Studies on the Natural Products (±)-Lingzhiol and Gulmirecin B

Studien zur Synthese der Naturstoffe (±)-Lingzhiol und Gulmirecin B

Dissertation

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To my parents

என்றும் என் இதயத்தில்...

"If you fail, never give up because F.A.I.L means *First Attempt In Learning*"

Dr. A.P.J. Abdul Kalam.

Publications:

"Total Synthesis of Lingzhiol and its Analogues through Wittig Reaction of an Oxocyclopentane Carboxylate"
Rengarasu, R.; Maier, M. E. *Asian J. Org. Chem*. **2017**, *6*, 108–117.

"Synthesis of a C1–C12 Fragment of Gulmirecin B"
Rengarasu, R.; Maier, M. E. *Manuscript accepted in Synlett.*

Poster presentation:

"Towards the total synthesis of Gulmirecin B"
43th International Summer School on Organic Synthesis, 11 June, **2018** at Gargnano, Italy.

"Towards the total synthesis of Gulmirecin B"
18th Tetrahedron Symposium on 26-30 June, **2017** at Budapest, Hungary.

"Total synthesis of (±)-Lingzhiol"
15th Belgian Organic Synthesis Symposium (BOSS) on 10-16 July, **2016** at Antwerp, Belgium.

Other Publications:

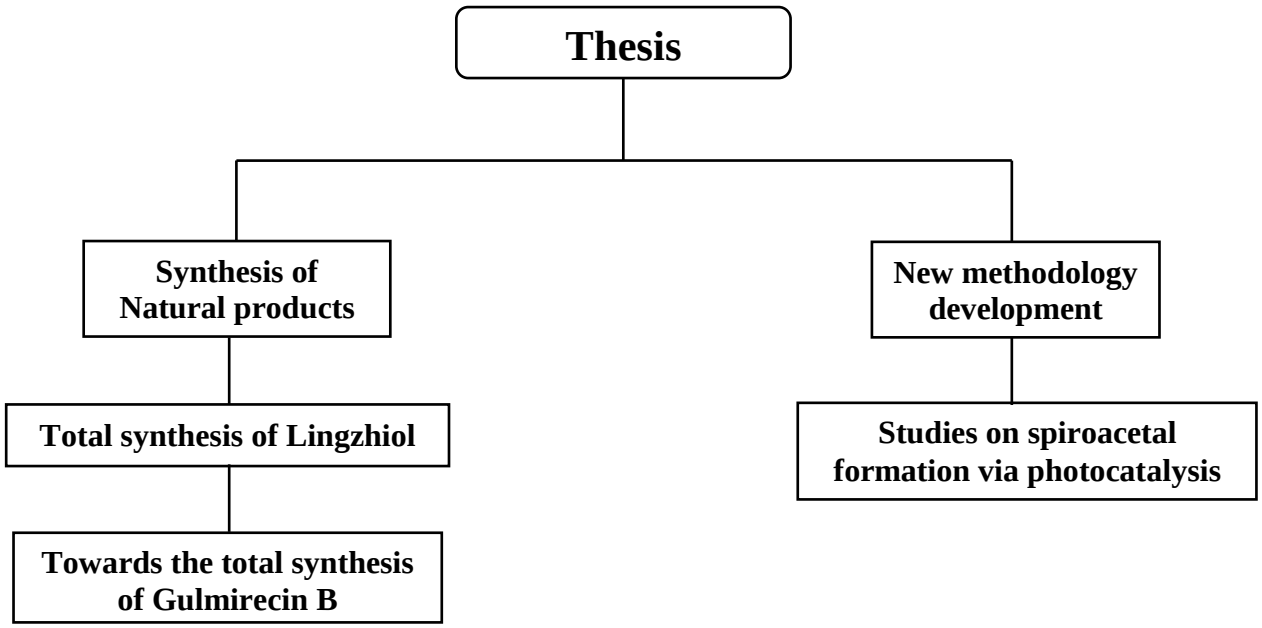
"Synthetic strategies for preparation of cyclen-based MRI contrast agents"
Cakić, N.; Gündüz, S.; Rengarasu, R.; Angelovski, G. *Tetrahedron Letters* **2015**, *56*, 759–765.

"Synthesis of 3,5-diaryl substituted indole derivatives and its selective iodide ion"
Rathikrishnan, K. R.; Indirapriyadharshini, V. K.; Ramakrishna, S.; Murugan, R. *Spectrochim. Acta A* **2012**, *86*, 640–644.

"4,7-Diaryl indole based fluorescent chemosensor for iodide ions"
Rathikrishnan, K. R.; Indirapriyadharshini, V. K.; Ramakrishna, S.; Murugan, R. *Tetrahedron* **2011**, *67*, 4025–4030.

Abstract (English)

This thesis contains several independent projects, covering two aspects of organic chemistry: natural product synthesis and investigation of new synthetic methodology. The first chapter contains the total synthesis of (±)-Lingzhiol, derivatives and their biological evaluation. The second chapter describes efforts towards the total synthesis of Gulmirecin B. The third chapter is about Spiroacetal formation by photocatalysis.



Chapter I:

Lingzhiol has an inhibitory effect on TGF-β-1 mediated Smad3 phosphorylation which is playing the main role in chronic kidney disease and diabetic problems. Besides biological activity, the structure of lingzhiol has a tetracyclic ring system and two consecutive quaternary carbons which are rather unusual. All this features attracted us to develop a synthesis for the polycyclic natural product (±)-Lingzhiol. The key steps consist of a Wittig olefination, an epoxide formation, intramolecular epoxide opening, and a benzylic oxidation.

Chapter II:

Gulmirecin A and B were isolated from the predatory bacterium *Pyxidicoccus fallax* HKI 727. They have strong activity against *Staphylococcus* species. Structurally, the gulmirecins are 12-membered macrolactones containing four stereocentres, two trisubstituted double bonds, and an α-arabinofuranose moiety attached at the C-7 position. All these features attracted us to the synthesis of Gulmirecin B.

The key intermediate C8-C12 was prepared from L-malic acid. The C1-C7 aldehyde building block was synthesized from hexenoic acid using an Evans alkylation, a cross metathesis, and an asymmetric dihydroxylation as key steps.

Chapter III:

Here we studied a method for spiroacetal formation via photocatalysis under blue LED irradiation. Different synthetic approaches to spiroacetal formation have been reported in the literature. However, the visible light induced spiroacetal formation via an alkoxy radical is unknown. Therefore, we decided to investigate such transformations via alkoxy radical generation using hypervalent iodine(III) reagents under photochemical conditions. The starting material was prepared by Swern oxidation, Horner-Wadsworth-Emmons reaction, and hydrogenation as key reactions.

Abstract (German)

Kapitel I:

Lingzhiol zeichnet sich durch eine hemmende Wirkung auf die durch TGF-β-1 vermittelte Smad3-Phosphorylierung aus, die eine Hauptrolle bei chronischen Nierenerkrankungen sowie bei Diabetes spielt. Neben der interessanten biologischen Aktivität weist Lingzhiol eine beachtenswerte Struktur auf. Lingzhiol hat ein tetracyclisches Ringsystem und zwei aufeinanderfolgende quaternäre Kohlenstoffzentren, welche eher als ungewöhnlich anzusehen sind. All diese Eigenschaften haben uns motiviert, eine Synthese für das polycyclische Naturprodukt von (±)-Lingzhiol zu entwickeln. Die entscheidenden Schritte dieser Synthese umfassen dabei eine Wittig-Olefinierung, eine Epoxidbildung, eine intramolekulare Epoxidöffnung sowie benzylische Oxidation.

Kapitel II:

Gulmirecin A und B wurden aus dem räuberischen Bakterium *Pyxidicoccus fallax* HKI 727 isoliert. Sie weisen eine starke Aktivität gegen *Staphylococcus*-Erreger auf. Strukturell handelt es sich bei den Gulmirecinen um 12-gliedrige Makrolactone, die vier Stereozentren, zwei trisubstituierte Doppelbindungen und einen α-Arabinofuranose-Rest an der C-7-Position enthalten. Diese strukturelle Eigenschaften machen die Gulmirecine zu interessanten Zielen für die Totalsynthese. Das Schlüsselintermediat C8-C12 wurde aus L-Äpfelsäure hergestellt. Der C1-C7-Aldehyd-Baustein wiederrum wurde aus Hexensäure unter Verwendung einer Evans-Alkylierung, einer Kreuzmetathese sowie einer asymmetrischen Dihydroxylierung als Schlüsselschritte synthetisiert.

Kapitel III:

Im Rahmen dieser Arbeit wurde eine neue Methode zur Synthese von Spiroacetalverbindungen durch Photokatalyse unter Bestrahlung mittels blauer LED-Lampen untersucht. In der Literatur wurden bereits verschiedene synthetische Ansätze zur Spiroacetal-Bildung beschrieben. Die durch sichtbares Licht induzierten Spiroacetal-synthesen über ein Alkoxy-Radikal sind allerdings bis heute unbekannt. Daher haben wir uns entschlossen, eine solche Umwandlung mittels Alkoxylradikalbildung unter Verwendung hypervalenter Iod(III)-Reagenzien unter photochemischen Bedingungen zu untersuchen. Das Ausgangsmaterial wurde mittels Swern-Oxidation, Wittig-Horner-Reaktion sowie einer Hydrierung als Schlüsselreaktion dargestellt .

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Chapter: II Synthesis of a C1-C12 Fragment of Gulmirecin B

Abbreviations

Ar	Aromatic
AcOH	Acetic acid
AD	Asymmetric dihydroxylation
abs	absolute
aq	aqueous
Ac	Acetyl
AIBN	Azobisisobutyronitrile
BPO	Dibenzoylperoxid
Bn	Benzyl
br	broad
con.	concentration
Cy	Cyclohexyl
°C	Temperature
COSY	Correlation Spectroscopy
COX	Cyclooxygenase
DMP	Dess-Martin periodinane
DMSO	Dimethylsulfoxide
DCM	Dichloromethane
DCE	Dichloroethane
DMF	*N*,*N*-Dimethylformamide
DMAP	4-Dimethylaminopyridine
DIBAL-H	Diisobutylaluminium hydride
DEPT	Distortionless Enhancement by Polarization Transfer
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIPEA	*N*,*N*-Diisopropylethylamine
dr	Diastereomeric ratio
de	Diastereomeric excess
d	Doublet (NMR)
ECM	Extracellular matrix
EC_{50}	Half maximal effective concentration
E	trans
ESI	Electronspray ionization

Et	Ethyl
eq	equivalents
ee	Enantiomeric excess
EtOAc	Ethyl acetate
EDCl	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
g	gram
Hex.	Hexane
HMPA	Hexamethylphosphoramide
h	hour(s)
HPLC	High perform liquid chromatography
HRMS	High-resolution mass spectrometry
HMBC	Heteronuclear Multiple Bond Correlation
IBX	2-Iodoxybenzoic acid
IC_{50}	Half maximal inhibitory concentration
J	coupling constant
KHMDS	Potassium bis(trimethylsilyl)amide
L	Liter(s)
LA	Lewis acid
LED	Light-emitting diode
MCP	Monocyte chemoattractant protein
m/z	Mass to charge ratio (MS)
m	Multiplet (NMR)
m-CPBA	*meta*-Chloroperbenzoic acid
Me	Methyl
MeOH	Methanol
mg	milligram
MVK	Methyl vinyl ketone
MeCN	Acetonitrile
MOMCl	Methoxymethyl chloride
MTMCl	Methylthiomethyl chloride
MLCT	Metal to ligand charge transfer
Nrf_2	Nuclear factor erythroid 2
NOE	Nuclear Overhauser effect
NBS	*N*-Bromosuccinimide
NHPI	*N*-hydroxyphthalimide

NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
OD	optical density
P	Protecting group
Ph	Phenyl
*p*TSA	*para*-Toluenesulfonic acid
Pyr	Pyridine
PE	Petroleum ether
PCC	Pyridinium chlorochromate
PMB	*para*-Methoxybenzyl
$PhNTf_2$	*N*-Phenyl-bis(trifluoromethanesulfonimide)
q	Quartet (NMR)
ROS	Reactive oxygen species
R_f	Retention factor (TLC)
r.t.	room temperature
s	Singlet (NMR)
SEM	2-(Trimethylsilyl)ethoxymethyl chloride
TBHB	*tert*-Butyl hydroperoxide
TMG	1,1,3,3-Tetramethylguanidine
t	Triplet (NMR)
TBS	*tert*-Butyldimethylsilyl
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
Tf_2O	Trifluoromethanesulfonic anhydride
TMS	Trimethylsilyl
TFA	Trifluoroacetic acid
TrCl	Triphenylmethyl chloride
TFAA	Trifluoroacetic anhydride
TBAF	Tetra-*n*-butylammonium fluoride
z	cis
δ	Chemical shift in ppm (NMR)

Chapter I

Total Synthesis of Lingzhiol and its Analogues through Wittig Reaction of an Oxocyclopentane Carboxylate

Asian J. Org. Chem. **2017**, 6, 108–117

1. Introduction

Bacteria and fungus are vast sources of biologically active compounds. They played a vital role in the development of modern medicines. Fungi have been used widely in East Asian medicine for a range of human disease conditions such as diabetics, chronic kidney problems, stomach ulcers, liver rot, and hypertension etc. A mushroom, named *Ganoderma lucidum,* has been used in Chinese medicine to prevent diabetic and kidney diseases. Most of the fungi are growing on woody plants, sawdust, grain and wood logs (**Figure 1**). More than 450 species of Ganoderma were recorded in the Chinese Pharmacopoeia. Particularly, the *Ganoderma lucidum* and *Ganoderma sinense* were listed as most beneficial fungus. Ganoderma species are rich sources of terpenoids. Most of the isolated terpenoids from them belong to meroterpenoids, which contain polycyclic substructures and polyunsaturated side chains.

Figure 1. Naturally occurring mushroom in wood logs.

Ganoderma meroterpenoids can be classified on the basis of chemical structures into three types[1]

1. Monocyclic with exocyclic chain

For examples: Fornicin D, Cochlearin H, Ganoleucin B etc.

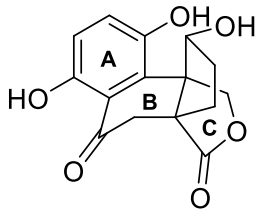
2. Polycyclic meroterpenoids

For examples: Lingzhine C, Lingzhiol, Spiroaplanatumine D etc.

3. Dimeric meroterpenoids

For examples: Sinensilactam A, (±)-Ganoapplanin etc.

Based on medicinal utility, the group of Cheng extracted Lingzhiol from the naturally available *Ganoderma lucidum.*[2] The extraction of 80 kg of the dried mushroom yielded 50 mg of racemic Lingzhiol (**1-1**). The enantiomers were separated using chiral HPLC, which provided pure enantiomers (–)-Lingzhiol and (+)-Lingzhiol (**1-1**). The isolated lingzhiol consists of an aromatic part and a terpene part. Structurally, lingzhiol has two phenolic groups, a tetracyclic ring system and two vicinal quaternary centers (**Figure 2**).



(±)-Lingzhiol (**1-1**)

Figure 2. Structure of (±)-Lingzhiol (**1-1**).

1.1 Monocyclic meroterpenoids with exocyclic chain

This kind of *Ganoderma* meroterpenoids has double bonds in the side chain. Due to that, redox reactions can take place at the allylic positions. For example, Fornicin D (**1-2**) and derivatives of Cochlearin H, G (**1-3**, **1-5**), and Ganomycin E (**1-8**) display significant antioxidant activity.[3] The compound Chizhine D (**1-4**) was isolated from *Ganoderma lucidum* and has shown a weak renoprotective effect.[4] Ganoleucin B (**1-6**) was isolated from *Ganoderma leuocontextum* and it does not show any inhibitory activities against COX-1, COX-2, HMG.[5] However, Ganomycin J (**1-7**) has shown strong inhibitory activity against HMG-CoA reductase with an IC_{50} value of 30.3 μM. The compounds (+)-Chizhine E and F (**1-10**, **1-9**) were isolated from *Ganoderma lucidum* and individual enantiomers have shown inhibitory effect on monocyte chemoattractant protein-1(MCP-1)[4](**Figure 3**).

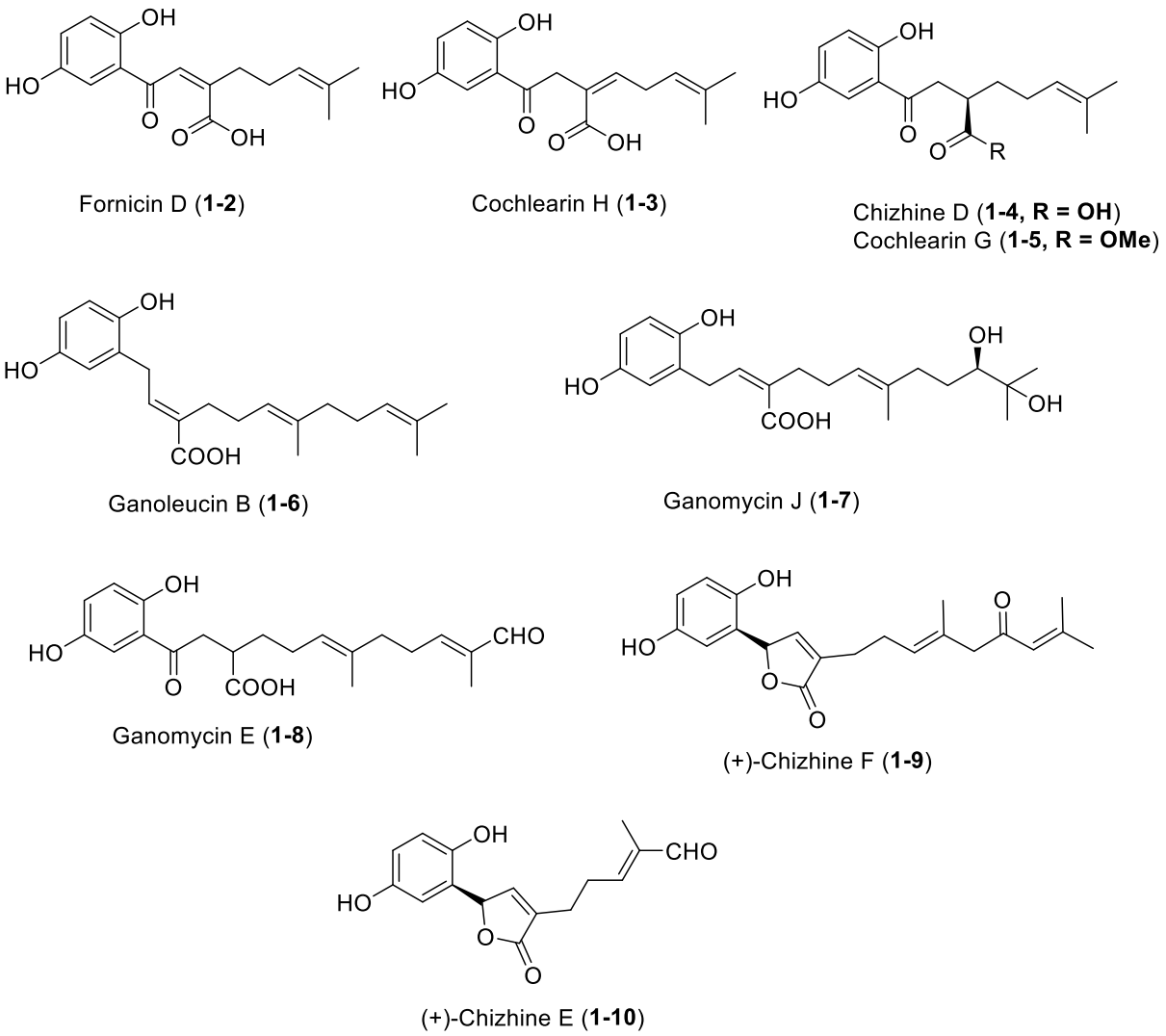


Figure 3. Structures of *Ganoderma* meroterpenoids with side chain.

1.2 Polycyclic meroterpenoids

These compounds have a polyunsaturated terpenoid part. It is supposed that free radical reactions driven by enzymes (or) light, lead to the formation of polycyclic structures (**Figure 4**). Lingzhine C (**1-11**) and (±)-Lingzhine B (**1-12**) were found to be potentially active against proliferation of neural stem cells (NSCs).[6] Furthermore, most of these *Ganoderma* meroterpenoids were found be inactive against COX-2 in vitro studies, but only (+)-Ganotheaecoloid J (**1-13**) had shown COX-2 inhibitory activity.[7] Biological evaluation of (+)-Cochlearin A (**1-14**) has shown a free radical scavenging activity.[8] The spiroaplanatumines D, F (**1-15**, **1-16**) were found to be JAK3 kinase inhibitores.[9]

Both enantiomers of (+)-Lingzhiol and (–)-Lingzhiol (**1-1**) have shown an inhibiting effect on TGF-β1-mediated Smad3 phosphorylation.[2] Cochlearol B (**1-17**), a novel meroterpenoid exhibits renoprotective activities.[10] Whereas, Applanatumol A (**1-18**) and (+)-Applanatumol A (**1-19**) were found inactive against anti-renal fibrosis.[11]

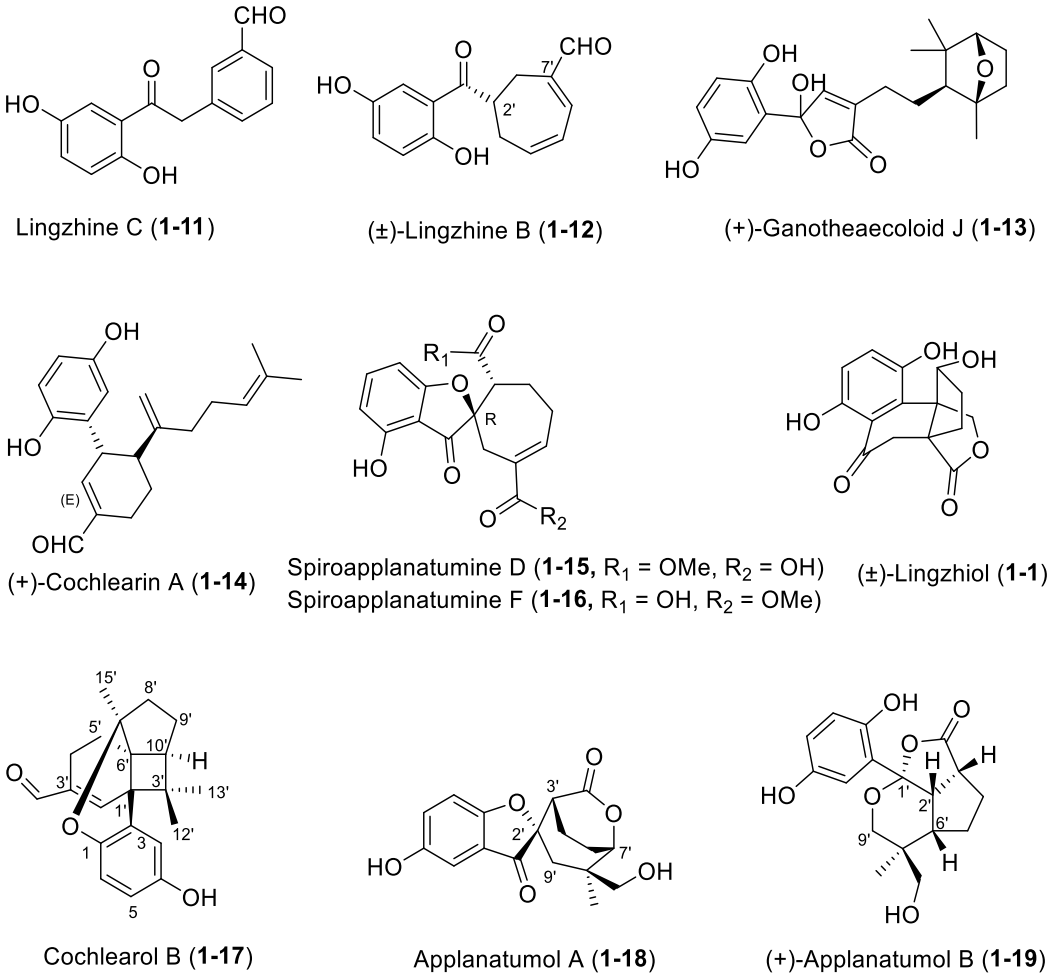


Figure 4. Chemical structures of polycyclic *Ganoderma* meroterpenoids.

1.3 Dimeric meroterpenoids

Dimeric *Ganoderma* meroterpenoids are formed via intra/intermolecular cyclization reactions (**Figure 5**). Both enantiomers (+)-Sinensilactam A and (–)-Sinensilactam A (**1-20**) were found to inhibit Smad3 phosphorylation, which is an integral part in the cure of chronic kidney disease and diabetic nephropathy.[12] Compound (±)-Ganoapplanin (**1-21**) has shown inhibitory activity against T-type voltage-gated calcium channels.[13] (+)-Ganodilactone (**1-22**) which features two chains has shown pancreatic lipase inhibitory activity.[14]

In addition, Cochlearoid H-K (**1-23** to **1-26**) and Cochlearoid F-G (**1-27**, **1-28**) were found to display renoprotective effect on HKC-8 cells.[15]

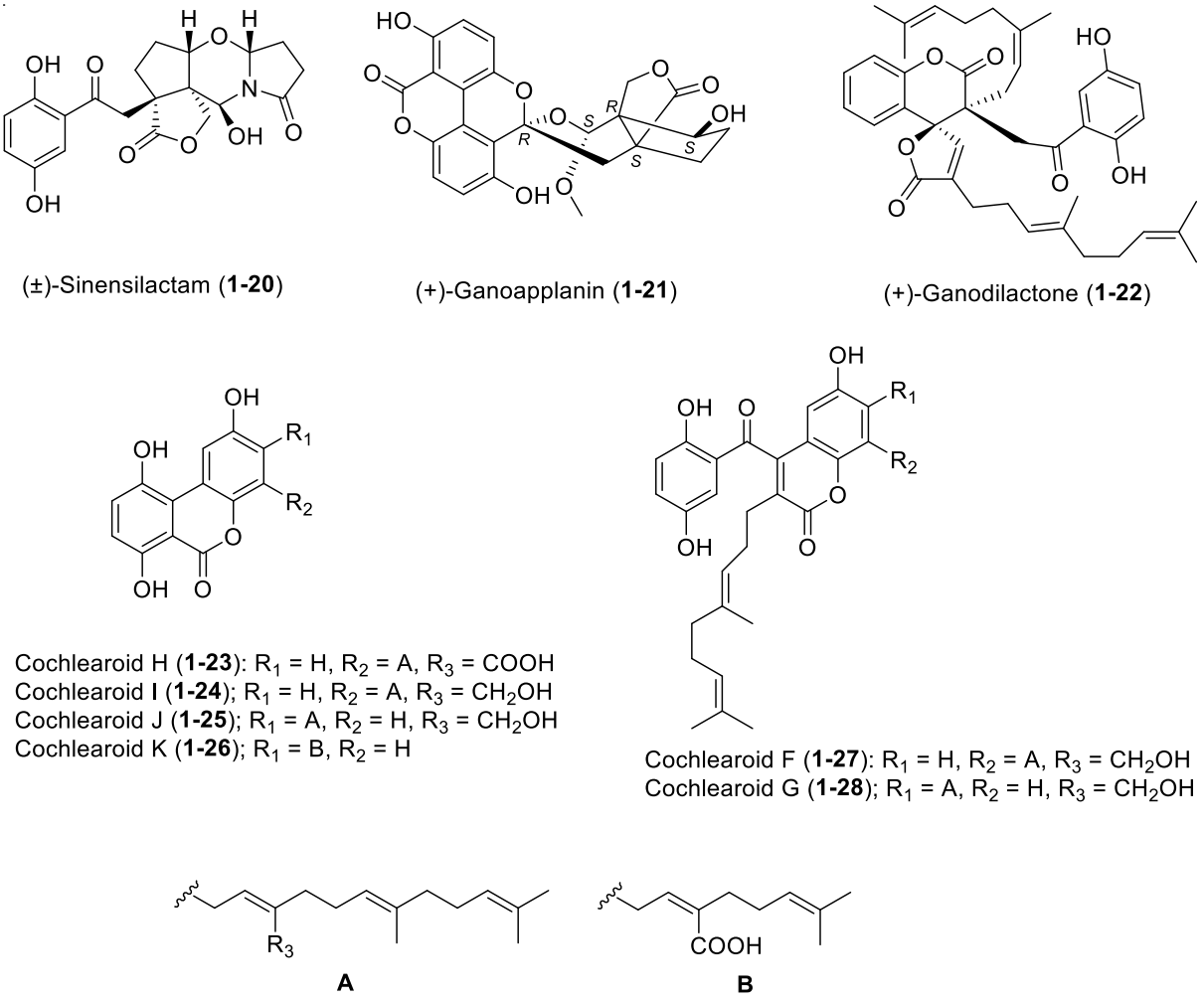


Figure 5. Structures of dimeric *Ganoderma* meroterpenoids.

1.4 Biological studies of Lingzhiol

Cheng *et al*. have investigated biological properties of Lingzhiol and found an interesting biological activity against renal fibrosis and diabetic nephropathy.[2] Diabetic nephropathy and renal fibrosis have been involved in liver failure and chronic kidney diseases. Pathogenic events contributing to renal fibrosis and diabetic nephropathy include oxidative stress,[16] accumulation of extracellular matrix (ECM), chronic inflammation and activated TGF-β/Smads signaling pathways.[17] The Smad2 and Smad3 proteins are associated with renal fibrosis and inflammatory processes. TGF-β/Smad signaling plays an important role in the development of chronic kidney disease.[18] Transforming Growth Factor β (TGF-β) is a cytokine protein belonging to the TGF superfamily. It is involved in the regulation of cell growth.[19] TGF-β expression is affected in many ways, including high levels of glucose.[20] There are many factors that could activate the TGF-β binding receptors such as pH medium, protease, reactive oxygen species (ROS), and integrins.[21] The signaling pathway of TGF-β family members occurs through type I (TβRI) and type II (TβRII) serine/threonine kinase receptors. The activated TβRI phosphorylates Smad3, which release the anchoring protein SARA and permits formation of Smads heteromeric complexes. These substrates can form a complex with Smad4 which can migrate into the nucleus (**Figure 6**).[22]

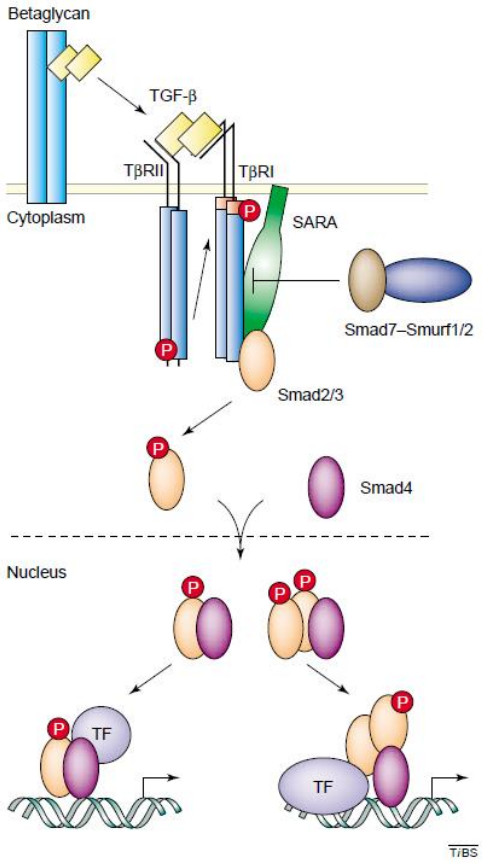
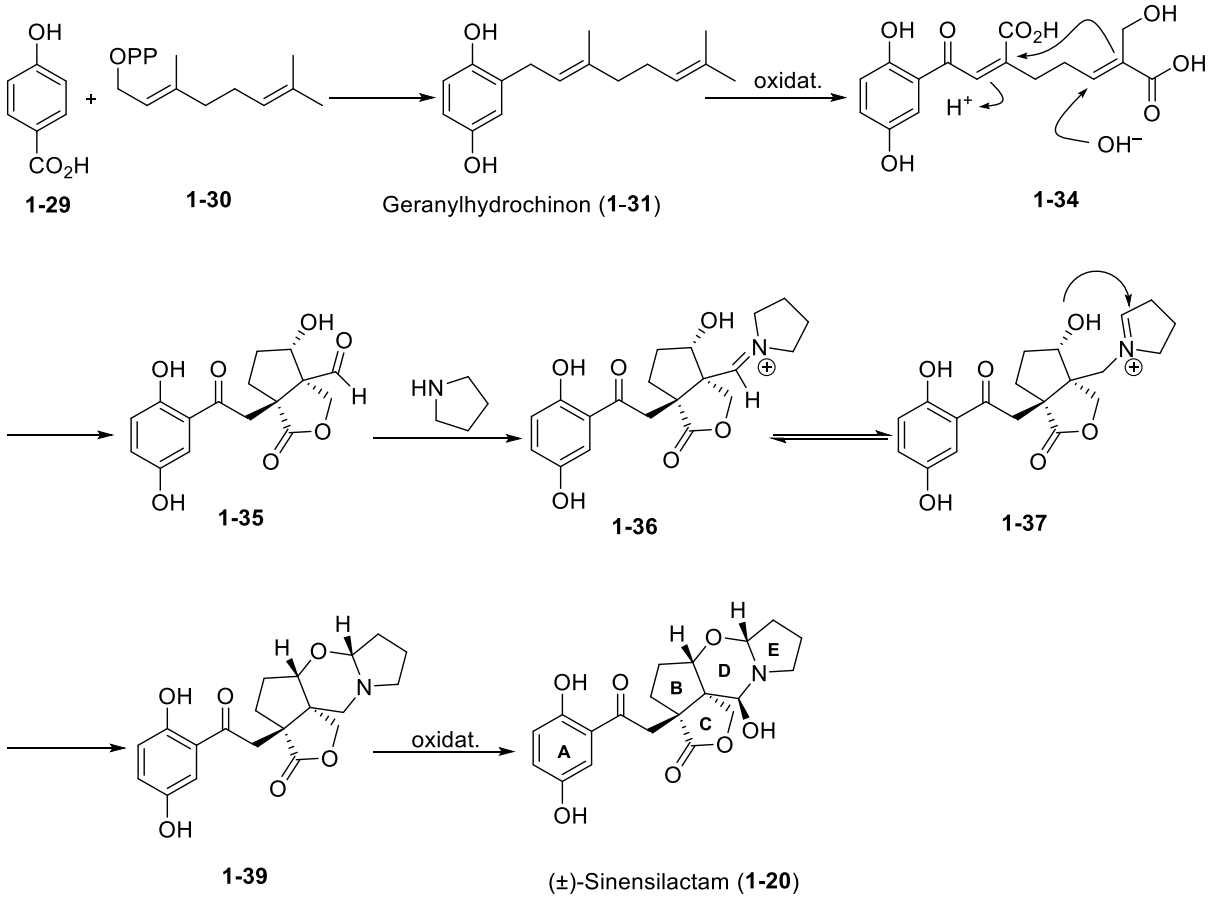


Figure 6. The TGF-β/Smad phosphorylation signaling pathway.

2. Literature

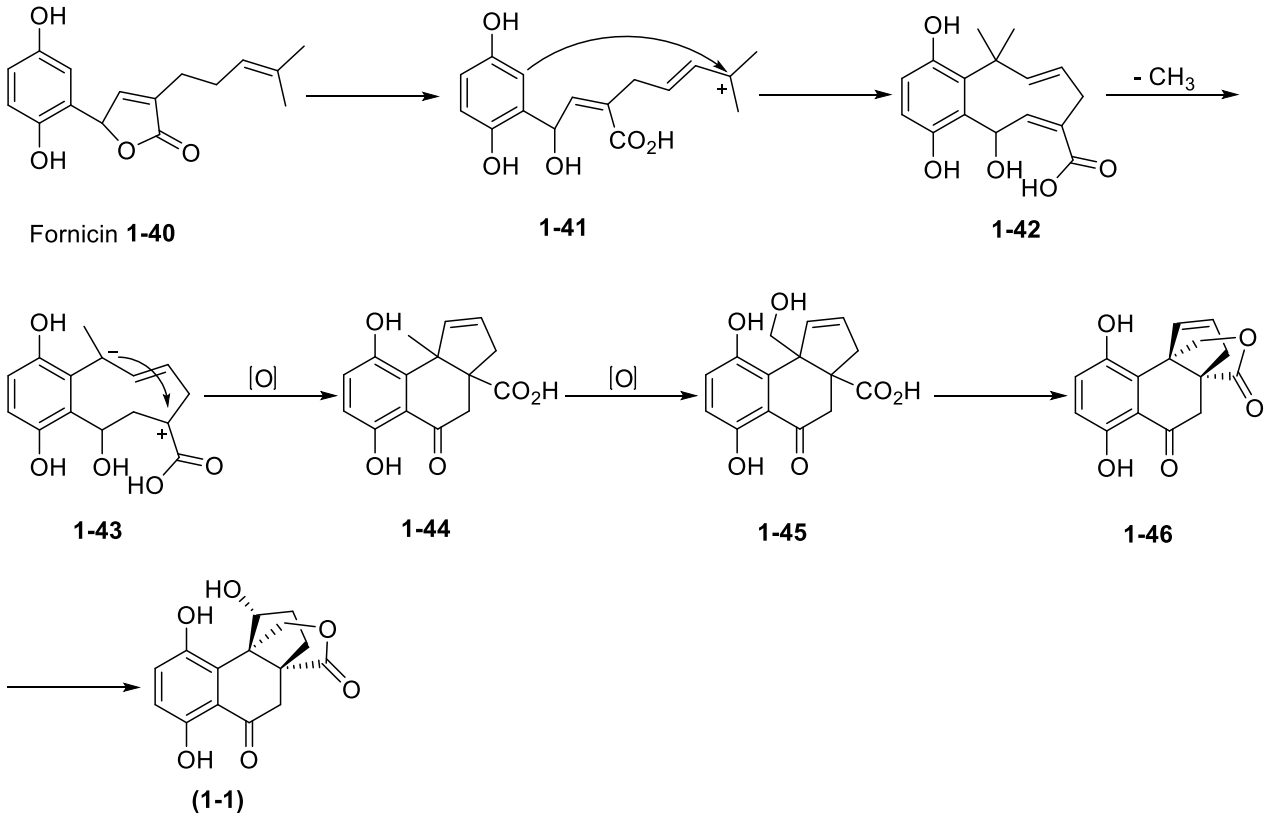
2.1 Biosynthesis of Lingzhiol

The biosynthesis of lingzhiol was proposed on the basis of a suggested biosynthesis of the related meroterpenoid (±)-Sinensilactam (**1-20**).[12] Structurally, it is related to Lingzhiol. It was suggested that (±)-Sinensilactam (**1-20**) originates from 4-hydroxybenzoic acid (**1-29**) formed via the shikimic acid pathway[23] and the monoterpene geranyl diphosphate (**1-30**). The geranylhydroquinone (**1-31**) was oxidized to generate intermediate **1-34**. The hydroxide induced domino-Michael addition to the oxidation product **1-34** could lead to cyclopentane **1-35**. Further, the biosynthesis involves the formation of intermediate **1-36** by the reaction of pyrrolidine with the aldehyde and hydroxyl function. The isomerization of iminium ion **1-36** to **1-37** involves a 1,3-hydride shift. Finally, the nucleophilic addition of the OH to the iminiumion followed by oxidation reactions would deliver the natural product (±)-Sinensilactam (**1-20**) (**Scheme 1**).



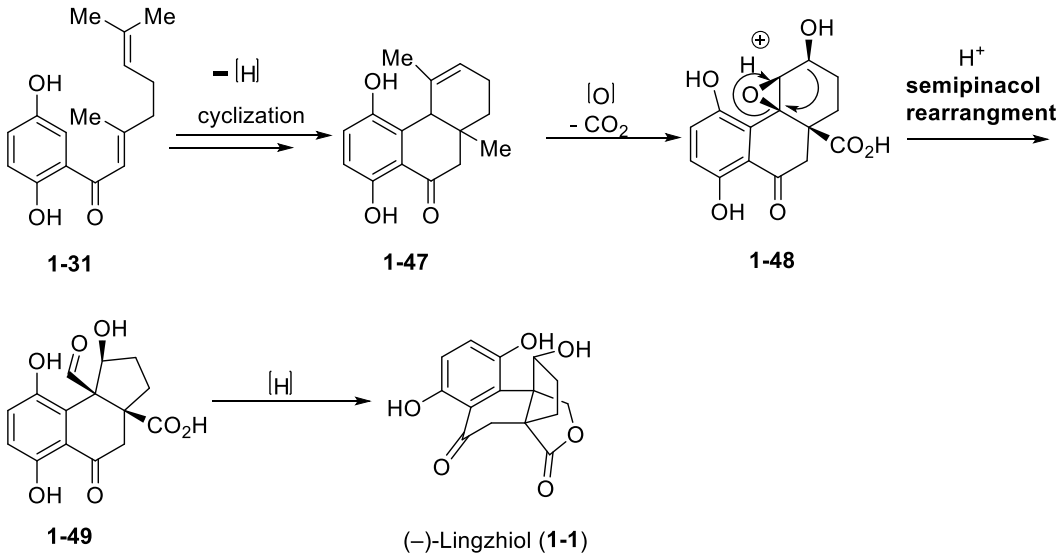
Scheme 1. Biosynthetic pathway related to (±)-Sinensilactam (**1-20**).

A first biosynthesis proposal for (±)-Lingzhiol was reported by Cheng *et al.* in 2013. It has been proposed based on Fornicin (**1-40**)[24] through a nucleophile substitution of benzene ring with a side chain allyl cation which would deliver macrocycle **1-42**. Loss of a methyl cation and transannular cyclization forms the tetracycle **1-44** featuring a cyclopentene ring. Oxidation reactions and lactonization would lead to Lingzhiol (**1-1**) (**Scheme 2**).



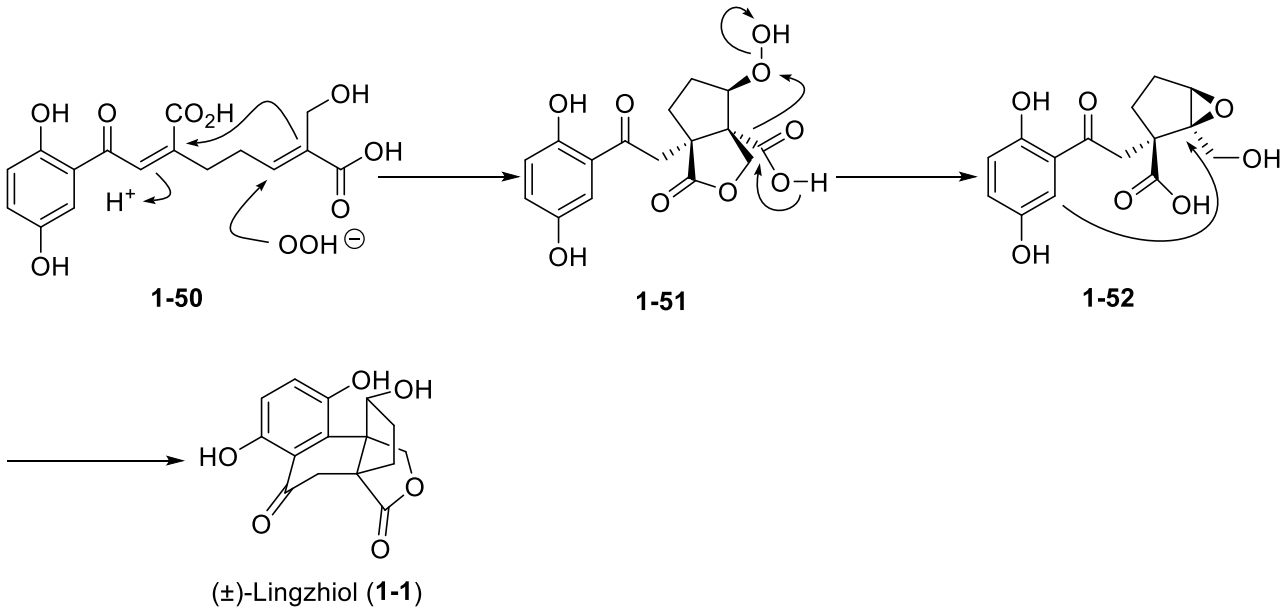
Scheme 2. A plausible biosynthesis pathway for (±)-Lingzhiol (**1-1**) by Cheng *et al*.

An alternative plausible biosynthesis pathway was proposed by Birman *et al*.[25] It was suggested that geranylhydroquinone **1-31** undergoes cyclization to produce enone **1-47**. After conversion of **1-47** into epoxy alcohol **1-48**, a semipinacol rearrangement would produce aldehyde **1-49**. Two further steps involving aldehyde reduction **1-49** and lactonization give (–)-Lingzhiol (**1-1**) (**Scheme 3**).



Scheme 3. Biosynthesis proposed via semipinacol rearrangement by Birman *et al*.

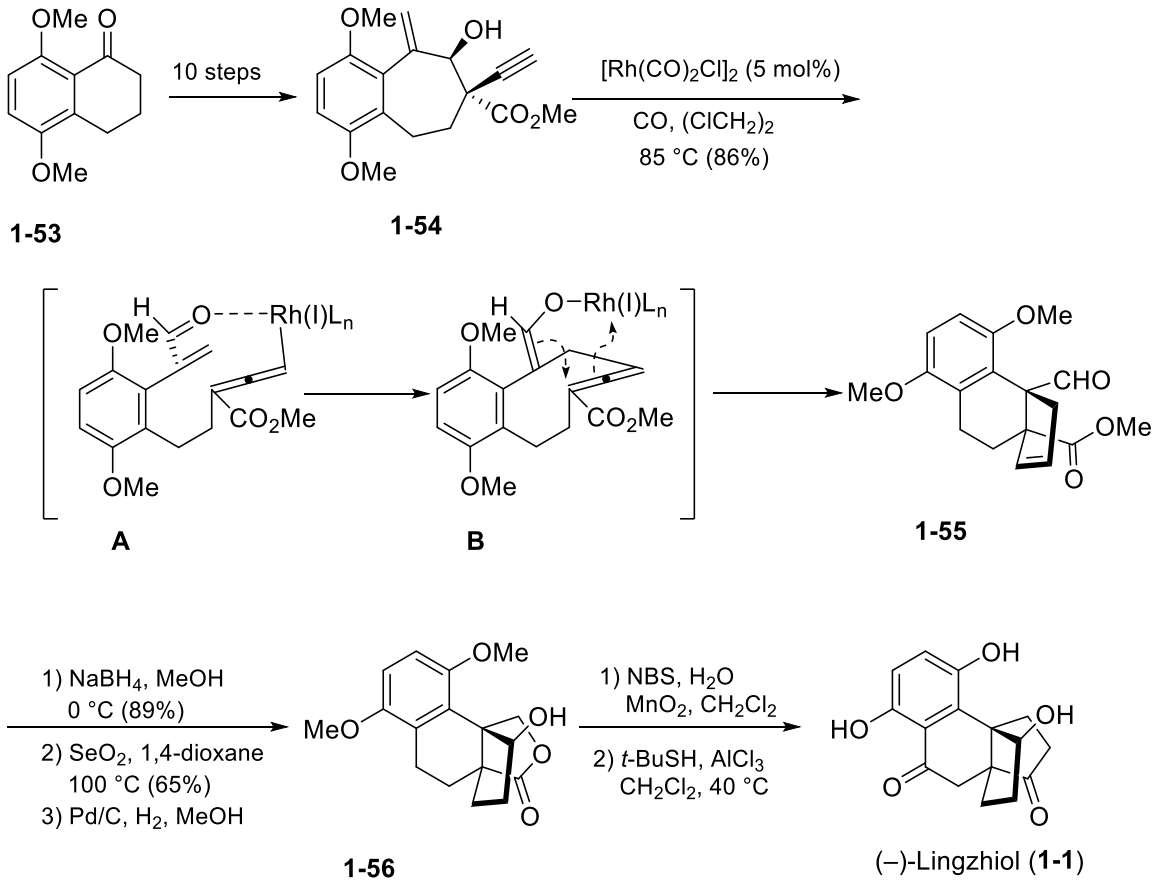
Our biosynthesis proposal is a modification of the pathway suggested for (±)-Sinensilactam for the formation of Lingzhiol (**1-1**).[26] In order to get lingzhiol in this way, the epoxide must be established in the cyclopentane ring **1-52**. We assumed that a related route to lingzhiol could involve the addition of hydroperoxide anion to the dicarboxylic acid **1-50**. The resulting cyclopentane carboxylic acid **1-51** might undergo decarboxylation to deliver epoxide **1-52**. A further step would be an intramolecular epoxide opening reaction with the aromatic ring as nucleophile that could lead to formation of Lingzhiol (**1-1**) (**Scheme 4**).



Scheme 4. Modified biosynthesis of (±)-Sinensilactam **1-20** for (±)-Lingzhiol (**1-1**).

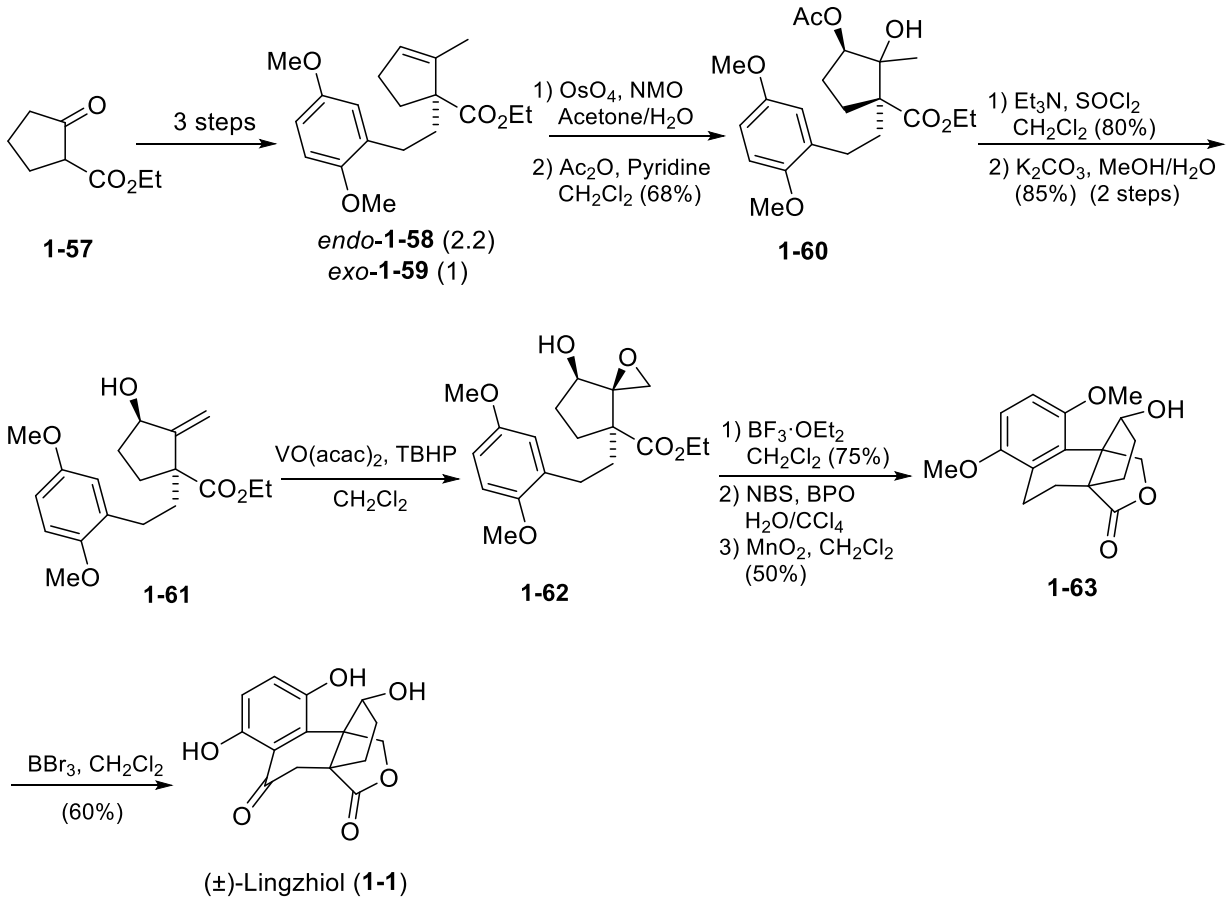
2.2 Previous syntheses of Lingzhiol

Up to now, six total syntheses of Lingzhiol have been reported in the literature. The isolated pure enantiomers of (+)-Lingzhiol and (–)-Lingzhiol from *Ganoderma lucidum* were described by Cheng *et al.* in 2013.[2] After that different groups have been investigating on the total synthesis of Lingzhiol (**1-1**). The first total synthesis was reported by Long *et al.*[27] and utilized an Rh-catalyzed [3+2] cycloaddition reaction of chiral homopropargyl alcohol **1-54** to give the tricyclic enal **1-55** through putative intermediates **A** and **B**. The key intermediate **1-54** was prepared from 5,8-dimethoxytetralone (**1-53**) in 10 steps. The aldehyde **1-55** was treated with $NaBH_4$ to induce lactone formation. Thereafter, allylic oxidation and reduction provided **1-56**. The stereochemistry of **1-56** was determined by NOE spectroscopy. Next steps involved benzylic oxidation reaction and demethylation to produce (–)-Lingzhiol (**1-1)**. The whole synthetic route comprises 17 steps (**Scheme 5**).



Scheme 5. Retrosynthetic analysis of (–)-Lingzhiol (**1-1**) by Long *et al.*

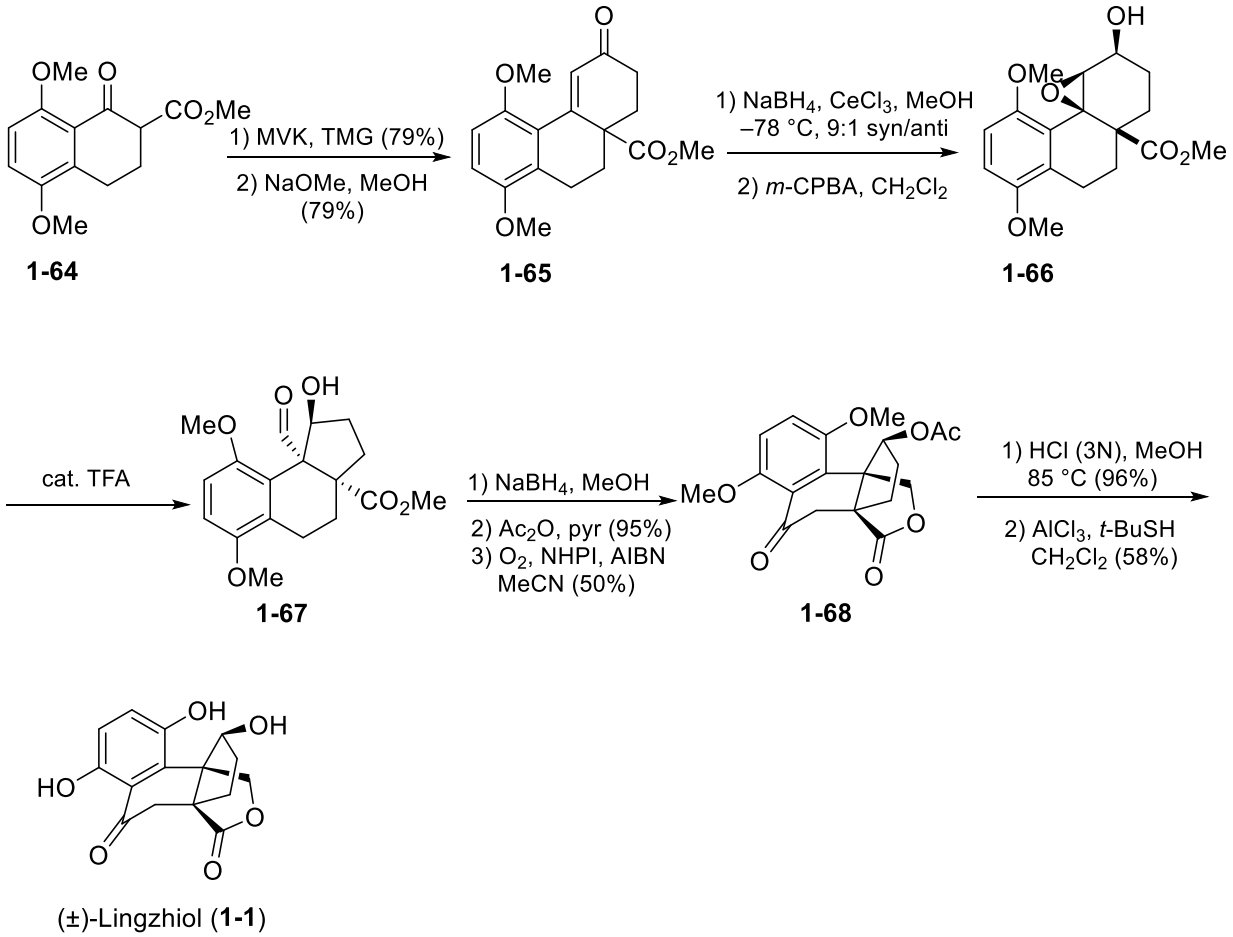
The second approach was reported by Qin *et al.* in 2015[28] and is outlined below. They have achieved the target molecule (±)-Lingzhiol (**1-1**) via an epoxy-arene cyclization reaction of epoxide **1-62** in the presence of Lewis acid. They have tried a classical Wittig olefination on an oxocyclopentane carboxylate which did not work in their hands. Therefore, they have developed a route to *endo*-**1-58** through Grignard addition and elimination to give a mixture of *endo/exo*-**1-58** (2.2:1). The major *endo*-**1-58** was oxidized using OsO_4/NMO and treated with acetic anhydride to give **1-60**. Further, elimination with $SOCl_2$, Et_3N and cleavage of the acetate group using basic conditions gave **1-61** in 4 steps. The next step is epoxide formation using $VO(acac)_2$, TBHB to give exclusively a single isomer of **1-62**. In this approach ethyl 2-oxocylco-pentanecarboxylate (**1-57**) was used as starting material. This route involved around 12 steps (**Scheme 6**).



Scheme 6. Synthesis of (–)-Lingzhiol (**1-1**) by Long *et al.*

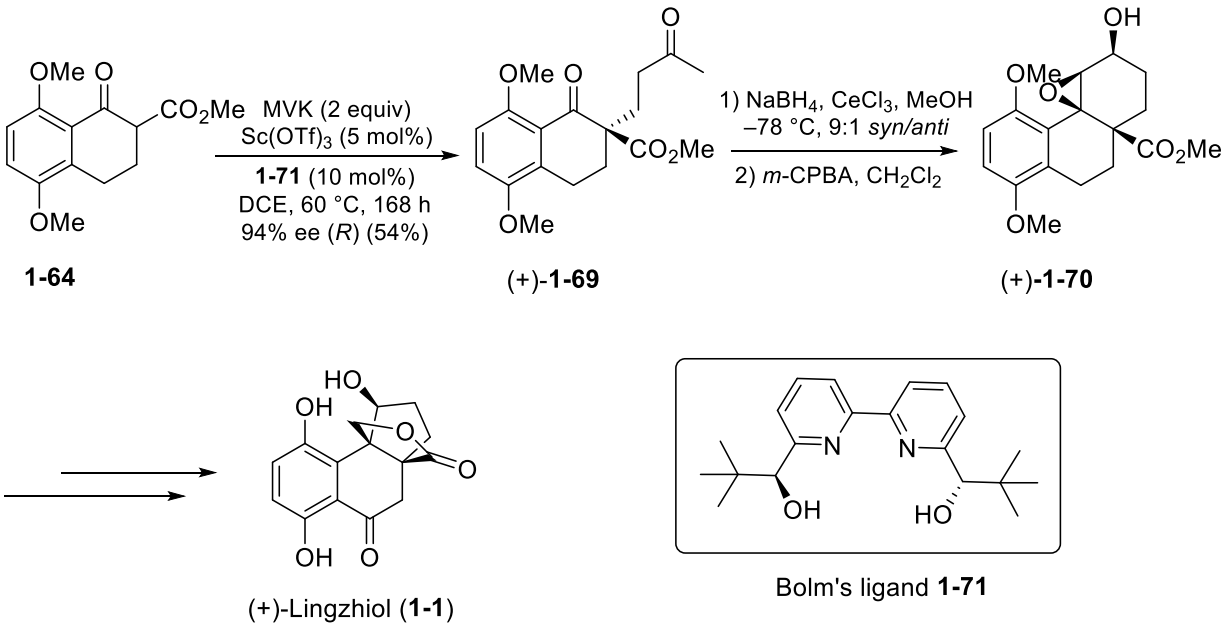
Thereafter, Birman *et al.*[25] and Xie *et al.*[29] groups reported conceptually similar synthetic approaches. The Birman group described a racemic as well as enantioselective synthesis of (+)-Lingzhiol through an acid-catalyzed semipinacol rearrangement of epoxyalcohol **1-66** to create the benzylic quaternary center of **1-67**.

The tricyclic enone **1-65** was obtained from tetralone **1-64** via a Robinson annulation reaction. This was followed by reduction of the enone and epoxidation of **1-65** which delivered a high diastereoselectivity of **1-66**. The glycidyl alcohol of **1-66** under goes on semipinacol rearrangement in the presence of TFA to produce aldehyde **1-67**. Further, reduction of the aldehyde and subsequent benzylic oxidation gave **1-68** and its deprotection secured **1-1** (**Scheme 7**).



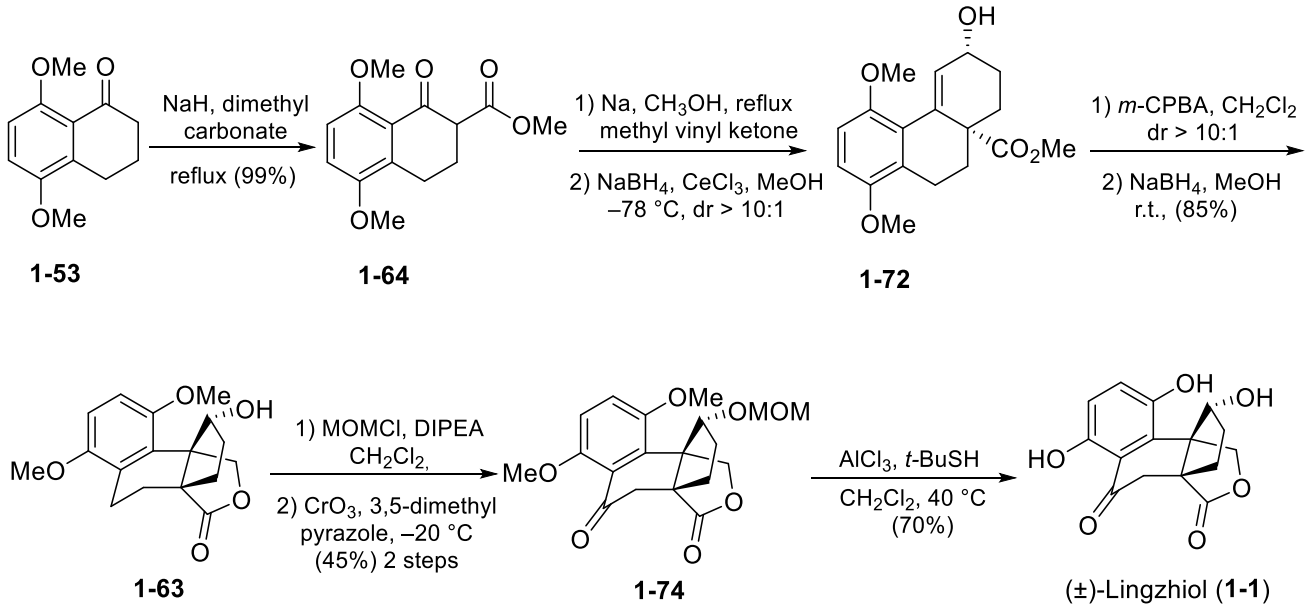
Scheme 7. Synthesis of **(±)**-Lingzhiol (**1-1**) according to Birman *et al.*

Furthermore, the same group has achieved the enantioselective synthesis of (+)-Lingzhiol (**1-1**) starting from known ketoester **1-64**[30] using an asymmetric catalytic Michael addition to MVK in the presence of scandium triflate and Bolm's ligand **1-71**[31] which produced the Michael adduct (+)-**1-69** in 94% *ee* (**Scheme 8**). Thereafter, they have used their initially established procedures to get enantioenriched (+)-Lingzhiol (**1-1)**.



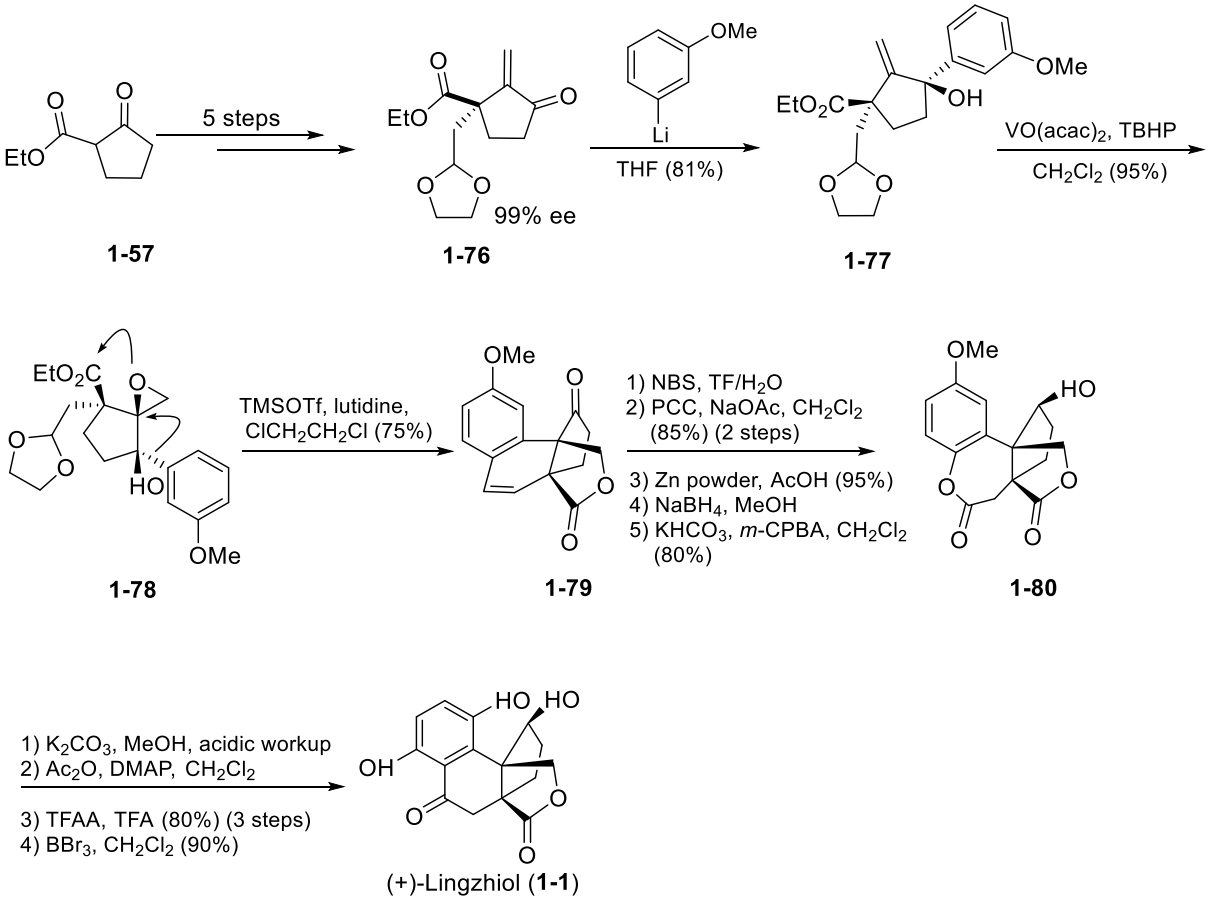
Scheme 8. Enantioselective synthesis of **(+)**-Lingzhiol (**1-1**) by Birman *et al*.

Xie *et al.*[29] have reported a similar synthesis like Birman[25] via semipinacol rearrangement under acidic conditions. Only the difference was in key intermediate **1-63**. The lactone **1-63** was treated with MOMCl followed by oxidization at the benzylic position with CrO_3 to deliver tetracyclic lactone **1-74** in 45% yield. Further, the demethylation and MOM cleavage from **1-74** produced the target molecule (**1-1**) in 74% yield (**Scheme 9**).



Scheme 9. Synthesis of **(±)**-Lingzhiol **(1-1)** by Xie *et al*.

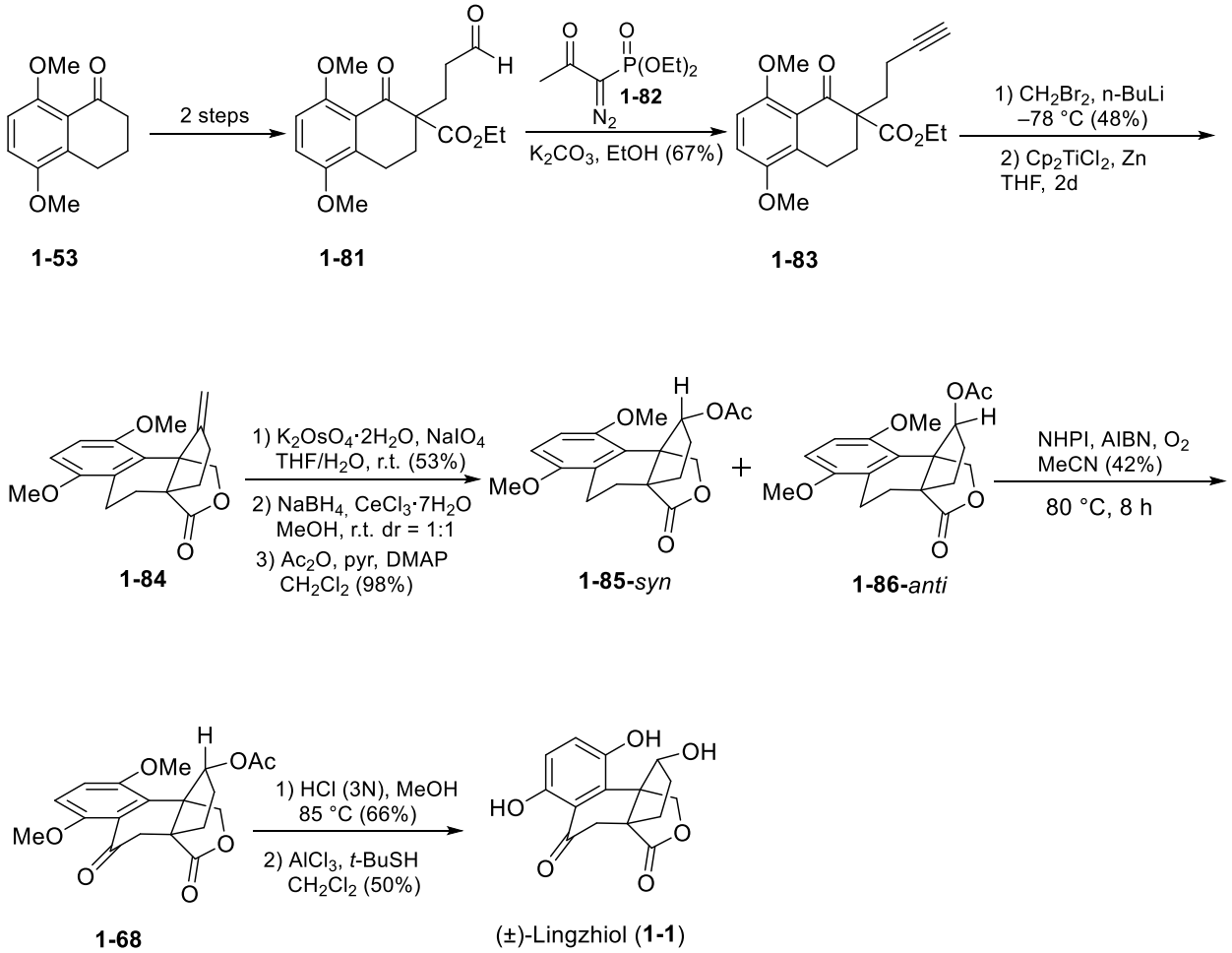
The group of Qin *et al.*[32] reported an enantioselective synthesis of (+)-Lingzhiol (**1-1)** in 17 steps. The intermediate **1-76** was obtained in high enantioselectivity (99% *ee*) *via* enzymatic resolution using baker's yeast. Nucleophilic addition of an aryllithium species to **1-76** gave **1-78**. This approach also involves a semipinacol rearrangement. The epoxy alcohol **1-78** obtained after rearrangement underwent an intramolecular Friedel-Crafts alkylation to close the B ring of **1-78**. Hydroquinone functionalities in ring A of **1-79** were created via Baeyer-Villiger oxidation. Thereafter, the aryl ester **1-80** was hydrolyzed into hydroquinone, which underwent spontaneously a meta Fries rearrangement to produce (+)-Lingzhiol (**1-1) (Scheme 10)**.



Scheme 10. Synthesis of **(+)**-Lingzhiol (**1-1**) by Qin *et al*.

Recently, the Maier group demonstrated a Lingzhiol synthesis[33] which utilizes a benzyl radical based cyclization approach. Tetralone **1-53** was reacted with diethyl carbonate to give ketoester **1-64** in 90% yield. The ketoester **1-64** was reacted with acrolein to give aldehyde **1-81** in 81% yield. Subsequently, the aldehyde **1-81** was treated with Ohira-Bestmann reagent **1-82** in the presence of a mild base to provide the alkyne **1-83**. Later, the keto group of **1-83** was converted into the corresponding spiro epoxide.

In the key step an intramolecular benzyl radical cyclization on to the alkyne using Cp_2TiCl_2/Zn produced polycycle **1-84**. After oxidative cleavage of the double bond, reduction of the derived ketone gave a separable mixture (1:1) of two diastereomeric alcohols. Further, benzylic oxidation of the acetate **1-85**-*syn* gave ketone **1-68**. Final deprotection delivered Lingzhiol (**1-1**). (**Scheme 11**).



Scheme 11. Synthesis of **(±)**-Lingzhiol (**1-1**) by Maier *et al*.

3. Goal of the research

The aim of this project was to investigate the total synthesis of Lingzhiol and analogues for testing their biologically activity. According to literature search Lingzhiol has an inhibitory effect on TGF-β-1 mediated Smad3 phosphorylation which is playing a main role in the chronic kidney disease and diabetes problems. Many methods have been reported in the literature. However, it is worthwhile to reinvestigate such species considering the developments in traditional medicine and the availability of more powerful analytical methods. Besides the interesting biological activity, the structure of lingzhiol has a tetracyclic ring system and two consecutive quaternary carbons are rather unusual. All the features attracted us to develop a synthesis for the polycyclic natural product of (±)-Lingzhiol (**1-1**).

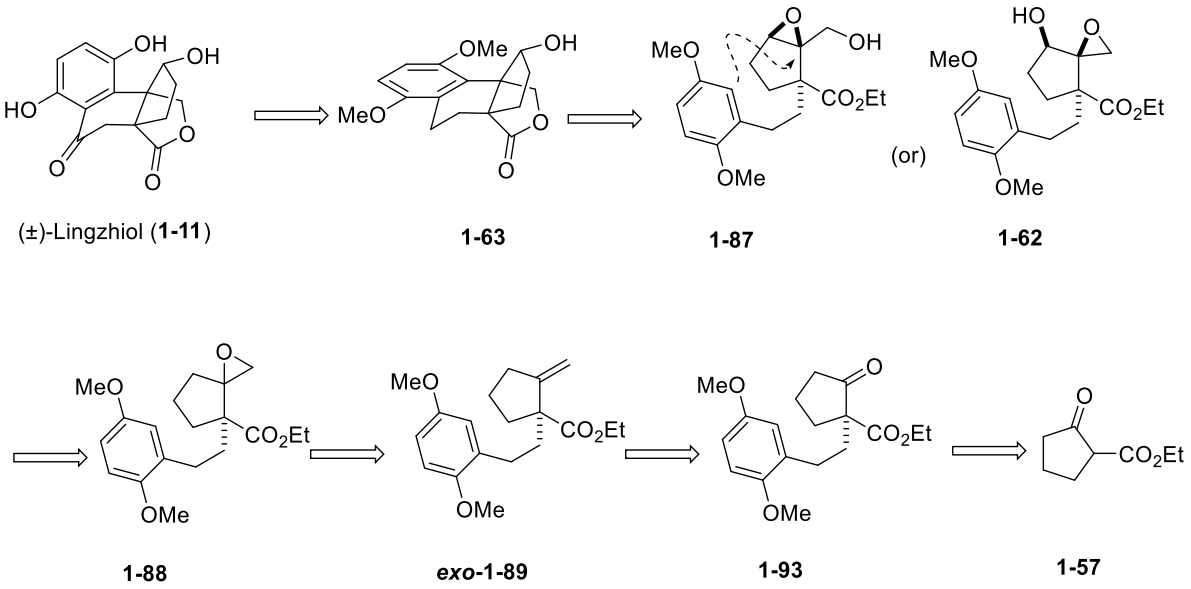


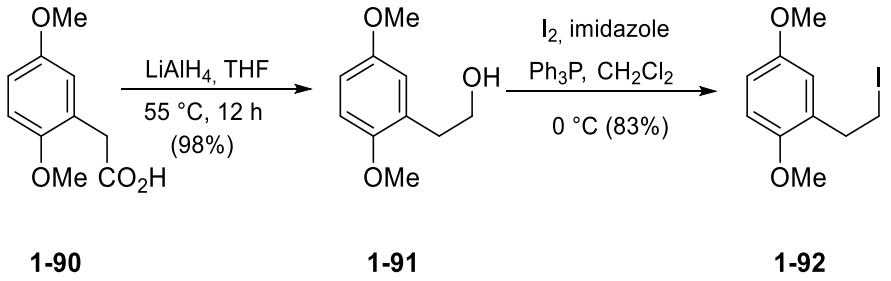
Figure 7. Retrosynthetic plan for synthesis of (±)-Lingzhiol (**1-1**).

Our general synthetic strategy for lingzhiol is outlined in **Figure 7**. Our initial plan was the formation of tetracycle **1-63** *via* intramolecular epoxide opening with the aromatic ring of **1-87** in the presence of Lewis acid. Alternatively, the spiro epoxide **1-62** was considered as another possible substrate.[28] The ketoester **1-93** was initiated from the β-ketoester **1-57** and a subsequent Wittig olefination reaction could deliver the *exo*-methylene compound **1-89**. After the crucial cyclization reaction to **1-63** benzylic oxidation[25] and demethylation should give (±)-Lingzhiol (**1-1**).

4. Results and Discussion

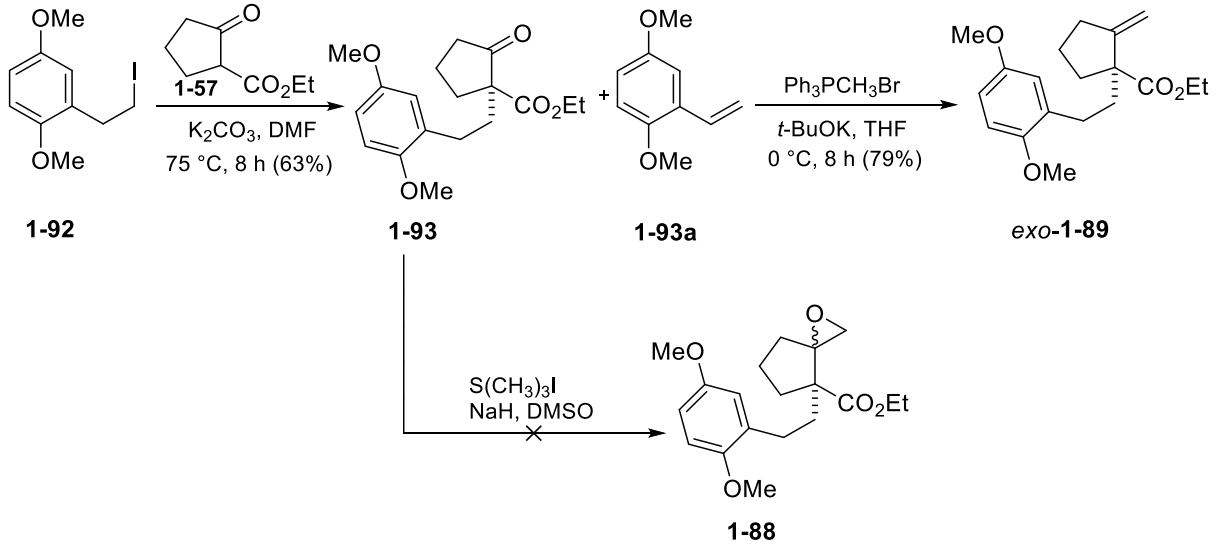
4.1 Synthesis of *exo*-double bond via Wittig olefination

According to the retrosynthetic plan, we have synthesized the alkyl iodide **1-92** from commercially available 2,5-dimethoxyphenyl acetic acid (**1-90**) which was reduced using $LiAlH_4$[34] in THF to alcohol **1-91** in 98% yield. Subsequently, alcohol **1-91** was treated with Ph_3P, I_2 under Appel-type conditions[35] which produced iodide **1-92** as brown oil in good yield (**Scheme 12**).



Scheme 12. Synthesis of 2-(2-iodoethyl)-1,4-dimethoxybenzene (**1-92**).

The next step was alkylation of ethyl 2-oxocyclopentane-1-carboxylate (**1-57**) with 2-iodoethyl-1,4-dimethoxybenzene (**1-92**) using K_2CO_3 as a base in DMF. This gave the alkylation product **1-93** in reasonable yield.[36] During this reaction, **1-93a** was formed as an elimination by-product.[37] Both compounds were separated by column chromatography on silica gel. As we were not able to convert ketone **1-93** into epoxide **1-88** by a Corey-Chaykovsky reaction using NaH, DMSO,[38] we wanted to prepare it by epoxidation of the corresponding alkene. Unfortunately, while working on this sequence, a similar synthetic approach was published by the Qin group.[28] They reported that the Wittig olefination reaction does not work in their hand.[28] But we have been able to find conditions for this crucial Wittig olefination reaction. Initially, we used a number of classical conditions such as 1) Ph_3PCH_3I (1.2 equiv), NaH (2.5 equiv), THF, 0 °C; 2) Ph_3PCH_3Br (2.5 equiv), *t*-BuOK (2.5 equiv), toluene, 100 °C; 3) Ph_3PCH_3Br (1.2 equiv), *n*-BuLi (1.5 equiv), THF, –10 °C and also Takai-Lombardo methylenation[39] but none of them gave the desired product *exo*-**1-89**. Eventually, we found that it is crucial to use around 3 equiv of methyl triphenylphosphonium bromide and 2.83 equiv of potassium *tert*-butoxide, both of them from freshly opened bottles and using distilled THF. Under these conditions, this Wittig reaction works well and it's reproducible easily. The maximum yield for this reaction was around 80% (**Scheme 13**).



Scheme 13. Synthesis of *exo*-**1-89** via Wittig olefination.

Furthermore, the formation of *exo*-**1-89** was proven by NMR and HRMS analysis. Particularly, the ^{1}H NMR spectrum shows two germinal vinyl protons as two triplets at δ values 5.03 and 5.10 ppm respectively (**Figure 8**).

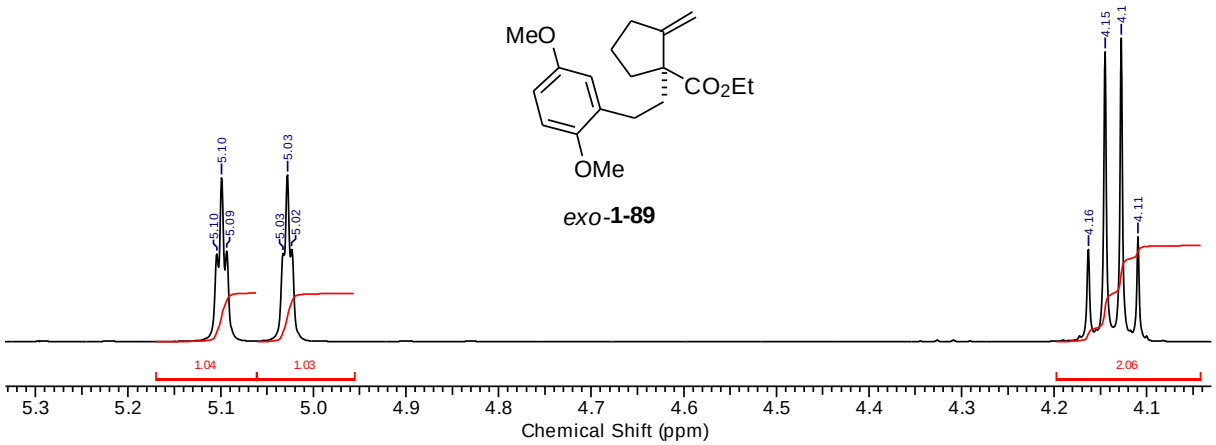
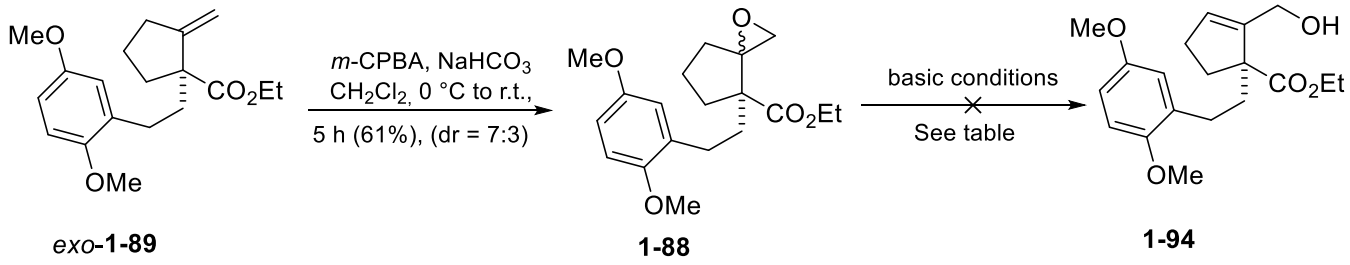


Figure 8. Confirmation of Wittig olefination to give *exo*-**1-89** by ^{1}H NMR spectrum.

4.2 Attempts for opening of epoxide under basic conditions

The intermediate *exo*-**1-89** was subjected for epoxide formation using *m*-CPBA (1.5 equiv), $NaHCO_3$ (2 equiv) in CH_2Cl_2 which delivered spiro epoxide **1-88** as a 7:3 mixture of diastereomers. Since both isomers would converge to the same allylic alcohols. we have subjected the mixture of isomers for further epoxide opening reaction using basic condition to get allylic alcohol **1-94**.

Initially, we have used a range of basic conditions for the opening of epoxide **1-88** (see **Table 1**).[40] However, all the conditions were not successful, only the starting material was recovered (**Scheme 14**).



Scheme 14. Attempts for opening of epoxide to get allyl alcohol **1-94**.

Table 1. Summary of basic conditions that were tried for opening of the epoxide **1-88**

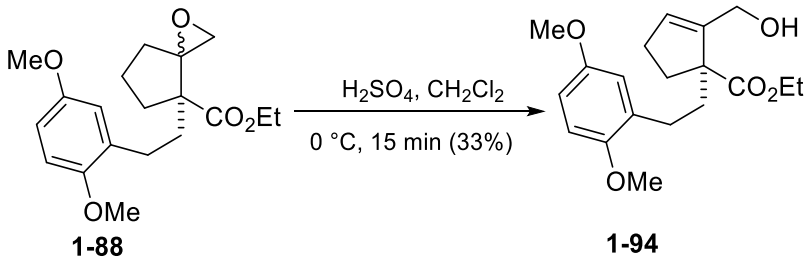
Entry	Reagents and conditions	Results
1	LDA (6.0 equiv), THF, –78 °C to r.t., 6 h	no reaction, SM was recovered
2	DATMP (1.0 equiv), toluene, –78 °C to r.t., 8 h	no reaction, SM was recovered
3	TMSiI (1.1 equiv), DBN (2.1 equiv), CH_3CN 60 °C, 12 h	no reaction, SM was recovered
4	$LiNEt_2$ (2.1 equiv), THF, –78 °C to r.t., 12 h	no reaction, SM was recovered
5	LDA (7.0 equiv), Et_2O, –78 °C to r.t., 8 h	no reaction, SM was recovered
6	LDA (3.0 equiv), THF, HMPA (5 drops), –78 °C to r.t., 6h	no reaction, SM was recovered

Substrate **1-88** was dissolved in the solvent (≈0.05 M) prior to addition of the base; SM = starting material.

4.3 Optimization of epoxide opening under acidic conditions

With enough amount of epoxide **1-88** in hand, we investigated opening of epoxide **1-88** using different Lewis acids.[41] However, it did not give an allylic alcohol **1-94**. Therefore, we decided to use a range of Brønsted acids such as HCl, H_2SO_4, TFA, H_3PO_4 and acetic acid. Surprisingly, we observed allylic alcohol **1-94** only in low yield using HCl (1M in 1,4-dioxane).[42] The reason for the low yield is decomposition of the substrate. This could be possible under strong acidic medium. In order to improve the yield, we investigated other weak acids such as TFA, acetic acid, and H_3PO_4. However, there was no product formation under these conditions (see the **Table 2**).

Interestingly, in the presence of H_2SO_4 (1 equiv, 2M in water) in CH_2Cl_2 at 0 °C for 15 min allyl alcohol **1-94** was formed in slightly higher yield (33%) (**Scheme 15**).



Scheme 15. Synthesis of allyl alcohol **1-94** using acidic conditions.

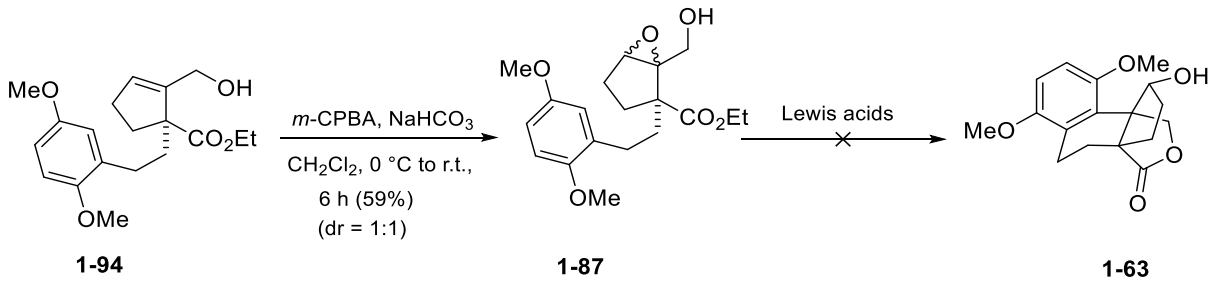
Table 2. Summary of acidic conditions that were tried for opening of the epoxide **1-88** to allylic alcohol **1-94**

Entry	Reagents and conditions	Results
1	$Al(OiPr)_3$ (2.7 equiv), 2-propanol, 85 °C, 8 h	no reaction, SM was recovered
2	$Al(OiPr)_3$ (5.0 equiv), toluene, 110 °C, 48 h	no reaction, SM was recovered
3	$BF_3{\cdot}OEt_2$ (1.8 equiv), CH_2Cl_2, 0 °C, 12 h	^{1}H NMR not comply
4	$Ti(OiPr)_4$ (2.5 equiv), CH_2Cl_2, 0 °C, 6 h	no reaction, SM was recovered
5	H_3PO_4 (1 drop), CH_2Cl_2, 0 °C to r.t., 1 h	multiple spots on TLC
6	AcOH (1 mL), H_2O, 80 °C, 8 h	no reaction, SM was recovered
7	**HCl (1M in dioxane), 0 °C to r.t., 2 h**	**20% yield of 1-94**
8	TFA (2.0 equiv), CH_2Cl_2, 0 °C to r.t., 12 h	no reaction, SM was recovered
9	**H_2SO_4 (0.5 mL), CH_2Cl_2, 0 °C, 15 min**	**33% yield of 1-94**

Substrate **1-88** was dissolved in the solvent (≈0.04 M) prior to addition of the Lewis or Brønsted acid, respectively.

The allylic alcohol **1-94** was treated with *m*-CPBA in the presence of $NaHCO_3$ in CH_2Cl_2 to give an inseparable mixture of diastereomers of **1-87** in reasonable yield. We believed that it would be possible to separate the diastereomers after the cyclization of **1-63**. Since only one of the isomer was expected to cyclize. Therefore, we have tested a range of Lewis acids[41] (**Table 3**) on the mixture of **1-87**. In this case, the aromatic ring would act as nucleophile and would undergo epoxide opening to get **1-63**.

However, the desired Lingzhiol precursor **1-63** was not formed, which was confirmed by ^{1}H NMR analysis. The NMR data showed the presence of three aromatic protons in all of the tested reactions (**Scheme 16**).



Scheme 16. Intramolecular Friedel–Crafts alkylation reaction of epoxide **1-87**.

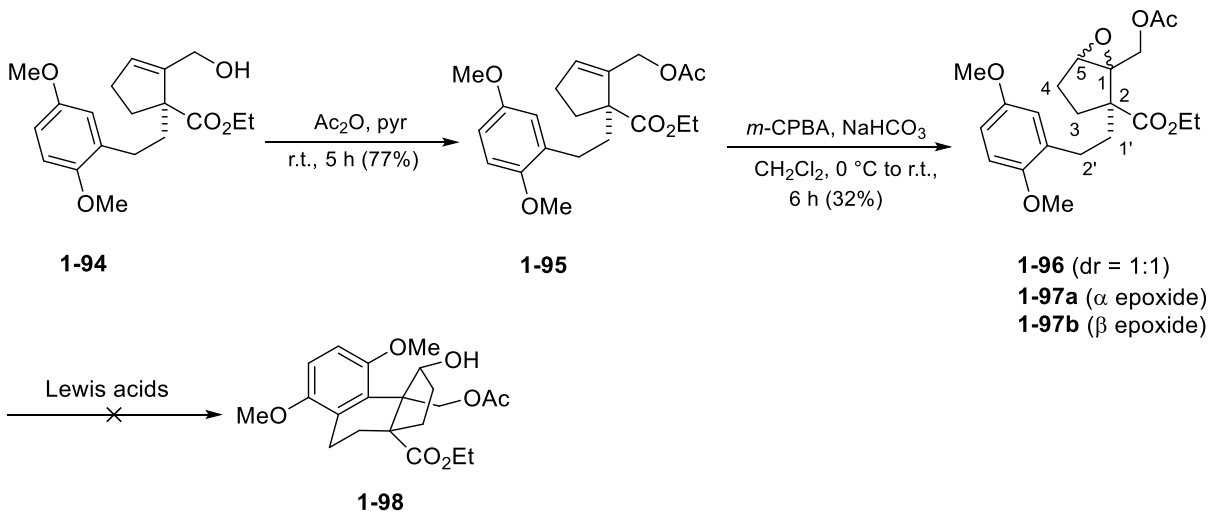
Table 3. Summary of conditions that were tried for cyclization of epoxides **1-87**.

Entry	epoxide	Reagents and conditions	Results
1	**1-87**	$AlCl_3$ (0.2 equiv), CH_2Cl_2, 0 °C to r.t., 30 min	no product formation
2	**1-87**	$BF_3{\cdot}Et_2O$ (1 equiv), CH_2Cl_2, 0 °C, 20 min	no product formation
3	**1-87**	$InCl_3$ (1 equiv), $ClCH_2CH_2Cl$, 90 °C, 20 min	many spots on TLC
4	**1-87**	$Sc(OTf)_3$ (2 equiv), $ClCH_2CH_2Cl$, 90 °C, 30 min	no product formation

The substrates were dissolved in the solvent (≈ 0.05M) prior to addition of the Lewis acid.

4.4 Intramolecular Friedel-Crafts cyclization of epoxide

We assumed that the unprotected allylic alcohol interfered with the cyclization process. Therefore, we have protected the allylic alcohol **1-94** using acetic anhydride and pyridine as a base to give allyl acetate **1-95** in 77% yield (**Scheme 17**). The **1-95** was treated with *m*-CPBA and $NaHCO_3$ to give **1-96** as a 1:1 mixture of diastereomers. Initially, we used a mixture of diastereomers **1-96** for the crucial cyclization reaction. But it did not work in my hands. At the same time, we have developed a suitable method for separation of the diastereomers to give pure compound **1-97a** and **1-97b**. Their relative stereochemistry was tentatively assigned based on NOESY data (**Figure 9**).



Scheme 17. Intramolecular Friedel-Crafts cyclization of epoxides **1-96** and **1-97a/b.**

Thus, one diastereotopic proton of the CH_2OAc group of **1-97a** showed a weak cross peak with one H-1', whilst the other CH_2OAc proton showed a weak cross peak with H-2' atom and a medium-sized cross peak with a H-1' atom. There were no cross-peaks with the H-3. If one would assume that there is also no cross peak with the H-3 atom, then the CH_2OAc and the aryl ethyl groups, which showed strong cross-peaks between the CH_2OAc protons and both H-1' atoms, should adopt a *cis* orientation in diasteroisomer **1-97b**. The problem here was that, in the spectrum of compound **1-97b**, the H-1' and H-3 atoms overlapped. Therefore, we were not completely sure about their relative stereochemistry (**Figure 9**).

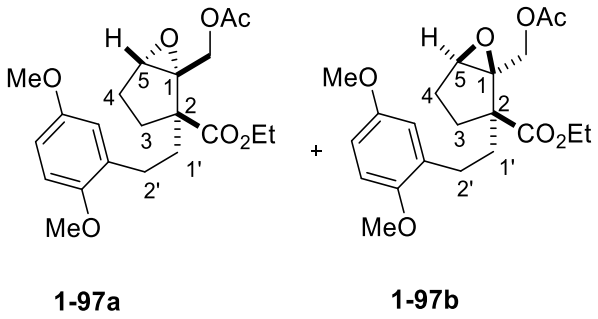


Figure 9. Key NOESY data of epoxide **1-97a** and **1-97b.**

Nevertheless, both isomers of **1-97a** and **1-97b** were studied in the intramolecular Friedel-Crafts reaction using a range of Lewis acids, including $AlCl_3$ (0.2 equiv), $BF_3{\cdot}Et_2O$ (1 equiv), $InCl_3$ (1 equiv), and $Sc(OTf)_3$[33] (2 equiv) in CH_2Cl_2 at 0 °C or 1,2-dichloroethane at 90 °C (**Table 4**). However, the epoxides of **1-97a/b** did not undergo the desired reaction to afford polycyclic **1-98**. Although these cyclization reactions would correspond to an allowed 6-*exo*-*tet* transformation,[43] stereoelectronic effects still may have thwarted this cyclization mode.

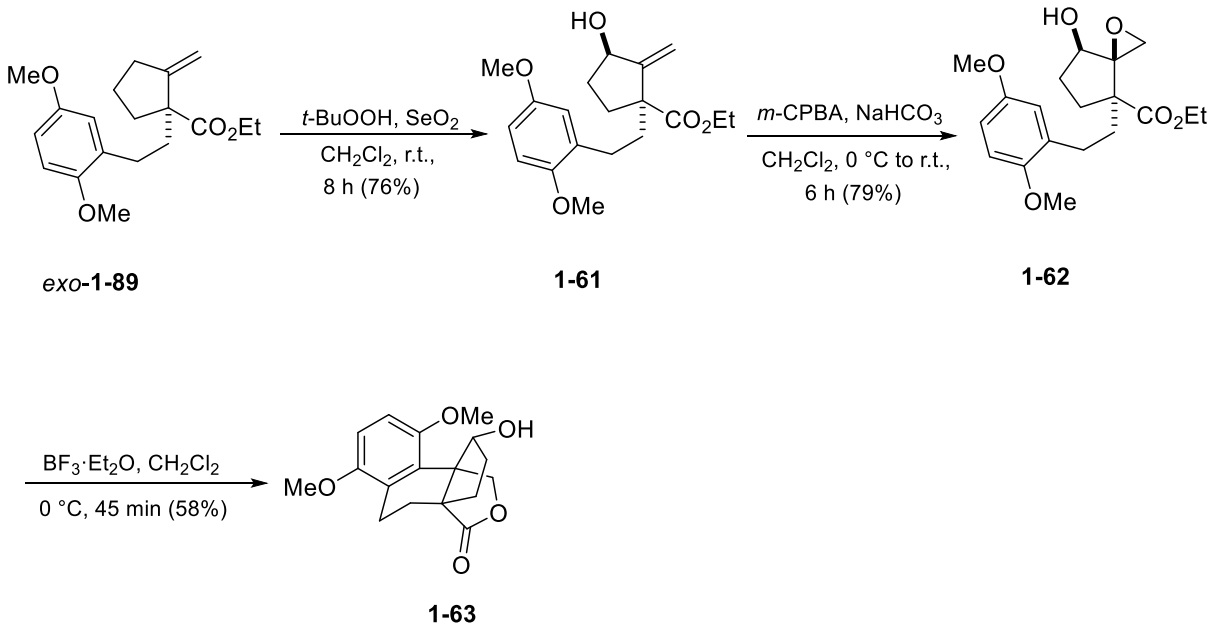
Table 4. Summary of conditions that were tried for cyclization of epoxides **1-96** and **1-97a/b**.

Entry	epoxide	Reagents and conditions	Results
1	**1-96 & 1-97a/b**	$AlCl_3$ (0.2 equiv), CH_2Cl_2, 0 °C, 30 min	SM disappeared, no product formation
2	**1-96 & 1-97a/b**	$BF_3{\cdot}Et_2O$ (1 equiv), CH_2Cl_2, 0 °C, 1 h	SM disappeared, no product formation
3	**1-96 & 1-97a/b**	$InCl_3$ (1 equiv), $ClCH_2CH_2Cl$, 90 °C, 2 h	SM disappeared, no product formation
4	**1-96 & 1-97a/b**	$Sc(OTf)_3$ (2 equiv), $ClCH_2CH_2Cl$, 90 °C, 1 h	SM disappeared, no product formation

The reactions were carried out both with the mixture **1-96** and individual diastereomers of **1-97a/b**.

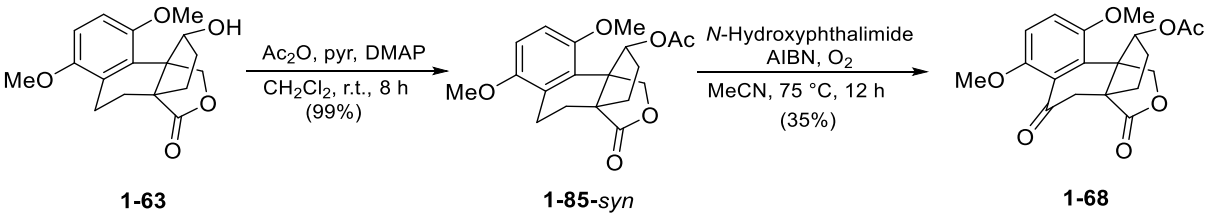
4.5 Synthesis of tetracyclic lactone

We could shorten the synthetic route of lingzhiol which was published by Qin *et al.*[28] while our work was underway. But our approach can directly produce olefin *exo*-**1-89** via classical Wittig olefination reaction without any addition and elimination reactions. Thus, the allylic oxidation of *exo*-**1-89** with *t*-BuOOH in the presence of selenium dioxide delivered the allylic alcohol **1-61** as a single diastereomer. Furthermore, the epoxidation using *m*-CPBA gave spiro epoxide **1-62** in 79% yield. A further step involves an intramolecular Friedel-Crafts alkylation of **1-62** in the presence of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 which gave tetracyclic lactone **1-63** as a white solid in 58% yield (**Scheme 18**).



Scheme 18. Synthesis of tetracyclic lactone **1-63**.

Initially, we have used a previously reported methods consisting of NBS, $(PhCO_2)_2$ in CCl_4/Water; then MnO_2, CH_2Cl_2 for the benzylic oxidation reaction.[27,28] Unfortunately, the crucial reaction did not work in our hands. Therefore, we have used the method of Birman and co-workers.[25] The key intermediate **1-63** in hand, the secondary alcohol was protected using acetic anhydride, pyridine and a catalytic amount of DMAP in CH_2Cl_2 to give acetate **1-85-***syn* in quantitative yield. Subsequently, the acetate **1-85-***syn* was treated with O_2, *N*-hydroxyphthalimide (NHPI), and AIBN in MeCN. After heating the mixture overnight the solvent was removed, and the crude phenone was directly loaded on a flash column for separation which produced ketone **1-68** in 35% yield (**Scheme 19**).

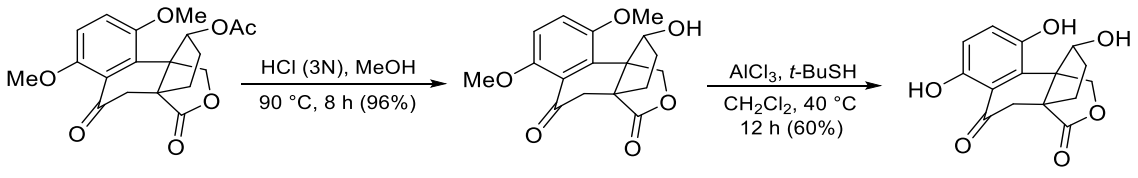


1-63 **1-85-*syn*** **1-68**

Scheme 19. Synthesis of phenone **1-68**.

4.6 Completion of the total synthesis of (±)-Lingzhiol (1-1)

After having a sufficient amount of tetracyclic **1-68** in hand, the next step was cleavage of the acetate group under acidic condition. For this reaction, we have used aqueous 3N HCl in MeOH at 85 °C to give hydroxy ketone **1-100** in 96% yield. Further, the demethylation reaction of **1-100** using $AlCl_3$ (2.2 equiv) in the presence of *t*-BuSH provided the target molecule **(±)-**Lingzhiol (**1-1**) in 60% yield as a yellow solid (**Scheme 20**). The ^1H NMR spectra showed two aromatic protons as two doublets at 7.22 ppm and 6.77 ppm and ^{13}C, and HMBC spectra clearly indicated the presence of the lactone and four quaternary centers as well. Also, the spectra of Lingzhiol (**1-1**) matched with previously published analytical data.



1-68 **1-100** **(±)-Lingzhiol (1-1)**

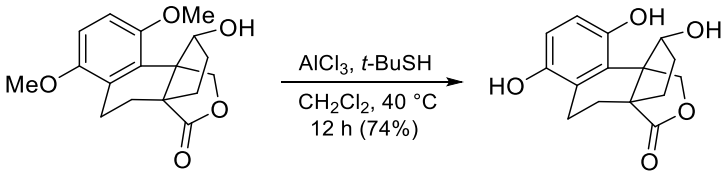
Scheme 20. Synthesis of (±)-Lingzhiol (**1-1**).

4.7 Synthesis of Lingzhiol derivatives

We have developed a quite efficient route to get (±)-Lingzhiol (**1-1**) in nine steps. This encouraged us to make various derivatives as Lingzhiol analogues. They include desoxylingzhiol **1-101**, obtained from tetracyclic lactone **1-63**, quinone derivative **1-102** from desoxy **1-101** and monomethoxy derivative **1-103** as well as ketone **1-104** from tetracyclic lactone **1-63**. All these compounds were submitted for preliminary screening.

4.7.1 Synthesis of desoxylingzhiol

Tetracyclic lactone **1-63** in hand, the next reaction involves the deprotection of the aryl methyl ethers using $AlCl_3$ and *t*-BuSH in CH_2Cl_2. After heating the reaction mixture for overnight at 40 °C Desoxy-lingzhiol (**1-101**) was obtained in 74% yield (**Scheme 21**). However, we did not observe the monomethoxy compound **1-103**.

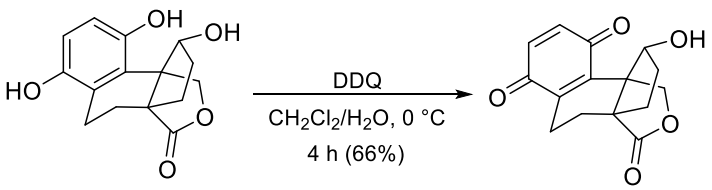


1-63 **1-101**

Scheme 21. Synthesis of desoxylingzhiol (**1-100**).

4.7.2 Synthesis of quinone derivative 1-102

It is well know that quinone derivatives are widely used in pharmaceutical industries. Because they are playing a main role in antibacterial activity.[44] Based on this kind of results, we have oxidized the phenol derivative **1-101** using DDQ in CH_2Cl_2/Water (25:1) to give quinone **1-102** as a yellow solid with a reasonable yield (**Scheme 22**).

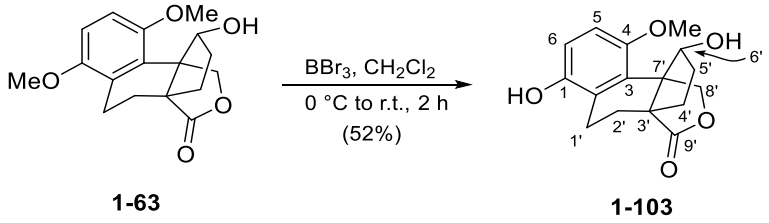


1-101 **1-102**

Scheme 22. Synthesis of quinone derivative **1-102**.

4.7.3 Synthesis of monomethoxy-deoxy derivative 1-103

We have made monomethoxy **1-103** from the tetracyclic lactone **1-63** using BBr_3 in CH_2Cl_2. Interestingly, we have observed that only one of the aryl methyl ethers was cleaved to afford monomethoxy analogue **1-103** in 52% yield (**Scheme 23**).



Scheme 23. Synthesis of monomethoxy derivative **1-103**.

The 1D and 2D NMR spectra of **1-103** showed that 1-OMe was selectively cleaved at the C1 position. ^{1}H NMR spectra showed OMe signal as a singlet at 3.76 ppm and HMBC spectrum exhibited cross-peaks between the protons of OCH_3 and carbon at C4 (three-bond correlation) and C5 atoms (four-bond correlation). All of the carbon atoms and protons in this compound were fully assigned (**Figure 10, 11**).

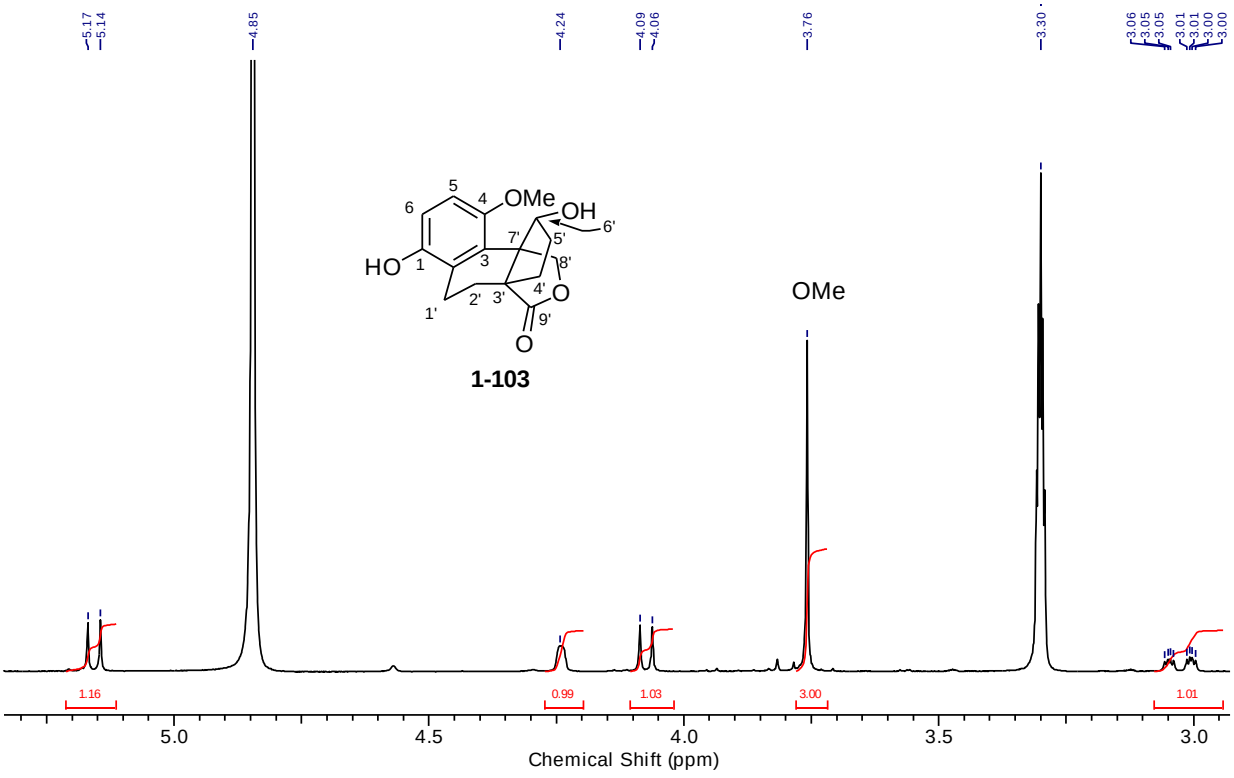


Figure 10. ^{1}H NMR (400 MHz) spectrum of monomethoxy **1-103** in CD_3OD (0.5 – 7.5 ppm).

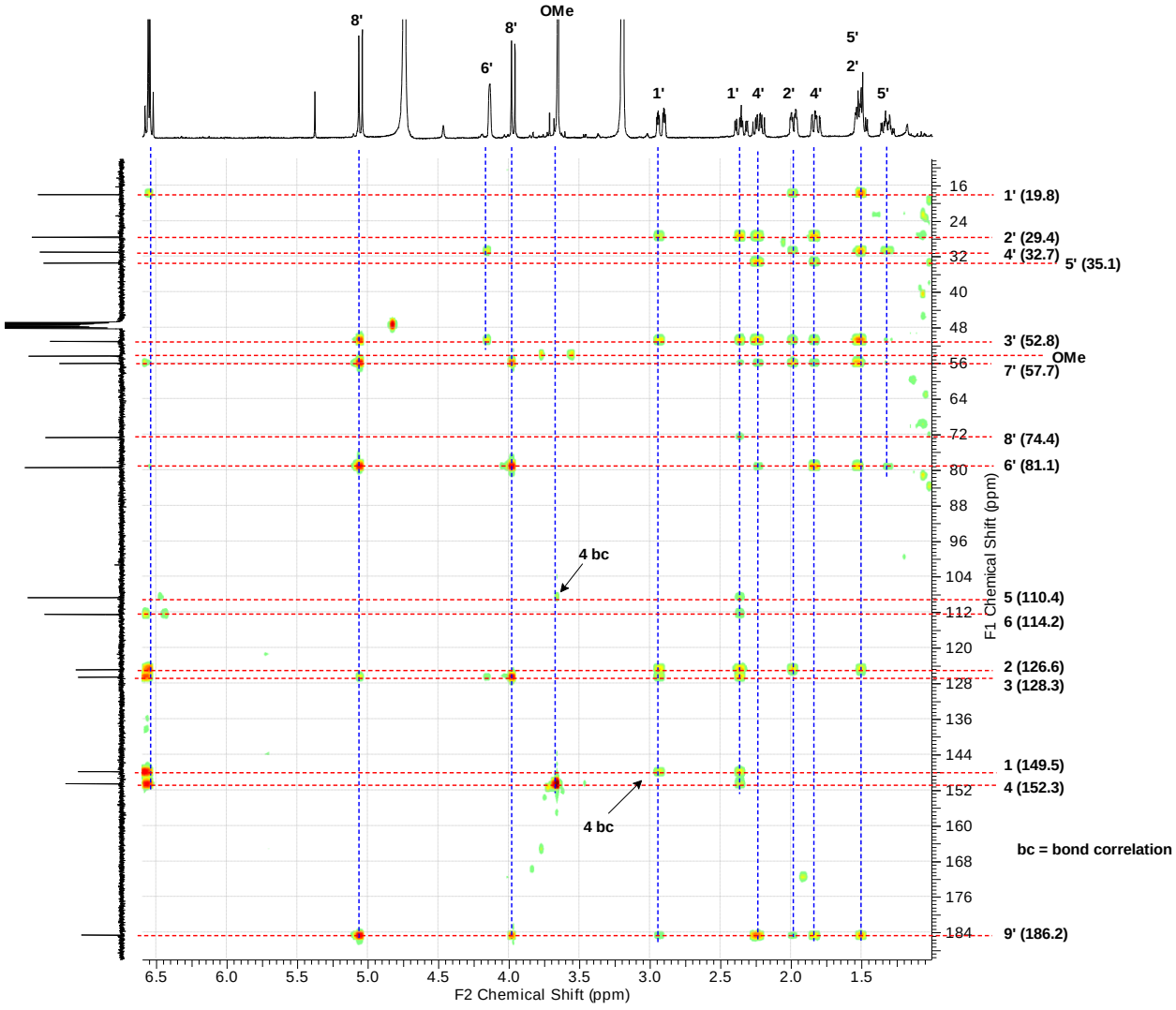
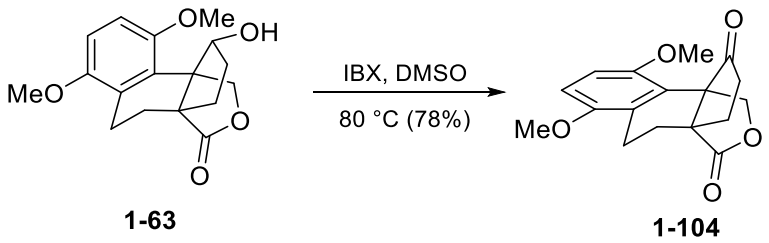


Figure 11. HMBC spectrum of monomethoxy **1-103** in CD_3OD.

4.7.4 Synthesis of ketone derivative 1-104

Finally, the ketone **1-104** was prepared easily by an oxidation reaction of **1-63** using IBX in DMSO. After heating the reaction mixture for 5 h at 80 °C ketone **1-104** was obtained as semisolid in 78% yield. Finally we have achieved five different compounds as Lingzhiol analogues for testing their biological activity (**Scheme 24**).



1-63 **1-104**

Scheme 24. Synthesis of ketone derivative **1-104**.

4.8 Biological Screening of Lingzhiol analogous

4.8.1 Antibiotic activity

In order to investigate structure activity relationship of Lingzhiol we have successfully synthesized a set of its analogues (**Scheme 21-24**). They are desoxylingzhiol (**1-101)**, quinone derivative **1-102**, monomethoxy-lingzhiol (**1-103)** and ketone **1-104**. The preliminary screening of these compounds against S. *aureus* (MRSA; RKI 11-02670), *E. coli* (DSM 1116), and p. *aeruginosa* (PA7; DSM 24068) suggested that they are inactive up to concentrations of 100 μM.

4.8.2 Antiproliferative activity

The compounds were tested on two different cell lines. In the first method, Human T-lymphoid (Cem) cells were seeded in 96-well plates at 60,000 cells/well in the presence of different concentrations of the compounds. The cells were allowed to proliferate for 72 h and then counted in a Coulter counter. The 50% inhibitory concentration (IC_{50}) was defined as the compound concentration required reducing cell proliferation by 50%. In a second method, human cervical carcinoma (HeLa) cells were seeded in 96-well plates at 15,000 cells/well in the presence of different concentrations of the compounds. After 4 days of incubation cell viability in the presence of the compounds was evaluated by the MTS method [(3-(4,5-dimethylthiazole-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium, Promega)]. Briefly, medium was replaced by 50 μ of 0.02% MTS in PBS and incubated for 2 h at 37 °C. The optical density (OD) was determined at 490 nm and the IC_{50} was calculated. Finally, all the compounds were found to be inactive. The results are summarized in **Table 5**.

4.8.3 Antiviral activity

Also, these compounds were tested against the following viruses: Respiratory syncytial virus (RSV) strain Long, influenza virus A (subtype H1N1), influenza virus B, human coronavirus strain 229E, yellow fever virus (17D vaccine strain). The antiviral assays were based on inhibition of virus-induced cytopathogenicity in human embryonic lung (HEL) fibroblasts, African green monkey cells (Vero), human cervical carcinoma cells (HeLa) or Madin-Darby canine kidney cells (MDCK). But there was no activity observed. Confluent cell cultures in microtiter 96-well plates were infected with the virus in the presence of varying concentrations of the test compounds. Viral cytopathogenicity was recorded as soon as it reached completion in the control virus-infected cell cultures that were not treated with the test compounds. Antiviral activity was expressed as the EC_{50} or compound concentration required to reducing virus-induced cytopathogenicity by 50%.

4.8.4 Other activities

Compounds active against yellow fever virus were subsequently tested against Zika virus (MR766 strain) and dengue virus serotype-2 (New Guinea C strain). Antiviral activity against Zika virus was measured using the MTS assay. Inhibition of DENV-2 infection of Vero cells was evaluated using flow cytometry. Confluent monolayers were infected with DENV-2 in the presence of different concentrations of the test compounds. DENV antigen expression was analyzed 24 h after infection by flow cytometry (FACS Calibur, BD Biosciences), using a specific anti-DENV-2 antibody (clone 3H5, Millipore). The EC_{50} value was determined as the compound concentration required to inhibit DENV-2 infection of Vero cells by 50%. Here also the results were found to be inactive.

Table 5. Results of biological activity for lingzhiol derivatives.

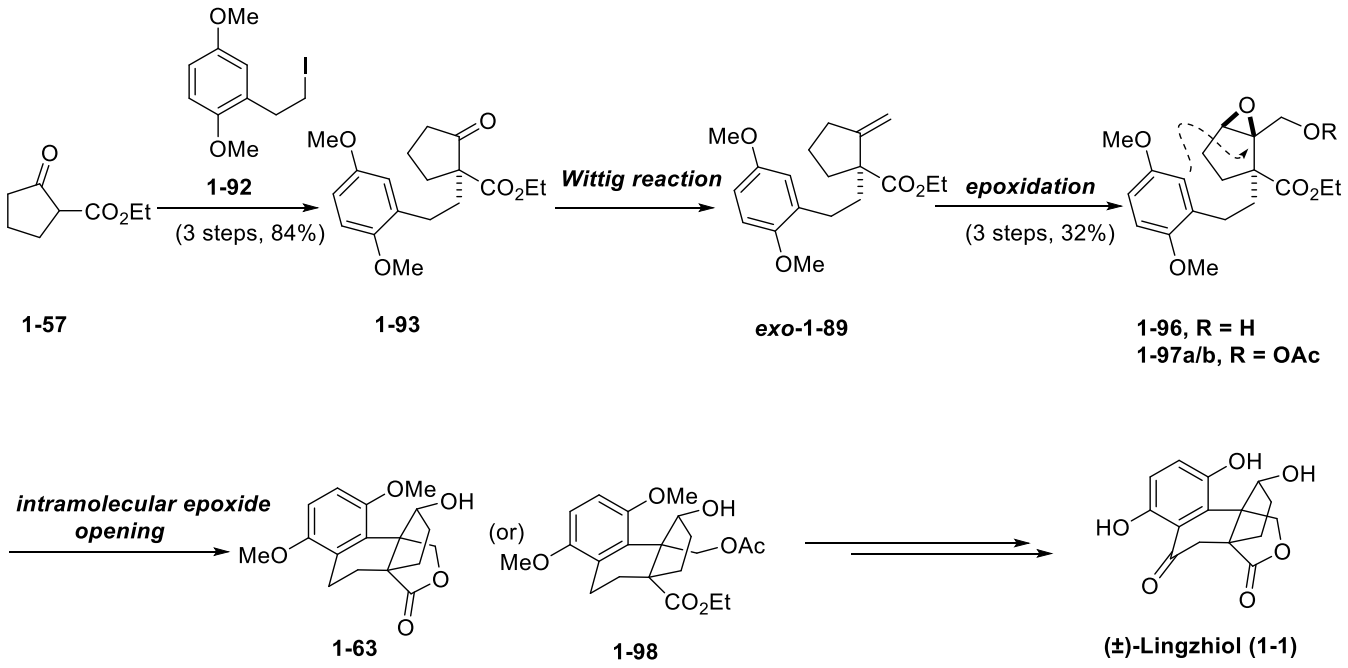
Compounds	**Antiproliferative activity** IC_{50} (μM)		**Antiviral activity** EC_{50} (μM)
	Cem	Hela	
1-1	>10	>10	>10
1-101	>10	>10	>10
1-102	>10	>10	>10
1-103	>10	>10	>10
1-104	>10	>10	>10

Results of antiproliferative activity IC_{50} in μM and antiviral activity EC_{50} in μM.

5. Conclusion

In overall summary, we have investigated two different approaches towards the total synthesis of (±)-Lingzhiol (**1-1**). The first approach was based on intramolecular Friedel-Crafts alkylation of **1-95** and **1-96a/b** using Lewis acids to get **1-63** as core molecule. In order to get key intermediate **1-95,** we started from commercially available **1-57** and alkyl iodide **1-92** (3 steps synthesis). A crucial reaction turned out to be the Wittig olefination to give *exo*-**1-89**. However, we have found appropriate conditions for this transformation of the ketone **1-93** to *exo*-**1-89** in good yield. Further steps involved epoxide formation, an opening of epoxide to give an allylic alcohol which was converted to **1-96** and **1-97a/b** (3 steps overall). Later, both isomers were used for the cyclization reaction using various Lewis acids. However, presumably owing to stereoelectronic effects the cyclization of these substrates into polycycles **1-63** and **1-97** were not successful (**Scheme 25**).

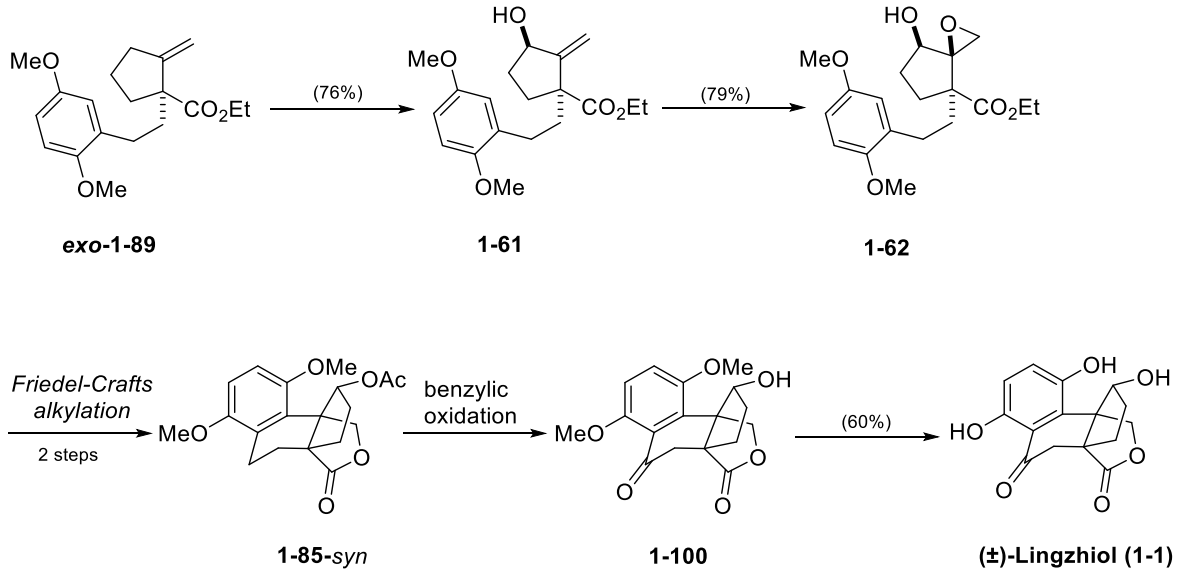
Approach: 1



Scheme 25. Attempts at intramolecular Friedel-Crafts alkylation of epoxides **1-96** and **1-97a/b**. These epoxides were prepared from the Wittig product *exo*-**1-89**.

A second approach was similar to the route published by Qin *et al*. However, the Wittig reaction to afford *exo*-**1-89** allowed us to shorten the previously reported route. The key intermediate *exo*-**1-89** delivered spiro epoxide **1-62** as a single diastereomer. Further, an intramolecular cyclization provided polycycle **1-63** in 58% yield. A subsequent, benzylic oxidation on acetate **1-85**-syn led to phenone **1-100**. Finally, treatment of **1-100** with $AlCl_3$ and *t*-BuSH delivered (±)-Lingzhiol (**1-1**) as a yellow solid (**Scheme 26**).

Approach: 2



Scheme 26. Synthesis of (±)-Lingzhiol (**1-1)** via spiro epoxide opening.

Finally, we have made five different compounds such as **1-1**, **1-101**, **1-102**, **1-103** and **1-104** as lingzhiol analogues for preliminary screening (**Figure 12**). All the compounds were tested with for biological activities such as antibiotic, antiviral and antiproliferative properties. The results are shown in **Table 5**. All compounds were eventually inactive.

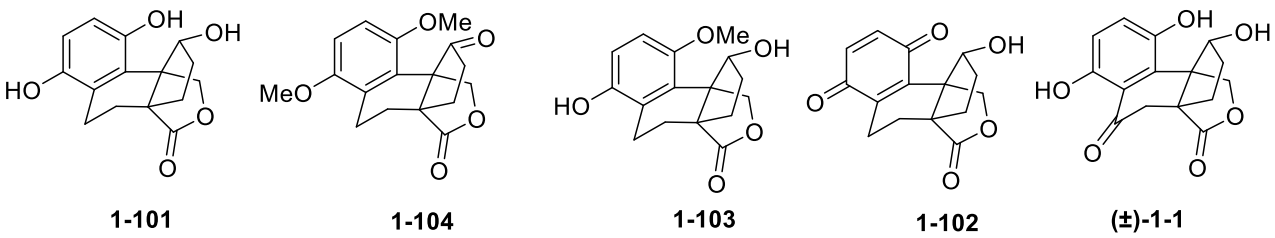


Figure 12. Analogues of lingzhiol for preliminary screening.

Chapter II

Synthesis of a C1-C12 Fragment of Gulmirecin B

6. Introduction

6.1 Macrolides as antibiotic drugs

The discovery of antibiotics was one of the key achievements of modern medicine. Antibiotics have been used enormously to human health for treating various bacterial infections. Many antibiotics bind to the 50S subunit of the bacterial ribosome and prevent translocation of peptidyl-t-RNA.[45] Still, natural products play a key role in the discovery of drugs against human diseases. For instance, naturally occurring macrolides and polyketides show interesting biological activities such as antibacterial, antifungal, prokinetic, and immunosuppressant properties. Macrolides usually have drug-like properties such as good solubility, tissue penetration, lipophilicity, and metabolic stability.[46] They are classified by the size from 12-membered to 60-membered lactones. Notably, 14-membered to 16-membered macrolides are most frequently used as antibiotics to treat skin and soft tissue infections.[47] Penicillin G (**2-1**) was isolated from the *Penicillium chrysogenum* by Alexander Fleming in 1928. It showed antibacterial activity against *Staphylococcus aureus* due to the β-lactam ring.[48] However, the antimicrobial spectrum of macrolides is broader than that of penicillins. Many macrocyclic based antibiotics are being used in the clinical practice. Among them, erythromycin (**2-2**) is a 14-membered macrolide that was isolated from the fungus *Saccharopolyspora erythraea*. It is used clinically for treatment of Gram-positive bacterial infections.[49] Clarithromycin (**2-3**) is a derivative of erythromycin and used for treatment of chronic bronchitis, and erysipelas.[50] Telithromycin (**2-4**), a synthetic derivative of erythromycin featuring an alkyl and hetaryl containing side contain linked to the macrolactone via a cyclic carbamate is used for the treatment of community-acquired pneumonia (CAP).[51] Fidaxomicin (**2-5**) was isolated from *Dactylosporangium aurantiacum* for the treatment of *clostridium difficile* associated diarrhea.[52] Spiramycin (**2-6**) is a glycomacrolide antibiotic is used for the treatment of bacterial infections.[53] Vancomycin (**2-7**), a peptide derivative where aryl ring of the side chains are cross-linked is mainly used for the treatment of Gram-positive bacterial infections such as methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin-resistant *Streptococcus pneumonia* (**Figure 13**).[54]

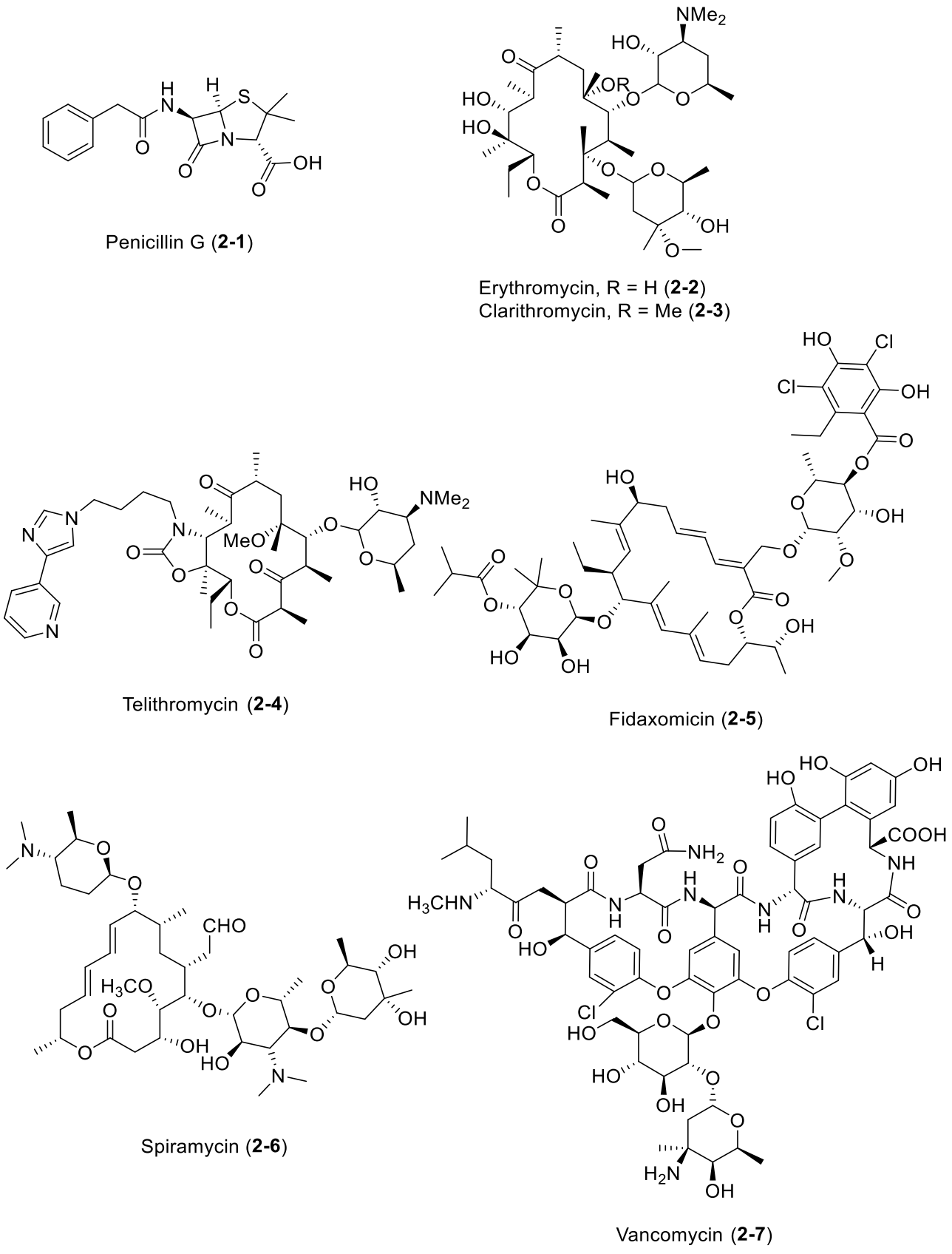


Figure 13. Examples of clinically used antibiotics.

6.2 Predatory bacteria

Myxobacteria are a promising source for the discovery of novel antibiotics. They produce several natural products such as Salimyxins,[55] Salimabromide,[56] Jahnellamides,[57] and Cystomanamides.[58] In recent years, further screening of various strains put forth novel antibiotics. Notably, predatory bacteria are a family of myxococcaceae that are able to feed on other microbes as sole nutrient source.[59] Furthermore in 2014, Müller *et al.*[60] reported that Disciformycin A (**2-8**) and B (**2-9**) were isolated from the *Pyxidicoccus fallax* stain AndGT8 (**Figure 14**). Structurally, Disciformycin A (**2-8**) has a double bond at C2-C3 position and B (**2-9**) has a double bond between at C3-C4 position. Both of them showed antibacterial activity against Gram-positive bacteria. However, Disciformycin B (**2-9**) displays a more inhibitory efficiency than Disciformycin A (**2-8**) in the range 0.6 to 1.2 μg mL^{-1} against *Staphylococcus aureus* including vancomycin-resistant *S. aureus* (VRSA) and methicillin-resistant *S. aureus* (MRSA) strains.[61] Moreover, these compounds don't show any cytotoxic effect on human cells with a concentration up to 10 μM.

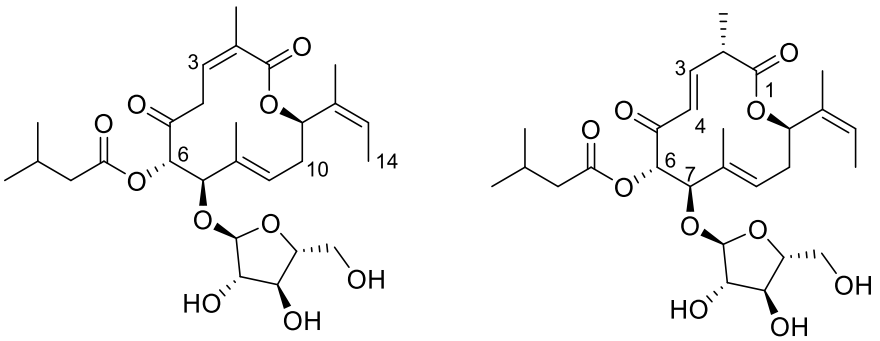


Figure 14. Disciformycin A (**2-8**) and B (**2-9**) were isolated by Müller *et al*.[60]

Likewise, Gulmirecin A (**2-8**) and B (**2-9**) reported by Nett *et al.*[62] were isolated from the Myxobacterium *Pyxidicoccus fallax* HKI 727. Structurally, Gulmirecins are related to Disciformycin A (**2-8**) and B (**2-9**). Interestingly, both families have an isovaleryl group at the C6 position and α-arabinofuranose moiety which is attached to the macrolactone ring. The antimicrobial activity of Gulmircein A (**2-10**) and B (**2-11**) were not varying from Disciformycin A (**2-8**) and B (**2-9**). However, the minimum inhibitory concentration (MIC) value of Gulmirecin A (**2-10**) and B (**2-11**) is larger than that of Disciformycin A (**2-8**) and B (**2-9**), respectively (**Figure 15**).

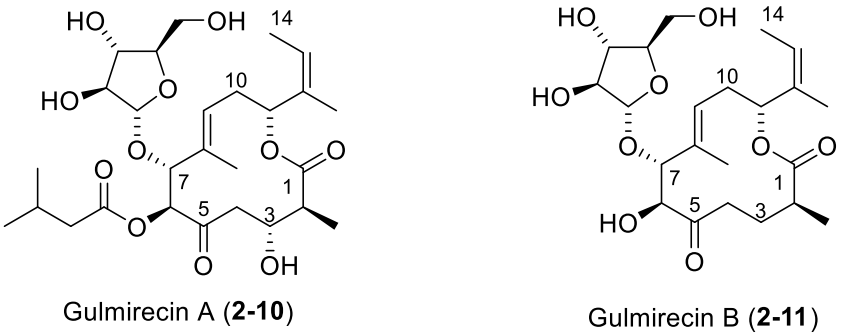


Figure 15. Gulmirecin A (**2-10**) and B (**2-11**) were isolated by Nett *et al.*[62]

7. Literature

7.1 Biosynthesis of Gulmirecins

The first biosynthesis proposals for Gulmirecins were reported by Nett *et al.* in 2014.[62] It was suggested that these macrolides were produced by the polyketide synthase (PKS) pathway.[63] The type I PKS process, a decarboxylative Claisen condensation takes place repeatedly between individual thioester monomers. Furthermore, linked monomers have several catalytic units with specific functions such as ketosynthase (KS), acyl transferase (AT), and acyl carrier protein (ACP) which are necessary to produce the β-ketoester intermediates.[64] Gulmirecin consist of six gene sequences in the PKS modules (gulA–gulF), which assembly the carbon chain. The stereocentres are introduced at C-3, C-7, and C-11 positions by NADPH-based reduction. After the polyketide synthesis and macrolactonization, a cytochrome P450-based oxidation introduce the hydroxyl group at C6. The modules may contain further domains (KR, DH, ER) to introduces further functionality after the Claisen condensation steps (**Figure 16**).

