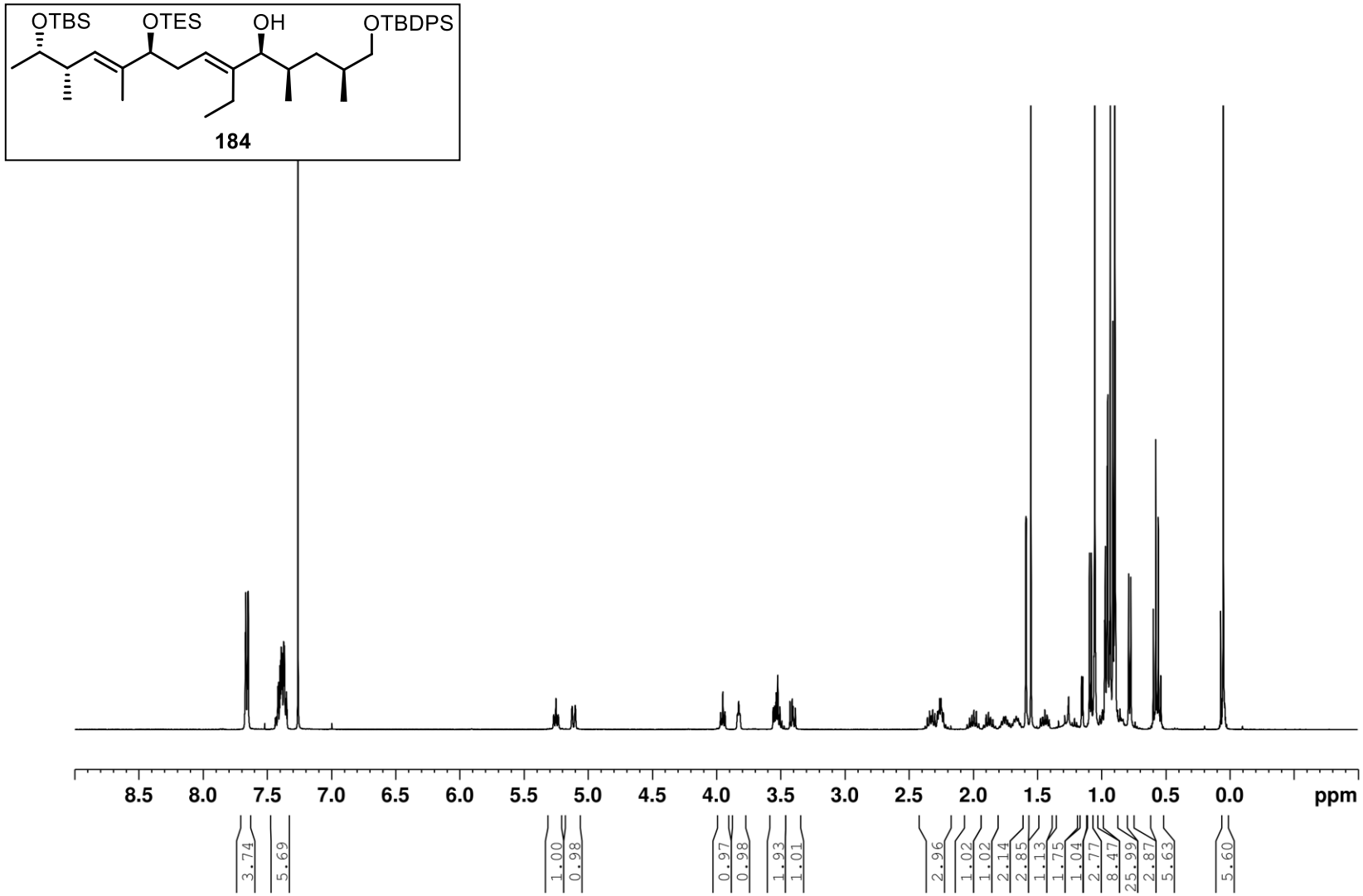
200
180
160
140
120
100
80
60
40
20
0
ppm


OTBS
OTES
OH
OTBDPS
184
8.5
8.0
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7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
3.74
5.69
1.00
0.98
0.97
0.98
1.93
1.01
2.96
1.02
1.02
2.14
2.85
1.13
1.75
1.04
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8.47
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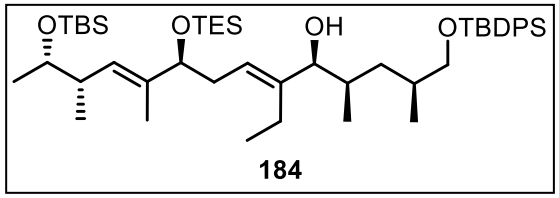
2.87
5.63
5.60


OTBS
OTES
OH
OTBDPS

184

143.535
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135.755
134.166
134.144
129.643
129.173
127.710
122.055
78.705
78.675
72.911
68.686
40.630
38.013
34.747
33.307
33.270
27.035
26.062
22.153
21.454
19.451
18.323
18.286
17.520
14.273
14.150
11.630
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200
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120
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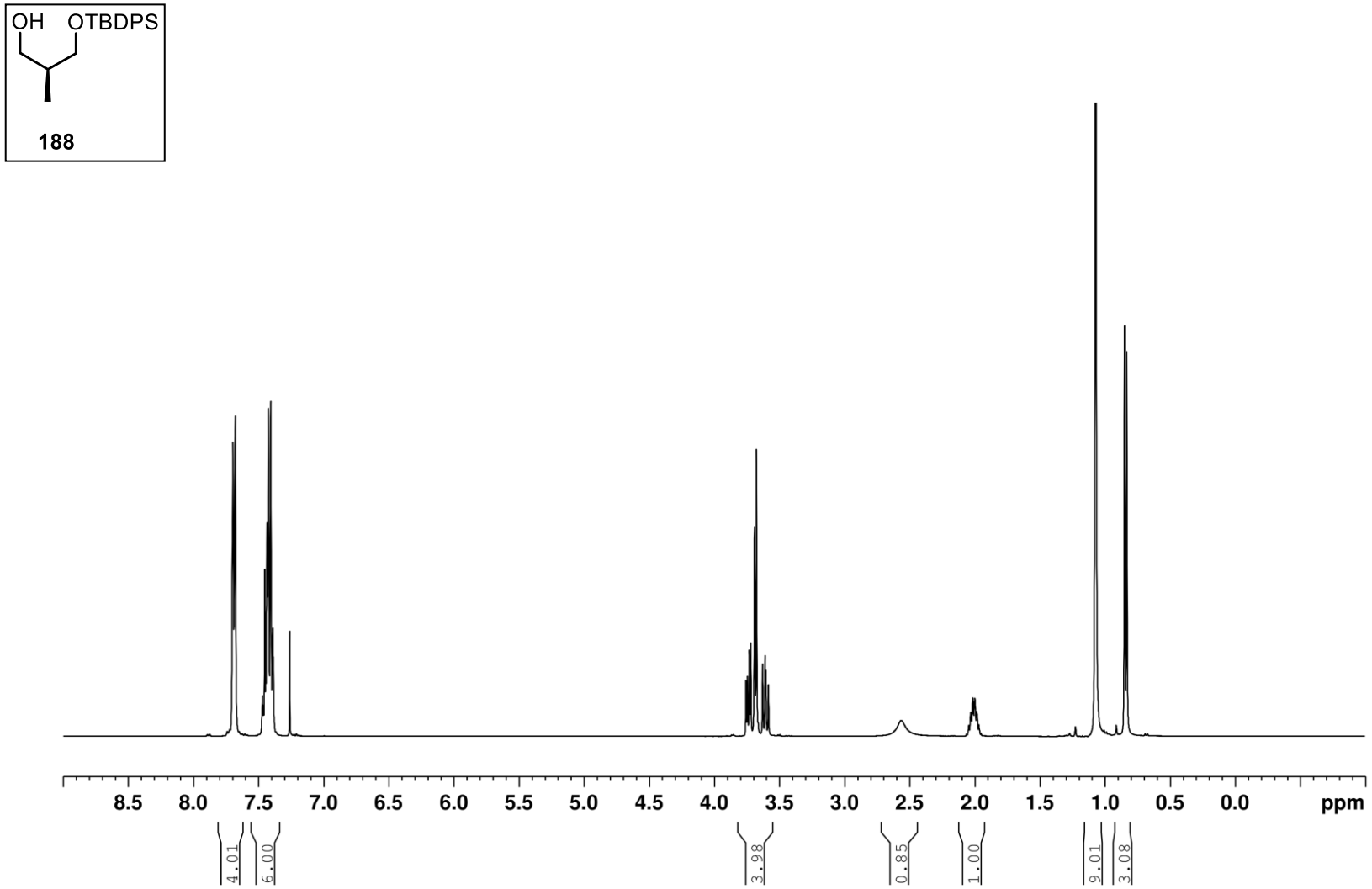
60
40
20
0
ppm


