Synthetic Studies Toward the Total Synthesis of Eunicin, Palau'amide and Asimitrin

A THESIS

SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

TO

UNIVERSITY OF PUNE

BY

SABITA NAYAK

UNDER THE GUIDANCE OF

DR M K GURJAR

ORGANIC CHEMISTRY:DIVISION

NATIONAL CHEMICAL LABORATORY

PUNE-411008, INDIA

DECEMBER-2007

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DECEMBER 2007

DEDICATED

TO MY BELOVED

PARENTS

DECLARATION

I here by declare that the research work presented in this thesis was carried out by me at the National Chemical Laboratory, Pune, India, under the guidance of **Dr. M. K. Gurjar**, Head and Deputy Director, Division of Organic Chemistry, National Chemical Laboratory, Pune-411008, submitted for the degree of Doctor of Philosophy in Chemistry to the University of Pune. This work is original and has not been submitted in part or full by me for any degree or diploma of this or any other university.

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CERTIFICATE

This is to certify that the work presented in this thesis entitled **"Synthetic Studies Toward the Total Synthesis of Eunicin, Palau'amide and Asimitrin"** Submitted by Miss Sabita Nayak, has been carried out by the candidate at National Chemical Laboratory, Pune, under my supervision. Such materials as obtained from other sources have been duly acknowledged in the thesis. This work is original and has not been submitted for any other degree or diploma of this or any other university.

Pune-411 008
December-2007

(Dr. M. K. Gurjar)
Research Guide

Acknowledgements

It gives me immense pleasure to express my deep sense of esteem and gratitude to my mentor, research guide ***Dr. M. K. Gurjar****, FNASc, Deputy Director and Head of Division of Organic Chemistry, National Chemical Laboratory, Pune for his excellent and inspiring guidance, never diminishing encouragement, sincere advice and unstinted support during all the times of my Ph.D. work. Working with him was a great pleasure and learning experience.*

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Finally, I thank the Director, National Chemical Laboratory, Pune for providing infrastructural facilities to complete my work successfully. I am also thankful to CSIR, New Delhi for the financial assistance in the form of fellowship.

SABITA NAYAK

ABBREVIATIONS

Ac	-	Acetyl
AcOH	-	Acetic acid
AIBN	-	2,2'-Azobisisobutyronitrile
Bn	-	Benzyl
BnBr	-	Benzyl bromide
$BH_3 \cdot Me_2S$	-	Boron dimethyl sulfide complex
BuLi	-	Butyl Lithium
COSY	-	Correlation spectroscopy
DCM	-	Dichloromethane
DDQ	-	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	-	Diisobutylaluminiumhydride
DMP	-	Dess–Martin periodinane
DMP	-	2,2-Dimethoxypropane
DMF	-	*N*, *N*′-Dimethylformamide
DMAP	-	*N*,*N*′-Dimethylaminopyridine
DMSO	-	Dimethyl sulfoxide
EtOH	-	Ethanol
Et	-	Ethyl
Et_2O	-	Diethyl ether
EtOAc	-	Ethyl acetate
Et_3N	-	Triethylamine
IBX	-	Iodoxybenzoic Acid
Im	-	Imidazole
LDA	-	Lithium diisopropylamide
MeOH	-	Methanol
MsCl	-	Methanesulfonyl chloride
Ms	-	Methanesulfonyl

Me	-	Methyl
MeI	-	Methyl iodide
MPM	-	*p*-Methoxyphenylmethyl
$NaBH_4$	-	Sodiumborohydride
NaH	-	Sodium hydride
NMR	-	Nuclear magnetic resonance
n*O*e	-	Nuclear Overhauser Effect
NOESY	-	Nuclear Overhauser Effect Spectroscopy
Ph	-	Phenyl
Py	-	Pyridine
PDC	-	Pyridiniumdichromate
RCM	-	Ring closing metathesis
TEA	-	Triethylamine
TBAI	-	Tetra-*n*-butylammonium iodide
TBAF	-	Tetra-*n*-butylammonium fluoride
TBDMSCl	-	*tert*-Butyldimethyl chlorosilane
THF	-	Tetrahydrofuran
TPP	-	Triphenylphosphine
p-TSA	-	*p*-Toluenesulphonic acid
TsCl	-	*p*-Toluenesulphonyl chloride

GENERAL REMARKS

- ^{1}H NMR spectra were recorded on AC-200 MHz, MSL-300 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, MSL-75 MHz, and DRX-125 MHz spectrometer
- EI Mass spectra were recorded on Finngan MAT-1020 spectrometer at 70 *eV* using a direct inlet system.
- The X-Ray Crystal data were collected on *Bruker SMART APEX* CCD diffractometer using Mo K radiation with fine focus tube with 50 kV and 30 mA.
- 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 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.

CONTENTS

ABSTRACT

Research Student : Sabita Nayak

Research Guide : Dr. Mukund K.Gurjar

Title of Thesis : **"Synthetic Studies Toward the Total Synthesis of Eunicin, Palau'amide and Asimitrin"**

Registration no. : E1/87/Ph.D/2005

Date of registration : 5-05-2004

Place of work : Division of Organic Chemistry: Technology, National Chemical Laboratory, Pune

Abstract

The thesis entitled "**Synthetic Studies Toward the Total Synthesis of Eunicin, Palau'amide and Asimitrin**" has been divided into three chapters and each chapter subdivided into following sections: Introduction, Experimental, Spectroscopic data and References. Chapter I describes the synthetic studies toward tricyclic cembranoids: a modular approach for the construction of the tricyclic, framework of eunicin. Chapter II deals with studies toward biologically active Palauamide. The final chapter III discusses synthetic studies toward Asimitrin using chiral pool strategy.

Chapter I: Synthetic studies toward tricyclic cembranoids: a modular approach for the construction of the tricyclic framework of eunicin

Cembranoids belongs to a class of diterpenoids possessing a 14-membered ring. Cembrane A forms the basic skeleton of these macrocyclic diterpenoids. Numerous cembranoids have been isolated from corals and other marine sources as well as from tobacco and other plants. Eunicin, Cuenicin, Eunicenolide and Uproeunicin (Figure 1) belong to the category of cembranes containing an oxa-bridged bicyclic ring. Basically these are potent cytotoxic

and antineoplastic agents. Recent studies shows that they are strong nicotine acetylcholine receptors (nAChR) and active against several human tumor cells. Literature survey reveals

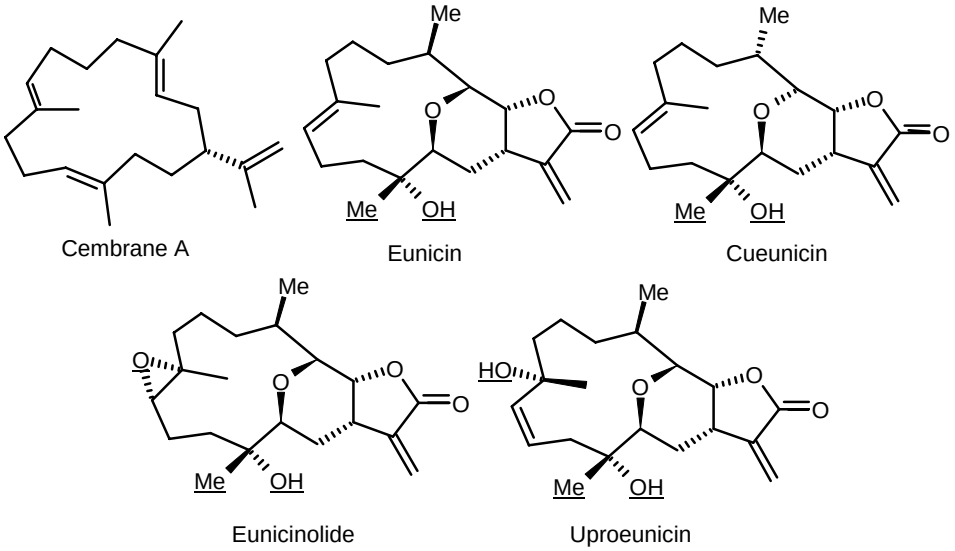


Figure 1

that though Eunicin was isolated in 1960's till now a single synthesis isn't reported. The interesting architectural features and promising biological activities attracted us to undertake its synthesis. In the beginning of our synthetic endeavor we planned to synthesize the tricyclic framework of Eunicin and its analogues.

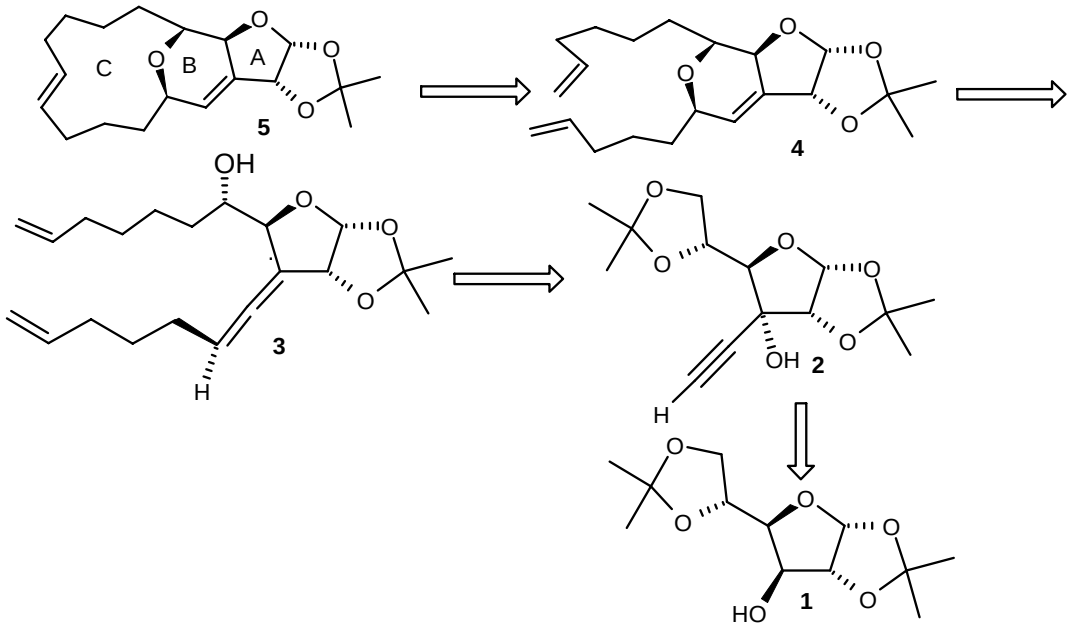
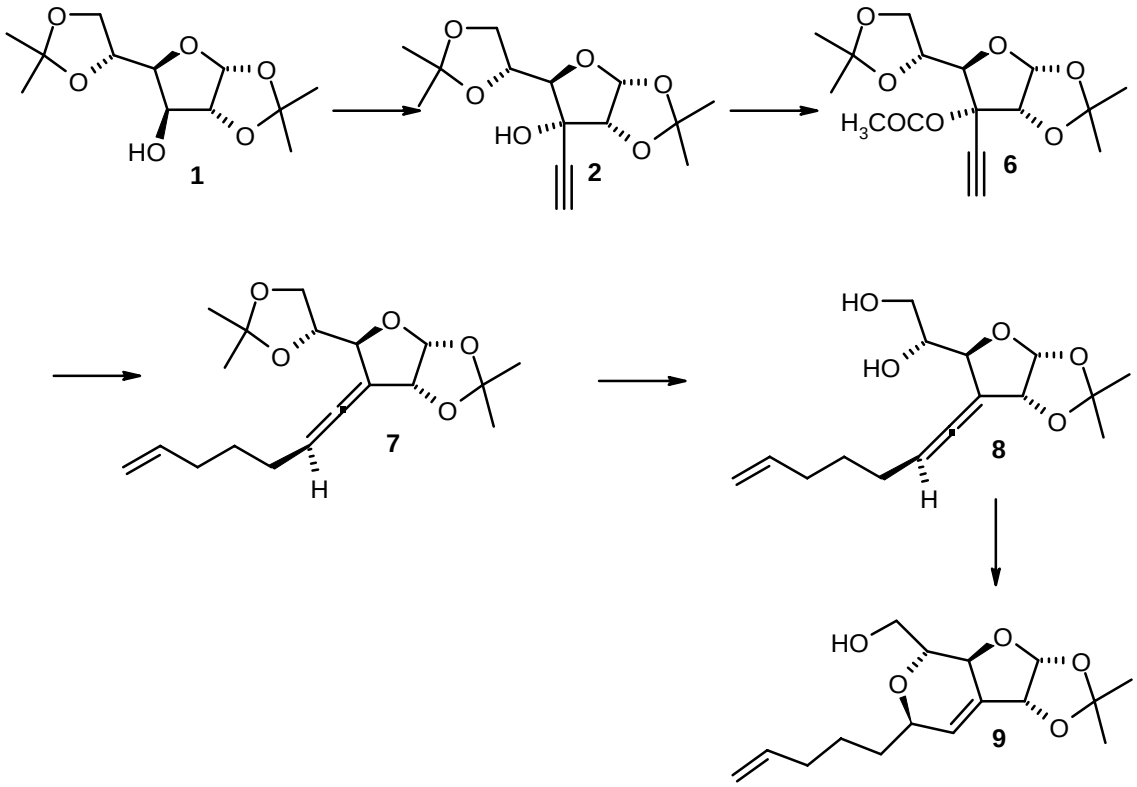


Figure 2. *Retrosynthetic analysis*

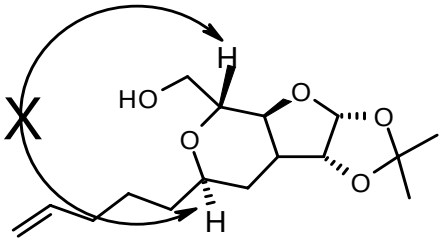
The retrosynthetic analysis of **5** is depicted in Figure 2. The key allene intermediate **3** can be synthesized from the known sugar alkyne moiety **2**, which can be prepared easily from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **1**.

Our synthesis commenced from the commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose. The alkyne group was stereoselectively introduced by oxidizing 3-hydroxyl group of **1** to its keto compound on treatment with PDC followed by Grignard reaction using acetylene magnesium chloride to provide 3-propargyl alcohol **2** exclusively. The tertiary alcohol of **2** was acylated by using Ac_2O, Py and DMAP (catalytic) to yield **6**, which was exposed to pentenyl magnesiumbromide in presence of CuBr (stochiometric) to furnish the allene **7** exclusively. Acidolytic cleavage of 5,6 isopropylidene of **7** gave diol **8**, which on cycloetherification with $AgNO_3$ afforded dihydropyran **9** in good yield (Scheme 1).