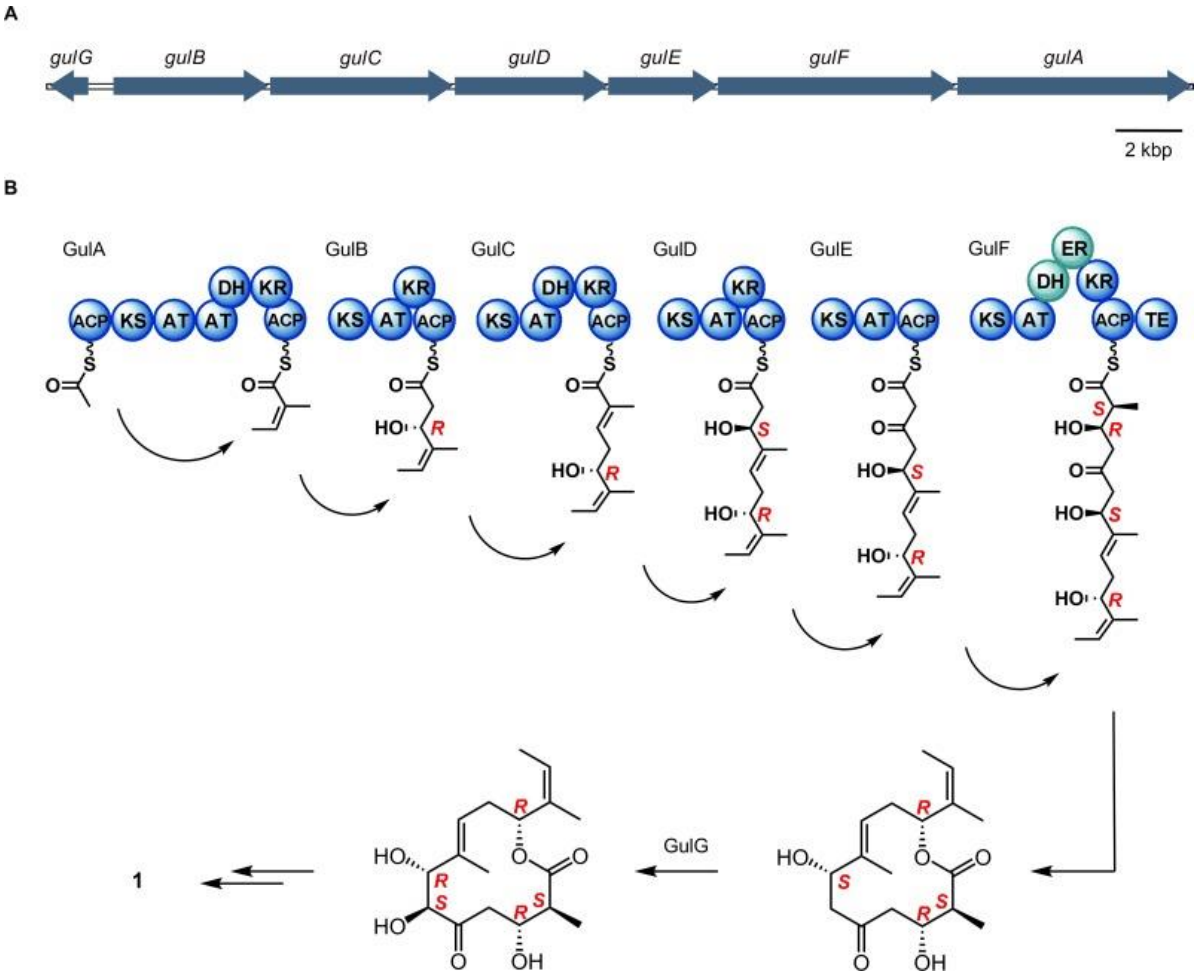


Figure 16. Biosynthesis of Gulmirecin A (**2-10**) according to Nett *et al.*[62]

The second biosynthesis proposals for Gulmirecins and Disciformycins were reported by Kirschning *et al.*[65] in 2018. Structurally, Gulmirecins are quite similar to Disciformycins. Accordingly, the biosynthesis of the gulmirecins is similar. The main difference relates to the introduction of the C3 hydroxyl group. Whereas in the Nett proposal this originates from a C3 ketone, in the Kirschning proposal 3-OH is introduced by oxidation. The intermediate **2-12** leads to macrolactone **2-13** by a thioesterase. Then, macrolactone **2-13** was oxidized to generate hydroxyl group at the C6 position. A further sequence involves an oxidation at C3 position and esterification at C6 position to furnish Gulmirecin A (**2-10**). Likewise, elimination of the hydroxyl group at C3 could lead to Disciformycin A (**2-8**) and B (**2-9**), respectively (**Figure 17**).

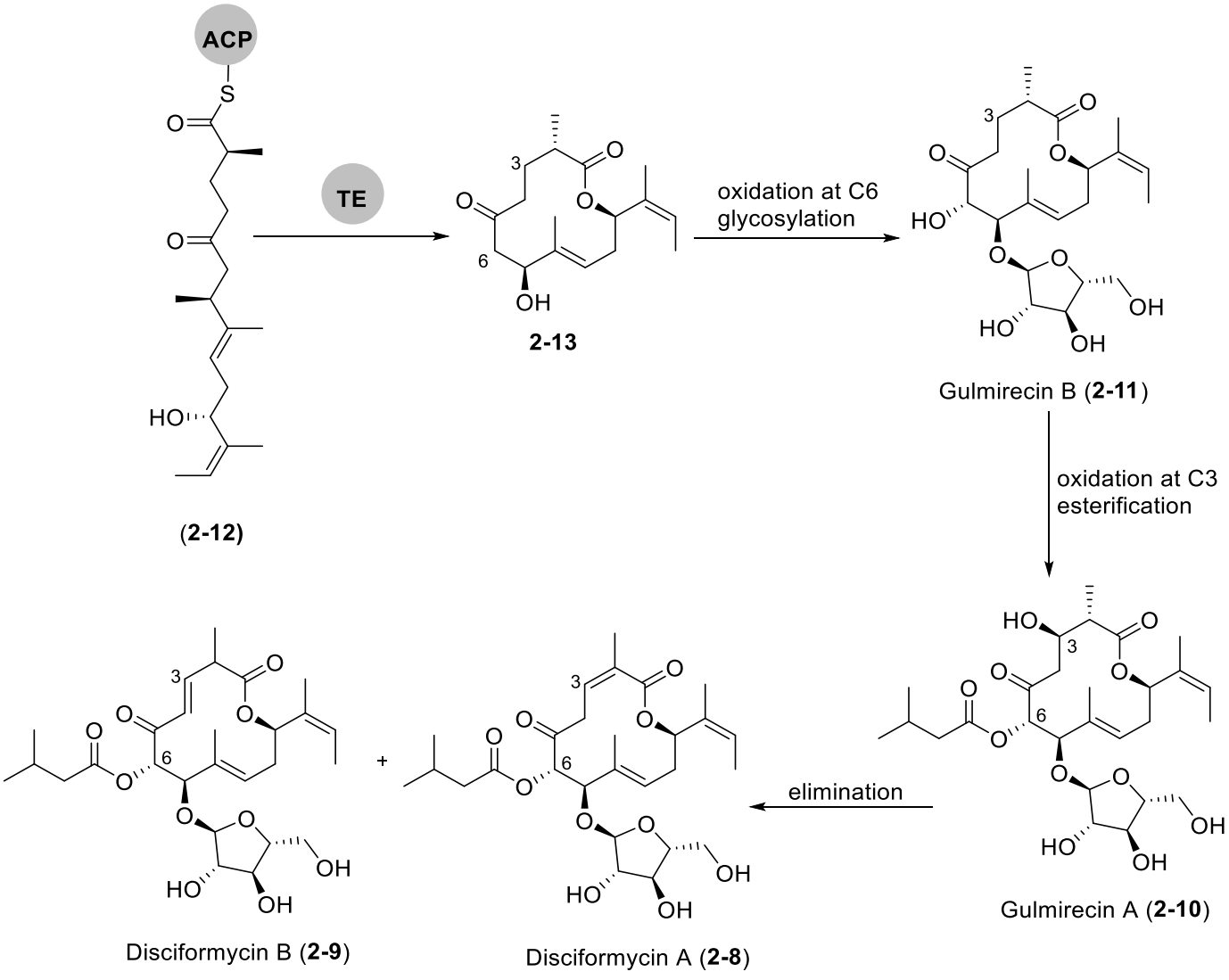
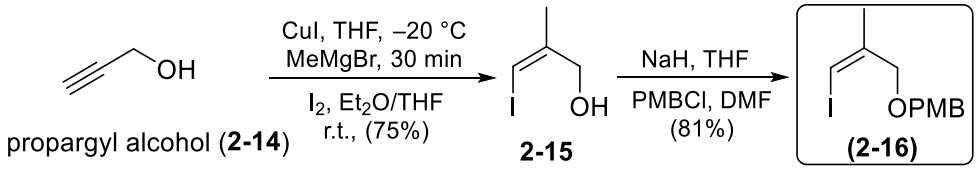


Figure 17. Biosynthetic relations between Gulmirecins and Disciformycins according to Kirschning *et al.*[65]

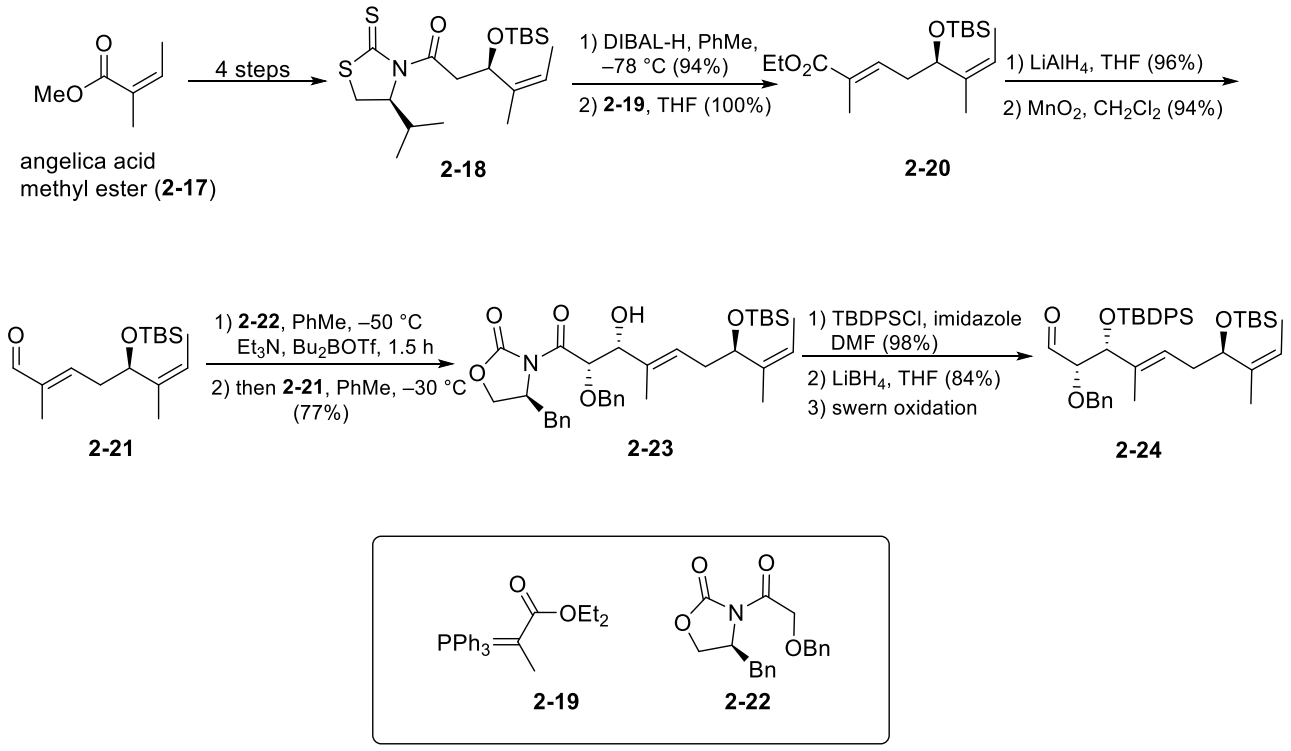
7.2 Known syntheses of Gulmirecins and Disciformycins

Gulmirecins and Disciformycins were described in a patent in 2016.[66] It is reported that these compounds have antimicrobial activity against Gram-positive bacteria. A total synthesis of Disciformycin A (**2-8**) was described utilizing an Evans aldol reaction and Yamaguchi macrolactonization. The key intermediate vinyl iodide **2-16**[67] was obtained from readily available propargyl alcohol (**2-14**) in a two step sequence. Propargyl alcohol (**2-14**) was converted to allyl alcohol **2-15** using CuI and MeMgBr followed by quenching of the vinyl metal intermediate with I_2. The resulting allyl alcohol **2-15** was treated with NaH, and PMBCl to furnish vinyl iodide **2-16** in 81% yield[68] (**Scheme 27**).



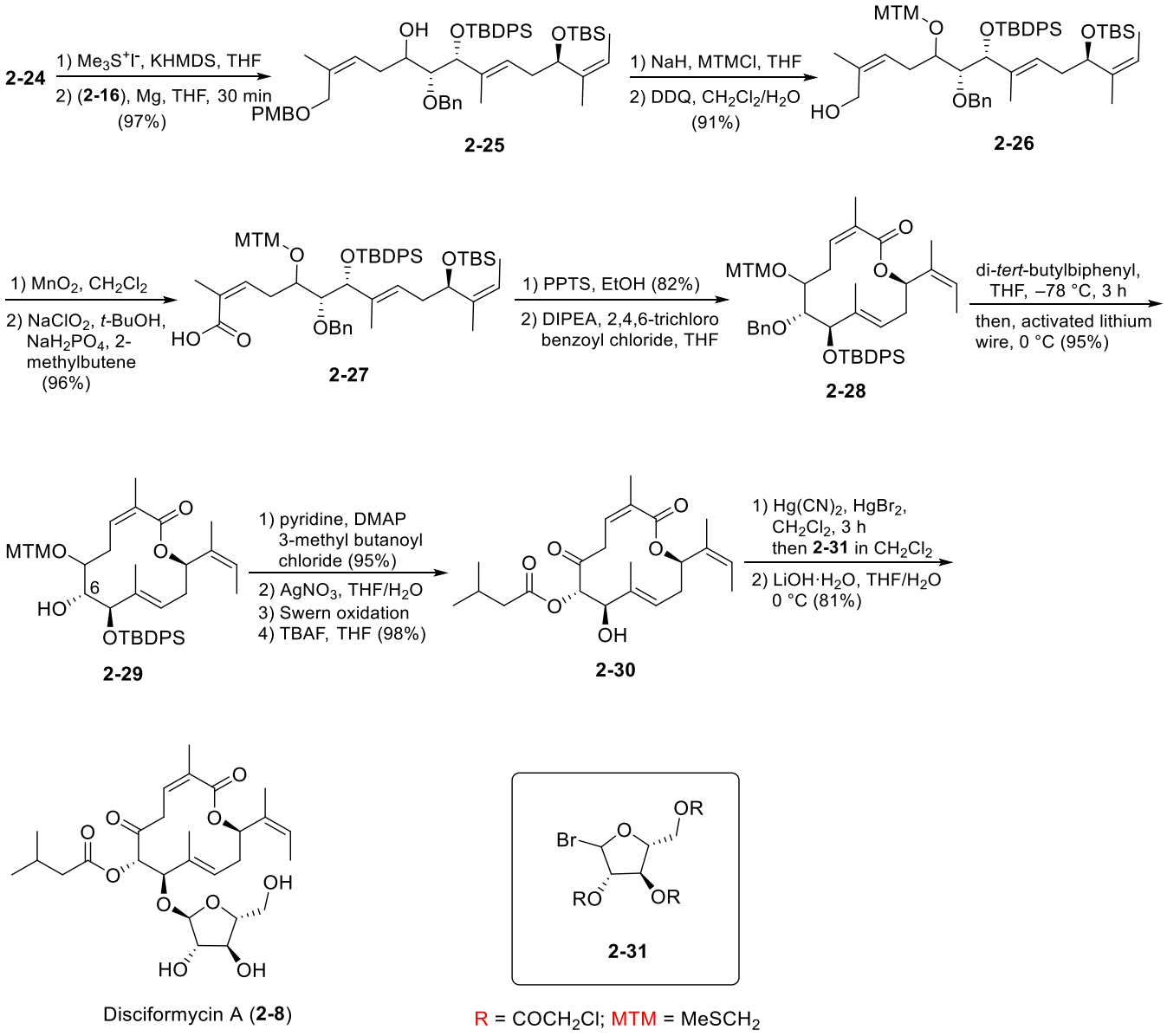
Scheme 27. Synthesis of (*Z*)-1-(((3-iodo-2-methylallyl)oxy)methyl)-4-methoxybenzene (**2-16**).

The required aldehyde **2-24** was prepared from (*Z*)-angelica acid methyl ester (**2-17**) in a 12 step sequence.[69] Thus, ester **2-17** was converted into amide **2-18** by reduction/oxidation and aldol reaction. Treatment of amide **2-18** with DIBAL-H at –78 °C, followed by the addition of Wittig reagent **2-19** provided ester **2-20** quantitatively.[70] Then, this ester **2-20** was transformed to aldehyde **2-21** by reduction/oxidation and an Evans aldol reaction furnished amide **2-23** in 77% yield. The next steps involve protection of secondary alcohol, reductive cleavage of the auxiliary and Swern oxidation to produce aldehyde **2-24** (**Scheme 28**).



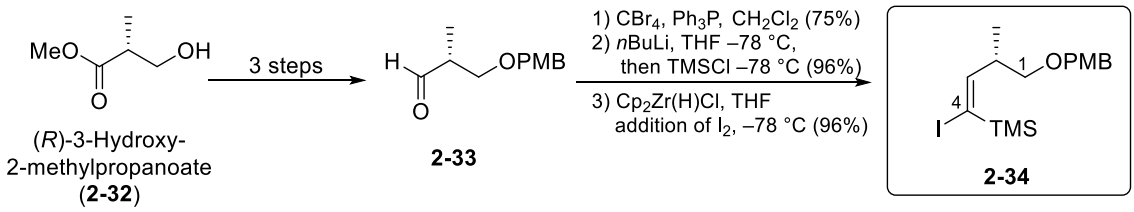
Scheme 28. Synthesis of aldehyde **2-24** from (*Z*)-angelica acid methyl ester (**2-17**).

Another key intermediate **2-25** was obtained from aldehyde **2-24** via Corey-Chaykovsky[71] reaction and opening of the resulting epoxide with **2-16**. Subsequently, protecting group manipulations delivered allyl alcohol **2-26**. Oxidation of allyl alcohol **2-26** gave seco acid **2-27** in 96% yield. This seco acid **2-27** was subjected to Yamaguchi esterification[72] using DIPEA, 2,4,6-trichloro benzoyl chloride to furnish macrolactone **2-28**. Further, the secondary alcohol **2-29** was generated by debenzylation of **2-28**.[73] The next step involved installation of the 3-methylbutanoyl group at the C6 hydroxy, which was achieved by Yamaguchi esterification of **2-28** with 3-methylbutanoyl chloride. This was followed by cleavage of the methylthiomethyl ether function at C5, Swern oxidation,[74] and TBAF mediated TBS ether cleavage which furnished macrolactone **2-30**. Finally, Disciformycin A (**2-8**) was received by attaching the arabinose derivative **2-31**[75] followed by hydrolysis of ester (**Scheme 29**).



Scheme 29. Total synthesis of Disciformycin A (**2-8**) displayed in a patent 2016.[66]

A second, total synthesis of Disciformycin A (**2-8**) and B (**2-9**) was reported by Fürstner *et al.*[76] in 2018 that is outlined below (**Schemes 31-35**). The key features of their synthesis are C-silyl building block **2-34** that can be easily functionalized at the C4 position and macrolactone formation via ring closing alkyne metathesis RCAM with formation of C8-C9 bond.[77] The key intermediate vinyl TMS compound **2-34** was obtained from easily available (*R*)-3-hydroxy-2-methylpropanoate (**2-32**). This ester was converted to aldehyde **2-33** in a three step sequence. Thereafter, Corey-Fuchs and Schwartz's reagent ($Cp_2Zr(H)Cl$)[78] were applied to afford TMS alkene **2-34** regioselectively (**Scheme 30**).



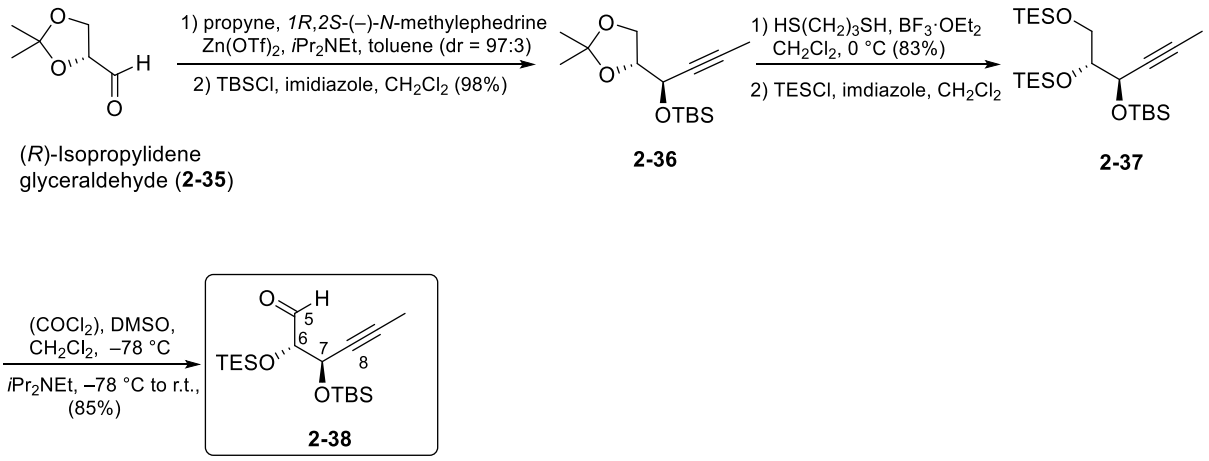
(*R*)-3-Hydroxy-2-methylpropanoate (**2-32**)

2-33

2-34

Scheme 30. Synthesis of C1-C4 building block featuring a vinyl silyl group **2-34**.

Another fragment, aldehyde **2-38** was efficiently prepared from (*R*)-isopropylideneglyceraldehyde (**2-35**) in a five step sequence. Thus, (*R*)-isopropylideneglyceraldehyde (**2-35**) was subjected to Carreira reaction protocol[79] using propyne, *1R,2S*-(–)-*N*-methylephedrine, and $Zn(OTf)_2$. The resulting secondary alcohol was protected with TBSCl in the presence of imidazole to give TBS ether **2-36**. Hydrolysis of the acetal under acidic conditions gave a diol which was converted to TES ether **2-37** by reacting it with TESCl in dichloromethane. A selective cleavage of the primary TES ether and Swern oxidation furnished aldehyde **2-38**[80] in 85% yield (**Scheme 31**).



(*R*)-Isopropylidene glyceraldehyde (**2-35**)

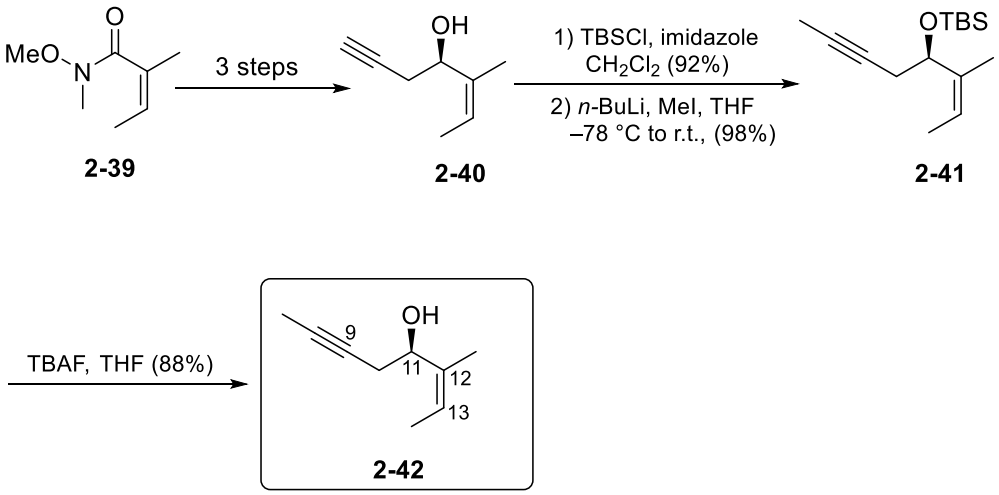
2-36

2-37

2-38

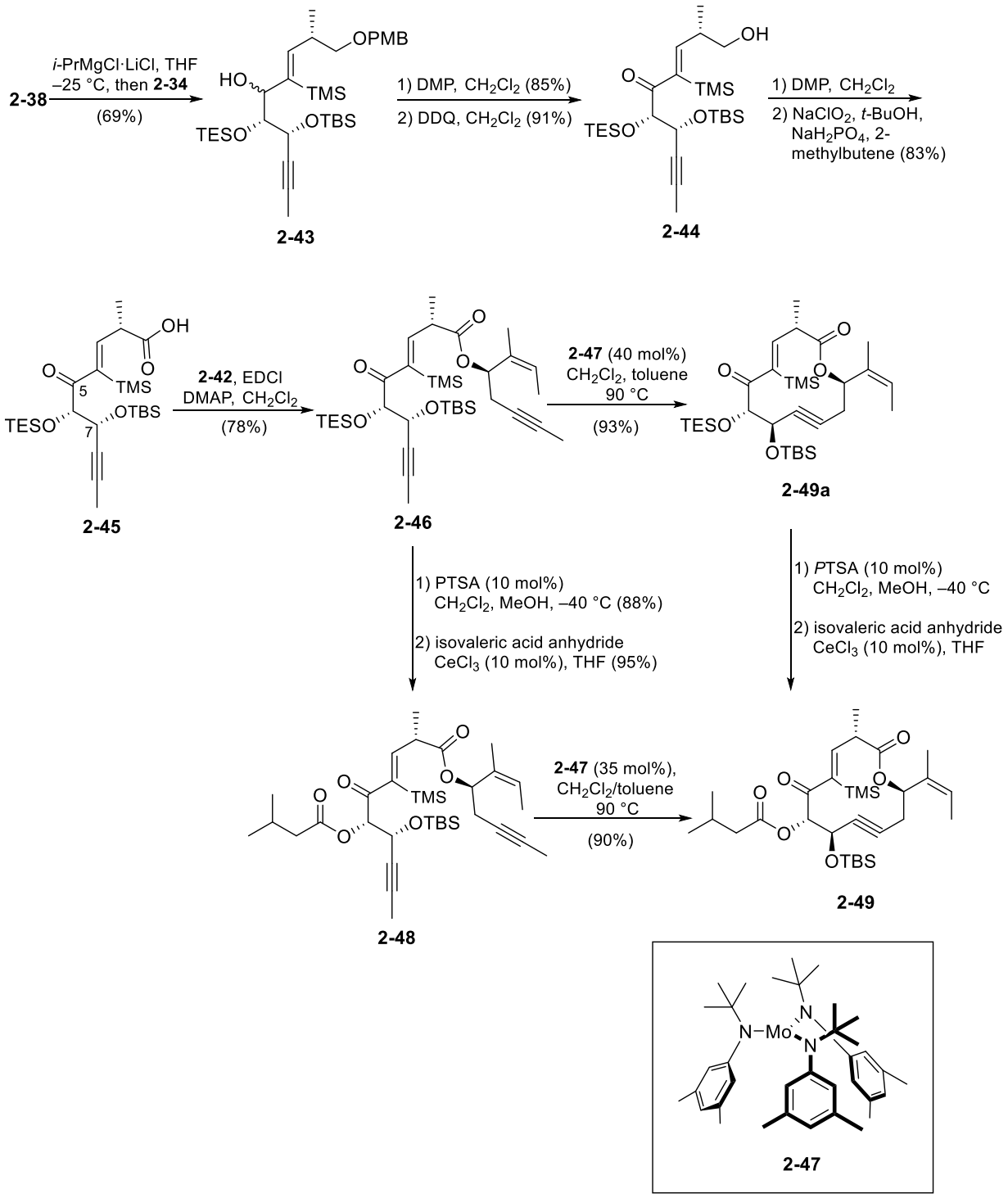
Scheme 31. Synthesis of intermediate **2-38** from (*R*)-isopropylideneglyceraldehyde (**2-35**).

The section containing the side chain **2-42** was prepared from the commercially available (*Z*)-2-methylbut-2-enoic acid. The derived Weinreb amide **2-39** was converted to alcohol **2-40** with 91% ee by Corey-Bakshi-Shibata reaction on the corresponding ketone.[81] The resulting secondary alcohol **2-40** was converted to the TBS ether and after that lithiation using *n*-BuLi, and addition of MeI furnished alkyne **2-41** in 98% yield. TBAF mediated cleavage of silyl ether **2-41** delivered the corresponding alcohol **2-42** in 88% yield (**Scheme 32**).



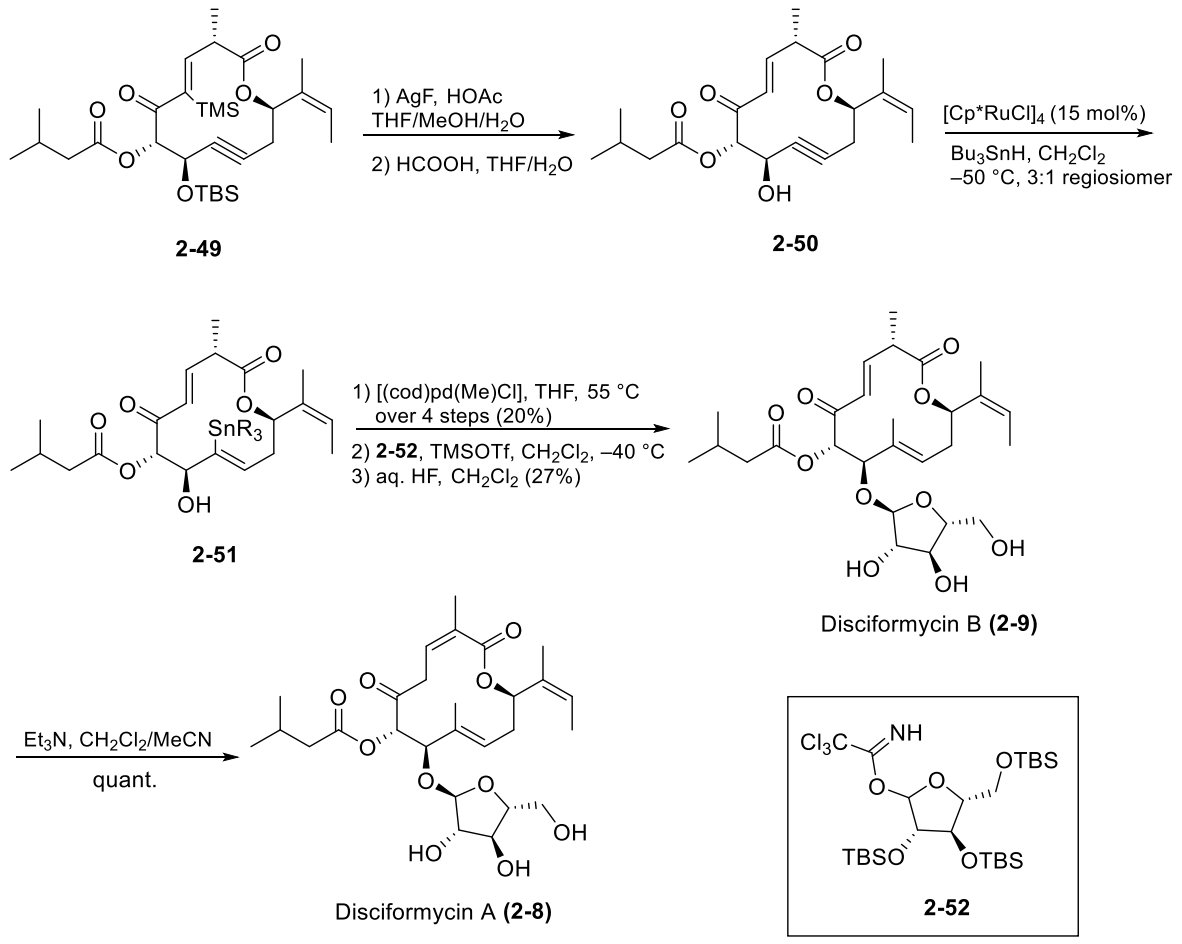
Scheme 32. Synthesis of key intermediate **2-42**.

Thereafter, key fragments **2-38** and **2-34** were coupled through metal-halogen exchange strategy.[82] Thus, vinyl iodosilane **2-34** was first treated with *i*PrMgCl·LiCl at –25 °C and the resulting Grignard reagent reacted with aldehyde **2-38** to furnish alcohol **2-43** in 69% yield.[83] Further, oxidization of the secondary alcohol, removal of the PMB group, and oxidation of primary alcohol gave secoacid **2-45**. Afterwards, the seco acid **2-45** was treated with EDCl, DMAP in the presence of alcohol **2-42** to deliver ester derivative **2-46** in 78% yield. After cleavage of TES ether, the isovalerate was attached at C6 position using $CeCl_3$ as a catalyst[84] and macrocyclization (rcam) gave **2-49**. Also, the authors described an alternative way to prepare lactone **2-49** where the rcam with molybdenum catalyst **2-47** was performed prior to attachment at the isovaleryl substituent (**Scheme 33**).



Scheme 33. Synthesis of macrolactone **2-49** via ring closing alkyne metathesis (RCAM).

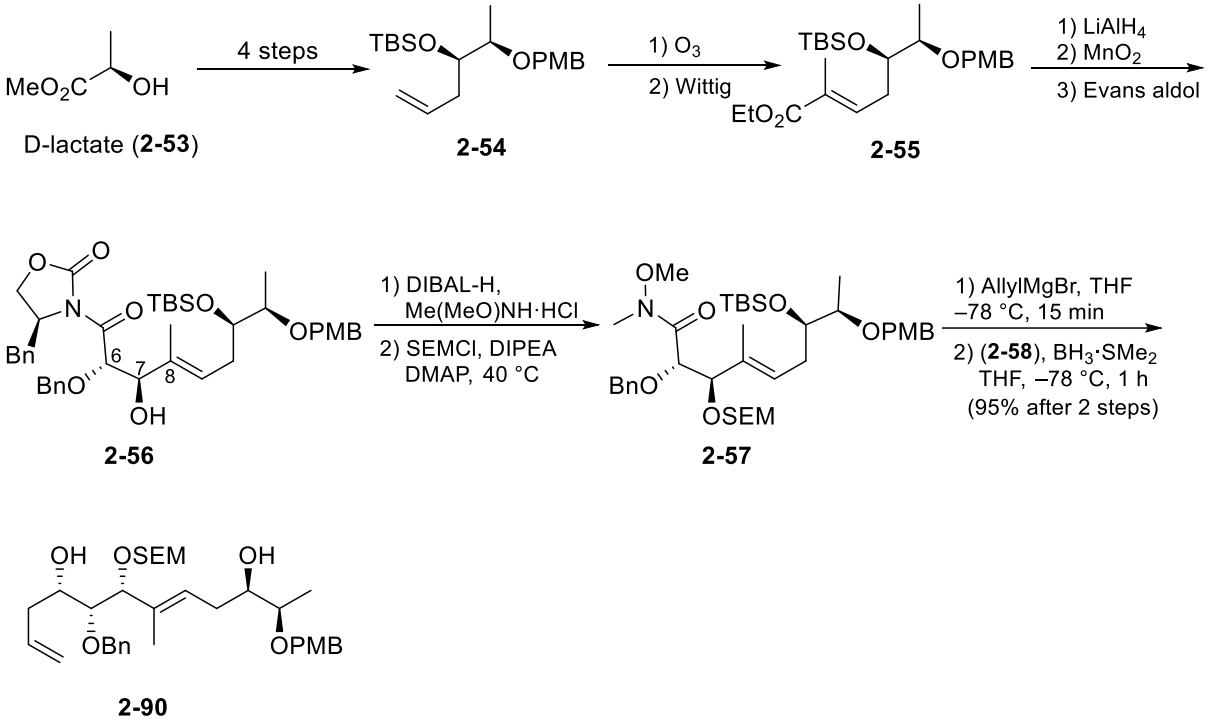
The formal trans hydromethylation of the triple bond proved quite challenging. First, the TMS group was removed from macrolactone **2-49** using AgF, HOAc in THF/MeOH/H_2O.[85] Then, the TBS ether was cleaved under acidic medium to furnish propargyl alcohol **2-50** without acyl group migration. Alcohol **2-50** was converted to tributyltin derivate **2-51** in high regioselectivity using 15mol% of $[Cp^*RuCl]_4$ as a catalyst.[86] Next, Stille coupling at C8 and glycosylation with arabinose derivate **2-52** at C7 position completed the target molecule Disciformycin B (**2-9**). Furthermore, Disciformycin B (**2-9**) was treated with Et_3N in CH_2Cl_2/MeCN to afford Disciformycin A (**2-8**) in quantitative yield (**Scheme 34**).



Scheme 34. Total synthesis of Disciformycin A (**2-8**) and B (**2-9**) by Fürstner *et al.*[76]

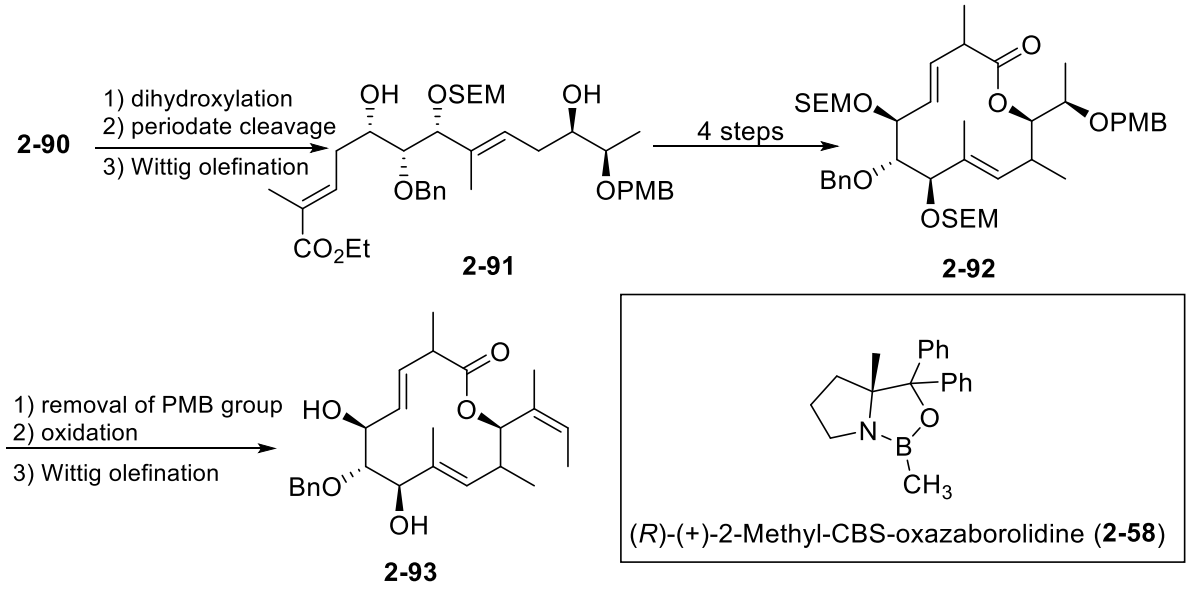
Kirschning *et al.*[65] described the total synthesis of the aglycon of Disciformycin B (**2-9**) in 2018. The required intermediate alkene **2-54** was synthesized from commercially available D-lactate (**2-53**) in 4 steps (**Scheme 35**). Further steps involved an ozonolysis[87] and Wittig olefination[88] which gave ethyl ester **2-55** in 10:1 diastereoselectivity. The ester **2-55** was converted to the aldehyde by reduction/oxidation and following an Evans aldol protocol[89] forming the C6-C7 bond, product **2-56** was obtained with in good diastereoselectivity. Next, formation of Weinreb amide by using DIBAL-H, and *N*,*O*-dimethylhydroxylamine hydrochloride was followed by protection of the C7

alcohol to give compound **2-57**. Towards macrolactone formation, allyl magnesium bromide was added to Weinreb amide **2-57** and stereoselective reduction of the resulting ketone using CBS-reagent (**2-58**) together with BH_3·DMS[90] furnished alcohol **2-90** in 95% yield.



Scheme 35. Synthesis of alcohol **2-90** from D-lactate (**2-53**) by Kirschning *et al.*[65]

Further synthetic sequence consisted of Sharpless dihydroxylation,[91] periodate cleavage, and Wittig olefination[88] which gave α,β-unsaturated ester **2-91**. Protecting group manipulations and Yamaguchi lactonization[92] resulted in macrolactone **2-92**. After the PMB cleavage the obtained alcohol was oxidized and the derived ketone subjected to Wittig olefination to provide the aglycon of Disciformycin B (**2-93**) in 6:1 *E*/*Z* ratio. This synthesis requires around 23 steps (**Scheme 36**).



Scheme 36. Synthesis of the aglycon of Disciformycin B (**2-93**) by Kirschning *et al.*[65]

8. Goal of the research

The aim of our project was to develop a total synthesis of Gulmirecin B (**2-11**) for biological activity studies. Gulmirecin A (**2-10**) and B (**2-11**) were isolated from the predatory bacterium *Pyxidicoccus fallax* HKI 727 by Nett *et al.*[62] They have strong antibacterial activity against *Staphylococcus* species. Structurally, the Gulmirecins are 12-membered macrolactones containing four stereocentres, two trisubstituted double bonds, and α-arabinofuranose attached at the C-7 position. All these features attracted us to embark on a synthesis of Gulmirecin B (**2-11**). Our retrosynthetic plan for Gulmirecin B (**2-11**) is outlined in **Figure 18**. Our initial plan was to make the macrolactone **2-94** by using two key fragments, the organozinc reagent **2-95** (C1-C4 building block) and the Weinreb amide **2-96** (C5-C14 building block), which contains the crucial trisubstituted double bond at C8/C9. Intermediate **2-95** can be synthesized from 5-hexenoic acid via asymmetric alkylation.[93] The C7-C8 bond formation to give **2-96** could be generated from ketone **2-98** via enolization and cross-coupling. Ketone **2-98** in turn should be available from tartrate derivative **2-99** and the Grignard reagent **2-101** (C9-C14 fragment).[94] The latter can be traced back to L-malic acid (**2-102**). Finally, Gulmirecin B (**2-11**) could be obtained by removal of the protecting group at C7 followed by attachment of the sugar moiety.

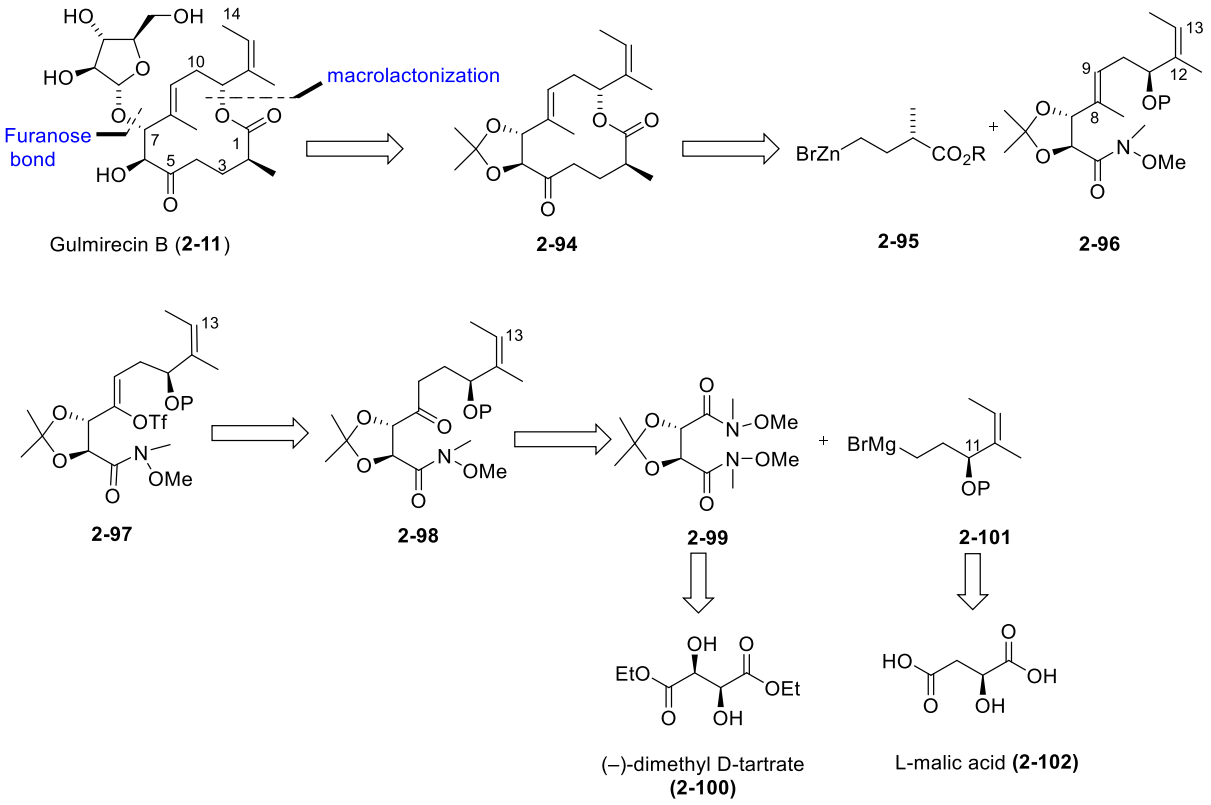


Figure 18. Retrosynthetic plan for Gulmirecin B (**2-11**).

From a synthetic point of view, the most challenging step would be the formation of the (*E*)-trisubstituted double bond between C8-C9 via cross-coupling. We were aware of the fact that vinyl triflate **2-97** could undergo an intramolecular Heck coupling to the C12/C13 double bond instead of the desired coupling with a methyl anion equivalent. To address these issues, we considered a model study with 5-bromopent-1-ene (**2-103**) (**Figure 19**).

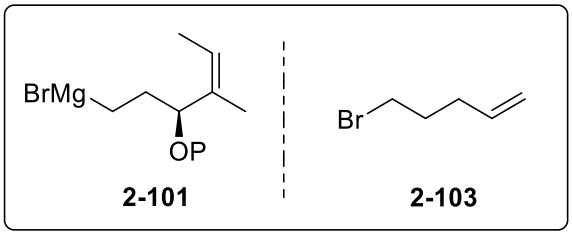
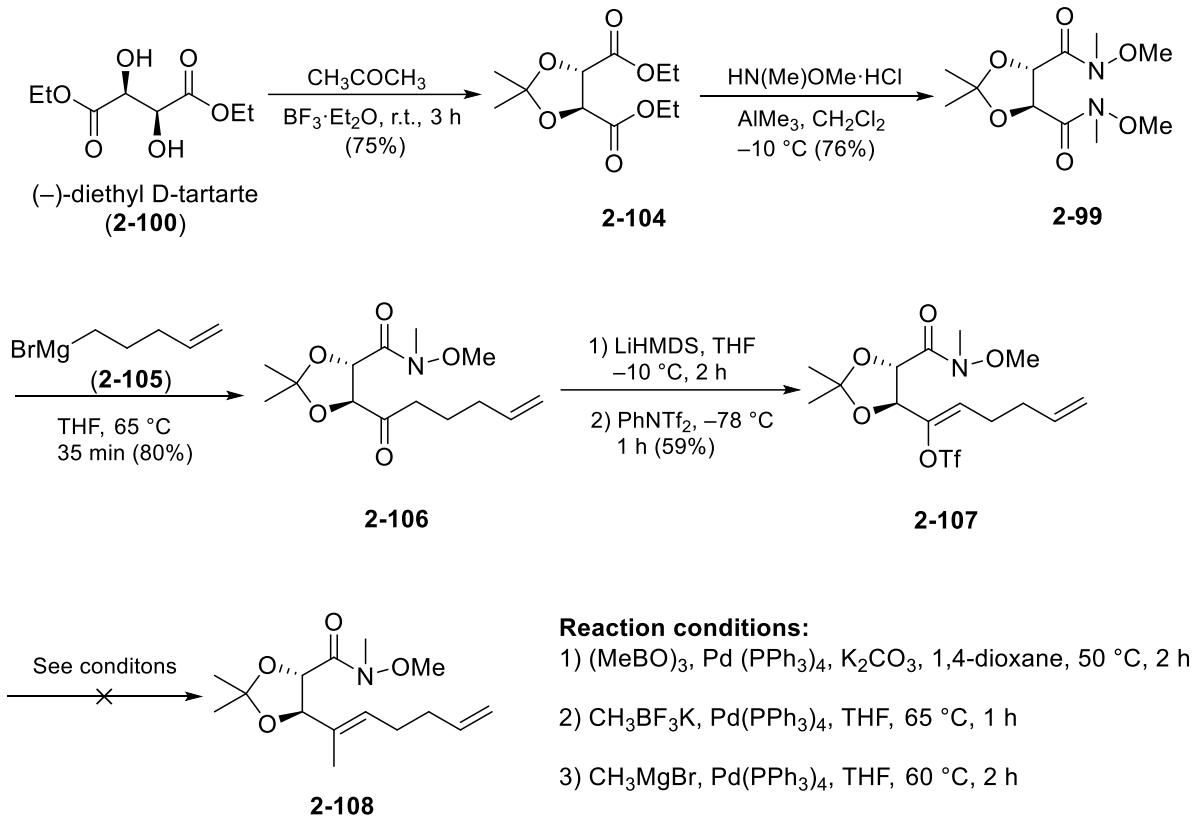


Figure 19. Model studies with 5-bromopent-1-ene (**2-103**) towards the total synthesis of Gulmirecin B (**2-11**).

9. Results and Discussion

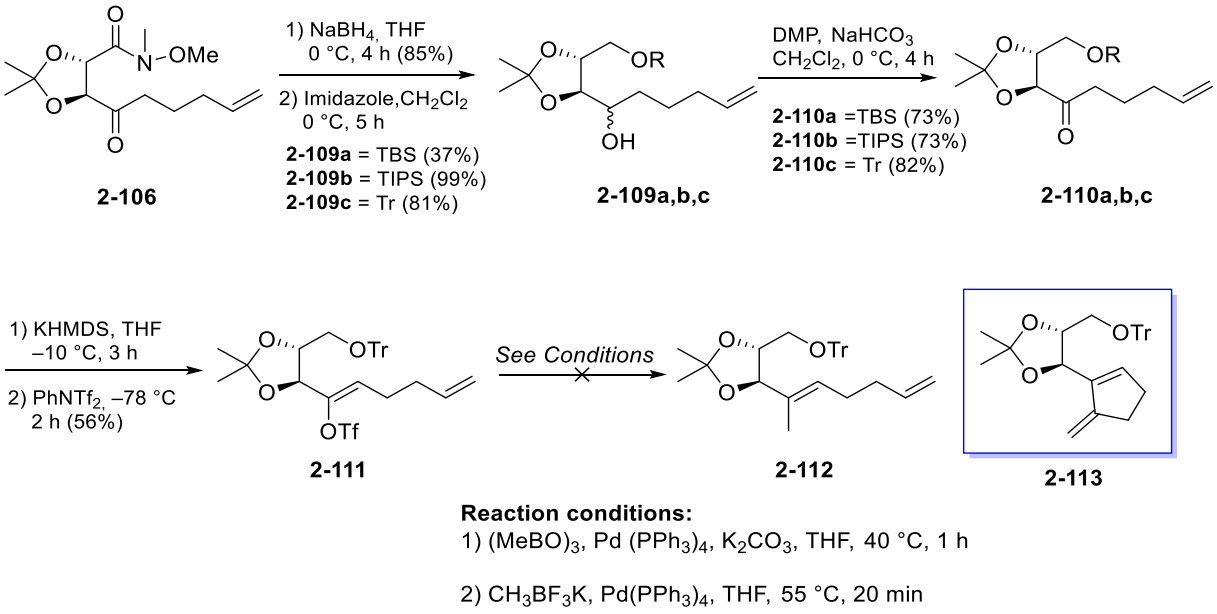
9.1 Model studies towards Gulmirecin B

As discussed in the retrosynthetic analysis, we synthesized bis-Weinreb amide **2-99** from commercially available (–)-diethyl-D-tartarte (**2-100**) using a literature procedure.[95] The starting material (–)-diethyl-D-tartarte was treated with acetone in the presence of $BF_3 \cdot OEt_2$ affording dimethoxy ester **2-104** in 75% yield.[96] Thereafter, dimethyl ester **2-104** was treated with *N,O*-dimethyl hydroxylamine and trimethyl aluminum (3M in toluene) at –10 °C, which gave us bis-Weinreb amide **2-99** as a white solid in 68% yield. The next step was the controlled addition of 4-pentenyl magnesium bromide (**2-105**) to bis-Weinreb amide **2-99** at 0 °C leading to the formation of mono keto with Weinreb-amide **2-106** in 80% yield. Mono additions of Grignard or organolithium reagent to bis-Weinreb amide **2-99** have been described in the literature.[97] Further reactions aimed at the formation of a trisubstituted double bond at C5 position. The mono ketone **2-106** was enolized using LiHMDS in THF at –78 °C and the resulting enolate was trapped by addition of $PhNTf_2$ to provide enol triflate **2-107** in 59% yield. Next step was the conversion of OTf to methyl group **2-108** via cross-coupling. Initially, we applied Kumada coupling conditions using MeMgBr in the presence of a palladium catalyst.[98] Unfortunately, we did not receive **2-108**. In parallel, we tried two different Suzuki conditions such as 1) $MeBF_3K$ (1.5 equiv), $Pd(PPh_3)_4$ in THF[99] and 2) $(MeBO)_3$, K_2CO_3, $Pd(PPh_3)_4$ in 1,4-dioxane at 50 °C. However, the crucial cross coupling reaction did not work in our hands. In all the cases, we received only a complex mixture as shown by TLC as well as ^{1}H NMR (**Scheme 37**).



Scheme 37. Model studies with 4-pentenyl magnesium bromide (**2-105**).

We assumed that vinyl triflate **2-107** in the presence of Weinreb amide was not suitable for a cross coupling by palladium catalysis. Therefore, we decided to reduce the ketone and Weinreb amide **2-106** simultaneously using $NaBH_4$ in THF[94] which gave a mixture of secondary and primary alcohols (**Scheme 38**). First, primary alcohol was converted into TBS ether **2-109a**, TIPS ether **2-109b** and trityl ether **2-109c** using classical conditions.[100] The next step was the oxidation of secondary alcohols **2-109a-c** using DMP, $NaHCO_3$ in CH_2Cl_2 which delivered ketones **2-110a-c** in good yield. With ketones **2-110a-c** in hand, we tested them for an enolization reaction using KHMDS or LiHMDS and addition of $PhNTf_2$.[98] However, we observed that enolization doesn't take place in the presence of silyl ether derivatives **2-110a-b**. Interestingly, trityl ether **2-110c** delivered OTf **2-111** using KHMDS in THF at –78 °C and addition of $PhNTf_2$ in 56% yield. In order to prepare **2-112**, vinyl triflate **2-111** was subjected for cross coupling using two different conditions such as 1) $(MeBO)_3$, anhydrous K_2CO_3, $Pd(PPh_3)_4$ in THF at 40 °C for 1 h, and 2) CH_3BF_3K, $Pd(PPh_3)_4$ in THF at 55 °C for 20 min. In both cases, we found that coupling occurred with the terminal double bond to give intramolecular Heck coupling product **2-113** which was confirmed by ^1H NMR and HRMS analysis (**Figure 20**).



Scheme 38. Attempts at cross coupling of **2-111** to get diene **2-112** with a trisubstituted double bond.

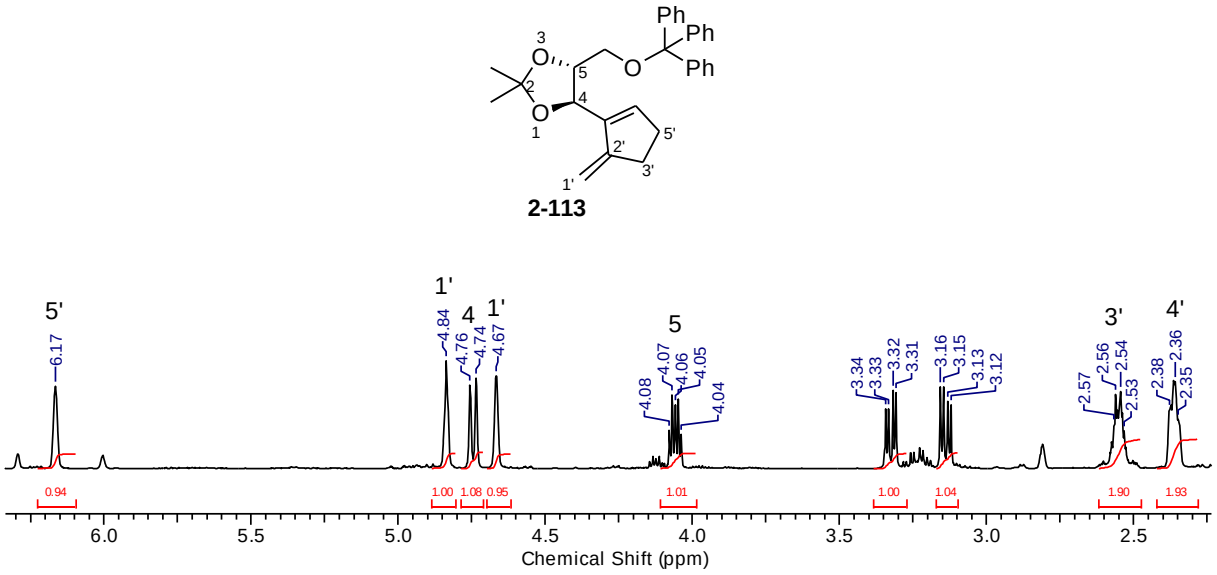
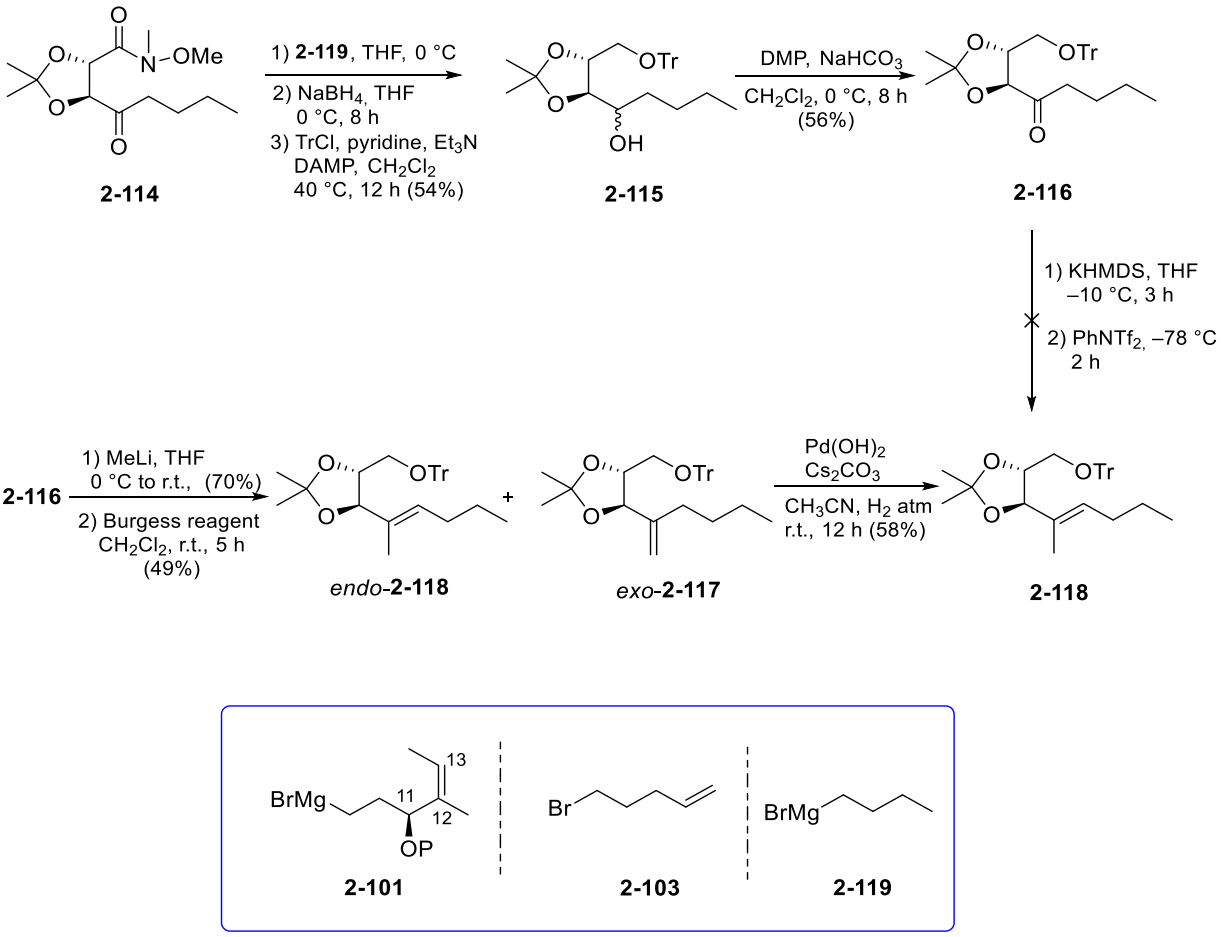


Figure 20. ^{1}H NMR spectrum of intramolecular Heck coupling product **2-113**.

Simultaneously, we did the enolization reaction without the double bond on the side chain (**Scheme 39**). We used our initially established procedures for all the transformation to get **2-116**. A freshly prepared solution of butylmagnesium bromide (**2-119**) was slowly added to bis-Weinreb amide **2-99** to give mono ketone **2-114** in good yield. Further steps were oxidation of alcohol **2-115** and

enolization of **2-116** using standard conditions. Surprisingly, the desired vinyl triflate **2-118** could not be obtained. Eventually, we decided to prepare **2-118** via Grignard addition and subsequent elimination. Hence, **2-114** was treated with MeLi in THF at 0 °C to provide a mixture of tertiary alcohols. Then, elimination of water using Burgess reagent ($MeO_2CN^-SO_2N^+Et_3$)[101] gave endo/exo **2-117** (1:0.78) which was subjected for isomerization in the presence of $Pd(OH)_2$, Cs_2CO_3[102] in CH_3CN to give **2-118** in 58% yield. However, we could not implement this strategy with real fragment **2-101** due to the double bond at the C11 position which could also isomerize during the process.



Scheme 39. Studies related to the construction of the trisubstituted double bond with ketone **2-166** lacking a terminal double bond.

9.2 Second retrosynthetic analysis featuring a Shapiro reaction

Our second retrosynthetic plan was based on the formation of vinyllithium reagent **2-122** via Shapiro reaction.[103] According to Shapiro reaction, the vinyllithium **2-122** could be obtained from sulfonylhydrazone **2-124** using *sec*-BuLi as a base. The required sulfonylhydrazone **2-124** can be synthesized from ketone **2-125** using 2,4,6-triisopropylbenzenesulfonylhydrazide (**Figure 21**).

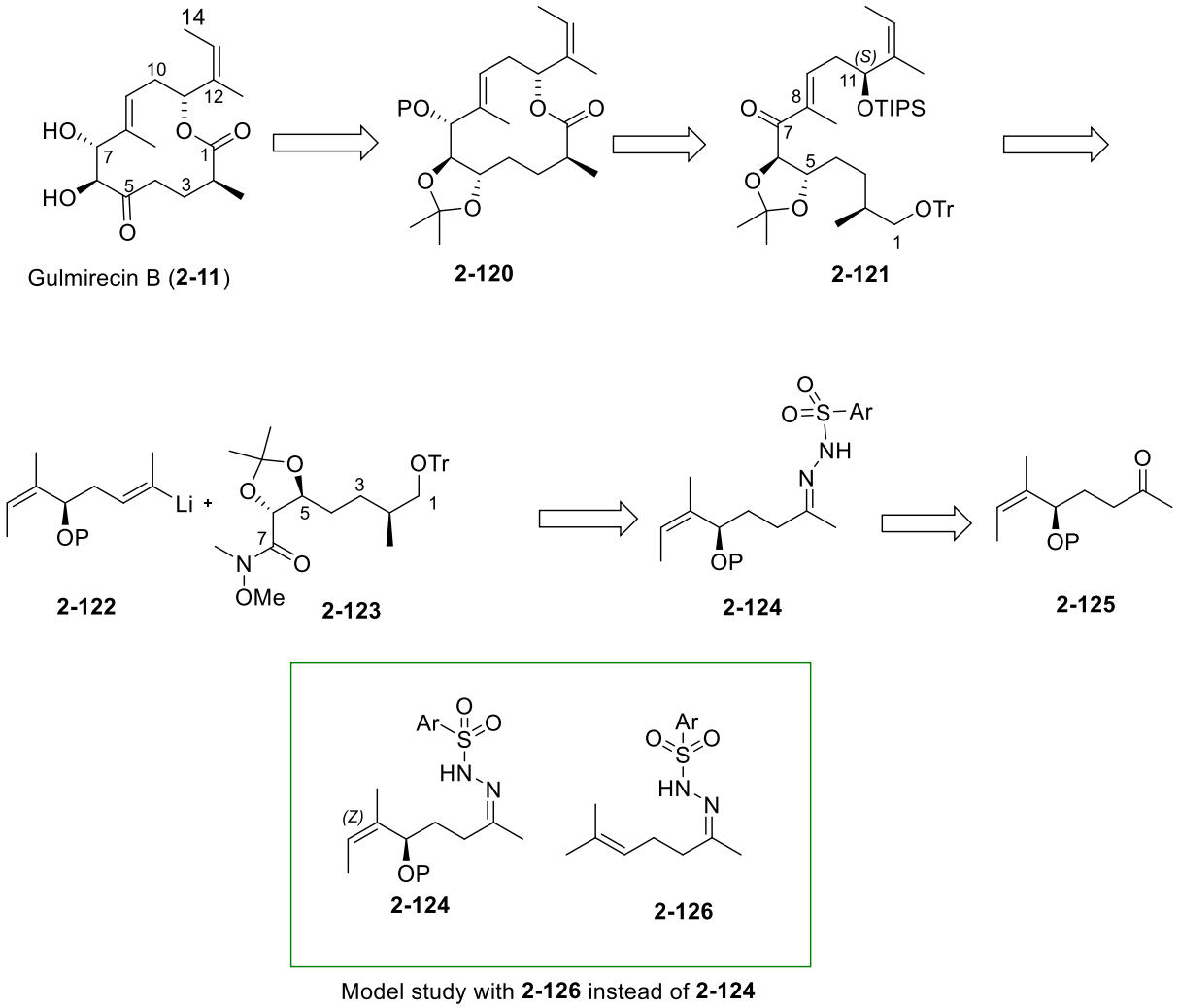
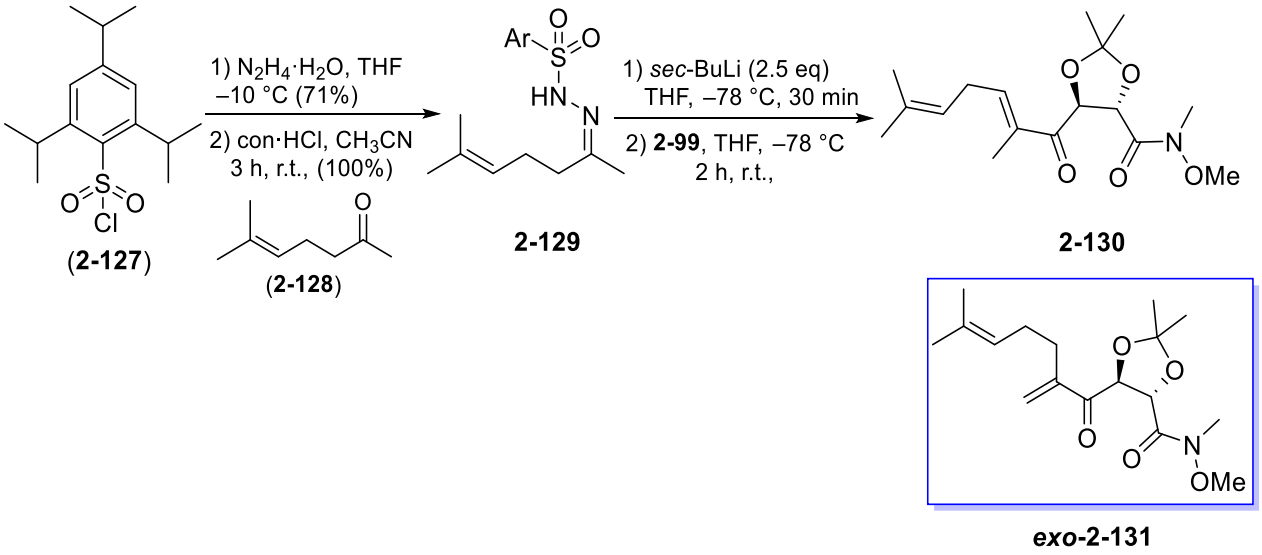


Figure 21. The second retrosynthetic analysis for Gulmirecin B (**2-1**) based on a Shapiro reaction to form the C7-C8 bond.

Before executing the above mentioned retrosynthetic plan, we aimed to make a model study with hydrazone derivative **2-126** instead of **2-124**. These studies would allow us to develop a precursor **2-124** towards Gulmirecin B (**2-11**). In order to prepare **2-126**, we started with 2,4,6-triisopropylbenzenesulfonyl chloride (**2-127**) which was treated with hydrazine hydrate under acidic condition affording 2,4,6-triisopropylbenzenesulfonylhydrazide[104] as a white solid.

Immediately, 2,4,6-triisopropylbenzenesulfonylhydrazide was condensed with 6-methylhept-5-en-2-one (**2-128**) in presence of aqueous HCl in CH_3CN which gave us hydrazone **2-129** as a white solid.[105] Hydrazone **2-129** was treated with 2.5 equiv of *sec*-BuLi in THF at –78 °C to generate the intermediate vinyllithium species which was added to bis-Weinreb amide **2-99** at –78 °C. Unfortunately, we obtained *exo*-**2-131** instead of **2-130**. The ^{1}H NMR spectrum showed two singlet protons at 5.92 and 6.22 ppm and missed the CH_3 group signal around at 1.45 ppm (**Figure 22**). It means that during the addition of *sec*-BuLi to **2-129**, deprotonation occurred from methyl group (**Scheme 40**).



Scheme 40. Model studies to form enone **2-130** by Shapiro reaction.

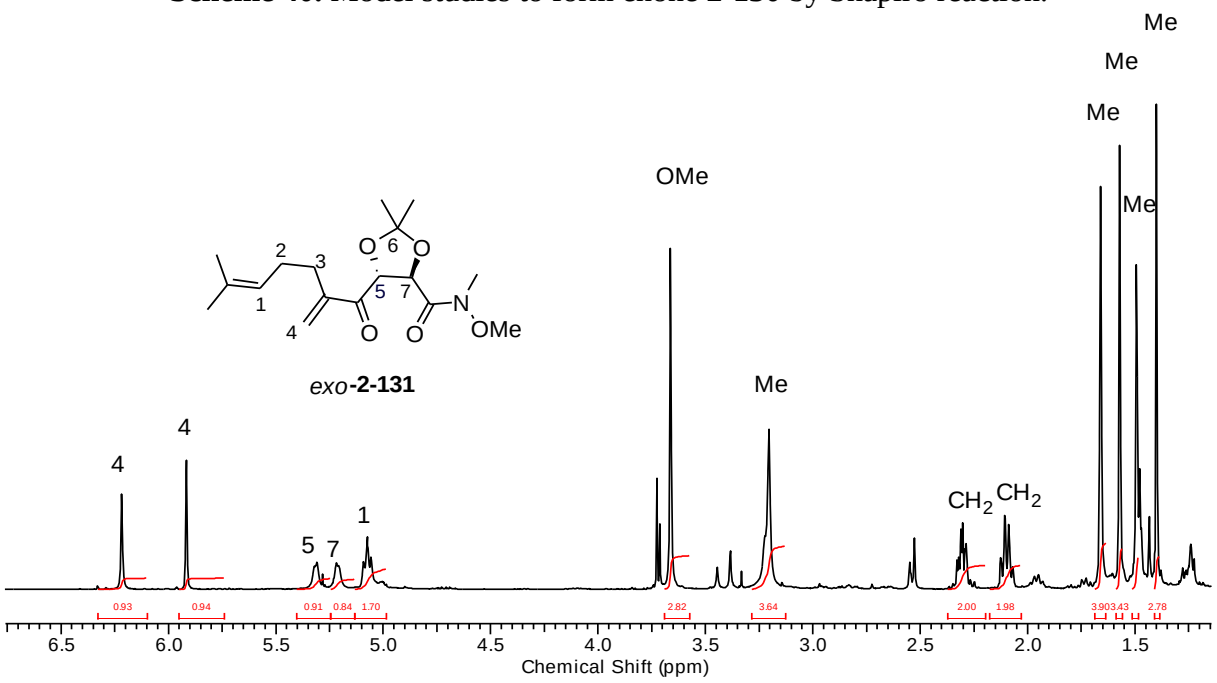
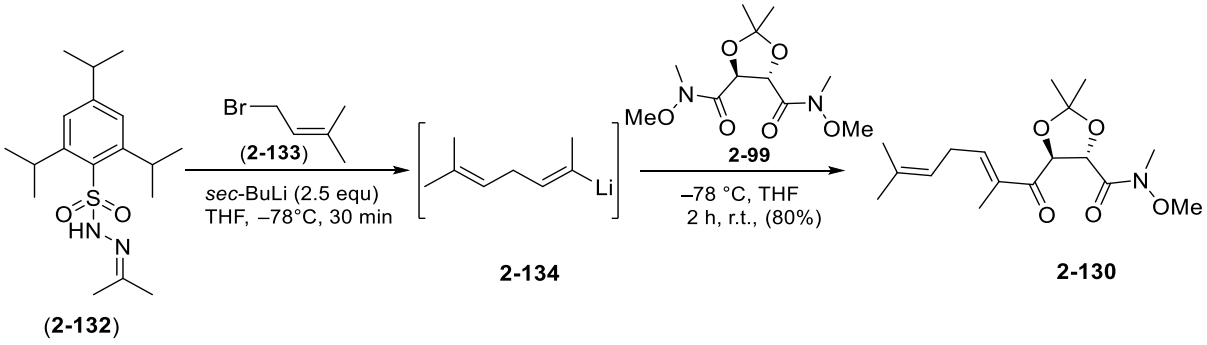


Figure 22. ^{1}H NMR spectrum of enone *exo*-**2-131**.

On the other hand, when we generated vinyllithium species **2-134** *in situ* from dimethylallyl bromide and the acetone sulfonylhydrazone[106] **2-132** and added the resulting vinyllithium species to bis-Weinreb amide **2-99** at –78 °C, the desired enone **2-130** was obtained. The ^{1}H NMR clearly indicates a CH_3 group signal at 1.40 as a singlet and there are no signals between 5.5 and 6.5 ppm (**Figure 23**). Since the third approach seemed more promising, we did not continue this approach towards the total synthesis of Gulmirecin B (**2-11**) (**Scheme 41**).



Scheme 41. Synthesis of vinyllithium **2-134** using the 3,3-dimethylallyl bromide (**2-133**).

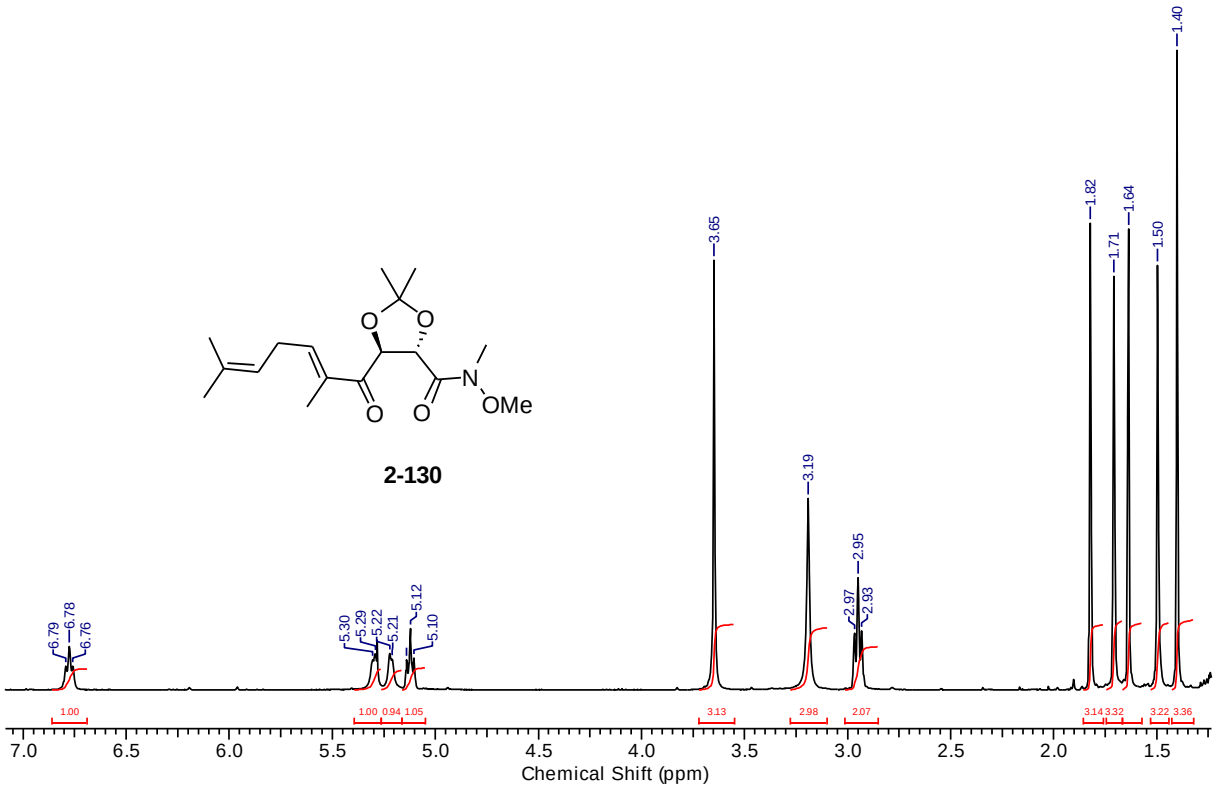


Figure 23. ^{1}H NMR spectrum indicates the desired compound **2-130**.

9.3 Third retrosynthetic analysis

In order to make the C7-C8 bond formation, our revised retrosynthetic plan is based on the addition of vinyllithium **2-138** to Weinreb amide **2-142** to get ketone **2-136**. In this case, further sequences consist of an oxidation/reduction to create a single configuration at C7. Alternatively, we considered the addition of vinyllithium **2-138** to aldehyde **2-143** to get alcohol **2-137**. Depending on the stereoselectivity of this reaction, the resulting C7 secondary alcohol could be used for attachment of the sugar. The ketone **2-136** would lead to macrolactone **2-120** via Mitsunobu lactonization (**Figure 24**).[107]

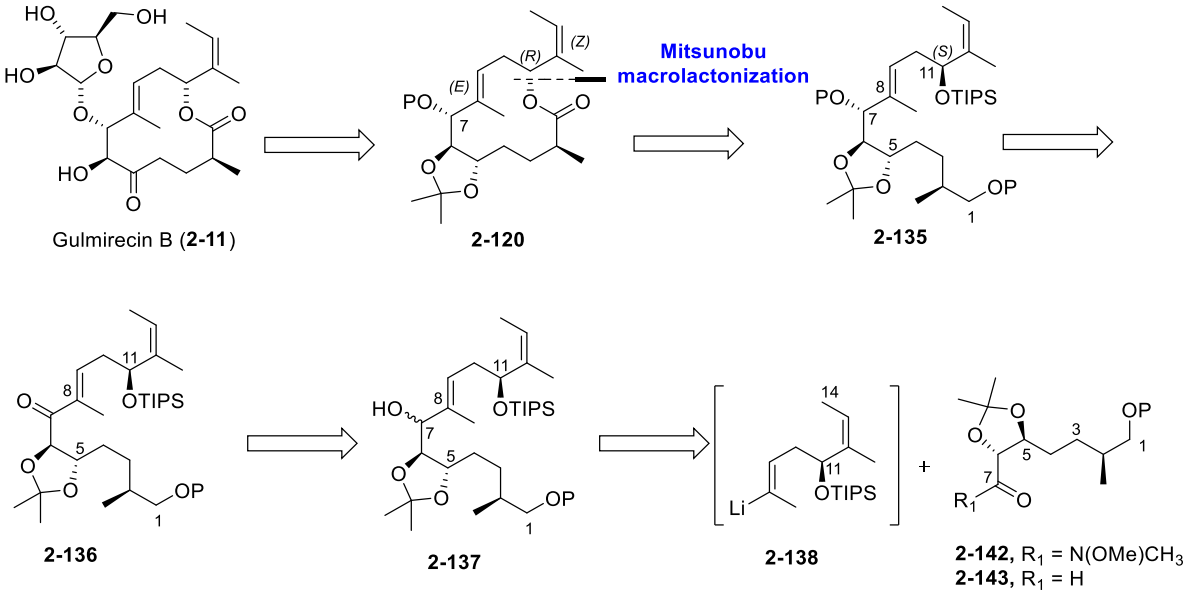


Figure 24. Third retrosynthetic plan towards Gulmirecin B (**2-11**).

The key fragment C8-C14 **2-139** can be synthesized from commercially available (*S*)-malic acid (**2-141**). The vinyl bromide functionality would come from an alkyne precursor whereas the C12-C13 double bond would be created by a Wittig reaction.[108] The required C1-C7 fragment **2-142/143** can be generated from commercially available 5-hexen-1-ol (**2-146**) via Jones oxidation,[109] asymmetric alkylation,[110] cross metathesis,[111] and Sharpless dihydroxylation[112] (**Figure 25**).

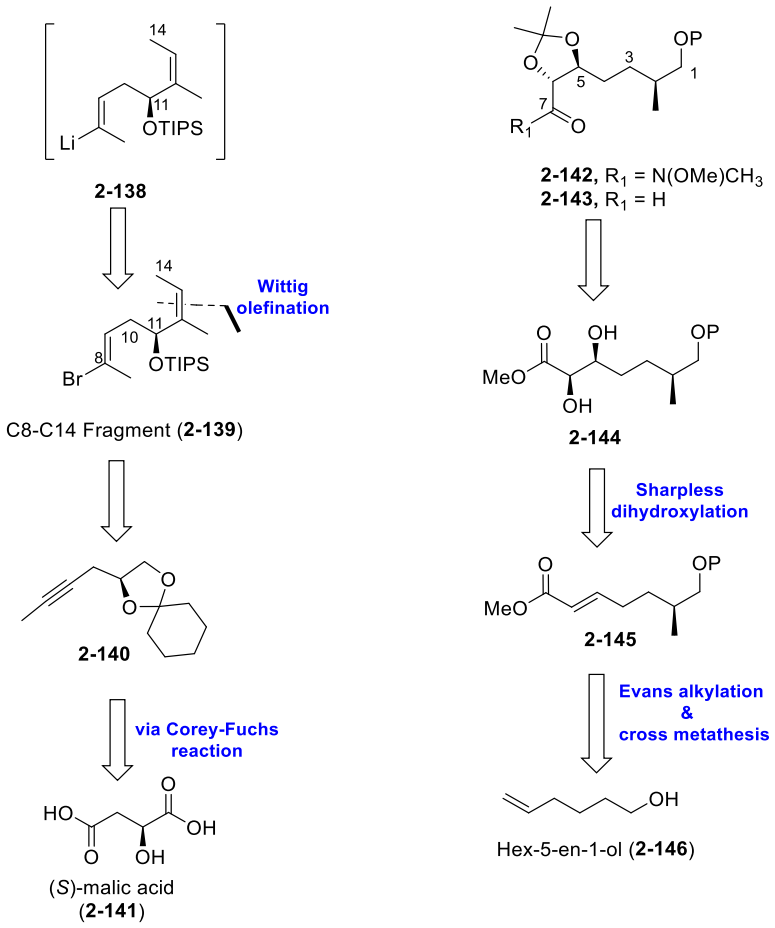
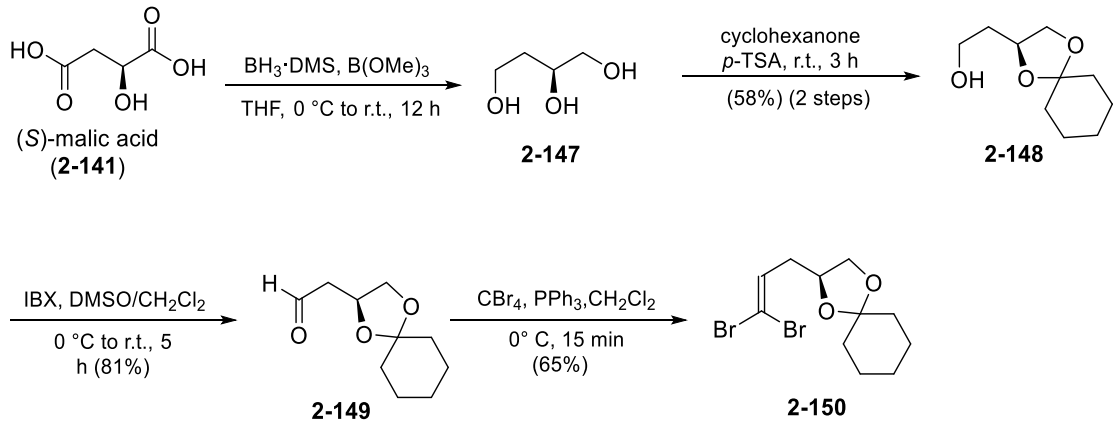


Figure 25. Third retrosynthetic plan towards the Gulmirecin B (**2-11**).

9.3.1 Synthesis of C8-C14 Fragment

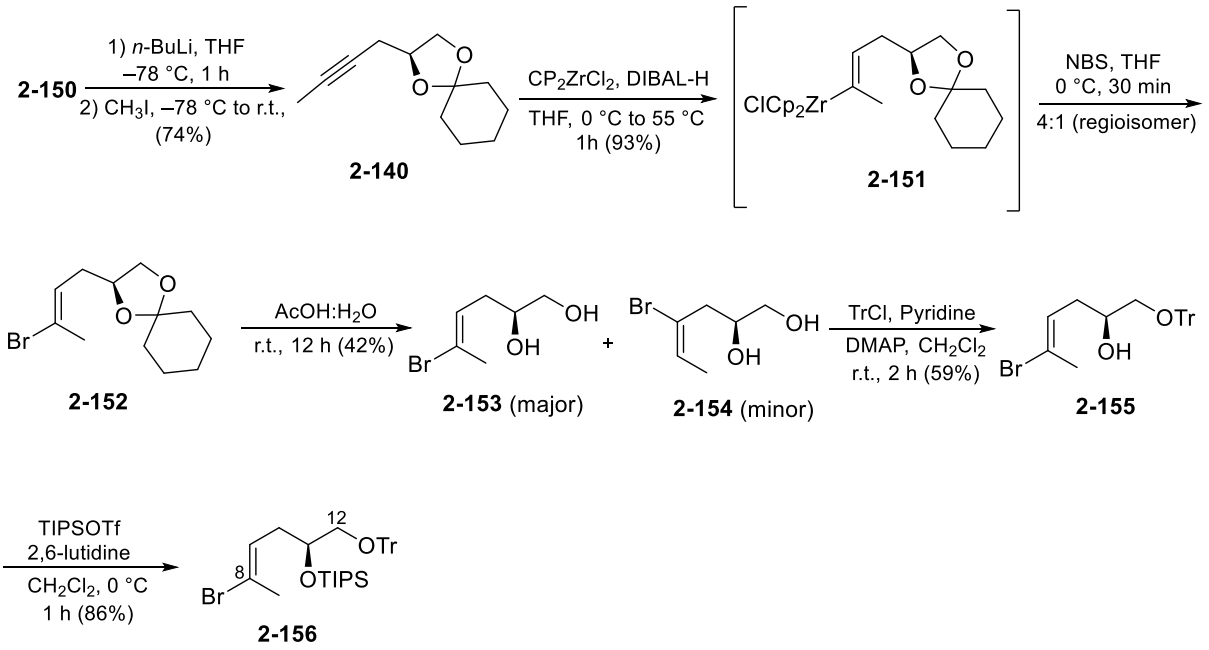
Initially, we prepared the C8-C14 fragment **2-139** using (*R*)-malic acid. Later, we decided to use (*S*)-malic acid (**2-141**) due to its cheaper price as compared to (*R*)-malic acid. Ideally one would aim at ent-**2-139** since with **2-139** the macrolactonization has to be performed under Mitsunobu condition.[107] The starting material (*S*)-malic acid (**2-141**) was reduced using BH_3·DMS and trimethyl borate to afford butanetriol **2-147**.[113] Due to the hydrophilic nature of butanetriol **2-147**, it was used without any further aqueous workup and column chromatography. The crude **2-147** was treated with cyclohexanone in acidic medium[113] which provided dioxolane **2-148** as colorless oil in 58% yield after two steps. Thereafter, the terminal alcohol **2-148** was oxidized using IBX to give the corresponding aldehyde **2-149**[114] which was further subjected for Corey-Fuchs reaction[115] using CBr_4, PPh_3 in CH_2Cl_2 to furnish dibromoalkene **2-150** in 65% yield (**Scheme 42**).



Scheme 42. Synthesis of dibromoalkene **2-150** starting from (*S*)-malic acid (**2-141**).

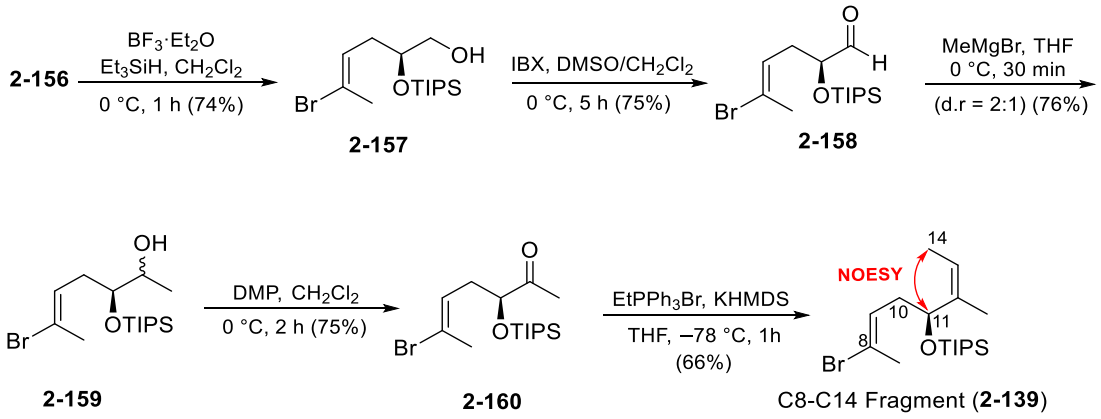
Treatment of **2-150** with *n*-BuLi in THF at –78 °C was followed by quenching the intermediate acetylide with iodomethane to provide alkyne **2-140**[115] in 74% yield. Further, alkyne **2-140** was added to a suspension of *in situ* generated Cp_2ZrHCl (Schwartz's reagent)[116] from the combination of Cp_2ZrCl_2 and DIBAL-H (1M in hexane) at 0 °C for 30 min. To complete the hydrometalation the reaction mixture was kept for 1 h at 55 °C and subsequently quenched by addition of NBS in THF at 0 °C to give vinyl bromide **2-152** with good regioselectivity (4:1). The mixture of regioisomers was subjected for deprotection without any flash chromatography. The cleavage of acetal **2-152** was accomplished with a mixture of CH_3COOH/H_2O mixture[117] at r.t.

At this point, the regioisomers were separated by flash chromatography to afford diol **2-154** (minor) and **2-153** as a major isomer in 42% yield. Thereafter, two different protecting groups were used to extend the side chain at C12-C14. Thus, primary alcohol **2-153** was converted to trityl ether **2-155** using trityl chloride, pyridine, DMAP in CH_2Cl_2 at r.t.[118] This was followed by protection of the secondary alcohol as TIPS ether **2-156** using TIPSOTf and 2,6-lutidine as base in 86% yield (**Scheme 43**).



Scheme 43. Synthesis of C8-C12 fragment **2-156** starting from dibromoalkene **2-150**.

In order to introduce the C12-C13 double bond, the trityl ether **2-156** was selectively cleaved under reductive conditions using $BF_3{\cdot}Et_2O$, Et_3SiH in CH_2Cl_2[119] to afford primary alcohol **2-157** in 75% yield. The resulting primary alcohol **2-157** was oxidized using IBX in $DMSO/CH_2Cl_2$ at r.t. Subsequently, the aldehyde **2-158** was treated with CH_3MgBr in THF to give **2-159** as a diasteromeric mixture (2:1) in 76% yield. The mixture of secondary alcohols **2-159** was oxidized using DMP to get methyl ketone **2-160** in 75% yield. Finally, methyl ketone **2-160** was subjected to Wittig olefination[108] using ethyltriphenylphosphonium bromide, and KHMDS (1M THF) in THF at –78 °C to produce (*Z*)-trisubstituted olefin **2-139** (C8-C14 fragment) in high stereoselectivity and in 66% yield (**Scheme 44**).



Scheme 44. Synthesis of C8-C14 fragment (**2-139**) via Wittig olefination.

Formation of Wittig product **2-139** was confirmed by ^{1}H NMR analysis (**Figure 26**). Confirmation of (*Z*)-trisubstituted double bond at C12 position was possible through a NOESY experiment, where we observed a relatively strong cross peak between the 11-H and 14-H (**Figure 27**).

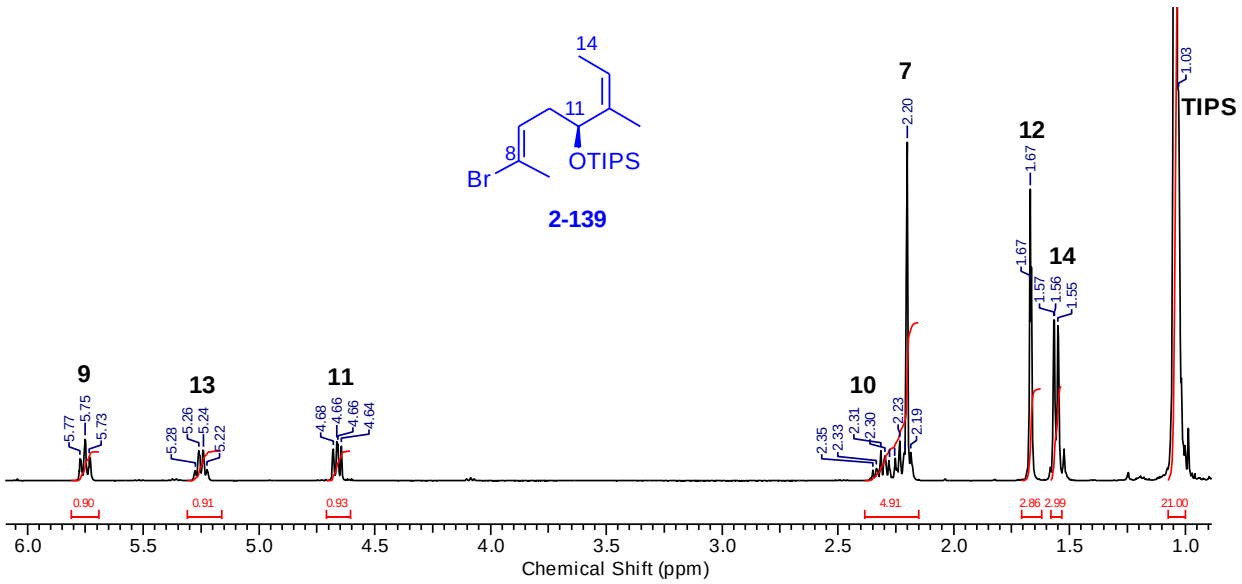


Figure 26. ^{1}H NMR spectrum of C8-C14 fragment (**2-139**).

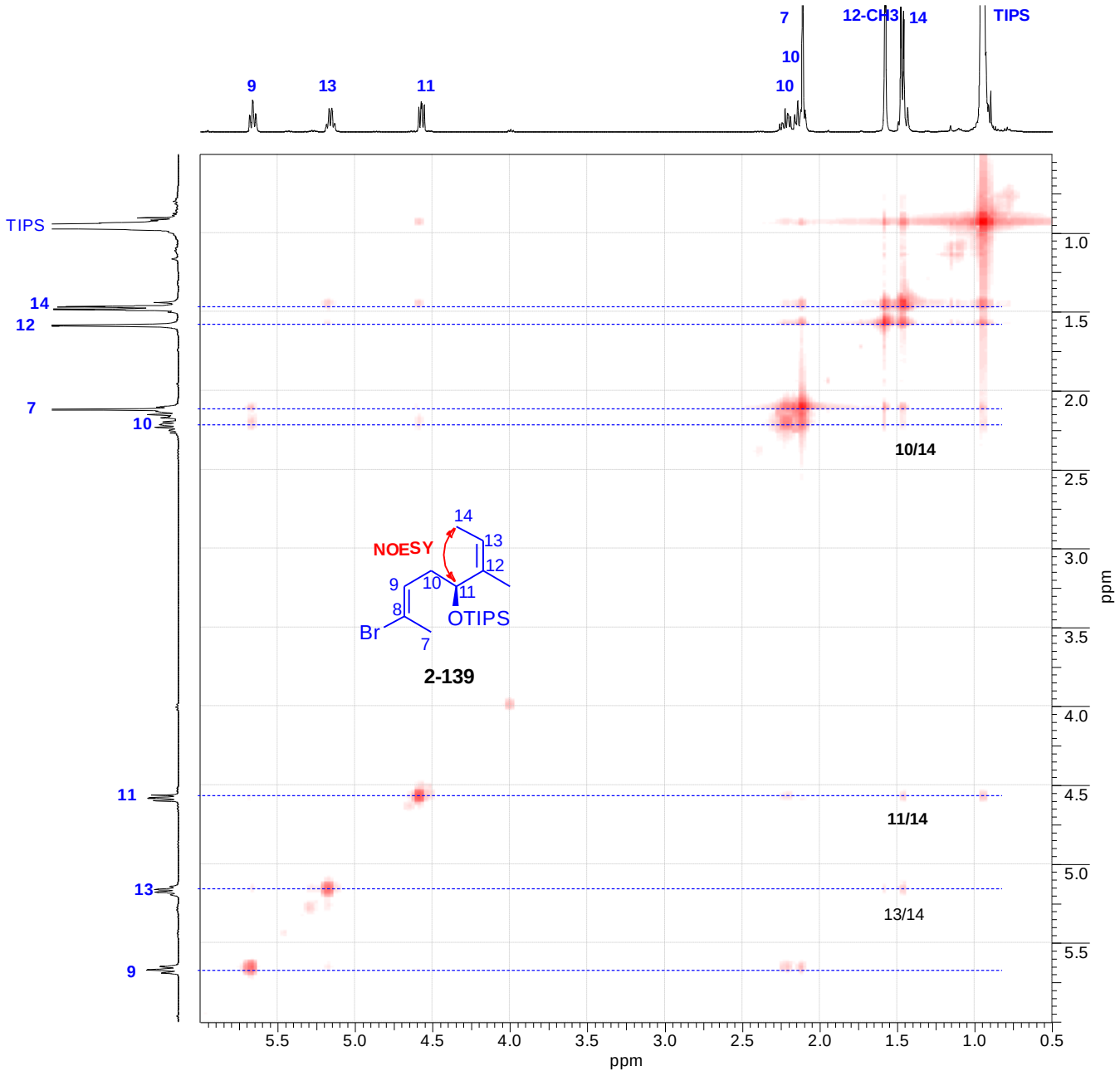
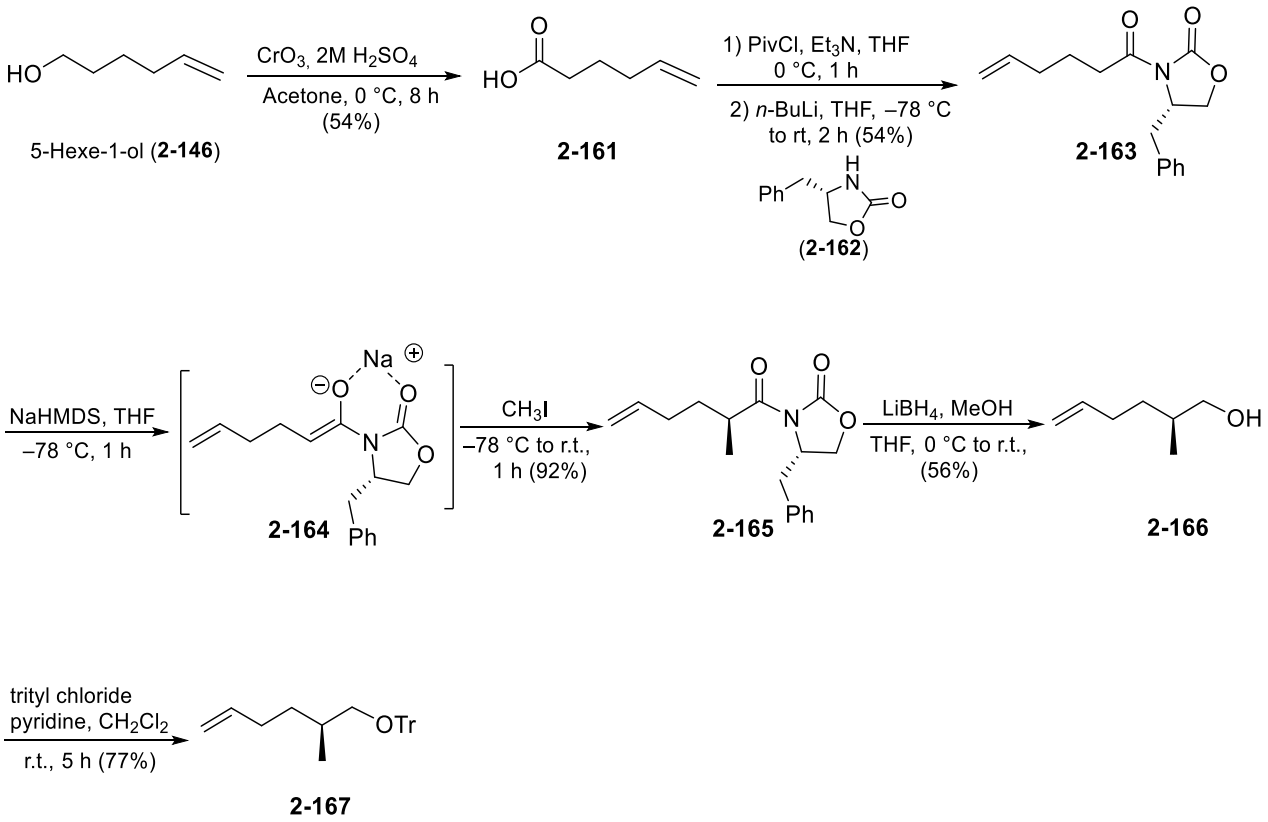


Figure 27. NOESY spectrum of C8-C14 fragment (**2-139**).

9.3.2 Synthesis of C1-C7 Fragment

We used 5-hexeonic acid (**2-161**) as a starting material to get key fragment C1-C7. However, commercially available 5-hexenoic acid (**2-161**) was slightly expensive. Therefore, we decided to make it by utilizing in-house chemicals. Initially, we synthesized 5-hexenoic acid (**2-161**) from easily available cyclohexanone using $H_2O_2/FeSO_4/CuSO_4$ conditions. However, in the oxidative ring cleavage **2-161** was obtained in only 15-20% yield.[120] Alternatively, Jones oxidization of 5-hexene-1-ol (**2-146**) using CrO_3, 2M H_2SO_4 at –10 °C affords 5-hexenoic acid (**2-162**) in 58%

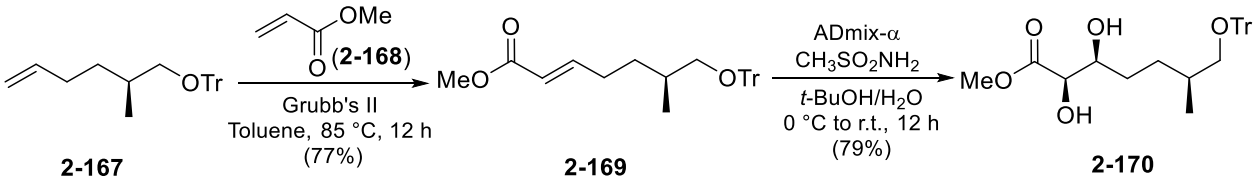
yield.[121] The next step was introduction of the stereocenter at the C2 position by asymmetric alkylation.[110] We used (*S*)-4-benzyl-2-oxazolidinone (**2-162**) as a chiral auxiliary to secure a stereoselective methylation of **2-165**. The chiral oxazolidinone (**2-162**) was treated with *n*-BuLi (2.5 M in hexane) in THF at –78 °C followed by the addition of freshly prepared mixed anhydride to afford *N*-acylated oxazolidinone **2-163** in 54% yield.[93] The mixed anhydride was prepared from 5-hexeonic acid (**2-161**) and pivaloyl chloride using Et_3N as a base. Thereafter, **2-163** was enolized using NaHMDS (2M in THF)[110] at –78 °C and the formed sodium enolate intermediate **2-164** was quenched with iodomethane affording the methylated product **2-165** in 92% yield. After reductive cleavage of auxiliary from **2-165** using $LiBH_4$ in THF and MeOH alcohol **2-166** was obtained as a volatile liquid together with the recovered Evans auxiliary **2-162** as well. Primary alcohol **2-166** was protected using trityl chloride, pyridine, and DMAP acquiring trityl ether **2-167** in good yield (**Scheme 45**).

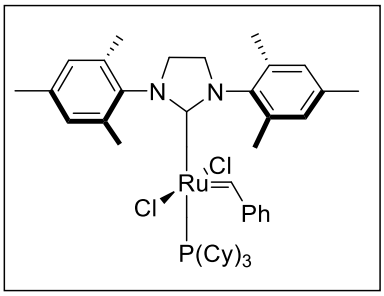


Scheme 45. Synthesis of trityl ether **2-167** via asymmetric alkylation.

9.3.3 Cross metathesis and Sharpless dihydroxylation

The cross metathesis reaction by ruthenium-based catalyst has proven to be one of the most powerful methods for the formation of carbon-carbon double bonds.[122] Taking advantage of this strategy, trityl ether **2-167** and methyl acrylate (**2-168**) were subjected to the cross metathesis reaction using Grubb's II catalyst in degassed toluene for 8 h at 80 °C. After completion of transformation, the black suspension was cooled to room temperature and the solvent was removed under reduced pressure. The crude product was directly loaded onto a silica column without any workup to afford metathesis product **2-169** as a colorless oil. The Sharpless asymmetric dihydroxylation has been developed as one of the most efficient methods for the preparation of enantiopure diols from olefins[123] by utilizing osmium-catalyst. Asymmetric dihydroxylation reactions were performed using commercially available AD-mix α (or) AD-mix β. They contain a mixture of $K_2[OsO_2(OH)_4]$ (0.4 mol%), $(DHQD)_2PHAL$ (or) $(DHQ)_2PHAL$ (1 mol%), $K_3[Fe(CN)_6]$ (3 equiv) and K_2CO_3 (3 equiv). Initially, we performed the asymmetric dihydroxylation with **2-169** using AD-mix α (1.4 g needed for 1 mmol of starting material) in a mixture of *t*-BuOH/H_2O at –10 °C for overnight. However, there was only trace amount of product formation shown by TLC. We realized that $MeSO_2NH_2$ is required to increase the reaction rate due to the hydrolysis of osmate esters.[123] Therefore, we used 2.5 equiv. of $MeSO_2NH_2$ and allowed the reaction to run for 1 day at r.t., which furnished diol **2-170** in high diastereoselectivity (**Scheme 46**).

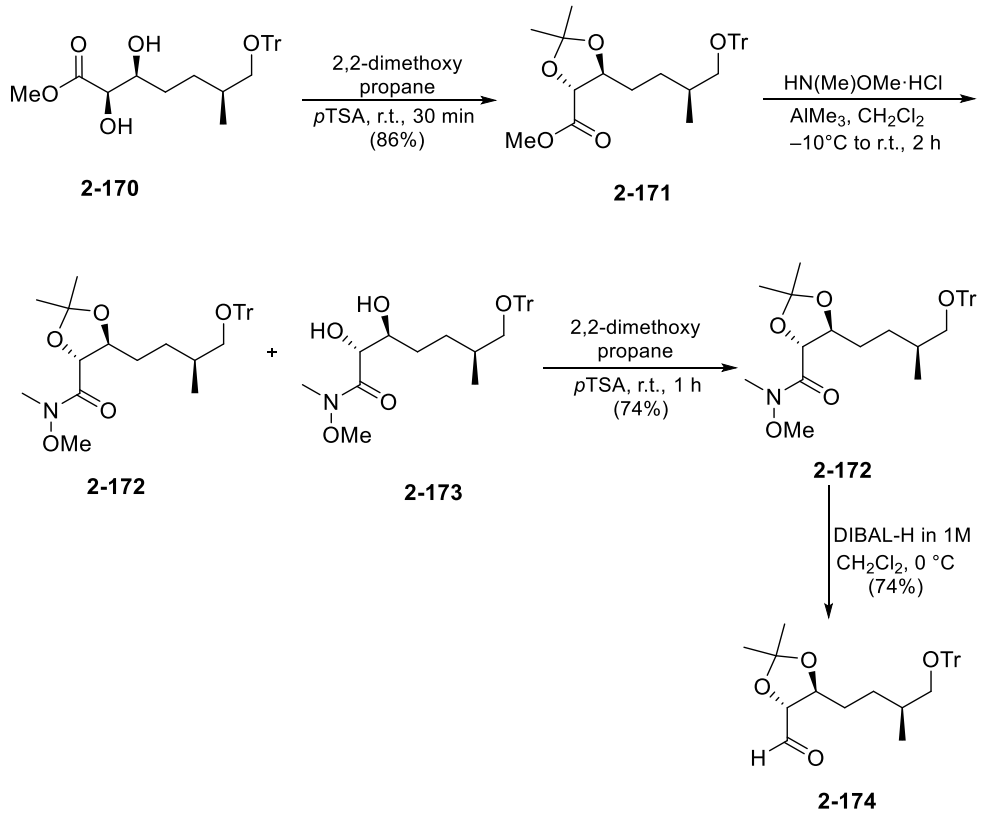




Grubb's II

Scheme 46. Synthesis of diol **2-170** via cross metathesis and Sharpless dihydroxylation.

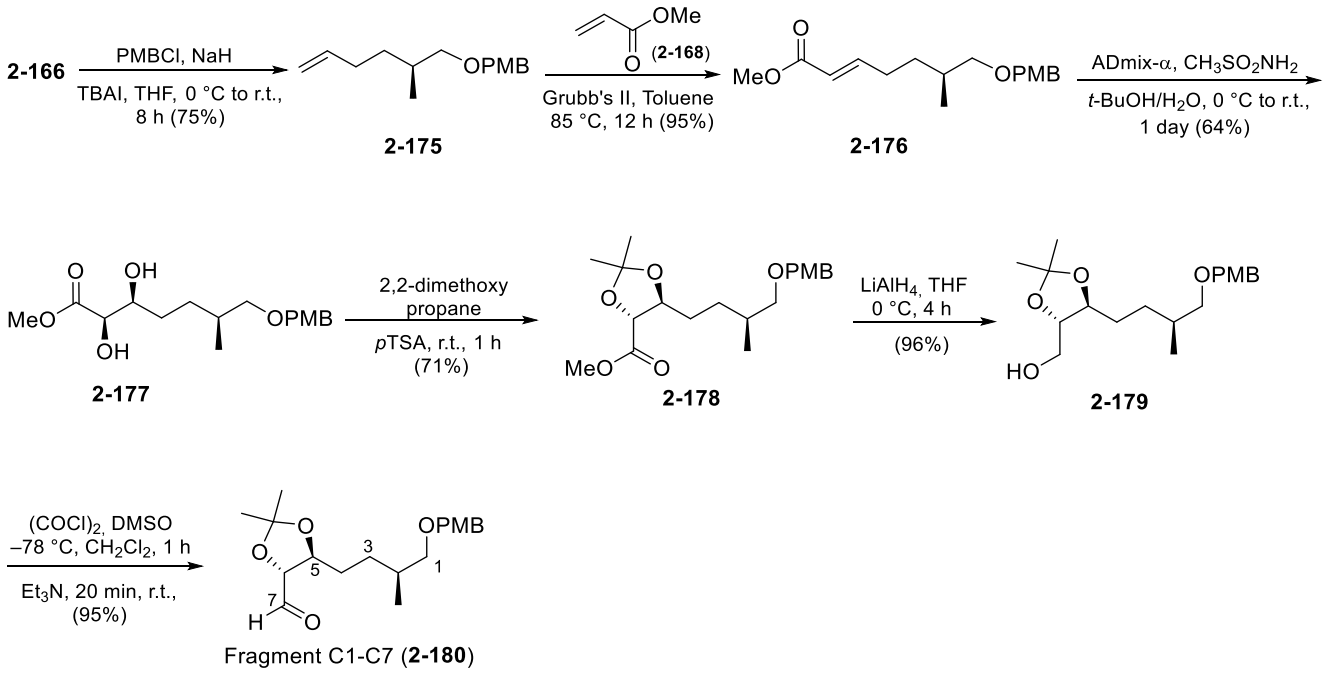
Diol **2-170** was protected using 2,2-dimethoxypropane under acidic medium to afford acetal **2-171** in 86% yield. Even though, we observed a trace amount of trityl cleavage product during this reaction by TLC. Methyl ester **2-171** was converted into Weinreb amide **2-172** using *N,O*-dimethyl hydroxylamine and trimethylaluminum at –10 °C. Due to acidic medium, we received a mixture of **2-172** and **2-173** as a protected and free diols respectively. Nevertheless, the resulting mixture was again treated with 2,2-dimethoxypropane in the presence of *p*-TSA to form the Weinreb amide **2-172**. In other hand, we considered that aldehyde **2-174** is a good electrophile for vinyllithium **2-138** addition. Therefore, Weinreb amide **2-172** was reduced into corresponding aldehyde **2-174** with DIBAL-H (1M in toluene)[124] in THF at 0 °C (**Scheme 47**).



Scheme 47. Synthesis of aldehyde **2-174** via cross metathesis and Sharpless dihydroxylation.

Due to the stability issue with trityl group, we decided to use a PMB protected alkene **2-175** for further transformations. Hence, primary alcohol **2-166** was treated with NaH, PMBCl, and TBAI that furnished PMB ether **2-175** in 75% yield. Further steps involved a cross metathesis, and Sharpless dihydroxylation which delivered methyl ester **2-177** in excellent yield.

After protection of the diol with 2,2-dimethoxypropane, the resulting methyl ester **2-178** was reduced using $LiAlH_4$ in THF at r.t. gave alcohol **2-179** in 96% yield. Thereafter, alcohol **2-179** was oxidized using Swern oxidation providing the required aldehyde **2-180** as an oil which was used without any further purification (**Scheme 48**).

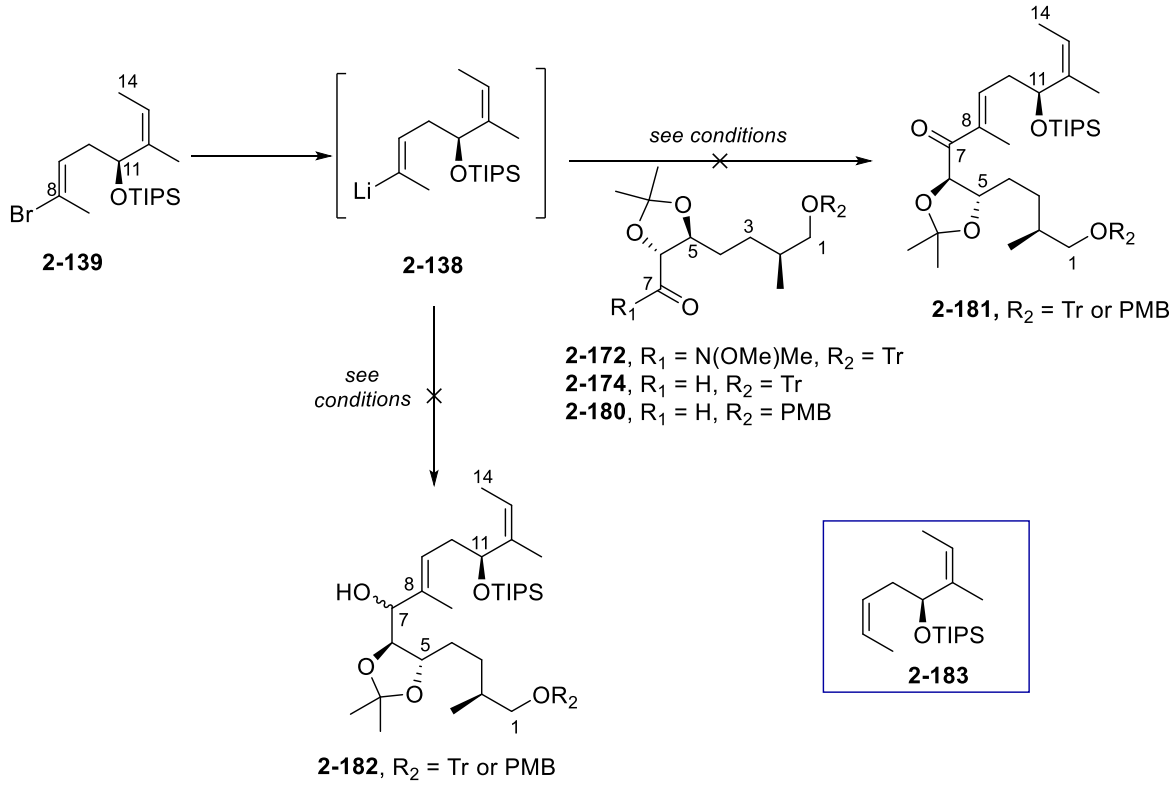


Scheme 48. Synthesis of aldehyde **2-180** with PMB ether.

9.3.4 Studies on the coupling of C1-C7 and C8-C14 Fragments

After this groundwork and the building blocks in hand, we focused to find suitable coupling conditions to assemble the available fragments **2-180** (C1-C7) and **2-139** (C8-C14). As discussed in the above retrosynthetic plan, our strategy involved two complementary approaches to assemble the vinyl bromide **2-139** and aldehyde **2-180** or **2-174** (**Scheme 49**). In the first attempt vinyllithium **2-138** generated from vinyl bromide **2-139** using *t*-BuLi in THF at –78° C, was treated with Weinreb amide **2-172** to get ketone **2-181**.[125] However, the reaction was not successful in our hand (see the **Table 6**). It is assumed that Weinreb amide **2-172** is not such a good electrophile as an aldehyde **2-180**.

The second approach involves the addition of vinyllithium **2-138** to more electrophilic aldehyde **2-180**. Initially, we used a number of classical conditions for the halogen-metal exchange, such as 1) *t*-BuLi (1.3 equiv) in THF at –78 °C, 1.5 h and 2) *t*-BuLi (1.5 equiv), $MgBr_2$ (1.5 equiv) in THF at –78 °C for 2 h. In all cases, we received only debrominated product **2-183** which was confirmed by ^{1}H NMR spectrum (**Figure 28**). This is an indication that the metalation had worked. It might be that the vinylmetal species gets protonated by the aldehyde instead of the addition reaction. Nevertheless, two alternative procedures were employed such as (i) Nozaki−Hiyama−Takai−Kishi protocol[126]using $CrCl_2$, $NiCl_2$ in DMF/THF, (ii) Turbo Grignard[127] using *i*PrMgCl·LiCl in THF at 0 °C. Even though both of these conditions were unsuccessful in our hands.



Scheme 49. Reaction between building blocks **2-139** and **2-172, 2-174, 2-180**.

Table 6. Summary of reaction conditions that were tried for coupling of the building blocks.

Entry	Reagents and conditions	Results
1	**2-139** (1.0 equiv), *t*-BuLi (2.2 equiv), THF, –78 °C to r.t., 1 h. then added **2-172**	No product formation, **2-183** was isolated as major compound
2	**2-139** (1.0 equiv), *sec*-BuLi (1.5 equiv), THF, –78 °C to r.t., 45 min, then added **2-172**	No product formation, **2-183** was isolated
3	**2-139** (1.0 equiv), *sec*-BuLi (1.5 equiv), THF, –78 °C to r.t., 15 min, then added **2-174**	No product formation, **2-183** was isolated
4	**2-139** (1.0 equiv), *i*-PrMgCl·LiCl (1.25 equiv), THF, –78 °C to r.t., 3 h, then addition of **2-180**	No reaction, both SM were recovered

5	**2-139** (2 equiv), **2-180** (1.2 equiv), $CrCl_2$ (5 equiv), $NiCl_2$ (1 equiv), DMF:THF (1:1 mL), r.t., 48 h	No reaction, SM was recovered
6	**2-139** (1.0 equiv), *n*-BuLi (1.5 equiv), Et_2O, –78 °C to r.t., 1 h, then added **2-180** at –78 °C	No product formation, **2-183** was isolated
7	**2-139** (1.0 equiv), *t*-BuLi (1.52 equiv), THF, –78 °C to r.t., 1 h, then added **2-180** at –78 °C	No product formation, **2-183** was isolated
8	**2-139** (1.0 equiv), *t*-BuLi (1.52 equiv), Et_2O, –78 °C to r.t., 30 min, then added **2-180** at –78 °C	No product formation, **2-183** was isolated
9	**2-139** (1.0 equiv), *t*-BuLi (1.5 equiv), $MgBr_2$ (1.5 equiv), THF, –78 °C , 2 h, then added **2-180** at –78 °C	No product formation, **2-183** was isolated

Substrate **2-139** was dissolved in the solvent (≈0.025M) prior to addition of the base; SM = starting material

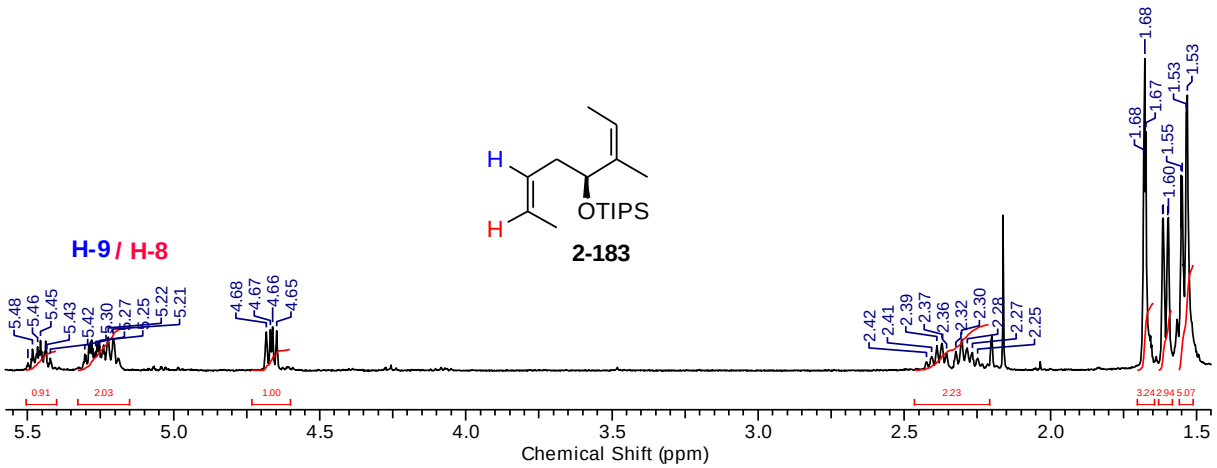
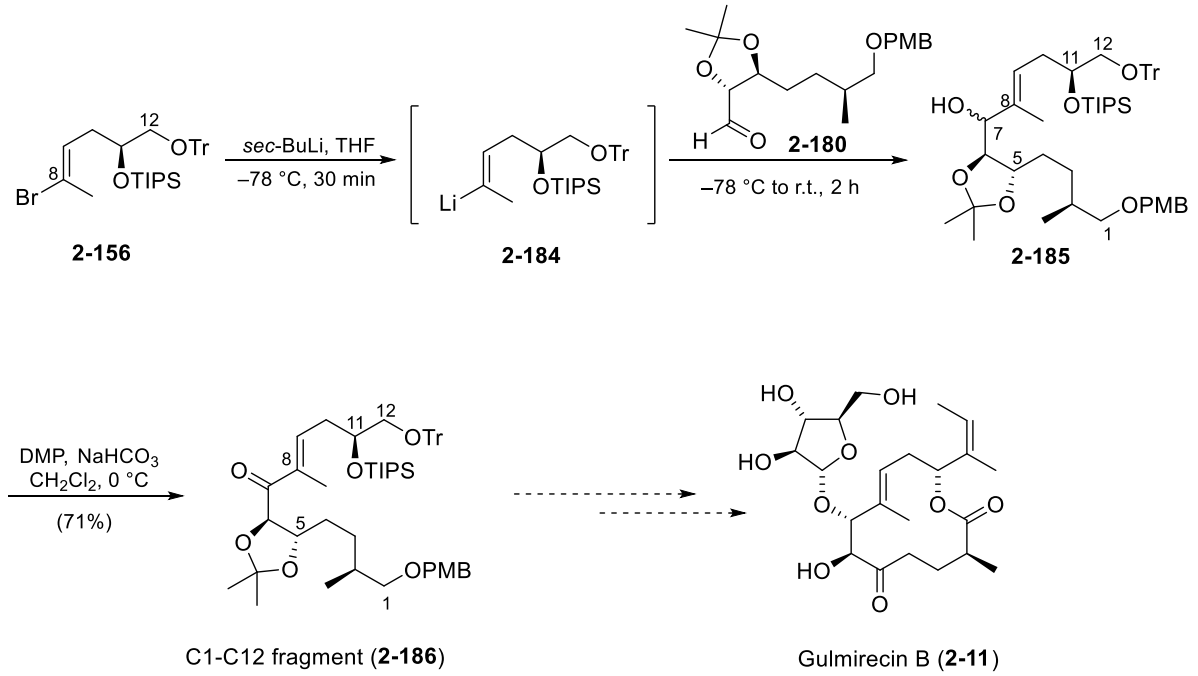


Figure 28. ^{1}H NMR spectrum of debrominated product **2-183**.

9.3.5 Synthesis of a C1-C12 Fragment

At this point decided to introduce the C12-C13 (*Z*)-trisubstituted double bond at a late stage of the total synthesis. With vinyl bromide **2-156** that lacks the trisubstituted double bond in hand, we investigated the crucial coupling step with different conditions (**Scheme 50**). Initially, vinyl bromide **2-156** was treated with *t*-BuLi in THF at –78 °C to give vinyllithium **2-184** which was added to aldehyde **2-180**. Notably, the desired alcohol **2-185** could be detected in the ^{1}H NMR spectrum. However, the yield was very small.

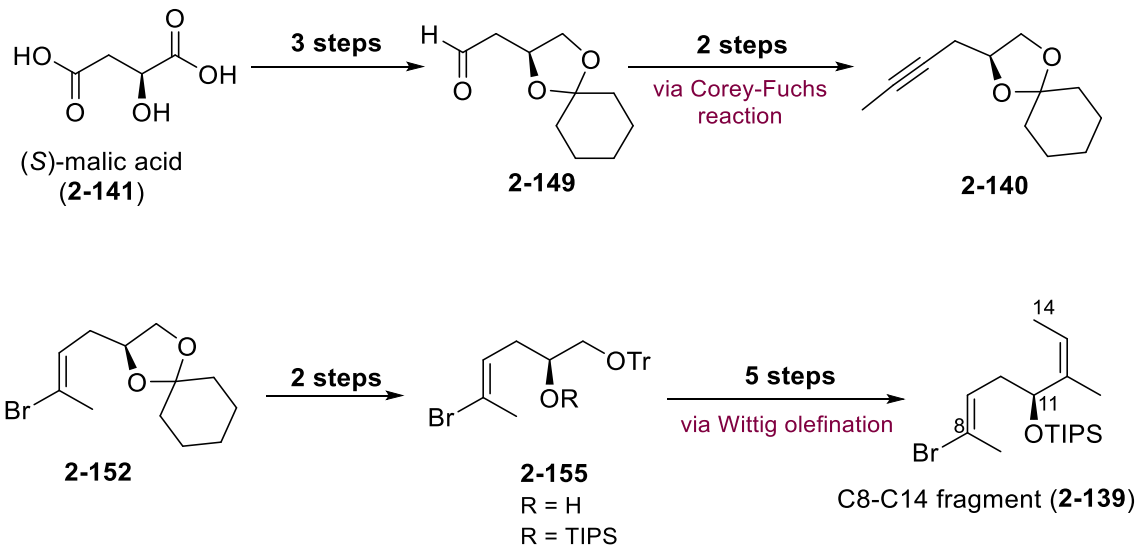
Consequently, we tuned the coupling step and observed that upon treating vinyl bromide **2-156** with *sec*-BuLi (1.2 equiv) in THF at –78 °C and using 1.7 equiv of aldehyde **2-180**, alcohol **2-185** was obtained as a 10:4 mixture of diastereomers in 40% yield. It is worth to mention that prior to formation of the vinyllithium species **2-184**, the corresponding vinyl bromide **2-156** was needed to be dried completely by evaporating the solvents from a benzene/toluene solution and placing the concentrate under high vacuum for 1 h. Alcohol **2-185** was oxidized using DMP, $NaHCO_3$ in CH_2Cl_2 which gave ketone **2-186** (C1-C12 fragment) as an oil in 71% yield. In order to complete the total synthesis of Gulmirecin B (**2-1**) the following steps would have to be performed: 1) selective reduction of ketone **2-186**, 2) cleavage of PMB group and oxidation of the alcohol to the acid 3) macrolactonization by Mitsunobu protocol, and 4) introduction of the (*Z*)-trisubstituted double bond at the C12 position.



Scheme 50. Synthesis of fragment C1-C12 (**2-186**) starting from the fragment C8-C12 (**2-156**).

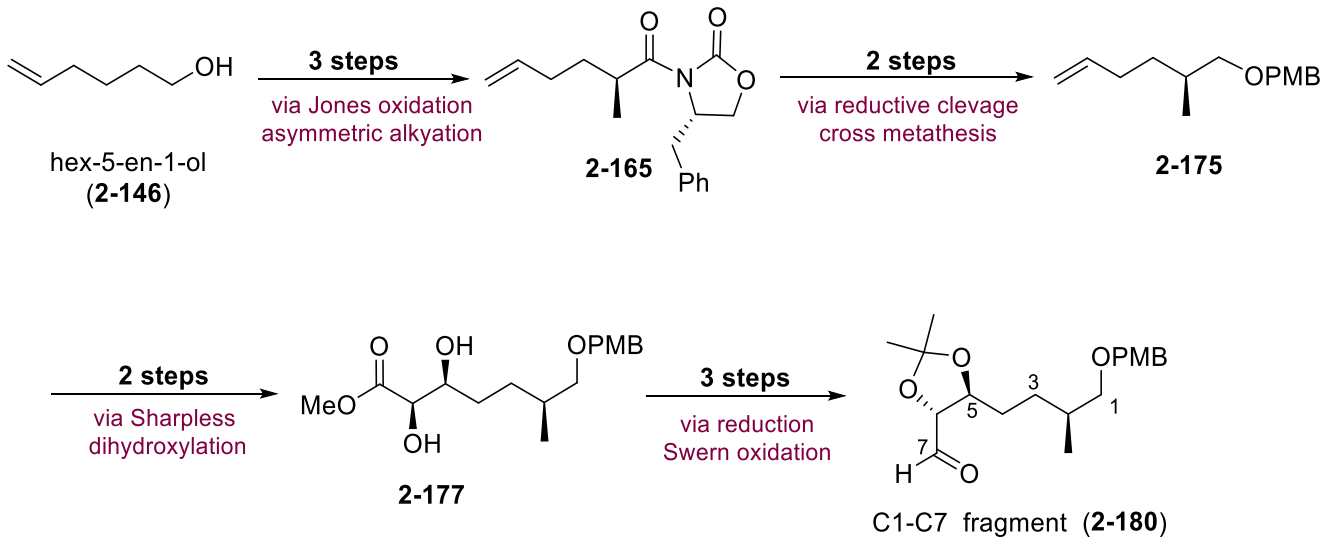
10. Conclusion

In summary, we investigated several approaches including model studies towards the total synthesis of Gulmirecin B (**2-11**). The first building block vinyl bromide **2-138** (C8-C14 fragment) was prepared from L-malic acid in 14 steps. The required aldehyde **2-149** was synthesized from (*S*)-malic acid (**2-141**) via reduction of the acid, protection of the diol and oxidation of the alcohol function. A Corey-Fuchs reaction on aldehyde **2-149** and iodomethane addition gave alkyne **2-140**. Further, alkyne **2-140** was subjected to hydrozirconation and addition of NBS furnished (*E*)-vinyl bromide **2-152** as a major regioisomer. Here, we used two different appropriate protecting groups for chain extension at the C12 position. After cleavage of the acetal, the primary and secondary alcohols were differentiated by protecting them with TrCl and TIPSOTf, which led to **2-155**. Thereafter, the trityl ether **2-155** was removed, the obtained alcohol oxidized to the aldehyde which upon reaction with MeMgBr led to a secondary alcohol. Oxidation of this alcohol to the methyl ketone and Wittig olefination delivered the required diene **2-139** (C8-C14 fragment) featuring the (*Z*)-trisubstituted double bond (**Scheme 51**).



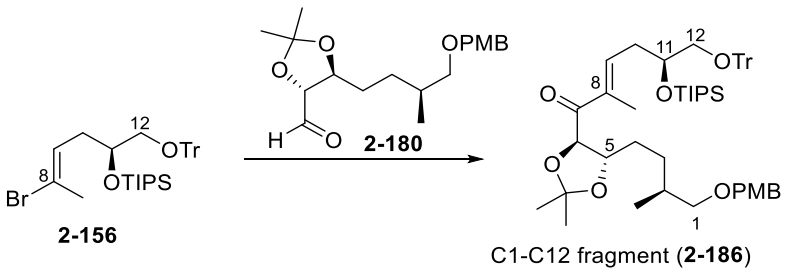
Scheme 51. Summary for the synthesis of fragment C8-C14 (**2-139**).

The second building block C1-C7 fragment **2-180** was made by asymmetric alkylation, cross metathesis, Sharpless dihydroxylation, and Swern oxidation. The amide derivative **2-165** was received from commercially available hex-5-en-1-ol (**2-146**) via Jones oxidation and Evans alkylation. Thereafter, reductive cleavage of the auxiliary gave a primary alcohol which was converted to PMB ether **2-175**. Further key steps involved a cross metathesis and Sharpless dihydroxylation to afford diol **2-177**. Then, reduction of methyl ester and Swern oxidation delivered aldehyde **2-180** as a C1-C7 fragment (**Scheme 52**).



Scheme 52. Summary of the synthesis of C1-C7 fragment (**2-180**).

Several reaction conditions were investigated for the coupling of C8-C14 fragment (**2-139**) and C1-C7 fragment (**2-180**). While metalated fragment **2-138** did not add to Weinreb amide **2-172** nor the aldehyde **2-174** or **2-180**, the addition of the vinyllithium derivative of truncated building **2-156** block was successful. This way C1-C12 fragment (**2-186**) could be obtained (**Scheme 53**).



Scheme 53. Received a key intermediate C1-C12 fragment **2-186** from **2-156** and **2-180**.

Chapter III

Studies on Spiroacetal Formation via Photocatalysis

11. Introduction

11.1 Photoredox catalysis

Visible light-mediated photoredox catalysis is a research field attracted by organic chemist due to its broad utility in organic transformations as well as for green chemistry.[128] This method is a more mild, safe, cost-effective, and environmentally friendly approach to promoting radical-based organic transformations.[129] Visible light irradiation of photocatalysts/chromophores enables one to convert solar energy to chemical energy by single-electron transfer (SET).[130] According to literature reports, a wide range of Ru/Ir polypyridyl complexes and various organic dyes are used as efficient catalysts in this field (**Figure 30**).[131] Furthermore, $Ru(bpy)_3^{2+}$ and related complexes have been utilized in different applications such as water splitting, organic light-emitting diodes, and proton-coupled electron transfer.[132] Upon irradiation of $Ru(bpy)_3^{2+}$ with visible light, an electron is transferred from the metal-centered t_{2g} orbital to ligand-centered π* orbital. This transition is called metal to ligand charge transfer (MLCT) and results in an excited triplet state. This lifetime of this triplet state is 1100 ns which allow the photocatalyst to engage in single electron transfer reaction with organic molecules. Also, photocatalysts have the dual nature of the excited state as being both oxidant and reductant on the basis of a simplified molecular orbital diagram (**Figure 29**).

