Studies toward the Total Synthesis of Xenovulene A

Von der Naturwissenschaftlichen Fakultät der

Gottfried Wilhelm Leibniz Universität Hannover

zur Erlangung des Grades

Doktor der Naturwissenschaften (Dr. rer. nat.)

genehmigte Dissertation

von

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2019

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Tag der promotion: 06.06.2019

To my family

Acknowledgement

First of all, I would like to thank my PhD thesis advisor, Prof. Dr. Andreas Kirschning for giving me the opportunity to conduct my PhD thesis in his research group and for support and enthusiasm over the past few years. I am very grateful for the freedom to develop my own ideas and projects. His passion and wisdom for all aspects of total synthesis and daily life have helped me become a better chemist.

I would like to thank Prof. Dr. Markus Kalesse for agreeing to be the reviewer for this thesis and as well Prof. Dr. Jürgen Caro for being on my PhD defense committee.

I am very thankful to Dr. Gerald Dräger for his help and assistance on crystallographic and mass analysis and many technical questions of the experimental instruments. I would like to thank Dr. Jörg Fohrer, Monika Rettstadt and Dagmar Körtje and all the members of the NMR and mass spectrometry department for their help and assistance with NMR and mass analysis.

I would like to thank all the people who have helped to improve this thesis with their excellent advice and suggestions: Alexandra Seemann, Sibel Türkkan, Samhita Banerjee, Janina Meyer, Christian Bartens, Dr. Matthew D. Norris, Helge Berneaud, Malte Moeller and Carsten Schotte.

I appreciate all current and former members of the Kirschning research group who contributed with theoretical and psychological help on my lab life and made it an enjoyable and memorable journey. Especially, I would like to thank all my labmates for making our laboratory a great working environment: Dr. Clara Oberhauser, Friederike Schaekel and Cong Duc Tran. In addition, I would like to acknowledge the people who have helped me to go through the tough beginning of my PhD: Dr. Michael Wolling, Dr. Egor Geist, Dr. Jonas Ammermann, Dr. Argyrios Kanakis, and Dr. Despoina Leivadiotou. During my time as a PhD student, I had the opportunity to mentor a few very talented master students: Christoph Etling, Konrad Kuhwald, and Catherine Victoria. I am very grateful for their contributions to my PhD work.

The staff at OCI and BMWZ is superb. I would like to thank Ms. Lovelock, Ms. Griese, Ms. Bartetzko and Ms. Kandil for their kind help and assistance on lots of general issues. My special thanks go to Ms. Roloff, whom I share the same birthday with, for help on everything which involves language issue, and celebrating birthday together.

Apart from work, I would like to thank Sibel and Samhita for help on solving lots of common problems with me and hanging out together after work. Thanks Nick and Hansi for inviting me to their awesome parties and celebrating holidays together which I really appreciate. Thanks Joseph for being my swimming and Chinese food tasting buddy, and Liping for teaching me how to cook and being my ping-pong partner.

Finally, I would like to give my special acknowledgements to my family, especially to my dearest parents, who had to support me, get along with those big changes of my life and get through all the ups and downs of my life with me over the past few years. Undoubtedly, this thesis would not have been possible without their love, encouragement and support.

Publication and conference contributions

Part of this thesis has been published in peer-reviewed journal:

- Pei-Jun Li, Gerald Dräger, and Andreas Kirschning; A General Biomimetic Hetero Diels-Alder Approach to the Core Skeletons of Xenovulene A, and the Sterhirsutins A and B. *Organic Letters*, **2019**, *21*, 998-1001.

Parts of this thesis have been presented at scientific conferences:

- Oral Presentations, *HSBDR Symposium*, Burg Warberg, Germany; July 2016, 2017 and 2018.
- Poster Presentation, The *3rd European Conference on Natural Products*, Frankfurt, Germany, September 2018.
- Poster Presentation, *ORCHEM 2018*, Berlin, Germany, September 2018.
- Poster Presentation, *Leibniz Symposium 2019*, Hannover, Germany, February 2019.

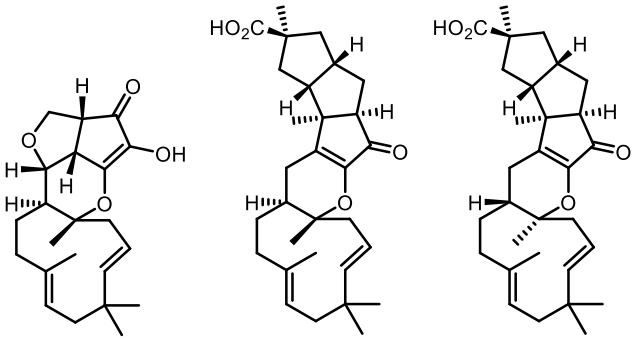
Abstract

Peijun Li

Studies toward the Total Synthesis of Xenovulene A

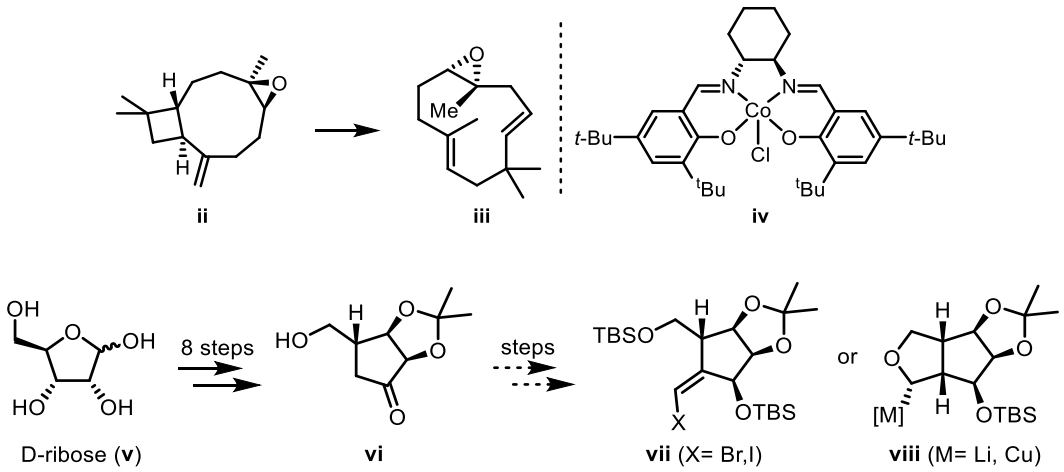
Keywords: total synthesis, natural product synthesis, meroterpenoid, epoxide ring opening, hetero Diels-Alder cycloaddition

Xenovulene A (**i**), an unusual meroterpenoid, was originally isolated by Chicarelli-Robinson and coworkers from the fungus *Acremonium strictum* in 1995. It comprises an unusual furocyclopentenone moiety fused to a humulene derived 11-memebered ring. This unusual molecular architecture combined with its significant biological activities has made it a highly attractive synthetic target. However, until now no total synthesis of it has been reported. As a consequence, interested in the novel and unique structure of xenovulene A (**i**) and to further probe its bioactivities, synthetic studies toward **i** were developed.

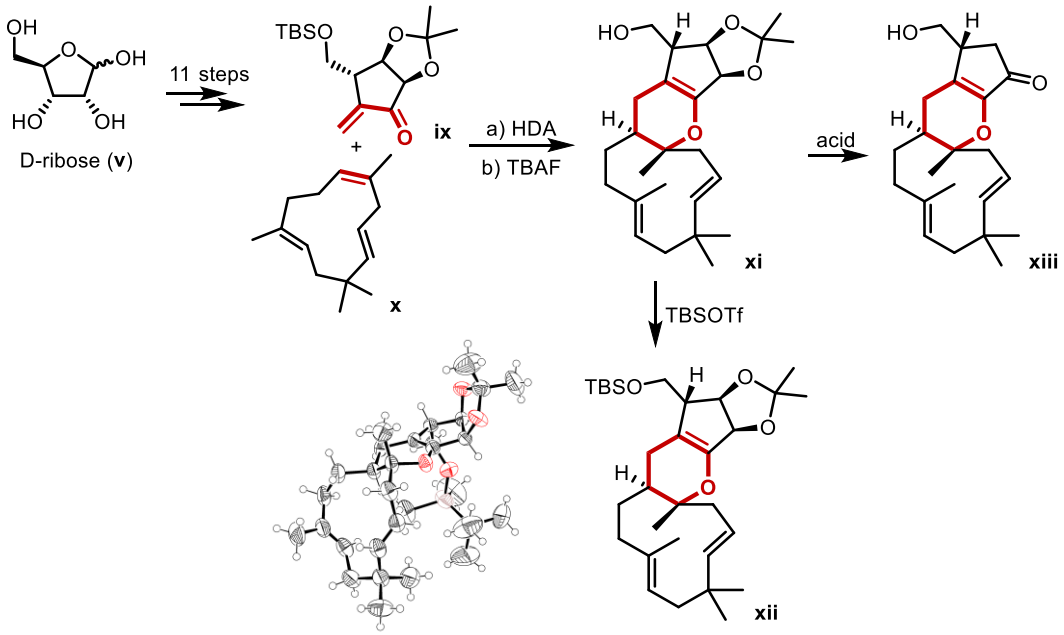


xenovulene A (**i**) sterhirsutins A (**xiv**) and B (**xv**)

The first synthetic approach towards xenovulene A (**i**) aimed to develop an epoxide ring opening reaction of humulene epoxide (**iii**) as one of the key steps. Firstly, as a literature known procedure, humulene epoxide (**iii**) can be synthesized through a Co(III)Cl (**iv**) catalyzed retrocycloisomerization of (-)-caryophyllene oxide (**ii**). The second goal of this approach was synthesis of the nucleophile fragments **(vii)** or **(viii)** for the proposed ring opening reaction of epoxide (**iii**). Despite several attempts to synthesize nucleophile fragments **(vii)** or **(viii)** from D-ribose (**v**), the desired fragments could not be obtained and hence the first strategy was abandoned.

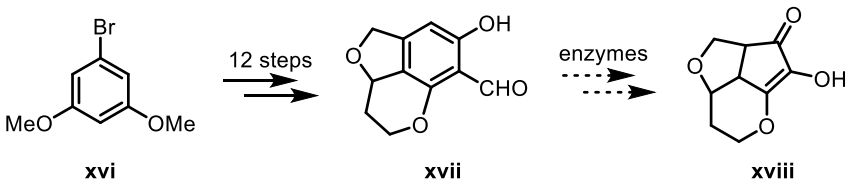


In the second synthetic approach towards xenovulene A (**i**), the key step was a biomimetic inverse electron demand hetero Diels-Alder cycloaddition (HDA) of α-humulene (**x**) and ribose-derived vinyl ketone (**ix**) which can be synthesized from D-ribose (**v**) in 10% yield over 11 steps. Using this biomimetic approach, a regio- and stereoselective synthesis of the full 5,6,11-tricyclic carbon skeleton of xenovulene A was accomplished. The absolute configuration of the advanced intermediate (**xi**) was confirmed by x-ray crystallographic analysis of its TBS-ether (**xii**), which could be obtained in crystalline form. In addition, a novel acid catalyzed rearrangement of 1,3-dioxolane (**xi**) to ketone (**xiii**) was discovered, demonstrating that Diels-Alder adducts such as **xi** might also be useful for the synthesis of the two xenovulene analogues, sterhirsutins A (**xiv**)and B (**xv**).



Finally, the last part of the thesis describes efforts toward the synthesis of a model system to mimic Simpson's biosynthetic proposal of xenovulene A (**i**). The model compound (**xvii**) was

successfully synthesized in 4% overall yield in 12 steps from **xvi**. The further studies on the biosynthesis of **xviii** through a unique pathway which involves the phenol (**xvii**) undergoes ring expansion to a tropolone followed by two successive ring contractions was still under investigation at the time of thesis submission.



xvi **xvii** **xviii**

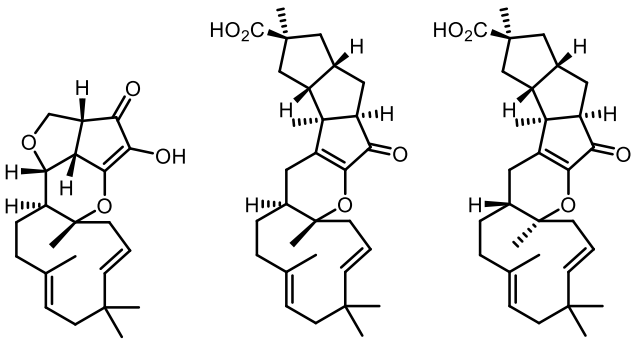
Zusammenfassung

Peijun Li

Studien zur Totalsynthese der Xenovulene A

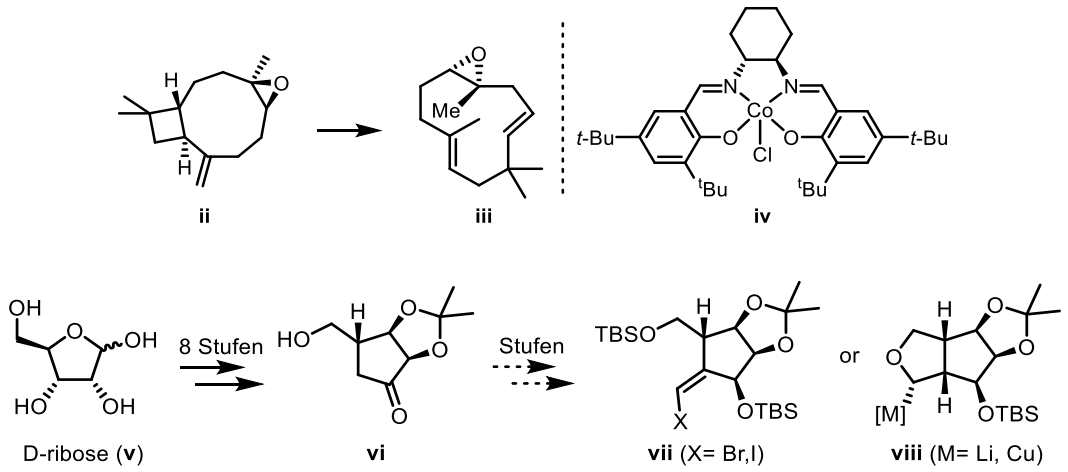
Schlagwörter: Totalsynthese, Naturstoffsynthese, Meroterpenoid, Epoxidringöffnung, Hetero-Diels-Alder-Cycloaddition

Xenovulene A (**i**), ein Hybrid-Polyketid-Terpenoid (Meroterpenoid), wurde ursprünglich von Chicarelli-Robinson und Mitarbeitern aus dem Pilz *Acremonium strictum* im Jahr 1995 isoliert. Die ungewöhnliche molekulare Architektur, bestehend aus einem komplexen Ringsystem, in kombination mit den signifikanten biologischen Eigenschaften, macht es zu einem sehr attraktiven Syntheseziel. Um weitere Untersuchung an der neuartigen und einzigartigen Struktur von Xenovulen A (**i**) und seiner Bioaktivität durchzuführen, wurden bereits synthetische Studien entwickelt.

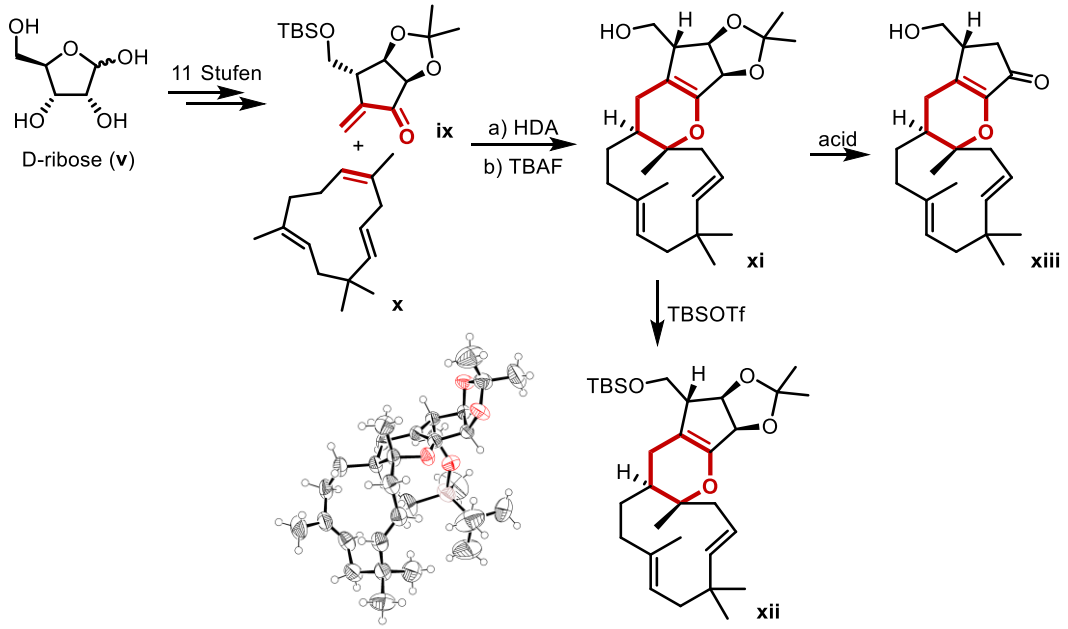


xenovulene A (**i**) sterhirsutins A (**xiv**) and B (**xv**)

Der erste synthetische Ansatz für Xenovulen A (**i**) beruhte auf einer Epoxidringöffnungsreaktion von Humulene epoxide (**iii**) als einen der zentralen Schlüsselschritte. Als erstes sollte Humulenepoxid (**iii**) durch eine Co(III)Cl (**iv**) katalysierte Retrocycloisomerisierung von (-)-Caryophyllenoxid (**ii**) synthetisiert werden. Das zweite Ziel war die Synthese von den Nukleophilfragmenten (**vii**) oder (**viii**) für die vorgeschlagene Ringöffnungsreaktion von Epoxid (**iii**). Trotz mehrerer Versuche, die Nucleophilfragmente (**vii**) oder (**viii**) aus D-Ribose (**v**) zu synthetisieren, konnten die gewünschten Fragmente nicht erhalten werden und die erste Strategie wurde aufgegeben.

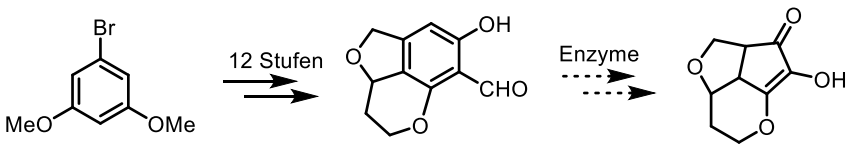


In der zweiten Synthesemethode für Xenovulen A (**i**) stellte der Schlüsselschritt eine Hetero-Diels-Alder-Cycloaddition (HDA) aus α-Humulen (**x**) und dem Ribose-abgeleitetem Vinylketon (**ix**) dar. Vinylketon (**ix**) kann aus D-Ribose (**v**) in eines Ausbeute von 10% über 11 Stufen synthetisiert werden. Mit diesem biomimetischen Ansatz wurde eine regio- und stereoselektive Synthese des gesamten 5,6,11-tricyclischen Kohlenstoffgerüsts von Xenovulen A durchgeführt. Die absolute Konfiguration des fortgeschrittenen Intermediats (**xi**) wurde durch röntgenkristallographische Analyse seines TBS-Ethers (**xii**) bestätigt, der in kristalliner Form erhalten werden konnte. Außerdem wurde eine neue säurekatalysierte Umlagerung von 1,3-Dioxolan (**xi**) entdeckt, die zeigt, dass Diels-Alder-Addukte wie **xi** auch für die Synthese der beiden Sterhirsutine A (**xiv**) und B (**xv**) von Nutzen sein kann.



Der letzte Teil der Arbeit beschreibt schließlich die Bemühungen der Synthese eines Modellsystems zur Nachahmung der Simpson-Biosynthese von Xenovulen A (**i**). Die

Modellverbindung (**xvii**) wurde erfolgreich in 4% Gesamtausbeute über 12 Stufen von **xvi** synthetisiert. Die weiteren Untersuchungen zur Biosynthese von **xviii** über einen einzigartigen Weg, bei dem das Phenol (**xvii**) einer Ringexpansion zu einem Tropolon unterzogen wird, gefolgt von zwei aufeinanderfolgenden Ringkontraktionen, wurden zum Zeitpunkt der Einreichung dieser Arbeit noch untersucht.



xvi **xvii** **xviii**

List of abbreviations and symbols

Ac	acetyl
Ar	aromatic
Bn	benzyl
Boc	*tert*-butoxycarbonyl
brsm	based on recovered starting material
Bu	butyl
c	concentration
conc.	concentrated
calcd	calculated
COSY	correlated spectroscopy
d	day(s)
DBU	1,8-diayobicyclo-[5,4,0]-undec-7-ene
DCM	dichloromethane
DCE	1,2-dichloroethane
DIBAL-H	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DIPA	diisopropylamine
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane or 1,1,1-Tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one)
DMSO	dimethylsulfoxide

DMS	dimethyl sulfide
dr	diastereomeric ratio
eq.	equivlent
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
g	gram
h	hour(s)
HMBC	heteronuclear multiple bond correlation
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence spectroscopy
Hz	Hertz
J	coupling constant
L	liter
LAH	lithium aluminium
LC	liquid chromatography
LDA	lithium diisopropylamide
LiHMDA	lithium bis(trimethylsilyl)amide
LUMO	lowest unoccupied molecular orbital
M	molar or metal
Me	methyl
mg	milligram

min	minute(s)
mL	milliliter
mol	mole(s)
mmol	millimole(s)
MOM	methoxymethyl
m. p.	melting point
MS	mass or molecular sieves
NBS	*N*-bromosuccinimide
NMO	4-methylmorpholine N-oxide
NMR	nuclear magnetic resonance
nm	namometer
NOE	nuclear Overhauser effect
o/n	overnight
p	*para*-
PE	petroleum ether
Ph	phenyl
PMB	*para*-methoxybenzyl
ppm	parts per million
Pr	propyl
Py	pyridine
RCM	ring-closing metathesis
R_f	retention factors
rt	room temperature

sat.	saturated
T	temperature
t	time
TBAF	*tetra*-n-butyl ammonium fluoride
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
T_f	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*para*-toluenesulfonyl
TS	transition state
UV	ultraviolet
Å	Ångström
δ	chemical shift
d	deutero
$h\nu$	irradiation
^{o}C	degree celsius

Contents

Chapter 1 Xenovulene A and the Meroterpenoids

1.1 Introduction

1.1.1 Polyketide

The polyketide natural products (Figure 1.1) are a remarkable class of compounds.[1] By definition, these molecules either contain alternating carbonyl and methylene groups (-CO-CH_2-), or are derived from precursors which contain such alternating groups. In addition, they exhibit a wide range of functional and structural diversity, and show a wealth of different bioactivities, including antibiotic, anticancer, antifungal, antiparasitic and immunosuppressive properties.[2]

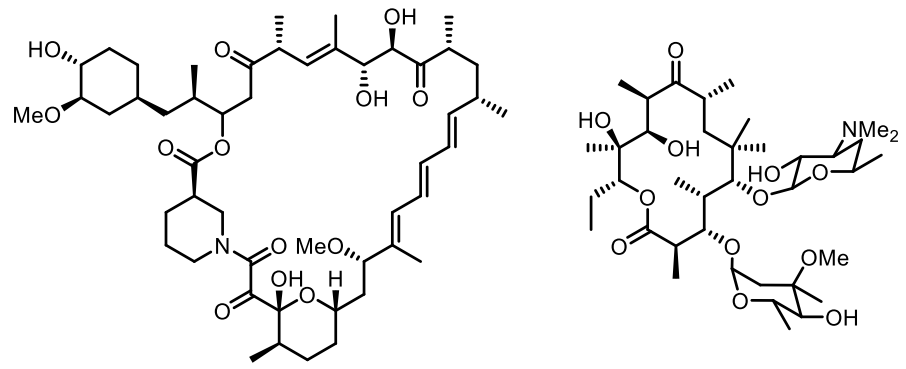


Figure 1.1: Examples of polyketide secondary metabolites.

[1] Staunton, J.; Weissman, K. J. *Nat. Prod. Rep.* **2001**, *18*, 380-416.
[2] Crump, M. P.; Crosby, J; Dempsey, C. E.; Parkinson, J. A.; Murray, M.; Hopwood, D. A.; Simpson, T. J. *Biochemistry*, **1997**, *36*, 6000-6006.

1.1.2 Terpenoid

The terpenoids (Figure 1.2), sometimes called isoprenoids, is one of the largest classes of naturally occurring bioactive compounds derived from terpenes. They are commonly multicyclic structures with oxygen-containing functional groups. Although sometimes used interchangeably with "terpenes", terpenoids contain additional functional groups, usually oxygen functionalities. Terpenes are hydrocarbons. Like polyketide natural products, the terpenoids exhibit extraordinary pharmacological importance including anticancer, antiviral, antibiotic, and immunosuppressive.[3]

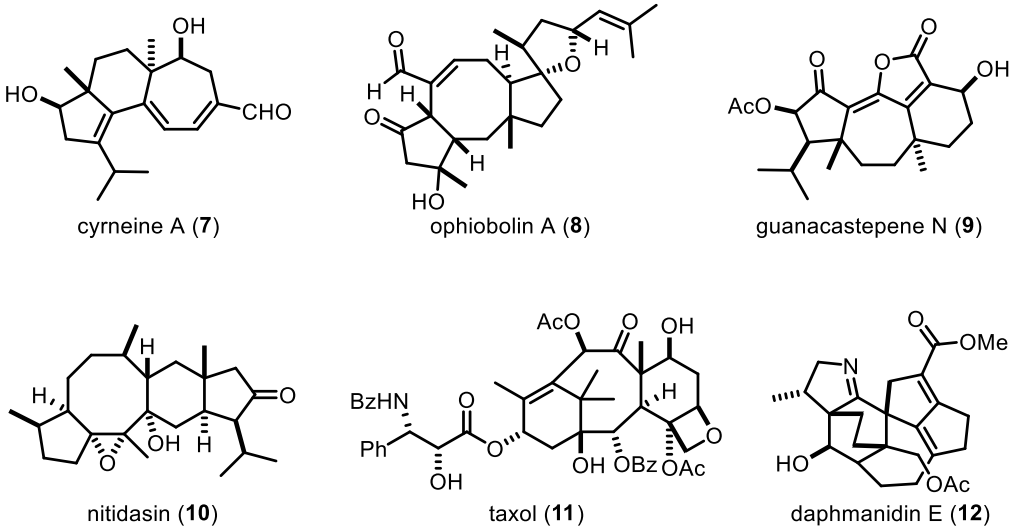


Figure 1.2: Examples of terpenoids.

1.1.3 Meroterpenoid (hybrid polyketide-terpenoid)

The prefix "*mero*" used for meroterpenoids means "part, partial, and fragment" in Greek, and as nature suggests, they are hybrid natural products partially derived from terpenoid pathways.[4] It was initially proposed by Cornforth in 1968 as "Compounds containing terpenoid elements along with structures of different biosynthetic origin".[5] Recently, Simpson defined meroterpenoids as a more limited group: "Compounds of mixed polyketide-terpenoid origin".[6] On the basis of their definition, there are a large number of compounds derived from animals, plants, bacteria, and fungi, which can be categorized as meroterpenoids and they exhibit a range of widely distributed molecules to species-specific secondary metabolites. For example, sponge-derived meroterpenoids are widely recognized for their various structural

[3] *Comprehensive Natural Products Chemistry*; Boston, D.; Nakanishi, K.; Meth-Cohn, O.; Eds.; Elsevier: Oxford, **1999**; Vol. *2*.
[4] Geris, R.; Simpson, T.J. *Nat. Prod. Rep.* **2009**, *26*, 1063-1094.
[5] Cornforth, J. W. *Chem. Ber.* **1968**, *4*, 102.
[6] Simpson, T.J. *Chem. Soc. Rev.* **1987**, *16*, 123.

features and potent bioactivities (Figure 1.3). Since the isolation of avarol (**13**), a rearranged drimane sesquiterpene hydroquinone, from *Dysidea avara*, compounds of this structural class have been obtained from several sponges of the group of Dictyoceratida. Structural variations occur at both the quinone (hydroquinone) and polyprenyl moieties, which have resulted in more than 100 novel compounds to date. The most frequently encountered bioactivities of these compounds are cytotoxicity along with anticancer-related activities. The most notable example of bioactivity of these meroterpenoids might be the significant anti-HIV activity of ilimaquinone (**14**), which has attracted considerable biomedical and synthetic interest.[7]

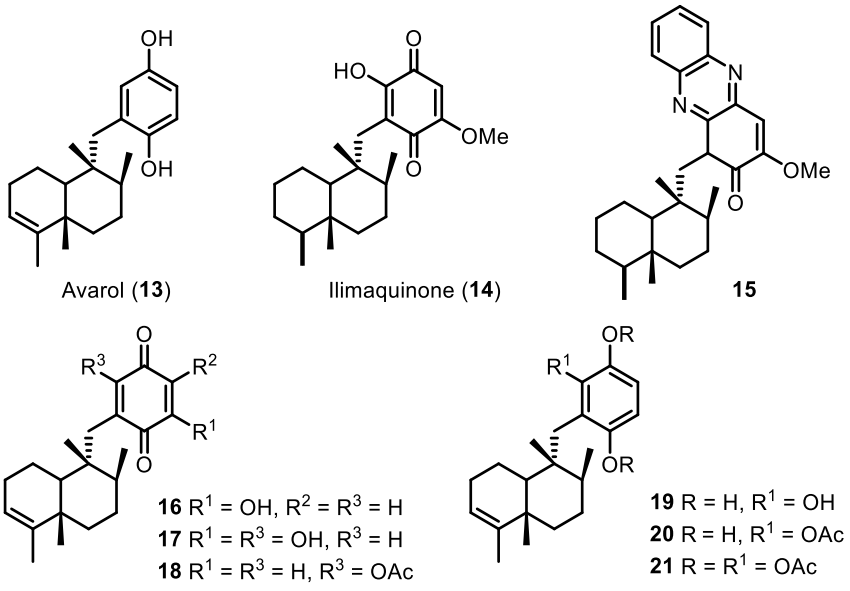


Figure 1.3: Examples of sponge-derived meroterpenoids

Another main class of well-known meroterpenoids with diverse chemical structures and a wide range of bioactivities is metabolite isolated from fungi (Figure 1.4).[8]

[7] Blunt, J. W.; Copp, B. R.; Keyzers, R. A.; Munro, M. H. G.; Prinsep, M. R. *Nat. Prod. Rep.* **2015**, *32*, 116-211.
[8] Morton, R. *Nature*, **1958**, *182*, 1764-1767.

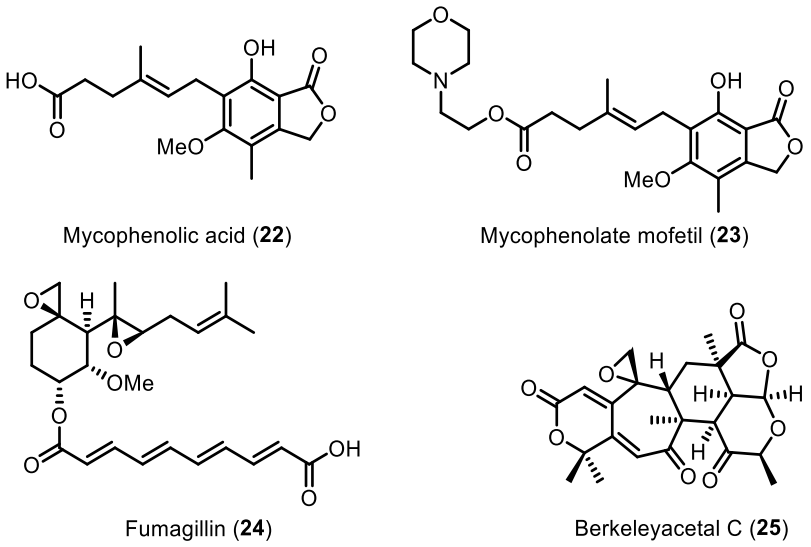


Figure 1.4: Examples of fungi-derived meroterpenoids

Mycophenolic acid (**22**), is a fungal secondary metabolite, which is produced by several Penicillium species. It was discovered by an Italian medical scientist Bartolomeo Gosio in 1893 as an antibiotic against *Bacillus anthracis*. Mycophenolic acid and its derivative, mycophenolate mofetil (**23**), are commercially used as frontline immunosuppressive agents to prevent rejection of transplant organs. Fumagillin (**24**), isolated from *Aspergillus fumigatus*, is used for the treatment of microsporidiosis and amebiasis, and has also been investigated as an anti-angiogenesis agent. Berkeleyacetal C (**25**) was originally isolated from *Penicillium rubrum*, and it shows anti-inflammatory activity by inhibiting nitric oxide (NO) production and inducible NO synthase, in which the target molecule of **25** was elucidated to be interleukin-1 receptor-associated kinase-4.[9]

1.1.4 Xenovulene A – an unusual meroterpenoid

1.1.4.1 Isolation and Structure

Xenovulene A (1) belongs to the xenovulene family of hybrid polyketide-terpenoids (meroterpenoids), a group of natural products produced by submerged fermentation of *Acremonium strictum* (Figure 1.5).

[9] (a) Sintchak, M. D.; Fleming, M. A.; Futer, O.; Raybuck, S. A.; Caron, P. R.; Murcko, M. A.; Wilson, K. P. *Cell* **1996**, *85*, 921-930. (b) McCowen, M. C.; Callender, M. E.; Lawlis, J. F. *Science* **1951**, *113*, 202-203.

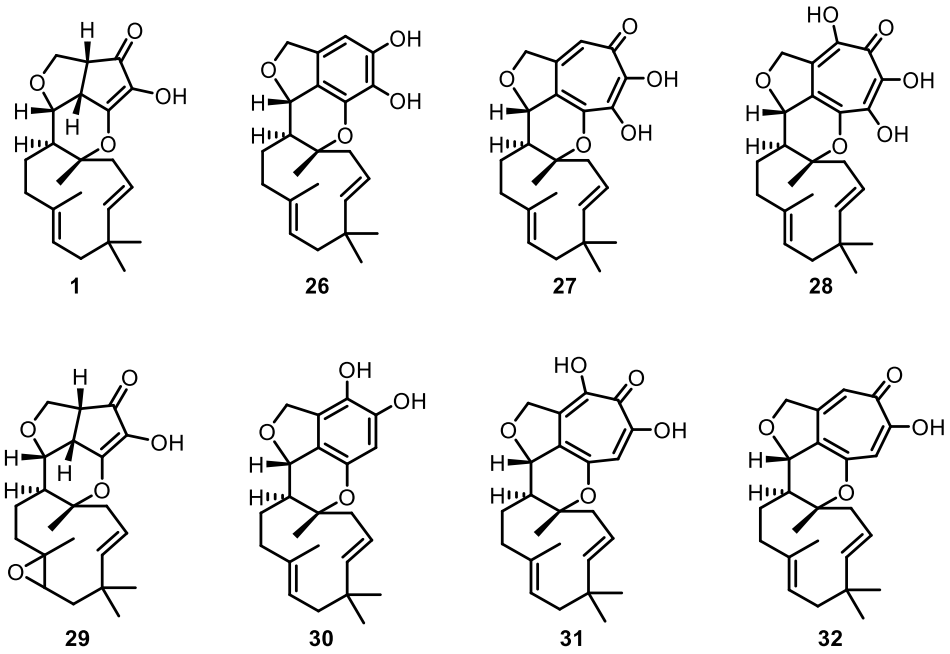


Figure 1.5: Structures of xenovulene A (**1**) and its analogues

Structurally, they all possess a common 5,6,11-tricyclic core. The unusual molecular architecture, consisting of a complex ring system, combined with their significant biological activities have made xenovulene A and related meroterpenoids challenging and popular targets for synthetic chemists.[10]

Xenovulene A (1) was initially isolated by Chicarelli-Robinson and coworkers in 1995 from the mycelium.[11] It consists of an unusual furocyclopentenone moiety fused to a humulene derived 11-membered ring. Conformationally, the humulene ring is restricted by the presence of two *trans* double bonds and the rigid 5,5,6-tricyclic system which contains five chiral centers present at the ring junctions. Based on the crystallographic analysis of xenovulene, Thomas and co-workers pointed out that the relative stereochemistry of these chiral centers leads to an overall concave conformation for the xenovulene A molecule.

[10] Thomas, P.; Sundaram, H.; Krishek, S. J.; Chazot, P.; Xie, X.; Bevan, P.; Brocchini, S. J.; Latham, C. J.; Charlton, P.; Moore, M.; Lewis, S. J.; Thornton, D. M.; Stephenson, F. A.; Smart, T. G. *J. Pharmacol. Exp. Ther.* **1997**, *282*, 513-520.

[11] Ainsworth, A. M.; Chicarelli-Robinson, M. I.; Copp, B. R.; Fauth, U.; Hyland, R. J.; Holloway, J. A.; Latif, M.; O'Beirne, G. B.; Poter, N.; Renno, D. V.; Richards, M.; Robinson, N. *J. Antibiot.* **1995**, *48*, 568-573.

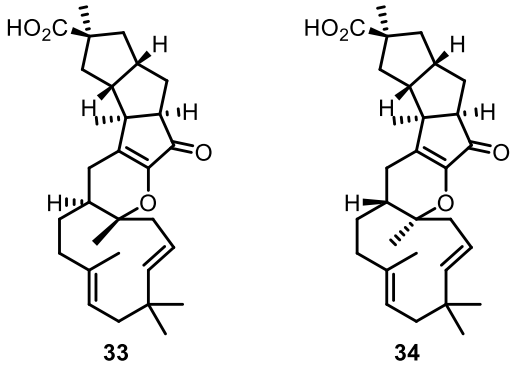


Figure 1.6: Structures of sterhirsutins A (**33**) and B (**34**)

Structurally related to xenovulenes are sterhirsutins A (**33**) and B (**34**) which were isolated by Liu and co-workers from *Stereum hirsutum* in 2014 (Figure 1.6).[12] Both diastereoisomers exhibit moderate antiproliferative activities against human myelogenous leukemia (K562) cells with IC_{50} values of 13 and 16 ug/mL, respectively. Although these meroterpenoids originate from different fungal species, they all share a similar tricyclic core structure including the humulene derived 11-membered ring.

1.1.4.2 Biological Activity

Benzodiazepines (**35**) are a class of well-known psychoactive drugs whose core chemical structure is the fusion of a benzene ring and a diazepine ring (Figure 1.7). The usefulness of the benzodiazepines as an antidepressant has been compromised by several well-known side effects, such as ataxia, sedation and chronic problem associated with benzodiazepine addiction. To obviate some of the side effects and improve the therapeutic potential of anxiolytic benzodiazepines, two approaches have been proposed: One of them is finding an inhibitor of benzodiazepine binding to the human γ-aminobutyric acid (GABA) receptor.

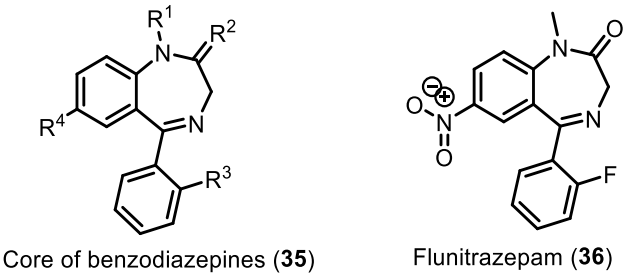


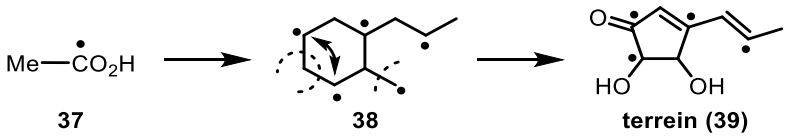
Figure 1.7: Structures of Benzodiazepines (**35**) and flunitrazepam (**36**)

[12] Qi, Q.-Y.; Bao, L.; Ren, J.-W.; Han, J.-J.; Zhang, Z.-Y.; Li, Y.; Yao, Y.-J.; Cao, R.; Liu, H.-W. *Org. Lett.* **2014**, *16*, 5092-5095.

After a screening programme for the new inhibitors of the binding of flunitrazepam (**36**) to the GABA benzodiazepine receptor, Chicarelli-Robinson and coworkers discovered that xenovulene A inhibited binding of the benzodiazepine, flunitrazepam (**36**), with an IC_{50} of 40 nM in an *in vivo* assay using bovine synaptosone membrane preparation. Additionally, antidepressant effects were encountered for xenovulene A (**1**).[10]

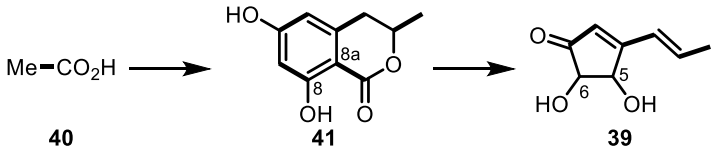
1.1.4.3 Biosynthesis of xenovulene A

Terrein (**39**) is a plant growth inhibitor and was initially isolated by Hirota and co-workers.[13] It is produced by *Aspergillus terreus* strain, C-520. Based on incorporation experiments of polyketide precursors, Birch and co-workers suggested that the biosynthesis of terrein (**39**) involves ring contraction of the six-membered ring of a polyketide intermediate (Scheme 1.1).[14]



Scheme 1.1: Proposed biosynthesis of terrein (**39**)

Staunton and co-workers confirmed this hypothesis by incorporation experiments with the aromatic precursor 3,4-dihydro-6,8-dihydroxy-3-methylisocoumarin (**41**) (Scheme 1.2).[15] The labelling pattern they proposed is shown in Scheme 1.2, where the intact acetate units are indicated by a heavy line. From this they concluded that C-5 and C-6 of terrain (**39**) are derived from C-8 and C-8a of intermediate (**41**) through a ring contraction.

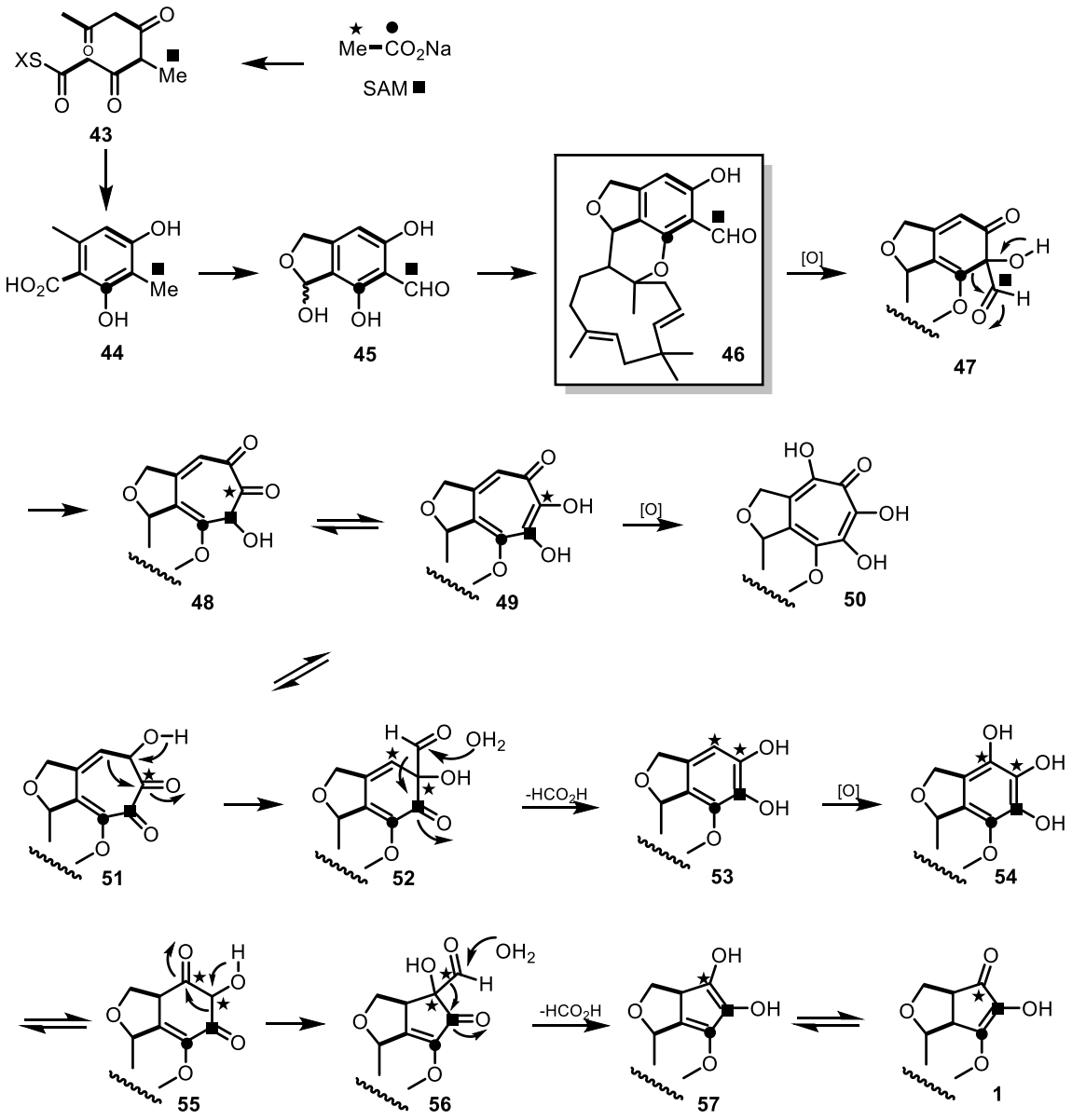


Scheme 1.2: Proposed biosynthesis of terrein

Certainly, it has been successfully proved that cyclopentanone or cyclopentane derivatives can be biosynthesized by the ring contraction of its corresponding aromatic precursor. Based on this fact and feeding experiments with labeled precursors, Simpson and co-workers suggested that the cyclopentenone moiety in xenovulene A (**1**) could be formed through a

[13] Kamata, S.; Sakai, H.; Hirota, A. *Agric. Biol. Chem.* **1983**, *47*, 2637-2638.
[14] Birch, A. J.; Cassera, A.; Jones, A. R. *J. Chem. Soc., Chem. Commun.* **1965**, 987-988.
[15] Holker, R. A.; Young, K. *J. Chem. Soc., Chem. Commun.* **1975**, 525-526.

unique pathway in which a phenolic precursor undergoes ring expansion to a tropolone followed by two successive ring contractions. Therefore, they proposed the first plausible biosynthetic pathway to xenovulene A as shown in Scheme 1.3.[16]

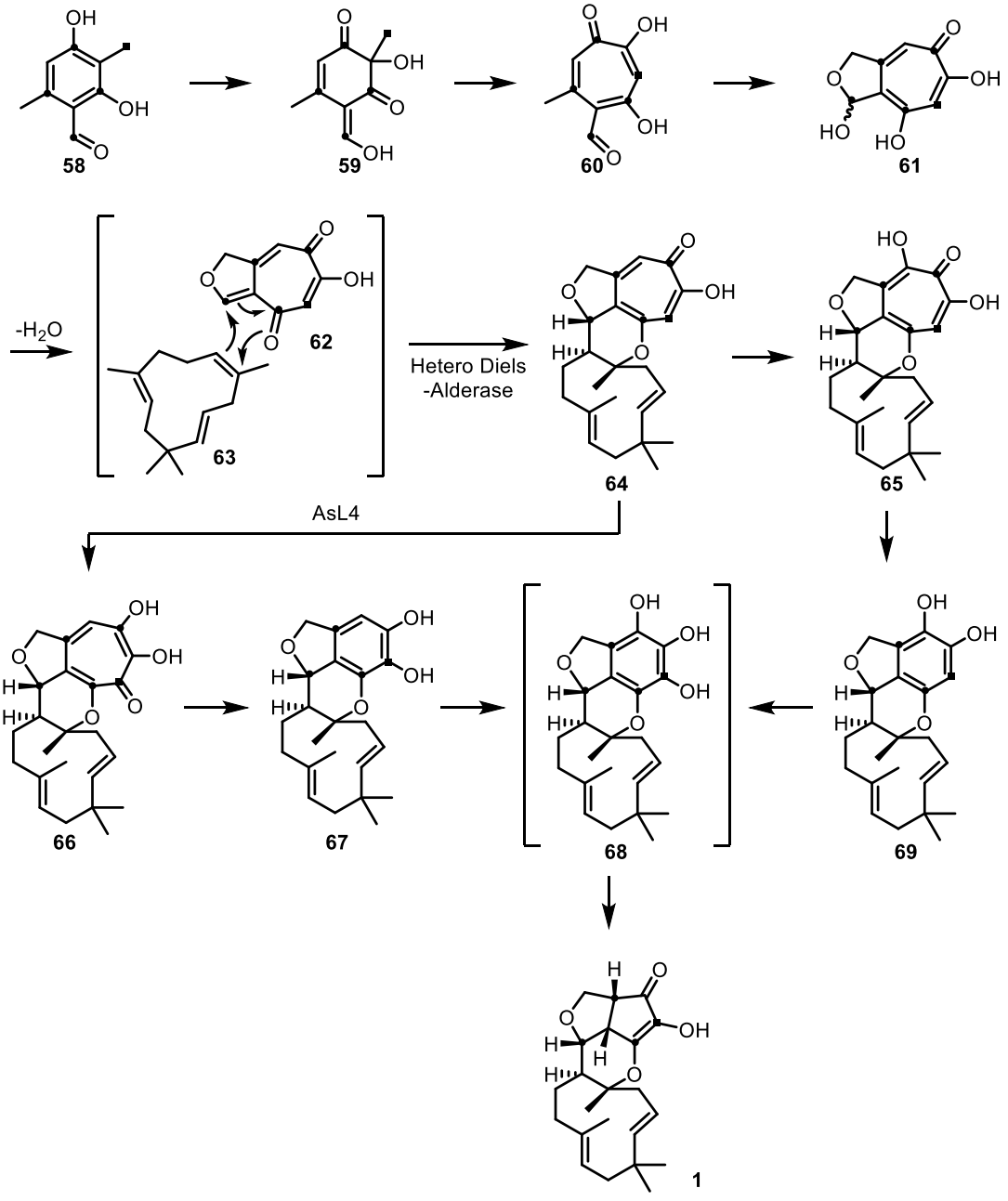


Scheme 1.3: Proposed biosynthetic pathway to xenovulene A by Simpson, et. al

It was proposed that the biosynthetic pathway to xenovulene A could occur via the polyketide-derived 3-methylorsellinic acid **44** which would be converted by standard biosynthetic modifications to lactol **45**. In turn, **45** would react with the 1,2 double bond of α-humulene, either by a carbocation mediated addition or an inverse hetero Diels-Alder reaction

[16] a) Raggatt, M. E.; Simpson, T. J.; Chicarelli-Robinson, M. I. *Chem. Commun*. **1997**, 2245-2246. b) Davison, J.; Fahad, A.; Cai, M.; Song, Z.; Yehia, S. Y.; Lazarus, C. M.; Bailey, A. M.; Simpson, T. J.; Cox, R. J. *PNAS* **2012**, *109*, 7642-7647. b) Liu, N.; Song, W.; Schienebeck, C. M.; Zhang, M.; Tang, W. *Tetrahedron* **2014**, *70*, 9281-9305.

to give the key tetracyclic intermediate **46**. The hydroxylation of **46** would allow ring expansion by an α-ketol rearrangement to give tropolone **48**. After further tautomeric adjustment, tropolone **49** would be converted to trioxygenated benzenoid intermediate **54** through ring contraction followed by decarboxylation. Further oxidation, α-ketol mediated ring contraction and decarboxylation would generate xenovulene A (**1**).



Scheme 1.4: Proposed biosynthetic pathway to xenovulene A by Cox, et. al

Recently, Cox and co-workers proposed an effective biosynthetic pathway to xenovulene A involving a hetero Diels-Alder reaction between α-humulene (**63**) and a tropolone

intermediate (**62**) which can be formed by the already well-known fungal tropolone pathway (Scheme 1.4). [17]

Based on their heterologous expression experiments, polyketide **58** can be synthesized through the expression of Aspks1 alone in the fungal host *A. oryzae* NSAR1. Compound **59** can be formed by an oxidative dearomatization of **58**. Then the tropolone intermediate **62** could be formed through a ring-expansion followed by a tautomerization of **59**. It in turn would react with the C1 and C2 double bond of α-humulene (**63**) via an inverse hetero Diels-Alder reaction to give the key tetracyclic intermediate **64**. The hydroxylation of **64** would give tropolones **65** and **66**, which could be converted to phenolic intermediates **69** and **67** via oxidative ring contraction, respectively. After further hydroxylation, phenolic intermediates **69** and **67** would be converted to the tetraoxygenated benzenoid intermediate **68**. Further oxidation, α-ketol mediated ring contraction and decarboxylation would generate xenovulene A (**1**).

1.1.5 α-Humulene

α-Humulene ((1*E*,4*E*,8*E*)-2,6,6,9-tetramethyl-1,4,8-cycloundecatriene or α-caryophyllene, **63**, Figure 1.8) is a naturally occurring monocyclic sesquiterpene ($C_{15}H_{24}$) consisting of three isoprene units containing three nonconjugated C=C double bonds, two of them being triply substituted and one being doubly substituted. It was first discovered in the essential oils of *Humulus lupulus* (Common Hop), from which its name is derived. [18]

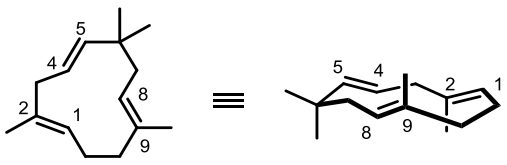


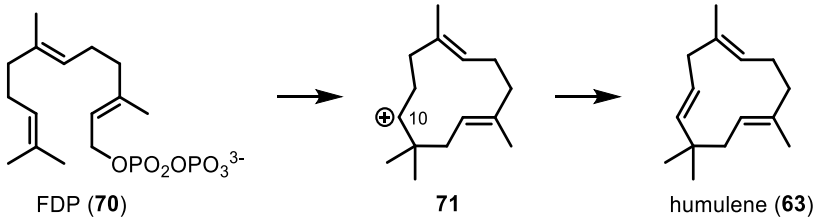
Figure 1.8: Structure of α-humulene (**63**)

1.1.5.1 Biosynthesis of α-Humulene

The α-humulene and the related sesquiterpenes are derived biologically from farnesol by anti-Markovnikov cyclization. The biosynthesis of α-humulene can be achieved in *Z. zerumbet* Smith from the sesquiterpene precursor farnesyl diphosphate (FDP, **70**) involving a ring-closing / deprotonation sequence (Scheme 1.5). The farnesyl diphosphate (FDP) was treated

[17] A Schor, R.; Schotte, C.; Wibberg, D.; Kalinowski, J.; Cox, R. J. *Nat. Commun.* **2018**, *9*, 1963-1969.
[18] AKatsiotis, S. T.; Langezaal, C. R.; Scheffe, J. J. C. *Planta Med*. **1989**, 55, 634-635.

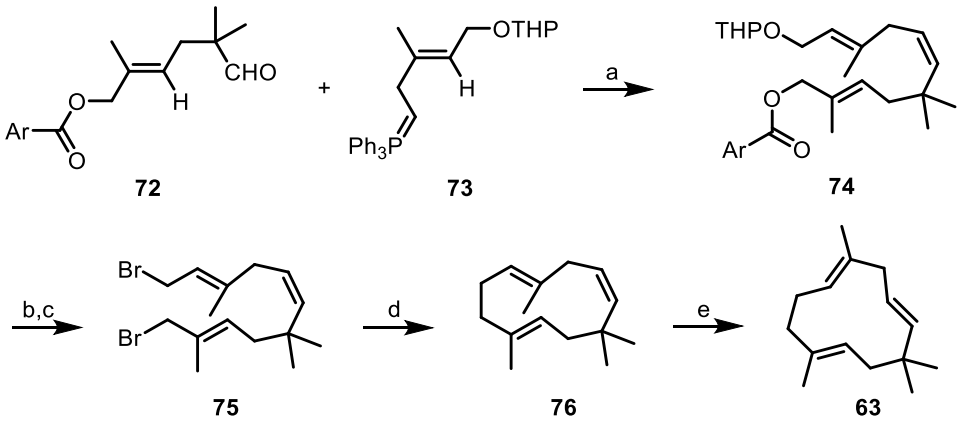
with α-humulene synthase (HUM) to give α-humulene (**63**) as the major product (95%) and β-caryophyllene as the minor product (5%).[19]



Scheme 1.5: Biosynthesis of α-humulene (**63**)

1.1.5.2 Synthesis of α-Humulene

Back in 1967, E. J. Corey and Edward K. W. Wat achieved the first total synthesis of humulene as show in Scheme 1.6 to 1.8.[20] Details on reaction conditions and yields of this work were not reported, but this work gave insights to the later synthesis of humulene and its derivatives. The key step is formation of the 11-membered ring by cyclization of a 1,11-dibromo-2,5,9-undecatriene derivative (**75**) using nickel carbonyl followed by the photochemical isomerization, as shown in Scheme 1.6. Compound **75** can be synthesized from **74**, which in turn can be prepared through the coupling of **72** and **73**.

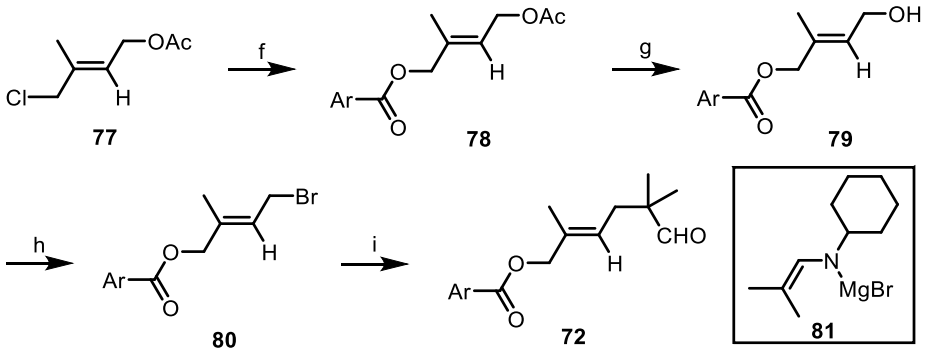


Scheme 1.6: The first synthesis of humulene (**63**). *Reagents: a) Wittig reaction; b) LAH and then acidic methanol; c) PBr_3; d) $Ni(CO)_4$; e) Ph_2S_2, cyclohexane, irradiation, 25°C, 2.5 h* .

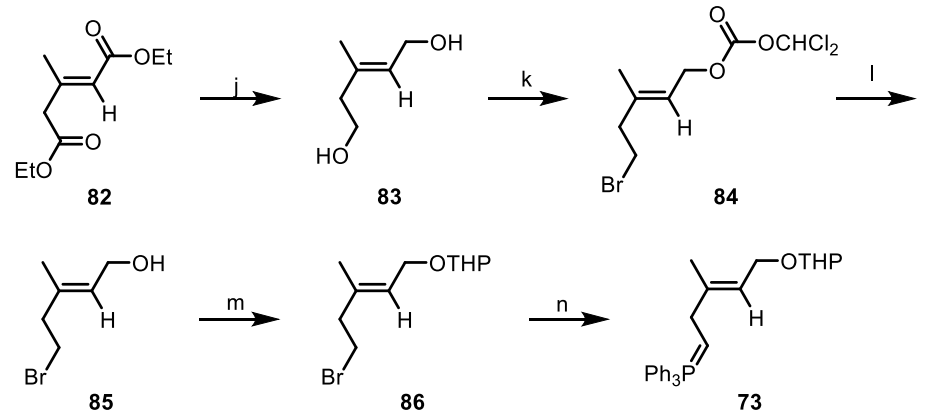
The first key intermediate, aldehyde (**72**), can be prepared from 1-chloro-2-methyl-4-acetoxy-2-butene (**77**) by a sequence involving (Scheme 1.7): (1) displacement of chlorine from **77** by trimethylbenzylammonium mesitoate to form **78**; (2) selective alkaline hydrolysis to **79**; (3) bromination of the primary alcohol of **79** with phosphorus tribromide to give **80**; (4) coupling

[19] Moss, G.P. International Union of Biochemistry and Molecular Biology Enzyme Nomenclature. **2011**.
[20] (a) Hamanaka, E.; Corey, E. J. *Org. Lett.* **1967**, *4*, 2758-2759.

of **80** and magnesium derivative **81**, which can be formed from N-(2-methylpropylidine) cyclohexylamine, to afford an imine which yielded **72** by hydrolysis with aqueous oxalic acid. The another key intermediate in the synthesis is the phosphonium ylide **73** which was obtained starting with dimethyl *trans*-3-methylglutaconate **82** by a sequence involving (Scheme 1.8) (1) reduction of **82** to the corresponding diol **83** using a mixture of lithium aluminum hydride and aluminum chloride (3:1); (2) conversion **83** to a dibromide intermediate, then selective displacement of the allylic bromine of it with trimethylbenzylammonium dichloroacetate to give **84**; (3) hydrolysis followed by protection of the alcohol with tetrahydropyran to form **86**; (4) reaction with triphenylphosphine to generate the phosphonium bromide **73**.



Scheme 1.7: Synthesis of intermediate **72**. *Reagents: f) trimethylbenzylammonium mesitoate, EtOH; g) alkaline hydrolysis; h) PBr_3; i) **81**, then aqueous oxalic acid.*

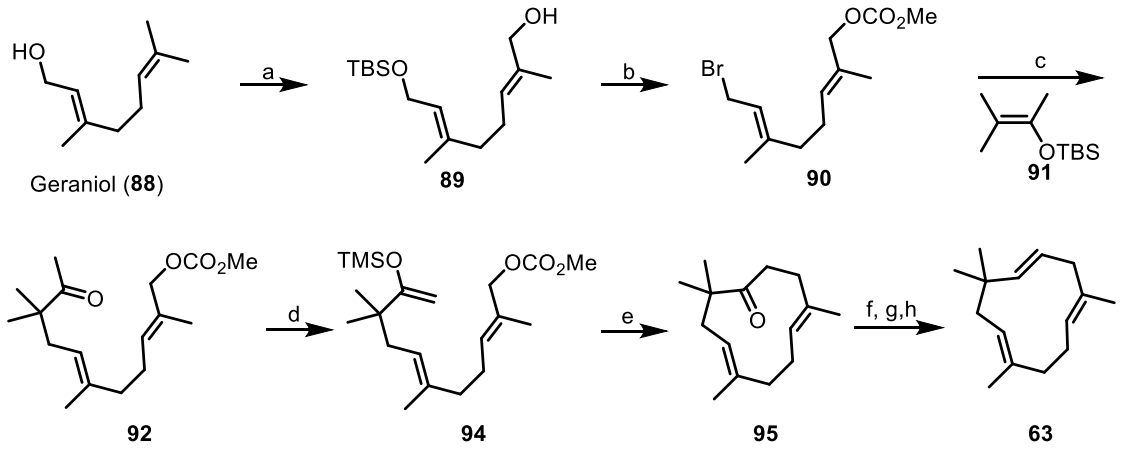


Scheme 1.8: Synthesis of intermediate **73**. *Reagents: j) $LiAlH_4/AlCl_3$, Et_2O (3/1); k) 1) Br_2; 2) trimethylbenzylammonium dichloroacetate; l) basic condition; m) dihydropyran; n) PPh_3.*

Since the first total synthesis of humulene by Corey group in 1967, several research groups have developed different approaches to humulene. They are simpler and more efficient, however, none of them are comparable with the second approach to humulene which was

completed by Corey group in 2002.[21] The synthesis of humulene (**63**) was carried out by an approach paralleling that used for araneosene, as shown in Scheme 1.9. The synthesis started with the protection of the hydroxyl group in geraniol (**88**) to TBS-ether, which was treated with SeO_2 followed by reduction with $NaBH_4$ to give allylic alcohol **89**. Esterification of **89** with methyl chloroformate followed by TBAF mediated TBS deprotection and bromination with PBr_3 generated bromide **90**.

Alkylation of the TBS enol ether (**91**) with bromide **90** afforded the keto carbonate **92** in 92% yield. In turn, **92** could be converted quantitatively into the corresponding TMS enol ether **94**. palladium-mediated cyclization of **94** directly generated the required cycloundecadienone **95** in 50% yield. Reduction of ketone **95** to the corresponding secondary alcohol by addition of isopropyl alcohol by portion to a well stirred suspension of sodium and **95** in toluene at 0 °C proceeded quantitatively. Reaction of this alcohol with methanesulfonyl chloride and triethylamine in CH_2Cl_2 at -35 °C for 30 min and at -20 °C for 30 min gave the mesylate, which was treated with silica gel in CH_2Cl_2 at 23 °C for 6 h to afford humulene (**63**) as a single isomer through the elimination of methanesulfonate.



Scheme 1.9: The simplest and most efficient synthesis of a-humulene (**63**). *Reagents and conditions: a) TBSCl, imidazole, DMF, rt, 1 h; then SeO_2, BuOOH, CH_2Cl_2, 0 ^oC to rt, 4 h; $NaBH_4$, EtOH, 0 ^oC to rt, 2 h. b) methyl chloroformate, pyridine, 0 ^oC to rt, 15 h; then TBAF, THF, 0 ^oC to rt, 1 h; PBr_3, Et_2O, 0 ^oC to rt, 1h; c) TAS-F, THF/DMF, -25 ^oC to 0 ^oC, 3 h, 92%; d) TMSOTf, i-PrNHEt, C_2H_3CN, 0 ^oC, 2 h, 99%; e) $Pd_2(dba)_3$, dppf, THF, 70 ^oC, 1 h, 50%; f) Na, i-PrOH, toluene, 0 ^oC, 12 h, 83%; g) MsCl, Et_3N, rt, 12h, 94%; h) SiO_2, CH_2Cl_2, rt, 6 h, 93%.*

[21] Hu, T.; Corey, E. J. *Org. Lett.* **2002**, *4*, 2441-2443.

1.2 Project aims

1.2.1 Total synthesis of xenovulene

Xenovulene A (**1**), structurally, comprises an unusual furocyclopentenone moiety fused to a humulene derived 11-membered ring and 5 contiguous stereocenters including a quaternary carbon atom. Biologically, it was found to be an inhibitor of benzodiazepine binding to the human γ-aminobutyric acid (GABA) receptor with an IC_{50}-value of 40 nM. Additionally, antidepressant effects with reduced addictive properties were encountered for **1**. This unusual molecular architecture combined with its significant biological activities has made it a highly attractive synthetic target. However, over the two decades since its first isolation, no synthetic approaches on this natural product have been reported.

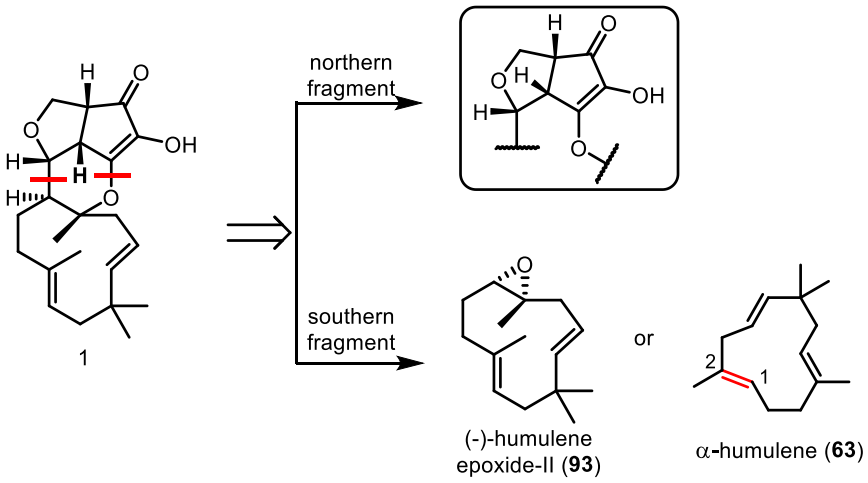
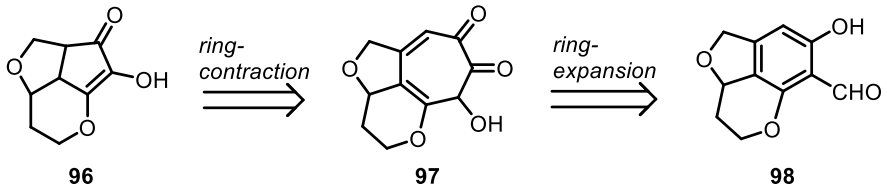


Figure 1.9: Strategies for the synthesis of xenovulene A (**1**)

Thus, interested in the unique and synthetically challenging structure of xenovulene A (**1**) and to further probe its bioactivity, the development of the total synthesis of **1** was envisaged. In addition, based on the fact that the 11-membered ring in **1** derived from α–humulene (**63**), two strategies for the total synthesis of xenovulene A were designed that either relying on a hetero Diels-Alder reaction of α,β-unsaturated ketone and α-Humulene (**63**) or utilize ring opening of (-)-humulene epoxide II (**93**) as the key step, respectively, as shown in Figure 1.9.

1.2.2 Model study on the cyclopentenone ring of xenovulene



96 **97** **98**

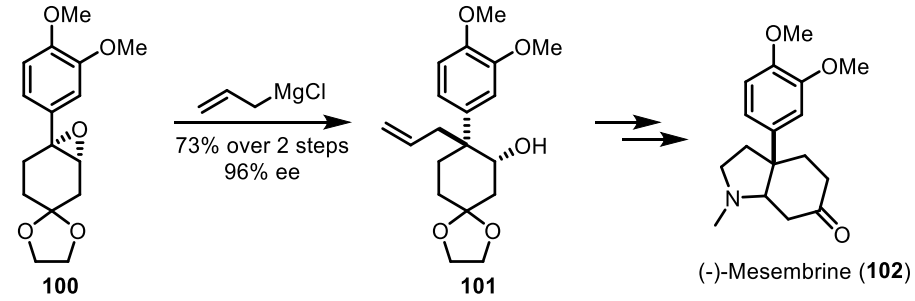
Figure 1.10: Synthesis of model compound **96**

Based on feeding experiments with labeled precursors, Simpson and coworkers proposed that the cyclopentanone moiety in xenovulene A (**1**) could be formed through a unique pathway in which a phenolic precursor undergoes ring expansion to a tropolone followed by two successive ring contractions. Therefore, the second project to be conducted in collaboration with the Cox research group was focused on the synthesis of a model compound (**98**) to mimic this unique biotransformation (Figure 1.10).

Chapter 2 Epoxide ring opening approach to xenovulene A

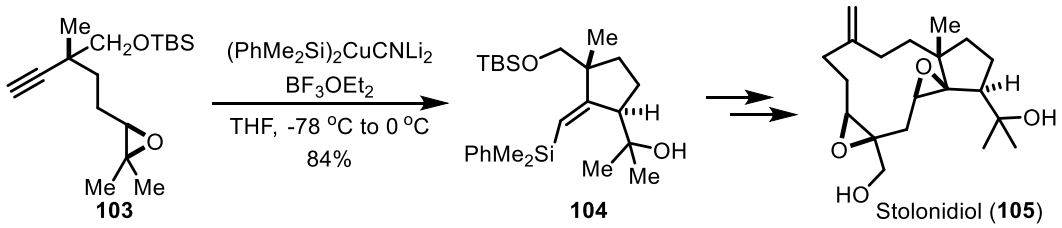
2.1 Introduction

The nucleophilic epoxide ring opening reaction is one of the most important transformations in synthetic chemistry. The formation of chiral alcohols by selective opening of epoxides and its application on total synthesis has been highly successful in recent years.[22] Among the organometallic reagents used in this reaction, the organocopper and Grignard reagents are known as the most popular and efficient to accomplish this transformation in a highly regio- and stereoselective manner. For example, in the total synthesis of (-)-mesembrine (**102**),[23] Taber and co-workers developed that epoxide **100** could be converted to alcohol **101** in 73% overall yield and 96% ee via epoxide ring opening with allylmagnesium chloride (Scheme 2.1).



Scheme 2.1: Synthesis of (−)-mesembrine (**102**)

In the synthetic studies toward stolonidiol (**105**),[24] Siegel and co-workers utilized epoxide **103** which was cyclized to vinylsilane **104** in 84% yield through a dilithium bis[dimethyl-(phenyl)silyl]-cyanocuprate catalyzed epoxide ring opening reaction (Scheme 2.2).

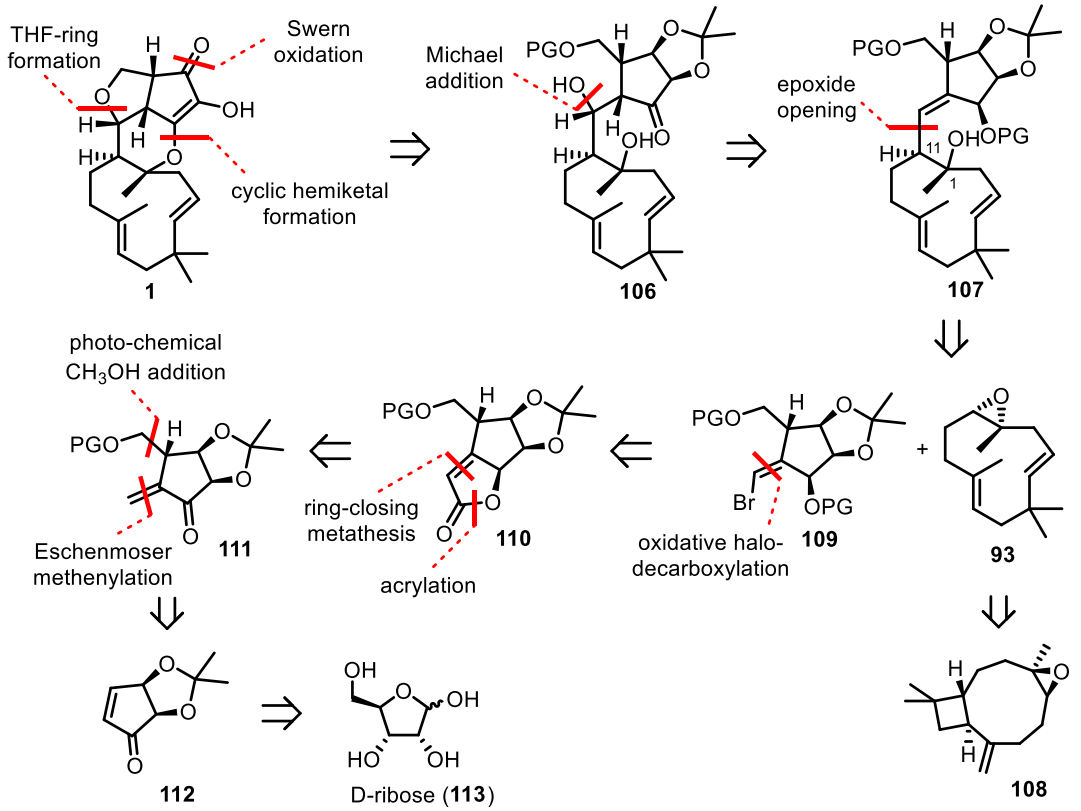


Scheme 2.2: Synthesis of stolonidiol (**105**)

[22] Zhu, Y.; Wang, Q.; Cornwall, R. G.; Shi, Y. *Chem. Rev.* **2014**, *114*, 8199-8256.
[23] Taber, D. F.; He, Y. *J. Org. Chem.* **2005**, *70*, 7711-7718.
[24] Barton, T.; Siegel, D. *Synthesis* **2012**, 44, 2770-2775.

2.2 Retrosynthetic analysis of xenovulene A

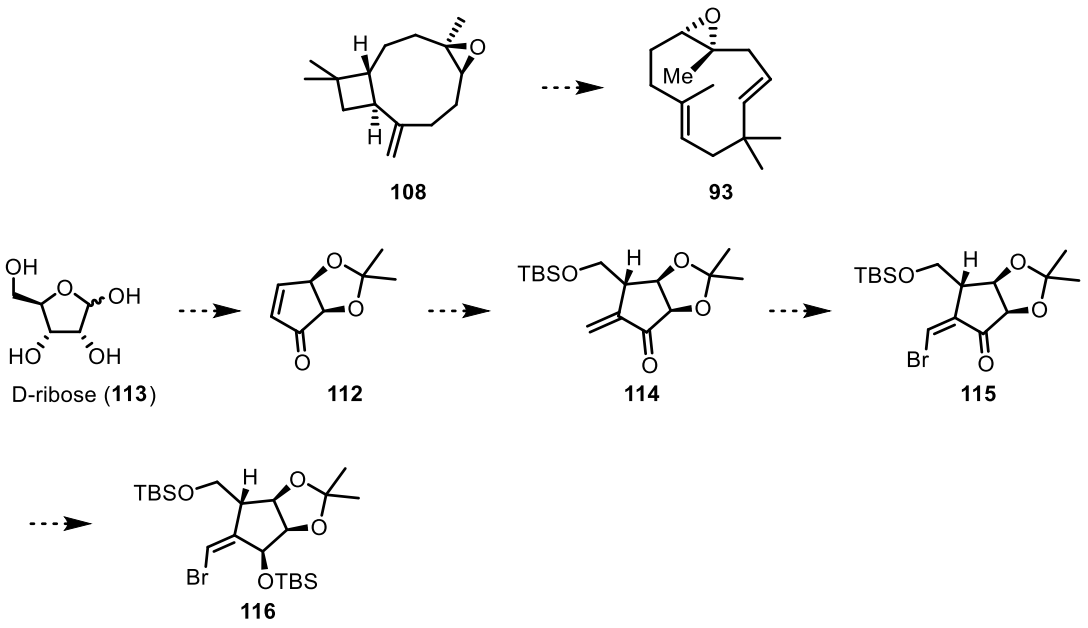
The first retrosynthetic analysis, shown in scheme 2.3, commenced with disconnecting the tetrahydrofuran ring and simplifying the cyclopentenone to diol leading to compound **106**. Compound **106** in turn could be synthesized by an oxidative sequence from enone **107**. Pivotal to this approach, it was expected that the advanced intermediate **107** with two contiguous stereogenic centers (C-1 and C-11) including a quaternary carbon could be established in a single step via a Grignard mediated epoxide ring opening between vinyl bromide **109** and (-)-humulene II epoxide (**93**). In turn the epoxide fragment **93** was envisioned to be constructed from the commercially available compound **108** through a transition metal-catalyzed retrocycloisomerization. Bromide **109** would be obtained from an acrylic acid or ester such as **110**, which could be constructed from **111** via an acrylation followed by a ring-closing metathesis. Next, the preparation of ketone **111** could be achieved by a short sequence of photochemical 1,4-addition and Eschenmoser methenylation of cyclopentenone **112**, which itself can be prepared from D-ribose (**113**).



Scheme 2.3: Retrosynthetic analysis towards xenovulene A

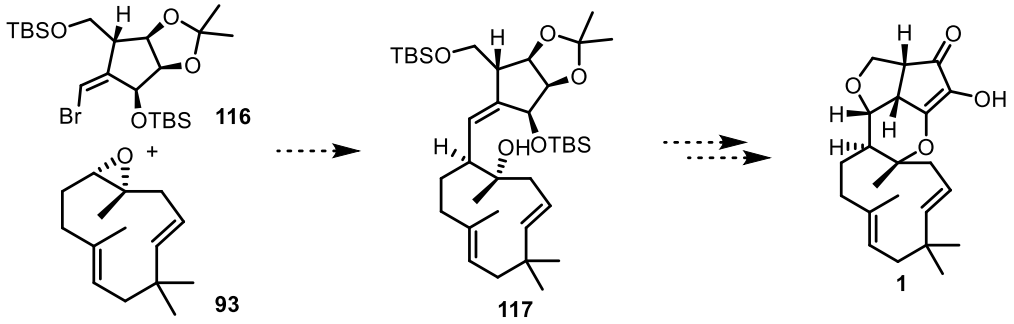
2.3 Project Outline

According to the retrosynthetic analysis the first goal was to synthesize two fragments: (-)-humulene II epoxide (**93**) and vinyl bromide (**116**) (Scheme 2.4). Next, both would be required to undergo the key epoxide ring opening reaction to form the full carbon skeleton of xenovulene A.



Scheme 2.4: Synthetic strategy for the fragments **93** and **116**

The second goal was the key step of this approach which involves the formation of Grignard reagent from bromide **116** followed by Grignard mediated ring opening of (-)-humulene II epoxide (**93**) to generate the advanced intermediate (**117**), which could be converted to the target xenovulene A (**1**) via few transformations (Scheme 2.5).

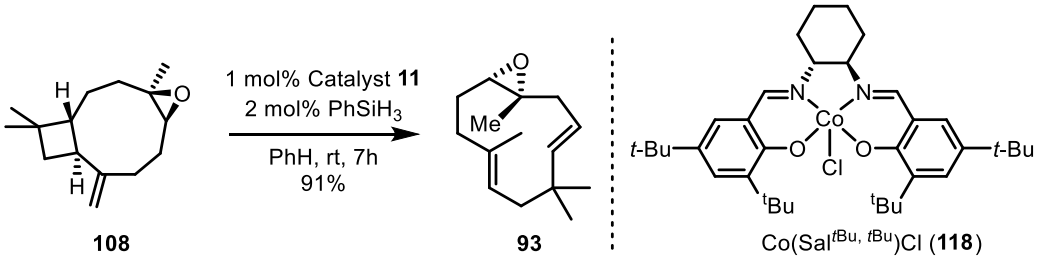


Scheme 2.5: Synthetic strategy for the epoxide opening

2.4 Results and Discussion

2.4.1 Preparation of epoxide **93**

The epoxide **93** was prepared form (-)-caryophyllene oxide **108** (Scheme 2.6). According to the Mukaiyama-type radical hydrofunctionalization and the methodology developed by Shenvi, et al., treatment of (-)-caryophyllene oxide **108** with a catalytic amount of Co(Sal$^{t\text{Bu, }t\text{Bu}}$)Cl (**118**) and phenylsilane yielded (-)-humulene II epoxide (**93**) in 91% yield.[25]



Scheme 2.6: Preparation of (-)-humulene II epoxide (**93**)

The proposed mechanism is shown in Figure 2.1. The reaction could be initiated with catalytic amounts of silane to generate the metal hydride (L_2CoH), which would then undergo hydrogen atom transfer (HAT) to alkene **108** to form **119**. Retrocycloisomerization of **119** followed by the inverse hydrogen atom transfer to **99** would generate **93**.[26]

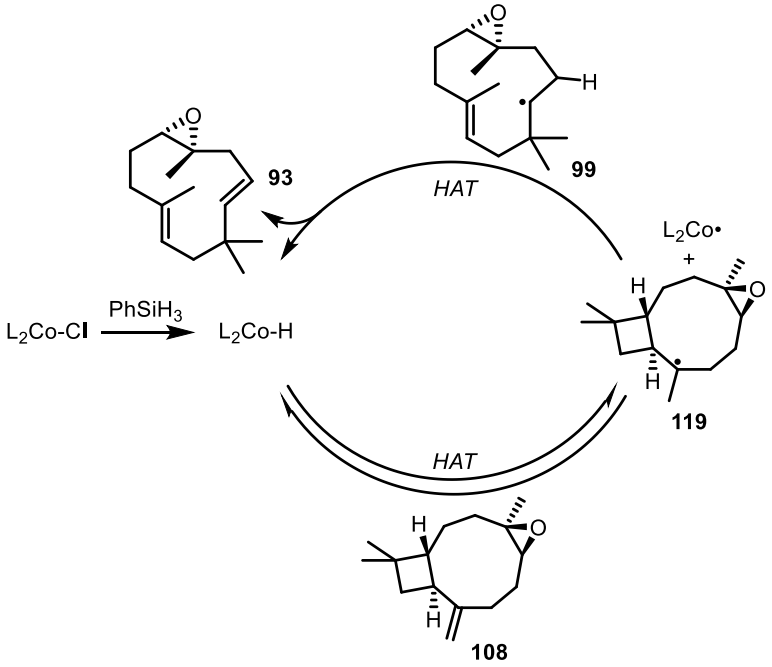
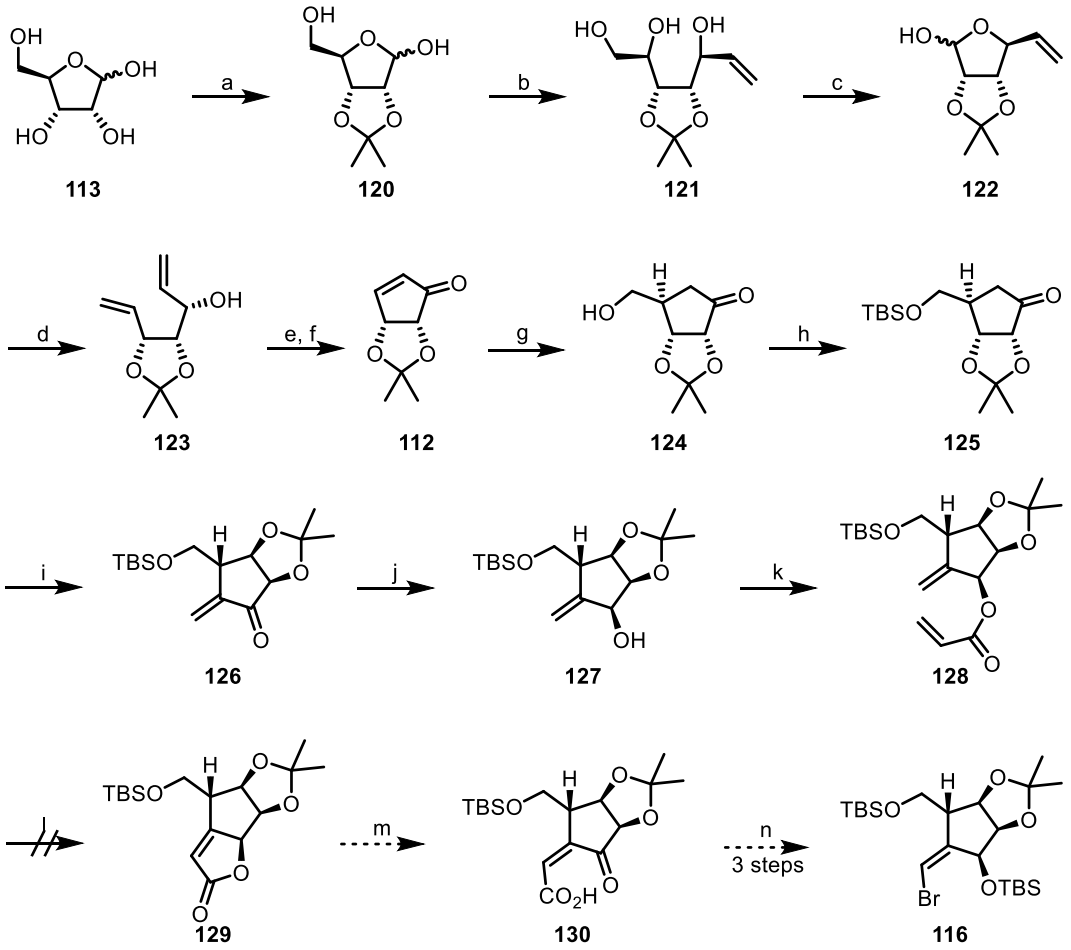


Figure 2.1: Hypothetical catalytic cycle

[25] Crossley, S. W. M.; Barabe, F.; Shenvi, R. A. *J. Am. Chem. Soc.* **2014**, *136*, 16788-16791.
[26] Crossley, S. W. M.; Obradors, C.; Martinez, R. M.; Shenvi, R. A. *Chem. Rev.* **2016**, *116*, 8912-9000.

2.4.2 Preparation of vinyl bromide **116**

The synthetic approach to vinyl bromide **116** started from D-ribose **113** and which is shown in Scheme 2.7.



Scheme 2.7: Preparation of vinyl bromide **116**. *Reagents and conditions: a) acetone, H_2SO_4, rt, 2.5 h, 93%; b) vinyl magnesium bromide, THF, -78 °C to 0 °C, 3 h, 81%; c) $NaIO_4$, CH_2Cl_2, H_2O, 0 °C to rt, 40 min, 85%; d) NaH, DMSO, $MePPh_3Br$, THF, 0 °C to reflux, 24 h, 88%; e) Grubbs I catalyst, $CHCl_3$, rt, 24 h; f) MnO_2, CH_2Cl_2, rt, 24 h, 60% for two steps; g) CH_3OH, Ph_2CO, hν, 1 h, 65%; h) TBSCl, DMAP, imidazole, DMF, rt, 24 h, 90%; i) LDA, C_3H_8NI, CH_3I, THF, -78 °C to rt, o/n, 65%; j) $NaBH_4$, $CeCl_3$, CH_3OH, -78 °C to 0 °C, 4 h, 80%; k) Et_3N, acryloyl chloride, CH_2Cl_2, -10 °C, 2h, 75%; l) see Table 2.1; m) NaOH.*

The synthesis of **116** commenced with the protection of 2,3-diol in D-ribose (**113**) to acetonide which was treated with vinylmagnesium bromide to give triol **121** in 80% yield. Oxidative cleavage of triol **121** with sodium metaperiodate followed by a Wittig reaction with methyltriphenylphosphonium bromide gave the diene **123** in good yield and with high

selectivity.[27] Ring-closing metathesis of diene **123** using Grubbs catalyst (first generation) gave the allylic alcohol, which was oxidized with MnO_2 to afford cyclopentenone **112** in 60% yield over two steps.[28] Next, photochemical activation of methanol and subsequent 1,4-addition to cyclopentenone **112** furnished alcohol **124** in 65% yield.[29] After protection as TBS-ether (90% yield), the resulting ketone **125** was treated with lithium diisopropylamide (LDA) and Eschenmoser's salt ($Me_2N{=}CH_2I$), followed by iodomethane to afford enone **126** in 70% yield after Hofmann elimination.[30] Reduction of **126** with $NaBH_4$ generated the alcohol **127** as a single isomer, which underwent an esterification with acryloyl chloride provided the desired ester **128** in 70% yield over two steps. Unfortunately, attempted ring-closing metathesis of ester **128** to lactone **129** failed (see Table 2.1), presumably due to the presence of bulky TBS group and the high ring strain of the 5,5,5-tricyclic system in **129**.

The attempted ring-closing metathesis of **128** is summarized in the Table 2.1. Initially, the reaction was carried out using Grubbs catalyst first generation (**131**) as catalyst in different solvents (e.g., CH_2Cl_2, $CHCl_3$). Unfortunately, these efforts either led to no reaction or the formation of an inseparable mixture (entries 1-2). Next, Grubbs catalyst (second generation) (**132**) and Hoveyda-Grubbs catalyst (second generation) (**133**) were also examined; both led to either no reaction or decomposition (entries 3-5).

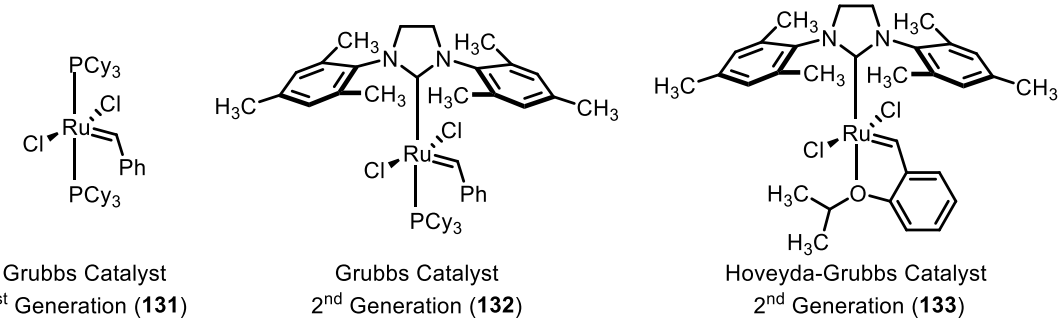


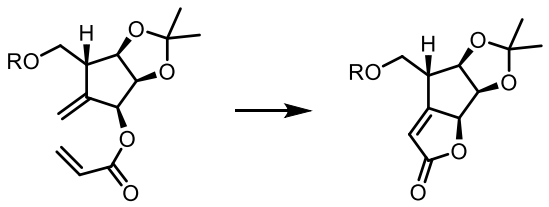
Figure 2.2: Structure of Grubbs catalysts tested in the ring-closing metathesis of **128**

In essence, attempted ring-closing metathesis of ester **128a** to lactone **129** failed under various conditions with different Grubbs catalysts. It was also postulated that the reason might be the presence of the bulky TBS group. Therefore, the ring-closing metathesis of **128b** was

[27] a) Parry, R. J.; Burns, M. R.; Skae, P. N.; Hoyt, J. C.; Pal, B. *Bioorg. Med. Chem.* **1996**, *4*, 1077-1088. b) Moon, H. R.; Choi, W. J.; Kim, H. O.; Jeong, L. S. *Tetrahedron: Asymm.* **2002**, *13*, 1189-1193.
[28] (10) Choi. W. J.; Park, J. G.; Yoo, S. J.; Kim, H. O.; Moon, H. R.; Chun, M. W.; Jung, Y. H.; Jeong, L. S. *J. Org. Chem.* **2001**, *66*, 6490-6494.
[29] Parry, R. J.; Burns, M. R.; Skae, P. N.; Hoyt, J. C.; Pal, B. *Bioorg. Med. Chem.* **1996**, *4*, 1077-1088.
[30] (11) a) Wang, P.; Agrofoglio, L. A.; Newton, M. G.; Chu, CK. *J. Org. Chem.* **1999**, *64*, 4173-4178. b) Jin, Y. H.; Liu, P.; Wang, J.; Baker, R.; Huggins, J.; Chu, C. K. *J. Org. Chem.* **2003**, *68*, 9012-9018. c) Gadthula, S.; Rawal, R. K.; Sharon, A.; Wu, D.; Korba, B.; Chu, C. K. *Bioorg. Med. Chem. Lett*. **2011**, *21*, 3982-3985.

investigated with a variety of Grubbs catalysts (entries 6-8). To be dismayed, no desired product was obtained.[31]

Table 2.1: Attempted ring-closing metathesis of **128**



128a R = TBS
128b R = H

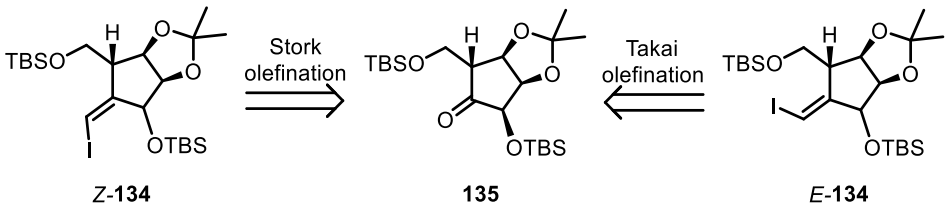
129a R = TBS
129b R = H

entry	reagent	condition	result
1	**128a**, cat. (**131**)	CH_2Cl_2, rt, 24h	no reaction
2	**128a**, cat. (**131**)	$CHCl_3$, 60 ^oC, 24h	complex mixture
3	**128a**, cat. (**132**)	DCE, rt, 24h	no reaction
4	**128a**, cat. (**132**)	DCE, 85 ^oC, 24h	decomposition
5	**128a**, cat. (**133**)	DCE, 85 ^oC, 24h	decomposition
6	**128a**, cat. (**131**)	DCE, 85 ^oC, 24h	no reaction
7	**128b**, cat. (**132**)	DCE, 85 ^oC, 24h	decomposition
8	**128b**, cat. (**133**)	DCE, 85 ^oC, 24h	decomposition

2.4.3 Preparation of vinyl iodide **134**

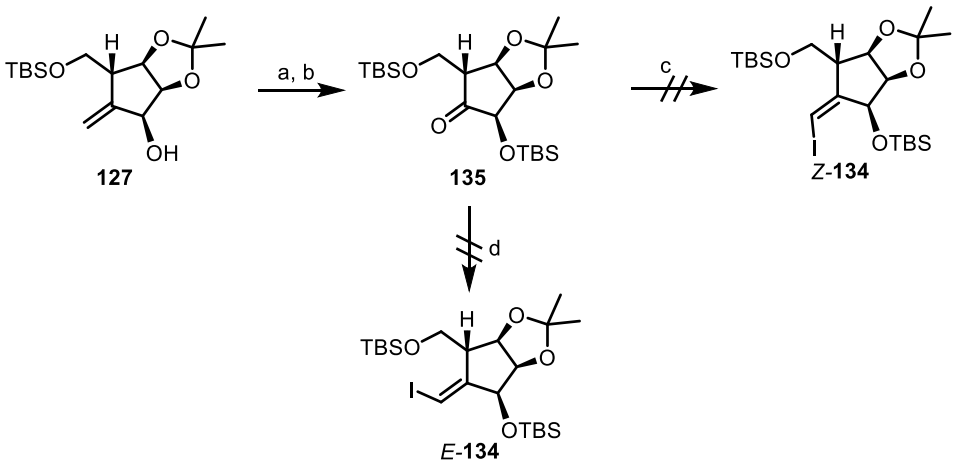
Due to the difficulties in obtaining vinyl bromide **116**, vinyl iodide **134** was chosen as a vinyl halide surrogate. It was postulated that vinyl iodide **134** could be generated from ketone **135** through Takai or Stork olefinations (Scheme 2.8).

[31] a) Bürki, C.; Bonjoch, J.; Bradshaw, B.; Villa, G.; Renaud, P. *Chem. Eur. J.* **2015**, *21*, 395-341. b) Vougioukalakis G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746-1787.



Scheme 2.8: Retrosynthetic analysis of **134** from **135**

Attempted preparation of vinyl iodide **134** started from alcohol **127** (Scheme 2.9). The TBS protection of **134** gave TBS-ether **136** (90%), which was treated with OsO_4 and NMO in a 3:1 mixture of THF and water overnight, followed by an aqueous $NaIO_4$ solution to afford ketone **135** in a one-pot operation in 65% yield.[32] Unfortunately, the subsequent Stork olefination of ketone **135** with Stork's iodophosphorane ($[Ph_3PCH_2I]^+I^-$, KHMDS) did not occur under various conditions.[33] It was postulated that the instability of the *Z*-isomer of **134** or the bulky TBS group might prevent the formation of *Z*-**134**. Then the Takai olefination of ketone **25** with $CH_3I/CrCl_2$ to *E*-**134** was investigated.[34] However, no desired product was obtained.



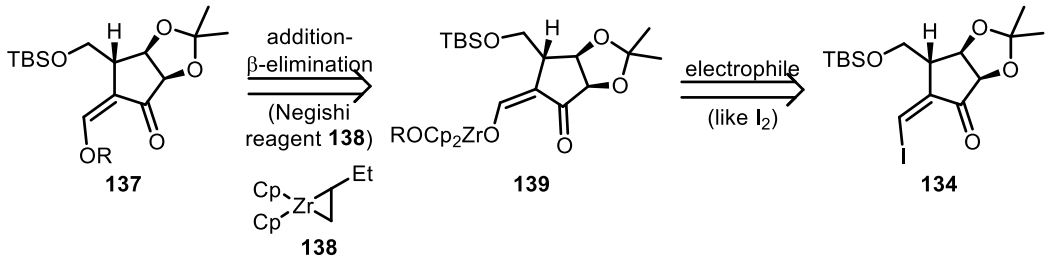
Scheme 2.9: Attempted preparation of vinyl iodide **134**. *Reagents and conditions: a) TBSCl, DMAP, imidazole, DMF, rt, 24 h, 90%; b) OsO_4, NMO; then $NaIO_4$, H_2O, rt, o/n, 65% c) KHMDS,* $[Ph_3PCH_2I]^+I$, *-30 to -78 °C to rt, 5 h; d) CHI_3, $CrCl_2$, THF, 0 °C to rt, 4 h.*

2.4.4 Modified preparation of vinyl iodide **134**

Because the transformation of ketone **135** to vinyl iodide **134** failed, it was expected to synthesize **134** from enolate **137**.

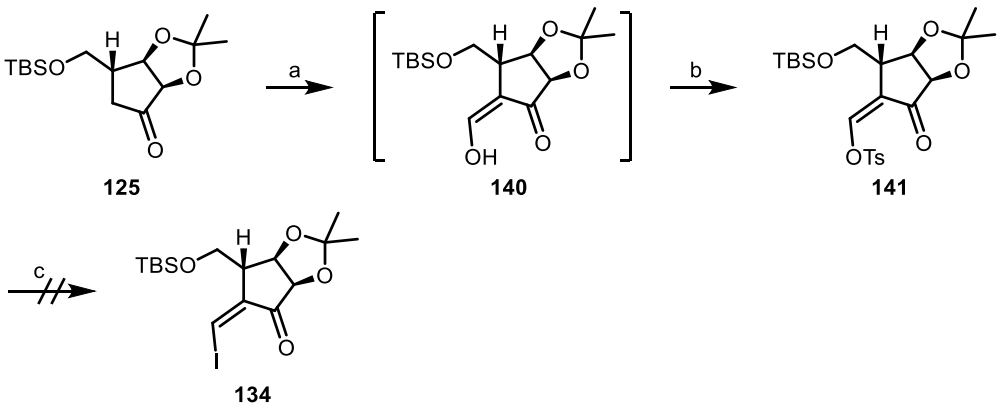
[32] Jana, N.; Das, D.; Nanda, S. *Tetrahedron*, **2013**, *69*, 2900-2908.
[33] a) Stork, G.; Zhang, K. *Tetrahedron Lett.*, **1989**, *30*, 2173-2174. b) Kim, H.; Choi, W. C.; Jung, J.; Kim, S.; Kim, D. *J. Am. Chem. Soc.*, **2003**, *125*, 10238–10240.
[34] a) Takai, K.; Nitta, N.; Utimoto, K. *J. Am. Chem. Soc.*, **1986**, *108*, 7408-7410. b) Smith, A. B.; Dong, S. *Org. Lett.*, **2009**, *11*, 1099-1102.

The synthesis of **134** was planned to start with a short sequence of addition-β-elimination of vinyl ether **137** with Negishi reagent **138** followed by trapping with iodine (Scheme 2.10).



Scheme 2.10: Modified retrosynthetic analysis of **134**

The second attempted preparation of vinyl iodide **134** started from ketone **125** (Scheme 2.11). Ketone **134** was treated with sodium hydride followed by ethyl formate to yield enol **140**, which was directly treated with *p*-toluenesulfonyl chloride to afford vinyl 4-methylbenzenesulfomate **141** in 36% yield over two steps.[35] Then the transformation of **141** to vinyl iodide **134** was investigated under a variety of conditions. To be dismayed, no desired product was obtained.[36] The reason might be the presence of the carbonyl group in **141**, both with respect to chemical stability and electronic properties. Thus, protection of the carbonyl group of **141** was investigated, however, no desired product was obtained.



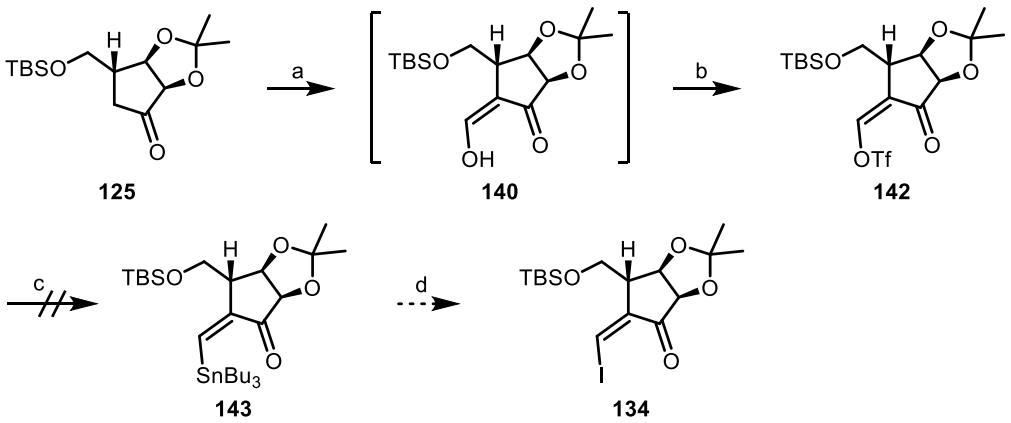
Scheme 2.11: Attempted preparation of vinyl iodide **134**. *Reagents and conditions: a) NaH, HCO_2Et, Et_2O, 0 °C to rt, o/n; b) p-TsCl, NMI, Et_3N, $PhCH_3$, rt, o/n, 36% for two steps; c) bis(cyclopentadienyl)zirconium dichloride, THF, -78 °C to rt; then I_2, -78 °C to rt.*

[35] a) Fischer, D. S.; Allan, G. M.; Bubert, C.; Vicker, N.; Smith, A.; Tutill, H. J.; Purohit, A.; Wood, L.; Packham, G.; Mahon, M. F.; Reed, M. J.; Potter, B. V. L. *J. Med. Chem.* **2005**, *48*, 5749-5770. b) Nakatsuji, H.; Nishikado, H.; Ueno, K.; Tanabe, Y. *Org. Lett.* **2009**, *11*, 4258-4261.