OH
OTBDPS
188
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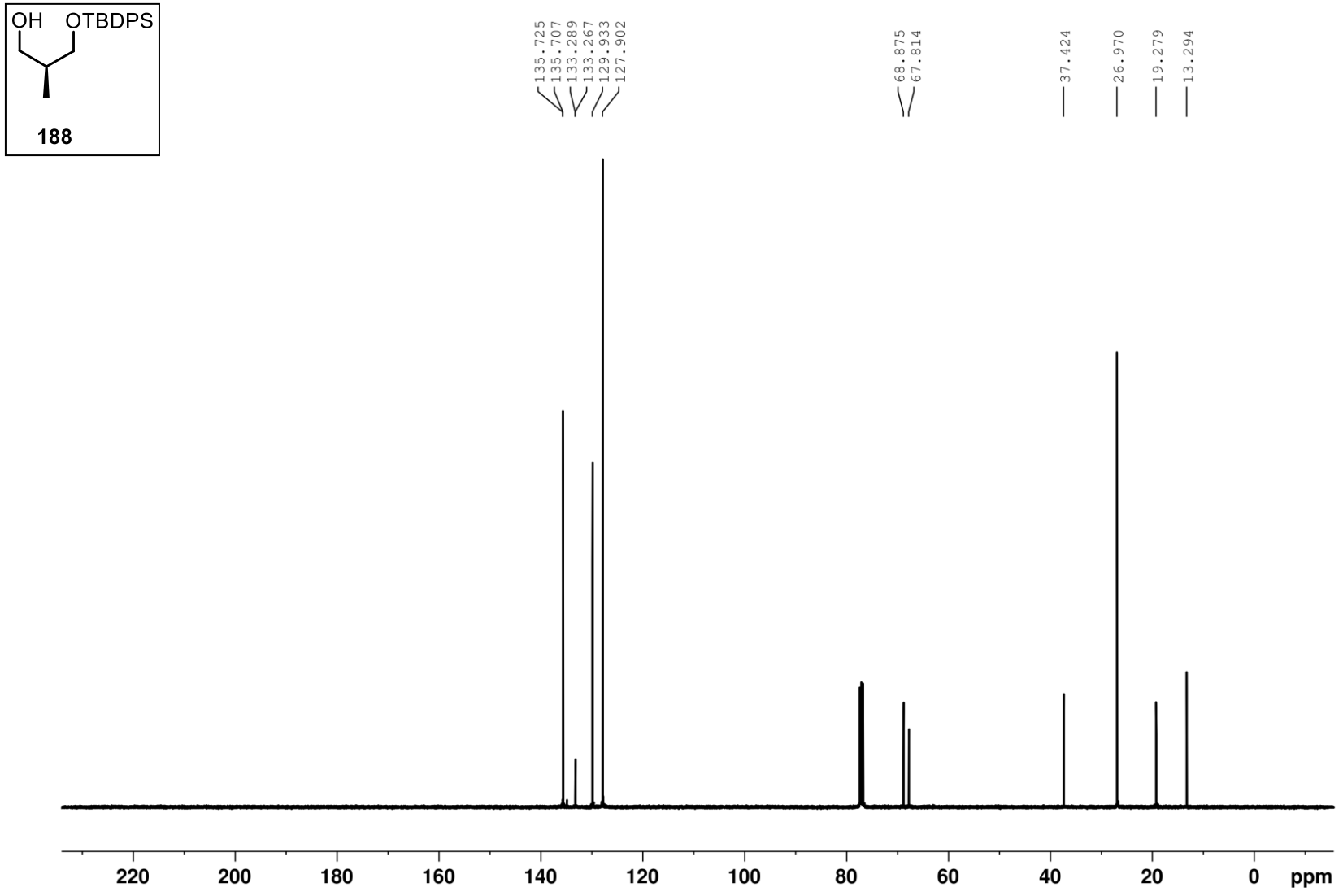
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
4.01
6.00
3.98
0.85
1.00
9.01
3.08


OH
OTBDPS
188
135.725
135.707
133.289
133.267
129.933
127.902
68.875
67.814
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19.279
13.294
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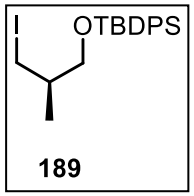
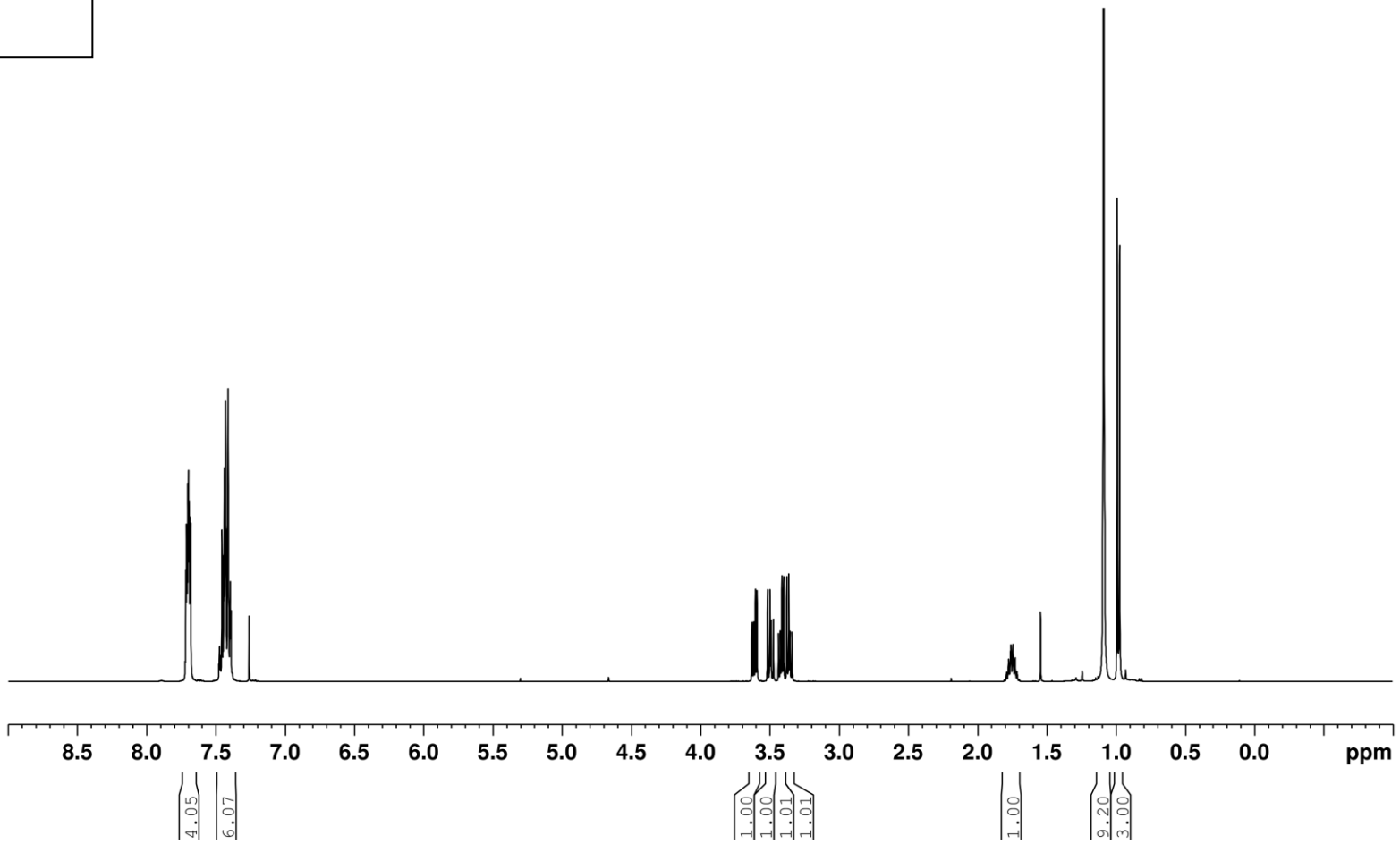
200
180
160
140
120
100
80
60
40
20
0
ppm


OTBDPS
189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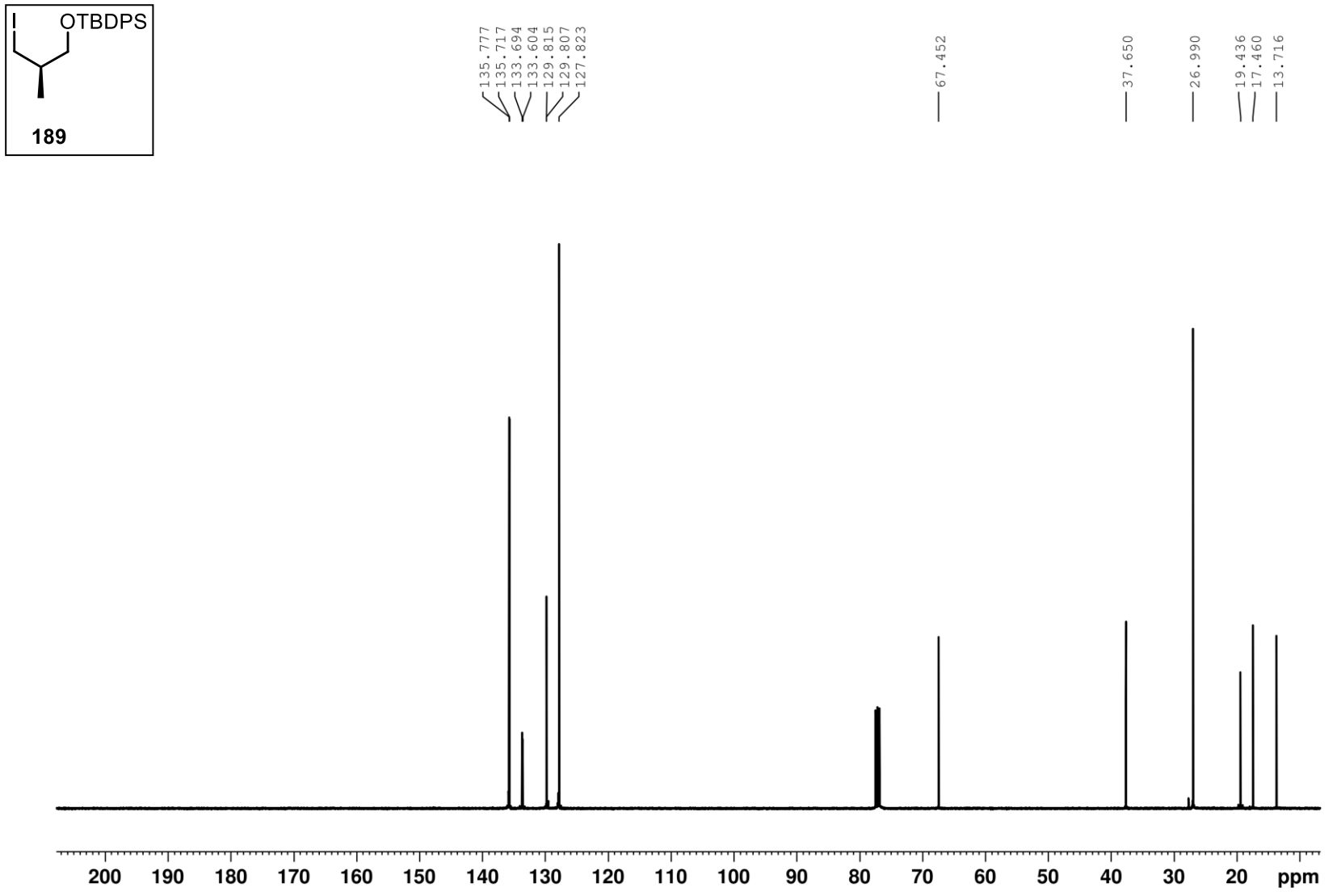
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
4.05
6.07
1.00
1.00
1.01
1.01
1.00
9.20
3.00