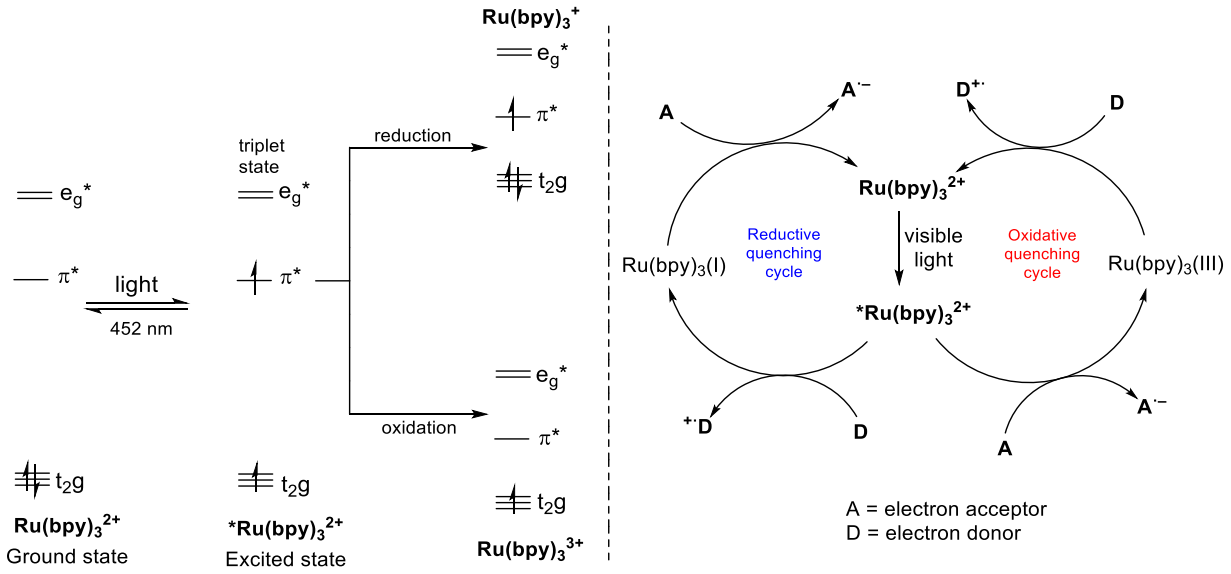


Figure 29. Simplified molecular orbital depiction of $Ru(bpy)_3^{2+}$ photochemistry.[132]

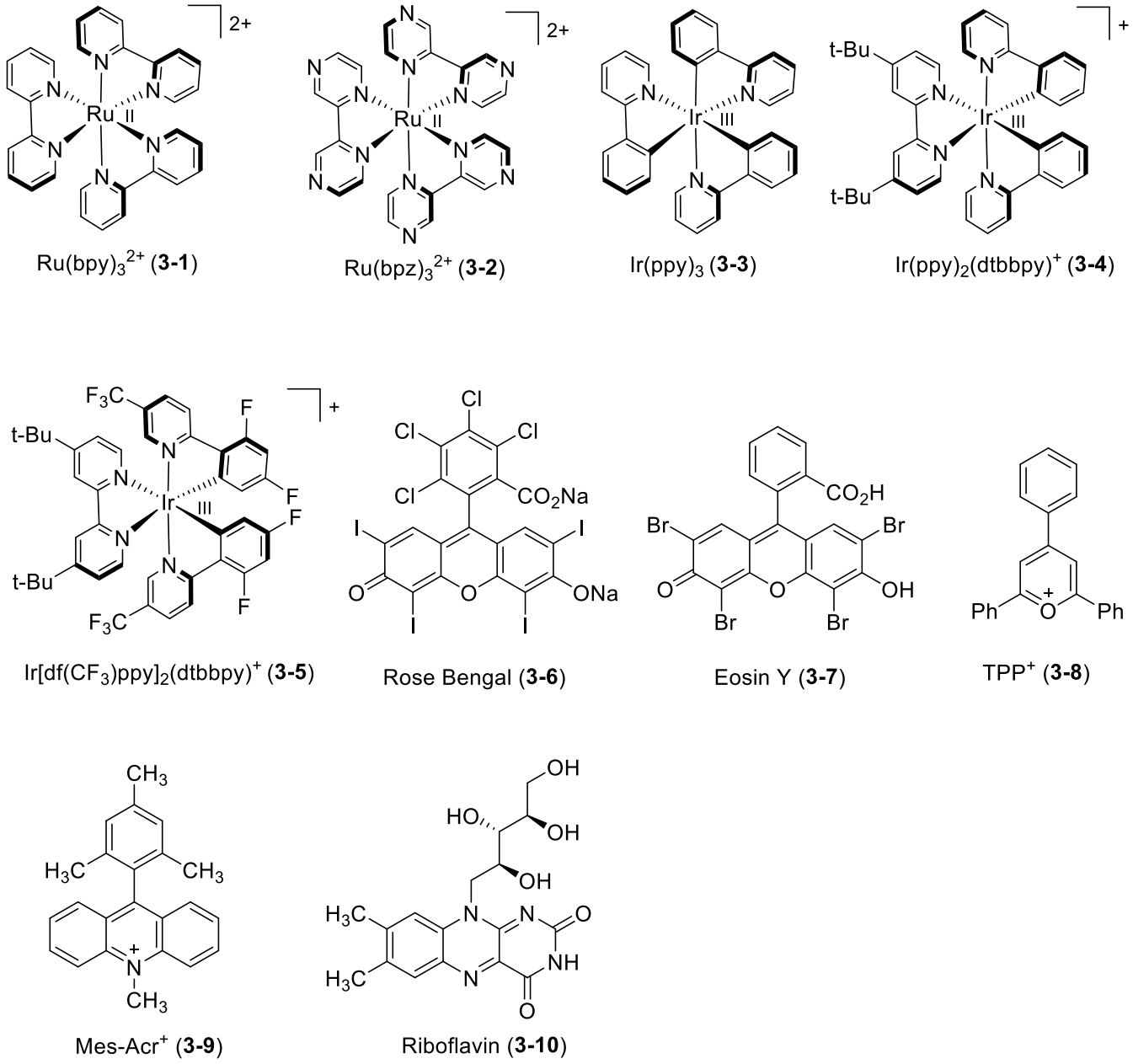


Figure 30. Chemical structures of most commonly used photoredox catalysts.

11.2 Hypervalent iodine(III) reagents used in photocatalysis

In recent years, hypervalent iodine(III) reagents have been used in organic synthesis for various oxidative transformations of organic molecules.[133] They display an ionic reactivity due to high electrophilicity and they also have the tendency to form radicals. Organic iodine(III) reagents can be classified based on the ligands attached to the iodine atom.[134] The most commonly used photoredox activating hypervalent iodine(III) reagents are displayed in **Figure 31**. Among the hypervalent iodine(III) reagents, five membered ring containing benziodoxoles have higher stability than acyclic derivatives. Besides having oxidizing ability, hypervalent iodine(III) reagents are used for cross-coupling reactions with more efficiency than transition-metal catalysis.[135]

In addition, the hypervalent iodine(III) compounds can generate radicals or electrophilic cationic species under thermal conditions.[136] The utilization of hypervalent iodine(III) reagents in visible-light photoredox catalysis is demonstrated in many synthetic methods. For example trifluoromethylation, alkynylation, azidation, and arylation are possible transformations.[137]

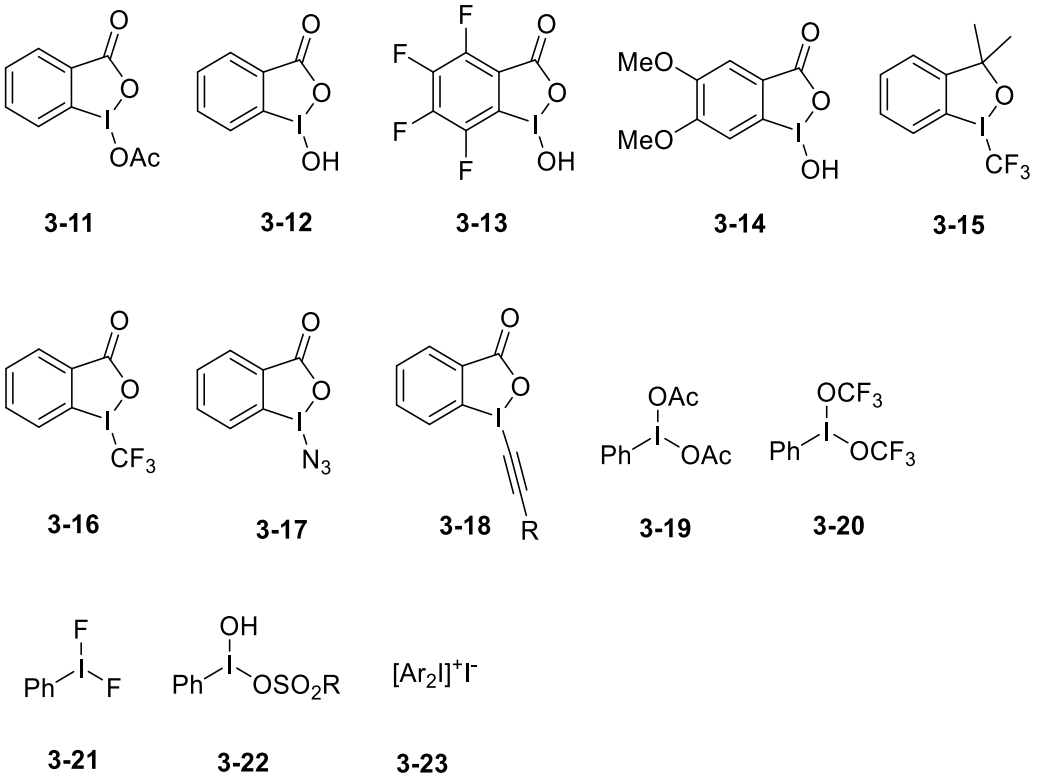


Figure 31. Examples of hypervalent iodine(III) reagents were used in photoredox catalysis.

12. Literature

12.1 General methods for spiroacetal formation

A variety of synthetic strategies are available for the synthesis of spiroacetal including

(i) Intramolecular hydrogen abstraction

(ii) Cycloisomerization

(iii) Oxa-Michael addition

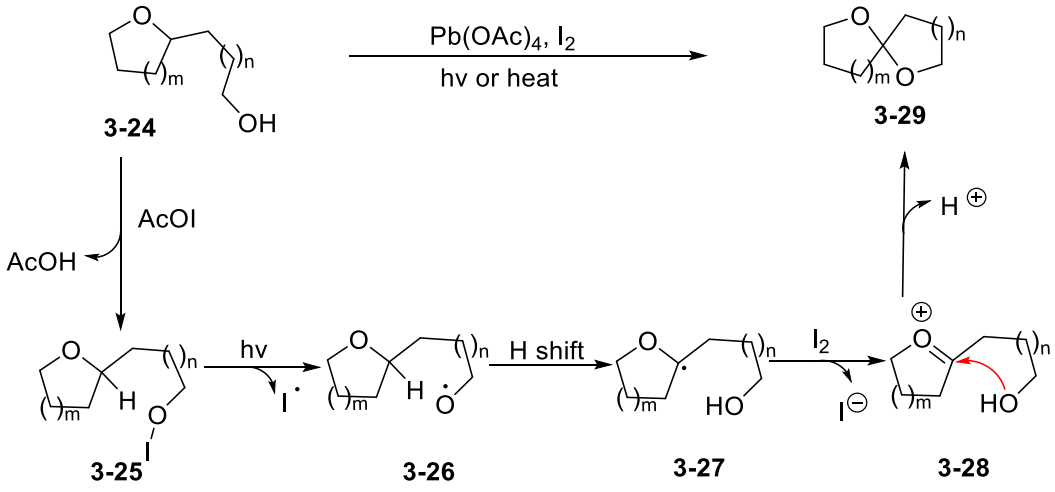
(iv) Furan oxidation

(v) Cycloaddition

(vi) Dehydration of ketodiols

12.1.1 Intramolecular hydrogen abstraction

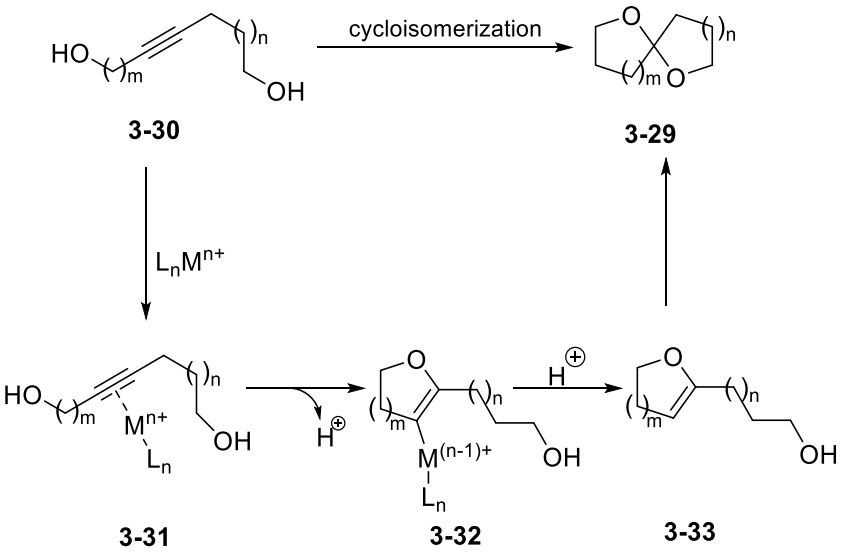
Intramolecular hydrogen abstraction is a powerful method in the area of spiroacetal synthesis.[138] The active alkoxy radical **3-26** is formed through the homolytic cleavage of an O–I bond of ether **3-25** via photochemical conditions. The required acetyl hypoiodite (AcOI) is formed *in situ* from the reaction between lead tetraacetate and iodine. The alkoxy radical of **3-26** undergoes an intramolecular hydrogen abstraction to form a carbon radical adjacent to the oxygen of **3-27** which is further oxidized by iodine to form oxocarbenium ion **3-28**. The subsequent attack of the alcohol to the electrophilic center of **3-28** affords spiroacetal derivative **3-29** (**Scheme 54**). Occasionally, this sequence is called Suarez reaction.



Scheme 54. Synthesis of spiroacetal derivatives **3-29** via intramolecular hydrogen abstraction.

12.1.2 Metal-catalyzed cycloisomerization

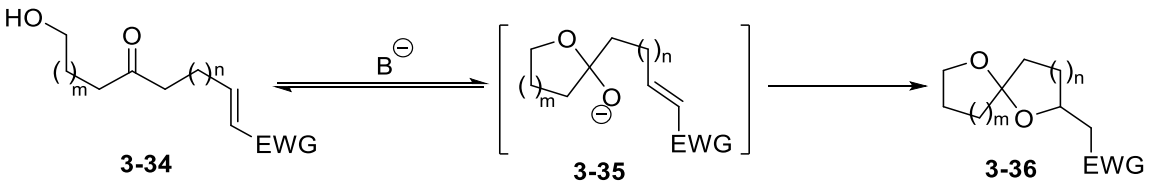
An alternative method for the synthesis of spiroacetal derivatives **3-29** is based on metal-catalyzed cycloisomerization[139] of alkyne diols **3-30** as shown in **Scheme 55**. The alkynediol **3-30** is activated by transition metal catalyst to form complex **3-31**. Then, the terminal alcohol attacks the alkyne in an *endo*-mode to give cyclic enol ether **3-32**. After protonolysis of **3-32**, the resulting intermediate **3-33** can cyclize to spiroacetal **3-29**.



Scheme 55. Synthesis of spiroacetal **3-29** via metal-catalyzed cycloismerization.

12.1.3 Oxa-Michael addition

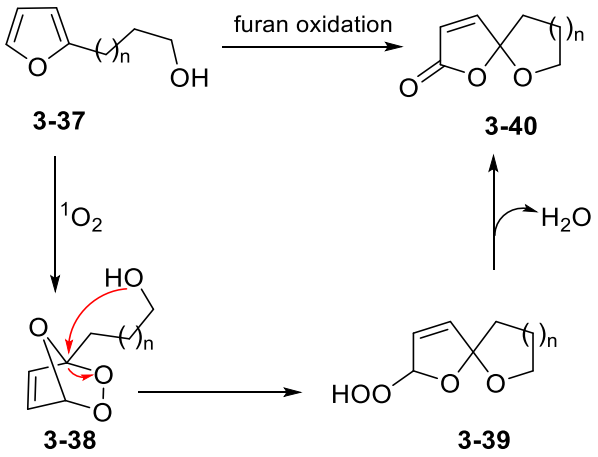
Another possibility to make the spiroacetal derivatives like **3-36** is via Oxa-Michael addition[140] as described in **Scheme 56**. In this case, treatment of ketone **3-34** with a suitable base may lead to anionic hemiacetal **3-35** which forms the spiroacetal derivative **3-36** via 1,4-addition reaction.



Scheme 56. Synthesis of spiroacetal derivatives **3-36** via oxa-Michael addition.

12.1.4 Furan oxidation

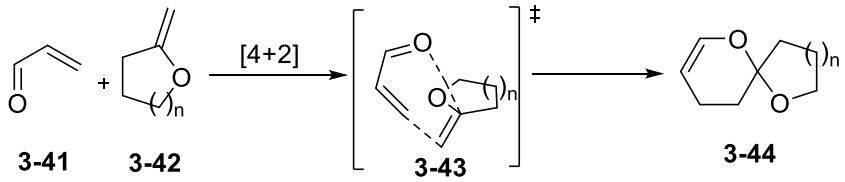
Furan derivatives can be easily transformed into spiroacetals by oxidation.[141] The mechanism involves [4+2]-cycloaddition between furan derivative **3-37** and singlet oxygen to result in cycloadduct **3-38**. Then, the terminal alcohol attacks the quaternary center to form a spirocyclic hydroperoxide **3-39** which undergoes a dehydration to afford the spirolactone derivative **3-40**. This can be easily transformed into the corresponding spiroacetal by reduction of the alkene as well as the carbonyl group (**Scheme 57**).



Scheme 57. Synthesis of spiroacetal **3-40** by oxidation of furan derivatives.

12.1.5 Cycloaddition

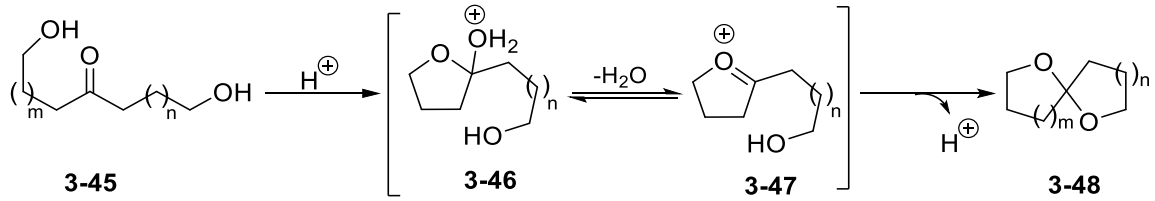
A very common method for synthesis of spiroacetal relies on a hetero Diels Alder reaction.[142] This protocol is used in the synthesis of various spiroacetal based natural products. The mechanism involves a [4+2]-cycloaddition reaction between electron-poor alkene **3-41** and the dienophile **3-42** to form 5,6-spiroacetal derivatives **3-44** (**Scheme 58**).



Scheme 58. Synthesis of spiroacetal **3-44** via [4+2]-cycloaddition reaction.

12.1.6 Dehydration of ketodiols

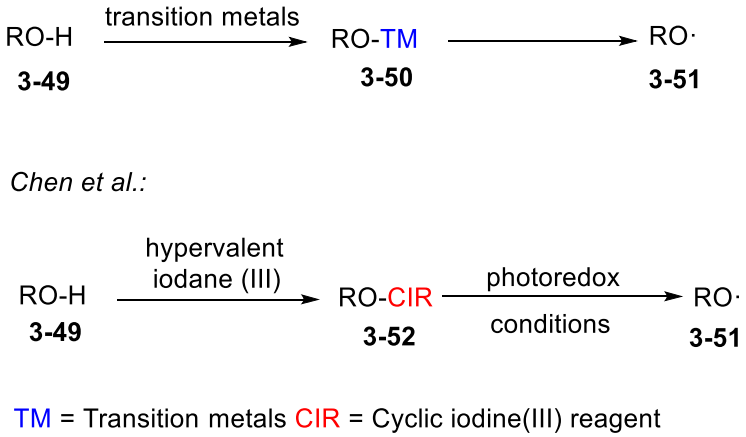
The treatment of ketodiols **3-45** with acid[143] induces the formation of protonated hemiacetal **3-46** which eliminates a water molecule to form a highly reactive oxocarbenium species **3-47**. Nucleophilic addition of the terminal alcohol to the electrophilic center of oxocarbenium **3-47** affords spiroacetal derivative **3-48** (**Scheme 59**).



Scheme 59. Synthesis of spiroacetal **3-48** by dehydration of ketodiols **3-45**.

12.2 Inspiration from previous work

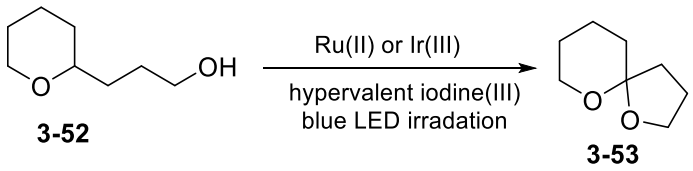
Chen *et al.*[144] utilized hypervalent iodine(III) reagents for generation of alkoxy radicals in the presence of a photocatalyst under visible light irradiation (**Scheme 60**). It is an example for visible light induced alkoxy radical mediated C-H bond activation. According to their mechanism, the alcohol derivative **3-49** was treated with hypervalent iodine(III) reagents to form complex **3-52** *in situ*. Then, photocatalytic conditions reduced the complex to provide alkoxy radical **3-51** which can make new bond formation by intramolecular hydrogen abstraction. We thought that the same strategy could be used to promote spiroacetal formation through an alkoxy radical using hypervalent iodine(III) reagents under visible light irradiation.



Scheme 60. Alkoxy radical generation by using hypervalent iodine(III) under visible-light photocatalysis.

13. Goal of the research

The aim of our project was to develop a new method for the synthesis of spiroacetal compounds via photocatalysis under blue LED irradiation. Spiroacetals are important structural components which can be found in many biologically active natural products. They are present in some sex pheromones, microtubule stabilizing agents (MSAs), and polyketide antibiotics.[145] Different synthetic approaches towards spiroacetal formation have been reported in the literature. However, the visible-light induced spiroacetal formation via alkoxy radical is unknown. Chen and co-workers developed a visible light induced alcohol oxidation to generate alkoxy radicals using hypervalent iodine(III) reagents.[144] Taking advantage of this strategy, we decided to investigate the spiroacetal formation via alkoxy radical generation using hypervalent iodine(III) reagents under photochemical conditions on model substrate **3-52** (**Scheme 61**).



3-52 **3-53**

Scheme 61. Synthesis of spiroacetal **3-53** by employing a photocatalysis strategy.

A plausible mechanism for spiroacetal formation is displayed in **Figure 32**. The alcohol **3-52** would react with hypervalent iodine(III) reagent (diacetoxyiodo)benzene to form intermediate (RO-I) **3-54** *in situ*. Then, single electron transfer of an electron from the excited Ru(II)* to the O-I bond would give alkoxy radical **3-55**, iodobenzene and acetate. Subsequently, the generated alkoxy radical **3-55** activates the C-H bond of the tetrahydropyran at C2 position by intramolecular hydrogen abstraction. The resulting stabilized C-centered radical species **3-56** further undergoes an oxidation process by Ru(III) which leads to the oxocarbenium ion **3-57**. Finally, the terminal alcohol attacks the electrophilic center of oxocarbenium **3-57** to afford spiroacetal **3-53**.

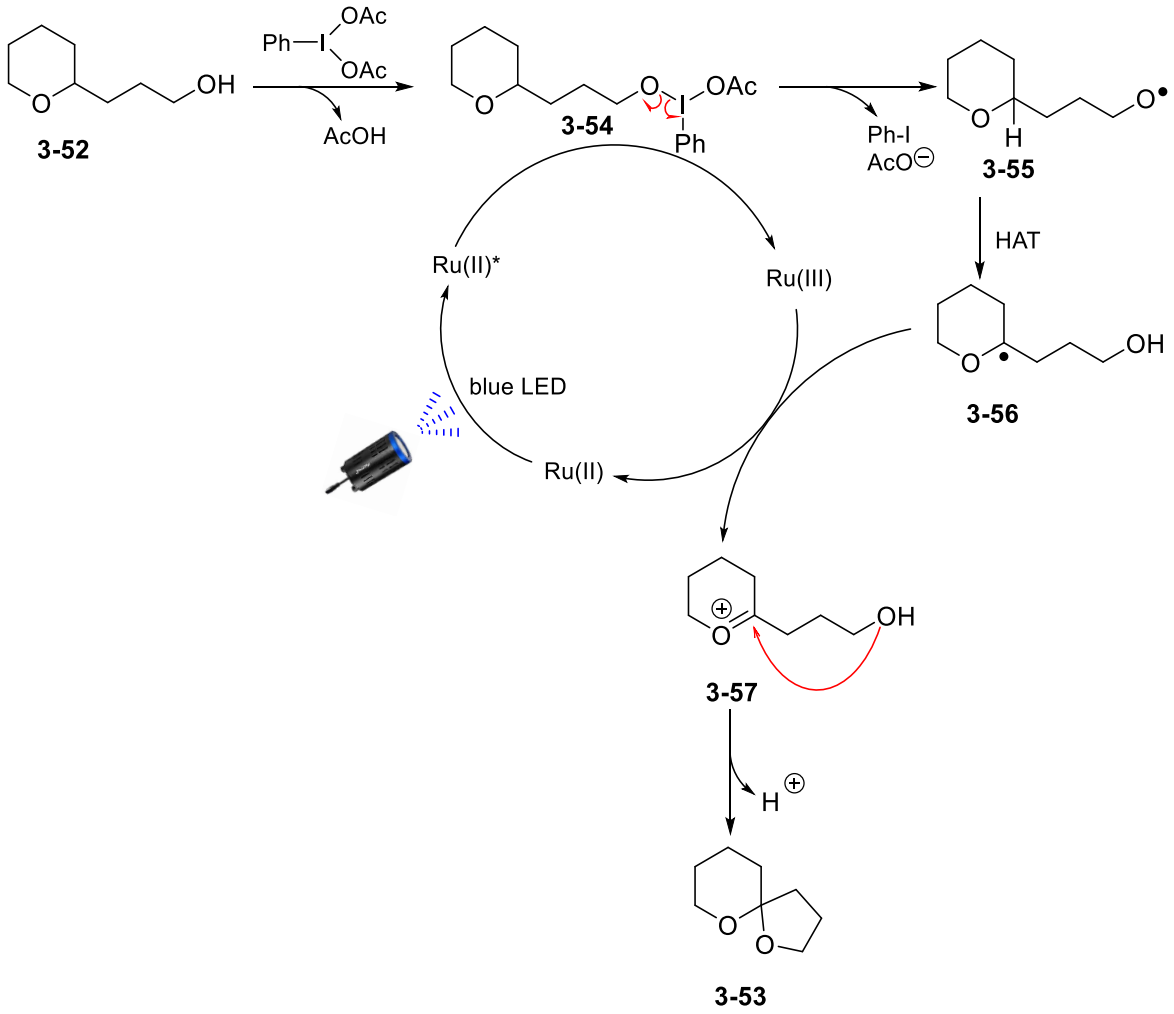
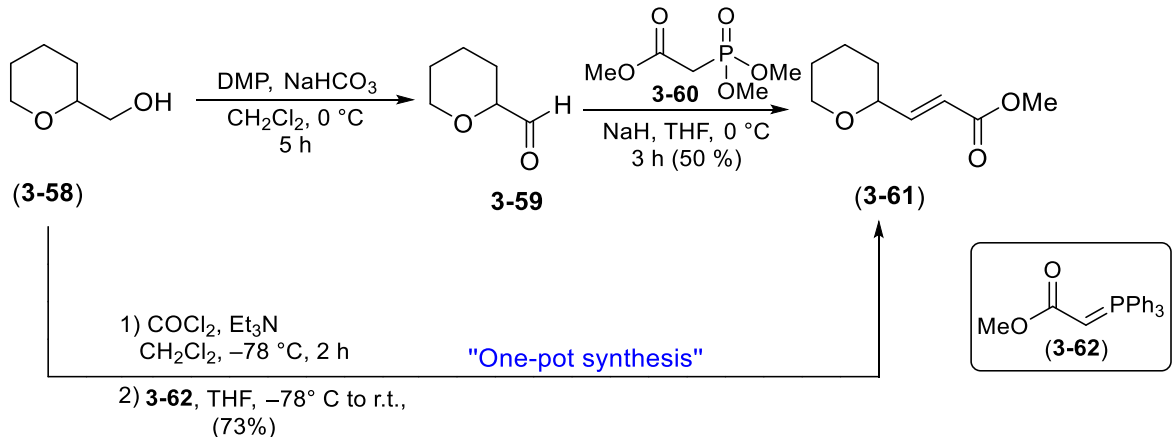


Figure 32. Proposed mechanism pathway for the formation of spiroacetal **3-53**.

14. Results and Discussion

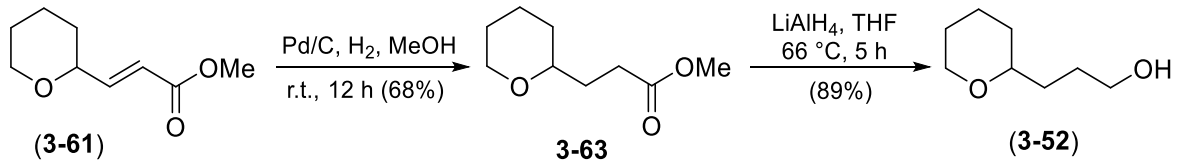
14.1 Synthesis of 3-(tetrahydro-2*H*-pyran-2-yl)propan-1-ol

According to our plan, 3-(tetrahydro-2*H*-pyran-2-yl)propan-1-ol (**3-52**) was prepared in four steps. The synthetic sequence involves Swern oxidation, Wittig-Horner reaction, hydrogenation, and reduction of the enoate. Initially, we performed a DMP oxidation of (tetrahydro-2*H*-pyran-2-yl)methanol (**3-58**) to give aldehyde **3-59**, which was used for the next step without any chromatography. Subsequently, aldehyde **3-59** was treated with methyl (dimethoxyphosphoryl)acetate (**3-60**) using NaH as a base to furnish Wittig-Horner product, (*E*)-α,β-unsaturated ester **3-61** in 50% yield.[146] However, we received around 10% of (*Z*)-α,β-unsaturated ester (**3-61**) as a minor product. An alternative method to make the (*E*)-α,β-unsaturated ester (**3-61**) is by an one-pot synthetic strategy.[147] Thus, the (tetrahydro-2*H*-pyran-2-yl)methanol (**3-58**) was subjected to Swern oxidation and subsequently we added methyl 2-(triphenyl-λ^5-phosphanylidene)acetate (**3-62**) in THF at –78 °C which afforded (*E*)-α,β-unsaturated ester (**3-61**) with 73% yield (**Scheme 62**).



Scheme 62. Synthesis of (*E*)-α,β-unsaturated ester **3-61**.

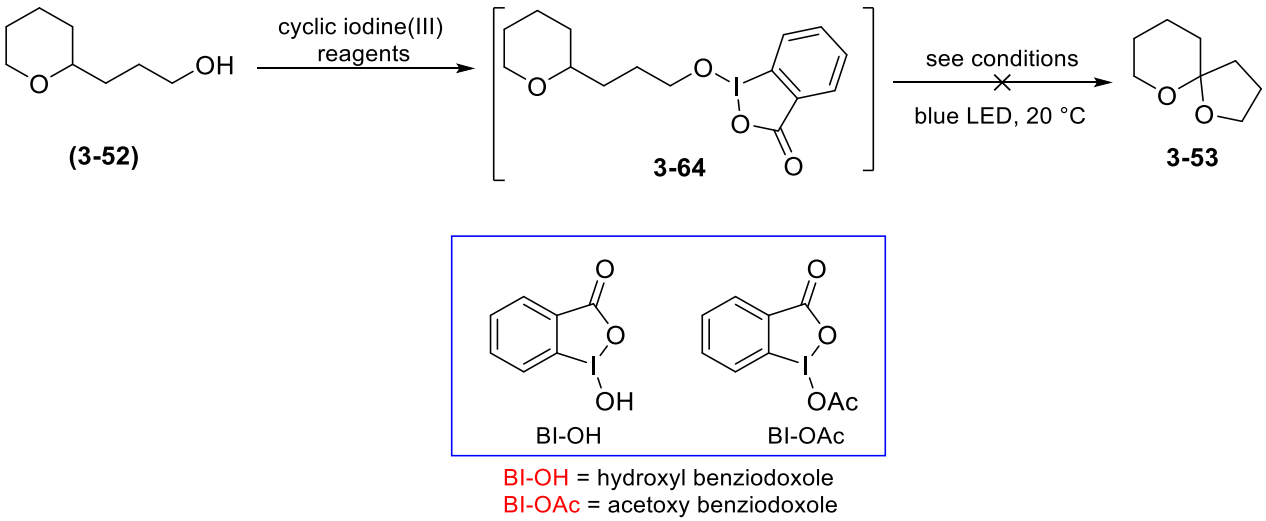
These (*Z*) and (*E*)-α,β-unsaturated ester **3-61** was reduced under hydrogenation conditions using Pd/C in MeOH to afford saturated methyl ester **3-63** in 68% yield. Treatment of saturated methyl ester **3-63** with $LiAlH_4$ in THF gave required 3-(tetrahydro-2*H*-pyran-2-yl)propan-1-ol (**3-52**) as a colorless oil in good yield (**Scheme 63**).



Scheme 63. Synthesis of starting material 3-(tetrahydro-2*H*-pyran-2-yl)propan-1-ol (**3-52**).

14.2 Investigation of spiroacetal/aminol formation under visible light irradiation

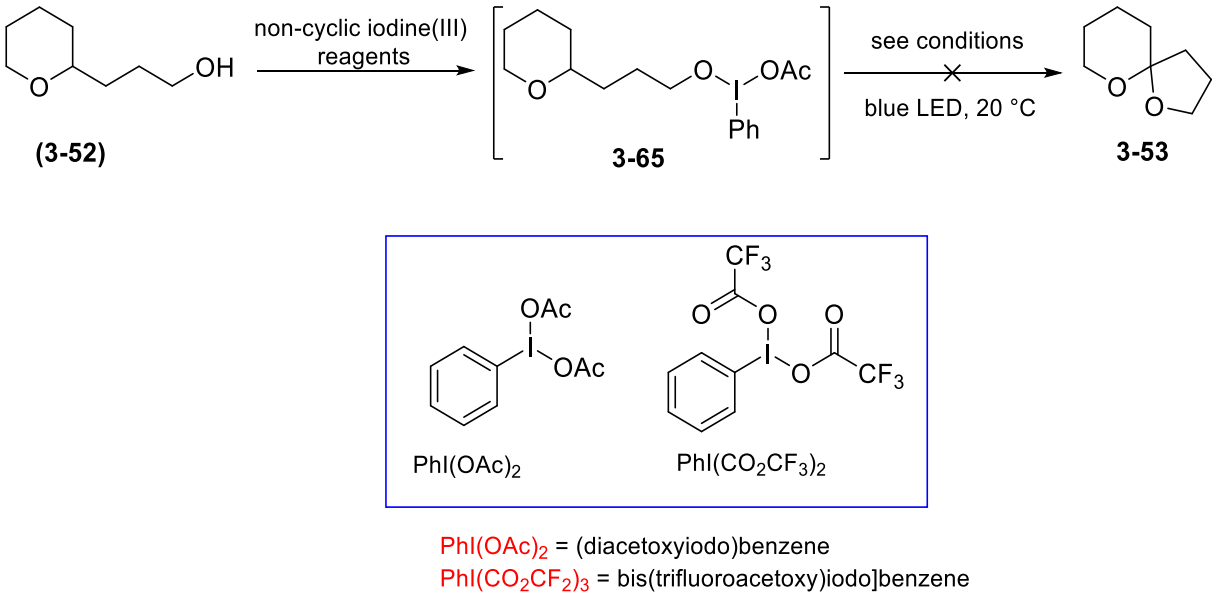
The required $[Ru(bpy)_3](PF_6)_2$ (**3-1**) and $Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (**3-5**) catalysts were synthesized using literature procedures.[148] Based on the above proposal, we started our investigation with 3-(tetrahydro-2*H*-pyran-2-yl)propan-1-ol (**3-52**) and benziodoxole derivatives (BI-OH, BI-OAc)[144] using DCE/H_2O as solvents to give complex mixture **3-64** *in situ*, which was subsequently reduced by $[Ru(bpy)_3]^{2+}$ under blue LED irradiation. However, all conditions were unsuccessful in our hand, only starting material was recovered (**Table 7**, entry 1-3) (**Scheme 64**).



Scheme 64. Attempts at spiroacetal formation using cyclic hypervalent iodine(III) reagents under blue LED light irradiation.

Thus, further experiments were performed. Alcohol **3-52** was reacted with various non-cyclic iodine(III) reagents, such as $PhI(OAc)_2$, and $PhI(CO_2CF_3)_2$ in the presence of $[Ru(bpy)_3]^{2+}$ under blue LED irradiation. However, none of them gave the desired product (entry 4,5). We also employed alternative photocatalyst, iridium complex $Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$. Again, the alcohol **3-52** was treated with $PhI(OAc)_2$ (1.5 equiv) in CH_3CN and stirred for 3 h, before

irradiation in presence of Ir{dF(CF$_3$)ppy}$_2$(dtbbpy)]PF$_6$ (0.01 equiv) using blue LED irradiation for overnight. In a further attempt alcohol **3-52** was reacted with PhI(CO$_2$CF$_3$)$_2$ in the presence of the Ir(III) species under blue LED light for 8 h. In both cases, we received only the starting material back. These results indicate that the alkoxy radical or the R-O-IX$_2$ **3-64/3-65** intermediate did not form during the reaction. (**Scheme 65**).



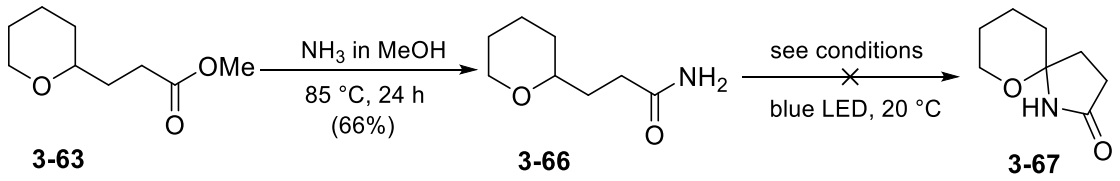
Scheme 65. Spiroacetal formation using non-cyclic hypervalent iodine(III) reagents under blue LED light irradiation.

Table 7. Summary of conditions that were tried for formation of spiroacetal

Entry	Reagents and conditions	Results
1	BI-OH (1.0 equiv), Ru(bpy)$_3$Cl$_2$ (0.02 equiv), DCE/H$_2$O, 20 °C, 8 h	No reaction; SM was observed
2	BI-OH (1.0 equiv), [Ru(bpy)$_3$](PF$_6$)$_2$ (0.02 equiv), DCE/H$_2$O, 20 °C, 2 days	No reaction; SM was observed
3	BI-OAc (1.2 equiv), [Ru(bpy)$_3$](PF$_6$)$_2$ (0.02 equiv), cyclohexane, 20 °C, 24 h	No reaction; SM was observed
4	PhI(OAc)$_2$ (1.2 equiv), [Ru(bpy)$_3$](PF$_6$)$_2$ (0.02 equiv), DCM/H$_2$O, 20 °C, 8 h	No reaction; SM was observed
5	PhI(OCF$_3$)$_2$ (1.0 equiv), [Ru(bpy)$_3$](PF$_6$)$_2$ (0.02 equiv), DCE, 20 °C, 24 h	No reaction; SM was observed
6	PhI(OAc)$_2$ (1.0 equiv), Ir{dF(CF$_3$)ppy}$_2$ (dtbbpy)]PF$_6$ (0.01 equiv), CH$_3$CN, 20 °C, 1 d	No reaction; SM was observed
7	PhI(OCF$_3$)$_2$ (1.0 equiv), Ir[df(CF$_3$)ppy)$_2$(dtbpy)]PF$_6$ (0.01 equiv), DCE, 20 °C, 8 h	No reaction; SM was observed

Substrate **3-52** was dissolved in the solvent (≈ 0.035M); SM = starting material

Also, we performed sprioaminal formation using the amide **3-66** (**Scheme 66**). Thus, methyl ester **3-63** was treated with ammonia (2N in MeOH) at 85 °C for 24 h to give amide **3-66** in good yield. Further the amide **3-66** was reacted with non-cyclic iodine(III) reagents, such as $PhI(OAc)_2$, $PhI(CO_2CF_3)_2$ in the presence of $[Ru(bpy)_3]^{2+}$ or $Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ under blue LED irradiation. However, none of them gave the desired spiroaminal **3-67** (**Table 8**).



Scheme 66. Attempts at spiroaminal formation using hypervalent iodine(III) reagents under blue LED light irradiation.

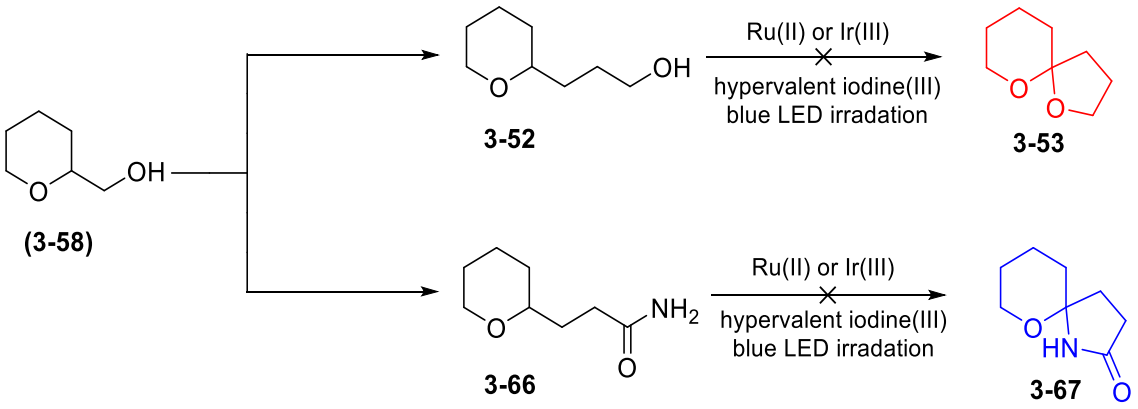
Table 8. Summary of conditions that were tried for formation of spiroaminal derivative **3-76**

Entry	Reagents and conditions	Results
1	$PhI(OAc)_2$ (1.2 equiv), $[Ru(bpy)_3](PF_6)_2$ (0.02 equiv), DCM, 20 °C, 24 h	No reaction; SM was observed
2	$PhI(OCF_3)_2$ (1.0 equiv), $[Ru(bpy)_3](PF_6)_2$ (0.02 equiv), EtOAc, 20 °C, 24 h	No reaction; SM was observed
3	$PhI(OAc)_2$ (2.0 equiv), $Ir\{dF(CF_3)ppy\}_2$ $(dtbbpy)]PF_6$ (0.01 equiv), CH_3CN, 20 °C, 2 days	No reaction; SM was observed
4	$PhI(OCF_3)_2$ (1.5 equiv), $Ir[df(CF_3)ppy)_2(dtbpy)]PF_6$ (0.01 equiv), cyclohexane, 20 °C, 16 h	No reaction; SM was observed

Substrate **3-66** was dissolved in the solvent (≈ 0.045M); SM = starting material

15. Conclusion

In summary, 3-(tetrahydro-2*H*-pyran-2-yl)propan-1-ol (**3-52**) was synthesized from commercially available (tetrahydro-2*H*-pyran-2-yl)methanol (**3-58**) involving a Swern oxidation, hydrogenation and reduction. We used a range of hypervalent iodine(III) reagents for spiroacetal **3-53** and spiroaminal **3-67** formation in the presence of a photocatalyst under blue LED irradiation. Unfortunately, all the attempts were not successful in our hands (**Scheme 67**).



Scheme 67. Summary of spiroacetal **3-53** and spiroaminal **3-67** formation via photocatalysis under blue LED irradiation.

16. Experimental Sections

16.1 General Remarks

16.1.1 Chemicals and working techniques

All the chemicals were purchased from TCI, Aldrich, and Acros. All reagents were used without further purification unless otherwise stated. All solvents were distilled and dried prior to use by standard methodology except for those, which were reagent grades. The applied petroleum ether fraction had a boiling point of 40-60 °C. Anhydrous solvents were obtained as follows: THF, diethyl ether and toluene by distillation from sodium and benzophenone; dichloromethane and chloroform by distillation from calcium hydride; acetone by distillation from phosphorous pentoxide. Absolute triethylamine, pyridine and diisopropylethylamine were distilled over calcium hydride prior to use. Unless and otherwise mentioned, all the reactions were carried out under a nitrogen atmosphere. Compounds that are not described in the experimental part were synthesized according to the literature.

16.1.2 NMR spectroscopy

All the spectra were measured on a Bruker Avance III HD spectrometer, which operated at 400 MHz for ^{1}H and 100 MHz for ^{13}C nuclei, respectively. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz): spectra were recorded at 295 K either in $CDCl_3$ or [D_4] MeOH; chemical shifts are calibrated to the residual proton and carbon resonance of the solvent: $CDCl_3$ (δ H = 7.25 ppm, δ C = 77.0 ppm), [D_4] MeOH (δ H = 2.49 ppm, δ C = 39.5 ppm). Data are reported as follows: chemical shift (multiplicity: s = singlet, d = doublet, t = triplet, ddd = doublet of doublet of doublet, dt = doublet of triplet, td = triplet of doublet, m = multiplet, br = broadened, *J* = coupling constant (Hz), integration, peak assignment in italic form).

16.1.3 Mass spectrometry

High–resolution mass spectra (HRMS) were recorded on a Bruker maXis 4G instrument with electron spray ionization (ESI) and a TOF mass detector (mass range: 50-20000 m/z, mass accuracy: 600 ppb RMS error). Some of the mass spectra were also measured on an Agilent 1100 series LC-MSD. Analytical HPLC-MS: HP 1100 Series connected with an ESI MS detector Agilent G1946C, positive mode with fragmentor voltage of 40 eV, column: Nucleosil 100–5, C–18 HD, 5 mm, 70 × 3 mm Machery Nagel, eluent: NaCl solution (5 mM)/acetonitrile, gradient: 0/10/15/17/20 min with 20/80/80/99/99% acetonitrile, flow: 0.6 mL min^{-1}.

High resolution mass (HRMS) are reported as follows: (ESI): calcd mass for the related compound followed by found mass.

16.1.4 Polarimetry

Optical rotations were measured on a JASCO Polarimeter P–1020. They are reported as follows: [α]temperature D (concentration, solvent). The unit of c is g/100 mL. Anhydrous CH_2Cl_2 or $CHCl_3$ were used as solvents. For the measurement the sodium D line = 589 nm was used.

16.1.5 Chromatographic Methods

High performance liquid chromatography (HPLC) analysis was performed on a Hewlett–Packard 1100 Series instrument equipped with a quaternary pump, using a Eurocell Knauer (250 × 4.6 mm). UV absorption was monitored at 220 nm or at 254 nm. Hexanes/isopropanol (65/25) mixture was used for elution (0.8 mL/min). Flash column chromatography was performed using flash silica gel (40–63 µm, 230–400 mesh ASTM) from Macherey–Nagel. Analytical thin layer chromatography (TLC) and preparative thin layer chromatography were performed on precoated silica gel 60 F254 plates (Merck) or Polygram Sil G/UV254 (Macherey Nagel). The compounds were visualized by UV254 light and the chromatography plates were developed with an aqueous solution of molybdophosphorous acid or an aqueous solution of potassium permanganate (heating with the heat gun). For preparation of the molybdate solution 20 g ammonium molybdate [$(NH_4)_6Mo_7O_{24}\cdot 4H_2O$] and 0.4 g $Ce(SO_4)_2\cdot 4H_2O$ were dissolved in 400 mL of 10% H_2SO_4. The potassium permanganate solution was prepared from 2.5 g $KMnO_4$ and 12.5 g Na_2CO_3 in 250 mL H_2O.

16.1.6 IR spectroscopy

FTIR spectra were measured on a JASCO FT/IR-4100 spectrophotometer.

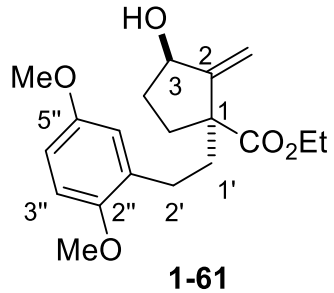
16.1.7 Photoreactor

Photochemical reactions were performed using the Kessill A160WE Tuna blue LED light. Two lamps were fixed around 10 cm away from the reaction vial (8 mL). Then, a cooling fan pointing towards the reaction vial was used to maintain the temperature between 20-25 °C during the reaction.

16.2 Experimental procedures

All the experimental procedures are arranged in the ascending order of number of the compounds.

Ethyl rel-(*1S,3R*)-1-(2,5-Dimethoxyphenethyl)-3-hydroxy-2-methylenecyclopentane-1-carboxylate (1-61)[28]

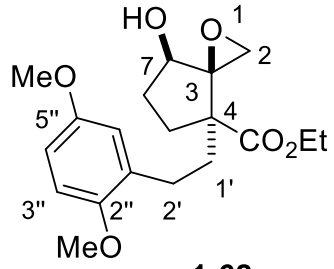


1-61

t-BuOOH (5.5 m in *n*-decane, 6.4 mL, 35.2 mmol) was added to a solution of SeO_2 (0.26 g, 2.35 mmol) in CH_2Cl_2 (30 mL) and the mixture was stirred for 30 min. Then, a solution of alkene *exo*-**1-89** (3.75 g, 11.80 mmol) in CH_2Cl_2 (10 mL) was added dropwise and the resulting suspension was stirred at r.t. for 8 h and then diluted with a saturated solution of $Na_2S_2O_3$ (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with an aqueous solution of $NaHCO_3$ (10 mL) and a saturated solution of NaCl (25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 2:1) to give allyl alcohol **1-61** (2.99 g, 76% yield) as a white solid.

R_f = 0.58 (petroleum ether/ethyl acetate, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.75–6.66 (m, 3H; ArH), 5.34 (d, *J* = 1.8 Hz, 1H; 2-CH_2), 5.32 (d, *J* = 2.0 Hz, 1H; 2-CH_2), 4.50–4.46 (m, 1H; H-3-H), 4.17–4.12 (m, 2H; $CO_2CH_2CH_3$), 3.76 (s, 3H; OCH_3), 3.75 (s, 3H; OCH_3), 2.60–2.50 (m, 2H; H-2', H-4), 2.45 (td, *J* = 4.9, 12.3 Hz, 1H; H-5), 2.20 (dt, *J* = 13.3, 4.9 Hz, 1H; H-4), 2.10–2.02 (m, 1H; H-1'), 1.80–1.67 (m, 3H; H-2', H-1', H-5), 1.27 (t, *J* = 7.2 Hz, 3H; $CO_2CH_2CH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 175.1 (CO_2Et), 156.8 (C-2), 153.5 (Ar), 151.6 (Ar), 131.6 (C-1"), 116.2 (C-6"), 111.2 (CH_2), 110.9 (Ar), 110.6 (2-CH_2), 75.7 (C-3), 61.0 ($CO_2CH_2CH_3$), 55.9 (OCH_3), 55.7 (OCH_3), 54.9 (C-1), 39.5 (C-4 or C-5), 34.1 (C-1'), 30.7 (C-5 or C-4), 26.2 (C-2'), 14.1 ($CO_2CH_2CH_3$); **HRMS** (ESI): calcd for $C_{19}H_{26}O_5$ $[M+Na]^+$ 357.1672; found: 357.1672.

Ethyl rel-(*3R,4S,7R*)-4-(2,5-Dimethoxyphenethyl)-7-hydroxy-1-oxaspiro[2.4]heptane-4-carboxylate (1-62)[28]

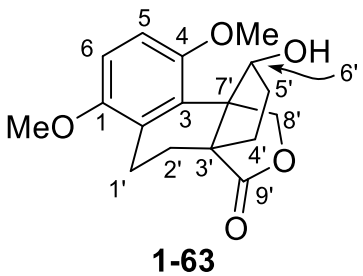


1-62

$NaHCO_3$ (0.81 g, 9.50 mmol) was added to a solution of allyl alcohol **1-61** (2.3 g, 6.88 mmol) in CH_2Cl_2 (40 mL) at 0 °C and a solution of *meta*-chloroperbenzoic acid (2.0 g, 11.9 mmol) in CH_2Cl_2 (20 mL, pre-dried with anhydrous Na_2SO_4) was added dropwise at the same temperature. After stirring for 6 h at r.t., a saturated solution of Na_2SO_3 (25 mL) was added and the mixture was stirred for a further 15 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 2:1) to give epoxide **1-62** (1.9 g, 79% yield) as a brown solid.

R_f = 0.54 (petroleum ether/ethyl acetate, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.75–6.67 (m, 3H; ArH), 4.16–4.11 (m, 3H; $CO_2CH_2CH_3$, H-7), 3.76 (s, 3H; OCH_3), 3.74 (s, 3H; OCH_3), 3.10 (d, *J* = 4.4 Hz, 1H; H-2), 2.83 (d, *J* = 4.5 Hz, 1H; H-2), 2.66–2.57 (m, 2H; CH_2), 2.35 (td, *J* = 12.2, 5.0 Hz 1H; H-6 or H-5), 2.23–2.10 (m, 2H; CH_2), 1.80–1.63 (m, 3H; CH_2, H-1'), 1.26 (t, *J* = 7.1 Hz, 3H; $CO_2CH_2CH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 171.7 (CO_2Et), 153.4, 151.5 (C-2",C-5"), 131.0 (C-1"), 116.2 (C-6"), 111.1, 111.1 (C-3", C-4"), 70.4 (C-7), 68.1 (C-3), 60.8 ($CO_2CH_2CH_3$), 55.8 (OCH_3), 55.6 (OCH_3), 52.2 (C-4), 47.4 (C-2), 36.8 (CH_2), 32.8 (CH_2), 28.0 (CH_2), 26.0 (CH_2), 14.2 ($CO_2CH_2CH_3$); **HRMS** (ESI): calcd for $C_{19}H_{26}O_6$ $[M+Na]^+$ 373.1621 ; found: 373.1621.

Lingzhiol derivative (1-63)[25]



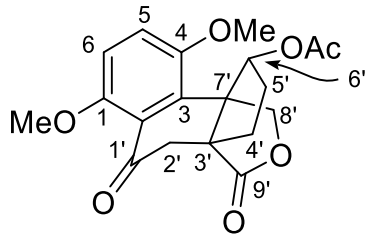
1-63

$BF_3{\cdot}Et_2O$ (0.46 mL, 3.25 mmol) was added to a solution of epoxide **1-62** (1.90 g, 5.42 mmol) in CH_2Cl_2 (45 mL) at 0 °C and the mixture was stirred for 40 min at 0 °C. Then, the reaction mixture was treated with a saturated aqueous solution of $NaHCO_3$ (15 mL), the layers were separated, and

the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were washed with a saturated solution of Na_2CO_3 (25 mL) and a saturated solution of NaCl (12 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 1:1) to give tetracyclic lactone **1-63** (0.96 g, 58% yield) as a white solid.

R_f = 0.36 (petroleum ether/ethyl acetate, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.74–6.67 (m, 2H; ArH), 5.20 (d, *J* = 9.9 Hz, 1H; H-8'), 4.15–4.12 (m, 1H; H-6'), 4.10 (d, *J* = 9.7 Hz, 1H; H-8'), 3.81 (s, 3H; OCH_3), 3.78 (s, 3H; OCH_3), 3.05 (dt, *J* = 17.2, 4.5 Hz, 1H; H-1'), 2.46 (ddd, *J* = 18.0, 13.4, 4.4 Hz, 1H; H-1'), 2.23–2.18 (m, 1H; H-4'), 2.10 (dt, *J* = 13.4, 4.4 Hz, 1H; H-2' or H-5'), 1.92–1.81 (m, 2H; H-4', H-2'), 1.65 (dd, *J* = 13.0, 4.6 Hz, 1H; H-4' or H-5'), 1.57–1.48 (m, 1H; H-2'); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 182.2 (C-9'), 151.3, 151.2 (C-1, C-4), 129.4 (C-3), 126.2 (C-2), 108.7, 108.2 (C-5, C-6), 81.8 (C-6'), 71.0 (C-8'), 55.9 (OCH_3), 55.8 (OCH_3), 53.6 (C-7'), 52.7 (C-3'), 32.4 (C-4' or C-5'), 30.1 (C-5' or C-4'), 26.7 (C-1'), 18.5 (C-2'); **IR** (ATR): $\tilde{n}$=3455, 2953, 2360, 1745, 1474, 1257, 1086, 963, 800, 738 cm^{-1}; **HRMS** (ESI): calcd for $C_{17}H_{20}O_5$ $[M+Na]^+$ 327.1208; found: 327.1206.

Ketone (1-68)[25]



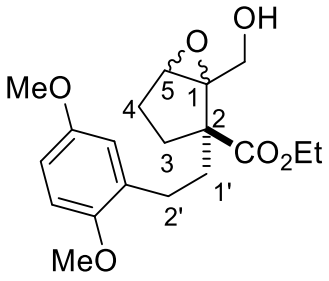
1-68

N-hydroxyphthalimide (NHPI; 106 mg, 0.65 mmol) and AIBN (21 mg, 0.13 mmol) were added to a solution of naphthalene derivative **1-99** (90 mg, 0.26 mmol) in CH_3CN (8 mL). Oxygen gas was bubbled through the mixture using a long steel needle and the mixture was stirred at 85° C for 12 h in a preheated oil bath. The mixture was cooled to r.t., and the solvent was removed under reduced pressure (without any workup). The crude product was directly purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 1:1) to give phenone **1-68** (33 mg, 35% yield) as a white solid.

R_f = 0.21 (petroleum ether/ethyl acetate, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.07 (d, *J* = 9.2 Hz, 1H; ArH), 7.01 (d, *J* = 9.2 Hz, 1H; ArH), 5.47 (br s, 1H; H-6'-H), 5.01 (d, *J* = 10.3 Hz, 1H; H-8'), 4.30 (d, *J* = 10.4 Hz, 1H; H-8'), 3.84 (s, 3H; OCH_3), 3.82 (s, 3H; OCH_3), 2.84 (d, *J* = 12.8 Hz, 1H; H-2'), 2.81 (d, *J* = 12.8 Hz, 1H; H-2'), 2.53–2.45 (m, 1H; H-4' or H-5'), 2.12 (s, 3H; $C(=O)CH_3$), 1.98–1.91 (m, 1H; H-5' or H-4'), 1.73–1.62 (m, 2H; H-4', H-5'); **^{13}C NMR** (100 MHz, $CDCl_3$): δ =

194.1 (C-1'), 179.4 (C-9'), 170.0 (*C*(=O)CH_3), 152.3, 150.3 (C-1, C-4), 130.2 (Ar), 122.9 (Ar), 117.0 (Ar), 112.5 (Ar), 81.6 (C-6'), 71.1 (C-8'), 56.5 (OCH_3), 55.9 (OCH_3), 55.2 (C-7'), 52.8 (C-3'), 44.3 (C-5' or C-4'), 31.8 (C-4' or C-5'), 31.5 (C-2''), 21.3 (C(=O)*C*H_3); **HRMS** (ESI): calcd for $C_{19}H_{20}O_7$ $[M+Na]^+$ 383.1101; found: 383.1104.

Ethyl rel-(*2S*)-2-(2,5-Dimethoxyphenethyl)-1-(hydroxymethyl)-6-oxabicyclo[3.1.0] hexane-2-carboxylate (1-87)

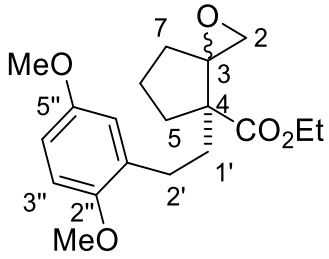


1-87 (dr = 1:1)

$NaHCO_3$ (91 mg, 1.07 mmol) was added to a solution of allyl alcohol **1-94** (0.120 g, 0.35 mmol) in CH_2Cl_2 (5 mL) at 0 °C, followed by the dropwise addition of a solution of meta-chloroperbenzoic acid (0.18 g, 1.07 mmol) in CH_2Cl_2 (3 mL, pre-dried with anhydrous Na_2SO_4) at the same temperature. After the addition was complete, the mixture was stirred for a further 6 h at r.t. Then, a saturated solution of Na_2SO_3 (5 mL) was added and the mixture was stirred for a further 15 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 1:1) to give a mixture of two epoxides **1-87** (74 mg, 59% combined yield, d.r = 1:1) as a colorless oil.

$\mathbf{R_f}$ = 0.47 (petroleum ether/ethyl acetate, 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.76–6.66 (m, 3H, ArH), 4.32 (d, *J* = 12.7 Hz, 0.5H, C*H*$_2$OH), 4.22–4.14 (m, 2H, $CO_2CH_2CH_3$), 3.90 (d, *J* = 12.8 Hz, 0.5H, C*H*$_2$OH), 3.80 (d, *J* = 11.7 Hz, 1H, C*H*$_2$OH), 3.77–3.74 (m, 6H, (2 × OCH_3), 3.60 (s, 0.5H, H-5), 3.53 (s, 0.5H, H-5), 2.70–2.50 (m, 2H, CH_2), 2.45 (dt, *J* = 12.5, 5.0 Hz, 0.5H, CH_2), 2.25–2.20 (m, 0.5H, CH_2), 2.11–1.75 (m, 5H, CH_2), 1.60–1.52 (m, 0.5H, CH_2), 1.30–1.24 (m, 3H, CO_2CH_2C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 175.0 (*C*O_2Et), 174.4 (*C*O_2Et), 153.4 (Ar), 151.6 (Ar), 151.4 (Ar), 131.6 (Ar), 130.6 (Ar), 116.3 (Ar), 116.1 (Ar), 111.1 (Ar), 111.1 (Ar), 70.3 (C-1), 69.4 (C-1), 61.9 (C-5), 61.2 (C-5), 60.9 (CO_2*C*H_2CH_3), 58.8 (*C*H_2OH), 58.5 (*C*H_2OH), 55.9 (OCH_3), 55.6 (OCH_3), 55.0 (C-1), 54.3 (C-1), 34.1 (CH_2), 33.1 (CH_2), 30.4 (CH_2), 28.2 (CH_2), 26.4 (CH_2), 26.2 (CH_2), 25.3 (CH_2), 14.3 (CO_2CH_2*C*H_3); **HRMS** (ESI): calcd for $C_{19}H_{26}O_6$ $[M+Na]^+$ 373.1621; found: 373.1621.

Ethyl 4-(2,5-Dimethoxyphenethyl)-1-oxaspiro[2.4]heptane-4-carboxylate (1-88)

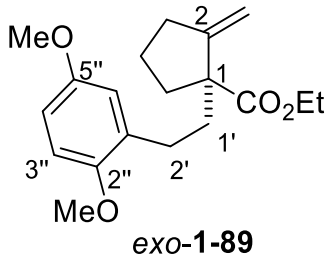


1-88 (dr = 7:3)

$NaHCO_3$ (0.81 g, 9.74 mmol) was added to a solution of alkene *exo*-**1-89** (1.55 g, 4.87 mmol) in CH_2Cl_2 (40 mL) at 0 °C, followed by the dropwise addition of a solution of *meta*-chloroperbenzoic acid (1.26 g, 7.30 mmol) in CH_2Cl_2 (20 mL, pre-dried with anhydrous Na_2SO_4) at the same temperature. After the addition was complete, the mixture was stirred for 5 h at r.t. Then, a saturated solution of sodium sulfite (Na_2SO_3; 25 mL) was added and the mixture was stirred for a further 15 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 4:1) to give a mixture of two epoxides **1-88** (1.0 g, 61% yield, d.r.= 7:3) as a white solid.

R_f = 0.58 (petroleum ether/ethyl acetate, 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.75–6.64 (m, 3H, ArH), 4.16–4.10 (m, 2H, $CO_2CH_2CH_3$), 3.76 (s,3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.02 (d, *J* = 4.8 Hz, 0.7H, H-2, major), 2.01 (d, *J* = 4.6 Hz, 0.3H, H-2, minor), 2.81 (d, *J* = 4.8 Hz, 0.3H, H-2, minor), 2.72 (d, *J* = 4.6 Hz, 0.7H, H-2, major), 2.67–2.44 (m, 2H, CH_2), 2.34 (dt, *J* = 12.1, 4.8 Hz, 1H, H-1'), 2.14–1.95 (m, 2H, CH_2), 1.90–1.72 (m, 3H, CH_2, H-6 or H-2'), 1.70–1.62 (m, 2H, CH_2), 1.30–1.25 (m, 3H, $CO_2CH_2CH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 175.0 (CO_2Et, minor), 172.2 (CO_2Et, major) 153.5, 151.6 (C-2", C-5"), 131.8 (Ar), 131.5 (Ar), 116.2 (Ar), 116.1 (Ar), 111.2 (C-3" or C-4"), 111.0 (C-4"or C-3"), 68.8 (C-3 or C-4), 60.7 ($CO_2CH_2CH_3$), 60.5 ($CO_2CH_2CH_3$), 55.9 (OCH_3), 55.7 (OCH_3), 54.9 (C-4 or C-3, minor), 54.4 (C-4 or C-3, major), 49.9 (C-2, minor), 48.9 (C-2), 35.2 (CH_2), 32.4 (CH_2), 26.1 (CH_2), 22.2 (CH_2), 21.6 (CH_2), 14.2 ($CO_2CH_2CH_3$); **HRMS** (ESI): calcd for $C_{19}H_{26}O_5$ $[M+Na]^+$ 357.1672; found: 357.1675.

Ethyl 1-(2,5-Dimethoxyphenethyl)-2-methylenecyclopentane-1-carboxylate (*exo*-1-89)

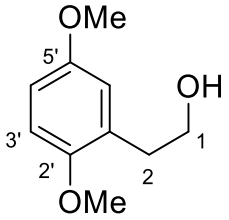


exo-**1-89**

Anhydrous potassium *tert*-butoxide (1.97 g, 17.61 mmol) was added to a solution of methyl triphenylphosphonium bromide (6.62 g, 18.53 mmol) in dry THF (50 mL) at 0 °C. The resulting yellow suspension was stirred for 30 min at 0 °C and then for 1 h at r.t. Then, the mixture was re-cooled to 0 °C and a solution of ketoester **1-93** (1.98 g, 6.17 mmol) in THF (30 mL) was added dropwise. The resulting yellow mixture was stirred at r.t. for 8 h and the reaction mixture was diluted with cold water (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×30 mL). The combined organic layers were washed with a saturated solution of NaCl (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 10:1) to give alkene *exo*-**1-89** (1.55 g, 79% yield) as a colorless liquid.

R_f = 0.44 (petroleum ether/ethyl acetate, 8:2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.75–6.72 (m, 2H, ArH), 6.70–6.66 (m, 1H, ArH), 5.10 (t, *J* = 2.0 Hz, 1H, 2-CH_2), 5.03 (t, *J* = 2.0 Hz, 1H, 2-CH_2), 4.15 (m, 2H, $CO_2CH_2CH_3$), 3.76 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 2.61 (dt, *J* = 12.9, 4.5 Hz, 1H, H-2'), 2.50–2.37 (m, 4H, H-3, H-2', H-4, H-5), 2.21 (td, *J* = 13.1, 4.8 Hz, 1H, H-1'), 1.82–1.68 (m, 4H, H-1', H-4, H-5, H-3), 1.26 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 175.1 (CO_2Et), 155.1 (C-2), 153.4, 151.6 (C-2", C-5"), 132.0 (C-1"), 116.1 (Ar), 111.2, 110.8 (C-3", C-4"), 107.5 (2-CH_2), 60.5 ($CO_2CH_2CH_3$), 56.4 (C-1), 55.9 (OCH_3), 55.6 (OCH_3), 39.1 (CH_2), 34.9 (C-1'), 33.8 (CH_2), 26.6 (C-2'), 24.1 (C-3), 14.1 ($CO_2CH_2CH_3$); **HRMS** (ESI): calcd for $C_{19}H_{26}O_4$ $[M+Na]^+$ 341.1723; found: 341.1728.

2-(2,5-Dimethoxyphenyl)ethan-1-ol (1-91)[34]



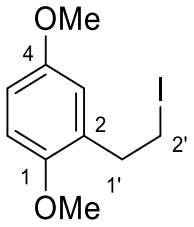
1-91

To a solution of $LiAlH_4$ (4.0 g, 100 mmol) in THF (150 mL) at 0 °C was added a solution of 2,5–dimethoxyphenyl acetic acid (10.0 g, 50.9 mmol) in dry THF (50 mL). Thereafter, the resulting

suspension was stirred at 45 °C for 8 h. The reaction mixture was cooled to 0 °C and quenched by adding H_2O (10 mL) and 15% aqueous NaOH (5 mL). The white suspension was filtered through celite and washed with hot ethyl acetate (2 × 50 mL). The obtained filtrate was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give crude alcohol **1-91** (9.1 g, 98%) as a colorless oil which was subjected for the next step without purification.

R_f = 0.25 (petroleum ether/ethyl acetate, 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.78−6.70 (m, 3H, ArH), 3.80 (t, *J* = 6.5 Hz, 2H, CH_2), 3.76 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 2.85 (t, *J* = 6.5 Hz, 2H, CH_2), 2.33 (s, 1H, OH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 153.4, 151.7 (C-2', C-5'), 128.2 (C-1'), 117.0 (Ar), 111.5, 111.2 (C-3', C-4'), 62.6 (C-1), 55.8 (OCH_3), 55.5 (OCH_3), 34.1 (C-2). **HRMS** (ESI): calcd for $C_{10}H_{14}O_3$ $[M+Na]^+$ 205.0835; found: 205.0838.

2-(2-Iodoethyl)-1,4-dimethoxybenzene (1-92)[35]

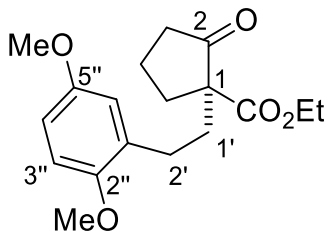


1-92

Iodine (23.0 g, 90.6 mmol) was added portionwise to a solution of imidazole (16.8 g, 247 mmol) and triphenylphosphine (23.7 g, 90.6 mmol) in CH_2Cl_2 (100 mL) at 0 °C. The resulting suspension was stirred for 5 min at the same temperature and then a solution of alcohol **1-91** (15.0 g, 82.4 mmol) in CH_2Cl_2 (50 mL) was added dropwise. After the addition was complete, the flask was covered with aluminum foil to protect it from light and the reaction mixture was stirred at r.t. for 4 h. The reaction mixture was diluted with a saturated aqueous solution of $Na_2S_2O_3$ (70 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 ×100 mL). The combined organic layers were washed with a saturated solution of NaCl (25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 10:1) to give alkyl iodide **1-92** (20.0 g, 83% yield) as a brown oil.

R_f = 0.3 (petroleum ether/ethyl acetate, 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.77–6.76 (m, 2H, ArH), 6.71–6.70 (m, 1H, ArH), 3.78 (s, 3H; OCH_3) 3.76 (s, 3H, OCH_3), 3.34 (t, *J* = 7.8 Hz, 2H, CH_2), 3.15 (t, *J* = 8.3 Hz, 2H, CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 153.3, 151.6 (C-1, C-4), 130.0 (C-2), 116.5 (C-3), 112.2, 111.3 (C-5, C-6), 55.8 (OCH_3), 55.7 (OCH_3), 35.7 (C-1'), 4.8 (C-2'); **HRMS** (ESI): calcd for $C_{10}H_{13}IO_2$ $[M+Na]^+$ 314.9853; found: 314.9850.

Ethyl 1-(2,5-Dimethoxyphenethyl)-2-oxocyclopentane-1-carboxylate (1-90)[28]

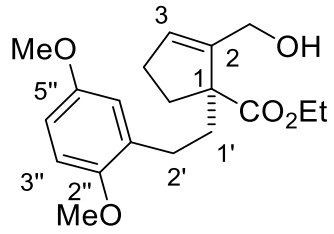


1-93

A solution of ethyl 2-oxocyclopentanecarboxylate (2.87 g, 18.04 mmol) and anhydrous K_2CO_3 (6.2 g, 53.06 mmol) in DMF (50 mL) was stirred for 15 min at r.t. A solution of alkyl iodide **1-92** (6.2 g, 21.2 mmol) in DMF (15 mL) was added and the mixture was stirred for 12 h at 75 °C. Then, the reaction was cooled to r.t., diluted with water (50 mL) and poured onto ethyl acetate (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with saturated solution of NaCl (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 10:1) to give ketoester **1-93** (3.70 g, 63% yield) as a colorless oil. Styrene **1-93a** was formed as a minor product (0.85 g, 24% yield, based on alkyl iodide) as colorless oil. ($\mathbf{R_f}$ = 0.78)

$\mathbf{R_f}$ = 0.52 (petroleum ether/ethyl acetate, 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.74–6.66 (m, 3H, ArH), 4.20–4.12 (m, 2H, $CO_2CH_2CH_3$), 3.75 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 2.64–2.50 (m, 3H, H-1', H-2', H-3), 2.45–2.37 (m, 1H, H-4), 2.31–2.16 (m, 2H, H-5, H-2'), 2.05–1.93 (m, 3H, H-5, H-3, H-4), 1.78 (ddd, *J* = 13.4, 11.6, 4.8 Hz, 1H, H-1'), 1.26 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 214.7 (C-2), 170.8 (CO_2Et), 153.5, 151.6 (C-2", C-5"), 131.0 (C-1"), 116.1 (C-6"), 111.4, 111.1 (C-3", C-4"), 61.3 ($CO_2CH_2CH_3$), 60.6 (C-1), 55.8 (OCH_3), 55.7 (OCH_3), 37.9 (C-3), 34.0 (C-1'), 32.6 (CH_2), 25.8 (C-2'), 19.6 (CH_2), 14.1 ($CO_2CH_2CH_3$); **HRMS** (ESI): calcd for $C_{18}H_{24}O_5$ $[M+Na]^+$ 343.1516; found: 343.1517.

Ethyl 1-(2,5-Dimethoxyphenethyl)-2-(hydroxymethyl)cyclopent-2-ene-1-carboxylate (1-94)

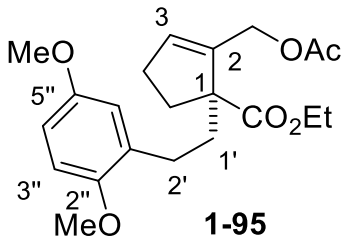


1-94

An aqueous solution of H_2SO_4 (2 m, 1 mL, 2.0 mmol) was added to a stirring solution of spiro epoxide **1-88** (0.7 g, 2.1 mmol) in CH_2Cl_2 (40 mL) at 0 °C and the stirring was continued for a further 15 min at the same temperature. Then, the reaction mixture was treated with a saturated aqueous solution of $NaHCO_3$ (10 mL) at 0 °C. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with a saturated solution of Na_2CO_3 (15 mL), a saturated solution of NaCl (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude alcohol was purified by flash chromatography (petroleum ether/ethyl acetate, 1:1) to give allyl alcohol **1-94** (0.231 g, 33% yield) as a white solid.

R_f = 0.46 (petroleum ether/ethyl acetate, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.75–6.67 (m, 3H, ArH), 5.90 (br s, 1H, H-3), 4.25–4.24 (m, 2H, C*H*$_2$OH), 4.17–4.10 (m, 2H, $CO_2CH_2CH_3$), 3.76 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 2.57–2.50 (m, 2H, CH_2), 2.48–2.40 (m, 2H, CH_2), 2.38–2.31 (m, 1H, H-2'), 2.18–2.10 (m, 1H, H-4), 2.07–2.00 (m, 1H, H-1'), 1.86 (dt, *J* = 12.1, 4.7 Hz, 1H, H-4), 1.26 (m, 3H,$CO_2CH_2CH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 176.8 (CO_2Et), 153.5, 151.6 (C-2", C-5"), 144.1 (C-2), 131.5 (C-3), 131.3 (C-1"), 116.3 (C-6"), 111.1 (C-3"), 111.0 (C-4"), 60.9 (C-1), 60.4 ($CO_2CH_2CH_3$), 59.7 (CH_2OH), 55.8 (OCH_3), 55.7 (OCH_3), 36.4 (C-4), 33.8 (C-1'), 30.3 (C-2'), 25.9 (C-5), 14.2 ($CO_2CH_2CH_3$); **HRMS** (ESI): calcd for $C_{19}H_{26}O_5$ $[M+Na]^+$ 357.1672; found: 357.1675.

Ethyl 2-(Acetoxymethyl)-1-(2,5-dimethoxyphenethyl)cyclopent-2-ene-1-carboxylate (1-95)

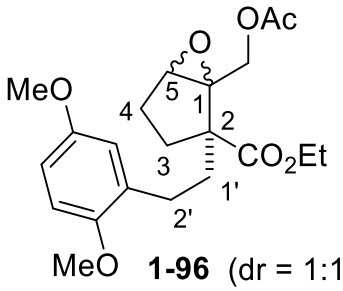


1-95

Acetic anhydride (0.158 g, 1.55 mmol) was added to a stirring solution of allyl alcohol **1-94** (0.26 g, 0.77 mmol) in pyridine (5 mL) at r.t. and the mixture was stirred for a further 8 h. The reaction mixture was diluted with water (15 mL) and extracted with CH_2Cl_2 (2 × 15 mL). The combined

organic layers were washed with HCl (1 m, 15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 3:1) to give allyl acetate **1-95** (0.225 g, 77% yield) as a yellow solid. **R_f** = 0.71 (petroleum ether/ethyl acetate, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.75–6.66 (m, 3H, ArH), 5.87 (br s, 1H, H-3), 4.72 (br s, 2H, C*H*$_2$OAc), 4.15–4.10 (m, 2H,$CO_2CH_2CH_3$), 3.76 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 2.61–2.50 (m, 2H, H-1', H-5), 2.48–2.34 (m, 3H, H-5, H-4, H-2'), 2.15 (dt, *J* = 13.4, 5.1 Hz, 1H, H-2'), 2.10–2.01 (m, 4H, OAc, H-1'), 1.80 (dt, *J* = 13.1, 4.5 Hz, 1H, H-4), 1.25 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 175.1 (CO_2Et), 170.7 (C=O, Ac), 153.4 (Ar), 151.6 (Ar), 139.4 (C-2), 131.9 (C-1''), 131.5 (C-3), 116.2 (C-6''), 111.0 (C-3'' or C-4''), 111.0 (C-4'' or C-3''), 61.2 (CH_2OAc), 60.6 ($CO_2CH_2CH_3$), 60.2 (C-1), 55.8 (OCH_3), 55.6 (OCH_3), 35.9 (C-4 or C-5), 33.4 (C-5 or C-4), 30.7 (C-1'), 25.9 (C-2'), 20.9 (O(C=O)CH_3), 14.2 ($CO_2CH_2CH_3$); **HRMS** (ESI): calcd for $C_{21}H_{28}O_7$ $[M+Na]^+$ 399.1778; found: 399.1780.

Ethyl rel-(*1S, 2S, 5S*)-1-(Acetoxymethyl)-2-(2,5-dimethoxyphenethyl)-6-oxabicyclo[3.1.0] hexane-2-carboxylate (1-97a) and Ethyl -(*1R, 2S, 5R*)-1-(Acetoxymethyl)-2-(2,5-dimethoxyphenethyl)-6- oxabicyclo[3.1.0]hexane-2-carboxylate (1-97b)



1-96 (dr = 1:1)
1-97a (α epoxide)
1-97b (β epoxide)

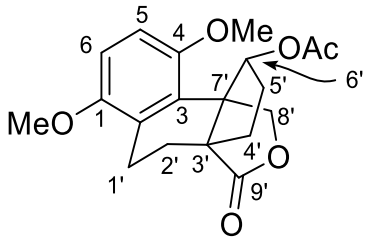
$NaHCO_3$ (0.17 g, 2.04 mmol) was added to a solution of compound **1-95** (0.22 g, 0.58 mmol) in CH_2Cl_2 (10 mL) at 0 °C and a solution of meta-chloroperbenzoic acid (0.35 g, 2.04 mmol) in CH_2Cl_2 (5 mL, pre-dried with anhydrous Na_2SO_4) was added dropwise at the same temperature. After the addition was complete, the mixture was stirred for a further 5 h at r.t. Then, a saturated solution of Na_2SO_3 (15 mL) was added and the mixture was stirred for a further 15 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 1:1) to give compound **1-97a** (37 mg, 16% yield) as a white solid and compound **1-97b** (36.4 mg, 16% yield) as a white solid.

Compound 1-97a: **R_f** = 0.22 (petroleum ether/ethyl acetate, 1:1); **1H NMR** (400 MHz, $CDCl_3$): δ = 6.72–6.65 (m, 2H; ArH), 6.64–6.57 (m,1H; ArH), 4.45 (d, *J* = 12.6 Hz, 1H; CH_2OAc), 4.25 (d, *J* =

12.6 Hz, 1H; CH_2OAc), 4.10 (q, *J* = 7.3 Hz, 2H; $CO_2CH_2CH_3$), 3.70 (s, 3H; OCH_3), 3.69 (s, 3H; OCH_3), 3.47 (s, 1H; H-5), 2.58–2.52 (m, 2H; H-1'), 2.23–2.16 (m, 1H; H-2'), 1.97 (s, 3H; OAc), 1.96–1.89 (m, 3H; H-3, H-4), 1.56–1.48 (m, 1H; H-4), 1.23 (t, *J* = 7.1 Hz, 3H; $CO_2CH_2CH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 174.1 ($CO_2CH_2CH_3$), 170.4 (C=O, Ac), 153.4, 151.6 (C-2", C-5"), 131.7 (C-1"), 116.1 (C-6"), 111.1, 111.0 (C-3", C-4"), 67.6 (C-5), 62.3 (C-1), 61.4 ($CO_2CH_2CH_3$), 60.9 (CH_2OAc), 55.9 (OCH_3), 55.7 (OCH_3), 54.5 (C-2), 32.8 (C-4), 30.6 (C-3), 26.6 (C-1'), 26.2 (C-2'), 20.7 ($O(C=O)CH_3$), 14.1 ($CO_2CH_2CH_3$); **HRMS** (ESI): calcd for $C_{21}H_{28}O_7$ $[M+Na]^+$ 415.1727; found: 415.1723.

Compound 1-97b: **R_f** = 0.19 (petroleum ether/Ethyl acetate, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.76–6.68 (m, 3H; ArH), 4.71–4.63 (m, 2H; CH_2 OAc), 4.22–4.17 (m, 2H; $CO_2CH_2CH_3$), 3.76 (s, 3H; OCH_3), 3.75 (s, 3H; OCH_3), 2.67 (td, *J* = 12.6, 4.0 Hz, 1H; H-2'), 2.43 (td, *J* = 12.6, 5.0 Hz, 1H; H-2'), 2.14–2.06 (m, 3H; H-1', H-3, H-4), 2.03 (s, 3H; OAc), 1.92–1.90 (m, 1H; H-4), 1.80–1.72 (m, 2H; H-1', H-3), 1.30 (t, *J* = 7.1 Hz, 3H; $CO_2CH_2CH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 173.8 (CO_2Et), 170.5 ($O(C=O)CH_3$), 153.5 (C-5"), 151.5 (C-2"), 130.7 (C-1"), 116.3 (C-6"), 111.3 (C-3"), 111.0 (C-4"), 67.4 (C-1), 61.2 (C-5), 61.0 ($CO_2CH_2CH_3$), 60.3 (CH_2OAc), 55.69 (OCH_3), 55.66 (OCH_3), 54.8 (C-2), 33.9 (C-1'), 27.7 (C-4), 26.2 (C-3), 25.2 (C-2'), 20.8 (OAc), 14.2 ($CO_2CH_2CH_3$); **HRMS** (ESI): calcd for $C_{21}H_{28}O_7$ $[M+Na]^+$ 415.1727; found: 415.1722.

Acetate (1-85-*syn*)[25]

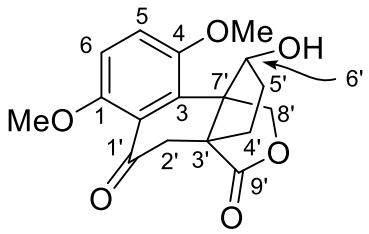


1-85-*syn*

A solution of alcohol **1-63** (0.30 g, 0.98 mmol) in CH_2Cl_2 (15 mL) was treated with acetic anhydride (0.3 mL, 2.95 mmol), pyridine (0.3 mL, 2.95 mmol), and DMAP (37 mg, 0.29 mmol) at 0 °C and the mixture was stirred for 8 h at r.t. Then, the mixture was diluted with CH_2Cl_2 (20 mL) and washed with HCl (1 m, 5 mL). The aqueous layer was further extracted with CH_2Cl_2 (30 mL) and the combined organic layers were washed with a saturated solution of NaCl (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 1:1) to give acetate **1-85** (0.34 g, 99% yield) as a white solid.

R_f = 0.63 (petroleum ether/ethyl acetate, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.70–6.66 (m, 2H; ArH), 5.46 (br s, 1H; H-6'), 4.91 (d, *J* = 4.8 Hz, 1H; H-8'), 4.10 (d, *J* = 4.0 Hz, 1H; H-8'), 3.78, (s, 3H; OCH_3), 3.76 (s, 3H; OCH_3), 3.10 (dd, *J* = 17.9, 4.5 Hz, 1H; H-1'), 2.43 (ddd, *J* = 17.6, 13.3, 4.4 Hz, 1H; H-1'), 2.37–2.31 (m, 1H; H-4' or H-5'), 2.20 (ddd, *J* = 17.4, 13.7, 4.2 Hz, 1H; H-2'), 2.11 (s, 3H; C(=O)CH_3), 2.01–1.93 (m, 1H; H-4' or H-5'), 1.76–1.52 (m, 3H; H-2', H-5', H-4'); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 182.5 (C-9'), 170.2 (*C*(=O)CH_3), 151.4, 150.7 (C-1, C-4), 127.2 (Ar), 125.7 (Ar), 109.0 (Ar), 108.3 (Ar), 82.2 (C-6'), 72.2 (C-8'), 55.8 (OCH_3), 55.4 (OCH_3), 54.9 (C-7' or C-3'), 51.6 (C-3' or C-7'), 32.2 (CH_2), 31.3 (CH_2), 27.4 (CH_2), 21.3 (C(=O)*C*H_3), 18.3 (C-1'); **HRMS** (ESI): calcd for $C_{19}H_{22}O_6$ $[M+Na]^+$ 369.1308; found: 369.1310.

Hydroxyketone (1-100)[25]

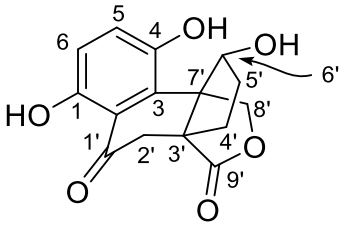


1-100

A mixture of acetate **1-85-***syn* (33 mg, 0.09 mmol) in MeOH (5 mL) and an aqueous solution of HCl (3 m, 5 mL) was heated at 85° C for 8 h. Then, the mixture was cooled to r.t. and the MeOH was removed under vacuum. The residue was diluted with water (25 mL) and then extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with a saturated solution of NaCl (2 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 1:1) to give alcohol **1-100** (28 mg, 96% yield) as light brown solid.

R_f = 0.12 (petroleum ether/ethyl acetate, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.10 (d, *J* = 9.1 Hz, 1H; ArH), 6.90 (d, *J* = 9.1 Hz, 1H; ArH), 5.30 (d, *J* = 10.0 Hz, 1H; H–8'), 4.26–4.21 (m, 2H; H-8', H-6'), 3.87 (s, 3H; OCH_3), 3.84 (s, 3H; OCH_3), 2.84 (d, *J* = 13.0 Hz, 1H; H-2'), 2.80 (d, *J* = 13.0 Hz, 1H; H-2'), 2.40–2.34 (m, 1H; H-4' or H-5'), 1.95–1.88 (m, 1H; H-5' or H-4'), 1.81–1.74 (m, 1H; H-5'), 1.58–1.50 (m, 1H; H-4'); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 194.7 (C-1'), 179.5 (C-9'), 152.6 (C-1), 150.1 (C-4), 134.0 (C-3), 122.4 (C-2), 117.0 (C-5), 111.6 (C-6), 81.6 (C-6'), 70.2 (C-8'), 56.5 (OCH_3), 56.4 (OCH_3), 53.5 (C-3'), 53.4 (C-7'), 44.1 (C-5'), 32.2 (C-4'), 31.5 (C-2'); **HRMS** (ESI): calcd for $C_{17}H_{18}O_6$ $[M+Na]^+$: 341.1001; found: 341.1001.

(±)-Lingzhiol (1-1)

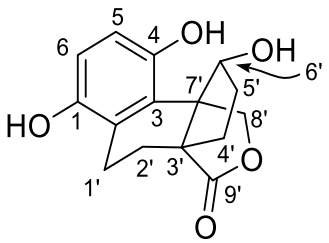


(±)-Lingzhiol (1-1)

t-BuSH (3 mL) was added to a solution of $AlCl_3$ (234 mg, 1.76 mmol) in CH_2Cl_2 (8 mL) at 0 °C and the mixture was stirred for 15 min at 0 °C. Subsequently, a solution of aryl ether **1-100** (28 mg, 0.08 mmol) in CH_2Cl_2 (5 mL) was added at the same temperature and the resulting suspension was heated at reflux for 12 h. Then, the mixture was cooled to 0 °C and treated with a saturated solution of NaH_2PO_4 (6 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with a saturated solution of NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 1:1) to give **(±)-Lingzhiol** (**1-1**) (15.3 mg, 60% yield) as a yellow solid.

R_f = 0.18 (petroleum ether/ethyl acetate, 1:1); **^{1}H NMR** (400 MHz, $(CD_3)_2CO$): δ = 11.57 (s, OH), 8.88 (s, OH), 7.20 (d, *J* = 8.9 Hz, 1H; ArH), 6.77 (d, *J* = 8.9 Hz, 1H; ArH), 5.20 (d, *J* = 9.7 Hz, 1H; H-8'), 4.87 (s, 1H; H), 4.64 (t, *J* = 4.3 Hz, 1H; H-6'), 4.45 (d, *J* = 9.7 Hz, 1H; H-8'), 3.10 (d, *J* = 16.0 Hz, 1H; H-2'), 2.80 (d, *J* = 16.0 Hz, 1H; H-2'), 2.46–2.41 (m, 1H; H-5' or H-4'), 1.81–1.68 (m, 3H; H-4', H-5'); **^{13}C NMR** (100 MHz, $(CD_3)_2CO$): δ = 202.4 (C-1'), 180.1 (C-9'), 156.4 (Ar), 148.0 (Ar), 129.2 (Ar), 127.6 (Ar), 118.0 (Ar), 116.5 (Ar), 80.8 (C-6'), 71.0 (C-8'), 56.2 (C-7'), 52.6 (C-3'), 42.4 (C-2'), 33.8 (C-5' or C-4'), 33.3 (C-4' or C-5'); **IR (ATR):** $\tilde{n}$= 2356, 2330, 1756, 1644, 1463, 1267, 740 cm^{-1}; **HRMS** (ESI): calcd for $C_{15}H_{13}O_6$ [M] 289.0717; found: 289.0722.

Hydroquinone (1-101)



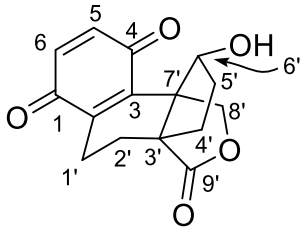
1-101

t-BuSH (5 mL) was added to a solution of $AlCl_3$ (613 mg, 4.65 mmol) in CH_2Cl_2 (15 mL) at 0 °C and a solution of aryl ether **1-63** (70 mg, 0.23 mmol) in CH_2Cl_2 (5 mL) was added at the same temperature. The resulting suspension was heated at reflux for 12 h, cooled to 0 °C, and treated with a saturated solution of NaH_2PO_4 (10 mL). The layers were separated and the aqueous layer was

extracted with ethyl acetate (2 × 20 mL), washed with a saturated solution of NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 1:1) to give lingzhiol analogue **1-101** (47 mg, 74% yield) as an off white solid.

R_f = 0.17 (petroleum ether/ethyl acetate, 1:1); **^{1}H NMR** (400 MHz, CD_3OD): δ = 6.53–6.48 (m, 2H; ArH), 5.23 (d, *J* = 9.8 Hz, 1H; H-8'), 4.38 (t, *J* = 3.4 Hz, 1H; H-6'), 4.16 (d, *J* = 9.9 Hz, 1H; H-8'), 3.01 (ddd, *J* = 17.1, 7.3, 4.3 Hz, 1H; H-1'), 2.46 (ddd, *J* = 17.2,13.1, 4.3 Hz, 1H;H-1'), 2.34–2.26 (m, 1H; H-4' or H-5'), 2.10 (td, *J* = 13.1, 4.0 Hz, 1H;H-2'), 2.01–1.90 (m, 1H; H-5' or H-5'), 1.67–1.50 (m, 3H; H-5', H-4', H-2'); **^{13}C NMR** (100 MHz, CD_3OD): δ = 186.0 (C-9'), 149.4 (C-4), 148.2 (C-1), 126.7 (C-3), 125.7 (C-2), 114.4 (Ar), 114.1 (Ar), 80.9 (C-6'), 74.1 (C-8'), 57.0 (C-7'), 52.8 (C-3'), 34.6 (C-5' or C-4'), 32.4 (C-4' or C-5'), 29.1 (C-2'), 19.6 (C-1'); **IR (ATR):** $\tilde{n}$ = 3364, 2947, 2834, 2360, 1742, 1407, 1024, 676 cm^{-1}; **HRMS** (ESI): calcd for $C_{15}H_{16}O_5$ $[M+Na]^+$ 299.0890; found: 299.0891.

Quinone (1-102)



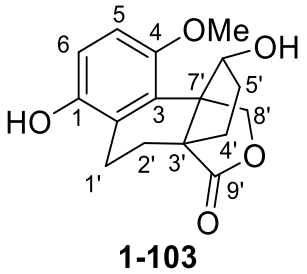
1-102

Water (0.2 mL) and 2,3-dichlor-5,6-dicyano-1,4-benzoquinone (DDQ; 51 mg, 0.22 mmol) were added to a stirring solution of hydroquinone **1-101** (25 mg, 0.09 mmol) in CH_2Cl_2 (5 mL) at r.t. The resulting suspension was stirred at r.t for 4 h. The reaction mixture was diluted with a saturated solution of $NaHCO_3$, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with a saturated solution of NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 1:1) to give quinone **1-102** (16.4 mg, 66% yield) as a yellow solid.

R_f = 0.37 (petroleum ether/ethyl acetate, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.84–6.77 (m, 2H; ArH) 5.10 (d, *J* = 10.1 Hz, 1H; H-8'), 4.01 (t, *J* = 7.9 Hz, 1H; H-6'), 3.90 (d, *J* = 10.2 Hz, 1H; H-8'), 3.30 (s, OH), 2.77 (td, *J* = 9.3, 4.8 Hz, 1H; H-1'), 2.41–2.32 (m, 1H; H-1'), 2.25–2.20 (m, 1H; H-4' or H-5'), 2.13–2.01 (m, 2H; H-2', H-5'), 1.80–1.71 (m, 2H; H-4', H-2'), 1.68–1.58 (m, 1H; H-5' or H-4'); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 188.9 (C=O), 185.8 (C=O), 180.0 (C-9'),143.9 (Ar), 142.6 (Ar), 136.9 (Ar), 136.6 (Ar), 79.5 (C-6'), 69.0 (C-8'),53.0 (C-3' or C-7'), 52.8 (C-7' or C-3'), 31.7 (C-

5'), 30.3 (C-4'), 25.5 (C-2'),18.8 (C-1'); **IR (ATR):** $\tilde{n}$=3730, 3444, 2360, 1758, 1653, 1302,1267, 1024, 739 cm^{-1}; **HRMS** (ESI): calcd for $C_{15}H_{14}O_5$ $[M+Na]^+$ 297.0733; found: 297.0732.

Phenol (1-103)

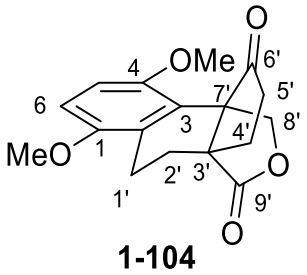


1-103

BBr_3 (1 m in CH_2Cl_2, 0.32 mL, 0.32 mmol) was added to a solution of aryl ether **1-63** (20 mg, 0.06 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The resulting mixture was stirred at r.t. for 2 h and then diluted with a saturated solution of $NaHCO_3$. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with a saturated solution of NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 1:1) to give phenol **1-103** (10 mg, 52% yield) as a yellow solid.

R_f = 0.25 (petroleum ether/ethyl acetate, 1:1); **^{1}H NMR** (400 MHz, CD_3OD): δ = 6.68–6.63 (m, 2H; ArH), 5.17 (d, *J* = 9.7 Hz, 1H; H-8'), 4.24 (t, *J* = 7.1 Hz, 1H; H-6'), 4.10 (d, *J* = 9.5 Hz, 1H; H-8'), 3.76 (s, 3H; OCH_3), 3.05 (ddd, *J* = 17.2, 4.4, 2.5 Hz, 1H; H-1'), 2.46 (ddd, *J* = 16.9, 12.5, 4.4 Hz, 1H; H-1'), 2.37–2.30 (m, 1H; H-4'), 2.11–2.06 (m, 1H; H-2'), 2.01–1.90 (m, 1H; H-4'), 1.65–1.56 (m, 2H; H-2', H-5'), 1.47–1.37 (m, 1H; H-5'); **^{13}C NMR** (100 MHz, CD_3OD): δ = 186.2 (C-9'), 152.3 (C-4), 149.5 (C-1), 128.3 (C-3), 126.6 (C-2), 114.2 (C-6), 110.4 (C-5), 81.1 (C-6'), 74.4 (C-8'), 57.7 (C-7'), 56.1 (OCH_3), 52.8 (C-3'), 35.1 (C-5'), 32.7 (C-4'), 29.4 (C-2'), 19.8 (C-1'); **IR (ATR):** $\tilde{n}$= 3436, 2360, 1748, 1267, 1026, 740, 677 cm^{-1}; **HRMS** (ESI): calcd for $C_{16}H_{18}O_5$$[M+Na]^+$ 313.1046; found: 313.1048.

Ketone (1-104)



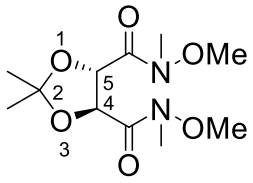
1-104

A mixture of alcohol **1-63** (25 mg, 0.082 mmol) and 2-iodoxybenzoic acid (46 mg, 0.16 mmol) in DMSO (5 mL) was stirred for 5 h at 80 °C. A saturated solution of $NaHCO_3$ (3 mL) was added and

the mixture was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with a saturated solution of NaCl (4 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 1:1) to give ketone **1-104** (19.4 mg, 78% yield) as a semi-solid.

R_f = 0.68 (petroleum ether/ethyl acetate, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.74 (s, 2H; ArH), 5.10 (d, *J* = 10.2 Hz, 1H; H-8'), 4.40 (d, *J* = 10.2 Hz, 1H; H-8'), 3.78 (s, 6H; 2 × OCH_3), 3.02 (td, *J* = 8.8, 4.5 Hz, 1H; H-1'), 2.58 (ddd, *J* = 16.9, 11.6, 4.9 Hz, 1H; H-1'), 2.44–2.27 (m, 3H; H-4', H-5'), 2.17–2.18 (m, 2H; H-2', H-4'), 1.80 (ddd, *J* = 18.2, 13.7, 4.9 Hz, 1H; H-2'); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 210.3 (C-6'), 180.6 (C-9'), 152.8 (Ar), 150.9 (Ar), 126.5 (Ar), 121.4 (Ar), 109.8 (Ar), 109.8 (Ar), 72.8 (C-8'), 56.6 (C-7' or C-3'), 56.2 (OCH_3), 55.8 (OCH_3), 49.7 (C-3' or C-7'), 36.0 (C-5'), 26.0 (C-2' or C-4'), 25.9 (C-4' or C-2'), 18.7 (C-1'); **IR (ATR):** $\tilde{n}$=3389, 2945, 2837, 2360, 1755, 1476, 1261, 1024, 676 cm^{-1}; **HRMS** (ESI): calcd for $C_{17}H_{18}O_5$ $[M+Na]^+$ 325.1046; found: 325.1050.

(*4S*,*5S*)-*N*4,*N*5-dimethoxy-*N*4,*N*5,2,2-tetramethyl-1,3-dioxolane-4,5-dicarboxamide (2-99)[94]

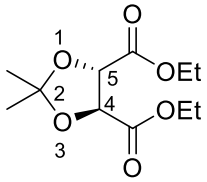


2-99

To a mixture of *N,O*-dimethylhydroxylamine hydrochloride (1.78 g, 18.3 mmol) in CH_2Cl_2 (20 mL) at –20 °C was added a solution of trimethylaluminum (2.0 M in hexane, 9.1 mL, 18.3 mmol) over 5 min. Then the mixture was stirred for 30 min at the same temperature before the dropwise addition of diethyl ester **2-104** (1.0 g, 4.1 mmol) in CH_2Cl_2 (5 mL). After addition, the cooling bath was removed and the mixture stirred for 2 h at r.t. Thereafter, the reaction mixture was carefully quenched with aqueous 1N HCl solution (10 mL) at 0 °C. Then, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 6:4) to give bis-weinreb amide **2-99** (0.86 g, 76%) as a colorless oil.

R_f = 0.26 (petroleum ether/ethyl acetate, 1:1); $[\alpha]_D^{20}$ = +13.2 (*c* = 2.15, CH_2Cl_2), **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.49 (s, 6H, 2 × CH_3), 3.20 (s, 6H, 2 × CH_3), 3.67 (s, 6H, 2 × OCH_3), 5.14 (s, br, 2H, 4-H, 5-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 26.6 (2 × $(CH_3)_2$), 32.4 (2 × $(CH_3)_2$), 61.6 (2 × (OCH_3), 74.9 (C-4, C-5), 112.9 (C-2), 170.0 (2 × C=O); **HRMS** (ESI): calculated for $[C_{16}H_{19}NO_3+Na]^+$: 296.1257; found: 296.1257.

Diethyl (*4S*,*5S*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (2-104)[96]

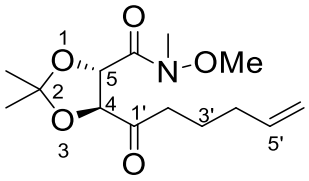


2-104

To a stirred solution of *R*-(+)-diethyl tartrate (5.0 g, 24.24 mmol) in acetone (50 mL) was added dropwise $BF_3 \cdot OEt_2$ (4.1 mL, 15.8 mmol) at r.t. The resulting yellow mixture was stirred for 3 h at r.t. During the reaction time the yellow mixture turned to red brown color. Thereafter, the reaction mixture was quenched with aqueous $NaHCO_3$ (15 mL) and extracted with ethyl acetate (2 × 40 mL). The combined organic layers were washed with NaCl solution (35 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by fractional distillation to give protected dimethyl tartrate **2-104** (4.5 g, 75%) as a yellow oil.

R_f = 0.72 (petroleum ether/ethyl acetate, 5:5); $[\alpha]_D^{20}$ = +47.5 (*c* = 2, CH_2Cl_2); {Lit[149] $[\alpha]_D^{20}$ = +48.8 (*c* = 1, MeOH}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 7.1 Hz, 6H, $(CO_2CH_2\mathit{CH_3})_2$), 1.48 (s, 6H, $C(CH_3)_2$), 4.26 (q, *J* = 7.1, 14.2 Hz, 4H, $(CO_2\mathit{CH_2}CH_3)_2$), 4.74 (s, 2H, 4-H, 5-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 13.9 (2 × $CO_2CH_2\mathit{C}H_3$), 26.2 (2 × CH_3), 61.7 (2 × $CO_2\mathit{C}H_2CH_3$), 76.5 (C-4, C-5), 113.6 (C-2), 169.5 (2 × $\mathit{C}O_2CH_2CH_3$); **HRMS** (ESI): calculated for $[C_{11}H_{18}O_6+Na]^+$: 269.0995; found: 269.0995.

(4*S*,5*S*)-5-(Hex-5-enoyl)-*N*-methoxy-*N*,2,2-trimethyl-1,3-dioxolane-4-carboxamide (2-106)[94]



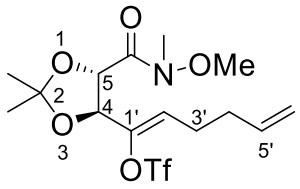
2-106

To a mixture of magnesium turnings (0.52 g, 21.7 mmol) in THF (5 mL) was added under argon atmosphere a solution of 5-bromo-1-pentene **2-105** (1.94 g, 13.0 mmol) in dry THF (6 mL) at 0 °C. After addition, the reaction mixture was stirred for 1 h at 45 °C. The resulting Grignard solution was added dropwise to a solution of bis-weinreb amide **2-99** (2.4 g, 8.68 mmol) in THF (8 mL) at 0 °C. The resulting mixture was stirred for further 30 min at 0 °C, before saturated NH_4Cl (10 mL) solution was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 15 mL). The combined organic layers were washed with NaCl solution (25 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash

chromatography (petroleum ether/ethyl acetate, 6:4) to give ketoamide **2-106** (2.0 g, 80%) as a colorless oil.

R_f = 0.46 (petroleum ether/ethyl acetate, 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.42 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.67–1.73 (m, 2H, 3'-H), 2.07 (q, *J* = 14.6, 7.1 Hz, 2H, 4'-H), 2.54–2.74 (m, 2H, 2'-H), 3.21 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 4.79–4.80 (m, 1H, 5-H), 4.95–5.03 (m, 3H, 6'-H, 4-H), 5.70–5.80 (m, 1H, 5'-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 22.0 (C-3'), 26.2 (CH_3), 26.6 (CH_3), 32.4 (CH_3), 32.9 (C-4'), 38.4 (C-2'), 61.6 (OCH_3), 73.9 (C-4), 82.2 (C-5), 112.7 (C-2), 115.3 (C-6'), 137.7 (C-5'), 169.7 (C=O), 206.1 (C-1'); **HRMS** (ESI): calculated for $[C_{14}H_{23}NO_5+Na]^+$: 308.14684; found: 308.14674.

(*Z*)-1-((*4S,5S*)-5-(Methoxy(methyl)carbamoyl)-2,2-dimethyl-1,3-dioxolan-4-yl)hexa-1,5-dien-1-yl trifluoromethanesulfonate (2-107)

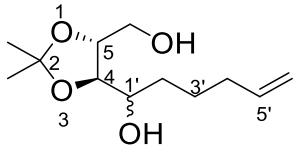


2-107

To a solution of hexamethyldisilazane (0.2 mL, 0.94 mmol) in THF (2 mL) at 0 °C was added *n*-BuLi (2.5 M in hexane, 0.3 mL, 0.52 mmol). The mixture was stirred for 30 min before the addition of amide **2-106** (0.15 g, 0.52 mmol) dissolved in THF (3 mL) at –78 °C. After addition, the reaction mixture was stirred for 1 h at –78 °C. Then, $PhNTf_2$ (0.28 g, 0.78 mmol) in THF (2 mL) solution was added at –78 °C. Again the resulting yellow mixture was stirred another 1 h at the same temperature and at r.t. for 30 min. The reaction mixture was quenched with saturated NH_4Cl solution (8 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 8 mL). The combined organic layers were washed with saturated NaCl solution (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The cured triflate was purified by flash chromatography (petroleum ether/ethyl acetate, 6:4) to give vinyl triflate **2-107** (0.13 g, 60%) as a colorless oil.

R_f = 0.64 (petroleum ether/ethyl acetate, 7:3); **^{1}H NMR** (400 MHz, C_6D_6): δ = 1.24 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.58–1.71 (m, 2H, 3'-H), 2.06–2.15 (m, 2H, 4'-H), 2.46–2.51 (m, 1H, 4-H), 2.64–2.75 (m, 1H, 5-H), 2.82 (s, 3H, CH_3), 3.24 (s, 3H, OCH_3), 4.05–5.08 (m, 2H, 6'-H), 5.66–5.76 (m, 1H, 5'-H), 6.07 (s, br, 1H, 2'-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 25.5 (CH_3), 26.3 (CH_3), 28.3 (CH_3), 32.5 (C-4'), 61.3 (OCH_3), 74.6 (C-5), 115.4 (C-4), 116.3 (C-2'), 117.2 (C-2), 120.4 (C-6'), 138.0 (C-5'), 148.3 (C=O), 167.1 (C-1'); **HRMS** (ESI): calculated for $[C_{15}H_{22}F_3NO_7S+Na]^+$: 440.0961; found: 440.0961.

1-((*4R*,*5R*)-5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)hex-5-en-1-ol (2-108)

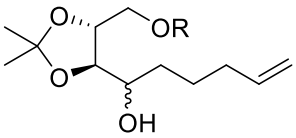


2-108

To a stirred solution of amide **2-106** (1.92 g, 6.73 mmol) in THF (40 mL) at 0 °C was added $NaBH_4$ (0.63 g, 16.65 mmol) portionwise over 10 min. After addition, the cooling bath was removed and the reaction mixture stirred at r.t. for 8 h. Then, the reaction mixture was quenched with aqueous NaOH solution (2.0 M, 15 mL). The aqueous phase was extracted with ethyl acetate (2 × 30 mL) and the combined organic layers were washed with saturated NaCl solution (35 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was purified by flash chromatography (petroleum ether/diethyl ether, 6:4) to give a 1:1 mixture of alcohol **2-108** (1.32 g, 85%) as a colorless oil.

R_f = 0.46 (petroleum ether/ethyl acetate, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.39 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.44–1.51 (m, 3H, 3'-H), 1.61–1.64 (m, 2H, 2'-H), 2.06–2.09 (m, 2.5H, 4'-H), 3.60–3.84 (m, 4H, *CH_2*OH, 1'-H, 4-H), 4.03–4.05 (m, 1H, 5-H), 4.94–5.03 (m, 2H, 6'-H), 5.75–5.85 (m, 1H, 5'-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 24.7 (C-3'), 24.9 (C-3'), 27.0 (CH_3), 27.2 (CH_3), 32.8 (C-2'), 33.5 (C-4'), 33.7 (C-4'), 63.9 (*CH_2*OH), 63.1 (*CH_2*OH), 70.3 (C-1'), 71.6 (C-1'), 77.6 (C-5), 78.6 (C-5), 79.9 (C-4), 80.5 (C-4), 108.8 (C-6'), 109.2 (C-6'), 114.7 (C-2), 114.8 (C-2), 138.4 (C-5'); **HRMS** (ESI): calculated for $[C_{12}H_{22}O_4+Na]^+$: 253.1410; found: 253.1410.

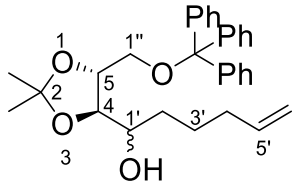
General procedure for synthesis of TBS, TIPS ether derivatives (2-109a and 2-109b)



2-109a R = TBS (37%)
2-109b R = TIPS (99%)

To a solution mixture of alcohol **2-108** (0.19 g, 0.85 mmol) in CH_2Cl_2 (8 mL) were added imidazole (0.07 g, 1.04 mmol) and TBSCl (0.15 g, 1.04 mmol) at 0 °C. The white suspension was stirred for 2 h at r.t. Then the reaction mixture was diluted with water (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 4 mL). The combined organic layers were washed with saturated NaCl solution (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/ethyl acetate, 60:40) to give silyl ethers **2-109a** and **2-109b** (d.r = 6:4) as a colorless oils.

1-((*4R,5R*)-2,2-Dimethyl-5-((trityloxy)methyl)-1,3-dioxolan-4-yl)hex-5-en-1-ol (2-109c)

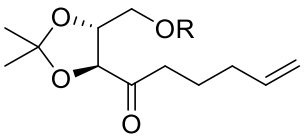


2-109c

To a mixture of secondary alcohols **2-109** (0.30 g, 1.30 mmol) in CH_2Cl_2 (10 mL) were added DMAP (16 mg, 0.13 mmol), pyridine (0.1 mL, 1.30 mmol) and trityl chloride (0.36 g, 1.30 mmol) at 0 °C. Then the reaction mixture was stirred for 8 h at r.t. before it was diluted with water (10 mL) and the aqueous layer extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with saturated NaCl solution (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude ether was purified by flash chromatography (petroleum ether/ethyl acetate, 8:2) to give trityl ether **2-109c** (0.50 g, 81%) as colorless oil.

R_f = 0.71 (petroleum ether/ethyl acetate, 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.35–1.44 (m, 9H, $(CH_3)_2$), 1.58–1.60 (m, 1.6H, 2'-H), 1.97–2.02 (m, 2H, 4'-H), 3.22–3.32 (m, 2H, 1'-H, 1''-H), 3.49–3.54 (m, 0.5H, 4-H), 3.69–3.70 (m, 0.7H, 4-H), 3.78–3.83 (m, 1H, 5-H), 4.90–4.98 (m, 2H, 6'-H), 5.69–5.82 (m, 1H, 5'-H), 7.21–7.31 (m, 10H, ArH), 7.42–7.47 (m, 6H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 24.8, (C(*CH_3*), 25.1 (C(*CH_3*), 29.7 (C-3'), 32.5 (C-2'), 33.1 (C-4'), 33.5 (C-4'), 65.4 (C-1''), 70.3 (C-1'), 73.1 (C-3'), 73.2 (C-2'), 73.7 (C-4'), 74.3 (C-5), 82.0 (C-4), 114.9 (C-6'), 127.2 (C-2), 127.2, 127.9, 128.6 (3 × Ar *C*), 138.3 (C-5'), 138.4 (C-5'), 146.8 (Ar *C*).

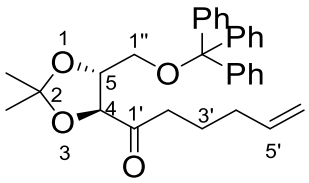
General procedure for synthesis ketones (2-110a and **2-110b)**



2-110a, R = TBS (73%)
2-110b, R = TIPS (81%)

To a solution of the secondary alcohol **2-109a,b** (0.18 g, 0.52 mmol) in CH_2Cl_2 (6 mL) at 0 °C were added DMP (0.44 g, 1.04 mmol) and $NaHCO_3$ (0.065 g, 0.78 mmol). The resulting mixture was stirred for 3 h at r.t. Then the reaction mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with saturated NaCl solution (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude ketones were purified by flash chromatography (petroleum ether/ethyl acetate, 8:2) to give ketone **2-110a** and **2-110b** as colorless oils.

1-((*4R,5S*)-2,2-dimethyl-5-((trityloxy)methyl)-1,3-dioxolan-4-yl)hex-5-en-1-one (2-110c)

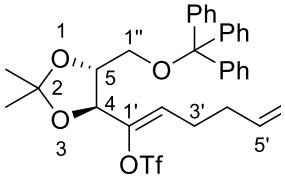


2-110c

To a solution of secondary alcohol **2-109c** (0.90 g, 1.90 mmol) in CH_2Cl_2 (20 mL) were added DMP (1.20 g, 2.85 mmol) and $NaHCO_3$ (0.40 g, 4.76 mmol) at 0 °C. The reaction mixture was stirred for 5 h at r.t. Then the reaction mixture was diluted with water (25 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were washed with saturated NaCl solution (25 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude ketone was purified by flash chromatography (petroleum ether/ethyl acetate, 85:15) to give ketone **2-110c** (0.74 g, 82%) as a colorless oil.

R_f = 0.52 (petroleum ether/ethyl acetate, 9:1); $[\alpha]_D^{20}$ = –1.5 (*c* = 1, CH_2Cl_2), **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.38 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.58–1.65 (m, 2H, 3'-H), 1.96–2.01 (m, 2H, 4'-H), 2.48–2.58 (m, 2H, 2'-H), 3.24 (dd, *J* = 4.9, 10.1 Hz, 1H, 1''-H), 3.32 (dd, *J* = 3.8, 10.2 Hz, 1H, 1''-H), 4.05–4.09 (m, 1H, 5-H), 4.14–4.17 (m, 1H, 4-H), 4.89–4.97 (m, 2H, 6'-H), 5.64–5.75 (m, 1H, 5'-H), 7.16 (m, 10H, ArH), 7.40–7.43 (m, 5H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 21.9 (C-3'), 26.4 (C(CH_3)$_2$, 27.0 (C(CH_3)$_2$, 32.9 (C-4'), 38.0 (C-2'), 64.1 (C-1''), 76.7 (C-5), 81.9 (C-4), 86.8 (CPh_3), 110.8 (C-2), 115.2 (C-6'), 127.8, 127.9, 128.7 (3 × Ar C), 137.9 (C-5'), 143.7 (Ar C), 209.5 (C-1').

(*Z*)-1-((*4S,5R*)-2,2-Dimethyl-5-((trityloxy)methyl)-1,3-dioxolan-4-yl)hexa-1,5-dien-1-yl trifluoromethanesulfonate (2-111)



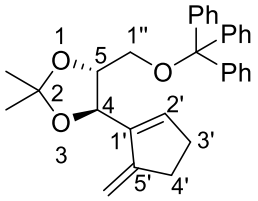
2-111

To a solution of ketone **2-110c** (0.10 g, 0.21 mmol) in THF (3 mL) at –78 °C was added a solution of KHMDS (1.0 M in THF, 0.42 mL, 0.21 mmol) dropwise over 5 min. The reaction mixture was stirred further 2 h at the same temperature, before it was treated with a solution of $PhNTf_2$ (0.11 g, 0.31 mmol) in THF (2 mL) at –78 °C for 45 min. Then the cooling bath was removed and the reaction mixture stirred for 30 min at r.t. Thereafter, the solvent was removed under reduced

pressure. The crude material purified by flash chromatography short column (petroleum ether/ethyl acetate, 7:3) to give triflate **2-111** (72 mg, 56%) as a colorless oil.

R_f = 0.56 (petroleum ether/ethyl acetate, 8:2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.42 (m, s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.96–2.05 (m, 2H, 3'-H), 2.13–2.31 (m, 2H, 4'-H), 3.18 (dd, *J* = 4.0, 10.2 Hz, 1H, 1''-H), 3.30 (dd, *J* = 4.4, 10.2 Hz, 1H, 1''-H), 4.01–4.05 (m, 1H, 5-H,), 4.45 (d, *J* = 8.2 Hz, 1H, 6'-H), 4.95–5.03 (m, 2H, 4-H, 6'-H), 5.50 (t, *J* = 7.3 Hz, 1H, 2'-H), 5.60–5.72 (m, 1H, 5'-H), 7.19–7.27 (m, 10H, ArH), 7.38–7.41 (m, 5H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 24.8 (C-4'), 26.4 (CH_3), 27.0 (CH_3), 32.1 (C-3'), 32.6 (C-4'), 62.6 (C-1''), 77.4 (C-5), 75.7 (C-4), 78.9 (C-1'), 86.8 (CPh_3), 110.5 (C-2), 115.9 (C-6'), 125.6 (C-2'), 127.8, 128.6, 128.7 (3 × Ar C), 136.5 (C-5'), 143.6 (Ar C); **HRMS** (ESI): calculated for $[C_{32}H_{33}F_3O_6S+Na]^+$: 625.1842; found: 625.1842.

(*4R*,*5R*)-2,2-Dimethyl-4-(5-methylenecyclopent-1-en-1-yl)-5-((trityloxy)methyl)-1,3-dioxolane (2-113)

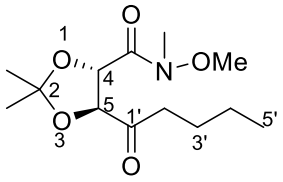


2-113

To a mixture of triflate **2-111** (20 mg, 0.03 mmol) in THF (2 mL) were added trimethylboroxine (6 mg, 0.05 mmol), anhydrous K_2CO_3 (18 mg, 0.13 mmol), and $Pd(PPh_3)_4$ (7 mg, 0.01 mmol) at 40 °C and the mixture was stirred for 1 h. The reaction mixture was cooled to r.t., and diluted with water (3 mL) and poured onto EtOAc (5 mL). The layers were separated and the organic layer washed with saturated NaCl solution (2 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/ethyl acetate, 80:20) to give diene **2-113** (10 mg, 66%) as a colorless oil.

R_f = 0.56 (petroleum ether/ethyl acetate, 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.47 (s, 3H, $C(CH_3)_2$), 1.48 (s, 3H, $C(CH_3)_2$), 2.35–2.40 (m, 2H, 4'-H), 2.53–2.60 (m, 2H, 3'-H), 3.15 (dd, *J* = 10.1, 4.3 Hz, 1H, 1''-H), 3.32 (dd, *J* = 10.3, 4.0 Hz, 1H, 1''-H), 4.05–4.10 (m, 1H, 5-H), 4.67 (s, 1H, $=CH_2$), 4.76 (d, *J* = 8.4 Hz, 1H, 4-H), 4.84 (s, 1H, $=CH_2$), 6.17 (s, 1H, 2'-H), 7.20–7.27 (m, 10H, ArH), 7.40–7.45 (m, 5H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 27.0 ($C(CH_3)_2$), 27.2 ($C(CH_3)_2$), 30.1 (C-4'), 39.5 (C-3'), 63.4 (C-1''), 74.3 (C-4 or C-5), 80.0 (C-5 or C-4), 86.3 (CPh_3), 101.8 (C-$=CH_2$), 109.0 (C-2), 126.7, 127.6, 128.8 (3 × Ar C), 132.0 (C-2'), 138.2 (C-5'), 143.8 (Ar C), 151.1 (C-1'); **HRMS** (ESI): *m/z* $[M + Na]^+$ calcd for $C_{31}H_{32}O_3$: 475.22437; found: 475.22433.

(*4S*,*5S*)-*N*-Methoxy-*N*,2,2-trimethyl-5-pentanoyl-1,3-dioxolane-4-carboxamide (2-114)

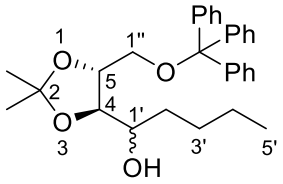


2-114

To magnesium turnings (0.26 g, 20.87 mmol) in THF (10 mL) was added under argon atmosphere a solution of 1-bromobutane (0.5 mL, 4.70 mmol) in dry THF (5 mL) at 0 °C. After addition, the reaction mixture was stirred for 1 h at 45 °C. The resulting Grignard solution was added dropwise to a solution of bis-Weinreb amide **2-99** (1.0 g, 3.66 mmol) in THF (8 mL) at 0 °C. The resulting mixture was stirred for further 1 h at 0 °C, before saturated NH_4Cl (15 mL) solution was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated NaCl solution (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude ketone was purified by flash chromatography (petroleum ether/ethyl acetate, 65:45) to give ketoamide **2-114** (0.70 g, 72%) as a colorless oil.

R_f = 0.5 (petroleum ether/ ethyl acetate, 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.3 Hz, 3H, 5'-H), 1.30–1.34 (m, 2H, CH_2), 1.41 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.52–1.60 (m, 2H, CH_2), 2.55–2.70 (m, 2H, CH_2), 3.21 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 4.80 (d, *J* = 5.2 Hz, 1H, 4-H or 5-H), 5.02 (d, *J* = 5.1 Hz, 1H, 5-H or 4-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 13.1 (CH_3), 22.2 (CH_2), 26.5 (C(CH_3)$_2$), 26.7 (C(CH_3)$_2$), 28.3 (CH_3), 32.5 (CH_2), 39.0 (CH_2), 61.7 (OCH_3), 73.8 (C-4 or C-5), 82.4 (C-5 or C-4), 113.3 (C-2), 172.0 (C=O), 208.4 (C=O).

1-((*4R*,*5R*)-2,2-Dimethyl-5-((trityloxy)methyl)-1,3-dioxolan-4-yl)pentan-1-ol (2-115)



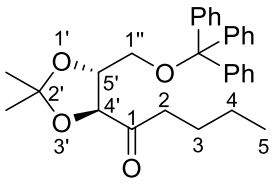
2-115

To a stirred solution of amide **2-114** (0.70 g, 2.56 mmol) in THF (40 mL) at 0 °C was added $NaBH_4$ (0.24 g, 6.40 mmol) portionwise. After addition, the reaction mixture was stirred at r.t. for 6 h. Then, the reaction mixture was quenched with aqueous NaOH solution (2.0 M, 8 mL). The aqueous phase was extracted with ethyl acetate (2 × 10 mL) and the combined organic layers were washed with saturated NaCl solution (15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced

pressure. The crude secondary alcohol was used further without any flash chromatography. To the crude secondary alcohols (0.54 g, 2.30 mmol) in CH_2Cl_2 (10 mL) were added DMAP (5.6 mg, 0.04 mmol), pyridine (5 mL) and trityl chloride (0.83 g, 2.30 mmol) at 0 °C. Then the reaction mixture was stirred for 12 h at r.t., before it was diluted with water (15 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with a saturated NaCl solution (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude alcohols was purified by flash chromatography (petroleum ether/ethyl acetate, 60:40) to give secondary alcohols **2-115** (0.67 g, 56%, after two steps, d.r = 1:1) as colorless oil.

R_f = 0.64 (petroleum ether/ethyl acetate, 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.78–0.83 (m, 3H, 5'-H), 1.18–1.23 (m, 5H, 3'-H, 2'-H), 1.35–1.38 (m, 7H, ($C(CH_3)_2$), 1.95–1.97 (m, 0.3H, 1'-H), 2.16–2.17 (m, 0.5H, 1'-H), 3.15–3.30 (m, 2H, CH_2), 3.44–3.50 (m, 0.5H, 4-H), 3.65–3.68 (m, 0.6H, 5-H), 4.06–4.10 (m, 1.5H, 1''-H), 7.17–7.27 (m, 11H, ArH), 7.40 –7.43 (m, 5H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 13.9 (C-5'), 14.1 (C-5'), 22.6 (CH_2), 27.0 ($C(CH_3)_2$), 27.1 ($C(CH_3)_2$), 27.8 ($C(CH_3)_2$), 32.2 (CH_2), 34.3 (CH_2), 60.4 (C-1'), 64.3 (C-1''), 64.7 (C-1''), 71.2 (CH_2), 76.5 (C-5 or C-4), 80.6 (C-4 or C-5), 81.4 (C-5 or C-4), 87.1 (CPh_3), 108.7 (C-2), 109.2 (C-2), 127.1, 127.8, 128.8, 143.4 (4 × Ar C).

1-((*4S*,*5R*)-2,2-dimethyl-5-((trityloxy)methyl)-1,3-dioxolan-4-yl)pentan-1-one (2-116)



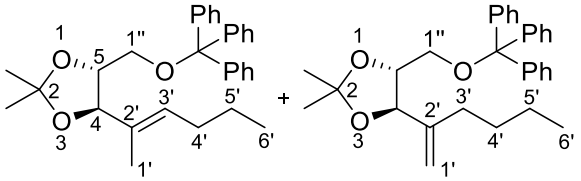
2-116

To a solution of secondary alcohols **2-115** (0.66 g, 1.43 mmol) in CH_2Cl_2 (10 mL) were added DMP (1.2 g, 2.86 mmol) and $NaHCO_3$ (0.36 g, 4.30 mmol) at 0 °C. The reaction mixture was stirred for 5 h at r.t. before it was diluted with water (15 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with a saturated NaCl solution (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude ketone was purified by flash chromatography (petroleum ether/ethyl acetate, 80:20) to give ketone **2-116** (0.37 g, 56%) as a colorless oil.

R_f = 0.54 (petroleum ether/ ethyl acetate, 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 7.3 Hz, 3H, 5'-H), 1.20–1.28 (m, 2H, CH_2), 1.40 (s, 3H, ($C(CH_3)_2$), 1.44–1.50 (m, 5H, ($C(CH_3)_2$), CH_2), 2.50–2.54 (td, *J* = 7.3, 3.1 Hz, 2H, CH_2), 3.24 (dd, *J* = 10.3, 4.9 Hz, 1H, 1''-H), 3.34 (dd, *J* = 10.2,

3.8 Hz, 1H, 1''-H), 4.16–4.18 (m, 1H, 5-H), 4.24–4.26 (m, 1H, 4-H), 7.16–7.28 (m, 10H, ArH), 7.41–7.43 (m, 5H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 13.8 (C-5'), 22.2 (C-4'), 25.0 (C-3'), 26.4 ($C(CH_3)_2$), 27.6 ($C(CH_3)_2$), 38.5 (C-2'), 64.1 (C-''), 77.4 (C-5), 81.2 (C-4), 86.8 (CPh_3), 110.8 (C-2), 127.0, 127.8, 128.7, 144.7 (4 × Ar C), 209.8 (C=O).

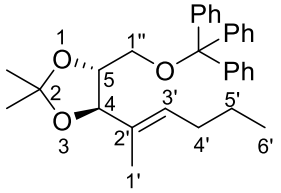
(*4R,5R*)-4-((*E*)-Hex-2-en-2-yl)-2,2-dimethyl-5-((trityloxy)methyl)-1,3-dioxolane (*endo*-2-118)
((*4R,5R*)-4-(Hex-1-en-2-yl)-2,2-dimethyl-5-((trityloxy)methyl)-1,3-dioxolan (*exo*-2-117)



To a solution of ketone **2-116** (100 mg, 0.27 mmol) in THF (2 mL) at 0 °C was added CH_3Li (1.6 M in Et_2O, 0.13 mL, 0.54 mmol) dropwise. After addition, the yellow suspension was stirred for 30 min at r.t. Then, the reaction was quenched with saturated NH_4Cl solution (2 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with statured NaCl solution (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. To the crude alcohol (85 mg, 0.17 mmol, d.r = 1:1) in CH_2Cl_2 (2 mL) was added Burgess reagent (18 mg, 0.08 mmol). The resulting mixture was heated at 40 °C for 8 h. Then, the reaction mixture was cooled to room temperature, diluted with water (3 mL) and poured onto ethyl acetate (2 × 5 mL). The layers were separated and the organic layer washed with saturated NaCl solution (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/ethyl acetate, 6:4) to give ***endo/exo*-2-177** (40 mg, 51%, 1:0.78) as a colorless oil.

R_f = 0.44 (petroleum ether/ethyl acetate, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.76 (t, J = 7.3 Hz, 3H, 6'-H, endo-major), 0.84 (t, J = 7.3 Hz, 2.5 H, 6'-H, exo-minor), 1.24–1.27 (m, 4H, 5'-H), 1.42–1.44 (m, 10H, ($C(CH_3)_2$), 1.57 (s, 3H, 1'-H), 1.86–2.00 (m, 3.5H, 4'-H), 3.10–3.14 (m, 2H, 1''-H), 3.20–3.30 (m, 2H, 1''-H), 3.86–3.90 (m, 1.7H, 5-H (or) 4-H), 4.25 (d, *J* = 8.6 Hz, 1H, 4-H (or) 5-H), 4.35 (d, *J* = 8.4 Hz, 5-H (or) 4-H), 4.83 (s, 0.7H, exo-minor), 4.95 (s, 0.7H, exo-minor), 5.35 (t, *J* = 7.2 Hz, 1H, 3'-H, endo-major), 7.16–7.27 (m, 17H, ArH), 7.41–7.45 (m, 11H, ArH).

(4*R*,5*R*)-4-((*E*)-hex-2-en-2-yl)-2,2-dimethyl-5-((trityloxy)methyl)-1,3-dioxolane (2-118)

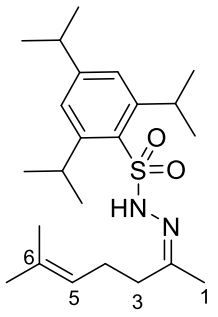


2-118

To a stirred solution of ***endo*-2188** and ***exo*-2-177** (20 mg, 0.04 mmol) in CH_3CN (2 mL) were added $Pd(OH)_2$ (2 mg) and Cs_2CO_3 (14 mg, 0.04 mmol). The suspension was kept under hydrogen atmosphere (balloon) for 8 h at r.t. Then, the reaction mixture was filtered through celite and the filtrate concentrated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 70:30) to give *endo*-**2-118** (10 mg, 55%) as a colorless oil.

R_f = 0.6 (petroleum ether/ethyl acetate, 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.78 (t, *J* = 7.3 Hz, 3H, 6'-H), 1.18–1.28 (m, 2H, 5'-H), 1.42–1.44 (m, 6H, $C(CH_3)_2$), 1.57 (s, 3H, 1'-H), 1.88–1.97 (m, 2H, 4'-H), 3.10 (dd, *J* = 10.1, 4.6 Hz, 1H, 1"-H), 3.24 (dd, *J* = 10.1, 3.9 Hz, 1H, 1"-H), 3.86–3.90 (m, 1H, 5-H (or) 4-H), 4.25–4.27 (m, 1H, 4-H (or) 5-H), 5.35 (t, *J* = 8.5 Hz, 1H, 3'-H), 7.17–7.27 (m, 10 ArH), 7.42–7.46 (m, 5H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 11.2 (C-6'), 13.8 (C-1'), 22.3 (C-5'), 26.5 ($C(CH_3)_2$), 26.7 ($C(CH_3)_2$), 30.7 (C-4'), 63.5 (C-1"), 79.6 (C-5), 81.2 (C-4), 86.6 (CPh_3), 108.6 (C-2), 126.8 (C-3'), 126.9, 127.7, 128.7 (3 × Ar C), 130.6 (C-2'), 144.5 (Ar C).

(*Z*)-2,4,6-triisopropyl-*N*'-(6-methylhept-5-en-2-ylidene)benzenesulfonohydrazide (2-129)[104]



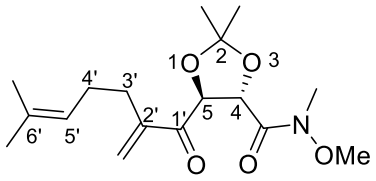
2-129

To a solution of 6-methyl-5-heptaen-2-one (0.5 mL, 3.35 mmol) in CH_3CN (10 mL) were added 2,4,6-triisopropylbenzenesulfonyl hydrazide (1.0 g, 3.35 mmol) and concentrated hydrochloric acid (0.3 mL) at r.t. The reaction mixture was stirred for 3 h at r.t. Then the white solid was filtered off, and washed with diethyl ether (30 mL) to afford hydrazone **2-129** (1.0 g, 73%) as a white solid.

R_f = 0.38 (CH_2Cl_2/MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.23–1.27 (m, 18H, $(CH(CH_3)_2)_3$), 1.47 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 2.07–2.12 (m, 2H, CH_2), 2.18–2.22 (m, 2H, CH_2), 2.87–2.90 (m, 1H, $CH(CH_3)_2)_3$), 4.20–4.25 (m, 2H, $CH(CH_3)_2)_3$), 4.86 (t, *J* = 7.1 Hz, 1H, 4-

H), 7.15 (s, 2H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 15.3 (CH_3), 17.5 (CH_3), 23.5 (CH_3), 24.5 (CH_3), 24.7 (2 × CH_3), 25.5 (CH_3), 29.8 (CH_3), 34.1 (*C*H(CH_3)$_2$)$_3$), 38.7 (C-3), 122.7 (C-5), 123.6 (2 × Ar C), 131.4 (C-6), 132.3 (Ar C), 151.3, 153.1 (2 × Ar C); **HRMS** (ESI): *m/z* $[M + Na]^+$ calcd for $C_{23}H_{38}N_2O_2S$: 429.25462; found: 429.25471.

(*4S*,*5S*)-*N*-Methoxy-*N*,2,2-trimethyl-5-(6-methyl-2-methylenehept-5-enoyl)-1,3-dioxolane-4-carboxamide (*exo*-2-131)

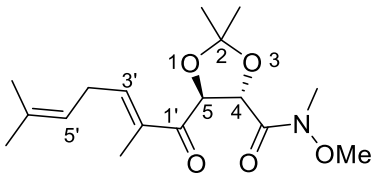


exo-2-131

Hydrazone **2-129** (100 mg, 0.24 mmol) was dissolved in THF (2 mL) under an argon atmosphere and the reaction flask was cooled to –78 °C. Then, *sec*-BuLi (1.4 M in cyclohexane, 0.5 mL, 0.70 mmol) was added dropwise and the reaction mixture stirred for 30 min at –78 °C. Then, the cooling bath was removed and the mixture was allowed to warm over 15 min until the nitrogen gas evolved (reaction mixture turned dark brown to yellow solution). Then, the solution was again re-cooled to –78 °C, before addition of bis-Weinreb amide **2-99** (70 mg, 0.24 mmol) in THF (1 mL). Later, the reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched with saturated NH_4Cl solution (2 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 5 mL). The combined organic layers were washed with saturated NaCl solution (2 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 30:70) to give ketone *exo*-**2-131** (60 mg, 76%) as a colorless oil.

R_f = 0.62 (petroleum ether/ethyl acetate, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.40 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 2.10–2.12 (m, 2H, 4'-H), 2.30–2.32 (m, 2H, 3'-H), 3.20 (s, 3H, OCH_3), 3.66 (s, 3H, CH_3), 5.10 (t, *J* = 7.1 Hz, 2H, 5'-H), 5.22 (d, *J* = 4.7 Hz, 1H, 5-H or 4-H), 5.31 (d, *J* = 4.7 Hz, 1H, 4-H or 5-H), 5.92 (s, 1H, 2'-CH_2), 6.22 (s, 1H, 2'-CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 17.7 (CH_3), 25.6 (CH_3), 26.4 (2 × CH_3), 26.6 (C-4'), 26.7 (CH_3), 31.2 (C-3'), 61.5 (OCH_3), 74.3 (C-4 or C-5), 78.6 (C-5 or C-4), 113.0 (C-2), 123.3 (C-5'), 127.8 (2'-CH_2), 132.4 (C-6'), 146.4 (C-2'), 170.2 (C=O), 196.4 (C=O); **HRMS** (ESI): *m/z* $[M + Na]^+$ calcd for $C_{17}H_{27}NO_5$: 348.17814; found: 348.17819.

(*4S*,*5S*)-5-((*E*)-2,6-Dimethylhepta-2,5-dienoyl)-*N*-methoxy-*N*,2,2-trimethyl-1,3-dioxolane-4-carboxamide (2-135)[142]

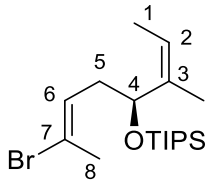


2-135

To a solution of acetone(2,4,6-triisopropylbenzyl)sulfonylhydrazone (0.20 g, 0.60 mmol) in THF (5 mL) at –78 °C was added *sec*-BuLi (1.4 M in cyclohexane, 0.9 mL, 1.30 mmol). The mixture was stirred for 30 min at the same temperature. After that l-bromo-3-methyl-2-butene (0.1 mL, 0.75 mmol) was added at –78 °C and the mixture stirred for 2 h. An additional portion of *sec*-BuLi (1.4 M in cyclohexane, 0.47 mL, 0.66 mmol) was added and the reaction stirred at –78° C another 20 min. Later, the cooling bath was removed and the reaction mixture was allowed to warm over 15 min until the nitrogen gas evolved. Then, the solution was re-cooled to –78 °C before addition of bis-Weinreb amide **2-99** (68 mg, 0.24 mmol) in THF (1 mL). The resulting mixture was stirred for another 1 h at –78 °C and warmed to room temperature within another 2 h. Finally, the reaction mixture was quenched with saturated NH_4Cl solution (5 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with saturated NaCl solution (8 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude ketoamide was purified by flash chromatography (petroleum ether/ethyl acetate, 60:40) to give ketoamide **2-135** (0.12 g, 61%) as a colorless oil.

R_f = 0.62 (petroleum ether/ethyl acetate, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.40 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 2.30 (t, *J* = 7.1 Hz, 2H, 4'-H), 3.20 (s, 3H, OCH_3), 3.65 (s, 3H, CH_3), 5.12 (t, *J* = 7.2 Hz, 1H, 5'-H), 5.21 (d, *J* = 5.0 Hz, 1H, 5-H or 4-H), 5.30 (d, *J* = 5.1 Hz, 1H, 4-H or 5-H), 6.80 (t, *J* = 7.0 Hz, 1H, 3'-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 11.5 (CH_3), 18.0 (CH_3), 25.6 (CH_3), 26.4 (CH_3), 26.6 (CH_3), 28.4 (CH_3), 32.4 (C-4'), 61.5 (OCH_3), 74.5 (C-4 or C-5), 78.0 (C-5 or C-4), 112.7 (C-2), 120.0 (C-5'), 134.0 ($C(CH_3)_2$), 135.2 (C-2'), 145.3 (C-3'), 170.3 (C=O), 196.2 (C=O).

(*S*,*2Z*,*6E*)-7-Bromo-3-methylocta-2,6-dien-4-yl)oxy)triisopropylsilane (2-139)



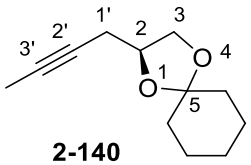
2-139

To a solution of ethyltriphenylphosphonium bromide (0.61 g, 1.65 mmol) in THF (5 mL) was added KHMDS (1.0 M in THF, 1.66 mL, 1.65 mmol) dropwise at –78 °C. The resulting yellow suspension was stirred for 45 min at the same temperature. Thereafter, a solution of ketone **2-160** (0.27 g, 0.74 mmol) in THF (2 mL) was added dropwise at –78 °C. After complete addition, the resulting yellow mixture was stirred for 1 h at –78 °C and then brought to r.t. The reaction mixture was diluted with water (10 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with saturated NaCl solution (8 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 75:15) to give vinyl bromide **2-139** (0.185 g, 66%) as a colorless oil.

R_f = 0.88 (petroleum ether/ethyl acetate, 9:1); $[\alpha]_D^{19}$ = +15.07 (*c* = 1.44, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.03–1.05 (m, 21H, $Si(CH(CH_3)_2)_3$), 1.55 (dd, *J* = 6.9, 1.4 Hz, 3H, 1-H), 1.67 (t, *J* = 1.4 Hz, 3H, 3-CH_3), 2.19–2.35 (m, 5H, 8-H, 5-H), 4.66 (dd, *J* = 8.0, 6.1 Hz, 1H, 4-H), 5.22–5.28 (m, 1H, 2-H), 5.75 (dt, *J* = 8.3, 1.3 Hz, 1H, 6-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 12.3 ($Si(CH(CH_3)_2)_3$), 13.2 (C-1), 17.5 (3-CH_3), 17.9 ($Si(CH(\mathit{C}H_3)_2)_3$), 18.0 ($Si(CH(\mathit{C}H_3)_2)_3$), 23.3 (C-8), 36.5 (C-5), 69.0 (C-4), 120.3 (C-2), 120.6 (C-7), 128.5 (C-6), 137.3 (C-3).