[36] a) Piers, E.; Grierson, J. R.; Lau, C. K.; Nagakura, I. *Can. J. Chem.* **1982**, *60*, 210-223. b) Liard, A.; Marek, A. *J. Org. Chem.* **2000**, *65*, 7218-7220.

2.4.5 Second modified preparation of vinyl iodide **134**

It has been well known that treating vinyl stannane with iodine or NIS could give vinyl iodide with high *Z*-selectivity and good yield. So it was expected that vinyl iodide **134** would be synthesized through a substitution of vinyl stannane **143** with iodine or NIS. The attempted preparation of **134** started from ketone **125** as shown in Scheme 2.12.



Scheme 2.12: Attempted preparation of vinyl iodide **134**. *Reagents and conditions: a) NaH,HCO_2Et, Et_2O, 0°C to rt, o/n; b) Tf_2O, DIPA, CH_2Cl_2, -78 °C, 1 h, 43% for two steps; c) LDA, THF; then n-Bu_3SnH, CuCN, -78 °C to -20 °C; d) iodine or NIS.*

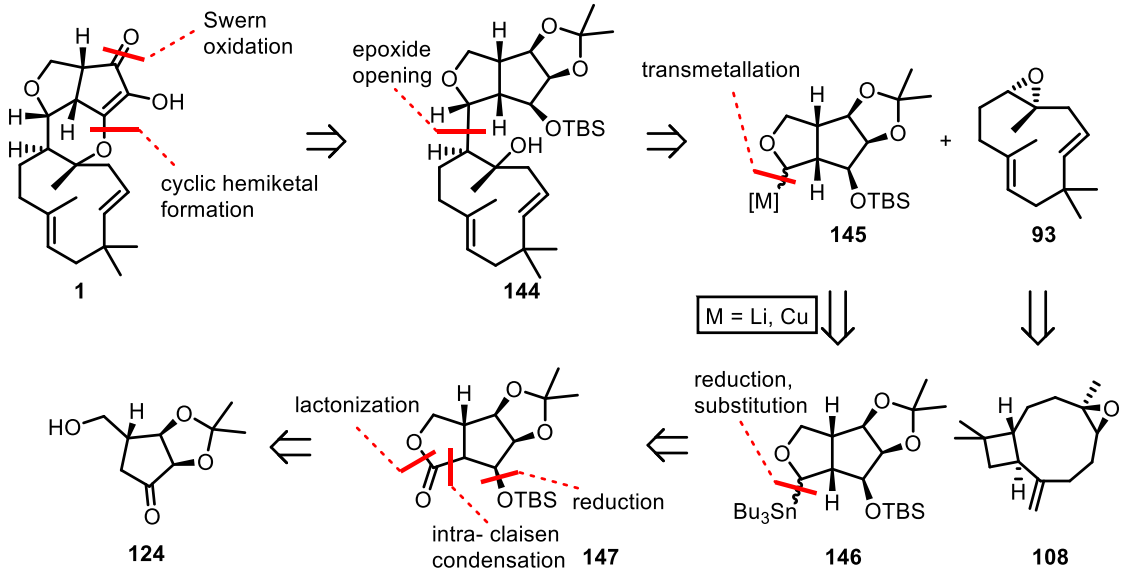
Enolization of **125** with ethyl formate gave enol **140**, which was treated with triflic anhydride to afford triflate **142** in 43% yield over two steps.[37] Then, the replacement of triflate **142** with a higher-order stannylcuprate reagent (n-$Bu_3Sn)_2CuCNLi_2$ was investigated.[38] Unfortunately, no desired product was obtained. In addition, the $Pd(PPh_3)_4$ catalyzed coupling of triflate **142** with hexabutylditin [(n-$Bu_3Sn)_2$] was also tested,[39] which led to an inseparable complex mixture.

Despite several attempts to synthesize vinyl bromide (**116**) and iodide (**134**) from D-ribose (**v**), the desired vinyl halide fragments could not be obtained. Therefore, the first strategy which involves Grignard mediated epoxide ring opening of humulene epoxide (**93**) was abandoned.

[37] Chassaing, S.; Speckin, S.; Weibel, J. M.; Pale, P. *Tetrahedron*, **2012**, *68*, 7245-7273.
[38] Williams, D. R.; Gladen, P. T.; Pinchman, J. R. *J. Org. Chem.*, **2015**, *80*, 5474–5493.
[39] Clark, J. S.; Northall, J. M.; Marlin, F.; Nay, B.; Wilson, C.; Blake, A. J.; Waring, M. J. *Org. Biomol. Chem.*, **2008**, *6*, 4012-4025.

2.5 Modified epoxide opening approach to xenovulene A

The modified retrosynthetic analysis of xenovulene A began with an oxidative adjustment of compound **144** (Scheme 2.13). As the key step, it was expected that the advanced intermediate **144** could be established via an epoxide ring opening between organocopper or organolithium reagent **145** and (-)-humulene II epoxide (**93**). The epoxide **93** is available from (-)-caryophyllene **108** through a transition metal-catalyzed retrocycloisomerization as described in the previous chapter. Organocopper or organolithium reagent **145** would be obtained via transmetallations of stannane **146**. In turn, stannane **146** could be synthesized from lactone **147** through reduction followed by substitution. Next, it was anticipated that lactone **147** could be generated through an intramolecular Claisen condensation of methyl ((3-oxocyclopentyl)methyl) carbonate, which could be synthesized from ketone **124**. Ketone **124** was successfully synthesized from D-ribose (**113**).

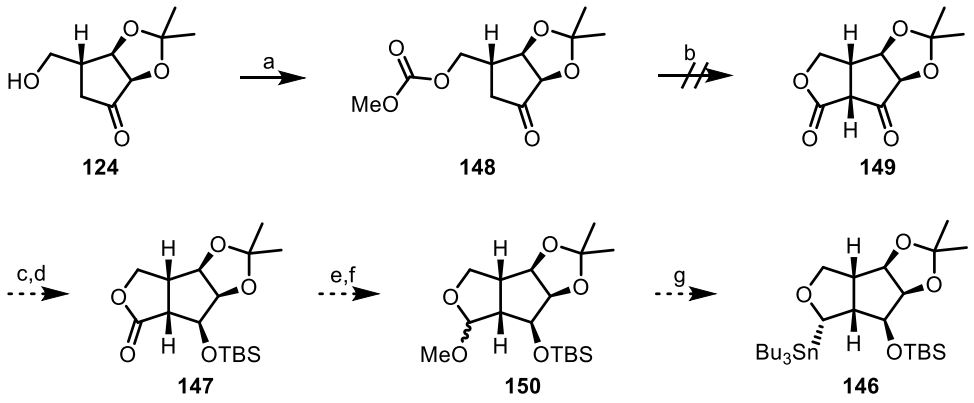


Scheme 2.13: Modified retrosynthetic analysis of xenovulene A

According to the previous strategy shown in Scheme 2.7, ketone **124** and epoxide **93** was successfully synthesized from commercially available D-ribose (**113**) and (−)-caryophyllene oxide (**108**), respectively. Therefore, this modified epoxide opening approach to xenovulene A (1) commenced with the synthesis of **146** from ketone **124**.

2.5.1 Preparation of stannane **146**

The synthesis of stannane **146** started from ketone **124** as shown in Scheme 2.14. Alcohol **124** was treated with methyl chloroformate to afford methyl carbonate **148** in 65% yield.[40] Then the intramolecular condensation of **148** to keto-lactone **149** was investigated.[41] However, this step did not succeed and the lactone-ring did not form. It was speculated that methyl carbonate of **148** might be unstable under the reaction conditions employed. Thus, the intramolecular condensation of ethyl carbonate **151** was investigated as shown in Scheme 2.15.

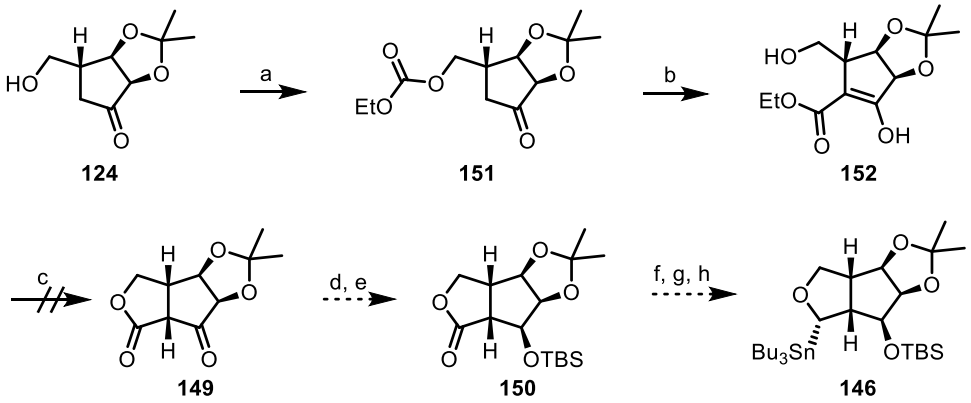


Scheme 2.14: Attempted preparation of stannane fragment **146**. *Reagents and conditions: a) $ClCO_2Me$, pyridine, rt, o/n, 65%; b) t-BuOK, toluene, rt, o/n; c) $NaBH_4$, $CeCl_3$, MeOH, -78 to 0 °C; d) TBSCl, DMAP, imidazole, DMF, rt; e) DIBAL-H, THF; f) H_2SO_4, methanol, rt; g) $LiSnBu_3$.*

2.5.2 Modified preparation of stannane **146**

The modified synthesis of stannane fragment **146** started with the esterification of **124** with ethyl chloroformate to afford ethyl carbonate **151** in 90% yield as shown in Scheme 2.15. As reported by Molander,[42] carbonate **151** was treated with t-BuOK to afford intermediate **152** in 72% yield; however, heating of compound **152** uner refluxing conditions in the presence of catalytic amount of *p*-TsOH did not give the desired keto-lactone product **149**, presumably due to the high ring strain of the 5,5,5-tricyclic system in **149**.

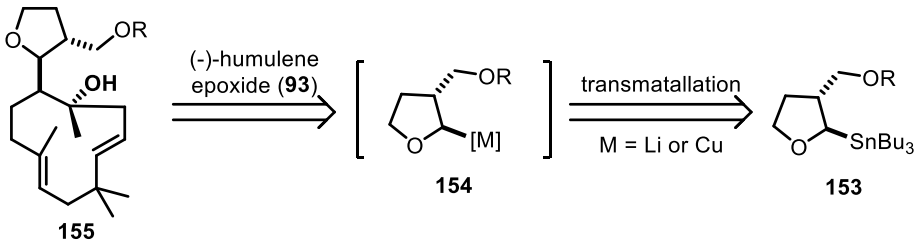
[40] a) Boeckman, Jr., R. K.; Naegely, R. C.; Arthur, S. D. *J. Org. Chem.* **1980**, *45*, 754-755. b) Goldsmith, D. J.; John, T. K.; Van Middlsworth, F. *Syn. Comm.* **1980**, *10*, 551-557.
[41] a) Tanimori, S.; Mitani, Y.; Chikai, M.; Ohira, S.; Nakayama, M. *Agric. Biol. Chem.* **1987**, *51*, 2861-2862. b) Honda, T.; Ishizone, H.; Mori, W.; Naito, K.; Suzuki, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3027-3032. c) Swarts, H. J.; Verstegen-Haaksma, A. A.; Jansen, B. J. M.; de Groot, A. *Tetrahedron Lett.* **1994**, *50*, 10083-10094.
[42] Molande, G. A.; Quirmbach, M. S.; Silva, L. F.; Spencer, K.; Balsells, J. *Org. Lett.* **2001**, *3*, 2257–2260.



Scheme 2.15: Attempted preparation of stannane fragment **146**. *Reagents and conditions: a) $ClCO_2Et$, pyridine, rt, o/n, 90%; b) t-BuOK, toluene, rt, o/n, 72%; c) p-TsOH, toluene, 110 °C; d) $NaBH_4$, $CeCl_3$, MeOH, -78 to 0 °C; e) TBSCl, DMAP, imidazole, DMF, rt; f) DIBAL-H, THF, -78 °C; g) H_2SO_4, methanol, rt; h) $LiSnBu_3$.*

2.5.3 Model study towards ring opening of (-)-humulene epoxide

In order to test the possibility and feasibility of ring opening of (-)-humulene epoxide (**93**) with organolithium or organocopper reagents, a model reaction was investigated (Scheme 2.16).



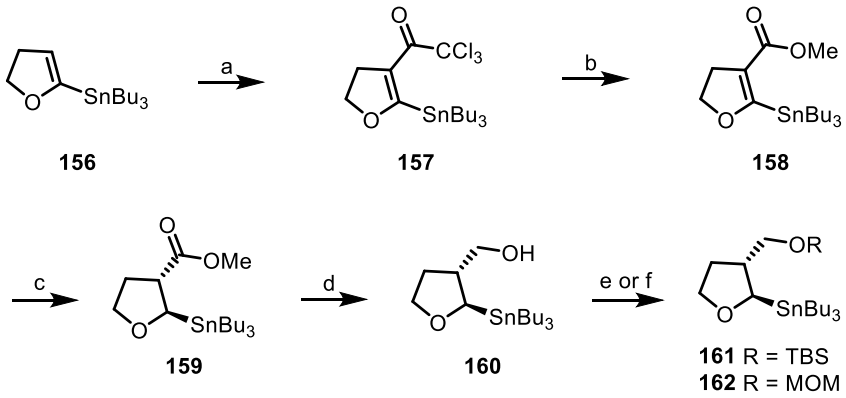
Scheme 2.16: Model studies toward epoxide opening of **93**.

2.5.3.1 Preparation of model stannanes **162** and **163**

The preparation of model stannanes **161** and **162** started from commercially available vinylstannane **156** as shown in Scheme 2.17. The reaction of **156** with trichloroacetyl chloride in the presence of *N*,*N*-diisopropylethylamine afforded the ester **157** in good yield, which upon exposure to methanolic triethylamine yielded the desired ester **158** in 76% yield.[43] Treating ester **158** with triethylsilane and trifluoroacetic acid resulted in the diastereoisomerically pure *trans*-disubstituted tetrahydrofuran **159** in 90% yield.[44] Reduction

[43] Booth, C.; Imanieh, H.; Quayle, P.; Lu, S. Y. *Tetrahedron Lett*. **1992**, *33*, 413-416.
[44] Quayle, P.; Zhao, Y. *Tetrahedron Lett*. **1994**, *35*, 4179-4182.

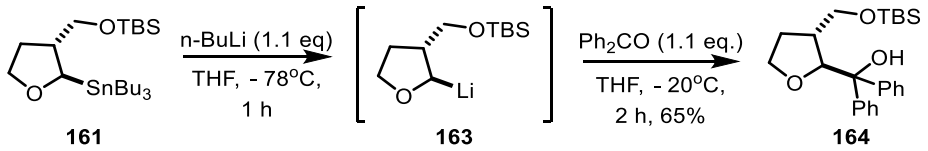
of **159** with DIBAL-H gave the alcohol **160**,[45] which was treated with TBSCl and MOMCl to afford model stannanes **161** and **162** in 90% and 97% yield, respectively.



Scheme 2.17: Attempted preparation of stannanes **161** and **162**. *Reagents and conditions: a) CCl_3COCl, DIPEA, CH_2Cl_2, 0 °C to rt, 12 h, 65%; b) Et_3N,CH_3OH, rt, 24 h, 76%; c) Et_3SiH, TFA, CH_2Cl_2, -78 °C to rt, 5 h, 90%; d) DIBAL-H, THF, 0 °C, 5 h, 81%; e) TBSCl, DMAP, imidazole, DMF, rt, o/n, 90%; f) MOMCl, DIPEA, CH_2Cl_2, 0 °C to rt, 16 h, 97%.*

2.5.3.2 (-)-Humulene epoxide opening with organolithium reagent

First of all, the transmetallation of stannane **161** with *n*-BuLi was investigated through the reaction with benzophenone (Scheme 2.18).[46] To be delighted, exposure of stannane **161** to *n*-BuLi in THF at -78 °C for an hour followed by adding the mixture of benzophenone in THF, and then allowing the reaction mixture to stir at -20°C for 2 h which furnished the desired alcohol **164** as a single product in 65% yield.



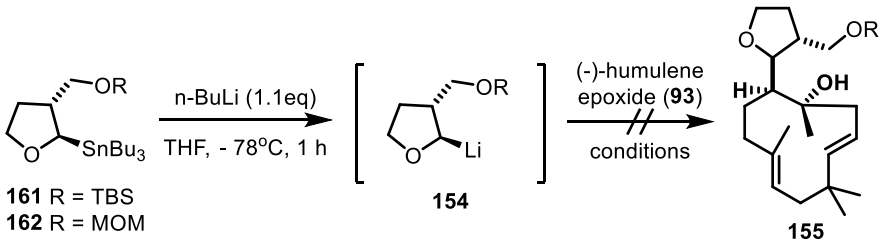
Scheme 2.18: Transmetallation of **161** with n-BuLi.

With the suitable transmetallation conditions of stannane **161** with *n*-BuLi to **163** in hand, various reaction conditions for the epoxide ring opening of **93** with organolithium reagents **154** were examined and some of them are shown in Table 2.2. Initially, the reaction was carried out at a lower reaction temperature. Unfortunately, even at 0 °C, no desired product

[45] Zhao, Y.; Beddoes, R. L.; Quayle, P. *Tetrahedron Lett.* **1994**, *35*, 4183-4186.
[46] Ryter, K.; Livinghouse, T. *J. Org. Chem.* **1997**, *62*, 4842-4844.

was observed (entries 1 and 3).[47] It was speculated that the bulky TBS group might affect the approach of the organolithium intermediate **163** to the epoxide ring of **93**. Therefore, stannane **162** was prepared and applied to this epoxide ring opening reaction. However, the outcome of this reaction was the same as TBS-ether stannane **161** with (-)-humulene epoxide (entry 2). When the reaction temperature was raised to room temperature, only decomposition was observed (entry 4). Ganem and co-workers reported that the mixture of organolithium and boron trifluoride etherate are reasonably stable together at low temperatures and react independently as potent nucleophile and strong Lewis acid, respectively.[48] Therefore, boron trifluoride etherate-assisted epoxide opening of (-)-humulene epoxide was also investigated, unfortunately, which resulted in an inseparable complex mixture (entries 5-6).

Table 2.2: Attempted epoxide ring opening of **93**



161 R = TBS
162 R = MOM

154

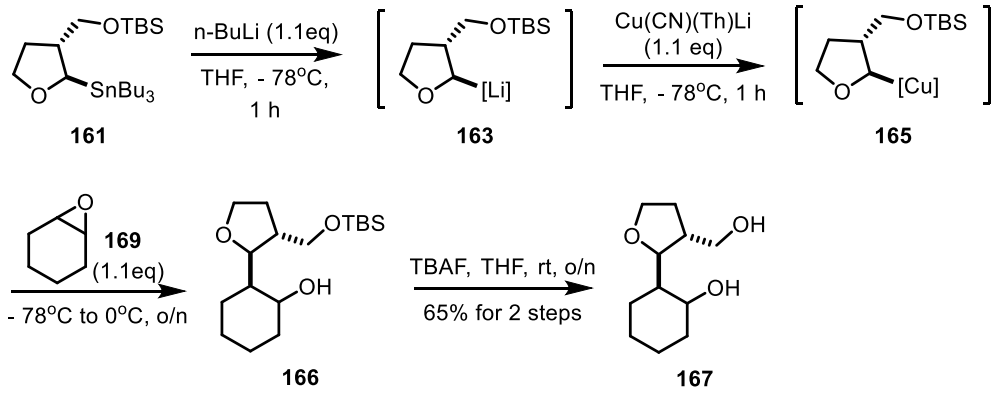
155

entry	reagent	conditions[a]	result[b]
1	**161**, THF	-78 °C, o/n; - 20 °C, 15h	no reaction
2	**162**, THF	-78 °C, o/n; - 20 °C, 15h	no reaction
3	**161**, THF	-78 °C, o/n; 0 °C, 15h	no reaction
4	**161**, THF	-78 °C, o/n; rt, 2h	decomposition
5	**161**, Et_2O, $BF_3{\cdot}Et_2O$ (1 eq.)	-78 °C, 2h	comlex mixture
6	**162**, Et_2O, $BF_3{\cdot}Et_2O$ (1 eq.)	-78 °C, 2h	complex mixture

[47] (a) Lipshutz, B. H.; Kozlowski, J.; Wilhelm, R. S. *J. Am. Chem. Soc.*, **1982**, *104*, 2305-2307. (b)Alexakis, A.; Jachiet, D.; Normant, J. F. *Tetrahedron*, **1986**, *42*, 5607-5619.
[48] (a) Eis, MJ.; Wrobel, JE.; Ganem, B. *J. Am. Chem. Soc.*, **1984**, *106*, 3693-3694. (b) Deng, X.; Mani, N. S. *Tetrahedron: Asymmetry*, **2005**, *16*, 661-664.

2.5.3.3 (-)-Humulene epoxide opening with organocopper reagent

Among the organometallic reagents used in the nucleophilic opening of epoxides, the organocopper reagents have been known to be the most efficient to accomplish this transformation. Therefore, the epoxide ring opening reaction with organocopper reagents were also investigated (Scheme 2.19).[49] Initially, as a model study, epoxide ring opening of cyclohexene oxide with copper reagent **165** was tested. To be delighted, treating stannane **161** with *n*-BuLi followed by Cu(CN)(Th)Li solution in THF, and then cyclohexene oxide afforded the desired product **166** which was then treated with TBAF at room temperature to yield diol **167** in 65% yield over all steps.[50]



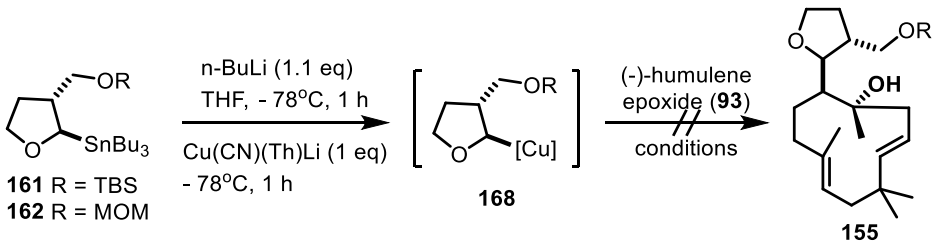
Scheme 2.19: epoxide ring opening of **169**

The epoxide ring opening of cyclohexene oxide (**169**) with organocopper reagent **165** succeeded, then various reaction conditions for the epoxide ring opening of (-)-humulene epoxide (**93**) were investigated and some presentative examples are shown in Table 2.3. Initially, the reaction was carried out under the same conditions as the cyclohexene oxide opening reaction conditions (Scheme 2.19), unfortunately, no reaction occurred (entry 1). It was speculated that the reason might be the bulky TBS group affecting the approach of intermediate **168** to epoxide ring of **93**. Therefore, stannane **162** was prepared and employed to this epoxide ring opening reaction. However, no desired product obtained (entry 2). Higher reaction temperature was not helpful for this transformation (entries 3 and 4). This reaction was also tested in diethyl ether as solvent which did not give any positive results either. Boron

[49] Alam, M.; Wise, C.; Baxter, C. A.; Cleator, E.; Walkinshaw, A. *Org. Process Res. Dev.*, **2012**, *16*, 435−441.
[50] (a) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737−799. (b) Rosowsky, A. Ethylene Oxides. In Chemistry of Heterocyclic Compounds; Weissberger, A., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 1964; Vol. 19, pp 1−523; (c) Rao, A. S.; Paknikar, S. K.; Kirtane, J. G. *Tetrahedron* **1983**, *39*, 2323−2367. (d) Smith, J. G. *Synthesis* **1984**, 629−656. (e) Bartok, M.; La´ ng, K. L. Oxiranes. In´ Chemistry of Heterocyclic Compounds; Hassner, A., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 1985; Vol. 42, Part 3, pp 1−196; (f) Pineschi, M. *Eur. J. Org. Chem.* **2006**, 4979−4988. (g) Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437−475. (h) Taylor, S. K. *Tetrahedron* **2000**, *56*, 1149−1163. (h) Zhao, Y.; Weix, D. Z. *J. Am. Chem. Soc.* **2014**, *136*, 48-51.

trifluoride etherate-assisted epoxide opening of (-)-humulene epoxide (**93**) with organocopper intermediate **168** was also investigated. Unfortunately, it resulted in an inseparable complex mixture (entries 7-8).[51]

Table 2.3: (-)-humulene epoxide opening with organocopper reagent

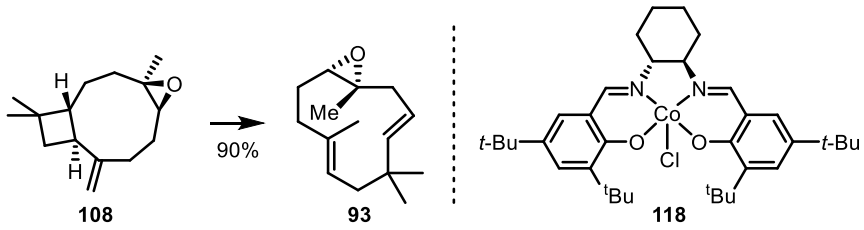


entry	reagent	conditions[a]	result[b]
1	**161**	THF, -78 °C to 0 °C, o/n	no reaction
2	**162**	THF, -78 °C to 0 °C, o/n	no reaction
3	**161**	THF, -78 °C to rt, o/n	no reaction
4	**162**	THF, -78 °C to rt, o/n	no reaction
5	**161**	Et_2O, -78 °C to 0 °C, o/n	no reaction
6	**161**	Et_2O, -78 °C to rt, o/n	no reaction
7	**162**, $BF_3{\cdot}Et_2O$ (1 eq.)	Et_2O, -78 °C to rt, 12h	complex mixture
8	**161**, $BF_3{\cdot}Et_2O$ (1 eq.)	Et_2O, -78 °C to rt, 12h	complex mixture

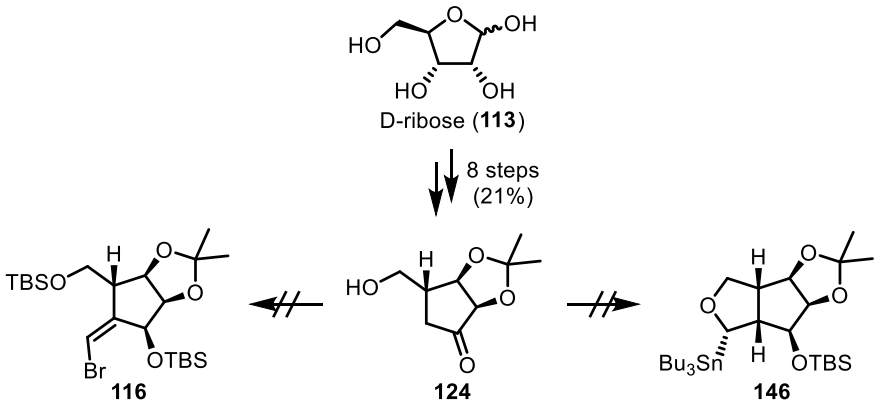
[51] (a) Pattenden, G. Comprehensive Organic Synthesis; Pergamon: Oxford, 1991; Vol. 3, pp. 733– 775; (b) Rao, A. S.; Paknikar, S. K.; Kirtune, J. G. *Tetrahedron*. **1983**, *39*, 2323–2367; (c) Taylor, S. K. *Tetrahedron*. **2000**, *56*, 1149–1163; (d) Posner, G. H.; Maxwell, J. P.; Kahraman, M. *J. Org. Chem*. **2003**, *68*, 3049–3054. (e) Torborg, C.; Hughes, D. D.; Buckle, R.; Robinson, M. W. C.; Bagley, M. C.; Graham, A. E. *Synthetic Comm*. **2008** *38*, 205-211.

2.6 Summary

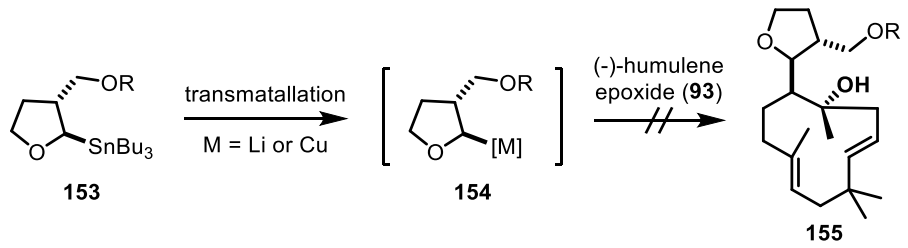
In summary, the first approach to the xenovulene A (**1**) has been discussed, employing the epoxide ring opening reaction as the key step. The epoxide fragment (**93**) has been successfully prepared by a Co(Sal$^{t\text{Bu, }t\text{Bu}}$)Cl (**118**) catalyzed retrocycloisomerization of (-)-caryophyllene oxide **(108)**.



The second goal was the synthesis of chiral vinyl bromide (**116**) and organostannane (**146**) to the epoxide ring opening of **93**. Both syntheses started from commercially available D-ribose (**113**). However, for both synthetic routes difficulties were encountered. The approach was finally not successful.



In addition, the model study towards the ring opening of (-)-humulene epoxide (**93**) with organolithium and organocopper reagents (**154**) was unsuccessful under various conditions.



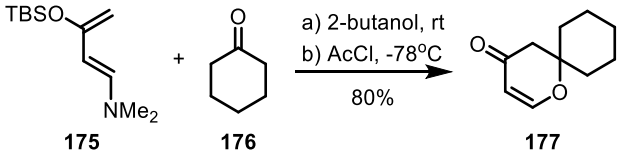
Therefore, another approach towards xenovulene A (**1**) in which a hetero Diels-Alder cycloaddition is the key step, has been proposed and will be presented in the next chapter.

Chapter 3 Hetero Diels-Alder approach to xenovulene A

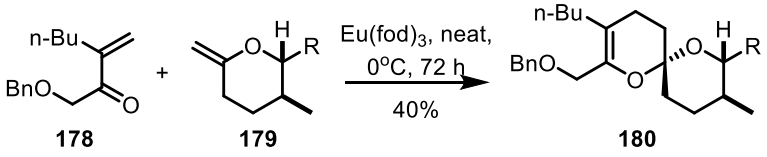
3.1 Introduction

3.1.1 Inverse Hetero-Diels-Alder (HDA) cycloaddition

Since the discovery of the Diels–Alder cycloaddition (DA) by Otto Diels and Kurt Alder in 1928,[52] increasingly appreciable attempts and endeavors have been made to develop this powerful methodology in different areas. Undoubtedly, one of the most interesting and significant developments was the discovery and establishment of Hetero Diels–Alder (HDA) cycloaddition. [53] Especially, the [4+2] cycloaddition between a diene and a carbonyl compound provides one of the most direct methods for the synthesis of dihydropyranone heterocycles. For example, Rawal and co-workers reported a hydrogen-bond promoted Hetero Diels–Alder reaction of dienes with unactivated ketone,[54] which was the first general method for achieving the HDA reaction of unactivated ketone (Scheme 3.1).



Scheme 3.1: HDA reaction of **175** and cyclohexanone (**176**)



Scheme 3.2: Inverse HDA reaction of **178** and **179**

The inverse Hetero Diels-Alder (HDA) cycloaddition between α,β-unsaturated carbonyl compound and dienophile is also a powerful method for the synthesis of 3,4-dihydro-*2H*-pyran heterocycles. For example, the Inverse HDA reaction between but-3-en-2-one **178** and

[52] Diels, O.; Alder, K. *Justus Liebigs Annalen der Chemie*., **1928**, *460*, 98–122.
[53] (a) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1. (b) Boger, D. L.; Weinreb, S. M. Hetero Diels-Alder Methodology in Organic Synthesis; Wasserman, H. H., Ed.; Academic Press: San Diego, CA, 1987; Vol. 47. c) Heravi, MM.; Ahmadi, T.; Ghavidel, M.; Heidari, B.; Hamidi, H. *RSC Adv*. **2015**, *5*, 101999-102075. d) Palasz, A. *Top. Curr. Chem*., **2016**, *24*, 3-37.
[54] Rawal, V. H.; Huang, Y. *J. Am. Chem. Soc*., **2002**, *124*, 9662-9663.

179 was treated with 15 mol% $Eu(fod)_3$ as catalyst, which provided the desired spiroketal **180** as a single diastereoisomer in moderate yield (Scheme 3.2). [55] Noticeably, the inverse HDA reactions generally proceed with high regio- and diastereoselectivity (generating 4 contiguous chiral centers in a single step) and in moderate to excellent yields. The geometry of the transition state of the HDA reactions influences the diastereoselectivity of cycloadditions. There are four different transition states for the HDA reaction of an α,β-unsaturated carbonyl compound with a dienophile, according to an *endo*- or *exo*-orientation of the dienophile and an (*E*)- or (*Z*)-configuration of the α,β-unsaturated carbonyl compound. The four transition structures of the HDA reaction providing the two diastereoisomers *syn* and *anti* are shown in Figure 3.1.

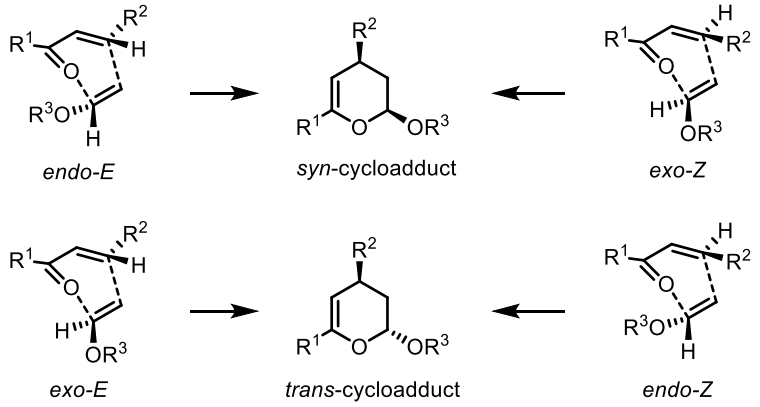


Figure 3.1: The four transition states of the HDA reaction of an alkene such as vinyl ether with 1-oxa-1,3-butadiene

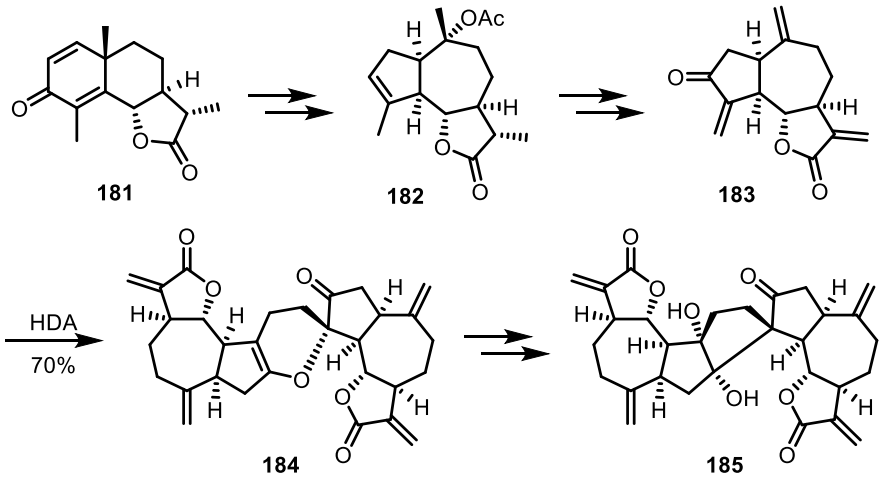
3.1.2 Application of inverse HDA reaction on natural product synthesis

Because the hetero Diels–Alder cycloaddition provides rapid and economic access to the construction of complex ring systems, it has become one of the most powerful strategies in the total synthesis of natural products with complex ring systems. In addition, as dihydro- and tetrahydropyran derivatives are prevalent structural subunits in a variety of natural compounds, including carbohydrates, alkaloids, and polyether antibiotics, the inverse hetero Diels–Alder cycloaddition has been widely and successfully applied in natural products synthesis.

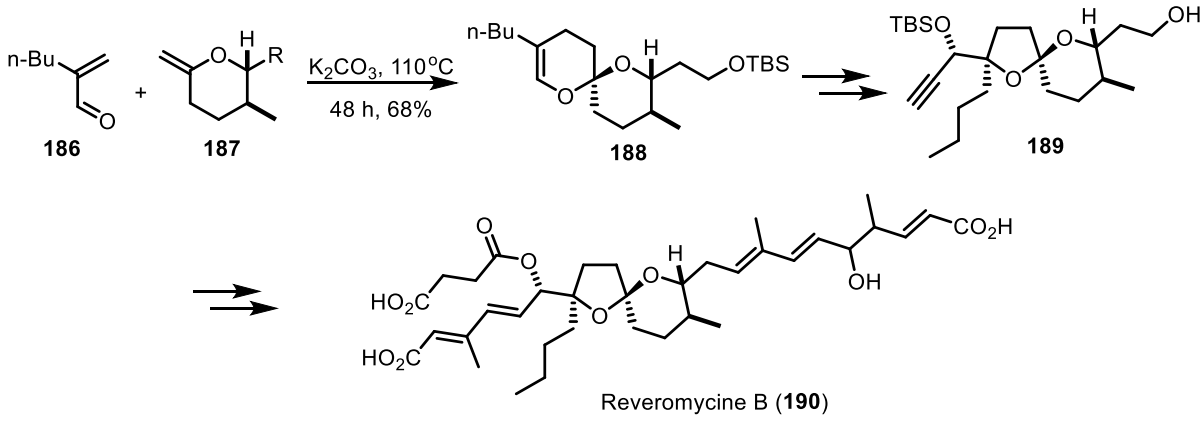
(+)-Ainsliadimer A (**185**), a new sesquiterpene lactone dimer with an exceptional carbon skeleton, was isolated from *Ainsliaea macrocephala* by Zhang and co-workers in 2008. It has

[55] Gong J.; Bonfand, E.; Brown, E.; Dujardin, G.; Michelet, V.; Genet, J. P. *Tetrahedron Lett*., **2004**, *44*, 2141–2144

been used in Chinese folk medicine for the treatment of different diseases, including angina and rheumatoid arthritis.[56] In 2010, Lei and co-workers achieved the first protecting free and biomimetic total synthesis of (+)-ainsliadimer A (**185**) utilizing a hydrogen bonding promoted HDA dimerization of **183** to provide the key homodimer intermediate (Scheme 3.3). This synthesis also confirmed the feasibility of employing nonenzymatic conditions to accomplish the suggested biosynthesis.[57]



Scheme 3.3: Synthesis of (+)-ainsliadimer A (**185**)



Scheme 3.4: Synthesis of Reveromycins B (**190**)

Spiroketals or spiroacetals are substructures that ensue in a wide variety of naturally occurring compounds from several and different sources such as, plants, fungi, marine organisms, insects and microbes. Reveromycins B (**190**) is specimen of natural products bearing a 5,6-spiroketal moiety. It was isolated from a soil actinomycete belonging to the *Sreptomyces*

[56] Wu, Z.-J.; Xu, X.-K.; Shen, Y.-H.; Su, J.; Tian, J.-M.; Liang, S.; Li, H.-L.; Liu, R.-H.; Zhang, W.-D. *Org. Lett*., **2008**, *10*, 2397-2401.
[57] Li, C.; Yu, X.; Lei, X. *Org. Lett*., **2010**, *20*, 4284-4287.

genus, and which has been found to act as epidermal growth factor inhibitor.[58] The total synthesis Reveromycins B has been accomplished in 25 linear steps starting from chiral methylene pyran **187** (Scheme 3.4).[59] The key step in this approach is an inverse electron demand HDA reaction between vinyl aldehyde **186** and methylene pyran **187** for constructing the 5,6-spiroketal **188**.

3.1.3 Application of α-humulene in the inverse HDA reaction

Since 1990s, a number of interesting natural products with 5-6-11, 6-6-11 or 7-6-11 tricyclic ring systems have been isolated, such as epolone B (**191**),[60] hypejapone A (**192**),[61] sterhirsutins A (**33**),[62] and xenovulenes A (**1**). All these natural products show a high degree of structural similarity, each featuring a ring system attached to a humulene-derived 11-membered sesquiterpene through a dihydropyran (Figure 3.2).

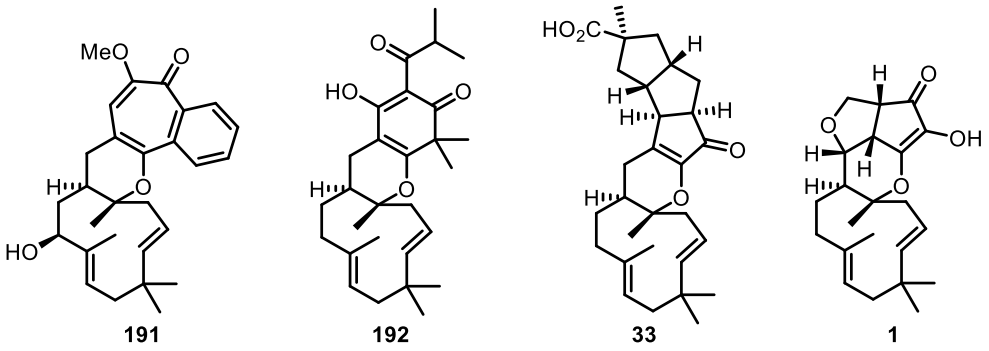


Figure 3.2: Structures of epolone B (**191**), hypejapone A (**192**), sterhirsutins A (**33**), and xenovulene A (**1**).

Obviously, the 11-membered sesquiterpene moiety derives from α-humulene. Biosynthetically, these tricyclic ring systems could be achieved by a single inverse hetero Diels-Alder reaction between an α,β-unsaturated ketone and commercially available α-humulene as dienophile. Studies toward the synthesis of epolone B (**191**) and hypejapone A (**192**) have proved this biosynthetic hypothesis.

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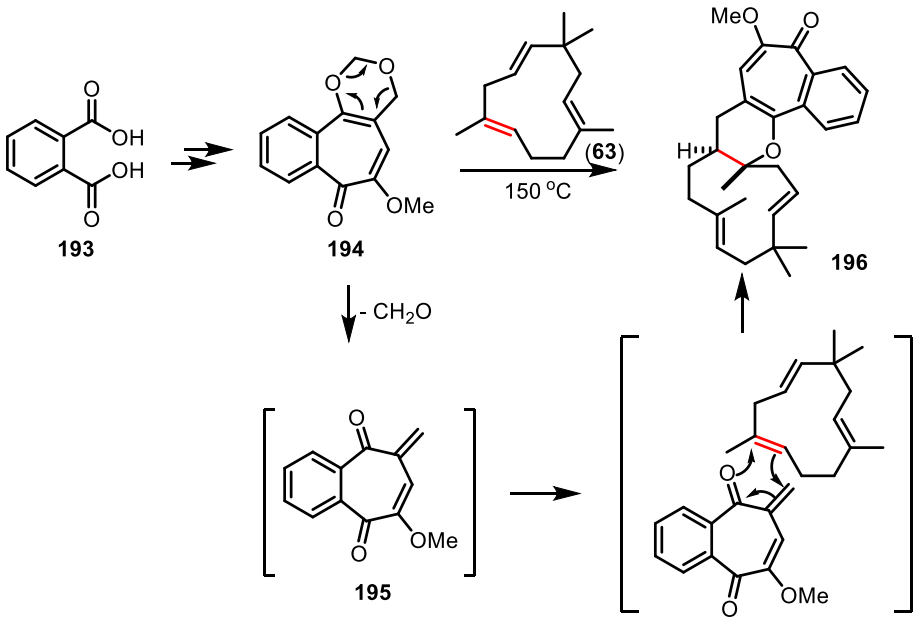
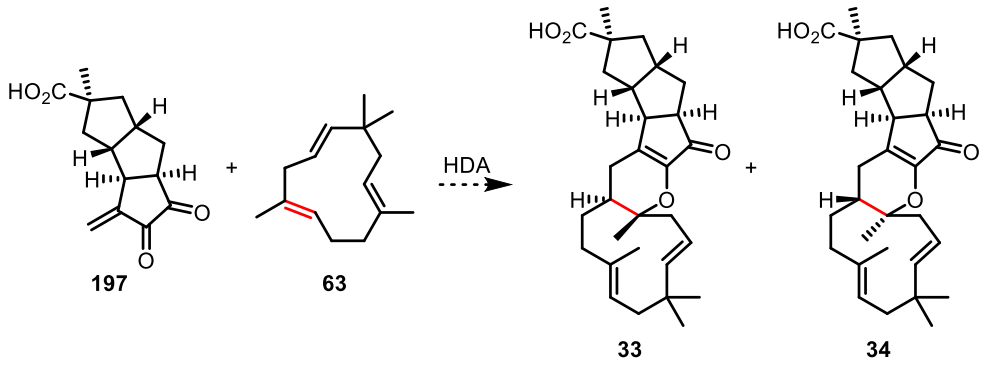
[58] Takahashi, H.; Osada, H.; Koshino, H.; Kudo, T.; Amano, S.; Shimizu, S.; Yoshihama, M.; Isono, K. *J. Antibiot.*, **1992**, *45*, 1409–1413.
[59] Cuzzupe, A. N.; Hutton, C. A.; Lilly, M. J.; Mann, R. K.; McRae, K. J.; Zammit, S. C.; Rizzacasa, M. A. *J. Org. Chem.*, **2001**, *66*, 2382–2393.
[60] (a) Cai, P.; Smith, D.; Cunningham, B.; Brown-Shimer, S.; Katz, B.; Pearce, C.; Venables, D.; Houck, D. *J. Nat. Prod.*, **1998**, 61, 791-794. (b) Harris, G. H.; Hoogsteen, K.; Silverman, K. C.; Raghoobar, S. L.; Bills, G. F.; Lingham, R. B.; Smith, J. L.; Dougherty, H. W.; Cascales, C.; Pala´ez, F. *Tetrahedron*, **1993**, *49*, 2139-2143.
[61] a) Yang, X.-W.; Li, Y.-P.; Su, J.; Ma, W.-G.; Xu, G. *Org.Lett.*, **2016**, *18*, 1876-1880. b) Hu, L.; Zhang, Y.; Zhu, H.; Liu, J.; Li, H.; Li, X.-N.; Sun, W.; Zeng, J.; Xue, Y.; Zhang, Y. *Org. Lett*. **2016**, *18*, 2272-2276.
[62] Qi, Q.-Y.; Bao, L.; Ren, J.-W.; Han, J.-J.; Zhang, Z.-Y.; Li, Y.; Yao, Y.-J.; Cao, R.; Liu, H.-W. *Org. Lett.* **2014**, *16*, 5092-5095.



Scheme 3.5: Synthesis of epolone B anologue (**196**)

In 1996, Baldwin and co-workers reported the first natural product synthesis which applied the hetero Diels-Alder reaction as key step using in situ generated tropolone quinone methide **195** as diene and α-humulene (**63**) as the dienophile (Scheme 3.5).[63] A thermal hetero Diels-Alder reaction of the protected benzotropolone **194**, with the extrusion of formaldehyde at 150 °C, generated the required tropolone quinone methide **195**. Sequentially, a hetero Diels-Alder reaction in situ with 1.5 equivalents of α-humulene (**63**) in *p*-xylene at 150 °C afforded the least hindered monosubstituted epolone B anologue **196** with correct regioselectivity in good yield. This synthesis and method provided a concise and efficient approach to construct the 7-6-11 tricyclic ring core skeleton of natural products.

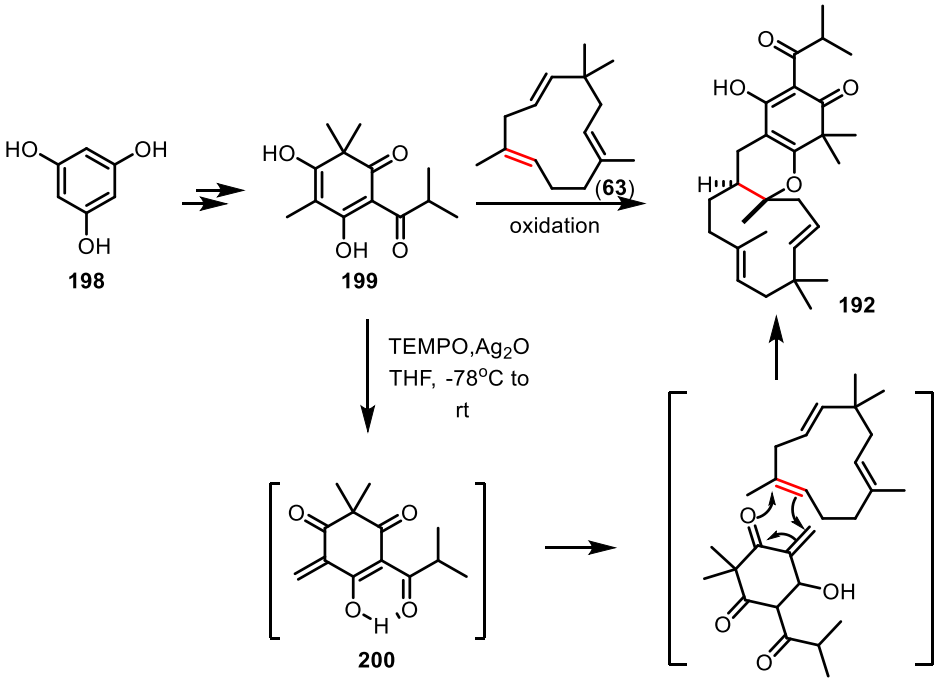


Scheme 3.6: Hypothetical biogenetic pathway of sterhirsutins A (**33**) and B (**34**)

[63] (a) Baldwin J. E.; Mayweg, A. V. W.; Neumann, K.; Pritchard, G. J. *Org. Lett.* **1999**, *1*, 1933-1935. (b) Adlington, R. M.; Baldwin J. E.; Mayweg, A. V. W.; Pritchard, G. J. *Org. Lett.* **2002**, *4*, 3009-3011.

In 2014, Liu and co-worker isolated and fully characterized two new cytotoxic sesquiterpenes of sterhirsutins A and B from the solid culture of *S. hirsutum*, which possess a new core skeleton of cyclopenta[5, 6]pentaleno[2, 1-*b*]cycloundeca[*e*]pyran. They proposed that these two natural products could be synthesized through a HDA reaction between α,β-unsaturated ketone **197** and α-humulene (**63**) as the dienophile (Scheme 3.6). To our knowledge, there have been no studies to confirm this hypothesis, so far.

In 2016, George and co-workers accomplished the first natural product synthesis which involves the hetero Diels-Alder reaction as one of the key steps using in situ generated α,β-unsaturated ketone **200** as diene and α-humulene (**63**) as dienophile (Scheme 3.7).[64] The synthesis of hypejapone A (**192**) began with a Friedel-Crafts acylation of phloroglucinol **198** with isobutyryl chloride followed by dearomatization to give norflavesone (**199**) in good yield over two steps. Oxidation of **199** with TEMPO and Ag_2O in the presence of α-humulene (**63**) generated hypejapone A (**192**) in 32% yield. It was presumed that this transformation went through a HDA reaction between the α,β-unsaturated ketone (**200**) generated in situ and α-humulene (**63**).



Scheme 3.7 Synthesis of hypejapone A (**192**)

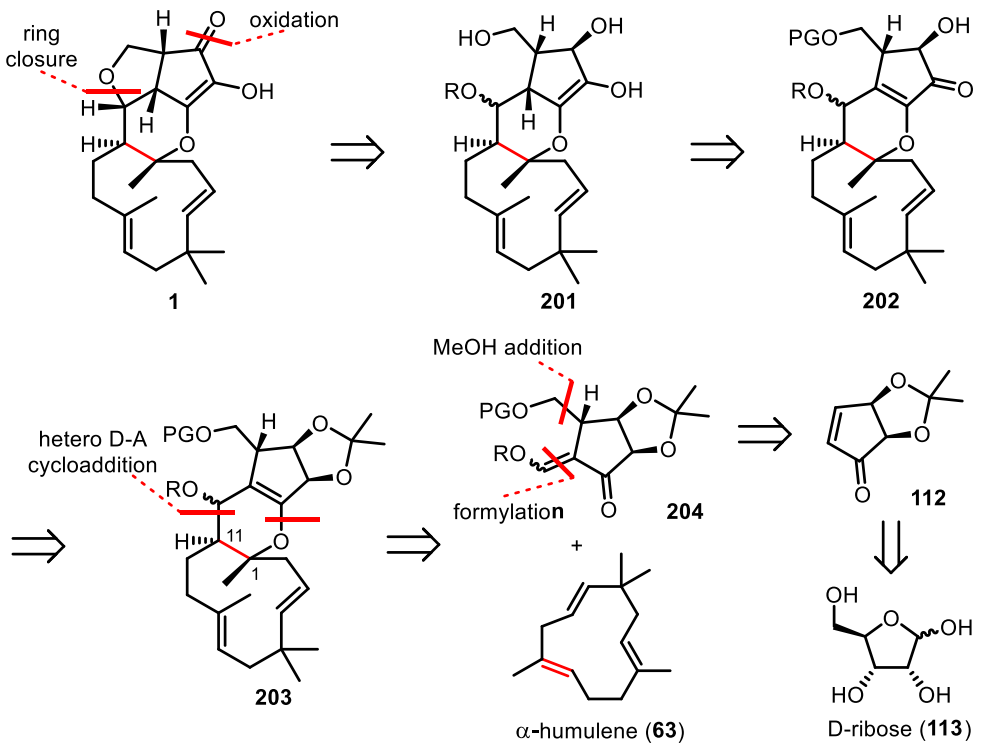
In conclusion, the hetero Diels-Alder approach allows for efficient coupling of suitable dienes with α-humulene (**63**) achieving complex polycyclic systems which are core skeletons of a

[64] Lam, H. C.; Spence, J. T. J.; George, J. H. *Angew. Chem. Int. Ed*. **2016**, *55*, 10368-10371.

number of complex natural products, such as our target molecules xenovulen A (**1**), and sterhirsutins A (**33**) and B (**34**), respectively.

3.2 Retrosynthetic Analysis

The first retrosynthetic analysis of xenovulene A (**1**) began by disconnecting the tetrahydrofuran ring and simplifying the cyclopentanone ring to diol leading to compound **201** as shown in scheme 3.8. Compound **201** in turn could be prepared from compound **202** by a 1,4-reduction using copper hydride reagents. It was expected that compound **202** could be synthesized through removal of the acetonide in compound **203** followed by selective allylic alcohol oxidization with MnO_2. Pivotal to this approach, the advanced intermediate **203** with two continuous stereogenic centers (C-1 and C-11) including a quaternary carbon could be established in a single step via a regioselective Hetero-Diels Alder cycloaddition of vinyl ketone **204** and α-humulene (**63**).[65] Formylation with ethyl formylate followed by tosylation of enol was envisaged to access **204** from enone **112** which itself could be synthesized from D-ribose (**113**).

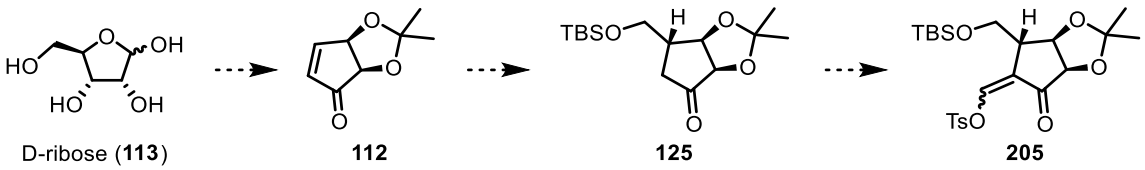


Scheme 3.8: Retrosynthetic analysis of xenovulene A (**1**)

[65] (a) Lei, X.; Johnson, R. P.; Porco, J. A., Jr. *Angew. Chem., Int. Ed*. **2003**, *42*, 3913-3917. (b) Li, C.; Johnson, R. P.; Porco, J. A., Jr. *J. Am. Chem. Soc*. **2003**, *125*, 5095-5999. (c) Lumb, J.; Trauner, D. *J. Am. Chem. Soc*. **2005**, *127*, 2870-2875.

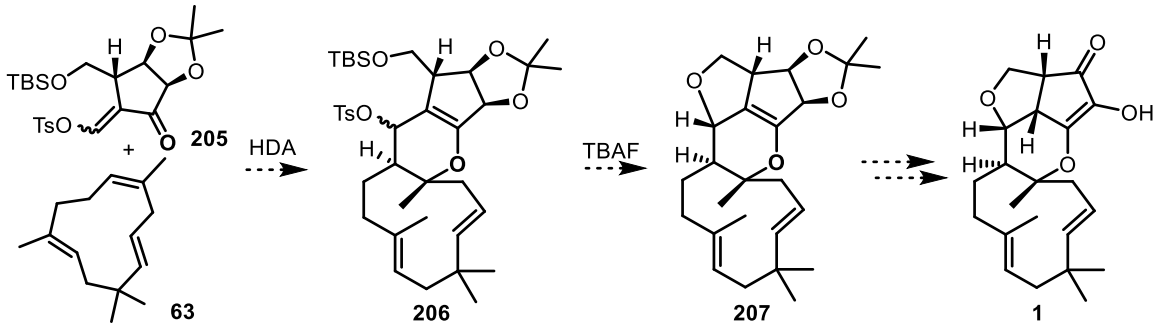
3.3 Project Outline

According to the retrosynthetic analysis of xenovulene A (**1**), the first goal was the synthesis of a suitable diene **205** , which then would be required to undergo the hetero Diels-Alder cycloaddition with α-humulene (**63**) to form the full carbon skeleton of xenovulene A. The vinyl tosylate (**205**) was chosen as the diene equivalent for the hetero Diels-Alder reaction with α-humulene (**63**), because the tosyl group would be the leaving group for the subsequent construction of the tetrahydrofuran ring of xenovulene A.



Scheme 3.9: Synthetic strategy for vinyl tosylate (**205**)

The second goal was the hetero Diels-Alder reaction between **205** and α-humulene (**63**) to form the advanced intermediate (**206**). Treatment of **206** with TBAF followed by few transformations could generate the target xenovulene A (**1**) (Scheme 3.10).

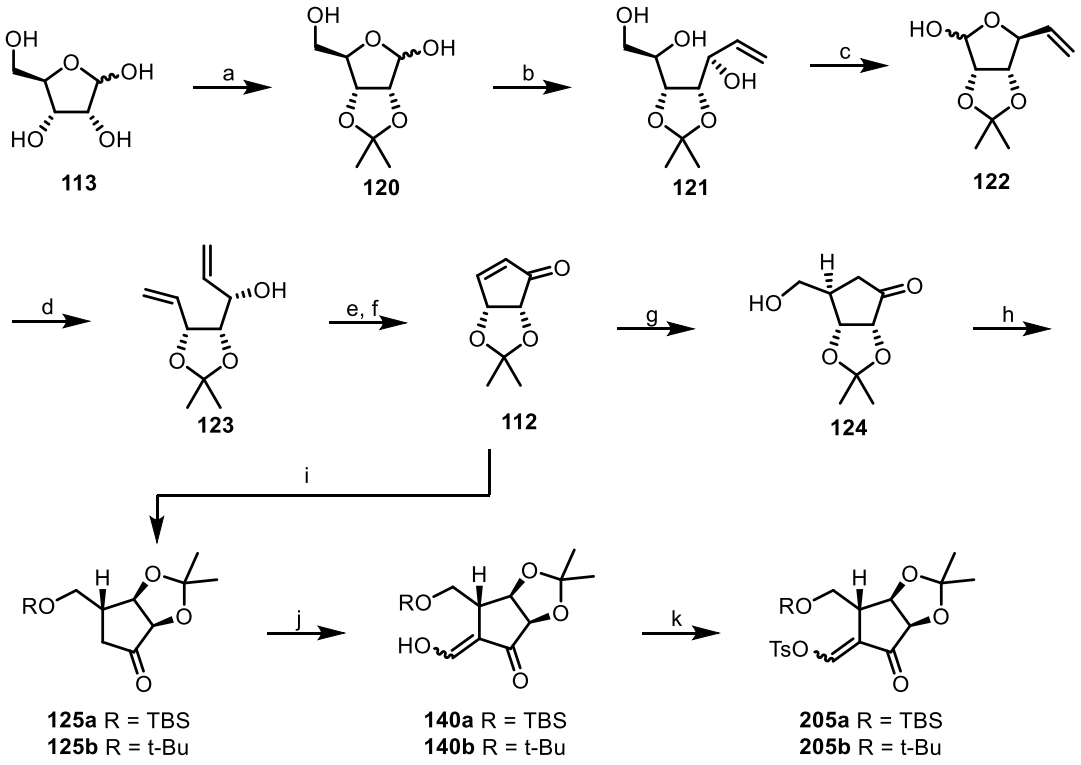


Scheme 3.10: Hetreo-DA approach to xenovulene A (**1**)

3.4 Results and Discussion

3.4.1 Preparation of vinyl tosylate **205**

The synthesis of vinyl tosylate **205** started from D-ribose (**113**) as shown in Scheme 3.11.[66] D-Ribose (**113**) was protected as the acetonide (**120**) which was treated with vinylmagnesium bromide to give triol **121** in 80% yield. Oxidative cleavage of 1,2-diol in **121** with sodium metaperiodate followed by Wittig reaction with methyltriphenylphosphonium bromide gave the diene **123** with good yield and high selectivity. Ring closure metathesis of diene **123** using Grubbs I catalyst gave the desired allylic alcohol, which was oxidized with MnO_2 to afford cyclopentenone **112** in 60% yield over two steps.



Scheme 3.11: Preparation of vinyl tosylate **205**. *Reagents and conditions: a) acetone, H_2SO_4, rt, 2.5 h, 93%; b) viny magnisium bromide, THF, -78 °C to 0 °C, 3 h, 81%; c) $NaIO_4$, CH_2Cl_2, H_2O, 0 °C to rt, 40 min, 85%; d) NaH, DMSO, $MePPh_3Br$, THF, 0 °C to reflux, 24 h, 88%; e) Grubbs I catalyst, $CHCl_3$, rt, 24 h; f) MnO_2, CH_2Cl_2, rt, 24 h, 60% for two steps; g) CH_3OH, Ph_2CO, hν, 1 h, 65%; h) TBSCl, DMAP, imidazole, DMF, 24 h, 90%; i) $(t\text{-}BuOCH_2)_2CuLi$, t-BuOMe/THF, -30 °C, 1 h, 85%. j) ethyl formate, t-BuOK, Et_2O, 2 h, 60%; k) p-toluenesulfonyl chloride, Et_3N, NMI, toluene, 12 h, 56%;*

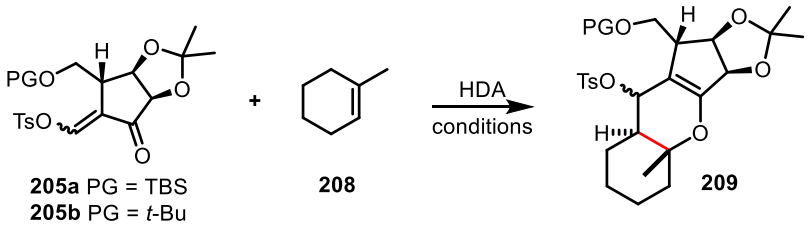
[66] See in chaper 2.

Photochemical methanol addition to cyclopentenone **112** gave alcohol **124** in 65% yield. Upon protection with TBS group (90% yield), compound **125a** was treated with *t*-BuOK and ethyl formate to give enol **140a**, which was subsequently tosylated with *p*-toluenesulfonyl chloride to give compound **205a** in moderate yield. After 1,4-reduction of **112** with (t-$BuOCH_2)_2CuLi$, compound **205b** was prepared via subsequent enolization followed by tosylation in an encouraging yield over three steps.[67]

3.4.2 HDA reaction of **205** with 1-methylcyclohexene

With compound **205** in hand, the hetero Diels-Alder reaction between it and humulene (**63**) was investigated. Initially, a test reaction between compound **205** and 1-methylcyclohexene (**208**) was examined (Table 3.3).[68] The reaction was carried out in benzene at room temperature for 24 h, unfortunately, no desired product was observed (entry 1). Under refluxing conditions in different solvents, such as benzene and toluene, only the decomposition of **205** was observed (entries 2-4). In addition, heating a solvent free mixture of **205** with an excess amount of 1-methylcyclohexene (**208**) at 110 ^{o}C for 2 h resulted in a inseparable mixture (entry 5).

Table 3.3: Hetero-DA reaction of **205** with 1-methylcyclohexene



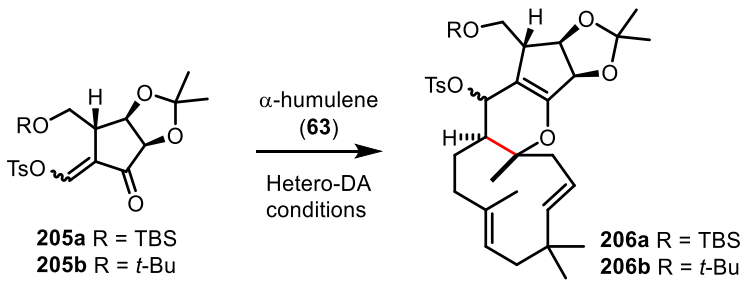
entry	reagent	conditions	result
1	**205a**, **208** (5 eq.)	benzene, 25 ^{o}C, 24h	-
2	**205a**, **208** (5 eq.)	benzene, 80 ^{o}C, 16h	decomposition
3	**205a**, **208** (5 eq.)	toluene, 110 ^{o}C, 24h	decomposition
4	**205b**, **208** (5 eq.)	toluene, 110 ^{o}C, 24h	decomposition
5	**205b**, **208** (20 eq.)	110 ^{o}C, 2h	complex mixture

[67] (a) Spengler, J.-P.; Schunack, W. *Arch. Pharm. (Weinheim)*, **1984**, *317*, 425-426. (b) Nakatsuji, H.; Nishikado, H.; Ueno, K.; Tanabe, Y. *Org. Lett*. **2009**, *11*, 4258-4261.
[68] Baldwin, J. E.; Mayweg, A. V. W.; Neumann, K.; Pritchard, G. J. *Org. Lett.* **1999**, *1*, 1933-1935.

3.4.3 HDA reaction of **205** with α-humulene

Even though the failure of the test Diels-Alder reaction of **205** with 1-methylcyclohexene (**208**), the cycloaddition between **205** with α-humulene (**63**) was examined (Table 3.4). Unfortunately, for both vinyl tosylate **205a** and **205b**, there were no transformations observed at room temperature in benzene for 48 h (entries 1 and 4). Only decomposition was occurred under refluxing conditions in benzene (entries 2 and 5), and as well under solvent free conditions (entries 3 and 6).

Table 3.4: Hetero Diels-Alder reaction of **205** with α-humulene (**63**)



205a R = TBS
205b R = *t*-Bu

206a R = TBS
206b R = *t*-Bu

entry	reagent	conditions[a]	result[b]
1	**205a**, **63** (10 eq.),	benzene, 25 °C, 48h	-
2	**205a**, **63** (10 eq.),	benzene, 80 °C, 16h	decomposition
3	**205a**, **63** (20 eq.),	80 °C, 5h	decomposition
4	**205b**, **63** (10 eq.),	benzene, 25 °C, 48h	-
5	**205b**, **63** (10 eq.),	benzene, 80 °C, 5h	decomposition
6	**205b**, **63** (20 eq.),	80 °C, 5h	decomposition

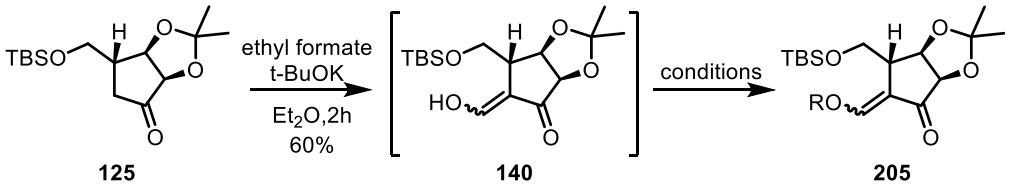
a: 0.05mmol scale reaction in sealed-tube. b: results refer to LC-MS and TLC.

In addition, several analogues of **205** were planned to be prepared and some representative examples are shown in Table 3.5. First of all, the PMB group was chosen to replace tosyl group, however, the protection of enol (**140**) with PMB protecting group failed under various conditions (entries 1 and 2).[69] Presumably, the reason for the failure of the hetero-DA reaction of **205** with alkenes might be associated with the tosyl group due to its Steric

[69] Stevens, A. T.; Bull, J. R.; Chibale, K. *Org. Biomol. Chem.* **2008**, *6*, 586–595.

hindrance. So mesylation of the enol **140** was investigated,[70] however, also in this case, no desired product was obtained (entry 3).

Table 3.5: Preparation of vinyl tosylate **205** analogues



125 140 205

entry	R	reagent	conditions[a]	result[b]
1	PMB	PMBCl (2.2 eq), NaH (1.1 eq),	DMF, rt, o/n	-
2	PMB	PMB-imidate (2.2 eq), $Sc(OTf)_3$ (0.1 eq)	toluene, rt, o/n	-
3	Ms	MsCl(1.5 eq), Et_3N(1.5 eq), NMI(0.1 eq.)	toluene, 0°C to rt, 12h	-
4	Ts	TsCl(1.5 eq), Et_3N(1.5 eq), NMI(0.1 eq)	toluene, 0°C to rt, 12h	36%

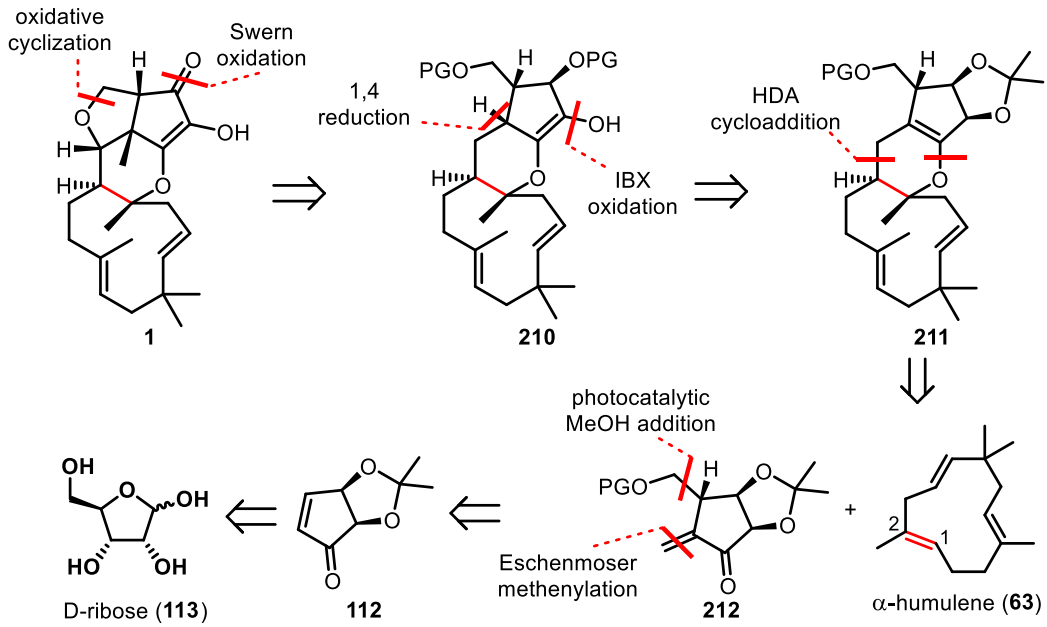
a: 0.05mmol scale. b: results refer to LC-MS and TLC.

[70] (a) Lim, M. I.; Klein, R. S.; Fox, J. J. *Tetrahedron Lett*. **1980**, *21*, 1013-1016. (b) Buchanan, J. G.; Craven, D. A.; Wightman, R. H.; Harnden, M. R. *J. Chem. Soc., Perkin. Trans. 1*, **1991**, 195-203.

3.5 Modified second generation of HDA approach

Due to the difficulties to develop a scalable synthesis of vinyl tosylate **205** and the failure of the hetero Diels-Alder reaction of **205** with α-humulene (**63**), vinyl ketone **212** was chosen as the modified diene component for the hetero Diels-Alder reaction with α-humulene (**63**).

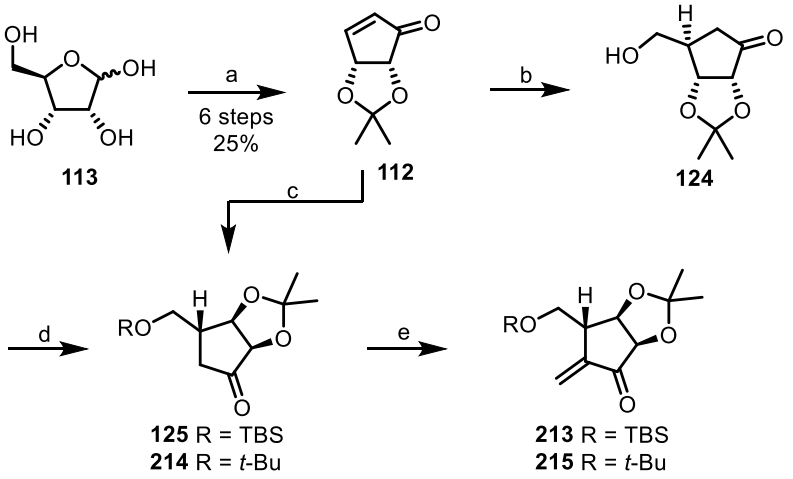
The modified second retrosynthetic analysis of xenovulene A is summarized in Scheme 3.12. It was envisioned that the tetrahydrofuran ring would be formed at a late stage in the synthesis by an oxidative cyclization from triol derivative **210**. In turn **210** could be formed through oxidative adjustment of intermediate **211**. As the key step of this approach, it was expected that the advanced intermediate **211** with two continuous stereogenic centers including a quaternary carbon could be established in a single step via a regio- and stereoselective hetero Diels Alder cycloaddition of vinyl ketone **212** with α-humulene (**63**). A key issue points to the regioselectivity of the cycloaddition with respect to the dienophile, α-humulene (**63**), as the sterically least congested double bond (the C_1=C_2 bond in α-humulene) has to react exclusively. Next, it was planned to prepare vinyl ketone **212** by a short sequence of photocatalytic 1,4-addition and methenylation of cyclopentenone **112**, which itself can be prepared from D-ribose (**113**).



Scheme 3.12: Modified second retrosynthetic analysis of xenovulene A

3.5.1 Preparation of vinyl ketone **212**

The synthesis of vinyl ketone **212** (**213**: R= TBS; **215**: R= *t*-Bu;) is described in Scheme 3.13. According to the first generation approach (scheme 3.11), enone **112** was successfully synthesized from D-ribose (**113**) in 25% yield over 6 steps.[71] Next, photochemical methanol addition to cyclopentenone **112** furnished alcohol **124** in 65% yield. Upon protection as TBS-ether (90% yield), the resulting ketone **125** was treated with lithium diisopropylamide (LDA) and Eschenmoser's salt ($Me_2N{=}CH_2I$)), followed by iodomethane to afford vinyl ketone **213** in 70% yield after Hofmann elimination. Alternatively, enone **215** was prepared from **112** by 1,4-addition with $(t\text{-}BuOCH_2)_2CuLi$ and subsequent Eschenmoser methenylation followed by Hofmann elimination in 65% yield over two steps.[72]



Scheme 3.13: Preparation of vinyl ketone **213** and **215**. *Reagents and conditions: a) see scheme 3.11; b) CH_3OH, Ph_2CO, hν, 1 h, 65%; c) $(t\text{-}BuOCH_2)_2CuLi$, t-BuOMe/THF, -30°C, 1 h, 85%. d) TBSCl, DMAP, imidazole, DMF, 24 h, 90%; e) LDA, C_3H_8NI, CH_3I, THF, -78 °C to rt,o/n (65% for **213**; 85% for **215**);*

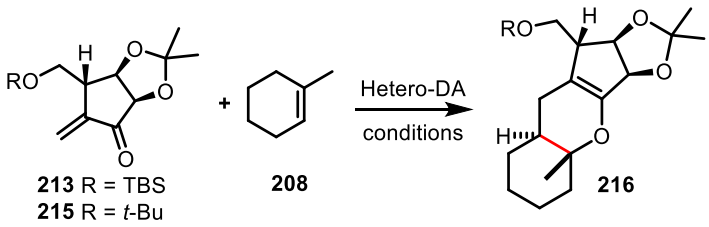
3.5.2 Model HDA reaction of **212** with 1-methylcyclohexene

With the vinyl ketones **213** and **215** in hand, the hetero Diels-Alder reaction of vinyl ketone with different alkenes was investigated. First, a test reaction using 1-methylcyclohexene (**208**) as dienophile was examined (Table 3.6). Initially, the reaction was carried out in benzene at room temperature for 24 h. Under this condition, the Hetero DA reaction did not take place

[71] Ref. 26-29.
[72] a) Wang, P.; Agrofoglio, L. A.; Newton, M. G.; Chu, CK. *J. Org. Chem*. **1999**, *64*, 4173-4178. b) Jin, Y. H.; Liu, P.; Wang, J.; Baker, R.; Huggins, J.; Chu, C. K. *J. Org. Chem*. **2003**, *68*, 9012-9018. c) Gadthula, S.; Rawal, R. K.; Sharon, A.; Wu, D.; Korba, B.; Chu, C. K. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3982-3985.

(entry 1). Then, the cycloaddition under refluxing condition in different solvents was investigated, however, only trace amount of adducts were observed as judged by LC-MS (entries 2, 3).[73] When the reaction temperature was raised to 150 °C, [4+2]-homodimerization of compound **213** took place referring to LC-MS results (entry 3). Surprisingly, heating **213** with 10 equivalents of 1-methylcyclohexene (**208**) under solvent free conditions at 150 °C for 48 to 72 h generated an inseparable mixture of adducts (**216**) and dimer derived from compound **213** (entries 5, 6). In contrast, the reaction of vinyl ketone **215** with α-humulene (**63**) was investigated, no desired product was obtained (entry 7).[74]

Table 3.6: Model hetero-DA reaction with 1-methylcyclohexene (**208**)



entry	reagent	conditions[a]	result[b]
1	**213**, **208** (5 eq.),	benzene, 25 °C, 24h	-
2	**213**, **208** (5 eq.),	benzene, 80 °C, 16h	trace
3	**213**, **208** (5 eq.),	toluene,110 °C, 24h	trace
4	**213**, **208** (5 eq.),	*p*-xylene, 150 °C, 48h	dimer of **213**
5	**213**, **208** (10 eq.),	150 °C, 48h	dimer of **213**
6	**213**, **208** (10 eq.),	150 °C, 72h	inseparable adducts & dimer of **213**
7	**215**, **208** (20 eq.),	150 °C, 72h	inseparable mixture

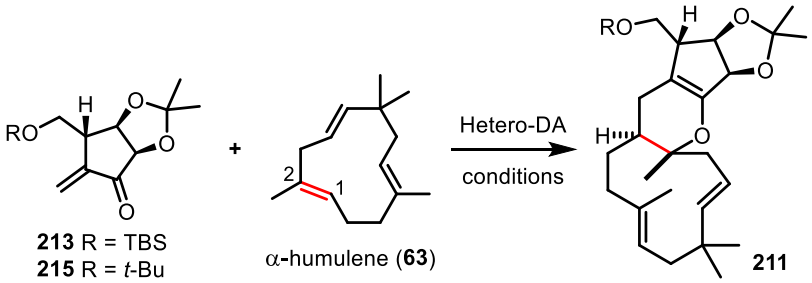
a: 0.05mmol scale in sealed-tube. b: results refer to LC-MS and TLC.

[73] (a) Baldwin J. E.; Mayweg, A. V. W.; Neumann, K.; Pritchard, G. J. *Org. Lett.* **1999**, *1*, 1933-1935. (b) Adlington, R. M.; Baldwin J. E.; Mayweg, A. V. W.; Pritchard, G. J. *Org. Lett.* **2002**, *4*, 3009-3011.
[74] Wu, Z.-J.; Xu, X.-K.; Shen, Y.-H.; Su, J.; Tian, J.-M.; Liang, S.; Li, H.-L.; Liu, R.-H.; Zhang, W.-D. *Org. Lett.* **2008**, *10*, 2397-2301.

3.5.3 Hetero Diels-Alder reaction of vinyl ketone with α-humulene

Inspired by the test reactions of **213** with 1-methylcyclohexene (**208**), as the key step of this approach, a number of conditions of the inverse hetero Diels Alder cycloaddition of **213** with α-humulene (**63**) were evaluated and some representative examples are shown in Table 3.7.

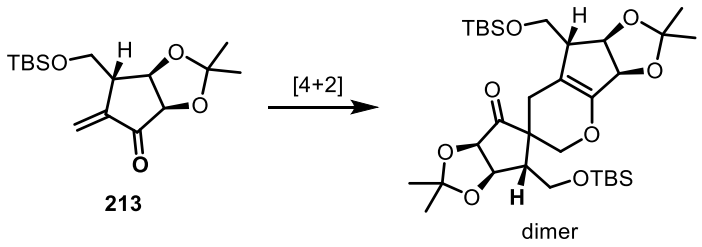
Table 3.7: Hetero-DA reaction of **213** with α-humulene (**63**)



entry	reagent	conditions[a]	result[b]
1	**213**, **63** (10 eq.), $AlCl_3$ (1.0 eq.)	toluene, rt, 16h	-
2	**213**, **63** (10 eq.), $AlCl_3$ (1.0 eq.)	toluene, 110 °C, 16h	decomposition
3	**213**, **63** (10 eq.), $Sc(OTf)_3$ (1 eq.)	toluene, 110 °C, 16h	decomposition
4	**213**, **63** (10 eq.), $Dy(OTf)_3$ (1 eq.)	toluene, 110 °C, 16h	decomposition
5	**213**, **63** (10 eq.)	toluene, 110 °C, 48h	dimer
6	**213**, **63** (10 eq.)	*p*-xylene, 150 °C, 48h	dimer
7	**213**, **63** (10 eq.)	nitrobenzene, 210 °C, 48h	dimer
8	**213**, **63** (20 eq.)	150 °C, 3d	adducts & dimer
9	**213**, **63** (20 eq.)	150 °C, 5d	adducts & trace dimer
10	**213**, **63** (20 eq.)	150 °C, 15d	adducts & trace dimer
11	**215**, **63** (20 eq.)	150 °C, 5d	adducts & trace dimer

a: 0.05mmol scale reaction in sealed-tube. b: dimers derived from vinyl ketone **213** or **215**.

Initially, the HDA cycloaddition was carried out in toluene with different Lewis Acids (e.g., $AlCl_3$, $Sc(OTf)_3$, and $Dy(OTf)_3$ at room temperature to refluxing conditions (entry 1 to 4);[75] These conditions resulted in either no conversion (entry 1) or decomposition (entries 2 to 4); The reaction was also carried out in high-boiling-point solvents (e.g., toluene xylene, and nitrobenzene) under refluxing condition.[76] In no case the desired product was obtained, but only dimerization of compound **213** was observed (entries 5 to 7). Interestingly, heating the mixture of **213** with excess amounts of α-humulene (**63**) without solvent at 150 ^oC for over 3 days gave a mixture of the desired adducts as the main products as well as trace amounts of dimer derived from **213**; Unfortunately, which was an inseparable mixture (entries 8 to 10). In contrast, the cycloaddition of **215** with 20 equivalents of α-humulene (**63**) at 150 ^oC was also investigated, which also yielded an inseparable mixture of adducts and dimer derived from **215** (entry 11). According to the total synthesis of (+)-ainsliadimer A (**185**),[56] a plausible dimerization of **215** was proposed as shown in Scheme 3.14.



Scheme 3.14: Proposed [4+2]-homodimerization of vinyl ketone **213**

3.5.4 The HDA reaction and TBS deprotection sequence

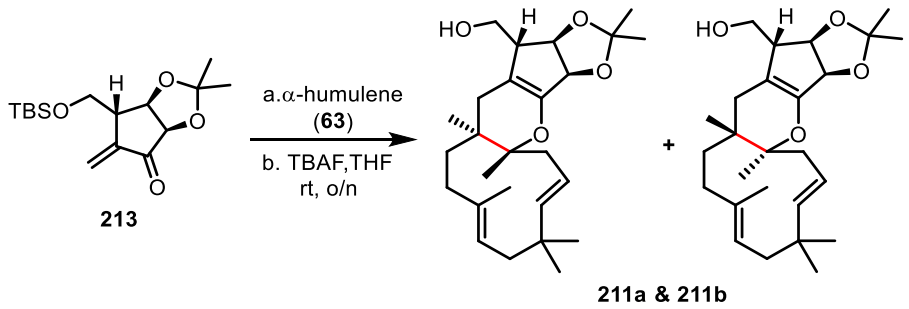
Due to the difficulties in separation of the desired HDA adducts from other byproducts, it was expected the separation and purification of adducts could be succeeded after a two-steps sequence of hetero Diels-Alder reaction followed by TBAF mediated TBS deprotection. It was rationalized that the polarity of adduct would be changed after the removal of TBS group, then the separation and purification of adducts could be feasible. The optimization of the HDA/TBS-deprotection sequence is shown in Table 3.8. To be delighted, it was found that heating vinyl ketone **213** with an excess amounts of α-humuleme (**63**) in the absence of

[75] (a) Gossinger, A. C. E.; Kalb, R.; Orglmeister, E.; Schwaiger, J. *Tetrahedron*, **2007**, *63*, 8326-8233. (b) Esmieu, W. R.; Worden, S. M.; Catterick, D.; Wilson, C.; Hayes, C. *J. Org. Lett.* **2008**, *10*, 3045-3050. c) Li, C.; Yu, X.; Lei, X. *Org. Lett*., **2010**, *12*, 4284-4287. (d) Weber, A.; Dehn, R.; Schläger, N.; Dieter, B.; Kirschning, A. *Org. Lett.* **2014**, *16*, 568-571. (e) Takao, K.; Noguchi, S.; Sakamoto, S.; Kimura, M.; Yoshida, K.; Tadano, K. *J. Am. Chem. Soc.* **2015**, *137*, 15971-15977.

[76] (a) Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 9662-9666. (b) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature*, **2003**, *424*, 146-147. (c) Thadani, A. N.; Stankovic, A. R.; Rawal, V. H. *Proc. Natl. Acad. Sci. U.S.A.*, **2004**, *101*, 5846-5856. (d) Unni, A. K.; Takenaka, N.; Yamamoto, H.; Rawal, V. H. *J. Am. Chem. Soc*. **2005**, *127*, 1336-1370. (e) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev*., **2007**, *107*, 5713-5748.

solvent in a sealed-tube at 150°C for 48 h followed by TBAF-mediated TBS deprotection, afforded the desired cycloadducts **211a** and **211b** with the diastereomeric ratio (d.r.) of 1:1 and in 20% combined yield over two steps (entry 1). As expected, the two distereoisomers **211a** and **211b** could be isolated and purified by silica gel column chromatography (**211a**: R_f = 0.60; **211b**: R_f = 0.55; ethyl acetate/petroleum ether = 1/1). Subsequently, a better yield (51%) and higher diastereoselectivty (2:1 d.r.) was achieved by extending the reaction time to 5 days (entry 2). Longer reaction times did not lead to a significantly improved result (entry 3). However, the excess amounts of α-humulene (**63**) could be decreased to five equivalents under these conditions without loss of yield (entry 5). If the amount of α-humulene (**63**) was decreased to 2 equivalents, both poor yield (5%) and low diastereoselectivty (1:1 d.r.) was observed (entry 6).

Table 3.8: A HDA reaction / TBS deprotection sequence



entry	**213** (mmol)	**63**	time	yield (d.r.) [a]
1	0.01	20 eq.	48h	22% (1:1)
2	0.07	20 eq.	5d	50% (2:1)
3	0.07	20 eq.	15d	51% (2:1)
4	0.20	10 eq.	5d	51% (2:1)
5	0.50	5 eq.	5d	50% (2:1)
6	0.50	2 eq.	5d	5% (1:1)

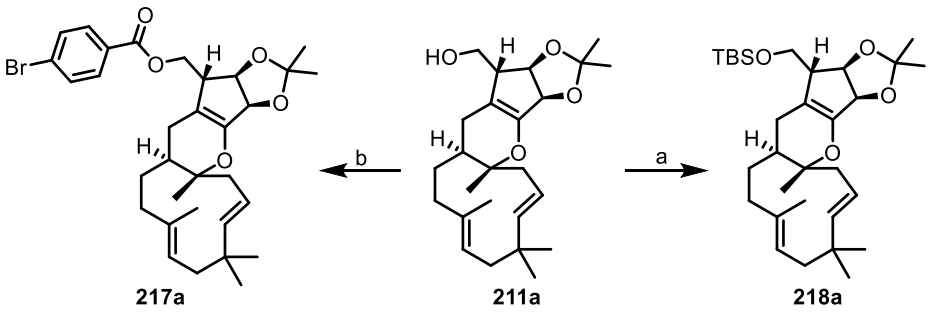
a: yields and d.r. refer to isolated, purified products over 2 steps.

The two diastereoisomers **211a** and **211b** were smoothly separated and purified by silica gel column chromatography and fully characterized by NMR analysis. However, NMR-analysis, including the nuclear Overhauser effects (NOE) experiments, was not sufficient to figure out

the absolute configuration of the newly formed stereogenic centers in the two distereoisomers **211a** and **211b**.

3.5.5 Structure elucidation of distereoisomers

Due to the difficulties in the elucidation of the absolute configuration of **211a** and **211b** through NMR-analysis, two crystalline derivatives of **211a** (**211a**: R_f = 0.6, ethyl acetate/petroleum ether = 1/1), namely the benzoate **217a** and the TBS-ether **218a** (Scheme 3.15), were prepared.[77] The structure of **211a** was confirmed and the absolute configuration assigned through single-crystal X-ray crystallographic analysis of the TBS-ether derivative (**218a**) (Figure 3.5).



Scheme 3.15: Preparation of **217a** and **218a**. *Reagents and conditions: a) TBOTf, 2,6-lutidine, CH_2Cl_2, rt, 2 h, 81%; b) 4-Bromobenzoyl chloride, DMAP, CH_2Cl_2/THF, rt, 16 h, 80%.*

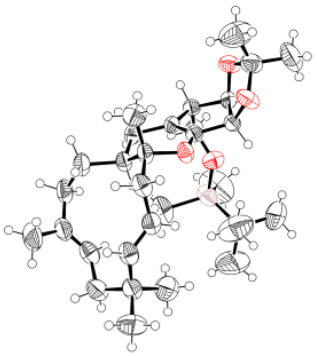
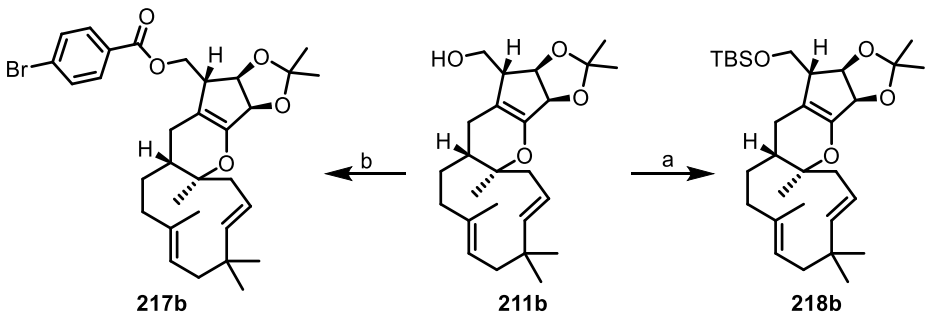


Figure 3.5: X-ray structure of **218a**

The same derivatizations were also conducted for the diastereoisomer **211b** (**211b**: R_f= 0.55, ethyl acetate/petroleum ether = 1/1) to generate **217b** and **218b** (Scheme 3.16). It was expected to pursue the same strategy as employed for isomer **211a**, namely X-ray crystallographic analysis, to figure out the absolute configuration of **211b**. However, it was unsuccessful to grow any high quality crystals from these two solid derivatives (**217b** and

[77] Deyrup, S. T.; Swenson, D. C.; Gloer, J. B.; Wicklow, D. T. *J. Nat. Prod.*, **2006**, *69* , 608–611.

218b) under various conditions. To be delighted, using NMR-analysis and comparison with the structural data of **211a**, the absolute configuration of compound **211b** could be confirmed as shown in scheme 3.16.



Scheme 3.16: Preparation of **217b** and **218b**. *Reagents and conditions: a) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 3 h, 85%; b) 4-Bromobenzoyl chloride, DMAP, CH_2Cl_2/THF, rt, 48 h, 60%.*

3.5.6 Transition states of the HDA reaction

The stereoselectivity of the hetero Diels-Alder cycloaddition of **213** with α-humulene (**63**) can at best be called to be moderate. According to the most populated two conformers of α-humulene (**63**), the transition states of this hetero-DA reaction were proposed to explain the stereochemical outcomes obtained.

α-Humulene (**63**) consists of an 11-membered ring and contains three nonconjugated C=C double bonds, two of them being triply substituted and one being doubly substituted. As observed by many groups, one of the two triply substituted C=C double bonds is significantly more reactive.[78] According to the calculation experiments by Hermans and co-workers, this peculiar regioselectivity has been explored computationally using various DFT functionals through the conformational space of α-humulene. Four different conformations were identified. Each conformation is chiral and has two enantiomeric forms, yielding a total of eight conformers (Figure 3.6).[79]

[78] Zigon, N.; Hoshino, M.; Yoshioka, S.; Inokuma, Y.; Fujita, M. *Angew. Chem. Int. Ed*. **2015**, *54*, 9033-9037.
[79] a) Shirahama, H.; Osawa, E.; Matsumoto, T. *J. Am. Chem. Soc.* **1980**, *102*, 3208-3213. b) Neuenschwander, U.; Czarniecki, B.; Hermans, I. *J. Org. Chem.* **2012**, *77*, 2865-2869.

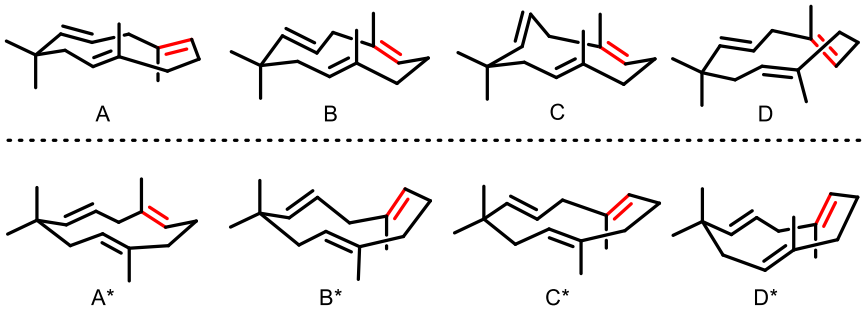


Figure 3.6: Lewis structures of the different humulene conformers

According to the calculation experiments by Hermans and co-workers, conformers A and B contribute nearly equally to the equilibrium population of α-humulene (**63**) conformations, i.e., 42.9% and 45.6% respectively, at room temperature. The temperature dependence of the equilibrium composition is shown in Figure 3.7.

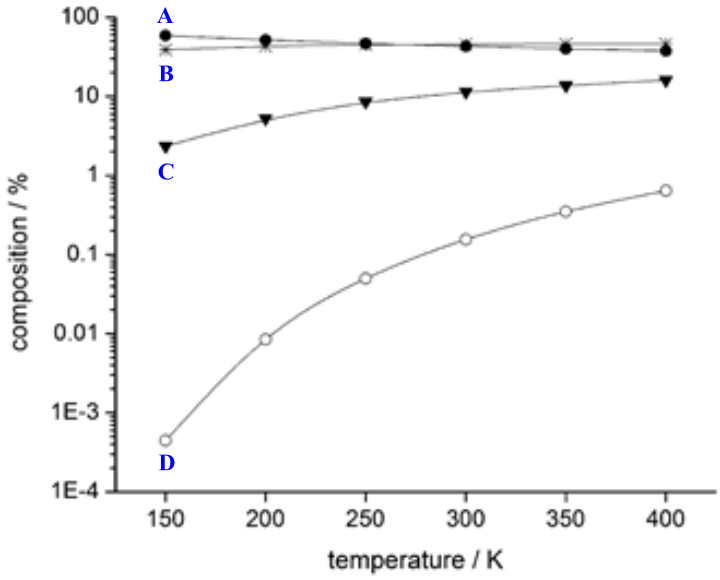


Figure 3.7: Equilibrium composition at different temperature

Therefore, based on Hermans' calculations and the Fujita's X-ray crystallographic studies on the conformation of α-humulene (**63**), the stereochemical outcomes obtained in the Hetero DA reaction of **213** with α-humulene (**63**) can be explained by the transition states as shown in Figure 3.8. The more stable conformer A of **63** is approached by the *Re-face* of vinyl ketone **213** inducing the steric repulsion of the methyl groups in **63** and the TBS group in **213** (TSA), whereas the approach of the *Si-face* of conformer A* is interrupted by the steric hindrance of the methyl groups in **63** and the TBS group in **213** (TSD). Approaching the *Si-face* of the conformer B has the strongest steric hindrance (TSC). Therefore, to avoid the

repulsion, the cycloaddition proceeds mainly via transition state TSB, forming **211a** as the major product.[80]

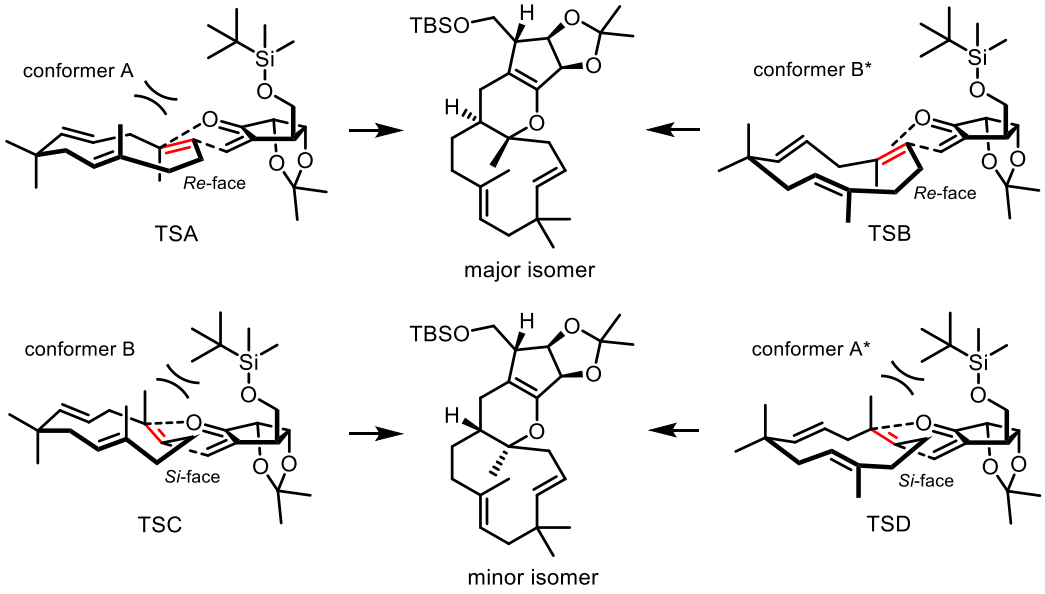
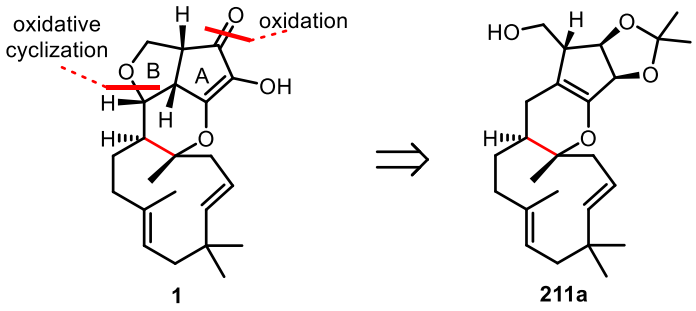


Figure 3.8 Proposed transition states of the HDA reaction of **213** with α-humulene (**63**)

In summary, a concise, regio- and stereoselective synthetic approach to the 5,6,11-tricyclic full carbon skeleton (**221a**) of xenovulene A (**1**) has been successfully developed. Next, the endgame would be the construction of two 5-membered rings (Scheme 3.17), namely the cyclopentanone ring (A ring) and the tetrahydrofuran ring (B ring).

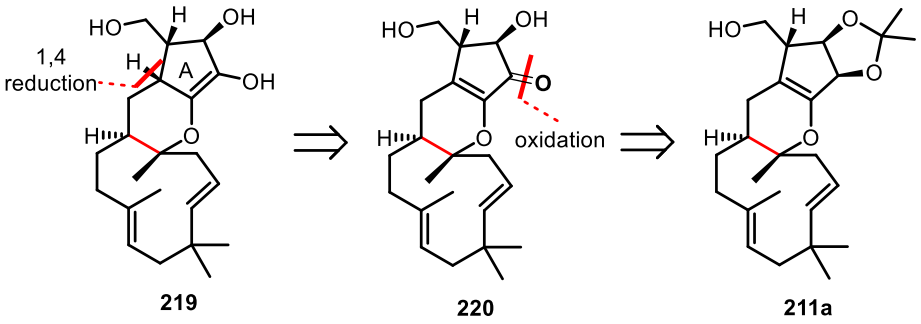


Scheme 3.17: Construction of two 5-membered rings of xenovulene A (**1**)

[80] (a) Takao, K.; Noguchi, S.; Sakamoto, S.; Kimura, M.; Yoshida, K.; Tadano, K. *J. Am. Chem. Soc.* **2015**, *137*, 15971-15977. (b) (d) Lam, H. C.; Spence, J. T. J.; George, J. H. *Angew. Chem. Int. Ed*. **2016**, *55*, 10368-10371.

3.5.7 Construction of the cyclopentenone ring

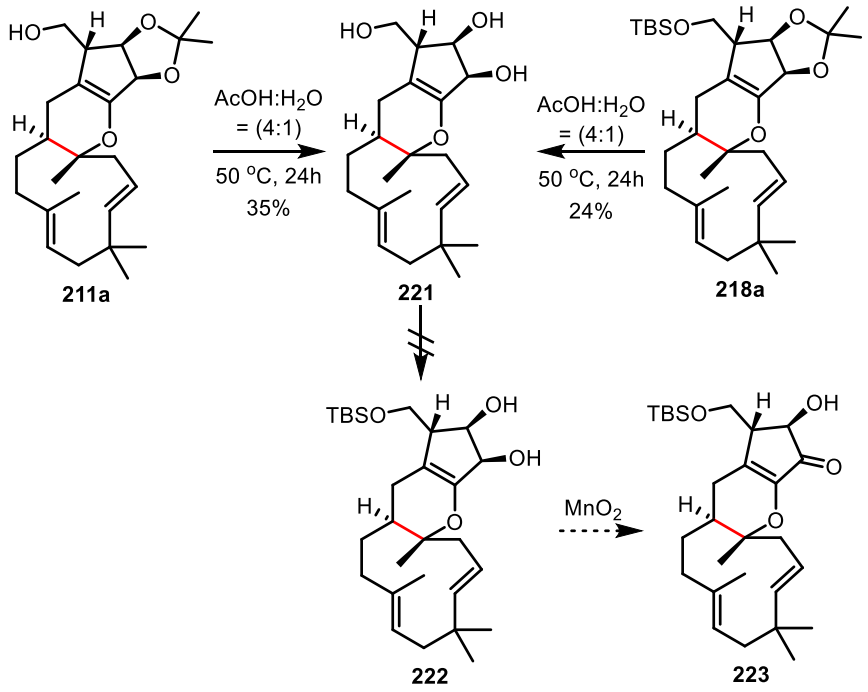
With the advanced intermediate **211a** in hand, in turn, the attention was turned to the construction of the cyclopentenone ring (**A** ring) of xenovulene A. The first retrosynthetic analysis of the cyclopentenone ring in xenovulene A is shown in Scheme 3.18. It was planned that the cyclopentenone ring could be installed through selective 1,4 reduction of enone **220**, which in turn could be generated by the removal of acetonide of **221a** followed by selective oxidation of the allylic hydroxyl group of the *sec*-1,2-diol.



Scheme 3.18: Retrosynthetic analysis of the cyclopentenone ring

3.5.7.1 Preparation of enone **220**

Initially, the acid catalyzed deprotection of acetonide **211a** to triol **221** was investigated (Scheme 3.19).