Scheme 1



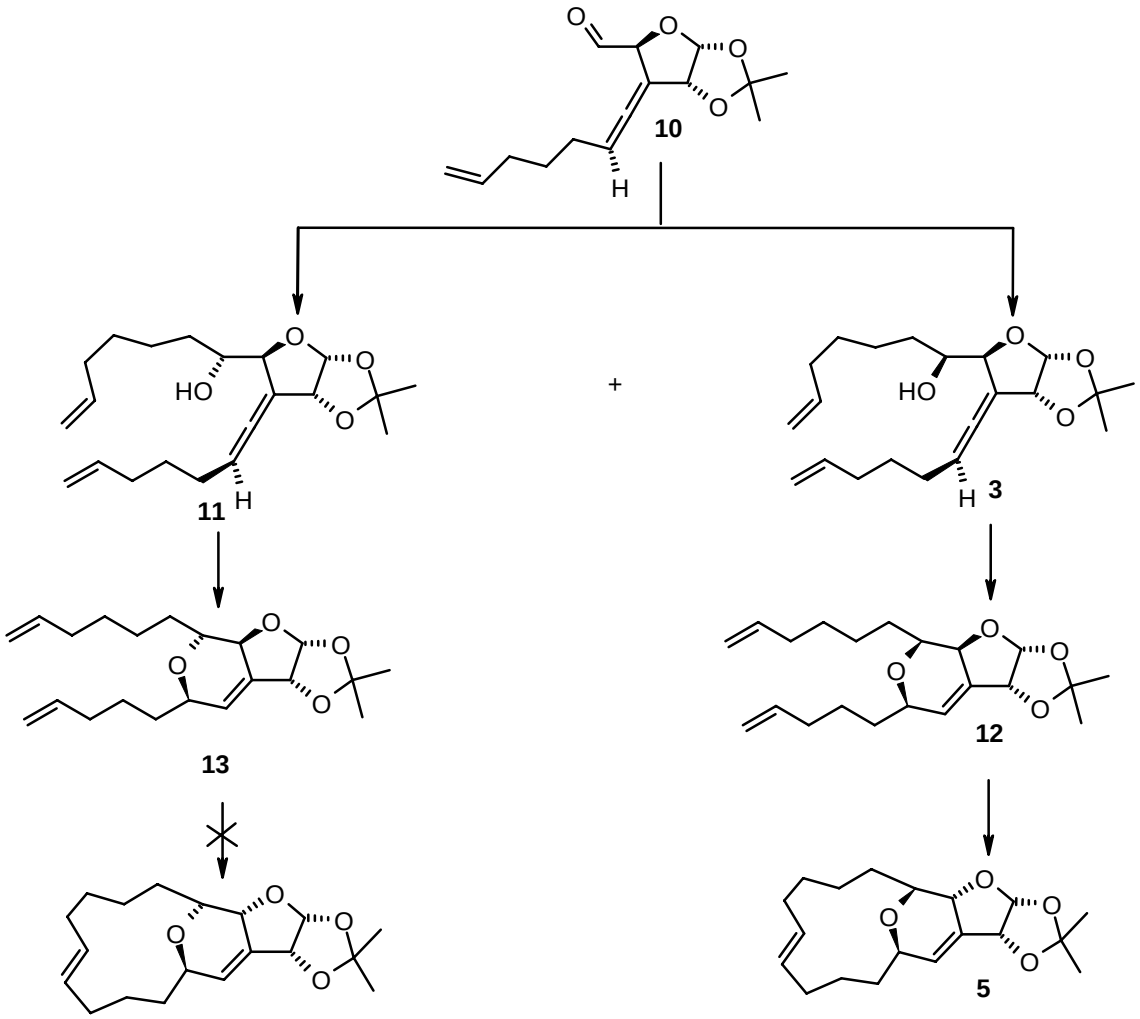
The stereochemistry of the substituted dihydropyran ring **9** was assigned as trans with the help of NOESY study. This observation indirectly justified the stereochemistry of the allene **7** which was shown in Scheme 1.



n*O*e of compound-**9**

Having established the stereochemistry of allene **7**, a model study was conducted to test the feasibility of RCM reaction to construct the requisite 12-membered ring (Scheme 2).

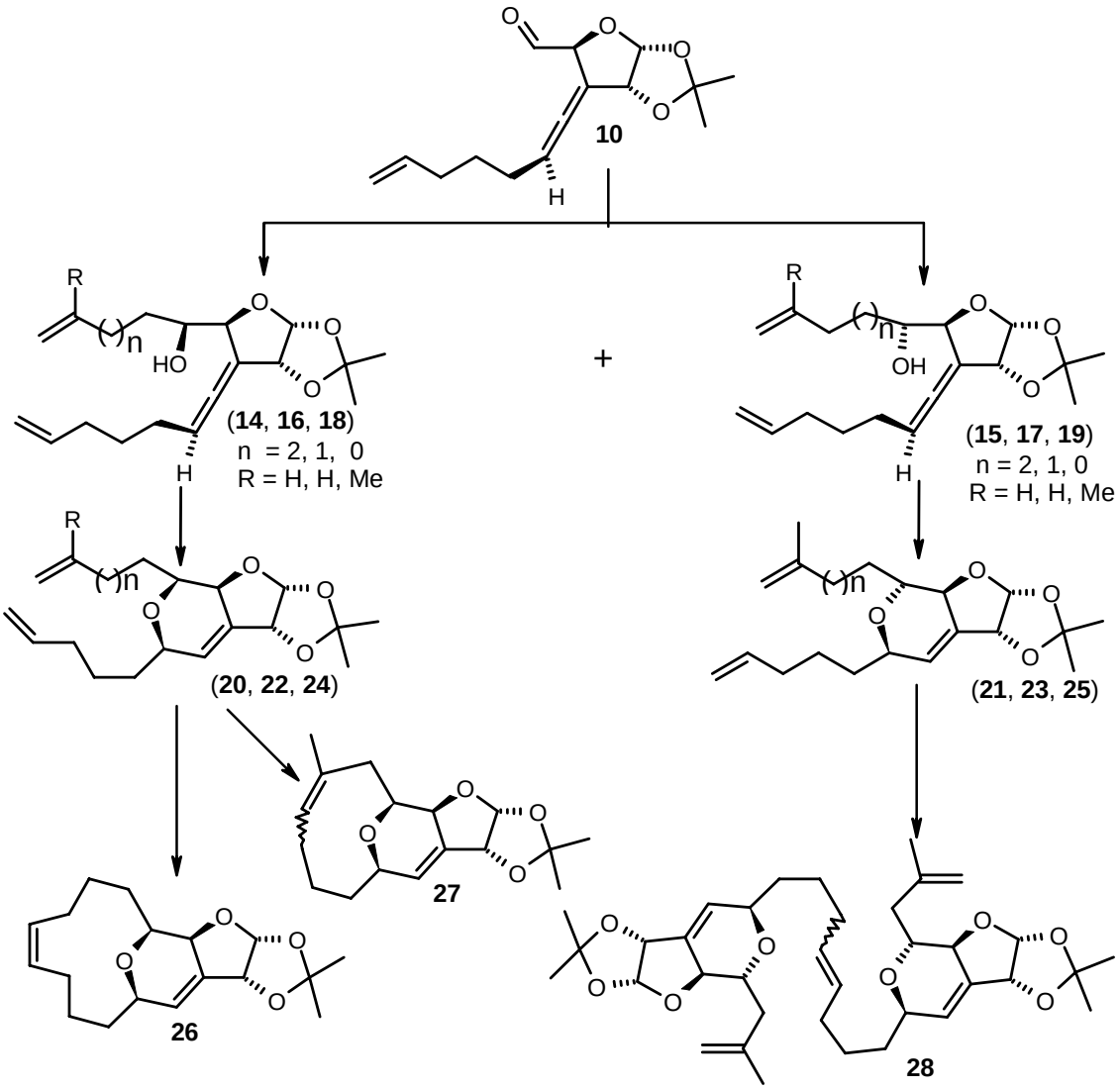
Scheme 2



Oxidative cleavage of diol **8** with sodium metaperiodate resulted in aldehyde **10** which on subsequent Grignard reaction with 5-hexenylmagnesium bromide in ether at 0 ^{o}C gave the dienes **3** and **11** in 7:3 ratio which were separated by simple column chromatography.

The silver nitrate mediated cyclo-etherification of dienes resulted in the bicyclic derivatives **12** and **13** exclusively. The stereochemistry of the newly formed dihydropyran rings in the bicyclic derivatives **12** and **13** were established as *cis* and *trans* respectively,

Scheme 3



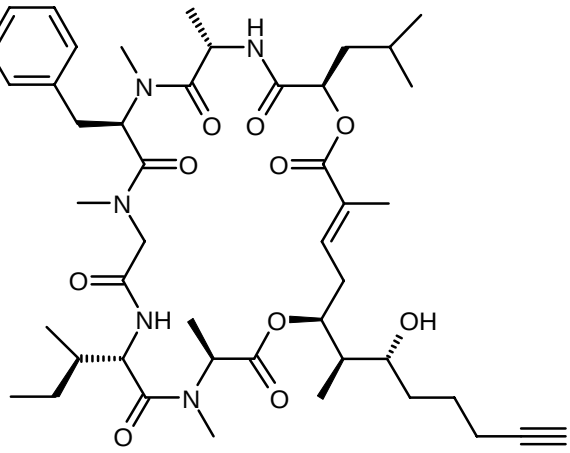
with the help of NOESY experiments. The RCM of **12** proceeded efficiently with the 1st generation Grubbs' catalyst in refluxing benzene gave the requisite *E* isomer **5**. However, the RCM of **13** was found to be sluggish and resulted in an intractable polymeric mixture (Scheme 2).

After establishing a strategy for the construction of the core structure of the Eunicin-like cembranoids, we next focused our attention on the generalization of our strategy for the synthesis of various analogues of Eunicin where the size of ring C could be modified.

Accordingly, treatment of suitable alkenyl Grignard reagent like pentenyl, butenyl and methallyl magnesium bromide, on **10** followed by cyclo-etherification resulted in 2,6-dihydropyran derivatives **20–25**. The RCM reaction was successful only for the 2,6-*cis*-dihydropyrans **20** and **24** and the corresponding tricyclic compounds **26** and **27** were obtained. RCM of **21** and **23** gave some intractable polymeric mixture. Surprisingly the RCM of **25** with 2nd generation Grubbs' catalyst gave a dimeric product **28** in good yield (Scheme 3).

In conclusion, we have accomplished the proposed core skeleton of Eunicin and its analogues starting from 1,2;5,6-di-*O*-isopropylidene glucofuranose employing silver-nitrate mediated cycloetherification and RCM as the key reactions.

Chapter II: Synthetic Studies Toward Palau'amide



Palau'amide (**29**)

Palau'amide (**29**), a cyclic depsipeptide was isolated by Moore and co-workers in 2000 from a species of the marine cyanobacterium *lyngbya*, which showed potent cytotoxicity to KB cells (IC_{50} = 13 nM). From this source, several potent antitumour agents such as lyngbyabellins and aparatoxins have been discovered. These compounds have become the focus of recent synthetic endeavors. The interesting structural features, and impressive biological activity of Palau'amide identified an appropriate target for total synthesis.Our retrosynthetic analysis for the synthesis of Palau'amide is depicted in Figure 3.

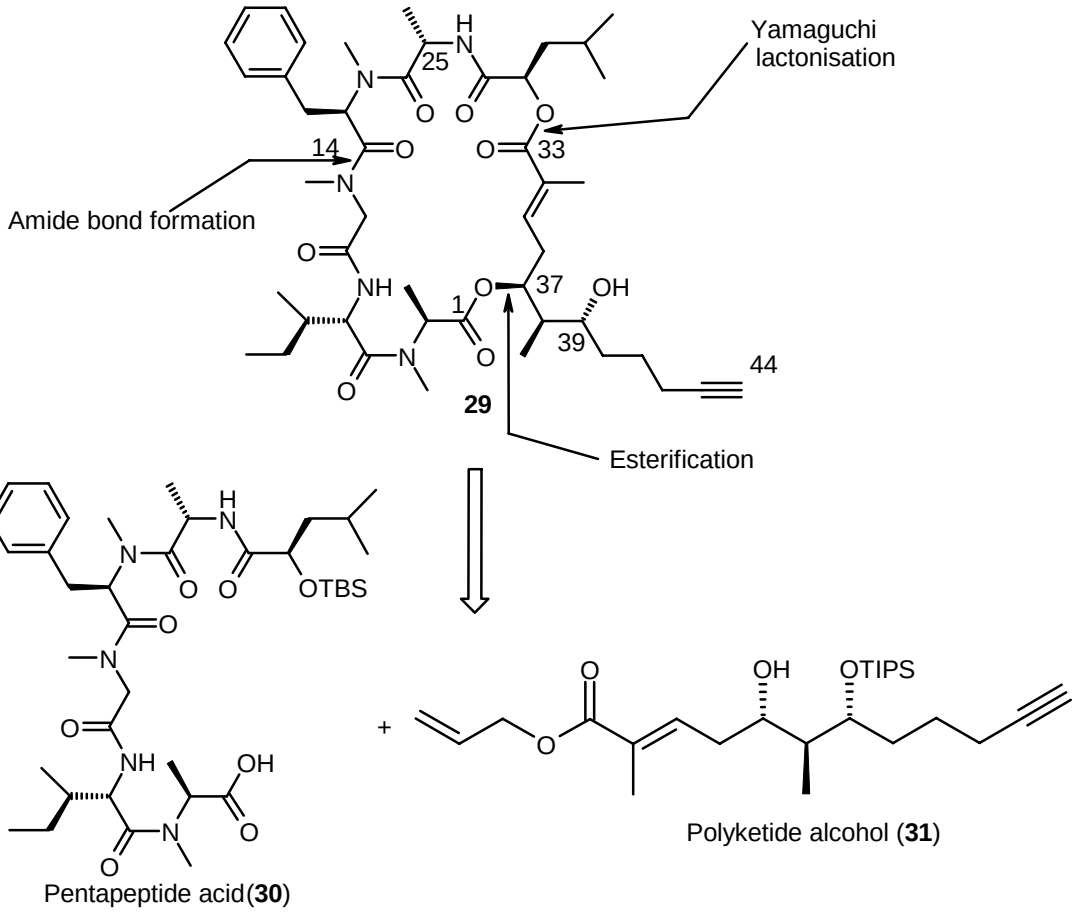
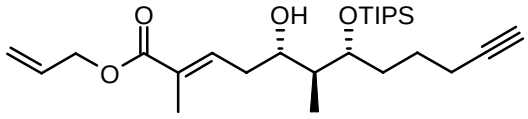


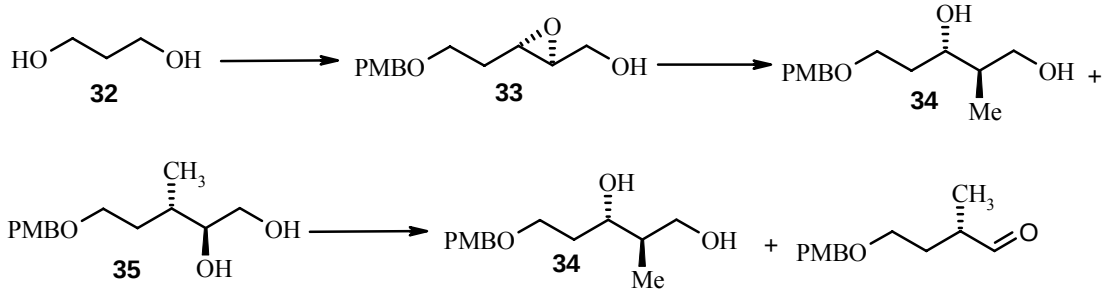
Figure 3. *Retrosynthetic analysis*

In the beginning of our synthetic endeavor we planned to synthesize the C33-C44 segment of Palauamide.**Synthesis of the C33 – C44 Fragment of Palauamide (31)**