Note: The same procedures were used for (*R*)-enantiomer.

(*S*)-2-(But-2-yn-1-yl)-1,4-dioxaspiro[4.5]decane (2-140)



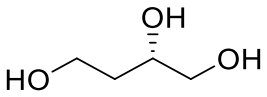
2-140

To a stirred solution of dibromide **2-150** (9.5 g, 27.9 mmol) in THF (80 mL) at –78 °C was added a solution of *n*-BuLi (2.5 M in THF, 27.9 mL, 69.8 mmol) over 15 min. The reaction mixture was stirred at –78 °C for 2 h, before iodomethane (7.0 mL, 112 mmol) was added dropwise. After addition, the reaction mixture was stirred at r.t. for 30 min. Then the reaction mixture was diluted with saturated NH_4Cl solution, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 35 mL). The combined organic layers were washed with saturated NaCl solution,

dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 9:1) to give alkyne **2-140** (4.0 g, 74%) as a colorless oil.

R_f = 0.75 (petroleum ether/ethyl acetate, 9:1); $[\alpha]_D^{22}$ = +33.01 (*c* =0.73, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.33–1.40 (m, 2H, CH_2), 1.52–1.63 (m, 8H, $(CH_2)_4$), 1.75 (t, *J* = 2.5 Hz, 3H, CH_3), 2.28–2.36 (m, 1H, 1'-H), 2.44–2.50 (m, 1H, 1'-H), 3.73 (dd, *J* = 8.2, 6.2 Hz, 1H, 3-H), 4.06 (dd, *J* = 8.3, 6.0 Hz, 1H, 3-H), 4.14–4.20 (m, 1H, 2-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 3.4 (4'-H), 23.7 (CH_2), 23.9 (C-1'), 24.1, 25.1, 35.1, 36.5 (4 × CH_2), 68.5 (C-3), 74.1 (C-2), 74.5 (C-2'), 77.4 (C-3'), 110.0 (C-5); **HRMS** (ESI): *m/z* $[M + Na]^+$ calcd for $C_{12}H_{18}O_2$: 217.1199; found: 217.1199.

(*S*)-Butane-1,2,4-triol (2-147)[113]

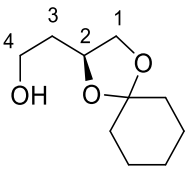


2-147

A mixture of $BH_3{\cdot}SMe_2$ complex (47.2 mL, 0.552 mol) and trimethyl borate (61.6 mL, 0.553 mol) in THF (50 mL) at 0 °C was added dropwise to a solution (*S*)-malic acid (**2-141**) (24.7 g, 0.184 mol) in THF (100 mL) at 0 °C over 20 min. After complete addition, the ice bath was removed and the mixture stirred for 12 h at r.t. Then, the reaction mixture was quenched by dropwise addition of MeOH (150 mL) at r.t. The solvent was removed under reduced pressure. The crude triol **2-147** (22.0 g) was used for the next reaction without further purification.

R_f = 0.42 (CH_2Cl_2/MeOH, 9:1); **HRMS** (ESI): *m/z* $[M + Na]^+$ calcd for $C_4H_{10}O_3$: 129.0522; found: 129.0522.

(*S*)-1,2-*O*-Cyclohexylidene-1,2,4-butanetriol (2-148)



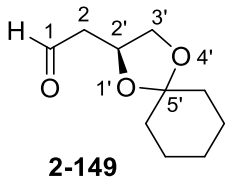
2-148

To a solution of triol **2-147** (22.0 g, 0.207 mol) in cyclohexanone (53 mL, 0.519 mol) was added *p*-toluenesulfonic acid (*p*TsOH·H_2O) (0.78 g, 4.10 mmol) followed by stirring of the mixture at r.t. for 3 h. Then the reaction mixture was diluted with saturated $NaHCO_3$ solution (55 mL) and H_2O (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 55 mL). The combined organic layers were washed with saturated NaCl solution (45 mL), dried over Na_2SO_4, filtered, and concentrated

under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 1:1) to give alcohol **2-148** (20.0 g, 58%, over two steps) as a colorless oil.

R_f = 0.72 (petroleum ether/ethyl acetate, 6:4); $[\alpha]_D^{18}$ = –12.7 (*c* = 0.5, CH_2Cl_2); {Lit.[113] $[\alpha]_D$ = –15.4 (*c* = 2.0, acetone)}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.36–1.37 (m, 2H, CH_2), 1.56–1.60 (m, 8H, $(CH_2)_4$), 1.78 (q, *J* = 5.8 Hz, 2H, 3-H), 2.44 (br s, 1H, OH), 3.58 (dd, *J* = 7.3, 7.3 Hz, 1H, 1-H), 3.78 (t, *J* = 6.2 Hz, 2H, 4-H), 4.05 (dd, *J* = 8.0, 5.9 Hz, 1H, 1-H), 4.21–4.27 (m, 1H, 2-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 23.8 (CH_2), 24.0 (CH_2), 25.0 (CH_2), 35.1 (CH_2), 35.6 (C-3), 36.4 (CH_2), 60.6 (C-4), 69.0 (C-1), 74.9 (C-2), 109.7 (acetal C). **HRMS** (ESI): *m/z* $[M + Na]^+$ calcd for $C_{10}H_{18}O_3$: 209.1147; found: 209.1147.

(*S*)-2-(1,4-Dioxaspiro[4.5]decan-2-yl)acetaldehyde (2-149)

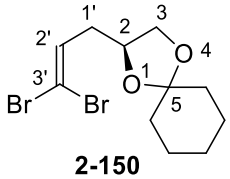


2-149

To a solution of oxalyl chloride (6.95 mL, 80.5 mmol) in CH_2Cl_2 (20 mL) was slowly added DMSO (11.4 mL, 161 mmol) at –78 °C. After being stirred for 15 min at this temperature, a solution of alcohol **2-148** (10.0 g, 53.7 mmol) in CH_2Cl_2 (50 mL) was added to the mixture over a period of 15 min. The reaction mixture was stirred at the same temperature for 1 h. Thereafter, Et_3N (45.3 mL, 322 mmol) was added dropwise. Then, the reaction mixture was brought to r.t. and stirred for 10 min. It was diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with saturated NaCl solution (80 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give aldehyde **2-149** (8.0 g, 81%) as a slightly brown oil. The aldehyde **2-149** was used for the next reaction without further purification.

R_f = 0.87 (petroleum ether/ethyl acetate, 6:4); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.33–1.40 (m, 2H, CH_2), 1.51–1.58 (m, 8H, $(CH_2)_4$), 2.57–2.60 (m, 1H, 2-H), 2.81 (ddd, *J* = 17.1, 6.5, 1.8 Hz, 1H, 2-H), 3.55 (dd, *J* = 8.3, 6.6 Hz, 1H, 3'-H), 4.14 (dd, *J* = 8.3, 6.0 Hz, 1H, 3'-H), 4.46–4.52 (m, 1H, 2'-H), 9.77 (t, *J* = 1.6 Hz, 1H, CHO); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 23.7 (CH_2), 23.9 (CH_2), 25.0 (CH_2), 34.8 (CH_2), 36.4 (CH_2), 47.9 (C-2), 68.7 (C-3'), 70.2 (C-2'), 109.8 (C-5'), 200.1 (C-1).

(*S*)-2-(3,3-Dibromoallyl)-1,4-dioxaspiro[4.5]decane (2-150)[150]

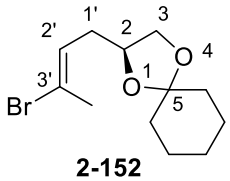


2-150

To a stirred solution of triphenylphosphine (54.1 g, 0.206 mol) in CH_2Cl_2 (70 mL) at 0 °C was added carbon tetrabromide (45.0 g, 0.136 mol) in small portions. After complete addition, the ice bath was removed and the reaction mixture stirred for 30 min at r.t. The reaction mixture was recooled to 0 °C before a solution of aldehyde **2-149** (10.0 g, 54.3 mmol) in CH_2Cl_2 (85 mL) was added dropwise over 15 min. After addition, the white suspension was stirred at r.t for 30 min. The reaction mixture was treated with hexane (250 mL) resulting of precipitation of phosphorus compounds. The obtained solid was removed by filtration of the mixture through a pad of celite and the filtrate concentrated under reduced pressure. The same procedure was repeated twice. Finally, the obtained oil was purified by flash chromatography (petroleum ether/ethyl acetate, 90:10) to give dibromide **2-150** (12.0 g, 65%) as a colorless oil.

R_f = 0.72 (petroleum ether/ethyl acetate, 9:1); $[\alpha]_D^{19}$ = –3.91 (*c* = 0.8, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.39–1.40 (m, 2H, CH_2), 1.56–1.62 (m, 8H, $(CH_2)_4$), 2.35–2.39 (m, 2H, 1'-H), 3.60 (dd, *J* = 8.2, 6.4 Hz, 1H, 3-H), 4.03 (dd, *J* = 8.2, 6.1 Hz, 1H, 3-H), 4.15–4.21 (m, 1H, 2-H), 6.49 (t, *J* = 7.1 Hz, 1H, 2'-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 23.8, 23.9, 25.1, 35.0, 36.5 (5 × CH_2), 37.3 (C-1'), 68.2 (C-3), 73.3 (C-2), 90.8 (C-3'), 109.9 (C-5), 134.0 (C-2').

(*S*,*E*)-2-(3-Bromobut-2-en-1-yl)-1,4-dioxaspiro[4.5]decane (2-152)



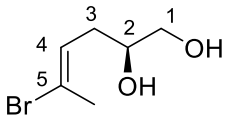
2-152

To a solution of Cp_2ZrCl_2 (19.25 g, 65.86 mmol) in THF (85 mL) at 0 °C was added DIBAL-H (1M hexane, 65.9 mL, 65.9 mmol) followed by stirring of the resulting white suspension of zirconocene hydrochloride at r.t. for 45 min. Thereafter, alkyne **2-140** (4.57 g, 23.5 mmol) in THF (10 mL) was added dropwise at 0 °C. The resulting mixture was heated for 1 h at 55 °C and then cooled to 0 °C before a solution of NBS (5.20 g, 29.4 mmol) in THF (15 mL) was added. After complete addition, the reaction mixture was stirred for another 30 min at 0 °C. The reaction mixture was carefully quenched with saturated $NaHCO_3$ solution (15 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, filtered

and concentrated under reduced pressure to give vinyl bromide **2-152** (6.0 g, 93%; 4:1 mixture of regioisomers). The crude brown oil was used for the next reaction without chromatography.

R_f = 0.92 (petroleum ether/ethyl acetate, 8:2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.34–1.38 (m, 3H, CH_2), 1.52–1.61 (m, 13H, CH_2), 2.21–2.35 (m, 5H, 3-CH_3, 1'-H), 3.54 (dd, *J* = 7.9, 6.5 Hz, 1.4H, 3-H), 4.03 (dd, *J* = 8.1, 6.0 Hz, 1.3H, 3-H), 4.08–4.14 (m, 1.5H, 2-H), 5.85 (td, *J* = 7.7, 1.2 Hz, 1H, 2'-H, major), 6.00–6.05 (m, 0.2H, 2'-H, minor); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 23.4 (CH_3), 23.8 (CH_2), 24.0 (C-1'), 25.1, 33.9, 35.0, 36.5 (4 × CH_2), 68.3 (C-3), 74.3 (C-2), 109.7 (C-5), 121.7 (C-3'), 127.0 (C-2').

(*S*,*E*)-5-Bromohex-4-ene-1,2-diol (2-153)

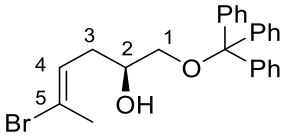


2-153

A solution of acetal **2-152** (1.24 g, 4.50 mmol) in a mixture of AcOH/H_2O (1:1, 16 mL) was stirred for 12 h at r.t. Thereafter, the reaction mixture was diluted with saturated $NaHCO_3$ solution (25 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with saturated NaCl solution (25 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The regioisomers were separated by flash chromatography (petroleum ether/ethyl acetate, 3:7) to give diol **2-153** (0.37 g, 42%) and a small amount of minor isomer (68 mg, 8%) as colorless oils.

R_f = 0.45 (petroleum ether/ethyl acetate, 2:8); $[\alpha]_D^{21}$ = –5.44 (*c* = 0.8, CH_2Cl_2); **^{1}H NMR** (400 MHz, C_6D_6): δ = 1.83–1.93 (m, 2H, 3-H), 2.00 (s, 3H, 5-CH_3), 2.85 (br s, 2H, OH), 3.20 (dd, *J* = 11.1, 7.1 Hz, 1H, 1-H), 3.32 (dd, *J* = 11.1, 2.5 Hz, 1H, 1-H), 3.41–3.46 (m, 1H, 2-H), 5.88 (td, *J* = 7.8, 1.2 Hz, 1H, 4-H); **^{13}C NMR** (100 MHz, C_6D_6): δ = 23.3 (*C*H_3), 33.5 (C-3), 66.0 (C-1), 71.4 (C-2), 121.7 (C-5), 129.9 (C-4); **HRMS** (ESI): *m/z* $[M + Na]^+$ calcd for $C_6H_{11}BrO_5$: 216.9836; found: 216.9836.

(*S*,*E*)-5-Bromo-1-(trityloxy)hex-4-en-2-ol (2-155)



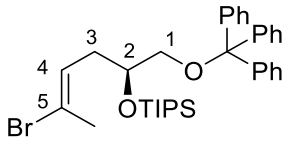
2-155

A solution of diol **2-153** (0.25 g, 1.28 mmol) in CH_2Cl_2 (10 mL) at r.t. was treated with pyridine (0.2 mL, 2.61 mmol), DMAP (55 mg, 0.45 mmol) and trityl chloride (0.72 g, 2.61 mmol). The resulting mixture was stirred for 2 h at r.t. Thereafter, the reaction mixture was diluted with water (20 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL).

The combined organic layers were washed with saturated NaCl solution (15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 7:3) to give trityl ether **2-155** (0.34 g, 59%) as a colorless oil.

R_f = 0.54 (petroleum ether/ethyl acetate, 8:2); $[\alpha]_D^{22}$ = –2.29 (*c* = 1.04, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.15–2.28 (m, 5H, CH_3, 3-H), 3.10 (dd, *J* = 9.5, 6.6 Hz, 1H, 1-H), 3.20 (dd, *J* = 9.4, 4.0 Hz, 1H, 1-H), 3.47 (br s, 1H, OH), 3.74–3.80 (m, 1H, 2-H), 5.80 (td, *J* = 7.7, 1.3 Hz, 1H, 4-H), 7.23–7.34 (m, 10H, ArH), 7.41–7.46 (m, 5H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 23.3 (CH_3), 33.7 (C-3), 66.8 (C-1), 70.1 (C-2), 86.8 (CPh_3), 121.4 (C-5), 127.2 (Ar C), 127.6 (C-4), 127.9, 128.6, 143.7 (3 × Ar C); **HRMS** (ESI): *m/z* $[M + Na]^+$ calcd for $C_{25}H_{25}BrO_2$: 459.0933; found: 459.0933.

(*S*,*E*)-((5-Bromo-1-(trityloxy)hex-4-en-2-yl)oxy)triisopropylsilane (2-156)

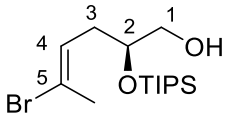


2-156

To a solution of alcohol **2-155** (1.10 g, 2.51 mmol) in CH_2Cl_2 (10 mL) at 0 °C were added 2,6-lutidine (0.58 mL, 5.03 mmol) and TIPSOTf (0.74 mL, 2.76 mmol) dropwise. The resulting mixture was stirred for 1 h at 0 °C before it was diluted with water (15 mL) and the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (15 mL), saturated NaCl solution (15 mL), dried with anhydrous Na_2SO_4, filtered and concentered under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 95:5) to give silyl ether **2-156** (1.29 g, 86%) as a colorless oil.

R_f = 0.77 (petroleum ether/ Et_2O, 9:1); $[\alpha]_D^{22}$ = –1.08 (*c* = 0.55, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.79–0.84 (m, 1H, $Si(CH(CH_3)_2)_3$), 0.92–0.94 (m, 20H, $Si(CH(CH_3)_2)_3$), 2.15 (s, 3H, CH_3), 2.35–2.47 (m, 2H, 3-H), 2.97 (dd, *J* = 8.9, 7.3 Hz, 1H, 1-H), 3.03 (dd, *J* = 9.0, 4.2 Hz, 1H, 1-H), 3.91–3.96 (m, 1H, 2-H), 5.83 (td, *J* = 7.1, 1.2 Hz, 1H, 4-H), 7.17–7.27 (m, 10H, Ar*H*), 7.36–7.40 (m, 5H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 12.3 ($Si(CH(CH_3)_2)_3$), 18.0 ($Si(CH(CH_3)_2)$), 23.5 (CH_3), 35.2 (C-3), 66.4 (C-1), 70.8 (C-2), 86.5 (CPh_3), 120.5 (C-5), 127.0, 127.7 (2 × Ar C), 128.3 (C-4), 128.7, 144.0 (2 × Ar C); **HRMS** (ESI): *m/z* $[M + Na]^+$ calcd for $C_{34}H_{45}BrO_2Si$: 615.2272; found: 615.2272.

(*S*,*E*)-5-Bromo-2-((triisopropylsilyl)oxy)hex-4-en-1-ol (2-157)

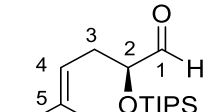


2-157

To a solution of trityl ether **2-156** (1.29 g, 2.17 mmol) in CH_2Cl_2 (15 mL) at 0 °C were added Et_3SiH (1.04 mL, 6.51 mmol) and $BF_3{\cdot}OEt_2$ (0.54 mL, 4.34 mmol) dropwise. The resulting mixture was stirred for 1 h at the same temperature before it was diluted with saturated $NaHCO_3$ solution (10 mL). The layers were separated and the organic layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated NaCl solution (10 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 7:3) to give alcohol **2-157** (0.57 g, 75%) as a colorless oil.

R_f = 0.37 (petroleum ether/ethyl acetate, 8:2); $[\alpha]_D^{20}$ = –3.02 (*c* = 0.21, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.06–1.08 (m, 21H, $Si(CH(CH_3)_2)_3$), 1.76 (br s, 1H, OH), 2.20–2.27 (m, 4H, CH_3, 3-H), 2.34–2.42 (m, 1H, 3-H), 3.50 (dd, *J* = 11.1, 3.8 Hz, 1H, 1-H), 3.60 (dd, *J* = 11.0, 3.8 Hz, 1H, 1-H), 3.87–3.92 (m, 1H, 2-H), 5.82–5.86 (m, 1H, 4-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 12.4 ($Si(CH(CH_3)_2)_3$), 18.0 ($Si(CH(CH_3)_2)_3$), 23.3 (CH_3), 34.1 (C-3), 65.2 (C-1), 71.7 (C-2), 121.5 (C-5), 127.6 (C-4); **HRMS** (ESI): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{31}BrO_2Si$: 373.1166; found: 373.1166.

(*S*,*E*)-5-Bromo-2-((triisopropylsilyl)oxy)hex-4-enal (2-158)



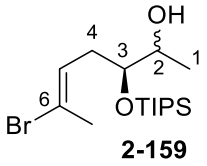
2-158

To a mixture of IBX (1.37 g, 4.90 mmol) in DMSO (8 mL) was added alcohol **2-157** (0.53 g, 1.50 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After complete addition, the ice bath was removed and the mixture stirred for 5 h at r.t. The suspension was diluted with CH_2Cl_2 (20 mL) and filtered through a pad of celite. The filtrate was washed with saturated $NaHCO_3$ solution (10 ml), saturated NaCl solution (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give aldehyde **2-158** (0.40 g, 76%) as yellow oil that was used for the next reaction without further purification.

R_f = 0.69 (petroleum ether/ethyl acetate, 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.05–1.11 (m, 21H, $Si(CH(CH_3)_2)_3$), 2.21 (s, 3H, 5-CH_3), 2.34–2.47 (m, 2H, 3-H), 4.12 (dt, *J* = 5.7, 1.8 Hz, 1H, 2-H), 5.90 (t, *J* = 7.2 Hz, 1H, 4-H), 9.64 (d, *J* = 1.8 Hz, 1H, CHO); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 12.1 ($Si(CH(CH_3)_2)_3$), 17.8 ($Si(CH(CH_3)_2)_3$), 23.4 (CH_3), 33.7 (C-3), 125.9 (C-2), 128.2 (C-5),

129.4 (C-4), 204.0 (C-1); **HRMS** (ESI): *m/z* [M + Na]$^+$ calcd for $C_{15}H_{29}BrO_2Si$: 403.1278; found: 403.1278.

(*3S,E*)-6-Bromo-3-((triisopropylsilyl)oxy)hept-5-en-2-ol (2-159)

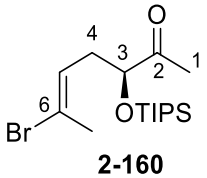


2-159

To a solution of aldehyde **2-158** (0.5 g, 1.43 mmol) in THF (10 mL) at 0 °C was added CH_3MgBr (3M in Et_2O, 0.71 mL, 2.14 mmol) dropwise. After addition, the white suspension was stirred for 30 min at 0 °C. Then, the reaction was quenched with saturated NH_4Cl solution (5 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with statured NaCl solution (15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/Et_2O, 6:4) to give of alcohol **2-159** (0.40 g, 76%) as a colorless oil.

R_f = 0.41 (petroleum ether/Et_2O, 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.04 (s, $Si(CH(CH_3)_2)_3$, major), 1.07–1.08 (m, $Si(CH(CH_3)_2)_3$, minor), 1.12 (d, *J* = 6.3 Hz, 1-H, minor), 1.18 (d, *J* = 6.2 Hz, 1-H, major), 2.15–2.27 (m, 7-H, 4-H, minor), 2.40–2.47 (m, 4-H, major), 3.61–3.70 (m, 2-H, 3-H minor), 3.80–3.86 (m, 3-H, major), 5.84–5.90 (m, 1H, 5-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 12.3 ($Si(\mathit{C}H(CH_3)_2)_3$), 12.7 (C-1, minor) 12.8 (C-1, major), 17.7 ($Si(CH(\mathit{C}H_3)_2)_3$, major), 18.1 ($Si(CH(\mathit{C}H_3)_2)_3$, minor), 23.4 (C-7, minor and major), 31.9 (C-4, minor), 34.1 (C-4, major), 68.7 (C-2, major), 70.3 (C-2, minor), 75.3 (C-3, minor), 75.6 (C-3, major), 120.5 (C-6, minor), 121.3 (C-6, major), 127.6 (C-5, major), 128.7 (C-5, minor); **HRMS** (ESI): *m/z* [M + Na]$^+$ calcd for $C_{16}H_{33}BrO_2Si$: 387.1331; found: 387.1331.

(*S,E*)-6-Bromo-3-((triisopropylsilyl)oxy)hept-5-en-2-one (2-160)



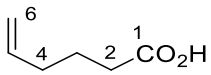
2-160

To a stirred solution of alcohol **2-159** (0.40 g, 1.09 mmol) in CH_2Cl_2 (10 mL) at 0 °C were added DMP (0.92 g, 2.18 mmol) and $NaHCO_3$ (0.27 g, 3.28 mmol). Thereafter, the reaction mixture was stirred for 1 h at r.t. The reaction mixture was treated with saturated $NaHCO_3$ solution (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with saturated NaCl solution (10 mL), dried over Na_2SO_4, filtered, and

concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/ethyl acetate, 8:2) to give methyl ketone **2-160** (0.30 g, 75%) as a colorless oil.

R_f = 0.43 (petroleum ether/ethyl acetate, 9:1); $[\alpha]_D^{22}$ = +1.88 (*c* = 0.25, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.02–1.07 (m, 21H, $Si(CH(CH_3)_2)_3$), 2.18–2.19 (m, 6H, 1-H, 7-H), 2.27–2.33 (m, 1H, 4-H), 2.40–2.47 (m, 1H, 4-H), 4.17 (t, *J* = 5.6 Hz, 1H, 3-H), 5.88 (t, *J* = 7.1 Hz, 1H, 5-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 12.2 ($Si(CH(CH_3)_2)_3$), 17.9 ($Si(CH(CH_3)_2)_3$), 23.4 (C-7 or C-1), 25.5 (C-1 or C-7), 35.4 (C-4), 78.1 (C-3), 122.0 (C-6), 126.1 (C-5), 211.8 (C-2); **HRMS** (ESI): *m/z* $[M + Na]^+$ calcd for $C_{16}H_{31}BrO_2Si$: 385.1169; found: 385.1169.

Hex-5-enoic acid (2-161)[109]

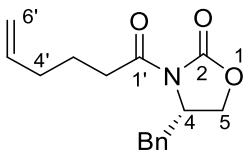


2-161

To a stirred solution of chromium trioxide (11.23 g, 112 mmol) in aqueous sulfuric acid (2M, 134 mL, 270 mmol) at –5 °C was added 5-hexen-1-ol **2-146** (3.0 g, 29.5 mmol) in acetone (100 mL) over 30 min. The resulting black suspension was stirred for 12 h at –5 °C. Thereafter, the reaction mixture was diluted with diethyl ether (100 mL) and the layers were separated. The organic layer was washed with aqueous NaOH solution (1M, 2 × 35 mL) and again the layers were separated. The combined aqueous layers were acidified with sulfuric acid (6M, 20 mL), and then extracted with diethyl ether (3 × 25 mL). The combined organic layers were washed with saturated NaCl solution (15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude acid was purified by flash chromatography (petroleum ether/ethyl acetate, 7:3) to give acid **2-161** (1.85 g, 54%) as a colorless liquid.

R_f = 0.26 (petroleum ether/ethyl acetate, 8:2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.73 (tt, apparent q, *J* = 7.5 Hz, 2H, 3–H), 2.12 (m, 2H, 4-H), 2.38 (t, *J* = 7.5 Hz, 2H, 2-H), 5.01–5.08 (m, 2H, 6-H), 5.77 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H, 5-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 23.7 (C-3), 32.9 (C-4), 33.1 (C-2), 115.2 (C-6), 137.5 (C-5), 179.3 (C-1).

(4*S*)-Benzyl-3-(hex-5-enoyl)-2-oxazolidinone (2-163) [110,151]



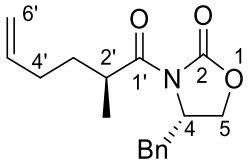
2-164

To a slurry of 5-hexenoic acid **2-161** (15.0 g, 131 mmol) in THF (80 mL) was added Et_3N (25.6 mL, 184 mmol) at 0 °C and the mixture was stirred for 30 min. Then, pivaloyl chloride (17.8 mL,

145 mmol) was added dropwise over 5 min at 0 °C. The resulting white suspension was stirred for 1 h at r.t. To a second flask, charged with (*S*)-4-benzyloxazolidin-2-one **2-162** (13.9 g, 118 mmol) in THF (125 mL) was added *n*-BuLi (2.5 M in hexane, 57.8 mL, 145 mmol) at –78 °C over 20 min. The resulting orange suspension was stirred at –78 °C for 1 h before the solution of the mixed anhydride in THF was added in a dropwise fashion. Thereafter, the reaction mixture was stirred for 1 h at –78 °C and then brought to r.t. The reaction mixture was treated with a saturated NH_4Cl solution (85 mL). Then, the layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 75 mL). The combined organic layers were washed with saturated NaCl solution (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 8:2) to give acylated oxazolidinone **2-163** (19.5 g, 54%) as a colorless oil.

R_f = 0.56 (petroleum ether/ethyl acetate, 1:1); $[\alpha]_D^{20}$ = +68.0 (*c* = 2, CH_2Cl_2); {Lit.[110] $[\alpha]_D^{23}$ = +56.7 (*c* = 1.2, $CHCl_3$)}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.76–1.84 (m, 2H, 3'-H), 2.16 (q, *J* = 7.3 Hz, 2H, 4'-H), 2.76 (dd, *J* = 13.4, 9.6 Hz, 1H, 5-H), 2.87–3.02 (m, 2H, 2'-H), 3.30 (dd, *J* =13.3, 3.2 Hz, 1H, 5-H), 4.10–4.21 (m, 2H, C*H*$_2$Ph), 4.63–4.68 (m, 1H, 4-H), 4.98 (d, *J* = 10.1 Hz, 1H, 6'-H), 5.05 (d, *J* = 17.1 Hz, 1H, 6'-H), 5.82 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H, 5'-H), 7.21–7.35 (m, 5H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 23.3 (C-3'), 32.9 (C-4'), 34.8 (C-2'), 37.9 (C-5), 55.1 (C-4), 66.1 (CH_2Ph), 115.3 (C-6'), 127.3, 128.9, 129.4, 135.2 (4 × Ar C), 135.8 (C-5'), 153.4 (C-2), 173.1 (C-1'); **HRMS** (ESI): *m/z* $[M + Na]^+$ calcd for $C_{16}H_{19}NO_3$: 296.1257; found: 296.1257.

(*S*)-4-Benzyl-3-((*S*)-2-methylhex-5-enoyl)oxazolidin-2-one (2-165)



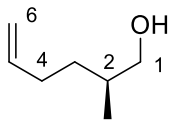
2-165

To a solution of *N*-acyloxazolidinone **2-163** (13.47 g, 49.28 mmol) in THF (80 mL) at –78 ° C was added a solution of NaHMDS (2M in THF, 37.0 mL, 73.9 mmol) over 30 min. The reaction mixture was stirred for 1 h at –78 °C before iodomethane (35 mL, 246 mmol) was added dropwise within 15 min. The resulting yellow mixture was stirred for another 1 h at –78 °C and another 30 min at r.t. Thereafter, the reaction mixture was diluted with AcOH (4 mL) and water (60 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 80 mL). The combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography gel

(petroleum ether/ethyl acetate, 9:1) to give methylated acid derivative **2-165** (11.82 g, 83%) as a colorless oil.

R_f = 0.38 (petroleum ether/ethyl acetate, 9:1); $[\alpha]_D^{20}$ = +91.5 (*c* = 1.05, CH_2Cl_2); {Lit.[110] $[\alpha]_D^{23}$ = +78.3 (*c* = 1.7, $CHCl_3$)}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.23 (d, *J* = 6.8 Hz, 3H, 2-CH_3), 1.47–1.55 (m, 1H, 3'-H), 1.83–1.92 (m, 1H, 3'-H), 2.09 (q, *J* = 6.9 Hz, 2H, 4'-H), 2.77 (dd, *J* = 13.4, 9.6 Hz, 1H, 5-H), 3.27 (dd, *J* = 13.4, 3.2 Hz, 1H, 5-H), 3.68–3.77 (m, 1H, 2'-H), 4.14–4.21 (m, 2H, CH_2Ph), 4.63–4.69 (m, 1H, 4-H), 4.95 (d, *J* = 10.2 Hz, 1H, 6'-H), 5.03 (d, *J* = 17.1 Hz, 1H, 6'-H), 5.73–5.83 (m, 1H, 5'-H), 7.20–7.21 (m, 2H, ArH), 7.30–7.34 (m, 3H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 17.4 (2-CH_3), 31.5 (C-4'), 32.4 (C-3'), 37.2 (C-2'), 37.9 (C-5), 55.3 (C-4), 66.0 (CH_2Ph), 114.9 (C-6'), 127.3, 128.9, 129.4, 135.3 (4 × Ar C), 138.1 (C-5'), 153.0 (C-2), 177.1 (C-1'); **HRMS** (ESI): *m/z* $[M + Na]^+$ calcd for $C_{17}H_{21}NO_3$: 310.1413; found: 310.1413.

(*S*)-2-Methylhex-5-en-1-ol (2-166)



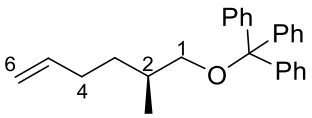
2-166

To a stirred solution of *N*-acyloxazolidinone **2-165** (11.82 g, 41.13 mmol) in THF (80 mL) and MeOH (1.58 mL, 49.36 mmol) was added a solution of lithium borohydride (4M in THF, 30.9 mL, 75.9 mmol) at 0 °C over 15 min. The resulting mixture was stirred for 2 h at r.t. Thereafter, the reaction mixture was quenched with aqueous NaOH (2M, 40 mL). The aqueous layer was extracted with diethyl ether (2 × 50 mL) and the combined organic layers were washed with a saturated NaCl solution (35 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

The residue was purified by flash chromatography (petroleum ether/diethyl ether, 90:10) to give primary alcohol **2-166** (2.92 g, 62%) as a colorless oil.

R_f = 0.27 (petroleum ether/ethyl acetate, 9:1); $[\alpha]_D^{20}$ = –11.2 (*c* = 3.0, CH_2Cl_2); {Lit.[152] $[\alpha]_D^{20}$ = –13.3 (*c* = 1.81, CH_2Cl_2)}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.93 (d, *J* = 6.7 Hz, 3H, 2-CH_3), 1.16–1.26 (m, 1H, 3-H), 1.43 (br s, 1H, OH), 1.47–1.55 (m, 1H, 3-H), 1.60–1.68 (m, 1H, 2-H), 2.00–2.17 (m, 2H, 4-H), 3.44 (dd, *J* = 10.5, 6.5 Hz, 1H, 1-H), 3.50 (dd, *J* = 10.5, 5.8 Hz, 1H, 1-H), 4.95 (dd, *J* = 10.1, 1.8 Hz, 1H, 6-H), 5.03 (dd, *J* = 17.1, 1.8 Hz, 1H, 6-H), 5.81 (ddt, *J* = 17.0, 10.1, 6.7 Hz, 1H, 5-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 16.4 (2-CH_3), 31.1 (C-4), 32.3 (C-3), 35.2 (C-2), 68.2 (C-1), 114.4 (C-6), 138.9 (C-5).

(*S*)-(((2-Methylhex-5-en-1-yl)oxy)methanetriyl)tribenzene (2-167)

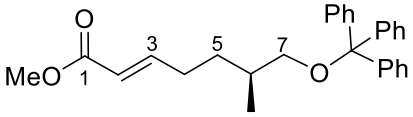


2-167

A solution of primary alcohol **2-166** (1.1 g, 9.63 mmol) in CH_2Cl_2 (10 mL) and pyridine (10 mL) at r.t. was treated with trityl chloride (4.0 g, 14.44 mmol) and DMAP (1.17 g, 9.63 mmol). The resulting mixture was stirred for 2 h at 40 °C. Thereafter, the reaction mixture was diluted with water (85 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layers were washed with saturated NaCl solution (35 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 9:1) to give trityl ether **2-167** (2.65 g, 77%) as a colorless oil.

R_f = 0.84 (petroleum ether/ethyl acetate, 9:1); $[\alpha]_D^{20}$ = +7.6 (*c* = 1, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.93 (d, *J* = 6.8 Hz, 3H, 2-CH_3), 1.20–1.25 (m, 1H, 3-H), 1.49–1.55 (m, 1H, 3-H), 1.72–1.77 (m, 1H, 2-H), 1.93–1.99 (m, 2H, 4-H), 2.84–2.97 (m, 1H, 1-H), 4.87–4.95 (m, 2H, 6-H), 5.72–5.79 (m, 1H, 5-H), 7.24–7.29 (m, 5H, ArH), 7.41–7.44 (m, 10H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 17.4 (2-CH_3), 31.2 (C-4), 32.9 (C-3), 33.4 (C-2), 68.1 (C-1), 86.1 (CPh_3), 114.2 (C-6), 126.8, 127.6, 128.8 (3 × Ar C), 139.1 (C-5), 144.5 (Ar C); **HRMS** (ESI): *m/z* $[M + Na]^+$ calcd for $C_{26}H_{28}O$: 379.20162 ; found: 379.20162.

Methyl (*S*,*E*)-6-methyl-7-(trityloxy)hept-2-enoate (2-169)



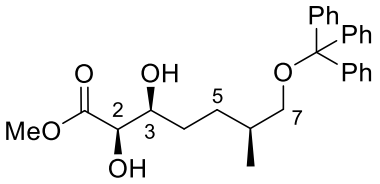
2-169

A solution of alkene **2-167** (1.5 g, 4.21 mmol) and methyl acrylate (1.5 mL, 16.84 mmol) in toluene (15 mL) was deoxygenated by bubbling argon through the solution for 2–5 min. Then, Grubbs II catalyst (0.17 g, 0.21 mmol, 5 mol%) in toluene (6 mL) was added dropwise at r.t. The dark red suspension was heated at 85 °C for 8 h. After the reaction mixture had cooled down to r.t., the solvent was removed under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 7:3) to give enoate **2-169** (1.45 g, 83%) as an off brown oil.

R_f = 0.26 (petroleum ether/ethyl acetate, 9:1); $[\alpha]_D^{20}$ = +6.0 (*c* = 1, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 6.7 Hz, 3H, 6-CH_3), 1.23–1.34 (m, 1H, 5-H), 1.58–1.62 (m, 1H, 5-H), 1.63–1.78 (m, 1H, 6-H), 2.10–2.15 (m, 2H, 7-H), 2.90–3.01 (m, 2H, 4-H), 3.71 (s, 3H, OCH_3), 5.82

(dt, *J* = 15.6 Hz, 1H, 2-H), 6.90–6.70 (m, 1H, 3-H), 7.20–7.31 (m, 10H, ArH), 7.42–7.44 (m, 5H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 17.2 (6-CH_3), 29.6 (C-4), 31.9 (C-5), 33.3 (C-6), 51.4 (OCH_3), 67.7 (C-7), 86.1 (CPh_3), 126.8, 127.7, 128.7, 144.4 (4 × Ar C), 167.1 (C=O); **HRMS** (ESI): *m/z* $[M + Na]^+$ calcd for $C_{28}H_{30}O_3$: 437.20872; found: 379.20905.

Methyl (*2R,3S,6S*)-2,3-dihydroxy-6-methyl-7-(trityloxy)heptanoate (2-170)

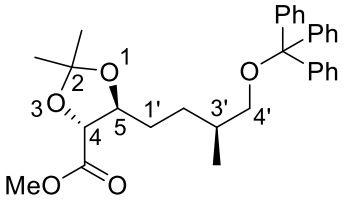


2-170

To a stirred solution of enoate **2-169** (100 mg, 0.24 mmol) in *t*-BuOH/H_2O (3:1, 5 mL) was added AD-mix α (0.33 g) and methyl sulfonamide (23 mg, 0.24 mmol) at 0 °C. The yellow suspension was stirred for 8 h at r.t. After that, the reaction mixture was quenched with sodium thiosulfate solution (5 mL) and the aqueous phase was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with saturated NaCl solution (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 6:4) to give dihydroxy ester **2-170** (60 mg, 55%) as a colorless oil.

R_f = 0.43 (petroleum ether/ethyl acetate, 1:1); $[\alpha]_D^{20}$ = –12.4 (*c* = 1, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.95 (d, *J* = 6.7 Hz, 3H, 6-CH_3), 1.50–1.58 (m, 3H, 5-H, 4-H), 1.75–1.87 (m, 2H, 4-H, 6-H), 2.92–3.01 (m, 2H, 7-H), 3.81 (s, 4H, OCH_3, 2-H), 4.04–4.06 (m, 1H, 3-H), 7.20–7.30 (m, 10H, ArH), 7.43–7.45 (m, 5H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 17.3 (6-CH_3), 29.4 (C-4), 31.1 (C-5), 33.7 (C-6), 52.8 (OCH_3), 68.0 (C-7), 72.7 (C-2), 73.1 (C-3), 86.1 (CPh_3), 126.8, 127.6, 128.7, 144.4 (4 × Ar C), 174.0 (C=O); **HRMS** (ESI): *m/z* $[M + Na]^+$ calcd for $C_{28}H_{32}O_5$: 471.21419; found: 471.21421.

Methyl (*4R,5S*)-2,2-dimethyl-5-((*S*)-3-methyl-4-(trityloxy)butyl)-1,3-dioxolane-4-carboxylate (2-171)



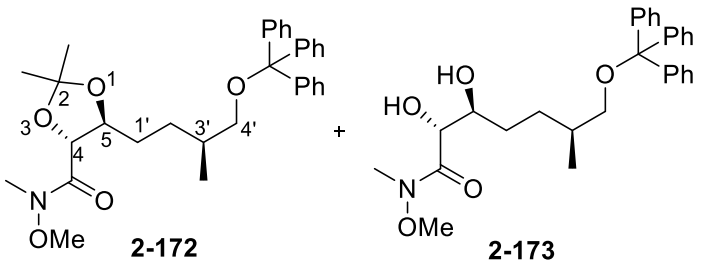
2-171

2,2-Dimethoxypropane (0.18 mL, 1.50 mmol) and *p*-toluenesulfonic acid (*p*TsOH·H_2O) (7 mg) were added to a stirred solution of dihydroxy ester **2-170** (0.56 g, 1.24 mmol) in acetone (12 mL) at r.t. followed by stirring of the mixture for 5 h. The reaction mixture was diluted with saturated

$NaHCO_3$ solution (8 mL) and H_2O (15 mL). The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated NaCl solution (15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude acetal was purified by flash chromatography (petroleum ether/ethyl acetate, 8:2) to give protected dihydroxy ester **2-171** (0.42 g, 68%) as a colorless oil.

R_f = 0.26 (petroleum ether/ethyl acetate, 9:1); $[\alpha]_D^{20}$ = –8.1 (*c* = 1, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.92 (d, J = 6.7 Hz, 3H, 3'-CH_3), 1.27–1.30 (m, 1H, 1'-H), 1.35 (s, 3H, $C(CH_3)_2$), 1.37 (s, 3H, $C(CH_3)_2$), 1.51–1.73 (4H, 2'-H, 1'-H, 3'-H), 2.84–2.88 (m, 2H, 4'-H), 3.60 (s, 3H, OCH_3), 4.06–4.03 (m, 2H, 4-H, 5-H), 7.16–7.25 (m, 10H, ArH), 7.27–7.42 (m, 5H, ArH).

(*4R,5S*)-*N*-methoxy-*N*,2,2-trimethyl-5-((*S*)-3-methyl-4-(trityloxy)butyl)-1,3-dioxolane-4-carboxamide (2-172)

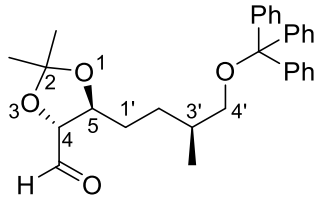


To a mixture of *N,O*-dimethylhydroxylamine hydrochloride (0.25 g, 2.43 mmol) in CH_2Cl_2 (50 mL) at –20 °C was added a solution of trimethylaluminum (2M in hexane, 1.2 mL, 6.80 mmol) over 5 min. Then the mixture was stirred for 30 min at the same temperature before the dropwise addition of dihydroxy ester **2-171** (0.42 g, 0.86 mmol) in CH_2Cl_2 (5 mL). After addition, the cooling bath was removed and the mixture stirred for 2 h at r.t. Thereafter, the reaction mixture was carefully quenched with water (10 mL) at –10 °C. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with saturated NaCl solution (25 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a mixture of **2-172/173** (1:1) as a colorless oil. Again, the crude mixture **2-172/173** (0.37 g, 0.76 mmol) was dissolved in acetone (8 mL) to which were added 2,2-dimethoxypropane (0.1 mL, 0.10 mmol) and *p*-toluenesulfonic acid (*p*TsOH·H_2O) (2 mg) followed by stirring of the mixture at r.t for 1 h. The reaction mixture was diluted with saturated $NaHCO_3$ solution (5 mL) and H_2O (10 mL). The aqueous phase was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with saturated NaCl solution (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude acetal was purified by flash chromatography (petroleum ether/ethyl acetate, 7:3) to give dihydroxy ester **2-172** (0.24 g, 60%) as a colorless oil.

R_f = 0.62 (petroleum ether/ethyl acetate, 9:1); $[\alpha]_D^{20}$ = –5.6 (*c* = 0.5, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.7 Hz, 3H, 3'-CH_3), 1.22–1.27 (m, 1H, 3'-H), 1.42 (s, 6H, $C(CH_3)_2$), 1.50–

1.75 (m, 4H, 1'-H, 2'-H), 2.84–2.93 (m, 2H, 4'-H), 3.17 (s, 3H, OCH_3), 3.65 (s, 3H, CH_3), 4.30–4.40 (m, 2H, 4-H, 5-H), 7.17–7.27 (m, 10H, ArH), 7.40–7.41 (m, 5H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 17.2 (3'-CH_3), 26.1 (C(*C*H_3)$_2$), 27.4 (C(*C*H_3)$_2$), 29.5 (C-1' or C-2'), 30.4 (C-2' or C-1'), 33.9 (C-3'), 68.2 (C-7), 86.1 (CPh_3), 110.4 (C(CH_3)$_2$), 126.7, 127.6, 128.7, 144.4 (4 × Ar C); **HRMS** (ESI): *m/z* $[M + Na]^+$ calcd for $C_{32}H_{39}NO_5$: 540.27204; found: 540.27218.

(*4R,5S*)-2,2-Dimethyl-5-((*S*)-3-methyl-4-(trityloxy)butyl)-1,3-dioxolane-4-carbaldehyde (2-174)

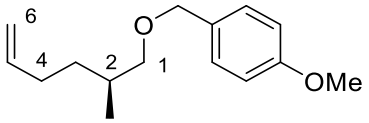


2-174

To a solution of amide **2-172** (110 mg, 0.21 mmol) in Et_2O (5 mL) at −78 °C was added DIBAL-H (1.0 M in hexane, 0.42 mL, 0.42 mmol) dropwise. The reaction mixture was stirred for 1 h at the same temperature. Then the reaction mixture was quenched with methanol (2 mL), and saturated NH_4Cl solution (5 mL). The layers were separated and the aqueous phase was extracted with diethyl ether (2 × 8 mL). The combined organic layers were washed with saturated NaCl solution (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The aldehyde **2-174** (85 mg, 87%) was obtained as a yellow oil which was used without flash chromatography.

R_f = 0.73 (petroleum ether/ethyl acetate, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.93 (d, *J* = 6.7 Hz, 3'-CH_3), 1.36 (s, 3H, (C(CH_3)$_2$), 1.42 (s, 3H, (C(CH_3)$_2$), 1.50–1.55 (m, 5H, 1'-H, 2'-H, 3'-H), 2.87–2.90 (m, 2H, 4'-H), 3.85–3.95 (m, 2H, 4-H, 5-H), 7.16–7.27 (m, 10H, ArH), 7.40–7.41 (m, 5H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 17.2 (3'-CH_3), 25.5 (C(CH_3)$_2$), 26.1 (C(CH_3)$_2$), 29.3 (C-2'), 30.8 (C-1'), 33.3 (C-3'), 67.8 (C-4'), 84.8 (C-4 or C-5), 86.1 (C-5 or C-4), 110.8 (*C*(CH_3)$_2$), 126.7, 127.8, 128.7, 144.3 (4 × Ar C), 201.1 (C=O).

(*S*)-1-Methoxy-4-(((2-methylhex-5-en-1-yl)oxy)methyl)benzene (2-175)



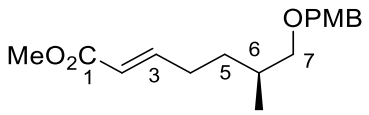
2-175

To a suspension of NaH (60% dispersion in mineral oil, 2.0 g, 51 mmol) in THF (10 mL) was added a solution of alcohol **2-166** (2.92 g, 25.6 mmol) in THF (15 mL) at 0 °C. The white suspension was stirred for 30 min before tetrabutylammonium iodide (TBAI, 0.94 g, 2.55 mmol) and 4-methoxybenzyl chloride (5.2 mL, 38.4 mmol) were added at 0 °C. The reaction mixture was

then stirred for 18 h at r.t. Thereafter, the reaction mixture was diluted with H_2O (45 mL). The aqueous phase was extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 9:1) to give PMB ether **2-175** (4.5 g, 75%) as a colorless oil.

R_f = 0.61 (petroleum ether/ethyl acetate, 9:1); $[\alpha]_D^{20}$ = +3.24 (*c* = 2.0, CH_2Cl_2); {Lit.[153] $[\alpha]_D^{20}$ = +3.0 (*c* = 1, $CHCl_3$)}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.7 Hz, 3H, 2-CH_3), 1.15–1.24 (m, 1H, 3-H), 1.48–1.57 (m, 1H, 3-H), 1.72–1.81 (m, 1H, 2-H), 1.96–2.14 (m, 2H, 4-H), 3.22 (dd, *J* = 9.0, 6.6 Hz, 1H, 1-H), 3.28 (dd, *J* = 9.1, 6.1 Hz, 1H, 1-H), 3.80 (s, 3H, OCH_3), 4.42 (s, 2H, CH_2Ar), 4.93 (dd, *J* = 10.1, 2.0 Hz, 1H, 6-H), 5.01 (dd, *J* = 17.1, 1.9 Hz, 1H, 6-H), 5.80 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1H, 5-H), 6.88 (d, *J* = 8.6 Hz, 2H, ArH), 7.25 (d, *J* = 8.6 Hz, 2H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 16.9 (2-CH_3), 31.1 (C-4), 32.8 (C-3), 55.2 (OCH_3), 72.6 (CH_2Ar), 75.5 (C-1), 113.7, 114.2, 129.0, 130.8 (4 × Ar C), 139.0 (C-5), 159.0 (Ar C(OMe)); **HRMS** (ESI): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{22}O_2$: 257.1512; found: 257.1512.

Methyl (*S*,*E*)-7-((4-methoxybenzyl)oxy)-6-methylhept-2-enoate (2-176)

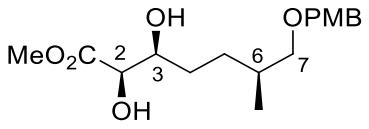


2-176

A solution of alkene **2-175** (1.0 g, 4.26 mmol) and methyl acrylate (1.46 mL, 17.1 mmol) in toluene (12 mL) was deoxygenated by bubbling argon through the solution for 2–3 min. Then, Grubbs II catalyst (0.18 g, 0.21 mmol, 5 mol%) in toluene (4 mL) was added dropwise at r.t. The dark red suspension was heated at 85 °C for 8 h. After the reaction mixture had cooled down to r.t., the solvent was removed under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 8:2) to give enoate **2-176** (1.18 g, 95%) as an off brown oil.

R_f = 0.33 (petroleum ether/ethyl acetate, 9:1); $[\alpha]_D^{20}$ = –1.65 (*c* = 1, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.7 Hz, 3H, 6-CH_3), 1.24–1.33 (m, 1H, 5-H), 1.58–1.67 (m, 1H, 5-H), 1.75–1.80 (m, 1H, 6-H), 2.13–2.29 (m, 2H, 4-H), 3.27 (dd, *J* = 6.3, 1.9 Hz, 2H, 7-H), 3.73 (s, 3H, OCH_3), 3.81 (s, 3H, $ArOCH_3$), 4.43 (s, 2H, CH_2Ar), 5.82 (dt, *J* = 15.7, 1.6 Hz, 1H, 2-H), 6.87 (d, *J* = 8.6 Hz, 2H, ArH), 6.93–7.01 (m, 1H, 2-H), 7.25 (d, *J* = 8.6 Hz, 2H, Ar*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 16.8 (6-CH_3), 29.6 (C-4), 31.8 (C-5), 32.9 (C-6), 51.3 (OCH_3), 55.2 (OCH_3), 72.6 (CH_2Ar), 75.1 (C-7), 113.7 (Ar C), 120.8 (C-3), 129.1 (Ar C), 130.6 (Ar C), 149.6 (C-2), 159.0 (Ar-C), 167.1 (C-1); **HRMS** (ESI): *m/z* $[M + Na]^+$ calcd for $C_{17}H_{24}O_4$: 315.1570; found: 315.1570.

Methyl (*2R*,*3S*,*6S*)-2,3-dihydroxy-7-((4-methoxybenzyl)oxy)-6-methylheptanoate (2-177)

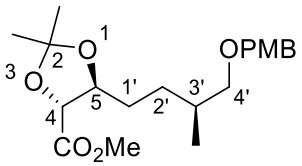


2-177

To a stirred solution of enoate **2-176** (1.18 g, 4.03 mmol) in *t*-BuOH/H_2O (3:1, 40 mL) was added solid of AD-mix α (5.65 g) and methyl sulfonamide (0.95 g, 10.1 mmol) at 0 °C. The yellow suspension was stirred for 36 h at r.t. After that, the reaction mixture was quenched with sodium thiosulfate solution (25 mL) and the aqueous phase was extracted with ethyl acetate (3 × 16 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 6:4) to give dihydroxy ester **2-177** (0.84 g, 64%) as a colorless oil.

R_f = 0.34 (petroleum ether/ethyl acetate, 1:1); $[\alpha]_D^{19}$ = –19.75 (*c* = 2, CH_2Cl_2), **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.7 Hz, 3H, 6-CH_3), 1.31–1.37 (m, 1H, 5-H), 1.47–1.58 (m, 2H, 4-H, 5-H), 1.63–1.70 (m, 1H, 4-H), 1.75–1.83 (m, 1H, 6-H), 3.25 (dd, *J* = 6.4, 1.8 Hz, 2H, 7-H), 3.79 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.83–3.87 (m, 1H, 3-H), 4.07 (d, *J* = 2.1 Hz, 1H, 2-H), 4.41 (s, 2H, CH_2Ar), 6.87 (d, *J* = 8.6 Hz, 2H, ArH), 7.23 (d, *J* = 7.8 Hz, 2H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 17.1 (6-CH_3), 29.9 (C-4), 31.0 (C-5), 33.2 (C-6), 43.4 (C-3), 52.8 (OCH_3), 55.3 (OCH_3), 72.7 (CH_2Ar), 73.2 (C-2), 75.4 (C-7), 113.7, 129.2, 130.6, 159.1 (4 × Ar C), 174.0 (C-1); **HRMS** (ESI): *m/z* $[M + Na]^+$ calcd for $C_{17}H_{26}O_6$: 349.1621; found: 349.1621.

Methyl (4*R*,5*S*)-5-((*S*)-4-((4-methoxybenzyl)oxy)-3-methylbutyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (2-178)



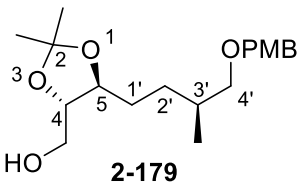
2-179

2,2-Dimethoxypropane (0.38 mL, 3.11 mmol) and *p*-toluenesulfonic acid (*p*TsOH·H_2O) (3 mg, 0.02 mmol) were added to a stirred solution of dihydroxy ester **2-177** (0.84 g, 2.57 mmol) in acetone (10 mL) at r.t. followed by stirring of the mixture for 2 h. The reaction mixture was diluted with saturated $NaHCO_3$ solution (5 mL) and H_2O (10 mL). The aqueous phase was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with saturated NaCl solution (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude acetal was

purified by flash chromatography (petroleum ether/ethyl acetate, 8:2) to give protected dihydroxy ester **2-178** (0.67 g, 71%) as a colorless oil.

R_f = 0.55 (petroleum ether/ethyl acetate, 8:2); $[\alpha]_D^{20}$ = –13.28 (c = 0.5, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.7 Hz, 3H, 3'-CH_3), 1.26–1.36 (m, 1H, 1'-H), 1.42 (s, 3H, C(CH_3)$_2$), 1.45 (s, 3H, C(CH_3)$_2$), 1.50–1.59 (m, 1H, 2'-H), 1.67–1.81 (m, 3H, 1'-H, 3'-H, 2'-H), 3.22–3.30 (m, 2H, 4'-H), 3.76 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.08–4.12 (m, 2H, 4-H, 5-H), 4.42 (s, 2H, CH_2Ar), 6.87 (d, *J* = 8.6 Hz, 2H, ArH), 7.25 (d, *J* = 8.6 Hz, 2H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 16.9 (3'-CH_3), 25.6 (C(*C*H_3)$_2$), 27.2 (C(*C*H_3)$_2$), 29.5 (C-1' or C-2'), 30.9 (C-2' or C-1'), 33.4 (C-3'), 52.3 (OCH_3), 55.2 (OCH_3), 72.6 (CH_2Ar), 75.4 (C-4'), 79.0 (C-4), 79.2 (C-5), 110.8, 113.7, 129.1, 130.7 (4 × Ar C), 159.1 (C-2), 171.3 (CO_2Me); **HRMS** (ESI): *m/z* $[M + Na]^+$ calcd for $C_{20}H_{30}O_6$: 389.1935; found: 389.1935.

((4*S*,5*S*)-5-((*S*)-4-((4-Methoxybenzyl)oxy)-3-methylbutyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (**2-179**)

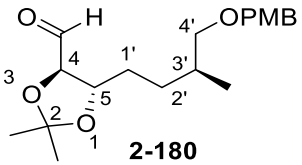


2-179

To a solution of $LiAlH_4$ (0.10 g, 2.61 mmol) in THF (3 mL) at 0 °C was added a solution of methyl ester **2-178** (0.64 g, 1.74 mmol) in THF (8 mL). After complete addition, the resulting suspension was stirred at r.t. for 2 h. The reaction mixture was quenched by adding H_2O (5 mL) and 15% aqueous NaOH (2 mL). The white suspension was filtered through a pad of celite, which was rinsed with ethyl acetate (10 mL). The obtained filtrate was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 5:5) to give primary alcohol **2-179** (0.57 g, 96%) as a colorless oil.

R_f = 0.23 (petroleum ether/ethyl acetate, 7:3); $[\alpha]_D^{21}$ = –14.64 (*c* = 2, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.93 (d, *J* = 6.7 Hz, 3H, 3'-CH_3), 1.29–1.40 (m, 6H, C(CH_3)$_2$, 2'-H), 1.46–1.53 (m, 2H, 2'-H, 1'-H), 1.71–1.79 (m, 1H, 1'-H), 1.93–1.96 (m, 1H, 3'-H), 3.26 (dd, *J* = 17.9, 9.0 Hz, 2H, 4'-H), 3.54–3.61 (m, 1H, C*H*$_2$OH), 3.69–3.79 (m, 5H, 5-H, 4-H, OCH_3), 3.81–3.86 (m, 1H, C*H*$_2$OH), 4.41 (s, 2H, CH_2Ar), 6.87 (d, *J* = 8.6 Hz, 2H, ArH), 7.25 (d, *J* = 8.6 Hz, 2H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 17.0 (3'-CH_3), 27.0 (C(CH_3)$_2$), 27.3 (C(CH_3)$_2$), 29.8 (C-2'), 30.5 (C-1'), 33.5 (C-3'), 55.2 (OCH_3), 62.0 (*C*H_2OH), 72.6 (CH_2Ar), 75.3 (C-4'), 77.0 (C-4 or C-5), 81.7 (C-5 or C-4), 108.5, 113.7, 129.1, 130.7 (4 × Ar C), 159.0 (C-2); **HRMS** (ESI): *m/z* $[M + Na]^+$ calcd for $C_{19}H_{30}O_5$: 361.1988; found: 361.1988.

(4*R*,5S)-5-((*S*)-4-((4-Methoxybenzyl)oxy)-3-methylbutyl)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (2-180)

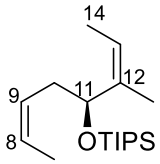


2-180

To a solution of oxalyl chloride (0.21 mL, 2.48 mmol) in CH_2Cl_2 (5 mL) was slowly added DMSO (0.35 mL, 4.96 mmol) at –78 °C. After being stirred for 15 min at this temperature, a solution of alcohol **2-179** (0.56 g, 1.65 mmol) in CH_2Cl_2 (8 mL) was added over a period of 5 min. The reaction mixture was stirred at the same temperature for 1 h. Thereafter, Et_3N (1.3 mL, 9.92 mmol) was added dropwise. Then the reaction mixture was warmed to r.t. The mixture was diluted with H_2O (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 8 mL). The combined organic layers were washed with saturated NaCl solution (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The aldehyde **2-180** (0.53 g, 95%) was used for the next step without chromatography.

R_f = 0.55 (petroleum ether/ethyl acetate, 7:3); $[\alpha]_D^{19}$ = –3.40 (*c* = 1.5, CH_2Cl_2); ^{1}H **NMR** (400 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.7 Hz, 3H, 3'-CH_3), 1.25–1.46 (m, 8H, $C(CH_3)_2$, 2'-H), 1.48–1.77 (m, 3H, 3'-H, 1'-H), 3.21–3.29 (m, 2H, 4'-H), 3.79 (s, 3H, OCH_3), 3.88–3.93 (m, 1H, 4-H), 3.98–4.03 (m, 1H, 5-H), 4.41 (s, 2H, CH_2Ar), 6.86 (d, *J* = 8.6 Hz, 2H, ArH), 7.23 (d, *J* = 7.7 Hz, 2H, ArH), 9.70 (s, 1H, CHO); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 16.9 (3'-CH_3), 26.1 ($C(CH_3)_2$), 27.0 ($C(CH_3)_2$), 29.4 (C-2'), 30.8 (C-1'), 33.3 (C-3'), 55.2 (OCH_3), 72.6 (CH_2Ar), 75.2 (C-4'), 77.1 (C-5), 84.8 (C-4), 110.8, 113.7, 129.1, 130.7 (4 × Ar C), 159.0 (C-2), 201.1 (CHO); **HRMS** (ESI): *m/z* [M + CH_3OH + Na]$^+$ calcd for $C_{19}H_{28}O_5$: 391.2090; found: 391.2090.

Triisopropyl(((*S*,*2Z*,*6Z*)-3-methylocta-2,6-dien-4-yl)oxy)silane (2-183)



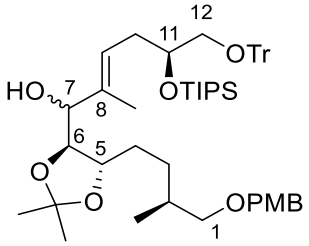
2-183

To a stirred solution of vinyl bromide **2-139** (25 mg, 0.06 mmol) in THF (0.5 mL) at –78 °C was added a solution of *t*-BuLi (1.7 M in pentane, 0.05 mL, 0.1 mmol) over 5 min. The reaction mixture was stirred at –78 °C for 1 h, before the addition of **2-180** (40 mg, 0.1 mmol) in THF (0.3 mL) dropwise. After addition, the reaction mixture was stirred at –78 °C for 30 min. Then the reaction mixture was stirred for 2 h at r.t. The reaction mixture was diluted with saturated NH_4Cl solution (3 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 3 mL).

The combined organic layers were washed with saturated NaCl solution (2 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The debrominated crude was purified by flash chromatography (petroleum ether/diethyl ether, 8:2) to give debrominated **2-184** (10 mg, 51%) as a major compound.

R_f = 0.7 (petroleum ether/diethyl ether, 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.05–1.04 (m, 21H, $Si(CH(CH_3)_2)_3$), 1.52–1.62 (m, 6H, 2 × CH_3), 1.68 (t, *J* = 1.5 Hz, 3H, 3-CH_3), 2.27–2.41 (m, 2H, 5-H), 4.66 (dd, *J* = 8.6, 5.5 Hz, 1H, 4-H), 5.20–5.31 (m, 2H, 6-H, 7-H), 5.44–5.50 (m, 1H, 2-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 12.4 ($Si(CH(CH_3)_2)$), 13.2 (C-1), 17.4 (3-CH_3), 17.9 ($Si(CH(CH_3)_2)_3$), 18.0 ($Si(CH(CH_3)_2)_3$), 29.7 (C-8), 34.0 (C-5), 69.5 (C-4), 119.6 (C-2), 125.2 (C-7), 126.2 (C-6), 138.0 (C-3).

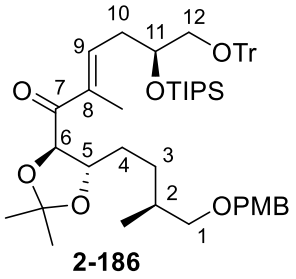
C1-C12 fragment (2-185)



2-185

Vinyl bromide **2-156** (0.15 g, 0.25 mmol) was dried by dissolving it in a mixture of benzene/toluene (3 mL, 1:1) followed by evaporation of the solvents using a rotavapor and placing it under high vacuum for 1 h. Thereafter, THF (1.5 mL) was added under an argon atmosphere and the reaction flask was cooled to –78 °C. Then, *s*-BuLi (1.4M in cyclohexane, 0.21 mL, 0.30 mmol) was added dropwise and the reaction mixture stirred for 30 min at –78 °C before aldehyde **2-180** (0.14 g, 0.43 mmol), dissolved in THF (1.5 mL), was added dropwise. After complete addition, the reaction mixture was stirred for 2 h at –78 °C and at r.t. for 1 h. Finally, the reaction mixture was treated with saturated NH_4Cl solution (5 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 8 mL). The combined organic layers were washed with saturated NaCl solution (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude allylic alcohol **2-185** (86 mg, dr = 10:4) was used for the next reaction without chromatography. **HRMS** (ESI): *m/z* $[M + Na]^+$ calcd for $C_{53}H_{74}O_7Si$: 873.5094; found: 873.5094.

Enone (2-186)

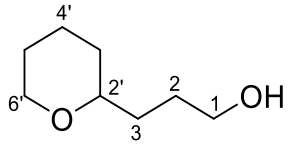


2-186

To a solution of alcohol **2-186** (70 mg, 0.08 mmol) in CH_2Cl_2 (5 mL) at 0 °C were added DMP (70 mg, 0.16 mmol) and $NaHCO_3$ (20 mg, 0.24 mmol). After addition, the cooling bath was removed and the mixture stirred for 2 h at r.t. Then the reaction mixture was diluted with saturated $NaHCO_3$ solution (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with saturated NaCl solution (8 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 85:15) to give enone **2-187** (50 mg, 71%) as a colorless oil.

R_f = 0.48 (petroleum ether/ethyl acetate, 9:1); $[\alpha]_D^{19}$ = –6.85 (*c* = 0.52, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.7 Hz, 3H, 2-CH_3), 0.94–0.96 (m, 21H, Si(CH(CH_3)$_2$)$_3$), 1.25–1.30 (m, 1H, 3-H), 1.30 (s, 3H, C(CH_3)$_2$), 1.37–1.44 (m, 4H, C(CH_3)$_2$, 3-H), 1.50–1.53 (m, 1H, 4-H), 1.56–1.60 (m, 1H, 4-H), 1.68–1.73 (m, 1H, 2-H), 1.80 (s, 3H, 8-CH_3), 2.70–2.73 (m, 2H, 10-H), 2.97 (t, *J* = 8.3 Hz, 1H, 12-H), 3.10–3.20 (m, 2H, 12-H, 1-H), 3.26 (dd, *J* = 9.0, 5.8 Hz, 1H, 1-H), 3.77 (s, 3H, OCH_3), 4.10–4.18 (m, 1H, 11-H), 4.22–4.26 (m, 1H, 5-H), 4.34 (d, *J* = 7.4 Hz, 1H, 6-H), 4.48 (d, *J* = 1.8 Hz, 2H, CH_2Ar), 6.86 (d, *J* = 8.6 Hz, 2H, ArH), 6.97 (t, *J* = 6.4 Hz, 1H, 9-H), 7.17–7.27 (m, 12H, ArH), 7.38–7.41 (m, 5H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 11.8 (8-CH_3), 12.3 (Si(*C*H(CH_3)$_2$)$_3$), 16.9 (2-CH_3), 18.0 (Si(CH(*C*H_3)$_2$)$_3$), 26.2 (C(*C*H_3)$_2$), 27.2 (C(*C*H_3)$_2$), 29.7 (C-3), 30.6 (C-4), 33.4 (C-2), 34.8 (C-1), 55.2 (OCH_3), 66.3 (C-12), 70.3 (C-11), 72.6 (CH_2Ar), 75.5 (C-1), 78.0 (C-5 or C-6), 80.3 (C-6 or C-5), 86.6 (CPh_3), 109.8 (*C*(CH_3)$_2$), 113.7, 127.0, 127.7, 128.6, 129.0, 130.8 (6 × Ar), 137.7 (C-8), 142.5 (C-9), 143.9 (Ar C), 159.0 (Ar C), 197.5 (C-7); **HRMS** (ESI): *m/z* [M + Na]$^+$ calcd for $C_{53}H_{72}O_7Si$: 871.4929; found: 871.4929.

3-(Tetrahydro-2*H*-pyran-2-yl)propan-1-ol (3-52)

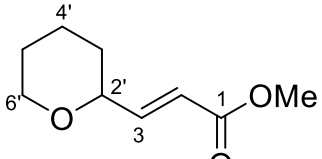


3-52

To a solution of $LiAlH_4$ (1.98 g, 52.29 mmol) in THF (5 mL) at 0 °C was added methyl ester **3-63** (4.50 g, 26.1 mmol) in THF (50 mL) dropwise. The reaction mixture was heated at 50 °C for 3 h. Thereafter, the reaction mixture was cooled to r.t. and then treated with 10% NaOH (20 mL), and water (5 mL). The resulting white suspension was filtered through a pad of celite, which was washed with hot ethyl acetate (35 mL), the filtrate was concentrated under pressure. The alcohol residue was purified by flash chromatography (petroleum ether/ethyl acetate, 60:40) to afford alcohol **3-52** (3.40 g, 89%) as a colorless oil.

R_f = 0.4 (petroleum ether/ethyl acetate, 1:1), **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.25–1.34 (m, 1H, 3'-H), 1.41–1.68 (m, 8H, 5'-H, 4'-H, 3'-H, 3-H, 2-H), 1.77–1.78 (m, 1H, 2-H), 2.68 (s, 1H, OH), 3.22–3.28 (m, 1H, 3-H), 3.40 (dt, *J* = 11.3, 2.8 Hz, 1H, 6'-H), 3.54–3.63 (m, 2H, 1-H), 3.94–3.98 (m, 1H, 6'-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 23.5 (C-4'), 25.8 (C-5'), 29.3 (C-2'), 31.9 (C-3'), 33.7 (C-3), 63.0 (C-1), 68.5 (C-6'), 78.0 (C-2); **HRMS** (ESI): calculated for $[C_8H_{16}O_2+Na]^+$: 167.1042; found: 167.1042.

Methyl (*E*)-3-(tetrahydro-2*H*-pyran-2-yl)acrylate (3-61)



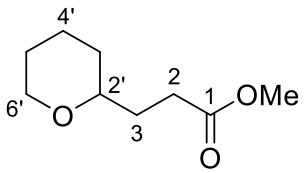
3-61

To a solution of oxalyl chloride (4.37 ml, 51.7 mmol) in CH_2Cl_2 (100 ml) at –78 °C was added DMSO (7.64 ml, 107 mmol) dissolved in CH_2Cl_2 (10 mL) dropwise. The solution was stirred for 15 min at–78 °C before the addition of tetrahydropyran-2-methanol (**3-58**) (5.0 ml, 43 mmol) in CH_2Cl_2 (25 ml). After addition, the reaction mixture was stirred for 1 h at –78 °C. After that Et_3N (29.8 ml, 101 mmol) was added dropwise at –78 °C and then the reaction mixture was warmed to 0 °C. Then, ylene **3-62** (18.0 g, 54.0 mmol) was added portionwise to the reaction mixture. The white suspension was stirred for 1 h at r.t. The reaction mixture was quenched with H_2O (50 mL) and then the layer were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 60 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over Na_2SO_4, filtered, and

concentrated under reduced pressure. The crude ester was purified by flash chromatography (petroleum ether/ethyl acetate, 65:35) to give methyl acrylate **3-61** (5.4 g, 73%) as a colorless oil.

R_f = 0.7 (petroleum ether/ethyl acetate, 7:3), **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.27–1.37 (m, 1H, 3'-H), 1.50–1.57 (m, 3H, 5'-H, 4'-H), 1.67–1.72 (m, 1H, 5'-H), 1.84–1.87 (m, 1H, 3'-H), 3.47 (m, 1H, 6'-H), 3.71 (s, 3H, OCH_3), 3.91–4.04 (m, 2H, 2'-H, 6'-H), 6.00 (dd, *J* = 15.8, 1.8 Hz, 1H, 2-H), 6.88 (dd, *J* = 15.8, 4.2 Hz, 1H, 3-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 23.4 (C-5'), 25.6 (C-4'), 31.4 (C-3'), 51.5 (OCH_3), 68.3 (C-6'), 76.1 (C-2'), 119.3 (C-2), 148.4 (C-3), 167.1 (CO_2Me).

Methyl 3-(tetrahydro-2*H*-pyran-2-yl)propanoate (3-63)

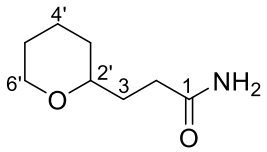


3-63

To a stirred solution of ester **3-61** (0.86 g, 5.05 mmol) in MeOH (10 mL) was added 10 mole% of Pd/C (86 mg). The suspension was kept under hydrogen atmosphere (Shaker hydrogenation apparatus) for 8 h. The reaction mixture was filtered through celite and filtrate concentrated under reduced pressure. The crude ester was purified by flash chromatography (petroleum ether/ethyl acetate, 60:40) to give methyl ester **3-63** (0.6 g, 68%) as a colorless oil.

R_f = 0.7 (petroleum ether/ethyl acetate, 7:3), **^{1}H NMR** (400MHz, $CDCl_3$): δ = 1.21–1.28 (m, 1H, 3-H), 1.42–1.56 (m, 4H, 4'-H, 5'-H), 1.68–1.80 (m, 3H, 3 (or) 2-H, 3'-H), 2.35–2.40 (m, 2H, 2 (or) 3-H), 3.20–3.22 (m, 2'-H), 3.31–3.37 (m, 1H, 6'-H), 3.63 (s, 3H, OCH_3), 3.90–3.94 (m, 1H, 6'-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 23.3 (C-4'), 26.0 (C-5'), 30.1 (C-3 or C-4), 31.4 (C-4 (or) C-3), 31.7 (C-3'), 51.4 (OCH_3), 68.3 (C-6'), 76.6 (C-2'), 174.2 (CO_2Me); **HRMS** (ESI): calculated for $[C_9H_{14}O_3+Na]^+$: 193.08352; found: 193.08345.

3-(Tetrahydro-2*H*-pyran-2-yl)propanamide (3-66)



3-66

Methyl ester **3-63** (0.2 g, 1.2 mmol) was dissolved in ammonia solution (7 N in MeOH, 10 mL). The reaction mixture was heated in a Parr bomb vessel for 2 days at 75 °C. Then, the mixture was slowly brought to r.t., and the solvent removed under reduced pressure. The crude amide was

washed with diethyl ether (2 × 15 mL), and dried under high vacuum for overnight to give **3-66** (0.12 g, 66% yield) as a white solid.

R_f = 0.38 (dichloromethane/MeOH, 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.25–1.32 (m, 1H, 3'-H), 1.45–1.60 (m, 4H, 5'-H, 4'-H), 1.66–1.72 (m, 1H, 5'-H), 1.78–1.84 (m, 2H, 2-H), 2.32–2.37 (m, 2H, 3-H), 3.25–3.30 (m, 1H, 2'-H), 3.40 (dt, *J* = 11.1, 3.0 Hz, 1H, 6'-H), 3.93–3.97 (m, 1H, 6'-H), 5.48 (br s, 2H, NH_2); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 23.4 (C-4'), 26.0 (C-5'), 31.8 (C-3'), 31.9 (C-2'), 32.0 (C-3), 68.4 (C-6'), 77.0 (CH_2), 175.7 (C=O); **HRMS** (ESI): calculated for $[C_8H_{15}NO_2+Na]^+$: 180.09950; found: 180.09975.

17. Appendix

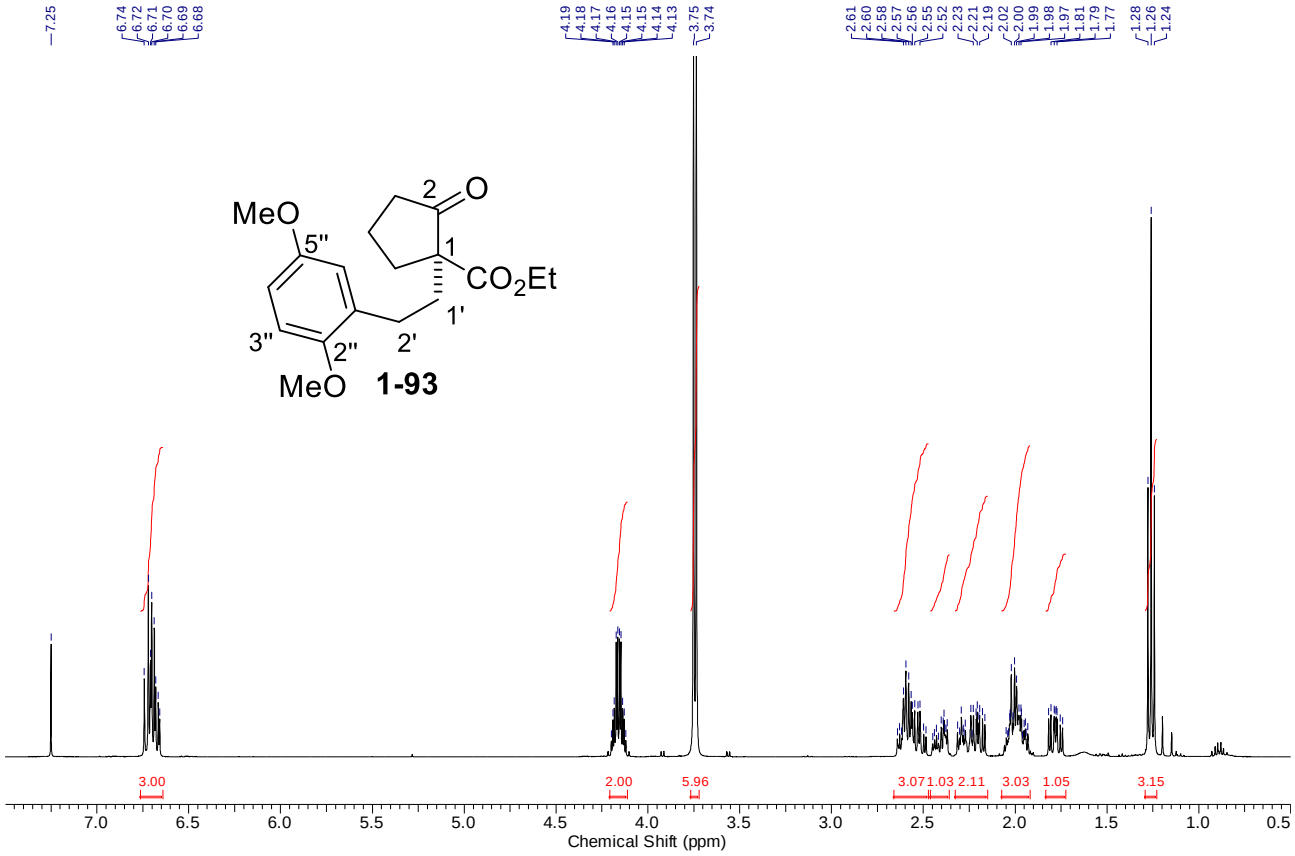
17.1 NMR Spectra for important compounds

Additional spectra are included in the supporting information of the published papers from this work and are available free of charge via Internet at DOI: 10.1002/ajoc.201600455 (*Asian J.Org. Chem*).

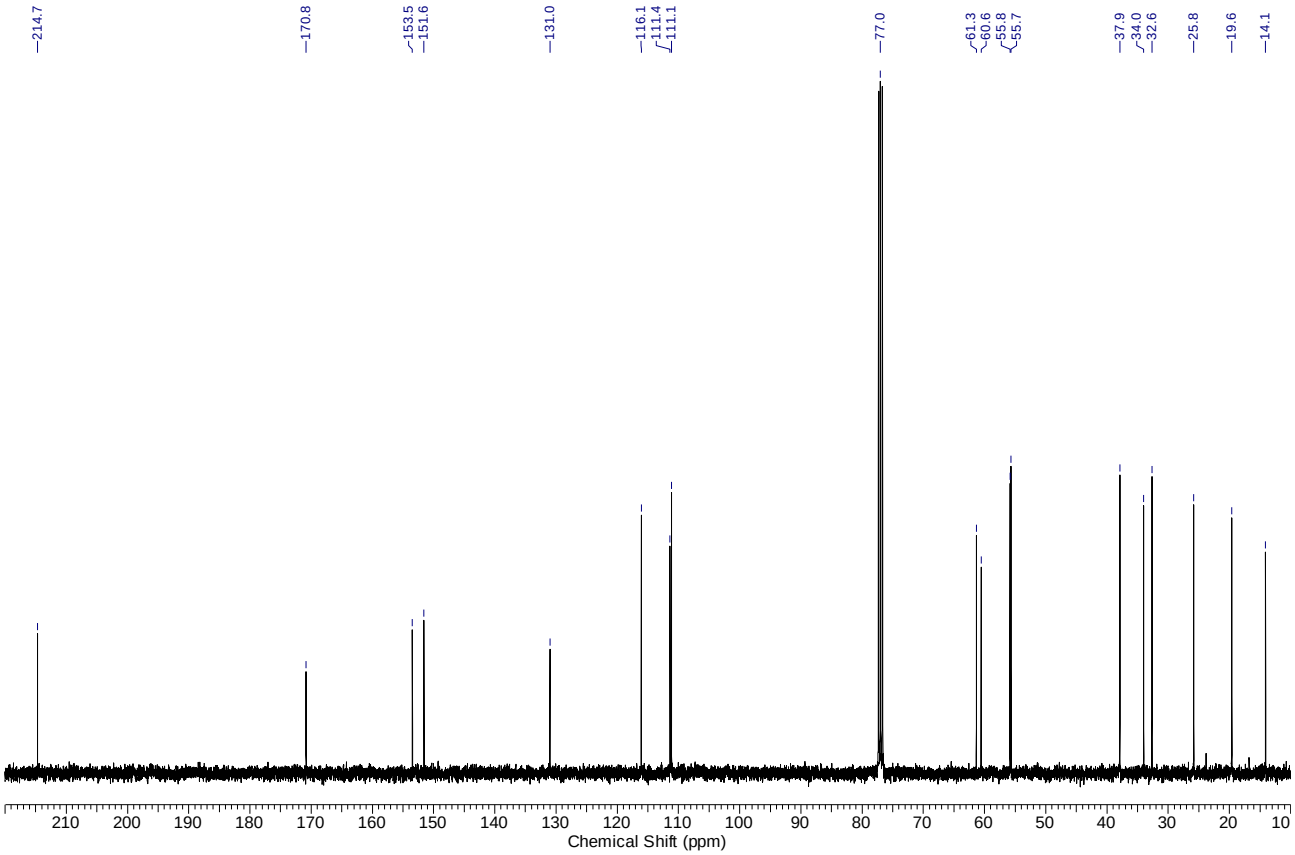
Chapter I. Total Synthesis of Lingzhiol and some Analogs via Wittig Reaction on an Oxocyclopentane Carboxylate. *Asian J. Org. Chem*. **2017**, 6, 108–117

Chapter II. Synthesis of a C1-C12 Fragment of Gulmirecin B

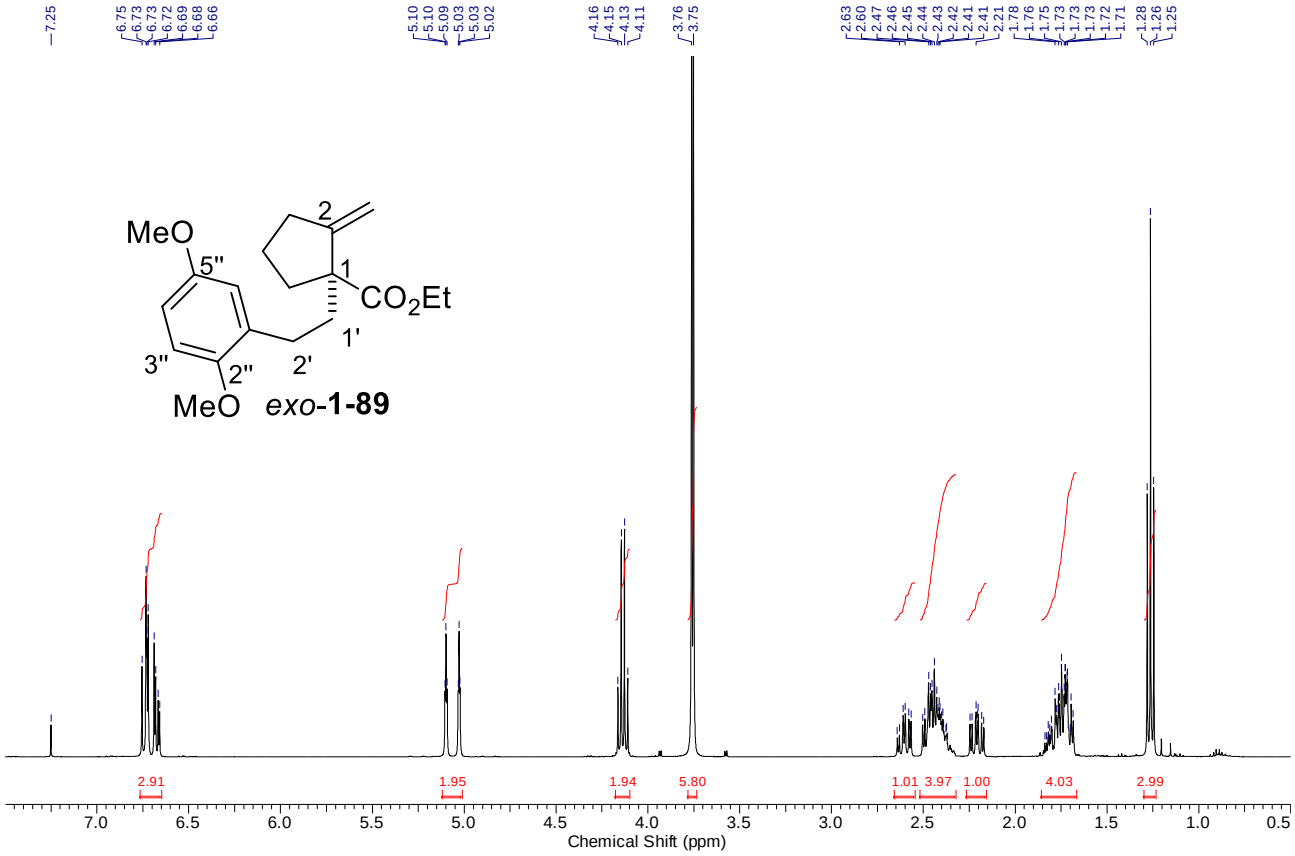
Chapter III. Studies on Spiroacetal Formation via Photocatalysis



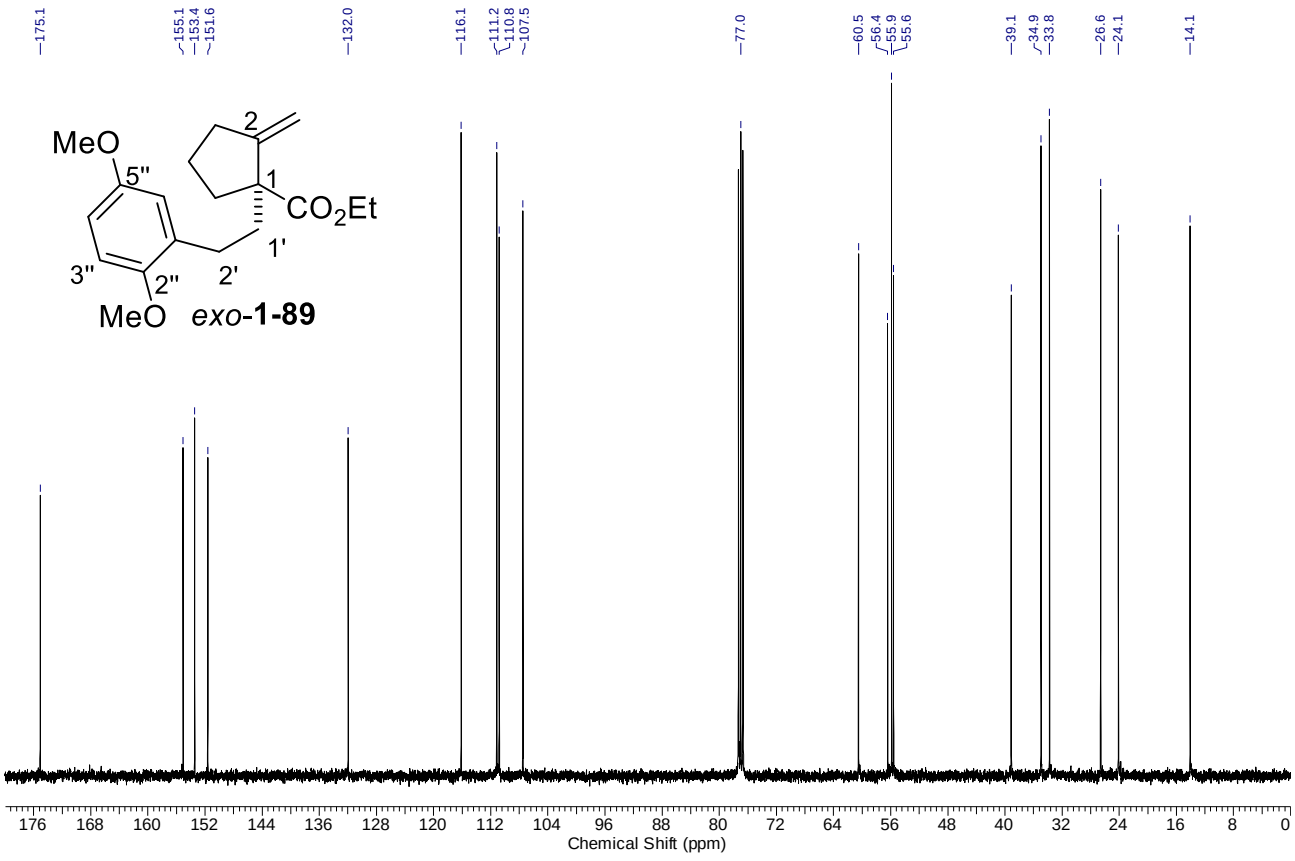
^{1}H NMR (400 MHz) spectrum of alkylated α-ketoester **1-93** in $CDCl_3$ (0.5 – 7.5 ppm)



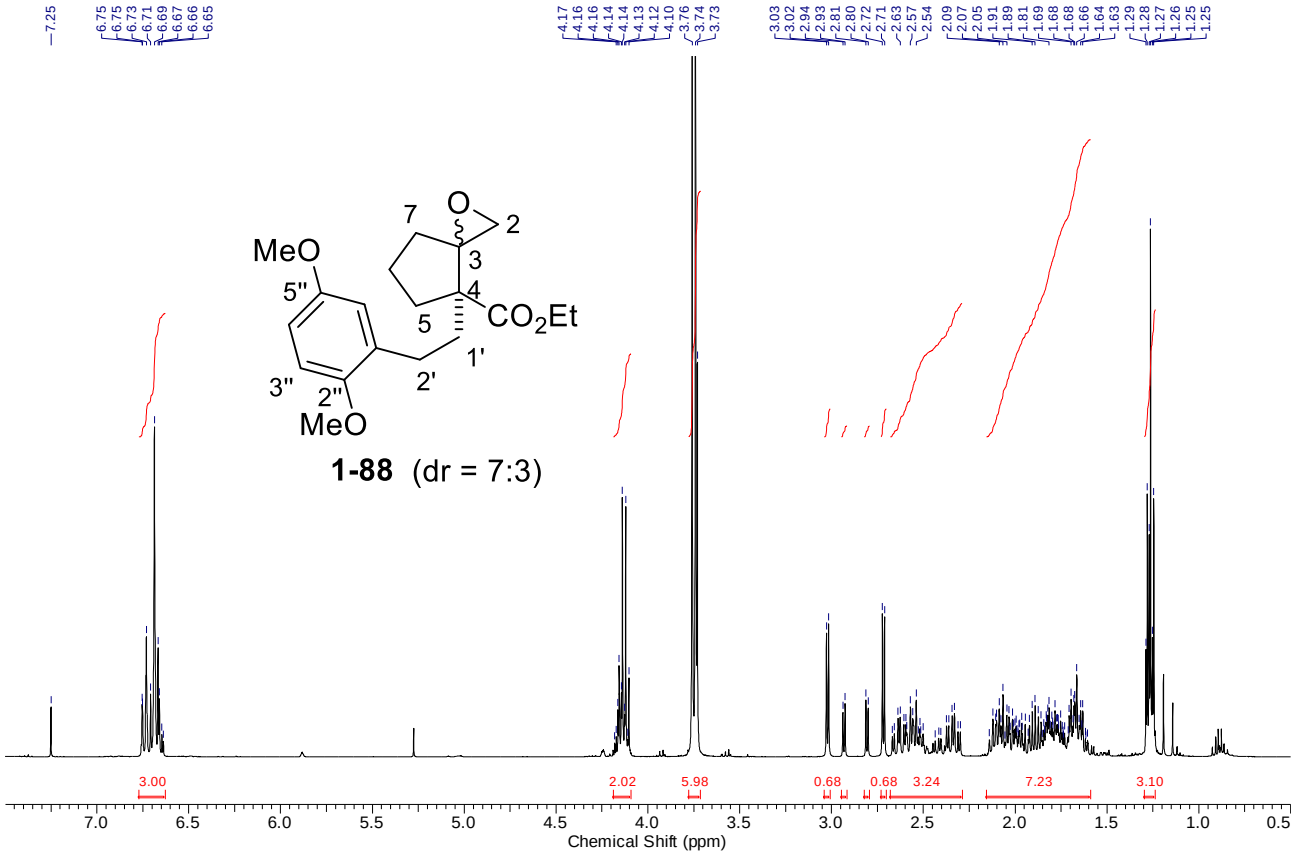
^{13}C NMR (100 MHz) spectrum of alkylated α–ketoester **1-93** in $CDCl_3$ (10 – 220 ppm)



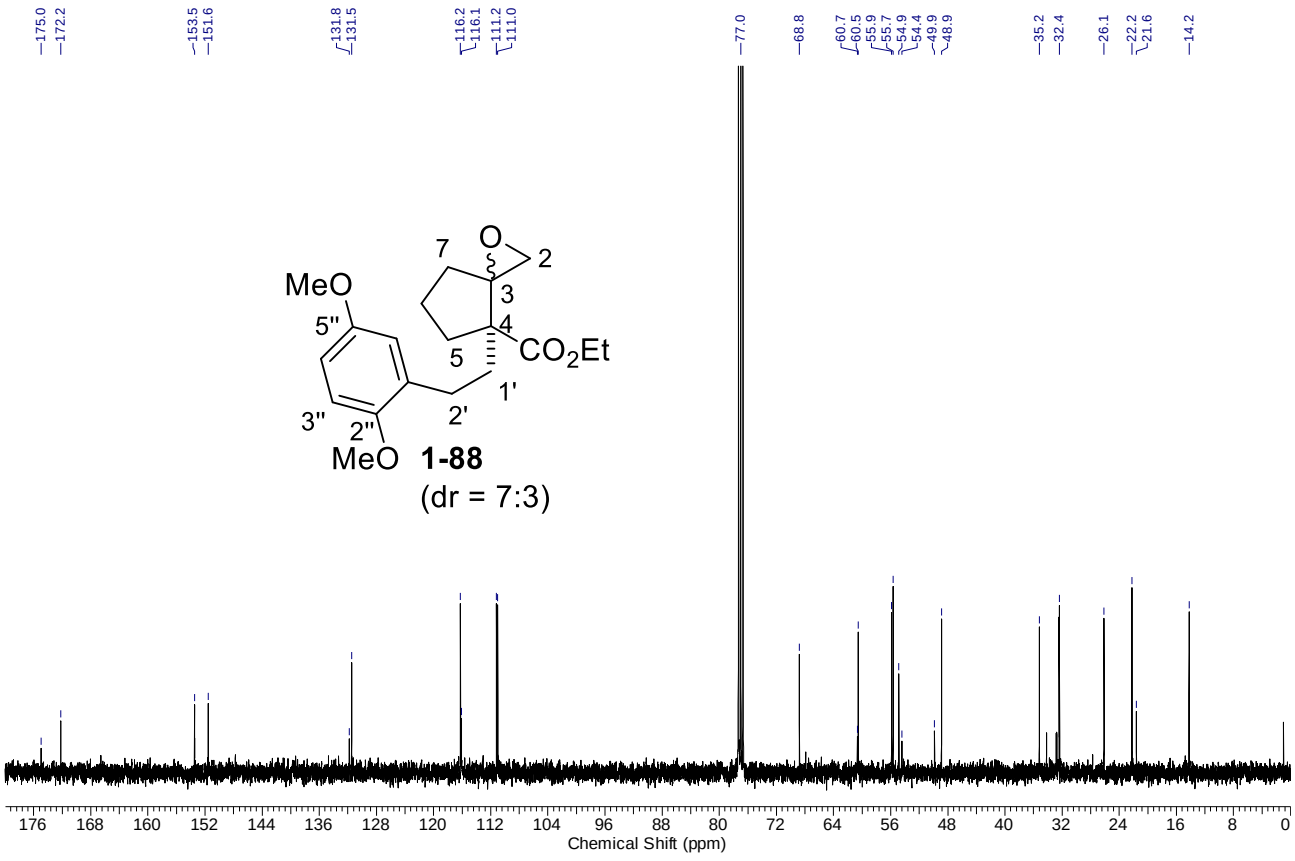
^{1}H NMR (400 MHz) spectrum of alkene *exo*–**1-89** in $CDCl_3$ (0.5 – 7.5 ppm)



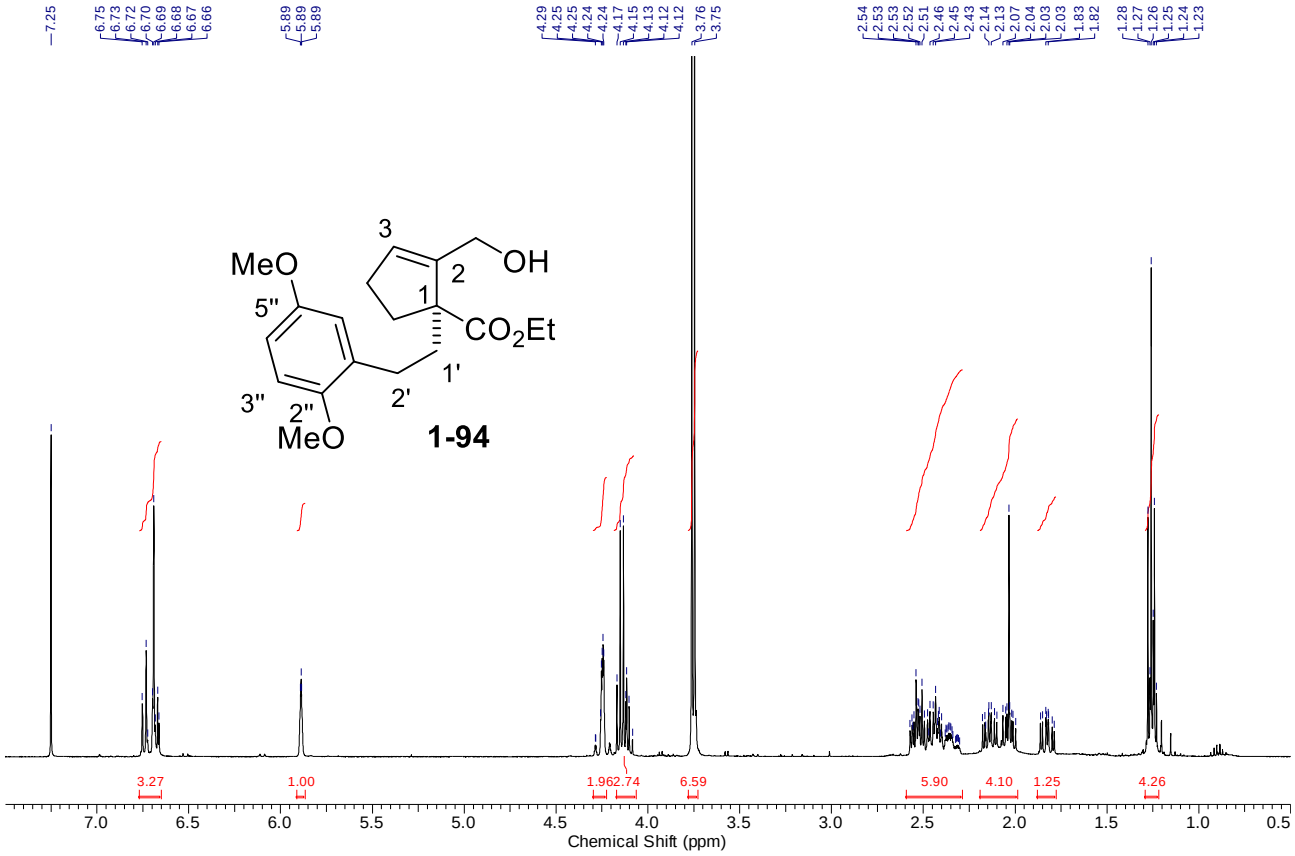
^{13}C NMR (100 MHz) spectrum of alkene *exo*–**1-89** in $CDCl_3$ (0 – 180 ppm)



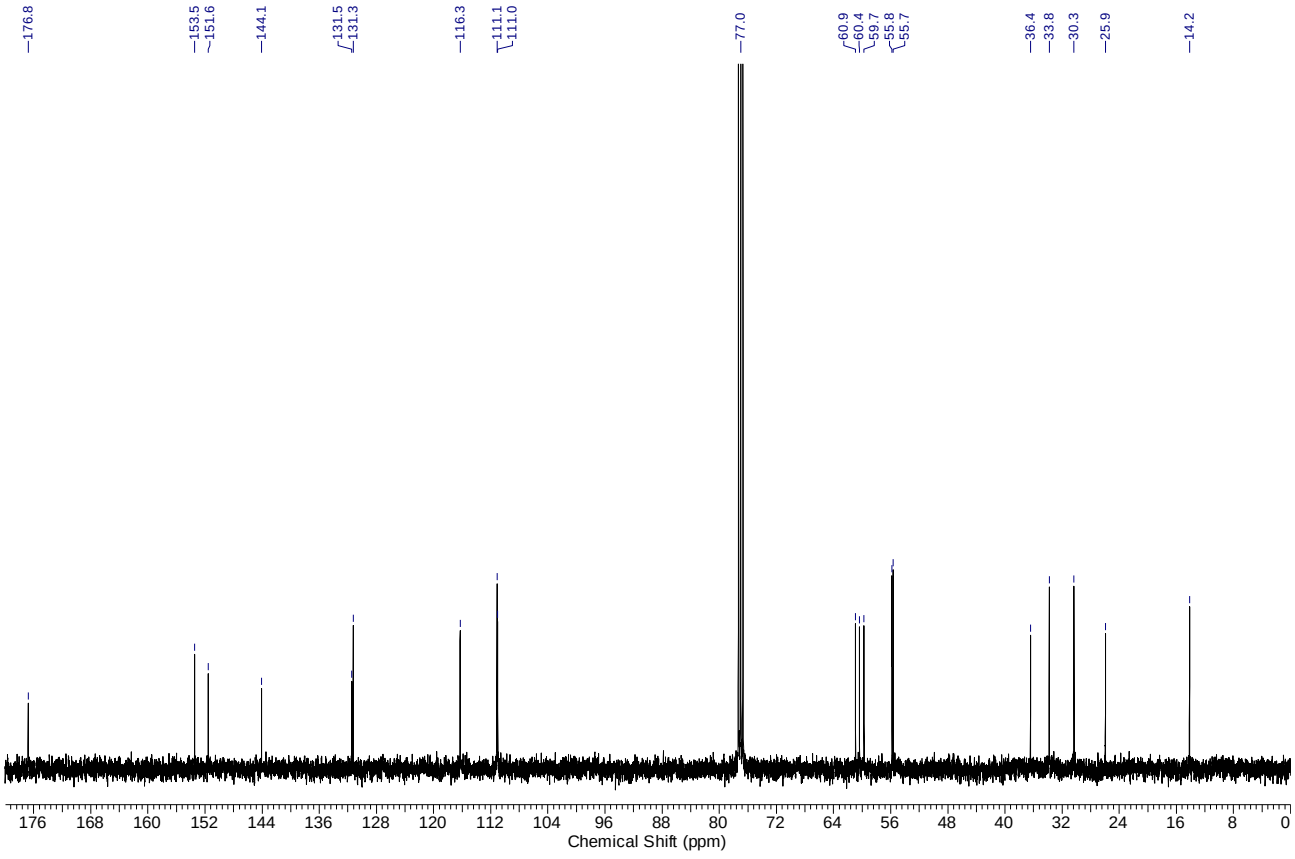
^{1}H NMR (400 MHz) spectrum of epoxide **1-88** (7/3 ration of d.r) in $CDCl_3$ (0.5 – 7.5 ppm)



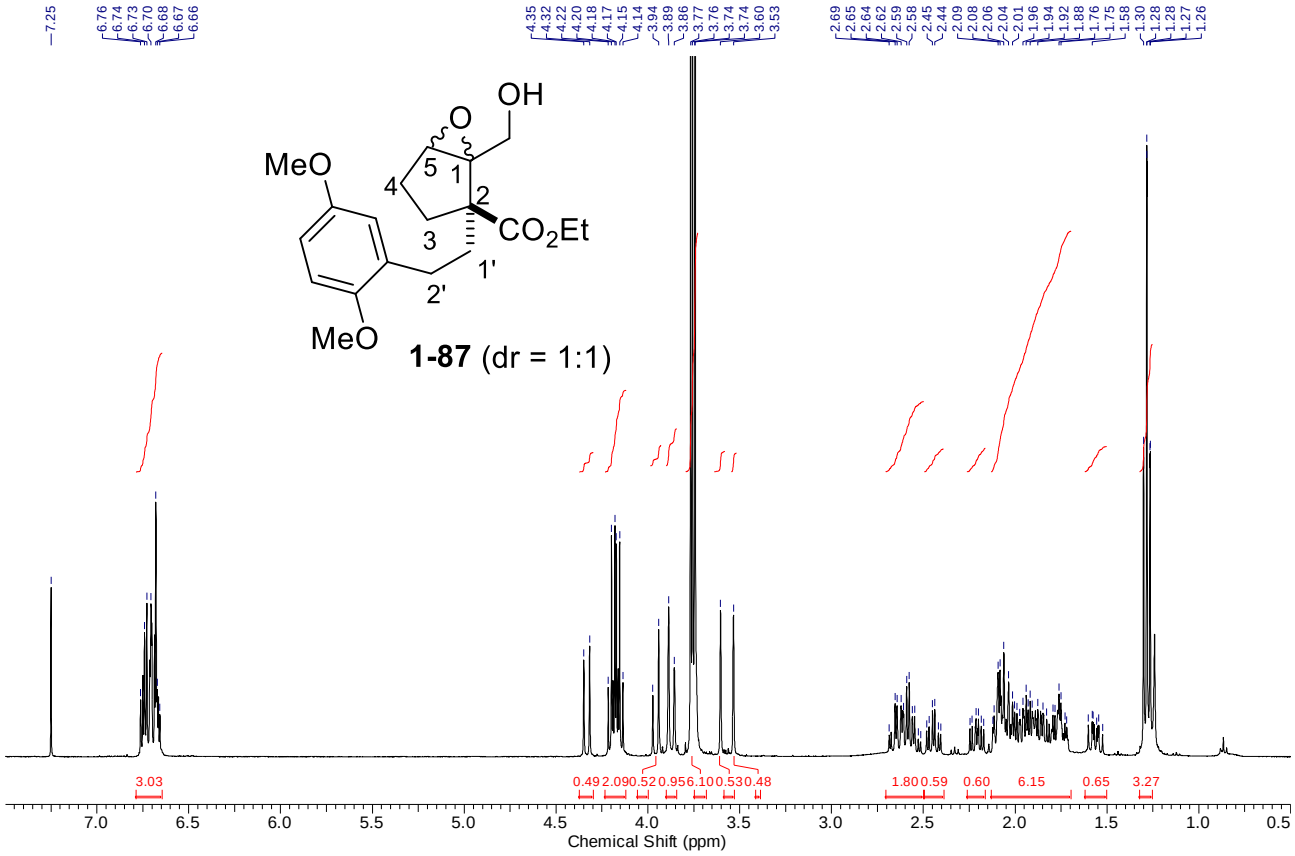
^{13}C NMR (100 MHz) spectrum of epoxide **1-88** (d.r =7;3) in $CDCl_3$ (0 – 180 ppm)



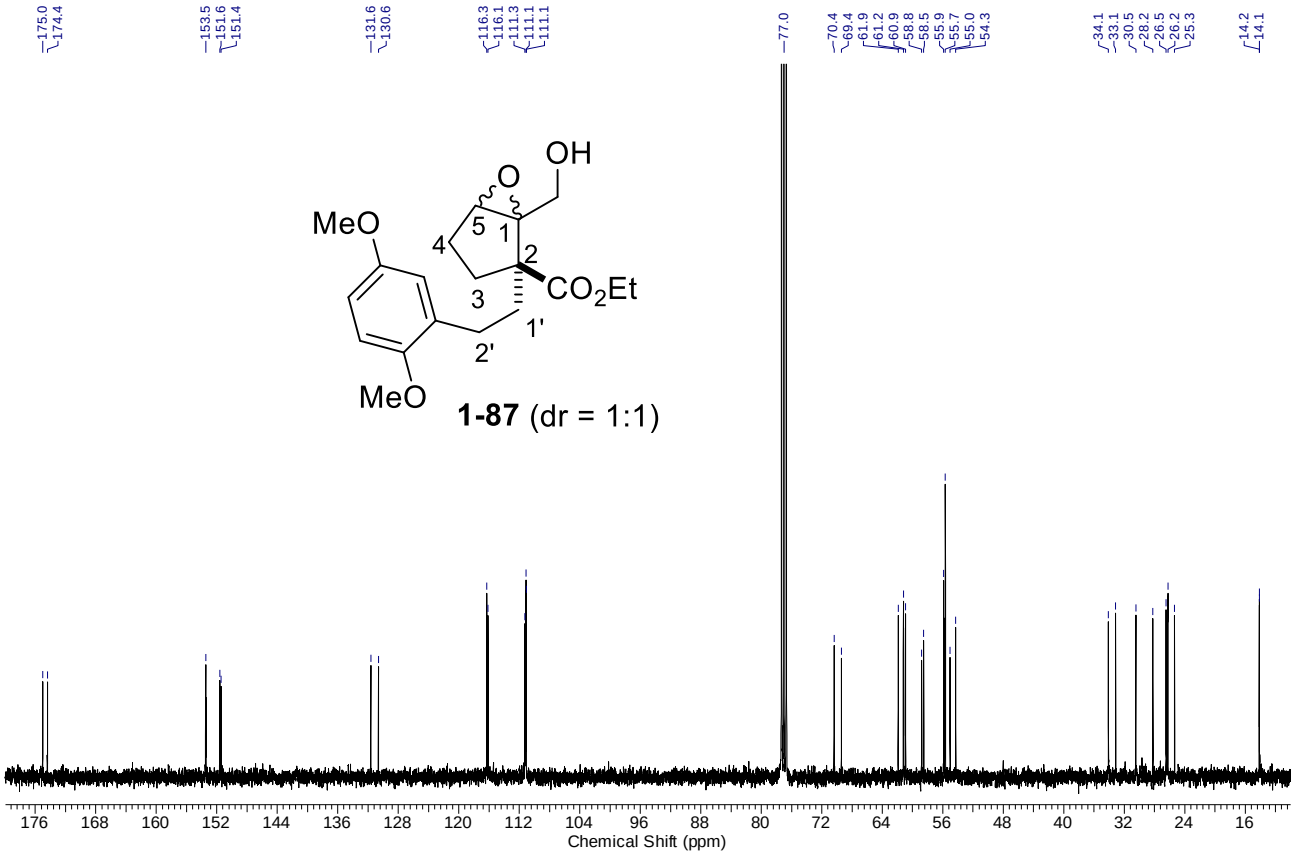
^{1}H NMR (400 MHz) spectrum of allyl alcohol **1-94** in $CDCl_3$ (0.5 – 7.5 ppm)



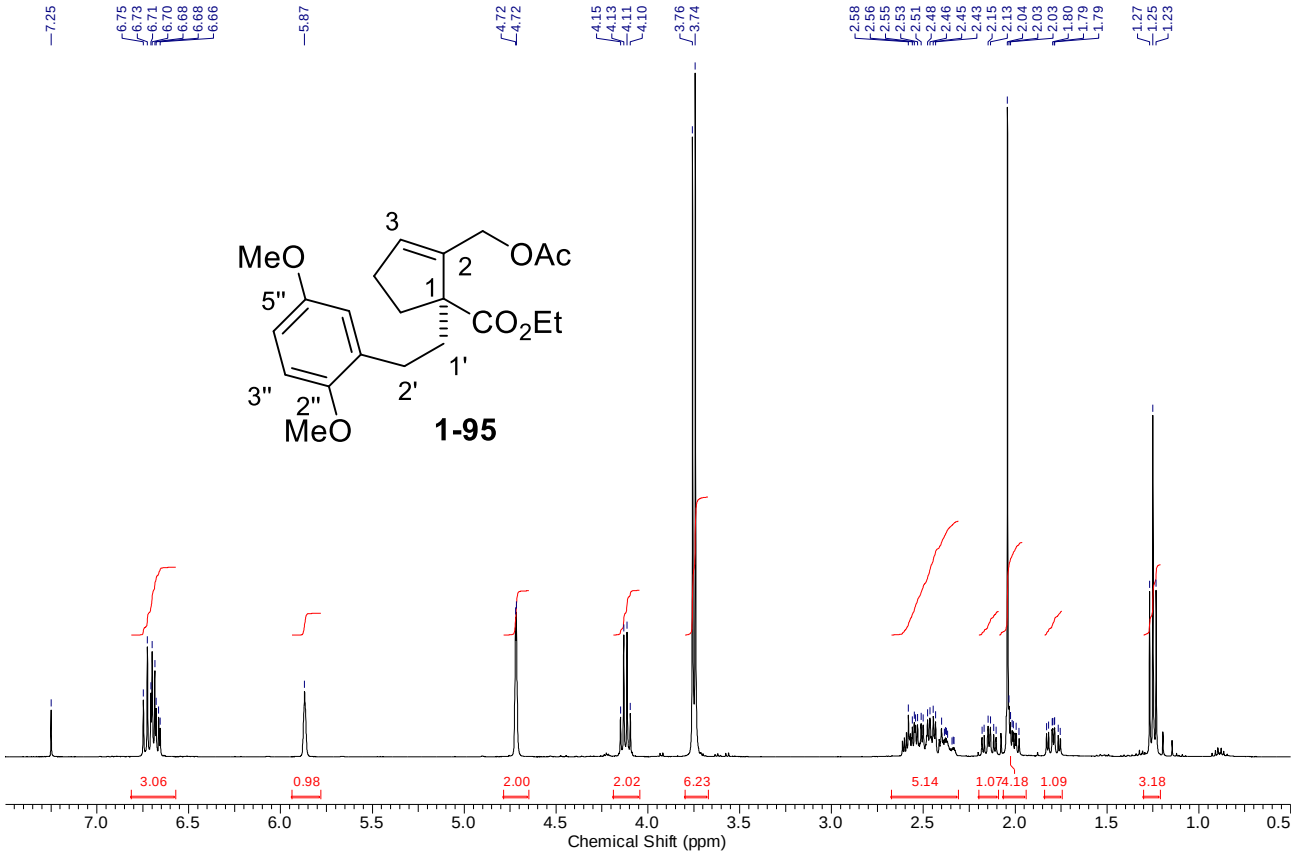
^{13}C NMR (100 MHz) spectrum of allyl alcohol **1-94** in $CDCl_3$ (0 – 180 ppm)



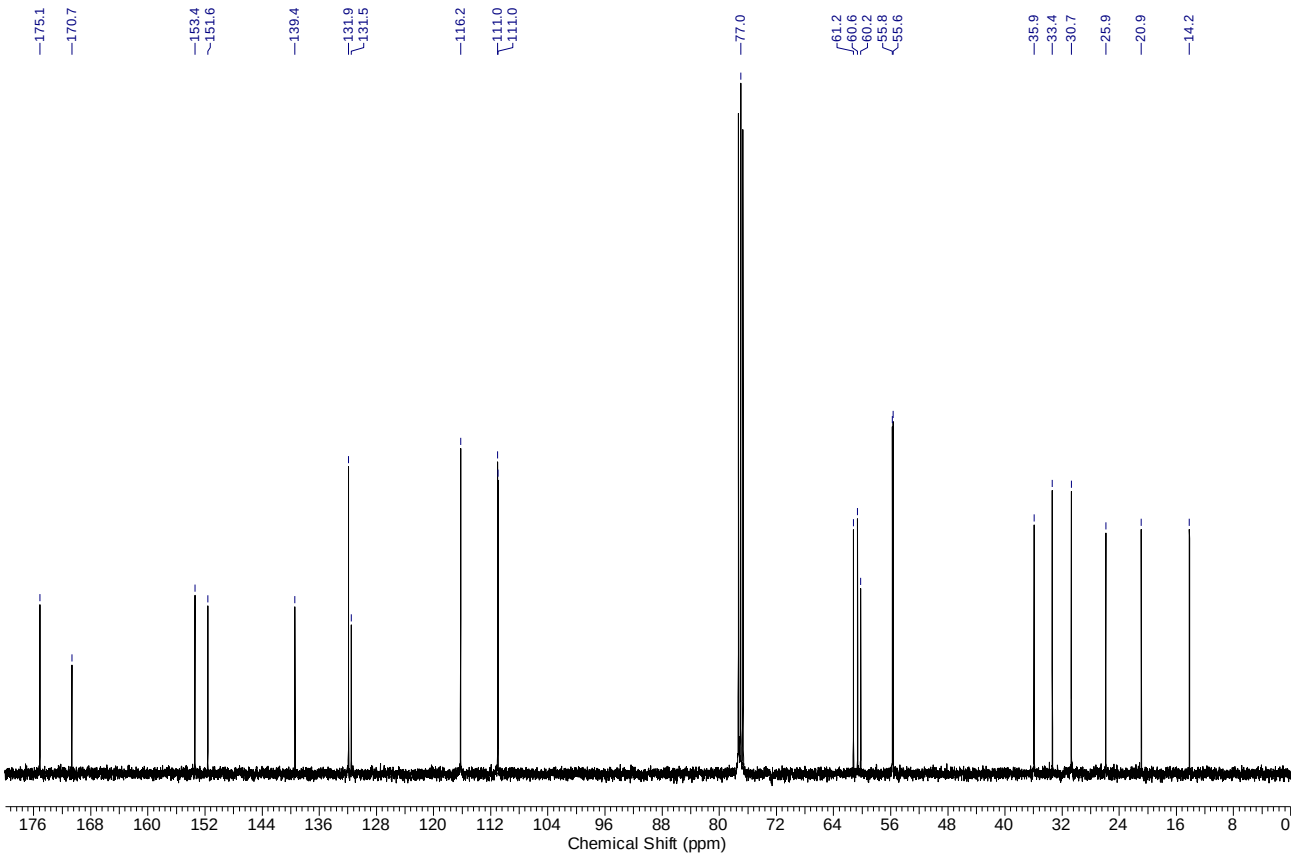
^{1}H NMR (400 MHz) spectrum of epoxide **1-87** in $CDCl_3$ (0.5 – 7.5 ppm)



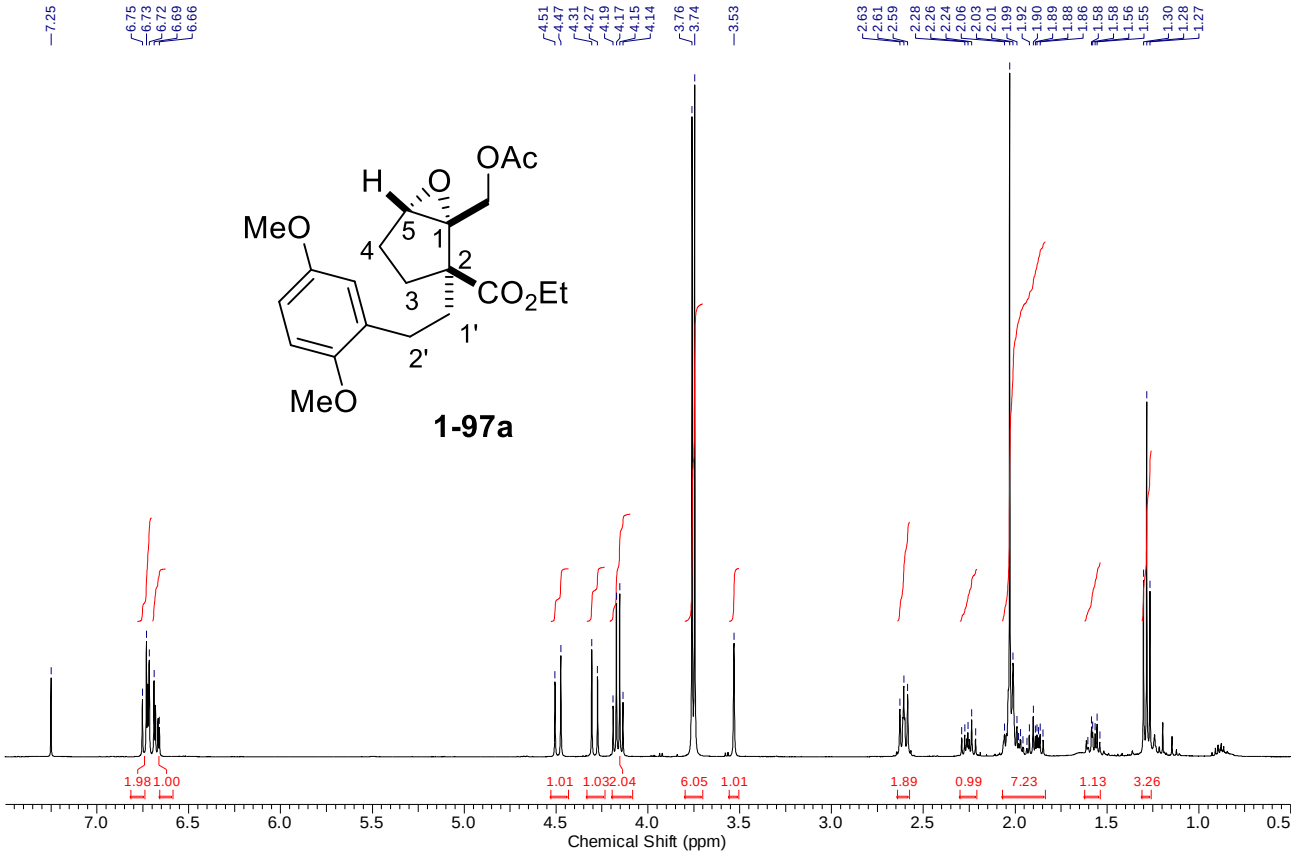
^{13}C NMR (400 MHz) spectrum of epoxide **1-87** in $CDCl_3$ (10 – 180 ppm)



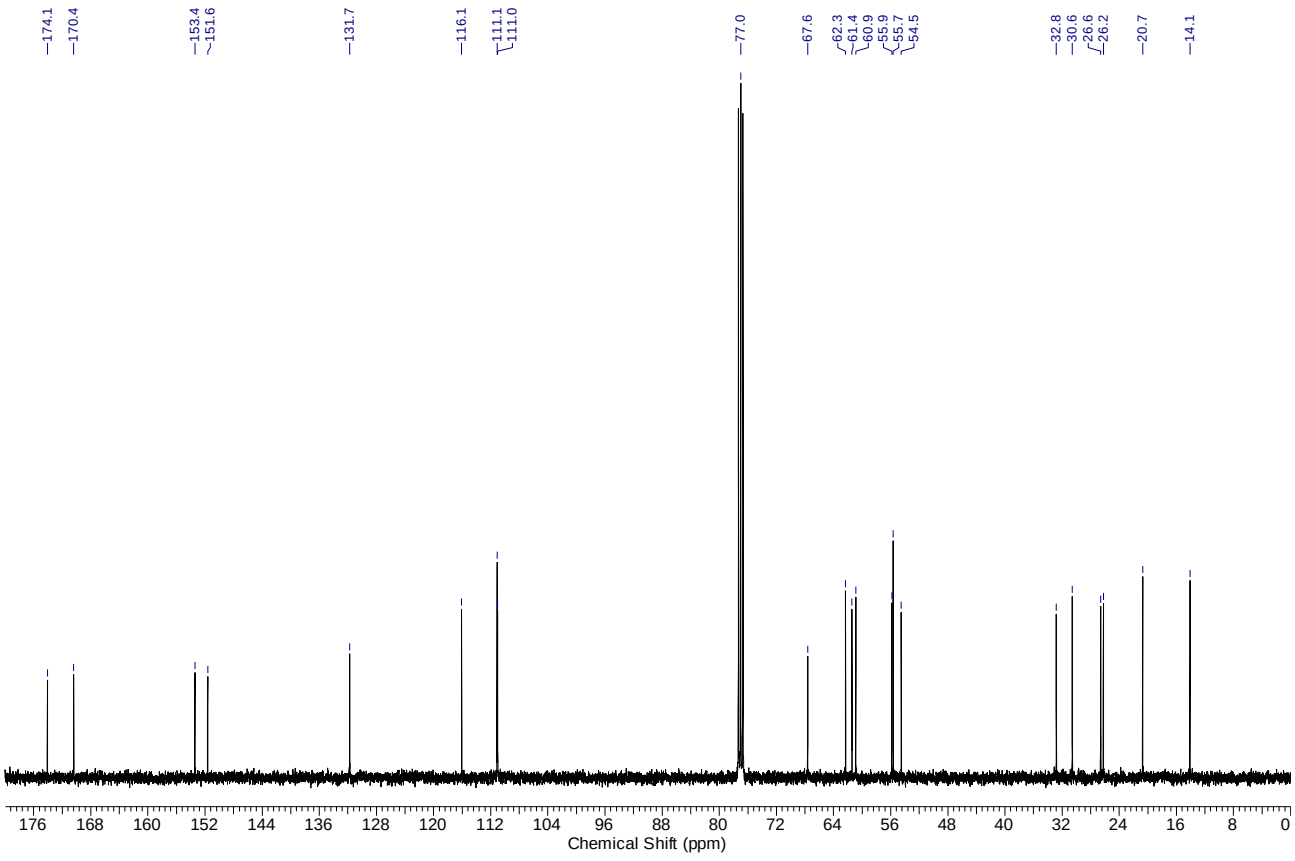
^{1}H NMR (400 MHz) spectrum of acetate **1-95** in $CDCl_3$ (0.5 – 7.5 ppm)



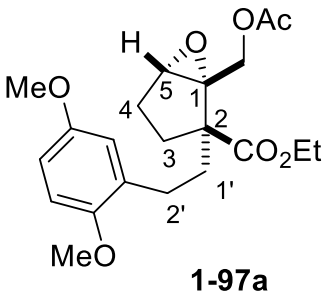
^{13}C NMR (100 MHz) spectrum of acetate **1-95** in $CDCl_3$ (0 – 180 ppm)



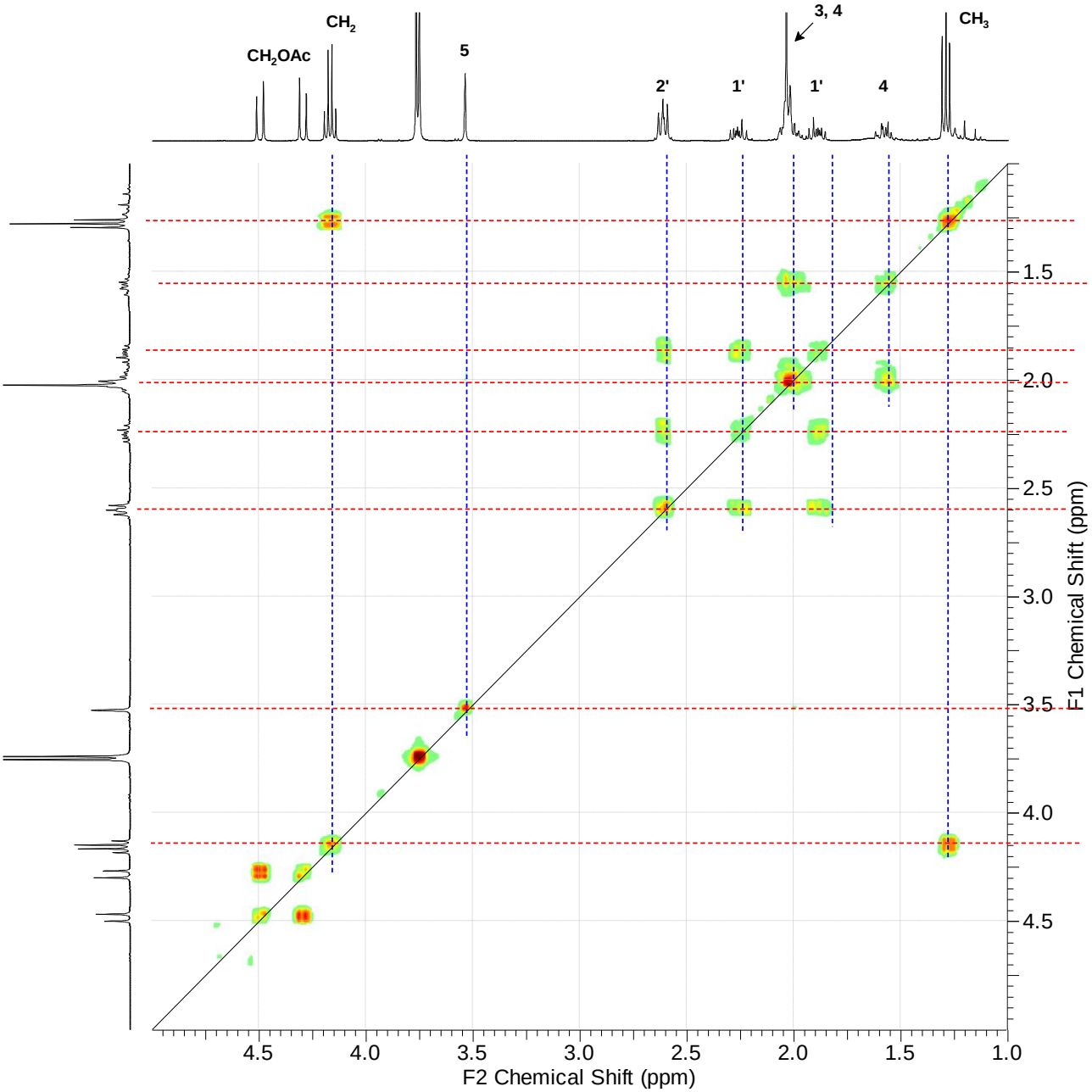
^{1}H NMR (400 MHz) spectrum of epoxide **1-97a** in $CDCl_3$ (0.5 – 7.5 ppm)



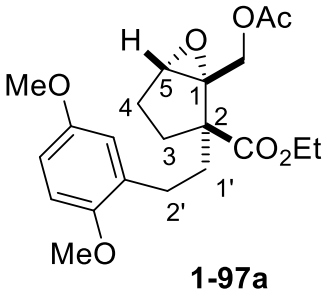
^{13}C NMR (100 MHz) spectrum of epoxide **1-97a** in $CDCl_3$ (0 – 180 ppm)



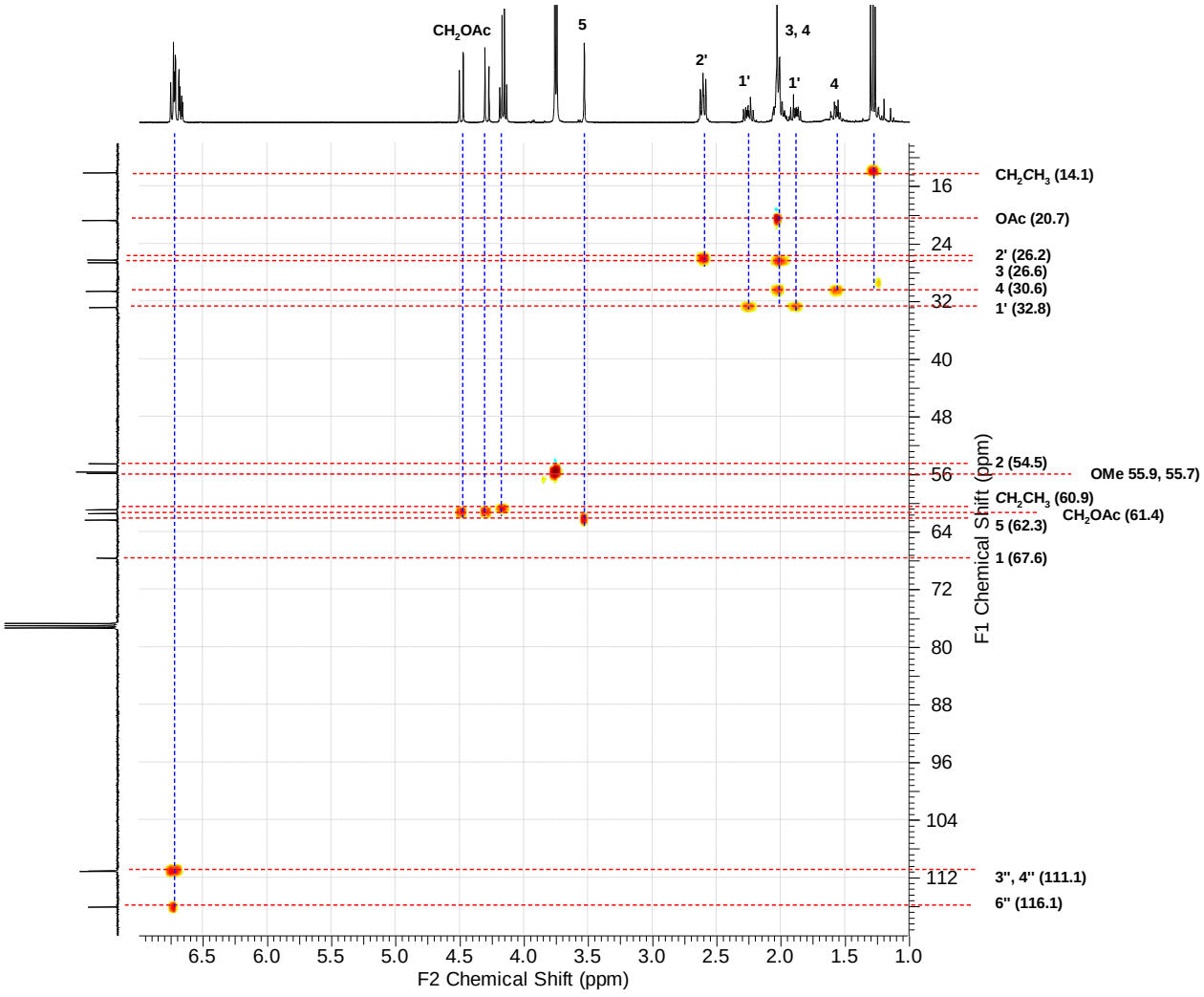
1-97a



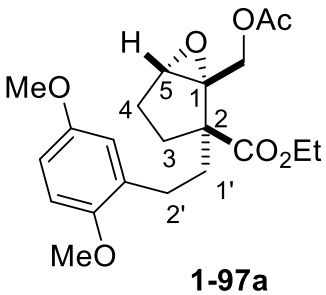
COSY (400 MHz) spectrum of epoxide **1-97a** in $CDCl_3$ (1.0 – 5.0 ppm)



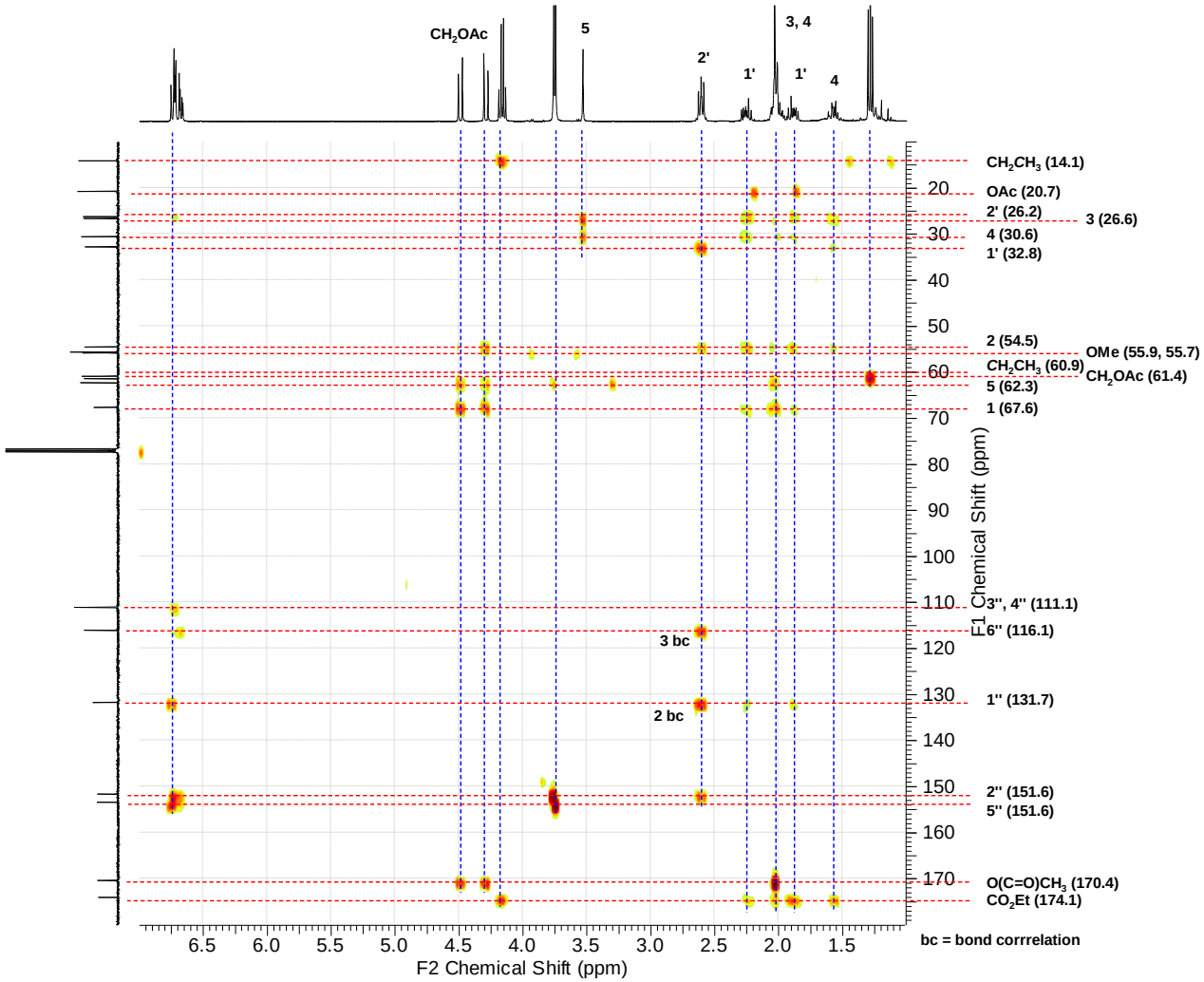
1-97a



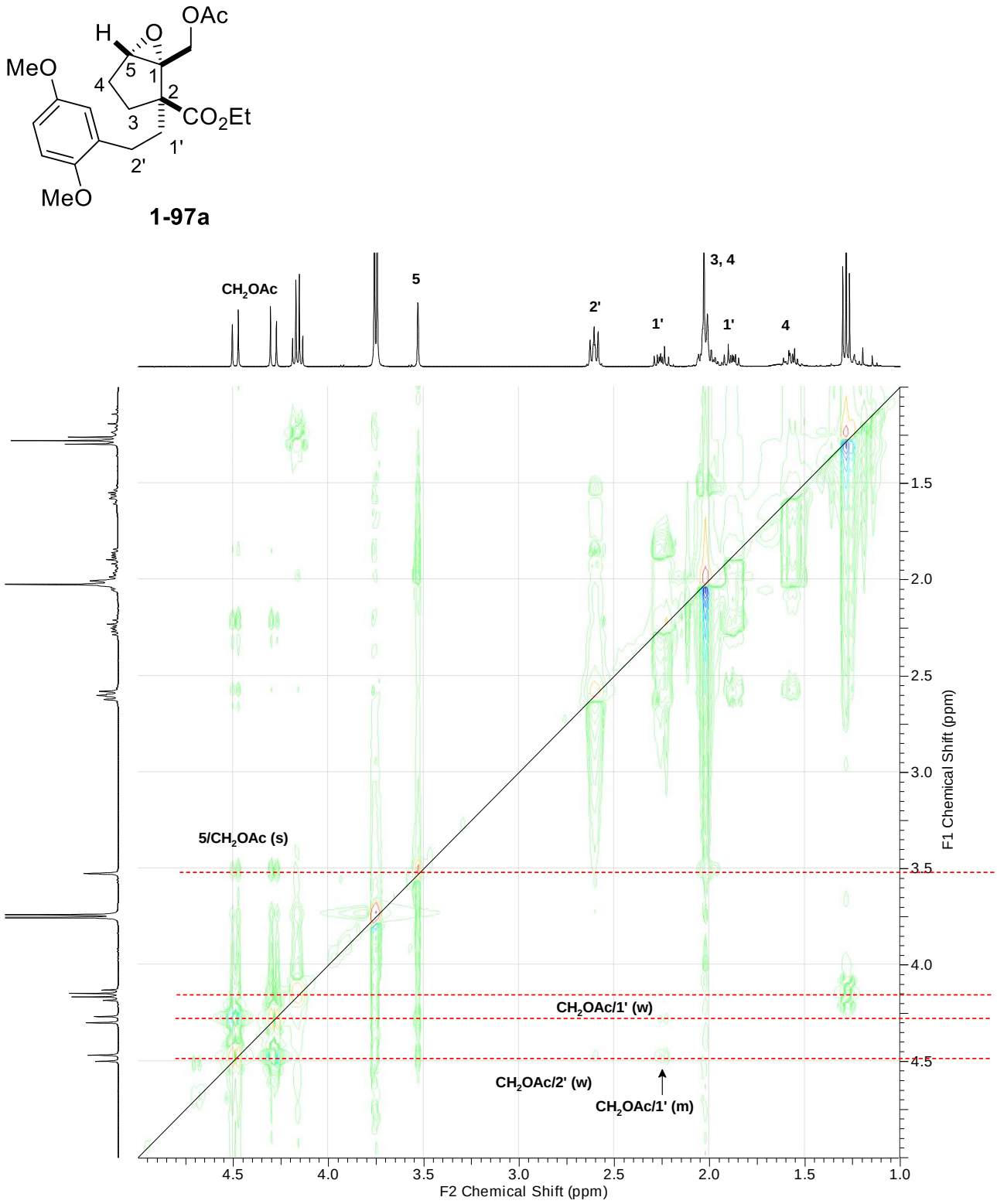
HSQC spectrum of epoxide **1-97a** (1.0 – 7.0 ppm, 10 – 120 ppm) in $CDCl_3$