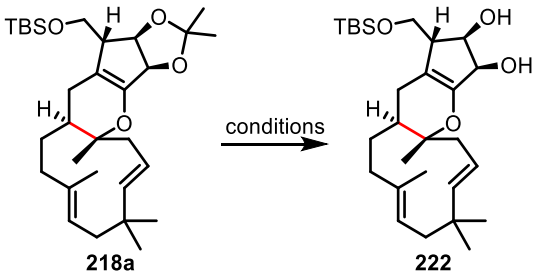
Scheme 3.19: Attempted preparation of 1,4 reduction precursor **223**

Compound **211a** was treated with a 4:1 mixture of acetic acid and water at 50 ^{o}C for 24 h to generate triol **221** in 35% yield. Even though the yield was only moderate, it was found that compound **211a** underwent to complete decomposition under other acidic conditions.[81] In order to perform the selective oxidation of the allylic hydroxyl group of the *sec*-1,2-diol of triol **221**, the protection of the primary hydroxyl group of triol **221** with TBSCl was investigated, however, no desired product was obtained. Due to the difficulties in obtaining TBS ether **222** from triol **221**, compound **218a** was chosen as a surrogate to generate TBS ether **222** after acetonide deprotection.[82]

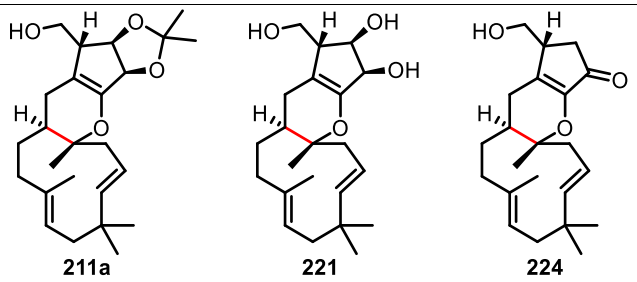
The transformation of TBS-ether **218a** into the diol **222** was investigated with a variety of different acids, some representative results of the screening are listed in Table 3.9. Initially, compound **218a** was treated with a 4:1 mixture of acetic acid and water at room temperature for few hours. Unfortunately, no desired product was obtained. After heating the mixture for 8 hours afforded desilylated alcohol **211a** in moderate yield (entry 1). Prolonged reaction times generated the triol **221** in 24% yield via the desilylation followed by acetonide deprotection (entry 2). Decreasing of the amount of acetic acid or lowering the reaction temperature did not result in an appreciable degree of conversion (entries 3 and 4). Stronger acidic condition such as TFA resulted in decomposition (entries 5-7). Interestingly, enone **224** was obtained in 59% yield when compound **218a** was treated with concentrated hydrochloric acid in THF at 50°C for 5 h or at room temperature for 24h (entries 8 and 9). Surprisingly, there was no conversion observed when compound **218a** was treated with chloric acid in methanol at room temperature for 24 h (entry 10). Lewis acids like $AlCl_3$ led to decomposition of compound **218a** (entry 11).[83]

[81] (a) Sung, W. L. *J. Org. Chem.*, **1982**, *47*, 3623-3628. (b) Wang, P.; Agrofoglio, L. A.; Newton, M. G.; Chu, C. K. *J. Org. Chem.*, **1999**, *64*, 4173–4178. (c) Wang, Q.; Sasaki, N. A. *J. Org. Chem.*, **2004**, *69*, 4767–4773.
[82] (a) King, S. M.; Calandra, N. A.; Herzon, S. B. *Angew. Chem. Int. Ed*., **2013**, *52*, 3642 –3645. (b) Nakao, M.; Tanaka, K.; Kitaike, S.; Sano, S. *Synthesis*, **2017**, *49*, 3654-3661.
[83] see ref. 80 and 81.

Table 3.9: Removal of acetonide of **218a**



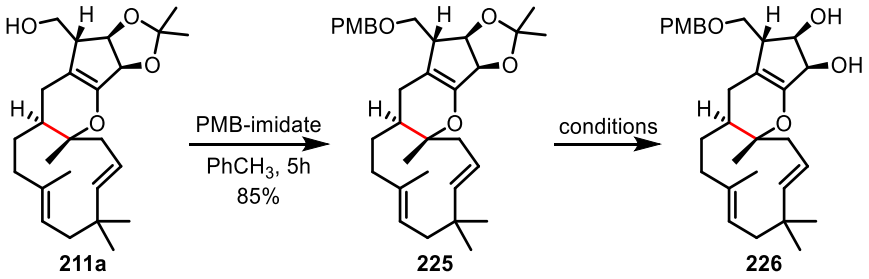
entry	reagent	conditions[a]	result[b]
1	AcOH : H_2O (4:1)	50 °C, 8h	50% (**211a**)
2	AcOH : H_2O (4:1)	50 °C, 24h	24% (**221**)
3	AcOH : H_2O (1:1)	0 °C, 24h	no reaction
4	AcOH : H_2O (1:1)	rt, 24h	no reaction
5	TFA : H_2O (2:1)	50 °C, 1h	decomposition
6	TFA : H_2O (2:1)	0 °C, 1h	decomposition
7	TsOH (1.5 eq.)	THF, rt, 16h	decomposition
8	HCl : THF (1:1)	50 °C, 5h	59% (**224**)
9	HCl (conc.)	THF, rt, 24h	65% (**224**)
10	2N HCl : MeOH (1:1)	rt, 24h	no reaction
11	$AlCl_3$ (1.5 eq.)	toluene, rt, 12h	decomposition



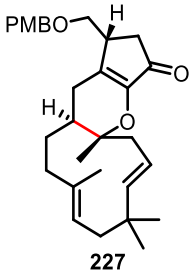
Because of the instability of the TBS protecting group under the employed acidic conditions, the PMB ether **225** was chosen as a surrogate for the next acetonide deprotection. The PMB protection of the **211a** with 4-methoxybenzyl-2,2,2-trichloroacetimidate (PMB-imidate)

afforded PMB ether **225** in 85% yield.[84] The next step, the acetonide deprotection of PMB ether **225** turned out to be a major hurdle. Some representative results of the validation are shown in Table 3.10.

Table 3.10: Removal of acetonide of **225**



entry	reagent	conditions[a]	result[b]
1	AcOH : H_2O (4:1)	50 °C, 24h	complex mixture
2	AcOH : H_2O (1:1)	50 °C, 24h	complex mixture
3	2N HCl : MeOH (1:1)	rt, 48h	no reaction
4	1N HCl : THF (1:1),	50 °C, 5h	67% (**227**)
5	HCl (conc.)	THF, 50°C, 24h	65% (**227**)
6	$AlCl_3$ (1.5 eq.)	toluene, rt, 12h	decomposition

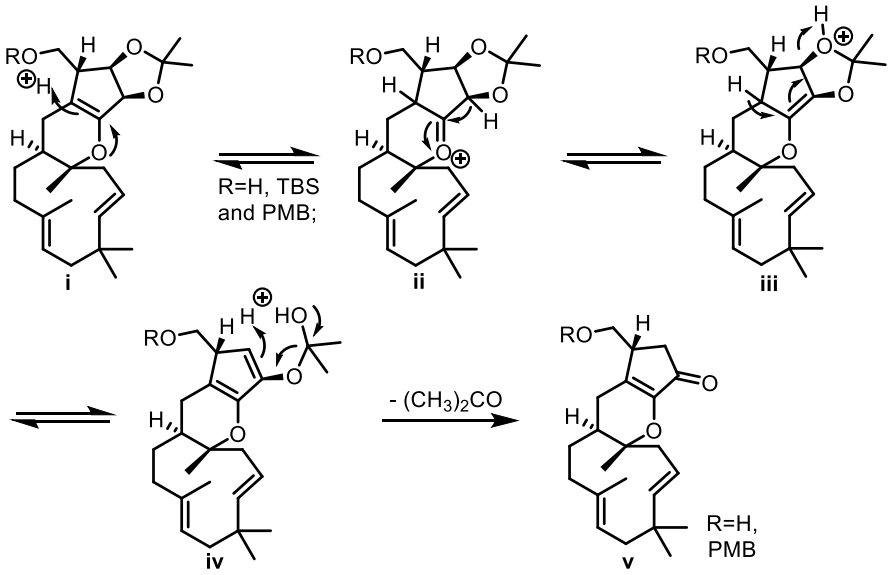


Treating PMB-ether **225** with differently concentrated solution of aqueous acetic acid at 50 °C for 24 h led to an inseparable complex mixture (entries 1 and 2). No conversion was observed when PMB-ether **225** was treated with a mixture of aqueous hydrochloric acid (HCl) and methanol at room temperature for 48 h (entry 3). Unexpectedly, treatment of PMB-ether **225** with 1 N solution of aqueous HCl or concentrated HCl in THF at 50 °C for 24 h afforded

[84] (a) Morra, N. A.; Pegenkopf, B. I. *Tetrahedron*, **2013**, *69*, 8632-8644. (b) Geist, E. PhD Thesis, **2017**.

enone **227** likely through an acid-catalyzed acetonide rearrangement in 67% and 65% yield, respectively (entries 4 and 5). Lewis acids like $AlCl_3$ led to decomposition (entry 6).

A plausible mechanism for this unique transformation is summarized in Scheme 3.20. Supported by the oxygen atom that neighbors the acetonide ring, proton-mediated migration of the tetrasubstituted olefin in compound (**i**) gives rise to enol ether (**ii**). Further protonation and opening of the 1,3-dioxolan ring leads to diene (**iv**), which collapses with loss of an acetone to yield enone (**v**).

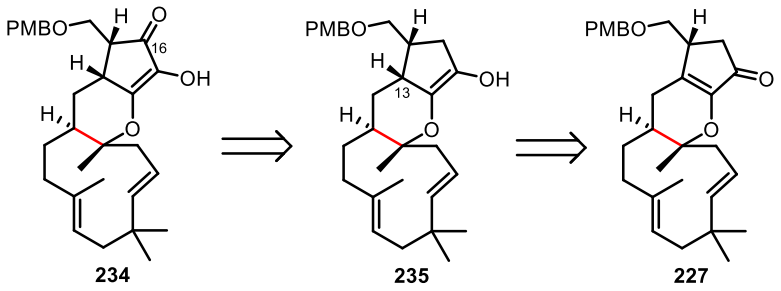


Scheme 3.19: Proposed mechanism of the acetonide rearrangement

The acid-catalyzed rearrangement of acetonides **211a**, **218a** and **225** provided enones **224** and **227**, respectively. This transformation was not initially expected, but to be delighted, it would provide a plausible pathway to the synthesis of sterhirsutins A (**33**) and B (**34**).

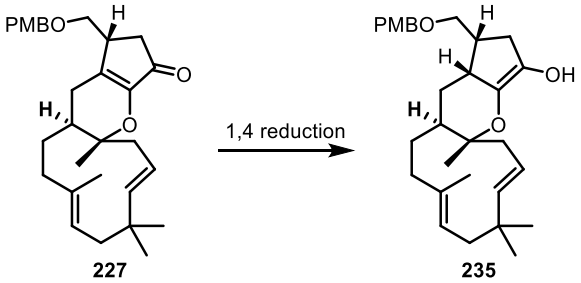
3.5.7.2 1,4-Reduction of enone **227**

Because of the difficulties to synthesize advanced intermediate **222** or **226**, a new approach to the cyclopentenone ring in xenovulene A from enone **227** was proposed. As shown in Scheme 3.21, the cyclopentenone could be installed by 1,4-reduction of **227** followed by allylic oxidation at C-16 position.



Scheme 3.21: Retrosynthetic analysis of the cyclopentenone ring in **234**

Table 3.11: 1,4-reduction of enone **227**



entry	reagent	condition[a]	result[b]
1	$[(Ph_3P)CuH]_6$ (0.4 eq.),Me_3SiCl (3 eq.)	C_6H_6, rt,	-
2	$[(Ph_3P)CuH]_6$ (1 eq.)	C_6H_6, rt,	-
3	Ph_2SiH_2 (1.2 eq.), $ZnCl_2$ (0.2 eq.), $Pd(PPh_3)_4$ (0.1 eq.),	$CHCl_3$, rt, 48h	decomposition
4	L-selectride (1 eq.)	THF, -78 ^oC, 2h	no reaction

Stryker and co-workers described that the remarkable tendency of the phosphine stabilized hexamer, $[(Ph_3P)CuH]_6$, to effect highly regioselective conjugate reductions of various carbonyl derivatives, including unsaturated ketones, esters and aldehydes.[85] Therefore the reduction of enone **227** was initially carried out under the Stryker conditions (entries 1 and 2). Unfortunately, no desired product was obtained. And a three-component system comprised of a soluble palladium catalyst, silicon hydride and zinc chloride was tried for the conjugate

[85] (a) Mahoney, W.S.; Brestensky, D.M.; Stryker, J.M. *J. Am. Chem. Soc*., **1988**, *110*, 291–293. (b) Pelss, A.; Kumpulainen, E. T. T., Koskinen, A. M. *J. Org. Chem*., **2009**, *74*, 7598-7601.

reduction of enone **227**.[86] However, it resulted in the decomposition of starting material (entry 3). Treatment of enone **227** with *l*-selectride (lithium tri-*sec*-butylborohydride) resulted in no conversion (enter 4).[87]

3.5.8 Proposed synthesis of sterhirsutins A and B

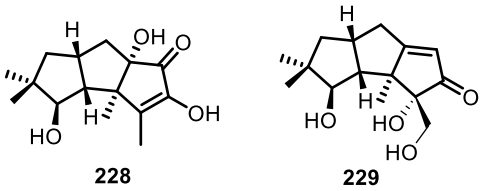
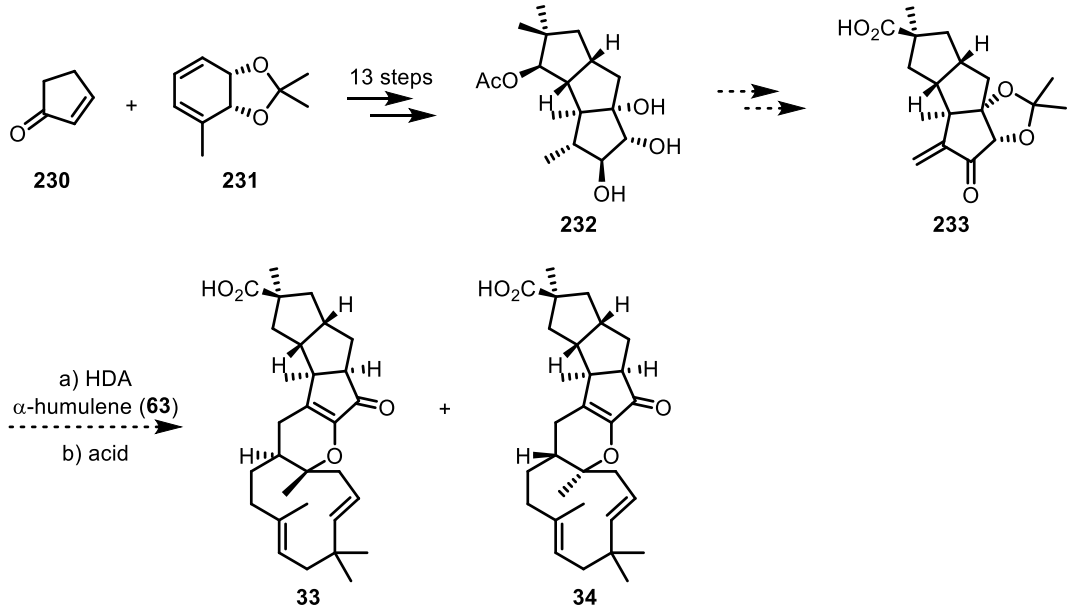


Figure 3.9 Structures of (+)-connatusin A (**228**) and B (**229**)

According to the synthesis of the natural products (+)-connatusin A (**228**) and B (**229**) by Banwell and co-workers in 2011,[88] advanced intermediate **232** can be synthesized from commercially available compounds **230** and **231**. Based on it, a plausible hetero DA approach to sterhirsutins A (**33**) and B (**34**) was proposed (Scheme 3.22).



Scheme 3.22: Proposed synthesis of sterhirsutins A (**33**) and B (**34**)

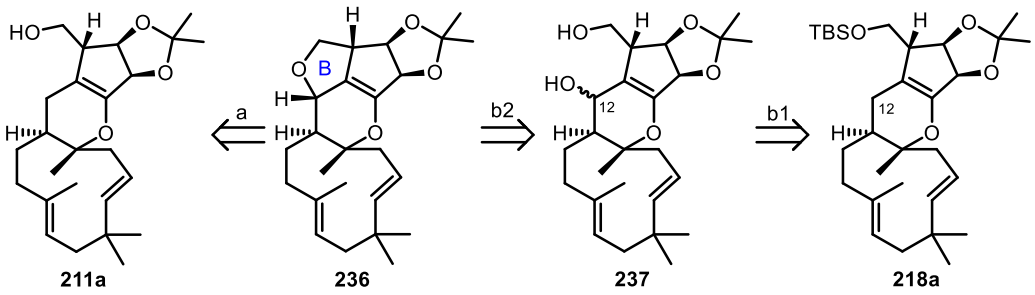
It was expected that vinyl ketone **233** could be established by just few transformations from alcohol **232**. Then, the hetero DA reaction of vinyl ketone **233** with α-humulene (**63**)

[86] (a) Keinan, E.; Greenspoon, N. *J. Am. Chem. Soc.*, **1986**, *108*, 7314–7325. (b) Shvartsbart, A.; Smith, III, A. B. *J. Am. Chem. Soc.*, **2014**, *136*, 870-873.
[87] (a) Miller, S. A.; Chamberlin, A. R. *J. Org. Chem.*, **1989**, *54*, 2502–2504. (b) Knight, S. T.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.*, **1993**, *115*, 9293–9294.
[88] Bon, D. J.-Y.-D.; Banwell, M. G.; Cade, I. A.; Willis, A. C. *Tetrahedron*, **2011**, *67*, 8348-8352.

followed by acid-catalyzed acetonide rearrangement could generate sterhirsutins A (**33**) and B (**34**).[89]

3.5.9 Construction of the tetrahydrofuran ring

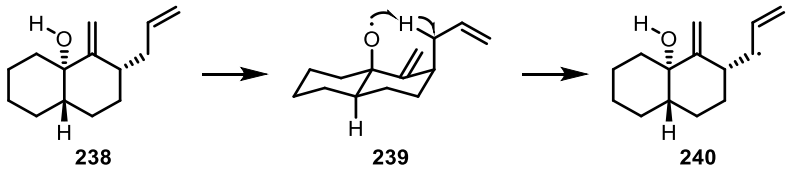
With advanced intermediates **211a** and **218a** in hand, on the one hand, the construction of the cyclohexanone ring of **1** was investigated. On the other hand, the formation of the THF ring of **1** was also investigated. As shown in Scheme 3.23, it was expected that the THF ring (B ring) in **236** could be constructed by two strategies: a) direct formation of the THF ring by an alkoxy-directed oxidative radical cyclization; b) allylic (C-12) functionalization followed by intramolecular ring closure.



Scheme 3.23: Retrosynthetic analysis for the THF ring in **236**

3.5.9.1 The THF ring formation via oxidative cyclization

Pattenden and co-workers found that γ-hydrogen abstraction of alcohol **238** could occur under the Suarez conditions to generate intermediate **240** involving the oxy-centered radical intermediate **239** and the side chain allylic hydrogen atoms (Scheme 3.24).[90]

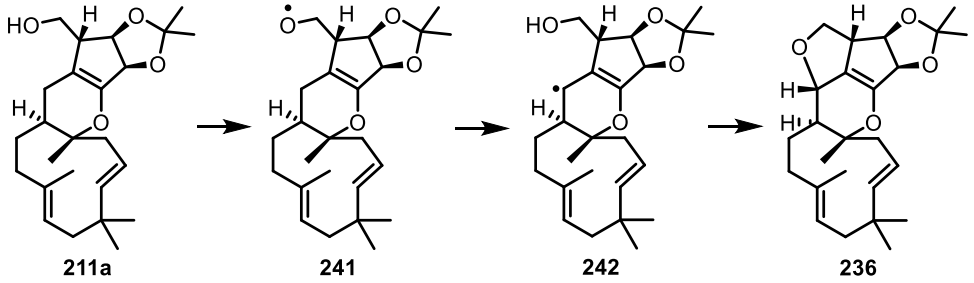


Scheme 3.24: Hydrogen abstraction of **238**

Therefore it was expected that the direct conversion of alcohol **211a** to **236** via alkoxy-directed cyclization would be possible (Scheme 3.25). For example, Treatment of 211a with I_2 and $PhI(OAc)_2$ under the irradiation conditions would generate oxy-radial **241**, which

[89] Li, P.-J.; Draeger, G.; Kirschning, A. *Org. Lett*., **2019**, *21*, 998-1001.
[90] (a) Mowbray, CE.; Pattenden, G. *Tetrahedron Lett*., **1993**, *34*, 127-130. (b) Boto, A.; Hernandez, R.; Velazquez, S. M.; Suarez, E. *J. Org. Chem*., **1998**, *63*, 14, 4697-4705. (c) Ravindar, K.; Reddy, M. S.; Lindqvist, L.; Pelletier, J.; Deslongchamps, P. *J. Org. Chem*., **2011**, *76*, 1269-1284.

undergoes an intramolecular abstraction of the allylic hydrogen and subsequent cyclization to generate the pentacyclic intermediate **236**.



Scheme 3.25: Proposed mechanism for the alkoxy-directed THF ring formation

The attempted oxidative cyclization of alcohol **221a** to pentacyclic intermediate **236** is shown in Table 3.12. Initially, the cyclization was carried out under Suarez oxidation conditions. However, instead of THF ring formation, only decomposition was observed (entries 1-3).[91]

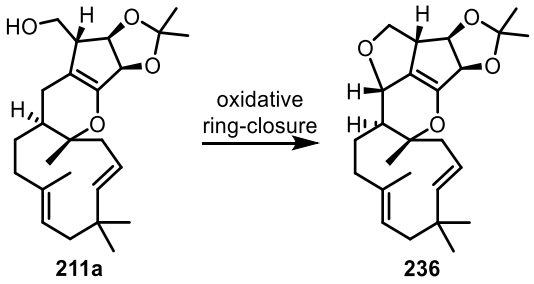


Table 3.12: Oxidative ring-closing of **211a**

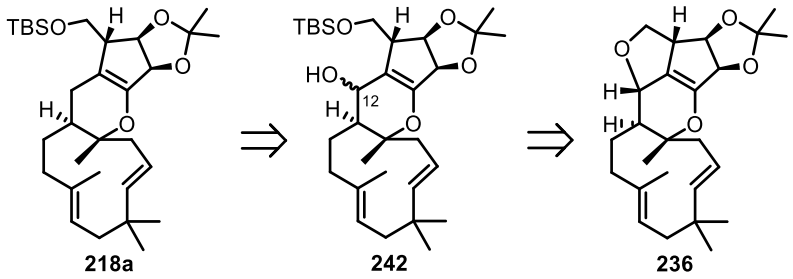
entry	reagents	conditions[a]	result[b]
1	$PhI(OAc)_2$ (1.2 eq.), I_2 (0.4 eq.)	cyclohexane, hν, 50 °C, 1h	decomposition
2	$PhI(OAc)_2$ (3 eq.), I_2 (1 eq.)	cyclohexane, hν, 50 °C, 1h	decomposition
3	$PhI(OAc)_2$ (1 eq.), I_2 (1 eq.)	cyclohexane, hν, 50 °C, 1h	decomposition
4	PhI(OH)OTs (2 eq.), 3 Å MS	CH_3CN, rt, 16h	-
5	$Pb(OAc)_4$ (1 eq.), BPO (1 eq.)	PhH, reflux, 2h	complex mixture
6	$Pd(OAc)_2$(0.2 eq.), BQ(2.2 eq.)	anisole, AcOH, 50 ^oC, 24h	complex mixture

[91] Condakes, M. L.; Hung, K.; Harwood, S. J.; Maimone, T. J. *J. Am. Chem. Soc.* **2017**, *139*, 17783-17786.

Koser's reagent [PhI(OH)OTs] led to either no reaction or decomposition (entry 4).[92] The intramolecular oxidative cyclization of **211a** in the presence of lead tetraacetate and benzoyl peroxide (BPO) was also investigated, but did not yield desired product (entry 5).[93] The palladium-catalyzed allylic acetoxylation to form the THF ring was also investigated,[94] again no desired product was obtained (entry 6). Unfortunately, all attempted cyclization of **211a** to intermediate **236** failed, presumably due to the high ring strain of the pentacyclic system.

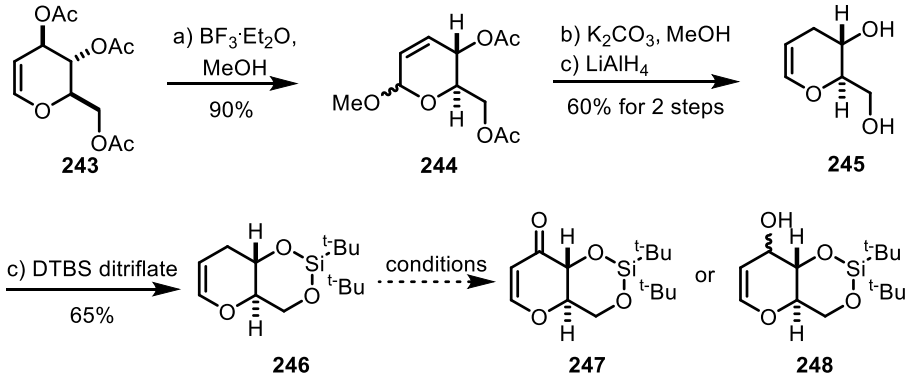
3.5.9.2 The THF ring formation via allylic oxidation

Due to the difficulties in the direct oxidative THF ring formation of **211a**, the two-step approach to **236** via a selective allylic (C-12) oxidation of **218a** followed by intramolecular ring closure was planned next (Scheme 3.26).



Scheme 3.26: Selective allylic oxidation followed by ring closure

Initially, a model 3,4-dihydro-2H-pyran **246** was prepared to figure out the most suitable allylic oxidation conditions. The model compound 3,4-dihydro-2H-pyran **246** was prepared from glucal derivative **243** (Scheme 3.27).



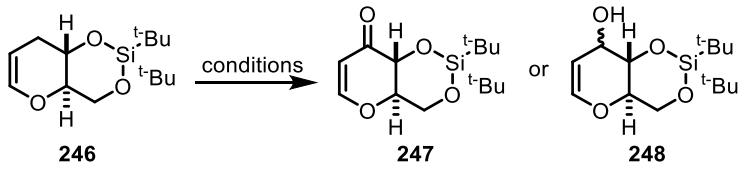
Scheme 3.27: Synthesis of model compound **246**

[92] (a) Kirschning, A. *Eur. J. Org. Chem*., **1998**, 2267-2274; (b) Kirschning, A., Domann, S., Dräger G. et al *Synlett*., **1995**, 767-769; (c) Kirschning, A. *J. Org. Chem*., **1995**, *60*, 1228-1232.
[93] Heusler, K.; Kalvoda, J. *Angew. Chem. Int. Ed*. **1964**, *3*, 525-596.
[94] Wilde, N. C.; Isomura, M.; Mendoza, A.; Baran, P. S. *J. Am. Chem. Soc.*, **2014**, *136*, 4909–4912.

Ferrier rearrangement of glucal **243** with methanol provided the 2,3-unsaturated glycoside **244** in 90% yield. Deprotection of the acetyl groups followed by subjecting to $LiAlH_4$ under reflux conditions afforded the 3-deoxyglucal **245**, which was treated with *di-tert*-butylsilyl bis(trifluoromethanesulfonate)benzylated (DTBS ditriflate) to afford the required 3,4-dihydro-2H-pyran **246** in 65% yield.[95]

With the 3,4-dihydro-2H-pyran **246** in hand, the allylic oxidation was investigated with a variety of oxidizing reagents as shown in Table 3.13. Unfortunately, in all cases no desired product was obtained. [96]

Table 3.13: Allylic oxidation of **246**



246 **247** **248**

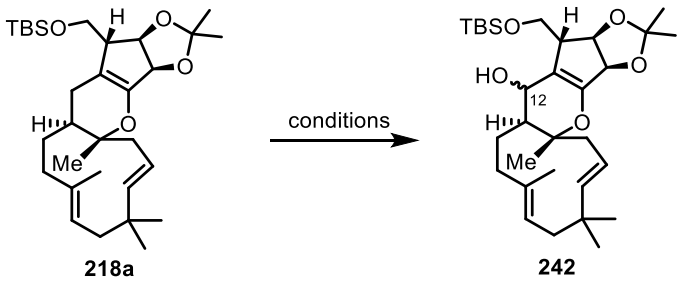
entry	reagent	condition[a]	result[b]
1	SeO_2 (0.5 eq.), *t*-BuO_2H (1.2 eq.)	CH_2Cl_2, rt, 16h	decomposition
2	SeO_2 (3 eq.)	CH_2Cl_2, reflux, 16h	decomposition
3	PhI(OH)OTs (1.2 eq.), 3 Å MS	CH_3CN, rt, 16h	decomposition
4	$PhI(OAc)_2$ (1.2 eq.), *p*-TsOH (1.2 eq.), 3 Å MS	CH_3CN, rt, 16h	decomposition
6	$Pd(OH)_2$/C (0.1eq.), Cs_2CO_3(5 eq.), *t*-BuO_2H (5 eq.)	CH_2Cl_2, rt, 3d	no reaction

Even though the attempted allylic oxidation of **246** failed, various oxidation conditions for the allylic oxidation at the C-12 position of TBS-ether **218a** were investigated and some representative examples are shown in Table 3.14.

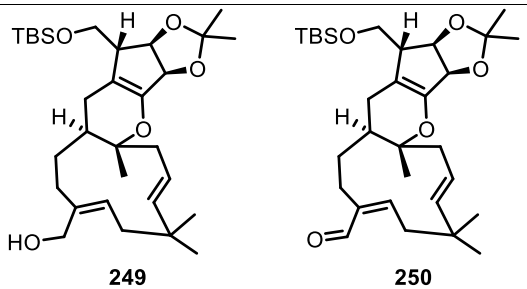
[95] (a) Clark, J. S.; Romiti, F.; Sieng, B.; Paterson, L. C.; Stewart, A.; Chaudhury, S.; Thomas, L. H. *Org. Lett.*, **2015**, *17*, 4694–4697. (b) Reddy, G. M.; Rao, B. U. M.; Sridhar, P. R. *J. Org. Chem.*, **2016**, *81*, 2782–2793.

[96] (a) Reley, H. L.; Morley, J. F.; Friend, N. A. *J. Chem. Soc*., **1932**, 1875-1883. (b) Corey, E. J.; Wu, L. I. *J. Am. Chem. Soc.*, **2014**, *136*, 4909–4912. (c) Kirschning, A. *J. Org. Chem.*, **1995**, *60*, 1228-1232.

Table 3.14: Selective allylic oxidation of **218a**



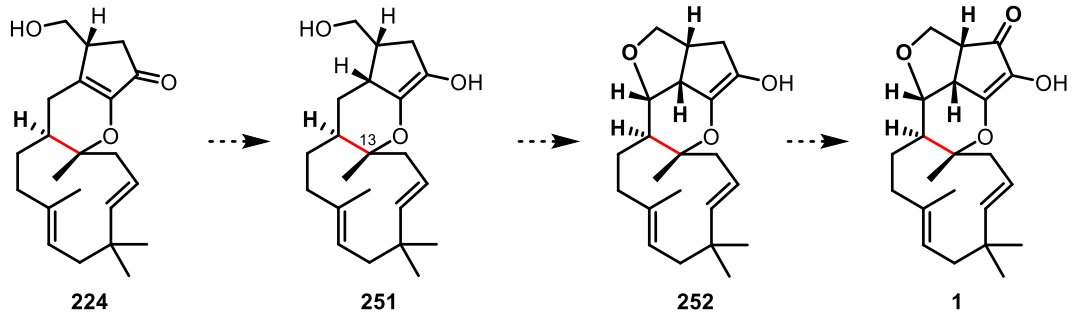
entry	reagent	condition	result
1	SeO_2 (0.5 eq.), *t*-BuO_2H in decane (1.5 eq.)	CH_2Cl_2, rt, 5h	21% **249** 30% **250**
2	SeO_2 (0.5 eq.), *t*-BuO_2H in water (1.5 eq.)	CH_2Cl_2, rt, 24h	16% **249** 20% **250**
3	SeO_2 (3 eq.)	CH_2Cl_2, reflux, 16h	decomposition
4	PhI(OH)OTs (1.2 eq.), 3 Å MS	CH_3CN, rt, 16h	complex mixture
5	$PhI(OAc)_2$ (1.2 eq.), *p*-TsOH (1.2 eq.), 3 Å MS	CH_3CN, 16h	complex mixture
6	$Pd(OH)_2$/C(0.1eq.), Cs_2CO_3 (5 eq.), *t*-BuO_2H in decane (5eq.)	CH_2Cl_2, rt, 3d	no reaction
7	$Pd(OH)_2$/C(0.1eq.), $CaCO_3$ (5 eq.), *t*-BuO_2H in decane(5eq.)	CH_2Cl_2, rt, 3d	no reaction
8	$Pd(OAc)_2$ (0.2 eq.), BQ (2.2 eq.),	AcOH, reflux, 24h	decomposition
9	LOX (5 mol %), CLA (1.2 eq)	acetone, 50 ^oC, 3d	**249**



Initial experiments were carried out under Riley selenium dioxide oxidation conditions (entries 1 and 2).[97] Surprisingly, two allylic oxidation byproducts **249** and **250** were formed in moderate yield. It is the fact that two allylic methyl groups in α-humulene (**63**) are the most reactive allylic positions. Treating **218a** with 3 equivalents of SeO_2 led to decomposition (entry 3). Hypervalent iodine reagents, such as Koser's reagent [PhI(OH)OTs] and $PhI(OAc)_2$, resulted in an inseparable complex mixture (entries 4 and 5). No reaction was observed when **218a** was treated with palladium catalysts (entries 6 and 7).[98] Akermark and Backvall developed Pd-catalyzed allylic acetoxylation was also employed to the allylic oxidation of **218a** (entry 8),[99] unfortunately, all the attempts were unsuccessful, leading to either decomposition or inseparable mixture. In addition, lipoxygenase (LOX) catalyzed oxidation of **218a** in the presence of conjugated linoleic acid (CLA) generated alcohol **249**.

3.5.10 1,4-reduction of enone **224**

Due to the difficulties in selectively allylic oxidation at C-12 position in TBS-ether **218a**, it was speculated that the best way to construct the THF ring in xenovulene A (**1**) would be the alkoxy-directed oxidative cyclization of intermediate **251** which could be synthesized by 1,4-reduction of enone **224**. And the last step would be a second selective allylic oxidation to target xenovulene A (**1**) as shown in Scheme 3.28. Unfortunately, due to the time constrains, this strategy could not be presented in the context of this thesis.

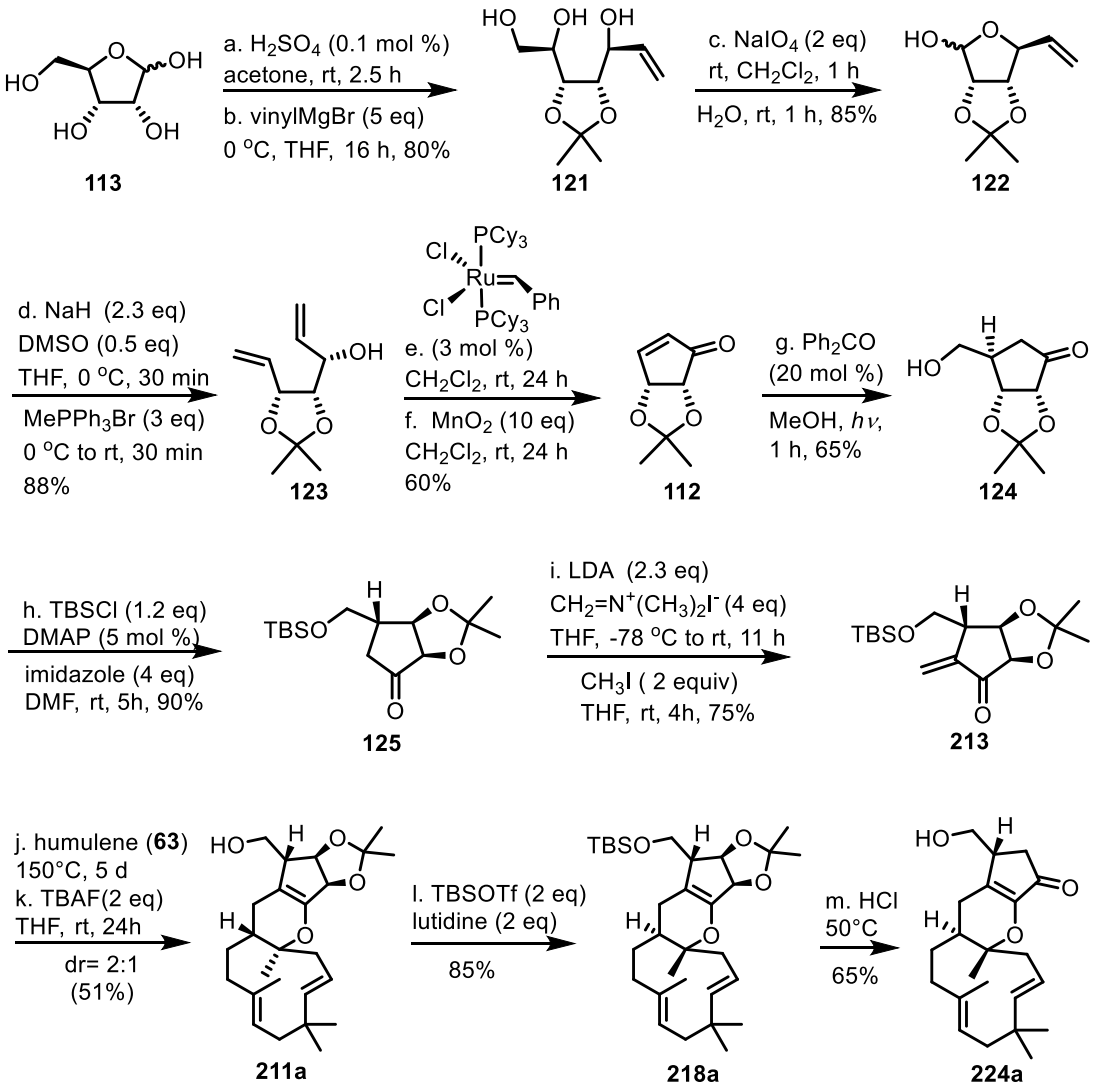


Scheme 3.28: Retrosynthetic analysis of xenovulene A (**1**) from **224**

[97] Ref. 94.
[98] (a) Baggaley, K. H.; Erdtman, H.; Norin, T. *Tetrahedron*, **1968**, *24*, 3399. (b) Brun, P.; Waegell, B. Tetrahedron, 1976, 32, 1137-1141. (c) Dorta, R. L.; Francisco, C. G.; Freire, R.; Suarez, E.´ *Tetrahedron Lett*., **1988**, *29*, 5429-5432. (d) Siler, D. A.; Mighion, J. D.; Sorensen, E. J. *Angew. Chem., Int. Ed.*, **2014**, *53*, 5332-5337. (e) Hung, K.; Condakes, M. L.; Morikawa, T.; Maimone, T. J. *J. Am. Chem. Soc*., **2016**, *138*, 16616-16619.
[99] (a) Encyclopedia of Reagents for Organic Synthesis (Ed.:L.A.Paquette), Wiley, NewYork, 1995. (b) Grennberg, H.; Baeckvall, J.-E. *Chem. Eur. J*., **1998**, *4*, 1083-1089.

3.6 Summary and Outlook

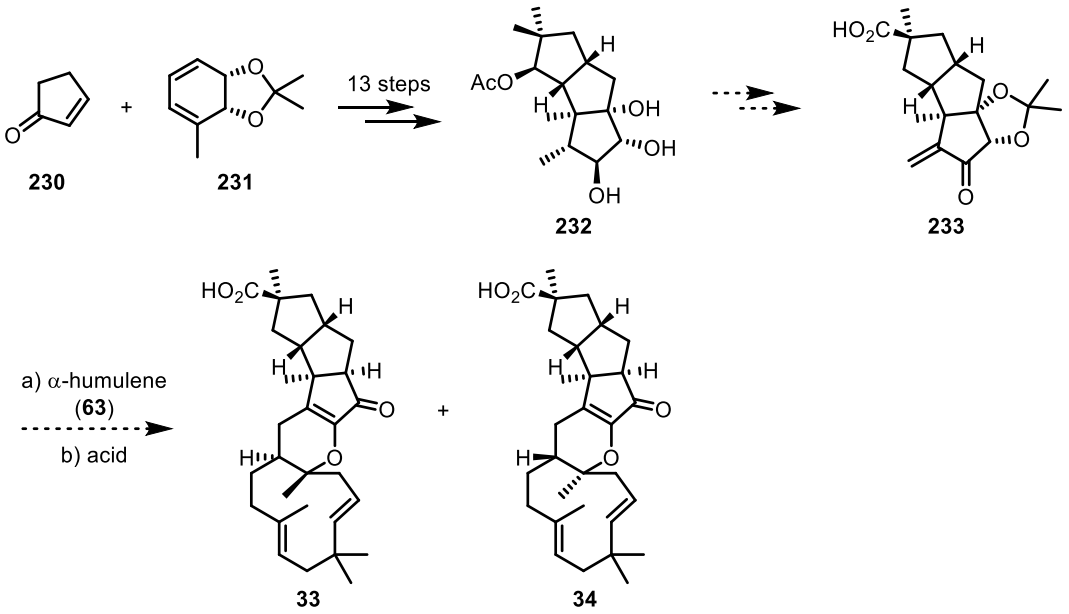
In summary, a regio- and stereoselective synthesis of the complete 5,6,11-tricyclic carbon skeleton of xenovulene A (**1**) was accomplished (Scheme 3.29). The key step was a biomimetic inverse electron demand hetero Diels-Alder cycloaddition (HDA) of α-humulene (**63**) and ribose-derived vinyl ketone (**213**) which was synthesized from D-ribose (**113**) in 10% yield over 11 steps. In addition, the absolute configuration was confirmed by the TBS-protection of diastereoisomer (**211a**), which provided compound (**218a**) as a crystalline solid and permitted X-ray crystallographic analysis.



Scheme 3.29: A hetero-DA approach to complete carbon skeleton of xenovulene A (**1**)

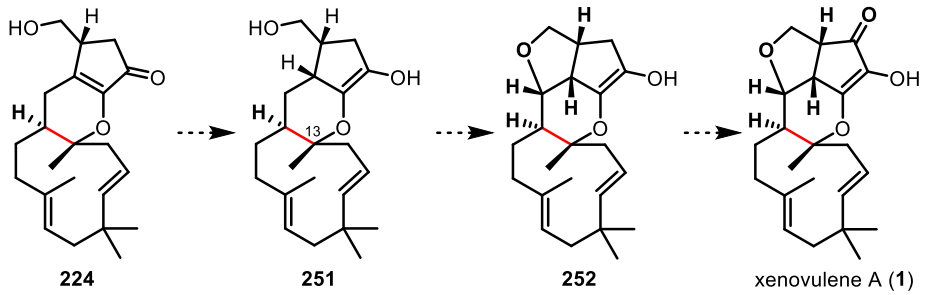
In addition, a novel acid catalyzed rearrangement of 1,3-dioxolane (**xi**) was discovered, demonstrating that Diels-Alder adducts such as **211a** might also be useful for the synthesis of the sterhirsutins A (**33**)and B (**34**). A plausible hetero DA approach to sterhirsutins A (**33**) and B (**34**) was proposed (Scheme 3.30). It was expected that vinyl ketone **233** could be

established through few transformations from compound **232**, which can be synthesized from commercially available **230** and **231**. Then the hetero DA reaction of vinyl ketone **233** with α-humulene (**63**) and followed by acid catalyzed acetonide arrangement could generate sterhirsutins A (**33**) and B (**34**).



Scheme 3.30: A proposed hetero-DA approach to sterhirsutins A (**33**) and B (**34**)

Next, we expected the total synthesis of xenovulene A (**1**) could be achieved from advanced intermediate (**224a**) through a 3-step sequence of 1,4-reduction, and subsequent oxidative radical cyclization followed by selective allylic oxidation (Scheme 3.31).

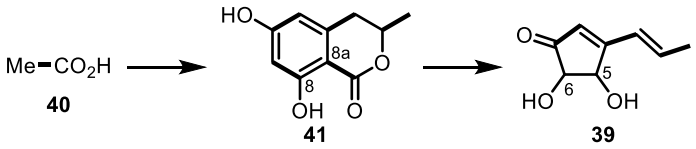


Scheme 3.31: Proposed synthesis of xenovulene A (**1**) from intermediate **224a**

Chapter 4 Model study on the cyclopentenone ring of xenovulene A

4.1. Introduction

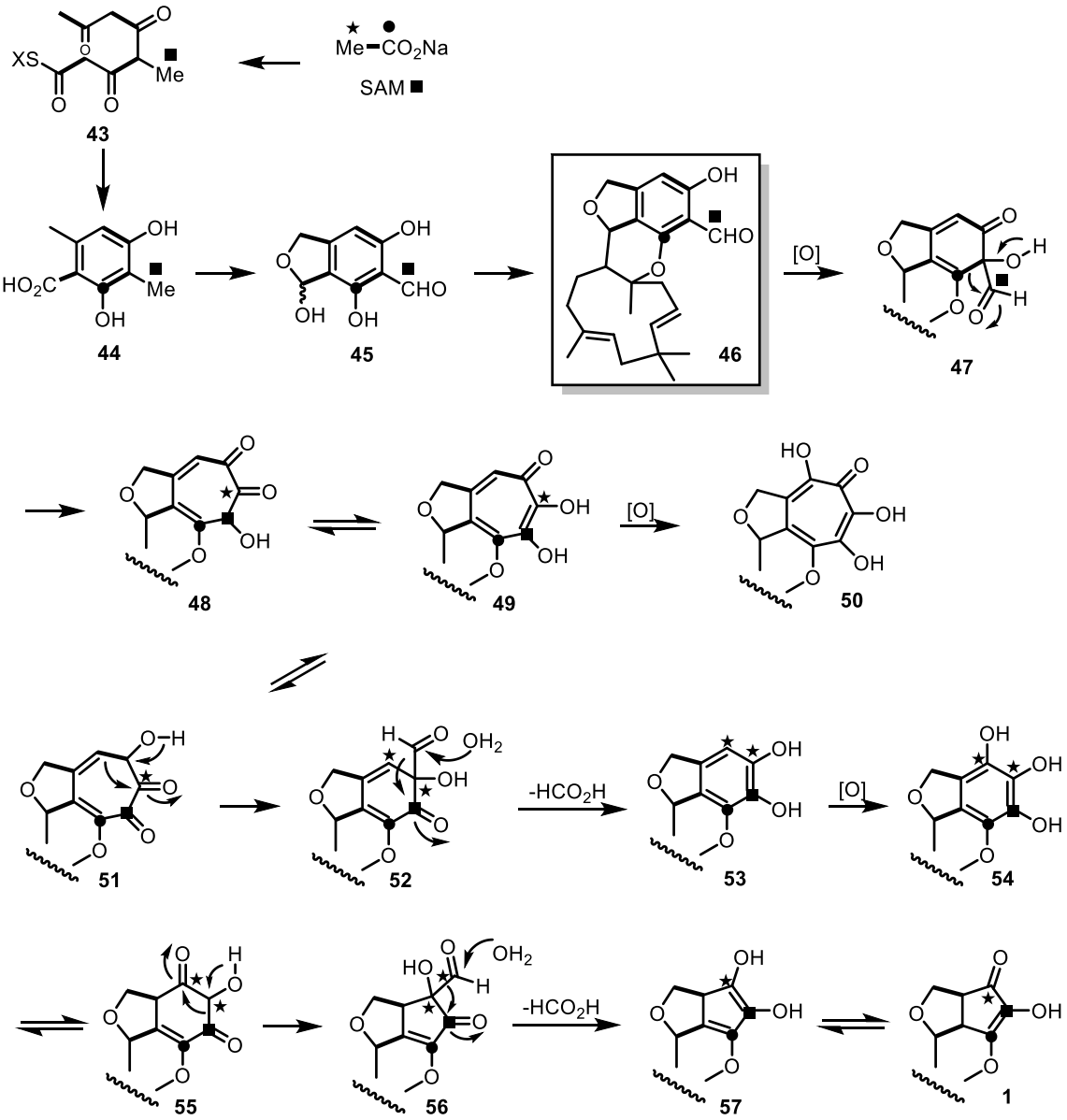
Terrein (**39**) is a plant growth inhibitor and was initially isolated by Hirota and coworkers, which is produced by a *Aspergillus terreus* strain, C-520. Based on incorporation experiments of suitable polyketide precursors, Birch and co-workers suggested that the biosynthesis of terrein involves ring contraction of the six-membered ring of a polyketide intermediate. Staunton and coworkers confirmed this hypothesis by incorporation experiments with the aromatic precursor 3,4-dihydro-6,8-dihydroxy-3-methylisocoumarin (**41**). The labelling pattern they proposed is shown in Scheme 4.1, where the intact acetate units are indicated by a heavy line. From there results they concluded that C-5 and C-6 of terrein are derived from C-8 and C-8a of the intermediate (**41**) by means of a ring contraction.



Scheme 4.1: Proposed biosynthesis of terrain (**39**)

Certainly, it has been successfully proven that cyclopentanone and cyclopentane derivatives can be biosynthesized by the ring contraction of the aromatic precursor. Based on this fact and feeding experiments with labeled precursors, Simpson and co-workers suggested that the cyclopentenone moiety in xenovulene A (**1**) could be formed through a unique pathway in which a phenolic precursor undergoes a ring expansion to a tropolone followed by two successive ring contractions. Consequently, the first plausible biosynthetic pathway to xenovulene A was proposed by Simpson research group as shown in Scheme 4.2.[100]

[100] Ref. 14-16.



Scheme 4.2: Proposed biosynthetic pathway to xenovulene A by Simpson

They proposed that the biosynthetic pathway to xenovulene A could commence via the polyketide-derived 3-methylorsellinic acid **44** which would be converted by standard biosynthetic modifications to lactol **45**. It in turn would react with the C-1 and C-2 double bond of α-humulene, either via a carbocation mediated addition or an inverse hetero Diels-Alder reaction to give the key tetracyclic intermediate **46**. The hydroxylation of **46** would allow ring expansion via an α-ketol rearrangement to give tropolone **48**. After further tautomeric adjustment, tropolone **49** would be converted to trioxygenated benzenoid intermediate **54** through ring contraction followed by decarboxylation. Further oxidation, α-ketol mediated ring contraction and decarboxylation would generate xenovulene A (**1**).

4.2 Project outline

It has been over two decades since xenovulene A was first isolated. However, until now neither a total synthesis nor the elucidation of the biosynthesis of xenovulene A has been reported. In order to confirm the biosynthesis of xenovulene A proposed by the Simpson research group, the biosynthetic route was planned to be established by a biomimetic approach thereby enriching the chemistry of ring expansion and ring contraction chemistry around the tropolone moiety using model compounds. The first goal of this project was synthesis of model compounds **97** or **98** (Figure 4.1).

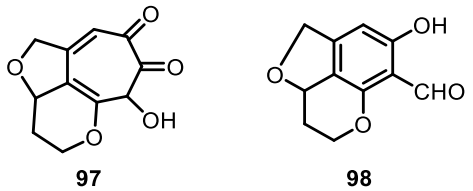
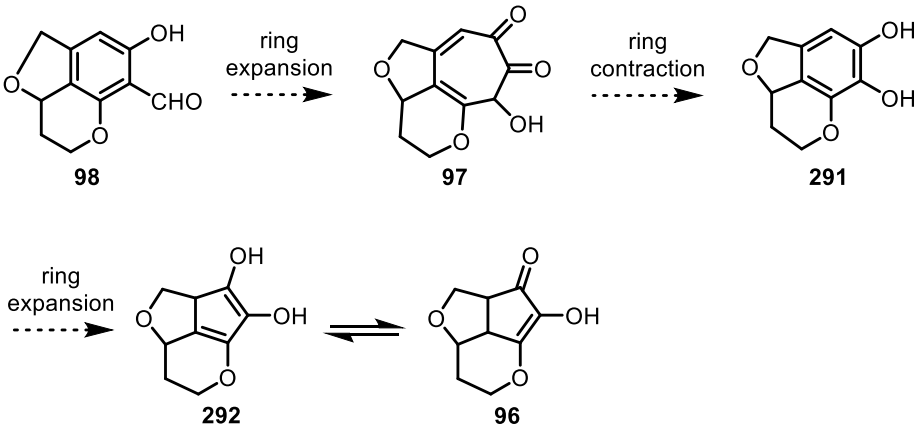


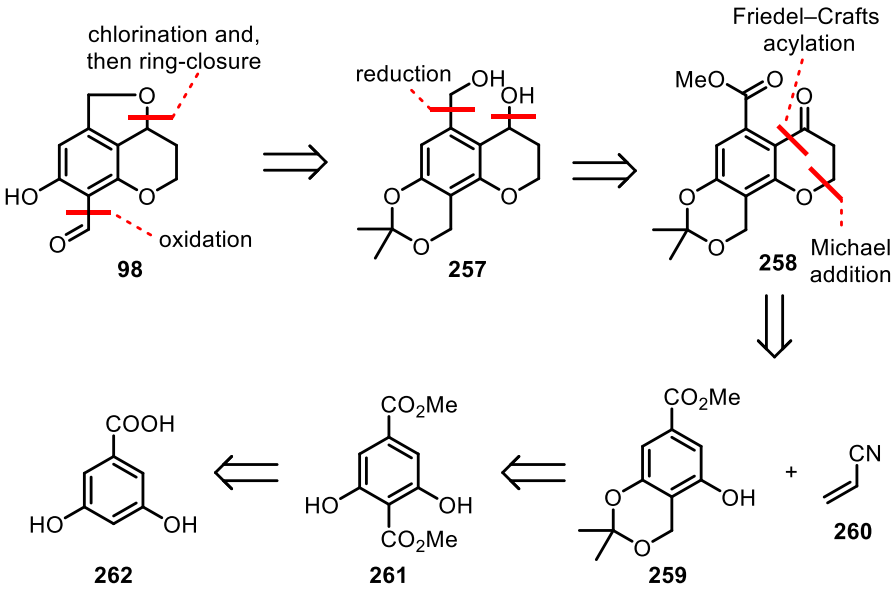
Figure 4.1: Structure of model compounds **97** and **98**

The second goal was study on the biosynthetically construction of cyclopentenone ring of **96** through a unique pathway which involves the phenolic compound (**98**) undergoes ring expansion to a tropolone (**97**) followed by two successive ring contractions. As a collaborative project, this part would be performed by the Cox research group.



4.3 Retrosynthetic Analysis

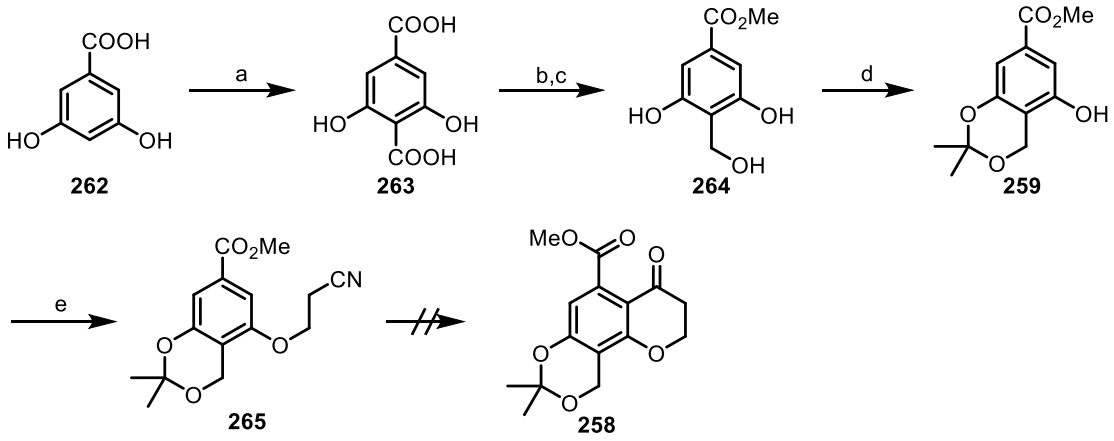
The first retrosynthetic analysis of **98** is shown in Scheme 4.3. It was postulated that the synthesis of **98** involves a late-stage nucleophilic ring-closure to form 2, 5-dihydronfuran followed by deprotection and subsequent oxidation of primary alcohol to aldehyde from diol **257**. In turn **257** could be synthesized from chroman-4-one **258** by a one-pot reduction of both ester and ketone. It was expected to synthesize chroman-4-one **258** through intramolecular Friedel-Crafts acylation of a cyanide intermediate, which would be obtained via *O*-Michael addition of phenol **259** with acrylonitrile (**260**). The preparation of phenol **259** would be achieved by a short sequence of selective reduction of ester **261** followed by protection with acetone. Ester **261** could be prepared through the esterification of 3,5-dihydroxybenzoic acid (**262**).



Scheme 4.3: Retrosynthetic analysis of **98**

4.3.1 Preparation of chroman-4-one **258**

The attempted preparation of chroman-4-one **258** is shown in Scheme 4.4. Carboxylation of 3,5-dihydroxybenzoic acid (**262**) with carbon dioxide gave terephthalic acid **263**, which was then converted to alcohol **264** via methylation followed by reduction. 1,3-Diol protection of **264** with 2,2-dimethoxypropane afforded phenol **259**.[101] *O*-Michael addition of **259** with acrylonitrile formed **265** in high yield. The intramolecular Friedel-Crafts acylation of cyanide intermediate **265** was investigated,[102] unfortunately, no desired product was obtained. We assumed that the aromatic ring system of **265** might be a poor nucleophile because of the electron-withdrawing group. Therefore, instead of using 3,5-dihydroxybenzoic acid (**262**), we decided to use 5-bromobenzene-1,3-diol (**266**) as starting material to synthesize model compound **98**.

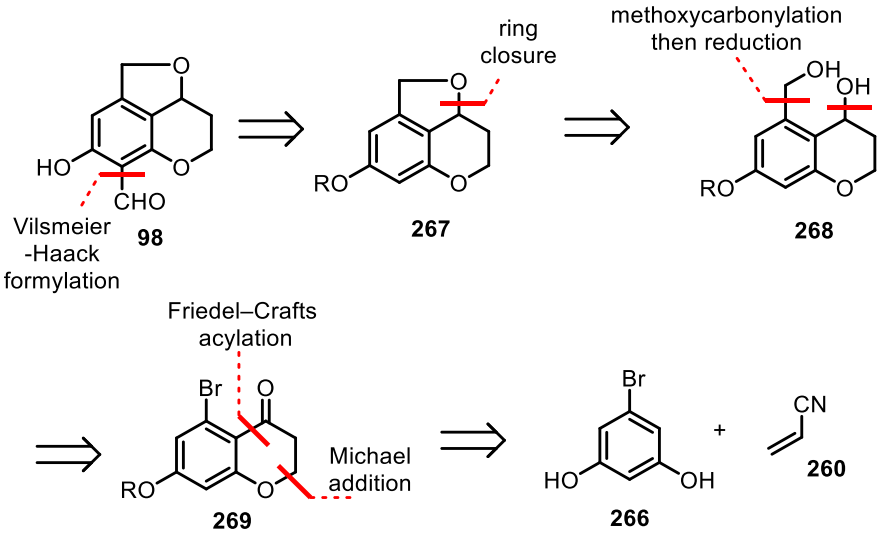


Scheme 4.4: Attempted preparation of chroman-4-one **258**. *Reagents and conditions: a) CO_2, $KHCO_3$, glycerol, 180 ^oC, 4 h, 55%; b) Me_2SO_4, $KHCO_3$, acetone, reflux, 24 h, 90%; c) $NaBH_4$, THF/H_2O, rt, 1 h, 70%; d) 2,2-dimethoxypropane, PTSA, 90%; e) C_2H_3CN, DBU, reflux, 48 h, 90%;*

[101] Sakurai, J.; Kikuchi, T.; Takahashi, O.; Watanabe, K.; Katoh, T. *Eur. J. Org. Chem*. **2011**, 2948–2957.
[102] Tatsuta, K.; Kasai, S.; Amano, Y.; Yamaguchi, T.; Seki, M.; Hosokawa, S. *Chem. Lett*. **2007**, *36*, 1-2.

4.4 Modified Retrosynthetic Analysis

The modified retrosynthetic analysis of **98** started from 5-bromobenzene-1,3-diol (**266**) is shown in Scheme 4.5. It was envisioned that target molecule **98** could be synthesized from **267** via Vilsmeier-Haack formylation, followed by deprotection. In turn **267** would be formed through the nucleophilic ring closure of diol **268**. Methoxycarbonylation of **269** could give a keto-ester, which could be reduced to generate diol **268**. It was expected that the synthesis of chroman-4-one **269** could be achieved by a short sequence of *O*-Michael addition of 5-bromobenzene-1,3-diol (**266**) with acrylonitrile (**260**) followed by intramocular Friedel-Crafts acylation.



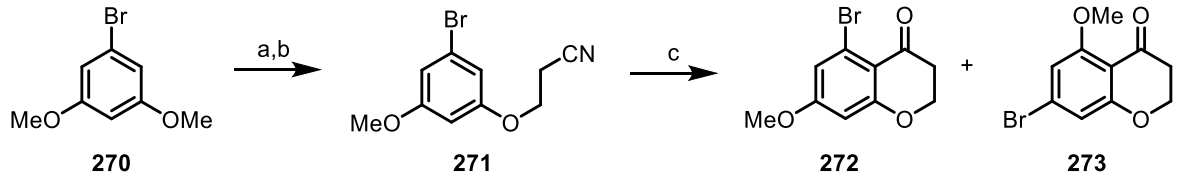
Scheme 4.5: Retrosynthetic analysis of **98**

4.5 Results and Discussion

Due to the high price of 5-bromobenzene-1,3-diol (**266**), the synthesis of target molecule (**98**) started with *O*-demethylation of 1-bromo-3,5-dimethoxybenzene (**270**).

4.5.1 Preparation of chroman-4-one **272**

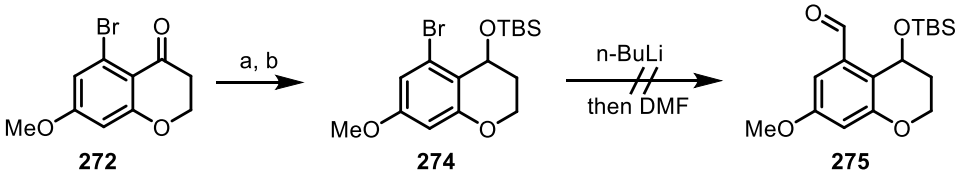
The intermediate **272** was prepared from 1-bromo-3,5-dimethoxybenzene **270** (Scheme 4.6). Demethylation of **270** with BBr_3 provided the 5-methoxyphenol, which underwent Michael addition with acrylonitrile to afford the desired product **271**.[103] Intramolecular Friedel-Crafts acylation of **271** gave the chroman-4-one with 2:1 regioselectivity, favoring the desired product **272**.[104]



Scheme 4.6: Preparation of chroman-4-one **272.** Reagents and conditions*: a) BBr_3, CH_2Cl_2, 0 °C to RT, 24 h, 80%; b) C_2H_3CN, DBU, reflux, 48 h, 76%; c) $AlCl_3$, CH_3NO_2, 60 °C, then H_2O, 56% (**272**) and 25% (**273**);*

4.5.2 Preparation of benzaldehyde **275**

Next, the preparation of benzaldehyde **275** was investigated (Scheme 4.7). Reduction of **272** with $NaBH_4$ gave the target alcohol, which was then protected with TBS group to afford TBS-ether **274** in 94% yield.[105] Unfortunately, attempted formylation of **274** to benzaldehyde **275** failed, presumably due to the high instability of chroman-4-ol.[106]

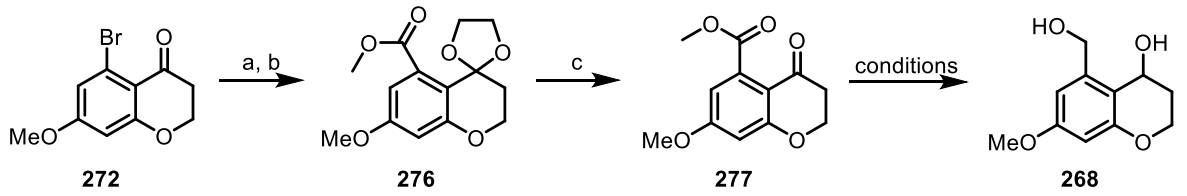


Scheme 4.7: Attempted synthesis of benzaldehyde **275**. *Reagents and conditions: a) $NaBH_4$, EtOH, 0 °C, 1 h, 94%; b) TBSCl, imidazole, DMAP, rt, overnight, 82%;*

[103] Camp, J. E. *Eur. J. Org. Chem*., **2017**, 425–433.
[104] Zhong, Z. L.; Boruta, D. T.; Gauthier, D. R.; Askin, D. *Tetrahedron Lett*., **2011**, 52, 4824-4826.
[105] Van Hoveln, R.; Hudson, B. M.; Wedler, H. B.; Bates, D. M.; Gros, G. L.; Tantillo, D. J.; Schomaker, J. M. *J. Am. Chem. Soc.*, **2015**, *137*, 5346–5354.
[106] Yuen, T.-Y.; Yang, S.-H.; Brimble, M. A. *Angew. Chem. Int. Ed*., **2011**, *50*, 8350 –8353.

Due to the difficulties in formylation of **274**, ester **277** was chosen as a surrogate to generate the desired diol **268**. The preparation of diol **268** started from chroman-4-one **272**. Protection of ketone of **272** with ethylene glycol followed by methoxycarbonylation with chloroformate under strong alkaline conditions gave ester **276** in high yield.[107] Deprotection of ester under acidic conditions afforded keto-ester **277** in 74% yield. Reduction of keto-ester **277** to diol **268** was screened as shown in Table 4.1.[108] Various reducing reagents were tested (entries 1-4), however, only $LiAlH_4$ in a mixed solvent of THF and diethyl ether at -78 ^oC provided a clean reaction and full conversion referred to LCMS results. Unfortunately, the target diol could not be isolated or purified due to its instability during the silica gel column chromatography (entry 5). To be delighted, the target product can be purified through simply washing with petroleum ether at 0^oC (entry 6).

Table 4.1: Reduction of keto-ester **277**; *a) $(CH_2OH)_2$, $HC(OMe)_3$, $PhCH_3$, reflux, 48 h, 83%; b) n-BuLi, $ClCO_2Me$, THF, -78 ^oC to rt, 3 d, 90%; c) HCl, MeOH, rt, 5 h, 74%; g) $LiAlH_4$, ether, -78 ^oC to RT, 1 h, 81%;*



272 **276** **277** **268**

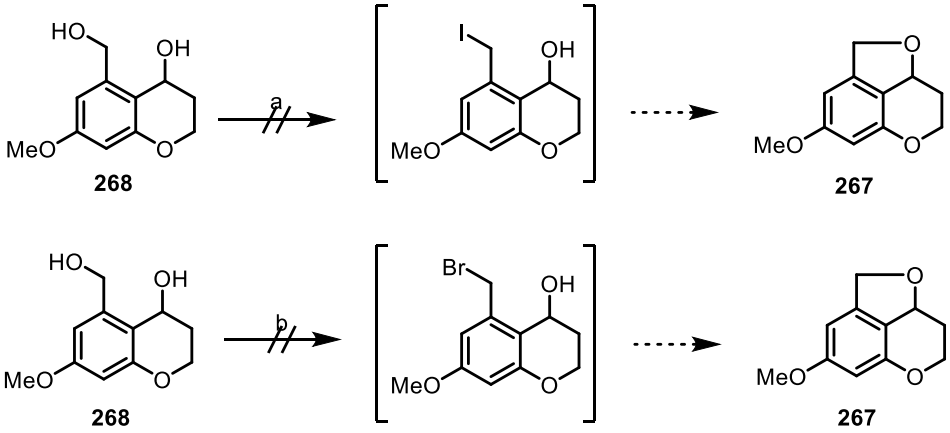
Entry	Reagents	Solvent	Temp.	Time	Result
1	$LiAlH_4$ (1.5 eq.)	THF	-78 ^oC to 25 ^oC	18h	decomposition
2	$LiAlH_4$ (4.0 eq.)	THF	0 ^oC	5h	decomposition
3	$NaBH_4$ (3.0 eq.)	EtOH	25 ^oC	24h	no reaction
4	DIBAL (3.0 eq.)	THF	25 ^oC	24h	no reaction
5	$LiAlH_4$ (4.0 eq.)	THF/Et_2O	-78 ^oC	3h	decomposition[a]
6	$LiAlH_4$ (4.0 eq.)	THF/Et_2O	-78 ^oC	3h	92%

a: Target diol product is unstable in silica gel column.

[107] a) Keisuke, H.; Ohmori, K.; Keisuke, S. *Synlett*., **2005**, *8*, 1311-1315. b) ref. 53.
[108] a) Greco, M. N.; Rasmussen, C. R. *J. Org. Chem.*, **1992**, *57*, 5532–5535. b) Celebuski, J. E.; Chan, C.; Jones, R. A. *J. Org. Chem.*, **1992**, *57*, 5535–5538.

4.5.3 Preparation of tetrahydrofuro-chromene **267**

With diol **268** in hand, the intramolecular nucleophilic cyclization to 2, 5-dihydronfuran **267** was examined (Scheme 4.8). First of all, it was planned to achieve the ring closure through a one-pot and two-step sequence of halogenation of the primary alcohol followed by intramolecular nucleophilic cyclization to form **268**. [109] Unfortunately, the attempted preparation failed. Instead of the desired product, two byproducts of 2*H*-chromene **278** and **279** were obtained respectively via the halogenation of the primary alcohol followed by the elimination of secondary alcohol of **268** (Figure 4.2).



Scheme 4.8: Attempted synthesis of tetrahydrofuro-chromene **267**. *Reagents and conditions: a) TsOH, NaI, CH_2Cl_2, rt; b) NBS, CH_2Cl_2, 0 ^oC to rt;*

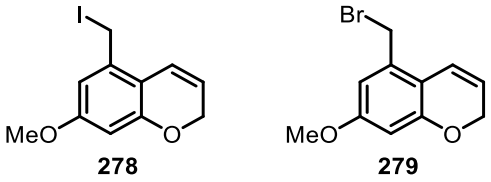
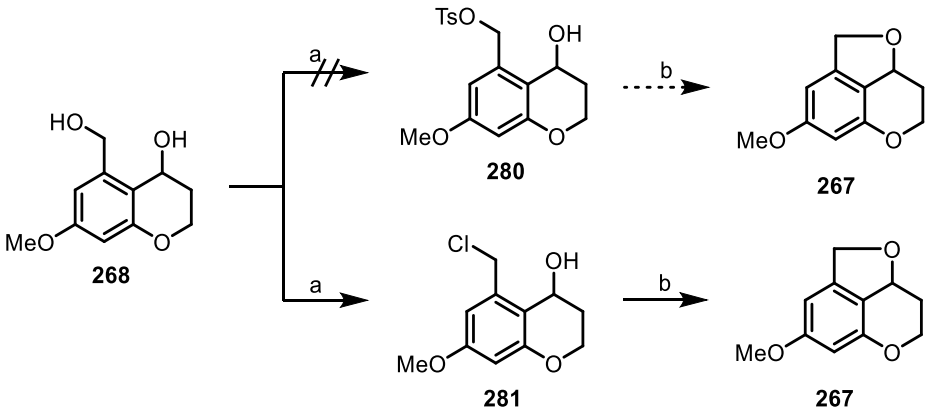


Figure 4.2: Sructures of 2*H*-chromene **278** and **279**

Because of the difficulties to prepare **267** by a direct cyclization of diol **268**, a two-step synthesis was proposed. This includes the conversion the primary alcohol in **268** to a leaving group followed by nucleophilic cyclization under basic conditions. Accordingly, tetrahydrofuro-chromene **267** was successfully prepared (Scheme 4.9). Tosylation of the primary alcohol of diol **268** to **280** was conducted,[110] but quite surprisingly, the chlorinated byproduct **281** was obtained. Even though the tosylated target product **280** was not formed,

[109] a) Arico, F.; Tundo, P.; Maranzana, A.; Tonachini, G. *ChemSusChem*, **2012**, *5*, 1578-1586. b) Rao. D. V.; Stuber, F. A. *Synthesis*, **1983**, 308.
[110] Kim, D.; Ahn, S. K.; Bae, H.; Choi, W. J.; Kim, H. S. *Tetrahedron Lett*., **1997**, *38*, 4437-4440.

fortunately, chloride **281** still could be applied for the subsequent nucleophilic cyclization to generate **267**. Treatment of **281** with sodium hydride in DMF under refluxing conditions for 2 h afforded tetrahydrofuro-chromene **267** in 83% yield.[111]



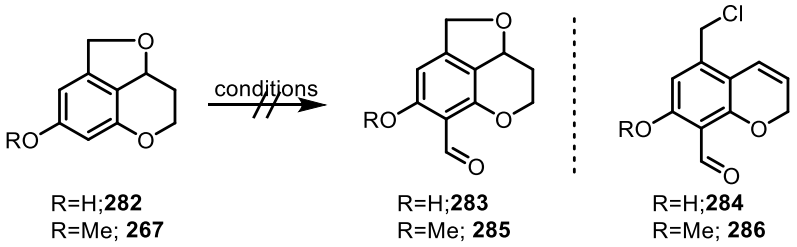
Scheme 4.9: Preparation of tetrahydrofuro-chromene **267**. *Reagents and conditions: a) p-TsCl, Et_3N, DMAP, CH_2Cl_2, 0 ^oC to RT, 4 h, 73%; b) NaH, THF, reflux, 2 h, 83%.*

4.5.4 Formylation and *O*-demethylation

With intermediate **267** in hand, various conditions were screened for the direct introduction of the formyl group to compounds **267** and **282** (Table 4.2). First of all, *O*-demethylation of **267** with BBr_3 generated **282** in high yield.[112] Then the formylation of compounds **267** and **282** were investigated, respectively. Lithiation of compounds **267** and **282** followed by electrophilic trapping with DMF, the most common method, was tested first;[113] however, **267** and **282** all decomposed under these conditions (entries 1-4). Oxalyl chloride in DMF conditions were also tested next (entries 5-6),[114] unfortunately, no conversion occurred, even at refluxing conditions for 24 hours. Next, the typical Vilsmeier–Haack conditions were investigated,[115] surprisingly, instead of target aldehyde **283** and **285**, five membered ring opening byproducts **284** and **286** were observed (entries 7-8). Finally, the Rieche formylation conditions were examined, no desired aldehyde was obtained (entry 9).[116]

[111] Mainkar, P. S.; Johny, K.; Rao, T. P.; Chandrasekhar, S. *J. Org. Chem.*, **2012**, *77*, 2519–2525.
[112] Ref. 53.
[113] Wang, L.; Wang, Y.; Guo, F.; Zheng, Y.; Bhadury, P. S.; Sun, Z. *Tetrahedron Lett*., **2013**, *54*, 6053-6054.
[114] a) Nicolaou, K. C.; Li, A. *Angew.Chem. Int. Ed*., **2008**, *47*, 6579-6584. b) Butler, J. R.; Wang, C.; Bian, J.; Ready, J. M. *J. Am. Chem. Soc.*, **2011**, *133*, 9956–9959.
[115] a) Fischer, O.; Muller, A.; Vilsmeier, A. *J. Prakt. Chem*., **1925**, *109*, 69-97. b) Vilsmeier, A.; Haack, A. *Ber*. **1927**, *60B*, 119-122. c) Deshpande, P. P.; Tagliaferri, F.; Victory, S. F.; Yan, S.; Baker, D. C. *J. Org. Chem*., **1995**, *60*, 2964-2965.
[116] (a) Rieche, A.; Gross, H.; Höft, E. *Chem. Ber.,* **1960**, *93*, 88-89. (b) Kraus, G. A.; Mengwasser, J.; Maury, W.; Oh, C. *Bioorg. Med. Chem. Lett*., **2011**, *21*, 1399-1402.

Table 4.2: Attempted formylation of **267**



R=H;**282**
R=Me; **267**

R=H;**283**
R=Me; **285**

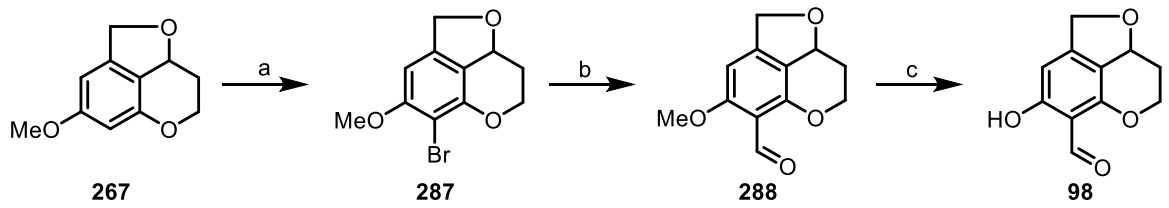
R=H;**284**
R=Me; **286**

Entry	R	Reagents	conditions	Result
1	H	TMEDA (2 eq.), n-BuLi (2 eq.), DMF (3 eq.)	THF, -78 ^{o}C, 1h	decomposition
2	Me	TMEDA (2 eq.), n-BuLi (2 eq.), DMF (3 eq.)	THF, -78 ^{o}C, 1h	decomposition
3	H	PhLi (1.1 eq.), DMF (3.0 eq.)	THF, -78 ^{o}C to rt, 24h	decomposition
4	Me	PhLi (1.1 eq.), DMF (3.0 eq.)	THF, -78 ^{o}C to rt, 2h	decomposition
5	H	$(COCl)_2$ (1.2 eq), DMF (1.2 eq)	CH_2Cl_2, 0 ^{o}C to rt, 24h	no reaction
6	Me	$(COCl)_2$ (1.2 eq), DMF (1.2 eq)	CH_2Cl_2, 0 ^{o}C to reflux, 24h	no reaction
7	H	$POCl_3$ (1.1 eq), DMF (2 eq.)	DCE, 0 ^{o}C to reflux, 18h	60% (**284**)
8	Me	$POCl_3$ (1.1 eq), DMF (2 eq.)	DCE, 0 ^{o}C to reflux, 18h	80% (**286**)
9	Me	$MeOCHCl_2$(1.5 eq), $TiCl_4$(1 eq.)	CH_2Cl_2, 0 ^{o}C to rt, 24h	no reaction

Due to the difficulties in introducing a formyl group into compound **267** in one-step, a two-step protocol was investigated which involves halogenation followed by lithium-halogen exchange and subsequent trapping by DMF (Scheme 4.10). Bromination of compound **267** with NBS generated bromobenzene **287** as single isomer in good yield.[117] Then the formylation of bromobenzene **287** to **288** was succeeded by the conditions of lithium-bromine

[117] Tarascou, I.; Barathieu, K.; Andre, Y.; Pianet, I.; Dufourc, E. J.; Fouquet, E. *Eur. J. Org. Chem.*, **2006**, 5367–5377.

exchange followed by trapping by DMF.[118] The last step of the synthesis was *O*-demethylation of compound **288** which worked well with BBr_3. Unfortunately, this reaction could not be repeated, even using the same procedure with new reagents and re-purified and re-dried solvents.



Scheme 4.10: Formylation of **267** followed by *O*-demethylation. *Reagents and conditions: a) NBS, CH_2Cl_2, reflux, 2 h, 77%; b) t-BuLi, DMF, ether, -78 °C to RT, 5 h, 85%; c) BBr_3, CH_2Cl_2, -78 °C to rt, overnight, 63%.*

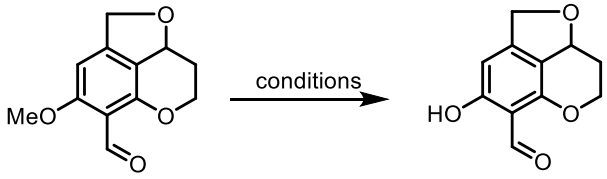
4.5.5 Modification of *O*-demethylation

Because of lack of reproduction of the *O*-demethylation of compound **288** with BBr_3 to **98**, various *O*-demethylation conditions were probed (Table 4.3). First of all, it was evident that the conditions with boron tribromide reagents gave the decomposition of starting material, no matter it is pure boron tribromide or stabilized boron tribromide dimethyl sulfide complex (entries 1 and 2).[119] It has been well known that all of the boron trihalides, except the fluorides, will cleave ethers with different efficiency.[120] However, the nucleophilic character of iodine coupled with the strong Lewis acidity of boron makes boron triiodide the most potent of these reagents. So the *O*-demethylation of compound **288** with BI_3 was also investigated,[121] unfortunately, no desired product was obtained (entry 3). It was postulated that the dihydroisobenzofuran the reason might be too reactive and sensitive under these acidic conditions. The result revealed that Lewis acids are not suited for this transformation (entries 4-6),[122] so that alkaline conditions were screened next (entry 7). However, all of Lewis or Bronsted bases tested gave no conversion. Since the nucleophilic thiolate reagents have been proven to be suitable for the *O*-demethylation of methyl aryl ether, various thiolates

[118] a) Stavrakov, G.; Keller, M.; Breit, B. *Eur. J. Org. Chem.*, **2007**, 5726 –5733. b) Ref. 57.
[119] a) McOmie, J. F. W.; Watts, M. L.; West, D. E. *Tetrahedron*, **1968**, *24*, 2289. b) Meyers, A. I.; Nolen, R. L.; Collington, E. W.; Narwid, T. A.; Strickland, R. C. *J. Org. Chem.*, **1973**, *38*, 1974. c) Teitel, S.; O'Brien, J.; Brossi, A. *J. Org. Chem.*, **1972**, *37*, 3368. (b) Teitel, S.; O'Brien, J. P. *J. Org. Chem.* **1976**, *41*, 1657.
[120] a) Weiberg, E.; Sutterlin, W. Z. *Anorg. Allg. Chem.*, **1931**, *202*, 22-23. b) Benton, F.; Dillon, T. *J. Am. Chem. Soc.* **1942**, *64*, 1128-1129.
[121] a) Lansinger, J. M.; Ronald, R. C. *Synth. Commun.*, **1979**, *9*, 341-343. b) Ronald, R. C.; Lansinger, J. M.; Lillie, T. S.; Wheeler, C. J. *J. Org. Chem.*, **1982**, *47*, 2541-2547.
[122] a) Bernard, A. M.; Ghiani, M. R.; Piras, P. P.; Rivoldini, A. *Synthesis*, **1989**, *4*, 287-289. b) Bao, K.; Fan, A.; Dai, Y.; Zhang, L.; Zhang, W.; Cheng, M.; Yao, X. *Org. Biomol. Chem.*, **2009**, *7*, 5084-5090.

and reaction conditions were investigated. Demethylation of **288** with pyridine HCl led to decomposition (entry 8)[123]. To be delighted, the *O*-demethylation of **288** with NaSPh worked well and gave the desired product in an encouraging yield (entry 9). Finally, it was found that NaSEt is the best choice for the demethylation of **288** to yield **98** (entries 10-12).[124]

Table 4.3: Screening of *O*-demethylation of **288**



288 **98**

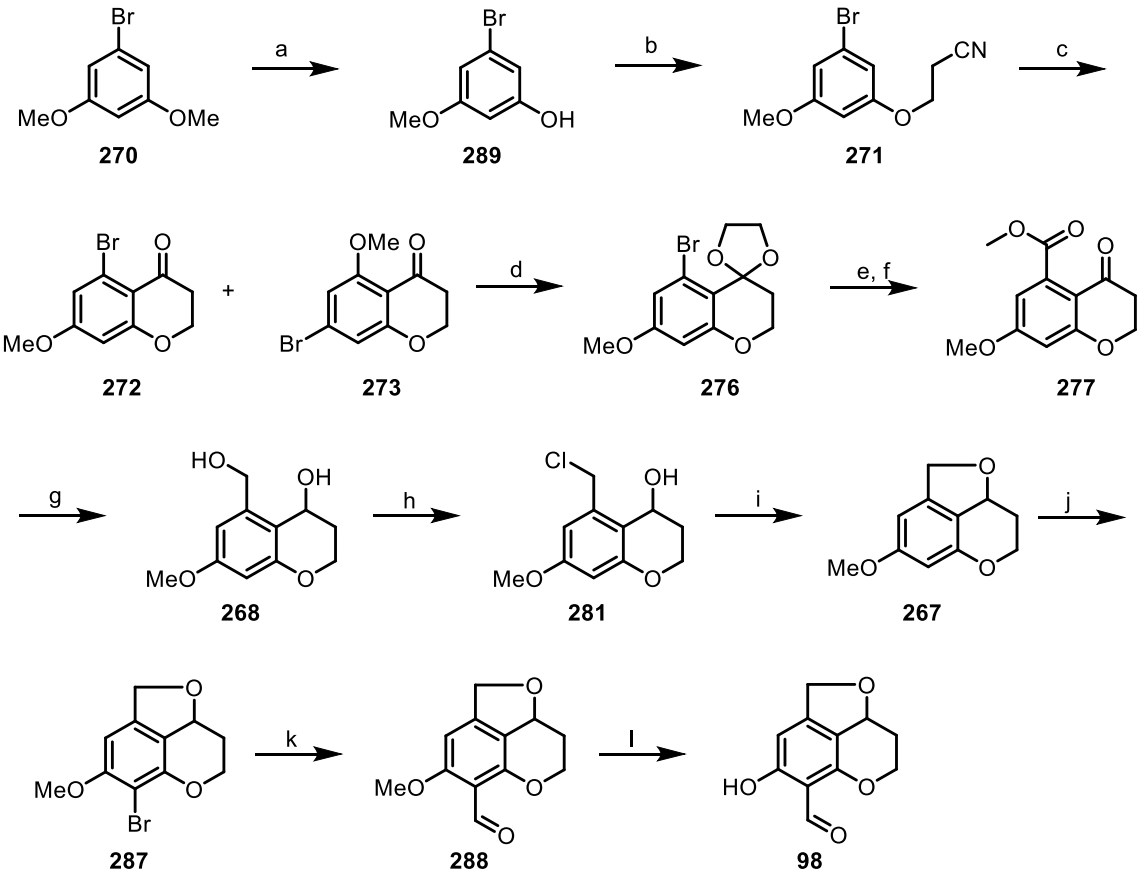
Entry	Reagents	conditions	Result
1	BBr_3 (1 eq.)	CH_2Cl_2, -78 °C to rt, 24h	decomposition
2	$BBr_3 \cdot S(CH_3)_2$(1 eq.)	CH_2Cl_2, -78 °C to rt, 24h	decomposition
3	BI_3 (1.5 eq.)	CH_2Cl_2, -78 °C to rt, 2h	decomposition
4	TMSI (1 eq.)	$CHCl_3$, 0 °C to reflux, 24h	no reaction
5	LiCl (3 eq.)	DMF, 0 °C to reflux, 24h	no reaction
6	AlCl3 (1.5 eq.)	CH_2Cl_2, 0 °C to reflux, 24h	no reaction
7	*t*-BuOK (2 eq.) 18-crown-6 (0.1 eq.)	$(CH_2OH)_2$, 200 °C (microwave), 2h	no reaction
8	pyridine-HCl (10 eq.)	200 °C	decomposition
9	NaH (2 eq.), PhSH (2 eq.)	DMF, 0 °C to reflux, 2h	22%
10	NaH (2 eq.),EtSH (2 eq.)	DMF, 0 °C to reflux, 2h	40%[a]
11	NaH (5 eq.), EtSH (6 eq.)	DMF, 0 °C to reflux, 2h	decomposition[b]
12	NaH (5 eq.), EtSH (6 eq.)	DMF, 0 °C to reflux, 2h	51%[a]

a: Twice chromatography purifications. b: termination by addition water.

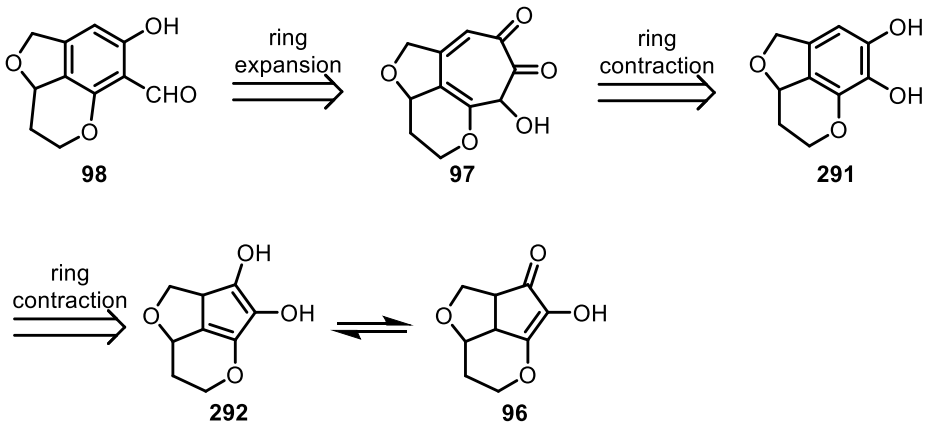
[123] Chapman, L. M.; Beck, J. C.; Wu, L.; Reisman, S. E. *J. Am. Chem. Soc*. **2016**, *138*, 9803-9806.
[124] Trost, B. M.; Shen, H. C.; Surivet, J. P. *Angew. Chem. Int. Ed*., **2008**, *47*, 6579-6584.

4.6 Summary and Outlook

In summary, model compound **98** was successfully synthesized in 4% overall yield over 12 steps from 1-bromo-3,5-dimethoxybenzene **270** (Scheme 4.11).



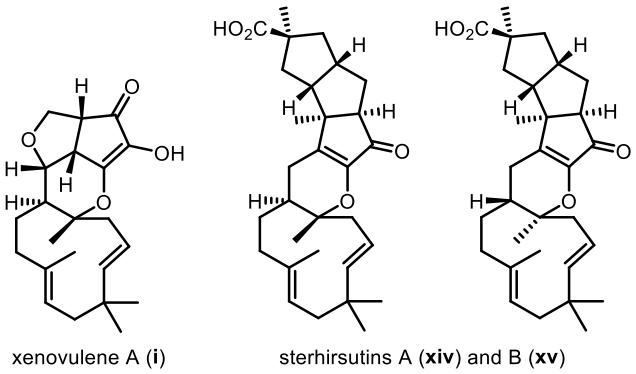
Scheme 4.11: Synthesis of model compound **98**. *Reagents and conditions: a) BBr_3, CH_2Cl_2, 0 ^oC to RT, 24 h, 80%; b) C_2H_3CN, DBU, reflux, 48 h, 76%; c) $AlCl_3$, CH_3NO_2, 60 ^oC, then H_2O, 56%; d) $(CH_2OH)_2$, $HC(OMe)_3$, $PhCH_3$, reflux, 48 h , 83%; e) n-BuLi, $ClCO_2Me$, THF, -78 ^oC to RT, 3 d; f) HCl, MeOH, rt, 5 h, 74% for 2 steps; g) $LiAlH_4$, ether, -78 ^oC to RT, 1 h, 81%; h) TsCl, Et_3N, DMAP, CH_2Cl_2, 0 ^oC to RT, 4 h, 73%; i) NaH, THF, reflux, 2 h, 83%; j) NBS, CH_2Cl_2, reflux, 2 h, 77%; k) t-BuLi, DMF, ether, -78 ^oC to RT, 5 h, 85%; l) NaH, EtSH, DMF, reflux, 2 h, 51%.*



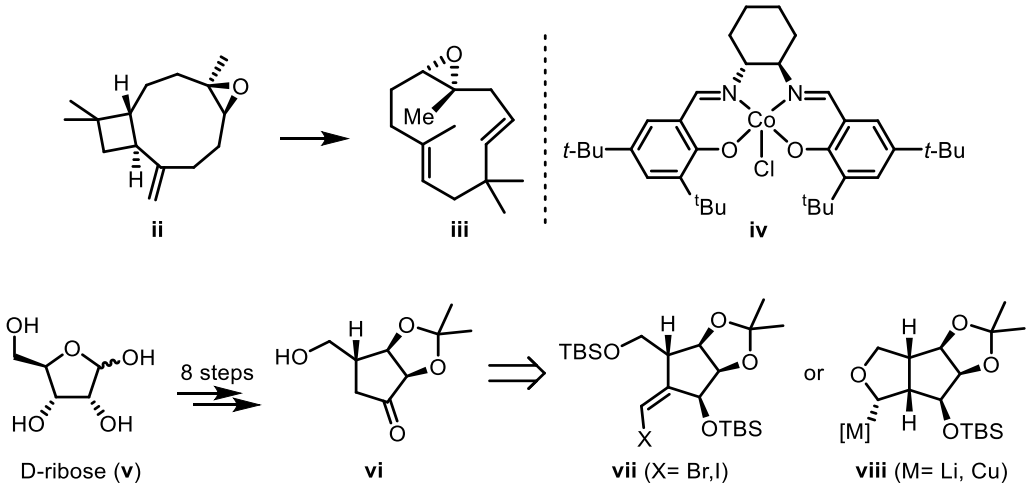
Further studies on the biosynthetic construction of the cyclopentenone ring in **96** through a unique pathway, which involves the phenolic precursor **98** that undergoes ring expansion to tropolone **97** followed by two successive ring contractions was still under investigation at the time of thesis submission.

Chapter 5 Conclusions

The objective of the work presented in this thesis has been a novel approach to the full carbon skeleton of xenovulene A (**i**) by chemical synthesis, which also paves the way for the total synthesis of sterhirsutins A (**xiv**) and B (**xv**).

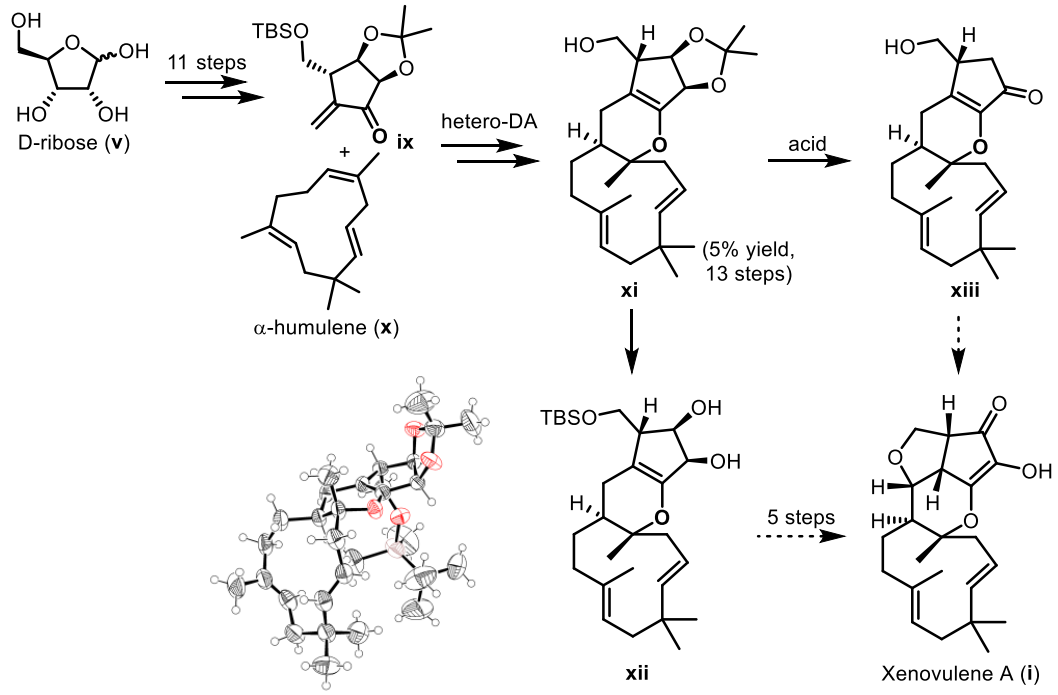


In chapter 2, an epoxide ring opening approach to xenovulene A (**i**) was presented. Firstly, a literature known procedure to humulene epoxide (**iii**) was carried out by using a Co(III)Cl (**iv**) -catalyzed retrocycloisomerization of (-)-caryophyllene oxide (**ii**). The second goal was the synthesis of nucleophile fragments **(vii)** or **(viii)** for the proposed ring opening reaction of epoxide (**iii**). Despite several attempts to synthesize nucleophile fragments **(vii)** or **(viii)** from D-ribose (**v**), the desired fragments could not be obtained and the first strategy was abandoned.

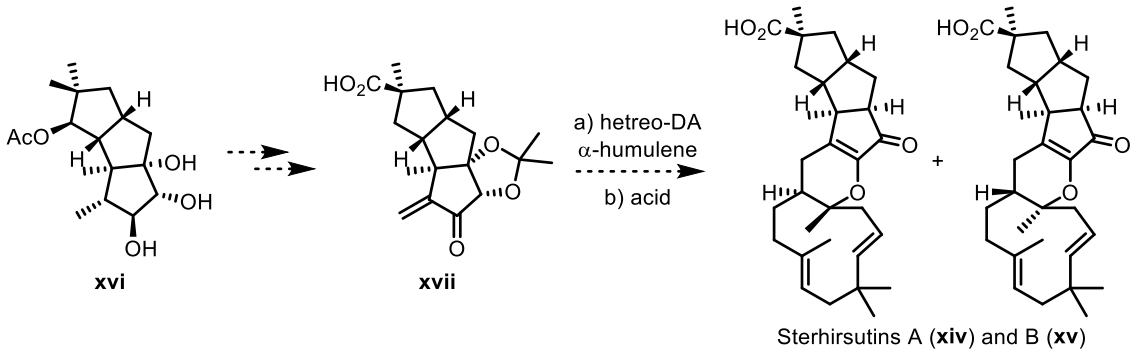


In chapter 3 a hetero Diels-Alder cycloaddition approach to xenovulene A was presented. The key step was a biomimetic inverse electron demand hetero Diels-Alder cycloaddition (HDA) of α-humulene (**x**) and ribose-derived vinyl ketone (**ix**) which can be synthesized from D-ribose (**v**) in 10% yield over 11 steps. Using this biomimetic approach, a regio- and

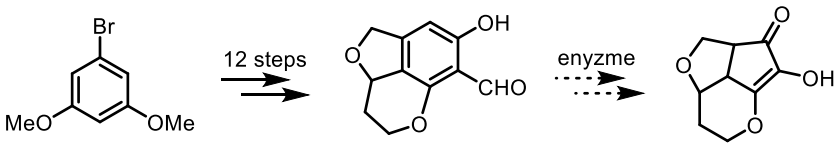
stereoselective synthesis of the full 5,6,11-tricyclic carbon skeleton of xenovulene A was accomplished. The absolute configuration of the advanced intermediate (**xi**) was confirmed by x-ray crystallographic analysis of its TBS-ether (**xii**), which was obtained in crystalline form.



In addition, a novel acid-catalyzed rearrangement of 1,3-dioxolane (**xi**) was discovered, demonstrating that the Diels-Alder cycloaddition products such as **xi** are suited for the synthesis of the two xenovulene analogues, sterhirsutins A (**xiv**) and B (**xv**). Following the discovery of this acetonide rearrangement and the literature known synthesis of advanced intermediate (**xvi**), a plausible synthesis of sterhirsutins A and B which involves a hetero Diels-Alder reaction of vinyl ketone (**xvii**) with α-humulene (**x**) followed by acid-catalyzed acetonide rearrangement was proposed.



Finally, in chapter 4 a synthesis of model compound (**xix**) for studying the biosynthesis of xenovulene A was presented. Model compound (**xix**) was successfully synthesized in 4% overall yield over 12 steps from 1-bromo-3,5-dimethoxybenzene (**xvii**).



xviii **xix** **xx**

Further studies on the biosynthetic construction of cyclopentenone ring of **xx** through a unique pathway which involves the phenolic compound (**xix**) undergoes ring expansion to a tropolone followed by two successive ring contractions was still under investigation at the time of thesis submission.

Chapter 6 Experimental section

6.1 General experimental details

All reactions in anhydrous solvents were conducted under an atmosphere of argon in glassware that was flame-dried. All commercially available reagents and dry solvents were used directly without further purification unless otherwise stated.

Analytical thin layer chromatography (TLC) was performed on precoated silica gel 0.25 mm silica gel 60 F254 plates (Merck, Darmstadt). Visualization was accomplished with UV light at 254 nm followed by heating after staining the plate with *p*-anisaldehyde solution, unless otherwise noted.

Product purification was performed by flash column chromatography using silica gel (Macherey-Nagel, 40–63 μm, 230–400 mesh). Unless otherwise stated, all isolated and characterized compounds were >95% pure as judged by ^{1}H-NMR spectroscopic analysis. ^{1}H-NMR spectra were recorded at 400 or 500 MHz, and 13C NMR spectra were recorded at 100 or 125 MHz, with Bruker Avance 400, DPX 400, or DRX 500 instruments. ^{1}H-NMR data are reported in the following format: chemical shift (multiplicity, coupling constants, and integration). Chemical shifts are reported in ppm with the residual solvent resonance as internal standard ($CDCl_3$: 7.26 ppm; C_6D_6: 7.16 ppm; CD_3OD: 3.31 ppm; $(CD_3)_2SO$: 2.50 ppm). Multiplicity is abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. 13C NMR spectra were recorded at 100 or 125 MHz, with Bruker Avance 400, DPX 400, or DRX 500 instruments. Chemical shifts are reported in ppm with the solvent resonance as internal standard ($CDCl_3$: 77.16 ppm; C_6D_6: 128.06 ppm; CD_3OD: 49.00 ppm; $(CD_3)_2SO$: 39.51 ppm). Some proton and carbon assignments were made with the aid of ^{1}H-^{1}H COSY, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC or NOE experiments.

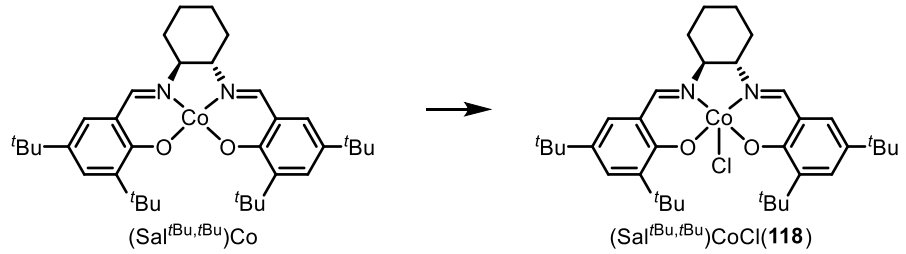
Melting points were measured on a SRS OptiMelt melting point apparatus and are uncorrected.

High resolution mass spectra (HRMS) were obtained at 70 eV with a type VG Autospec spectrometer (Micromass), with a type LCT (ESI) (Micromass), with a type Q-TOF (Micromass) spectrometer in combination with a Waters Aquity Ultraperformance LC (UPLC) system, with a UPLC/Q-TOF-MS combination (Dionex Ultimate 3000/BrukerMaxis HD) or as a gas chromatography with a HP6890.

Optical rotations were measured on a Perkin-Elmer polarimeter type 341 in a quartz glass cuvette with a Na lamp and are reported as: $[\alpha]_D^{T(°C)} = XX°$ (c (g/100 mL), solvent).

6.2 Supporting information for chapter 2

Synthesis of Co(III) catalyst **(118)**



(*R,R*)-*N,N′′*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexane-diaminato Co(III)Cl (118)

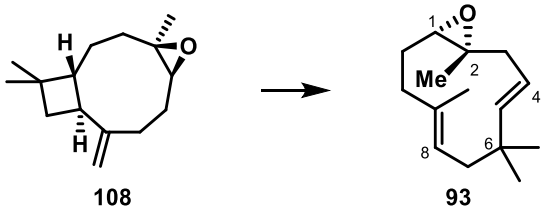
The commercially available (*R,R*)-*N,N′′*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexane-diaminato cobalt(II) complex (603.7 mg, 1.00 mmol) was added to a 250 mL round-bottomed flask containing CH_2Cl_2 (50 mL) to give a red suspension. TsOH•H_2O (190.1 mg, 1.00 mmol) was added, and the resulting mixture was stirred vigorously for 1 h. The resulting dark green solution was washed with brine, dried with Na_2SO_4, filtered through *Celite*, and concentrated *in vacuo* to give a dark green solid. This was suspended in pentane (50 mL), filtered, and washed with additional pentane to give the (salen$^{tBu,\ tBu}$)CoCl complex as a dark green solid (418.1 mg, 0.64 mmol, 64%). (Note: In yield calculations, one molecule of coordinated H_2O is assumed. The resulting (salen$^{tBu,\ tBu}$)CoCl complex generally yields readily interpretable ^{1}H-NMR spectra in dilute solutions of DMSO-d_6 (<1 mg/mL). ^{1}H NMR spectra of more concentrated solutions can result in significant peak broadening and appearance of new peaks, possibly due to paramagnetic aggregates.)