OTBDPS
189
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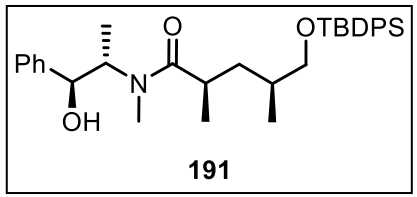
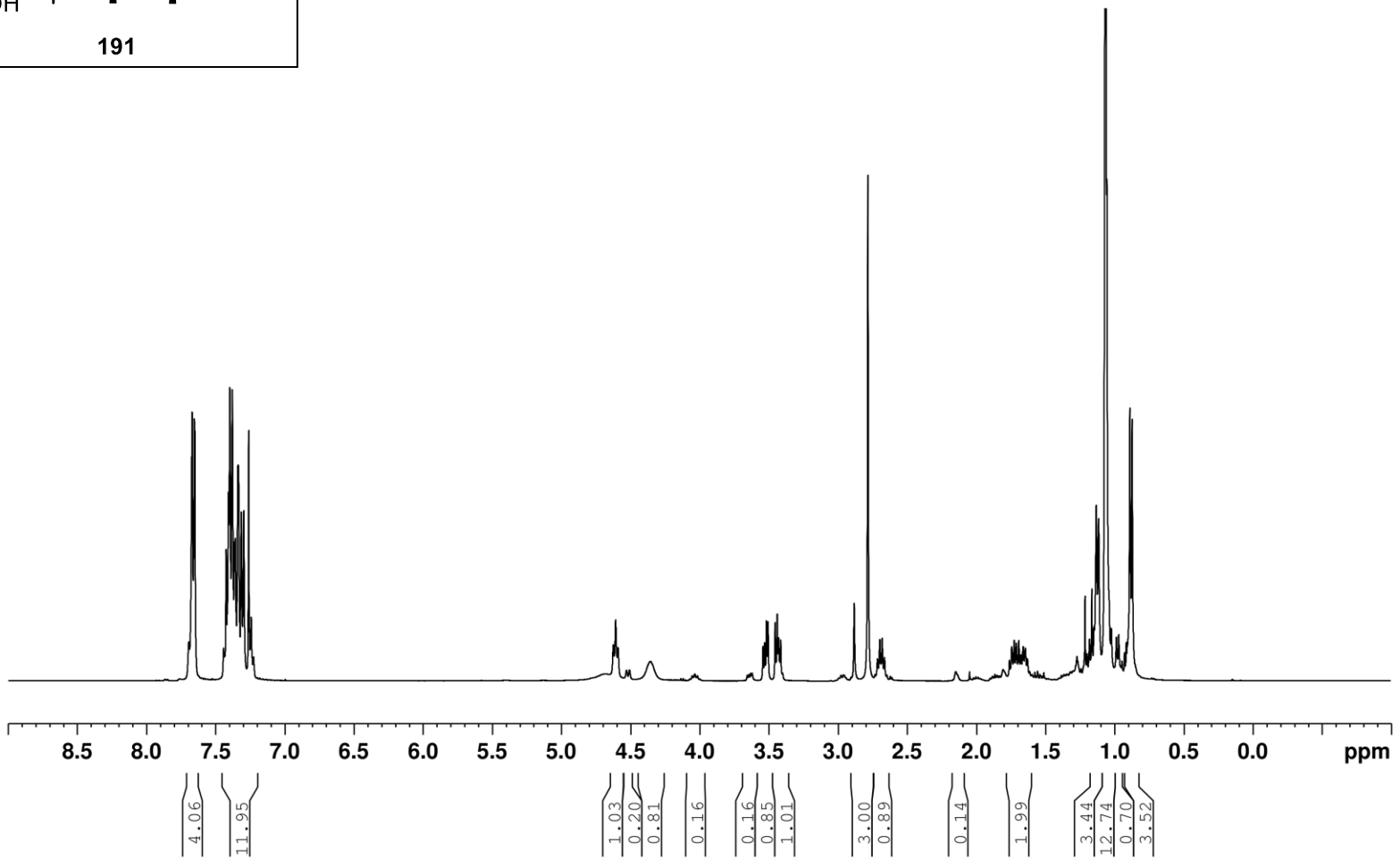
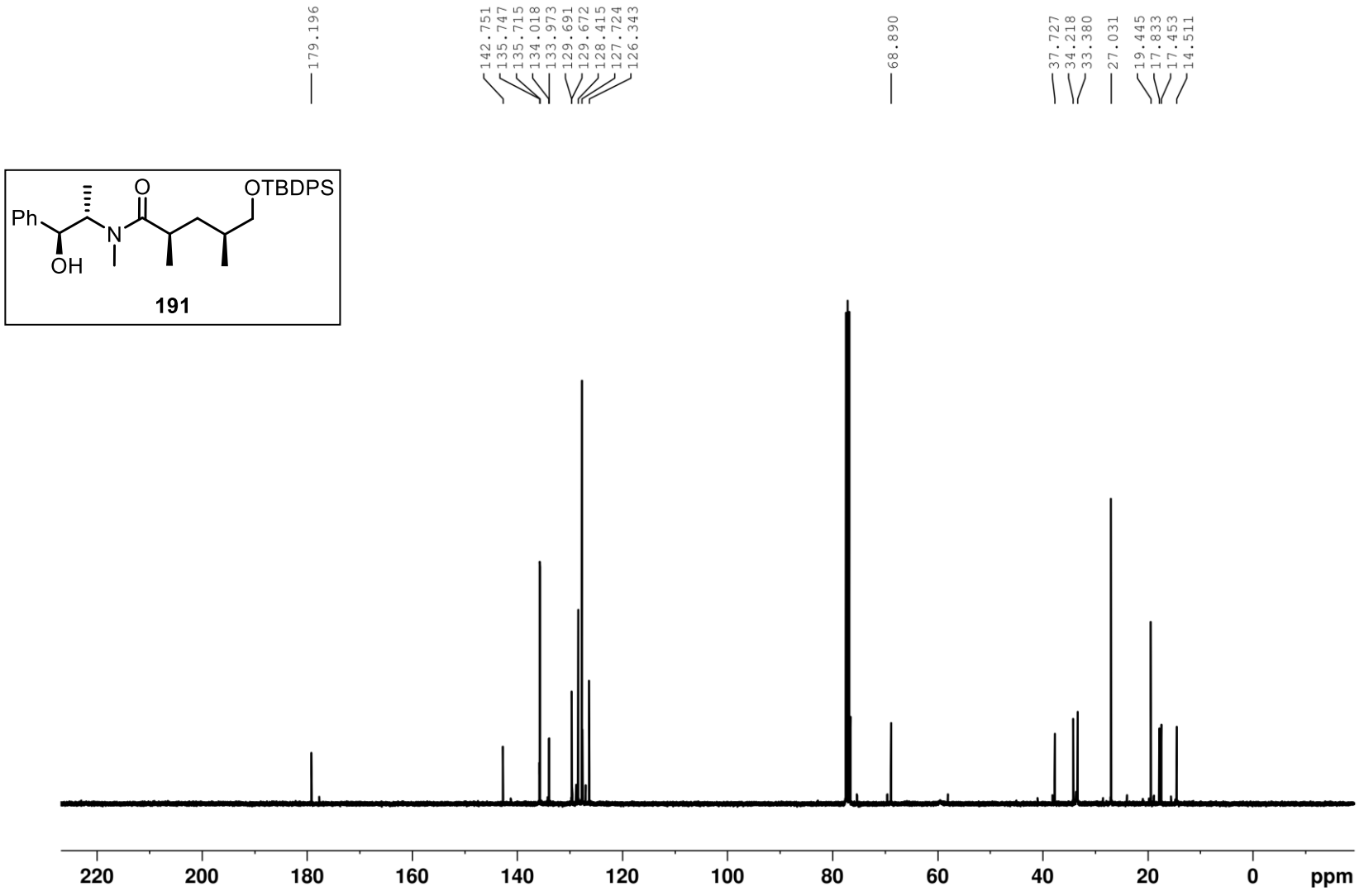
133.694
133.604
129.815
129.807
127.823
67.452
37.650
26.990
19.436
17.460
13.716
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


