Studies Directed Towards the Synthesis of Polyketides, Lactones, Mono Acetogenins and Development of New Methodologies Involving C-S and C-N Bond Formations

Thesis Submitted to AcSIR
For the Award of the Degree of
DOCTOR OF PHILOSOPHY
In
Chemical Sciences

By
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Under the guidance of
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October-2016

Dedicated to…..

My beloved Parents, Lovely Wife

&

Little Daughter

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75 Years of CSIR Touching Lives

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THESIS CERTIFICATE

This is to certify that the work incorporated in this Ph.D. thesis entitled "**Studies Directed Towards the Synthesis of Polyketides, Lactones, Mono Acetogenins and Development of New Methodologies Involving C-S and C-N Bond Formations**" submitted by **Mr. Ummidisetti Nookaraju** to Academy of Scientific and Innovative Research (AcSIR) in fulfillment of the requirements for the award of the Degree of Doctor of Philosophy, embodies original research work under my supervision. I further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material obtained from other sources has been duly acknowledged in the thesis. Any text, illustration, table *etc*., used in the thesis from other sources, have been duly cited and acknowledged.

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CANDIDATE'S DECLARATION

I hereby declare that the original research work embodied in this thesis entitled "**Studies Directed Towards the Synthesis of Polyketides, Lactones, Mono Acetogenins and Development of New Methodologies Involving C-S and C-N Bond Formations**" submitted to Academy of Scientific and Innovative Research for the award of degree of Doctor of Philosophy (Ph.D.) is the outcome of experimental investigations carried out by me under the supervision of **Dr. Pradeep Kumar**, Chief Scientist and Chair, Organic Chemistry Division, CSIR-National Chemical Laboratory, Pune. I affirm that the work incorporated is original and has not been submitted to any other academy, university or institute for the award of any degree or diploma.

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Though only my name appears on the cover of this dissertation, a great many people have contributed to its production. I owe my gratitude to all those people who have made this dissertation possible and because of whom my graduate experience has been one that I will cherish forever.

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Ummidisetti Nookaraju

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Abbreviations

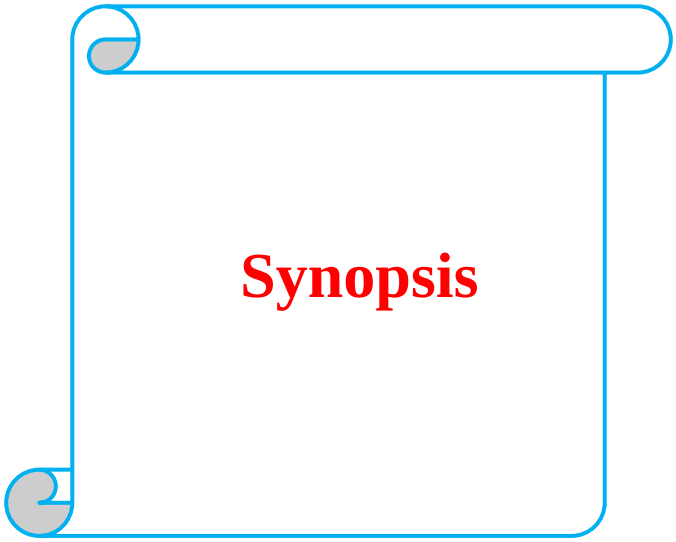
Ac	-	Acetyl
AcOH	-	Acetic acid
Ac_2O	-	Acetic anhydride
ACN	-	Acetonitrile
Bn	-	Benzyl
BnBr	-	Benzyl bromide
Boc	-	*tert*-Butoxy carbonyl
$(Boc)_2O$	-	Di-*tert*-butyl dicarbonate
BuLi	-	Butyl lithium
^tBuOH	-	*Tert*-butanol
Cat.	-	Catalytic
$CDCl_3$	-	Deuterated chloroform
Claycop	-	Clay supported copper nitrate
Clayfen	-	Clay supported ferric nitrate
Clayan	-	Clay supported ammonium nitrate
COSY	-	Correlation spectroscopy
DABCO	-	1,4-Diazabicyclo[2.2.2]octane
DBU	-	1,8-Diazabicyclo[5.4.0]undecene-7
DCM	-	Dichloromethane
DCC	-	N,N'-Dicyclohexylcarbodiimide
DCE	-	1,2-Dichloroethane
DDQ	-	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
$(DHQ)_2PHAL$	-	1,4-Bis(dihydroquinin-9-*O*-yl)phthalazine
$(DHQD)_2PHAL$	-	1,4-Bis(dihydroquinindin-9-*O*-l)phthalazine
DIAD	-	Diisopropyl azodicarboxylate
DIPT	-	Diisopropyl D-tartrate
DIBAL-H	-	Diisobutylaluminiumhydride
DIPEA	-	N,N-Diisopropylethylamine
DMF	-	*N*, *N'*-Dimethylformamide

DMAP	-	*N*,*N'*-Dimethylaminopyridine
DMSO	-	Dimethyl sulfoxide
ee	-	Enantiomeric excess
equiv.	-	Equivalents
EtOH	-	Ethanol
Et	-	Ethyl
Et_2O	-	Diethyl ether
EtOAc	-	Ethyl acetate
Et_3N	-	Triethylamine
G-II	-	Grubbs second generation catalyst
HG-II	-	Hoveda Grubbs second generation catalyst
Hz	-	Hertz
HRMS	-	High resolution mass spectroscopy
HMPA	-	Hexamethylphosphoramide
HMBC	-	Heteronuclear Multiple Bond Correlation
HPLC	-	High pressure liquid chromatography
HSQC	-	Heteronuclear Single Quantum Coherence
Im	-	Imidazole
Ipc	-	Diisopinocampheyl
KHMDS	-	Potassium bis(trimethylsilyl)amide
Me	-	Methyl
MeOH	-	Methanol
mg	-	Milligram
min	-	Minutes
mL	-	Millilitre
mmol	-	Millimole
m-CPBA	-	*meta*-Chloroperoxybenzoic acid
M. P.	-	Melting point
Ms	-	Methanesulfonyl
MS	-	Molecular seives
MsCl	-	Methanesulfonyl chloride

Me	-	Methyl
MeI	-	Methyl iodide
MOM	-	Methoxymethyl
MEM	-	2-Methoxyethoxymethyl
$NaBH_4$	-	Sodiumborohydride
NaH	-	Sodium hydride
NaHMDS	-	Sodium bis(trimethylsilyl)amide
NBS	-	*N*-Bromosuccinimide
NOE	-	Nuclear Overhauser effect
PivCl	-	Pivaloyl chloride
Ph	-	Phenyl
Py	-	Pyridine
PNBA	-	*para*-Nitro benzoic acid
PMB	-	*para*-Methoxy benzyl
p-TSA	-	*par*a-Toluenesulfonic acid
PPTS	-	Pyridinium p-toluenesulfonate
TBAI	-	Tetra-*n*-butylammonium iodide
TBAF	-	Tetra-*n*-butylammonium fluoride
TBDMS	-	*tert*-Butyldimethyl silyl
TBHP	-	*tert*-Butyl hydroperoxide
TBSCl	-	*tert*-Butyldimethyl silyl chloride
TBDPSCl	-	*tert*-Butyl(chloro)diphenylsilane
TEMPO	-	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TEA	-	Triethyl amine
TFA	-	Trifluoroacetic acid
THF	-	Tetrahydrofuran
TPP	-	Triphenylphosphine
p-TSA	-	*p*-Toluenesulfonic acid
TsCl	-	*p*-Toluenesulfonyl chloride

General remarks

- ^{1}H NMR spectra were recorded on AC-200 MHz, AC-400 MHz, Jeol-400 MHz and DRX-500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C NMR spectra were recorded on AC-50 MHz, AC-100 MHz, Jeol-100 MHz and DRX-125 MHz spectrometer.
- EI Mass spectra were recorded on Finnigan MAT-1020 spectrometer at 70 *eV* using a direct inlet system.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected.
- All reactions are monitored by Thin layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV light, I_2, ninhydrin and anisaldehyde in ethanol as development reagents.
- All solvents and reagents were purified and dried by according to procedures given in Vogel's Text Book of Practical Organic Chemistry. All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 40 °C.
- Silica gel (60–120) used for column chromatography was purchased from ACME Chemical Company, Mumbai, India.
- All melting points and boiling points are uncorrected and the temperatures are in centigrade scale.
- The compounds, scheme and reference numbers given in each section of chapter refer to that particular section of the chapter only.


Synopsis

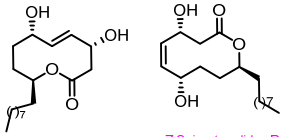
Synopsis of the Thesis to be submitted to the Academy of Scientific and Innovative Research for Award of the Degree of Doctor of Philosophy in Chemistry	
Name of the Candidate	**UMMIDISETTI NOOKARAJU**
Degree Enrolment No. & Date	**Ph. D in Chemical Sciences (10CC11A26038); August 2011**
Title of the Thesis	**Studies Directed Towards the Synthesis of Polyketides, Lactones, Mono Acetogenins and Development of New Methodologies Involving C-S and C-N Bond Formations**
Research Supervisor	**Dr. Pradeep Kumar**

The thesis is divided into four chapters. **Chapter 1** describes the studies in the synthesis of lactones and mono acetogenins, **Chapter 2:** describes THF ring construction *via* tandem iodocyclizations: synthesis of Hagen's gland lactones and its epimers, pheromone of *Idea Leuconoe*, oxylipid and valuable synthons, **Chapter 3** describes the studies towards the synthesis of Polyketides and **Chapter 4** describes the development of new methodologies involving C-S and C-N bond formations.

Chapter 1: Studies in the synthesis of lactones and mono acetogenins

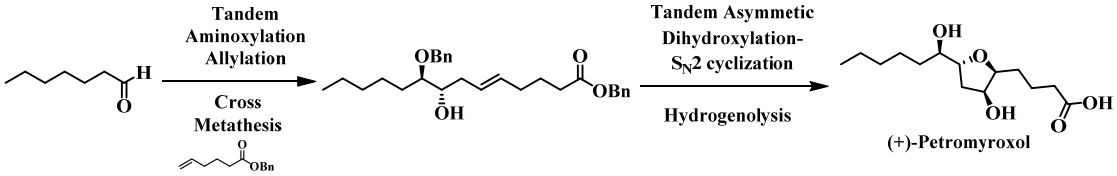
Section A: First total synthesis of seimatopolide B

Seimatopolides A and B were isolated[1a] from an ethyl acetate extract of *Seimatosporium discosioides* culture medium. Seimatopolides show therapeutic potential in the treatment of type 2 diabetes and inflammatory disease. The first enantioselective total synthesis of seimatopolide B has been achieved, using ring-closing metathesis and DCC coupling as key steps. The stereogenic centres were generated by means of iterative hydrolytic kinetic resolution (HKR) of racemic epoxides. Here, we studied the protecting group directed RCM[1b].



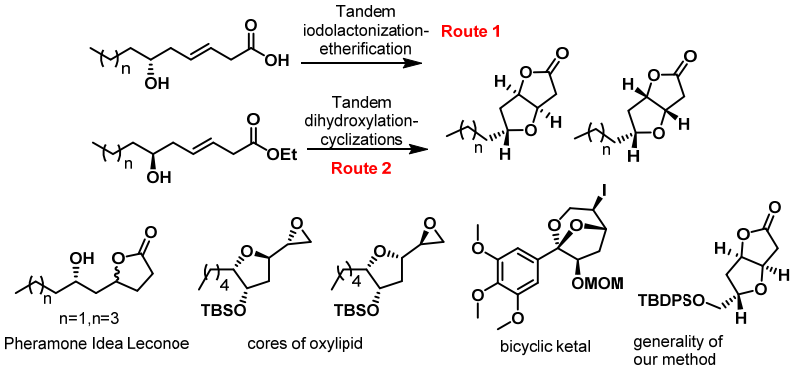
Section B: Total synthesis of (+)-petromyroxol *via* tandem α-aminoxylation–allylation and asymmetric dihydroxylation–S_N2 cyclization approach

A non-racemic mixture of petromyroxol (2.9 mg) has been isolated from >100 000 L of water conditioned with the larvae of Petromyzon marinus.[2a] The (+)-enantiomer was found to be just 0.9 mg (36%) of the isolated mixture, nevertheless, was found to trigger a better olfactory response among the lamprey fish than it's (-)-antipode. The present synthesis employs a tandem α-aminoxylation-allylation, cross metathesis and tandem asymmetric dihydroxylation-S_N2 cyclization as key steps.[2b]



Chapter 2: THF ring construction *via* tandem iodocyclizations: synthesis of Hagen's gland lactones and its epimers, pheromone of *Idea Leuconoe*, oxylipid and valuable synthons[2c]

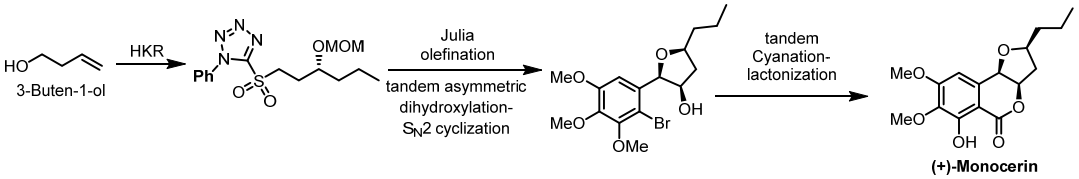
Fused THF-γ-lactone motif is a significant synthon to access the class of acetogenins and several other natural products of similar type. We devised two short and protecting group free approaches towards the synthesis of Hagen's gland lactones and its epimers. Our synthetic efforts towards the Hagen's gland lactones as well as observations made during the course of synthesis are disclosed here.



Chapter 3: Studies towards the synthesis of polyketides

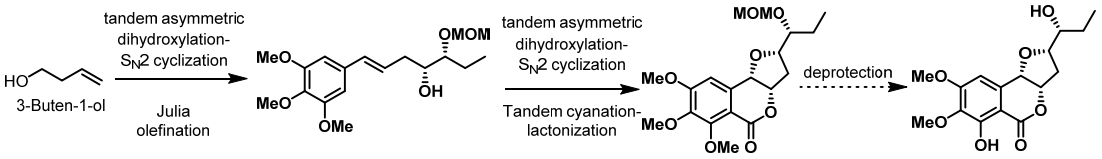
Section A: Total synthesis of (+)-monocerin via tandem dihydroxylation-S_N2 cyclization and a copper mediated tandem cyanation–lactonization approach

Monocerin was isolated by Aldridge *et al.* in 1970 from culture filtrates of *Helminthosporium monoceras*.[3a] A simple and novel synthesis of (+)-monocerin was achieved from 3-buten-1-ol employing hydrolytic kinetic resolution, Julia olefination, intramolecular tandem Sharpless asymmetric dihydroxylation-S_N2 cyclization and a novel copper mediated tandem cyanation–cyclization as the key steps.[3b]



Section B: Studies towards the synthesis of 11-hydroxy monocerin

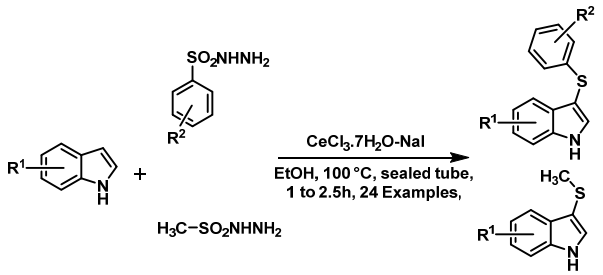
11-Hydroxymonocerin was isolated from the plant endophytic Fungus *Exserohilum rostratum.*[3c] *11-Hydroxymonocerin displayed activity against Plasmodium falciparum (K1, multidrug-resistant strain) with* IC_{50} *values of 7.70 μM.* On the similar lines we attempted the total synthesis of 11-hydroxy monocerin.



Chapter 4: Development of new methodologies involving C-S and C-N bond formations

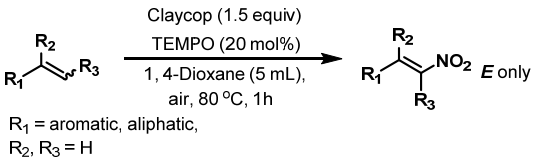
Section A: $CeCl_3.7H_2O$-NaI promoted regioselective sulfenylation of indoles with sulfonylhydrazides

A simple and highly efficient method has been developed for the selective sulfenylation of a wide variety of indoles with sulfonylhydrazides through the cleavage of sulfur–oxygen and sulfur–nitrogen bonds using $CeCl_3.7H_2O$-NaI as an inexpensive and readily available reagent system.[4a]



Section B: Clay-supported copper nitrate (claycop): A mild reagent for the selective nitration of aromatic olefins

A straightforward and highly selective method has been developed for the synthesis of selective nitration of a wide variety of aromatic and aliphatic olefins using clay supported copper nitrate "Claycop" and catalytic amount of TEMPO as an inexpensive and eco-friendly reagent system.[4b]



Noteworthy Findings:

- We have achieved the first total synthesis of seimatopolide B using protecting group directed RCM.
- Petromyroxol synthesis was achieved using tandem aminoxylation-allylation and dihydroxylation-cyclization.
- Two short and protecting group free approaches towards the synthesis of Hagen's gland lactones and its epimers were developed. During the course of this study, we also achieved the total synthesis of pheromone of *Idea Leuconoe*, formal synthesis of oxylipid and a valuable key intermediate bicylic ketal.
- We have achieved the total synthesis of (+)-monocerin. We are at the final stage of total synthesis of 11-hydroxy monocerin.
- We developed new methodologies involving C-S and C-N bond formations *i.e.* Indole 3-sulfenylation and nitration of aromatic olefins.

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4. a) **U. Nookaraju,** Eeshwaraiah Begari, Ravikiran Reddy Yetra, and Pradeep Kumar, ChemistrySelect, 2016, 1, 81–84. b) Eeshwaraiah Begari, Chandani Singh, **U. Nookaraju** Pradeep Kumar, Synlett 2014, 14, 1997-2000.

To the field of synthetic chemistry belongs an array of responsibilities which are crucial for the future of mankind, not only with regard to the health and needs of our society, but also for the attainment of a deep understanding of matter, chemical change, and life.

Elias James Corey

Chapter-1

Studies in the Synthesis of Lactones and Mono Acetogenins

1.1. SECTION A

First Total Synthesis of Seimatopolide B

1.1.1. Introduction

Jang and Lee *et al.*[1] recently isolated seimatopolide A and B, a polyhydroxylated 10-membered macrolide from an EtOAc extract of *Seimatosporium discosioides* culture medium, along with three known compounds monosporascone, arthrinone and 3a,9a-deoxy-3a-hydroxy-1-dehydroxyarthrinone. Seimatopolides belong to a family of novel class of 10-membered lactones, such as members of deacarestrictine,[2] microcarpalide[3] and pinolidoxin[4] *etc.* (**Figure 1**). These compounds are structurally related to each other based on their physico-chemical properties. Owing to their strong and interesting biological profile including inhibition of cholesterol biosynthesis,[5] antimalarial and antibacterial activity,[6] microfilament formation,[3] these compounds have attracted a great deal of interest among synthetic organic chemists worldwide as an attractive synthetic targets towards developing new therapeutic agents. Seimatopolides exhibited significant activity in a reporter gene assay for activation of peroxisome proliferator-activated receptor γ (PPAR-γ)[7a] with EC_{50} values of 11.05 μM, which has therapeutic potential target in treatment of type 2 diabetes, inflammatory disease and certain cancers.[7b]

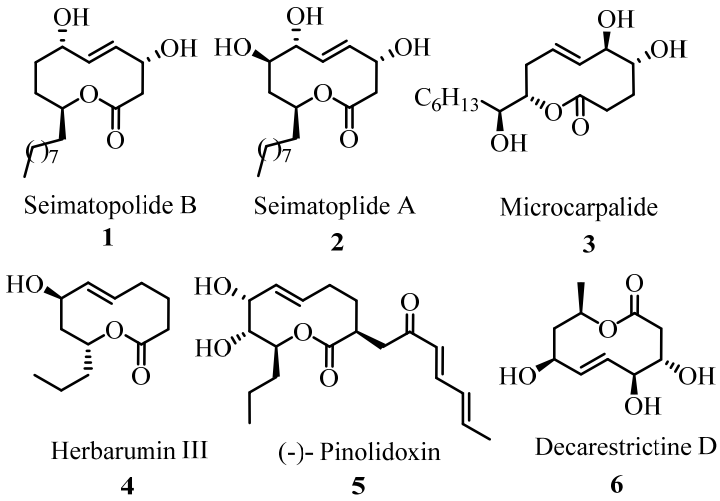


Figure 1: Some selected examples of 10-membered lactones

1.1.2. Introduction to key step (Hydrolytic Kinetic Resolution reaction)

Enantiomerically pure epoxides are very useful building blocks in asymmetric organic synthesis. Due to this fact lot of research has been aroused for making chiral epoxides during last decade and many advanced methods have been developed in this area. Among them Sharpless asymmetric epoxidation[8] proved to be profound method to access enantiopure epoxy alcohols. However it requires allylic alcohol handle, thus limiting the scope of this reaction. Later another advanced strategy was developed for the epoxidation of olefins using chiral dioxiranes intermediates.[9] Apart from these methods, no other general methods are available for making enantiomerically pure epoxides.

In 1997, Jacobsen discovered the powerful and reliable general method to resolve the racemic terminal epoxides into chiral pure epoxides and diols using salen cobalt (III) acetate complex as a catalyst.[10] By using this method we can have easy access to the both chiral pure epoxides and diols. The chiral epoxides are very useful building blocks in asymmetric synthesis and they find tremendous applications in the total synthesis of biologically active natural products.[11] It is pertinent to mention here that we can also access chiral pure 1, 2-diols in this reaction, which are generally not readily accessible from dihydroxylation method (*i.e*. low *ee* of 1,2-diols).

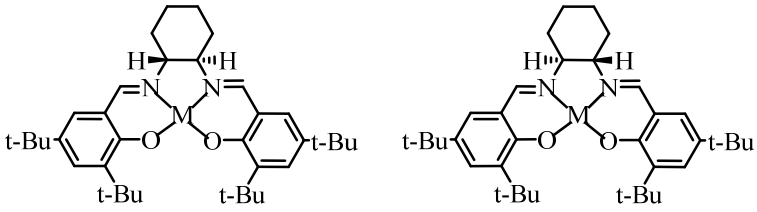
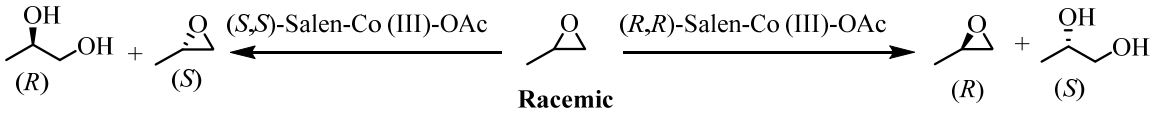


Figure 2: Catalysts used in Hydrolytic Kinetic Resolution

The beauty lies in the fact that it requires low catalyst loadings (0.2 mol %) that can be recycled. Water acts as a nucleophile. Epoxide ring opening reaction can be controlled by

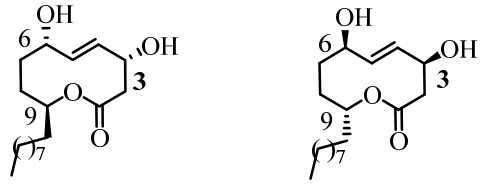
the rate of addition of water to the reaction mixture containing catalyst. Jacobsen HKR method has proved to be a general method as virtually any terminal epoxide can be resolved by using this protocol.



Scheme 1: Hydrolytic Kinetic Resolution reaction

1.1.3. Review of Literature

Post synthesis and structural revision: Our group accomplished and published the first total synthesis of proposed structure of seimatopolide B.[12a] The publication of our work was immediately followed by the structural revision of seimatopolide B and subsequent one total synthesis of the revised natural product. The absolute configuration of seimatopolide B was initially assigned as 3*R*, 6*S*, 9*S*. Later isolation group revised its structure as 3*S*, 6*R*, 9*R* (**Figure 3**). We synthesized the initially proposed structure of seimatopolide B which happened to be the opposite enantiomer of the revised structure. Raji Reddy and co-workers[12b] synthesized seimatopolide B (revised structure) using almost the similar strategy as reported by us.



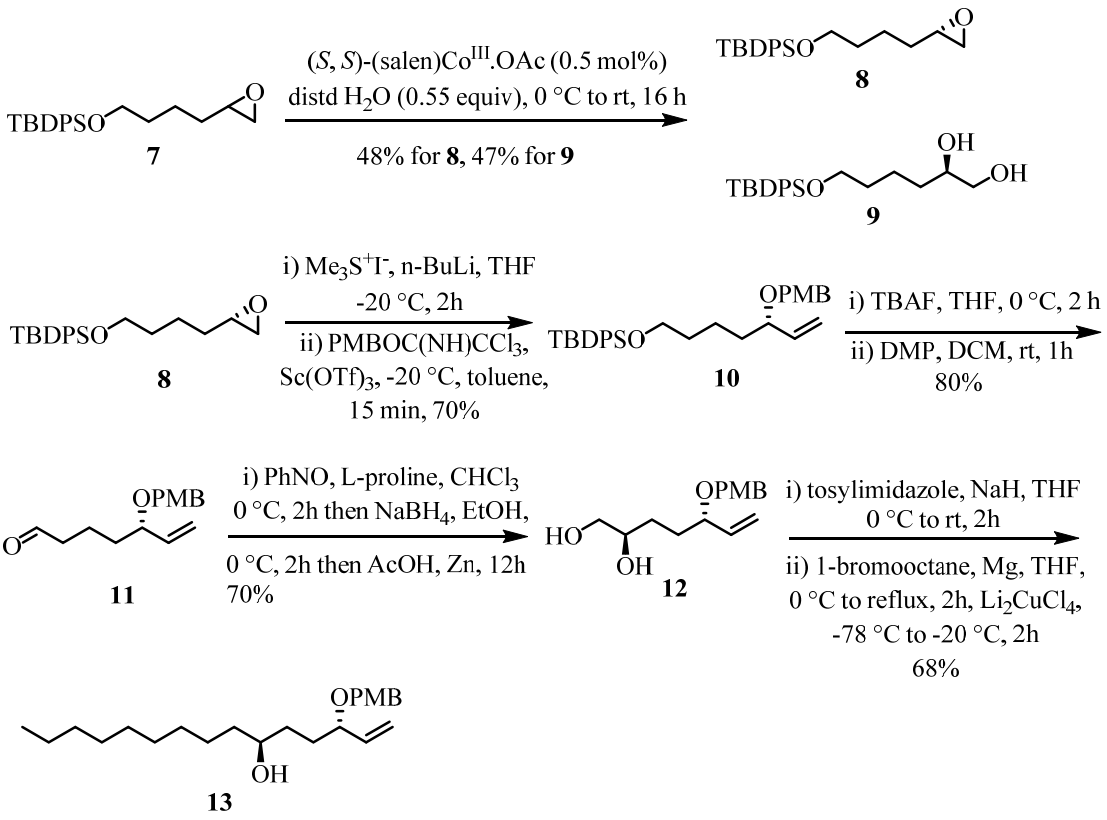
Initially proposed structure | **After revision**

3*R*, 6*S*, 9*S* | 3*S*, 6*R*, 9*R*

Figure 3: Structural revision of seimatopolide B

Raji Reddy *et al.* (2013)[12b] accomplished the first synthesis of revised structure of seimatopolide B by coupling the acid and alcohol fragments using Yamaguchi esterification as key step and RCM for macro-lactonization. Synthesis of alcohol fragment (**Scheme-2**)

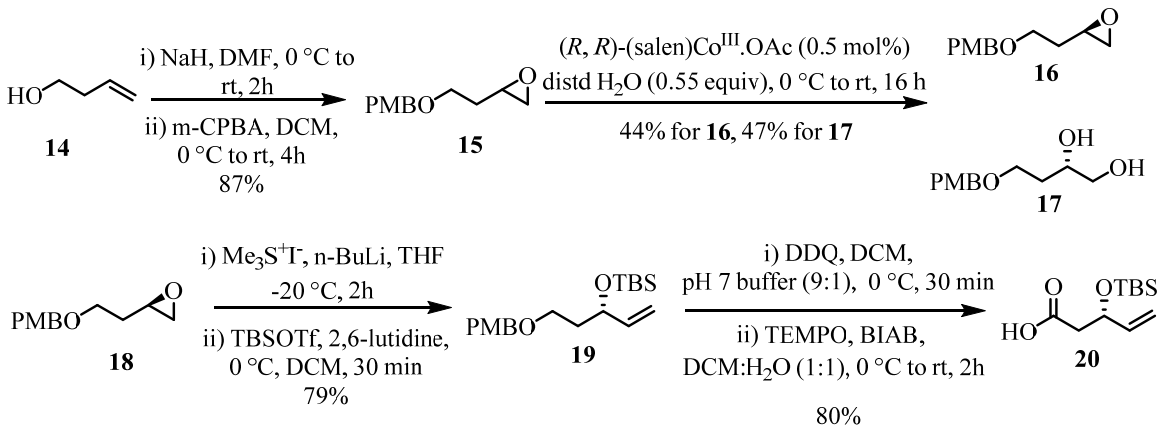
started from known epoxide **7**, which was subjected to Jacobson's HKR condition using *(S,S)*-Salen Co^{III}-OAc catalyst to give the required enantio pure epoxide **8**, which upon treatment with dimethyl sulfonium methylide resulted in the allylic alcohol and further protected as its PMB ether **10.** Subsequent desilylation and oxidation gave the aldehyde **11**. The aldehyde **11** was subjected to proline catalysed aminoxylation followed by reduction using $NaBH_4$ to give the diol **12**. The diol was converted to epoxide using tosylimaidazole. Subsequent epoxide opening with octyl Grignard gave the alcohol fragment **13** (**Scheme 2**).



Scheme 2: Synthesis of alcohol fragment **13**

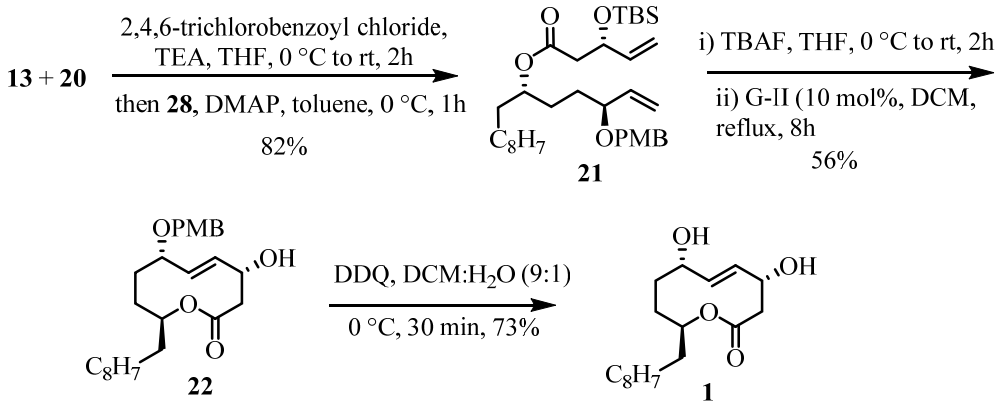
Synthesis of acid fragment commenced from 3-buten-1-ol **14**, which was protected as its PMB ether and subsequent epoxidation using *m*-CPBA gave the rac-epoxide **15**. To get the chiral pure epoxide **16**, the compound **15** was treated with catalyst-*(R, R)*-Salen Co^{III}-OAc. The chiral epoxide **16** was treated with trimethylsulfonium iodide using ^{n}BuLi as base to afford the allylic alcohol which upon protection gave the TBS ether **19**. The TBS ether **19**

was subjected to oxidative cleavage of PMB ether using DDQ followed by the oxidation of primary alcohol using TEMPO, BAIB to give the acid fragment **20** (**Scheme 3**).



Scheme 3: Synthesis of acid fragment **20**

Now both the acid **20** and alcohol **13** were coupled using Yamaguchi esterification reaction to give the diene ester **21**. The ester **21** was subjected to desilylation followed by RCM to afford the cyclized product **22**, which upon deprotection of PMB ether using DDQ resulted in the target molecule seimatopolide B **1** (**Scheme 4**).



Scheme 4: Synthesis of Seimatopolide B **1**

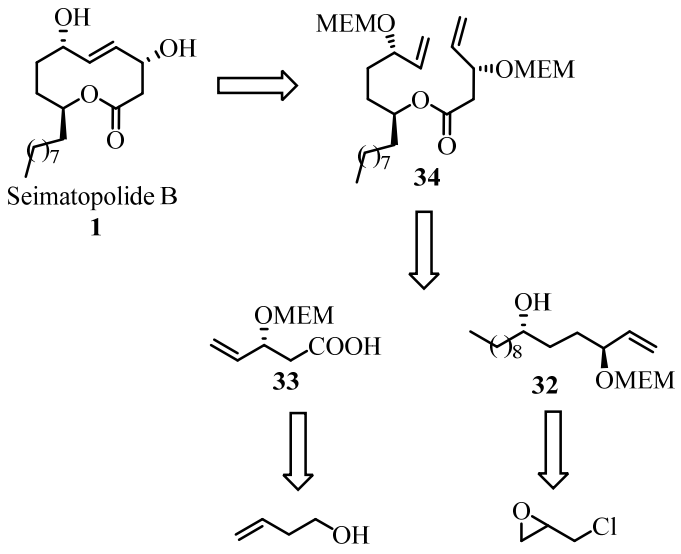
1.1.4. Present work

Objective

As a part of our research programme aimed at developing enantioselective synthesis of biologically active natural products based on hydrolytic kinetic resolution (HKR),[13] we considered developing a simple and concise first total synthesis of seimatopolide B, employing HKR, DCC coupling and ring- closing metathesis (RCM)[14] as the key steps. The details of findings are presented below.

1.1.5. Results and discussion

In continuation of our ongoing interest in exploiting HKR method to install the stereocentres and ring-closing metathesis for making cyclic compounds *viz.* 10-membered lactone rings based upon protecting group directed ring-closing metathesis protocol[15] and generalizing its substrate based selectivity, we planned to synthesize seimatopolide B.



Scheme 5: Retrosynthetic route to Seimatopolide B

Our retrosynthetic analysis for seimatopolide B is based on convergent approach as outlined is **Scheme 5**. We envisioned that the natural product **1** could be obtained by ring-closing metathesis of diene precursor **34,** which in turn could be prepared by intermolecular DCC

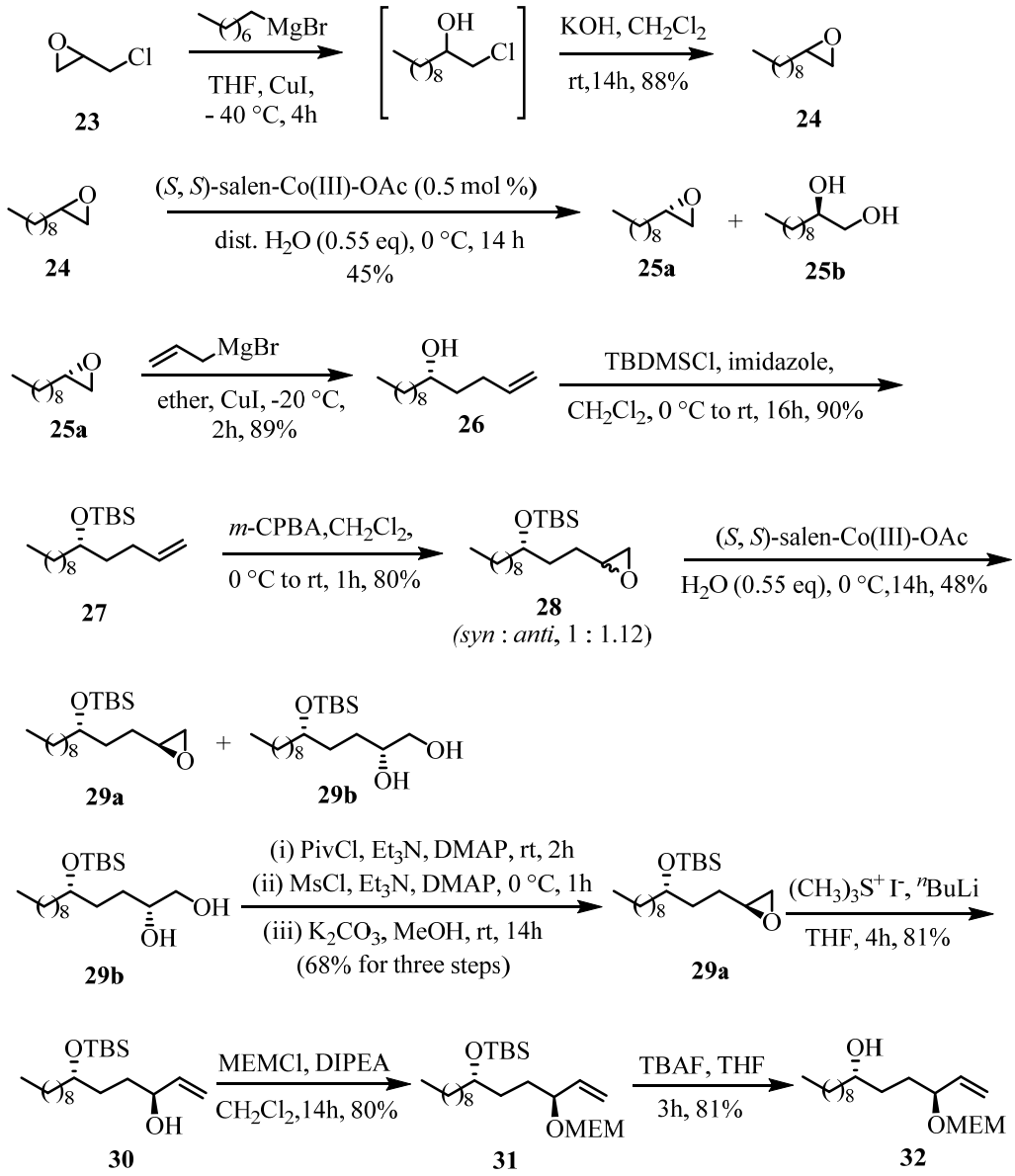
coupling of acid **33** and alcohol **32.** Acid **33** could be obtained from 3-butene-1-ol while the alcohol fragment **32** could be prepared from *rac*-epichlorohydrin **23** *via* iterative HKR.

The acid fragment **33** was synthesized by another colleague in our group starting from commercially available 3-butene-1-ol using HKR as key step. (Ph.D. thesis of Dr. Ankush Kumar Bhise[12c])

Synthesis of the alcohol fragment 32:

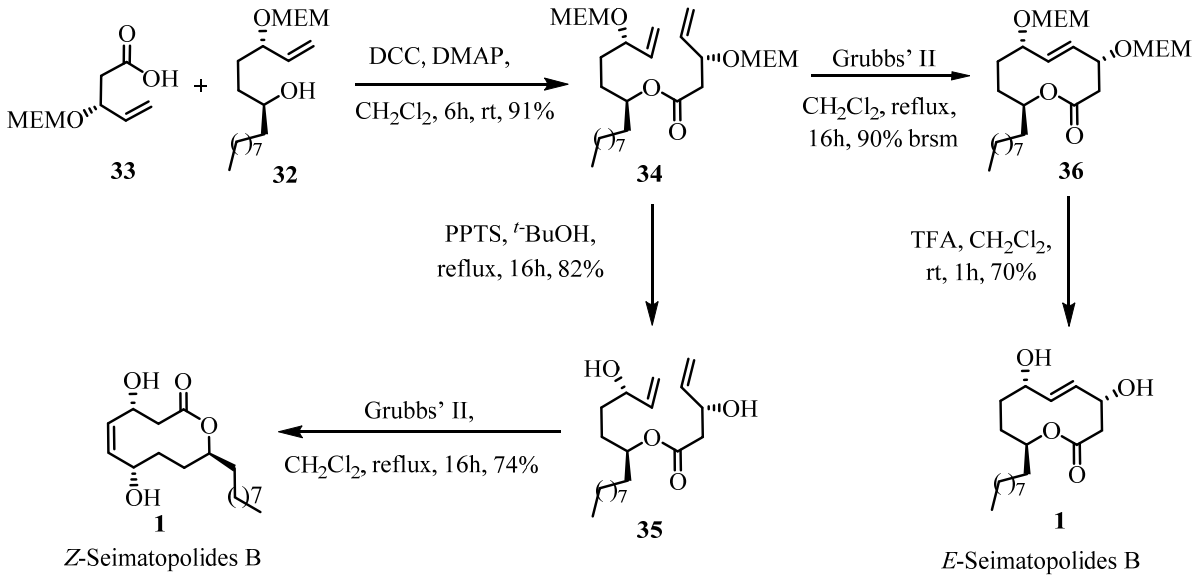
As illustrated in **Scheme 6**, synthesis of alcohol fragment **32** started from commercially available (±) epichlorohydrin **23** which was converted to racemic epoxide **24** by known procedure.[13m] The racemic epoxide **24** was resolved using Jacobson HKR catalyst-*(S,S)*-Salen Co^{III}-OAc to give enantiopure epoxide[16] **25a** in 45% yield and diol **25b** in 43% yield. The enantiomerically pure epoxide **25a** was then opened with allyl magnesium bromide in the presence of catalytic amount of CuI, to give the alcohol **26** in 89% yield. The IR spectrum of **26** gave broad hydroxyl absorption at 3381$cm^{-1}$and the ^1H NMR spectrum gave olefin peaks at δ 5.75-5.95 (m, 1H), 4.93-5.10 (m, 2H). The hydroxyl group was protected as its TBS ether using TBDMSCl and imadazole to afford **27** in 90% yield. The IR spectrum of **27** showed absence of hydroxyl group. The olefin was oxidized using *m*-CPBA, which gave the epoxide **28** as mixture of *syn* and *anti* compounds (*syn*:*anti*, 1:1.12).[17] The two diastereomers were inseparable on TLC. In order to get the diastereomerically pure epoxide, the epoxide **28** was resolved using *(S,S)*-Salen Co^{III}-OAc and water in THF to give the diastereomerically pure epoxide **29a** in 48% yield. As the HKR method provided the desired epoxide **29a** along with unwanted diol **29b**, we thought it appropriate to convert diol **29b** into required epoxide **29a** *via* internal nucleophilic substitution of secondary mesylate.[18] Accordingly, chemoselective pivalation of diol **29b** with pivaloyl chloride was followed by mesylation of the secondary hydroxy group. Treatment of the crude mesylate with potassium carbonate in methanol led to deprotection of the pivaloyl ester and concomitant ring closure *via* intramolecular S_N2 displacement of the mesyl group to furnish epoxide **29a** in 68% overall yield.

With substantial amount of epoxide **29a** in hand we further proceeded for the synthesis of alcohol fragment **32** by ring opening of epoxide with dimethylsulfonium methylide to get the one carbon homologated allylic alcohol **30** in excellent yield. The IR spectrum of **30** gave broad hydroxyl absorption at 3367 cm^{-1}. The ^1H NMR spectrum of **30** gave olefin peaks at 5.87 (ddd, *J*= 6.11, 10.38, 17.09 Hz, 1H), 5.23 (dt, *J* = 1.53, 17.40 Hz, 1H), 5.10 (dt, *J* = 1.22, 10.38Hz, 1H). Subsequently, hydroxyl group was protected as its MEM ether **31** using MEMCl and Hunigs base.



Scheme 6: Synthesis of the alcohol fragment **32**

Further desilylation of the compound **31** was achieved using TBAF to furnish the alcohol fragment **32** in 81% yield (**Scheme 6**). With substantial amount of both the fragments in hand, the coupling of acid **33** and alcohol **32** was achieved by using the intermolecular DCC coupling to afford the diene ester **34** in 91% yield (**Scheme 7**). The IR spectrum of **34** gave ester carbonyl absorption at 1732 cm^{-1}. The ^{1}H NMR spectrum of **34** gave the peak at 4.85-4.92 (m, 1H), indicating that both fragments were coupled and further ^{13}C value at δ 170.4 confirmed the presence of ester. Subsequently the cyclization was attempted using ring closing metathesis,[15] by two different ways: one with protection and the other without protection of allylic alcohols.



Scheme 7: Synthesis of the *E*-Seimatopolide and *Z*-Seimatopolide

The deprotection of MEM groups was achieved using PPTS in *t*-BuOH to give the naked diol ester **35.** Subsequent ring-closing metathesis using Grubb's 2nd generation catalyst in CH_2Cl_2 resulted into the unnatural isomer, *Z*-Seimatopolide B **1** exclusively in 74% yield (**Scheme 7**). *Z*-Seimatopolide B **1** was well characterized by physical and spectroscopic methods. The ^{1}H NMR spectrum of **1** gave the olefinic peaks at 5.94 (dd, J = 10.55, 9.78 Hz, 1H), 5.74 (dd, J = 10.29, 11.04 Hz, 1H). From the coupling constant values it was observed that the outcome of RCM reaction without protecting allylic alcohols was a *cis* olefin.

Seimatopolide B isolated Spectroscopic data (500MHz, *Pyridine-d_5*)		**Seimatopolide B (*E* isomer)** Spectroscopic data (500 MHz, *Pyridine-d_5*)		**Seimatopolide B (*Z* isomer)** Spectroscopic data (400MHz, *Pyridine-d_5*)	
^{13}C	**^{1}H (*J* in Hz)**	**^{13}C**	**^{1}H (*J* in Hz)**	**^{13}C**	**^{1}H (*J* in Hz)**
170.5	6.56, dd	170.6	6.56,dd	170.6	7.02 (brs)
133.4	(8.5,16.0)	133.4	(8.54,16.17)	135.2	6.58 (brs)
133.4	5.98, dd	133.4	5.98,dd	133.9	5.94, t
76.5	(3.0,16.0)	76.5	(3.05,16.17)	74.8	(10.55,9.78)
74.9	5.06, ddd	74.9	5.09,m	66.6	5.74,t
67.8	(7.0,7.0,13.0)	67.8	4.99,m	65.1	(10.29,11.04)
45.7	4.96,m	45.8	4.64,m	44.6	5.51, m
38.5	4.62, dd (7.5,7.5)	38.6	2.90,dd(3.36,1	33.2	5.33, m
36.3	2.89, dd	36.4	1.60)	32.6	5.12, m
32.4	(3.0,11.5)	32.4	2.74,dd	31.6	3.36,dd
31.0	2.72, dd	31.2	(3.97,11.60)	30.5	(14.05,6.02)
30.2	(3.0,11.5)	30.3	2.32,m	30.3	2.78, m
30.2	2.30,m	30.2	2.00,m	30.2	2.35-2.44, m
30.1	2.00,m	30.1	2.00,m	30.1	2.02-2.12, m
29.9	2.00,m	29.9	1.72,m	28.4	1.70-1.82, m
26.0	1.72,m	26.1	1.63,m	26.8	1.50-1.59, m
23.2	1.62,m	23.3	1.51,m	23.5	1.23 (brs)
14.6	1.51,m	14.6	1.23,m	14.8	0.88, t
	1.22,m		1.23,m		(6.52,7.03)
	1.22,m		1.23,m		
	1.22,m		1.23,m		
	1.22,m		1.23,m		
	1.22,m		1.23,m		
	1.22,m		1.23,m		
	1.22,m		0.88, t		
	0.86, dd (7.0,7.0)		(6.71,7.02)		

Table 1: NMR data comparison of isolated seimatopolide B and synthesized (*E* & *Z*) seimatopolide B

With an aim to synthesize the natural *E*-Seimatopolide B **1,** we extended our studies to explore the protecting group directed ring-closing metathesis (RCM). Accordingly the diene

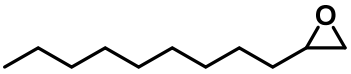
ester **35** was subjected to ring-closing metathesis conditions using Grubb's 2nd generation catalyst in CH_2Cl_2 under reflux conditions. To our delight, the reaction led to the formation of cyclised product **36** albeit in only 50% conversion only even after prolonging times (90% yield brsm). The ^{1}H NMR spectrum of **36** gave the olefinic peaks at δ 5.70 (dd, *J*=3.01, 16.32 Hz, 1H), 5.58 (dd, *J*=8.29, 16.57 Hz, 1H). From the values of coupling constants, it was observed that the outcome of RCM reaction without protecting allylic alcohols was *trans* double bond. Subsequent deprotection of MEM ethers using TFA in CH_2Cl_2 afforded the natural product, Seimatopolide B **1** exclusively as *trans*-isomer. The natural *E*-Seimatopolide B **1** was well characterized by ^{1}H & ^{13}C NMR, mass and IR spectral data. In ^{1}H NMR the coupling constant between H4 and H5 clearly demonstrated the *trans* nature of the double bond (**Scheme 7**).

1.1.6. Conclusion

In conclusion, a convergent and efficient first total synthesis of seimatopolide B, both natural and unnatural isomers has been accomplished with high enantioselectivities in which the stereocentres were generated by means of iterative Jacobsen's hydrolytic kinetic resolution and cyclization was achieved by ring-closing metathesis. The protecting group directed ring closing metathesis was successfully applied to synthesize selective *E* and *Z* seimatopolides. This approach could be used for the synthesis of other members of this class of macrolides for structure-activity relationship.

1.1.7. Experimental Section

2-Nonyloxirane 24:

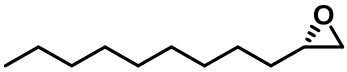


A round bottom flask was charged with copper (I) iodide (4.1 g, 21.62 mmol), gently heated under vaccum, and slowly cooled with a flow of argon after which dry THF (50 mL) was added. This suspension was cooled to -40 °C and vigorously stirred after which octyl magnesium bromide solution (prepared from octylbromide (74.7 mL, 432.34 mmol) and Mg turnings (15.75 g, 648.51 mmol) in dry THF (250 mL) was injected to it. A solution of (±)-epichlorohydrin (20.0 g, 216.16 mmol) in THF (40 mL) was added slowly to the above

reagent and the mixture were stirred at -40 °C for 4h. The reaction mixture was quenched with a saturated solution of NH_4Cl. The layers were separated. Aqueous layer was extracted with EtOAc. The combined organic layers was washed with brine, dried over Na_2SO_4 and concentrated to dryness.

To a solution of above crude compound (44.6 g, 216.2 mmol) in CH_2Cl_2 (200 mL) was added finely powdered KOH (28.57 g, 509.3mmol). The mixture was stirred vigorously for 14 h and poured into 500 mL water. After separation of the layers, the aqueous layer was extracted with CH_2Cl_2 (3 x 200mL) and the combined organic layers were dried over Na_2SO_4. Evaporation of the solvent and silica gel column chromatographic purification petroleum ether:EtOAc, (98:2) of the crude product gave **24** (30.0 g, 88%) as a colorless liquid. Then, we proceeded with the crude material to further reaction without any characterization.

(*S*)-2-Nonyloxirane 25a:



A solution of epoxide **24** (20.0g, 117.89 mmol) and (*S*,*S*)-Salen-Co(III)-OAc (0.39 g, 0.59 mmol) in isopropyl alcohol (2 mL) was stirred at 0 °C for 5 min and then distilled water (1.16 mL, 64.84 mmol) was added. After stirring for 14h, it was concentrated and purified by silica gel column chromatography using pet ether to afford **25a** as a yellow color liquid. Continued chromatography with petroleum ether:EtOAc, 60:40 provided the diol **25b** as a brown color solid.

Yield: 9.0 g, 45%

Mol. Formula: $C_{11}H_{22}O$

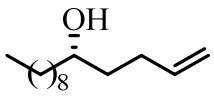
$[\alpha]_D^{25}$: -6.9 (*c* 1, $CHCl_3$) {***ent*-25a**: *Lit.*[16] $[\alpha]_D^{24}$: +6.34 (*c* 1, $CHCl_3$)}

IR (neat, cm^{-1}): ν_{max} 2925, 2855, 1465, 1017, 836, 478.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.86-2.95 (m, 1H), 2.74 (dd, *J* = 4.17, 5.06 Hz, 1H), 2.46 (dd, *J* = 2.78, 5.06 Hz, 1H), 1.52-1.42 (m, 3H), 1.27 (s, 13H), 0.88 (t, *J* = 6.06, 6.70Hz, 3H)

^{13}CNMR (50 MHz, $CDCl_3$): δ 52.5, 47.3, 32.6, 32.0, 29.69, 29.65, 29.59, 29.4, 26.1, 22.8, and 14.2

(*S*)-Tetradec-1-en-5-ol 26:



To a stirred solution of **25a** (9.0g, 53.05 mmol) and CuI (1.01 g, 5.31mmol) in dry ether (150 mL), was added, 1 M solution of allylmagnesium bromide in ether (3.07 g, 79.58mmol, 79.58 ml, 1M solution in ether) drop-wise over a period of 30 min. at -20 °C and stirred for 2 h. The mixture was allowed to warm up to 0 °C, before it was quenched with a saturated NH_4Cl solution (20 mL). The layers were separated, the aqueous layer extracted with EtOAc (3 x 100 mL), the combined organic extracts were washed with brine (50 mL) and dried over Na_2SO_4, evaporated to dryness followed by silica gel column chromatographic purification petroleum ether:EtOAc, (96:4) of the crude product to give **26** as a colorless oil.

Yield: 10.0 g, 89%

Mol. Formula: $C_{14}H_{28}O$

$[\alpha]_D^{25}$: +0.6 (*c* 1.0, $CHCl_3$)

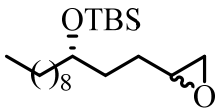
IR (neat, cm^{-1}): ν_{max} 3381, 2925, 2854, 1641, 1465, 909, 461

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.75-5.95 (m, 1H), 4.93-5.10 (m, 2H), 3.55-3.68 (m, 1H), 2.10-2.25 (m, 1H), 1.27 (m, 14H), 1.43-1.47 (m, 2H), 1.50-1.60 (m, 3H), 0.88(t, *J* = 6.19, 6.70Hz, 3H)

^{13}CNMR (50 MHz, $CDCl_3$): δ 138.8, 114.8, 71.6, 37.6, 36.6, 32.02, 30.2, 29.8, 29.76, 29.71, 29.4, 25.7, 22.8, 14.2

LC–MS: m/z = 257.95 $[M + HCOO]^-$

Tert-butyldimethyl(((3*S*)-1-(oxiran-2-yl)dodecan-3-yl)oxy)silane 28:



To a stirred solution of alcohol **26** (9.0 g, 42.52 mmol) in CH_2Cl_2 (80 mL) was added imidazole (7.23 g, 106.31 mmol). To this solution *t*-butyl dimethylchlorosilane (7.05 g, 46.77 mmol) was added at 0 °C and reaction was stirred at room temperature for 16h. The reaction mixture was quenched with a saturated solution of NH_4Cl and extracted with CH_2Cl_2 (4 x 100mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Silica gel column chromatography of the crude product using petroleum ether:EtOAc, (98:2) as eluent provided **27** as colorless liquid (12.45 g, 90%).

To a stirred solution of TBS protected alcohol **27** (9.5 g, 29.08 mmol) in CH_2Cl_2 (75 mL) at 0 °C was added *m*-CPBA (50%) (17.06 g, 49.44 mmol). The reaction mixture was stirred at room temperature for 1h and quenched by saturated Na_2CO_3 solution, extracted with CH_2Cl_2, washed with sat.$NaHCO_3$ and brine, dried over Na_2SO_4, concentrated and purified by silica gel column chromatography using petroleum ether:EtOAc, (96:4) as eluent to yield the epoxide **28** as *syn*/*anti* (1:1.12) a colorless liquid.

Yield: 7.86 g, 80%

Mol. Formula: $C_{20}H_{42}O_2Si$

$[\alpha]_D^{25}$: +2.0 (*c* 0.4, $CHCl_3$)

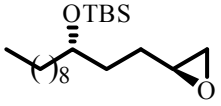
IR (neat, cm^{-1}): ν_{max} 2927, 2856, 1463, 1254, 1070, 835, 773, 478

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.60-3.75 (m, 1H), 2.86-2.95 (m, 1H), 2.74 (q, *J* = 4.17, 4.93 Hz, 1H), 2.44-2.49 (m, 1 H), 1.35-1.54 (m, 4H), 1.26 (s, 16H), 0.88 (s, 12H), 0.04 (s, 6H)

^{13}CNMR (125 MHz, $CDCl_3$): δ 72.0, 71.9, 52.1, 52.6, 47.34, 47.28, 37.4, 37.1, 33.1, 32.9, 32.0, 29.97, 29.78, 29.72, 29.47, 28.7, 28.2, 26.11, 26.05, 25.44, 25.37, 22.8, 18.3, 14.2, -4.24, -4.32

LC–MS: m/z = 365.31 $[M+Na]^+$

Tert-butyldimethyl(((*S*)-1-((*S*)-oxiran-2-yl)dodecan-3-yl)oxy)silane 29a:



A solution of epoxide **29** (5.9 g, 17.22 mmol) and (*S*,*S*)-Salen-Co(III)-OAc (0.057 g, 0.086 mmol) in isopropyl alcohol (2 mL) was stirred at 0 °C for 5 min, and then distilled water (0.17 mL, 9.47 mmol) was added. After stirring for 14h, it was concentrated and purified by silica gel column chromatography using petroleum ether:EtOAc, (98:2) to afford **29a** as a yellow color liquid. Continued chromatography with pet ether:EtOAc (60:40) provided the diol **29b** as a brown color solid.

Yield: 2.83 g, 48%

Mol Formula: $C_{20}H_{42}O_2Si$

$[\alpha]_D^{25}$: +0.8 (*c* 0.4, $CHCl_3$)

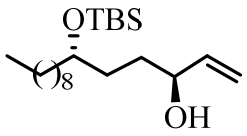
IR (neat, cm^{-1}): ν_{max} 2928, 2856, 1463, 1254, 1070, 835,774, 483

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.61-3.74 (m, 1H), 2.87-2.98 (m, 1H), 2.74 (q, *J* = 4.04, 4.93 Hz, 1H), 2.44-2.48 (m, 1H), 1.39-1.54 (m, 4H), 1.26 (s, 16H), 0.85-0.88 (s, 12H), 0.04 (s, 6H)

^{13}CNMR (125 MHz, $CDCl_3$): δ 72.0, 52.7, 47.3, 37.4, 33.2, 32.0, 29.97, 29.72, 29.47, 29.78, 28.72, 26.0, 25.4, 22.8, 18.3, 14.3, -4.3, -4.2

LC–MS: m/z = 365.31 $[M+Na]^+$

(3*S*,6S)-6-((Tert-butyldimethylsilyl)oxy)pentadec-1-en-3-ol 30:



To a -20 °C suspension of trimethylsulfonium iodide (6.21 g, 30.46 mmol) in Dry THF (30 mL) was added *n*-BuLi (19.03 mL, 1.6 M, 30.46 mmol). After 40 min. **29a** (2.0 g, 6.09 mmol) in THF (10 mL) was added drop wise. The reaction mixture was stirred at -20 °C for 4h and quenched by saturated solution of ammonium chloride. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water (4 x 50 mL), brine, dried over Na_2SO_4 and

concentrated. The residual oil was purified by silica gel column chromatography using petroleum ether:EtOAc, (93:7) as eluent to furnish the allylic alcohol **30** as colorless oil.

Yield: 1.68 g, 81%

Mol. Formula: $C_{21}H_{44}O_2Si$

$[\alpha]_D^{25}$: -4.4 (*c* 0.4, $CHCl_3$)

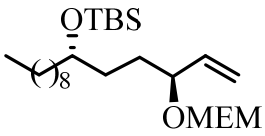
IR (neat, cm^{-1}): ν_{max} 3367, 2928, 2856, 1463, 1254, 1058, 835, 773

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.87 (ddd, *J*= 6.11, 10.38, 17.09 Hz, 1H), 5.23 (dt, *J*= 1.53, 17.40 Hz,1H), 5.10 (dt, *J* = 1.22, 10.38Hz, 1H), 4.04-4.10 (m, 1H), 3.68-3.72 (m, 1H), 2.38 (brs, 1H), 1.44-1.46 (m, 2H), 1.49-1.55 (m, 2H), 1.59-1.62 (m, 2H), 1.26 (m, 14H), 0.89 (brs, 9H), 0.88 (t, *J*=7.02, 3H), 0.06 (s, 6H)

^{13}CNMR (125 MHz, $CDCl_3$): δ 141.4, 114.5, 73.5, 72.3, 36.7, 32.9, 32.76, 32.0, 29.93, 29.78, 29.72, 29.47, 26.0, 25.6, 22.8, 18.3, 14.2, -4.3

LC–MS: m/z = 379.34 $[M+Na]^+$

(8*S*,11*S*)-13,13,14,14-Tetramethyl-11-nonyl-8-vinyl-2,5,7,12-tetraoxa-13-silapentadecane 31:



To a solution of allylic alcohol **30** (0.90 g, 2.52 mmol) in dry CH_2Cl_2 (8 mL) was added DIPEA (0.96 mL, 5.82 mmol) at 0 °C. To this mixture MEM chloride (0.6 mL, 5.28 mmol) was added slowly with further stirring for 14h at room temperature. The reaction mixture was quenched with addition of cold water at 0 °C. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with water (3 x 20 mL), brine, dried over Na_2SO_4 and concentrated to give crude MEM ether. It was purified by silica gel column chromatography using petroleum ether:EtOAc, (96:4) as eluent to furnish the MEM ether **31** as colorless oil.

Yield: 0.9 g, 80%

Mol. Formula: $C_{25}H_{52}O_4Si$

$[\alpha]_D^{25}$: -0.3 (*c* 1.0, $CHCl_3$)

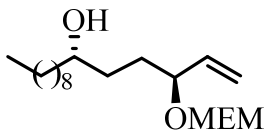
IR (neat, cm^{-1}): ν_{max} 3419, 2927, 2856, 1463, 1254, 1107, 1039, 926, 835, 773, 491

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.61-5.70 (ddd, *J* = 7.53, 10.29, 17.56 Hz, 1H), 5.16-5.21 (m, 2H), 4.77 (d, *J* = 6.77 Hz, 1H), 4.66 (d, *J* = 7.02, 1H), 3.97-4.03 (m, 1H), 3.76-3.81 (m, 1H), 3.54-3.65 (m, 4H), 3.39 (s, 3H), 1.35-1.47 (m, 4H), 1.25 (s, 16H), 0.88 (m, 12H), 0.03 (s, 6H)

^{13}CNMR (100 MHz, $CDCl_3$): δ 138.5, 117.4, 39.9, 92.9, 77.9, 72.4, 71.9, 67.0, 59.1, 37.3, 32.86, 32.0, 31.2, 29.9, 29.79, 29.73, 29.4, 26.0, 25.4, 22.8, 18.2, 14.2, -4.24, -4.28

LC–MS: m/z = 467.35 $[M + Na]^+$

(3*S*,6*S*)-3-((2-Methoxyethoxy)methoxy)pentadec-1-en-6-ol 32:



A solution of TBAF (9.31mL, 1M in THF, 9.31 mmol) was added to a stirred solution of **31** (0.8 g, 1.86 mmol). The mixture was stirred at room temperature for 3h. The solvent was evaporated and extracted with EtOAc (3 x 20 mL). Evaporation of the solvent and purification of crude product by silica gel column chromatography using petroleum ether:EtOAc, (84:16) provided the compound **32** as a brown color liquid.

Yield: 0.48 g, 81%

Mol. Formula: $C_{19}H_{38}O_4$

$[\alpha]_D^{25}$: -61.3 (*c* 1.0, $CHCl_3$)

IR (neat, cm^{-1}): ν_{max} 3447, 2926, 2855, 1642, 1458, 1106, 1039, 926, 728, 489

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.64-5.71 (ddd, *J* = 7.63, 10.07, 17.39Hz, 1H), 5.19 (m, 2H), 4.71 (q, $^2J_{ab}$ = 7.02Hz, 2H), 4.08-4.14 (m, 1H), 3.81-3.85 (m, 1H), 3.55-3.63 (m, 4H),

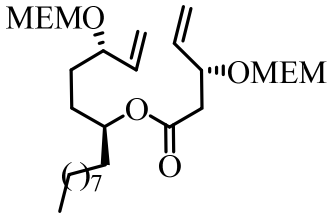
3.39 (s, 3H), 1.85 (brs, 1H), 1.97 (m, 2H), 1.43 (m, 4H), 1.26 (brs, 14H), 0.88 (t, *J* = 6.41, 7.02Hz, 3H)

^{13}CNMR (125 MHz, $CDCl_3$): δ 138.2, 117.4, 93.0, 72.0, 71.8, 67.2, 59.1, 37.74, 33.1, 32.0, 31.7, 29.85, 29.78, 29.72, 29.47, 25.8, 22.8, 14.2

LC–MS: m/z = 353.17 $[M+Na]^+$

HRMS (ESI) for $C_{19}H_{39}O_4$ $(M+H)^+$ found 331.2835, calcd 31.2843

(*R*)-(3*S*,6*S*)-3-((2-Methoxyethoxy)methoxy)tetradec-1-en-6-yl-3-((2-methoxyethoxy)methoxy)pent-4-enoate 34:



To a stirred solution of **33** (0.54 g, 2.67 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C, DCC (0.66 g, 3.175 mmol) was added portion-wise and white precipitate was formed. Then DMAP was added followed by the solution of **32** (0.400 g, 1.27 mmol) in dry CH_2Cl_2 (5mL) and solution stirred for 6 h at room temperature. The reaction mixture was evaporated to dryness. The crude product was purified by column chromatography using petroleum ether:EtOAc, (80:20) as eluent to afford **34** as a colorless liquid.

Yield: 0.6 g, 91%

Mol. Formula: $C_{28}H_{52}O_8$

$[\alpha]_D^{25}$: -5.3 (*c* 0.8, $CHCl_3$)

IR (neat, cm^{-1}): ν_{max} 3418, 2926, 1732, 1455, 1190, 1108, 1036, 930,850

^{1}H NMR(400 MHz, $CDCl_3$): δ 5.69-5.77 (ddd, *J* = 7.58, 10.27, 17.61 Hz, 1H), 5.59-5.68 (ddd, *J* = 7.58, 10.27, 17.61 Hz, 1H), 5.17-5.33 (m, 4H), 4.85-4.92 (m, 1H), 4.75 (dd, *J* = 2.93, 6.85 Hz, 2H), 4.65 (dd, *J* = 7.09, 9.29 Hz, 2H), 4.50 (m, 1H), 3.98 (m, 1H), 3.73-3.80 (m, 2H), 3.51-3.64 (m, 6H), 3.39 (s, 6H), 2.62 (dd, *J* = 8.07, 15.16 Hz, 1H), 2.47 (dd, *J* =

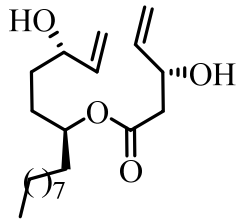
5.62, 15.16 Hz, 1H), 1.63-1.70 (m, 1H), 1.49-1.55 (m, 4H), 1.25 (s, 15H), 0.88 (t, *J* = 6.60, 7.10, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 138.0, 136.8, 118.5, 117.72, 93.1, 92.9, 74.6, 74.0, 71.93, 71.90, 67.1, 59.1, 41.2, 34.3, 32.0, 31.28, 30.10, 29.85, 29.68, 29.65, 29.46, 25.4, 22.2, 14.2

LC–MS: m/z = 539.39 $[M + Na]^+$

HRMS (ESI) for $C_{28}H_{52}O_8$ $(M + Na)^+$ found 539.3535, calcd 539.3554

(*R*)-(3*S*,6*S*)-3-Hydroxytetradec-1-en-6-yl 3-hydroxypent-4-enoate 35:



To a solution of **34** (0.100g, 0.193 mmol) in *t*-BuOH, PPTS was added (0.974 g, 3.88 mmol) and refluxed for 16h. The reaction mixture was quenched with water and extracted with ethyl acetate. Organic layer was separated, washed with brine, dried over Na_2SO_4, concentrated and purified by column chromatography using petroleum ether:EtOAc, (70:30) to afford **35**.

Yield: 54 mg, 82%

Mol. Formula: $C_{20}H_{37}O_4$

$[\alpha]_D^{25}$: +0.97 (*c* 0.6, $CHCl_3$)

IR (neat, cm^{-1}): ν_{max} 3408, 2926, 2855, 1714, 1174, 990, 923

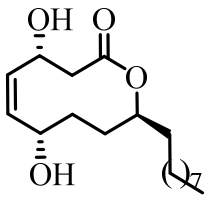
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.80-5.93 (m, 2H), 5.10-5.34 (m, 4H), 4.95 (m, 1H), 4.55 (m, 1H), 4.10 (m, 1H), 2.54 (m, 2H), 1.58-1.73 (m, 6H), 1.25 (s, 14H), 0.87 (dd, *J* = 6.53, 7.03 Hz, 3H)

^{13}CNMR (100 MHz, $CDCl_3$): δ 172.3, 140.9, 138.4, 115.58, 115.18, 75.0, 73.0, 69.1, 41.5, 34.2, 32.6, 32.01, 30.0, 29.84, 29.65, 29.59, 29.43, 25.4, 22.8 and 14.2

LC–MS: m/z = 363.20 $[M + Na]^+$

HRMS (ESI) for $C_{20}H_{37}O_4$ $(M + H)^+$ found 341.2678, calcd 341.2686

***Z*-Seimatopolide B 1:**



To a stirred solution of **35** (0.030 g, 0.088 mmol, 0.001 M) in freshly distilled degassed anhydrous CH_2Cl_2 (90 mL) was added Grubbs' second generation catalyst (0.015 g, 0.017 mmol) and heated under reflux for 16h under an argon atmosphere until the complete consumption of the starting material (monitored by TLC). The solvent was evaporated to a brown residue, which was purified by silica gel column chromatography using petroleum ether:EtOAc (53:47) to afford *Z*-seimatopolide B **1** as a white sticky solid.

Yield: 0.020 g, 74%

Mol. Formula: $C_{18}H_{32}O_4$

$[\alpha]_D^{25}$: -118.5 (*c* 0.049, MeOH)

IR (neat, cm^{-1}): ν_{max} 3243, 2911, 2852, 1722

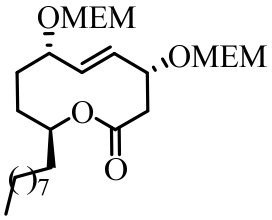
^{1}H NMR (400 MHz, *pyridine-d_5*): δ 7.02 (brs, 1H), 6.58 (brs, 1H), 5.94 (dd, *J* = 10.55, 9.78 Hz, 1H), 5.74 (dd, *J* = 10.29, 11.04 Hz, 1H), 5.51 (m, 1H), 5.33 (m, 1H), 5.12 (m, 1H), 3.36 (dd, *J* = 14.05, 6.02 Hz, 1H), 2.78 (m, 1H), 2.35–2.44 (m, 1H), 2.02–2.12 (m, 1H), 1.70–1.82 (m, 2H), 1.50–1.59 (m, 2H), 1.23 (brs, 14H), 0.88 (t, *J* = 7.03 Hz, 3H)

^{13}C NMR (100 MHz, *pyridine-d_5*): δ 170.6, 135.2, 133.9, 74.8, 66.6, 65.1, 44.6, 33.2, 32.6, 31.6, 30.3, 30.2, 30.1, 28.4, 26.8, 23.5, 14.8, 30.5

LC–MS: m/z = 335.17 $[M + Na]^+$

HRMS (ESI) for $C_{18}H_{32}O_4Na$ $(M + Na)^+$ found 335.2187, calcd 335.2193

(4*R*,7*S*,10*S*,*E*)-4,7-bis((2-Methoxyethoxy)methoxy)-10-octyl-3,4,7,8,9,10-hexahydro-2*H*-oxecin-2-one 36:



To a solution of **34** (0.10 g, 0.193 mmol, 0.001M) in freshly distilled degassed anhydrous CH_2Cl_2 (276mL) was added Grubb's second generation catalyst (0.033 g, 0.038 mmol, 20 mol%) and heated at reflux for 16h under an argon atmosphere. The solvent was evaporated to a brown residue, which was purified by column chromatography using (petroleum ether :EtOAc, 70:30) as eluent to afford **36** (0.048 g, 90% based on recovery of starting material) as a colorless liquid.

$[\alpha]_D^{25}$: +3.3 (c = 0.73, $CHCl_3$)

IR (neat, cm^{-1}): ν_{max} 2926, 2855, 1735, 1109, 1042,850

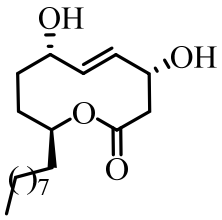
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.70 (dd, *J*=3.01, 16.32 Hz,1H), 5.58 (dd, *J*=8.29, 16.57 Hz, 1H), 4.70-4.81(m, 4H), 4.63 (m, 1H), 4.10-4.18 (m, 1H), 3.60-3.68 (m, 1H), 3.60-3.78 (m, 4H), 3.53-3.56 (m, 4H), 3.39 (s, 6H), 2.68 (dd, *J*= 3.01, 12.05 Hz, 1H), 2.48 (dd, *J*= 3.76, 12.05 Hz, 1H), 2.25-2.38 (m, 1H), 1.72-2.02 (m, 4H), 1.25 (s, 15H), 0.86 (dd, *J*=7.02, 7.28 Hz, 3H)

^{13}CNMR (100 MHz, $CDCl_3$): δ 169.71, 141.4, 132.5, 93.7, 92.7, 71.9, 71.8, 71.0, 67.3, 67.0, 59.1, 42.6, 35.75, 32.0, 29.85, 29.82, 29.76, 29.67, 29.59, 29.44, 25.3, 22.8, 14.2

LC–MS: m/z = 511.336 $[M+Na]^+$

HRMS (ESI) for $C_{26}H_{48}O_8$ $(M + Na)^+$ found 511.3289, calcd 511.3241

***E*-Seimatopolide B 1:**



To a solution of compound **36** (0.040 g, 0.082 mmol) in CH_2Cl_2, was added TFA (0.062 mL, 0.82 mmol) and stirred at room temperature for 16h. The reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$, extracted with EtOAc and the organic layer was separated, washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography using EtOAc:petroleum ether (1:1) as eluent to afford *E*-Seimatopolide B **1** (0.018 g, 70%) as white sticky solid.

$[\alpha]_D^{25}$: -212.6 (*c* 0.035, MeOH) {*Lit*[1]. $[\alpha]_D^{25}$-125.3 (*c* 0.03, MeOH)}

IR (neat, cm^{-1}): ν_{max} 3242, 2912, 2853, 1721

^{1}H NMR (500 MHz, *Pyridine-d_5*): δ 6.56 (dd, *J*=8.54, 16.17 Hz 1H), 5.98 (dd, *J*=3.05, 16.17 Hz 1H), 5.09 (m, 2H), 4.99 (m, 1H), 4.64 (m, 1H), 2.90 (dd, *J*=3.36, 11.60 Hz, 1H), 2.74 (dd, *J*= 3.97, 11.60, Hz, 1H), 2.32 (m, 1H), 2.00 (m, 2H), 1.72 (m, 1H), 1.63 (m, 1H), 1.51 (m, 1H), 1.23 (m, 14H), 0.88 (t, *J*= 6.71, 7.02 Hz, 3H)

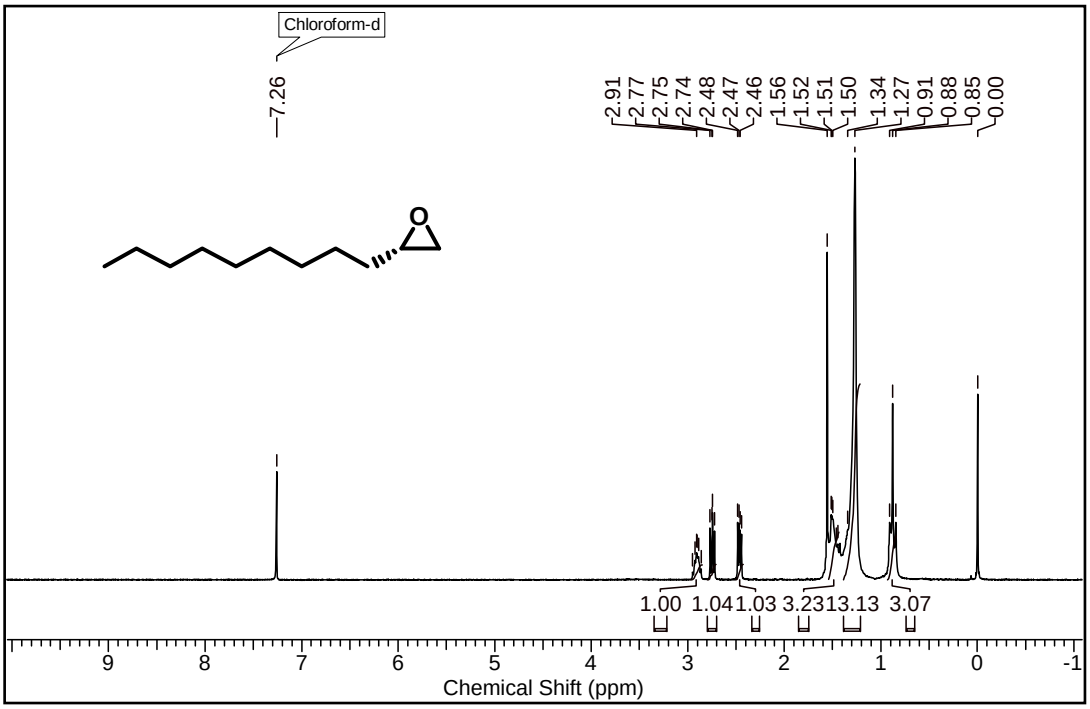
^{13}C NMR (125 MHz, *Pyridine-d_5*): δ 170.6, 133.4, 76.5, 74.9, 67.8, 45.8, 38.6, 36.4, 32.4, 31.2, 30.3, 30.2, 30.1, 29.9, 26.1, 23.3, 14.6

LC–MS: m/z = 335.17 $[M + Na]^+$

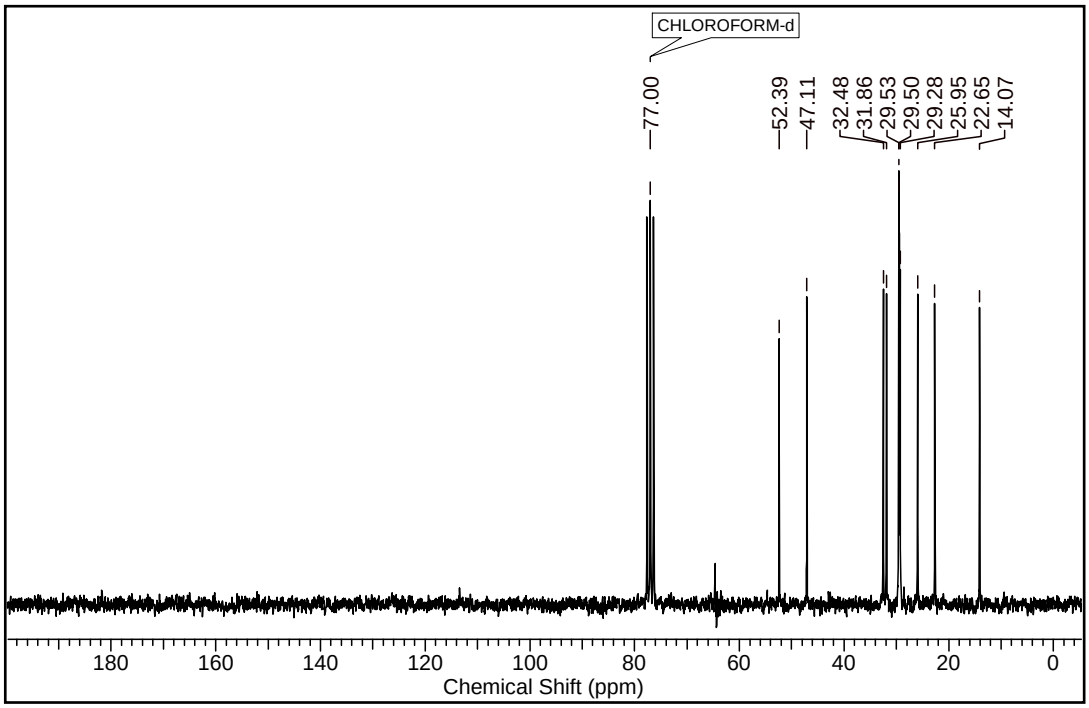
HRMS (ESI) for $C_{18}H_{32}O_4$ $(M + Na)^+$ found 335.2187, calcd 335.2193.

1.1.8. Spectra:

(*S*)-2-Nonyloxirane25a:

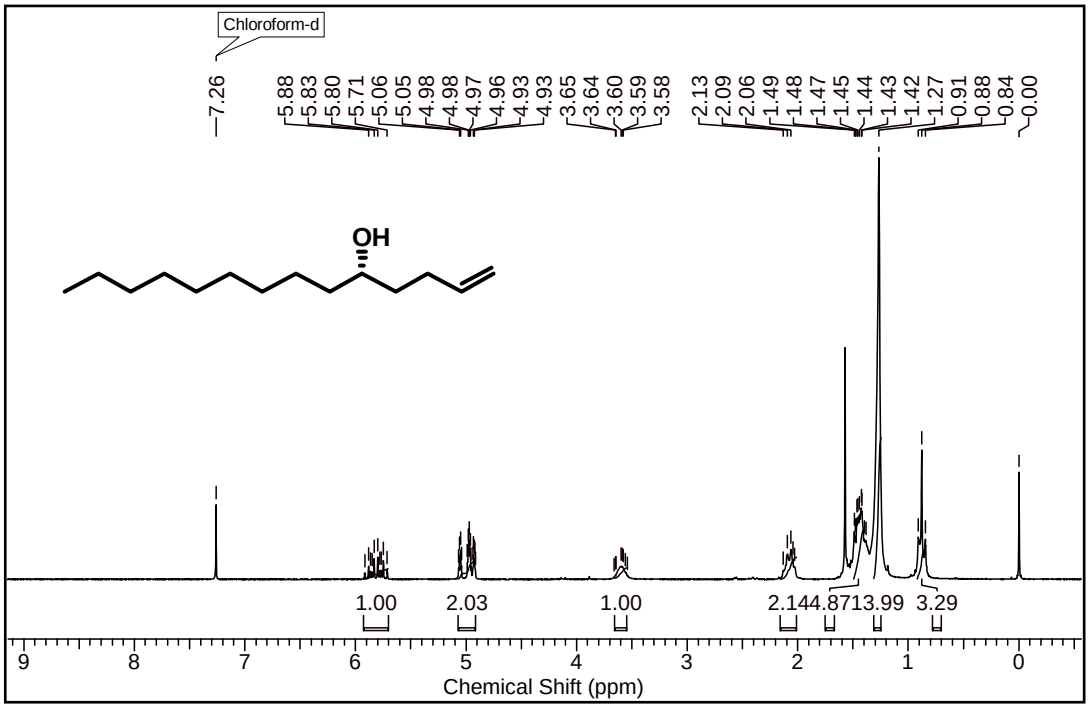


- **^{1}H NMR of the compound 25a in $CDCl_3$**

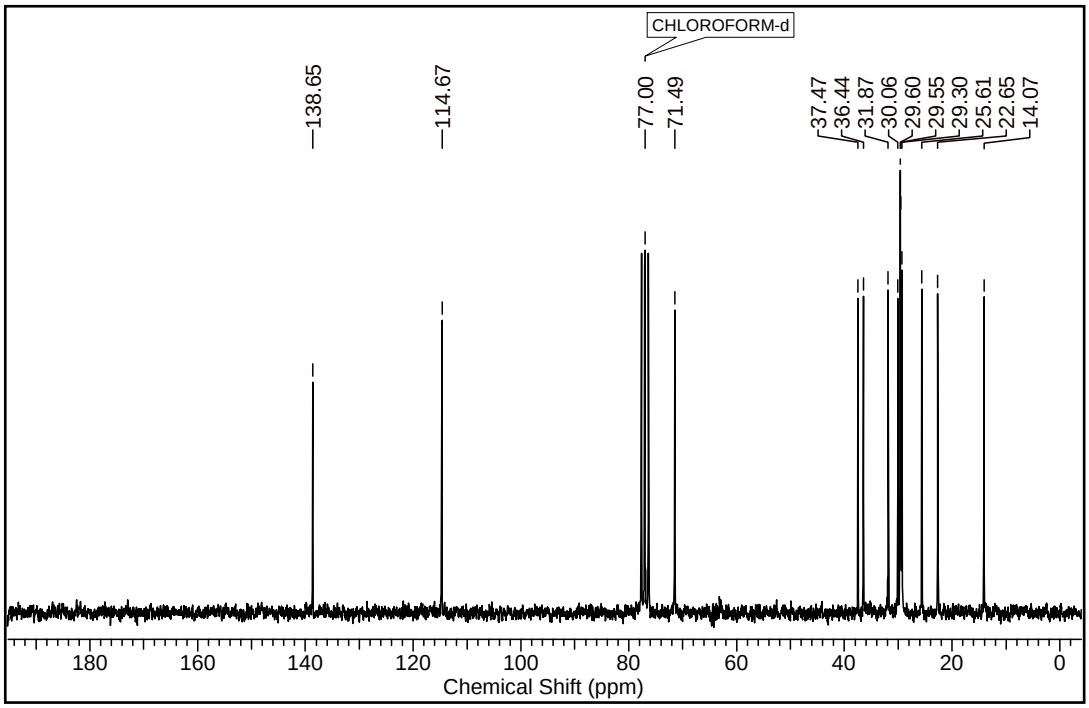


- **^{13}C NMR of the compound 25a in $CDCl_3$**

(*S*)-Tetradec-1-en-5-ol 26:

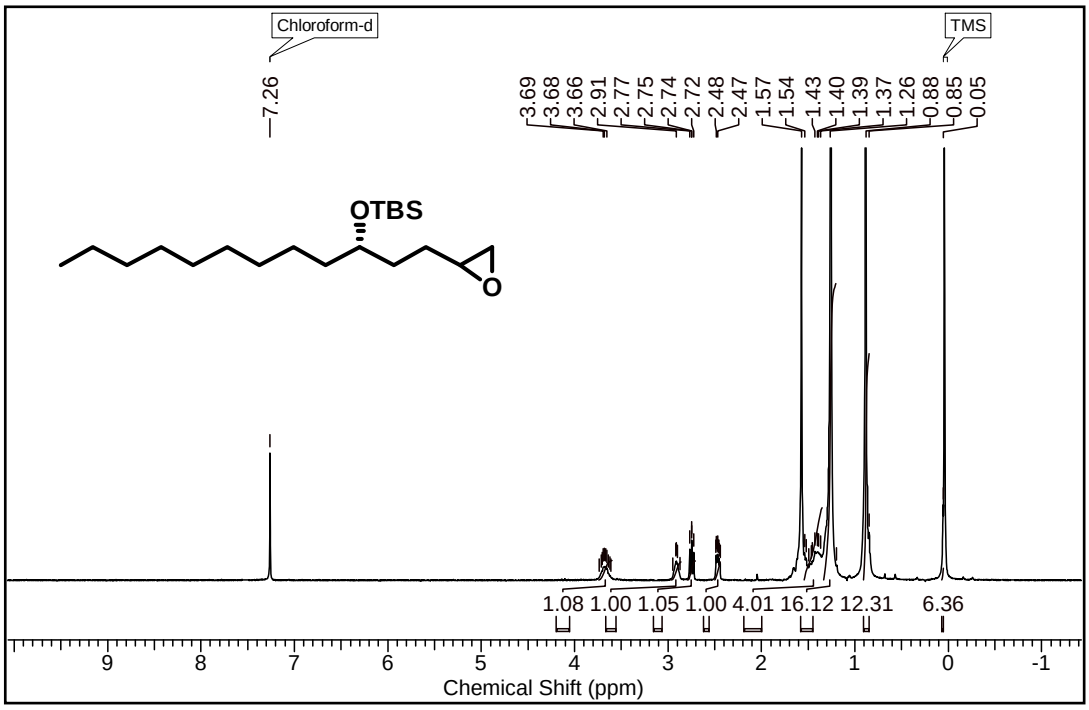


➢ **^{1}H NMR of the compound 26 in $CDCl_3$**

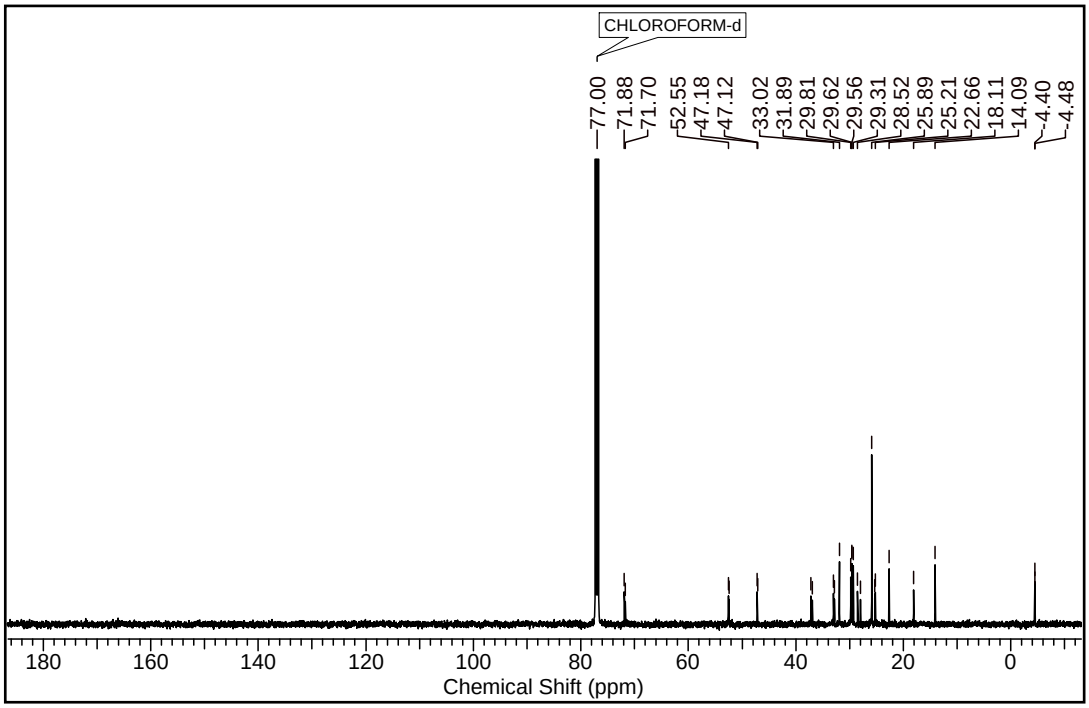


➢ **^{13}C NMR of the compound 26 in $CDCl_3$**

Tert-butyldimethyl(((3*S*)-1-(oxiran-2-yl)dodecan-3-yl)oxy)silane 28:

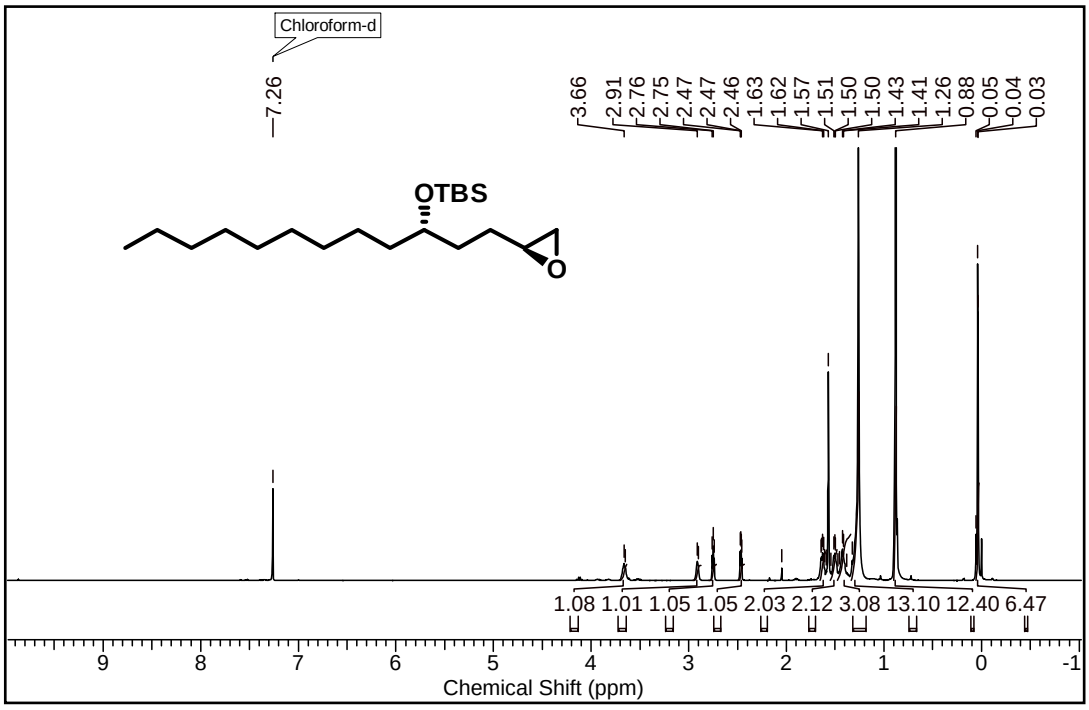


- **^{1}H NMR of the compound 28 in $CDCl_3$**

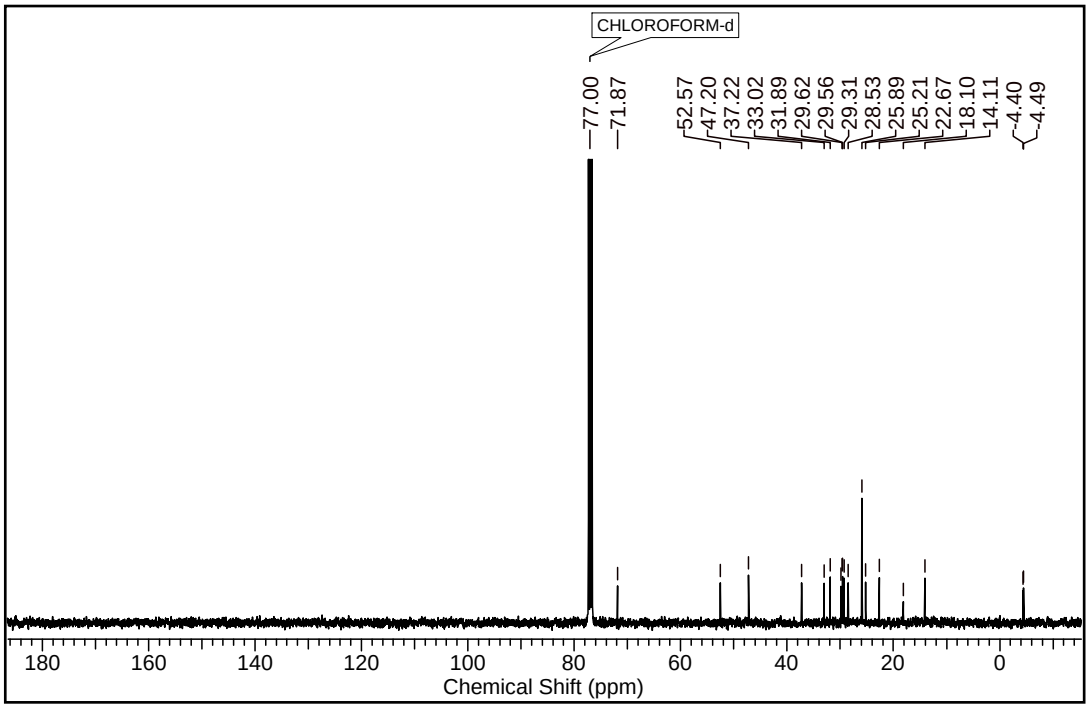


- **^{13}C NMR of the compound 28 in $CDCl_3$**

Tert-butyldimethyl(((*S*)-1-((*S*)-oxiran-2-yl)dodecan-3-yl)oxy)silane 29a:

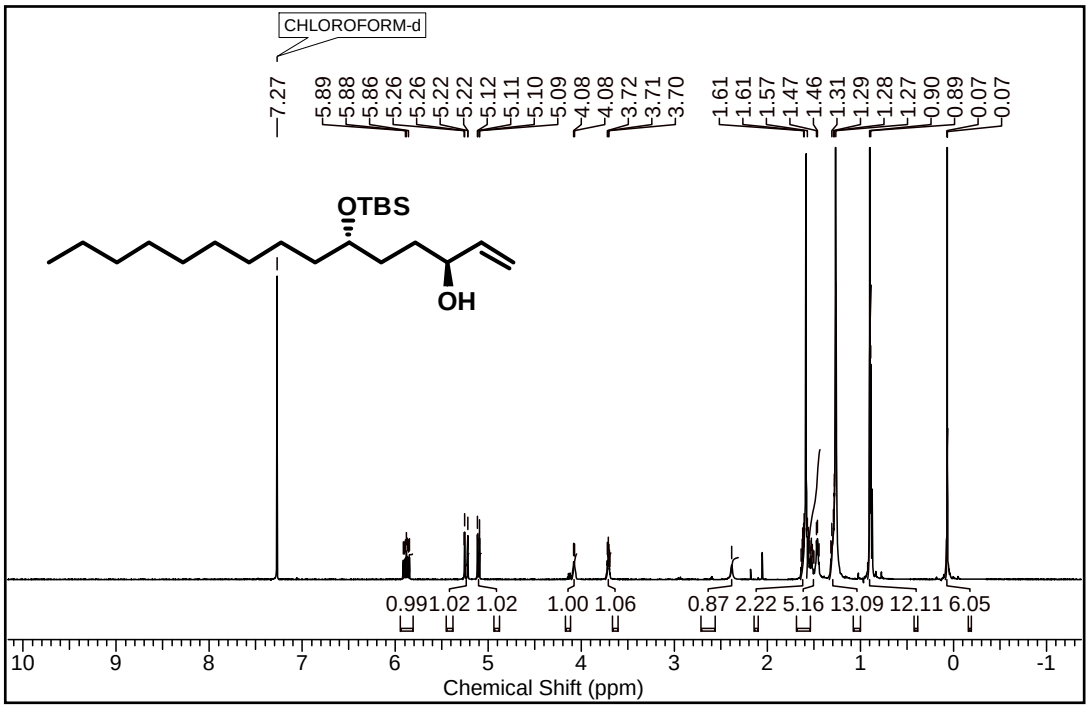


- **^{1}H NMR of the compound 29a in $CDCl_3$**

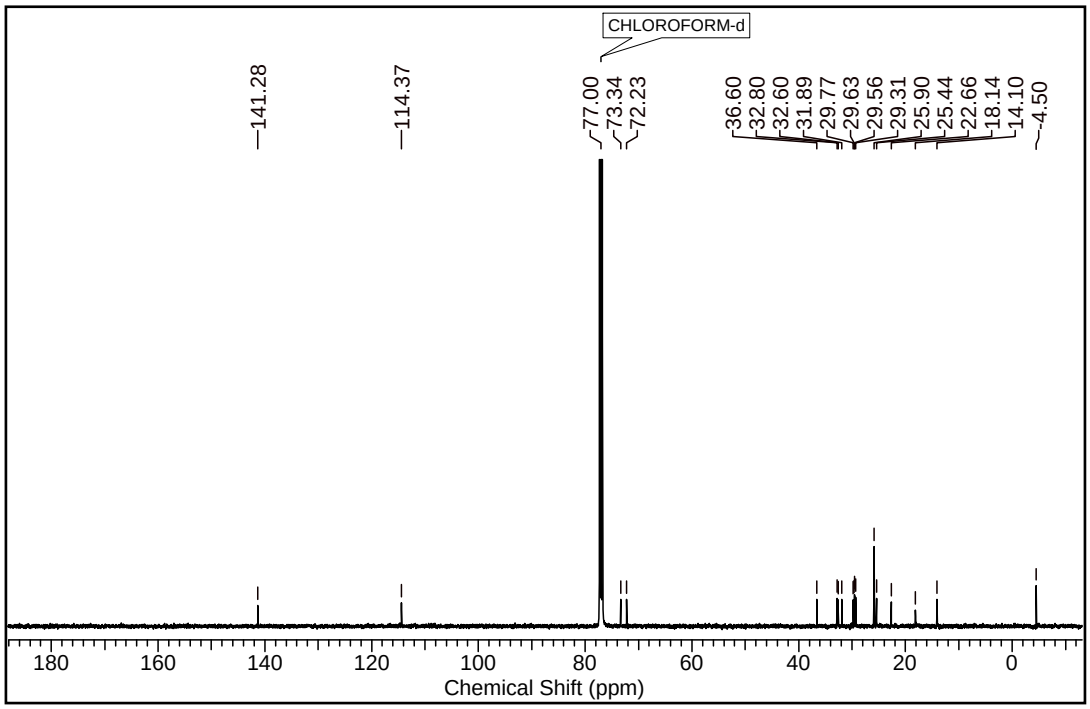


- **^{13}C NMR of the compound 29a in $CDCl_3$**

(3*S*,6*S*)-6-((Tert-butyldimethylsilyl)oxy)pentadec-1-en-3-ol 30:

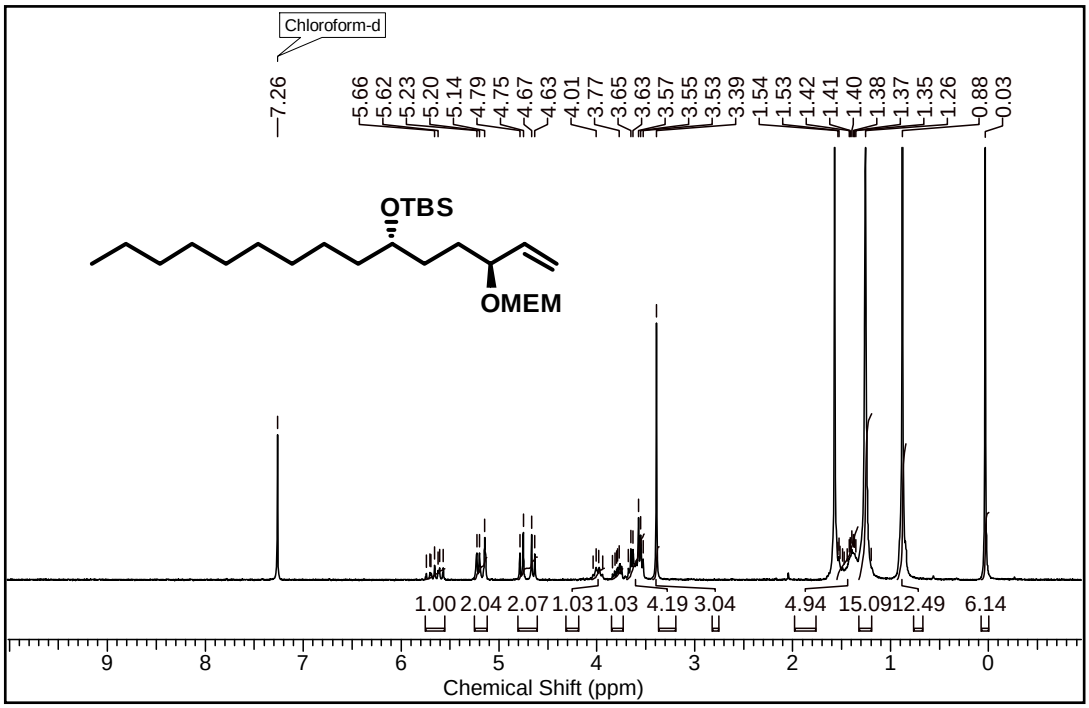


➢ **^{1}H NMR of the compound 30 in $CDCl_3$**

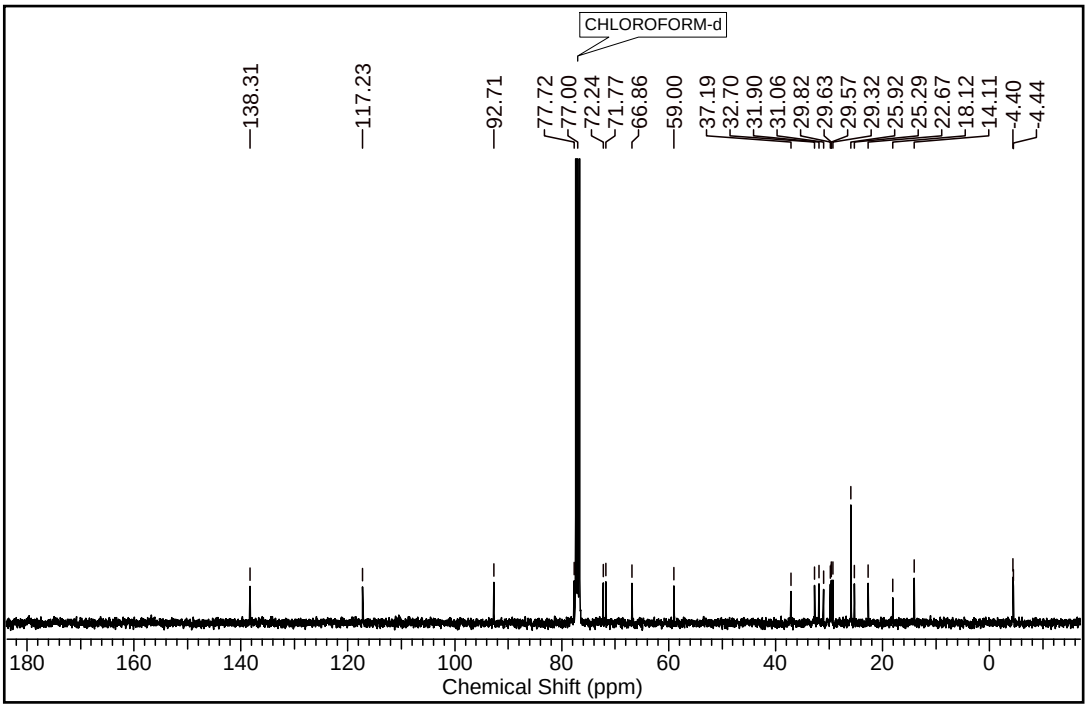


➢ **^{13}C NMR of the compound 30 in $CDCl_3$**

(8*S*,11*S*)-13,13,14,14-Tetramethyl-11-nonyl-8-vinyl-2,5,7,12-tetraoxa-13-silapentadecane 31:

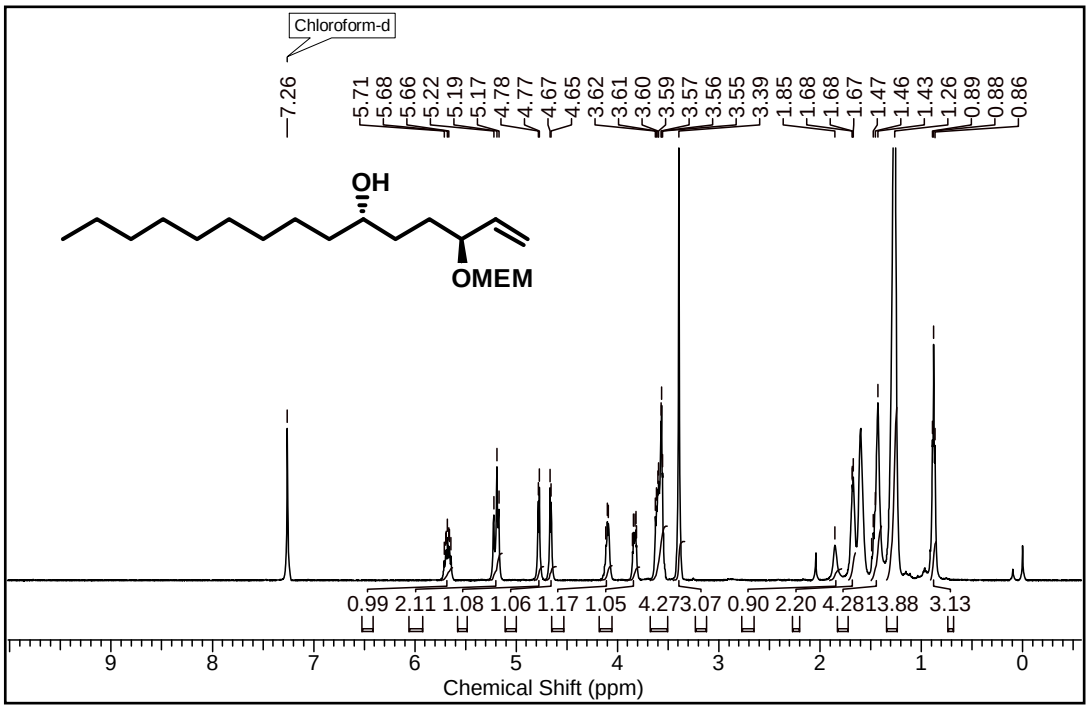


- **^{1}H NMR of the compound 31 in $CDCl_3$**

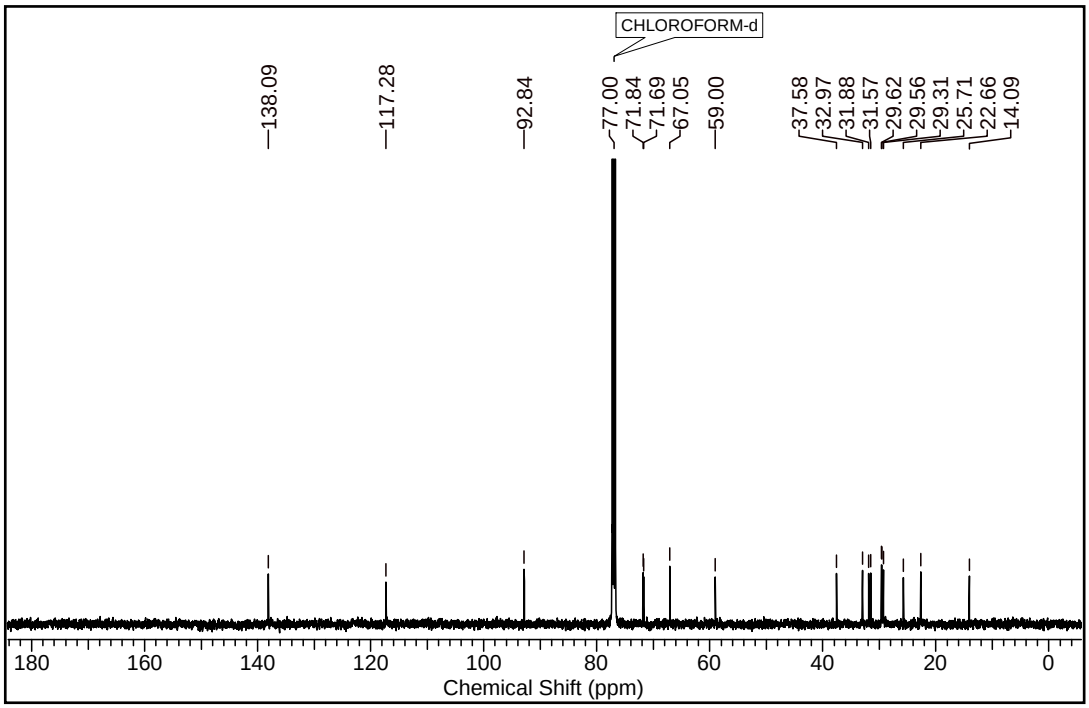


- **^{13}C NMR of the compound 31 in $CDCl_3$**

(3*S*,6*S*)-3-((2-Methoxyethoxy)methoxy)pentadec-1-en-6-ol 32:

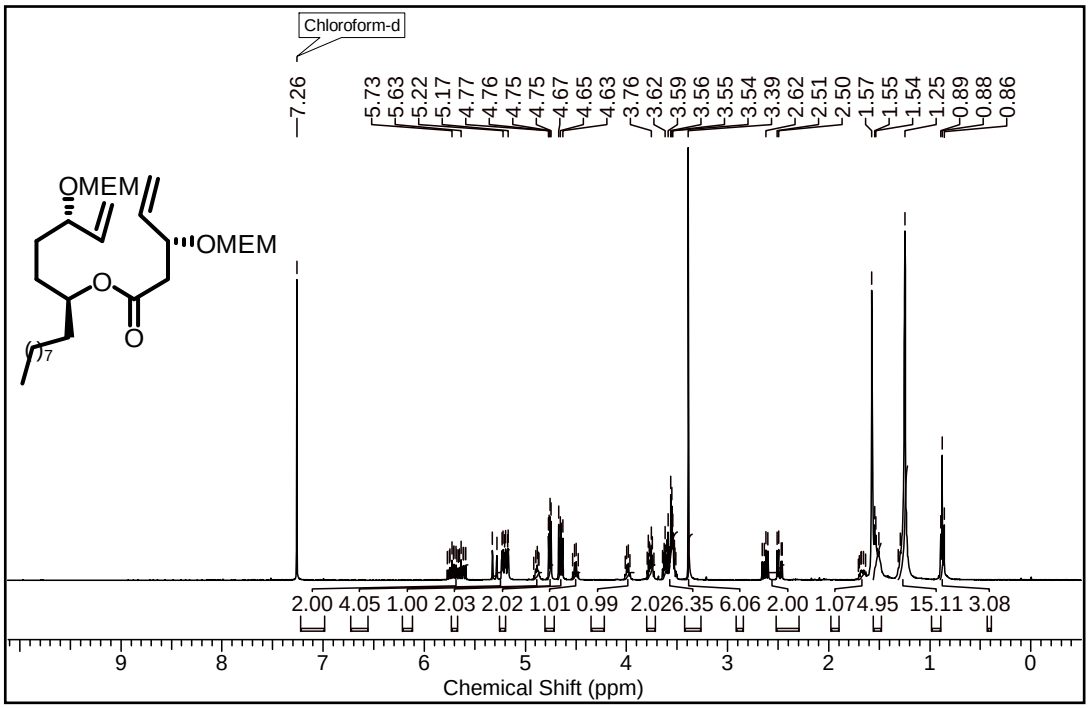


- **^{1}H NMR of the compound 32 in $CDCl_3$**

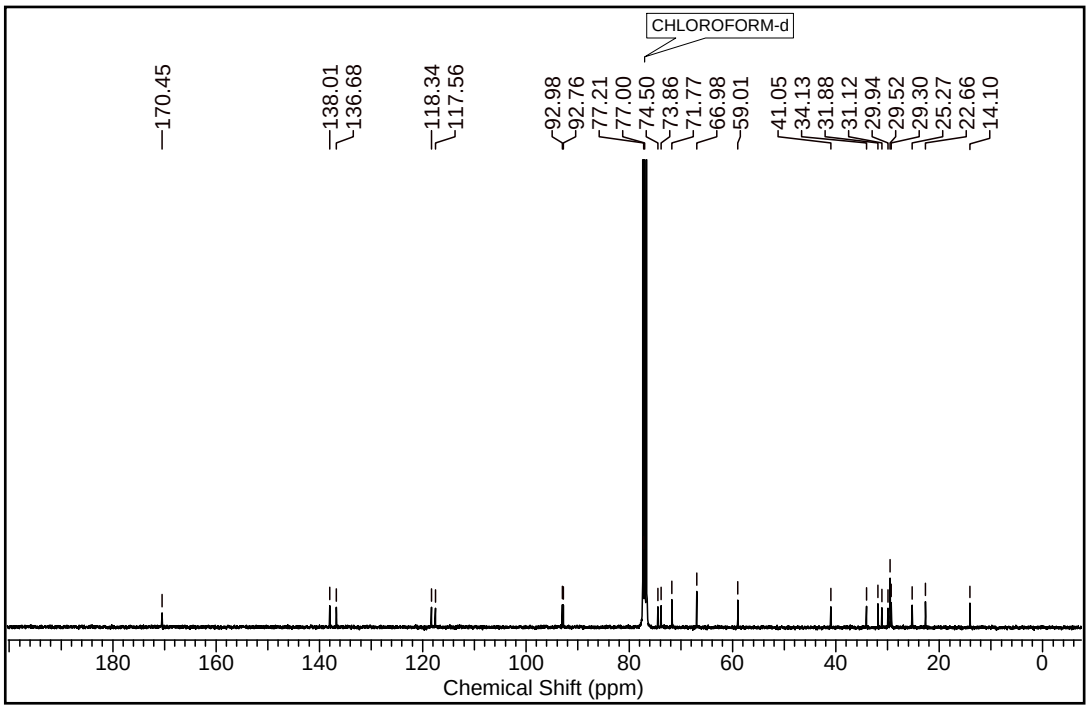


- **^{13}C NMR of the compound 32 in $CDCl_3$**

(3*S*,6*S*)-3-((2-Methoxyethoxy)methoxy)pentadec-1-en-6-yl(*R*)-3-((2-methoxyethoxy)methoxy)pent-4-enoate 34:

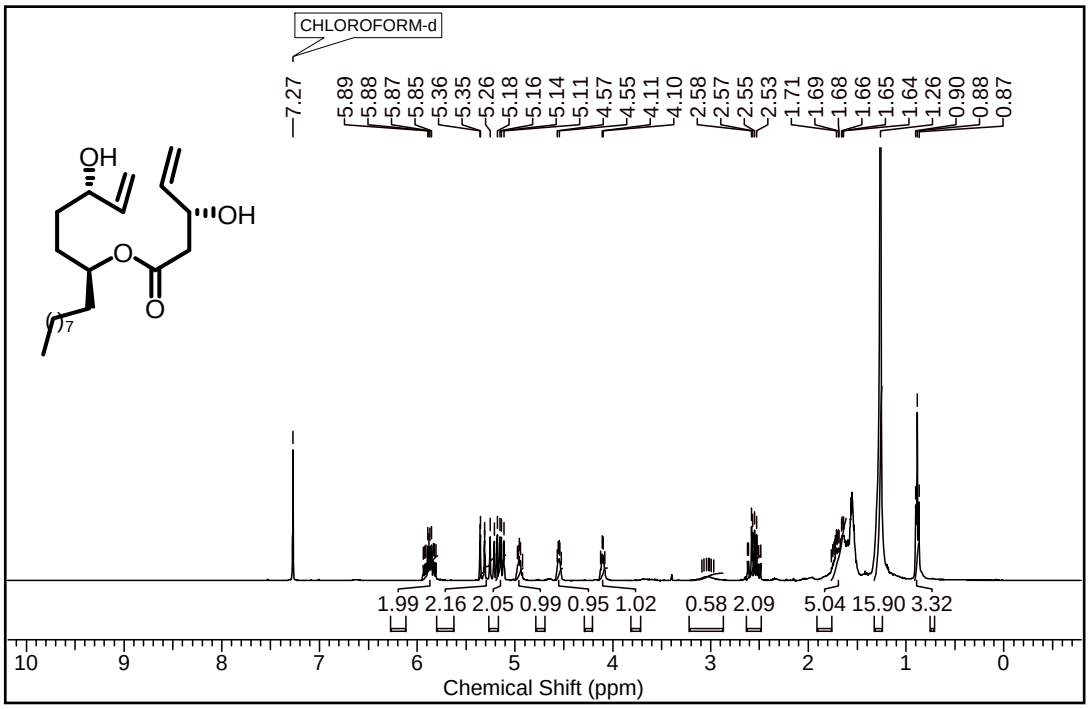


- **^{1}H NMR of the compound 34 in $CDCl_3$**

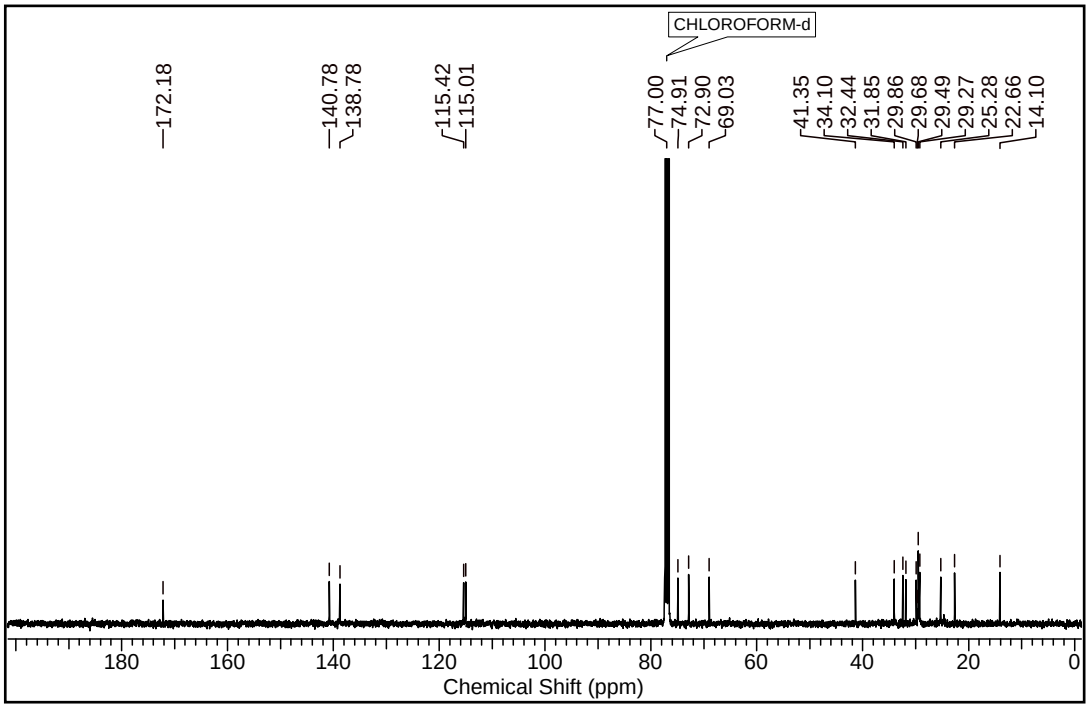


- **^{13}C NMR of the compound 34 in $CDCl_3$**

(3*S*,6*S*)-3-Hydroxypentadec-1-en-6-yl (*R*)-3-hydroxypent-4-enoate 35:

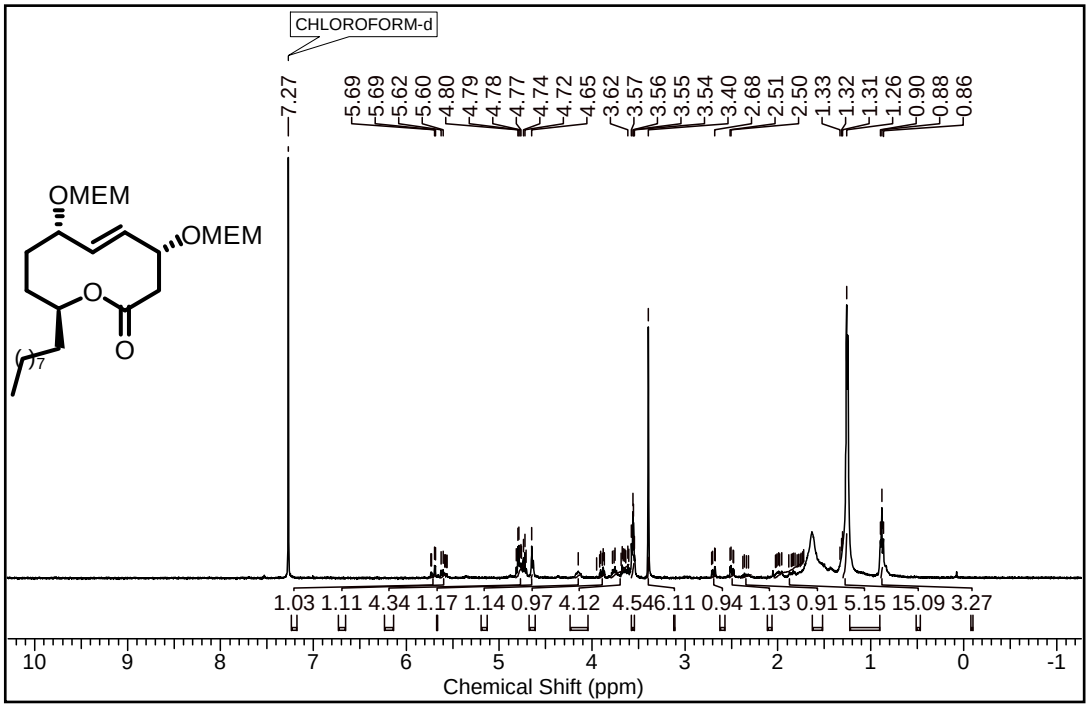


➢ **^{1}H NMR of the compound 35 in $CDCl_3$**

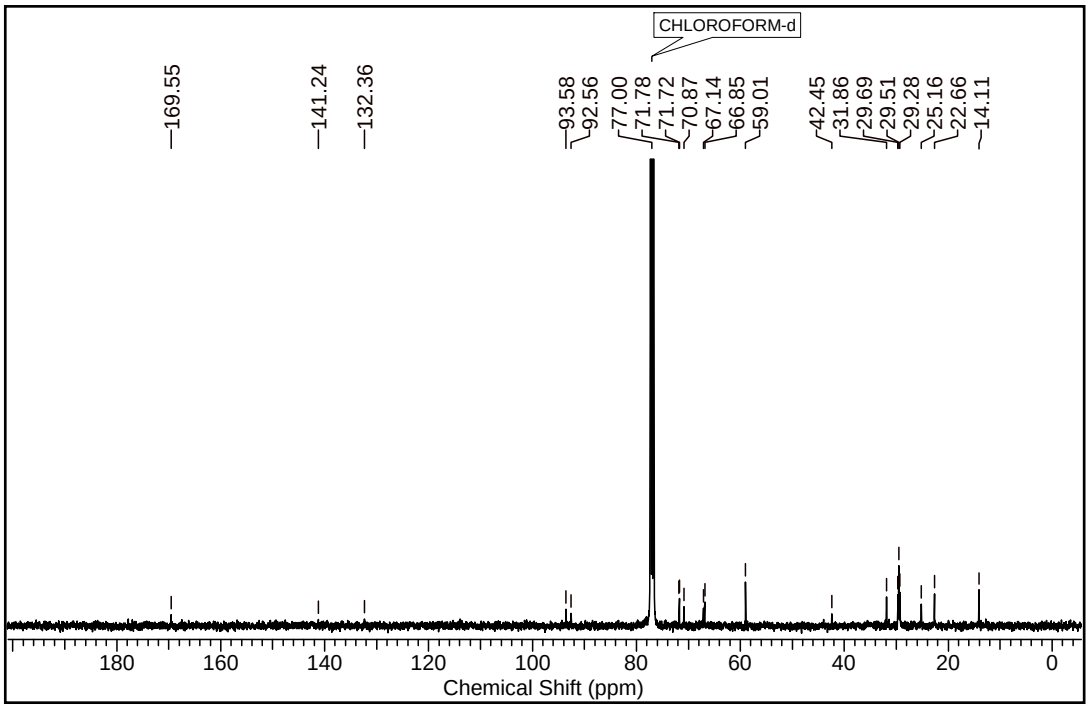


➢ **^{13}C NMR of the compound 35 in $CDCl_3$**

(4*R*,7*S*,10*S*,*E*)-4,7-Bis((2-methoxyethoxy)methoxy)-10-nonyl-3,4,7,8,9,10-hexahydro-2*H*-oxecin-2-one 36:

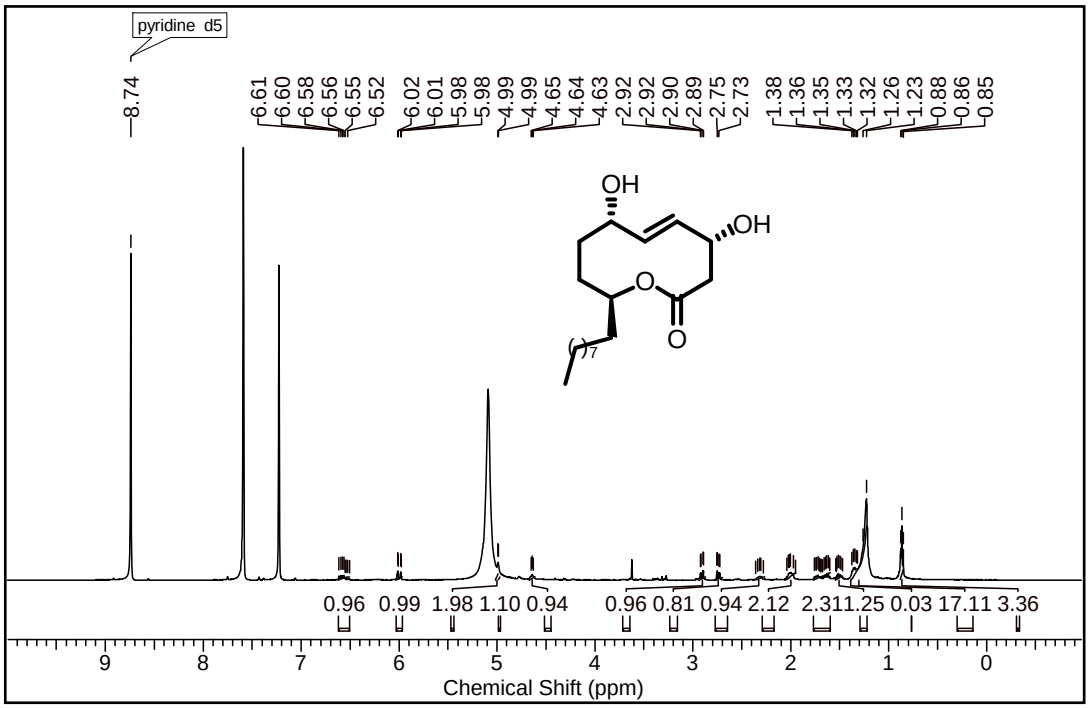


➢ **^{1}H NMR of the compound 36 in $CDCl_3$**

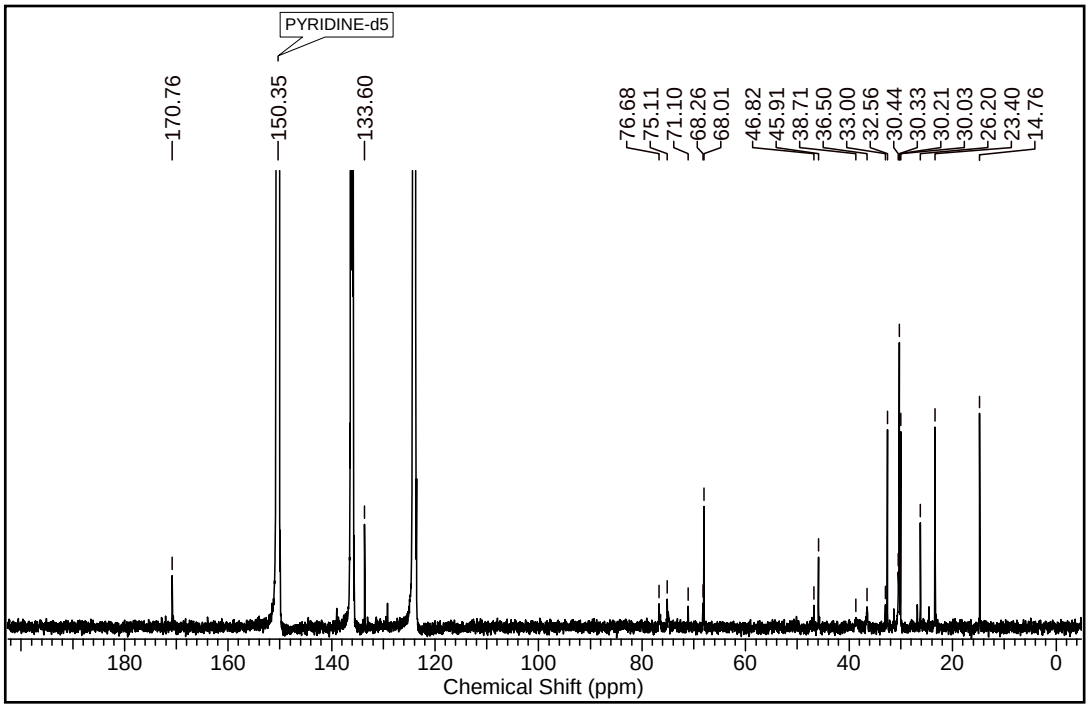


➢ **^{13}C NMR of the compound 36 in $CDCl_3$**

(4*R*,7*S*,10*S*,*E*)-4,7-Dihydroxy-10-nonyl-3,4,7,8,9,10-hexahydro-2*H*-oxecin-2-one 1:

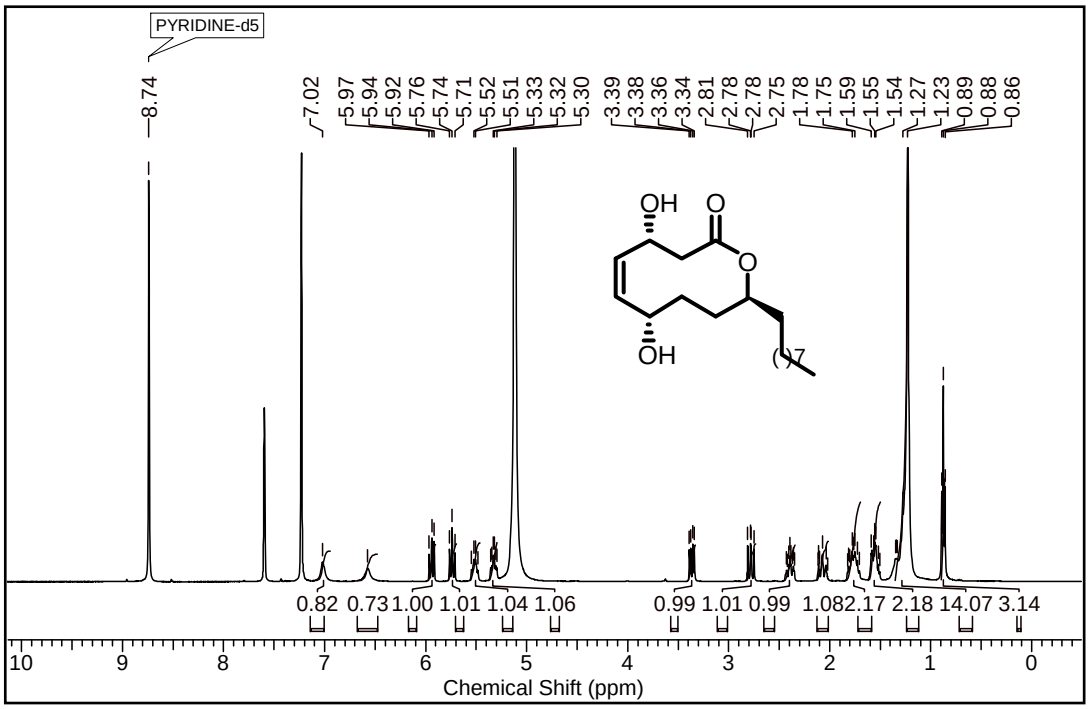


➢ **^{1}H NMR of the compound *E*-seimatopolide B in *Pyridine-d$_5$***

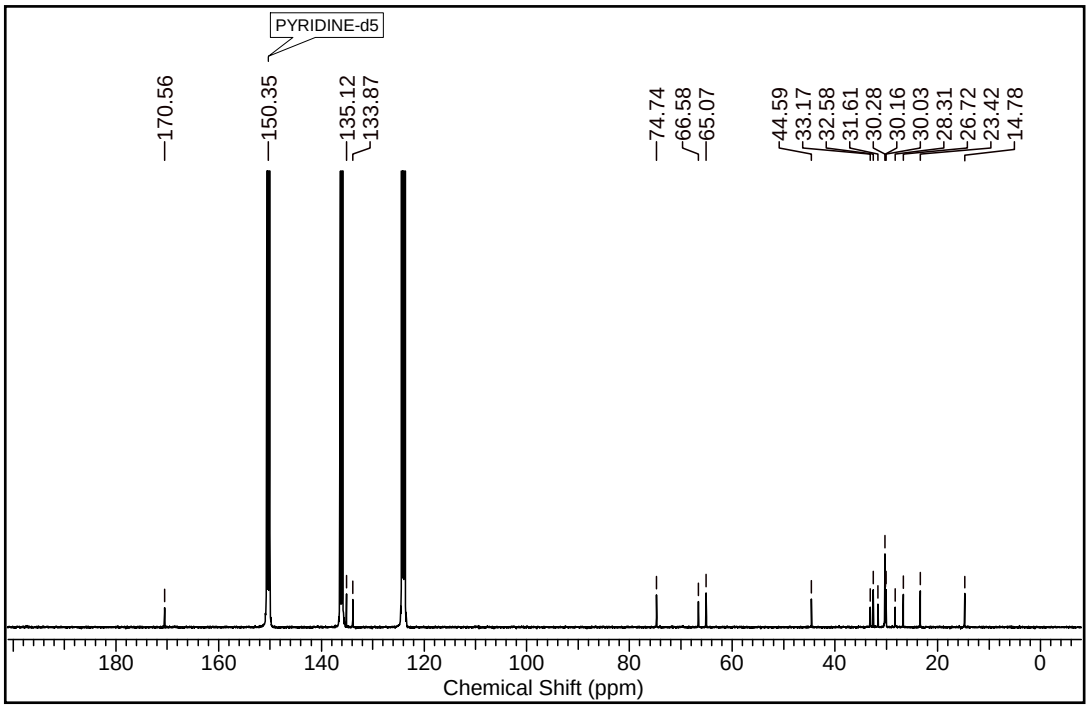


➢ **^{13}C NMR of the compound *E*-seimatopolide B in *Pyridine-d$_5$***

(4*R*,7*S*,10*S*,*Z*)-4,7-Dihydroxy-10-nonyl-3,4,7,8,9,10-hexahydro-2*H*-oxecin-2-one 1:



- **^{1}H NMR of the compound *Z*-seimatopolide B in *Pyridine-d$_5$***



- **^{13}C NMR of the compound *Z*-seimatopolide B in *Pyridine-d$_5$***

1.1.9. References:

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16. The enantiomeric purity of epoxide **25a** was determined by comparing optical rotation with known literature values: Compound **25a**: $[\alpha]_D^{25}$: -6.96 (*c* 1.0, $CHCl_3$) compound ***ent*-25a** : *Lit.*[13b] $[\alpha]_D^{24}$: +6.34 (*c* 1.0, $CHCl_3$);

17. Diastereomeric ratio (*syn*/*anti* ratio) was determined by ^1H and ^{13}C NMR analysis.

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1.2. SECTION B

Total Synthesis of (+)-Petromyroxol *via* Tandem α-Aminoxylation-Allylation and Tandem Dihydroxylation-S_N2 Cyclization Approach

1.2.1. Introduction

Acetogenins, an important class of compounds containing tetrahydrofuran ring systems (**Fig 1**), were isolated from *Annonaceae* plants. They are known to exhibit a wide range of biological activities such as antifeedant, antitumor, immunosuppressive and most significantly pesticidal and pheromonal activities.[1] This interesting biological profile along with varied structural features of the acetogenin family has aroused a lot of research interest in the synthesis of this class of compounds among the organic chemists worlwide.[2] Isolation of one such mono acetogenin, petromyroxol containing a single THF ring has been reported recently by Li *et al*.[3] Petromyroxol was known to have a possible biochemical role in study of communication among the sea lamprey, which are parasitic fish that are known to cause damage to the fish population especially in Great lakes area of North America.

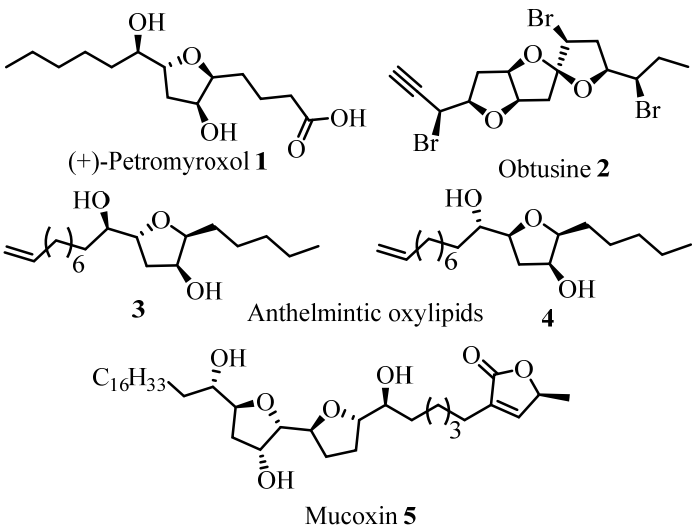


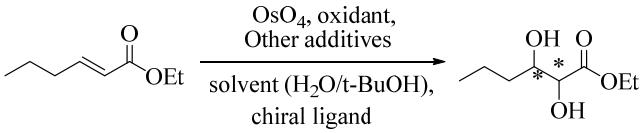
Figure 1: Some of the acetogenins based natural products

Significant efforts have been made to maintain the ecological balance and minimize the havoc caused by these invasive species.

Towards this, many strategies have been employed to control the growth of sea lamprey and one such study was to understand the olfactory responses in these species. A non-racemic mixture of petromyroxol (2.9 mg) has been isolated from >100 000 L of water conditioned with the larvae of *Petromyzon marinus*. The (+)-enantiomer was found to be just 0.9 mg (~ 36%) of the isolated mixture, nevertheless, was found to trigger a better olfactory response among the lamprey fish than it's (–)-antipode. The scarcity of the material has hampered further research in this area. The use of sex pheromones as a tool for biological control of pests has been under active consideration and along these lines petromyroxol is expected to be a part of sex pheromones,[3] of sea lamprey and could possibly help in development of eco-friendly pest controlling agents.

1.2.2. Introduction to the key step Sharpless asymmetric dihydroxylation (AD)

Sharpless asymmetric dihydroxylation is a powerful and predictable olefin functionalization in organic synthesis. Sharpless discovered the catalytic dihydroxylation of an olefin, which uses the catalytic (0.2 mol %) OsO_4 as an oxidant, $K_3Fe(CN)_6$ (3 equiv) as co-oxidant, K_2CO_3 (3 equiv), *tert*-butanol and water (1:1) combination as a solvent (0.1 M) and Cinchona alkaloids (1 mol%) as a source of chirality, methane sulfonamide (1 equiv) to increase the rate of hydrolysis of osmate ester thus to increase the rate of reaction[14b].



Scheme 1: Sharpless asymmetric dihydroxylation reaction

The discovery of ligands with two independent cinchona alkaloid units by Hartung[14b] (phthalazine core) and Crispino[14c] (diphenylpyrimidine core) attached to a heterocyclic spacer, has led to a considerable increase in both the enantioselectivity and scope of the reaction. Depending upon the substrate, the ligands used in the dihydroxylation reaction are

$(DHQ)_2$ PHAL, $(DHQD)_2$PHAL, $(DHQ)_2$PYR, $(DHQD)_2$PYR, $(DHQ)_2$AQN, $(DHQD)_2$AQN…*etc.* (**Figure 2**)

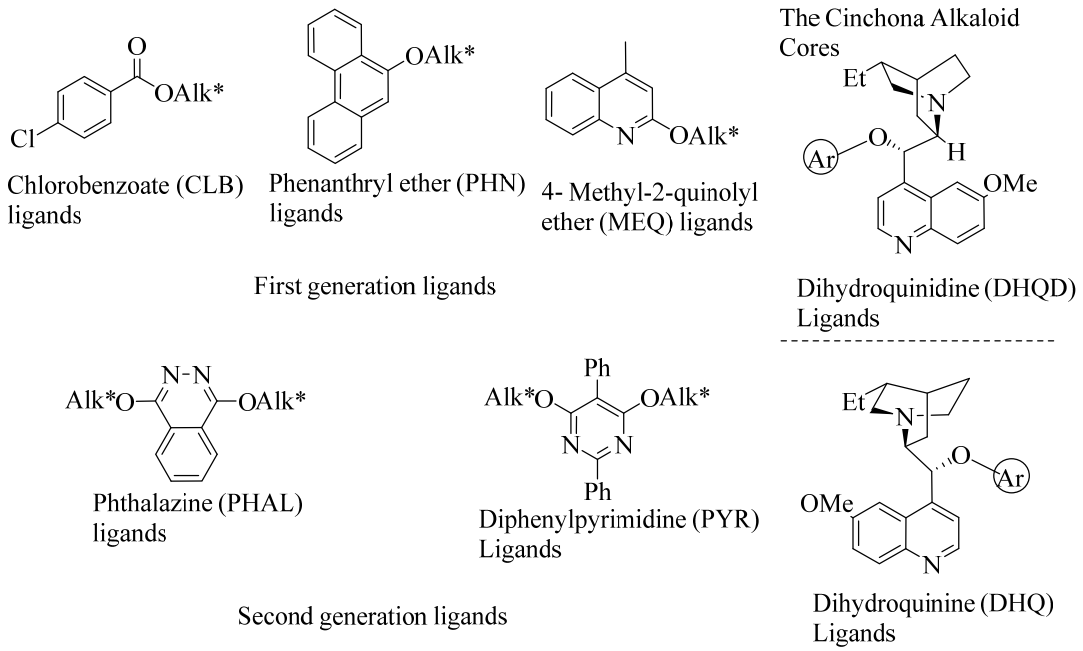
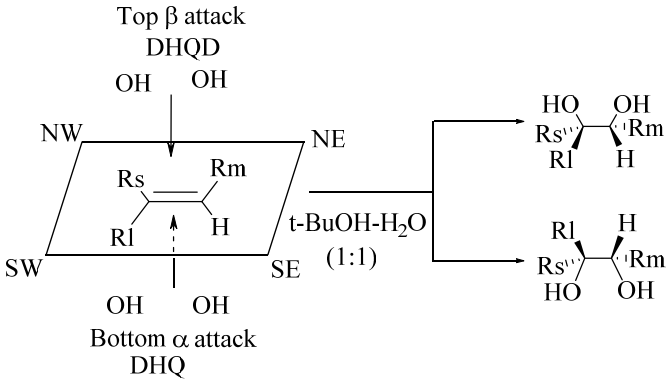


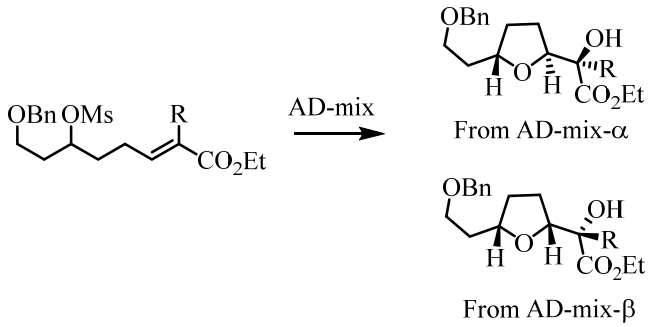
Figure 2: The latest generation of "dimeric" PHAL and PYR ligands and their predecessors (Alk* = DHQD or DHQ)

The stereochemical outcome of the dihydroxylation reaction can be predictable using pneumonic device. If we arrange our substrate according to pneumonic device, and use DHQD ligands, we will get β hydroxyl groups *i.e.* attack from top side and if we use DHQ ligands we will get α hydroxyl groups *i.e.* attack from bottom side.



Scheme 2: Empirical rules for determining the phase selectivity of dihydroxylation

Following discovery of AD reaction, there has been tremendous application of this asymmetric reaction in total synthesis of natural products, among several applications known in the literature. Marshall and co-workers developed a tool box for making *cis* and *trans* THF rings using dihydroxylation reaction.[13a,b] Accordingly, they designed a substrate (α,β-unsaturated-ε-mesyloxy ester) in such way that after dihydroxylation, it will be cyclized in preference to ligands used in the AD-mixes. If we use AD-mix-α, we will get *trans* 2,5-substituted THF ring and if we use AD-mix-β, we will end up with *cis* 2,5-substituted THF ring.



Scheme 3: Tool box for making *cis* and *trans* THF rings

1.2.3. Review of Literature

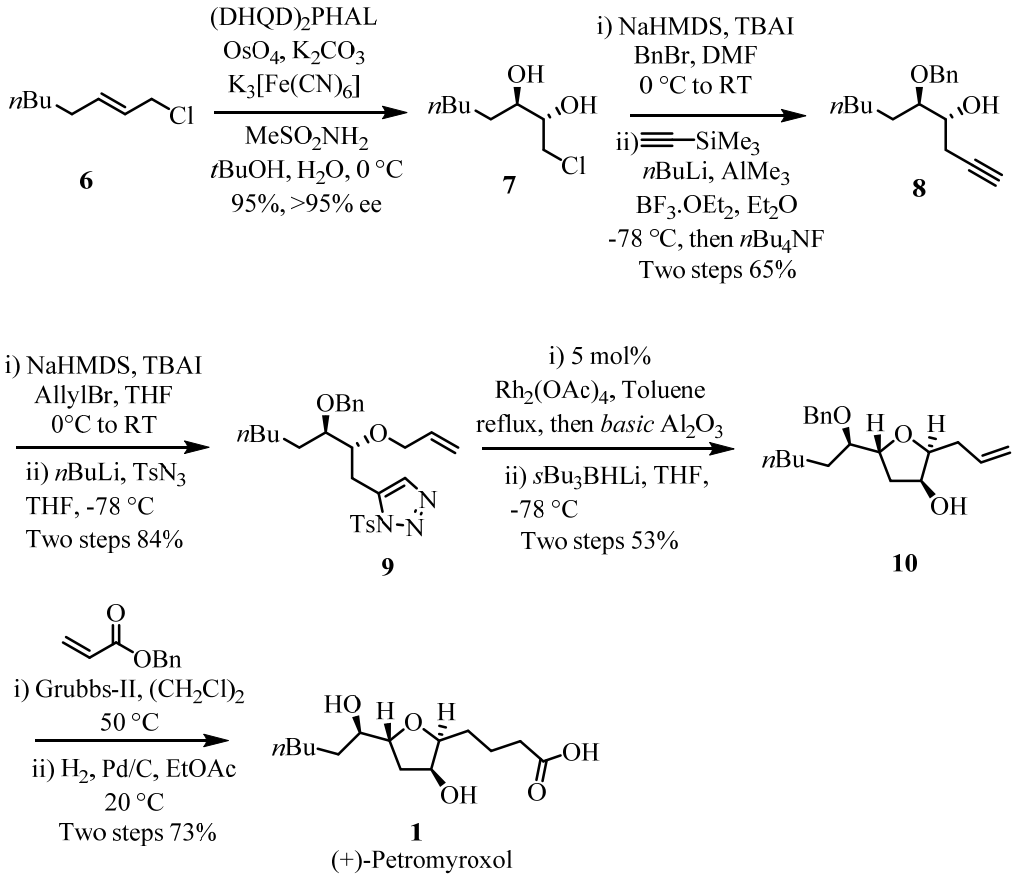
Due to the attractive structural features along with biological importance and low abundance of petromyroxol, this molecule attracted attention of many synthetic groups worldwide. As a result two syntheses were reported one after another. A detailed report of these syntheses is described below.

Synthesis of (+)-petromyroxol

Alistair Boyer (2015)[7a]

Alistair Boyer synthesized (+)-petromyroxol starting from *trans*-1-chloro-2-octene **6**, which was subjected to Sharpless asymmetric dihydroxylation to give 1, 2-diol **7** in 95% yield. The diol **7** was treated with NaHMDS and BnBr to give benzyl protected epoxy alcohol which

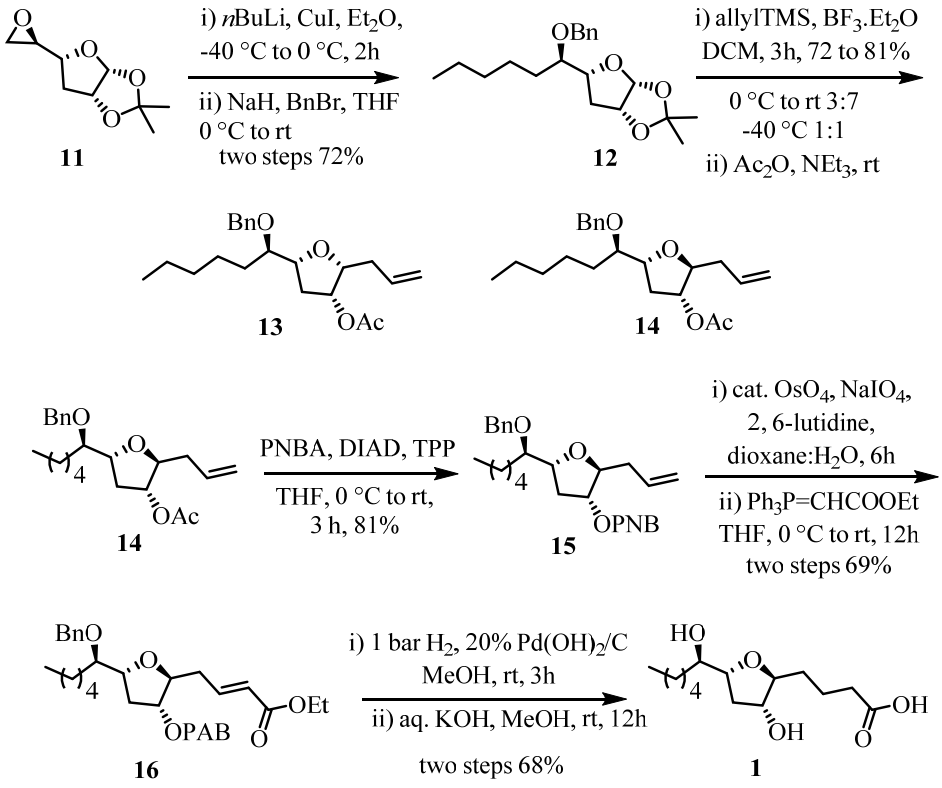
upon treatment with aluminium acetylide afforded the terminal alkyne **8**. Then, the alcohol **8** was converted into allylether followed by treatment with ^{n}BuLi and TsN_3 to give the triazole moity **9**. Compound **9** was treated with rhodium (II) acetate in toluene under reflux conditions to furnish the furanone ring with *trans*-2,5-configuration *via* denitrogenation, rearrangement. Subsequent reduction using $^{s}Bu_3BHLi$ resulted in desired alcohol **10** with 10:1 selectivity. The alcohol **10** was subjected to cross metathesis reaction with benzyl acrylate followed by the reduction of double bond and benzyl deprotection leading to the target molecule (+)-Petromyroxol **1**.



Scheme 4: Synthesis of (+)-petromyroxol (Alistair Boyer method)

C. V. Ramana *et al.* (2015)[7d]

Ramana and co-workers used chiral pool approach to synthesize **1**. The synthesis commenced with the known epoxide **11**, derived from D-glucose in 7 steps. The epoxide **11** was opened with *n*-BuLi using copper iodide to give the free alcohol, which was protected as its benzyl ether **12**. Further it was subjected to C-allyaltion using allylTMS and BF_3-Et_2O at 0 °C to furnish the allyl glycosides **13** and **14** in 3:7 ratio. Next the alcohol was subjected to Mitsunobu conditions to invert the center at C-2, to yield the **15**. Further olefin **15** was cleaved using OsO_4 and $NaIO_4$ conditions to give aldehyde, which was trapped *insitu* with 2C Wittig ylide to give the α,β unsaturated ester **16**. Now the ester was subjected to reduction and hydrogenolysis reaction using $Pd(OH)_2$/C under 1 bar followed by hydrolysis eventually to furnish (+)-petromyroxol **1**.



Scheme 5: Synthesis of (+)-petromyroxol (Ramana method)

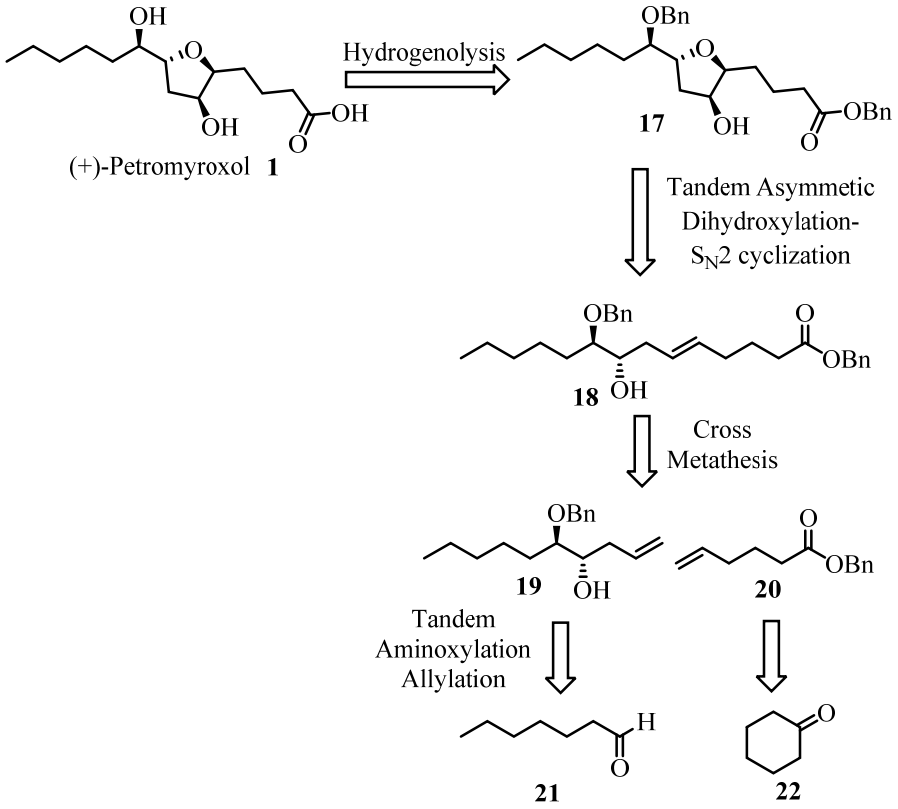
1.2.4. Present work

Objective

Petromyroxol is structurally interesting molecule with trisubstituted tetrahydrofurandiol. The construction of stereochemically defined THF ring has always been a major challenge which is evident from various literature reports.[2] The attractive structural features of petromyroxol along with biological importance and its low abundance drew our attention towards its synthesis. Accordingly we devised a simple and efficient route to (+)-petromyroxol *via* organocatalytic tandem process.

1.2.5. Results and discussion

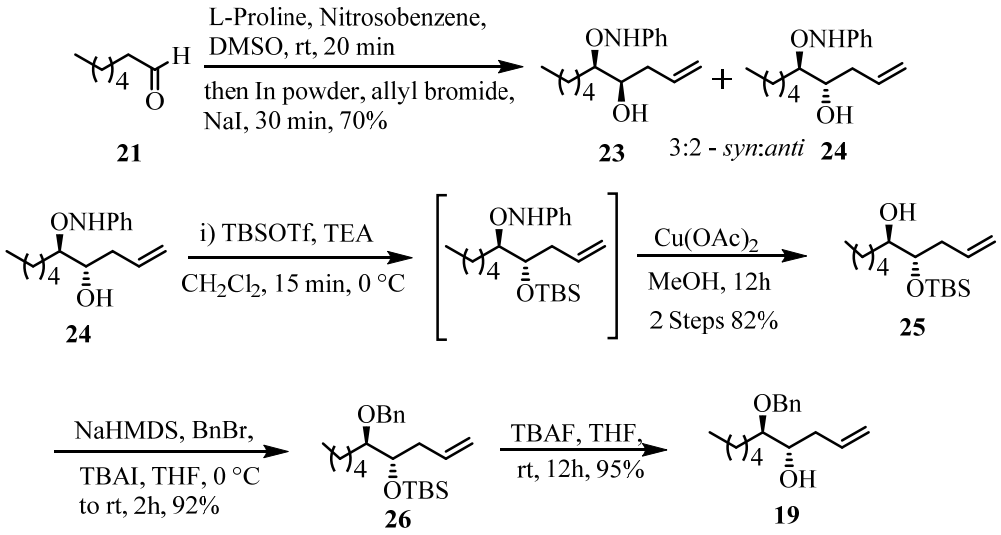
Our synthetic strategy for the synthesis of **1** is outlined in **Scheme 6**. We envisioned that the target molecule could be achieved by hydrogenolysis of THF alcohol **17**. The key tri-substituted THF moiety could be constructed diastereoselectively by using tandem-



Scheme 6: Retrosynthetic analysis of (+)-petromyroxol **1**

-asymmetric dihydroxylation-S_N2 cyclization of an olefin **18** which in turn could be derived from the cross metathesis of ester **20** and homoallylic alcohol **19**. The homo allylic alcohol **19** could be synthesized from commercially available heptanal **21** *via* oragano catalytic tandem α–aminoxylation-allylation protocol[8] developed by Zhong. The ester fragment **20** could be readily accessible from cyclohexanone **22**.

As illustrated in **Scheme 7**, synthesis of petromyroxol started from commercially available heptanal **21**, which was subjected to α-aminoxylation using L-proline as a catalyst and nitrosobenzene as an oxygen source to provide chiral *O*-*N*-phenylaminoxyaldehyde. This intermediate was then subjected to *in situ* indium mediated allylation (In/allylbromide/NaI) to afford a mixture of O-amino-substituted allylic alcohols **23** & **24** respectively with a diastereomeric ratio of 3:2 (*syn*:*anti*) in 70% overall yield with excellent enantioselectivities.[9] The IR spectrum of **23** and **24** gave broad hydroxyl absorption at 3394 cm^{-1}. The ^1H NMR spectrum of **23** gave olefin peaks at δ {5.95 - 5.85 (m, 1 H), 5.21 - 5.14 (m, 2 H)}, aromatic peaks at δ 7.28 (s, 2 H), 7.02 - 6.97 (m, 3 H). Both compounds **23** and **24** were cleanly separated by silica gel chromatography and fully characterized by spectroscopic means.