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.29 (s, 18H), 1.55–1.60 (m, 2H), 1.73 (s, 18H), 1.88–1.93 (m, 2H), 1.98–2.02 (m, 2H), 3.04–3.07 (m, 2H), 3.57–3.60 (m, 2H), 7.43 (s, 2H), 7.46 (s, 2H), 7.83 (s, 2H) ppm.

Spectral information obtained matched those previously reported.[125]

[125] Crossley, S. W. C.; Barabe, F.; Shenvi, R. A. *J. Am. Chem. Soc.* **2014**, *136*, 16788−16791.

Synthesis of (-)-humulene epoxide (**93**)



108 **93**

((1*R*,3*E*,7*E*,11*R*)-1,5,5,8-Tetramethyl-12-oxabicyclo[9.1.0]dodeca-3,7-diene) (93)

To a flame dried 150 mL round bottom flask equipped with a stir bar was added (salen$^{tBu,\ tBu}$)CoCl (1.5 mol %, 23.6 mg), (-)-caryophyllene oxide (528.0 mg, 2.40 mmol), and dry benzene (24 mL). The reaction was degassed with argon, followed by the addition of phenylsilane (2 mol%, 11.7 μL). The dark green solution turned a red-orange color and the reaction was monitored by LCMS. After completion at 6.5 hours, the reaction mixture was concentrated directly *in vacuo* and the residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 1/1 to 1/2) to give the epoxide **93** as a yellow oil (475.1 mg, 2.16 mmol, 90%).

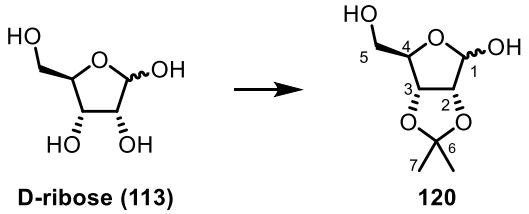
$\mathbf{R_f}$ = 0.31 (petroleum ether /EtOAc = 1/1); $\mathbf{[\alpha]_D^{20}}$ = - 110.1 °(*c* = 0.88, $CHCl_3$);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 5.28 (ddd, *J* = 15.5, 10.1, 5.2 Hz, 1H, H-8), 5.15 (d, *J* = 15.8 Hz, 1H, H-5), 5.07-4.92 (m, 1H, H-4), 2.62-2.48 (m, 2H, H-3), 2.24 (m, 1H, H-1), 2.14 (m, 2H, H-7), 1.99 (dd, *J* = 13.7, 9.2 Hz, 1H, H-10), 1.92-1.81 (m, 1H, H-10'), 1.68-1.60 (m, 1H, H-11), 1.35 (m, 1H, H-11'), 1.30 (s, 3H), 1.11 (s, 3H), 1.08 (s, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 143.25 (d, C-8), 132.05 (d, C-4), 125.86 (d, C-5), 122.23 (s, C-9), 63.37 (s, C-2), 62.09 (d, C-1), 42.74 (t, C-3), 40.37 (t, C-7), 36.77 (t, C-10), 36.66 (t, C-11), 29.86 (q, -CH_3), 24.90 (q, -CH_3), 17.35 (q, -CH_3), 15.24 (q, -CH_3) ppm.

HRMS (ESI): *m/z* calcd. for $C_{15}H_{24}ONa$ $[M+Na]^+$: 243.1725; found: 243.1727.

Synthesis of acetonide **120**



D-ribose (113) **120**

2,3-*O*-Isopropylidene-D-ribose (120)

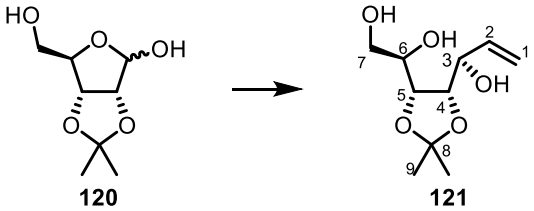
To a stirred suspension of D-ribose (20.1 g, 133.20 mmol) in acetone (250 mL) was added conc. H_2SO_4 (0.6 mL) dropwise at room temperature and the reaction mixture was stirred at room temperature for 5 h. The mixture was neutralized with solid $NaHCO_3$, filtered and evaporated *in vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether /EtOAc = 1/1 to 1/2) to afford the target acetonide **120** as a colorless syrup (23 g, 121.10 mmol, 91%).

$\mathbf{R}_f$ = 0.30 (petroleum ether /EtOAc = 1/1); $\mathbf{[\alpha]_D^{20}}$ = - 37.1 °(*c* = 1.08, acetone);

^{1}H-NMR (400 MHz, MeOH-*d4*): δ_H = 5.26 (s, 1H, H-1), 4.84 (brs, 2H, OH), 4.76 (d, *J* = 5.92 Hz, 1H, H-2), 4.52 (d, *J* = 5.96 Hz, 1H, H-3), 4.19 (t, *J* = 5.55 Hz, 1H, H-4), 3.70-3.55 (m, 2H, H-5), 1.43 (s, 3H, H-7), 1.30 (s, 3H, H-7) ppm;

Spectral information obtained matched those previously reported.[126]

Synthesis of triol **121**



120 **121**

(*R*)-1-((4*R*,5*S*)-5-((*R*)-1-Hydroxyallyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol (121)

To a stirred solution of **120** (20.2 g, 107.10 mmol) in THF (800 mL) was added dropwise vinylmagnesium bromide (1.0 M solution in THF, 482 mL, 482.00 mmol) at −78°C and the

[126] Moon, R. N.; Choi, W. J.; Kim, H. O.; Jeong, L. S. *Tetrahedron: Asymmetry* **2002**, *13*, 1189-1195.

reaction mixture was stirred at 0°C overnight. After adding water (160 mL) at 0°C, the resulting precipitate was removed through a short pad of *Celite*. The filtrate was extracted with ethyl acetate, dried, filtered, and evaporated *in vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 1/1 to 1/2) to afford the target product as a white solid (19.2 g, 87.80 mmol, 82%).

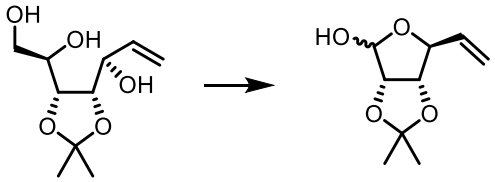
R_f = 0.24 (petroleum ether/EtOAc = 1/2); **M. p. =** 72-74 °C; **$[\alpha]_D^{20}$** = - 30.6 °(*c* = 0.89, $CHCl_3$);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 6.04 (ddd, *J* =17.2, 10.4, 6.1 Hz, 1H, H-2), 5.39 (d, *J* = 17.2 Hz, 1H, H-1), 5.30 (d, *J* = 10.4 Hz, 1H, H-1), 4.33 (dd, *J* = 9.2, 6.1 Hz, 1H, H-3), 4.14 (dd, *J* = 9.5, 5.4 Hz, 1H, H-5), 4.05 (dd, *J* = 9.2, 5.4 Hz, 1H, H-4), 3.95 (ddd, *J* = 9.5, 3.4, 6.1 Hz, 1H, H-6), 3.89 (dd, *J* = 11.2, 3.4 Hz, 1H, H-7), 3.72 (dd, *J* = 11.2, 6.1 Hz, 1H, H-7), 2.90 (br., 3H, -OH), 1.39 (s, 3H, $-CH_3$), 1.33 (s, 3H, $-CH_3$) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 137.7 (d, C-2), 117.2 (t, C-1), 109.2 (s, C-8), 80.0 (d, C-4), 77.8 (d, C-5), 70.9(d, C-3), 69.5(d, C-6), 64.6 (t, C-7), 28.0 (q, $-CH_3$), 25.6 (q, $-CH_3$) ppm;

HRMS (ESI): *m/z* calcd. for $C_{10}H_{18}O_5Na$ $[M+Na]^+$: 241.1052; found: 241.1051.

Synthesis of alcohol **122**



121 **122**

(3a*S*,6*S*,6a*S*)-2,2-Dimethyl-6-vinyltetrahydrofuro[3,4-d][1,3]dioxol-4-ol (122)

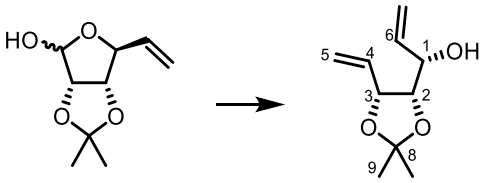
To a stirred solution of **122** (18.1 g, 82.90 mmol) in CH_2Cl_2 (330 mL) was added dropwise an aqueous solution of $NaIO_4$ (0.65 M solution, 191 mL, 124.40 mmol) at 0°C and the reaction mixture was stirred at room temperature for 40 min. After water (210 mL) was added, the mixture was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 10/1 to 2/1) to give the target alcohol **122** as a colorless oil (14.1 g, 70.50 mmol, 85%).

R_f = 0.50 (petroleum ether/EtOAc = 2/1);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 6.09-5.91 (m, 0.8H), 5.87-5.70 (m, 0.2H), 5.48(d, *J* = 2.9 Hz, 0.9H), 5.36-5.18 (m, 2.1H), 4.71-4.54 (m, 3H), 3.94(d, *J* = 10.3 Hz, 0.1H), 2.99-2.95 (m, 0.9 H), 1.57 (s, 0.4H), 1.49 (s, 2.6H), 1.38 (s, 0.4H), 1.32 (s, 2.6H) ppm;

Spectral information obtained matches those previously reported.[127]

Synthesis of diene **123**



(1*S*,2*S*,3*R*)-(-)-1-(2,2-Dimethyl-5-vinyl[1,3]dioxolan-4-yl)-prop-2-en-1-ol (123)

To a suspension of sodium hydride (60% dispersion in mineral oil, 112.1 mg, 2.30 mmol) in THF (2.5 mL) was added dimethyl sulfoxide (0.41 mL, 5.00 mmol) at 0 °C, and the mixture was stirred at room temperature for 0.5 h. Then a suspension of methyltriphenylphosphonium bromide (1.1 g, 3.00 mmol) in THF (4.5 mL) was added at 0 °C, and the reaction mixture was stirred for 1 h at room temperature. To this reaction mixture was added a solution of **122** (186.0 mg, 1.00 mmol) in THF (3.5 mL) at 0 °C, and then the mixture was heated under refluxing conditions overnight. After it was cooled down to room temperature, diethyl ether was added to the mixture, and a white solid was precipitated out. The mixture was filtered through a short pad of silica gel, washed with diethyl ether, and evaporated. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc 20/1 to 10/1 to 5/1) to give the target diene **123** as a colorless oil (162.1 mg, 0.88 mmol, 88%).

$\mathbf{R_f}$ = 0.21 (petroleum ether/EtOAc = 10/1); $\mathbf{[\alpha]_D^{20}}$ = - 51 °(*c* = 1.10, $CHCl_3$);

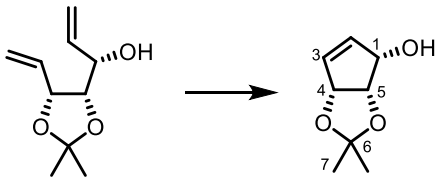
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 6.10-5.98 (m, 2H, H-4 and H-6), 5.43 (ddd, *J* = 17.2, 1.5, 1.0, 1H, H-7), 5.34 (ddd, *J* = 17.4, 1.4, 1.4, 1H, H-1), 5.29 (d, *J* = 10.2, 1H, H-7'), 5.23 (d, *J* = 10.7, 1H, H-1'), 4.67 (dd, *J* = 7.0, 6.8 Hz ,1H, H-2), 4.15 (dd, *J* = 7.5, 5.9 Hz ,1H, H-3), 4.02 (dd, *J* = 7.5, 6.8 Hz 1H, H-1), 1.95 (br, 1H, -OH), 1.49 (s, 3H, H-9), 1.37 (s, 3H, H-10) ppm;

[127] Choi, W. J.; Jeong, L. S. et al. *J. Org. Chem.* **2001,** *66,* 6490-6494.

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 137.7 (d, C-4), 134.1 (d, C-6), 118.5 (t, C-5), 116.7 (t, C-7), 109.0 (s, C-8), 80.6 (d, C-2), 78.8 (d, C-3), 71.2 (d, C-1), 27.7 (q, C-9), 25.4 (q, C-10) ppm.

HRMS (ESI): *m/z* calcd. for $C_{10}H_{16}O_3Na$ $[M+Na]^+$: 207.0997; found: 207.0998.

Synthesis of alcohol **97**



(1*S*,4*R*,5*S*)-4,5-*O*-Isopropylidenecyclopenten-1-ol (97)

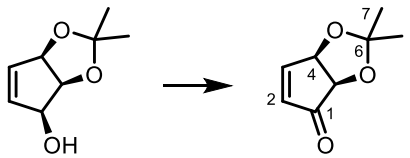
A round-bottomed flask charged with the Grubbs I catalyst (364.4 mg, 0.44 mmol) was vacuumed and filled with argon gas three times before the addition of a solution of **123** (2.7 g, 14.76 mmol) in degassed CH_2Cl_2 or $CHCl_3$ (55 mL). The resulting pink solution was stirred overnight at room temperature. The solvent was removed *in vacuo*, and the dark residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 10/1 to 4/1) to give the target alcohol **97** as a yellow oil (421.1 mg, 0.39 mmol, 89%).

$\mathbf{R_f}$ = 0.21 (petroleum ether = 4/1);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 5.86 (s, 2H, H-2 and H-3), 4.98(d, *J* = 5.52 Hz, 1H, H-5), 4.72 (t, *J* = 5.48 Hz, 1H, H-4), 4.55-4.51 (m, 1H, H-1), 2.73(d, *J* = 9.88 Hz, 1H, -OH), 1.41 (s, 3H, H-7), 1.38 (s, 3H, H-7') ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 136.5 (d, C-2), 132.1 (d, C-3), 112.5 (s, C-6), 83.7 (d, C-5), 77.3 (d, C-1), 74.3 (d, C-4), 27.8 (q, C-7), 26.7 (q, C-7') ppm.

Synthesis of enone **112**



(4*R*,5*R*)-4,5-*O*-Isopropylidene-2-cyclopentenone (112)

To a stirred solution of alcohol **97** (300.1 mg, 1.92 mmol) in dichloromethane (10 mL) was added activated manganese oxide (1.7 g, 19.20 mmol), and the mixture was vigorously stirred overnight at room temperature. The reaction mixture was filtered through a pad of *Celite*, and the filter cake was washed with dichloromethane. The filtrates were concentrated *in vacuo*, and the residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 4/1) to afford the target enone **112** as a colorless crystalline solid (224.1 mg, 1.48 mmol, 77%).

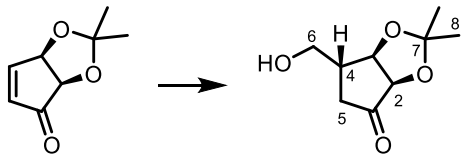
$\mathbf{R_f}$ = 0.25 (petroleum ether/EtOAc = 4/1); **M. p. =** 68-70 ^{o}C; $\mathbf{[\alpha]_D^{20}}$ = -70.5 °(*c* = 1.10, $CHCl_3$);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 7.60 (dd, *J* = 2.29, 5.39 Hz, 1H, H-2), 6.20(d, *J* = 5.88 Hz, 1H, H-2), 5.27-5.24 (m, 1H, H-4), 4.45 (d, 1H, *J* = 5.88, H-5), 1.41 (s, 3H, H-7), 1.40 (s, 3H, H-7') ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 203.1 (s, C-1), 159.7 (d, C-3), 134.5 (d, C-2), 115.7 (s, C-6), 78.7 (d, C-4), 76.6 (d, C-5), 27.6 (q, C-7), 26.3 (q, C-7') ppm;

HRMS (ESI): *m/z* calcd. for $C_8H_{10}O_3Na$ $[M+Na]^+$: 177.0528; found: 177.0528.

Synthesis of ketone **124**



112 **124**

(2*R*,3*R*,4*R*)-2,3-Dihydroxy-2,3-O-isopropylidene-4-hydroxymethylcyclopentan-l-one (124)

A solution of (-)-enone **112** (77.1 mg, 0.5 mmol) and benzophenone (15.2 mg, 0.08 mmol) in CH_3OH (32 mL) was degassed by flushing with argon for 1 h. Then, the solution was irradiated using a high pressure Hg lamp for 1 h. The solvent was evaporated *in vacuo*, and the residue was purified by column chromatography (Florisil, EtOAc/hexane = 10/1 to 1/1) to give the target ketone **124** as a colorless oil (60.1 mg, 0.33 mmol, 65%);

$\mathbf{R_f}$ = 0.35 (hexane /EtOAc = 1/1); $\mathbf{[\alpha]_D^{20}}$ = -145 °(*c* = 1.00, CH_3OH);

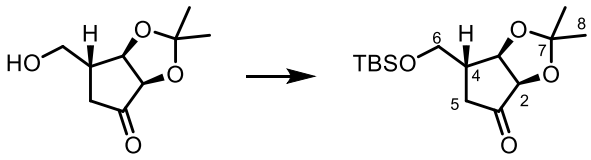
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 4.71 (d, *J* = 5.36 Hz, 1H, H-2), 4.29 (d, *J* = 5.32 Hz, 1H, H-3), 3.86-3.68 (m, 2H, H-6), 2.79-2.72 (m, 1H, H-5), 2.55-2.52 (m, 1H, H-5), 2.18-2.14 (m, 1H, H-4), 1.43 (s, 3H, H-8), 1.35 (s, 3H, H-8') ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 213.9 (s, C-1), 111.4 (s, C-7), 81.3 (d, C-2), 79.0 (d, C-3), 64.4 (t, C-6), 38.8 (t, C-5), 37.2 (d, C-4), 26.8 (q, C-8), 24.7 (q, C-8') ppm;

Spectral information obtained matched those previously reported.[128]

[128] Perry, R. J. et al. *Bio. Med. Chem.* **1996,** *4*, 1077-1088.

Synthesis of TBS-ether **125**



124 **125**

(3aR,6R,6aR)-6-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydro-4H-cyclo -penta[d][1, 3]dioxol-4-one (125)

To a solution of alcohol **124** (96.6 mg, 0.52 mmol) in DMF (2.1 mL) was added TBSCl (94.1 mg, 0.62 mmol), imidazole (127.5 mg, 1.87 mmol) and DMAP (3.2 mg, 0.03 mmol). After the mixture was stirred at room temperature for 5 h, it was diluted with diethyl ether, and successively washed with saturated aqueous NaHCO3 solution, water and brine. Then, the solvent was evaporated *in vacuo*, and the residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 20/1 to 10/1) to give the target TBS-ether **125** as a colorless oil (117.1 mg, 0.39 mmol, 75%).

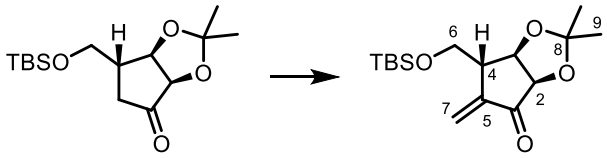
$\mathbf{R_f}$ = 0.45 (petroleum ether/EtOAc = 20/1);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 4.63 (d, *J* = 5.4 Hz, 1H, H-2), 4.21 (d, *J* = 4.8 Hz, 1H, H-3), 3.82 (dd, *J* = 9.7, 7.2 Hz, 1H, H-6), 3.62 (dd, *J* = 9.7, 7.6 Hz, 1H, H-6'), 2.72 (dd, *J* = 18.1, 9.0 Hz, 1H, H-4), 2.50 (d, *J* = 8.8 Hz, 1H, H-5), 2.08 (d, *J* = 18.1 Hz, 1H, H-5), 1.43 (s, 3H, H-8), 1.34 (s, 3H, H-8'), 0.84 (s, 9H, $SiC(CH_3)_3$), 0.03 (s, 3H, Si-CH_3), -0.01 (s, 3H, Si-CH_3) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 213(s, C-1), 111.1 (s, C-7), 82.1 (d, C-2), 79.2 (d, C-3), 65.4 (t, C-6), 39.2 (t, C-5), 37.3 (d, C-4), 26.9 (q, C-8), 25.9 (q, C- 8'), 24.7(q, $SiC(\underline{C}H_3)_3$), 18.3(s, $Si\underline{C}(CH_3)_3$), -3.4(q, Si-CH_3), -5.68(q, Si-CH_3) ppm;

HRMS (ESI): *m/z* calcd. for $C_{15}H_{28}O_4SiNa$ $[M+Na]^+$: 323.1655; found: 323.1658.

Synthesis of vinyl ketone **126**



125 **126**

(3a*R*,6*R*,6a*R*)-6-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-5-methylenetetrahy -dro-4H-cyclopenta[d][1,3]dioxol-4-one (126)

n-BuLi (1M in THF, 1.6 mL, 1.61 mmol) was added dropwise to stirred anhydrous THF (6.1 mL) at -20 °C under argon atmosphere. To the resulting solution was added diisopropylamine (0.24 mL, 1.71 mmol) under the same conditions and stirring was continued for 1 h. The mixture was cooled to -78 °C and was added a solution of ketone **125** (366.1 mg, 1.22 mmol) in anhydrous THF (2.1 mL) through a cannula. The resulting mixture was stirred for 3 h at -78 °C and then Eshenmoser's salt (903.2 mg, 4.91 mmol) was added in one portion. The mixture was stirred for additional 3 h at -78 °C and for 8 h at room temperature. Then iodomethane (2.6 mL) was added and the mixture was stirred for another 4 h at room temperature. The reaction was terminated by addition of a 10% of aqueous $NaHCO_3$ solution (10 mL) and stirred for 1 h. The mixture was extracted with diethyl ether. The combined ether extracts were washed with 10% aqueous $NaHCO_3$ solution followed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 95/5) to afford the target vinyl ketone **126** as a light yellow solid (280.1 mg, 0.91 mmol, 74%).

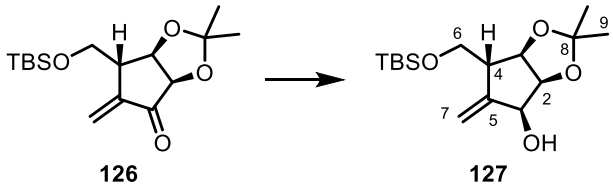
R_f = 0.25 (petroleum ether/EtOAc = 95/5); **M. p. =** 67-69 °C; **$[\alpha]_D^{20}$** = - 165° (*c* = 0.6, $CHCl_3$);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 6.28-6.26 (m, 1H, H-6), 5.54-5.53 (m, 1H, H-6), 4.62 (d, *J* = 5.3 Hz, 1H, H-7), 4.47 (d, *J* = 5.3 Hz, 1H, H-7), 3.92 (dd, *J* = 9.9, 3.0 Hz, 1H, H-2), 3.74 (dd, *J* = 9.6, 3.4 Hz, 1H, H-3), 3.08-3.08 (m, 1H, H-4), 1.37 (s, 3H, H-9), 1.35 (s, 3H, H-10), 0.83 (s, 9H, SiC(C$\underline{H}_3$)$_3$), 0.01 (s, 3H, Si-C$\underline{H}_3$), -0.03 (s, 3H, Si-C$\underline{H}_3$) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 203.2 (s, C-1), 144.4 (s, C-5), 122.4 (t, C-6), 111.4 (s, C-8), 80.2 (d, C-2), 79.3 (d, C-3), 66.5 (t, C-7), 46.4 (d, C-4), 27.4 (q, SiC($\underline{C}H_3$)$_3$), 25.9 (q, C-9), 25.5 (q, C-9), 18.4 (s, Si$\underline{C}$(CH$_3$)$_3$), -5.5 (q, Si-CH$_3$), -5.6 (q, Si-CH$_3$) ppm;

HRMS (ESI): *m/z* calcd. for $C_{16}H_{28}O_4SiNa$ $[M+Na]^+$: 335.1655; found: 335.1656.

Synthesis of vinyl alcohol **127**



(3a*S*,4*S*,6*R*,6a*R*)-6-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-5-methylenetetra -hydro-4H-cyclopenta[d][1,3]dioxol-4-ol (127)

To a solution of compound **126** (40.1 mg, 0.13 mmol) in anhydrous CH_3OH (0.5 mL) was added $CeCl_3.7H_2O$ (65.2 mg, 0.18 mmol) at -78 ^oC. After stirring for 10 minutes, $NaBH_4$ (6.5 mg, 0.17 mmol) was added in one portion. After stirring at -78 ^oC for 15 min, the reaction mixture was allowed to warm to 0 ^oC. Then, a saturated aqueous NH_4Cl solution (20 mL) was added and the mixture was allowed to be stirred for 1 h. The solvent was removed *in vacuo* at room temperature. The remaining residue was extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 20/1) to give the target alcohol **127** as a white solid (34.1 mg, 0.09 mmol, 75%).

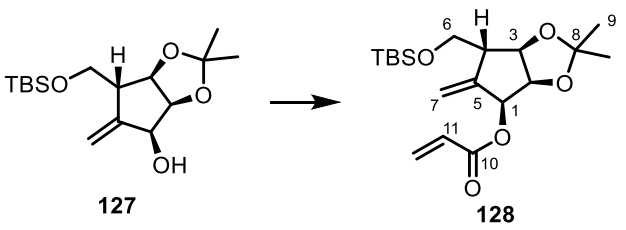
$\mathbf{R}_f$ = 0.25 (petroleum ether/EtOAc = 20/1);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 5.28-5.27 (m, 1H, H-7), 5.12-5.10 (m, 1H, H-7), 4.54-4.52 (m, 2H, H-6), 4.45-4.44 (m, 1H, H-1), 3.74-3.70 (m, 1H, H-2), 3.56-3.52 (m, 1H, H-3), 2.60-2.57 (m, 1H, H-4), 2.28 (d, *J* = 10.6 Hz,1H, OH), 1.40 (s, 3H, H-9), 1.34 (s, 3H, H-9'), 0.86 (s, 9H, Si-C$(CH_3)_3$), 0.02 (s, 3H, Si-CH_3), 0.01 (s, 3H, Si-CH_3) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 153.4 (s, C-5), 110:4 (t, C-7), 109.9 (s, C-8), 81.3 (d, C-2), 79.3 (d, C-3), 73.9 (d C-1), 66.0 (t, C-6), 51.5(d, C-4), 26.5 (q, C-9), 25.9 [s, Si-$\underline{C}(CH_3)_3$], 24.8 (q, C-9'),18.2 [q, Si-C($\underline{C}H_3)_3$], -5.57 (q, Si-CH_3), -5.58 (q, Si-CH_3) ppm;

HRMS (ESI): *m/z* calcd. for $C_{16}H_{30}O_4SiNa$ $[M+Na]^+$: 337.1913; found: 337.1915.

Synthesis of diene **128**



(3a*R*,4*S*,6*R*,6a*R*)-2,2-Dimethyl-5-methylene-6-(((trimethylsilyl)oxy)methyl)tetrahydro-4H -cyclopenta[d][1,3]dioxol-4-yl acrylate (128)

To a mixture of alcohol **127** (100.1 mg, 0.32 mmol) and triethylamine (0.13 mL, 0.95 mmol) in CH_2Cl_2 (5.1 mL) a solution of acryloyl chloride (0.075 mL, 0.95 mmol) in CH_2Cl_2 (7.5 mL) was added at -10 ^oC. The reaction mixture was stirred for 1 h, then water was added, and washed with saturated aqueous $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 10/1) to give the target diene **128** as a light yellow oil (79.1 mg, 0.21 mmol, 67%).

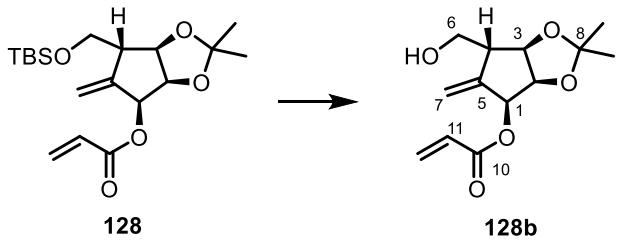
$\mathbf{R_f}$ = 0.35 (petroleum ether /EtOAc = 10/1); $\mathbf{[\alpha]_D^{20}}$ = - 186^o (*c* = 1.0, $CHCl_3$);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 6.49 (dd, *J* = 1.4, 17.4 Hz, 1H, H-12), 6.24 (dd, *J* = 10.4, 17.3 Hz, 1H, H-11), 5.86 (dd, *J* = 1.4, 10.4 Hz, 1H, H-12), 5.47-5.45 (m, 1H, H-12), 5.20-5.17 (m, 2H, H-12 and H-1), 4.77 (t, *J* = 5.68 Hz, 1H, H-2), 4.55 (d, *J* = 5.36 Hz, 1H, H-3), 3.75 (dd, *J* = 3.70, 9.64 Hz, 1H, H-6), 3.60 (dd, *J* = 4.08, 9.64 Hz, 1H, H-6), 2.73-2.69 (m, 1H, H-4), 1.39 (s, 3H, H-9), 1.32 (s, 3H, H-9'), 0.89 [s, 9H, Si-$(CH_3)_3$], 0.05 (s, 3H, Si-CH_3), 0.04 (s, 3H, Si-CH_3) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 165.8 (s, C-10), 148.8 (s, C-11), 131.3 (s, C-12), 128.4 (s, C-7), 111.1 (s, C-5), 110.7 (s, C-8), 82.2 (s, C-1), 78.8 (s, C-2), 75.1 (s, C-3), 66.0 109.9 (s, C-6), 51.3 (s, C-8), 26.8 (s, C-9), 26.0 [s, Si-$\underline{C}(CH_3)_3$], 25.5 (s, C-9'),18.4 [s, Si-C($\underline{C}H_3)_3$],, -5.45 (s, Si-$\underline{C}H_3$), -5.47 (s, Si-$\underline{C}H_3$) ppm;

HRMS (ESI): *m/z* calcd. for $C_{19}H_{32}O_5SiNa$ $[M+Na]^+$: 391.2019; found: 391.2021.

Synthesis of alcohol **128b**



(3a*R*,4*S*,6*R*,6a*R*)-6-(Hydroxymethyl)-2,2-dimethyl-5-methylenetetrahydro-4H cyclopenta -[d] [1,3]dioxol-4-yl acrylate (128b)

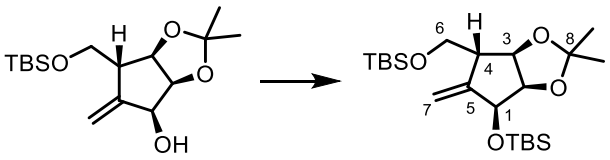
To a solution of compound **128** (20.1 mg, 0.05 mmol) in THF (0.41 mL) was added TBAF (1M solution in THF, 0.11 mL, 0.11 mmol) at room temperature under an argon atmosphere. After stirring for 3 h, the solvent was removed *in vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 10/1) to give the target alcohol **128b** as a yellow oil (21.7 mg, 0.04 mmol, 79%).

$\mathbf{R}_f$ = 0.21 (petroleum ether /EtOAc = 10/1);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 6.51 (dd, *J* = 1.44, 17.32 Hz, 1H, H-12), 6.25 (dd, *J* = 10.54, 17.32 Hz, 1H, H-11), 5.89 (dd, *J* = 1.45, 10.48 Hz, 1H, H-12), 4.30-5.44 (m, 1H, H-1), 4.27-5.20 (m, 2H, H-7), 4.80 (t, *J* = 5.60 Hz, 1H, H-2), 4.58 (dd, *J* = 0.92, 5.44 Hz, 1H, H-3), 3.72-3.61 (m, 2H, H-6), 2.83-2.76 (m, 1H, H-4), 1.64 (broad, 1H, OH),1.41 (s, 3H, H-9), 1.32 (s, 3H, H-9') ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 165.8 (s, C-10), 147.3 (s, C-5), 131.7 (t, C-12), 128.2 (d, C-11), 111.9 (s, C-8), 111.7 (t, C-7), 81.4 (d, C-1), 78.5 (d, C-2), 74.7 (d, C-3), 64.4 (t, C-6), 51.2 (d, C-4), 26.8 (q, C-9), 25.4(q, C-9') ppm.

Synthesis of TBS-ether **136**



127 **136**

***tert*-Butyl(((3a*R*,4*R*,6*S*,6a*R*)-6-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethyl-5-methylenetetra hydro-4H-cyclopenta[d][1,3]dioxol-4-yl)methoxy)dimethylsilane (136)**

A solution of alcohol **127** (100.1 mg, 0.32 mmol) in DMF (1.5 mL) was added TBSCl (57.5 mg, 0.38 mmol), imidazole (77.9 mg, 1.15 mmol) and DMAP (1.9 mg, 0.02 mmol). After the mixture was stirred at room temperature for 5 h, it was diluted with diethyl ether, and successively washed with saturated aqueous $NaHCO_3$ solution, water and brine. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc 20/1 to 10/1) to give the target TBS-ether **136** as a light yellow oil (134.4 mg, 0.32 mmol, 99%).

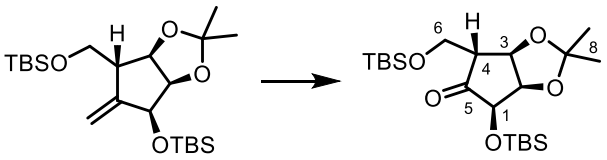
$\mathbf{R_f}$ = 0.40 (petroleum ether/EtOAc=10/1); $\mathbf{[\alpha]_D^{20}}$ = - 101° (*c* = 1.5, $CHCl_3$);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 5.25-5.20 (m, 1H, H-7), 5.10-5.04 (m, 1H, H-7), 4.64-5.537 (m, 1H, H-1), 5.54-4.43 (m, 2H, H-2 and H-3), 3.78 (dd, *J* = 3.80, 9.64 Hz, 1H, H-6), 3.60 (dd, *J* = 3.96, 9.64 Hz, 1H, H-6), 2.60-2.55 (m, 1H, H-4), 1.44 (s, 3H, H-9), 1.36 (s, 3H, H-9'), 0.89 (s, 9H, Si-$(CH_3)_3$), 0.91 (s, 9H, Si-$(CH_3)_3$), 0.17 (s, 3H, Si-CH_3), 0.16 (s, 3H, Si-CH_3), 0.07 (s, 3H, Si-CH_3), 0.06 (s, 3H, Si-CH_3) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 152.9 (s, C-5), 110.9 (s, C-8), 108.4 (t, C-7), 152.9 (s, C-5), 81.0 (d, C-1), 80.8 (d, C-2), 75.4 (d, C-3), 66.4 (t, C-6), 51.5 (d, C-4), 27.3 (s, C1-O-Si-$\underline{C}(CH_3)_3$), 26.1 (q, C1-O-Si-C($\underline{C}H_3)_3$), 26.0 (q, C6-O-Si-C($\underline{C}H_3)_3$), 25.7 (s, C1-O-Si-$\underline{C}(CH_3)_3$), 18.7 (q, C-9), 18.4 (q, C-9'), -4.49 (q, Si-$\underline{C}H_3$), -4.63 (q, Si-$\underline{C}H_3$)), -5.41 (q, Si-$\underline{C}H_3$), -5.46 (q, Si-$\underline{C}H_3$) ppm;

HRMS (ESI): *m/z* calcd. for $C_{22}H_{44}O_4Si_2Na$ $[M+Na]^+$: 451.2778; found: 451.2777.

Synthesis of ketone **135**



136 **135**

(3a*R*,4*R*,6*R*,6a*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-6-(((*tert*-butyldimethylsilyl)oxy)methyl) -2,2-dimethyltetrahydro-5H-cyclopenta[d][1,3]dioxol-5-one (135)

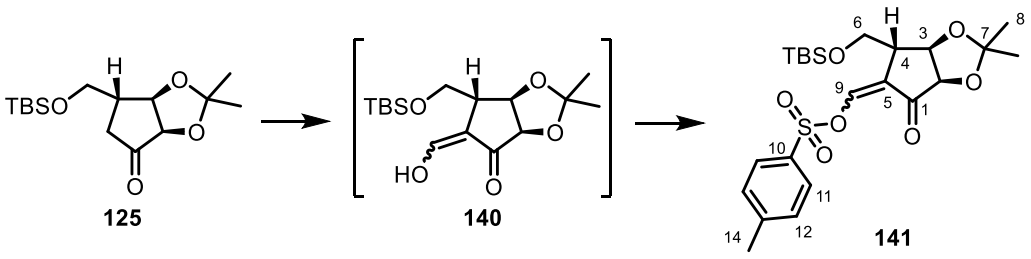
To a mixture of the olefin **136** (28.1 mg, 0.07 mmol) in THF/H_2O (4 mL, 3:1) at room temperature was added NMO (22.8 mg, 0.20 mmol), OsO_4 (2.5 wt. % solution in *t*-BuOH, 3.3 mg, 0.01 mmol), and $NaIO_4$ (41.7 mg, 0.20 mmol) sequentially. The mixture was stirred vigorously at room temperature for 3 h. The reaction was terminated by the addition of saturated aqueous Na_2SO_3 solution. The solution was extracted then with EtOAc. The combined organic layers were washed with an aqueous $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Then the residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 10/1) to give the target product **135** as a light yellow solid (13.2 mg, 0.03 mmol, 49%).

$\mathbf{R}_f$ = 0.40 (petroleum ether/EtOAc =10/1);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 4.72-4.64 (m, 2H, H-1 and H-2), 4.27 (d, *J* = 4.84 Hz, 1H, H-3), 3.91 (dd, *J* = 2.48, 9.46 Hz, 1H, H-6), 3.80 (dd, *J* = 2.86, 9.64 Hz, 1H, H-6), 2.40 (q, *J* = 2.60 Hz, 1H, H-4), 1.44 (s, 3H, H-8), 1.40 (s, 3H, H-8'), 0.96 (s, 9H, Si-$(CH_3)_3$), 0.88 (s, 9H, Si-$(CH_3)_3$), 0.19 (s, 3H, Si-CH_3), 0.13 (s, 3H, Si-CH_3) 0.07 (s, 3H, Si-CH_3), 0.03 (s, 3H, Si-CH_3) ppm;

HRMS (ESI): *m/z* calcd. for $C_{21}H_{42}O_5Si_2Na$ $[M+Na]^+$: 453.2469; found : 453.2469.

Synthesis of tosylate **141**



((3a*R*,4*R*,6a*R*)-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-6-oxotetrahydro-5H-cyclopenta[d][1,3]dioxol-5-ylidene)methyl 4-methylbenzenesulfonate (141)

To a solution of **125** (10.1 mg, 0.07 mmol) in anhydrous toluene (1.1 mL) was added *t*-BuOK (11.3 mg, 0.11 mmol) portionwise and it was stirred at room temperature for 20 min. Then ethyl formate (0.038 mL, 0.47 mmol) was added, and the resulting suspension was stirred at room temperature for 6 h. The final mixture was poured into icy water (1.1 mL) and acidified with 1 M HCl at 0 °C. The organic phase was extracted with EtOAc, washed with water and then brine, dried with Na_2SO_4, filtered, and concentrated *in vacuo*. Then the residue was purified by column chromatography (silica gel, petroleum ether/EtOAc 10/1) to give enol **140** mixed with some inseparable byproducts as a yellow oil, which was applied for the next tosylation without further purification.

To a mixture of the impure enol **140** obtained above (4.0 mg, 0.02 mmol) in toluene (0.5 mL) was added TsCl (5 mg, 0.023 mmol) in toluene (0.5 mL) at 0 °C and it was stirred for 15 min. Then this mixture was successively added dropwise to a solution of *N*-methylimidazole (NMI) (0.0018 mL, 0.023 mmol) and Et_3N (0.0032 mL, 0.023 mmol) in toluene (0.5 mL) at 0° C, and then the temperature was slowly warmed up to room temperature and the mixture was stirred overnight at room temperature. Water was added to the mixture, which was extracted twice with AcOEt. The combined organic phases were washed with brine, dried with Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, petroleum ether /EtOAc = 100/1) to give tosylate **141** as a yellow oil (9.7 mg, 0.02 mmol, 30%).

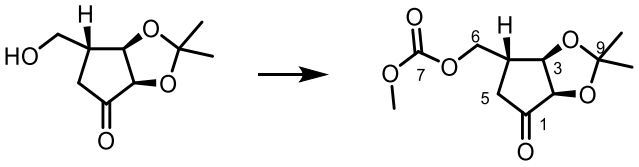
$\mathbf{R_f}$ = 0.10 (petroleum ether /EtOAc =100/1);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 7.85 (d, *J* = 8.53Hz, 2H, H-11 and H-11'), 7.38 (d, *J* = 2.88 Hz, 1H, H-9), 7.34 (d, *J* = 8.53Hz, 2H, H-12 and H-12'), 3.68 (dd, *J* = 5.48, 9.48 Hz, 1H, H-6), 3.57 (dd, *J* = 6.44, 9.76 Hz, 1H, H-6), 3.11-2.99 (m, 1H, H-2), 2.48-2.40 (m, 4H, H-3

and H-14), 2.12 (dd, *J* = 1.95, 1.88 Hz, 1H, H-4), 1.55 (s, 6H, H-8 and H-8'), 0.87 (s, 9H, Si-$(CH_3)_3$), 0.04 (s, 3H, Si-CH_3), 0.036 (s, 3H, Si-CH_3) ppm;

HRMS (ESI): *m/z* calcd. for $C_{23}H_{34}O_7SSiNa$ $[M+Na]^+$: 505.1692; found: 505.1695.

Synthesis of methyl carbonate **148**



((3a*R*,4*R*,6a*R*)-2,2-Dimethyl-6-oxotetrahydro-4H-cyclopenta[d][1,3]dioxol-4-yl)methyl methyl carbonate (148)

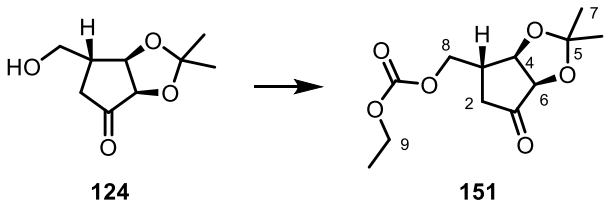
To a solution of alcohol **124** (15.1 mg, 0.08 mmol) in 0.5 mL pyridine was added methyl chloroformate (75.6 mg, 0.80 mmol) at 0 °C. After stirring for 15 min, the reaction was warmed to room temperature. Then the mixture was stirred overnight. After dilution with ice-water, the mixture was acidified with a 20% aqueous HCl solution, extracted with CH_2Cl_2. The combined organic phases were dried with $NaSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 10/1) to give target product **148** as a yellow oil (16.6 mg, 0.068 mmol, 85%).

$\mathbf{R_f}$ = 0.25 (petroleum ether/EtOAc= 10/1);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 5.46 (d, *J* = 5.36 Hz, 1H, H-2), 4.29 (d, *J* = 5.32 Hz, 1H, H-3), 4.28-4.16 (m, 2H, H-6), 3.76 (s, 3H, H-8), 2.87-2.69 (m, 2H, H-4 and H-5), 2.17 (d, *J* = 17.9 Hz, 1H, H-5'), 1.43 (s, 3H, H-10), 1.34 (s, 6H, H-10') ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 212.6 (s, C-1), 155.4 (s, C-7), 112.1 (s, C-9), 80.5 (d, C-2), 78.8 (d, C-3), 69.3 (t, C-6), 55.2 (q, C-8), 39.1 (t, C-5), 36.6 (d, C-4), 26.9 (q, C-10), 24.9 (q, C-10') ppm.

Synthesis of ethyl carbonate **151**



124 **151**

((3a*R*,4*R*,6a*R*)-2,2-Dimethyl-6-oxotetrahydro-4H-cyclopenta[d][1,3]dioxol-4-yl)methyl ethyl carbonate (151)

To a solution of alcohol **124** (18.5 mg, 0.11 mmol), DMAP (3.0 mg, 0.02 mmol) and pyridine (16.6 mg, 0.21 mmol) in THF (0.5 mL) ethyl chloroformate (13.0 mg, 0.01 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 18 h. The mixture was diluted with ethyl acetate (5 mL), and then washed with a 1 M aqueous solution of HCl and brine. The organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 2/1) to give target product **151** as a colorless oil (19.2 mg, 0.08mmol, 76%).

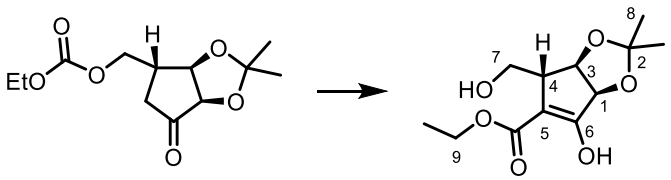
$\mathbf{R_f}$ = 0.30 (petroleum ether/EtOAc = 2/1); $\mathbf{[\alpha]_D^{20}}$ = -126 °(*c* = 0.5, CH_3Cl);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 4.67 (d, *J* = 5.36 Hz, 1H, H-6), 4.30 (d, *J* = 5.36 Hz, 1H, H-3), 4.26-4.14 (m, 4H, H-8 and H-9), 2.85-2.71 (m, 2H, H-4 and one of H-2), 2.17 (d, *J* = 17.8 Hz, 1H, another one of H-2), 1.43 (s, 3H, H-7), 1.34 (s, 3H, H-7), 1.29 (t, 3H, *J* = 7.15 Hz, H-10) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 212.7 (s, C-1), 154.9(s, -COO-), 112.1(s, C-5), 80.4(d, C-6), 78.9(d, C-3), 69.0(t, C-8), 64.6(t, C-9), 37.1 (t, C-2), 36.6 (d, C-4), 26.9 (q, C-10), 24.9 (q, C-7), 14.3 (s, C-7') ppm;

HRMS (ESI): *m/z* calcd. for $C_{12}H_{18}O_6Na$ $[M+Na]^+$: 281.1103; found: 281.1104.

Cyclization of **151**



151 **152**

Ethyl (4*R*)-6-hydroxy-4-(hydroxymethyl)-2,2-dimethyl-3a,6a-dihydro-4H-cyclopenta[d][1,3]dioxole-5-carboxylate (152)

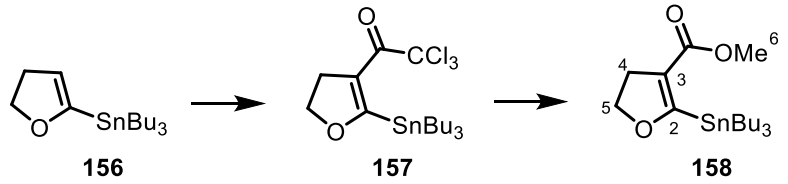
To a solution of ester **151** (18.0 mg, 0.07 mmol) in anhydrous THF (3.5 mL) was added NaH (60% in mineral oil, 33.0 mg, 0.85 mmol) portionwise at room temperature. The mixture was stirred at room temperature for 5 h. Then it was terminated by addition of saturated aqueous NH_4Cl solution. Then the mixture was extracted with EtOAc; The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 1/1) to give a byproduct **152** as a colorless oil (6.0 mg, 0.02 mmol, 31%).

$\mathbf{R}_f$ = 0.20 (petroleum ether/EtOAc = 1/1);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 10.18 (s, 1H, -OH), 5.02 (d, *J* = 5.36 Hz, 1H, H-1), 4.57 (d, *J* = 5.32 Hz, 1H, H-3), 4.29-4.22 (m, 2H, H-9), 3.85 (dd, *J* = 3.44, 10.56 Hz, 1H, H-7), 3.68 (dd, *J* = 4.76, 10.92 Hz, 1H, H-7), 3.08 (t, *J* = 4.00Hz, 1H, H-7), 1.45 (s, 3H, H-8), 1.37 (s, 6H, H-8), 1.31 (t, 3H, *J* = 7.15 Hz, H-10) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 172.3 (s, C-6), 169.5 (s, -COO-), 111.3 (s, C-5), 99.8 (s, C-2), 80.9 (d, C-1), 79.4 (d, C-3), 63.0 (t, C-7), 60.8 (t, C-9), 47.9 (d, C-4), 27.4 (q, C-8) 25.5 (q, C-8'), 14.4 (q, C-10) ppm.

Synthesis of ester **158**



Methyl 2-(tributylstannyl)-4,5-dihydrofuran-3-carboxylate (158)

To a solution of stannane **156** (179.6 mg, 0.51 mmol) and DIPEA (6.5 mg, 0.11 mmol) in dry CH_2Cl_2 (2.0 mL) at 0 °C was added trichloroacetyl chloride (90.9 mg, 0.51 mmol) portionwise over a period of 5 minutes. Then the mixture was slowly warmed to room temperature to continue stirring for 12 hours. Then the reaction was terminated by pouring into water (kept at slightly basic PH by the addition of 10% of aqueous $NaHCO_3$). The mixture was extracted with CH_2Cl_2, and then washed with brine. The organic phase was dried over Na_2SO_4 and filtered. The solvent was removed *in vacuo* to furnish crude compound **157** which was directly applied to the next step without further purification.

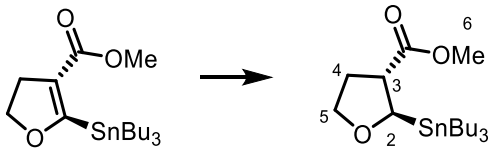
A solution of the crude ketone **157** (200.1 mg, 0.40 mmol) in 10% methanolic triethylamine (40.1 mL) was stirred at room temperature for 48 h. The solvent was removed *in vacuo* and the residue was dissolved in EtOAc (10 mL). And then the mixture was neutralized with 1M aqueous HCl, washed with water and brine. The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 20/1) to give the target ester **158** as a colorless oil (115.1 mg, 0.28 mmol, 70%).

$\mathbf{R_f}$ = 0.40 (petroleum ether/EtOAc = 20/1);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 4.48 (t, *J* = 5.36 Hz, 1H, H-5), 3.69 (s, 3H, H-6), 2.78 (t, *J* = 5.36 Hz, 1H, H-4), 1.50 (m, 6H, -$\underline{CH_2}CH_2CH_2CH_3$), 1.29 (m, 6H, -$CH_2\underline{CH_2}CH_2CH_3$), 1.05 (m, 6H, -$CH_2CH_2\underline{CH_2}CH_3$), 0.88 (m, 9H, -$CH_2CH_2CH_2\underline{CH_3}$) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 184.7(s, -$\underline{C}OO$-), 167.2 (s, C-2), 118.7 (s, C-3), 74.3 (t, C-5), 50.9 (q, C-6), 29.0 (t, -$\underline{CH_2}CH_2CH_2CH_3$), 27.4 (t, -$CH_2\underline{CH_2}CH_2CH_3$), 17.7 (t, C-4),, 13.8(t, -$CH_2CH_2\underline{CH_2}CH_3$),10.8 (q, -$CH_2CH_2CH_2\underline{CH_3}$) ppm.

Synthesis of compound **159**



Methyl (2*R*,3*R*)-2-(tributylstannyl)tetrahydrofuran-3-carboxylate (159)

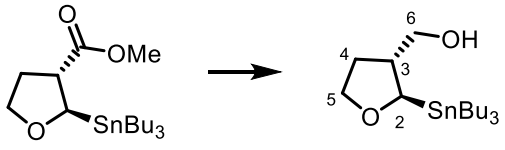
To a solution of vinyl stannane **158** (115.1 mg, 0.28 mmol) in dry CH_2Cl_2 (2.0 mL) at -78 °C was added TFA (63.9 mg, 0.56 mmol) followed by triethylsilane (325.6 mg, 2.81 mmol). After stirring for an hour at -78 °C and another 30 mins at 0 °C, the mixture was allowed to warm to room temperature and continued stirring for 5 h. Then the reaction was terminated by addition of saturated aqueous $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2, and washed with brine. The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 20/1) to give the target product **159** as a colorless oil (80.1 mg, 0.20 mmol, 69%).

$\mathbf{R}_f$ = 0.30 (petroleum ether/EtOAc = 20/1);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 3.90 (m, 1H, H-2), 3.81 (m, 1H, H-5), 3.71-3.64 (m, 4H, H-6 and H-5'), 3.08-3.01 (m, 1H, H-6), 2.22-2.01 (m, 2H, H-4), 1.50 (m, 6H, -$\underline{CH_2}CH_2CH_2CH_3$), 1.29 (m, 6H, -$CH_2\underline{CH_2}CH_2CH_3$) and 0.95-0.87 (m, 15H, -$CH_2CH_2\underline{CH_2}\underline{CH_3}$) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 174.6 (s, -$\underline{C}$OO-), 75.2 (d, C-2), 69.3 (t, C-5), 51.8 (q, C-6), 48.5 (d, C-3), 30.8 (t, C-4), 29.1 (t, -$\underline{CH_2}CH_2CH_2CH_3$), 27.4 (t, -$CH_2\underline{CH_2}CH_2CH_3$), 13.7(t, -$CH_2CH_2\underline{CH_2}CH_3$),8.7 (q, -$CH_2CH_2CH_2\underline{CH_3}$) ppm.

Synthesis of compound **160**



159 **160**

2-(Tributylstannyl)-tetrahydrofuran-3-yl methanol (160)

To a solution of ester **159** (360.1 mg, 0.86 mmol) in anhydrous THF (8.0 mL) was added DIBAL-H (1.8 mL, 1.72 mmol) at 0 °C. The mixture was allowed to stir for 3 h, and then diethyl ether (20.0 ml), water (0.07 ml), 15% of aqueous solution NaOH (0.07 ml) and water (0.07 ml) were added successively. The mixture was warmed up to room temperature, dried with $MgSO_4$ and filtered with a short pad *Celite*. The solvent was removed *in vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 5/1) to give the target product **160** as a colorless oil (277 mg, 0.708 mmol, 82%).

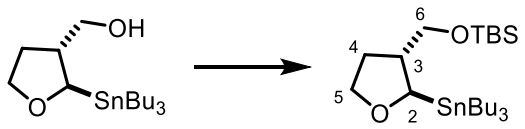
$\mathbf{R}_f$ = 0.30 (petroleum ether/EtOAc = 5/1);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 3.82-3.77 (m, 1H, H-2), 3.62-3.68 (m, 2H, H-5), 3.58 (m, 2H, H-6), 2.50-2.40 (m, 1H, H-3), 2.04-1.96 (m, 1H, H-4), 1.62-1.69 (m, 1H, H-4), 1.50 (m, 6H, -$\underline{CH_2}CH_2CH_2CH_3$), 1.29 (m, 6H, -$CH_2\underline{CH_2}CH_2CH_3$) and 0.95-0.87 (m, 15H, -$CH_2CH_2\underline{CH_2}\underline{CH_3}$) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 75.3 (d, C-2), 68.7 (t, C-6), 65.3 (t, C-5), 46.8 (d, C-3), 30.5 (t, C-4), 29.3 (t, -$\underline{CH_2}CH_2CH_2CH_3$), 27.6 (t, -$CH_2\underline{CH_2}CH_2CH_3$), 13.9(t, -$CH_2CH_2\underline{CH_2}CH_3$), 8.9 (q, -$CH_2CH_2CH_2\underline{CH_3}$) ppm;

HRMS (ESI): *m/z* calcd. for $C_{17}H_{36}O_2SnNa$ $[M+Na]^+$: 415.3615; found: 415.3621.

Synthesis of compound **161**



160 **161**

***tert*-Butyldimethyl(((2*R*,3*R*)-2-(tributylstannyl)tetrahydrofuran-3-yl)methoxy)silane (161)**

To a solution of alcohol **160** (80.1 mg, 0.21 mmol) in anhydrous DMF (1.5 mL) was added TBSCl (40.2 mg, 0.25 mmol), imidazole (50.0 mg, 1.87 mmol) and DMAP (1.2 mg, 0.01 mmol). After the mixture was stirred for 5 h at room temperature, it was diluted with diethyl ether, and washed successively with a saturated aqueous $NaHCO_3$ solution, water and brine. Then the solvent was evaporated *in vacuo*, and the residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 1/0 to 50/1) to give the target TBS-ether **161** (99.1 mg, 0.196 mmol, 96%) as a colorless oil.

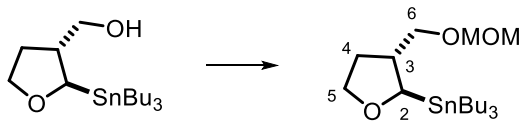
$\mathbf{R}_f$ = 0.20 (petroleum ether/EtOAc = 50/1);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 3.78-3.71 (m, 2H, H-2 and one of H-5), 3.64-3.58 (m, 1H, another one of H-5), 3.58-3.54 (m, 1H, H-6), 3.50-3.446 (m, 1H, H-6), 2.50-2.40 (m, 1H, H-3), 1.97-1.88 (m, 1H, H-4), 1.70-1.62 (m, 1H, H-4), 1.55-1.45 (m, 6H, -$\underline{CH_2}CH_2CH_2CH_3$), 1.35-1.25 (m, 6H, -$CH_2\underline{CH_2}CH_2CH_3$) , 0.92-0.87 (m, 25H, -$CH_2CH_2\underline{CH_2CH_3}$ and Si-C($\underline{CH_3}$)$_3$), 0.04 (d, 6H, Si-($\underline{CH_3}$)$_2$) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 74.6 (d, C-2), 68.6 (t, C-6), 65.1 (t, C-5), 46.8 (d, C-3), 30.5 (t, C-4), 29.4 (t, -$\underline{CH_2}CH_2CH_2CH_3$), 27.6 (t, -$CH_2\underline{CH_2}CH_2CH_3$), 26.1 (s, Si-$\underline{C}(CH_3)_3$) 18.6 (q, - Si-C($\underline{C}H_3$)$_3$), 13.9(t, -$CH_2CH_2\underline{CH_2}CH_3$), 8.8 (q, -$CH_2CH_2CH_2\underline{CH_3}$) , -5.1 (q, Si-C($\underline{C}H_3$)$_2$), -5.2 (q, Si-($\underline{C}H_3$)$_2$) ppm;

HRMS (ESI): *m/z* calcd. for $C_{23}H_{50}O_2SiSnNa$ $[M+Na]^+$: 528.2602; found: 528.2607.

Synthesis of compound **162**



160 **162**

Tributyl((2*R*,3*R*)-3-((methoxymethoxy)methyl)tetrahydrofuran-2-yl)stannane (162)

To a solution of the alcohol **160** (95.1 mg, 0.24 mmol) and DIPEA (0.11 mL, 0.96 mmol) in CH_2Cl_2 (0.5 mL) was added MOM chloride (0.08 mL, 0.72 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 48 h and then treated with a saturated $NaHCO_3$ solution. Following extraction of the aqueous phase with CH_2Cl_2, the combined organic phases were washed with brine, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 20/1) to give the target MOM-ether **162** as a colorless oil (90.0 mg, 0.21 mmol, 88%).

$\mathbf{R}_f$ = 0.40 (petroleum ether/EtOAc = 20/1);

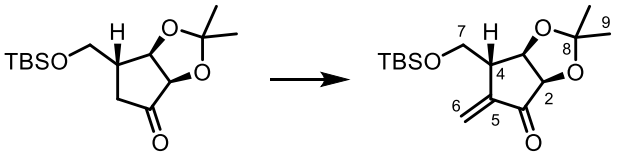
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 4.60 (s, 2H, -OC$\underline{H_2}$OCH$_3$), 3.84-3.77 (m, 1H, H-2), 3.66-3.60 (m, 2H, H-5), 3.52-3.40 (m, 2H, H-6), 4.60 (s, 3H, -OCH$_2$OC$\underline{H_3}$), 2.61-2.50 (m, 1H, H-3), 2.04-1.96 (m, 1H, H-4), 1.60-1.56 (m, 1H, H-4), 1.55-1.45 (m, 6H, -$\underline{CH_2}$CH$_2$CH$_2$CH$_3$), 1.35-1.25 (m, 6H, -CH$_2\underline{CH_2}$CH$_2$CH$_3$), 0.93-0.87 (m, 15H, -CH$_2$CH$_2\underline{CH_2}\underline{CH_3}$) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C= 96.7 (t, -O$\underline{C}$H$_2$OCH$_3$), 75.9 (d, C-2), 70.2 (q, -O$\underline{C}$H$_3$), 68.7 (t, C-6), 55.3 (t, C-5), 44.3 (d, C-3), 30.9 (t, C-4), 29.3 (t, -$\underline{CH_2}$CH$_2$CH$_2$CH$_3$), 27.6 (t, -CH$_2\underline{CH_2}$CH$_2$CH$_3$), 13.9 (t, -CH$_2$CH$_2\underline{CH_2}$CH$_3$) and 8.8 (t, -CH$_2$CH$_2$CH$_2\underline{CH_3}$) ppm;

HRMS (ESI): *m/z* calcd. for $C_{19}H_{40}O_3SnNa$ $[M+Na]^+$: 459.1999; found: 459.2003.

6.3 Supporting information for chapter 3

Synthesis of vinyl ketone **213**



(3a*R*,6*R*,6a*R*)-6-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-5-methylenetetrahydro-4H-cyclopenta[d][1,3]dioxol-4-one (213)

n-BuLi (1M in THF, 1.6 mL, 1.61 mmol) was added dropwise to stirred anhydrous THF (6.1 mL) at -20 °C. To the resulting solution was added diisopropylamine (0.24 mL, 1.71 mmol) under the same conditions and stirring was continued for 1 h. The mixture was cooled to -78 °C and was added a solution of ketone **125** (366.1 mg, 1.22 mmol) in anhydrous THF (2.1 mL) through a cannula. The resulting mixture was stirred for 3 h at -78 °C and then Eschenmoser's salt (903.2 mg, 4.91 mmol) was added in one portion. The mixture was stirred for additional 3 h at -78 °C and for 8 h at room temperature. Then iodomethane (2.6 mL) was added and the mixture was stirred for another 4 h at room temperature. The reaction was terminated by addition of 10% aqueous $NaHCO_3$ solution (10 mL) and stirred for 1 h. The mixture was extracted with diethyl ether. The combined ether extracts were washed with 10% aqueous $NaHCO_3$ solution followed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 95/5) to afford the target vinyl ketone **213** as a light yellow solid (280.1 mg, 0.91 mmol, 74%).

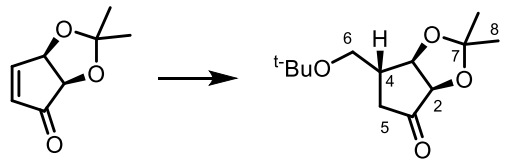
R_f = 0.25 (petroleum ether/EtOAc = 95/5); **M. p.** = 67-69 °C; **$[\alpha]_D^{20}$** = -165° (*c* = 0.6, $CHCl_3$);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 6.28-6.26 (m, 1H, H-6), 5.54-5.53 (m, 1H, H-6), 4.62 (d, *J* = 5.3 Hz, 1H, H-7), 4.47 (d, *J* = 5.3 Hz, 1H, H-7), 3.92 (dd, *J* = 9.9, 3.0 Hz, 1H, H-2), 3.74 (dd, *J* = 9.6, 3.4 Hz, 1H, H-3), 3.08-3.08 (m, 1H, H-4), 1.37 (s, 3H, H-9), 1.35 (s, 3H, H-10), 0.83 (s, 9H, SiC($C\underline{H}_3$)$_3$), 0.01 (s, 3H, Si-$C\underline{H}_3$), -0.03 (s, 3H, Si-$C\underline{H}_3$);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 203.2 (s, C-1), 144.4 (s, C-5), 122.4 (t, C-6), 111.4 (s, C-8), 80.2 (d, C-2), 79.3 (d, C-3), 66.5 (t, C-7), 46.4 (d, C-4), 27.4 (q, SiC($\underline{C}H_3$)$_3$), 25.9 (q, C-9), 25.5 (q, C-9), 18.4 (s, Si$\underline{C}$(CH_3)$_3$), -5.5 (q, Si-$\underline{C}H_3$), -5.6 (q, Si-$\underline{C}H_3$) ppm;

HRMS (ESI): *m/z* calcd. for $C_{16}H_{28}O_4SiNa$ $[M+Na]^+$: 335.1655; found: 335.1656.

Synthesis of ketone **214**



112 **214**

(3a*R*,6*R*,6a*R*)-6-(*tert*-Butoxymethyl)-2,2-dimethyltetrahydro-4H-cyclopenta[d][1,3]dioxol-4-one (214)

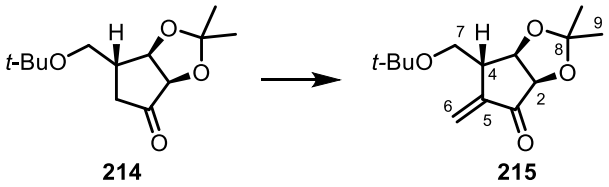
t-BuOK (168.1 mg, 1.51 mmol) was suspended in anhydrous *tert*-butylmethyl ether (5 mL) under argon atmosphere. After being cooled to -78 °C, the well-stirred mixture was treated with *sec*-BuLi (1.3 M in cyclohexane, 1.2 mL, 1.51 mmol) over 10 min. After the mixture was stirred for 2.5 h at -78 °C, a solution of LiBr (2 M in THF, 3.1 mL) was added dropwise over 10 min at -78 °C, and the resulting solution was stirred at -15 °C for 30 min. Upon recooling to -78 °C, a solution of $CuBr_2 \cdot SMe_2$ (148 mg, 0.75 mmol) in *iso*-propyl sulfide (1.1 mL) was added dropwise over 10 min. The resulting viscous dark solution was stirred for 1 h at -78 °C and treated with a solution of the enone **112** (74 mg, 0.48 mmol) in THF (7 mL) over 5 min. The reaction mixture was allowed to warm to -30 °C over 15 min. After 30 min at -30 °C, a 1:1 mixture of acetic acid and methanol (168 mL) was added and the mixture poured into 20 mL of an aqueous NH_4Cl/NH_4OH solution (pH = 9). After removal of the aqueous layer, the organic layer was washed with a 1:1 mixture of saturated NH_4Cl solution and 3% of aqueous NH_4OH solution (30 mL) and then brine. The organic phase was dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified by column chromatography (silica gel , petroleum ether/EtOAc = 20/1) to afford the target ketone **214** as a light yellow oil (101.7 mg, 0.42 mmol, 87%).

$\mathbf{R_f}$ = 0.25 (petroleum ether/EtOAc = 10/1); $\mathbf{[\alpha]_D^{20}}$ = - 176° (*c* = 1.5, $CHCl_3$);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 4.60 (d, J = 5.40 Hz, 1H, H-6), 4.20 (d, J = 5.40 Hz, 1H, H-6), 3.51(dd, J = 8.5, 2.4 Hz, H-2), 3.33(dd, J = 8.5, 2.4 Hz, H-3), 2.69 (dd, J = 17.9, 8.9 Hz, 1H, H-7), 2.51(d, J = 8.8 Hz, 1H, H-7), 2.02 (m, 1H, H-4), 1.40 (q, 3H, H-9), 1.32 (q, 3H, H-10), 0.83 (q, 9H, $OC(C\underline{H}_3)_3$) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 213.1 (s, C-1), 111.0 (s, C-7), 82.2(t, C-6), 79.2 (d, C-2), 73.6 (d, C-3), 63.2 (s, $O\underline{C}(CH_3)_3$),) 37.7 (d, C-4), 37.5 (t, C-5), 27.2 (q, $OC\text{-}\underline{C}H_3$), 26.9 (t, C-8), 24.7 (t, C-9) ppm.

Synthesis of vinyl ketone **215**



(3a*R*,6*R*,6a*R*)-6-(*tert*-Butoxymethyl)-2,2-dimethyl-5-methylenetetrahydro-4Hcyclopenta-[d][1,3]dioxol-4-one (215)

n-BuLi (1.6 M in THF, 0.21 mL, 0.29 mmol) was added dropwise to stirred anhydrous THF (2.1 mL) at -20 °C. To the resulting solution was added diisopropylamine (0.04 mL, 0.31 mmol) under the same conditions and stirring was continued for 1 h. The mixture was cooled to -78 °C and a solution of ketone **214** (53 mg, 0.22 mmol) in anhydrous THF (2 mL) was added through a cannula. The mixture was stirred for 3 h at -78 °C and Eschenmoser's salt (163 mg, 0.88 mmol) was added in one portion. The mixture was stirred for additional 3 h at -78 °C and warmed up to room temperature and stirring was continued for 8 h. Then iodomethane (0.3 mL, excess) was added and the mixture was stirred for 4 h at room temperature. The reaction was terminated by addition of 10% of an aqueous $NaHCO_3$ solution and the mixture was stirred for 1 h. The mixture was extracted with diethyl ether. The combined organic phases were washed with 10% aqueous $NaHCO_3$ solution followed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 95/5) to afford the target vinyl ketone **215** as a light yellow semisolid (34.8 mg, 0.14 mmol, 64%).

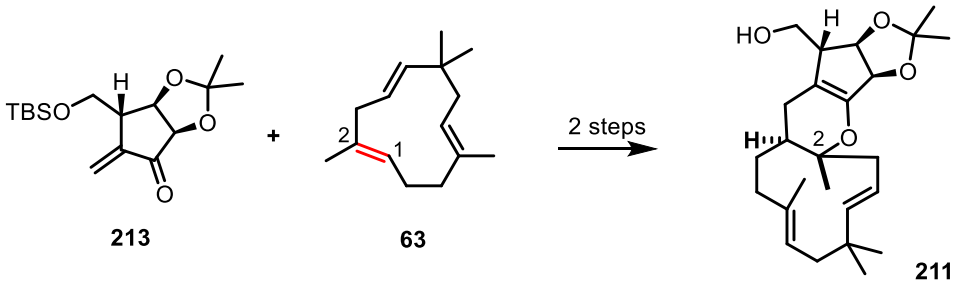
$\mathbf{R_f}$ = 0.20 (petroleum ether/EtOAc = 10/1); $\mathbf{[\alpha]_D^{20}}$ = - 105° (*c* = 0.5, $CHCl_3$);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 6.22 (m, 1H, H-6), 5.51 (dd, J = 1.6, 0.6 Hz, 1H, H-6), 4.54 (dd, J = 43.1, 5.3 Hz, 2H, H-7), 3.63 (dd, J = 8.3, 3.1 Hz, 1H, H-2), 3.74 (dd, J = 8.3, 3.4 Hz, 1H, H-3), 3.10-3.06 (m, 1H, H-4), 1.36 (s, 3H, H-9), 1.34 (s, 3H, H-9'), 1.07 (s, 9H, $OC(C\underline{H}_3)_3$) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 203.5 (s, C-1), 144.9 (s, C-5), 121.7 (t, C-6), 111.3 (s, C-8), 80.3 (d, C-2), 79.5 (d, C-3), 73.3 (t, C-7), 64.7 (s, $O\underline{C}(CH_3)_3$), 44.8 (d, C-4), 27.2 (q, $OC(\underline{C}H_3)_3$), 26.9 (t, C-9), 24.7 (t, C-10) ppm;

HRMS (ESI): *m/z* calcd. for $C_{14}H_{22}O_4Na$ $[M+Na]^+$: 277.1414; found: 277.1416.

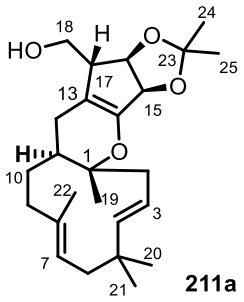
Synthesis of intermediate **211**



((3a*R*,4a*R*,6*E*,10*E*,13a*S*,15*R*,15a*R*)-2,2,4a,8,8,11-Hexamethyl3a,4a,8,9,12,13,13a,14,15,15a-decahydro-5H-[1,3]dioxolo[4',5':4,5]cyclopenta[1,2-b]cycloundeca[e]pyran-15yl)metha–nol (211)

To a 5 mL sealed-tube was added **213** (23 mg, 0.07 mmol) and α-humulene (0.3 mL), the mixture was heated under refluxing conditions for 5 d. After cooling to room temperature, the mixture was concentrated *in vacuo*. Excess of α-humulene was removed by column chromatography (silica gel, petroleum ether/EtOAc = 1/0 to 10/1) to furnish an inseparable mixture of adducts and additional byproducts (25.8 mg), which was directly applied for next step without further purification.

This mixture of adducts and byproducts (25.8 mg) in anhydrous THF (1 mL) was treated with TBAF (1 M in THF, 0.10 mL, 0.10 mmol) at 0 ^{o}C. After warmed up to room temperature, the mixture was stirred at same temperature for 24 h. The reaction was terminated by addition of a saturated aqueous $NaHCO_3$ solution. The mixture was extracted with diethyl ether. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 10/1 to 5/1) to afford two isomers: **211a** as a colorless oil (6.9 mg, 0.017 mmol, 25%), and **211b** as a colorless oil (5.9 mg, 0.015 mmol, 21%).



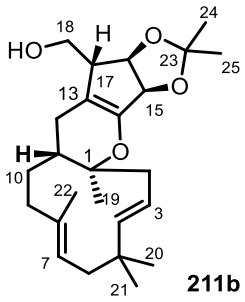
211a

$\mathbf{R_f}$ = 0.60 (petroleum ether/EtOAc = 1/1); $\mathbf{[\alpha]_D^{20}}$ = - 18.1^{o} (c = 0.5, CH_3OH);

^{1}H-NMR (400 MHz, MeOD): δ_H = 5.20-5.09 (m, 2H, H-3 and H-4), 5.05 (dd, *J* = 13.0, 3.0 Hz, 1H, H-7), 4.93 - 4.85 (m, 1H, H-15), 4.55 (dd, *J* = 6.1, 0.9 Hz, 1H, H-16), 3.72 (dd, *J* = 11.0, 4.1 Hz, 1H, H-18), 3.48 (dd, *J* = 11.1, 6.8 Hz, 1H, H-18), 2.65-2.60 (m, 1H, H-17), 2.42-2.39 (m, 1H, H-2), 2.36-2.26 (m, 2H, H-2 and H-12), 2.20 (t, *J* = 12.6 Hz, 1H, H-6), 2.05 (dd, *J* = 12.6, 7.6 Hz, 1H, H-9), 1.80 (dd, *J* = 12.3, 10.8 Hz, 1H, H-9), 1.79-1.69 (m, 2H, H-6' and H-11), 1.59 (s, 3H, H-22), 1.60-1.51 (m, H-12'), 1.36 (s, 3H, H-24), 1.33 (s, 3H, H-25), 1.36-1.31 (overlapped, 1H, H-10), 1.15-1.09 (m, 1H, H-10'), 1.05 (s, 3H, H-19), 1.04 (s, 3H, H-20), 1.03 (s, 3H, H-21) ppm;

^{13}C-NMR (100 MHz, MeOD): δ_C = 150.7 (s, C-14), 142.8 (d, C-4), 137,8 (s, C-8), 123.8 (d, C-7), 122.0 (d, C-3), 111.5 (s, C-23), 109.0 (s, C-13), 82.6 (s, C-1), 82.3 (d, C-15), 81.5 (d, C-16), 63.2 (t, C-18), 53.1 (d, C-17), 43.5 (t, C-2), 42.4 (t, C-6), 39.1 (s, C-9), 38.8 (t, C-5), 37.4 (d, C-11), 31.8 (t, C-10), 30.8 (q, C-20), 27.9 (q, C-24), 26.6 (t, C-12), 26.2 (q, C-25), 24.6 (q, C-21), 19.6 (q, C-19), 17.3 (q, C-22) ppm;

HRMS (ESI): *m/z* calcd. for $C_{25}H_{38}O_4Na$ $[M+Na]^+$: 425.2668; found: 425.2665.



211b

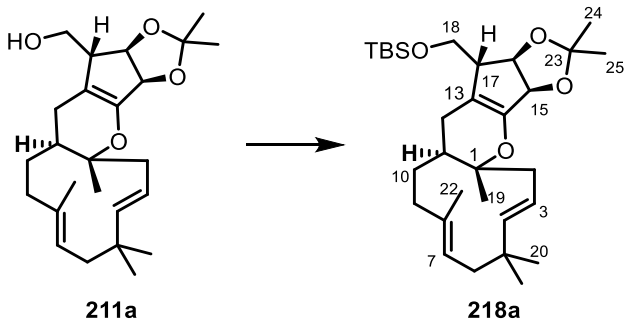
R_f = 0.50 (petroleum ether/EtOAc = 1/1); **$[\alpha]_D^{20}$ =** - 15 ^{o} (*c* = 0.4, CH_3OH);

^{1}H-NMR (400 MHz, C_6D_6): δ_H = 5.49 (ddd, *J* = 16.0, 10.6, 2.5 Hz, 1H, H-3), 5.05 (dd, *J* = 16.0, 1.7 Hz, 1H, H-4), 5.05- 4.95 (m, overlapped, 2H, H-7 and H-16), 4.45 (d, *J* = 5.7 Hz, 1H, H-15), 3.42 (d, *J* = 6.4 Hz, 1H, H-18), 3.22 (dd, *J* = 10.2, 5.7 Hz, 1H, H-18), 2.77 (t, *J* = 4.5 Hz, 1H, H-17), 2.60 (dt, *J* = 14.2, 2.2 Hz, 1H, H-2), 2.15 (t, *J* = 12.4 Hz, 1H, H-9), 2.11 (dd, *J* = 14.2, 10.7 Hz, 1H, H-2'), 2.00 (dd, *J* = 16.7, 5.3 Hz, 1H, H-12), 1.93 (dd, *J* = 12.6, 7.3 Hz, 1H, H-6), 1.86-1.78 (m, 1H, H-11), 1.77-1.68 (m, 2H, H-9' and 6'), 1.59 (s, 3H, H-24), 1.48 (s, 3H, H-22), 1.46-1.41 (m, 1H, H-12'), 1.41 (s, 3H', H-25), 1.11-1.05 (m, 1H, H-10), 1.04 (s, 6H, H-20 and H-21), 0.91 (s, 3H, H-19), 0.82-0.75 (m, 1H, H-10') ppm;

^{13}C-NMR (100 MHz, C_6D_6): δ_C = 150.6 (s, C-14), 141.4 (d, C-4), 136.0 (s, C-8), 123.2 (d, C-7), 121.4 (d, C-3), 110.2 (s, C-23), 106.2 (s, C-13), 82.2 (t, C-16), 80.9 (s, C-1), 80.2 (d, C-15), 63.0 (t, C-18), 53.0 (d, C-17), 42.6 (t, C-2), 41.6 (t, C-9), 38.0 (t, C-6), 37.7 (s, C-5), 35.8 (d, C-11), 30.1 (t, C-10), 30.1 (q, C-20), 28.2 (q, C-24), 26.5 (q, C-25), 26.0 (t, C-12), 23.8 (q, C-21), 19.2 (q, C-19), 16.9 (q, C-22) ppm;

HRMS (ESI): *m/z* calcd. for $C_{25}H_{38}O_4Na$ $[M+Na]^+$: 425.2668; found: 425.2668.

Synthesis of TBS-ether **218a**



211a **218a**

***tert*-Butyl(((3a*R*,4a*R*,6*E*,10*E*,13a*S*,15*R*,15a*R*)-2,2,4a,8,8,11-hexamethyl 3a,4a,8,9, 12,13, 13a,14,15,15a-decahydro-5H-[1,3]dioxolo[4',5':4,5]cyclopenta[1,2-b]cycloundeca[e]pyra n-15-yl)methoxy)dimethylsilane (218a)**

To a solution of **211a** (4.2 mg, 0.011 mmol) in dry CH_2Cl_2 (1.1 mL) 2,6-Lutidine (3.1 mg, 0.022 mmol) was added dropwise followed by the addition of TBSOTf (6.1 mg, 0.022 mmol) at -78 ^oC. The mixture was stirred at -78 ^oC for 2 h. The reaction was terminated with saturated aqueous $NaHCO_3$ solution (5 mL). The mixture was warmed up to room temperature and extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over anhydrous $NaSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 1/0 to 70/1) to furnish the target TBS-ether **218a** as a crystalline solid (4.6 mg, 0.009 mmol, 81%).

R_f = 0.55 (petroleum ether/EtOAc = 20/1); **M. p. =** 109-111 ^oC;

$[\alpha]_D^{25}$ = - 16^o (*c* = 0.26, CH_3OH);

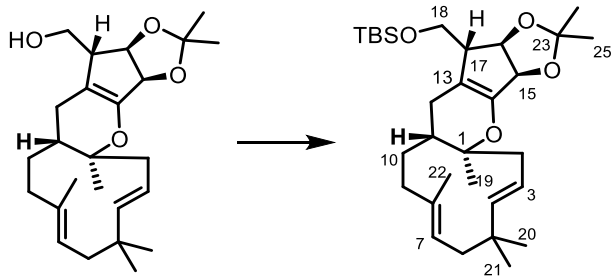
^{1}H-NMR (400 MHz, MeOD): δ_H = 5.20-5.05 (m, 2H, H-3 and H-4), 5.01 (dd, *J* = 12.0, 3.0 Hz, 1H, H-7), 4.81 - 4.84 (m, 1H, H-15), 4.52 (d, *J* = 5.9 Hz, 1H, H-16), 3.75 (ddd, *J* = 15.9, 3.5, 3.3 Hz, 2H, H-18), 2.60 (t, *J* = 3.7 Hz, 1H, H-17), 2.41 (m, 1H, H-2), 2.35-2.25 (m, 2H, H-2 and H-12), 2.21 (t, *J* = 12.5 Hz, 1H, H-6), 2.17 (dd, *J* = 12.7, 7.7 Hz, 1H, H-9), 1.82-1.67 (m, 3H, H-9', H-6' and H-11), 1.61 (s, 3H, H-22), 1.60-1.50 (m, H-12'), 1.38-1.34 (m, 1H, H-10), 1.35 (s, 3H, H-24), 1.32 (s, 3H, H-25), 1.15-1.08 (m, 1H, H-10'), 1.04(s, 9H, H-19, H-20 and H-21), 0.90 (s, 9H, $SiC(C\underline{H}_3)_3$), 0.07 (s, 3H, $Si\text{-}C\underline{H}_3$), 0.06 (s, 3H, $Si\text{-}C\underline{H}_3$).

^{13}C-NMR (100 MHz, MeOD): δ_C = 150.9 (s, C-14), 142.9 (d, C-4), 138.0 (s, C-8), 123.7 (d, C-7), 122.0 (d, C-3), 111.4 (s, C-23), 108.5 (s, C-13), 82.6 (s, C-1), 82.4 (d, C-15), 81.7 (d, C-16), 63.2 (t, C-18), 52.6 (d, C-17), 43.5 (t, C-2), 42.3 (t, C-6), 39.1 (s, C-5), 39.0 (t, C-9), 37.5

(d, C-11), 31.7 (t, C-10), 30.7 (q, C-19), 28.1 (q, C-24), 26.5 (t, C-12), 26.4 (q, SiC($\underline{C}H_3)_3$), 26.3 (q, C-25), 24.9 (q, C-20), 19.5 (q, C-21), 19.0 (s, Si$\underline{C}(CH_3)_3$), 17.3 (q, C-22), -5.0 (q, Si-$\underline{C}H_3$), -5.3 (q, Si-$\underline{C}H_3$).

HRMS (ESI): *m/z* calcd. for $C_{31}H_{52}O_4SiNa$ $[M+Na]^+$: 539.3525; found: 539.3528.

Synthesis of TBS-ether **218b**



211b **218b**

***tert*-Butyl(((3a*R*,4a*R*,6*E*,10*E*,13a*S*,15*R*,15a*R*)-2,2,4a,8,8,11-hexamethyl 3a,4a,8,9, 12,13, 13a,14,15,15a-decahydro-5H-[1,3]dioxolo[4',5':4,5]cyclopenta[1,2-b]cycloundeca[e]pyran-15-yl)methoxy)dimethylsilane (218b)**

To a solution of **211b** (8.4 mg, 0.022 mmol) in CH_2Cl_2 (2 mL) 2,6-lutidine (6.1 mg, 0.044 mmol) was added dropwise followed by the addition of TBSOTf (12 mg, 0.044 mmol) at -78 ^oC. The mixture was stirred at -78 ^oC for 2 h. The reaction was terminated by addition of a saturated aqueous $NaHCO_3$ solution (5 mL). The mixture was warmed to room temperature and extracted with CH_2Cl_2; The combined organic phases were washed with brine, dried over anhydrous $NaSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 1/0 to 70/1) to furnish the target TBS-ether **218b** as a crystalline solid (4.6 mg, 0.01 mmol, 85%).

$\mathbf{R_f}$ = 0.60 (petroleum ether/EtOAc = 20/1); $\mathbf{[\alpha]_D^{25}}$ = - 18^o (*c* = 0.26, CH_3OH);

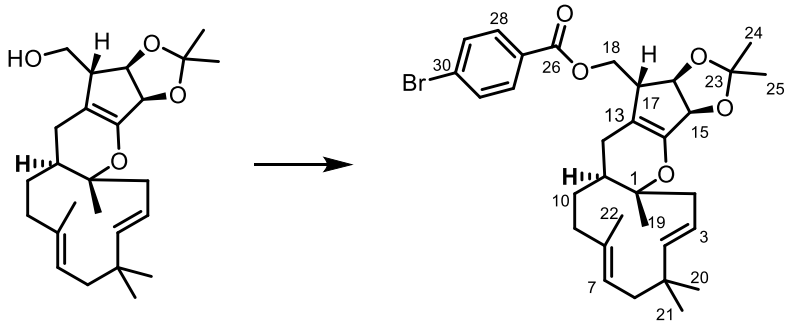
^{1}H-NMR (400 MHz, MeOD): δ_H = 5.20 (ddd, *J* = 15.9, 9.6, 2.5 Hz, 1H, H-3), 5.12 (dd, *J* = 15.9, 1.4 Hz, 1H, H-4), 5.02 (dd, *J* = 11.9, 3.2 Hz, 1H, H-7), 4.83 - 4.79 (m, 1H, H-16), 4.44 (d, *J* = 2.6 Hz, 1H, H-15), 3.74 (dd, *J* = 9.9, 3.9 Hz, 1H, H-18), 3.58 (dd, *J* = 9.9, 4.6 Hz, 1H, H-18'), 2.64 (t, *J* = 4.0 Hz, 1H, H-17), 2.42-2.26 (m, 2H, H-2), 2.21 (t, *J* = 12.4 Hz, 1H, H-6), 2.17 (dd, *J* = 16.6, 5.2 Hz, 1H, H-12), 2.06 (dd, *J* = 12.8, 7.5 Hz, 1H, H-9), 1.85-1.77 (m, 2H, H-9' and H-11), 1.77-1.71 (m, 1H, H-6'), 1.70-1.628 (m, H-12'), 1.62 (s, 3H, H-22), 1.40 (s,

3H, H-24), 1.38-1.26 (m, 1H, H-10), 1.34 (s, 3H, H-25), 1.12-1.06 (m, 1H, H-10'), 1.04 (s, 3H, H-19), 1.02 (s, 6H, H-20 and H-21), 0.88 (s, 9H, SiC($C\underline{H}_3$)$_3$), 0.07 (s, 3H, Si-$C\underline{H}_3$), 0.04 (s, 3H, Si-$C\underline{H}_3$);

^{13}C-NMR (100 MHz, MeOD): δ_C = 150.6 (s, C-14), 142.8 (d, C-4), 137.9 (s, C-8), 123.8 (d, C-7), 122.3 (d, C-3), 111.5 (s, C-23), 108.8 (s, C-13), 83.6 (d, C-15), 82.7 (s, C-1), 81.6 (d, C-16), 64.1 (t, C-18), 53.8 (d, C-17), 43.4 (t, C-2), 42.5 (t, C-6), 39.2 (s, C-5), 38.3 (t, C-9), 37.2 (d, C-11), 31.3 (t, C-10), 30.7 (q, C-19), 28.5 (q, C-20), 27.0 (q, C-21), 26.8 (t, C-12), 26.3 (q, SiC($\underline{C}H_3$)$_3$), 24.6 (q, C-24), 20.1 (q, C-25), 18.9 (s, Si$\underline{C}$(CH_3)$_3$), 17.3 (q, C-22), -5.4 (q, Si-$\underline{C}H_3$), -5.5 (q, Si-$\underline{C}H_3$);

HRMS (ESI): *m/z* calcd. for $C_{31}H_{52}O_4SiNa$ $[M+Na]^+$: 539.3525; found: 539.3528.

Synthesis of benzoate **217a**



((3a*R*,4a*R*,6*E*,10*E*,13a*S*,15*R*,15a*R*)-2,2,4a,8,8,11-hexamethyl-3a,4a,8,9,12,13,13a,14,15,15 1a-decahydro-5H-[1,3]dioxolo[4',5':4,5]cyclopenta[1,2-b]cycloundeca[e]pyran-15yl)meth yl-4-bromobenzoate (217a)

To a solution of **211a** (6.5 mg, 0.016 mmol) in anhydrous THF (1 mL) was added DMAP (3.1 mg, 0.024 mmol) and 4-bromobenzoyl chloride (6.1 mg, 0.026 mmol) at room temperature. CH_2Cl_2 (3 mL) was added to aid in the dissolution of the reagents. The mixture was stirred at room temperature for 5 h. And then the reaction was terminated by addition of water (2 ml). The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over anhydrous $NaSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 1/0 to 10/1) to furnish the target benzoate **217a** as a light yellow oil (9.1 mg, 0.015 mmol, 95%).

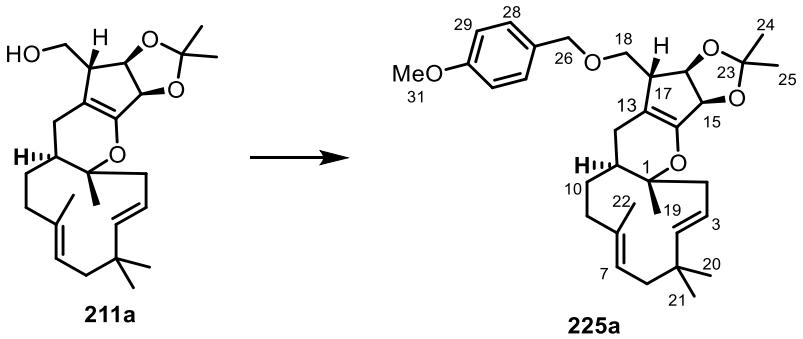
$\mathbf{R_f}$ = 0.60 (petroleum ether/EtOAc = 10/1);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 7.88 (d, *J* = 8.6 Hz, 2H, H-28), δ_H = 7.60 (d, *J* = 8.6 Hz, 2H, H-29), 5.20-4.90 (overlapped, 3H, H-3, H-4 and H-15), 4.88 (dd, *J* = 11.5, 4.2 Hz, 1H, H-7), 4.64 (d, *J* = 6.0 Hz, 1H, H-16), 4.56 (dd, *J* = 11.2, 5.4 Hz, 1H, H-18), 4.38 (dd, *J* = 11.2, 3.3 Hz, 1H, H-18), 2.98 (t, *J* = 4.2 Hz 1H, H-17), 2.60-2.41 (m, 1H, H-2), 2.40-2.30 (m, 1H, H-12), 2.23 (d, *J* = 10.0 Hz, 1H, H-2), 2.15 (dd, *J* = 24.7, 12.4 Hz, 1H, H-6), 2.05 (dd, *J* = 12.6, 7.7 Hz, 1H, H-9), 1.76 (t, *J* = 12.0 Hz 1H, H-9), 1.72-1.67 (m, 1H, H-6'), 1.65-1.55 (overlapped, 5H, H-2', H-11 and H-22), 1.44 (s, 3H, H-24), 1.39 (s, 3H, H-25), 1.22-1.20 (m, 1H, H-10), 1.15-1.09 (m, 1H, H-10'), 1.07 (s, 3H, H-19), 1.03 (s, 3H, H-20), 0.8 (s, 3H, H-21) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 165.7 (s, C-26), 150.5 (s, C-14), 141.2 (d, C-4), 136.7 (s, C-8), 132.1 (d, C-28), 131.1 (d, C-29), 129.0 (s, C-30), 128.4 (s, C-27), 123.0 (d, C-7), 120.1 (d, C-3), 111.0 (s, C-23), 105.7 (s, C-13), 81.8 (s, C-1), 81.2 (d, C-15), 80.3 (d, C-16), 64.6 (t, C-18), 49.4 (d, C-17), 42.4 (t, C-2), 41.5 (t, C-6), 38.2 (t, C-9), 37.9 (s, C-5), 36.3 (d, C-11), 30.5 (t, C-10), 30.4 (q, C-20), 27.8 (q, C-24), 26.1 (q, C-25), 25.4 (t, C-12), 24.2 (q, C-21), 19.4 (q, C-19), 17.3 (q, C-22) ppm;

HRMS (ESI): *m/z* calcd. for $C_{32}H_{41}O_4BrO_5Na$ $[M+Na]^+$: 607.2038; found: 607.2040.

Synthesis of PMB-ether **225a**



211a 225a

(3a*R*,4a*R*,6*E*,10*E*,13a*S*,15*R*,15a*R*)-15-(((4-Methoxybenzyl)oxy)methyl)-2,2,4a,8,8,11-hexamethyl-3a,4a,8,9,12,13,13a,14,15,15a-decahydro-5H [1,3]dioxolo[4',5':4,5]cyclopenta[1,2-b]cycloundeca[e]pyran (225a)

To a solution of **211a** (20.1 mg, 0.05 mmol) in anhydrous toluene (0.5 mL) was added $Sc(OTf)_3$ (2.5 mg, 0.005 mmol) and 4-methoxybenzyl-2,2,2-trichloroacetimidate (21.1 mg,

0.075 mmol) at 0 °C. After the mixture was stirred at 0 ℃ for 30 min, it was allowed to warm to room temperature and stirred for 4 h. The reaction was terminated by addition of water (2 mL), and then the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 1/0 to 20/1) to furnish the target PMB-ether **225a** as a colorless oil (15.1 mg, 0.029 mmol, 58%).

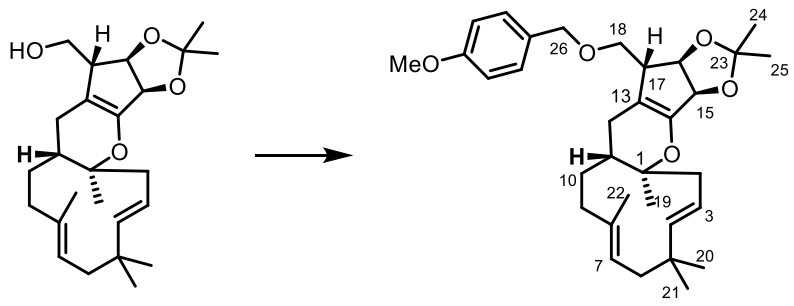
$\mathbf{R_f}$ = 0.60 (petroleum ether/EtOAc = 5/1); $\mathbf{[\alpha]_D^{20}}$ = -15 ^{o} (*c* = 0.88 , $CHCl_3$);

^{1}H-NMR (400 MHz, C_6D_6): δ_H = 7.19 (d, *J* = 9.2 Hz, 2H, H-28), 6.83 (d, *J* = 8.7 Hz, 2H, H-29), 5.45 (ddd, *J* = 15.9, 10.7, 2.5 Hz , 1H, H-3), 5.11-4.95 (overlapped, 3H, H-4, H-7 and H-15), 4.58 (d, *J* = 6.1 Hz, 1H, H-16), 4.28 (dd, *J* = 35.9, 11.8 Hz, 2H, H-26), 3.38 (dd, *J* = 9.2, 4.6 Hz, 1H, H-18), 3.32 (s, 3H, H-31), 3.23 (dd, *J* = 9.2, 4.6 Hz, 1H, H-18), 3.00 (t, *J* = 5.0 Hz 1H, H-17), 2.66 (dt, *J* = 14.4, 2.5 Hz, 1H, H-2), 2.26 (ddd, *J* = 16.9, 5.5, 2.0 Hz , 1H, H-12), 2.14 (t, *J* = 12.4 Hz, 1H, H-6), 2.13 (dd, *J* = 14.5, 10.7 Hz, 1H, H-2'), 1.96 (dd, *J* = 12.5, 7.6 Hz, 1H, H-9), 1.88-1.76 (overlapped, 2H, H-11 and H-9'), 1.70 (dd, *J* = 12.8, 4.3 Hz, 1H, H-6'), 1.55 (s, 3H, H-24), 1.49 (s, 3H, H-22), 1.46-1.38 (m, 1H, H-12'), 1.35 (s, 3H, H-25), 1.13-1.07 (m, 1H, H-10), 1.06 (s, 3H, H-19), 1.01 (s, 3H, H-20), 0.95 (s, 3H, H-21), 0.82 (m, 1-H, H-10') ppm.

^{13}C-NMR (100 MHz, C_6D_6): δ_C = 159.8 (s, C-30), 150.5 (s, C-14), 141.9 (d, C-4), 136.7 (s, C-8), 131.2 (s, C-27), 129.3 (d, C-28), 123.3 (d, C-7), 121.7 (d, C-3), 114.2 (d, C-29), 110.6 (s, C-23), 107.7 (s, C-13), 81.7 (d, C-15), 81.2 (s, C-1), 80.9 (d, C-16), 73.0 (t, C-26), 70.7 (t, C-18), 54.8 (q, C-31), 50.4 (d, C-17), 43.0 (t, C-2), 41.8 (t, C-6), 38.3 (s, C-5), 38.3 (t, C-9), 36.6 (d, C-11), 31.0 (t, C-10), 30.5 (q, C-20), 28.2 (q, C-24), 26.3 (q, C-25), 26.2 (t, C-12), 24.4 (q, C-21), 19.5 (q, C-19), 17.3 (q, C-22) ppm;

HRMS (ESI): *m/z* calcd. for $C_{33}H_{46}O_5Na$ $[M+Na]^+$: 545.3243; found: 545.3243.

Synthesis of PMB-ether **225b**



211b **225b**

(3a*R*,4a*S*,6*E*,10*E*,13a*R*,15*R*,15a*R*)-15-(((4-Methoxybenzyl)oxy)methyl)-2,2,4a,8,8,11-hexamethyl-3a,4a,8,9,12,13,13a,14,15,15a-decahydro-5H[1,3]dioxolo[4',5':4,5]cyclopenta[1,2-b]cycloundeca[e]pyran (225b)

To a suspension of NaH (60% in mineral oil, 4.1 mg, 0.101 mmol) in anhydrous DMF (0.5 mL) was added a solution of **211b** (37 mg, 0.092 mmol) in anhydrous DMF (1.5 mL), and the mixture was stirred at 0 °C for 30 min. After the addition of PMBCl (0.015 mL, 0.11 mmol), the mixture was allowed to warm to room temperature, and then stirred for 48 h. The reaction was terminated by addition of water (2 mL), and then the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 1/0 to 20/1) to furnish the target PMB-ether **225b** as a colorless oil (24.1 mg, 0.046 mmol, 50%);

$\mathbf{R_f}$ = 0.43 (petroleum ether/EtOAc = 5/1); $\mathbf{[\alpha]_D^{20}}$ = -16.2° (*c* = 0.45 , $CHCl_3$);

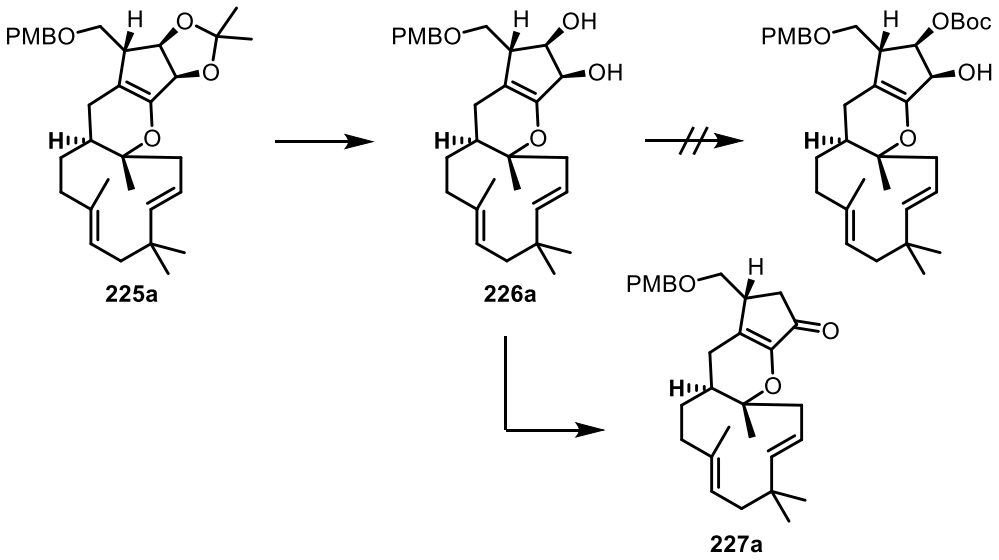
^{1}H-NMR (400 MHz, C_6D_6): δ_H = 7.19 (d, *J* = 8.7 Hz, 2H, H-28), 6.80 (d, *J* = 8.7 Hz, 2H, H-29), 5.15 (ddd, *J* = 16.0, 10.6, 2.4 Hz , 1H, H-3), 5.12-4.95 (overlapped, 3H, H-4, H-7 and H-15), 4.60 (d, *J* = 5.8 Hz, 1H, H-16), 4.32 (d, *J* = 3.7 Hz, 2H, H-26), 3.38 (dd, *J* = 9.4, 4.4 Hz, 1H, H-18), 3.31 (s, 3H, H-31), 3.21 (dd, *J* = 9.0, 5.6 Hz, 1H, H-18), 3.01 (t, *J* = 5.1 Hz 1H, H-17), 2.66-2.58 (m, 1H, H-2), 2.22-2.09 (overlapped, 2H, H-6 and H-2'), 2.05 (dd, *J* = 16.8, 5.3 Hz, 1H, H-12), 1.91 (dd, *J* = 12.6, 7.4 Hz, 1H, H-9), 1.84 (dd, *J* = 9.1, 5.4 Hz, 1H, H-11), 1.78-1.68 (overlapped, 2H, H-9' and H-6'), 1.62 (s, 3H, H-24), 1.58-1.51 (m, 1H, H-12'), 1.48 (s, 3H, H-22), 1.43 (s, 3H, H-25), 1.13-1.06 (m, 1H, H-10), 1.05 (s, 6H, H-20 and H-21), 0.99 (s, 3H, H-19), 0.82 (m, 1H, H-10') ppm;

^{13}C-NMR (100 MHz, C_6D_6): δ_C = 159.8 (s, C-30), 150.5 (s, C-14), 141.7 (d, C-4), 136.4 (s, C-8), 131.1 (s, C-27), 129.3 (d, C-28), 123.5 (d, C-7), 121.9 (d, C-3), 114.1 (d, C-29), 110.7 (s,

C-23), 107.6 (s, C-13), 82.8 (d, C-15), 81.2 (s, C-1), 80.8 (d, C-16), 73.0 (t, C-26), 71.0 (t, C-18), 54.8 (q, C-31), 51.3 (d, C-17), 43.0 (t, C-2), 42.0 (t, C-6), 38.4 (s, C-5), 38.1 (t, C-9), 36.2 (d, C-11), 30.5 (t, C-10), 30.4 (q, C-20), 28.6 (q, C-24), 27.1 (q, C-25), 26.6 (t, C-12), 24.2 (q, C-21), 19.7 (q, C-19), 17.2 (q, C-22) ppm;

HRMS (ESI): *m/z* calcd. for $C_{33}H_{46}O_5Na$ $[M+Na]^+$: 545.3243; found: 545.3243.

Deprotection of **225a** and selective protection of **226a**

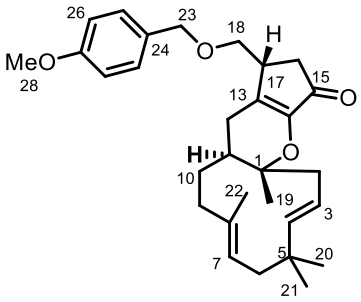


(1*R*,4a*R*,6*E*,10*E*,13a*S*)-1-(((4-Methoxybenzyl)oxy)methyl)-4a,8,8,11-tetramethyl-1,2,4a,5,8,9,12,13,13a,14-decahydro-3H-cyclopenta[b]cycloundeca[e]pyran-3-one (227a)

To a mixture of **225a** (5.1 mg, 0.01 mmol) in THF was added HCl (1 N, 1 mL) at room temperature, and then the mixture was stirred at 50 °C for 12 h. The mixture was diluted with EtOAc (5 mL), and a saturated aqueous $NaHCO_3$ solution (2mL) was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was applied in the next reaction without further purification.