Ph
OH
N
O
OTBDPS

191


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
4.06
11.95
1.03
0.20
0.81
0.16
0.16
0.85
1.01
3.00
0.89
0.14
1.99
3.44
12.74
0.70
3.52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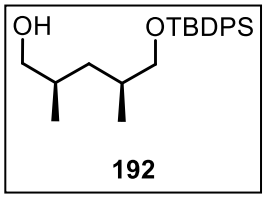
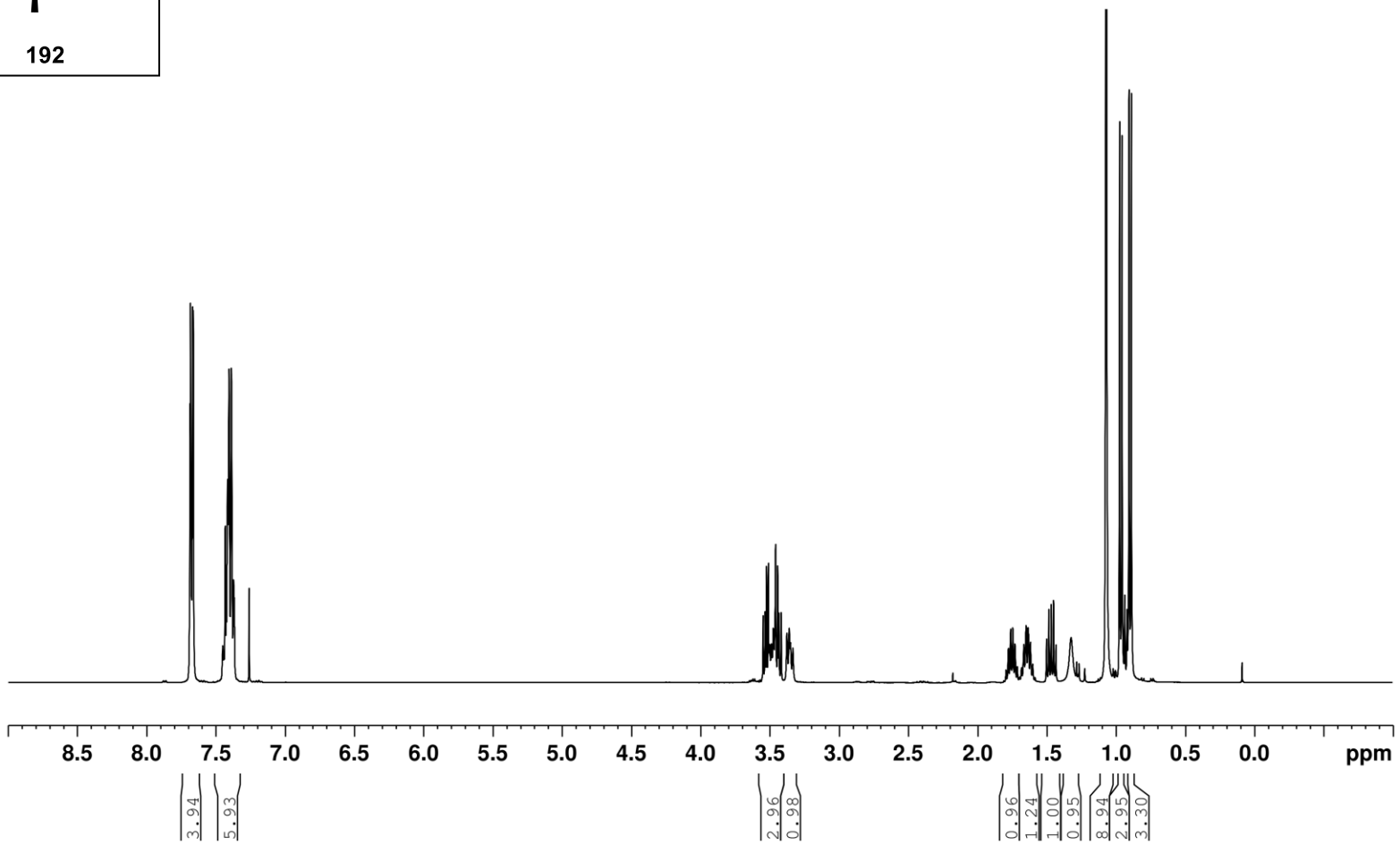
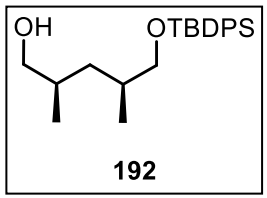
126.343
68.890
37.727
34.218
33.380
27.031
19.445
17.833
17.453
14.511
Ph
OH
N
O
OTBDPS
191
220
200
180
160
140
120
100
80
60
40
20
0
ppm

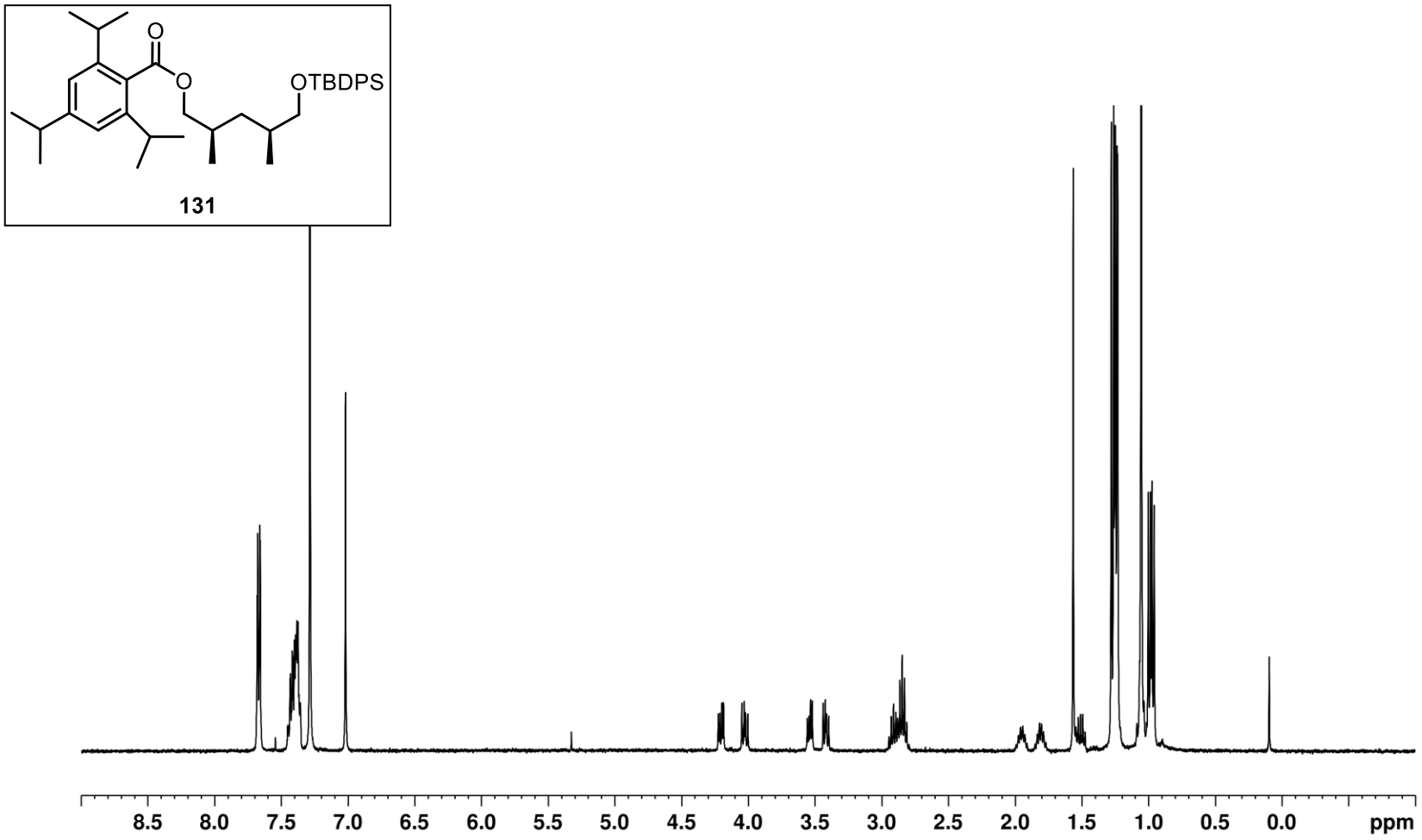

OH
OTBDPS

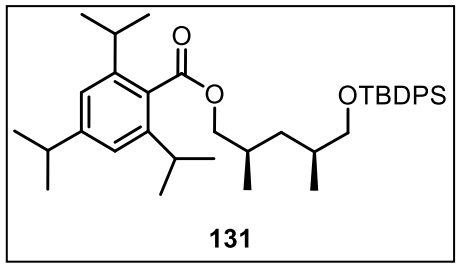
192


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
3.94
5.93
2.96
0.98
0.96
1.24
1.00
0.95
8.94
2.95
3.30


OH
OTBDPS
192

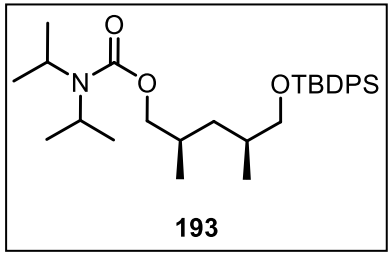
135.777
135.763
134.107
134.098
129.676
127.734
127.724
68.850
68.425
37.279
33.295
33.283
27.026
19.432
18.042
17.553
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
O
OTBDPS
131
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