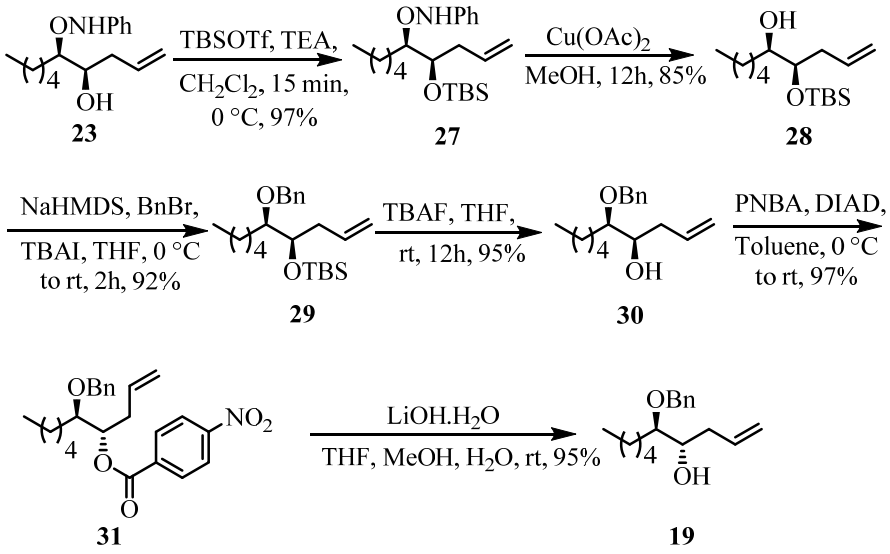
Scheme 7: Synthesis of alcohol fragment **19**

The anti compound **24** was then protected as its TBS ether using TBSOTf and NEt_3 to furnish the silyl ether followed by N–O bond cleavage[10] using copper (II) acetate in

methanol to get compound **25** in 82% yield (2 steps). The IR spectrum of **25** gave broad hydroxyl absorption at 3568 cm^{-1}.

Further, the free alcohol was protected as its benzyl ether using NaHMDS and benzyl bromide at 0 °C to furnish the compound **26**, which was then desilylated using TBAF in THF to obtain homoallylic alcohol **19.** The IR spectrum of **19** gave broad hydroxyl absorption at 3425 cm^{-1}.

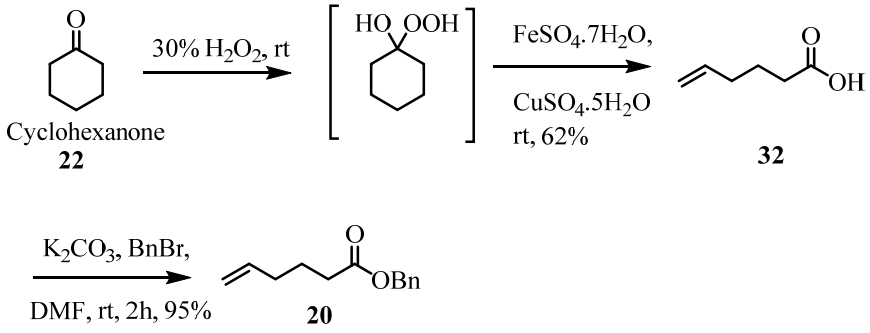
Our next task was to convert the major *syn* compound **23** into the required homoallylic alcohol **19** (**Scheme 8**). Towards this end compound **30** was synthesized from **23** using a similar sequence of reactions as described in **Scheme 7**. Subsequently compound **30** was smoothly converted to the required fragment **19** *via* Mitsunobu inversion (**Scheme 8**).



Scheme 8: Conversion of *syn* isomer **23** to desired *anti* alcohol fragment **19**

We then proceeded next to prepare the ester fragment, for that cyclohexanone **22** was treated with 30% H_2O_2 to give hydroperoxide intermediate which was decomposed using ferrous sulfate-copper sulfate system to give the acid **32** in 62% yield[11] (**Scheme 9**). The IR spectrum of **32** gave broad acid carbonyl absorption at 1711 cm^{-1}. The olefinic acid **32** was subjected to esterification using K_2CO_3/BnBr to furnish the benzyl ester **20** in 95% yield. The IR spectrum of **20** gave ester carbonyl absorption at 1737 cm^{-1}.

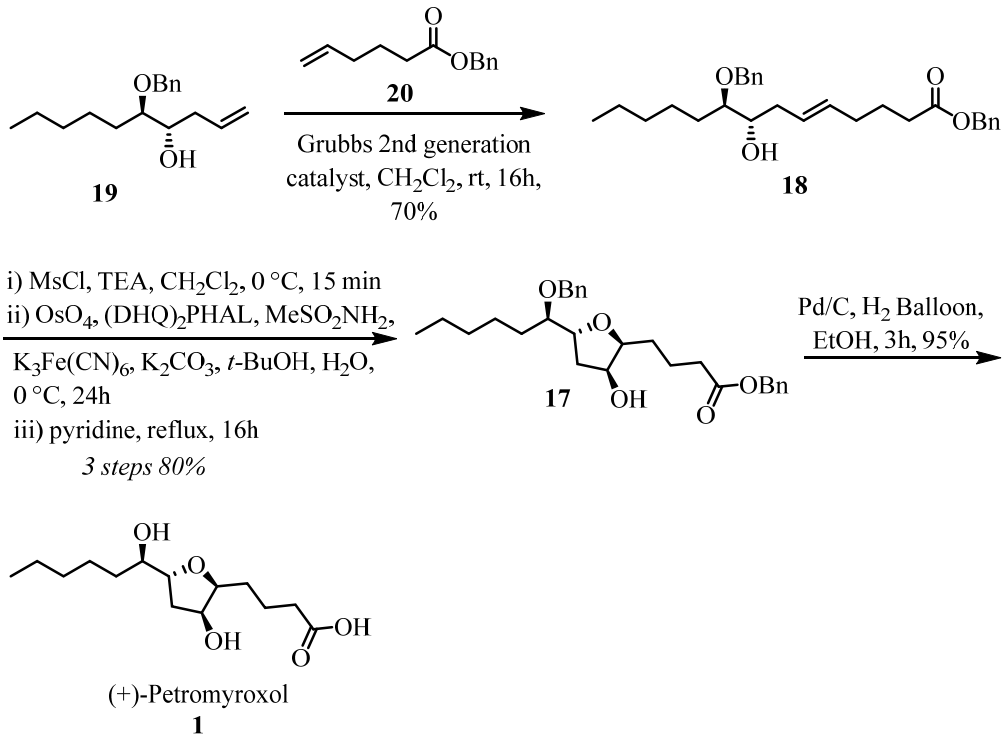
After few optimizations with temperature and catalyst loading, the cross metathesis[12] reaction was performed between alcohol **19** (1 equiv) and **20** (5 equiv) in CH_2Cl_2 using 15 mol% Grubb's catalyst, resulting in the cross coupled **18** as major product in 70% yield (**Scheme 10**). The IR spectrum of **18** gave ester carbonyl absorption at 1734 cm^{-1} and alcohol absorption at 3456 cm^{-1}. ^1H NMR gave the internal olefin peak at δ 5.56 - 5.40 (m, 2 H) and ^{13}C NMR gave the ester carbonyl carbon at δ 173.4.



Scheme 9: Synthesis of ester fragment **20**

After having substantial amounts of olefinic alcohol **18**, the time was set for the construction of *trans* trisubstituted tetrahydrofuran ring **17** *via* intramolecular tandem Sharpless asymmetric dihydroxylation-S_N2 cyclization according to Marshall's protocol.[13] Thus, the alcohol **18** was first converted into its mesylate and then subjected to Sharpless asymmetric dihydroxylation[14] using commercially available AD-mix-α in *t*-BuOH–H_2O (1:1), however the reaction did not work.

So we considered optimizing the dihydroxylation reaction conditions with respect to ligand and OsO_4. Initially we carried out the reaction with standard conditions of Sharpless asymmetric dihydroxylation using 1 mol% ligand $(DHQ)_2PHAL$ and 0.4 mol% OsO_4, but reaction did not work even after prolonged reaction time for a week at 0 °C. This prompted us to increase the amount of OsO_4 to 5 mol% in a phased manner and to our delight starting material was completely consumed to give the crude diol. This crude product, without any extensive characterization, was immediately subjected to cyclization using pyridine as solvent. Though the reaction did not proceed at room temperature, refluxing the same in pyridine for 16h furnished the desired cyclized compound **17** in 80% yield (3 steps) with excellent selectivity (single diastereomer, confirmed by ^1H and ^{13}C NMR).



Scheme 10: Synthesis of (+)-petromyroxol **1**

Finally debenzylation of compound **17** using 10% wt/wt Pd/C under hydrogen balloon pressure gave the target molecule (+)-petromyroxol **1** in 95% yield. All the spectroscopic data matched well with isolated (+)-petromyroxol.

Synthetic (+)-Petromyroxol spectroscopic data (500MHz, $CDCl_3$)			**Natural (+)-Petromyroxol spectroscopic data (500MHz, $CDCl_3$)**	
S.No	**(δ_H, *J* in Hz)**	**δ_C**	**(δ_H, *J* in Hz)**	**δ_C**
1		177.7		177.6, C
2	2.49 - 2.37 m	33.5	2.43, m	33.7, CH_2
3	1.80 - 1.63 m	21.2	1.77 m, 1.70 m	21.4, CH_2
4		28.2	1.72 m, 1.67 m	28.4, CH_2
5	3.82 - 3.77 ddd (*J* = 2.4, 6.5, 6.5)	82.4	3.79 ddd (*J* = 2.5, 6.5, 6.5)	82.5, CH
6	4.32 - 4.27 dd (*J* = 3.5, 3.5)	73.3	4.30 dd (*J* = 3.5,3.5)	73.5, CH
7	1.89 ddd (*J* = 4.6, 9.1, 13.5) 2.04 dd (*J* = 6.6, 13.3)	37.6	1.89 ddd (*J* = 4.6,9.2, 13.7) 2.02 dd (*J* = 6.6, 13.4)	37.8, CH_2
8	4.10 - 4.04 ddd (*J* = 6.4, 6.7, 8.9)	80.5	4.06 ddd (*J* = 6.5, 6.5, 8.9)	80.7, CH
9	3.43 - 3.37 ddd (*J* =	74.1	3.39 m	74.3, CH

	4.0, 6.4, 7.3)			
10	1.55 - 1.47 m	33.1	1.40 m	33.3, CH_2
11		25.2	1.51 m. 1.38 m	25.4, CH_2
12	1.44 - 1.28 m	31.8	1.29 m	32.0, CH_2
13		22.6	1.31 m	22.8, CH_2
14	0.89 t (J = 6.9)	14.0	0.89 t (J = 6.9)	14.2, CH_2

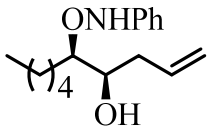
Fig 2: Comparison of ^{1}H and ^{13}C NMR data of both natural and synthetic (+)-petromyroxol

1.2.6. Conclusion

In summary, we achieved the asymmetric synthesis of (+)-petromyroxol in 10 steps with an overall yield of 26.6% from easily accessible starting materials. Depending upon the catalyst (D/L-proline) used in the tandem aminoxylation-allylation step along with variation in chain length and the ligands (DHQ/DHQD) in the Sharpless asymmetric dihydroxylation step, one can have easy access to various stereoisomers of petromyroxol and its synthetic analogues.

1.2.7. Experimental Section

(4*R*, 5*R*)-5-((Phenylamino)oxy)hept-1-en-4-ol 23:



To a stirred solution of heptanal (6.4 g, 56.0 mmol) and nitrosobenzene (5.0, 46.6 mmol) in DMSO (94 mL), L-proline (1.07 g, 9.3 mmol) was added. After being stirred for 20 min at rt (The endpoint of the reaction was monitored by its color change from green to orange), allyl bromide (6.05 ml, 70.0 mmol), NaI (10.5 g, 70.0 mmol), and indium powder (8.03 g, 70.0 mmol) were added at rt. The stirring was kept at room temperature for 30 min. The reaction mixture was quenched with 0.5 M aq HCl (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash column

chromatography EtOAc-petrolium ether, (3:97) to afford the title compound (4*R*, 5*R*)-5-((phenylamino)oxy)hept-1-en-4-ol **23** as yellow liquid and the more quickly eluting (4*S*, 5*R*)-isomer **24** as yellow liquid. The diastereomeric ratios of the products were determined by weighing the separated isomers. The enantiomeric excess of the *anti* and the *syn*-diastereomer was measured by HPLC analysis after separation of the isomers using column chromatography.

***Syn* 23:**

Yield: 5.1g, 42%

Mol. Formula: $C_{16}H_{25}O_2N$

$[\alpha]_D^{26.6}$: +28.7° (*c* 1.58, $CHCl_3$)

IR (neat, cm^{-1}): ν_{max} 3394, 3275, 3074, 2929, 2863, 1640, 1600, 1484, 1459, 1375, 1320, 1041

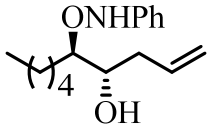
^{1}H NMR (500MHz, $CDCl_3$) δ = 7.28 (s, 2 H), 7.09 (s, 1 H), 7.02 - 6.97 (m, 3 H), 5.95 - 5.85 (m, 1 H), 5.21 - 5.14 (m, 2 H), 4.03 (t, *J* = 5.6 Hz, 1 H), 3.89 (td, *J* = 2.9, 8.5 Hz, 1 H), 2.57 (br. s., 1 H), 2.32 (t, *J* = 6.9 Hz, 2 H), 1.76 - 1.66 (m, 2 H), 1.65 - 1.56 (m, 2 H), 1.55 - 1.36 (m, 4 H), 0.93 - 0.90 (m, 3 H)

^{13}C NMR (125MHz, $CDCl_3$) δ = 148.3, 135.1, 129.0, 122.4, 117.7, 114.9, 85.8, 72.2, 36.9, 31.9, 28.2, 26.0, 22.5, 14.0

HRMS (ESI) for $C_{16}H_{25}O_2N$ $(M + Na)^+$ found 286.1782, calcd 286.1778

HPLC {Chiralcel OD-H (250mm x 4.6 mm), *i*PrOH/hexane (10:90), flow rate 1 mL min^{-1}, λ = 230 nm, t_R = 5.40 (major), t_R = 6.31 (minor)}

***Anti* 24**:



Yield: 3.5 g, 28%

Mol. Formula: $C_{16}H_{25}O_2N$

$[\alpha]_D^{26.6}$: +20.4° (*c* 1.43, $CHCl_3$)

IR (neat, cm^{-1}): ν_{max} 3396, 3285, 3075, 2929, 2863, 1640, 1600, 1480, 1459, 1375, 1320, 1041

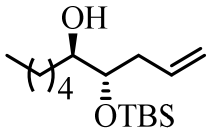
^1H NMR (500MHz, $CDCl_3$) δ = 7.31 - 7.27 (m, 2 H), 7.04 - 6.98 (m, 3 H), 5.98 - 5.82 (m, 1 H), 5.21 - 5.12 (m, 2 H), 3.87 (ddd, *J* = 4.1, 5.7, 8.2 Hz, 1 H), 3.79 (q, *J* = 5.8 Hz, 1 H), 2.51 - 2.38 (m, 1 H), 2.33 - 2.25 (m, 1 H), 1.75 - 1.61 (m, 2 H), 1.53 - 1.42 (m, 2 H), 1.38 - 1.30 (m, 4 H), 0.90 (t, *J* = 6.9 Hz, 3 H)

^{13}C NMR (125MHz, $CDCl_3$) δ = 148.0, 134.6, 129.0, 122.6, 117.9, 115.3, 85.4, 72.7, 38.2, 32.0, 29.4, 25.3, 22.5, 14.0

HRMS (ESI) for $C_{16}H_{25}O_2N$ $(M + Na)^+$ found 286.1782, calcd 286.1778

HPLC {Chiralcel OD-H (250 mm x 4.6 mm), ^{i}PrOH/hexane (10:90), flow rate 1 mL min^{-1}, λ = 230 nm, t_R = 6.32 (major), t_R = 7.35 (minor)}

(4*S*, 5*R*)-4-((Tert-butyldimethylsilyl)oxy)dec-1-en-5-ol 25:



To a stirred solution of compound **24** (3.0 g, 10.48 mmol) in CH_2Cl_2 (30.0 mL) at 0 °C was added Et_3N (3.5 mL, 25.09 mmol), followed by TBDMSOTf (3.2 mL, 13.6 mmol) and the mixture was stirred for 15 min. The reaction mixture was quenched with sat. NH_4Cl solution (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the crude silyl ether as yellow oil.

To a stirred solution of the crude silyl ether in MeOH (50 mL) was added $Cu(OAc)_2$ (720 mg, 3.96 mmol). The mixture was stirred at rt for 12h. The reaction mixture was quenched with a cold sat.NH_4Cl solution and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was

purified by flash column chromatography on silica gel EtOAc-petrolium ether, (2:98) to afford compound **25** as yellow oil.

Yield: 2.4 g, 2 steps 82%

Mol. Formula: $C_{16}H_{34}O_2Si$

$[\alpha]_D^{27.7}$: +0.24° (*c* 1.74, $CHCl_3$

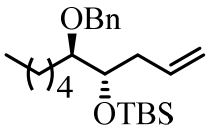
IR (neat, cm^{-1}): ν_{max} 3566, 3460, 3076, 2942, 2862, 1462, 1392, 1258, 1080

^{1}H NMR (400MHz, $CDCl_3$) δ = 5.90 - 5.77 (m, 1 H), 5.12 - 5.01 (m, 2 H), 3.70 - 3.64 (m, 1 H), 3.61 - 3.56 (m, 1 H), 2.35 - 2.26 (m, 1 H), 2.25 - 2.17 (m, 1 H), 1.92 (br. s., 1 H), 1.45 - 1.39 (m, 2 H), 1.37 - 1.29 (m, 6 H), 0.91 (s, 12H), 0.08 (s, 6 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 135.6, 116.8, 75.1, 74.6, 35.9, 31.9, 31.8, 25.8, 25.8, 22.6, 18.1, 14.0, -4.3, -4.6

HRMS (ESI) for $C_{16}H_{34}O_2Si$ $(M + Na)^+$ found 309.2228, calcd 309.2220

(((4*S*, 5*R*)-5-(Benzyloxy)dec-1-en-4-yl)oxy)(tert-butyl)dimethylsilane 26:



Sodium bis(trimethylsilyl)amide (1M solution in THF, 10.48 mL, 10.48 mmol) was added to a stirred solution of **25** (2.0 g, 6.9 mmol), tetrabutylammonium iodide (258 mg, 0.69 mmol) and benzyl bromide (1.24 mL, 10.48 mmol) in THF (30 mL) at 0 °C. The mixture was stirred at ambient temperature for 2h. The reaction was quenched by the addition of saturated aqueous ammonium chloride (25 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash column chromatography EtOAc-pet ether, (1.5:98.5) to yield the title compound **26** as colourless oil.

Yield: 2.37 g, 92%

Mol. Formula: $C_{23}H_{40}O_2Si$

$[\alpha]_D^{28.9}$: +15.67° (*c* 1.31, $CHCl_3$)

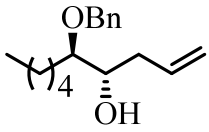
IR (neat, cm^{-1}): ν_{max} 3075, 3029, 2940, 2861, 1462, 1370, 1317, 1252, 1208, 1095

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.38 - 7.28 (m, 5 H), 5.88 (tdd, *J* = 7.2, 10.1, 17.1 Hz, 1 H), 5.11 - 5.02 (m, 2 H), 4.71 (d, *J* = 11.5 Hz, 1 H), 4.51 (d, *J* = 11.5 Hz, 1 H), 3.79 (td, *J* = 4.3, 6.3 Hz, 1 H), 3.38 (td, *J* = 3.6, 7.5 Hz, 1 H), 2.45 - 2.36 (m, 1 H), 2.32 - 2.24 (m, 1 H), 1.54 - 1.48 (m, 2 H), 1.36 - 1.24 (m, 6H), 0.92 - 0.87 (m, 12 H), 0.07 (s, 6 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 139.1, 135.8, 128.2, 127.8, 127.4, 116.7, 82.3, 74.2, 72.5, 37.8, 32.0, 30.7, 25.9, 25.5, 22.6, 18.1, 14.1, -4.4, -4.4

HRMS (ESI) for $C_{23}H_{40}O_2$ Si $(M + Na)^+$ found 399.2699, calcd 399.2690

(*4S*, 5*R*)-5-(Benzyloxy)dec-1-en-4-ol 19:



To a stirred solution of **26** (2.0 g, 5.3 mmol) in THF (10 mL) was added 1.0 M TBAF in THF (10.6 mL, 10.6 mmol) at 0 °C. After being stirred for 12 h at rt, the reaction mixture was quenched with H_2O (10 mL) and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash column chromatography EtOAc–hexane, (5:95) to afford compound **19** as colourless oil.

Yield: 1.3 g, 95%

Mol. Formula: $C_{17}H_{26}O_2$

$[\alpha]_D^{28.9}$: -1.95° (*c* 0.6, $CHCl_3$)

IR (neat, cm^{-1}): ν_{max} 3425, 3076, 3030, 2926, 2865, 1696, 1635, 1455, 1372, 1084, 1037.

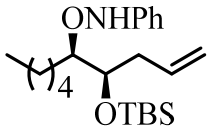
^{1}H NMR (500MHz, $CDCl_3$) δ = 7.36-7.28 (m, 5 H), 5.95 - 5.79 (m, 1 H), 5.19 - 5.11 (m, 2 H), 4.64 - 4.56 (m, 2 H), 3.87 - 3.81 (m, 1 H), 3.44 - 3.38 (m, 1 H), 2.35 - 2.25 (m, 2 H),

1.93 (br. s., 1 H), 1.69 - 1.60 (m, 1 H), 1.50 (d, *J* = 7.6 Hz, 2 H), 1.38 - 1.25 (m, 5 H), 0.92 - 0.87 (m, 3 H)

^{13}C NMR (125MHz, $CDCl_3$) δ = 138.5, 135.1, 128.4, 127.8, 127.7, 117.6, 81.7, 77.3, 76.7, 72.1, 71.4, 36.9, 32.0, 29.1, 25.2, 22.6, 14.0

HRMS (ESI) for $C_{17}H_{26}O_2$ $(M + Na)^+$ found 285.1830, calcd 285.1825

O-((4*R*,5*R*)-4-((Tert-butyldimethylsilyl)oxy)dec-1-en-5-yl)-N-phenylhydroxylamine 27:



Procedure as described in the preparation of **25**.

Yield: 5.57 g, 97%

Mol. Formula: $C_{22}H_{39}O_2$ N Si

$[\alpha]_D^{25.8}$: +22.7° (*c* 1.7, $CHCl_3$)

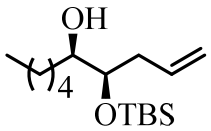
IR (neat, cm^{-1}): ν_{max} 3296, 3074, 2942, 2861, 1641, 1601, 1463, 1421, 1372, 1252, 1081, 1010, 913, 835, 772, 728, 687

^{1}H NMR (500MHz, $CDCl_3$) δ = 7.32 - 7.26 (m, 3 H), 7.02 - 6.94 (m, 3 H), 5.90 (tdd, *J* = 7.2, 10.0, 17.1 Hz, 1 H), 5.15 - 5.06 (m, 2 H), 4.00 (ddd, *J* = 2.1, 5.0, 7.2 Hz, 1 H), 3.87 - 3.82 (m, 1 H), 2.41 (td, *J* = 7.1, 14.3 Hz, 1 H), 2.34 - 2.27 (m, 1 H), 1.73 - 1.62 (m, 2 H), 1.56 - 1.44 (m, 2 H), 1.42 - 1.34 (m, 4 H), 0.98 - 0.93 (m, 12 H), 0.13 (s, 6 H)

^{13}C NMR (125MHz, $CDCl_3$) δ = 148.8, 135.7, 128.8, 121.6, 116.9, 114.3, 86.6, 74.0, 37.6, 32.0, 29.4, 26.2, 25.9, 22.6, 18.2, 14.1, -4.3, -4.4

HRMS (ESI) for $C_{22}H_{39}O_2$ N Si $(M+H)^+$ found 378.2830, calcd 378.2823

(4*R*, 5*R*)-4-((Tert-butyldimethylsilyl)oxy)dec-1-en-5-ol 28:



Procedure as described in the preparation of **25**.

Yield: 3.2 g, 85%

Mol. Formula:

$[\alpha]_D^{26.0}$: -7.8° (*c* 1.61, $CHCl_3$)

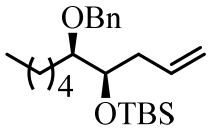
IR (neat, cm^{-1}): ν_{max} 3568, 3460, 3076, 2942, 2862, 1463, 1392, 1255, 1079

^{1}H NMR (500MHz, $CDCl_3$) δ = 5.80 (tdd, *J* = 7.1, 10.1, 17.2 Hz, 1 H), 5.12 - 5.05 (m, 2 H), 3.56 (td, *J* = 4.3, 7.0 Hz, 1 H), 3.47 - 3.43 (m, 1 H), 2.43 (td, *J* = 7.1, 14.1 Hz, 1 H), 2.25 - 2.18 (m, 1 H), 1.91 (br. s., 1 H), 1.53 - 1.44 (m, 1 H), 1.43 - 1.39 (m, 2 H), 1.37 - 1.28 (m, 5 H), 0.92 - 0.89 (m, 12 H), 0.10 (d, *J* = 7.3 Hz, 6 H)

^{13}C NMR (125MHz, $CDCl_3$) δ = 134.4, 117.4, 74.6, 72.4, 38.7, 33.9, 31.9, 25.9, 25.5, 22.6, 18.1, 14.1, -4.1, -4.7

HRMS (ESI) for $C_{16}H_{34}O_2$ Si $(M + Na)^+$ found 309.2226, calcd 309.2220

(((4*R*, 5*R*)-5-(Benzyloxy)dec-1-en-4-yl)oxy)(tert-butyl)dimethylsilane 29:



Procedure as described in the preparation of **26**.

Yield: 3.4 g, 92 %

Mol. Formula: $C_{23}H_{40}O_2$ Si

$[\alpha]_D^{27.6}$: +22.3° (*c* 2.8, $CHCl_3$)

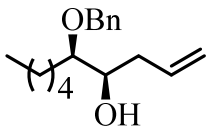
IR (neat, cm^{-1}): ν_{max} 3074, 3029, 2941, 2862, 1462, 1370, 1319, 1253, 1208, 1094

^{1}H NMR (500MHz, $CDCl_3$) δ = 7.37 - 7.28 (m, 5 H), 5.84 (tdd, *J* = 7.2, 10.0, 17.2 Hz, 1 H), 5.09 - 5.01 (m, 2 H), 4.62 (d, *J* = 11.9 Hz, 1 H), 4.55 (d, *J* = 11.6 Hz, 1 H), 3.81 (td, *J* = 3.9, 8.3 Hz, 1 H), 3.33 (ddd, *J* = 2.9, 4.4, 9.2 Hz, 1 H), 2.41 (dddd, *J* = 1.8, 3.4, 5.1, 14.0 Hz, 1 H), 2.17 - 2.10 (m, 1 H), 1.67 - 1.61 (m, 1 H), 1.55 - 1.48 (m, 1 H), 1.42 (dtd, *J* = 4.6, 9.0, 13.5 Hz, 1 H), 1.34 - 1.27 (m, 5 H), 0.89 (s, 12 H), 0.02 (s, 3 H), 0.04 (s, 3 H)

^{13}C NMR (125MHz, $CDCl_3$) δ = 139.3, 136.7, 128.5, 128.1, 127.8, 116.7, 82.3, 77.3, 72.8, 72.6, 36.7, 32.2, 29.0, 26.3, 26.1, 22.9, 18.3, 14.3, -4.2, -4.2

HRMS (ESI) for $C_{23}H_{40}O_2$ Si $(M + Na)^+$ found 399.2699, calcd 399.2690

(4*R*, 5*R*)-5-(Benzyloxy)dec-1-en-4-ol 30:



Procedure as described in the preparation of **27**.

Yield: 1.3 g, 95%

Mol. Formula: $C_{17}H_{26}O_2$

$[\alpha]_D^{28.8}$: -18.6° (*c* 2.27, $CHCl_3$)

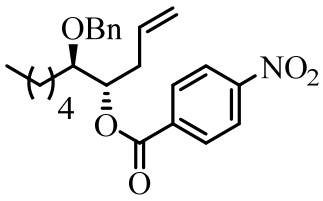
IR (neat, cm^{-1}): ν_{max} 3421, 3073, 3030, 2927, 2862, 1638, 1695, 1457, 1373, 1080

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.38 - 7.29 (m, 5 H), 5.88 (tdd, *J* = 7.0, 10.3, 16.9 Hz, 1 H), 5.16 - 5.07 (m, 2 H), 4.67 (d, *J* = 11.2 Hz, 1 H), 4.52 (d, *J* = 11.2 Hz, 1 H), 3.65 (td, *J* = 4.8, 7.8 Hz, 1 H), 3.35 (q, *J* = 5.5 Hz, 1 H), 2.40 - 2.31 (m, 1 H), 2.30 - 2.21 (m, 1 H), 2.16 (br. s., 1 H), 1.72 - 1.53 (m, 2 H), 1.43 - 1.28 (m, 6 H), 0.91 (t, *J* = 6.8 Hz, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 138.4, 135.0, 128.4, 127.8, 127.7, 117.3, 81.4, 72.3, 72.0, 38.1, 32.1, 30.1, 24.8, 22.6, 14.0

HRMS (ESI) for $C_{17}H_{26}O_2$ $(M + Na)^+$ found 285.1831, calcd 285.1825

(4*S*, 5*R*)-5-(Benzyloxy)dec-1-en-4-yl 4-nitrobenzoate 31:



To a stirred solution of alcohol **30** (1.0 g, 3.8 mmol) in dry toluene (15 mL) were added PPh_3 (0.393 g, 15.2 mmol), *p*-nitrobenzoic acid (PNBA) (0.143 g, 19.0 mmol) and diisopropylazodicarboxylate (DIAD) (0.29 ml, 15.2 mmol) at 0 °C and it was stirred for 2h at rt. Toluene was concentrated and crude product was purified by silica gel column chromatography using EtOAc-petroleum ether, (3:97) as eluent to furnish **31** as a yellow colour oil.

Yield: 1.5 g, 97%

Mol. Formula: $C_{24}H_{29}O_5\,N$

$[\alpha]_D^{28.9}$: +9.13° (*c* 1.18, $CHCl_3$)

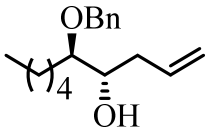
IR (neat, cm^{-1}): ν_{max} 3074, 3027, 2937, 2863, 1724, 1643, 1641, 1530, 1456, 1348, 1275

^{1}H NMR (400MHz, $CDCl_3$) δ = 8.32 - 8.26 (m, *J* = 8.8 Hz, 2 H), 8.22 - 8.16 (m, *J* = 8.8 Hz, 2 H), 7.38 - 7.27 (m, 5 H), 5.82 (tdd, *J* = 7.0, 10.0, 17.1 Hz, 1 H), 5.41 (td, *J* = 4.0, 8.4 Hz, 1 H), 5.17 - 5.04 (m, 2 H), 4.70 (d, *J* = 11.5 Hz, 1 H), 4.55 (d, *J* = 11.5 Hz, 1 H), 3.64 (td, *J* = 3.7, 7.8 Hz, 1 H), 2.66 - 2.56 (m, 1 H), 2.56 - 2.48 (m, 1 H), 1.73 - 1.48 (m, 4 H), 1.46 - 1.29 (m, 4 H), 0.89 (t, *J* = 6.8 Hz, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 164.2, 150.5, 138.2, 135.8, 133.6, 130.7, 128.4, 127.9, 127.7, 123.5, 118.1, 79.6, 75.7, 72.4, 34.2, 31.8, 30.5, 25.3, 22.5, 14.0

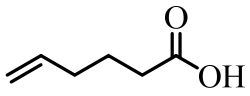
HRMS (ESI) for $C_{24}H_{29}O_5\,N\,(M + Na)^+$ found 434.1949, calcd 434.1938

Conversion of nitrobenzoate 31 to alcohol fragment 19:



To a stirred solution of *p*-nitrobenzoate ester **31** (1.1 g, 2.6 mmol) in THF:MeOH:H_2O (3:2:1, 12 mL) was added LiOH.H_2O (0.168 g, 4.0 mmol) and stirred at rt for 1h. After completing the starting material (monitored by TLC), reaction was quenched with water and extracted with EtOAc (3 x 10 ml). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuum. The crude was purified by column chromatography using an eluent EtOAc-petroleum ether, (5:95) to give **19** as colourless oil (659 mg, 95%).

Hex-5-enoic acid 32:



To a stirred solution of cyclohexanone (20.0 g, 203.7 mmol) in MeOH (20 mL), hydrogen peroxide (46 mL, 407.4 mmol) was added slowly at rt. The mixture was then added to a stirred solution of $FeSO_4.7H_2O$ (56.7 g, 203.7 mmol) and $CuSO_4.5H_2O$ (51 g, 203.7 mmol) in water (370 mL), maintaining the reaction temperature at 18-20 °C. The aqueous phase was separated and extracted with Et_2O (3 x 40 mL). The combined Et_2O extracts were washed with 20% NaOH (3 x 20 mL). The alkaline extract was acidified with 20% H_2SO_4 to pH 2 and extracted with Et_2O (3 x 40 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (EtOAc–petroleum ether, 10:90) to afford compound **32** as colourless oil.

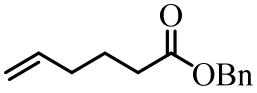
Yield: 14.4 g, 62%

Mol. Formula: $C_6H_{10}O_2$

IR (neat, cm^{-1}): ν_{max} 3077, 2933, 2670, 1711, 1420, 1251, 1110

^{1}H NMR (200MHz, $CDCl_3$) δ = 5.95 - 5.67 (m, 1 H), 5.14 - 4.96 (m, 2 H), 2.45 - 2.33 (m, 2 H), 2.13 (q, *J* = 7.1 Hz, 2 H), 1.75 (quin, *J* = 7.4 Hz, 2 H)

Benzyl hex-5-enoate 20:



To a stirred solution of compound **20** (4.0 g, 35.04 mmol), in DMF (50 mL), K_2CO_3 (12.1 g, 87.6 mmol) was added under argon atmosphere at 0 °C. After 10 min stirring at 0 °C, BnBr (6.2 mL, 52.5 mmol) was added to the reaction mixture and stirred for 2h at rt. After completion of reaction, cold water was added into the reaction mixture and extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (EtOAc-petrolium ether, 5:95) to yield the title compound **32** as colourless oil.

Yield: 6.8 g, 95%

Mol. Formula: $C_{13}H_{16}O_2$

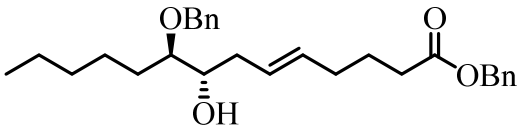
IR (neat, cm^{-1}): ν_{max} 3074, 2940, 1737, 1638, 1596, 1451, 1234, 1162, 1111

^{1}H NMR (200MHz, $CDCl_3$) δ = 7.47 - 7.32 (m, 5 H), 5.91 - 5.65 (m, 1 H), 5.13 (s, 2 H), 5.09 - 4.94 (m, 2 H), 2.39 (t, *J* = 7.5 Hz, 2 H), 2.10 (q, *J* = 7.3 Hz, 2 H), 1.88 - 1.65 (m, 2 H)

^{13}C NMR (50MHz, $CDCl_3$) δ = 173.4, 137.6, 136.0, 128.5, 128.2, 115.4, 66.1, 33.5, 33.0, 24.0

HRMS (ESI) for $C_{13}H_{16}O_2$ $(M + Na)^+$ found 227.1047, calcd 227.1043

Benzyl (8*S*, 9*R*, *E*)-9-(benzyloxy)-8-hydroxytetradec-5-enoate 18:



To a stirred solution of **19** (600 mg, 2.28 mmol) in CH_2Cl_2 (7.0 mL) was added compound **20** (2.3 g, 11.44 mmol) and degassed for 15 min. Then Grubb's II catalyst (290 mg, 15 mol %) was added to the reaction mixture and stirred for 16h at rt. After completion of reaction, solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (EtOAc–petroleum ether, 8:92) to afford compound **18** as yellow colour oil

Yield: 700 mg, 70%

Mol. Formula: $C_{28}H_{38}O_4$

$[\alpha]_D^{28.9}$: -1.11° (*c* 1.64, $CHCl_3$)

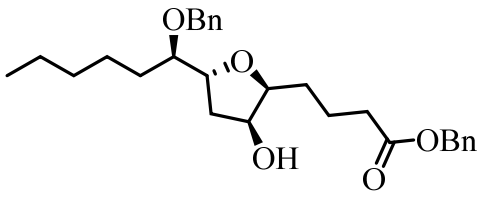
IR (neat, cm^{-1}): ν_{max} 3456, 3030, 2930, 2861, 1734, 1598, 1454, 1378, 1219, 1155, 1083

^1H NMR (400MHz, $CDCl_3$) δ = 7.42 - 7.28 (m, 10 H), 5.56 - 5.40 (m, 2 H), 5.15 - 5.10 (m, 2 H), 4.64 - 4.53 (m, 2 H), 3.82 - 3.72 (m, 1 H), 3.45 - 3.33 (m, 1 H), 2.41 - 2.34 (m, 2 H), 2.29 - 2.16 (m, 2 H), 2.14 - 2.01 (m, 2 H), 1.92 - 1.84 (m, 1 H), 1.74 (quin, *J* = 7.5 Hz, 2 H), 1.68 - 1.57 (m, 1 H), 1.54 - 1.45 (m, 2 H), 1.36 - 1.28 (m, 5 H), 0.89 (t, *J* = 6.8 Hz, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 173.4, 138.5, 136.0, 132.5, 131.4, 128.5, 128.4, 128.2, 127.8, 127.6, 127.4, 126.7, 81.7, 72.1, 71.6, 66.1, 35.6, 33.6, 32.0, 31.9, 29.1, 25.2, 24.5, 22.6, 14.0

HRMS (ESI) for $C_{28}H_{38}O_4$ $(M + Na)^+$ found 461.2672, calcd 461.2662

Benzyl 4-((2*S*, 3*S*, 5*R*)-5-((*R*)-1-(benzyloxy)hexyl)-3-hydroxytetrahydrofuran-2-yl)butanoate 17:



To a stirred solution of compound **18** (72 mg, 0.164 mmol) in dry CH_2Cl_2 was added triethylamine (0.057 ml, 0.41 mmol), followed by slow addition of mesyl chloride (0.018 ml, 0.246 mmol) at 0 °C, with further stirring for 15 min at the room temperature. The reaction mixture was quenched with addition of cold water at 0 °C. The two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with water (3 x 5 mL), brine, dried over Na_2SO_4 and concentrated to give crude mesylate.

To a mixture of $K_3Fe(CN)_6$ (0.192 g, 0.580 mmol), K_2CO_3 (0.081 g, 0.58 mmol) and $(DHQ)_2PHAL$ (1.5 mg, 0.002 mmol, 1 mol%) in *t*-BuOH–H_2O (1:1, 10 mL) at 0 °C was added osmium tetroxide (95 μL, 0.1 M solution in toluene, 5 mol%), followed by methane

sulfonamide (0.079 g, 0.83 mmol). After stirring for 5 min at 0 °C, the crude mesylate (0.100 g, 0.19 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 24h and then quenched with solid sodium sulfite (286 mg, 1.48 mg/mmol). Stirring was continued for an additional 15 min and then the solution was extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give the crude diol.

The crude diol was refluxed in pyridine as a solvent at 150 °C for 16h. After completion of the reaction 10% $CuSO_4.5H_20$ solution was added to the reaction mixture and extracted with EtOAc. The combined organic layers were washed with water (2 x 5 mL), brine, dried over Na_2SO_4 and concentrated to give crude cyclized compound. The crude material was purified by flash column chromatography (EtOAc–petroleum ether, 15:85) to afford compound **17** as colourless oil.

Yield: 59 mg, 80%

Mol. Formula: $C_{28}H_{38}O_5$

$[\alpha]_D^{24.8}$: +15.2° (*c* 1.49, $CHCl_3$)

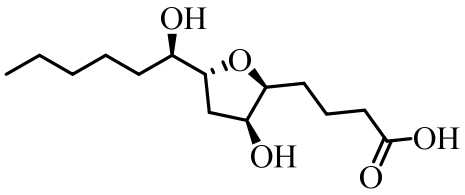
IR (neat, cm^{-1}): ν_{max} 3441, 2928, 2861, 1733, 1455, 1249, 1161, 1083

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.38 - 7.28 (m, 10 H), 5.13 (s, 2 H), 4.70 (d, *J* = 11.7 Hz, 1 H), 4.63 (d, *J* = 11.7 Hz, 1 H), 4.32 (td, *J* = 6.2, 9.1 Hz, 1 H), 4.27 (t, *J* = 2.9 Hz, 1 H), 3.81 (dt, *J* = 2.6, 6.5 Hz, 1 H), 3.34 - 3.28 (m, 1 H), 2.53 - 2.38 (m, 2 H), 2.05 - 1.83 (m, 5 H), 1.83 - 1.57 (m, 6 H), 1.53 - 1.41 (m, 4 H), 0.88 (s, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 173.7, 139.0, 135.9, 128.5, 128.2, 127.9, 127.4, 82.1, 81.1, 79.3, 72.9, 72.7, 66.3, 37.5, 33.9, 32.0, 30.6, 28.4, 25.3, 22.6, 21.3, 14.0

HRMS (ESI) for $C_{28}H_{38}O_5$ $(M + Na)^+$ found 477.2621, calcd 477.2611

(+)-Petromyroxol 1:



To a stirred solution of **17** (14 mg, 0.03 mmol) in EtOH (3 mL) was added 10% w/w Pd/C (2 mg, 0.1 w/w) and the mixture was stirred for 3h under H_2 atmosphere. Then, the Pd/C was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (MeOH:CH_2Cl_2, 15:85) to afford compound **1** as a colourless liquid.

Yield: 8 mg, 95%

Mol. Formula: $C_{14}H_{26}O_5$

$[\alpha]_D^{25.9}$: +8.5° (*c* 0.64, $CHCl_3$) {(lit[3]. $[\alpha]_D^{25}$ = +17° (*c* 0.36, $CHCl_3$)}

IR (neat, cm^{-1}): ν_{max} 3400, 2935, 2861, 1710, 1408, 1248, 1072, 1065.

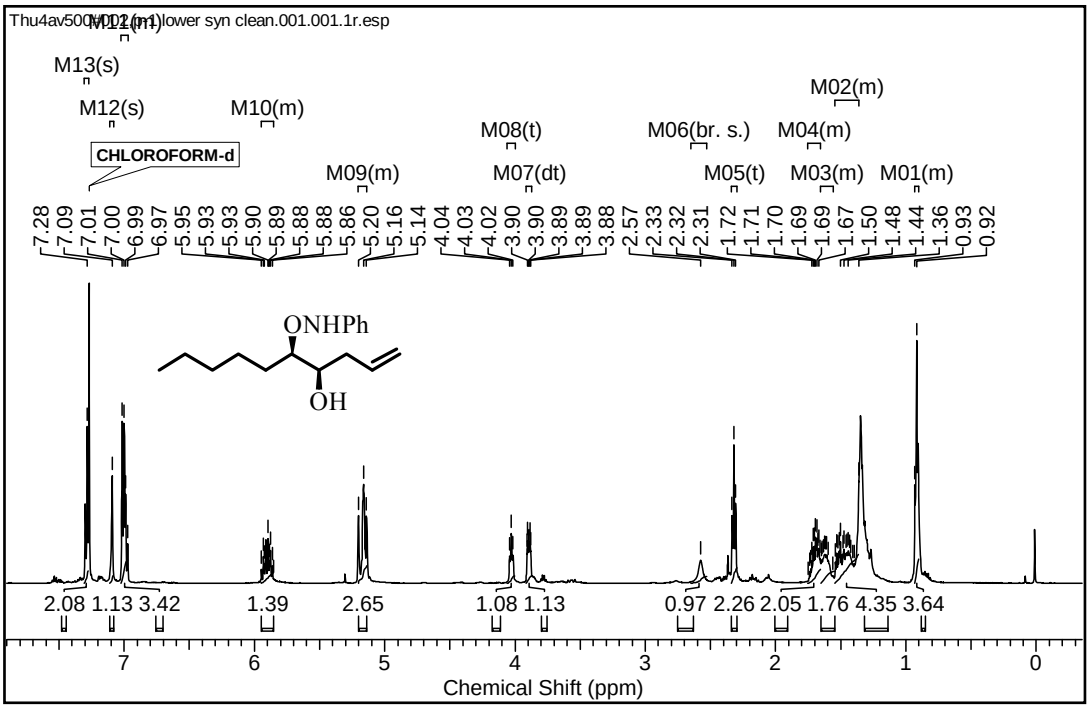
^{1}H NMR (500MHz, $CDCl_3$) δ = 4.32 - 4.27 (m, 1 H), 4.10 - 4.04 (m, 1 H), 3.82 - 3.77 (m, 1 H), 3.43 - 3.37 (m, 1 H), 2.49 - 2.37 (m, 2 H), 2.04 (dd, *J* = 6.6, 13.3 Hz, 1 H), 1.89 (ddd, *J* = 4.6, 9.1, 13.5 Hz, 1 H), 1.80 - 1.63 (m, 4 H), 1.55 - 1.47 (m, 1 H), 1.44 - 1.28 (m, 7 H), 0.89 (t, *J* = 6.9 Hz, 3 H)

^{13}C NMR (125MHz, $CDCl_3$) δ = 177.7, 82.4, 80.5, 74.1, 73.3, 37.6, 33.5, 33.1, 31.8, 28.2, 25.2, 22.6, 21.2, 14.0

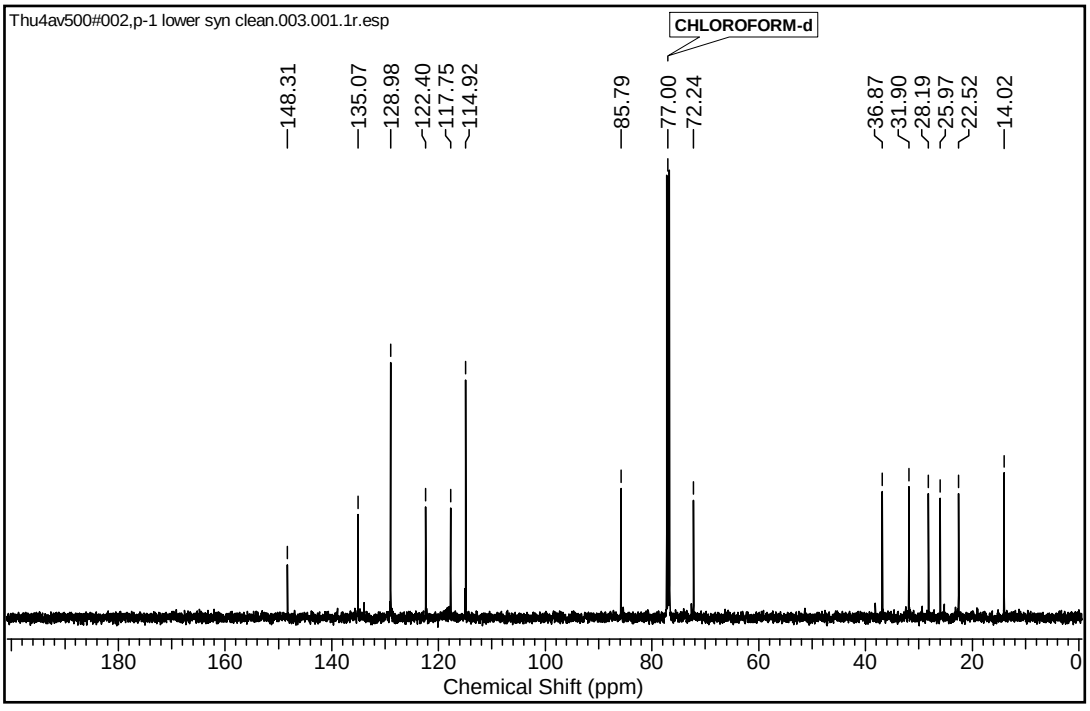
HRMS (ESI) for $C_{14}H_{26}O_5$ $(M + Na)^+$ found 297.1678, calcd 297.1672

1.2.8. Spectra:

(4*R*, 5*R*)-5-((Phenylamino)oxy)dec-1-en-4-ol 23:

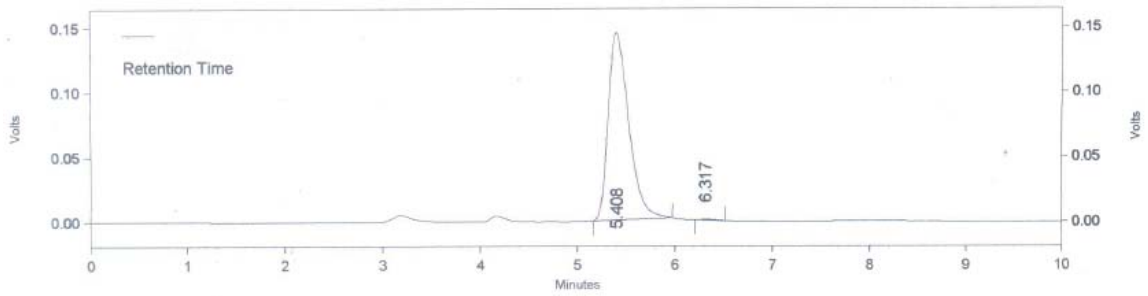


- **^{1}H NMR of the compound 23 in $CDCl_3$**



- **^{13}C NMR of the compound 23 in $CDCl_3$**

HPLC (*ee*) of the compound (4*R*,5*R*)-5-((phenylamino)oxy)dec-1-en-4-ol 23:

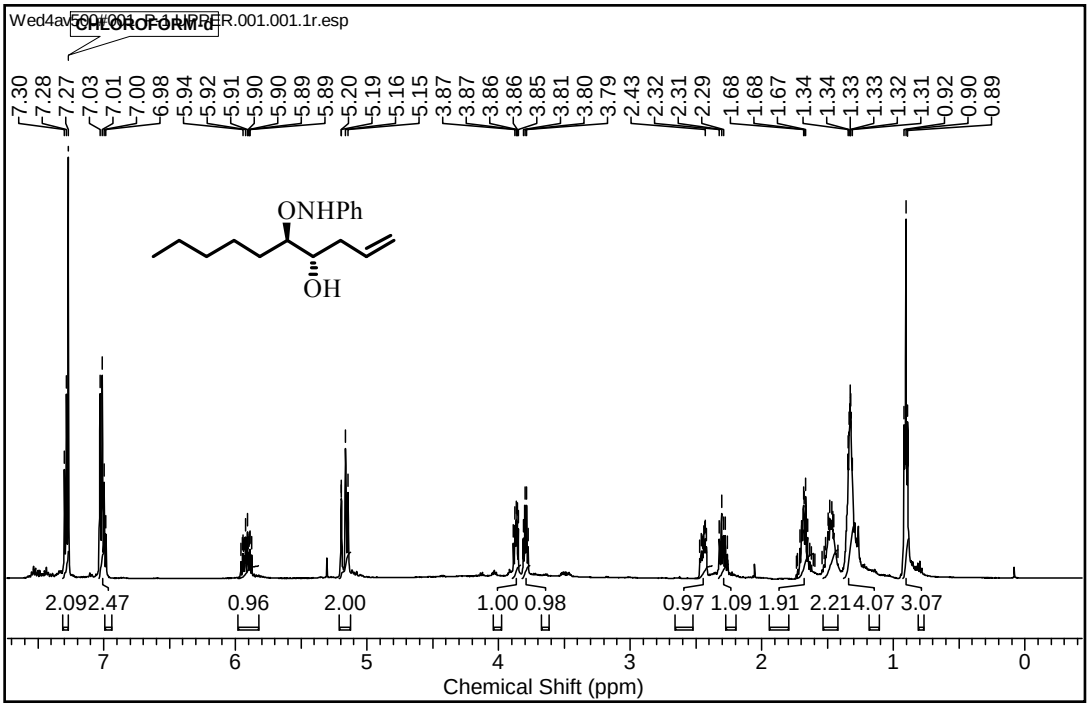


Detector A - 1 (230nm)

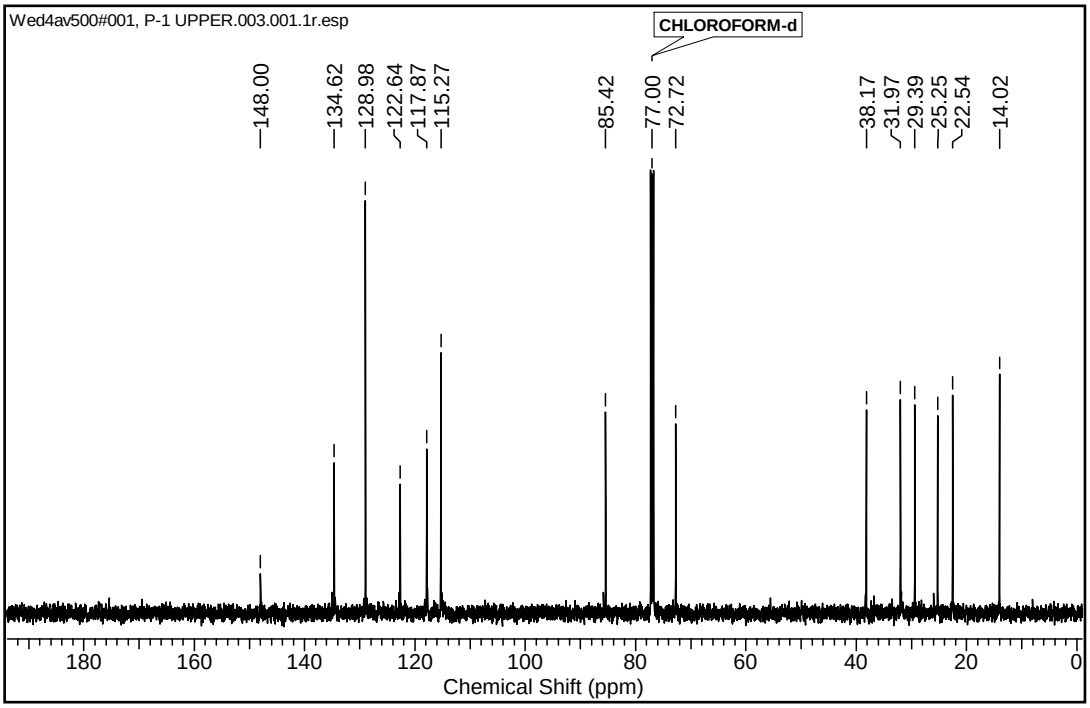
Pk #	Retention Time	Area	Area %
1	5.408	2119412	99.713
2	6.317	6108	0.287
Totals		2125520	100.000

Project Leader :Dr.Tripathi P.K.
Column :Chiralcel OD-H (250mm x 4.6mm)
Mobile Phase :IPA:n-Hexane (10 : 90)
Wavelength : 230nm
Flow Rate :1mL/min (620psi)
Conc. : 1mg/1ml
Inj vol- : 2uL

(4*S*,5*R*)-5-((Phenylamino)oxy)dec-1-en-4-ol 24:

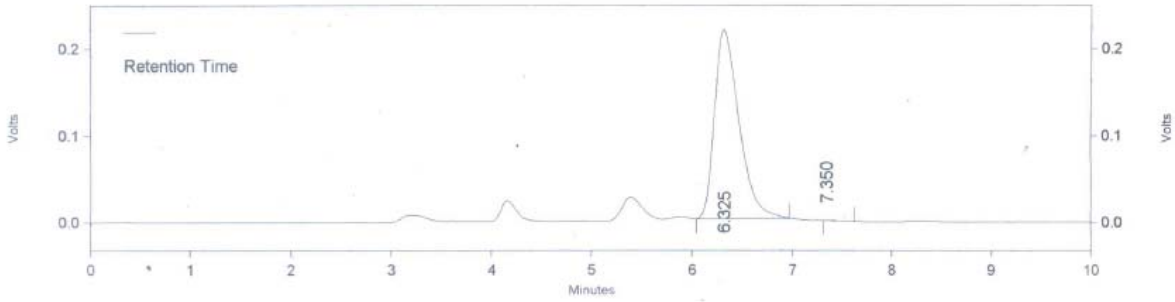


- **^{1}H NMR of the compound 24 in $CDCl_3$**



- **^{13}C NMR of the compound 24 in $CDCl_3$**

HPLC (*ee*) of the compound (4*S*,5*R*)-5-((phenylamino)oxy)dec-1-en-4-ol 24:

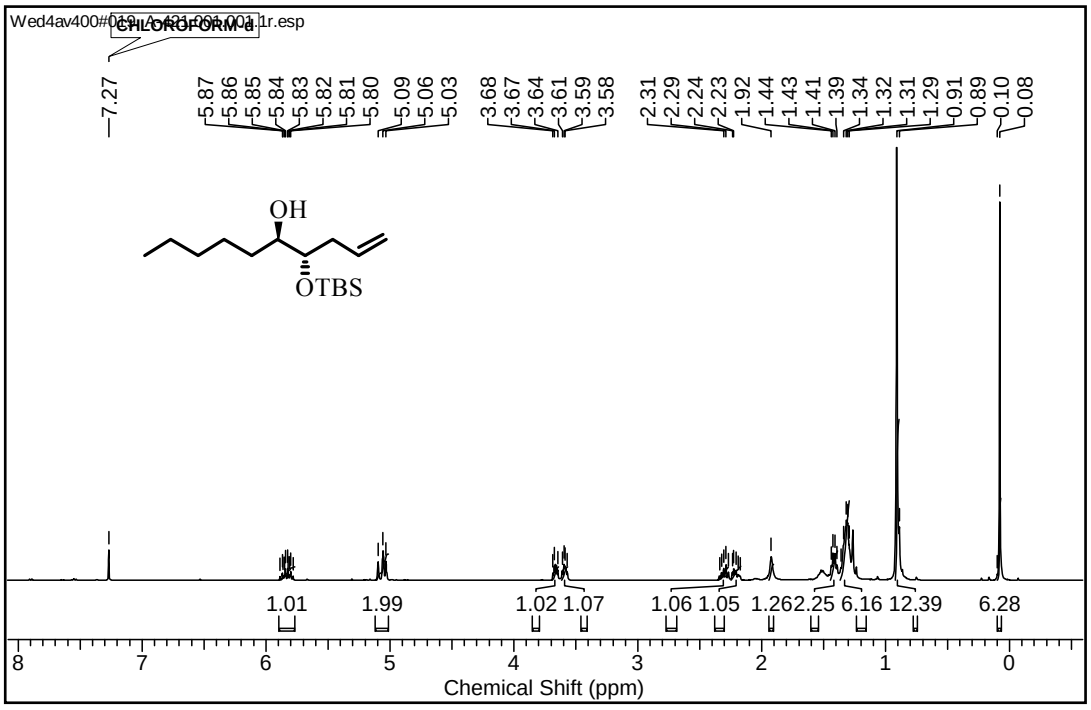


Detector A - 1 (230nm)

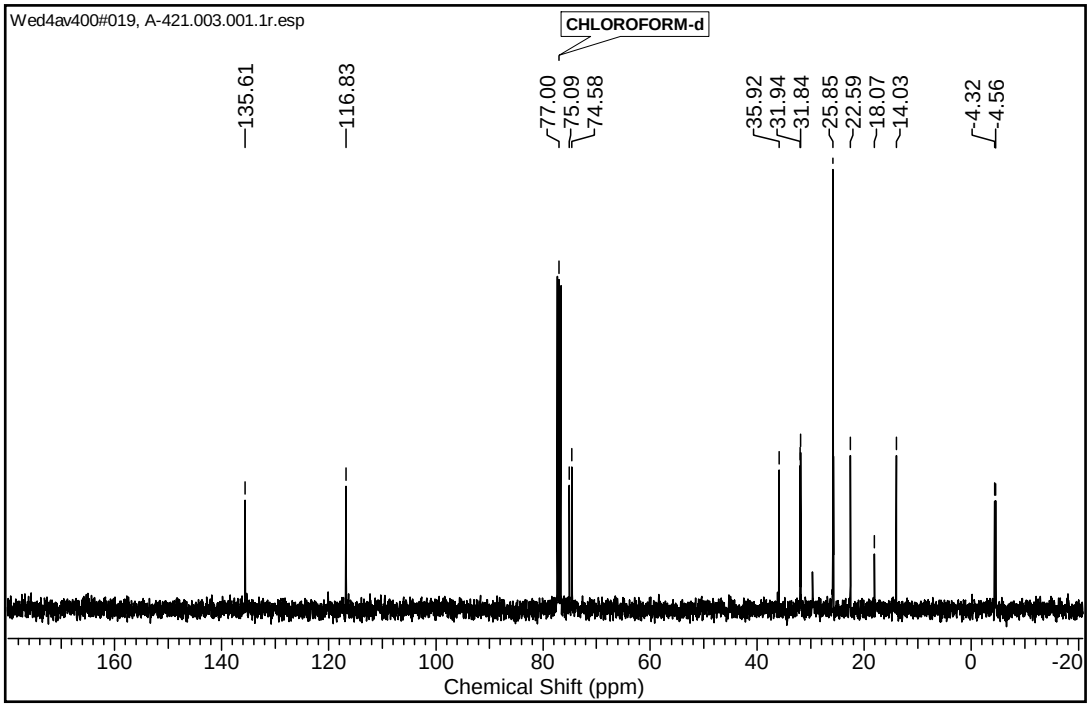
Pk #	Retention Time	Area	Area %
1	6.325	3693207	99.915
2	7.350	3129	0.085
Totals		3696336	100.000

Project Leader :Dr.Tripathi P.K.
Column :Chiralcel OD-H (250mm x 4.6mm)
Mobile Phase :IPA:n-Hexane (10 : 90)
Wavelength : 230nm
Flow Rate :1mL/min (620psi)
Conc. : 1mg/1ml
Inj vol- : 2uL

(4*S*,5*R*)-4-((Tert-butyldimethylsilyl)oxy)dec-1-en-5-ol 25:

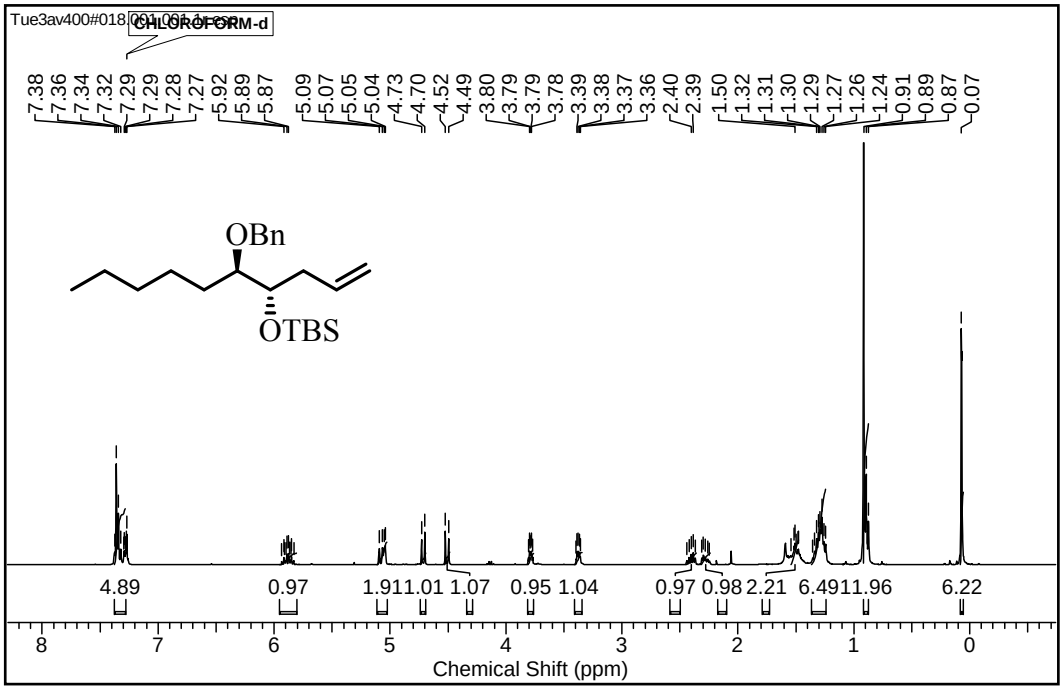


- **^{1}H NMR of the compound 25 in $CDCl_3$**

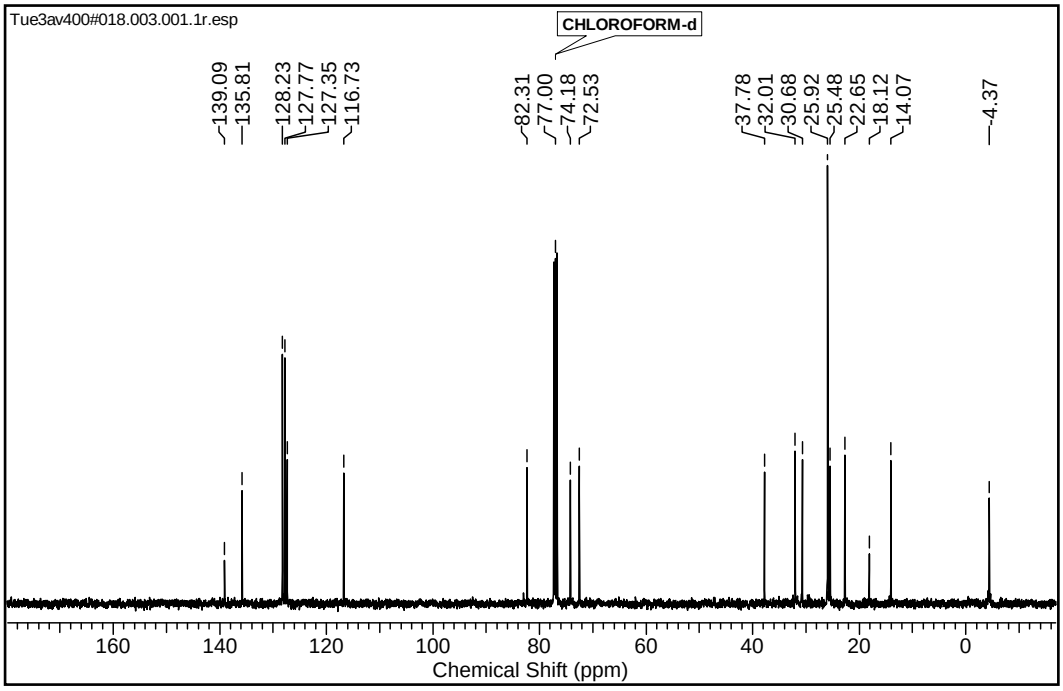


- **^{13}C NMR of the compound 25 in $CDCl_3$**

(((4*S*,5*R*)-5-(Benzyloxy)dec-1-en-4-yl)oxy)(*tert*-butyl) dimethylsilane 26:

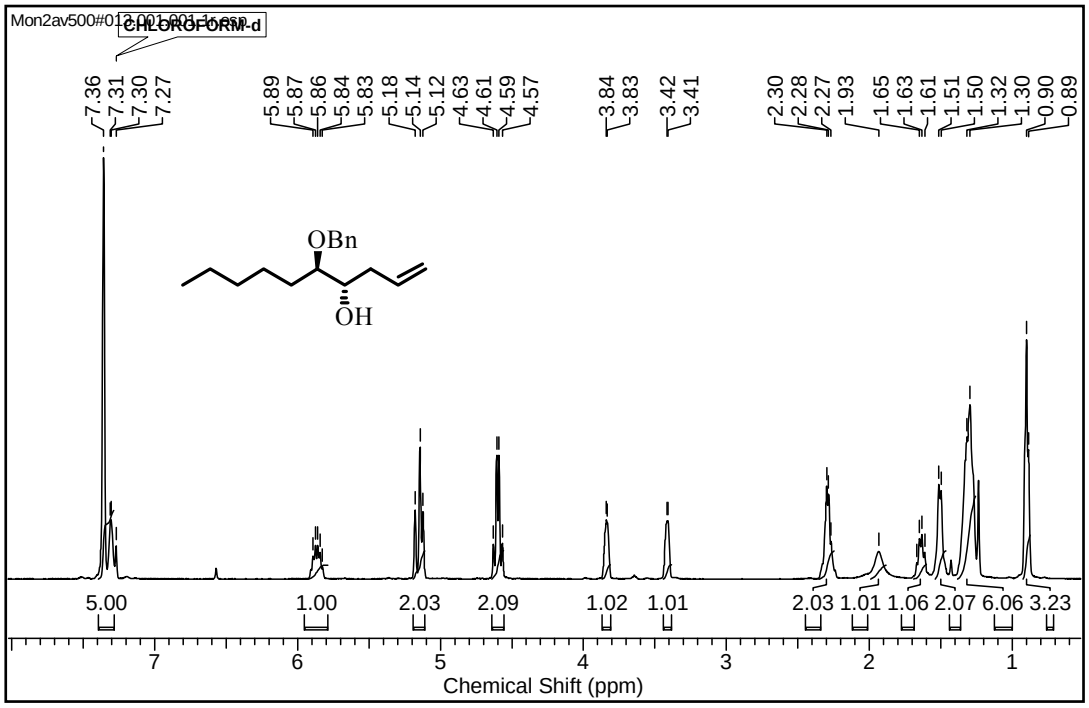


- **^{1}H NMR of the compound 26 in $CDCl_3$**

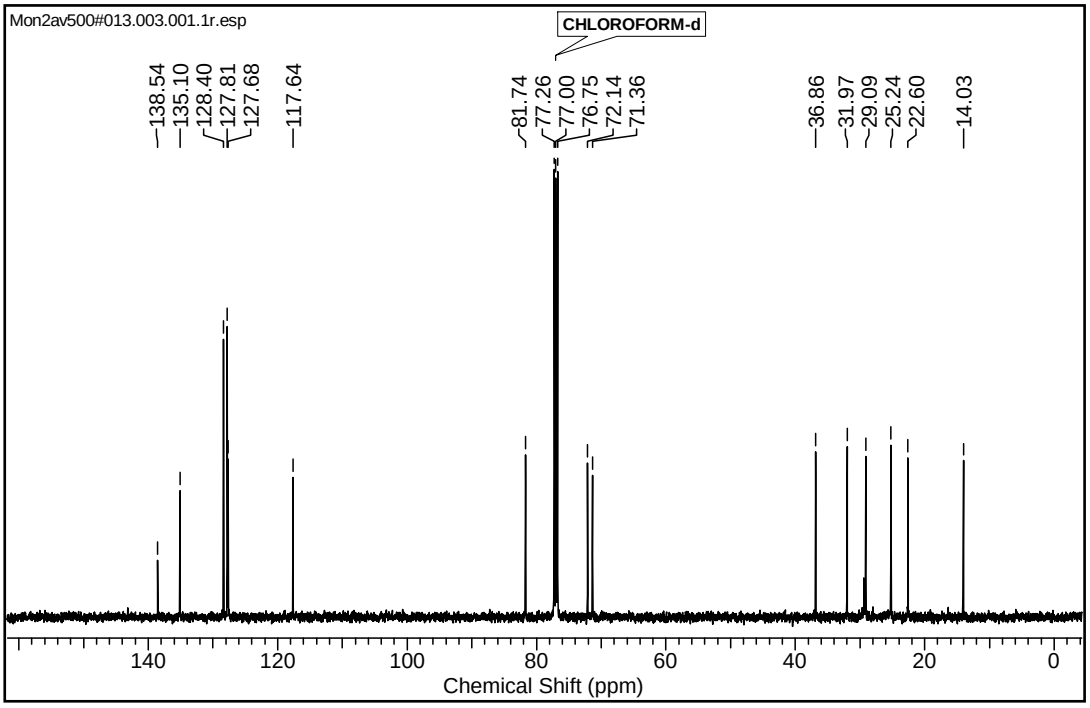


- **^{13}C NMR of the compound 26 in $CDCl_3$**

(4*S*,5*R*)-5-(Benzyloxy)dec-1-en-4-ol 19:

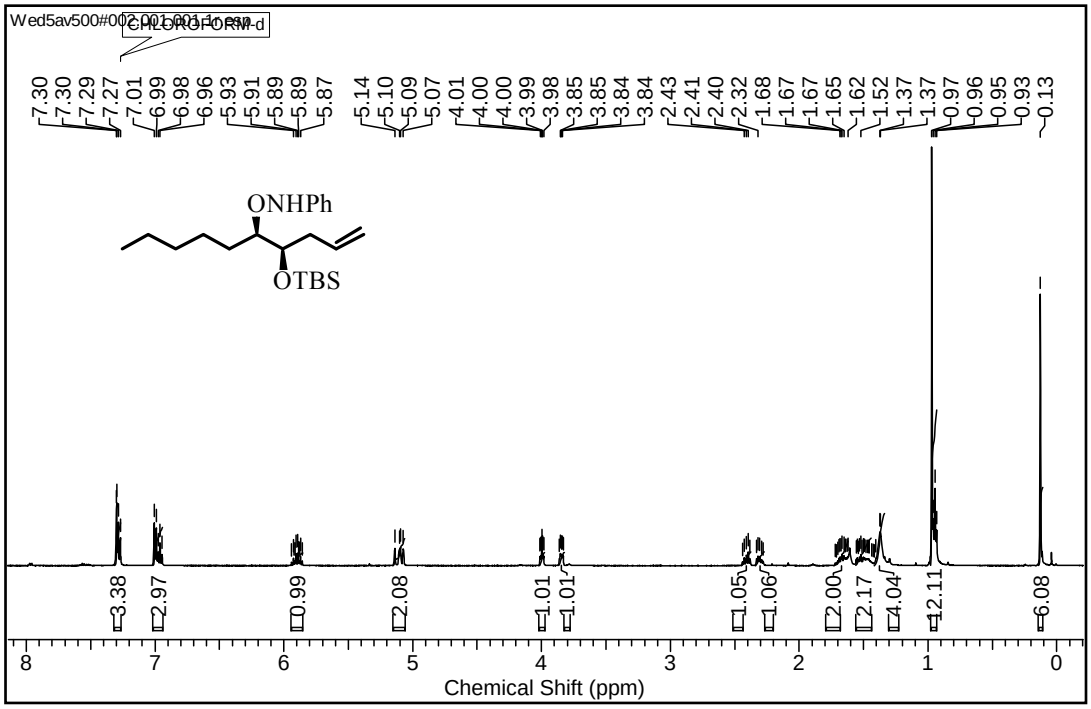


➢ **^{1}H NMR of the compound 19 in $CDCl_3$**

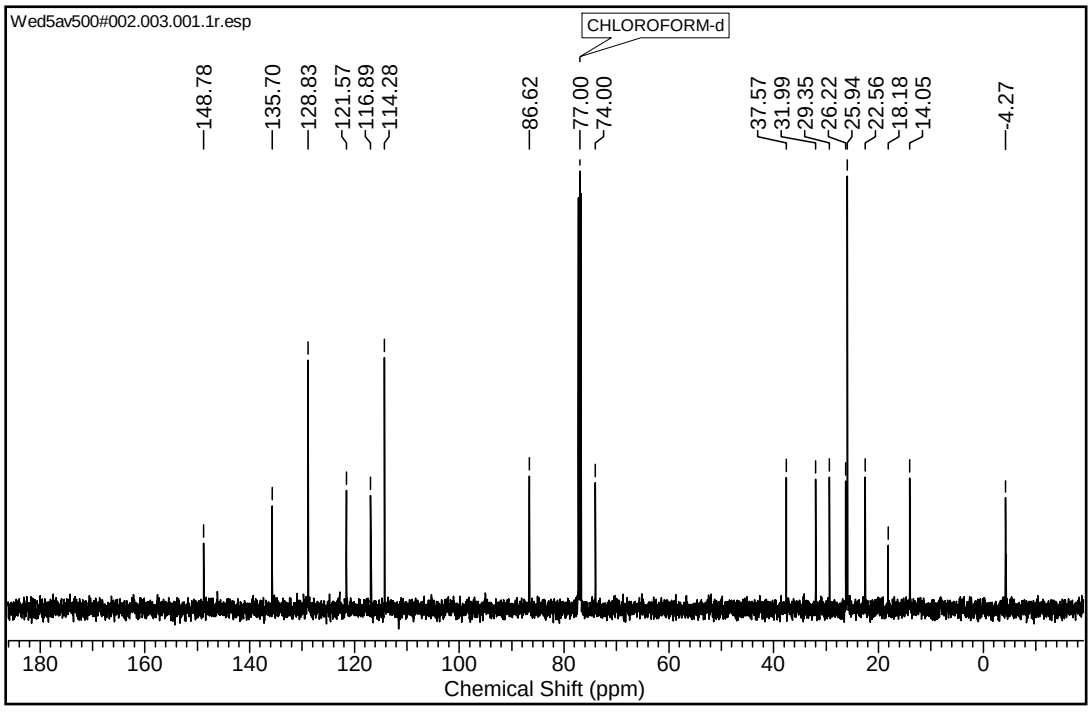


➢ **^{13}C NMR of the compound 19 in $CDCl_3$**

O-((4*R*,5*R*)-4-((Tert-butyldimethylsilyl)oxy)dec-1-en-5-yl)-N-phenylhydroxylamine 27:

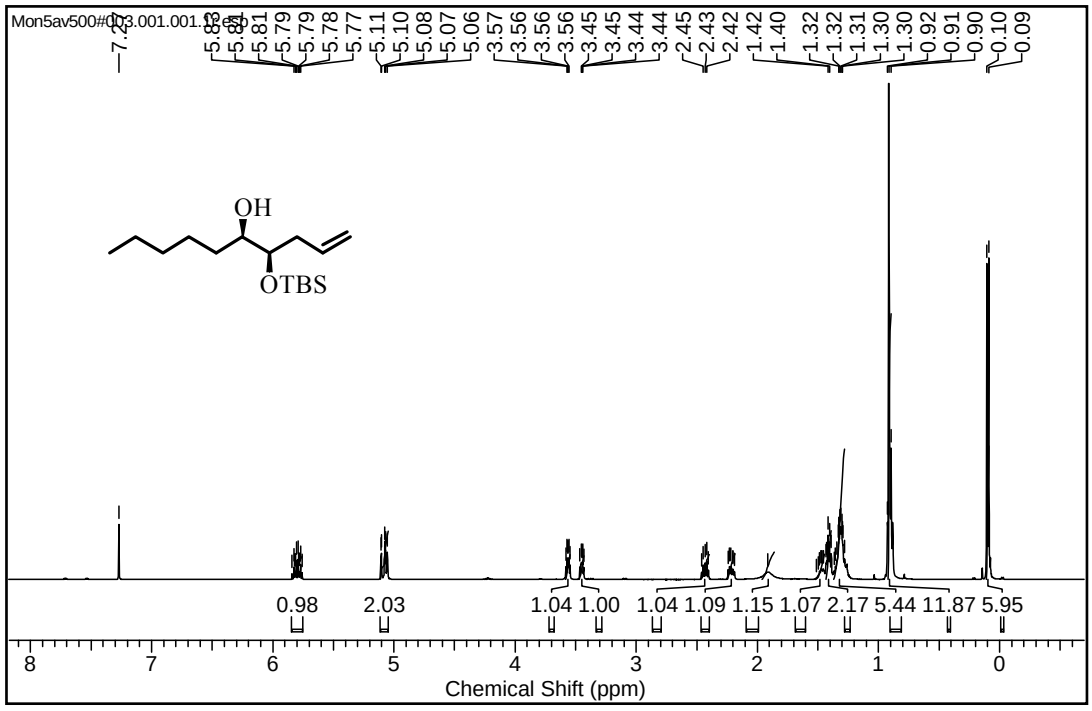


- **^{1}H NMR of the compound 27 in $CDCl_3$**

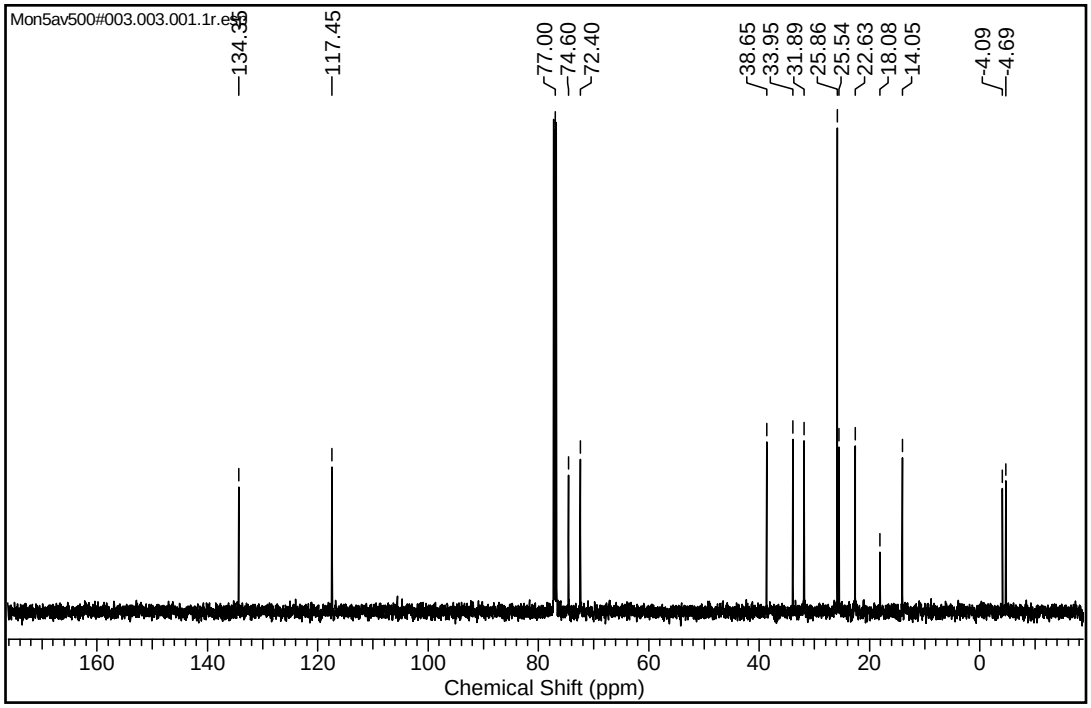


- **^{13}C NMR of the compound 27 in $CDCl_3$**

(4*R*,5*R*)-4-((Tert-butyldimethylsilyl)oxy)dec-1-en-5-ol 28:

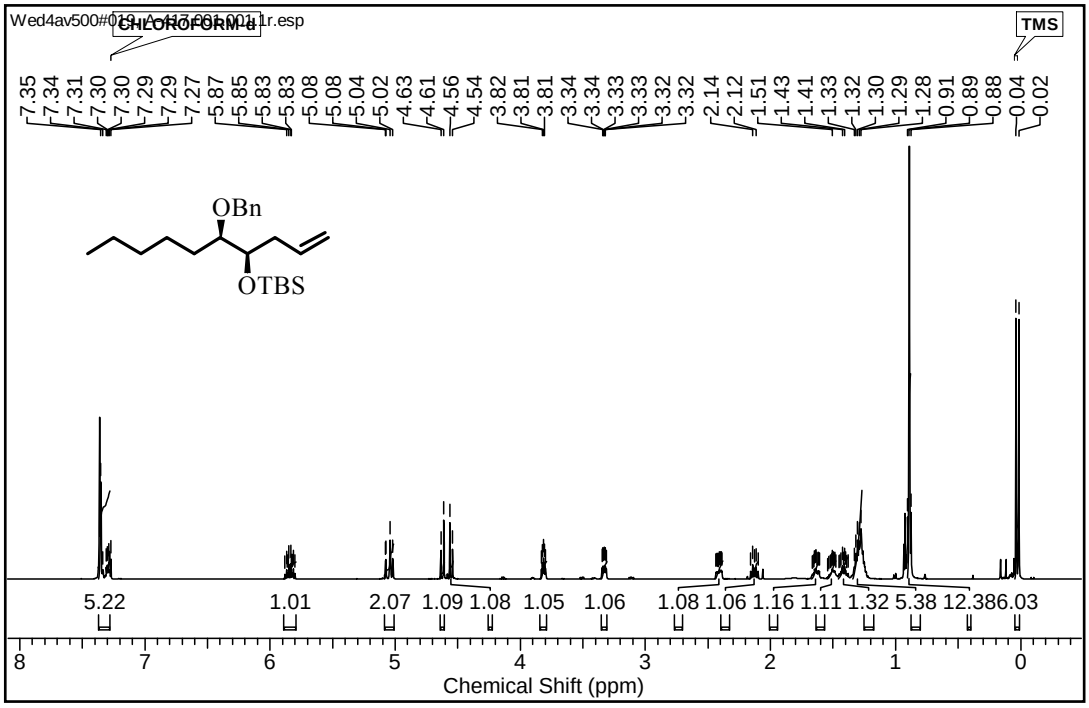


- **^{1}H NMR of the compound 28 in $CDCl_3$**

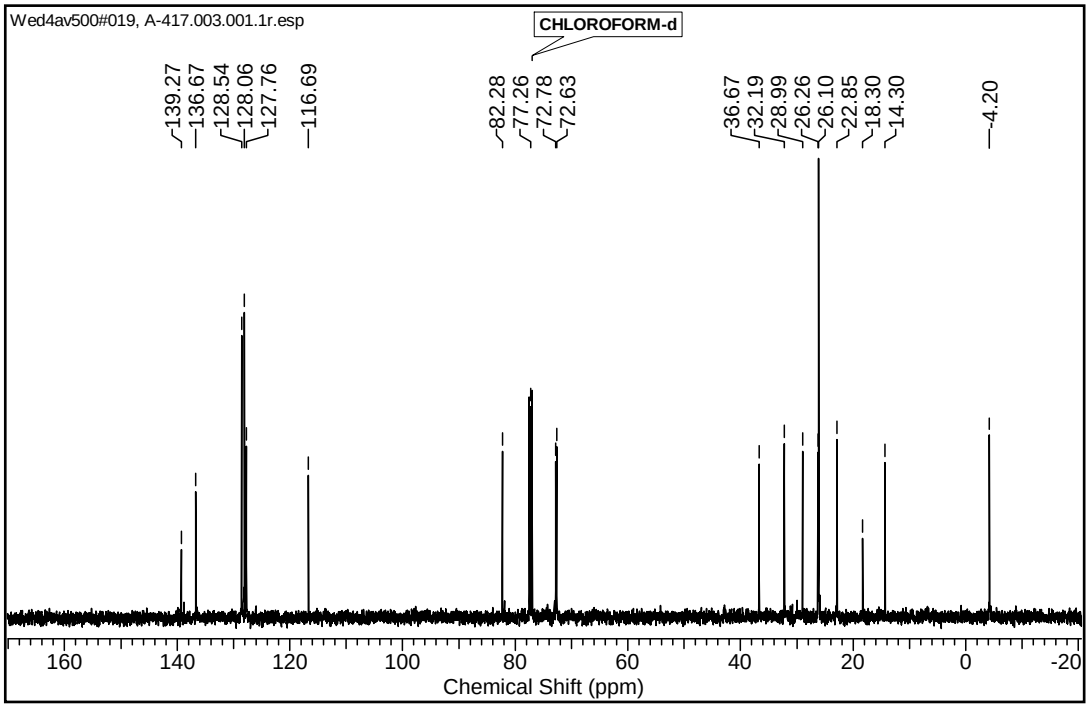


- **^{13}C NMR of the compound 28 in $CDCl_3$**

(((4*R*,5*R*)-5-(Benzyloxy)dec-1-en-4-yl)oxy)(tert-butyl)dimethylsilane 29:

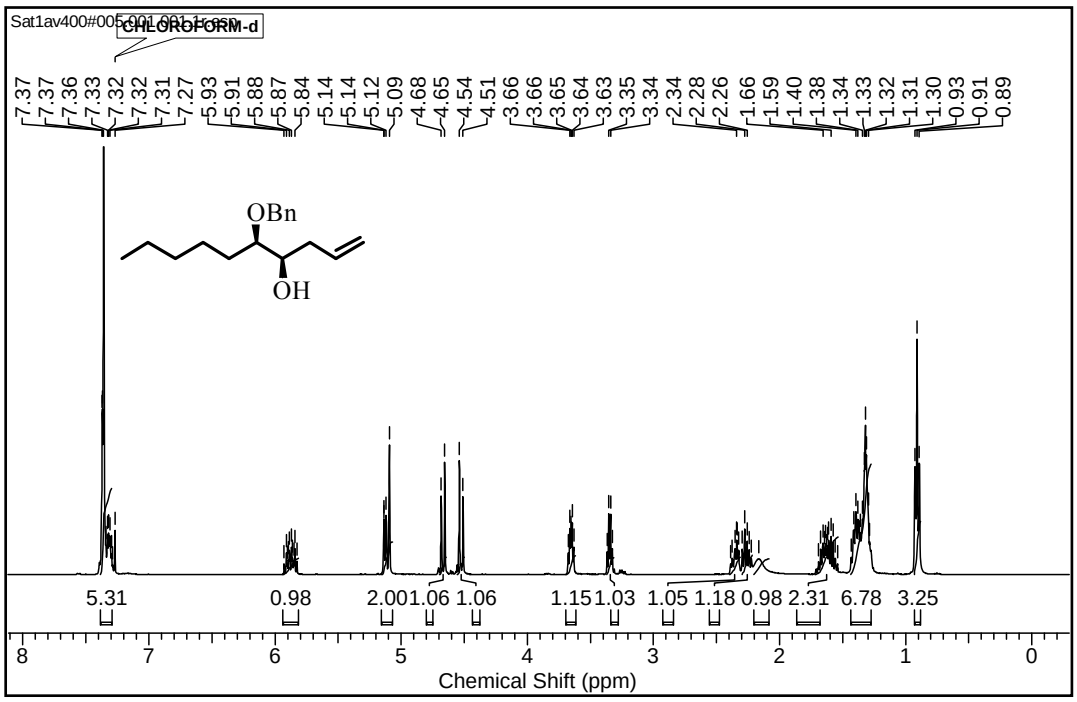


- **^{1}H NMR of the compound 29 in $CDCl_3$**

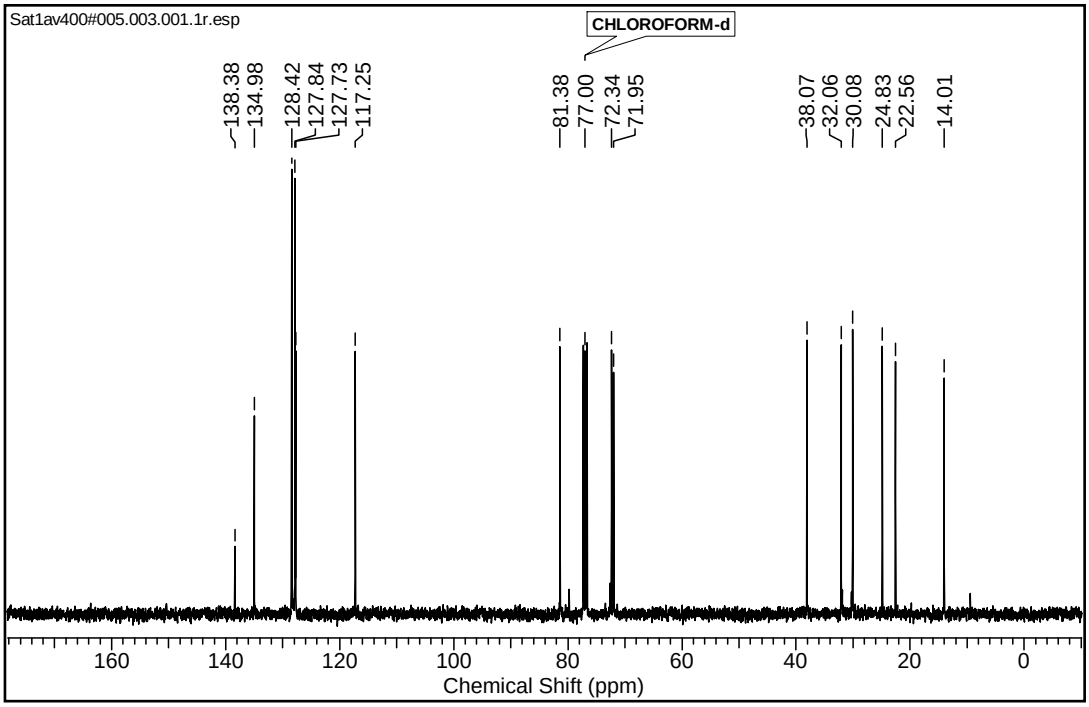


- **^{13}C NMR of the compound 29 in $CDCl_3$**

(4*R*,5*R*)-5-(Benzyloxy)dec-1-en-4-ol 30:

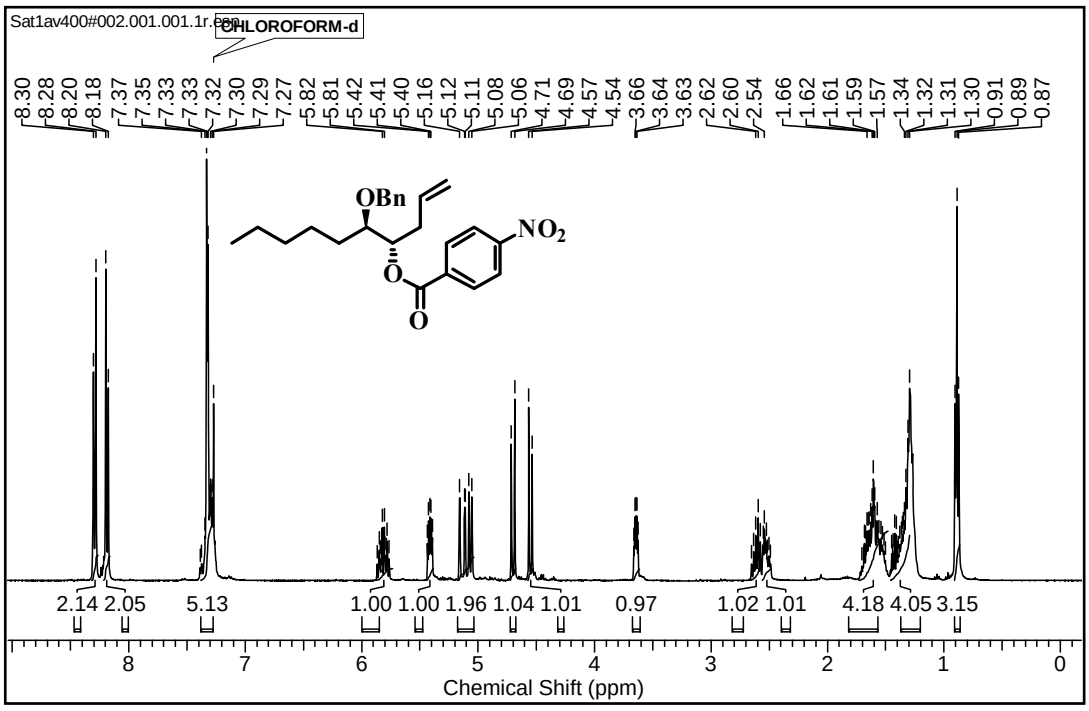


- **^{1}H NMR of the compound 30 in $CDCl_3$**

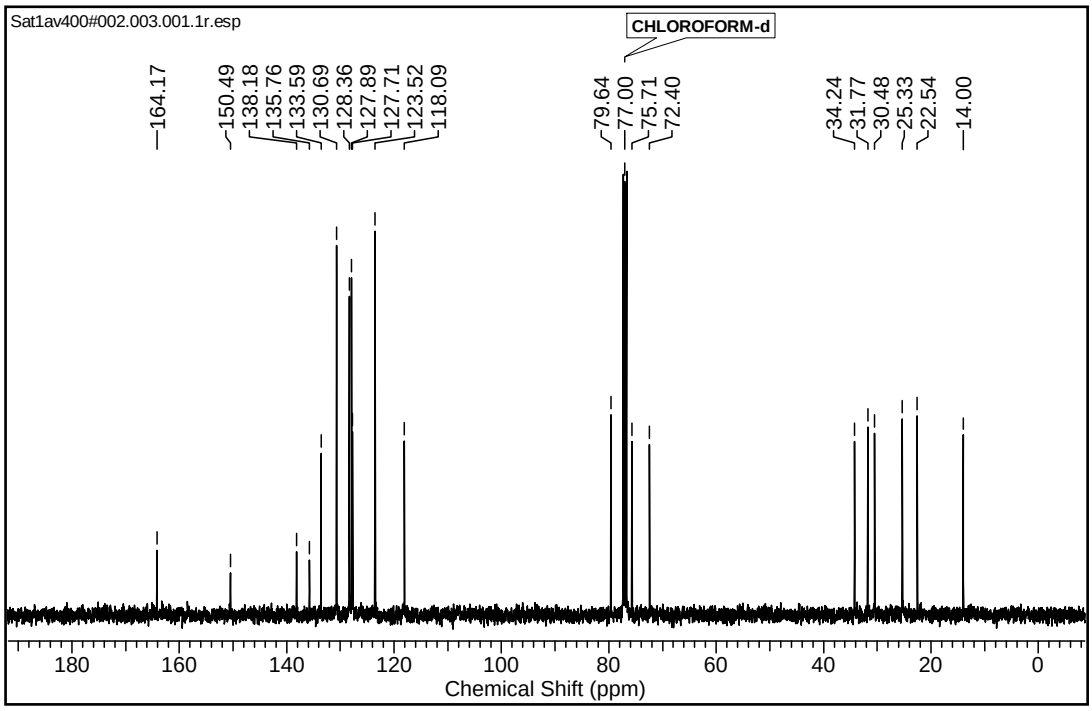


- **^{13}C NMR of the compound 30 in $CDCl_3$**

(4*S*,5*R*)-5-(Benzyloxy)dec-1-en-4-yl 4-nitrobenzoate 31:

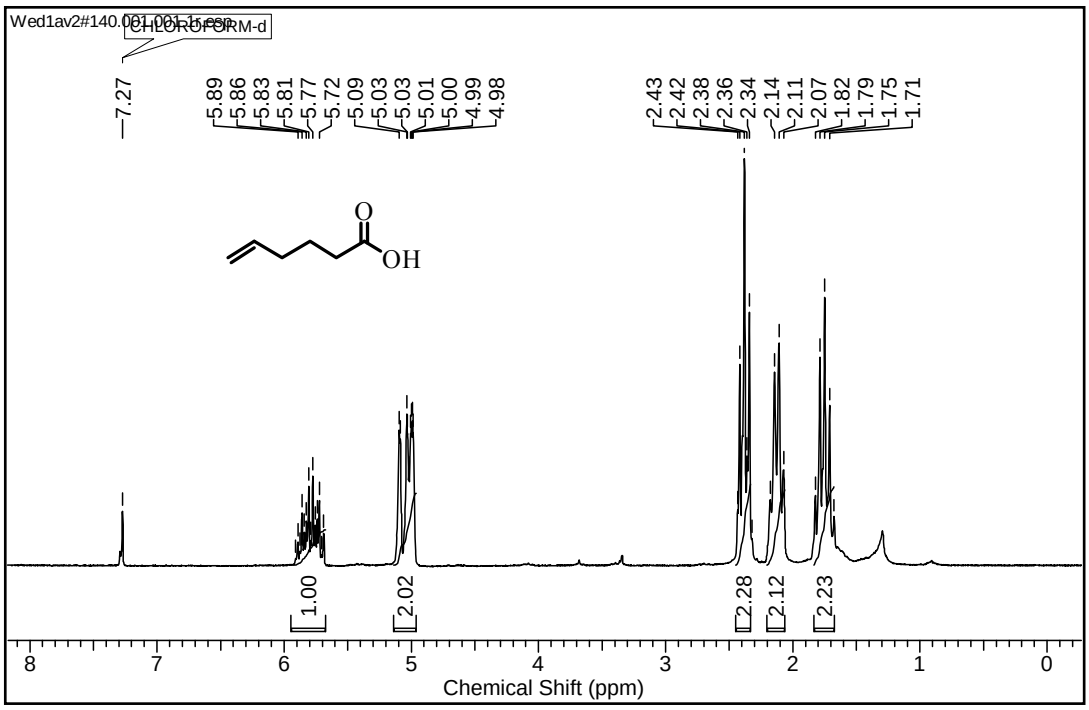


- **^{1}H NMR of the compound 31 in $CDCl_3$**



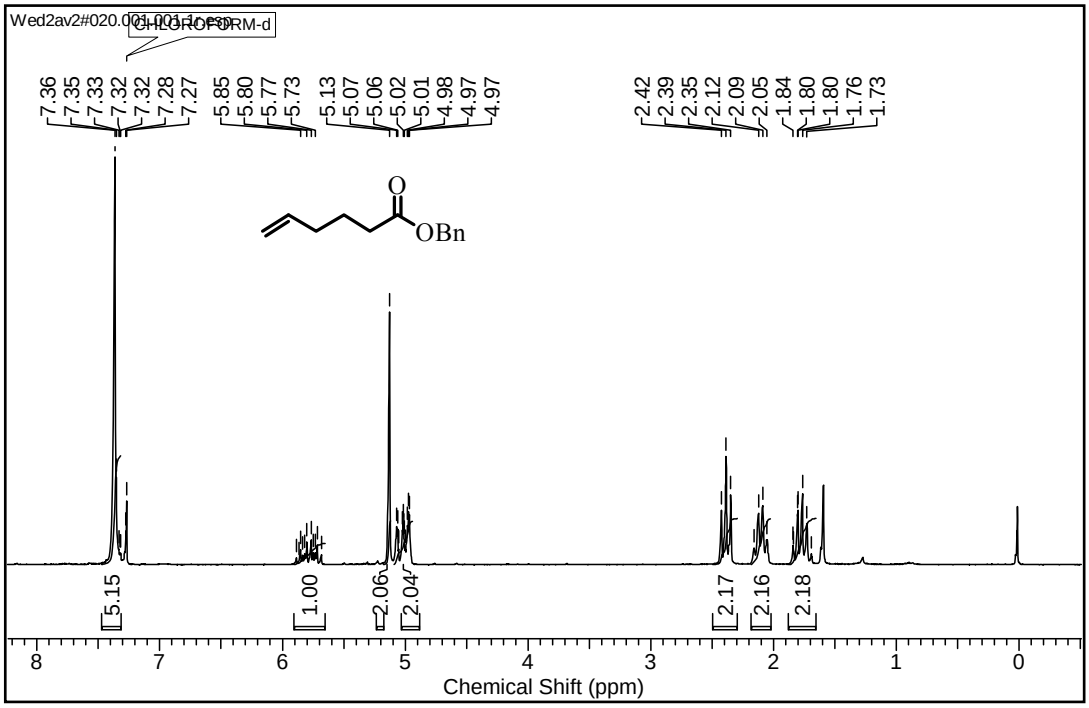
- **^{13}C NMR of the compound 31 in $CDCl_3$**

Hex-5-enoic acid 32:

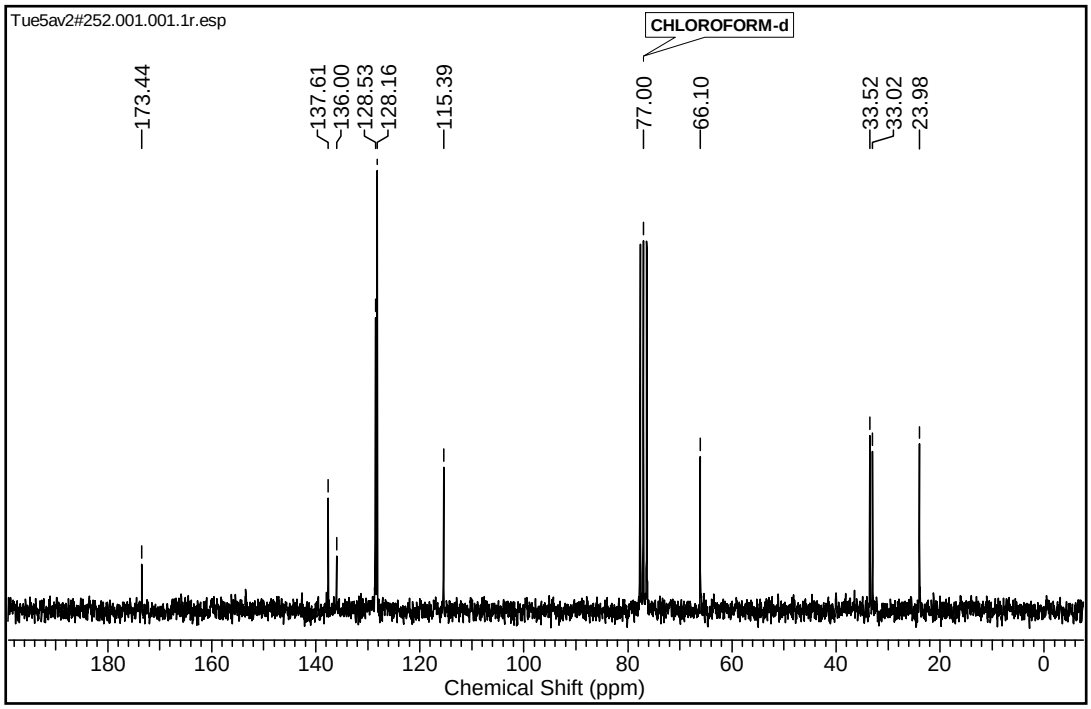


- **^{1}H NMR of the compound 32 in $CDCl_3$**

Benzyl hex-5-enoate 20:

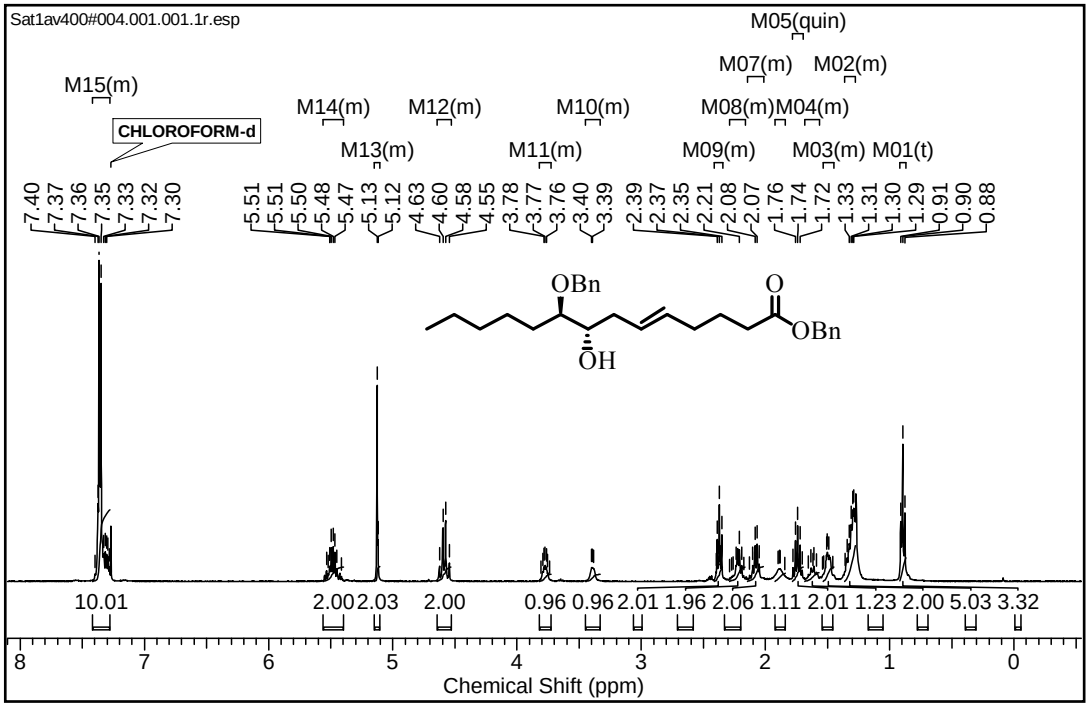


- **^{1}H NMR of the compound 20 in $CDCl_3$**

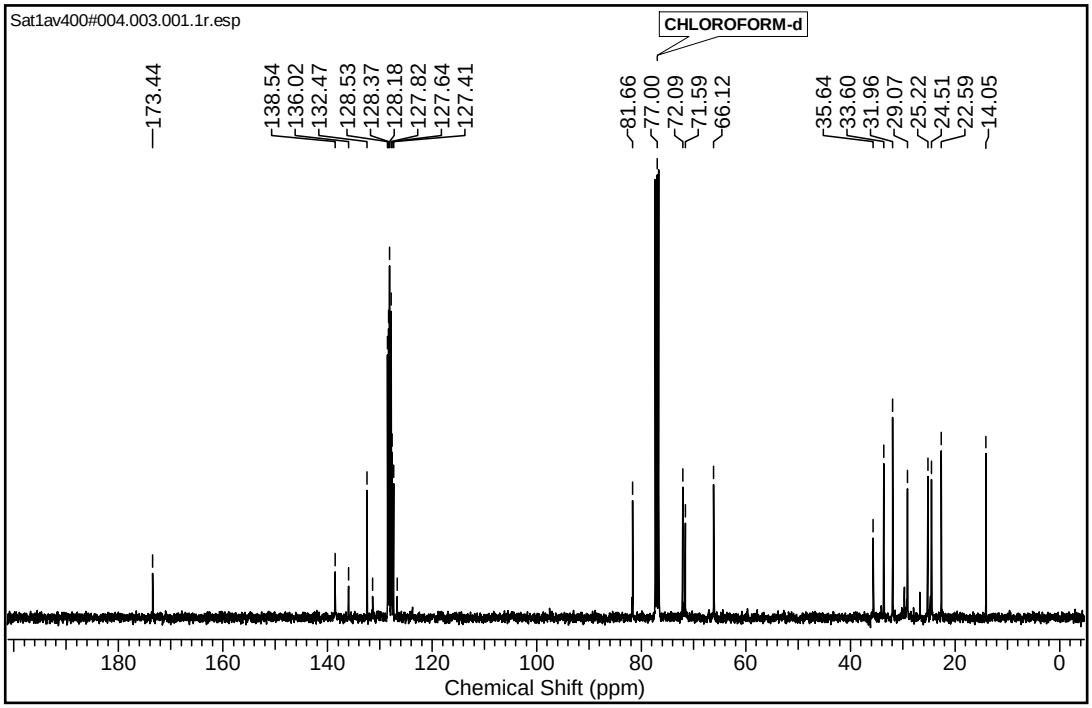


- **^{13}C NMR of the compound 20 in $CDCl_3$**

Benzyl (8*S*,9*R*,*E*)-9-(benzyloxy)-8-hydroxytetradec-5-enoate 18:

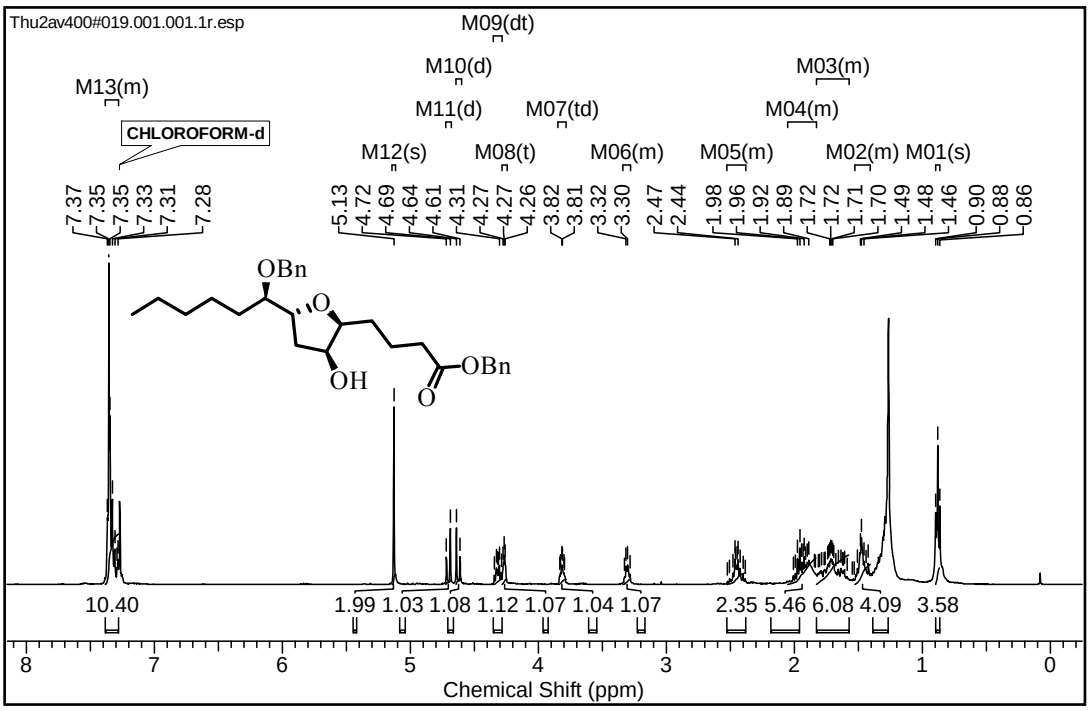


➢ **^{1}H NMR of the compound 18 in $CDCl_3$**

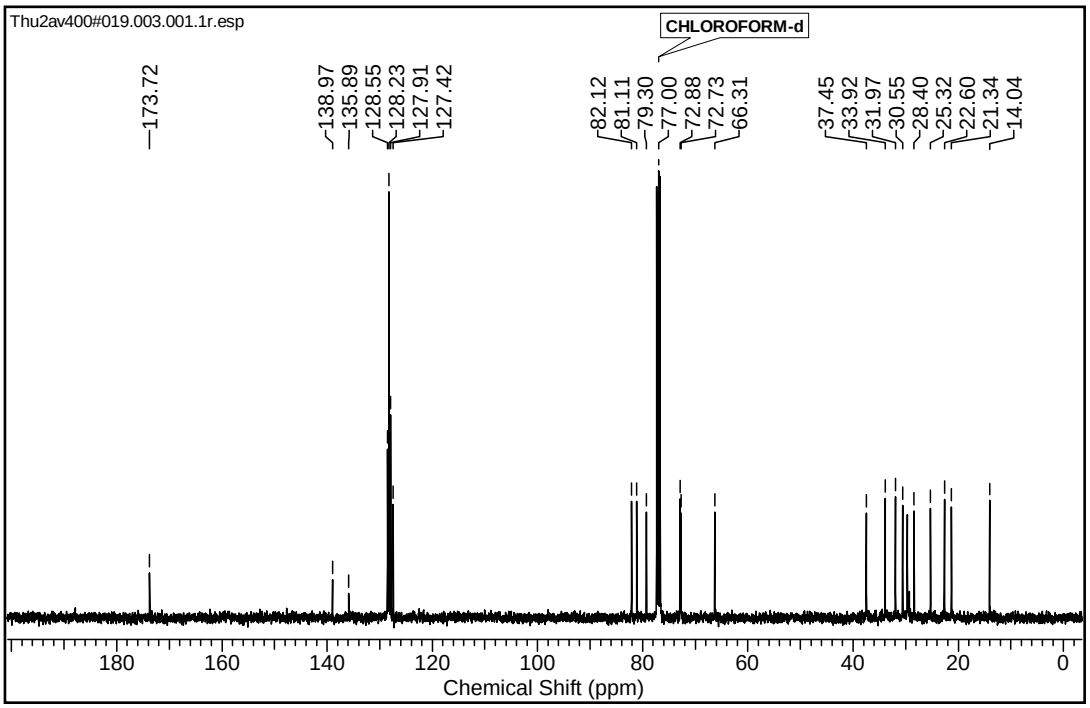


➢ **^{13}C NMR of the compound 18 in $CDCl_3$**

Benzyl 4-((2*S*,3*S*,5*R*)-5-((R)-1-(benzyloxy)hexyl)-3-hydroxytetrahydrofuran-2-yl)butanoate 17:

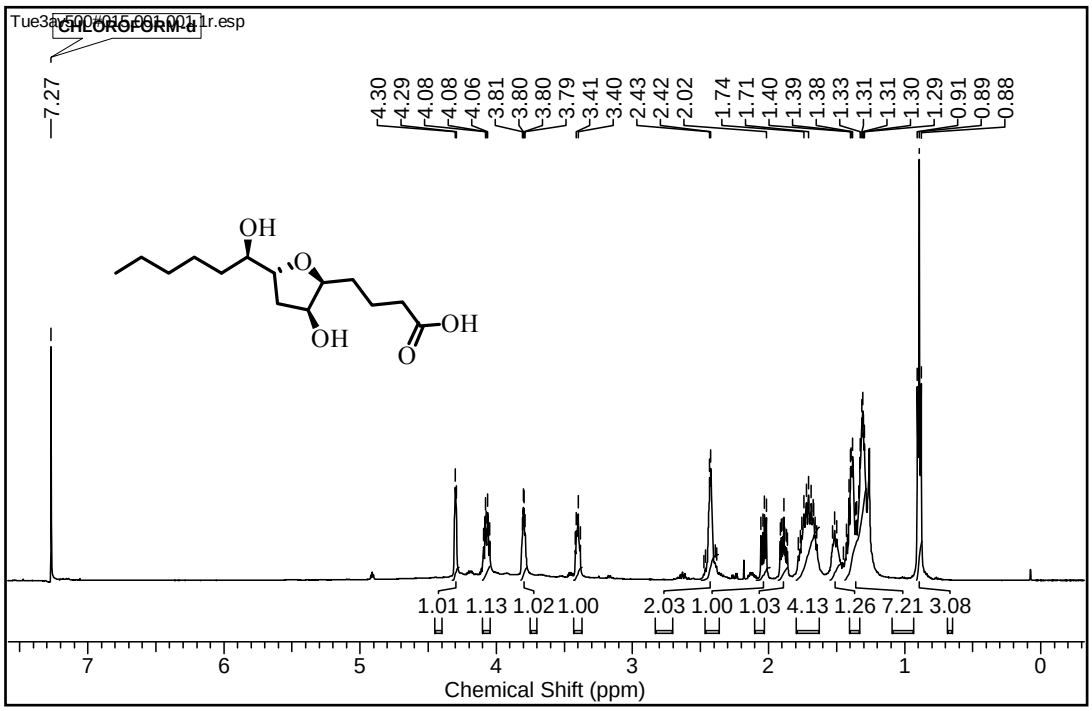


- **^{1}H NMR of the compound 17 in $CDCl_3$**

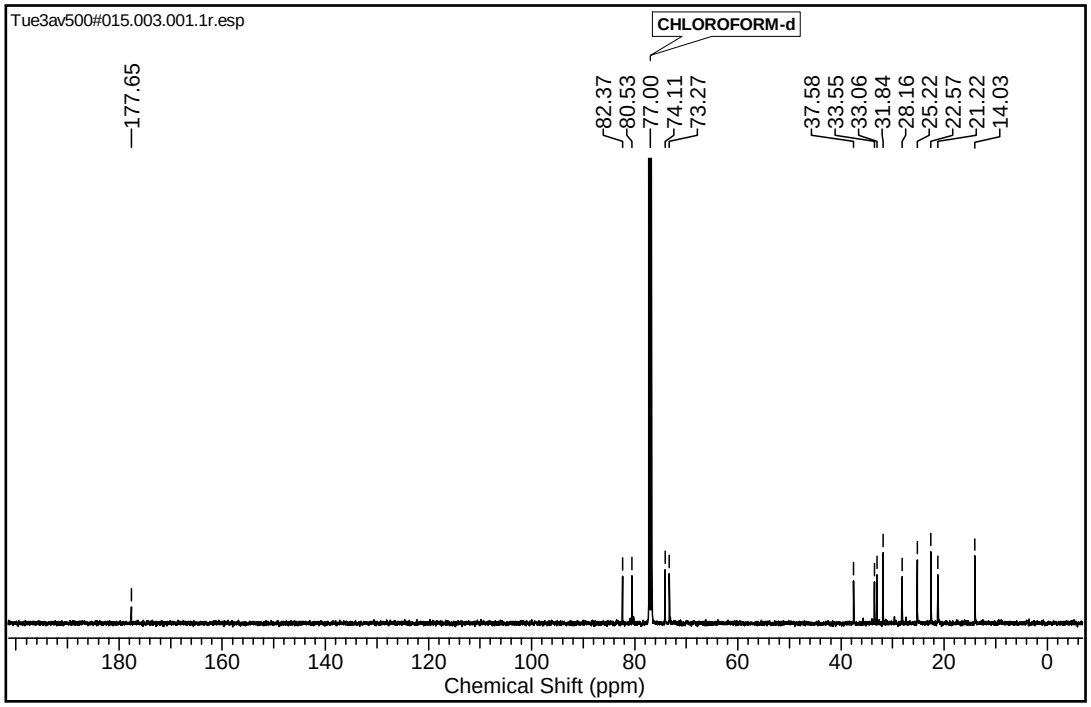


- **^{13}C NMR of the compound 17 in $CDCl_3$**

(+)-Petromyroxol 1:



➢ **^{1}H NMR of the compound 1 in $CDCl_3$**



➢ **^{13}C NMR of the compound 1 in $CDCl_3$**

1.2.9. References

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2. (a) J. P. Wolfe and M. B. Hay, *Tetrahedron,* 2007, **63**, 261; (b) N. Li, Z. Shi, Y. Tang, J. Chen and X. Li, *Beilstein J. Org. Chem.,* 2008, **4**, 48; (c) G. Jalce, X. Franck and B. Figadère, *Tetrahedron: Asymmetry,* 2009, **20**, 2537; (d) N. Kojima and T. Tanaka, *Molecules,* 2009, **14**, 3621; (e) B. S. Ian and C. D. B. Richard *Molecules,* 2010, **15**, 460; (f) A. Lorente, J. Lamariano-Merketegi, F. Albericio and M. Álvarez, *Chem. Rev.,* 2013, **113**, 4567.

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9. The enantioselectivity of compound **23** was determined as 98% *ee* using chiral HPLC {Chiralcel OD-H (250mm x 4.6 mm), ^{i}PrOH/hexane (10:90), flow rate 1 mL min^{-1}, λ = 230 nm, t_R = 5.40 (major), t_R = 6.31 (minor)}. The enantioselectivity of compound **24** was determined as 98% *ee* using chiral HPLC {Chiralcel OD-H (250mm x 4.6 mm), ^{i}PrOH/hexane (10:90), flow rate 1 mL min^{-1}, λ = 230 nm, t_R = 6.32 (major), t_R = 7.35 (minor)}.

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Chapter-2

THF Ring Construction *via* Tandem Iodocyclizations: Synthesis of Hagen's Gland Lactones and its Epimers, Pheromone of *Idea Leuconoe*, Oxylipid and Valuable Synthons

THF Ring Construction *via* Tandem Iodocyclizations: Synthesis of Hagen's Gland Lactones, Pheromone of *Idea Leconoe*, Oxylipid and Valuable Synthons

2.1. Introduction

THF ring containing natural products are known to exhibit a wide range of biological activities for instance, they act as excellent antifeedant, antimalarial, antitumor, immunosuppressive and notably pesticidal and pheromonal activities.[1] Its excellent biological profile & fascinating architecture has attracted a great deal of the attention of synthetic chemists worldwide.[2] The beauty of THF ring containing natural products lies in the fact that with change in substituent's on the THF ring (2, 3, 5 *cis*/*trans* substituted), they show remarkable variety in its biological activities. Hence we became interested in choosing a variety of targets containing THF ring system either fused or substituted (**Fig. 1**)

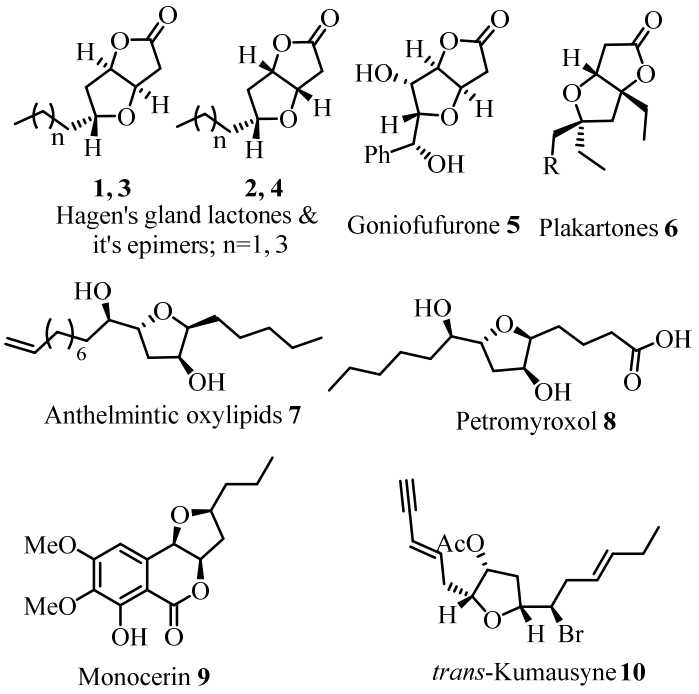


Figure 1: Some of the THF ring based natural products

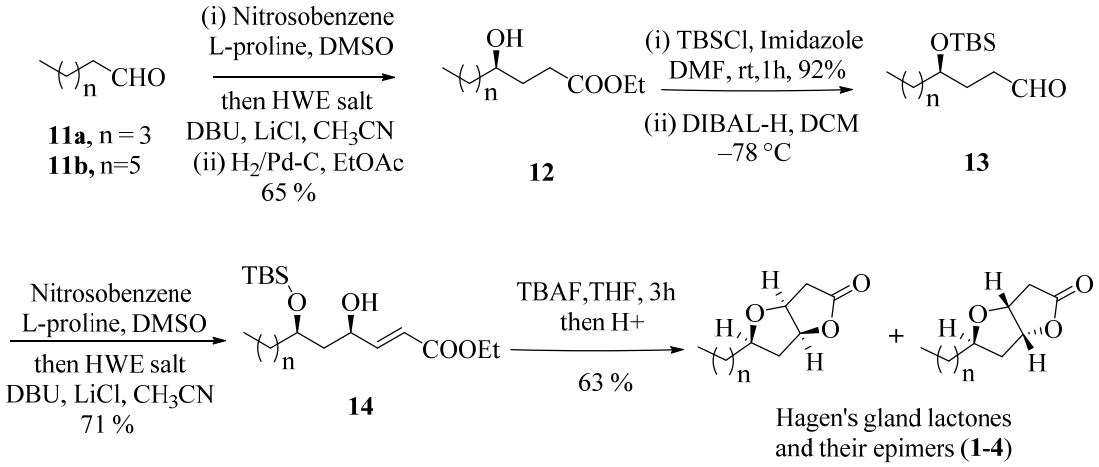
One such fused THF-γ-lactones were secreted from the glands near abdominal tips of braconid wasps (*D. longicaudata* (Ashmead), D. *tryoni* (Cameron) and *Fopius arisanus* (Biosteres)).[3] As these wasps are natural enemies of the Queensland fruit-fly, a known pest in Hawaii and eastern Queensland region,[3] their secretions were expected to show excellent pest control properties. Accordingly, the biological studies revealed that these lactones have a potential role in pest management to control the Queensland fruit fly. These observations were first made by Hagen and co-workers (1953), hence named as Hagen's Gland lactones.

2.2. Review of Literature

Fused THF-γ-lactone motif is a significant synthon to access the class of acetogenins and several other natural products of similar type.[4] Due to this fact a lot of research has been done for the synthesise of Hagen's gland lactones. So far 15 syntheses were reported in the literature. The first synthesis of Hagen's gland lactones was documented by Kitching *et al.* [5a,b] using a protocol involving $PdCl_2$-catalyzed oxy carbonylation–lactonization. Later several chiral pool approaches and enantioselective syntheses were reported. [5c-m] Among them recent reports include short protecting group free synthesis.[5i,n] Recently, our group also synthesized the Hagen's gland lactones using iterative aminoxylation and oxa-Michael reactions as key step.[5m] A detailed report of recent syntheses is described below.

Kumar *et al.* (2015)[5m]

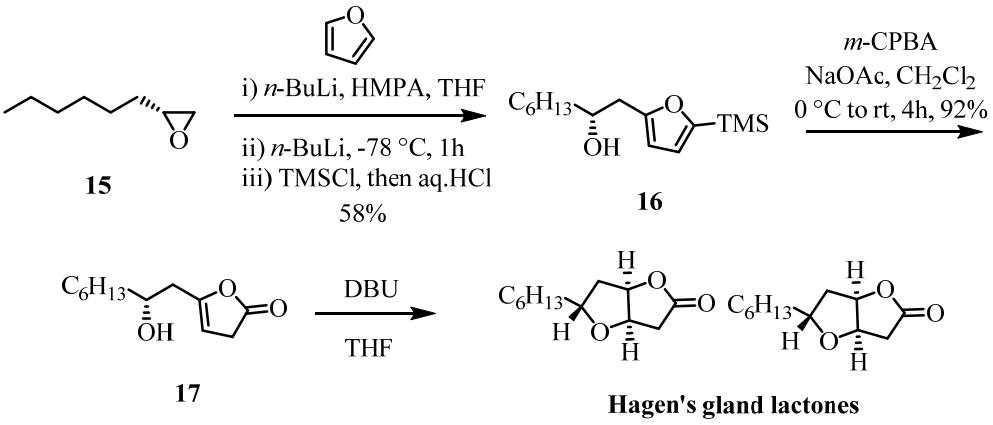
Our own group has synthesized Hagen's lactones starting from hexanal **11a,** which upon α-aminoxylation followed by HWE olefination and subsequent hydrogenation furnished the γ–hydroxy ester **12**. Free hydroxyl group was protected as its TBS followed by reduction using DIBAL-H to furnish the aldehyde **13**. The crude aldehyde **13** was further subjected to α-aminoxylation followed by HWE-olefination to yield compound **14**. It was further subjected to tandem desilylation-oxa-Michael addition-lactonization leading to *cis* and *trans* Hagen's gland lactones in the ratio 5:1.



Scheme 1: Synthesis of Hagen's gland lactones

Kim *et al.* (2014) [5n]

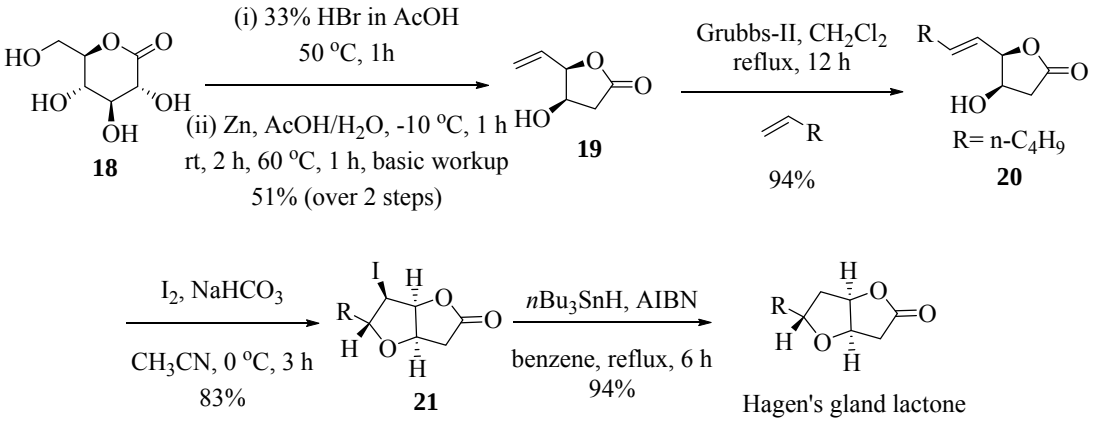
Kim and coworkers synthesized Hagen's gland lactones in three steps starting from commercially available (±)-1,2-epoxyoctane. The epoxide **15** was opened using 2-lithiofuran to afford hydroxy TMS-furan **16.** The hydroxybutenolide **16** was treated with *m*-CPBA and NaOAc to afford hydroxybutenolide **17**. It was subsequently subjected to a DBU promoted sequential isomerization/intramolecular oxa-Michael addition of a hydroxybutenolide to give the target molecule (±) Hagen's gland lactone.



Scheme 2: Synthesis of Hagen's gland lactones

Fernandes *et al.* (2012)[5i]

Fernandes and coworkers synthesized the Hagen's gland lactone using chiral pool approach. D-Glucono-*δ*-lactone **18** was converted to γ-lactone **19** over two steps. Further it was subjected to cross metathesis reaction with 1-hexene using Grubbs second-generation catalyst to afford the lactone **20.** Lactone **20** upon iodoetherification gave the iodo lactone **21**. Subsequent reductive removal of iodine using AIBN and n-Bu_3SnH provided the Hagen's gland lactone.



Scheme 3: Synthesis of Hagen's gland lactone

2.3. Present work

Objective

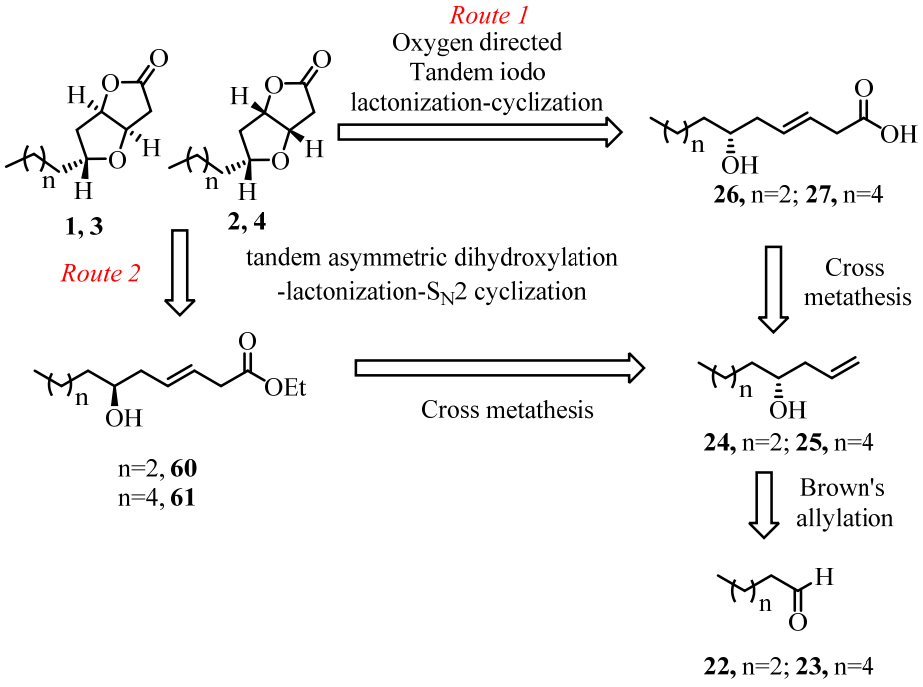
As a part of our ongoing research program on the synthesis of THF ring containing natural products, we considered Hagen's gland lactones as a target molecule for our study due to its structural and biological importance. Even though there are ample literature reports available, still there is a need for developing a new and efficient strategy for the target molecules with high yields and reduced number of steps.

Our synthetic efforts towards the Hagen's gland lactones as well as observations made during the course of synthesis are disclosed here. We devised two short and protecting group

free approaches towards the synthesis of Hagen's gland lactones and it's epimers, one of them using Brown's allylation,[6] cross-metathesis reaction[7] and oxygen directed tandem iodolactonization-etherification,[8] The other approach differs in the fact that tandem asymmetric dihydroxylation-lactonization-S_N2 cyclization has been used as key features in the synthesis. Our strategy is based on concept of using the alcohol chiral centre as a handle to generate the fused ring junction stereochemistry.

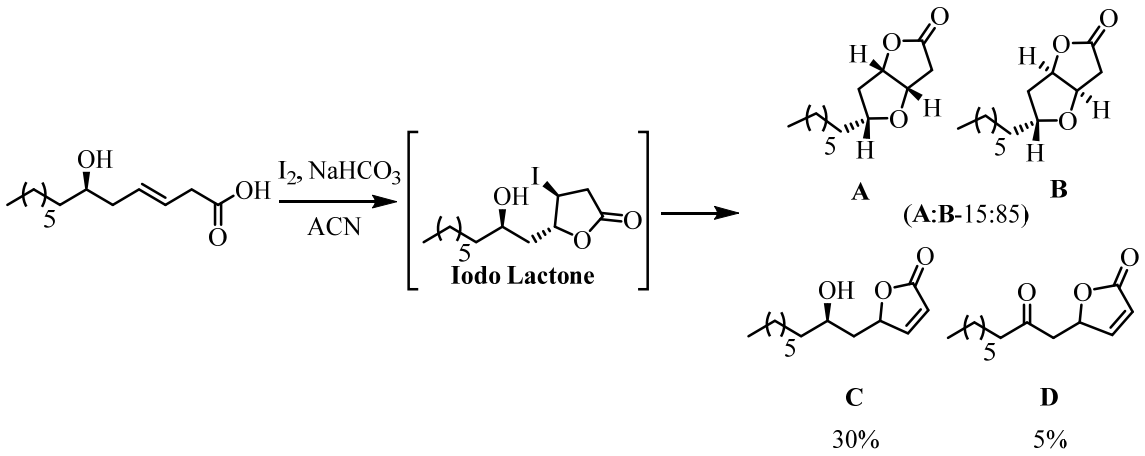
2.4. Results and discussion

Our first synthetic strategy for the synthesis of Hagen's gland lactones and its epimer is delineated in **Scheme 4**. We envisioned that the target molecules (**1**, **2**, **3**, **4**) could be achieved *via* the key step involving oxygen directed tandem iodolactonization-etherification of *seco* acid (**26**/**27**), which in turn could be synthesized from cross metathesis reaction of homo allylic alcohol (**24/25**) and vinyl acetic acid. The alcohol (**24**/**25**) could be derived from Brown allylation of pentanal and heptanal.



Scheme 4: Retrosynthesis of Hagen's gland lactones & its epimers

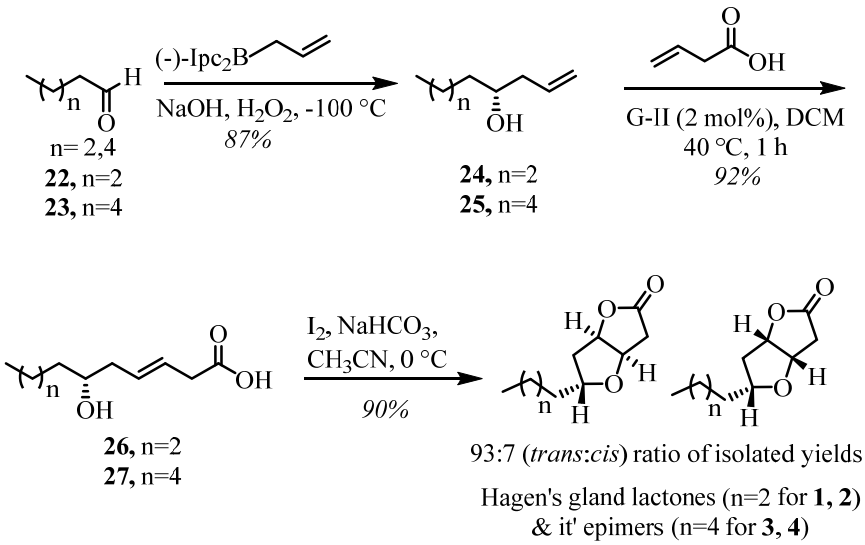
Initially we tried a model reaction with *seco* acid as shown in the **Scheme 5**. We carried out the reaction with 6 equiv of I_2 and 6 equiv of $NaHCO_3$ in acetonitrile at 0 °C which resulted in the formation of required lactones **A**, **B** (55%) along with the undesired lactones **C**, **D** (30%, 5%). The products **A**, **B** can be formed *via* S_N2 displacement of iodine in the intermediate **iodolactone**. The formation of oxidized product **D** can be explained by the literature reports that iodine in basic medium acts as oxidizing agent,[9] thus facilitating oxidation of **C** to **D**. Formation of the compound **C** can be explained *via* elimination reaction of iodine from **iodolactone**. To minimize these by products we further reduced the equivalents of I_2 and $NaHCO_3$ to 3 equivalents, however still we could not avoid the formation of the side products (15%). The desired product is formed as a result of an intramolecular reaction, so we believed that increase in dilution could have an effect on products ratio and thus carried out reaction at the concentration 0.01M. To our delight the formation of side product **D** was completely eliminated and minor quantity of **C** (6%) was obtained and the ratio of Hagen's gland lactones **A** and **B** formed was found to be 85:15 (*trans*:*cis*). We then maintained the reaction temperature at 0 °C for 6h before allowing it to warm to room temperature, this resulted in formation of **A** and **B** in 7:93 ratio respectively (ratio of isolated yields).



Scheme 5: Initial attempt for tandem iodo lactonization-etherification

Synthesis of Hagen's gland lactones started from commercially available heptanal/pentanal (**23**/**22**), which were subjected to Brown's allylation protocol by using (-)-B-allyldiisopinocampheylborane to get the homo allylic alcohol (**24**/**25**) in 87% yield (*ee* was

confirmed by Mosher analysis, 94%, 80% *ee* respectively). The IR spectrum of **24** gave broad hydroxyl absorption at 3366 cm^{-1}. The ^{1}H NMR spectrum of **24** gave olefin peaks at δ {5.90 - 5.77 (m, 1 H), 5.19 - 5.10 (m, 2 H)}. Our next task was to perform a cross-metathesis reaction between the homoallylic alcohol (**24**/**25**) and commercially available vinyl acetic acid (2.0 equiv) in DCM using 2 mol% Grubb's 2nd generation catalyst to furnish the *seco* acid (**26**/**27**) in 92% yield. The IR spectrum of **26** gave broad hydroxyl and carbonyl absorptions at 3416, 1710 cm^{-1} respectively. The ^{1}H NMR spectrum of **26** gave internal olefin peaks at δ {5.73 - 5.56 (m, 2 H)}. The ^{13}C NMR spectrum of **26** gave carbonyl peak at δ 177.2 indicating the presence of acid functionality. After having *seco* acid in our hand, the segment was set for the construction of stereochemically defined THF ring fused with a γ-lactone *via* oxygen directed tandem iodo lactonization-etherification reaction (olefin activation as iodonium ion).



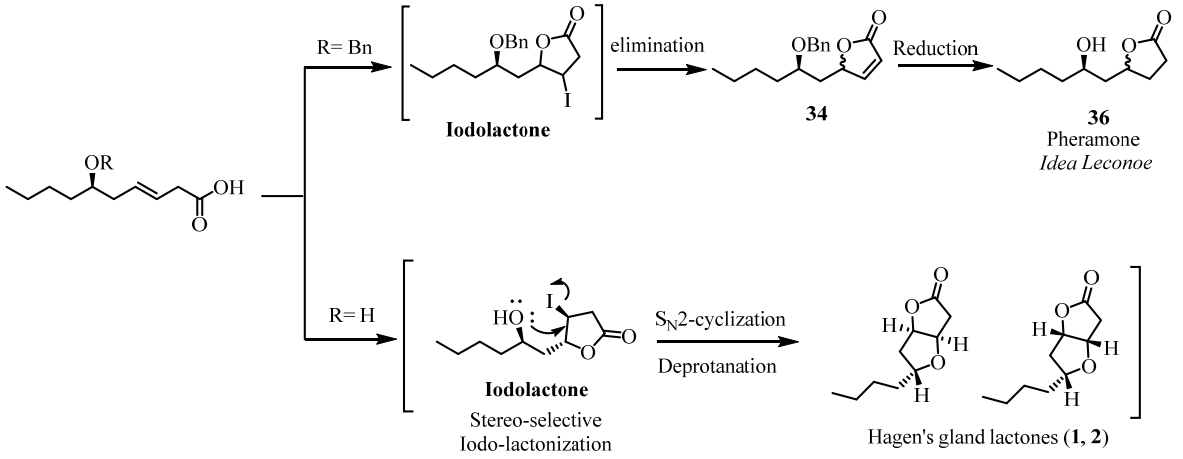
Scheme 6: Synthesis of Hagen's gland lactones (**1**, **2**) and its epimers (**3**, **4**)

Towards this end, the *seco* acid (**26**, **27**) in acetonitrile was treated with iodine (3 equiv), $NaHCO_3$ (3 equiv) at 0 °C for 16 h, to give the desired target molecules **1** & **2** and its epimers **3** & **4** with 93:7 (*anti*:*syn*) ratio (based on isolated yields) in 90% yield (**Scheme 6**). The IR spectrum of **1** gave carbonyl absorption at 1781cm^{-1} indicating the presence of cyclic

ester group and it was further evident by the peak at δ 176.1 in ^{13}C NMR spectrum. The spectral data of Hagen's gland lactones **1**, **2**, **3**, **4** matched well with the literature reports.

The reason for selectivity can be attributed to a free hydroxyl group directing the iodonium ion formation through hydrogen bonding that facilitates the attack of carboxylate anion in S_N2 fashion to give the intermediate **iodolactone** *via* the stereo-selective iodolactonization. This on further S_N2 displacement reaction by the internal free hydroxyl group (acting as nucleophile) resulted in the major *trans* isomer and minor *cis* isomer (**Scheme 7**). Thus we can synthesize both the enantiomers of the natural product by simply varying the stereochemistry of the homoallylic alcohol moiety.

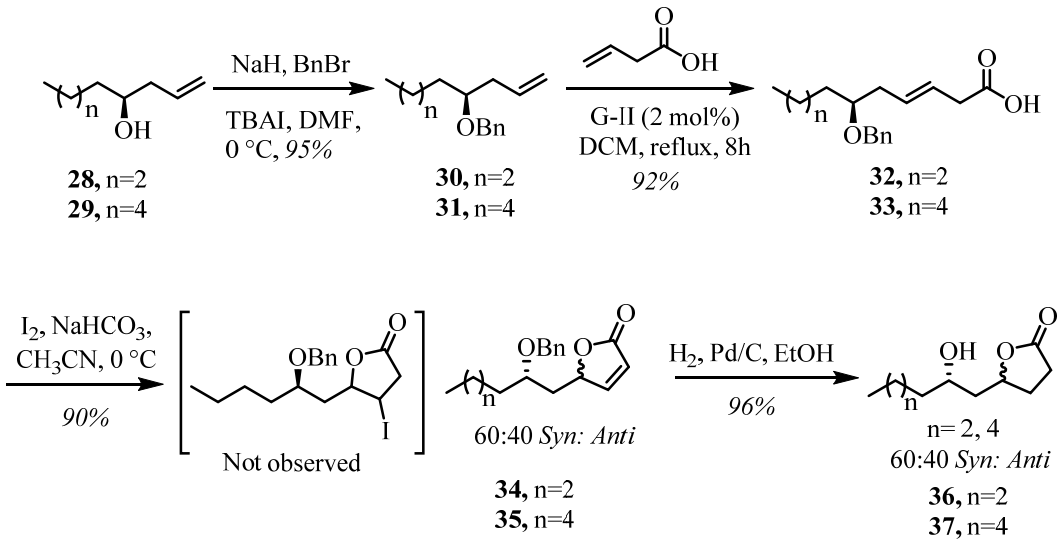
While studying the effect of free hydroxyl group in the formation of **A**, we thought it would be useful to simultaneously study the formation of **C**, a useful γ-butyro hydroxyl lactone. This moiety was found to be very useful skeleton among many natural products. For this we protected the free hydroxyl group of **28** & **29** (**Scheme 8**) as its benzyl ether (**30**/**31**) using NaH and benzyl bromide. The IR spectrum of **30/31** shows the absence of hydroxyl absorption.



Scheme 7: Plausible transition state for stereo-chemical outcome

Then we carried out the cross metathesis between benzyl ether and vinyl acetic acid to yield the acid **32**/**33**. The IR spectrum of **32** gave broad hydroxyl absorption at 3032 cm^{-1} and carbonyl absorption at 1712 cm^{-1}. The ^{1}H NMR spectrum of **32** gave internal olefin peaks at δ {5.71 - 5.55 (m, 2 H)}. The ^{13}C NMR spectrum of **32** gave carbonyl peak at δ 177.6 indicating the presence of acid functionality. Next we attempted at the iodocyclization reaction on the benzyl protected *seco* acid (**32**/**33**), surprisingly instead of forming **iodolactone**, we ended up with *non-racemic* mixture (60:40) (confirmed by ^{1}H NMR) of α, β–unsaturated γ-lactones **34**, **35**. We tried to isolate the **iodolactone**, by carrying out reaction with reduced amount of I_2 and $NaHCO_3$ (equivalents 2 & 1), however we could only observe the formation of unsaturated lactones. In literature several synthetic methodologies have been described to prepare the α, β-unsaturated γ-lactones.[10]

Thus the above findings led to the development of an elegant approach for the synthesis of α, β-unsaturated γ-lactones for the first time using simple molecular iodine therefore avoiding the use of metals and oxidants.[11] We realized that this serendipitous discovery could find its application in the synthesis of several natural products especially the sex pheromones containing hydroxyl lactone moiety.



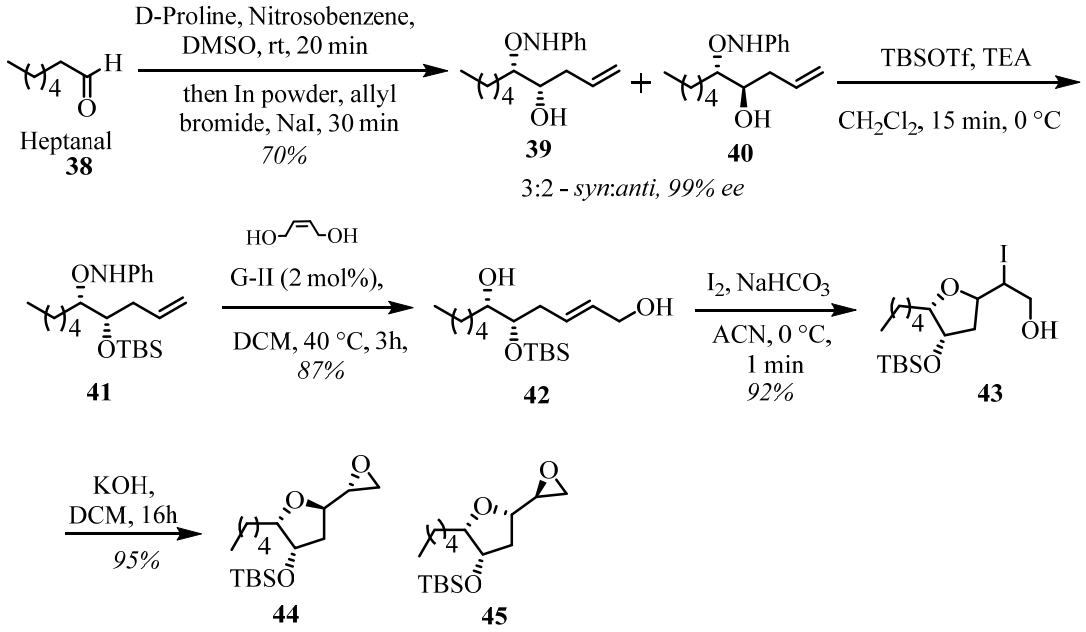
Scheme 8: Synthesis of pheromone lactones of *Idea Leuconoe*

One such pheromone components are the 6-hydroxy-4-dodecanolides with chain lengths between 10 and 13 carbon atoms. The reduced form of the **34** is a sex pheromone of *Idea Leuconoe* (giant butterfly) that releases a mixture of volatiles from their pheromone glands (hairpencils) during courtship. Accordingly we successfully transformed the compound (**34**/**35**) to a natural product (**36**/**37**) (60:40 as a non separable and non racemic mixture (**Scheme 8**). The IR spectrum of **36** gave broad hydroxyl and lactone absorptions at 3441and 1771 cm^{-1} respectively and it was further evident by the carbonyl peak at δ 177.2 in ^{13}C NMR. To date only two syntheses are reported in literature (one racemic and the other chiral).[12] Thus we can conclude that the presence of free -OH group is responsible for major *trans* lactone formation. If we protect the free –OH, no selectivity was observed and we ended up with *non-racemic* mixture of relatively stable α, β-unsaturated γ–lactone. Thus without protection we could access the Hagen's gland lactones (**Scheme 7**) and with protection one can generate the pheromone lactones of *Idea Leuconoe* (**Scheme 8**).

Product **D**, the over oxidized product **(Scheme 5)** as discussed, was observed in a very small amounts. We then decided to investigate this reaction further and with a suitable substrates containing aliphatic, aromatic substituent (**42**, **52**) under the same conditions and see the fate of the over oxidation product. Here we have chosen these substrates in such a way that the substrate **42** can generate the *oxylipid* family and the aryl substrate **52** the monocerin family, through iodine mediated reaction. The results are presented below.

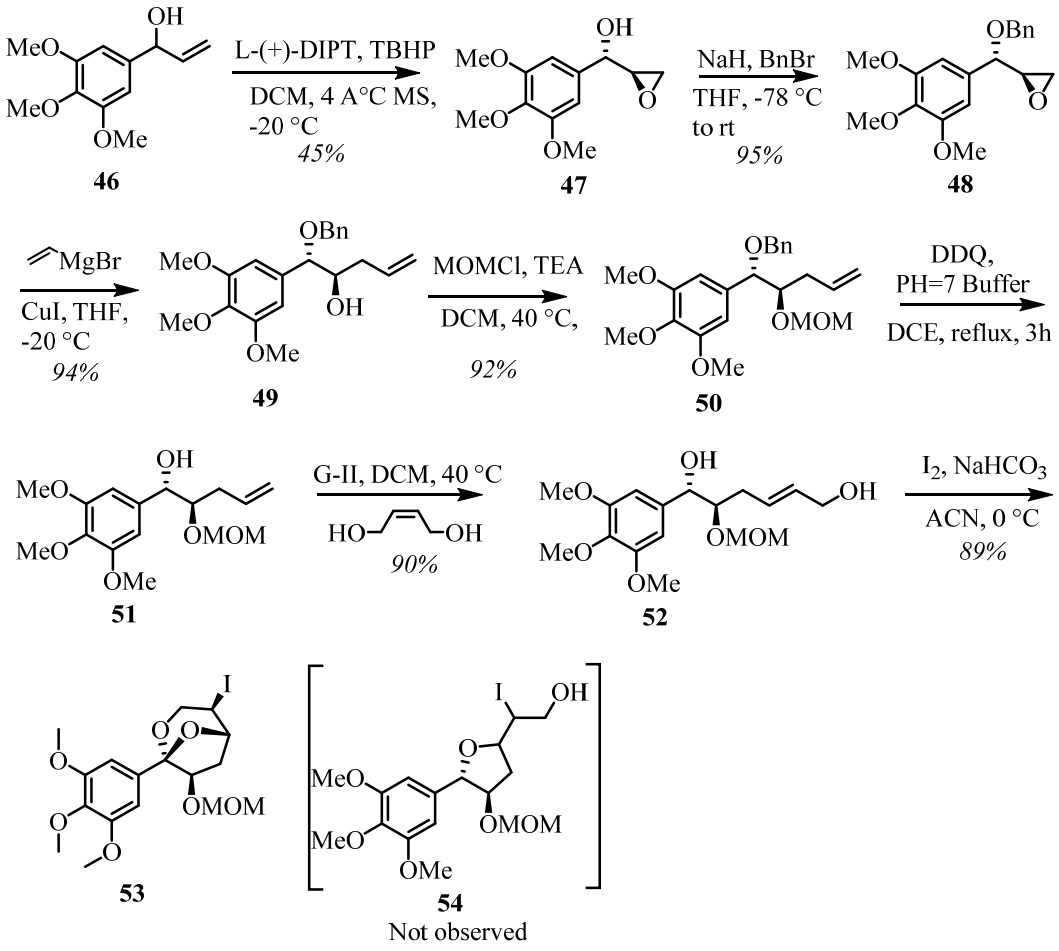
The preparation of the compound **42** started from commercially available heptanal **38** which was subjected to tandem aminoxylation-allylation protocol.[13] Heptanal was treated with D-proline as an organocatalyst, nitroso benzene as an oxygen source, DMSO as a solvent to afford the α-aminoxyaldehyde. The *in situ* trapping of this intermediate using indium, allyl bromide and NaI combination provided the *O*-amino-substituted allylic alcohols **39** & **40** with 3:2 ratio. The IR spectrum of **39** and **40** gave broad hydroxyl absorption at 3394 and 3396 cm^{-1}. The ^{1}H NMR spectrum of **39** gave olefin peaks at δ {5.96 - 5.87 (m, 1 H), 5.20 - 5.14 (m, 2 H)}, aromatic peaks at δ {7.31 - 7.27 (m, 2 H), 7.03 - 6.99 (m, 3 H)}. The *syn* compound **39** was protected as its silyl ether **41** and subjected to cross metathesis reaction

with *cis* 1, 4-butenediol to produce the allylic alcohol **42** in 90% yield. The IR spectrum of **42** gave broad hydroxyl absorption at 3355 cm^{-1}. The ^1H NMR of **42** gave internal olefin peaks at δ {5.75 - 5.63 (m, 2 H)}. It was interesting to note that during cross metathesis reaction we observed the O-N bond cleavage.[14] Now, the stage was set for tandem iodoetherification. Thus the compound **42** was treated with iodine and $NaHCO_3$ in acetonitrile to provide the inseparable *trans* and *cis* THF-iodo alcohols **43** in 85:15 ratio (confirmed by ^1H NMR). The IR spectrum of **43** gave broad hydroxyl absorption at 3384 cm^{-1}. From this study it was clear that over oxidation product was not formed even after prolonging times with the alkyl substituent and it led only to the THF ring formation. To extend the scope of this reaction, we further considered synthesizing the core moiety of epoxy furan present in *oxylipid* family. Towards this, the intermediate **43** was further subjected to S_N2 displacement reaction with free alcohol using KOH in DCM to provide the column separable *trans* and *cis* THF-epoxides (**44**, **45**) in 95% yield (**Scheme 9**). The stereochemistry of THF-epoxides was confirmed by 2D NMR (see experimental section). Thus, we accomplished the formal synthesis [15a, b] of oxylipid **44**, **45** in just 5 steps.

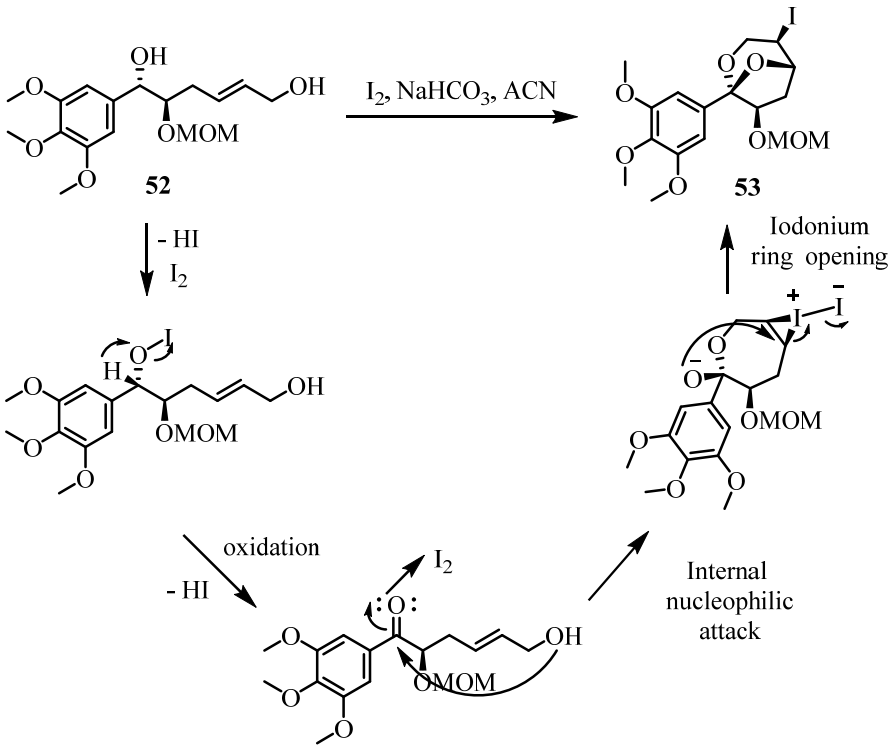


Scheme 9: Formal synthesis of oxylipid

Having succeeded with aliphatic precursor, the preparation of aromatic substrate **52** (**Scheme 10**) started from the known alcohol **46**,[16] which was subjected to Sharpless epoxidation[17] conditions using (L)-DIPT & TBHP to give the epoxy alcohol **47**. The IR spectrum of **47** gave broad hydroxyl absorption at 3458 cm^{-1}. The ^1H NMR spectrum of **47** gave epoxide peaks at δ {2.96 (dd, J = 2.8, 4.8 Hz, 1 H), 2.79 (dd, J = 4.0, 4.9 Hz, 1 H), 2.36 (s, 1 H)}. The epoxy alcohol **47** was protected as its benzyl ether using NaH and BnBr to furnish the compound **48**. The IR spectrum of **48** shows the absence hydroxyl absorption. The epoxide **48** was subjected to vinyl Grignard to afford the homoallylic alcohol **49**. The IR spectrum of **49** gave broad hydroxyl absorption at 3458 cm^{-1}. The ^1H NMR spectrum of **49** gave terminal olefin peaks at δ {6.00 - 5.77 (m, 1 H), 5.20 - 5.07 (m, 2 H)}.