To a mixture of diol **226a** (5 mg, 0.01 mmol, 1.0) obtained above in CH_2Cl_2 (0.5 mL) was added $Yb(OTf)_3$ (6.2 mg, 0.01 mmol) and Boc anhydride (11.3 mg, 0.04 mmol) at 0 °C. The resulting cloudy pale yellow solution was stirred at 0 °C for 3 h. The reaction was terminated by addition of water (5 mL). The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, petroleum

ether/EtOAc = 1/0 to 5/1) to afford enone **227a** (4.0 mg, 0.086 mmol, 86% over 2 steps) as a colorless oil;



227a

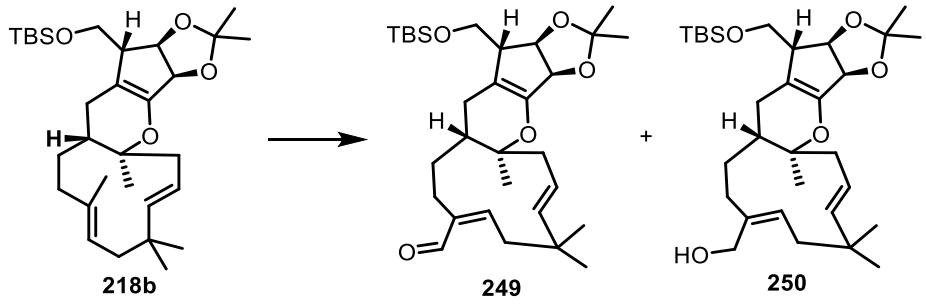
$\mathbf{R_f}$ = 0.65 (petroleum ether/EtOAc = 1/1); $\mathbf{[\alpha]_D^{20}}$ = -40 (*c* = 0.2, $CHCl_3$);

^{1}H-NMR (400 MHz, MeOD): δ_H = 7.23 (d, *J* = 8.7 Hz, 2H, H-25), 6.88 (d, *J* = 8.7 Hz, 2H, H-26), 5.15-5.05 (m, 2H, H-3 and H-4), 5.04-4.95 (m, 1H, H-7), 4.46 (dd, *J* = 22.6, 11.8 Hz, 2H, H-23), 3.80 (s, 3H, H-28), 3.55 (dd, *J* = 9.1, 5.6 Hz, 1H, H-18), 3.49 (dd, *J* = 9.1, 5.6 Hz, 1H, H-18), 2.95 (dd, *J* = 11.5, 5.6 Hz, 1H, H-17), 2.68 (dd, *J* = 18.6, 4.9 Hz, 1H, H-12), 2.62 (d, *J* = 14.6 Hz, 1H, H-2), 2.54 (dd, *J* = 18.7, 6.3 Hz, 1H, H-16), 2.25-2.13 (overlapped, 3H, H-2', H-16' and H-6), 2.08 (dd, *J* = 12.7, 7.7 Hz, 1H, H-9), 1.88-1.80 (m, 1H, H-12'), 1.79-1.70 (overlapped, 3H, H-6', H-9' and H-11), 1.62 (s, 3H, H-22), 1.31-1.26 (m, 1H, H-10), 1.11-1.07 (m, 1H, H-10'), 1.03 (s, 3H, H-20), 1.00 (s, 3H, H-21) and 0.96 (s, 3H, H-19) ppm;

^{13}C-NMR (100 MHz, MeOD): δ_C = 230.2 (s, C-15), 160.9 (s, C-27), 151.1 (s, C-14), 148.2 (s, C-13), 143.4 (d, C-4), 137.8 (s, C-8), 131.5 (s, C-24), 130.6 (s, C-26), 124.1 (d, C-7), 121.6 (d, C-3), 114.9 (d, C-25), 83.4 (s, C-1), 73.9 (t, C-23), 70.9 (t, C-18), 55.6 (q, C-28), 43.2 (t, C-2), 42.4 (t, C-6), 39.1 (s, C-5), 38.6 (t, C-9), 38.4 (t, C-16), 38.2 (d, C-17), 37.0 (d, C-11), 31.4 (t, C-10), 30.7 (q, C-20), 28.1 (t, C-12), 24.7 (q, C-21), 19.8 (q, C-19) and 17.3 (q, C-22) ppm;

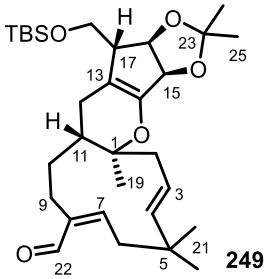
HRMS (ESI): *m/z* calcd. for $C_{30}H_{40}O_4Na$ $[M+Na]^+$: 487.0887; found: 487.0887.

Allylic oxidation of **218b**



(3a*R*,4a*S*,6*E*,10*Z*,13a*R*,15*R*,15a*R*)-15-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,2,4a,8,8-pentamethyl-3a,4a,8,9,12,13,13a,14,15,15a-decahydro-5[1,3]dioxolo[4',5':4,5]cyclopenta [1,2-b]cycloundeca[e]pyran-11-carbaldehyde (249)

To a solution of **218b** (13.1 mg, 0.025 mmol) in dry CH_2Cl_2 (1 mL) was added SeO_2 (4.2 mg, 0.036 mmol) and a *t*-butyl hydroperoxide solution in decane (3 drops) at room temperature. The mixture was stirred for 5 h. The reaction was terminated by addition of water (5 mL). The mixture was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over anhydrous $NaSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 20/1 to 5/1) to furnish aldehyde **249** as a light yellow oil (3.7 mg, 0.007 mmol, 28%) and alcohol **250** as a colorless oil (5.1 mg, 0.01 mmol, 40%);



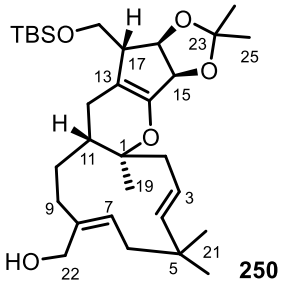
$\mathbf{R}_f$ = 0.60 (petroleum ether/EtOAc = 10/1);

^{1}H-NMR (400 MHz, MeOD): δ_H = 10.09 (s, 1H, H-22), 6.47 (dd, *J* = 11.9, 3.2 Hz, 1H, H-7), 5.26 (ddd, *J* = 15.9, 9.6, 2.5 Hz, 1H, H-3), 5.08 (dd, *J* = 15.9, 1.4 Hz, 1H, H-4), 4.81 (d, 1H, H-16), 4.44 (d, *J* = 2.6 Hz, 1H, H-15), 3.74 (dd, *J* = 9.9, 3.9 Hz, 1H, H-18), 3.58 (dd, *J* = 9.9, 4.6 Hz, 1H, H-18'), 3.10 (t, *J* = 12.4 Hz, 1H, H-6), 2.65 (m, 1H, H-9), 2.64 (m, 1H, H-17), 2.37 (d, *J* = 2.6 Hz, 1H, H-2), 2.26-2.20 (m, 2H, H-2' and H-12), 2.17 (dd, *J* = 16.6, 5.2 Hz, 1H, H-6'), 1.70-1.56 (m, 3H, H-9', H-12' and H-11), 1.40 (s, 3H, H-24), 1.33 (s, 3H, H-25),

1.20-1.17 (m, 2H, H-10), 1.17 (s, 3H, H-20), 1.15 (s, 3H, H-21), 1.00 (s, 3H, H-19), 0.89 (s, 9H, SiC(C$\underline{H}_3$)$_3$), 0.07 (s, 3H, Si-C$\underline{H}_3$), 0.05 (s, 3H, Si-C$\underline{H}_3$);

^{13}C-NMR (100 MHz, MeOD): δ_C = 192.7 (d, C-22), 150.6 (s, C-14), 149.2 (d, C-7), 143.9 (s, C-8), 143.9 (d, C-4), 122.9 (d, C-3), 111.5 (s, C-23), 109.0 (s, C-13), 83.6 (d, C-15), 82.3 (s, C-1), 81.6 (d, C-16), 64.1 (t, C-18), 53.8 (d, C-17), 43.2 (t, C-2), 40.1 (t, C-6), 38.2 (s, C-5), 37.1 (d, C-11), 33.1 (t, C-10), 30.7 (q, C-20), 28.8 (t, C-9), 28.4 (q, C-24), 26.7 (t, C-12), 26.6 (q, C-25), 26.3 (q, SiC($\underline{C}$H$_3$)$_3$), 24.7 (q, C-21), 19.9 (s, Si$\underline{C}$(CH$_3$)$_3$), 19.0 (q, C-19), -5.4 (q, Si-$\underline{C}$H$_3$), -5.5 (q, Si-$\underline{C}$H$_3$);

HRMS (ESI): *m/z* calcd. for $C_{31}H_{50}O_5SiNa$ $[M+Na]^+$: 553.3325; found: 553.3327.



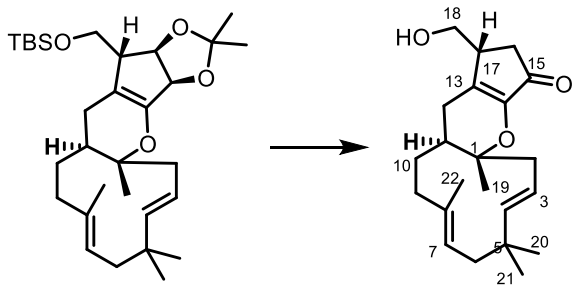
250

R$_f$ = 0.11 (PE/EtOAc = 10/1);

^{1}H-NMR (400 MHz, MeOD, CD_2HOD = 3.31 ppm): δ_H = 5.57 (dd, *J* = 11.9, 3.2 Hz, 1H, H-7), 5.55-5.45 (m, 2H, H-3 and H-4), 4.80 (d, 1H, H-16), 4.44 (d, *J* = 2.6 Hz, 1H, H-15), 3.97 (dd, *J* = 9.9, 3.9 Hz, 2H, H-22), 3.74 (dd, *J* = 9.9, 3.9 Hz, 1H, H-18), 3.61(dd, *J* = 9.9, 4.6 Hz, 1H, H-18'), 2.65 (t, *J* = 3.9 Hz,, H-17), 2.45-2.42 (m, 1H), 2.32 (m, 1H), 2.22-2.18 (m, 2H), 2.08 (m, 1H), 1.99 (m, 1H), 1.92-1.90 (m, 1H), 1.82-1.60 (m, 2H), 1.57-1.49 (m, 1H), 1.44 (s, 3H, H-24), 1.41-1.39 (m, 1H), 1.35 (s, 6H, H-25 and H-20), 1.15 (s, 3H, H-21), 1.00 (s, 3H, H-19), 0.91 (s, 9H, SiC(C$\underline{H}_3$)$_3$), 0.09 (s, 3H, Si-C$\underline{H}_3$), 0.07 (s, 3H, Si-C$\underline{H}_3$);

HRMS (ESI): *m/z* calcd. for $C_{31}H_{52}O_5SiNa$ $[M+Na]^+$: 555.3482; found: 555.3488.

Attempted removal of acetonide of **218a**



218a **224a**

(1*R*,4a*R*,6*E*,10*E*,13a*S*)-1-(Hydroxymethyl)-4a,8,8,11-tetramethyl 1,2,4a,5,8,9,12,13,13a, 14 -decahydro-3H-cyclopenta[b]cycloundeca[e]pyran-3-one (224a)

To a mixture of **218a** (10 mg, 0.02 mmol) in THF (1 mL) was added aqueous HCl (1 M, 0.5 mL) at room temperature, and then the mixture was stirred at 50 °C for 12 h. The reaction was terminated by addition of saturated aqueous $NaHCO_3$ (2mL). The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 10/1 to 1/1) to afford ketone **224a** as a yellow oil (5.1 mg, 0.014 mmol, 72%);

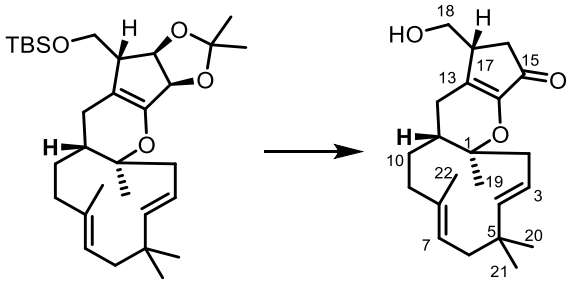
$\mathbf{R}_f$ = 0.10 (petroleum ether/EtOAc = 1/1); $\mathbf{[\alpha]_D^{20}}$ = -106 (*c* = 0.5, $CHCl_3$);

^{1}H-NMR (400 MHz, MeOD): δ_H = 5.19-5.09 (m, 2H, H-3 and H-4), 5.07-5.02 (m, 1H, H-7), 3.72 (d, *J* = 4.7 Hz, 2H, H-18), 2.89 (d, *J* = 4.3 Hz, 1H, H-17), 2.81 (dd, *J* = 13.9, 4.1 Hz, 1H, H-12), 2.54-2.43 (m, overlapped, 2H, H-2 and H-16), 2.34 (dd, *J* = 9.5, 8.6 Hz, 1H, H-2'), 2.27-2.15 (m, overlapped, 2H, H-16' and H-6), 2.09 (d, *J* = 7.5 Hz, 1H, H-9), 1.97 (m, *J* = 9.0 Hz, 1H, H-12'), 1.92-1.83 (m, overlapped, 2H, H-11 and H-9'), 1.74 (dd, *J* = 12.8, 4.0 Hz, 1H, H-6'), 1.63 (s, 3H, H-22), 1.42-1.35 (m, 1H, H-10), 1.22-1.17 (m, 1H, H-10'), 1.04 (s, 6H, H-20 and H-21), 1.02 (s, 3H, H-19) ppm;

^{13}C-NMR (100 MHz, MeOD): δ_C = 203.4 (s, C-15), 151.1 (s, C-14), 148.1 (s, C-13), 143.5 (d, C-4), 137.8 (s, C-8), 123.9 (d, C-7), 121.6 (d, C-3), 83.6 (s, C-1), 63.9 (t, C-18), 43.2 (t, C-2), 42.4 (t, C-6), 41.4 (s, C-5), 39.1 (t, C-9), 38.7 (t, C-16), 37.8 (d, C-17), 36.9 (d, C-11), 31.5 (t, C-10), 30.7 (q, C-20), 29.2 (t, C-12), 24.6 (q, C-21), 19.6 (q, C-19), 17.3 (q, C-22) ppm;

HRMS (ESI): *m/z* calcd. for $C_{22}H_{32}O_3Na$ $[M+Na]^+$: 367.2249; found: 367.2250.

Attempted removal of acetonide of **218b**



218b **224b**

(1*R*,4a*S*,6*E*,10*E*,13a*R*)-1-(Hydroxymethyl)-4a,8,8,11-tetramethyl-1,2,4a,5,8,9,12,13,13a, 14-decahydro-3H-cyclopenta[b]cycloundeca[e]pyran-3-one (224b)

To a mixture of **218b** (5 mg, 0.01 mmol) in THF (1 mL) was added aqueous HCl (1 M, 0.5 mL) at room temperature, and then the mixture was stirred at 50 °C for 12 h. The reaction was terminated by addition of a saturated aqueous $NaHCO_3$ solution (2mL). The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 10/1 to 1/1) to afford ketone **224b** as a yellow oil (3 mg, 0.009 mmol, 90%);

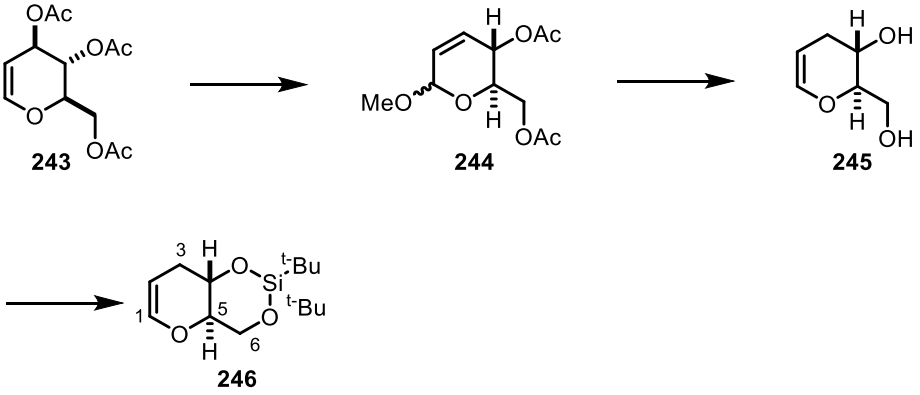
$\mathbf{R}_f$ = 0.10 (petroleum ether/EtOAc = 1/1); $\mathbf{[\alpha]_D^{20}}$ = +108 (*c* = 0.12, $CHCl_3$);

^{1}H-NMR (400 MHz, MeOD): δ_H = 5.19-5.09 (m, 2H, H-3 and H-4), 5.07-5.03 (m, 1H, H-7), 3.69 (dd, *J* = 5.3, 4.7 Hz, 1H, H-18), 3.64 (dd, *J* = 5.3, 4.7 Hz, 1H, H-18), 2.89 (d, *J* = 4.7 Hz, 1H, H-17), 2.64 (dd, *J* = 18.6, 4.9 Hz, 1H, H-12), 2.54-2.43 (m, overlapped, 2H, H-2 and H-16), 2.34 (dd, *J* = 10.0, 9.7 Hz, 1H, H-2'), 2.27-2.15 (m, overlapped, 2H, H-16' and H-6), 2.14-2.07 (m, overlapped, 2H, H-12' and H-9), 1.88-1.79 (m, overlapped, 2H, H-11 and H-9'), 1.80-1.72 (m, 1H, H-6'), 1.63 (s, 3H, H-22), 1.42-1.35 (m, 1H, H-10), 1.22-1.17 (m, 1H, H-10'), 1.04 (s, 6H, H-20) and H-21), 1.03 (s, 3H, H-19) ppm.

^{13}C-NMR (100 MHz, MeOD): δ_C = 203.4 (s, C-15), 151.1 (s, C-14), 148.1 (s, C-13), 143.5 (d, C-4), 137.8 (s, C-8), 123.91 (d, C-7), 121.6 (d, C-3), 83.6 (s, C-1), 63.7 (t, C-18), 43.2 (t, C-2), 42.4 (t, C-6), 41.4 (s, C-5), 39.1 (t, C-9), 38.7 (t, C-16), 37.8 (d, C-17), 36.9 (d, C-11), 31.5 (t, C-10), 30.7 (q, C-20), 29.2 (t, C-12), 24.6 (q, C-21), 19.6 (q, C-19), 17.3 (q, C-22) ppm.

HRMS (ESI): *m/z* calcd. for $C_{22}H_{32}O_3Na$ $[M+Na]^+$: 367.2249; found: 367.2249.

Synthesis of model compound **246**



(4a*R*,8a*S*)-2,2-Di-tert-butyl-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3,2]dioxasiline (246)

To a solution of tri-*O*-acetyl-D-glucal **243** (4.1 g, 14.80 mmol) in CH_2Cl_2 was added CH_3OH (0.7 mL, 16.10 mmol) and $BF_3{\cdot}OEt_2$ (0.8 mL, 6.5 mmol) at room temperature. The mixture was stirred at rt for 1.5 h. The reaction was terminated by addition of a saturated aqueous $NaHCO_3$ solution (50 mL). And the mixture was diluted with water, and extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over $MgSO_4$, and filtered. The resulting brown mixture was filtered through a short pad of silica gel, the filter cake was washed with a 1:1 mixture of petroleum ether and Et_2O. The mixture was concentrated *in vacuo* to give the crude acetal **244**, which was used directly in the next step without further purification.

To a solution of crude acetal **244** in CH_3OH (50 mL) was added anhydrous solid K_2CO_3 (132.1 mg, 0.94 mmol) and stirred at room temperature for 2 h. The mixture was concentrated and coevaporated with toluene (20 mL). The crude compound was vacuumed for 20 min and then dissolved in anhydrous dioxane (30 mL). To this mixture was added $LiAlH_4$ (0.76 g, 20.0 mmol) at 0 ^oC. The mixture was refluxed overnight. The reaction was terminated at 0 °C by addition of saturated aqueous NH_4Cl solution (10 mL) and stirred for another 30 min at room temperature. The precipitated solid material was removed by filtration over a pad of *Celite*. The filtrate was dilute with EtOAc and washed with aqueous NH_4Cl, brine dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was used in the next step without further purification.

To a mixture of the residue described above in DMF (30 mL) was slowly added *t*-$Bu_2Si(OT_f)_2$ (5.0 mL, 15.4 mmol) at −45 °C, and then the mixture was stirred at −45 °C for 1 h. The reaction was terminated by addition of pyridine (2 mL). The mixture was extracted with Et_2O.

The combined organic phases were washed with water and then brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/Et_2O = 99/1) to give the enol ether **246** as a colorless solid (2.51 g, 63% over 3 steps).

R_f = 0.25 (petroleum ether/Et_2O = 99/1); **M.p.** = 38–40 °C;

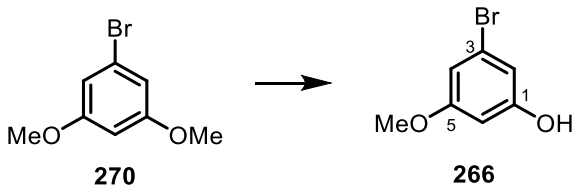
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 6.26 (1H, ddt, *J* = 5.9, 2.4, 1.4 Hz, H-1), 4.69 (1H, ddd, *J* = 5.9, 5.8, 2.0 Hz, H-2), 4.19 (1H, dd, *J* = 10.3, 4.8 Hz, H-6), 4.11 (1H, ddd, *J* = 9.5, 9.5, 6.0 Hz H-6'), 3.92 (1H, dd, *J* = 10.3, 10.3 Hz, H-4), 3.68 (1H, ddd, *J* = 10.3, 9.5, 4.8 Hz, H-5), 2.38 (1H, dddd, *J* = 16.5, 6.0, 5.8, 1.4 Hz, H-3), 2.07 (1H, dddd, *J* = 16.5, 9.5, 2.4, 2.0 Hz, H-3'), 1.06 (s, 9H, -$C(CH_3)_3$), 0.99 (s, 9H, -$C(CH_3)_3$) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) 142.6 (s, C-1), 98.9 (s, C-2), 73.9 (s, C-4), 71.4 (s, C-5), 66.4(s, C-6), 30.2 (s, C-3), 27.5 (s, -$\underline{C}(CH_3)_3$), 27.0 (s, -$\underline{C}(CH_3)_3$), 22.7 (s, -$C(\underline{C}H_3)_3$), 19.9 (s, -$C(\underline{C}H_3)_3$) ppm;

HRMS (ESI): *m/z* calcd. for $C_{14}H_{27}O_3Si$ $[M+H]^+$: 271.1729; found: 271.1731.

6.4 Supporting information for chapter 4

Synthesis of phenol **266**



270 **266**

3-Bromo-5-methoxyphenol (266)

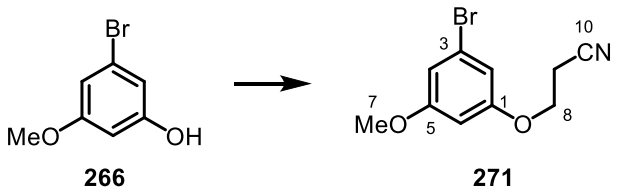
To a solution of 1-bromo-3,5-dimethoxybenzene (4.3 g, 20.00 mmol) in dry CH_2Cl_2 (15 ml) BBr_3 (1 M solution in THF, 6.6 ml, 6.60 mmol) was added dropwise at 0 °C. While continuing stirring, the mixture was slowly warmed to room temperature. After stirring for another 24 h, the reaction was terminated by addition of methanol, and then the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 5/1) to give the target phenol **266** as a light brown solid (3.3 g, 16.10 mmol, 80%).

$\mathbf{R_f}$ = 0.15 (petroleum ether/EtOAc = 5/1); **M**.**p**. 103-105 ^{o}C

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 6.65 (dd, *J* = 2.2, 1.6 Hz, 1H, H-2), 6.61 (dd, *J* = 2.2, 1.6 Hz, 1H, H-4), 6.33 (t, *J* = 2.2 Hz, 1H, H-6), 4.94 (s, 1H, -OH), 3.76 (s, 3H, -OCH_3) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 161.5 (s, C-5), 157.3 (s, C-1), 123.0 (s, C-3), 111.6 (d, C-2), 110.2 (d, C-4), 101.0 (d, C-6), 55.7 (q, -OCH_3) ppm.

Synthesis of nitrile **271**



266 **271**

3-(3-Bromo-5-methoxyphenoxy)propanenitrile (271)

To a solution of 3-bromo-5-methoxyphenol (1.1 g, 5.57 mmol) in vinyl cyanide (25 ml) was added DBU (1.3 mL, 8.40 mmol) at room temperature under an argon atmosphere. Then the mixture was heated up to reflux for 48 h. After cooled to room temperature, the mixture was

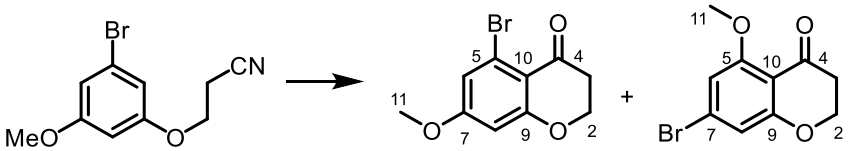
concentrated *in vacuo*, and then the residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 10/1) to give the target nitrile **271** as a colorless solid (0.7 g, 4.23 mmol, 76%).

R_f = 0.20 (petroleum ether/EtOAc = 10/1); **M**.**p**. 71-73 °C

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 6.71 (dd, *J* = 2.2, 1.6 Hz, 1H, H-2), 6.66 (dd, *J* = 2.2, 1.6 Hz, 1H, H-4), 6.39 (t, *J* = 2.2 Hz, 1H, H-6), 4.15 (t, *J* = 6.3 Hz, 1H, H-8), 3.77 (s, 3H, H-7), 2.82 (t, *J* = 6.4 Hz, 1H, H-9) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 161.5 (s, C-5), 159.3 (s, C-1), 123.2 (s, C-3), 117.0 (s, C-10), 111.1 (d, C-2), 110.4 (d, C-4), 100.7 (d, C-6), 62.9 (t, C-8), 55.8 (q, C-7) and 18.7 (t, C-9) ppm.

Synthesis of chromanone **272**



5-Bromo-7-methoxychroman-4-one (272) and **7-Bromo-5-methoxychroman-4-one (273)**

To a solution of 3-(3-bromo-5-methoxyphenoxy)propanenitrile (350.1 mg, 1.37 mmol) in CH_3NO_2 (5 mL) was added aluminum trichloride (365.1 mg, 2.74 mmol). The mixture was stirred at 60 °C overnight. Water (5 mL) was added and stirring was continued for 1 h. After the mixture was cooled down to room temperature, the mixture was extracted with CH_2Cl_2, dried with $NaSO_4$, filtered and concentrated *in vacuo*, and then the residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 1/0 to 5/1) to give **272** as a yellow solid (146.1 mg, 0.63 mmol, 46%) and **273** as a colorless oil (81.2 mg, 0.32 mmol, 23%).

5-Bromo-7-methoxychroman-4-one (272):

R_f = 0.60 (petroleum ether/EtOAc = 1/1); **M**.**p**. 89-92 °C

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 6.87 (d, *J* = 2.5 Hz, 1H, H-6), 6.41 (d, *J* = 2.6 Hz, 1H, H-8), 4.48 (t, *J* = 6.3 Hz, 1H, H-2), 3.82 (s, 3H, H-11), 2.79 (t, *J* = 6.4 Hz, 1H, H-3) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 188.8 (s, C-4), 164.8 (s, C-7), 164.3 (s, C-9), 123.2 (s, C-5), 116.8 (s, C-10), 113.6 (d, C-6), 101.3 (d, C-8), 66.9 (t, C-2), 55.9 (q, C-11), 38.4 (t, C-3) ppm.

HRMS (ESI): *m/z* calcd. for $C10H9BrO_3Na$ $[M+Na]^+$: 278.9633; found: 278.9634.

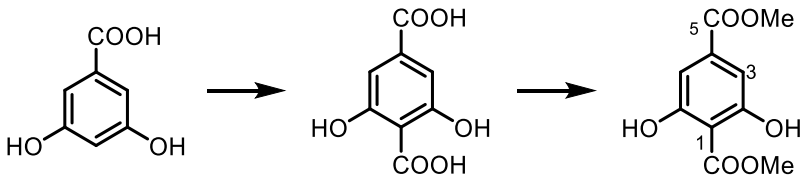
7-Bromo-5-methoxychroman-4-one (273):

R_f = 0.50 (petroleum ether/EtOAc = 1/1);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 6.78 (d, *J* = 1.7 Hz, 1H, H-6), 6.66 (d, *J* = 2.6 Hz, 1H, H-8), 4.47 (t, *J* = 6.1 Hz, 1H, H-2), 3.90 (s, 3H, H-11) and 2.76 (t, *J* = 6.5 Hz, 1H, H-3) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 189.8 (s, C-4), 163.7 (s, C-9), 161.1 (s, C-5), 130.2 (s, C-7), 113.6 (s, C-10), 110.7 (d, C-6), 108.1 (d, C-8), 66.9 (t, C-2), 56.7 (q, C-11), 39.0 (t, C-3) ppm.

Synthesis of diester **263**



262 **263**

Dimethyl 2,6-dihydroxyterephthalate (263)

A stirred suspension of 3,5-dihydroxybenzoic acid (5.0 g, 32.11 mmol) in glycerol (25 mL) was heated at 100 °C for 1 h. After cooling to room temperature, $KHCO_3$ (150 g, 1.5 mol) was added in small portions to the mixture, and then the resulting suspension was heated at 180°C under an atmosphere of CO_2 for 3 h. Then the mixture was cooled to room temperature, and hot water and concentrated HCl were added. The resulting mixture was extracted three times with Et_2O. The combined organic phases were washed with brine, and then dried over Na_2SO_4 and filtered. Concentration of the solvent *in vacuo* afforded a pale yellow solid, which was applied for the next reaction without further purification.

To a mixture of 2,6-dihydroxyterephthalic acid (4.5 g, 25.21 mmol) and $KHCO_3$ (6.3 g, 63.11 mmol) in acetone (30 mL) Me_2SO_4 (6.1 mL, 63.21 mmol) was added dropwise at room

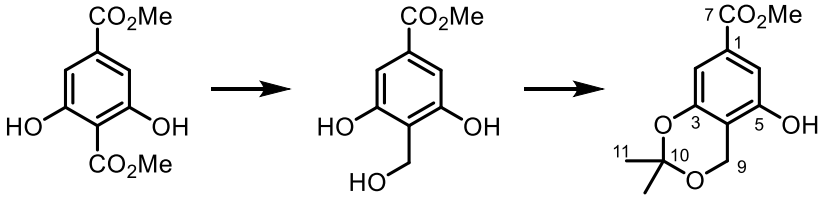
temperature, and then the mixture was heated under refluxing condition for 10 h. After cooling, the mixture was concentrated *in vacuo* to give a residue, which was diluted with saturated aqueous $NaHCO_3$ solution. The resulting mixture was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over Na_2SO_4 and filtered. Concentration of the solvent *in vacuo* afforded a pale yellow solid, which was purified by recrystallization from CH_3OH to give dimethyl 2,6-dihydroxyterephthalate **263** as pale yellow solid (4.7 g, 20.81 mmol, 64%, over 2 steps).

M. p. 146–149°C;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 9.67 (brs, 2H, OH), 7.12 (s, 2H, H-3), 4.11 (s, 3H, -CH_3), 3.91 (s, 3H, -CH_3) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 169.7 (s, C-1), 169.7 (s, C-4), 160.9 (s, C-2), 137.3 (s, C-2), 109.3 (d, C-3), 109.2 (d, C-4), 53.4 (q, -CH_3), 52.7 (q, -CH_3) ppm.

Synthesis of phenol **259**



Methyl 5-hydroxy-2,2-dimethyl-4H-benzo[d][1,3]dioxine-7-carboxylate (259)

To a solution of dimethyl 2,6-dihydroxyterephthalate (50.6 mg, 224.10 mmol) in THF (2.5 mL) was dropwise added a mixture of $NaBH_4$ (17.1 mg, 448.20 mmol) in water (1.0 mL) at 0°C. After stirring at 0°C for 1 h, the reaction was terminated by addition of 1 M aqueous HCl (0.1 mL) at 0°C, and the resulting mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was filtered through a short-pass column (silica gel, EtOAc) to give methyl 3,5-dihydroxy-4-(hydroxymethyl)benzoate (10.1 mg), which was used in the next reaction without further purification.

To a solution of residue obtained above in 2,2-dimethoxypropane (1.0 mL) was added *p*-TsOH (2.1 mg, 0.0025 mmol) at room temperature, and the mixture was stirred for 5 h. Then

the mixture was concentrated *in vacuo* to afford a residue, which was diluted with saturated aqueous $NaHCO_3$ (2.1 mL) at 0°C. The resulting mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (silica gel, petroleum ether/EtOAc = 1/2) to give the target phenol **259** as a light yellow oil (29.3 mg 123.3 mmol, 55%, over 2 steps).

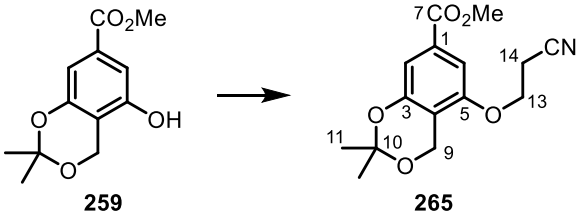
$\mathbf{R_f}$ = 0.15 (petroleum ether/EtOAc = 1/1);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 7.12 (s, 1H, H-6), 7.07 (s, 1H, H-2), 4.85 (s, 2H, H-9), 3.88 (s, 3H, H-8), 1.55 (s, 6H, H-11) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 167.1 (s, C-7), 152.4 (s, C-5), 130.0 (s, C-3), 112.6 (d, C-1), 110.7 (d, C-4), 107.7 (d, C-1), 99.8 (d, C-4), 65.1 (d, C-10), 58.2 (d, C-8), 52.4 (d, C-9), 31.1 (q, -CH_3), 24.7(q, -CH_3) ppm.

HRMS (ESI): *m/z* calcd. for $C_{12}H_{14}O_5Na$ $[M+Na]^+$: 261.0739; found: 261.0742.

Synthesis of nitrile **265**



Methyl 5-(2-cyanoethoxy)-2,2-dimethyl-4H-benzo[d][1,3]dioxine-7-carboxylate (265)

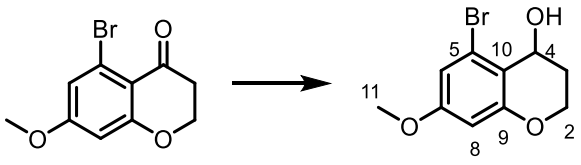
To a solution of methyl 5-hydroxy-2,2-dimethyl-4H-benzo[d][1,3]dioxine-7-carboxylate (10.1 mg, 0.042 mmol) in vinyl cyanide (25 ml) was added DBU (1.3 mL, 8.40 mmol) at room temperature under argon atmosphere. Then the mixture was heated under refluxing condition for 48 h. The mixture was cooled to room temperature, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 10/1) to give the target nitrile **265** as a colorless oil (8.9 mg, 0.041 mmol, 74%).

$\mathbf{R_f}$ = 0.25 (petroleum ether/EtOAc = 10/1);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 7.11 (s, 2H, H-2 and H-6), 5.46-5.35 (m, 2H, H-9), 4.15 (t, J = 6.3 Hz, 2H, H-13), 3.88 (s, 3H, H-8), 2.82 (t, J = 6.4 Hz, 2H, H-14), 1.53 (s, 3H, H-11), 1.54 (s, 3H, H-12) ppm;

HRMS (ESI): *m/z* calcd. for $C_{15}H_{17}NO_5Na$ $[M+Na]^+$: 314.1263; found: 314.1265.

Synthesis of alcohol **272b**



272 **272b**

5-Bromo-7-methoxychroman-4-ol (272b)

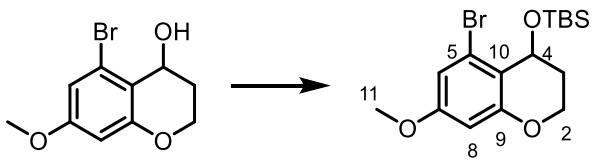
To a solution of 5-bromo-7-methoxychroman-4-one (13.1 mg, 0.05 mmol) in ethanol (1.0 mL) was added $NaBH_4$ (3.5 mg, 0.09 mmol) at room temperature, then the mixture was stirred for 12 h. Then the reaction was terminated by addition of a saturated aqueous NH_4Cl solution. The mixture was concentrated *in vacuo*, and the residue was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried with $NaSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 5/1) to give 5-bromo-7-methoxychroman-4-ol (**272b**) as a colorless oil (12.2 mg, 0.047 mmol, 94%).

$\mathbf{R_f}$ = 0.40 (petroleum ether/EtOAc = 5/1);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 6.75 (d, J = 2.5 Hz, 1H, H-6), 6.37 (d, J = 2.4 Hz, 1H, H-8), 4.89 (t, J = 2.6 Hz, 1H, H-4), 4.30-4.15 (m, 2H, H-2), 3.75 (s, 3H, H-11), 2.18-2.12 (m, 2H, H-3) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 160.8 (s, C-7), 156.9 (s, C-9), 125.8 (s, C-5), 116.5 (s, C-6), 112.0 (s, C-8), 101.5 (s, C-10), 62.2 (s, C-2), 61.8 (s, C-4), 55.7 (s, C-11), 30.0 (s, C-3) ppm.

Synthesis of TBS-ether **274**



272b **274**

(5-Bromo-7-methoxychroman-4-yl)oxy)(tert-butyl)dimethylsilane (274)

To a solution of 5-bromo-7-methoxychroman-4-ol (10.1 mg, 0.04 mmol) in CH_2Cl_2 (0.5 mL) was added imidazole (11.1 mg, 0.16 mmol), DMAP (2.2 mg, 0.02 mmol), and then TBSCl (24.1 mg, 0.16 mmol). After the mixture was stirred overnight at room temperature, it was diluted with CH_2Cl_2, and successively washed with saturated aqueous $NaHCO_3$ solution, water and brine. The combined organic phases were washed with brine, dried with $NaSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 20/1) to give a light yellow oil (11.9 mg, 0.03 mmol, 82%).

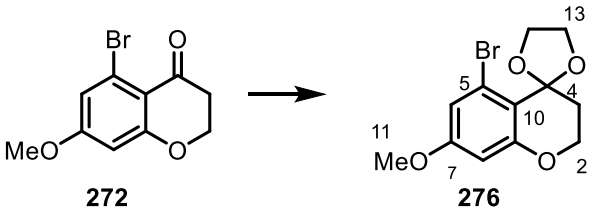
R_f = 0.30 (petroleum ether/EtOAc = 20/1);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 6.75 (d, *J* = 2.5 Hz, 1H, H-6), 6.37 (d, *J* = 2.4 Hz, 1H, H-8), 4.89 (t, *J* = 2.6 Hz, 1H, H-4), 4.30-4.15 (m, 2H, H-2), 3.75 (s, 3H, H-11), 2.00-192 (m, 2H, H-3), 0.88 (s, 9H, Si-C($C\underline{H}_3)_3$), 0.21 (s, 3H, Si-$C\underline{H}_3$), 0.20 (s, 3H, Si-$C\underline{H}_3$) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 160.5 (s, C-7), 156.5 (s, C-9), 125.9 (s, C-5), 117.0 (s, C-6), 111.8 (s, C-8), 101.4 (s, C-10), 63.3 (s, C-2), 61.3 (s, C-4), 55.6 (s, C-11), 31.6 (s, C-3), 26.1 (s, Si-$\underline{C}(CH_3)_3$), 18.3 (s, Si-C($\underline{C}H_3)_3$), -3.7 (s, Si-$\underline{C}H_3$), -4.0 (s, Si-$\underline{C}H_3$) ppm.

HRMS (ESI): *m/z* calcd. for $C_{16}H_{25}BrO_3SiNa$ $[M+Na]^+$: 395.0654; found: 395.0655.

Synthesis of dioxolane **276**



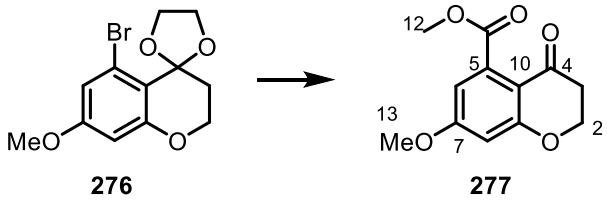
5-Bromo-7-methoxyspiro[chromane-4,2'-[1,3]dioxolane] (276)

To a solution of 5-bromo-7-methoxychroman-4-one (56.1 mg, 0.21 mmol) in anhydrous toluene (2.0 mL) was added ethylene glycol (0.2 mL, 2.11 mmol), *p*-TsOH (10 mg, 0.05 mmol), and trimethyl orthoformate (0.2 mL, 1.50 mmol) at room temperature. The mixture was heated under refluxing condition for 48 h. After cooling down to room temperature, water (1.0 mL) was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over $NaSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 1/0 to 10/1) to yield the target dioxolane **276** as a yellow oil (48.1 mg, 0.15 mmol, 72%).

$\mathbf{R}_f$ = 0.55 (petroleum ether/EtOAc = 10/1);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 6.82 (d, *J* = 2.6 Hz, 1H, H-6), 6.32 (d, *J* = 2.6 Hz, 1H, H-8), 4.40-4.30 (m, 2H, H-2), 4.25-4.18 (m, 2H, H-12), 4.14-4.05 (m, 2H, H-13), 3.74 (s, 3H, H-11) and 2.17-2.11 (m, 2H, H-3) ppm;

Synthesis of ester **277**



Methyl 7-methoxy-4-oxochromane-5-carboxylate (277)

To a solution of 5-bromo-7-methoxyspiro[chromane-4,2'-[1,3]dioxolane] (22.1 mg, 0.07 mmol) in dry THF (0.5 mL) was added *n*-BuLi (2 M in THF, 0.05 mL, 0.1 mmol) at -78 °C. After the mixture was stirred for 5 min, methyl chloroformate (0.1 mL, 3.10 mmol) was added under the same conditions. Then the mixture was slowly warmed to room temperature and

stirred for 3 d. The reaction was terminated by addition of water (1 mL) and the mixture was extracted with EtOAc. The organic phases were washed with brine, dried over $NaSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 5/1) to yield the target ester **277** as a light pink solid (13.1 mg, 0.05 mmol, 73%).

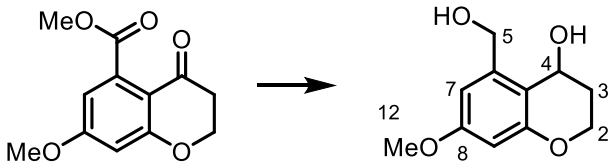
R_f = 0.30 (petroleum ether/EtOAc = 1/1); **M**.**p**. 103-105.

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 6.55 (d, *J* = 2.4 Hz, 1H, H-6), 6.46 (d, *J* = 2.4 Hz, 1H, H-8), 4.53 (t, *J* = 6.4 Hz, 2H, H-2), 3.93 (s, 3H, H-12), 3.86 (s, 3H, H-13), 2.76 (t, *J* = 6.4 Hz, 3H, H-3) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 189.1 (s, C-4), 169.8 (s, C-11), 165.3 (s, C-7), 164.1 (s, C-9), 136.3 (s, C-5), 112.4 (s, C-10), 109.3 (d, C-6), 102.3 (d, C-8), 67.4 (t, C-2), 56.0 (q, C-13), 53.1 (q, C-12), 37.5 (t, C-3) ppm.

HRMS (ESI): *m/z* calcd. for $C_{12}H_{12}O_5Na$ $[M+Na]^+$: 259.0582; found: 259.0582.

Synthesis of diol **268**



5-(Hydroxymethyl)-7-methoxychroman-4-ol (268)

To a suspension of $LiAlH_4$ (12 mg, 0.32 mmol) in diethyl ether (2.0 mL) was added dropwise a solution of methyl 7-methoxy-4-oxochromane-5-carboxylate (50.1 mg, 0.21 mmol) in THF (1.0 mL) at -78 ^oC. After stirring for 3 hours at -78 ^oC, the mixture was slowly warmed to room temperature, and stirring was continued for 1 h. Then the reaction was terminated by addition of a saturated aqueous Na_2SO_4 solution at 0 ^oC until hydrogen evolution had ceased. The mixture was filtered through a short pad of *Celite*, and the filter cake was washed with diethyl ether and the filtrate was dried with anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo* and the residue was washed with petroleum ether to yield the target product as a white solid (41.1 mg, 0.20 mmol, 92%).

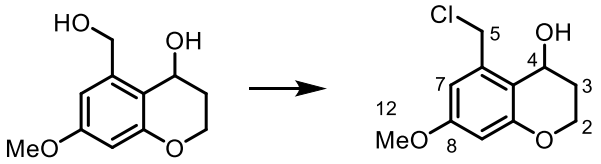
R_f = 0.10 (petroleum ether/EtOAc = 1/1); **M**.**p**. 117-119 °C

^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ_H = 6.60 (d, *J* = 2.6 Hz, 1H, H-7), 6.23 (d, *J* = 2.6 Hz, 1H, H-9), 5.18 (t, *J* = 5.6 Hz, 1H, H-4), 5.03 (d, *J* = 4.9 Hz, 1H, C^5-OH), 4.66 (bs, 1H, C^4-OH), 4.59 (ddd, *J* = 5.7, 13.9, 19.5 Hz, 2H, H-5), 4.18-4.05 (m, 2H, H-2), 3.69 (s, 3H, H-12) and 1.87-1.85 (m, 2H, H-3) ppm;

^{13}C-NMR (100 MHz, $(CD_3)_2SO$): δ_C = 159.4 (s, C-8), 155.1 (s, C-10), 144.0 (s, C-6), 114.5 (s, C-11), 105.9 (d, C-7), 99.5 (d, C-9), 60.6 (d, C-4), 60.1 (t, C-2), 57.5 (q, C-12), 55.0 (t, C-5) and 31.1 (t, C-3) ppm.

HRMS (ESI): *m/z* calcd. for $C_{11}H_{14}O_2Na$ $[M+Na]^+$: 233.0790; found: 233.0786.

Synthesis of chloride **281**



268 **281**

5-(Chloromethyl)-7-methoxychroman-4-ol (281)

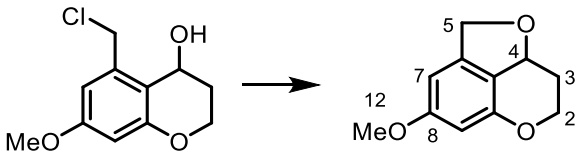
To a solution of 5-(hydroxymethyl)-7-methoxychroman-4-ol (48.1 mg, 0.23 mmol) in CH_2Cl_2 (3.0 ml) was successively added dry Et_3N (28.1 mg, 0.27 mmol), DMAP (4.2 mg, 0.034 mmol), and then *p*-toluenesulfonyl chloride (52.1 mg, 0.27 mmol) at 0 °C. After the mixture was stirred for 3 h, it was warmed up to room temperature and stirring was continued for 1 hour. Then the reaction was terminated by addition of water, the mixture was extracted with CH_2Cl_2. The organic phase was successively washed with a saturated aqueous $NaHCO_3$ solution, water and brine, and then dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo* and the residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 10/1 to 1/1) to yield the target chloride **281** as a yellow oil (38.1 mg, 0.17 mmol, 73%).

R_f = 0.60 (petroleum ether/EtOAc = 1/1);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 6.57 (d, *J* = 2.5 Hz, 1H, H-7), 6.38 (d, *J* = 2.5 Hz, 1H, H-9), 5.02 (d, *J* = 2.2 Hz, 1H, H-4), 4.72 (dd, *J* = 11.2, 41.5 Hz, 2H, H-5), 5.29-4.25 (m, 2H, H-2), 3.77 (s, 3H, H-12), 2.17 (bs, 1H, -OH), 2.02-2.07 (m, 2H, H-3) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 160.6 (s, C-8), 156.5 (s, C-10), 138.6 (s, C-6), 115.0 (s, C-11), 110.3 (d, C-7), 102.3 (d, C-9), 61.2(d, C-4), 59.4 (t, C-2), 55.5 (q, C-12), 43.6 (t, C-5), 30.7 (t, C-3) ppm.

Synthesis of chromene **267**



268 **267**

7-Methoxy-2,3,3a,5-tetrahydrofuro[2,3,4-de]chromene (267)

To a suspension of NaH (60% in mineral oil, 10.1 mg, 0.26 mmol,) in anhydrous THF (1.0 mL) was dropwise added a solution of 5-(chloromethyl)-7-methoxychroman-4-ol (38.2 mg, 0.17 mmol) in anhydrous THF (4 mL) at 0 ^oC. After 10 min, the mixture was warmed to room temperature, and stirring was continued for 30 min. Then the reaction mixture was heated under refluxing conditions for 1 h. After the mixture was cooled to 0 ^oC, the reaction was terminated by addition of several drops of water. The mixture was extracted with EtOAc, and then the combined organic phases were washed with brine, dried over anhydrous $NaSO_4$, filtered and concentrated in *vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 10/1 to 5/1) to give the target product **267** as a light yellow oil (27.1 mg, 0.14 mmol, 83%).

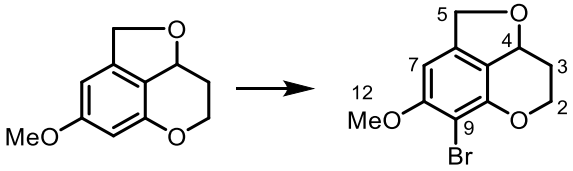
$\mathbf{R}_f$ = 0.55 (petroleum ether/EtOAc = 5/1);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 6.40 (s, 1H, H-7), 6.22 (s, 1H, H-9), 5.06 (d, *J* = 11.4 Hz, 1H, H-5), 5.03-4.97 (m, 1H, H-4), 4.80 (d, *J* = 11.4 Hz, 1H, H-5), 4.48 (ddd, *J* = 2.2, 4.1, 11.6 Hz, 1H, H-2), 4.14-4.07 (m, 1H, H-2), 3.77 (s, 3H, H-12), 2.36-2.30 (m, 1H, H-3), 1.80-1.70 (m, 1H, H-3) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 162.4 (s, C-8), 152.4 (s, C-10), 142.2 (s, C-6), 119.0 (s, C-11), 100.3 (d, C-9), 98.3 (d, C-7), 75.2(d, C-4), 73.2(t, C-5), 65.6(t, C-2), 55.9(q, C-12), 30.1(t, C-3) ppm.

HRMS (ESI): *m/z* calcd. for $C_{11}H_{12}O_3Na$ $[M+Na]^+$: 215.0685; found: 205.0684.

Synthesis of bromide **287**



8-Bromo-7-methoxy-2,3,3a,5-tetrahydrofuro[2,3,4-de]chromene (287)

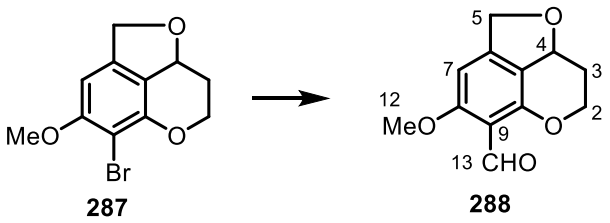
To a solution of 7-methoxy-2,3,3a,5-tetrahydrofuro[2,3,4-de]chromene (55.1 mg, 0.27 mmol) in dry CH_2Cl_2 (5.0 mL) was added dropwise a solution of NBS (77.2 mg, 0.27 mmol) in dry CH_2Cl_2 (2.0 mL) at –78 °C. The reaction mixture was warmed up to room temperature and then heated under refluxing conditions for 2 h until the starting material was totally consumed. The mixture was extracted with EtOAc, and then the organic phase was washed with brine and dried over anhydrous $NaSO_4$, filtered and concentrated in *vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 10/1) to give the target product **287** as a light yellow oil (50.2 mg, 0.18 mmol, 66%).

$\mathbf{R_f}$ = 0.15 (petroleum ether/EtOAc = 10/1);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 6.25 (s, 1H, H-7), 5.11-5.08 (m, 1H, H-4), 5.04 (dd, *J* = 1.6, 12.4 Hz, 1H, H-5), 4.84 (d, *J* = 1.6, 12.4 Hz, 1H, H-5), 4.48 (ddd, *J* = 2.2, 4.1, 11.9 Hz, 1H, H-2), 4.13-4.05 (m, 1H, H-2), 3.85 (s, 3H, H-12), 2.36-2.30 (m, 1H, H-3), 1.82-1.71 (m, 1H, H-3) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm): δ_C = 157.7 (s, C-8), 151.6 (s, C-10), 142.7 (s, C-6), 119.6 (s, C-11), 97.9 (d, C-7), 95.5 (s, C-9), 76.3 (d, C-4), 74.1 (t, C-5), 65.8 (t, C-2), 56.9 (q, C-12), 30.0 (t, C-3) ppm.

Synthesis of aldehyde **288**



7-Methoxy-2,3,3a,5-tetrahydrofuro[2,3,4-de]chromene-8-carbaldehyde (288)

To a solution of 8-bromo-7-methoxy-2,3,3a,5-tetrahydrofuro[2,3,4-de]chromene (100.1 mg, 0.37 mmol) in dry diethyl ether (20 mL) was dropwise added *t*-BuLi (0.41 mL, 0.78 mmol) at -78 °C under argon atmosphere. After stirring for 30 min, a solution of DMF (0.17 mL, 2.31 mmol) in anhydrous diethyl ether (5 mL) was added and the mixture was stirred for 30 min. Then, the reaction mixture was slowly warmed up to room temperature and was stirred until the starting material was completely consumed. The reaction mixture was terminated by addition of a saturated aqueous NH_4Cl solution. Then the mixture was extracted with EtOAc, the organic phase was washed with brine, dried with anhydrous $NaSO_4$, filtered and concentrated in *vacuo*. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 10/1 to 5/1) to give the target aldehyde **288** as a white solid (50 mg, 0.23 mmol, 62%).

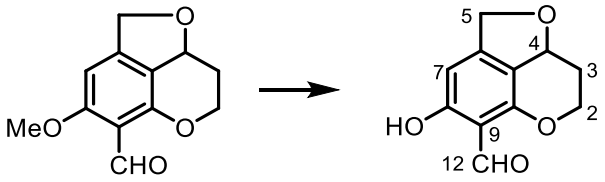
R_f = 0.35 (petroleum ether/EtOAc = 5/1); **M. p.** 112-115 °C

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 10.29 (s, 1H, H-13), 6.25 (s, 1H, H-7), 5.23 (ddd, *J* = 2.7, 14.4, 17.4 Hz, 2H, H-5), 4.95-5.01 (m, 1H, H-4), 4.55 (ddd, *J* = 2.1, 4.2, 11.9 Hz, 1H, H-2), 4.17 (ddd, *J* = 2.1, 4.2, 11.9 Hz, 1H, H-2), 3.88 (s, 3H, H-12), 2.43-2.37 (m, 1H, H-3), 1.82-1.71 (m, 1H, H-3) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 188.7 (d, C-13), 165.2 (s, C-8), 157.6 (s, C-10), 144.9 (s, C-6), 119.6 (s, C-11), 115.0 (s, C-9), 96.3 (d, C-7), 74.7 (d, C-4), 74.1 (t, C-5), 66.5 (t, C-2), 56.4 (q, C-12), 30.0 (t, C-3) ppm.

HRMS (ESI): *m/z* calcd. for $C_{12}H_{12}O_4Na$ $[M+Na]^+$: 243.0633; found: 243.0635.

Synthesis of target compound **98**



288 **98**

7-Hydroxy-2,3,3a,5-tetrahydrofuro[2,3,4-de]chromene-8-carbaldehyde (98)

To a suspension of sodium hydride (60% in mineral oil, 26.1 mg, 0.66 mmol) in anhydrous DMF (1.1 mL) was added ethyl thiolate (37.2 mg, 0.60 mmol) at 0 °C. After 10 min, it was warmed up to room temperature and stirred for 0.5 h. To the resulting mixture was added 7-methoxy-2,3,3a,5-tetrahydrofuro[2,3,4-de]chromene-8-carbaldehyde (13.1 mg, 0.06 mmol) in DMF (1.1 mL). The mixture was heated at 120 °C for 3 h. After the mixture was cooled to room temperature, it was purified by column chromatography (silica gel, petroleum ether/EtOAc = 10/1 to 5/1) to afford phenol **98** as a yellow oil (5.0 mg, 0.024 mmol, 40%).

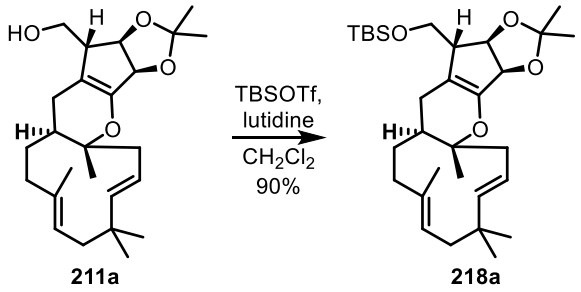
$\mathbf{R}_f$ = 0.55 (petroleum ether/EtOAc = 1/1);

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 11.45 (s, 1H, -OH), 9.70 (s, 1H, H-12), 6.23 (s, 1H, H-7), 5.20 (ddd, *J* = 2.2, 12.3, 44.4 Hz, 2H, H-5), 5.02-4.99 (m, 1H, H-4), 4.65-4.45 (m, 1H, H-2), 4.30-4.10 (m, 1H, H-2), 2.53-2.35 (m, 1H, H-3), 1.90-1.75 (m, 1H, H-3) ppm;

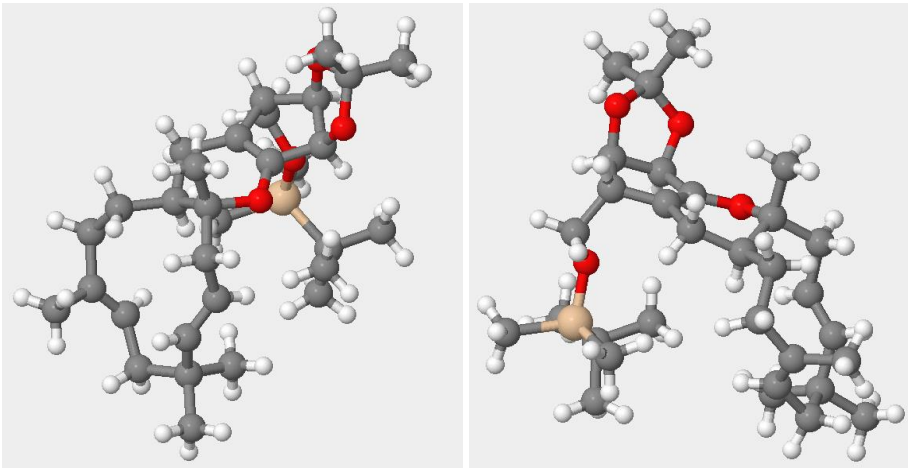
^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 190.8 (d, C-12), 165.8 (s, C-8), 159.2 (s, C-10), 145.5 (s, C-6), 119.6 (s, C-11), 110.6 (s, C-9), 101.1 (d, C-7), 75.1 (d, C-4), 71.6 (t, C-5), 66.4 (t, C-2), 30.0 (t, C-3) ppm;

HRMS (ESI): *m/z* calcd. for $C_{11}H_9O_4$ $[M-H]^-$: 205.0501; found: 205.0500.

Appendix I. X-ray crystallographic analysis



211a **218a**



CCDC 1884756 contains the supplementary crystallographic data for the compound **218a**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing da-ta_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Table S1. Sample and crystal data for compound **218a**.

Identification code	**Peijun2a**	
Chemical formula	$C_{2.30}H_{3.85}O_{0.30}Si_{0.07}$	
Formula weight	38.28 g/mol	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal size	0.130 x 0.300 x 0.670 mm	
Crystal system	orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 12.126(4) Å	α = 90°
	b = 12.283(5) Å	β = 90°
	c = 22.106(8) Å	γ = 90°
Volume	3293.(2) $Å^3$	
Z	54	
Density (calculated)	1.043 g/cm^3	
Absorption coefficient	0.101 mm^{-1}	
F(000)	1136	
Theta range for data collection	2.36 to 21.17°	
Index ranges	-12<=h<=11, -12<=k<=12, -22<=l<=22	
Reflections collected	26187	
Independent reflections	3612 [R(int) = 0.1276]	
Coverage of independent reflections	99.6%	
Absorption correction	multi-scan	
Max. and min. transmission	0.9870 and 0.9360	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2014/7 (Sheldrick, 2014)	
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	3612 / 0 / 336	
Goodness-of-fit on F^2	0.993	
Final R indices	2751 data; I>2σ(I)	R1 = 0.0481, wR2 = 0.0989
	all data	R1 = 0.0716, wR2 = 0.1076
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0443P)^2]$ where $P=(F_o^2+2F_c^2)/3$	
Absolute structure parameter	0.0(2)	
Largest diff. peak and hole	0.117 and -0.153 $eÅ^{-3}$	
R.M.S. deviation from mean	0.029 $eÅ^{-3}$	

Table S2. Atomic coordinates and equivalent isotropic atomic displacement parameters (Å2) for compound **218a**.

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x/a	**y/b**	**z/c**	**U(eq)**
Si01	0.42939(16)	0.19242(15)	0.33063(8)	0.0725(6)
O002	0.2919(2)	0.3914(3)	0.53196(17)	0.0487(10)
O003	0.4472(3)	0.1039(3)	0.58949(16)	0.0600(11)
O004	0.4357(3)	0.1680(3)	0.40271(15)	0.0588(10)
O005	0.2745(3)	0.1747(3)	0.59059(17)	0.0619(11)
C006	0.4222(4)	0.1256(4)	0.5279(2)	0.0466(14)
C007	0.1778(4)	0.6720(5)	0.3653(3)	0.0591(16)
C008	0.3178(4)	0.1946(4)	0.5320(2)	0.0432(13)
C009	0.3611(4)	0.3054(5)	0.5236(2)	0.0404(12)
C00A	0.5126(4)	0.1970(4)	0.5006(2)	0.0441(13)
C00B	0.4659(4)	0.3098(4)	0.5081(2)	0.0423(13)
C00C	0.3469(5)	0.1034(5)	0.6221(3)	0.0636(17)
C00D	0.1998(4)	0.6662(5)	0.4319(3)	0.0557(16)
C00E	0.3463(4)	0.4968(4)	0.5395(2)	0.0486(14)
C00F	0.4390(4)	0.5091(4)	0.4923(2)	0.0462(14)
C00G	0.2813(5)	0.7263(5)	0.3363(3)	0.0691(18)
C00H	0.2084(4)	0.5778(5)	0.4663(3)	0.0551(16)
C00I	0.5224(4)	0.4158(4)	0.4969(2)	0.0508(15)
C00J	0.4998(4)	0.6190(4)	0.4946(3)	0.0592(16)
C00K	0.3868(5)	0.6792(5)	0.3616(3)	0.0612(16)
C00L	0.4531(5)	0.7247(5)	0.4020(3)	0.0661(17)
C00M	0.5398(4)	0.6587(5)	0.4333(3)	0.0642(17)
C00N	0.2517(4)	0.5779(5)	0.5296(3)	0.0558(16)
C00O	0.3874(5)	0.5041(5)	0.6042(3)	0.0677(18)
C00P	0.5363(4)	0.1666(5)	0.4361(2)	0.0555(15)
C00Q	0.0777(5)	0.7456(6)	0.3521(3)	0.090(2)
C00R	0.1589(5)	0.5603(6)	0.3365(3)	0.088(2)
C00S	0.2975(6)	0.9912(6)	0.6233(4)	0.111(3)
C00T	0.2804(6)	0.1829(6)	0.3120(3)	0.092(2)
C00U	0.3685(6)	0.1496(7)	0.6836(3)	0.116(3)
C00V	0.4406(6)	0.8395(5)	0.4253(3)	0.107(3)
C00W	0.2416(8)	0.0655(7)	0.3177(4)	0.149(4)
C00X	0.2604(9)	0.2221(8)	0.2465(4)	0.174(5)
C00Y	0.5126(8)	0.0884(7)	0.2910(3)	0.148(4)
C00Z	0.4881(8)	0.3289(7)	0.3149(4)	0.154(4)
C010	0.2134(7)	0.2537(7)	0.3554(4)	0.141(4)

Table S3. Bond lengths (Å) for compound **218a**.

Si01-O004	1.623(4)	Si01-C00Y	1.849(8)
Si01-C00Z	1.855(7)	Si01-C00T	1.856(8)
O002-C009	1.362(6)	O002-C00E	1.463(6)
O003-C00C	1.413(6)	O003-C006	1.419(6)
O004-C00P	1.426(6)	O005-C008	1.419(6)
O005-C00C	1.422(6)	C006-C008	1.526(7)
C006-C00A	1.529(7)	C006-H006	1.0
C007-C00D	1.497(8)	C007-C00R	1.531(8)
C007-C00Q	1.542(8)	C007-C00G	1.559(7)
C008-C009	1.470(7)	C008-H008	1.0
C009-C00B	1.316(6)	C00A-C00P	1.500(6)
C00A-C00B	1.506(7)	C00A-H00A	1.0
C00B-C00I	1.491(7)	C00C-C00U	1.495(8)
C00C-C00S	1.503(8)	C00D-C00H	1.330(7)
C00D-H00D	0.95	C00E-C00O	1.516(7)
C00E-C00N	1.535(7)	C00E-C00F	1.541(7)
C00F-C00I	1.531(7)	C00F-C00J	1.539(7)
C00F-H00F	1.0	C00G-C00K	1.511(8)
C00G-H00B	0.99	C00G-H00C	0.99
C00H-C00N	1.494(7)	C00H-H00H	0.95
C00I-H00E	0.99	C00I-H00G	0.99
C00J-C00M	1.520(7)	C00J-H00I	0.99
C00J-H00J	0.99	C00K-C00L	1.324(8)
C00K-H00K	0.95	C00L-C00M	1.496(8)
C00L-C00V	1.510(8)	C00M-H00L	0.99
C00M-H00M	0.99	C00N-H00N	0.99
C00N-H00O	0.99	C00O-H00P	0.98
C00O-H00Q	0.98	C00O-H00R	0.98
C00P-H00S	0.99	C00P-H00T	0.99
C00Q-H00U	0.98	C00Q-H00V	0.98
C00Q-H00W	0.98	C00R-H00$	0.98
C00R-H00	0.98	C00R-H00S	0.98
C00S-H00$	0.98	C00S-H00	0.98
C00S-H00S	0.98	C00T-C00W	1.522(10)
C00T-C010	1.528(10)	C00T-C00X	1.545(9)
C00U-H00$	0.98	C00U-H00	0.98
C00U-H00S	0.98	C00V-H00$	0.98
C00V-H00	0.98	C00V-H00S	0.98
C00W-H00$	0.98	C00W-H00	0.98
C00W-H00S	0.98	C00X-H00$	0.98

C00X-H00	0.98	C00X-H00S	0.98
C00Y-H00$	0.98	C00Y-H00	0.98
C00Y-H00S	0.98	C00Z-H00$	0.98
C00Z-H00	0.98	C00Z-H00S	0.98
C010-H01A	0.98	C010-H01B	0.98
C010-H01C	0.98		

Table S4. Bond angles (°) for compound **218a**.

O004-Si01-C00Y	108.2(3)	O004-Si01-C00Z	109.5(3)
C00Y-Si01-C00Z	109.1(4)	O004-Si01-C00T	104.6(3)
C00Y-Si01-C00T	112.5(4)	C00Z-Si01-C00T	112.9(4)
C009-O002-C00E	115.1(3)	C00C-O003-C006	107.8(4)
C00P-O004-Si01	123.4(3)	C008-O005-C00C	109.0(4)
O003-C006-C008	103.0(4)	O003-C006-C00A	109.5(4)
C008-C006-C00A	107.4(4)	O003-C006-H006	112.2
C008-C006-H006	112.2	C00A-C006-H006	112.2
C00D-C007-C00R	113.1(5)	C00D-C007-C00Q	110.8(5)
C00R-C007-C00Q	109.2(5)	C00D-C007-C00G	106.4(5)
C00R-C007-C00G	109.5(5)	C00Q-C007-C00G	107.8(5)
O005-C008-C009	114.1(5)	O005-C008-C006	105.3(4)
C009-C008-C006	102.1(4)	O005-C008-H008	111.6
C009-C008-H008	111.6	C006-C008-H008	111.6
C00B-C009-O002	126.7(5)	C00B-C009-C008	114.6(5)
O002-C009-C008	118.7(4)	C00P-C00A-C00B	114.0(4)
C00P-C00A-C006	111.7(4)	C00B-C00A-C006	102.4(4)
C00P-C00A-H00A	109.5	C00B-C00A-H00A	109.5
C006-C00A-H00A	109.5	C009-C00B-C00I	121.5(5)
C009-C00B-C00A	110.7(5)	C00I-C00B-C00A	127.7(4)
O003-C00C-O005	106.2(4)	O003-C00C-C00U	108.2(5)
O005-C00C-C00U	108.6(6)	O003-C00C-C00S	110.8(5)
O005-C00C-C00S	109.0(5)	C00U-C00C-C00S	113.7(6)
C00H-C00D-C007	128.0(6)	C00H-C00D-H00D	116.0
C007-C00D-H00D	116.0	O002-C00E-C00O	107.9(4)
O002-C00E-C00N	102.8(4)	C00O-C00E-C00N	110.0(5)
O002-C00E-C00F	109.7(4)	C00O-C00E-C00F	113.1(4)
C00N-C00E-C00F	112.6(4)	C00I-C00F-C00J	109.8(4)
C00I-C00F-C00E	111.3(4)	C00J-C00F-C00E	114.4(4)
C00I-C00F-H00F	107.0	C00J-C00F-H00F	107.0
C00E-C00F-H00F	107.0	C00K-C00G-C007	111.4(5)
C00K-C00G-H00B	109.3	C007-C00G-H00B	109.3
C00K-C00G-H00C	109.3	C007-C00G-H00C	109.3

H00B-C00G-H00C	108.0	C00D-C00H-C00N	124.3(6)
C00D-C00H-H00H	117.9	C00N-C00H-H00H	117.9
C00B-C00I-C00F	111.2(4)	C00B-C00I-H00E	109.4
C00F-C00I-H00E	109.4	C00B-C00I-H00G	109.4
C00F-C00I-H00G	109.4	H00E-C00I-H00G	108.0
C00M-C00J-C00F	113.9(5)	C00M-C00J-H00I	108.8
C00F-C00J-H00I	108.8	C00M-C00J-H00J	108.8
C00F-C00J-H00J	108.8	H00I-C00J-H00J	107.7
C00L-C00K-C00G	127.0(6)	C00L-C00K-H00K	116.5
C00G-C00K-H00K	116.5	C00K-C00L-C00M	120.6(6)
C00K-C00L-C00V	124.3(6)	C00M-C00L-C00V	114.7(6)
C00L-C00M-C00J	111.2(5)	C00L-C00M-H00L	109.4
C00J-C00M-H00L	109.4	C00L-C00M-H00M	109.4
C00J-C00M-H00M	109.4	H00L-C00M-H00M	108.0
C00H-C00N-C00E	113.3(4)	C00H-C00N-H00N	108.9
C00E-C00N-H00N	108.9	C00H-C00N-H00O	108.9
C00E-C00N-H00O	108.9	H00N-C00N-H00O	107.7
C00E-C00O-H00P	109.5	C00E-C00O-H00Q	109.5
H00P-C00O-H00Q	109.5	C00E-C00O-H00R	109.5
H00P-C00O-H00R	109.5	H00Q-C00O-H00R	109.5
O004-C00P-C00A	109.0(4)	O004-C00P-H00S	109.9
C00A-C00P-H00S	109.9	O004-C00P-H00T	109.9
C00A-C00P-H00T	109.9	H00S-C00P-H00T	108.3
C007-C00Q-H00U	109.5	C007-C00Q-H00V	109.5
H00U-C00Q-H00V	109.5	C007-C00Q-H00W	109.5
H00U-C00Q-H00W	109.5	H00V-C00Q-H00W	109.5
C007-C00R-H00$	109.5	C007-C00R-H00	109.5
H00$-C00R-H00	109.5	C007-C00R-H00S	109.5
H00$-C00R-H00S	109.5	H00-C00R-H00S	109.5
C00C-C00S-H00$	109.5	C00C-C00S-H00	109.5
H00$-C00S-H00	109.5	C00C-C00S-H00S	109.5
H00$-C00S-H00S	109.5	H00-C00S-H00S	109.5
C00W-C00T-C010	108.8(8)	C00W-C00T-C00X	108.9(7)
C010-C00T-C00X	109.2(7)	C00W-C00T-Si01	110.0(6)
C010-C00T-Si01	110.0(5)	C00X-C00T-Si01	110.0(6)
C00C-C00U-H00$	109.5	C00C-C00U-H00	109.5
H00$-C00U-H00	109.5	C00C-C00U-H00S	109.5
H00$-C00U-H00S	109.5	H00-C00U-H00S	109.5
C00L-C00V-H00$	109.5	C00L-C00V-H00	109.5
H00$-C00V-H00	109.5	C00L-C00V-H00S	109.5
H00$-C00V-H00S	109.5	H00-C00V-H00S	109.5
C00T-C00W-H00$	109.5	C00T-C00W-H00	109.5

H00$-C00W-H00	109.5	C00T-C00W-H00S	109.5
H00$-C00W-H00S	109.5	H00-C00W-H00S	109.5
C00T-C00X-H00$	109.5	C00T-C00X-H00	109.5
H00$-C00X-H00	109.5	C00T-C00X-H00S	109.5
H00$-C00X-H00S	109.5	H00-C00X-H00S	109.5
Si01-C00Y-H00$	109.5	Si01-C00Y-H00	109.5
H00$-C00Y-H00	109.5	Si01-C00Y-H00S	109.5
H00$-C00Y-H00S	109.5	H00-C00Y-H00S	109.5
Si01-C00Z-H00$	109.5	Si01-C00Z-H00	109.5
H00$-C00Z-H00	109.5	Si01-C00Z-H00S	109.5
H00$-C00Z-H00S	109.5	H00-C00Z-H00S	109.5
C00T-C010-H01A	109.5	C00T-C010-H01B	109.5
H01A-C010-H01B	109.5	C00T-C010-H01C	109.5
H01A-C010-H01C	109.5	H01B-C010-H01C	109.5

Table S5. Anisotropic atomic displacement parameters (Å2) for compound **218a**.

The anisotropic atomic displacement factor exponent takes the form: -2π2[h2 a*2 U11 + ... + 2 h k a* b* U12]

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Si01	0.1057(14)	0.0570(12)	0.0547(11)	0.0031(10)	0.0055(10)	-0.0037(12)
O002	0.0353(18)	0.039(2)	0.072(3)	0.007(2)	0.0078(18)	0.001(2)
O003	0.046(2)	0.076(3)	0.058(3)	0.021(2)	-0.001(2)	0.009(2)
O004	0.051(2)	0.076(3)	0.049(2)	-0.003(2)	0.0007(19)	0.006(2)
O005	0.054(2)	0.065(3)	0.067(3)	0.029(2)	0.014(2)	0.015(2)
C006	0.046(3)	0.038(3)	0.056(4)	0.005(3)	-0.006(3)	-0.006(3)
C007	0.055(3)	0.051(4)	0.071(4)	0.007(4)	0.006(3)	0.000(3)
C008	0.037(3)	0.044(4)	0.048(3)	0.010(3)	-0.001(3)	-0.001(3)
C009	0.035(3)	0.041(3)	0.046(3)	0.004(3)	-0.001(3)	0.002(3)
C00A	0.036(3)	0.042(3)	0.054(4)	0.006(3)	-0.004(3)	0.006(3)
C00B	0.031(3)	0.044(4)	0.052(3)	0.006(3)	-0.002(2)	-0.005(3)
C00C	0.051(4)	0.077(5)	0.063(5)	0.018(4)	0.003(3)	0.003(4)
C00D	0.055(3)	0.041(4)	0.072(4)	-0.002(3)	0.012(3)	0.007(3)
C00E	0.041(3)	0.038(4)	0.066(4)	0.005(3)	0.008(3)	-0.006(3)
C00F	0.039(3)	0.035(3)	0.064(4)	0.003(3)	0.004(3)	-0.001(3)
C00G	0.074(4)	0.057(4)	0.076(4)	0.013(3)	0.002(4)	0.003(4)
C00H	0.040(3)	0.048(4)	0.077(5)	0.001(4)	0.008(3)	0.003(3)
C00I	0.036(3)	0.053(4)	0.064(4)	-0.004(3)	0.005(3)	-0.007(3)
C00J	0.053(3)	0.043(4)	0.081(4)	-0.001(3)	0.002(3)	-0.010(3)
C00K	0.066(4)	0.049(4)	0.069(4)	0.009(4)	0.022(3)	0.002(4)
C00L	0.061(4)	0.047(4)	0.090(5)	0.013(4)	0.000(4)	-0.010(3)

C00M	0.052(3)	0.054(4)	0.087(5)	0.008(3)	0.011(3)	-0.019(3)
C00N	0.052(3)	0.044(4)	0.071(4)	0.003(3)	0.016(3)	0.005(3)
C00O	0.070(4)	0.073(4)	0.060(4)	-0.002(4)	0.004(3)	-0.001(4)
C00P	0.041(3)	0.058(4)	0.068(4)	0.001(3)	0.007(3)	0.002(3)
C00Q	0.080(4)	0.099(5)	0.093(5)	0.016(4)	-0.011(4)	0.032(4)
C00R	0.098(5)	0.080(5)	0.087(5)	-0.008(4)	-0.012(4)	-0.006(4)
C00S	0.078(5)	0.080(6)	0.174(9)	0.061(6)	0.009(5)	-0.006(4)
C00T	0.131(6)	0.073(5)	0.072(5)	-0.016(5)	-0.039(4)	-0.003(6)
C00U	0.099(5)	0.184(10)	0.066(5)	-0.005(5)	0.002(4)	0.006(6)
C00V	0.110(5)	0.038(4)	0.173(8)	0.002(4)	-0.034(6)	-0.007(4)
C00W	0.162(8)	0.107(7)	0.178(10)	0.004(7)	-0.069(7)	-0.063(7)
C00X	0.239(12)	0.195(11)	0.088(7)	0.016(7)	-0.080(7)	-0.023(10)
C00Y	0.202(9)	0.148(8)	0.094(6)	-0.018(6)	0.079(6)	0.043(8)
C00Z	0.192(9)	0.114(8)	0.158(9)	0.058(7)	-0.049(7)	-0.073(7)
C010	0.117(6)	0.161(9)	0.145(9)	-0.029(7)	-0.043(6)	0.043(6)

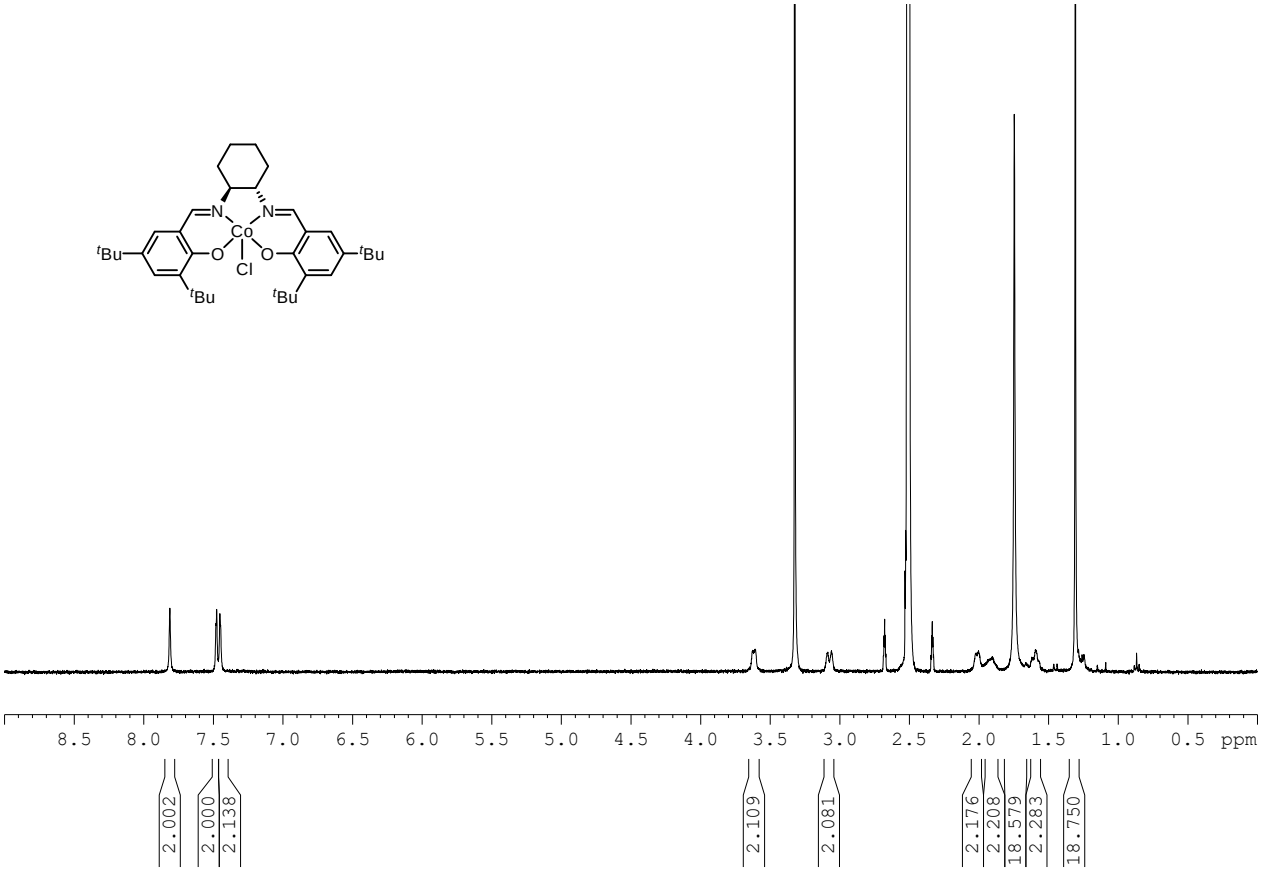
Table S6. Hydrogen atomic coordinates and isotropic atomic displacement parameters (Å2) for compound **218a**.

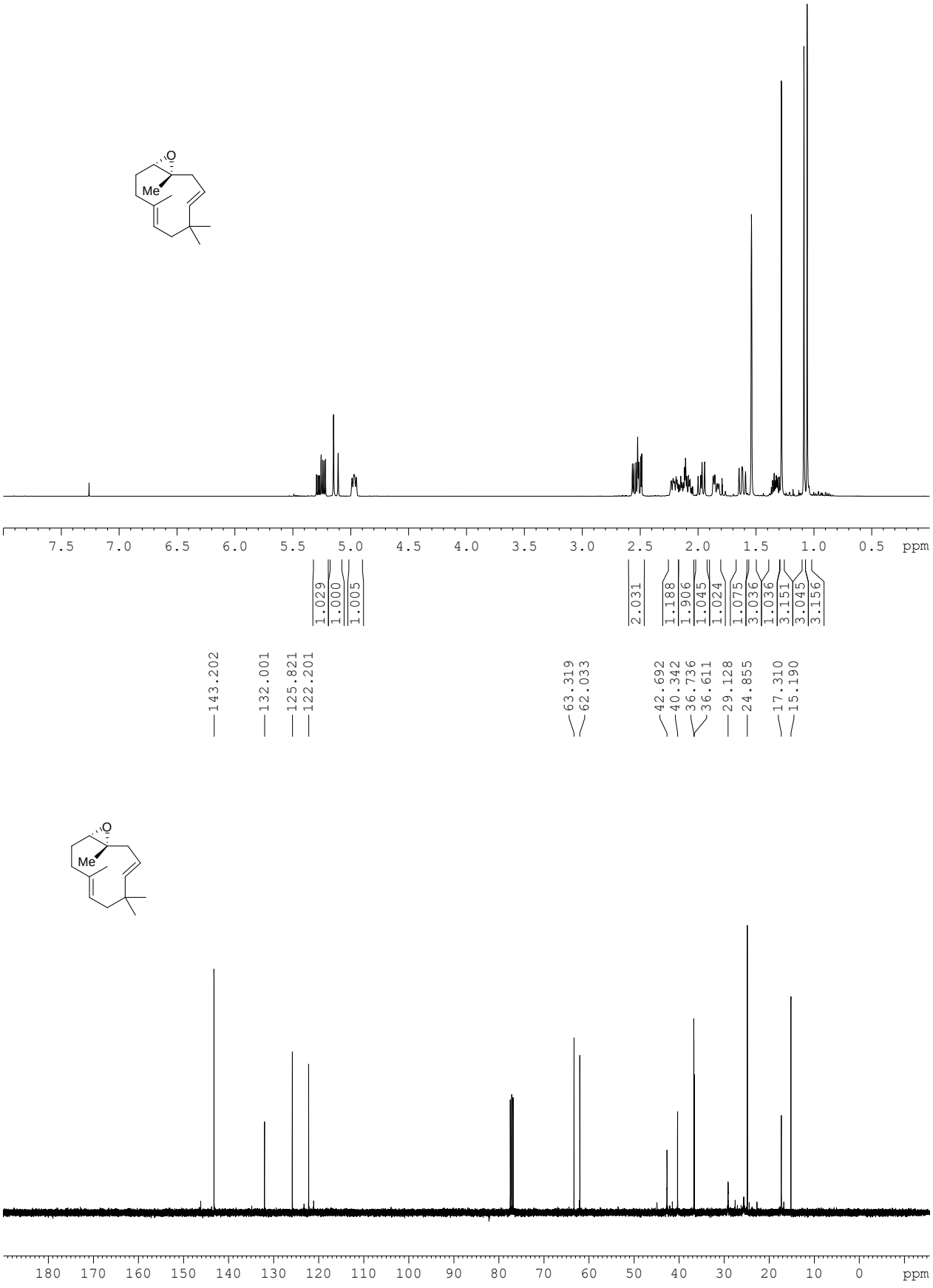
	x/a	**y/b**	**z/c**	**U(eq)**
H006	0.4102	0.0573	0.5042	0.056
H008	0.2637	0.1749	0.4997	0.052
H00A	0.5814	0.1900	0.5252	0.053
H00D	0.2086	0.7340	0.4520	0.067
H00F	0.4038	0.5037	0.4515	0.055
H00B	0.2796	0.7151	0.2920	0.083
H00C	0.2795	0.8056	0.3441	0.083
H00H	0.1855	0.5102	0.4496	0.066
H00E	0.5652	0.4111	0.4589	0.061
H00G	0.5746	0.4307	0.5303	0.061
H00I	0.4496	0.6744	0.5120	0.071
H00J	0.5640	0.6122	0.5220	0.071
H00K	0.4077	0.6094	0.3471	0.073
H00L	0.6068	0.7036	0.4387	0.077
H00M	0.5594	0.5953	0.4078	0.077
H00N	0.1908	0.5600	0.5577	0.067
H00O	0.2780	0.6521	0.5396	0.067
H00P	0.3264	0.4891	0.6321	0.102
H00Q	0.4162	0.5774	0.6118	0.102
H00R	0.4462	0.4506	0.6105	0.102
H00S	0.5892	0.2190	0.4183	0.067

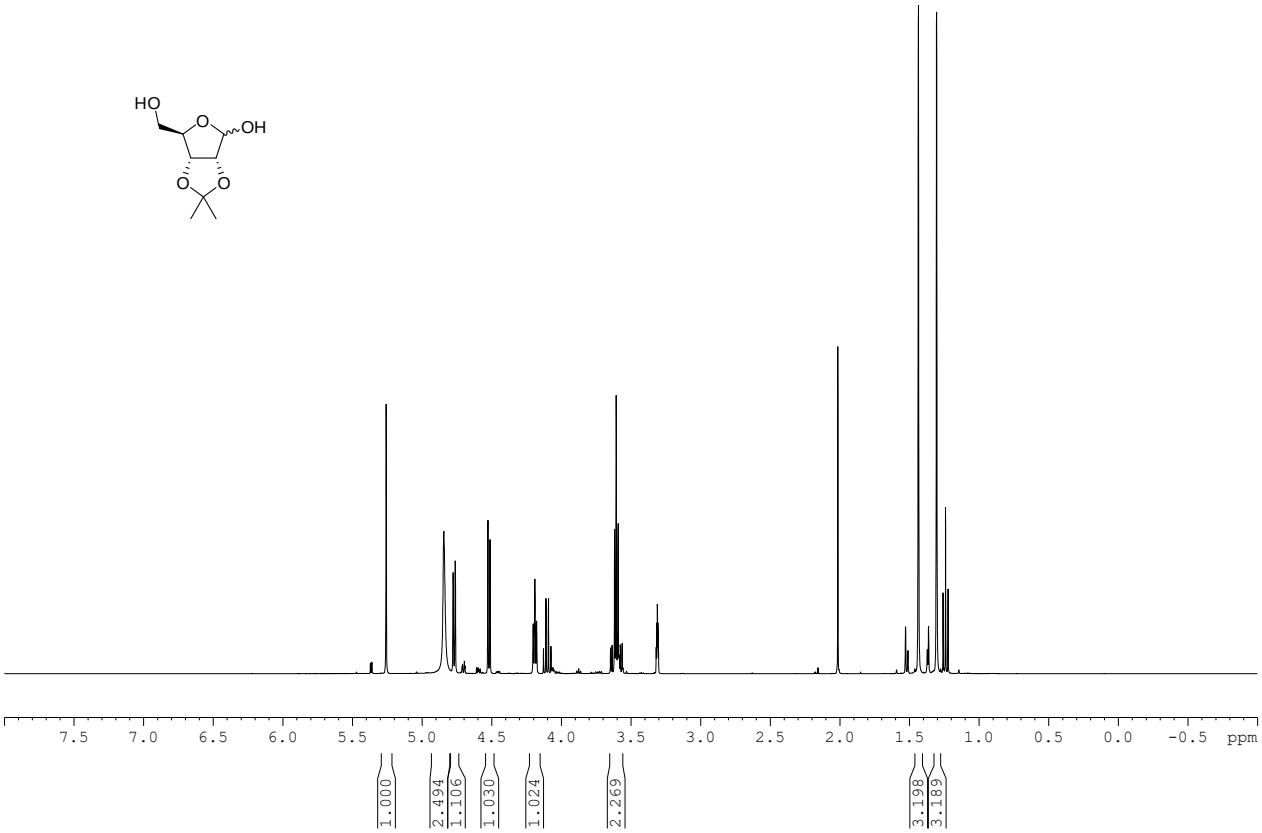
H00T	0.5696	0.0931	0.4345	0.067
H00U	0.0110	0.7123	0.3689	0.136
H00V	0.0692	0.7541	0.3082	0.136
H00W	0.0892	0.8171	0.3706	0.136
H00$	0.2258	0.5161	0.3407	0.133
H00	0.1413	0.5694	0.2936	0.133
H00S	0.0974	0.5237	0.3569	0.133
H00$	0.2284	-0.0074	0.6462	0.166
H00	0.3492	-0.0593	0.6425	0.166
H00S	0.2827	-0.0328	0.5818	0.166
H00$	0.3935	0.2252	0.6797	0.174
H00	0.4256	0.1065	0.7038	0.174
H00S	0.3005	0.1475	0.7075	0.174
H00$	0.5120	0.8768	0.4234	0.16
H00	0.4149	0.8376	0.4673	0.16
H00S	0.3869	0.8787	0.4004	0.16
H00$	0.2400	0.0448	0.3605	0.223
H00	0.2925	0.0176	0.2958	0.223
H00S	0.1675	0.0586	0.3005	0.223
H00$	0.1869	0.1991	0.2333	0.261
H00	0.3162	0.1903	0.2197	0.261
H00S	0.2654	0.3016	0.2449	0.261
H00$	0.5905	0.1095	0.2920	0.222
H00	0.4880	0.0828	0.2489	0.222
H00S	0.5033	0.0179	0.3111	0.222
H00$	0.4603	0.3811	0.3448	0.232
H00	0.4663	0.3523	0.2742	0.232
H00S	0.5687	0.3255	0.3174	0.232
H01A	0.1349	0.2478	0.3455	0.211
H01B	0.2369	0.3297	0.3516	0.211
H01C	0.2255	0.2288	0.3970	0.211

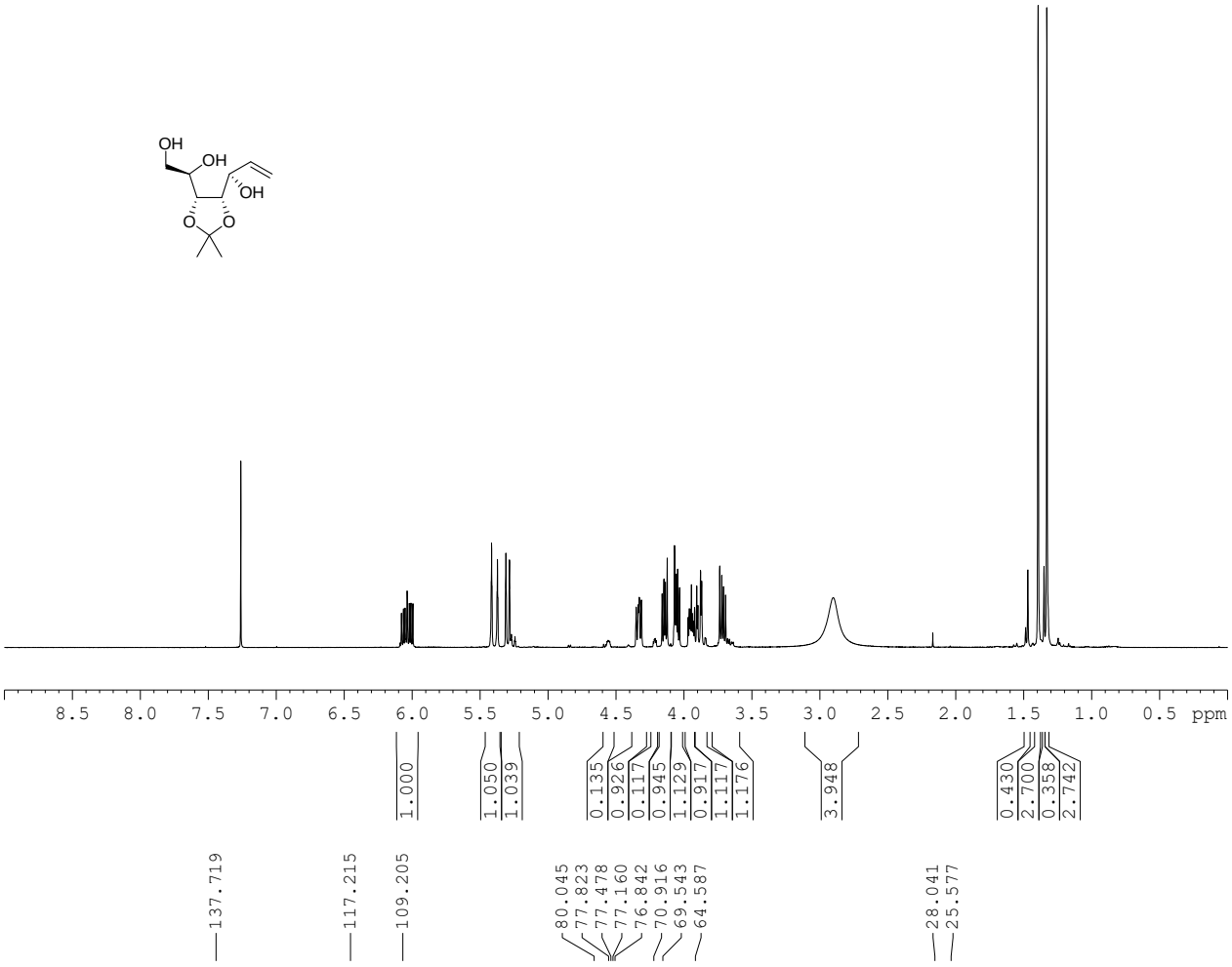
Appendix II. NMR Spectra

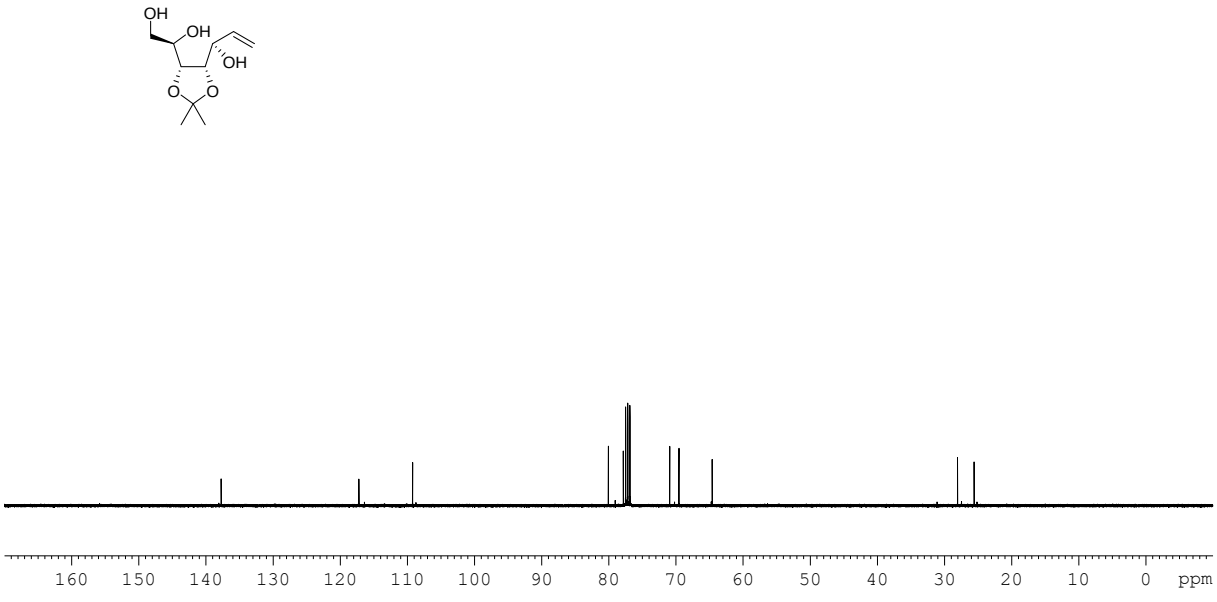
8.1 NMR Spectra for chapter 2

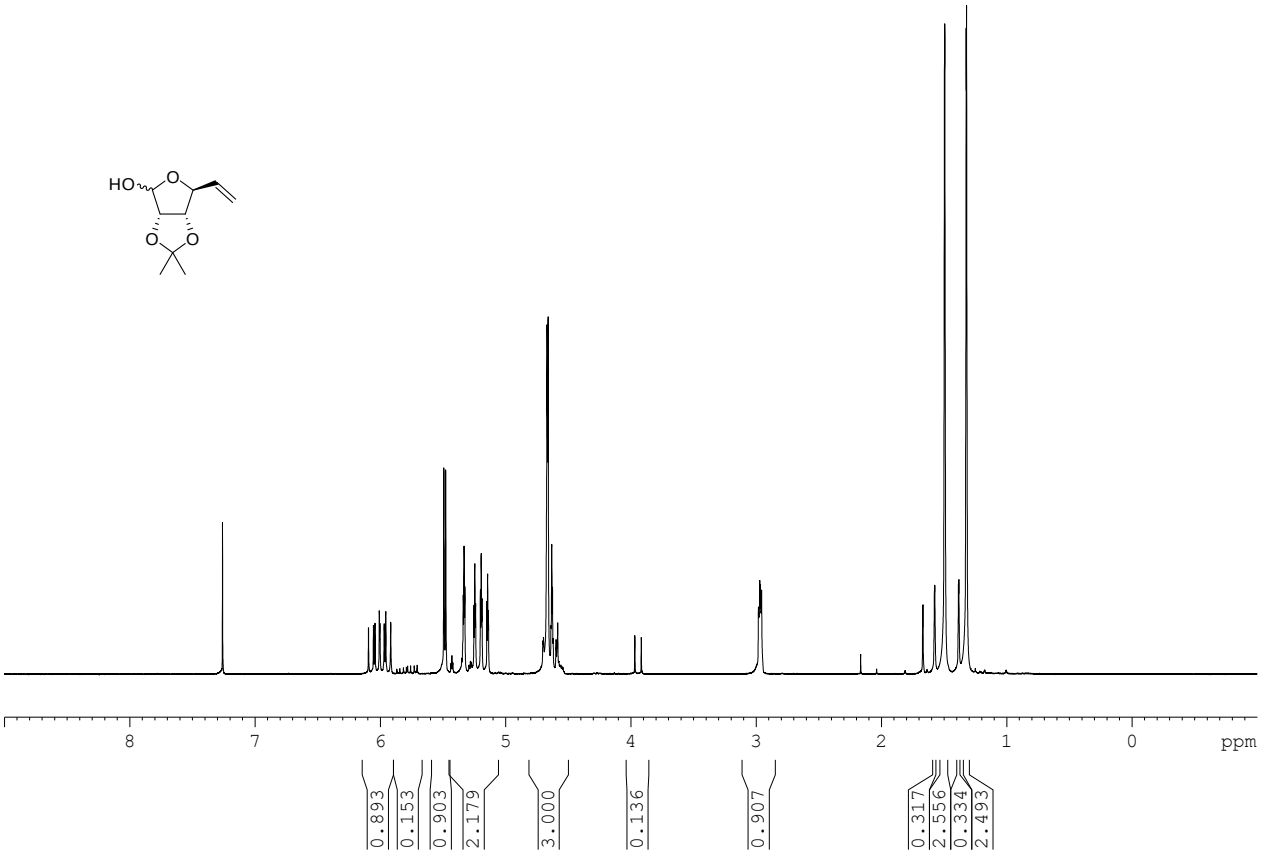


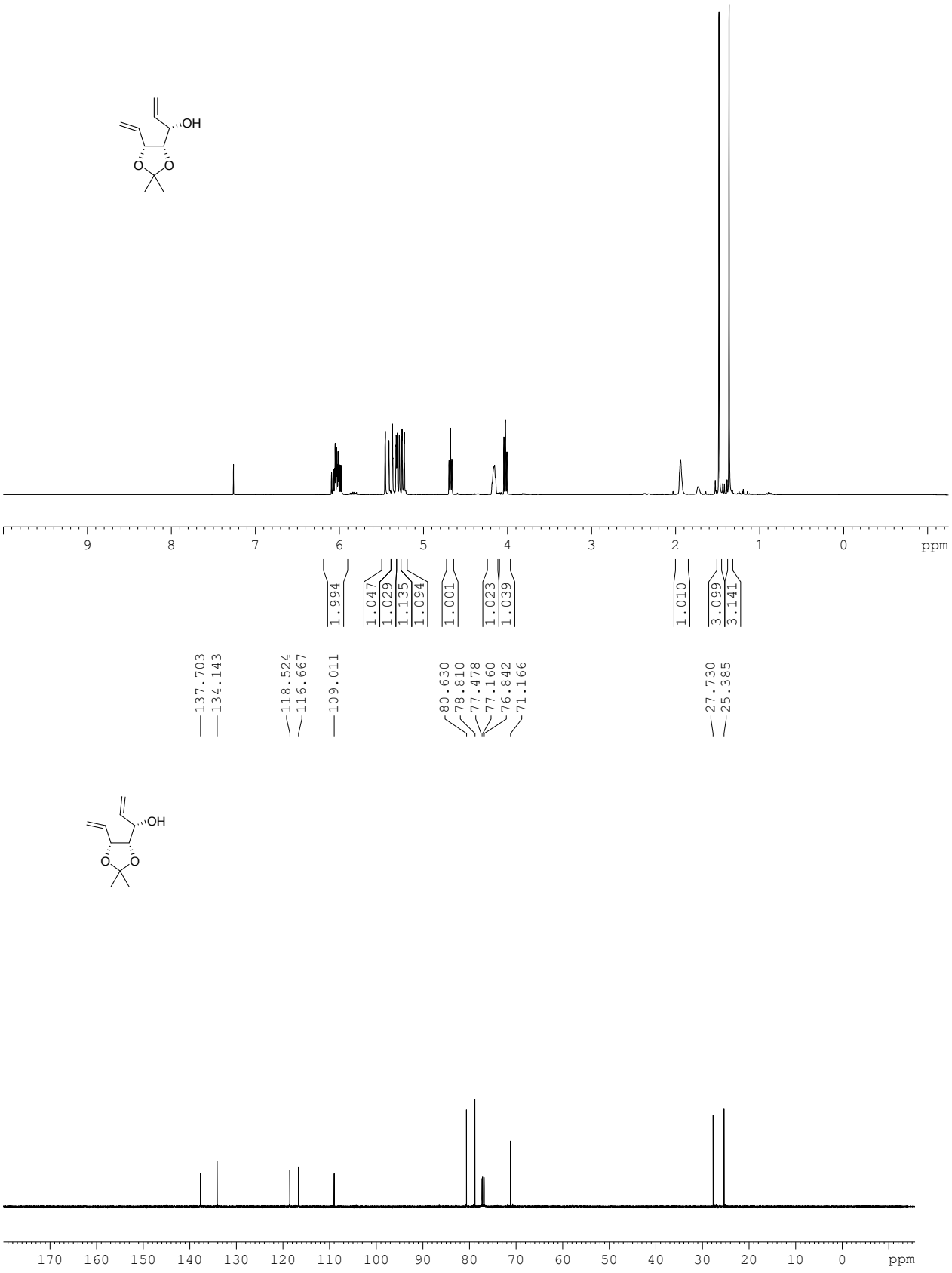

O
Me
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.029 1.000 1.005 2.031 1.188 1.906 1.045 1.024 1.075 3.036 1.036 3.151 3.045 3.156
143.202 132.001 125.821 122.201 63.319 62.033 42.692 40.342 36.736 36.611 29.128 24.855 17.310 15.190
O
Me
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