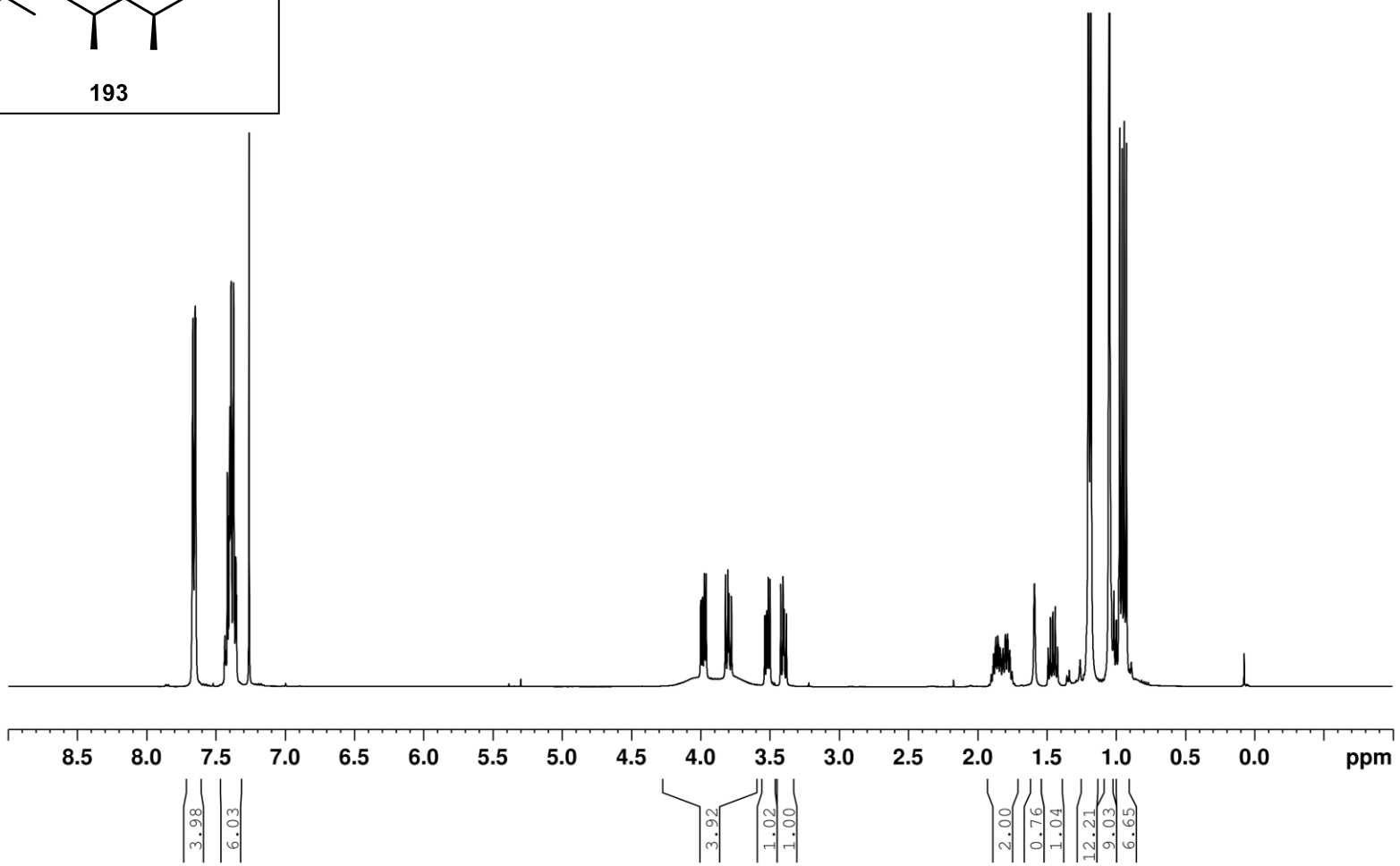

O
O
OTBDPS

131

136.585
135.577
134.823
133.830
133.824
129.658
129.649
127.645
127.641
126.605
68.781
67.871
35.044
30.342
26.885
26.816
26.585
25.983
19.310
16.901
13.956
1.047
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
N
O
OTBDPS

193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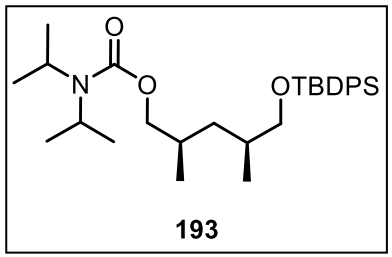
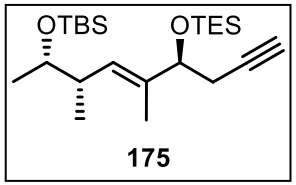
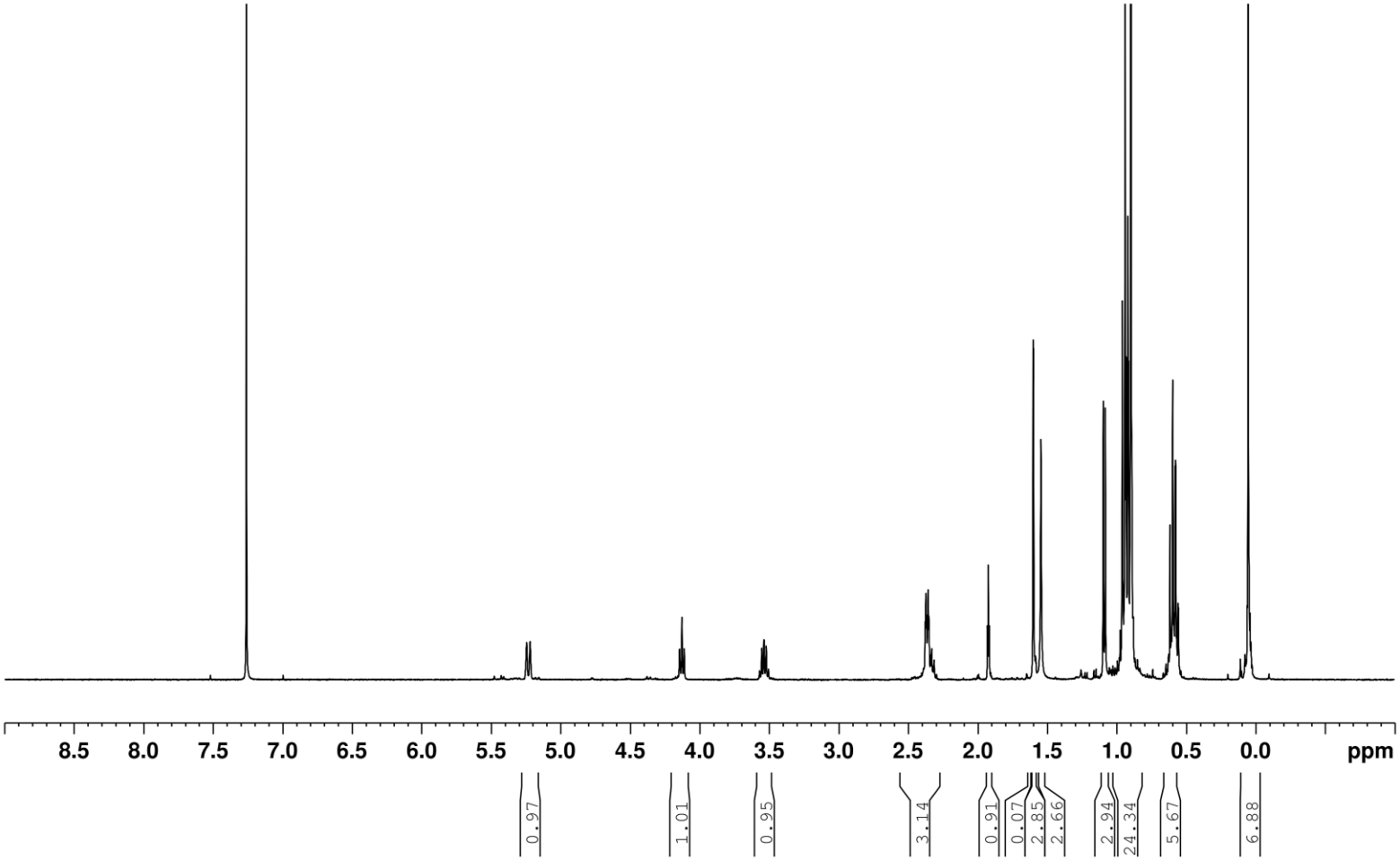
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
3.98
6.03
3.92
1.02
1.00
2.00
0.76
1.04
12.21
9.03
6.65

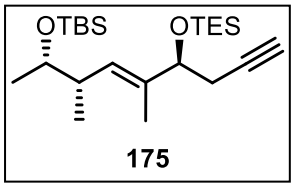

O
N
O
OTBDPS

193

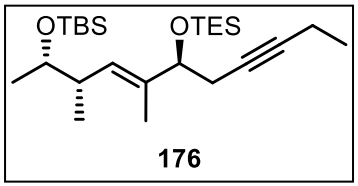
156.137
135.752
134.112
129.644
127.716
69.862
69.090
45.897
37.856
33.198
30.479
27.009
21.248
19.434
18.308
17.803
220
200
180
160
140
120
100
80
60
40
20
0
ppm