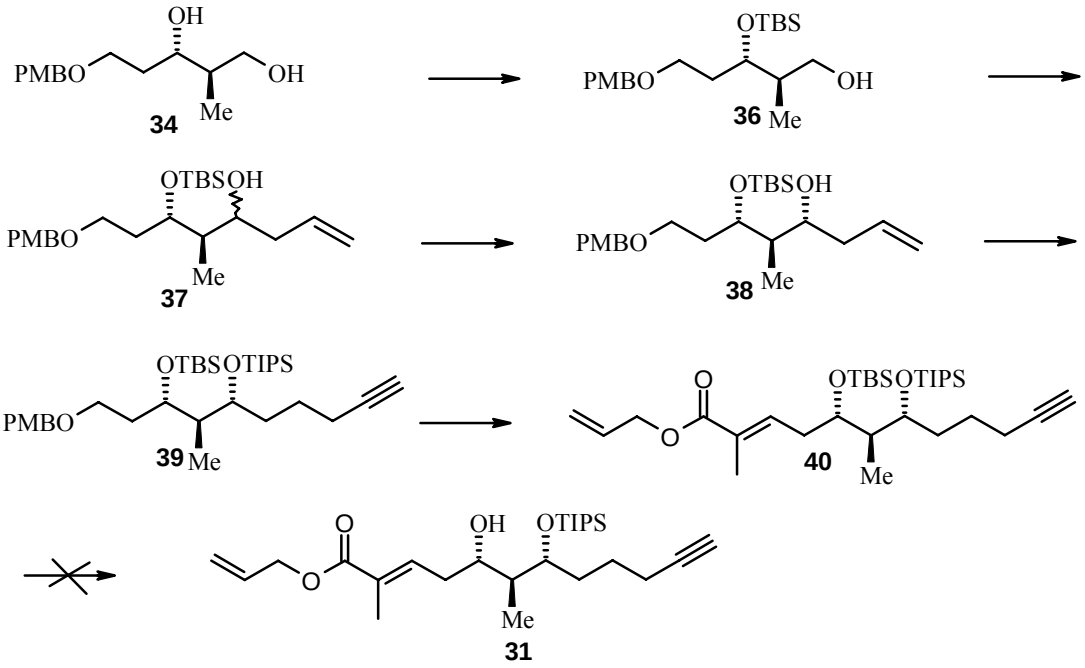
We initiated our synthesis from commercially available 1,3 propane diol (**32**), which was transformed into key epoxide intermediate **33** in five steps synthesis, (i) mono-PMB-protection (ii) Swern oxidation (iii) twocarbon stable Wittig olefination (iv) reduction of ester using DIBAL-H and (iv) Sharpless asymmetric epoxidation using L-diethyltartrate. Epoxide **33** was subjected to $Me_2CuCNLi_2$ furnishing an inseperable mixture of **34** and in7:1 ratio, which on treatment with $NaIO_4$ resulted in an aldehyde and 1,3 diol. Both were separated easily by silicagel chromatography (Scheme 4).

Scheme 4



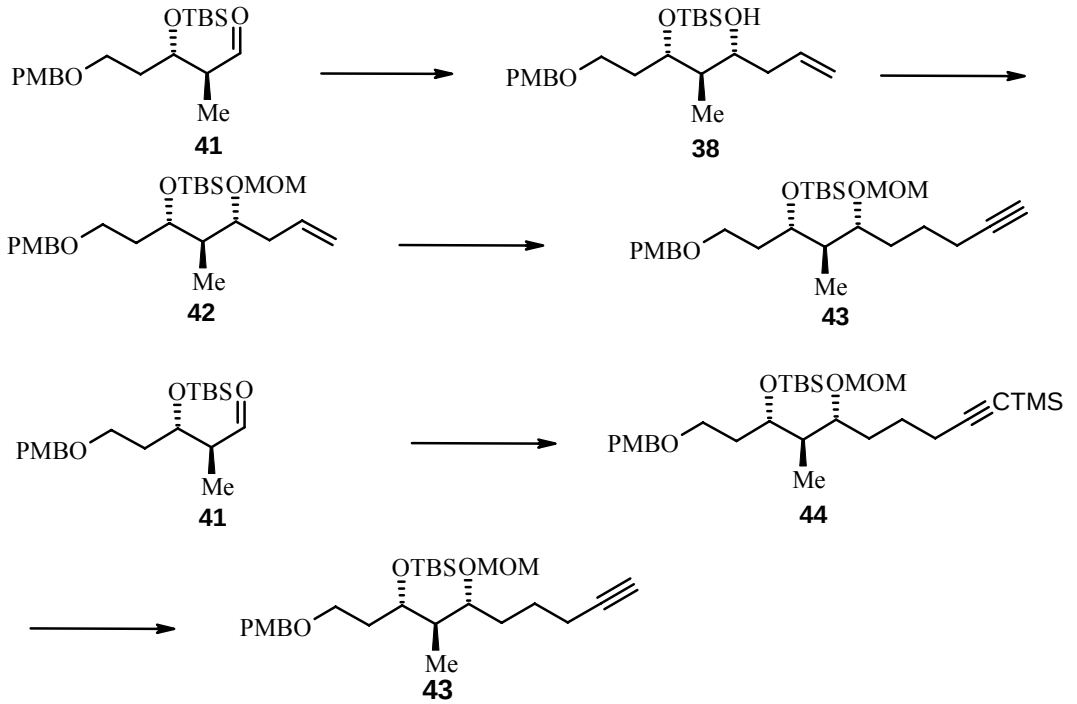
In order to get compound **36**, the diol **34** was subjected to a sequence of reactions, benzoylation of primary alcohol, TBS protection of secondary hydroxyl group and hydrolysis of benzoate ester. The primary alcohol **36** underwent swernoxidation to give aldehyde, which on subsequent treatment with allylmagnesium bromide furnished diastereomeric mixture of homoallylic alcohols **37**. Further oxidation of secondary alcohol **37** in swern condition and Luche's stereoselective reduction at –100 ^{o}C to give **38** exclusively. The compound **38** underwent a sequence of simple and straightforward reactions involving TIPS protection of secondary hydroxyl group, hydroboration-oxidation of terminal olefin, bromination of primary alcohol and conversion of bromo to alkyne by Lithiumacetylide:EDTA complex to provide pentynyl appended product **39**. DDQ mediated PMB deprotection, oxidation of primary alcohol with IBX followed by 3C-wittig olefination with PPh_3=CH(CH_3)COOAllyl in refluxing THF gave α,β unsaturated ester **40**. Selective deprotection of TBS ether in **40** with various reagents failed to give **31** (Scheme 5).

Scheme 5



Methoxymethylether group was replaced by TIPS group in **38** and the same series of reaction was carried out as shown in (Scheme 6).

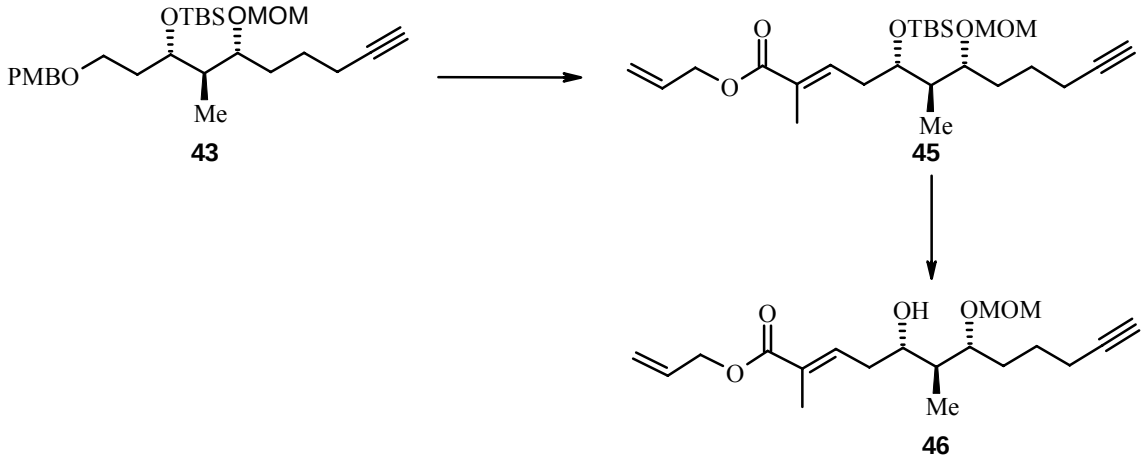
Scheme 6



Compound **38** was treated with MOMCl, DIPEA in presence of catalytic $AgNO_3$ furnished **42,** which followed same sequence of reaction conditions as that for **38** to **39** to yield **43**. Having **43** in hand, a scalable approach was devised following a sequence of reactions, involving Grignard reaction by using TMS-pentynylmagnesiumbromide on aldehyde **41**, deprotection of TMS group and MOM-protection to provide **43** in good yield (Scheme 6).

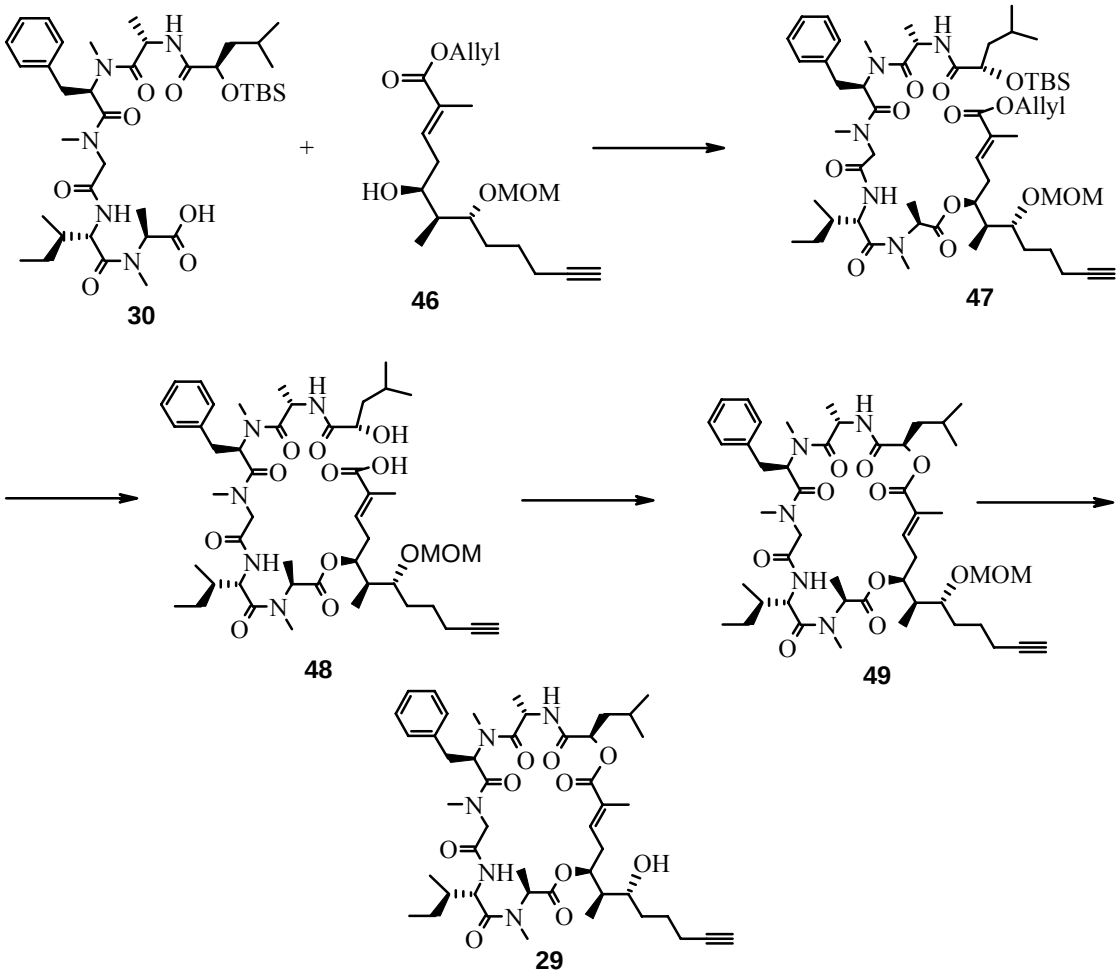
The α,β-unsaturated-Allylester **45** was obtained by DDQ mediated PMB-ether deprotection of **43,** followed by oxidation and subsequent Wittig reaction. Finally TBS ether deprotection was accomplished with TBAF, THF and AcOH (catalytic) furnished **46** in good yield (Scheme 7).

Scheme 7



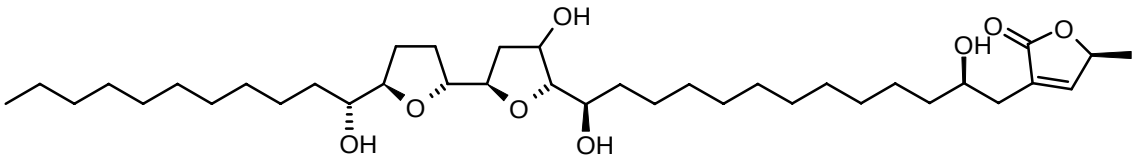
Having free hydroxyl polyketide chain in hand, we focussed our attention for coupling with the necessary pentapeptide acid **30**, which was already synthesized in our group. EDCI, DMAP mediated coupling of pentapeptide acid and polyketide alcohol to give the ester unit **47**. Further TBS-ether deprotection with TBAF, THF, AcOH (catalytic) and allyl deprotection by Pd(0), Morpholine to give the hydroxy acid **48**. Finally intramolecular Yamaguchi lactonization of **48** resulted in MOM-protected palauamide **49**, which was assigned by LC-MS and ^{1}H NMR study to be a mixture of two diastereomers (Scheme 8). Since the adjacent position of acid group in **48** was not occupied by chiral centre, so we assumed that racemisation might have occurred during esterification step rather than lactonisation step. Seperation of mixture compound and analyzing the requisite isomer is currently undergoing in our laboratory.

Scheme 8



In conclusion, a fragment corresponding to C33-C44 fragment of Palau'amide has been successfully synthesized using SAE, regioselective epoxide opening by Gillmann reagent, Luche's stereoselective reduction and Grignard reaction as our key reactions. In addition, we attempted the synthesis of MOM-protected Palau'amide **49**, following ECDI esterification and Yamaguchi lactonization.