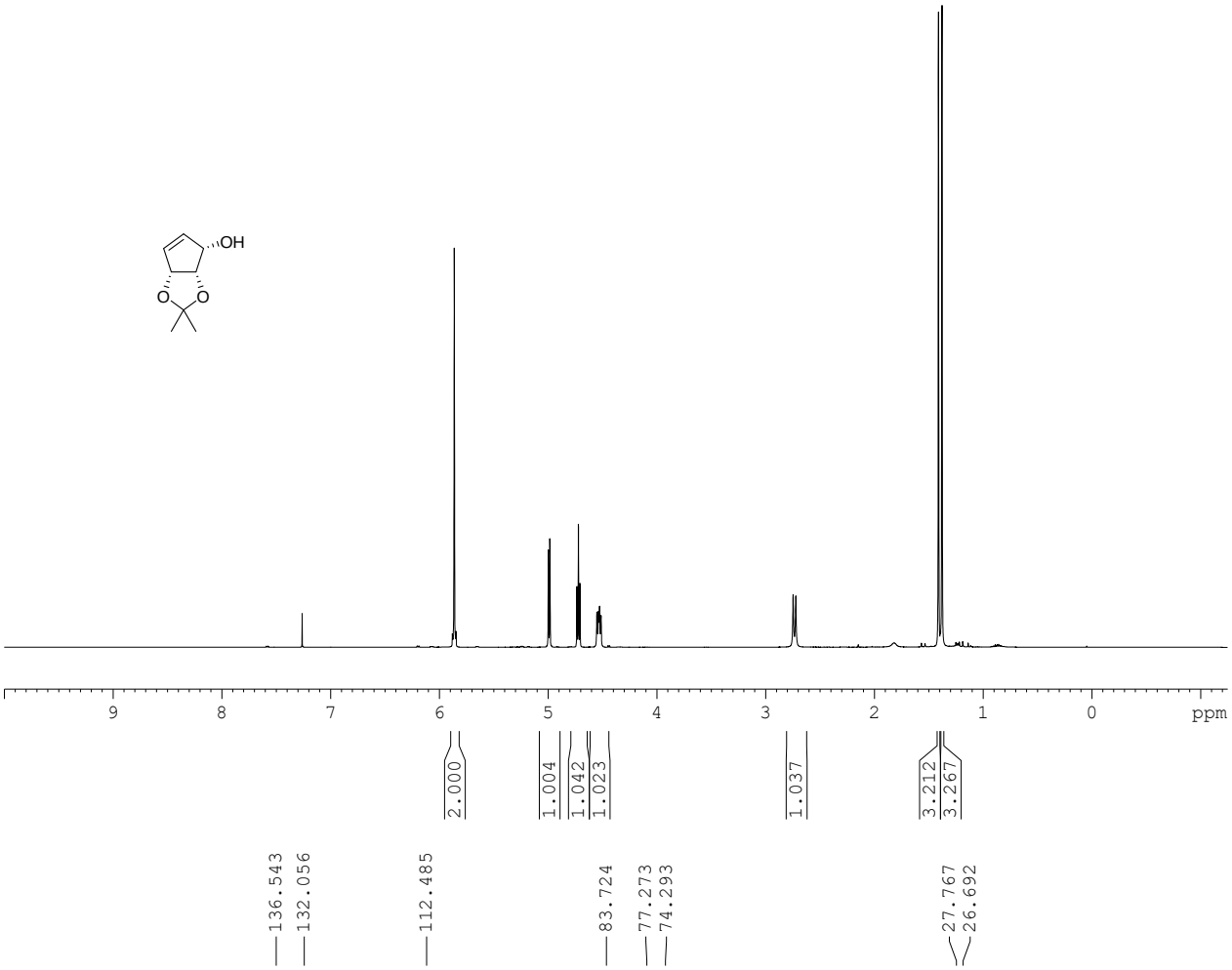

HO
O
OH
O
O
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm
1.000
2.494
1.106
1.030
1.024
2.269
3.198
3.189

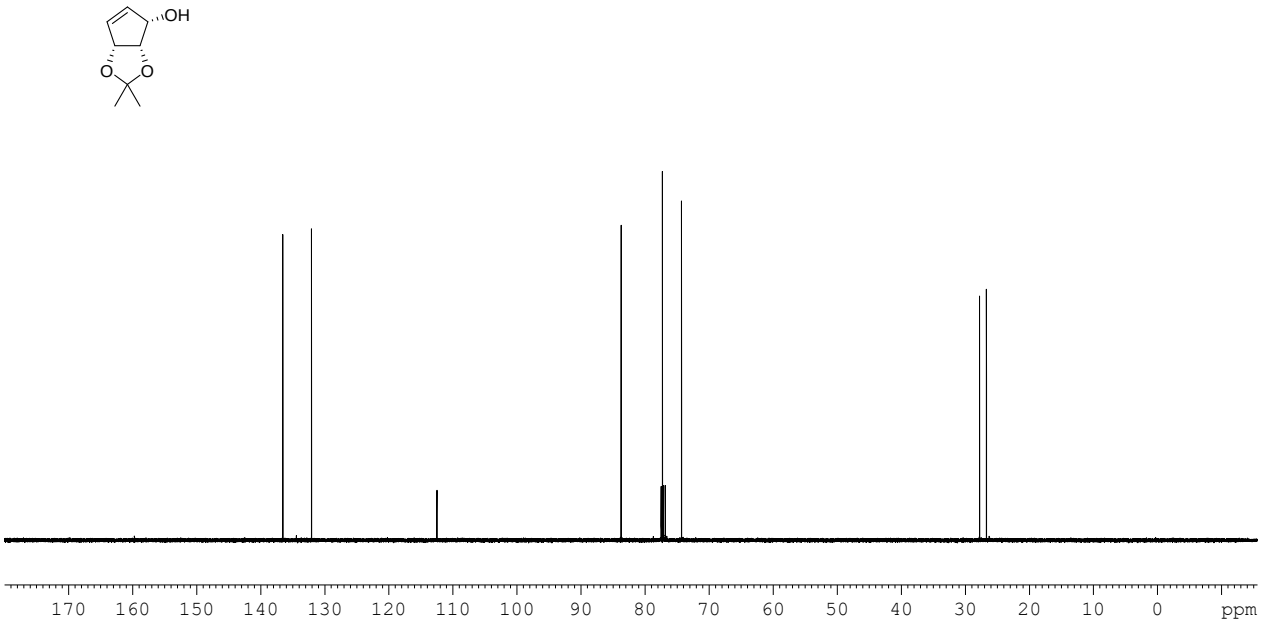

OH
OH
OH
O
O
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.000
1.050
1.039
0.135
0.926
0.117
0.945
1.129
0.917
1.117
1.176
3.948
0.430
2.700
0.358
2.742
137.719
117.215
109.205
80.045
77.823
77.478
77.160
76.842
70.916
69.543
64.587
28.041
25.577

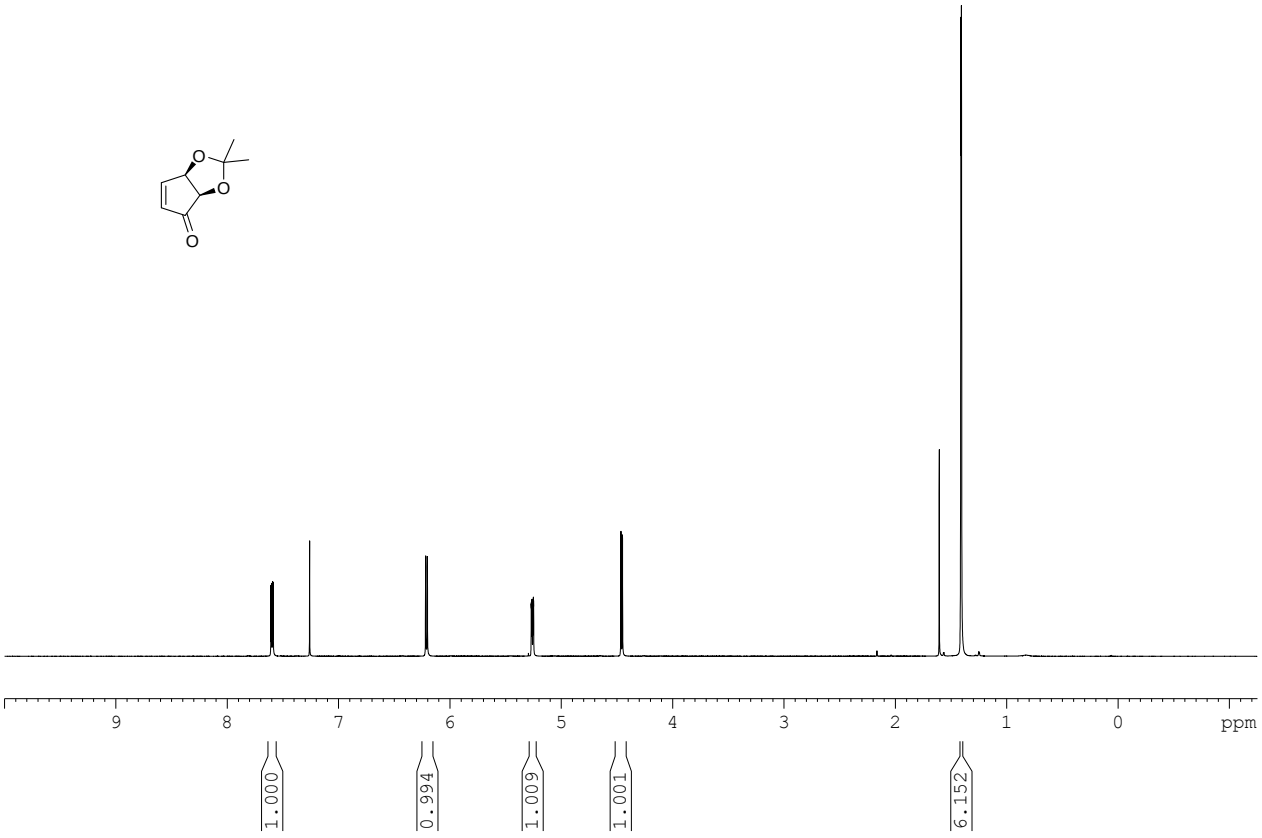

OH
OH
OH
O
O
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

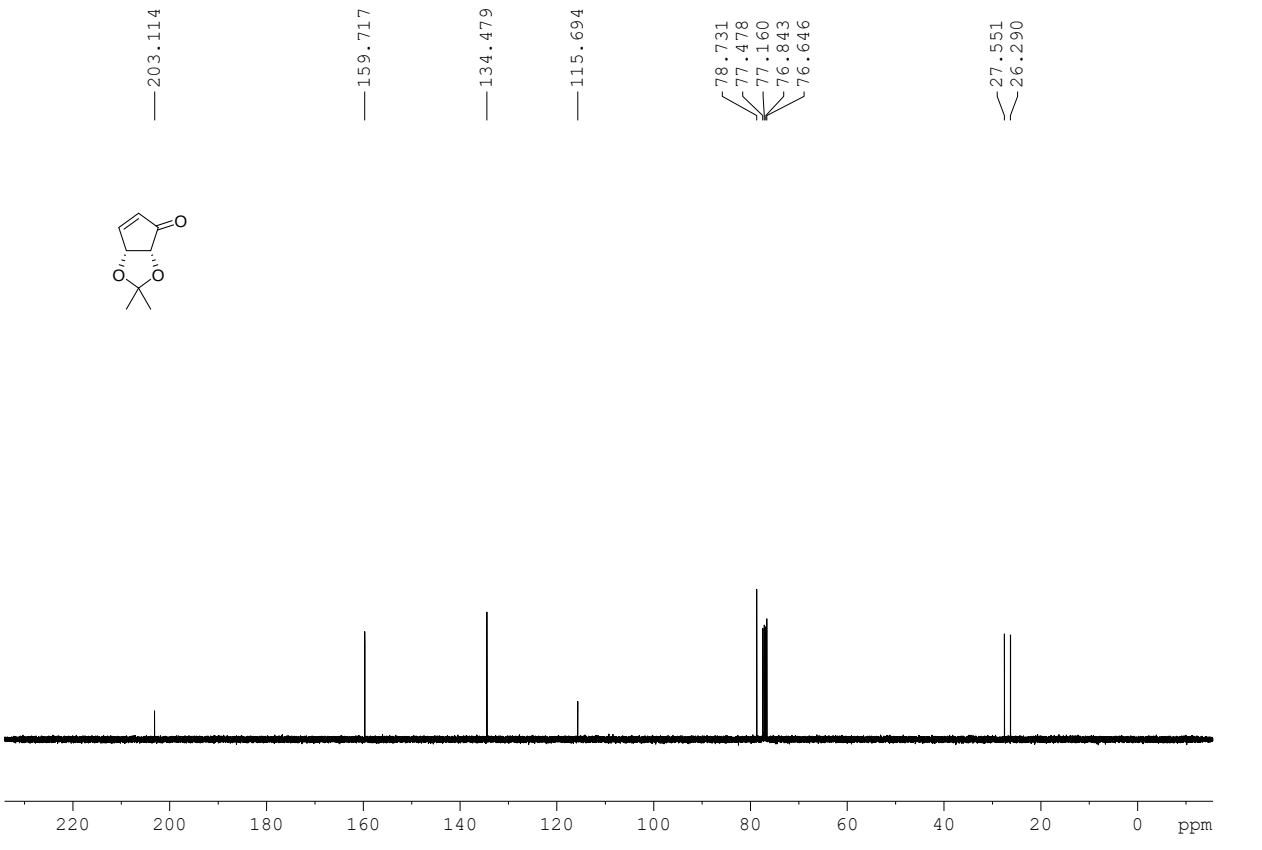

HO
O
O
O
8
7
6
5
4
3
2
1
0
ppm
0.893
0.153
0.903
2.179
3.000
0.136
0.907
0.317
2.556
0.334
2.493

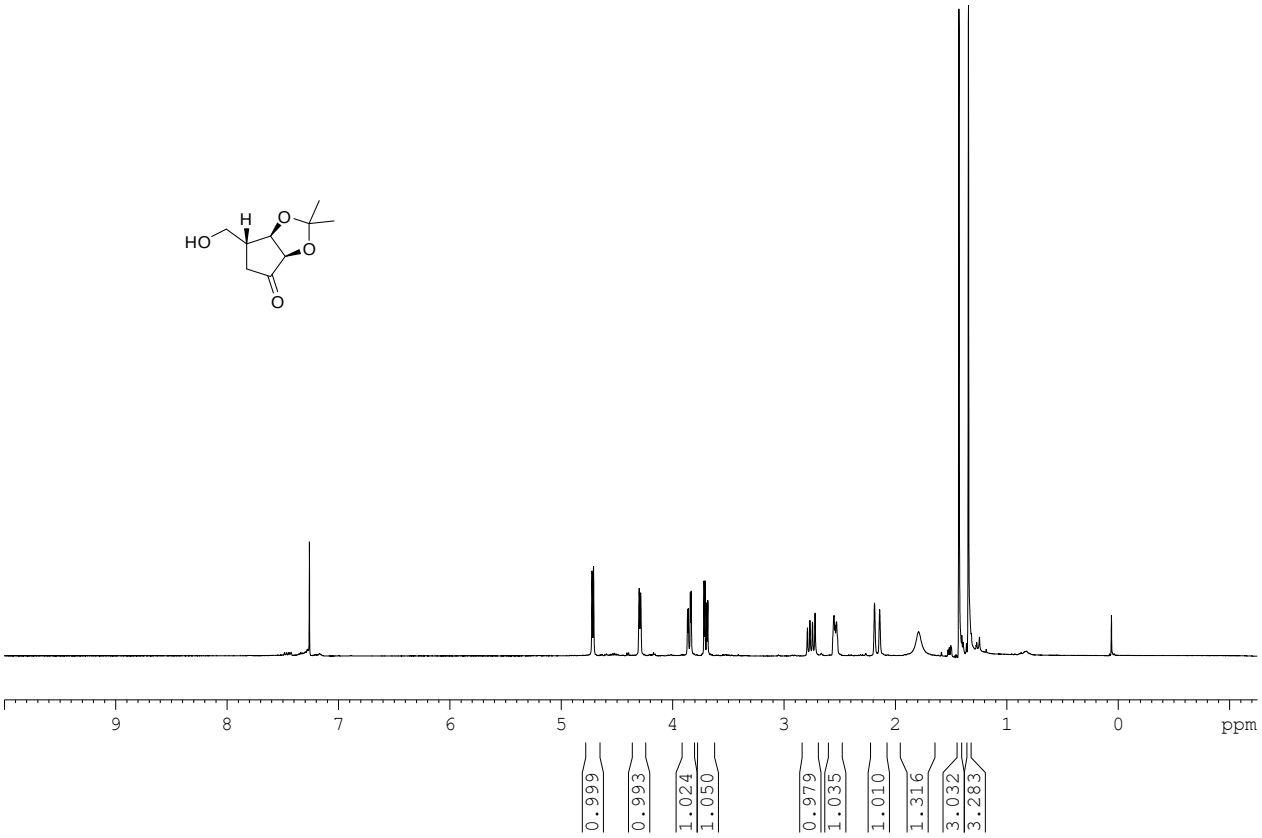

OH
O
O
9
8
7
6
5
4
3
2
1
0
ppm
1.994
1.047
1.029
1.135
1.094
1.001
1.023
1.039
1.010
3.099
3.141
137.703
134.143
118.524
116.667
109.011
80.630
78.810
77.478
77.160
76.842
71.166
27.730
25.385
OH
O
O
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

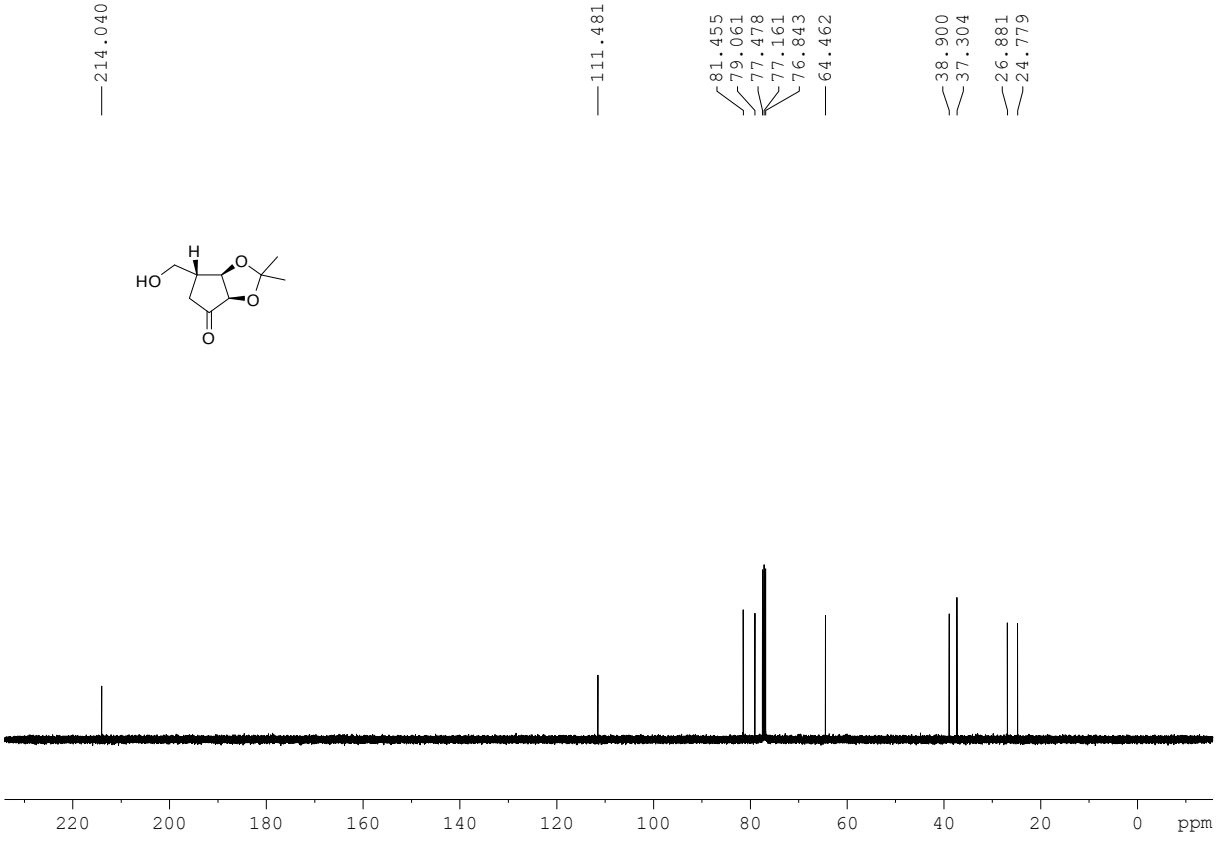

OH
O
O
9
8
7
6
5
4
3
2
1
0
ppm
2.000
1.004
1.042
1.023
1.037
3.212
3.267
136.543
132.056
112.485
83.724
77.273
74.293
27.767
26.692

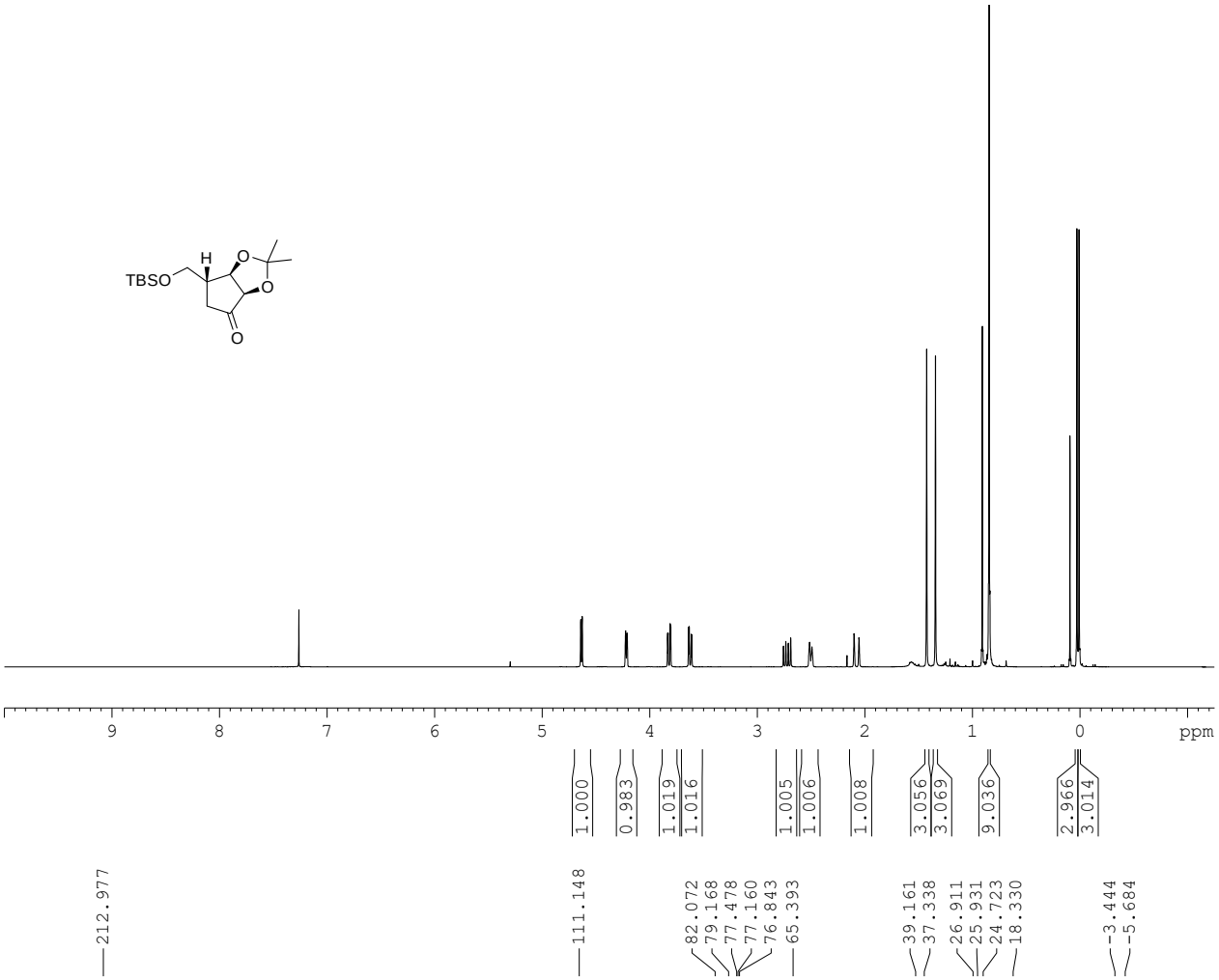

OH
O
O
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


9
8
7
6
5
4
3
2
1
0
ppm
1.000
0.994
1.009
1.001
6.152

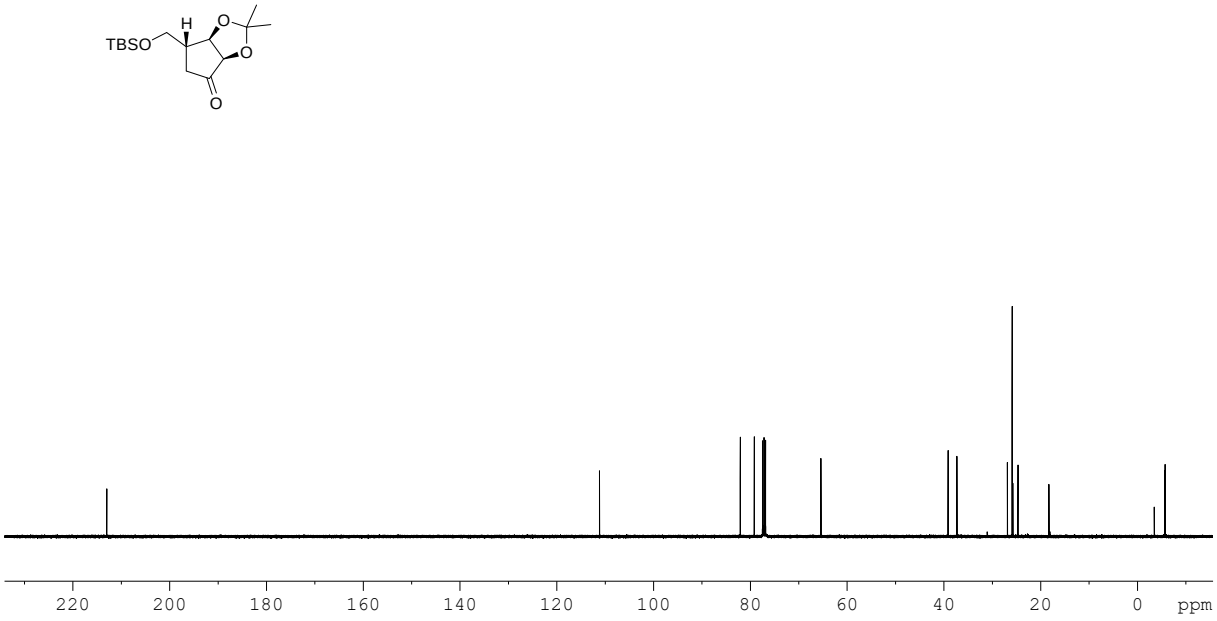

203.114
159.717
134.479
115.694
78.731
77.478
77.160
76.843
76.646
27.551
26.290
220
200
180
160
140
120
100
80
60
40
20
0
ppm

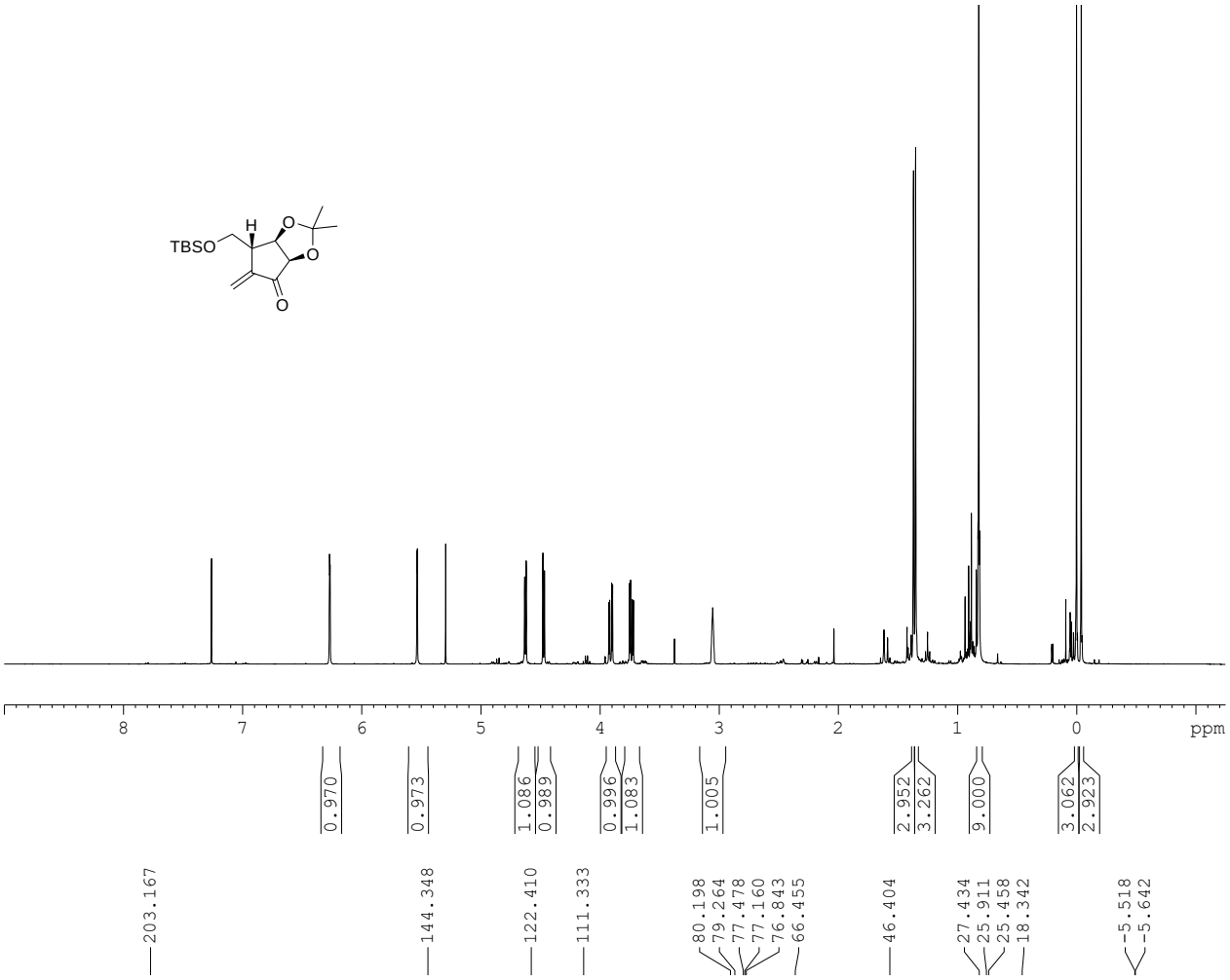

HO
H
O
O
O
9
8
7
6
5
4
3
2
1
0
ppm
0.999
0.993
1.024
1.050
0.979
1.035
1.010
1.316
3.032
3.283

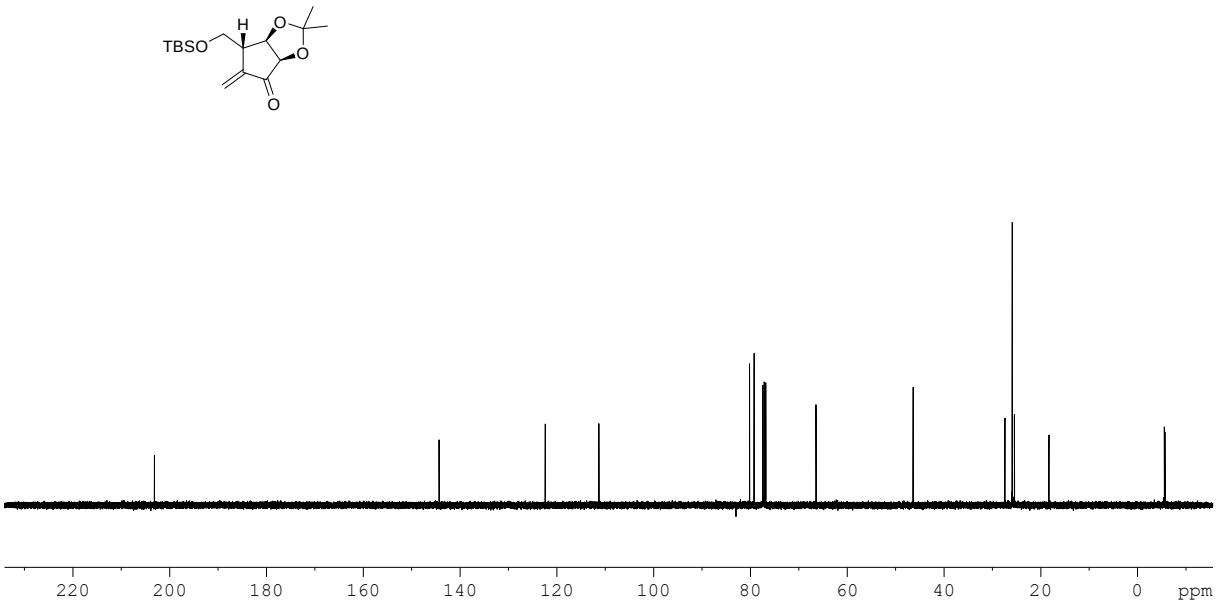

214.040
111.481
81.455
79.061
77.478
77.161
76.843
64.462
38.900
37.304
26.881
24.779
HO
H
O
O
O
220
200
180
160
140
120
100
80
60
40
20
0
ppm

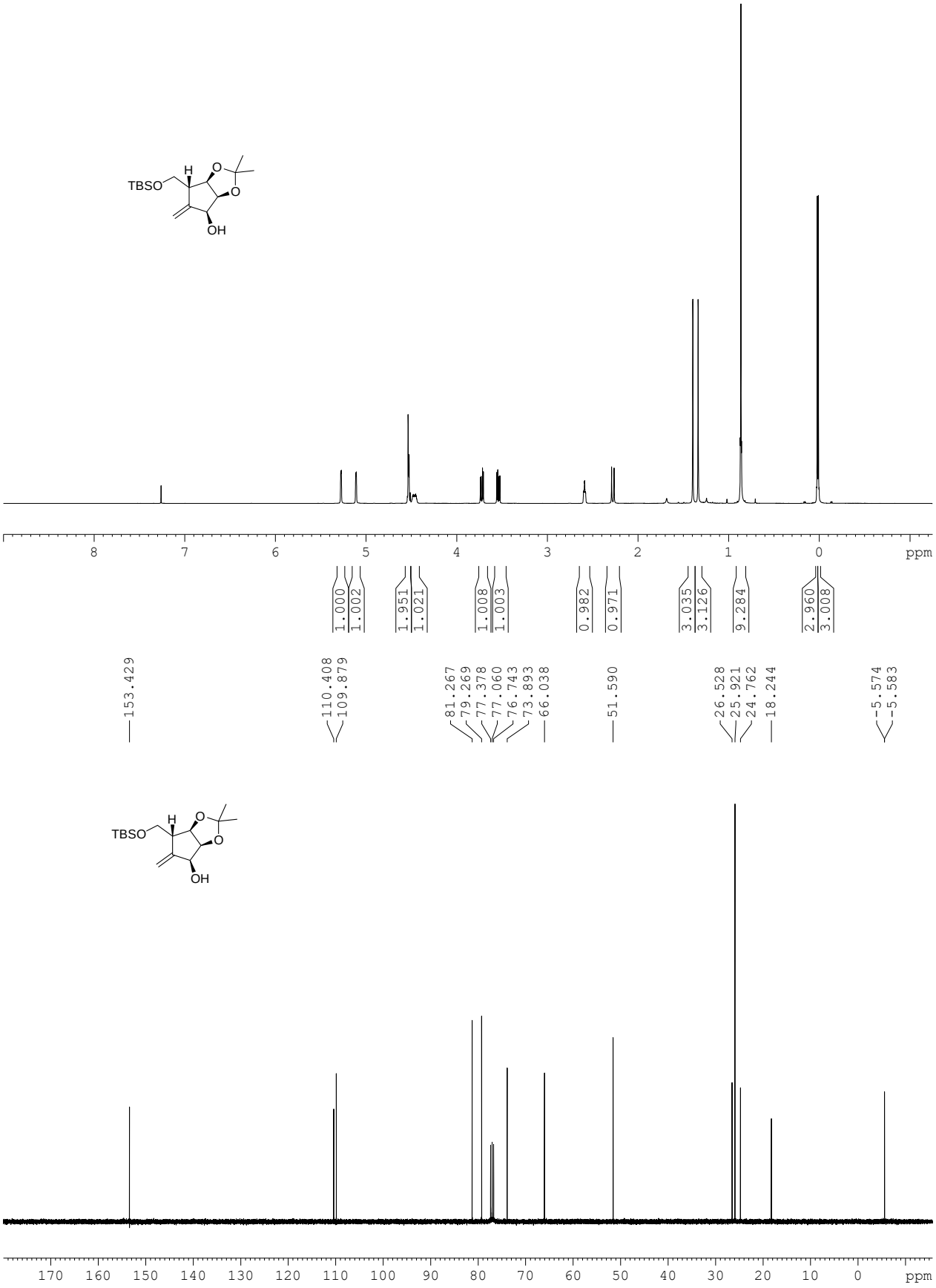


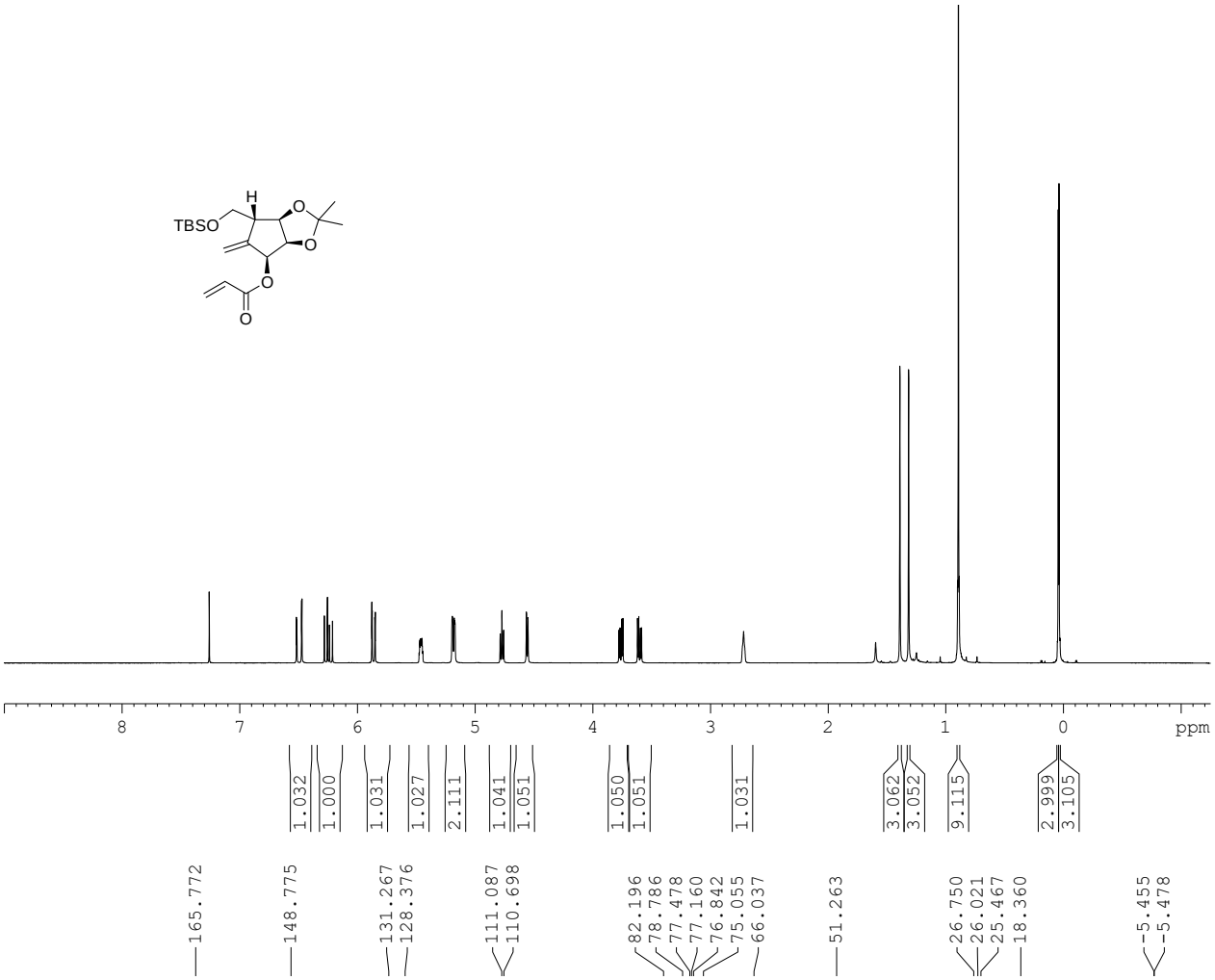
212.977
111.148
82.072
79.168
77.478
77.160
76.843
65.393
39.161
37.338
26.911
25.931
24.723
18.330
-3.444
-5.684

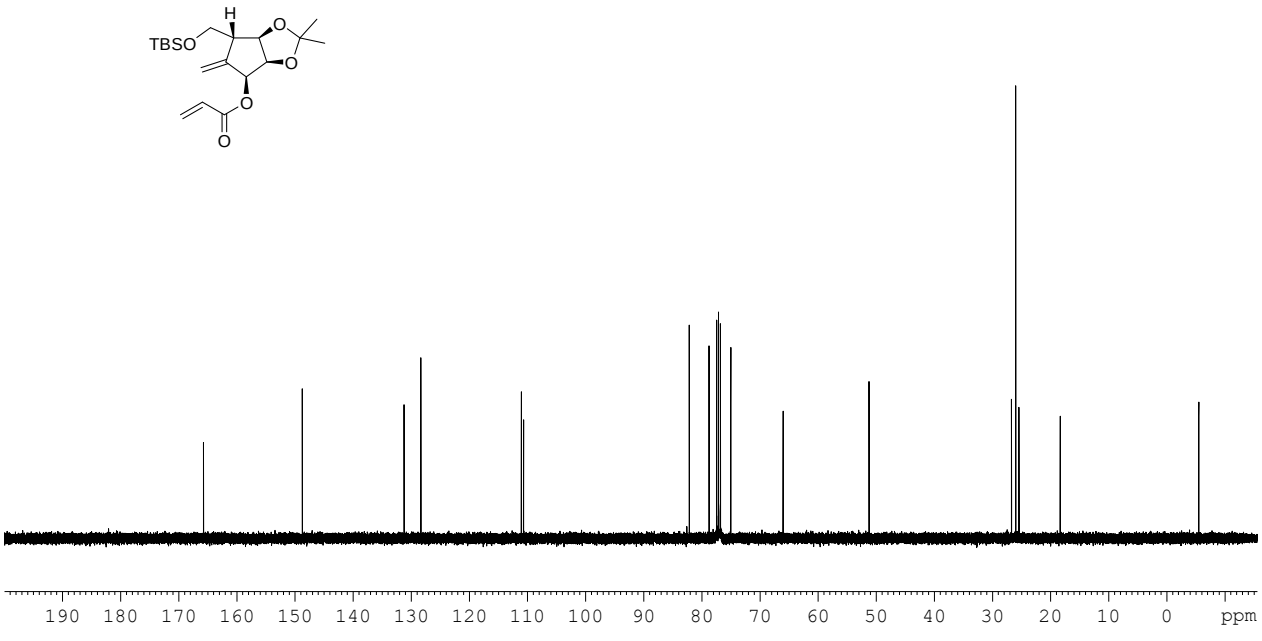


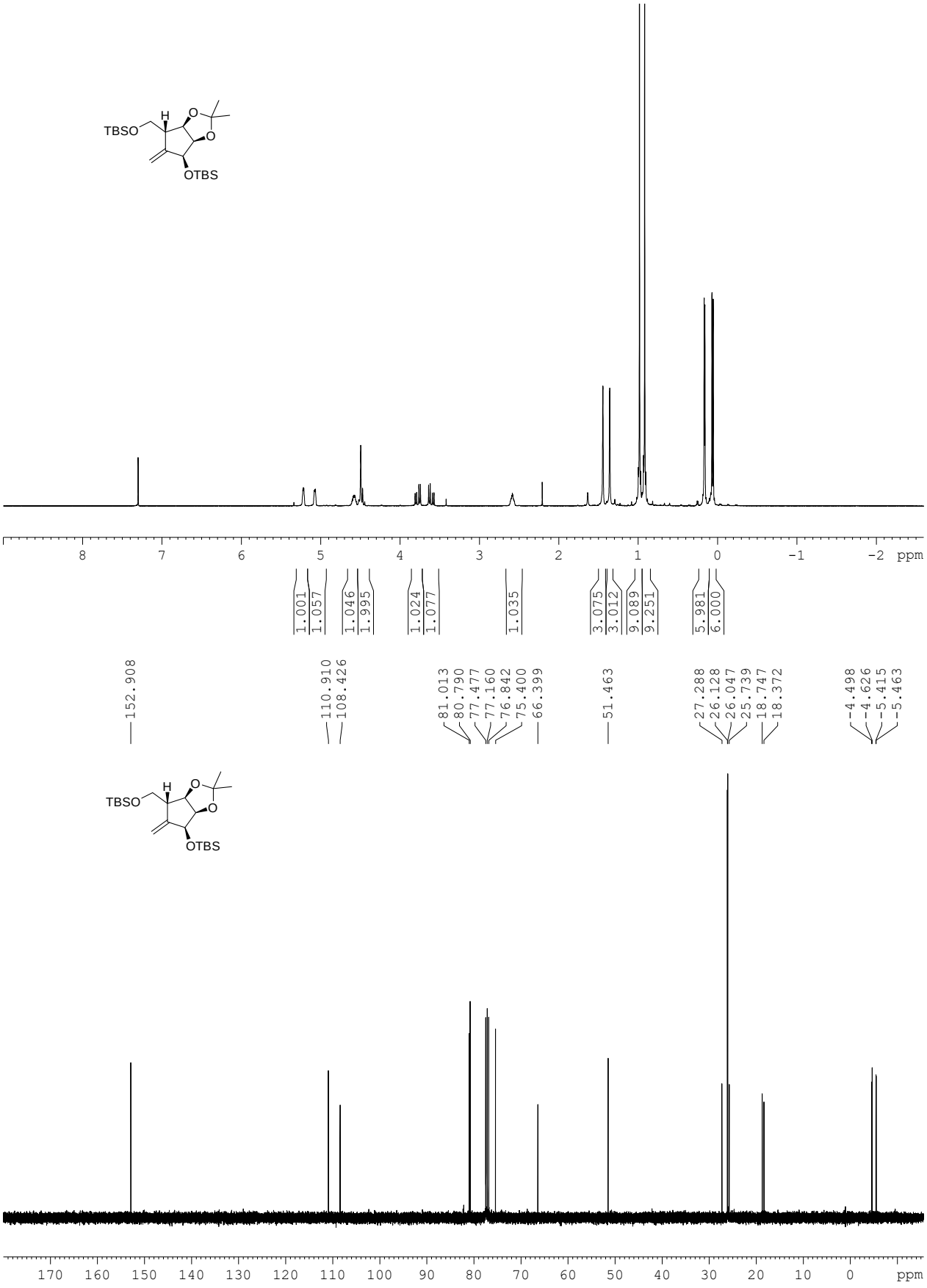

TBSO
H
O
O
O
8
7
6
5
4
3
2
1
0
ppm
0.970
0.973
1.086
0.989
0.996
1.083
1.005
2.952
3.262
9.000
3.062
2.923

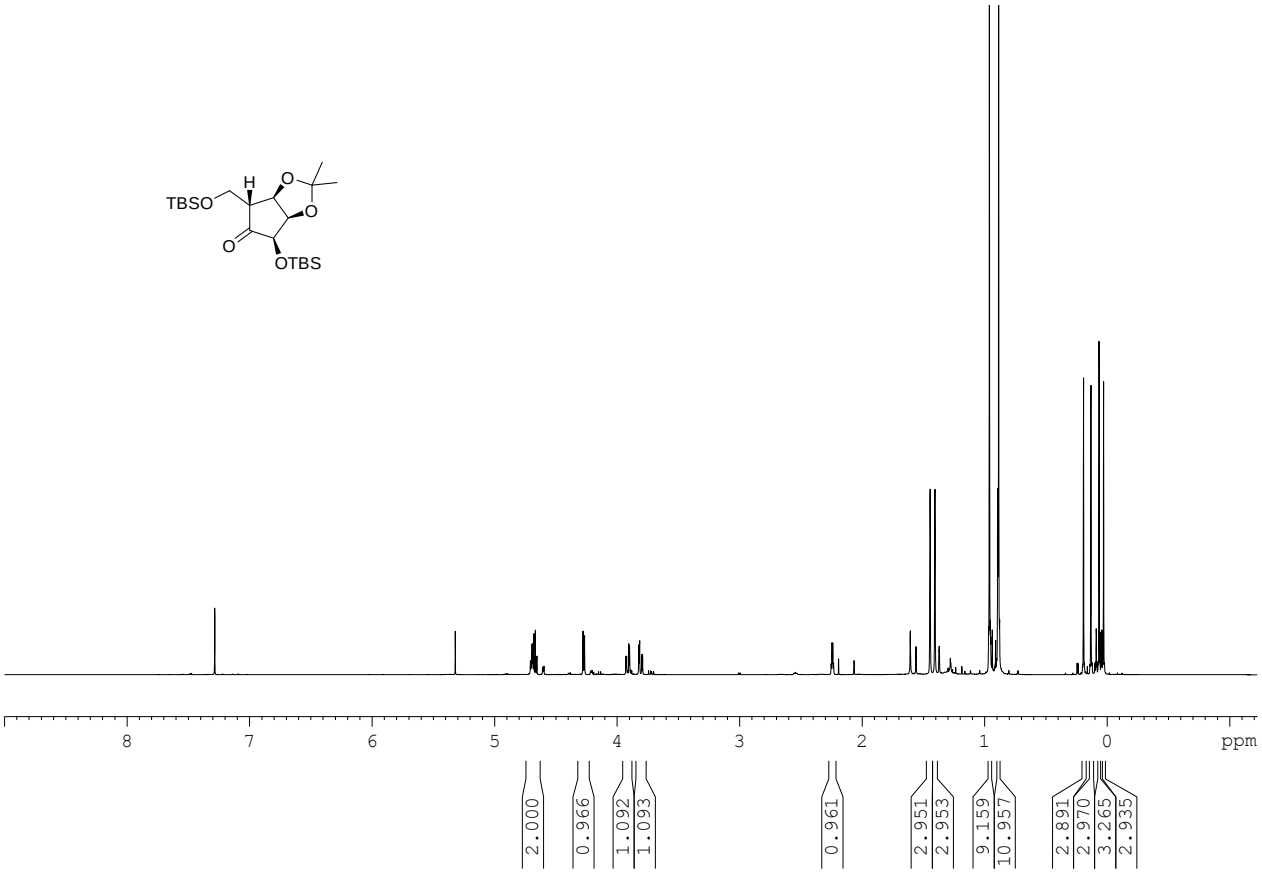

203.167
144.348
122.410
111.333
80.198
79.264
77.478
77.160
76.843
66.455
46.404
27.434
25.911
25.458
18.342
-5.518
-5.642
TBSO
H
O
O
O
220
200
180
160
140
120
100
80
60
40
20
0
ppm

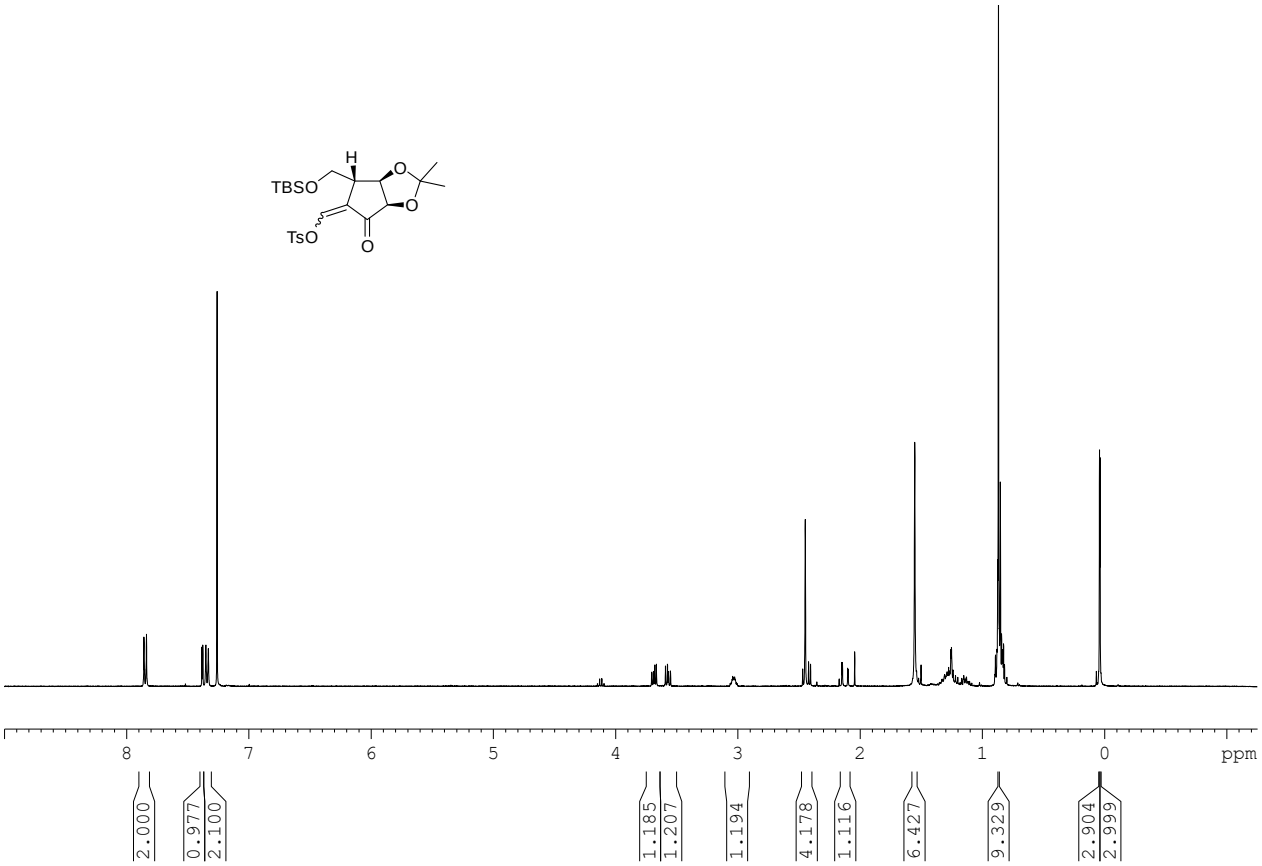

TBSO
H
O
O
OH
8
7
6
5
4
3
2
1
0
ppm
1.000
1.002
1.951
1.021
1.008
1.003
0.982
0.971
3.035
3.126
9.284
2.960
3.008
153.429
110.408
109.879
81.267
79.269
77.378
77.060
76.743
73.893
66.038
51.590
26.528
25.921
24.762
18.244
-5.574
-5.583
TBSO
H
O
O
OH
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

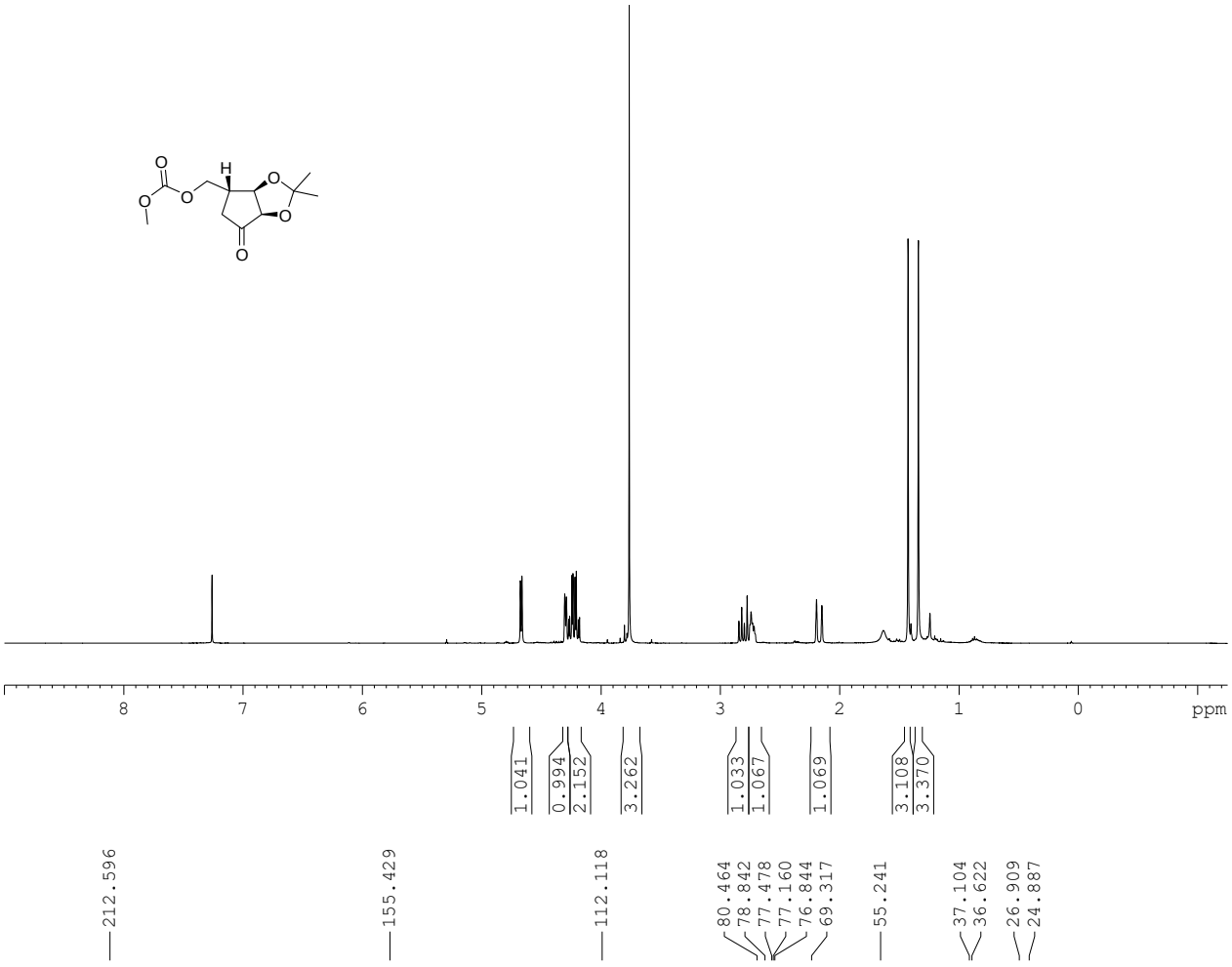

TBSO
H
O
O
O
O
8
7
6
5
4
3
2
1
0
ppm
1.032
1.000
1.031
1.027
2.111
1.041
1.051
1.050
1.051
1.031
3.062
3.052
9.115
2.999
3.105
165.772
148.775
131.267
128.376
111.087
110.698
82.196
78.786
77.478
77.160
76.842
75.055
66.037
51.263
26.750
26.021
25.467
18.360
-5.455
-5.478


TBSO
H
O
O
O
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

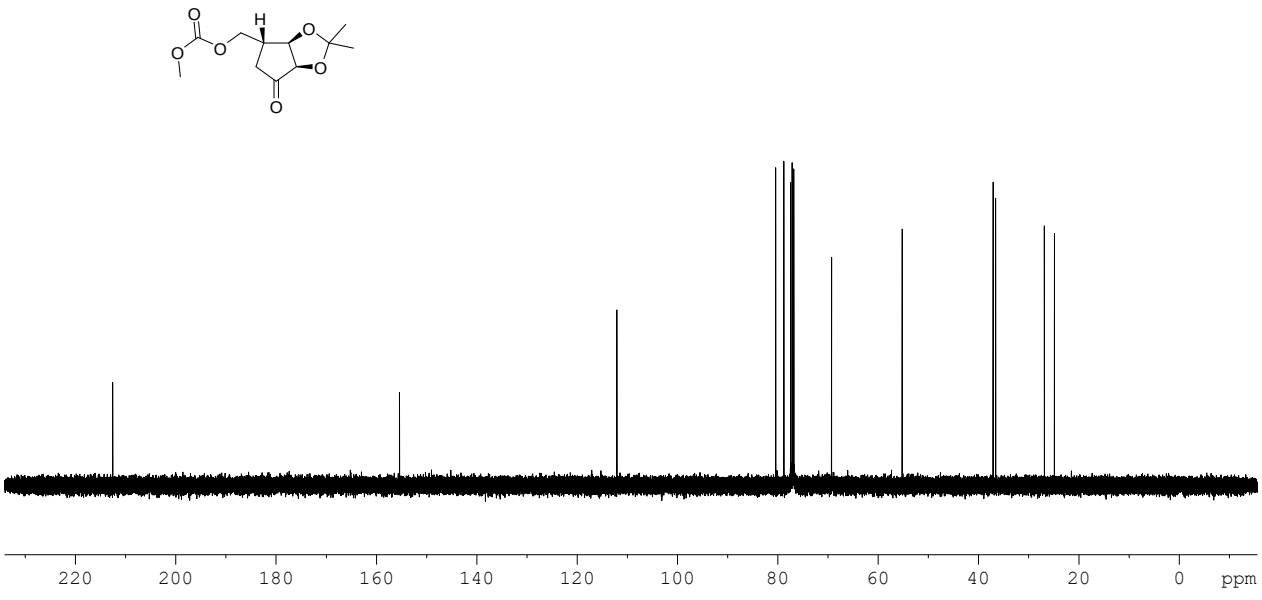

TBSO
H
O
O
OTBS
8 7 6 5 4 3 2 1 0 -1 -2 ppm
1.001 1.057 1.046 1.995 1.024 1.077 1.035 3.075 3.012 9.089 9.251 5.981 6.000
152.908
110.910 108.426
81.013 80.790 77.477 77.160 76.842 75.400 66.399
51.463
27.288 26.128 26.047 25.739 18.747 18.372
-4.498 -4.626 -5.415 -5.463
TBSO
H
O
O
OTBS
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

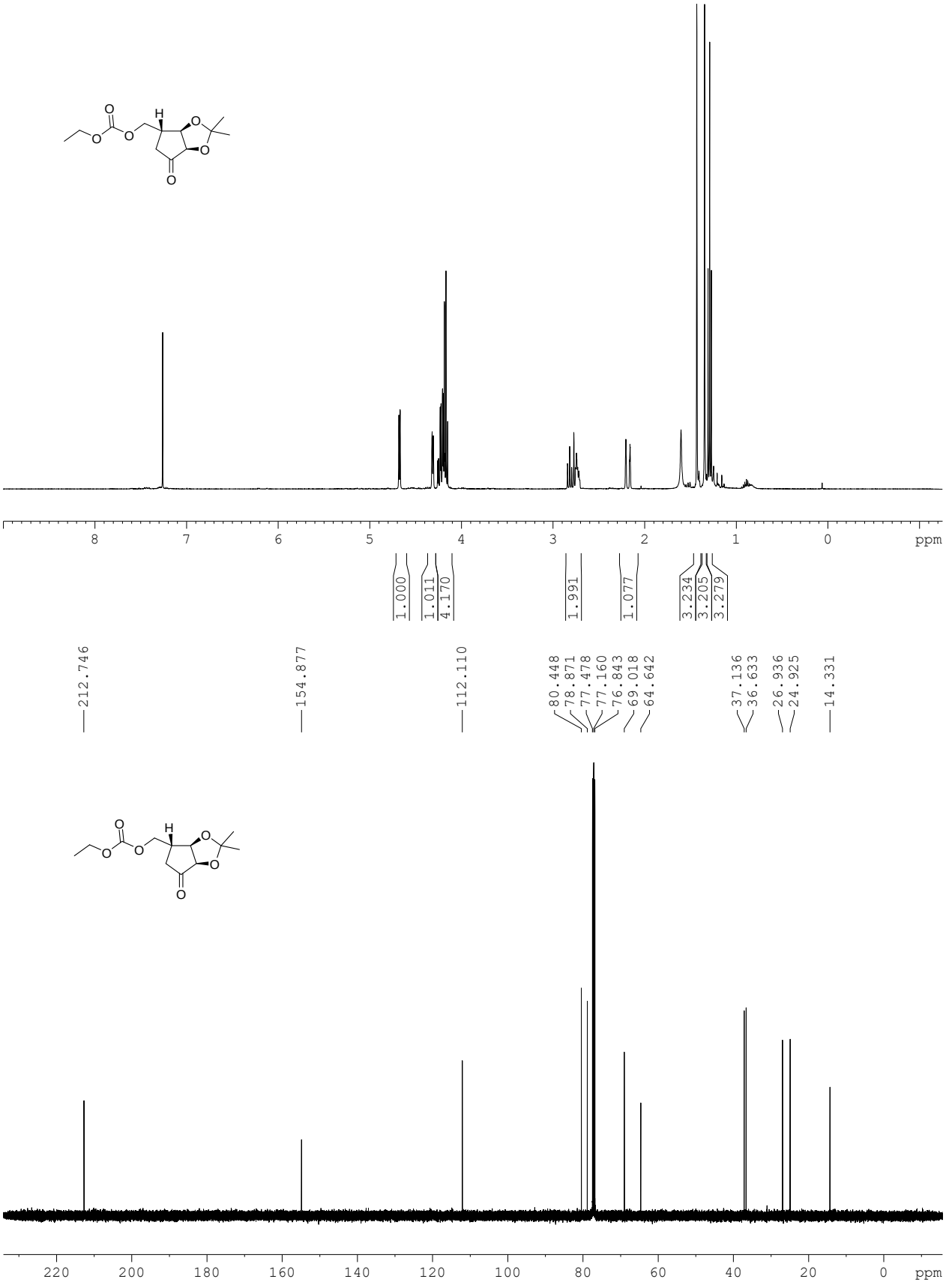

TBSO
H
O
O
O
OTBS
8
7
6
5
4
3
2
1
0
ppm
2.000
0.966
1.092
1.093
0.961
2.951
2.953
9.159
10.957
2.891
2.970
3.265
2.935

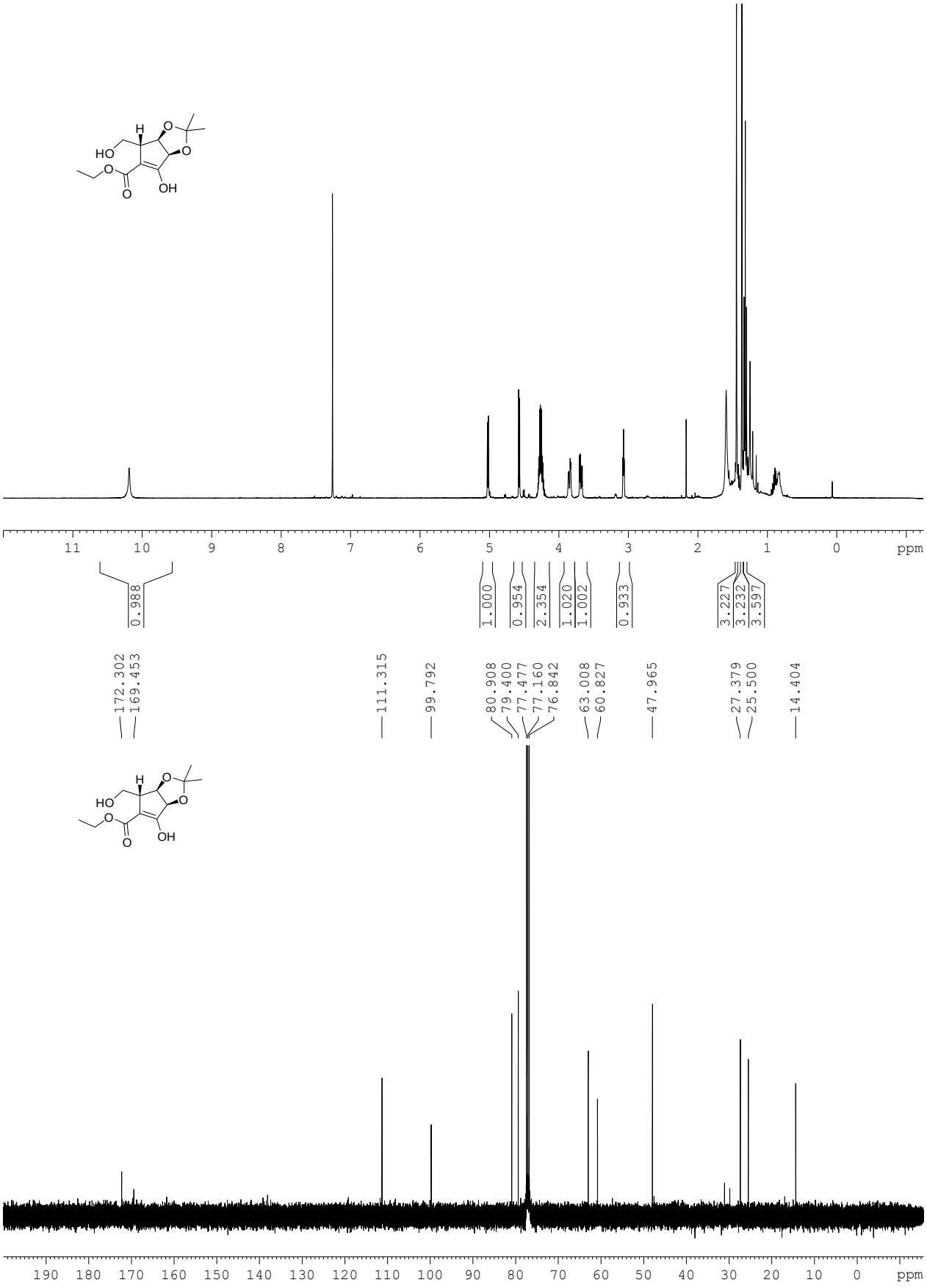

TBSO
H
O
O
TsO
O
8
7
6
5
4
3
2
1
0
ppm
2.000
0.977
2.100
1.185
1.207
1.194
4.178
1.116
6.427
9.329
2.904
2.999

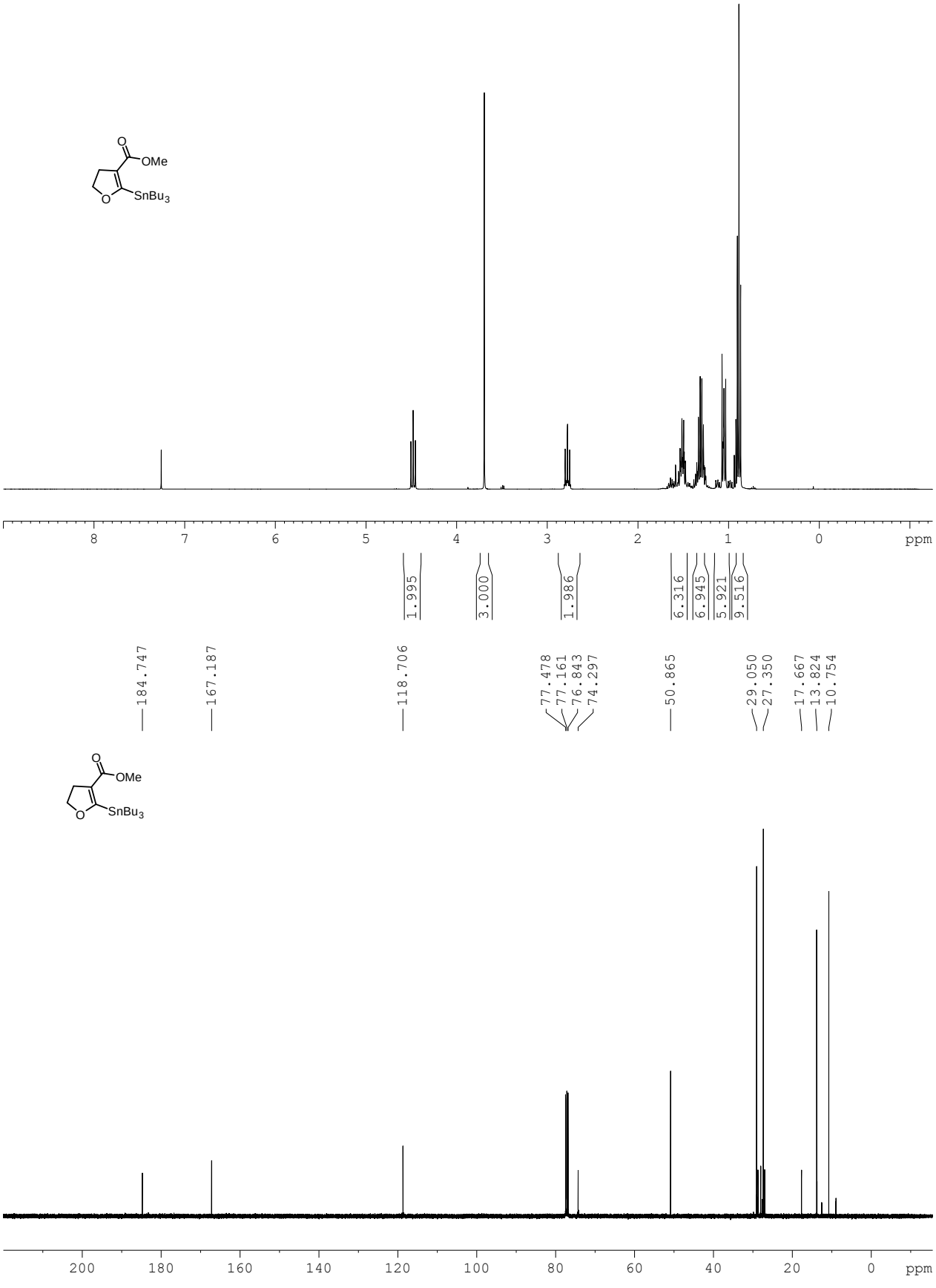

8
7
6
5
4
3
2
1
0
ppm
1.041
0.994
2.152
3.262
1.033
1.067
1.069
3.108
3.370

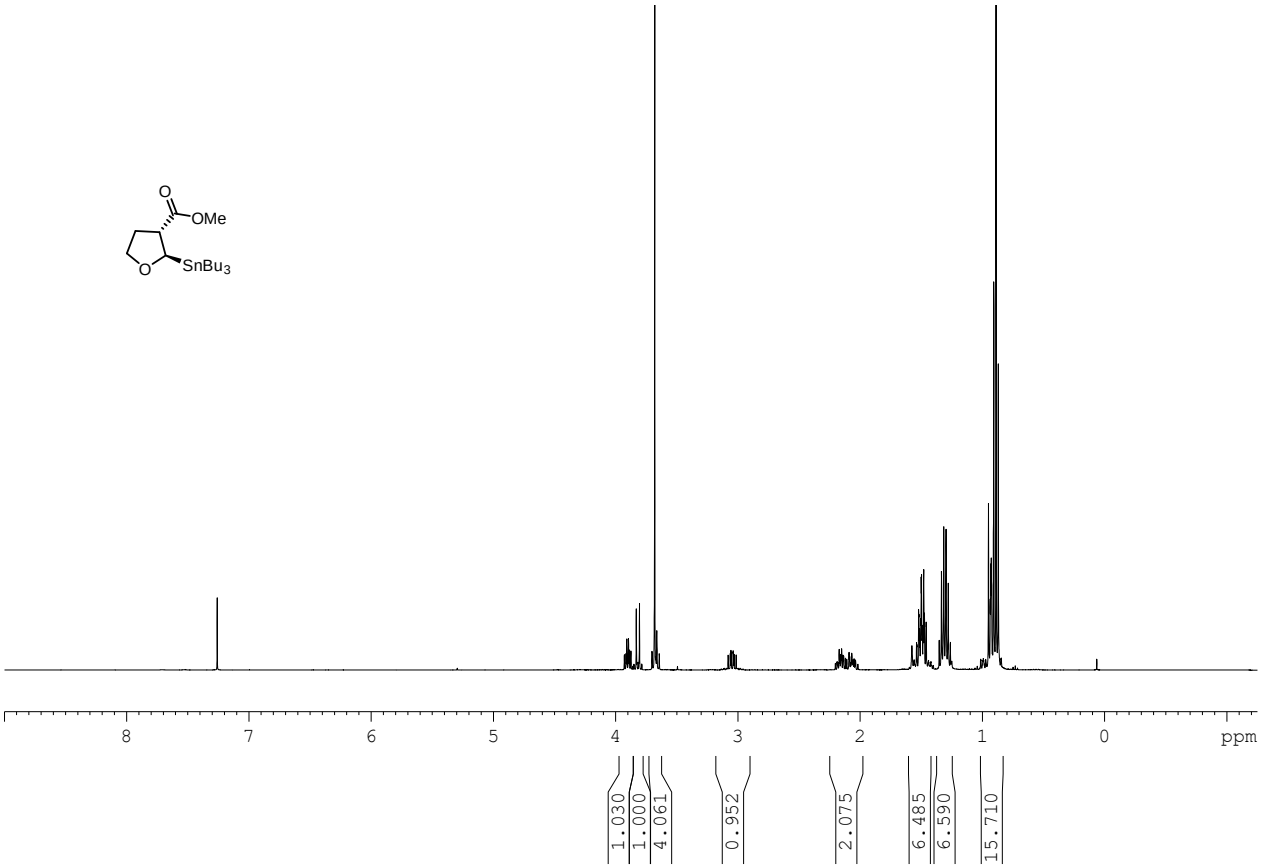
212.596
155.429
112.118
80.464
78.842
77.478
77.160
76.844
69.317
55.241
37.104
36.622
26.909
24.887

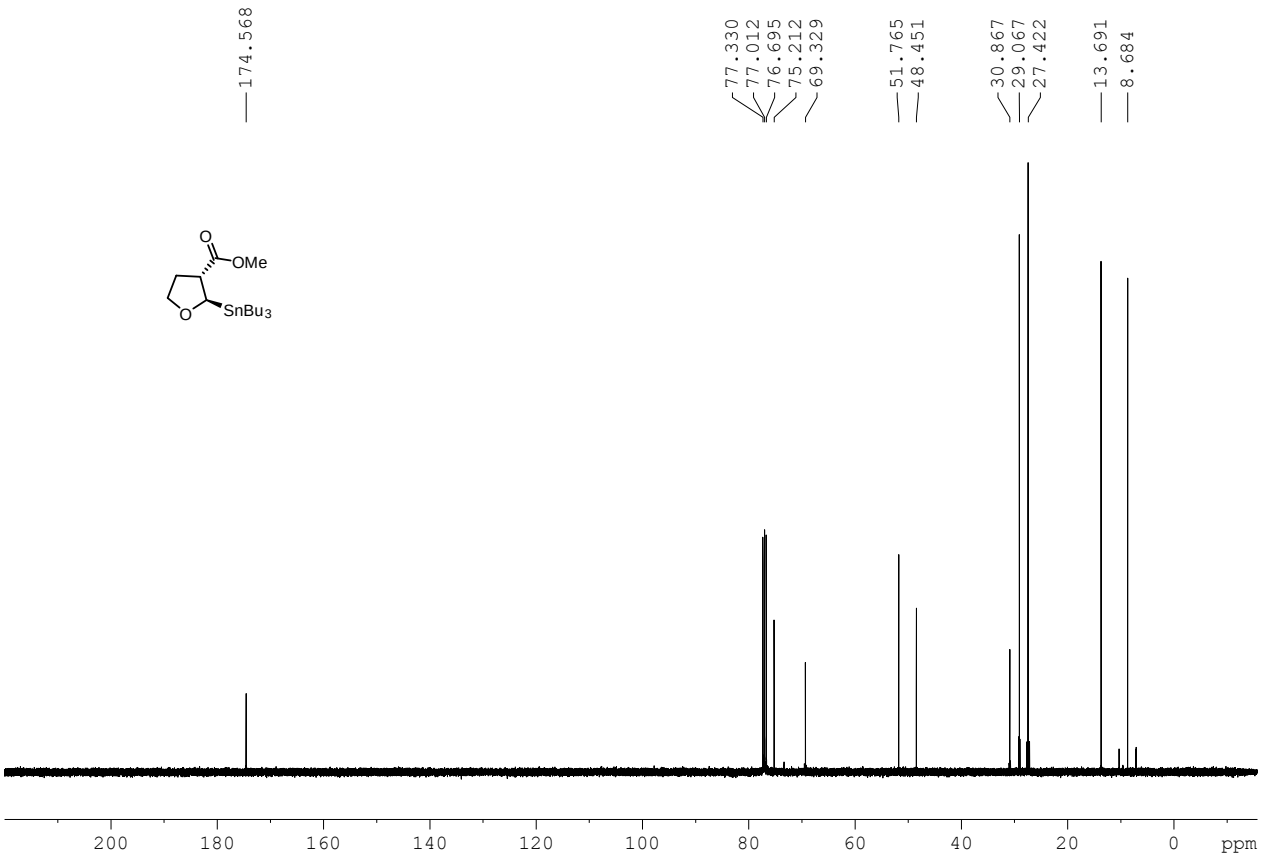

220
200
180
160
140
120
100
80
60
40
20
0
ppm

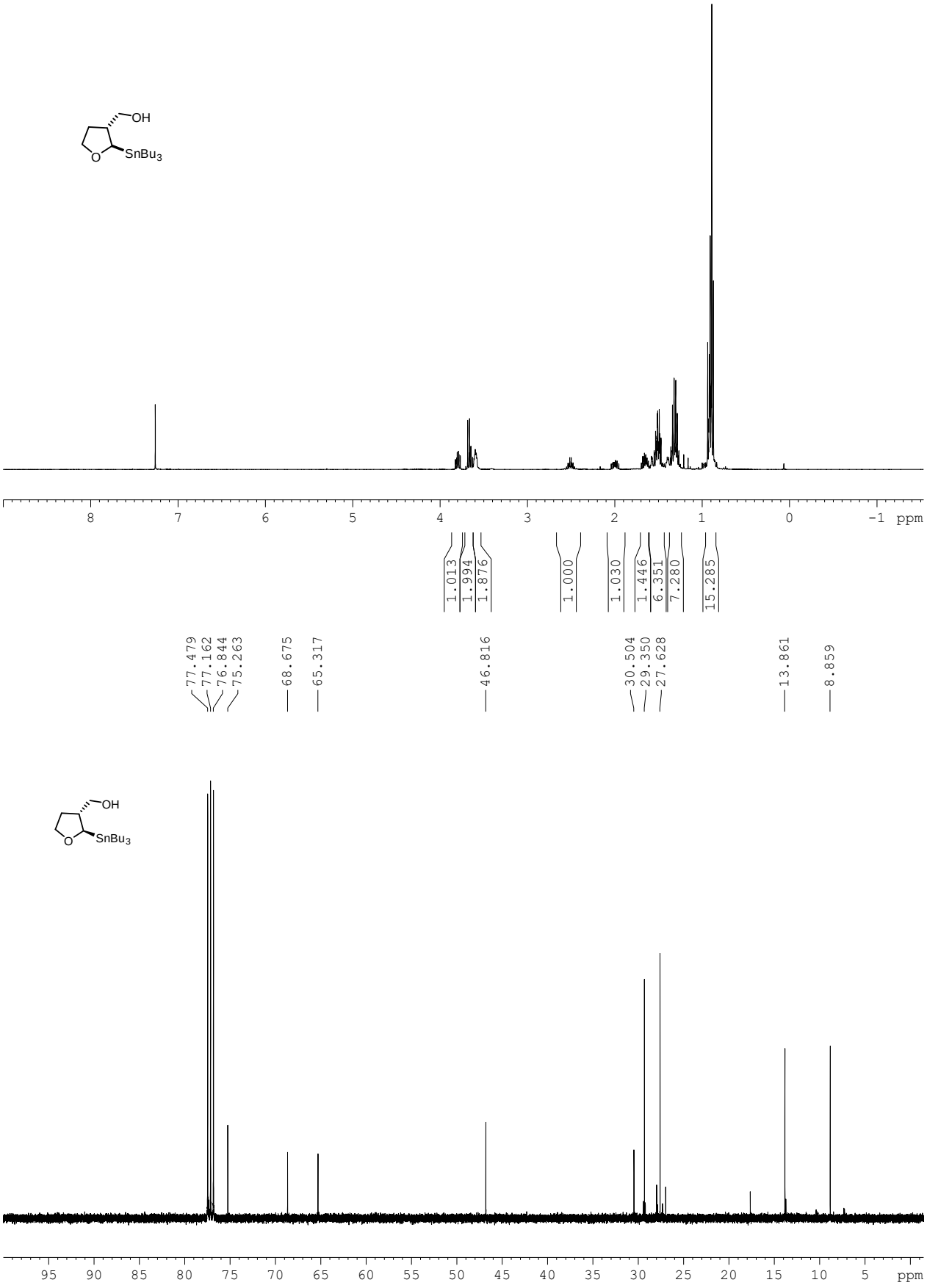

8
7
6
5
4
3
2
1
0
ppm
1.000
1.011
4.170
1.991
1.077
3.234
3.205
3.279
212.746
154.877
112.110
80.448
78.871
77.478
77.160
76.843
69.018
64.642
37.136
36.633
26.936
24.925
14.331
220
200
180
160
140
120
100
80
60
40
20
0
ppm

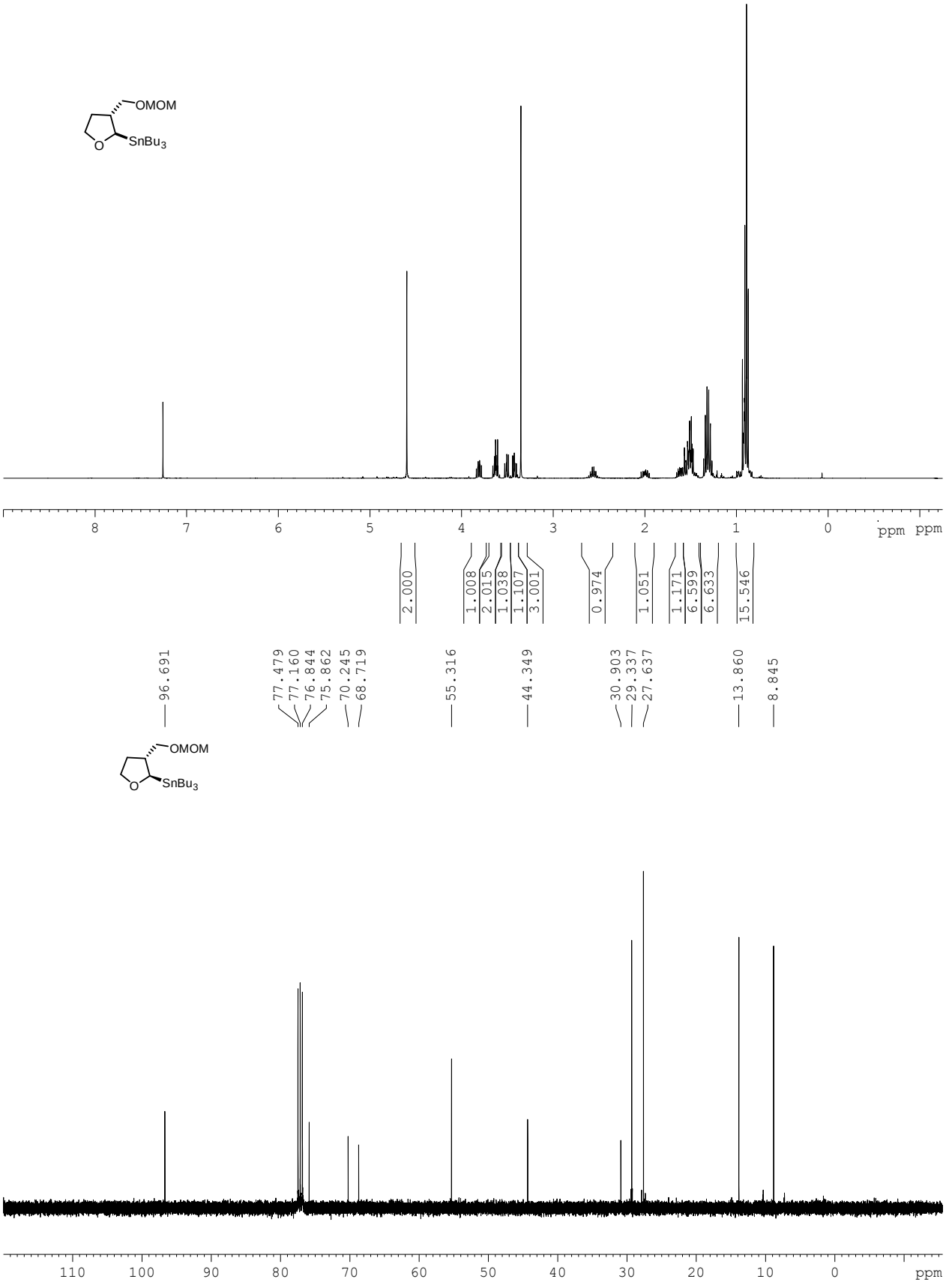

H
O
HO
O
O
OH
O
11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.988
1.000
0.954
2.354
1.020
1.002
0.933
3.227
3.232
3.597
172.302
169.453
111.315
99.792
80.908
79.400
77.477
77.160
76.842
63.008
60.827
47.965
27.379
25.500
14.404
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

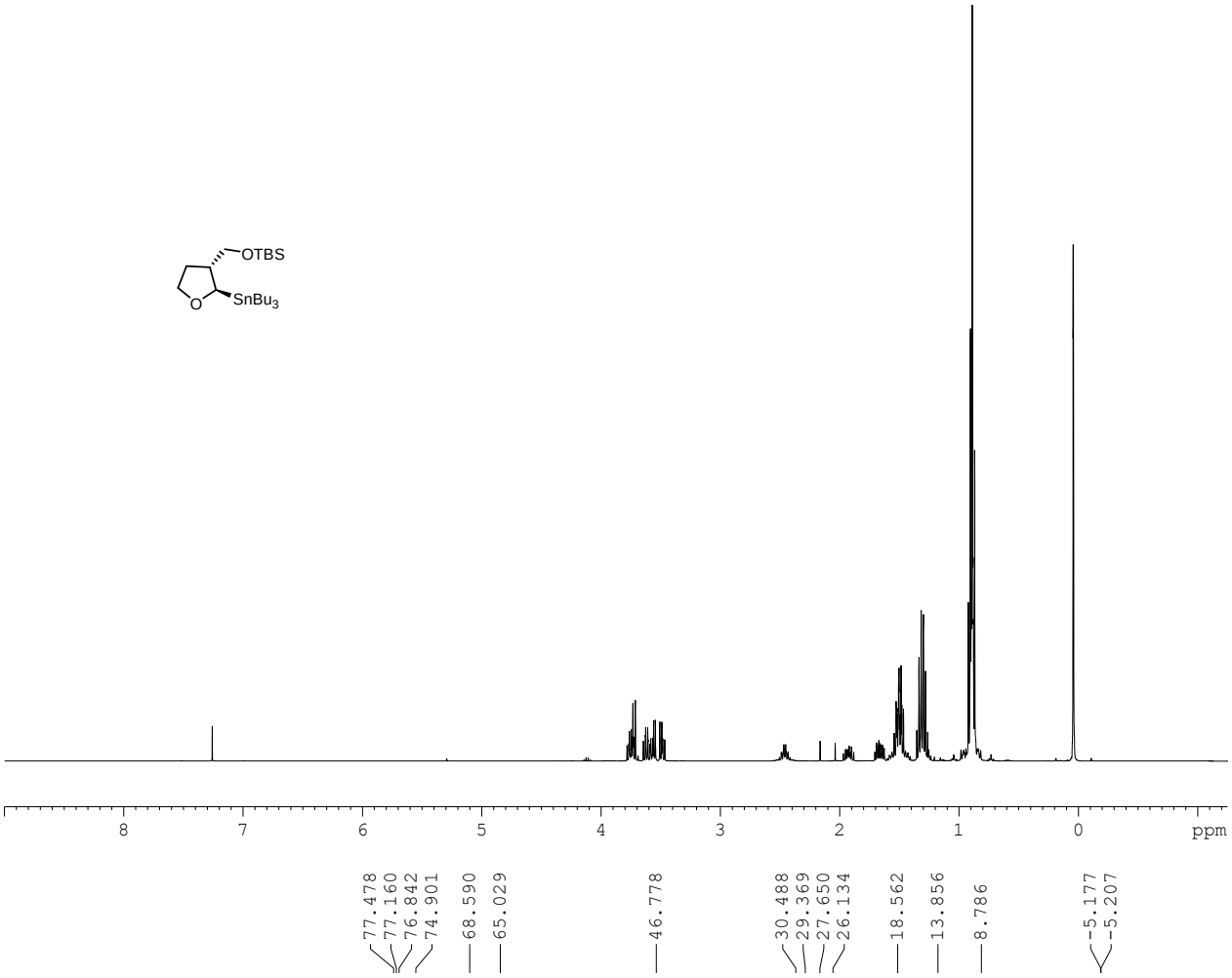

OMe
SnBu3
8
7
6
5
4
3
2
1
0
ppm
1.995
3.000
1.986
6.316
6.945
5.921
9.516
184.747
167.187
118.706
77.478
77.161
76.843
74.297
50.865
29.050
27.350
17.667
13.824
10.754
OMe
SnBu3
200
180
160
140
120
100
80
60
40
20
0
ppm

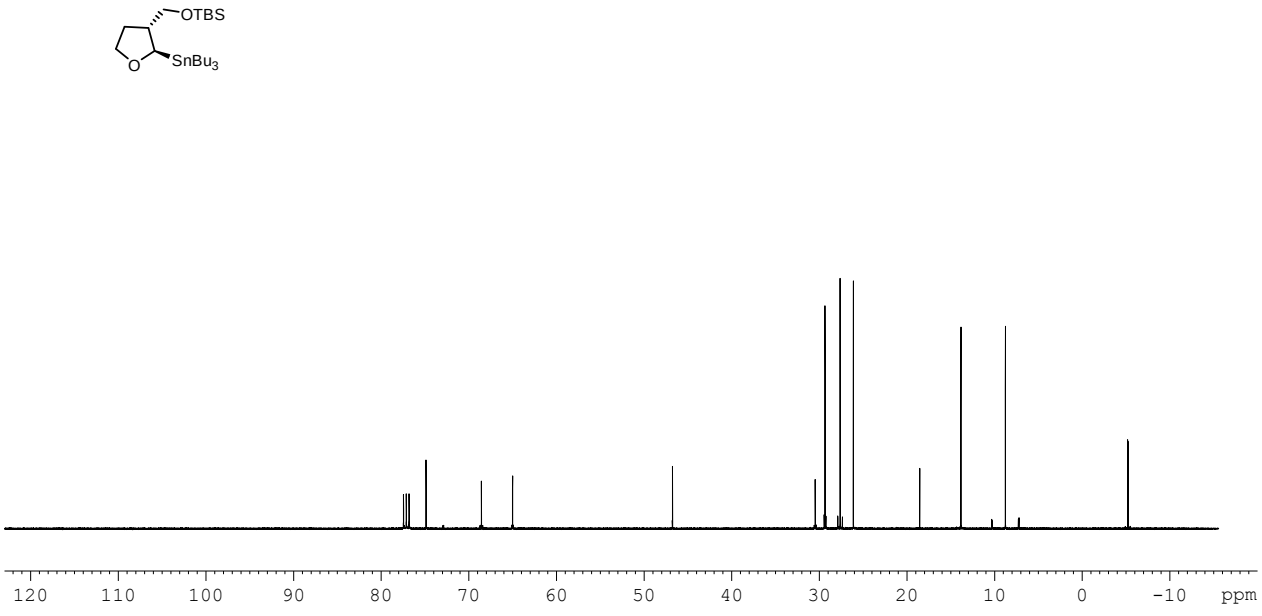

OMe
SnBu3
8
7
6
5
4
3
2
1
0
ppm
1.030
1.000
4.061
0.952
2.075
6.485
6.590
15.710


174.568
77.330
77.012
76.695
75.212
69.329
51.765
48.451
30.867
29.067
27.422
13.691
8.684
OMe
SnBu3
200
180
160
140
120
100
80
60
40
20
0
ppm

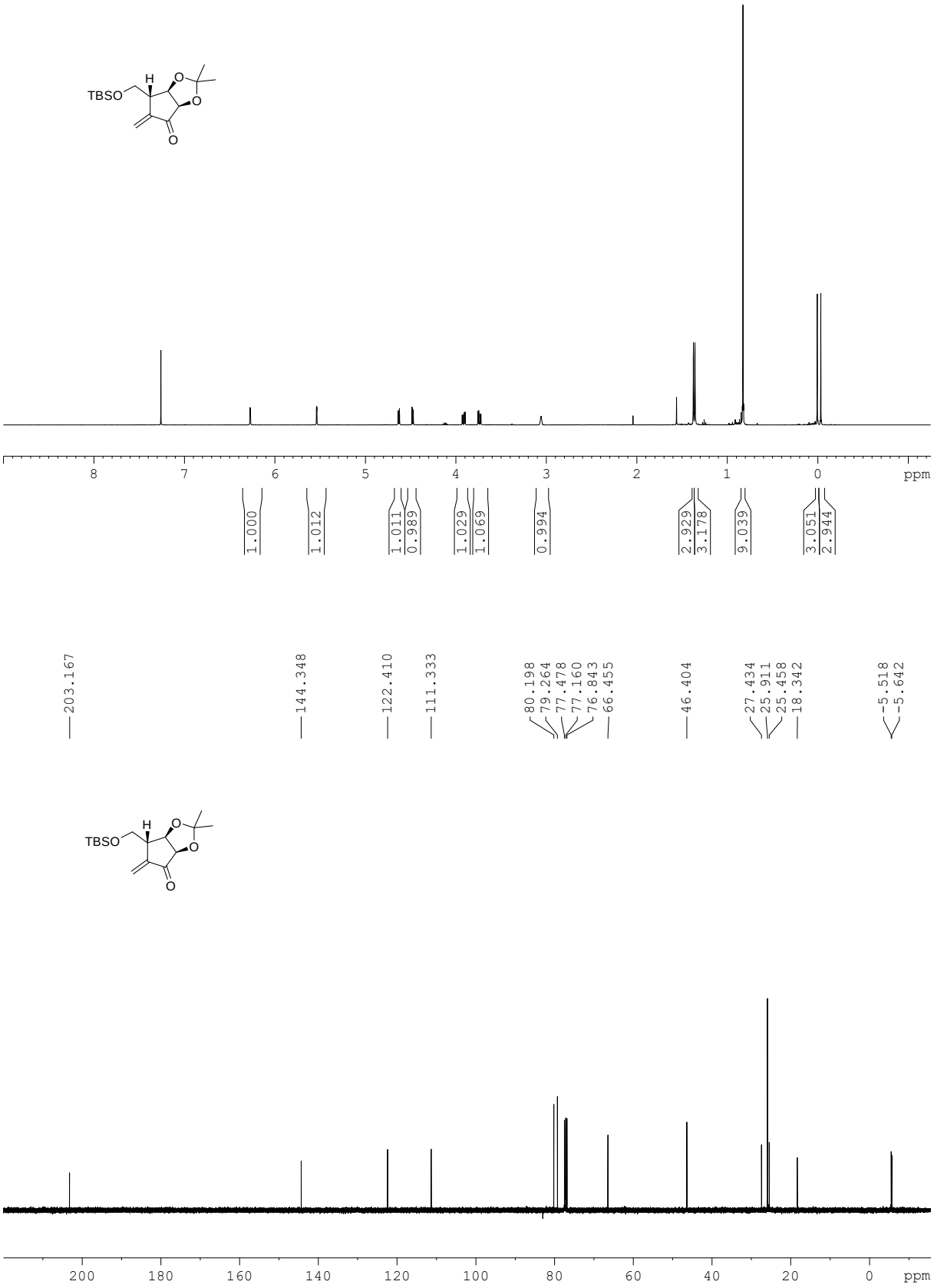

OH
SnBu3
8
7
6
5
4
3
2
1
0
-1 ppm
1.013
1.994
1.876
1.000
1.030
1.446
6.351
7.280
15.285
77.479
77.162
76.844
75.263
68.675
65.317
46.816
30.504
29.350
27.628
13.861
8.859
OH
SnBu3
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
ppm

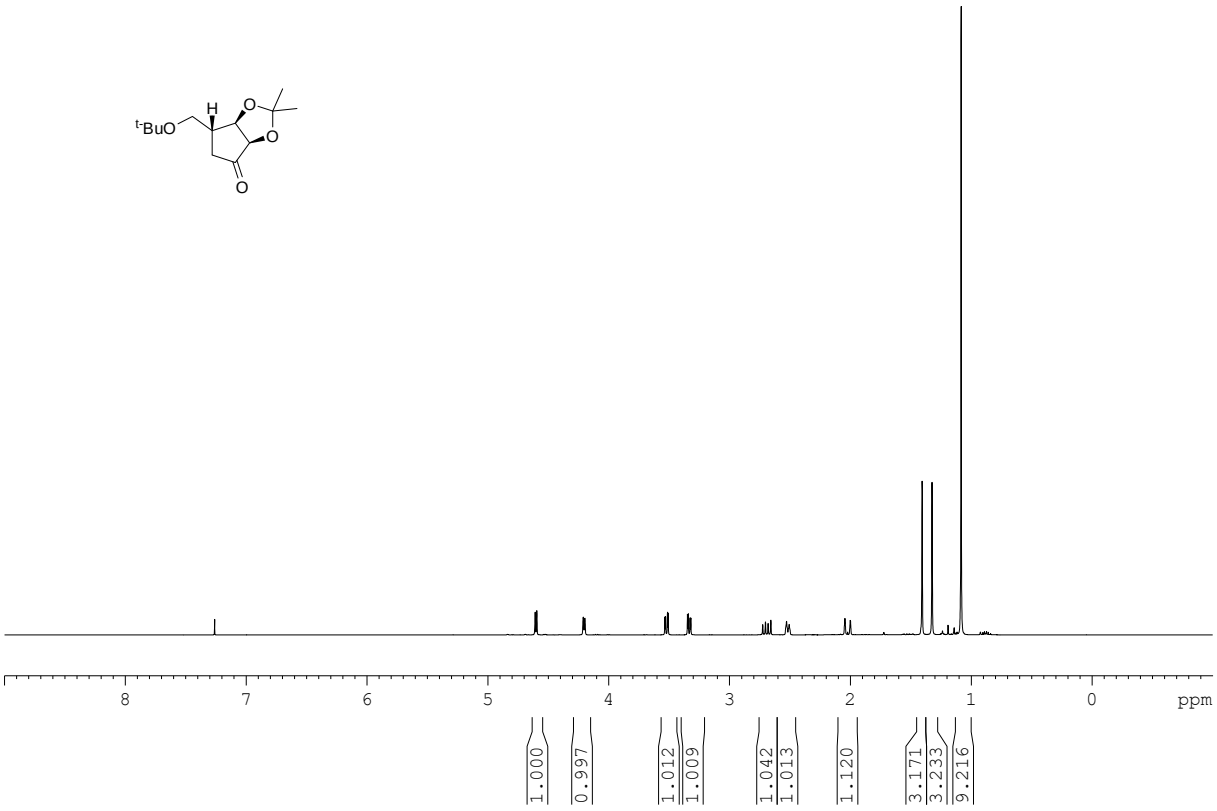

OMOM
SnBu3
8
7
6
5
4
3
2
1
0
ppm
2.000
1.008
2.015
1.038
1.107
3.001
0.974
1.051
1.171
6.599
6.633
15.546
96.691
77.479
77.160
76.844
75.862
70.245
68.719
55.316
44.349
30.903
29.337
27.637
13.860
8.845
OMOM
SnBu3
110
100
90
80
70
60
50
40
30
20
10
0
ppm