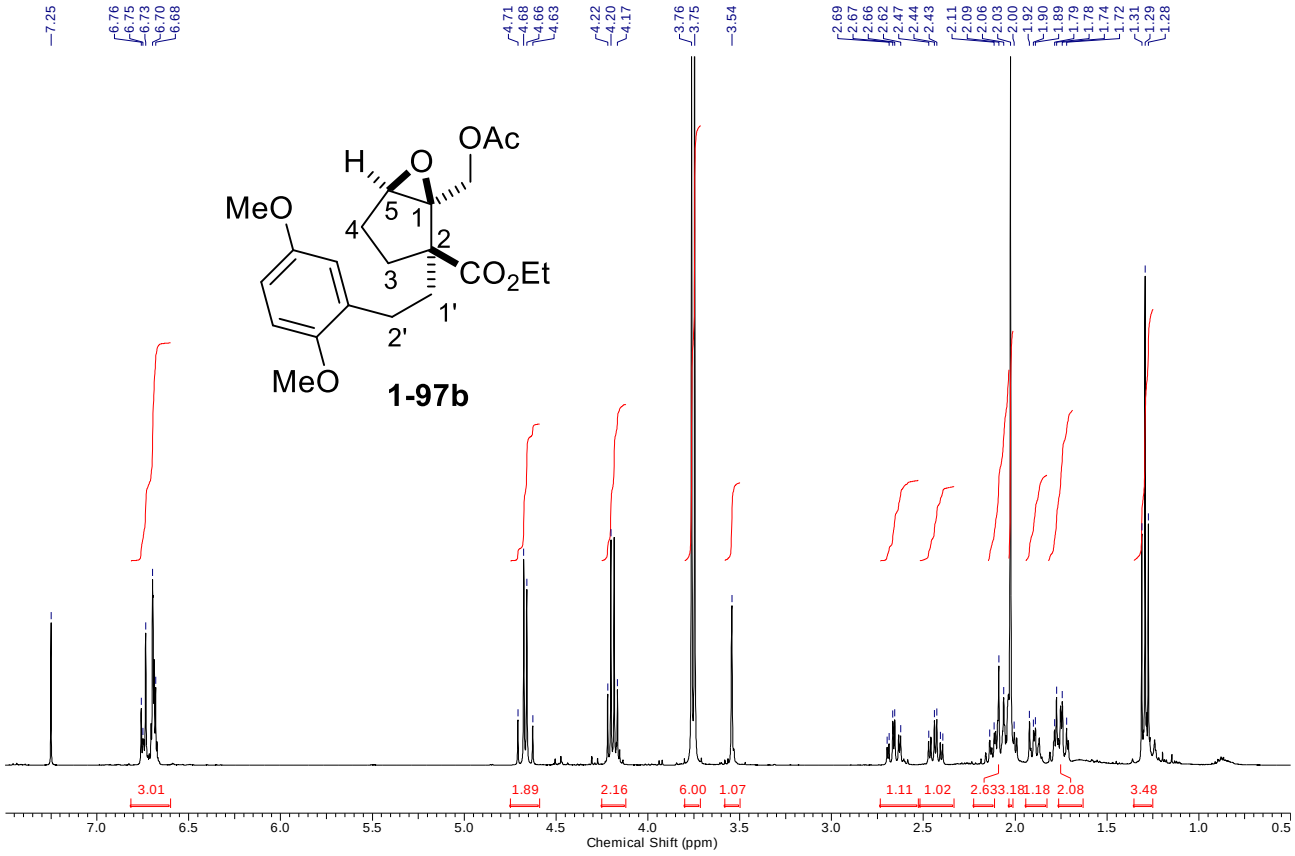
1-97a



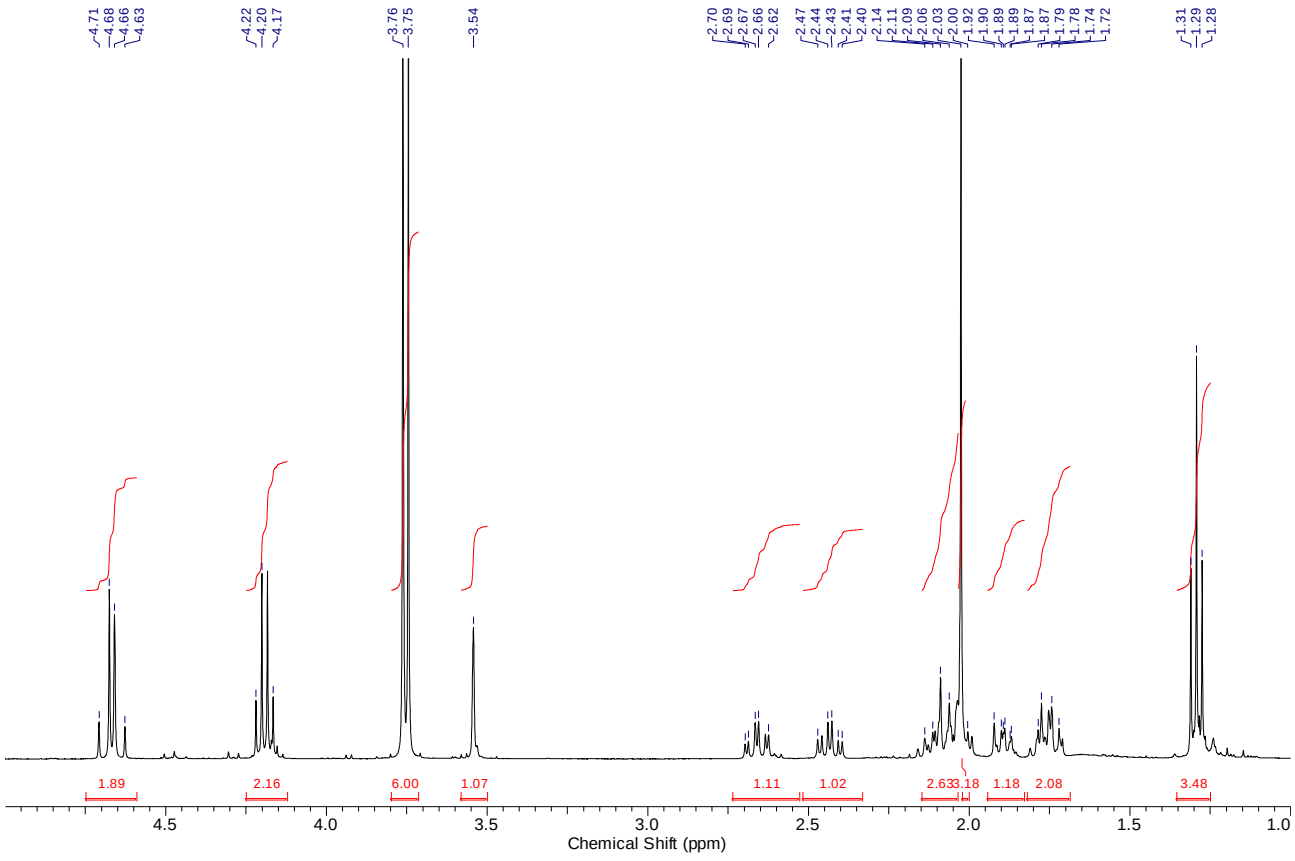
HMBC spectrum of epoxide **1-97a** (1.0 – 7.0 ppm, 10 – 180 ppm) in $CDCl_3$



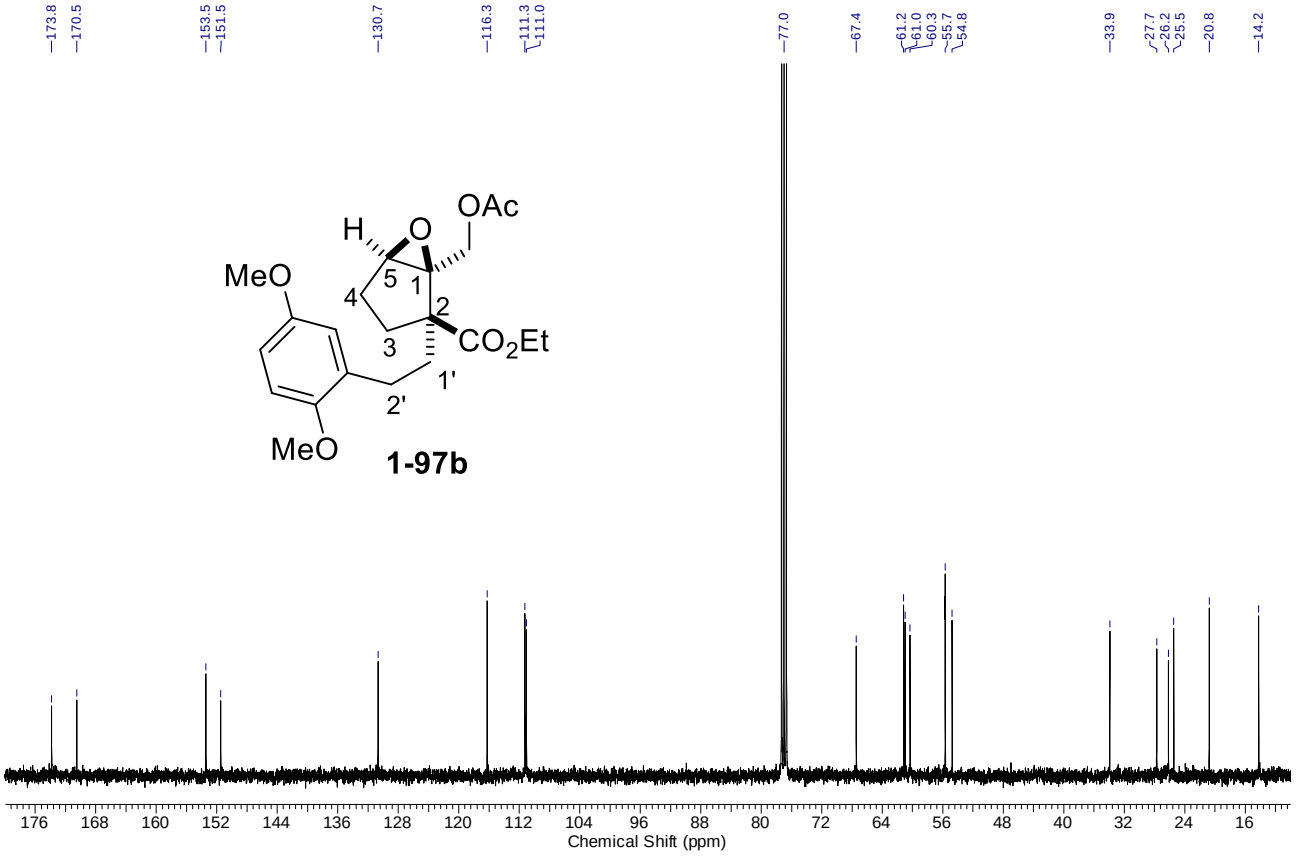
NOESY (400 MHz) spectrum of epoxide **1-97a** in $CDCl_3$ (1.0 – 5.0 ppm)



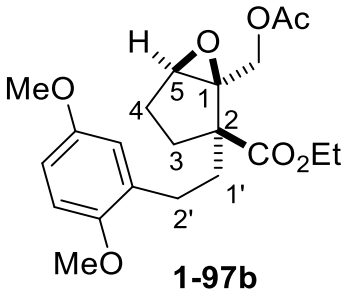
^{1}H NMR (400 MHz) spectrum of epoxide **1-97b** in $CDCl_3$ (0.5 – 7.5 ppm)



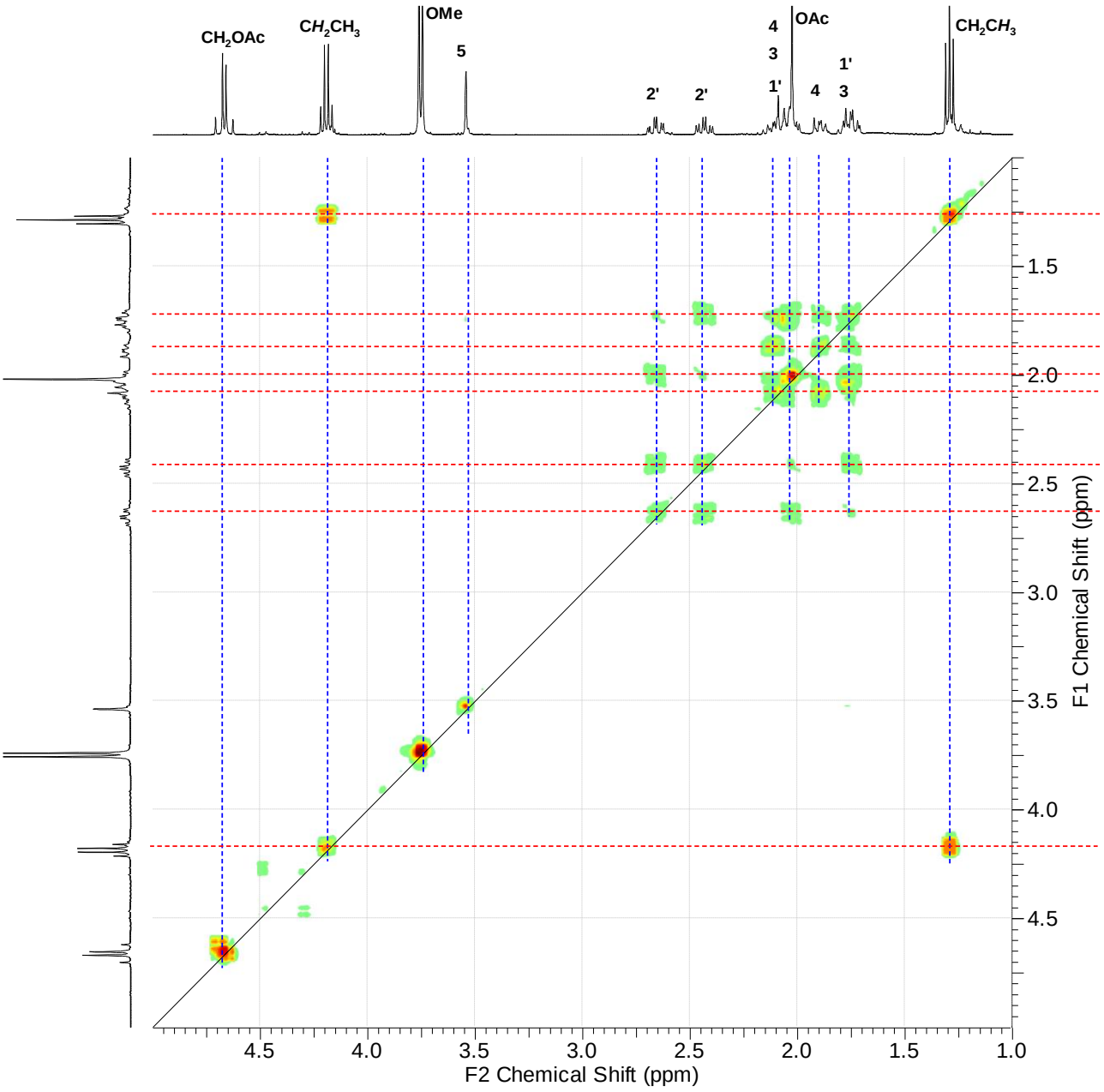
^{1}H NMR (400 MHz) spectrum of epoxide **1-97b** in $CDCl_3$ (1.0 – 5.0 ppm)



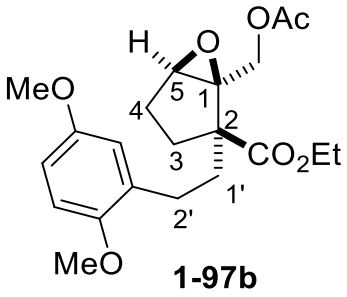
^{13}C NMR (100 MHz) spectrum of epoxide **1-97b** in $CDCl_3$ (10 – 180 ppm)



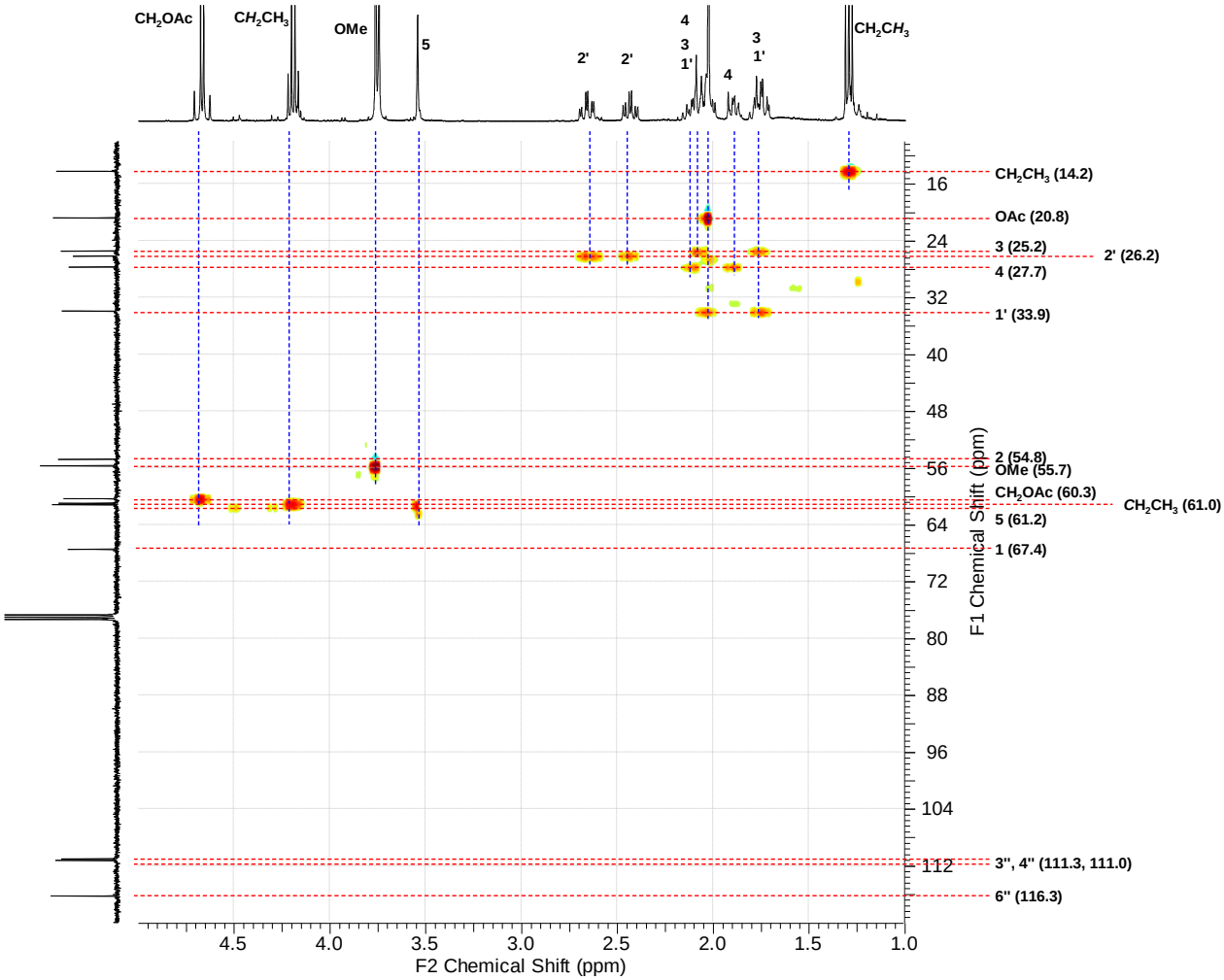
1-97b



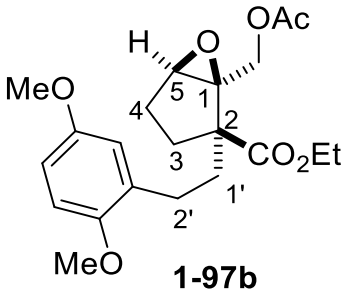
COSY (400 MHz) spectrum of epoxide **1-97b** in $CDCl_3$ (1.0 – 5.0 ppm)



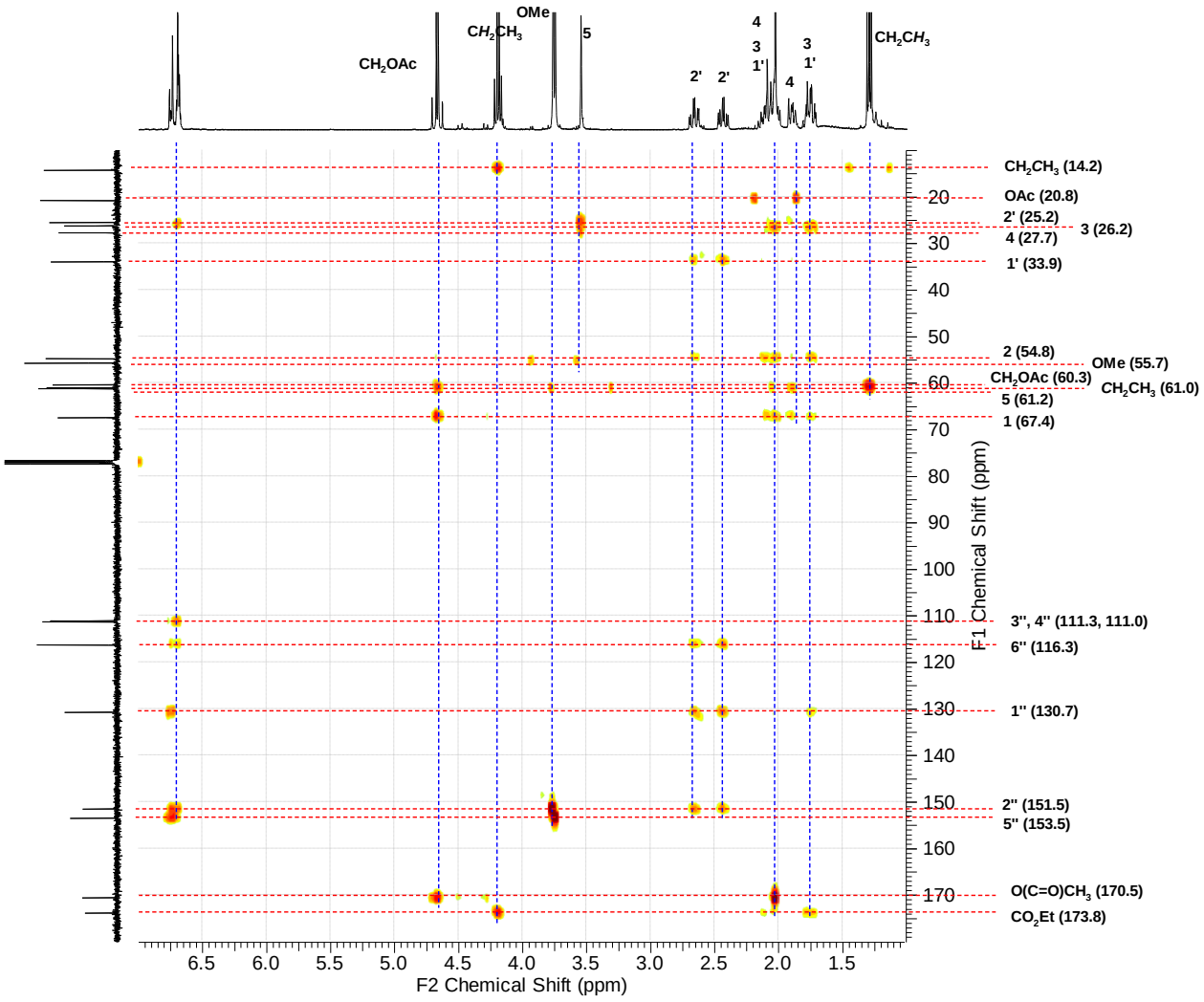
1-97b



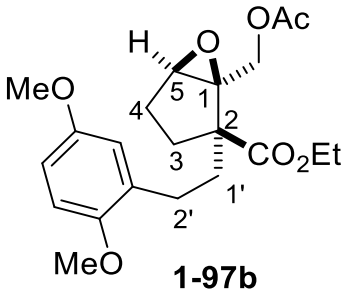
HSQC spectrum of epoxide **1-97b** (1.0 – 5.0 ppm, 10 – 120 ppm) in $CDCl_3$



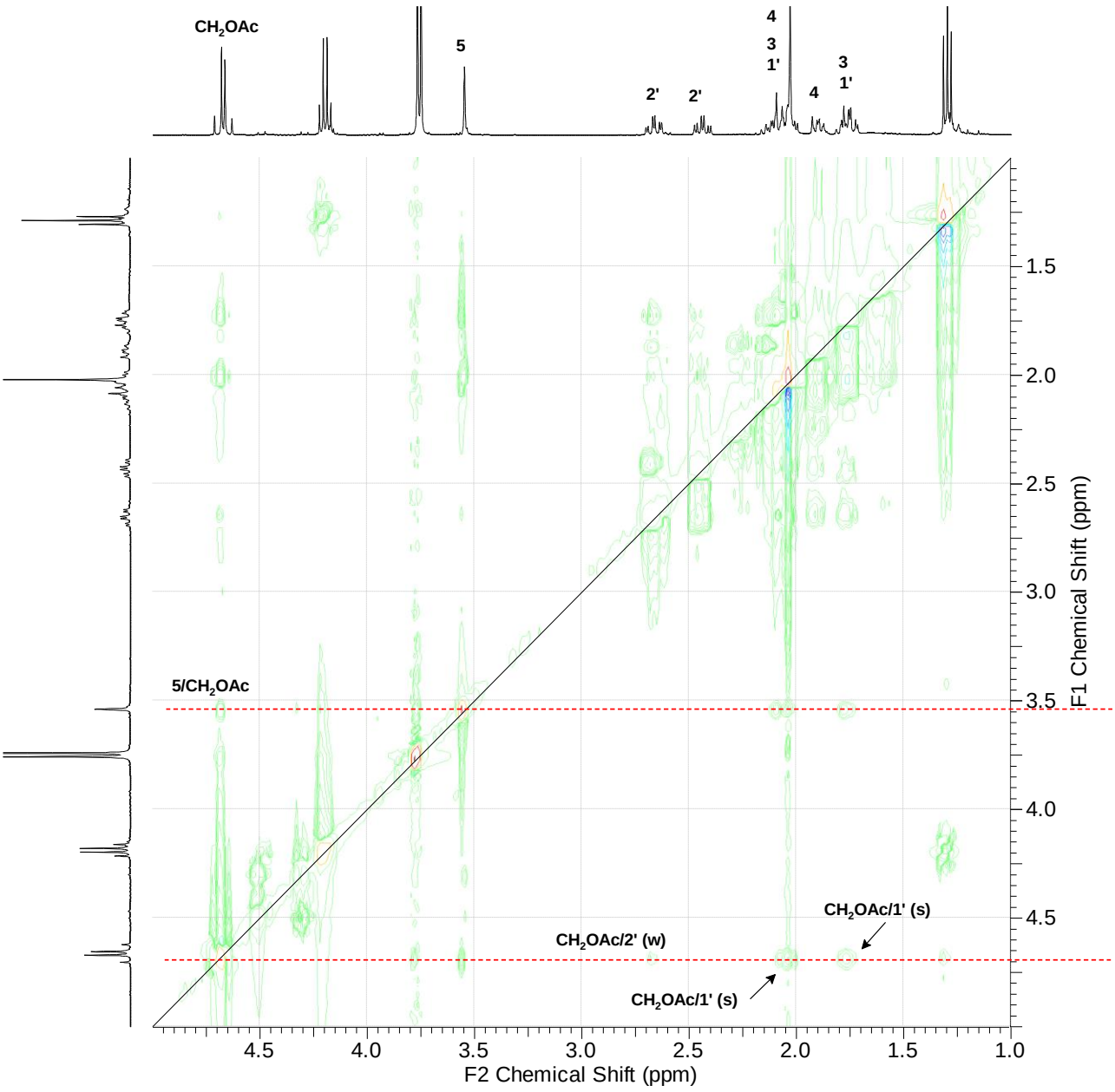
1-97b



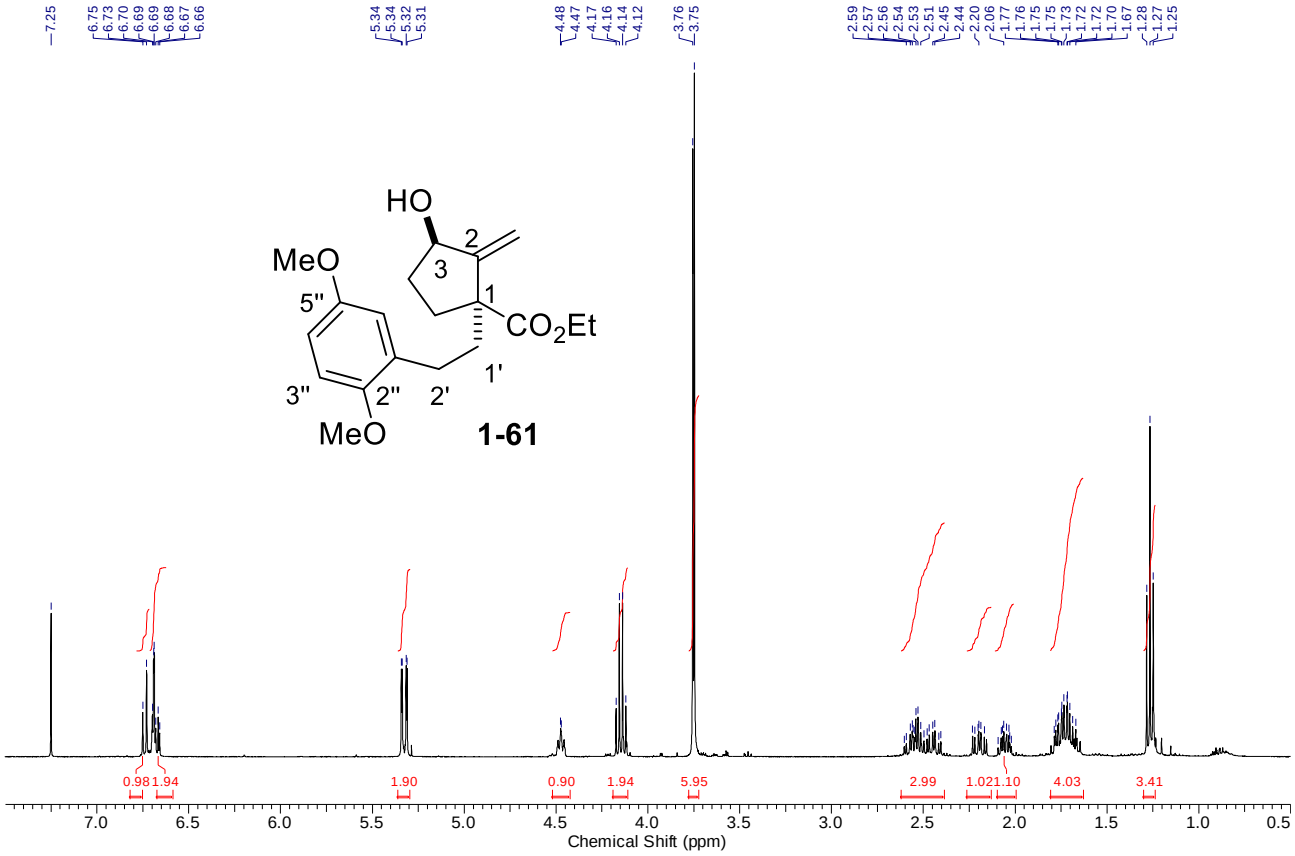
HMBC spectrum of epoxide **1-97b** (1.0 – 7.0 ppm, 10 – 180 ppm) in $CDCl_3$



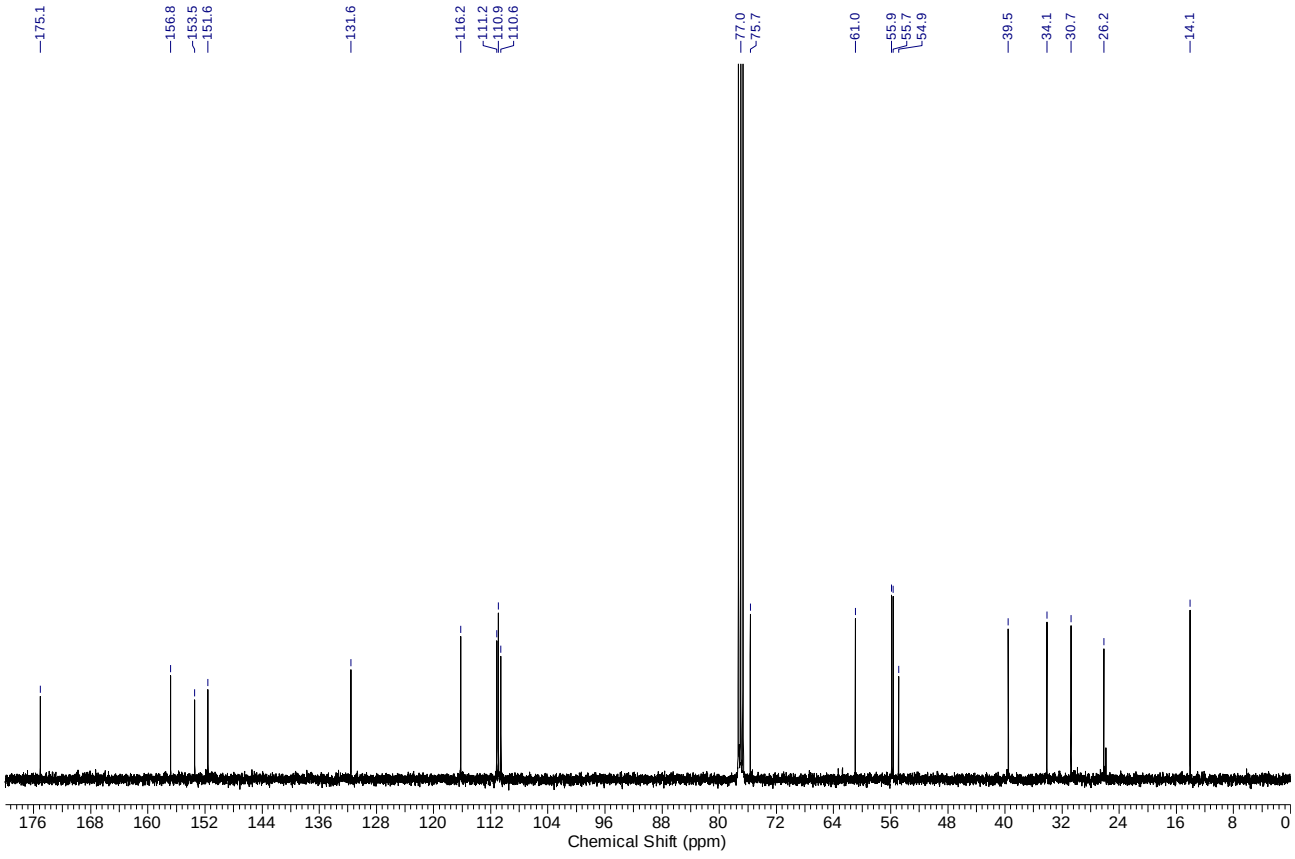
1-97b



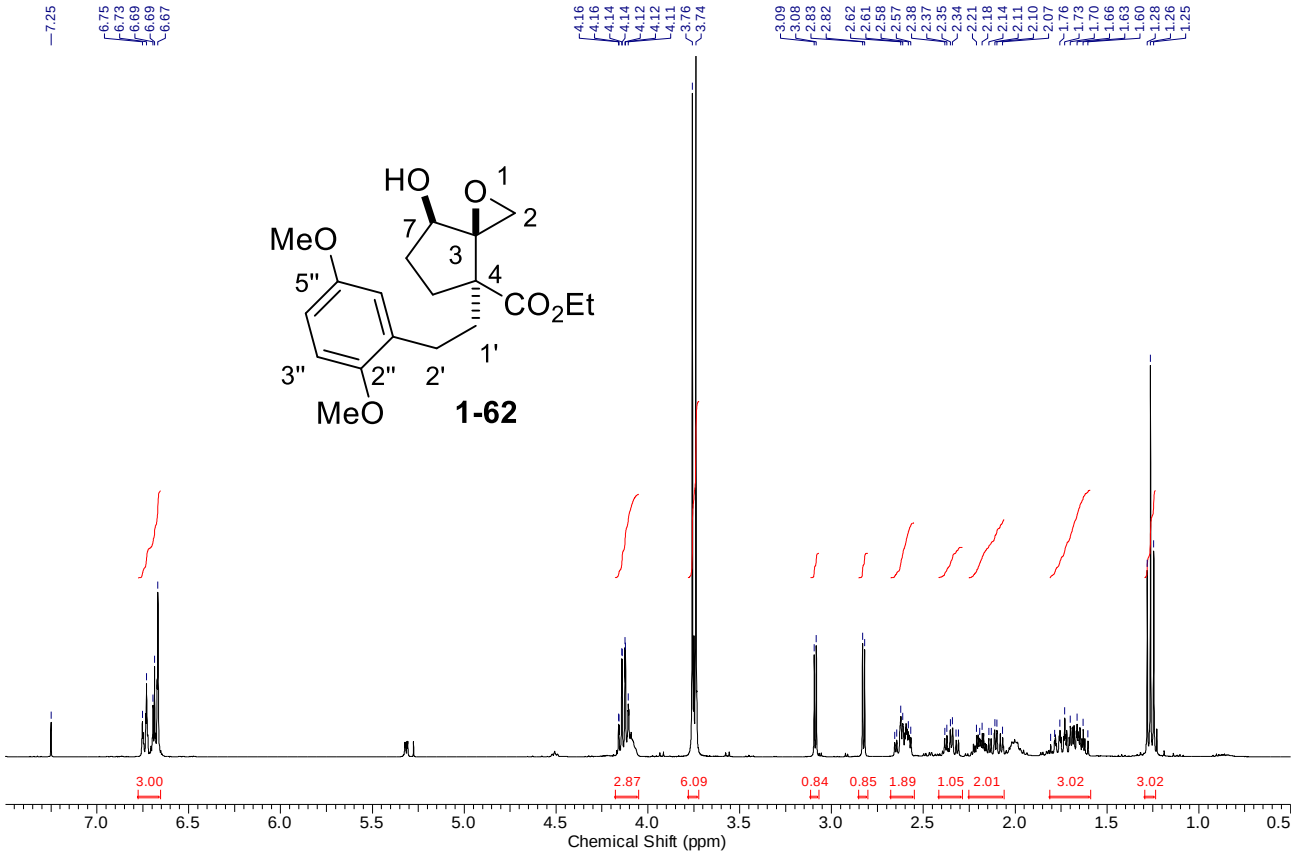
NOESY (400 MHz) spectrum of epoxide **1-97b** in $CDCl_3$ (1.0 – 5.0 ppm)



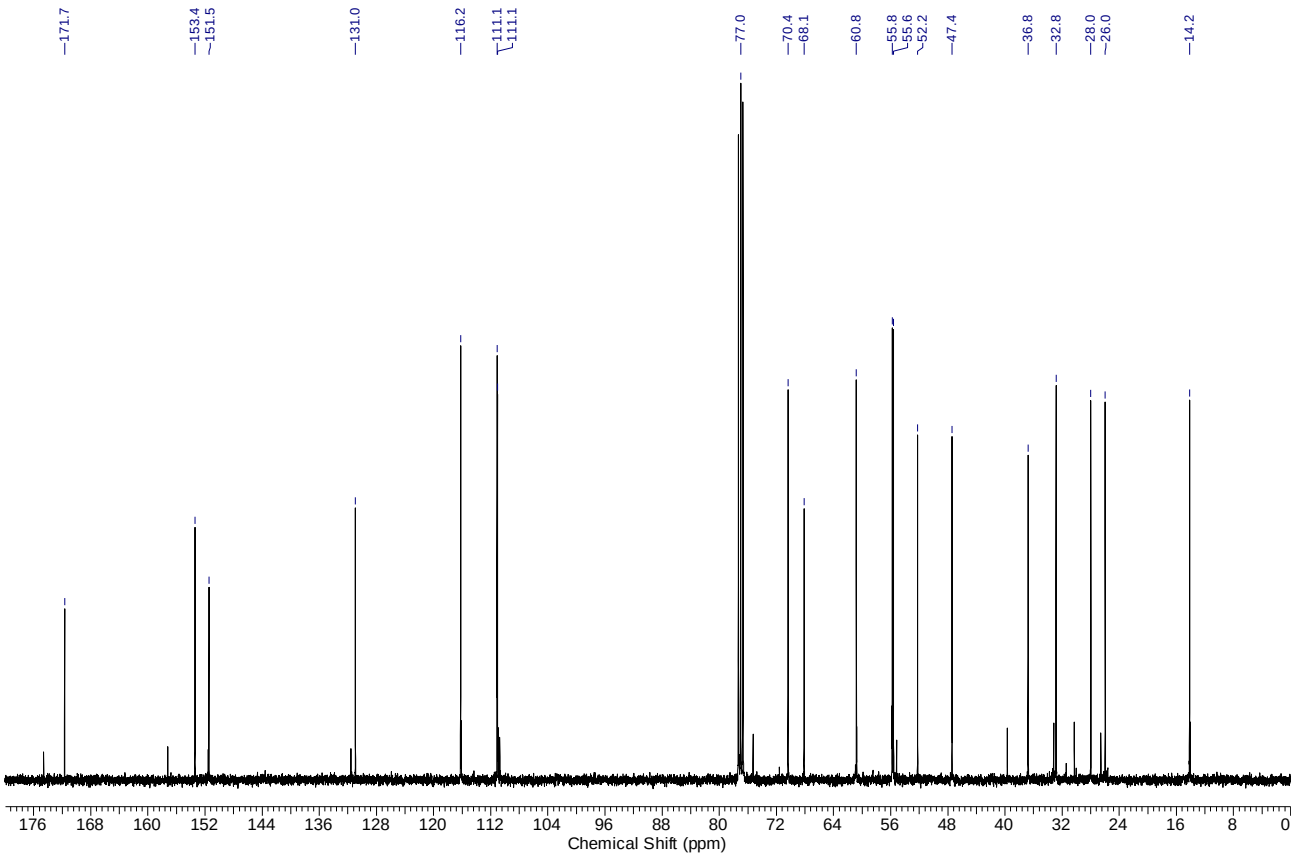
^{1}H NMR (400 MHz) spectrum of allyl alcohol **1-61** in $CDCl_3$ (0.5 – 7.5 ppm)



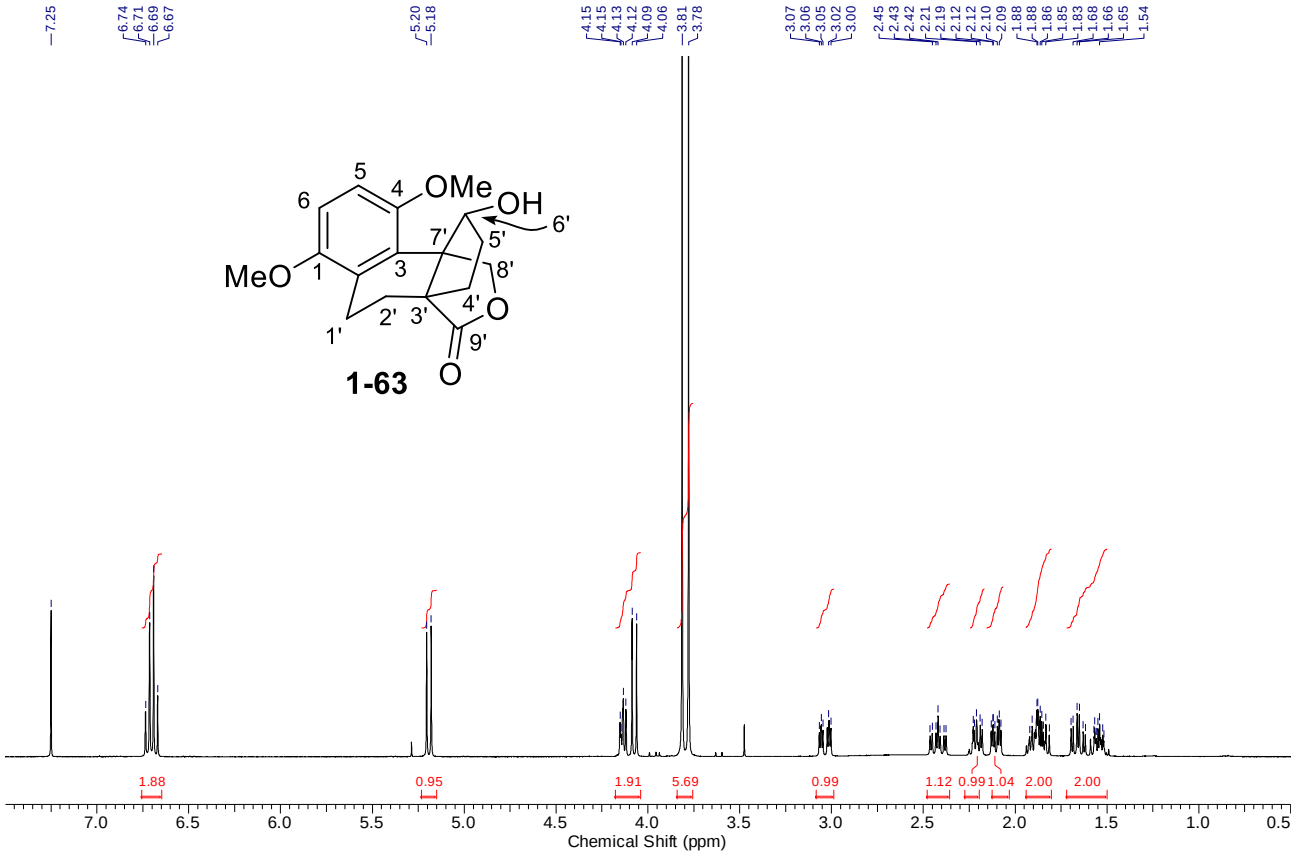
^{13}C NMR (100 MHz) spectrum of allyl alcohol **1-61** in $CDCl_3$ (0 – 180 ppm)



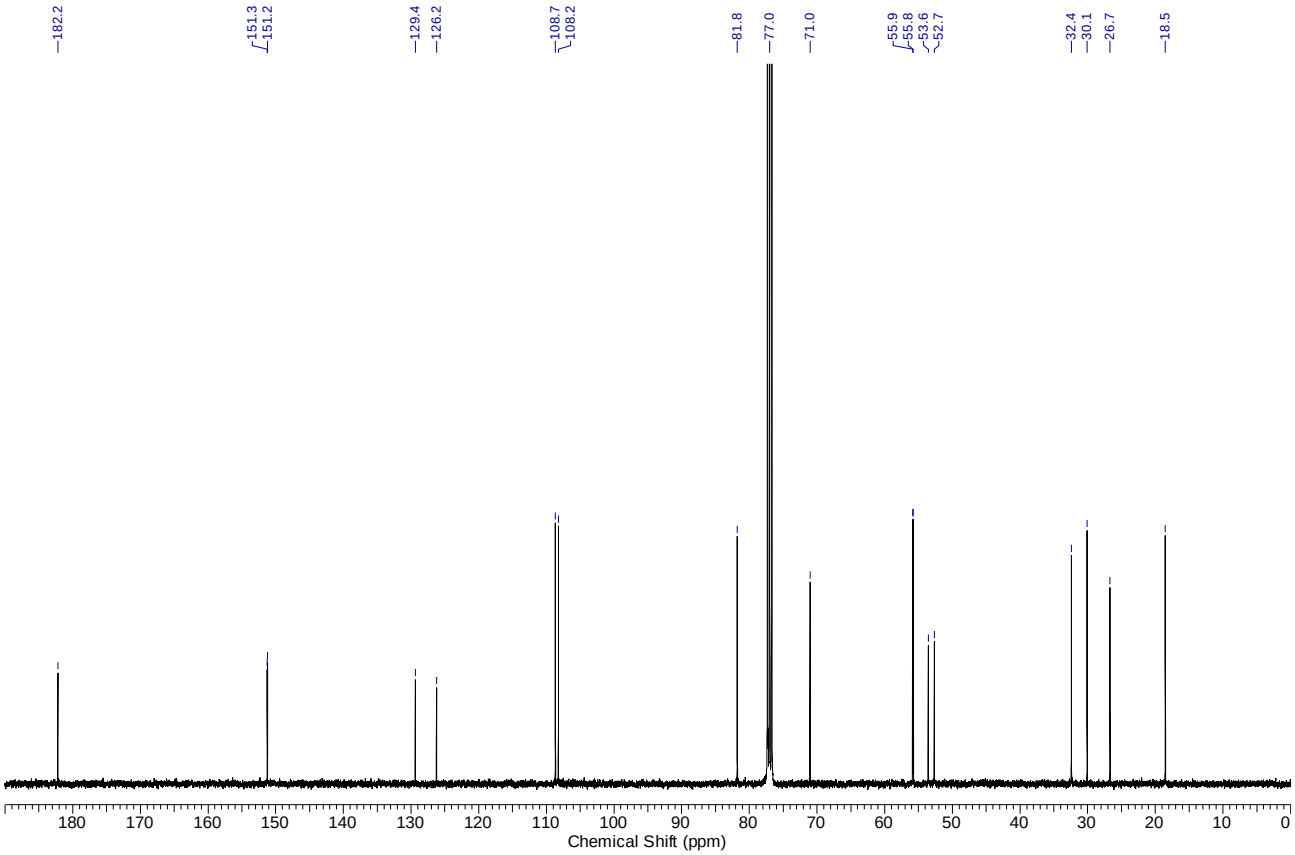
^{1}H NMR (400 MHz) spectrum of epoxide **1-62** in $CDCl_3$ (0.5 – 7.5 ppm)



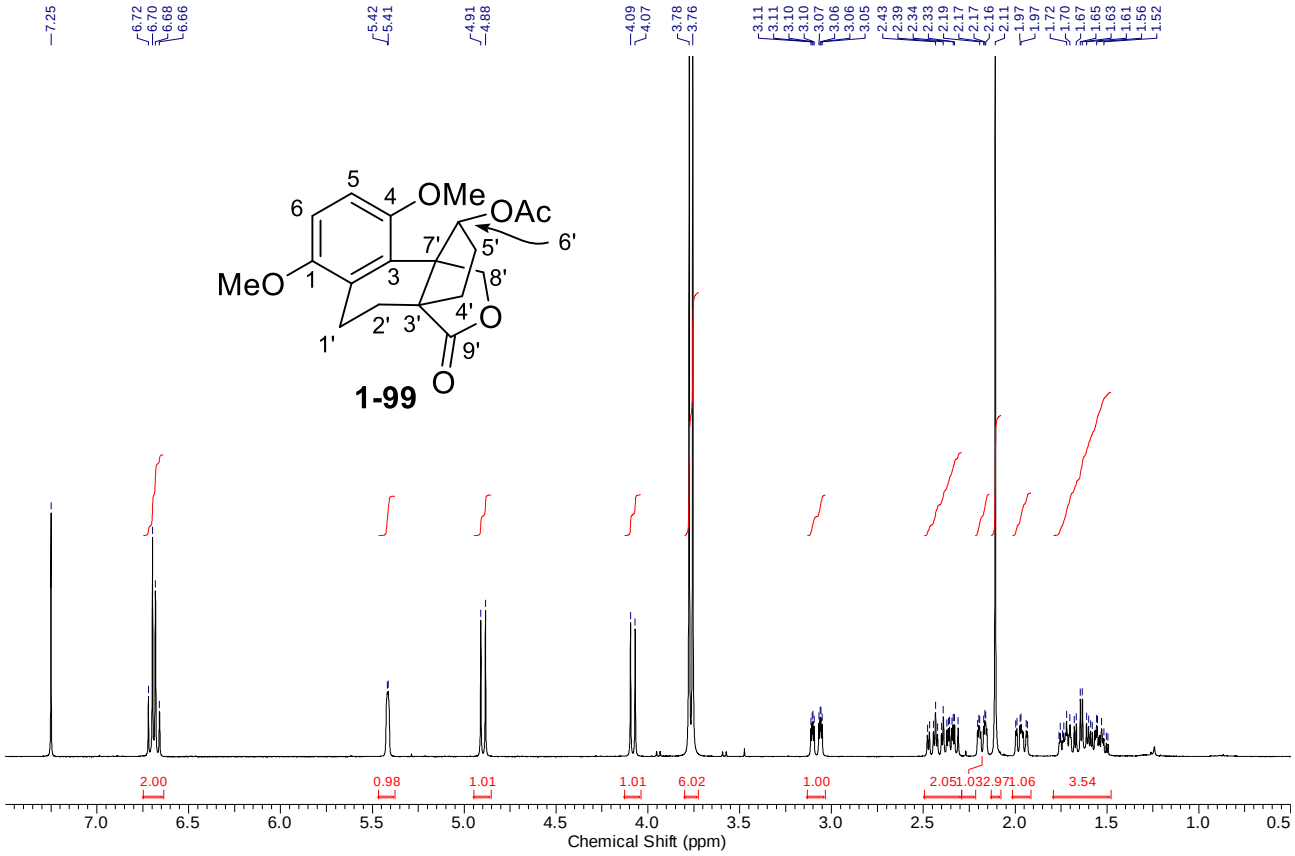
^{13}C NMR (100 MHz) spectrum of epoxide **1-62** in $CDCl_3$ (0 – 180 ppm)



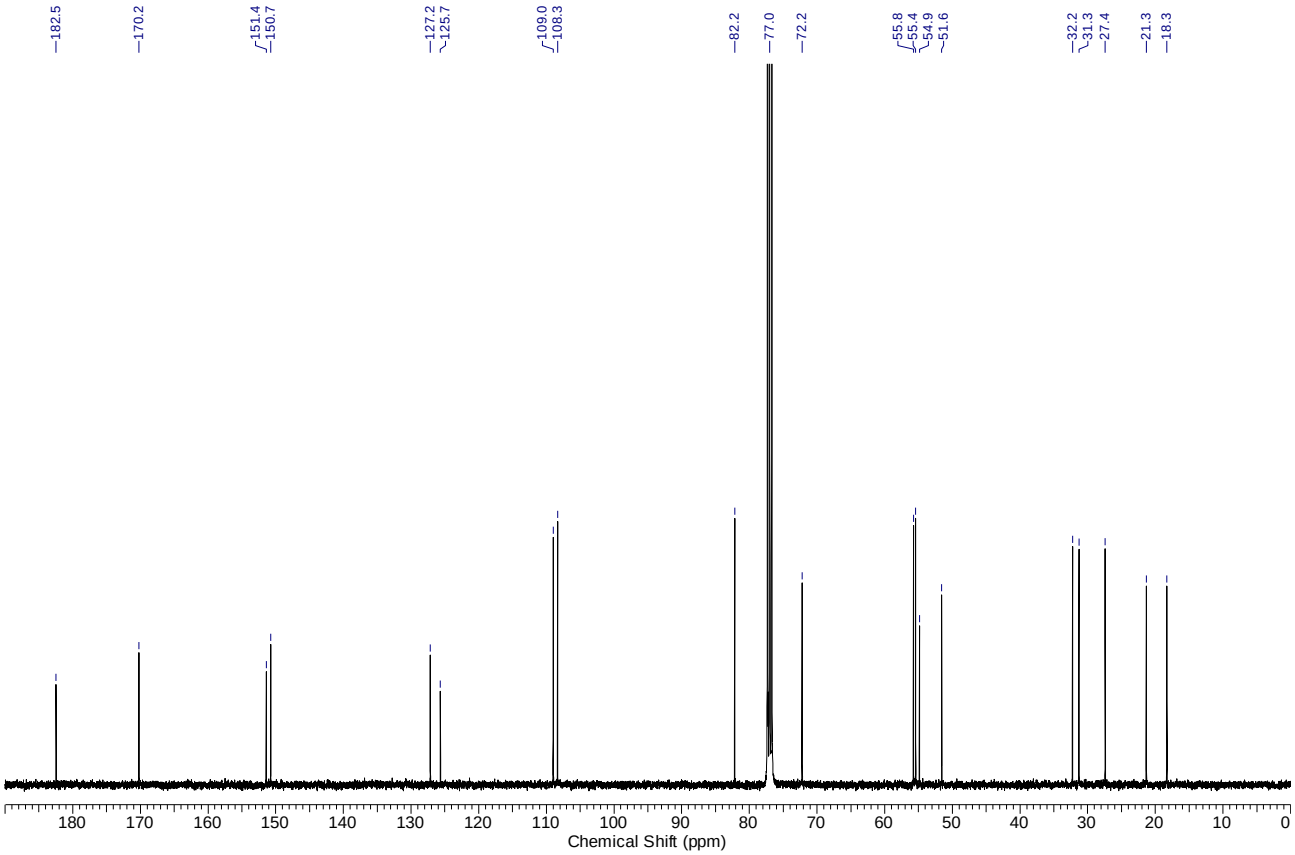
^{1}H NMR (400 MHz) spectrum of polycycle **1-63** in $CDCl_3$ (0.5 – 7.5 ppm)



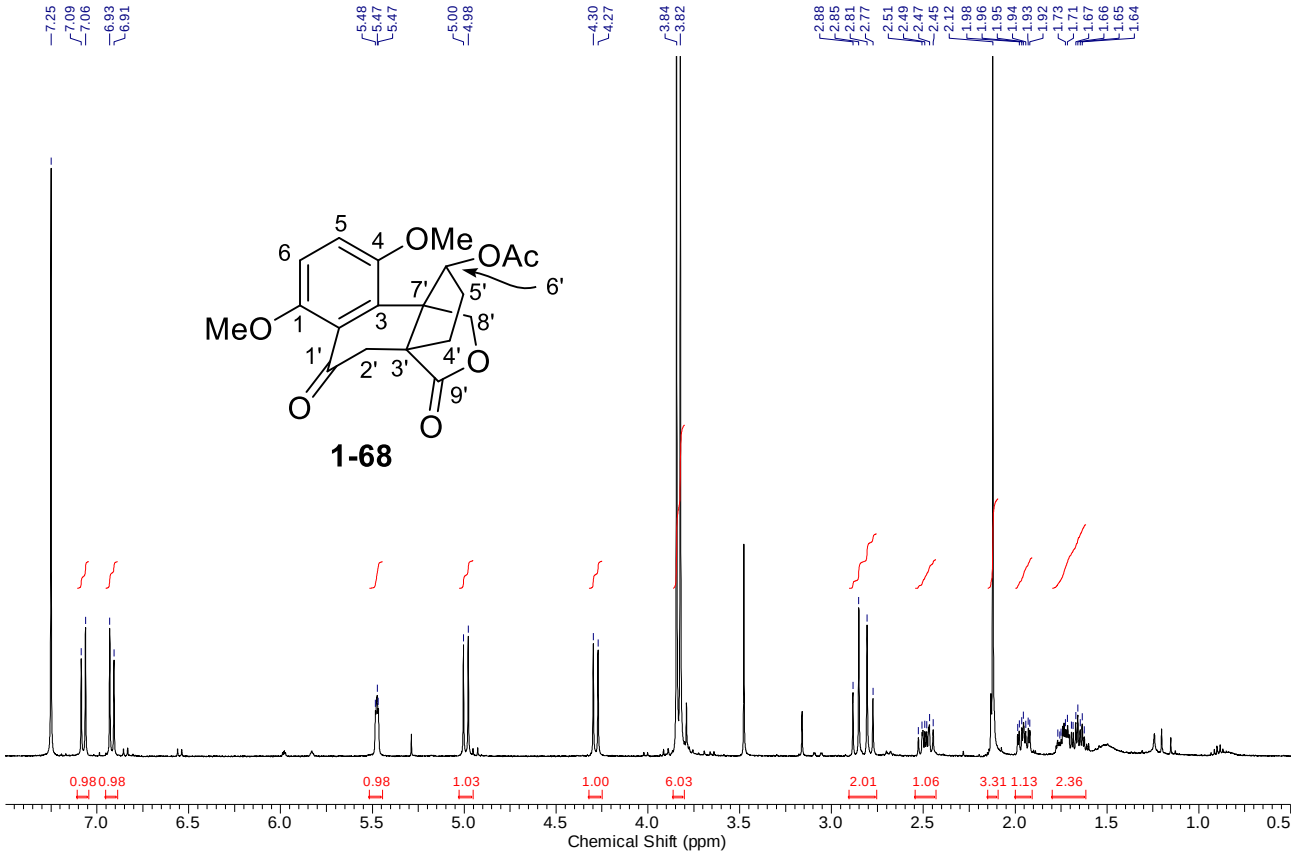
^{13}C NMR (100 MHz) spectrum of polycycle **1-63** in $CDCl_3$ (0 – 190 ppm)



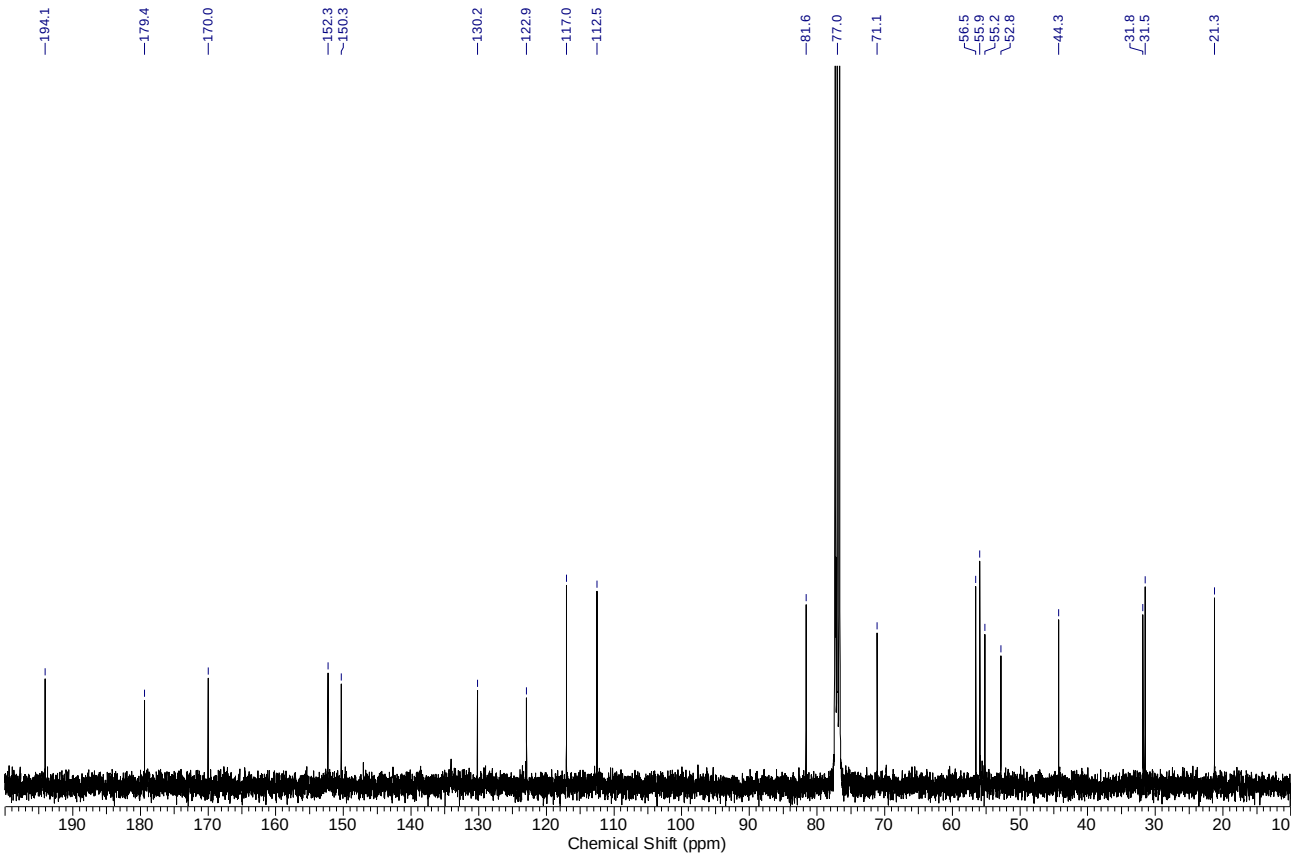
^{1}H NMR (400 MHz) spectrum of acetate **1-99** in $CDCl_3$ (0.5 – 7.5 ppm)



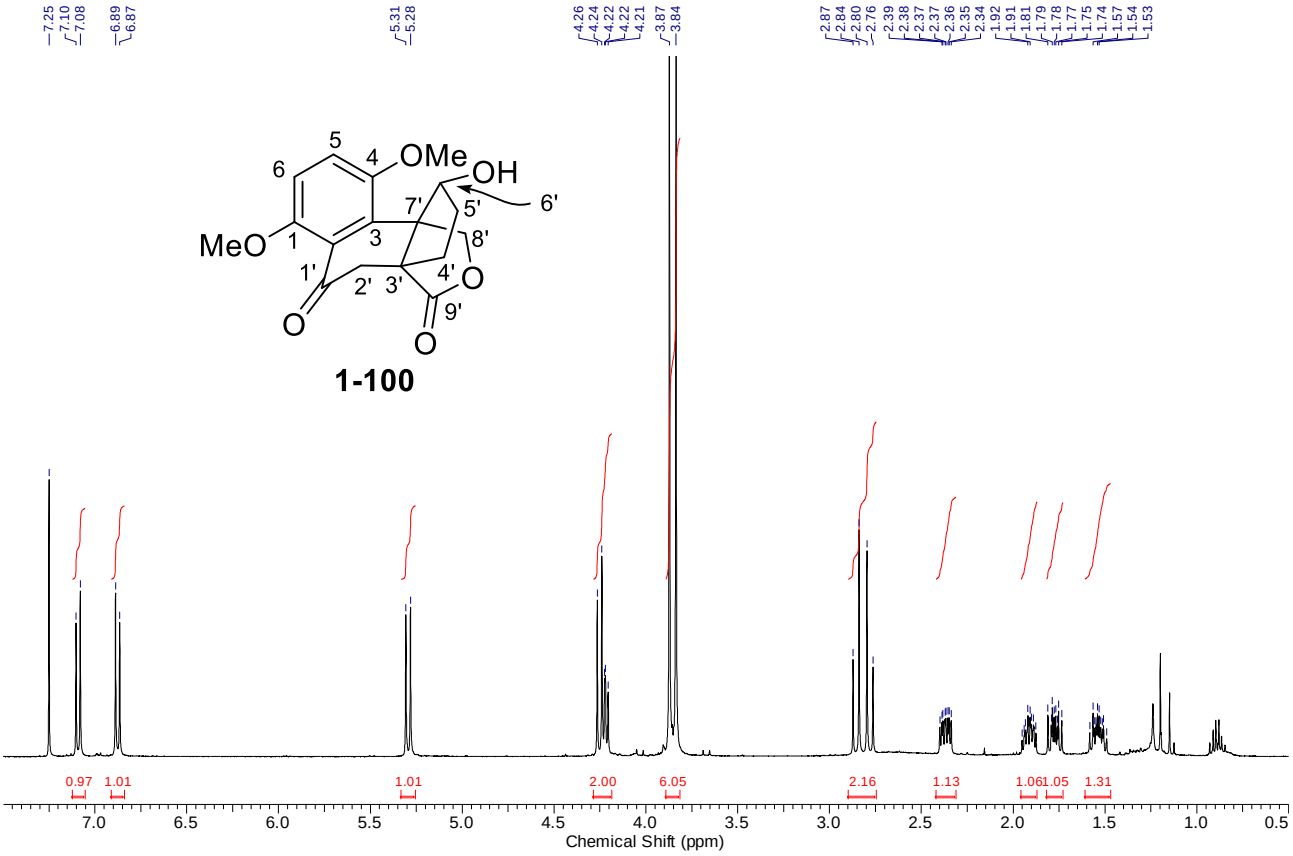
^{13}C NMR (100 MHz) spectrum of acetate **1-99** in $CDCl_3$ (0 – 190 ppm)



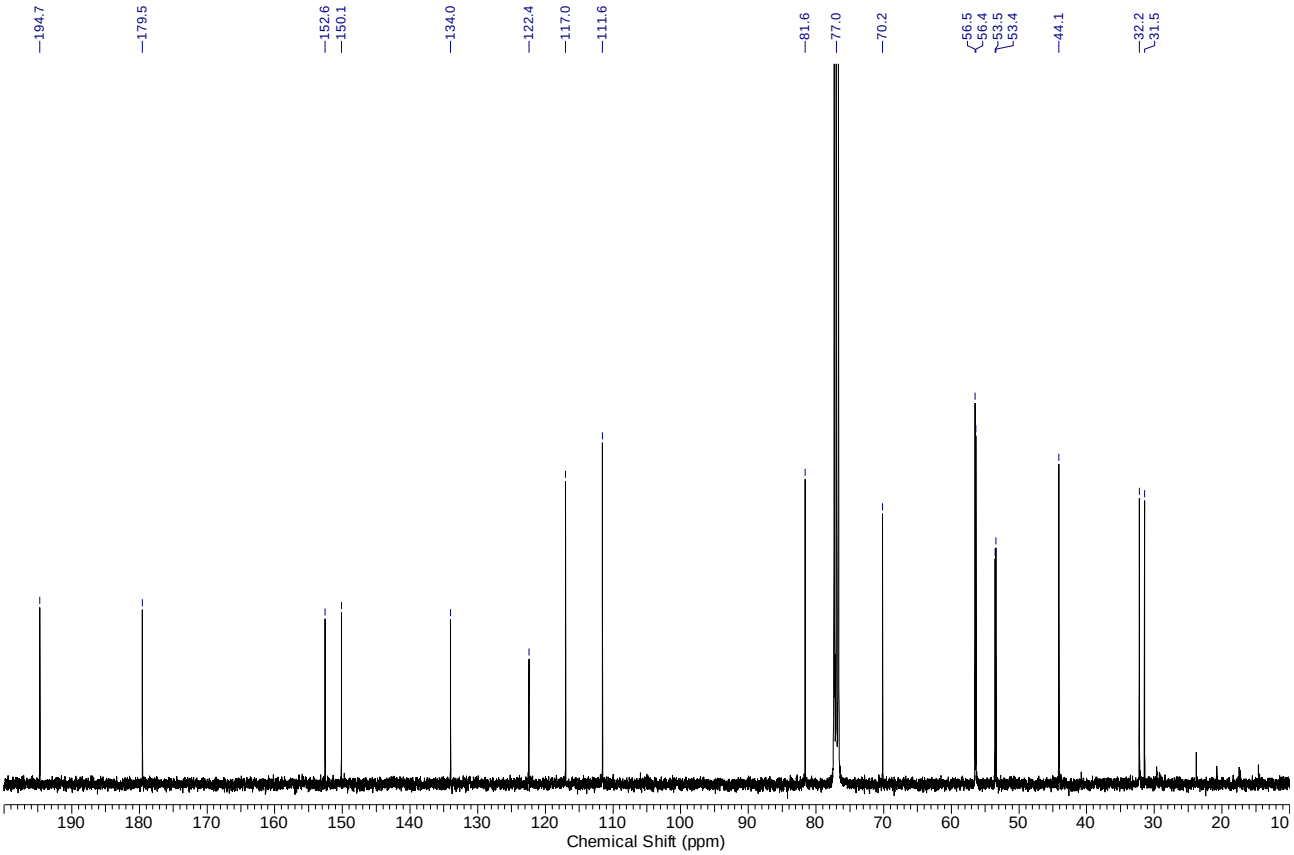
^{1}H NMR (400 MHz) spectrum of phenone **1-68** in $CDCl_3$ (0.5 – 7.5 ppm)



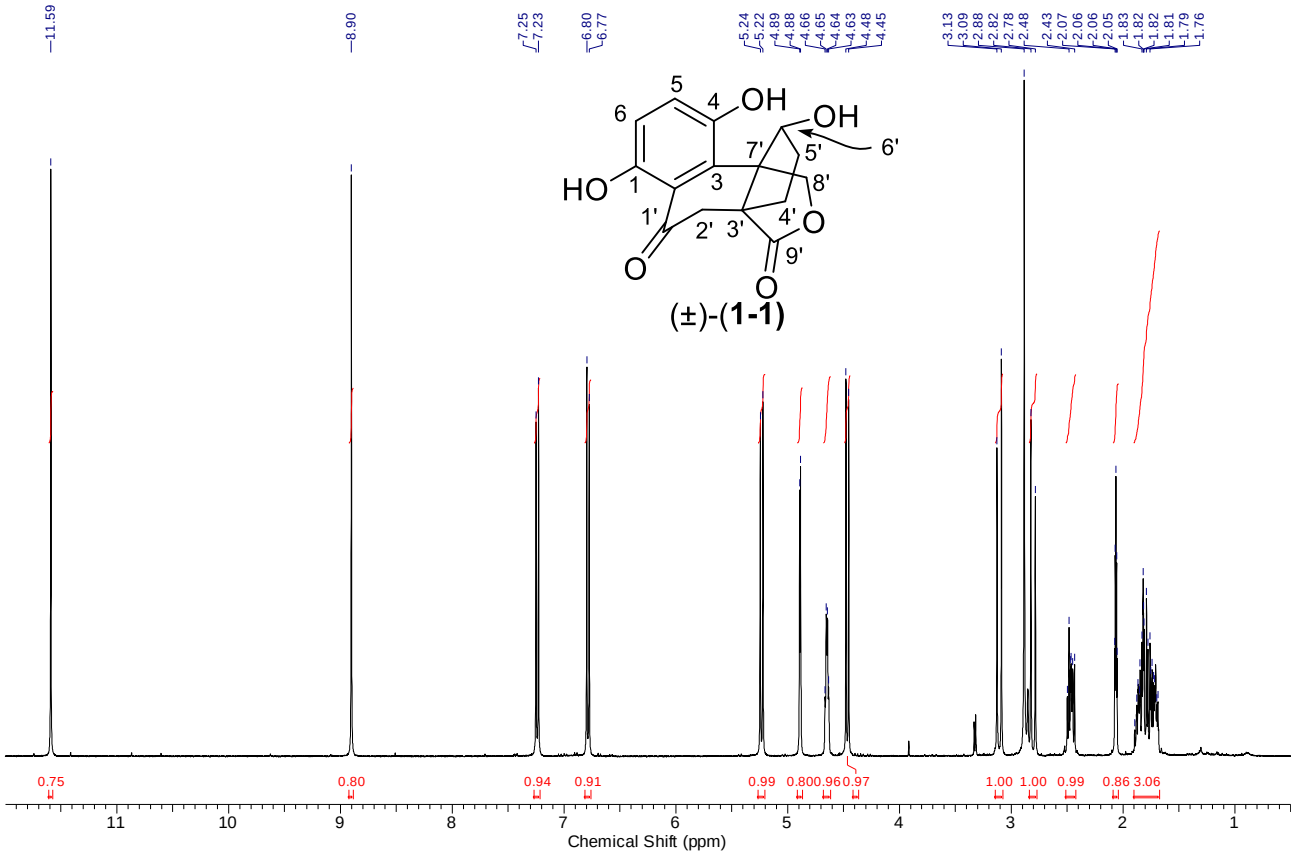
^{13}C NMR (100 MHz) spectrum of phenone **1-68** in $CDCl_3$ (10 – 200 ppm)



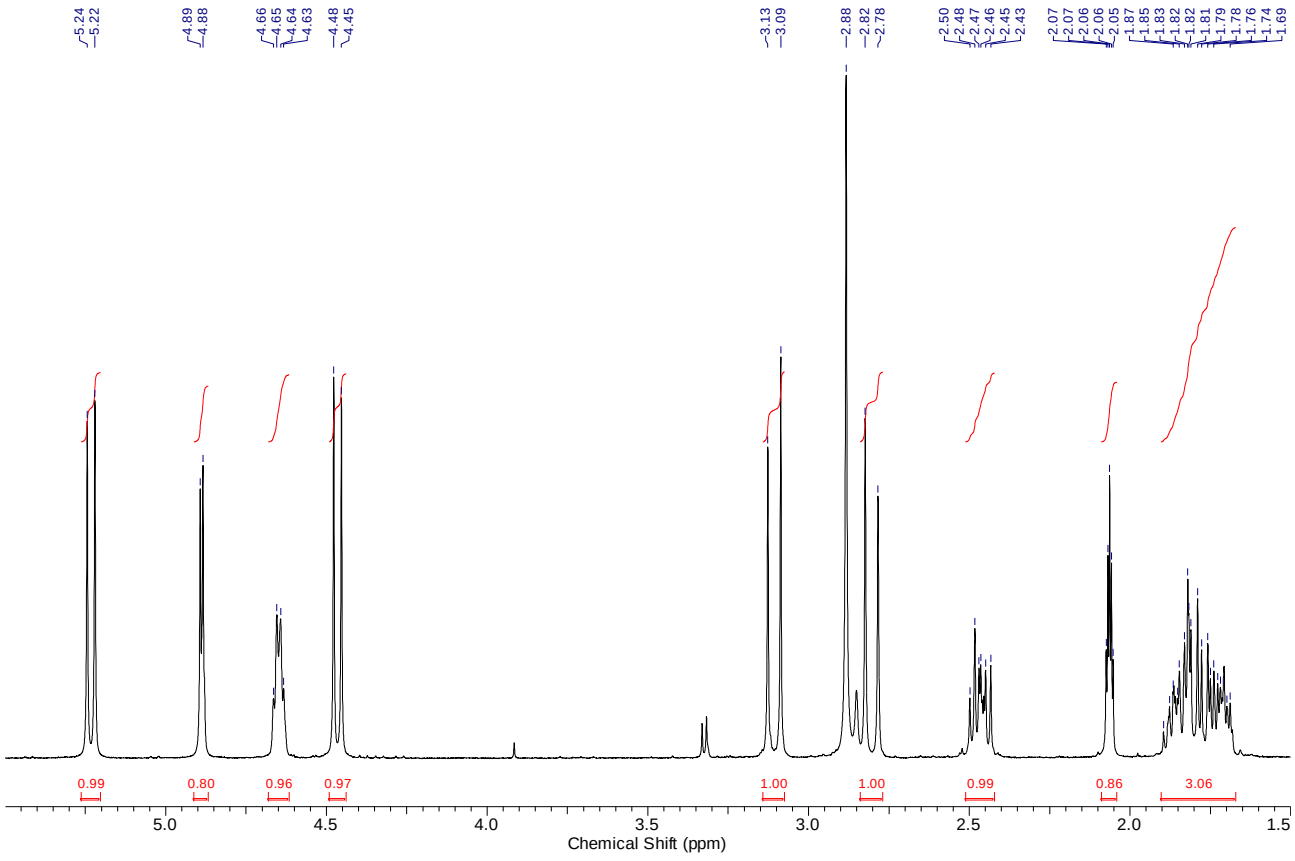
^{1}H NMR (400 MHz) spectrum of hydroxyketone **1-100** in $CDCl_3$ (0.5 – 7.5 ppm)



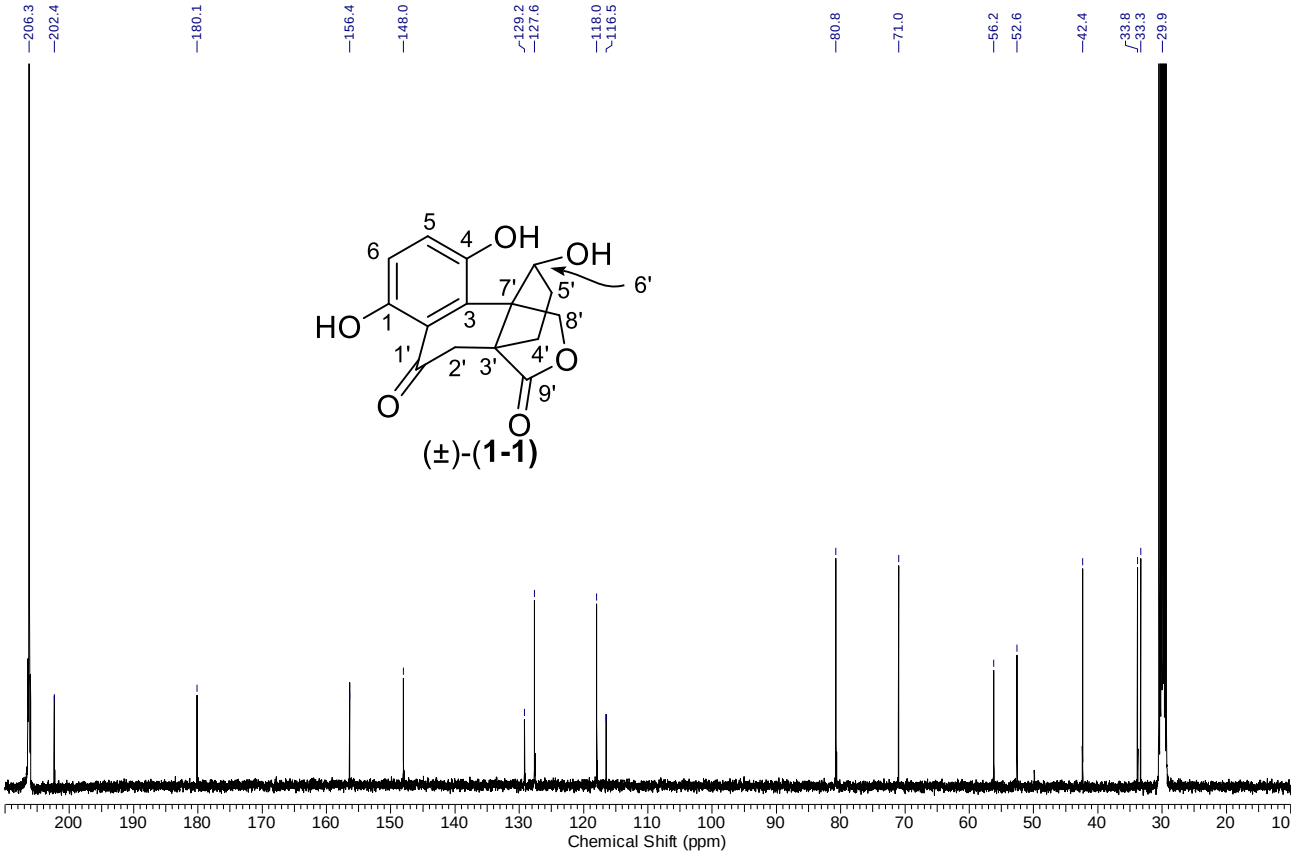
^{13}C NMR (100 MHz) spectrum of hydroxyketone **1-100** in $CDCl_3$ (10 – 200 ppm)



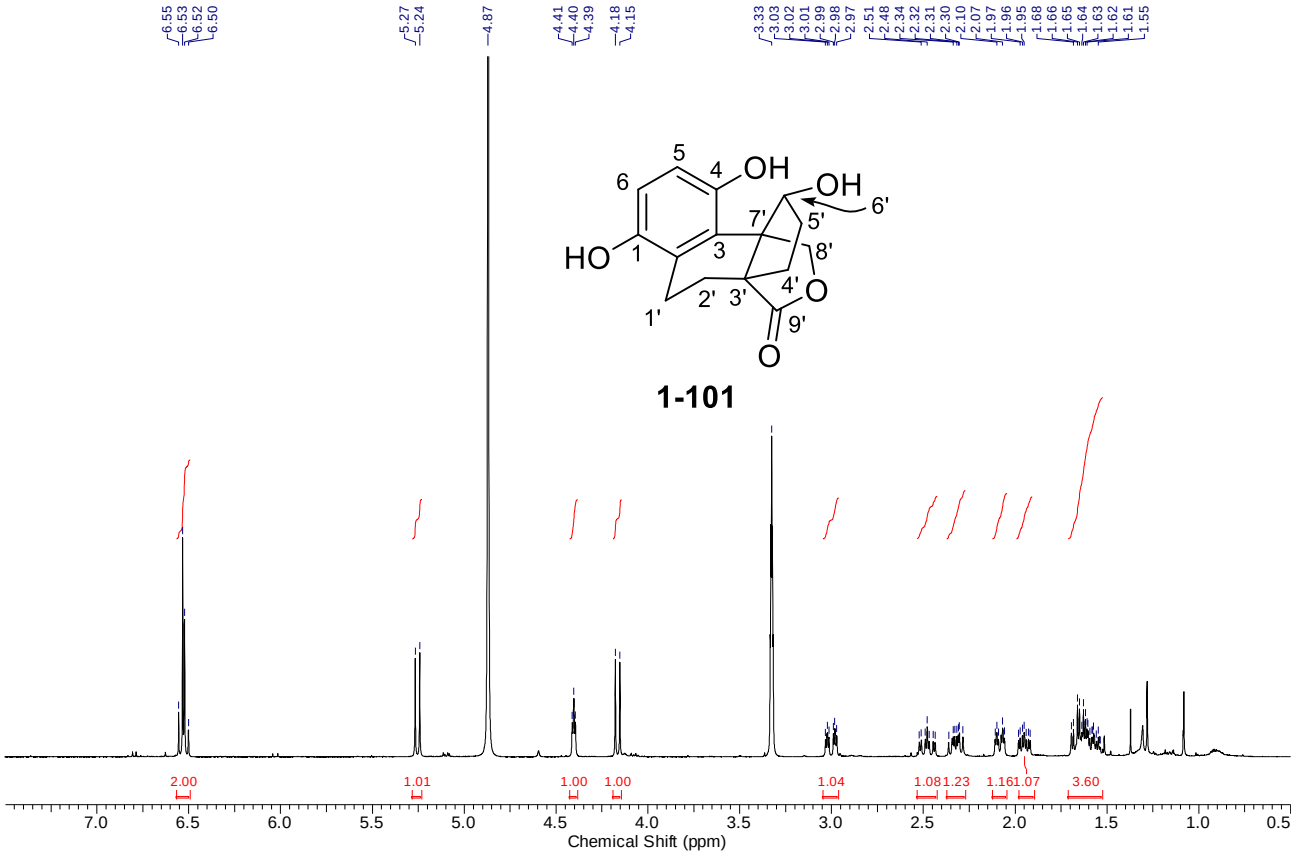
^{1}H NMR (400 MHz) spectrum of lingzhiol [(±)–**1-1**] in $(CD_3)_2CO$ (0.5 – 12.0 ppm)



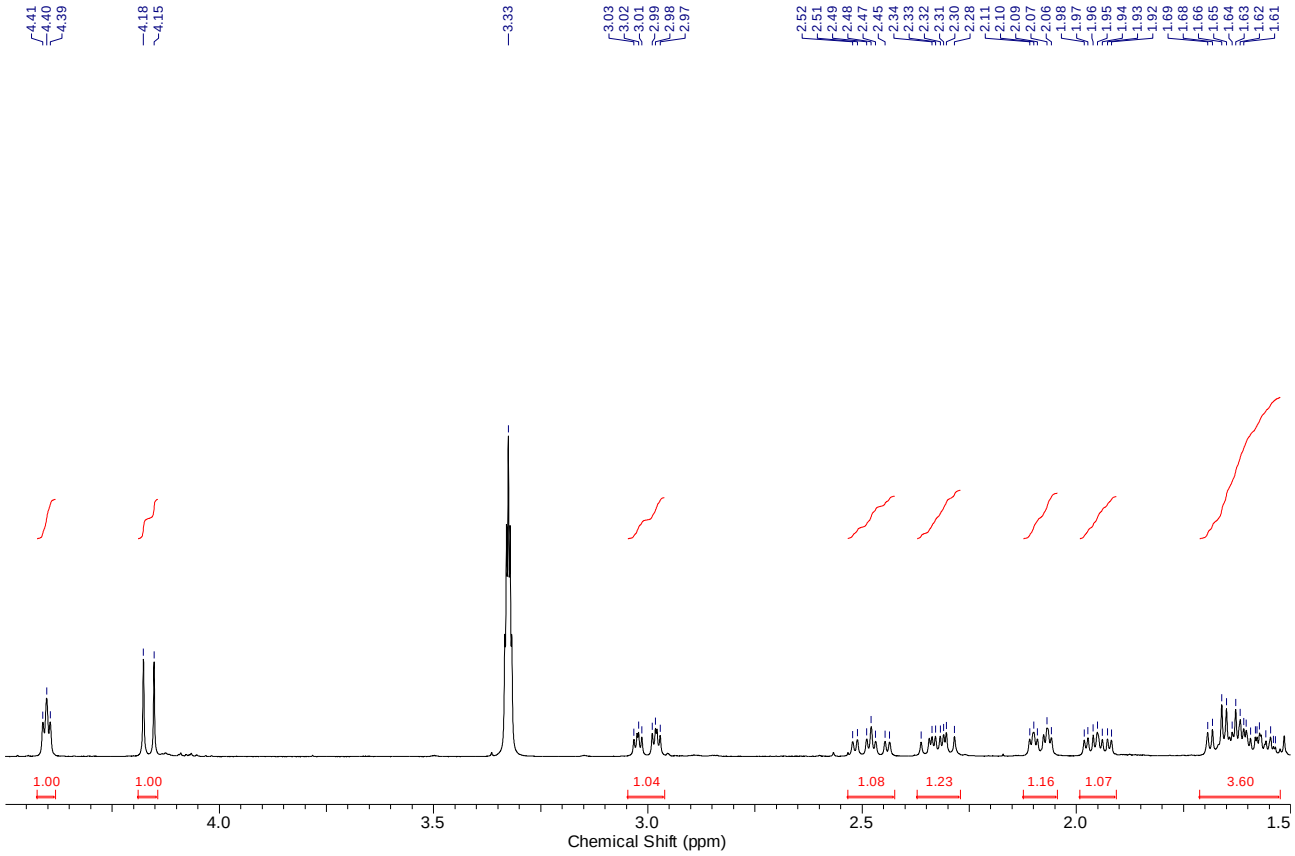
^{1}H NMR (400 MHz) spectrum of lingzhiol [(±)–**1-1**] in $(CD_3)_2CO$ (1.5 – 5.5 ppm)



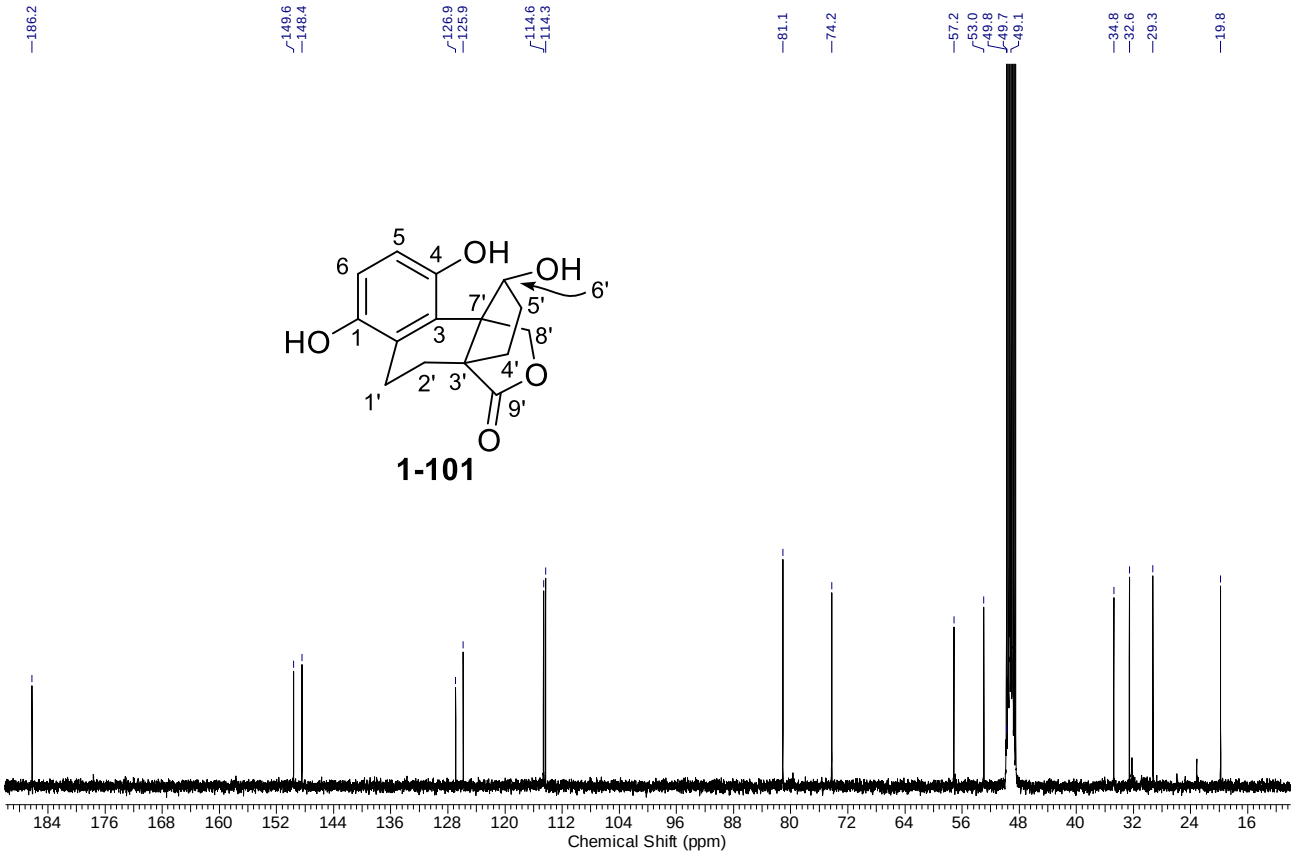
^{13}C NMR (100 MHz) spectrum of lingzhiol [(±)–**1-1**] in $(CD_3)_2CO$ (10 – 210 ppm)



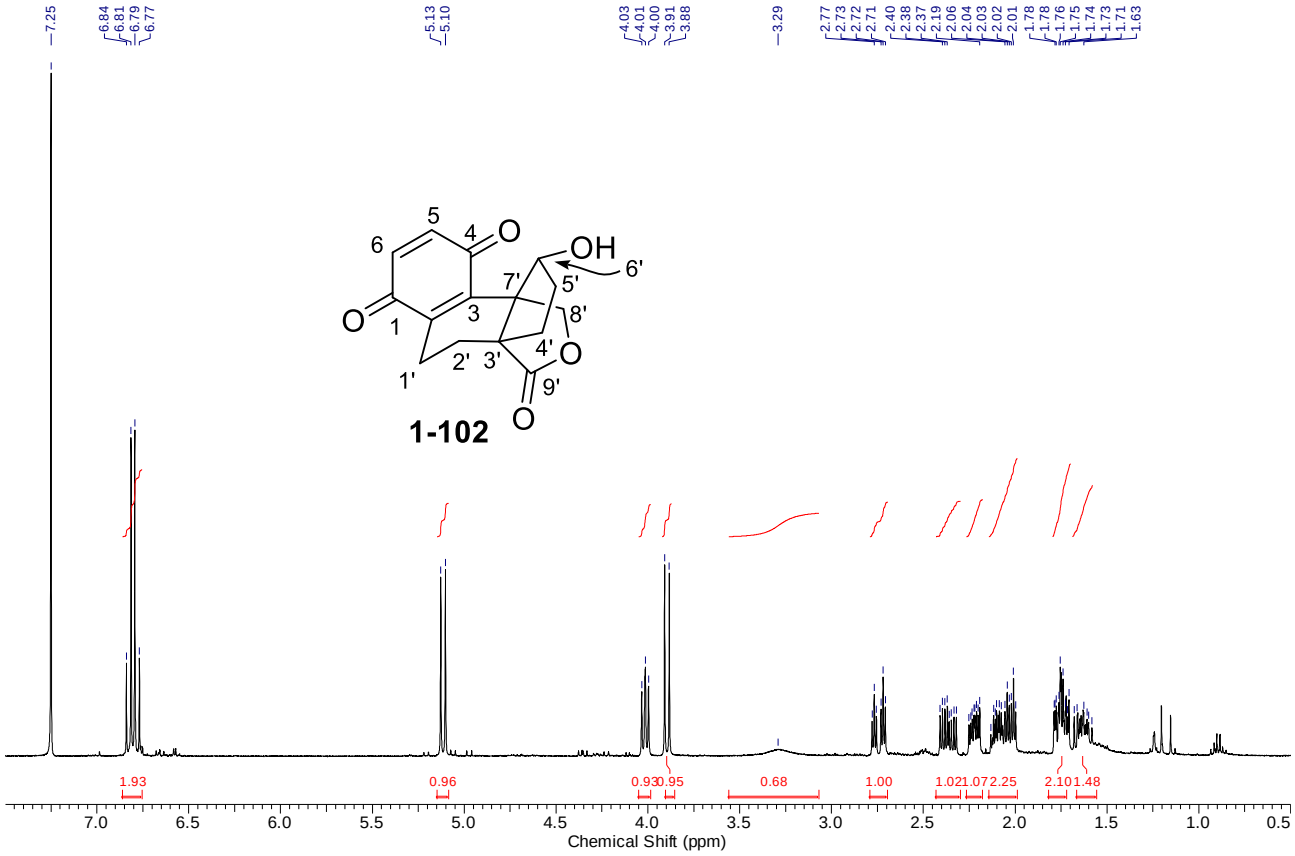
^{1}H NMR (400 MHz) spectrum of hydroquinone **1-101** in CD_3OD (0.5 – 7.5 ppm)



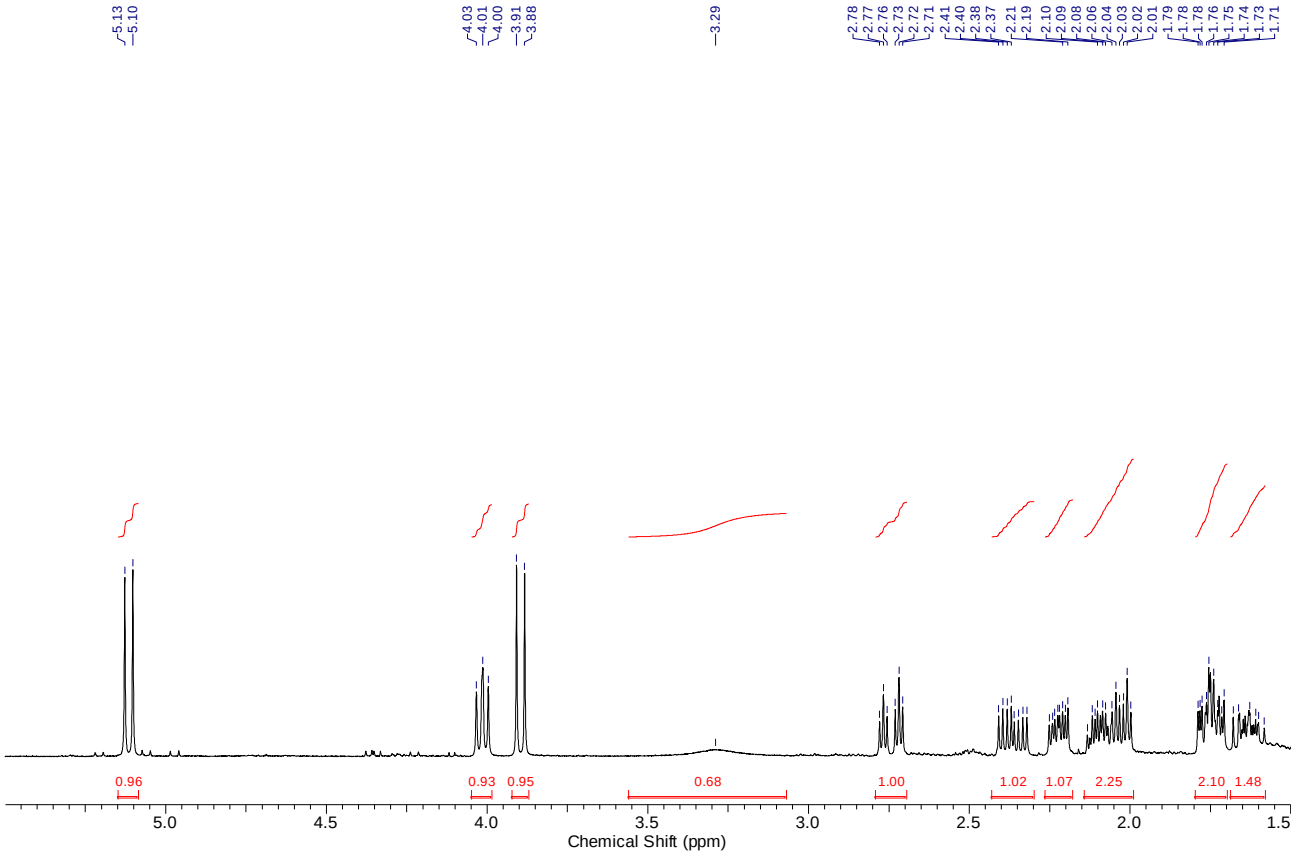
^{1}H NMR (400 MHz) spectrum of hydroquinone **1-101** in CD_3OD (1.5 – 4.5 ppm)



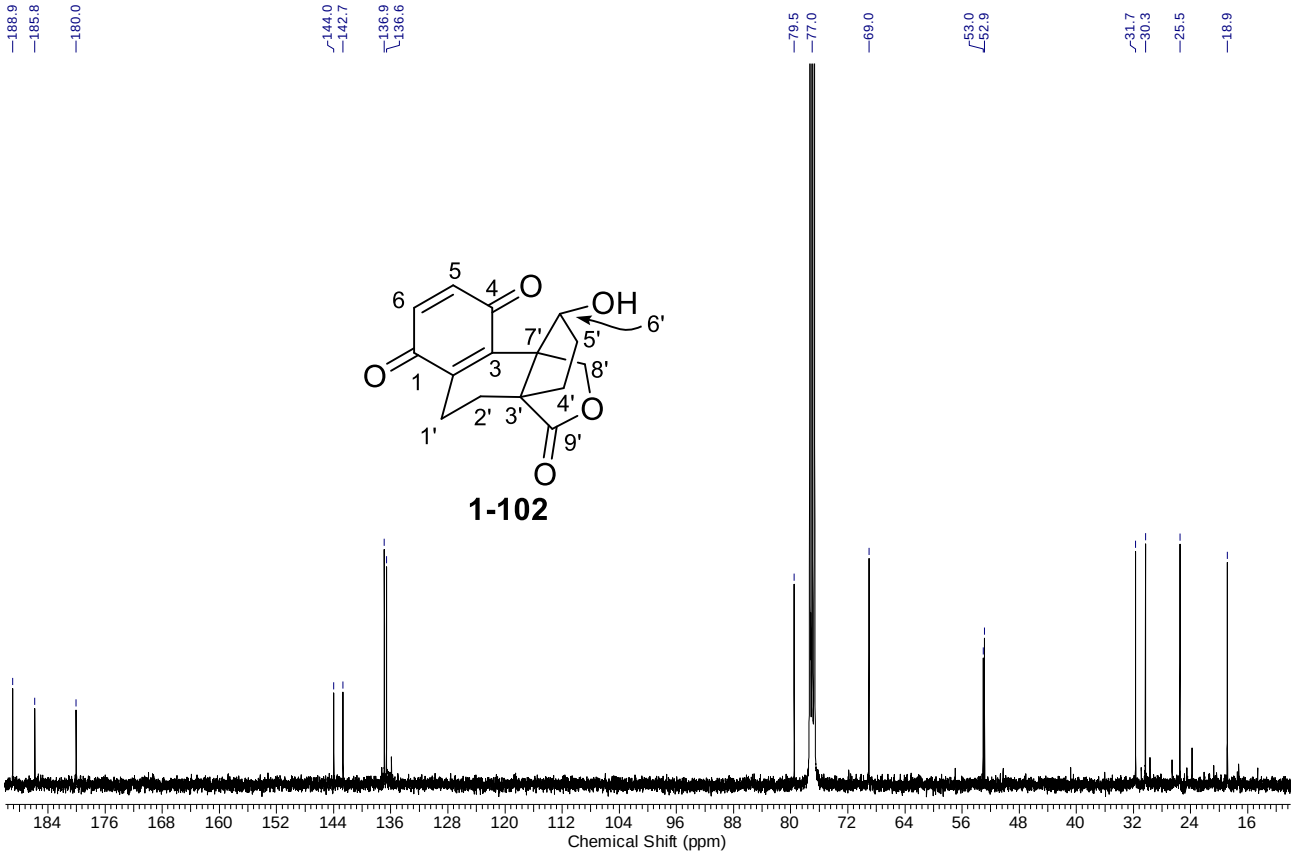
^{13}C NMR (100 MHz) spectrum of hydroquinone **1-101** in CD_3OD (10 – 190 ppm)



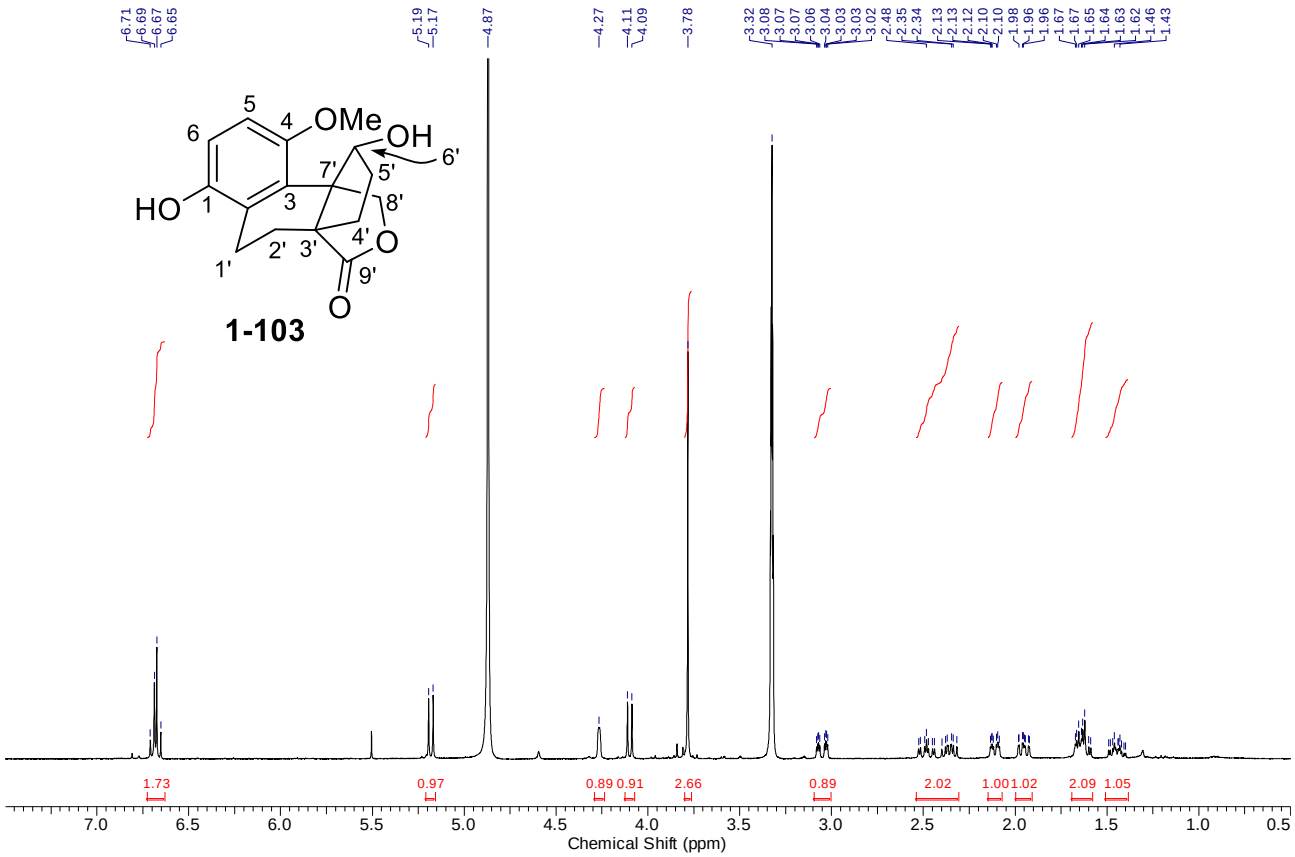
^{1}H NMR (400 MHz) spectrum of quinone **1-102** in $CDCl_3$ (0.5 – 7.5 ppm)



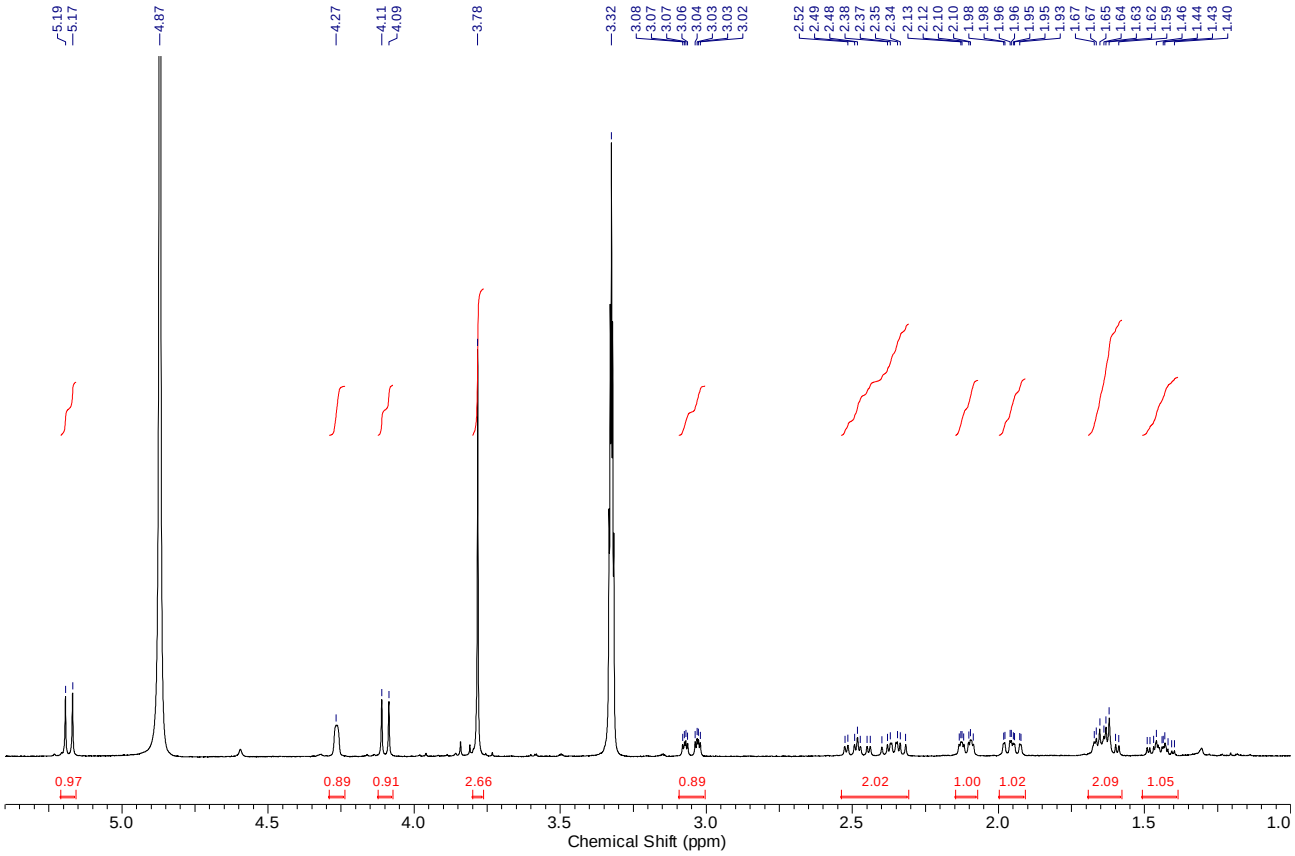
^{1}H NMR (400 MHz) spectrum of quinone **1-102** in $CDCl_3$ (1.5 – 5.5 ppm)



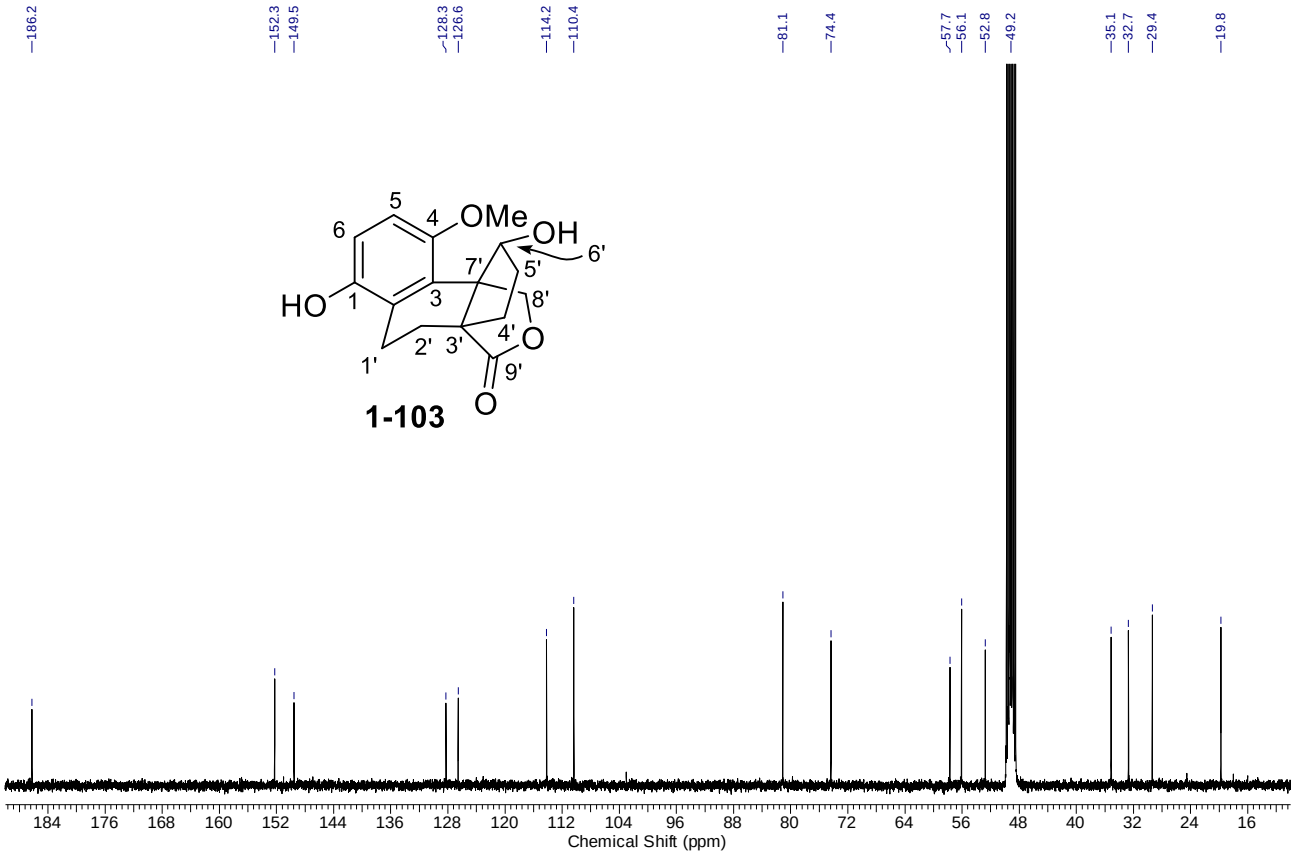
^{13}C NMR (100 MHz) spectrum of quinone **1-102** in $CDCl_3$ (10 – 190 ppm)



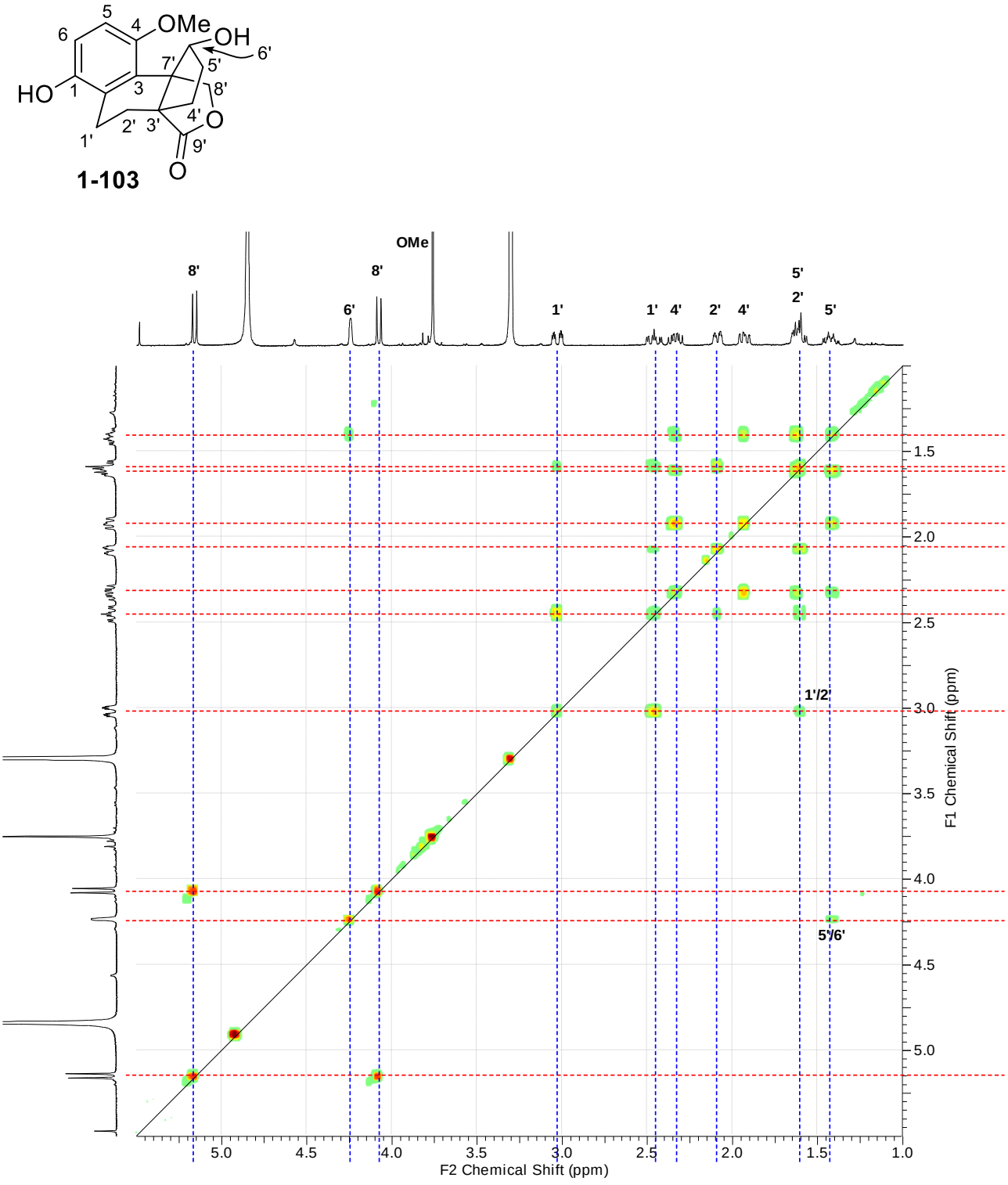
^{1}H NMR (400 MHz) spectrum of lingzhiol analog **1-103** in CD_3OD (0.5 – 7.5 ppm)



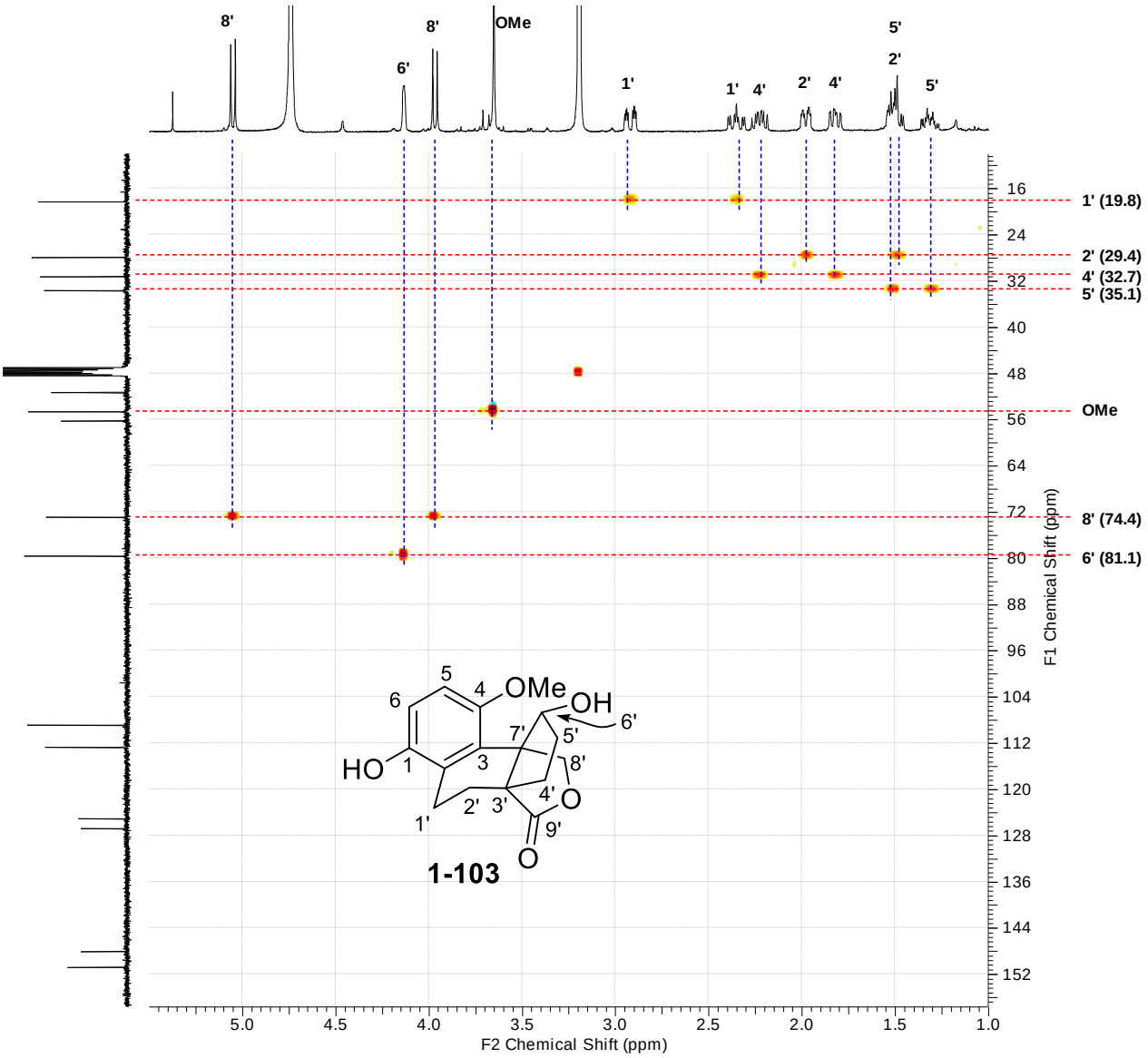
^{1}H NMR (400 MHz) spectrum of lingzhiol analog (phenol) **1-103** in CD_3OD (1.0 – 5.5 ppm)



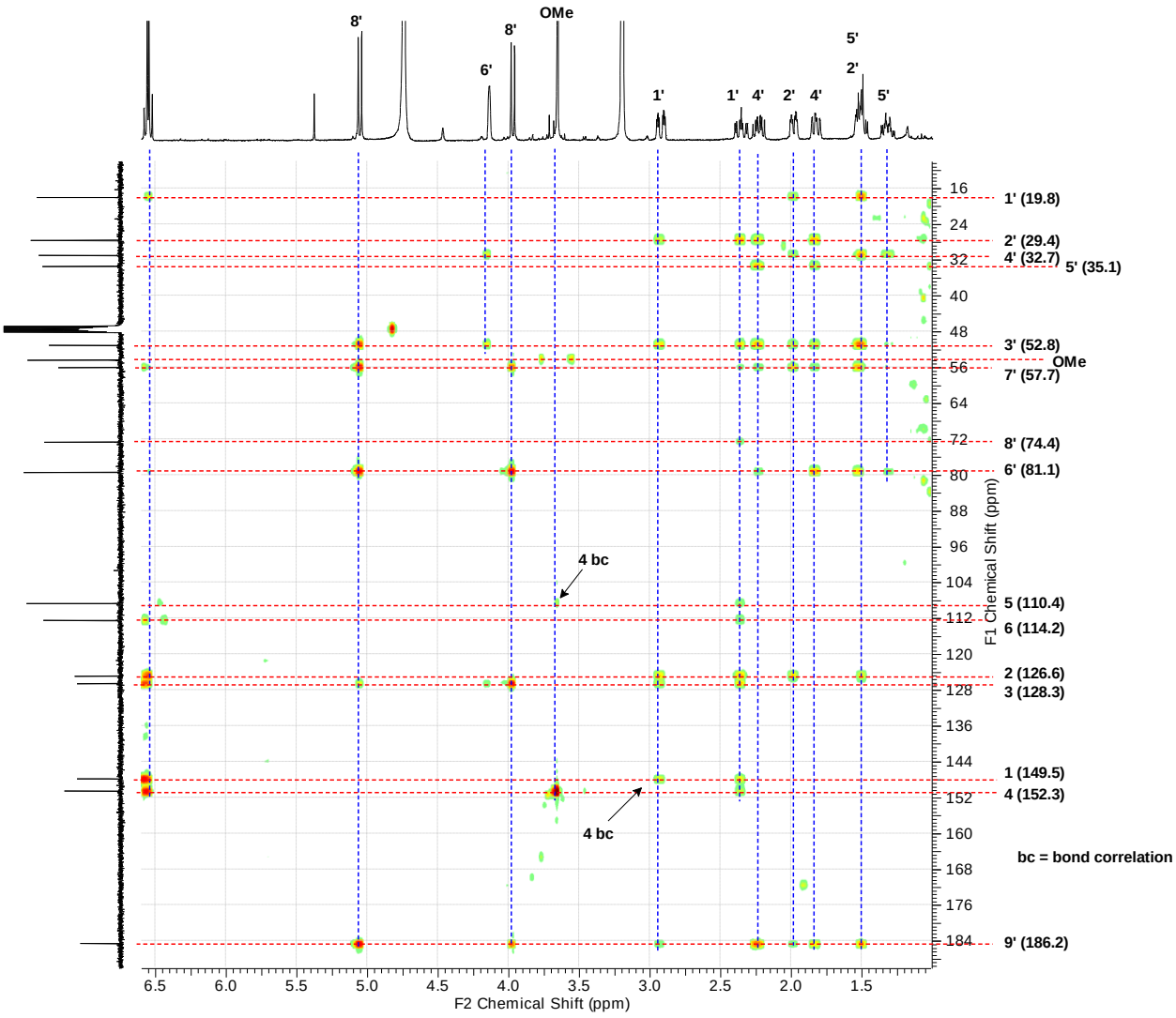
^{13}C NMR (100 MHz) spectrum of lingzhiol analog **1-103** in CD_3OD (10 – 190 ppm)



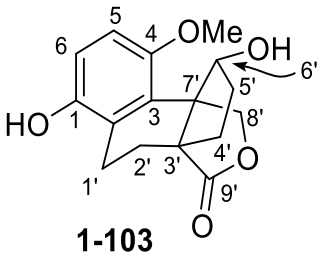
COSY (400 MHz) spectrum of lingzhiol analog **1-103** in CD_3OD (1.0 – 5.5 ppm)



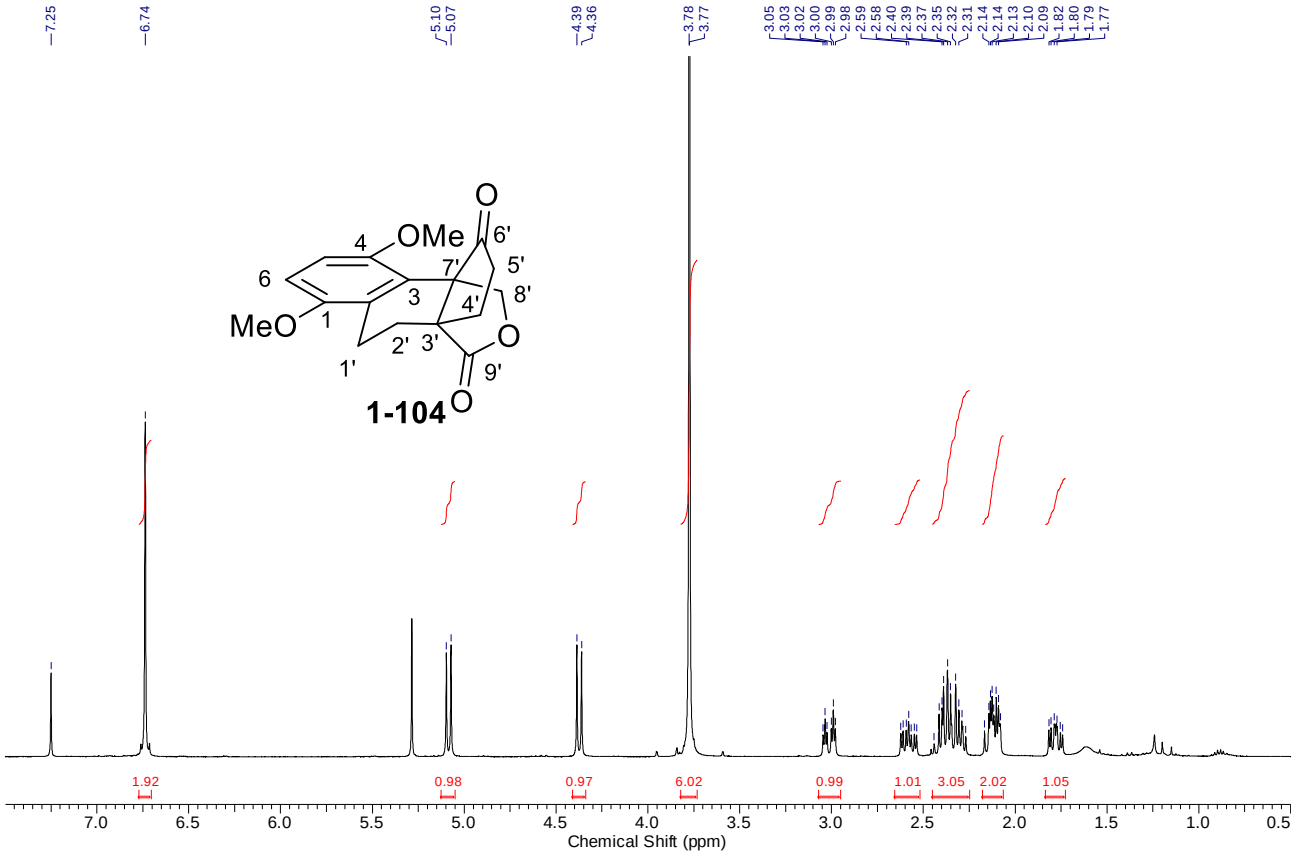
HSQC spectrum of lingzhiol analog **1-103** (1.0 – 5.5 ppm, 10 – 160 ppm) in CD_3OD



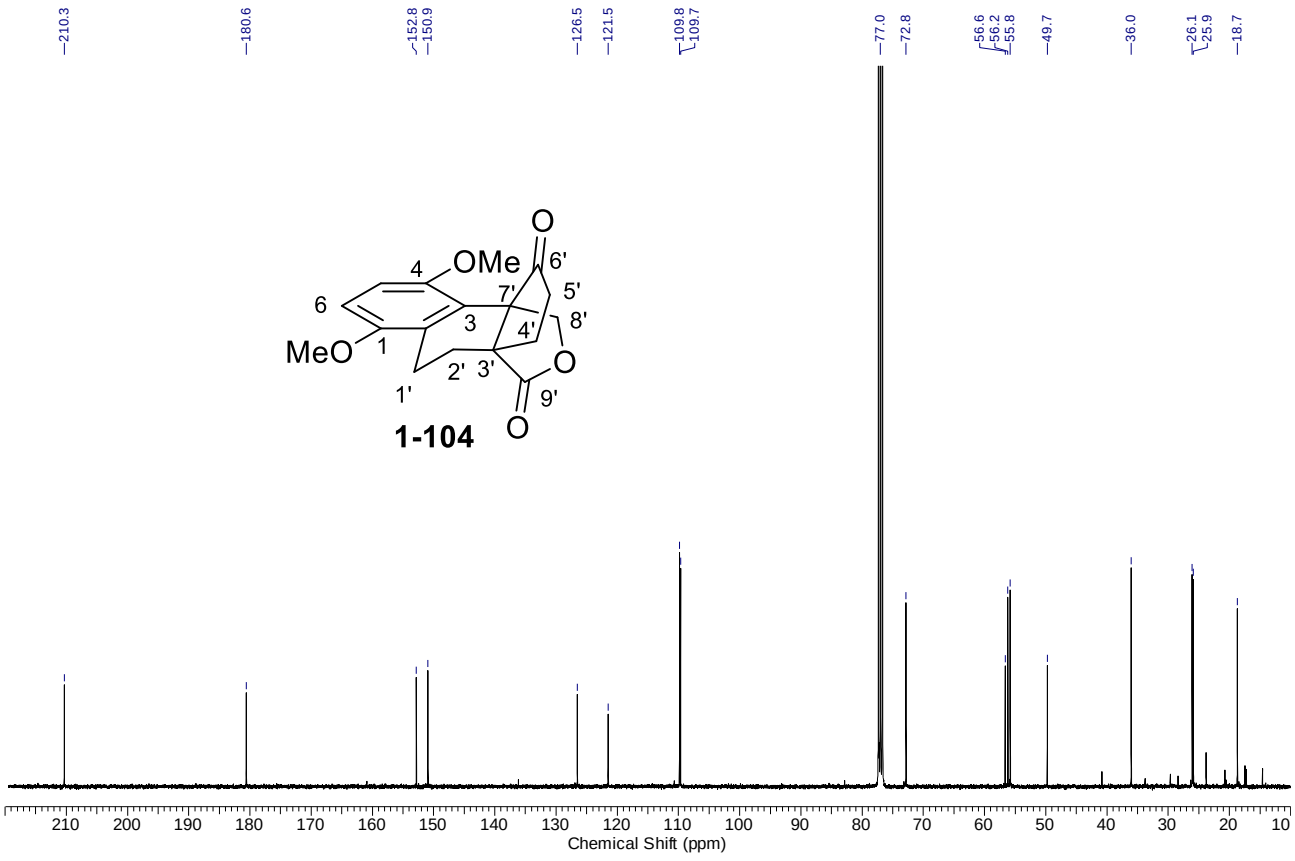
HMBC spectrum of lingzhiol analog **1-103** (1.0 – 6.6 ppm, 10 – 190 ppm) in CD_3OD



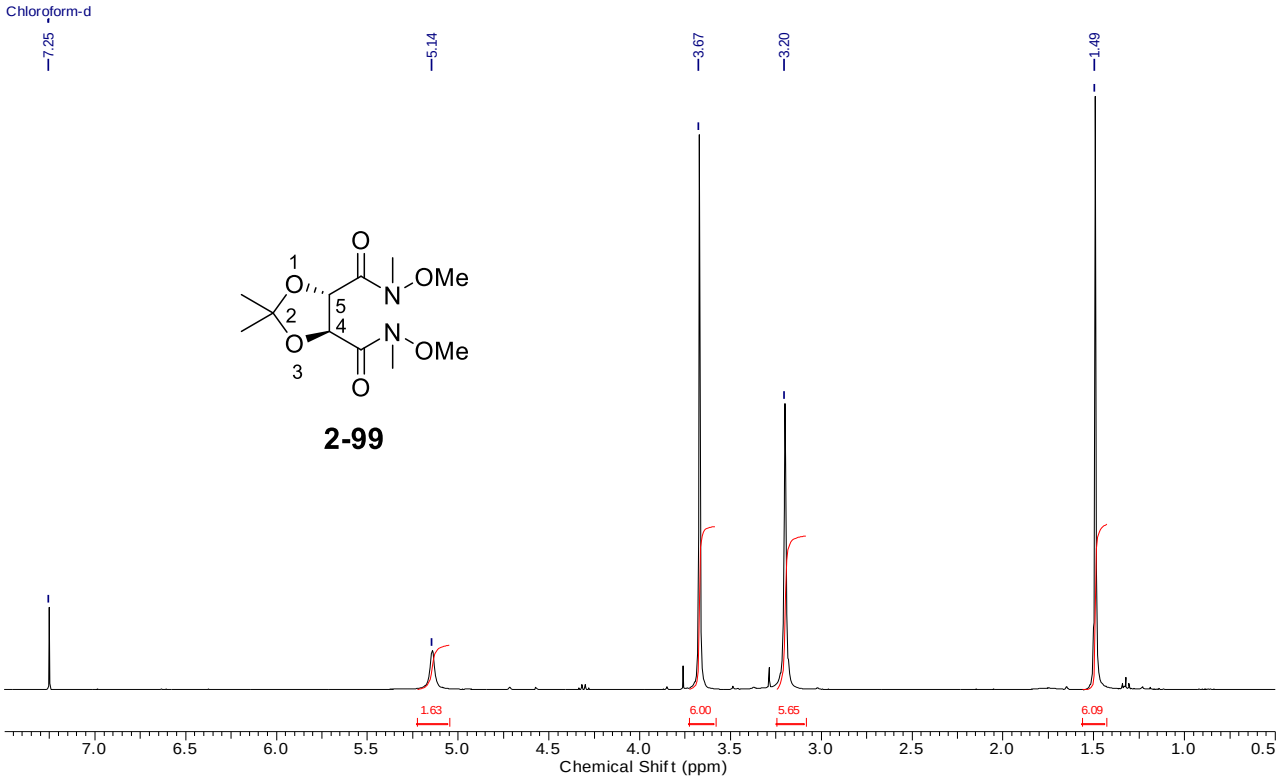
1-103



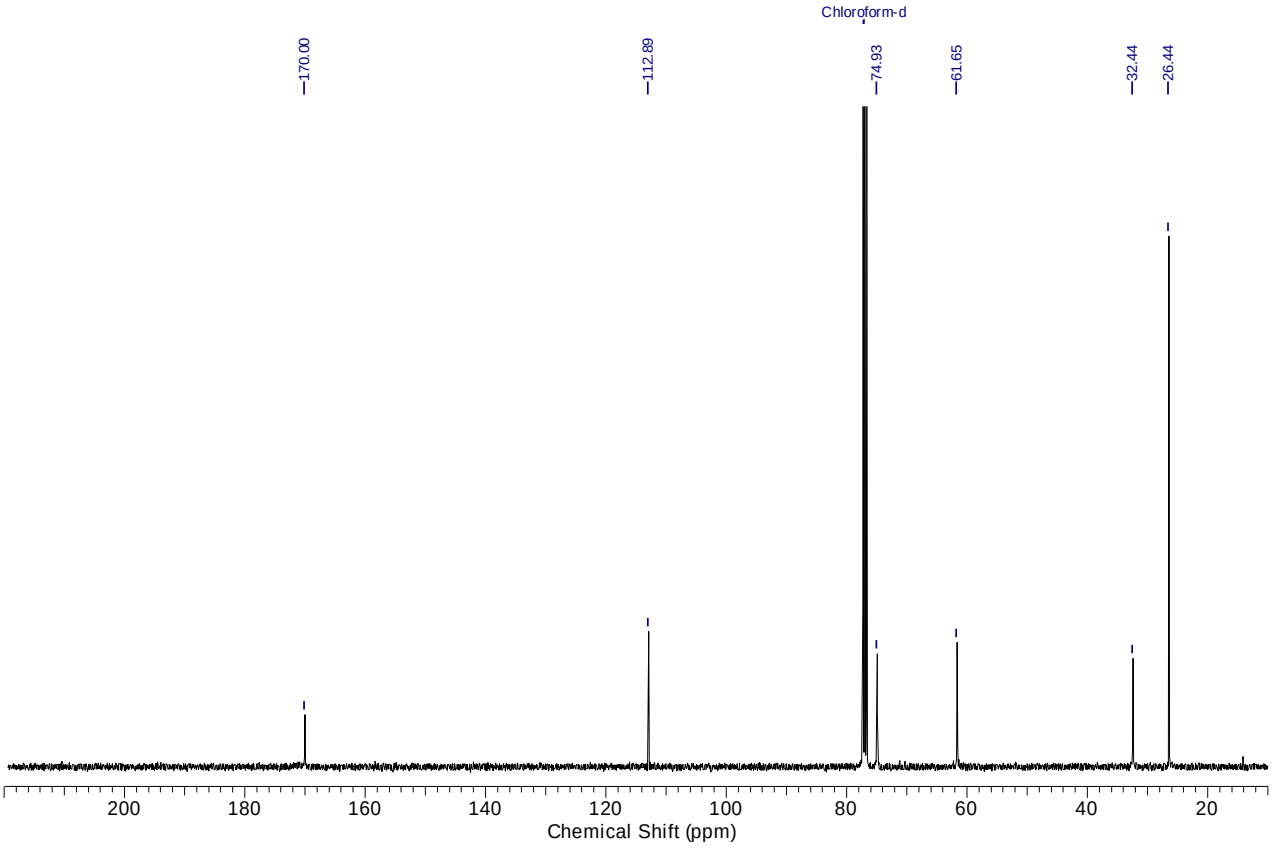
^{1}H NMR (400 MHz) spectrum of ketone **1-104** in $CDCl_3$ (0.5 – 7.5 ppm)