Chapter III: Synthetic Studies Toward Asimitrin



Asimitrin (**50**)

Asimitrin (**50**) a ring hydroxylated unsymmetrical bis-tetrahydrofuran acetogenin was isolated from the seeds of Asimina triloba by Mi Hee Woo in 2005. This novel type of acetogenin was found to be cytotoxic selectively against prostate carcinoma (PC-3) at about 10,000 times and colon adenocarcinoma (HT-29) at about 100 times the potency of adriamycin. Such powerful antitumor activity and the unique structure of **50** attracted us to undertake its total synthesis.

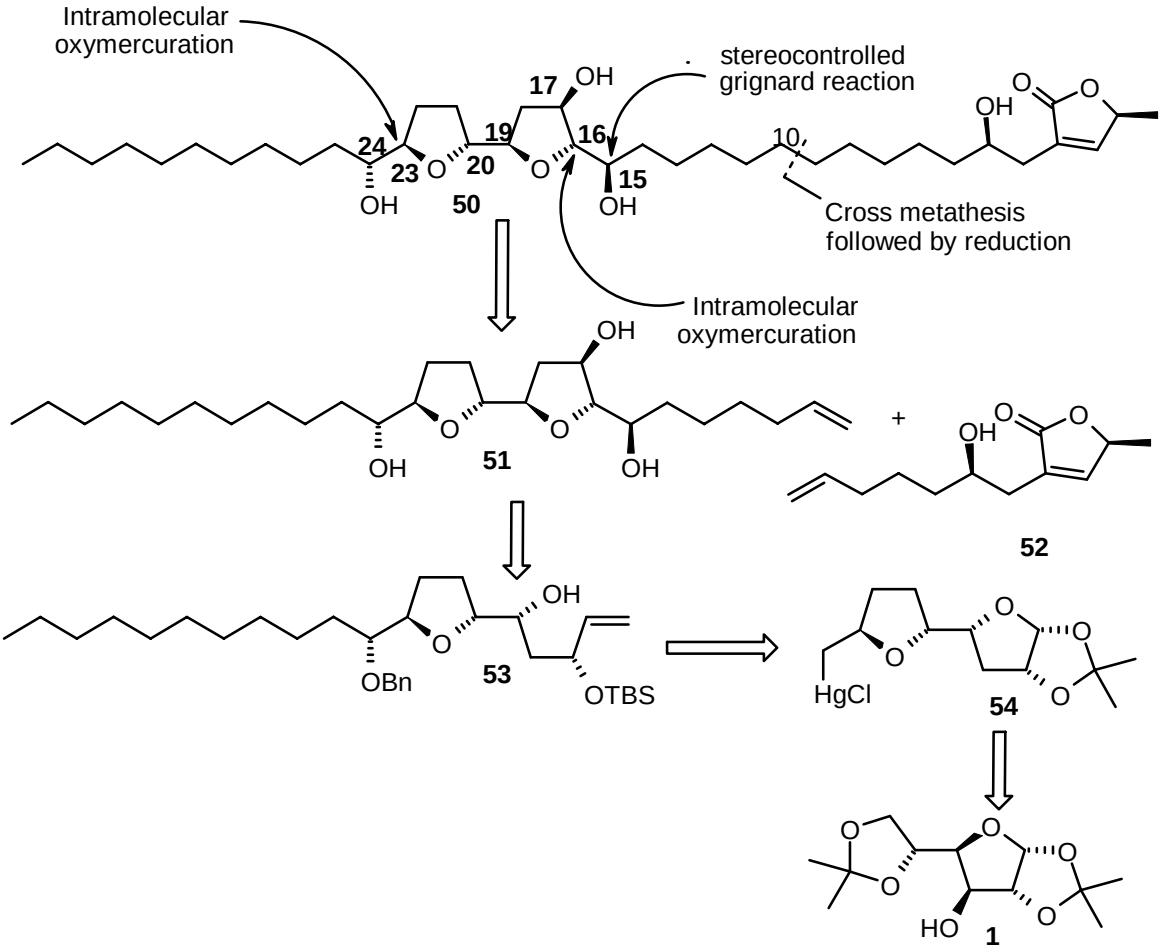
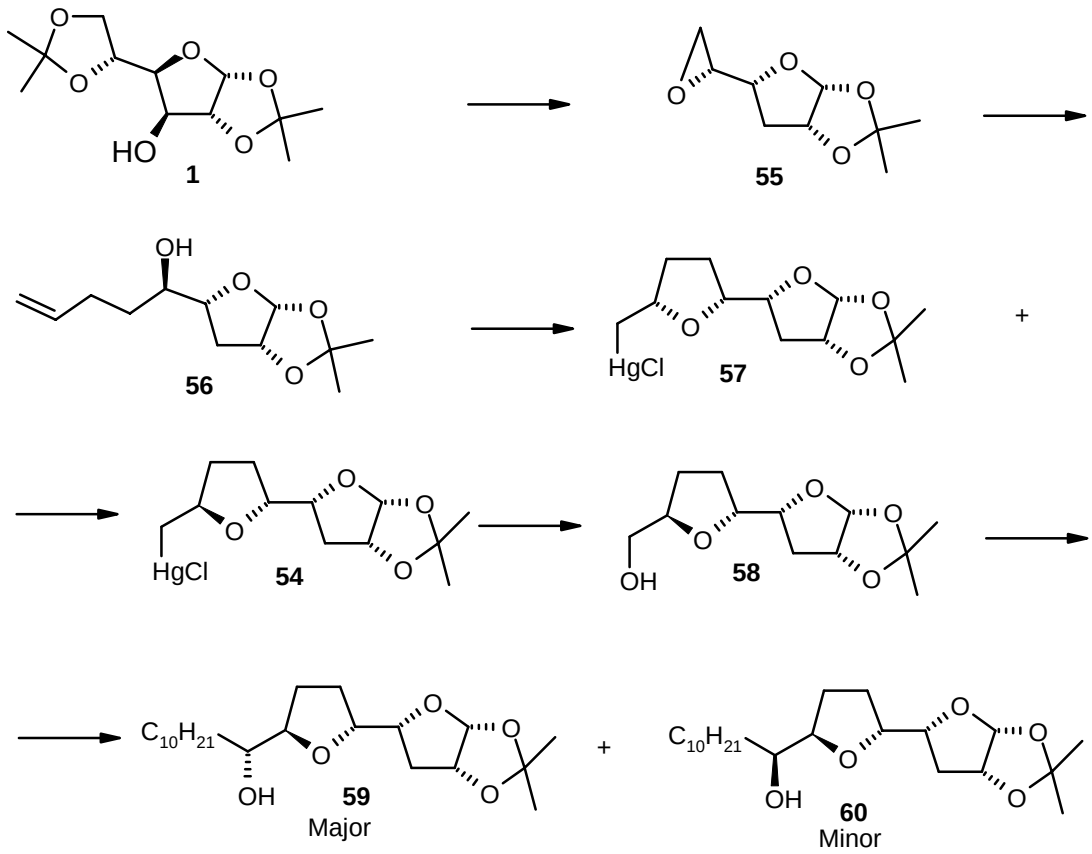


Figure 4. *Retrosynthetic analysis of Asimitrin* **50**

After a thorough literature study we realized a chiral pool approach will be the suitable one to fix the desired stereocentres of Asimitrin and 3-deoxy-1,2:5,6-di-*O*-isopropylidene xylofuranose will be a suitable precursor. The retrosynthetic analysis of **50** was discussed in Figure 4.

According to retrosynthetic analysis our synthetic strategy directed toward **50** was based on a convergent approach involving cross metathesis of the bis-THF core **51** with γ-lactone segment **52**. We planned to made bis-THF core in a systematic manner from a chiral pool, like glucosediacetonide **1**, which is a source of chiral centers like C17, C19 and C20 and also a setting stage for introducing C16 and C23 stereocentres through stereoselective intramolecular oxymercuration and chelation controlled Grignard reaction.

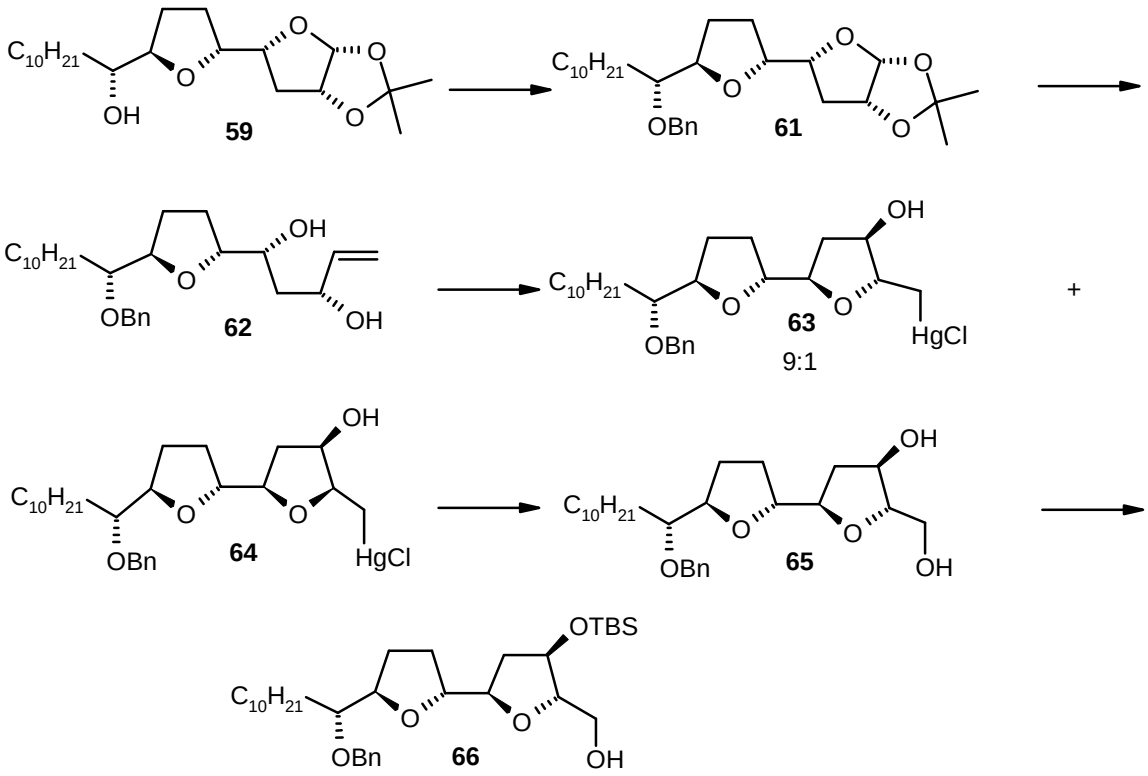
Scheme 9



The synthetic endeavor commenced from commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **1**, which underwent a sequence of simple and straightforward reactions, includes tosylation of secondary hydroxyl group, elimination of tosyl group to form olefin, double bond reduction, regioselective 5,6 isopropylidene

cleavage and insitu formation of epoxide **55**. Allylmagnesium bromide and CuCN mediated epoxide opening resulted in homoallylic alcohol **56**. Intramolecular oxymercuration of **56** using $Hg(OAc)_2$ in dichloromethane resulted in diastereomeric mixture of chloromercurated compound **54** and **57** in 8:2 ratio. The stereochemistry around the tetrahydrofuran ring was assigned by n*O*e study and further confirmed by X-ray crystallography. Demercuration of desired isomer **54** resulted in primary alcohol **58**. Ten carbon appendages was incorporated in **58** by two step synthesis i,e. oxidation of primary alcohol and subsequent treatment of decylmagnesiumbromide in presence of CuBr.DMS to give diastereomeric mixture of **59** and **60** in 7:3 ratio. Both the alcohols were separated by flash silicagel chromatography and the major isomer formed was expected due to chelation-controlled product (Scheme 9).

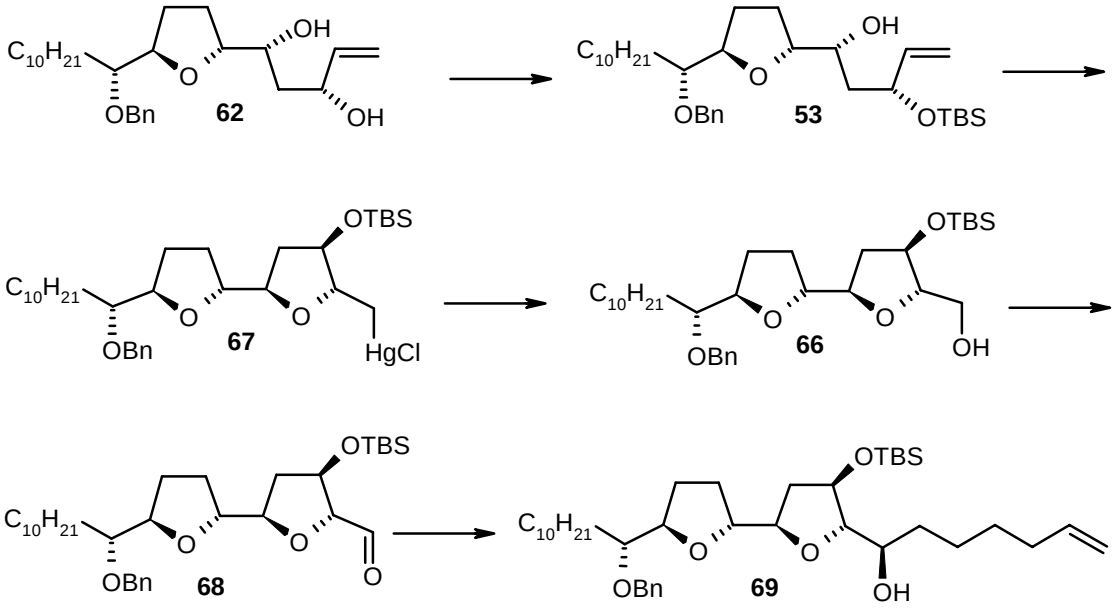
Scheme 10



The stereochemistry of the newly generated center in **59** was assigned by modified Mosher's method which clearly indicates that it was the required one. The minor isomer was oxidized and reduced by L-selectride provides **59** and **60** in 9:1 ratio (Scheme 10).

The secondary hydroxyl group of **59** was protected as benzylether using NaH and benzylbromide to furnish **61**. Acid hydrolysis of 1,2 isopropylidene in **61** by *p*-TSA, THF: H_2O in refluxing condition gave lactol, which was subjected to one carbon wittig olefination resulted in α-hydroxy homoallylic alcohol **62**. Oxymercuration of **62** by using $Hg(OAc)_2$ in dichloromethane yielded a mixture of chloromercurated bis-THF compound **63** and **64** in 9:1 ratio.

Scheme 11



The major isomer **63** was demercurated by $NaBH_4$-DMF in the presence of O_2 to give **65**. In order to get TBS-protected bis-THF alcohol **66**, the diol **65** underwent three steps of reactions like (i) primary alcohol.acylation (ii) deprotection of acetate by K_2CO_3, MeOH (iii) TBS protection of secondary hydroxyl group giving poor yield of **66** (Scheme 10).