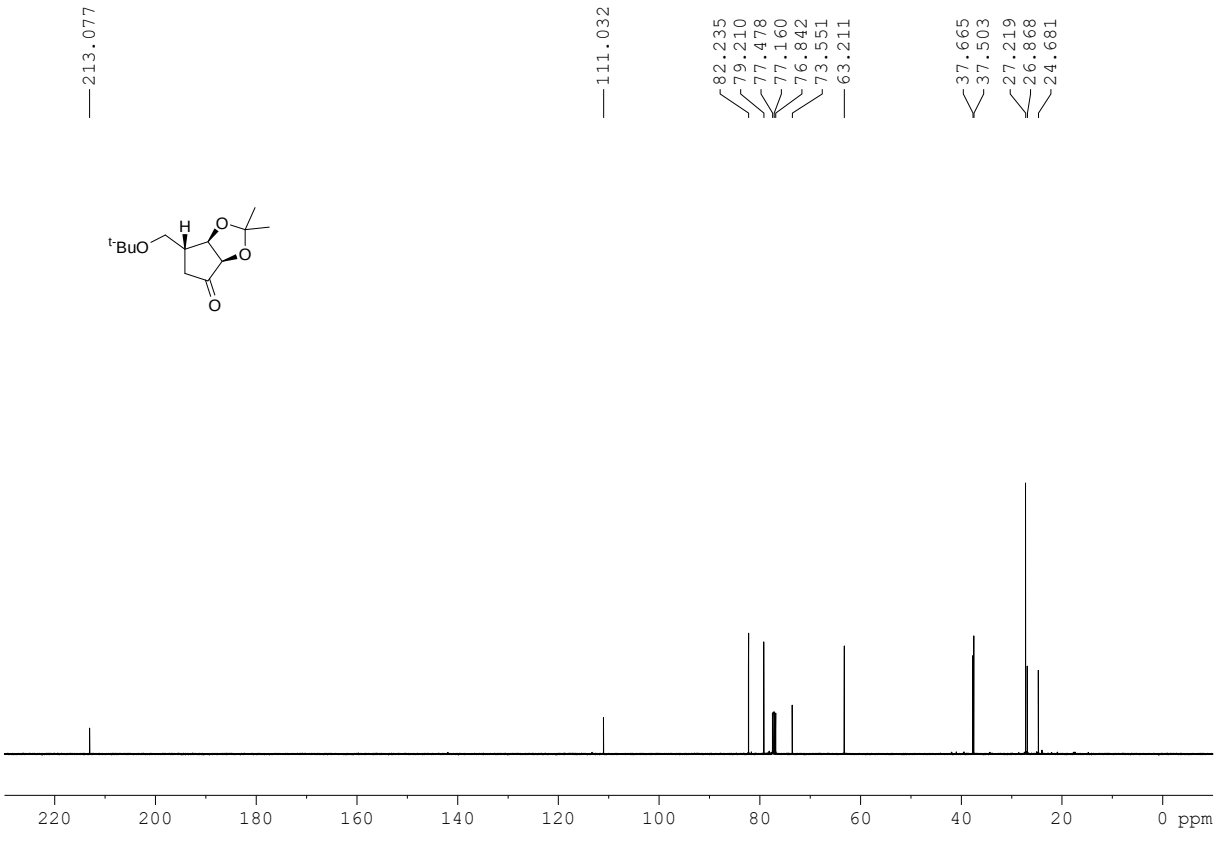

OTBS
SnBu3
O
8
7
6
5
4
3
2
1
0
ppm
77.478
77.160
76.842
74.901
68.590
65.029
46.778
30.488
29.369
27.650
26.134
18.562
13.856
8.786
-5.177
-5.207

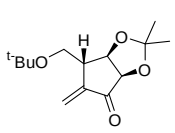

OTBS
SnBu3
O
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm

8.2 NMR Spectra for chapter 3

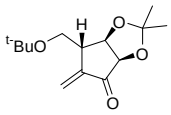


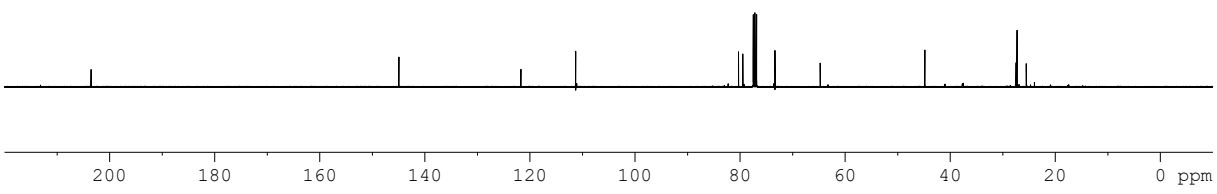

t-BuO
H
O
O
O
8
7
6
5
4
3
2
1
0
ppm
1.000
0.997
1.012
1.009
1.042
1.013
1.120
3.171
3.233
9.216

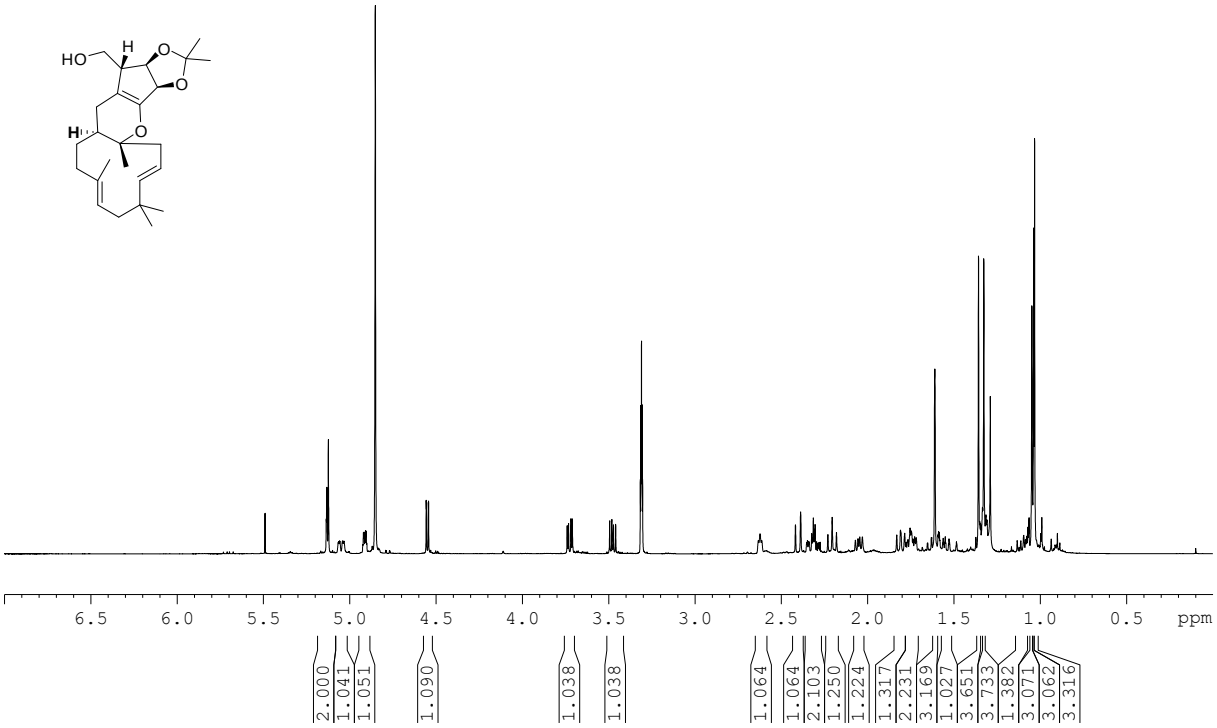

213.077
111.032
82.235
79.210
77.478
77.160
76.842
73.551
63.211
37.665
37.503
27.219
26.868
24.681
t-BuO
H
O
O
O
220
200
180
160
140
120
100
80
60
40
20
0 ppm

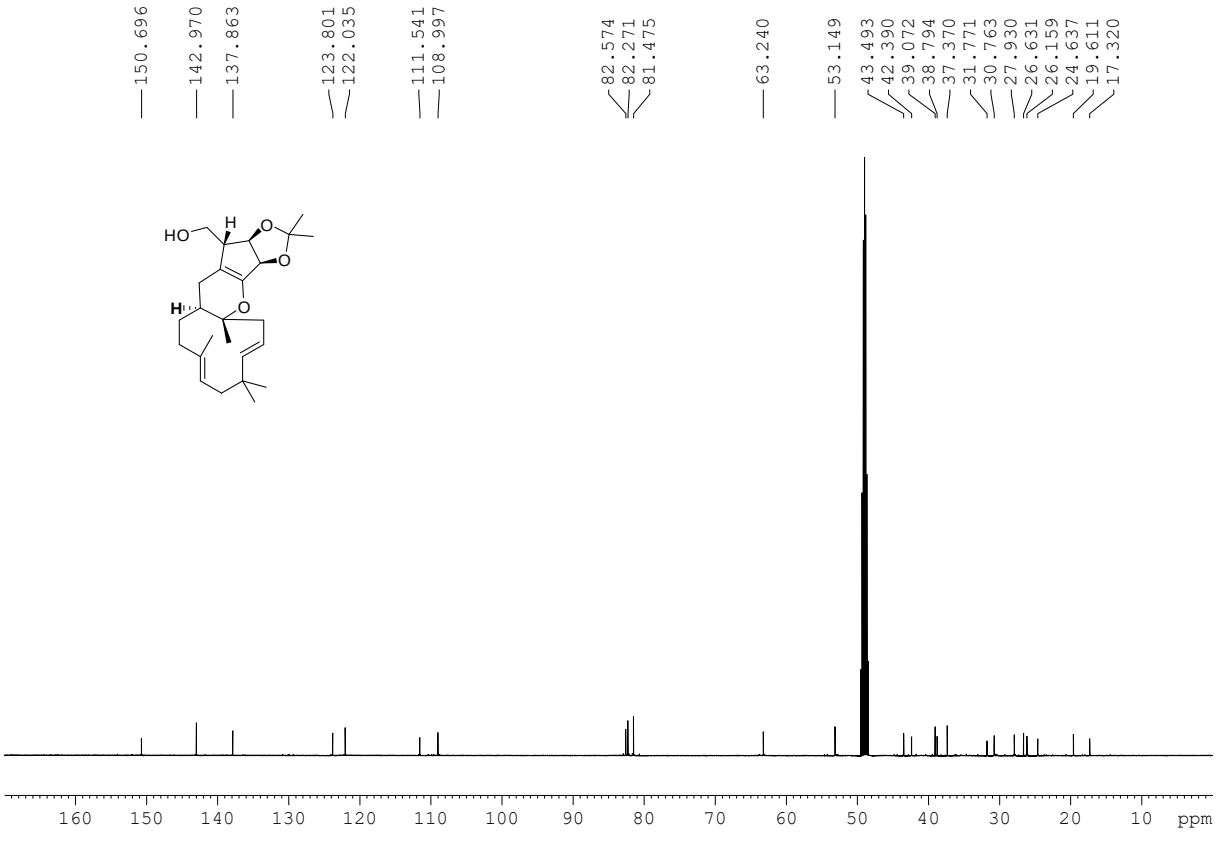


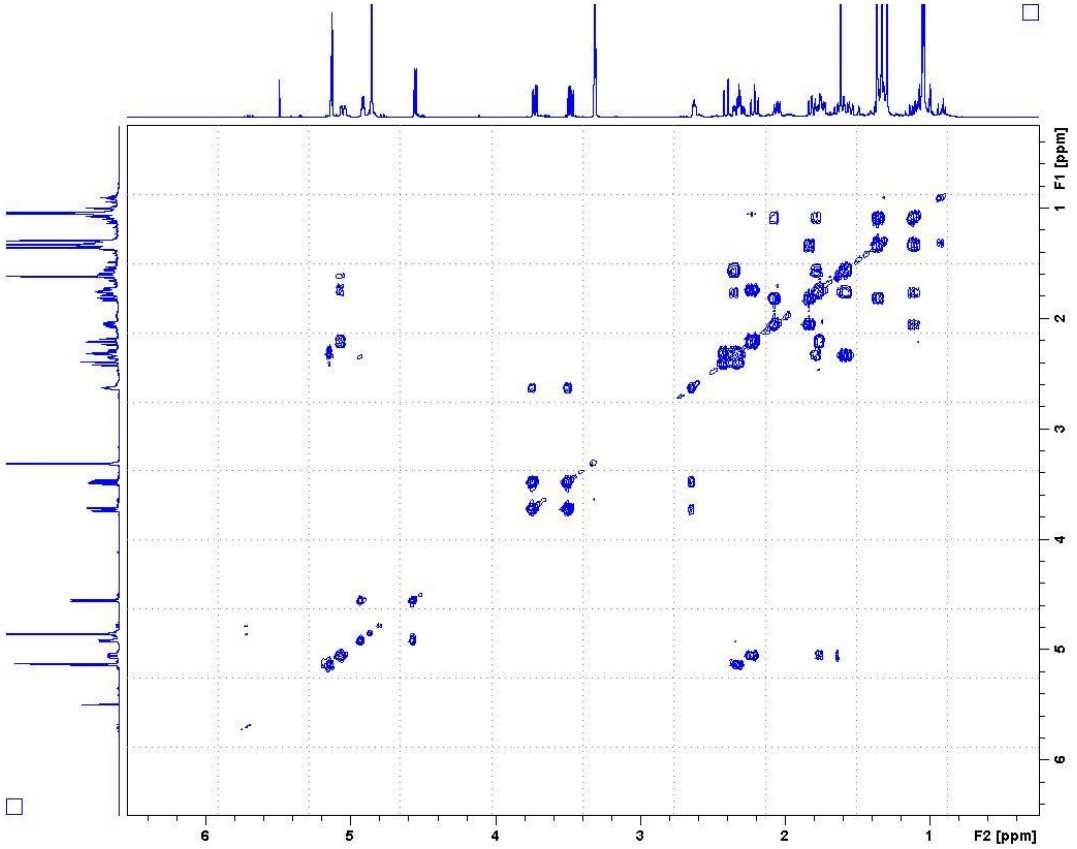
203.479
144.889
121.707
111.269
80.288
79.467
77.479
77.161
76.844
73.338
64.741
44.831
27.467
27.282
25.522



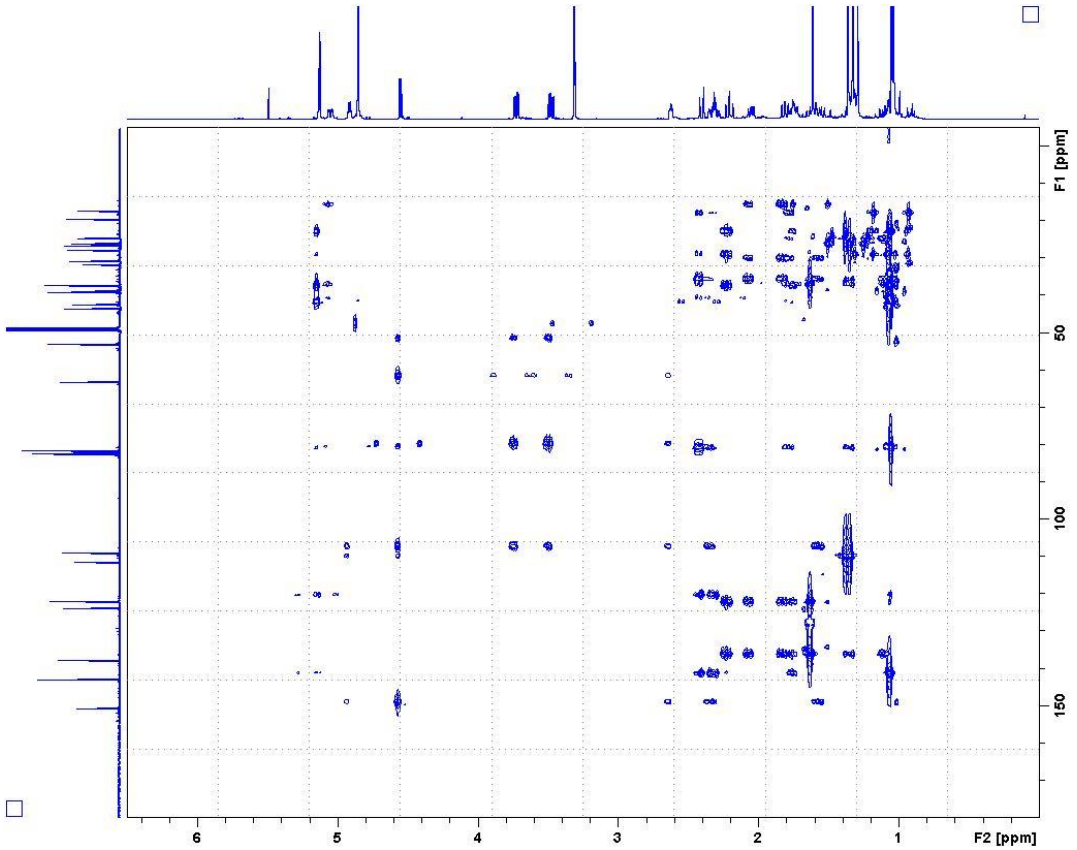



HO
H
O
O
H
O
6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.000 1.041 1.051 1.090 1.038 1.038 1.064 1.064 2.103 1.250 1.224 1.317 2.231 3.169 1.027 3.651 3.733 1.382 3.071 3.062 3.316

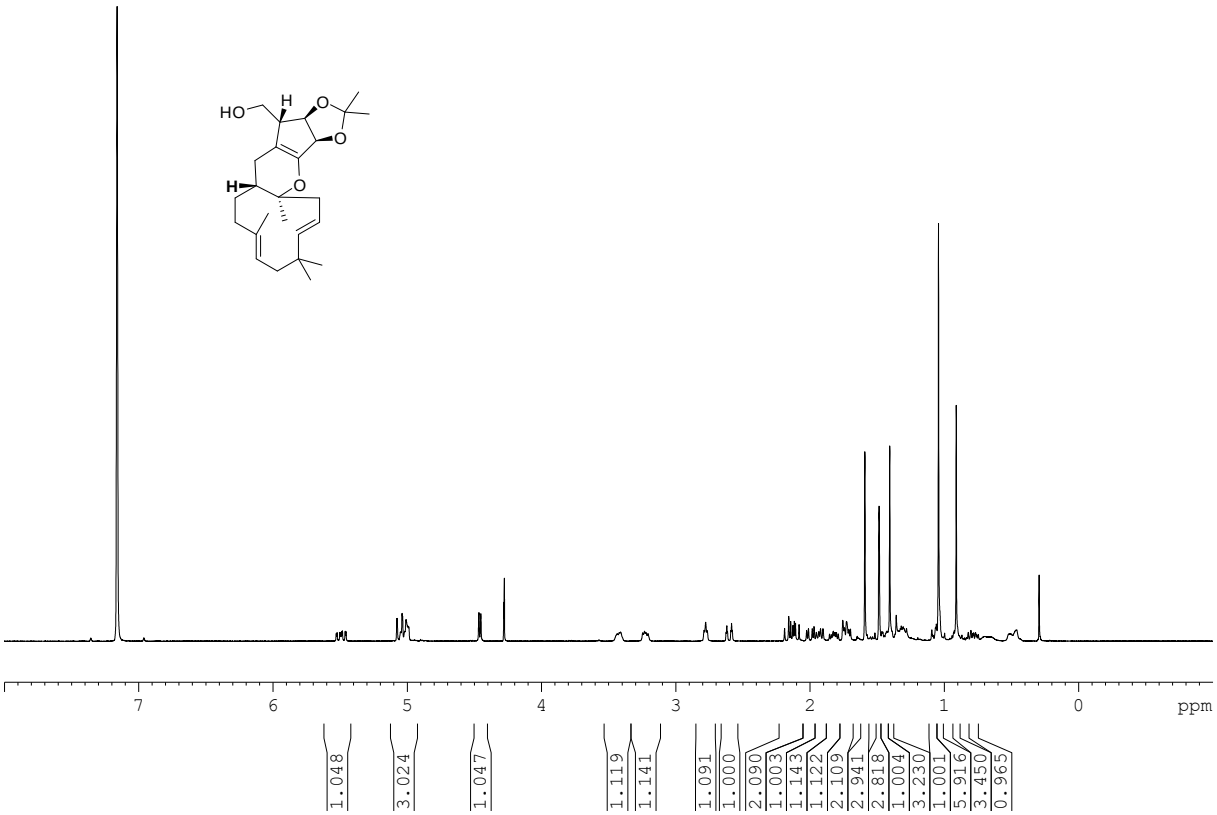

150.696
142.970
137.863
123.801
122.035
111.541
108.997
82.574
82.271
81.475
63.240
53.149
43.493
42.390
39.072
38.794
37.370
31.771
30.763
27.930
26.631
26.159
24.637
19.611
17.320
HO
H
O
O
H
O
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

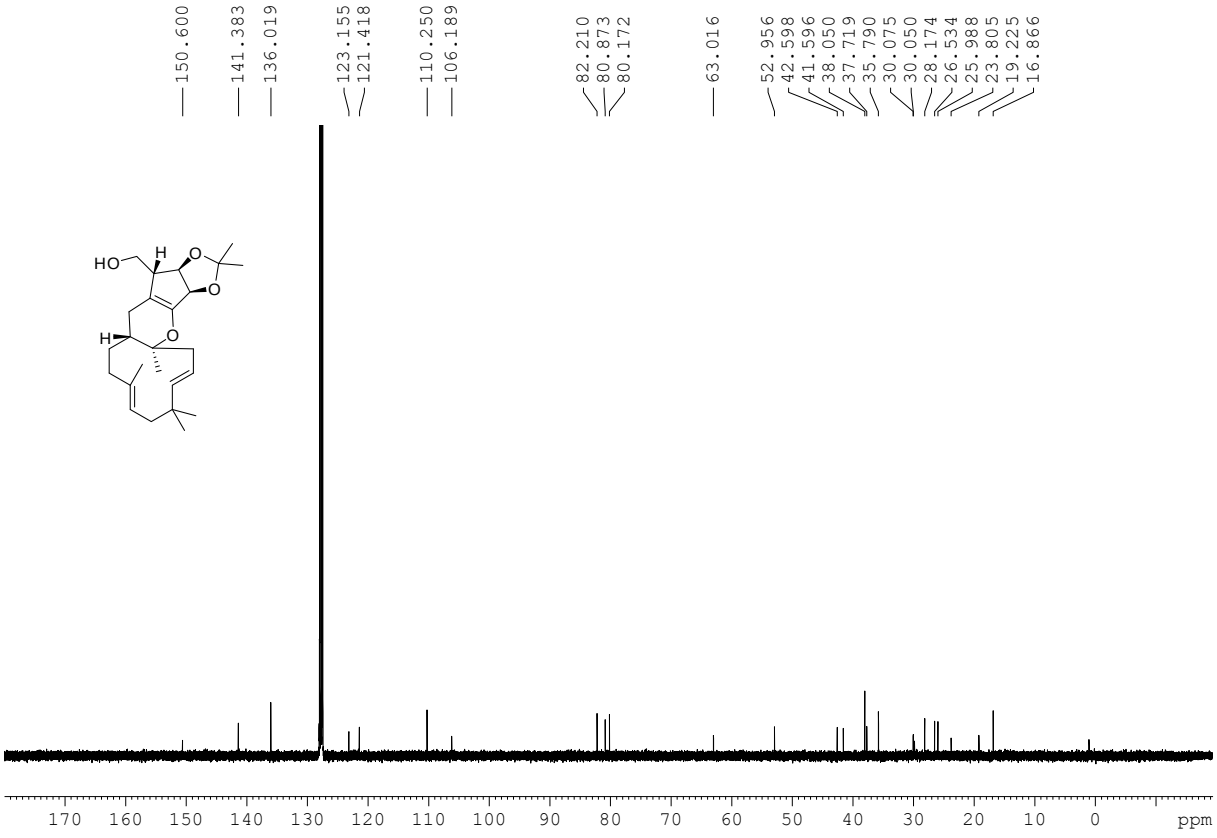


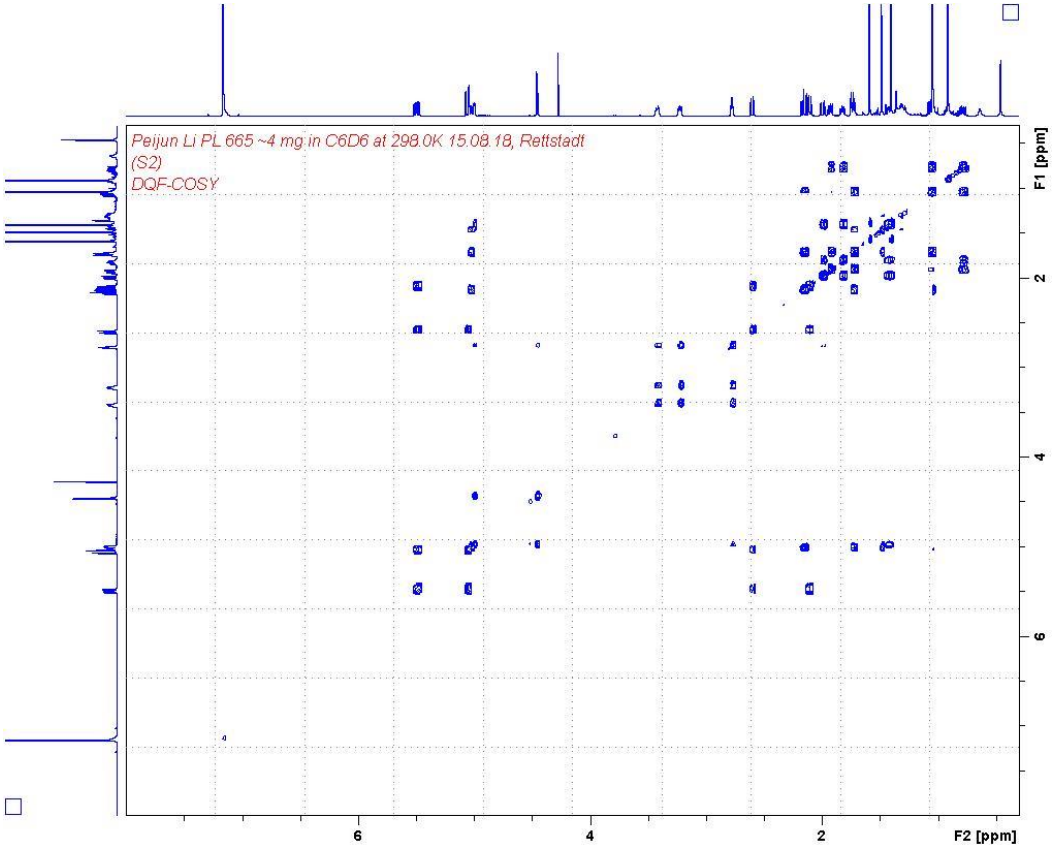
^{1}H, ^{1}H COSY NMR of **211a**



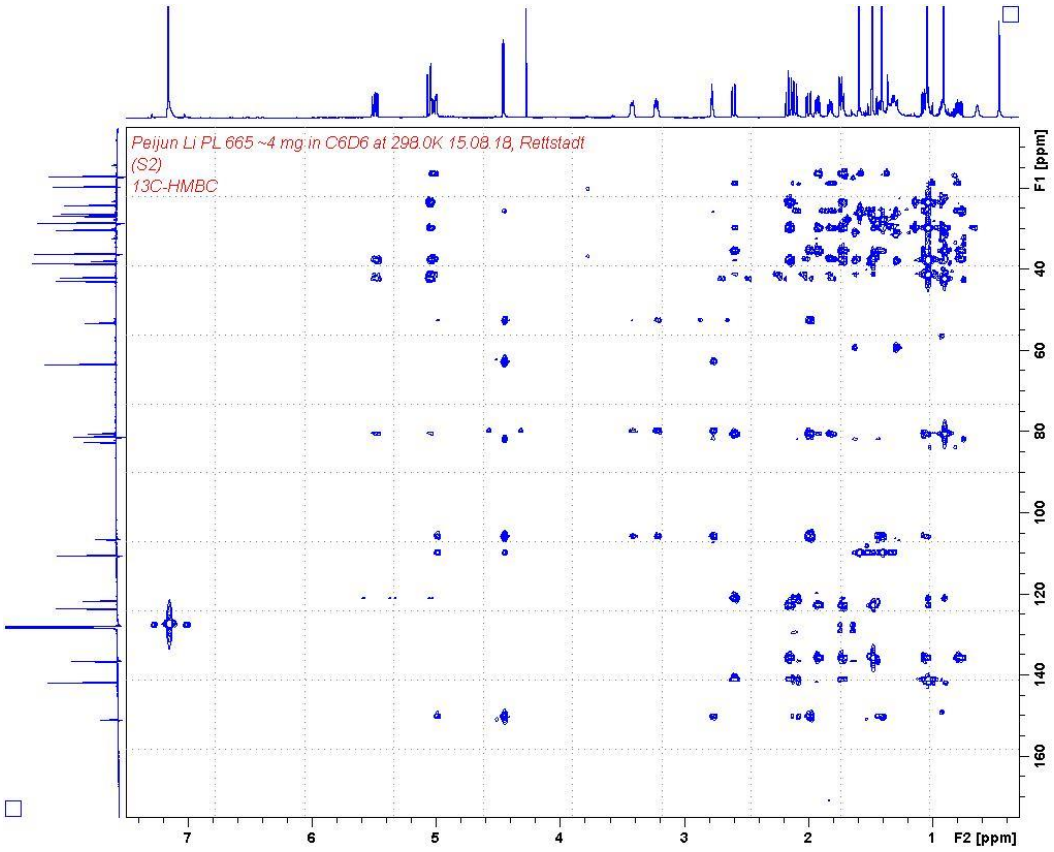
^{1}H, ^{13}C HMBC NMR of **211a**


HO
H
O
O
H
O
7
6
5
4
3
2
1
0
ppm
1.048
3.024
1.047
1.119
1.141
1.091
1.000
2.090
1.003
1.143
1.122
2.109
2.941
2.818
1.004
3.230
1.001
5.916
3.450
0.965

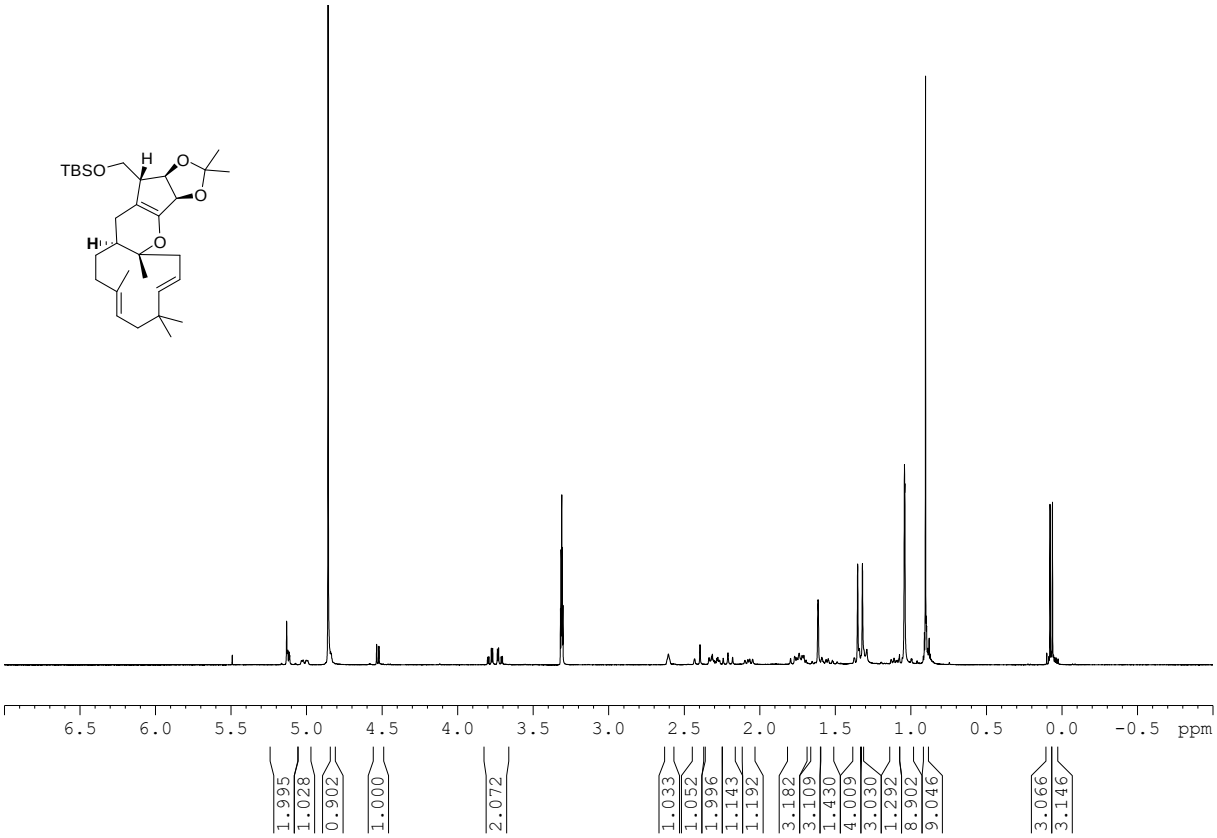

150.600
141.383
136.019
123.155
121.418
110.250
106.189
82.210
80.873
80.172
63.016
52.956
42.598
41.596
38.050
37.719
35.790
30.075
30.050
28.174
26.534
25.988
23.805
19.225
16.866
HO
H
O
O
H
O
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

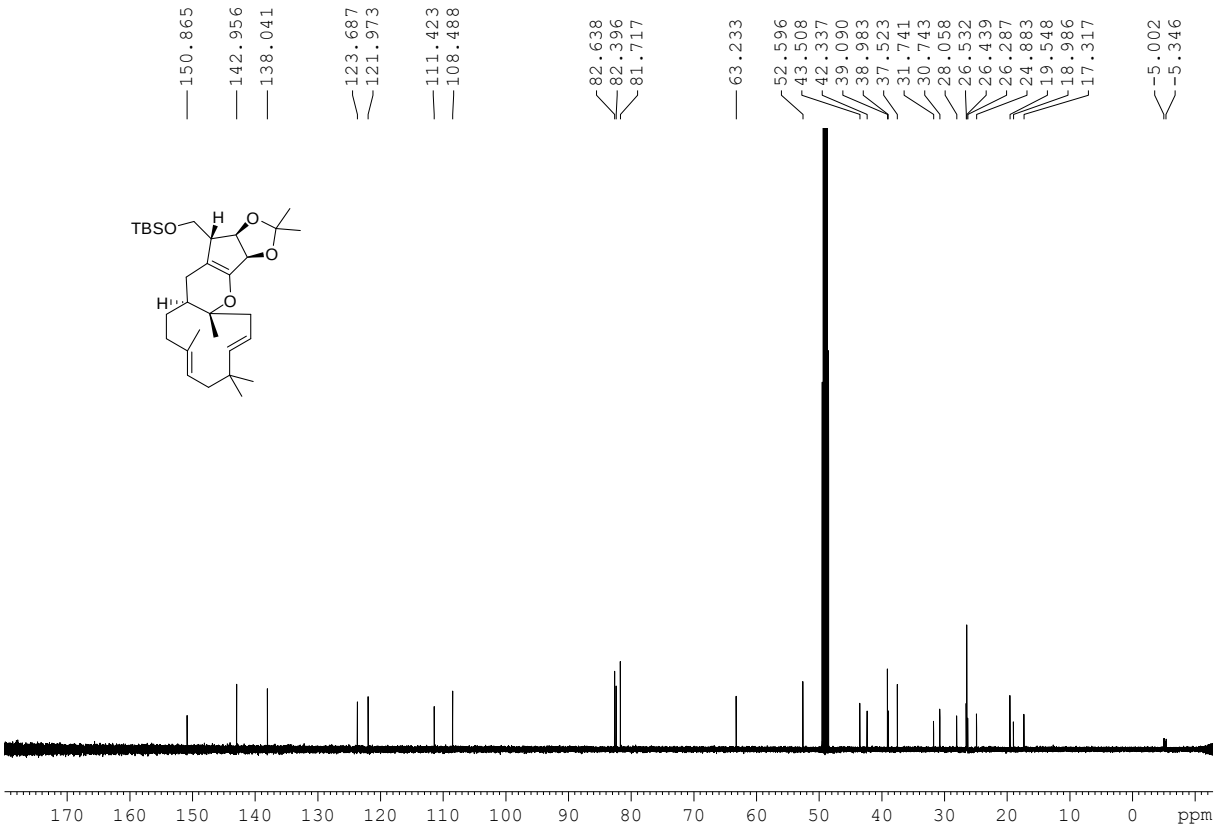


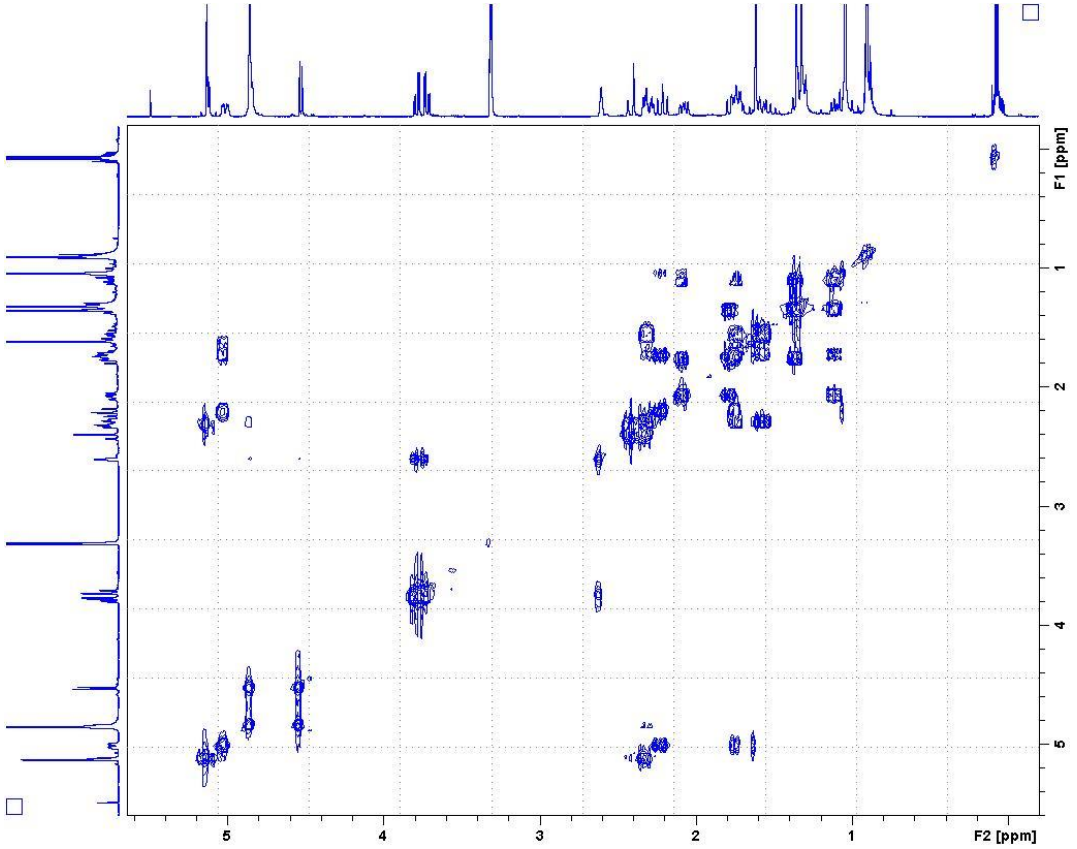
^{1}H, ^{1}H COSY NMR of **211b**



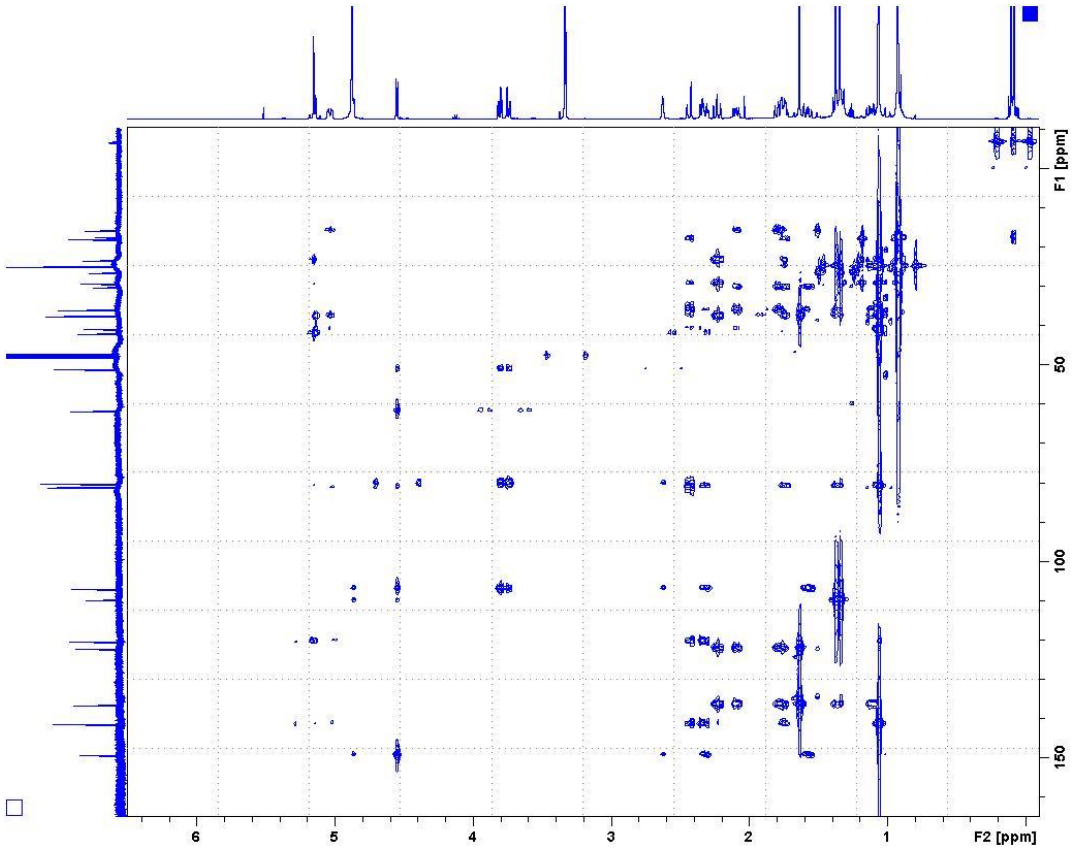
^{1}H, ^{13}C HMBC NMR of **211b**


TBSO
H
O
O
H
O
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 -0.5 ppm
1.995
1.028
0.902
1.000
2.072
1.033
1.052
1.996
1.143
1.192
3.182
3.109
1.430
4.009
3.030
1.292
8.902
9.046
3.066
3.146

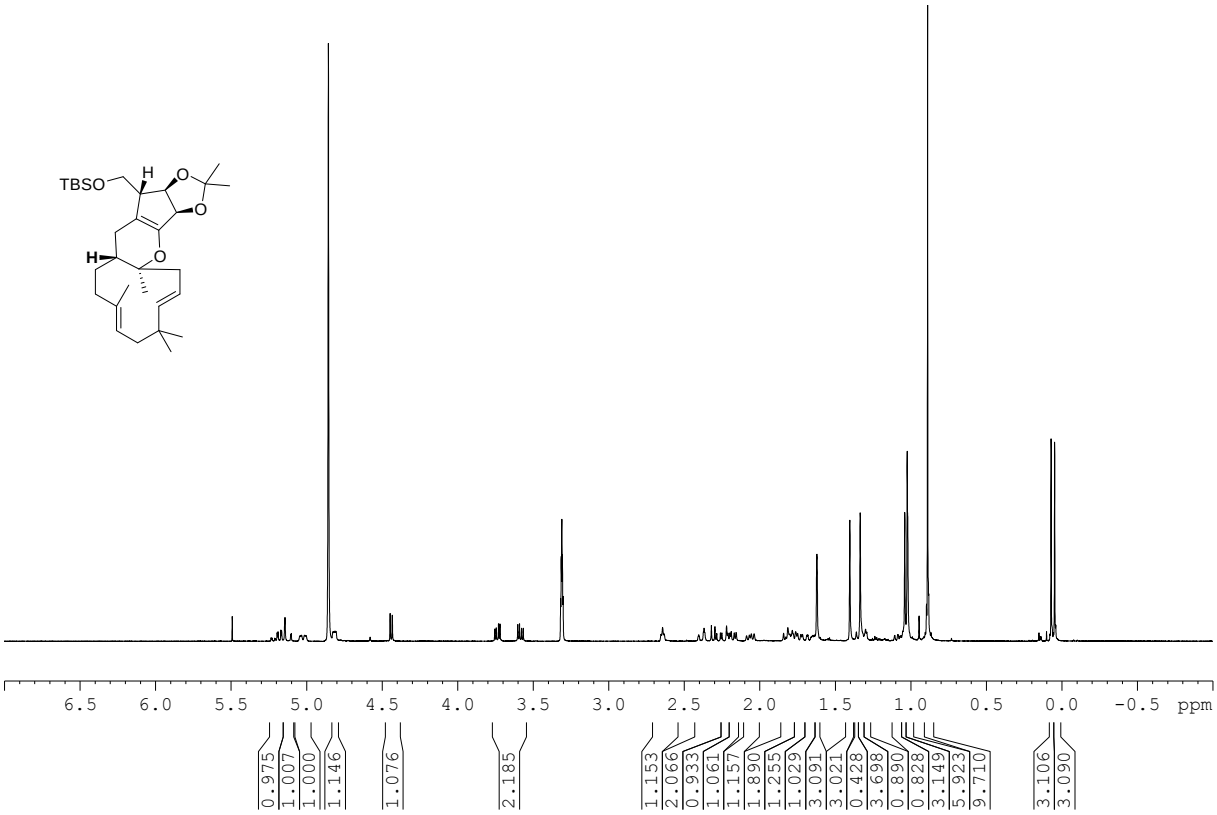

150.865
142.956
138.041
123.687
121.973
111.423
108.488
82.638
82.396
81.717
63.233
52.596
43.508
42.337
39.090
38.983
37.523
31.741
30.743
28.058
26.532
26.439
26.287
24.883
19.548
18.986
17.317
-5.002
-5.346
TBSO
H
O
O
H
O
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

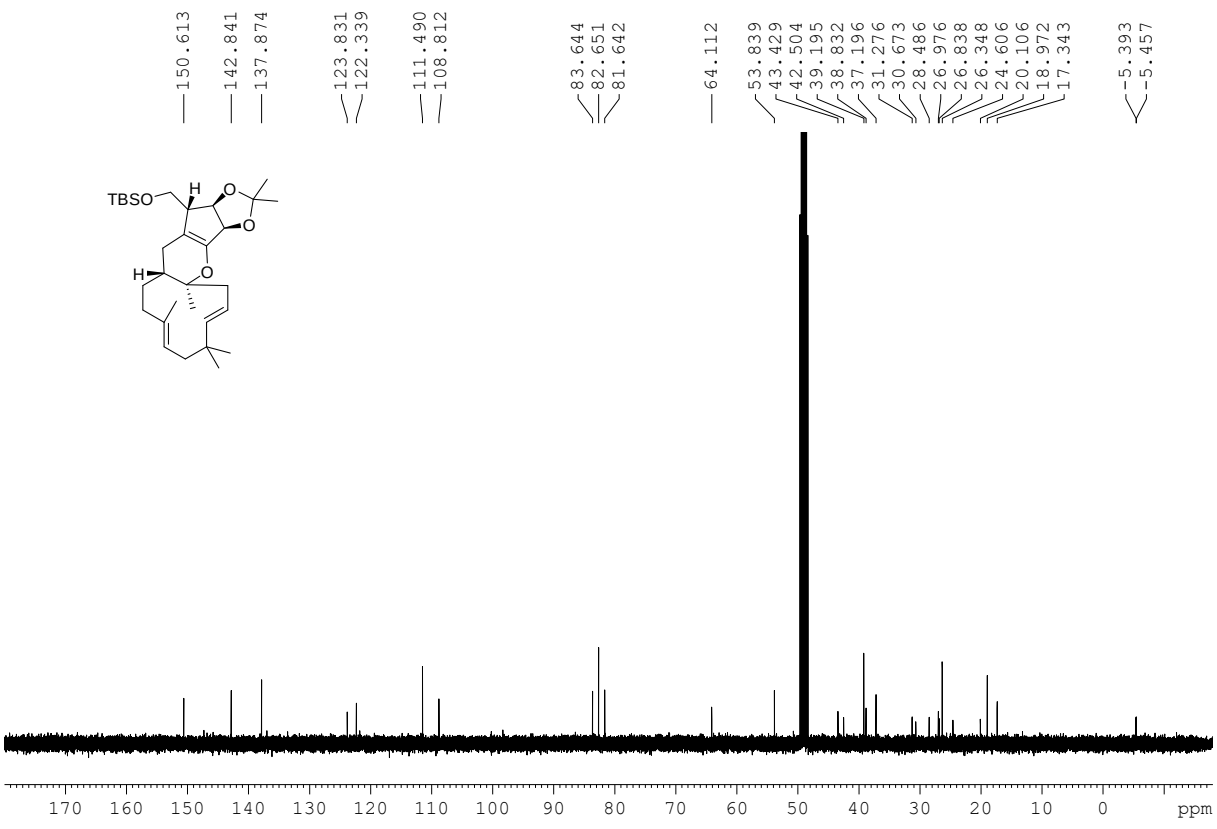


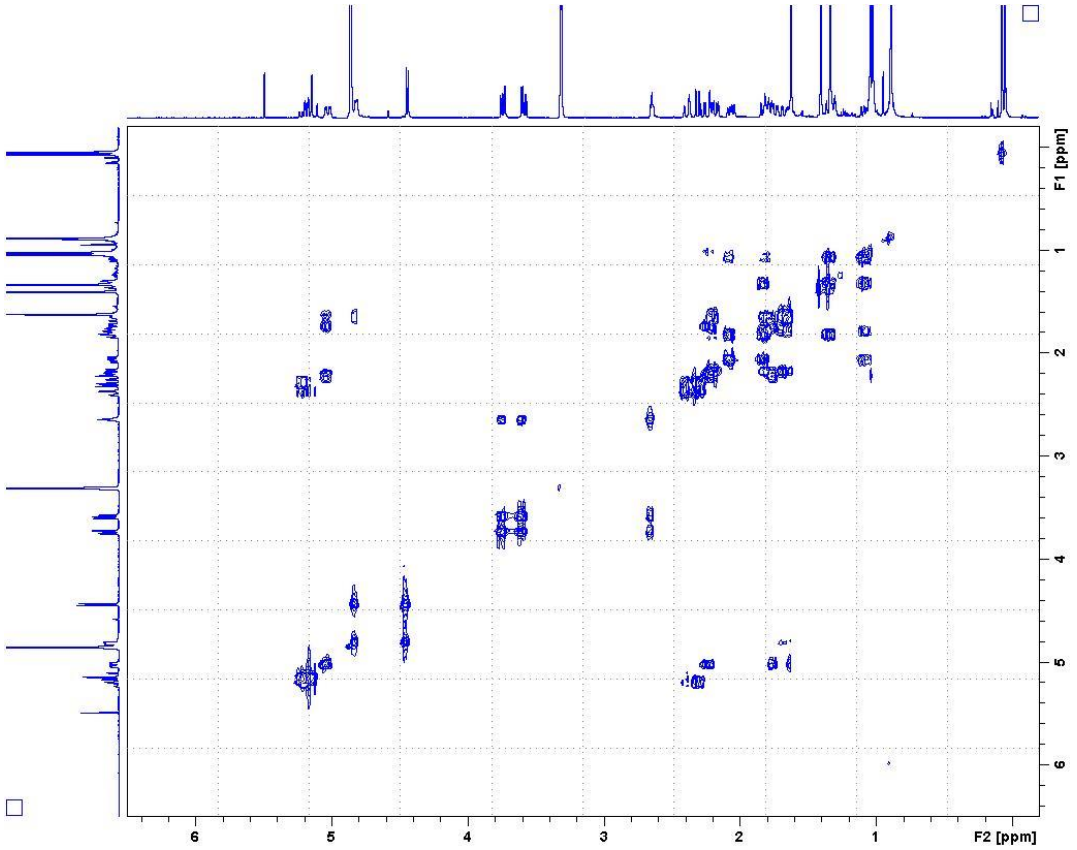
^{1}H, ^{1}H COSY NMR of **218a**



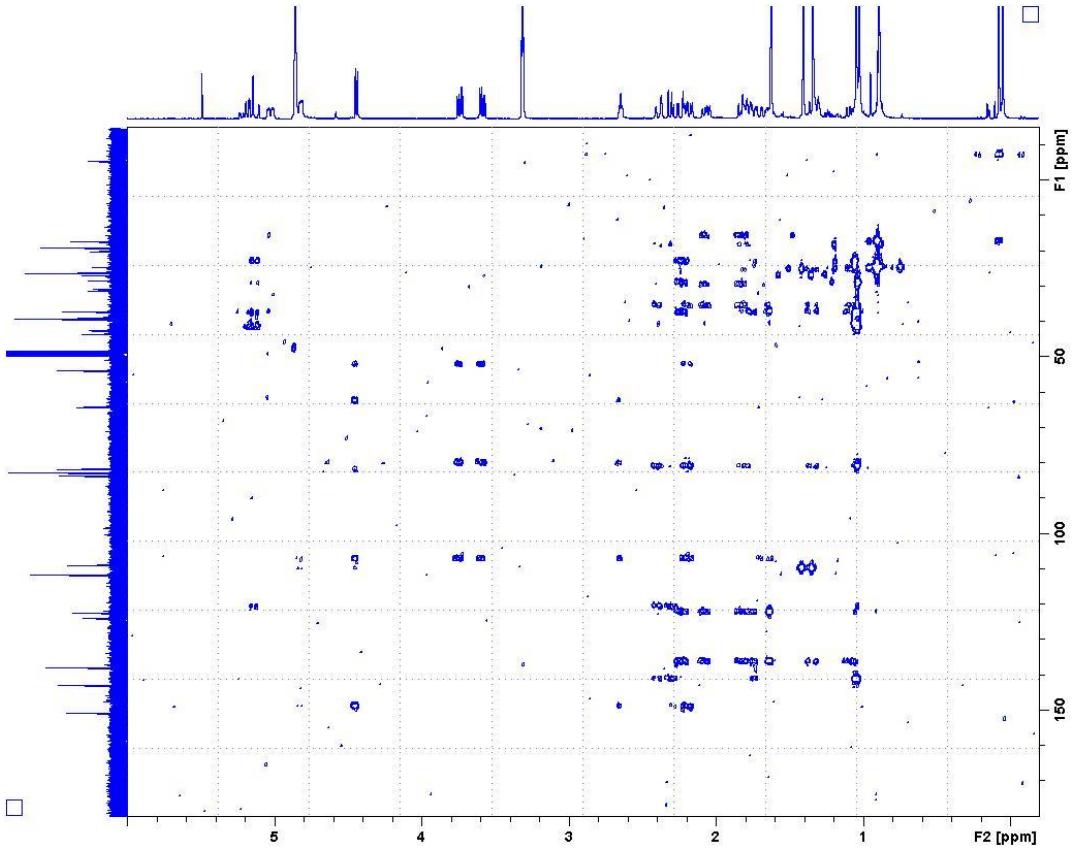
^{1}H, ^{13}C HMBC NMR of **218a**


TBSO
H
O
O
H
O
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 -0.5 ppm
0.975
1.007
1.000
1.146
1.076
2.185
1.153
2.066
0.933
1.061
1.157
1.890
1.255
1.029
3.091
3.021
0.428
3.698
0.890
0.828
3.149
5.923
9.710
3.106
3.090

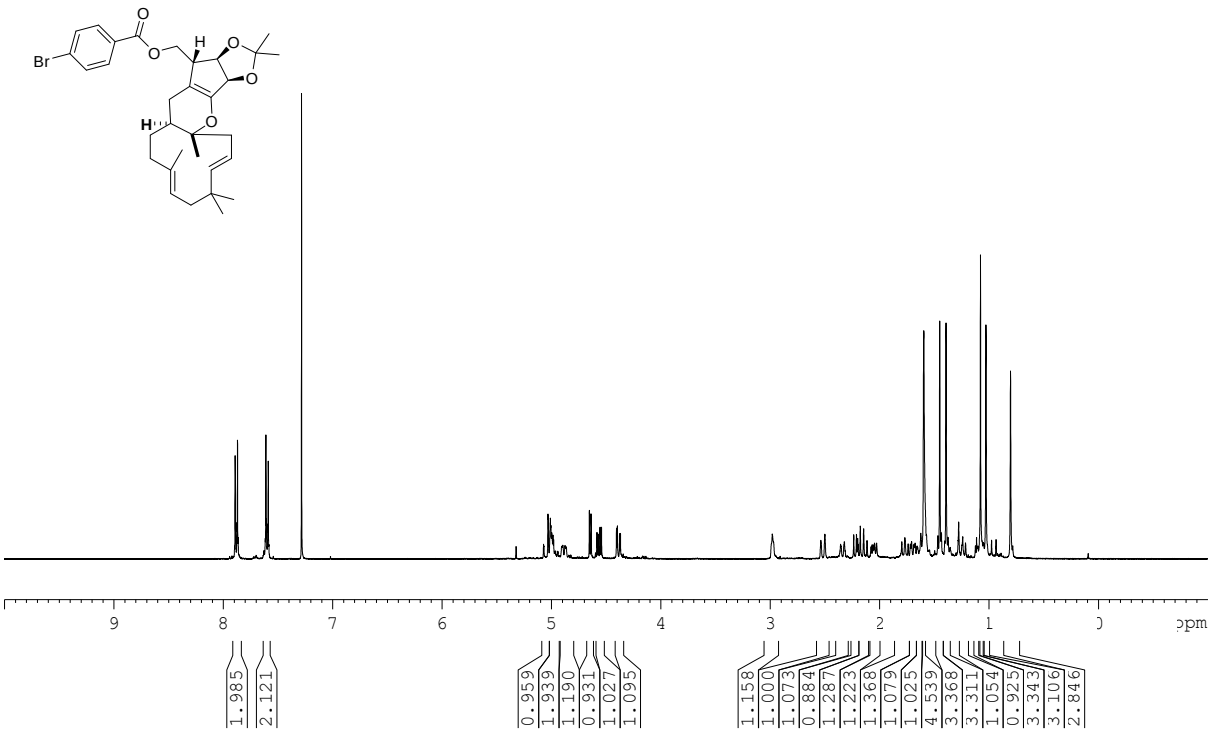

150.613
142.841
137.874
123.831
122.339
111.490
108.812
83.644
82.651
81.642
64.112
53.839
43.429
42.504
39.195
38.832
37.196
31.276
30.673
28.486
26.976
26.838
26.348
24.606
20.106
18.972
17.343
-5.393
-5.457
TBSO
H
O
O
H
O
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

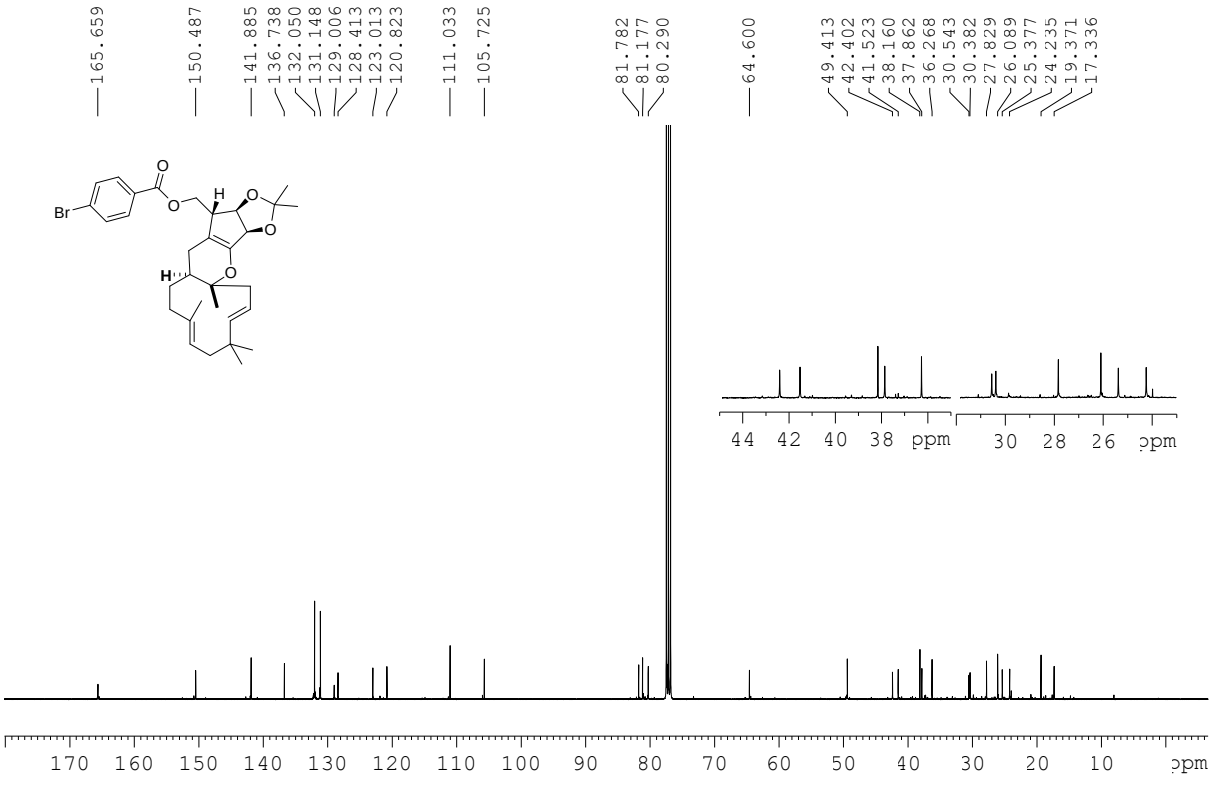


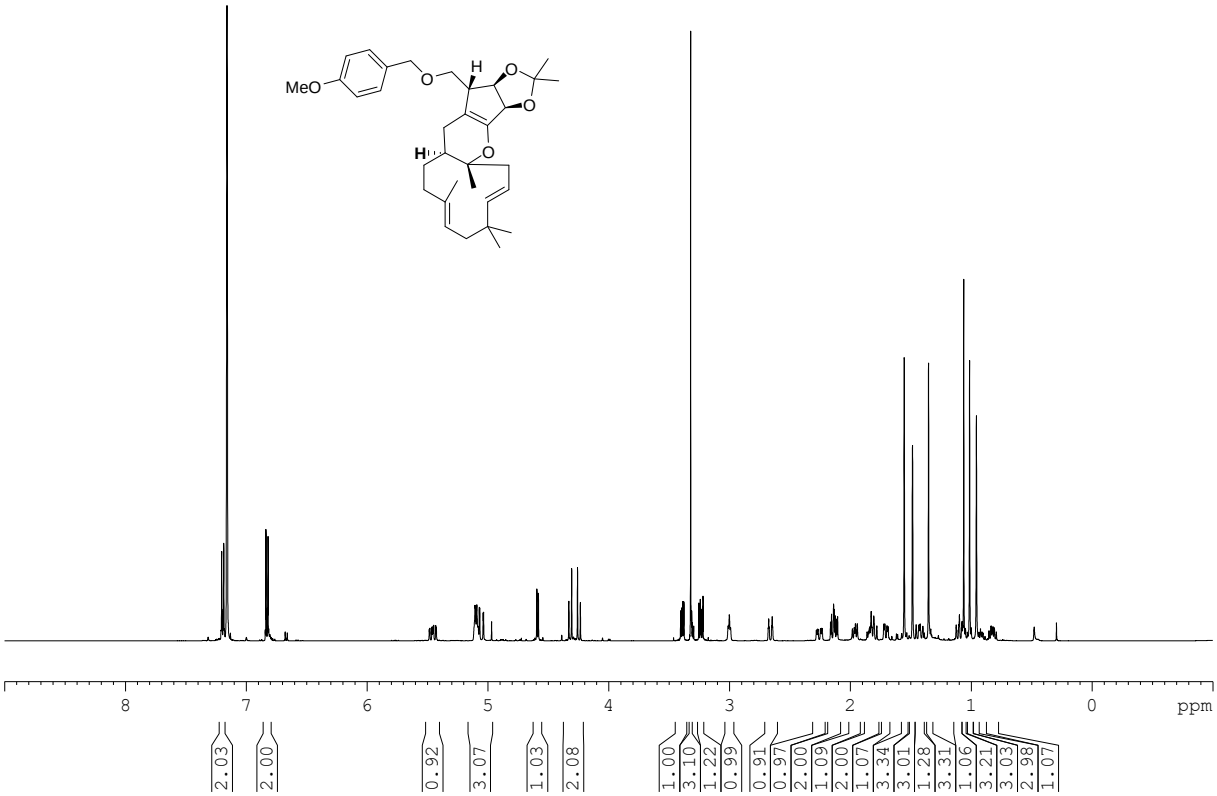
^{1}H, ^{1}H COSY NMR of **218b**



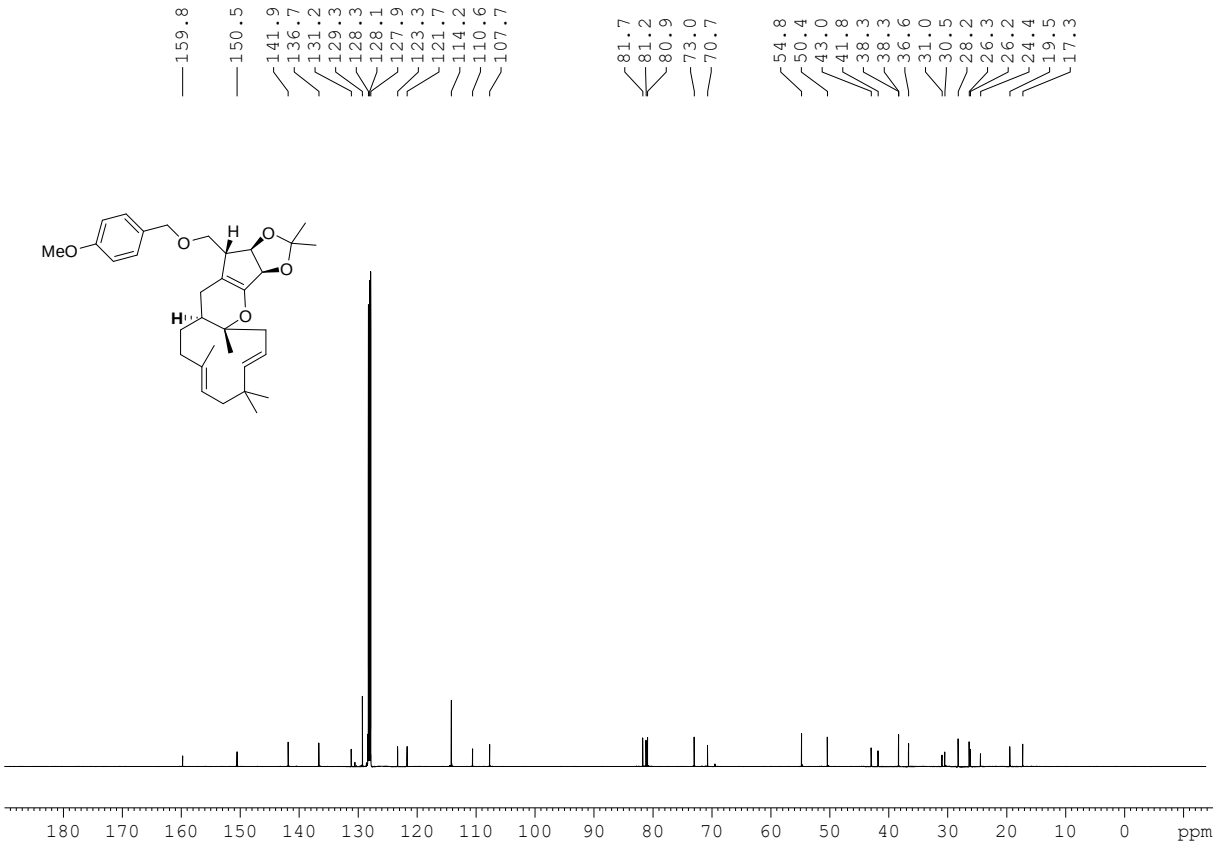
^{1}H, ^{13}C HMBC NMR of **218b**

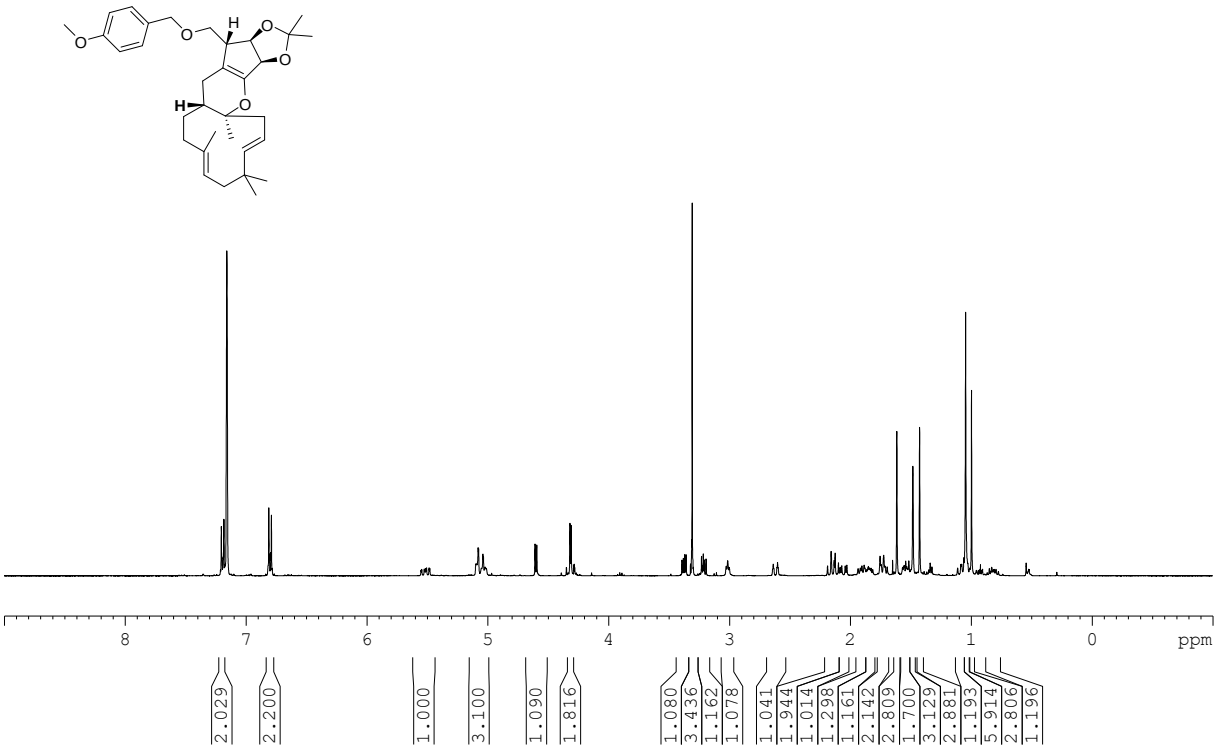

Br
O
H
O
O
H
O
9
8
7
6
5
4
3
2
1
0
ppm
1.985
2.121
0.959
1.939
1.190
0.931
1.027
1.095
1.158
1.000
1.073
0.884
1.287
1.223
1.368
1.079
1.025
4.539
3.368
3.311
1.054
0.925
3.343
3.106
2.846


165.659
150.487
141.885
136.738
132.050
131.148
129.006
128.413
123.013
120.823
111.033
105.725
81.782
81.177
80.290
64.600
49.413
42.402
41.523
38.160
37.862
36.268
30.543
30.382
27.829
26.089
25.377
24.235
19.371
17.336
Br
O
H
O
O
H
O
44
42
40
38
ppm
30
28
26
ppm
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

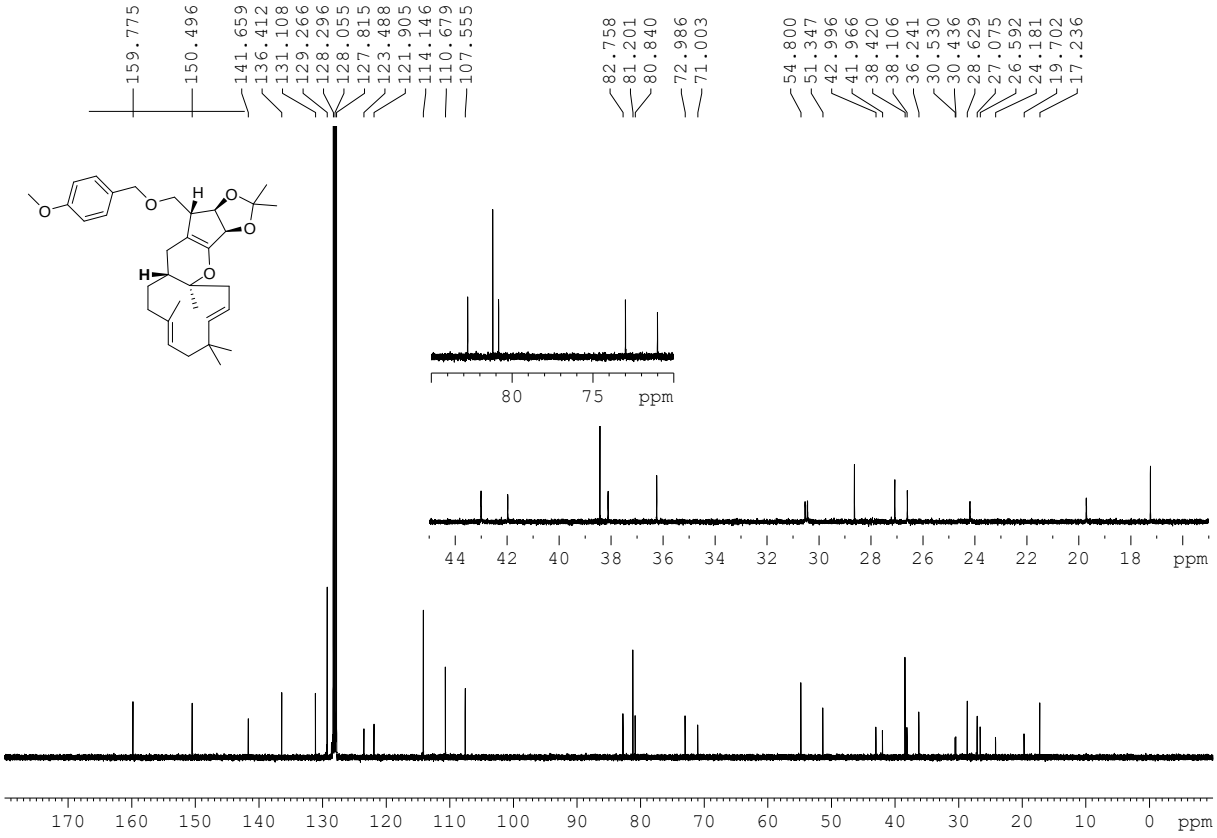

MeO
H
O
H
O
O
8
7
6
5
4
3
2
1
0
ppm
2.03
2.00
0.92
3.07
1.03
2.08
1.00
3.10
1.22
0.99
0.91
0.97
2.00
1.09
2.00
1.07
3.34
3.01
1.28
3.31
1.06
3.21
3.03
2.98
1.07

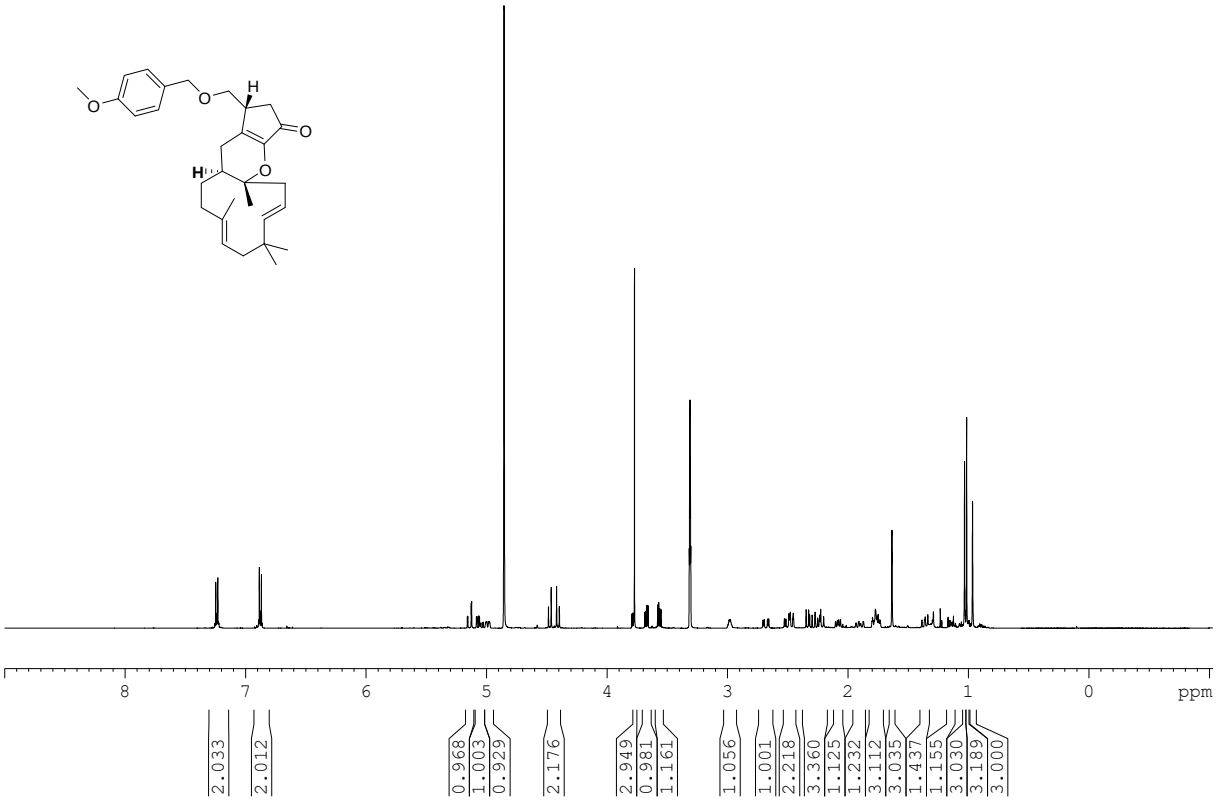
I

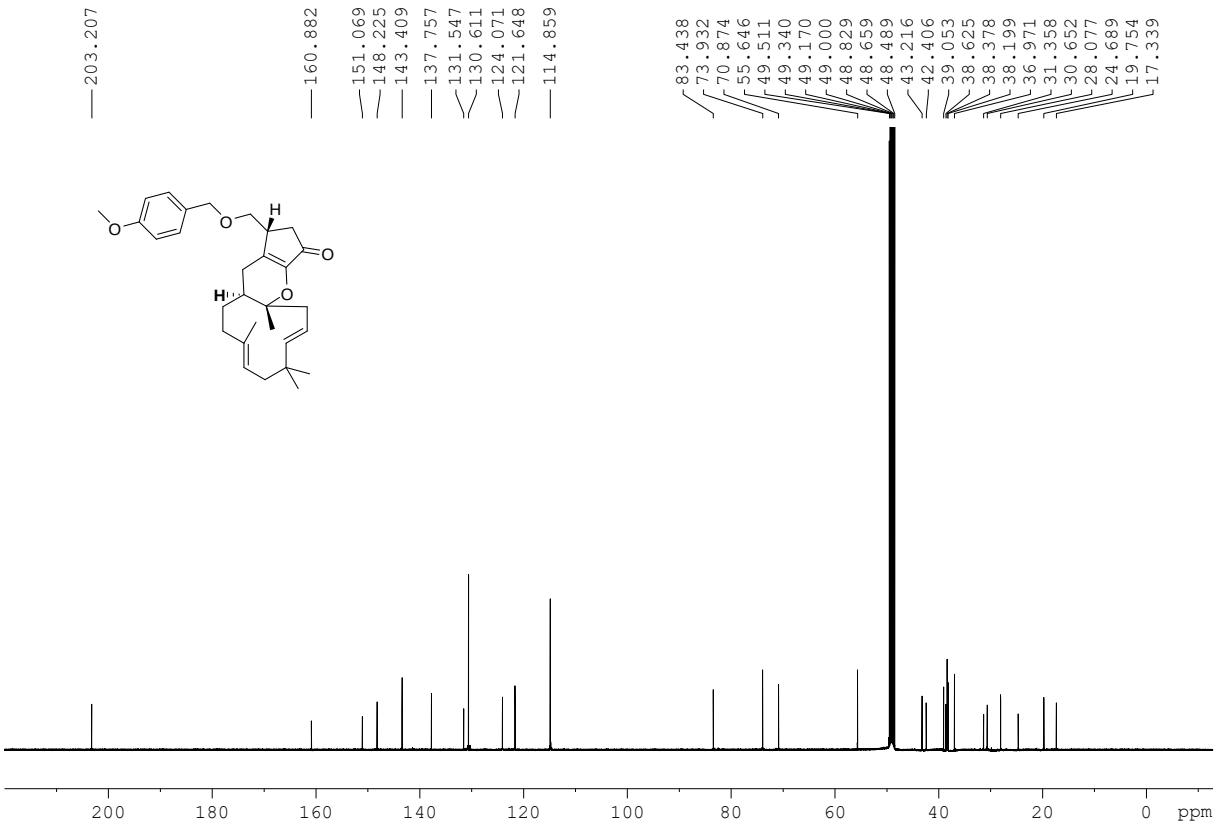

159.8
150.5
141.9
136.7
131.2
129.3
128.3
128.1
127.9
123.3
121.7
114.2
110.6
107.7
81.7
81.2
80.9
73.0
70.7
54.8
50.4
43.0
41.8
38.3
38.3
36.6
31.0
30.5
28.2
26.3
26.2
24.4
19.5
17.3
MeO
H
O
H
O
O
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

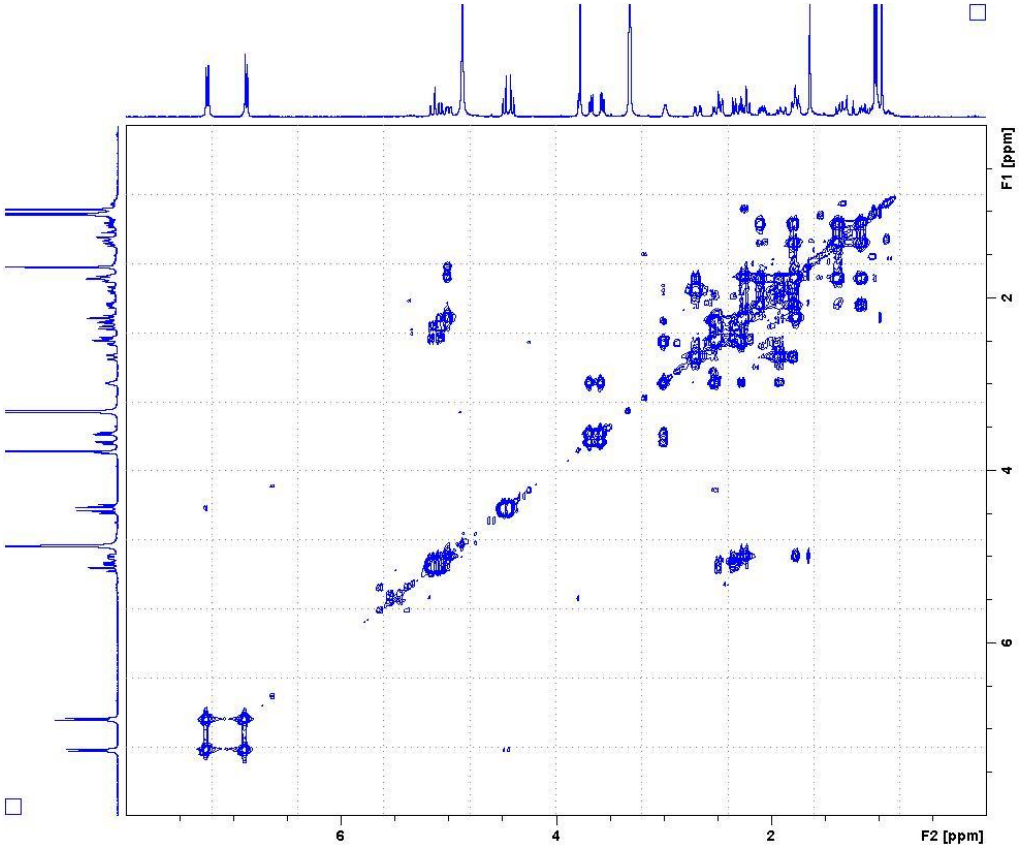

8 7 6 5 4 3 2 1 0 ppm
2.029 2.200 1.000 3.100 1.090 1.816 1.080 3.436 1.162 1.078 1.041 1.944 1.014 1.298 1.161 2.142 2.809 1.700 3.129 2.881 1.193 5.914 2.806 1.196

1

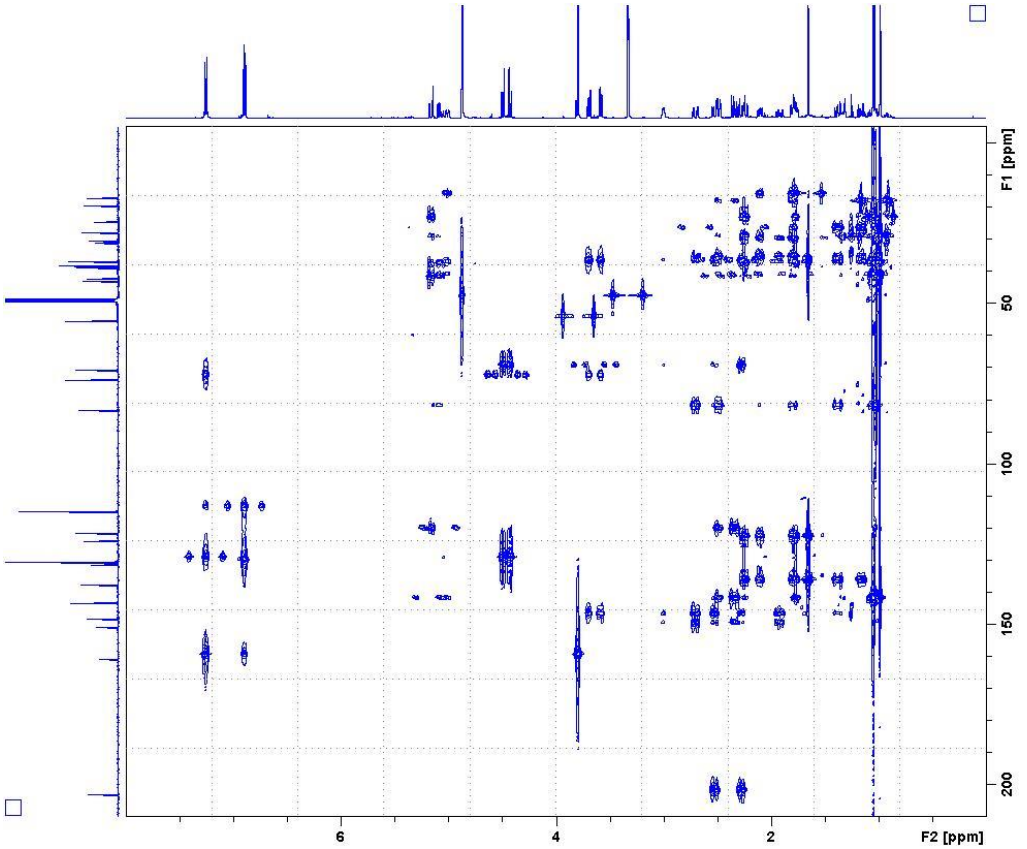

159.775 150.496 141.659 136.412 131.108 129.266 128.296 128.055 127.815 123.488 121.905 114.146 110.679 107.555
82.758 81.201 80.840 72.986 71.003
54.800 51.347 42.996 41.966 38.420 38.106 36.241 30.530 30.436 28.629 27.075 26.592 24.181 19.702 17.236
80 75 ppm
44 42 40 38 36 34 32 30 28 26 24 22 20 18 ppm
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


8
7
6
5
4
3
2
1
0
ppm
2.033
2.012
0.968
1.003
0.929
2.176
2.949
0.981
1.161
1.056
1.001
2.218
3.360
1.125
1.232
3.112
3.035
1.437
1.155
3.030
3.189
3.000

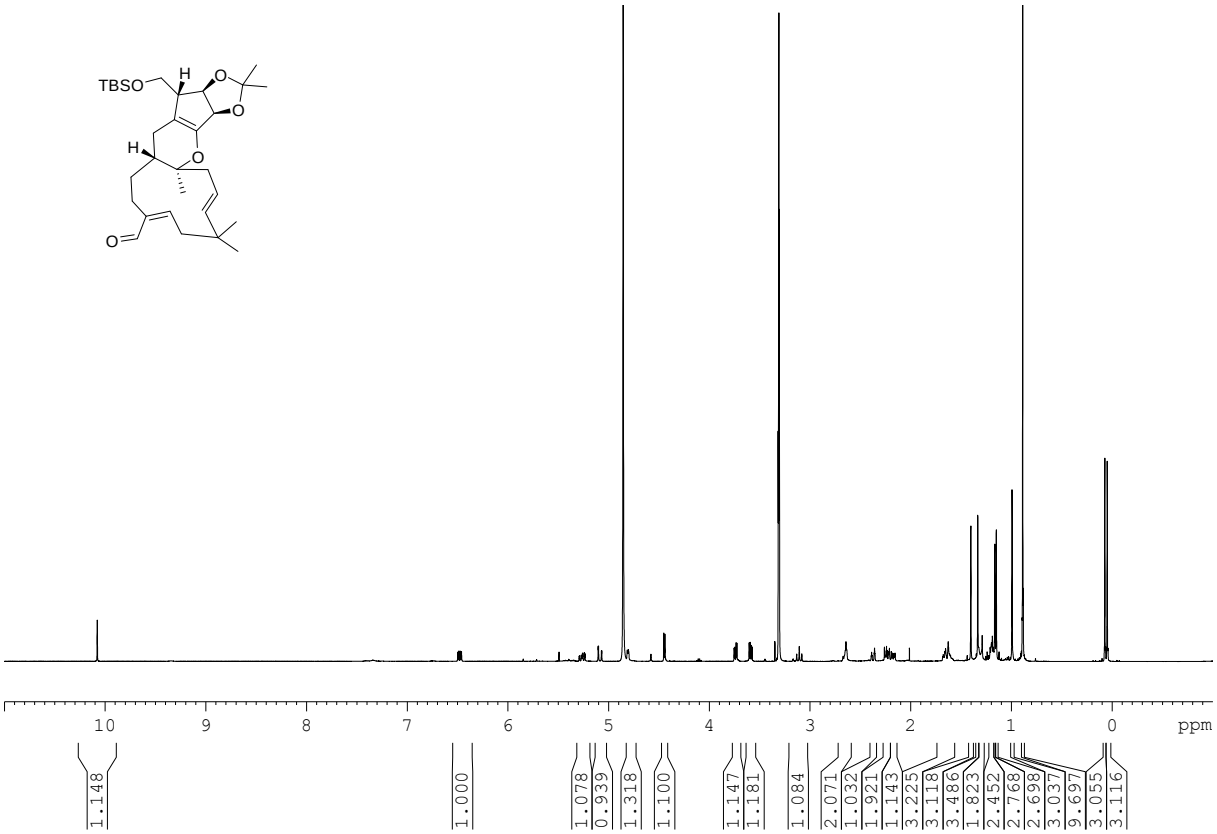

203.207
160.882
151.069
148.225
143.409
137.757
131.547
130.611
124.071
121.648
114.859
83.438
73.932
70.874
55.646
49.511
49.340
49.170
49.000
48.829
48.659
48.489
43.216
42.406
39.053
38.625
38.378
38.199
36.971
31.358
30.652
28.077
24.689
19.754
17.339
200
180
160
140
120
100
80
60
40
20
0
ppm

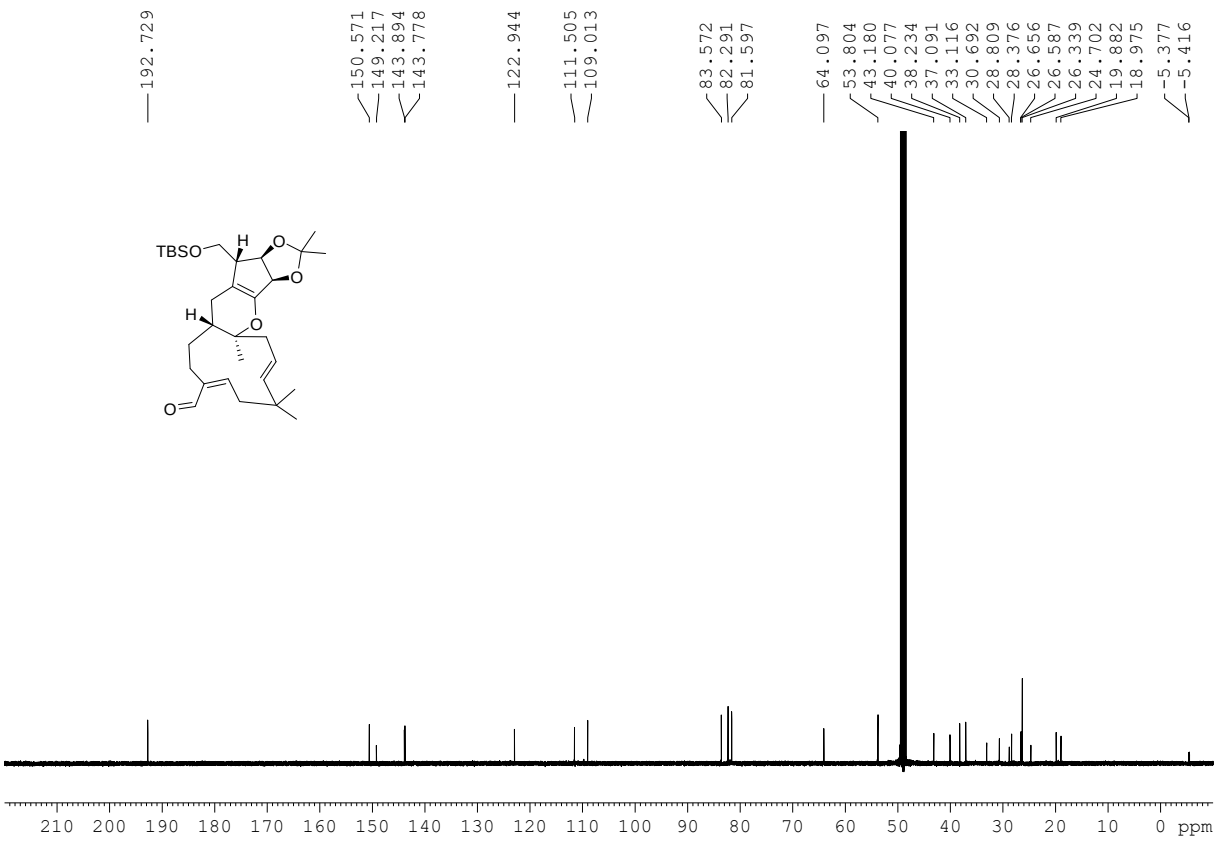


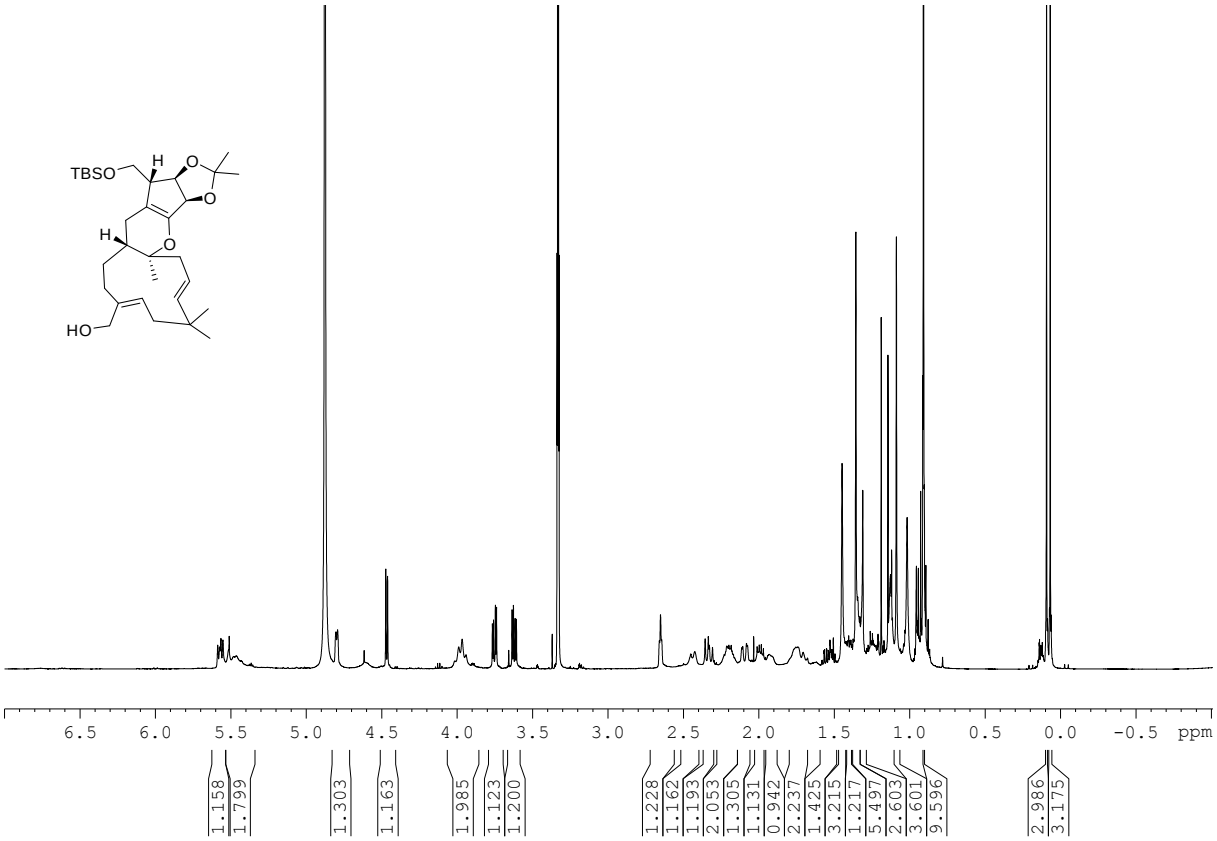
^{1}H, ^{1}H COSY NMR of **227a**

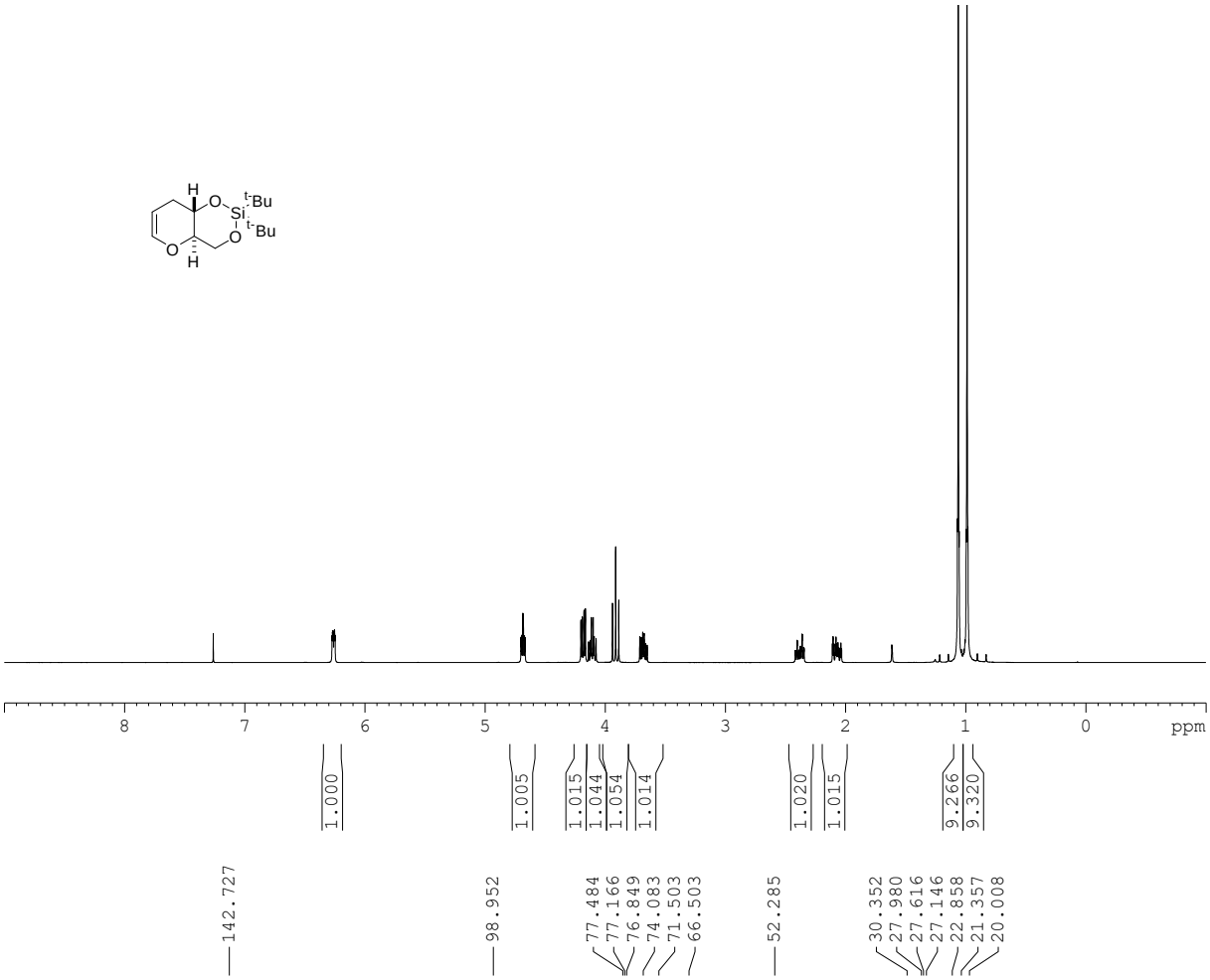


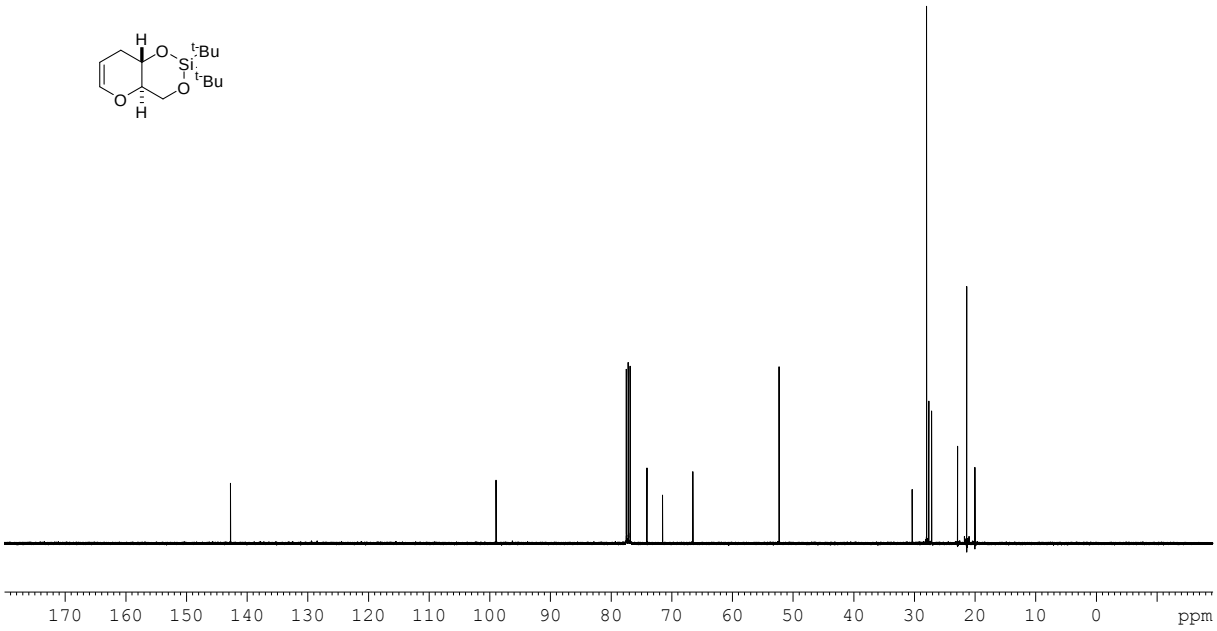
^{1}H, ^{13}C HMBC NMR of **227a**

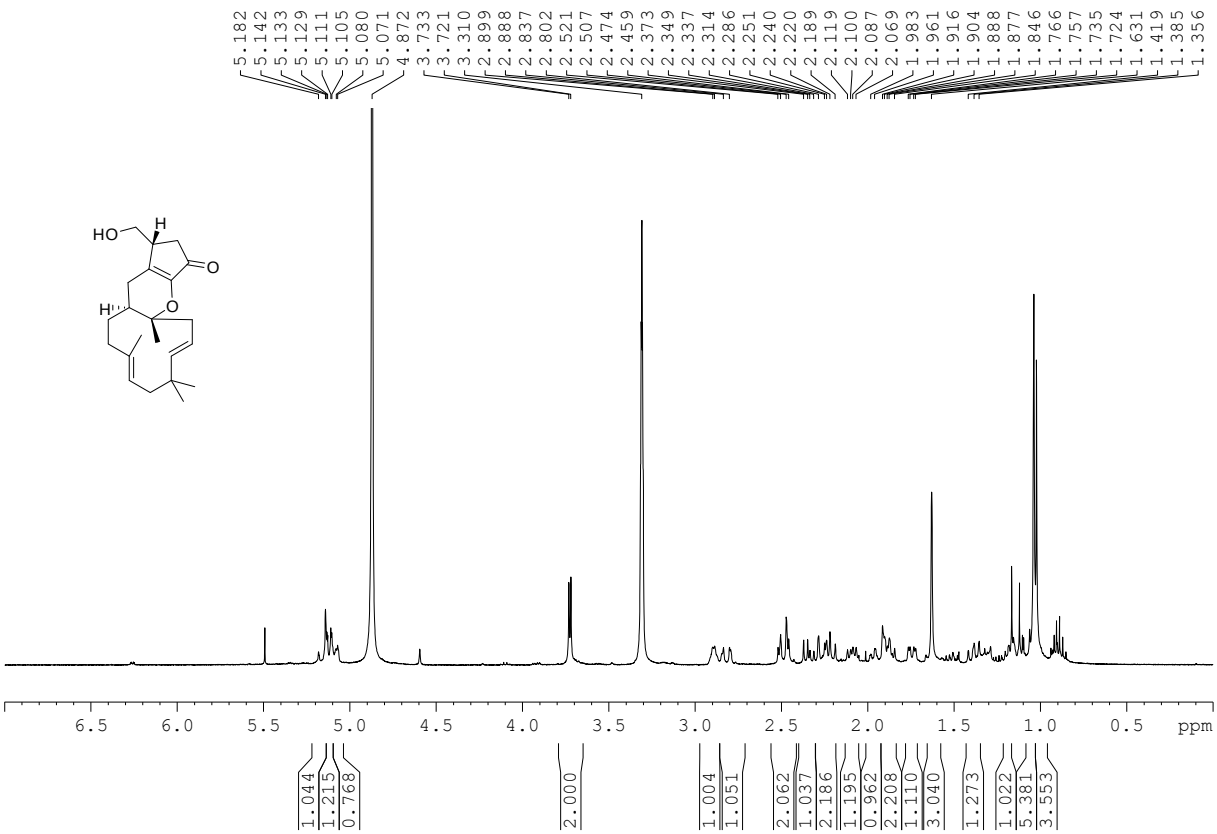

TBSO
H
O
O
H
O
O
10 9 8 7 6 5 4 3 2 1 0 ppm
1.148
1.000
1.078
0.939
1.318
1.100
1.147
1.181
1.084
2.071
1.032
1.921
1.143
3.225
3.118
3.486
1.823
2.452
2.768
2.698
3.037
9.697
3.055
3.116