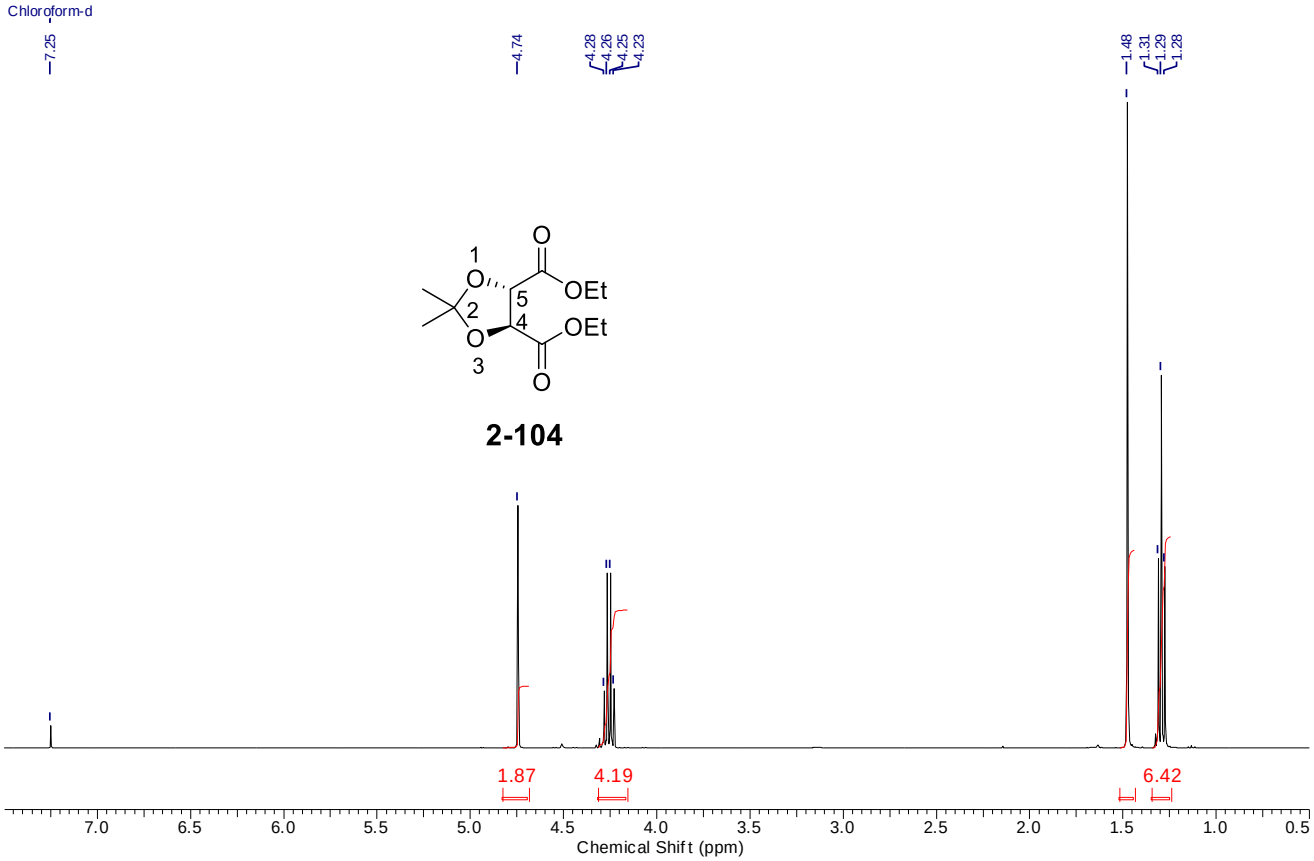
^{13}C NMR (100 MHz) spectrum of ketone **1-104** in $CDCl_3$ (0.5 – 7.5 ppm)



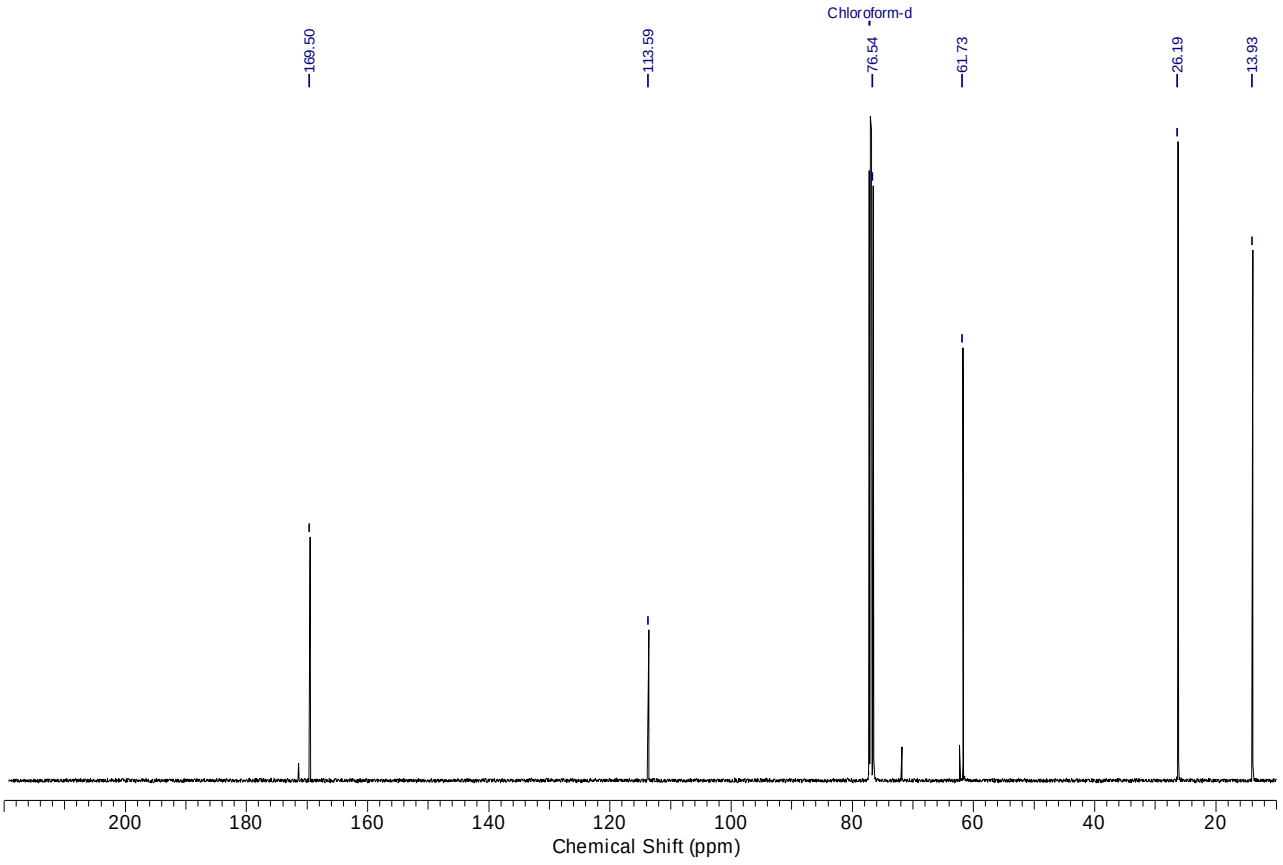
^{1}H NMR (400 MHz) spectrum of bis-Weinreb amide **2-99** in $CDCl_3$ (0.5 – 7.5 ppm)



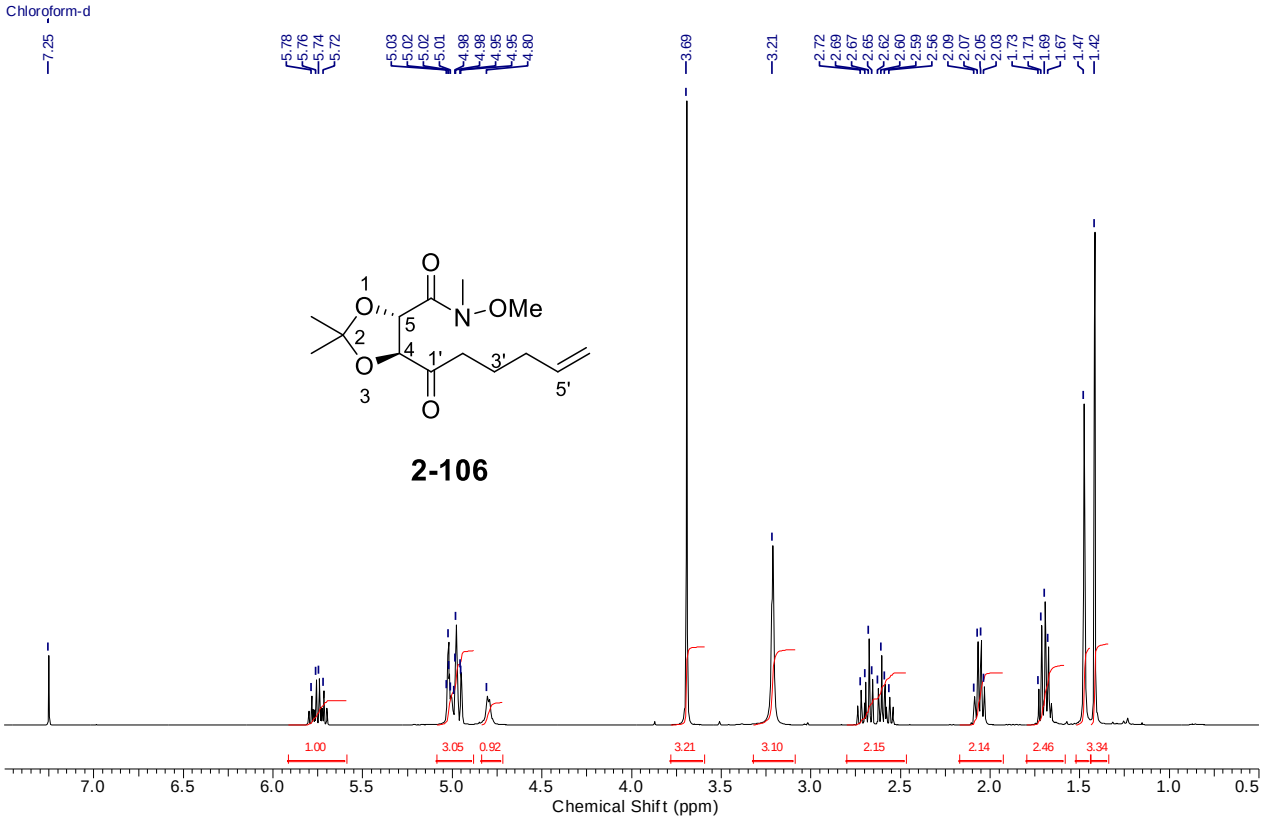
^{13}C NMR (100 MHz) spectrum of bis-Weinreb amide **2-99** in $CDCl_3$ (10 – 220 ppm)



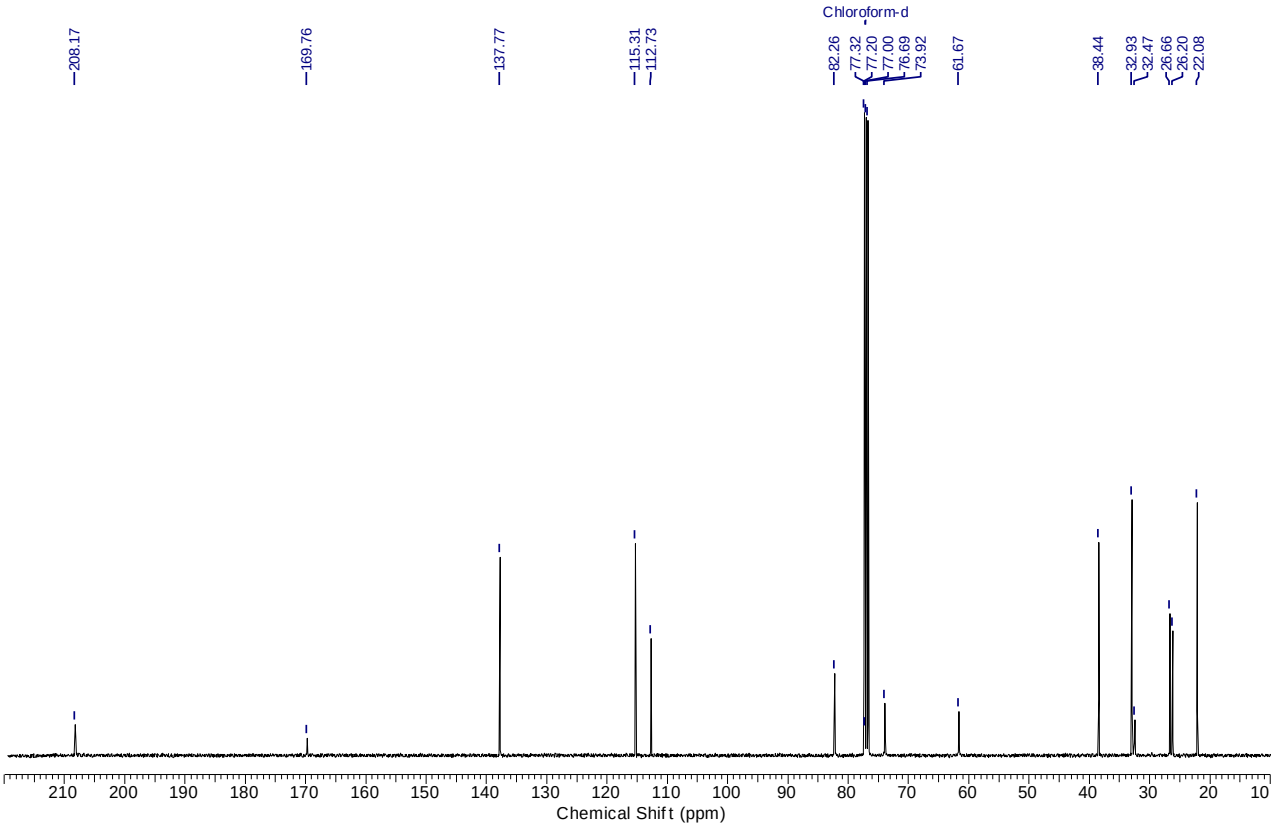
^{1}H NMR (400 MHz) spectrum of ketone **2-104** in $CDCl_3$ (0.5 – 7.5 ppm)



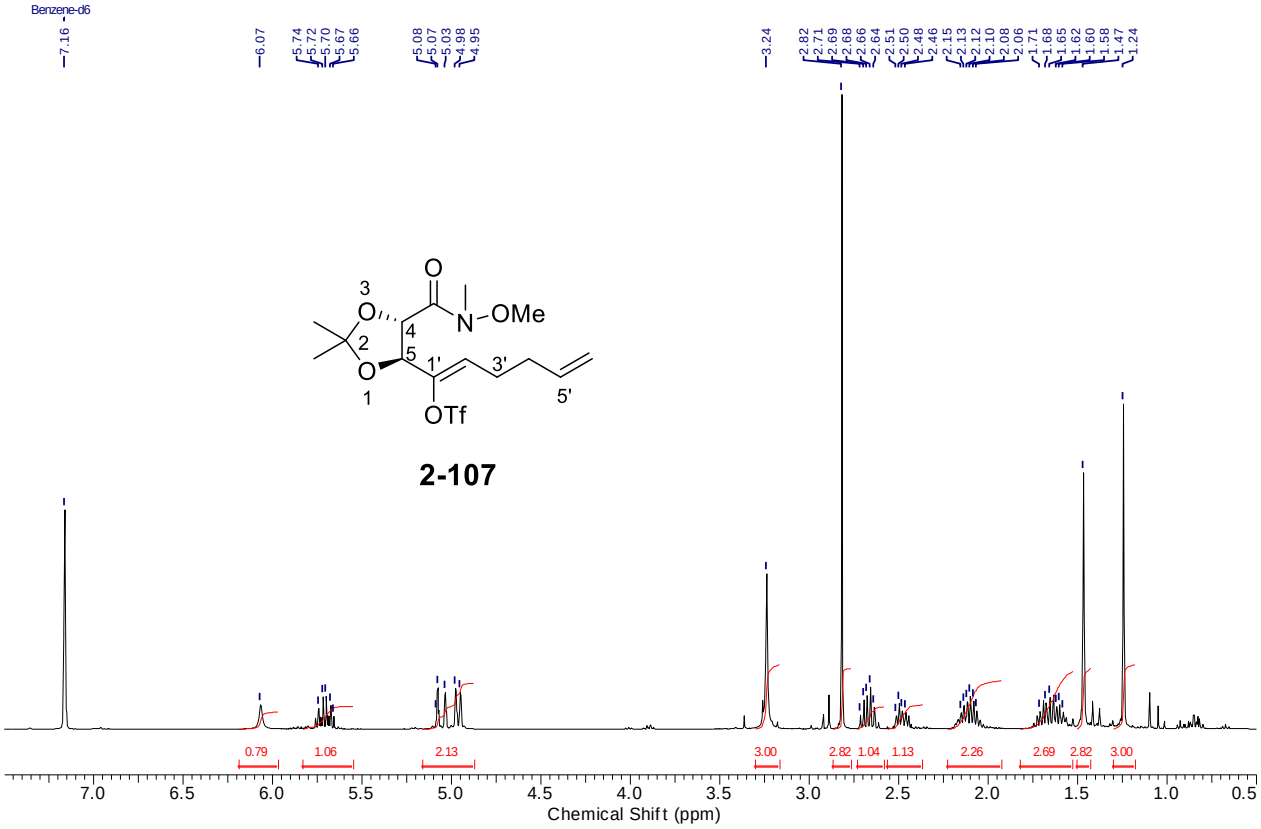
^{13}C NMR (100 MHz) spectrum of ketone **2-104** in $CDCl_3$ (10 – 220 ppm)



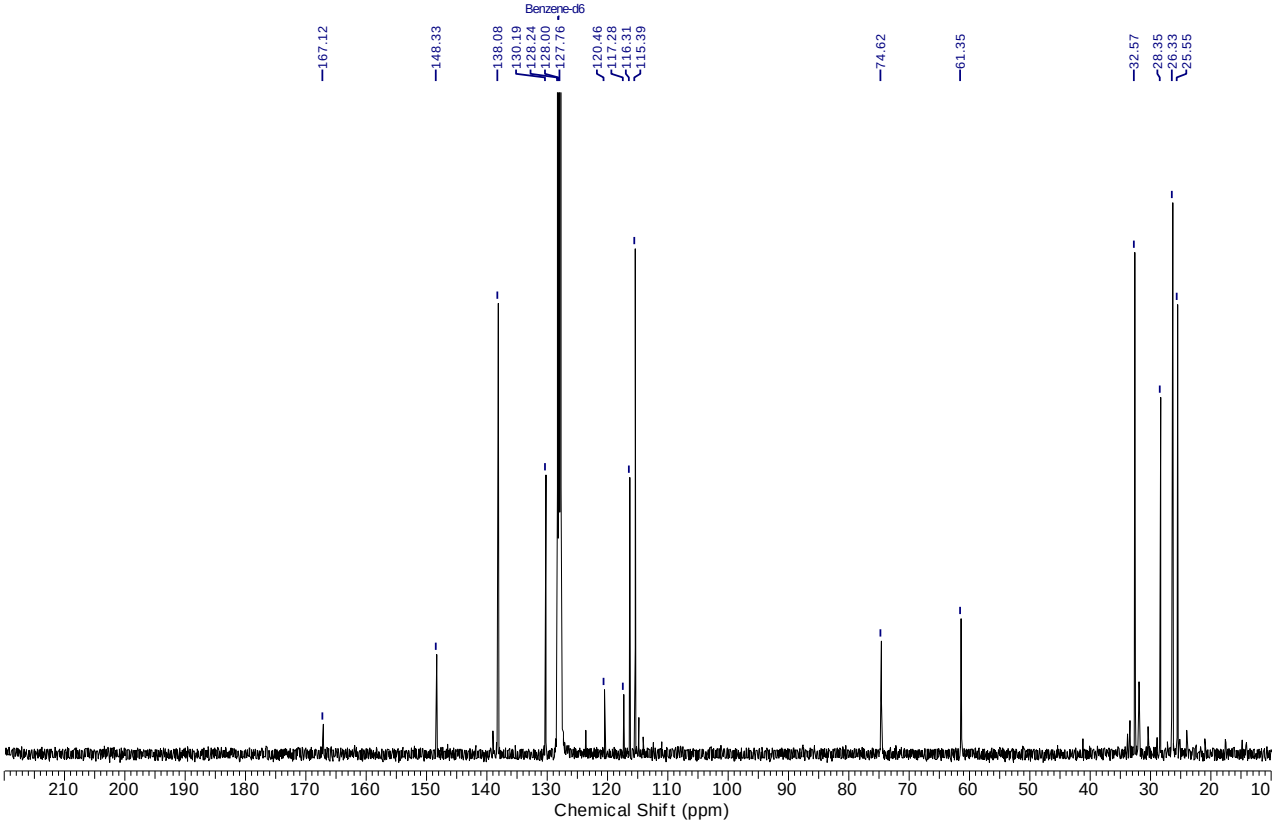
^{1}H NMR (400 MHz) spectrum of mono alkylation **2-106** in $CDCl_3$ (0.5 – 7.5 ppm)



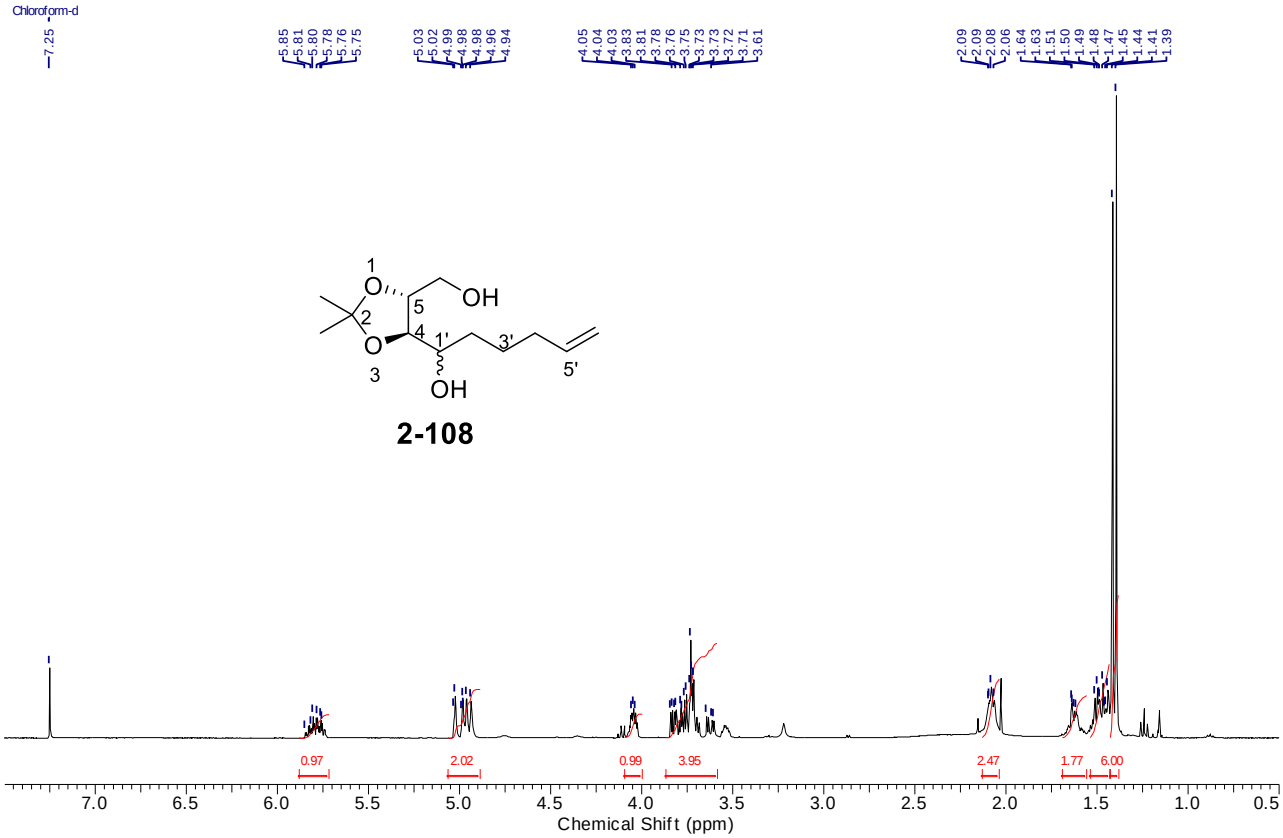
^{13}C NMR (100 MHz) spectrum of mono alkylation **2-106** in $CDCl_3$ (10 – 220 ppm)



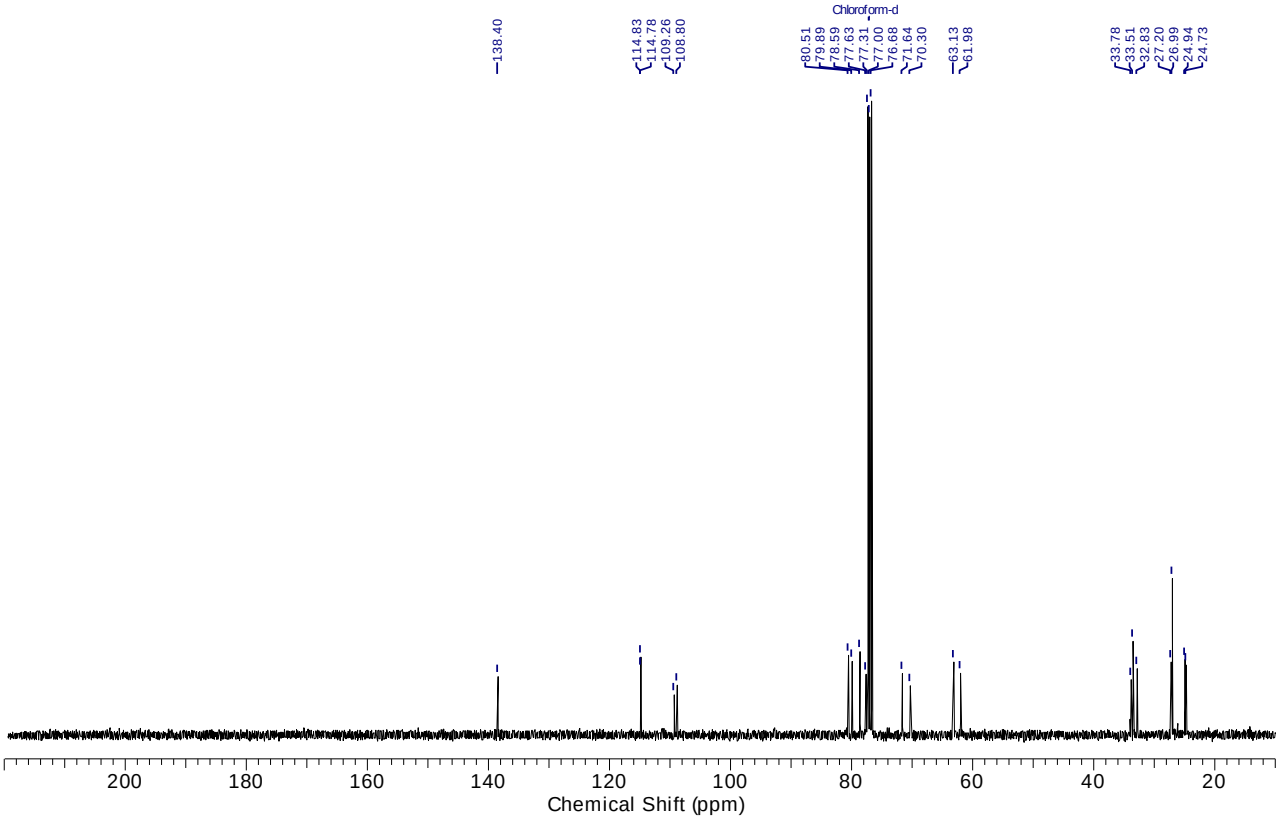
^{1}H NMR (400 MHz) spectrum of vinyl triflate **2-107** in $CDCl_3$ (0.5 – 7.5 ppm)



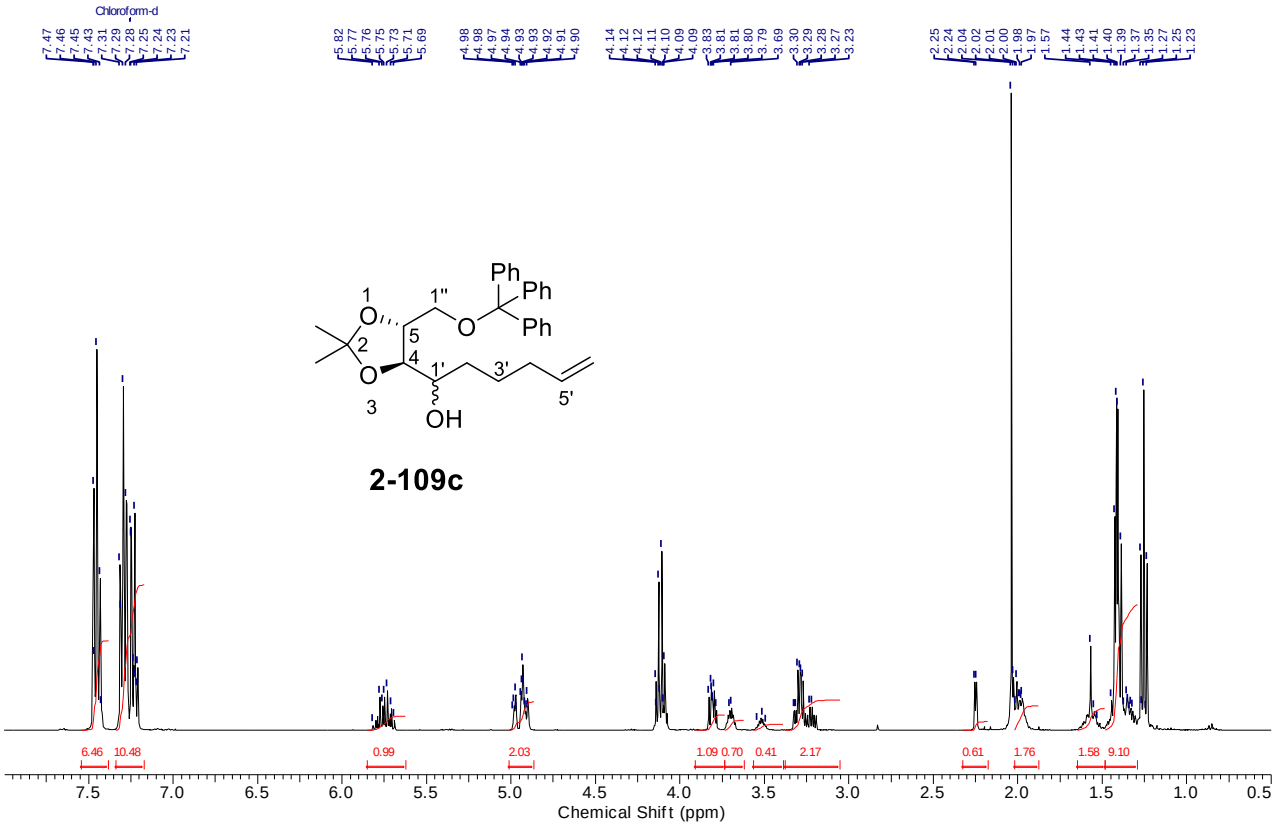
^{13}C NMR (100 MHz) spectrum of vinyl triflate **2-107** in $CDCl_3$ (10 – 220 ppm)



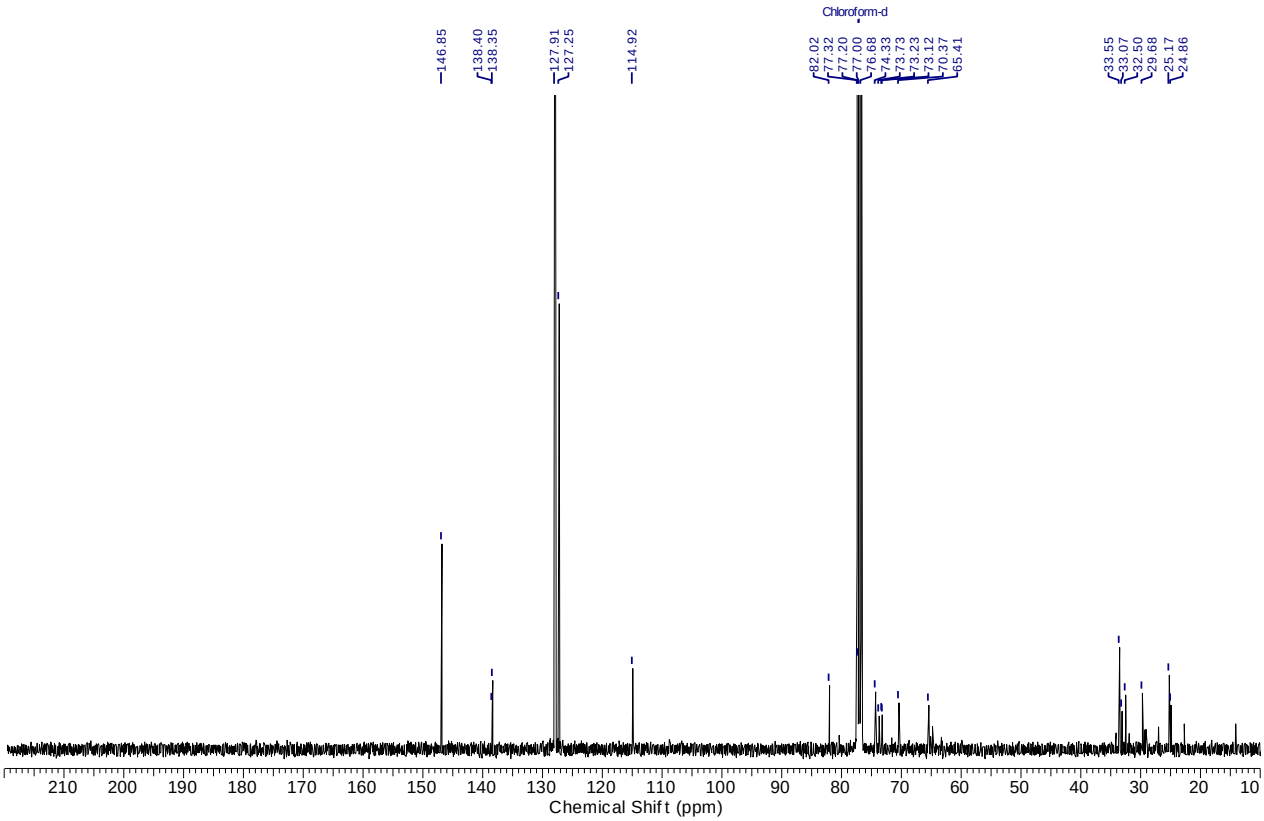
^{1}H NMR (400 MHz) spectrum of alcohols **2-108** in $CDCl_3$ (0.5 – 7.5 ppm)



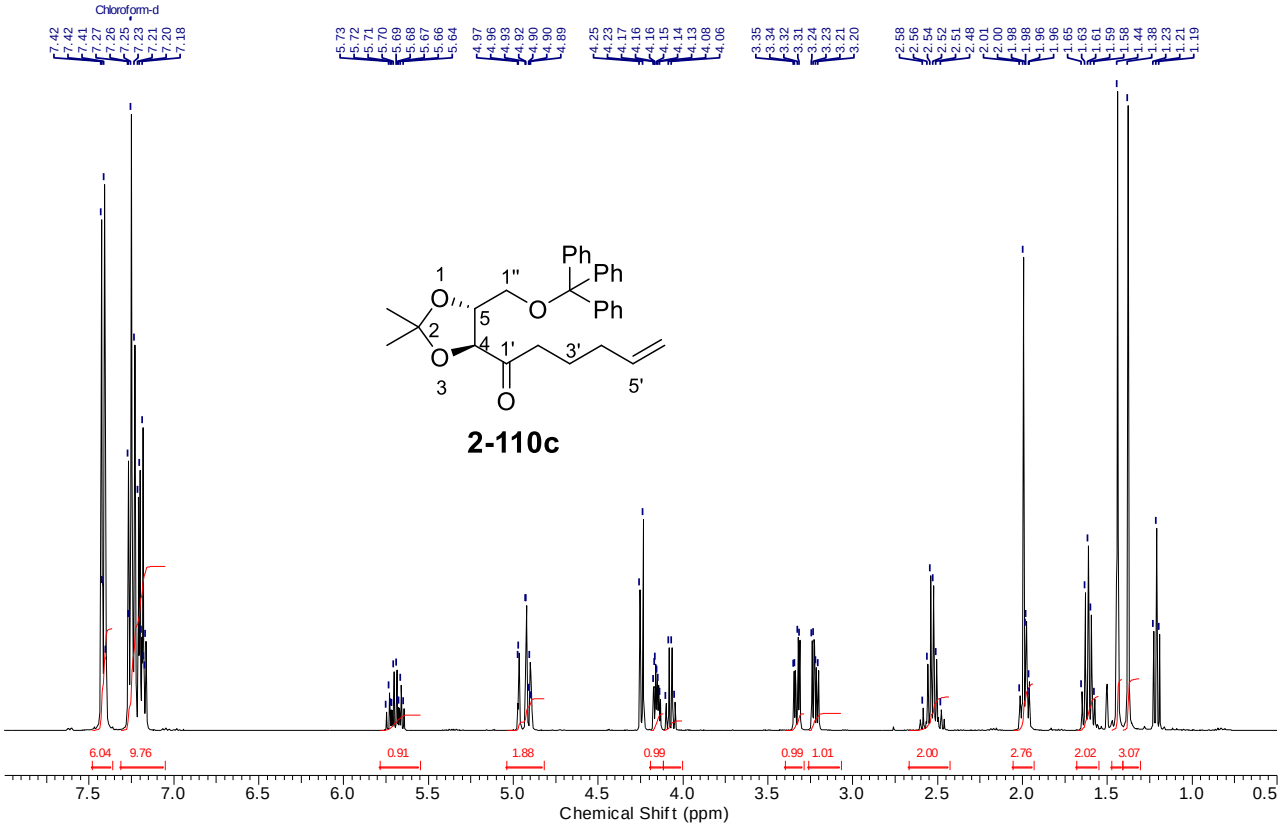
^{13}C NMR (100 MHz) spectrum of alcohols **2-108** in $CDCl_3$ (10 – 220 ppm)



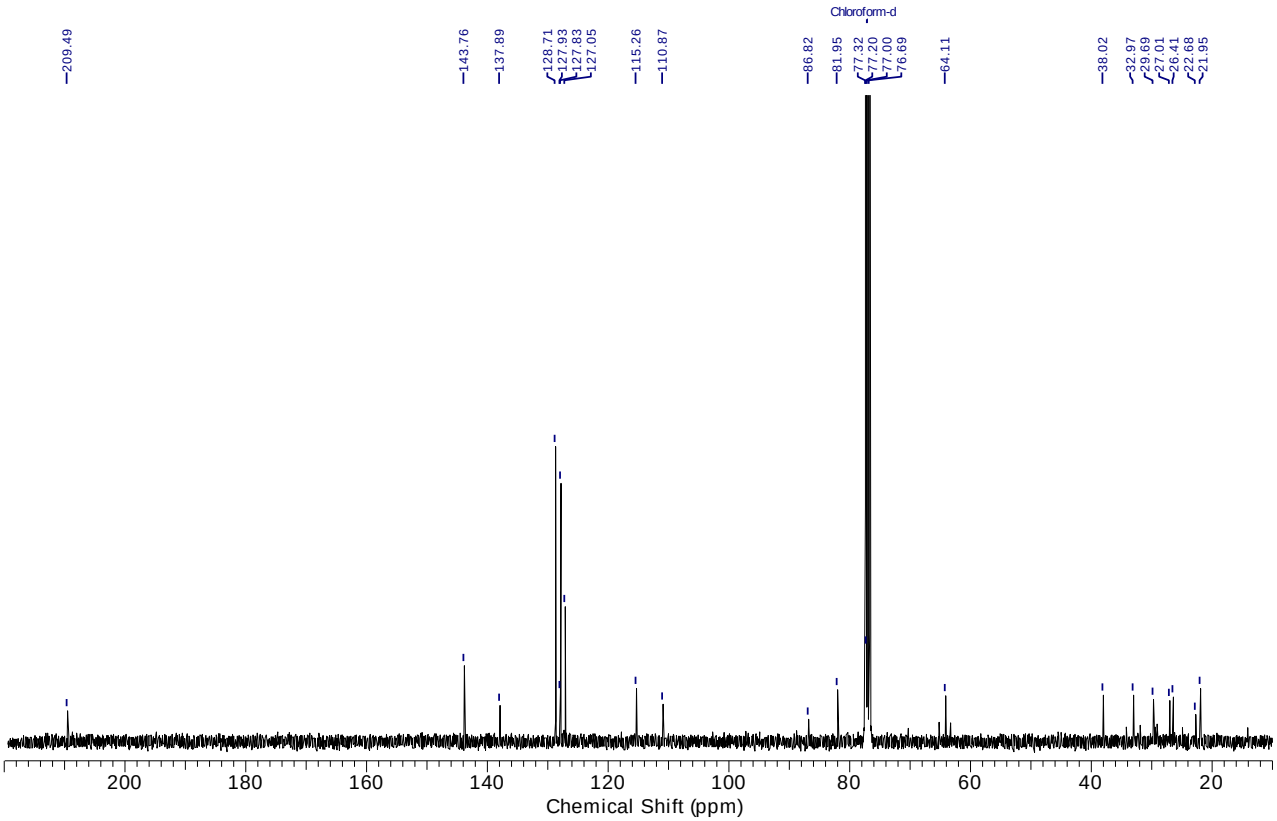
^{1}H NMR (400 MHz) spectrum of alcohol **2-109c** in $CDCl_3$ (0.5 – 7.5 ppm)



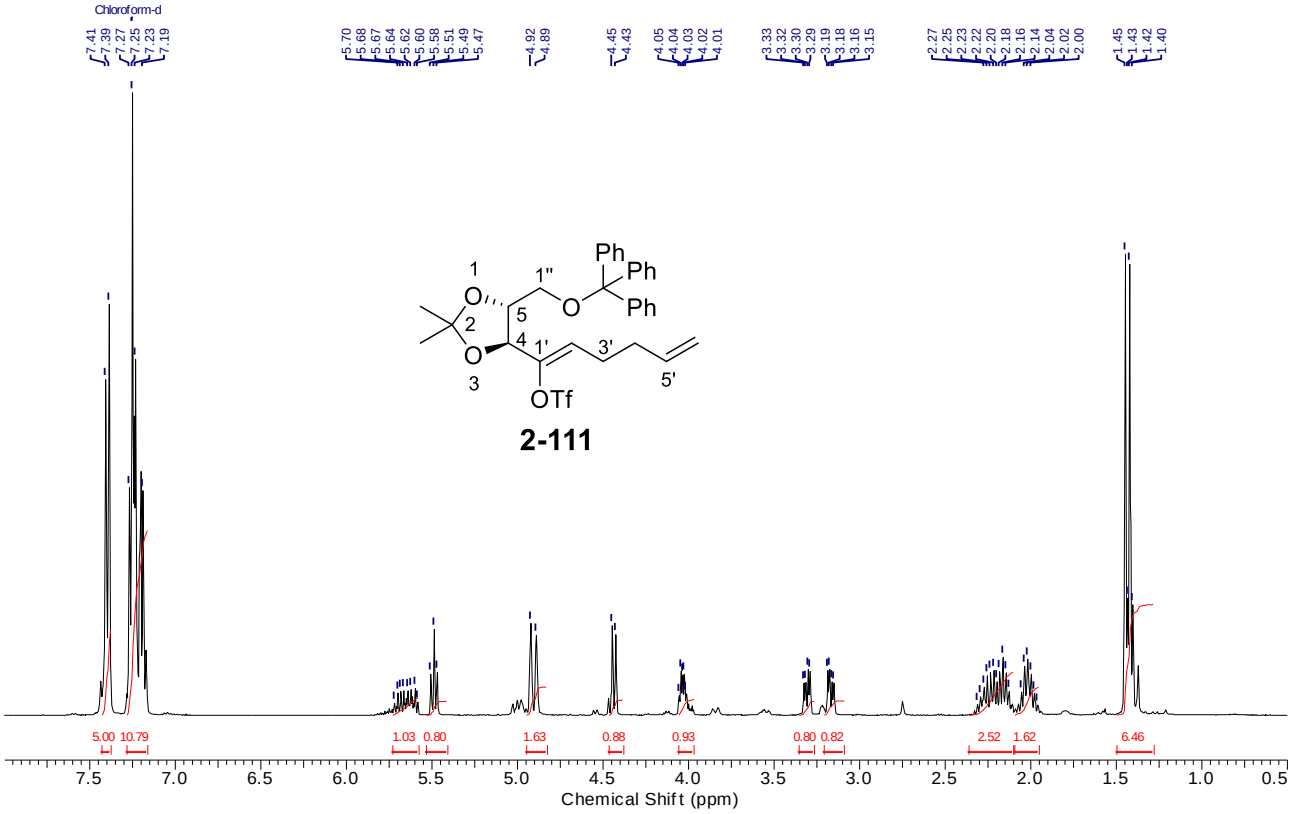
^{13}C NMR (100 MHz) spectrum of alcohol **2-109c** in $CDCl_3$ (10 – 220 ppm)



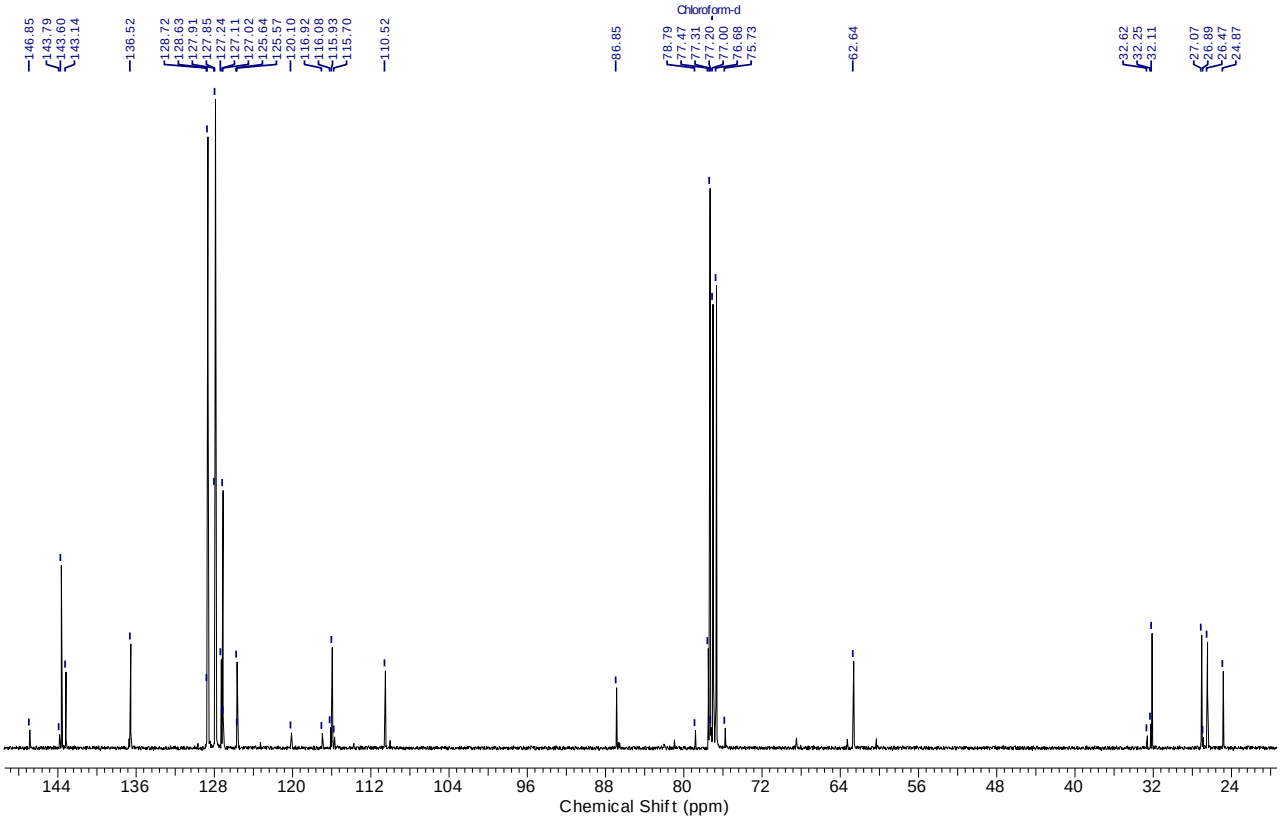
^{1}H NMR (400 MHz) spectrum of trityl ether **2-110c** in $CDCl_3$ (0.5 – 7.5 ppm)



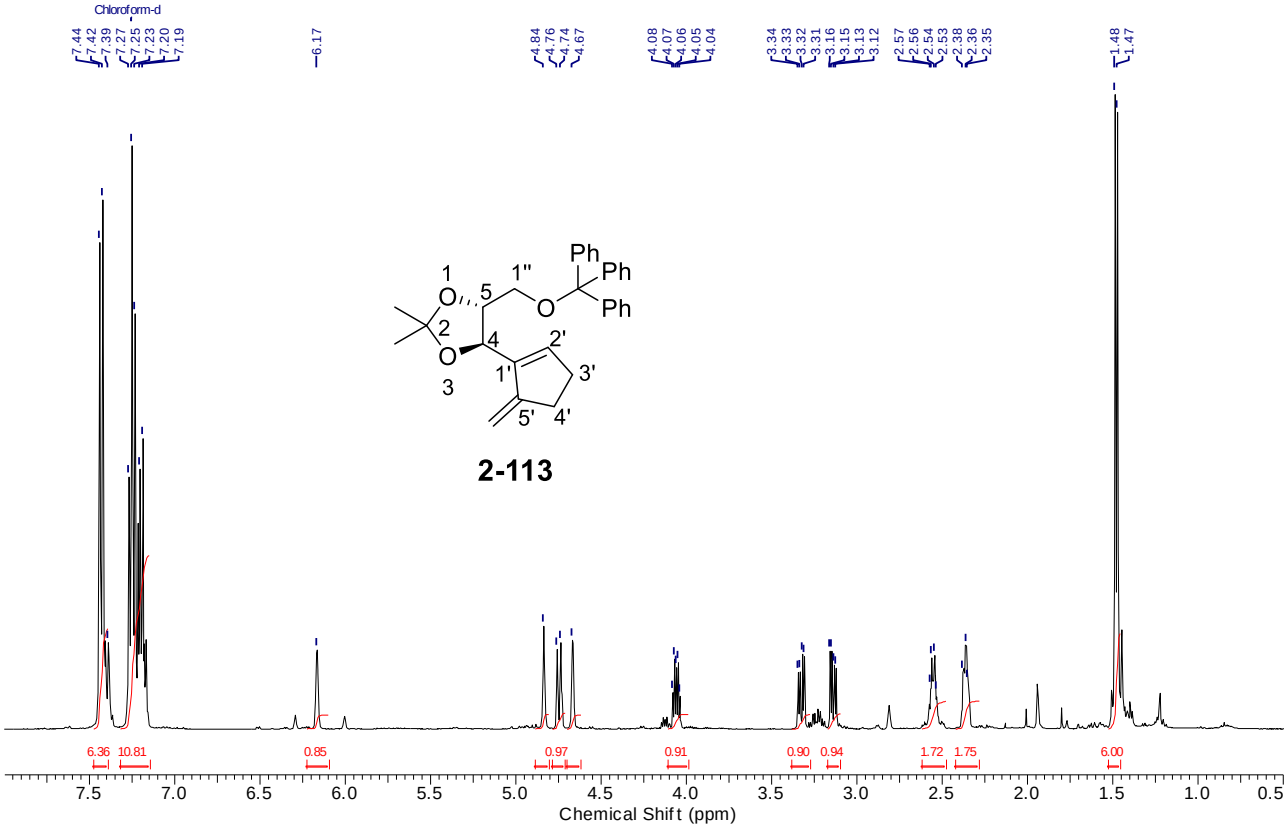
^{13}C NMR (100 MHz) spectrum of trityl ether **2-110c** in $CDCl_3$ (10 – 220 ppm)



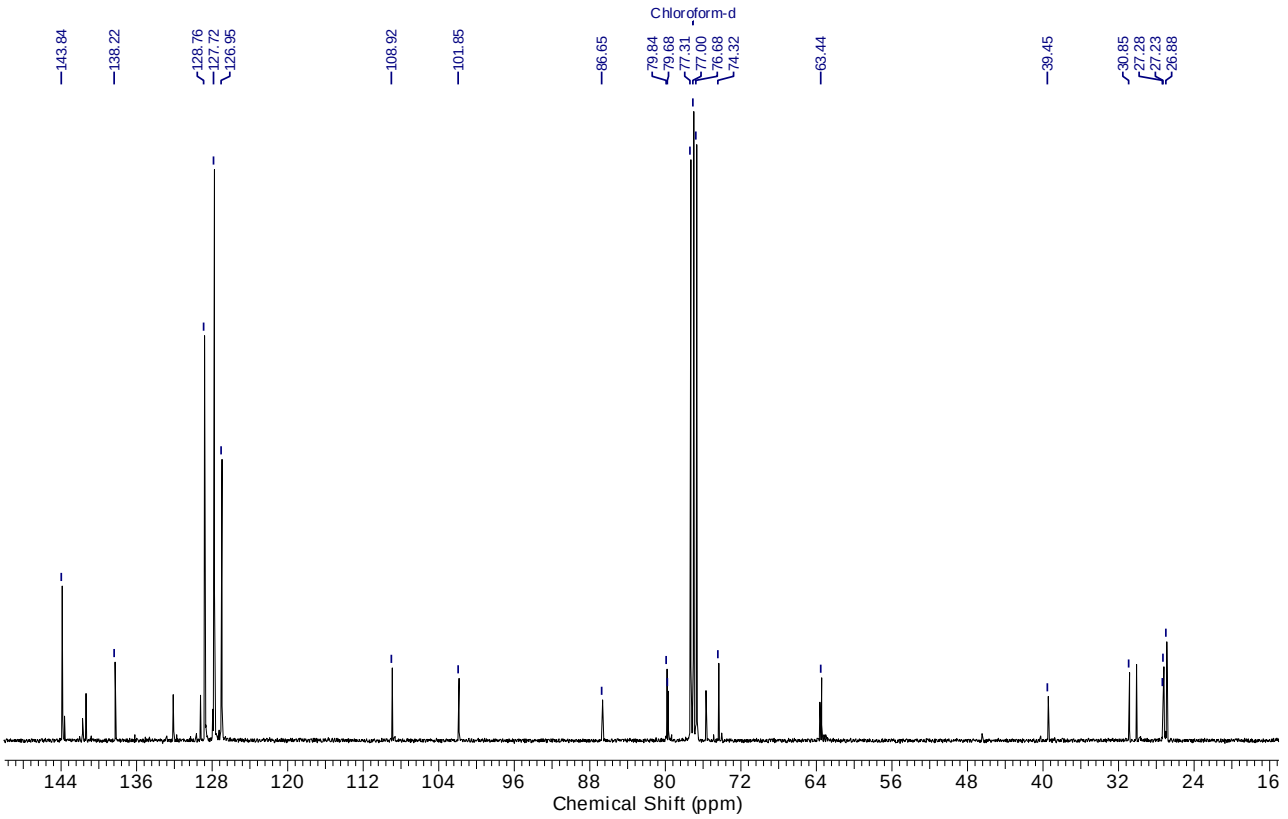
^{1}H NMR (400 MHz) spectrum of vinyl triflate **2-111** in $CDCl_3$ (0.5 – 8 ppm)



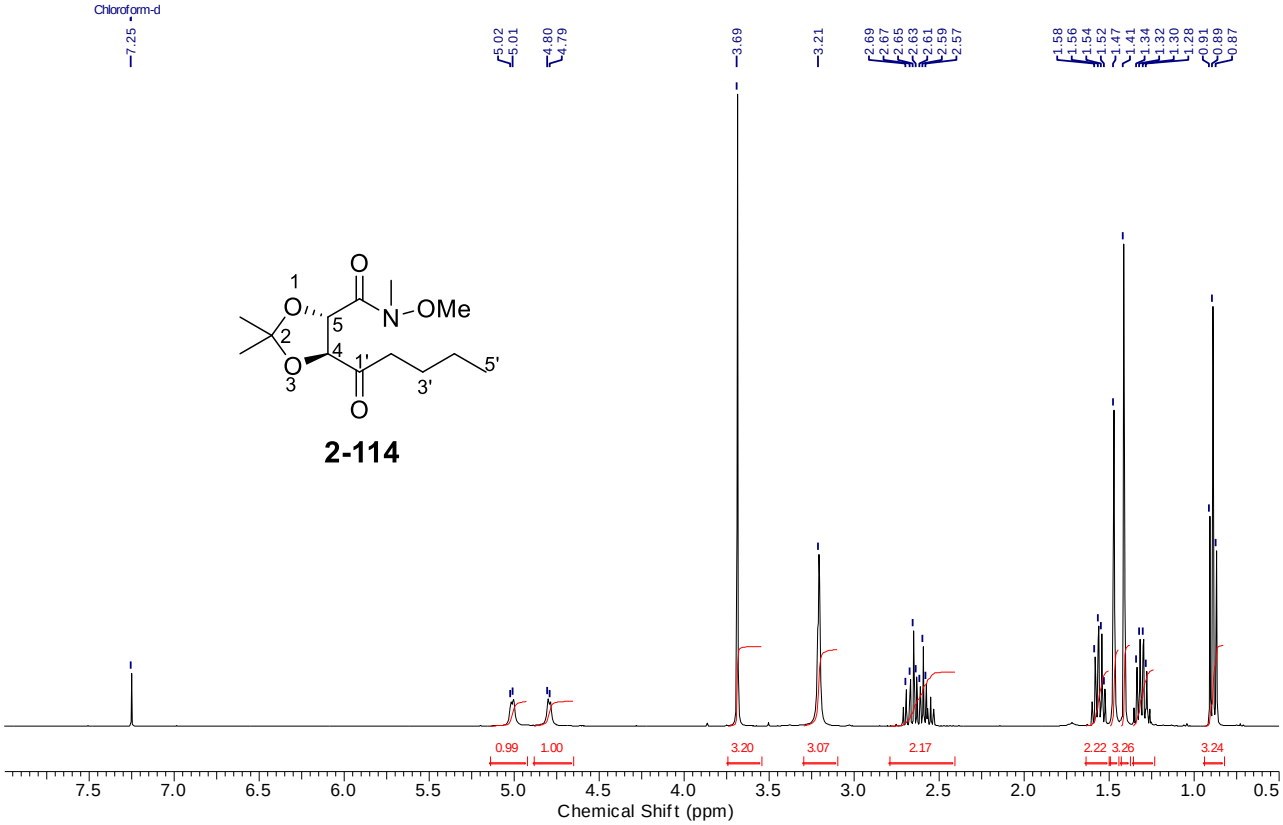
^{13}C NMR (100 MHz) spectrum of vinyl triflate **2-111** in $CDCl_3$ (15 – 200 ppm)



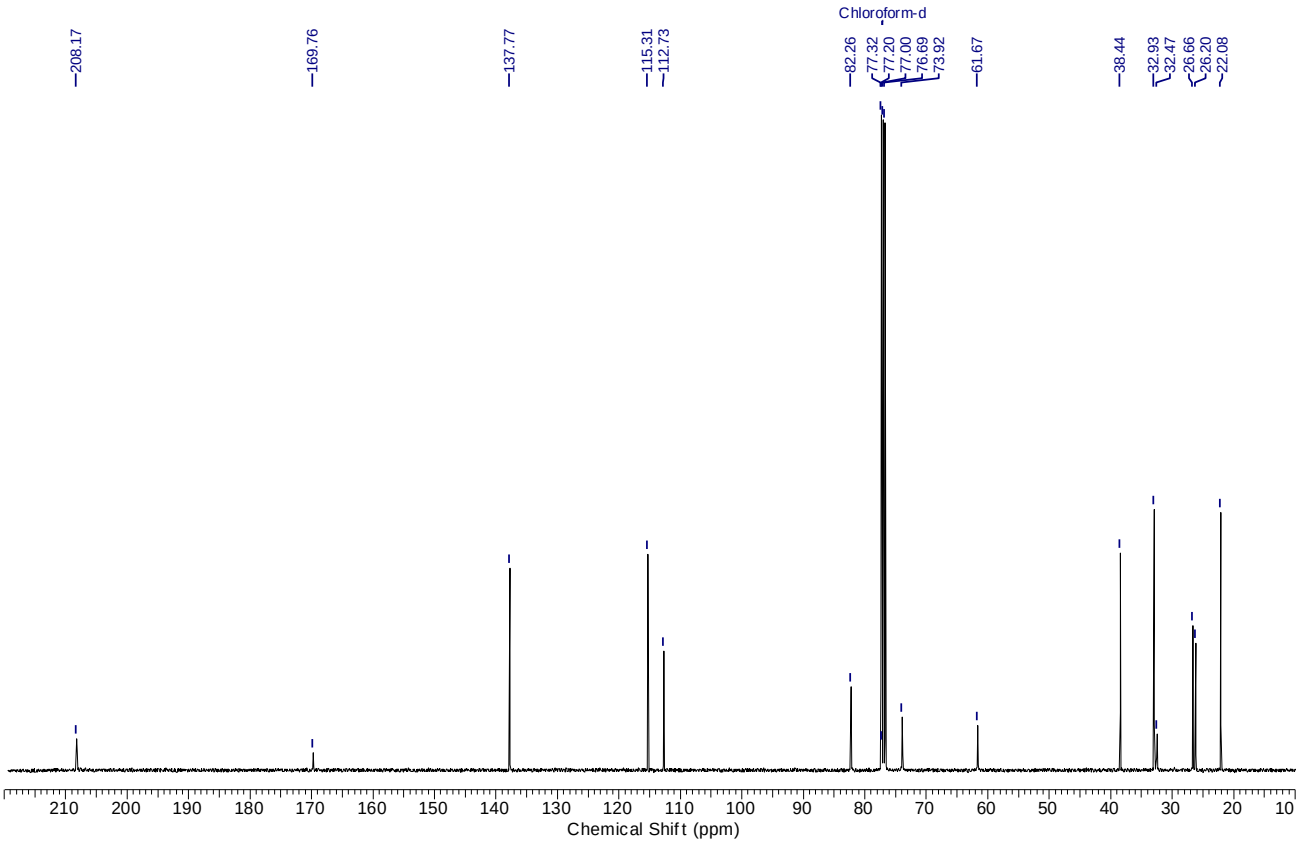
^{1}H NMR (400 MHz) spectrum of diene **2-113** in $CDCl_3$ (0.5 – 8 ppm)



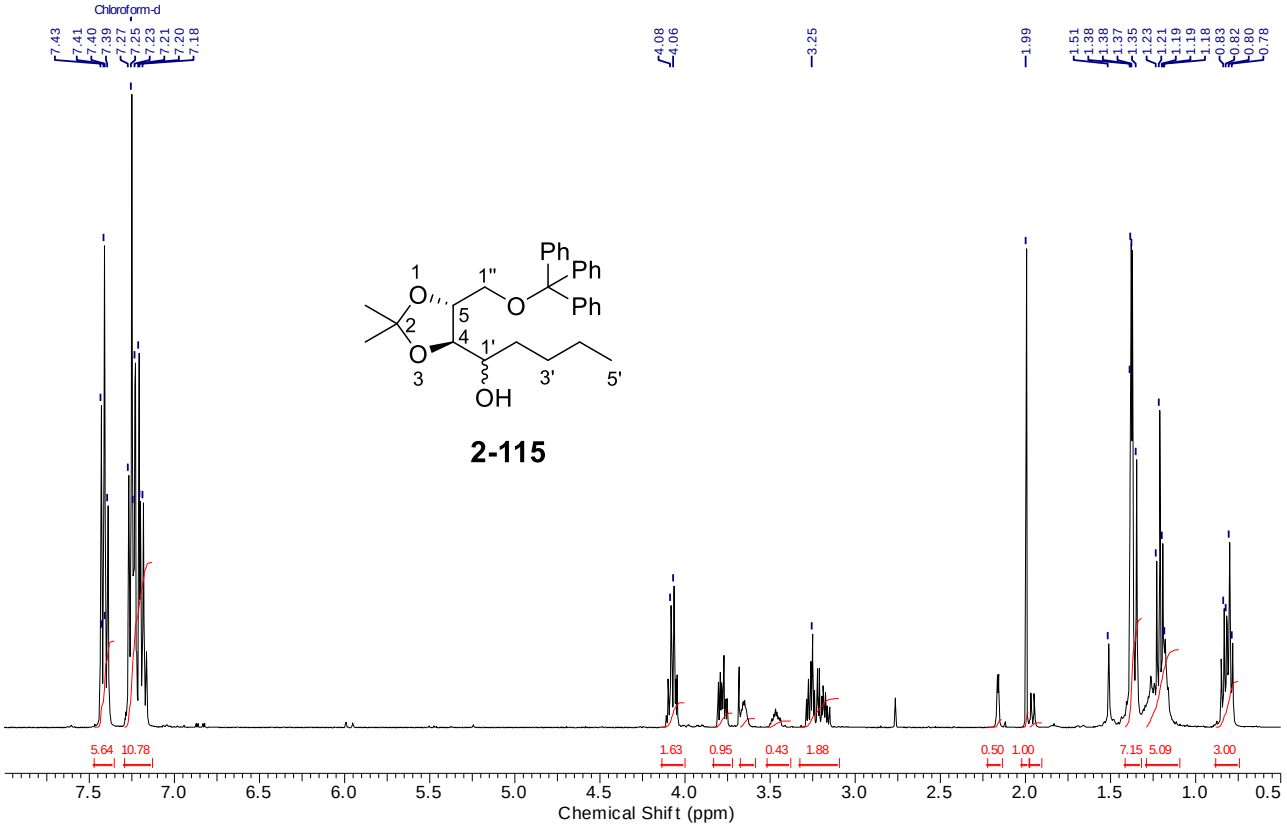
^{13}C NMR (100 MHz) spectrum of diene **2-113** in $CDCl_3$ (15 – 150 ppm)



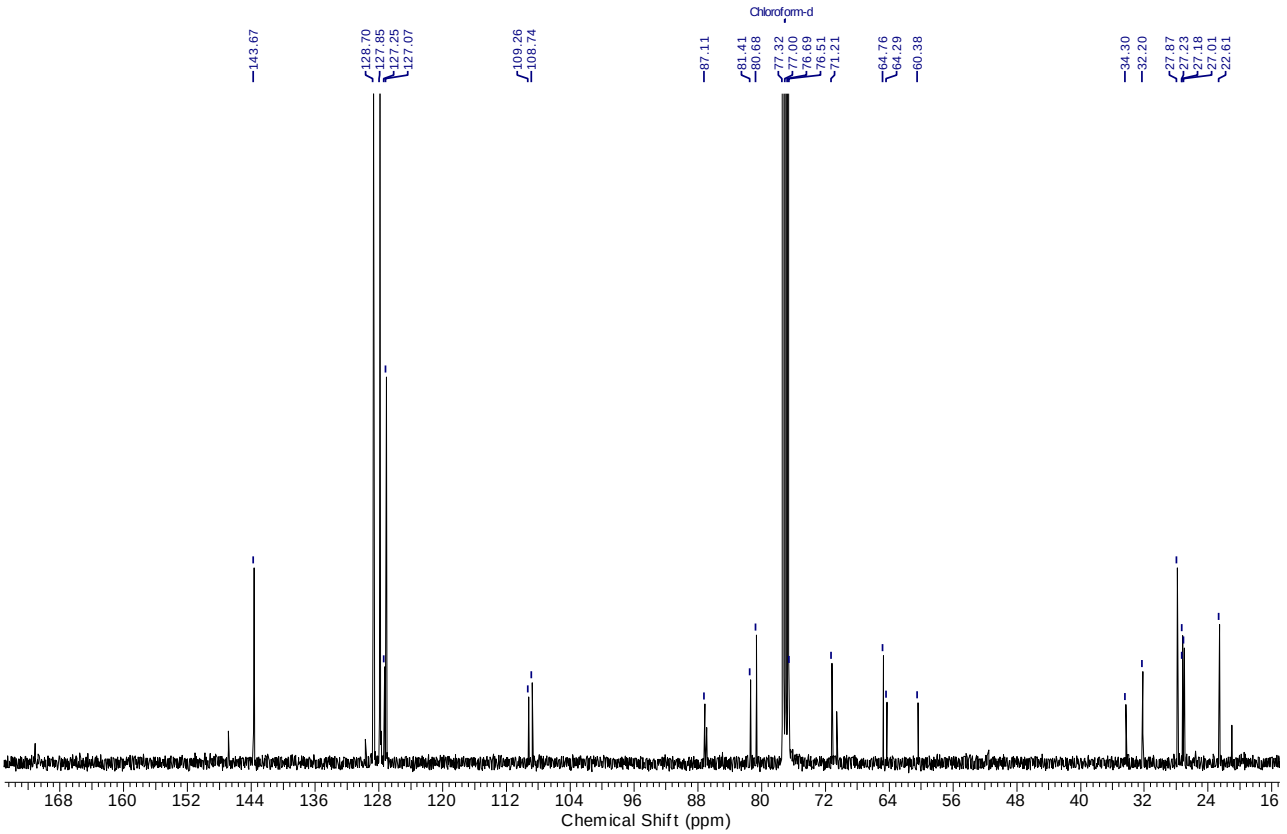
^{1}H NMR (400 MHz) spectrum of ketone **2-114** in $CDCl_3$ (0.5 – 8 ppm)



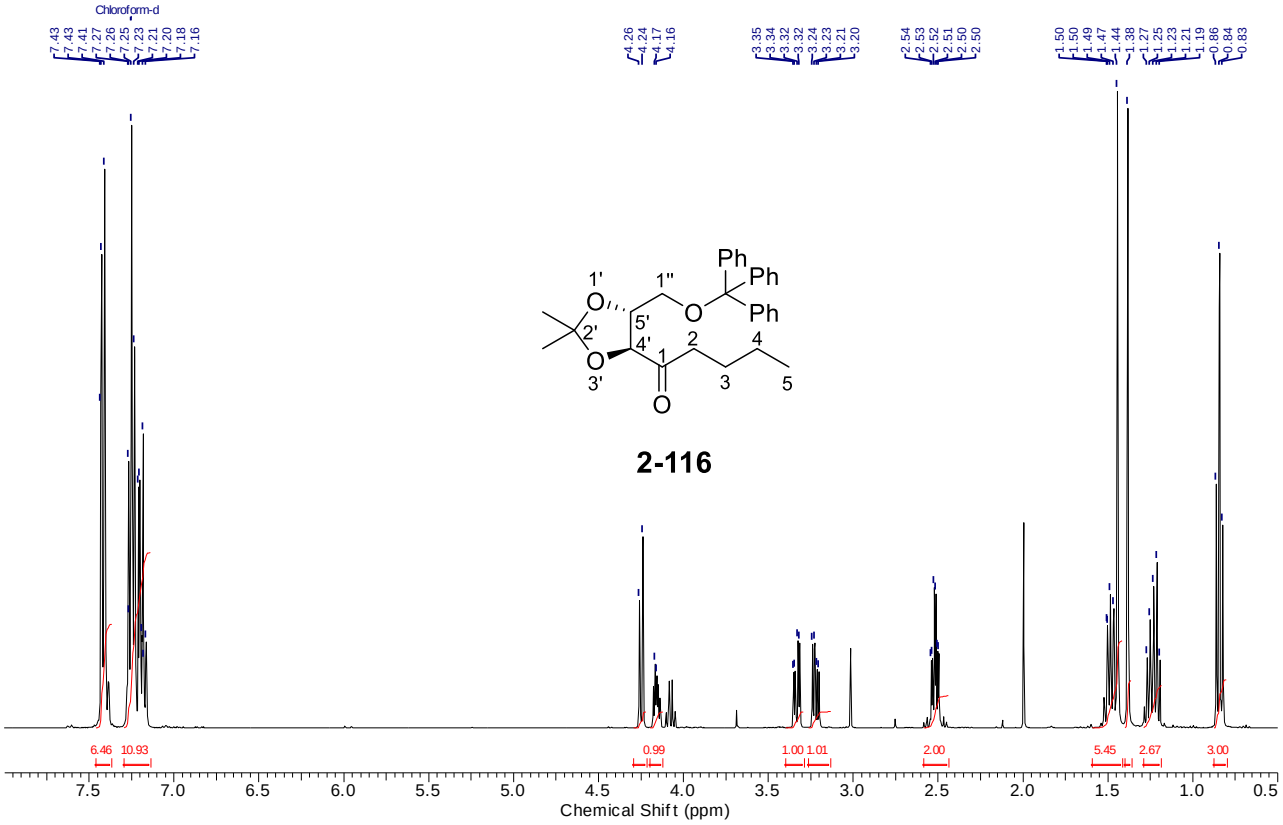
^{13}C NMR (100 MHz) spectrum of ketone **2-114** in $CDCl_3$ (15 – 220 ppm)



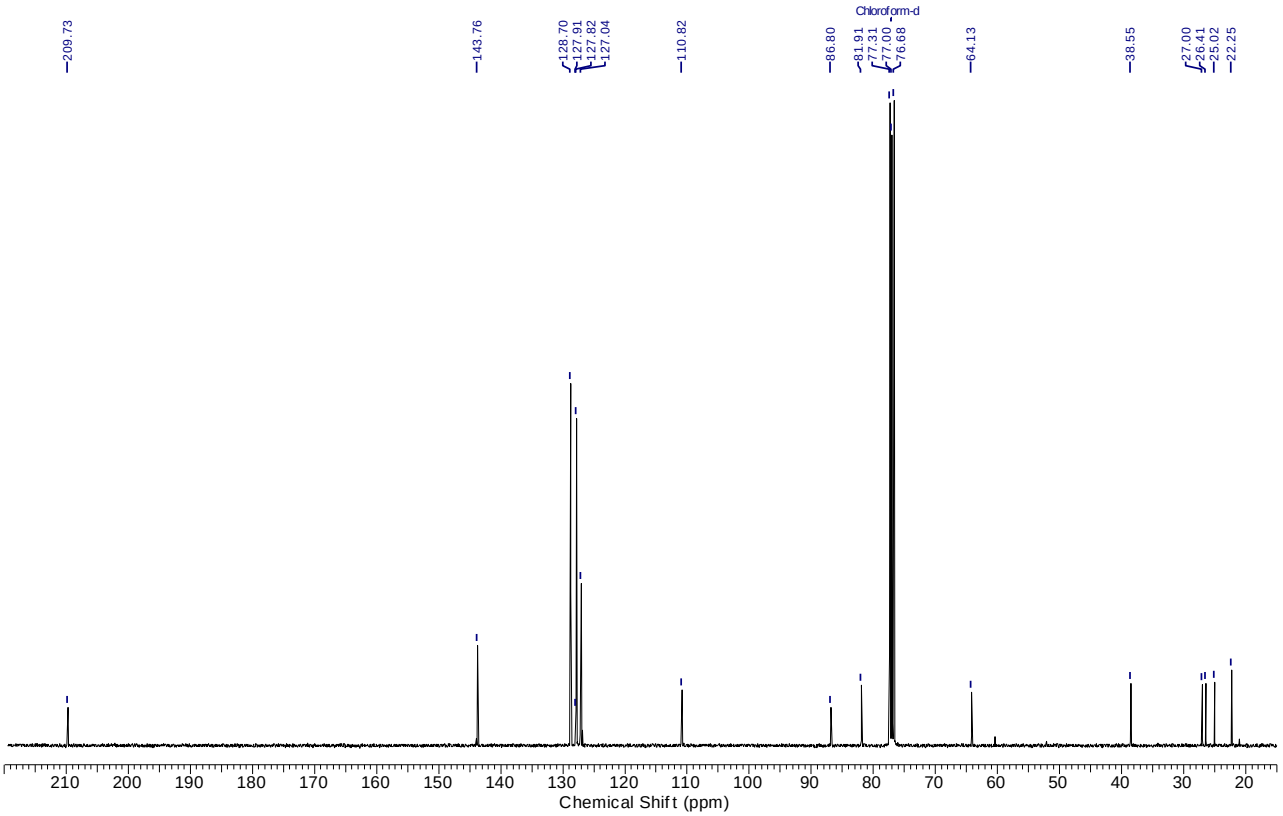
^{1}H NMR (400 MHz) spectrum of alcohols **2-115** in $CDCl_3$ (0.5 – 8 ppm)



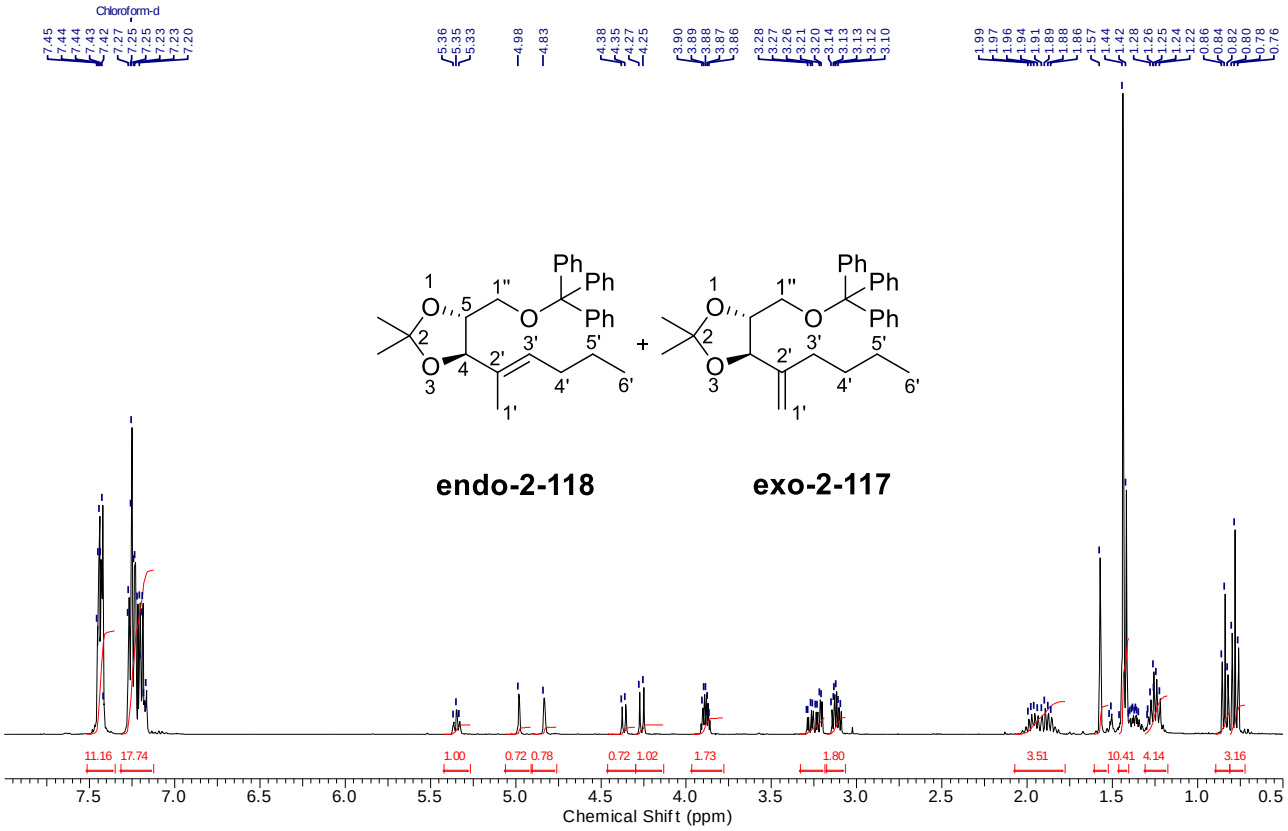
^{13}C NMR (100 MHz) spectrum of alcohols **2-115** in $CDCl_3$ (20 – 160 ppm)



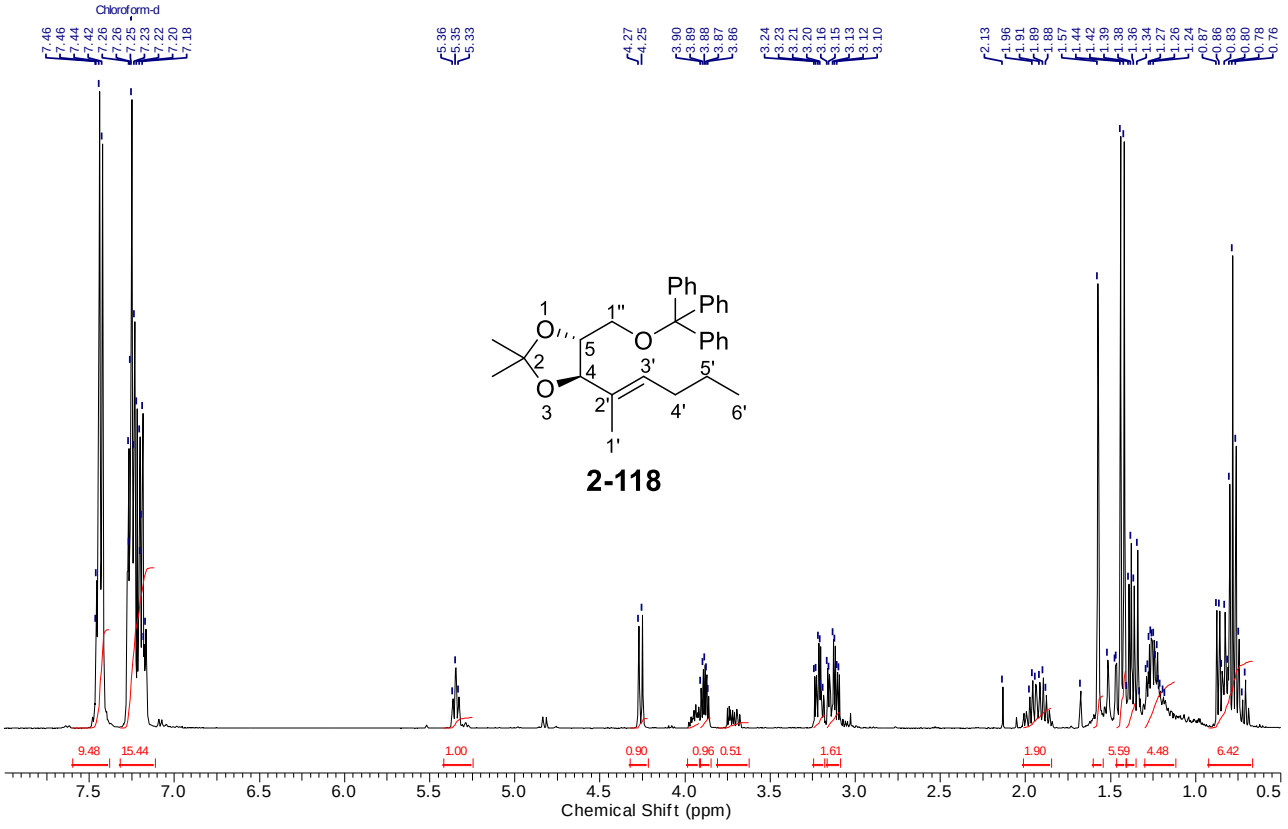
^{1}H NMR (400 MHz) spectrum of ketone **2-116** in $CDCl_3$ (0.5 – 8 ppm)



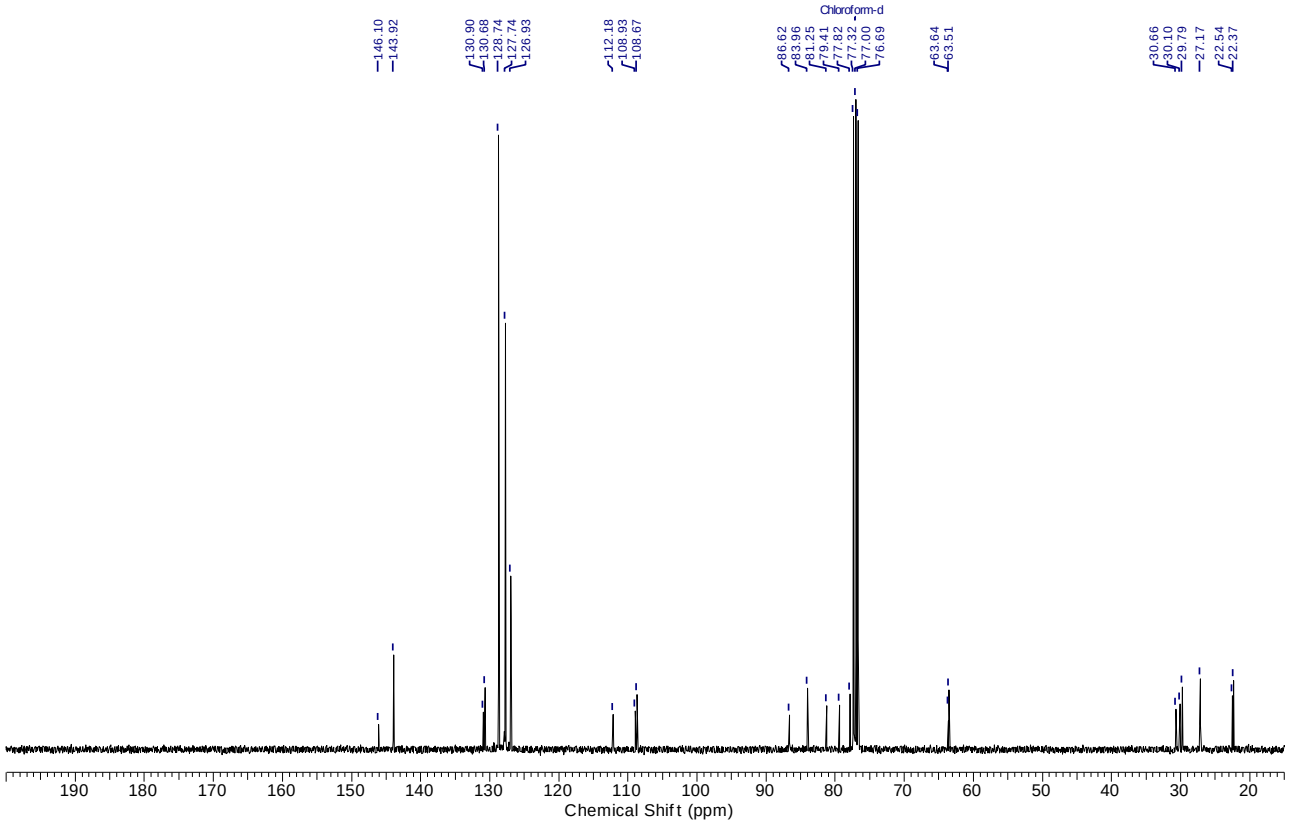
^{13}C NMR (100 MHz) spectrum of alcohol **2-116** in $CDCl_3$ (15 – 220 ppm)



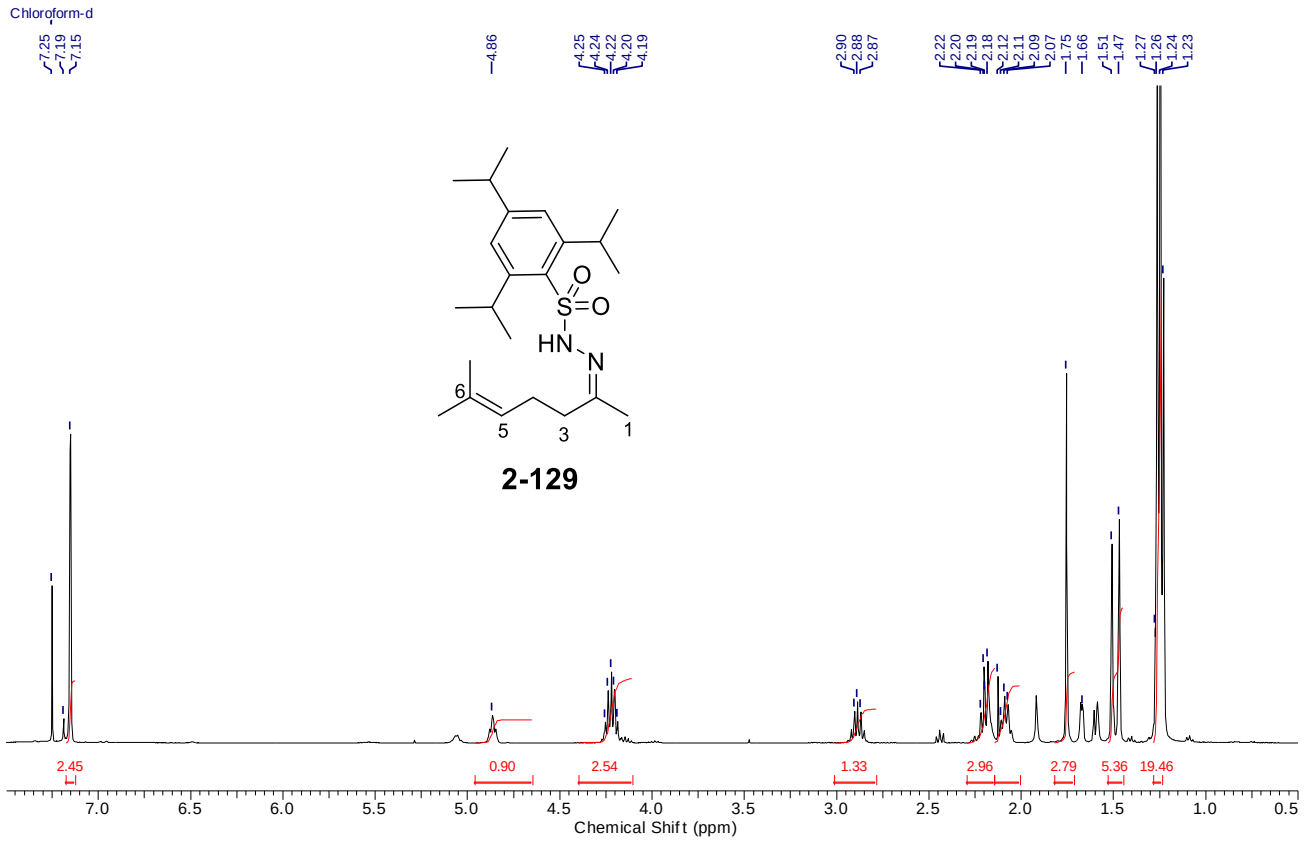
^{1}H NMR (400 MHz) spectrum of exo/endo-**2-117** in $CDCl_3$ (0.5 – 8 ppm)



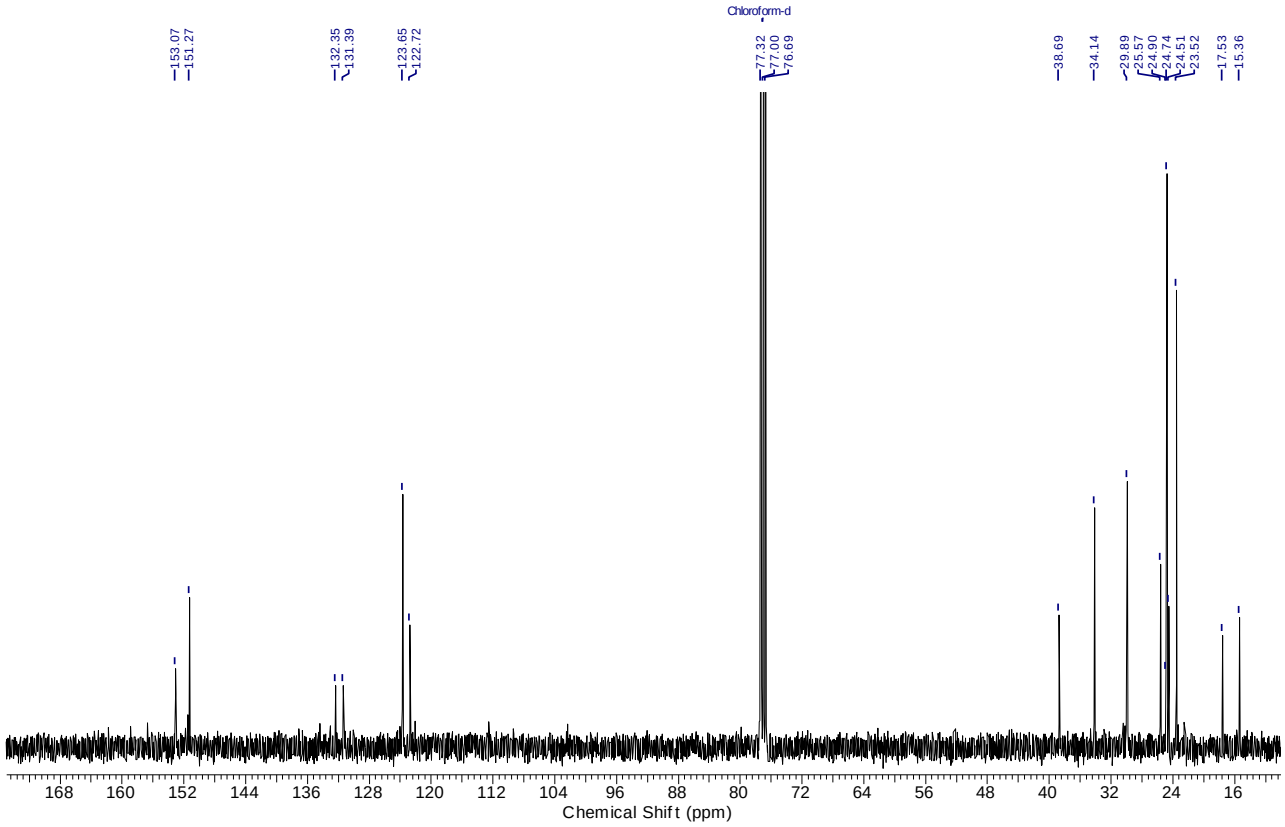
^{1}H NMR (400 MHz) spectrum of (*E/Z*)-**2-118** in $CDCl_3$ (0.5 – 8 ppm)



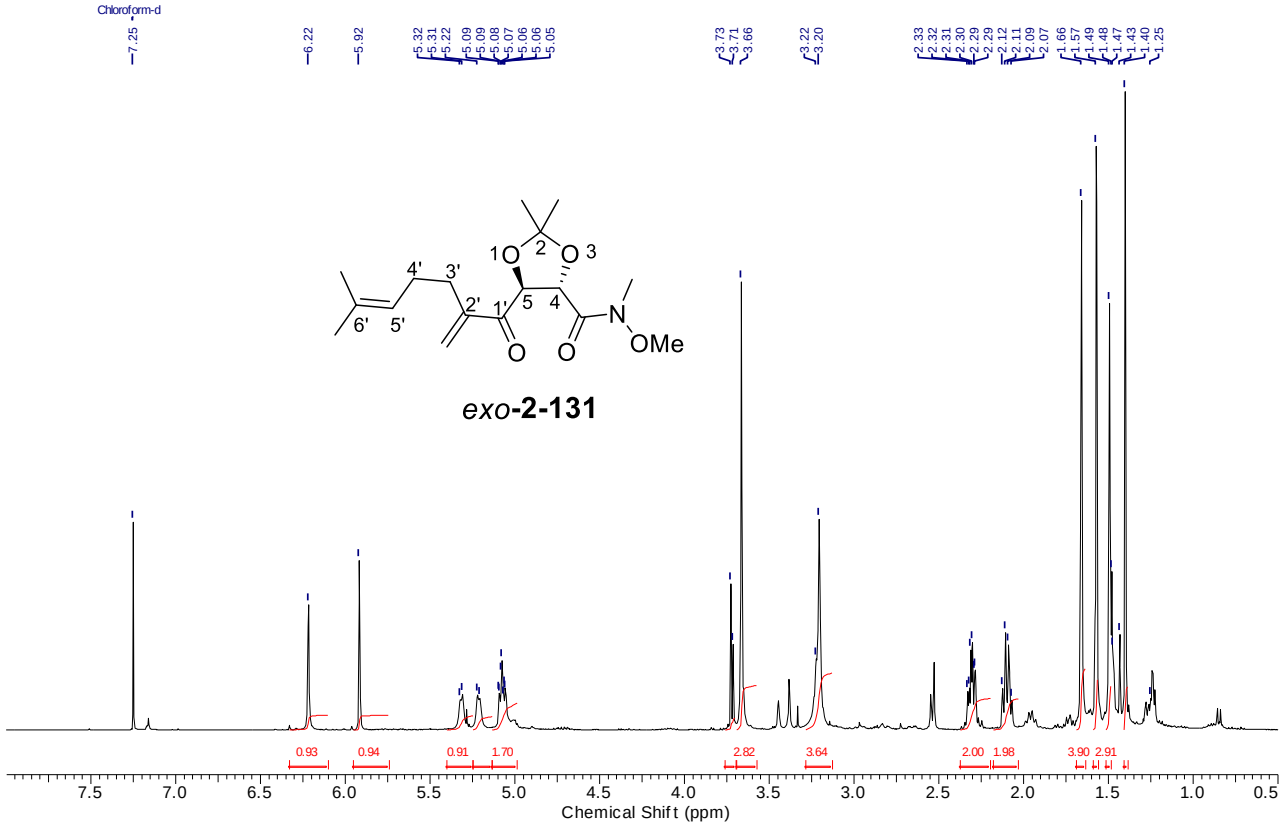
^{13}C NMR (100 MHz) spectrum of (*E/Z*)-**2-118** in $CDCl_3$ (15 – 200 ppm)



^{1}H NMR (400 MHz) spectrum of hydrazone **2-129** in $CDCl_3$ (0.5 – 8 ppm)

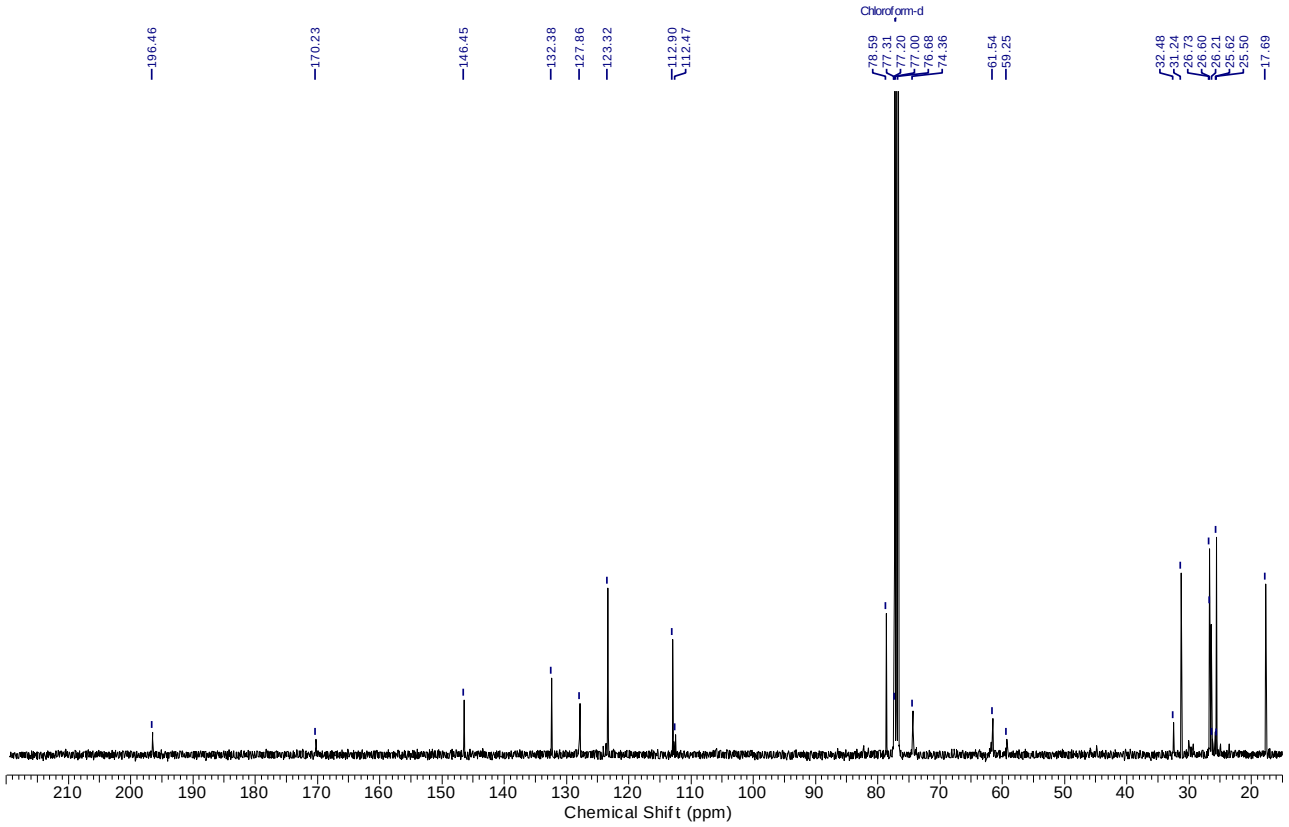


^{13}C NMR (100 MHz) spectrum of hydrazone **2-129** in $CDCl_3$ (15 – 175 ppm)

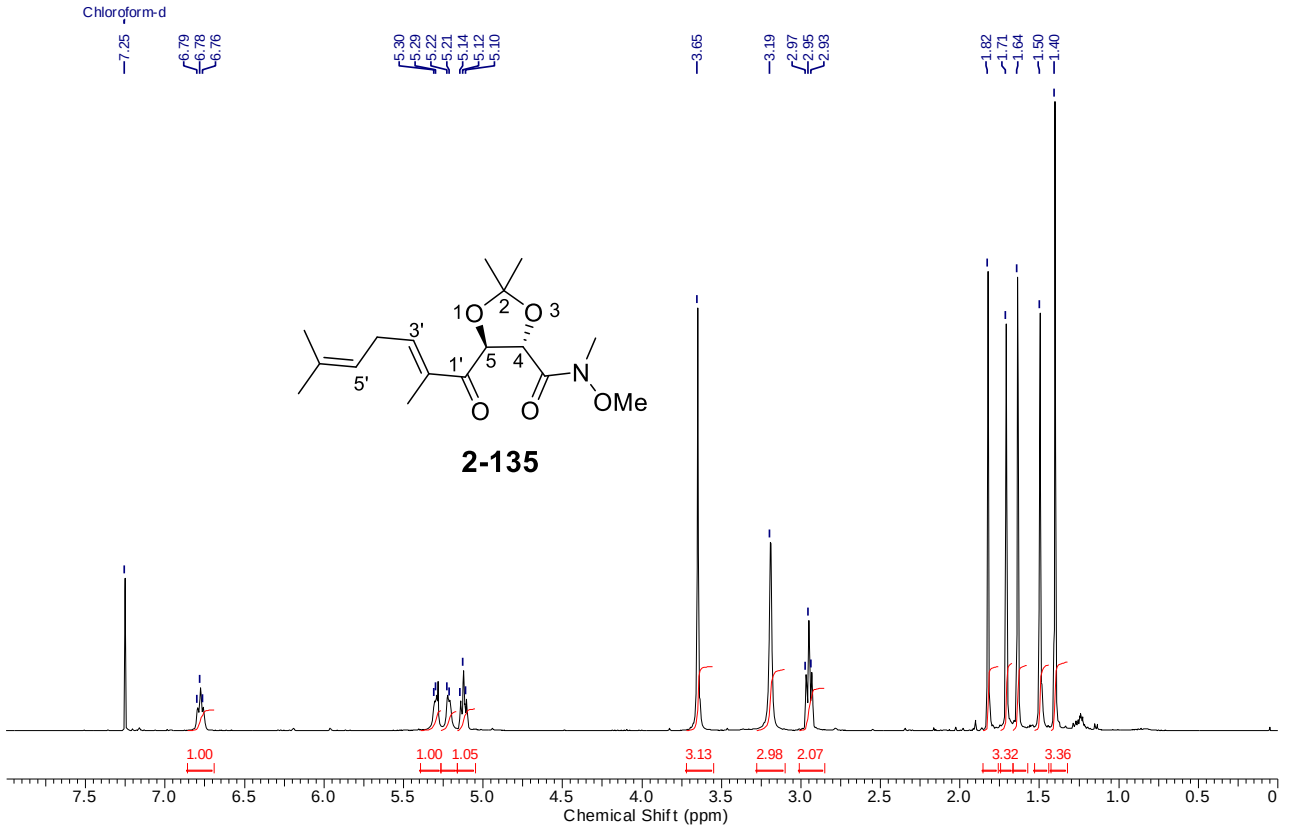


exo-**2-131**

^{1}H NMR (400 MHz) spectrum of *exo*-**2-131** in $CDCl_3$ (0.5 – 8 ppm)

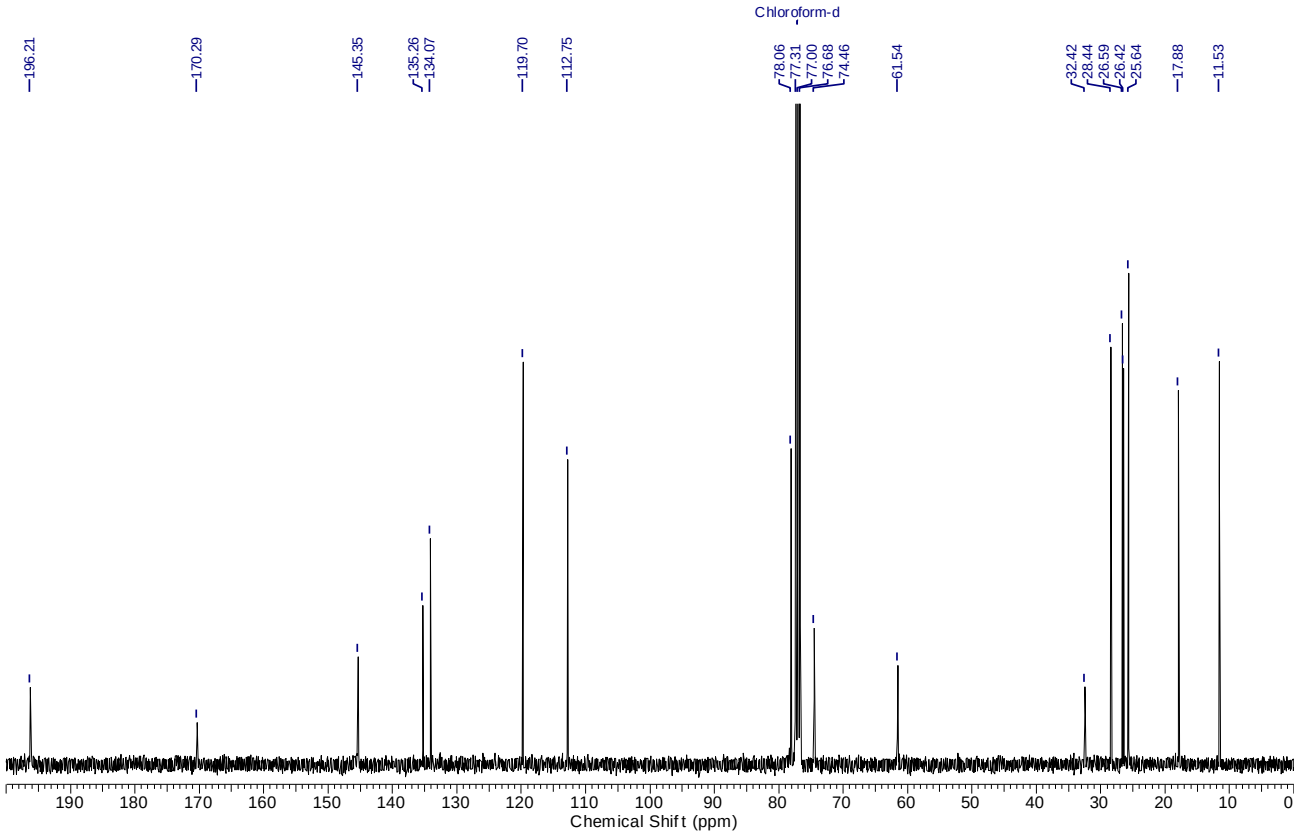


^{13}C NMR (100 MHz) spectrum of exo-**2-131** in $CDCl_3$ (15 – 220 ppm)

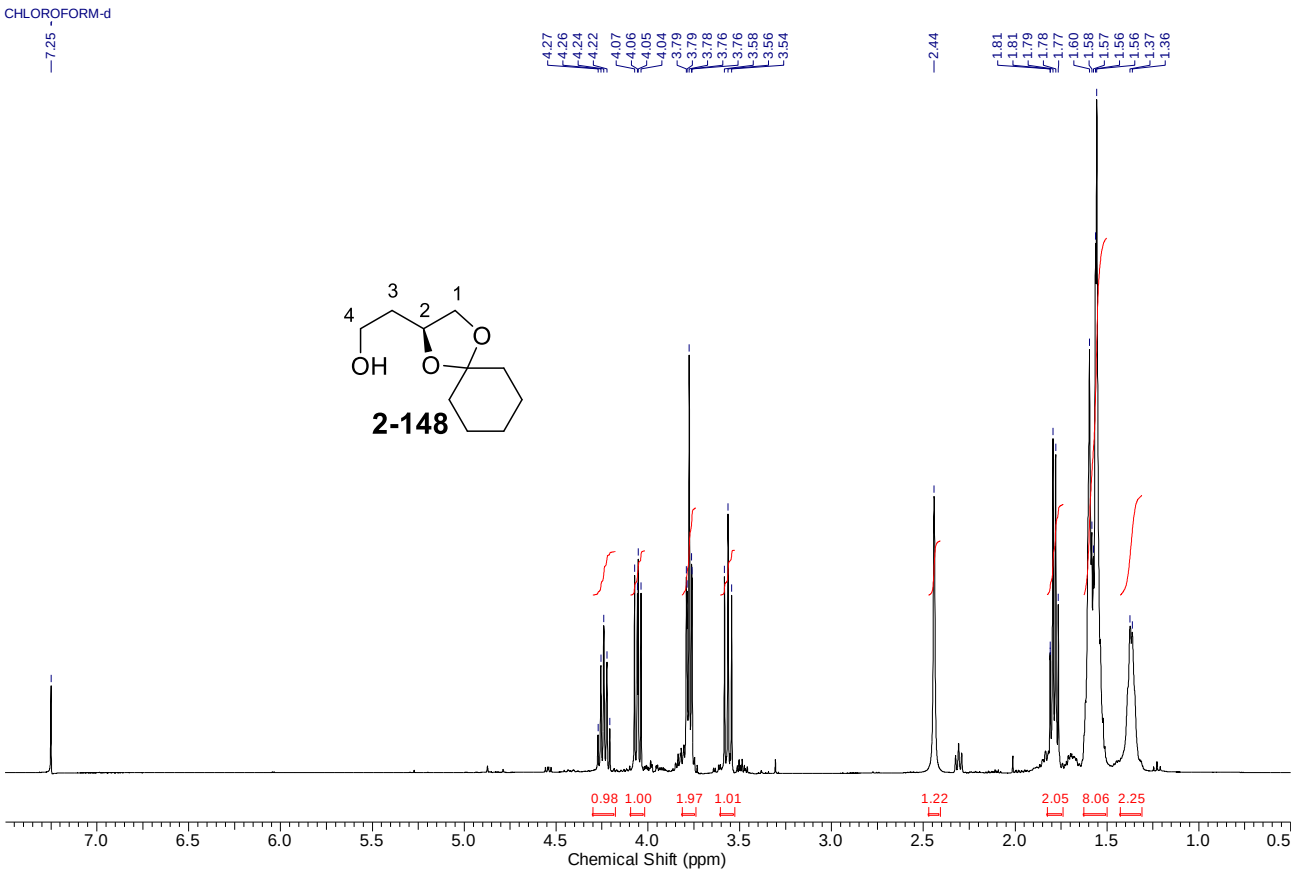


2-135

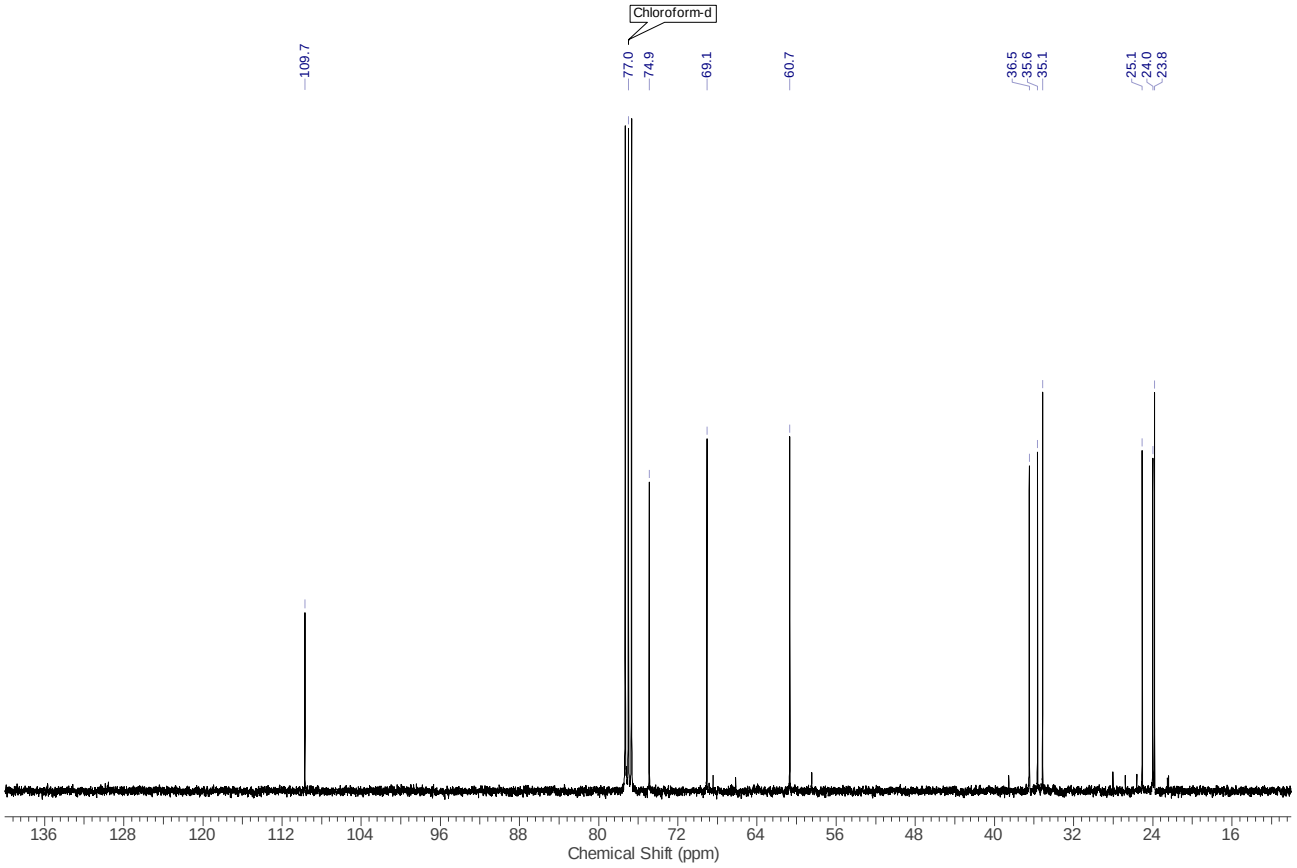
^{1}H NMR (400 MHz) spectrum of enone **2-135** in $CDCl_3$ (0 – 8 ppm)



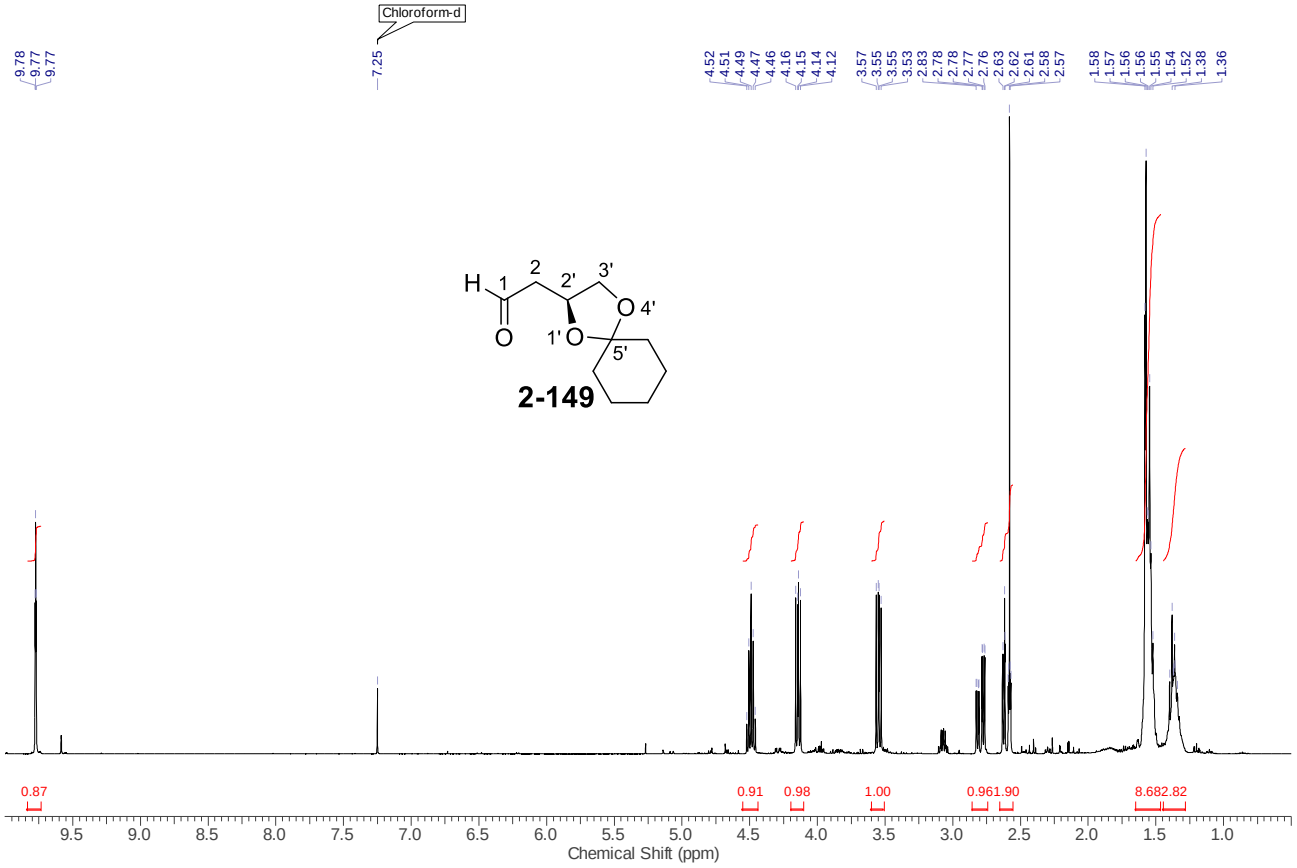
^{13}C NMR (100 MHz) spectrum of enone **2-130** in $CDCl_3$ (0 – 200 ppm)



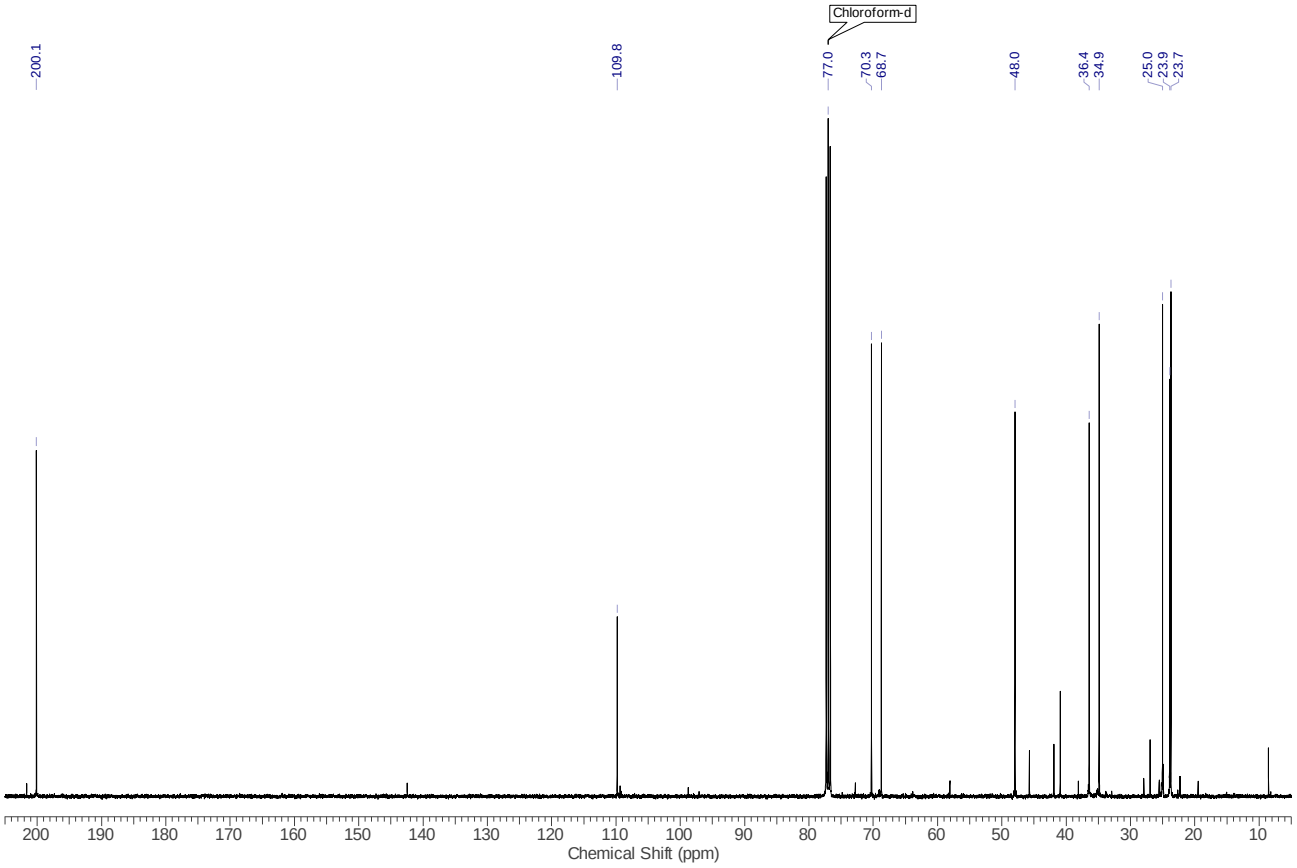
^{1}H NMR (400 MHz) spectrum of acetal **2-148** in $CDCl_3$ (0.5 – 7.5 ppm)



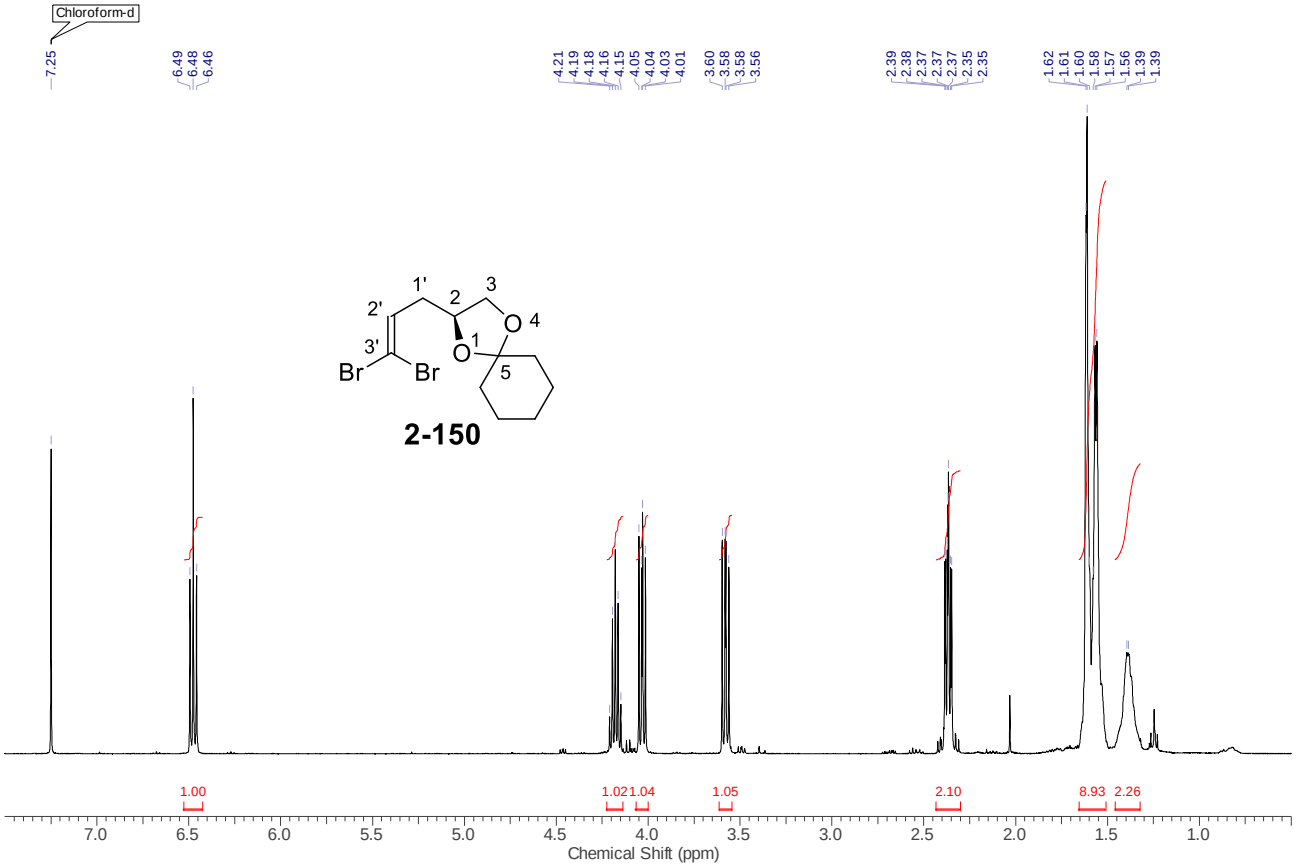
^{13}C NMR (100 MHz) spectrum of acetal **2-149** in $CDCl_3$ (10 – 140 ppm)



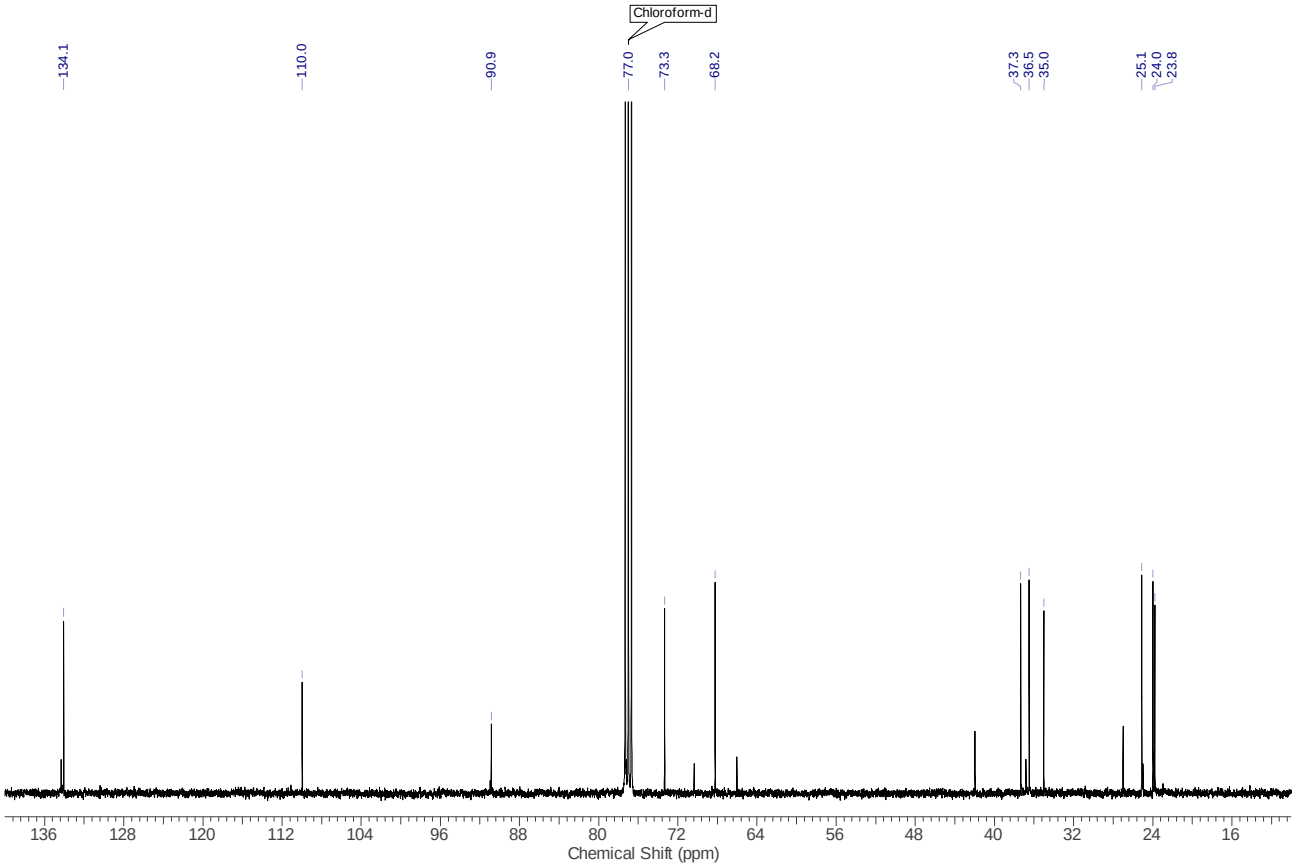
^{1}H NMR (400 MHz) spectrum of aldehyde **2-149** in $CDCl_3$ (0.5 – 10.0 ppm)



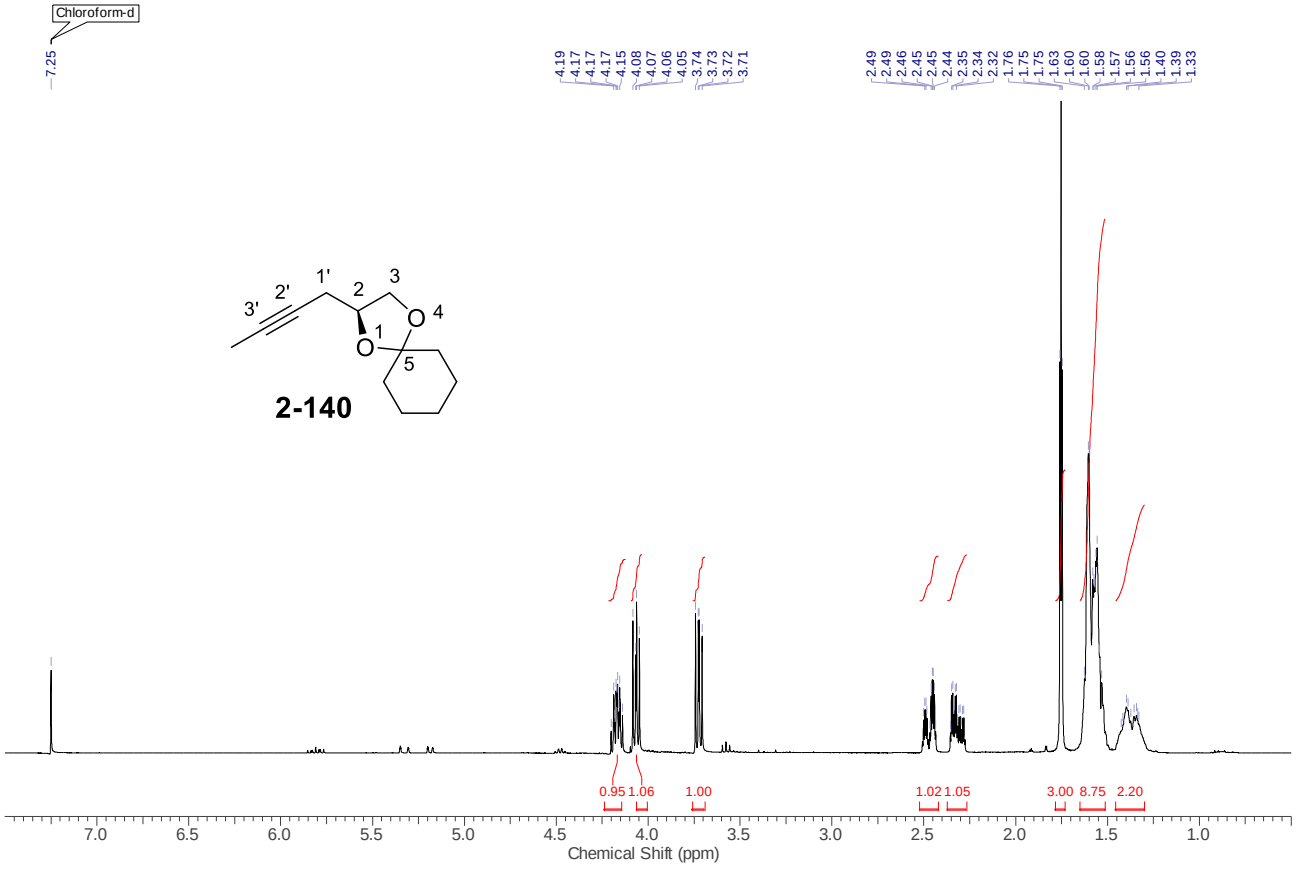
^{13}C NMR (100 MHz) spectrum of aldehyde **2-149** in $CDCl_3$ (5 – 205 ppm)



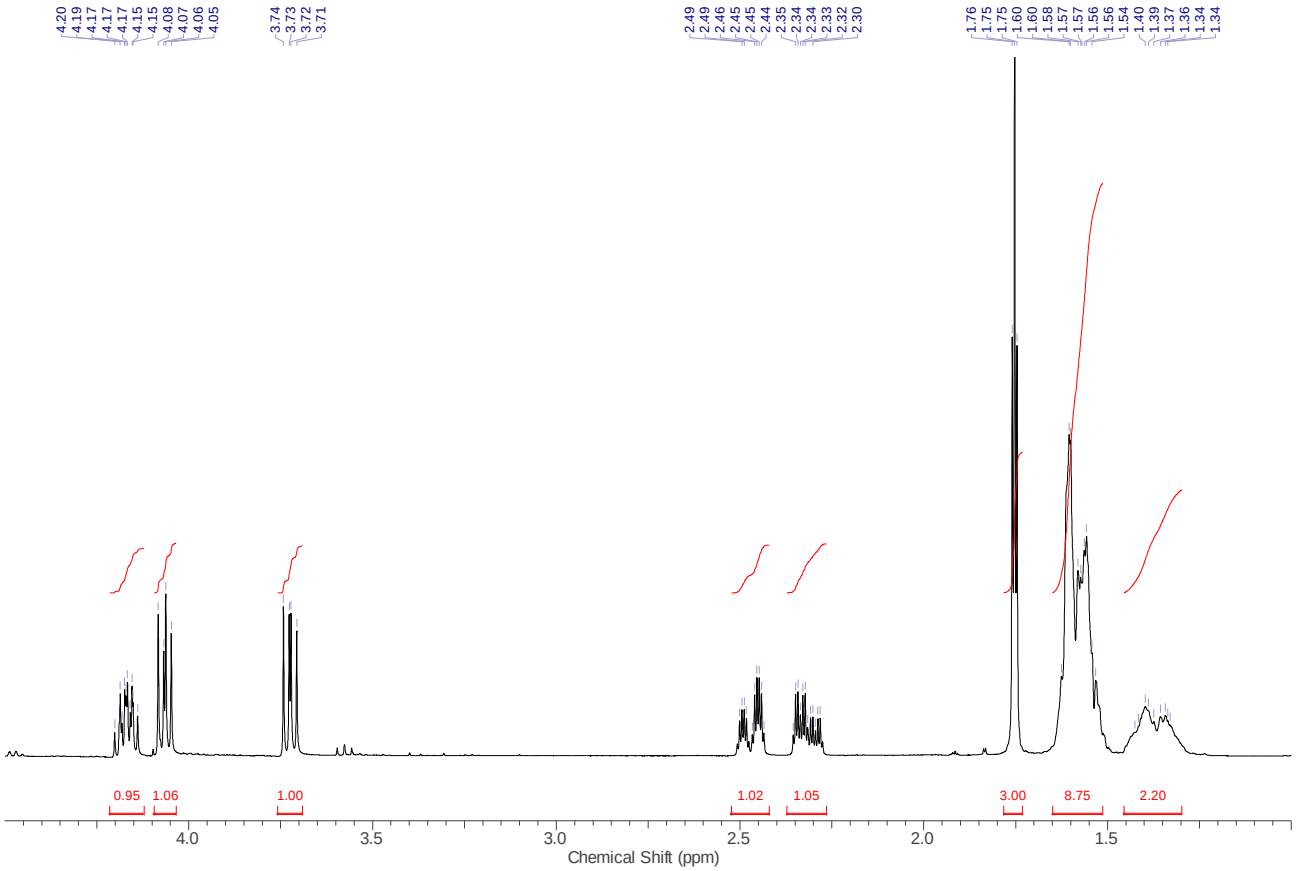
^{1}H NMR (400 MHz) spectrum of dibromoalkene **2-150** in $CDCl_3$ (0.5 – 7.5 ppm)