To overcome this difficulty, the allylic alcohol of **62** was selectively protected as TBS ether using TBSCl, imidazole and DMAP (catalytic) to give **53**. Oxymercuration of **53** with mercuric acetate gave single chloromercurated compound **67**, which was demercuration with $NaBH_4$, DMF in presence of O_2 furnished the bis-THF alcohol **66** in good yield. Finally Swern oxidation of primary alcohol of **66** and subsequent Grignard reaction of aldehyde **68** using hexenylmagnesium bromide in the presence of CuBr.DMS at –100 ^oC gave secondary alcohol **69** as a single product. The newly generated stereo center was assigned by modified Mosher's method (Scheme 11).

In conclusion, we have developed a systematic straightforward route for the stereoselective synthesis of C10-C34 segment **69** of Asimitrin following a chiral pool approach. Here in the double intramolecular oxymercuration reaction was explored as a key reaction, stereochemically chelation controlled Grignard reaction also assisted us to achieve the target.

Note: Compound numbers in the abstract are different from those in thesis.

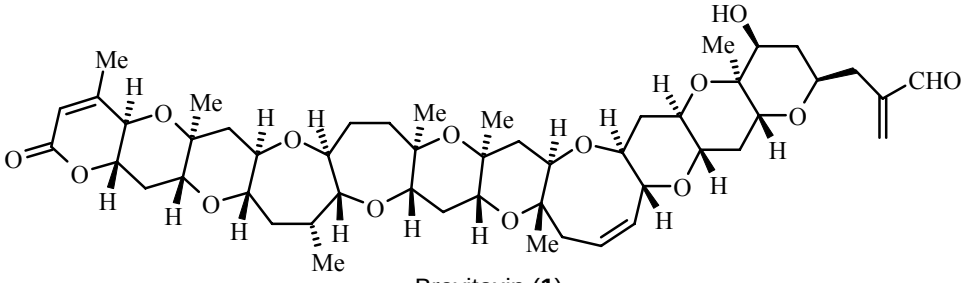
CHAPTER –I

Synthetic studies toward tricyclic cembranoids: a modular approach for the construction of the tricyclic framework of eunicin

INTRODUCTION

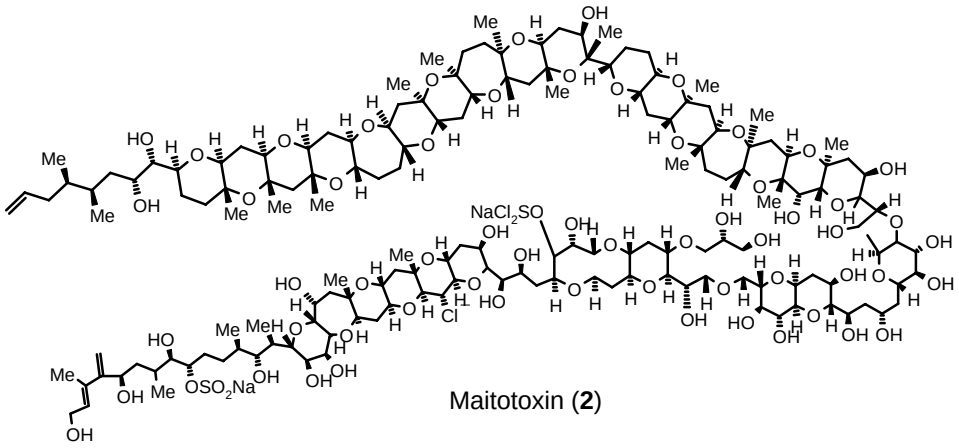
Introduction

Natural products are the most consistently successful source of drug leads and continue to provide greater structural diversity than standard combinatorial chemistry. Current commercial evidence also supports this statement. More than 60% of the available anticancer drugs were either directly based on or developed from natural products. Early history reveal that five decades back most of the terrestrial plants and organisms were the sources of the inspiration of pharmaceutical drugs, which indirectly meant that peoples were less aware about the ocean waters which contains 70% inhabitats of our biosphere. The historical paradigm of the deep ocean as a biological 'desert' has shifted to one of a 'rainforest' owing to the isolation of many novel bioactive compounds. Although deep ocean exploration is still in its infancy, many scientists now believe that it is a inexhaustible source of complex natural products, which will be a tremendous potential for human benefit. Marine natural products chemistry is essentially a child of the 1970's that developed rapidly during the 1980's and matured in the last decade. During1975, there were already three parallel tracks in marine natural products chemistry: marine toxins, marine biomedicinals and marine chemical ecology has developed. Due to the integration of the three fields of study marine natural products chemistry proceed in vigour. Initially Japanese researchers have started studies on marine natural products. The isolation of 'ladder-like' skeleton of the polyether toxins Brevetoxin B (**1**),[1] Maitotoxin (**2**),[2] Palytoxin,[3] from the dinoflagellate *Gymnodinium breve* and their interesting biological



Brevitoxin (**1**)

activities fascinated the world wide chemists and elicited their interest for further exploration of marine organisms from different areas.

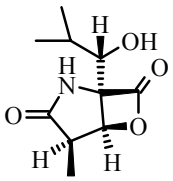


Maitotoxin (**2**)

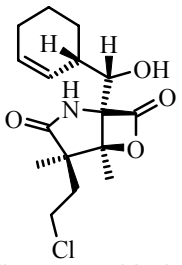
Currently more than 15,000 natural products have been discovered from marine microbes, algae, and invertebrates, and the number continues to grow. Most of the drugs are in different phages of clinical trials.[3] For example Omuralide (**3**, IC_{50}¼ = 49 nm),[4] Salinosporamide A (**4**, proteasomal chymotrypsin-like proteolytic activity with an IC_{50} value of 1.3 nm),[5] Spongothymidine (**5**, Caribbean sponge *Cryptotheca crypta,* an antiviral drug),[6] spongouridine (**6**, anticancer drug),[6] Dictyostatin (**7**, anticancer agent similar activity to taxol),[7] Prostaglandins **8**,[8a] Peluroside (**9**, anti cancer drug),[8b] Eleutherobin (**10**, anti cancer agent),[9] Discodermolide (**11**, Sponge *Discodermia dissolute,* anti cancer drug, more potent than Taxol),[7] Norzoanthamine (**12**, an alkaloid isolated from *Zoanthus* sp., can suppress the loss of bone weight and strength in ovariectomized mice and has been considered a promising candidate for an antiosteoporotic drug),[10] Sarcodictyin (**13**, a rare natural substances originally found by Pietra and his group in the mediterranean stoloniferan coral *Sarcodictyon roseum* showed potent antitumor activity),[11]and Bryostatin (**14**) [12]are some of the natural products which were in advanced clinical trials for the above mentioned medicinal applications.

Soft corals are a largest producer of steroid, diterpene and sesquiterpenes. Day by day isolation of diterpene class of compound is growing on increasing. Though the isolation, characterization and biological study of these classes of compounds is tedious but its complex artechitectural features attracted several groups to isolate and study their structure and activity in details.

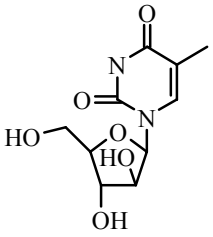
Bioactive metabolites from marine resources



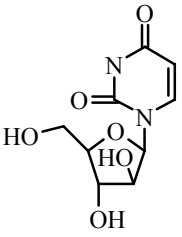
Omuralide (**3**)



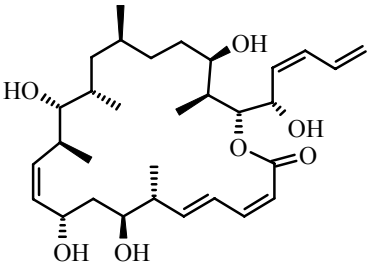
Salinosporamide (**4**)



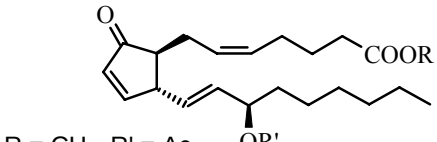
Spongothymidine (**5**)



Spongouridine (**6**)

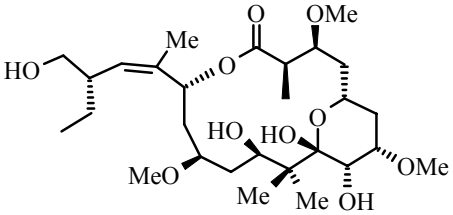


Dictyostatin (**7**)

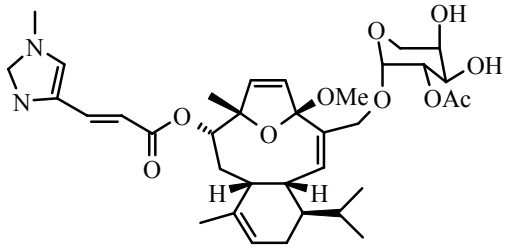


R = CH_3, R' = Ac
R = CH_3, R' = H
R = R' = H

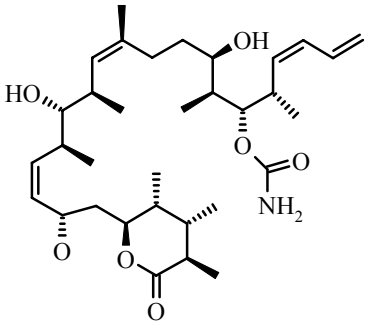
Prostaglandin (**8**)



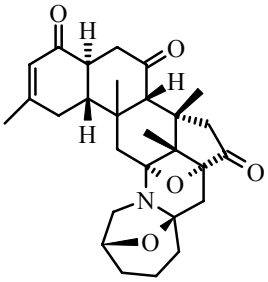
Peloruside (**9**)



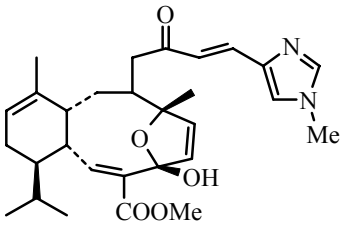
Eleuthrobin (**10**)



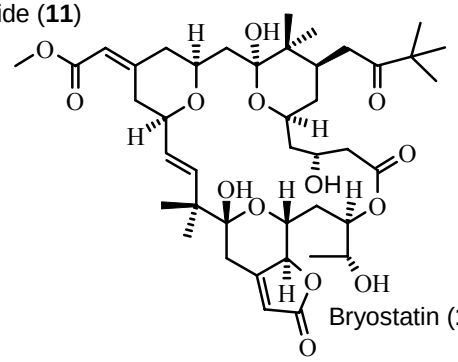
Discodermolide (**11**)



Norzoanthamine (**12**)



Sarcodictyn (**13**)



Bryostatin (**14**)

Figure 1

Cembranoids belong to a structurally unique family of diterpene natural products characterized by the presence of a 14-membered ring, and have been isolated from various marine sources as well as some terrestrial organisms since the 1960's.[13] These diterpenoids have become of great interest to synthetic chemists and biologists because of their unusual structural features and remarkably wide range of biological activities.[14]

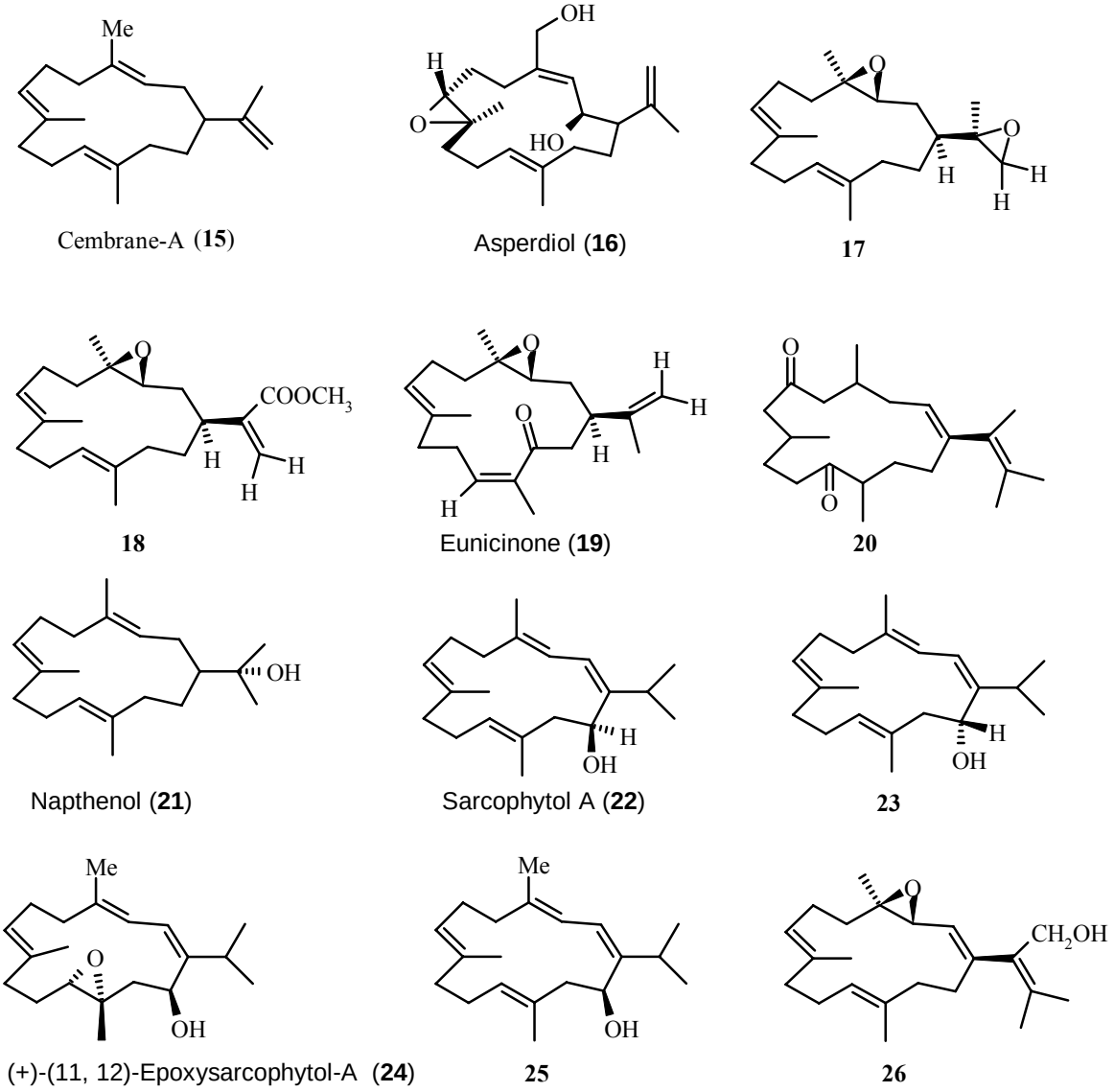
According to their structural features they have categorized into three diffent groups like:

1. Monocyclic 14-membered-ring diterpenes (Simple cembrane)
2. Bicyclic 14-membered-ring diterpenes (γ-lactone cembranoid)
3. Fused tricyclic cembranoids

Monocyclic 14-membered-ring diterpenes (Simple cembrane)