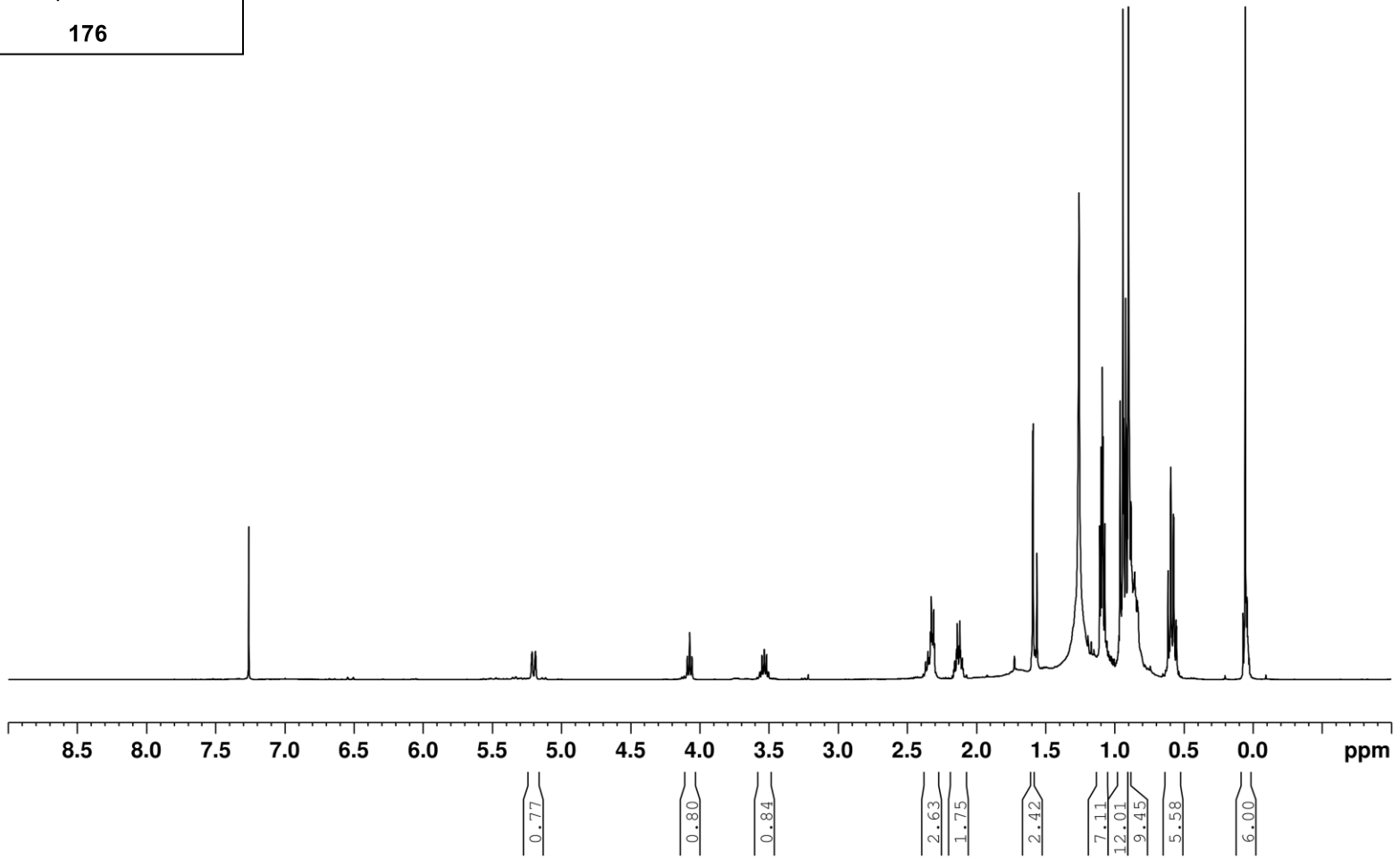

OTBS
OTES
175

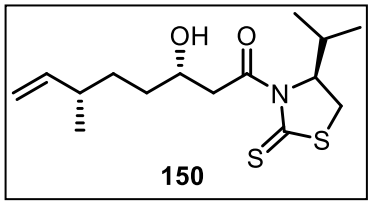

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
0.97
1.01
0.95
3.14
0.91
0.07
2.85
2.66
2.94
24.34
5.67
6.88

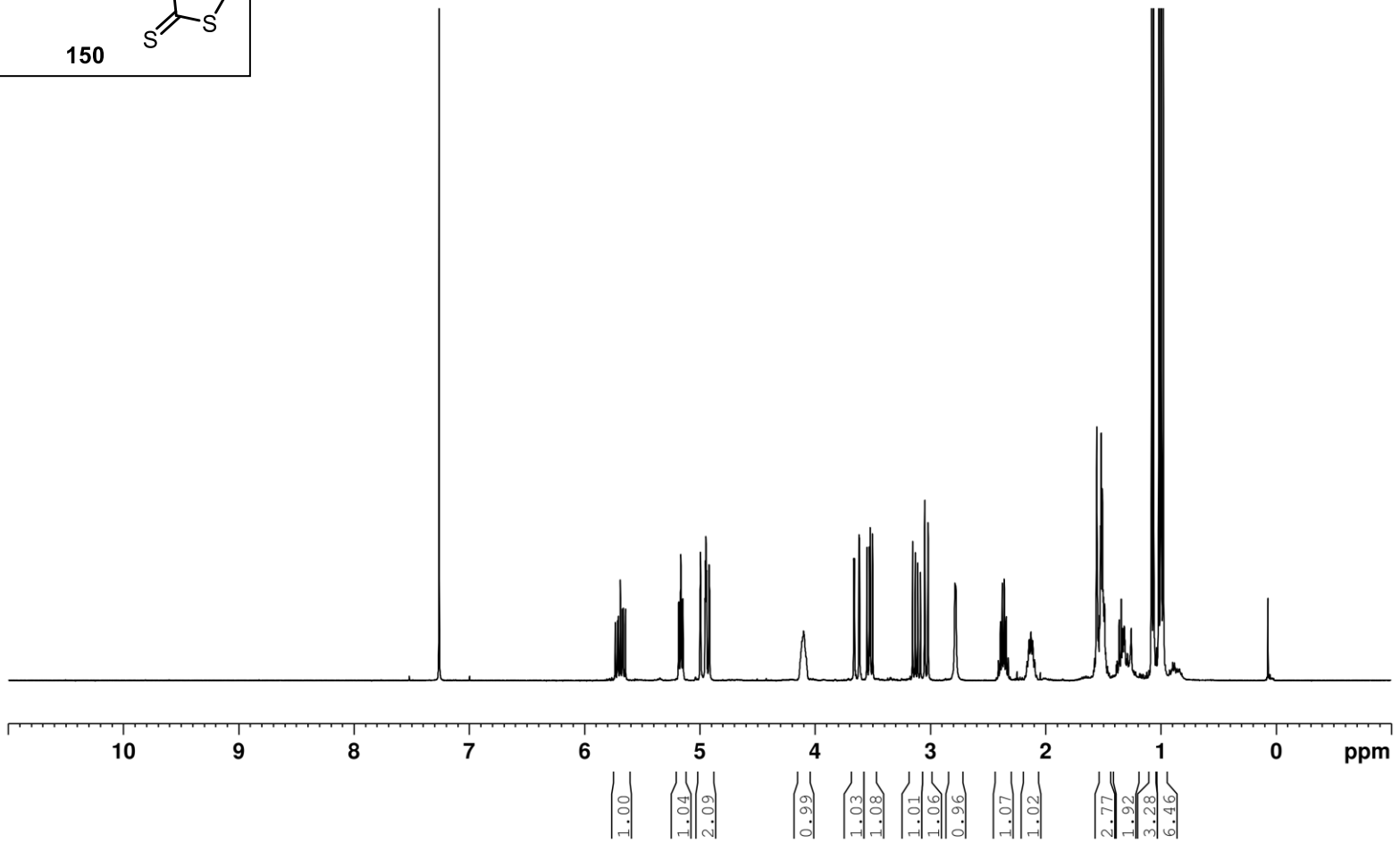

OTBS
OTES
175

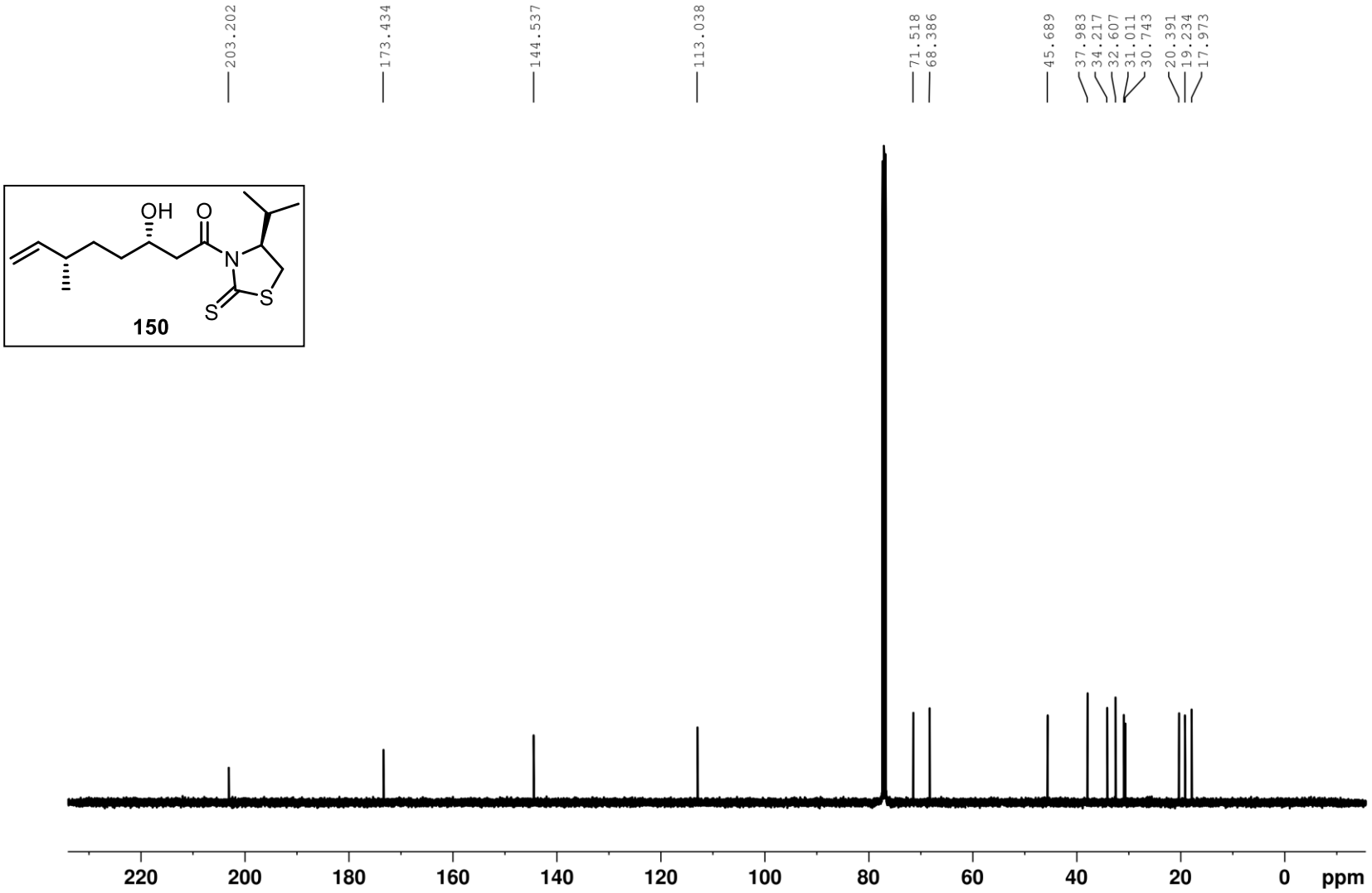
135.420
130.082
82.042
77.007
72.868
69.784
40.767
27.217
26.063
22.128
18.285
17.344
11.535
7.004
4.902
-4.060
-4.622
220
200
180
160
140
120
100
80
60
40
20
0
ppm