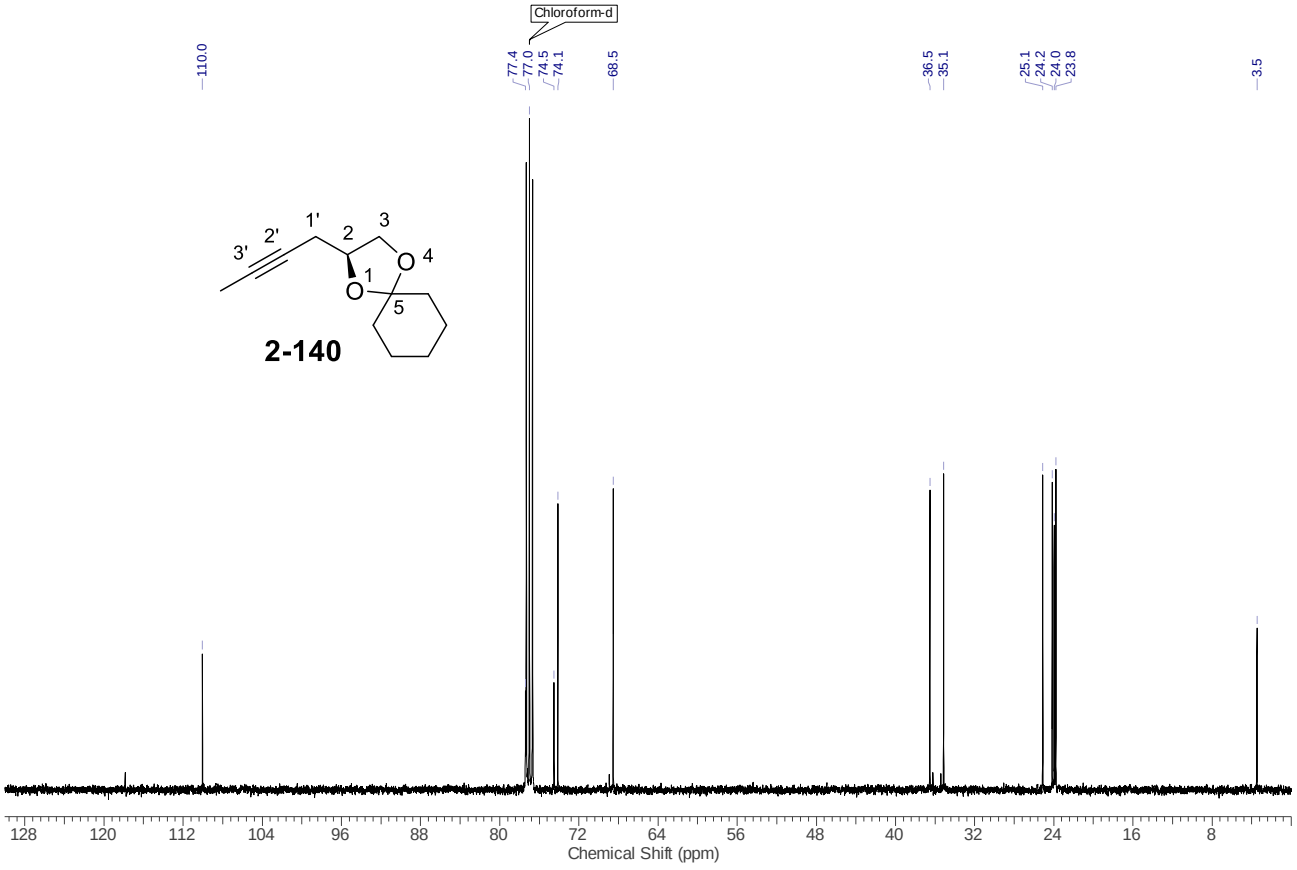
^{13}C NMR (100 MHz) spectrum of dibromoalkene **2-150** in $CDCl_3$ (10 – 140 ppm)



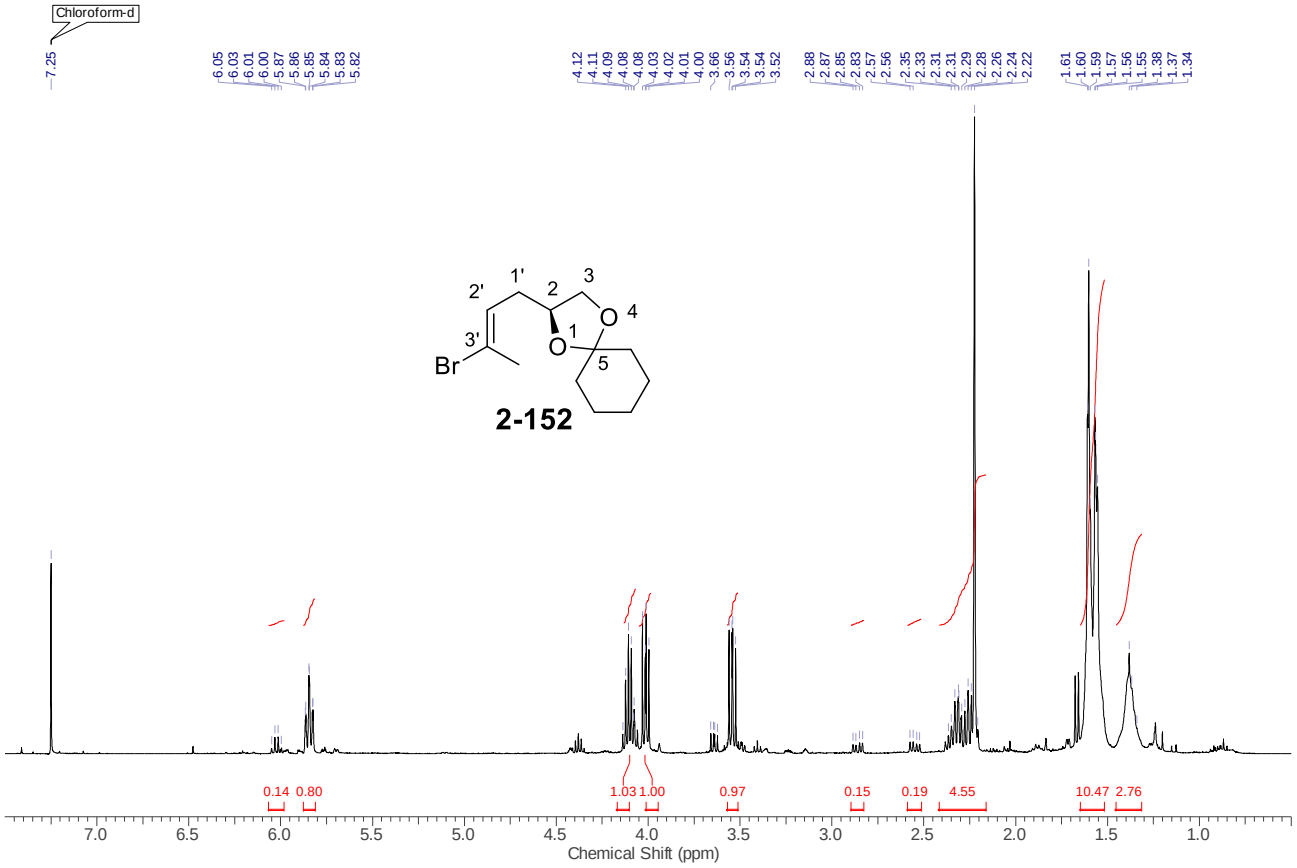
^{1}H NMR (400 MHz) spectrum of alkyne **2-140** in $CDCl_3$ (0.5 – 7.5 ppm)



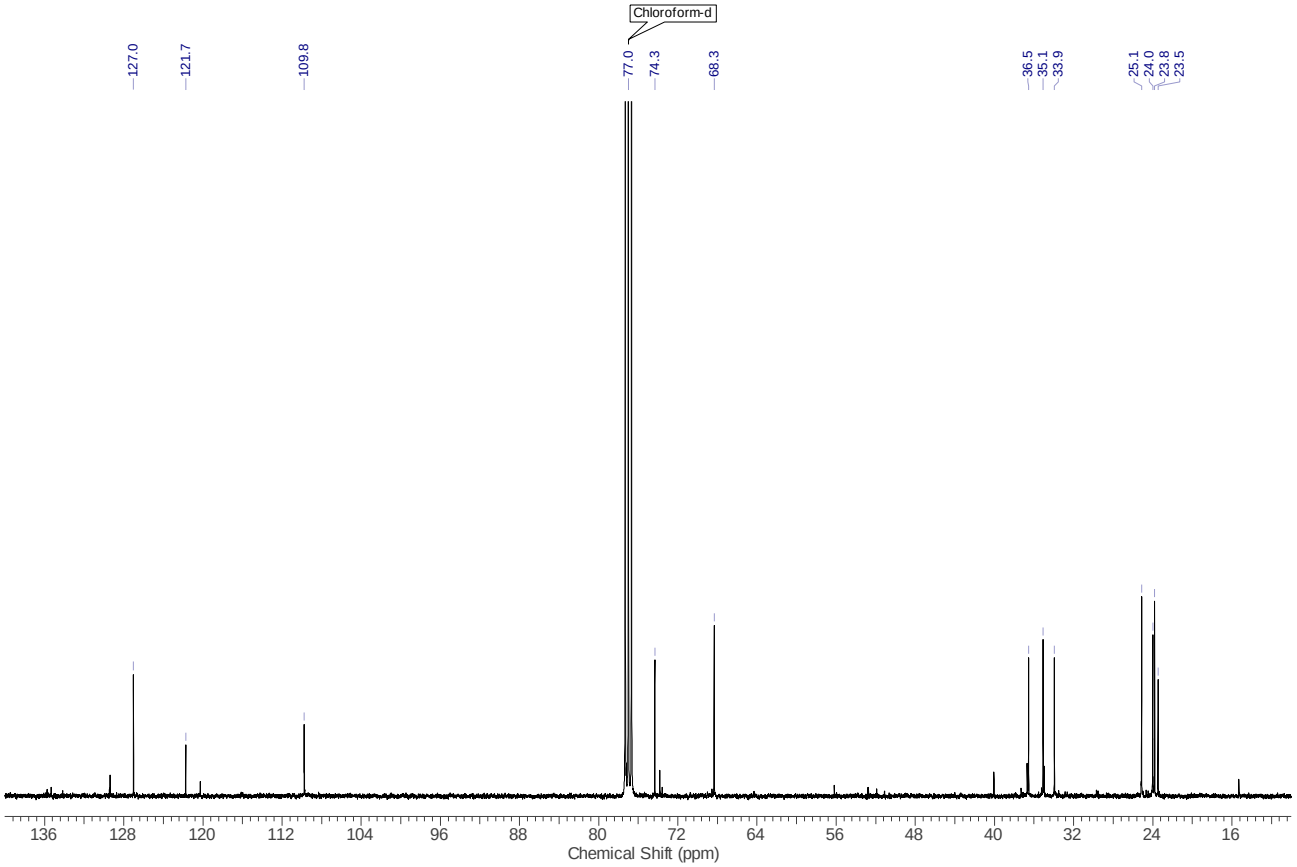
^{1}H NMR (400 MHz) spectrum of alkyne **2-140** in $CDCl_3$ (1.0 – 4.5 ppm)



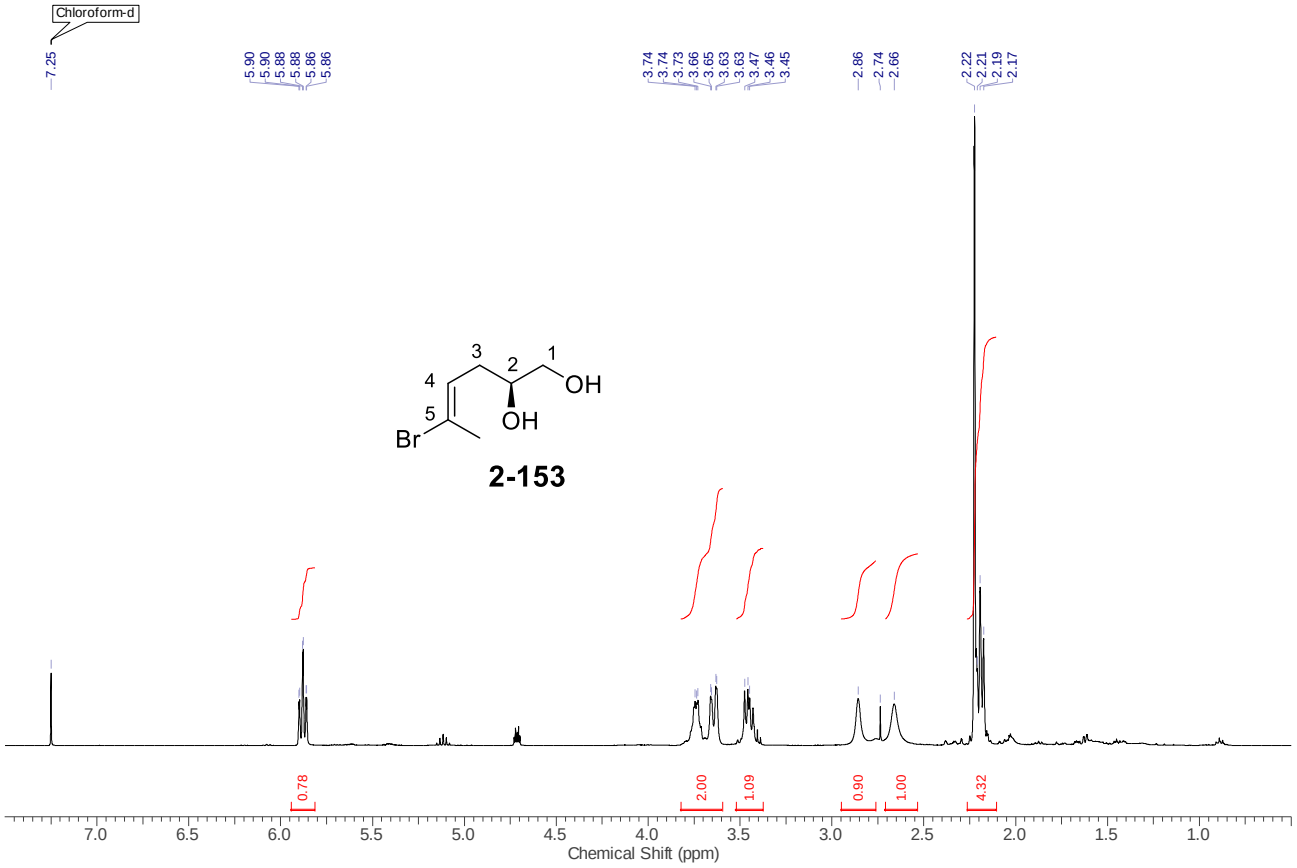
^{13}C NMR (100 MHz) spectrum of alkyne **2-140** in $CDCl_3$ (0 – 130 ppm)



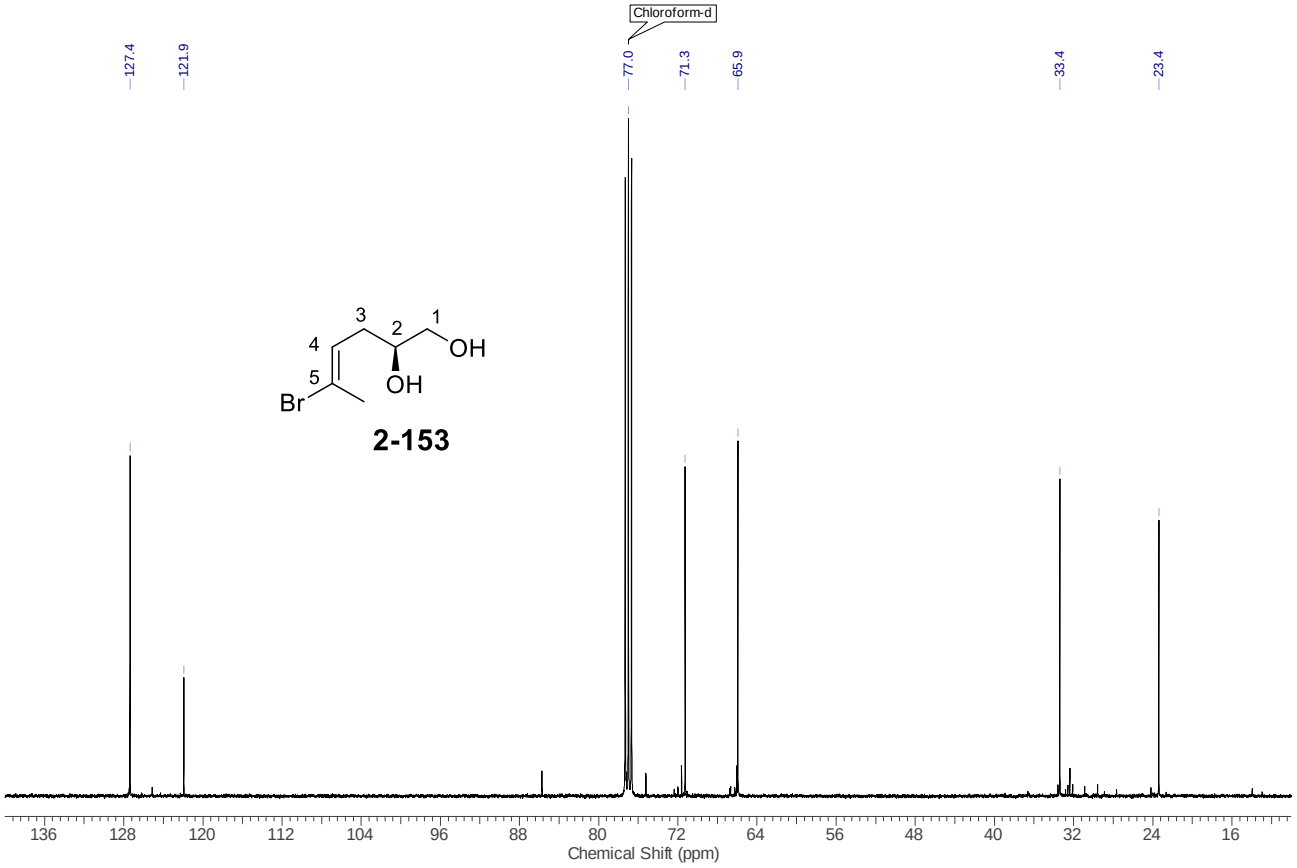
^{1}H NMR (400 MHz) spectrum of vinyl bromide **2-152** in $CDCl_3$ (0.5 – 7.5 ppm)



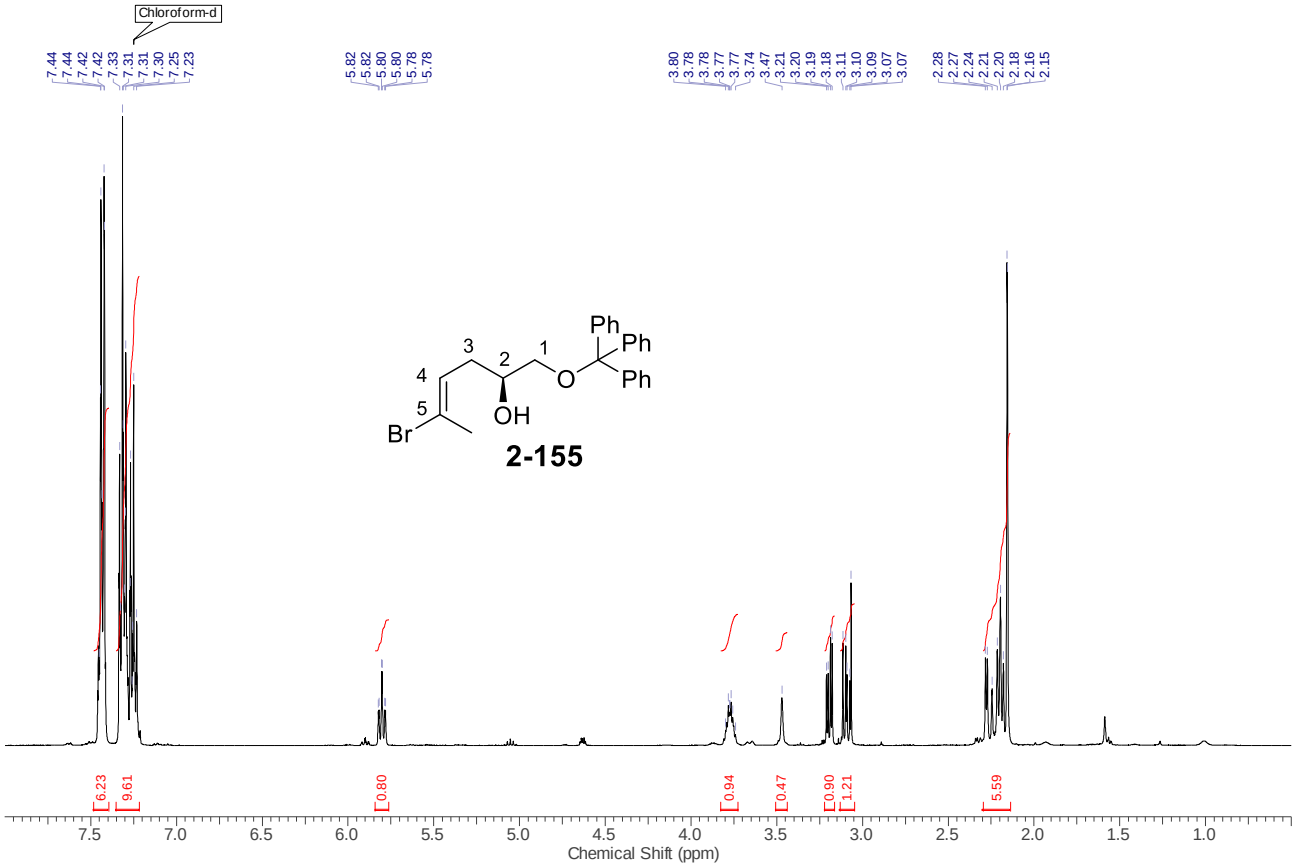
^{13}C NMR (100 MHz) spectrum of vinyl bromide **2-152** in $CDCl_3$ (10 – 140 ppm)



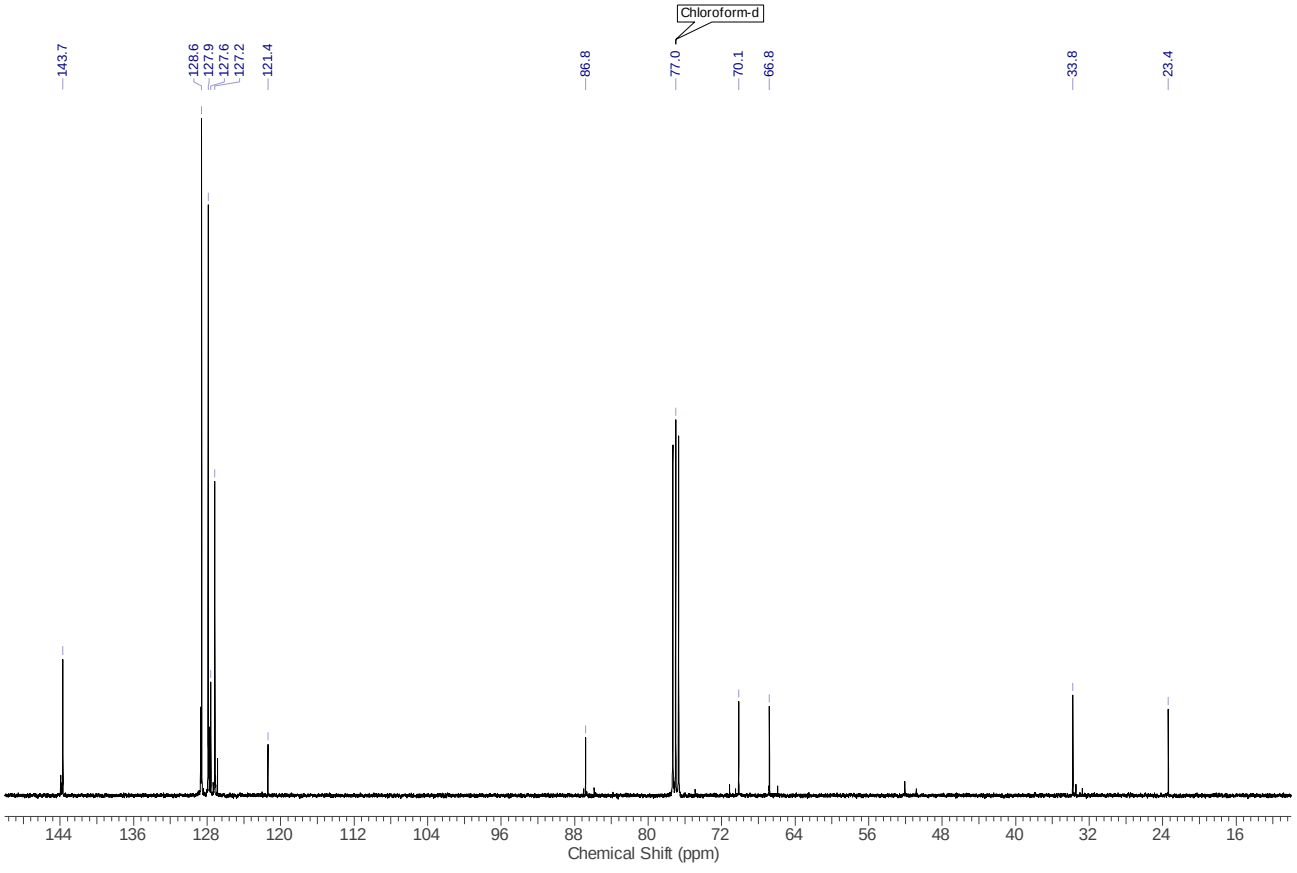
^{1}H NMR (400 MHz) spectrum of vinyl bromide **2-153** in $CDCl_3$ (0.5 – 7.5 ppm)



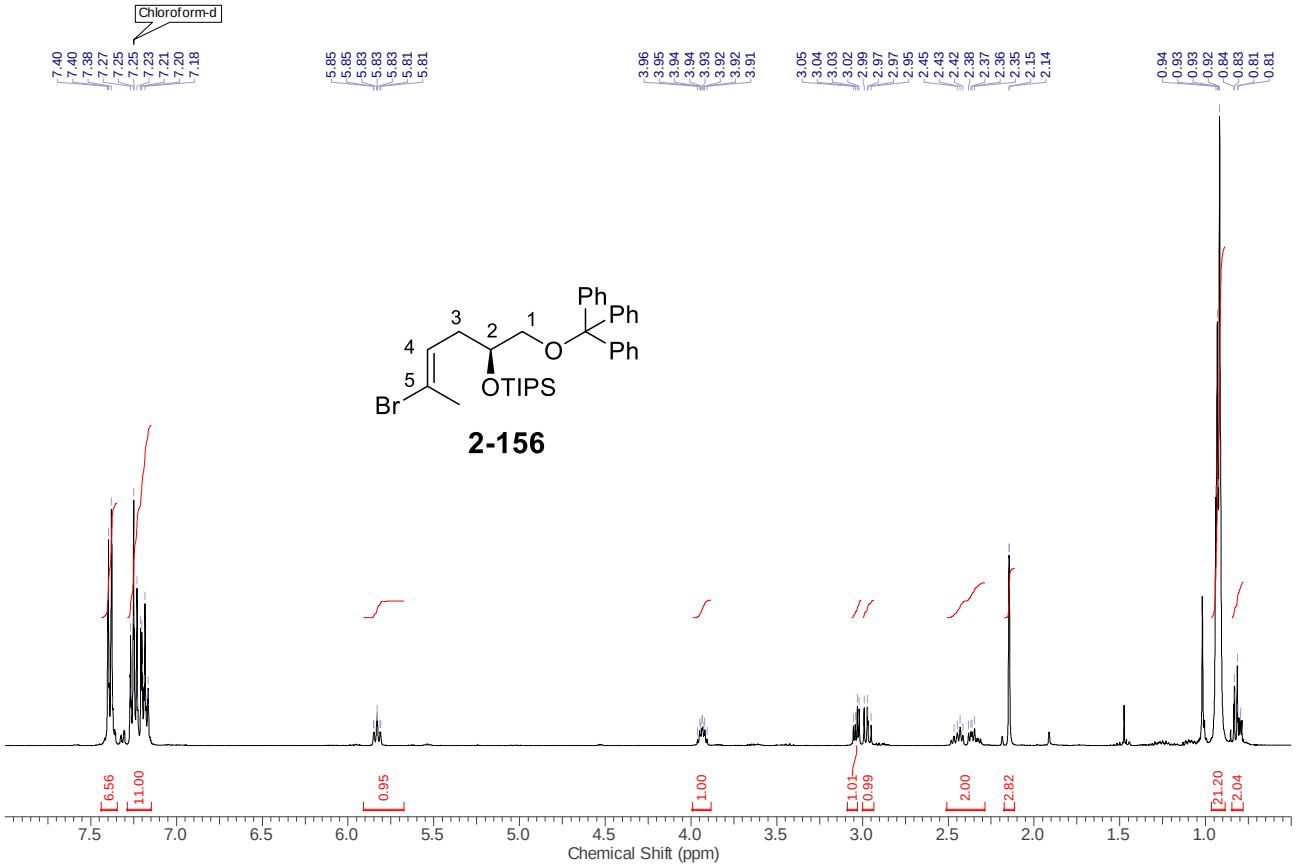
^{13}C NMR (100 MHz) spectrum of vinyl bromide **2-153** in $CDCl_3$ (10 – 140 ppm)



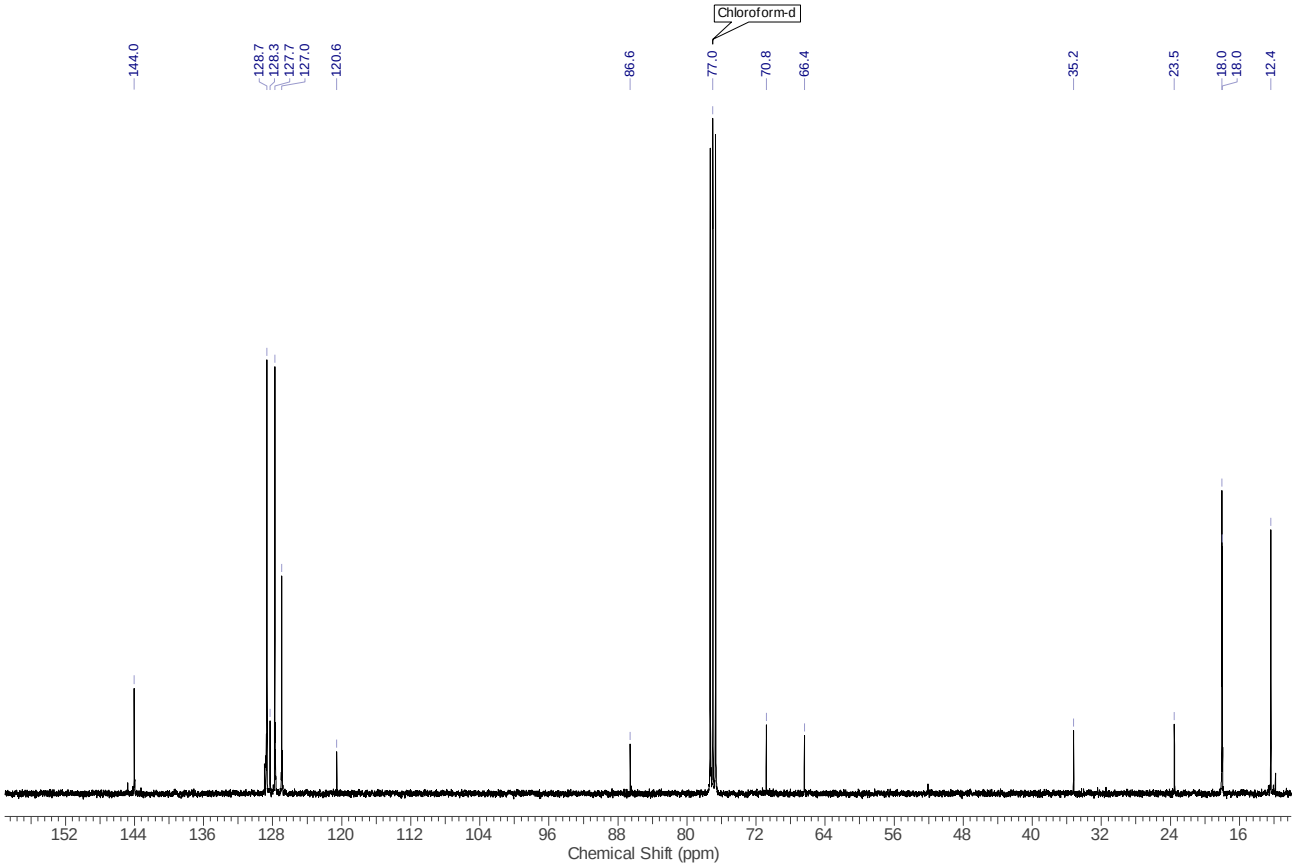
^{1}H NMR (400 MHz) spectrum of trityl ether **2-155** in $CDCl_3$ (0.5 – 8.0 ppm)



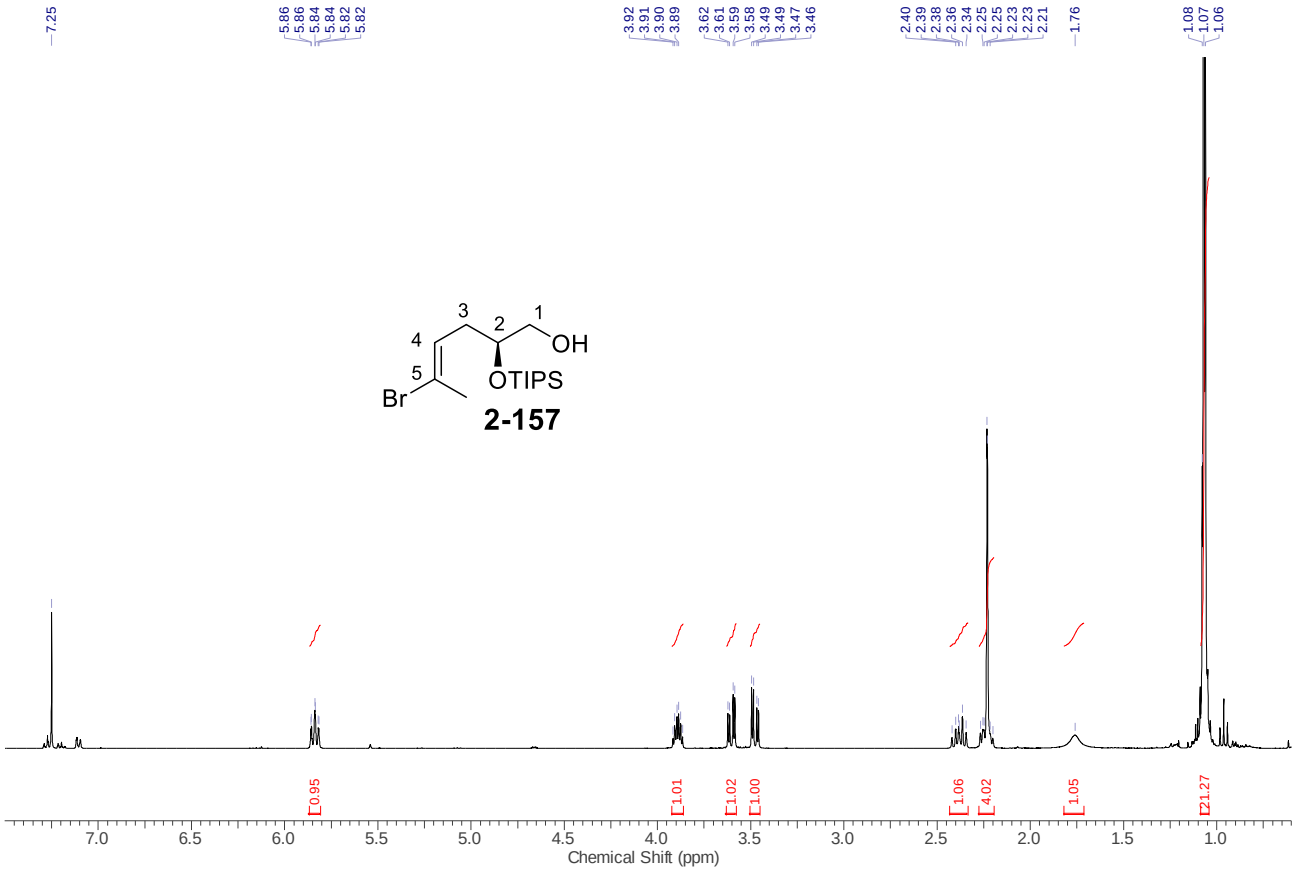
^{13}C NMR (100 MHz) spectrum of trityl ether **2-155** in $CDCl_3$ (10 – 150 ppm)



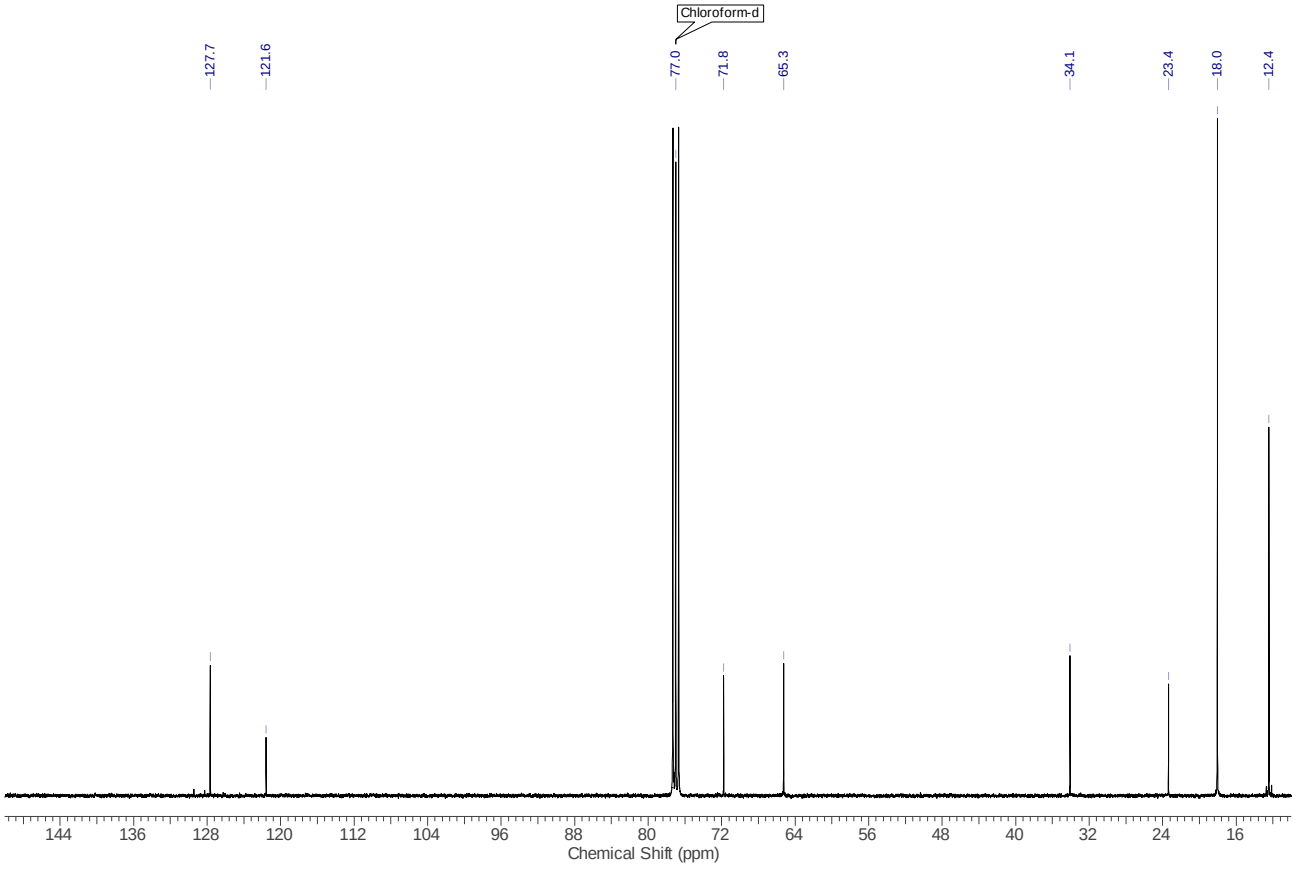
^{1}H NMR (400 MHz) spectrum of silyl ether **2-156** in $CDCl_3$ (0.5 – 8.0 ppm)



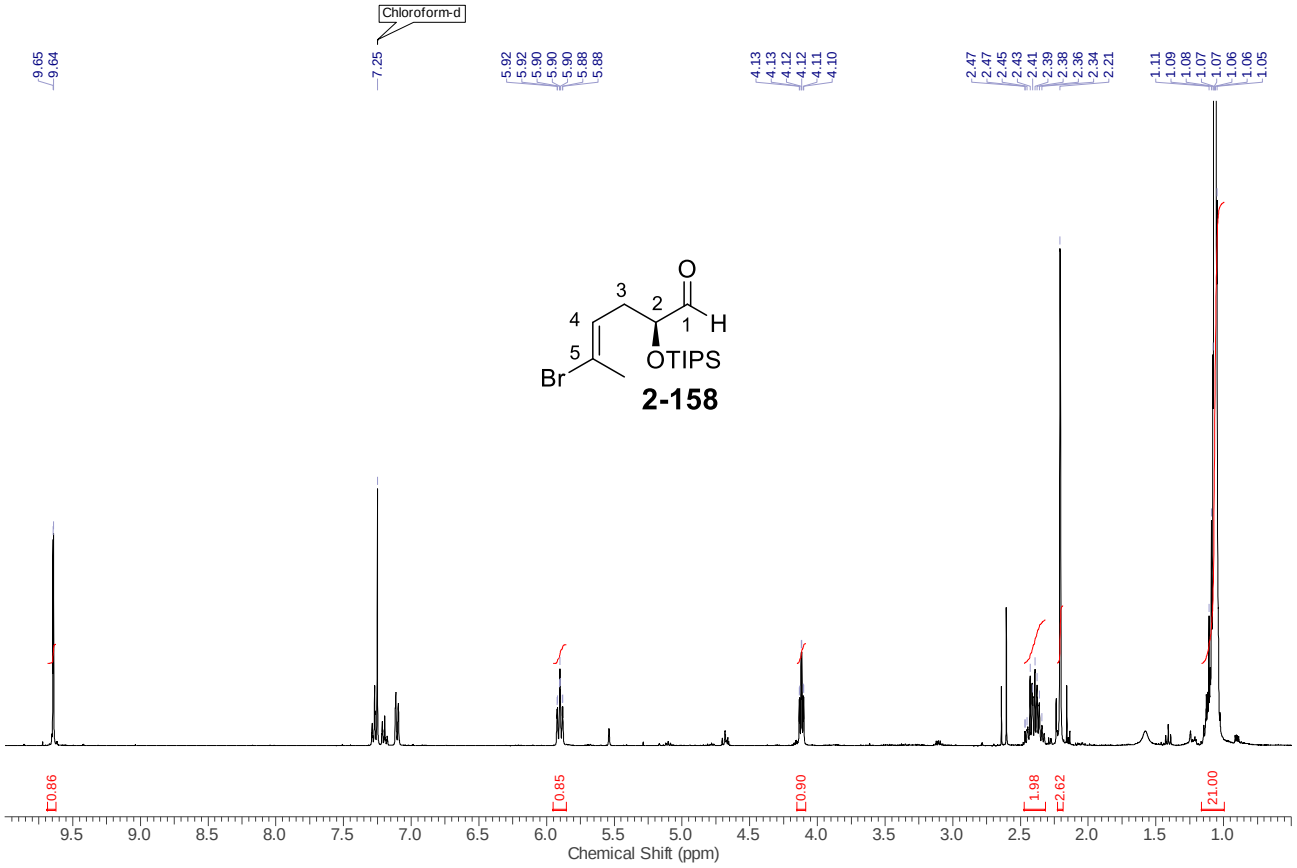
^{13}C NMR (100 MHz) spectrum of silyl ether **2-156** in $CDCl_3$ (10 – 150 ppm)



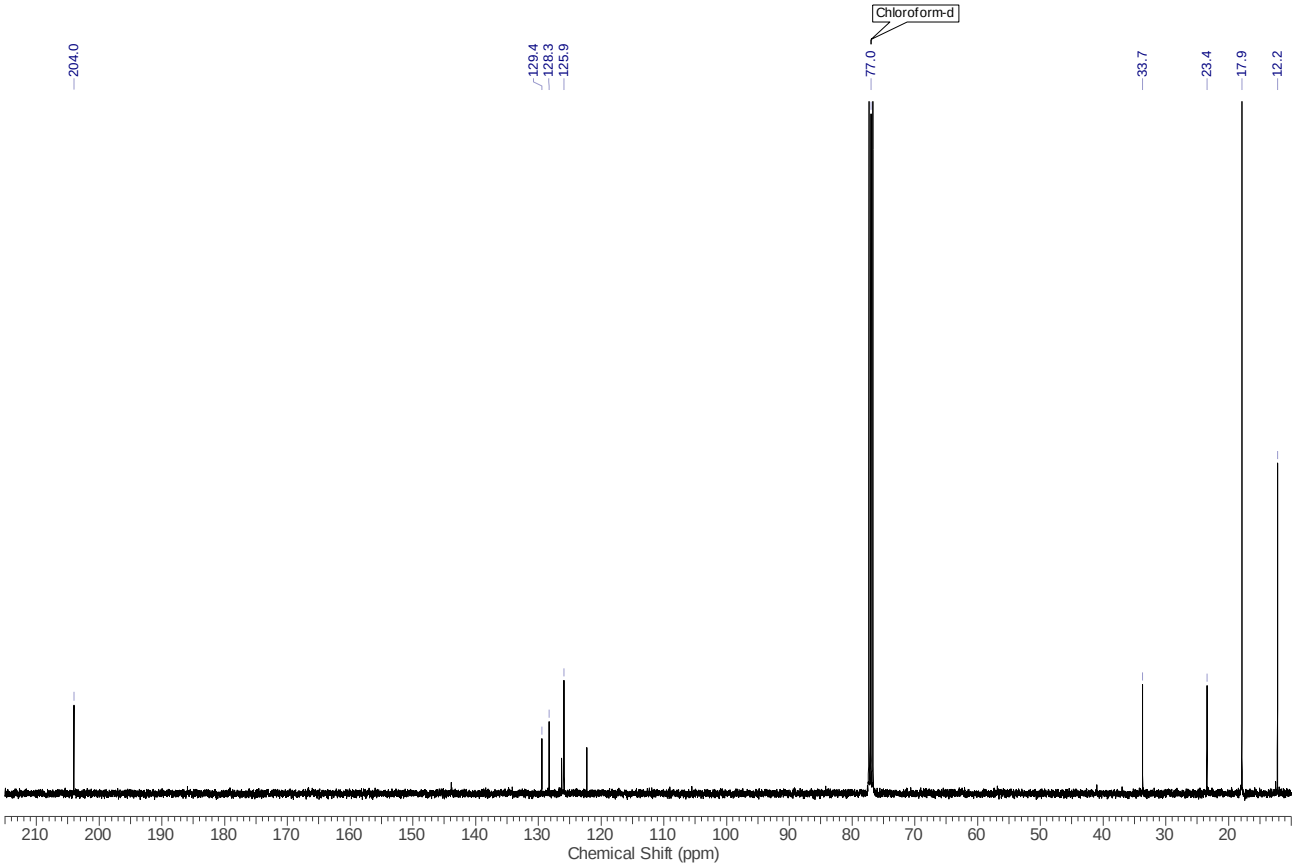
^{1}H NMR (400 MHz) spectrum of primary alcohol **2-157** in $CDCl_3$ (0.5 – 7.5 ppm)



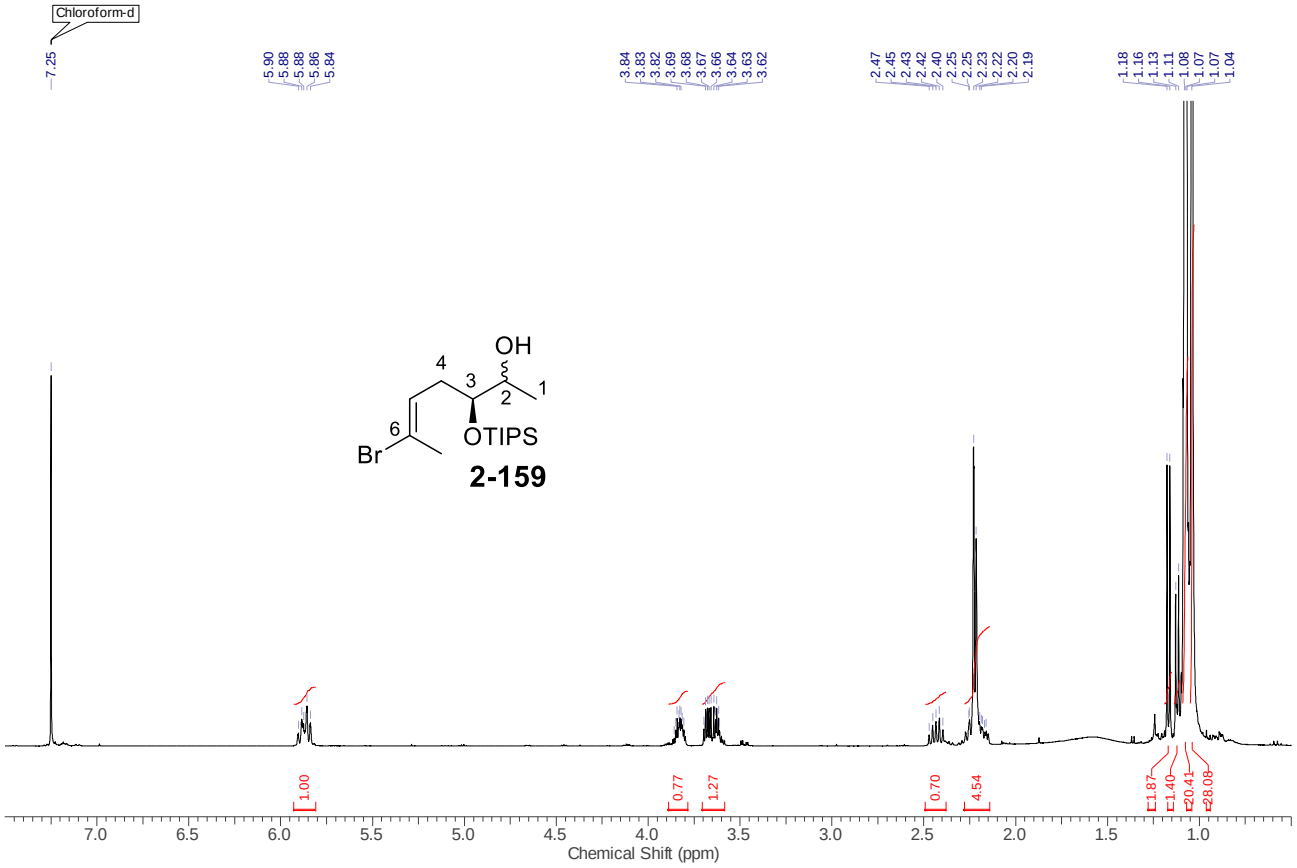
^{13}C NMR (100 MHz) spectrum of alcohol **2-157** in $CDCl_3$ (10 – 150 ppm)



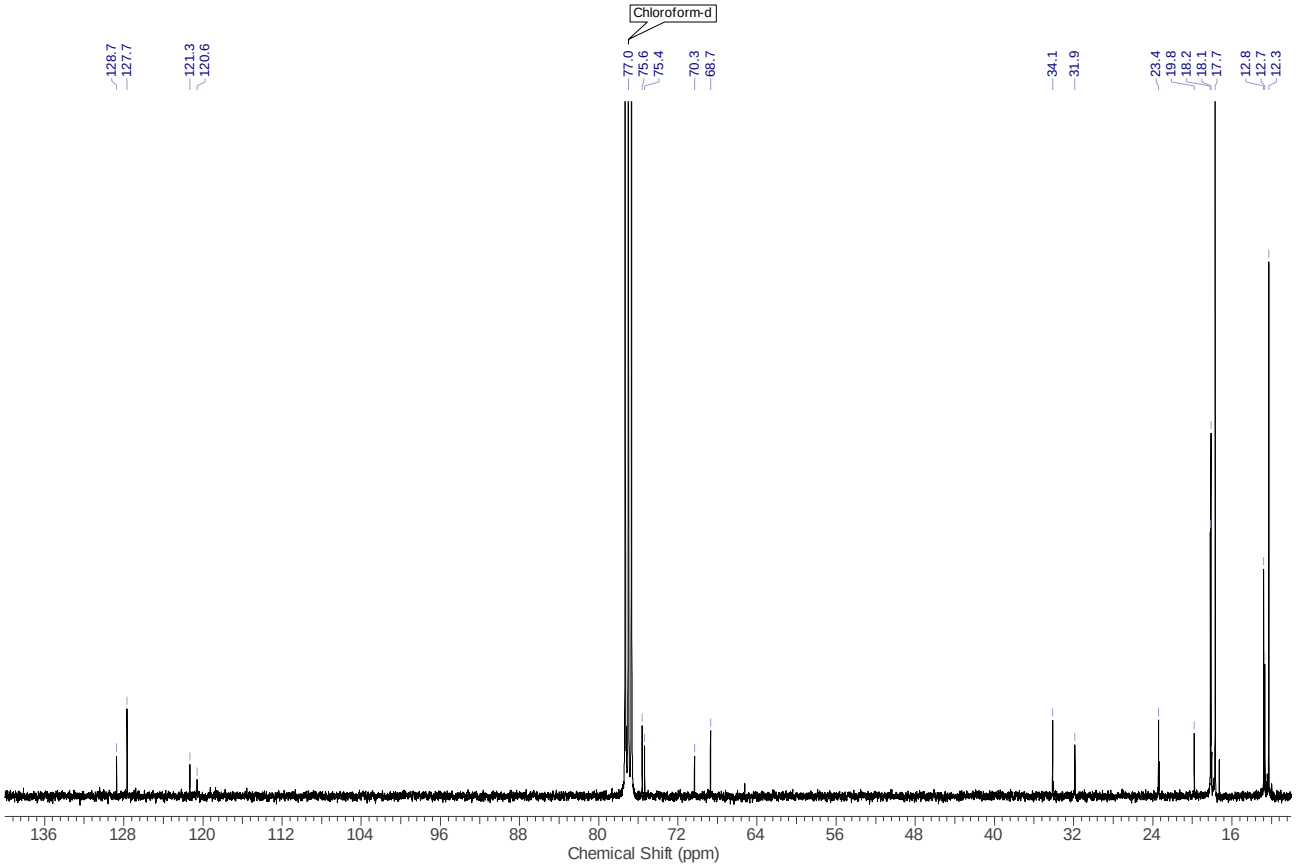
^{1}H NMR (400 MHz) spectrum of aldehyde **2-158** in $CDCl_3$ (0.5 – 10.0 ppm)



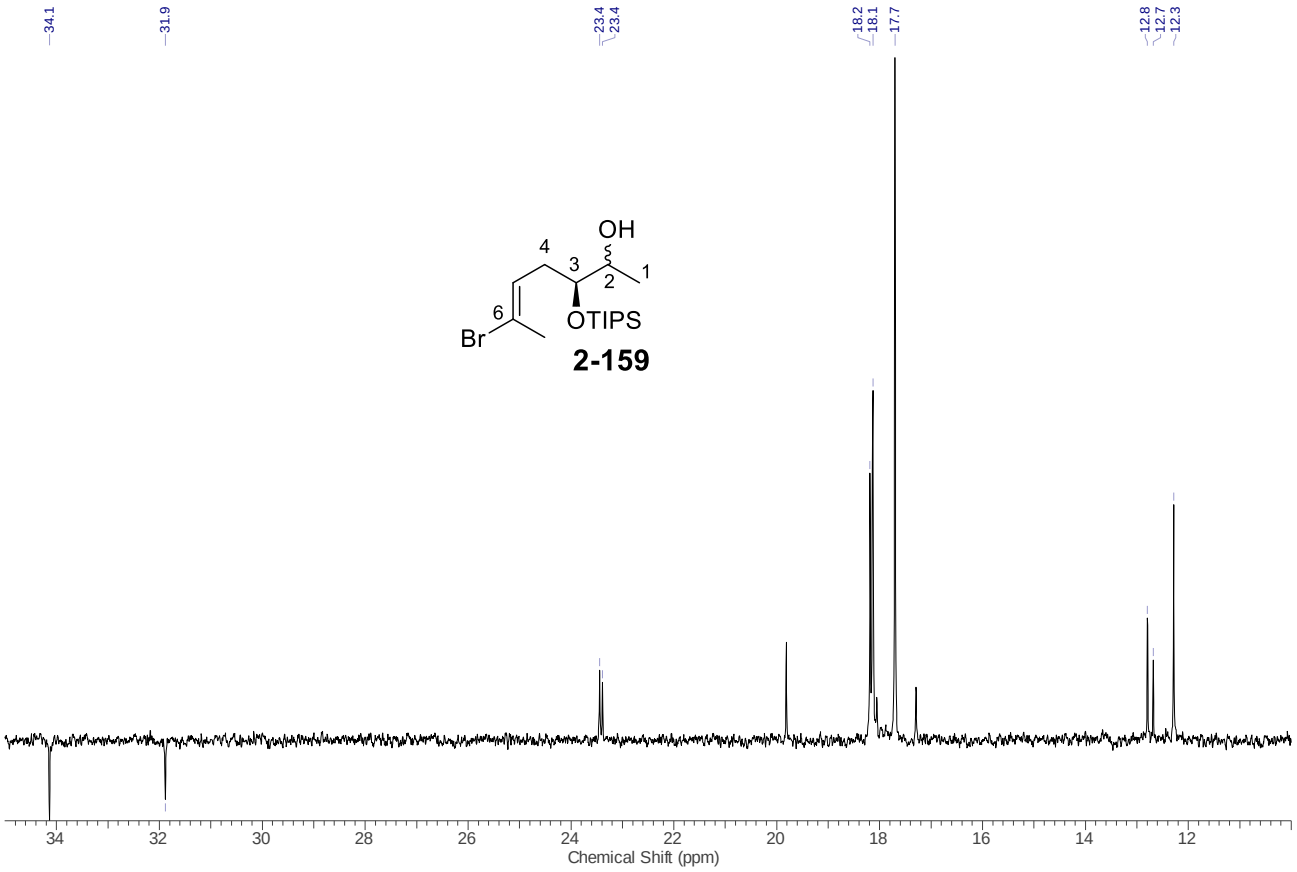
^{13}C NMR (100 MHz) spectrum of aldehyde **2-158** in $CDCl_3$ (10 – 215 ppm)



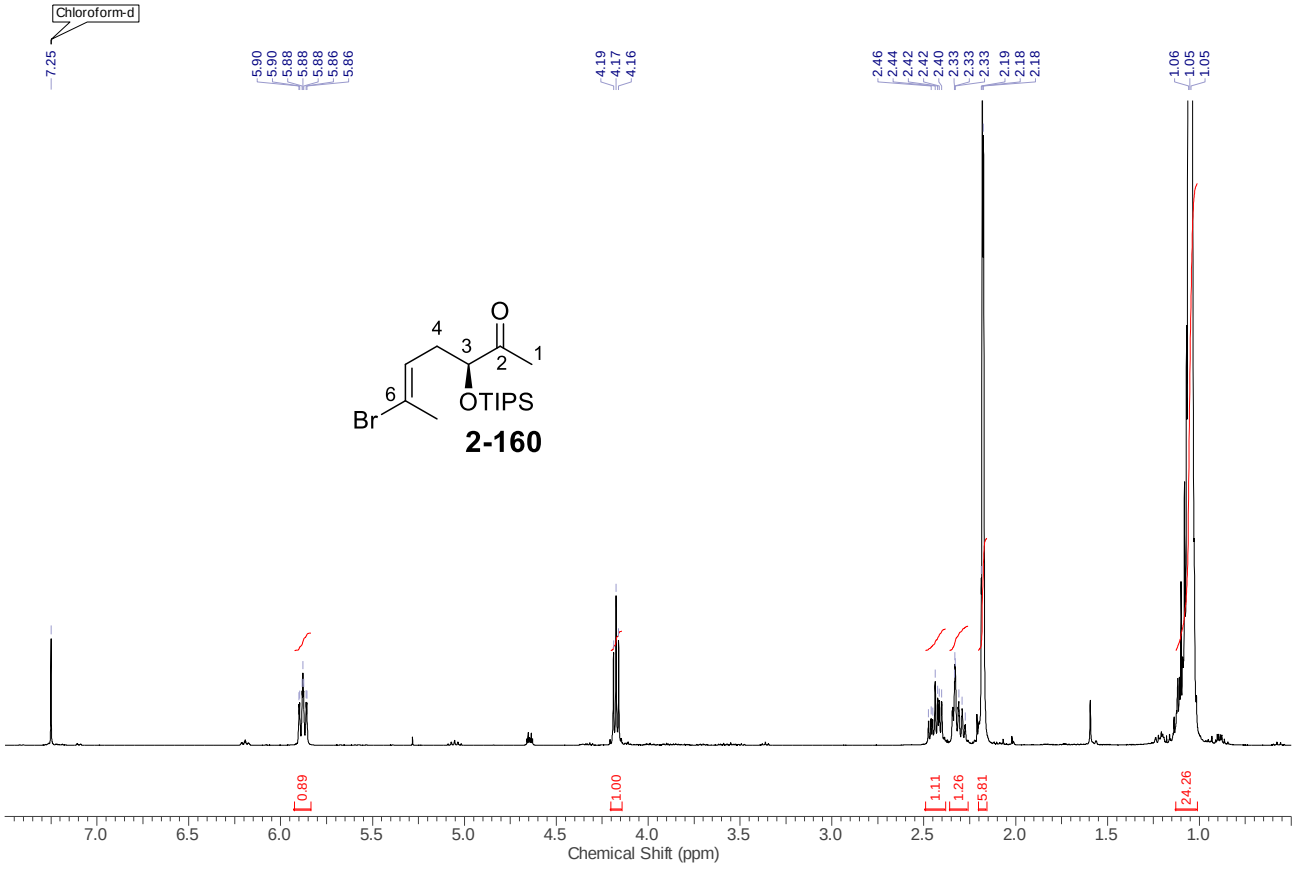
^{1}H NMR (400 MHz) spectrum of alcohol **2-159** in $CDCl_3$ (0.5 – 7.5 ppm)



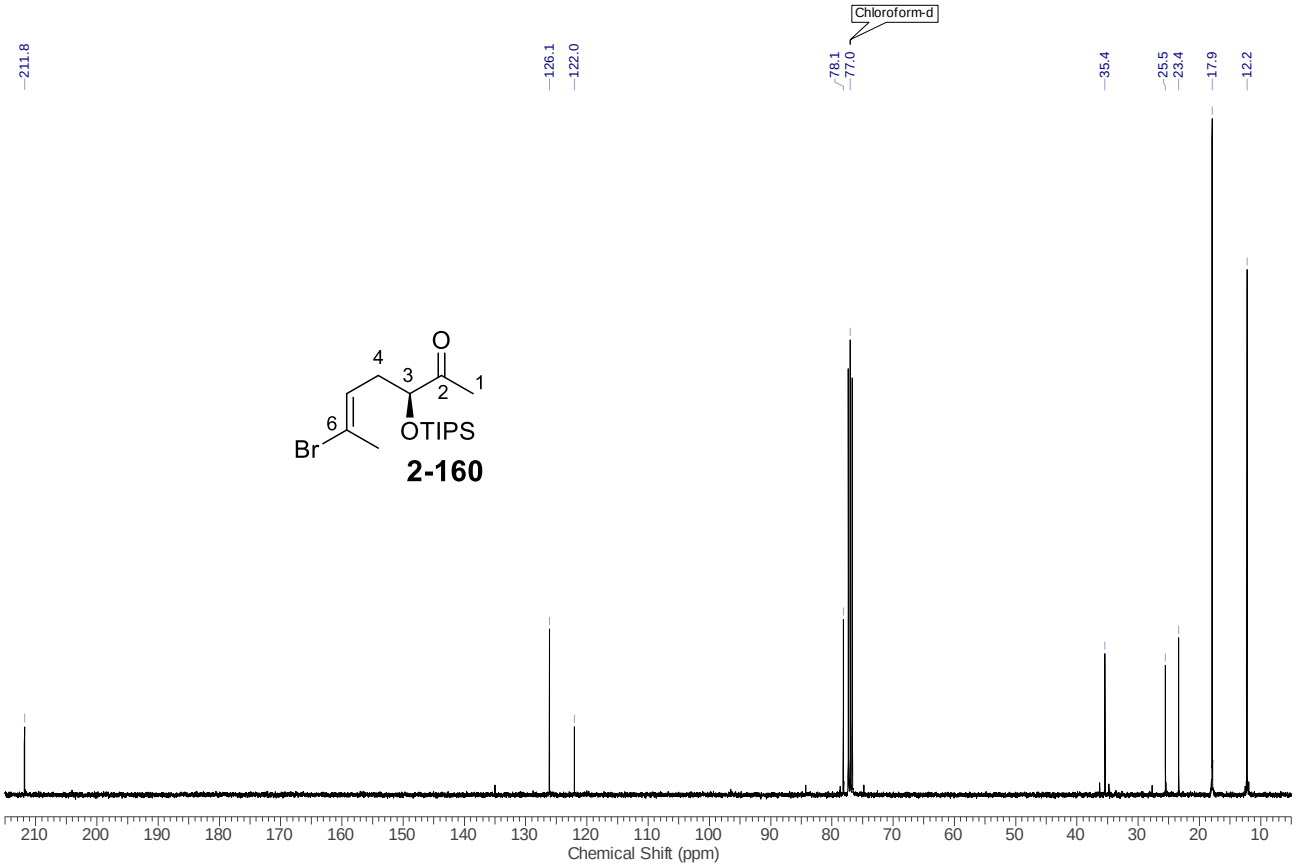
^{13}C NMR (100 MHz) spectrum of alcohol **2-159** in $CDCl_3$ (10 – 140 ppm)



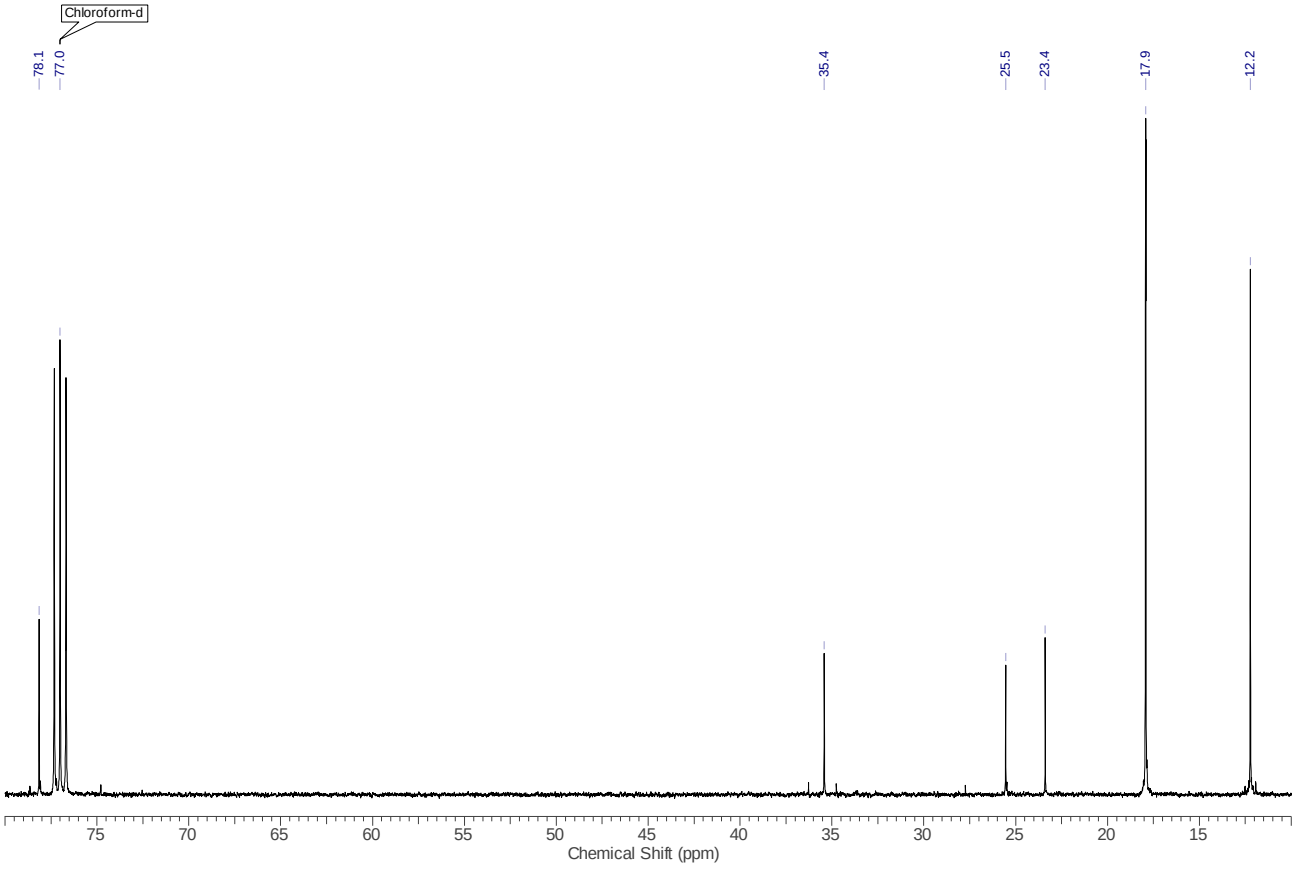
DEPT-135 (100 MHz) spectrum of alcohol **2-159** in $CDCl_3$ (10 – 35 ppm)



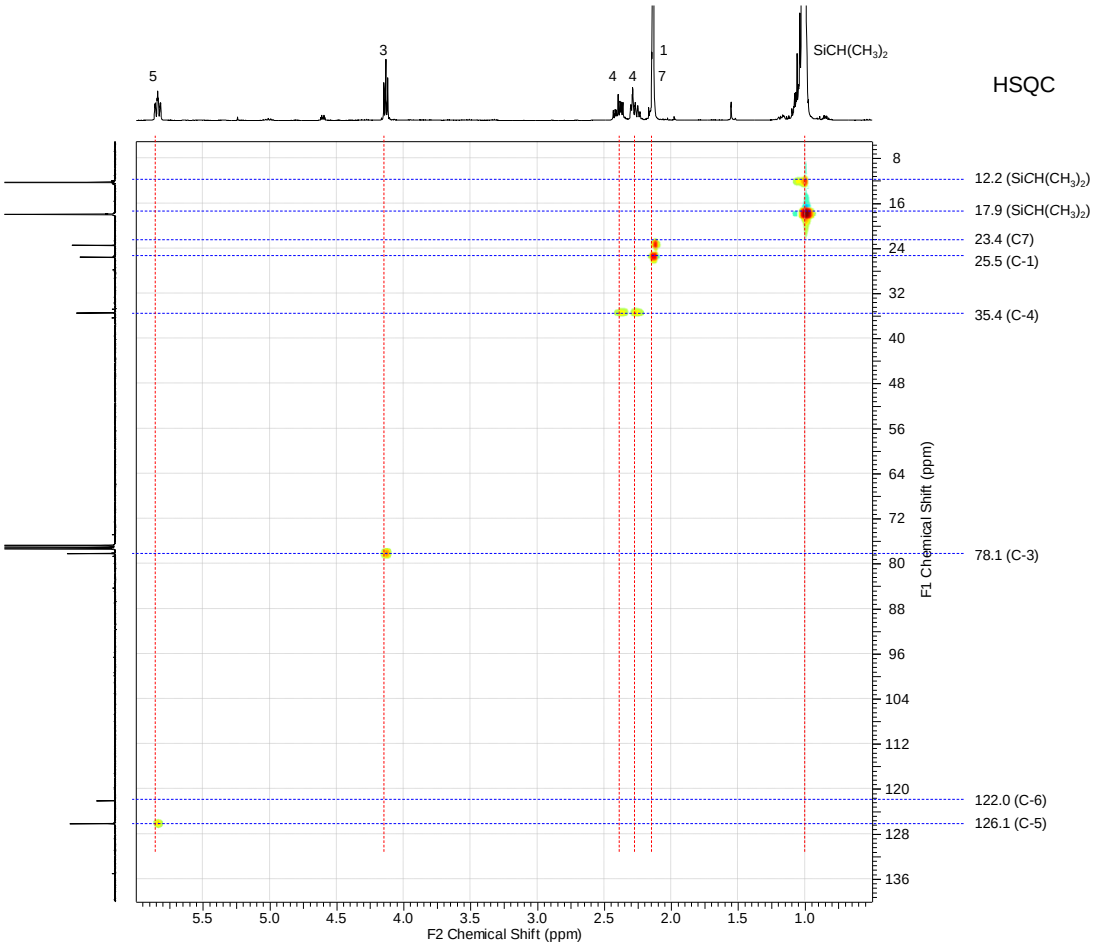
^{1}H NMR (400 MHz) spectrum of methyl ketone **2-160** in $CDCl_3$ (0.5 – 7.5 ppm)



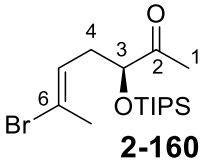
^{13}C NMR (100 MHz) spectrum of methyl ketone **2-160** in $CDCl_3$ (5 – 215 ppm)



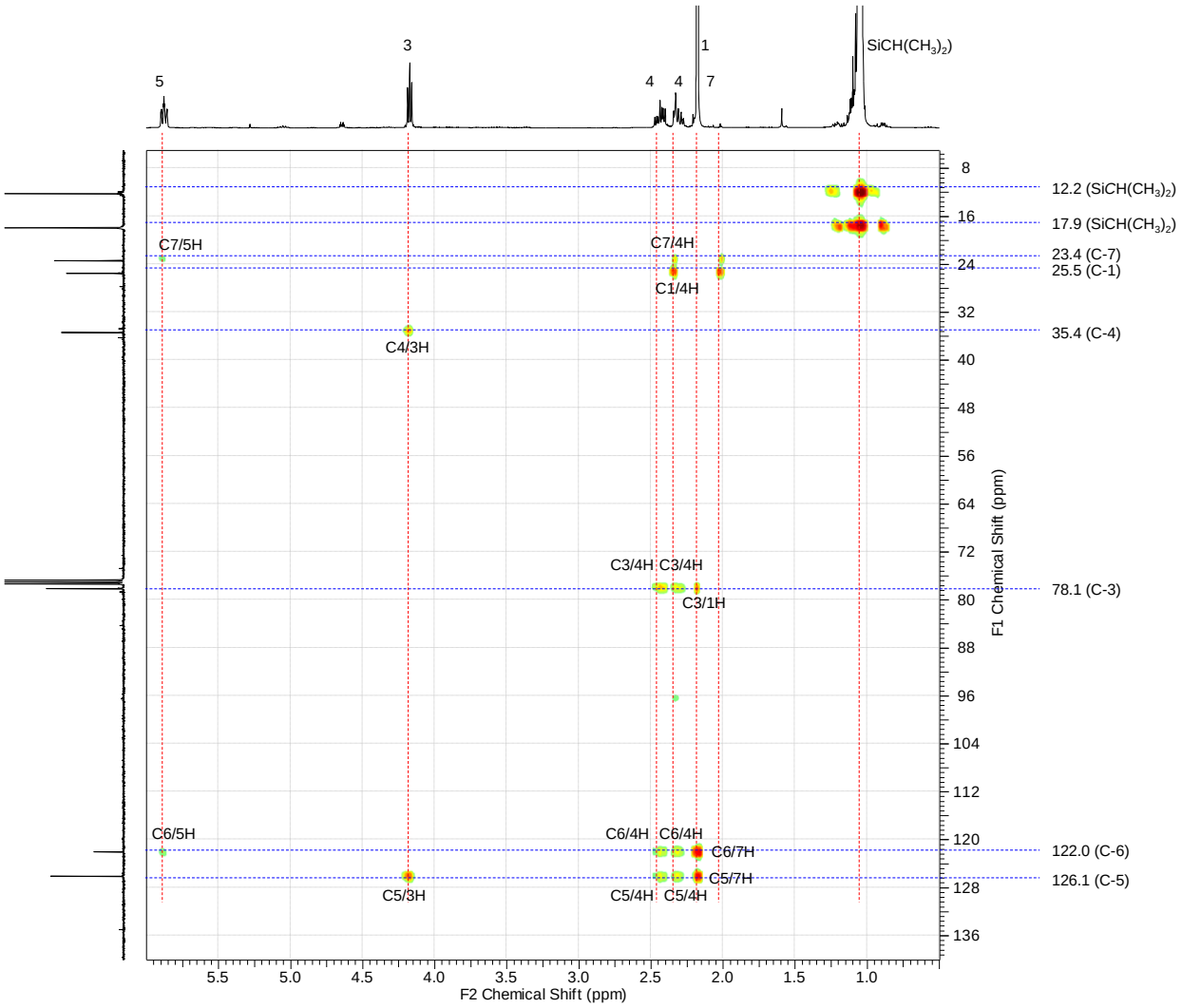
^{13}C NMR (100 MHz) spectrum of methyl ketone **2-160** in $CDCl_3$ (10 – 80ppm)



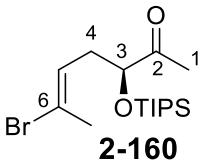
HSQC spectrum of methyl ketone **2-160** in $CDCl_3$ (0.5 – 6.0, 5 – 140 ppm)



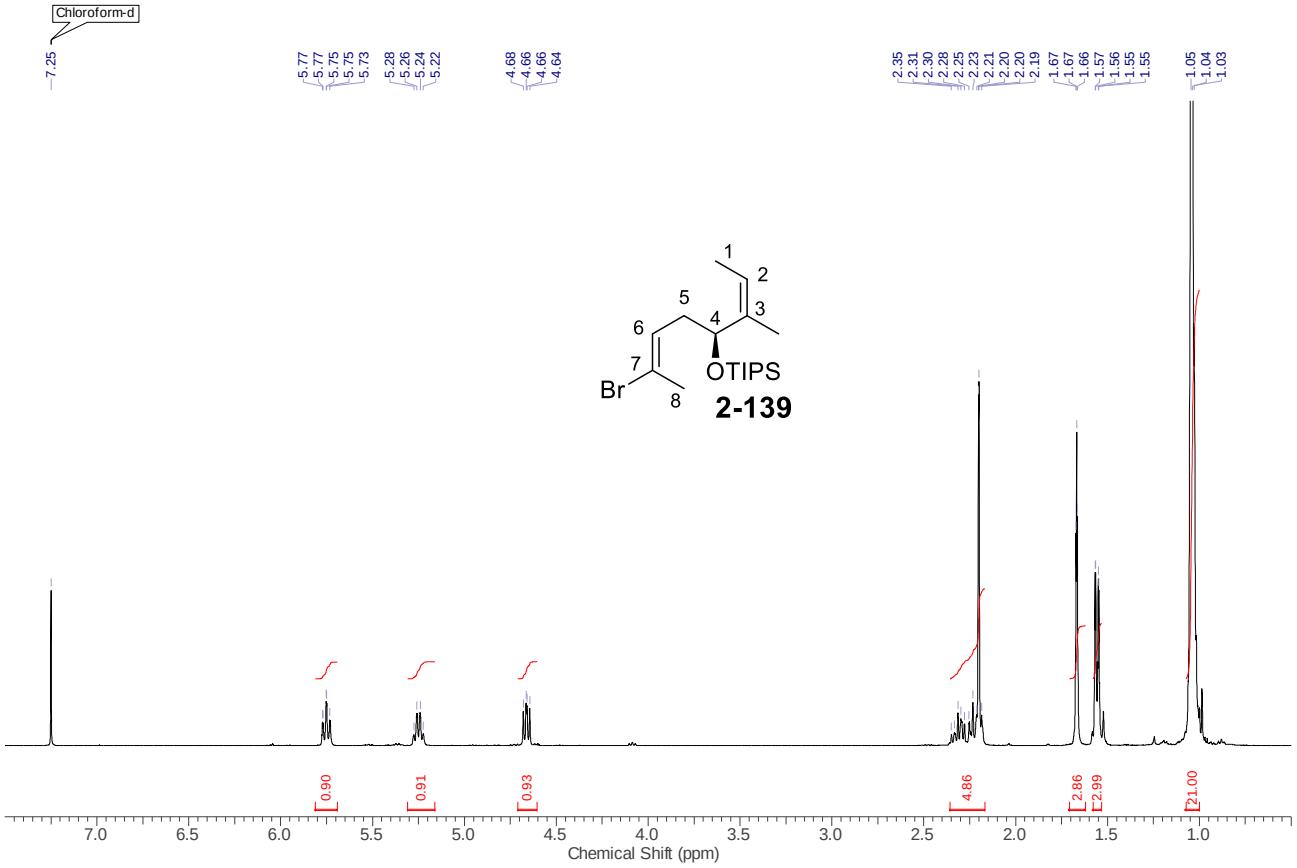
2-160



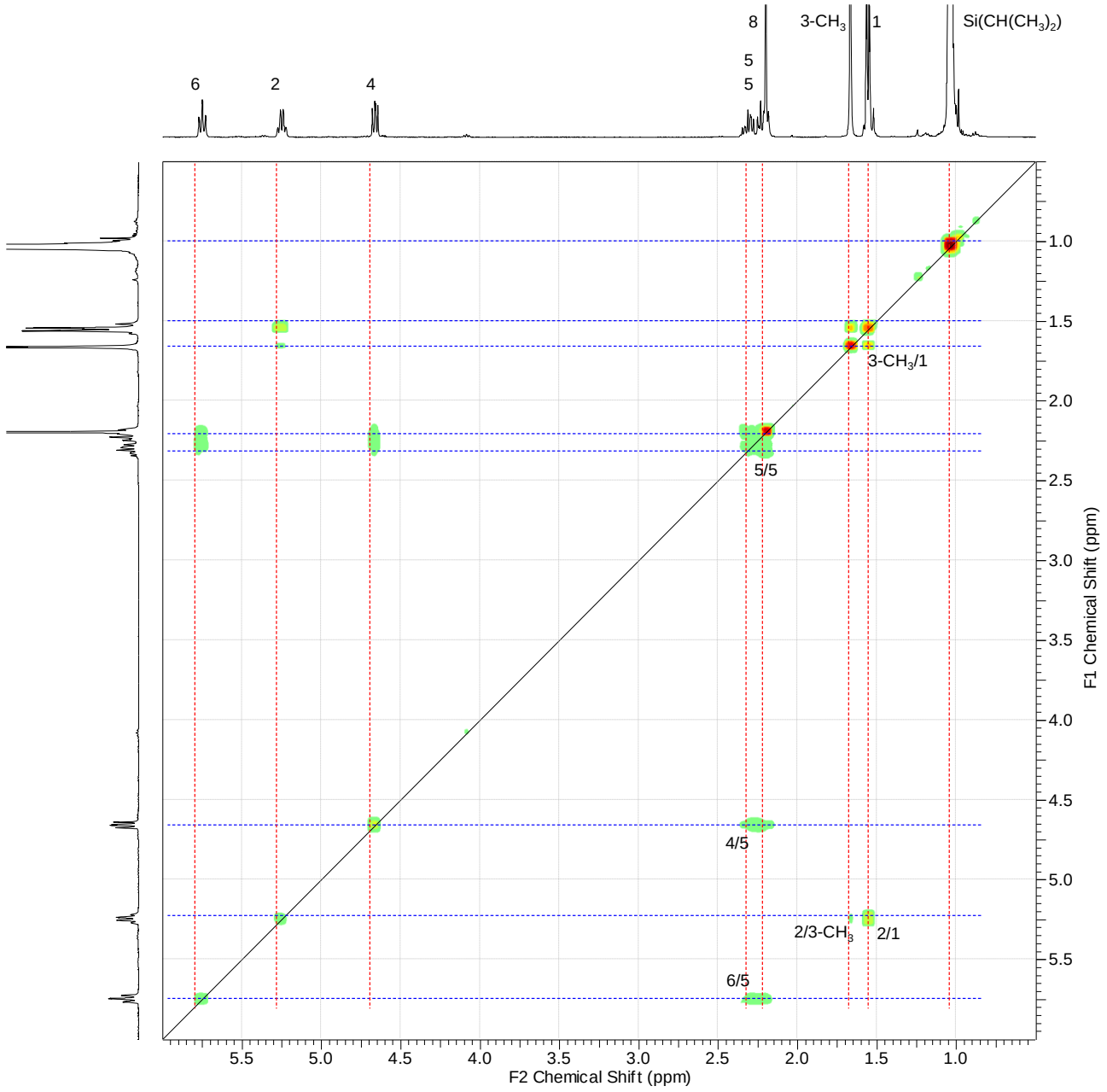
HMBC spectrum of methyl ketone **2-160** in $CDCl_3$ (0.5 – 6.0, 5 – 140 ppm)



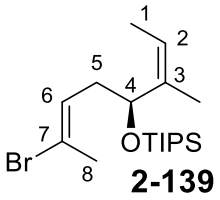
2-160



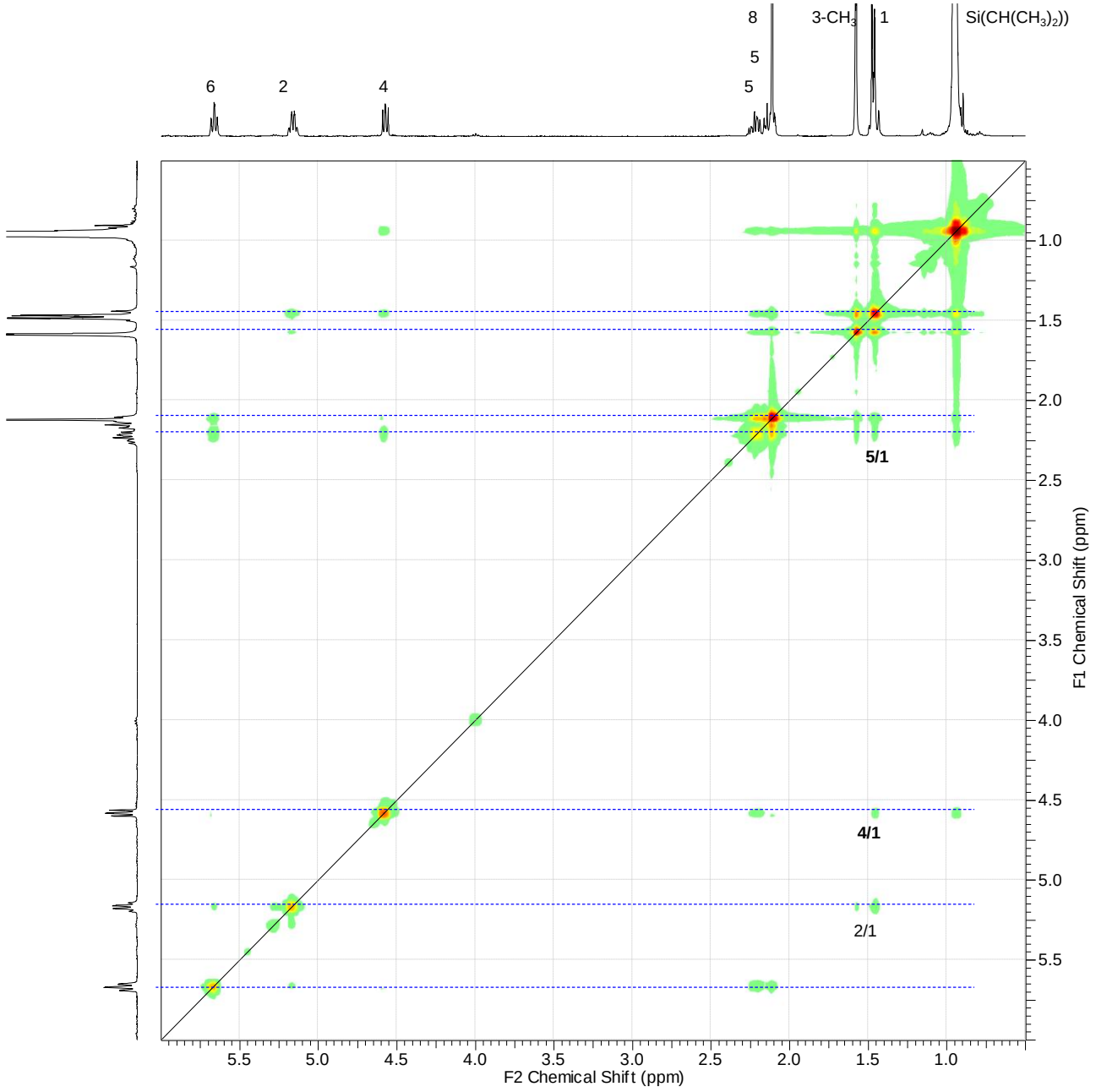
^{1}H NMR (400 MHz) spectrum of alkene **2-139** in $CDCl_3$ (0.5 – 7.5 ppm)



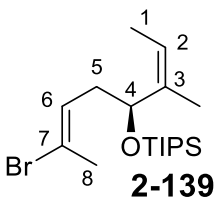
COSY spectrum of alkene **2-139** in $CDCl_3$ (0.5 – 6.0 ppm)



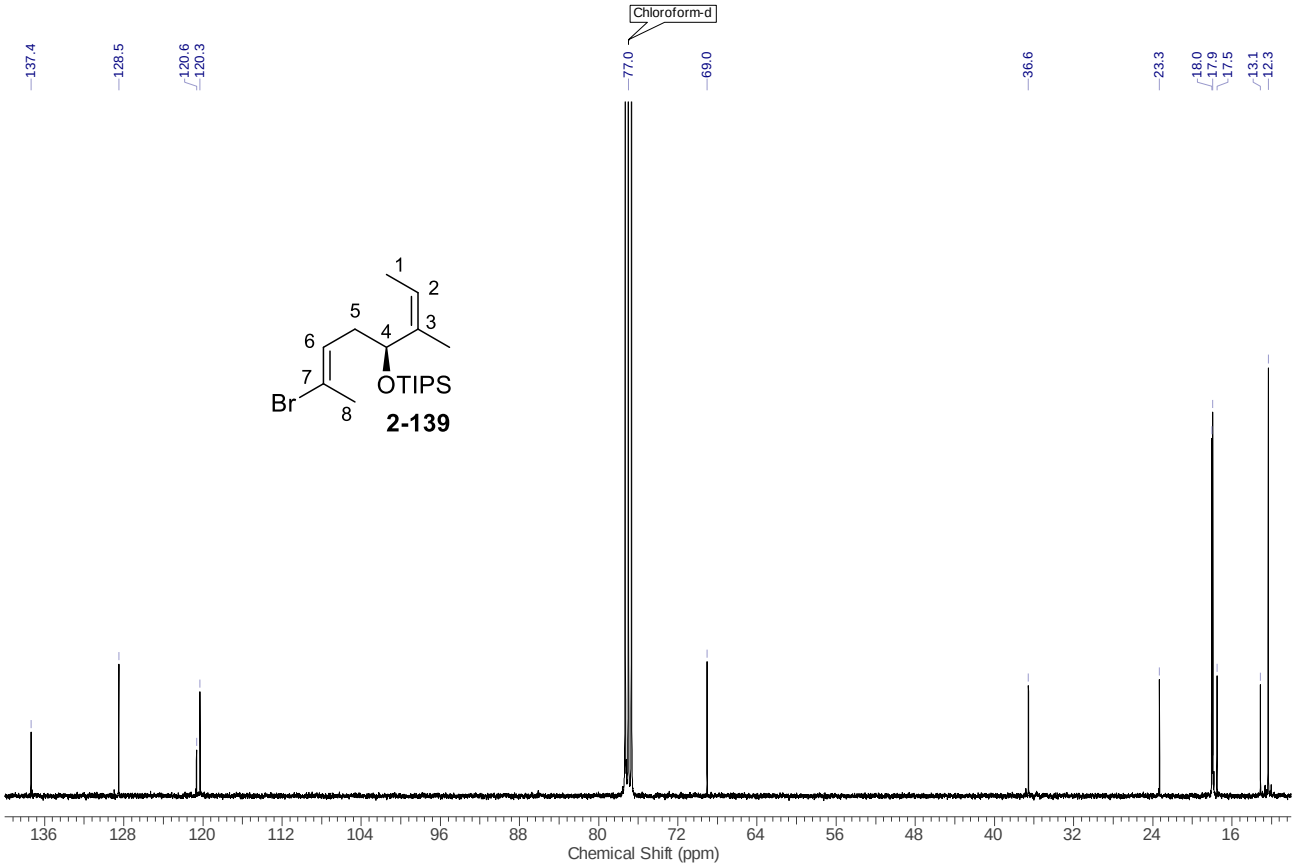
2-139



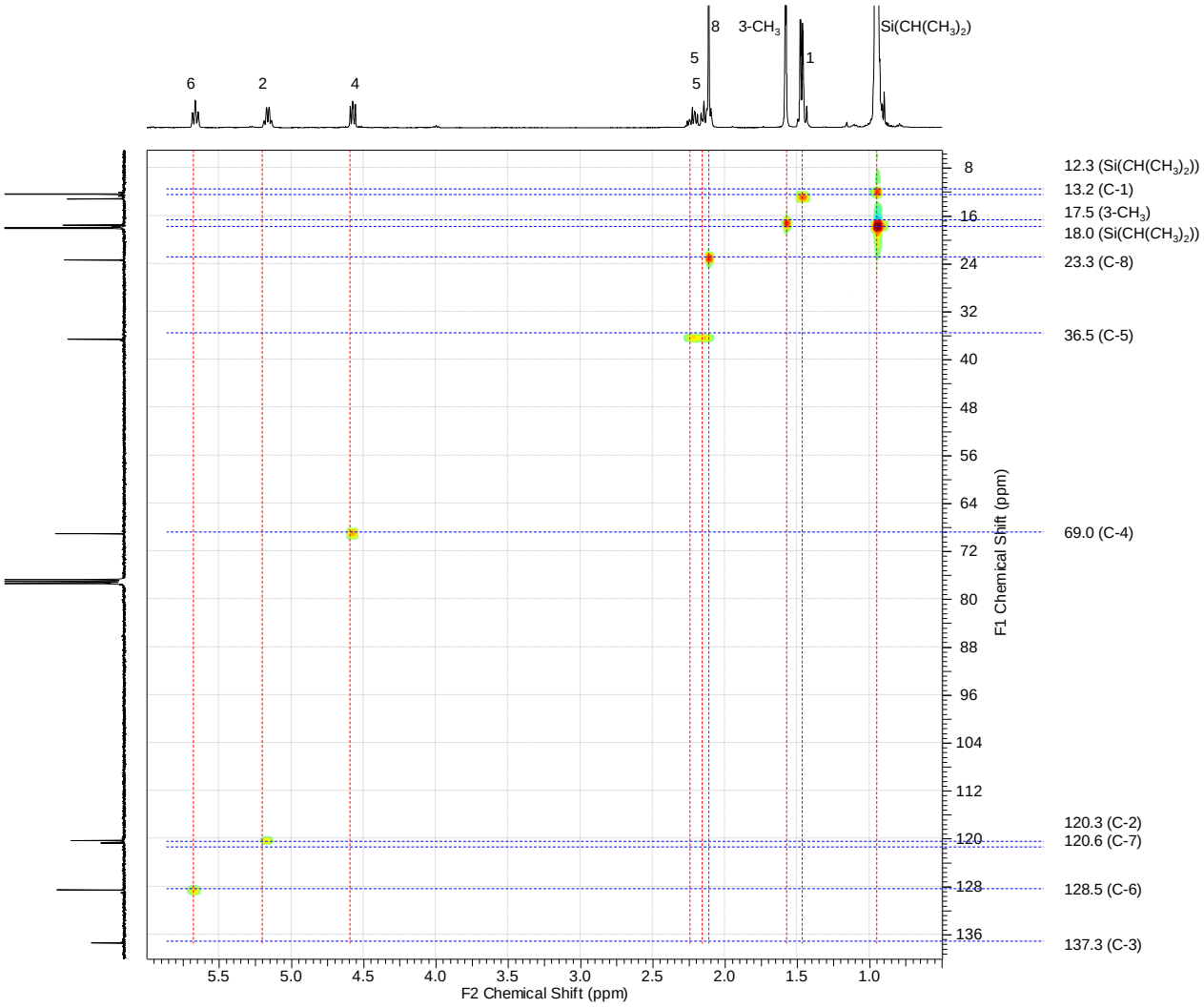
NOESY spectrum of alkene **2-139** in $CDCl_3$ (0.5 – 6.0 ppm)



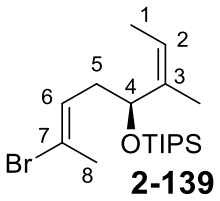
2-139



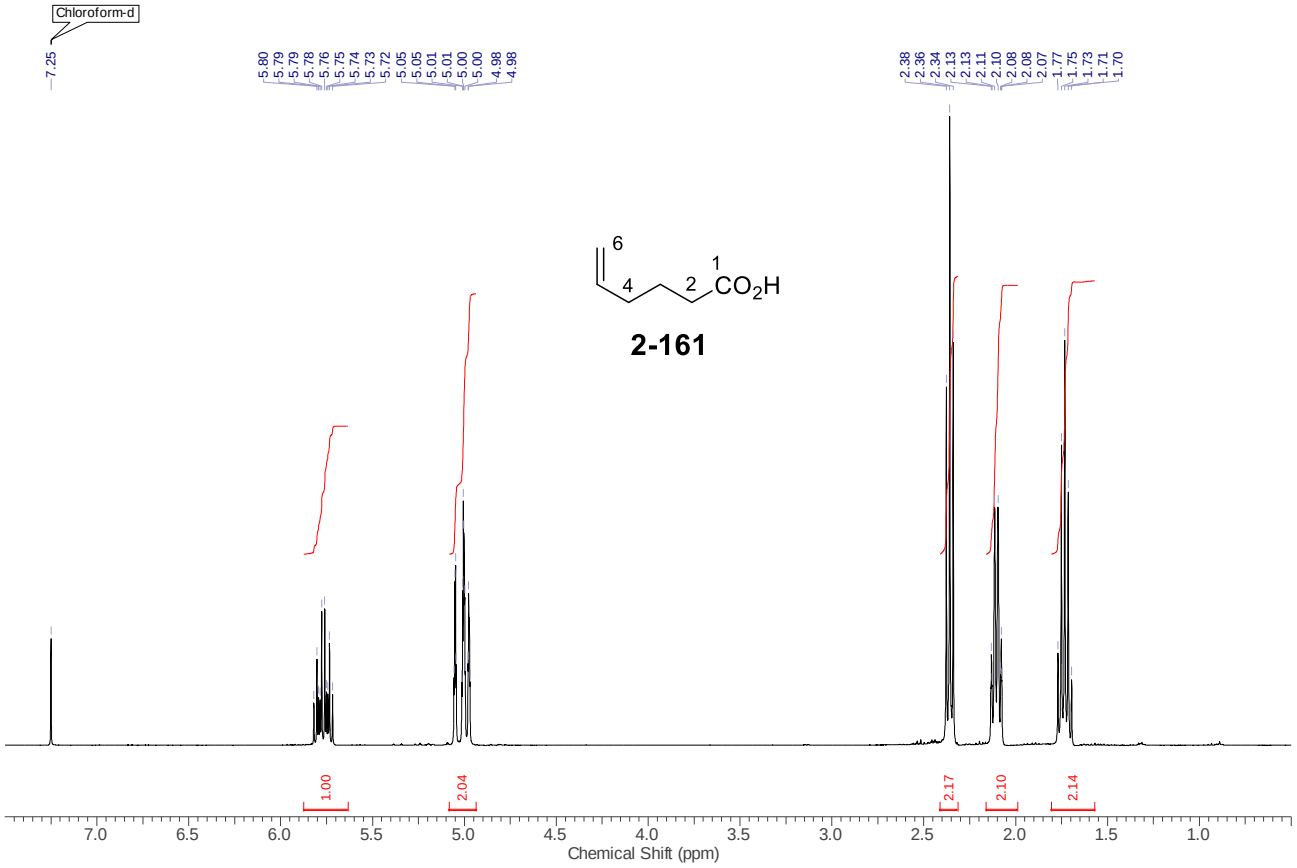
^{13}C NMR (100 MHz) spectrum of alkene **2-139** in $CDCl_3$ (10 – 140 ppm)



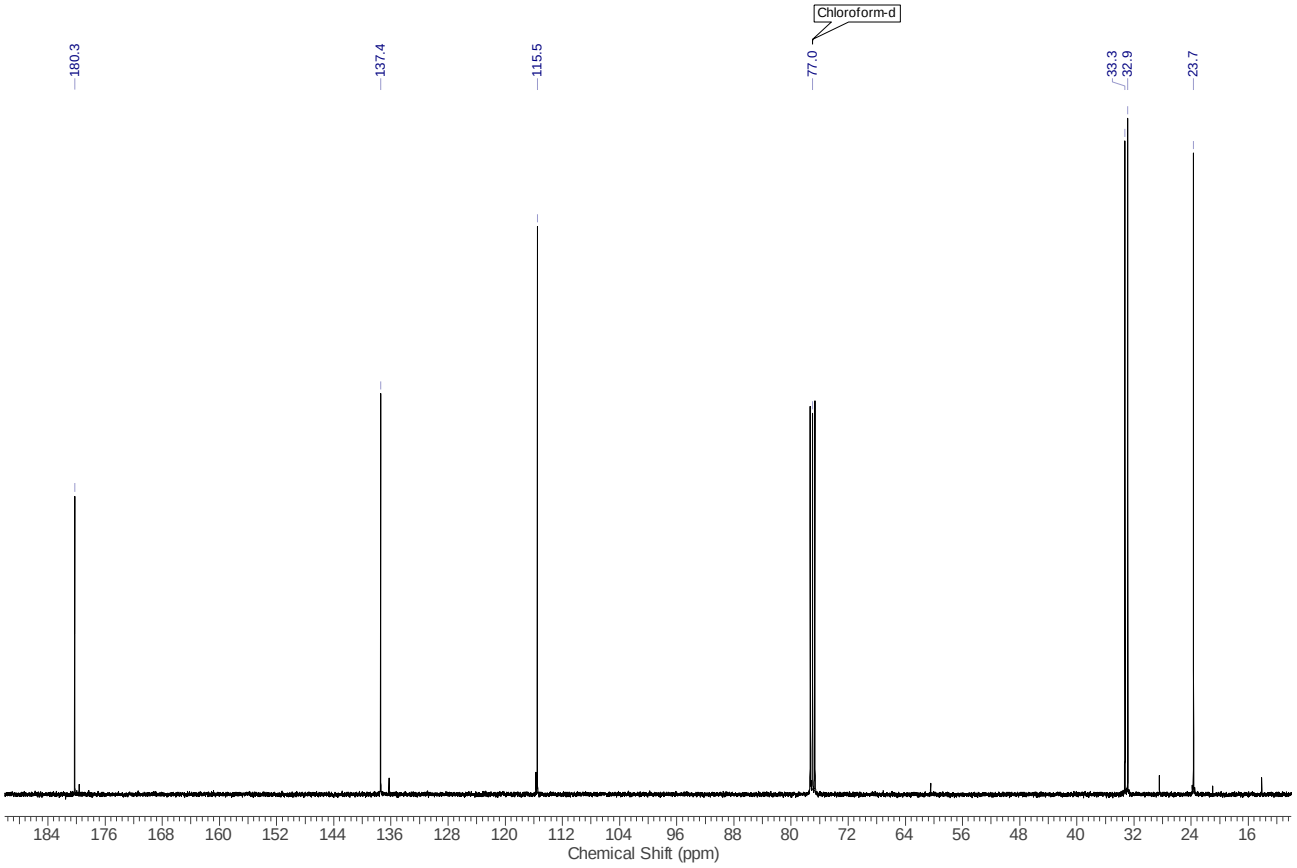
HSQC spectrum of alkene **2-139** in $CDCl_3$ (0.5 – 6.0, 5 – 140 ppm)



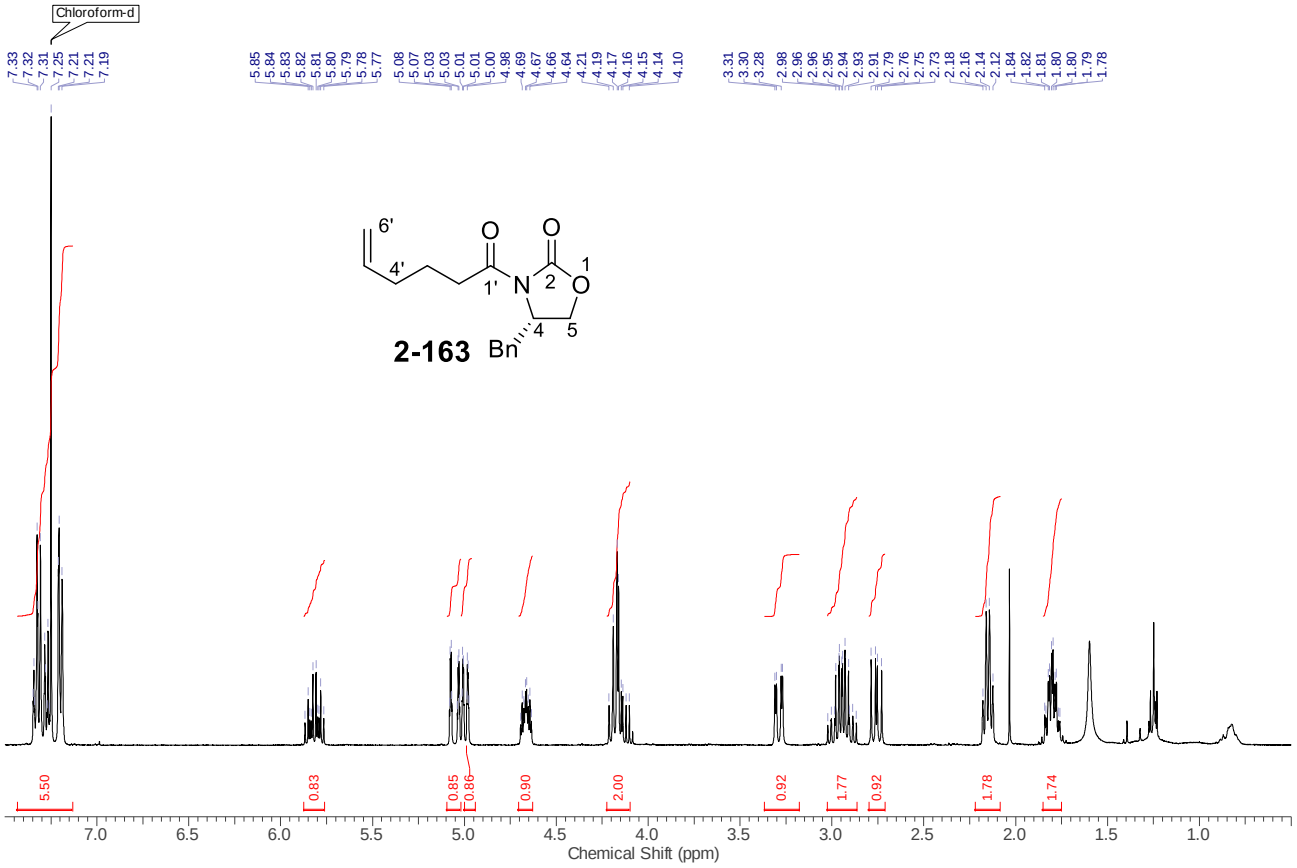
2-139



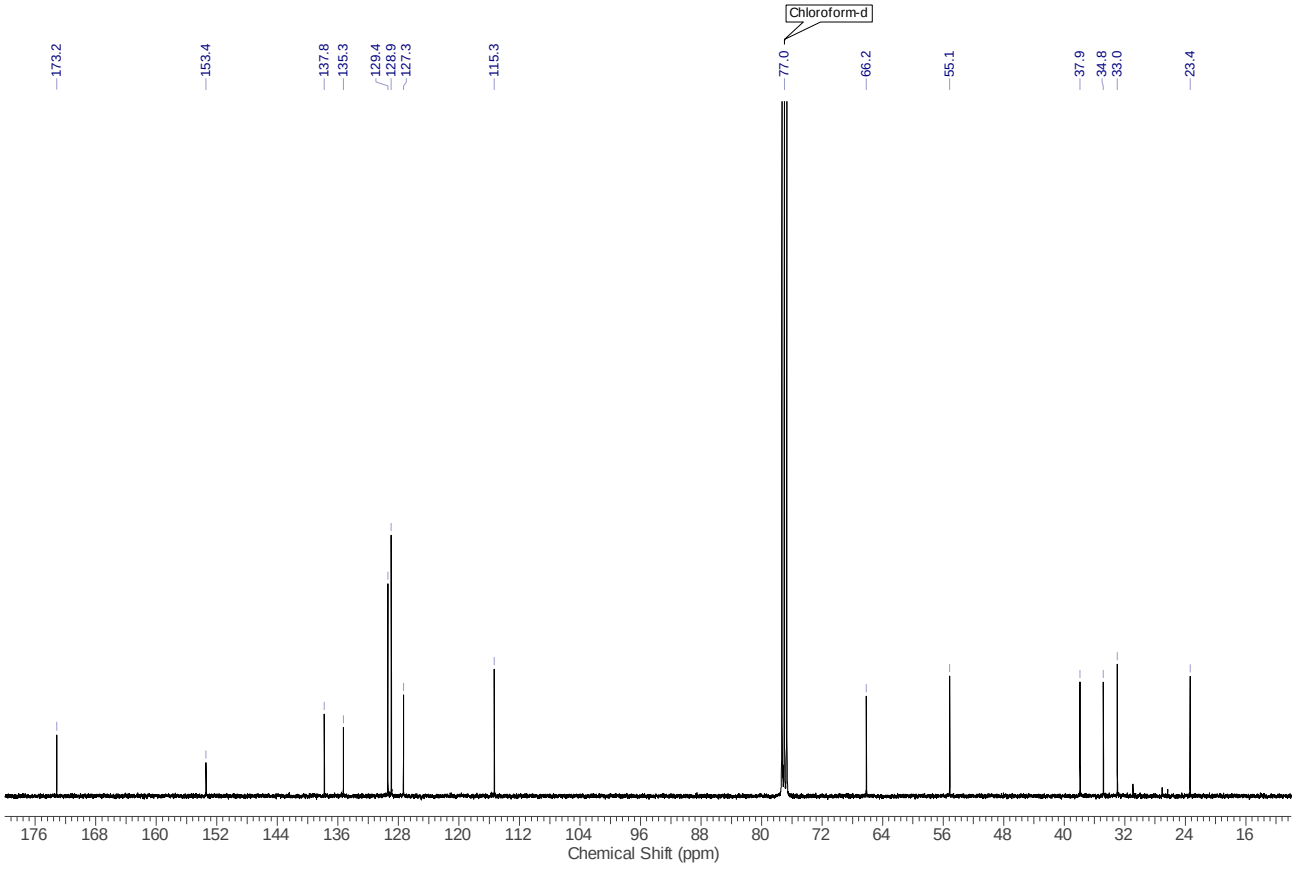
^{1}H NMR (400 MHz) spectrum of hexenoic acid **2-161** in $CDCl_3$ (0.5 – 7.5 ppm)



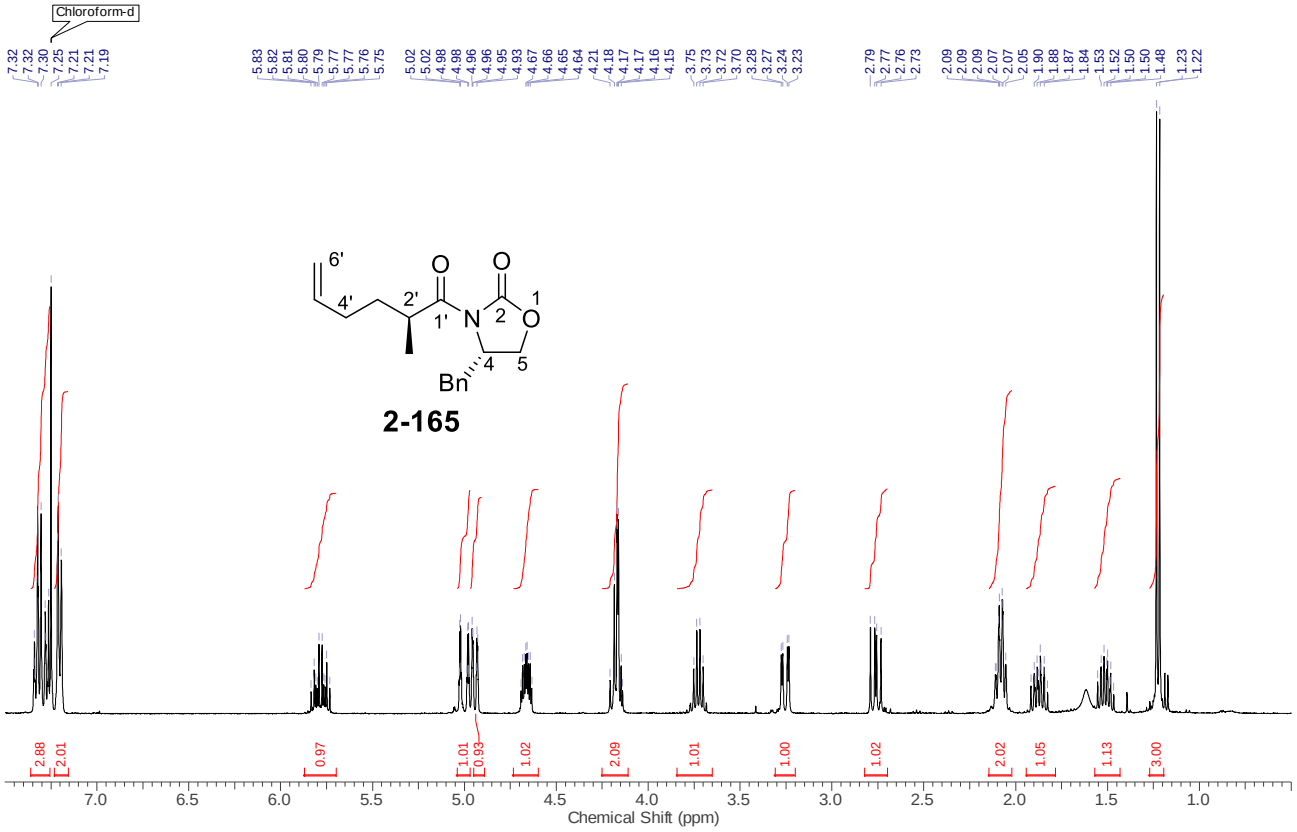
^{13}C NMR (100 MHz) spectrum of hexenoic acid **2-161** in $CDCl_3$ (10 – 190 ppm)



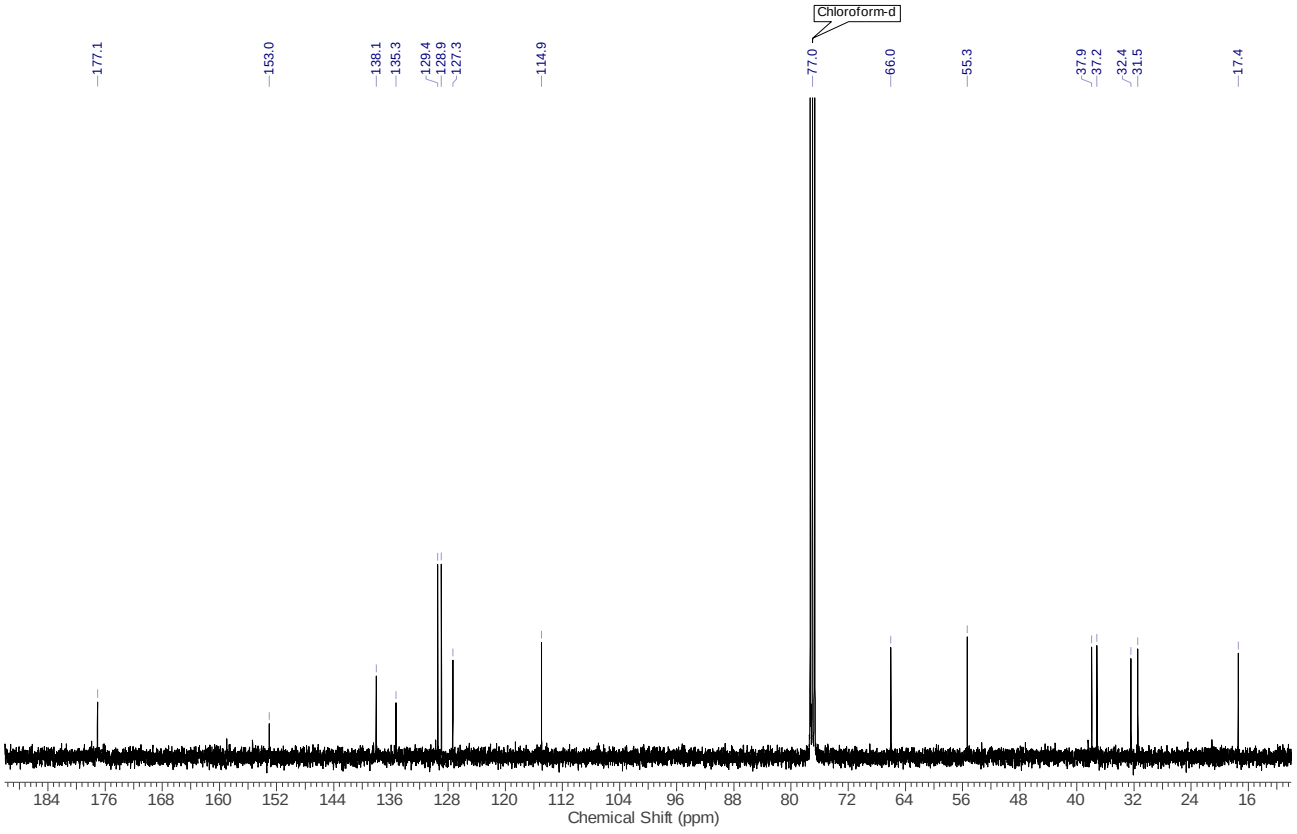
^{1}H NMR (400 MHz) spectrum of acyloxazolidinone **2-163** in $CDCl_3$ (0.5 – 7.5 ppm)



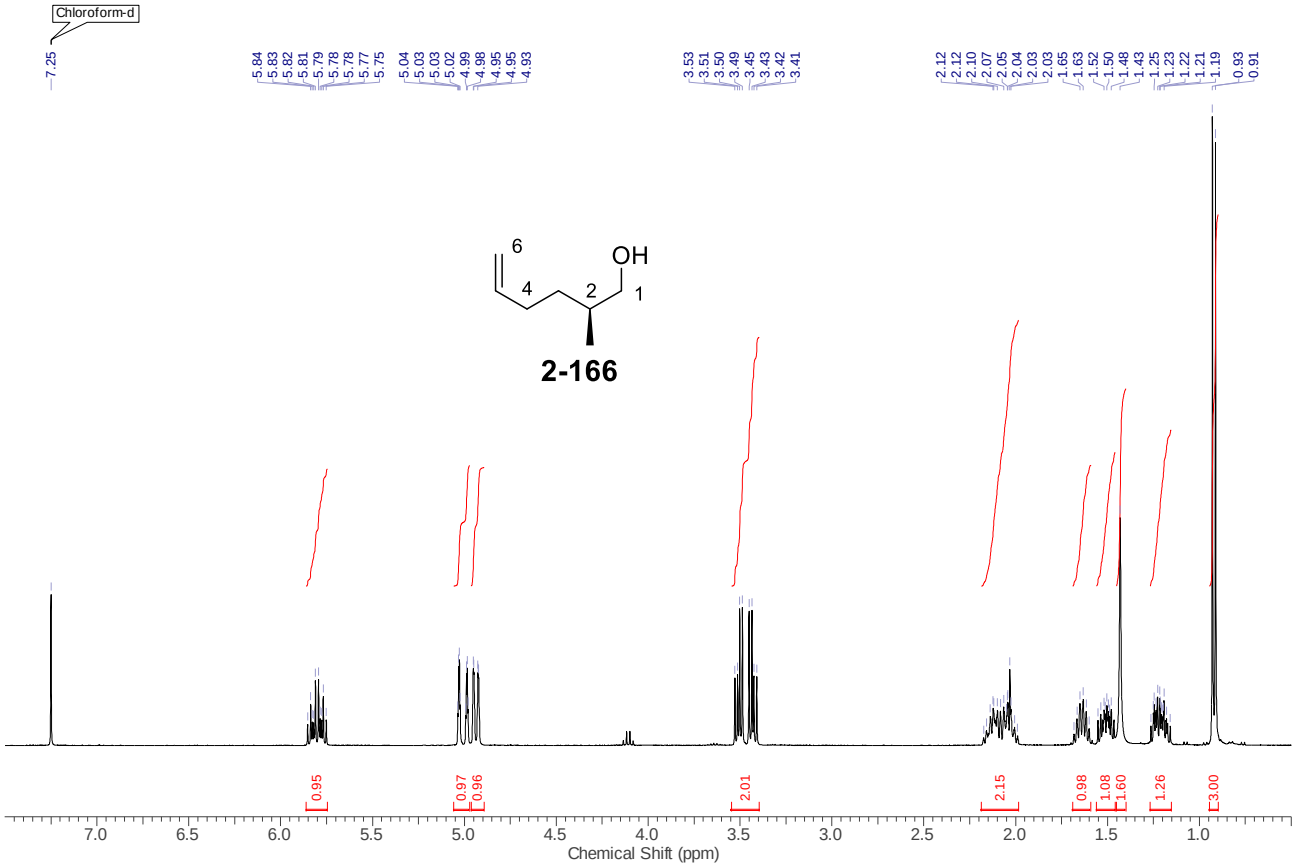
^{13}C NMR (100 MHz) spectrum of acyloxazolidinone **2-163** in $CDCl_3$ (10 – 180 ppm)



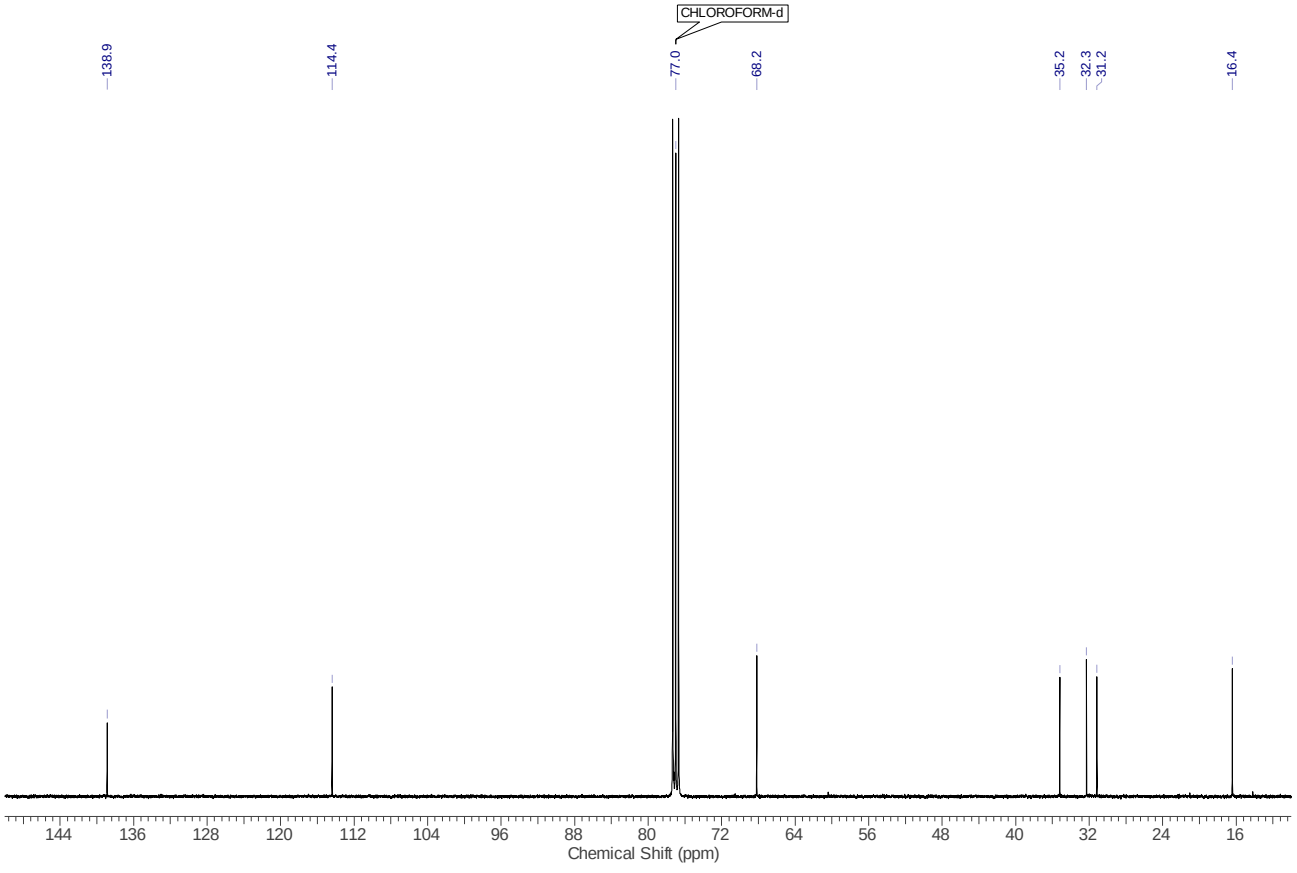
^{1}H NMR (400 MHz) spectrum of 2-methylhexenoic acid derivative **2-165** in $CDCl_3$ (0.5 – 7.5 ppm)



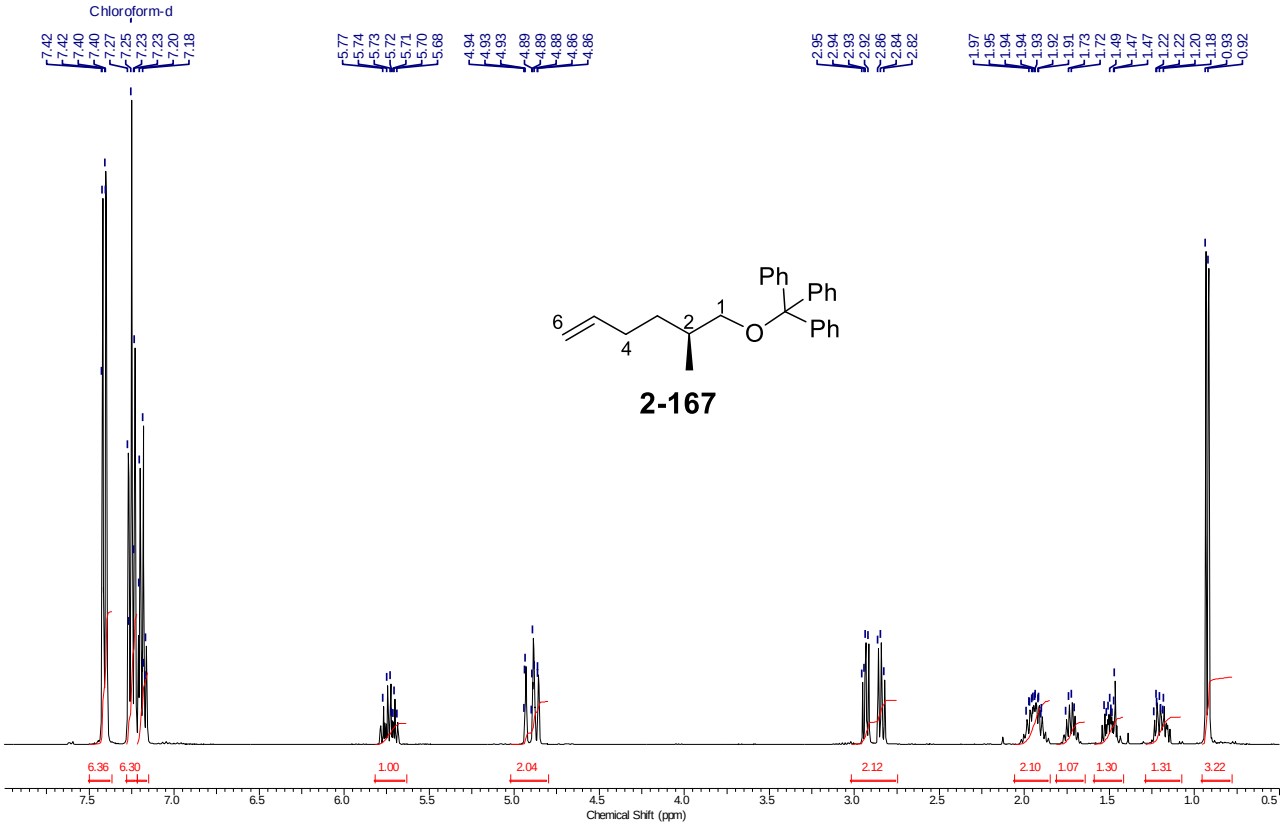
^{13}C NMR (100 MHz) spectrum of 2-methylhexenoic acid derivative **2-165** in $CDCl_3$ (10 – 190 ppm)



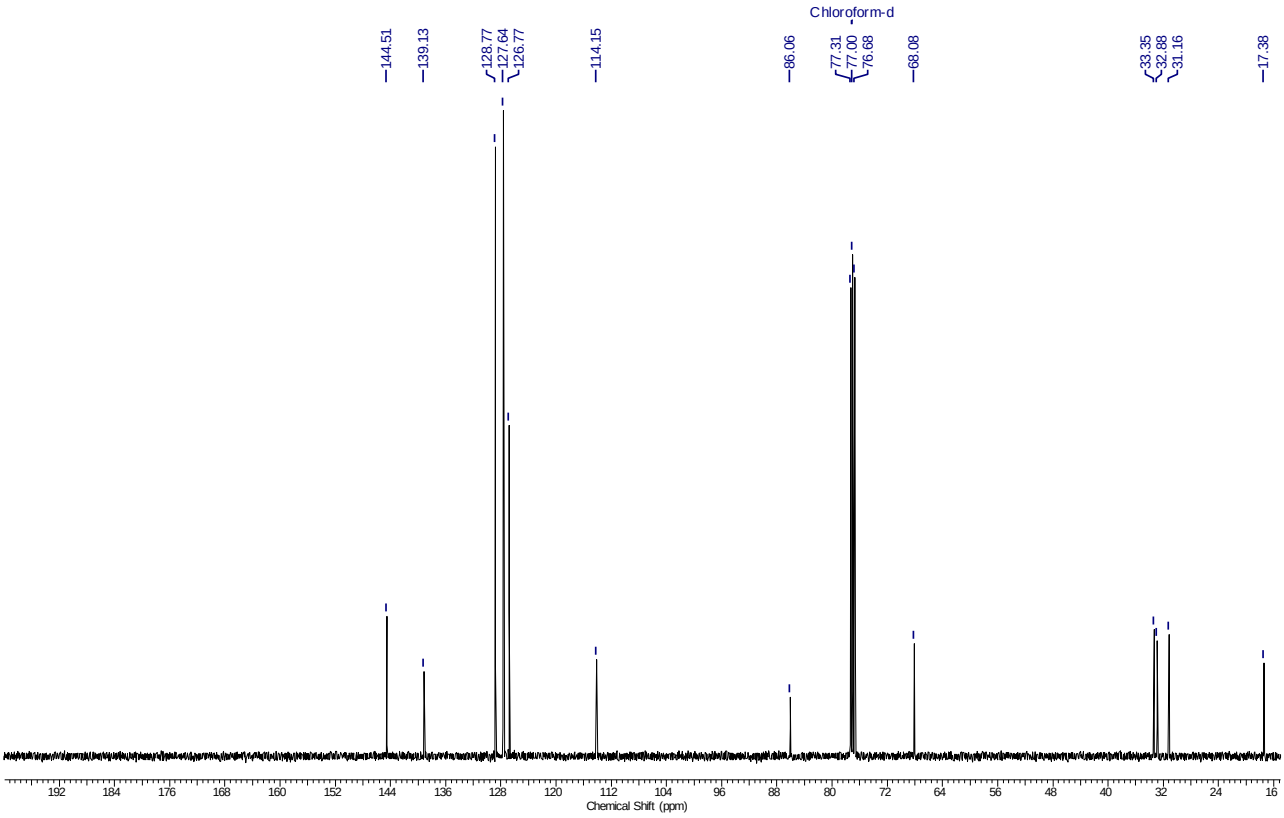
^{1}H NMR (400 MHz) spectrum of alkenol **2-166** in $CDCl_3$ (0.5 – 7.5 ppm)



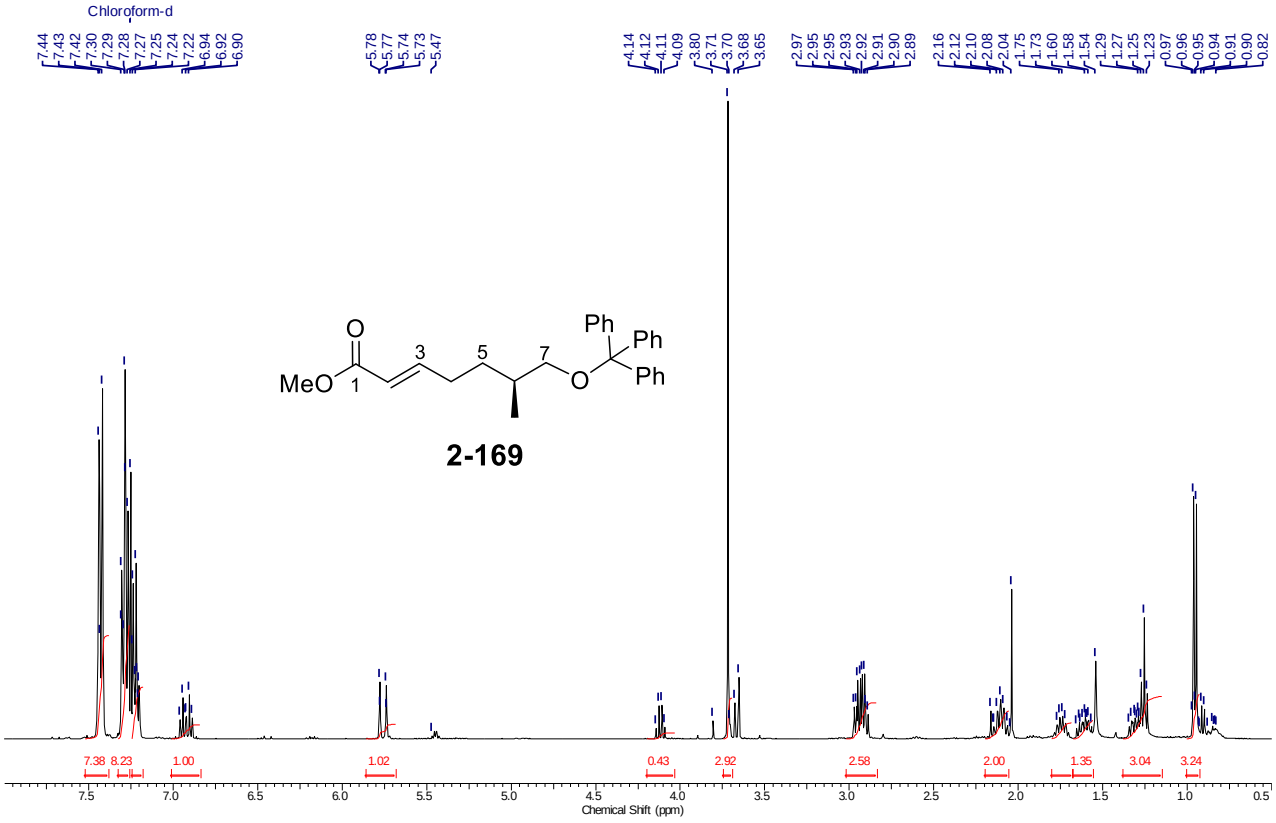
^{13}C NMR (100 MHz) spectrum of alkenol **2-166** in $CDCl_3$ (10 – 150 ppm)



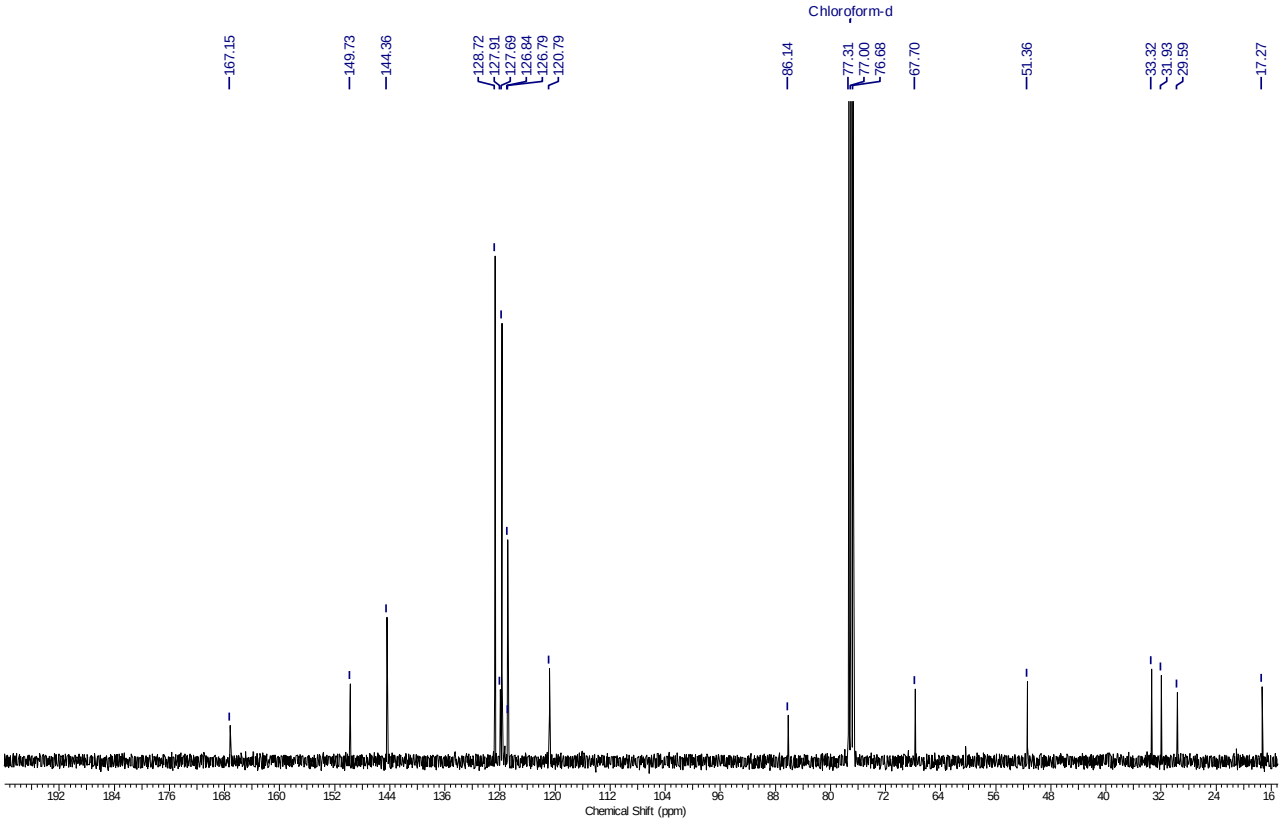
^{1}H NMR (400 MHz) spectrum of trityl ether **2-167** in $CDCl_3$ (0.5 – 8 ppm)