The first member of this class of compounds, cembrene A (**15**) was initially isolated from terrestrial plant pine oleoresins and termites of the species *Nasutitermes exitiosus* by Schmidt et al in 1970 and latter on by same group it was also isolated from marine soft coral, *Nephthea* species in 1978. [15, 16] Basically this class of compounds contains a single cyclic ring hence considered as simple cembrane. Some of these compounds are highly oxygenated and functionalized on the periphery. Asperdiol **16**,[17] a potent anticancer compound, was isolated from several marine coral sources like gorgonian coral *Eunicea* knighti, *Eunicea asperula* and *Eunicea tourneforti* in the Caribbean region. It was the first non lactonic cembrane isolated from gorgonians and displayed *in vitro* anticancer activity against PS, KB and LE cell lines. The promising antitumor actvity displayed by asperdiol has culminated in its total synthesis as well as its derivatives for detailed structure activity studies.[18] Eunicenone **19**, a rare cembranoid diterpene having the uncommon 11-cis double bond, was found to be the (-)-antipode of a known cembranoid isolated from a South Pacific soft coral. Both **19** and **20** showed significant cytotoxicity against CHO-K1 cells. Nephthenol **21** was isolated from soft coral *Nephthea* species by Schmitz et al in 1974 shows antitumor activity.[19, 20] Sarcophytol A **22**, its antipode (-)-Sarcophytol **23** and its congenor epoxy Sarcophytol **24** was isolated by Bowden and co-workers in 1983 from australian soft coral Lobophytum species.[21] Biological study reveals that **22** is a potent anticarcinogen. Pseudoplexaurol **26**, was isolated from a specimen of *P. porosa* collected in Puerto Rico, displayed a potent antitumor activity when screened against a small panel of five human tumor cell lines.[22]

Figures of monocyclic diterpene cembranes



Cembrane-A (**15**) Asperdiol (**16**) **17**

18 Eunicinone (**19**) **20**

Napthenol (**21**) Sarcophytol A (**22**) **23**

(+)-(11, 12)-Epoxysarcophytol-A (**24**) **25** **26**

Figure 2

Bicyclic14-membered-ring diterpenes (γ-lactone cembranoid)

Bicyclic cembranes are structurally more complex than simple cembrane and shows potent cytotoxic activity by virtue of the presence of a γ-lactone ring. Sinulariolide **27** is a lactone cembranoid was isolated from the soft corals alcyonarian Sinularia flexibilis exhibited remarkable antineoplastic activity in vitro PS and KB tests.[23] Eupalmerin **28** and its acetate **29** have been isolated from *E. mammosa* from Puerto Rico. The acetate derivative **29** showed *in vitro* cytotoxicity against CHO-K1 cells and antimicrobial activity against

Shigella flexneri and Proteus vulgaris (MIC = 1 ~tg /mL) while Eupalmerin **28** inhibits a similar potency to the muscle (IC_{50}=6.4 ~tM) and electric organ (IC_{50} = 4.9 IxM) acetylcholine receptors (AChR's) expressed in *Xenopus laevis* oocytes.[24,25,26] Euniolide **30** has been found in significant amounts in specimens of *E. mammosa* collected off the west coast of Puerto Rico, which showed significant cytotoxicity against CHO-K1 cells.[27]

Bicyclic diterpene cembranolides

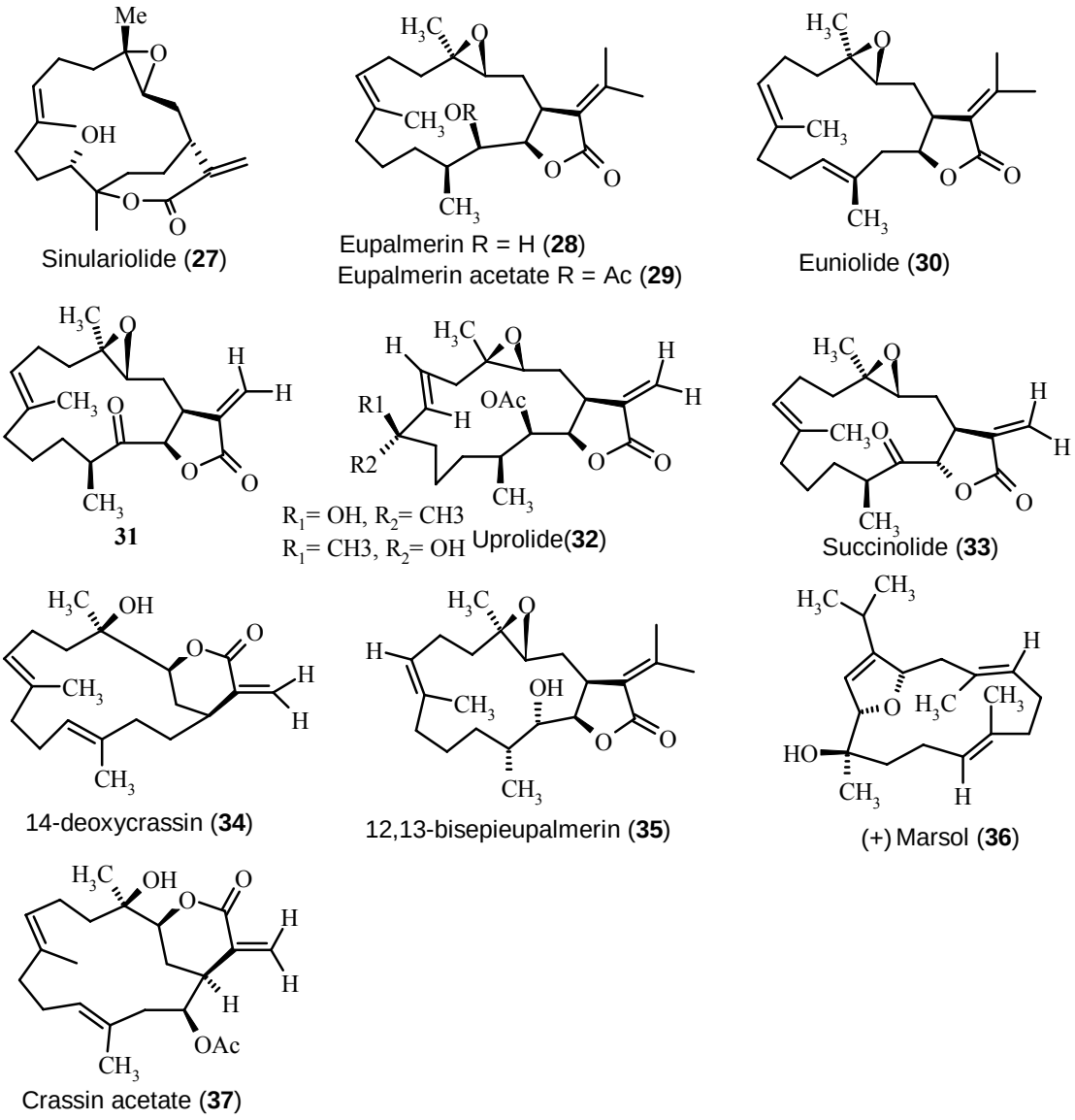


Figure 3

Eupalmerone **31** having keto functionality in peripherry, isolated from *E. mammosa* collected in Desecheo Island near Puerto Rico. Uprolides **32** and its derivative isolated from *E. mammosa* near Puerto Rico show *in vitro* toxicity to several human tumor cell lines. [28,29] The cembranolide 12,13-bisepieupalmerin **35** was isolated from specimens of E. *succinea* collected in St.Croix, U.S. Virgin Islands, and a biosynthetic precursor for the related cembranolides eunicin **38** and jeunicin **41** displayed strong *in vitro* cytotoxicity against CHO-KI cells and a very good nicotinic acetylcholine receptor (AChR). [30] Succinolide **33** isolated from E. *succinea* from Puerto Rico a potent antitumor promoter.

Fused tricyclic cembranoids

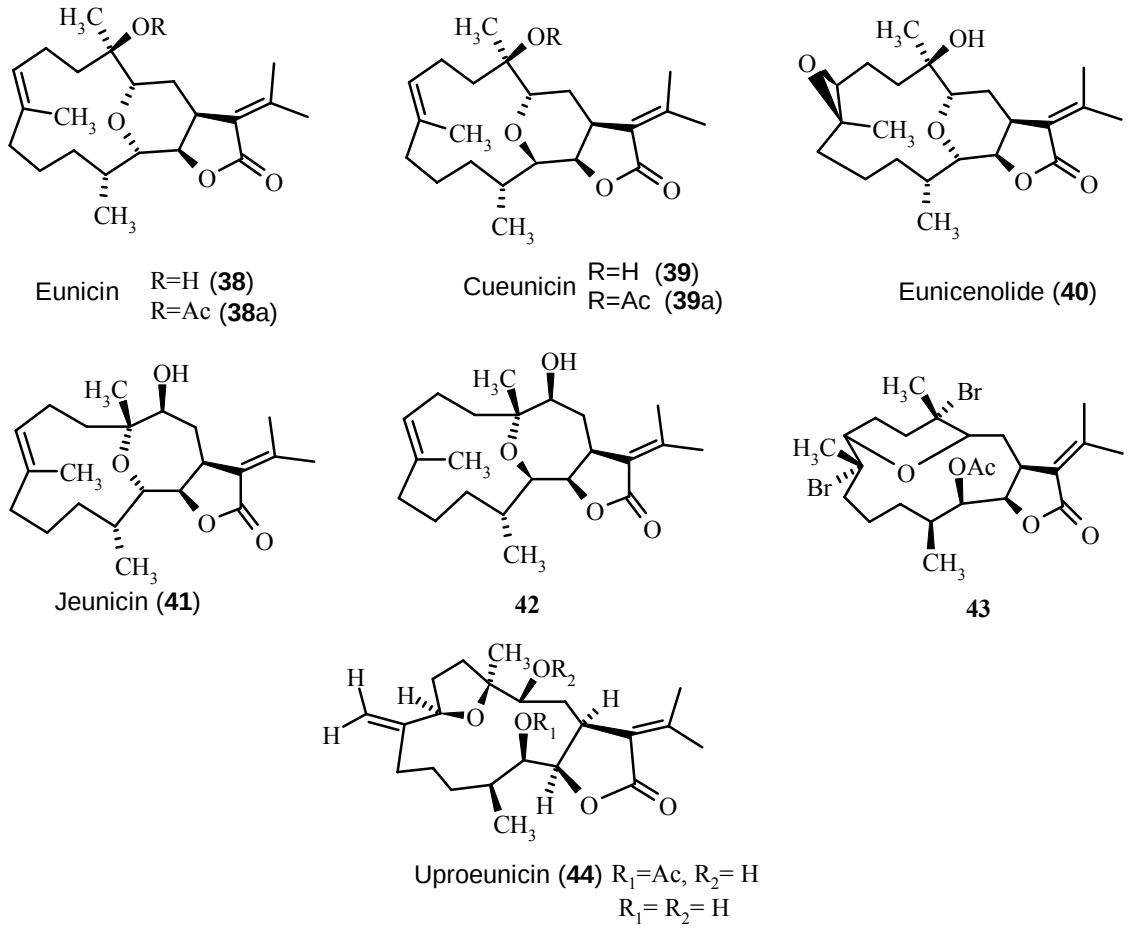


Figure 4

The bicyclic oxa-bridged 2,5-dihydrofuran-containing cembranoid diterpene (+)-marasol **36** was isolated from the gorgonian *Plexauraflexuosa* from Puerto Rico, showed strong

cytotoxicity against CHO-K1 and HeLa cells. 14-deoxy crassin **34** and Crassin acetate **37** are the major constituent of the Caribbean gorgonian *Pseudoplexaura porosa,* were the first cembranolide possesses a α–methylene-δ- lactone ring to be isolated from marine sources shows cytotoxic activity.

The tricyclic cembranoids are most complex one having fused lactone ring with oxabridged bicyclic skeleton and the periphery is highly functionalized. Cembranoids belonging to these categories are eunicin **38**, cuenicin **39**, eunicenolide **40,** jeunicin **41**, **42**, **43** and uproeunicin **44** etc. Cembranoids belonging to this class contains a fused tricyclic core having 14-membered macrocyclic ring, an internal tetrahydropyran ring with fused tetrahydrofuran lactone and a highly functionalized peripherry. The cembranolides cueunicin **39** and cueunicin acetate **39a** were isolated from the hexane extract of the Caribbean gorgonians, eunicea mammosa lamouroux collected in Bahamas.[31]

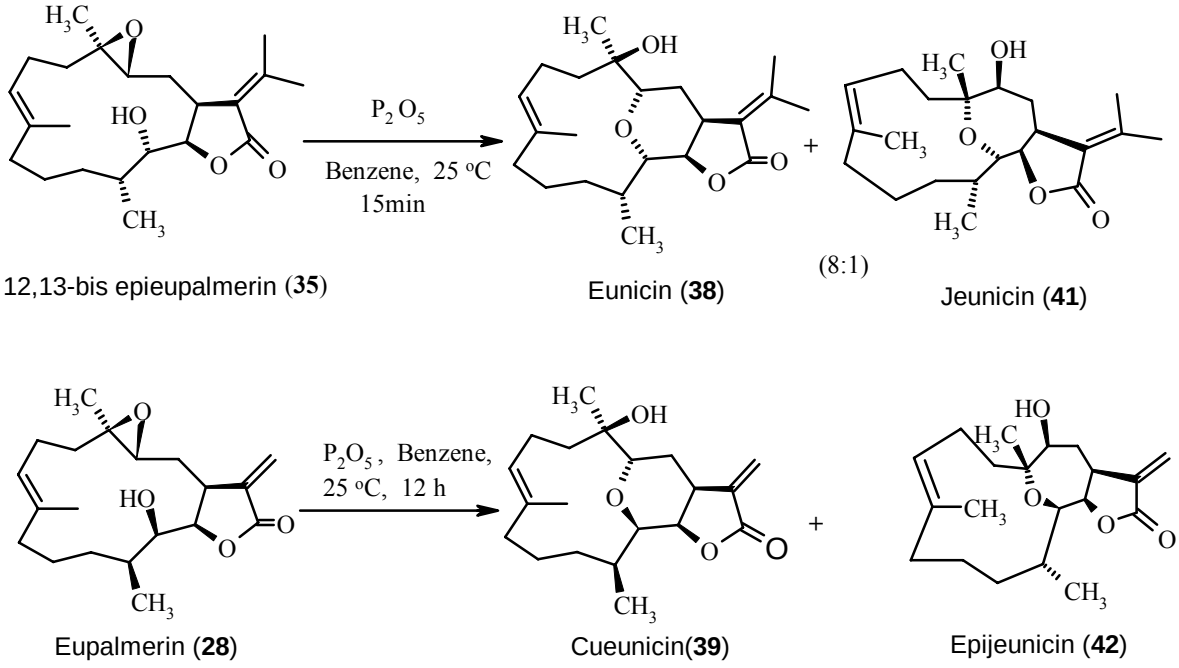
Cueunicin acetate **39a** was a crystalline solid and its structure was unambiguously confirmed by the crystallographic study (Gupta etal, 1986).[32] This study also reveals that Cueunicin is the only example where the cis fused γ-lactone assumes a planar geometry. Epipeunicin is an unstable 7-1actonic-cembranolide diterpene isolated from the same specimen of E. *succinea,* and its proposed structure is based on spectral data. 12,13-Bisepieupalmerin possesses the correct stereochemistry to be a biosynthetic precursor for the related cembranolides eunicin **38** and jeunicin **41**.