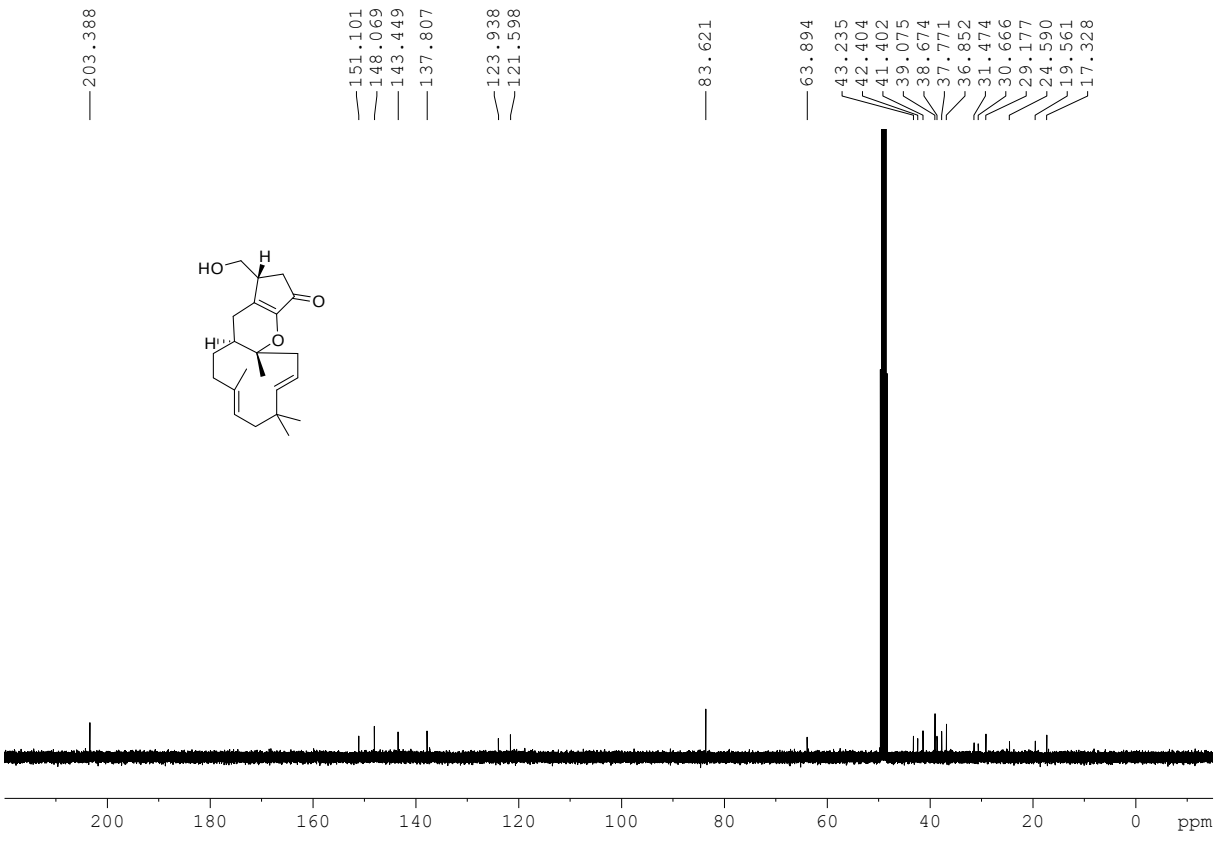

192.729
150.571
149.217
143.894
143.778
122.944
111.505
109.013
83.572
82.291
81.597
64.097
53.804
43.180
40.077
38.234
37.091
33.116
30.692
28.809
28.376
26.656
26.587
26.339
24.702
19.882
18.975
-5.377
-5.416
TBSO
H
O
O
H
O
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

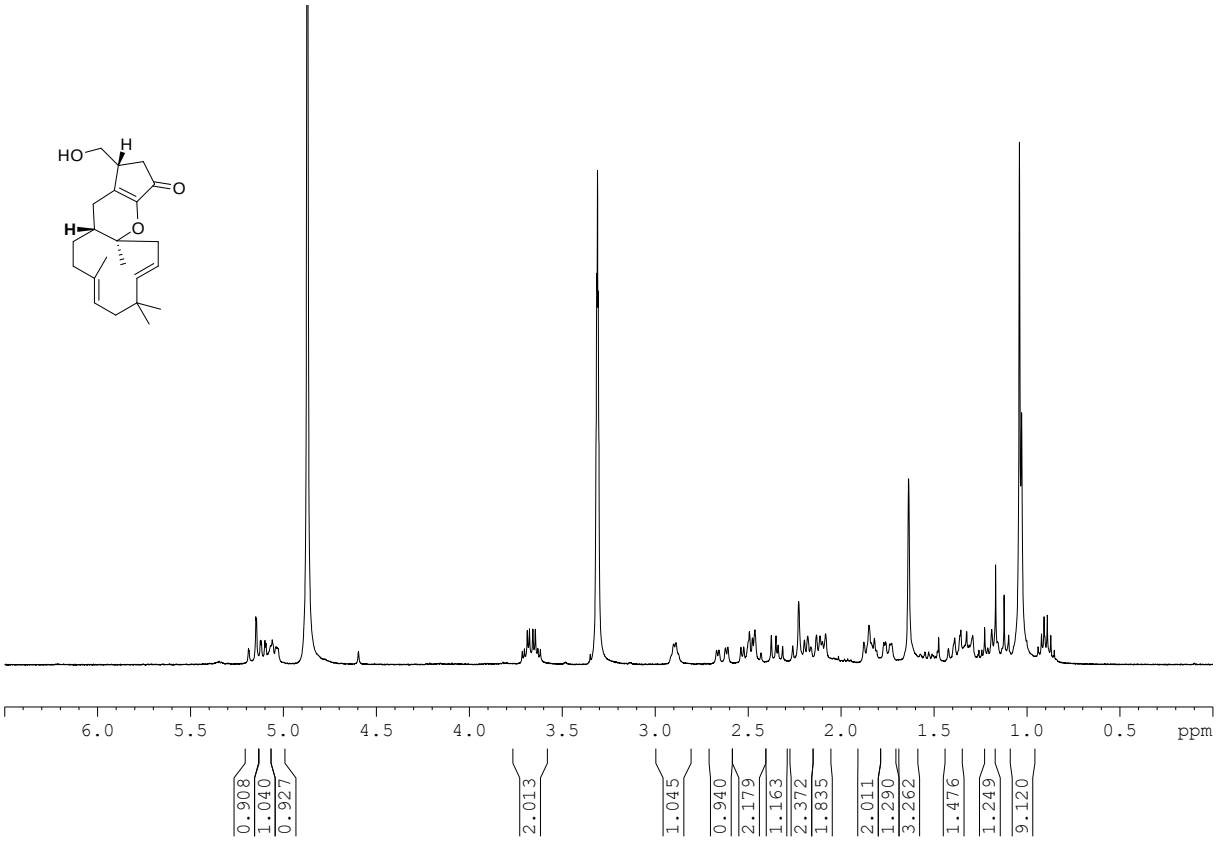

TBSO
H
O
O
H
O
HO
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm
1.158
1.799
1.303
1.163
1.985
1.123
1.200
1.228
1.162
1.193
2.053
1.305
1.131
0.942
2.237
1.425
3.215
1.217
5.497
2.603
3.601
9.596
2.986
3.175

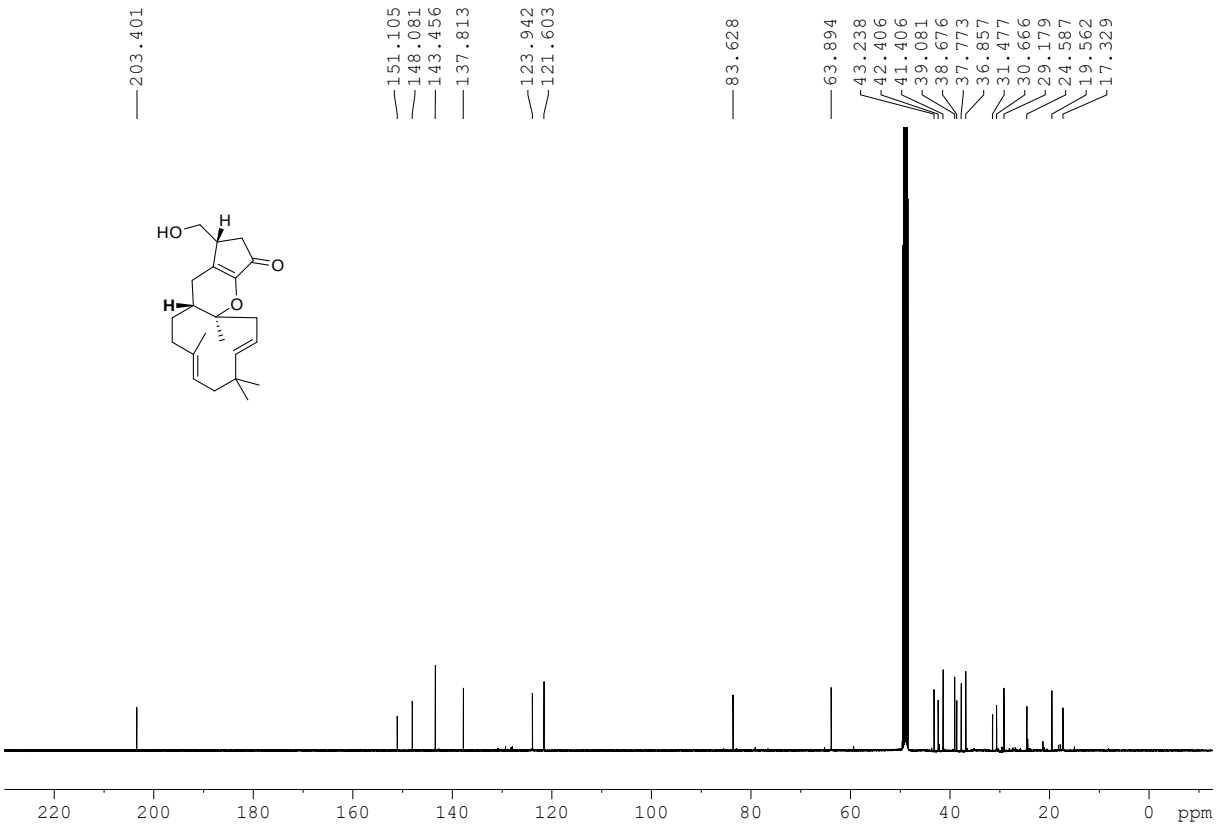

8
7
6
5
4
3
2
1
0
ppm
1.000
1.005
1.015
1.044
1.054
1.014
1.020
1.015
9.266
9.320
142.727
98.952
77.484
77.166
76.849
74.083
71.503
66.503
52.285
30.352
27.980
27.616
27.146
22.858
21.357
20.008

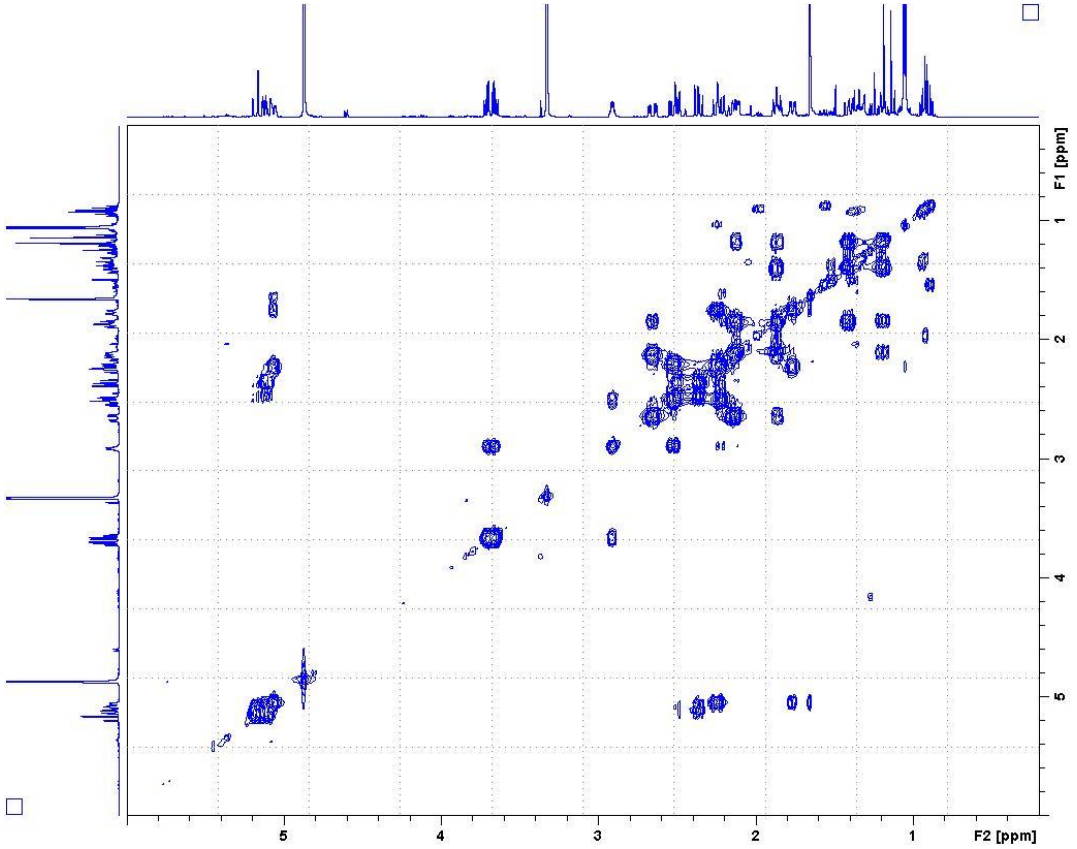

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


5.182
5.142
5.133
5.129
5.111
5.105
5.080
5.071
4.872
3.733
3.721
3.310
2.899
2.888
2.837
2.802
2.521
2.507
2.474
2.459
2.373
2.349
2.337
2.314
2.286
2.251
2.240
2.220
2.189
2.119
2.100
2.087
2.069
1.983
1.961
1.916
1.904
1.888
1.877
1.846
1.766
1.757
1.735
1.724
1.631
1.419
1.385
1.356
HO
H
O
H
O
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
ppm
1.044
1.215
0.768
2.000
1.004
1.051
2.062
1.037
2.186
1.195
0.962
2.208
1.110
3.040
1.273
1.022
5.381
3.553

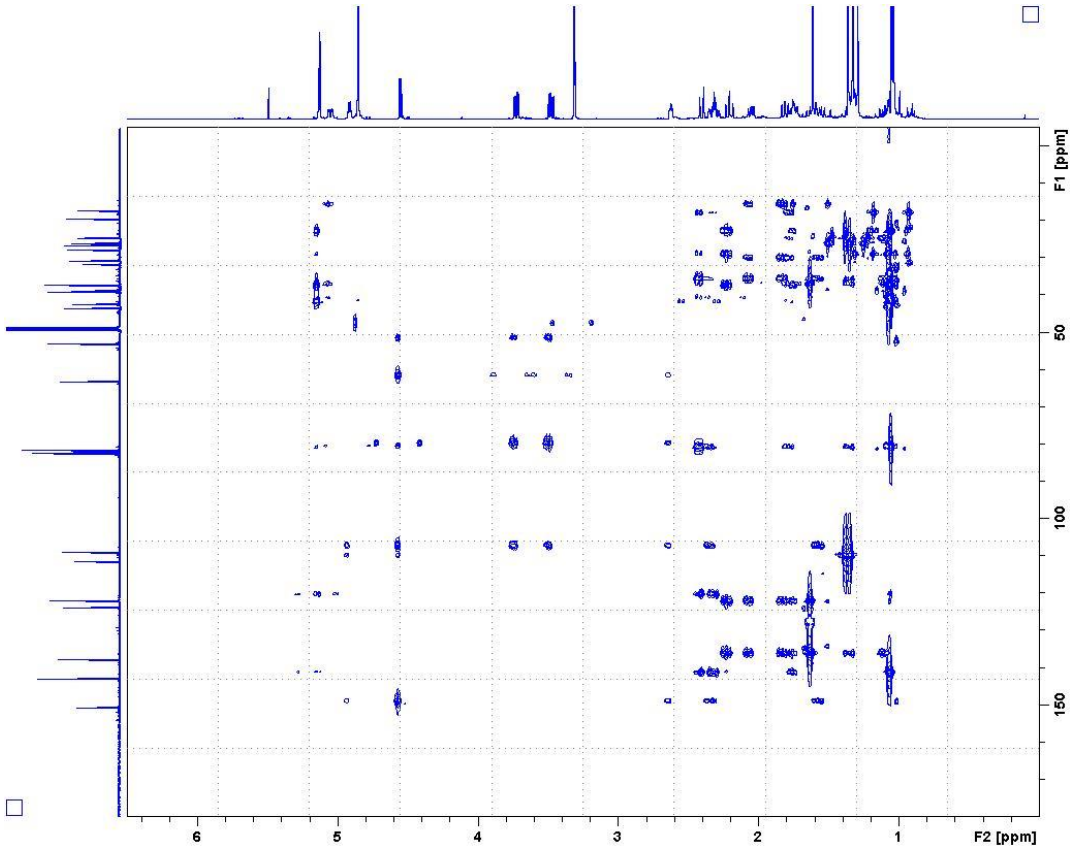

203.388
151.101
148.069
143.449
137.807
123.938
121.598
83.621
63.894
43.235
42.404
41.402
39.075
38.674
37.771
36.852
31.474
30.666
29.177
24.590
19.561
17.328
HO
H
O
H
O
200
180
160
140
120
100
80
60
40
20
0
ppm


HO
H
O
H
O
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.908
1.040
0.927
2.013
1.045
0.940
2.179
1.163
2.372
1.835
2.011
1.290
3.262
1.476
1.249
9.120


203.401
151.105
148.081
143.456
137.813
123.942
121.603
83.628
63.894
43.238
42.406
41.406
39.081
38.676
37.773
36.857
31.477
30.666
29.179
24.587
19.562
17.329
HO
H
O
H
O
220
200
180
160
140
120
100
80
60
40
20
0
ppm

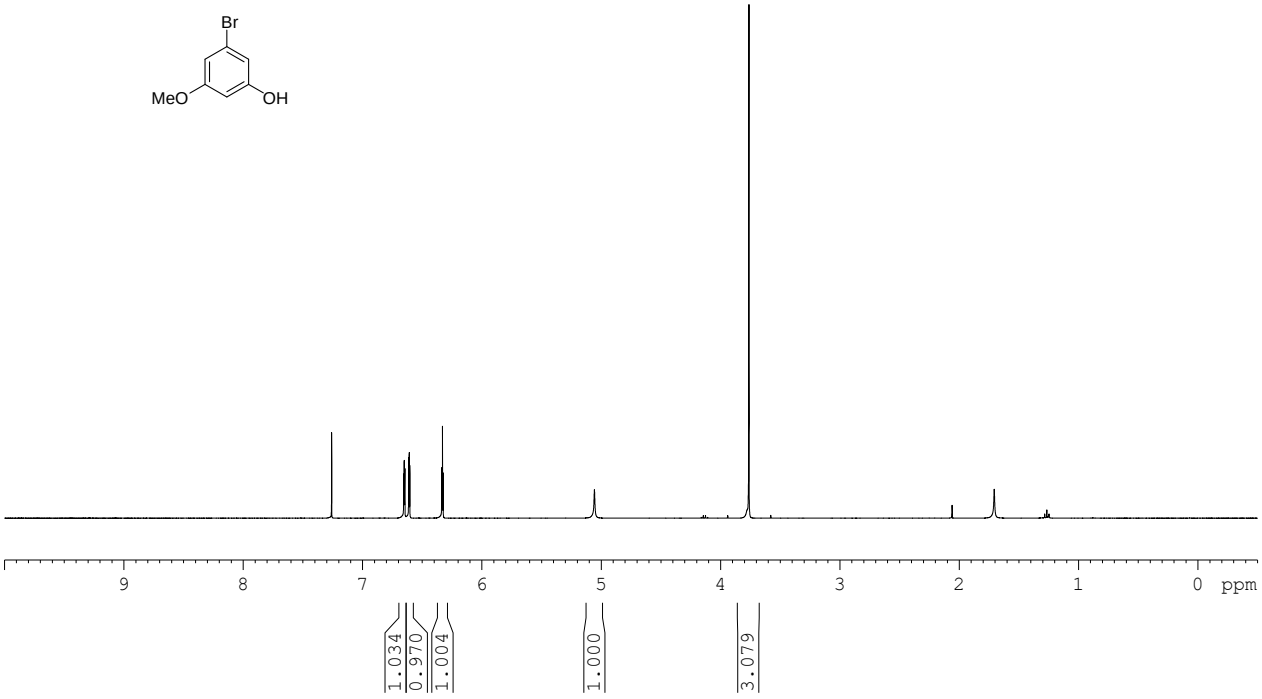


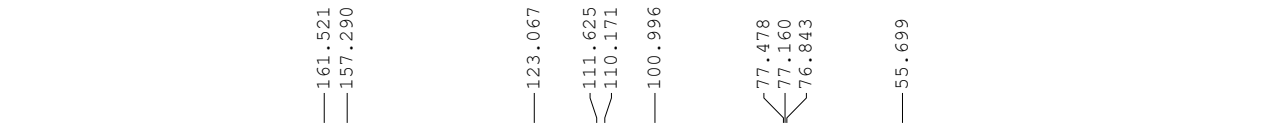
^{1}H, ^{1}H COSY NMR of **224b**

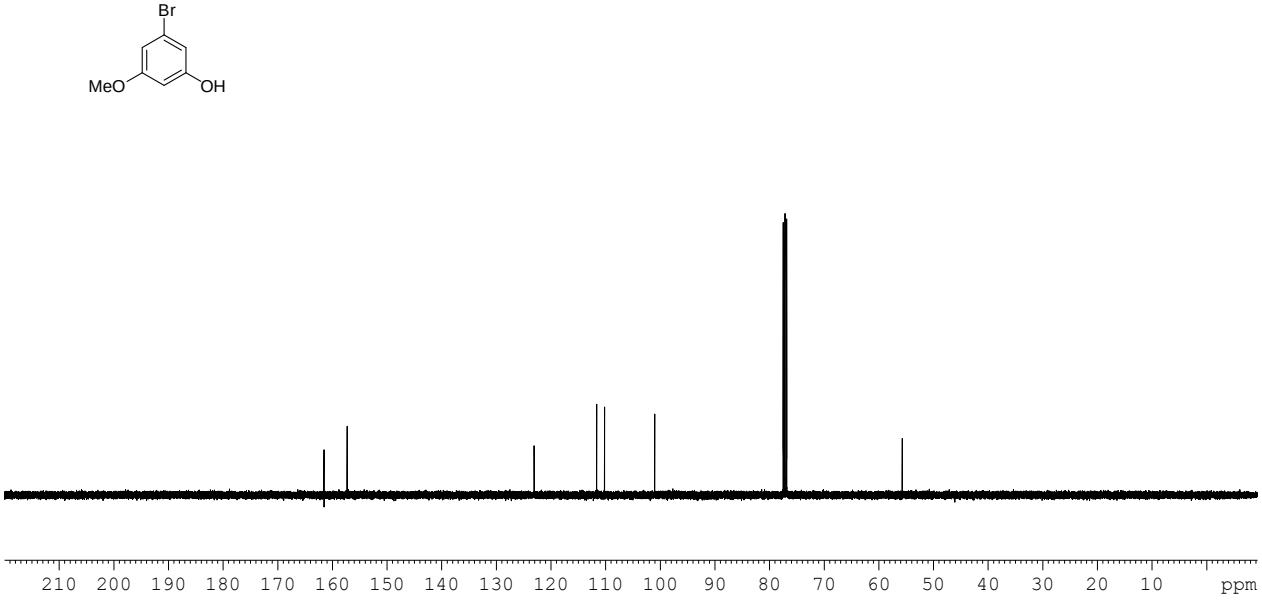


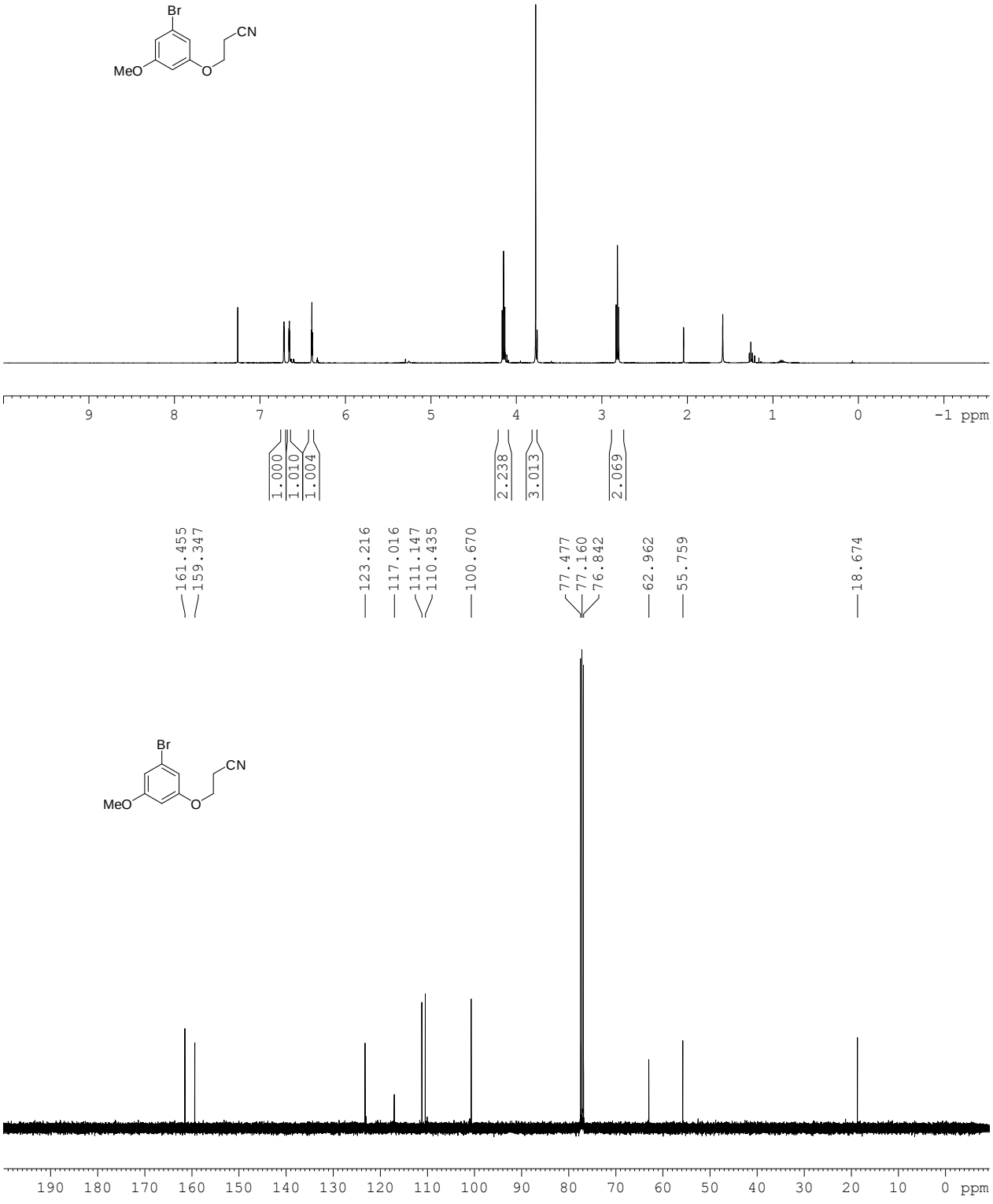
^{1}H, ^{13}C HMBC NMR of **224b**

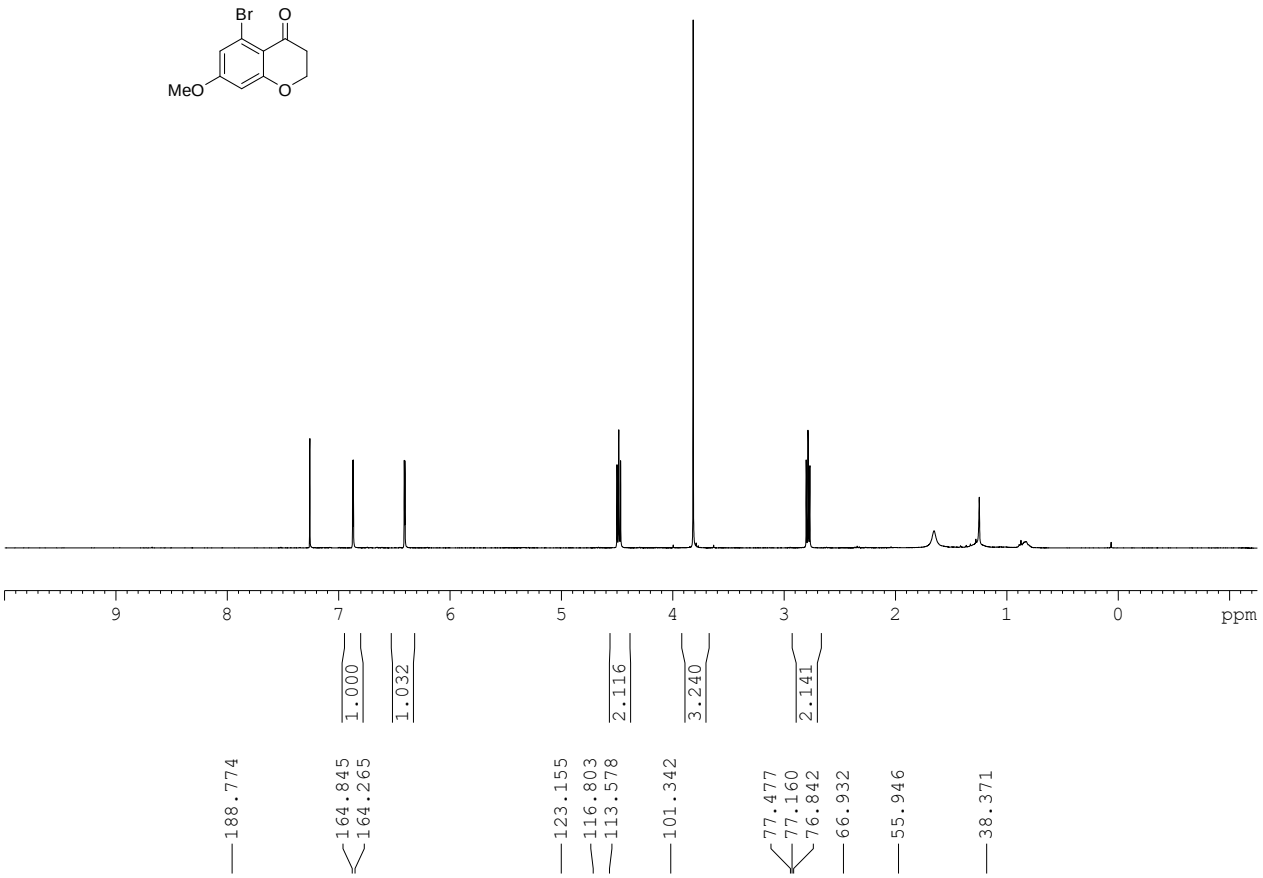
8.3 NMR Spectra for chapter 4

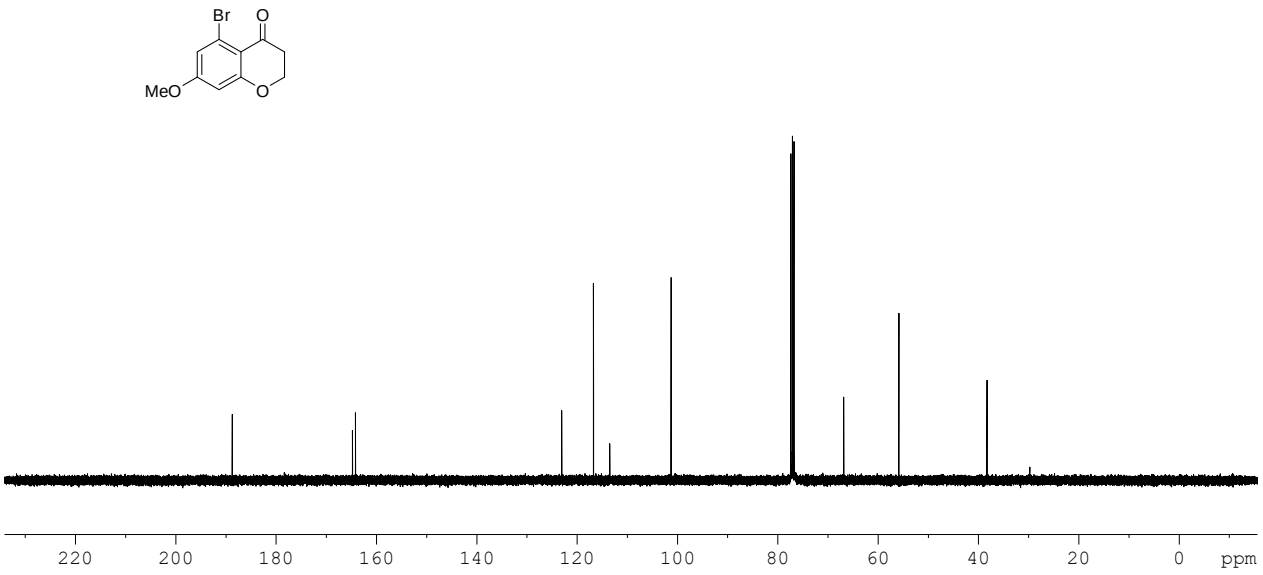


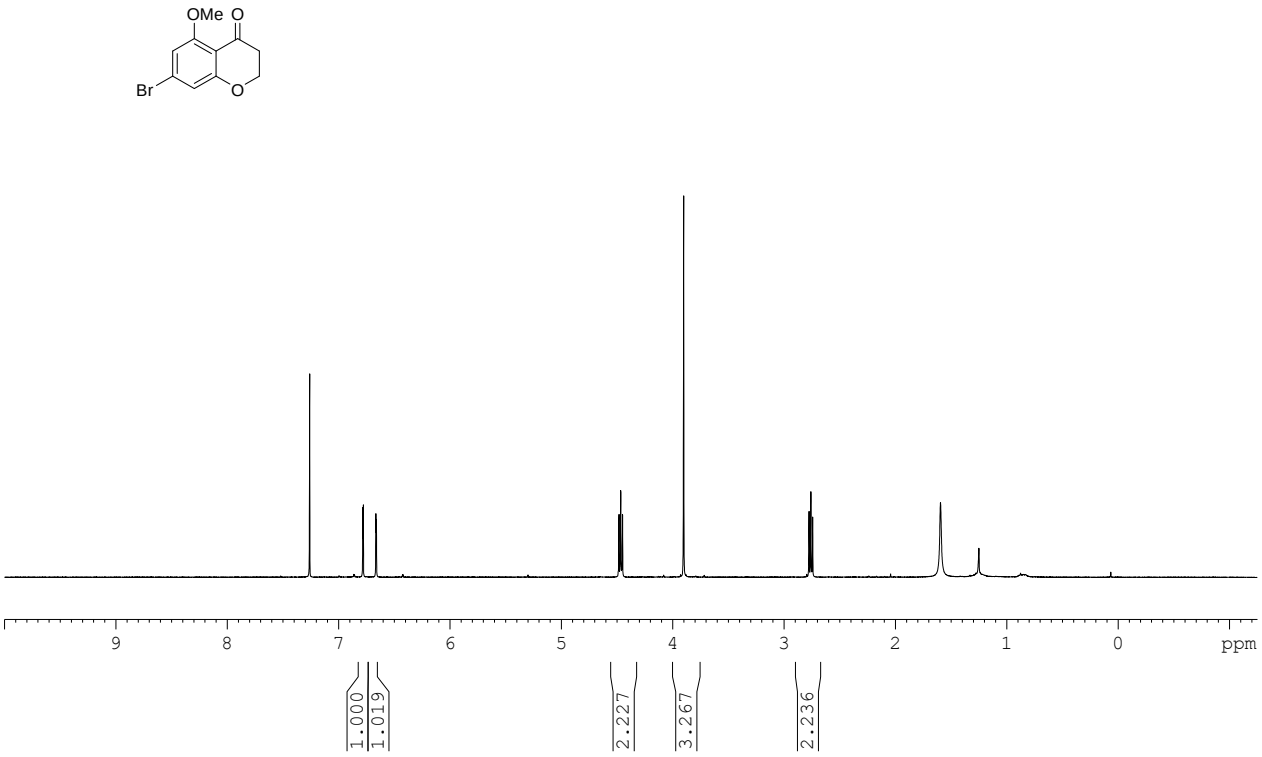


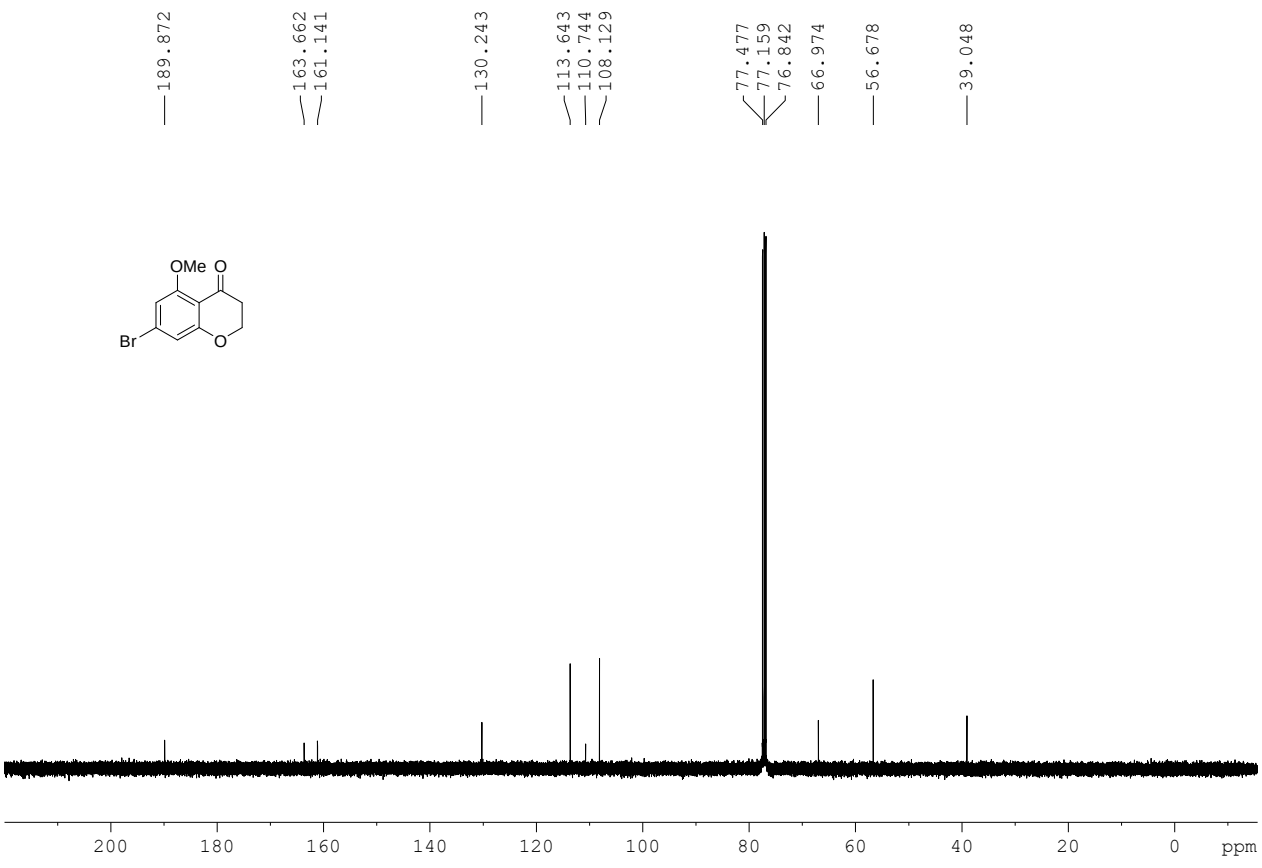


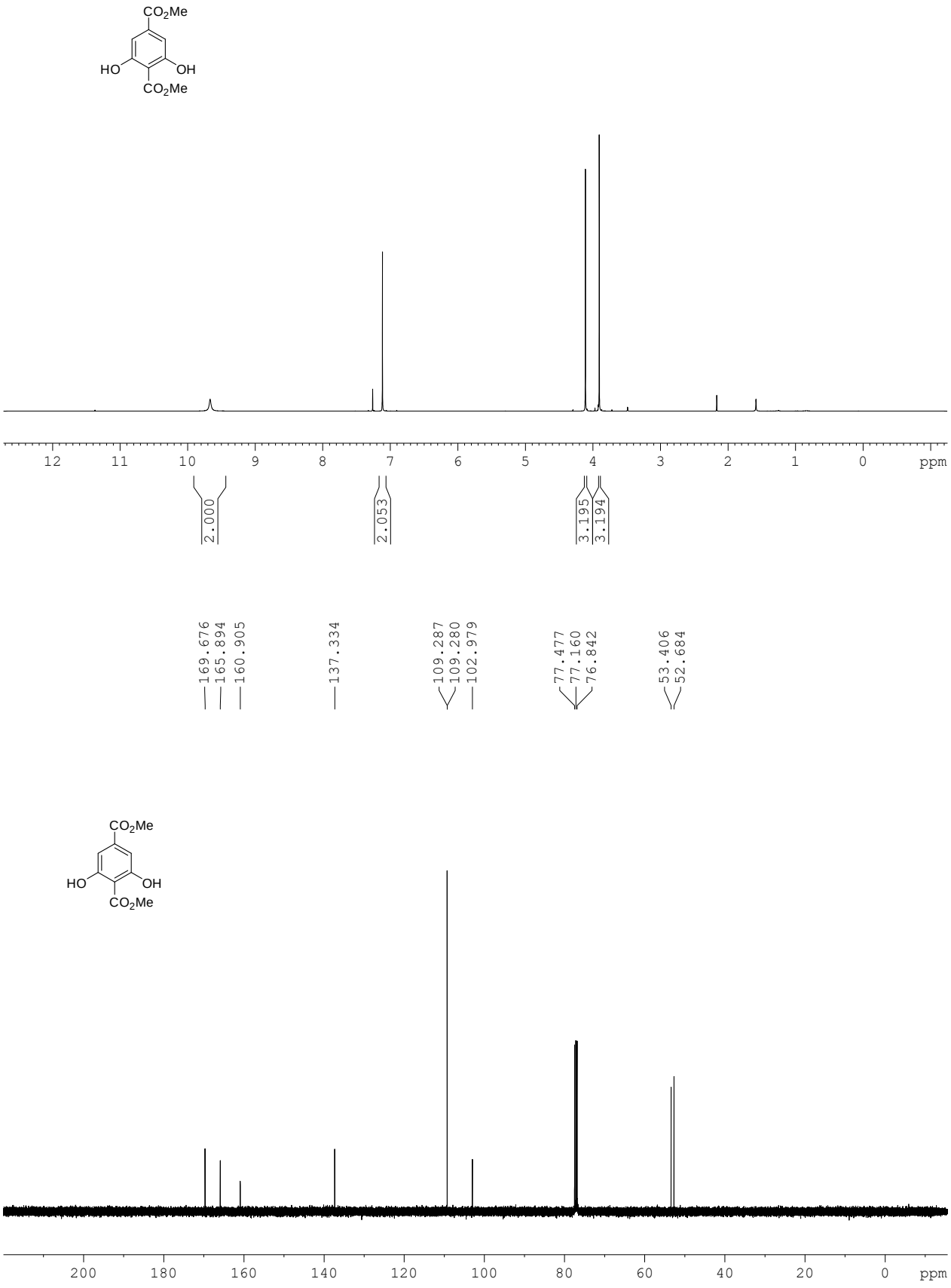

Br
CN
MeO
O
9 8 7 6 5 4 3 2 1 0 -1 ppm
1.000
1.010
1.004
2.238
3.013
2.069
161.455
159.347
123.216
117.016
111.147
110.435
100.670
77.477
77.160
76.842
62.962
55.759
18.674
Br
CN
MeO
O
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

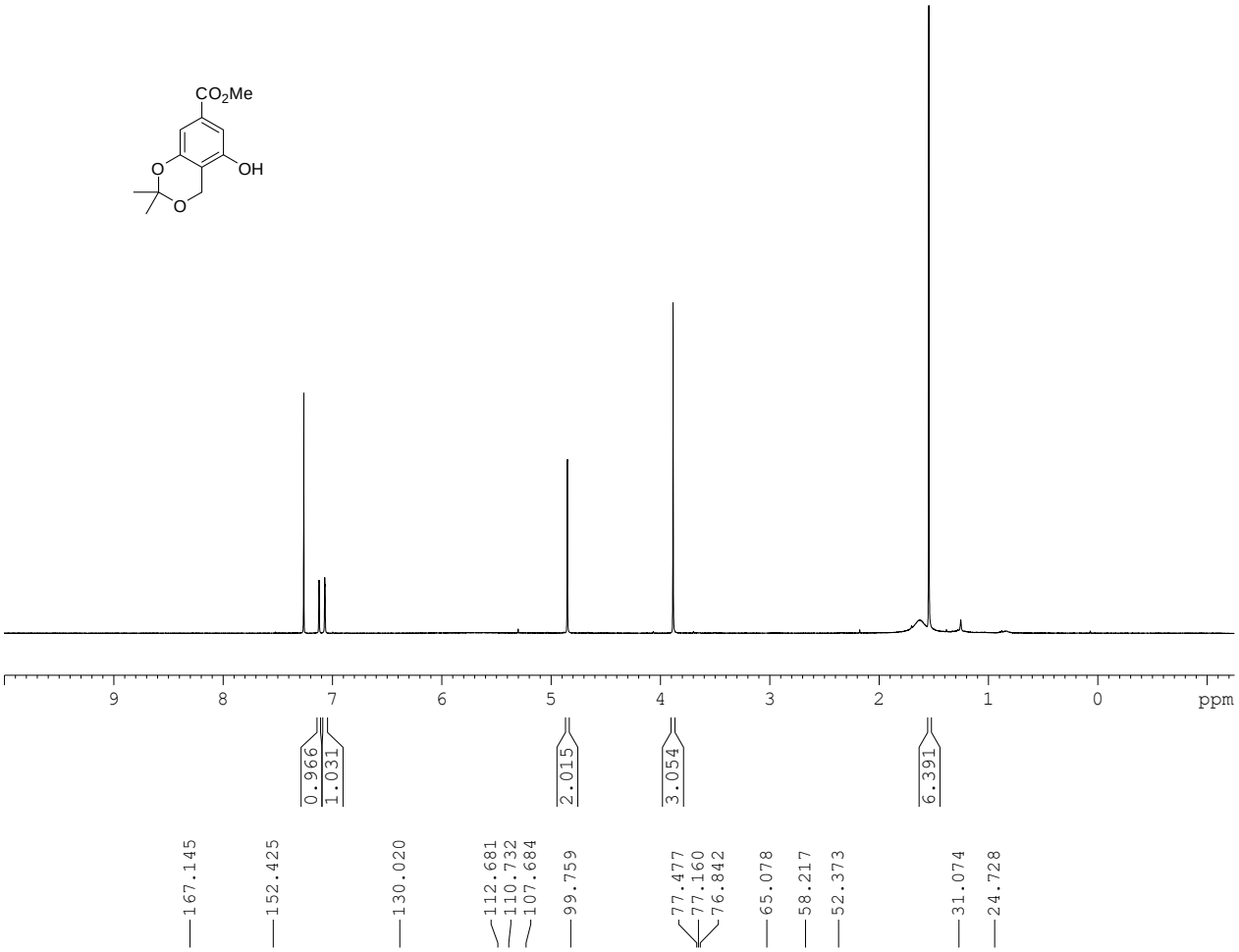

Br
O
MeO
O
9
8
7
6
5
4
3
2
1
0
ppm
1.000
1.032
2.116
3.240
2.141
188.774
164.845
164.265
123.155
116.803
113.578
101.342
77.477
77.160
76.842
66.932
55.946
38.371


Br
O
MeO
O
220
200
180
160
140
120
100
80
60
40
20
0
ppm

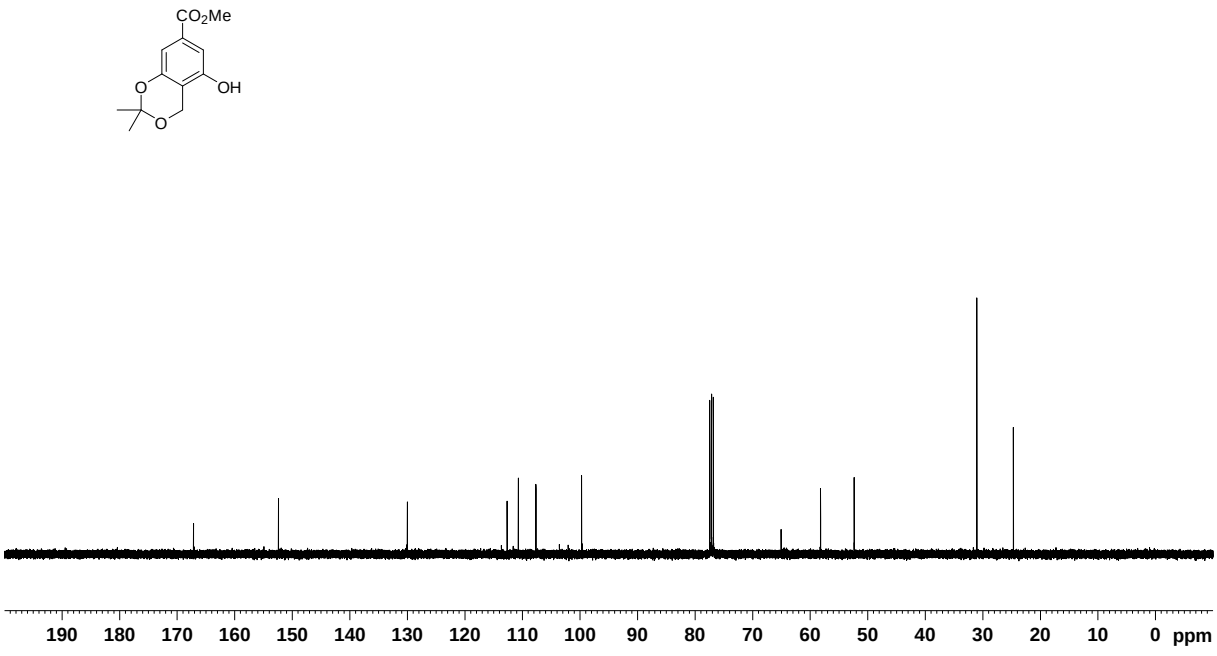

OMe O
Br
O
9
8
7
6
5
4
3
2
1
0
ppm
1.000
1.019
2.227
3.267
2.236

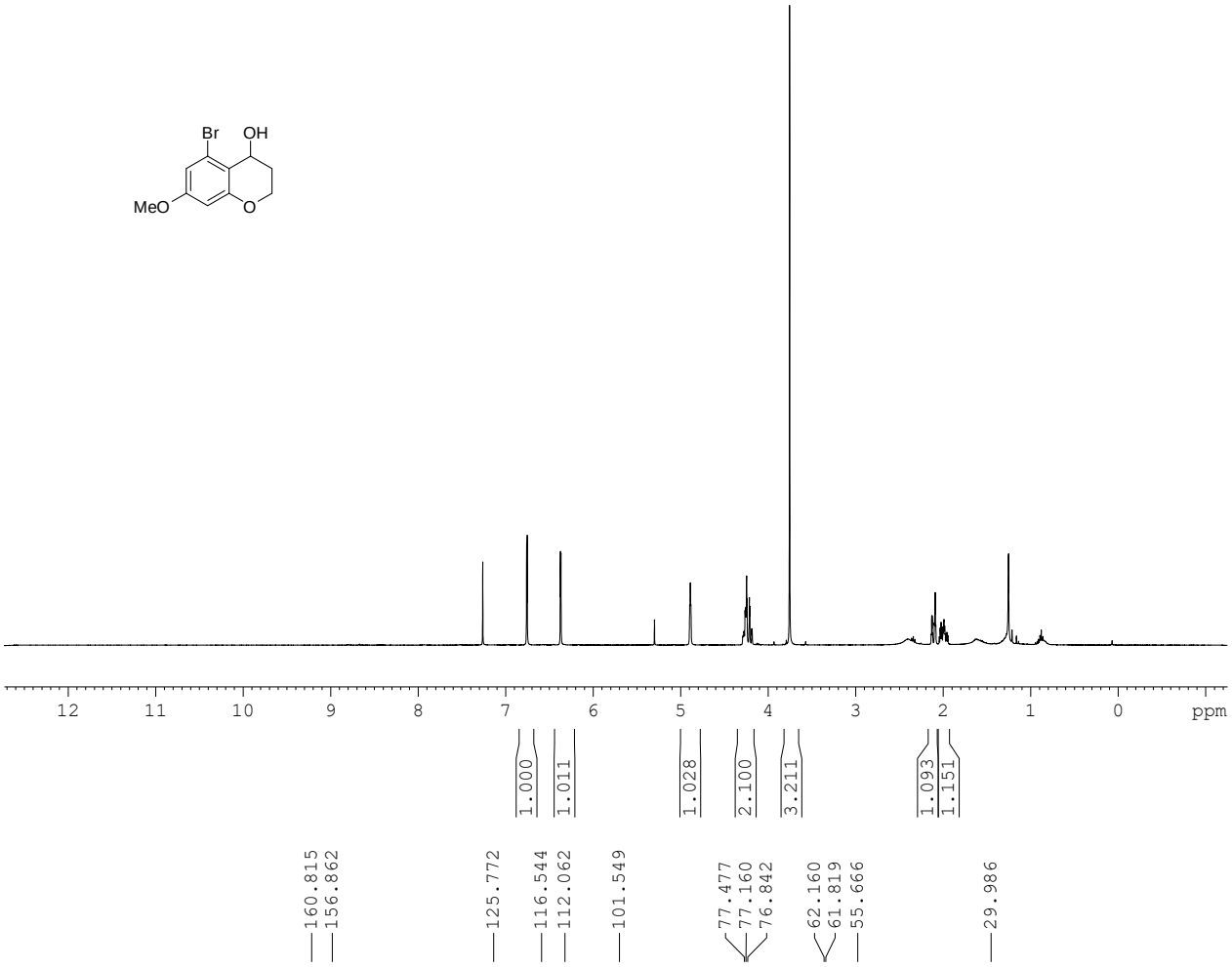

189.872
163.662
161.141
130.243
113.643
110.744
108.129
77.477
77.159
76.842
66.974
56.678
39.048
OMe O
Br
O
200
180
160
140
120
100
80
60
40
20
0
ppm

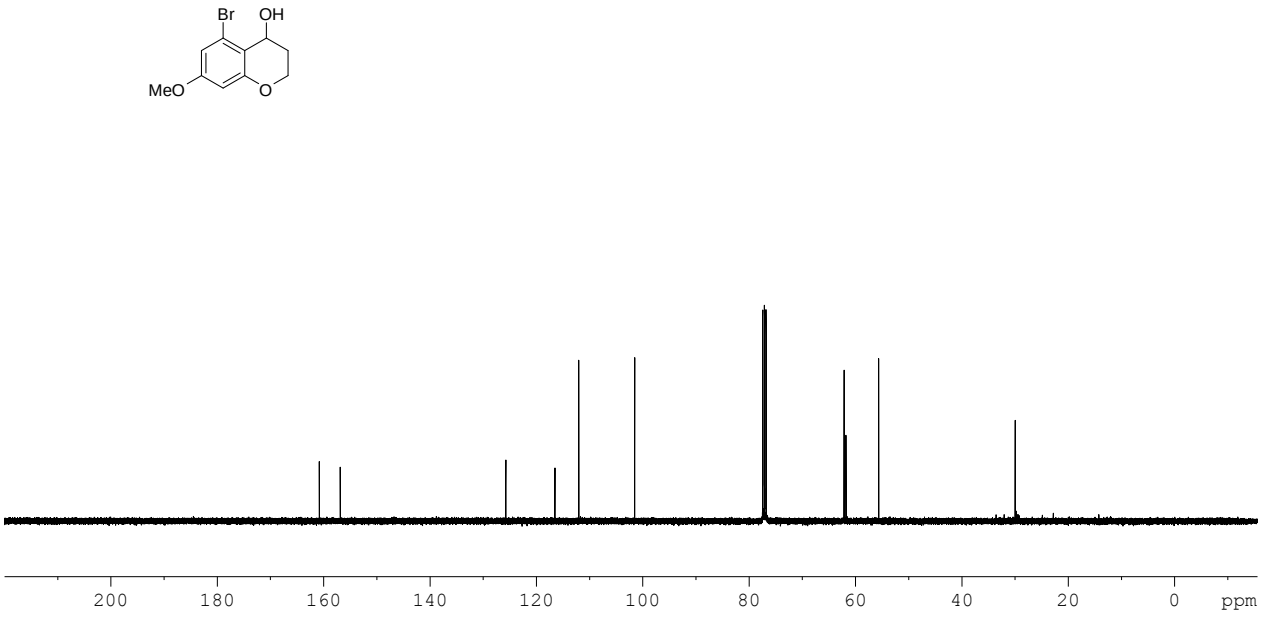

CO2Me
HO
OH
CO2Me
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
2.000
2.053
3.195
3.194
169.676
165.894
160.905
137.334
109.287
109.280
102.979
77.477
77.160
76.842
53.406
52.684
CO2Me
HO
OH
CO2Me
200
180
160
140
120
100
80
60
40
20
0
ppm



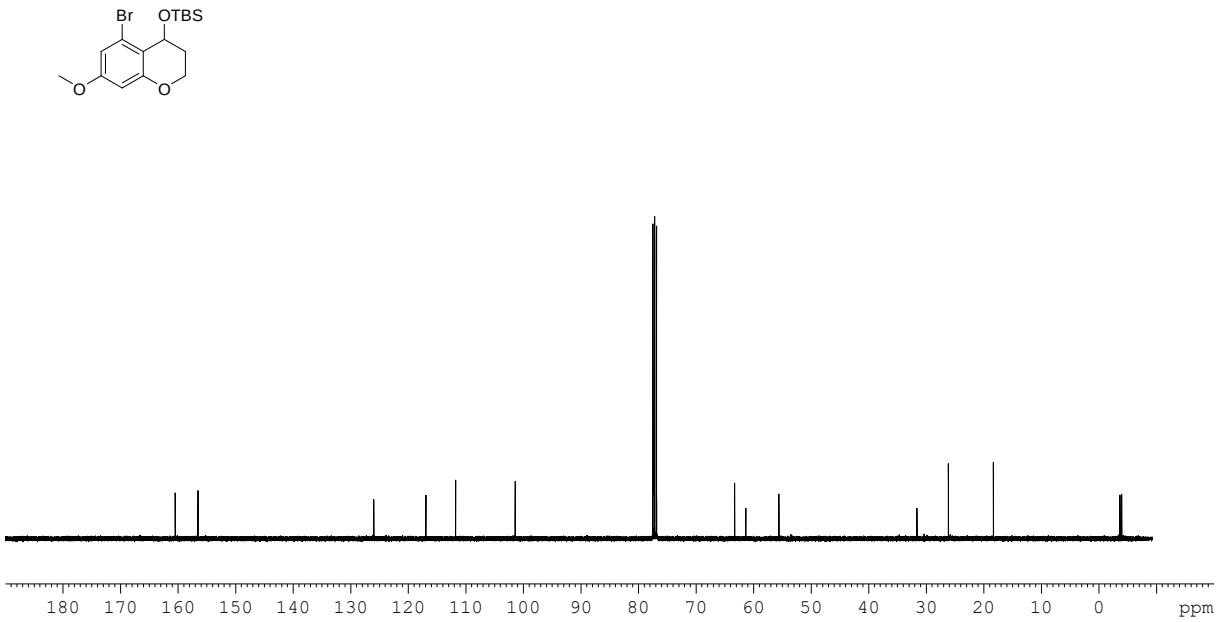
167.145
152.425
130.020
112.681
110.732
107.684
99.759
77.477
77.160
76.842
65.078
58.217
52.373
31.074
24.728

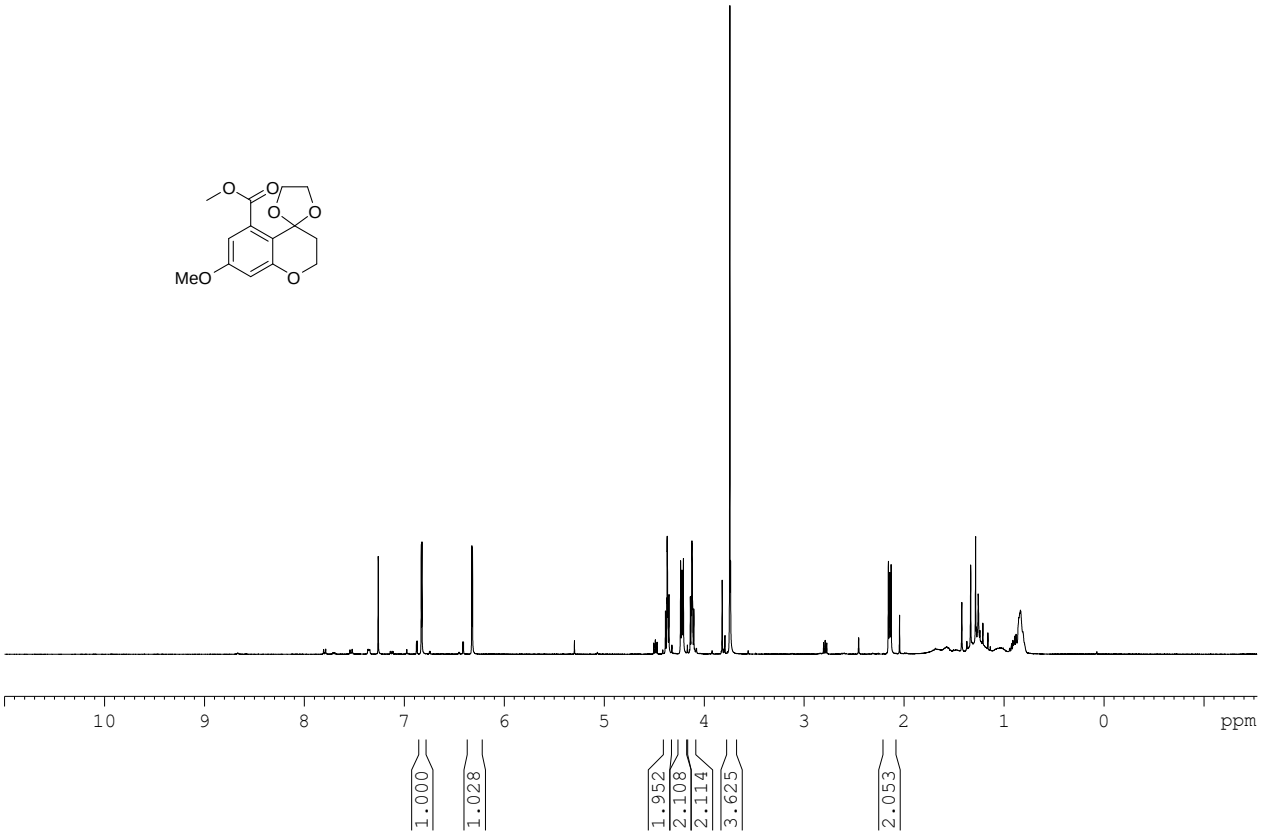


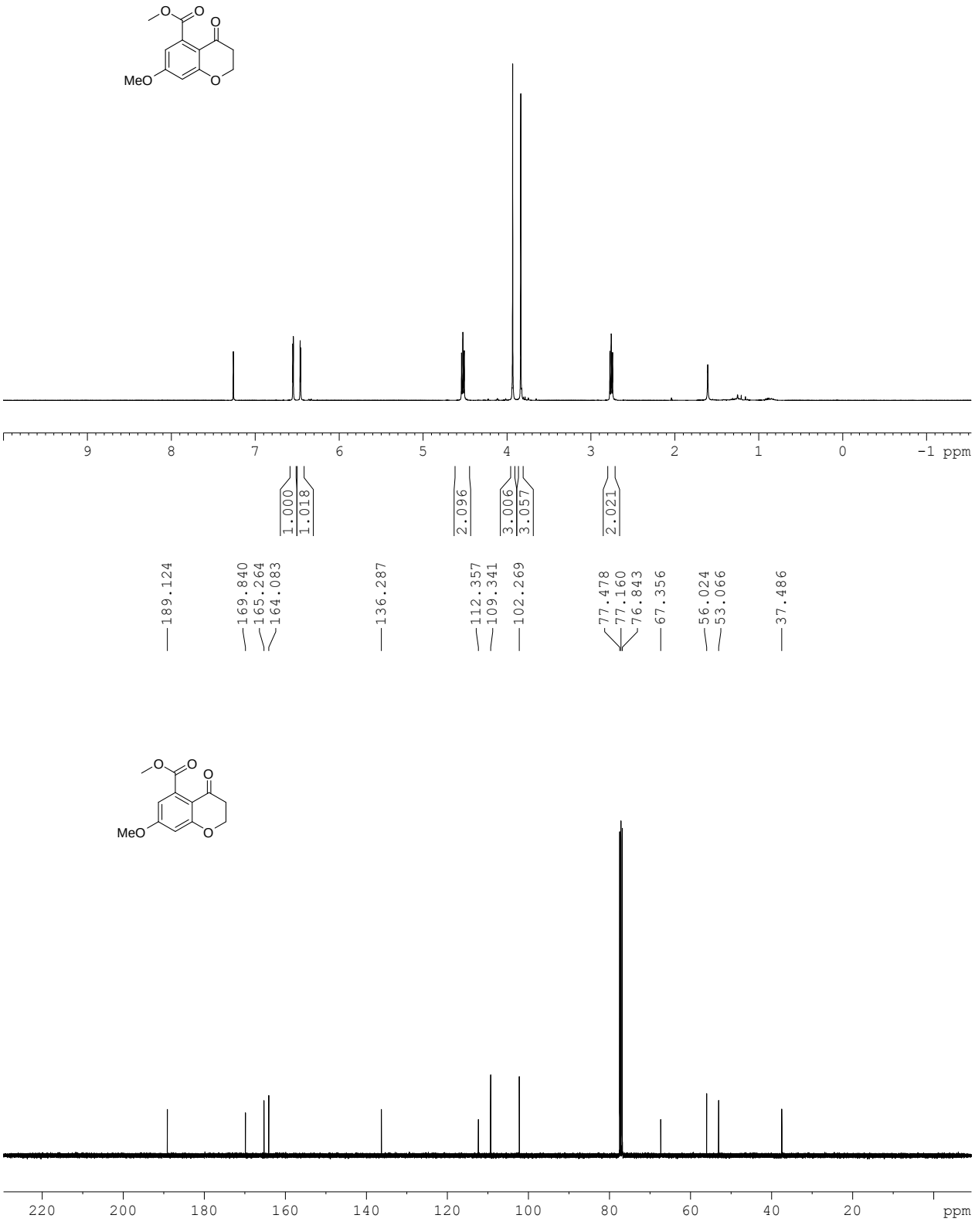

Br
OH
MeO
O
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.000
1.011
1.028
2.100
3.211
1.093
1.151
160.815
156.862
125.772
116.544
112.062
101.549
77.477
77.160
76.842
62.160
61.819
55.666
29.986

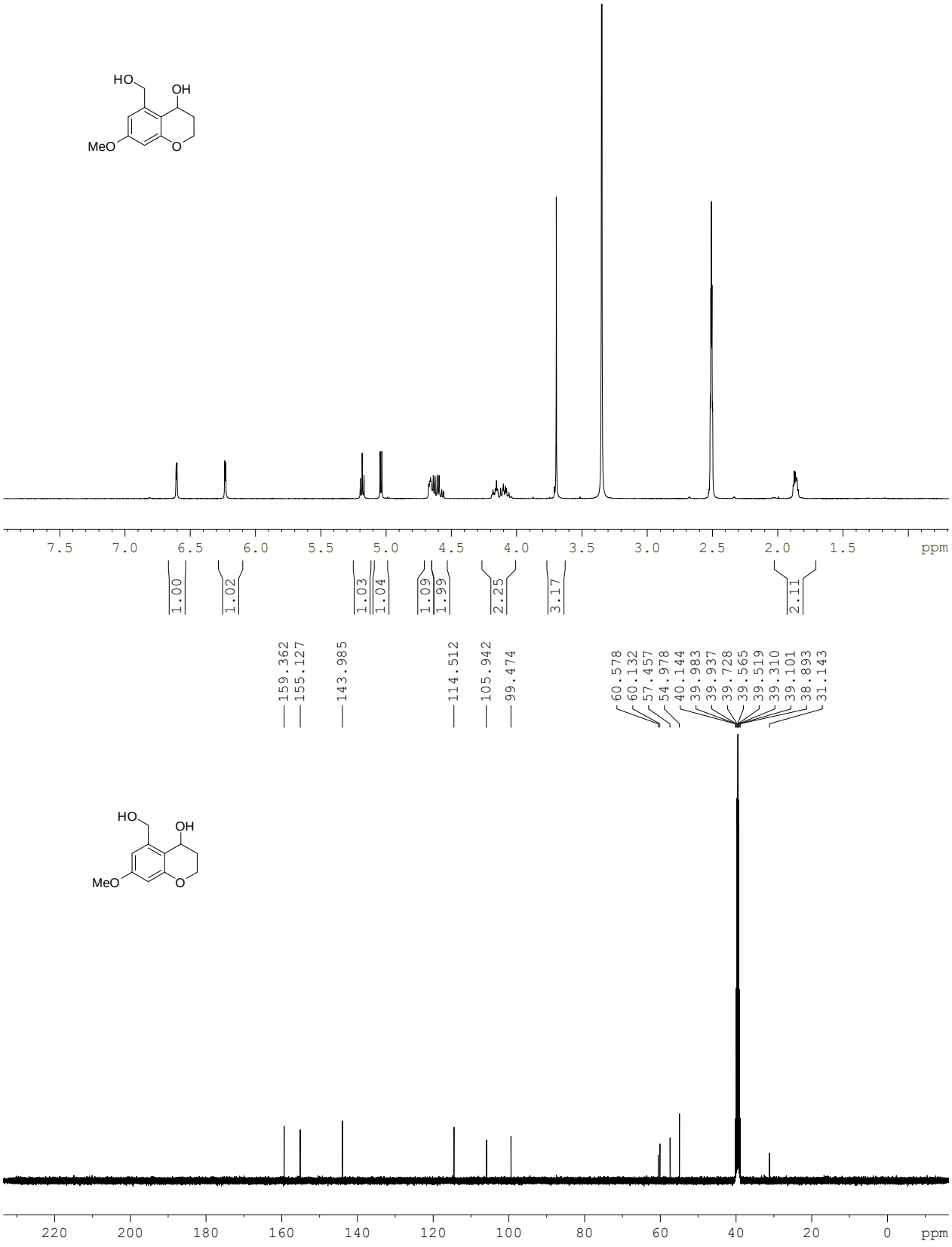

Br
OH
MeO
O
200
180
160
140
120
100
80
60
40
20
0
ppm

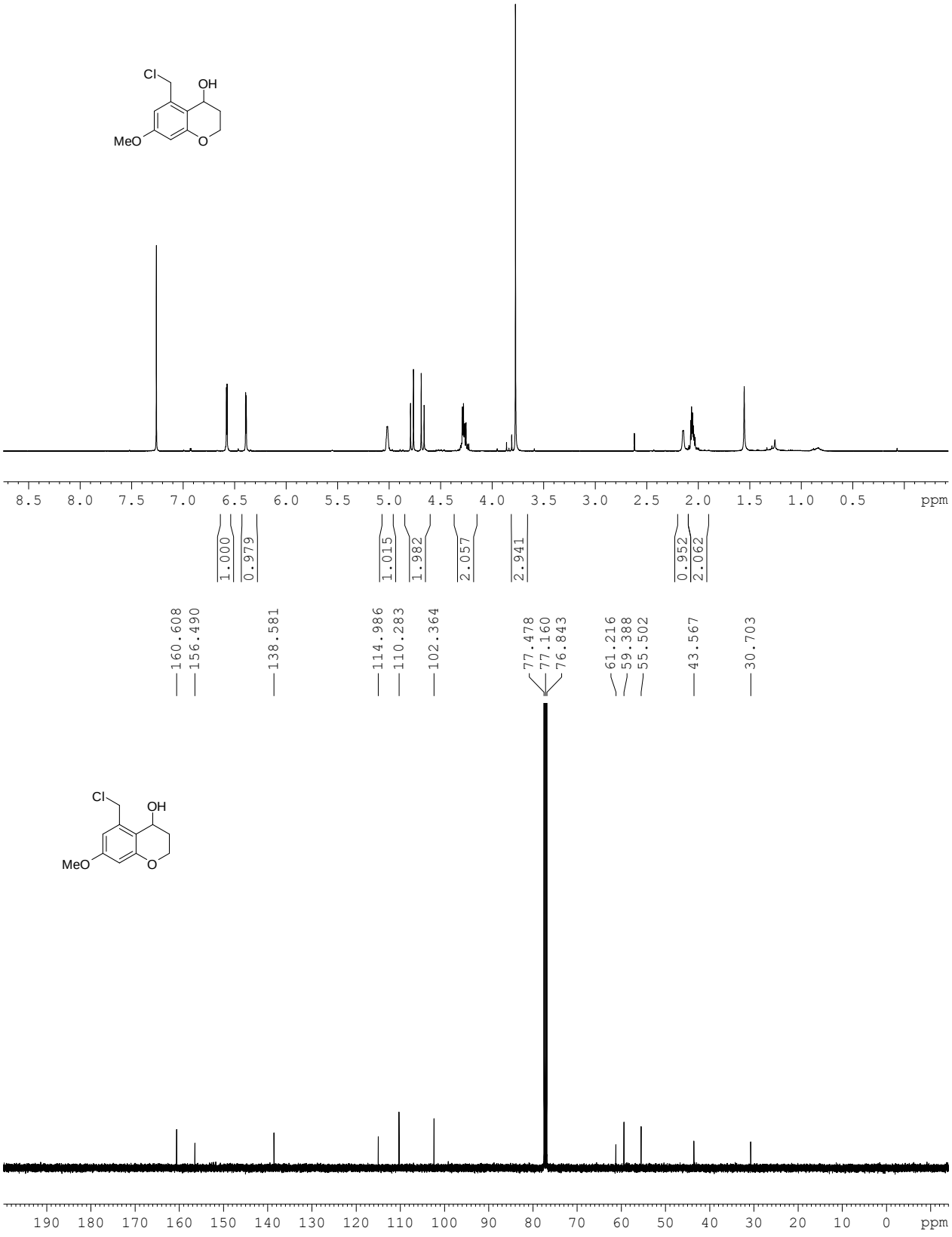

Br
OTBS
O
O
8
7
6
5
4
3
2
1
0
ppm
1.028
1.054
1.003
0.996
1.014
3.000
2.044
9.394
2.645
3.101
160.491
156.532
125.987
116.927
111.752
101.411
77.477
77.160
76.842
63.269
61.326
55.575
31.593
26.120
18.315
-3.697
-3.990

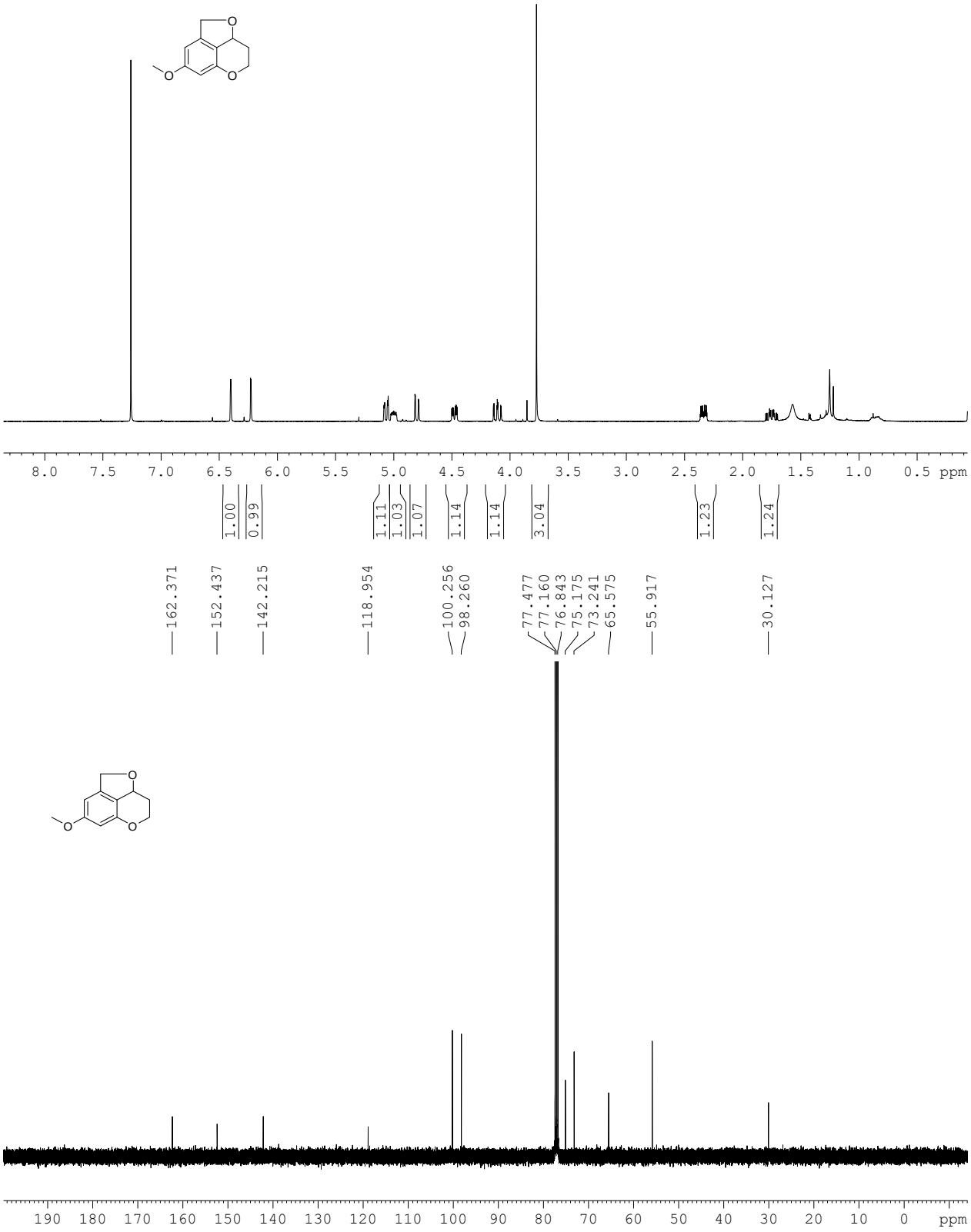

Br
OTBS
O
O
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

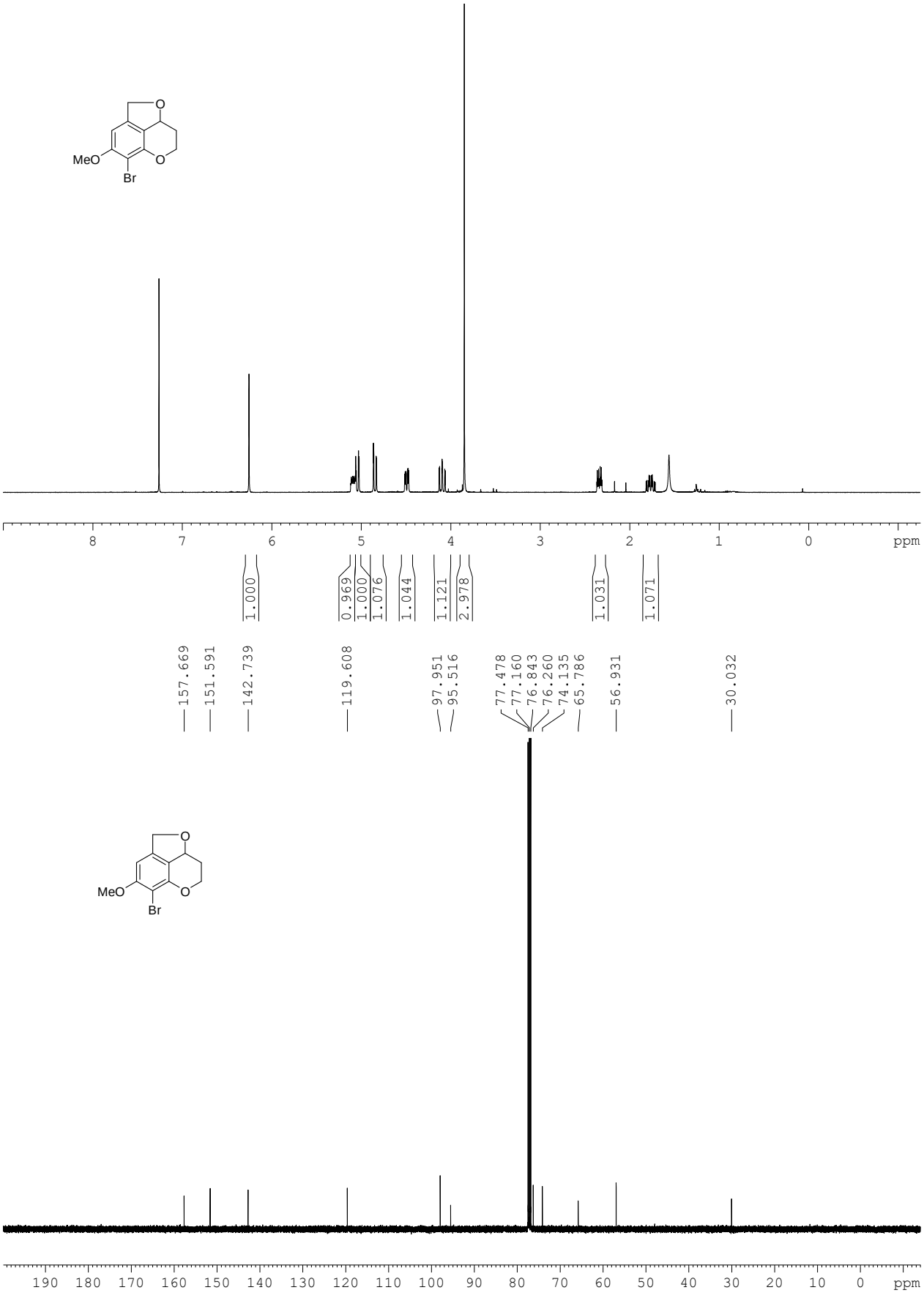

MeO
10
9
8
7
6
5
4
3
2
1
0
ppm
1.000
1.028
1.952
2.108
2.114
3.625
2.053

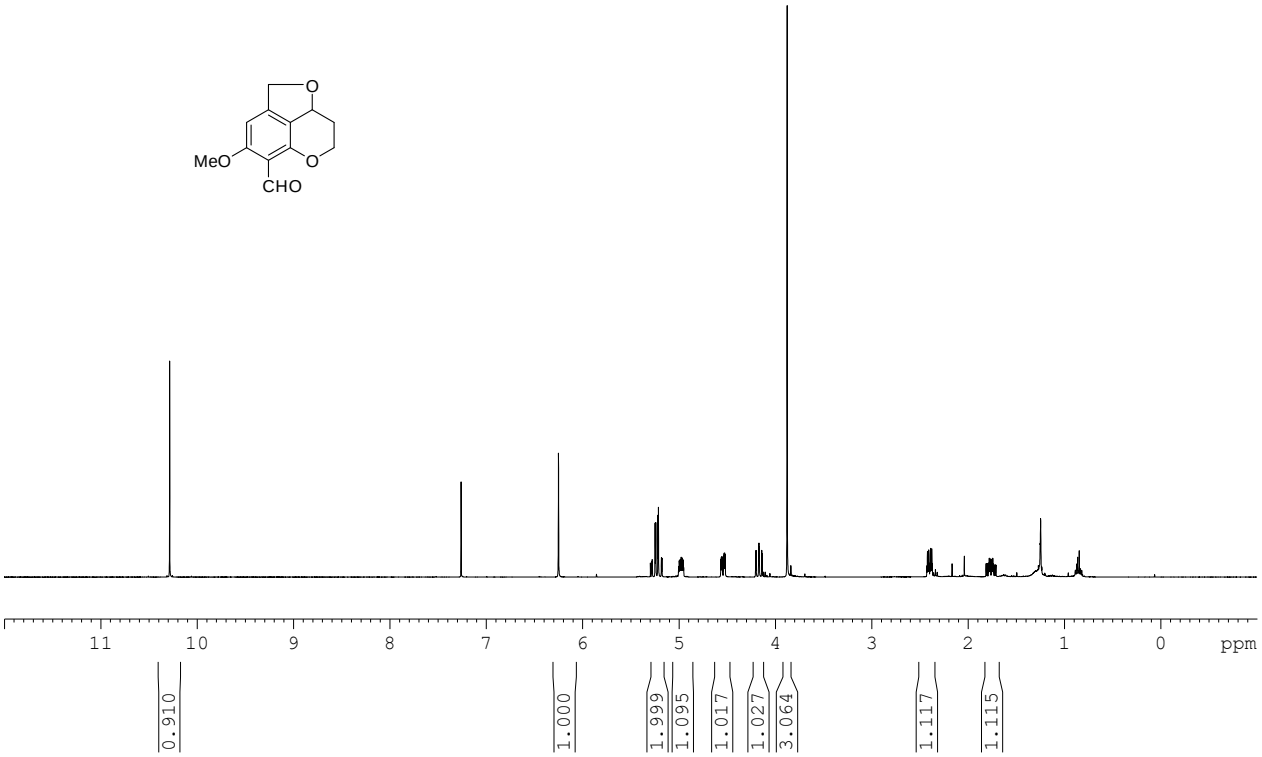

MeO
9
8
7
6
5
4
3
2
1
0
-1 ppm
1.000
1.018
2.096
3.006
3.057
2.021
189.124
169.840
165.264
164.083
136.287
112.357
109.341
102.269
77.478
77.160
76.843
67.356
56.024
53.066
37.486
MeO
220
200
180
160
140
120
100
80
60
40
20
ppm

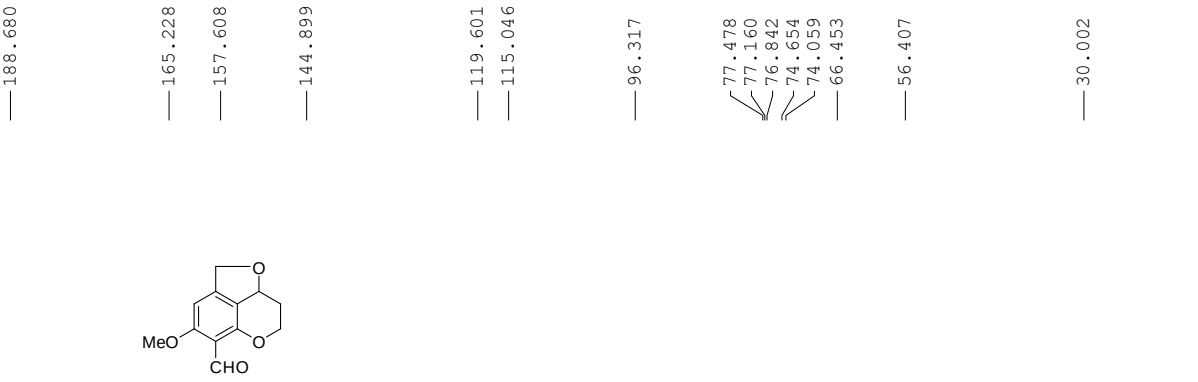

HO
OH
MeO
O
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.00
1.02
1.03
1.04
1.09
1.99
2.25
3.17
2.11
159.362
155.127
143.985
114.512
105.942
99.474
60.578
60.132
57.457
54.978
40.144
39.983
39.937
39.728
39.565
39.519
39.310
39.101
38.893
31.143
220
200
180
160
140
120
100
80
60
40
20
0
ppm

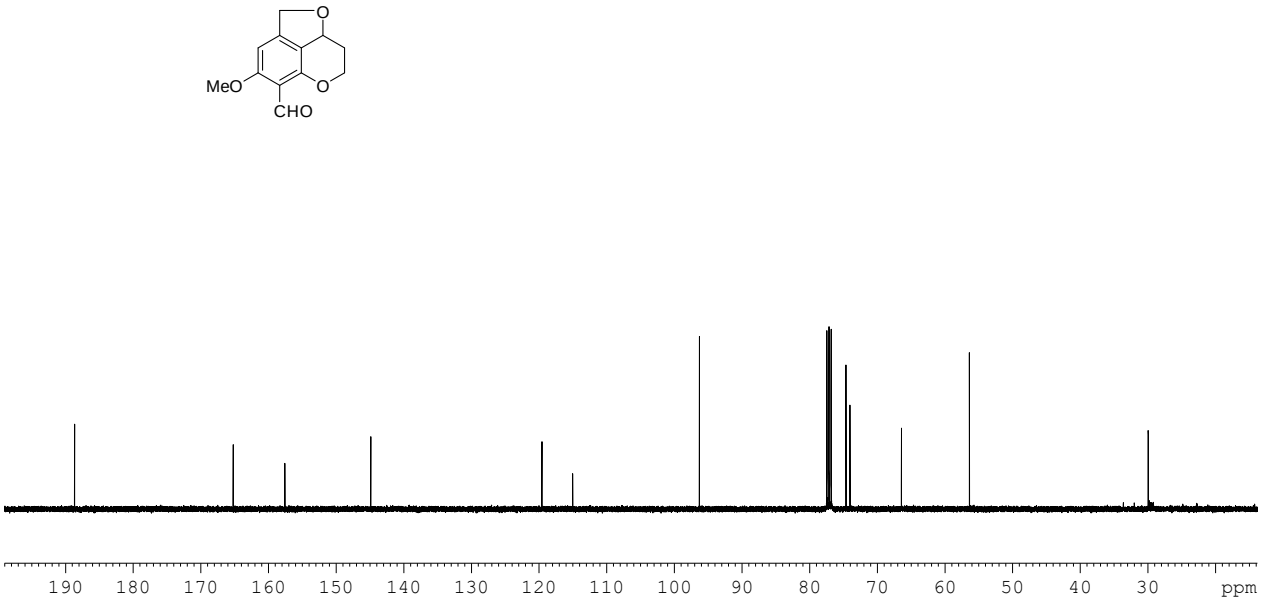

Cl
OH
MeO
O
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.000
0.979
1.015
1.982
2.057
2.941
0.952
2.062
160.608
156.490
138.581
114.986
110.283
102.364
77.478
77.160
76.843
61.216
59.388
55.502
43.567
30.703
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

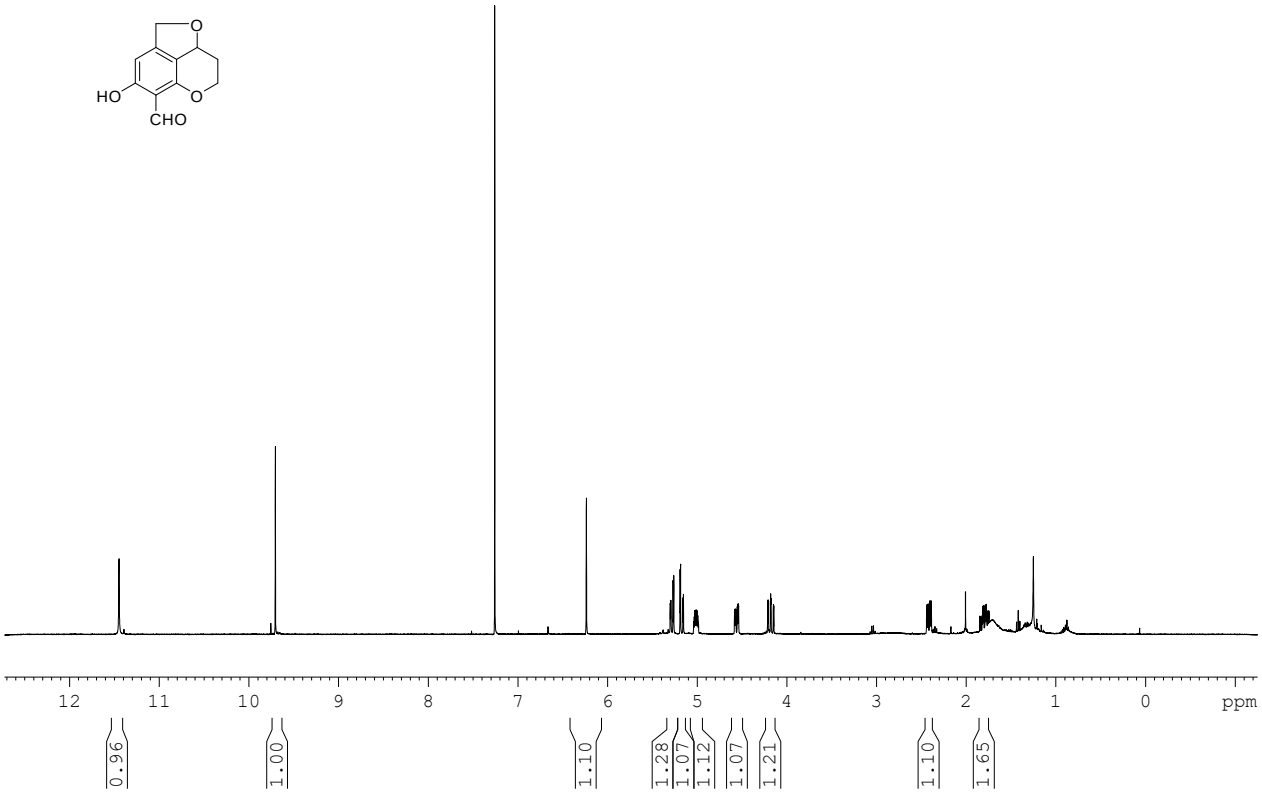

8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
0.99
1.11
1.03
1.07
1.14
1.14
3.04
1.23
1.24
162.371
152.437
142.215
118.954
100.256
98.260
77.477
77.160
76.843
75.175
73.241
65.575
55.917
30.127
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

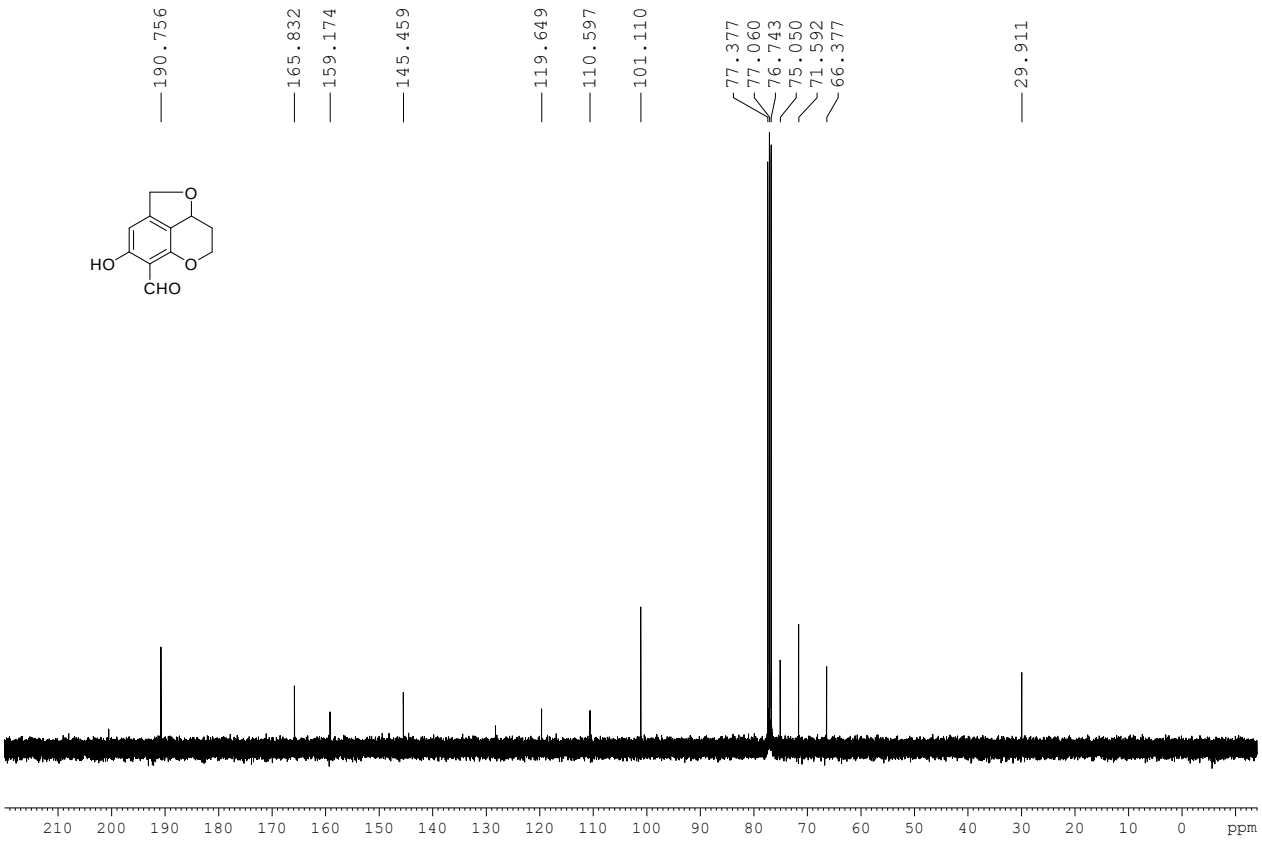

MeO
Br
O
O
8
7
6
5
4
3
2
1
0
ppm
1.000
0.969
1.000
1.076
1.044
1.121
2.978
1.031
1.071
157.669
151.591
142.739
119.608
97.951
95.516
77.478
77.160
76.843
76.260
74.135
65.786
56.931
30.032
MeO
Br
O
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


MeO
CHO
11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.910
1.000
1.999
1.095
1.017
1.027
3.064
1.117
1.115


188.680
165.228
157.608
144.899
119.601
115.046
96.317
77.478
77.160
76.842
74.654
74.059
66.453
56.407
30.002


MeO
CHO
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 ppm


HO
O
O
CHO
12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.96
1.00
1.10
1.28
1.07
1.12
1.07
1.21
1.10
1.65


190.756
165.832
159.174
145.459
119.649
110.597
101.110
77.377
77.060
76.743
75.050
71.592
66.377
29.911
HO
O
O
CHO
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

Curriculum Vitae

Peijun Li
lipeijun0716@gmail.com
Nationality: Chinese
Date and place of birth: 16/07/1986; Xining, China

EDUCATION

07/2015 – 06 /2019 **Ph.D., Leibniz University Hannover**
Hannover, Germany

- Scholarship: HSBDR Scholarship (07/2015-07/2018)
- Projects: **a)** Total synthesis of xenovulene A and sterhirsutins A and B. **b)** Probing the biosynthesis of xenovulene A by chemical synthesis.

09/2007 – 10 /2010 **M. Sc., University of Chinese Academy of Sciences**
Beijing, China

- Scholarship: CAS Graduate Scholarship
- Projects: **a)** Chiral ketones catalyzed asymmetric epoxidation of olefins. **b)** Catalytic oxidative C-H bond amination of arenes under metal-free conditions.

09/2003 – 07 /2007 **B. Sc., Sichuan Normal University**
Chengdu, China

- Bachelor Thesis: Synthesis and evaluation of novel antioxidants and antiozonants for polymeric materials.

PROFESSIONAL EXPERIENCE

01/2011 – 12 /2014 Scientist, **Pharmaron, Inc. & Institute of Chemistry, CAS**
Beijing, China

- Project: Scalable synthesis of biologically active compounds: (+)-ambrisentan and (-)-clausenamide.
- Development and optimization of synthesis processes.
- Supervision of lab courses and thesis of bachelor and master students.

PUBLICATION

- P.-J. Li, G. Draeger and A. Kirschning*. A Biomimetic Hetero-Diels–Alder Approach to the Core Skeletons of Xenovulene A and the Sterhirsutins A and B. *Organic Letters*, **2019**, *21*, 998-1001.