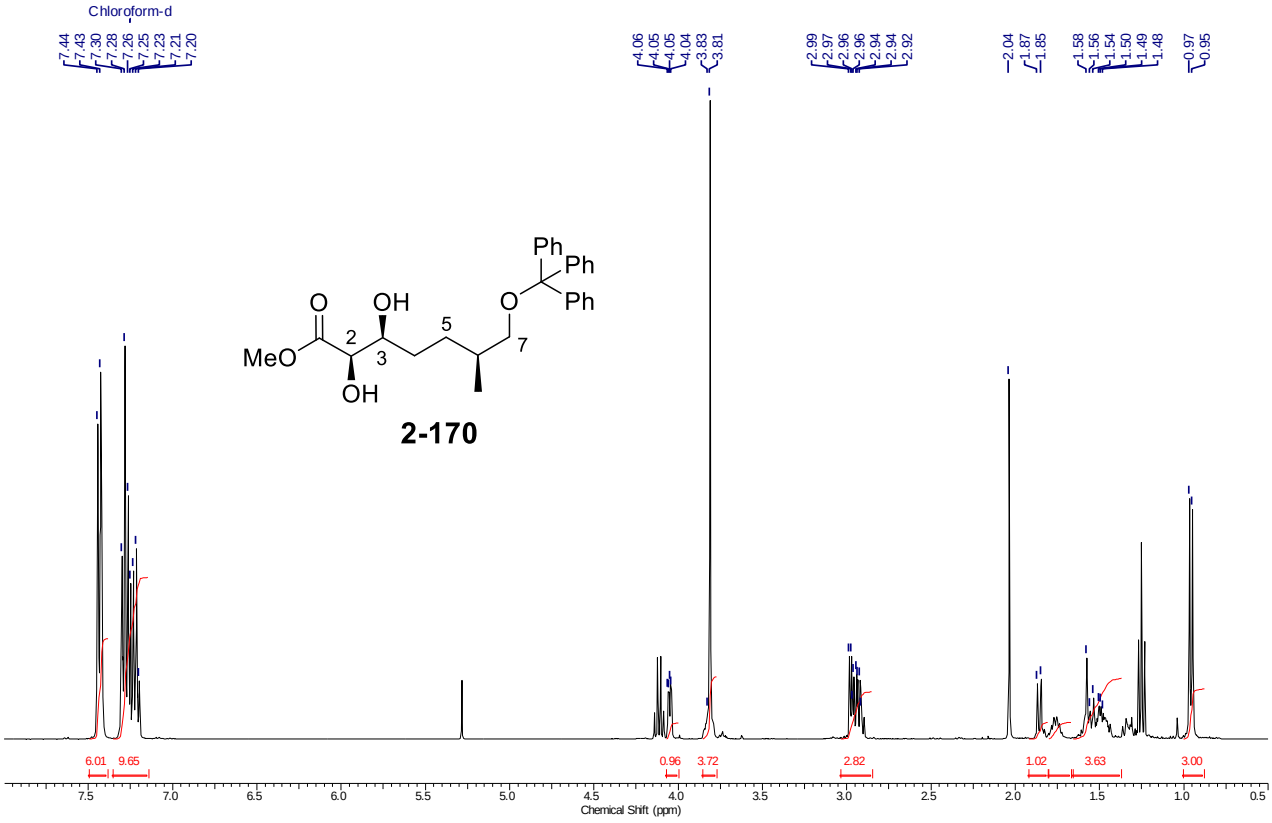
^{13}C NMR (100 MHz) spectrum of trityl ether **2-167** in $CDCl_3$ (15 – 200 ppm)



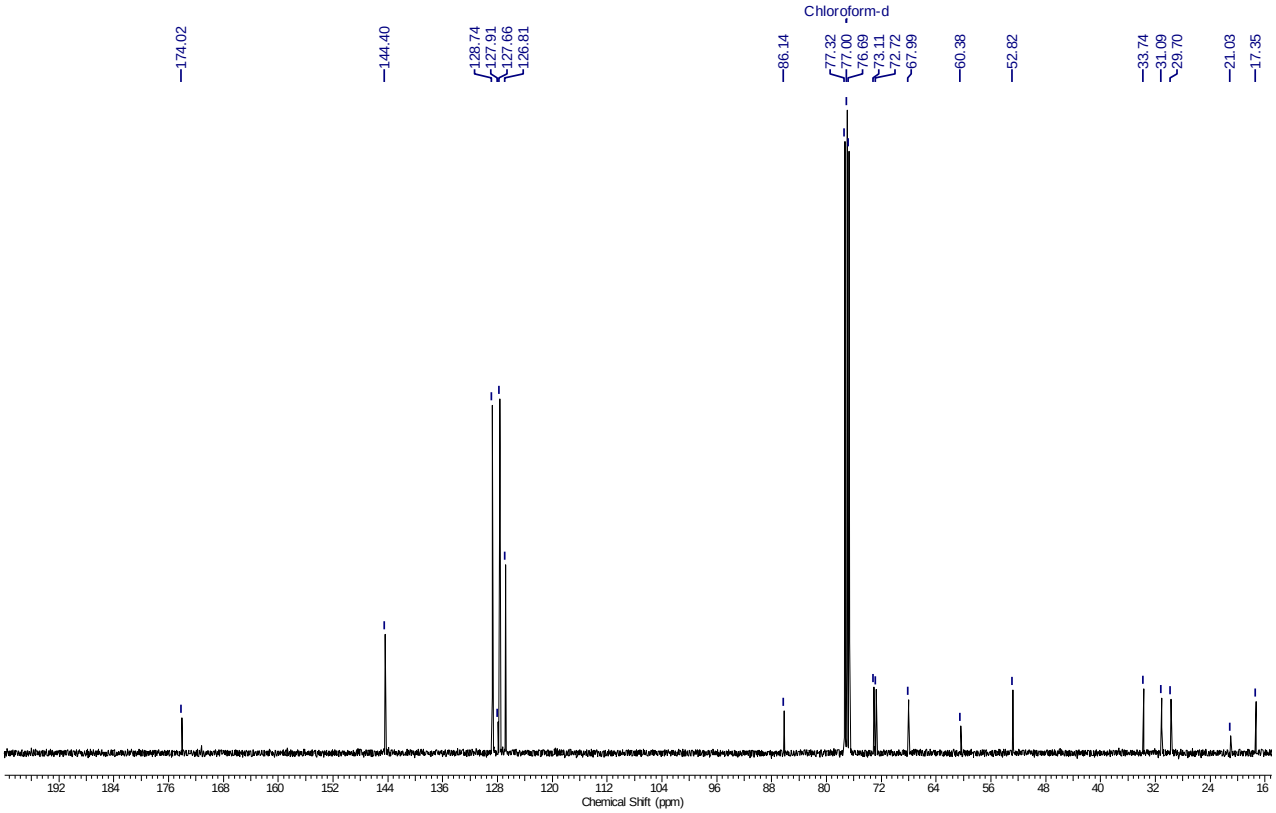
^{1}H NMR (400 MHz) spectrum of alkene **2-169** in $CDCl_3$ (0.5 – 8 ppm)



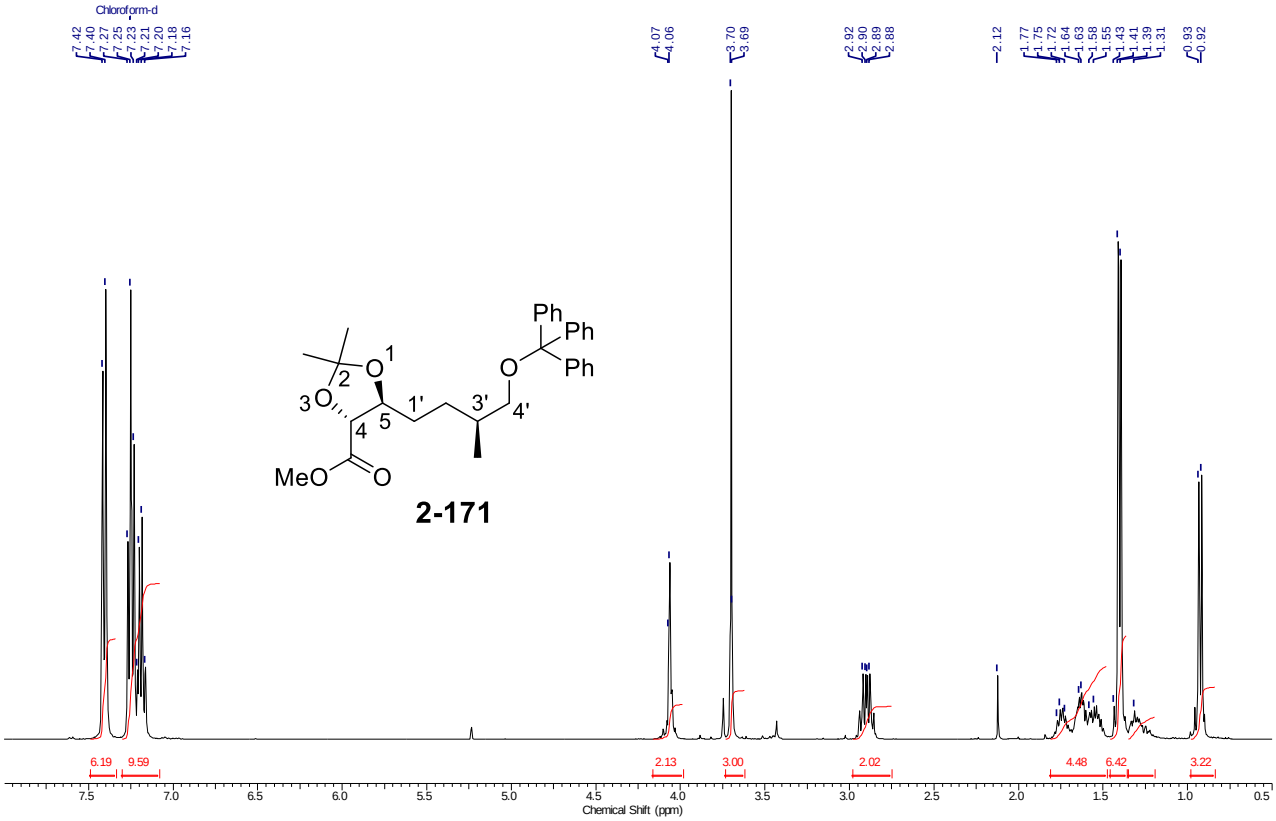
^{13}C NMR (100 MHz) spectrum of alkene **2-169** in $CDCl_3$ (15 – 200 ppm)



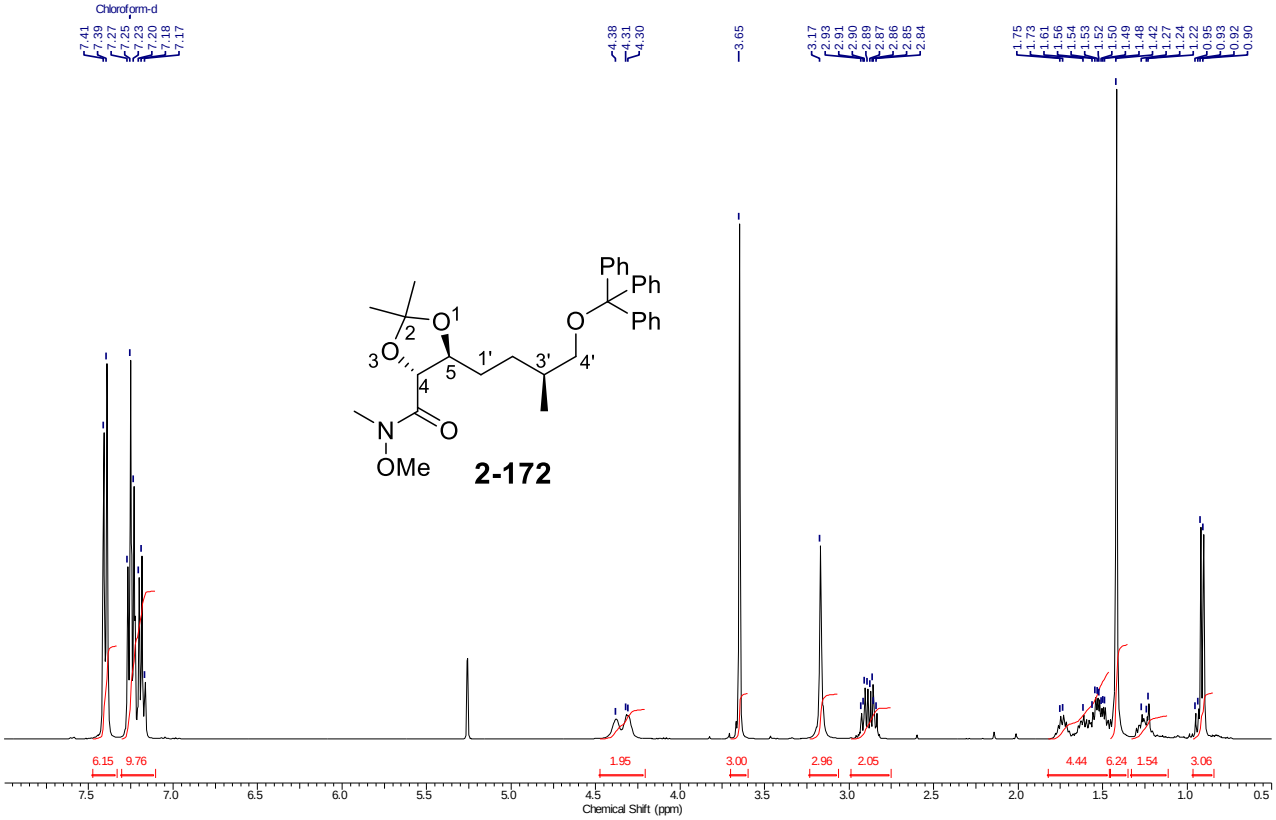
^{1}H NMR (400 MHz) spectrum of diols **2-170** in $CDCl_3$ (0.5 – 8 ppm)



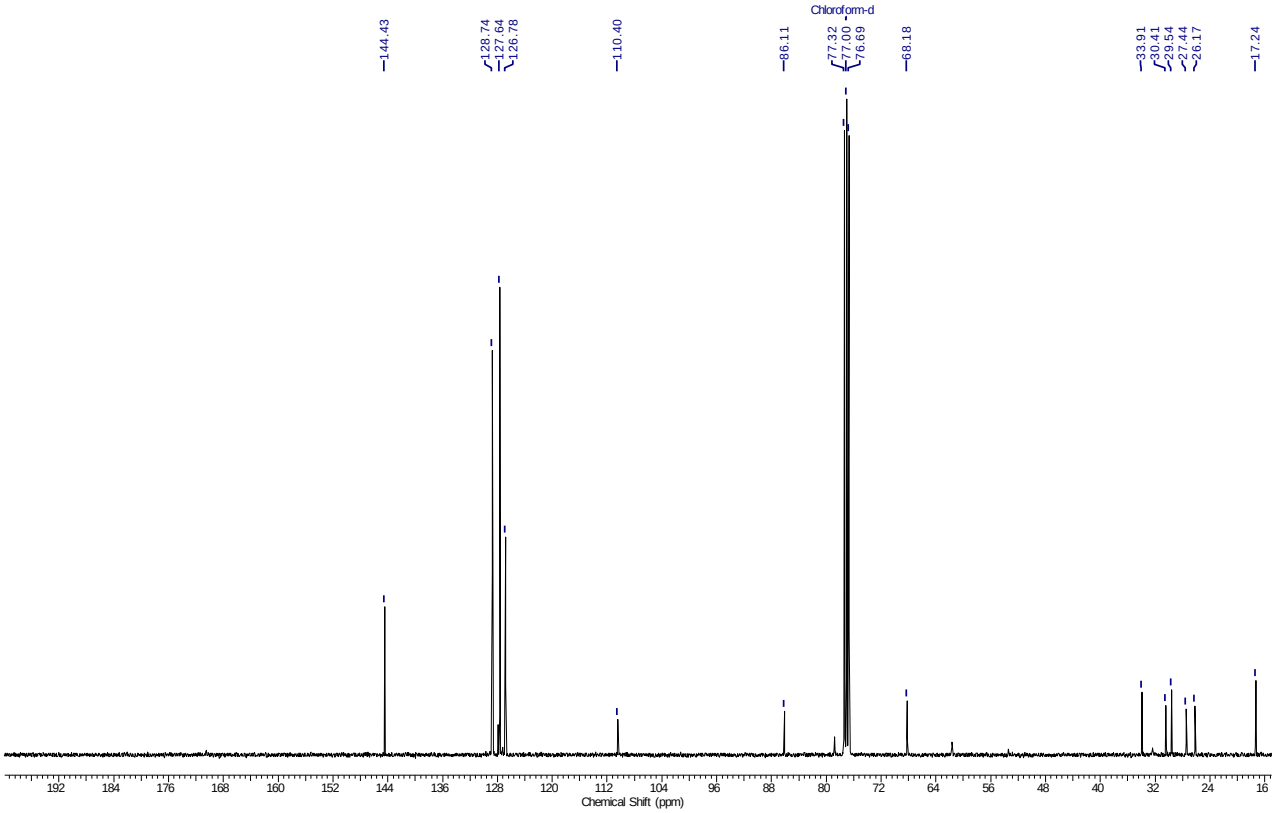
^{13}C NMR (100 MHz) spectrum of diols **2-170** in $CDCl_3$ (15 – 200 ppm)



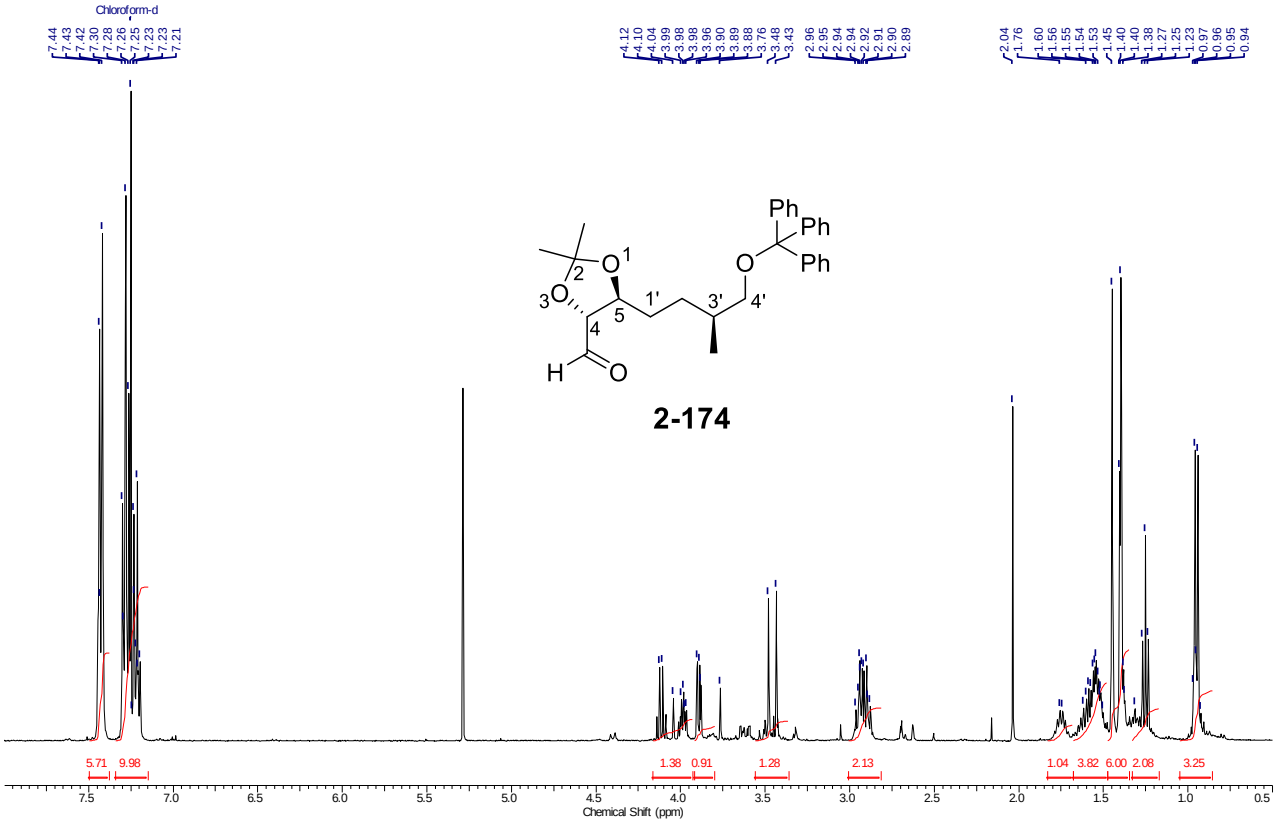
^{1}H NMR (400 MHz) spectrum of methyl ester **2-171** in $CDCl_3$ (0.5 – 8 ppm)



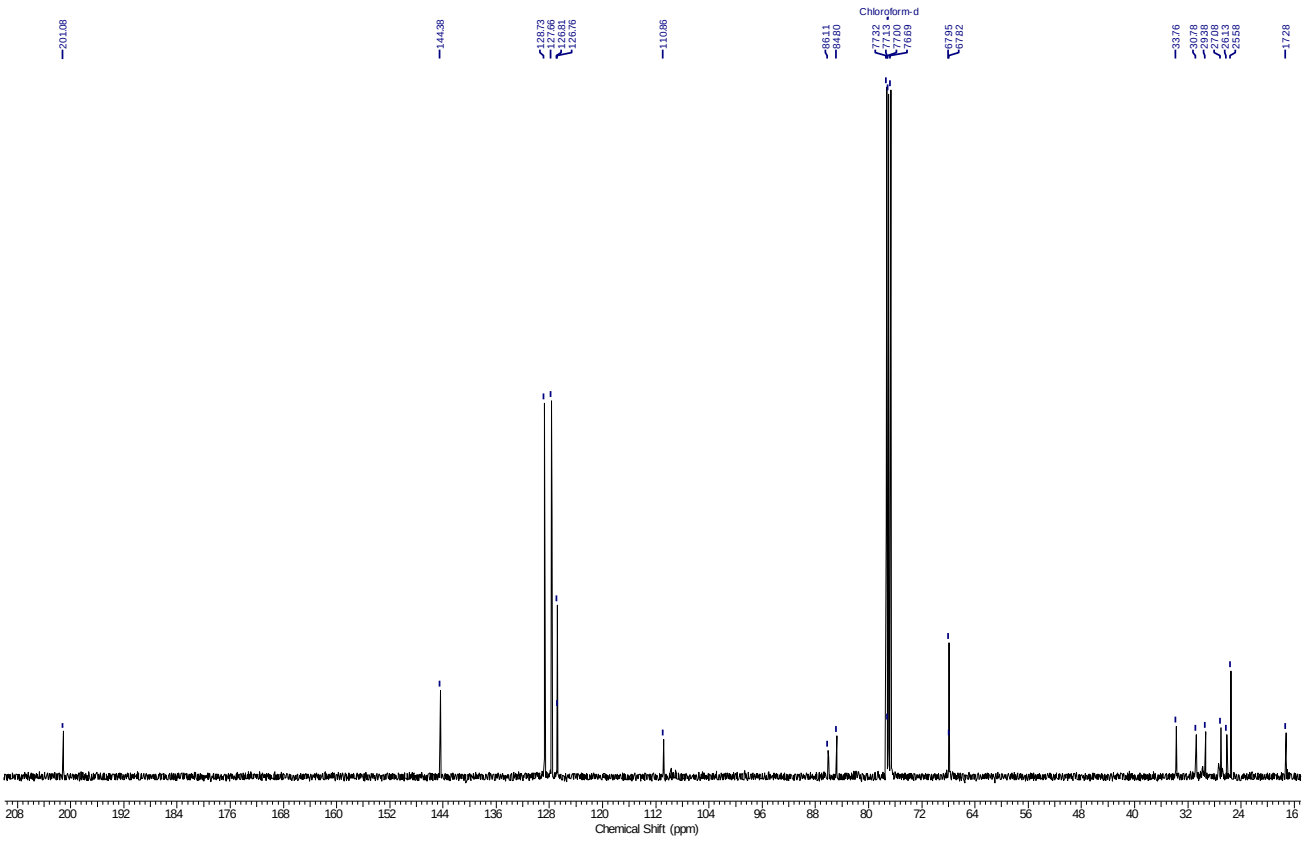
^{1}H NMR (400 MHz) spectrum of Weinreb amide **2-172** in $CDCl_3$ (0.5 – 8 ppm)



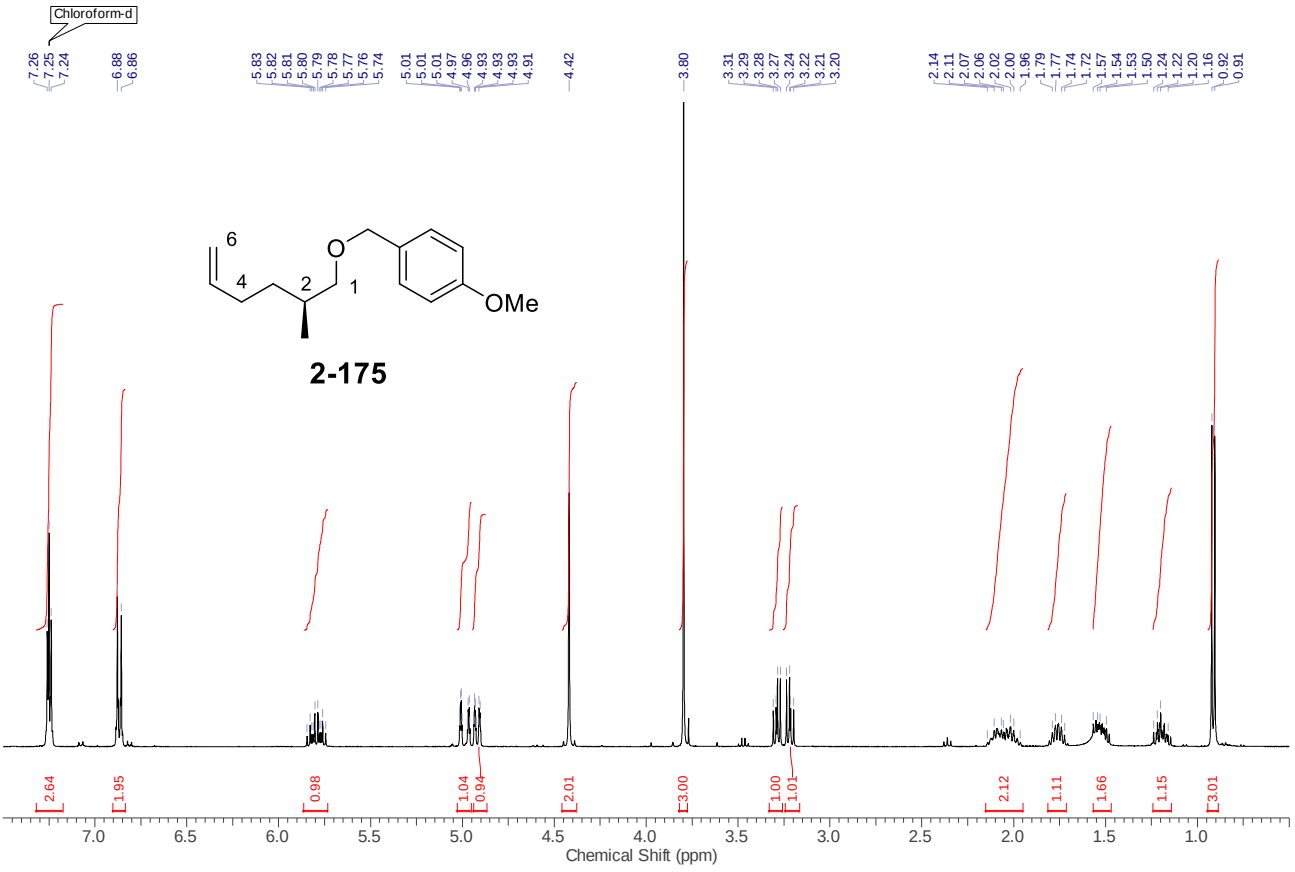
^{13}C NMR (100 MHz) spectrum of Weinreb amide **2-172** in $CDCl_3$ (15 – 200 ppm)



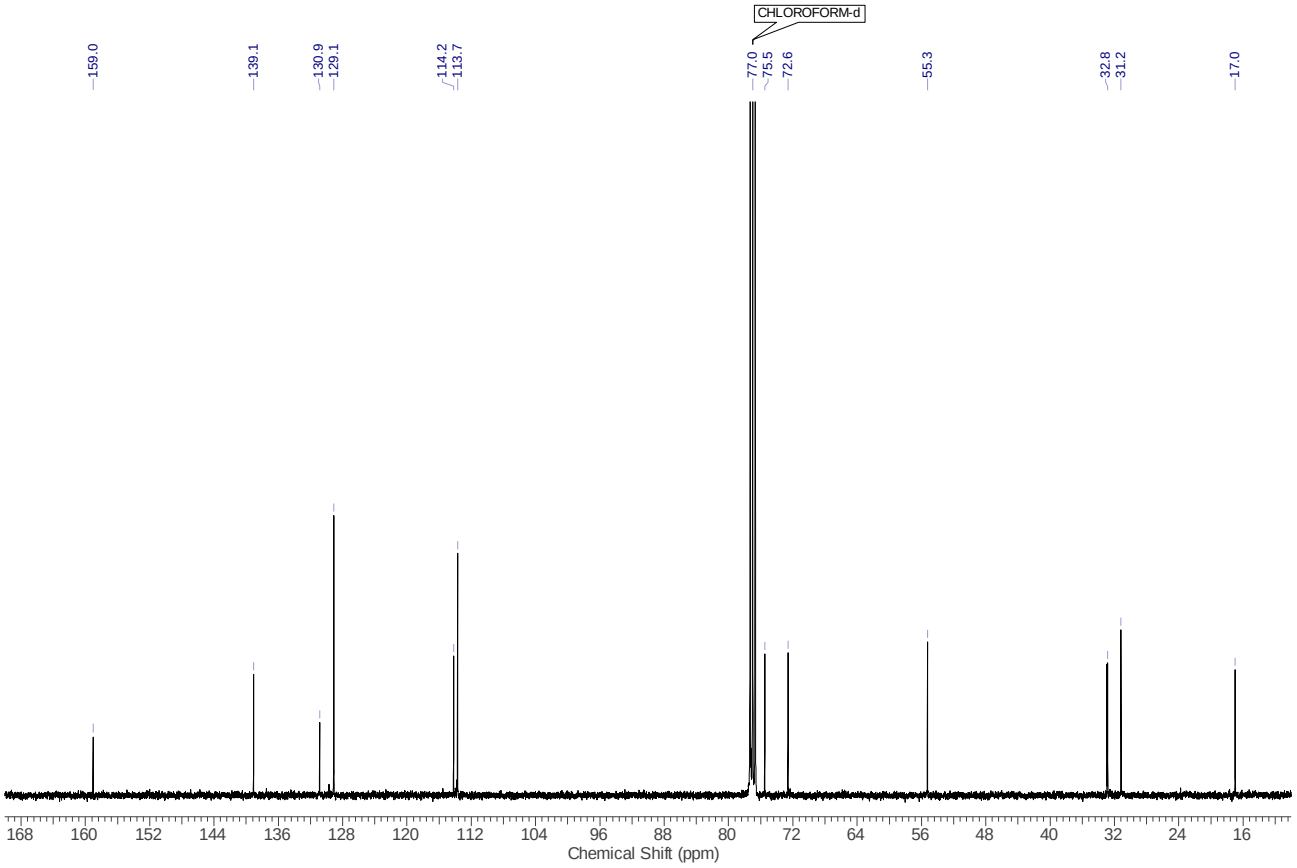
^{1}H NMR (400 MHz) spectrum of aldehyde **2-174** in $CDCl_3$ (0.5 – 8 ppm)



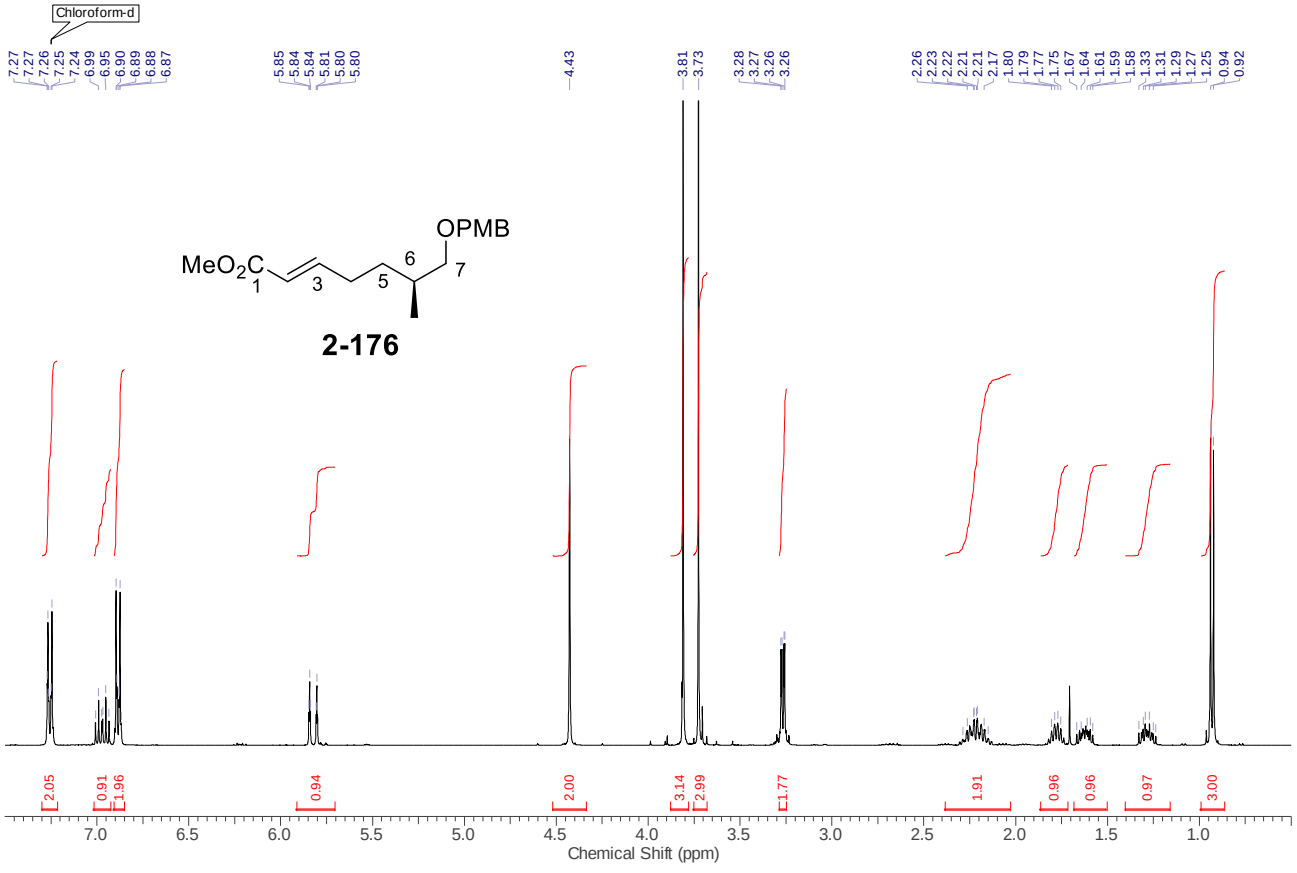
^{13}C NMR (100 MHz) spectrum of aldehyde **2-174** in $CDCl_3$ (15 – 200 ppm)



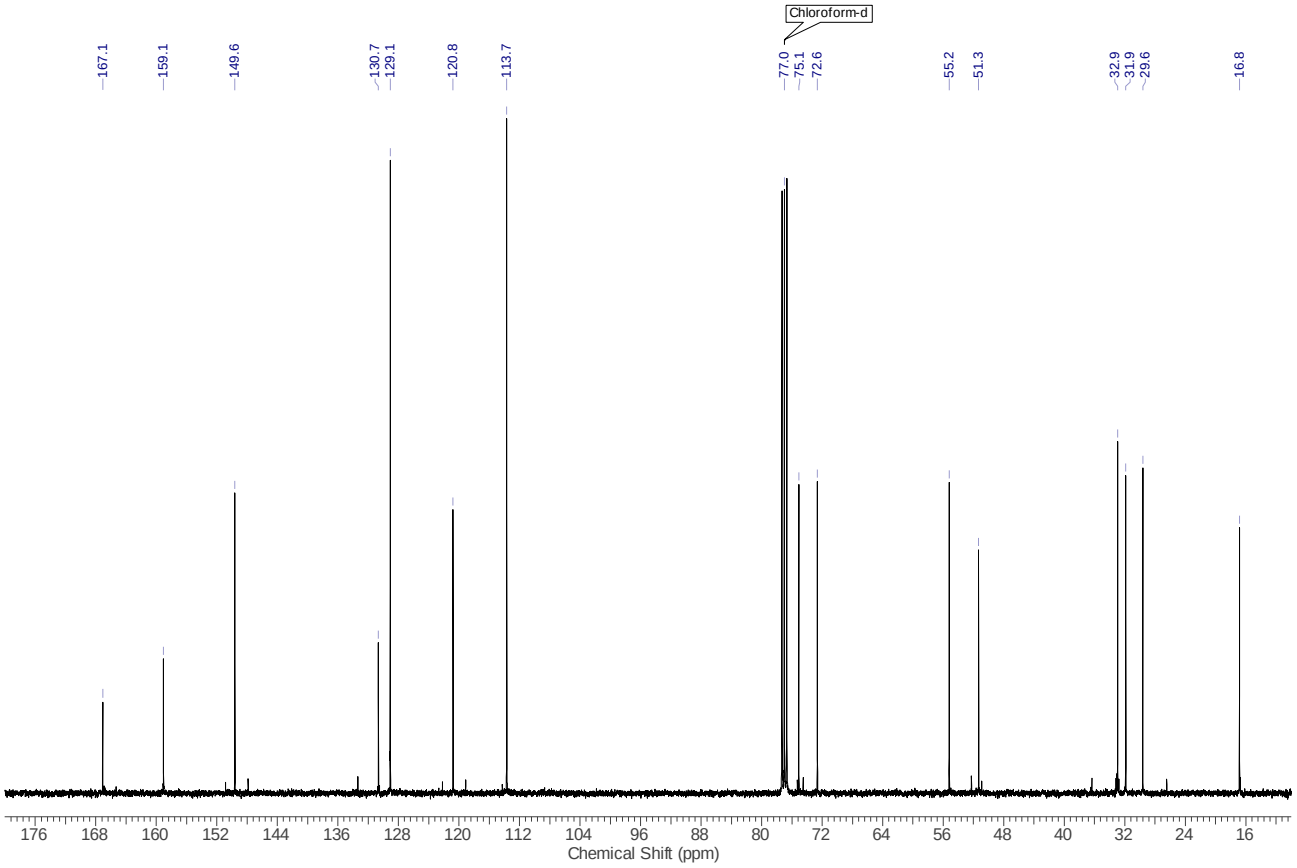
^{1}H NMR (400 MHz) spectrum of PMB ether **2-175** in $CDCl_3$ (0.5 – 7.5 ppm)



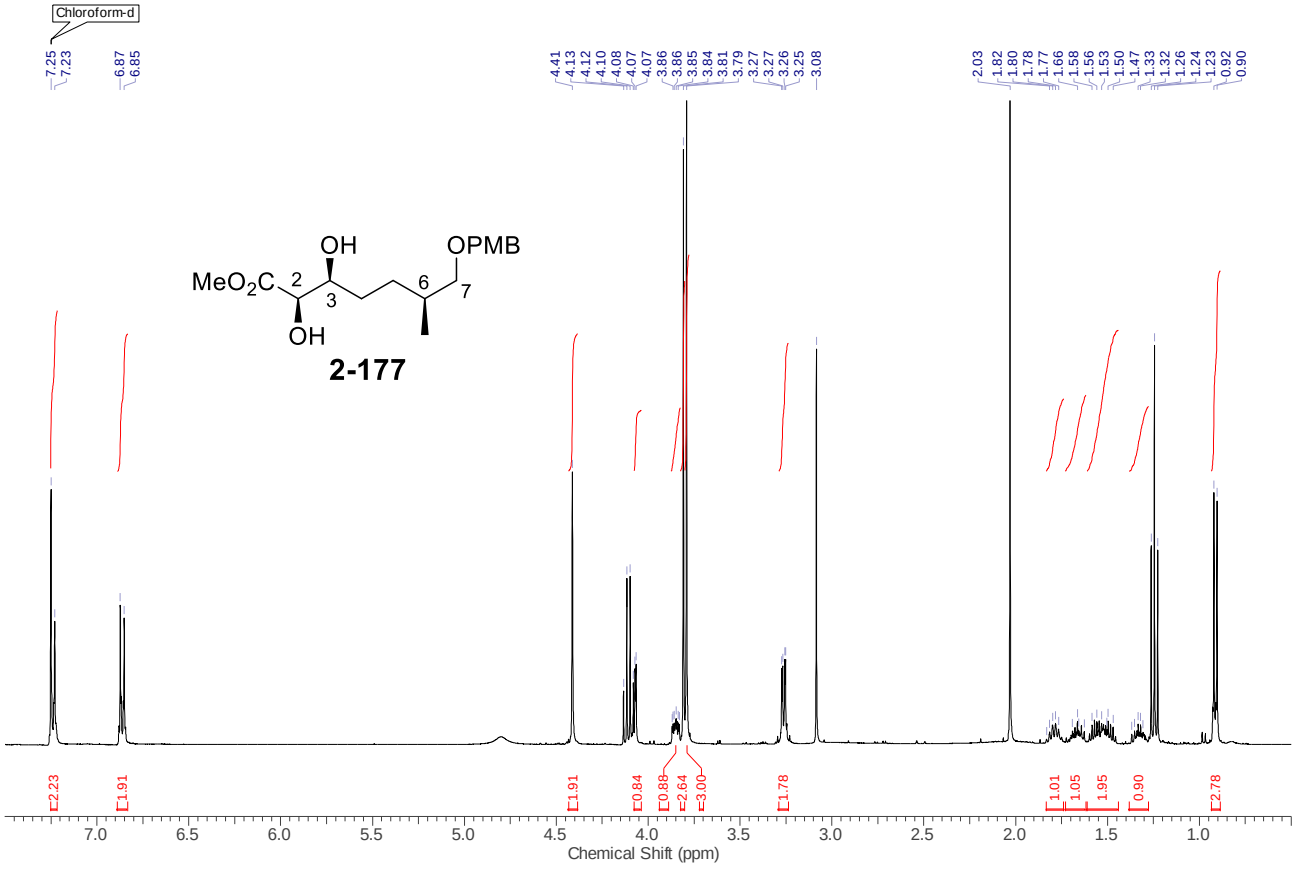
^{13}C NMR (100 MHz) spectrum of PMB ether **2-175** in $CDCl_3$ (10 – 170 ppm)



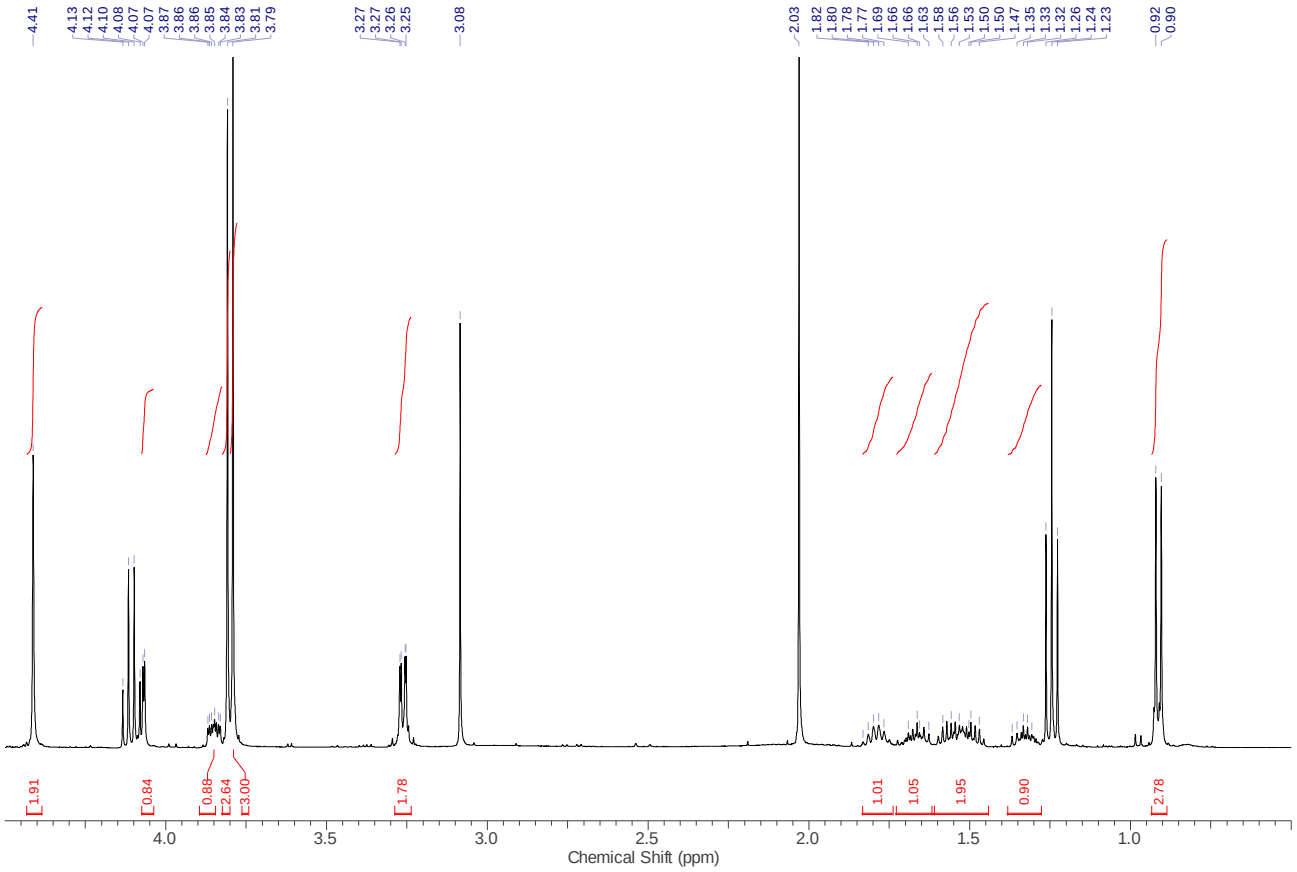
^{1}H NMR (400 MHz) spectrum of enoate **2-176** in $CDCl_3$ (0.5 – 7.5 ppm)



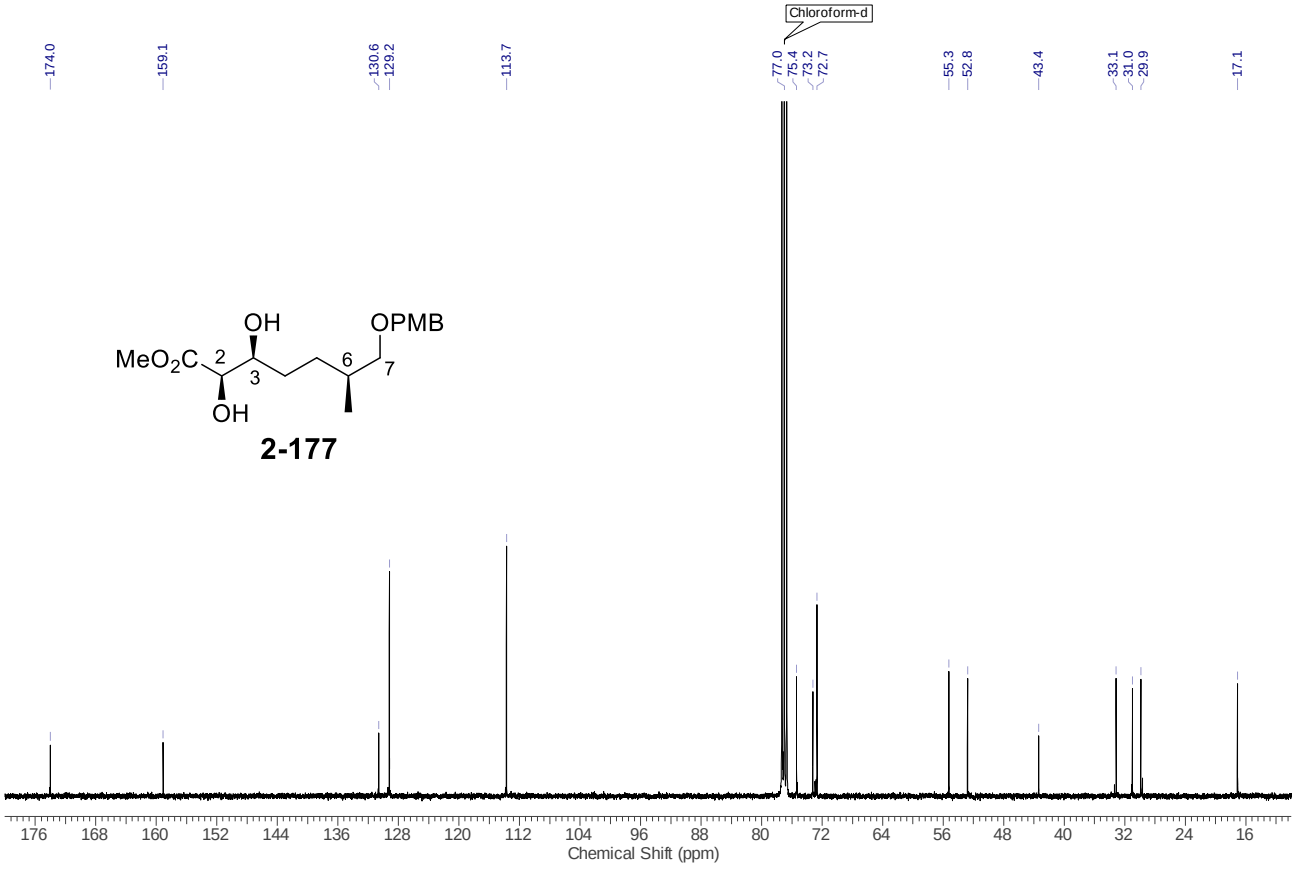
^{13}C NMR (100 MHz) spectrum of enoate **2-176** in $CDCl_3$ (10 – 180 ppm)



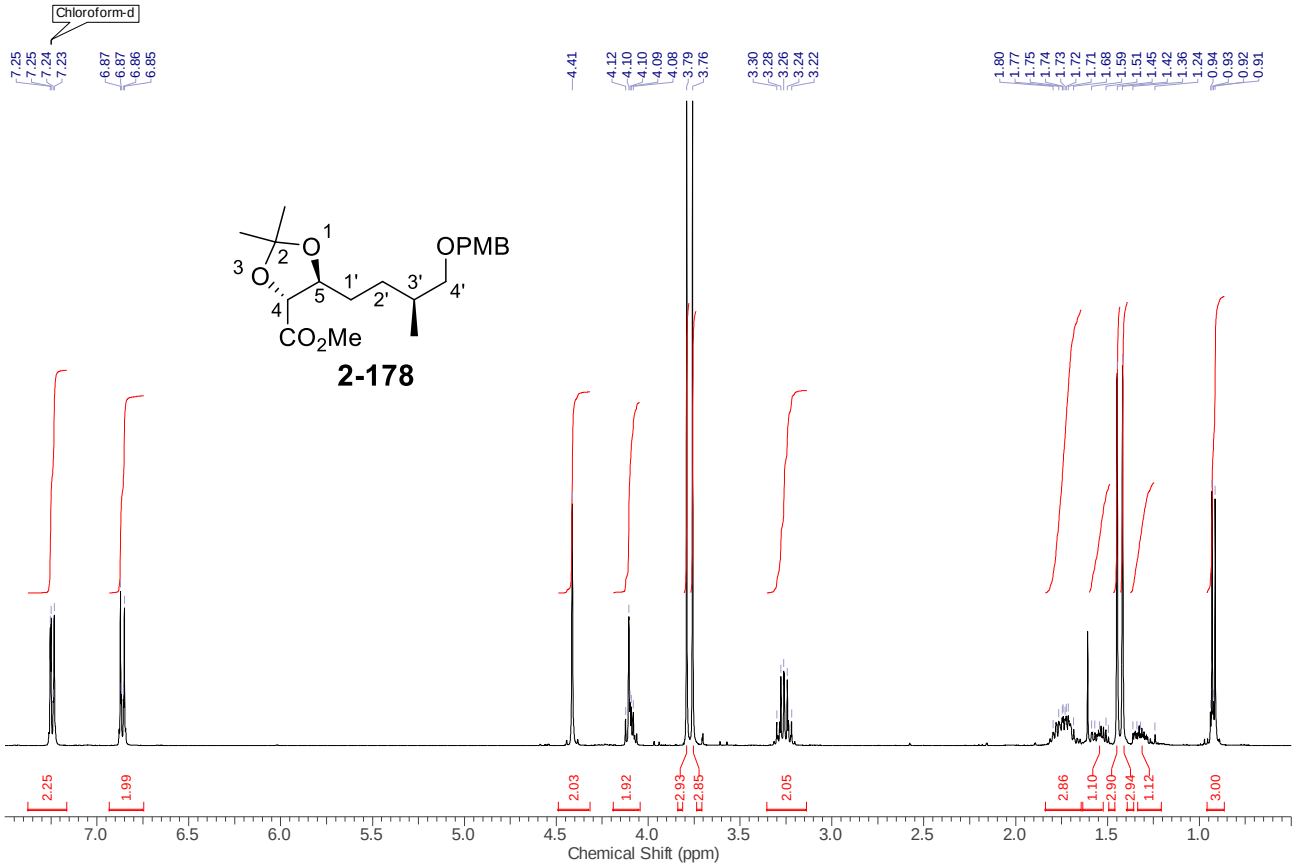
^{1}H NMR (400 MHz) spectrum of diol **2-177** in $CDCl_3$ (0.5 – 7.5 ppm)



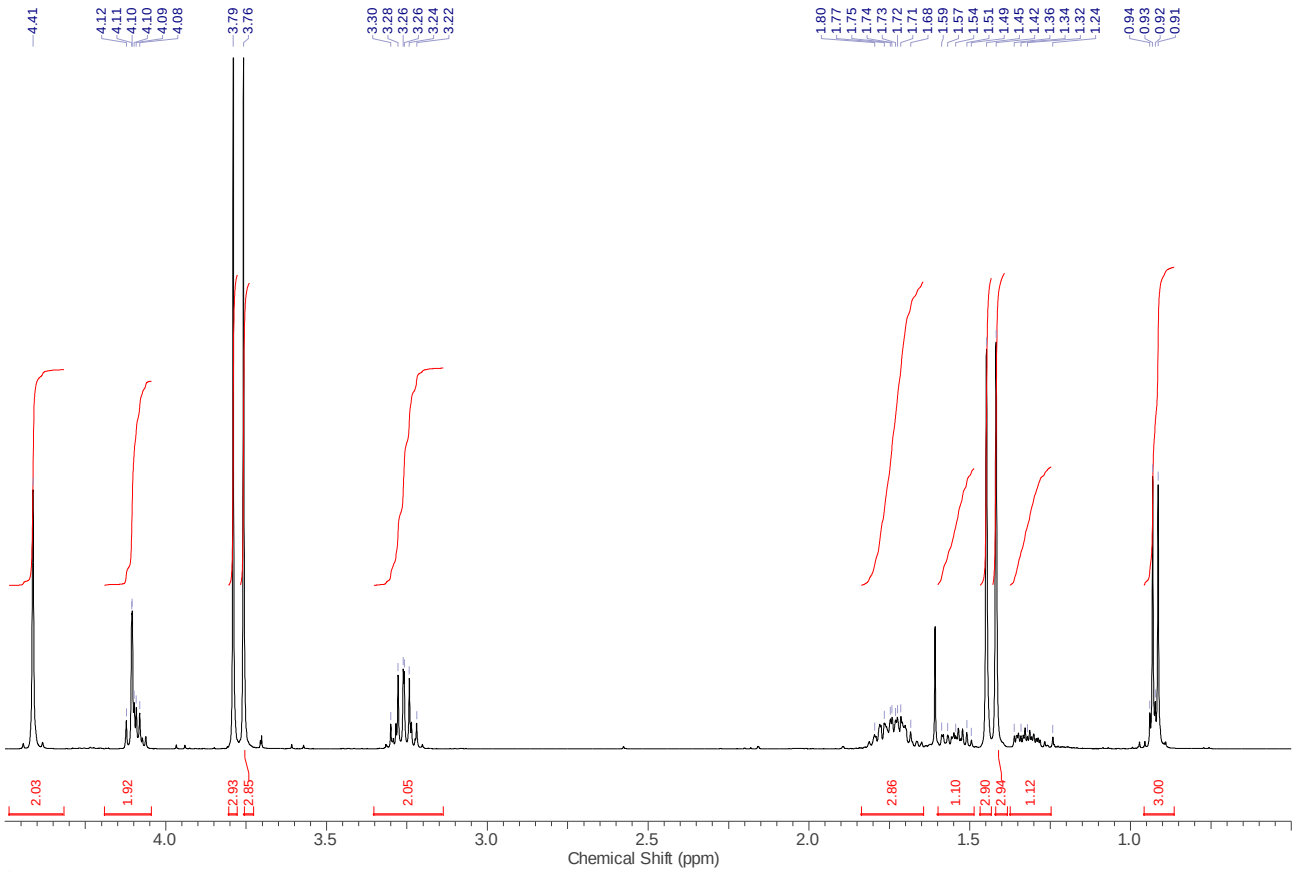
^{1}H NMR (400 MHz) spectrum of diol **2-177** in $CDCl_3$ (0.5 – 4.5 ppm)



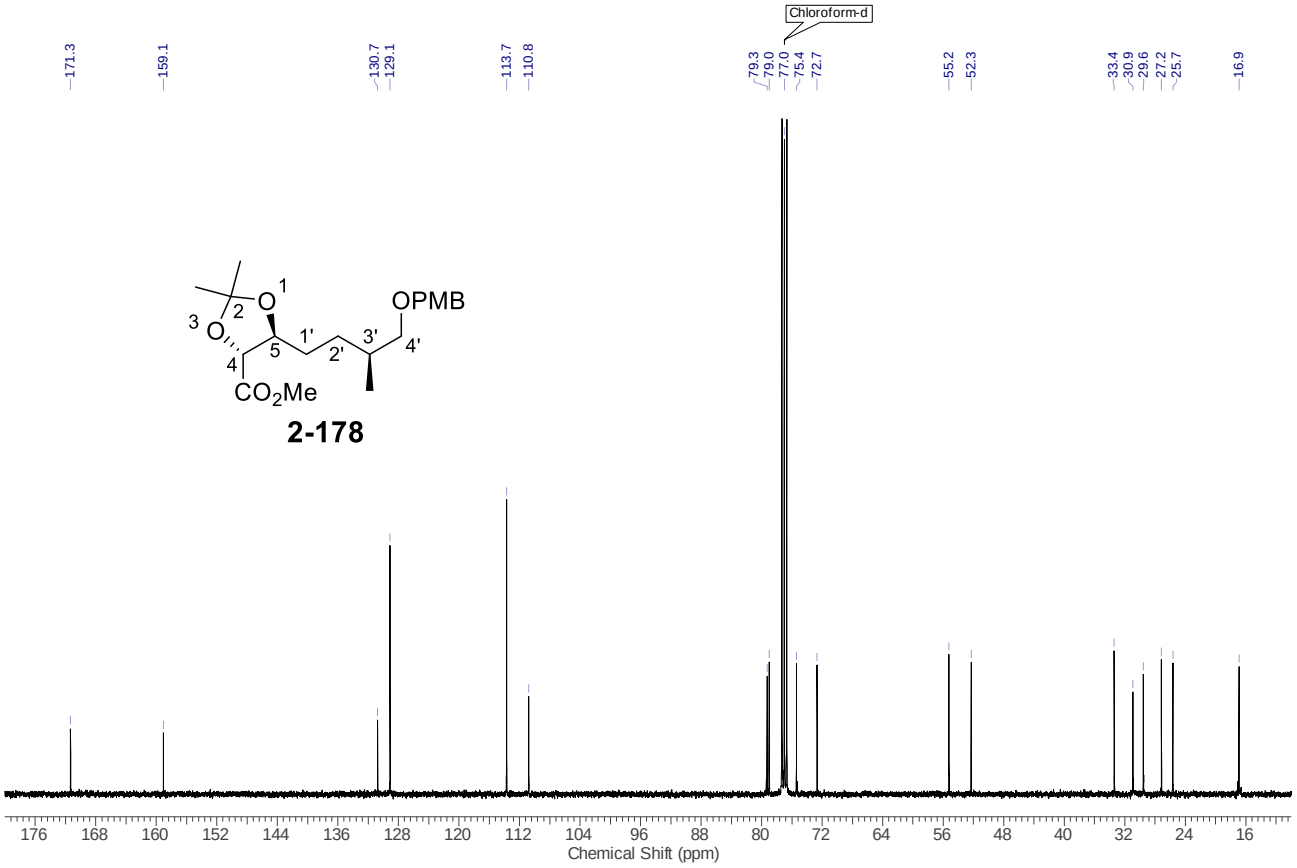
^{13}C NMR (100 MHz) spectrum of diol **2-177** in $CDCl_3$ (10 – 180 ppm)



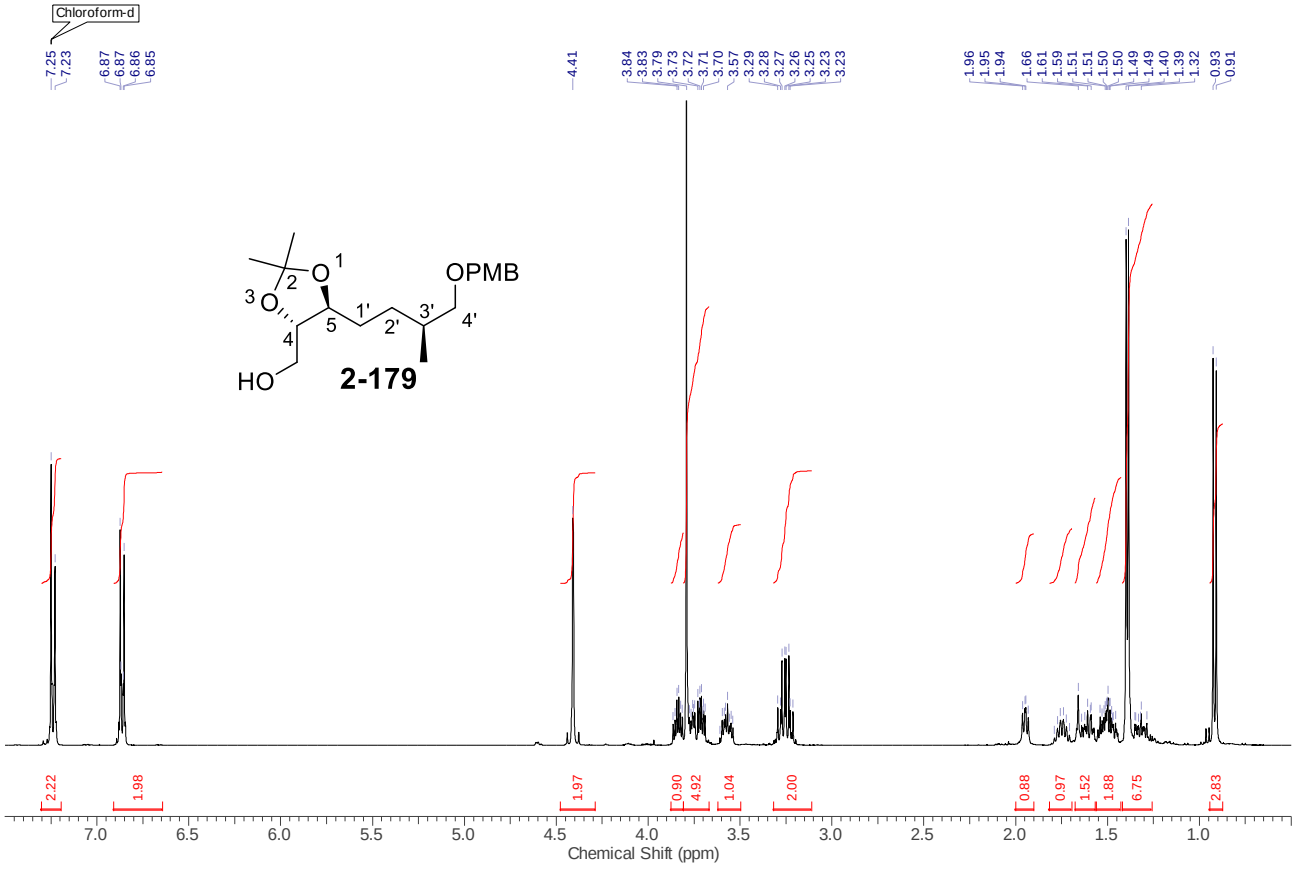
^{1}H NMR (400 MHz) spectrum of acetonide **2-178** in $CDCl_3$ (0.5 – 7.5 ppm)



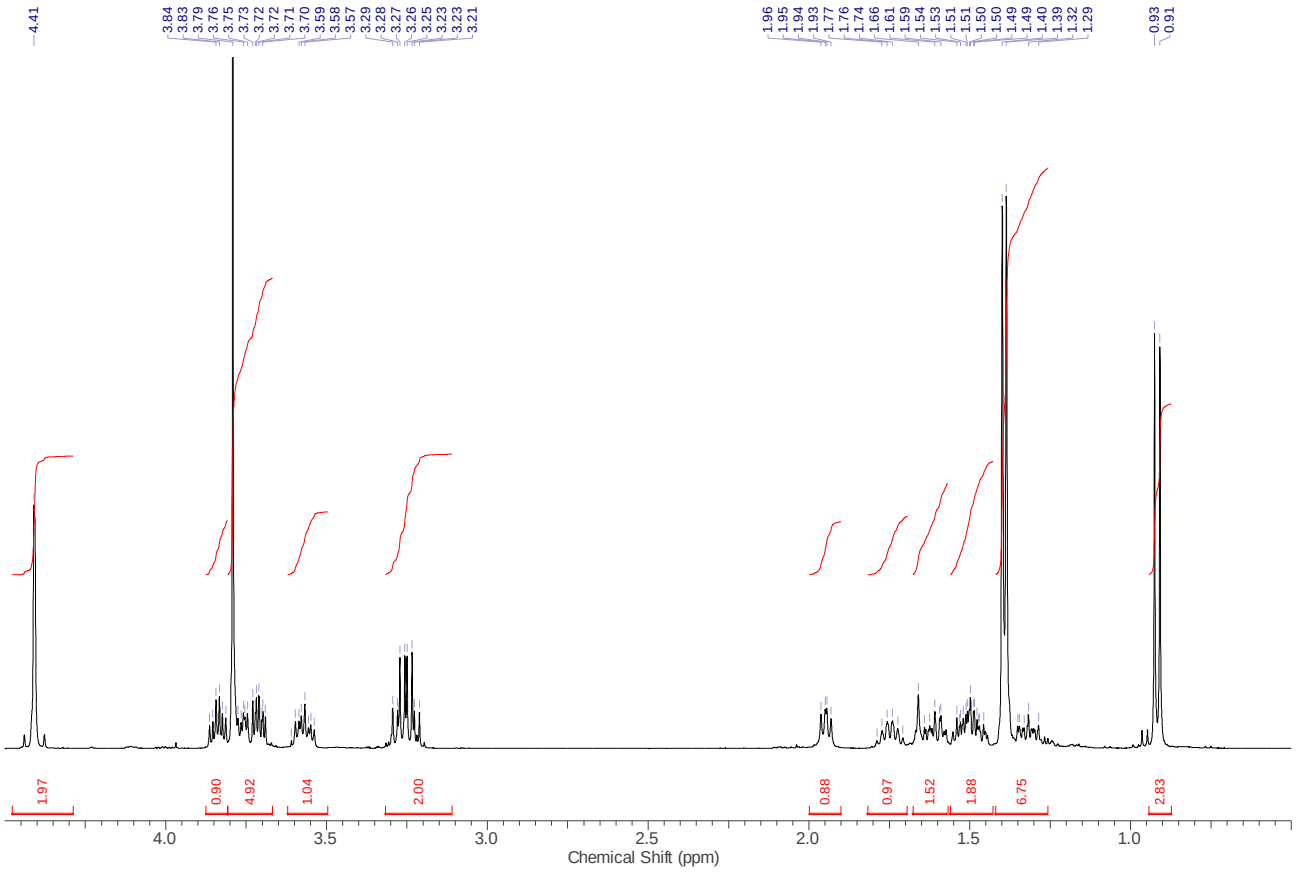
^{1}H NMR (400 MHz) spectrum of acetonide **2-178** in $CDCl_3$ (0.5 – 4.5 ppm)



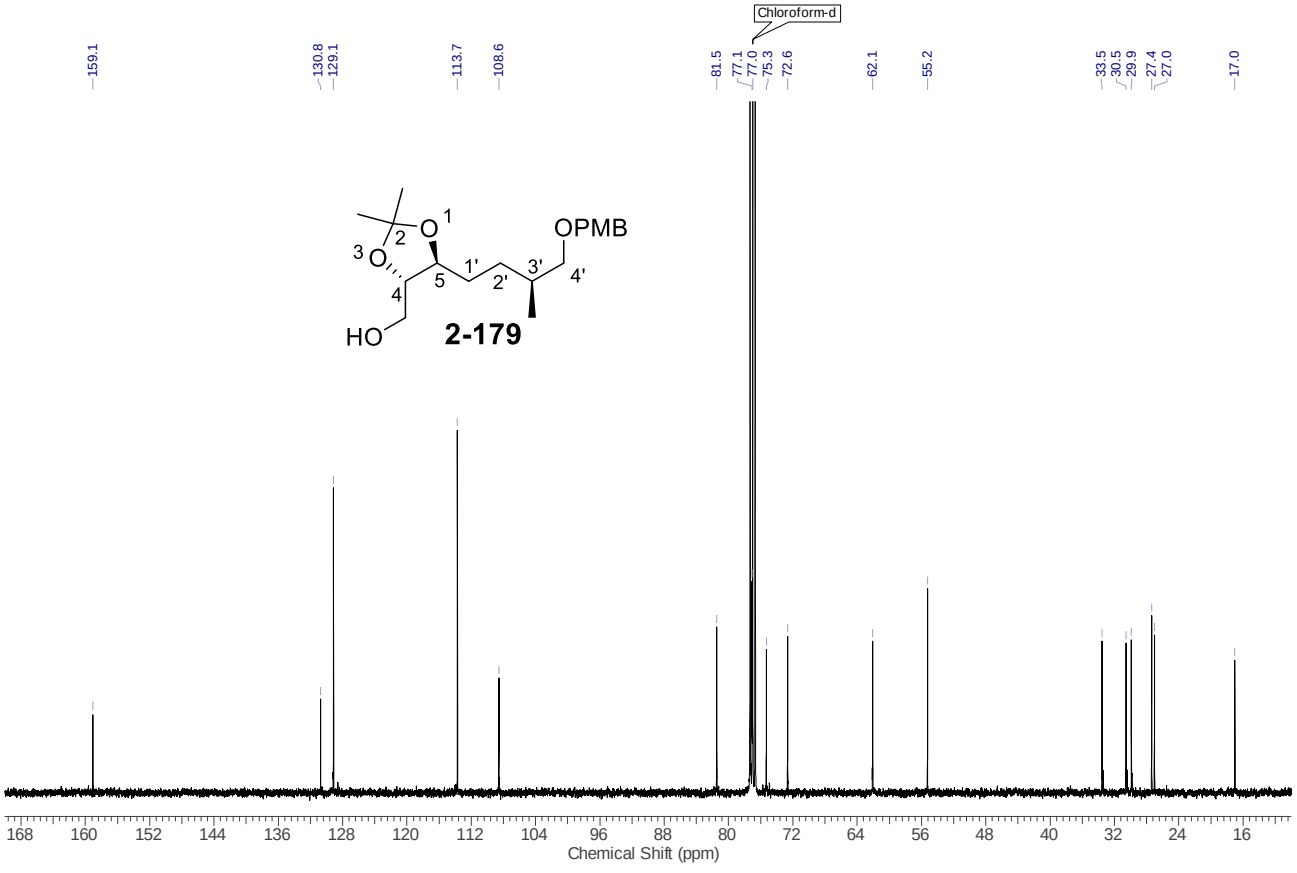
^{13}C NMR (100 MHz) spectrum of acetonide **2-178** in $CDCl_3$ (10 – 180 ppm)



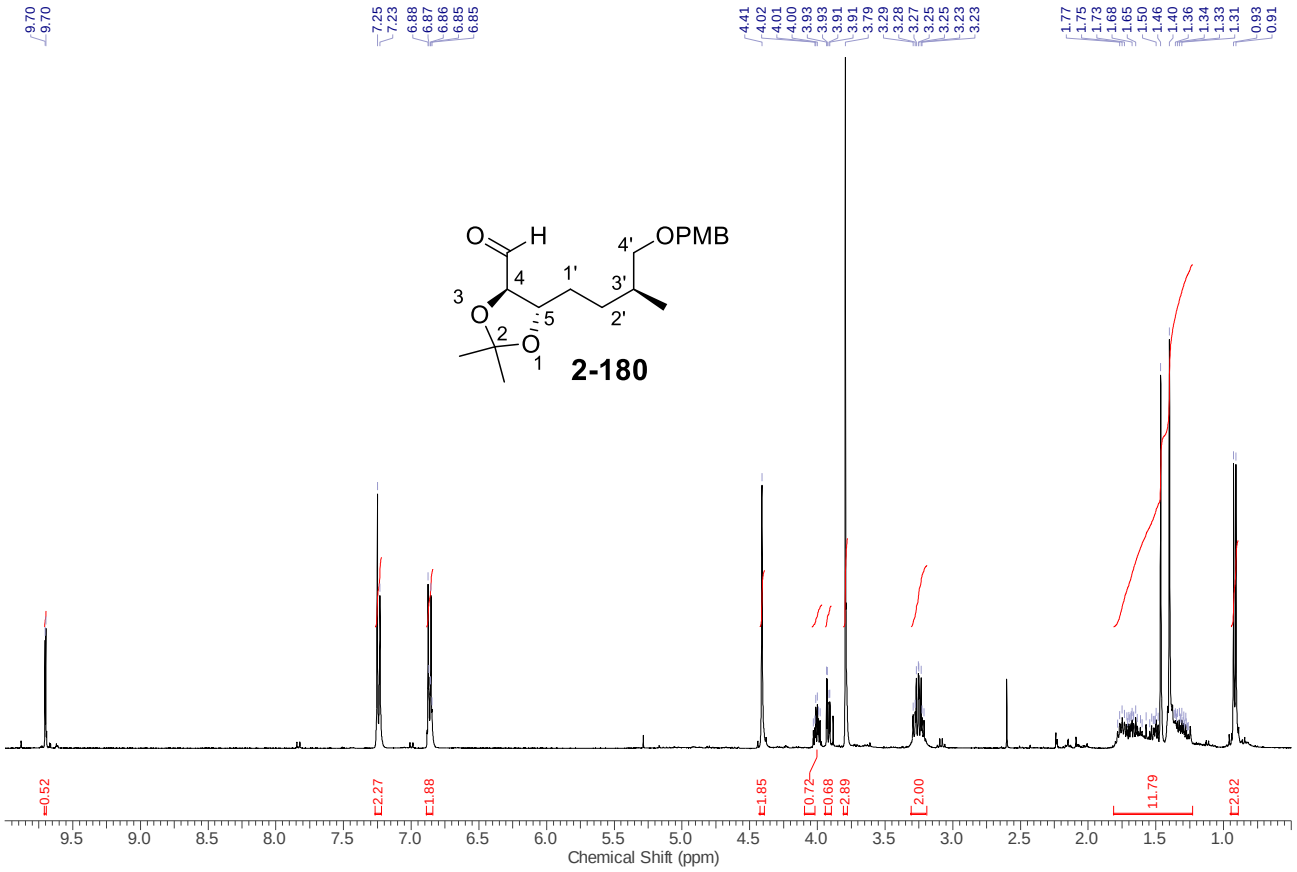
^{1}H NMR (400 MHz) spectrum of alcohol **2-179** in $CDCl_3$ (0.5 – 7.5 ppm)



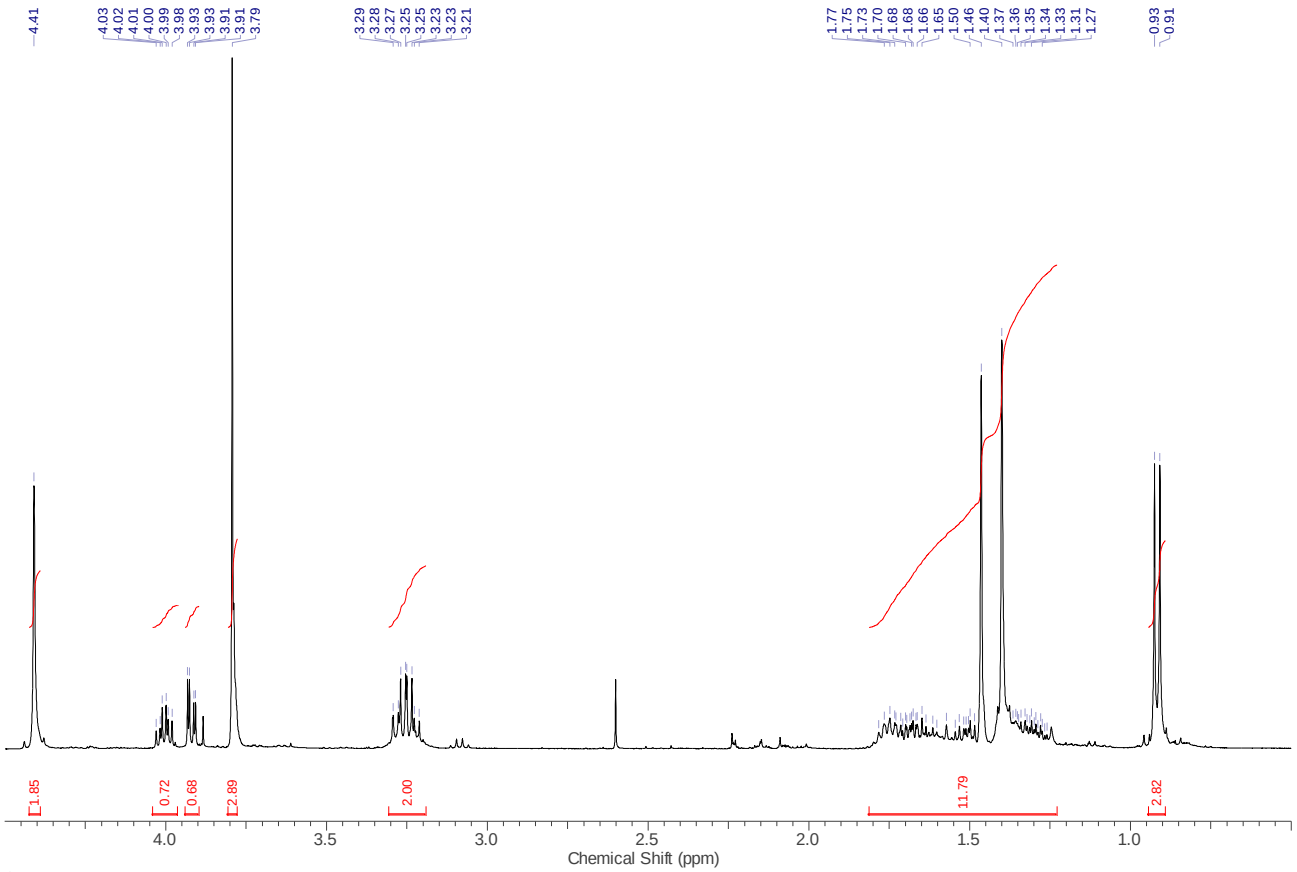
^{1}H NMR (400 MHz) spectrum of alcohol **2-179** in $CDCl_3$ (0.5 – 4.5 ppm)



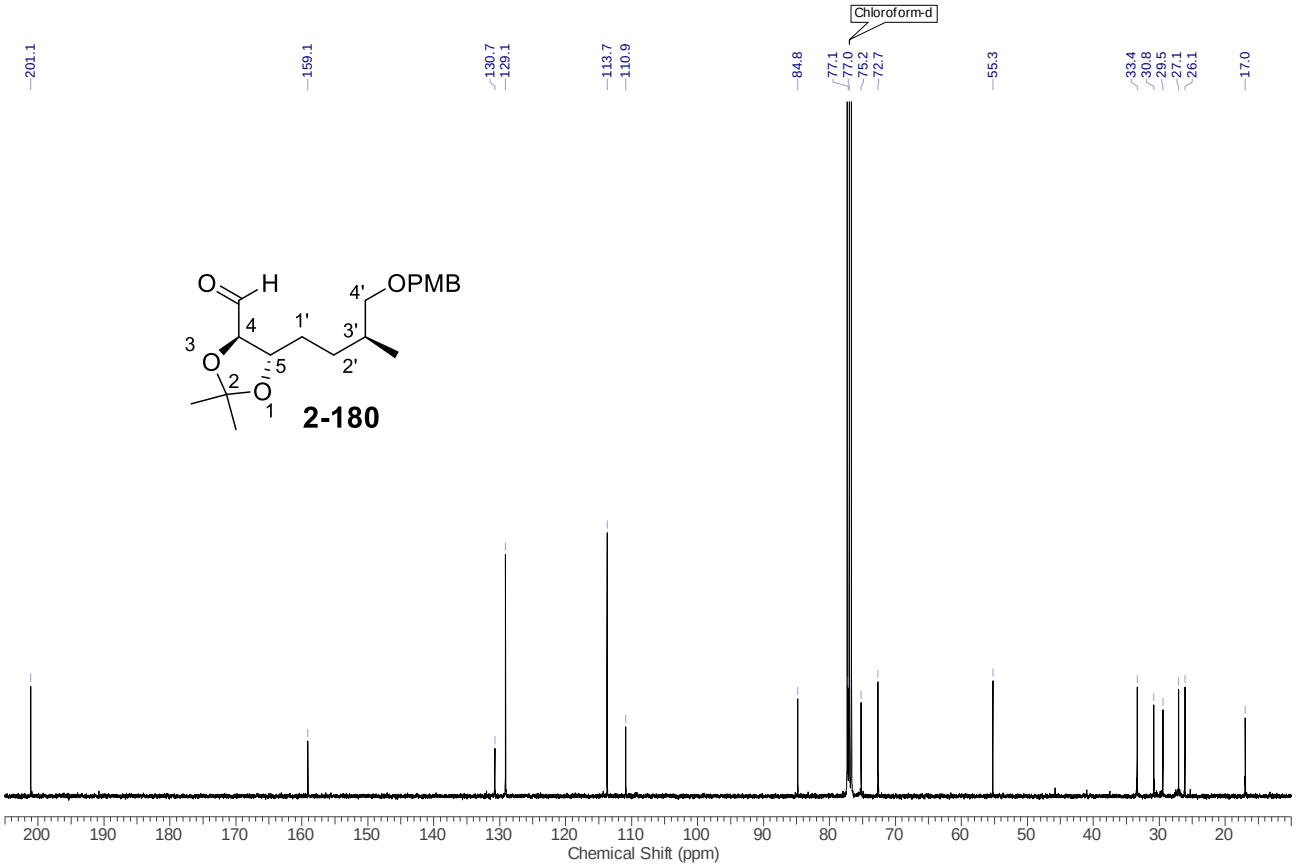
^{13}C NMR (100 MHz) spectrum of alcohol **2-179** in $CDCl_3$ (10 – 170 ppm)



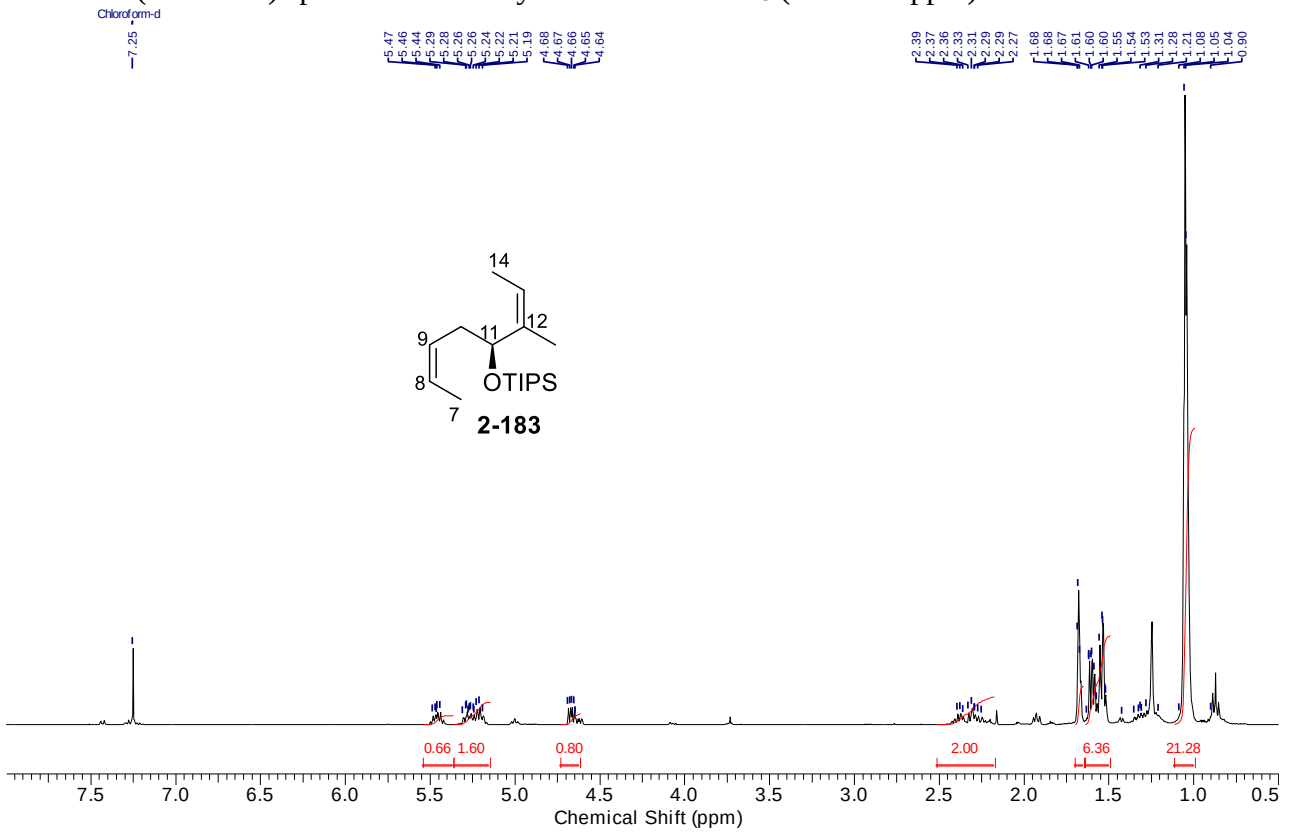
^{1}H NMR (400 MHz) spectrum of aldehyde **2-180** in $CDCl_3$ (0.5 – 10.0 ppm)



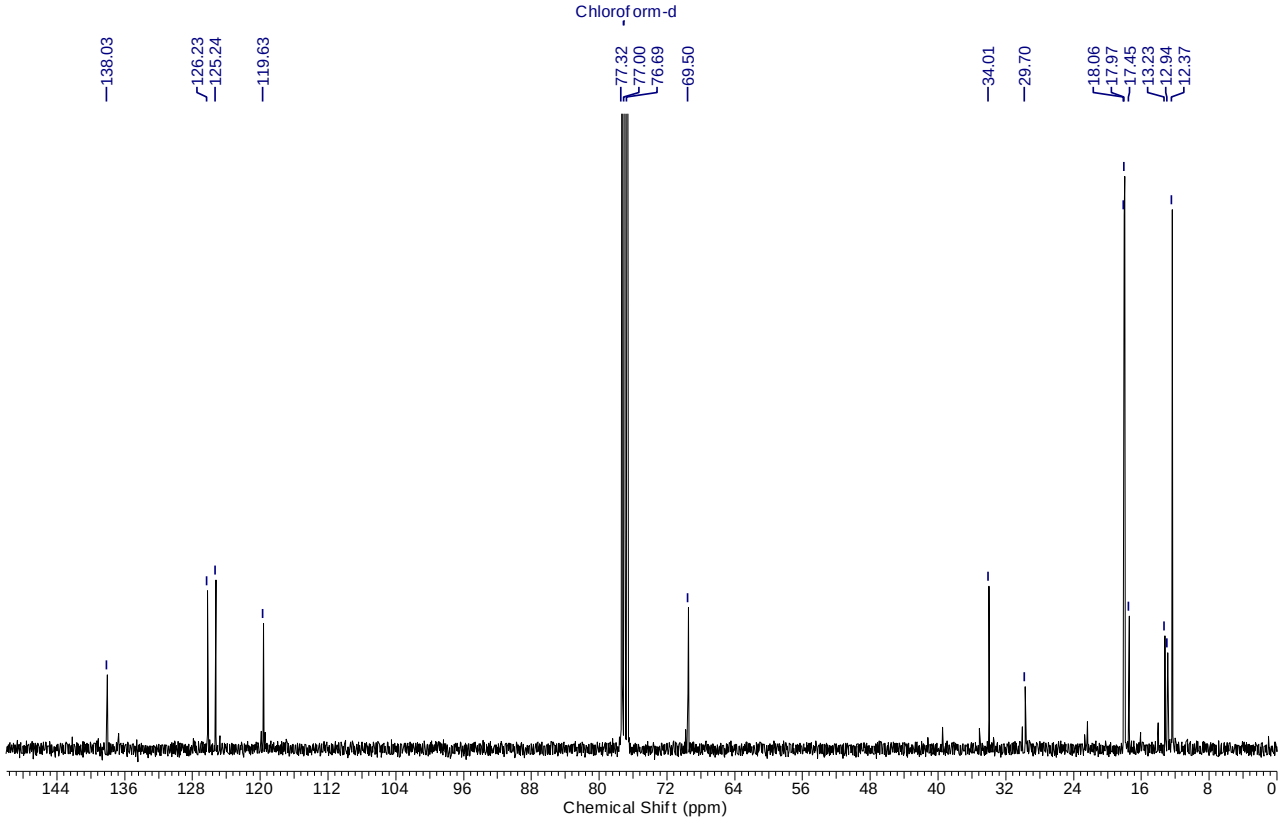
^{1}H NMR (400 MHz) spectrum of aldehyde **2-180** in $CDCl_3$ (0.5 – 4.5 ppm)



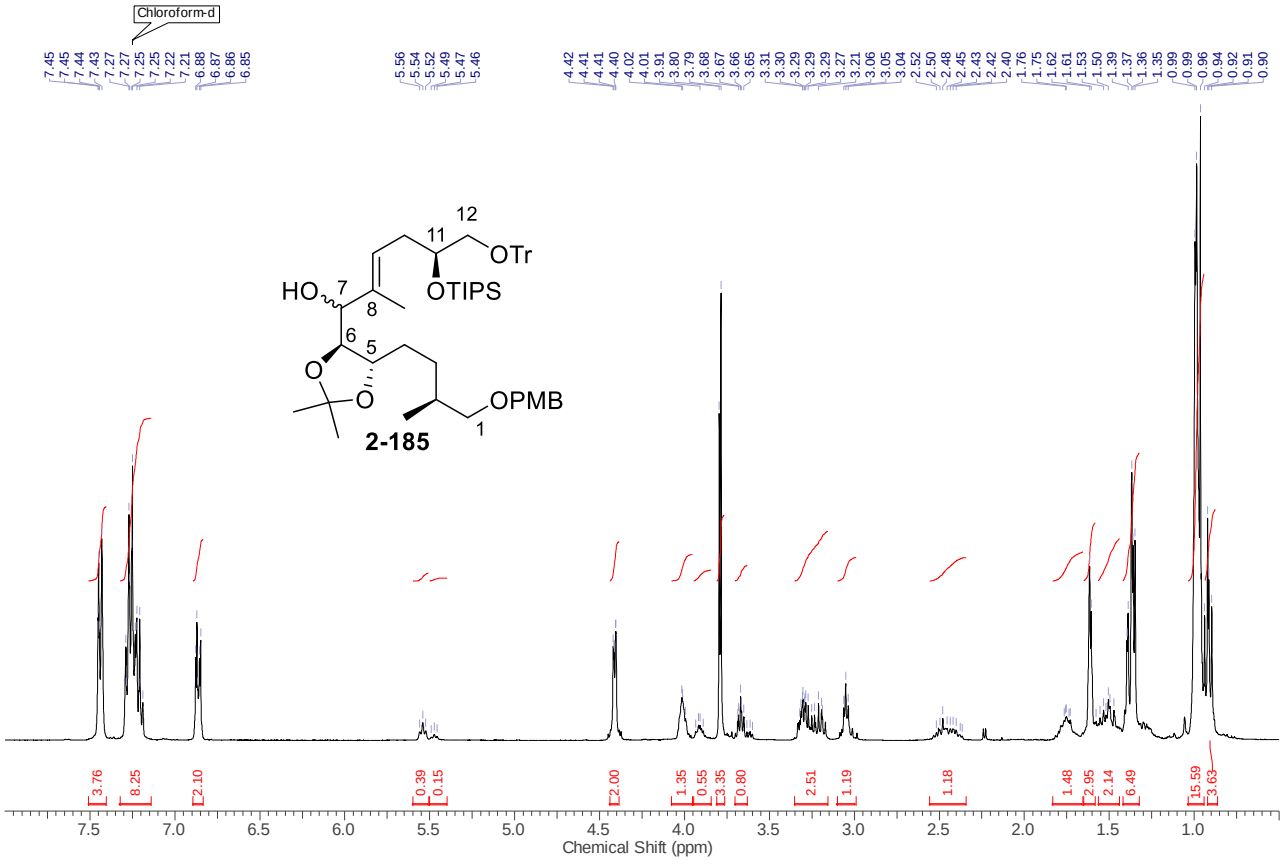
^{13}C NMR (100 MHz) spectrum of aldehyde **2-180** in $CDCl_3$ (10 – 205 ppm)



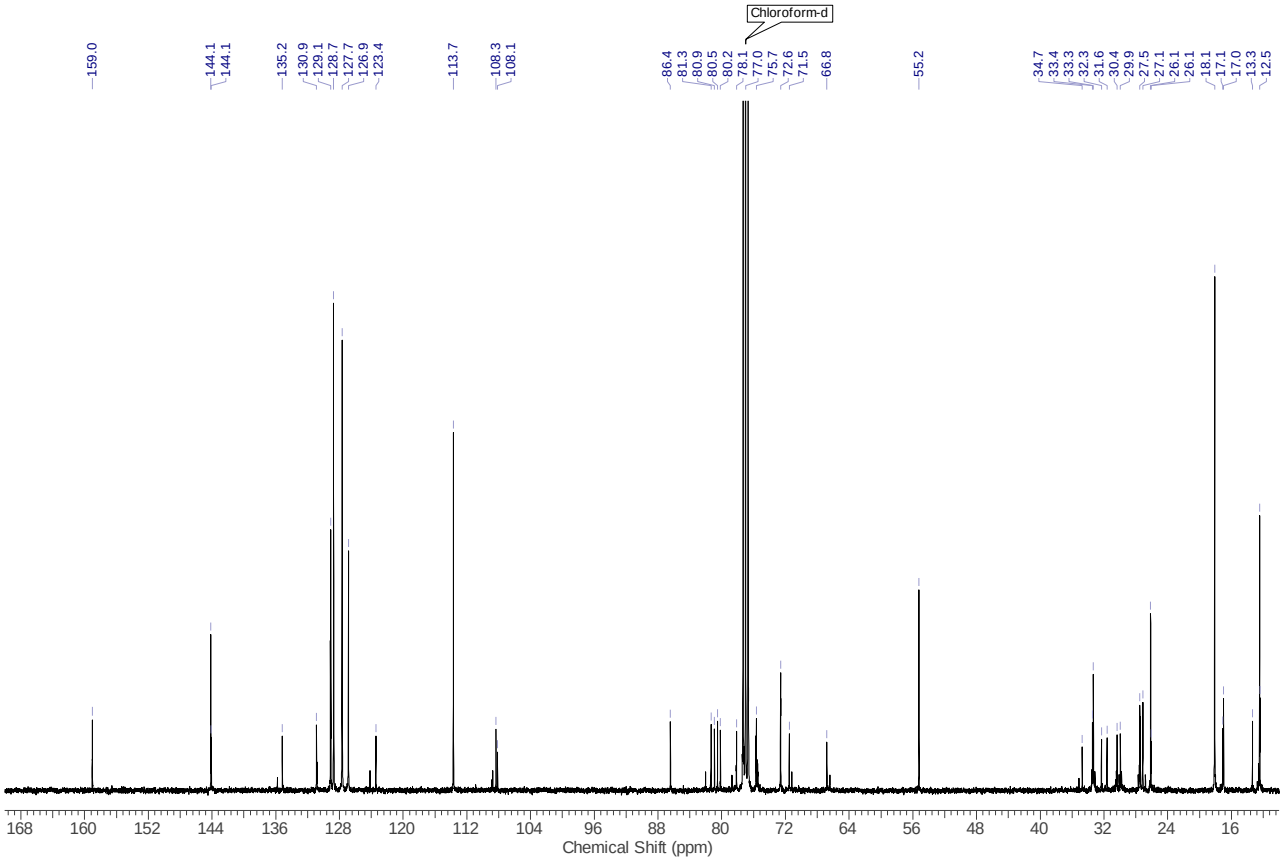
^{1}H NMR (400 MHz) spectrum of debrominated **2-183** in $CDCl_3$ (0.5 – 8 ppm)



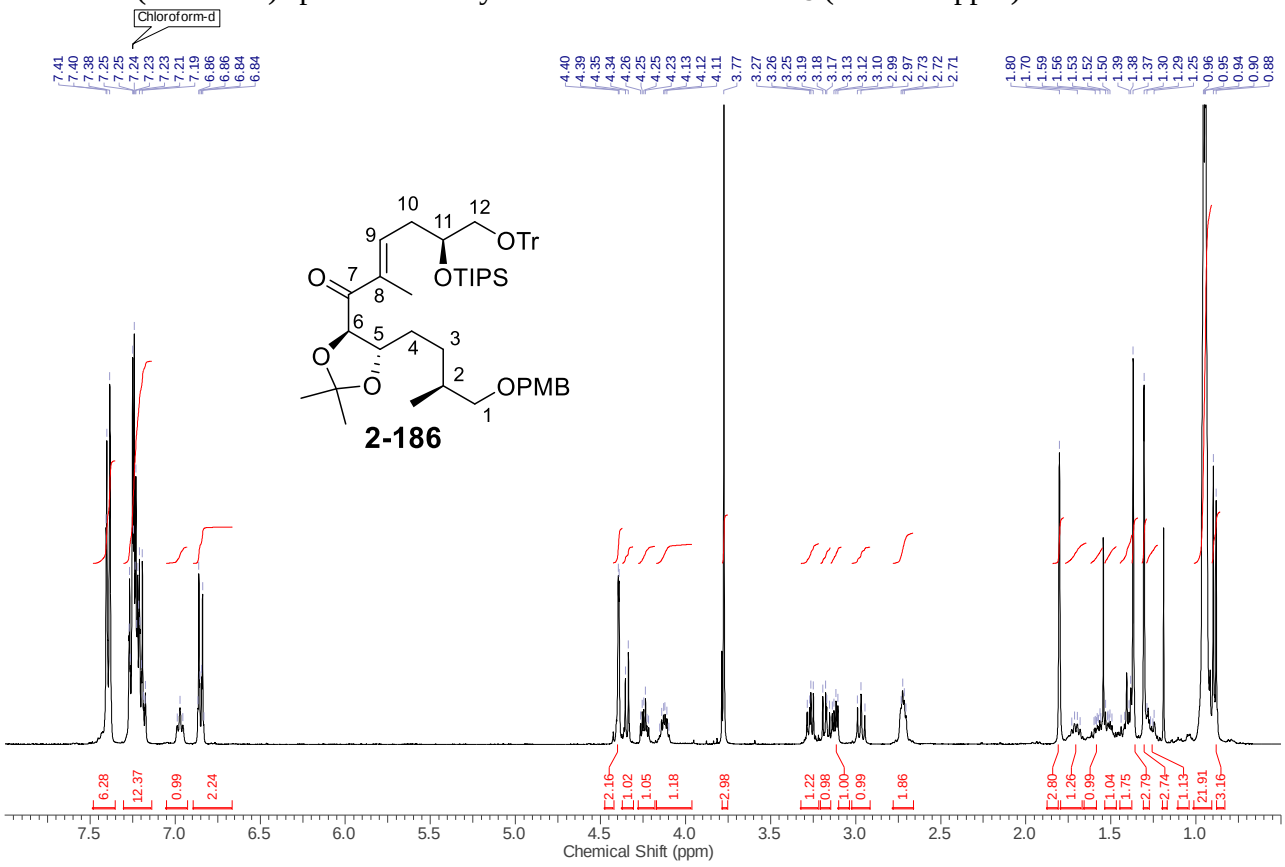
^{13}C NMR (100 MHz) spectrum of debrominated **2-183** in $CDCl_3$ (10 – 150 ppm)



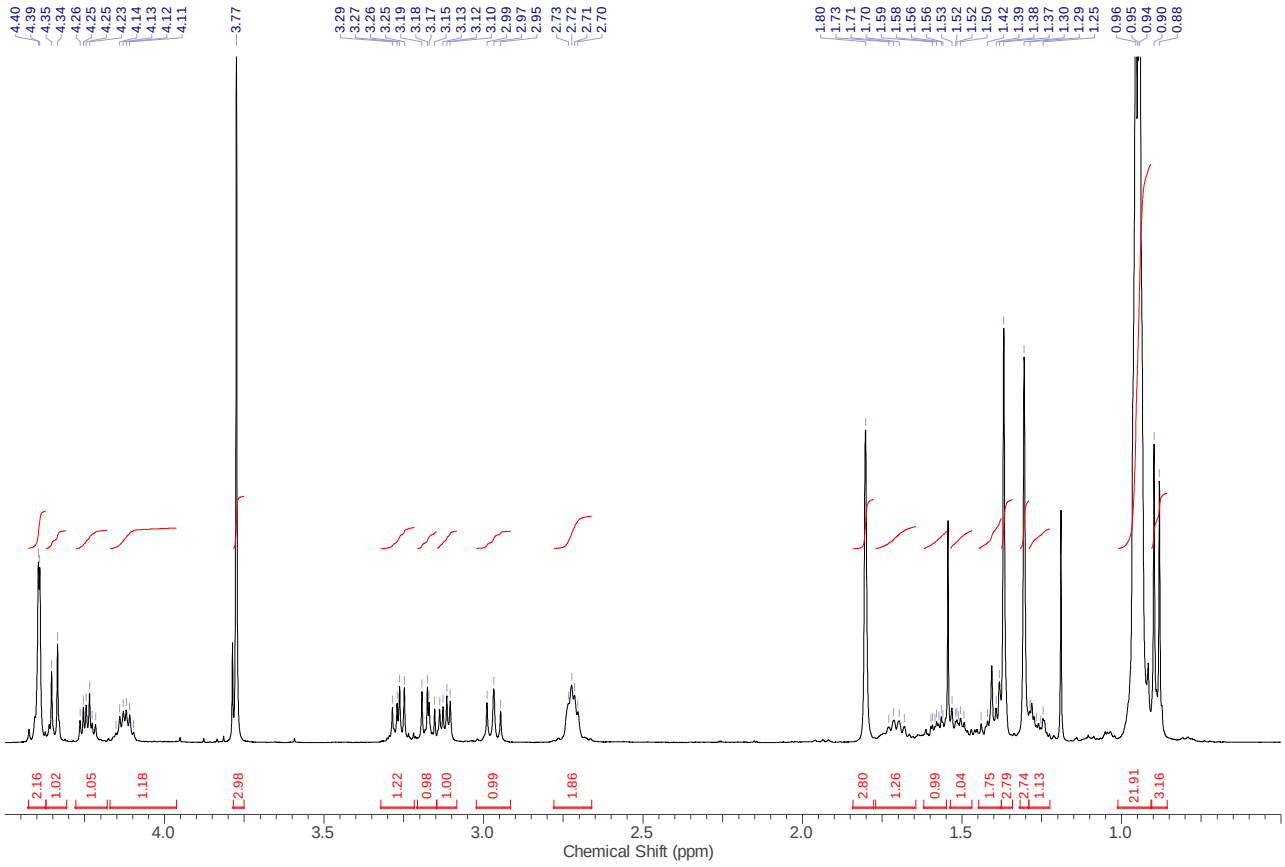
^{1}H NMR (400 MHz) spectrum of allyl alcohol **2-185** in $CDCl_3$ (0.5 – 8.0 ppm)



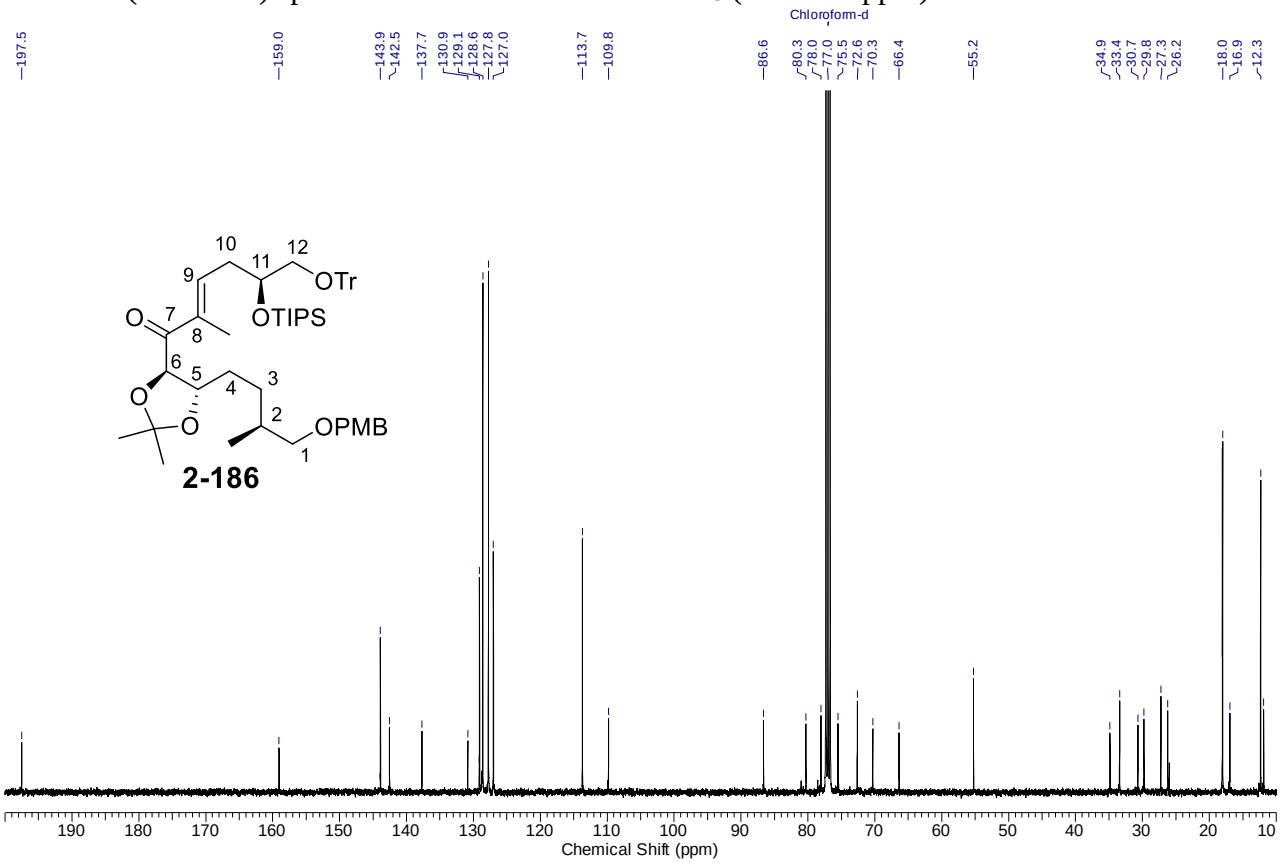
^{13}C NMR (100 MHz) spectrum of allyl alcohol **2-185** in $CDCl_3$ (10 – 170 ppm)



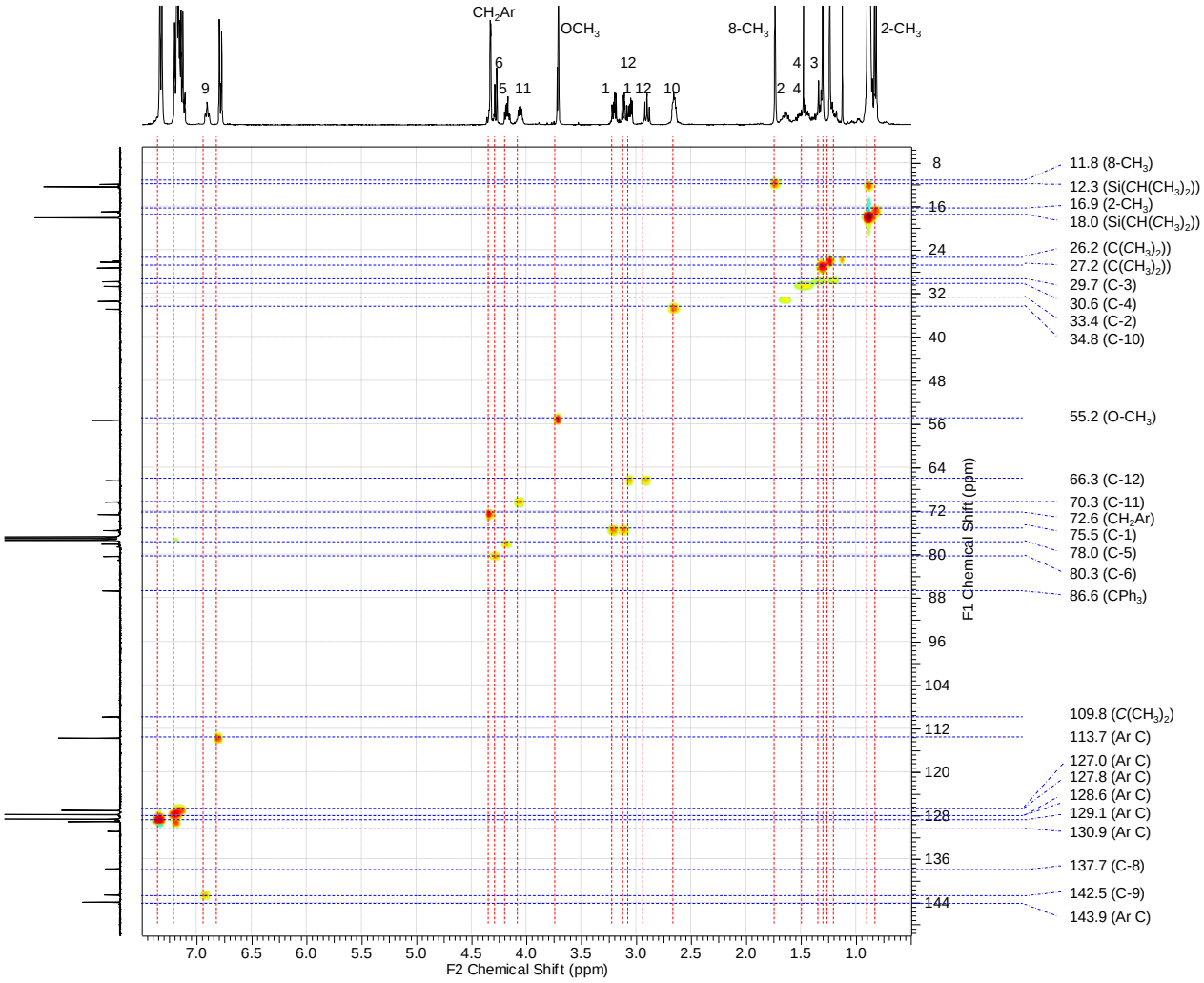
^{1}H NMR (400 MHz) spectrum of enone **2-186** in $CDCl_3$ (0.5 – 8.0 ppm)



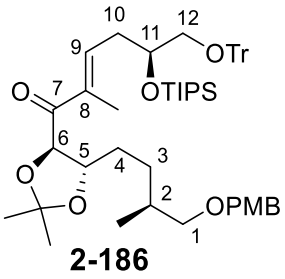
^{1}H NMR (400 MHz) spectrum of enone **2-186** in $CDCl_3$ (0.5 – 4.5 ppm)



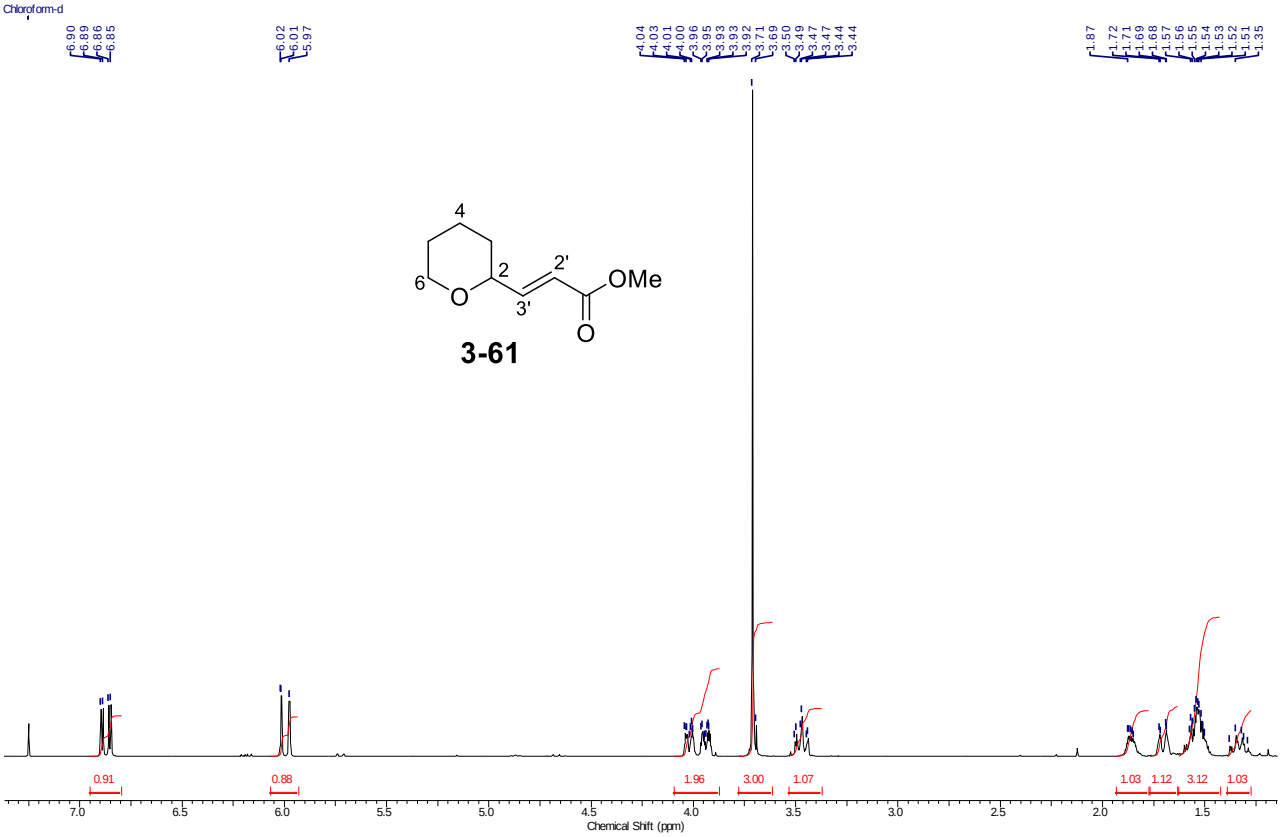
^{13}C NMR (100 MHz) spectrum of enone **2-186** in $CDCl_3$ (10 – 200 ppm)



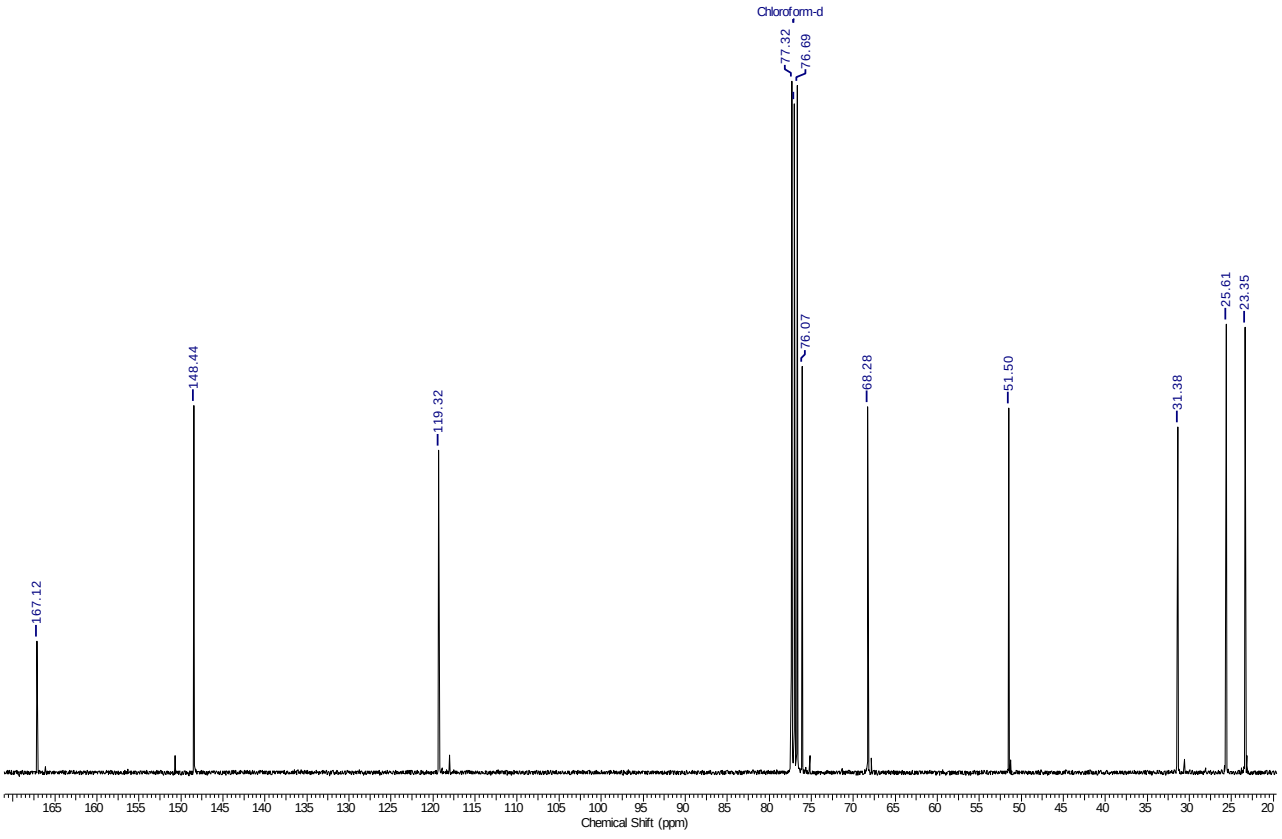
HSQC spectrum of enone **2-186** in $CDCl_3$ (0.5 – 7.5, 5 – 150 ppm)



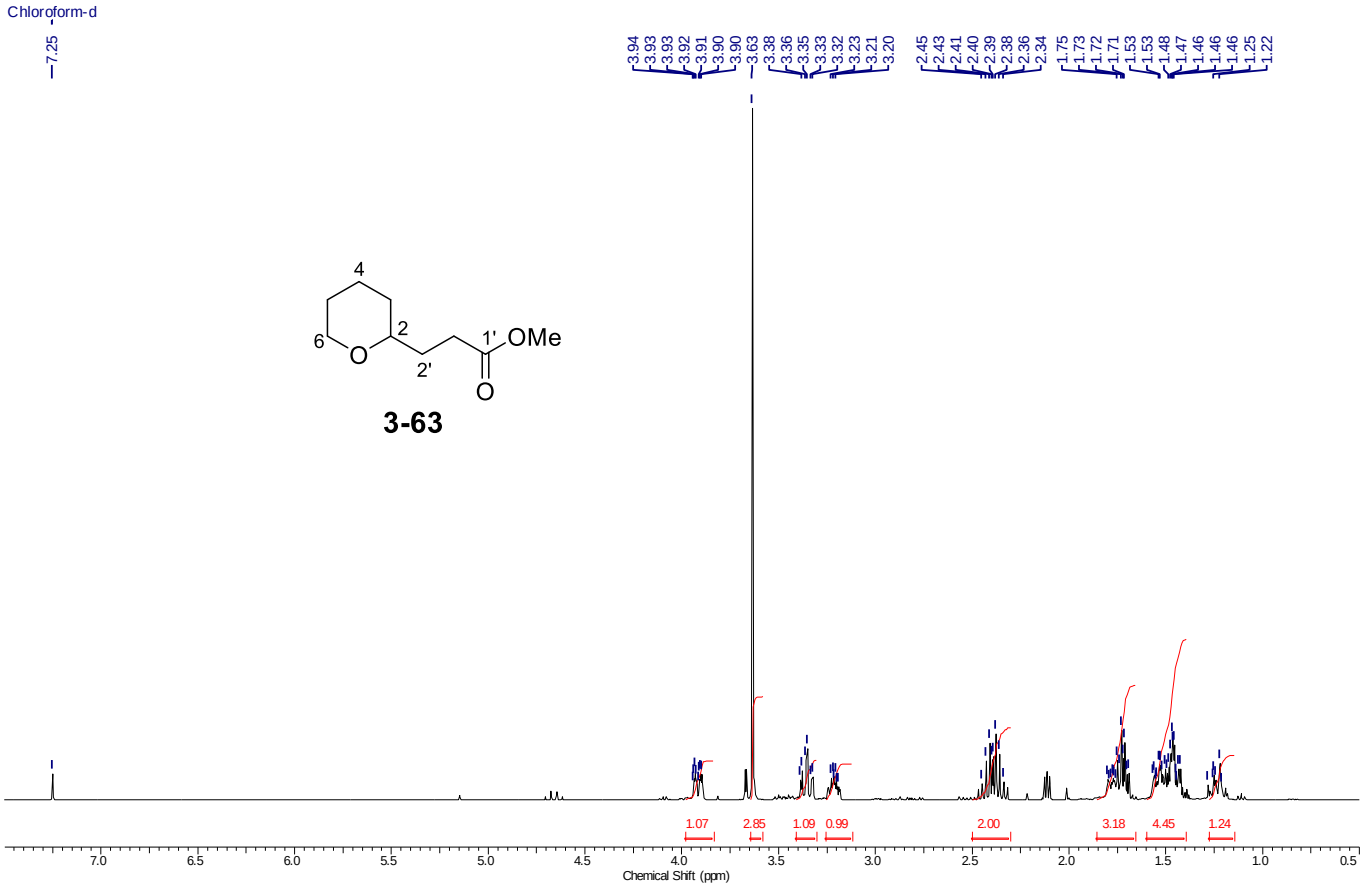
2-186



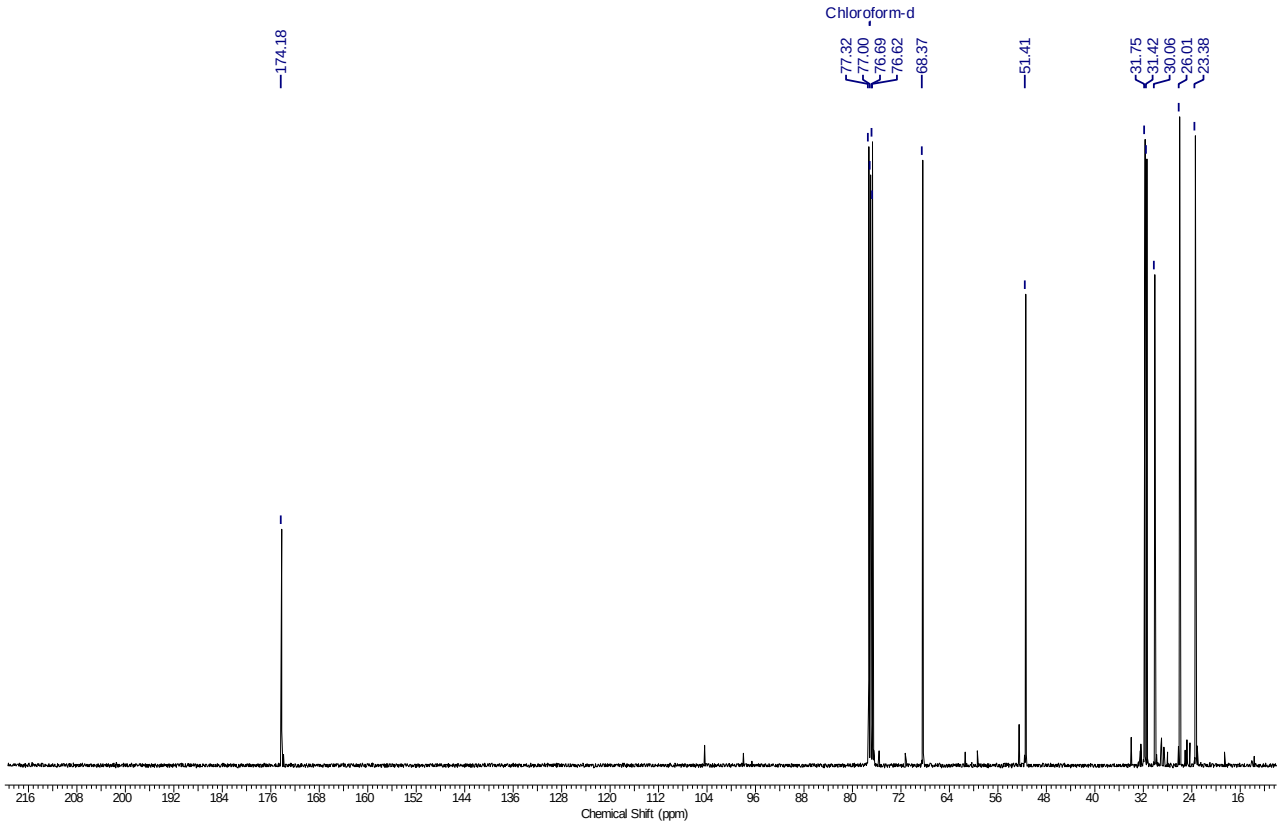
^{1}H NMR (400 MHz) spectrum of methyl acrylate **3-61** in $CDCl_3$ (0.5 – 8 ppm)



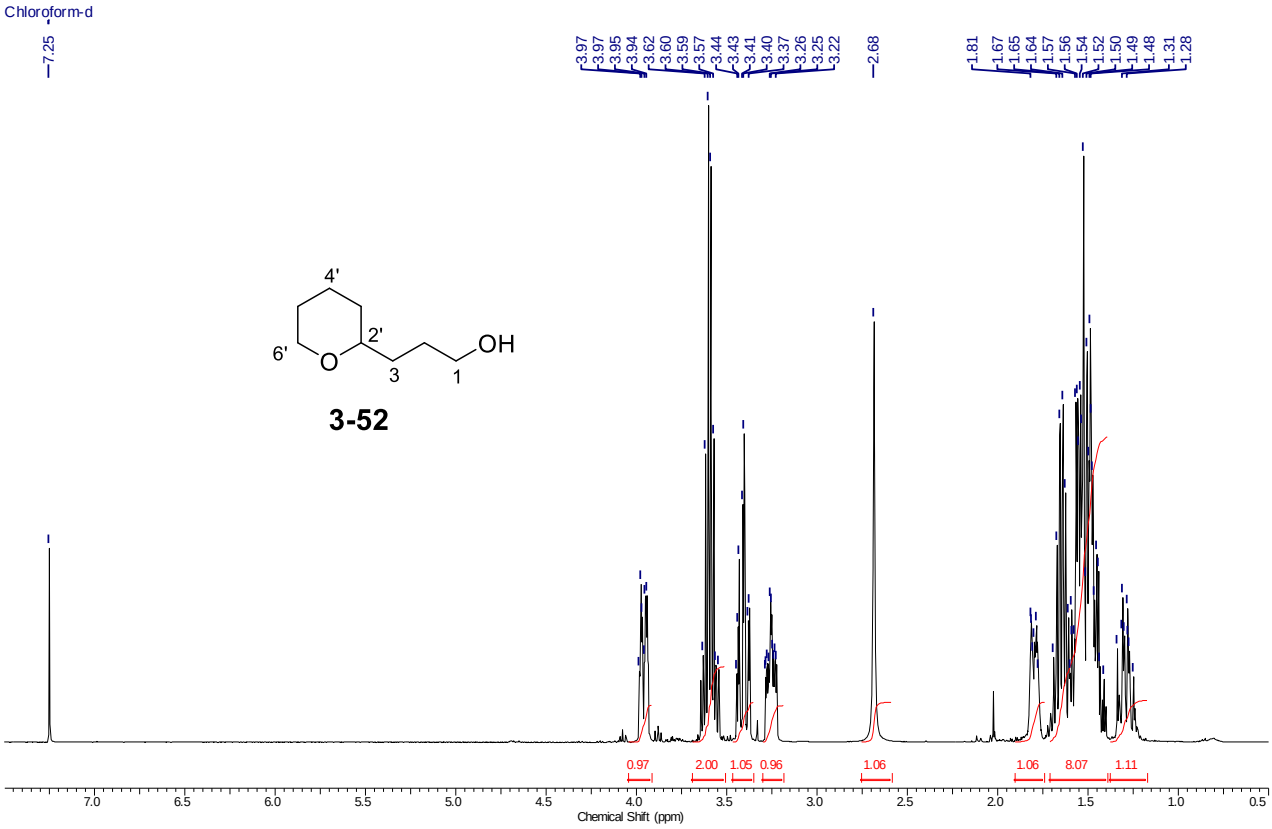
^{13}C NMR (100 MHz) spectrum of methyl acrylate **3-61** in $CDCl_3$ (15 – 200 ppm)



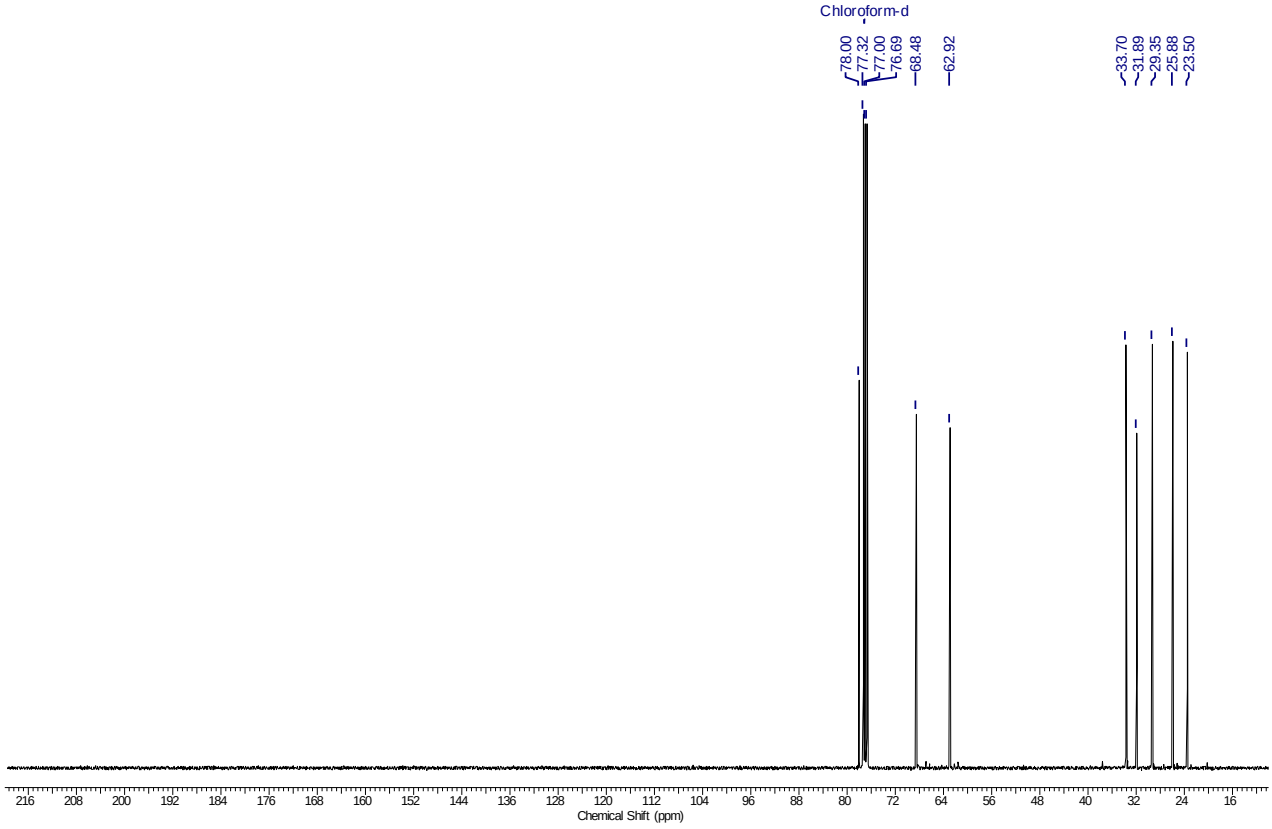
^{1}H NMR (400 MHz) spectrum of methyl ester **3-63** in $CDCl_3$ (0.5 – 8 ppm)



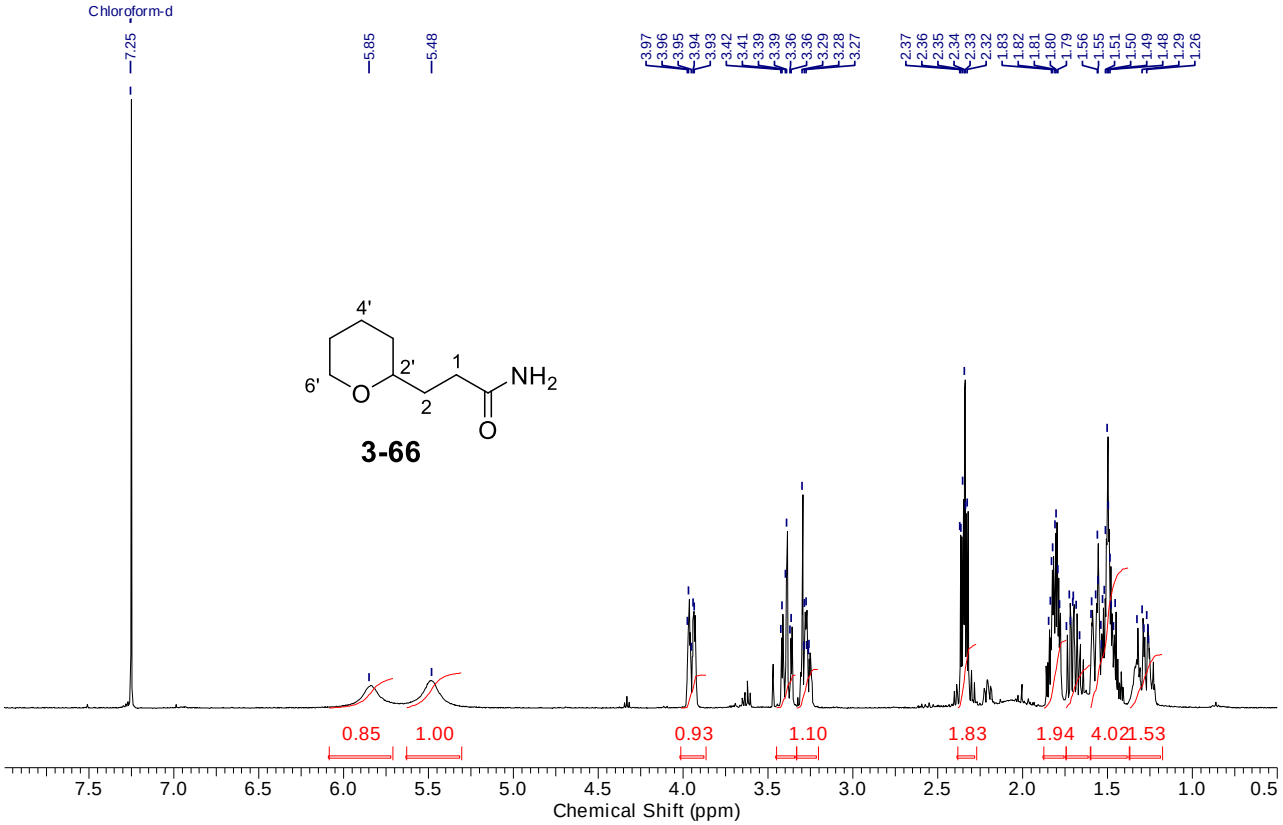
^{13}C NMR (100 MHz) spectrum of methyl ester **3-63** in $CDCl_3$ (15 – 200 ppm)



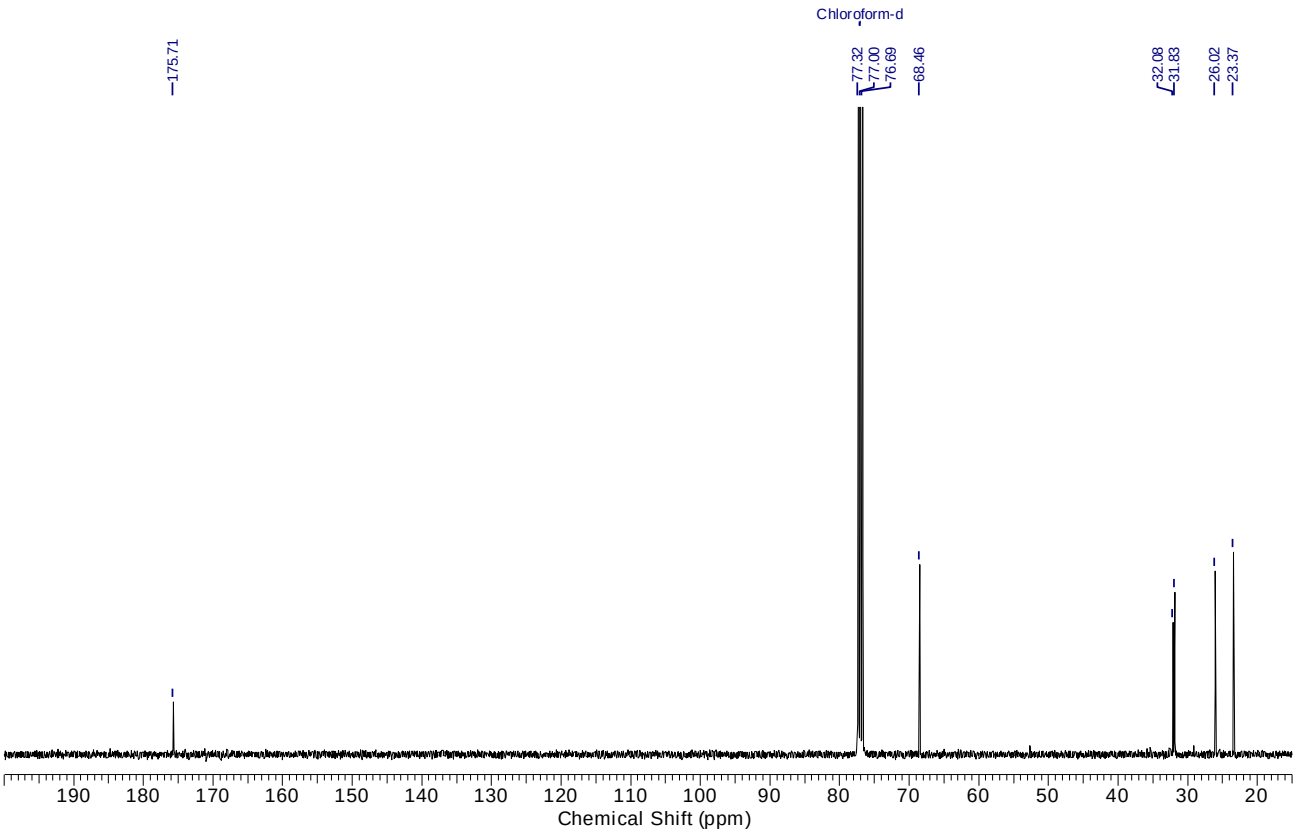
^{1}H NMR (400 MHz) spectrum of alcohol **3-52** in $CDCl_3$ (0.5 – 8 ppm)



^{13}C NMR (100 MHz) spectrum of alcohol **3-52** in $CDCl_3$ (15 – 200 ppm)



^{1}H NMR (400 MHz) spectrum of amide **3-66** in $CDCl_3$ (0.5 – 8 ppm)



^{13}C NMR (100 MHz) spectrum of amide **3-66** in $CDCl_3$ (15 – 200 ppm)

17.2 Bibliography

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