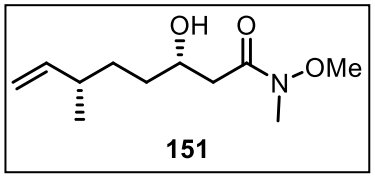

OTBS
OTES
176


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
0.77
0.80
0.84
2.63
1.75
2.42
7.11
12.01
9.45
5.58
6.00

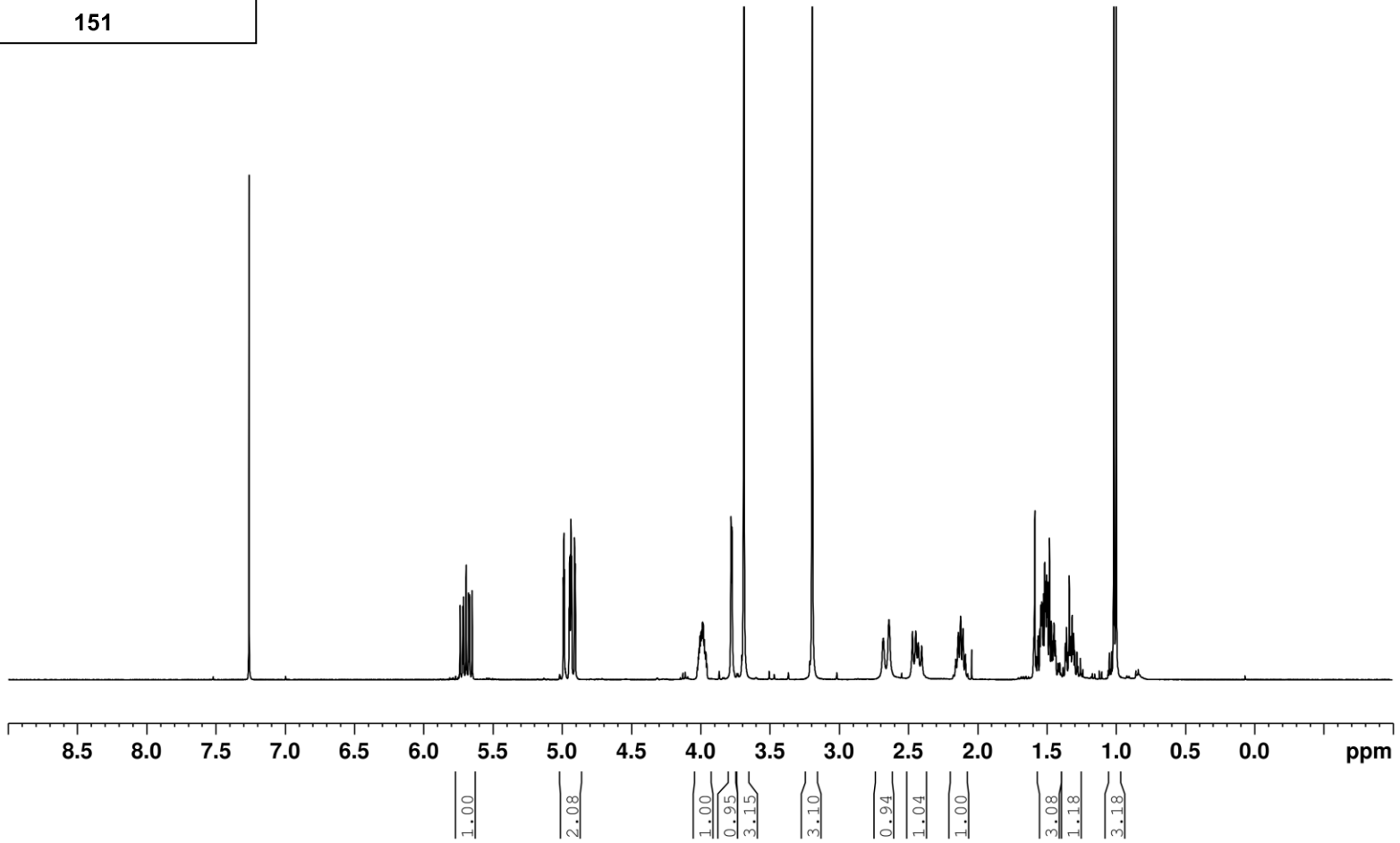

OH
O
N
S
S
150

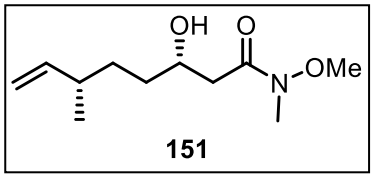

10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.04
2.09
0.99
1.03
1.08
1.01
1.06
0.96
1.07
1.02
2.77
1.92
3.28
6.46


203.202
173.434
144.537
113.038
71.518
68.386
45.689
37.983
34.217
32.607
31.011
30.743
20.391
19.234
17.973
OH
O
N
S
S
150
220
200
180
160
140
120
100
80
60
40
20
0
ppm