Scheme 10: Synthesis of core bicyclic ketal **53**



Scheme 11: Plausible mechanism for the formation of bicyclic ketal **53** (**Path A**)

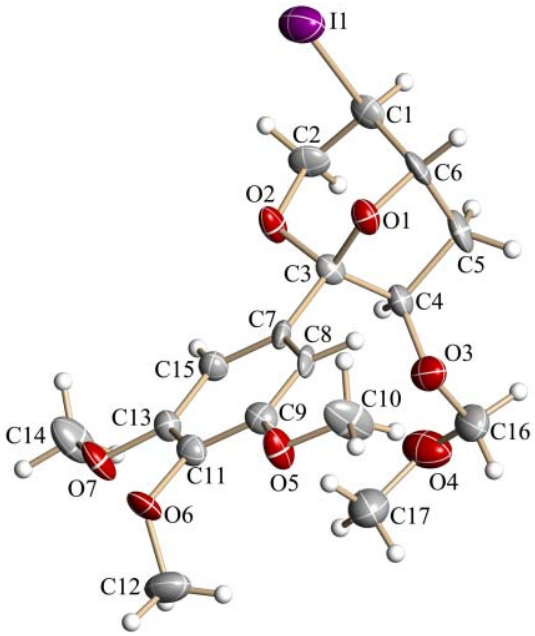


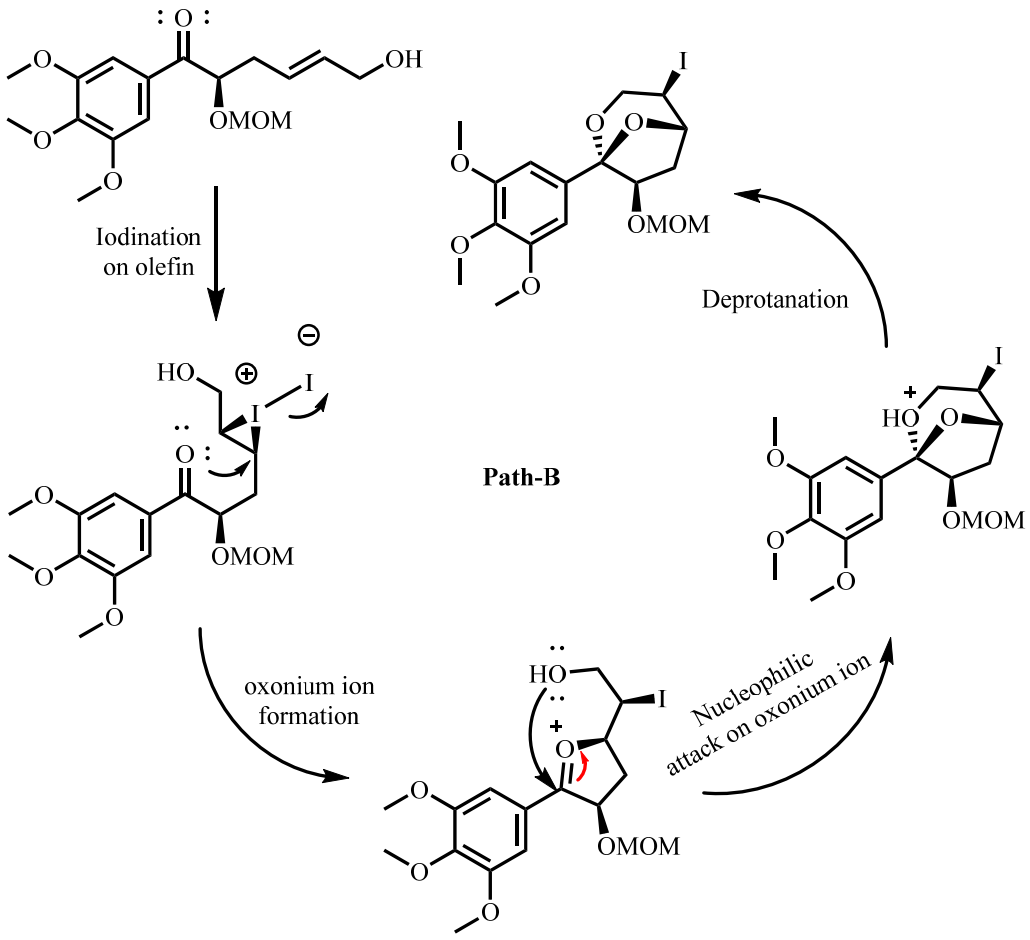
Figure 2: ORTEP diagram of **53**

Homoallylic alcohol **49** was protected as its MOM ether (**50)** using MOM chloride. The deprotection of benzyl group was achieved using DDQ, P^H=7 buffer in DCE under reflux conditions to afford compound **51** in 70% yield, which was subjected to cross metathesis reaction with *cis* 1, 4-butendiol to give the allylic alcohol **52.** The IR spectrum of **52** gave broad hydroxyl absorption at 3478 cm^{-1}. The ^1H NMR spectrum of **52** gave internal olefin peaks at δ {5.73 - 5.64 (m, 2 H)}. Further iodo etherification of **52** resulted in the formation of bicyclic ketal **53** instead of **54,** as a single diastereomer. The absolute stereochemistry and structure was confirmed unambiguously by X-ray crystallography. The ORTEP diagram is as shown in the **Figure 2**.

Literature survey revealed the presence of this type of skeleton in the (+)-Wailupemycin B, a less abundant polyketide natural product.[18] Based on the product **(53)** formation, the possible mechanism can be explained *via* the two proposed pathways (scheme **11**, **12**). Path A involves the oxidation of benzylic alcohol to ketone in the presence of I_2. Further coordination of iodine with ketone triggers the nucleophilic attack at carbonyl carbon followed by the ring opening of iodonium ion with oxyanion to give the compound **53**, whereas path B involves the oxidation of benzylic alcohol to ketone in presence of I_2 followed by iodonium ion ring opening by carbonyl oxygen leading to the formation of oxonium ion. This further facilitates the internal nucleophilic attack of free alcohol at the benzylic position, followed by deprotonation resulting in the formation of the bicylic ketal **53**. From this study we can conclude that over oxidation product will be the sole product in the aryl substituent.

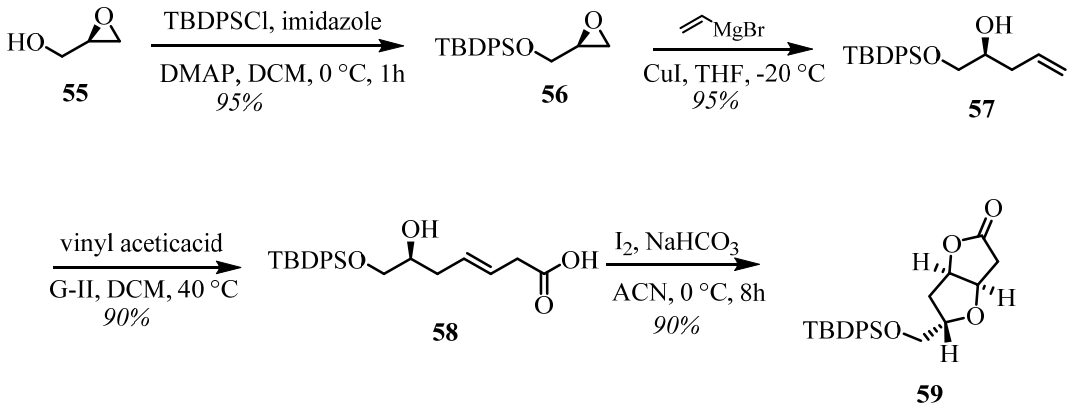
To show the generality of our synthetic strategy, we considered synthesizing the key intermediate **59**, a precursor in the synthesis of *trans*-Kumausallene (**Scheme 13**). Our synthesis started with (*R*)-glycidol ether **55**, which was protected using TBDPS chloride and imidazole to give **56**, followed by the ring opening of epoxide using vinyl Grignard and CuI to afford the homoallylic alcohol **57** in 95% yield. The IR spectrum of **57** gave broad hydroxyl absorptions at 3365 cm^{-1}. The ^1H NMR spectrum of **57** gave terminal olefin peaks at δ {5.81 (tdd, J = 7.2, 10.1, 17.1 Hz, 1 H), 5.13 - 5.03 (m, 2 H)}.

Now we performed the cross metathesis reaction between the alcohol **57** and vinyl acetic acid using G-II, dichloromethane under reflux conditions to give the *seco* acid **58** in 90% yield. The IR spectrum of **58** gave broad hydroxyl absorption at 3420, 3024 cm^{-1} and carbonyl absorption at 1727 cm^{-1}. The ^{1}H NMR spectrum of **58** gave internal olefin peaks at δ {5.63 - 5.54 (m, 2 H)}. The ^{13}C NMR spectrum of **58** gave carbonyl peak at δ 177.4 indicating the presence of acid functionality. Now the stage was set to perform the tandem iodolactonization-etherification strategy developed by us. Thus the compound **58** was treated with iodine and $NaHCO_3$ to afford the *trans* fused THF-γ-lactone **59** in 90% yield. The IR spectrum of **59** shows the absence of hydroxyl absorptions and presence of carbonyl absorption at 1783 cm^{-1}. The ^{13}C NMR spectrum of **59** gave carbonyl peak at δ 175.8.

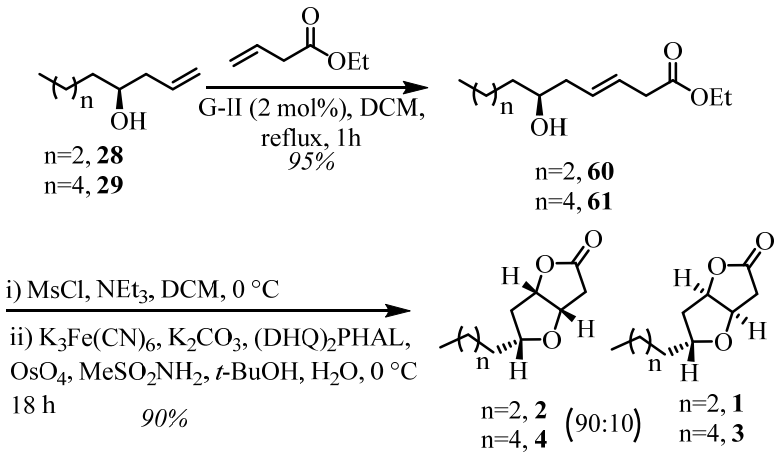


Scheme 12: Plausible mechanism for the formation of bicyclic ketal **53 (path B)**

indicating the presence of ester functionality. The ^{1}H NMR spectrum of **59** gave THF ring protons at δ {5.14 (t, *J* = 4.8 Hz, 1 H), 4.83 (t, *J* = 4.6 Hz, 1 H), 4.35 - 4.28 (m, 1 H)}. The data of **59** was fully consistent with the literature values.



Scheme 13: Synthesis of key synthon **59**



Scheme 14: Protecting group free strategy for the synthesis of Hagen's gland lactones & its epimers

Encouraged by above findings, we considered devising another protecting group-free strategy for the synthesis of Hagen's gland lactones as shown in **scheme 14**. In this

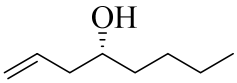
approach, we used tandem asymmetric dihydroxylation-lactonization-S_N2 cyclization as key step. The synthesis starts from the homo allylic alcohol (**28**/**29**) which underwent cross metathesis with vinyl ethyl acetate, to afford the hydroxyl ester (**60**/**61**). The IR spectrum of **60** gave the hydroxyl absorption at 3445 cm^{-1} and ester carbonyl absorption at 1732 cm^{-1}. The ^1H NMR spectrum of **60** gave internal olefin peaks at δ {5.76 - 5.48 (m, 2 H)}. The ^{13}C NMR spectrum of **60** gave carbonyl peak at δ 171.9 indicating the presence of ester functionality. Subsequent hydroxyl protection as its mesylate and asymmetric dihydroxylation[19] following Marshall's[19b-d] protocol using $(DHQ)_2PHAL$ as a ligand, OsO_4 as an oxygen source resulted in the formation of *cis* (**2**, **4**) & *trans* (**1**, **3**) Hagen's gland lactones (90:10) {ratio based on isolated yields}.

2.5. Conclusion

In conclusion we developed two protecting group free, scalable routes towards Hagen's gland lactones in just 3 and 4 steps with 72%, 70% overall yields. We also developed a method to prepare α, β-unsaturated γ-butyrolactones. This protocol was successfully used in the synthesis of pheromone lactones of *Idea Leuconoe*. We prepared the key precursor **59** in 4 steps with 60% overall yield. The formal synthesis of oxylipid was achieved in just 5 steps from heptanal. We prepared the useful chiral bicyclic ketal **53** framework presented in the ployketides and proposed a plausible mechanism for its formation.

2.6. Experimental Section

(*R*)-Oct-1-en-4-ol 24:



To a cooled mixture of (-)-Ipc_2(allyl)borane (8.33 g, 25.57 mmol) in dry diethyl ether (15 mL) at -100 °C, a solution of freshly distilled pentanal (2 g, 23.25 mmol) in diethyl ether (20 mL) was added drop wise over 10 min *via* syringe (maintaining the temperature below -90 °C). The resulting mixture was stirred vigorously at -100 °C for 1.5 h and warmed to

room temperature over 1 h. A solution of 3M NaOH (5.17 mL) and 30% aq. H_2O_2 (17 mL) was carefully added *via* the dropping funnel, keeping the temperature below 15 °C, followed by addition of saturated aqueous $NaHCO_3$ (20 mL). The resulting mixture was stirred for 10 h at the same temperature to completely hydrolyze boronate ester product. Organic phase was then diluted with diethyl ether, extracted with the same solvent (3 x 20 mL) and combined organic layers were washed with brine (2 x 10 mL). The resulting layers then dried over anhyd. Na_2SO_4 and concentrated by rotary evaporation to afford light yellow oil which was purified by column chromatography with hexane: ethyl acetate, (95:5) to provide pure homoallylic alcohol **24.**

Yield: 2.59 g, 87%

Mol. Formula: $C_8H_{16}O$

$[\alpha]_D^{25}$: +8.01 (*c* 3, $CHCl_3$)

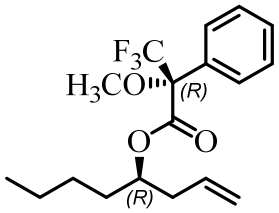
IR (neat, cm^{-1}): ν_{max} 3366, 2927, 2863, 1639, 1456, 1125, 1029

^{1}H NMR (500MHz, $CDCl_3$) δ = 5.90 - 5.77 (m, 1 H), 5.19 - 5.10 (m, 2 H), 3.65 (dtd, *J* = 4.1, 6.0, 7.9 Hz, 1 H), 2.31 (tddd, *J* = 1.3, 4.2, 6.5, 13.9 Hz, 1 H), 2.19 - 2.10 (m, 1 H), 1.51 - 1.32 (m, 6 H), 0.91 (t, *J* = 7.2 Hz, 3 H)

^{13}C NMR (125MHz, $CDCl_3$) δ = 134.9, 118.1, 70.6, 41.9, 36.5, 27.8, 22.7, 14.0

HRMS (ESI) for $C_8H_{16}O$ $(M + Na)^+$ found 151.1095, calcd 151.1094

(*R*)-Oct-1-en-4-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate:



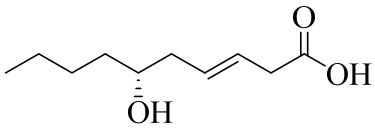
Yield: 25 mg, 92%

Mol. Formula: $C_{18}H_{23}F_3O_3$

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.64 - 7.49 (m, 2 H), 7.45 - 7.33 (m, 3 H), 5.86 - 5.56 (m, 1 H), 5.22 - 5.07 (m, 3 H), 3.61 - 3.53 (m, 3 H), 2.48 - 2.33 (m, 2 H), 1.67 - 1.56 (m, 2 H), 1.32 - 1.12 (m, 4 H), 0.83 (t, *J* = 7.1 Hz, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 166.2, 133.2, 133.0, 132.4, 129.5, 128.3, 127.3, 124.8, 121.9, 118.3, 84.6, 76.5, 55.5, 38.3, 32.9, 26.9, 22.3, 13.8

(*R*, *E*)-6-Hydroxydec-3-enoic acid 26:



To a stirred solution of **24** (500 mg, 3.9 mmol) in CH_2Cl_2 (7.0 mL) was added the compound vinyl acetic acid (672 mg, 7.81 mmol) and degassed for 15 min. Then Grubb's II catalyst (66.3 mg, 2 mol %) was added to the reaction mixture and stirred for 1h at reflux. After completion of reaction, solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (EtOAc–petroleum ether, 32:68) to afford compound *seco* acid **26** as yellow oil.

Yield: 668 mg, 92%

Mol. Formula: $C_{10}H_{18}O_3$

$[\alpha]_D^{24.8}$: +2.5 (*c* 1.2, $CHCl_3$)

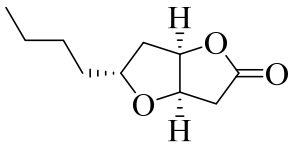
IR (neat, cm^{-1}): ν_{max} 3416, 3021, 2928, 2862, 1728, 1410, 1278, 1173

^{1}H NMR (400MHz, $CDCl_3$) δ **=** 5.73 - 5.56 (m, 2 H), 5.0-5.63(br m, 1H), 3.71 - 3.61 (m, 1 H), 3.21 - 3.06 (m, 2 H), 2.34 - 2.24 (m, 1 H), 2.20 - 2.09 (m, 1 H), 1.51 - 1.28 (m, 6 H), 0.91 (t, *J* = 7.0 Hz, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 177.2, 131.2, 124.7, 70.9, 40.4, 37.7, 36.4, 27.8, 22.7, 14.0

HRMS (ESI) for $C_{10}H_{18}O_3$ $(M + Na)^+$ found 209.1150, calcd 209.1148

(3a*R*, 5*R*, 6a*R*)-5-Butyltetrahydrofuro[3,2-b]furan-2(3*H*)-one 1:



To a solution of **26** (100 mg, 0.54 mmol) in MeCN (10 mL) were added sequentially $NaHCO_3$ (135 mg, 1.61 mmol, 3.0 equiv) and iodine (204 mg, 1.61 mmol, 3.0 equiv) at 0 °C and the mixture stirred for 6 h before allowing it to rt. The reaction was quenched with aqueous $Na_2S_2O_3$, and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/ EtOAc (85:15) to give **1** (82.1 mg, 83%) as a colorless oil. Further elution with petroleum ether/EtOAc (84:16) gave **2** (6.9 mg, 7%) {(3a*S*, 5*R*, 6a*S*)-5-butyltetrahydrofuro[3,2-b]furan-2(3*H*)-one}.

Yield: 82.1 mg, 83%

Mol. Formula: $C_{10}H_{16}O_3$

$[\alpha]_D^{25.2}$: +49.5° (*c* 1.0, $CHCl_3$)

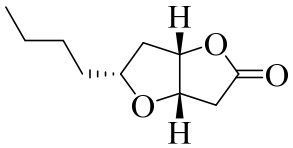
IR (neat, cm^{-1}): ν_{max} 2930, 2864, 1781, 1459, 1345, 1180, 1065

^{1}H NMR (200MHz, $CDCl_3$) δ = 5.13 (t, *J* = 4.7 Hz, 1 H), 4.84 - 4.79 (m, 1 H), 4.07 (dt, *J* = 6.3, 10.8 Hz, 1 H), 2.77 (dd, *J* = 6.6, 18.8 Hz, 1 H), 2.65 (d, *J* = 18.6 Hz, 1 H), 2.38 (dd, *J* = 4.6, 13.7 Hz, 1 H), 1.71 - 1.65 (m, 1 H), 1.57 - 1.43 (m, 2 H), 1.43 - 1.29 (m, 4 H), 0.90 (t, *J* = 7.0 Hz, 3 H)

^{13}C NMR (125MHz, $CDCl_3$) δ = 176.1, 84.9, 78.2, 77.3, 38.8, 36.6, 34.3, 28.1, 22.6, 13.9

HRMS (ESI) for $C_{10}H_{16}O_3$ $(M + Na)^+$ found 207.0994, calcd 207.0992

(3a*S*, 5*R*, 6a*S*)-5-Butyltetrahydrofuro[3,2-b]furan-2(3*H*)-one 2:



Yield: 6.9 mg, 7%

Mol. Formula: $C_{10}H_{16}O_3$

$[\alpha]_D^{24.5}$: -52.81° (*c* 0.6, $CHCl_3$)

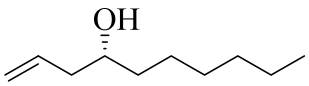
IR (neat, cm^{-1}): ν_{max} 2930, 2862, 1780, 1458, 1344, 1179, 1064

^{1}H NMR (400MHz, $CDCl_3$) δ = 5.02 (ddd, *J* = 2.1, 4.4, 6.8 Hz, 1 H), 4.55 - 4.49 (m, 1 H), 3.99 - 3.89 (m, 1 H), 2.73 (d, *J* = 3.3 Hz, 2 H), 2.43 (td, *J* = 7.1, 14.2 Hz, 1 H), 1.88 (ddd, *J* = 2.1, 7.9, 14.3 Hz, 1 H), 1.70 - 1.64 (m, 1 H), 1.60 - 1.50 (m, 1 H), 1.42 - 1.29 (m, 4 H), 0.93 - 0.88 (m, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 175.5, 84.7, 80.3, 78.2, 38.3, 36.4, 35.2, 28.2, 22.6, 13.9

HRMS (ESI) for $C_{10}H_{16}O_3$ $(M + Na)^+$ found 207.0993, calcd 207.0992

(*R*)-Dec-1-en-4-ol 25:



To a cooled mixture of (-)-Ipc_2(allyl)borane (6.28 g, 19.28 mmol) in dry diethyl ether (15 mL) at -100 °C, a solution of heptanal (2.0 g, 17.5 mmol) in diethyl ether (20 mL) was added dropwise over 10 min *via* syringe (maintaining the temperature below -90 °C). The resulting mixture was stirred vigorously at -100 °C for 1.5 h and warmed to room temperature over 1 h. A solution of 3M NaOH (3.9 mL) and 30% aq. H_2O_2 (12.8 mL) was carefully added *via* the dropping funnel, keeping the temperature below 15 °C, followed by addition of saturated aqueous $NaHCO_3$ (20 mL). The resulting mixture was stirred for 10 h at the same temperature to completely hydrolyze boronate ester product. Organic phase was then diluted with diethyl ether, extracted with the same solvent (3 x 20 mL) and combined organic layers were washed with brine (2 x 10 mL). The resulting layers then dried over anhyd. Na_2SO_4 and concentrated by rotary evaporation to afford light yellow oil which was purified by column chromatography with hexane:ethyl acetate, (96:4) to provide pure homoallylic alcohol **25**.

Yield: 2.4 g, 88%

Mol. Formula: $C_{10}H_{20}O$

$[\alpha]_D^{25}$: +6.98 (*c* 1.0, $CHCl_3$)

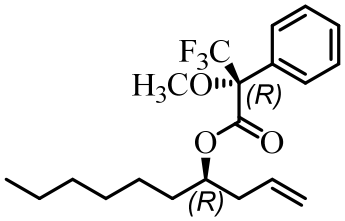
IR (neat, cm^{-1}): ν_{max} 3365, 2929, 2865, 1637, 1458, 1128, 1024

^{1}H NMR (400MHz, $CDCl_3$) δ = 5.90 - 5.78 (m, 1 H), 5.18 - 5.11 (m, 2 H), 3.70 - 3.60 (m, 1 H), 2.31 (td, *J* = 5.4, 13.7 Hz, 1 H), 2.18 - 2.10 (m, 1 H), 1.62 (d, *J* = 15.7 Hz, 2 H), 1.51 - 1.43 (m, 3 H), 1.38 (br. s., 5 H), 0.89 (t, *J* = 6.6 Hz, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 134.9, 118.1, 70.7, 41.9, 36.8, 31.8, 29.3, 25.6, 22.6, 14.1

HRMS (ESI) for $C_{10}H_{20}O$ $(M + Na)^+$ found 179.1404 , calcd 179.1406

(*R*)-Dec-1-en-4-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate:



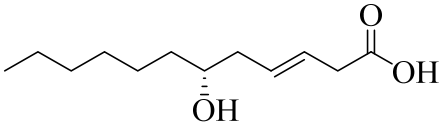
Yield: 24 g, 91%

Mol. Formula: $C_{20}H_{27}F_3O_3$

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.62 - 7.53 (m, 2 H), 7.45 - 7.36 (m, 3 H), 5.83 - 5.59 (m, 1 H), 5.25 - 5.07 (m, 3 H), 5.07 - 4.89 (m, 1 H), 3.61 - 3.51 (m, 3 H), 2.47 - 2.30 (m, 2 H), 1.74 - 1.57 (m, 2 H), 1.36 - 1.18 (m, 8 H), 0.97 - 0.79 (m, 4 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 166.2, 133.2, 132.8, 132.4, 129.5, 128.3, 127.3, 124.8, 121.9, 118.3, 84.3, 76.5, 55.5, 38.4, 33.2, 31.6, 28.9, 24.8, 22.5, 14.0

(*R*, *E*)-6-Hydroxydodec-3-enoic acid 27:



Procedure as described in the synthesis of **26**.

Yield: 630 mg, 92%

Mol. Formula: $C_{12}H_{22}O_3$

$[\alpha]_D^{25.4}$: +3.46 (*c* 2.4, $CHCl_3$)

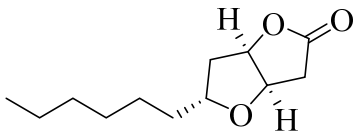
IR (neat, cm^{-1}): ν_{max} 3414, 3024, 2929, 2862, 1728, 1409, 1276, 1175

^{1}H NMR (400MHz, $CDCl_3$) δ = 5.78 - 5.57 (m, 2 H), 4.68 - 4.49 (m, 1 H), 4.49 - 4.18 (m, 1 H), 3.75 - 3.54 (m, 1 H), 3.22 - 3.03 (m, 2 H), 2.37 - 2.00 (m, 2 H), 1.53 - 1.36 (m, 3 H), 1.36 - 1.25 (m, 7 H), 0.96 - 0.76 (m, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 177.0, 131.2, 124.7, 70.9, 40.4, 37.6, 36.8, 31.8, 29.3, 25.6, 22.6, 14.1.

HRMS (ESI) for $C_{12}H_{22}O_3$ $(M + Na)^+$ found 237.1463, calcd 237.1461

(3a*R*, 5*R*, 6a*R*)-5-Hexyltetrahydrofuro[3,2-b]furan-2(3*H*)-one 3:



Procedure as described in the synthesis of **1**.

Yield: 41 mg, 83%

Mol. Formula: $C_{12}H_{20}O_3$

$[\alpha]_D^{29.4}$: +48.1 (*c* 1.0, $CHCl_3$)

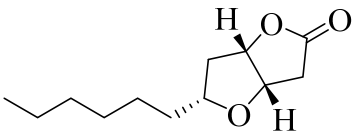
IR (neat, cm^{-1}): ν_{max} 2931, 2864, 1782, 1458, 1345, 1177, 1063

^{1}H NMR (500MHz, $CDCl_3$) δ = 5.13 (t, *J* = 4.7 Hz, 1 H), 4.84 - 4.79 (m, 1 H), 4.07 (dt, *J* = 6.3, 10.8 Hz, 3 H), 2.77 (dd, *J* = 6.6, 18.8 Hz, 1 H), 2.65 (d, *J* = 18.6 Hz, 1 H), 2.38 (dd, *J* = 4.6, 13.7 Hz, 1 H), 1.71 - 1.65 (m, 1 H), 1.64 - 1.57 (m, 1 H), 1.57 - 1.47 (m, 1 H), 1.43 - 1.29 (m, 4 H), 0.90 (t, *J* = 7.0 Hz, 3 H)

^{13}C NMR (125 MHz, $CDCl_3$) δ = 176.1, 84.9, 78.2, 77.3, 38.8, 36.6, 34.7, 31.7, 29.2, 26.0, 22.5, 14.0

HRMS (ESI) for $C_{12}H_{20}O_3$ $(M + Na)^+$ found 235.1306, calcd 235.1305

(3a*S*, 5*R*, 6a*S*)-5-Hexyltetrahydrofuro[3,2-b]furan-2(3*H*)-one 4:



Yield: 3.4 mg, 7%

Mol. Formula: $C_{12}H_{20}O_3$

$[\alpha]_D^{24.8}$: -38.0 (*c* 0.3, $CHCl_3$)

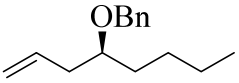
IR (neat, cm^{-1}): ν_{max} 2928, 2861, 1783, 1456, 1343, 1175, 1066

^{1}H NMR (200 MHz, $CDCl_3$) δ = 5.02 (ddd, *J* = 2.2, 4.5, 6.9 Hz, 1 H), 4.52 (td, *J* = 3.3, 4.4 Hz, 1 H), 3.94 (quin, *J* = 7.0 Hz, 1 H), 2.74 (d, *J* = 3.3 Hz, 2 H), 2.44 (td, *J* = 7.1, 14.2 Hz, 1 H), 1.89 (ddd, *J* = 2.3, 7.9, 14.2 Hz, 1 H), 1.76 - 1.60 (m, 4 H), 1.41 - 1.31 (m, 6 H), 0.89 (s, 3 H)

^{13}C NMR (125 MHz, $CDCl_3$) δ = 175.6, 84.7, 80.4, 78.2, 38.3, 36.4, 35.5, 31.7, 29.2, 26.0, 22.6, 14.0

HRMS (ESI) for $C_{12}H_{20}O_3$ $(M+Na)^+$ found 235.1307, calcd 235.1305

(*S*)- ((Oct-1-en-4-yloxy)methyl)benzene 30:



Sodium Hydride (60 % in Oil, 10 mg, 5.8 mmol) was added to a stirred solution of **28** (0.5 g, 3.9 mmol), tetrabutylammonium iodide (144 mg, 0.39 mmol) and benzyl bromide (0.56 mL, 4.68 mmol) in DMF (5 mL) at 0 °C. The mixture was stirred at ambient temperature for 2 h. The reaction was quenched by the addition of saturated aqueous ammonium chloride (5 mL) and extracted with EtOAc (3x 10 mL). The combined organic layers were dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash column chromatography (EtOAc–pet ether, 2:98) to yield compound **30** as colourless oil.

Yield: 808 mg, 95%

Mol. Formula: $C_{15}H_{22}O$

$[\alpha]_D^{25.0}$: -15.68 (*c* 1.63, $CHCl_3$)

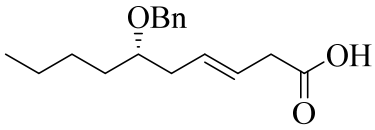
IR (neat, cm^{-1}): ν_{max} 2929, 2863, 1456, 1414, 1293, 1125, 1066

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.39 - 7.27 (m, 5 H), 5.88 (tdd, *J* = 7.0, 10.1, 17.2 Hz, 1 H), 5.14 - 5.04 (m, 2 H), 4.61 - 4.49 (m, 2 H), 3.50 - 3.42 (m, 1 H), 2.35 (tddd, *J* = 1.4, 2.8, 5.7, 7.1 Hz, 2 H), 1.64 - 1.53 (m, 2 H), 1.38 - 1.27 (m, 4 H), 0.91 (t, *J* = 7.1 Hz, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 138.9, 135.1, 128.3, 127.7, 127.4, 116.8, 78.6, 70.9, 38.3, 33.5, 27.5, 22.8, 14.1

HRMS (ESI) for $C_{15}H_{22}O$ $(M + Na)^+$ found 241.1564, calcd.241.1563

(*S*, *E*)-6-(Benzyloxy)dec-3-enoic acid 32:



Procedure as described in the synthesis of **26**. The crude compound was eluted over silica gel column chromatography using the solvent system EtOAc-pet ether (15:85).

Yield: 580 mg, 92%

Mol. Formula: $C_{17}H_{24}O_3$

$[\alpha]_D^{25.1}$: -11.72 (*c* 1.01, $CHCl_3$)

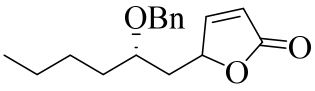
IR (neat, cm^{-1}): ν_{max} 3032, 2929, 2863, 1712, 1453, 1414, 1293, 1070

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.39 - 7.27 (m, 5 H), 5.71 - 5.55 (m, 2 H), 4.60 - 4.46 (m, 2 H), 3.43 (quin, *J* = 5.8 Hz, 1 H), 3.18 - 3.05 (m, 2 H), 2.38 - 2.27 (m, 2 H), 1.60 - 1.45 (m, 2 H), 1.44 - 1.28 (m, 5 H), 0.90 (t, *J* = 7.0 Hz, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 177.6, 138.8, 131.4, 128.3, 127.8, 127.5, 123.2, 78.5, 70.9, 37.8, 36.8, 33.5, 27.5, 22.8, 14.1

HRMS (ESI) for $C_{17}H_{24}O_3$ $(M + Na)^+$ found 299.1618, calcd 299.1618

5-((*S*)-2-(Benzyloxy)hexyl)furan-2(5*H*)-one 34:



Procedure as described in the synthesis of **3**. The crude compound was eluted from silica gel column chromatography using the solvent system EtOAC-pet ether (7:93).

Yield: 89 mg, 90%

Mol. Formula: $C_{17}H_{22}O_3$

$[\alpha]_D^{29.7}$: +97.52 (*c* 0.86, $CHCl_3$)

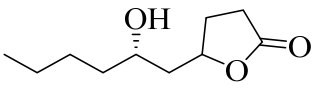
IR (neat, cm^{-1}): ν_{max} 2925, 2859, 1749, 1458, 1369, 1293, 1169, 1099, 1040

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.44 (ddd, *J* = 1.4, 5.8, 19.8 Hz, 1 H), 7.39 - 7.27 (m, 5 H), 6.12 - 5.95 (m, 1 H), 5.31 - 5.15 (m, 1 H), 4.67 (d, *J* = 11.0 Hz, 1 H), 4.51 (d, *J* = 6.4 Hz, 1 H), 4.33 (d, *J* = 11.4 Hz, 1 H), 3.52 - 3.44 (m, 1 H), 2.12 - 2.01 (m, 1 H), 2.01 - 1.87 (m, 1 H), 1.65 - 1.53 (m, 2 H), 1.37 - 1.30 (m, 4 H), 0.95 - 0.87 (m, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 173.2, 173.2, 157.3, 157.2, 138.3, 138.2, 128.5, 127.9, 127.8, 127.8, 121.0, 120.3, 81.0, 80.8, 76.0, 74.6, 71.9, 70.6, 39.0, 37.4, 33.7, 33.0, 27.2, 26.9, 22.8, 22.8, 14.0

HRMS (ESI) for $C_{17}H_{22}O_3$ $(M + Na)^+$ found 297.1461, calcd 297.1461

5-((*S*)-2-Hydroxyhexyl)dihydrofuran-2(3*H*)-one 36:



To a stirred solution of **34** (50 mg, 0.18 mmol) in EtOH (3 mL) was added 10% w/w Pd/C (5 mg, 0.1 w/w) and the mixture was stirred for 3 h under H_2 atmosphere. Then, the Pd/C was

filtered off and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (EtOAC-petether, 30:70) to afford compound **36** as a colorless liquid.

Yield: 32.5 mg, 96%

Mol. Formula: $C_{10}H_{18}O_3$

$[\alpha]_D^{25.2}$: +13.55 (*c* 0.81, $CHCl_3$)

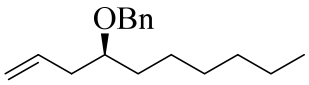
IR (neat, cm^{-1}): ν_{max} 3441, 2926, 2859, 1771, 1458, 1361, 1185, 1032

^{1}H NMR (500MHz, $CDCl_3$) δ = 4.70 (tt, *J* = 6.1, 7.9 Hz, 1 H), 3.84 - 3.78 (m, 1 H), 2.58 - 2.52 (m, 2 H), 2.44 - 2.33 (m, 1 H), 1.98 - 1.86 (m, 2 H), 1.84 - 1.73 (m, 2 H), 1.73 - 1.64 (m, 1 H), 1.54 - 1.31 (m, 7 H), 0.91 (dt, *J* = 1.5, 7.0 Hz, 3 H)

^{13}C NMR (125MHz, $CDCl_3$) δ = 177.2, 176.9, 79.5, 78.1, 69.4, 68.4, 43.1, 42.6, 37.7, 37.2, 29.7, 28.9, 28.5, 28.5, 28.3, 27.6, 27.6, 22.6, 22.6, 14.0

HRMS (ESI) for $C_{10}H_{18}O_3$ $(M + Na)^+$ found 209.1149, calcd 209.1148

(*S*)-((Dec-1-en-4-yloxy)methyl)benzene 31:



Procedure as described in the synthesis of **29**. The crude product was purified by flash column chromatography (EtOAc–pet ether, 2:98) to yield compound **31** as colourless oil.

Yield: 749 mg, 95%

Mol. Formula: $C_{17}H_{26}O$

$[\alpha]_D^{24.2}$: -8.83 (*c* 1.02, $CHCl_3$)

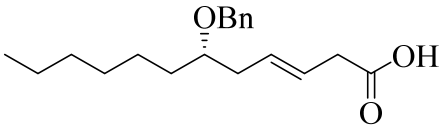
IR (neat, cm^{-1}): ν_{max} 2927, 2864, 1458, 1412, 1291, 1129, 1068

^{1}H NMR (200MHz, $CDCl_3$) δ = 7.41 - 7.33 (m, 5 H), 5.88 (tdd, *J* = 7.1, 10.1, 17.2 Hz, 1 H), 5.18 - 5.02 (m, 2 H), 4.63 - 4.46 (m, 3 H), 3.45 (quin, *J* = 5.7 Hz, 1 H), 2.40 - 2.29 (m, 2 H), 1.54 - 1.29 (m, 10 H), 0.93 - 0.88 (m, 3 H)

^{13}C NMR (50MHz, $CDCl_3$) δ = 139.0, 135.1, 128.2, 127.7, 116.7, 78.5, 70.8, 38.3, 33.8, 31.8, 29.4, 25.3, 22.6, 14.1

HRMS (ESI) for $C_{17}H_{26}O$ $(M + Na)^+$ found 269.1877, calcd 269.1876

(*S*, *E*)-6-(Benzyloxy)dodec-3-enoic acid 33:



Procedure as described in the synthesis of **26**. The crude compound was eluted over silica gel column chromatography using the solvent system EtOAc-pet ether (14:86).

Yield: 552 mg, 90%

Mol. Formula: $C_{19}H_{28}O_3$

$[\alpha]_D^{26.2}$: -8.8 (*c* 3.2, $CHCl_3$)

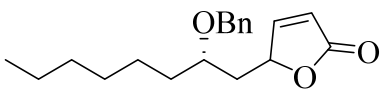
IR (neat, cm^{-1}): ν_{max} 3034, 2928, 2863, 1710, 1454, 1412, 1295, 1072

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.39 - 7.26 (m, 5 H), 5.77 - 5.54 (m, 2 H), 4.63 - 4.44 (m, 2 H), 3.52 - 3.37 (m, 1 H), 3.18 - 3.03 (m, 2 H), 2.40 - 2.22 (m, 2 H), 1.58 - 1.45 (m, 2 H), 1.44 - 1.27 (m, 9 H), 0.90 (t, *J* = 6.6 Hz, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 178.1, 138.8, 131.4, 128.3, 127.8, 127.5, 123.2, 78.5, 77.3, 76.7, 70.9, 37.8, 36.8, 33.8, 31.8, 29.4, 25.3, 22.6, 14.1

HRMS (ESI) for $C_{19}H_{28}O_3$ $(M + Na)^+$ found 327.1932, calcd 327.1931

5-((*S*)-2-(Benzyloxy)octyl)furan-2(5*H*)-one 35:



Procedure as described in the synthesis of **1**. The crude compound was eluted over silica gel column chromatography using the solvent system EtOAc-petether (6:94).

Yield: 90.4 mg, 91%

$[\alpha]_D^{26.4}$: +41.8 (*c* 2.3, $CHCl_3$)

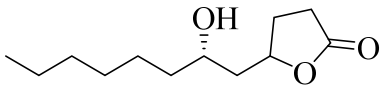
IR (neat, cm^{-1}): ν_{max} 2929, 2862, 1750, 1457, 1368, 1294, 1167, 1096, 1042

^{1}H NMR (200MHz, $CDCl_3$) δ = 7.42 - 7.32 (m, 1 H), 7.30 - 7.21 (m, 6 H), 6.03 - 5.92 (m, 1 H), 5.26 - 5.06 (m, 1 H), 4.64 - 4.44 (m, 1 H), 4.44 - 4.34 (m, 1 H), 4.34 - 4.21 (m, 1 H), 3.56 - 3.35 (m, 1 H), 2.09 - 1.75 (m, 2 H), 1.62 - 1.40 (m, 3 H), 1.34 (br. s., 1 H), 1.22 (br. s., 6 H), 0.84 - 0.78 (m, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 173.3, 173.2, 157.3, 157.2, 138.3, 138.2, 128.4, 128.3, 127.9, 127.8, 127.7, 127.5, 121.0, 120.3, 81.0, 80.8, 78.3, 76.0, 74.6, 71.9, 71.0, 70.6, 38.9, 37.4, 34.0, 33.8, 33.3, 31.9, 31.8, 31.7, 29.4, 29.3, 25.3, 25.0, 24.7, 22.7, 22.5, 14.0

HRMS (ESI) for $C_{19}H_{26}O_3$ $(M + Na)^+$ found 325.1774, calcd 325.177

5-((*S*)-2-Hydroxyoctyl)dihydrofuran-2(3*H*)-one 37:



Procedure as described in the synthesis of **35**. The crude compound was eluted over silica gel column chromatography using the solvent system EtOAc-pet ether (30:70)

Yield: 34 mg, 96%

Mol. Formula: $C_{12}H_{22}O_3$

$[\alpha]_D^{26.29}$: +4.04 (*c* 1.3, $CHCl_3$)

IR (neat, cm^{-1}): ν_{max} 3443, 2926, 2863, 1774, 1459, 1364, 1187, 1039

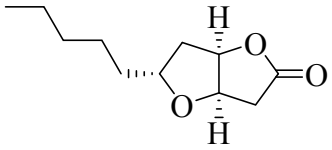
^{1}H NMR (400MHz, $CDCl_3$) δ = 4.86 - 4.65 (m, 1 H), 3.93 - 3.76 (m, 1 H), 2.61 - 2.49 (m, 2 H), 2.45 - 2.33 (m, 1 H), 2.00 - 1.85 (m, 2 H), 1.84 - 1.63 (m, 2 H), 1.55 - 1.39 (m, 3 H), 1.29 (br. s., 7 H), 0.89 (t, *J* = 6.4 Hz, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 177.2, 176.9, 79.5, 78.1, 69.4, 68.5, 43.1, 42.6, 38.0, 37.5, 31.7, 29.7, 29.2, 28.9, 28.54, 28.49, 28.3, 25.4, 22.6, 14.0

HRMS (ESI) for $C_{12}H_{22}O_3$ $(M + Na)^+$ found 237.1463, calcd 237.1461

Tandem Iodolactonization-etherification optimization:

(3a*R*, 5*R*, 6a*R*)-5-Pentyltetrahydrofuro[3,2-b]furan-2(3*H*)-one A:



Procedure as described in the synthesis of **3**.

Mol. Formula: $C_{11}H_{18}O_3$

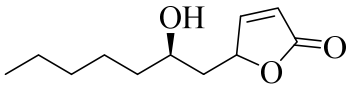
$[\alpha]_D^{24.9}$: +38.25 (*c* 0.44, $CHCl_3$)

^{1}H NMR (400MHz, $CDCl_3$) δ = 5.13 (t, *J* = 4.8 Hz, 1 H), 4.82 (t, *J* = 5.3 Hz, 1 H), 4.08 (dt, *J* = 5.7, 10.8 Hz, 1 H), 2.82 - 2.72 (m, 1 H), 2.65 (d, *J* = 18.6 Hz, 1 H), 2.38 (dd, *J* = 4.5, 13.8 Hz, 1 H), 1.72 - 1.65 (m, 1 H), 1.56 - 1.28 (m, 8 H), 0.92 - 0.87 (m, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 176.0, 84.9, 78.3, 77.3, 38.8, 36.6, 34.6, 31.7, 25.7, 22.5, 14.0

HRMS (ESI) for $C_{11}H_{18}O_3$ $(M + H)^+$ found 199.1331, calcd 199.1329

5-((*R*)-2-Hydroxyheptyl)furan-2(5*H*)-one C:



Mol. Formula: $C_{11}H_{18}O_3$

$[\alpha]_D^{25.2}$: -9.92 (*c* 0.4, $CHCl_3$)

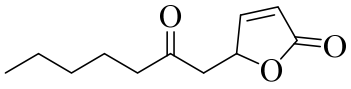
IR (neat, cm^{-1}): ν_{max} 3440, 3097, 2926, 2859, 1750, 1457, 1368, 1167, 1090, 1042

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.57 (ddd, *J* = 1.4, 5.6, 18.2 Hz, 1 H), 6.11 (dt, *J* = 2.1, 6.1 Hz, 1 H), 5.36 - 5.22 (m, 1 H), 4.00 - 3.89 (m, 1 H), 1.97 - 1.87 (m, 1 H), 1.69 - 1.62 (m, 1 H), 1.56 - 1.43 (m, 3 H), 1.39 - 1.30 (m, 5 H), 0.92 - 0.88 (m, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 177.0, 173.2, 157.4, 156.9, 121.1, 121.1, 81.7, 81.2, 68.9, 68.7, 40.9, 40.4, 38.1, 37.5, 31.8, 31.7, 25.2, 25.2, 22.7, 14.1

HRMS (ESI) for $C_{11}H_{18}O_3$ $(M + Na)^+$ found 221.1150, calcd 221.1148

5-(2-Oxoheptyl)furan-2(5*H*)-one D:



Mol. Formula: $C_{11}H_{16}O_3$

$[\alpha]_D^{25.1}$: -1.5 (*c* 0.19, $CHCl_3$)

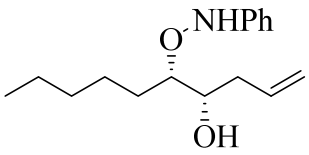
IR (neat, cm^{-1}): ν_{max} 2926, 2863, 1748, 1710, 1458, 1367, 1166, 1091 1045

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.65 - 7.57 (m, 1 H), 6.14 (dd, *J* = 2.1, 5.7 Hz, 1 H), 5.49 - 5.40 (m, 1 H), 3.05 (dd, *J* = 6.4, 17.4 Hz, 1 H), 2.65 (dd, *J* = 7.6, 17.2 Hz, 1 H), 2.47 (dt, *J* = 3.2, 7.3 Hz, 2 H), 1.39 - 1.30 (m, 6 H), 0.90 (s, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 206.7, 176.1, 156.1, 121.7, 79.0, 45.2, 43.4, 31.2, 23.2, 22.4, 13.9

HRMS (ESI) for $C_{11}H_{16}O_3$ $(M + Na)^+$ found 219.0994, calcd 219.0992

(4*S*, 5*S*)-5-((Phenylamino)oxy)dec-1-en-4-ol 39:



To a stirred solution of heptanal (3.2 g, 28.0 mmol) and nitrosobenzene (2.5, 23.3 mmol) in DMSO (47 mL), L-proline (0.5 g, 4.65 mmol) was added. After being stirred for 20 min at rt (The endpoint of the reaction was monitored by its colour change from green to orange), allyl bromide (3.0 ml, 35.0 mmol), NaI (5.25 g, 35.0 mmol), and indium powder (4.01 g, 35.0 mmol) were added at rt. The stirring was kept at room temperature for 30 min. The reaction mixture was quenched with 0.5 M aq HCl (25 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash column chromatography (EtOAc-petroleum ether, 3:97) to afford the title compound (4*S*, 5*S*)-5-((phenylamino)oxy)hept-1-en-4-ol **39** (2.55 g, 42%) and the more quickly eluting (4R, 5S)-5-((phenylamino)oxy)dec-1-en-4-ol **40** (1.75 g, 28%). The diastereomeric ratios of the products were determined by weighing the separated isomers.

***Syn* 39:**

Yield: 2.55 g, 42%

Mol. Formula: $C_{16}H_{25}O_2N$

$[\alpha]_D^{26.2}$: -28.4° (*c* 1.6, $CHCl_3$)

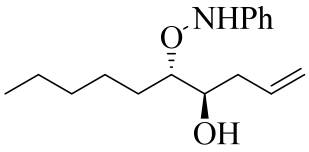
IR (neat, cm^{-1}): ν_{max} 3394, 3275, 3074, 2929, 2863, 1640, 1600, 1484, 1459, 1375, 1320, 1041

^{1}H NMR (500MHz, $CDCl_3$) δ = 7.31 - 7.27 (m, 2 H), 7.09 (s, 1 H), 7.02 - 6.97 (m, 3 H), 5.90 (tdd, *J* = 7.1, 10.1, 17.2 Hz, 1 H), 5.21 - 5.13 (m, 2 H), 4.03 (t, *J* = 5.6 Hz, 1 H), 3.89 (td, *J* = 2.9, 8.5 Hz, 1 H), 2.57 (br. s., 1 H), 2.32 (t, *J* = 6.9 Hz, 2 H), 1.76 - 1.65 (m, 2 H), 1.65 - 1.52 (m, 2 H), 1.52 - 1.36 (m, 4 H), 0.94 - 0.90 (m, 3 H)

^{13}C NMR (125MHz, $CDCl_3$) δ = 148.3, 135.1, 129.0, 122.4, 117.7, 114.9, 85.8, 72.2, 36.9, 31.9, 28.2, 26.0, 22.5, 14.0

HRMS (ESI) for $C_{16}H_{25}O_2N$ $(M + Na)^+$ found 286.1782, calcd 286.1778

***Anti* 40:**



Yield: 1.75 g, 28%

Mol. Formula: $C_{16}H_{25}O_2N$

$[\alpha]_D^{26.4}$: -20.2° (*c* 1.4, $CHCl_3$)

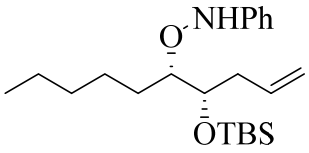
IR (neat, cm^{-1}): ν_{max} 3396, 3285, 3075, 2929, 2863, 1640, 1600, 1480, 1459, 1375, 1320, 104

^1H NMR (500 MHz, $CDCl_3$) δ = 7.31 - 7.27 (m, 2 H), 7.03 - 6.99 (m, 3 H), 5.96 - 5.87 (m, 1 H), 5.20 - 5.14 (m, 2 H), 3.87 (ddd, *J* = 4.1, 5.7, 8.2 Hz, 1 H), 3.79 (q, *J* = 5.8 Hz, 1 H), 2.48 - 2.41 (m, 1 H), 2.33 - 2.25 (m, 1 H), 1.74 - 1.63 (m, 2 H), 1.52 - 1.44 (m, 2 H), 1.37 - 1.31 (m, 4 H), 0.90 (t, *J* = 6.9 Hz, 3 H)

^{13}C NMR (125 MHz, $CDCl_3$) δ = 148.0, 134.6, 129.0, 122.6, 117.9, 115.3, 85.4, 72.7, 38.2, 32.0, 29.4, 25.3, 22.5, 14.0

HRMS (ESI) for $C_{16}H_{25}O_2N$ $(M + Na)^+$ found 286.1782, calcd 286.1778

O-((4*S*, 5*S*)-4-((tert-butyldimethylsilyl)oxy)dec-1-en-5-yl)-N-phenylhydroxylamine 41:



To a stirred solution of compound **39** (2.4 g, 9.1 mmol) in CH_2Cl_2 (30.0 mL) at 0 °C was added Et_3N (2.8 mL, 20.07 mmol), followed by TBDMSOTf (2.5 mL, 10.9 mmol) and the mixture was stirred for 15 min. The reaction mixture was quenched with sat. NH_4Cl solution (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the crude **41** as yellow liquid.

Yield: 3.33 g, 97%

Mol. Formula: $C_{22}H_{39}O_2$

$[\alpha]_D^{26}$: -22.2° (*c* 1.6, $CHCl_3$)

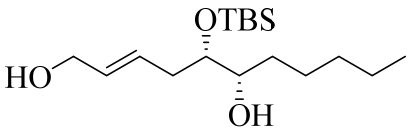
IR (neat, cm^{-1}): ν_{max} 3296, 3074, 2942, 2861, 1641, 1601, 1463, 1421, 1372, 1252, 1081

^{1}H NMR (500MHz, $CDCl_3$) δ = 7.32 - 7.27 (m, 3 H), 7.03 - 6.94 (m, 3 H), 5.90 (tdd, *J* = 7.2, 10.0, 17.1 Hz, 1 H), 5.16 - 5.06 (m, 2 H), 4.00 (ddd, *J* = 2.1, 5.0, 7.2 Hz, 1 H), 3.88 - 3.82 (m, 1 H), 2.41 (td, *J* = 7.1, 14.3 Hz, 1 H), 2.34 - 2.27 (m, 1 H), 1.73 - 1.61 (m, 2 H), 1.57 - 1.43 (m, 2 H), 1.42 - 1.34 (m, 4 H), 0.98 - 0.93 (m, 12 H), 0.13 (s, 6 H)

^{13}C NMR (125 MHz, $CDCl_3$) δ = 148.8, 135.7, 128.8, 121.6, 116.9, 114.3, 86.6, 74.0, 37.6, 32.0, 29.4, 26.2, 25.9, 22.6, 18.2, 14.1, -4.3, -4.4

HRMS (ESI) for $C_{22}H_{39}O_2$ $(M + H)^+$ found 378.2830, calcd 378.2823

(5*S*, 6*S*, *E*)-5-((Tert-butyldimethylsilyl)oxy)undec-2-ene-1,6-diol 42:



To a stirred solution of **41** (300 mg, 0.79 mmol) in CH_2Cl_2 (5.0 mL) was added compound (*Z*)-but-2-ene-1,4-diol (0.140 g, 1.59 mmol) and degassed for 15 min. Then Grubb's II catalyst (13.5 mg, 2 mol %) was added to the reaction mixture and stirred for 1h at reflux. After completion of reaction, solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (EtOAc–pet ether, 30:70) to afford compound **42** as yellow oil.

Yield: 213 mg, 87%

Mol. Formula: $C_{17}H_{36}O_3Si$

$[\alpha]_D^{26.83}$: +0.16 (*c* 1.18, $CHCl_3$)

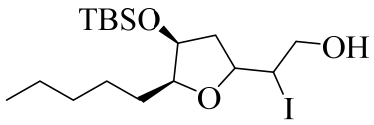
IR (neat, cm^{-1}): ν_{max} 3355, 2951, 2861, 1462, 125, 1080, 1009

^{1}H NMR (500MHz, $CDCl_3$) δ = 5.75 - 5.63 (m, 2 H), 4.10 (d, *J* = 4.3 Hz, 2 H), 3.56 (ddd, *J* = 3.7, 4.7, 7.2 Hz, 1 H), 3.43 (td, *J* = 4.0, 8.2 Hz, 1 H), 2.42 (td, *J* = 6.7, 13.2 Hz, 1 H), 2.21 (td, *J* = 5.5, 13.5 Hz, 1 H), 1.87 (br. s., 3 H), 1.48 - 1.37 (m, 3 H), 1.36 - 1.24 (m, 7 H), 0.92 - 0.89 (m, 13 H), 0.09 (d, *J* = 4.6 Hz, 6 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 131.9, 128.2, 74.5, 72.4, 63.5, 37.0, 34.0, 31.9, 25.8, 25.5, 22.6, 18.1, 14.0, -4.1, -4.7

HRMS (ESI) for $C_{17}H_{36}O_3Si$ $(M + H)^+$ found 317.2507, calcd 317.2506

2-((4*S*, 5*S*)-4-((Tert-butyldimethylsilyl)oxy)-5-pentyltetrahydrofuran-2-yl)-2-iodoethan-1-ol 43:



Procedure as described in the synthesis of **3**. The residue was purified by silica gel column chromatography using EtOAc–petether, 8:92 to give **43** (182 mg, 92%) as yellow oil.

Yield: 182 mg, 92%

Mol. Formula: $C_{17}H_{35}O_3ISi$

$[\alpha]_D^{24.8}$: +28.24 (*c* 2.6, $CHCl_3$)

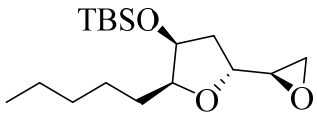
IR (neat, cm^{-1}): ν_{max} 3384, 2929, 2861, 1463, 1359, 1145, 1089, 1029, 753, 514

^{1}H NMR (400MHz, $CDCl_3$) δ = 4.40 (dt, *J* = 6.1, 9.4 Hz, 1 H), 4.20 - 4.15 (m, 1 H), 4.04 - 3.89 (m, 4 H), 2.30 (dd, *J* = 6.2, 13.1 Hz, 1 H), 1.84 (ddd, *J* = 4.2, 9.4, 13.3 Hz, 1 H), 1.66 - 1.41 (m, 3 H), 1.41 - 1.29 (m, 6 H), 0.94 - 0.89 (m, 13 H), 0.08 (d, J = 9.5 Hz, 6 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 86.0, 84.9, 82.9, 82.0, 77.2, 72.7, 72.0, 68.7, 68.5, 44.4, 42.1, 38.7, 38.2, 32.0, 31.9, 29.9, 29.4, 25.9, 25.9, 25.8, 25.7, 22.6, 18.1, 14.0, -4.5, -5.1, -5.2

HRMS (ESI) for $C_{17}H_{35}O_3ISi$ $(M + Na)^+$ found 465.1292, calcd 465.1292

Tert-butyldimethyl(((2*S*,3*S*,5*R*)-5-((*R*)-oxiran-2-yl)-2-pentyltetrahydrofuran-3-yl)oxy)silane 44:



To a solution of crude compound **43** (150 mg, 0.34 mmol) in CH_2Cl_2 (10 mL) was added finely powdered KOH (57 g, 1.01 mmol). The mixture was stirred vigorously for 16h and poured into 10mL water. After separation of the layers, the aqueous layer was extracted with CH_2Cl_2 (3 x 5mL) and the combined organic layers were dried over Na_2SO_4 Evaporation of the solvent and silica gel column chromatographic purification (EtOAc–pet ether, 6:94) of the crude product gave the separable compounds **44** and **45** (102 mg, 96 %) as a colourless liquid.

Yield: 102 mg, 81 %

Mol. Formula: $C_{17}H_{34}O_3Si$

$[\alpha]_D^{27}$: +28.48 (*c* 0.8, $CHCl_3$)

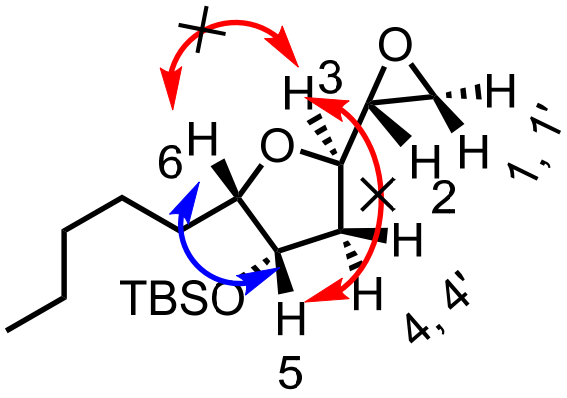
IR (neat, cm^{-1}): ν_{max} 2929, 2863, 1592, 1458, 1355, 1110, 1080

^{1}H NMR (500MHz, $CDCl_3$) δ = 4.27 - 4.23 (m, 1 H), 4.15 (ddd, *J* = 4.3, 7.0, 8.9 Hz, 1 H), 3.77 (dt, *J* = 3.1, 6.7 Hz, 1 H), 3.02 - 2.98 (m, 1 H), 2.83 - 2.76 (m, 2 H), 2.05 - 1.96 (m, 2 H), 1.60 - 1.48 (m, 2 H), 1.46 - 1.28 (m, 7 H), 0.95 - 0.88 (m, 13 H), 0.08 (d, *J* = 7.6 Hz, 6 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 84.1, 75.6, 73.0, 54.2, 44.7, 38.8, 32.1, 29.4, 26.0, 25.7, 22.6, 18.0, 14.1, -4.5, -5.1

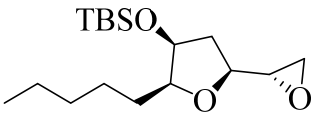
HRMS (ESI) for $C_{17}H_{34}O_3Si$ $(M + Na)^+$ found 337.2169, calcd 337.2169

NOESY:



In NOESY analysis of compound *tans* THF-epoxide, H5 proton shows nOe correlation with both methine proton H6 indicating *syn* stereochemistry among them. H3 proton does not show any nOe correlation with H5 and H6 indicating that H3 is relatively *anti* to both H5 and H6. Furthermore there is no correlation between H3 and H6 indicating *anti* stereochemistry.

Tert-butyldimethyl(((2*S*,3*S*,5*S*)-5-((*S*)-oxiran-2-yl)-2-pentyltetrahydrofuran-3-yl)oxy)silane 45:



Yield: 15%

Mol. Formula: $C_{17}H_{34}O_3Si$

$[\alpha]_D^{24}$: +27.33 (*c* 1.44, $CHCl_3$)

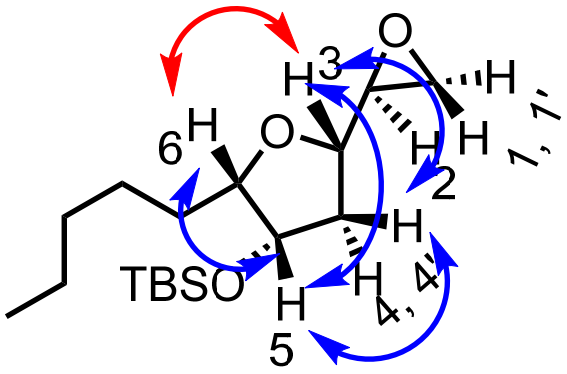
IR (neat, cm^{-1}): ν_{max} 2928, 2861, 1594, 1456, 1354, 1115, 1084

^{1}H NMR (400MHz, $CDCl_3$) δ = 4.21 (ddd, *J* = 2.2, 3.4, 5.2 Hz, 1 H), 3.69 (dt, *J* = 3.7, 6.6 Hz, 1 H), 3.55 (ddd, *J* = 4.6, 7.3, 8.8 Hz, 1 H), 3.21 (ddd, *J* = 2.8, 4.2, 7.2 Hz, 1 H), 2.78 (t, *J* = 4.5 Hz, 1 H), 2.54 (dd, *J* = 2.7, 4.9 Hz, 1 H), 2.27 (ddd, *J* = 5.3, 8.7, 13.6 Hz, 1 H), 1.83 - 1.74 (m, 1 H), 1.71 - 1.54 (m, 3 H), 1.49 - 1.34 (m, 2 H), 1.31 (br. s., 3 H), 0.93 - 0.88 (m, 13 H), 0.09 - 0.06 (m, 6 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 84.4, 79.6, 72.4, 54.8, 43.9, 38.7, 32.1, 29.5, 26.0, 25.7, 22.7, 18.0, 14.1, -4.5, -5.1

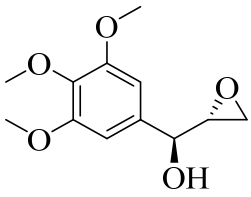
HRMS (ESI) for $C_{17}H_{34}O_3Si$ $(M + Na)^+$ found 337.2169, calcd 337.2169

NOESY:



In NOESY analysis of compound ***cis* THF**-epoxide, H5 proton shows nOe correlation with both methine protons H3 and H6 indicating *syn* stereochemistry among them. The relative stereochemistry was also confirmed with the help of methylene group which shows two different signals for two protons (H4 and H4'). The H3 and H5 methine protons showed nOe correlations only with H4' proton (1.66 ppm), but it does not show any correlation with H4 (2.4 ppm) proton indicating all the three methine protons (H3, H4' and H5) being *syn* to each other.

(*S*)-((*R*)-Oxiran-2-yl)(3,4,5-trimethoxyphenyl)methanol 47:



To a solution of 4 Å MS powder (6.0 g) in anhydrous CH_2Cl_2 (50.0 mL) was added (+) DIPT (2.8 mL, 13.4 mmol) at –20 ˚C, followed by $Ti(O\text{-}i\text{-}Pr)_4$ (3.96 mL, 13.4 mmol) and stirred for 30 min, to this mixture was added allyl alcohol **46** (3.0 g, 13.4 mmol) in anhydrous CH_2Cl_2 (10.0 mL) drop wise at same temperature and stirred for 30 min, ^{t}BuOOH (6.0 M in decane, 4.46 mL, 26.8 mmol) was added drop wise and the resultant RM was kept

without disturbing in refrigerator at –20 ˚C, after 18 h (reaction was monitored by TLC for ~50% conversion) saturated aqueous Na_2SO_4 (30 mL), was added and allowed to warm to rt, stirred for 3 h, solids formed were filtered through a pad of celite and concentrated in vacuo. The crude product was purified by flash chromatography over 200-400 mesh silica gel (30-50% EtOAc-pet ether) to afford compound **47** as yellow oil.

Yield: 1.44 g, 45%

Mol. Formula: $C_{12}H_{16}O_5$

$[\alpha]_D^{25.4}$: +57.9840 (*c* 2.0, $CHCl_3$)

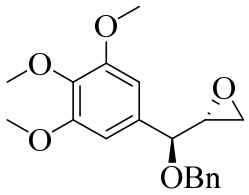
IR (neat, cm^{-1}): ν_{max} 3458, 2941, 2839, 1592, 1504, 1461, 1330, 1236, 1001

^{1}H NMR (500MHz, $CDCl_3$) δ = 6.62 (s, 2 H), 4.84 (d, *J* = 2.7 Hz, 1 H), 3.88 (s, 6 H), 3.84 (s, 3 H), 3.27 - 3.18 (m, 1 H), 2.96 (dd, *J* = 2.8, 4.8 Hz, 1 H), 2.79 (dd, *J* = 4.0, 4.9 Hz, 1 H), 2.36 (s, 1 H)

^{13}C NMR (50 MHz, $CDCl_3$) δ = 153.3, 137.6, 135.3, 103.2, 77.2, 71.1, 60.7, 56.0, 55.0, 43.8

HRMS (ESI) for $C_{12}H_{16}O_5$ $(M+Na)^+$ found 263.0885, calcd 263.0890

(*R*)-2-((*S*)-(Benzyloxy)(3,4,5-trimethoxyphenyl)methyl)oxirane 48:



Sodium Hydride (60 % in Oil, 0.25g, 6.25 mmol) was added to a stirred solution of **47** (1.0 g, 4.1 mmol), tetrabutylammonium iodide (154 mg, 0.41 mmol) and benzyl bromide (0.74 mL, 6.25 mmol) in DMF (10 mL) at -78 °C to 0 °C. The mixture was stirred at ambient temperature for 1 h. The reaction was quenched by the addition of saturated aqueous ammonium chloride (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified

by flash column chromatography (EtOAc–pet ether, 20:80) to yield compound **48** as yellow oil.

Yield: 1.32 g, 95%

Mol. Formula: $C_{19}H_{22}O_5$

$[\alpha]_D^{25.5}$: +60.1 (*c* 2.4 , $CHCl_3$)

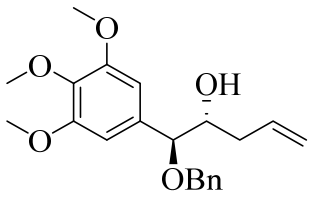
IR (neat, cm^{-1}): ν_{max} 2938, 2840, 1592, 1460, 1335, 1235, 1125, 1009

^{1}H NMR (200MHz, $CDCl_3$) δ = 7.40 - 7.29 (m, 5 H), 6.61 (s, 2 H), 4.59 (d, *J* = 11.9 Hz, 1 H), 4.42 (d, *J* = 11.9 Hz, 1 H), 4.25 (d, *J* = 4.5 Hz, 1 H), 3.87 (d, *J* = 1.0 Hz, 10 H), 3.18 (dt, *J* = 2.7, 4.2 Hz, 1 H), 2.86 - 2.74 (m, 2 H)

^{13}C NMR (50MHz, $CDCl_3$) δ = 153.3, 137.9, 137.7, 133.9, 128.3, 127.7, 104.1, 80.2, 70.8, 60.7, 56.0, 54.4, 45.4

HRMS (ESI) for $C_{19}H_{22}O_5$ $(M + Na)^+$ found 353.1351, calcd 353.1359

(1*S*, 2*R*)-1-(Benzyloxy)-1-(3,4,5-trimethoxyphenyl)pent-4-en-2-ol 49:



To a solution of CuI (0.058 g, 3.03 mmol) in anhydrous THF (5 mL) was added vinylmagnesium bromide (1.6 M in THF, 2.84 mL, 4.54 mmol) at –20 ˚C and stirred for 10 min, followed by a solution of above obtained epoxide **48** (1.0 g, 30.3 mmol) in anhydrous THF (10 mL) was added dropwise and stirred at same temperature for 2 h, RM was quenched by adding saturated aqueous NH_4Cl (10 mL), extracted with EtOAc (3 x 10 mL), combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash chromatography over 230-400 mesh silica gel (15% EtOAc-Pet ether) to afford alcohol **49** as yellow oil.

Yield: 1.03 g, 95%

Mol. Formula: $C_{21}H_{26}O_5$

$[\alpha]_D^{25.6}$: + 57.7 (*c* 1.0, $CHCl_3$)

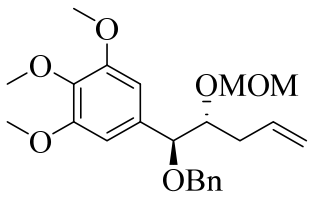
IR (neat, cm^{-1}): ν_{max} 3458, 2928, 2851, 1590, 1458, 1336, 1240, 1128, 1020

^{1}H NMR (200MHz, $CDCl_3$) δ = 7.39 - 7.30 (m, 5 H), 6.61 (s, 2 H), 6.00 - 5.77 (m, 1 H), 5.20 - 5.07 (m, 2 H), 4.53 (d, *J* = 11.6 Hz, 1 H), 4.32 (d, *J* = 11.6 Hz, 1 H), 4.22 (d, *J* = 6.1 Hz, 1 H), 3.90 - 3.85 (m, 10 H), 2.56 - 2.41 (m, 1 H), 2.33 - 2.16 (m, 1 H), 1.81 (d, *J* = 4.4 Hz, 1 H)

^{13}C NMR (50MHz, $CDCl_3$) δ = 153.4, 138.0, 134.9, 134.0, 128.4, 127.9, 127.8, 117.6, 104.5, 84.0, 73.8, 70.9, 60.8, 56.1, 37.2

HRMS (ESI) for $C_{21}H_{26}O_5$ $(M + Na)^+$ found 381.1663, calcd 381.1672

5-((1*S*, 2*R*)-1-(Benzyloxy)-2-(methoxymethoxy)pent-4-en-1-yl)-1,2,3-trimethoxybenzene 50:



To a solution of alcohol **49** (0.9 g, 8.4 mmol) in dry CH_2Cl_2 (10 mL) was added diisopropylethylamine (1.3 mL, 7.54 mmol) at 0 °C. To this mixture MOM chloride (0.29 ml, 3.77 mmol) was added slowly with further stirring for 18 h at 40 °C. The reaction mixture was quenched with the addition of cold water at 0 °C. The two phases were separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with water (3 × 10 mL), brine, dried over Na_2SO_4 and concentrated to give crude **50**. It was purified by silica gel column chromatography using EtOAc–pet ether, (10:90) as the eluent to furnish **50** as colourless oil.

Yield: 0.93 g, 92%

Mol. Formula: $C_{23}H_{30}O_6$

$[\alpha]_D^{25.7}$: +28.18 (*c* 2.19, $CHCl_3$)

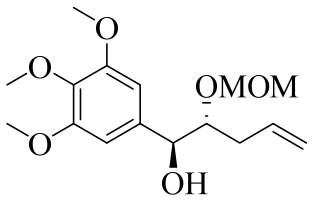
IR (neat, cm^{-1}): ν_{max} 2956, 2929, 1584, 1507, 1420, 1325, 1148, 1006

^{1}H NMR (200MHz, $CDCl_3$) δ = 7.37 - 7.30 (m, 5 H), 6.62 (s, 2 H), 5.89 (tdd, *J* = 7.1, 10.1, 17.1 Hz, 1 H), 5.20 - 5.05 (m, 2 H), 4.54 - 4.44 (m, 2 H), 4.34 - 4.22 (m, 3 H), 3.86 (s, 10 H), 3.85 - 3.77 (m, 1 H), 3.11 (s, 3 H), 2.50 (dd, *J* = 5.6, 6.8 Hz, 2 H)

^{13}C NMR (50MHz, $CDCl_3$) δ = 153.1, 138.1, 137.4, 135.1, 134.7, 128.3, 127.8, 127.6, 117.3, 104.7, 96.0, 82.4, 79.6, 70.7, 60.8, 56.1, 55.4, 35.7

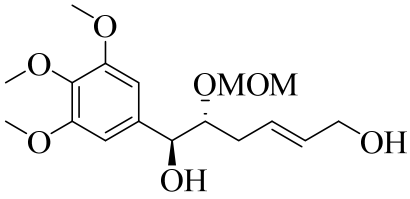
HRMS (ESI) for $C_{23}H_{30}O_6$ $(M + Na)^+$ found 425.1927, calcd 425.1935

(1*S*, 2*R*)-2-(Methoxymethoxy)-1-(3,4,5-trimethoxyphenyl)pent-4-en-1-ol 51:



To a solution of benzyl ether **50** (0.9 g, 2.23 mmol) in DCE-P^H=7 buffer (19 : 1) mL was added DDQ (0.762 g, 3.35 mmol) at rt with further stirring for 3 h under reflux conditions. The reaction mixture was quenched with addition of cold water, stirred for 30 min, then sat. $NaHCO_3$ solution was added, stirred for 30 min, and then filtered through celite. The two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with sat. $NaHCO_3$ (2 × 10 mL), brine, dried over Na_2SO_4 and concentrated to give crude **51**. It was purified by silica gel column chromatography using EtOAc–pet ether (15:85) as the eluent to furnish **51** as yellow oil. Crude compound was taken to the next step without any characterization.

(5*R*, 6*S*, *E*)-5-(Methoxymethoxy)-6-(3, 4, 5-trimethoxyphenyl)hex-2-ene-1,6-diol 52:



To a stirred solution of **51** (100 mg, 3.2 mmol) in CH_2Cl_2 (5.0 mL) was added compound (*Z*)-but-2-ene-1,4-diol (0.056 g, 6.41 mmol) and degassed for 15 min. Then Grubb's II catalyst (5.5 mg, 2 mol %) was added to the reaction mixture and stirred for 1h at reflux. After completion of reaction, solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (EtOAc–petroleum ether, 40:60) to afford compound **52** as yellow oil.

Yield: 100 mg, 90%

Mol. Formula: $C_{17}H_{26}O_7$

$[\alpha]_D^{25.98}$: +23.3 (*c* 1.47, $CHCl_3$)

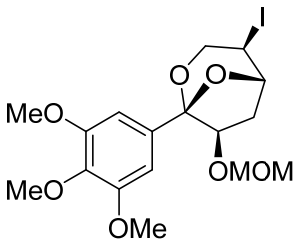
IR (neat, cm^{-1}): ν_{max} 3478, 2934, 2854, 1683, 1585, 1459, 1328, 1120, 1038

^{1}H NMR (200MHz, $CDCl_3$) δ = 7.22 (s, 2 H), 5.73 - 5.64 (m, 2 H), 4.88 (dd, *J* = 5.6, 6.9 Hz, 1 H), 4.65 (q, *J* = 7.0 Hz, 2 H), 4.07 - 4.01 (m, 2 H), 3.88 (d, *J* = 1.9 Hz, 9 H), 3.81 (s, 2 H), 3.30 (s, 3 H), 2.64 - 2.47 (m, 2 H), 2.42 - 2.05 (m, 1 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 153.1, 143.0, 132.8, 130.3, 126.7, 106.2, 96.2, 78.3, 77.3, 77.0, 76.7, 63.3, 61.0, 56.4, 56.2, 56.1, 36.2

HRMS (ESI) for $C_{17}H_{26}O_7$ $(M + Na)^+$ found 365.1573, calcd 365.1576

(1*S*, 4*S*, 5*R*, 7*R*)-4-Iodo-7-(methoxymethoxy)-1-(3,4,5-trimethoxyphenyl)-2,8-dioxabicyclo[3.2.1]octane 53:



To a solution of **52** (80 mg, 0.233 mmol) in MeCN (5 mL) were added sequentially $NaHCO_3$ (0.059 g, 0.7 mmol, 3.0 equiv) and iodine (90 mg, 0.7 mmol, 3.0 equiv) at 0 °C and the mixture stirred for 30 min. The reaction was quenched with aqueous $Na_2S_2O_3$, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/ EtOAc (84:16) to give **53** as a colorless solid. This was recrystallized using diethyl ether and EtOAc combination.

Yield: 100 mg, 89%

Mol. Formula: $C_{17}H_{24}O_7I$

Melting point: 71 °C

$[\alpha]_D^{25.4}$: -28.7 (*c* 1.99, $CHCl_3$)

IR (neat, cm^{-1}): ν_{max} 2933, 1670, 1588, 1459, 1334, 1236, 1123, 759

^{1}H NMR (400MHz, $CDCl_3$) δ = 6.82 (s, 2 H), 4.87 (d, *J* = 7.8 Hz, 1 H), 4.43 (dd, *J* = 2.9, 6.8 Hz, 1 H), 4.32 (dd, *J* = 3.4, 13.7 Hz, 1 H), 4.20 (d, *J* = 7.3 Hz, 1 H), 4.13 (d, *J* = 13.7 Hz, 1 H), 4.11 - 4.04 (m, 2 H), 3.91 - 3.85 (m, 7 H), 3.83 (s, 3 H), 3.12 (s, 3 H), 2.44 (dd, *J* = 7.1, 13.9 Hz, 1 H), 2.20 (ddd, *J* = 2.7, 7.9, 13.8 Hz, 1 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 152.6, 138.0, 132.3, 107.3, 103.7, 95.0, 79.8, 79.3, 77.2, 67.6, 60.8, 56.1, 55.5, 39.0, 25.3

HRMS (ESI) for $C_{17}H_{24}O_7I$ $(M + Na)^+$ found 467.0561, calcd 467.0561

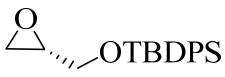
Crystal data:

X-ray intensity data measurements of compound Bicylic ketal **53** was carried out on a Bruker SMART APEX II CCD diffractometer with graphite-monochromatized (MoK_α= 0.71073Å) radiation at 200(2) K. The X-ray generator was operated at 50 kV and 30 mA. A preliminary set of cell constants and an orientation matrix were calculated from three sets of 36 frames. Data were collected with ω scan width of 0.5° at different settings of φ and 2θ with a frame time of 20 secs keeping the sample-to-detector distance fixed at 5.00 cm. The

X-ray data collection was monitored by APEX2 program (Bruker, 2006).[1] All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2006). SHELX-97 was used for structure solution and full matrix least-squares refinement on F^2.[20] All the hydrogen atoms were placed in geometrically idealized position and constrained to ride on their parent atoms. The crystals belong to monoclinic space group $P2_1$ containing two molecules in the asymmetric unit. The O-methoxy methyl ether (O-MOM) moiety one of the molecules exhibited statistical disorder at two positions having occupancies 0.65 and 0.35. Two molecules An *ORTEP* III[3] view of both compounds were drawn with 50% probability displacement ellipsoids and H atoms are shown as small spheres of arbitrary radii.

Crystal data of Bicylic ketal **53**, $C_{17}H_{23}IO_7$, M = 466.25, colourless plate, 0.37 x 0.25 x 0.20 mm^3, monoclinic, space group $P2_1$, a = 9.452(3) Å, b = 19.677(7) Å, c = 10.900(4) Å, β = 112.274(5)°, V = 1876.0(11) $Å^3$, Z = 4, T = 200(2) K, $2\theta_{max}$=50.00°, D_{calc} (g cm^{-3}) = 1.651, $F(000)$ = 936, μ (mm^{-1}) = 1.741, 18987 reflections collected, 6586 unique reflections (R_{int}=0.0716), 5390 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.565, T_{max} = 0.722, 488 refined parameters, restraints = 92, S = 1.065, $R1$ = 0.0559, $wR2$ = 0.1130 (all data R = 0.0713, $wR2$ = 0.1196), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 1.45, $\Delta\rho_{min}$= -0.73 ($eÅ^{-3}$). The absolute configuration was established by the structure determination of Bicylic ketal **53** which contain a chiral reference molecule of known absolute configuration and confirmed by anomalous dispersion effects in diffraction measurements on the crystal.

(*S*)-Tert-butyl(oxiran-2-ylmethoxy)diphenylsilane 56:



To a stirred solution of compound (*R*)-Glycidol ether **55** (1.0 g, 13.5 mmol) in CH_2Cl_2 (30.0 mL) at 0 °C was added imidazole (1.9 g, 28.38 mmol), followed by TBDPSCl (3.8 mL, 14.86 mmol) and DMAP. The mixture was stirred for 1h. The reaction mixture was quenched with sat. NH_4Cl solution (20 mL) and the aqueous layer were extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the crude **56** as yellow oil.

The crude material was purified by flash column chromatography (EtOAc–petroleum ether, 5:95) to afford compound **56** as yellow colour oil.

Yield: 4.0 g, 95%

Mol. Formula: $C_{19}H_{24}O_2Si$

$[\alpha]_D^{25}$: -3.0 (*c* 2.49, $CHCl_3$)

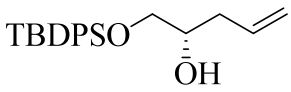
IR (neat, cm^{-1}): ν_{max} 2931, 2863, 1468, 1111

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.73 - 7.68 (m, 4 H), 7.47 - 7.38 (m, 7 H), 3.87 (dd, *J* = 3.2, 11.7 Hz, 1 H), 3.73 (dd, *J* = 4.8, 11.9 Hz, 1 H), 3.17 - 3.12 (m, 1 H), 2.76 (t, *J* = 4.5 Hz, 1 H), 2.63 (dd, *J* = 2.6, 5.0 Hz, 1 H), 1.07 (s, 9 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 135.6, 135.5, 133.3, 129.7, 127.7, 64.3, 52.3, 44.4, 26.7, 19.2

HRMS (ESI) for $C_{19}H_{24}O_2Si$ $(M + Na)^+$ found 335.1435, calcd 335.1437

(*S*)-1-((Tert-butyldiphenylsilyl)oxy)pent-4-en-2-ol 57:



To a solution of CuI (0.062 g, 0.32 mmol) in anhydrous THF (20 mL) was added vinylmagnesium bromide (1.6 M in THF, 3 mL, 4.8 mmol) at –20 ˚C and stirred for 10 min, followed by a solution of above obtained epoxide **56** (1.0 g, 3.21 mmol) in anhydrous THF (10 mL) was added drop wise and stirred at same temperature for 1 h, RM was quenched by adding saturated aqueous NH_4Cl (15 mL), extracted with EtOAc (3 x 10 mL), combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash chromatography over 230-400 mesh silica gel (7% EtOAc/Petroleum ether) to afford alcohol **57** as a yellow oil.

Yield: 1.03 g, 95%

Mol. Formula: $C_{21}H_{28}O_2Si$

$[\alpha]_D^{24.7}$: +2.08 (*c* 2.18, $CHCl_3$)

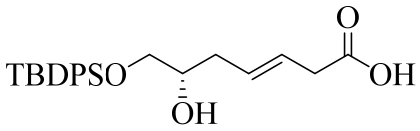
IR (neat, cm^{-1}): ν_{max} 3365, 3072, 2931, 2863, 1449, 1124, 1030

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.72 - 7.65 (m, 4 H), 7.49 - 7.38 (m, 6 H), 5.81 (tdd, *J* = 7.2, 10.1, 17.1 Hz, 1 H), 5.13 - 5.03 (m, 2 H), 3.80 (dq, *J* = 3.7, 6.6 Hz, 1 H), 3.69 (dd, *J* = 3.9, 10.3 Hz, 1 H), 3.57 (dd, *J* = 7.1, 10.3 Hz, 1 H), 2.29 - 2.23 (m, 2 H), 1.09 (s, 9 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 135.5, 134.3, 133.1, 129.8, 127.8, 117.4, 71.2, 67.3, 37.5, 26.8, 19.2

HRMS (ESI) for $C_{21}H_{28}O_2Si$ $(M + Na)^+$ found 363.1752, calcd 363.1751

(*S*, *E*)-7-((Tert-butyldiphenylsilyl)oxy)-6-hydroxyhept-3-enoic acid 58:



Procedure as described in the synthesis of **26**. The crude material was purified by flash column chromatography (EtOAc–petroleum ether, 20:80) to afford compound **58** as yellow colour oil.

Yield: 210 mg, 90%

Mol. Formula: $C_{21}H_{26}O_5$

$[\alpha]_D^{25.0}$: +1.76 (*c* 2.4, $CHCl_3$)

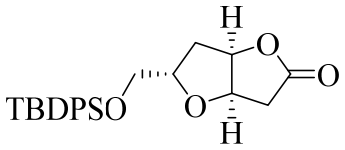
IR (neat, cm^{-1}): ν_{max} 3420, 3024, 2928, 2863, 1727, 1457, 1429, 1276, 1175, 1025

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.69 - 7.66 (m, 4 H), 7.46 - 7.40 (m, 6 H), 5.63 - 5.54 (m, 2 H), 3.81 - 3.74 (m, 1 H), 3.69 - 3.65 (m, 1 H), 3.60 - 3.49 (m, 2 H), 3.11 - 3.04 (m, 2 H), 2.27 - 2.22 (m, 2 H), 1.08 (s, 9 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 177.4, 135.7, 135.5, 133.1, 129.8, 127.8, 71.3, 67.2, 37.6, 36.1, 26.8, 19.2

HRMS (ESI) for $C_{21}H_{26}O_5$ $(M + Na)^+$ found 381.1663, calcd 381.1672

(3a*R*,5*S*,6a*R*)-5(((Tertbutyldiphenylsilyl)oxy)methyl)tetrahydrofuro[3,2-b]furan-2(3*H*)-one 59:



Procedure as described in the synthesis of **3**. The residue was purified by silica gel column chromatography using petroleum ether/ EtOAc (90:10) to give as yellow oil.

Yield: 89.5 mg, 90%

Mol. Formula: $C_{23}H_{28}O_4$

$[\alpha]_D^{26.2}$: +22.6 (*c* 1.94, $CHCl_3$)

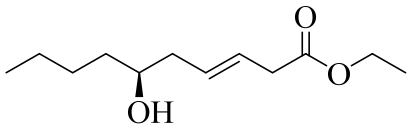
IR (neat, cm^{-1}): ν_{max} 2935, 2862, 1783, 1468, 1431, 1143, 1112

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.69 - 7.65 (m, 4 H), 7.46 - 7.39 (m, 6 H), 5.14 (t, *J* = 4.8 Hz, 1 H), 4.83 (t, *J* = 4.6 Hz, 1 H), 4.35 - 4.28 (m, 1 H), 3.82 (ddd, *J* = 1.4, 3.4, 11.2 Hz, 1 H), 3.68 - 3.63 (m, 1 H), 2.76 - 2.70 (m, 2 H), 2.36 (dd, *J* = 6.2, 14.0 Hz, 1 H), 2.24 - 2.17 (m, 1 H), 1.07 (s, 9 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 175.8, 135.8, 135.5, 133.1, 129.8, 127.8, 85.1, 79.4, 78.6, 65.4, 36.9, 34.4, 26.8, 19.2

HRMS (ESI) for $C_{23}H_{28}O_4$ $(M + Na)^+$ found 419.1649, calcd 419.1649

Ethyl (*S*, *E*)-6-hydroxydec-3-enoate 60:



To a stirred solution of **28** (200 mg, 1.56 mmol) in CH_2Cl_2 (7.0 mL) was added compound ethyl but-3-enoate (356 mg, 3.12 mmol) and degassed for 15 min. Then Grubb's II catalyst (26 mg, 2 mol %) was added to the reaction mixture and stirred for 1h at reflux. After completion of reaction, solvent was removed under reduced pressure. The crude material

was purified by flash column chromatography (EtOAc–petether, 20:80) to afford compound **60** as yellow colour oil.

Yield: 317 mg, 95%

Mol. Formula: $C_{12}H_{22}O_3$

$[\alpha]_D^{26.7}$: -0.71 (*c* 1.97, $CHCl_3$)

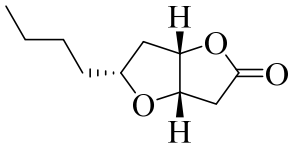
IR (neat, cm^{-1}): ν_{max} 3445, 2927, 2864, 1732, 1458, 1375, 1256, 1166, 1029

^{1}H NMR (400MHz, $CDCl_3$) δ = 5.76 - 5.48 (m, 2 H), 4.14 (q, *J* = 6.8 Hz, 2 H), 3.62 (td, *J* = 5.9, 11.7 Hz, 1 H), 3.12 - 3.01 (m, 2 H), 2.28 (td, *J* = 5.0, 14.1 Hz, 1 H), 2.18 - 2.08 (m, 1 H), 1.52 - 1.39 (m, 3 H), 1.36 - 1.28 (m, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 0.90 (t, *J* = 6.8 Hz, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 171.9, 130.7, 125.3, 70.8, 60.6, 40.5, 38.1, 36.5, 27.8, 22.7, 14.2, 14.0

HRMS (ESI) for $C_{12}H_{22}O_3$ $(M + Na)^+$ found 237.1463, calcd 237.1461

(3a*S*, 5*R*, 6a*S*)-5-Butyltetrahydrofuro[3,2-b]furan-2(3*H*)-one 2:



To a stirred solution of compound **60** (100 mg, 0.46 mmol) in dry CH_2Cl_2 was added triethylamine (0.14 ml, 0.98 mmol), followed by slow addition of mesyl chloride (0.04 ml, 0.51 mmol) at 0 °C, with further stirring for 15 min at the room temperature. The reaction mixture was quenched with addition of cold water at 0 °C. The two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with water (3 x 5 mL), brine, dried over Na_2SO_4 and concentrated to give crude mesylate.

To a mixture of $K_3Fe(CN)_6$ (0.767 g, 2.32 mmol), K_2CO_3 (0.321 g, 2.32 mmol) and $(DHQ)_2PHAL$ (3.6 mg, 0.002 mmol, 1 mol%) in *t*-BuOH–H_2O (1:1, 6 mL) at 0 °C was

added osmium tetroxide (0.23 mL, 0.1 M solution in toluene, 5 mol%), followed by methane sulfonamide (0.079 g, 0.83 mmol). After stirring for 5 min at 0 °C, the crude mesylate (0.136 g, 0.46 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 18h and then quenched with solid sodium sulphite (690 mg, 1.48 g/mmol). Stirring was continued for an additional 15 min and then the solution was extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure gave the crude bicylic lactone. The crude material was purified by flash column chromatography (EtOAc–petether, 16:84) to afford compound **2** as yellow colour oil.

Yield: 77 mg, 90%

Mol. Formula: $C_{10}H_{16}O_3$

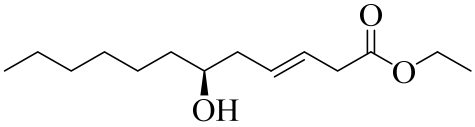
$[\alpha]_D^{24.5}$: -52.44° (*c* 2.24, $CHCl_3$)

^{1}H NMR (400MHz, $CDCl_3$) δ = 5.01 (br. s., 1 H), 4.51 (br. s., 1 H), 3.93 (t, *J* = 6.4 Hz, 1 H), 2.74 - 2.67 (m, 2 H), 2.43 (td, *J* = 6.7, 13.8 Hz, 1 H), 1.88 (dd, *J* = 8.1, 13.6 Hz, 1 H), 1.55 (br. s., 1 H), 1.41 - 1.27 (m, 5 H), 0.89 (br. s., 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 175.5, 84.7, 80.3, 78.2, 38.2, 36.3, 35.2, 28.2, 22.5, 13.9

HRMS (ESI) for $C_{10}H_{16}O_3$ $(M + Na)^+$ found 207.0993, calcd 207.0992

Ethyl (*S*, *E*)-6-hydroxydodec-3-enoate 61:



Procedure as described in the synthesis of **60**. The crude material was purified by flash column chromatography (EtOAc–pet ether, 20:80) to afford compound **61** as yellow colour oil.

Yield: 295 mg, 95%

Mol. Formula: $C_{14}H_{27}O_3$

$[\alpha]_D^{25.1}$: -0.68 (*c* 2.64, $CHCl_3$)

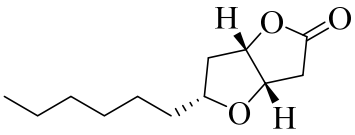
IR (neat, cm^{-1}): ν_{max} 3446, 2929, 2863, 1734, 1456, 1374, 1255, 1168, 1027

^{1}H NMR (400MHz, $CDCl_3$) δ = 5.71 - 5.51 (m, 2 H), 4.13 (dq, *J* = 1.6, 7.1 Hz, 2 H), 3.67 - 3.55 (m, 1 H), 3.13 - 2.99 (m, 2 H), 2.44 - 2.32 (m, 1 H), 2.31 - 2.22 (m, 1 H), 2.17 - 2.07 (m, 1 H), 1.44 (t, *J* = 5.0 Hz, 3 H), 1.39 - 1.25 (m, 10 H), 0.87 (t, *J* = 6.4 Hz, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 171.9, 130.7, 125.3, 70.8, 60.6, 40.5, 38.1, 36.8, 31.8, 29.3, 25.6, 22.6, 14.1, 14.0

HRMS (ESI) for $C_{14}H_{27}O_3$ $(M + H)^+$ found 243.1955, calcd 243.1955

(3a*S*, 5*R*, 6a*S*)-5-Hexyltetrahydrofuro[3,2-*b*]furan-2(3*H*)-one 4:



Procedure as described in the synthesis of **2**. The crude material was purified by flash column chromatography (EtOAc–pet ether, 16:84) to afford compound **4** as yellow colour oil.

Yield: 79 mg, 90%

Mol. Formula: $C_{12}H_{20}O_3$

$[\alpha]_D^{24.7}$: -39.9 (*c* 1.2, $CHCl_3$)

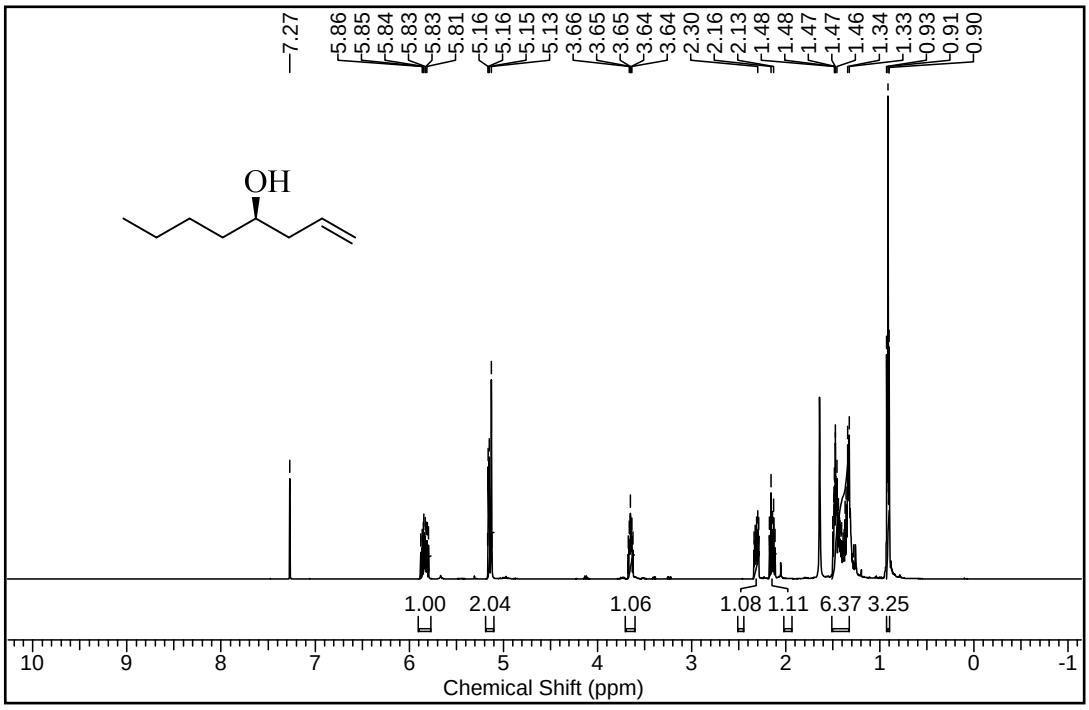
^{1}H NMR (400MHz, $CDCl_3$) δ = 5.01 (tt, *J* = 2.2, 4.6 Hz, 1 H), 4.54 - 4.47 (m, 1 H), 3.98 - 3.89 (m, 1 H), 2.73 (t, *J* = 2.5 Hz, 2 H), 2.46 - 2.38 (m, 1 H), 1.88 (tdd, *J* = 2.3, 7.8, 14.2 Hz, 1 H), 1.48 - 1.33 (m, 3 H), 1.28 (br. s., 8 H), 0.90 - 0.86 (m, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 175.5, 84.7, 80.3, 78.2, 38.3, 36.4, 35.5, 31.7, 29.1, 26.0, 22.5, 14.0

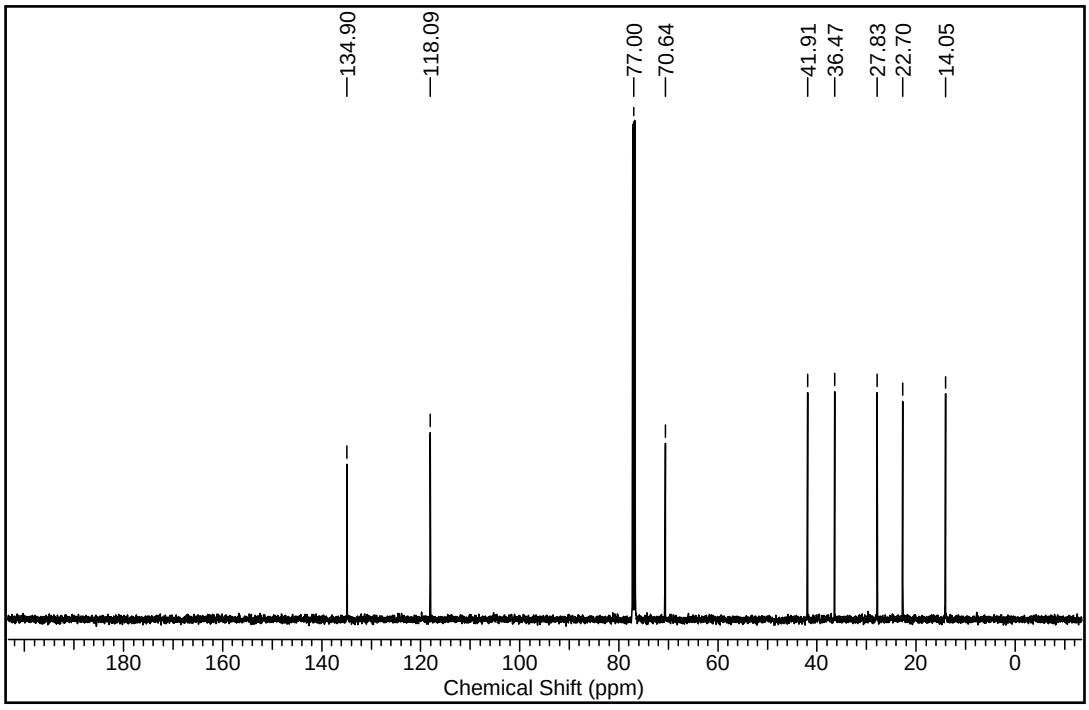
HRMS (ESI) for $C_{12}H_{20}O_3$ $(M + Na)^+$ found 235.1307, calcd 235.1305

2.7. Spectra:

(*R*)-Oct-1-en-4-ol 24:

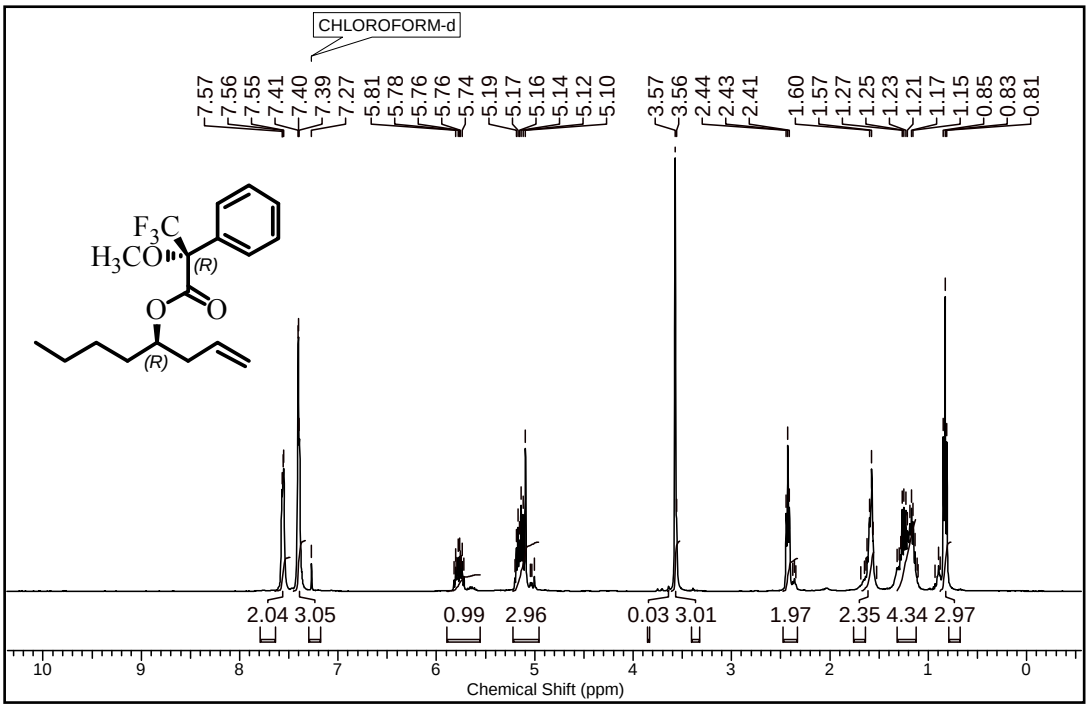


➢ **^{1}H NMR of the compound 24 in $CDCl_3$**

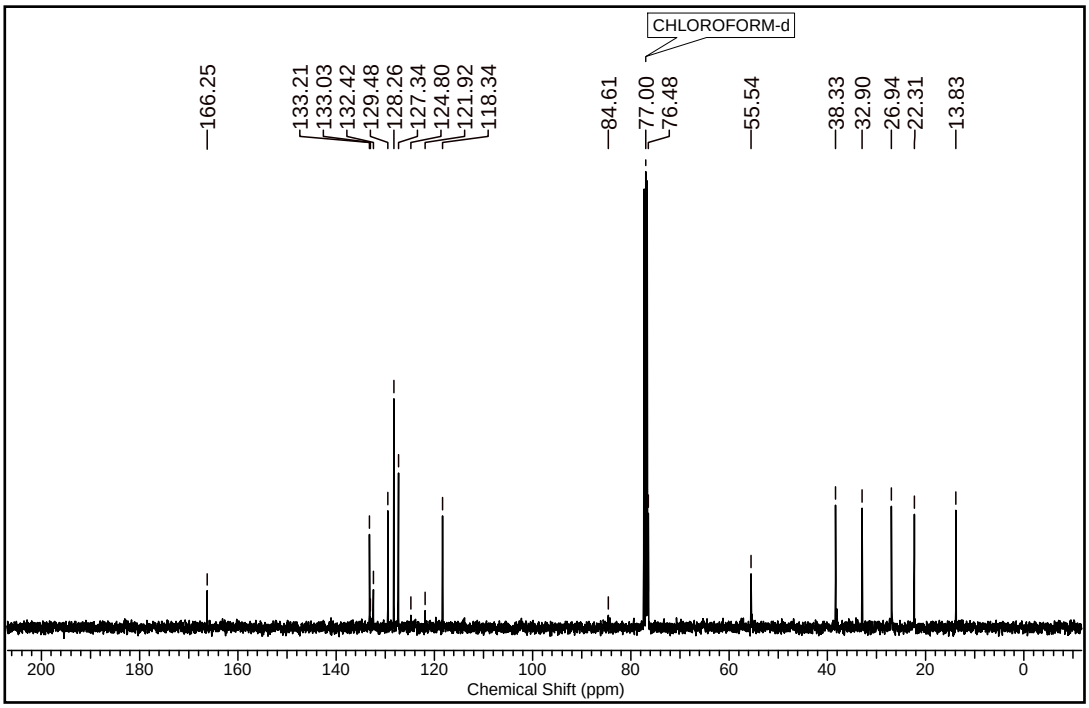


➢ **^{13}C NMR of the compound 24 in $CDCl_3$**

(*R*)-Oct-1-en-4-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate:

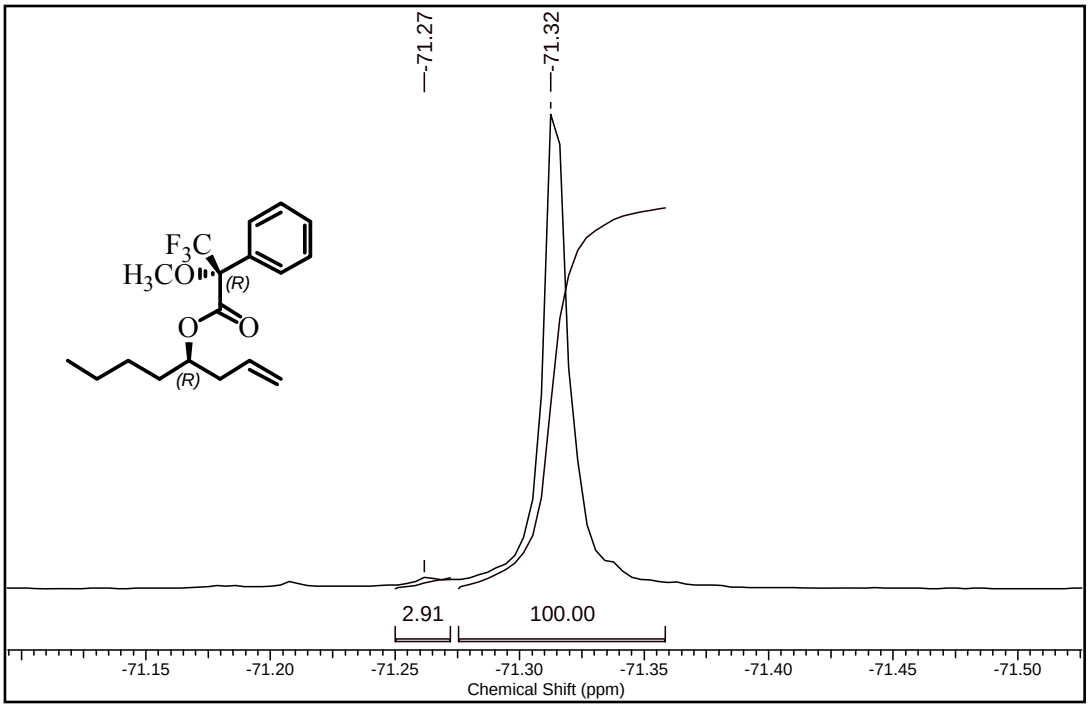


➢ **^{1}H NMR of the compound in $CDCl_3$**

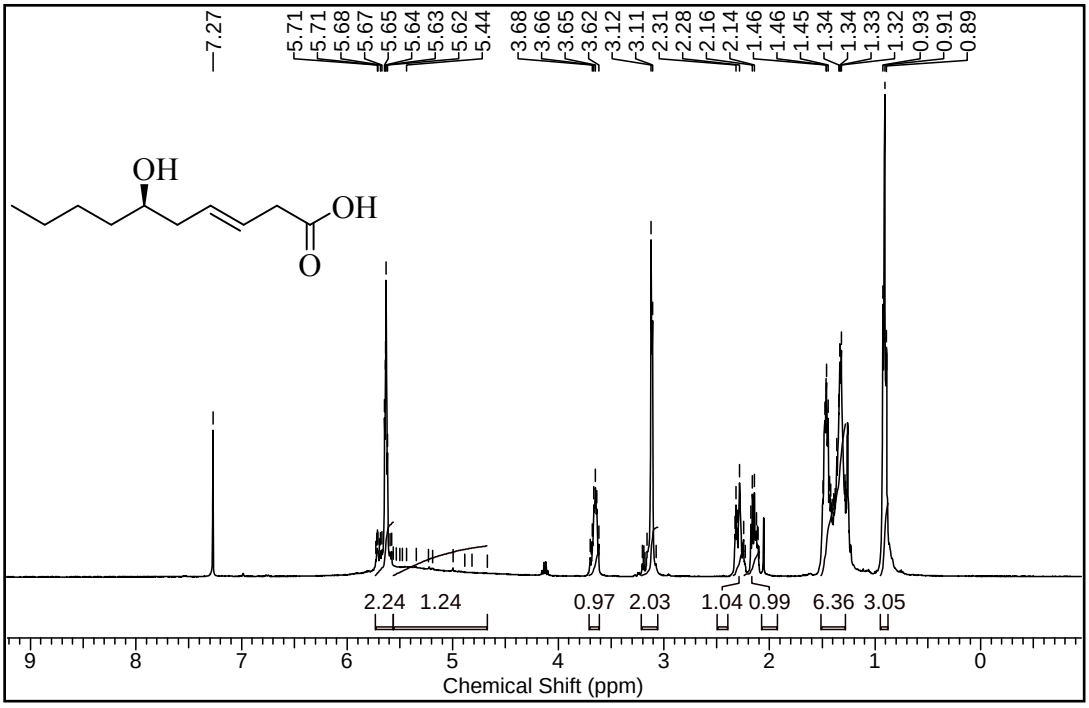


➢ **^{13}C NMR of the compound in $CDCl_3$**

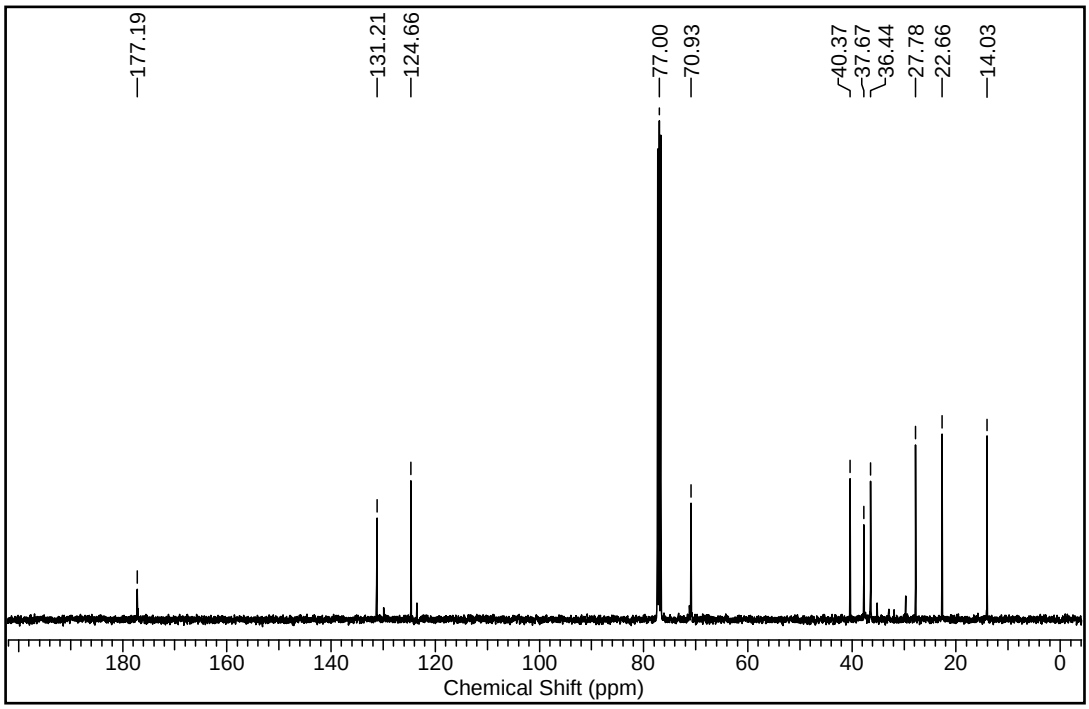
^{19}F spectra:


-71.27
-71.32
F3C
H3CO
(R)
O
O
(R)
2.91
100.00
-71.15
-71.20
-71.25
-71.30
-71.35
-71.40
-71.45
-71.50
Chemical Shift (ppm)

(*R*,*E*)-6-Hydroxydec-3-enoic acid 26:

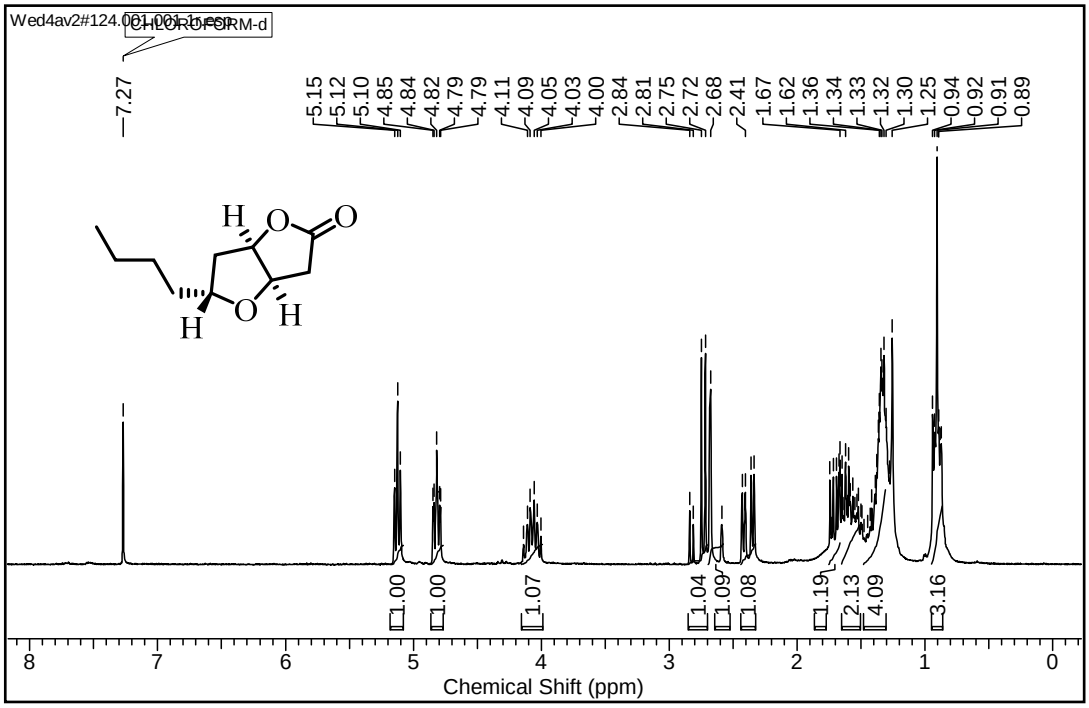


➢ **^{1}H NMR of the compound 26 in $CDCl_3$**

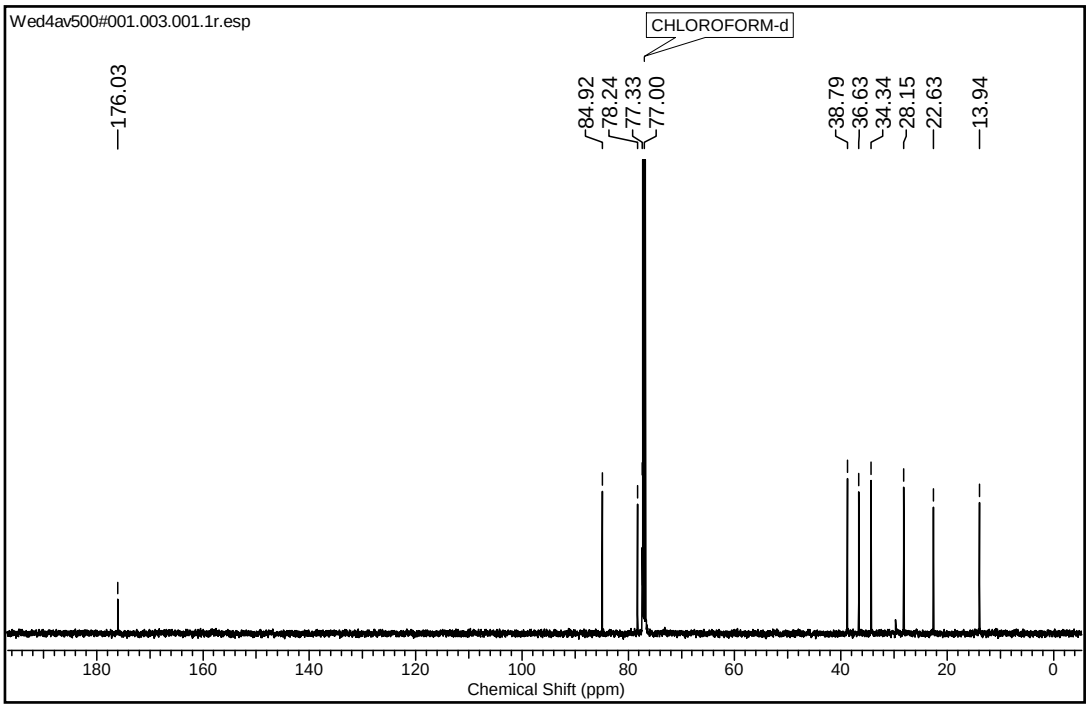


➢ **^{13}C NMR of the compound 26 in $CDCl_3$**

(3a*R*,5*R*,6a*R*)-5-Butyltetrahydrofuro[3,2-b]furan-2(3*H*)-one 1:

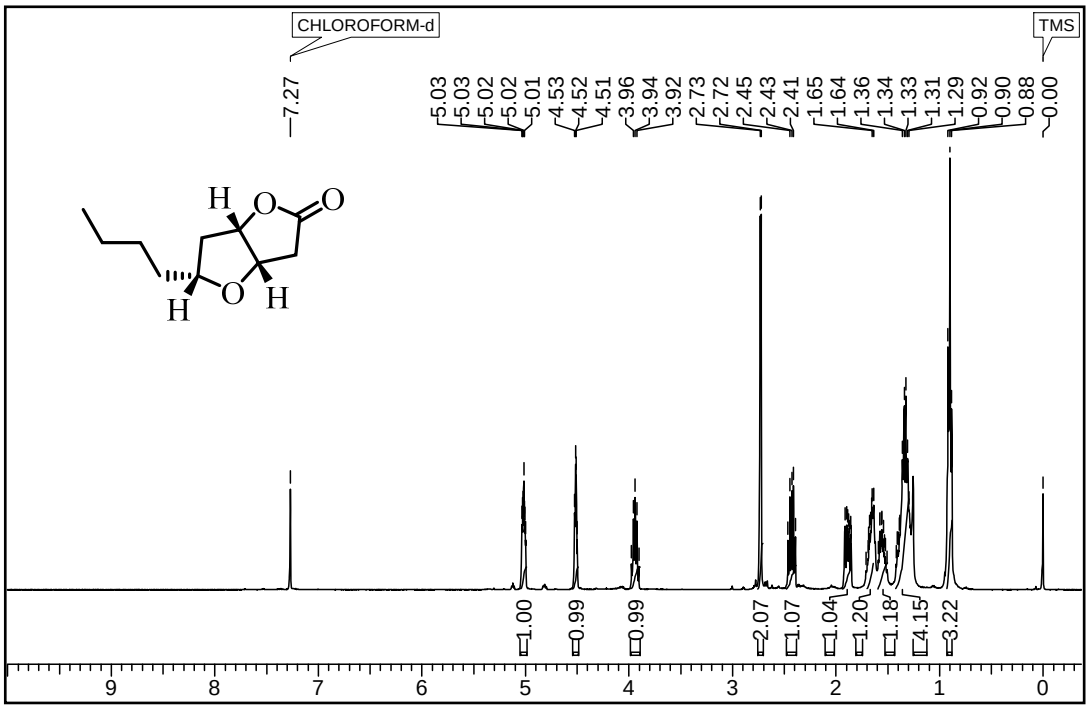


➢ **^{1}H NMR of the compound 1 in $CDCl_3$**

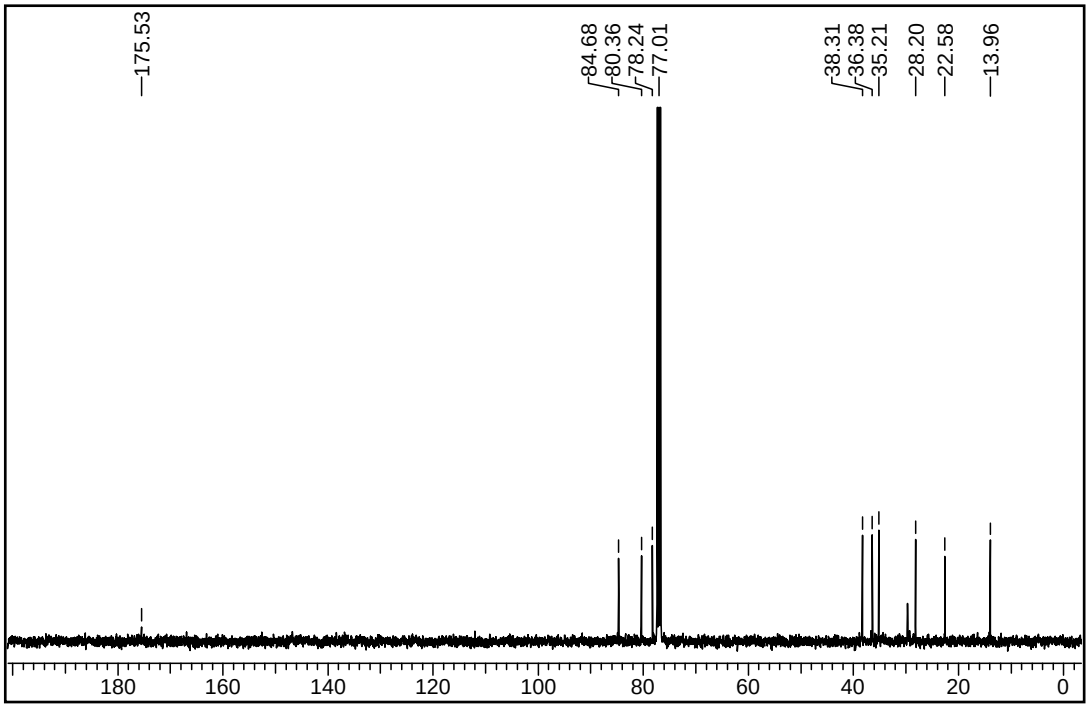


➢ **^{13}C NMR of the compound 1 in $CDCl_3$**

(3a*S*,5*R*,6a*S*)-5-Butyltetrahydrofuro[3,2-b]furan-2(3*H*)-one 2:

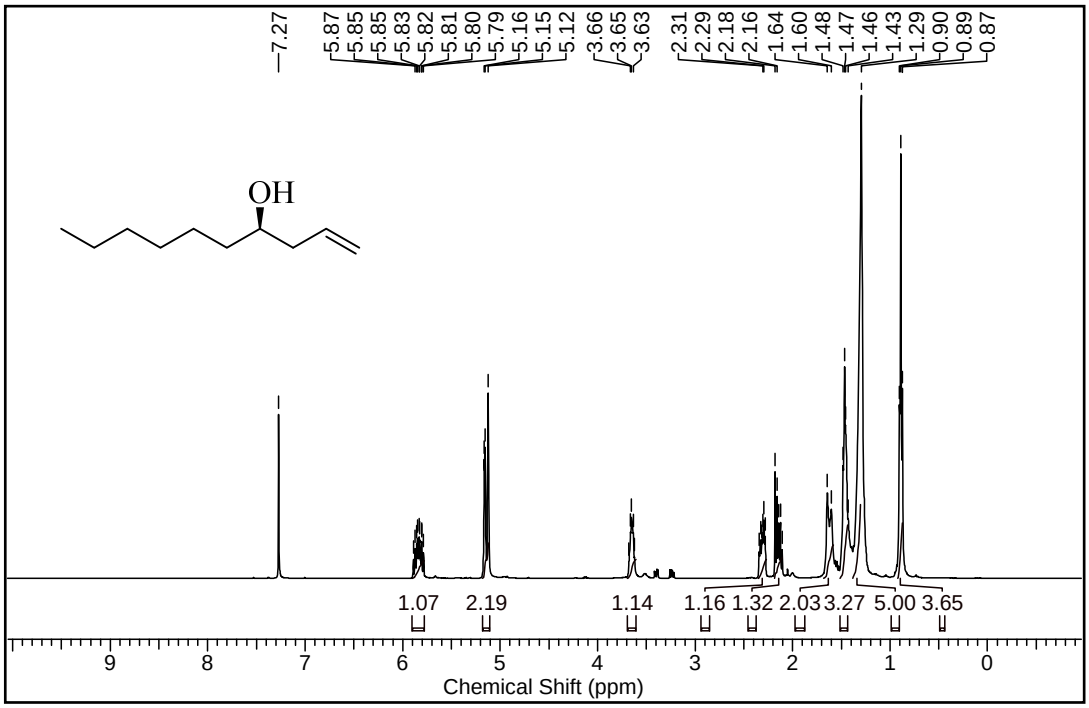


➢ **^{1}H NMR of the compound 2 in $CDCl_3$**

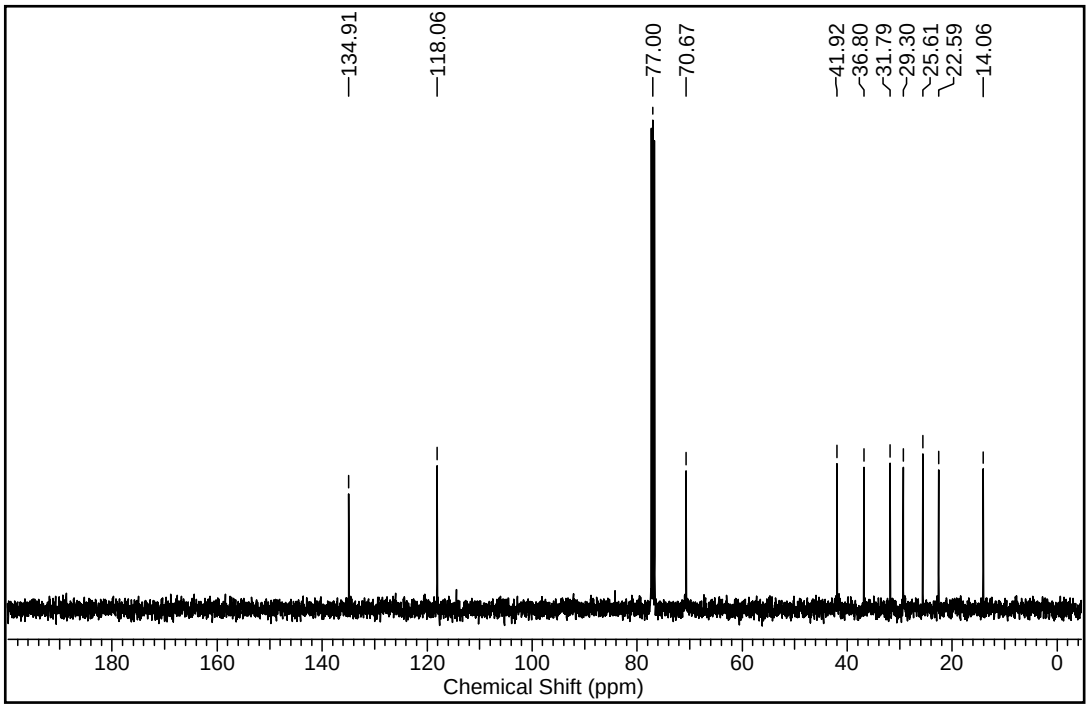


➢ **^{13}C NMR of the compound 2 in $CDCl_3$**

(*R*)-Dec-1-en-4-ol 25:

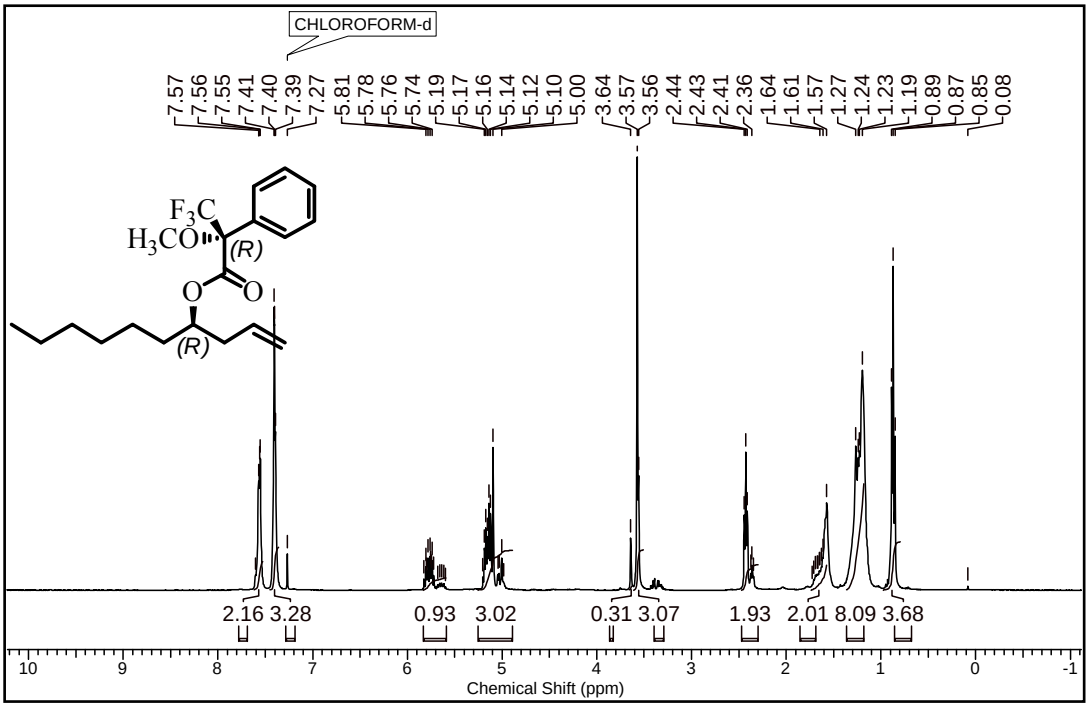


➢ **^{1}H NMR of the compound 25 in $CDCl_3$**

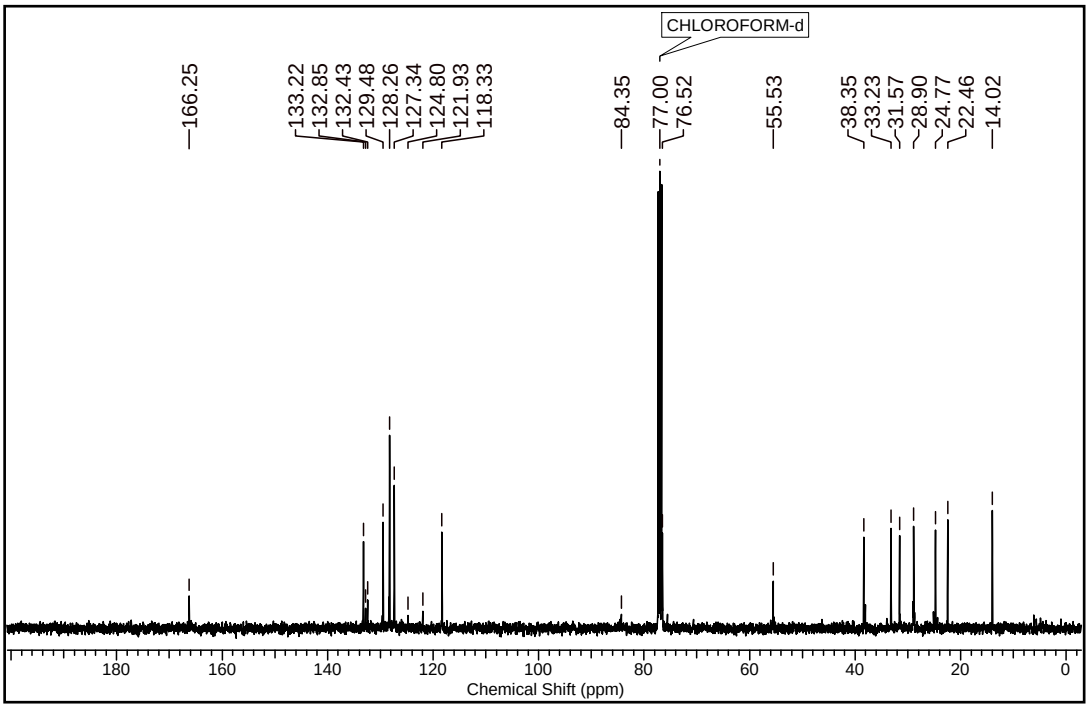


➢ **^{13}C NMR of the compound 25 in $CDCl_3$**

(*R*)-Dec-1-en-4-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate:

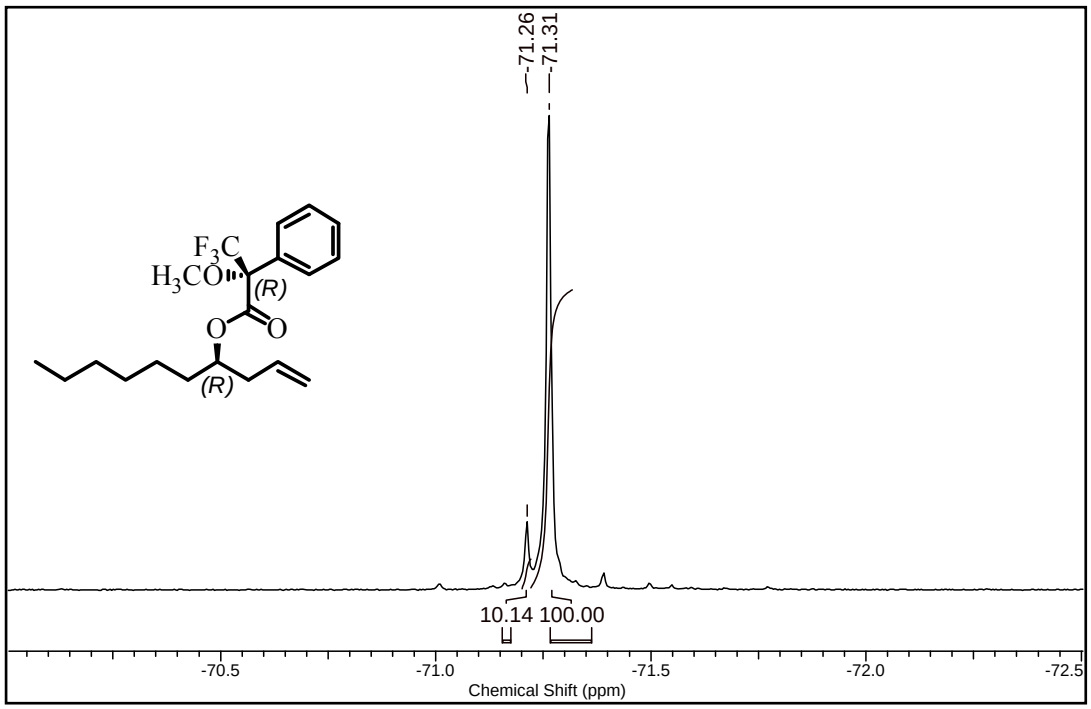


➢ **^{1}H NMR of the compound 25 in $CDCl_3$**

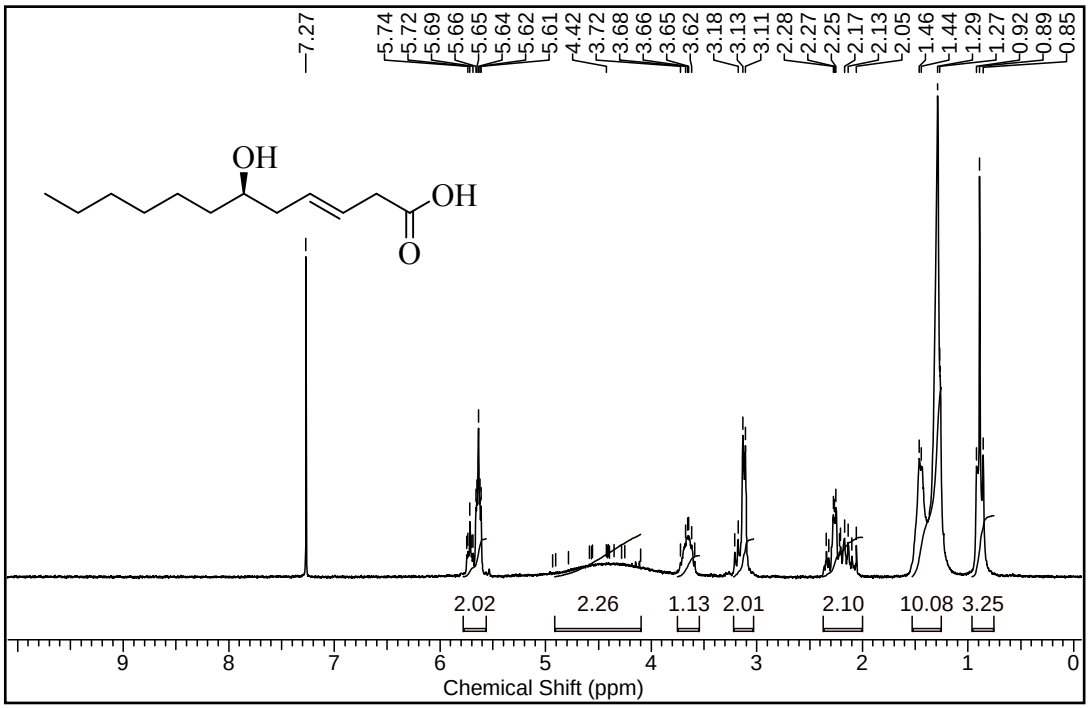


➢ **^{13}C NMR of the compound in $CDCl_3$**

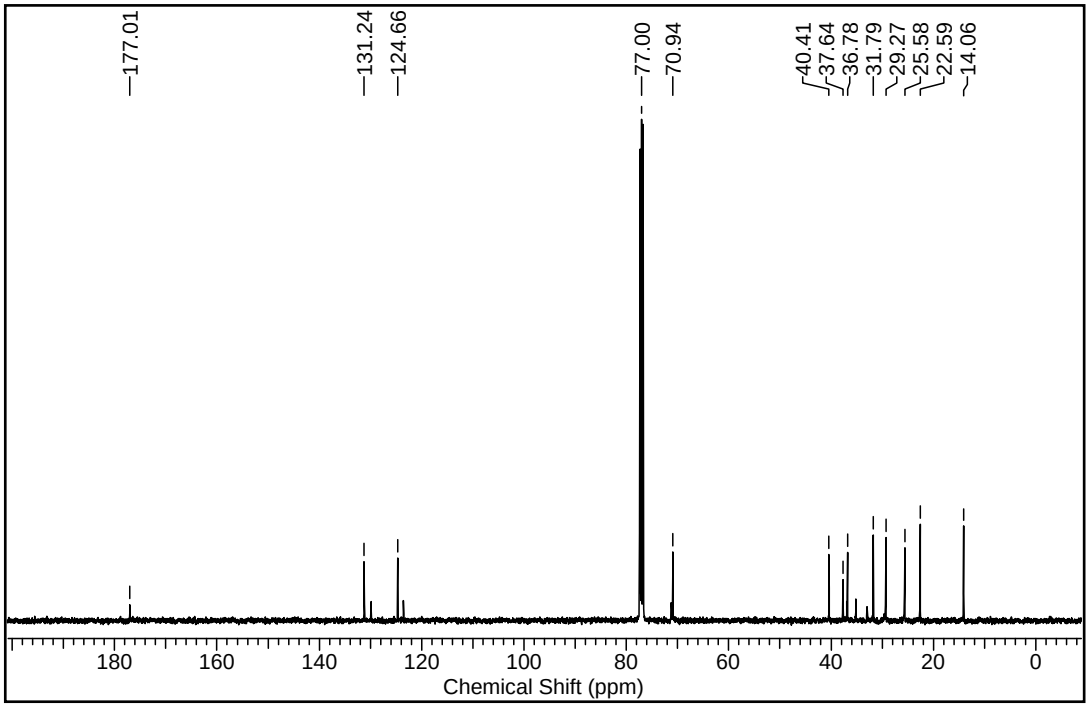
^{19}F spectra:


-71.26
-71.31
F3C
H3CO
(R)
O
O
(R)
10.14 100.00
-70.5
-71.0
-71.5
-72.0
-72.5
Chemical Shift (ppm)

(*R*,*E*)-6-Hydroxydodec-3-enoic acid 27:

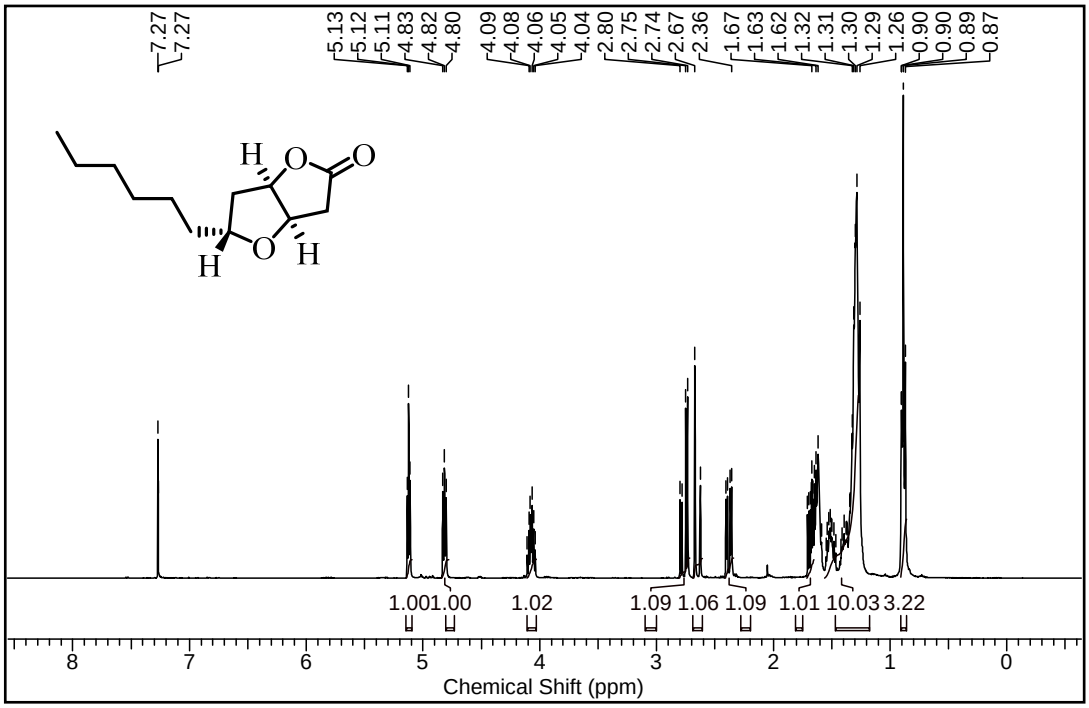


➢ **^{1}H NMR of the compound 27 in $CDCl_3$**

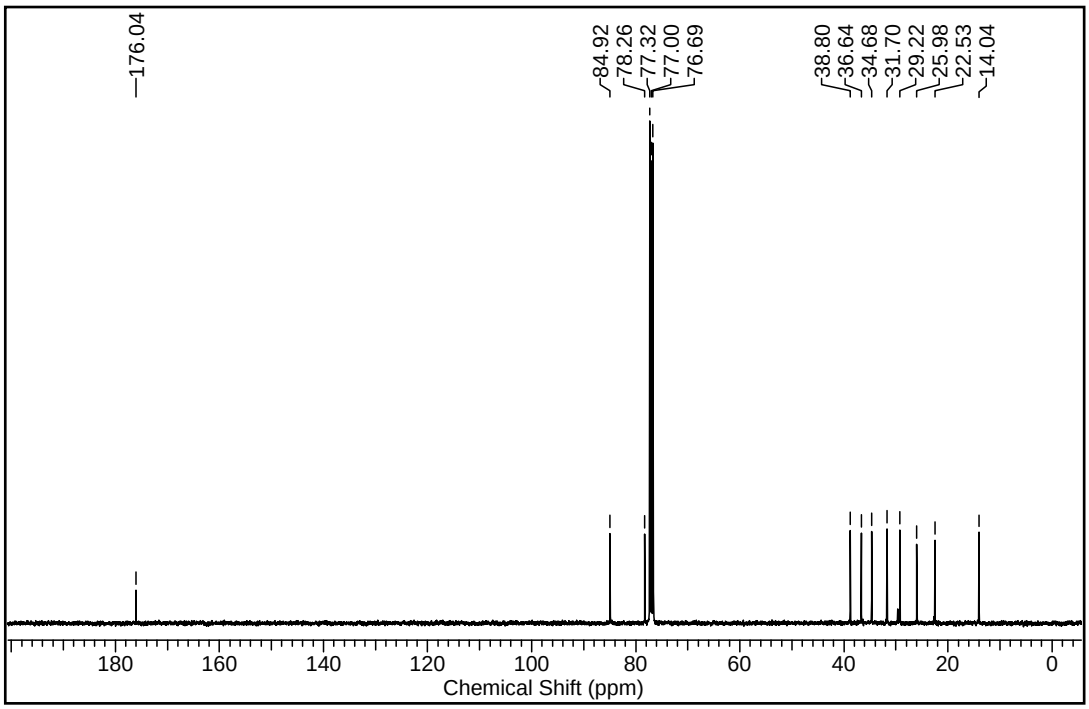


➢ **^{13}C NMR of the compound 27 in $CDCl_3$**

(3a*R*,5*R*,6a*R*)-5-Hexyltetrahydrofuro[3,2-b]furan-2(3*H*)-one 3:

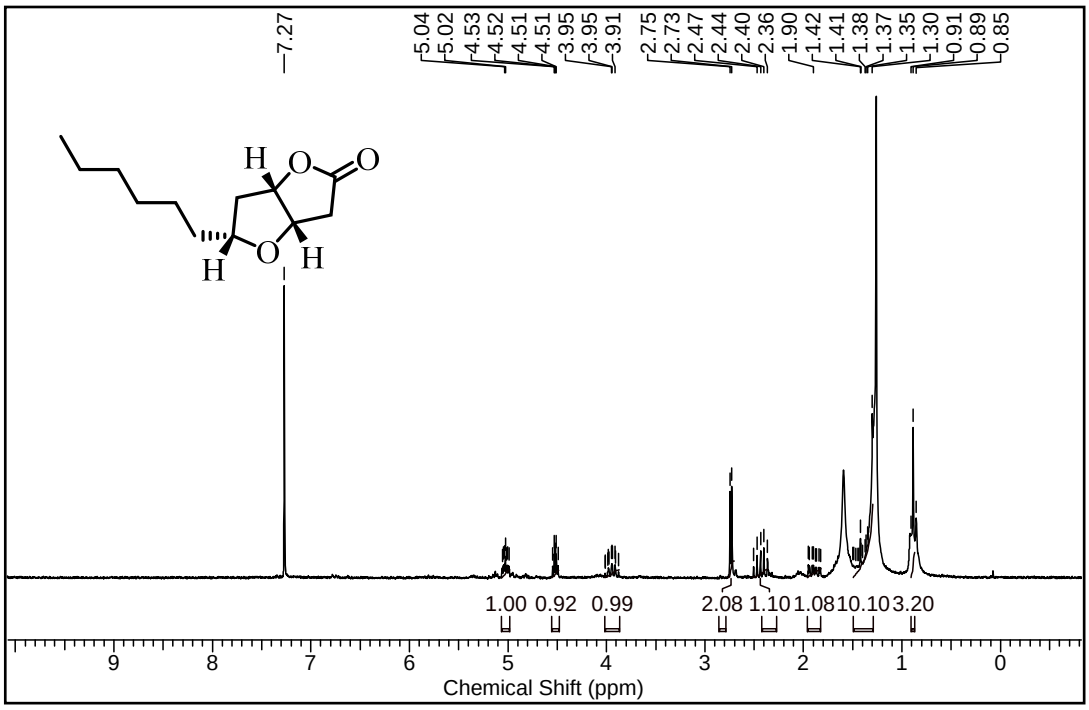


➢ **^{1}H NMR of the compound 3 in $CDCl_3$**

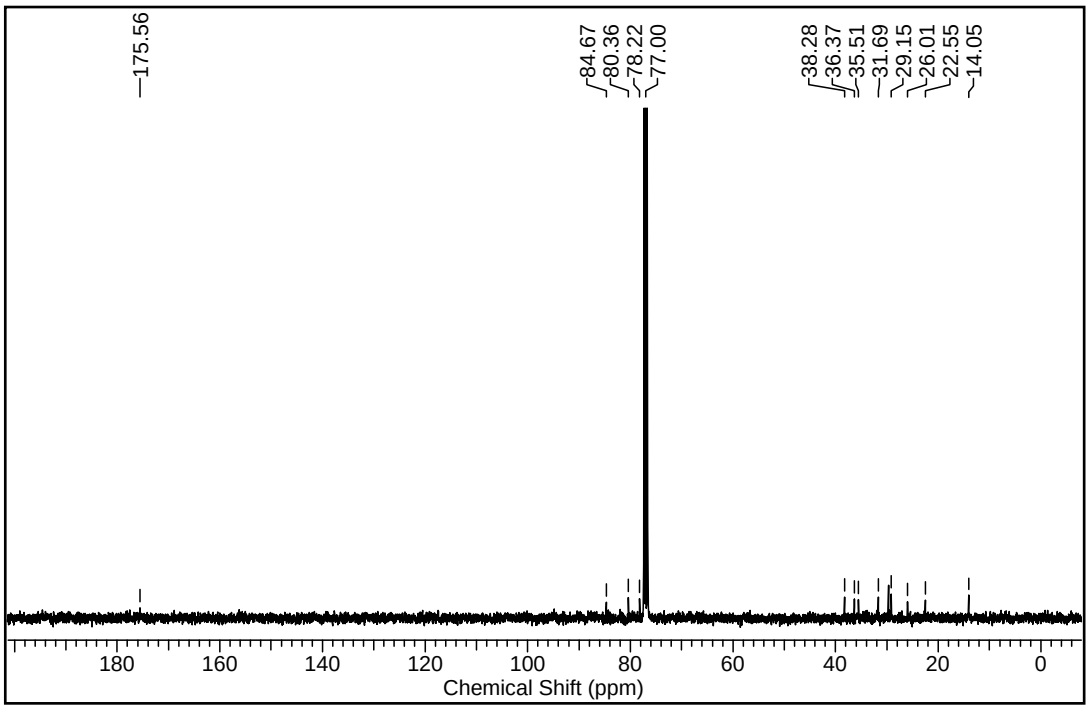


➢ **^{13}C NMR of the compound 3 in $CDCl_3$**

(3a*S*,5*R*,6a*S*)-5-Hexyltetrahydrofuro[3,2-b]furan-2(3*H*)-one 4:

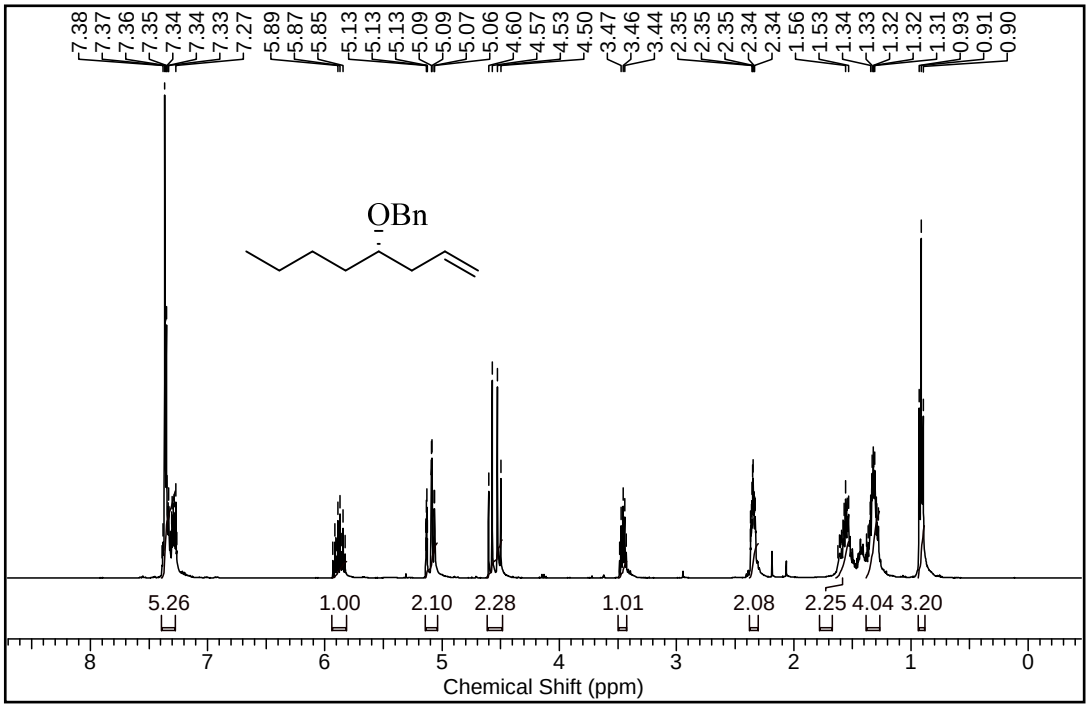


➢ **^{1}H NMR of the compound 4 in $CDCl_3$**

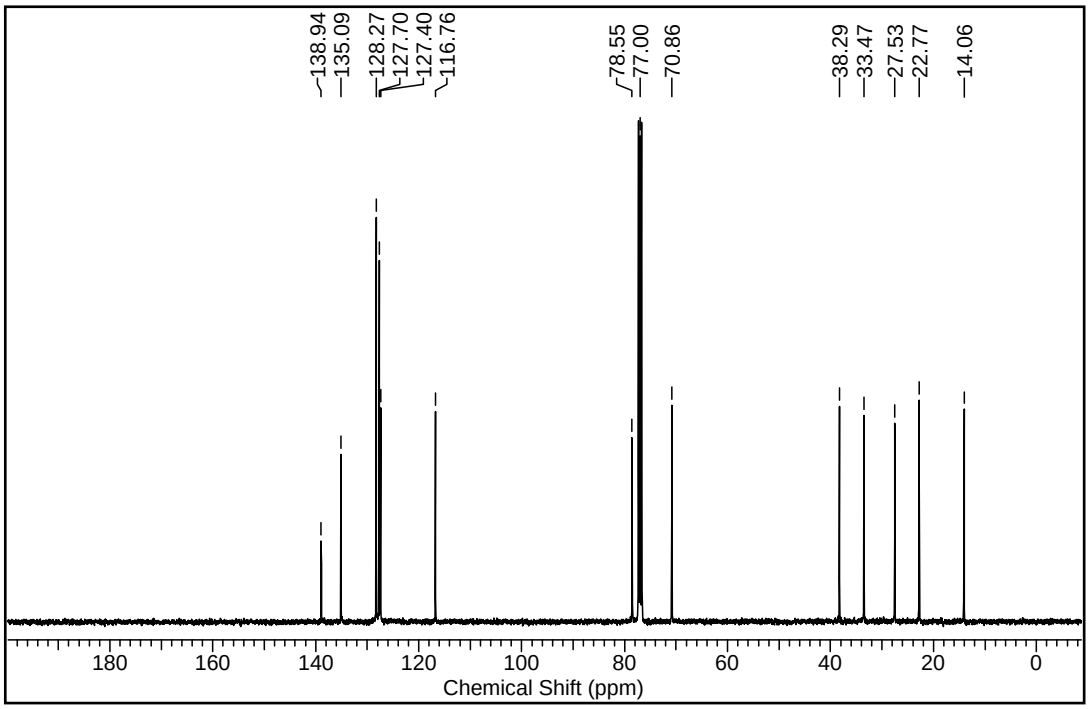


➢ **^{13}C NMR of the compound 4 in $CDCl_3$**

(*S*)-((Oct-1-en-4-yloxy)methyl)benzene 30:

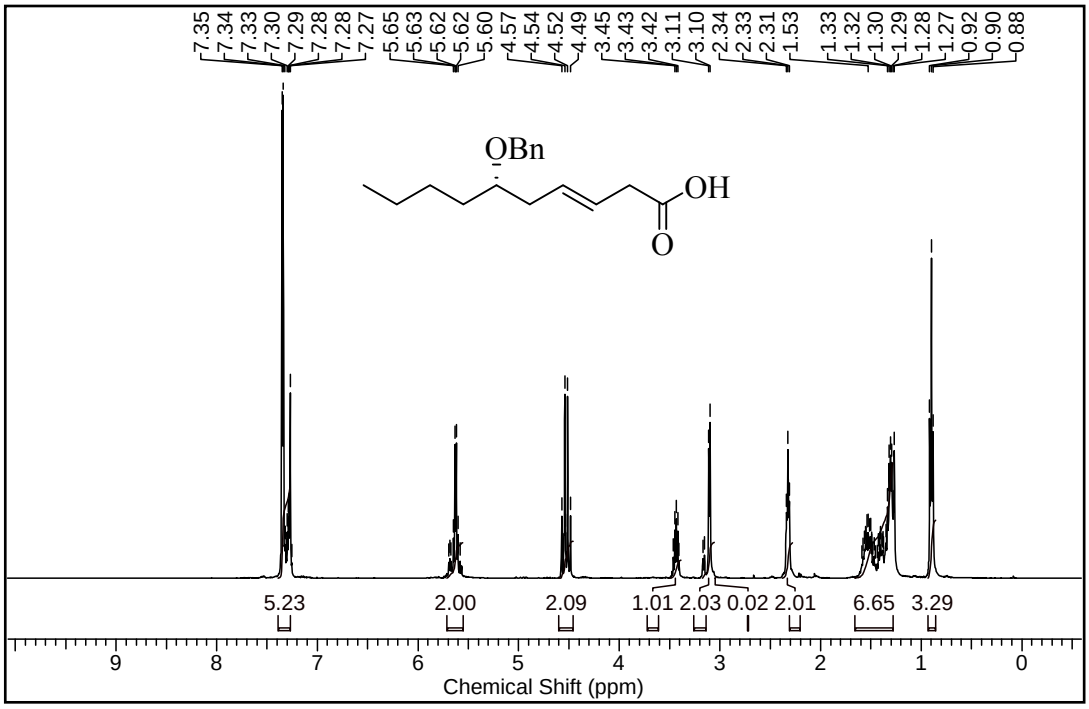


➢ **^{1}H NMR of the compound 30 in $CDCl_3$**

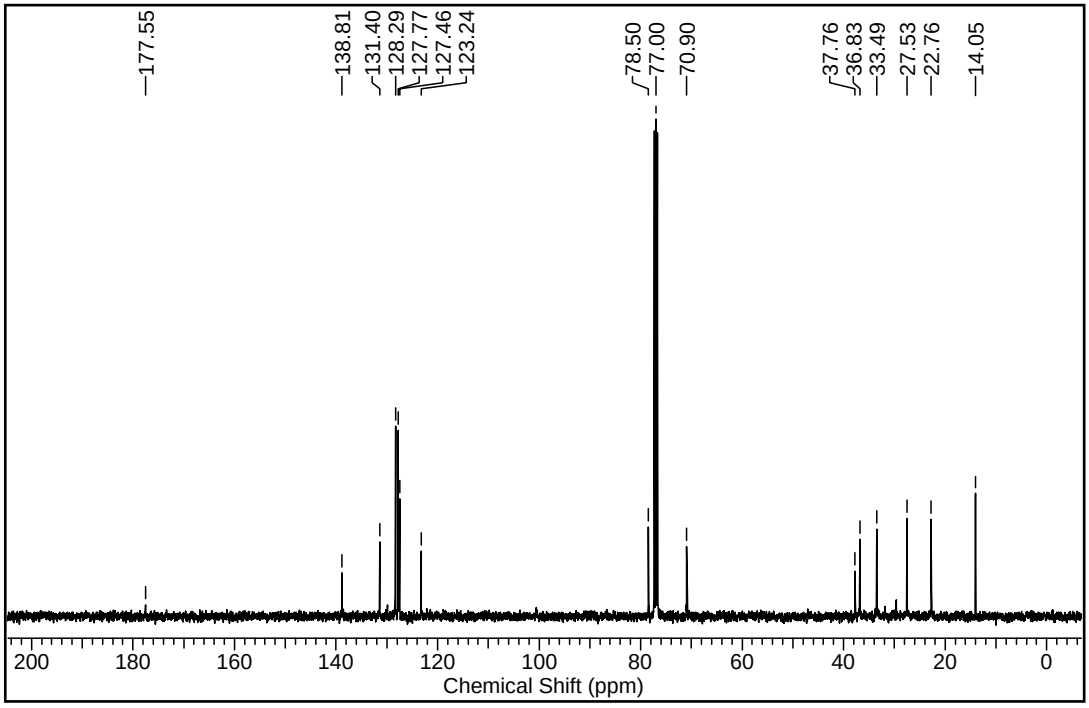


➢ **^{13}C NMR of the compound 30 in $CDCl_3$**

(*S*,*E*)-6-(Benzyloxy)dec-3-enoic acid 32:

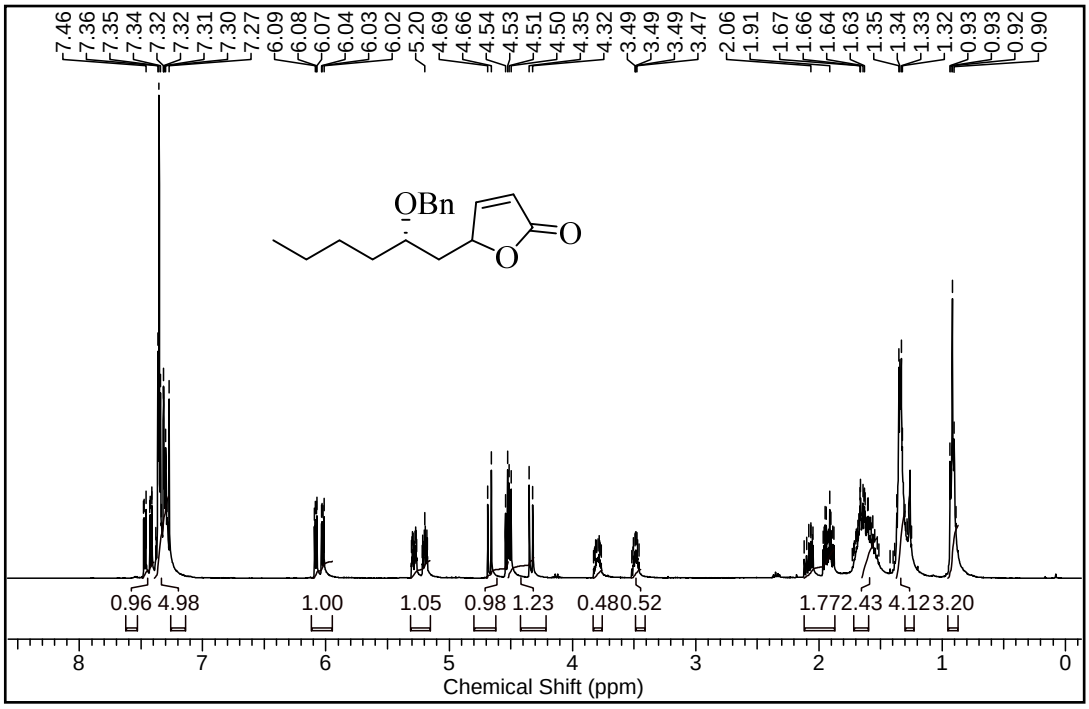


➢ **^{1}H NMR of the compound 32 in $CDCl_3$**

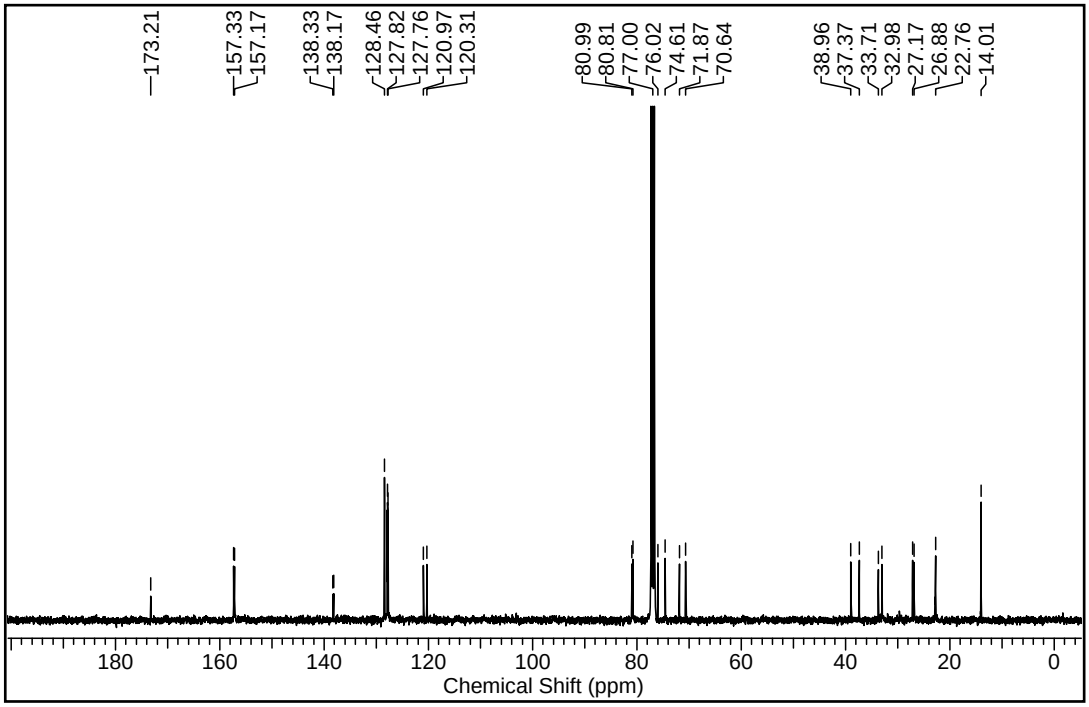


➢ **^{13}C NMR of the compound 32 in $CDCl_3$**

5-((*S*)-2-(Benzyloxy)hexyl)furan-2(5*H*)-one 34:

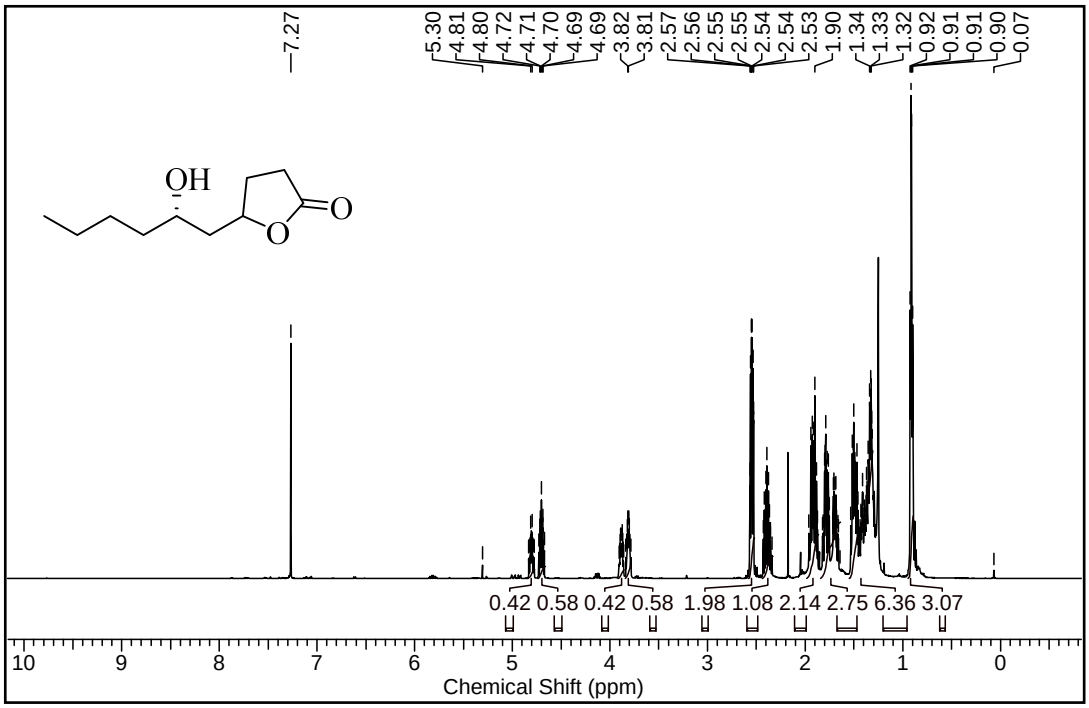


➢ **^{1}H NMR of the compound 34 in $CDCl_3$**

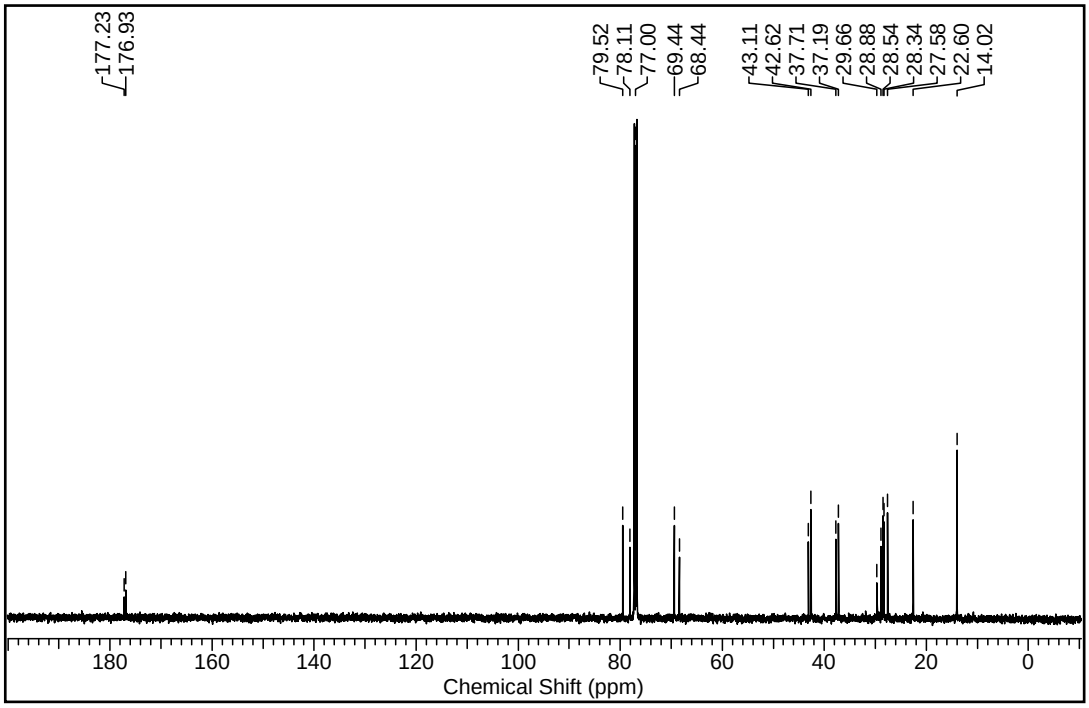


➢ **^{13}C NMR of the compound 34 in $CDCl_3$**

5-((*S*)-2-Hydroxyhexyl)dihydrofuran-2(3*H*)-one 36:

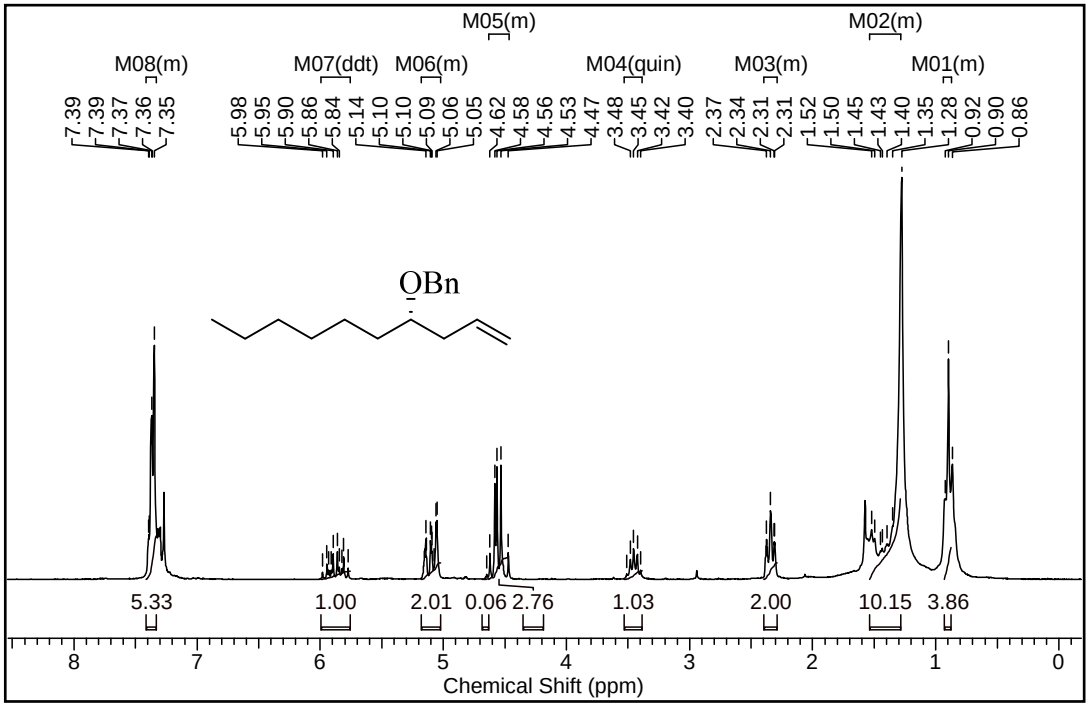


➢ **^{1}H NMR of the compound 36 in $CDCl_3$**

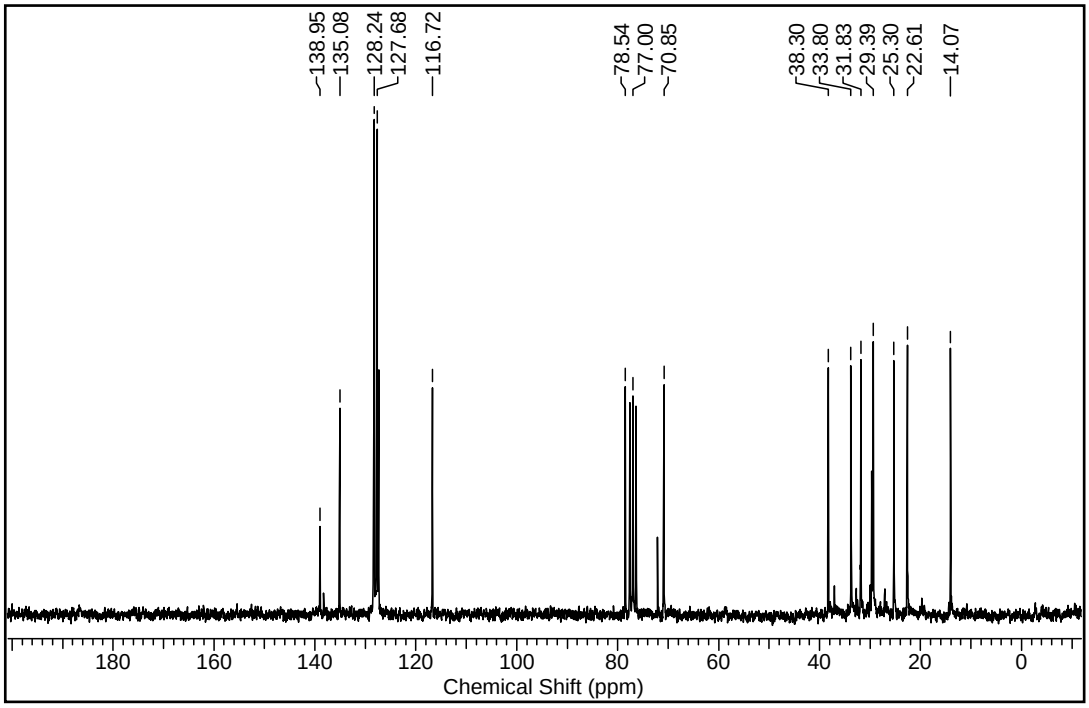


➢ **^{13}C NMR of the compound 36 in $CDCl_3$**

(*S*)-((Dec-1-en-4-yloxy)methyl)benzene 31:

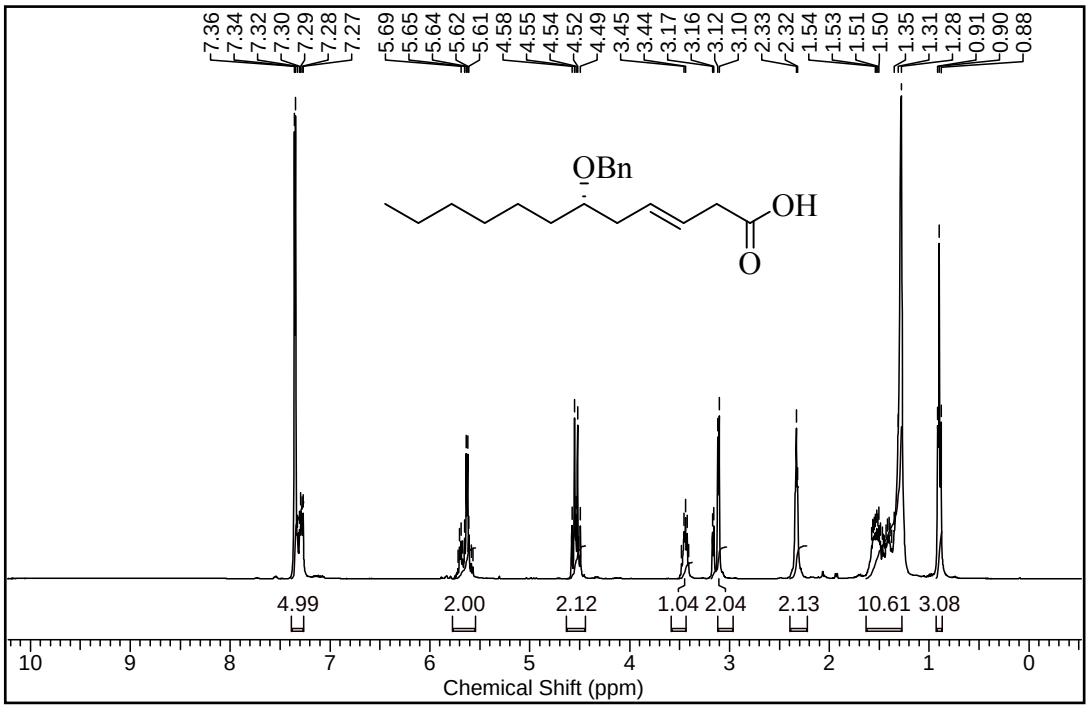


➢ **^{1}H NMR of the compound 31 in $CDCl_3$**

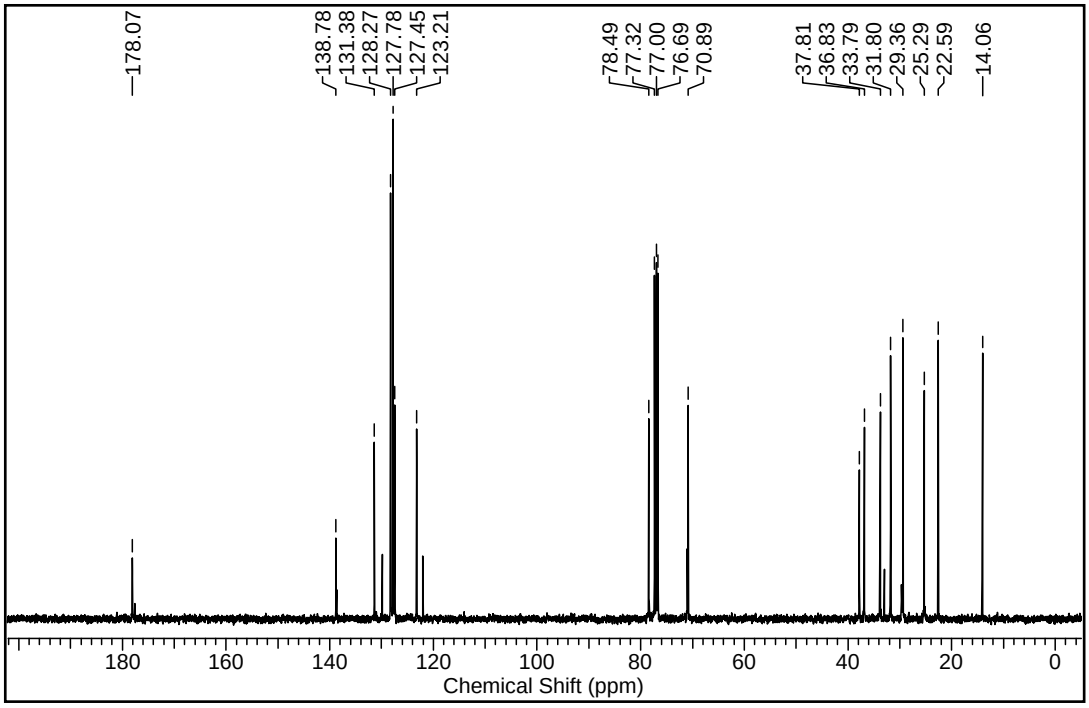


➢ **^{13}C NMR of the compound 31 in $CDCl_3$**

(*S*,*E*)-6-(Benzyloxy)dodec-3-enoic acid 33:

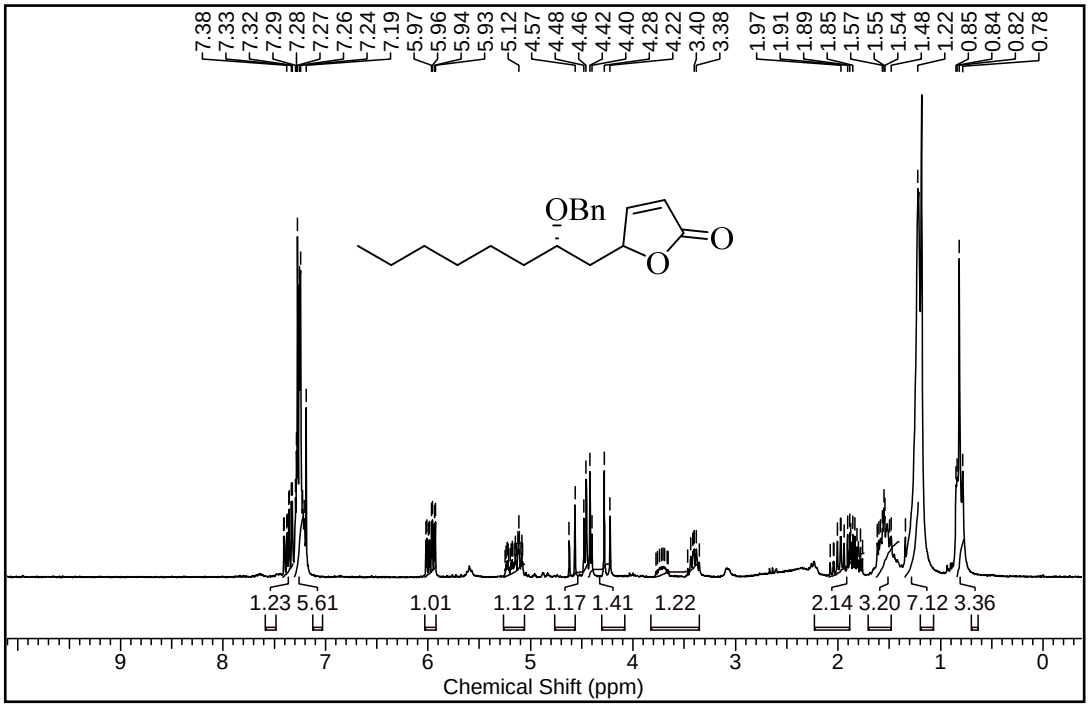


➢ **^{1}H NMR of the compound 33 in $CDCl_3$**

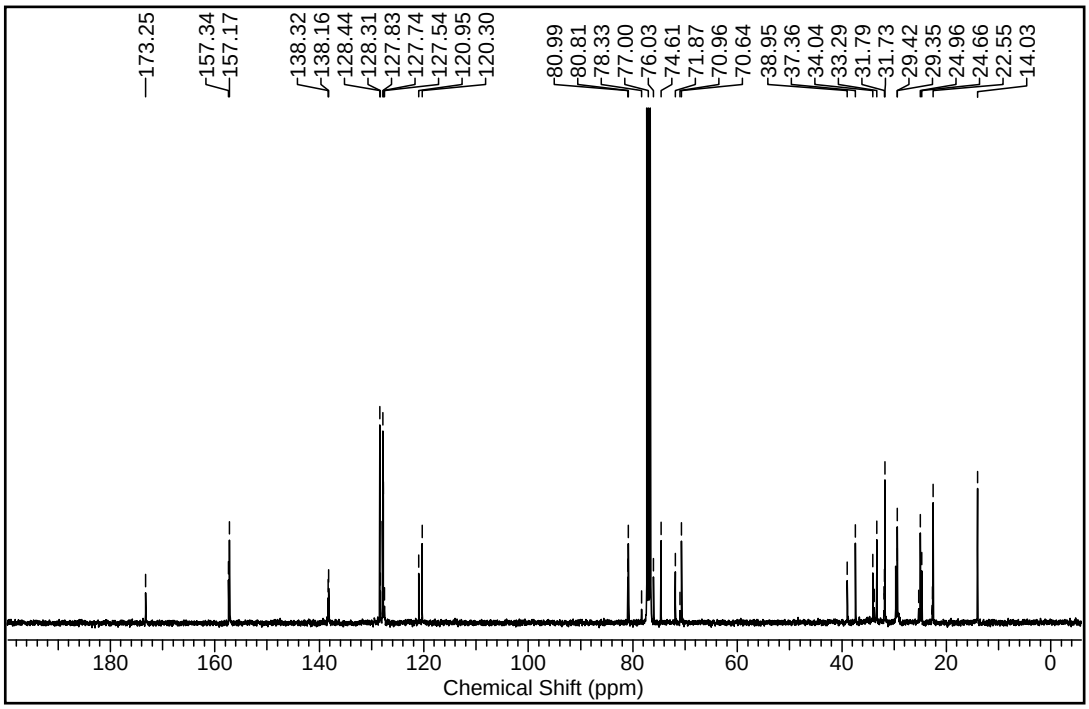


➢ **^{13}C NMR of the compound 33 in $CDCl_3$**

5-((*S*)-2-(Benzyloxy)octyl)furan-2(5*H*)-one 35:

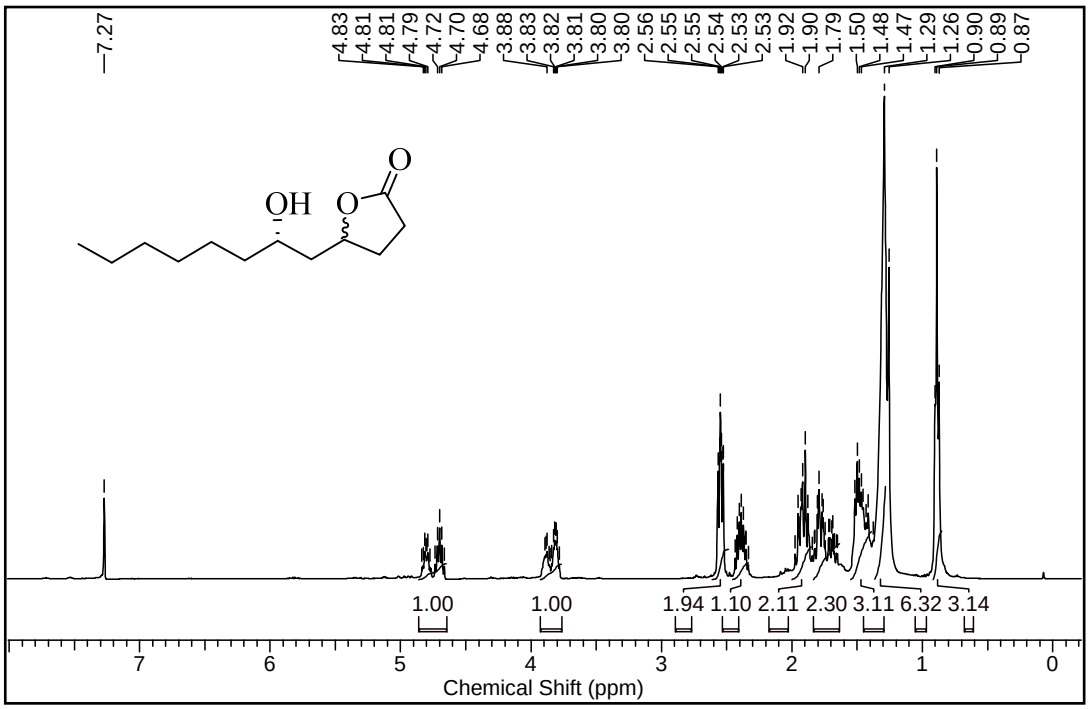


➢ **^{1}H NMR of the compound 35 in $CDCl_3$**

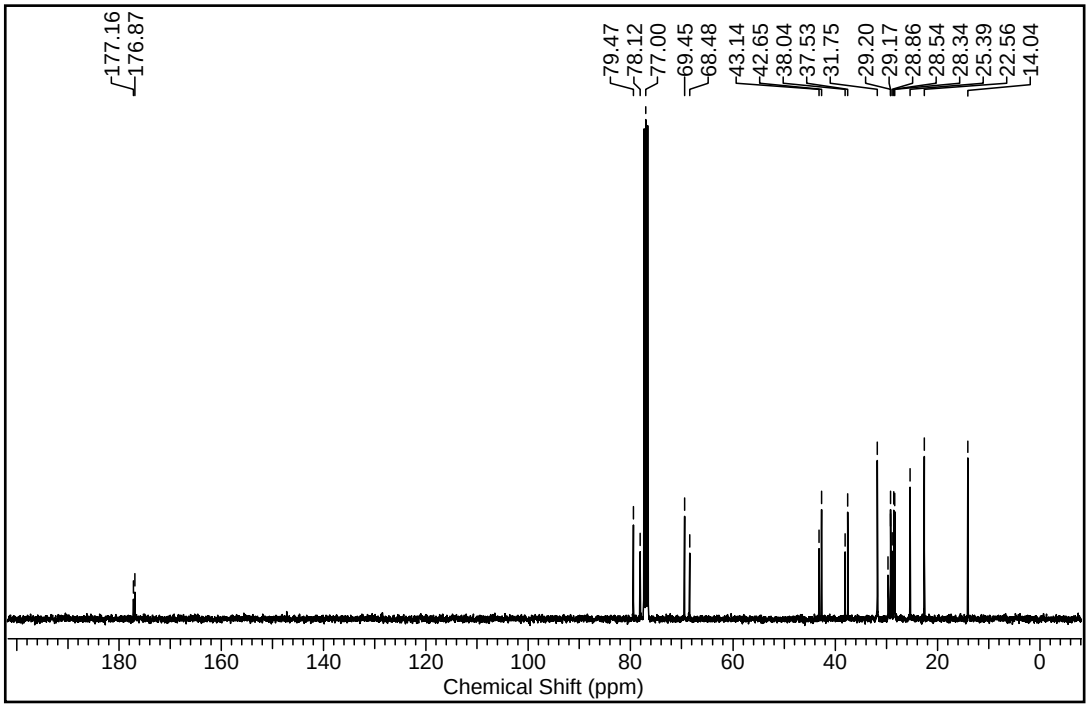


➢ **^{13}C NMR of the compound 35 in $CDCl_3$**

5-((*S*)-2-Hydroxyoctyl)dihydrofuran-2(3*H*)-one 37:

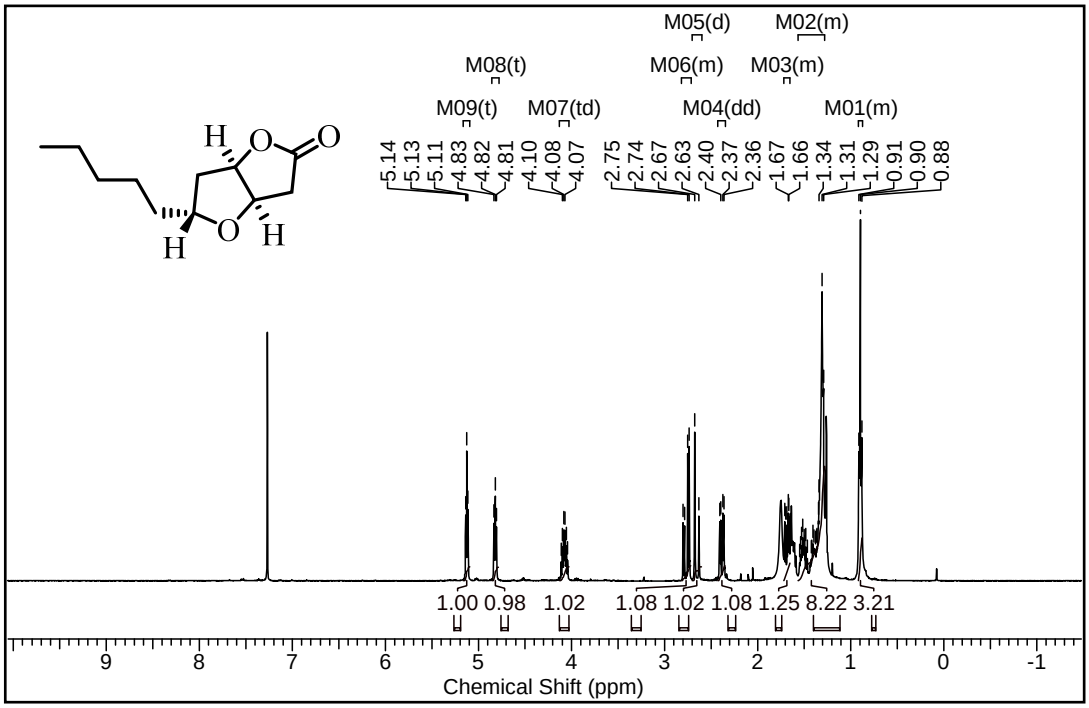


➢ **^{1}H NMR of the compound 37 in $CDCl_3$**

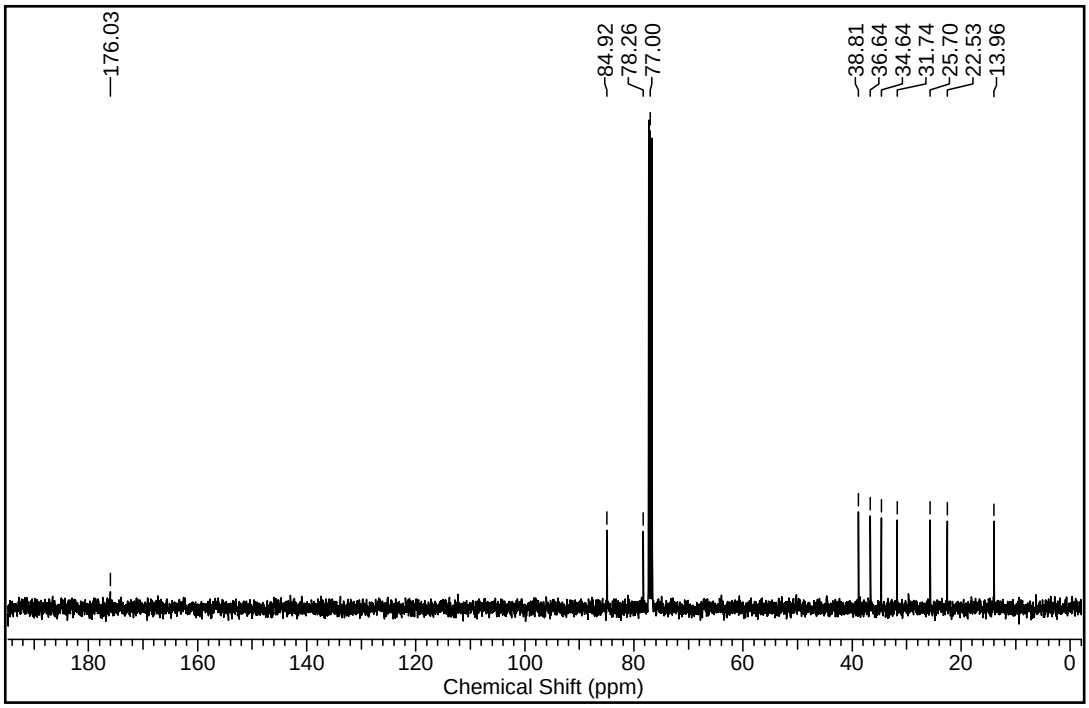


➢ **^{13}C NMR of the compound 37 in $CDCl_3$**

(3a*R*,5*R*,6a*R*)-5-Pentyltetrahydrofuro[3,2-b]furan-2(3*H*)-one A:

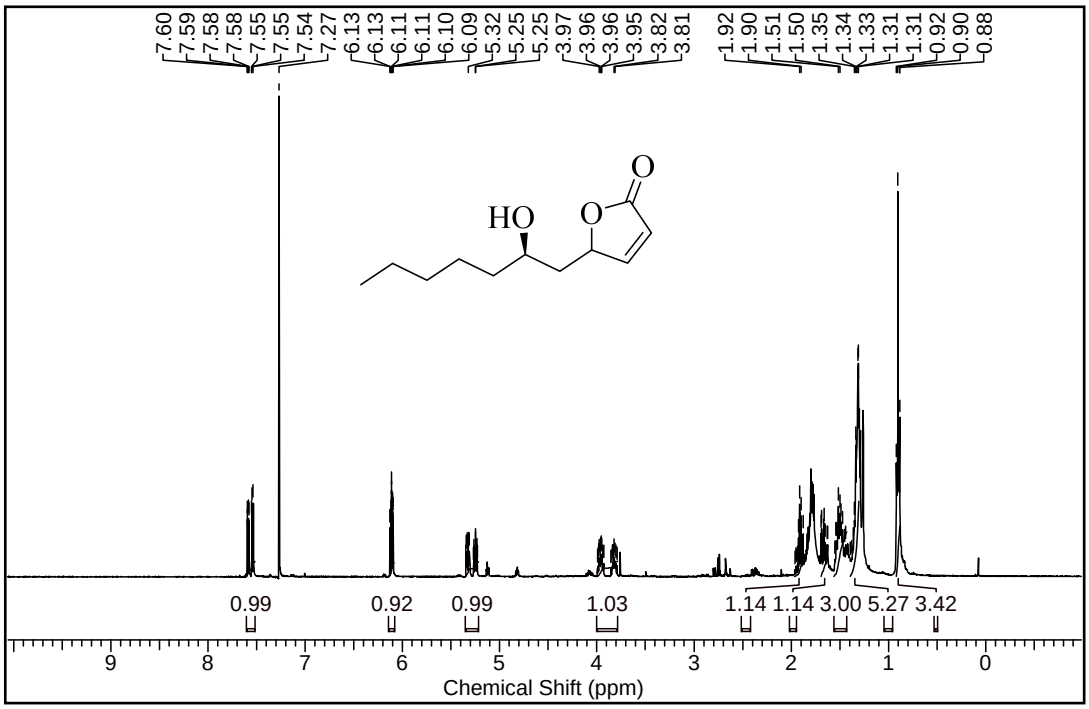


➢ **^{1}H NMR of the compound A in $CDCl_3$**

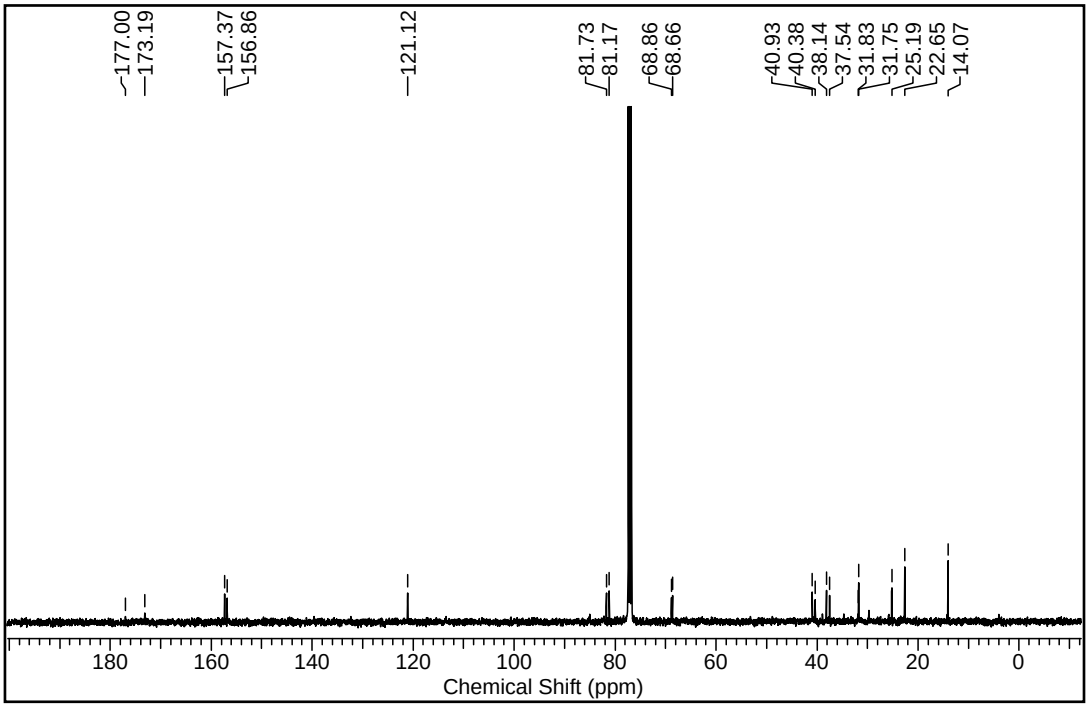


➢ **^{13}C NMR of the compound A in $CDCl_3$**

5-((*R*)-2-Hydroxyheptyl)furan-2(5*H*)-one C:

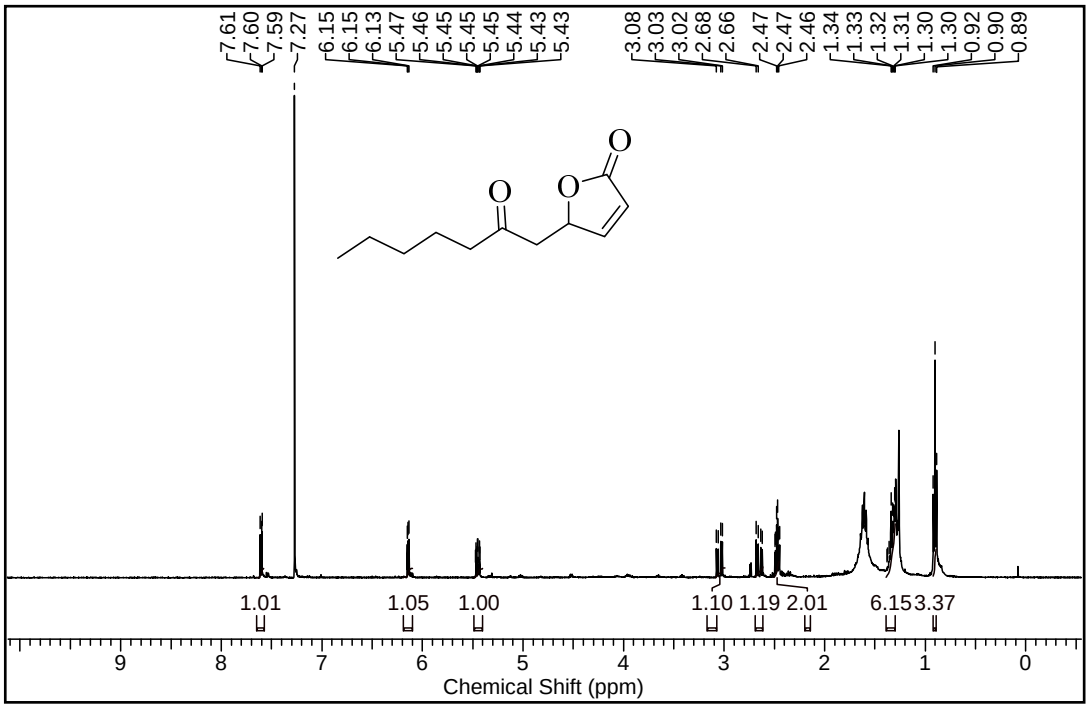


➢ **^{1}H NMR of the compound C in $CDCl_3$**

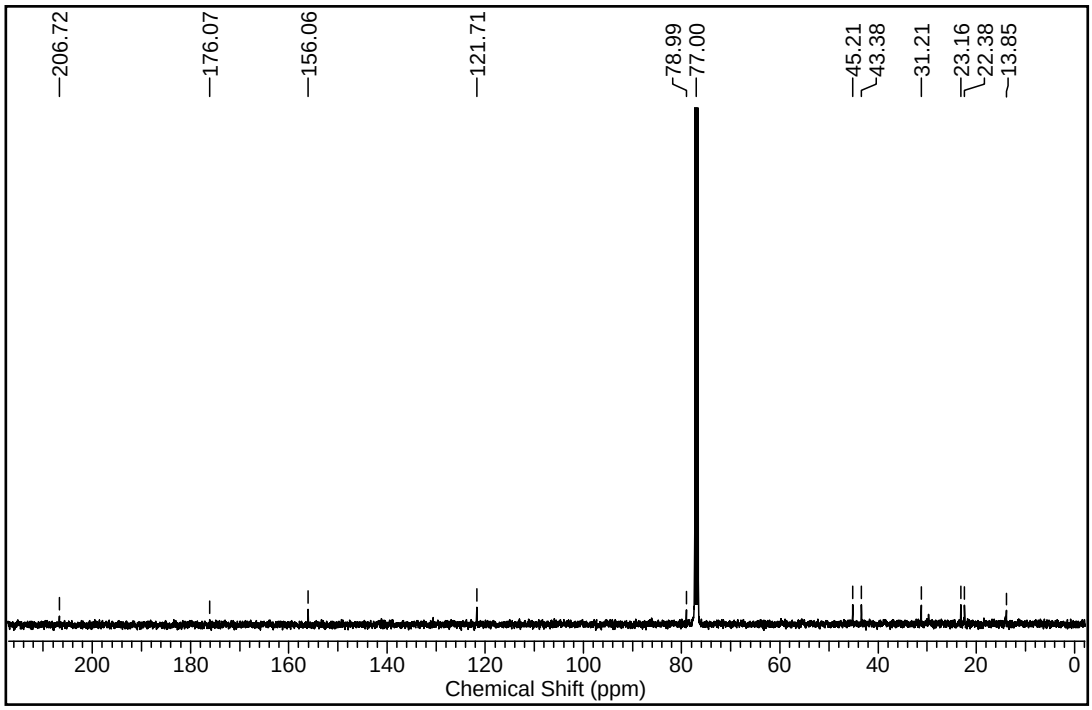


➢ **^{13}C NMR of the compound C in $CDCl_3$**

5-(2-Oxoheptyl)furan-2(5*H*)-one D:

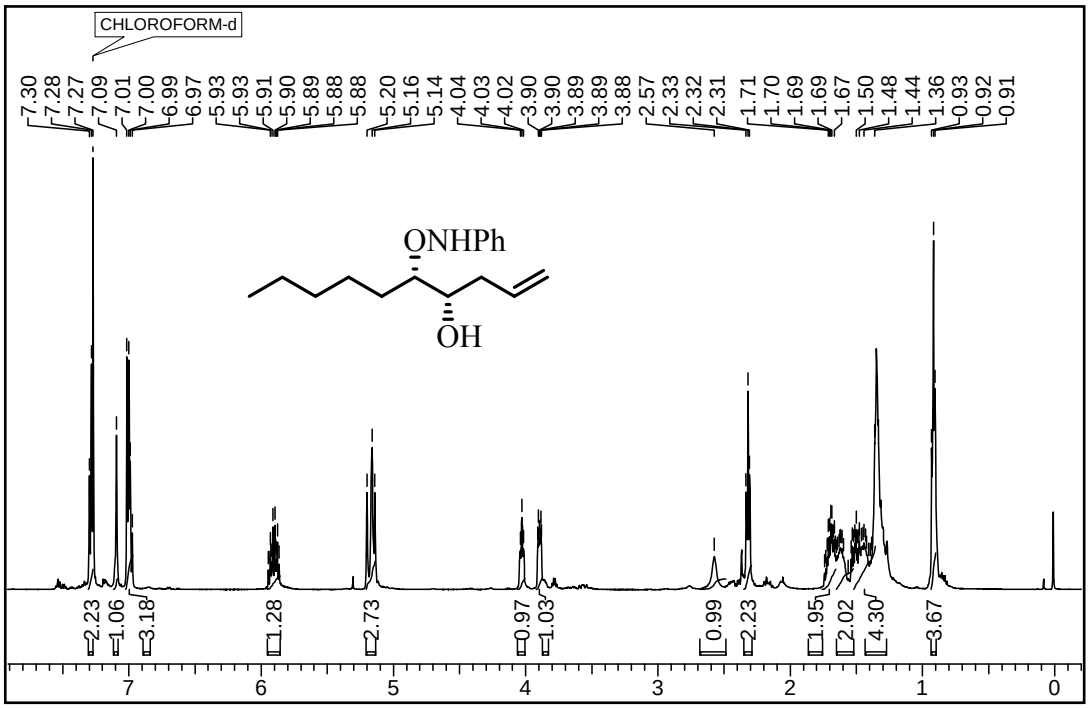


➢ **^{1}H NMR of the compound D in $CDCl_3$**

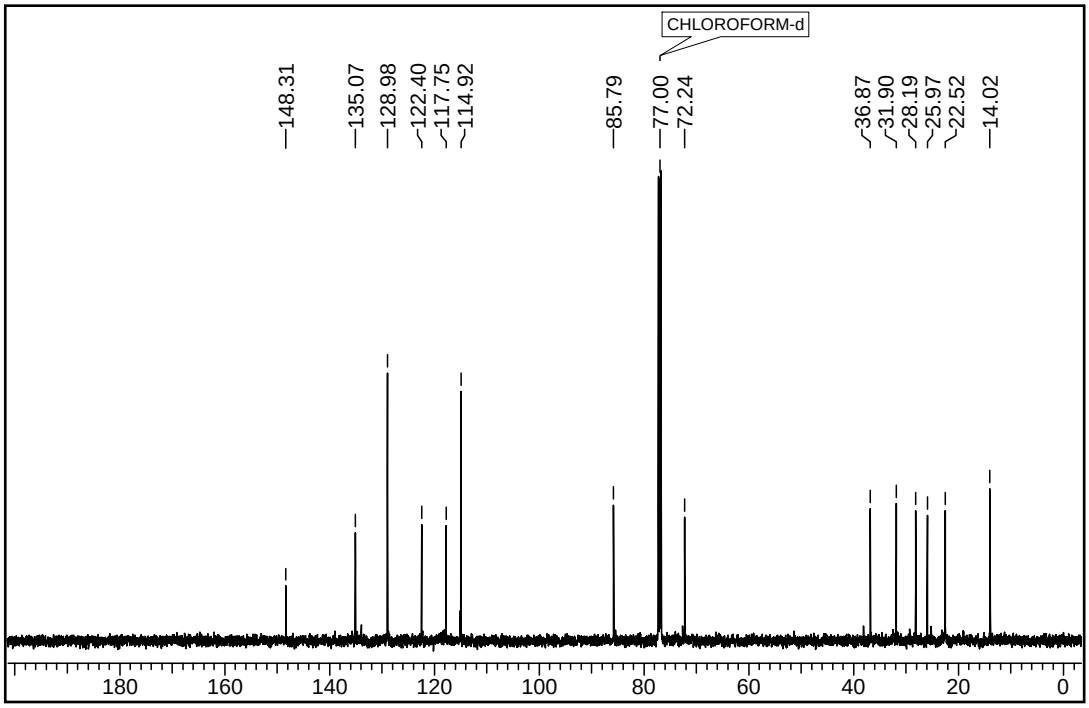


➢ **^{13}C NMR of the compound D in $CDCl_3$**

(4*S*,5*S*)-5-((Phenylamino)oxy)dec-1-en-4-ol 39:

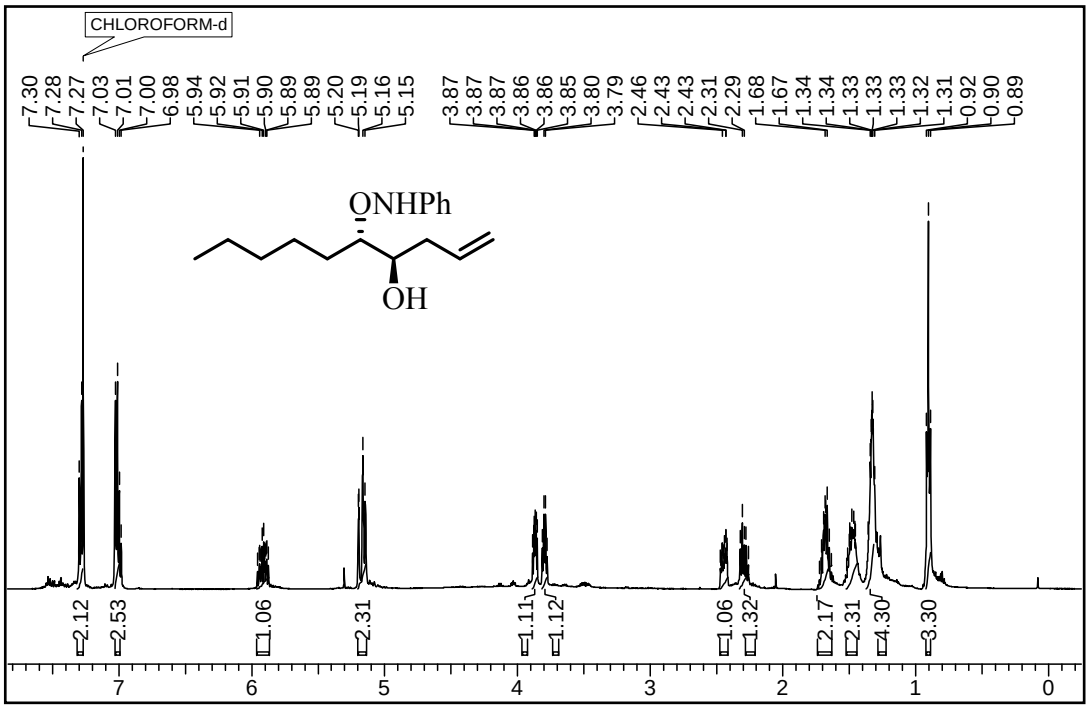


➢ **^{1}H NMR of the compound 39 in $CDCl_3$**

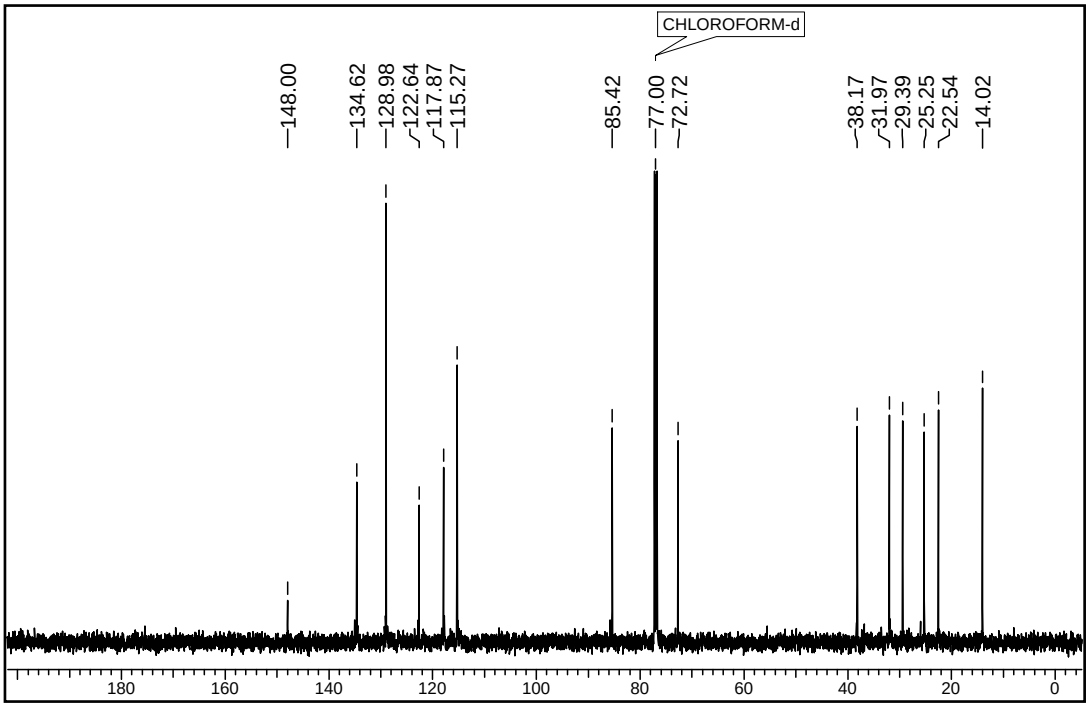


➢ **^{13}C NMR of the compound 39 in $CDCl_3$**

(4*R*,5*S*)-5-((Phenylamino)oxy)dec-1-en-4-ol 40:

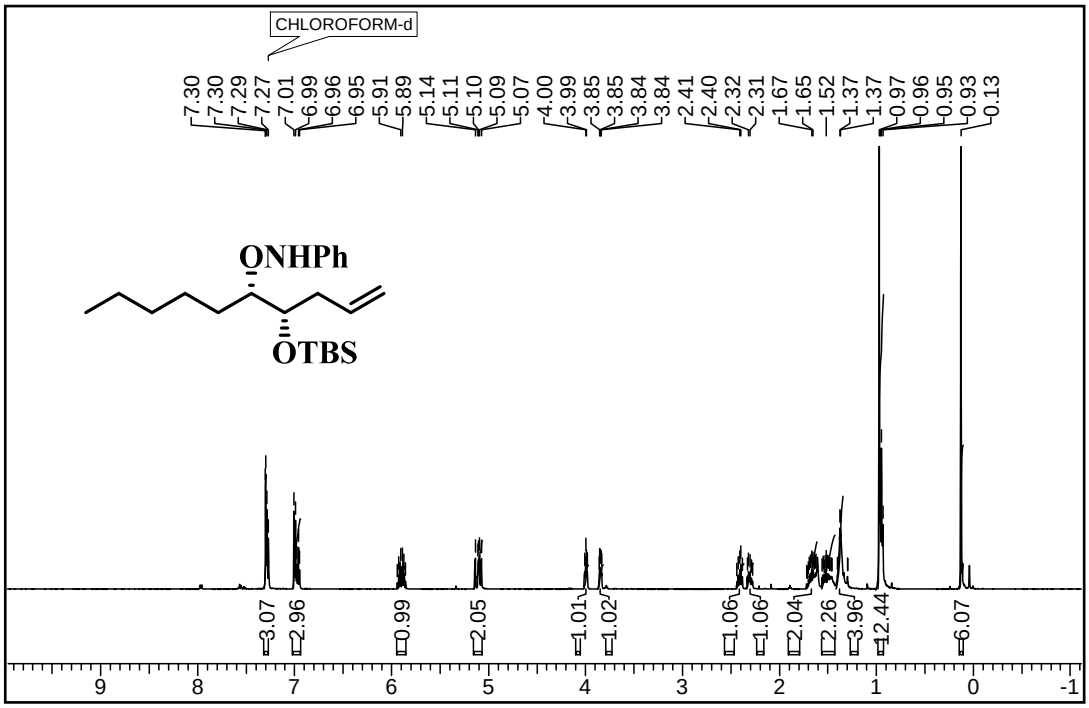


➢ **^{1}H NMR of the compound 40 in $CDCl_3$**

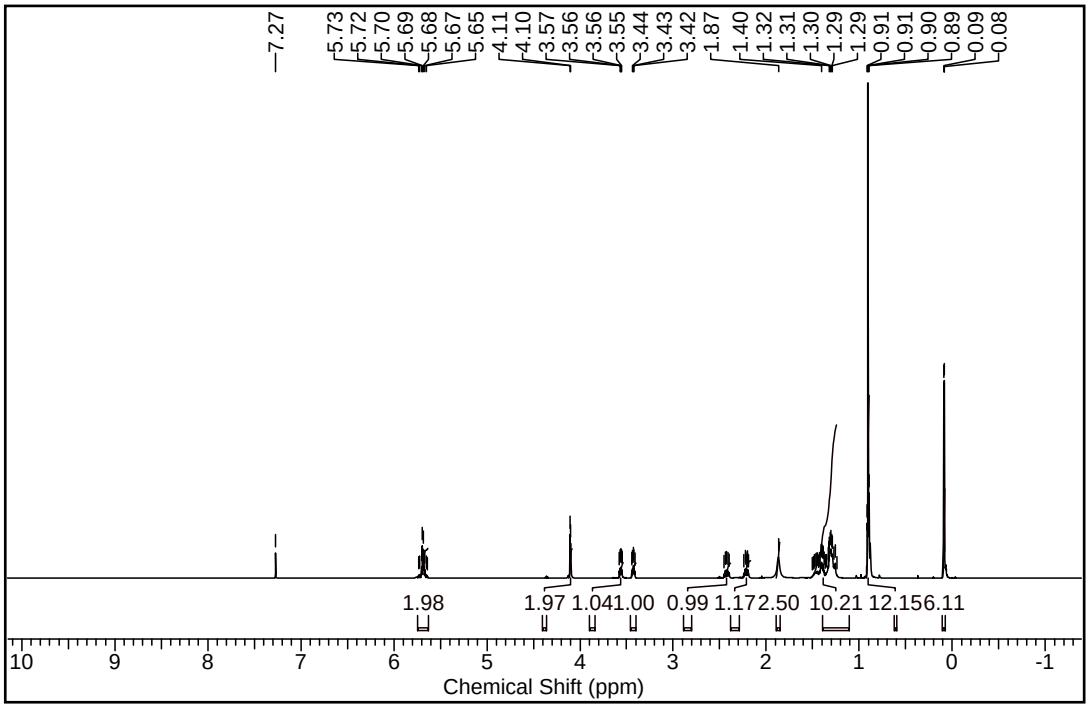


➢ **^{13}C NMR of the compound 40 in $CDCl_3$**

O-((4*S*,5*S*)-4-((Tert-butyldimethylsilyl)oxy)dec-1-en-5-yl)-N-phenylhydroxylamine 41:

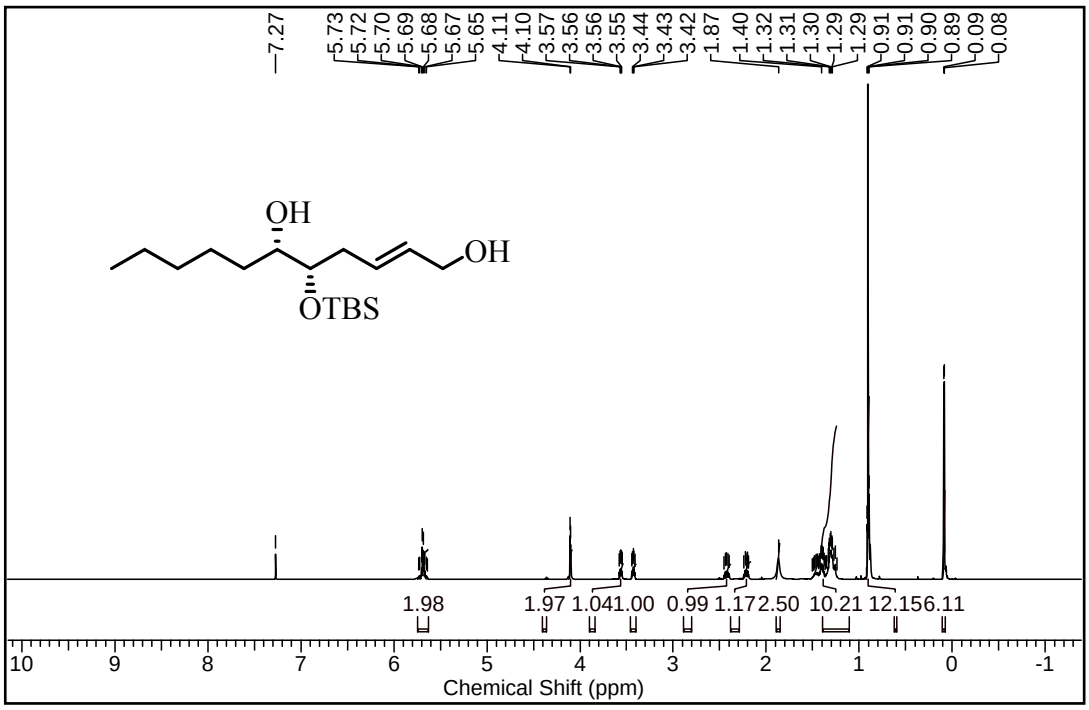


- **^{1}H NMR of the compound 41 in $CDCl_3$**

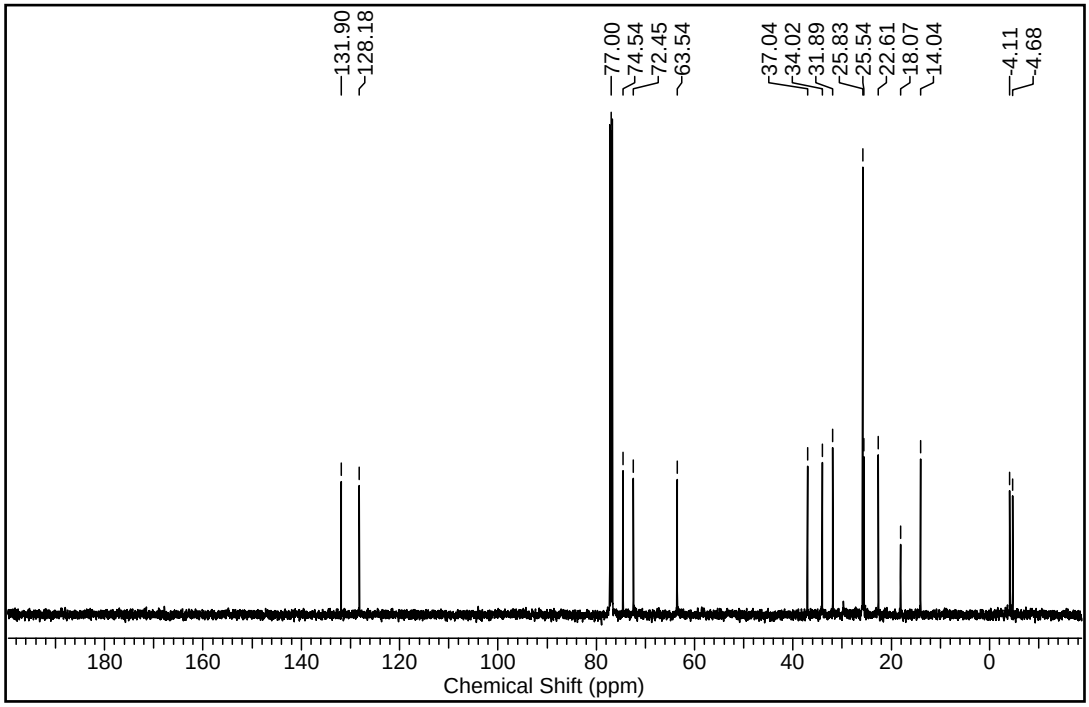


- **^{13}C NMR of the compound 41 in $CDCl_3$**

(5*S*,6*S*,*E*)-5-((Tert-butyldimethylsilyl)oxy)undec-2-ene-1,6-diol 42:

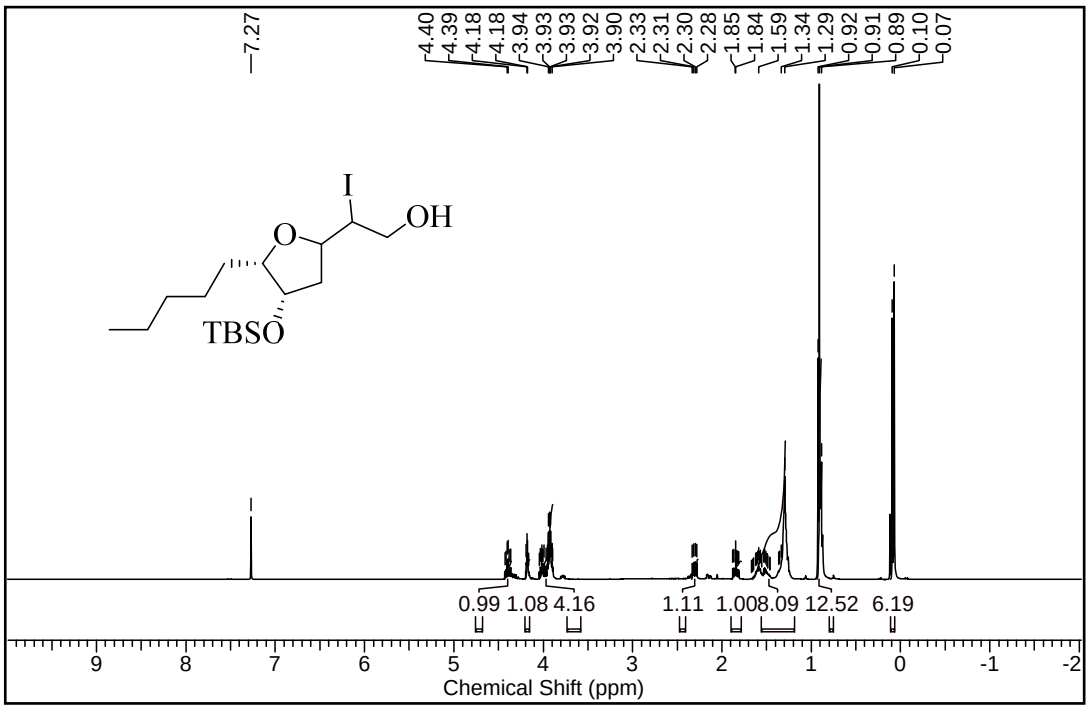


➢ **^{1}H NMR of the compound 42 in $CDCl_3$**

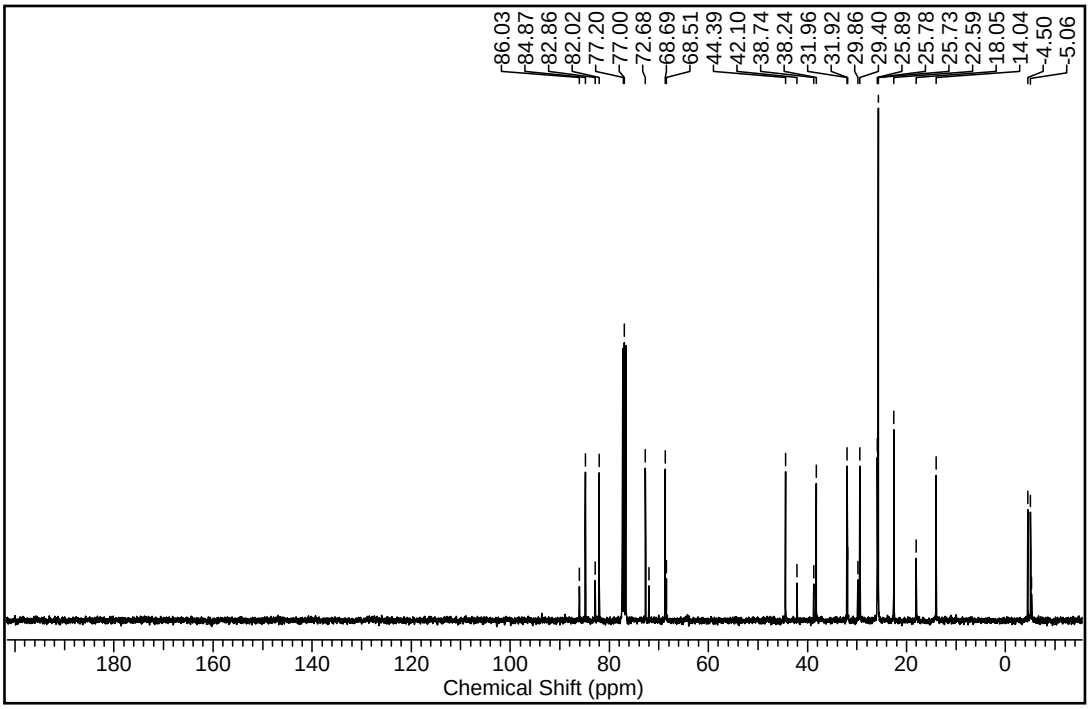


➢ **^{13}C NMR of the compound 42 in $CDCl_3$**

2-((4*S*,5*S*)-4-((Tert-butyldimethylsilyl)oxy)-5-pentyltetrahydrofuran-2-yl)-2-iodoethan-1-ol 43:

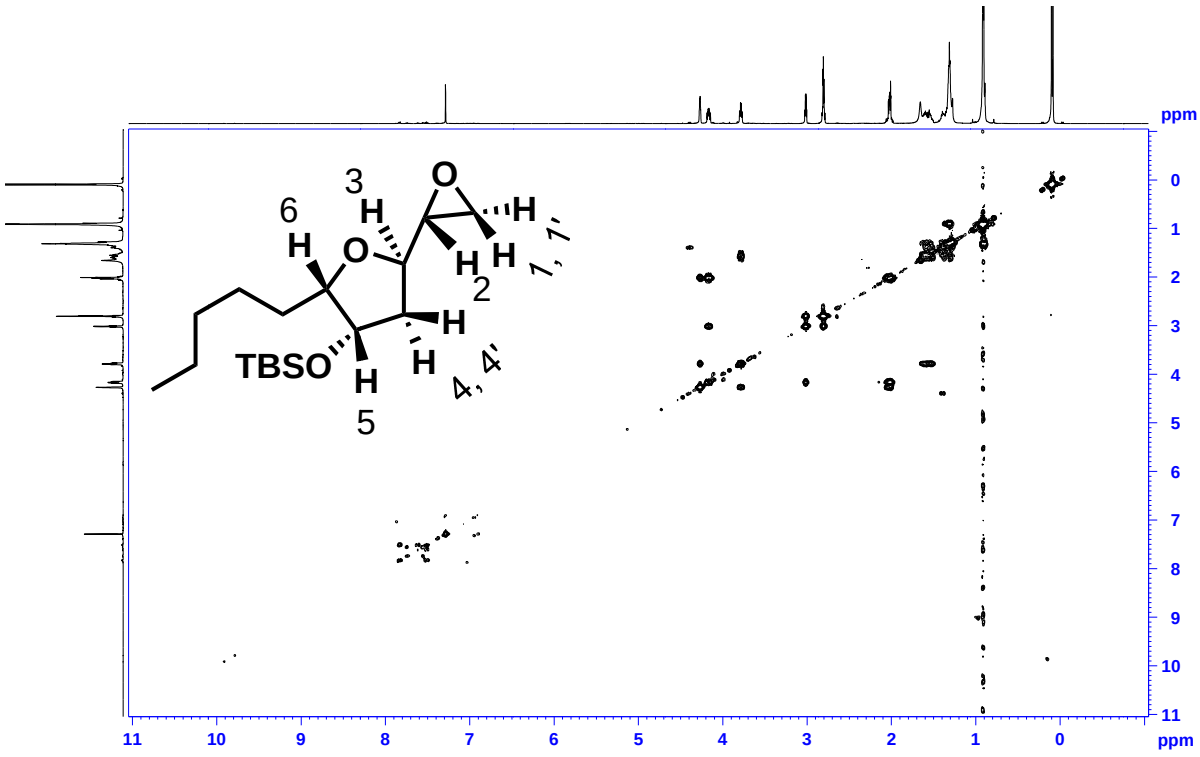


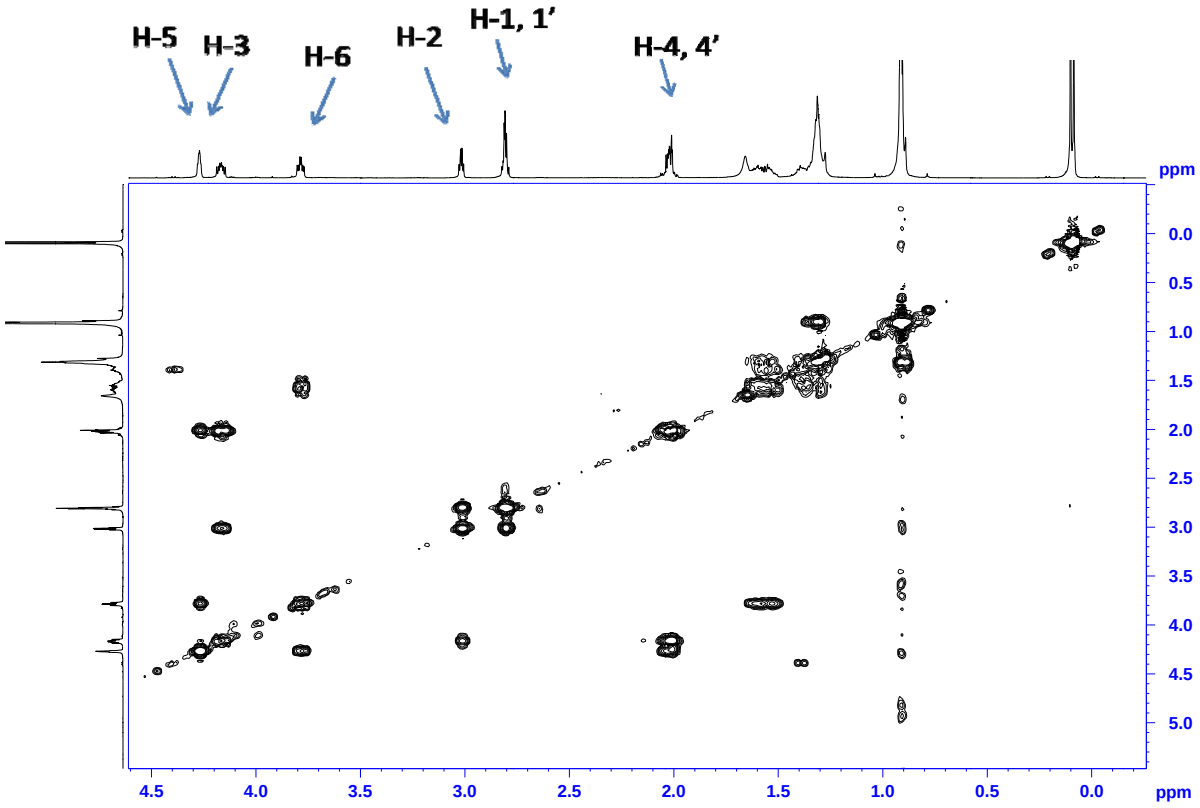
➢ **^{1}H NMR of the compound 43 in $CDCl_3$**



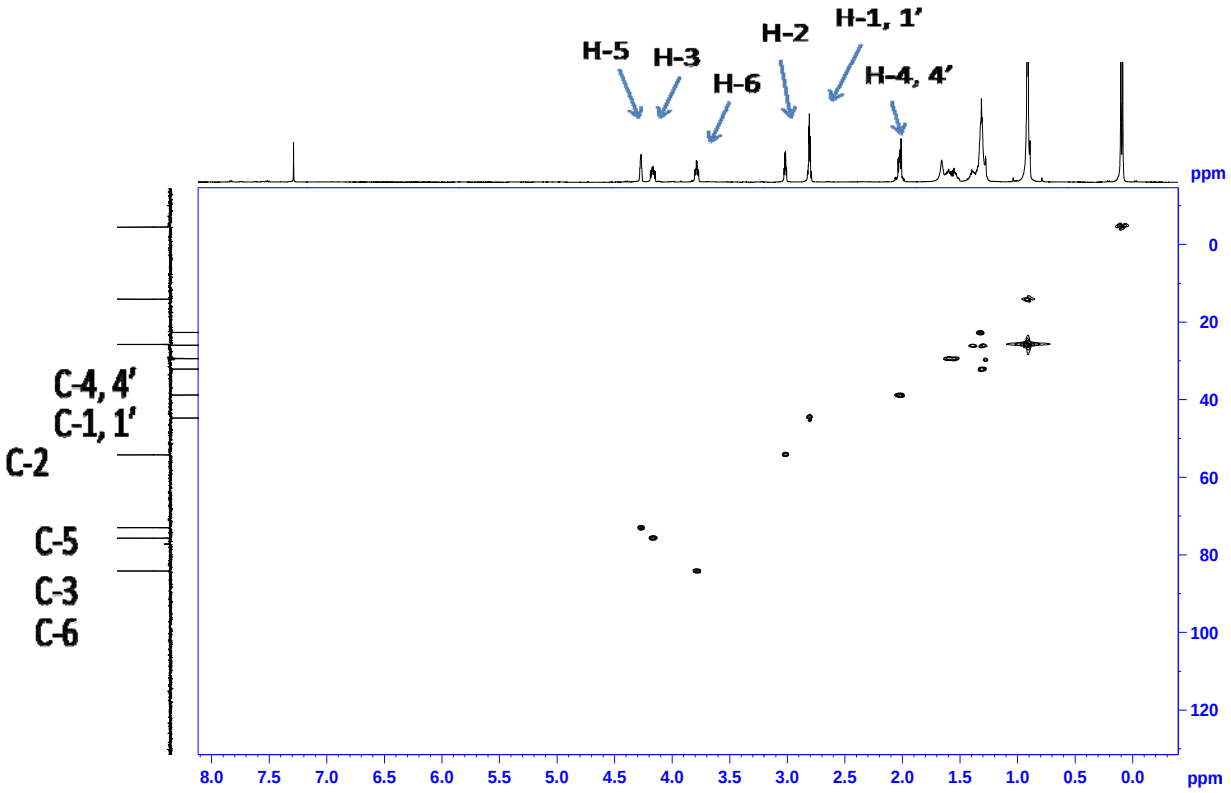
➢ **^{13}C NMR of the compound 43 in $CDCl_3$**

COSY of the compound 44 in $CDCl_3$:

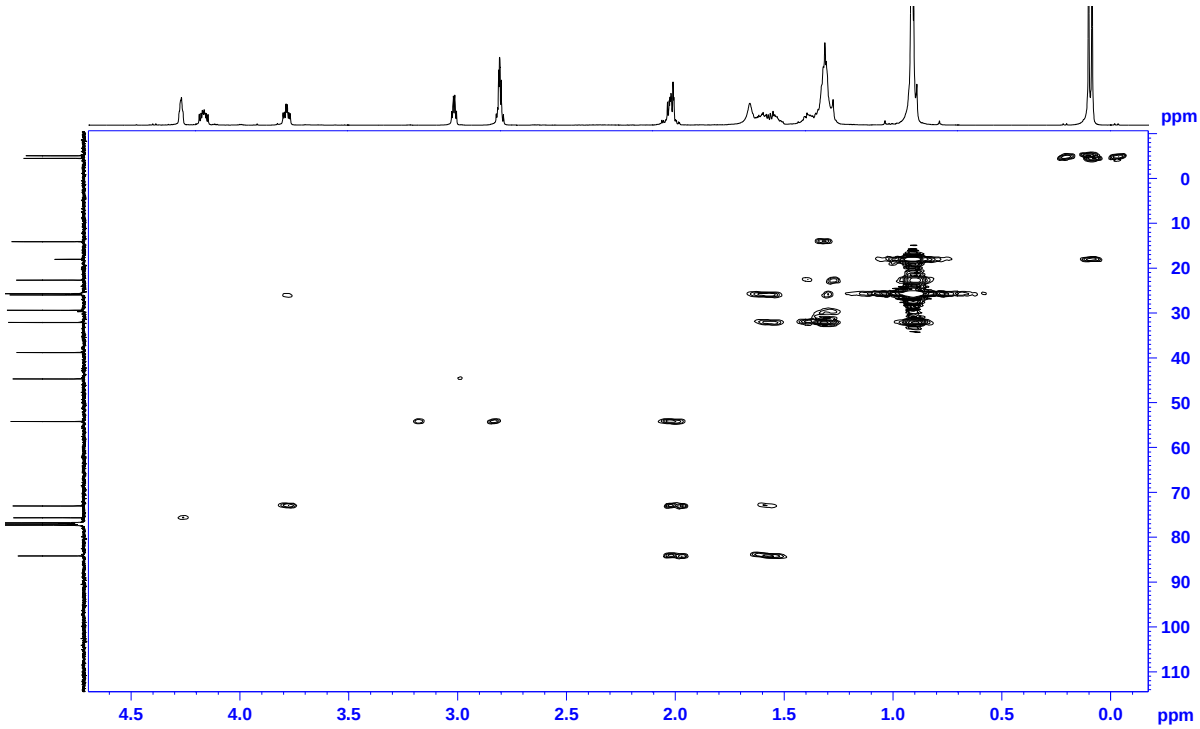




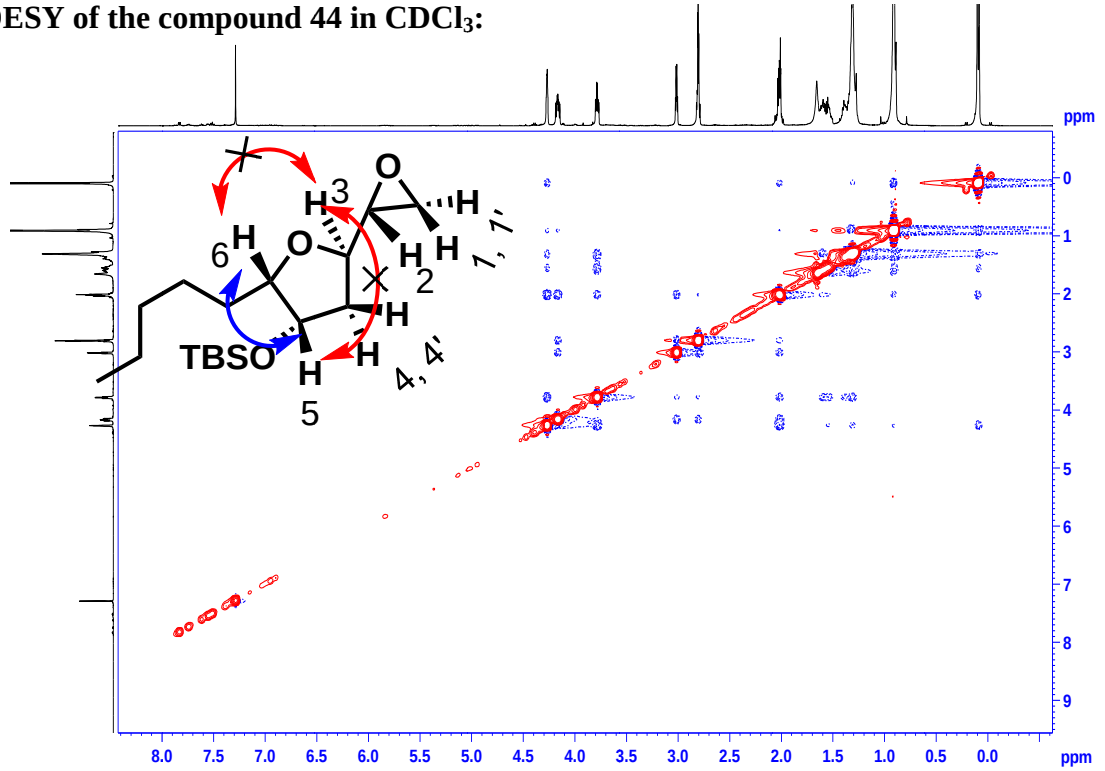
HSQC of the compound 44 in $CDCl_3$:

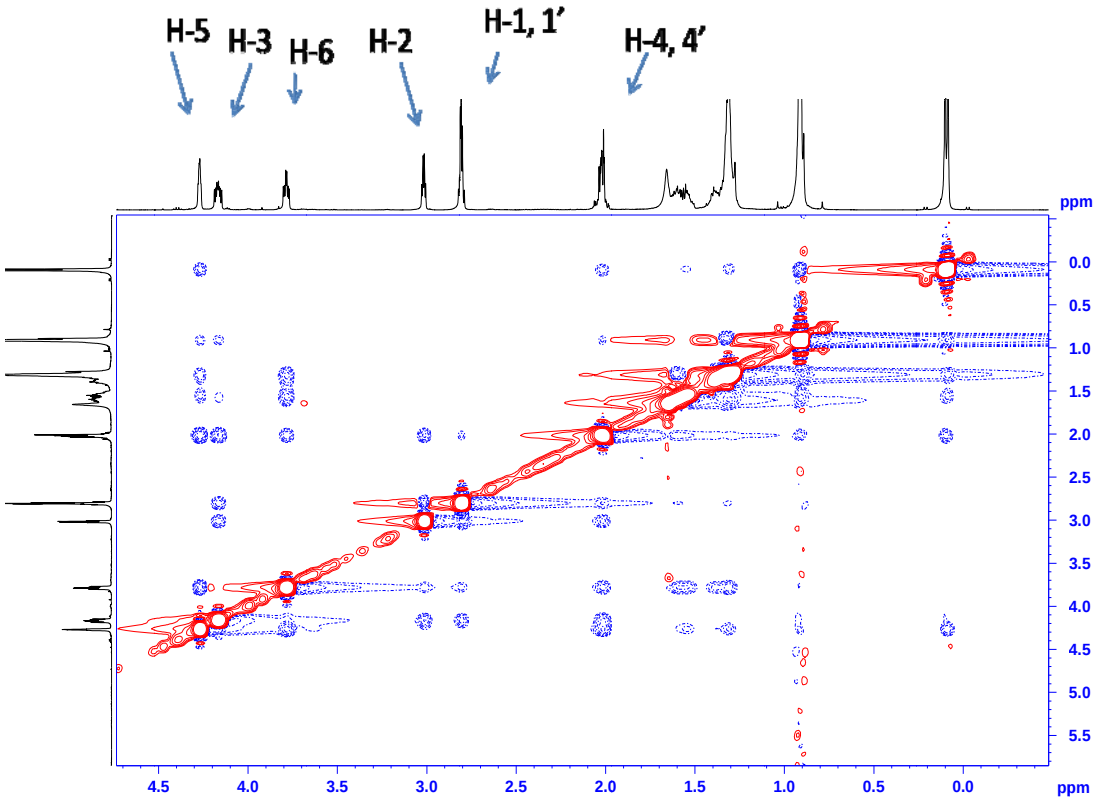


HMBC of the compound 44 in $CDCl_3$:

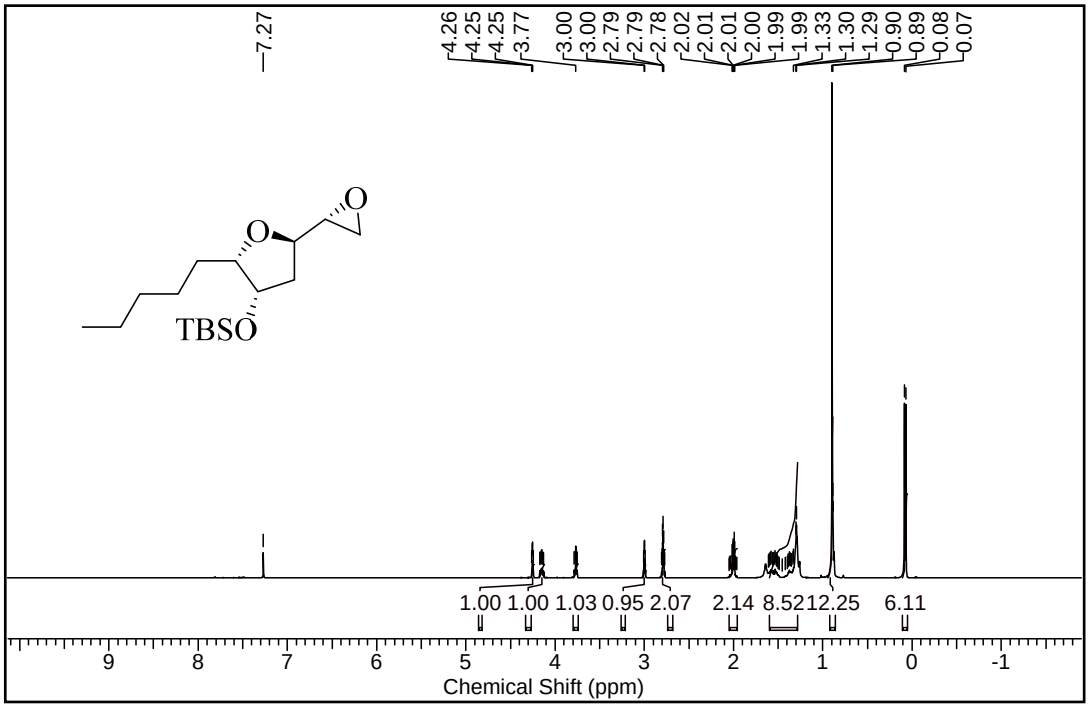


NOESY of the compound 44 in $CDCl_3$:

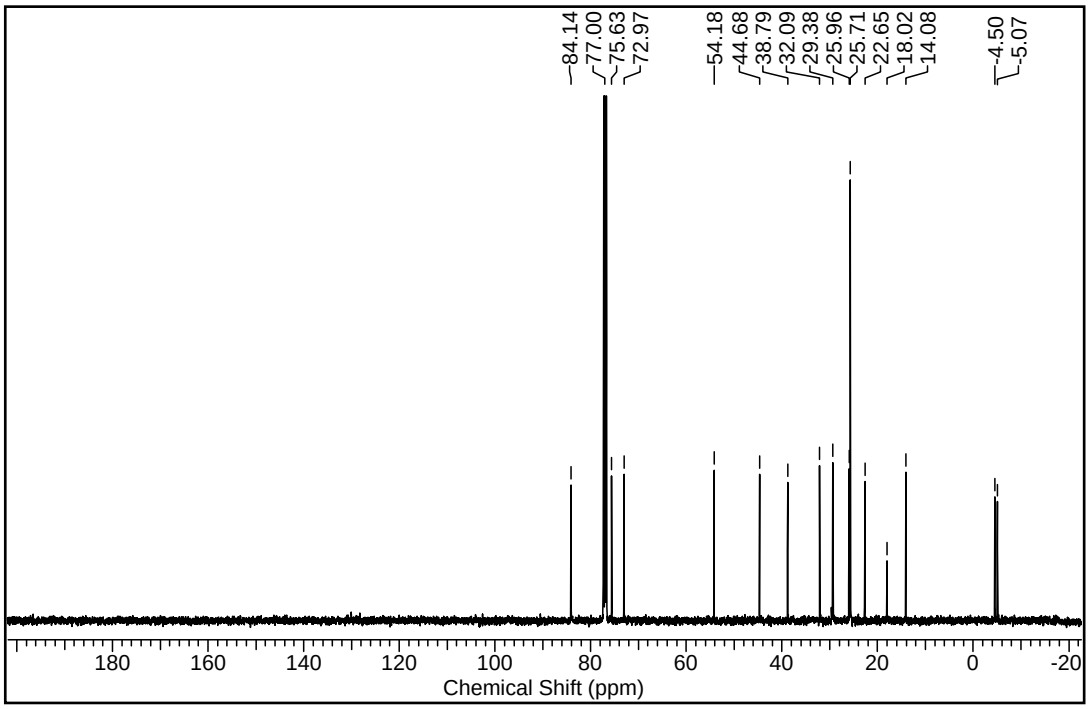




Tert-butyldimethyl(((2*S*,3*S*,5*R*)-5-((*R*)-oxiran-2-yl)-2-pentyltetrahydrofuran-3-yl)oxy)silane 44:

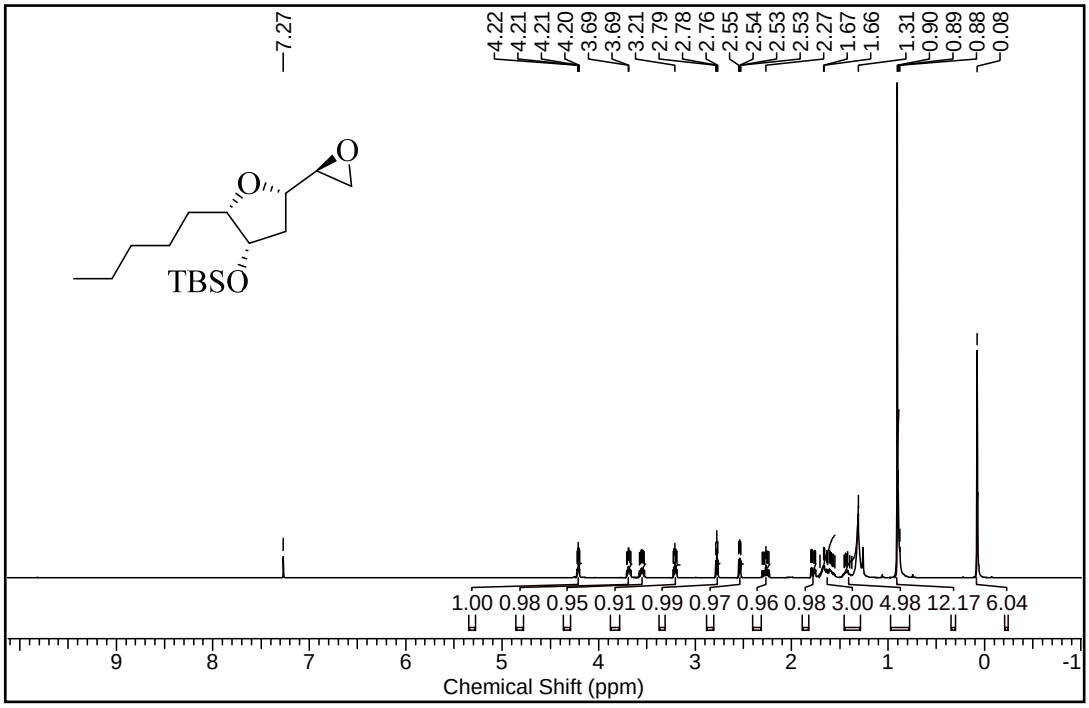


➢ **^{1}H NMR of the compound 44 in $CDCl_3$**

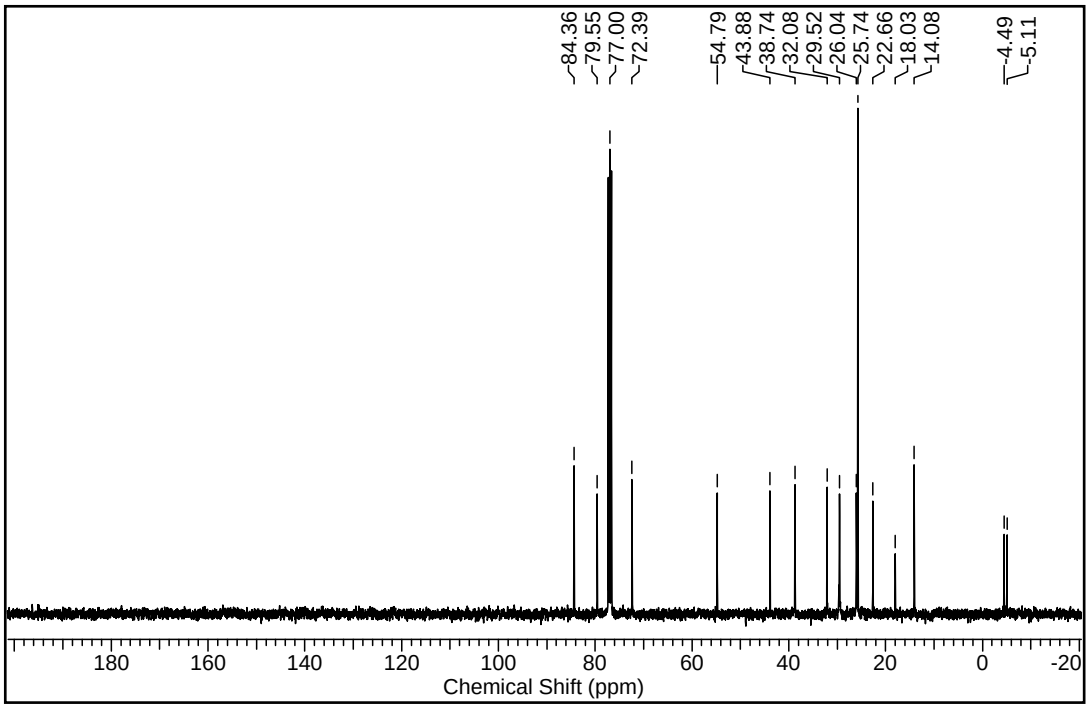


➢ **^{13}C NMR of the compound 44 in $CDCl_3$**

Tert-butyldimethyl(((2*S*,3*S*,5*S*)-5-((*S*)-oxiran-2-yl)-2-pentyltetrahydrofuran-3-yl)oxy)silane 45:

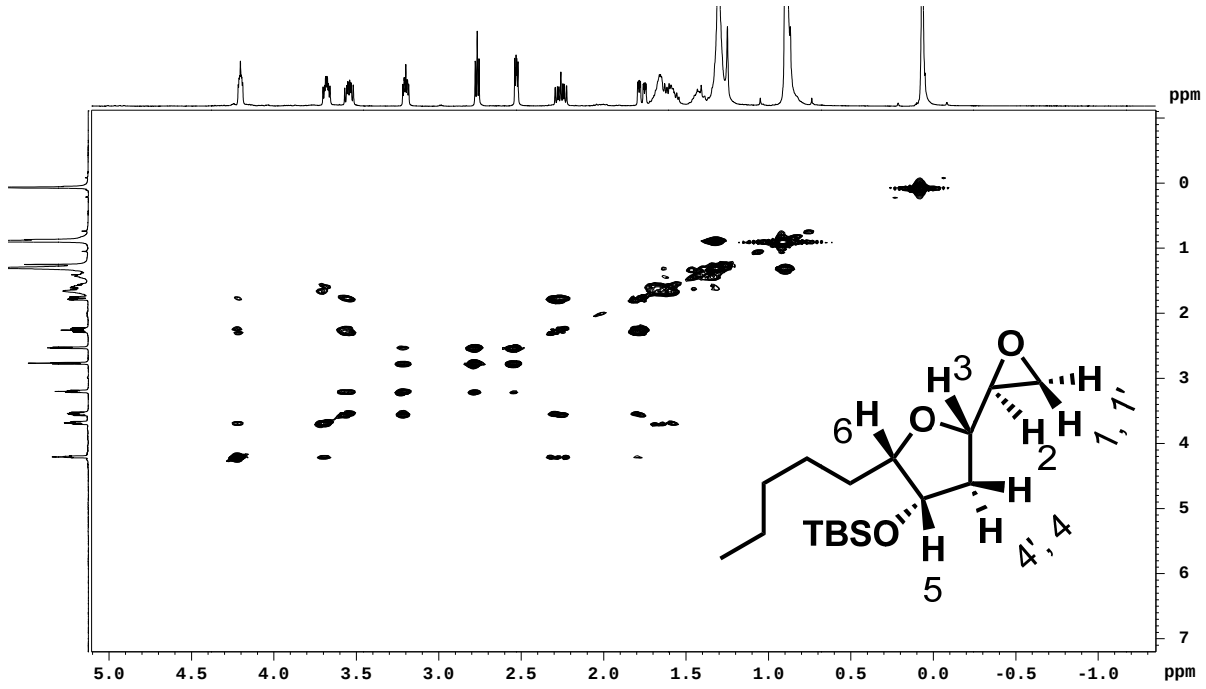


➢ **^{1}H NMR of the compound 45 in $CDCl_3$**

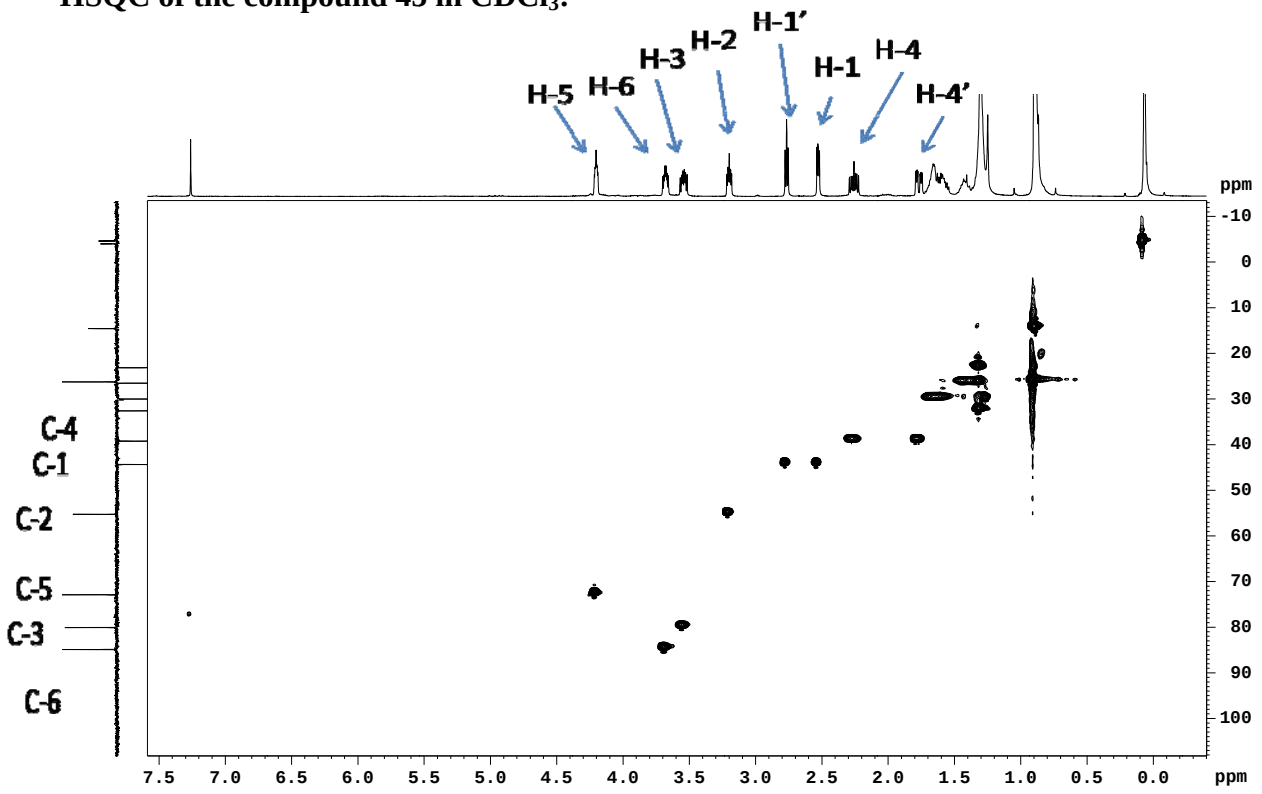


➢ **^{13}C NMR of the compound 45 in $CDCl_3$**

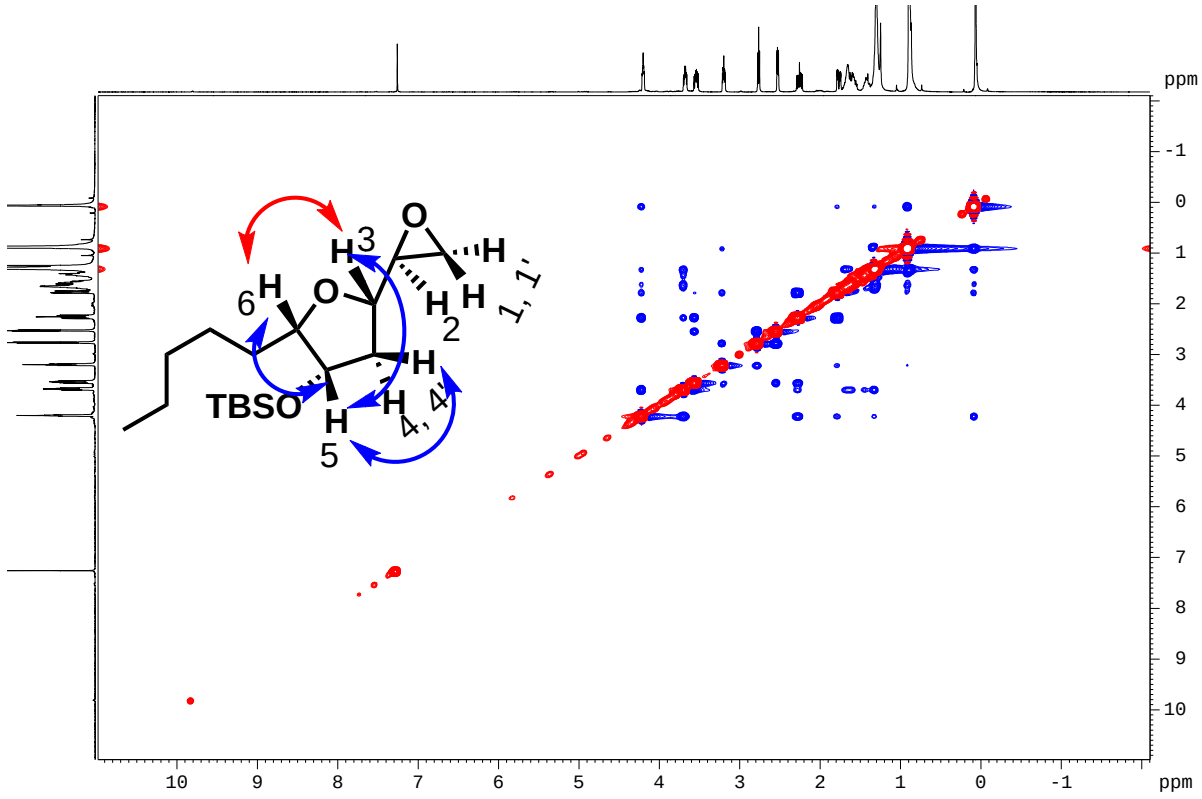
COSY of the compound 45 in $CDCl_3$:

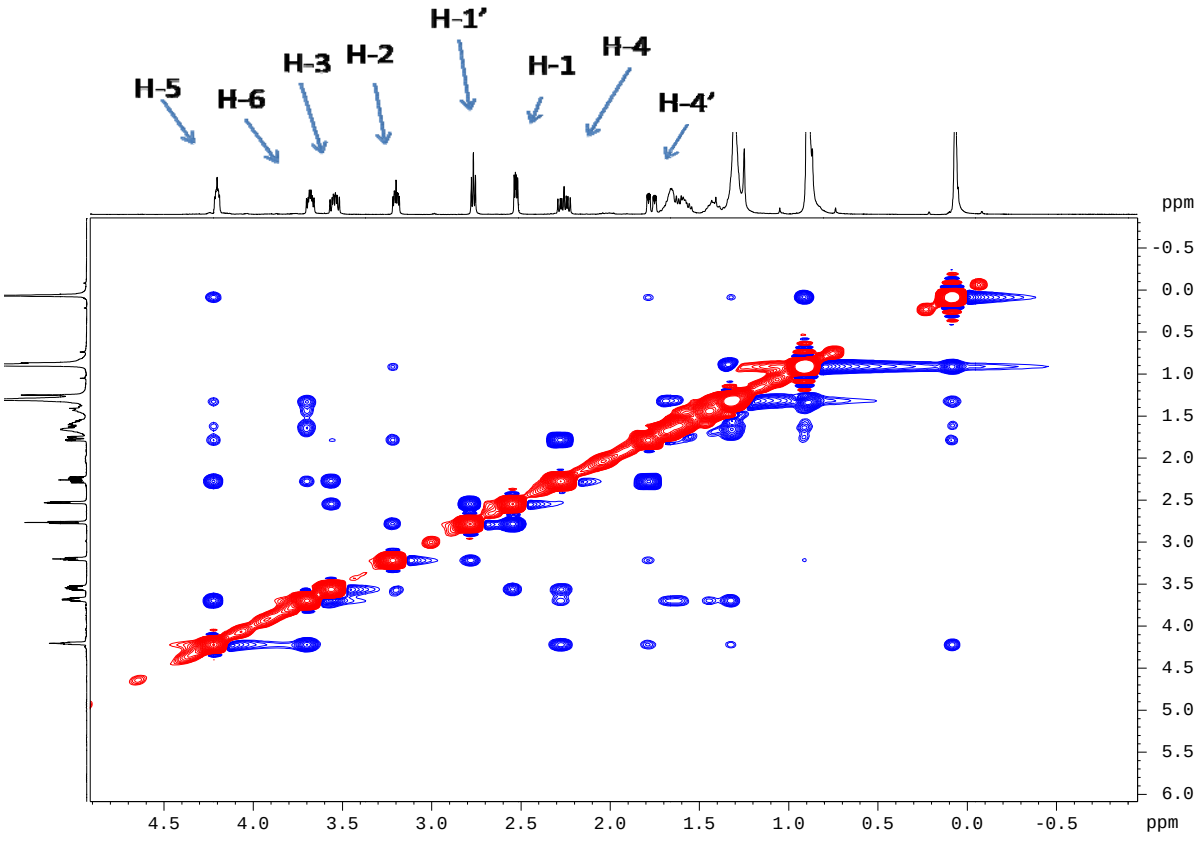


HSQC of the compound 45 in $CDCl_3$:

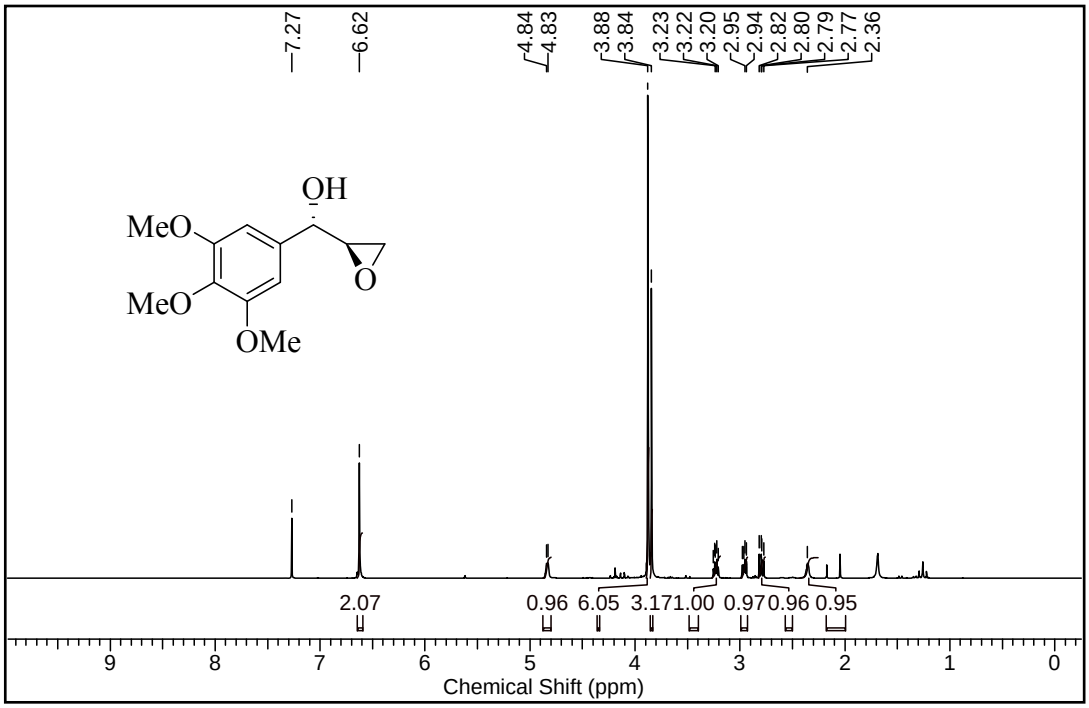


NOESY of the compound 45 in $CDCl_3$:

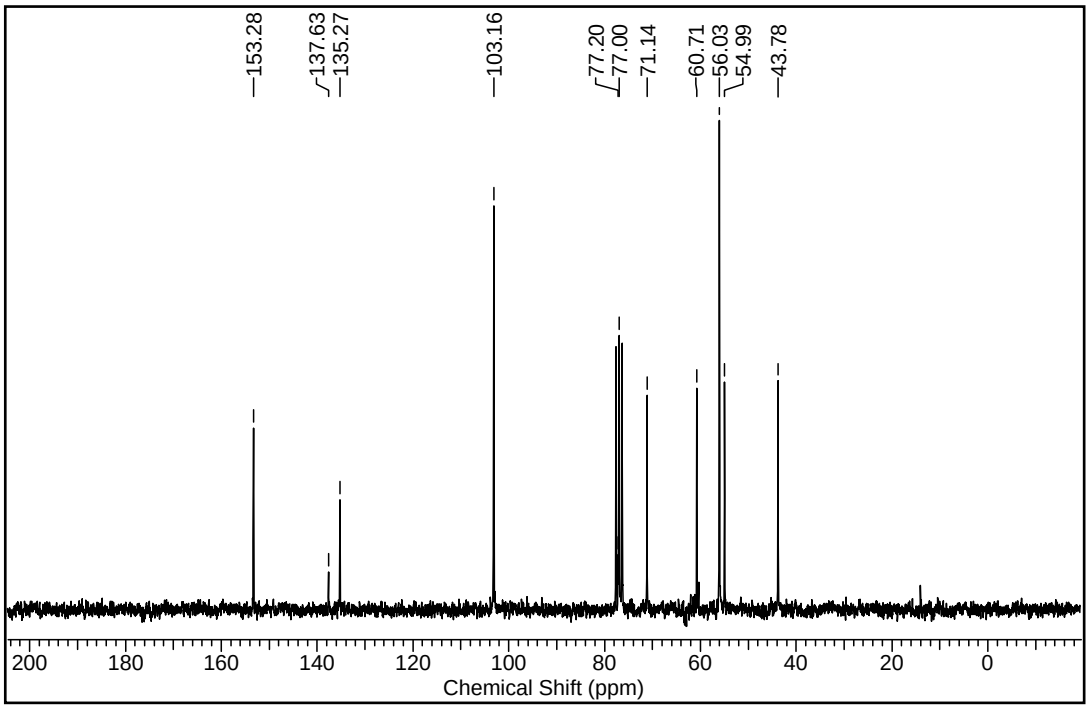




(*S*)-((*R*)-Oxiran-2-yl)(3,4,5-trimethoxyphenyl)methanol 47:

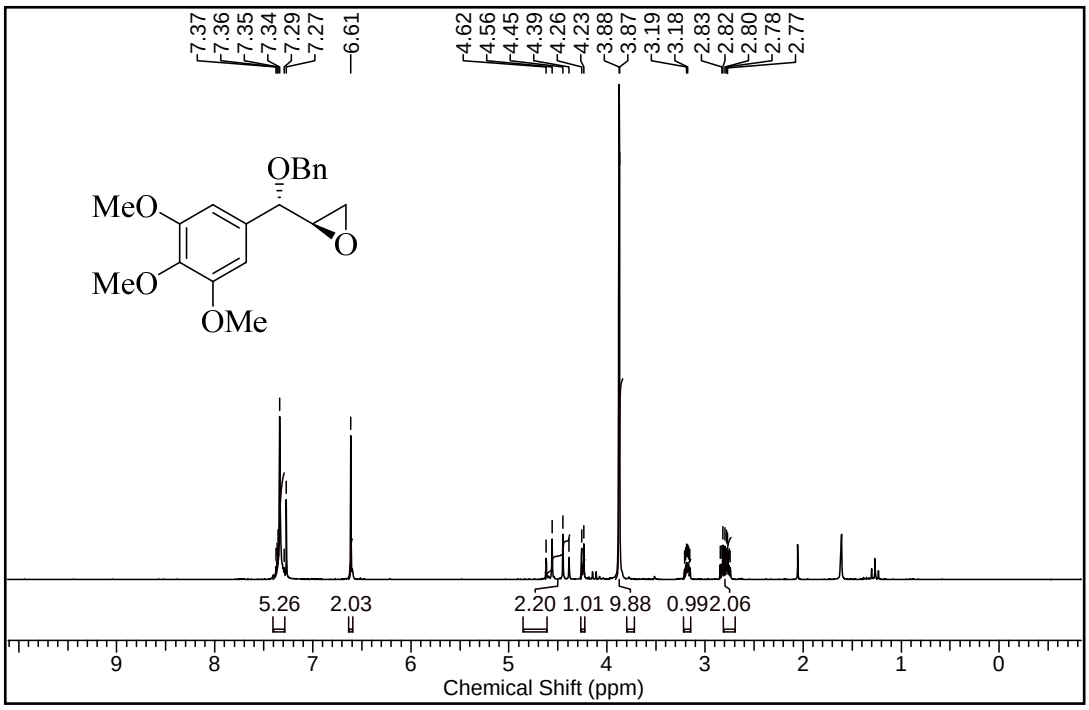


➢ **^{1}H NMR of the compound 47 in $CDCl_3$**

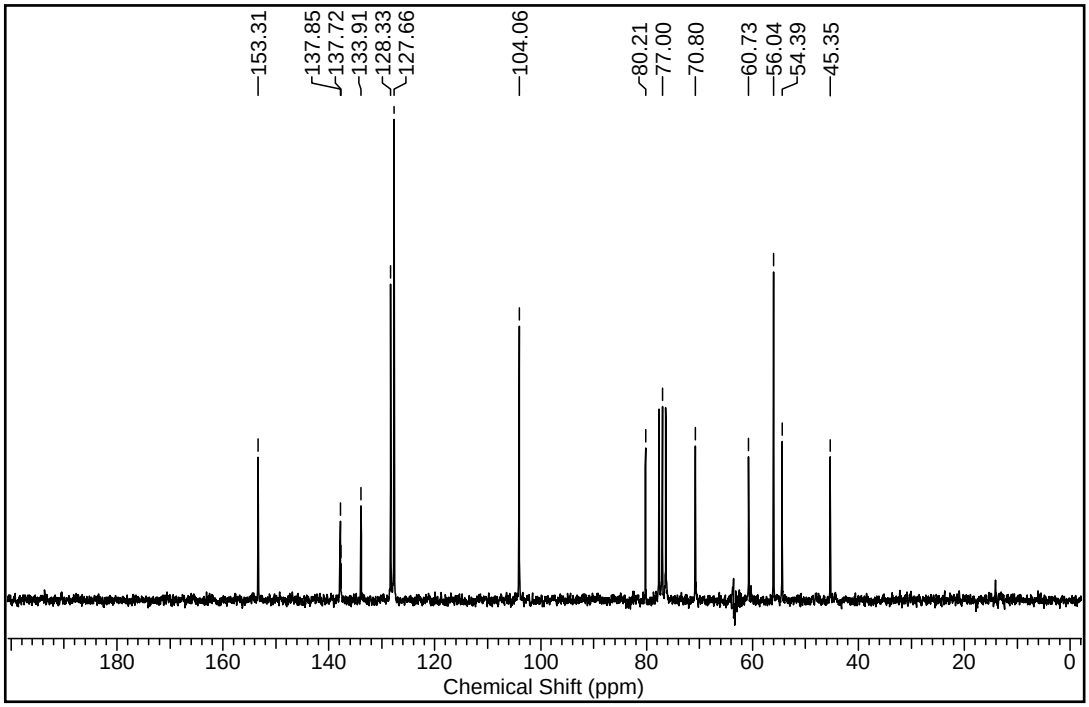


➢ **^{13}C NMR of the compound 47 in $CDCl_3$**

(*R*)-2-((*S*)-(Benzyloxy)(3,4,5-trimethoxyphenyl)methyl)oxirane 48:

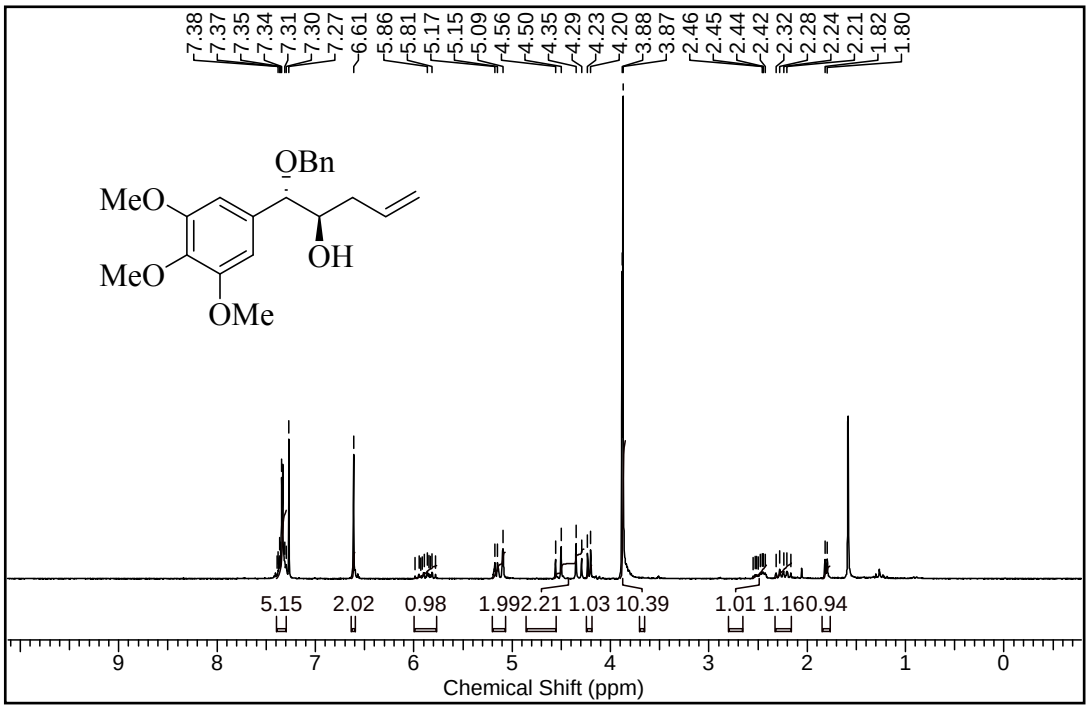


➢ **^{1}H NMR of the compound 48 in $CDCl_3$**

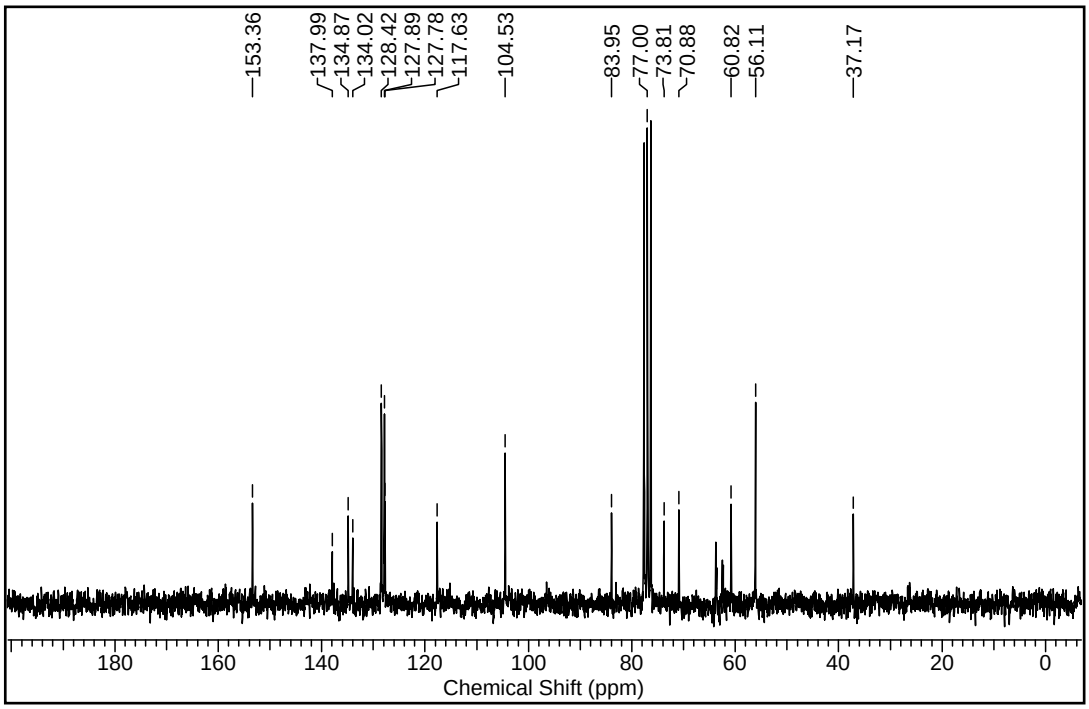


➢ **^{13}C NMR of the compound 48 in $CDCl_3$**

(1*S*,2*R*)-1-(Benzyloxy)-1-(3,4,5-trimethoxyphenyl)pent-4-en-2-ol 49:

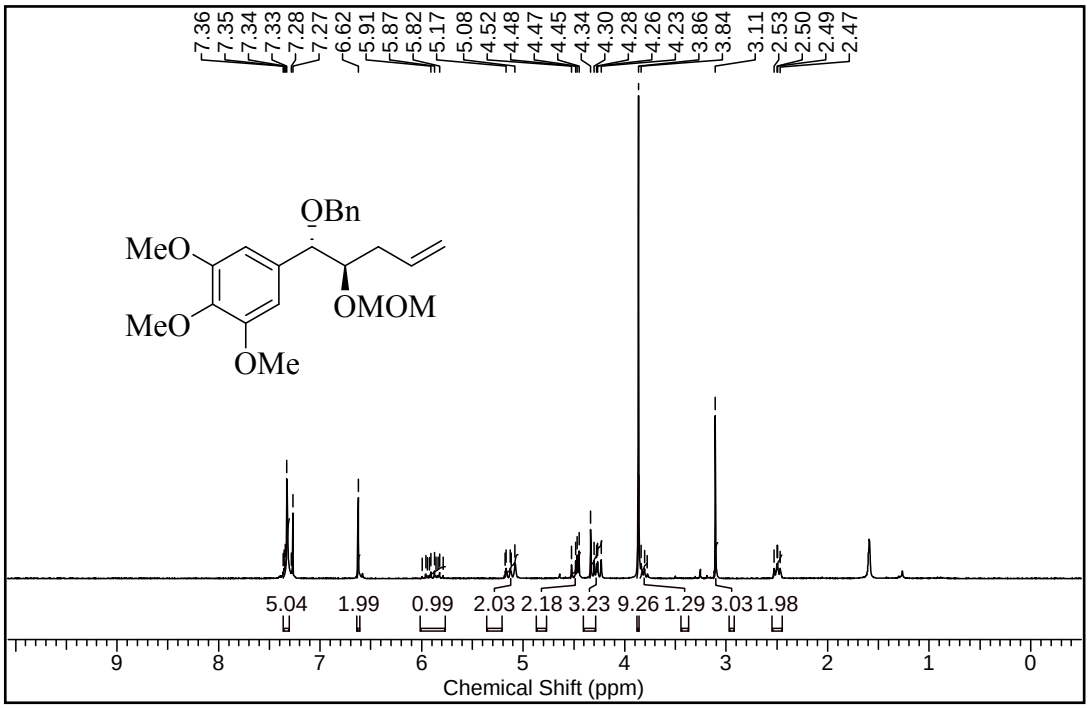


➢ **^{1}H NMR of the compound 49 in $CDCl_3$**

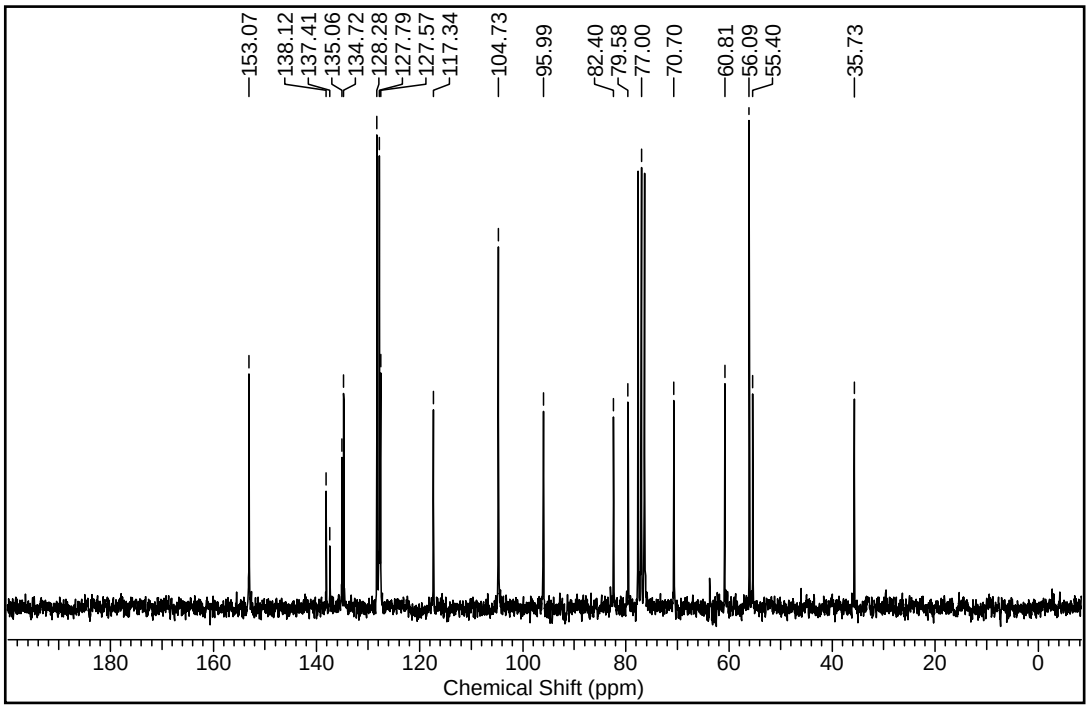


➢ **^{13}C NMR of the compound 49 in $CDCl_3$**

5-((1*S*,2*R*)-1-(Benzyloxy)-2-(methoxymethoxy)pent-4-en-1-yl)-1,2,3-trimethoxybenzene 50:

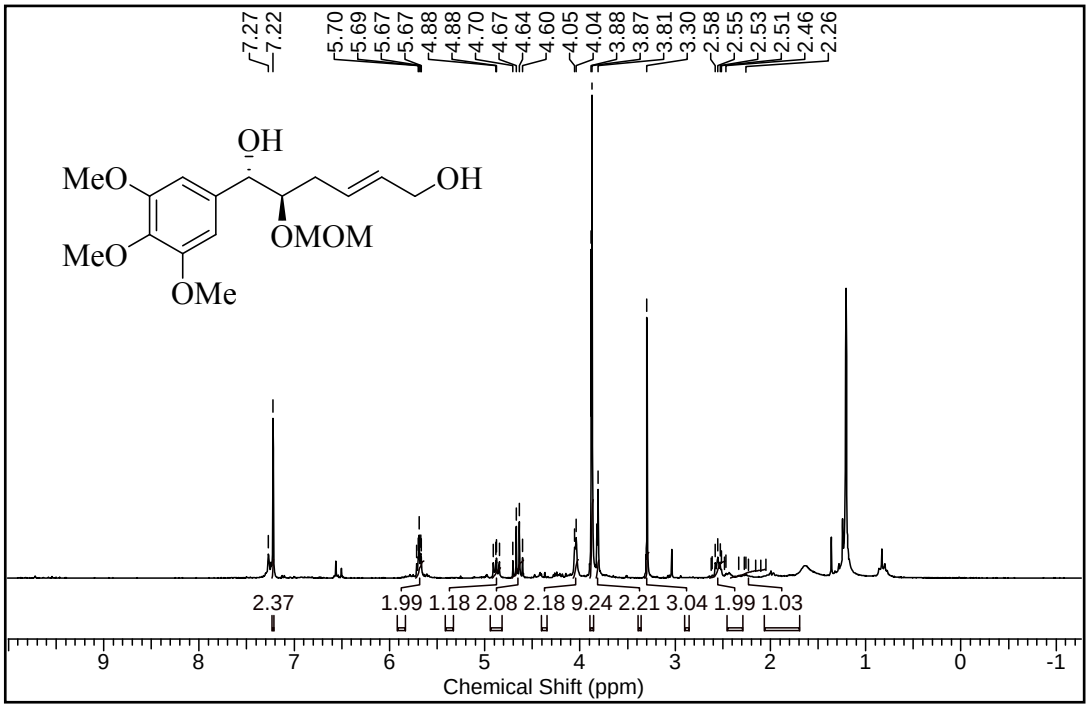


➢ **^{1}H NMR of the compound 50 in $CDCl_3$**

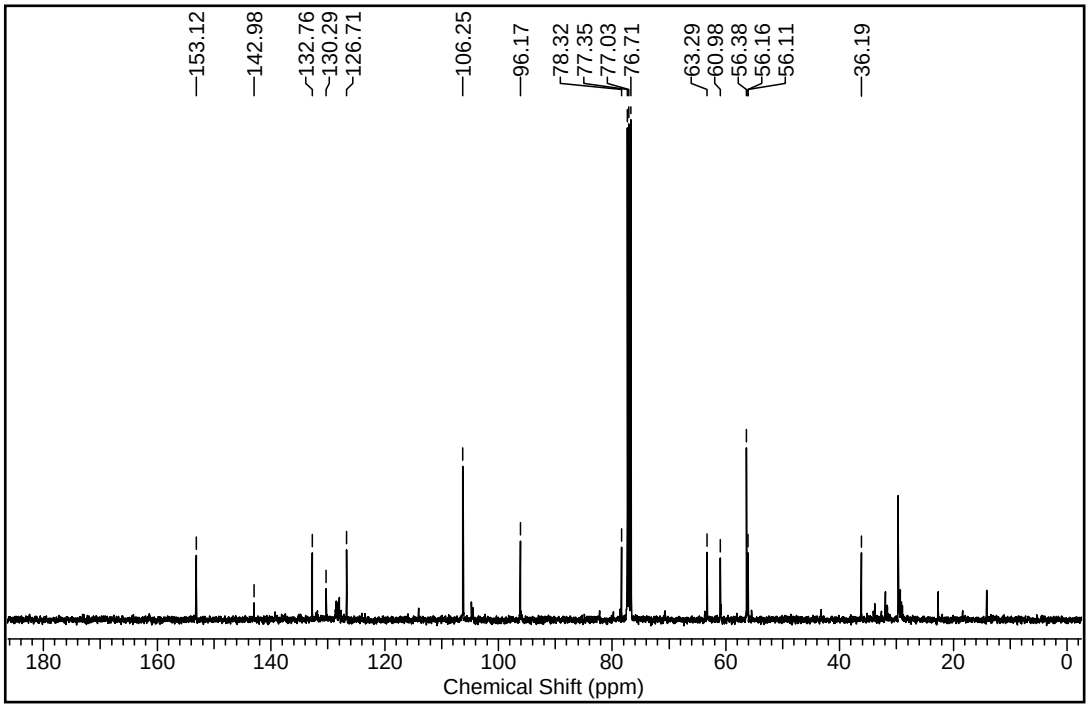


➢ **^{13}C NMR of the compound 50 in $CDCl_3$**

(5*R*,6*S*,*E*)-5-(Methoxymethoxy)-6-(3,4,5-trimethoxyphenyl)hex-2-ene-1,6-diol 52:

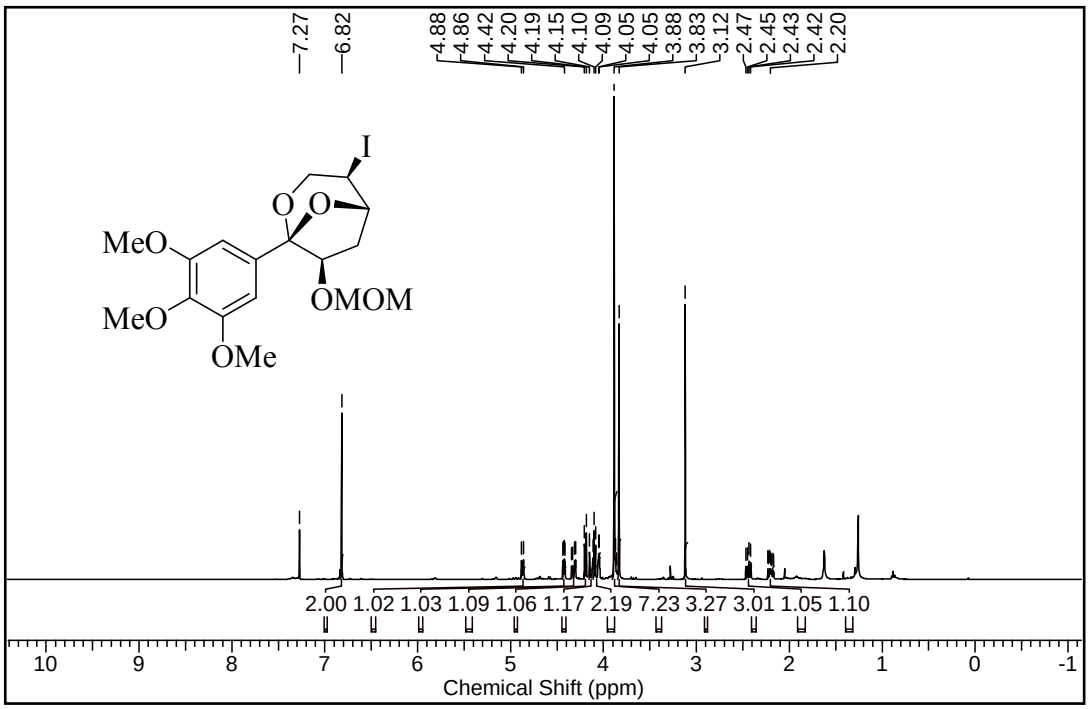


➢ **^{1}H NMR of the compound 52 in $CDCl_3$**

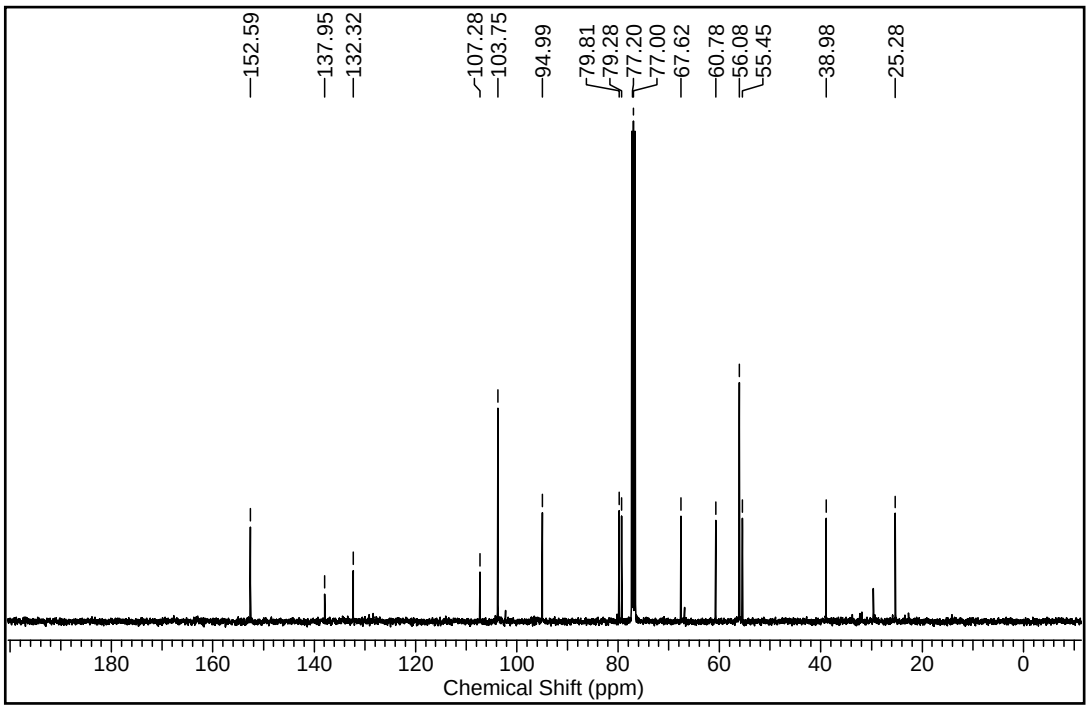


➢ **^{13}C NMR of the compound 52 in $CDCl_3$**

(1*R*,4*R*,5*S*,7*R*)-4-Iodo-7-(methoxymethoxy)-1-(3,4,5-trimethoxyphenyl)-2,8-dioxabicyclo[3.2.1]octane 53:

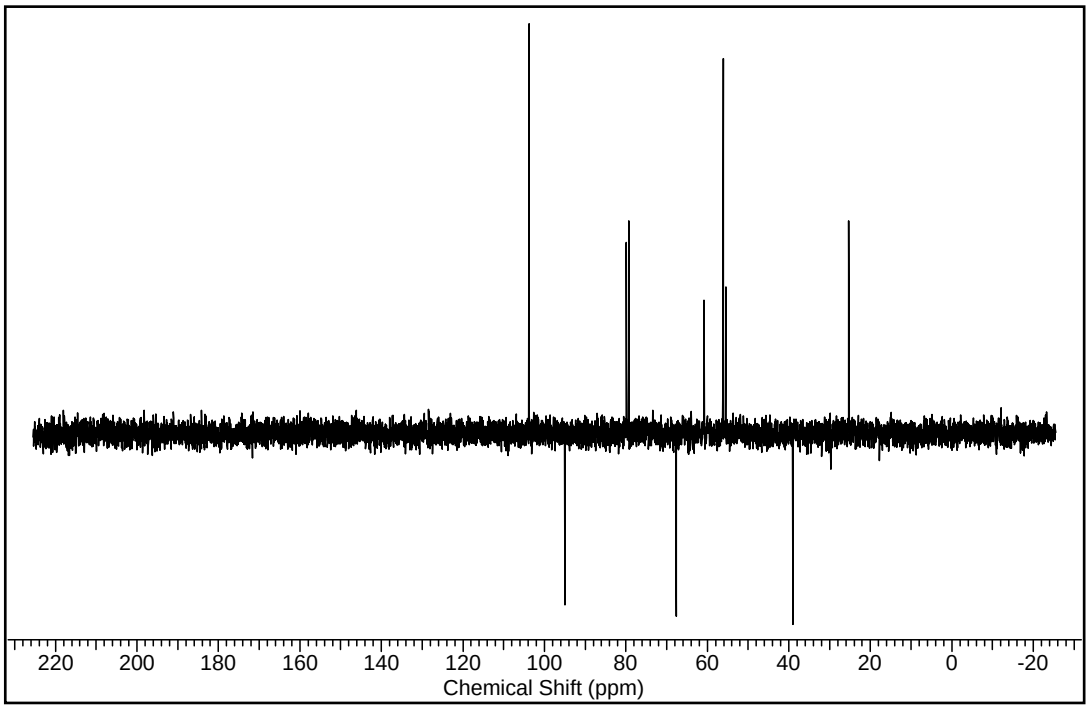


➢ **^{1}H NMR of the compound 53 in $CDCl_3$**

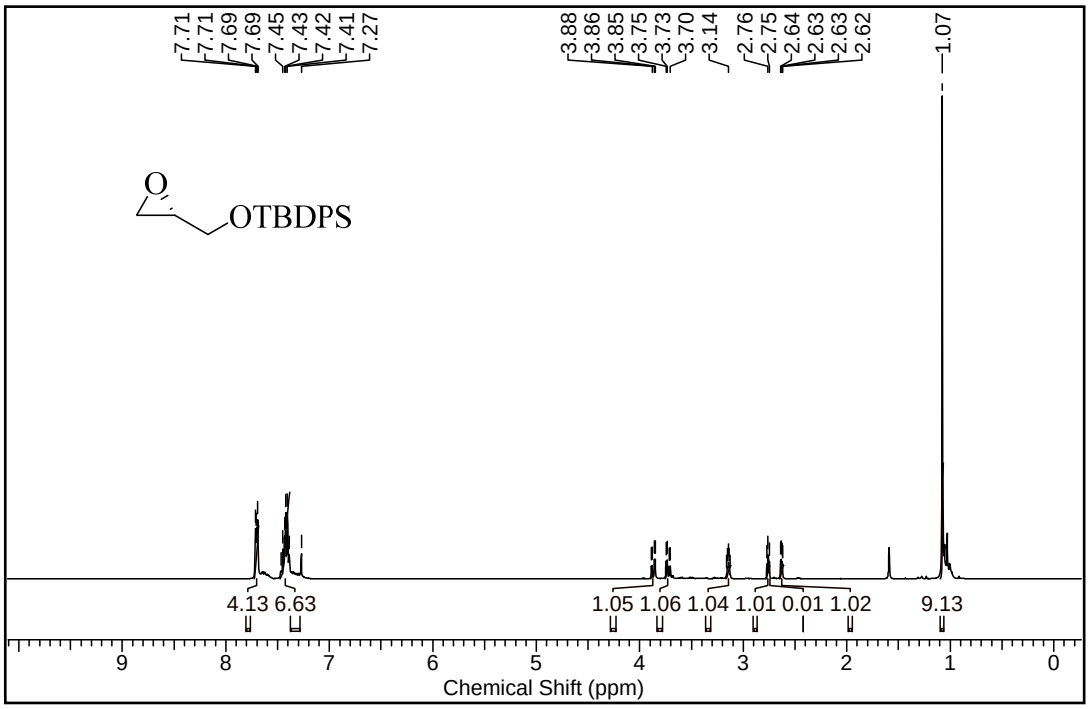


➢ **^{13}C NMR of the compound 53 in $CDCl_3$**

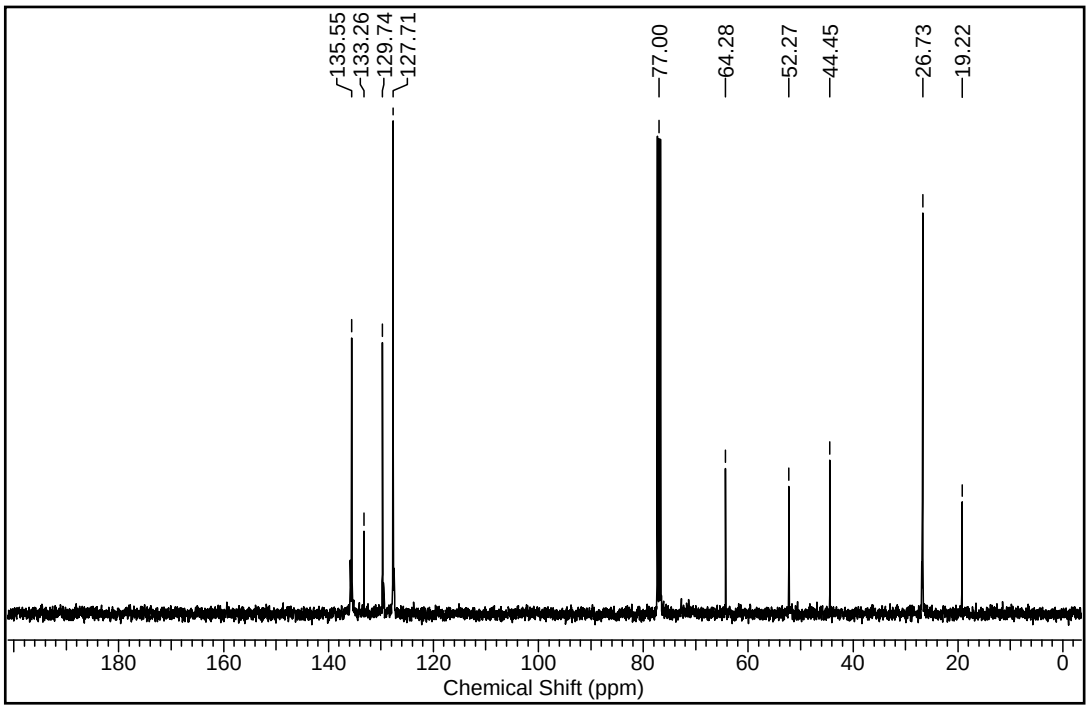
- **DEPT NMR of the compound 53 in $CDCl_3$**



(*S*)-Tert-butyl(oxiran-2-ylmethoxy)diphenylsilane 56:

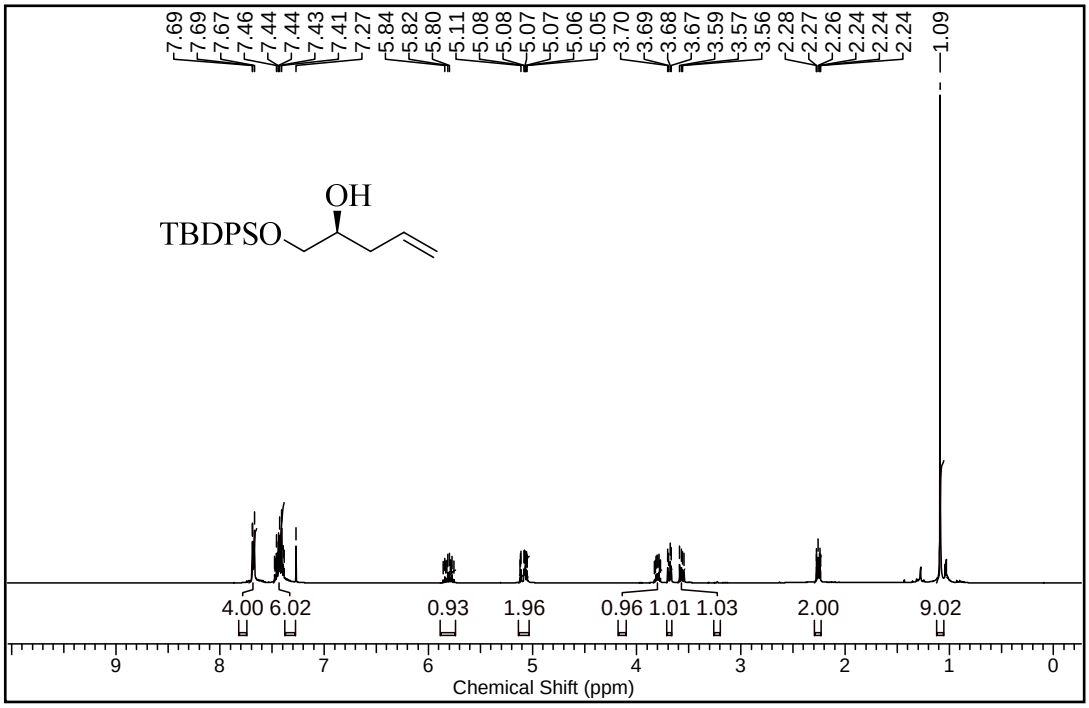


- **^{1}H NMR of the compound 56 in $CDCl_3$**

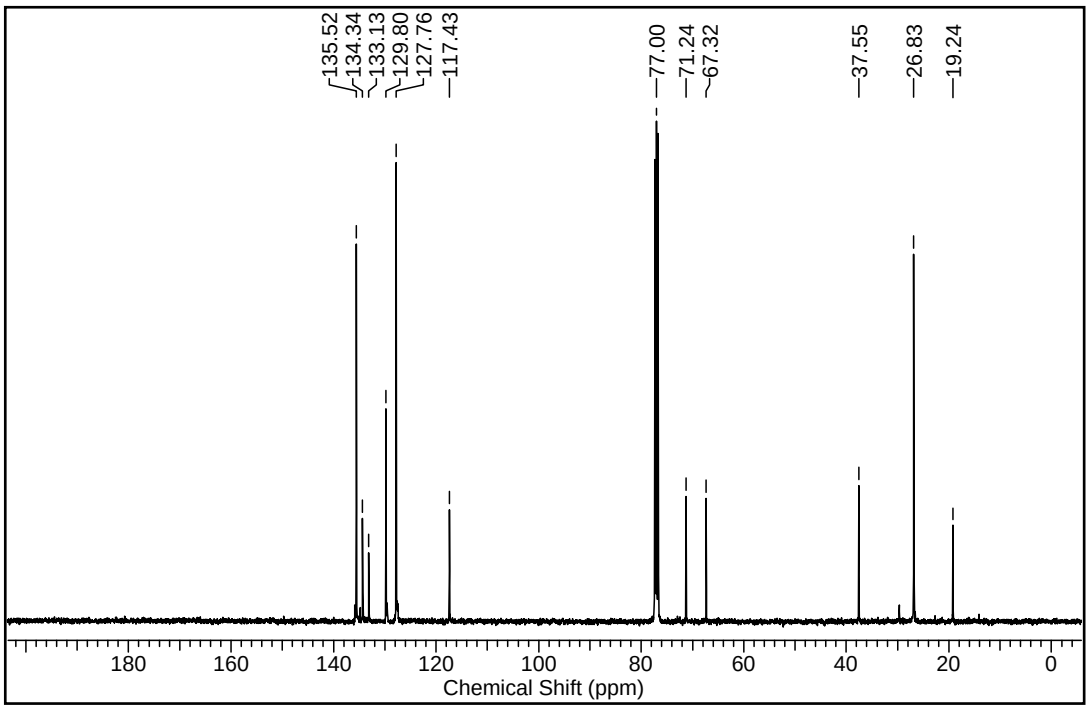


- **^{13}C NMR of the compound 56 in $CDCl_3$**

(*S*)-1-((Tert-butyldiphenylsilyl)oxy)pent-4-en-2-ol 57:

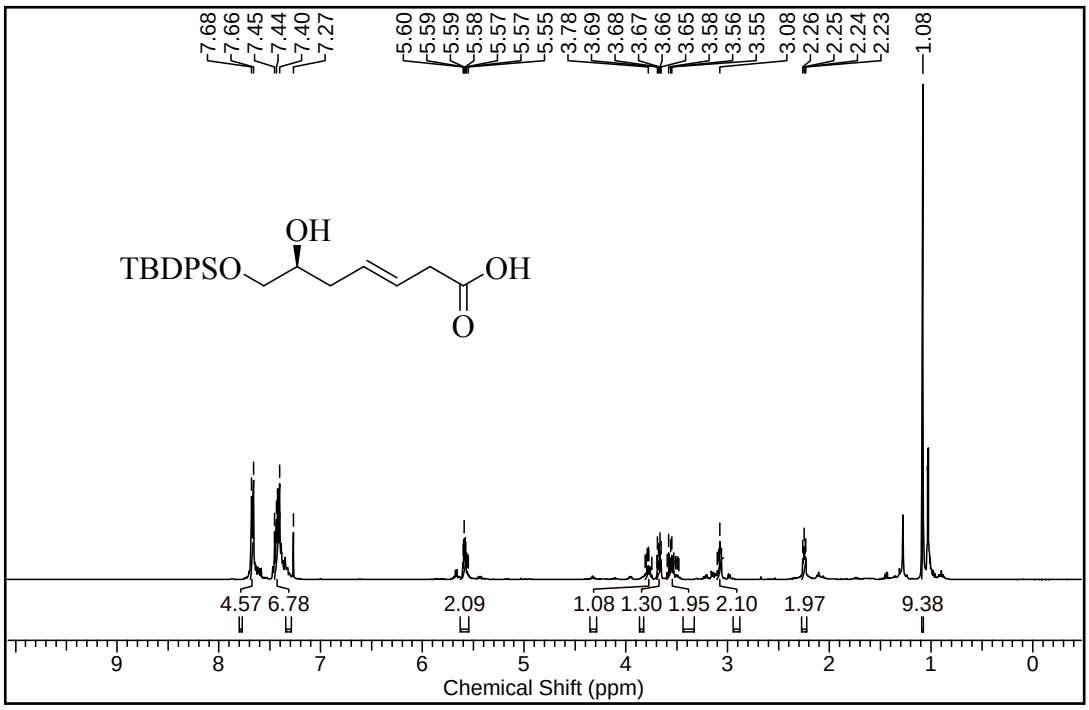


➢ **^{1}H NMR of the compound 57 in $CDCl_3$**

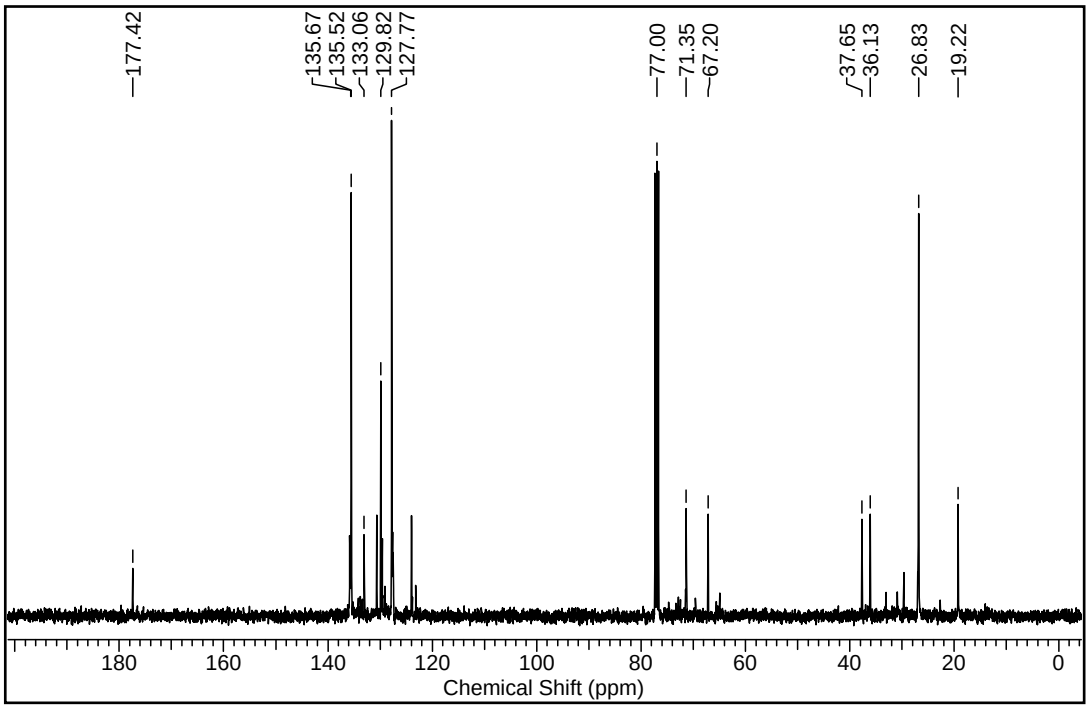


➢ **^{13}C NMR of the compound 57 in $CDCl_3$**

(*S*,*E*)-7-((Tert-butyldiphenylsilyl)oxy)-6-hydroxyhept-3-enoic acid 58:

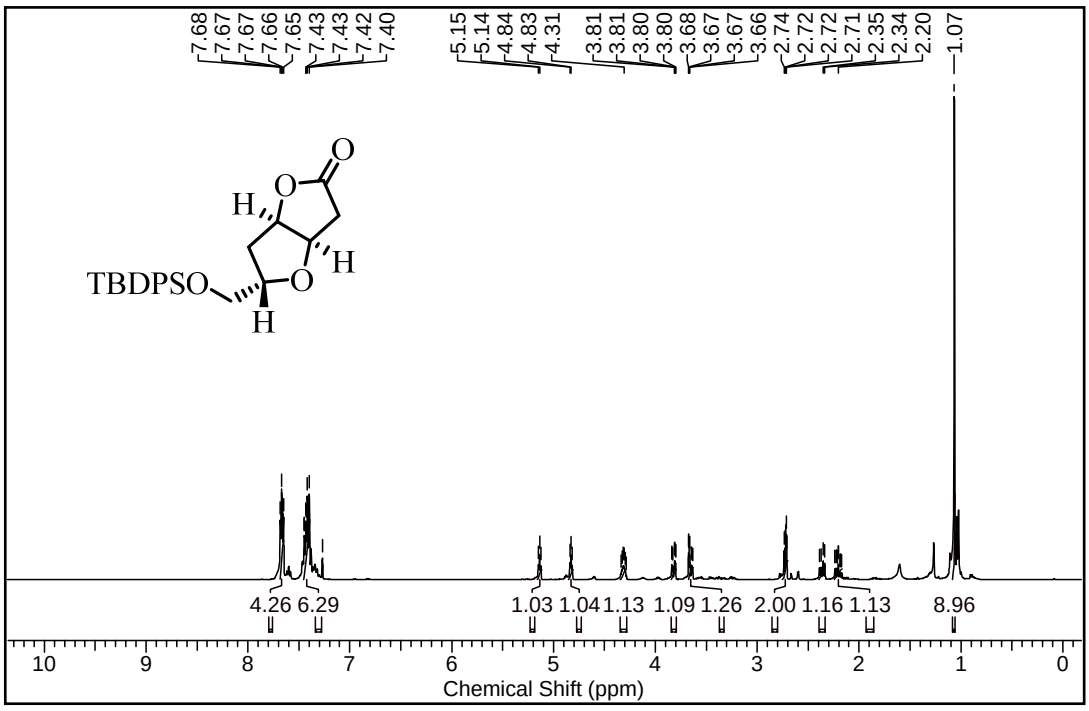


➢ **^{1}H NMR of the compound 58 in $CDCl_3$**

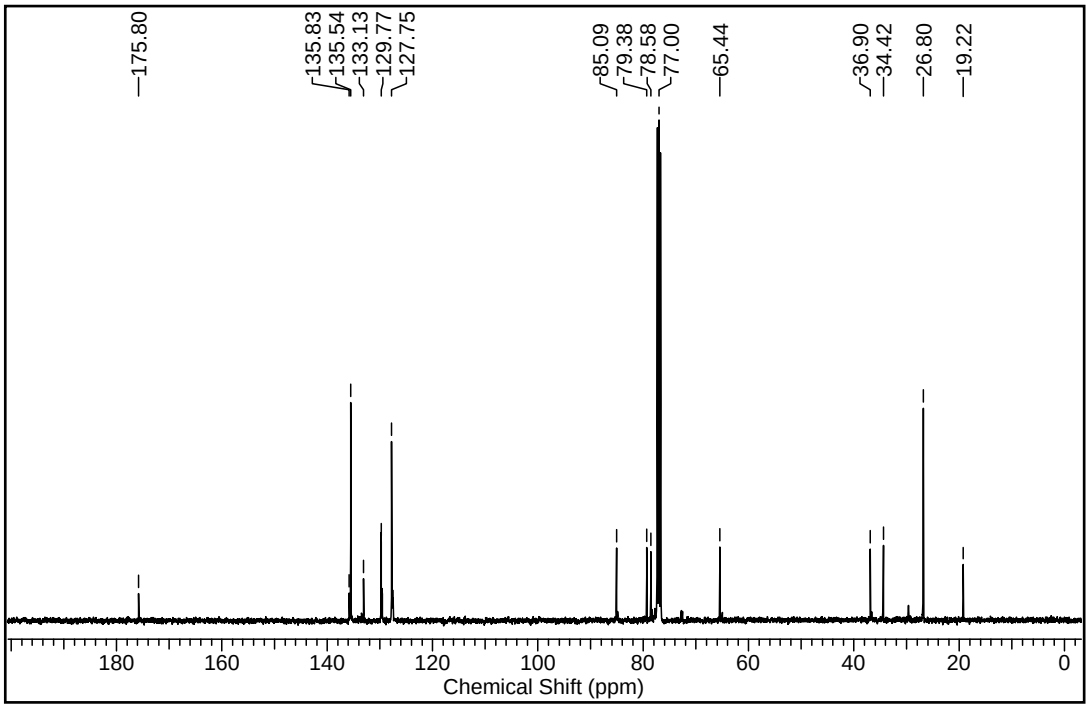


➢ **^{13}C NMR of the compound 58 in $CDCl_3$**

(3a*R*,5*S*,6a*R*)-5-(((Tert-butyldiphenylsilyl)oxy)methyl)tetrahydrofuro[3,2-b]furan-2(3*H*)-one 59:

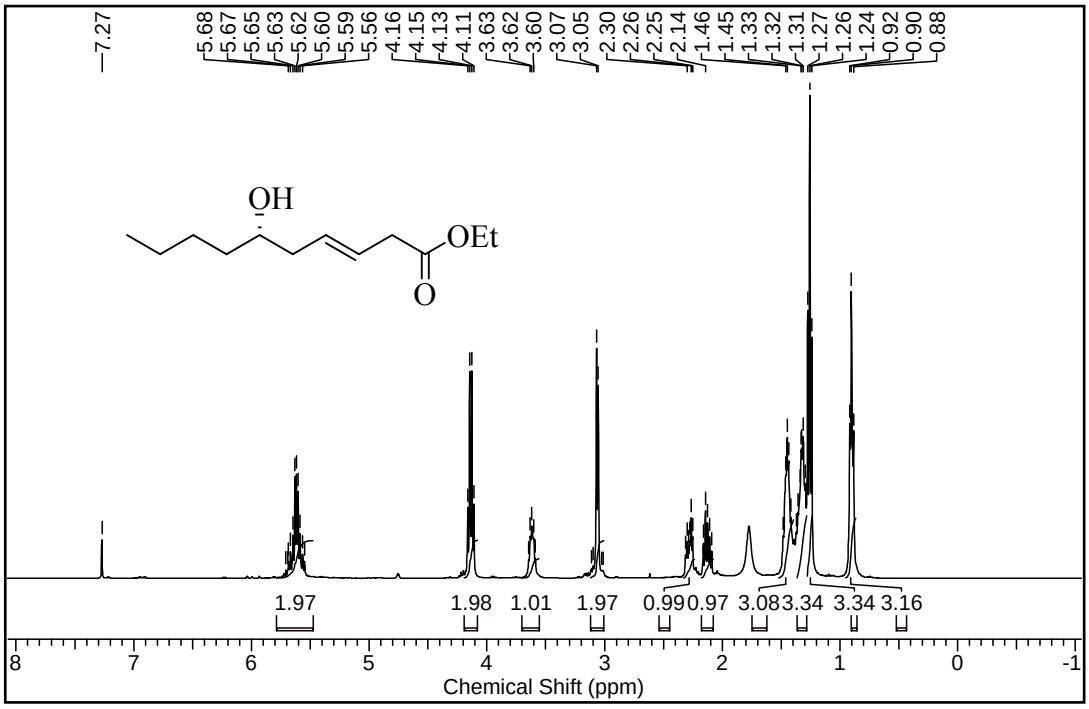


➢ **^{1}H NMR of the compound 59 in $CDCl_3$**

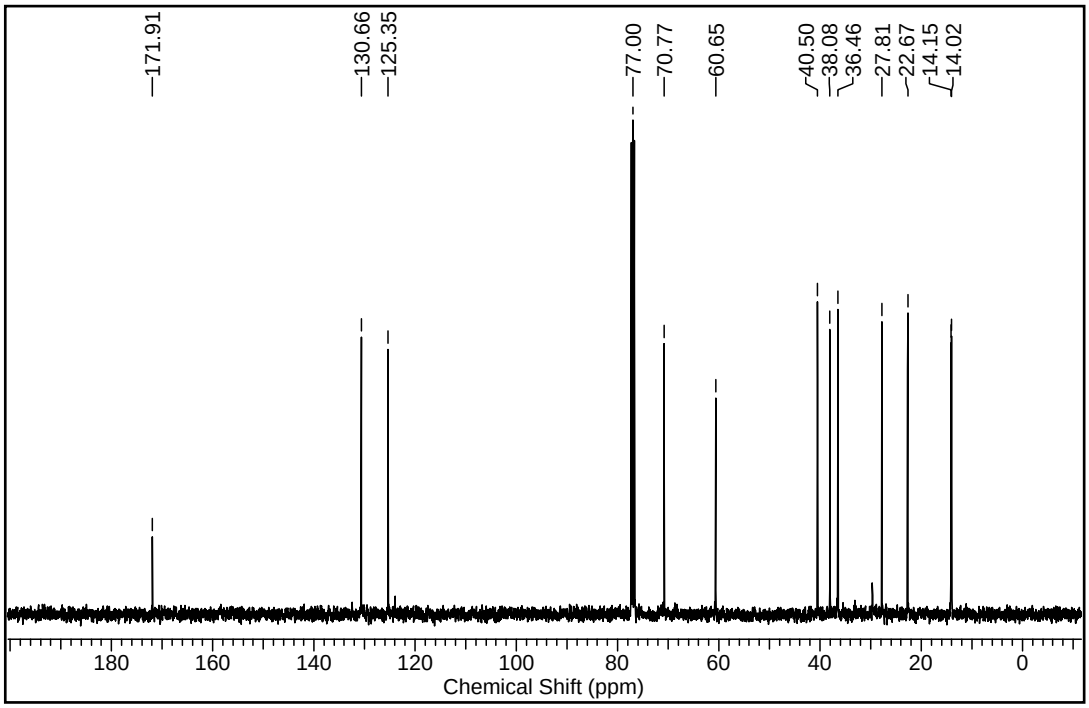


➢ **^{13}C NMR of the compound 59 in $CDCl_3$**

Ethyl (*S*,*E*)-6-hydroxydec-3-enoate 60:

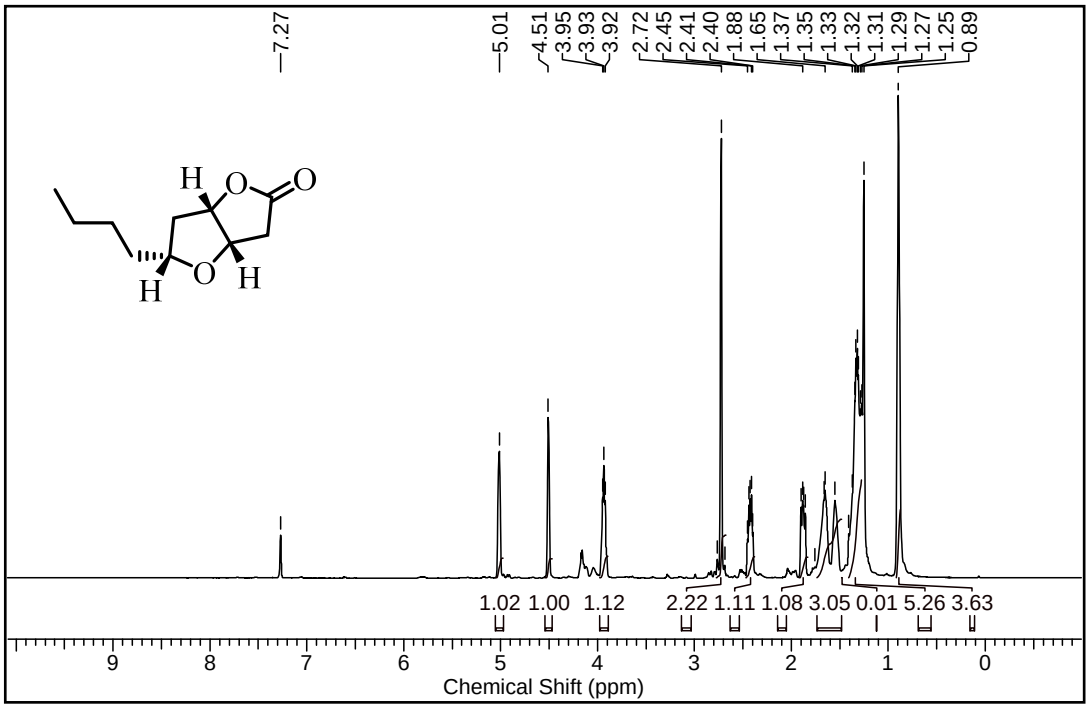


➢ **^{1}H NMR of the compound 60 in $CDCl_3$**

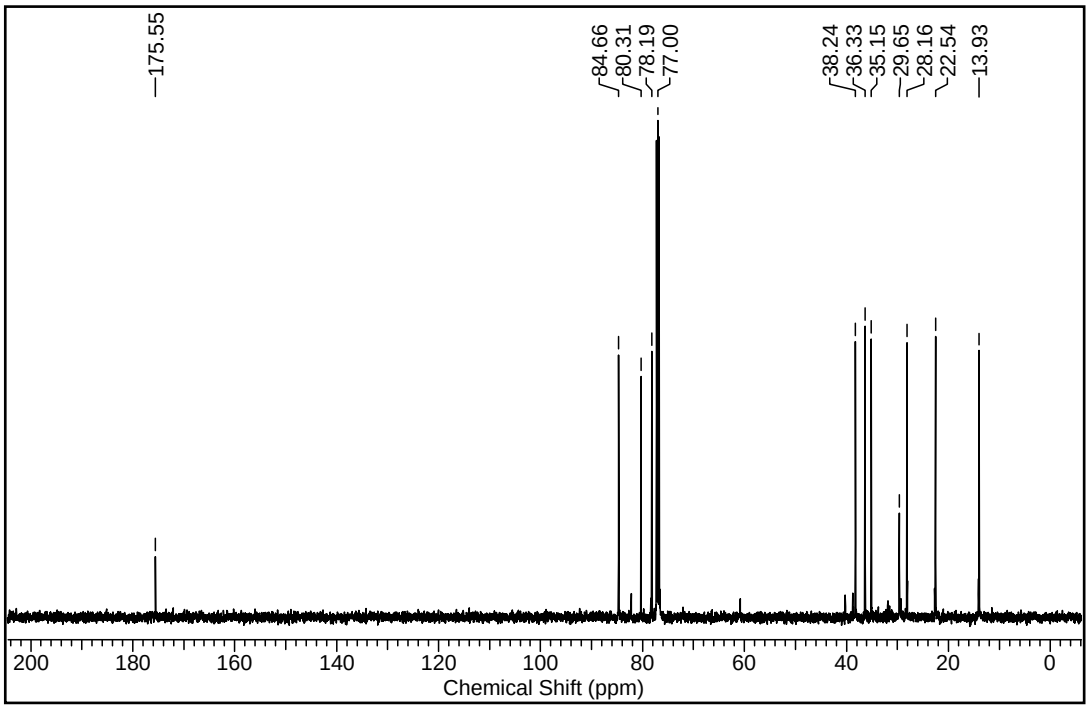


➢ **^{13}C NMR of the compound 60 in $CDCl_3$**

(3a*S*,5*R*,6a*S*)-5-Butyltetrahydrofuro[3,2- b]furan-2(3*H*)-one 2:

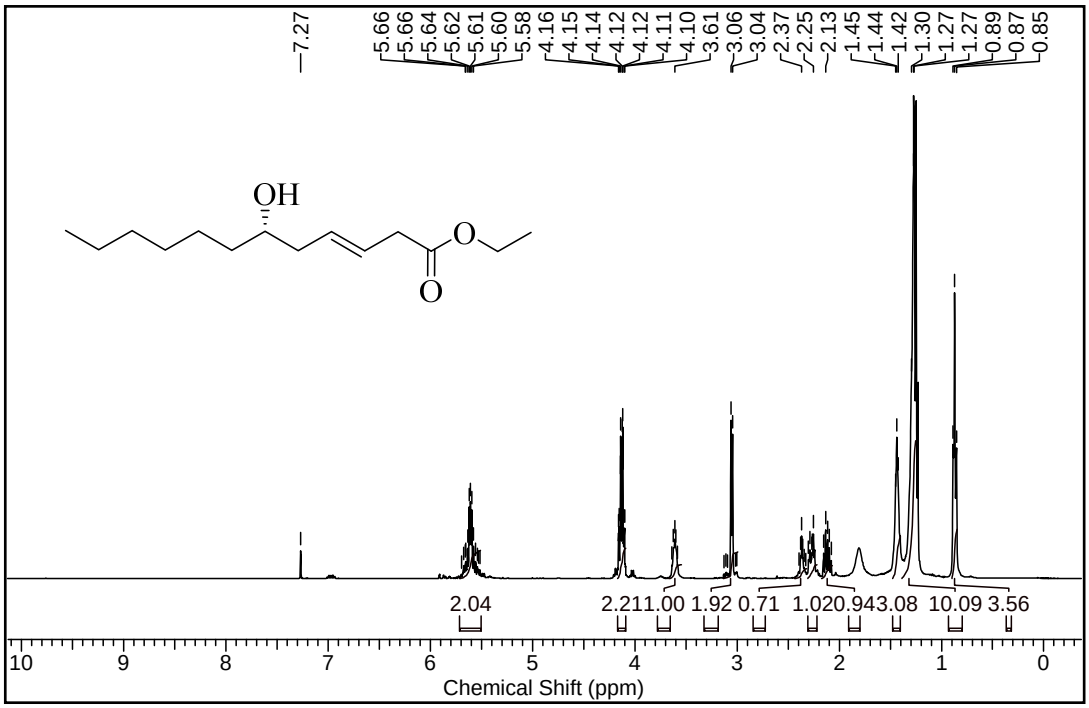


➢ **^{1}H NMR of the compound 2 in $CDCl_3$**

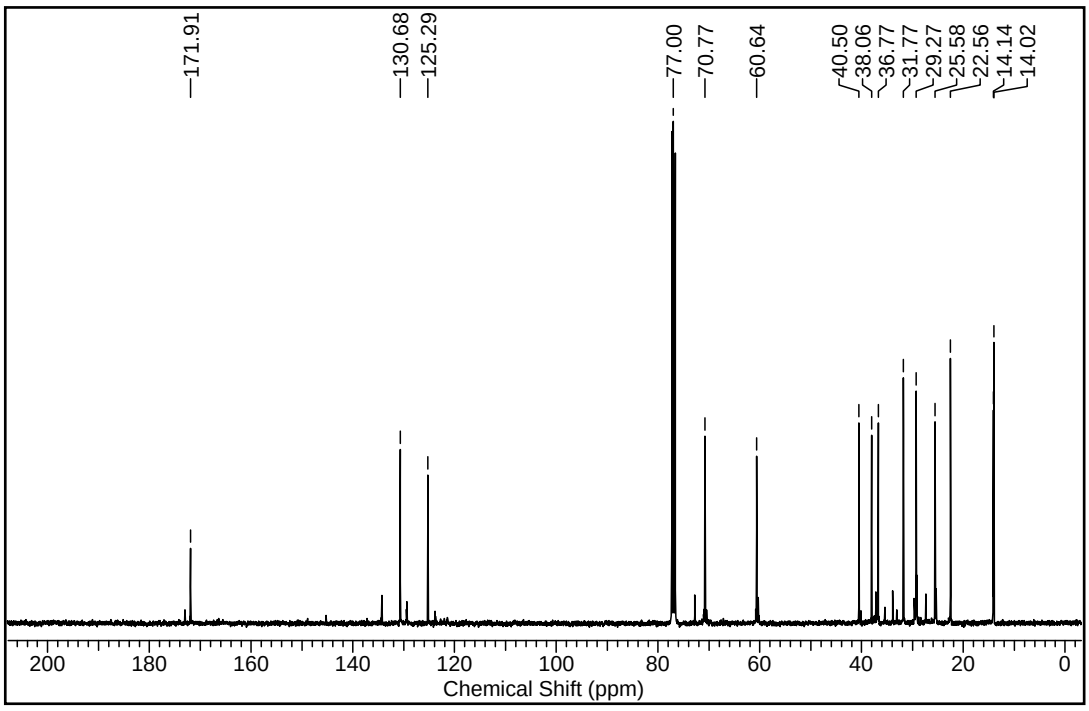


➢ **^{13}C NMR of the compound 2 in $CDCl_3$**

Ethyl (*S*,*E*)-6-hydroxydodec-3-enoate 61:

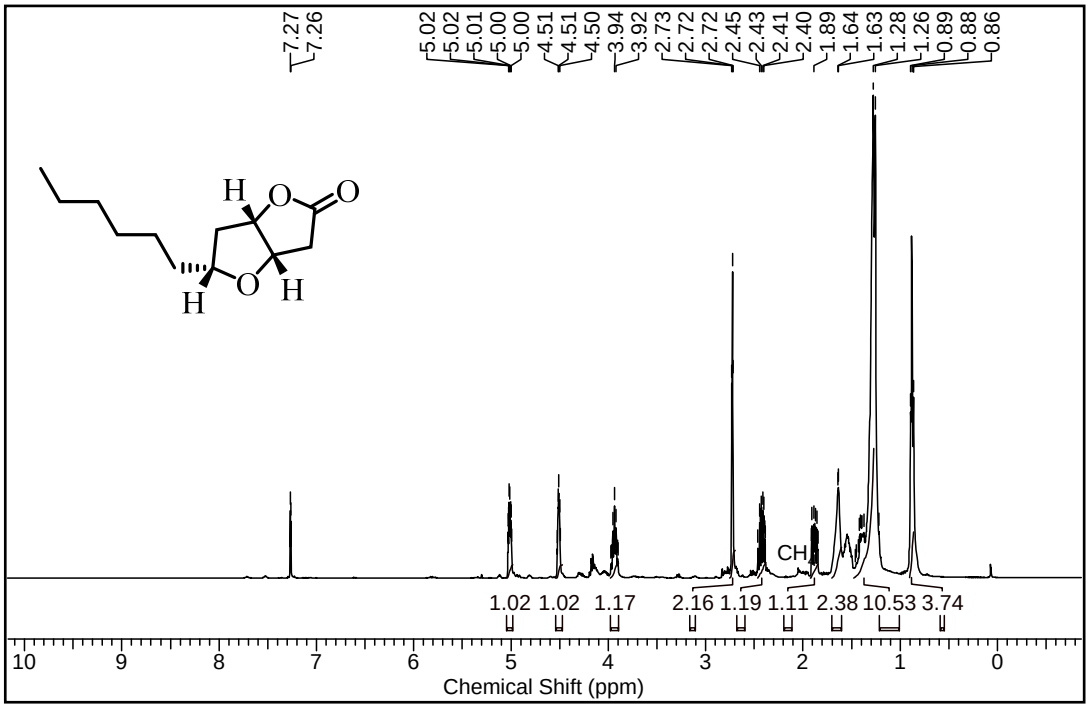


➢ **^{1}H NMR of the compound 61 in $CDCl_3$**

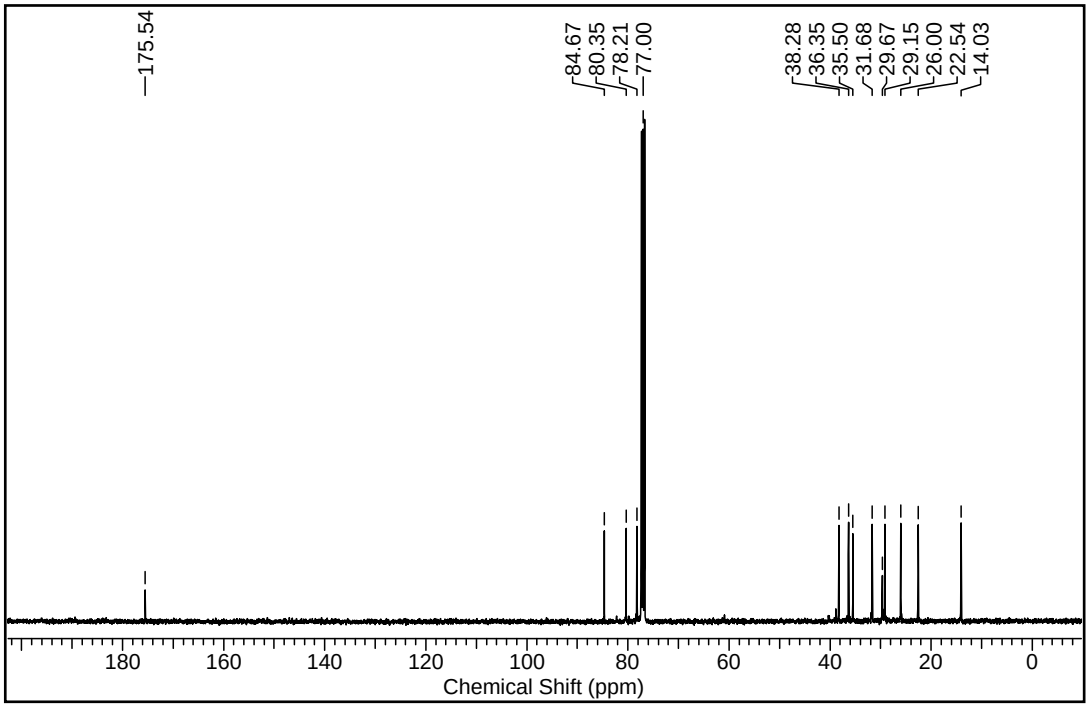


➢ **^{13}C NMR of the compound 61 in $CDCl_3$**

(3a*S*,5*R*,6a*S*)-5-Hexyltetrahydrofuro[3,2-b]furan-2(3*H*)-one 4:



➢ **^{1}H NMR of the compound 4 in $CDCl_3$**



➢ **^{13}C NMR of the compound 4 in $CDCl_3$**

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Chapter-3

Studies towards the Synthesis of Polyketides

3.1. SECTION A

Total Synthesis of (+)-Monocerin *via* Tandem Dihydroxylation-S_N2 Cyclization and a Copper Mediated Tandem Cyanation-Lactonization Approach

3.1.1. Introduction

Natural products symbolize the significant portion of current drug market and they play a crucial role in the discovery of new drug therapies. Hence total synthesis of biologically active natural products is a constant challenge for many scientists in the area of drug discovery around the globe. Monocerin **1** and its analogues are polyketide natural products[1] which are attractive synthetic targets due to their fascinating architecture (**Figure 1**). Monocerin was first isolated by Aldridge *et al*. in 1970 from the culture filtrates of *Helminthosporium monoceras* as an anti-powdery mildew (Erisyphe graminis) of wheat.[2] In 1979, Grove and co-workers noticed monocerin as an insecticidal constituent of the entomogenous fungus Fusarium larvarum Fukel.[3]

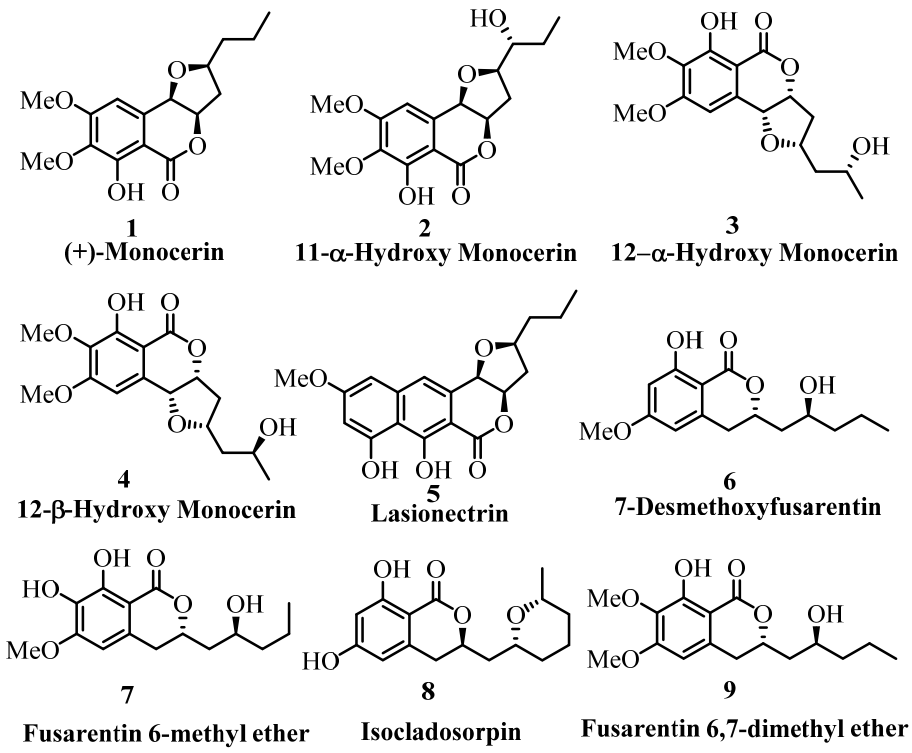


Figure 1: Polyketide (**1**–**5**) and dihydroisocoumarin (**6**–**9**) natural products

Later on monocerin, dihydroisocoumarins and their analogues (**Figure 1**) were isolated from several other fungal species[3,4] exhibiting a broad spectrum of biological activities like antifungal,[4a] phytotoxic,[4b] plant pathogenic[4c] and insecticidal activity.[5] In 2008, Sriubolmas and co-workers identified the antiplasmodial activity[6] of monocerin 1 (IC_{50} value of 0.68 μM) against the multidrug-resistant K1 strain of *Plasmodium Falciparum.* Monocerin and its analogues were proved to be non specific toxic and nonspecific inhibitor of seed germination by interference with selected stages of the cell division cycles.[7]

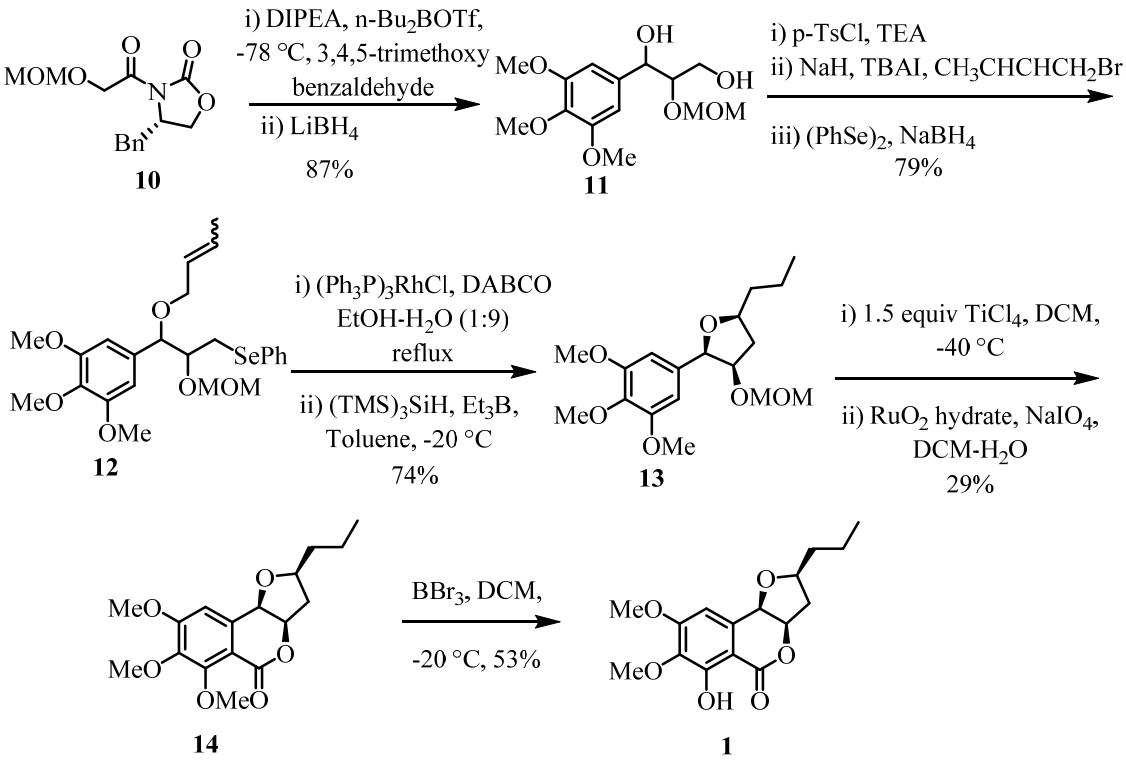
3.1.2. Review of Literature

While the first synthesis of monocerin was reported by Mori *et al.* in 1989,[8] the Simpson group subsequently described its biomimetic synthetic path way.[9] In recent years monocerin and its analogues have attracted a great deal of interest, consequently several syntheses of this molecule were reported.[10] A detailed report of recent syntheses is described below.

Synthesis of (+)-Monocerin

Eun Lee *et al.* (2008) [10b]

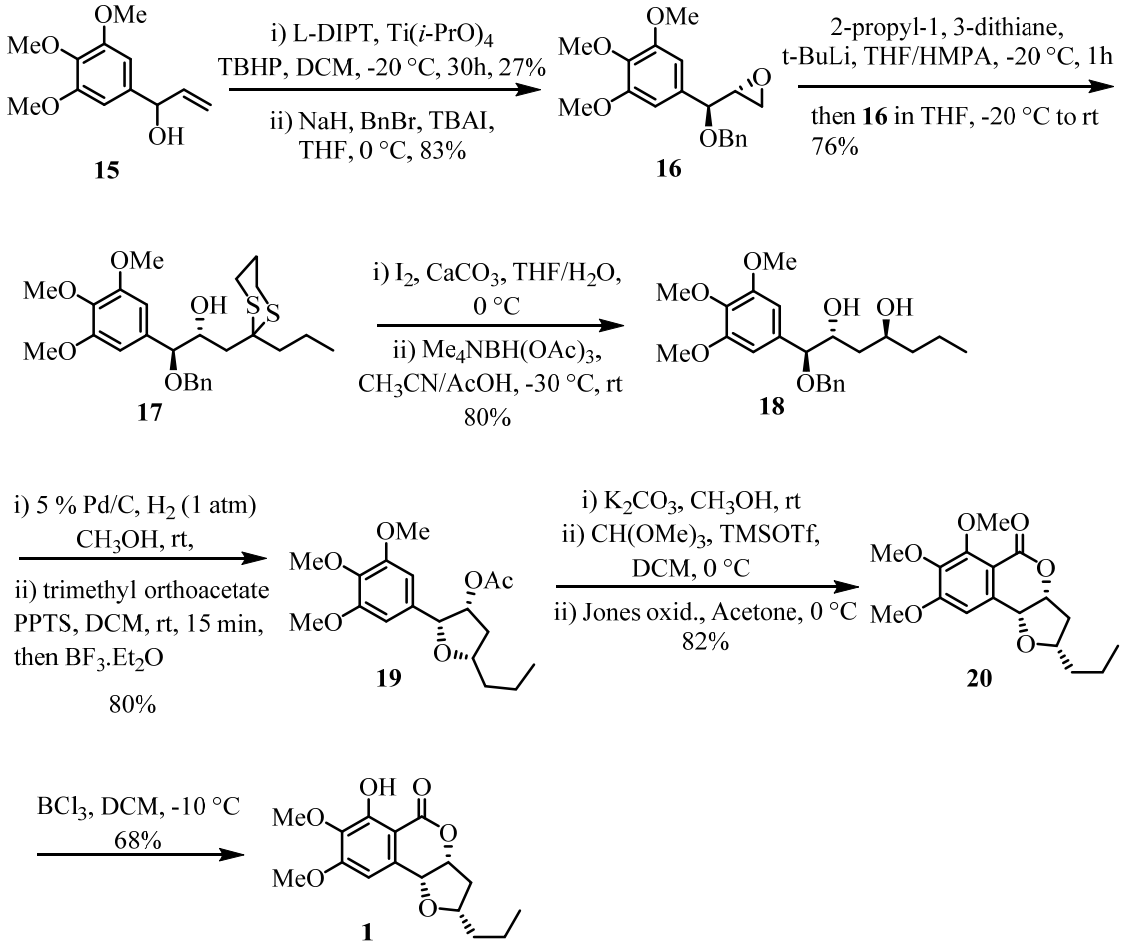
Synthesis of monocerin commenced from 3,4,5-trimethoxy benzaldehyde. A stereoselective aldol reaction between chiral imide **10** and 3,4,5-trimethoxy benzaldehyde, followed by reduction using $LiBH_4$ gave the triol **11**. The compound **11** was further subjected to selective tosylation of the primary hydroxyl group followed by O-alkylation with 1-bromo-2-butene and phenyl selenide substitution gave the selenide **12**. Then, it was treated with Wilkinson catalyst which leads to double bond migration followed by treatment with tris(trimethylsilyl)silane in the presence of triethylborane to give the key THF motif **13**. The compound **13** was treated with $TiCl_4$ to give dioxatricycle which on Ru-catalysed benzylic oxidation gave the lactone **14**. Selective demethylation resulted in (+)-monocerin **1**.



Scheme1: Synthesis of (+)-Monocerin

Xuegong She *et al.* (2013)[10d]

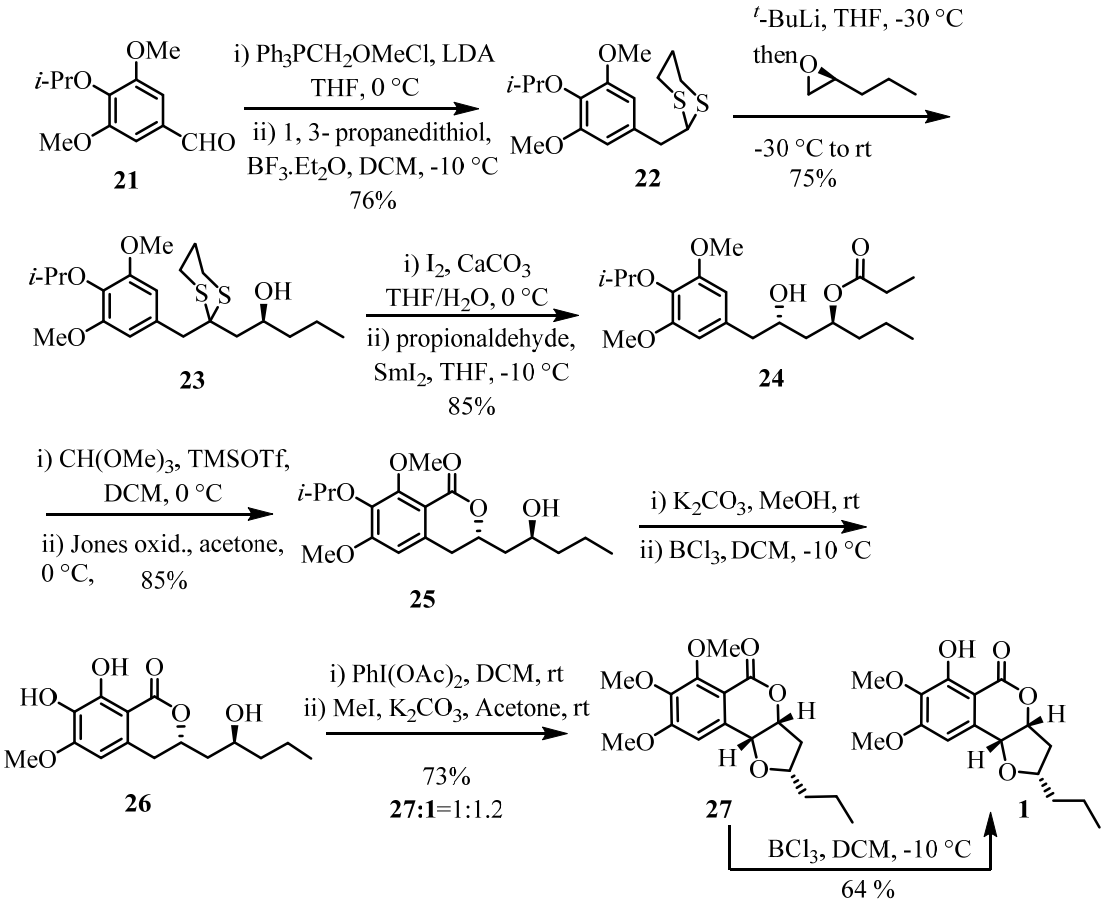
Synthesis of monocerin started from the known allylic alcohol **15**. It was subjected to Sharpless asymmetric epoxidation followed by benzyl protection to give the epoxide **16**. The epoxide was treated with 2-propyl-1,3-dithiane and ^{t}BuLi to furnish the *β*-hydroxy dithiane **17**. The compound was subjected to dithiane deprotection using I_2 and $CaCO_3$ followed by $Me_4NBH(OAc)_3$ reduction to give the desired anti diol **18**. Subsequent debenzylation was achieved using Pd/C, H_2 condition to give triol, which on reaction with trimethyl orthoacetate in the presence of catalytic amount of PPTS followed by addition of BF_3–OEt_2 led to cyclized product **19** as a single diastereomer in 85% yield. The acetate was hydrolyzed using K_2CO_3, followed by oxa-Pictet-Spengler reaction, Jones oxidation to furnish lactone **20**. Selective demethylation gave the target monocerin **1.**



Scheme 2: Synthesis of (+)-Monocerin

Xuegong She *et al.*(2013)[10a]

The synthesis of Monocerin **1** commenced from the known 4-isopropoxy-3,5-dimethoxybenzaldehyde **21,** which was subjected to homologation reaction *via* Wittig reaction followed by treatment with 1,3-propane thiol and BF_3-OEt_3 to give the dithiane **22.** The epoxide (*S*)-2-propyloxirane ring opening with the anion of dithiane **22** afforded the alcohol **23.** Then dithiane was removed using iodine and $CaCO_3$ followed by treatment with SmI_2 to afford the homo benzylic alcohol **24.** The alcohol **24** was subjected to Oxa-Pictet-Spengler reaction followed by Jones oxidation to give δ-valerolactone **2**5. The propionyl group was removed under basic conditions followed by selective demthylation to give fusarentin 6-methyl ether **26**, which on treatment with $PhI(OAc)_2$ followed by methylation and selective demthylation gave the target molecule Monocerin **1**.

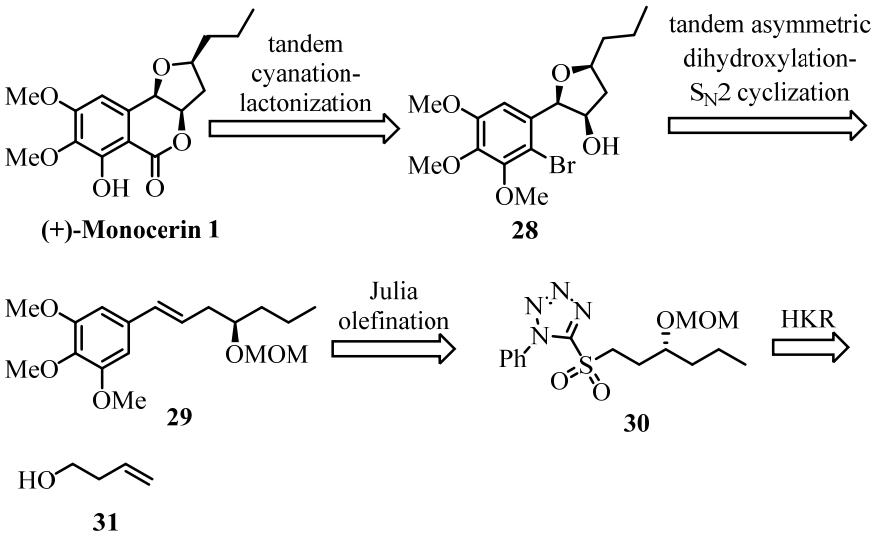


Scheme 3: Synthesis of (+)-Monocerin

3.1.3. Present work

Objective

Due to its structural features such as 4-oxyisochroman-1-one skeleton and a 2,3,5-trisubstituted tetrahydrofuran moiety, fused in *cis*-fashion, monocerin and its analogues have attracted a great deal of interest. Also majority of the syntheses of monocerin involve large number of steps and low overall yields. Therefore, it is highly desirable to develop a concise and general synthetic route with desired stereochemical variations. In continuation of our research interest in the synthesis of polyketides and related compounds, we developed a simple and efficient synthesis of (+)-monocerin employing hydrolytic kinetic resolution, Julia-Kochienski olefination, intramolecular tandem Sharpless asymmetric dihydroxylation-S_N2 cyclization and novel copper-mediated tandem cyanation-lactonization of a substituted bromo benzene derivative as the key steps.



Scheme 4: Retrosynthetic route to (+)-Monocerin

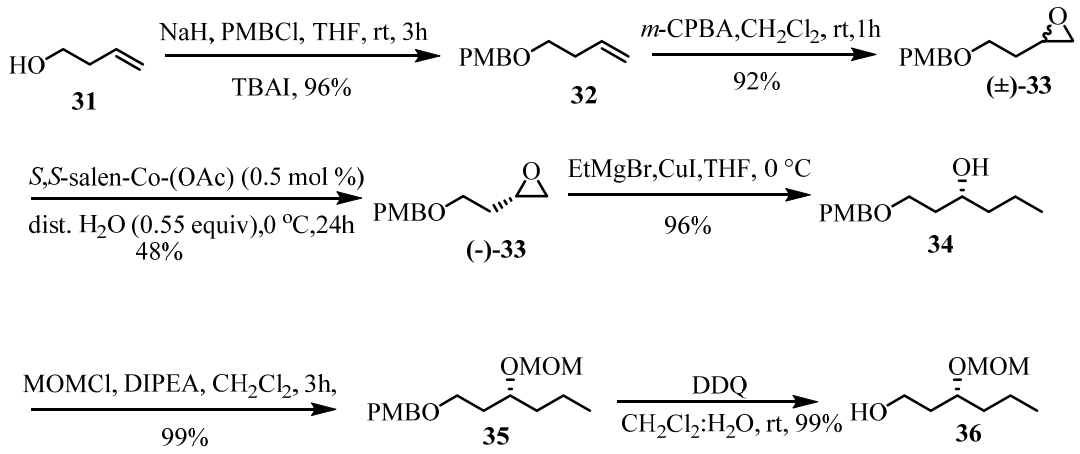
3.1.4. Results and discussion

The retrosynthetic analysis of (+)-monocerin **1** was visualized based on the linear approach as outlined in **Scheme 4**. We envisioned that the target molecule **1** could be prepared by tandem cyanation-cyclization of a substituted tetrahydrofuran alcohol **28** which could be derived *via* tandem Sharpless asymmetric dihydroxylation-S_N2 cyclization of olefin **29**. The olefin **29** could be prepared by Julia–Kocienski olefination reaction between trimethoxy benzaldehyde and sulfone **30.** Compound **30** in turn could be derived from commercially available 3-buten-1-ol **31**.

As illustrated in **Scheme 5**, our synthesis began with the commercially available 3-buten-1-ol **31**. This upon hydroxy group protection using PMBCl and NaH gave the PMB ether **32.** The olefin **32** was oxidized using *m*-CPBA to give the racemic epoxide (±**33**). The disappearance of olefin peaks in ^{1}H NMR at δ 5.86 (tdd, J = 6.7, 10.3, 17.1 Hz, 1 H), 5.20–5.01 (m, 2 H) and appearance of new peaks at δ 3.16–2.96 (m, 1 H), 2.79 (t, J = 4.5 Hz, 1 H), 2.53 (dd, J = 2.7, 4.9 Hz, 1 H) confirmed the presence of epoxide. Racemic epoxide **33** was subjected to Jacobsen's HKR[11] protocol using (*S*,*S*)-salen-Co^{III}(OAc) catalyst to give the enantiopure epoxide (-)-**33**[12] and diol. The epoxide ring opening[12,13] with ethyl magnesium bromide ((-)-**33**→**34**) yielded the free alcohol **34.** The IR spectrum of **34** gave broad hydroxyl absorption at 3444 cm^{-1}. Protection of hydroxy group was carried out with MOM chloride using diisopropylethylamine as a base to give the MOM ether **35** in almost quantitative yield. The IR spectrum of **35** shows the

absence of hydroxyl absorption. Subsequent oxidative removal of 4-methoxy benzyl group with DDQ afforded the alcohol **36** in excellent yield. The IR spectrum of **36** gave broad hydroxyl absorption at 3385 cm^{-1}.

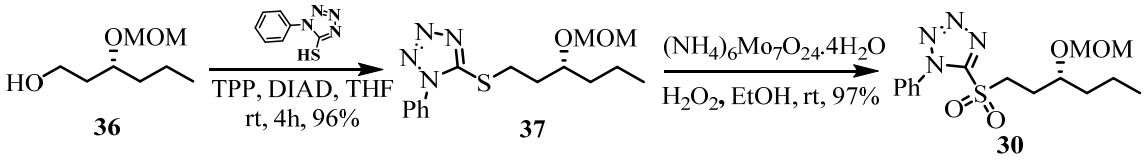
Next, we sought to synthesize the olefin fragment **29**. Initially we attempted at the Horner-Wittig reaction of 3,4,5-trimethoxy phenylmethylenephosphonate with aldehyde derived from **36** under various conditions to obtain **29**. For example, use of different bases such as NaH (1.5 to 6 equiv), *n*-BuLi, KO^{t}Bu and NaHMDS (2 equiv) ...*etc.* to bring the above transformation was a total failure. Raising the temperature from 0 °C to rt and reflux temperature in various solvents such as THF or DMF also did not work.



Scheme 5: Synthesis of compound **36**

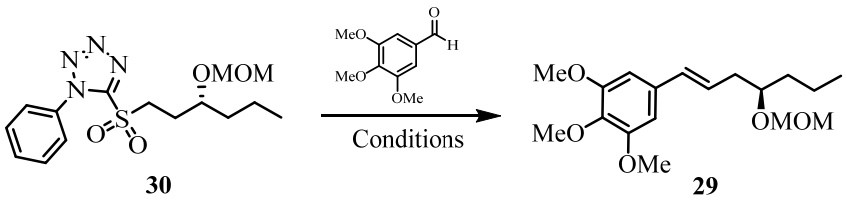
Hence we modified the strategy and proceeded with Julia-Kocienski olefination reaction to obtain the required olefin **29** (**Scheme 6**). Thus the primary alcohol **36** was converted to sulfide **37** under Mitsunobu conditions using 1-phenyl-*1H*-tetrazole-5-thiol as a nucleophile in the presence of TPP/DIAD. The IR spectrum of **37** shows the absence of hydroxyl absorption. In ^{1}H NMR aromatic peaks appeared at δ 7.64 - 7.51 (m, 5 H) and also peaks corresponding to S-CH_2-were seen at δ 3.61 - 3.41 (m, 2 H). Oxidation of sulfide **37** with ammonium heptamolybdate and H_2O_2 afforded sulfone **30**[14] (**Scheme 6**). In ^{1}H NMR aromatic peaks appeared at δ 7.82 - 7.53 (m, 5 H) and also peaks corresponding to SO_2-CH_2-were visible at δ 3.99 - 3.69 (m, 2 H). Having sulfone **30** in hand we further proceeded to optimize the Julia–Kocienski[15] olefination conditions. To

this end, various bases such as KHMDS, NaHMDS were screened under prematallate conditions at -78 °C to 0 °C.



Scheme 6: Synthesis of compound **30**

However under none of above conditions the product formation could be observed. Then we switched over to the Barbier conditions using NaHMDS as a base and carried out reaction at -78 °C to 0 °C, however it gave only 10% of the desired product. Notably increasing the temperature from -78 °C to rt under Barbier conditions resulted in improvement of yields up to 30%. Eventually, further raising the temperature from 0 °C to rt, afforded the desired product **29** in 88% yield (**Table 1, entry 7**). In ^{1}H NMR the internal olefin peaks were observed at δ 6.36 (d, J = 15.6 Hz, 1 H), 6.24 - 6.08 (m, 1 H) and from coupling constant (J = 15.6 Hz) value, the presence of *trans* double bond was confirmed.

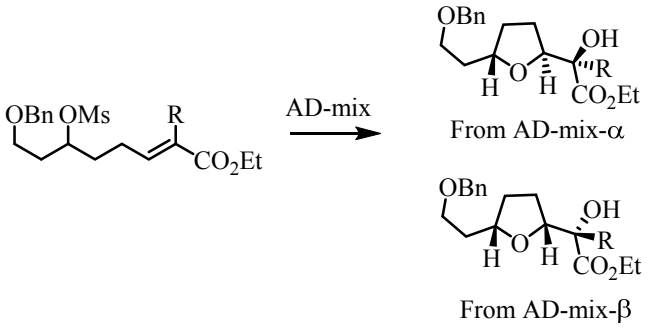


S.No.	Reaction Conditions	Yield (%)	*E*:*Z*
1	Premetallate[a] KHMDS, THF,-78 °C	No reaction	-
2	Premetallate KHMDS, THF,-78 °C to 0 °C	No reaction	-
3	Premetallate NaHMDS, THF,-78 °C to rt	No reaction	-
4	Premetallate NaHMDS, THF, 0 °C to rt	No reaction	-
5	Barbier[b]	10%[c]	*E* only

	NaHMDS, THF,-78 °C to 0 °C		
6	Barbier NaHMDS, THF,-78 °C to rt	30%[c]	*E* only
7	**Barbier** **NaHMDS, THF, 0 °C to rt**	**88%[c]**	***E* only**
[a] base first added to sulfone followed by aldehyde addition, [b] base added to a mixture of sulfone and aldehyde [c]isolated yield			

Table 1: Optimization of Julia-Kocienski olefination reaction conditions

Now the stage was set for the synthesis of *cis*-substituted tetrahydrofuran hydroxyl compound **39** *via* intramolecular tandem Sharpless asymmetric dihydroxylation-S_N2 cyclization following Marshall's protocol (**Scheme** 7).[12a]

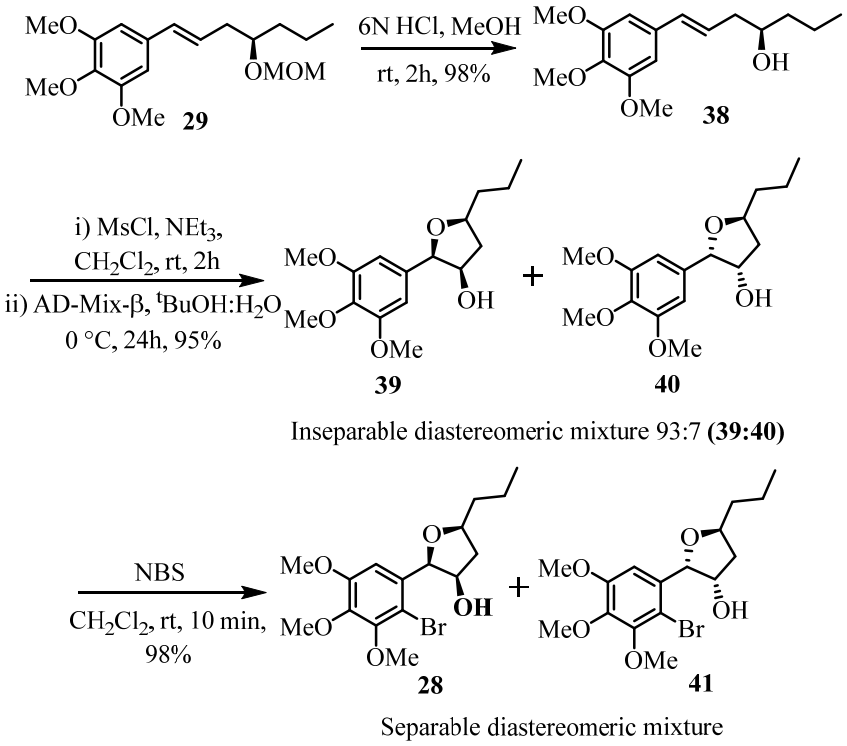


Scheme 7: Marshall's protocol for making *cis* and *trans* THF rings

According to Marshall`s protocol, both *cis* and *trans* substituted THF rings can be constructed from δ-mesyloxy α, β-unsaturated esters by tandem dihydroxylation and in situ S_N2 cyclization sequence. If we use AD-mix-α, we will end up with *trans* 2,5-substituted THF ring and if we use AD-mix-β, we will get *cis* 2,5-substituted THF ring (**Scheme 7**).

Following the above protocol, compound **29** was first subjected to MOM deprotection with 6 N HCl to give the alcohol **38** in 98% yield (**Scheme 8**). In ^{1}H NMR peaks at δ 3.40 (s, 3 H), 4.76 - 4.66 (m, 2 H) corresponding to MOM disappeared. The IR spectrum of **38** gave broad hydroxyl absorption at 3412 cm^{-1}. Further the alcohol **38** was converted into its mesylate followed by Sharpless asymmetric dihydroxylation[16] using AD-mix-*β* in ^{t}BuOH/H_2O (1:1) to afford the inseparable mixture of key *cis* and *trans*-substituted tetrahydrofuran **39** and **40** (93:7) respectively in 95% yield. The IR spectrum of **39** gave

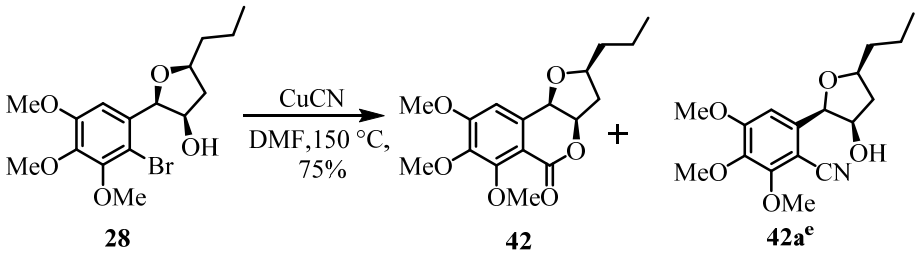
broad hydroxyl absorption at 3470 cm^{-1}. The ^1H NMR of **39** showed peaks at δ 4.75 (d, *J* = 3.7 Hz, 1 H), 4.40 - 4.33 (m, 1 H), 4.09 - 3.99 (m, 1 H), 2.49 - 2.39 (m, 1 H), 1.90 - 1.81 (m, 1 H) confirms the presence of THF ring. The formation of major *cis*-substituted tetrahydrofuran alcohol thus obtained could be attributed to the well-established steric preference of the AD-mix reagents and presumed S_N2 nature of cyclization reaction leading to the inversion of configuration at the reacting centre. It may be pertinent to mention here that this protocol is amenable to the other stereoisomers of monocerin by simply taking the (*R*)-enantiomer of epoxide **33** and changing the ligand in the dihydroxylation step. Selective aromatic bromination of **39** & **40** with NBS in CH_2Cl_2 afforded the bromobenzene derivatives **28** & **41** in 98% yield. At this stage the two diastereomers could be separated easily by silica gel column chromatography (**Scheme 8**). The ^1H NMR of **28** showed peak at δ 7.07 (s, 1 H) suggesting the monobromination of aromatics.



Scheme 8: Synthesis of compound **28**

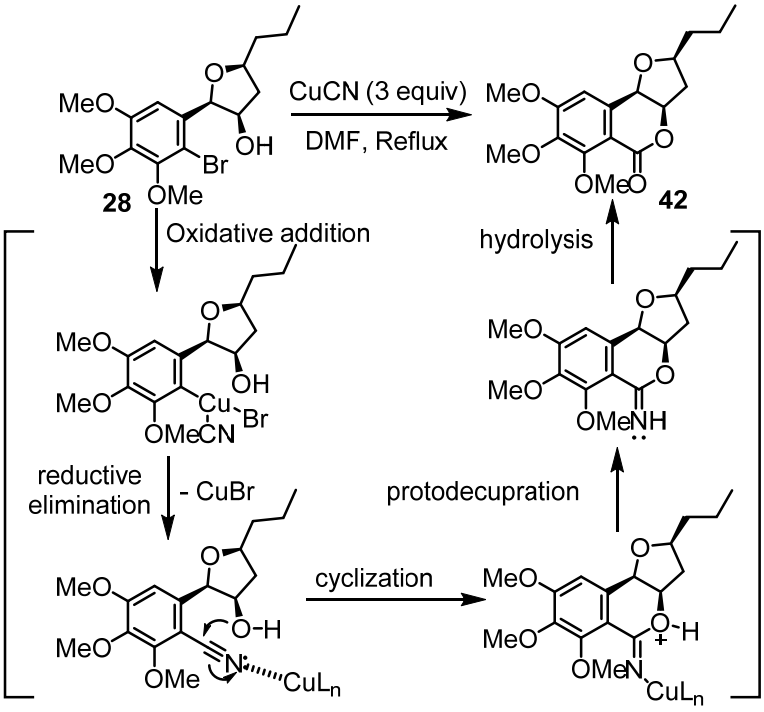
With substantial amount of bromo compound **28** in hand, our next task was to convert this into the corresponding cyano using CuCN in DMF[17] at reflux temperature followed by acid mediated cyclization[18] to give the desired product **42**. Initially the formation of desired product **42** was not observed by attempting the reaction of **28** with CuCN (1.0

equiv.) in DMF at 100 °C and only the starting material was recovered (**Table 2**, entry 1).



S.No	Equiv. of CuCN	Temperature	Yield[a] (%) (42)
1	1	100 °C	0[b]
2	1	150 °C	22%[c]
3	2	150 °C	46%[d]
4	**3**	**150 °C**	**75%**
[a]isolated yield,[b]Quantitative recovery of the starting material.[c,d]Recovery of most of the starting material.[e]In none of above cases, cyano product **42a** was observed			

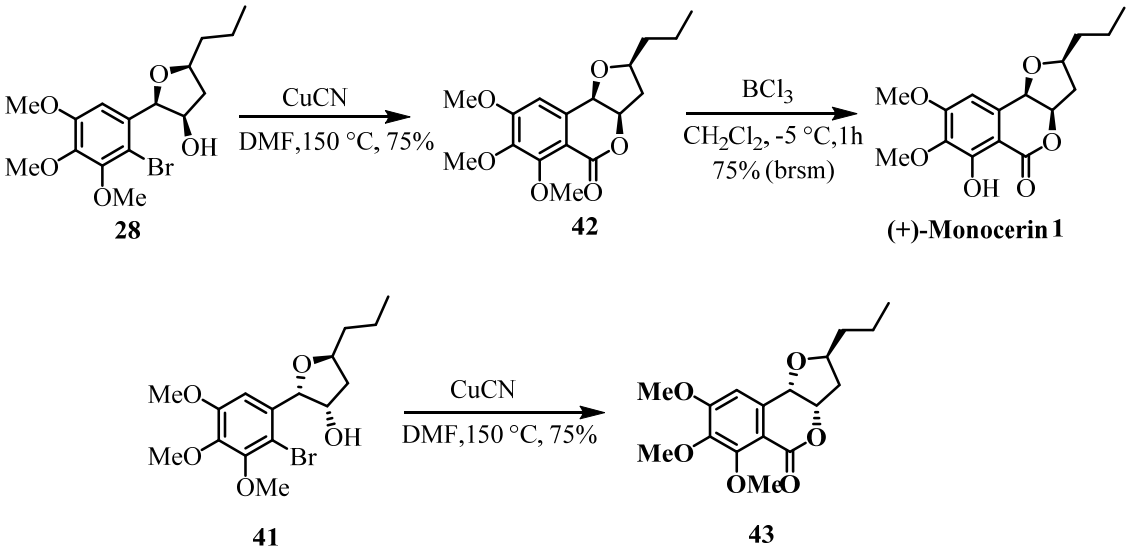
Table 2: Optimization for copper cyanide mediated tandem cyanation-lactonization



Scheme 9: Plausible mechanism for copper mediated tandem cyanation-lactonization

Surprisingly, when the reaction was carried out at 150 °C, instead of the expected product **43**, the cyclized product **42** was directly obtained albeit in low yield (**Table 2**, entry 2)**.** This prompted us to explore the copper-mediated tandem cyanation-lactonization of **28.** To improve the yield, when 2 equiv of CuCN was used, we could isolate compound **42** in moderate yield (**Table 2**, entry 3). When the same reaction was carried out with 3 equiv of CuCN at 150 °C, the desired cyclized product **42** was obtained in 75% yield (**Table 2**, entry 4). The IR spectrum of **42** gave carbonyl absorption at 1717 cm^{-1}. ^{13}C NMR of **42** showed ester carbonyl carbon peak at 159.9. To the best of our knowledge, there have been no reports of the synthesis of 6-membered lactone ring through copper-mediated tandem cyanation-cyclization of a substituted bromo benzene tetrahydrofuran alcohol.

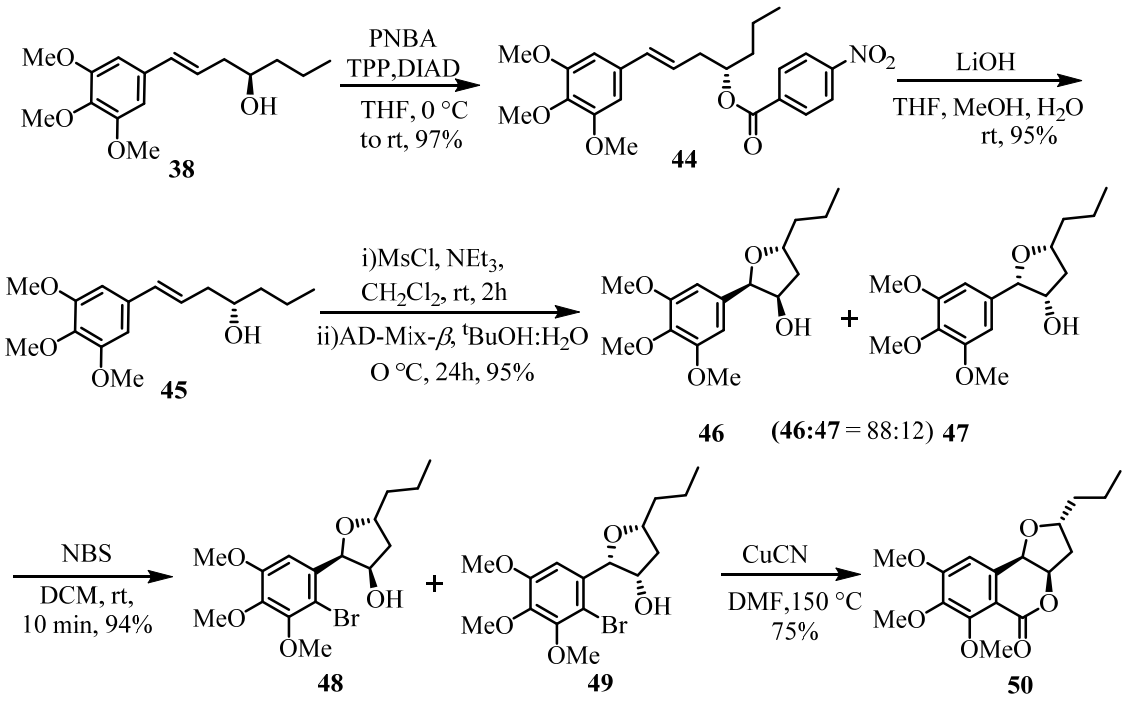
Mechanistically, the reaction is expected to proceed *via* the formation of oxidative addition of aryl bromide with copper cyanide followed by reductive elimination to give the cyano intermediate. This on further coordination with copper as Lewis acid facilitates the attack of alcoholic group. Subsequent protodecupration and hydrolysis eventually leads to the desired cyclized product **42** (**Scheme 9**).



Scheme 10: Synthesis of Monocerin and its analogue **43**

Finally selective demethylation of methoxy group from **42** using boron trichloride gave the target molecule monocerin **1** in 75% yield. The spectral data of (+)-monocerin was matched well with the reported values. Similarly **41** was also subjected to tandem cyanation-lactonization reaction to get the monocerin analogue **43** (**Scheme 10**).

In the same manner, we have also accomplished the synthesis of (*R*,*R*,*R*) isomer (**50**) of monocerin (**Scheme 11**). Feasibility of our developed route was checked by preparing the other stereoisomers of monocerin by simply changing the ligands in the dihydroxylation step.



Scheme 11: Synthesis of (2*R*,3a*R*,9b*R*)-6,7,8-trimethoxy-2-propyl-2,3,3a,9b-tetrahydro-5H-furo[3,2-c]isochromen-5-one **50**

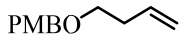
In our method, the synthesis of target molecule **1** was accomplished in 15 steps in an overall 15.5% yield. Our synthesis of **1** proved to be efficient in comparison with literature reports (Mori *et al.*[8] 14 steps, 6.6% yield; She *et al.*[10a] 12 steps, 12.25% yield; Lee *et al.*[10b] 10 steps, 7.7% yield; Stephen *et al.*[10c] 8 steps, 6.5% yield; Fang *et al.*[10d] 11 steps 5% yield).

3.1.5. Conclusion:

In summary, we have developed a novel copper mediated tandem cyanation–cyclization method for the synthesis of (+)-monocerin and its stereoisomers. The present method is applicable for the preparation of polyketide and dihydroisocoumarin natural products containing a lactone moiety through the intramolecular carbonylative coupling of aryl halide and alcohol. Our approach is suitable for the large-scale synthesis of **1** and its analogues. Depending upon catalyst used in HKR reaction and the ligand in dihydroxylation step we can have easy access to the other stereoisomers of monocerin.

3.1.6. Experimental Section

1-((But-3-en-1-yloxy)methyl)-4-methoxybenzene 32:



To a stirred solution of but-3-en-1-ol **31** (5.0 g, 69.33 mmol) in THF (100 mL) was added NaH (4.0 g, 90.14 mmol) at 0 °C and this was stirred well for 20 min at rt. Then PMBCl (11.8 ml, 83.22 mmol) was added to the reaction mixture at 0 °C, followed by addition of TBAI (2.5 g, 6.9 mmol), and this was stirred at rt for 3 h. The reaction mixture was quenched with ice water and extracted with EtOAc (3 × 50 mL). The extract was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether–EtOAc (91:9) as the eluent provided the PMB protected compound **32** as a colorless liquid.

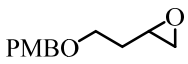
Yield: 12.8 g, 96%

Mol. Formula: $C_{12}H_{16}O_2$

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36–7.25 (m, 2 H), 6.97–6.85 (m, 2 H), 5.86 (tdd, *J* = 6.7, 10.3, 17.1 Hz, 1 H), 5.20–5.01 (m, 2 H), 4.48 (s, 2 H), 3.83 (s, 3 H), 3.52 (t, *J* = 6.8 Hz, 2 H), 2.39 (tq, *J* = 1.3, 6.7 Hz, 2 H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 135.3, 130.5, 129.2, 116.3, 113.7, 72.5, 69.3, 55.2, 34.2

2-(2-((4-Methoxybenzyl)oxy)ethyl)oxirane (±)-32:



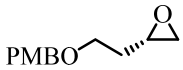
To a stirred solution of the compound **32** (12.0 g, 62.4 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added *m*-CPBA (50%) (32.31 g, 93.62 mmol). The reaction mixture was stirred at room temperature for 1 h, quenched by a saturated Na_2CO_3 solution, extracted with CH_2Cl_2, washed with sat. $NaHCO_3$ and brine, dried (Na_2SO_4), concentrated and purified by silica gel column chromatography using petroleum ether–EtOAc (9:1) as the eluent to yield the epoxide (±)-**33** as a colorless liquid.

Yield: 11.9 g, 92%

Mol. Formula: $C_{12}H_{16}O_3$

^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.35–7.22 (m, 2 H), 6.96–6.85 (m, 2 H), 4.49 (s, 2 H), 3.83 (s, 3 H), 3.68–3.56 (m, 2 H), 3.15–3.03 (m, 1 H), 2.85–2.76 (m, 1 H), 2.54 (dd, *J* = 2.8, 5.1 Hz, 1 H), 2.03–1.69 (m, 2 H)

(*S*)-2-(2-((4-Methoxybenzyl)oxy)ethyl)oxirane (−)-33:



Epoxide (±)-**33** (6 g, 28.83 mmol) and (*S*,*S*)-salen-Co(III)-OAc (95.7 mg, 0.0144 mmol) in isopropyl alcohol (0.285 ml) were stirred at 0 °C for 5 min, and then distilled water (0.285 ml, 15.84 mmol) was added. After stirring for 24 h, the solution was concentrated and purified by silica gel column chromatography using petroleum ether–EtOAc (9:1) to afford (−)-**33** as a yellow liquid. Continued chromatography with petroleum ether–EtOAc (1:1) provided the diol as a brown colour liquid.

Yield: 2.88 mg, 48%

Mol. Formula: $C_{12}H_{16}O_3$

$[\alpha]_D^{27}$: −13.1 (*c* 1.0, $CHCl_3$) {lit.[19] $[\alpha]_D^{26}$: −13.9° (*c* 1.0, $CHCl_3$)}

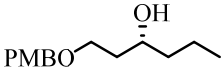
IR (neat, cm^{-1}): ν_{max} 2997, 2924, 1611, 1511, 1416, 1316, 1243, 1174, 1088, 906, 817, 753, 709

^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.28 (d, *J* = 8.6 Hz, 2 H), 6.89 (d, *J* = 8.6 Hz, 2 H), 4.47 (s, 2 H), 3.82 (s, 3 H), 3.67–3.54 (m, 2 H), 3.16–2.96 (m, 1 H), 2.79 (t, *J* = 4.5 Hz, 1 H), 2.53 (dd, *J* = 2.7, 4.9 Hz, 1 H), 2.03–1.70 (m, 2 H)

^{13}C NMR (50 MHz, $CDCl_3$) δ = 159.2, 130.3, 129.2, 113.8, 72.7, 66.7, 55.2, 50.1, 47.1, 32.9

HRMS (ESI) for $C_{12}H_{16}O_3Na$ $(M + Na)^+$ found 231.0992, calcd 231.0992

***(R)*-1-((4-Methoxybenzyl)oxy)hexan-3-ol 34:**



To a stirred solution of epoxide (-)-**33**[11] (2.0 g, 9.61 mmol) and CuI (183 mg, 0.961mmol) in dry THF (60 mL), was added, 1M solution of ethyl magnesium bromide in THF (14.4 ml, 14.4 mmol, 1M solution in THF) drop-wise at 0 °C and stirred for 1 h. The mixture was quenched with a saturated NH_4Cl solution (5 mL). The layers were

separated, the aqueous layer extracted with EtOAc (3 x 10 mL), the combined organic extracts were washed with brine (2 X 5 mL), followed by 25% NH_4OH solution (5 ml) and dried over Na_2SO_4, evaporated to dryness and silica gel column chromatographic purification (petroleum ether:EtOAc, 89:11) of the crude product gave **34** as a yellow colour oil.

Yield: 2.2 g, 96%

Mol. Formula: $C_{14}H_{22}O_3$

$[\alpha]_D^{26.4}$: + 8.41° (*c* 0.53, $CHCl_3$)

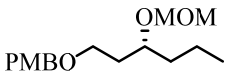
IR (neat, cm^{-1}): ν_{max} 3444, 2956, 1612, 1512, 1245, 1085, 1032, 817, 707

^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.32 - 7.20 (m, 2 H), 6.96 - 6.83 (m, 2 H), 4.46 (s, 2 H), 3.81 (s, 4 H), 3.74 - 3.57 (m, 2 H), 3.00 - 2.81 (m, 1 H), 1.80 - 1.66 (m, 2 H), 1.55 - 1.24 (m, 4 H), 1.03 - 0.81 (m, 3 H)

^{13}C NMR (50MHz, $CDCl_3$) δ = 143.2, 137.5, 129.5, 127.3, 96.1, 77.6, 76.4, 58.3, 54.7, 35.4, 32.4, 25.0, 23.2, 21.5

HRMS (ESI) for $C_{14}H_{22}O_3Na$ $(M + Na)^+$ found 261.1461, calcd 261.1461

(*R*)-1-Methoxy-4-(((3 (methoxymethoxy)hexyl)oxy)methyl)benzene 35:



To a solution of alcohol **34** (2.0 g, 8.4 mmol) in dry CH_2Cl_2 (40 mL) was added diisopropylethylamine (3.12 mL, 17.64 mmol) at 0 °C. To this mixture MOM chloride (0.94 ml, 12.6 mmol) was added slowly with further stirring for 3 h at the room temperature. The reaction mixture was quenched with addition of cold water at 0 °C. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water (3 x 20 mL), brine, dried over Na_2SO_4 and concentrated to give crude **35**. It was purified by silica gel column chromatography using petroleum ether:EtOAc, (93:7) as eluent to furnish **35** as colourless oil.

Yield: 2.34 g, 99%

Mol. Formula: $C_{16}H_{26}O_4$

$[\alpha]_D^{26.6}$: - 4.39° (*c* 1.02, $CHCl_3$)

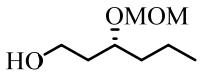
IR (neat, cm^{-1}): $\nu_{max.}$ 2933, 1512, 1246, 1138, 1034, 951, 821, 750, 606

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.26 (br. s., 2 H), 6.88 (d, *J* = 8.2 Hz, 2 H), 4.64 (s, 2 H), 4.44 (s, 2 H), 3.81 (s, 3 H), 3.71 (t, *J* = 5.6 Hz, 1 H), 3.54 (t, *J* = 6.4 Hz, 2 H), 3.37 (s, 3 H), 1.85 - 1.75 (m, 2 H), 1.54 - 1.32 (m, 4 H), 0.92 (t, *J* = 7.2 Hz, 3 H)

^{13}C NMR (125 MHz, $CDCl_3$) δ = 159.1, 130.5, 129.3, 113.7, 95.7, 74.9, 72.6, 66.7, 55.5, 55.3, 37.0, 34.7, 18.4, 14.2

HRMS (ESI) for $C_{16}H_{26}O_4Na$ $(M + Na)^+$ found 305.1723, calcd 305.1723

(*R*)-3-(Methoxymethoxy)hexan-1-ol 36:



To a solution of PMB ether **35** (2.0 g, 7.08 mmol) in dry CH_2Cl_2 : H_2O (38 : 2) mL was added DDQ (1.93 g, 8.5 mmol) at 0 °C with further stirred for 2 h at the room temperature. The reaction mixture was quenched with addition of cold water, stirred for 30 min then sat.$NaHCO_3$ solution was added, stirred for 30 min. Then reaction mixture was filtered through celite. The two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with sat.$NaHCO_3$ (2 x 15 mL), brine, dried over Na_2SO_4 and concentrated to give crude **36**. It was purified by silica gel column chromatography using petroleum ether:EtOAc, (86:14) as eluent to furnish the **36** as a yellow colour oil.

Yield: 1.12 g, 99%

Mol. Formula: $C_8H_{18}O_3$

$[\alpha]_D^{26.7}$: - 58.22° (*c* 1.08, $CHCl_3$)

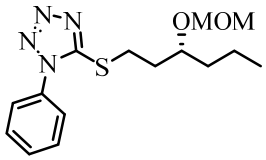
IR (neat, cm^{-1}): $\nu_{max.}$ 3385, 2956, 2933, 1095, 1029, 915

^{1}H NMR (500 MHz , $CDCl_3$) δ = 4.70 (d, *J* = 6.7 Hz, 1 H), 4.66 (d, *J* = 7.0 Hz, 1 H), 3.86 - 3.70 (m, 3 H), 3.41 (s, 3 H), 2.15 - 1.91 (m, 1 H), 1.86 - 1.79 (m, 1 H), 1.73 - 1.65 (m, 1 H), 1.62 - 1.55 (m, 1 H), 1.53 - 1.45 (m, 1 H), 1.41 - 1.32 (m, 2 H), 0.93 (t, *J* = 7.2 Hz, 3 H)

^{13}C NMR (125 MHz, $CDCl_3$) δ = 95.9, 76.4, 59.9, 55.8, 36.8, 36.5, 18.5, 14.2

HRMS (ESI) for $C_8H_{18}O_3Na$ $(M + Na)^+$ found 185.1148, calcd 185.1148

(*R*)-5-((3-(Methoxymethoxy)hexyl)thio)-1-phenyl-1*H*-tetrazole 37:



To the solution of resulting alcohol **36** (0.5 g, 3.08 mmol) in dry THF (5 mL) were added PPh_3 (1.78 g, 6.78 mmol), 1-phenyl-1*H*-tetrazole-5-thiol (0.824 g, 4.62 mmol) and DIAD (1.33 ml, 6.78 mmol) at 0 °C and allowed to stir for 4 h at room temperature. THF was concentrated and crude directly purified by silica gel column chromatography using petroleum ether:EtOAc, (91:9) as eluent to furnish **37** as a yellow colour oil.

Yield: 954 mg, 96%

Mol. Formula: $C_{15}H_{22}O_2N_4S$

$[\alpha]_D^{26.3}$: - 14.06° (*c* 1.48, $CHCl_3$)

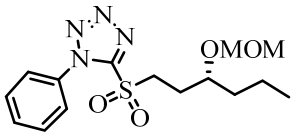
IR (neat, cm^{-1}): ν_{max} 2955, 2931, 1596, 1499, 1385, 1032, 915, 759, 711

^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.64 - 7.51 (m, 5 H), 4.72 - 4.60 (m, 2 H), 3.78 - 3.63 (m, 1 H), 3.61 - 3.41 (m, 2 H), 3.40 - 3.35 (m, 3 H), 2.18 - 1.88 (m, 2 H), 1.61 - 1.25 (m, 4 H), 0.97 - 0.86 (m, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.3, 133.7, 130.0, 129.7, 123.8, 95.6, 76.0, 55.7, 36.4, 33.8, 29.5, 18.4, 14.1

HRMS (ESI) for $C_{15}H_{22}O_2N_4NaS$ $(M + Na)^+$ found 345.1353, calcd 345.1356

(*R*)-5-((3-(Methoxymethoxy)hexyl)sulfonyl)-1-phenyl-1*H*-tetrazole 30:



To a solution of compound **37** (0.9 g, 2.79 mmol) in absolute EtOH (10 mL) was added $(NH_4)_6Mo_7O_{24}.4H_2O$ (1.72 g, 1.39 mmol) followed by addition of H_2O_2 (1.47 mL, 12.55 mmol) at 0 °C. The mixture was allowed to stir for 8 h at room temperature. The reaction mixture was quenched with addition of cold sat.Na_2SO_3 solution at 0 °C, filtered through celite. The solvent was evaporated and then the residue was extracted with EtOAc,

washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to get the crude product which was purified by silica gel column chromatography using petroleum ether:EtOAc, (90:10) as eluent to furnish **30** as a light yellow colour semi solid.

Yield: 960 mg, 97%

Mol. Formula: $C_{15}H_{22}O_4N_4S$

$[\alpha]_D^{25.4}$: - 4.43° (*c* 1.0, MeOH) {lit.[13c] for *S* isomer $[\alpha]_D^{23}$= + 8.60° (*c* 0.91, $CHCl_3$)

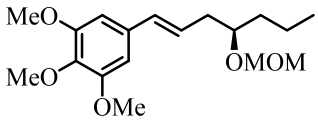
IR (neat, cm^{-1}): ν_{max} . 2958, 2932, 1595, 1339, 1149, 1036, 761, 688

^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.82 - 7.53 (m, 5 H), 4.71 - 4.61 (m, 2 H), 3.99 - 3.69 (m, 3 H), 3.40 (s, 3 H), 2.35 - 1.97 (m, 2 H), 1.52 - 1.28 (m, 4 H), 0.99 - 0.89 (m, 3 H)

^{13}C NMR (50 MHz, $CDCl_3$) δ = 133.0, 131.4, 129.7, 125.1, 95.7, 75.2, 55.8, 52.6, 36.3, 26.6, 18.4, 14.0

HRMS (ESI) for $C_{15}H_{22}O_4N_4NaS$ $(M + Na)^+$ found 377.1254, calcd 377.1254

(*R*,*E*)-1,2,3-Trimethoxy-5-(4-(methoxymethoxy)hept-1-en-1-yl)benzene 29:



To a mixture of compound **30** (930 mg, 2.62 mmol) and trimethoxybenzaldehyde (514 mg, 2.62 mmol) in dry THF (10 mL) was added NaHMDS (4.64 mL, 1M in THF, 4.64 mmol) dropwise at 0 °C and it was stirred at room temperature for 3 h. The reaction mixture was quenched with addition of sat.NH_4Cl solution. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to give crude **29**. It was purified by silica gel column chromatography using petroleum ether: EtOAc, (90:10) as eluent to furnish **29** as colourless oil (*E* only).

Yield: 749 mg, 88%

Mol. Formula: $C_{18}H_{28}O_5$

$[\alpha]_D^{26.3}$: + 18.46° (*c* 1.31, $CHCl_3$)

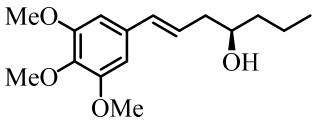
IR (neat, cm^{-1}): ν_{max} 2956, 2930, 1581, 1506, 1416, 1327, 1150, 1124, 1006, 966, 838, 779

^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.58 (s, 2 H), 6.36 (d, *J* = 15.6 Hz, 1 H), 6.24 - 6.08 (m, 1 H), 4.76 - 4.66 (m, 2 H), 3.91 - 3.83 (m, 9 H), 3.74 - 3.66 (m, 1 H), 3.40 (s, 3 H), 2.53 - 2.37 (m, 2 H), 1.58 - 1.35 (m, 4 H), 1.01 - 0.91 (m, 3 H)

^{13}C NMR (125 MHz, $CDCl_3$) δ = 153.2, 137.3, 133.3, 132.0, 126.1, 103.0, 95.4, 60.9, 56.0, 55.5, 38.0, 36.6, 18.7, 14.1

HRMS (ESI) for $C_{18}H_{28}O_5Na$ $(M + Na)^+$ found 347.1826, calcd 347.1829

***(R,E)*-1-(3,4,5-Trimethoxyphenyl)hept-1-en-4-ol 38:**



To a solution of compound **29** (700 mg, 2.15 mmol) in methanol (14 ml), was added 6N HCl (14 ml) drop wise at rt and stirring was continued for 2 h (reaction was monitored by TLC).The reaction was quenched by using sat.$NaHCO_3$ solution The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to give crude **38**. It was purified by silica gel column chromatography using petroleum ether:EtOAc, (85:15) as eluent to furnish **38** as a white solid.

Yield: 592 mg, 98%

Mol. Formula: $C_{16}H_{24}O_4$

mp: 70-71 °C

$[\alpha]_D^{27.3}$: - 11.27° (*c* 1.8, $CHCl_3$)

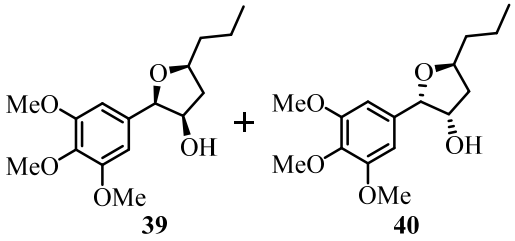
IR (neat, cm^{-1}): ν_{max} 3412, 2955, 2929, 1580, 1453, 1237, 1150, 1006, 966, 838

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.60 (s, 2 H), 6.41 (d, *J* = 15.7 Hz, 1 H), 6.17 (td, *J* = 7.5, 15.4 Hz, 1 H), 3.90 - 3.81 (m, 9 H), 3.79 - 3.72 (m, 1 H), 2.53 - 2.39 (m, 1 H), 2.38 - 2.24 (m, 1 H), 1.68 - 1.62 (m, 1 H), 1.54 - 1.37 (m, 4 H), 0.96 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.0, 137.2, 132.7, 132.5, 125.6, 102.8, 70.6, 60.6, 55.7, 40.7, 38.8, 18.6, 13.7

HRMS (ESI) for $C_{16}H_{24}O_4Na$ $(M + Na)^+$ found 303.1566, calcd 303.1567

(2*R*,3*R*,5*S*)-5-Propyl-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran 39:



39 **40**

To a solution of compound **38** (200 mg, 0.713 mmol) in dry CH_2Cl_2 was added tri ethylamine (0.4 ml, 2.84 mmol) at 0 °C. To this mixture mesyl chloride (0.11 ml, 1.42 mmol) was added slowly with further stirring for 2 h at the room temperature. The reaction mixture was quenched with addition of cold water at 0 °C. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 8 mL). The combined organic layers were washed with water (3 x 8 mL), brine, dried over Na_2SO_4 and concentrated to give crude mesylate.

To a solution of compound crude mesylate in $^tBuOH/H_2O$ (1:1, 12 mL) were added AD-mix-β (357 mg, 1.4 gm/mmol) and methanesulfonamide (25.5 mg, 100 mg/mmol) at 0 °C and the reaction mixture was allowed to stir for 24 h at that temperature. The reaction was quenched by addition of Na_2SO_3 (360 mg, 1.48 mg/mmol) and stirred for 1 h at room temperature until it became colourless. EtOAc was used for extraction and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to get the crude product which was purified by silica gel column chromatography using petroleum ether:EtOAc, (80:20) as eluent to furnish **39** as a colourless oil, which contains 7% of other diastereomer **40** (inseparable) confirmed by ^1H NMR spectroscopy.

Yield: 200 mg, 95%

Mol. Formula: $C_{16}H_{24}O_5$

$[\alpha]_D^{27.7}$: - 51.35° (*c* 1.85, $CHCl_3$)

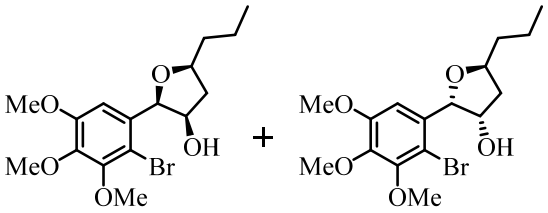
IR (neat, cm^{-1}): ν_{max} 3470, 2955,2940, 1590, 1418, 1232, 1125, 920, 781

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.63 (s, 2 H), 4.75 (d, *J* = 3.7 Hz, 1 H), 4.40 - 4.33 (m, 1 H), 4.09 - 3.99 (m, 1 H), 3.87 (s, 6 H), 3.84 (s, 3 H), 2.49 - 2.39 (m, 1 H), 1.90 - 1.81 (m, 1 H), 1.80 - 1.73 (m, 1 H), 1.70 - 1.40 (m, 4 H), 0.99 (t, *J* = 7.2 Hz, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.4, 137.4, 132.4, 103.7, 103.4, 84.9, 84.3, 78.6, 78.1, 77.2, 74.6, 73.9, 60.8, 56.1, 40.7, 40.2, 38.5, 38.3, 19.4, 19.1, 14.1

HRMS (ESI) for $C_{16}H_{24}O_5Na$ $(M + Na)^+$ found 319.1514, calcd 319.1516

(2*R*,3*R*,5*S*)-2-(2-Bromo-3,4,5-trimethoxyphenyl)-5-propyltetrahydrofuran-3-ol 28:



28 **41**

To a solution of alcohol **39 & 40** (100 mg, 0.337 mmol) in CH_2Cl_2 (3 mL) was added NBS (66 mg, 0.371 mmol) and the mixture was stirred at 25 °C for 10 min. After the reaction was complete (monitored by TLC), it was quenched with sat. $Na_2S_2O_3$ (3 mL) and extracted with CH_2Cl_2 (3 x 4 mL), washed with water and combined organic phases were dried over Na_2SO_4 and concentrated to give the crude bromo compound, which was then purified by column chromatography over silica gel using petroleum ether:EtOAc (90:10) to give the brominated alcohol **28** (124 mg, 98%) as a colourless oil. It contained 8.7 mg of other diastereomer **41.**

Yield: 124 mg, 98%

Mol. Formula: $C_{16}H_{23}O_5Br$

$[\alpha]_D^{27.8}$: -55.00° (*c* 2.2, $CHCl_3$)

IR (neat, cm^{-1}): ν_{max} 2935, 2866, 1569, 1481, 1428, 1166, 1012, 812, 773

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.07 (s, 1 H), 4.99 (d, *J* = 4.1 Hz, 1 H), 4.76 - 4.69 (m, 1 H), 4.02 (td, *J* = 6.9, 13.7 Hz, 1 H), 3.91 - 3.85 (m, 9 H), 2.50 (td, *J* = 6.8, 14.3 Hz, 1 H), 1.90 - 1.81 (m, 1 H), 1.76 - 1.62 (m, 3 H), 1.56 - 1.41 (m, 2 H), 0.99 (t, *J* = 7.3 Hz, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.8, 150.5, 142.4, 132.1, 108.1, 107.4, 84.3, 77.7, 71.8, 61.0, 56.0, 40.5, 38.3, 19.4, 14.2

HRMS (ESI) for $C_{16}H_{23}O_5BrNa$ $(M + Na)^+$ found 397.0618, calcd 397.0621

(2*S*,3*S*,5*S*)-2-(2-Bromo-3,4,5-trimethoxyphenyl)-5-propyltetrahydrofuran-3-ol 40:

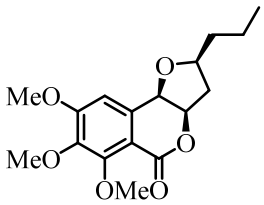
It was a by product in the preperation of compound **28**.

$[\alpha]_D^{26.6}$: + 39.58° (*c* 0.92, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.03 (s, 1 H), 5.26 (d, *J* = 3.2 Hz, 1 H), 4.78 (t, *J* = 3.7 Hz, 1 H), 4.52 - 4.44 (m, 1 H), 3.91 - 3.88 (m, 9 H), 2.25 (dd, *J* = 5.5, 13.3 Hz, 1 H), 1.93 - 1.85 (m, 1 H), 1.78 - 1.71 (m, 1 H), 1.54 - 1.44 (m, 3 H), 1.01 - 0.97 (m, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.9, 150.6, 142.4, 132.5, 107.8, 107.5, 83.8, 78.5, 72.4, 61.0, 56.1, 40.8, 38.1, 19.2, 14.1

(2*S*,3a*R*,9b*R*)-6,7,8-Trimethoxy-2-propyl-2,3,3a,9b-tetrahydro-5*H*-furo[3,2c]isochromen-5-one 42:



Bromo alcohol **28** (100 mg, 0.267 mmol) was taken in dry DMF (1.0 mL) and CuCN (71 mg, 0.802 mmol) was added to it. The entire solution was refluxed under N_2 for 12 h (monitored by TLC). The reaction mixture was then cooled to room temperature, and diluted with water (3 mL) and EtOAc (5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product which was purified by column chromatography using an eluent dichloromethane:EtOAc (95:5) to give cyclized product **42** as a colourless oil.

Yield: 64 mg, 75%

Mol. Formula: $C_{17}H_{23}O_6$

$[\alpha]_D^{27.2}$: + 23.2° (*c* 0.53, $CHCl_3$) {(lit.[8] $[\alpha]_D^{21}$ = + 22.8° (*c* 2.76, $CHCl_3$)}

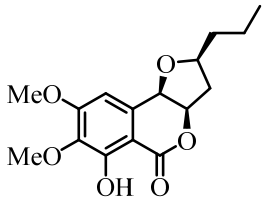
IR (neat, cm^{-1}): ν_{max} 2923, 2853, 1717, 1592, 1461, 1366, 1256, 1110, 1009, 844, 754.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.79 (s, 1 H), 5.01 - 4.92 (m, 1 H), 4.52 (d, *J* = 2.7 Hz, 1 H), 4.19 - 4.10 (m, 1 H), 3.97 (s, 3 H), 3.95 (s, 3 H), 3.89 (s, 3 H), 2.52 (ddd, *J* = 5.7, 8.6, 14.2 Hz, 1 H), 2.16 (dd, *J* = 5.4, 14.2 Hz, 1 H), 1.77 - 1.68 (m, 1 H), 1.64 - 1.56 (m, 1 H), 1.48 - 1.34 (m, 2 H), 0.91 (t, *J* = 7.3 Hz, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.9, 157.9, 156.5, 144.3, 132.5, 111.2, 108.1, 79.5, 79.0, 75.1, 61.8, 61.1, 56.2, 39.0, 38.1, 19.2, 13.9

HRMS (ESI) for $C_{17}H_{23}O_6$ $(M + H)^+$ found 323.1483, calcd 323.1489

(2*S*,3a*R*,9b*R*)-6-Hydroxy-7,8-dimethoxy-2-propyl-2,3,3a,9b-tetrahydro-5*H*-furo[3,2-c]isochromen-5-one 1:



To a solution of lactone **42** (48 mg, 0.148 mmol) in dry CH_2Cl_2 (1 mL) was added BCl_3 (1.0 M, 0.163 mL, 0.163 mmol) at -10 °C under Argon. The mixture was stirred at -5 °C for 1 h and quenched with saturated aqueous $NaHCO_3$ (1 mL). The mixture was extracted with CH_2Cl_2 (3 x 4 mL), and the organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuum, purified by column chromatography using an eluent petroleum ether:EtOAc (60:40) to give **(+)-monocerin 1** as colourless oil.

Yield: 11.3 mg, 75% yield

Mol. Formula: $C_{16}H_{21}O_6$

$[\alpha]_D^{26}$: + 53° (*c* 1, $CHCl_3$) {(lit^2. $[\alpha]_D^{25}$ = +53° (*c* 1, $CHCl_3$)}

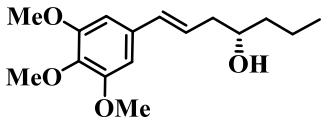
IR (neat, cm^{-1}): ν_{max} 2956, 2924, 1663, 1520, 1456, 1274, 1119, 1013, 759

^{1}H NMR (400 MHz, $CDCl_3$) δ = 11.29 (s, 1 H), 6.60 (s, 1 H), 5.06 (dd, *J* = 3.1, 5.3 Hz, 1 H), 4.55 (d, *J* = 3.2 Hz, 1 H), 4.17 - 4.08 (m, 1 H), 3.96 (s, 3 H), 3.91 (s, 3 H), 2.60 (ddd, *J* = 6.4, 8.4, 14.5 Hz, 1 H), 2.17 (dd, *J* = 6.0, 14.5 Hz, 1 H), 1.74 - 1.67 (m, 1 H), 1.63 - 1.59 (m, 1 H), 1.45 - 1.35 (m, 2 H), 0.93 (t, *J* = 7.3 Hz, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.8, 158.7, 156.3, 137.3, 131.1, 104.3, 102.0, 81.2, 78.7, 74.5, 60.7, 56.2, 39.0, 38.0, 19.1, 14.0

HRMS (ESI) for $C_{16}H_{21}O_6$ $(M + H)^+$ found 309.1331, calcd 309.1333

(*S*,*E*)-1-(3,4,5-Trimethoxyphenyl)hept-1-en-4-ol 45:



To the solution of alcohol **38** (0.2 g, 0.713 mmol) in dry THF (5 mL) were added PPh_3 (0.393 g, 1.49 mmol), *p*-nitrobenzoic acid (PNBA) (0.143 g, 0.856 mmol) and diisopropylazodicarboxylate (DIAD) (0.29 ml, 1.49 mmol) at 0 °C and it was allowed to stir for 1 h at room temperature. THF was concentrated and crude product thus obtained was purified by silica gel column chromatography using petroleum ether:EtOAc, (94:6) as eluent to furnish **44** as yellow colour oil.

Yield: 297 mg, 97%

Mol. Formula: $C_{23}H_{27}O_7N$

$[\alpha]_D^{27.4}$: + 39.8° (*c* 1.03, $CHCl_3$)

IR (neat, cm^{-1}): ν_{max} 2959, 2936, 1718, 1581, 1505, 1416, 1270, 1184, 1011, 964, 872, 694

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 - 8.26 (m, *J* = 8.7 Hz, 2 H), 8.23 - 8.18 (m, *J* = 8.7 Hz, 2 H), 6.53 (s, 2 H), 6.39 (d, *J* = 15.6 Hz, 1 H), 6.15 - 6.06 (m, 1 H), 5.32 - 5.24 (m, 1 H), 3.88 - 3.83 (m, 9 H), 2.62 (t, *J* = 6.6 Hz, 2 H), 1.82 - 1.71 (m, 2 H), 1.53 - 1.40 (m, 2 H), 0.97 (t, *J* = 7.3 Hz, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.4, 153.3, 150.5, 137.7, 136.0, 133.1, 132.9, 130.6, 124.4, 123.5, 103.2, 75.4, 60.9, 56.1, 37.9, 35.8, 18.7, 13.9

HRMS (ESI) for $C_{23}H_{27}O_7NNa$ $(M + Na)^+$ found 452.1676, calcd 452.1680

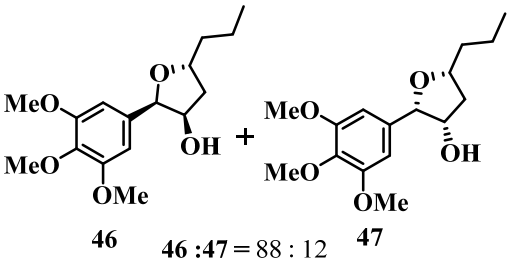
To the solution of ester **44** (0.25 g, 0.582 mmol) in THF:MeOH:H_2O (3:2:1) (6 mL) was added $LiOH.H_2O$ (0.029 g, 0.699 mmol) at rt and it was allowed to stir for 1 h at room temperature. Solvent was concentrated and to the residue was added Sat.$NaHCO_3$ (5 ml) and extracted with EtOAc (3 x 5 ml) and the organic layer was washed with brine, dried

over anhydrous Na_2SO_4 and concentrated in vacuum. Purification by column chromatography using an eluent petroleum ether:EtOAc (85:15) gave **45** as colourless oil.

Yield: 153 mg, 95%

$[\alpha]_D^{27}$: + 11.16° (*c* 1.8, $CHCl_3$)

(2*R*,3*R*,5*R*)-5-Propyl-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-ol 46:



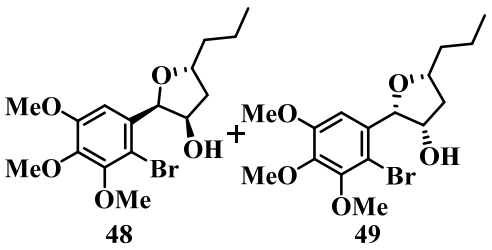
46 **46 :47** = 88 : 12 **47**

For the preparation of above compounds, the same procedure was used as described for the compound **39.** Compound **45** (40 mg, 0.142 mmol) was subjected to tandem Sharpless asymmetric dihydroxylation-S_N2 cyclization to give **46** & **47** as a colourless oil, which contains 12% of other diastereomer **47** (inseparable) as confirmed by proton spectroscopy.

Yield: 40 mg, 95%

^{1}H NMR (200 MHz, $CDCl_3$) δ 0.92 - 1.05 (m, 3 H) 1.36 - 1.61 (m, 4 H) 1.79 - 1.90 (m, 1 H) 2.27 (dd, *J*=13.07, 5.75 Hz, 1 H) 3.84 (s, 3 H) 3.87 (s, 6 H) 4.35 - 4.55 (m, 2 H) 5.00 (d, *J*=3.03 Hz, 1 H), 6.60 (s, 2 H)

(2*R*,3*R*,5*R*)-2-(2-Bromo-3,4,5-trimethoxyphenyl)-5-propyltetrahydrofuran-3-ol 48:



48 **49**

The same procedure was used for preparing compound **48** as described for the compound **28.** Bromination of alcohol **46** & **47** (20 mg, 0.202 mmol) yielded the brominated alcohol **48** as a colourless oil. It contained 3 mg of other diastereomer **49.**

Yield: 22 mg, 98%

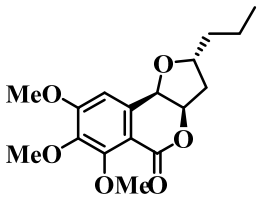
Mol. Formula: $C_{16}H_{23}O_5Br$

$[\alpha]_D^{25.3}$: - 43.54° (*c* 2.6, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.02 (s, 1 H), 5.25 (d, *J* = 3.1 Hz, 1 H), 4.77 (t, *J* = 3.2 Hz, 1 H), 4.51 - 4.45 (m, 1 H), 3.90 - 3.87 (m, 9 H), 2.23 (dd, *J* = 5.5, 13.1 Hz, 1 H), 1.91 - 1.85 (m, 1 H), 1.77 - 1.70 (m, 1 H), 1.53 - 1.38 (m, 3 H), 0.98 (t, *J* = 7.2 Hz, 3 H)

^{13}C NMR (125 MHz, $CDCl_3$) δ = 152.9, 150.6, 142.4, 132.5, 107.7, 107.5, 83.7, 78.4, 72.4, 61.0, 56.1, 40.8, 38.1, 19.2, 14.1

(2*R*,3a*R*,9b*R*)-6,7,8-Trimethoxy-2-propyl-2,3,3a,9b-tetrahydro-5*H*-furo[3,2-c]isochromen-5-one 50 :



The same procedure as described for the preperation of compound **42.** Bromo alcohol **48** (10 mg, 0.026 mmol) yielded cyclised product **50** as a colourless oil.

Yield: 6.4 mg, 75%

Mol. Formula: $C_{17}H_{23}O_6$

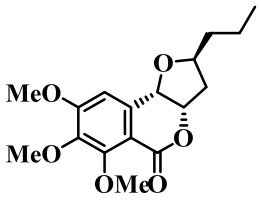
$[\alpha]_D^{27.6}$: + 11.34° (*c* 0.45, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.96 (t, *J*=7.21 Hz, 3 H) 1.48 - 1.59 (m, 2 H) 1.71 - 1.76 (m, 2 H) 1.94 (ddd, *J*=13.63, 9.60, 3.91 Hz, 1 H) 2.60 (dd, *J*=13.69, 5.87 Hz, 1 H) 3.89 (s, 3 H) 3.97 (s, 3 H) 3.96 (s, 3 H) 4.38 - 4.47 (m, 1 H) 4.76 (d, *J*=2.69 Hz, 1 H) 5.04 (t, *J*=3.06 Hz, 1 H) 6.77 (s, 1 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.2, 158.1, 156.6, 144.2, 133.4, 108.0, 80.2, 79.5, 73.9, 61.8, 61.2, 56.2, 40.2, 38.3, 19.2, 14.0

HRMS (ESI) for $C_{17}H_{23}O_6$ $(M + H)^+$ found 323.1484, calcd 323.1489

(2*S*,3a*S*,9b*S*)-6,7,8-Trimethoxy-2-propyl-2,3,3a,9b-tetrahydro-5*H*-furo[3,2-c]isochromen-5-one 43:



For preparing compound **43** the same procedure was used as described for compound **42.** Bromo alcohol **41** (6 mg, 0.0801 mmol) yielded cyclized product **43** as a colourless oil.

Yield: 3.8 mg, 75%

Mol. Formula: $C_{17}H_{23}O_6$

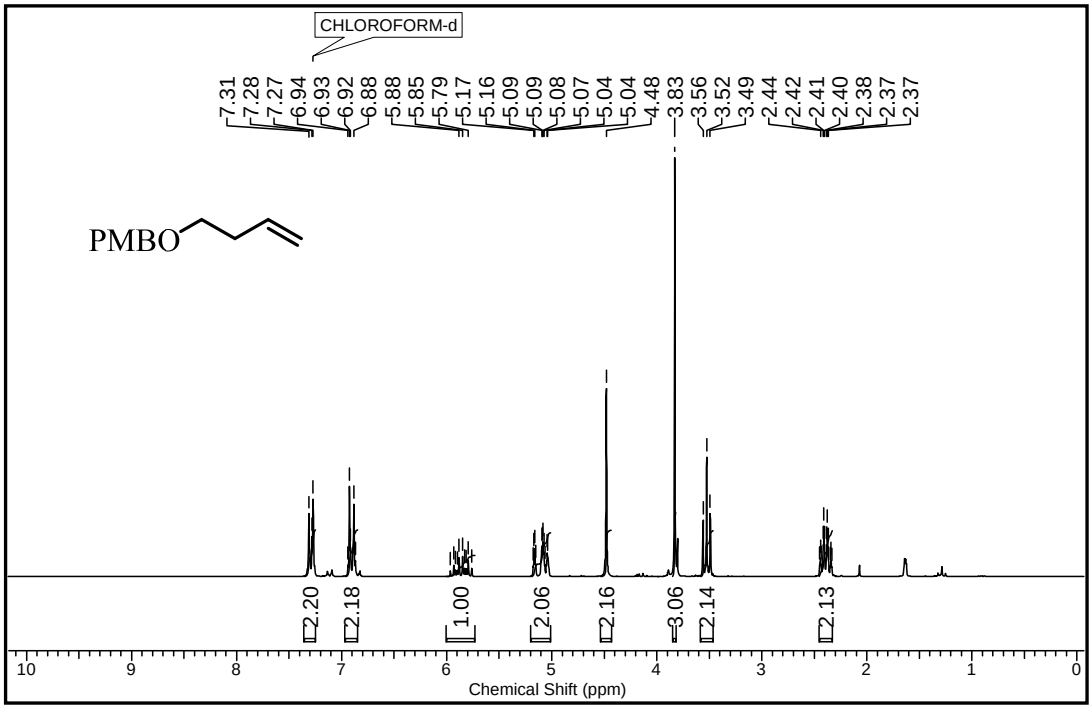
$[\alpha]_D^{27.5}$: - 10.5° (*c* 0.2, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.94 - 0.97 (m, 3 H) 1.49 - 1.57 (m, 2 H) 1.67 - 1.75 (m, 2 H) 1.94 (ddd, *J*=13.66, 9.69, 4.12 Hz, 1 H) 2.59 (dd, *J*=13.43, 5.80 Hz, 1 H) 3.89 (s, 3 H) 3.97 (d, *J*=4.27 Hz, 7 H) 4.39 - 4.46 (m, 1 H) 4.76 (d, *J*=2.75 Hz, 1 H) 5.04 (t, *J*=2.90 Hz, 1 H) 6.78 (s, 1 H)

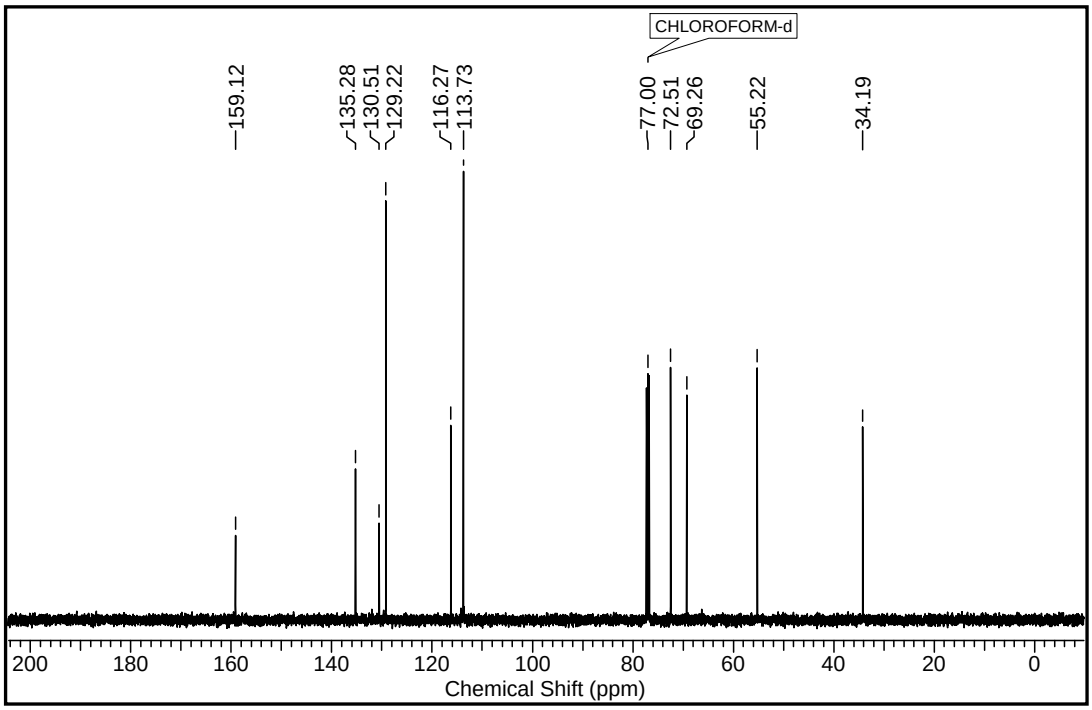
^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.2, 158.1, 156.5, 144.1, 133.4, 108.0, 80.2, 79.5, 73.9, 61.8, 61.2, 56.2, 40.1, 38.3, 19.2, 14.1

3.1.7. Spectra:

1-((But-3-en-1-yloxy)methyl)-4-methoxybenzene 32:

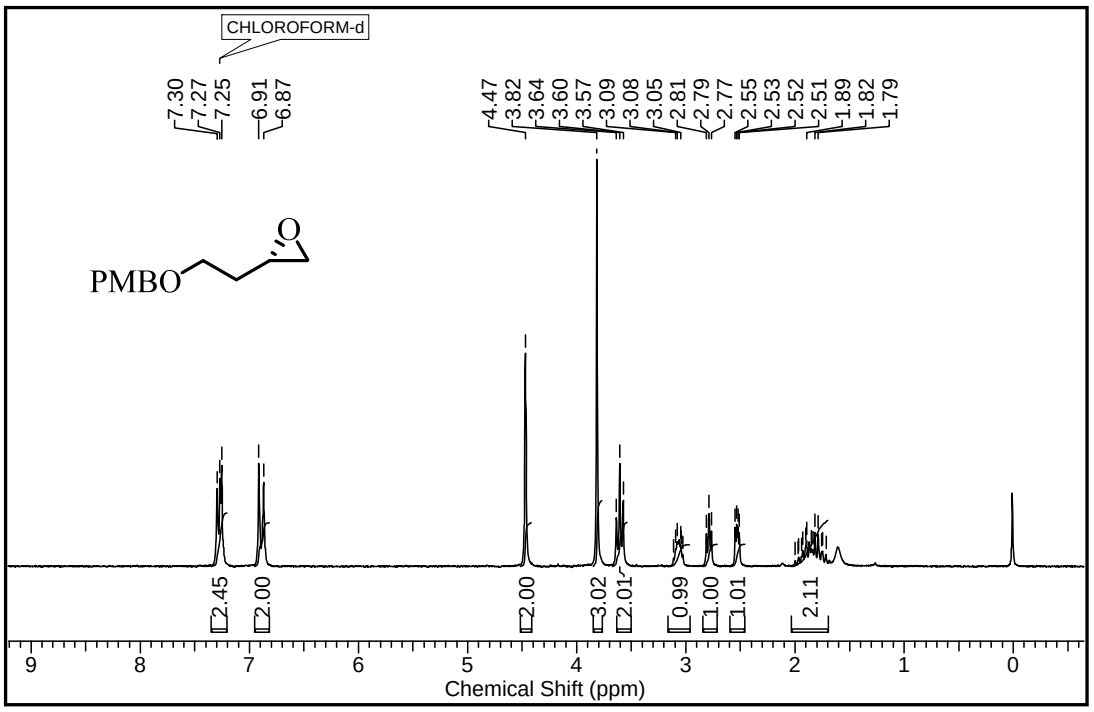


➢ **^{1}H NMR of the compound 32 in $CDCl_3$**

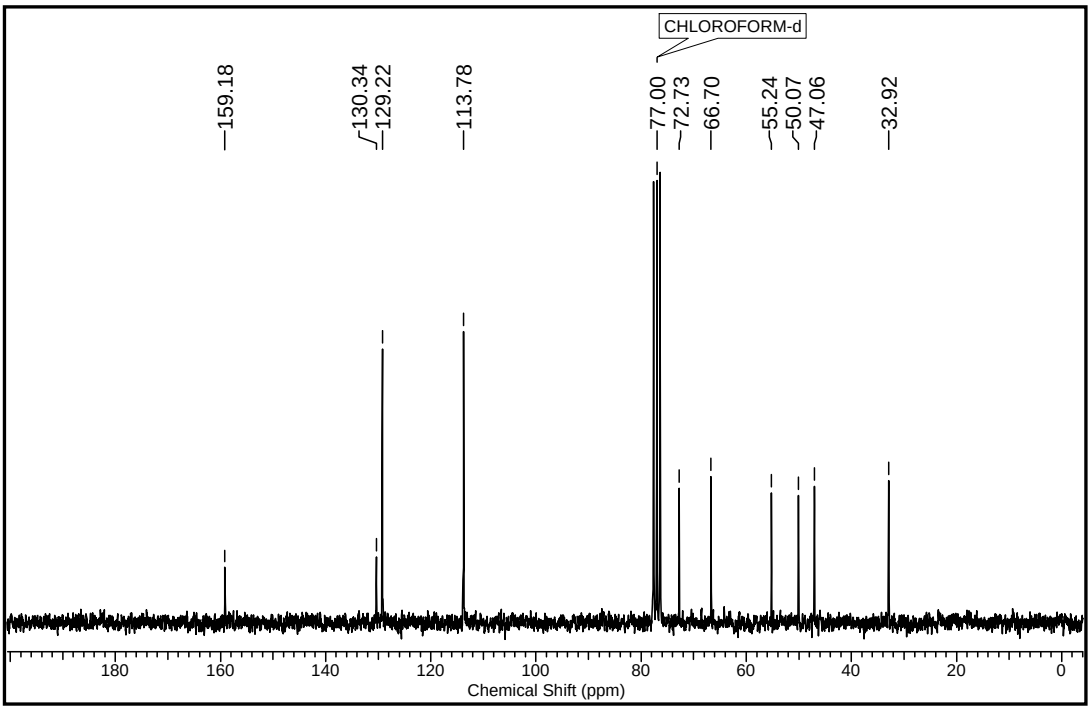


➢ **^{13}C NMR of the compound 32 in $CDCl_3$**

(*S*)-2-(2-((4-Methoxybenzyl)oxy)ethyl)oxirane (-)-33:

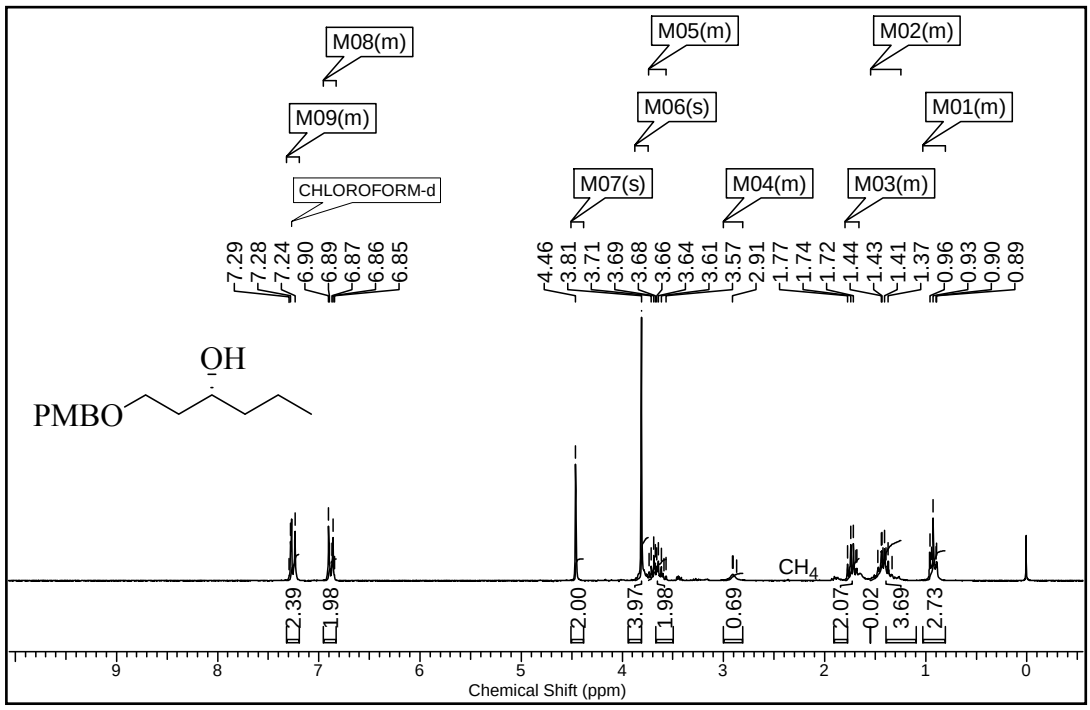


➢ **^{1}H NMR of the compound (-)-33 in $CDCl_3$**

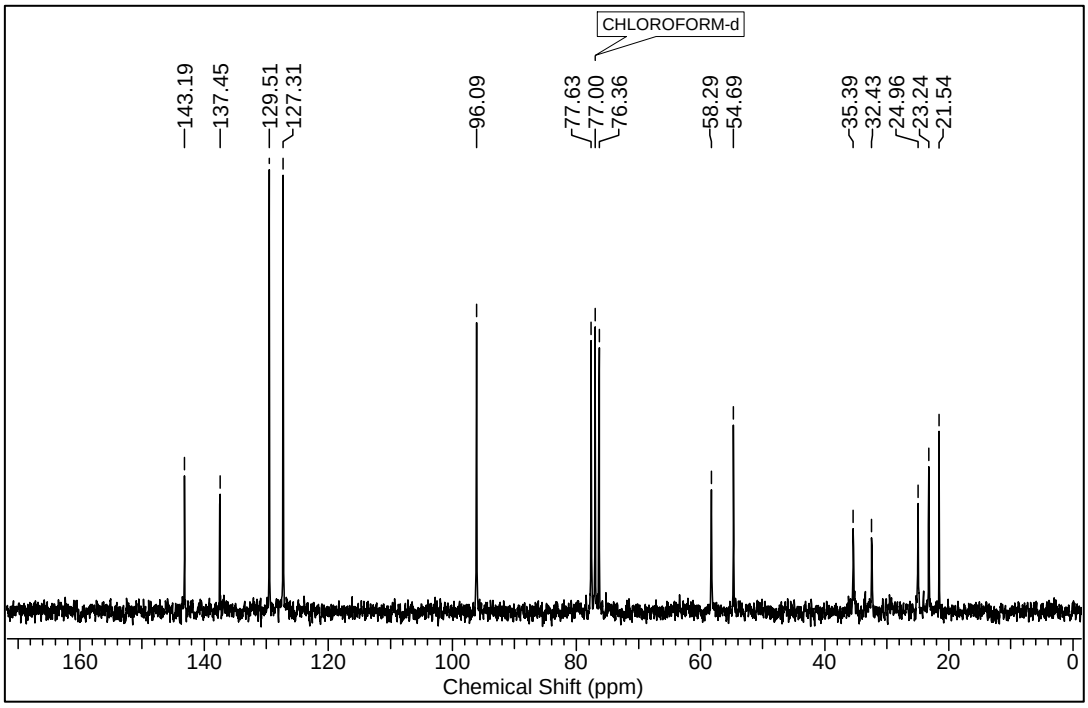


➢ **^{13}C NMR of the compound (-)-33 in $CDCl_3$**

(*R*)-1-((4-Methoxybenzyl)oxy)hexan-3-ol 34:

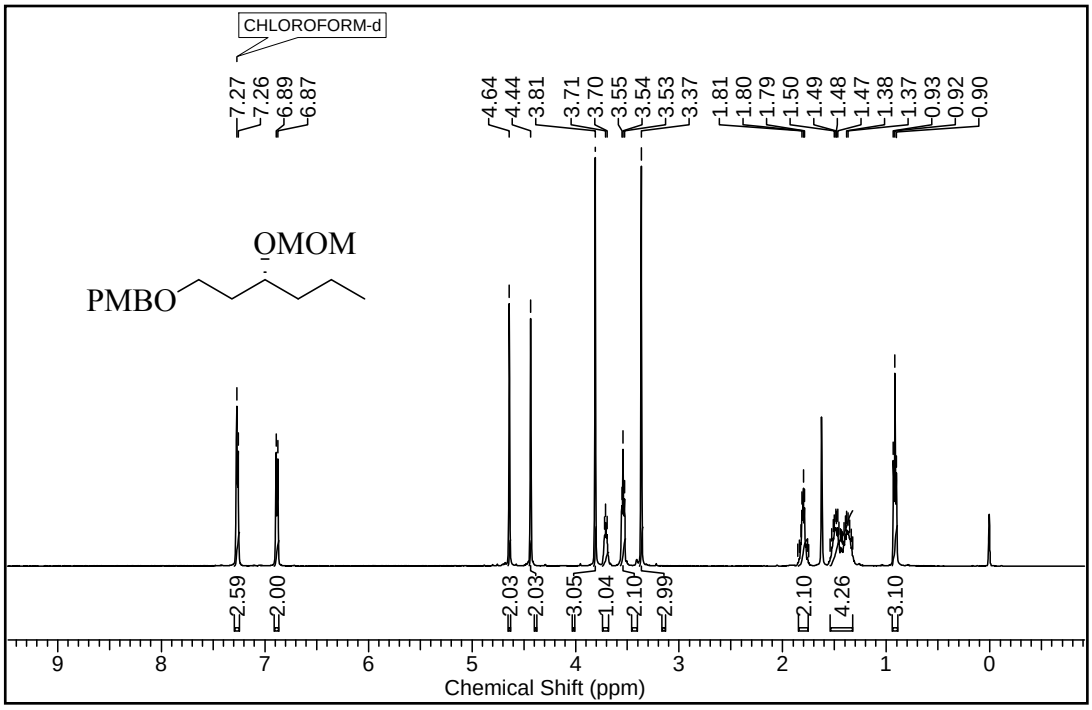


- **^{1}H NMR of the compound 34 in $CDCl_3$**

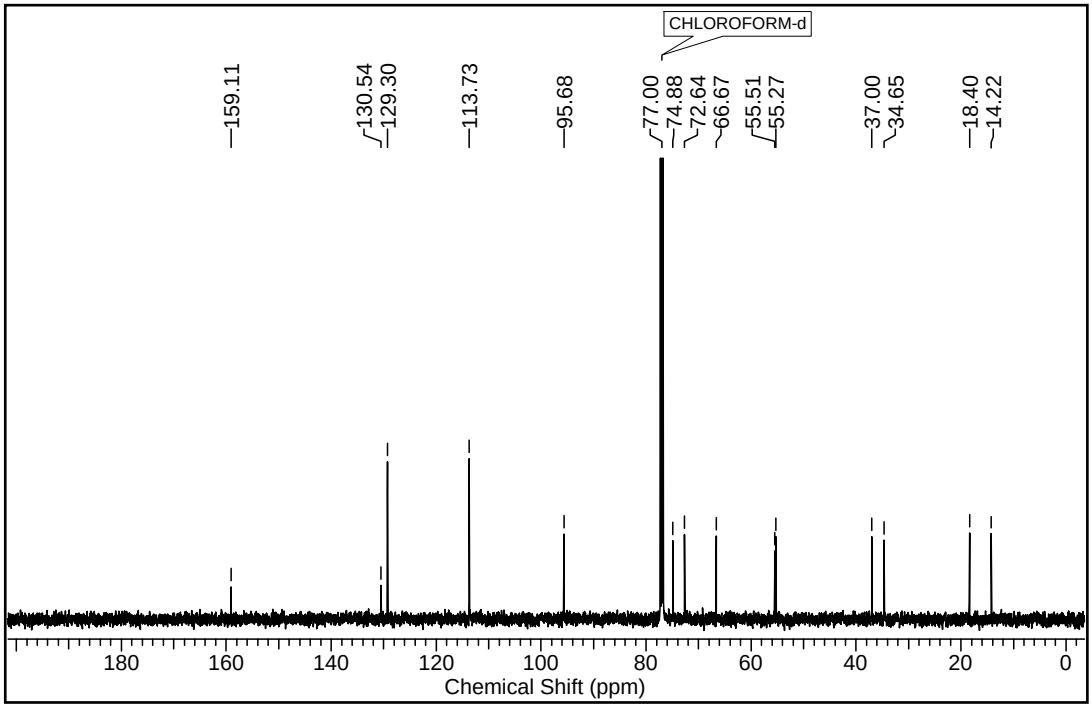


- **^{13}C NMR of the compound 34 in $CDCl_3$**

(*R*)-1-Methoxy-4-(((3-(methoxymethoxy)hexyl)oxy)methyl)benzene 35:

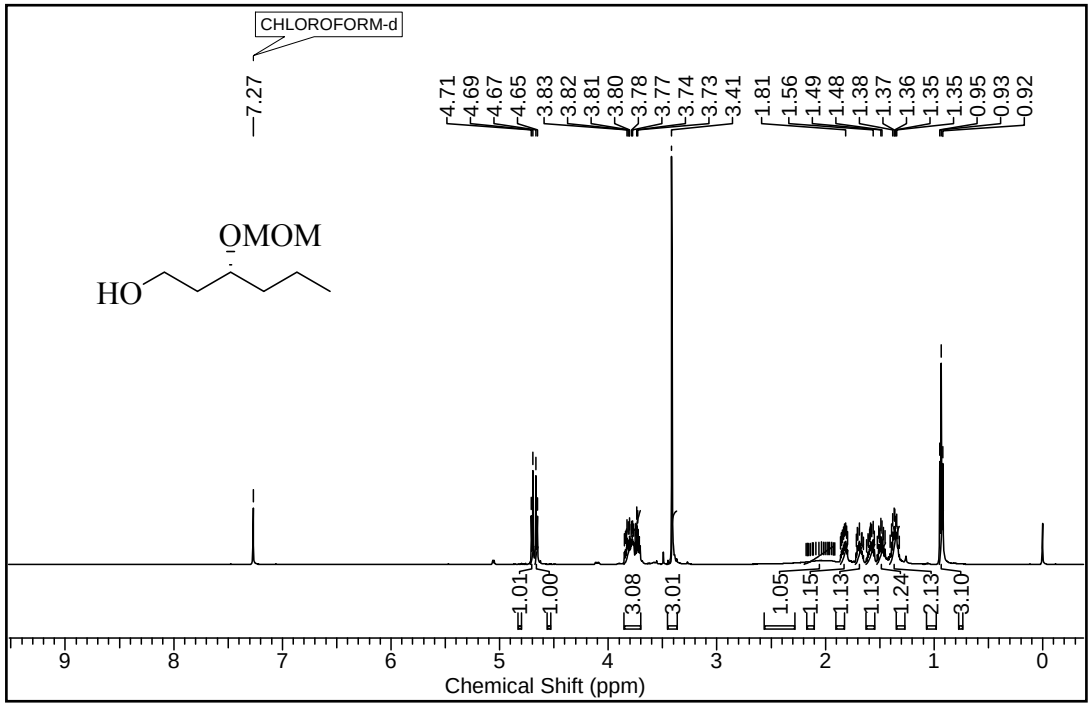


- **^{1}H NMR of the compound 35 in $CDCl_3$**

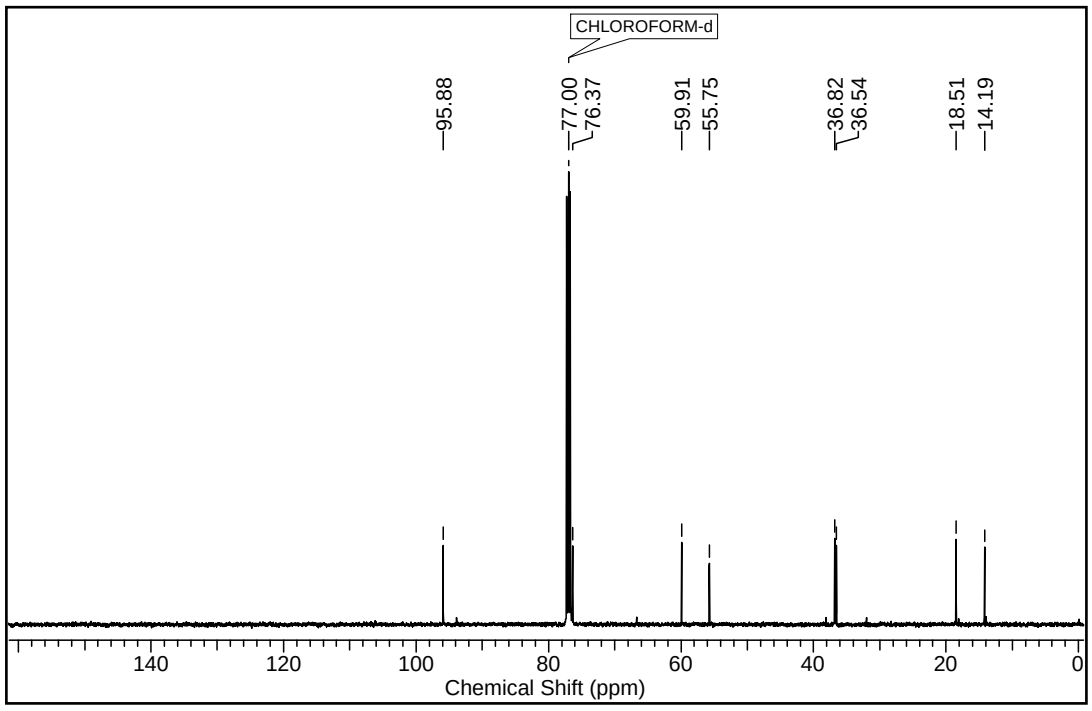


- **^{13}C NMR of the compound 35 in $CDCl_3$**

(*R*)-3-(Methoxymethoxy)hexan-1-ol 36:

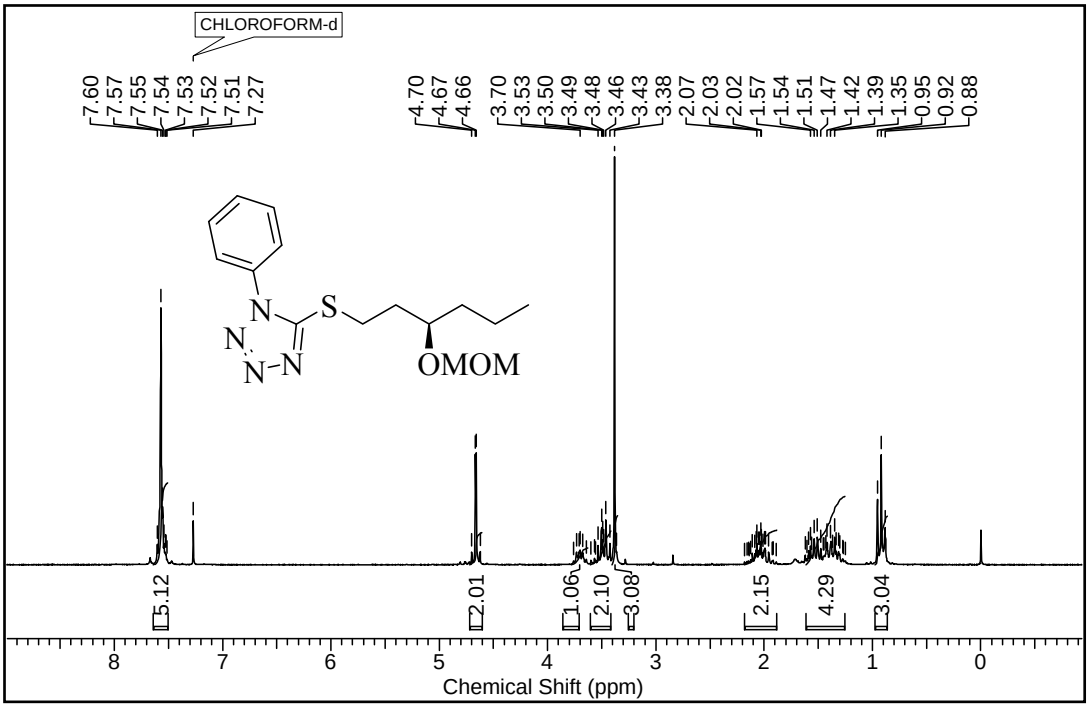


- **^{1}H NMR of the compound 36 in $CDCl_3$**

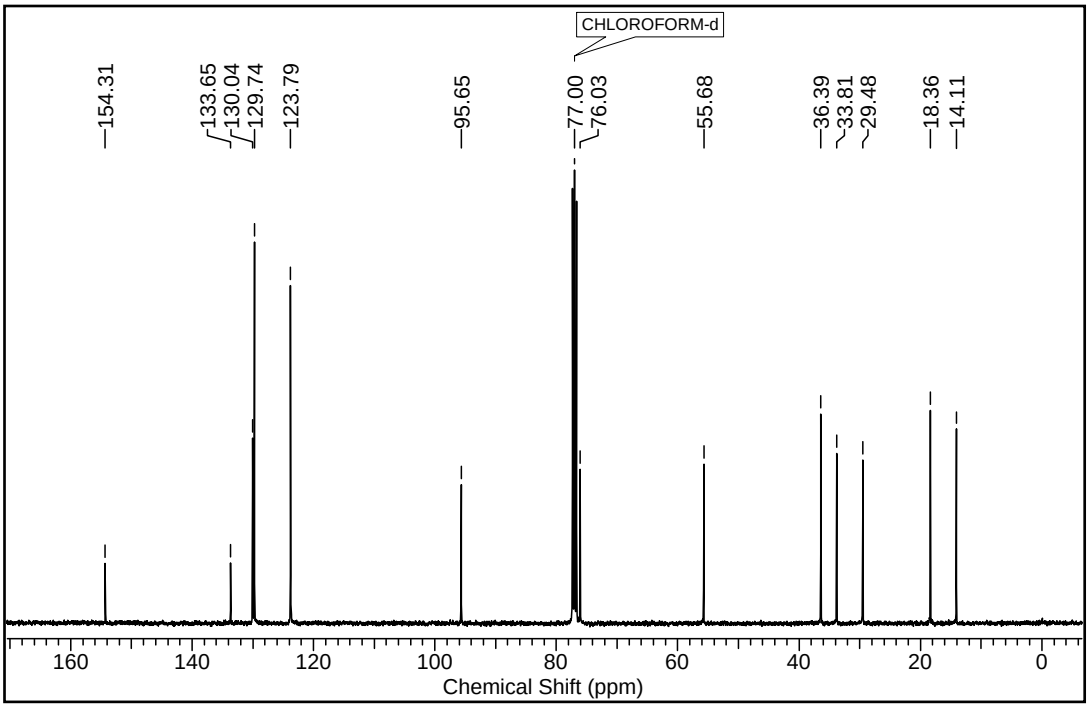


- **^{13}C NMR of the compound 36 in $CDCl_3$**

(*R*)-5-((3-(Methoxymethoxy)hexyl)thio)-1-phenyl-1*H*-tetrazole 37:

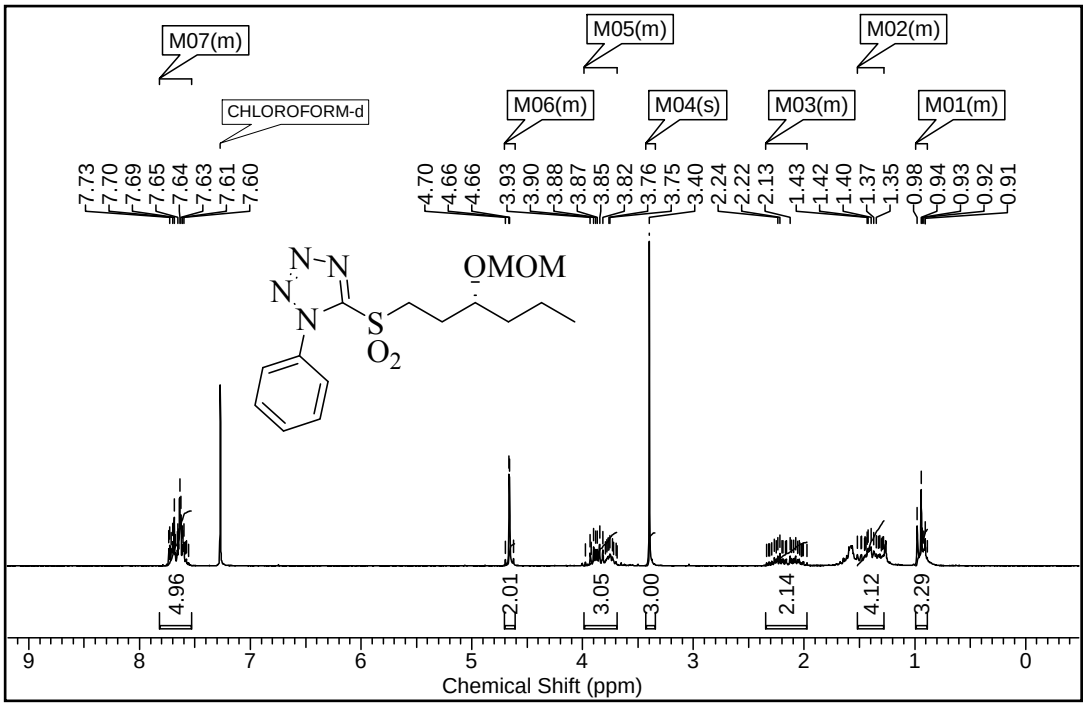


➢ **^{1}H NMR of the compound 37 in $CDCl_3$**

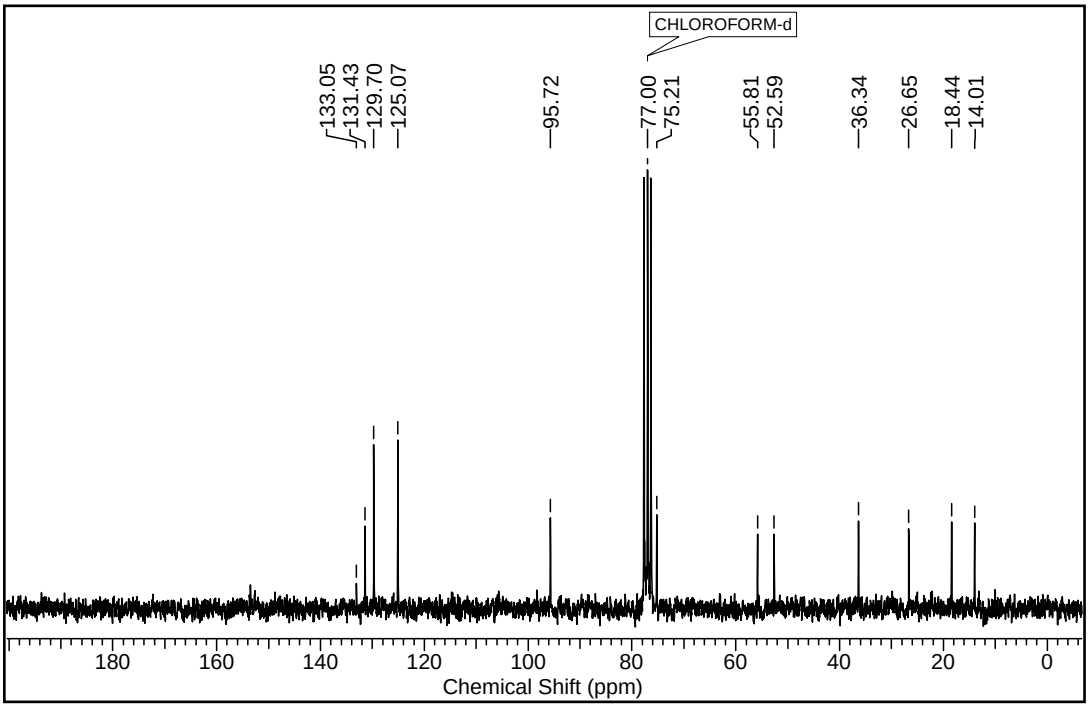


➢ **^{13}C NMR of the compound 37 in $CDCl_3$**

(*R*)-5-((3-(Methoxymethoxy)hexyl)sulfonyl)-1-phenyl-1*H*-tetrazole 30:

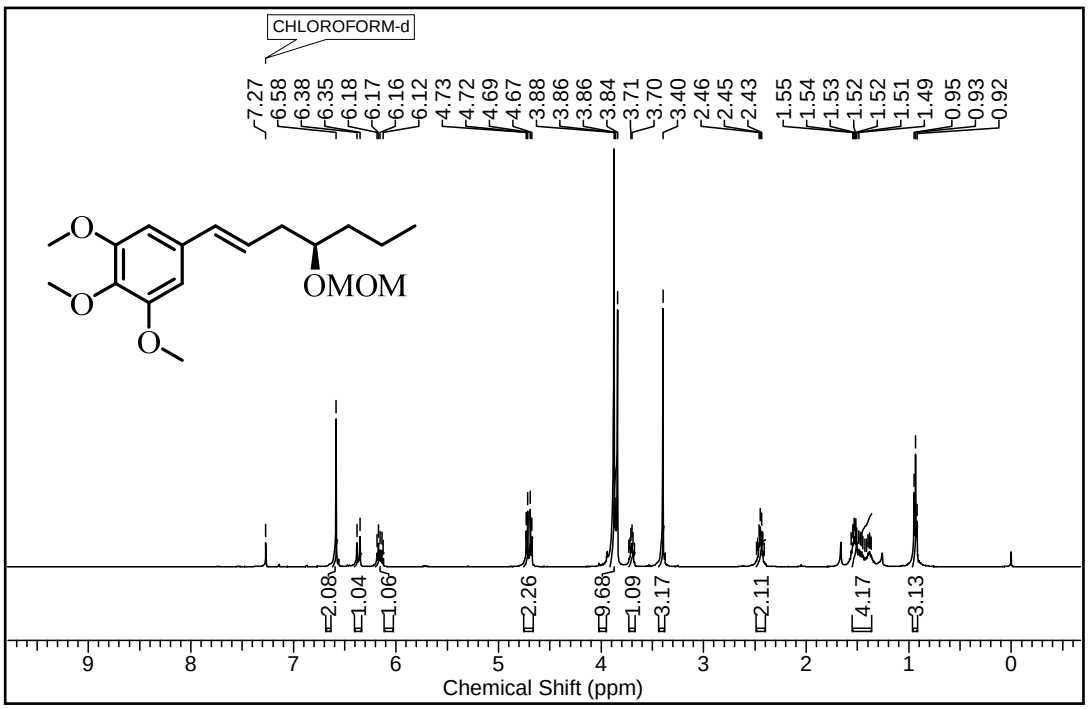


➢ **^{1}H NMR of the compound 30 in $CDCl_3$**

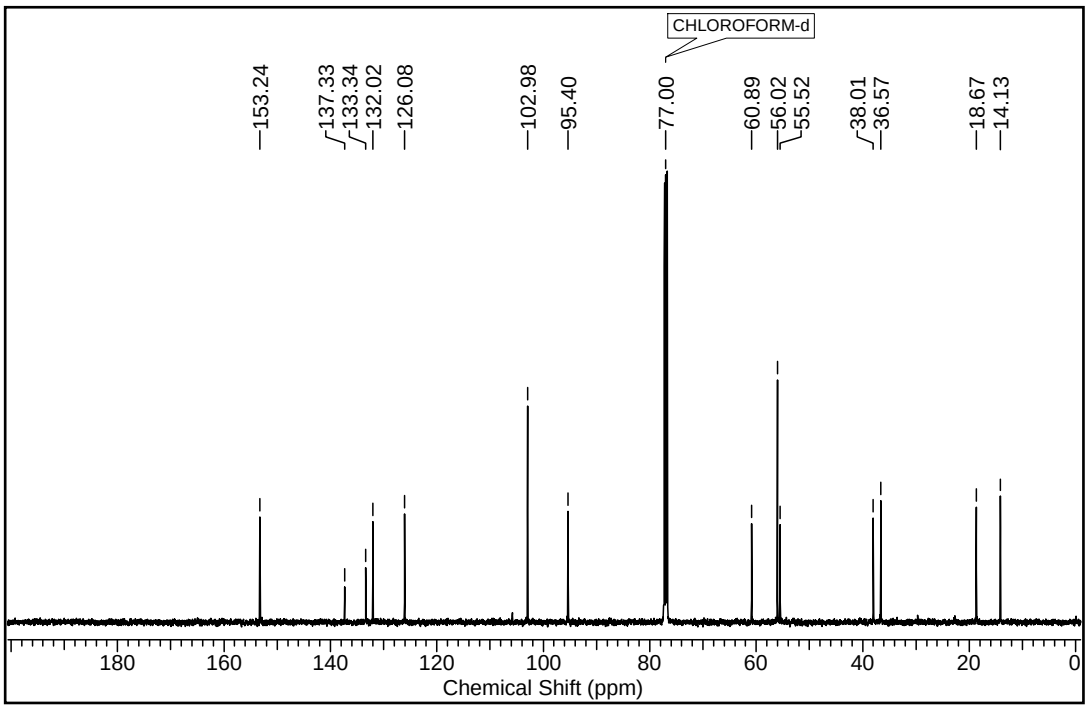


➢ **^{13}C NMR of the compound 30 in $CDCl_3$**

(*R*,*E*)-1,2,3-Trimethoxy-5-(4-(methoxymethoxy)hept-1-en-1-yl)benzene 29:

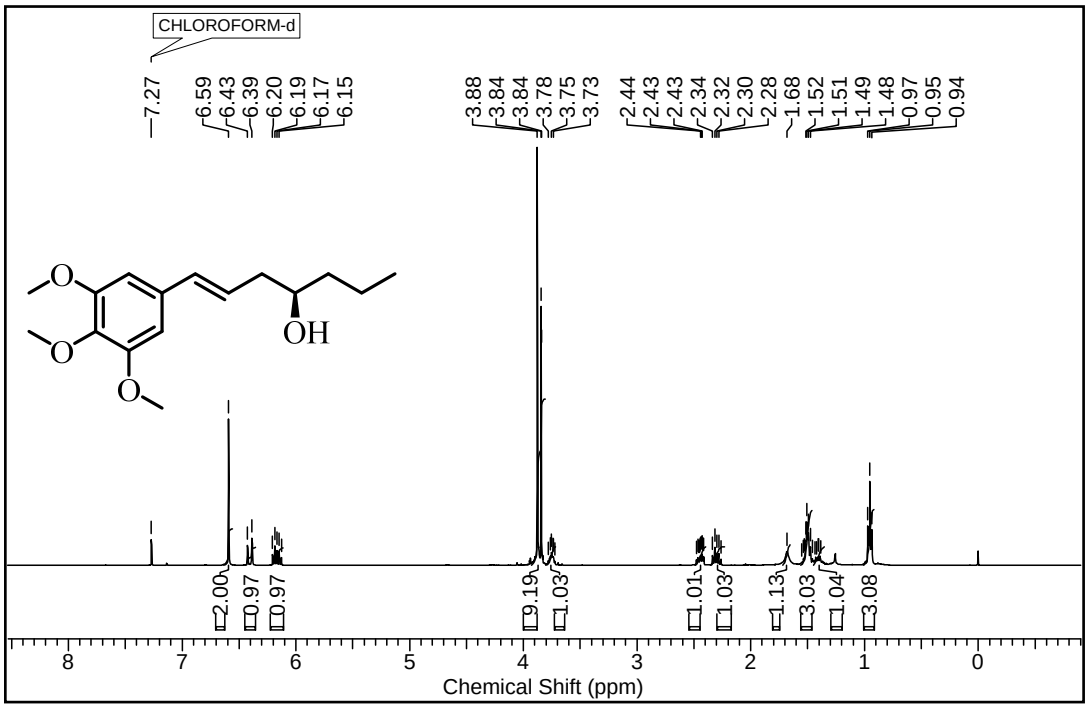


➢ **^{1}H NMR of the compound 29 in $CDCl_3$**

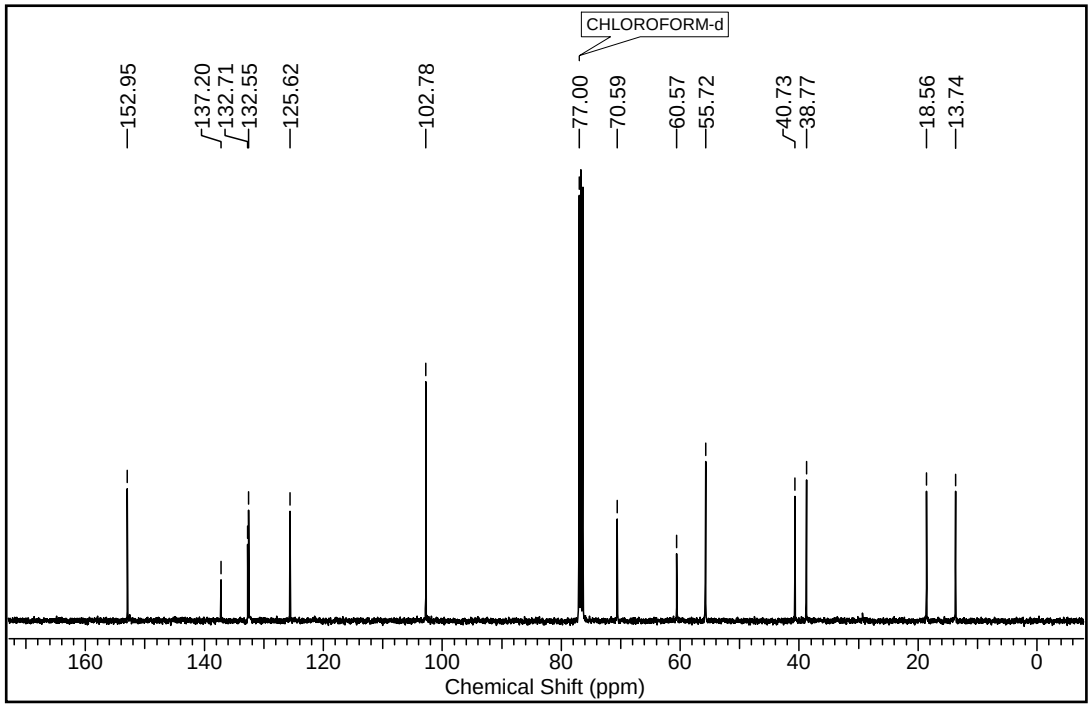


➢ **^{13}C NMR of the compound 29 in $CDCl_3$**

(*R*,*E*)-1-(3,4,5-Trimethoxyphenyl)hept-1-en-4-ol 38:

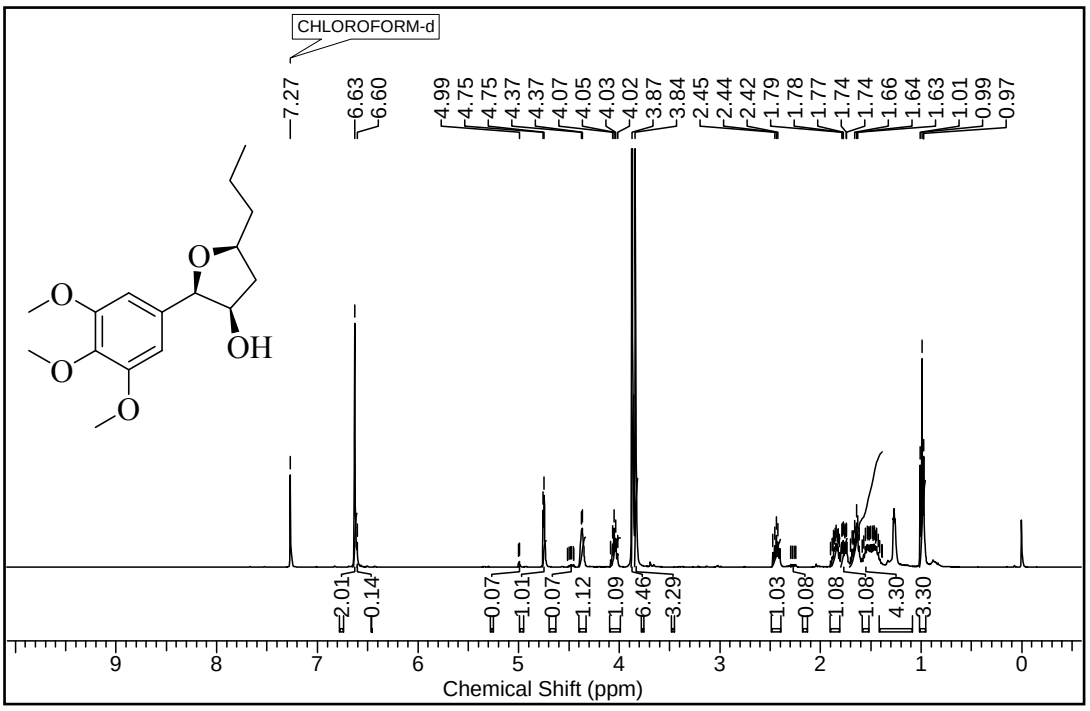


➢ **^{1}H NMR of the compound 38 in $CDCl_3$**

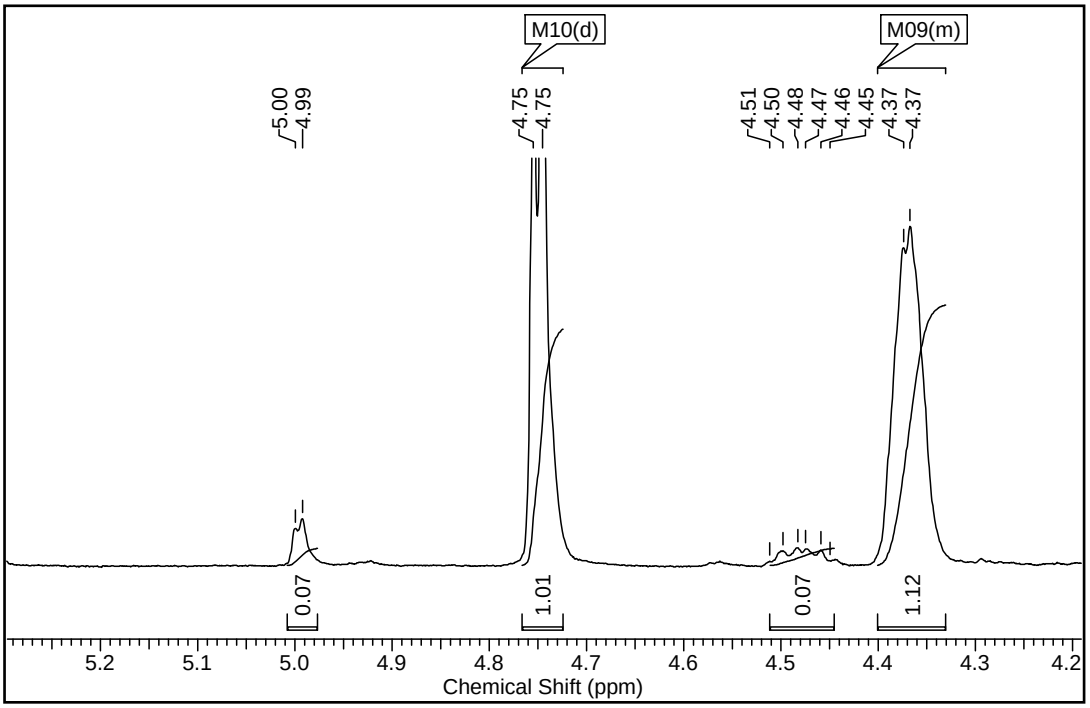


➢ **^{13}C NMR of the compound 38 in $CDCl_3$**

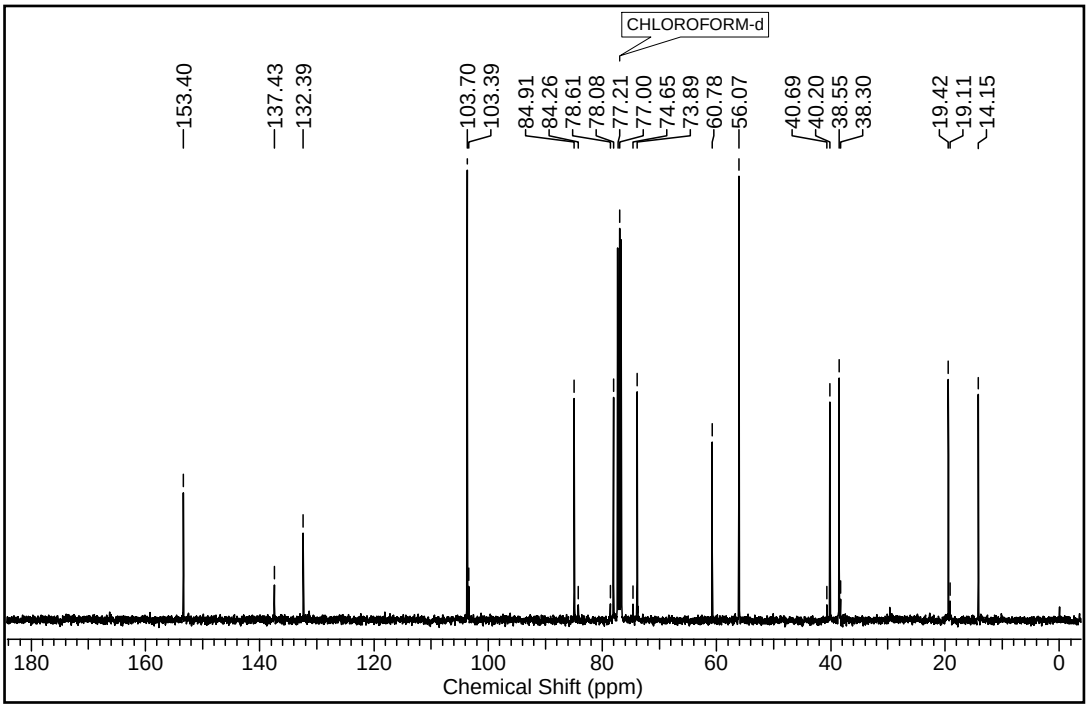
(2*R*,3*R*,5*S*)-5-Propyl-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-ol 39:



- **^{1}H NMR of the compound 39 in $CDCl_3$**

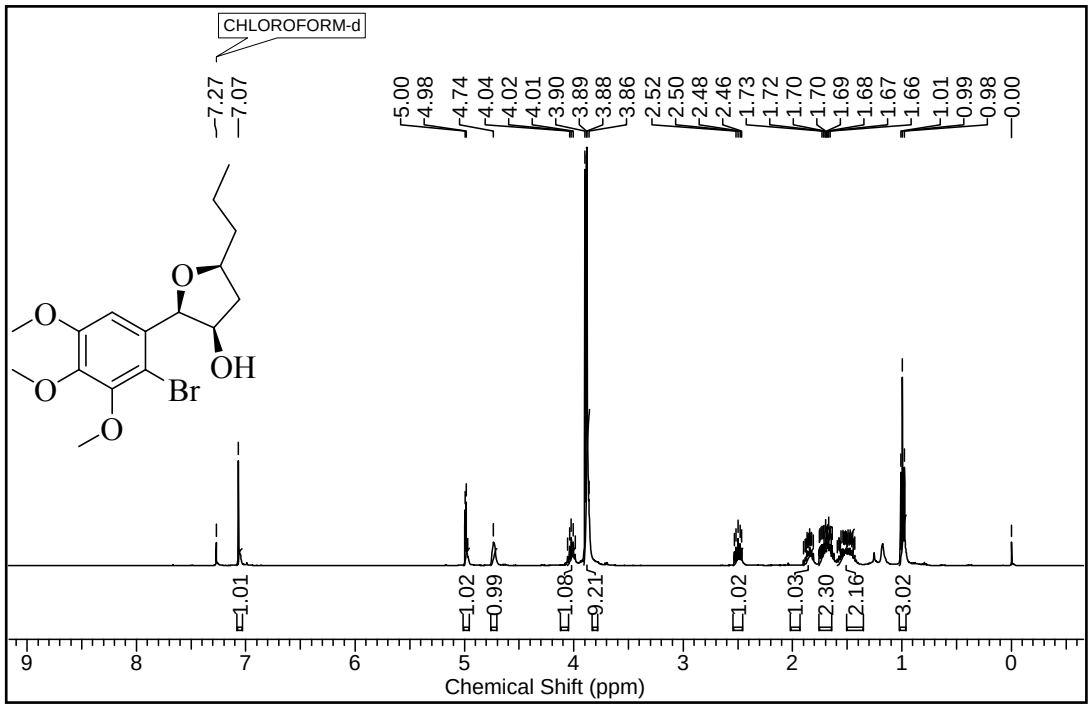


(2*R*,3*R*,5*S*)-5-Propyl-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-ol 39:

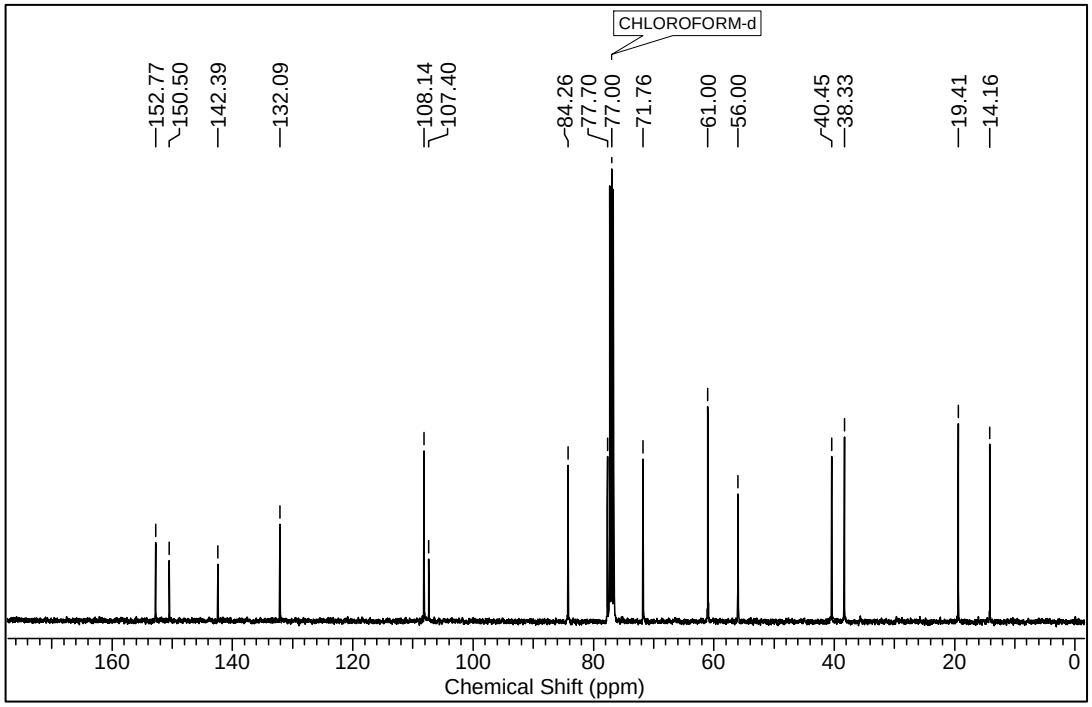


- **^{13}C NMR of the compound 39 in $CDCl_3$**

(2*R*,3*R*,5*S*)-2-(2-Bromo-3,4,5-trimethoxyphenyl)-5-propyltetrahydrofuran-3-ol 28:

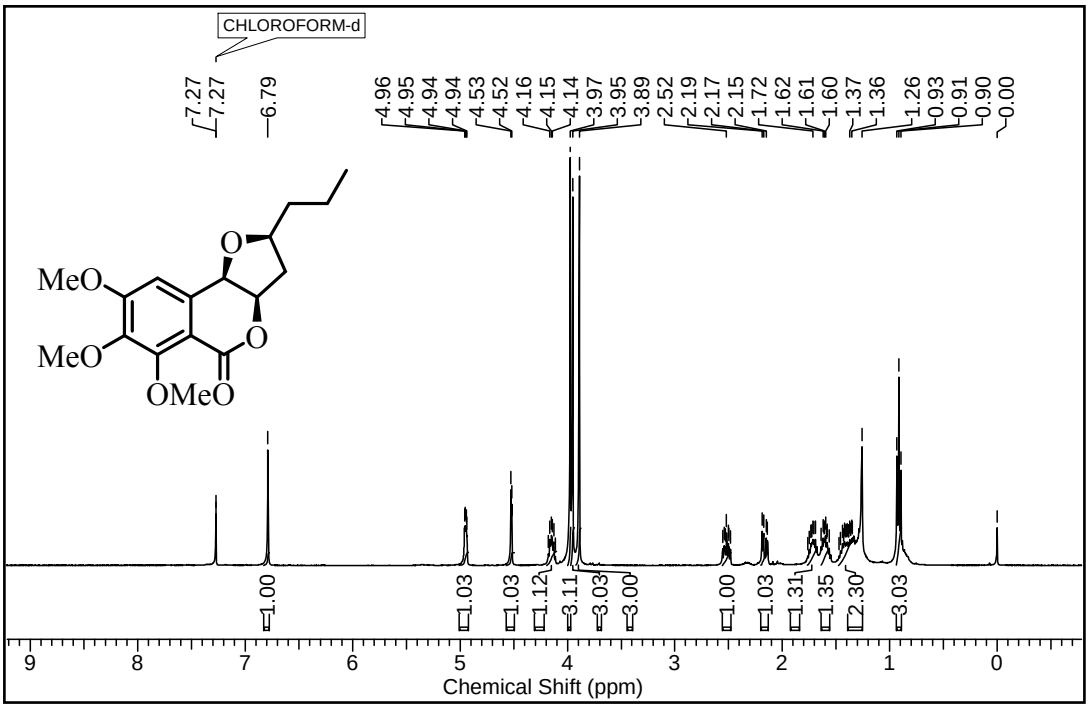


➢ **^{1}H NMR of the compound 28 in $CDCl_3$**

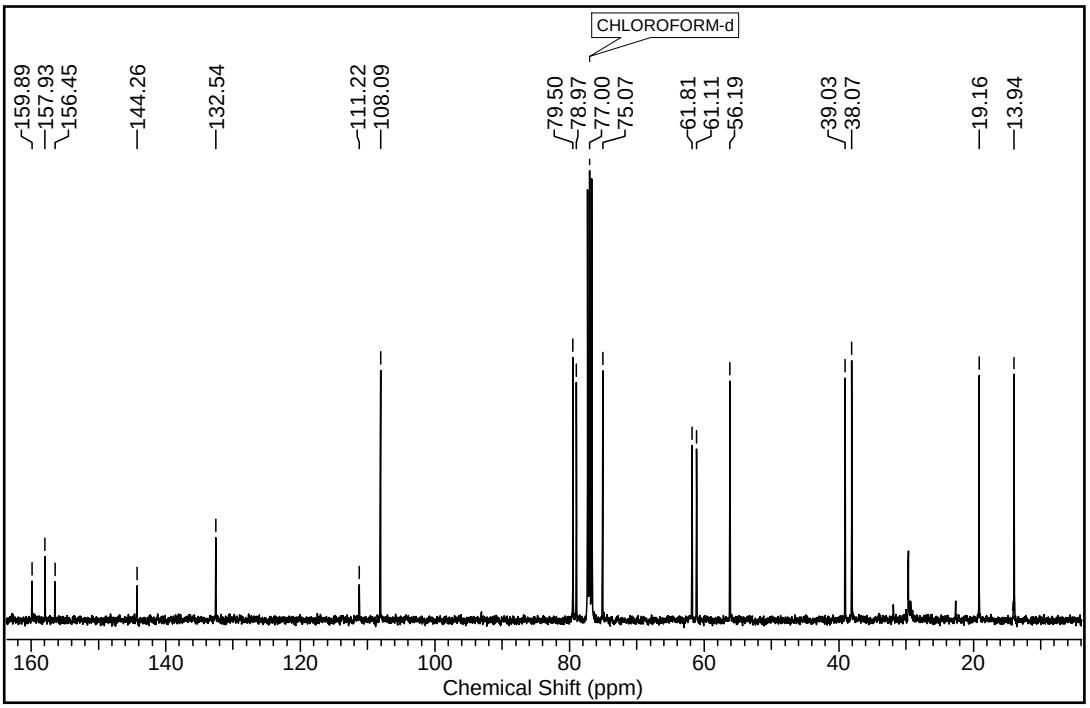


➢ **^{13}C NMR of the compound 28 in $CDCl_3$**

(2*S*,3a*R*,9b*R*)-6,7,8-Trimethoxy-2-propyl-2,3,3a,9b-tetrahydro-5*H*-furo[3,2-c]isochromen-5-one 42:

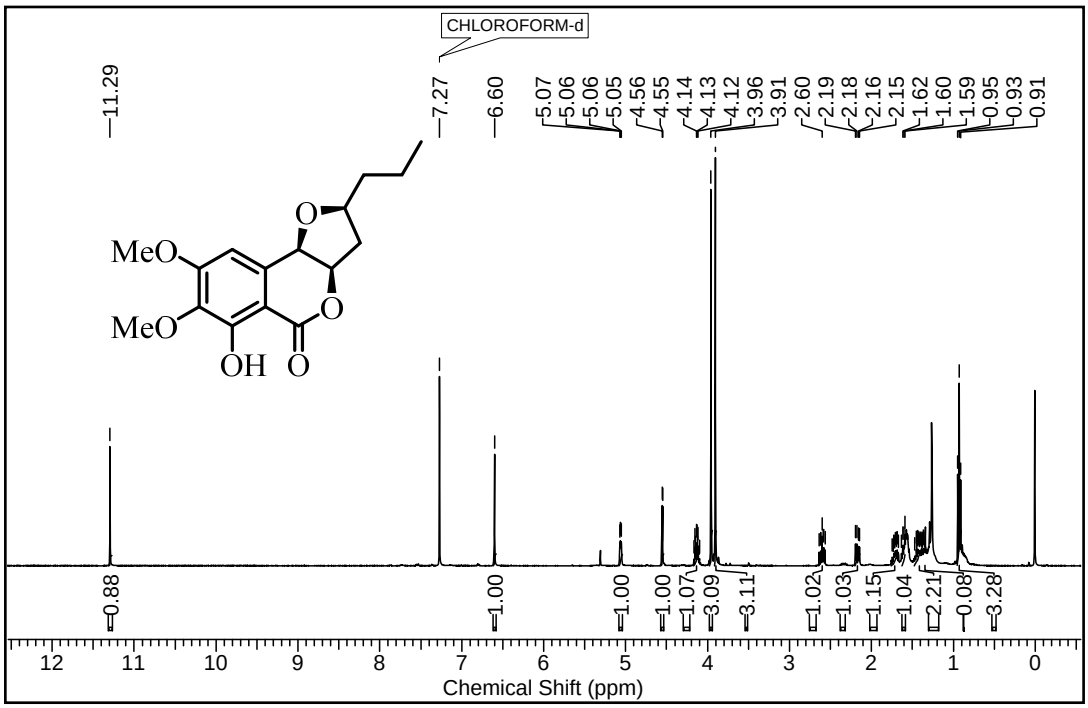


➢ **^{1}H NMR of the compound 42 in $CDCl_3$**

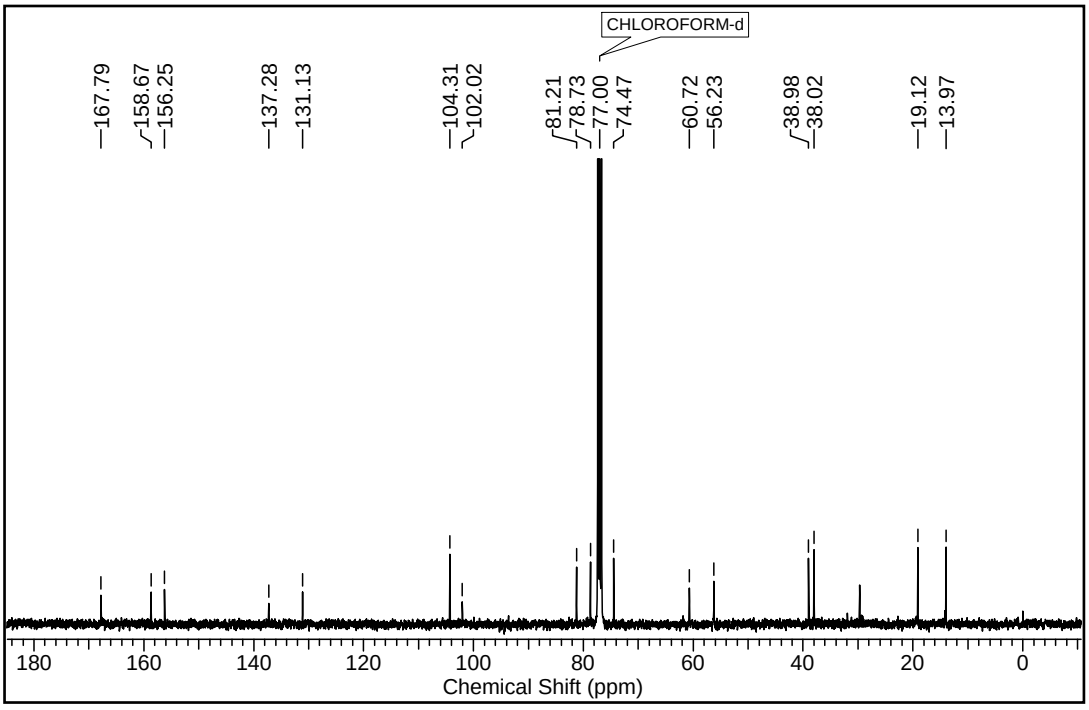


➢ **^{13}C NMR of the compound 42 in $CDCl_3$**

(2*S*,3a*R*,9b*R*)-6-Hydroxy-7,8-dimethoxy-2-propyl-2,3,3a,9b-tetrahydro-5*H*-furo[3,2-c]isochromen-5-one 1:

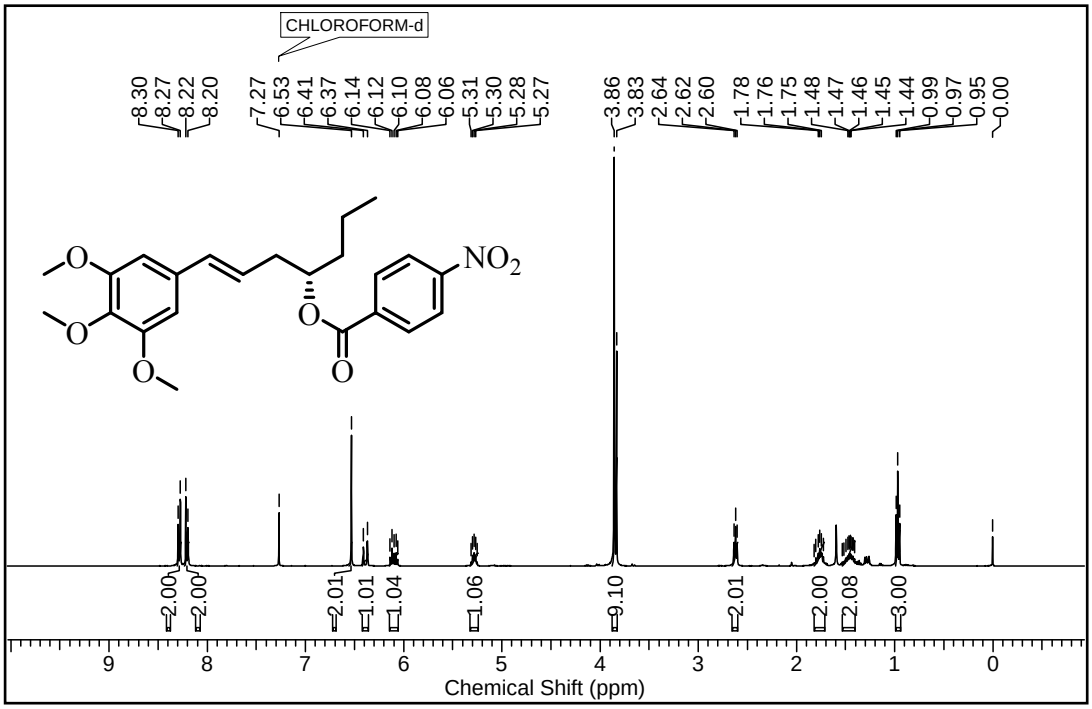


➢ **^{1}H NMR of the compound 1 in $CDCl_3$**

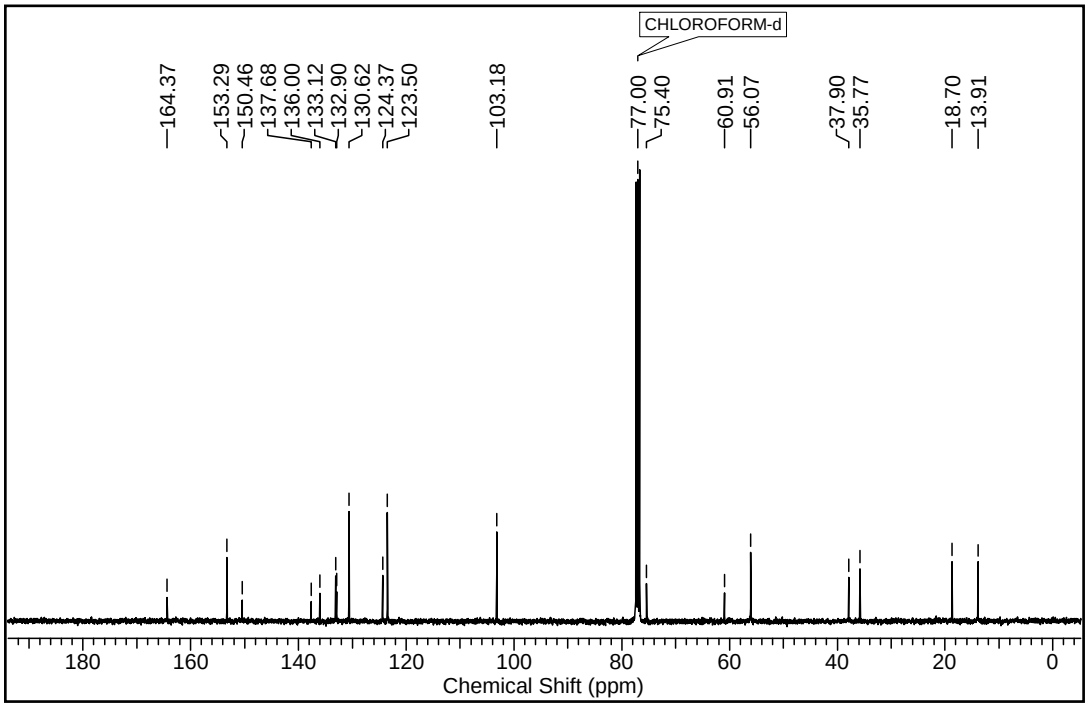


➢ **^{13}C NMR of the compound 1 in $CDCl_3$**

(*S*,*E*)-1-(3,4,5-Trimethoxyphenyl)hept-1-en-4-yl 4-nitrobenzoate 44:

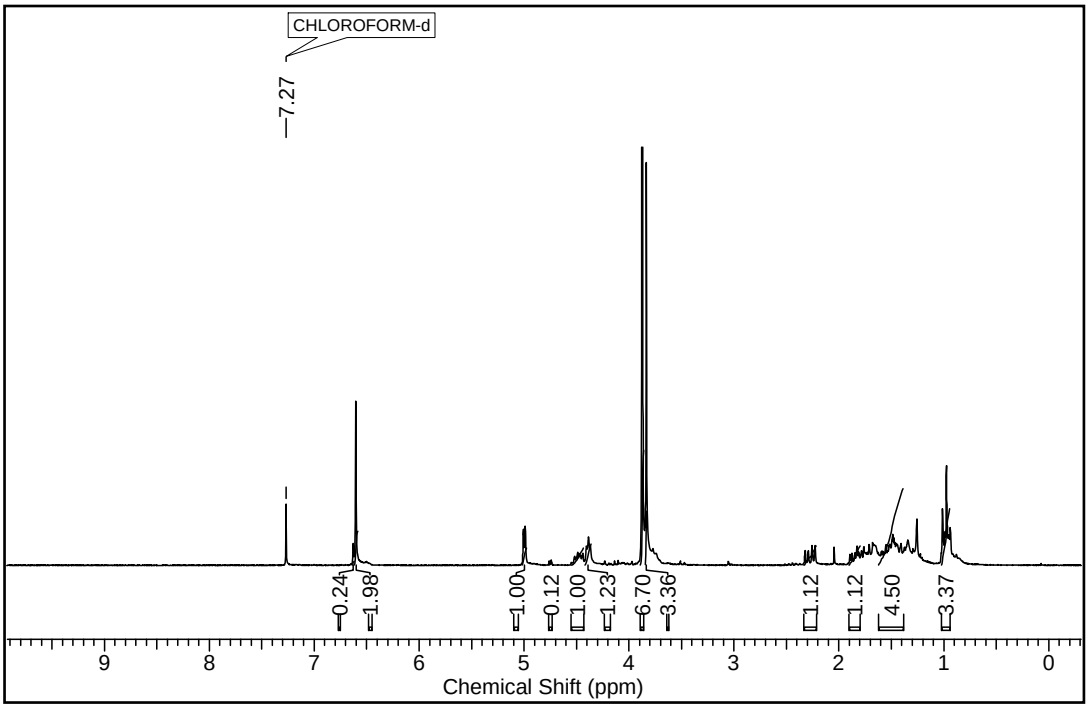


➢ **^{1}H NMR of the compound 44 in $CDCl_3$**

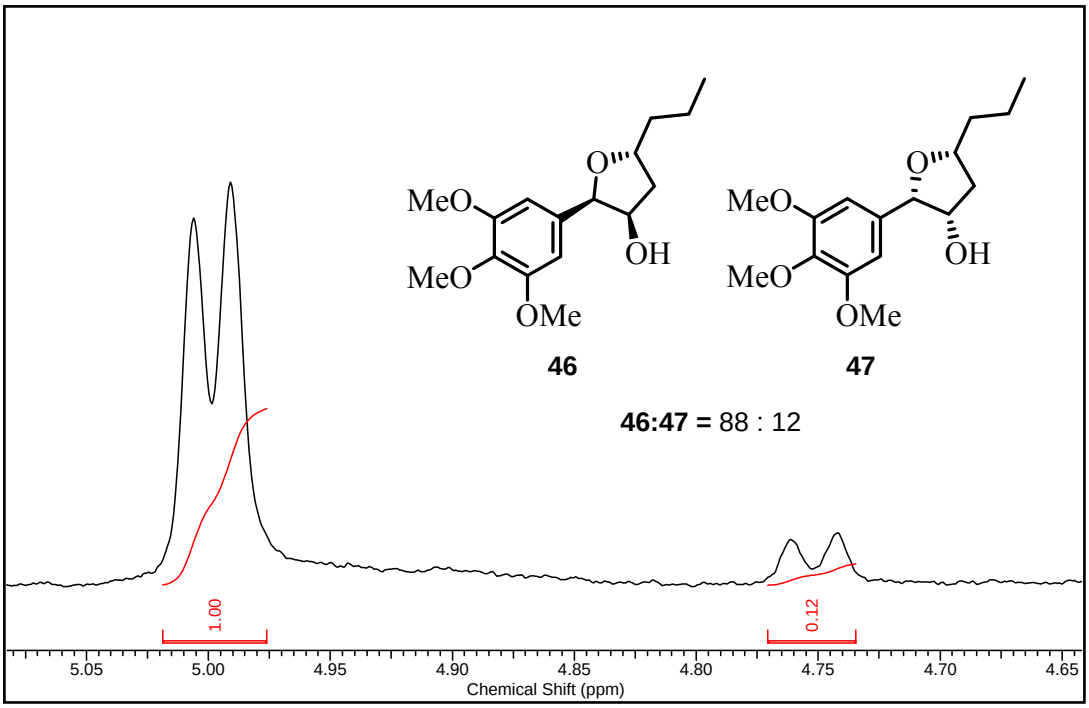


➢ **^{13}C NMR of the compound 44 in $CDCl_3$**

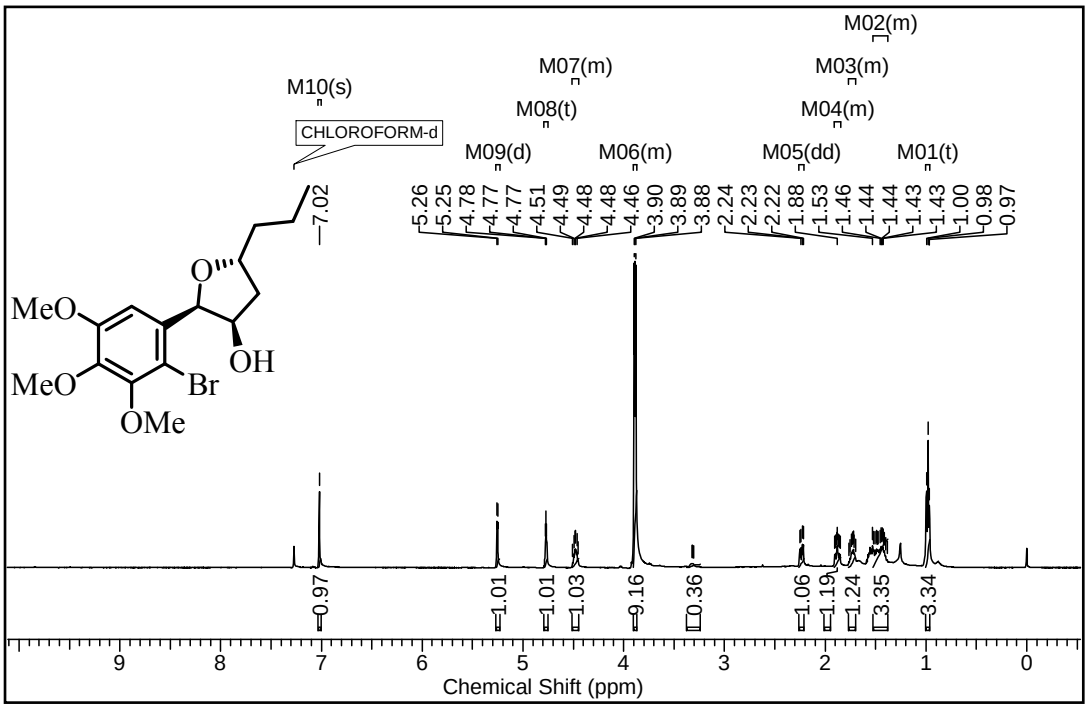
(2*R*,3*R*,5*R*)-5-Propyl-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-ol 46:



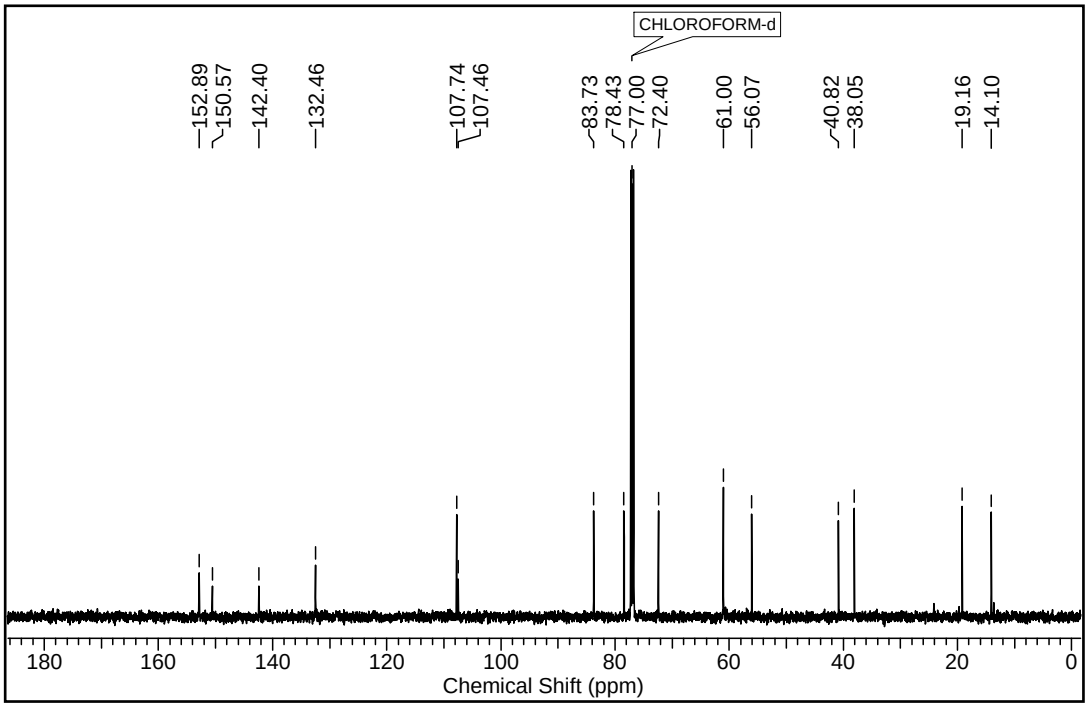
➢ **^{1}H NMR of the compound 46 in $CDCl_3$**



(2*R*,3*R*,5*R*)-2-(2-Bromo-3,4,5-trimethoxyphenyl)-5-propyltetrahydrofuran-3-ol 48:

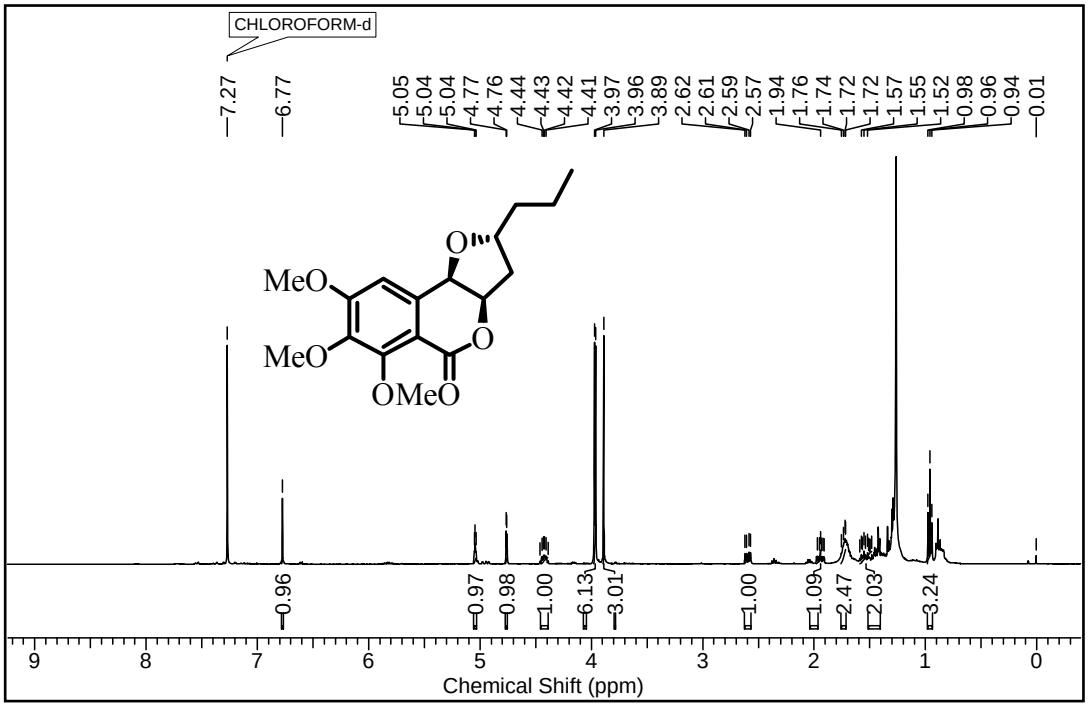


➢ **^{1}H NMR of the compound 48 in $CDCl_3$**

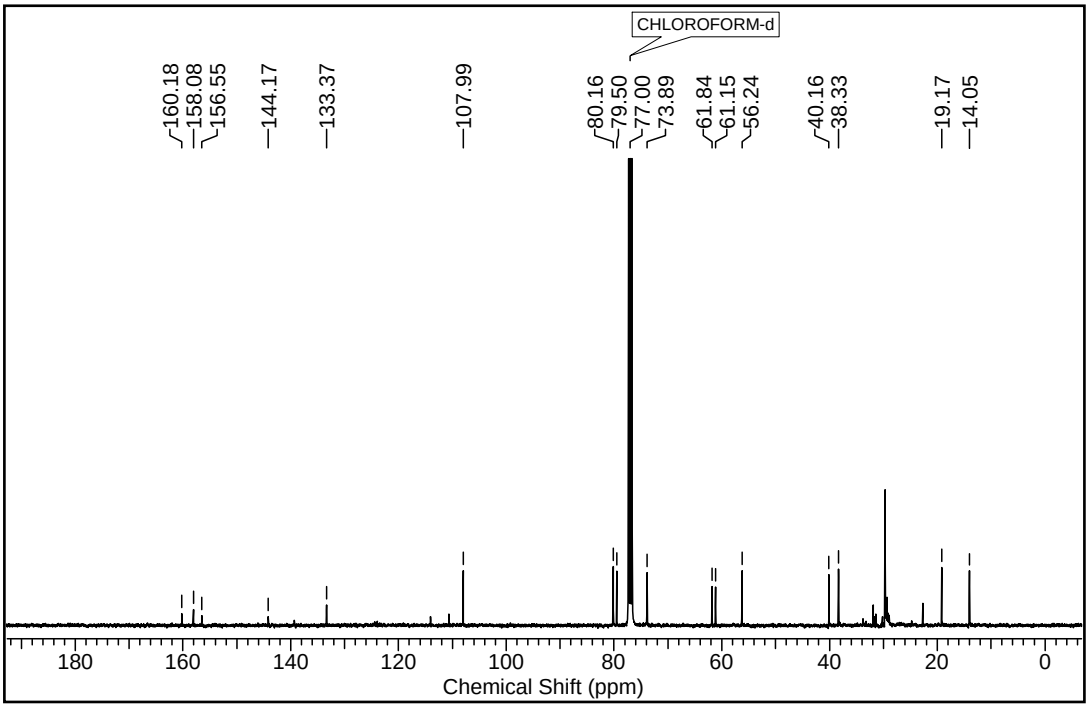


➢ **^{13}C NMR of the compound 48 in $CDCl_3$**

(2*R*,3a*R*,9b*R*)-6,7,8-Trimethoxy-2-propyl-2,3,3a,9b-tetrahydro-5*H*-furo[3,2-c]isochromen-5-one 50:

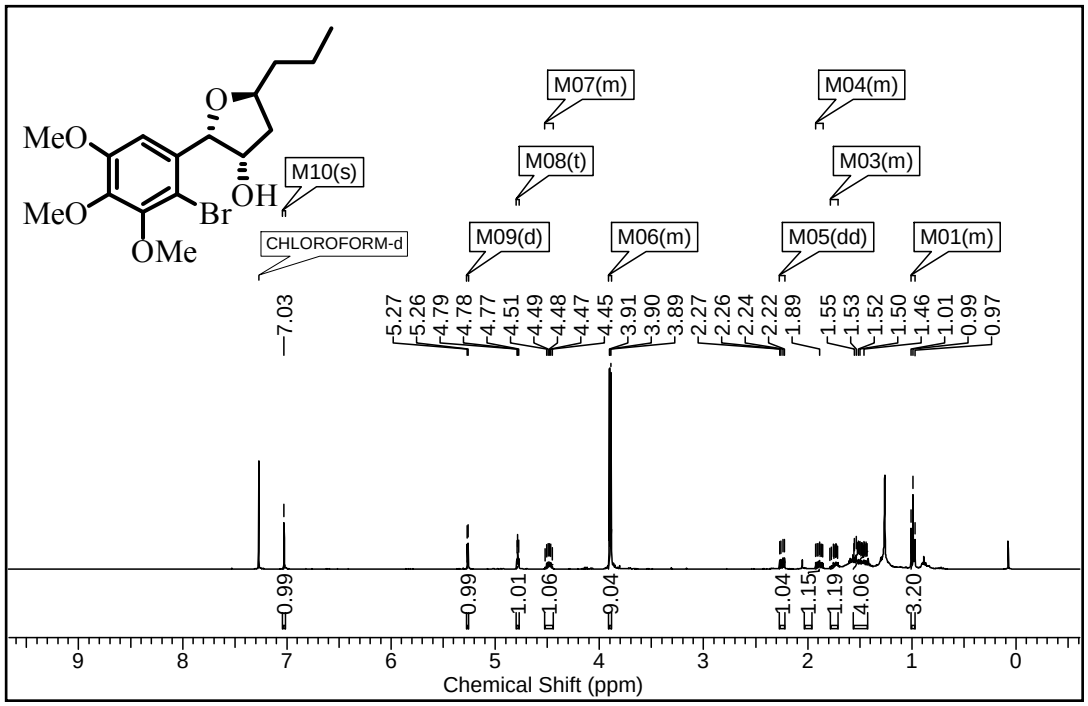


➢ **^{1}H NMR of the compound 50 in $CDCl_3$**

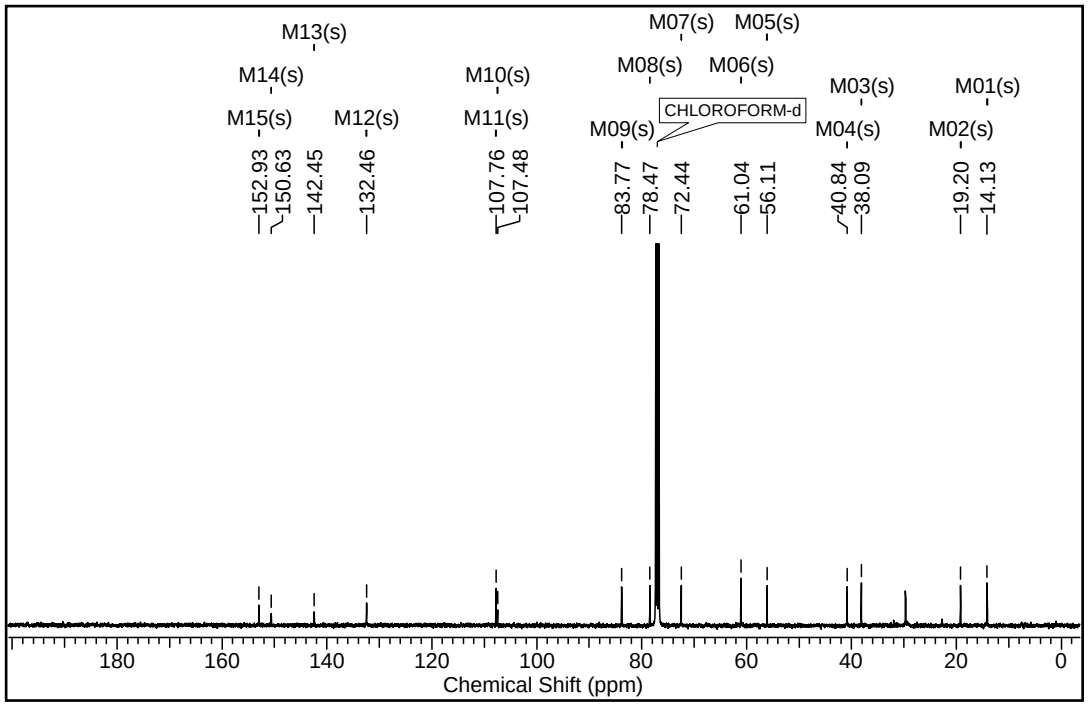


➢ **^{13}C NMR of the compound 50 in $CDCl_3$**

(2*S*,3*S*,5*S*)-2-(2-Bromo-3,4,5-trimethoxyphenyl)-5-propyltetrahydrofuran-3-ol 41:

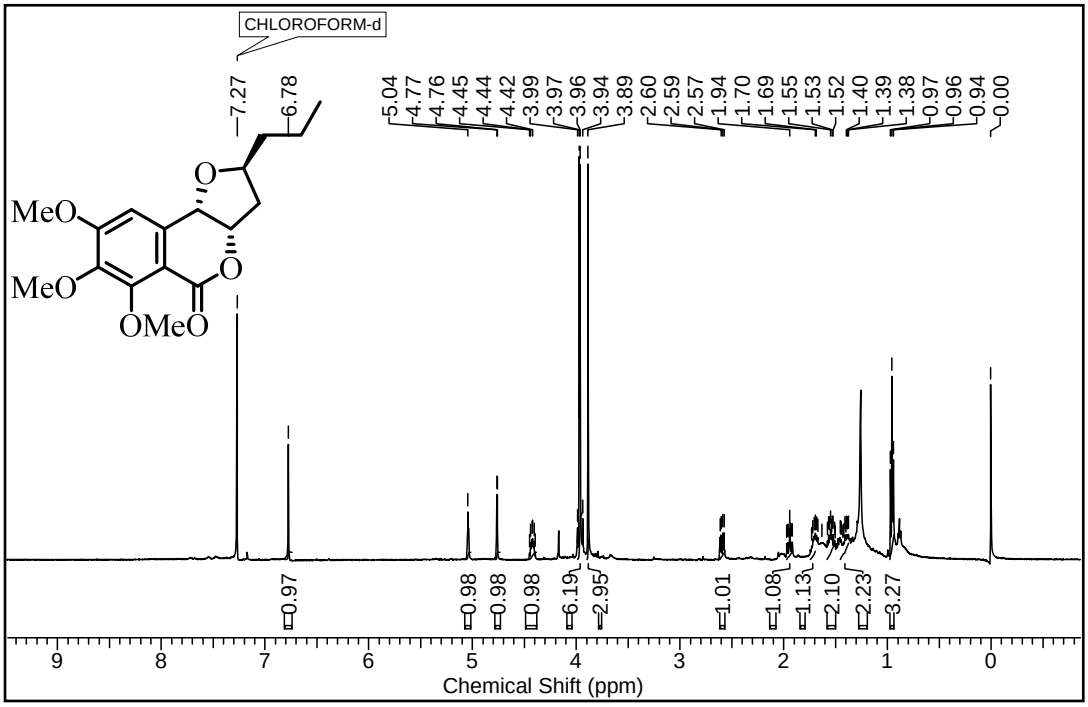


➢ **^{1}H NMR of the compound 41 in $CDCl_3$**

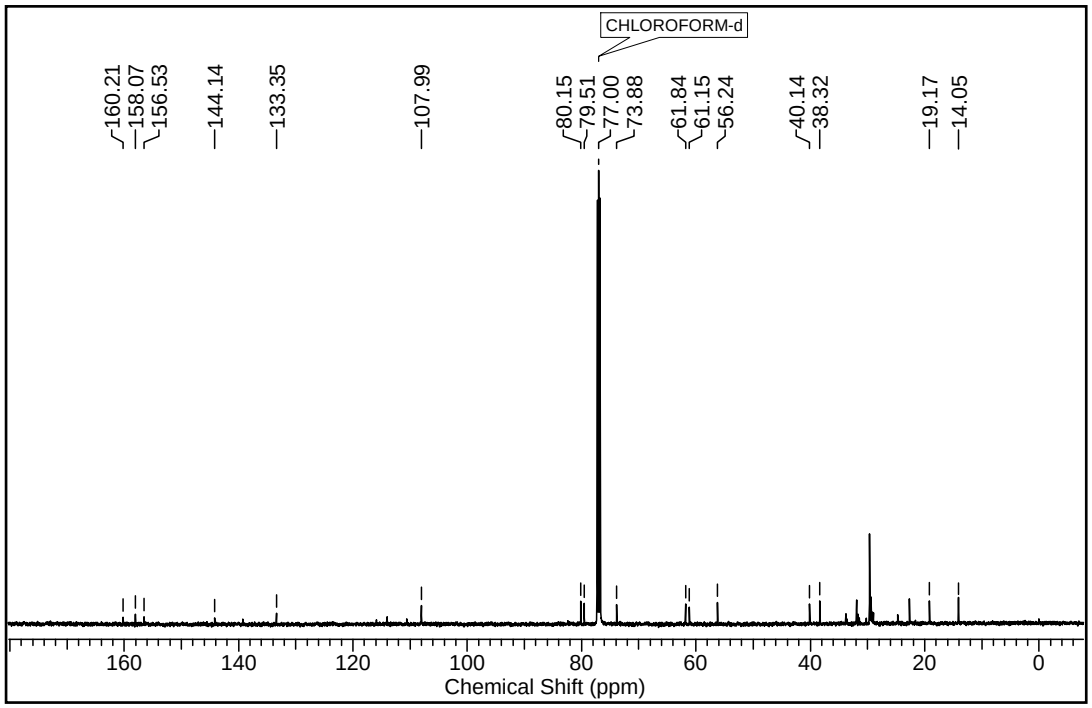


➢ **^{13}C NMR of the compound 41 in $CDCl_3$**

(2*S*,3a*S*,9b*S*)-6,7,8-Trimethoxy-2-propyl-2,3,3a,9b-tetrahydro-5*H*-furo[3,2-c]isochromen-5-one 43:



➢ **^{1}H NMR of the compound 43 in $CDCl_3$**



➢ **^{13}C NMR of the compound 43 in $CDCl_3$**

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3.2. SECTION B

Studies towards the Synthesis of 11-Hydroxy Monocerin

3.2.1. Introduction

Monocerin[1] and their analogues were isolated from several fungal species and were known to possess various biological activities like antifungal, phytotoxic, plant pathogenic and insecticidal activity.[2-4] They becomes attractive targets due to their structural features like- 4-oxyisochroman-1-one skeleton and a 2,3,5-trisubstituted tetrahydrofuran with all-*cis* stereochemistry along with broad biological activities especially, anti-malarial activity with IC_{50} value 0.68 µM against the multidrug-resistant K1 strain of *Plasmodium Falciparum.*[5] Recently, 11-hydroxy monocerin was isolated[5] along with the known monocerin **1** and 12-hydroxy monocerin **(3**, **4**) from EtOAc extract of the culture *Exserohilum rostratum*, a fungal strain endophytic in the leaves of a *stemona sp.* Monocerin and 11-hydroxy monocerin showed biological activity against antiplasmodial activity (IC_{50} values of 0.68 and 7.70 µM, respectively) but none of them showed cytotoxic activities.[5]

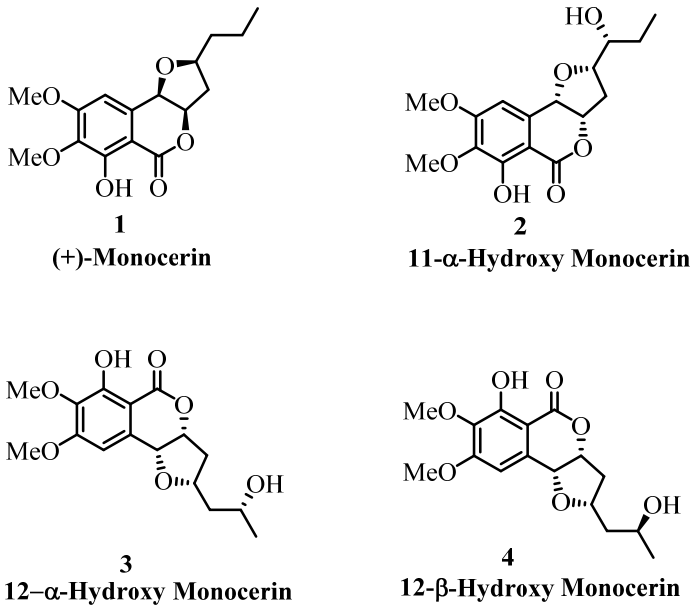


Figure 1: Monocerin family

11-Hydroxy monocerin was isolated as a white solid and its structure was confirmed by 2D NMR experiments. The absolute configuration of 11-hydroxy monocerin was confirmed by modified Mosher method.[6]

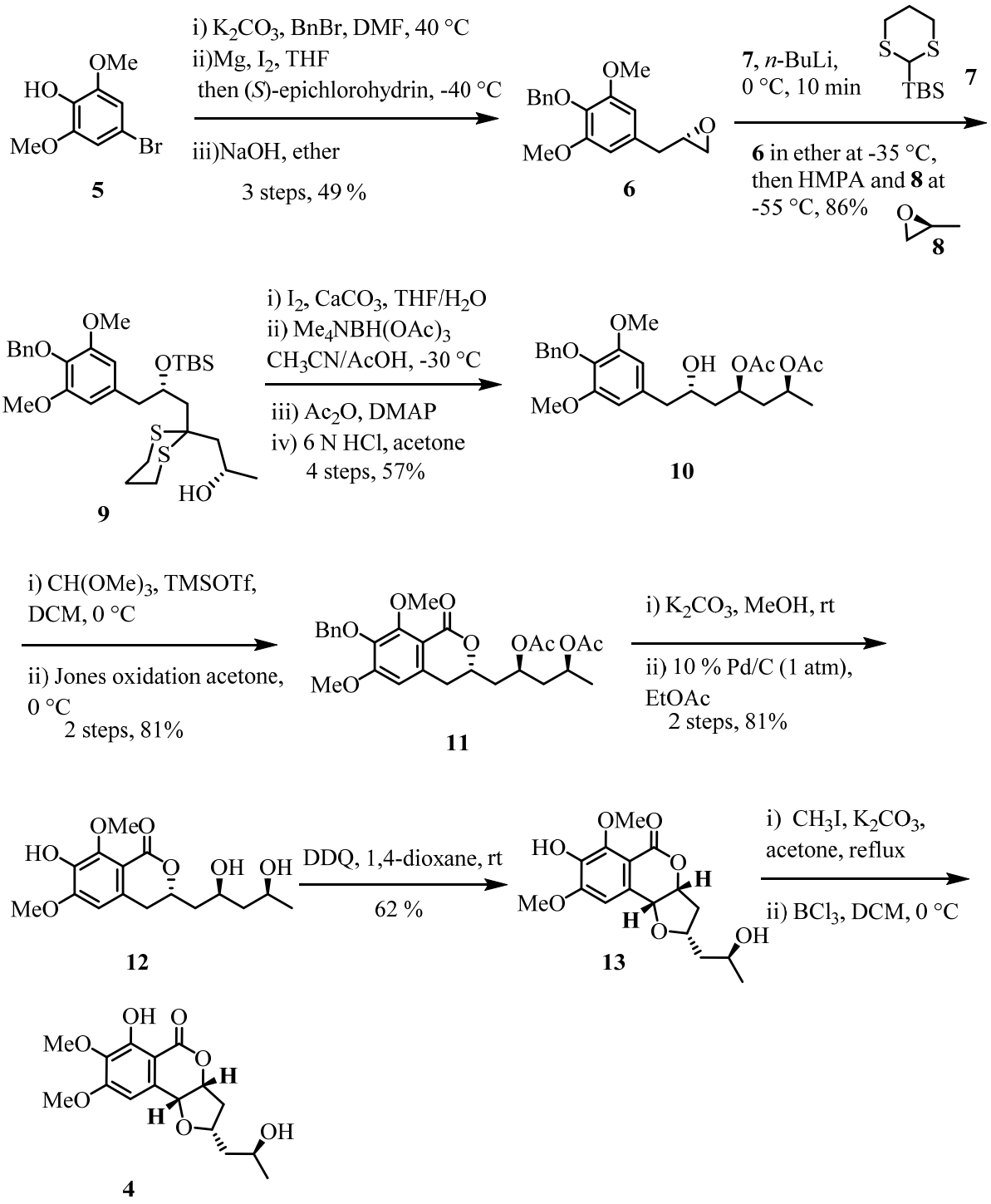
3.2.2. Review of Literature

Though there is no synthesis of 11-hydroxy monocerin reported in literature, but the synthesis of its close analogue 12-hydroxy monocerin has been described. The detailed report is discussed below.

Synthesis of 12-hydroxy monocerin:

Fang and co-workers [7]

The synthesis of (12*S*)-12-hydroxymonocerin **4** commenced from the known 4-bromo-2,6-dimethoxyphenol **5.** The compound **5** was protected as its benzyl ether followed by its Grignard reaction with epichlohydrin and subsequent epoxide ring opening and closing of chloro hydrin under basic medium to give eventually the benzylic epoxide **6.** The epoxide **6** was subjected to three-component Linchpin coupling using *tert*-butyl(1,3-dithian-2-yl)dimethylsilane **7** with (*S*)-2-methyloxirane **8** and epoxide **6** to afford β-hydroxydithiane **9.** Compound **9** was subjected to dithiane removal followed by *syn*-diastereoselective reduction to afford the β-hydroxyketone, which upon acetate protection followed by desilylation gave the bis-acetate **10.** The bis-acetate **10** was subjected to oxa-Pictet-Spengler reaction to give the cylic acetal which on Jones oxidation gave δ-valerolactone **11.** Removal of acetate group was achieved under basic medium followed by debenzylation under hydrogenolysis to afford the phenol **12. 12** was oxidized using DDQ to give the *cis*-fused furobenzopyranone **13** *via* an intramolecular nucleophilic trapping of a quinonemethide intermediate. Furobenzopyranone **13** was subjected to O-methylation followed by selective demethylation to give the target molecule **4**.



Scheme 1: Total synthesis of 12-hydroxy monocerin

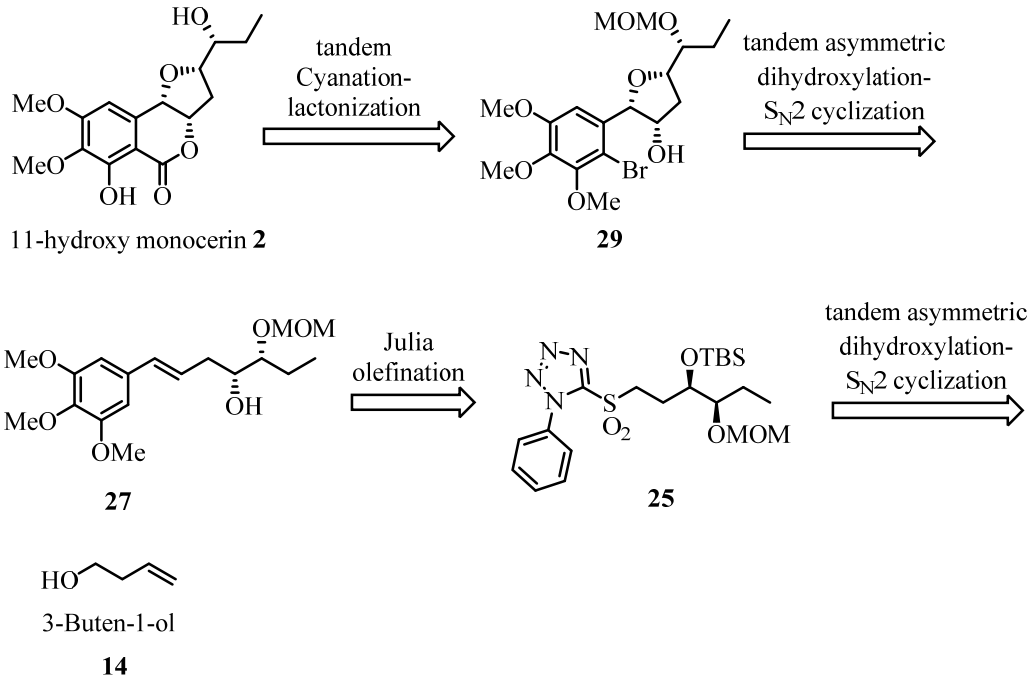
3.2.3. Present work

Objective

As a part of our research program in the synthesis of polyketides and related compounds, we aimed at developing an efficient strategy for the synthesis of 11-hydroxy monocerin. The results are discussed below.

3.2.4. Results and discussion

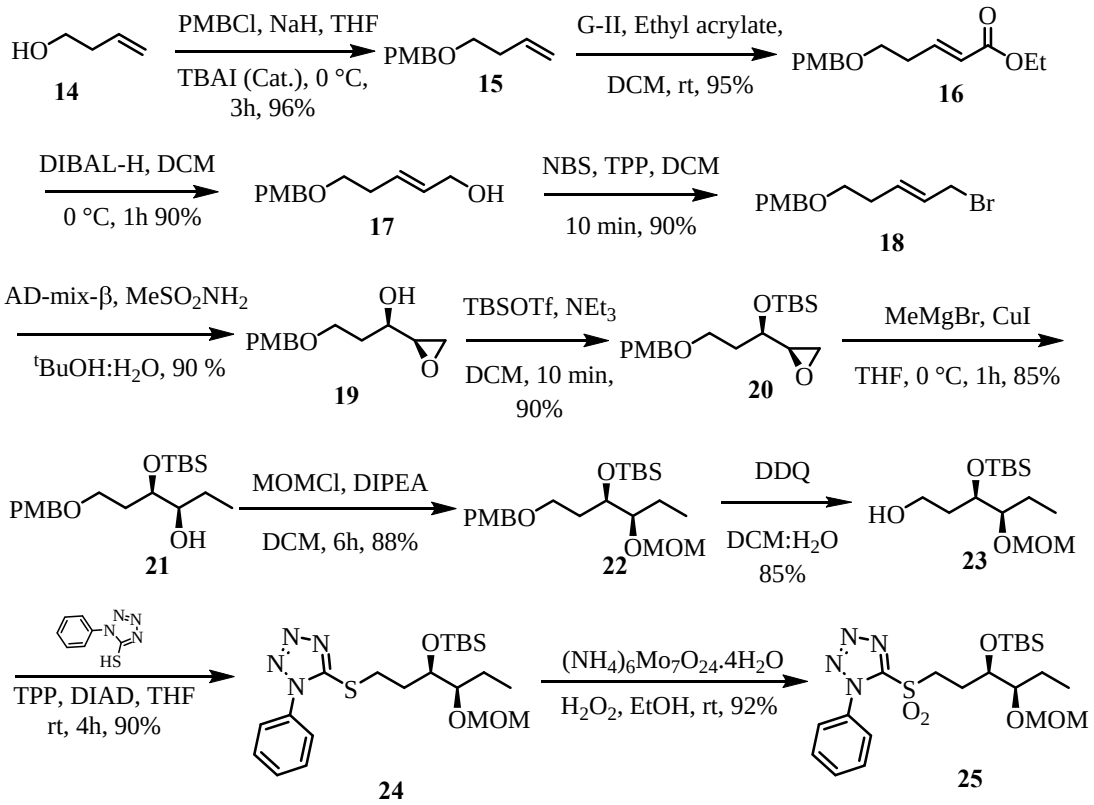
Retrosynthetic analysis of 11-hydroxy monocerin is shown in **Scheme 2**. We envisioned that the target molecule **2** could be prepared by tandem cyanation-cyclization of a substituted tetrahydrofuran alcohol **29** which could be derived *via* tandem Sharpless asymmetric dihydroxylation-S_N2 cyclization of olefin **27**. The olefin **27** could be prepared by Julia–Kocienski olefination reaction between trimethoxy benzaldehyde and sulfone **25.** Compound **25** in turn could be derived from commercially available 3-buten-1-ol.



Scheme 2: Retrosynthetic analysis of 11-hydroxy monocerin

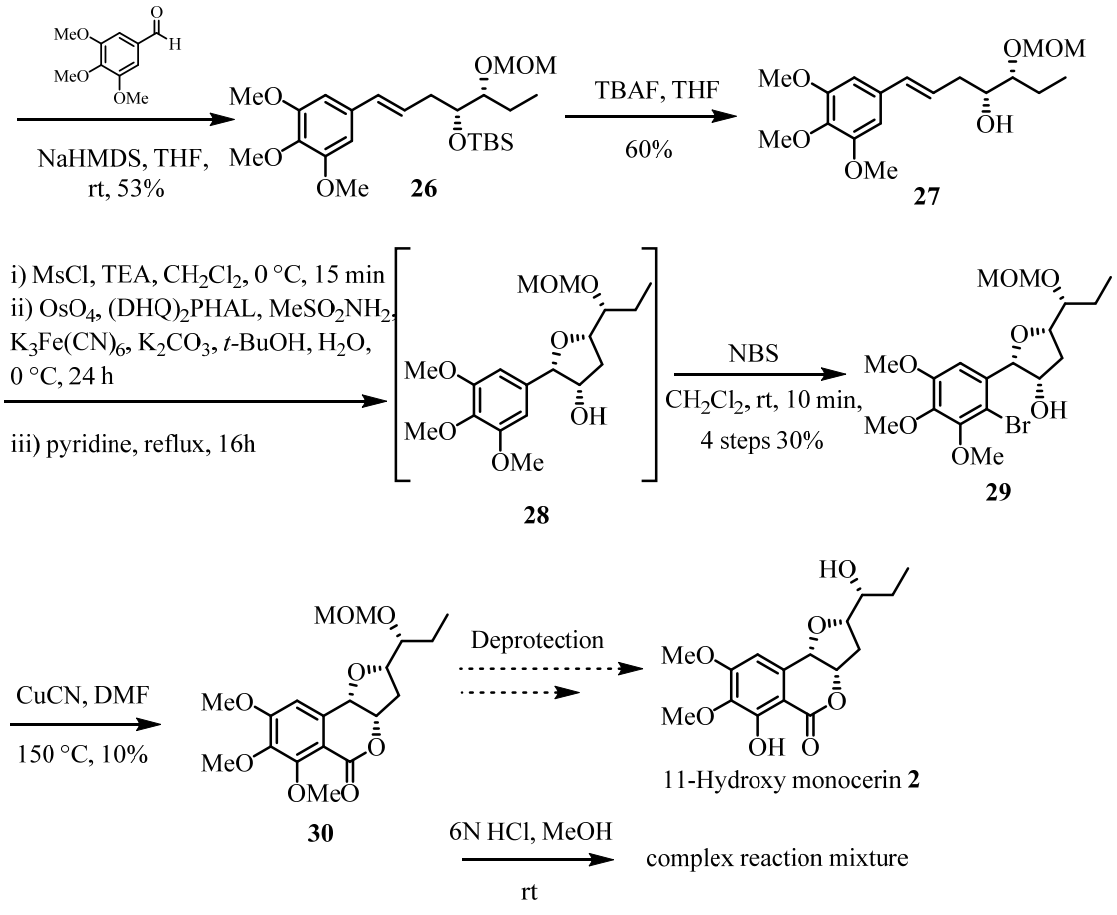
Synthesis of 11-hydroxy monocerin started from 3-buten-1-ol **14 (Scheme 3)**, which was protected as its PMB ether using PMBCl and NaH to give the PMB ether **15**. PMB ether **15**

was subjected to cross metathesis reaction with ethyl acrylate to yield the α,β-unsaturated ester **16**. The IR spectrum of **16** shows the ester carbonyl absorption at 1735 cm^{-1}. The ^{1}H NMR shows the peaks at δ 7.07 - 6.91 (m, 1 H), 5.89 (td, *J* = 1.5, 15.7 Hz, 1 H) and carbonyl peak at δ 166.4 in ^{13}C NMR further confirming the presence of ester. Now the ester **16** was reduced using DIBAL-H to afford the alcohol **17**. The IR spectrum of **17** shows the alcohol absorption at 3430 cm^{-1}. The allylic alcohol **17** was subjected to bromination using NBS and TPP to yield the allyl bromide **18**. The IR spectrum of **18** shows the absence of alcohol absorption. Allyl bromide **18** was subjected to tandem dihydroxylation-S_N2 cyclization[9,10] reaction using AD-mix-*β* to afford the epoxy alcohol **19** as a single diastereomer. The IR spectrum of **19** shows the alcohol absorption at 3420 cm^{-1}. The ^{1}H NMR of **19** shows the peaks at δ 2.83 - 2.78 (m, 1 H), 2.77 - 2.73 (m, 1 H), 2.68 (d, *J* = 4.9 Hz, 1 H) confirming the presence of epoxide.



Scheme 3: Preparation of sulfone fragment **25**

The epoxy alcohol **19** was protected using TBSOTf and Et_3N to afford the TBS ether **20**. The IR spectrum of **20** shows the absence of alcohol absorption. The TBS ether **20** was subjected to epoxide ring opening[8,9] reaction with methyl Grignard to give the alcohol **21**. The IR spectrum of **21** shows the alcohol absorption at 3425 cm^{-1}. The ^1H NMR of **21** shows the peaks at δ 1.53 - 1.40 (m, 2 H), 0.96 (t, *J* = 7.3 Hz, 3 H) corresponding to the -CH_2CH_3 protons. The alcohol **21** was protected as its MOM ether using MOMCl followed by *p*-methoxy benzyl deprotection using DDQ to give the alcohol **23**. The IR spectrum of **23** shows the alcohol absorption at 3433 cm^{-1}. The alcohol **23** was subjected to Mitsunobu reaction using TPP, DIAD and *N*-phenyl-1*H*-tetrazole-1-thiol to afford the sufide **24**. The IR spectrum of **24** shows the absence of alcohol absorption. The ^1H NMR of **24** shows peaks at δ 3.55 - 3.49 (m, 1 H), 3.45 - 3.39 (m, 1 H) corresponding to –S-CH_2 protons.



Scheme 4: Attempted synthesis of 11-hydroxy monocerin **2**

The sufide **24** was readily oxidized to sulfone **25** using ammonium heptamolybdate and hydrogen peroxide to give the sulfone **25**.[11] The ^{1}H NMR of **25** shows peaks at δ 3.74 (m, 2 H) corresponding to $–SO_2$-CH_2 protons. Now stage was set for Julia olefination[12] reaction to get the *E*-olefin, accordingly sulfone **25** was treated with 3,4,5-trimethoxy benzaldehyde under basic conditions leading to the *E*-olefin **26** albeit in (53%) moderate yield. The ^{1}H NMR of **26** shows peaks at δ 6.34 (d, *J* = 15.9 Hz, 1 H), 6.22 - 6.15 (m, 1 H) corresponding to *trans*-olfin protons. Desilylation of **26** was achieved using TBAF to give the homoallylic alcohol **27** in 60% yield (**Scheme 4)**. The IR spectrum of **27** shows the alcohol absorption at 3410 cm^{-1}.

With substantial amounts of homoallylic alcohol **27** in hand, the stage was set to employ the Marshall,'s protocol,[9] as the key step for the construction of the required THF ring. Accordingly the compound **27** was mesylated using MsCl and triethyl amine and subjected to dihydroxylation reaction using AD-mix-α, but the reaction did not work under normal conditions. Then we decided to optimize the dihydroxylation reaction using osmium tetraoxide and ligands. Initially we carried out the reaction using 1 mol% ligand $(DHQ)_2$PHAL and 0.4 mol% OsO_4, but reaction did not work even after prolonging the reaction time. Then we thought of increasing the amount of OsO_4 to 5 mol% and to our delight reaction was completed (SM was completely consumed) to give the more diol along with trace amounts of cyclized compound. So the crude diol was subjected to cyclization reaction with pyridine under reflux conditions leading to the THF alcohol **28** albeit in low yield (40%) only. Like monocerin, this step did not work efficiently in this case. The crude THF alcohol **28** was carried forward without any characterization and subjected for mono bromination using NBS to yield the mono brominated THF alcohol **29** as a single isomer (80% yield). The ^{1}H NMR of **29** shows peaks at δ = 6.99 (s, 1 H) suggesting monobromination.

We further proceeded with the aim to construct the lactone ring by the cyclization reaction, accordingly compound **29** was treated with CuCN and DMF[13] under reflux conditions to yield the valero-lactone **30** albeit in very low yield (10%) and rest of the material was either

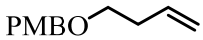
a decomposed or complex reaction mixture. The IR spectrum of **30** shows the ester carbonyl absorption at 1718 cm^{-1}. Carbonyl peak at δ 164.7 in ^{13}C NMR further confirmed the presence of cyclic ester. Further we tried to deprotect the MOM ether using 6N HCl but unfortunately we ended up with complex reaction mixture. The present strategy gives an access to the synthesis of core structures of 11-hydroxy monocerin and related analogues. Further work is in progress to optimize these conditions and improve the yield.

3.2.5. Conclusion

In conclusion we attempted at the synthesis of 11-hydroxy monocerin and were successful to get it in its protected form. The route optimized for monocerin was not suitable for the synthesis of 11-hydroxy monocerin due to poor yields in the key steps. A suitable convergent, high yielding strategy for the synthesis of this class of polyketides is still desirable.

3.2.6. Experimental Section

1-((But-3-en-1-yloxy)methyl)-4-methoxybenzene 15:



To a stirred solution of but-3-en-1-ol **14** (5.0 g, 69.33 mmol) in THF (100 mL) was added NaH (4.0 g, 90.14 mmol) at 0 °C and this was stirred well for 20 min at rt. Then PMBCl (11.8 ml, 83.22 mmol) was added to the reaction mixture at 0 °C, followed by addition of TBAI (2.5 g, 6.9 mmol), and this was stirred at rt for 3 h. The reaction mixture was quenched with ice water and extracted with EtOAc (3 × 50 mL). The extract was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether–EtOAc (91:9) as the eluent provided the PMB protected compound **15** as a colourless liquid.

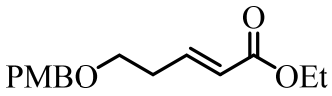
Yield: 12.8 g, 96%

Mol. Formula: $C_{12}H_{16}O_2$

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36–7.25 (m, 2 H), 6.97–6.85 (m, 2 H), 5.86 (tdd, *J* = 6.7, 10.3, 17.1 Hz, 1 H), 5.20–5.01 (m, 2 H), 4.48 (s, 2 H), 3.83 (s, 3 H), 3.52 (t, *J* = 6.8 Hz, 2 H), 2.39 (tq, *J* = 1.3, 6.7 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 135.3, 130.5, 129.2, 116.3, 113.7, 72.5, 69.3, 55.2, 34.2

Ethyl (*E*)-5-((4-methoxybenzyl)oxy)pent-2-enoate 16:



To a stirred solution of **15** (5.0 g, 26.0 mmol) in CH_2Cl_2 (50 mL) was added compound ethyl acrylate (13.85 mL, 130.0 mmol) and degassed for 10 min. Then Grubb's II catalyst (221 mg, 1 mol %) was added to the reaction mixture and stirred for 1h at rt. After completion of reaction, solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (EtOAc–pet ether, 16:85) to afford compound **16** as yellow colour oil.

Yield: 6.5 g, 95%

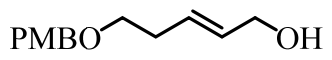
Mol. Formula: $C_{15}H_{20}O_4$

^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.31 - 7.21 (m, 2 H), 7.07 - 6.91 (m, 1 H), 6.91 - 6.85 (m, 2 H), 5.89 (td, *J* = 1.5, 15.7 Hz, 1 H), 4.46 (s, 2 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 3.81 (s, 4 H), 3.56 (t, *J* = 6.6 Hz, 2 H), 2.50 (dq, *J* = 1.5, 6.6 Hz, 2 H), 1.29 (t, *J* = 7.1 Hz, 3 H)

^{13}C NMR (50MHz, $CDCl_3$) δ = 166.4, 159.1, 145.6, 130.1, 129.2, 122.8, 113.7, 72.6, 67.9, 60.1, 55.2, 32.5, 14.2

HRMS (ESI) for $C_{15}H_{20}O_4$ $(M + Na)^+$ found 287.1255, calcd 287.1253

(*E*)-5-((4-Methoxybenzyl)oxy)pent-2-en-1-ol 17:



To a solution of **16** (6 g, 22.7 mmol) in CH_2Cl_2 (100 mL), was added DIBAL-H (50 mL 1M solution in toluene, 50 mmol) at 0 °C under argon atmosphere. The reaction was stirred at

this temperature for 1 h. Then saturated solution of ammonium chloride was added. The resulting mixture was warmed to ambient temperature and was then diluted with 0.2 M aqueous HCl followed by EtOAc and organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL), the combined organic layers were dried (Na_2SO_4), filtered and evaporated under reduced pressure to give alcohol **17** as a colorless liquid.

Yield: 4.5 g, 90%

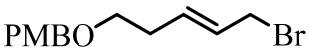
Mol. Formula: $C_{13}H_{18}O_3$

^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.33 - 7.21 (m, 3 H), 6.95 - 6.82 (m, 2 H), 5.82 - 5.61 (m, 2 H), 4.45 (s, 2 H), 4.14 - 4.06 (m, 2 H), 3.50 (t, *J* = 6.7 Hz, 2 H), 2.43 - 2.30 (m, 2 H)

^{13}C NMR (50 MHz, $CDCl_3$) δ = 159.1, 130.9, 130.3, 129.2, 113.7, 72.5, 69.2, 63.4, 55.2, 32.5

HRMS (ESI) for $C_{13}H_{18}O_3$ $(M + Na)^+$ found 245.1149, calcd 245.1148

(*E*)-1-(((5-Bromopent-3-en-1-yl)oxy)methyl)-4-methoxybenzene 18:



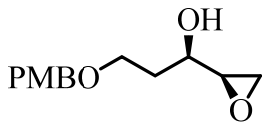
To the compound **17** (4.0, 18.0 mmol) in DCM, cooled at -15 °C, TPP (5.2 g, 19.8 mmol) was added followed by addition of freshly crystallized NBS (3.5 g, 19.8 mmol) and stirred for 10 min. The reaction mixture was quenched with hypo solution and extracted with EtOAc (3 × 20 mL). The extract was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether–EtOAc (6:94) as the eluent provided the allyl bromide compound **18** as a colorless liquid.

Yield: 4.6 g, 90%

Mol. Formula: $C_{13}H_{17}BrO_2$

^{1}H NMR (200 MHz , $CDCl_3$) δ = 7.37 - 7.18 (m, 2 H), 6.95 - 6.81 (m, 2 H), 5.95 - 5.60 (m, 2 H), 4.44 (s, 2 H), 4.06 - 3.89 (m, 2 H), 3.81 (s, 3 H), 3.49 (t, *J* = 6.6 Hz, 2 H), 2.54 - 2.27 (m, 2 H)

(*R*)-3-((4-Methoxybenzyl)oxy)-1-((*R*)-oxiran-2-yl)propan-1-ol 19:



To a solution of compound allyl bromide **18** (4.6 g, 16.2 mmol) (in ^{t}BuOH/H_2O (1:1, 100 mL) were added AD-mix-β (22.7 g, 1.4 gm/mmol) and methanesulfonamide (1.6 g, 100 mg/mmol) at 0 °C and the reaction mixture was allowed to stir for 24 h at that temperature. The reaction was quenched by addition of Na_2SO_3 (23 g, 1.48 mg/mmol) and stirred for 1 h at room temperature until it became colourless. EtOAc was used for extraction and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to get the crude product which was purified by silica gel column chromatography using petroleum ether:EtOAc, (75:25) as eluent to furnish **19** as a colourless oil

Yield: 3.66 g, 95%

Mol. Formula: $C_{13}H_{18}O_4$

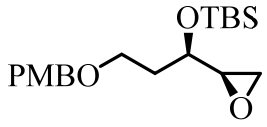
$[\alpha]_D^{24.1}$: - 10.3° (*c* 1.5, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (s, 3 H), 6.91 (d, *J* = 8.3 Hz, 2 H), 4.53 - 4.44 (m, 2 H), 3.84 (s, 4 H), 3.79 - 3.63 (m, 4 H), 3.06 - 3.01 (m, 1 H), 2.83 - 2.78 (m, 1 H), 2.77 - 2.73 (m, 1 H), 2.68 (d, *J* = 4.9 Hz, 1 H), 1.92 (q, *J* = 5.9 Hz, 2 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.3, 130.0, 129.3, 113.9, 113.8, 77.3, 76.7, 72.9, 70.0, 67.3, 55.3, 55.1, 44.5, 33.8

HRMS (ESI) for $C_{13}H_{18}O_4$ $(M + Na)^+$ found 261.1097, calcd 261.1097

T*ert*-butyl((*R*)-3-((4-methoxybenzyl)oxy)-1-((*R*)-oxiran-2-yl)propoxy)dimethylsilane 20:



To a stirred solution of compound **19** (3.0 g, 12.6 mmol) in CH_2Cl_2 (30.0 mL) at 0 °C was added Et_3N (3.8 mL, 27.7 mmol), followed by TBDMSOTf (3.2 mL, 13.8 mmol) and the mixture was stirred for 15 min. The reaction mixture was quenched with sat. NH_4Cl solution (20 mL) and the aqueous layer were extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the crude silyl ether as yellow oil and silica gel column chromatographic purification (petroleum ether:EtOAc, 92:8) of the crude product gave **20** as a yellow color oil.

Yield: 4.0 g, 90%

Mol. Formula: $C_{19}H_{32}O_4Si$

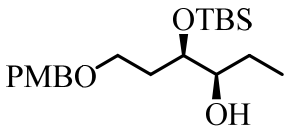
$[\alpha]_D^{24.2}$: +2.2° (*c* 1.73, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.25 (d, *J* = 8.6 Hz, 2 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 4.47 - 4.37 (m, 2 H), 3.81 (s, 4 H), 3.56 (t, *J* = 6.1 Hz, 2 H), 3.51 - 3.45 (m, 1 H), 2.97 - 2.93 (m, 1 H), 2.76 (t, *J* = 4.5 Hz, 1 H), 2.55 (dd, *J* = 2.7, 4.9 Hz, 1 H), 1.82 (q, *J* = 6.3 Hz, 2 H), 0.91 (s, 9 H), 0.13 (s, 3 H), 0.07 (s, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.2, 130.4, 129.3, 113.8, 72.7, 71.8, 65.9, 56.0, 55.3, 44.8, 34.8, 25.8, 25.8, 18.1, -4.4, -5.2

HRMS (ESI) for $C_{19}H_{32}O_4Si$ $(M + Na)^+$ found 375.1981, calcd 375.1982

(3*R*,4*R*)-4-((Tert-butyldimethylsilyl)oxy)-6-((4-methoxybenzyl)oxy)hexan-3-ol 21:



To a stirred solution of epoxide **20** (3.5 g, 9.9 mmol) and CuI (183 mg, 0.99 mmol) in dry THF (50 mL), was added, 1M solution of methyl magnesium bromide in THF (12.9 mL, 12.9 mmol, 1M solution in THF) drop-wise at 0 °C and stirred for 1 h. The mixture was quenched with a saturated NH_4Cl solution (5 mL). The layers were separated, the aqueous layer extracted with EtOAc (3 x 15 mL), the combined organic extracts were washed with

brine (2 x 10 mL), followed by 25% NH_4OH solution (10 ml) and dried over Na_2SO_4, evaporated to dryness. Silica gel column chromatographic purification (petroleum ether:EtOAc, 88:12) of the crude product gave **21** as a yellow color oil.

Yield: 3.1 g, 85%

Mol. Formula: $C_{20}H_{36}O_4Si$

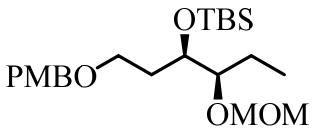
$[\alpha]_D^{24.2}$: - 2.8° (*c* 1.63, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.25 (d, *J* = 8.5 Hz, 2 H), 6.88 (d, *J* = 8.5 Hz, 2 H), 4.43 (q, *J* = 11.5 Hz, 2 H), 3.81 (s, 3 H), 3.77 - 3.72 (m, 1 H), 3.51 (dt, *J* = 3.4, 6.3 Hz, 2 H), 3.32 (td, *J* = 3.9, 7.9 Hz, 1 H), 2.40 - 2.17 (m, 1 H), 1.98 - 1.88 (m, 1 H), 1.82 - 1.74 (m, 1 H), 1.53 - 1.40 (m, 2 H), 0.96 (t, *J* = 7.3 Hz, 3 H), 0.90 (s, 9 H), 0.08 (d, *J* = 3.1 Hz, 6 H)

^{13}C NMR (125 MHz, $CDCl_3$) δ = 159.2, 130.4, 129.2, 113.8, 74.7, 72.6, 72.3, 66.2, 55.3, 34.0, 26.7, 25.9, 18.1, 10.5, -4.3, -4.6

HRMS (ESI) for $C_{20}H_{36}O_4Si$ $(M + Na)^+$ found 391.2274, calcd 391.2275

(5*R*,6*R*)-5-Ethyl-6-(2-((4-methoxybenzyl)oxy)ethyl)-8,8,9,9-tetramethyl-2,4,7-trioxa-8-siladecane 22:



To a solution of alcohol **21** (3.0 g, 8.1 mmol) in dry CH_2Cl_2 (30 mL) was added diisopropylethylamine (3.12 mL, 17.9 mmol) at 0 °C. To this mixture MOM chloride (0.94 ml, 12.2 mmol) was added slowly with further stirring for 2 h at the room temperature. The reaction mixture was quenched with addition of cold water at 0 °C. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water (3 x 20 mL), brine, dried over Na_2SO_4 and concentrated to give crude **22**. It was purified by silica gel column chromatography (petroleum ether:EtOAc, 90:10 as eluent) to furnish **22** as colourless oil.

Yield: 2.95 g, 88%

Mol. Formula: $C_{22}H_{40}O_5Si$

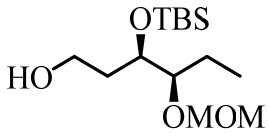
$[\alpha]_D^{24.2}$: +21.8 ° (*c* 2.27, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 - 7.23 (m, 2 H), 6.91 - 6.83 (m, 2 H), 4.69 (d, *J* = 6.8 Hz, 1 H), 4.62 (d, *J* = 6.8 Hz, 1 H), 4.47 - 4.39 (m, 2 H), 3.95 (ddd, *J* = 2.9, 4.5, 9.2 Hz, 1 H), 3.81 (s, 3 H), 3.59 - 3.47 (m, 2 H), 3.41 - 3.31 (m, 4 H), 2.00 - 1.89 (m, 1 H), 1.77 - 1.65 (m, 1 H), 1.62 - 1.55 (m, 1 H), 1.44 - 1.32 (m, 1 H), 0.97 (t, *J* = 7.3 Hz, 3 H), 0.90 - 0.85 (m, 9 H), 0.06 (d, *J* = 8.6 Hz, 6 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.0, 130.8, 129.1, 113.7, 97.0, 82.9, 72.4, 69.9, 67.0, 55.5, 55.2, 31.3, 25.8, 21.7, 18.0, 10.9, -4.5, -4.9

HRMS (ESI) for $C_{22}H_{40}O_5Si$ $(M + Na)^+$ found 435.2536, calcd 435.2537

(3*R*,4*R*)-3-((Tert-butyldimethylsilyl)oxy)-4-(methoxymethoxy)hexan-1-ol 23:



To a solution of PMB ether **22** (2.5 g, 6.06 mmol) in dry CH_2Cl_2:H_2O (38:2) mL was added DDQ (1.65 g, 7.2 mmol) at 0 °C with further stirring for 2 h at the room temperature. The reaction mixture was quenched with addition of cold water, stirred for 30 min then sat.$NaHCO_3$ solution was added, stirred for 30 min. Then reaction mixture was filtered through celite. The two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with sat.$NaHCO_3$ (2 x 15 mL), brine, dried over Na_2SO_4 and concentrated to give crude **23**. It was purified by silica gel column chromatography using petroleum ether:EtOAc, (86:14) as eluent to furnish **23** as a yellow colour oil.

Yield: 1.5 g, 85%

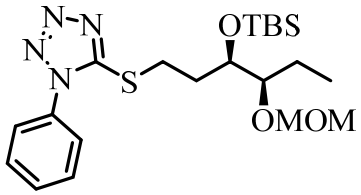
Mol. Formula: $C_{14}H_{32}O_4Si$

$[\alpha]_D^{25.1}$: +5.9° (*c* 0.8, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.75 - 4.60 (m, 2 H), 4.04 - 3.91 (m, 1 H), 3.80 - 3.67 (m, 2 H), 3.46 - 3.34 (m, 4 H), 2.11 - 1.97 (m, 1 H), 1.97 - 1.77 (m, 2 H), 1.76 - 1.68 (m, 1 H), 1.52 - 1.32 (m, 1 H), 1.03 - 0.93 (m, 3 H), 0.92 - 0.85 (m, 10 H), 0.14 - 0.06 (m, 6 H)

HRMS (ESI) for $C_{14}H_{32}O_4Si$ $(M + Na)^+$ found 315.1961, calcd 315.1962

5-(((3*R*,4*R*)-3-((Tert-butyldimethylsilyl)oxy)-4-(methoxymethoxy)hexyl)thio)-1-phenyl-1*H*-tetrazole 24:



To the solution of resulting alcohol **23** (1.4 g, 4.8 mmol) in dry THF (30 mL) were added PPh_3 (2.5 g, 9.5 mmol), 1-phenyl-1*H*-tetrazole-5-thiol (1.0 g, 5.75 mmol) and DIAD (1.9 mL, 9.5 mmol) at 0 °C and it was allowed to stir for 4 h at room temperature. THF was concentrated and directly transferred into silica gel column. It was purified by silica gel column chromatography using petroleum ether:EtOAc, (88:12) as eluent to furnish **24** as a yellow colour oil.

Yield: 1.95 g, 90%

Mol. Formula: $C_{21}H_{36}N_4O_3SSi$

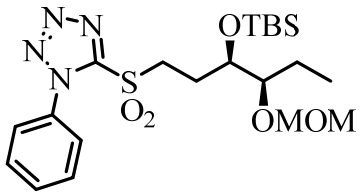
$[\alpha]_D^{24.4}$: + 25.4° (*c* 1.75, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.59 - 7.53 (m, 5 H), 4.69 - 4.60 (m, 2 H), 3.94 (ddd, *J* = 3.1, 4.4, 9.0 Hz, 1 H), 3.55 - 3.49 (m, 1 H), 3.45 - 3.39 (m, 1 H), 3.39 - 3.35 (m, 1 H), 3.34 (s, 3 H), 2.16 - 2.08 (m, 1 H), 1.87 (dtd, *J* = 5.2, 8.8, 13.8 Hz, 1 H), 1.75 - 1.67 (m, 1 H), 1.40 - 1.31 (m, 1 H), 0.96 (t, *J* = 7.5 Hz, 3 H), 0.89 (s, 9 H), 0.08 (d, *J* = 1.8 Hz, 6 H)

^{13}C NMR (125 MHz, $CDCl_3$) δ = 154.2, 133.8, 130.0, 129.7, 123.8, 97.3, 82.9, 72.0, 55.7, 30.8, 30.4, 25.8, 21.7, 18.0, 10.8, -4.4, -4.7

HRMS (ESI) for $C_{21}H_{36}N_4O_3SSi$ $(M + Na)^+$ found 475.2169, calcd 475.2170

5-(((3*R*,4*R*)-3-((Tert-butyldimethylsilyl)oxy)-4-(methoxymethoxy)hexyl)sulfonyl)-1-phenyl-1*H*-tetrazole 25:



To a solution of compound **24** (1.9 g, 4.2 mmol) in absolute EtOH (20 mL) was added $(NH_4)_6Mo_7O_{24}.4H_2O$ (2.45 g, 2.1 mmol) followed by H_2O_2 (2.8 mL, 21.0 mmol) at 0 °C and it was allowed to stir for 8 h at room temperature. The reaction mixture was quenched with addition of cold sat.Na_2SO_3 solution at 0 °C, filtered through celite. The solvent was evaporated and then the residue was extracted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to get the crude product which was purified by silica gel column chromatography using petroleum ether:EtOAc, (85:15) as eluent to furnish **25** as a light yellow colour semi solid.

Yield: 1.8 g, 92%

Mol. Formula: $C_{21}H_{36}N_4O_5SSi$

$[\alpha]_D^{24.5}$: +17.1° (*c* 1.78, $CHCl_3$)

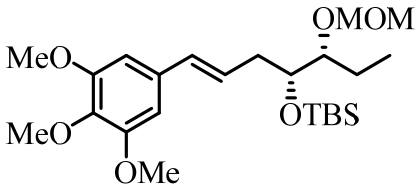
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.74 - 7.59 (m, 5 H), 4.72 - 4.60 (m, 2 H), 3.96 (td, *J* = 4.2, 8.6 Hz, 1 H), 3.90 - 3.74 (m, 2 H), 3.45 - 3.33 (m, 4 H), 2.34 - 2.16 (m, 1 H), 2.11 - 1.94 (m, 1 H), 1.78 - 1.65 (m, 1 H), 1.44 - 1.32 (m, 1 H), 0.97 (t, *J* = 7.4 Hz, 3 H), 0.92 - 0.88 (m, 9 H), 0.15 - 0.08 (m, 6 H)

^{13}C NMR (100MHz, $CDCl_3$)

δ = 153.4, 133.0, 131.4, 129.7, 125.0, 97.3, 82.7, 71.5, 55.8, 53.5, 25.7, 24.2, 21.6, 17.9, 10.7, –4.5, –4.8

HRMS (ESI) for $C_{21}H_{36}N_4O_5SSi$ $(M + H)^+$ found 507.2066, calcd 507.2068

(5*R*,6*R*)-5-Ethyl-8,8,9,9-tetramethyl-6-((*E*)-3-(3,4,5-trimethoxyphenyl)allyl)-2,4,7-trioxa-8-siladecane 26:



To a mixture of compound **25** (1.7 g, 3.5 mmol) and trimethoxybenzaldehyde (688 mg, 3.5 mmol) in dry THF (20 mL) was added NaHMDS (5.26 ml, 1M in THF, 5.26 mmol) dropwise at 0 °C and it was stirred at room temperature for 3 h. The reaction mixture was quenched with addition of sat.NH_4Cl solution. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to give crude **26**. It was purified by silica gel column chromatography using petroleum ether:EtOAc, (84:16) as eluent to furnish **26** as colourless oil (*E* only).

Yield: 0.84 g, 53%

Mol. Formula: $C_{24}H_{42}O_6Si$

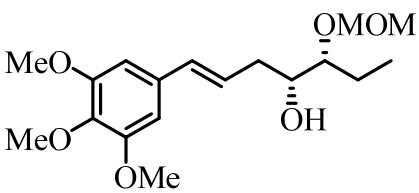
$[\alpha]_D^{24.65}$: +16.1° (*c* 1.02, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.57 (s, 2 H), 6.34 (d, *J* = 15.9 Hz, 1 H), 6.22 - 6.15 (m, 1 H), 4.74 (d, *J* = 6.7 Hz, 1 H), 4.67 (d, *J* = 7.0 Hz, 1 H), 3.88 - 3.84 (m, 10 H), 3.41 (s, 3 H), 3.40 - 3.36 (m, 1 H), 2.52 - 2.46 (m, 1 H), 2.31 - 2.23 (m, 1 H), 1.80 - 1.71 (m, 1 H), 1.48 - 1.40 (m, 1 H), 1.00 (t, *J* = 7.3 Hz, 3 H), 0.91 (s, 9 H), 0.07 (d, *J* = 5.2 Hz, 6 H)

^{13}C NMR (125 MHz, $CDCl_3$) δ = 153.3, 133.6, 131.5, 127.8, 103.0, 97.2, 83.1, 77.3, 76.7, 73.7, 60.9, 56.0, 55.6, 35.2, 25.8, 22.0, 18.1, 10.8, -4.5

HRMS (ESI) for $C_{24}H_{42}O_6Si$ $(M + Na)^+$ found 477.2644, calcd 477.2643

(4*R*,5*R*,*E*)-5-(Methoxymethoxy)-1-(3,4,5-trimethoxyphenyl)hept-1-en-4-ol 27:



To a stirred solution of **26** (0.7 g, 1.5 mmol) in THF (10 mL) was added 1.0 M TBAF in THF (3.0 mL, 3.0 mmol) at 0 °C. After being stirred for 12 h at rt, the reaction mixture was quenched with H_2O (10 mL) and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (EtOAc–hexanes, 20:80) to afford compound **27** as colourless oil.

Yield: 314 mg, 60%

Mol. Formula: $C_{18}H_{28}O_6$

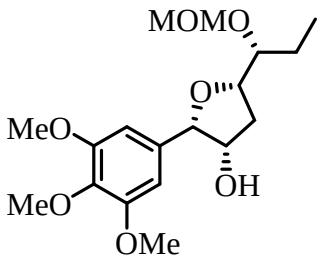
$[\alpha]_D^{25.1}$: -7.9° (*c* 0.88, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.60 (s, 2 H), 6.44 - 6.38 (m, 1 H), 6.29 - 6.20 (m, 1 H), 4.76 - 4.71 (m, 2 H), 3.90 - 3.83 (m, 10 H), 3.74 - 3.67 (m, 1 H), 3.45 (s, 3 H), 3.42 - 3.36 (m, 1 H), 2.95 - 2.76 (m, 1 H), 2.53 - 2.45 (m, 1 H), 2.41 - 2.33 (m, 1 H), 1.78 - 1.68 (m, 1 H), 1.60 - 1.52 (m, 1 H), 0.97 (t, *J* = 7.5 Hz, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.3, 137.5, 133.2, 132.2, 126.0, 103.2, 97.1, 83.8, 72.2, 60.9, 56.1, 55.9, 37.0, 23.8, 9.5

HRMS (ESI) for $C_{18}H_{28}O_6$ $(M + Na)^+$ found 363.1774, calcd 363.1778

(2*S*,3*S*,5*S*)-5-((*R*)-1-(Methoxymethoxy)propyl)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-ol 28:



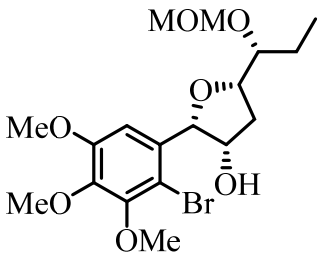
To a stirred solution of compound **27** (250 mg, 0.73 mmol) in dry CH_2Cl_2 was added triethylamine (0.22 ml, 1.61 mmol), followed by slow addition of mesyl chloride (0.099 mL, 0.88 mmol) at 0 °C, with further stirring for 15 min at the room temperature. The reaction mixture was quenched with addition of cold water at 0 °C. The two phases were separated

and the aqueous phase was extracted with CH_2Cl_2 (3x5 mL). The combined organic layers were washed with water (3x5 mL), brine, dried over Na_2SO_4 and concentrated to give crude mesylate.

To a mixture of $K_3Fe(CN)_6$ (0.706 g, 2.2 mmol), K_2CO_3 (0.295 g, 2.2 mmol) and $(DHQ)_2PHAL$ (4.8 mg, 0.007 mmol, 1 mol%) in *t*-BuOH–H_2O (1:1, 30 mL) at 0 °C was added osmium tetroxide (250 µL, 0.1 M solution in toluene, 5 mol%), followed by methane sulfonamide (0.071 g, 0.7 mmol). After stirring for 5 min at 0 °C, the crude mesylate (0.25 g, 0.7 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 24h and then quenched with solid sodium sulphite (1.0 g, 1.48 mg/mmol). Stirring was continued for an additional 15 min and then the solution was extracted with EtOAc (3 × 20 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give the crude diol.

The crude diol was refluxed in pyridine as solvent at 150 °C for 16h. After completion of the reaction 10% $CuSO_4.5H_20$ solution was added to the reaction mixture and extracted with EtOAc. The combined organic layers were washed with water (2 x 5 mL), brine, dried over Na_2SO_4 and concentrated to give crude cyclized compound **28** which was passed through filter column and carried out for next step without any characterization.

(2*S*,3*S*,5*S*)-2-(2-Bromo-3,4,5-trimethoxyphenyl)-5-((*R*)-1-(methoxymethoxy)propyl)tetrahydrofuran-3-ol 29:



To a solution of alcohol **28** (100 mg, 0.28 mmol) in CH_2Cl_2 (3 mL) was added NBS (56 mg, 0.3 mmol) and the mixture was stirred at 25 °C for 10 min. After the reaction was complete (reaction was monitored by TLC), it was quenched with sat. $Na_2S_2O_3$ (3 mL) and extracted with CH_2Cl_2 (3 x 4 mL), washed with water and combined organic phases were dried over Na_2SO_4 and concentrated to give the crude bromo compound, which was then purified by

column chromatography over silica gel using petroleum ether:EtOAc (75:25) to give the brominated alcohol **29** (single diastereomer) as a colourless oil.

Yield: 97 mg, 80%

Mol. Formula: $C_{18}H_{27}BrO_7$

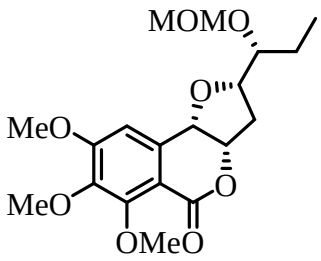
$[\alpha]_D^{25.1}$: +30.8° (*c* 1.53, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.99 (s, 1 H), 4.95 (d, *J* = 2.7 Hz, 1 H), 4.94 - 4.85 (m, 2 H), 4.61 (d, *J* = 2.7 Hz, 1 H), 4.26 - 4.19 (m, 1 H), 3.92 - 3.84 (m, 11 H), 3.45 (s, 3 H), 2.49 - 2.39 (m, 1 H), 2.13 (dd, *J* = 4.2, 13.9 Hz, 1 H), 1.71 (td, *J* = 6.9, 14.2 Hz, 1 H), 1.54 (d, *J* = 7.1 Hz, 1 H), 1.02 (t, *J* = 7.6 Hz, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.5, 150.4, 142.3, 132.0, 107.9, 97.4, 84.5, 81.0, 78.5, 70.6, 61.0, 56.2, 55.9, 35.1, 25.1, 10.2

HRMS (ESI) for $C_{18}H_{27}BrO_7$ $(M + Na)^+$ found 457.0835 , calcd 457.0832

(2*S*,3a*S*,9b*S*)-6,7,8-Trimethoxy-2-((*R*)-1-(methoxymethoxy)propyl)-2,3,3a,9b-tetrahydro-5*H*-furo[3,2-c]isochromen-5-one 30:



Bromo alcohol **29** (80 mg, 0.184 mmol) was taken in dry DMF (2.0 mL) and CuCN (49 mg, 0.552 mmol) was added to it. The entire solution was refluxed under N_2 for 12 h (monitored by TLC). The reaction mixture was then cooled to room temperature, and diluted with water (3 mL) and EtOAc (5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product which was purified by column chromatography using an eluent dichloromethane:EtOAc (93:7) to give cyclized product **30** as a colourless oil.

Yield: 7 mg, 10%

Mol. Formula: $C_{19}H_{26}O_8$

$[\alpha]_D^{25.2}$: +26.2° (*c* 0.7, $CHCl_3$)

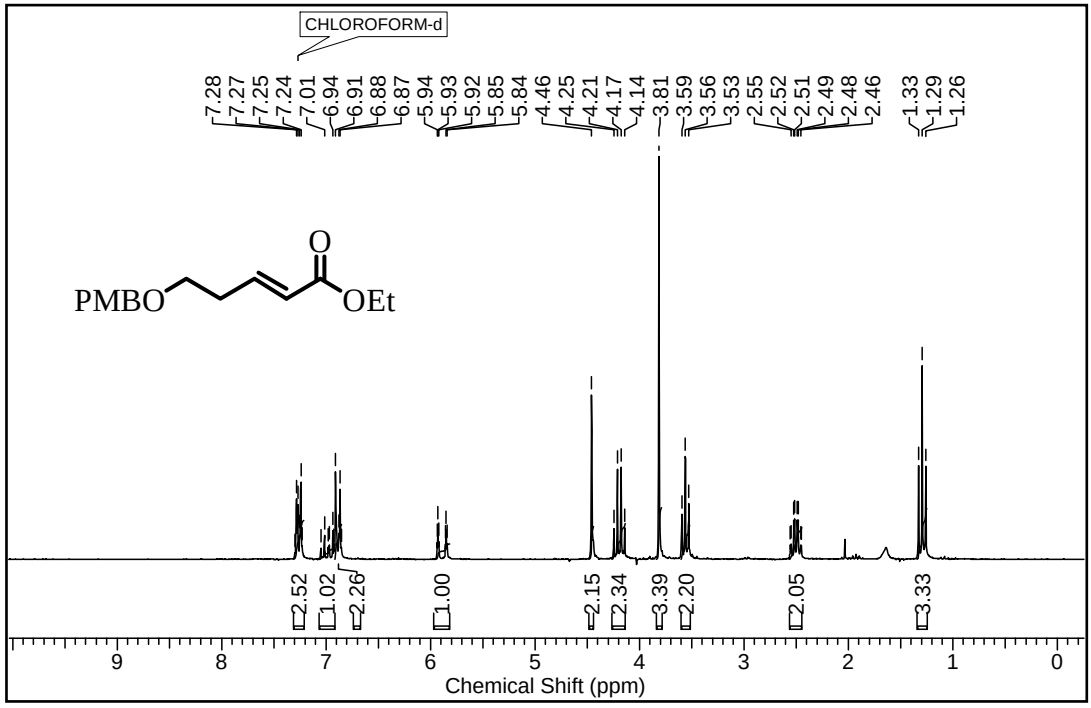
^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.68 (s, 1 H), 4.80 (d, *J* = 6.8 Hz, 1 H), 4.70 (d, *J* = 6.8 Hz, 1 H), 4.19 (s, 3 H), 4.10 - 4.04 (m, 1 H), 3.98 - 3.92 (m, 1 H), 3.88 (s, 3 H), 3.89 (s, 3 H), 3.85 (d, *J* = 7.8 Hz, 1 H), 3.58 (td, *J* = 3.9, 7.8 Hz, 1 H), 3.49 - 3.44 (m, 3 H), 2.99 - 2.85 (m, 2 H), 1.71 - 1.63 (m, 2 H), 1.01 (t, *J* = 7.3 Hz, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.7, 156.5, 149.7, 141.1, 138.7, 124.9, 104.1, 97.5, 96.3, 85.0, 77.3, 77.2, 76.7, 71.1, 61.6, 60.8, 56.4, 55.9, 31.3, 23.8, 10.3

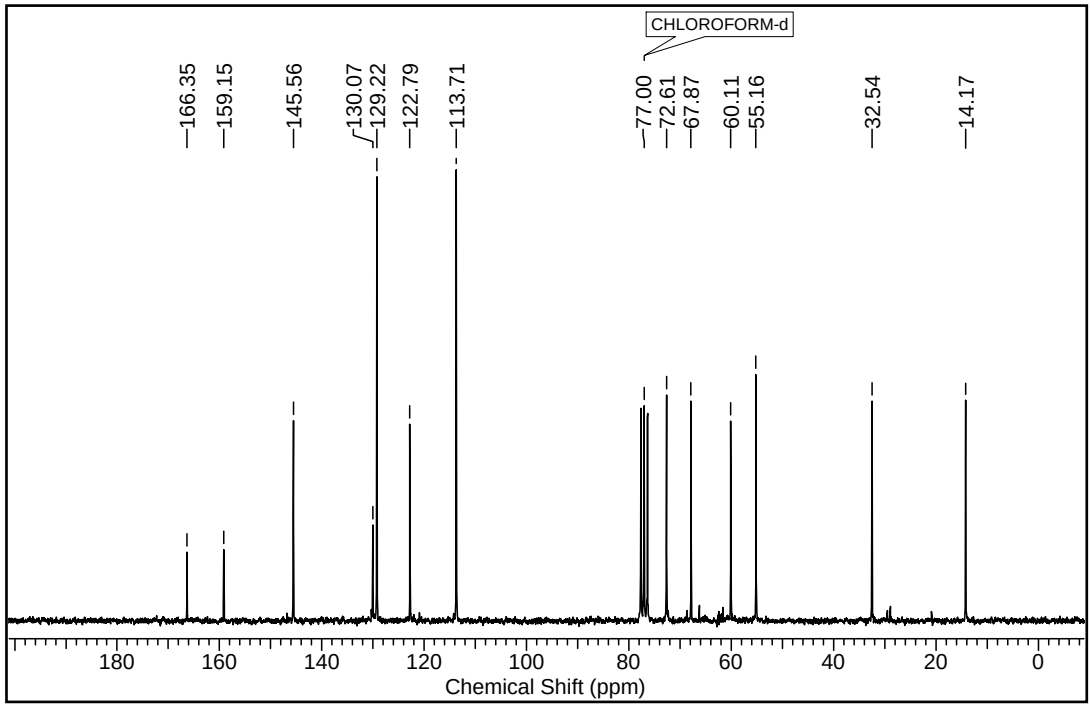
HRMS (ESI) for $C_{19}H_{26}O_8$ $(M + Na)^+$ found 405.1520, calcd 405.1519

3.2.7. Spectra:

Ethyl (*E*)-5-((4-methoxybenzyl)oxy)pent-2-enoate 16:

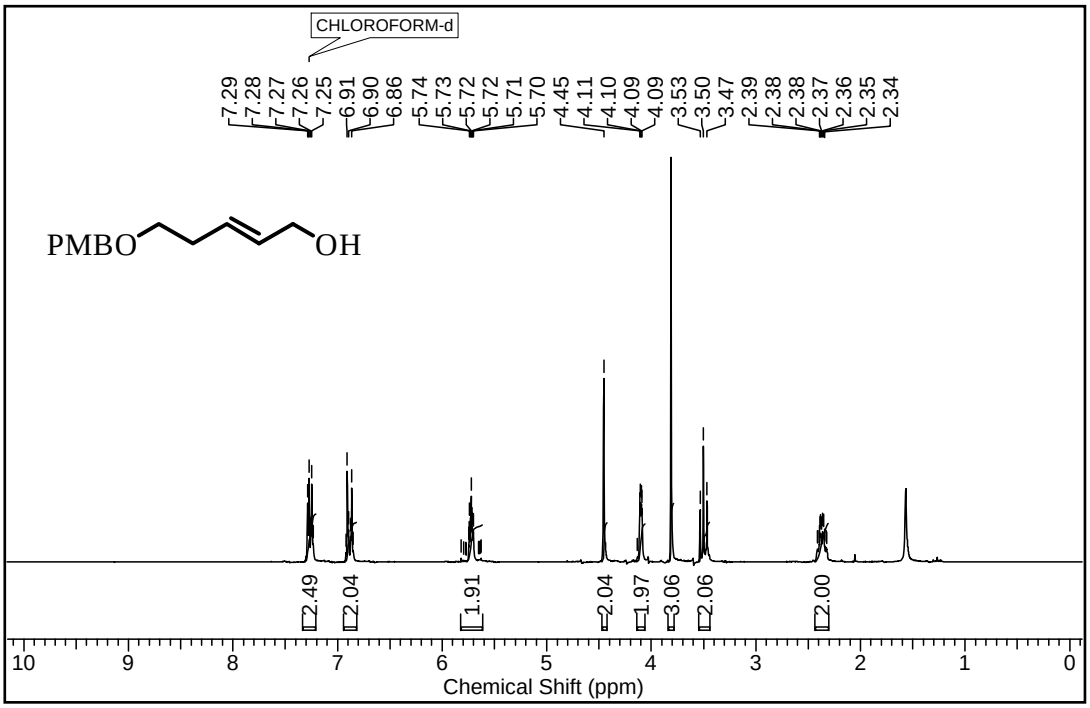


➢ **^{1}H NMR of the compound 16 in $CDCl_3$**

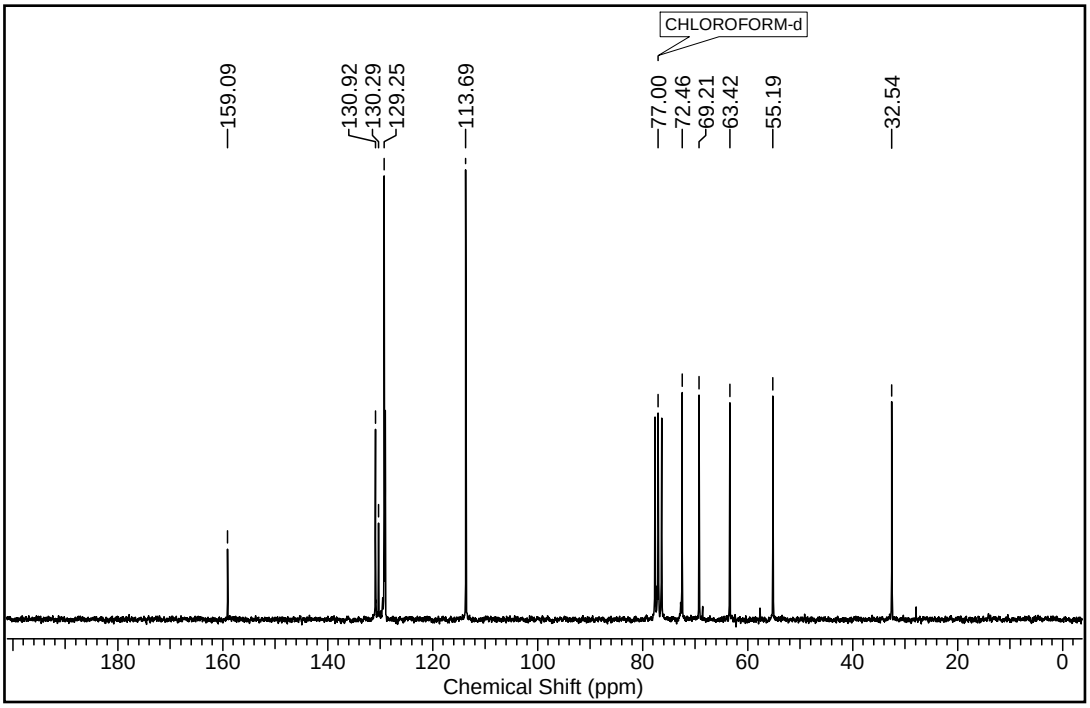


➢ **^{13}C NMR of the compound 16 in $CDCl_3$**

(*E*)-5-((4-Methoxybenzyl)oxy)pent-2-en-1-ol 17:

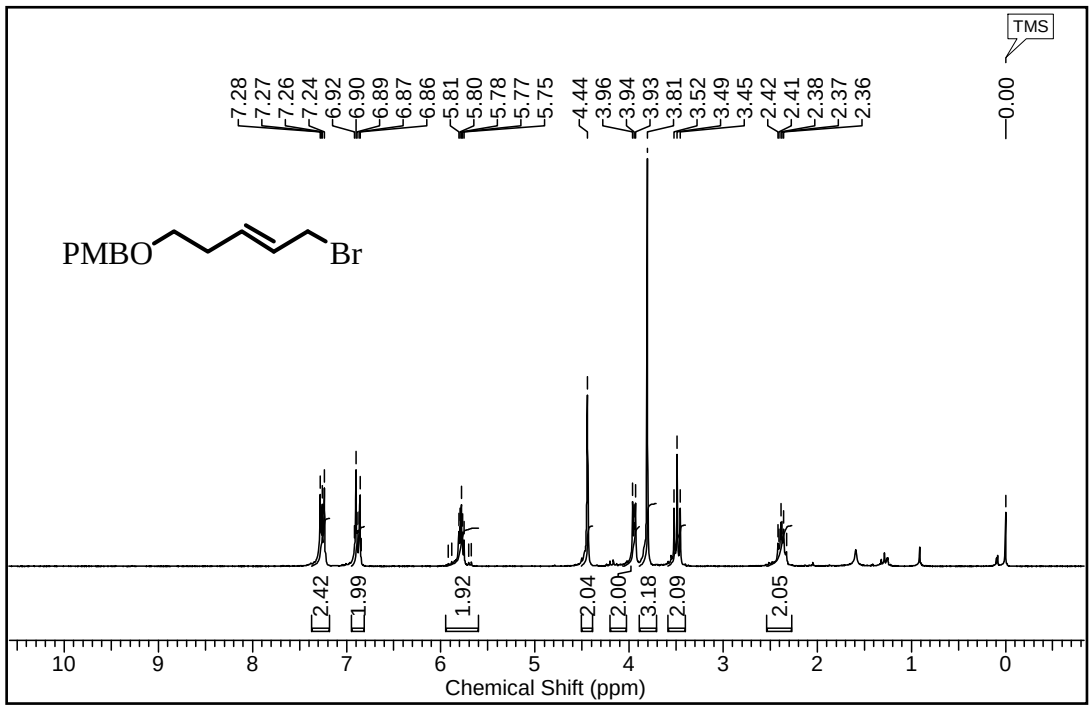


➢ **^{1}H NMR of the compound 17 in $CDCl_3$**



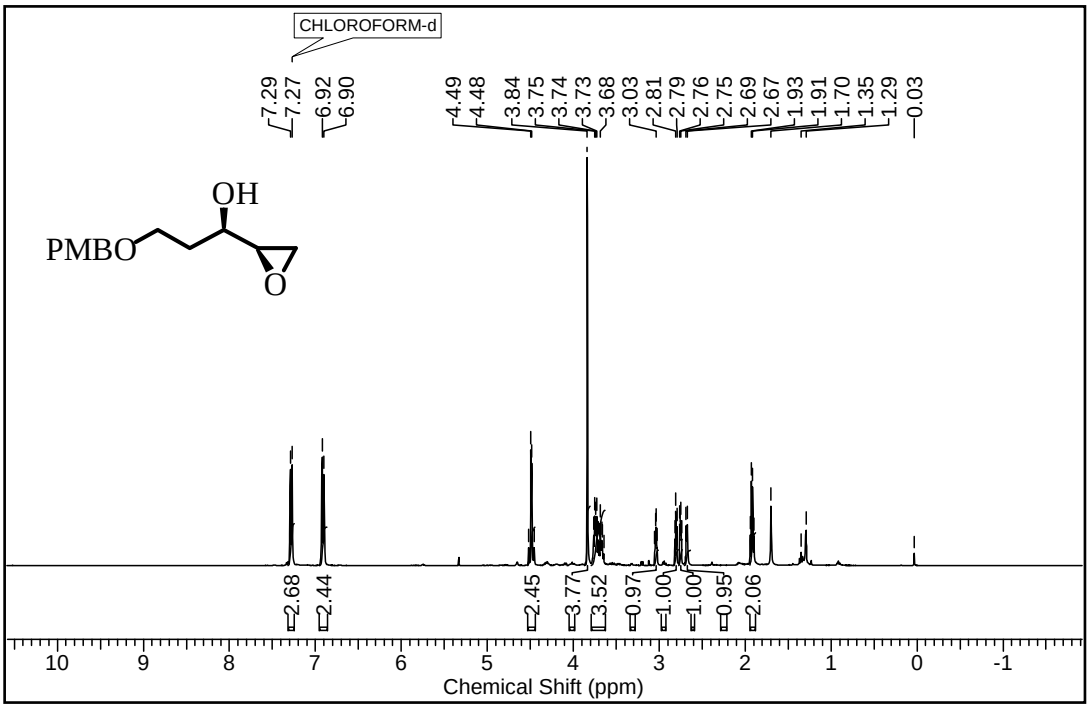
➢ **^{13}C NMR of the compound 17 in $CDCl_3$**

(*E*)-1-(((5-Bromopent-3-en-1-yl)oxy)methyl)-4-methoxybenzene 18:

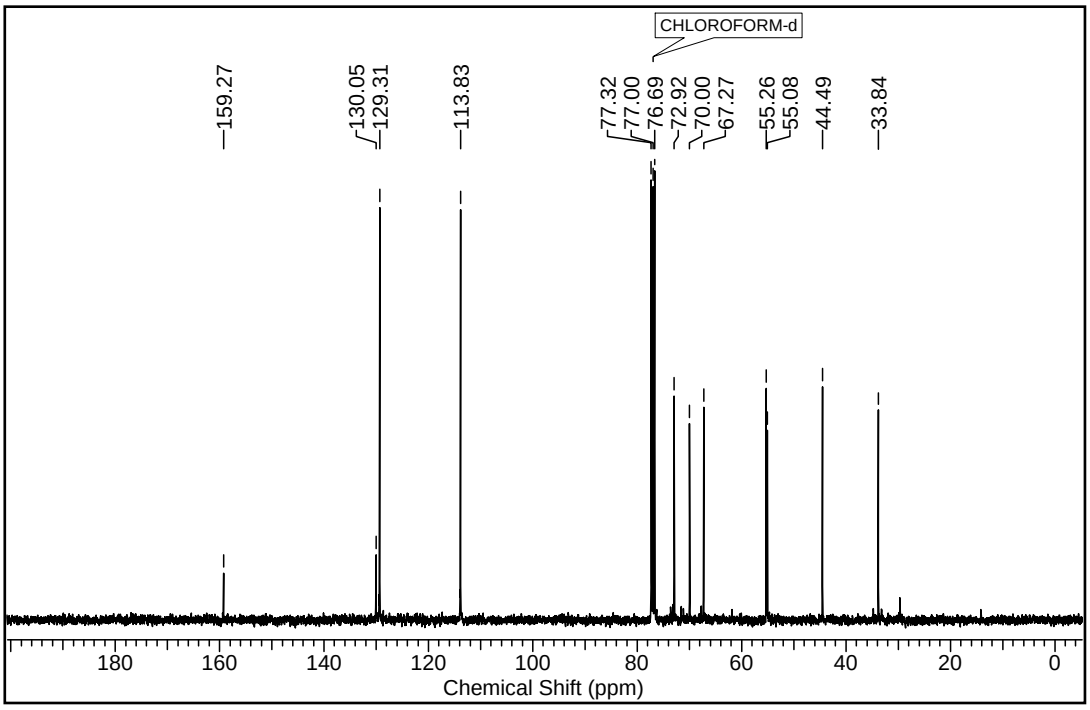


- **^{1}H NMR of the compound 18 in $CDCl_3$**

(*R*)-3-((4-Methoxybenzyl)oxy)-1-((R)-oxiran-2-yl)propan-1-ol 19:

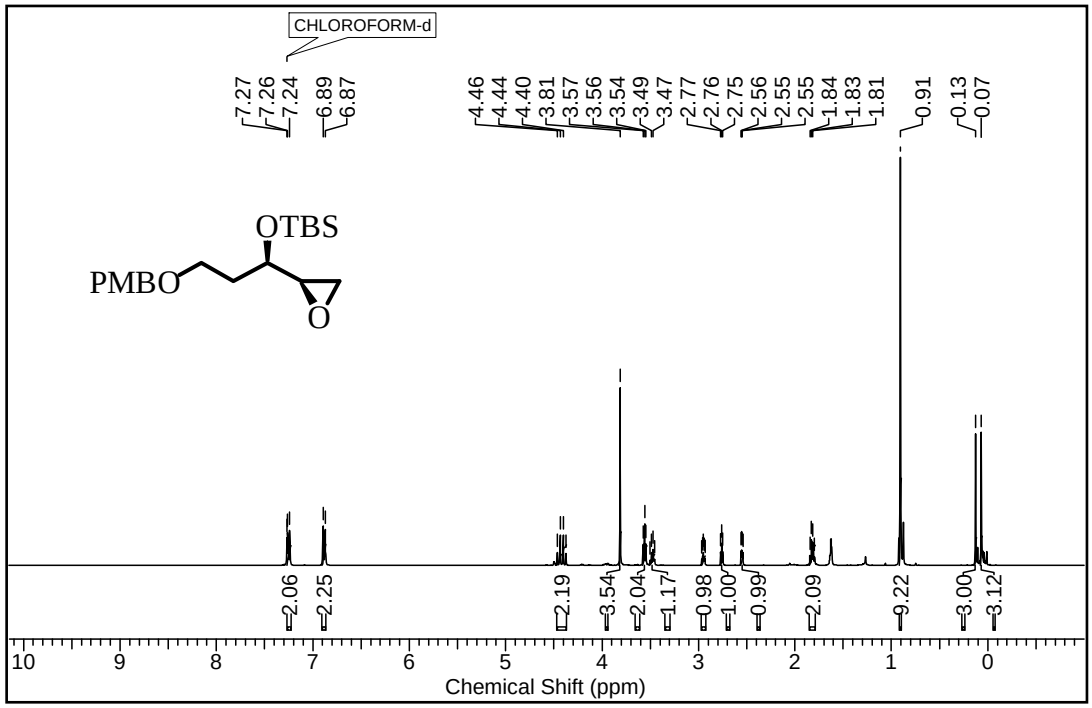


- **^{1}H NMR of the compound 19 in $CDCl_3$**

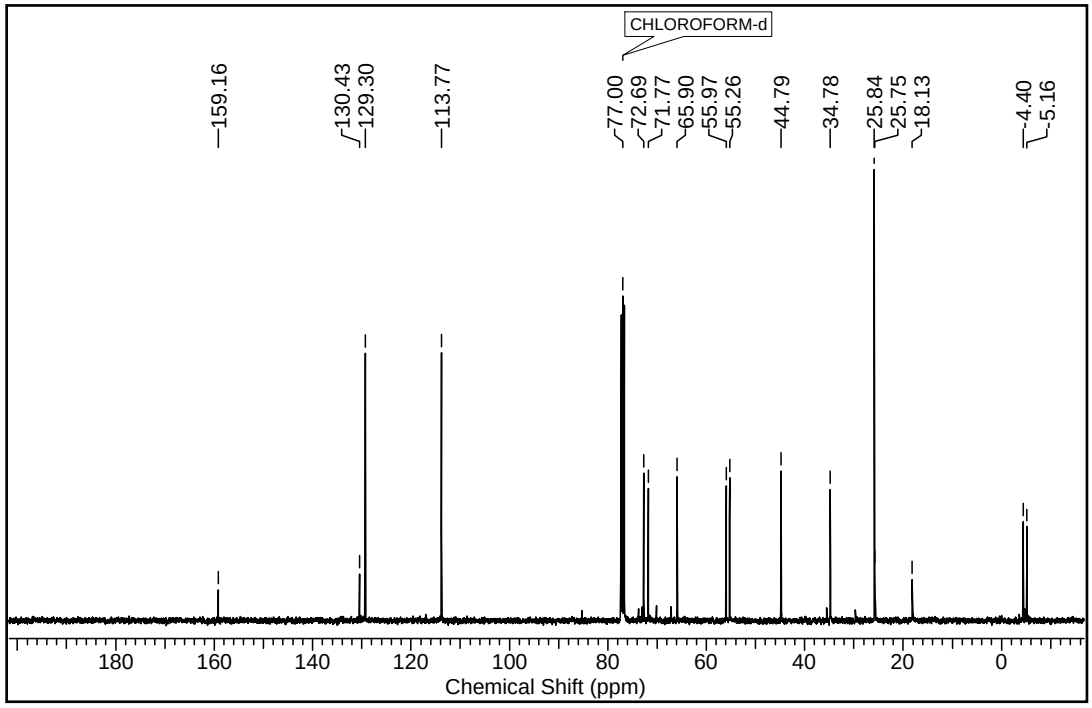


- **^{13}C NMR of the compound 19 in $CDCl_3$**

Tert-butyl((*R*)-3-((4-methoxybenzyl)oxy)-1-((*R*)-oxiran-2-yl)propoxy)dimethylsilane 20:

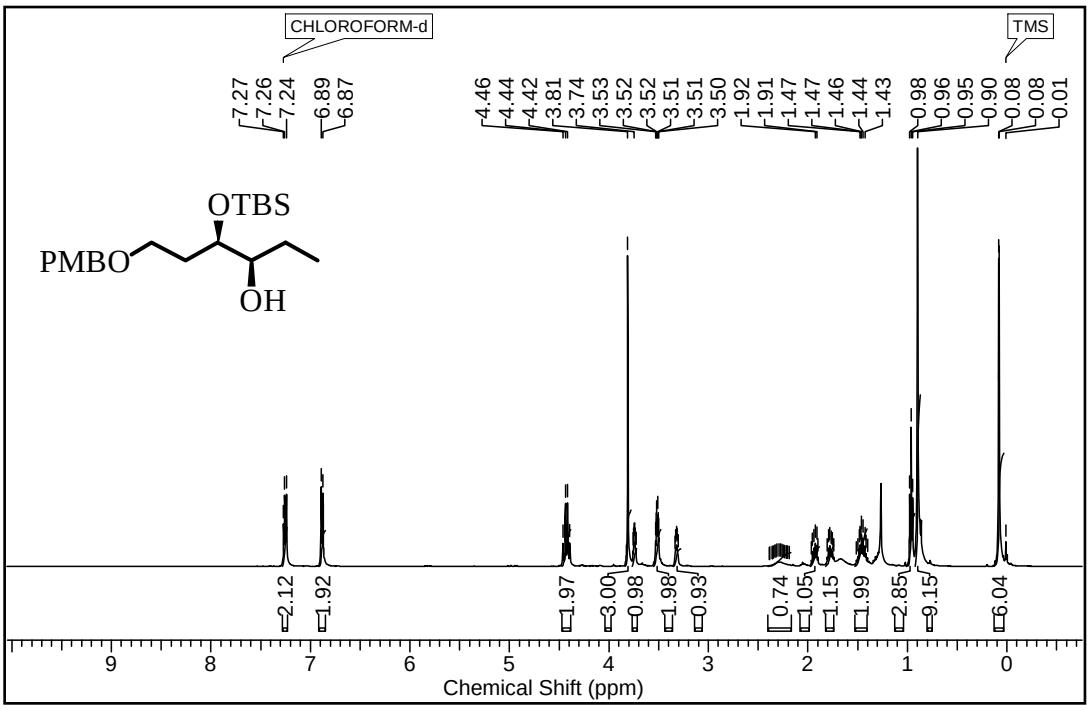


➢ **^{1}H NMR of the compound 20 in $CDCl_3$**

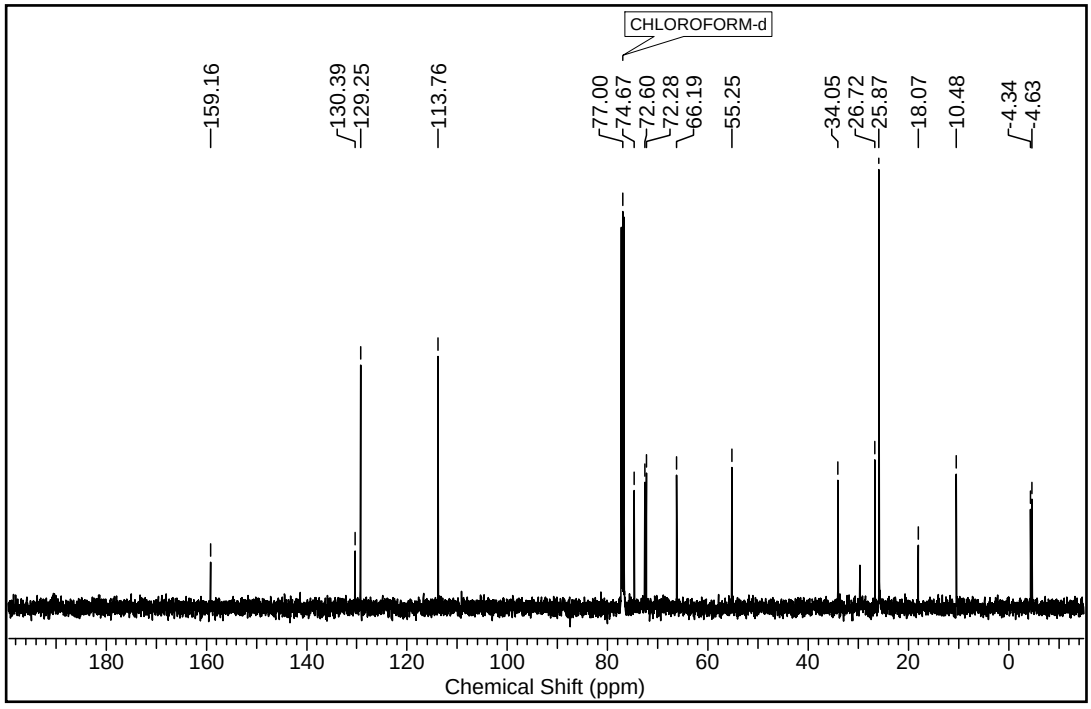


➢ **^{13}C NMR of the compound 20 in $CDCl_3$**

(3*R*,4*R*)-4-((Tert-butyldimethylsilyl)oxy)-6-((4-methoxybenzyl)oxy)hexan-3-ol 21:

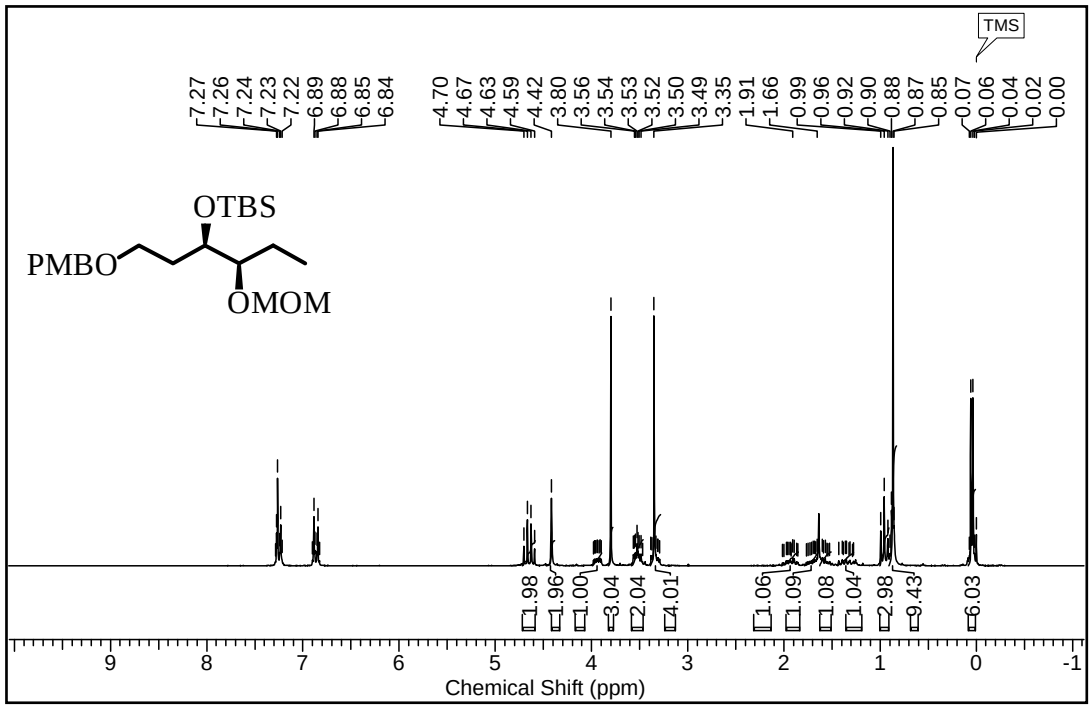


- **^{1}H NMR of the compound 21 in $CDCl_3$**

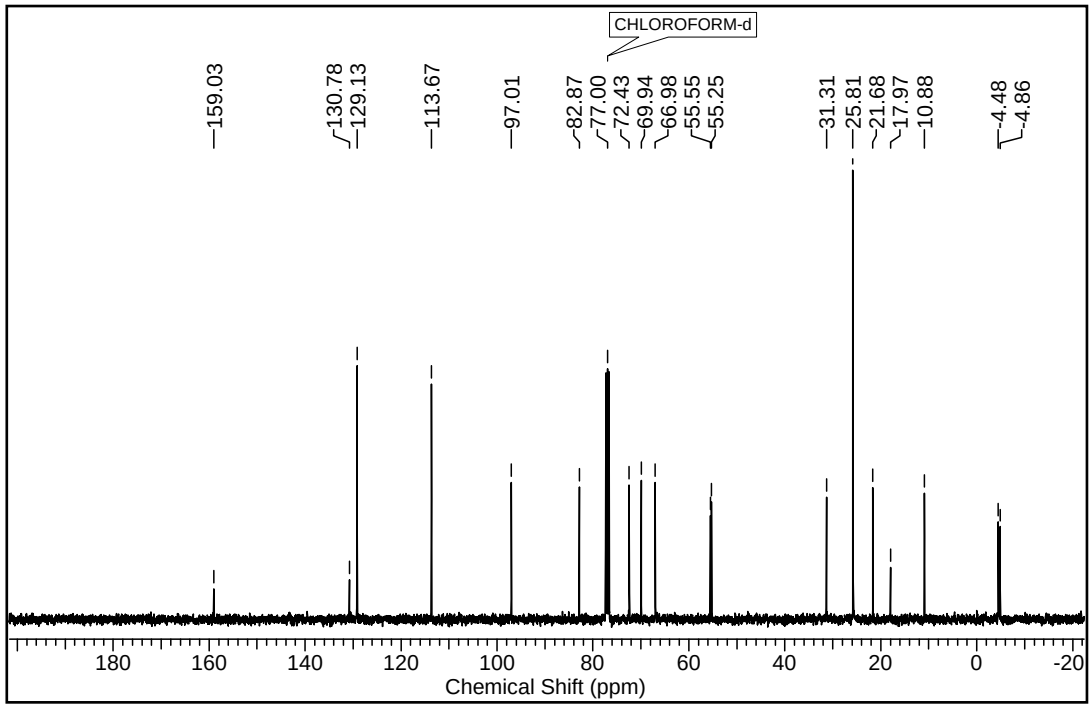


- **^{13}C NMR of the compound 21 in $CDCl_3$**

(5*R*,6*R*)-5-Ethyl-6-(2-((4-methoxybenzyl)oxy)ethyl)-8,8,9,9-tetramethyl-2,4,7-trioxa-8-siladecane 22:

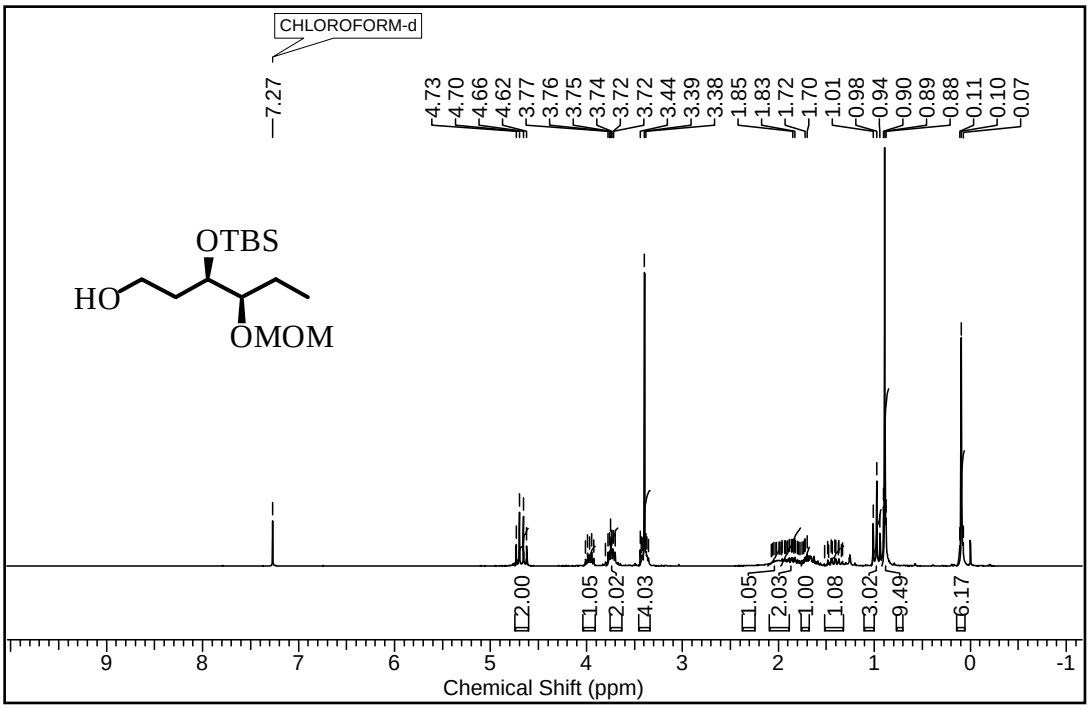


- **^{1}H NMR of the compound 22 in $CDCl_3$**



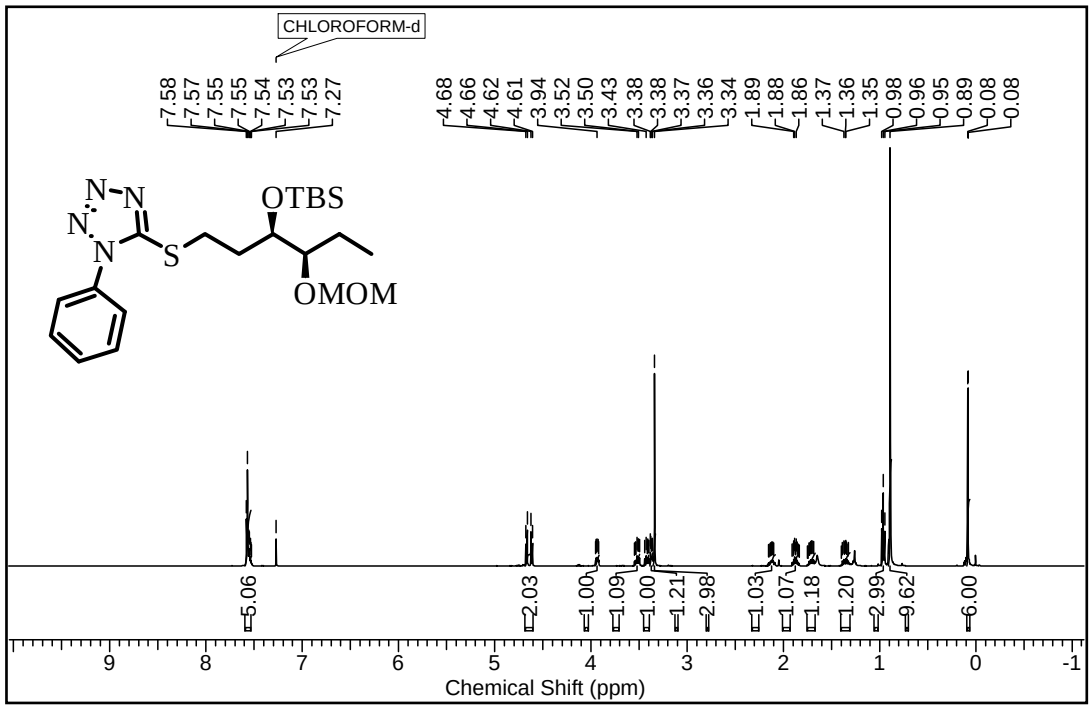
- **^{13}C NMR of the compound 22 in $CDCl_3$**

(3*R*,4*R*)-3-((Tert-butyldimethylsilyl)oxy)-4-(methoxymethoxy)hexan-1-ol 23:

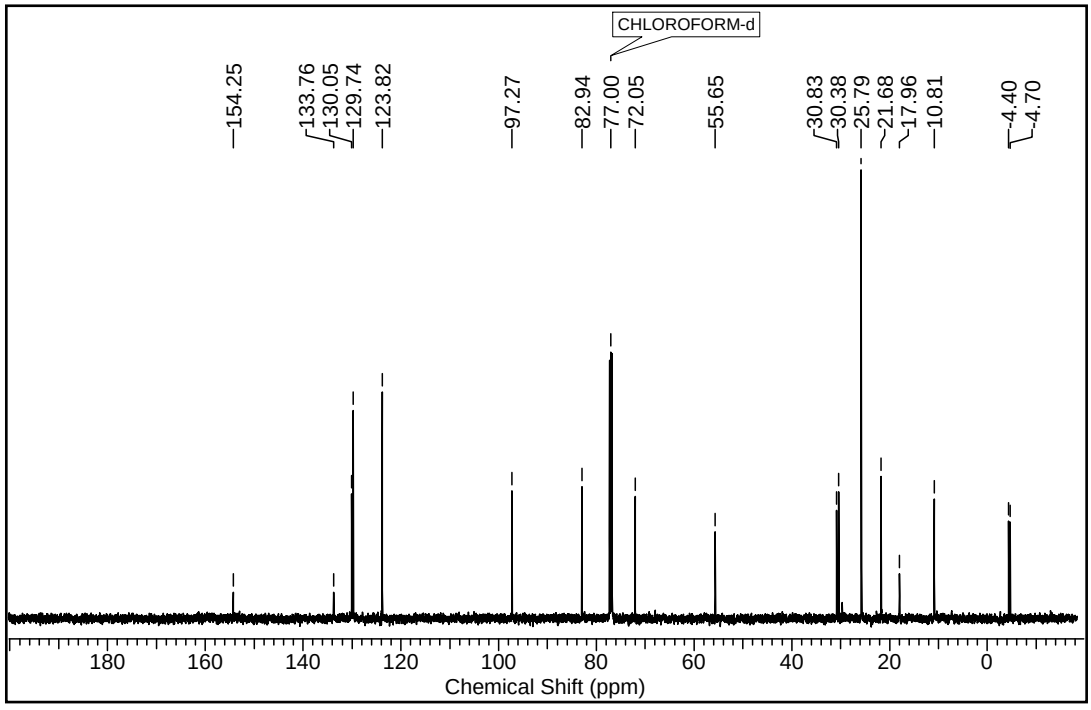


- **^{1}H NMR of the compound 23 in $CDCl_3$**

5-(((3*R*,4*R*)-3-((Tert-butyldimethylsilyl)oxy)-4-(methoxymethoxy)hexyl)thio)-1-phenyl-1*H*-tetrazole 24:

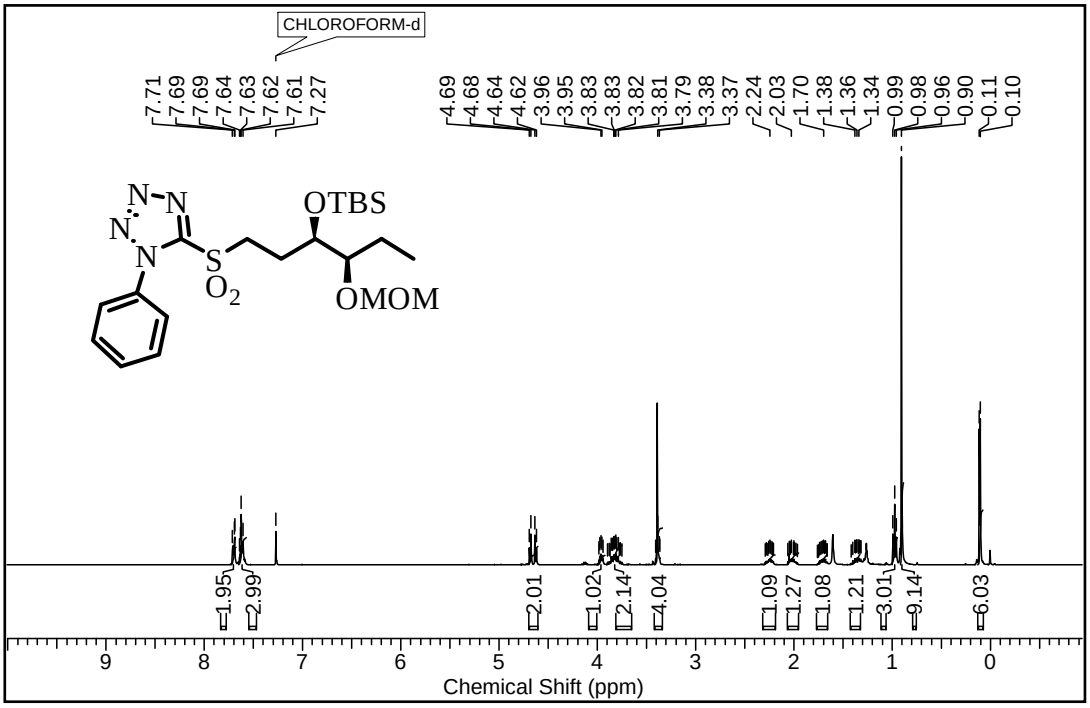


➢ **^{1}H NMR of the compound 24 in $CDCl_3$**

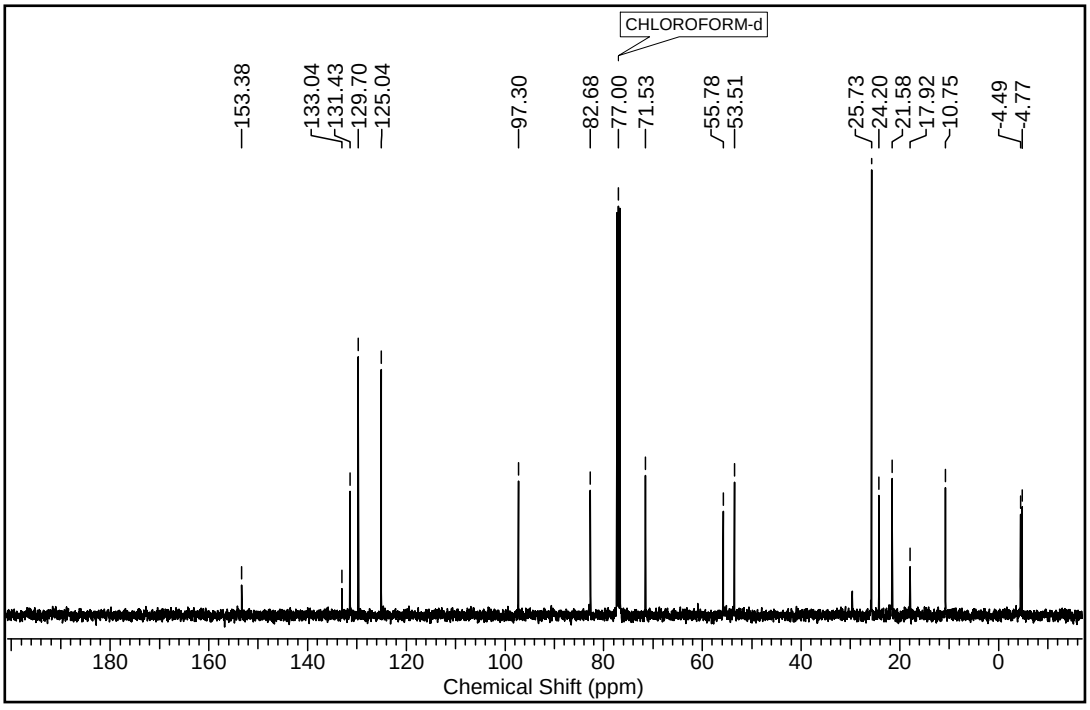


➢ **^{13}C NMR of the compound 24 in $CDCl_3$**

5-(((3*R*,4*R*)-3-((Tert-butyldimethylsilyl)oxy)-4-(methoxymethoxy)hexyl)sulfonyl)-1-phenyl-1*H*-tetrazole 25:

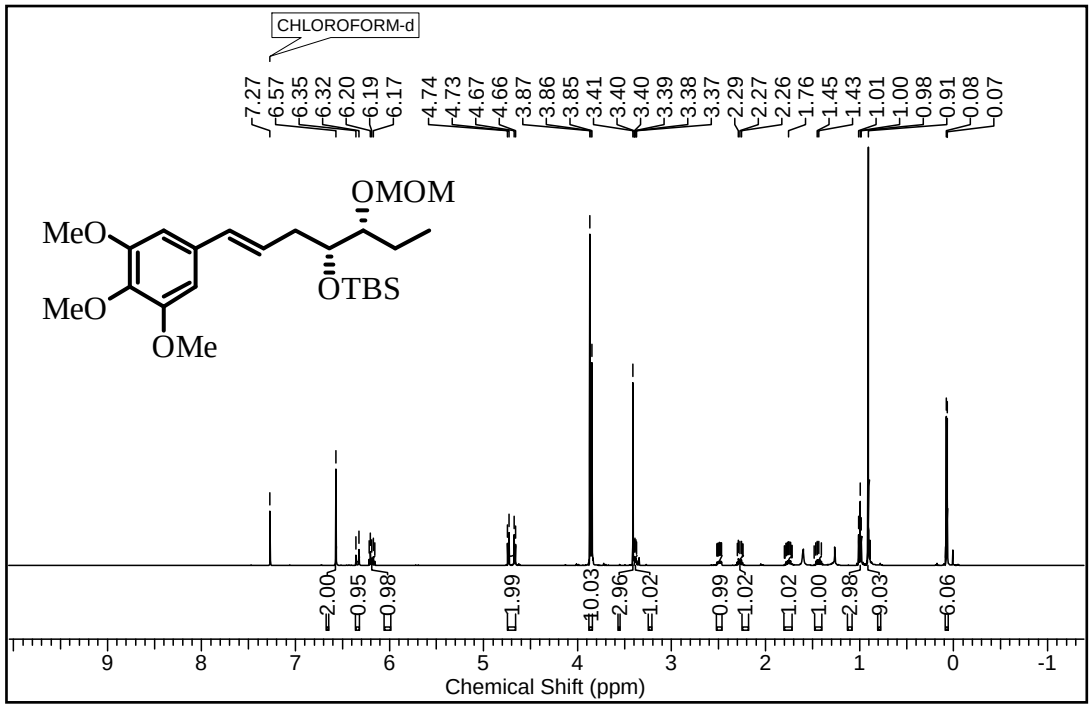


- **^{1}H NMR of the compound 25 in $CDCl_3$**

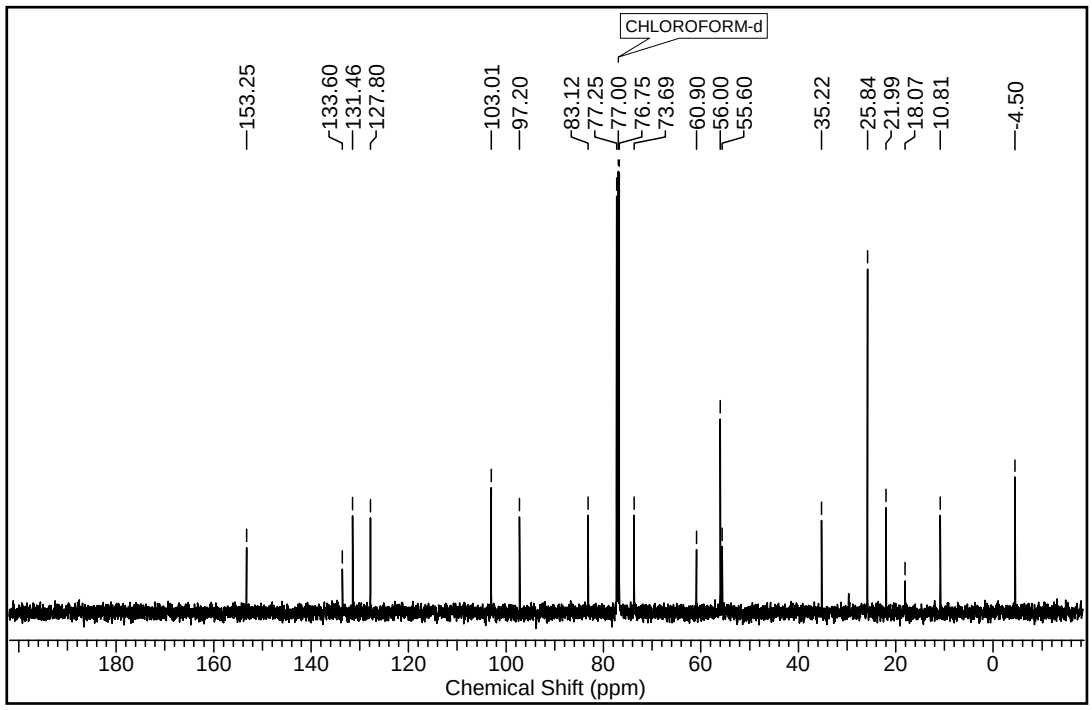


- **^{13}C NMR of the compound 25 in $CDCl_3$**

(5*R*,6*R*)-5-Ethyl-8,8,9,9-tetramethyl-6-((E)-3-(3,4,5-trimethoxyphenyl)allyl)-2,4,7-trioxa-8-siladecane 26:

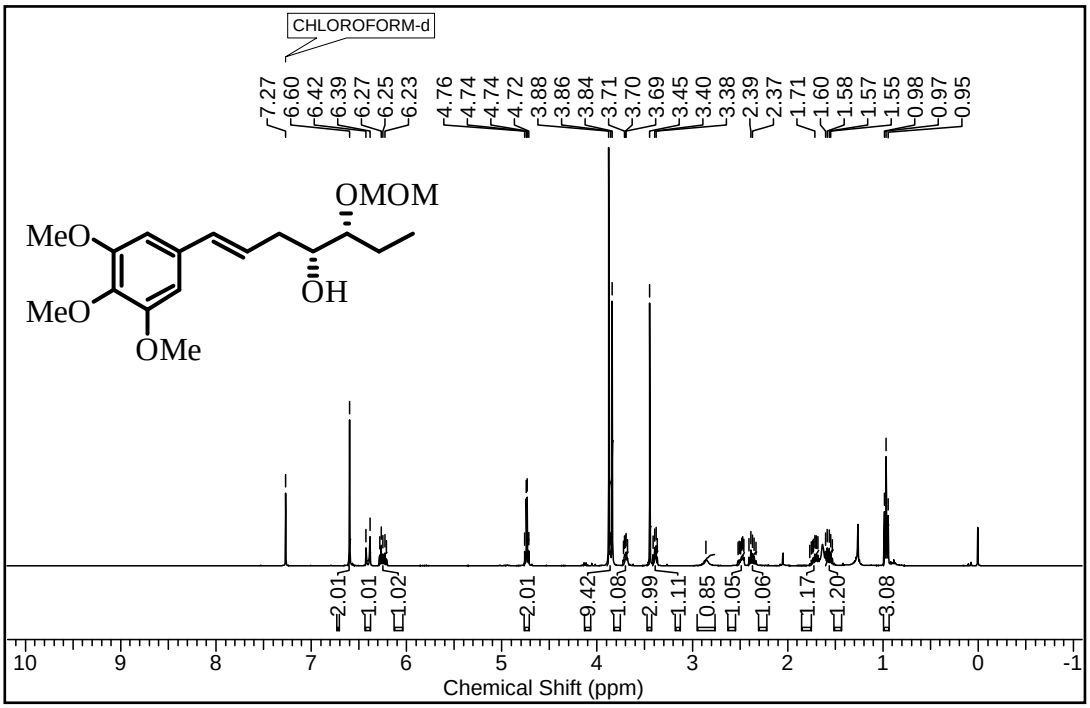


- **^{1}H NMR of the compound 26 in $CDCl_3$**

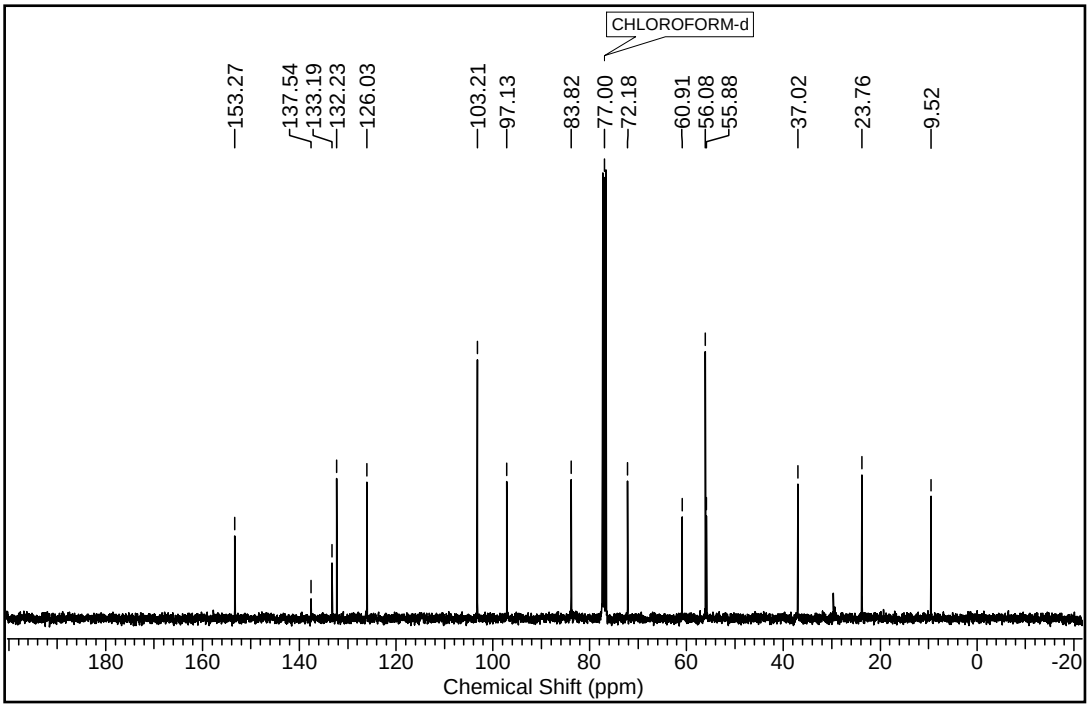


- **^{13}C NMR of the compound 26 in $CDCl_3$**

(4*R*,5*R*,*E*)-5-(Methoxymethoxy)-1-(3,4,5-trimethoxyphenyl)hept-1-en-4-ol 27:

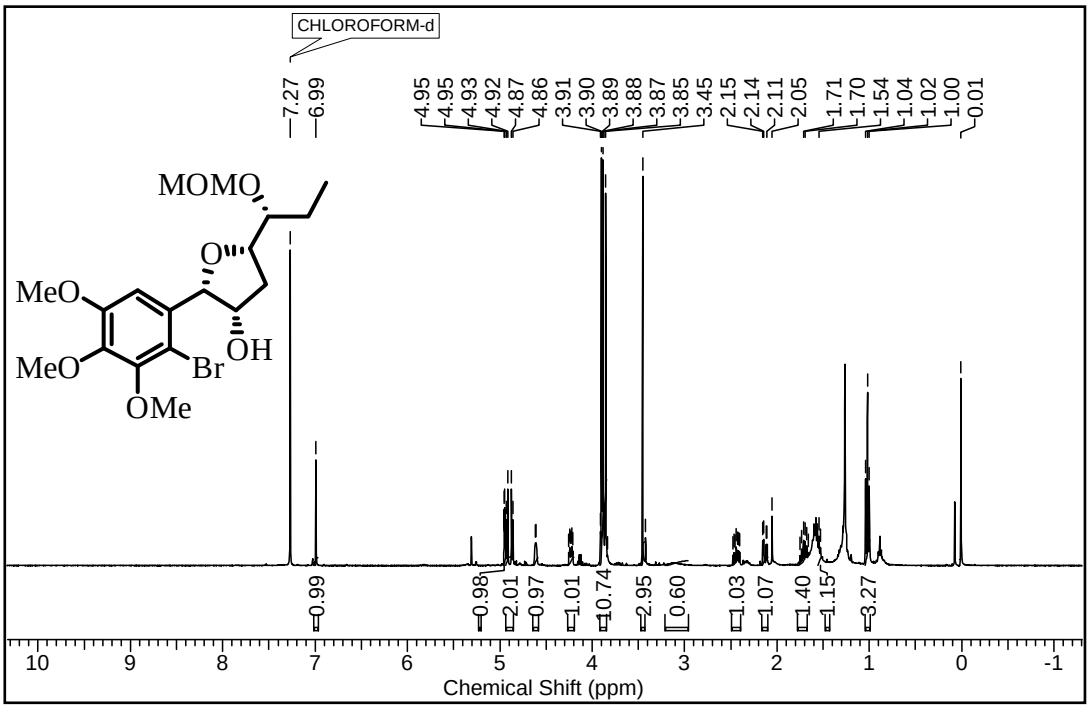


➢ **^{1}H NMR of the compound 27 in $CDCl_3$**

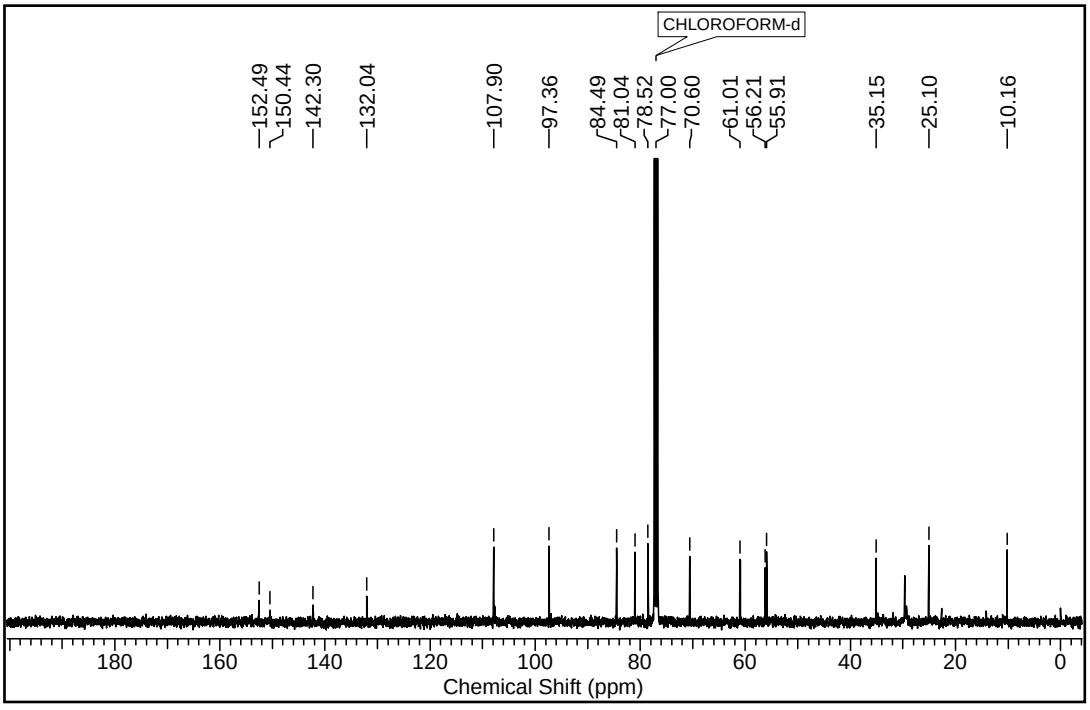


➢ **^{13}C NMR of the compound 27 in $CDCl_3$**

(2*S*,3*S*,5*S*)-2-(2-Bromo-3,4,5-trimethoxyphenyl)-5-((*R*)-1-(methoxymethoxy)propyl)tetrahydrofuran-3-ol 29:

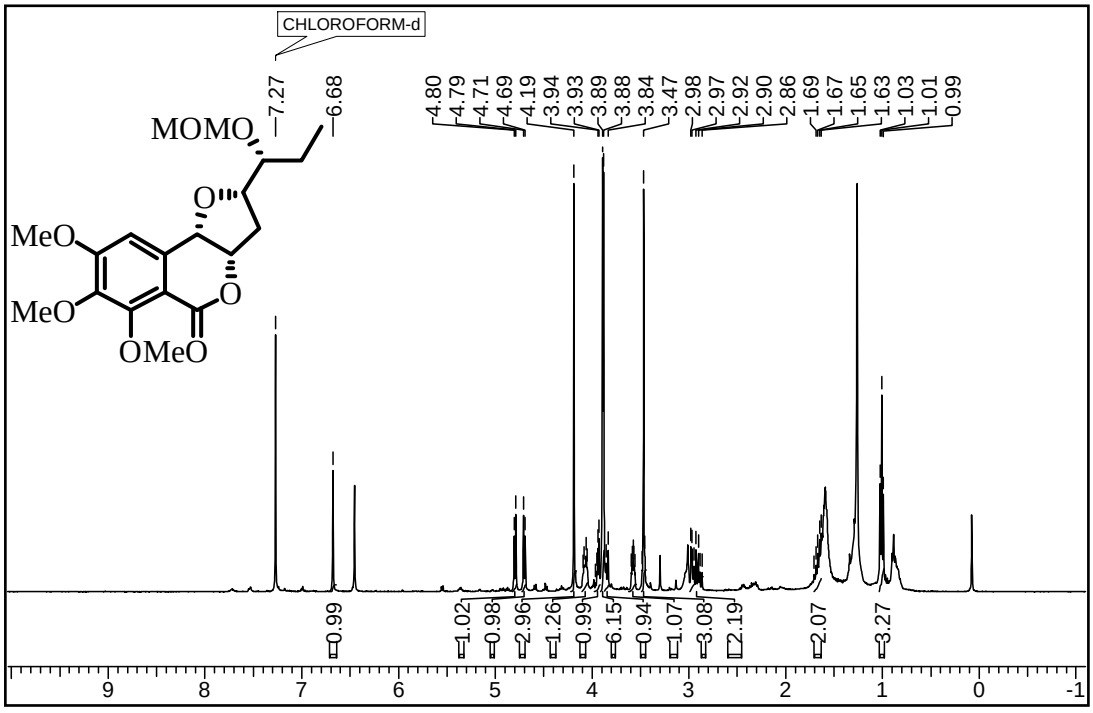


- **^{1}H NMR of the compound 29 in $CDCl_3$**

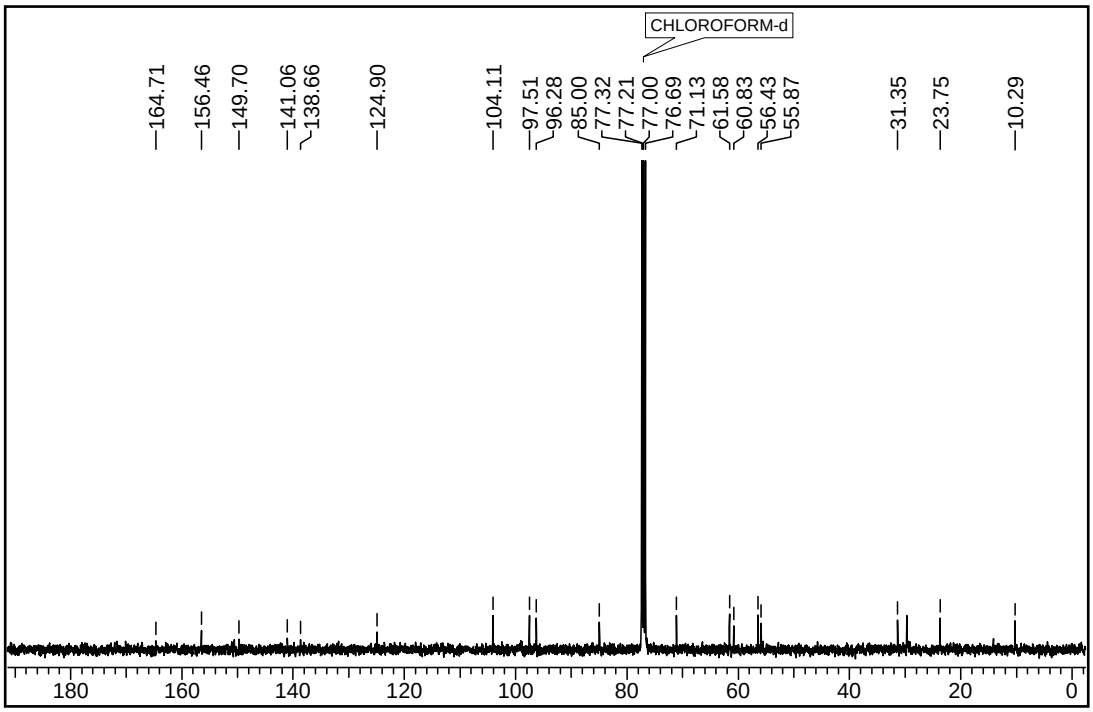


- **^{13}C NMR of the compound 29 in $CDCl_3$**

(2*S*,3a*S*,9b*S*)-6,7,8-Trimethoxy-2-((*R*)-1-(methoxymethoxy)propyl)-2,3,3a,9b-tetrahydro-5*H*-furo[3,2-c]isochromen-5-one 30:



➢ **^{1}H NMR of the compound 30 in $CDCl_3$**



➢ **^{13}C NMR of the compound 30 in $CDCl_3$**

3.2.7. References

1. a) L. C. Axford, T. J. Simpson and C. L. Willis, *Angew. Chem. Int. Ed.*, 2004, **43**, 727; b) D. C. Aldridge and W. B. Turner, *J. Chem. Soc. C: Organic*, 1970, 2598; c) J. F. Grove and M. *J*. Pople, *Chem. Soc. Perkin Trans I.*, 1979, 2048.
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Chapter-4

Development of New Methodologies Involving C-S and C-N Bond Formations

4.1. SECTION A

$CeCl_3.7H_2O$-NaI Promoted Regioselective Sulfenylation of Indoles with Sulfonylhydrazides

4.1.1. Introduction

Indoles, a prominent class of alkaloids, constitute enthusiastic structures in a myriad of natural products.[1] The indole derivatives have been well-known as wide variety of significant substances and intermediates of many medicinal, pharmaceuticals as well as human healthcare industry.[2] Particularly, 3-sulfenylated indole pharmacophores are extremely delightful due to their utility in the treatment of HIV, [3] obesity, [4] cancer, [5] heart disease, [6] and allergies.[7] They are also used as cyclooxygenase-2 (COX-2) inhibitors and as potent inhibitor of tubulin polymerization,[8] antinociceptive,[9a] and organic nonlinear optical materials.[9b] (**Fig 1**).