Eunicenolide **40**, an epoxy cembranoid containing oxabridged bicyclic skeleton has been isolated from Caribbean gorgonian *Eunicea succinea* (phylum Coelenterate, class Anthozoa, subclass Octocorallia, order Gorgonacea, familyPlexauridae) collected near Mona Island off the westcoast of Puerto Rico (Abimael D. Rodrı´guez and Ana L. Acosta in 1998). A structure of 40 was carefully established by a combination of chemical and spectroscopic methods in addition to detailed NMR spectral comparisons with known cembranolide models. The biological study reveals that eunicenolide was the least toxic, displaying moderate cytotoxicity against only one ovarian (IGROV1), one nonsmall celllung (NCI-H522), and two leukemia (CCRF-CEM and RPMI-8226) cancer cell lines at concentrations of 10^{-5} M. Eunicin **38**, an oxabridged bicyclic type cembranoid diterpene, was first isolated by Ciereszko and Weinheimer in 1960 from a marine soft coral Eunicea mammosa.[33] The 3,13-oxabridged γ-lactone structure was proposed initially on

chemical and spectral grounds. Later on, the structural confirmation has been carried out by X-ray crystallographic analysis of the corresponding acetate.[34] Biological study reveals that it is a potent cytotoxic and antineoplastic agent. Recent study shows that it is a strong nicotine acetylcholine receptor (nAChR) and active against several human tumor cells.[35]

After a thorough literature study of cembranoids, we noticed that though the tricyclic cembranoids like Eunicin and its analogues isolated in early 1960's but a single synthesis hasn't been reported till date, only few partial syntheses from known cembranolides has been reported. Many synthetic studies have been addressed for the synthesis of simple cembrane or epoxy cembrane, which contains only macrocyclic ring, but semi synthesis of fused tricyclic cembranoid has been reported by simple conversion of naturally isolated cembranes. The semi synthesis has been explained as follows: Rodriguez et al in 1995,

Scheme 1

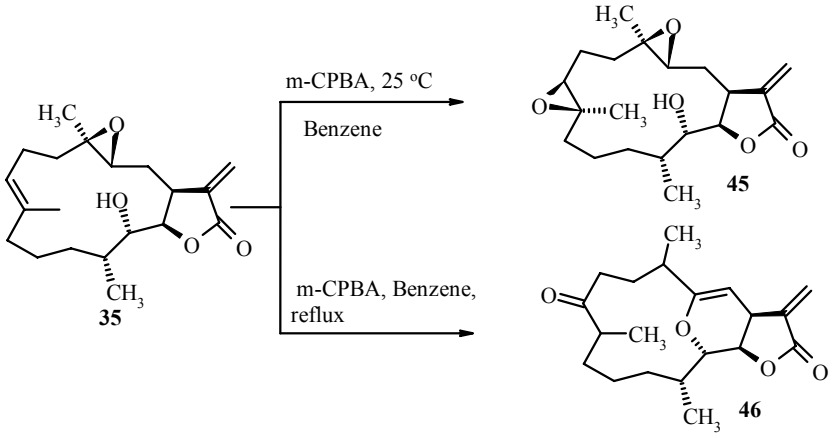


12,13-bis epieupalmerin (**35**) Eunicin (**38**) Jeunicin (**41**)

Eupalmerin (**28**) Cueunicin(**39**) Epijeunicin (**42**)

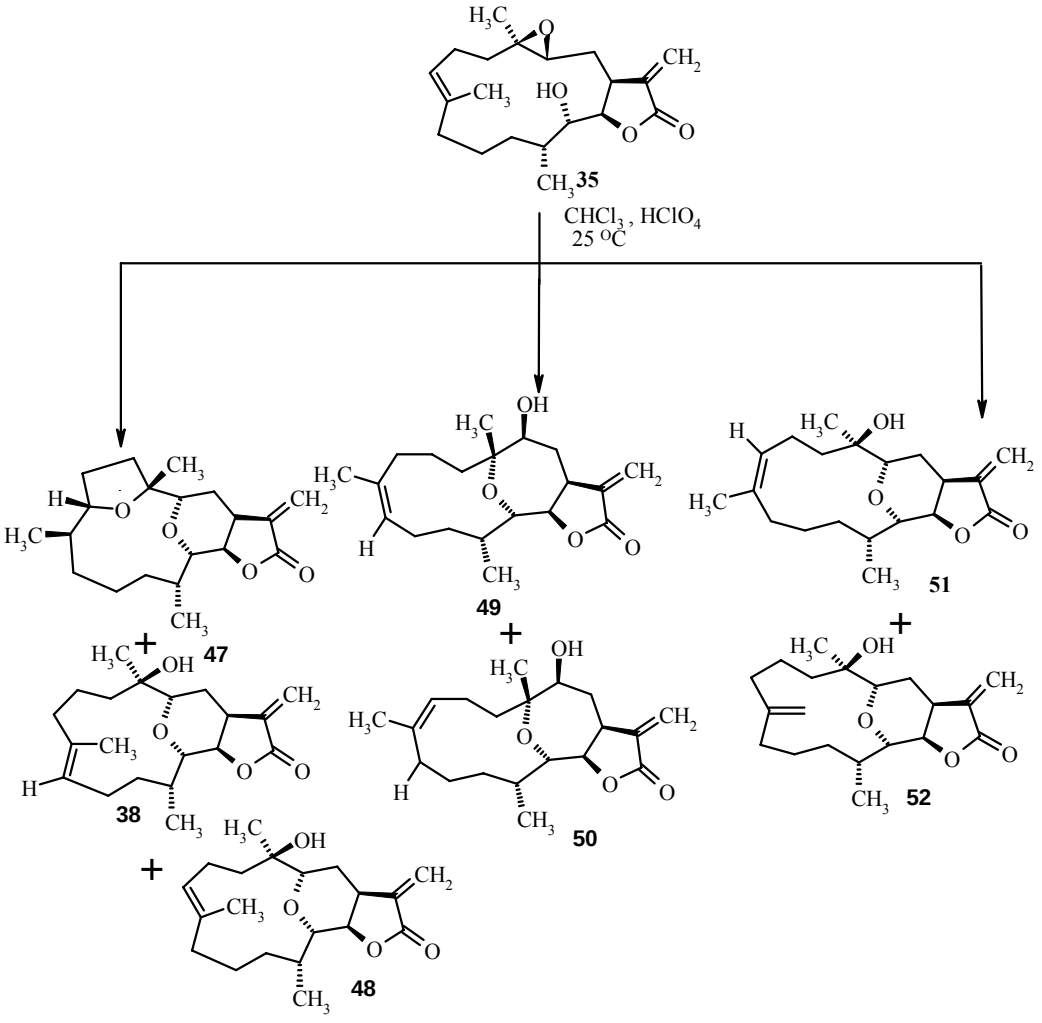
have reported the semi synthesis of Eunicin and Jeunicin from 12,13-bisepieupalmerin via transannular back–side attack of the C13 hydroxyl group at C-3 of the epoxide and epimer of cueunicin **39** and epijeunicin **42** from eupalmerin **28**.[36]

Scheme 2



Rodriguez et al in 2001 synthesized compound **45** and **46** from **35** by treatment of *m*-CPBA as acid catalyst in benzene.

Scheme 3

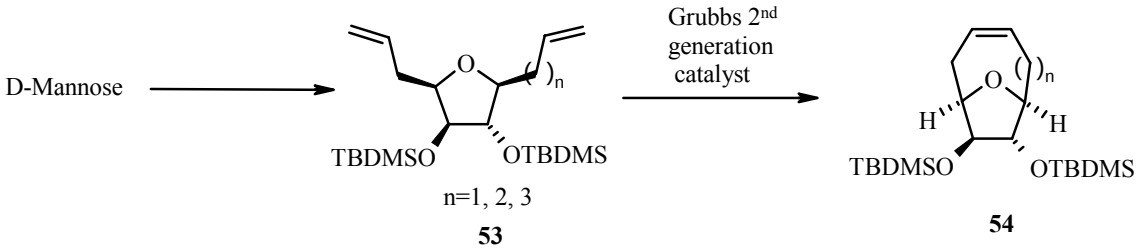


Rodriguez et al in 2001 reported the acidolytic cleavage of the epoxide **35** using perchloric acid in chloroform at ambient temperature in 2h resulted in a mixture of complex products like **38**, **47**, **48**, **49**, **50**, **51** and **52.**

Short review on oxa/aza bridged bicyclic systems using RCM reaction:

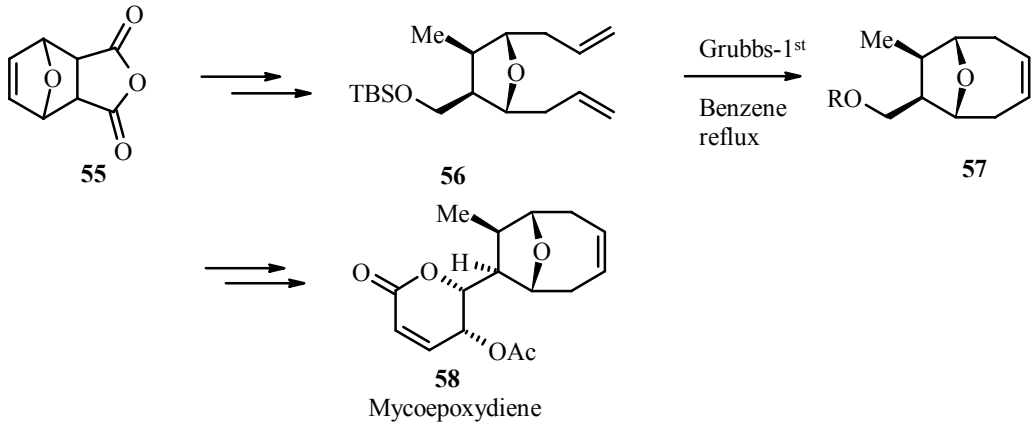
RCM reaction has been found a wide use in the construction of medium ring-sized carbo- and heterocycles, its use in the construction of medium sized bridged compound is scare. The review of the literature for making medium sized (**7-9**) ring–bridged oxa/aza bicycles by ring closing metathesis are mentioned below:

Scheme 4



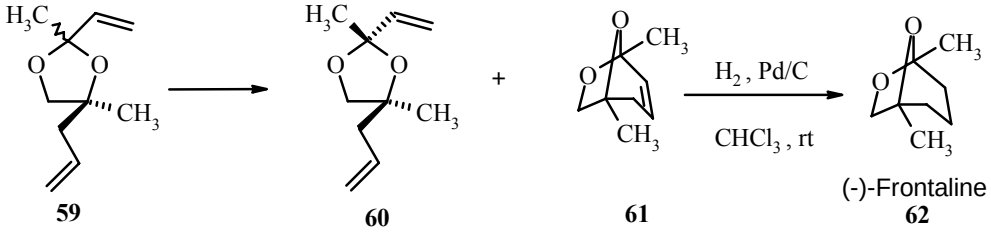
Pedro de Armas et al[37] synthesized the oxa bridged bicycles [4.2.1], [5.2.1] and [6.2.1] using a ring closing metathesis reaction of the suitably substituted 2,5-*cis*-dialkenyl tetrahydrofuran derivatives **53**. The dienes **53** was easily synthesized in a stereospecific fashion from inexpensive, commercially available carbohydrates D-mannose using straightforward procedure. Upon treatment with Grubbs' catalyst (2nd generation) in refluxing benzene, underwent metathesis to afford the bicyclic products **54** in good yields.

Scheme 5



Tadano and co-workers[38] prepared the core of Mycoepoxydiene, which was isolated from a fungal metabolite by fermentation of a fungus in the year1999.[39] The synthesis of the 2,5-diallyl tetrahydrofuran precursors **56** involved nine steps synthesis from the Diels-Alder adduct of furan and maleic anhydride **55**. Treatment of Grubbs'1st generation catalyst in refluxing benzene resulted in the formation of bicyclic compound **57**.

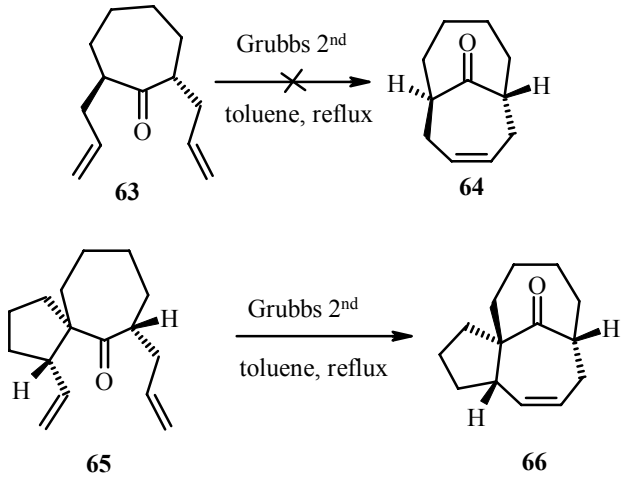
Scheme 6



59 **60** **61** **62**

Grubbs et al [40] reported a synthesis of the bicyclic ether (-)-frontalin **62** employing an approach that featured a RCM reaction. The metathesis substrate **59** was prepared as a mixture of C-5 epimer, stereochemistry at C-1 was set by an asymmetric Mukaiyama allylation. When this mixture was treated with Grubbs'1st generation catalyst in benzene at room temperature, (1*S*, 5*S*) **60** and the cyclized product **61** were obtained.The uncyclized (1*S*,5*S*) **60** was equilibrated under acidic conditions to provide a mixture of (1*S*, 5*S*) **60** and (1*S*,5*R*) **60** that was resubjected to RCM conditions synthesizes **61.** Hydrogenation of the double bond resuled in compound **62**.

Scheme 7

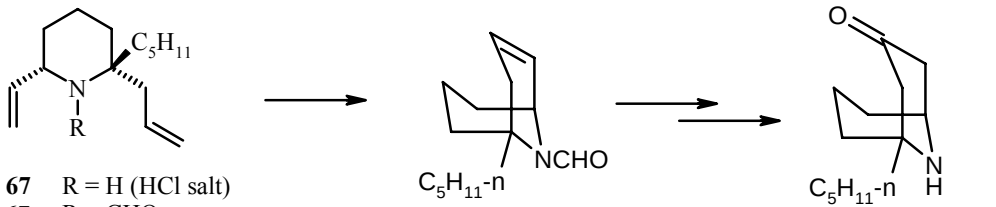


63 **64** **65** **66**

Kigoshi et al[41] reported an attempt to synthesize a trans bicycle [4.4.1] undecanone by means of ring closing metathesis. Trans 2,7-diallyl cycloheptanone was subjected to RCM

reaction by using 2nd generation Grubbs' catalyst in refluxing toluene failed to provide the bicyclic enone **64** This led to the hypothesis that the intramolecular distance between the terminal double bonds is a key feature. Where as reducing bond distance 3.8 A^o to 3.6 A^o by some structural modification, the substrate **65** underwent ring-closing metathesis at a high temperature to yield compound **66** in 20% yield.