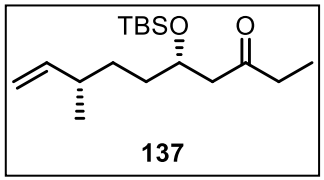

OH
O
N
OMe

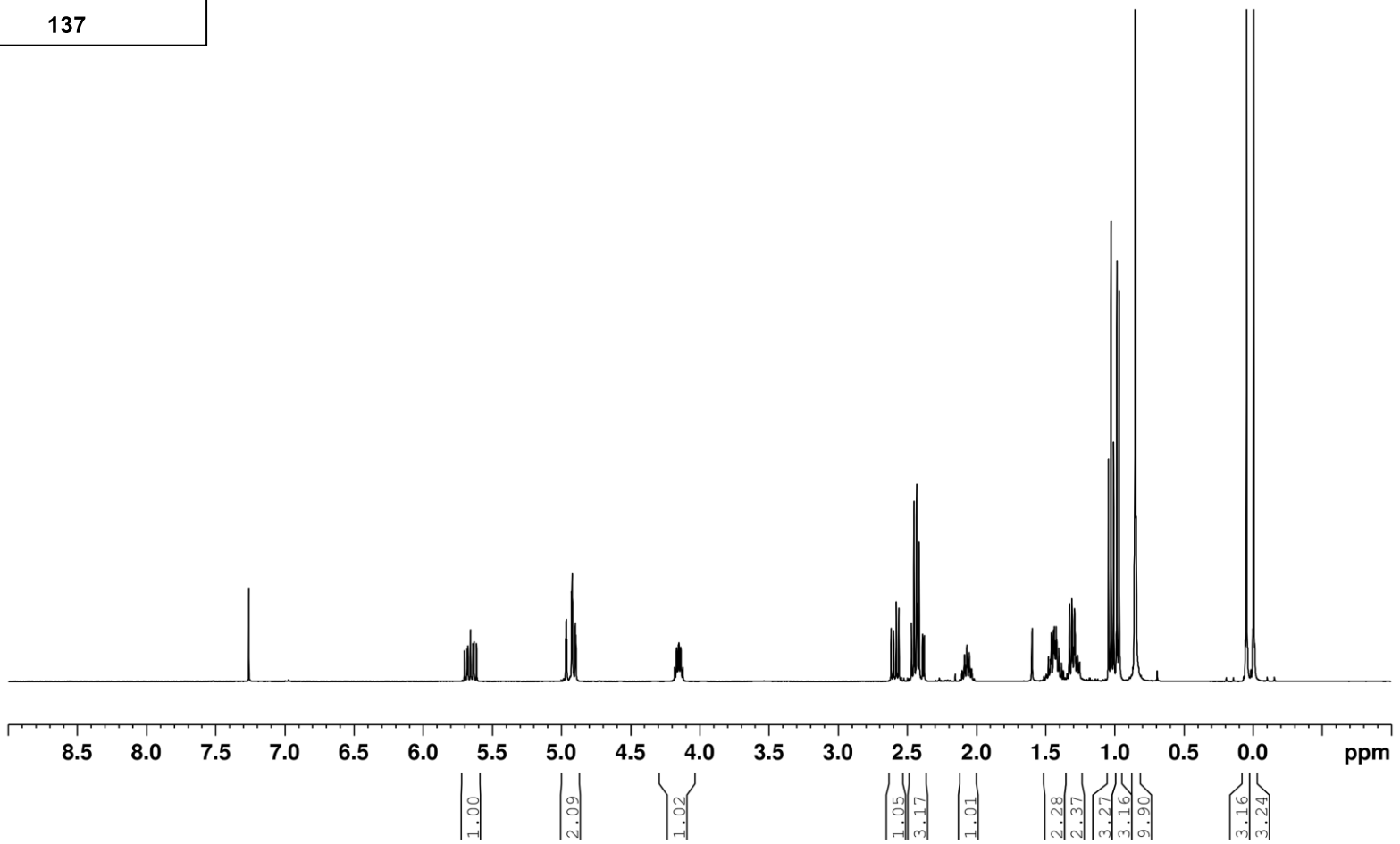
151

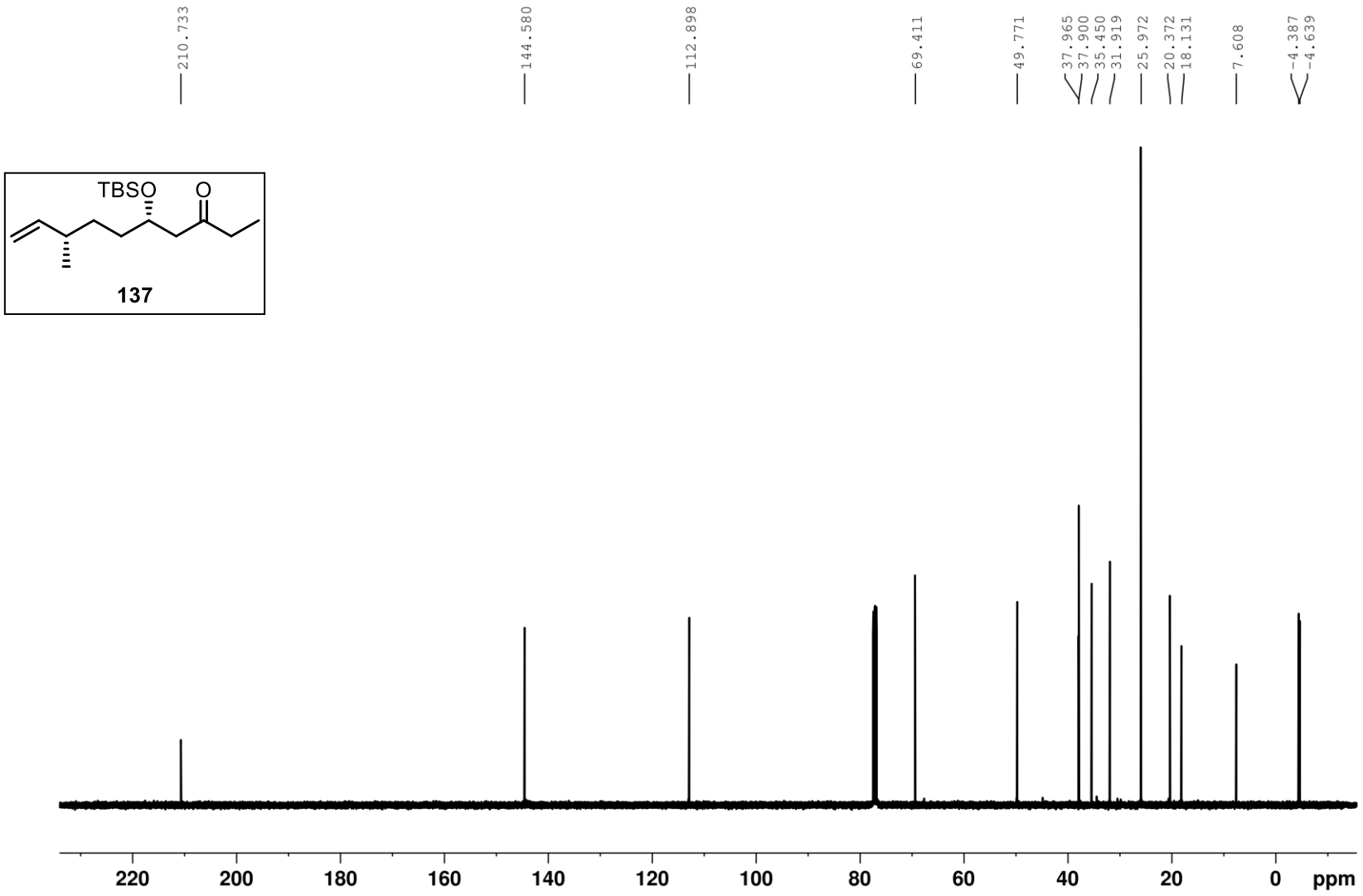

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.00
2.08
1.00
0.95
3.15
3.10
0.94
1.04
1.00
3.08
1.18
3.18


OH
O
N
OMe
151

174.103
144.678
112.896
68.293
61.382
38.372
38.082
34.502
32.622
31.994
20.384
220
200
180
160
140
120
100
80
60
40
20
0
ppm


TBSO
O
137


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.00
2.09
1.02
1.05
3.17
1.01
2.28
2.37
3.27
3.16
9.90
3.16
3.24


210.733
144.580
112.898
69.411
49.771
37.965
37.900
35.450
31.919
25.972
20.372
18.131
7.608
-4.387
-4.639
TBSO
O
137
220
200
180
160
140
120
100
80
60
40
20
0
ppm

6.2 Curriculum Vitae

Andi Kipper

Education

09/2014- present day — **Leibniz University Hannover, PhD in Organic Chemistry**
Hannover, Germany
Areas of Resesarch: Synthetic organic chemistry, natural products
Publications and Conferences: See page 2
PhD Thesis: "Towards the Total Synthesis of Meridamycins"

09/2011 – 06/2013 — **University of Tartu, MSc. in Chemistry (*cum laude*)**
Tartu, Estonia
Core Courses: Organic chemistry, analytical chemistry, computational chemistry
Scholarships: Kristjan Jaak Scholarship for 3-month exchange in Notre Dame University, USA; DORA scholarship for 3-week exchange in University of Nice, France; Estonian-Revelia Academic Fund scholarship
Master's Thesis: "The Synthesis of CH_2-skipped Pyridine-Piperazine Homologue"

09/2008 – 06/2011 — **University of Tartu, BSc. in Chemistry**
Tartu, Estonia
Core Courses: General chemistry, organic chemistry
Bachelor's Thesis: "The Synthesis of Grapevine Moth Sex Pheromone (7*E*,9*Z*)-dodeca-7,9-diene-1-yne acetate and Separation of Its *E*,*E* and *E*,*Z* Isomers by Urea Inclusion Complex"

Work

09/2014 – 03/2018 — **Institute of Organic Chemistry, Scientific Researcher**
Leibniz University Hannover, Hannover, Germany
- Prepared a large variety of chemical compounds
- Supervised lab courses, exercise classes and Bachelor's theses
- Presented my work at scientific conferences and institute seminars

09/2013 – 08/2014 — **Chemist/Project Manager**
TBD Biodiscovery, Tartu, Estonia
- Planned a project preparing 10 kg of a starting material for API synthesis
- Discussed the progress on the project with the client on weekly basis
- Composed the relevant documentation (work plan, risk assessment, change management etc.) for projects

09/2011 – 01/2014 — **Institute of Chemistry, Chemist**
University of Tartu, Tartu, Estonia
- Supervised organic chemistry exercise classes
- Maintained and performed experiments on NMR spectrometer
- Organized a course on transition metal catalysis

Skills

Languages: Estonian (native), English (fluent), German (intermediate), Russian (basic), Spanish (basic)

Computer: MS Office, Mozilla Firefox, ChemOffice, MestReNova, TopSpin, Reaxys, Scifinder, Citavi

Certificates: Promotion Plus+ skills for careers outside academia – team work and team leadership, conversation and conflict resolution skills, management practice

Participation in conferences and courses:

"A. Corbella" XLII International Summer School on Organic Synthesis with **oral presentation** in Gargnano, Italy, 18-22th July 2017

BMWZ Symposium with **oral presentation** in Hannover, Germany, 29th Septemeber, 2016

HSBDR Symposium with **oral presentation** in Burg Warberg, Germany, 16-17th June, 2016

Natural Products: From Genome Mining to Chemical Synthesis conference with **poster presentation** in Leiden, Netherlands, 16-18th September 2015

29th Organisk Kjemisk Vintermote with **poster presentation** in Skeikampen, Norway, 9-12th January 2014

Paul Helquist course "*Synthetic Methods of the XXI Century*", May 2012

European Symposium of Organic Chemistry ESOC 2011 with **poster presentation** in Hersonissos, Greece, 10-15th July, 2011

Abstracts/Publications:

Kalesse, M.; Böhm, A.; Kipper, A.; Wandelt, V. Synthesis of Antibiotics. In *How to Overcome the Antibiotic Crisis*; Stadler, M.; Dersch, P., Eds. Springer: Cham, 2016; pp 419-446.

A. Kipper, I. Kalvet, L. Sikk, K. Tämm, P. Burk, K. Kõiv, U. Mäeorg, Synthesis of unprotected CH_2-skipped piperazine-pyridine alternating cycles with azide end-group, *Heterocycles*, **2014**.