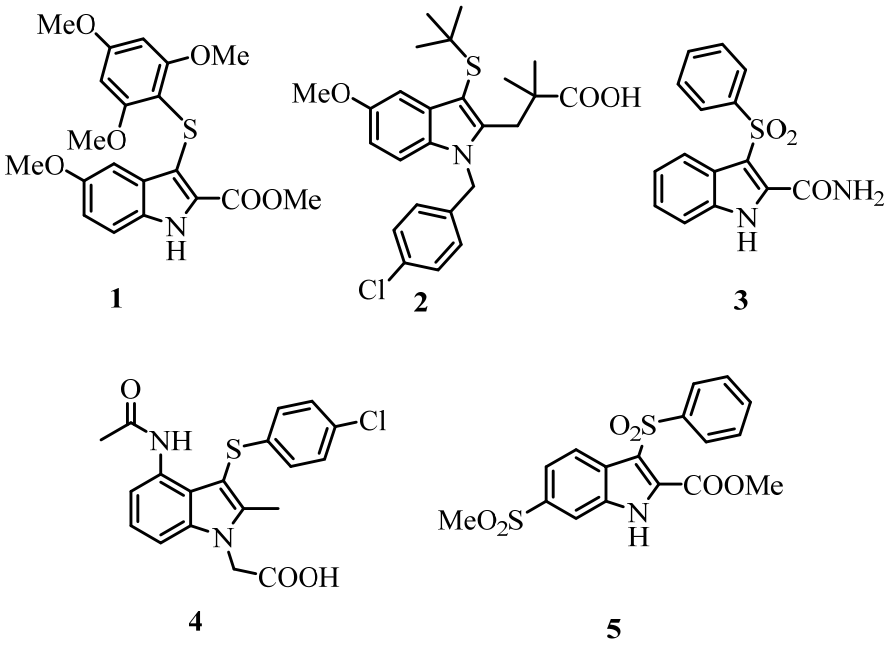


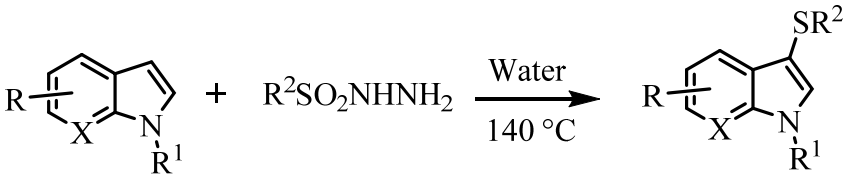
Figure 1: Biologically active thioindole derivatives

4.1.2. Review of Literature

In view of their biological significance, different methods have been developed towards the synthesis of 3-sulfenylated indole. Normally, 3-arylthioindoles are prepared through electrophilic substitution of indoles with thiols. While Ranken and co-workers developed a method for 3-sulfenylation of indoles using $AlCl_3$ as a catalyst,[10] Uemura *et al.* have reported the synthesis of 3- sulfenylindoles from indoles and thiols using heterogeneous vanadium as a catalyst.[11] Tudge group has reported the direct 3-arylthiolation of indoles from *N*-thioarylphthalimides using halide-containing salts.[12a,b] Additionally various other methods of sulfenylation at the 3-position of indoles have been reported using a variety of reagents such as thiols,[13a] quinone mono-*O*,*S*-acetal,[13b] sulfenyl chlorides,[13c, d] arylsulfonyl chlorides,[13e] acyloxysulfonium salt [13f] *etc*. A detailed report of recent methods is described below.

Zhiyong Wang (2016)[13g]

Zhiyong Wang and co-workers developed a green protocol, catalyst free water promoted indole 3-sulfenylation using aryl sulfonylhydrazides as sulfur source. No additional catalyst and ligands were utilized for this transformation.



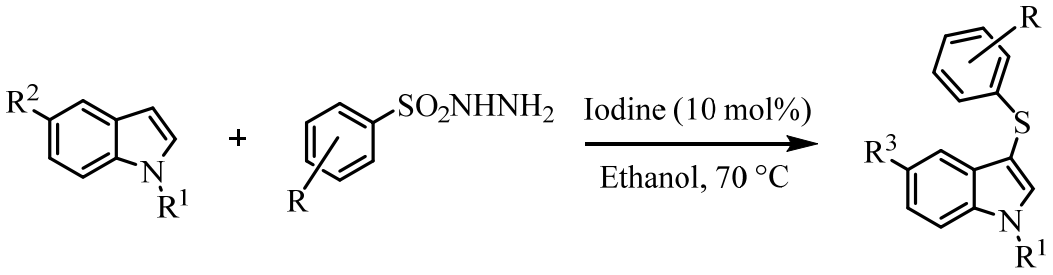
X= CH, N
R^1 =H, Me

Scheme 3: Catalyst free indole 3-sulfenylation using arylsulfonyl hydrazides

Tian and co-workers (2013)[14]

More recently, Tian and co-workers[14] have reported an iodine catalyzed reaction between indoles and sulfonyl hydrazides affording structurally diverse indole thioethers. The same

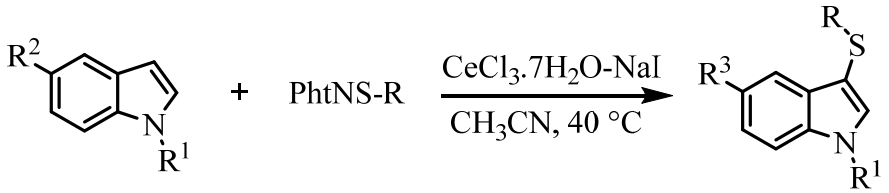
group attempted the reaction replacing the iodine with other iodine source reagents like *N*-bromosuccinimide (NBS), *N*-chlorosuccinimide (NCS), *N*-iodosuccinimide (NIS) and Bu_4NI. While *N*-iodosuccinimide gave very low yield of the required product, no desired product was obtained with other iodine source reagents.



Scheme 3: Iodine catalyzed indole 3-sulfenylation using arylsulfonyl hydrazides

Enrico Marcantoni *et al.* (2013)[12b]

Enrico Marcantoni and co-worker developed efficient catalytic protocol, regio-selective sulfenylation of electron rich aza aromatics (*i.e.* indoles and pyrroles) using *S*-alkyl- and *S*-arylthiophthalimides as sulfenylating agents. They have used catalytic amounts of $CeCl_3.7H_2O$-NaI to accelerate the regio-selective C-S bond formation.

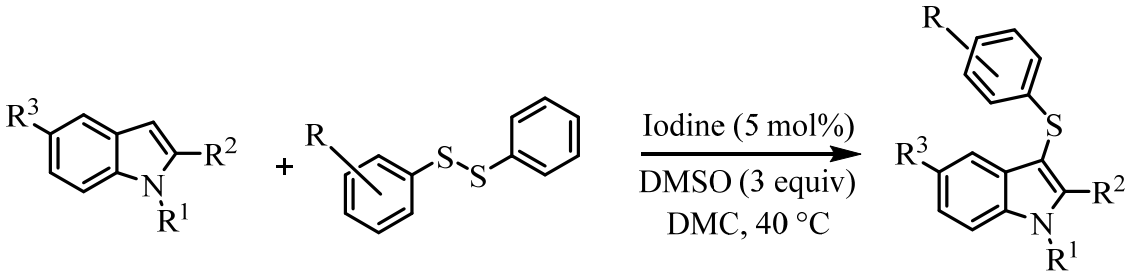


Scheme 3: $CeCl_3.7H_2O$-NaI catalyzed indole 3-sulfenylation using *S*-arylthiophthalimide

Wei and Ge *et al.* (2012)[12c]

Wei and Ge have reported a green protocol, iodine-catalyzed selective sulfenylation of indoles using disulfides as sulfenylating agent and DMSO as oxidant under ambient conditions. In

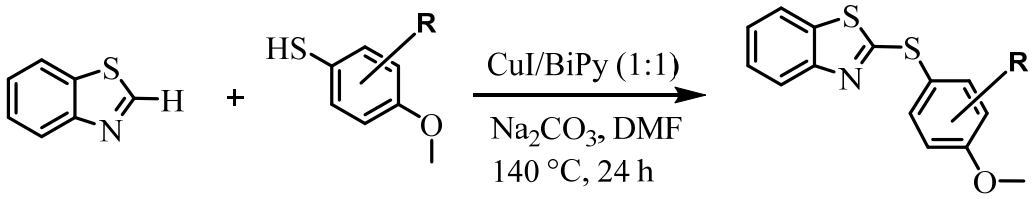
this protocol, 0.5 mmol of sulfenylating agent (disulfides) is sufficient for sulfenylation of 1.0 mmol of indole. This method was applicable for both *N*-protected and unprotected indoles.



Scheme 3: Iodine catalysed indole 3-sulfenylation using phenyl disulfides

Kuo-Wei Huang *et al.* (2011) [13a]

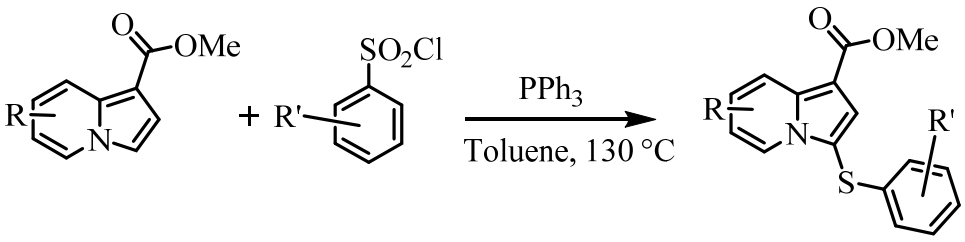
Kuo-Wei Huang and co-workers developed efficient protocol for the selective thiolation of benzothiazoles with aryl or alkyl thiols *via* copper-mediated aerobic C−H bond activation. Alkyl and aryl thiols were used as sulfenylating agents and stoichiometric amounts of CuI, 2,2′-bipyridine and Na_2CO_3 employed as a reagent system to achieve the thiolation of benzothiols. Further this methodology was extended to synthesize thiazoles, benzimidazole and indole based compounds.



Scheme 4: Copper mediated direct sulfurization of benzothiazole with thiols

Jingsong You *et al.* (2011) [13e]

Jingsong You and co-workers developed a protocol for the preparation of di(hetero)aryl sulfides as these molecules were important building blocks in both medicinal chemistry and natural product synthesis. They used aryl sulfonyl chlorides as sulfenylating agent and TPP for the sulfenylation of indolizines.



Scheme 5: Sulfenylation of indolizines (hetero arenes) using arylsulfonyl chlorides

4.1.3. Present work

Objective

Literature review described above revealed that most of the methods involve extra steps to prepare activated thiols and many of the sulfenylating agents are expensive and unstable to air and moisture, or possess unpleasant odors. In addition, earlier reported indole sulfenylation reactions require excess sulfenylating agents, excess additives, high temperature, suffer from a limited substrate scope or environmentally unfriendly formation of by products with often relatively low yields of products. To deal with such problems, it is highly desirable to develop a simple, convenient, and general methodology for the regioselective sulfenylation of indoles using stable and eco-friendly sulfenylating agents. In view of above, we considered developing a simple and efficient protocol for 3-sulfenylation of indoles using sulfonyl hydrazides as sulfenylating agent.

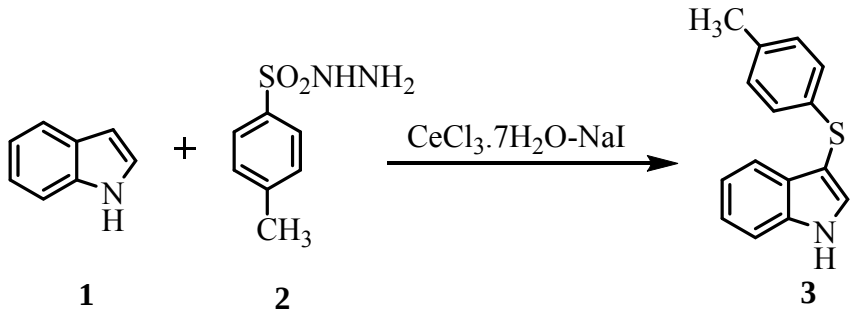
Lanthanide compounds, being environmentally friendly and stable, have become attractive aspirant for use as Lewis acid reagents in organic chemistry.[16] More than ever, cerium reagents are readily available at a low cost, relatively nontoxic, and water-tolerant Lewis acidic promoter. Among lanthanide compounds, $CeCl_3.7H_2O$ has been widely used for a variety of organic transformations.[17, 18] The reactivity of commercially available $CeCl_3.7H_2O$

increases dramatically in the presence of NaI. In recent years, Marcantoni research group has extensively worked on the application of the $CeCl_3 \cdot 7H_2O$-NaI system especially in the classical carbon-carbon bond forming reactions like, Knoevenagel condensation, allylation reaction and Michael additions *etc*.[18] However, there are no reports on the use of $CeCl_3.7H_2O$-NaI reagent system for the synthesis of 3-sulfenylindoles using arylsulfonylhydrazides as a sulfur source.[17e-g]

4.1.4. Results and discussion

Initially, we attempted at the sulfenylation of indole **1** with *p*-toluenesulfonylhydrazide **2** using a stoichiometric amount of $CeCl_3.7H_2O$ in ethanol which gave the desired product **3** in 13% yield (**Table 1**, entry 1). The ^{1}H NMR of **3** showed peaks at δ 8.54 - 8.29 (m, 1 H), 7.63 (d, J = 7.7 Hz, 1 H), 7.53 - 7.39 (m, 2 H), 7.35 - 7.11 (m, 2 H), 7.09 - 6.92 (m, 4 H), 2.26 (s, 3 H) which confirms the product **3**. HRMS (ESI) for the compound **3** with molecular formula $C_{15}H_{13}NS$ $(M+H)^+$ the found value 240.0841 matched exactly with calcd value (240.0841). We then carried out the same reaction without $CeCl_3.7H_2O$ using only NaI in ethanol. To our delight, the reaction gave the desired product **3** albeit in 26% yield only (**Table 1**, entry 2). We also performed the reactions using $CeCl_3.7H_2O$ & NaI individually under oxygen atmosphere which gave the product **3** in 5 and 30% yields respectively (**Table 1**, entry 3 & 4). Encouraged by our initial findings, we considered investigating the synergistic effects of both cerium & NaI, using different combinations of $CeCl_3.7H_2O$-NaI systems. The use of combination of both $CeCl_3.7H_2O$ and NaI either of 0.8 or 1.0 equiv provided 95% yield of the desired compound (**Table 1**, entries 6, 7).

Further decreasing the equiv of $CeCl_3.7H_2O$-NaI to 0.2 and 0.3, we observed the low yields of product. After extensive experimentation, we found that even $CeCl_3.7H_2O$ (50 mol %) in combination with NaI (50 mol %) was sufficient under the optimal conditions (2.5 h, 100 °C). The reaction of indole **1** with *p*-methyl sulfonylhydrazide **2** in ethanol gave the desired product **3** in 95% yield (**Table 1**, entry 7). Similarly we did the same reaction using optimized condition but under N_2 atmosphere we observed the product formation **(Table 1**, entry 10). It is important to note that this reaction is quite regioselective and we did not observe the formation of any 2-sulfenylated product.



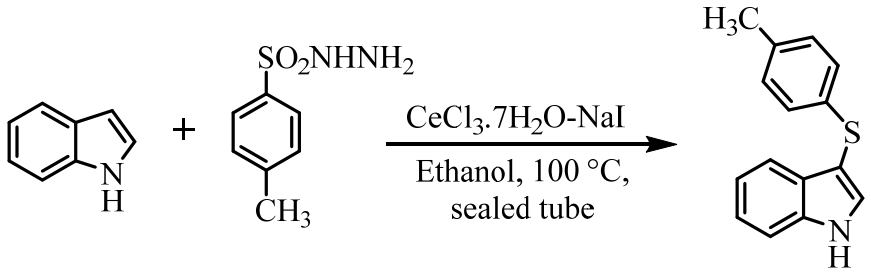
1 **2** **3**

Entry	**Catalyst**	**[O]**	**Equiv**	**Time (h)**	**Yield (%)**
1	$CeCl_3.7H_2O$	air	1.0	16	13
2	NaI	air	1.0	16	26
3	$CeCl_3.7H_2O$	O_2	1.0	16	5
4	NaI	O_2	1.0	16	30
5	NaI	N_2	1.0	16	NR
6	$CeCl_3.7H_2O$-NaI	air	1.0/1.0	2.5	95
7	$CeCl_3.7H_2O$-NaI	air	0.8/0.8	2.5	95
8	**$CeCl_3.7H_2O$-NaI**	**air**	**0.5/0.5**	**2.5**	**95**
9	$CeCl_3.7H_2O$-NaI	air	0.3/0.3	2.5	80
10	$CeCl_3.7H_2O$-NaI	air	0.2/0.2	2.5	55

11	$CeCl_3.7H_2O$-NaI	N_2	0.5/0.5	4.0	95
General reaction conditions: Indole (1.0 mmol), *p*-toluenesulfonylhydrazide (1.0 mmol), catalyst $CeCl_3.7H_2O$-NaI (50 mol%- 50 mol %), ethanol (5 mL) in sealed tube at 100 °C, [a] Isolated yield of pure product.					

Table 1: Optimization of reaction conditions

In order to examine the role of solvents, next we screened various solvents. In toluene there was no reaction (**Table 2**, entry 3). Use of solvents such as DMSO, DMF, CH_3CN, 1, 4-dioxane, THF gave only low yields of desired product **(Table 2**, entries1, 2, 4, 5, 6). The best results were obtained using solvents methanol and ethanol (**Table 2**, entries 7, 8). Among these, ethanol was found to be the best solvent providing 95% yield of the product.



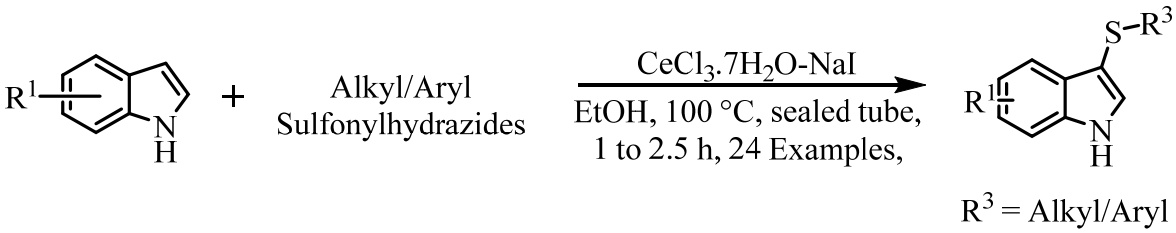
Entry	solvent	Yield (%)
1	DMSO	25
2	DMF	35
3	Toluene	NR[b]

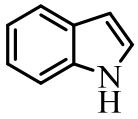
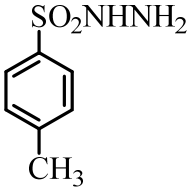
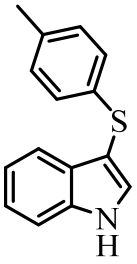
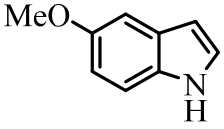
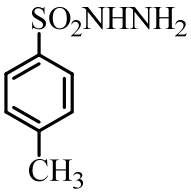
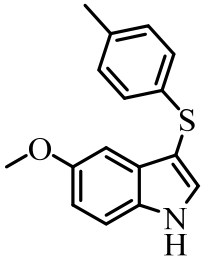
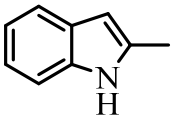
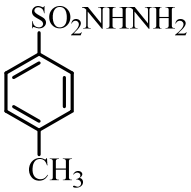
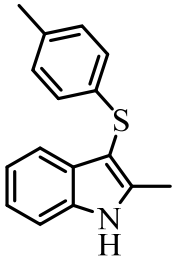
4	CH_3CN	40
5	1, 4-Dioxane	46
6	THF	30
7	**Ethanol**	**95**
8	MeOH	80
[a]Isolated yield of pure product. [b] No reaction		

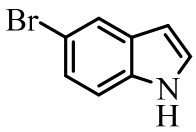
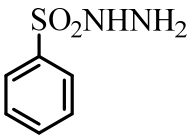
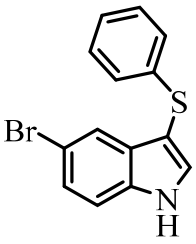
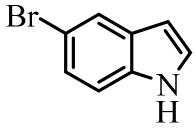
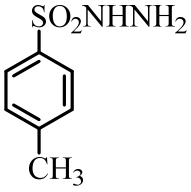
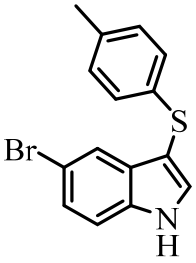
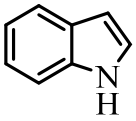
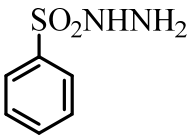
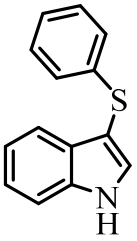
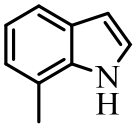
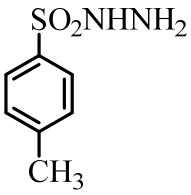
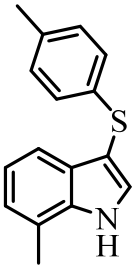
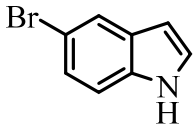
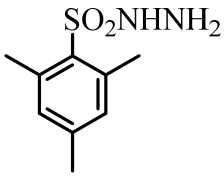
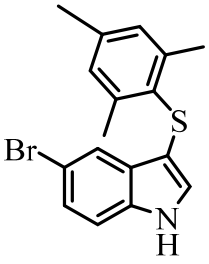
Table 2: Screening of solvents

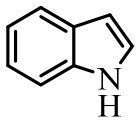
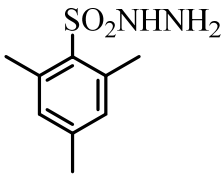
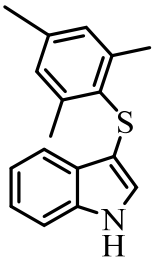
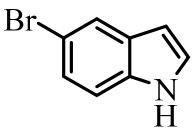
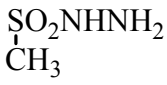
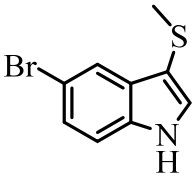
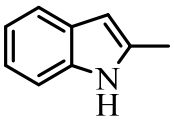
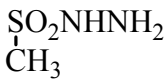
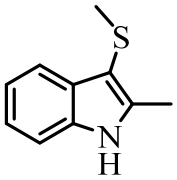
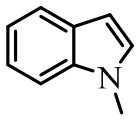
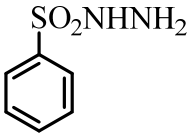
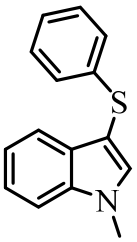
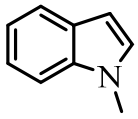
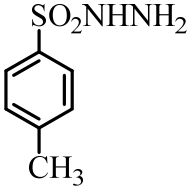
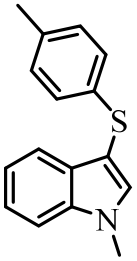
Having optimized the reaction conditions, we further explored the substrate scope with respect to various indoles and sulfonylhydrazides. Interestingly, the reaction of 5-bromoindole with substituted hydrazides such as benzenesulfonylhydrazide, *p*-toluenesulfonylhydrazide, *p*-methoxybenzenesulfonyl hydrazide, methylsulfonylhydrazide and mesitylsulfonylhydrazide compounds afforded the corresponding 3-arylthioindole derivatives in excellent yields (**Table 3**, entries 4, 5, 8, 10, 15, 22). Indoles containing electron donating groups were smoothly converted to 3-arylthioindoles (**Table 3**, entries 4, 5, 9, 13, 19, 23). Indoles containing electron withdrawing groups such as 5-nitro and 4-cyano indoles were less reactive compared to indoles containing electron donating groups & we observed 30% conversion only, the remaining starting material was recovered back (**Table 3**, entries 18, 19, 20, 23). Notably, indole-2-carboxylate was efficiently converted into 3-sulfenylated indole (entry 24) with excellent yield, which is an important biologically active COX2 inhibitor. In addition, *N*-methylindole also participated in this reaction with same efficiency (**Table 3**, entries 12, 13, and 16). This method worked equally well with electron deficient hydrazides and electron rich

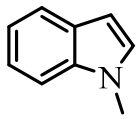
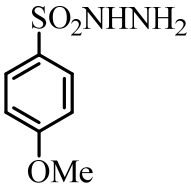
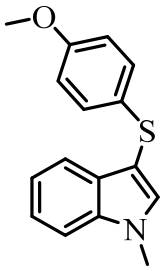
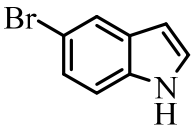
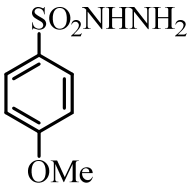
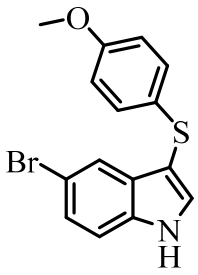
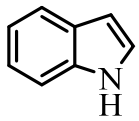
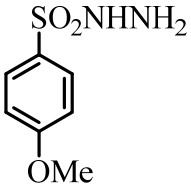
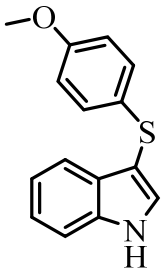
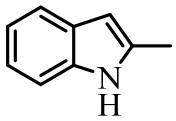
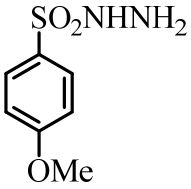
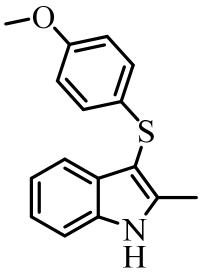
hydrazides. Furthermore, alkyl hydrazide also participated well in this reaction (**Table 3**, entries 10, 11).

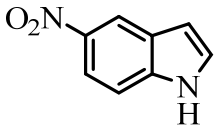
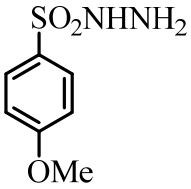
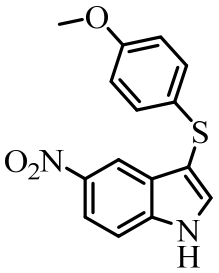
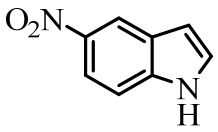
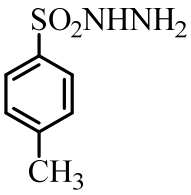
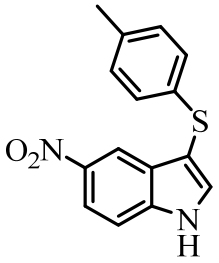
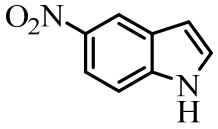
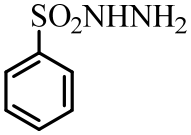
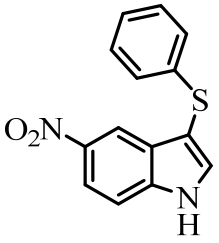
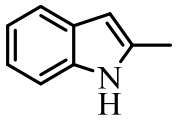
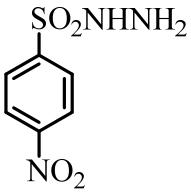
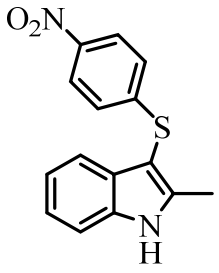


S. No.	Indoles	Hydrazides	Product	Time & yield
1				(2.5 h, 91%)
2				(2.5 h, 90%)
3				(2.5 h, 91%)

4				(2.5 h, 94%)
5				(2.5 h, 92%)
6				(2.5 h, 95%)
7				(2.5 h, 95%)
8				(2.5 h, 93%)

9				(2.5 h, 90%)
10				(2 h, 94%)
11				(2 h, 91%)
12				(2.5 h, 96%)
13				(2.5 h, 92%)

14				(2.5 h, 94%)
15				(2 h, 92%)
16				(2 h, 91%)
17				(2.5 h, 93%)

18				(1 h, 32%)
19				(1 h, 30%)
20				(1 h, 30%)
21				(1.5 h, 94%)

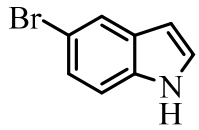
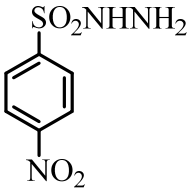
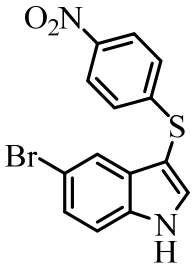
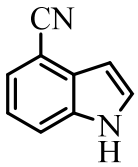
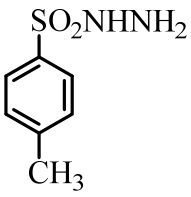
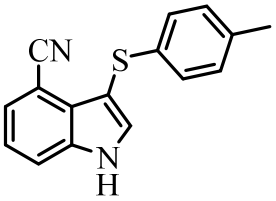
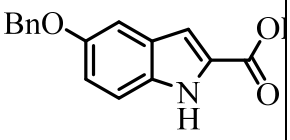
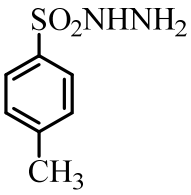
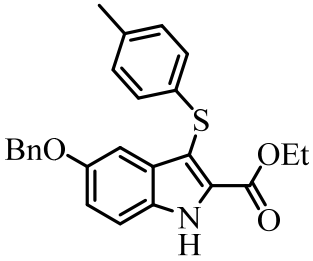
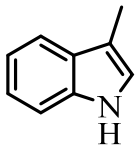
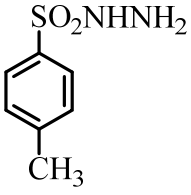
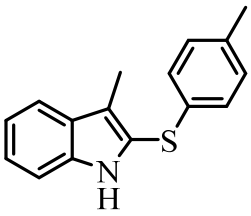
22				(1.5 h, 95%)
23				(2 h, 33%)
24				(1.5 h, 93%)
25				(2.5 h, 90%)

Table 3: Reaction of various indoles with sulfonylhydrazides in the presence of $CeCl_3.7H_2O$-NaI

Alkoxy, aryloxy, bromo, nitro, cyano, ester functional groups were well tolerated under the reaction conditions. Generally, Indole C3 position is more nucleophilic centre than C2, however when C3 is blocked by a substituent the reaction site will be the C2 position of

Indole (**Table 3**, entry 25). The reactions proceeded rapidly at 100 °C affording 3-sulfenylated indoles in excellent yields.

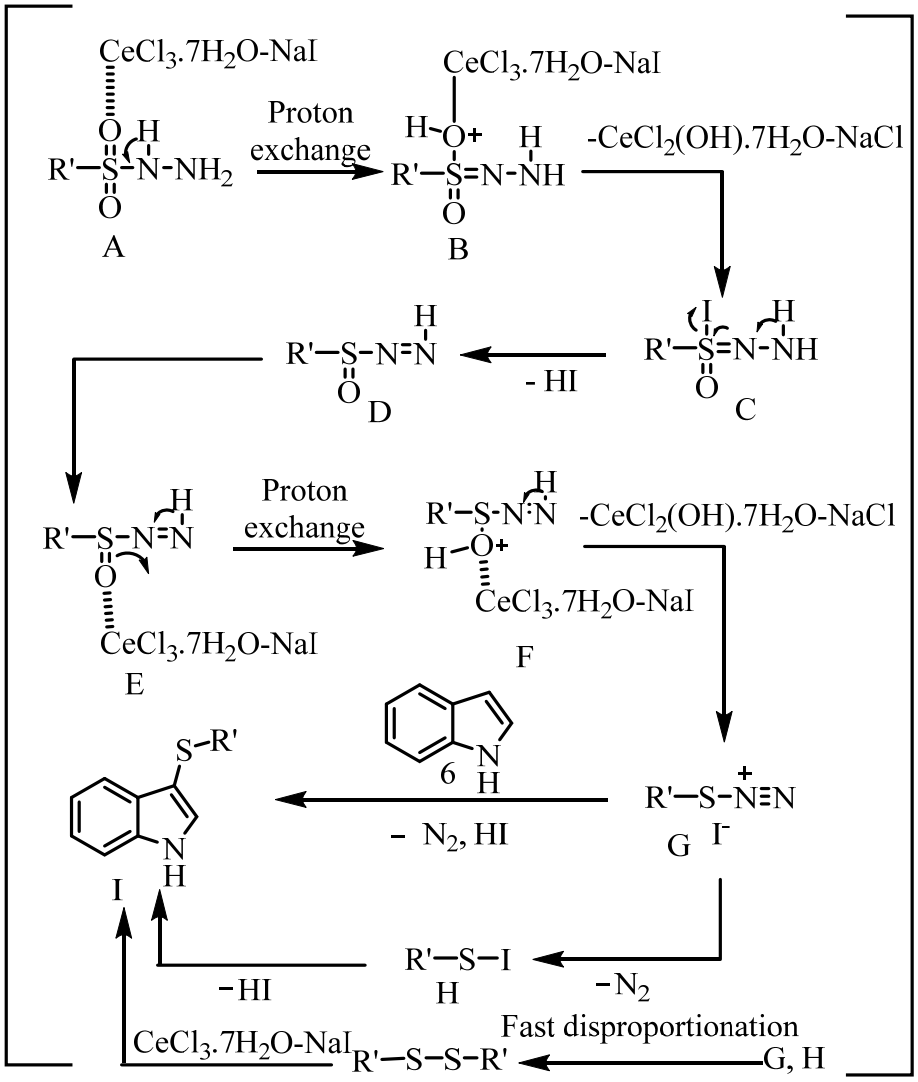


Figure 2: The plausible mechanism for regioselective sulfenylation of indoles

To find out the reactive intermediate responsible for reaction, we took the GC-MS of the crude reaction after 10 min of the addition of all the reagents. We observed the formation of phenyldisufide (**Fig. 2**). It should be noted that the high lability of sulfenyl iodide, and their fast disproportionation gives the corresponding disulfide. Based on the above results we proposed a plausible reaction mechanism for the formation of product as depicted in Figure 2. The exact nature of reactive species using $CeCl_3.7H_2O$–NaI combination is not yet known.

Even studies like X-ray photoelectron spectroscopy (XPS) could not deduce the coordination environment of the Ce(III) ion. However the monomeric $CeCl_3.7H_2O$–NaI combination is known to have enhanced Lewis acid properties.[20] As illustrated in Figure 2, $CeCl_3.7H_2O$–NaI system first coordinates with the oxygen atom of sulfonylhydrazide A followed by proton transfer from nitrogen to oxygen leading to the intermediate B. Subsequent nucleophilic attack of iodide on the sulfur atom of B gives rise C. HI is liberated from the intermediate C to give iodosulfinyl diazene D which again coordinates with $CeCl_3.7H_2O$–NaI nitrogen to oxygen (E→F) followed by attack of iodide ion furnishing the thiodiazonium intermediate G. This intermediate undergoes regioselective Friedel Craft's reaction with indole to generate the required product I. On the other hand displacement of molecular nitrogen from G gives the sulfenyl iodide H, which is attacked by indole **6** to give the required product 3-aryl sulfenyl indole derivatives I. A similar mechanism for sulfenylation of *N*-methyl amides with arene sulfoylhydrazides has been proposed using Mn(II)acetate.[19]

4.1.5. Conclusion

In summary we developed a simple, convenient and efficient protocol for the sulfenylation of indoles via cleavage of sulfur–oxygen and sulfur–nitrogen bonds using $CeCl_3.7H_2O$-NaI as a novel reagent system. This method offers several advantages such as broad substrate scope, functional group tolerance, high yields and excellent regioselectivity. The experimental simplicity makes it a useful and attractive strategy for the preparation of 3-sulfenyl indoles.

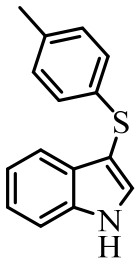
4.1.6. Experimental Section

General experimental procedure:

To a stirred solution of *p*-toluenesulfonylhydrazide (186 mg, 1 mmol) in ethanol (5 mL), cerium chloride heptahydrate (186 mg, 1 mmol) and sodium iodide (75 mg, 1 mmol) were added at rt and refluxed to 100 °C in a sealed tube (15 mL) for 10 min (color of reaction mixture turns to pale yellow color). Then indole (117 mg, 1 mmole) was added in one shot and continued the reaction for 2.5 h in a sealed tube at 100 °C. Reaction monitoring was done by TLC. After completion of the reaction, it was quenched with water and extracted with

EtOAc (2 x 5 mL). The combined organic layers were dried over Na_2SO_4, and concentrated under vaccum. The crude product was purified using silica gel column chromatography. Yield 217.5 mg, 91%. All reactions are performed on 1 mmol scale.

3-(*p*-Tolylthio)-1*H*-indole 1:



Yield: 91%, White solid.

Mol. Formula: $C_{15}H_{13}NS$

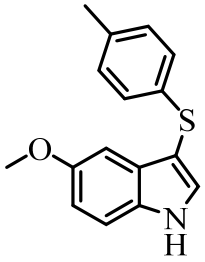
Mp =124-126 °C (*Lit.*[14] 124-126 °C)

^{1}H NMR (200MHz, $CDCl_3$) δ = 8.54 - 8.29 (m, 1 H), 7.63 (d, *J* = 7.7 Hz, 1 H), 7.53 - 7.39 (m, 2 H), 7.35 - 7.11 (m, 2 H), 7.09 - 6.92 (m, 4 H), 2.26 (s, 3 H)

^{13}C NMR (50MHz, $CDCl_3$) δ = 136.4, 135.4, 134.6, 1304, 129.5, 129.1, 126.2, 122.9, 120.8, 119.6, 111.5, 103.4, 20.8

HRMS (ESI) for $C_{15}H_{13}NS$ $(M+H)^+$ found 240.0841, calcd 240.0841

5-Methoxy-3-(*p*-tolylthio)-1*H*-indole 2:



Yield: 90%, Brown oily liquid

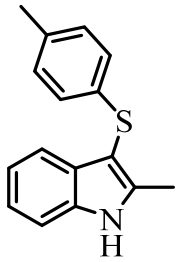
Mol. Formula: $C_{16}H_{15}ONS$

^{1}H NMR (200MHz, $CDCl_3$) δ = 8.32 (br. s., 1 H), 7.44 (d, *J* = 2.5 Hz, 1 H), 7.32 (d, *J* = 8.7 Hz, 1 H), 7.11 - 6.95 (m, 5 H), 6.92 (dd, *J* = 2.5, 8.8 Hz, 1 H), 3.80 (s, 3 H), 2.27 (s, 3 H)

^{13}C NMR (50 MHz, $CDCl_3$) δ = 155.1, 135.6, 134.5, 131.3, 131.1, 130.0, 129.5, 126.0, 113.5, 112.3, 102.8, 100.8, 55.8, 20.8

HRMS (ESI) for $C_{16}H_{15}ONS$ $(M + H)^+$ found 270.0945, calcd 270.0947

2-Methyl-3-(*p*-tolylthio)-1*H*-indole 3:



Yield: 91%, White solid

Mp = 102-103 °C (*Lit.*[21] 98.2-100 °C)

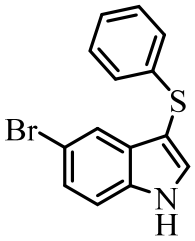
Mol. Formula: $C_{16}H_{15}NS$

^{1}H NMR (400MHz, $CDCl_3$) δ = 8.20 (br. s., 1 H), 7.57 (d, *J* = 7.6 Hz, 1 H), 7.34 (d, *J* = 8.1 Hz, 1 H), 7.23 - 7.17 (m, 1 H), 7.16 - 7.11 (m, 1 H), 7.00 - 6.97 (m, 4 H), 2.53 (s, 3 H), 2.26 (s, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 140.8, 135.7, 135.4, 134.3, 130.3, 129.4, 125.8, 122.1, 120.6, 119.0, 110.5, 100.0, 20.8, 12.1

HRMS (ESI) for $C_{16}H_{15}NS$ $(M + H)^+$ found 254.0995, calcd 254.0998

5-Bromo-3-(phenylthio)-1*H*-indole 4:



Yield: 94%, Orange solid

Mp: 120-121 °C (*Lit.*[12c] 120-121 °C)

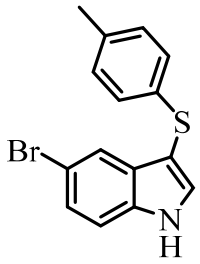
Mol. Formula: $C_{14}H_{10}NBrS$

^{1}H NMR (400MHz, $CDCl_3$) δ = 8.45 (br. s., 1 H), 7.77 (s, 1 H), 7.49 (d, *J* = 2.4 Hz, 1 H), 7.39 - 7.29 (m, 2 H), 7.23 - 7.16 (m, 2 H), 7.13 - 7.05 (m, 3 H)

^{13}C NMR (125MHz, $CDCl_3$) δ = 138.7, 135.1, 131.8, 130.9, 128.8, 126.1, 125.8, 125.0, 122.2, 114.5, 113.1, 102.7

HRMS (ESI) for $C_{14}H_{10}NBrS$ $(M + H)^+$ found 302.9710, calcd 302.9712

5-Bromo-3-(*p*-tolylthio)-1*H*-indole 5:



Yield: 92%, Brown solid

Mol. Formula: $C_{15}H_{12}NBrS$

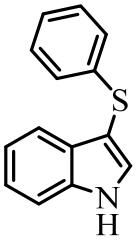
Mp: 121-124 °C (*Lit.*[21a] 123-125 °C)

^{1}H NMR (500MHz, $CDCl_3$) δ = 8.43 (br. s., 1 H), 7.77 (s, 1 H), 7.47 (br. s., 1 H), 7.38 - 7.28 (m, 2 H), 7.07 - 6.98 (m, 4 H), 2.28 (s, 3 H)

^{13}C NMR (125MHz, $CDCl_3$) δ = 135.1, 134.9, 134.9, 131.6, 130.9, 129.6, 126.3, 126.0, 122.2, 114.4, 113.0, 103.4, 20.8

HRMS (ESI) for $C_{15}H_{12}NBrS$ $(M + H)^+$ found 317.9949, calcd 317.9947

3-(Phenylthio)-1*H*-indole 6:



Yield: 95%, White solid

Mol. Formula: $C_{14}H_{11}NS$

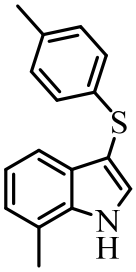
Mp: 150-152 °C (*Lit.*[14] 150-152 °C)

^{1}H NMR (400MHz, $CDCl_3$) δ = 8.40 (br. s., 1 H), 7.64 (d, *J* = 8.1 Hz, 1 H), 7.53 - 7.42 (m, 2 H), 7.33 - 7.27 (m, 1 H), 7.22 - 7.15 (m, 3 H), 7.15 - 7.11 (m, 2 H), 7.10 - 7.05 (m, 1 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 139.2, 136.5, 130.6, 129.1, 128.7, 125.8, 124.7, 123.0, 120.9, 119.6, 111.5, 102.8

HRMS (ESI) for $C_{14}H_{11}NS$ $(M + H)^+$ found 226.0684, calcd 226.0685

7-Methyl-3-(*p*-tolylthio)-1*H*-indole 7: [21c]



Yield: 95%, White solid

Mol. Formula: $C_{16}H_{15}NS$

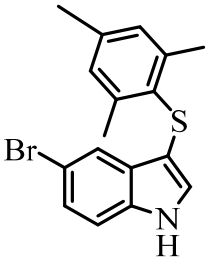
Mp : 113-114 °C

^{1}H NMR (400MHz, $CDCl_3$) δ = 8.29 (br. s., 1 H), 7.53 - 7.48 (m, 1 H), 7.47 (s, 1 H), 7.15 - 7.04 (m, 4 H), 7.03 - 6.97 (m, 2 H), 2.54 (s, 3 H), 2.28 (s, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 136.0, 135.5, 134.6, 130.1, 129.4, 128.7, 126.2, 123.5, 121.0, 120.7, 117.4, 103.8, 20.8, 16.4

HRMS (ESI) for $C_{16}H_{15}NS$ $(M + H)^+$ found 254.0995, calcd 254.0998

5-Bromo-3-(mesitylthio)-1*H*-indole 8:



Yield: 93%, Brown solid

Mol. Formula: $C_{17}H_{16}NBrS$

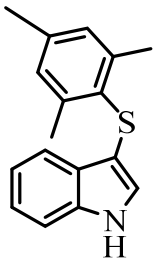
Mp : 102-103 °C.

^{1}H NMR (400MHz, $CDCl_3$) δ = 8.10 (br. s., 1 H), 7.69 (s, 1 H), 7.27 (dd, *J* = 1.7, 8.6 Hz, 1 H), 7.19 (dd, *J* = 1.5, 8.6 Hz, 1 H), 7.00 - 6.97 (m, 1 H), 6.94 (s, 2 H), 2.53 (s, 6 H), 2.28 (s, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 142.2, 138.1, 134.7, 129.8, 129.7, 129.2, 126.5, 125.4, 122.1, 113.4, 112.7, 108.1, 22.0, 20.9

HRMS (ESI) for $C_{17}H_{16}NBrS$ $(M + H)^+$ found 346.0258, calcd 346.0260

3-(Mesitylthio)-1*H*-indole 9:



Yield: 90%, Orange solid

Mol. Formula: $C_{17}H_{17}NS$

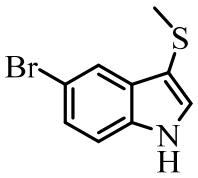
Mp: 124-126 °C (*Lit.*[14] 125-127 °C)

^{1}H NMR (400MHz, $CDCl_3$) δ = 8.09 (br. s., 1 H), 7.54 (d, *J* = 7.8 Hz, 1 H), 7.35 (d, *J* = 8.1 Hz, 1 H), 7.20 (t, *J* = 7.6 Hz, 1 H), 7.15 - 7.08 (m, 1 H), 7.05 (d, *J* = 2.4 Hz, 1 H), 6.93 (s, 2 H), 2.55 (s, 6 H), 2.28 (s, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 142.2, 137.8, 136.1, 130.0, 129.2, 128.2, 125.5, 122.5, 120.0, 119.5, 111.2, 108.0, 22.1, 20.9

HRMS (ESI) for $C_{17}H_{17}NS$ $(M + H)^+$ found 268.1149, calcd 268.1154.

5-Bromo-3-(methylthio)-1*H*-indole 10:



Yield: 94%, Yellow sticky liquid

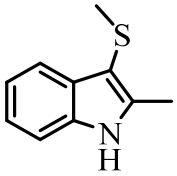
Mol. Formula: C_9H_8NBrS

^{1}H NMR (400MHz, $CDCl_3$) δ = 8.29 (br. s., 1 H), 7.92 (br. s., 1 H), 7.38 - 7.17 (m, 3 H), 2.39 (s, 3 H).

^{13}C NMR (100MHz, $CDCl_3$) δ = 134.8, 130.5, 129.0, 125.6, 121.8, 113.7, 113.0, 107.8, 20.3

HRMS (ESI) for C_9H_8NBrS $(M + H)^+$ found 240.9554, calcd 240.9555

2-Methyl-3-(methylthio)-1*H*-indole 11:



Yield: 91%, Yellow sticky liquid

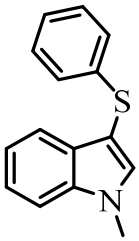
Mol. Formula: $C_{10}H_{11}NS$

^{1}H NMR (400MHz, $CDCl_3$) δ = 8.03 (br. s., 1 H), 7.82 - 7.75 (m, 1 H), 7.37 - 7.29 (m, 1 H), 7.29 - 7.22 (m, 2 H), 2.57 (s, 3 H), 2.34 (s, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 138.9, 135.1, 129.9, 121.7, 120.1, 118.5, 110.6, 104.1, 19.7, 11.9

HRMS (ESI) for $C_{10}H_{11}NS$ $(M + H)^+$ found 178.0683, calcd 178.0685

1-Methyl-3-(phenylthio)-1*H*-indole 12:



Yield: 96%, Brown solid

Mol. Formula: $C_{15}H_{13}NS$

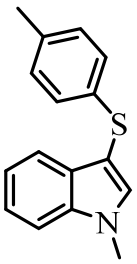
Mp : 88-90 °C (*Lit.*[12a] 84-86 °C)

^{1}H NMR (500MHz, $CDCl_3$) δ = 7.64 (d, *J* = 7.9 Hz, 1 H), 7.41 (d, *J* = 8.2 Hz, 1 H), 7.36 - 7.30 (m, 2 H), 7.21 - 7.15 (m, 3 H), 7.15 - 7.11 (m, 2 H), 7.09 - 7.04 (m, 1 H), 3.86 (s, 3 H)

^{13}C NMR (125MHz, $CDCl_3$) δ = 139.6, 137.5, 135.0, 129.8, 128.6, 125.7, 124.6, 122.5, 120.5, 119.7, 109.7, 100.5, 33.1

HRMS (ESI) for $C_{15}H_{13}NS$ $(M + H)^+$ found 240.0841, calcd 240.0841

1-Methyl-3-(*p*-tolylthio)-1*H*-indole 13:



Yield: 92%, White solid

Mol. Formula: $C_{16}H_{15}NS$

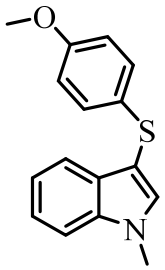
Mp : 88-90 °C (*Lit.*[21d] 86-88 °C)

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.58 (d, *J* = 8.1 Hz, 1 H), 7.35 - 7.30 (m, 1 H), 7.27 - 7.20 (m, 2 H), 7.15 - 7.09 (m, 1 H), 6.98 (d, *J* = 8.3 Hz, 2 H), 6.92 (d, *J* = 8.1 Hz, 2 H), 3.78 (s, 3 H), 2.20 (s, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 137.5, 135.9, 134.8, 134.5, 129.8, 129.4, 126.2, 122.5, 120.4, 119.7, 109.6, 101.3, 33.1, 20.8

HRMS (ESI) for $C_{16}H_{15}NS$ $(M + H)^+$ found 254.0995, calcd 254.0998

3-((4-Methoxyphenyl)thio)-1-methyl-1*H*-indole 14:[12a, 21a]



Yield: 94%, Semi solid

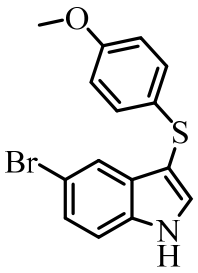
Mol. Formula: $C_{16}H_{15}ONS$

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.70 - 7.63 (m, 1 H), 7.38 - 7.24 (m, 3 H), 7.23 - 7.11 (m, 3 H), 6.78 - 6.69 (m, 2 H), 3.75 (s, 3 H), 3.71 (s, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 157.6, 137.4, 134.4, 129.9, 129.6, 128.3, 122.3, 120.2, 119.5, 114.3, 109.6, 102.1, 55.2, 32.9

HRMS (ESI) for $C_{16}H_{15}ONS$ $(M + H)^+$ found 270.0945, calcd 270.0947

5-Bromo-3-((4-methoxyphenyl)thio)-1*H*-indole 15:



Yield: 92%, Yellow solid.

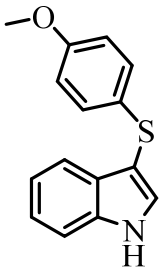
Mol. Formula: $C_{15}H_{12}BrNOS$

Mp: 100-103 °C (*Lit.*[21b] 99-100 °C)

^{1}H NMR (400MHz, $CDCl_3$) δ = 8.43 (br. s., 1 H), 7.79 (s, 1 H), 7.43 (d, *J* = 2.4 Hz, 1 H), 7.33 (dd, *J* = 2.0, 8.6 Hz, 1 H), 7.25 (d, *J* = 8.6 Hz, 1 H), 7.17 - 7.12 (m, 2 H), 6.80 - 6.74 (m, 2 H), 3.75 (s, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 157.9, 135.0, 131.2, 130.8, 128.9, 128.7, 125.9, 122.0, 114.6, 114.2, 113.0, 104.3, 55

3-((4-Methoxyphenyl)thio)-1*H*-indole 16:



Yield: 91%. Yellow solid

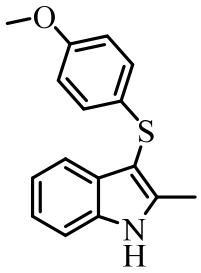
Mol. Formula: $C_{15}H_{13}NOS$

Mp: 105-108 °C (*Lit.*[12c] 111-112 °C)

^{1}H NMR (400MHz, $CDCl_3$) δ = 8.33 (br. s., 1 H), 7.68 (d, *J* = 7.6 Hz, 1 H), 7.45 - 7.37 (m, 2 H), 7.28 (dt, *J* = 1.0, 7.6 Hz, 1 H), 7.25 - 7.15 (m, 3 H), 6.82 - 6.74 (m, 2 H), 3.75 (s, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 157.7, 136.4, 130.0, 129.4, 128.9, 128.5, 122.8, 120.7, 119.5, 114.4, 111.5, 104.3, 55.3

3-((4-Methoxyphenyl)thio)-2-methyl-1*H*-indole 17:



Yield: 93%, White solid

Mol. Formula: $C_{16}H_{15}ONS$

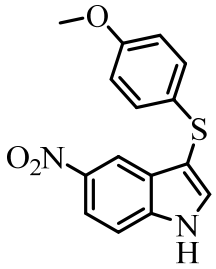
Mp : 110-112 °C (*Lit.*[21a] 119-120 °C)

^{1}H NMR (400MHz, $CDCl_3$) δ = 8.19 (br. s., 1 H), 7.59 (d, *J* = 7.6 Hz, 1 H), 7.33 (d, *J* = 8.1 Hz, 1 H), 7.24 - 7.11 (m, 2 H), 7.10 - 7.03 (m, 2 H), 6.78 - 6.71 (m, 2 H), 3.74 (s, 3 H), 2.54 (s, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 157.5, 141.0, 140.6, 135.3, 130.2, 129.9, 127.9, 122.1, 120.6, 118.9, 114.4, 110.5, 55.3, 12.1

HRMS (ESI) for $C_{16}H_{15}ONS$ $(M + H)^+$ found 270.0941, calcd 270.0947

3-((4-Methoxyphenyl)thio)-5-nitro-1H-indole 18:



Yield: 92%, Yellow solid.

Mol. Formula: $C_{15}H_{12}O_3N_2S$

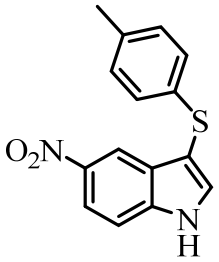
Mp: 169-170 °C

^{1}H NMR (400MHz, $CDCl_3$) δ = 8.86 (br. s., 1 H), 8.59 (d, *J* = 2.0 Hz, 1 H), 8.15 (dd, *J* = 2.0, 9.0 Hz, 1 H), 7.62 (s, 1 H), 7.47 (d, *J* = 8.8 Hz, 1 H), 7.24 - 7.16 (m, *J* = 8.8 Hz, 2 H), 6.84 - 6.74 (m, *J* = 8.6 Hz, 2 H), 3.75 (s, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 158.4, 142.7, 139.4, 132.6, 129.8, 128.7, 127.8, 118.6, 116.9, 114.7, 111.8, 108.8, 55.4

HRMS (ESI) for $C_{15}H_{12}O_3N_2S$ $(M + Na)^+$ found 323.0459, calcd 323.0461

5-Nitro-3-(*p*-tolylthio)-1*H*-indole 19:



Yield: 92%, Yellow solid

Mol. Formula: $C_{15}H_{12}O_2N_2S$

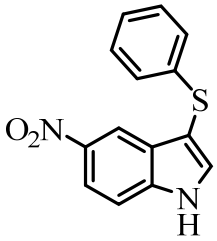
Mp: 194-195 °C (*Lit.*[21a] 189-193 °C)

^{1}H NMR (400MHz, $CDCl_3$) δ = 8.80 (br. s., 1 H), 8.58 (d, *J* = 2.0 Hz, 1 H), 8.17 (dd, *J* = 2.1, 8.9 Hz, 1 H), 7.65 (d, *J* = 2.2 Hz, 1 H), 7.49 (d, *J* = 9.0 Hz, 1 H), 7.10 - 6.96 (m, 4 H), 2.27 (s, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 142.8, 139.4, 135.6, 133.9, 133.1, 130.4, 129.7, 128.8, 127.1, 118.7, 116.9, 111.8, 20.9

HRMS (ESI) for $C_{15}H_{12}O_2N_2S$ $(M + Na)^+$ found 307.0510, calcd 307.0512

5-Nitro-3-(phenylthio)-1*H*-indole 20:



Yield: 95%, Yellow solid

Mol. Formula: $C_{14}H_{10}O_2N_2S$

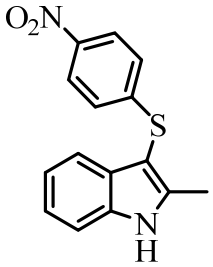
Mp : 93-94 °C (*Lit.*[14] 93-95 °C)

^{1}H NMR (400MHz, $CDCl_3$) δ = 8.93 (br. s., 1 H), 8.58 (d, *J* = 2.0 Hz, 1 H), 8.18 (dd, *J* = 2.2, 9.0 Hz, 1 H), 7.68 (d, *J* = 2.4 Hz, 1 H), 7.52 (d, *J* = 9.0 Hz, 1 H), 7.24 - 7.17 (m, 2 H), 7.16 - 7.07 (m, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 139.4, 137.8, 133.6, 128.9, 128.8, 126.4, 125.5, 118.7, 116.9, 111.9, 106.5

HRMS (ESI) for $C_{14}H_{10}O_2N_2S$ $(M + Na)^+$ found 293.0354, calcd 293.0355

2-Methyl-3-((4-nitrophenyl)thio)-1*H*-indole 21:



Yield: 94%, Yellow solid

Mp : 132-136 °C (*Lit.*[21e] 133 °C)

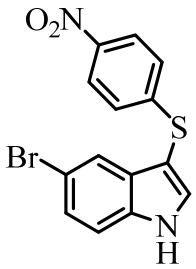
Mol. Formula: $C_{15}H_{12}O_2N_2S$

^{1}H NMR (400MHz, $CDCl_3$) δ = 8.45 (br. s., 1 H), 8.05 - 7.98 (m, 2 H), 7.50 - 7.38 (m, 2 H), 7.29 - 7.22 (m, 1 H), 7.19 - 7.14 (m, 1 H), 7.12 - 7.07 (m, 2 H), 2.53 (s, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 149.8, 144.8, 141.6, 135.5, 129.5, 124.9, 123.9, 122.7, 121.1, 118.5, 111.0, 96.9, 12.1

HRMS (ESI) for $C_{15}H_{12}O_2N_2S$ $(M + Na)^+$ found 307.0510, calcd 307.0512

5-Bromo-3-((4-nitrophenyl)thio)-1*H*-indole 22:



Yield: 95%, Yellow solid

Mp : 172-173 °C

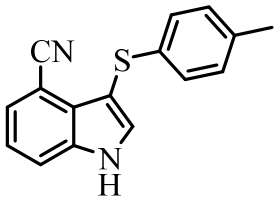
Mol. Formula: $C_{14}H_9O_2N_2BrS$

^{1}H NMR (400MHz, $CDCl_3$) δ = 8.75 (br. s., 1 H), 8.07 - 7.99 (m, 2 H), 7.67 (s, 1 H), 7.56 (d, *J* = 2.7 Hz, 1 H), 7.43 - 7.36 (m, 2 H), 7.16 - 7.08 (m, 2 H)

^{13}C NMR (100MHz $CDCl_3$) δ = 149.2, 145.0, 135.2, 132.4, 130.3, 126.6, 125.0, 124.0, 121.8, 114.9, 113.5, 99.9

HRMS (ESI) for $C_{14}H_9O_2N_2BrS$ $(M + Na)^+$ found 370.9457, calcd 370.9460

3-(*p*-Tolylthio)-1*H*-indole-4-carbonitrile 23:



Yield: 90%, White solid

Mol. Formula: $C_{16}H_{12}N_2S$

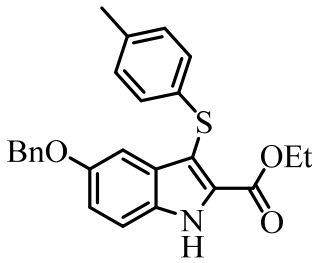
Mp: 168-170 °C

^{1}H NMR (400MHz, $CDCl_3$) δ = 9.30 (br. s., 1 H), 7.68 (d, *J* = 8.3 Hz, 1 H), 7.62 (s, 1 H), 7.53 (d, *J* = 7.3 Hz, 1 H), 7.30 - 7.23 (m, 1 H), 7.07 (d, *J* = 8.1 Hz, 2 H), 6.98 (d, *J* = 8.1 Hz, 2 H), 2.24 (s, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 136.9, 135.4, 135.2, 134.3, 129.6, 128.5, 128.0, 126.8, 122.3, 118.2, 116.9, 103.5, 102.5, 20.8

HRMS (ESI) for $C_{16}H_{12}N_2S$ $(M + Na)^+$ found 287.0611, calcd 287.0613

Ethyl 5-(benzyloxy)-3-(*p*-tolylthio)-1*H*-indole-2-carboxylate 24:



Yield: 93%, White solid.

Mol. Formula: $C_{25}H_{23}O_3NS$

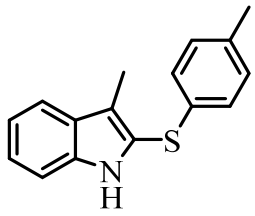
Mp: 133-135 °C

^{1}H NMR (400MHz, $CDCl_3$) δ = 9.19 (br. s., 1 H), 7.46 - 7.31 (m, 6 H), 7.17 - 7.07 (m, 4 H), 7.02 (d, *J* = 8.1 Hz, 2 H), 4.98 (s, 2 H), 4.41 (q, *J* = 7.1 Hz, 2 H), 2.30 (s, 3 H), 1.35 (t, *J* = 7.1 Hz, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 172.6, 161.2, 154.3, 137.0, 135.3, 134.0, 130.9, 130.7, 129.5, 128.8, 128.5, 127.9, 127.7, 118.4, 113.0, 110.6, 102.8, 70.4, 61.3, 20.9, 14.2

HRMS (ESI) for $C_{25}H_{23}O_3NS$ $(M + Na)^+$ found 440.1290, calcd 440.1291

3-Methyl-2-(*p*-tolylthio)-1*H*-indole 25:



Yield: 90%, White solid

Mol. Formula: $C_{16}H_{15}NS$

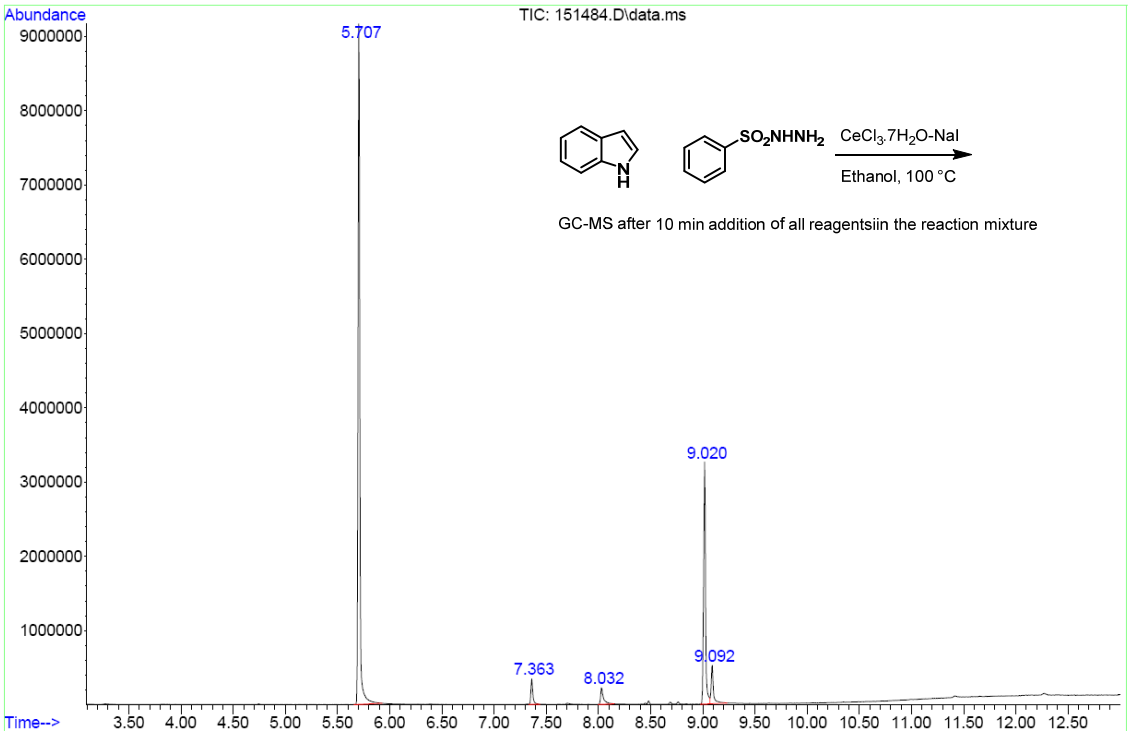
Mp: 93-95 °C

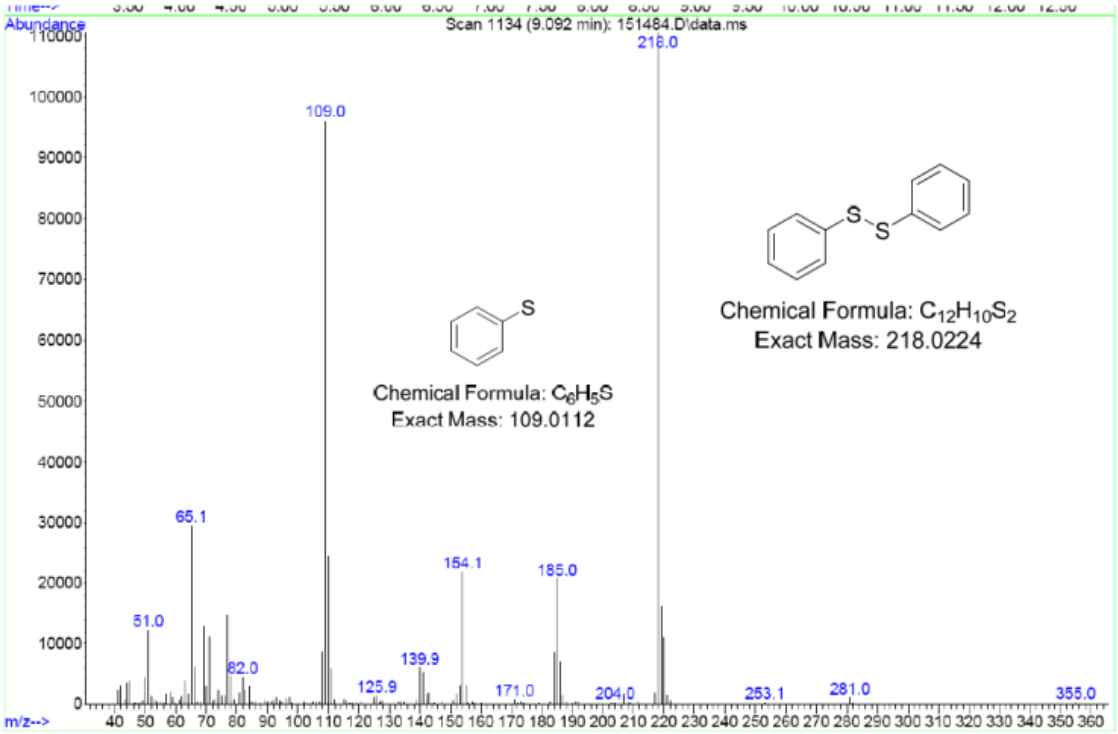
^{1}H NMR (200MHz, $CDCl_3$) δ = 7.83 (br. s., 1 H), 7.55 - 7.46 (m, 1 H), 7.22 - 7.11 (m, 2 H), 7.05 (ddd, *J* = 2.4, 5.7, 7.8 Hz, 1 H), 6.98 - 6.84 (m, 4 H), 2.31 (s, 3 H), 2.18 (s, 3 H)

^{13}C NMR (125MHz, $CDCl_3$) δ = 136.7, 135.7, 133.2, 130.1, 129.8, 128.4, 127.0, 123.3, 122.2, 119.5, 119.3, 110.8, 20.9, 9.4

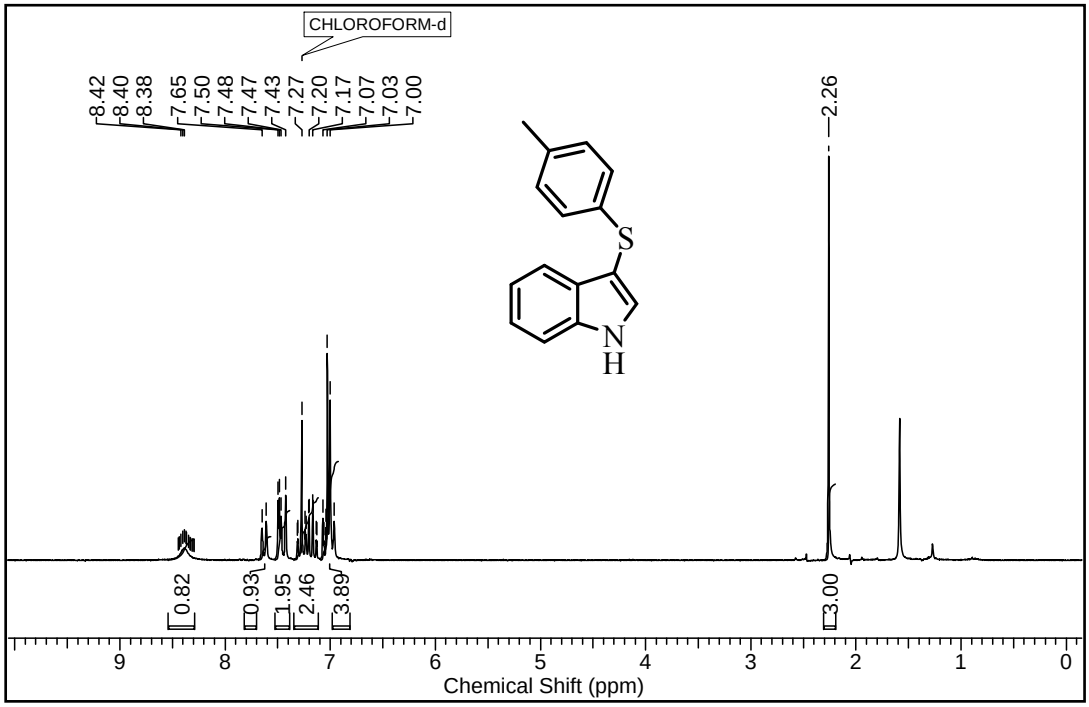
4.1.7. Spectra:

GC spectrum of crude reaction mixture containing indole and benzenesulfonylhydrazide

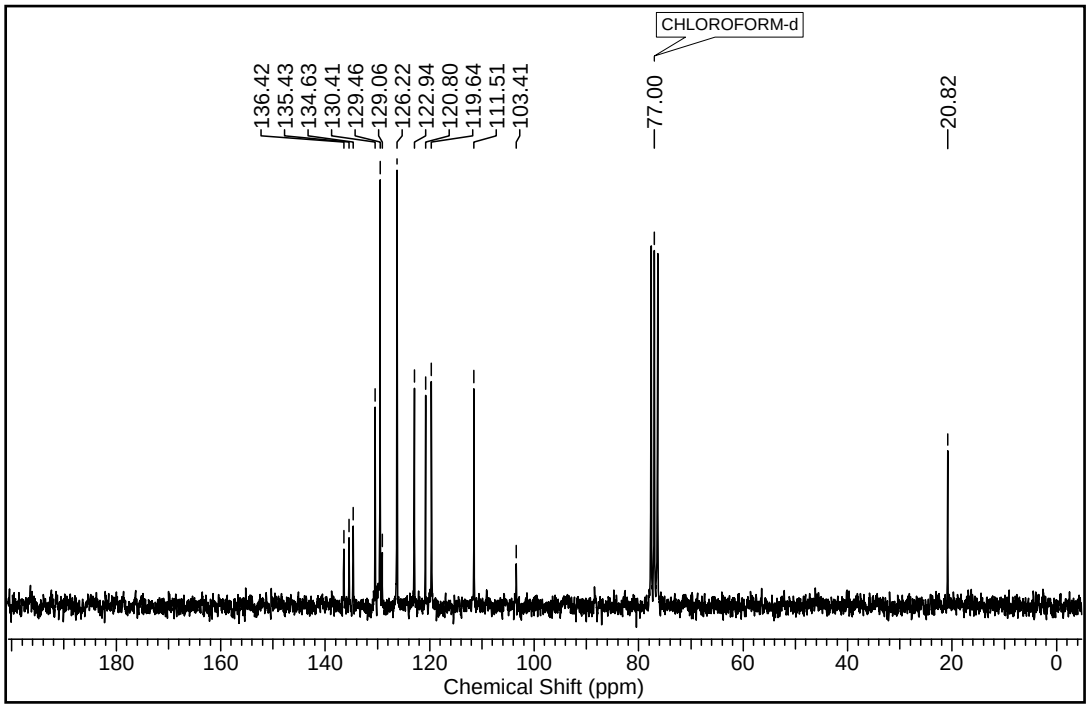




3-(*p*-Tolylthio)-1*H*-indole 1:

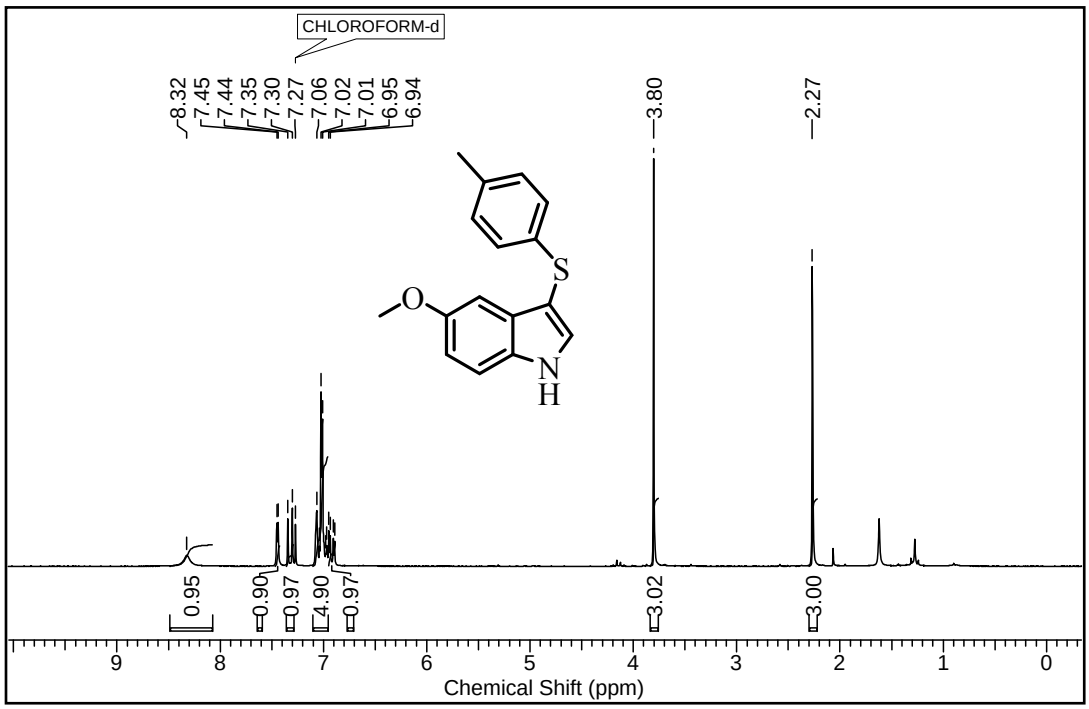


➢ **^{1}H NMR of the compound 1 in $CDCl_3$**

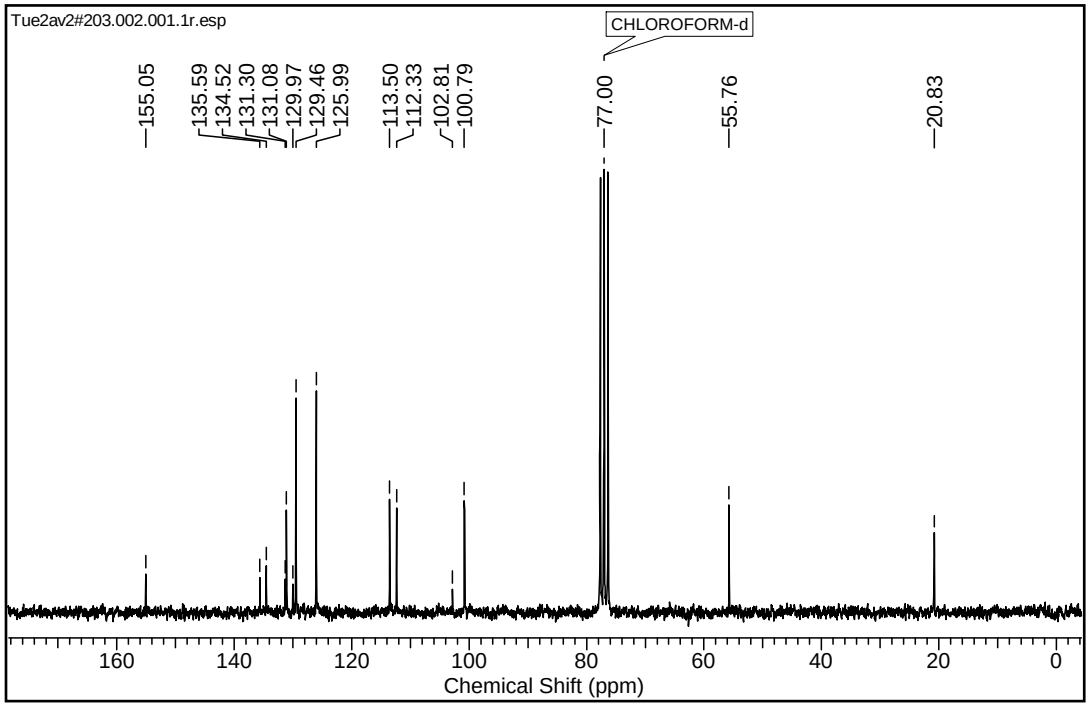


➢ **^{13}C NMR of the compound 1 in $CDCl_3$**

5-Methoxy-3-(*p*-tolylthio)-1*H*-indole 2:

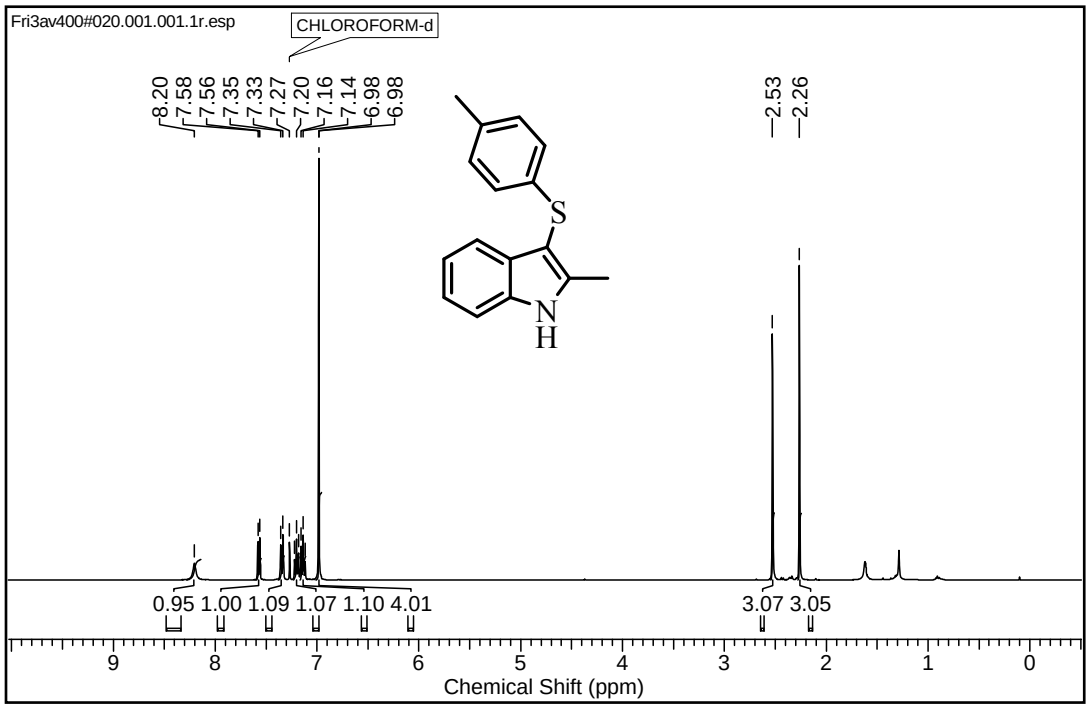


➢ **^{1}H NMR of the compound 2 in $CDCl_3$**

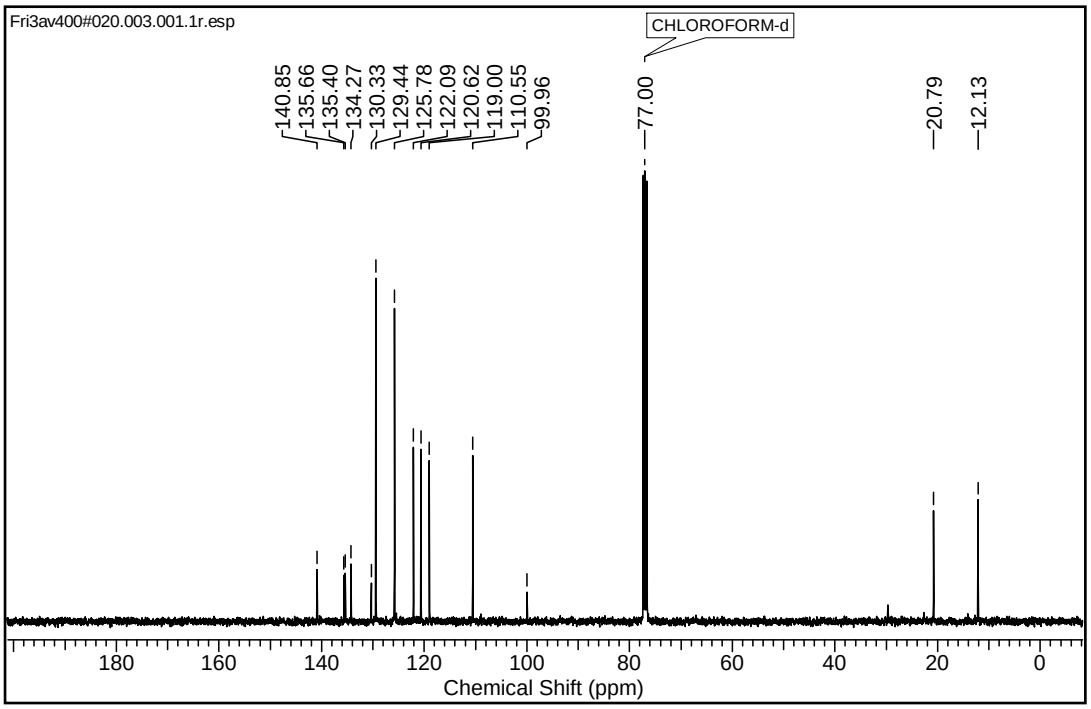


➢ **^{13}C NMR of the compound 2 in $CDCl_3$**

2-Methyl-3-(*p*-tolylthio)-1*H*-indole:

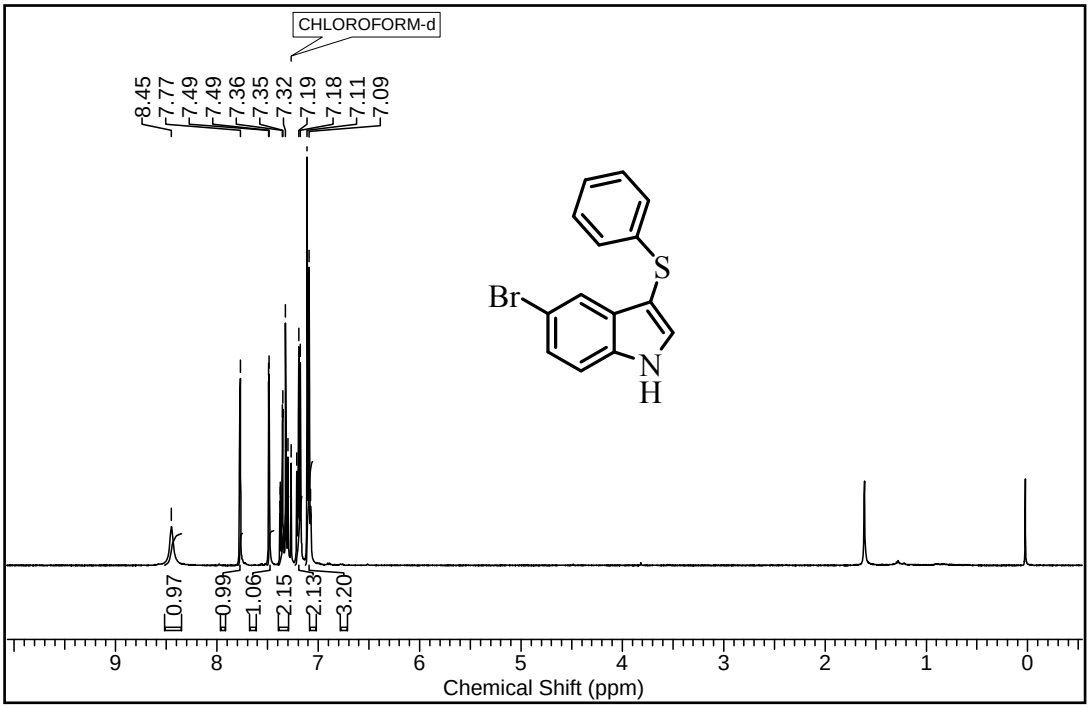


- **^{1}H NMR of the compound 3 in $CDCl_3$**

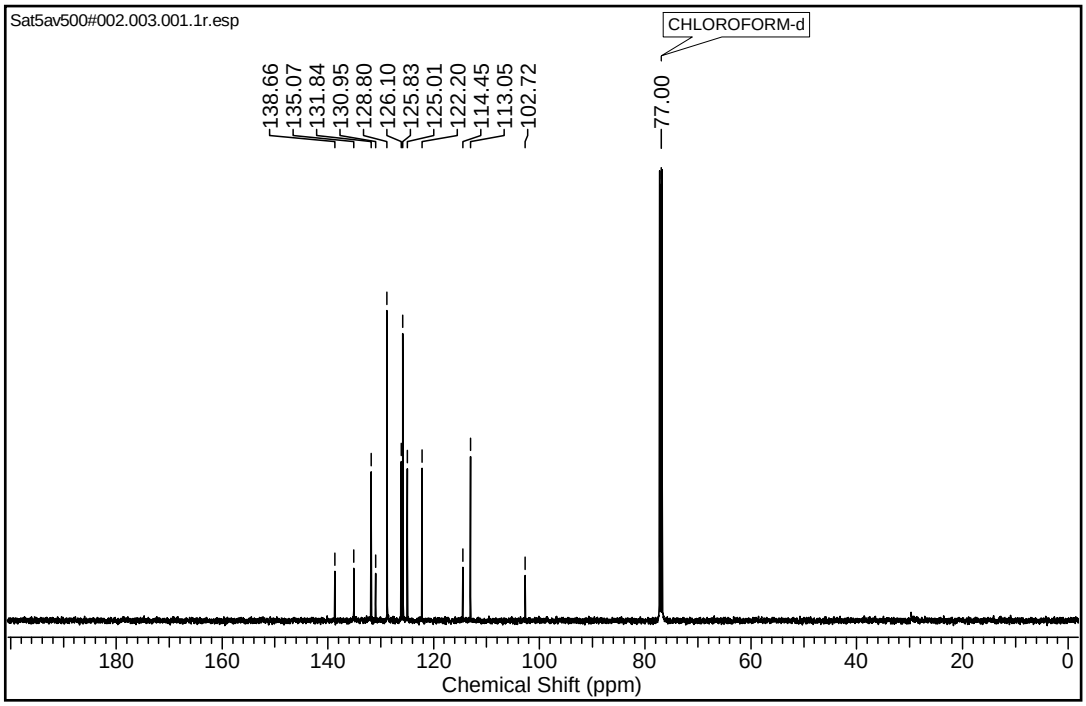


- **^{13}C NMR of the compound 3 in $CDCl_3$**

5-Bromo-3-(phenylthio)-1*H*-indole 4:

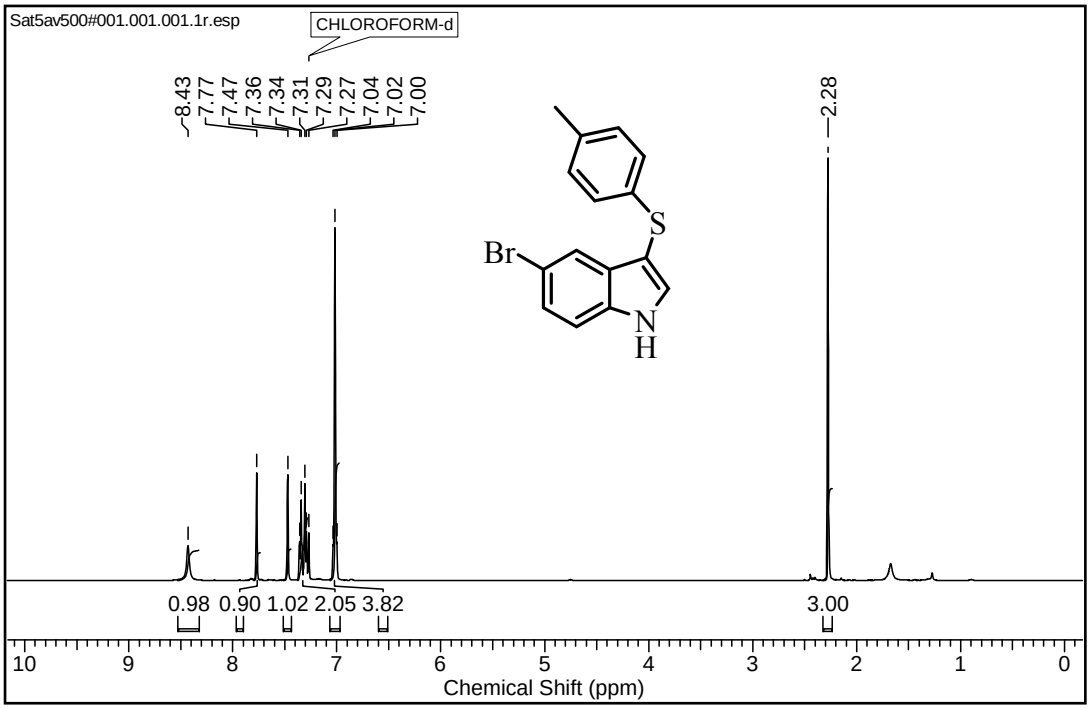


➢ **^{1}H NMR of the compound 4 in $CDCl_3$**

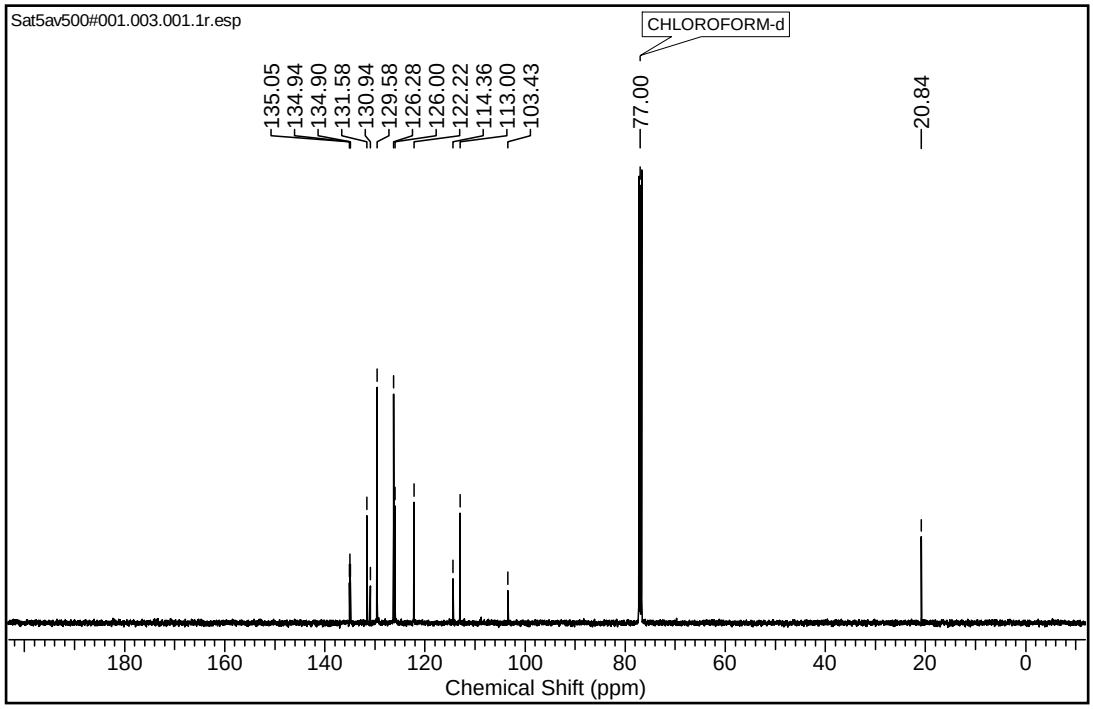


➢ **^{13}C NMR of the compound 4 in $CDCl_3$**

5-Bromo-3-(*p*-tolylthio)-1*H*-indole 5:

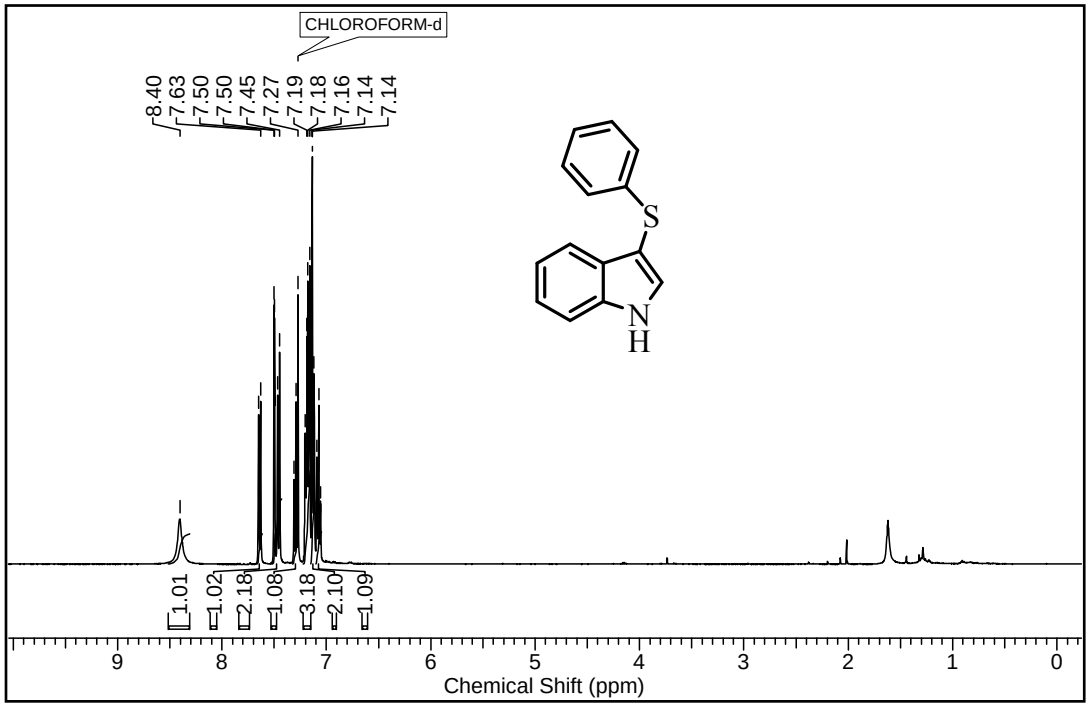


➢ **^{1}H NMR of the compound 5 in $CDCl_3$**

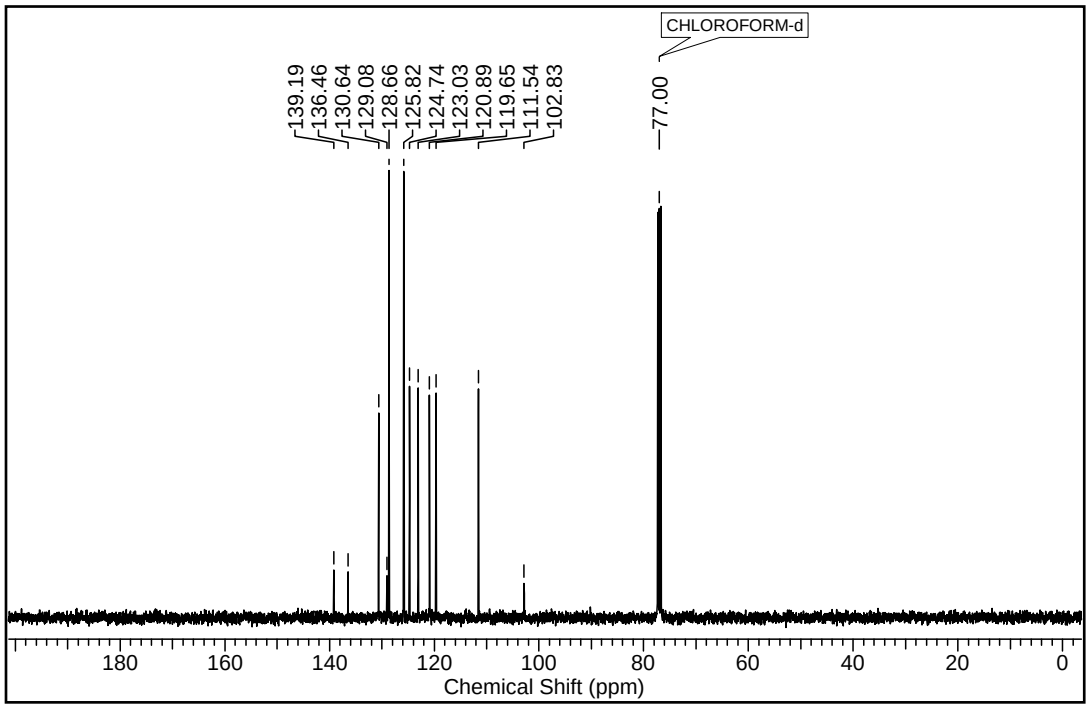


➢ **^{13}C NMR of the compound 5 in $CDCl_3$**

3-(Phenylthio)-1*H*-indole 6:

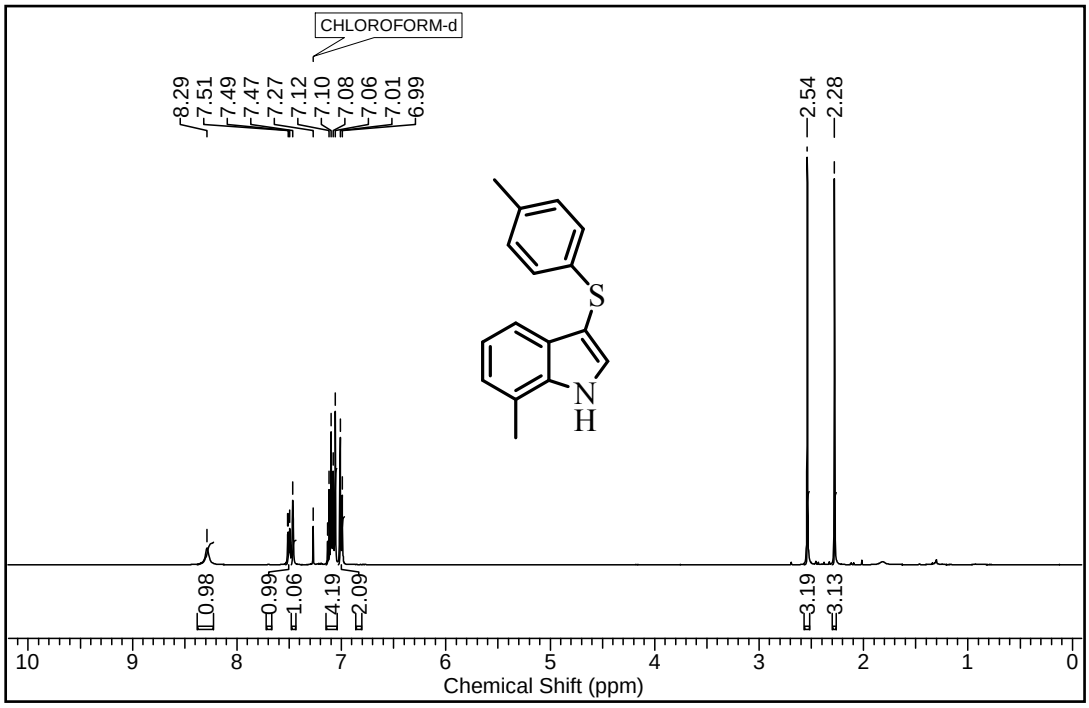


➢ **^{1}H NMR of the compound 6 in $CDCl_3$**

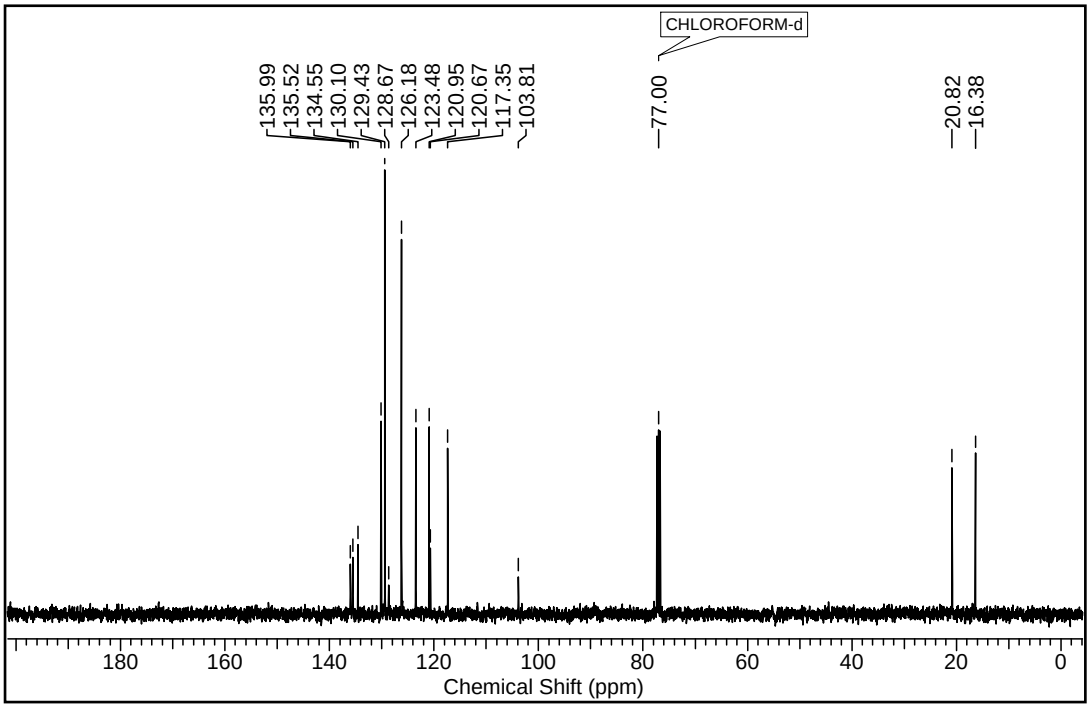


➢ **^{13}C NMR of the compound 6 in $CDCl_3$**

7-Methyl-3-(*p*-tolylthio)-1*H*-indole 7:

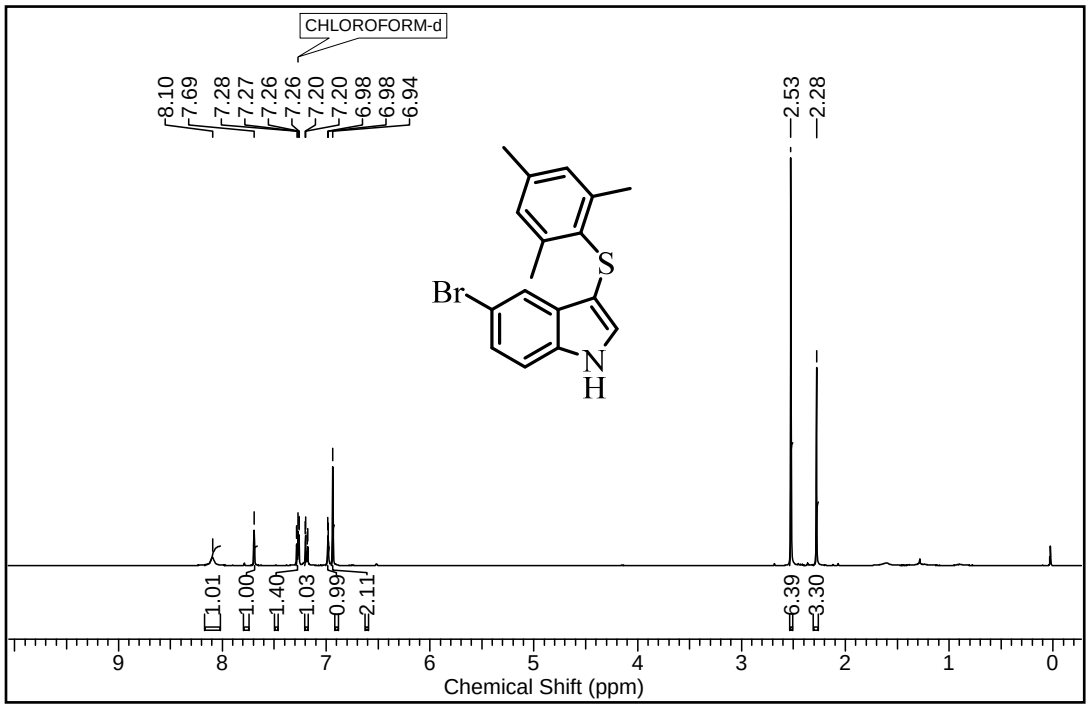


➢ **^{1}H NMR of the compound 7 in $CDCl_3$**

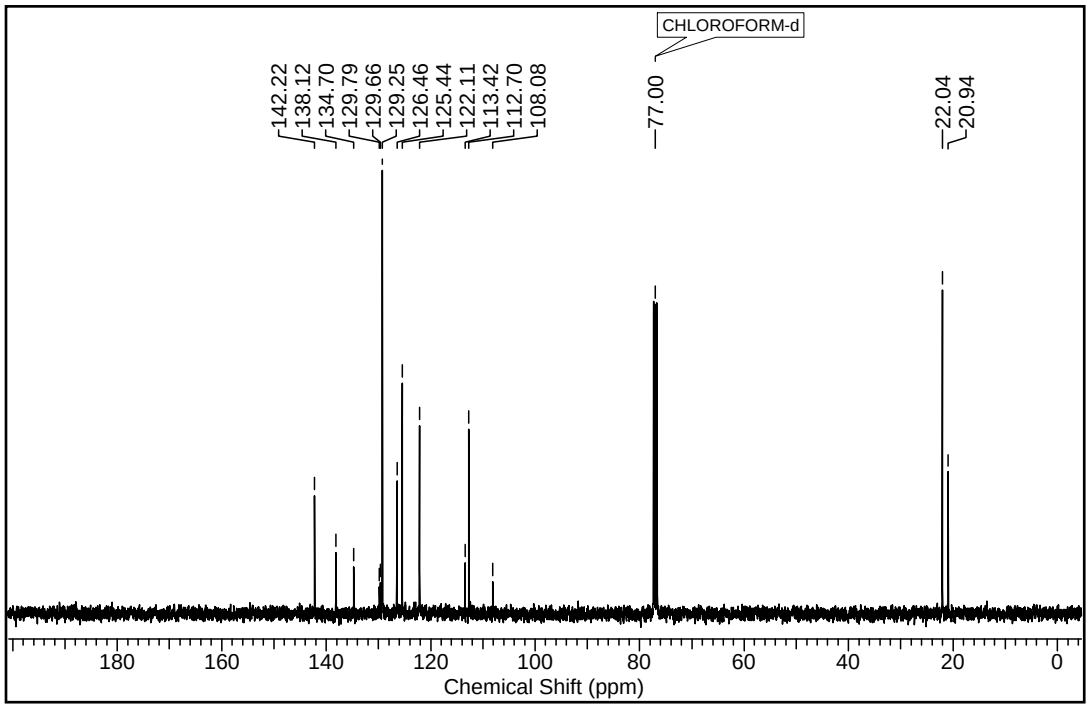


➢ **^{13}C NMR of the compound 7 in $CDCl_3$**

5-Bromo-3-(mesitylthio)-1*H*-indole 8:

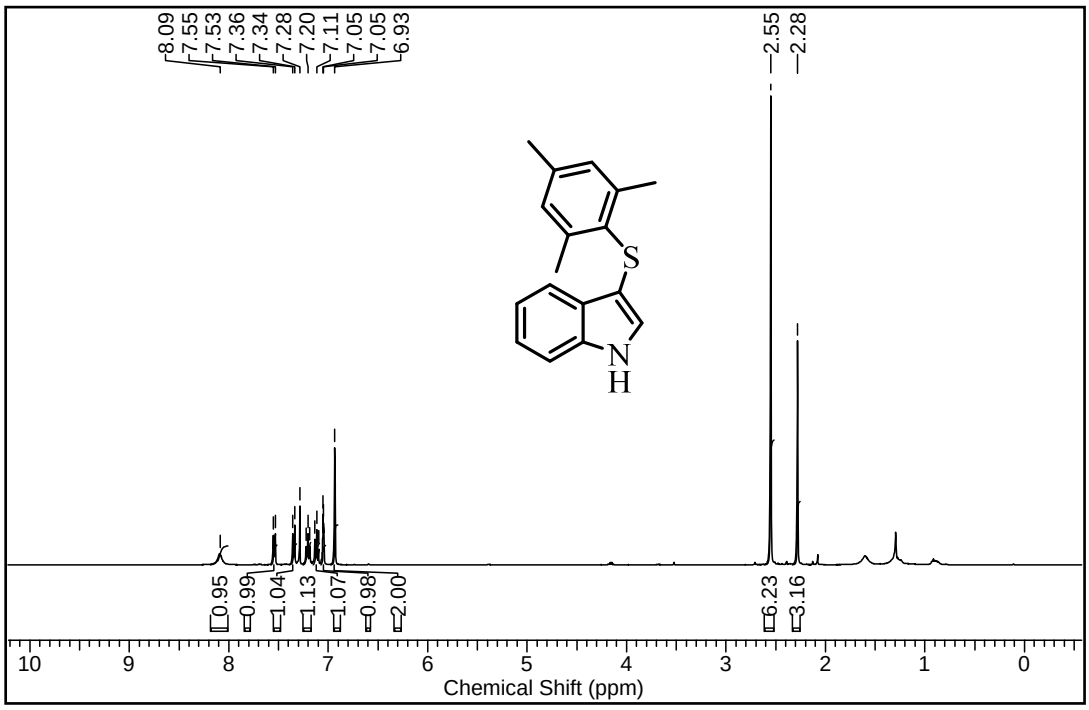


➢ **^{1}H NMR of the compound 8 in $CDCl_3$**

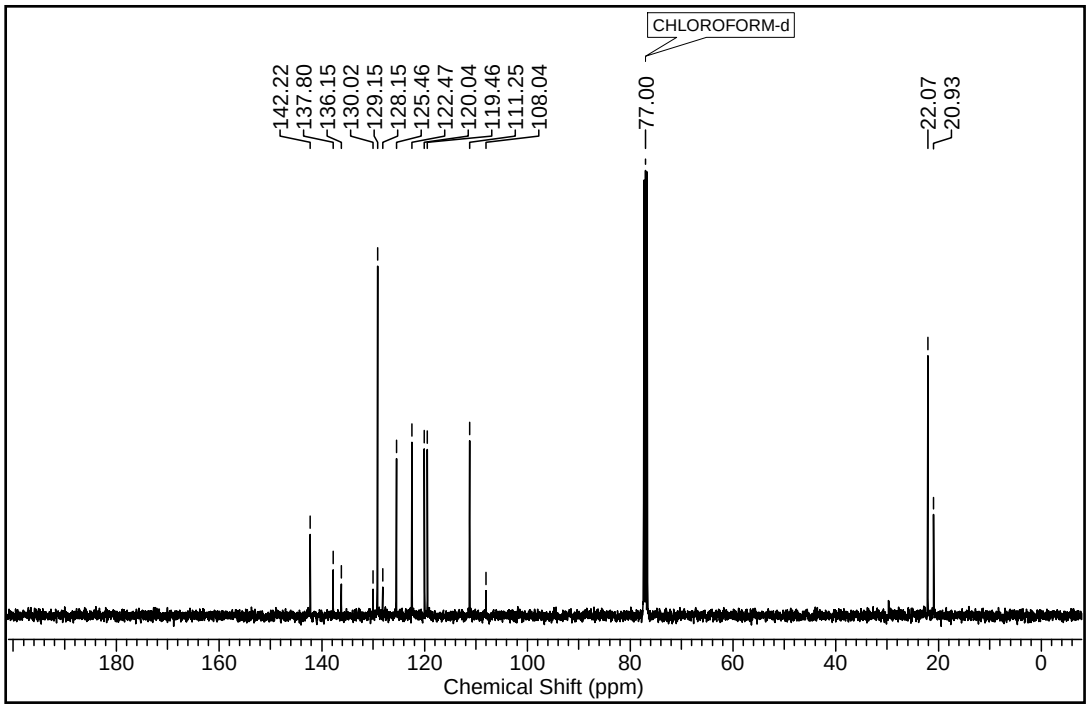


➢ **^{13}C NMR of the compound 8 in $CDCl_3$**

3-(Mesitylthio)-1*H*-indole 9:

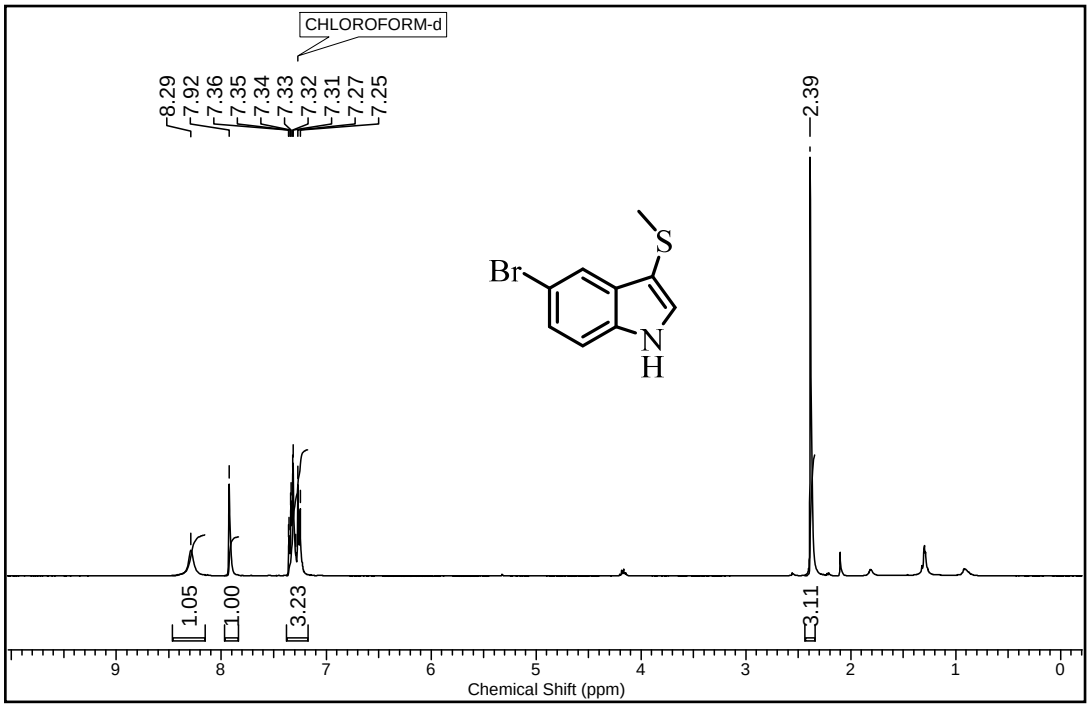


- **^{1}H NMR of the compound 9 in $CDCl_3$**

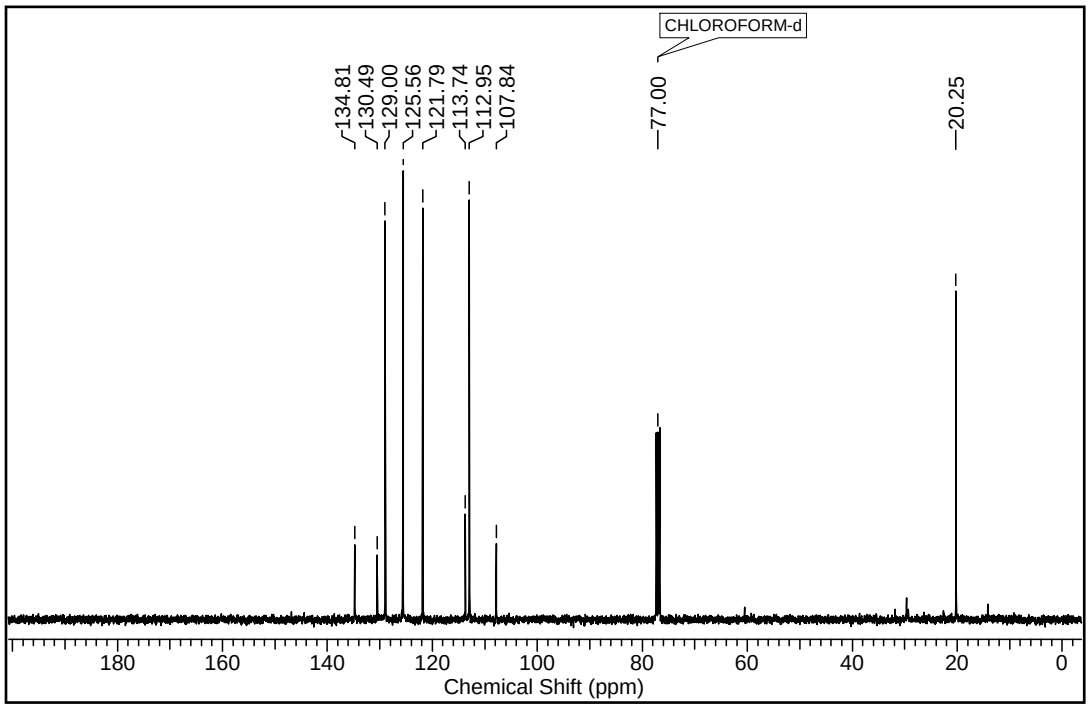


- **^{13}C NMR of the compound 9 in $CDCl_3$**

5-Bromo-3-(methylthio)-1*H*-indole 10:

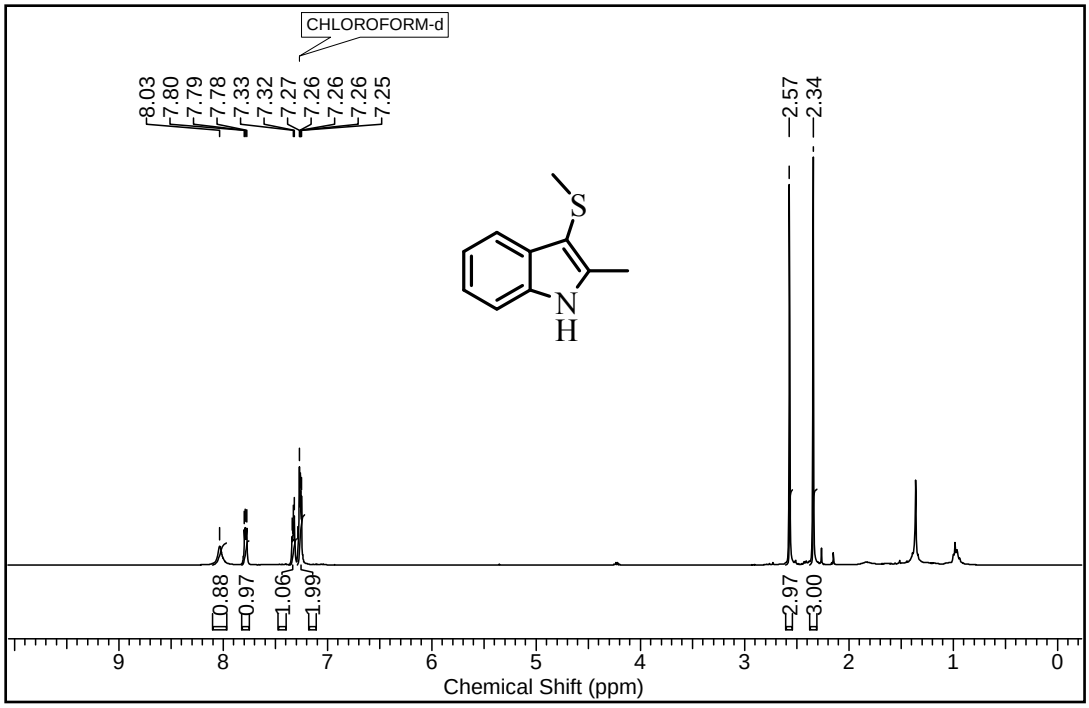


➢ **^{1}H NMR of the compound 10 in $CDCl_3$**

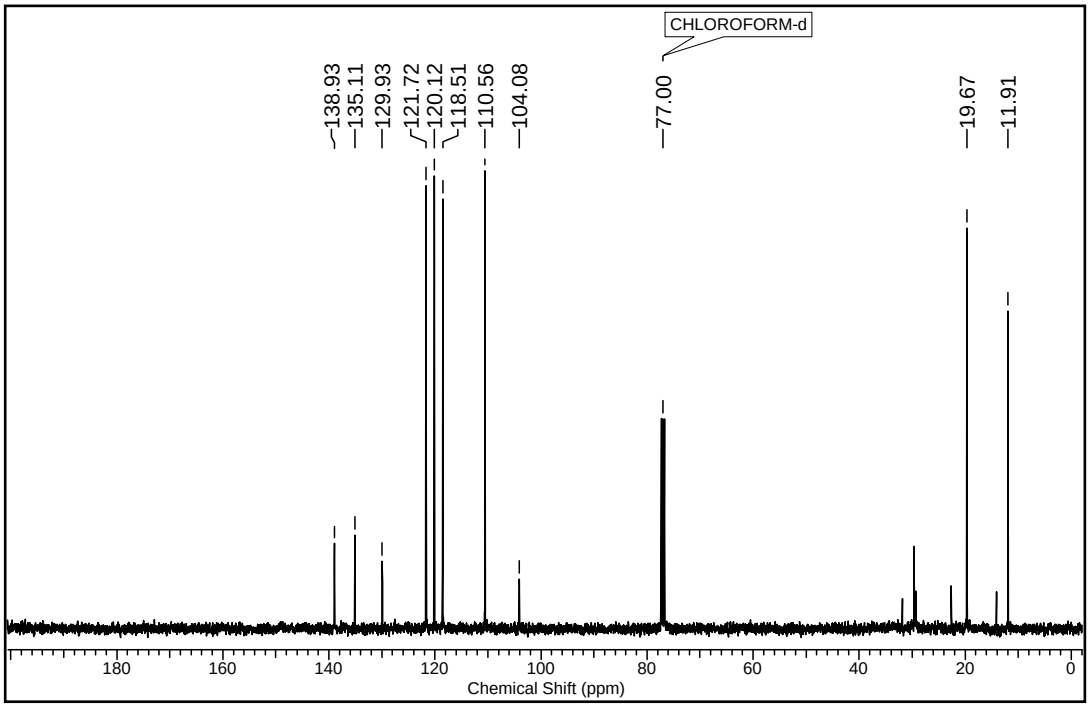


➢ **^{13}C NMR of the compound 10 in $CDCl_3$**

2-Methyl-3-(methylthio)-1*H*-indole 11:

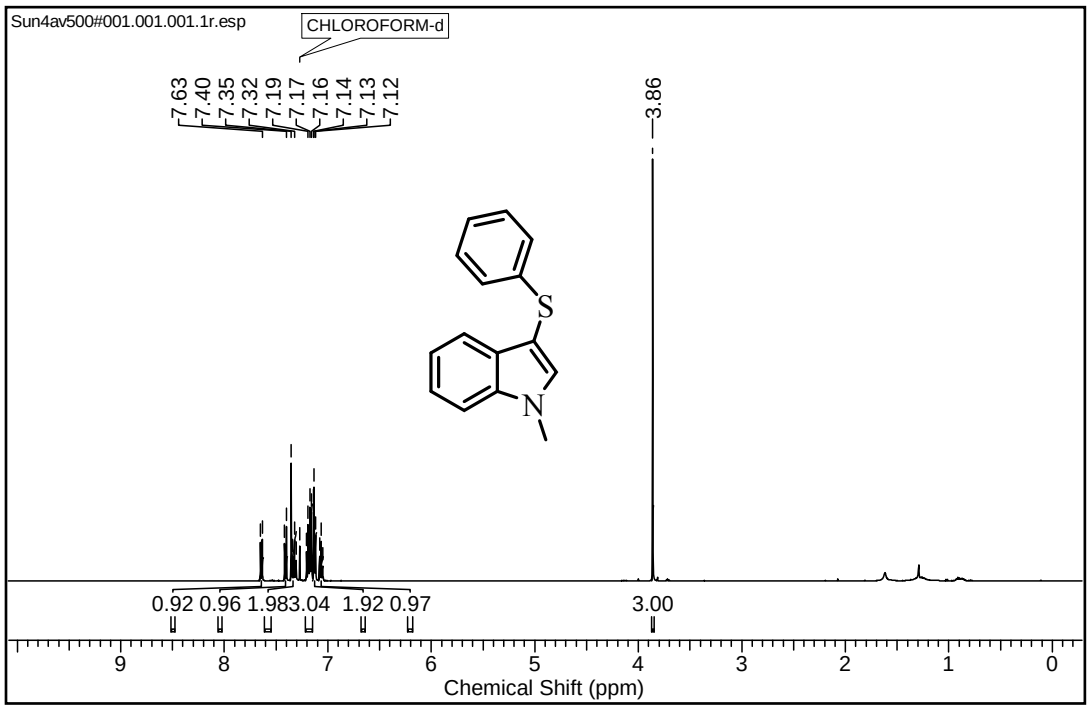


➢ **^{1}H NMR of the compound 11 in $CDCl_3$**

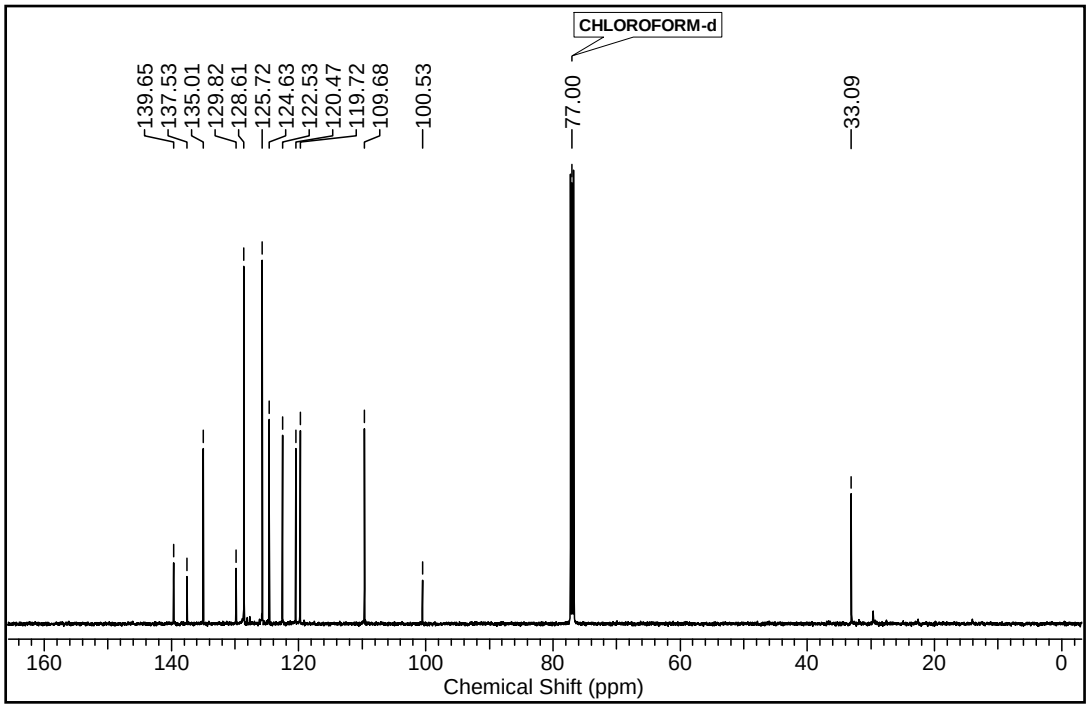


➢ **^{13}C NMR of the compound 11 in $CDCl_3$**

1-Methyl-3-(phenylthio)-1*H*-indole 12:

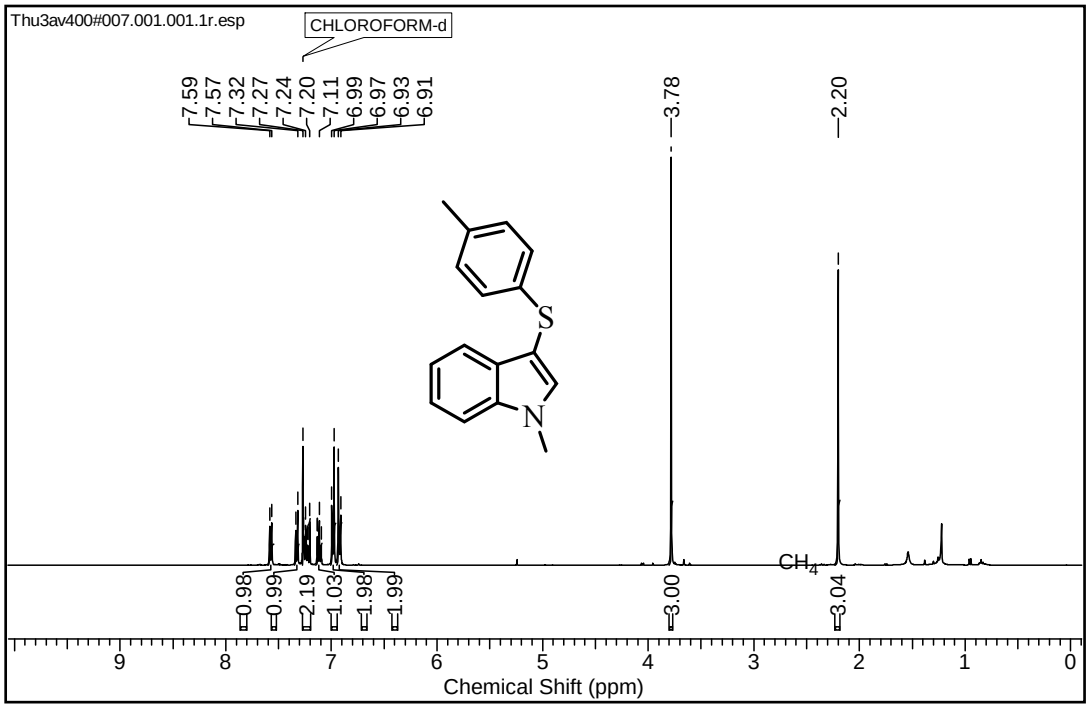


➢ **^{1}H NMR of the compound 12 in $CDCl_3$**

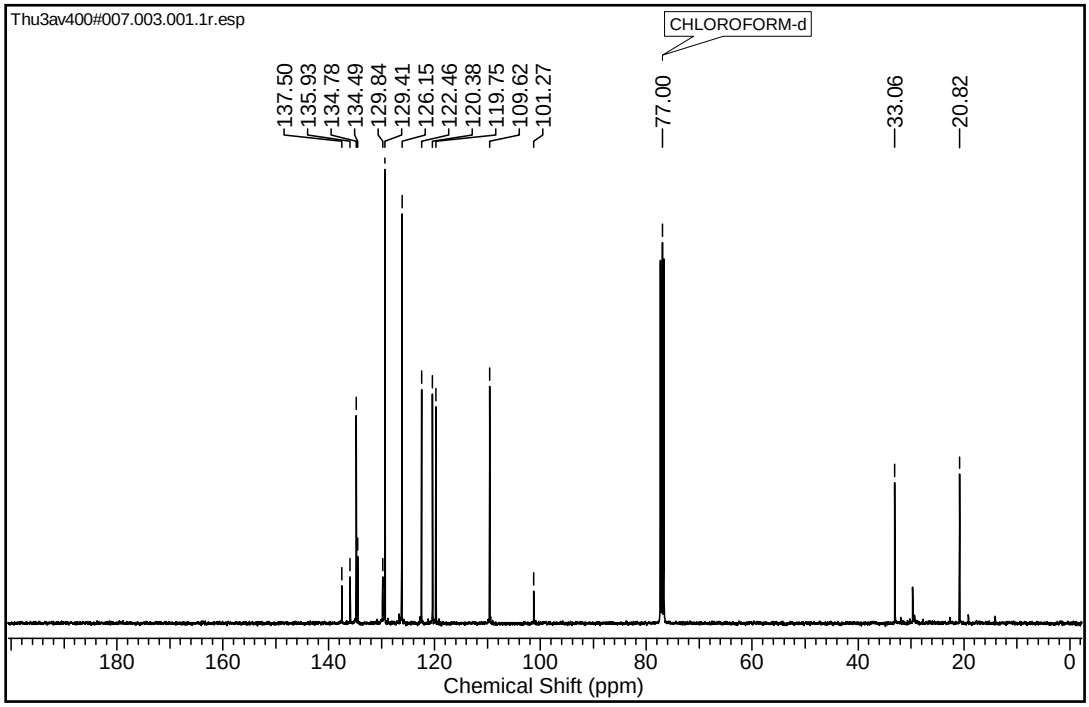


➢ **^{13}C NMR of the compound 12 in $CDCl_3$**

1-Methyl-3-(*p*-tolylthio)-1*H*-indole 13:

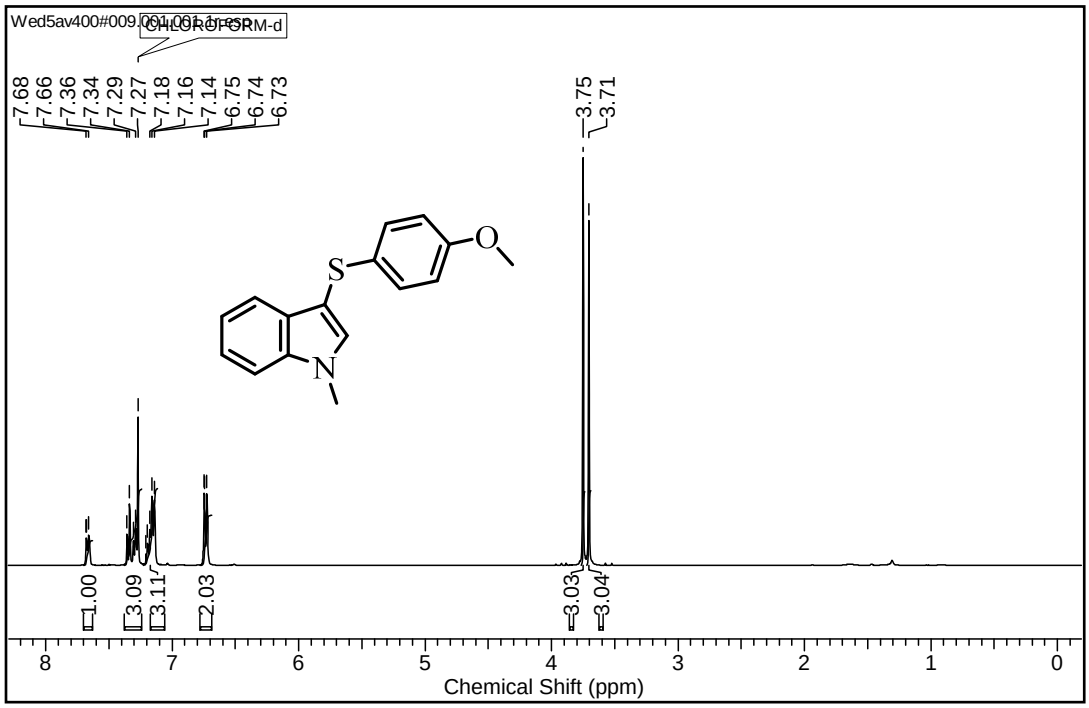


➢ **^{1}H NMR of the compound 13 in $CDCl_3$**

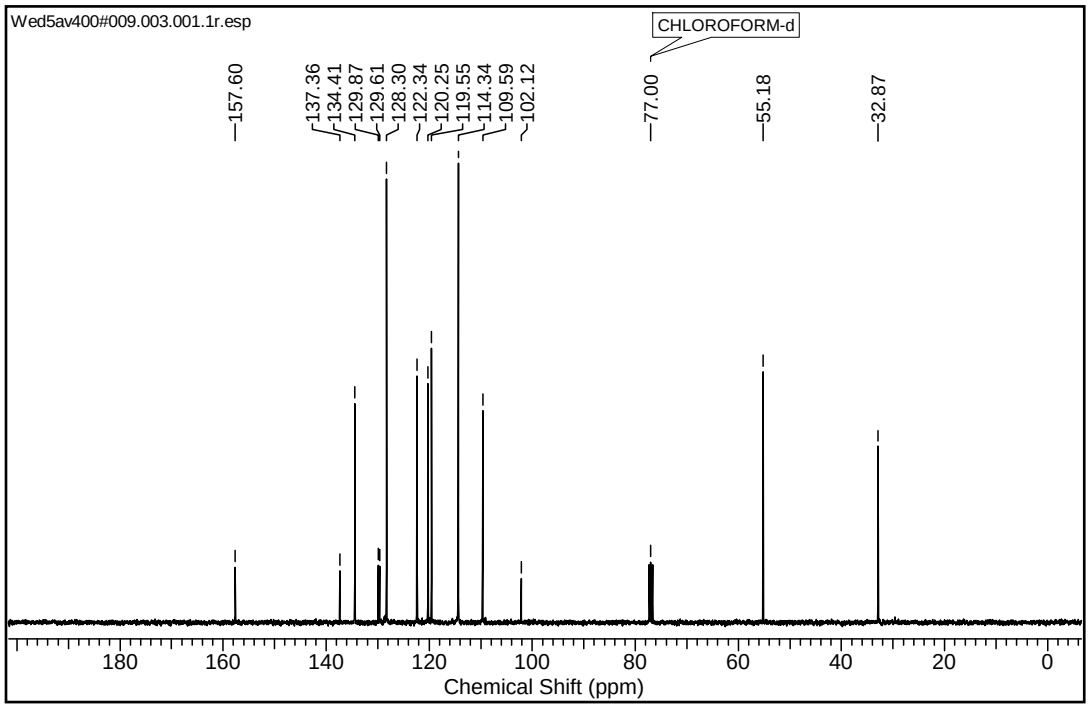


➢ **^{13}C NMR of the compound 13 in $CDCl_3$**

3-((4-Methoxyphenyl)thio)-1-methyl-1*H*-indole 14:

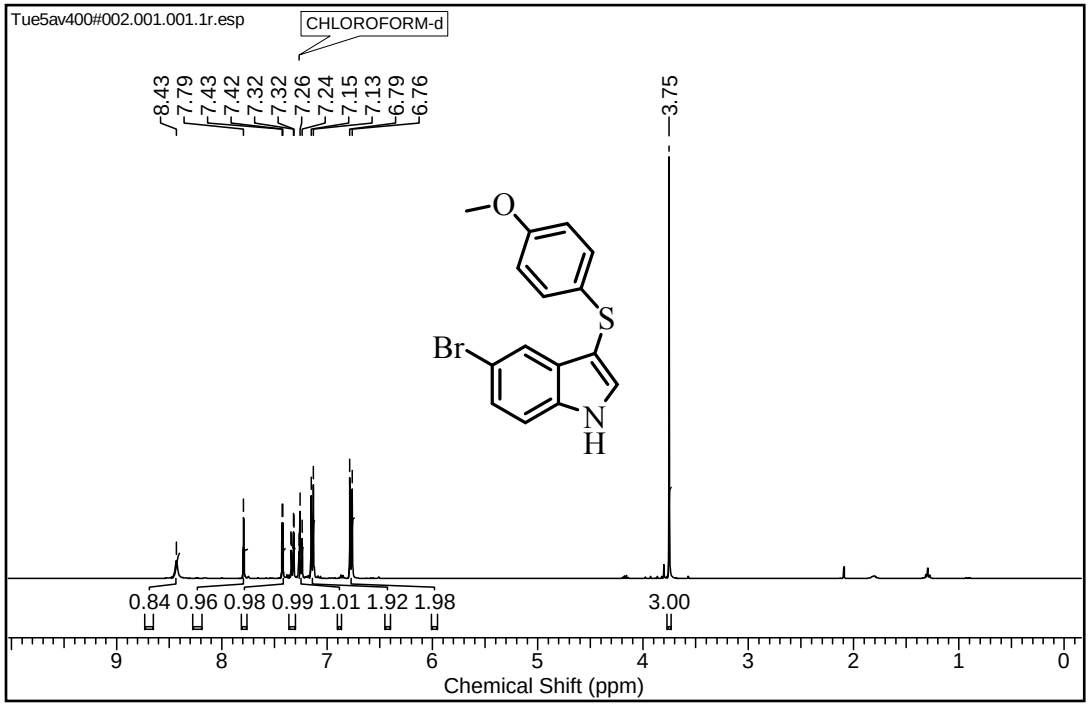


- **^{1}H NMR of the compound 14 in $CDCl_3$**

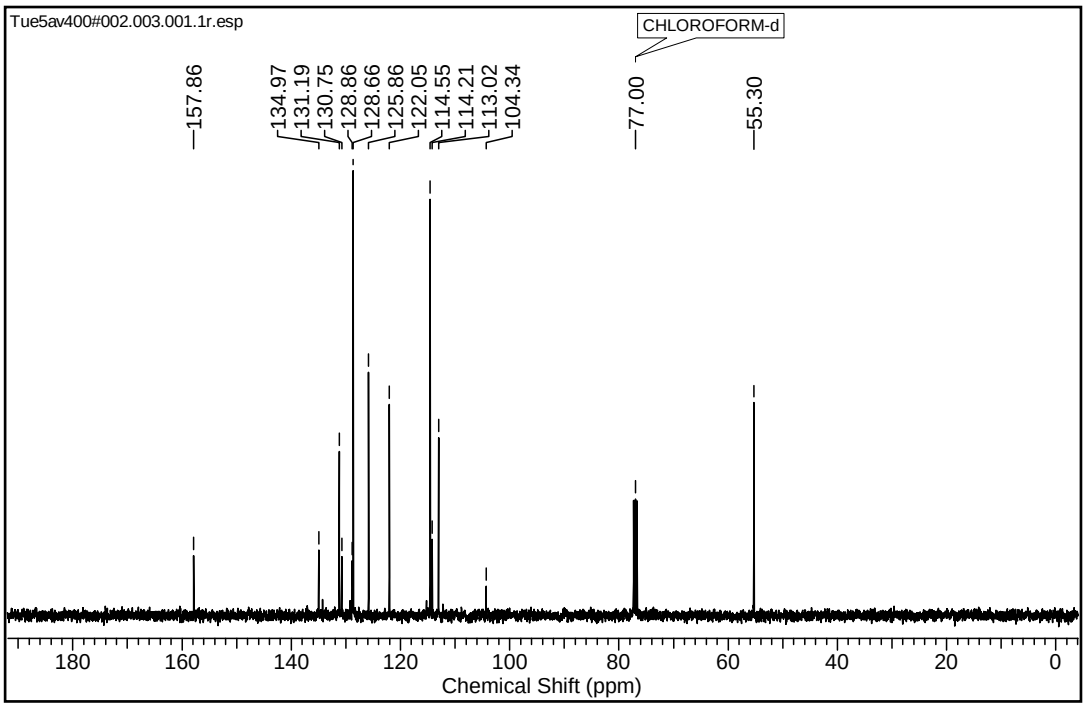


- **^{13}C NMR of the compound 14 in $CDCl_3$**

5-Bromo-3-((4-methoxyphenyl)thio)-1*H*-indole 15:

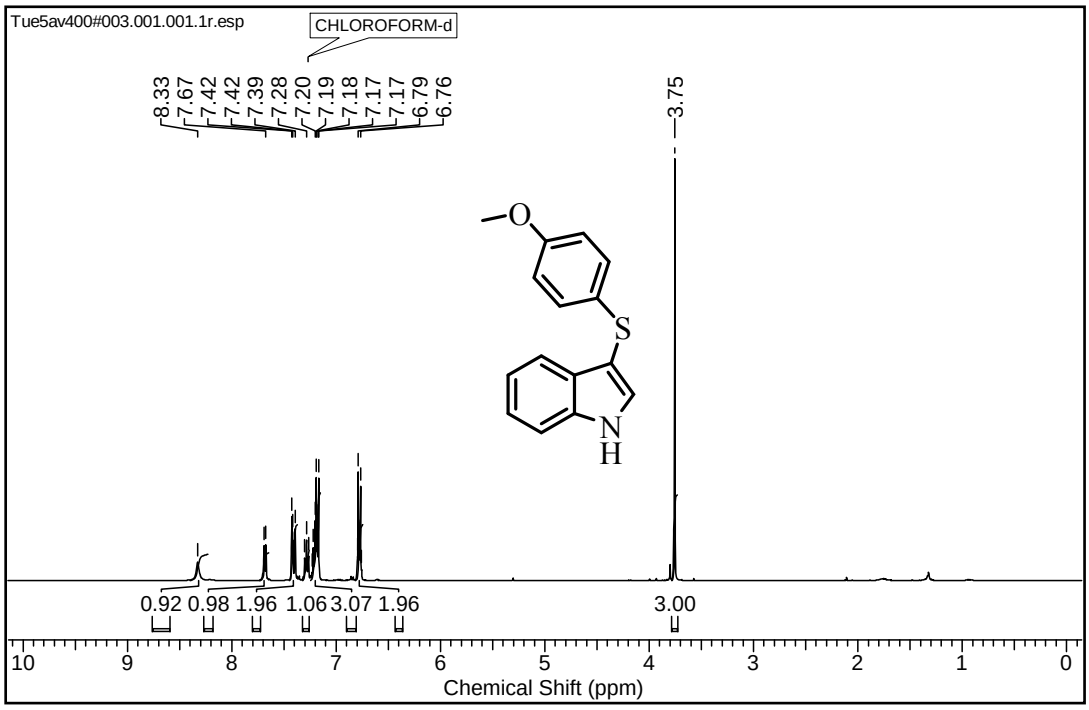


➢ **^{1}H NMR of the compound 15 in $CDCl_3$**

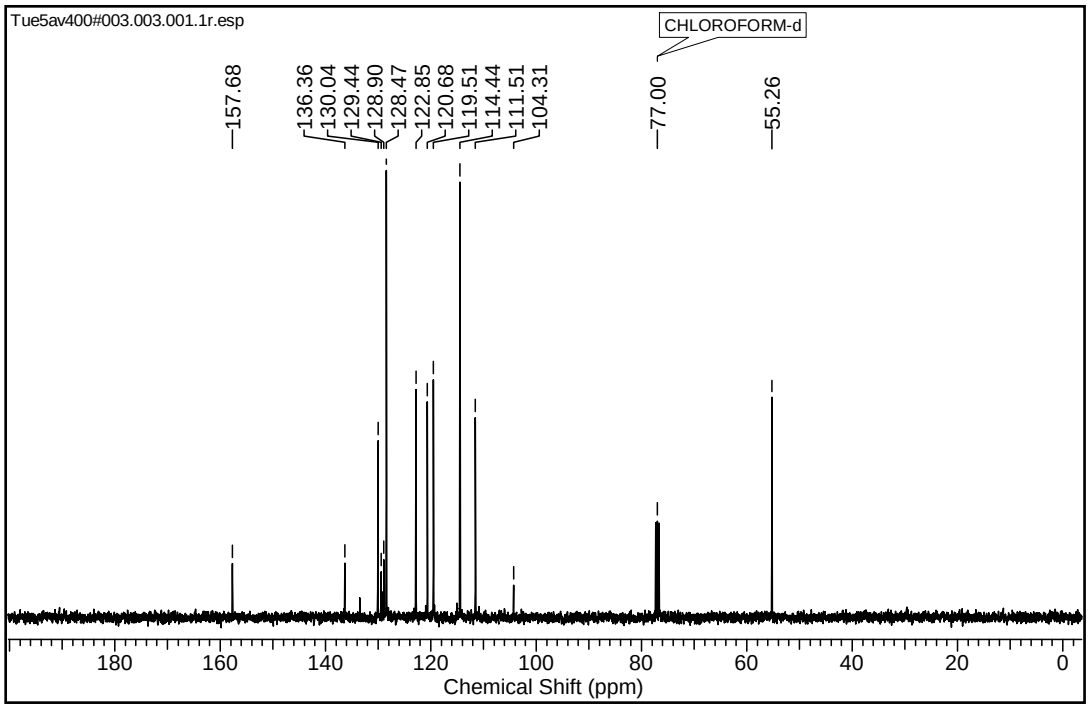


➢ **^{13}C NMR of the compound 15 in $CDCl_3$**

3-((4-Methoxyphenyl)thio)-1*H*-indole 16:

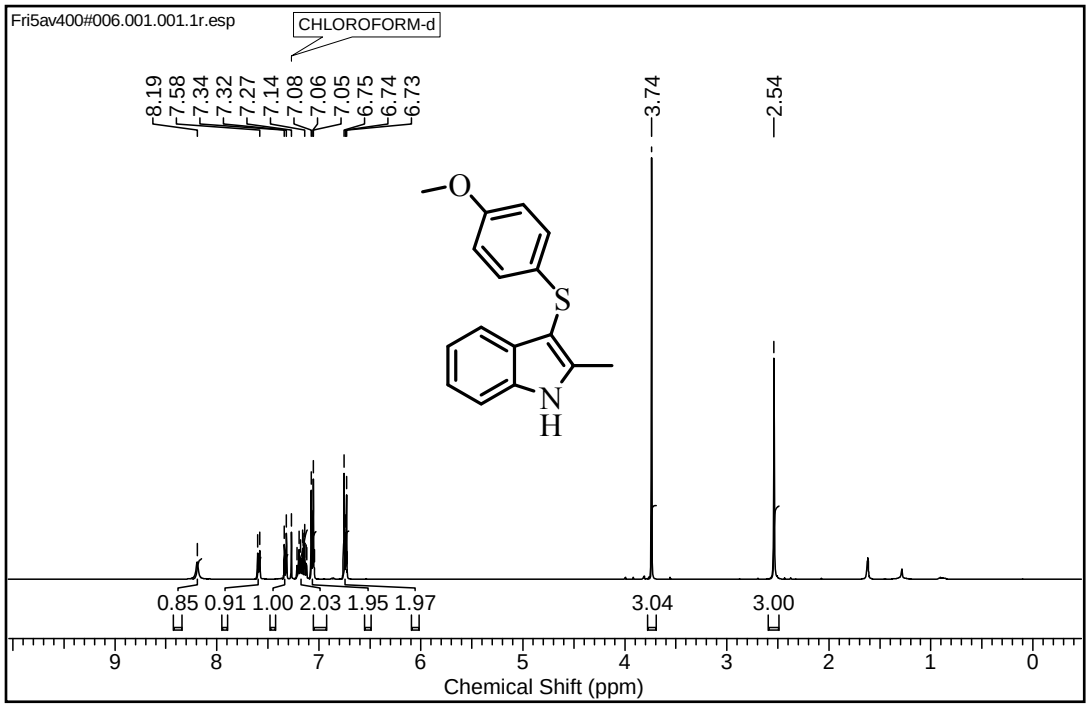


➢ **^{1}H NMR of the compound 16 in $CDCl_3$**

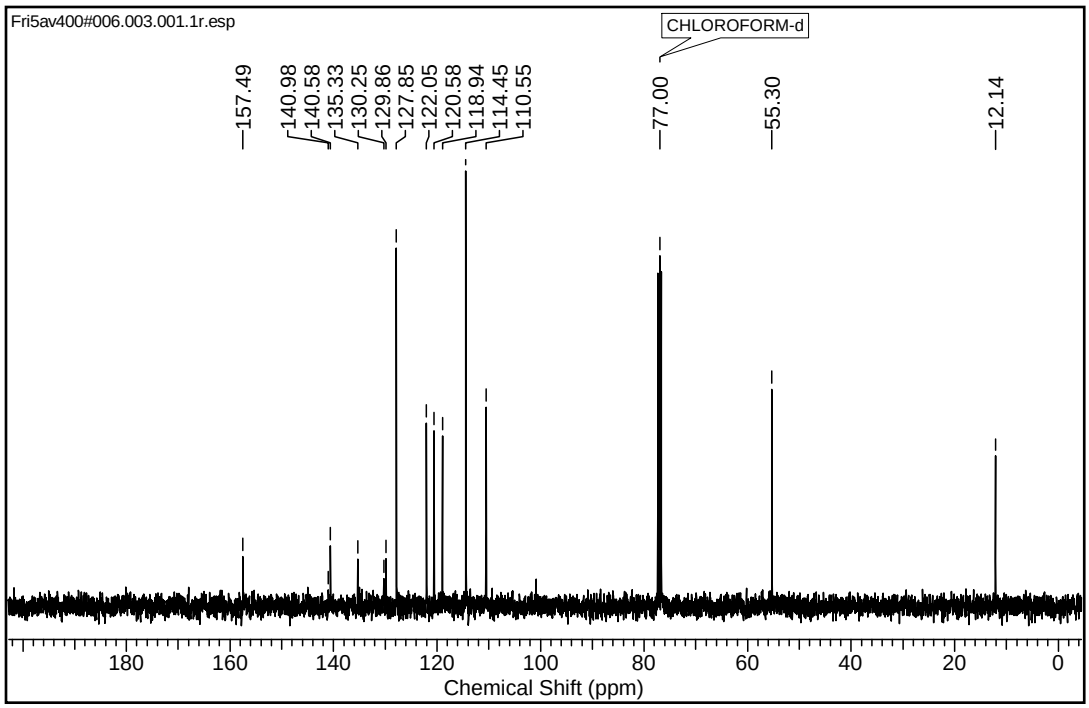


➢ **^{13}C NMR of the compound 16 in $CDCl_3$**

3-((4-Methoxyphenyl)thio)-2-methyl-1*H*-indole 17:

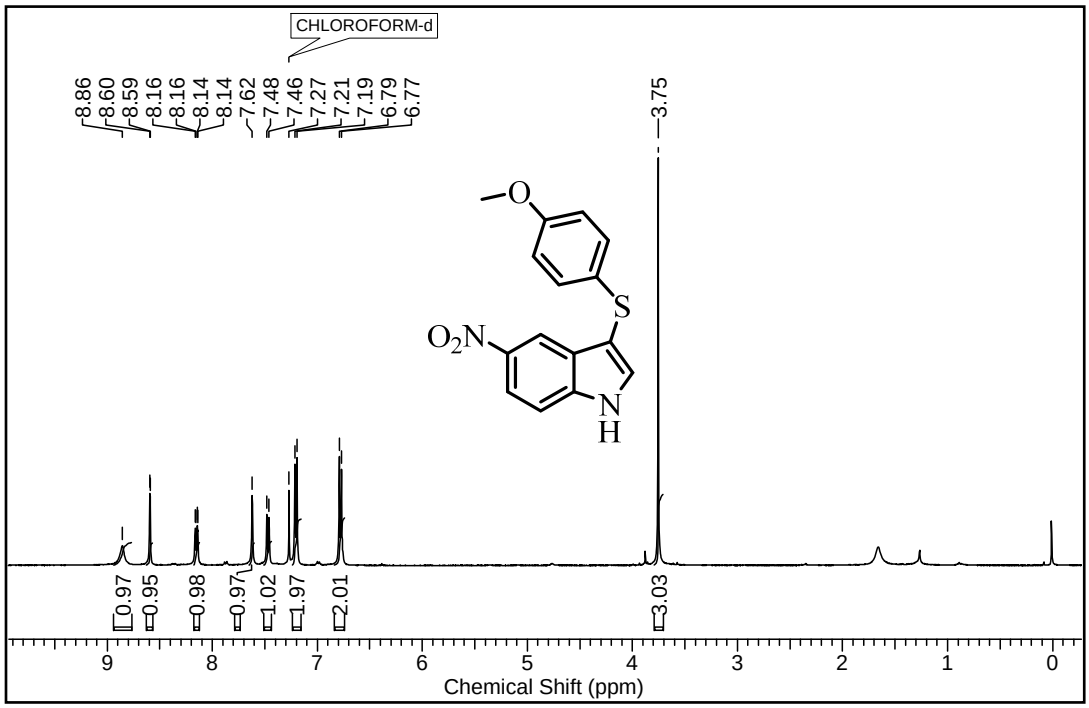


- **^{1}H NMR of the compound 17 in $CDCl_3$**

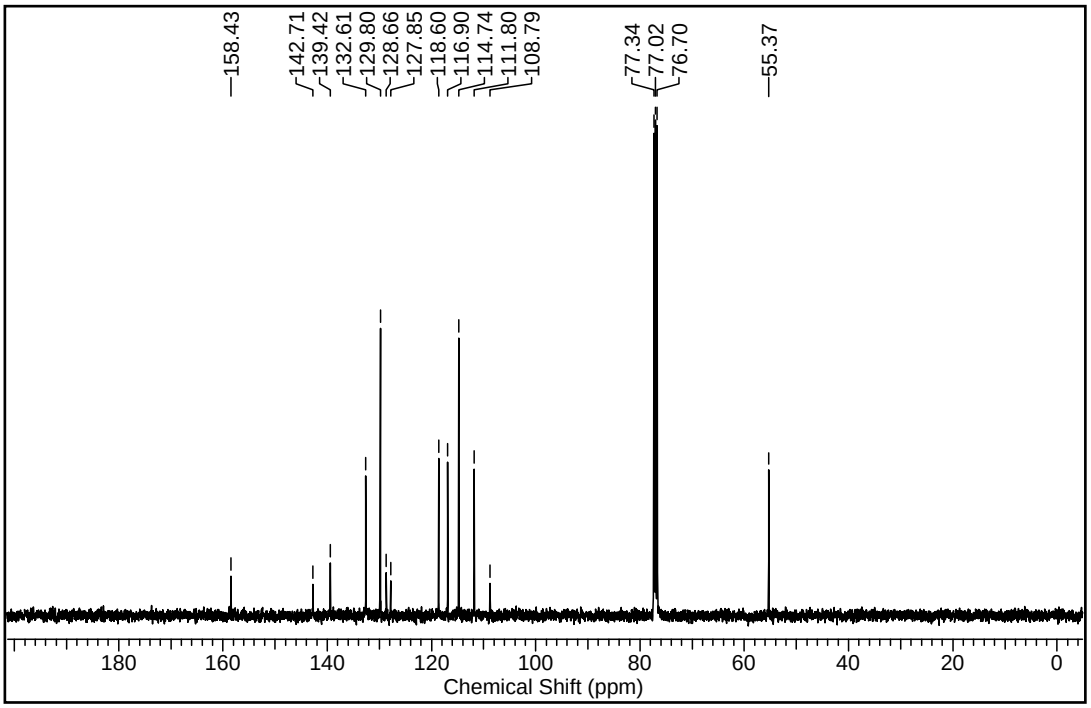


- **^{13}C NMR of the compound 17 in $CDCl_3$**

3-((4-Methoxyphenyl)thio)-5-nitro-1*H*-indole 18:

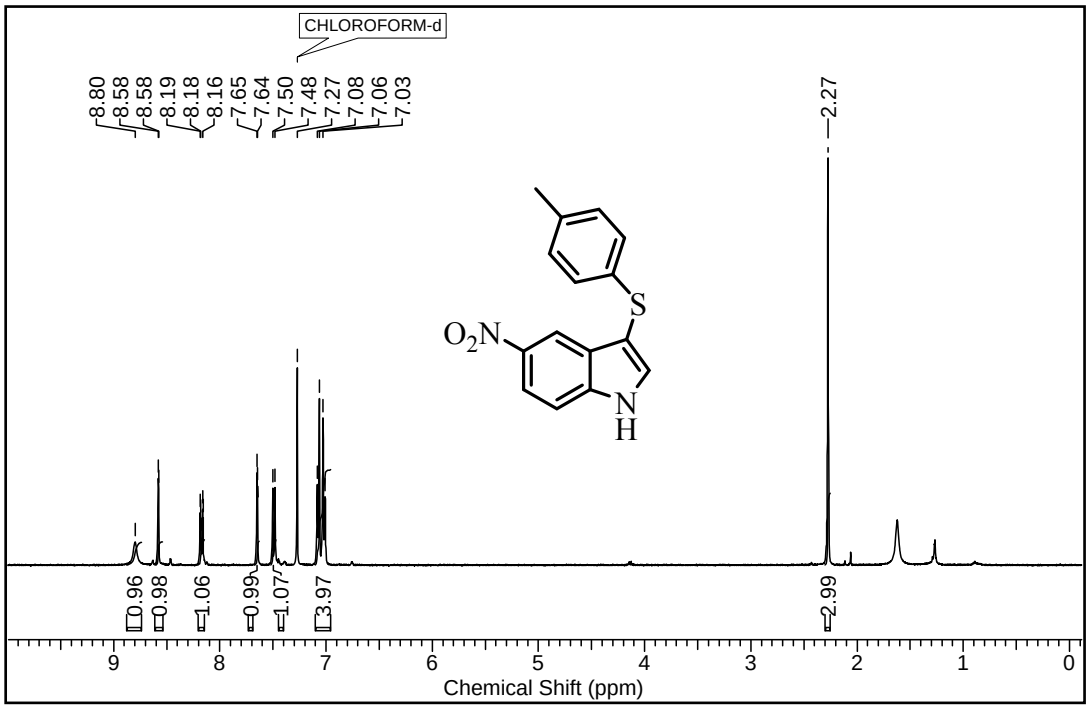


➢ **^{1}H NMR of the compound 18 in $CDCl_3$**

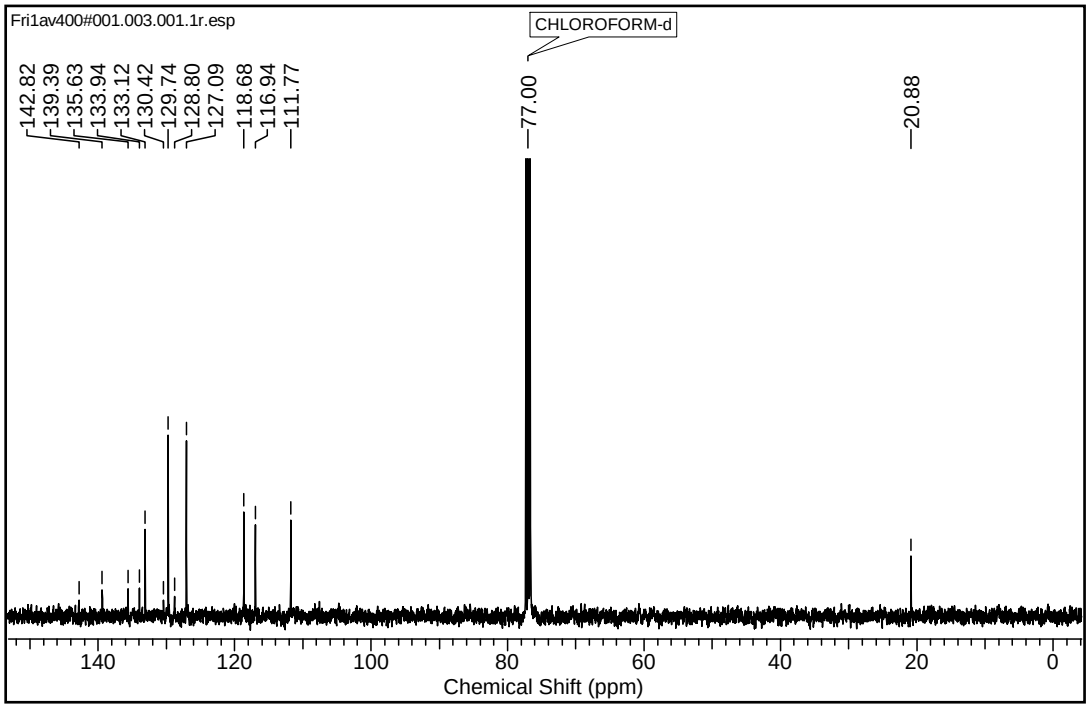


➢ **^{13}C NMR of the compound 18 in $CDCl_3$**

5-Nitro-3-(*p*-tolylthio)-1*H*-indole 19:

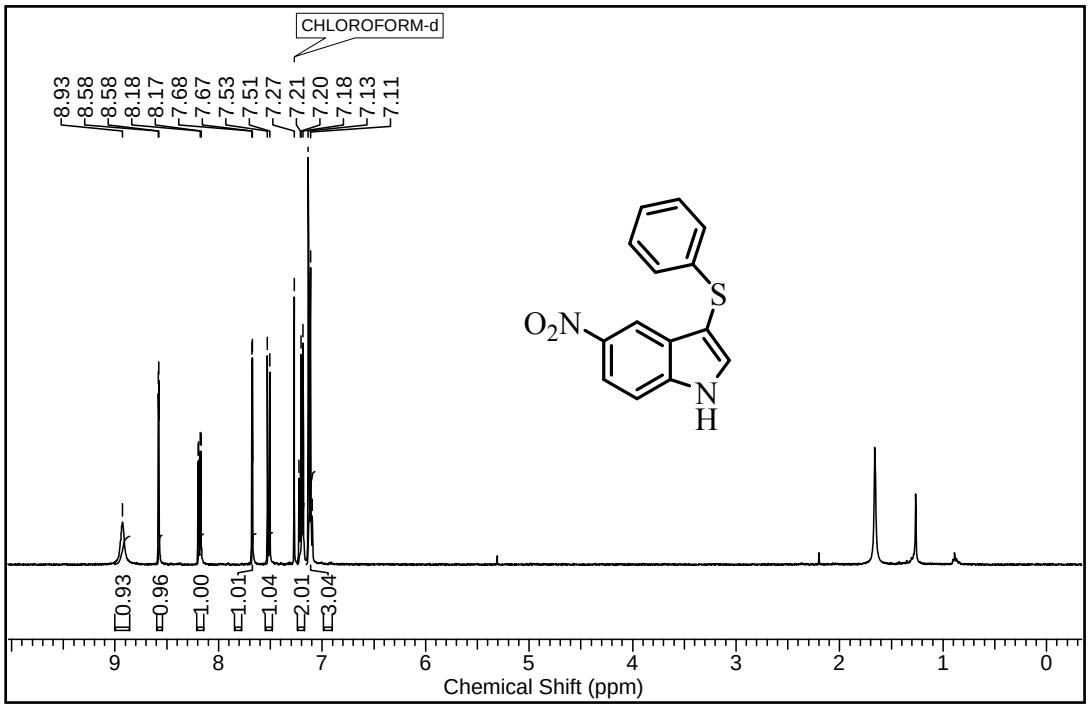


- **^{1}H NMR of the compound 19 in $CDCl_3$**

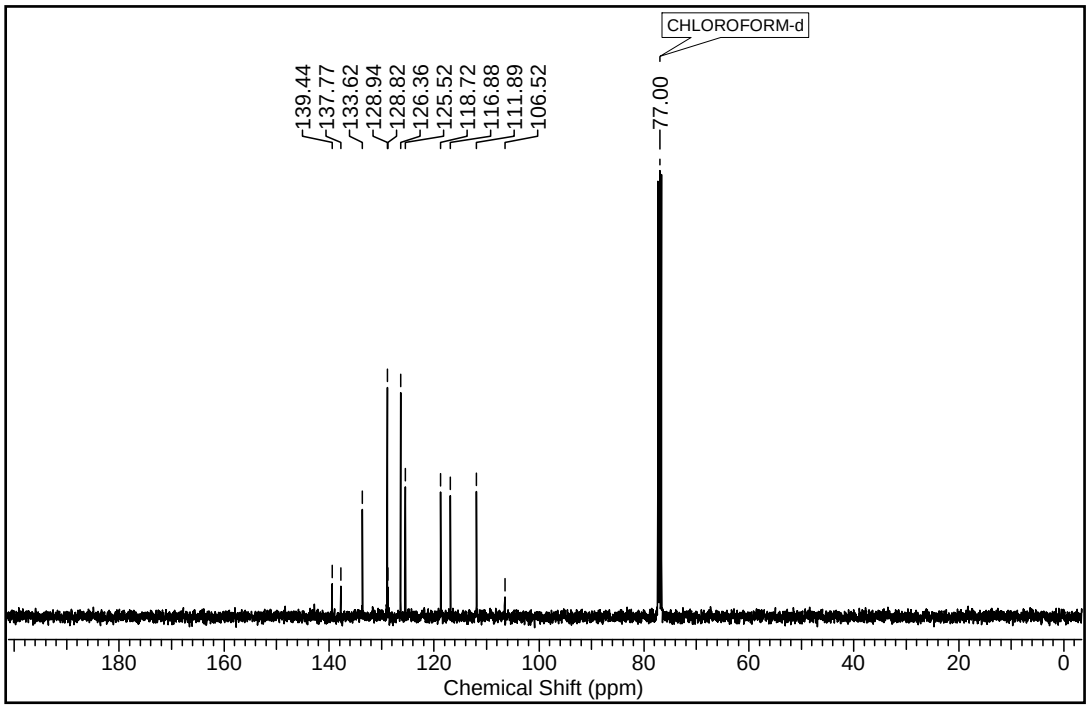


- **^{13}C NMR of the compound 19 in $CDCl_3$**

5-Nitro-3-(phenylthio)-1*H*-indole 20:

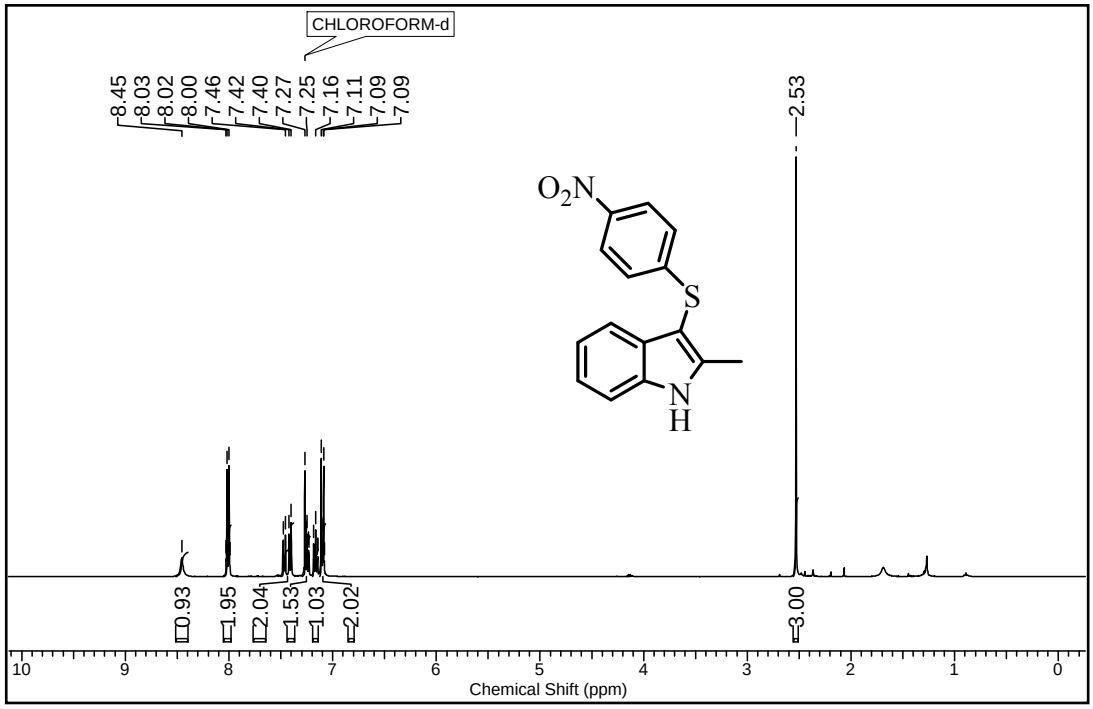


➢ **^{1}H NMR of the compound 20 in $CDCl_3$**

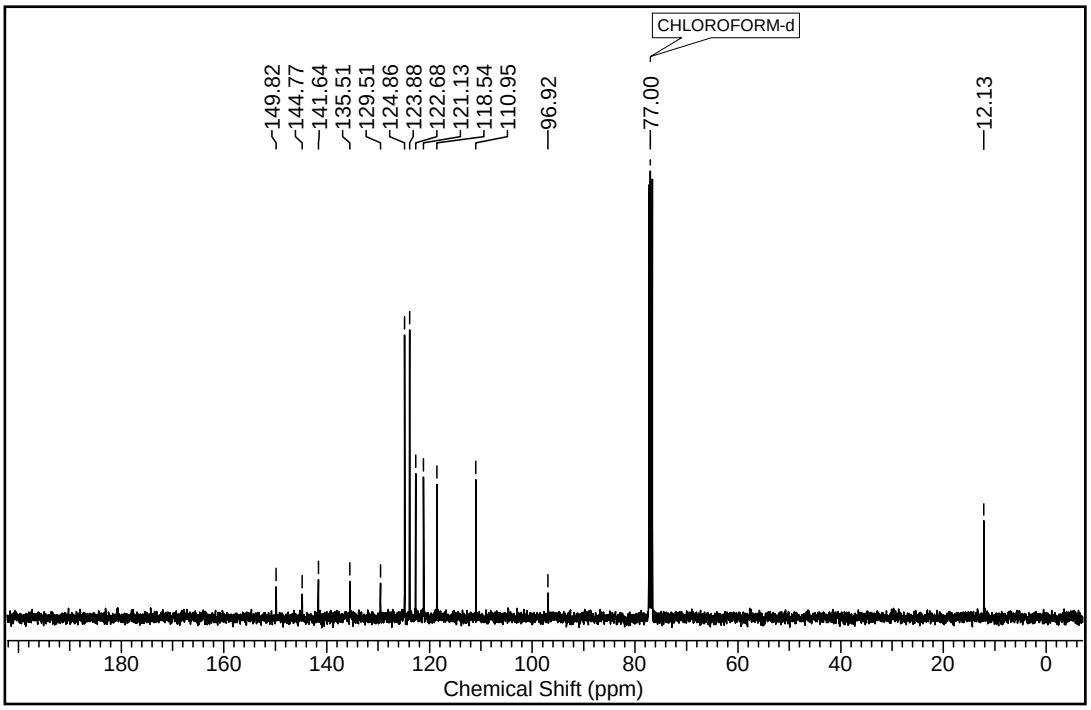


➢ **^{13}C NMR of the compound 20 in $CDCl_3$**

2-Methyl-3-((4-nitrophenyl)thio)-1*H*-indole 21:

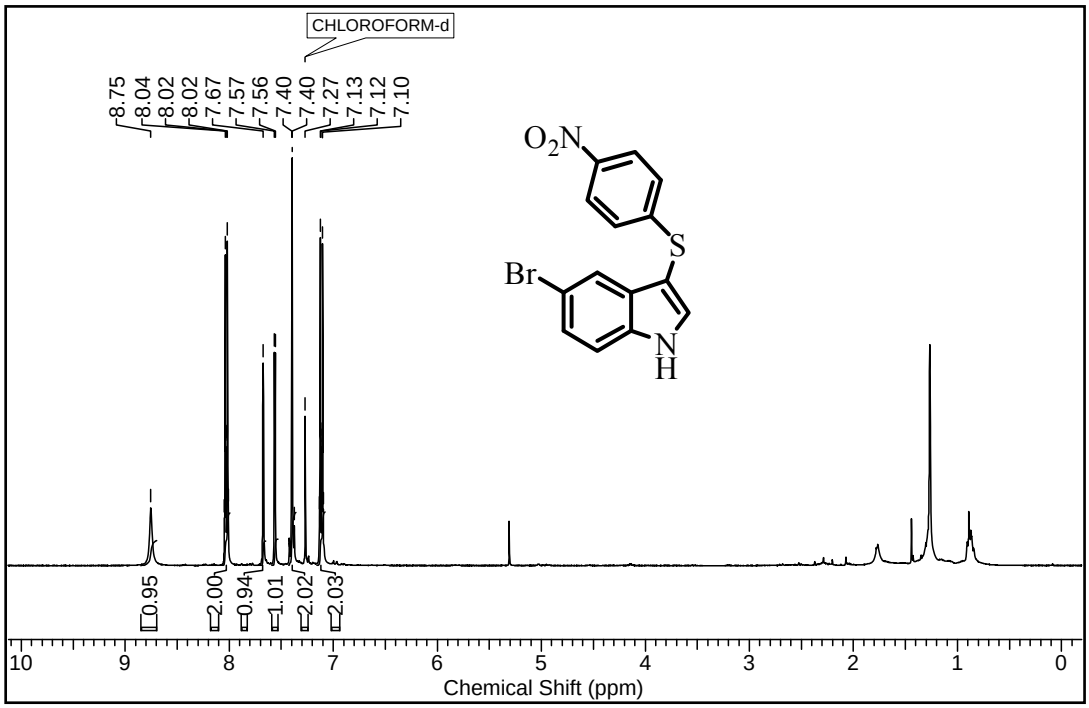


- **^{1}H NMR of the compound 21 in $CDCl_3$**

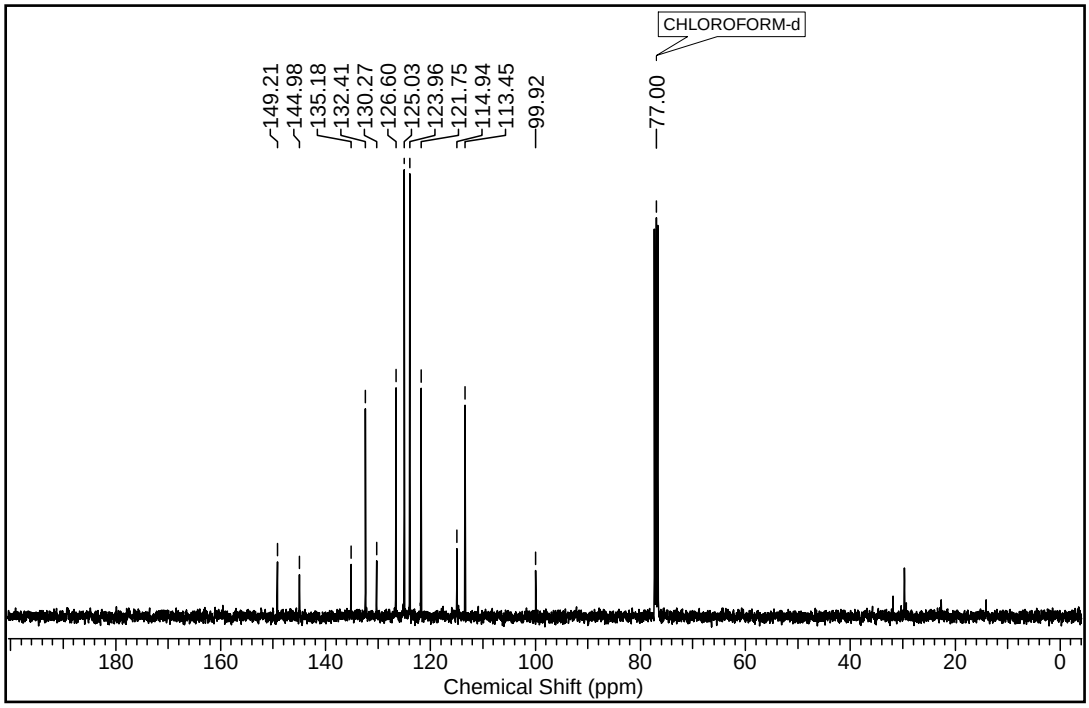


- **^{13}C NMR of the compound 21 in $CDCl_3$**

5-Bromo-3-((4-nitrophenyl)thio)-1*H*-indole 22:

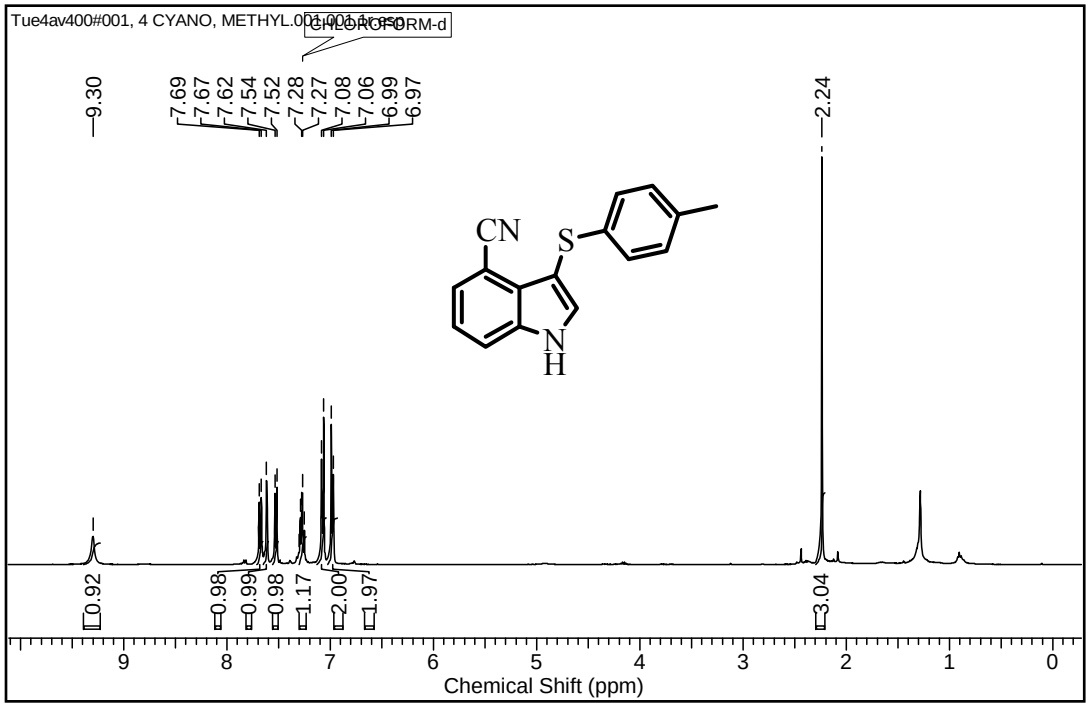


➢ **^{1}H NMR of the compound 22 in $CDCl_3$**

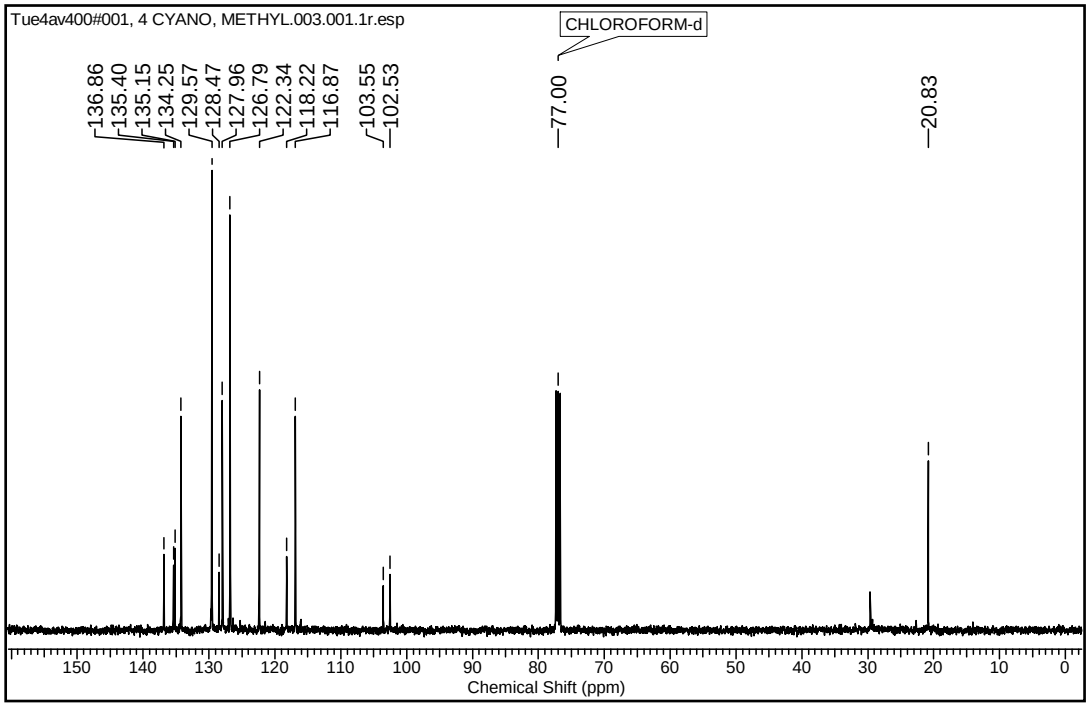


➢ **^{13}C NMR of the compound 22 in $CDCl_3$**

3-(*p*-Tolylthio)-1*H*-indole-4-carbonitrile 23:

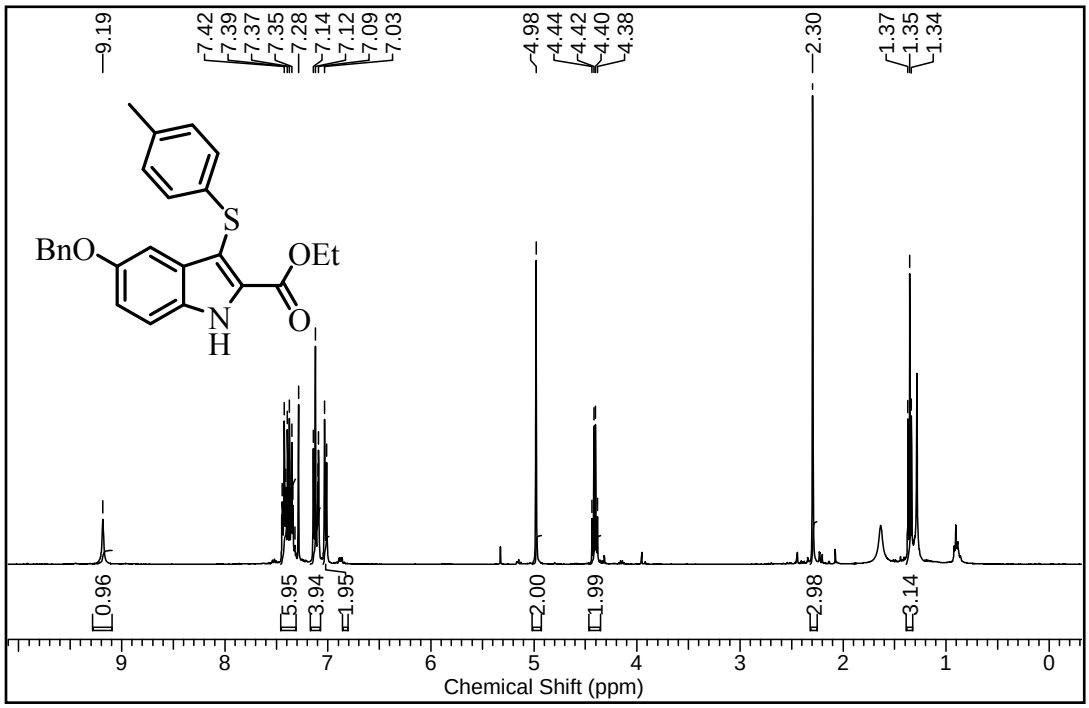


➢ **^{1}H NMR of the compound 23 in $CDCl_3$**

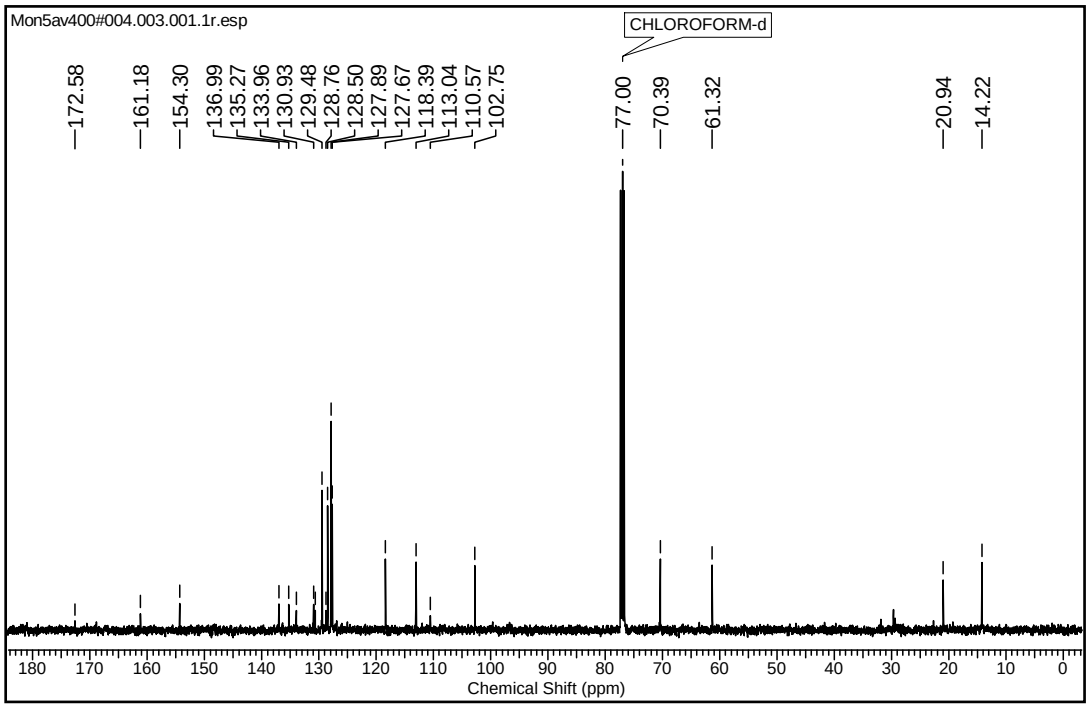


➢ **^{13}C NMR of the compound 23 in $CDCl_3$**

Ethyl 5-(benzyloxy)-3-(*p*-tolylthio)-1*H*-indole-2-carboxylate 24:

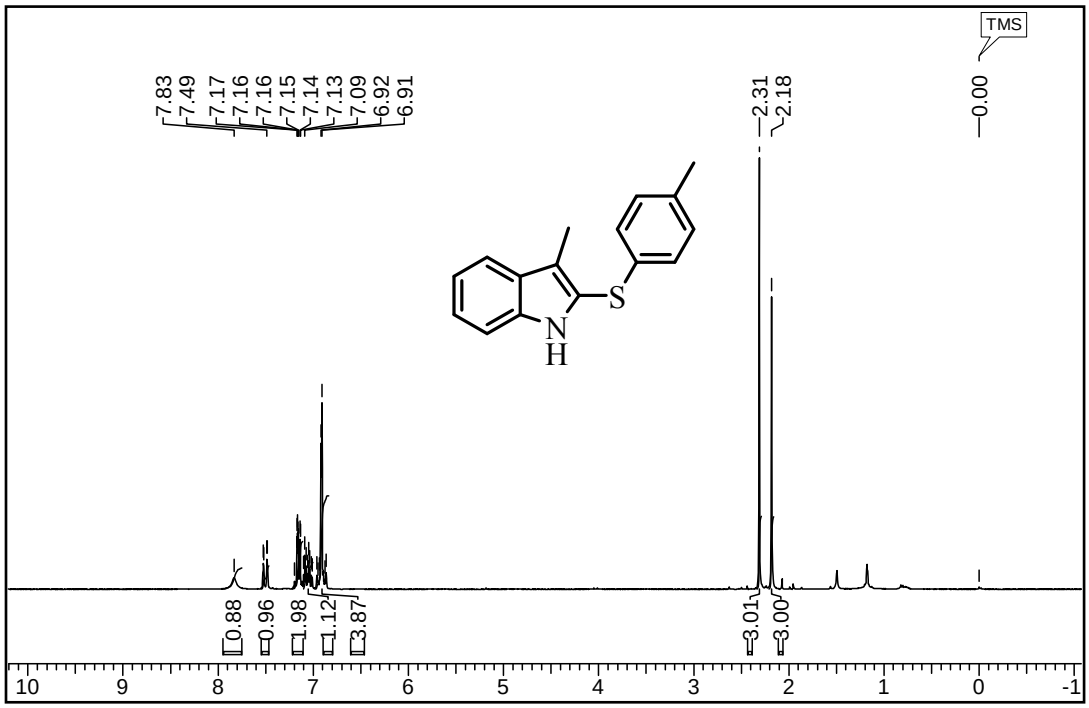


➢ **^{1}H NMR of the compound 24 in $CDCl_3$**

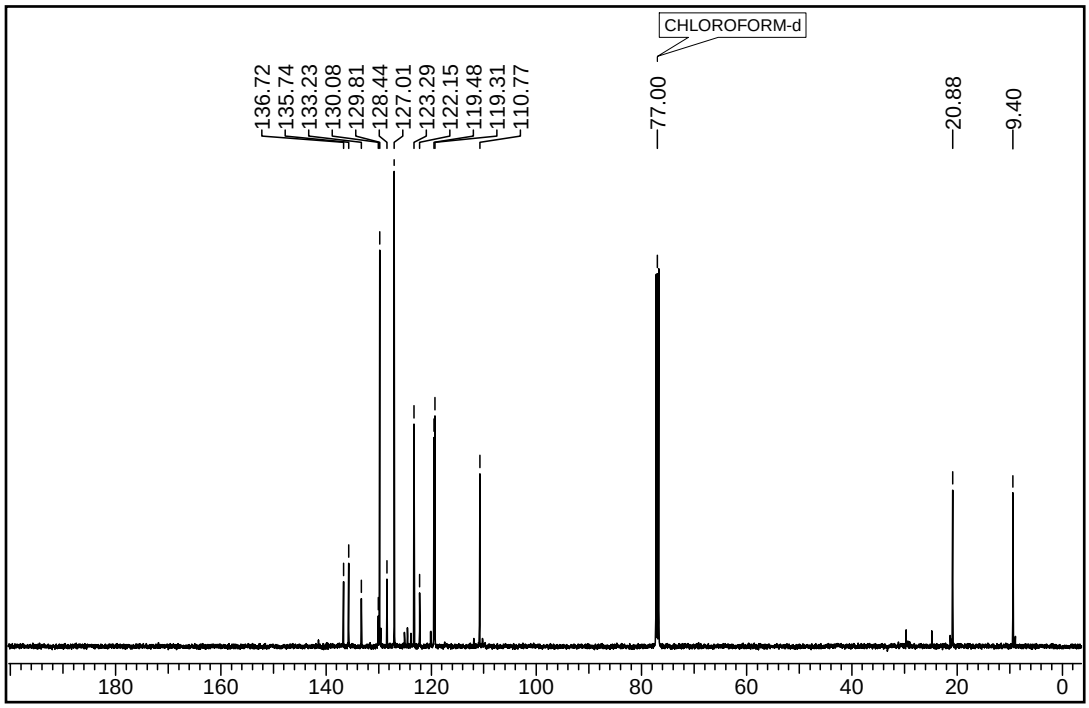


➢ **^{13}C NMR of the compound 24 in $CDCl_3$**

3-Methyl-2-(*p*-tolylthio)-1*H*-indole 25:



➢ **^{1}H NMR of the compound 25 in $CDCl_3$**



➢ **^{13}C NMR of the compound 25 in $CDCl_3$**

4.1.8. References

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4.2. SECTION B

Clay-Supported Copper Nitrate (ClayCop): A Mild Reagent for the Selective Nitration of Aromatic Olefins

4.2.1. Introduction

Nitro compounds are incredibly important synthetic intermediates, with nitro olefins and their derivatives having been utilized for the synthesis of a wide variety of biologically and medicinally important compounds.[1] They are essential starting materials for a variety of useful building blocks; for example: amines, ketoximes, nitroalkanes, hydroxylamines, aldoximes and also carbon-carbon bond forming reactions such as Morita-Baylis-Hillman reaction, Michael reaction and cycloaddition reactions.[2] So far a number of methods have been reported to give nitro olefins directly from olefins.[3] One of the well known methods for the synthesis of nitro olefins is by the condensation of nitroalkanes with aldehydes or ketones in the presence of base followed by dehydration.[4] However, many of these methods are associated with several drawbacks such as the use of hazardous and expensive reagents, long reaction time, limited scope, formation of a mixture of *E* & *Z* isomers and among others the yields reported are far from satisfactory.

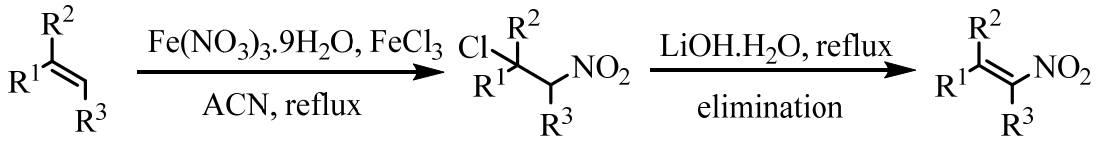
4.2.2. Review of Literature

The direct nitration of the olefinic C–H bond is of considerable interest & has generated lot of interest among synthetic chemists. A detailed report of recent reports was described below.

Taniguchi and co-workers (2010)[3p]

Taniguchi and co-workers developed practical and nontoxic method for the halo-nitration of alkenes. This reaction goes *via* radical mechanism. Alkenes react with NO_2 radical which are generated under thermal decomposition of iron (III) nitrate nonahydrate, followed by the radical trapping by chlorine atom generated from iron chloride leading to the formation of

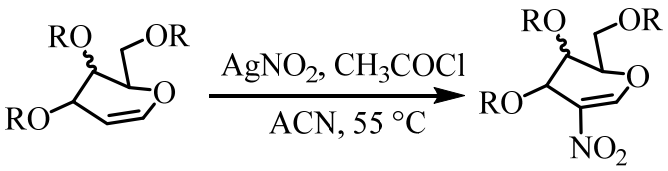
chloro-nitro alkanes. Under basic conditions chloro nitro alkanes are converted into nitro-alkenes *via* elimination reaction.



Scheme 1: Chloro-Nitration of alkenes

Y. D. Vankar and co-workers (2011)[3i]

Y. D. Vankar and co-workers developed a protocol for the selective nitration of glycals employing $AgNO_2$-AcCl-acetonitrile system. They found that the combination of silver nitrite and acetyl chloride produces the nitronium ion. Olefin attacks on this nitronium ion followed by elimination to give 2- nitro-glycals.

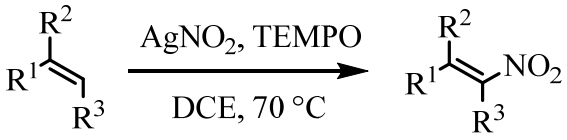


Scheme 2: Selective nitration of glycals

D. Maiti and co-workers (2013)[3b]

Maiti and co-workers developed efficient protocol for the stereoselective nitration of mono and di-substituted olefins using silver nitrite and TEMPO combination. The group has successfully applied this methodology to several alkyl, aryl terminal olefins and internal olefins. This reaction involves a radical mechanism; under thermal conditions. $AgNO_2$ produces the nitro radical. Nitro olefin is formed *via* the elimination of TEMPOH from the

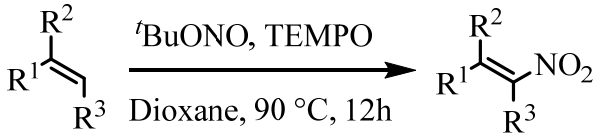
intermediate TEMPO−alkane−NO_2. It was further concluded that mono substituted olefins are more reactive towards this transformation compared to disubstituted olefins which in turn are more reactive than trisubstituted olefins.



Scheme 3: Nitration of olefins using $AgNO_2$ and TEMPO

D. Maiti and co-workers (2013)[3c]

D. Maiti and co-workers also developed a metal free protocol for the selective nitration of olefins using *tert*-butyl nitrite and TEMPO combination under thermal conditions. Here *tert*-butyl nitrite generates the NO radical under thermal conditions followed by aerobic oxidation to produce the NO_2 radical, which is responsible for the nitro alkenes formation.



Scheme 4: Metal free nitration of olefins using ^{t}BuONO and TEMPO

4.2.3. Present work

Objective

Based on the literature survey and our interest in new methodologies, we considered developing an environmentally benign method[5] for nitro olefin using inexpensive reagents. In last few decades, there has been a tremendous upsurge of interest in organic synthesis using

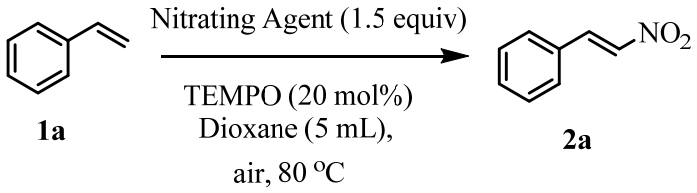
solid support.[6-8] In particular, clay supported reagents[9] have gained wide applications because of their simple work up, inexpensive, environmentally safe, and mild procedure.

Among the clay supported reagents, "claycop"[8] (clay supported nitrating agent) and clayfen (clay supported ferric nitrate) are known to be an efficient reagents for ring nitration for a wide variety of phenols, anilines and nitrogen heterocycles.[10] However, there has been no reports on the use of the clay supported nitrating agent/TEMPO for the selective nitration of olefins. Here we present the use of clay supported copper nitrate "claycop"/TEMPO as a suitable reagent for the synthesis of β-nitroolefin derivatives from the corresponding olefin.

4.2.4. Results and discussion

Initially, we decided to screen various nitrating agents and optimise the reaction conditions for the selective conversion of styrene (**1a**) into *β*-nitro styrene (**2a**) (**Table-1**). When copper nitrate was used in the presence of TEMPO, we observed the formation nitro olefin in very poor yield (30%) (**Table 1, entry 1**). In ^{1}H NMR of the internal olefin peaks were observed at δ 8.03 (d, *J*=13.6 Hz, 1H), 7.53 - 7.66 (m, 1H) and from coupling constant (*J* = 13.6 Hz) value, the presence of *trans* double bond was confirmed. In GC-MS (m/z), peak observed 149.1 $[M]^+$ which corresponds to the molecular formula $C_8H_7NO_2$. Melting point of the compound **2a** was consistent with the literature **(**56-58 °C; lit.[3c] Mp 58 °C). This provided the incentive for a study to explore the solid supported nitrating reagents such as clay supported ammonium nitrate clayan, clayfen and claycop. Subsequently, we performed the above reaction with clayan, as it can be seen from **Table-1**, the reaction took a long time and gave only moderate yield of the desired product. Under similar reaction conditions, clayfen showed a little improvement in the yield. We then examined the reaction of styrene with claycop in the presence of a catalytic amount of TEMPO. The reaction proceeded smoothly in 1,4-dioxane at 80 °C in 1 h and the product (*E*)-β-nitrostyrene (**2a)** was isolated exclusively in 95% yield (**Table 1, entry 4**). Thus, claycop was found to be the best reagent as the reaction was complete within 1 h and it gave essentially quantitative yield of the product. It may be pertinent to mention here that Varma *et al.* have reported the use of clayan for nitration of styrene and *p*-substituted styrenes ((*E*)-1-methoxy-4-(2-nitrovinyl)benzene), however reaction gave only 14% of desired product along with unidentified and polymeric compound as the

major product.[9] Thus claycop was found to be the best nitrating reagent when compared with earlier reports in terms of reaction time and yields (**Table 1**).



S.No	Nitrating agent	Time (h)	Yield (%)
1	$Cu(NO_3)_2.H_2O$	12.0	30
2	Clayan	12.0	60
3	Clayfen	12.0	76
4	**Claycop**	**1.0**	**95**

[a]Reaction conditions: **1a** (1.0 mmol), nitrating agent (1.5 mmol), TEMPO (0.2 mmol), 80 °C, 1,4-Dioxane (5 mL).

Table 1: Screening of various nitrating agents in the formation of product **2a**[a] from styrene

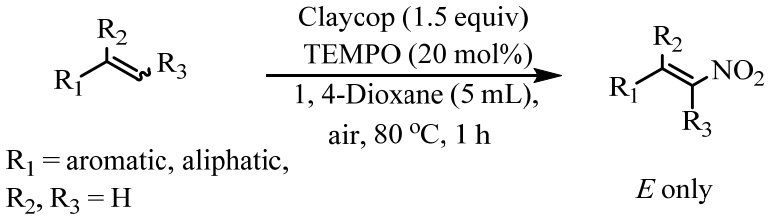
In order to examine the role of solvents, next the reaction was performed in various solvents such as tetrahydrofuran, toluene, 1, 2-dichloroethane, DMF and 1,4-dioxane *etc.* (**Table 2**). Among these, 1, 4-dioxane was found to be the best solvent providing 95% yield of the product.

Entry	Solvent	Yield (%)
1	THF	50
2	Toluene	54
3	$ClCH_2CH_2Cl$	70

4	DMF	NR
5	**1,4-Dioxane**	**95**
[a]Reaction conditions: 1a (0.5 mmol), nitrating agent (1.0 mmol), TEMPO (0.2 mmol), 80 °C, solvent (5 mL).		

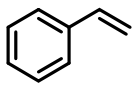
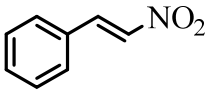
Table 2: Effect of various solvents in the selective nitration of olefin[a]

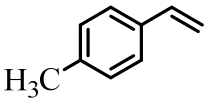
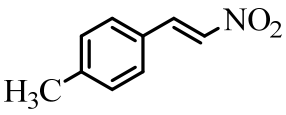
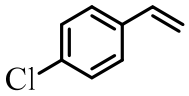
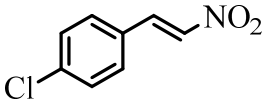
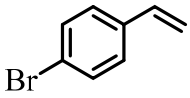
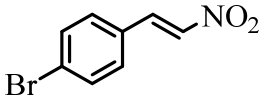
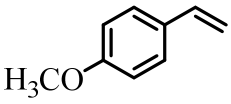
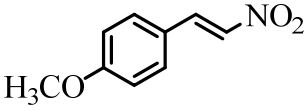
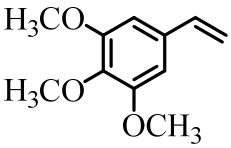
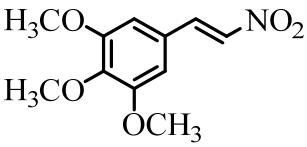
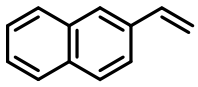
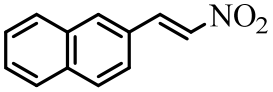
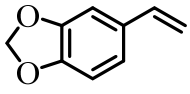
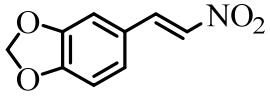
Having established the optimal reaction conditions for selective nitration of olefins with claycop, we then examined the scope and limitations of this reaction with various olefins, the results are presented in **Table 3**. Remarkably only the *E* isomer was observed in all these cases. Aromatic olefins afforded excellent yield of products in comparison to aliphatic olefins. It should be noted that *p*-substituted styrenes with claycop gave the excellent yield of product (entries **2**, **3**, **4**, **5**, **17**, **Table 3**) whereas the same reaction with clayan & clayfen in the presence of catalytic amount of TEMPO gave mainly the polymeric compounds with desired product only in low yield. Thus claycop was found to be the superior reagent for the selective nitration of styrene derivatives when compared with clayfen and clayan.[9]

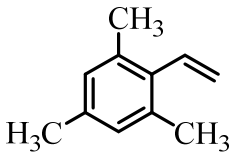
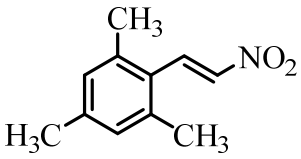
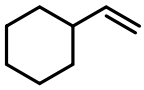
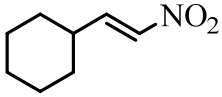
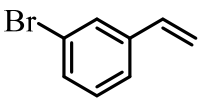
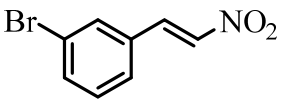
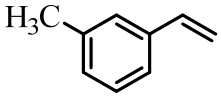
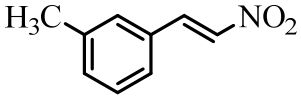
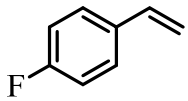
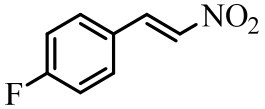
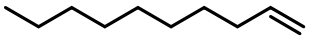
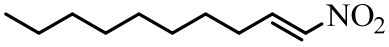
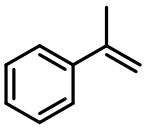
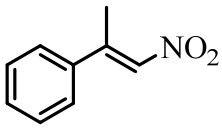


R_1 = aromatic, aliphatic,
R_2, R_3 = H

E only

Entry	**Alkene**	**Product**	**Yield (%)**
1			95

2			89
3			85
4			84
5			87
6			92
7			90
8			95

9			88
10			60
11			84
12			82
13			84
14			70
15			65

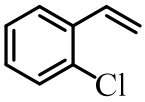
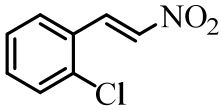
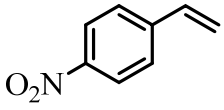
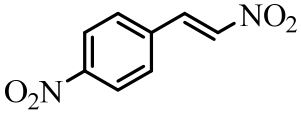
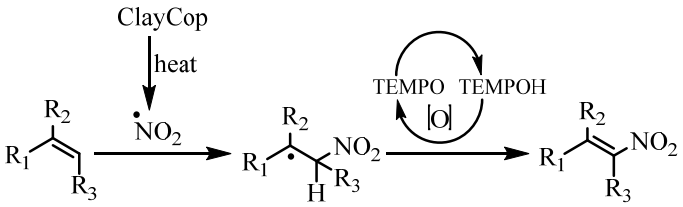
16			80
17			82
[a]The reactions were performed at 1 mmol scale. [b] All the products were characterized by ^{1}H and ^{13}C NMR, and GC mass spectroscopy. [c] Yield refers to pure products after column chromatography.			

Table 3: Selective nitration of aromatic olefins[a]

We also carried out nitration reaction without TEMPO, but it was a failure. The present method is simple, affording excellent yield of (*E*)-β-nitro olefin derivatives. In addition, the workup is simple, because product separation requires only a simple filtration to remove the depleted claycop reagent.



Scheme 5: Plausible mechanism for the nitration of aromatic olefins

Mechanistically, the reaction is expected to proceed *via* the formation of nitro radical ($^{\bullet}NO_2$).[11] The nitro radical ($^{\bullet}NO_2$) can be generated thermally from claycop and the olefin is

eventually converted to β-nitro olefin derivative in the presence of catalytic amount of TEMPO under aerobic conditions according to the proposed mechanism (**Scheme 5**).[3a-c]

4.2.5. Conclusion

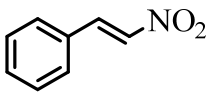
In conclusion, we have demonstrated an alternative, convenient, and general method for the selective nitration of a variety of alkenes using claycop. Additionally the clay supported reagent and aqueous medium with minimum waste effluent makes this a very attractive and environmentally benign process.

4.2.6 Experimental Section:

Preparation of claycop: A solution of copper (II) nitrate trihydrate (26 g) was stirred in acetone (400 mL). To this, K10 clay (30 g) was added, and stirring is continued for 5-10 minutes and the solvent was removed on a rotary evaporator at 50 °C. After removal of the solvent, a dry solid crust adheres to the walls of the flask which was flaked off with a spatula, and the rotary drying under vacuum is resumed for 50 min at the same temperature. This yields the clay-supported copper nitrate reagent as a blue free-flowing powder, which shows no loss of reactivity for several months.

General procedure: In a round bottom flask a mixture of styrene (0.104g, 1.0 mmol), claycop (0.605g, 1.5 mmol, 1.5 equiv, copper (II) nitrate present in the reagent), TEMPO (0.0156g, 20 mol%) and 1,4-dioxane (5 mL) was stirred under heating at 80 °C. After 1 h, the mixture was cooled to room temperature and the claycop was removed by filtration and washed with 1, 4-dioxane (3 x 5 mL). The crude product obtained by the removal of the solvent under vaccum was purified by recrystallisation or column chromatography using ethyl acetate/hexanes to yield *β*-nitro styrene derivatives.

(*E*)-(2-Nitrovinyl)benzene 1:



Crystalline yellow solid

Yield: 95 %

Mol. Formula: $C_8H_7NO_2$

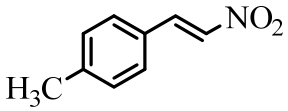
Mp: 56-58 °C; lit.[3c] Mp 58 °C

^{1}H NMR (200MHz, $CDCl_3$): δ = 8.03 (d, *J*=13.6 Hz, 1H), 7.53 - 7.66 (m, 3H), 7.41 - 7.53 (m, 3H)

^{13}C NMR (100MHz, $CDCl_3$): δ = 139.1, 137.1, 132.1, 130.0, 129.4, 129.1

GC-MS (m/z) 149.1 $[M]^+$

(*E*)-1-Methyl-4-(2-nitrovinyl)benzene 2:



Yellow solid

Yield: 89 %

Mol. Formula: $C_9H_9NO_2$

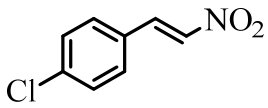
Mp: 106-108 °C; lit.[3c] Mp 108 °C

^{1}HNMR (400MHz, $CDCl_3$,): δ = 8.00 (d, *J*=13.7 Hz, 1H), 7.58 (d, *J*=13.7 Hz, 1H), 7.46 (d, *J*=8.1 Hz, 2H), 7.27 (d, *J*=8.1 Hz, 2H), 2.42 (s, 3H)

^{13}C NMR (100MHz, $CDCl_3$): δ = 143.1, 139.2, 136.2, 130.1, 129.2, 127.2, 21.6

GC-MS (m/z) 163.1 $[M]^+$

(*E*)-1-Chloro-4-(2-nitrovinyl)benzene 3:



Yellow solid

Yield: 85 %

Mol. Formula: $C_8H_6ClNO_2$

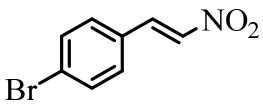
Mp: 113-114 °C; lit.[3c] 113-114 °C

^{1}H NMR (200MHz, $CDCl_3$): δ = 7.98 (d, *J*=13.8 Hz, 1H), 7.57 (d, *J*=13.6 Hz, 1H), 7.41 - 7.53 (m, 4H)

^{13}C NMR (50MHz, $CDCl_3$): δ = 138.3, 137.6, 137.4, 130.2, 129.8, 128.8

GC-MS (m/z) 183.1 $[M]^+$

(*E*)-1-Bromo-4-(2-nitrovinyl)benzene 4:



Yellow solid

Yield: 84 %

Mol. Formula: $C_8H_6BrNO_2$

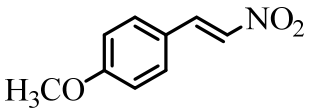
Mp: 149-150 °C; lit.[3d] 148-150 °C

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.96 (d, *J*=13.7 Hz, 1H), 7.59 - 7.62 (m, 2H), 7.52 - 7.58 (m, 1H), 7.43 (d, *J*=7.9 Hz, 2H)

^{13}C NMR (125MHz, $CDCl_3$): δ = 137.8, 137.5, 132.8, 130.4, 128.9, 126.8

GC-MS (m/z) 228.0 $[M]^+$

(*E*)-1-Methoxy-4-(2-nitrovinyl)benzene 5:



Yellow solid

Yield: 87 %

Mol. Formula: $C_9H_9NO_3$

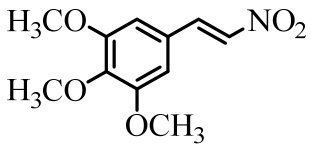
Mp: 84-86 °C; lit.[3c] 85-86 °C

^{1}H NMR (200MHz, $CDCl_3$): δ = 7.99 (d, *J*=13.5 Hz, 1H), 7.48 - 7.58 (m, 3H), 6.93 - 7.00 (m, 2H), 3.88 (s, 3H)

^{13}C NMR (100MHz, $CDCl_3$): δ = 162.9, 139.0, 135.0, 131.1, 122.5, 114.9, 55.5

GC-MS (m/z) 179.1 $[M]^+$

(*E*)-1,2,3-Trimethoxy-5-(2-nitrovinyl)benzene 6:



Crystalline yellow solid

Yield: 92 %

Mol. Formula: $C_{11}H_{13}NO_5$

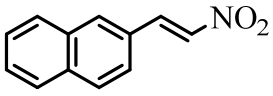
Mp: 120-122 °C; lit.[3d] 121 °C

^{1}H NMR (500MHz, $CDCl_3$): δ = 7.95 (d, *J*=13.7 Hz, 1H), 7.54 (d, *J*=13.4 Hz, 1H), 6.77 (s, 2H), 3.90 - 3.93 (m, 9H)

^{13}C NMR (125MHz, $CDCl_3$): δ = 153.7, 139.3, 136.4, 125.3, 106.5, 61.1, 56.3

GC-MS (m/z) 239.2 $[M]^+$

(*E*)-2-(2-Nitrovinyl)naphthalene 7:



Yellow solid

Yield: 90 %

Mol. Formula: $C_{12}H_9NO_2$

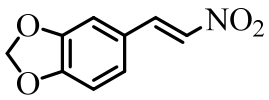
Mp 129-130 °C; lit.[3a-c] 130 °C

^{1}H NMR (500MHz, $CDCl_3$): δ = 8.18 (d, *J*=13.7 Hz, 1H), 8.04 (brs, 1H), 7.86 - 7.94 (m, 3H), 7.72 (d, *J*=13.4 Hz, 1H), 7.55 - 7.63 (m, 3H)

^{13}C NMR (100MHz, $CDCl_3$): δ = 138.9, 136.8, 134.6, 132.9, 132.8, 132.0, 129.1, 128.5, 128.1, 127.6, 127.0, 123.0

GC-MS (m/z) 199.2 $[M]^+$

(*E*)-5-(2-Nitrovinyl)benzo[d][1,3]dioxole 8:



Dark yellow solid

Yield: 95 %

Mol. Formula: $C_9H_7NO_4$

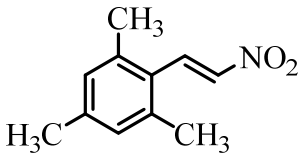
Mp 140-141 °C; lit.[3d] 144 °C

^{1}H NMR (200MHz, $CDCl_3$): δ = 7.94 (d, *J*=13.6 Hz, 1H), 7.48 (d, *J*=13.6 Hz, 1H), 7.06 - 7.13 (m, 1H), 7.01 (d, *J*=1.6 Hz, 1H), 6.88 (d, *J*=8.1 Hz, 1H), 6.06 - 6.10 (m, 2H)

^{13}C NMR (100MHz, $CDCl_3$): δ =151.4, 148.7, 139.1, 135.4, 126.6, 124.2, 109.1, 107.0, 102.0

GC-MS (m/z) 193.5 $[M]^+$

(*E*)-1,3,5-Trimethyl-2-(2-nitrovinyl)benzene 9:



Crystalline yellow solid

Yield: 88 %

Mol. Formula: $C_{11}H_{13}NO_2$

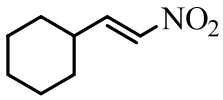
Mp: 122-124 °C; lit.[3a-c] 123-124 °C

^{1}H NMR (200MHz, $CDCl_3$): δ 8.29 (d, *J*=14.0 Hz, 1H), 7.32 (d, *J*=14.0 Hz, 1H), 6.96 (s, 2H), 2.40 (s, 6H), 2.32 (s, 3H)

^{13}C NMR (50MHz, $CDCl_3$): δ 140.8, 139.7, 138.4, 136.6, 129.9, 125.7, 21.5, 21.2

GC-MS (m/z) 191.23 $[M]^+$

(*E*)-(2-Nitrovinyl)cyclohexane 10:



Yellow liquid

Yield: 60 %

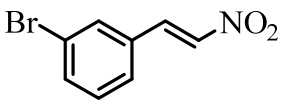
Mol. Formula: $C_8H_{13}NO_2$

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.23 (dd, *J*=13.7, 7.3 Hz, 1H), 6.94 (dd, *J*=13.7, 1.4 Hz, 1H), 2.26 (tdtd, *J*=10.9, 7.3, 3.5, 1.4 Hz, 1H), 1.67 - 1.88 (m, 7H), 1.15 - 1.23 (m, 5H)

^{13}C NMR (100MHz, $CDCl_3$): δ = 147.3, 138.3, 37.5, 31.4, 25.6, 25.4

GC-MS (m/z) 155.01 $[M]^+$

(*E*)-1-Bromo-3-(2-nitrovinyl)benzene 11:



Yellow solid

Yield: 84 %

Mol. Formula: $C_8H_6BrNO_2$

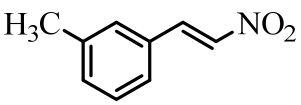
Mp: 149-152 °C

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.94 (d, *J*=13.7 Hz, 1H), 7.71 (s, 1H), 7.64 (d, *J*=7.8 Hz, 1H), 7.57 (d, *J*=13.7 Hz, 1H), 7.49 (d, *J*=7.8 Hz, 1H), 7.35 (t, *J*=7.8 Hz, 1H)

^{13}C NMR (100MHz, $CDCl_3$): δ = 138.1, 137.3, 134.9, 132.0, 131.7, 130.8, 127.6, 123.4

GC-MS (m/z) 228.7 $[M]^+$

(*E*)-1-Methyl-3-(2-nitrovinyl)benzene 12:



Yellow liquid

Yield: 82 %

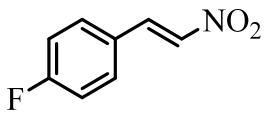
Mol. Formula: $C_9H_9BrNO_2$

^{1}H NMR (200MHz, $CDCl_3$): δ = 7.98 (d, *J*=13.6 Hz, 1H), 7.58 (d, *J*=13.6 Hz, 1H), 7.29 - 7.39 (m, 4H), 2.41 (s, 3H)

^{13}C NMR (100MHz, $CDCl_3$): δ = 139.2, 139.1, 136.8, 133.0, 129.9, 129.6, 129.2, 126.3, 21.2

GC-MS (m/z) 163.1 $[M]^+$

(*E*)-1-Fluoro-4-(2-nitrovinyl)benzene 13:



Crystalline yellow solid

Yield: 84 %

Mol. Formula: $C_8H_6FNO_2$

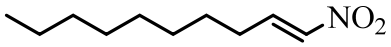
Mp: 99-100 °C; lit.[3c] 101 °C.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.99 (d, *J*=13.7 Hz, 1H), 7.52 - 7.60 (m, 3H), 7.13 - 7.20 (m, 2H)

^{13}C NMR (100MHz, $CDCl_3$): δ = 166.3, 137.9, 136.9, 131.4, 131.3, 126.4, 117.0, 116.8

GC-MS (m/z) 167.1 $[M]^+$

(*E*)-1-Nitrodec-1-ene 14:



Yellow liquid

Yield: 70 %

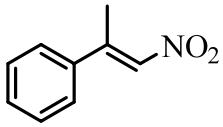
Mol. Formula: $C_{10}H_{19}NO_2$

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.33 - 7.27 (m, 1 H), 7.02 - 6.96 (m, 1 H), 2.31 - 2.24 (m, 2 H), 1.34 - 1.27 (m, 10 H), 0.91 - 0.88 (m, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 142.8, 139.5, 31.8, 29.7, 29.2, 29.1, 28.4, 27.7, 22.6, 14.1

GC-MS (m/z) 185.2 $[M]^+$

(*E*)-(1-Nitroprop-1-en-2-yl)benzene 15:



Yellow liquid

Yield: 65 %

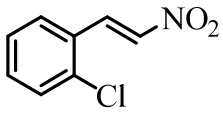
Mol. Formula: $C_9H_9NO_2$

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.47 (d, *J* = 2.4 Hz, 5 H), 7.32 (d, *J* = 1.5 Hz, 1 H), 2.66 (d, *J* = 1.2 Hz, 3 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 149.9, 138.3, 136.3, 130.4, 129.0, 126.8, 18.6

GC-MS (m/z) 163.1 $[M]^+$

(*E*)-1-Chloro-2-(2-nitrovinyl)benzene 16:



Yellow liquid

Yield: 80 %

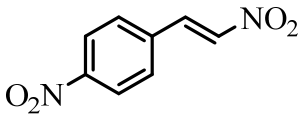
Mol. Formula: $C_8H_6ClNO_2$

^{1}H NMR (200MHz, $CDCl_3$) δ = 8.43 (d, *J* = 13.6 Hz, 1 H), 7.66 - 7.56 (m, 2 H), 7.54 - 7.48 (m, 1 H), 7.44 - 7.37 (m, 1H), 7.35 - 7.29 (m, 1 H)

^{13}C NMR (100MHz, $CDCl_3$) δ =138.8, 136.1, 135.1, 132.8, 130.8, 128.6, 128.5, 127.5

GC-MS (m/z) 183.1 $[M]^+$

(*E*)-1-Nitro-4-(2-nitrovinyl)benzene 17:



Yellow solid

Yield: 82 %

Mol. Formula: $C_8H_6N_2O_4$

Mp: 205 °C

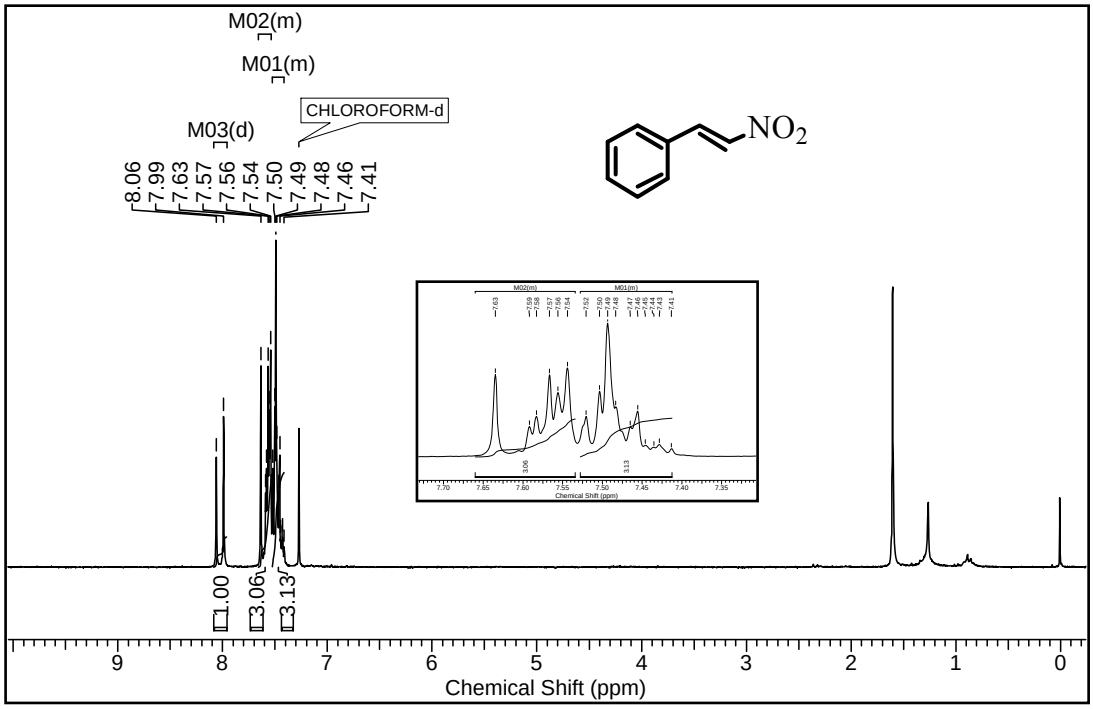
^{1}H NMR (200MHz, $CDCl_3$) δ = 8.40 - 8.28 (m, 2 H), 8.05 (d, *J* = 13.8 Hz, 1 H), 7.81 - 7.70 (m, 2 H), 7.65 (d, *J* = 13.8 Hz, 1 H)

^{13}C NMR (100MHz, $CDCl_3$) δ = 149.5, 139.8, 136.1, 136.0, 129.8, 124.5

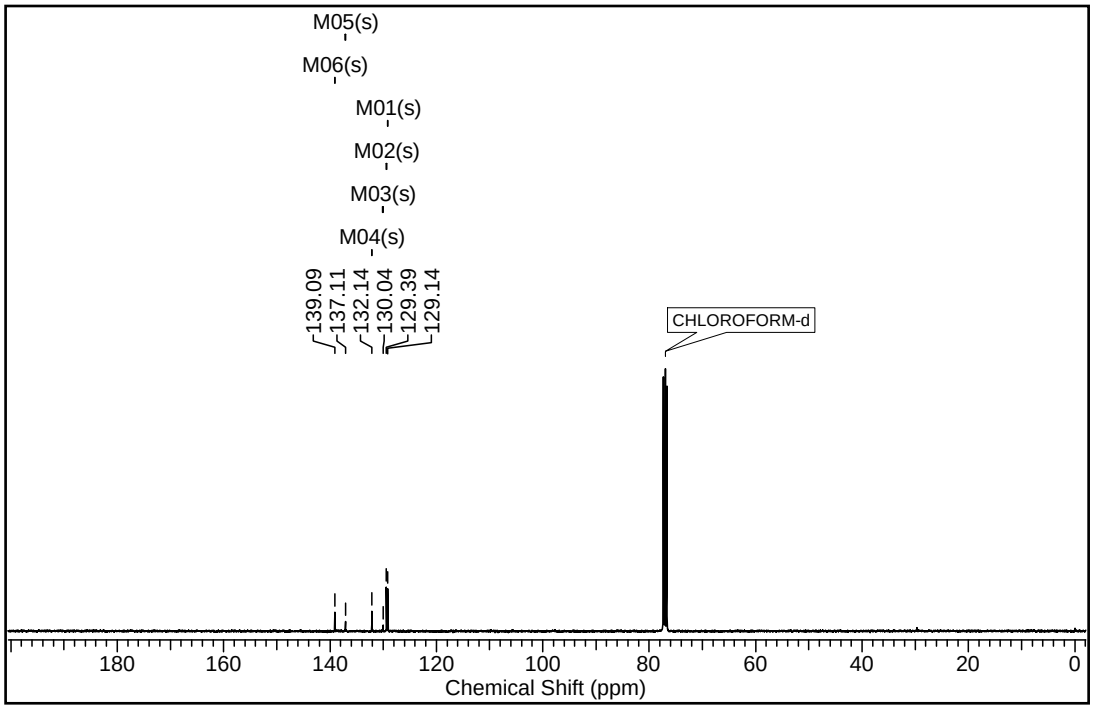
GC-MS (m/z) 194.1 $[M]^+$

4.2.7 Spectra:

(*E*)-(2-Nitrovinyl)benzene 1:

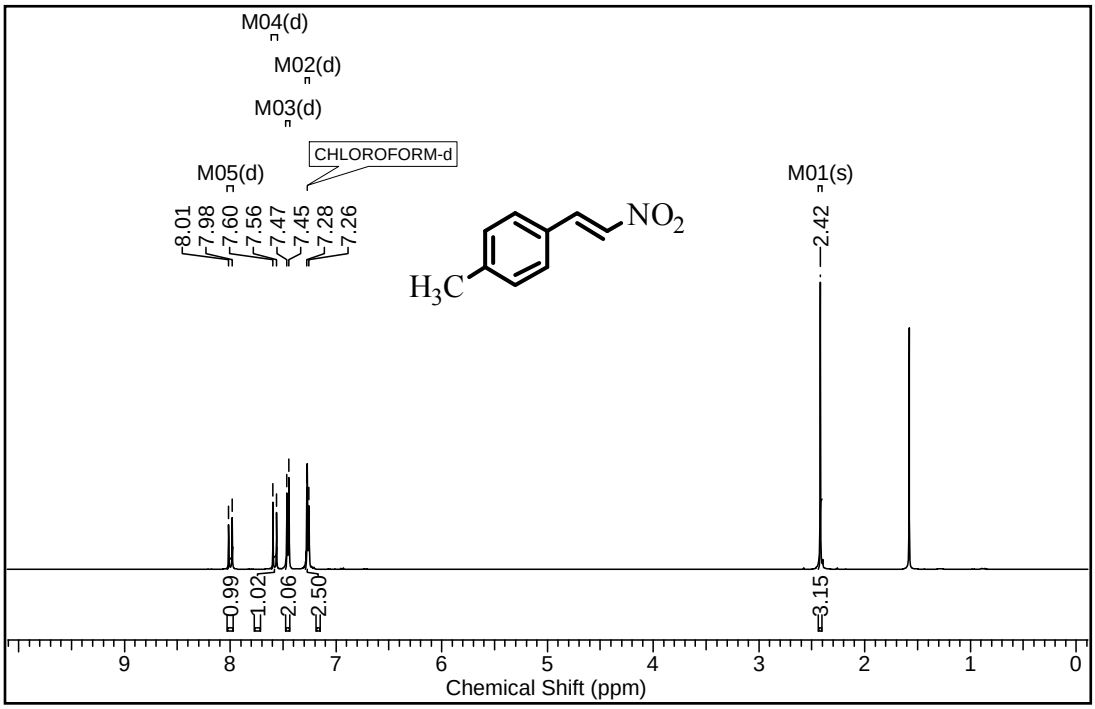


- **^{1}H NMR of the compound 1 in $CDCl_3$**

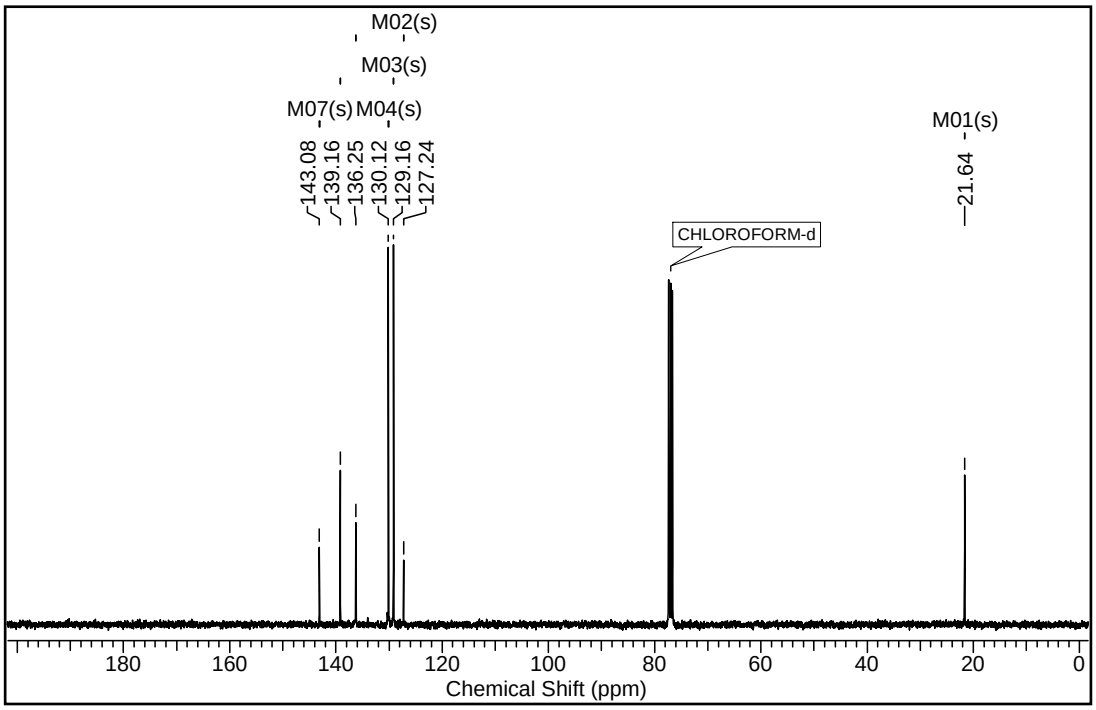


- **^{13}C NMR of the compound 1 in $CDCl_3$**

(*E*)-1-Methyl-4-(2-nitrovinyl)benzene 2:

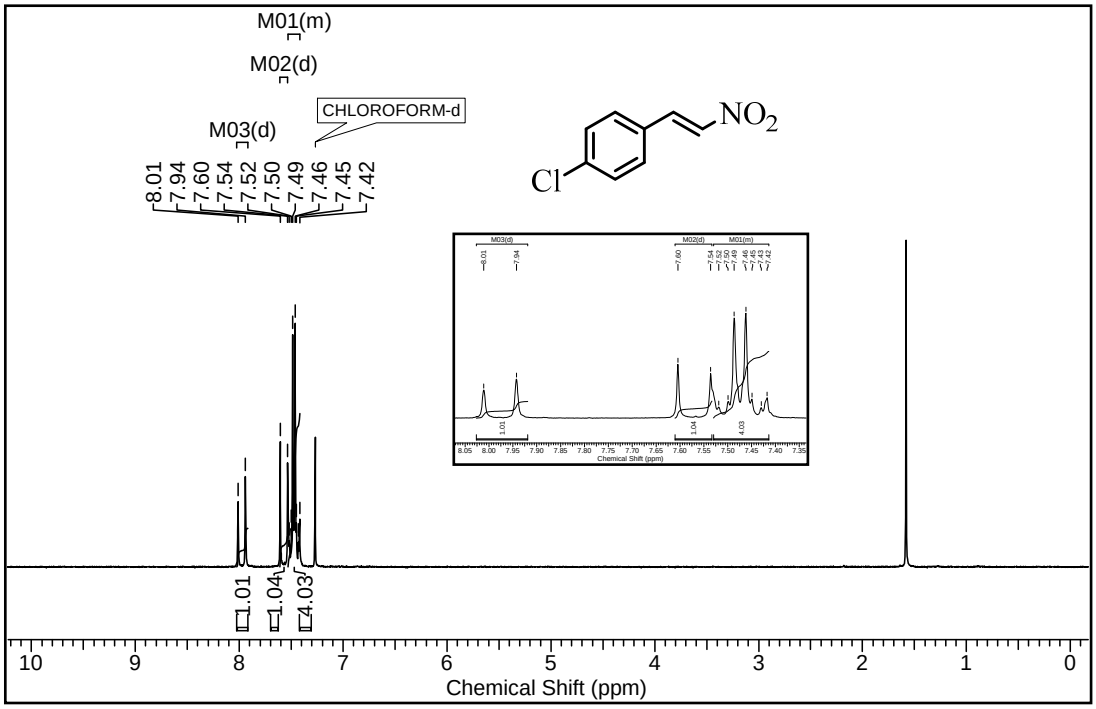


➢ **^{1}H NMR of the compound 2 in $CDCl_3$**

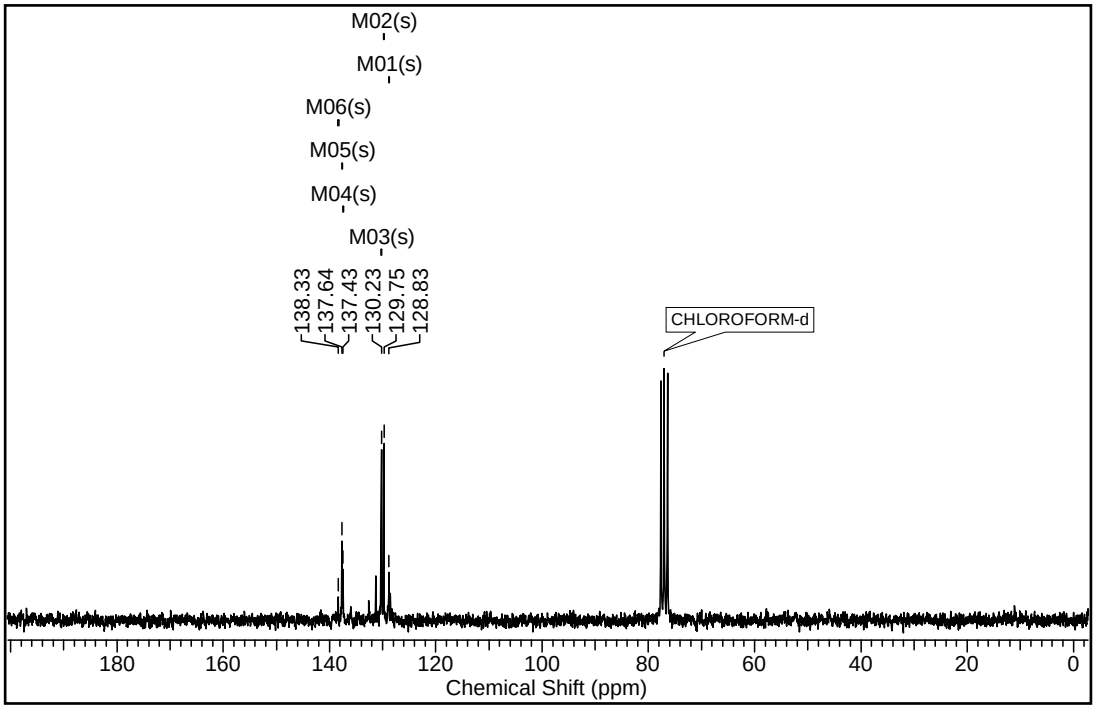


➢ **^{13}C NMR of the compound 2 in $CDCl_3$**

(*E*)-1-Chloro-4-(2-nitrovinyl)benzene 3:

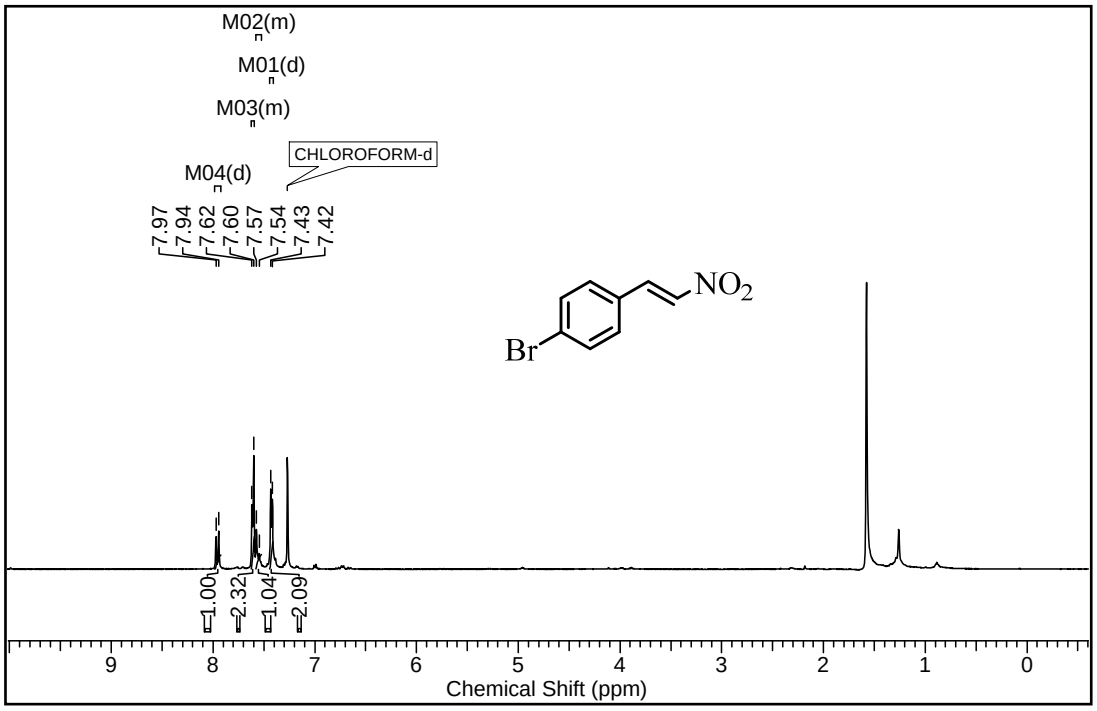


➢ **^{1}H NMR of the compound 3 in $CDCl_3$**

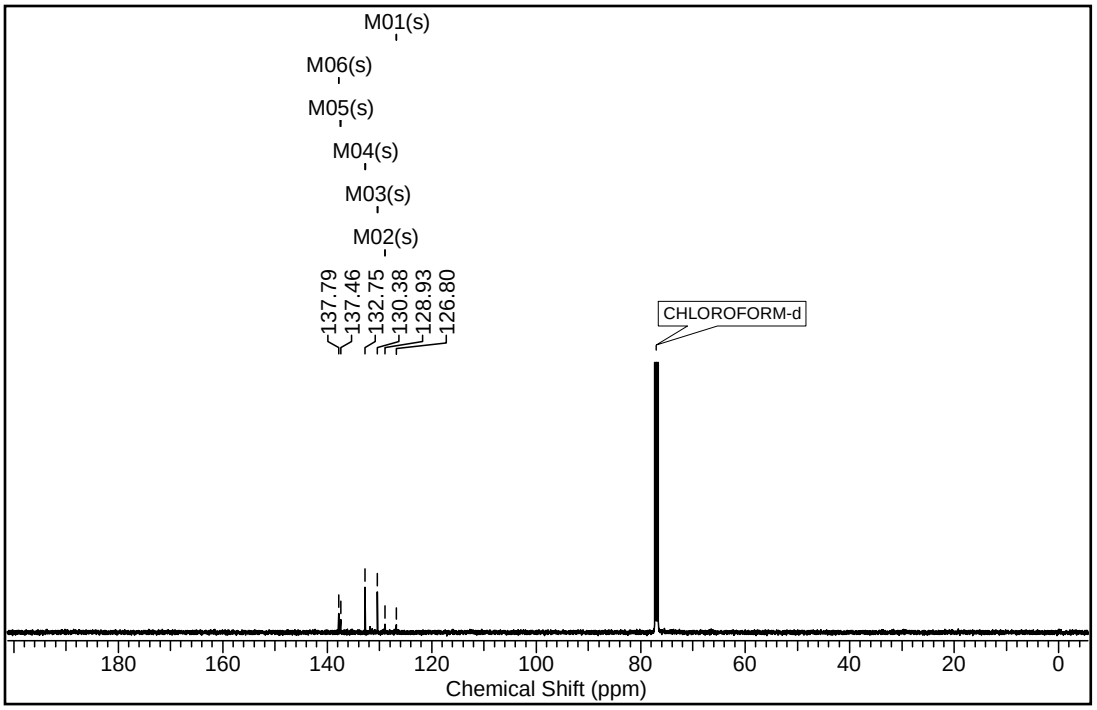


^{13}C NMR of the compound 3 in $CDCl_3$

(*E*)-1-Bromo-4-(2-nitrovinyl)benzene 4:

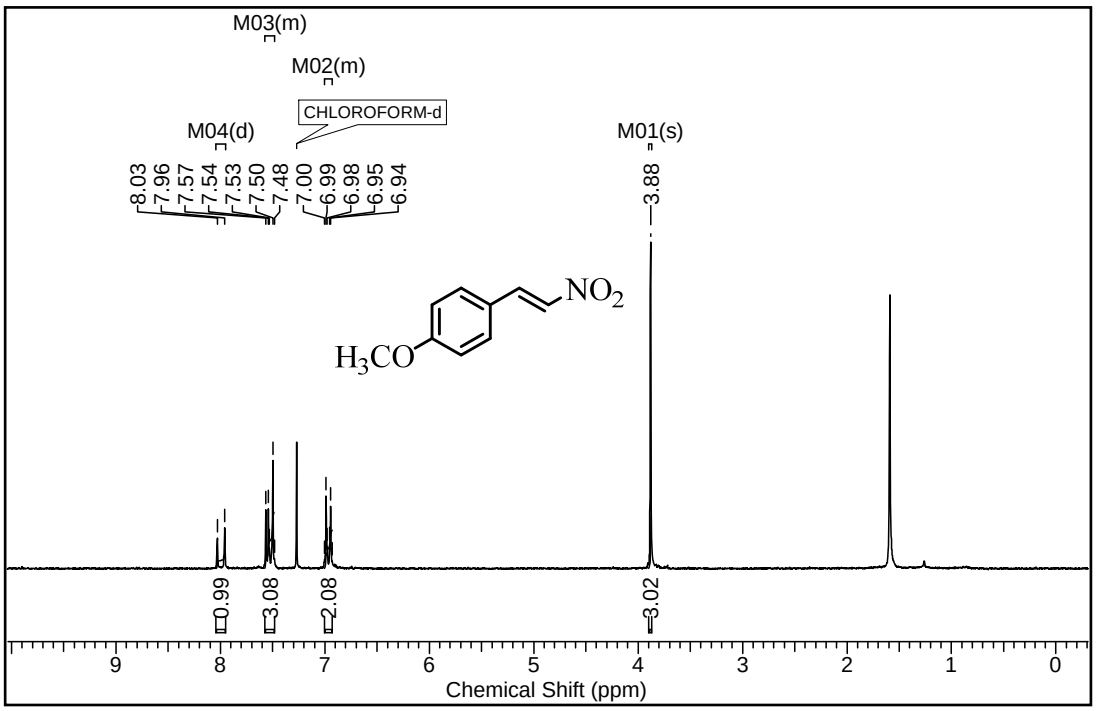


- **^{1}H NMR of the compound 4 in $CDCl_3$**

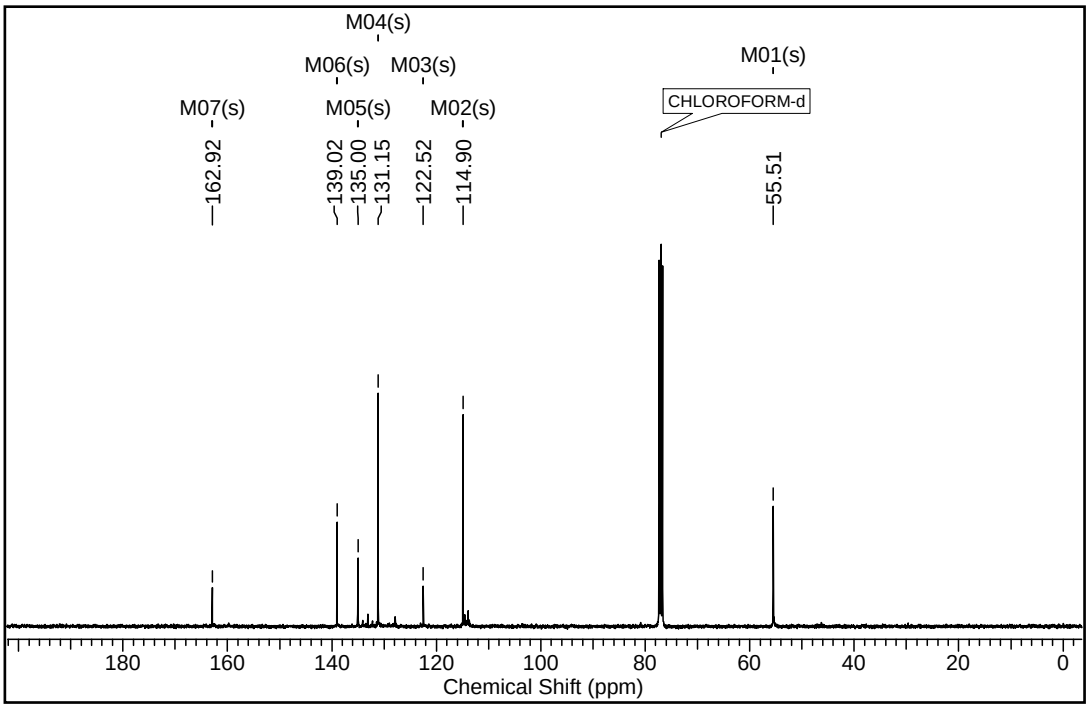


- **^{13}C NMR of the compound 4 in $CDCl_3$**

(*E*)-1-Methoxy-4-(2-nitrovinyl)benzene 5:

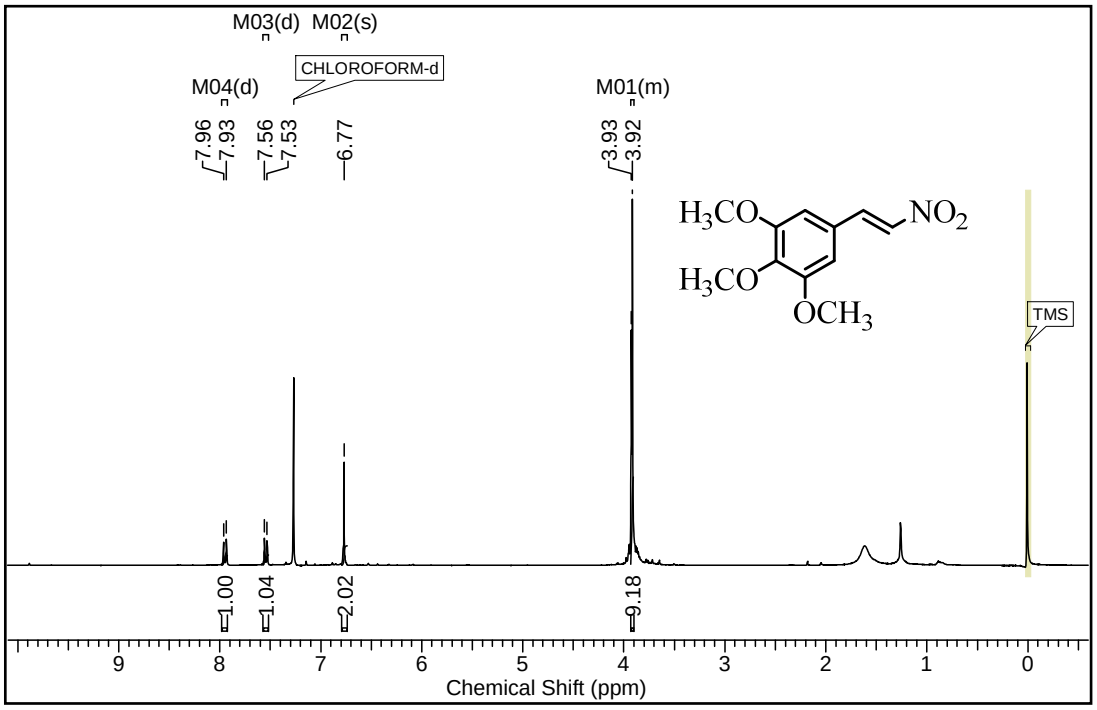


- **^{1}H NMR of the compound 5 in $CDCl_3$**

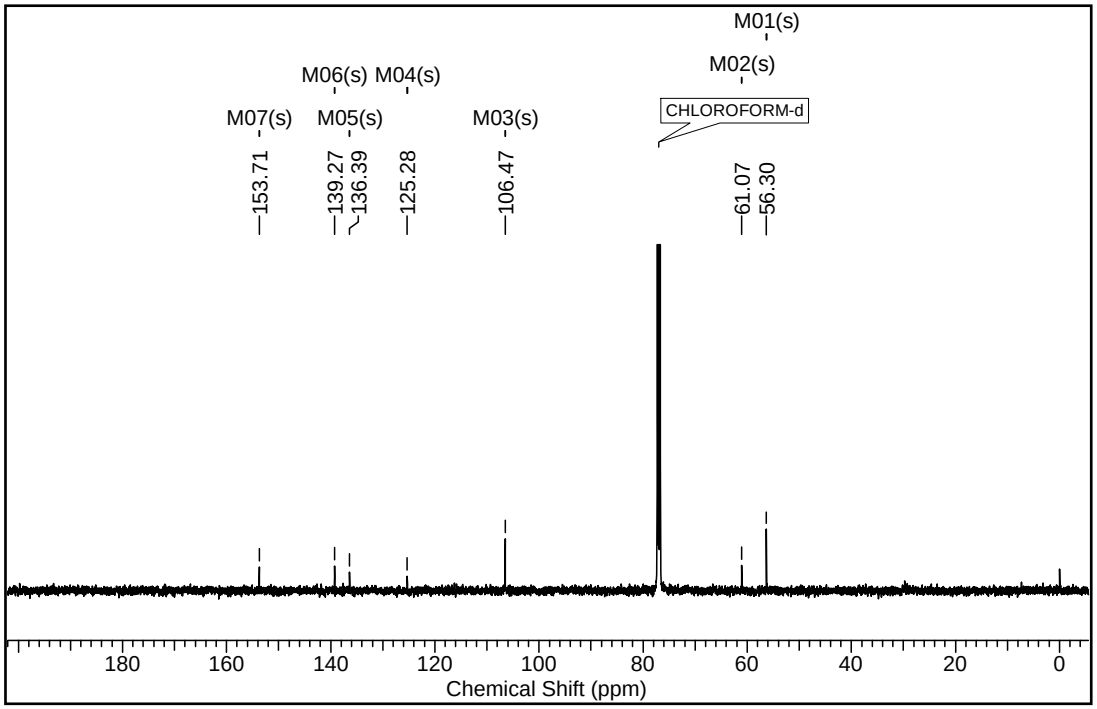


- **^{13}C NMR of the compound 5 in $CDCl_3$**

(*E*)-1,2,3-Trimethoxy-5-(2-nitrovinyl)benzene 6:

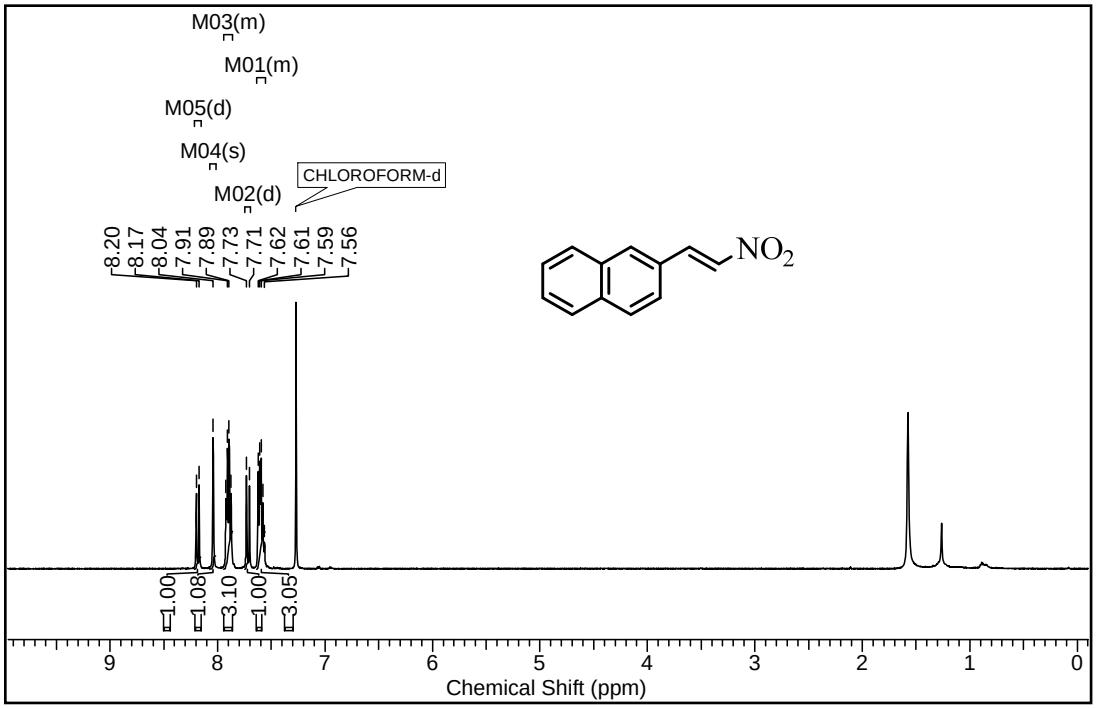


➢ **^{1}H NMR of the compound 6 in $CDCl_3$**

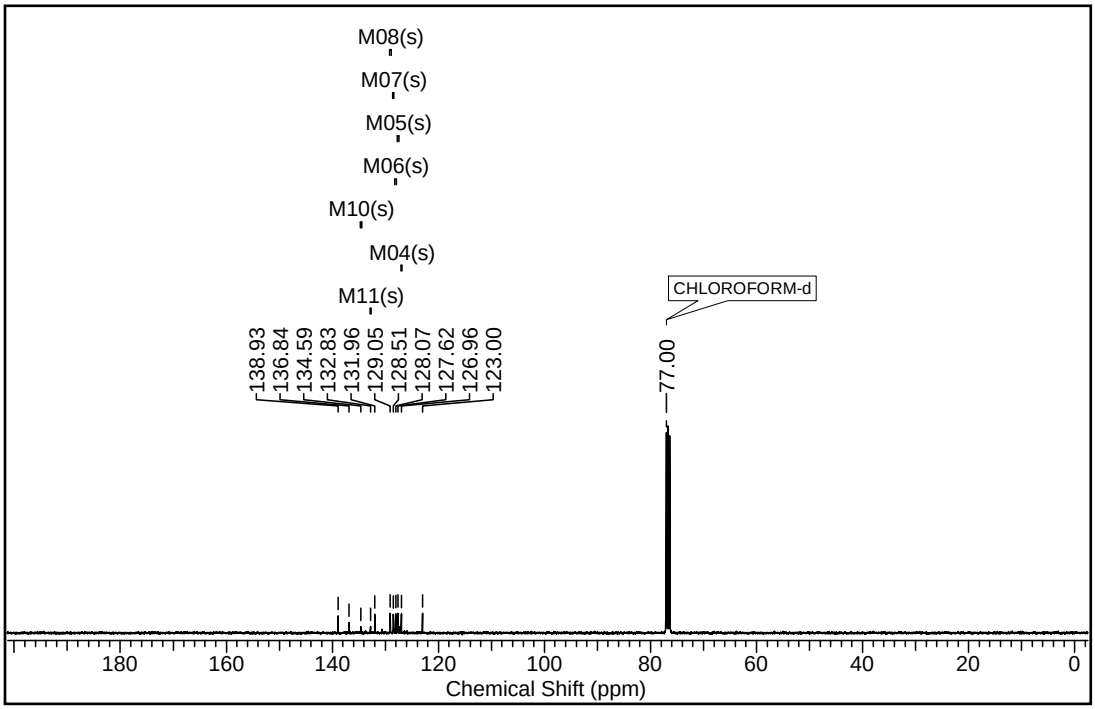


➢ **^{13}C NMR of the compound 6 in $CDCl_3$**

(*E*)-2-(2-Nitrovinyl)naphthalene 7:

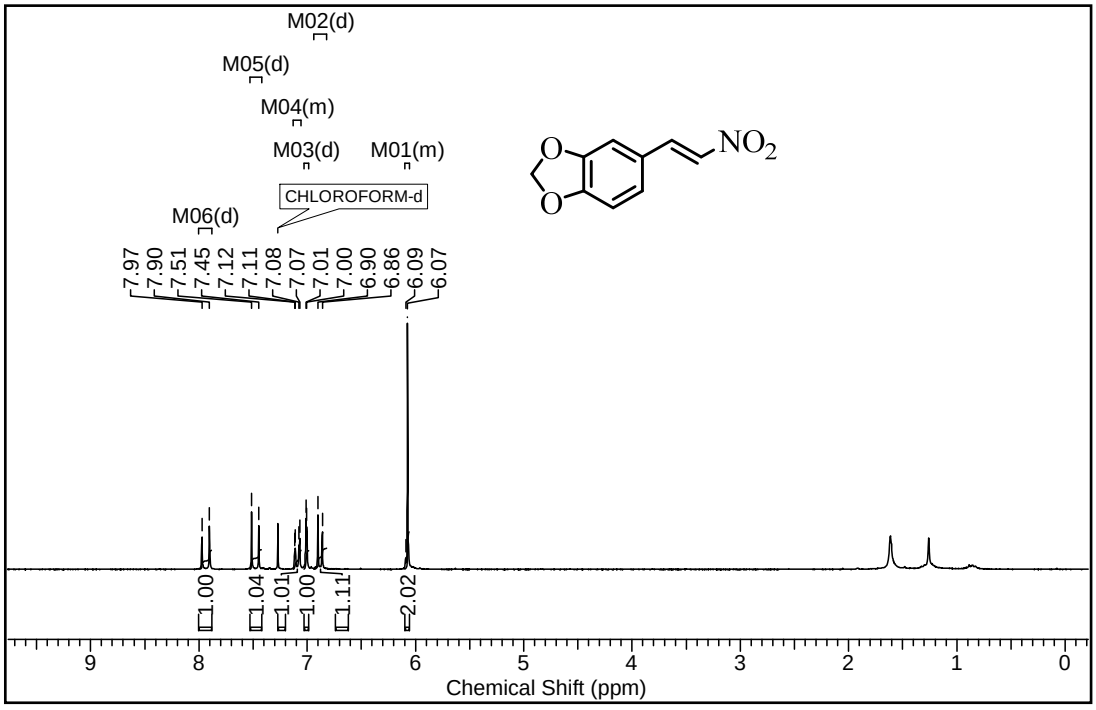


- **^{1}H NMR of the compound 7 in $CDCl_3$**

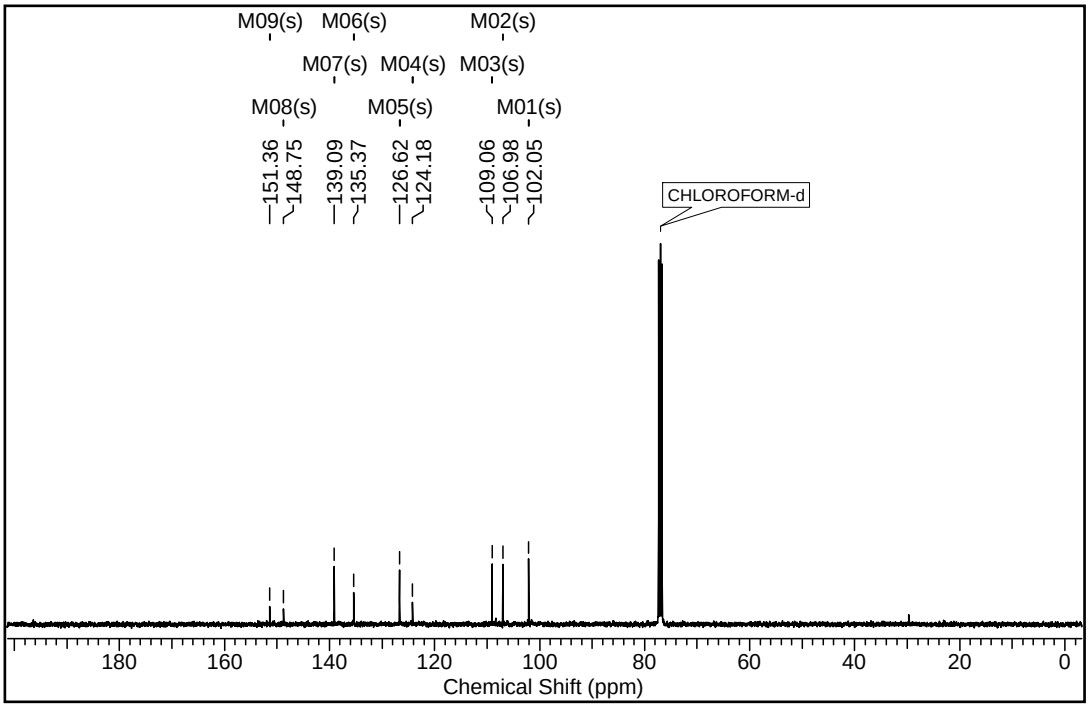


- **^{13}C NMR of the compound 7 in $CDCl_3$**

(*E*)-5-(2-Nitrovinyl)benzo[d][1,3]dioxole 8:

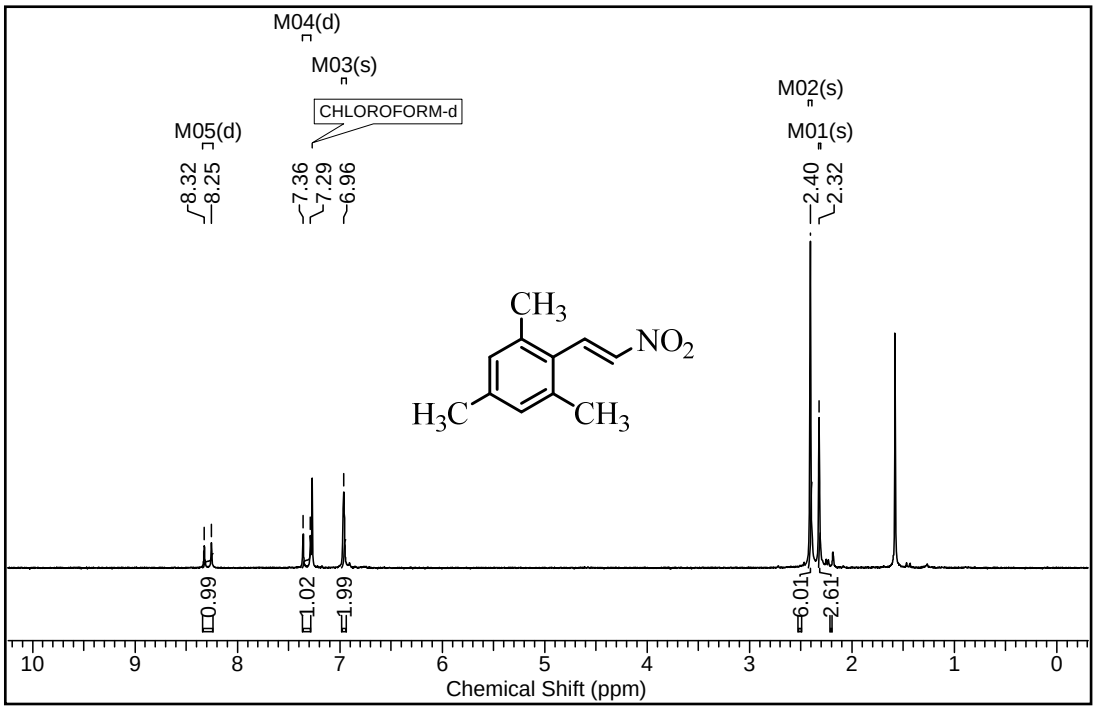


➢ **^{1}H NMR of the compound 8 in $CDCl_3$**

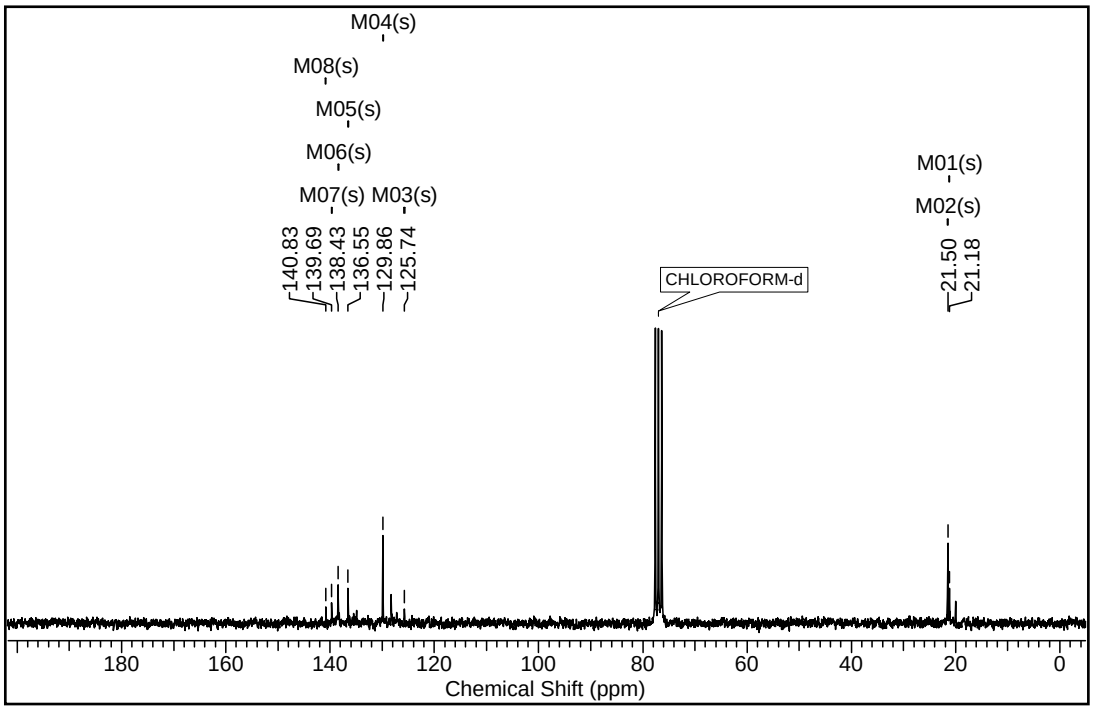


➢ **^{13}C NMR of the compound 8 in $CDCl_3$**

(*E*)-1,3,5-Trimethyl-2-(2-nitrovinyl)benzene 9:

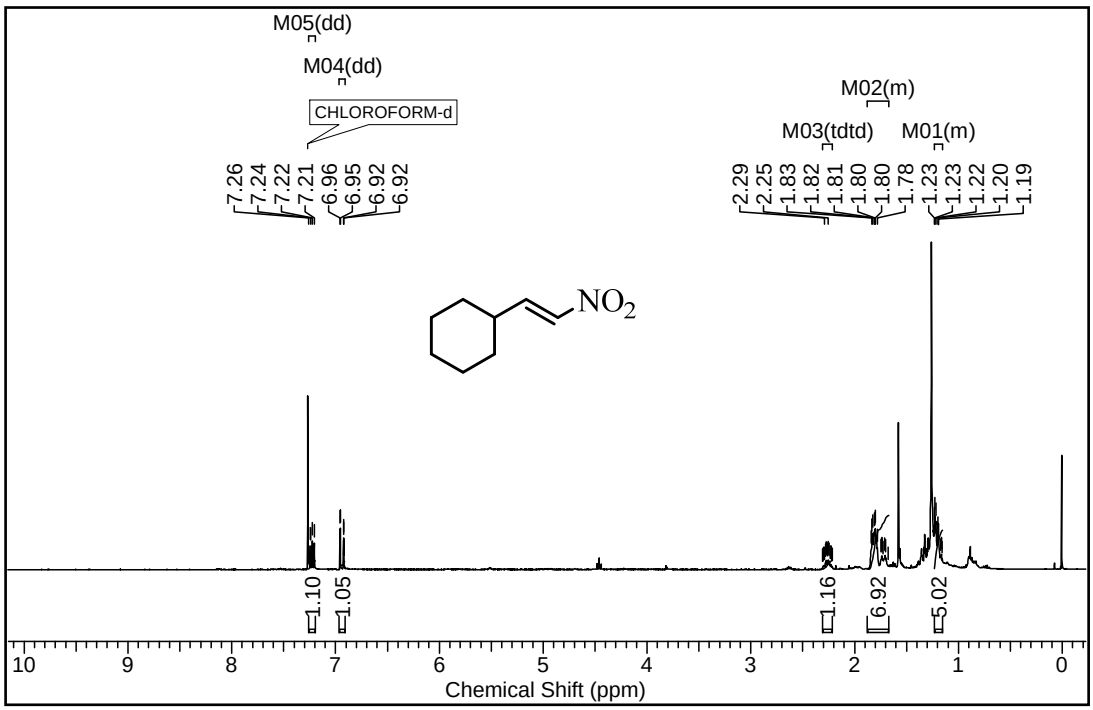


➢ **^{1}H NMR of the compound 9 in $CDCl_3$**

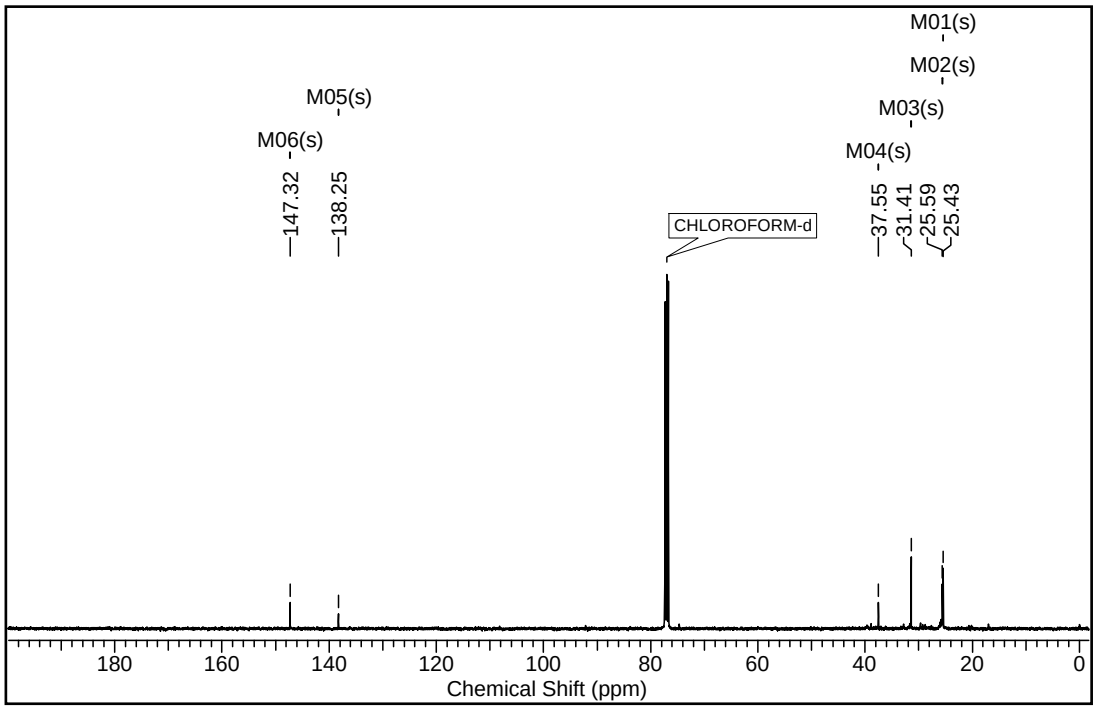


➢ **^{13}C NMR of the compound 9 in $CDCl_3$**

(*E*)-(2-Nitrovinyl)cyclohexane 10:

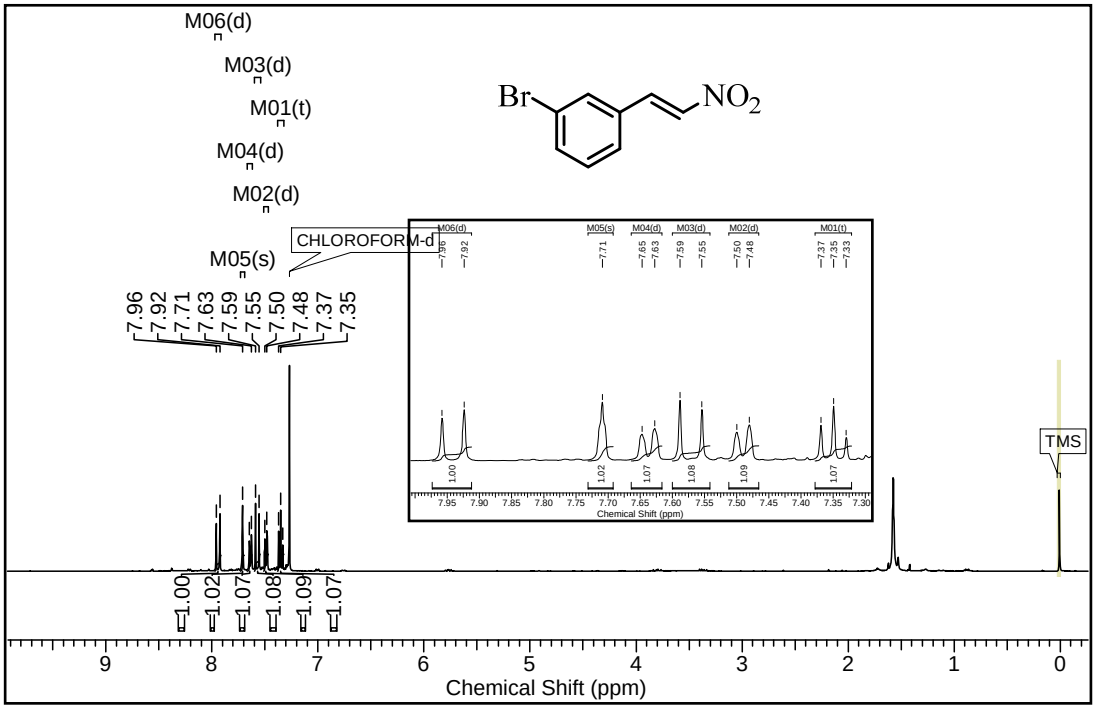


➢ **^{1}H NMR of the compound 10 in $CDCl_3$**

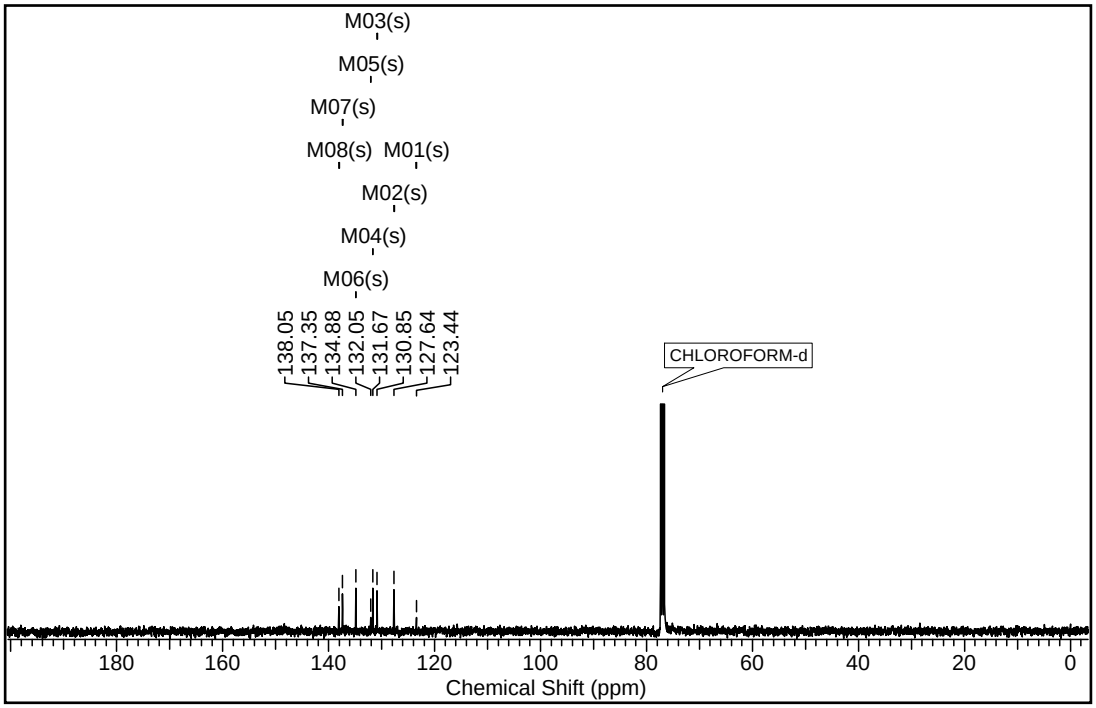


➢ **^{13}C NMR of the compound 10 in $CDCl_3$**

(*E*)-1-Bromo-3-(2-nitrovinyl)benzene 11:

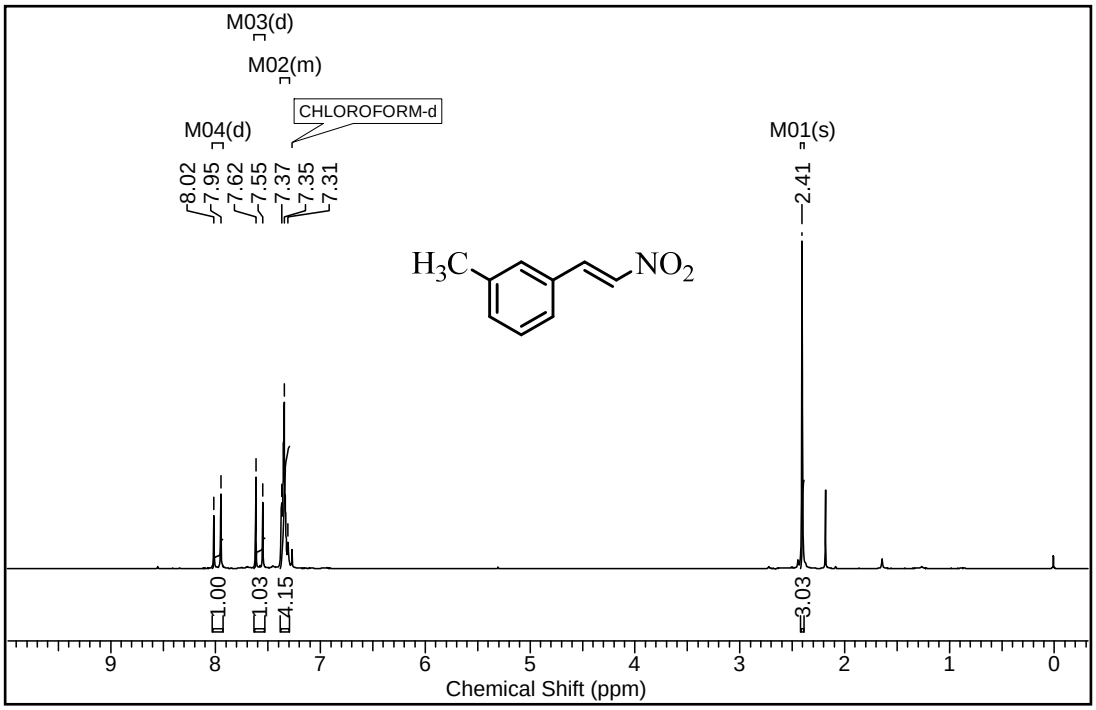


- **^{1}H NMR of the compound 11 in $CDCl_3$**

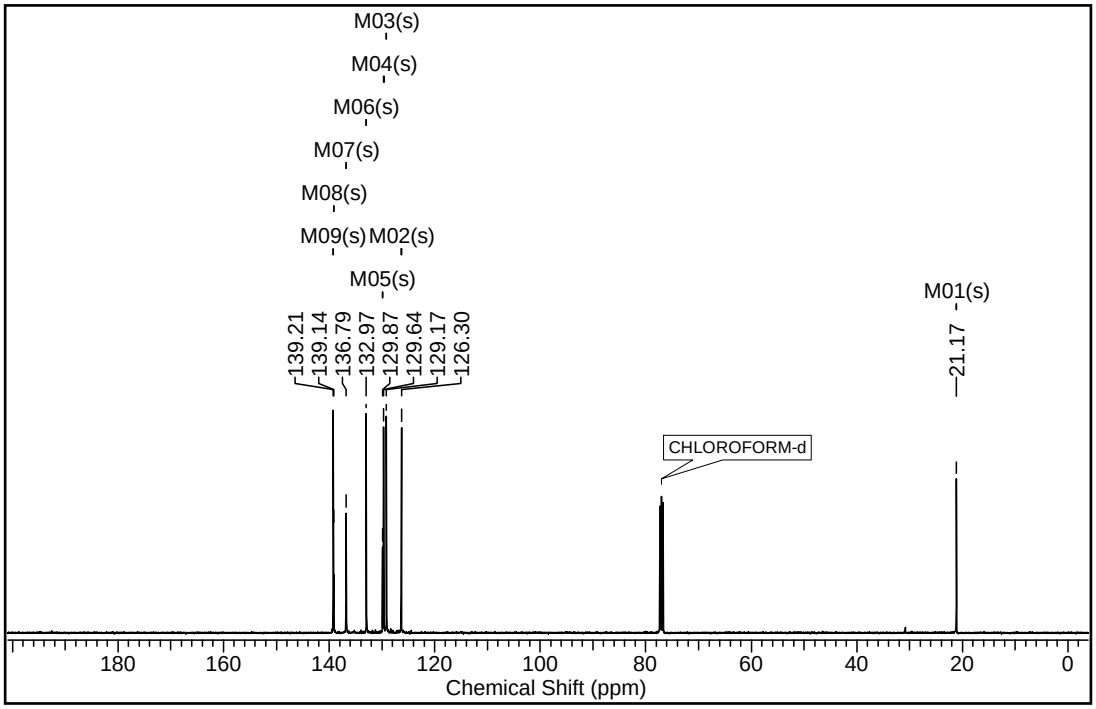


- **^{13}C NMR of the compound 11 in $CDCl_3$**

(*E*)-1-Methyl-3-(2-nitrovinyl)benzene 12:

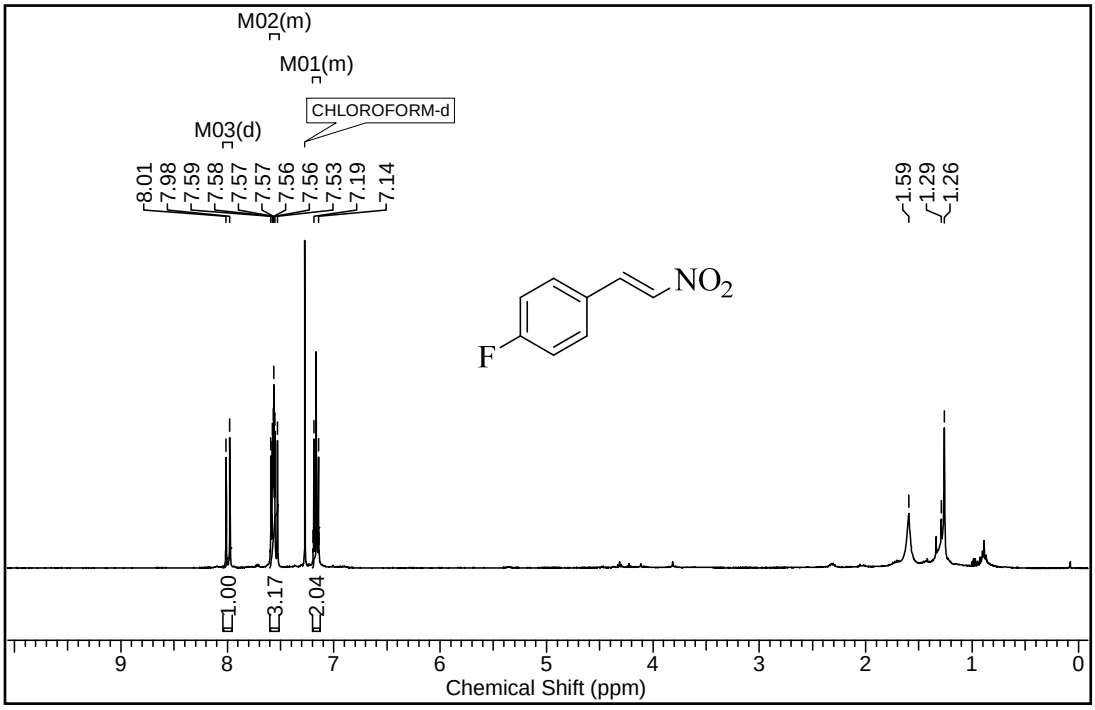


➢ **^{1}H NMR of the compound 12 in $CDCl_3$**

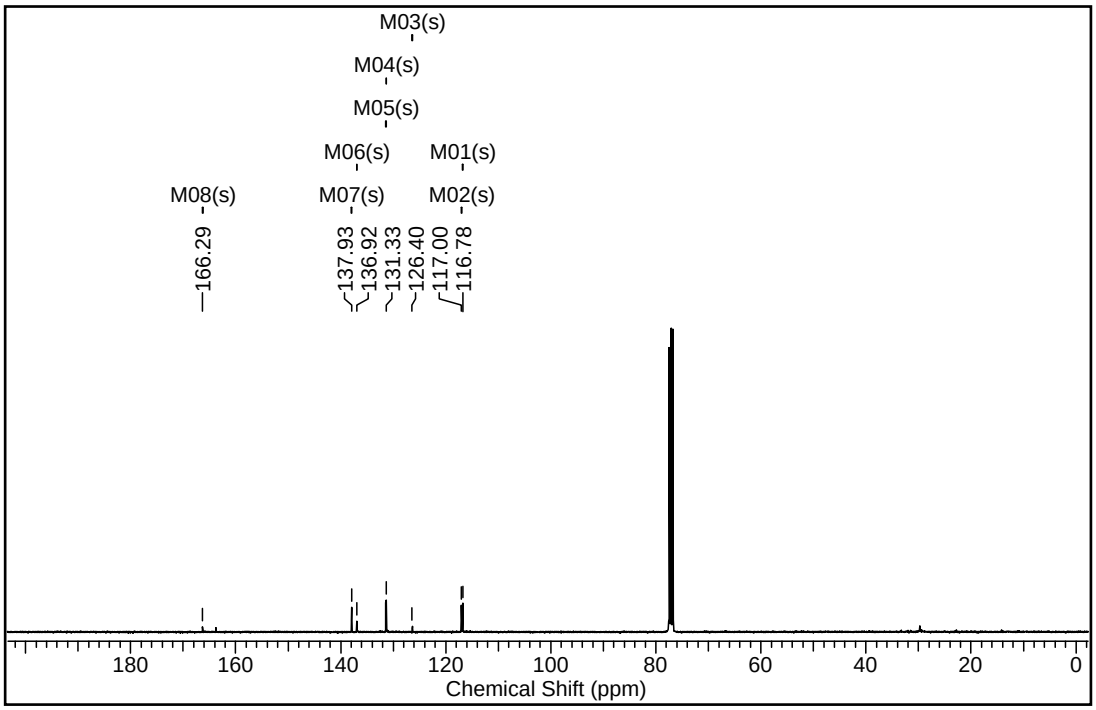


➢ **^{13}C NMR of the compound 12 in $CDCl_3$**

(*E*)-1-Fluoro-4-(2-nitrovinyl)benzene 13:

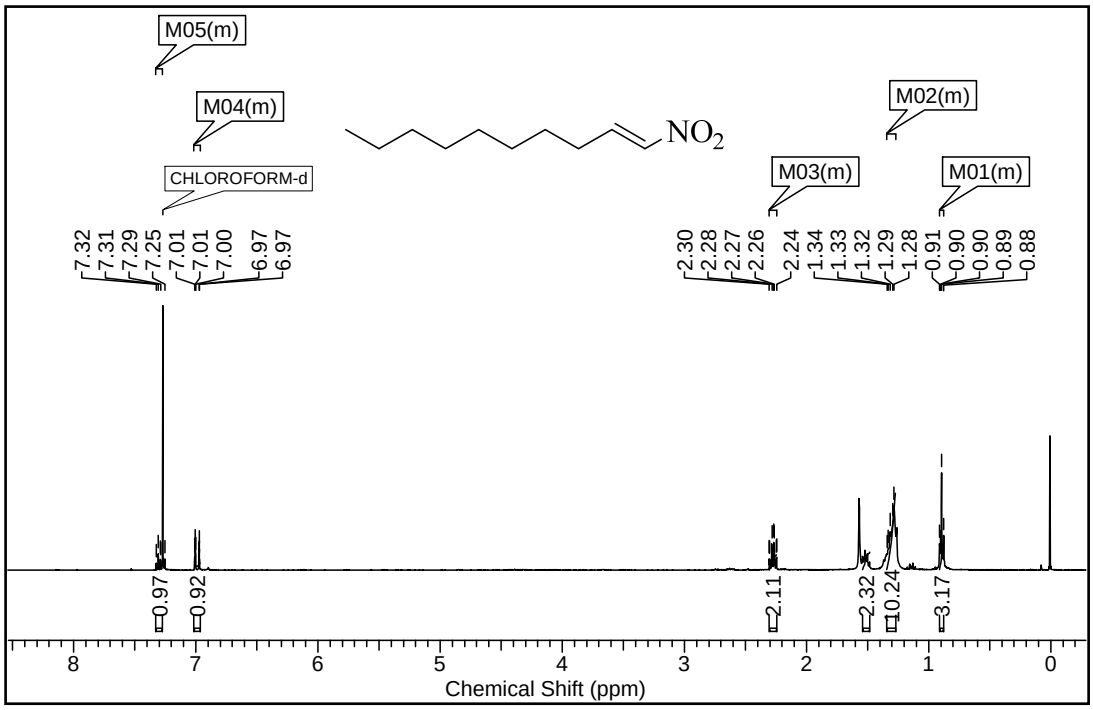


- **^{1}H NMR of the compound 13 in $CDCl_3$**

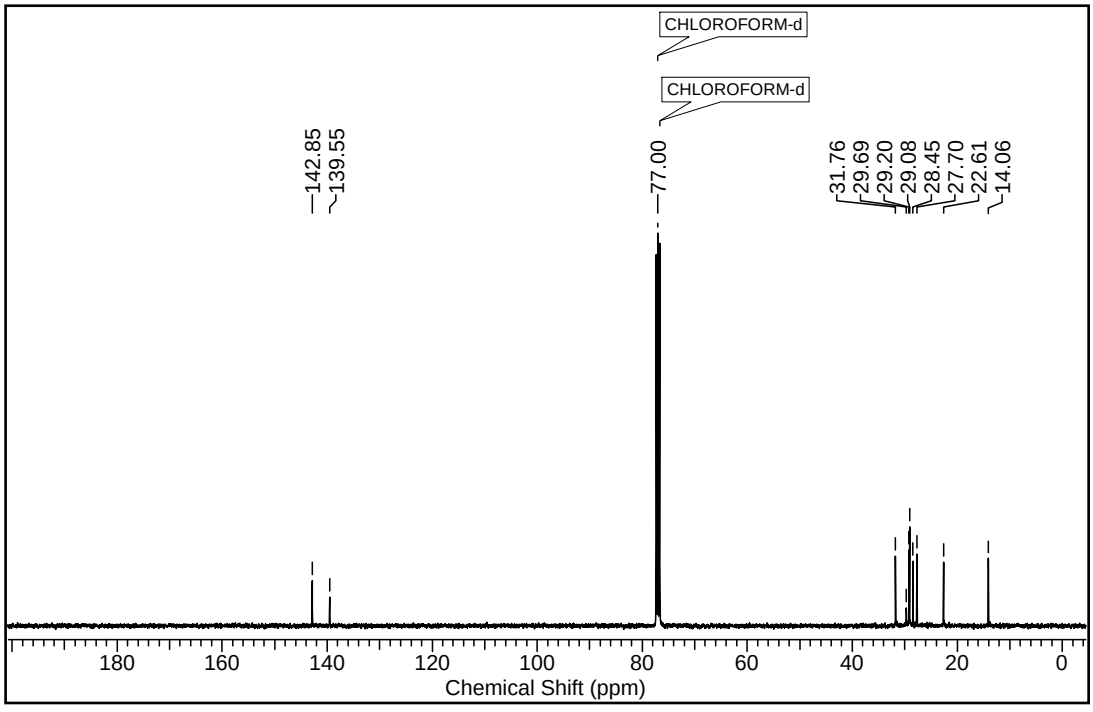


- **^{13}C NMR of the compound 13 in $CDCl_3$**

(*E*)-1-Nitrodec-1-ene 14:

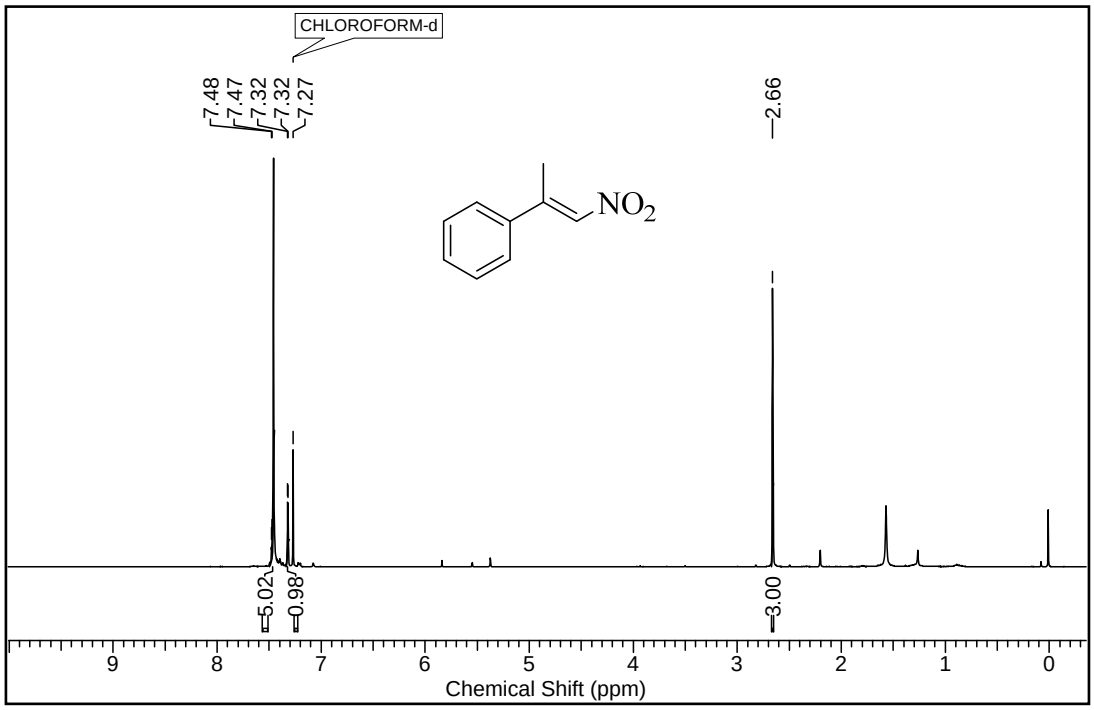


- **^{1}H NMR of the compound 14 in $CDCl_3$**

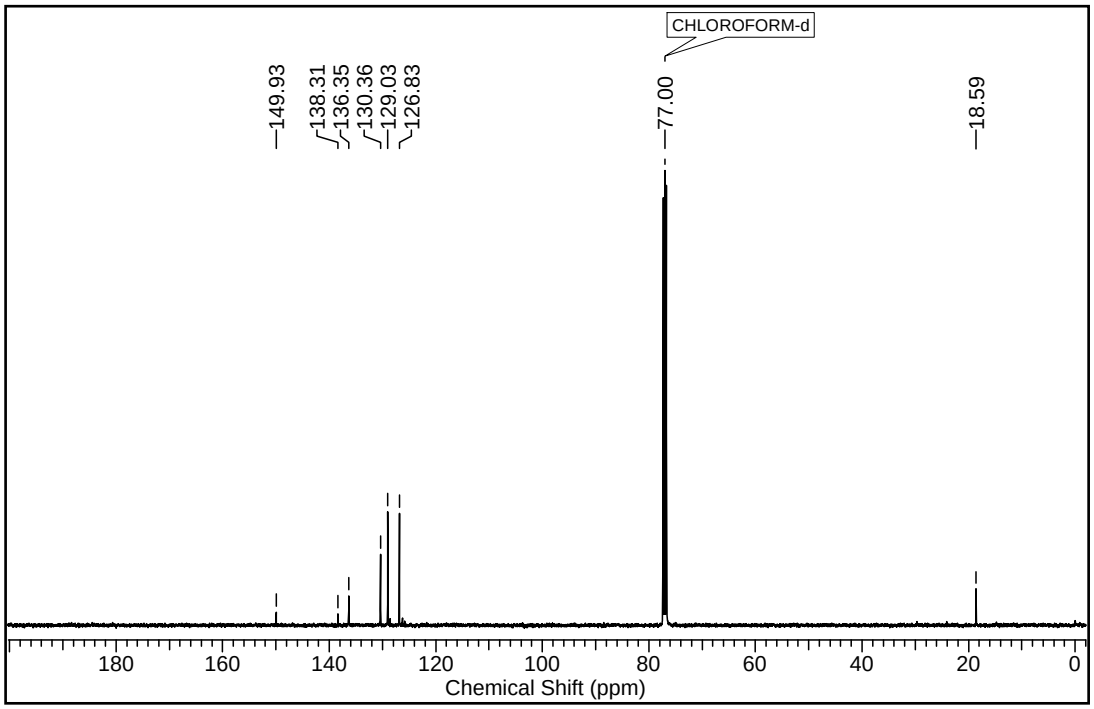


- **^{13}C NMR of the compound 14 in $CDCl_3$**

(*E*)-(1-Nitroprop-1-en-2-yl)benzene 15:

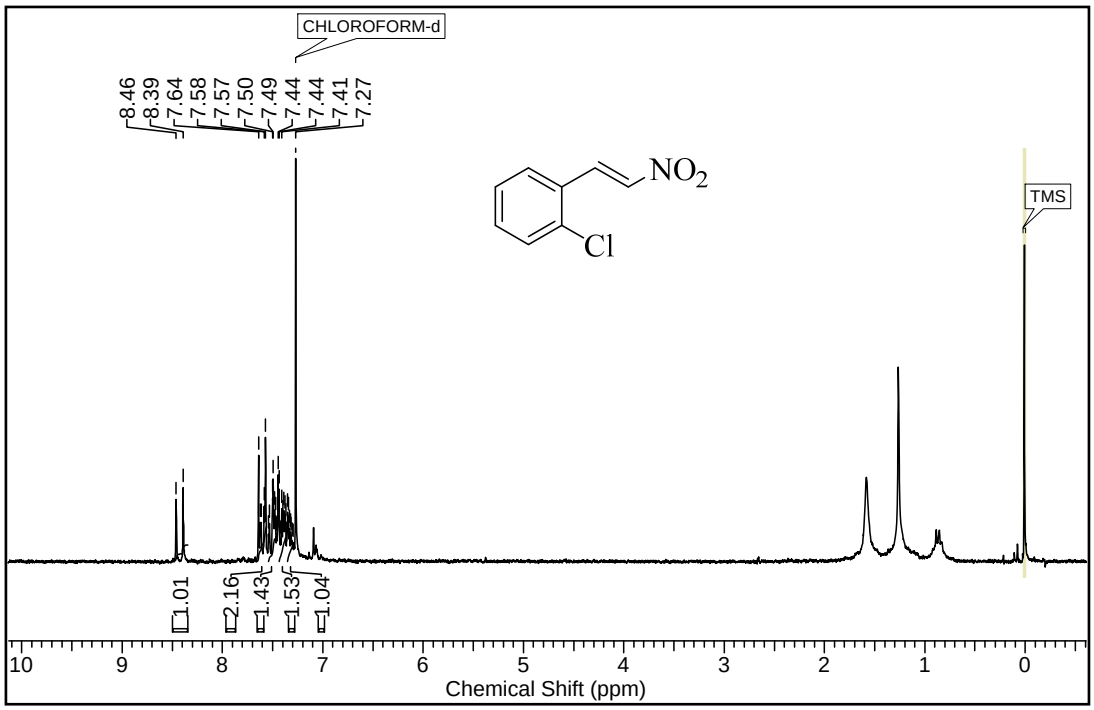


- **^{1}H NMR of the compound 15 in $CDCl_3$**

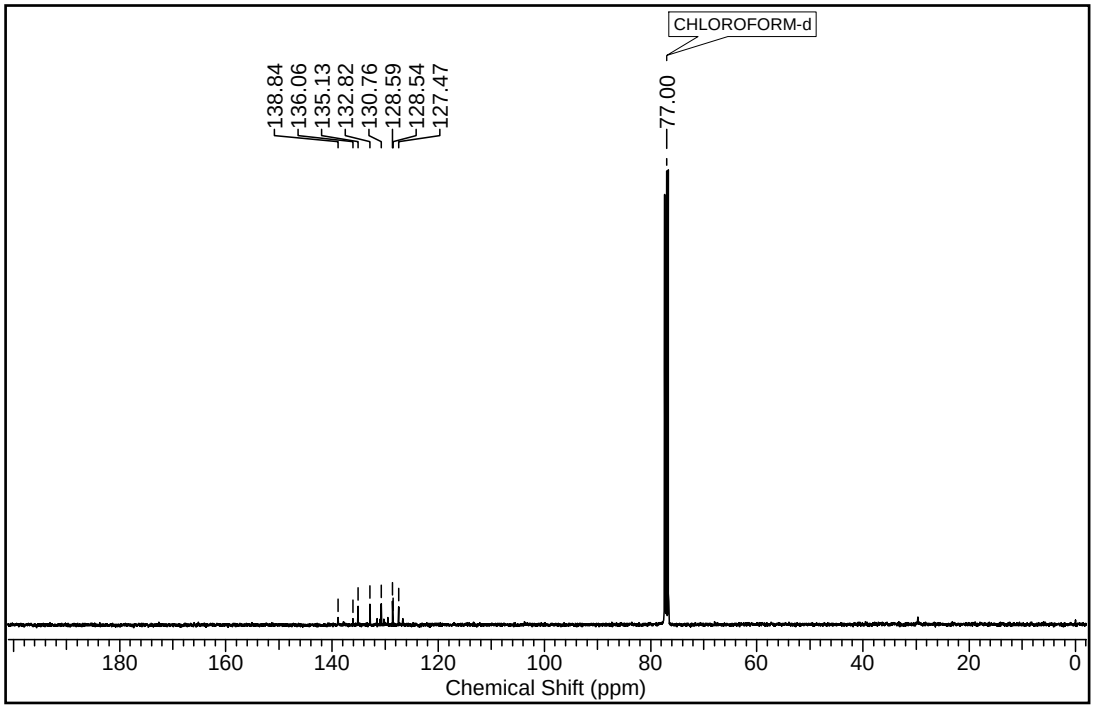


- **^{13}C NMR of the compound 15 in $CDCl_3$**

(*E*)-1-Chloro-2-(2-nitrovinyl)benzene 16:

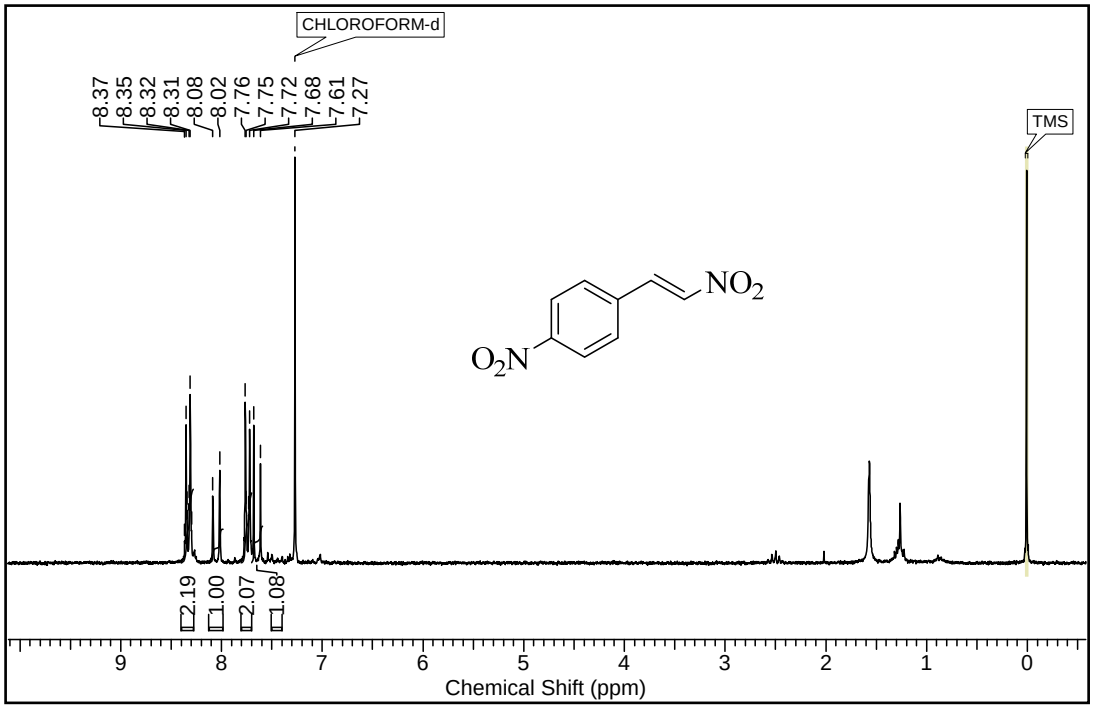


➢ **^{1}H NMR of the compound 16 in $CDCl_3$**

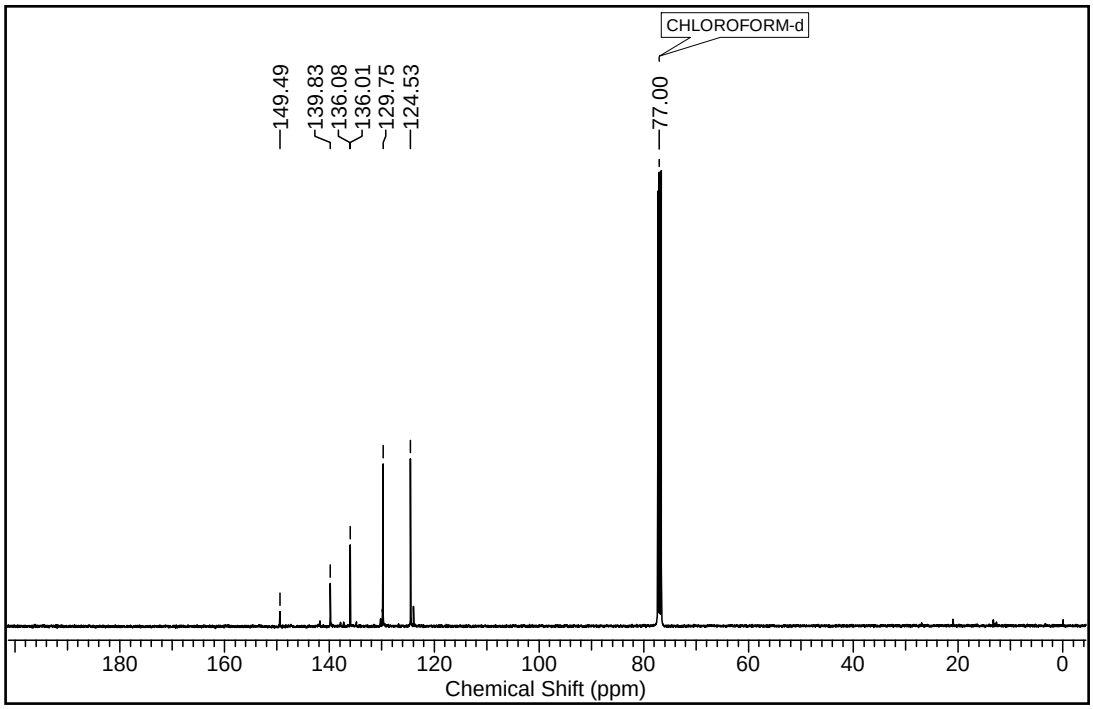


➢ **^{13}C NMR of the compound 16 in $CDCl_3$**

(*E*)-1-Nitro-4-(2-nitrovinyl)benzene 17:



➢ **^{1}H NMR of the compound 17 in $CDCl_3$**



➢ **^{13}C NMR of the compound 17 in $CDCl_3$**

4.2.8. References

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- **Xth J-NOST Conference**, held at Dept. of Chemistry, IIT-Madras, **December 4-6, 2014** "Total synthesis of (+)-Monocerin *via* tandem asymmetric dihydroxylation-S_N2 cyclization and copper mediated tandem cyanation-lactonization approach" ***(poster)***
- **National Science Day 2014** Poster presented on occasion at National Chemical Laboratory on **February 25-27, 2015.** "Total synthesis of (+)-Monocerin *via* tandem asymmetric dihydroxylation-S_N2 cyclization and copper mediated tandem cyanation-lactonization approach" ***(poster)***
- **National Science Day 2013** Poster presented on occasion at National Chemical Laboratory on **February 26-27, 2013.** "**First total synthesis of Seimatopolide B**" ***(poster)***
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1. First total synthesis of seimatopolide B

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   U.Nookaraju and Pradeep Kumar, 2016 (***To be communicated)***

7. Total synthesis of 11-hydroxy Monocerin

   U.Nookaraju and Pradeep Kumar (***manuscript under preparation***)