Scheme 8



67 R = H (HCl salt)
67a R = CHO

69

(-)-Adaline **70**

The bicyclic nitrogen heterocycles (-)-adaline**70** is a major defensive alkaloid of the European ladybug Adalia bipunctata. *Kibayashi et al* [42] synthesized compound **70** following RCM from the diene precursor **67**. Where as **67** didn't undergo RCM in the presence of the Grubbs' 1st generation catalyst. This failure was attributed to the diequatorial arrangement of the two alkenyl side chain. Converting R = H to formyl derivative **67a** underwent facile RCM with Grubbs' 1st generation catalyst results **69**, which was subsequently transformed into the natural product **70**.

PRESENT WORK

Present Work

Presence of *syn*- or *anti*-oxa brigded bicyclic ring in a tricyclic core is an important feature of the Cembranoid class of compounds. It is an intriguing unit present in many natural products such as eunicin, cueunicin, epieunicin and eunicenolide etc, and have attracted immense attention of organic chemists because of their complex architectural features and promising biological activities. [43]

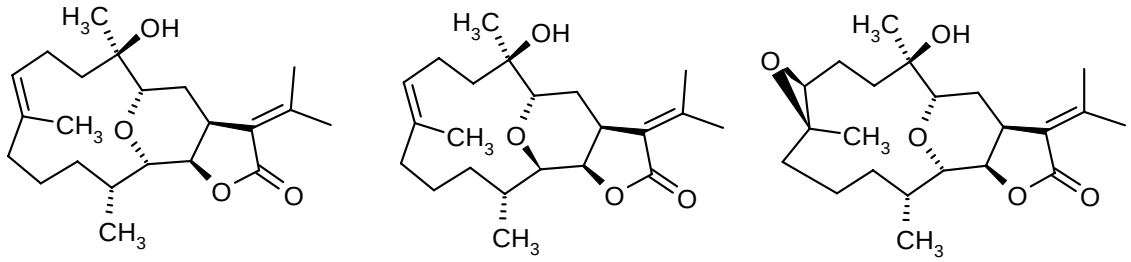


Figure 5

As a part of our ongoing efforts directed towards the synthesis of natural products containing oxabridged bicyclic ring system, we envisioned that a furo [2,3-*c*] pyran diene linked to carbohydrate backbone would be a potential precursor. There are several protocols available in literature for the cyclisation. One of the preferred methods to prepare oxa-bridged bicyclic ring exploits a ring closing metathesis reaction using Grubbs'catalysts. As the literature study accounted us higher membered (>10membered ring) heteroatom containg bridged bicycles synthesis, using RCM condition wasn't reported till date, so we thought of making a 14-membered cyclic ring of eunicin and its analogues employing RCM reaction (Figure 6).

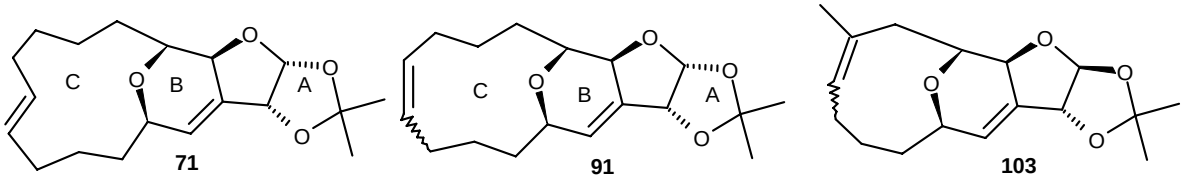


Figure 6

In the beginning of our synthetic endeavor, we planned to synthesize the tricyclic core skeleton of Eunicin like cembranoid and its analogues (Figure 6) using RCM as the key reaction. Here a retrosynthetic analysis was planned, which was depicted in Figure 7.

Retrosynthetic analysis:

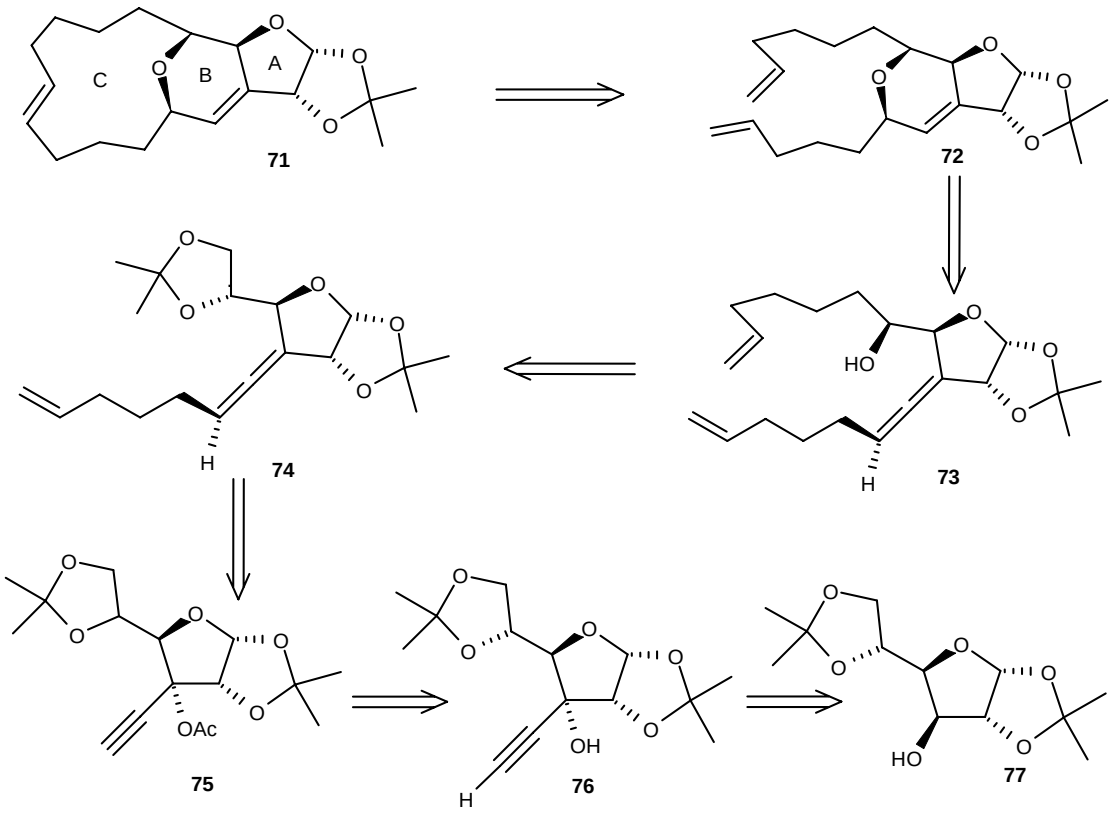
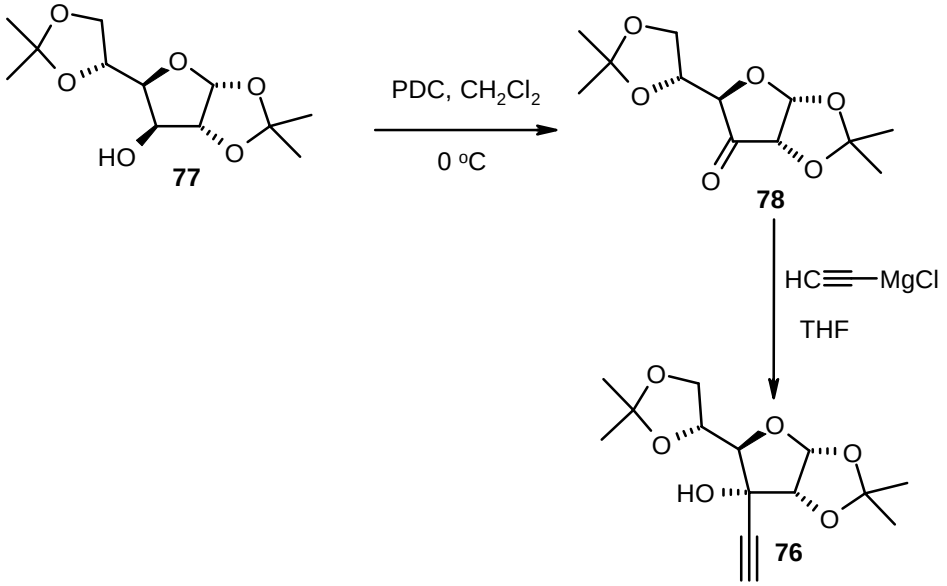


Figure 7

According to retrosynthetic analysis it was envisaged to cleave the double bond of ring C in **71** led to the furo [2,3-c] pyran diene **72**. The dihydropyran ring **72** can be synthesized by silver(I) mediated cycloetherification of β-allenic alcohol **73**, where as **73** could be obtained from allenenic precursor **74** by regular transansformations. Compound **74** can be synthesized by organocuprate mediated S_N2' reaction of propargyl acetate **75**, which inturn synthesized from known propargyl alcohol **76**. Propargyl alcohol **76** can be synthesized from 1,2:5,6–di-*O*-isopropylidine-D(+)-glucose **77.**

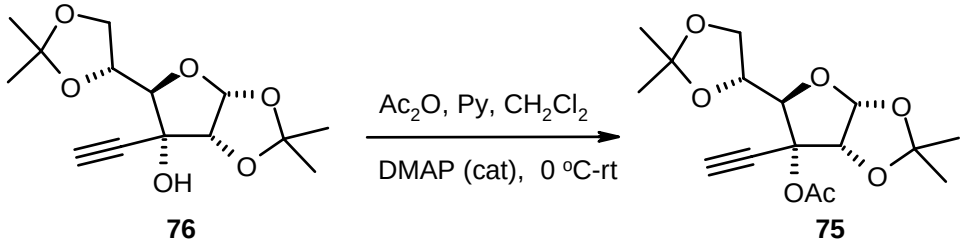
According to retrosynthetic analysis our synthesis started from alkyne precursor **76**, which was synthesized from glucosediacetonide in a two step synthesis following known literature procedure.[44]

Scheme 9



The commercially available diacetonide glucofuranose (**77)** was oxidized using Pyridiniumdichromate in presence of 4A° molecular sieves powder and Ac_2O (cat) in anhydrous dichloromethane to give 1,2:5,6-di-*O*-isopropylidiene-α-D-*ribo-hexofuranose*-3-ulose **78**, which was treated with acetylene magnesium chloride (prepared by the exchange of butylmagnesium chloride and acetylene gas) in tetrahydrofuran at 0 °C to room temperature for 1 h afforded propargyl alcohol **76** in good yield. ^1H, ^{13}C NMR, IR, melting point and optical rotation of **76** were identical to the reported values (Scheme 9).

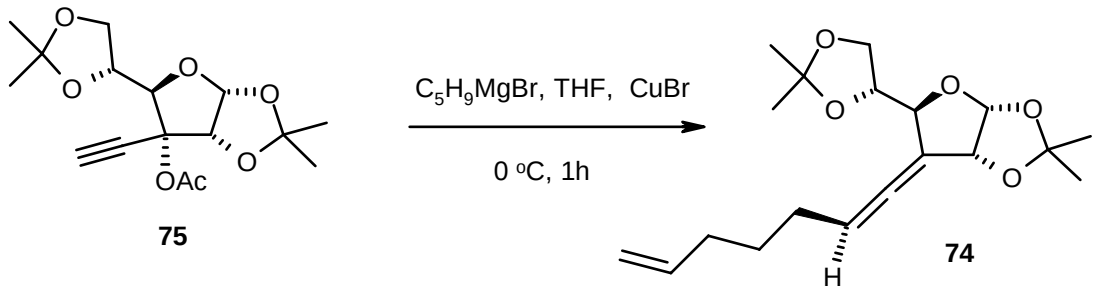
Scheme 10



The tertiaryalcohol of **76** was acylated by using Ac_2O, pyridine and DMAP (catalytic) in dichloromethane to yield **75**. In the ^1H NMR spectrum of compound **75**, the characteristic methyl proton signal of acetate group was appeared as a singlet at δ 2.12 ppm and the acetylinic proton signal observed at δ 2.72 ppm as a singlet. The other proton resonances of **75** were in accordance with the assigned structure. In the ^{13}C NMR spectrum resonances

due to distinguishing carbonyl carbon signal of acetate group was observed at δ 168.4 ppm confirmed the assigned structure (Scheme 10).

Scheme 11



Having compound **75** in hand, our immediate concern was to carryout organocuprate-induced 1, 3-substitution reaction to result in allenic moiety **74**. Thus acetate **75** was subjected with Pentenylmagnesiumbromide[45] inpresence of CuBr (cat) at –10 ^{o}C furnished 3-allenic moiety **74** in moderate yield, where as using CuBr stochiometrically, **74** was obtained with good yield as a single product.[46] In the ^{1}H NMR spectrum of **74** resonances corresponding to the allenic proton was apparent at δ 5.78 ppm as a multiplet. In addition, the olefinic methine proton signal was observed at δ 5.52 ppm as a multiplet integrating to one proton whilst terminal methylene protons of alkene was found at δ 5.04-4.94 ppm. In the ^{13}C NMR spectrum three allenic carbons signals were resonated at 198.5, 101.9, 96.2 ppm whilst in the DEPT spectrum the disappearance of signal at δ 198.5, 101.9 indicating quaternary carbon of allene. In the ^{13}C NMR spectrum the –CH and –CH_2 carbons of olefin was resonated at δ 138.1 and 115.1 ppm, where the –CH_2 carbon signals was unambiguously identified at 115.1 ppm in the DEPT spectrum. The structure was further confirmed by elemental and mass analysis (Scheme 11).

Stereochemical Rationale: The S_N2' substitution of progargyl derivatives by organocuprates was proposed to proceed through a copper(III) intermediate **75a** (Figure 8).[47] The *in situ* generated organocuprate coordinated with the acetylenic moiety of the propargyl derivative to form a copper(III) π-complexes **75a**, which underwent subsequent elimination of the leaving group when the copper and the leaving group possessed an antiperiplanar disposition. Besides the interaction between the copper p, d orbitals and acetylenic π, π* orbitals, the electron donation from a copper d orbital to the antibonding orbital of the C-O σ* bond is also conceivable. It was proposed that this latter interaction

initiated the dissociation of the leaving group. The resulting allenic cuprate **75b** collapsed by reductive elimination, regenerating the halocopper and giving the allene product **74** with an overall *anti*-S_N2' stereochemistry. In some special cases an overall *syn* S_N2' stereochemistry was observed, probably due to *syn* elimination of the Π-complex.

Mechanistic explanation on stereochemistry

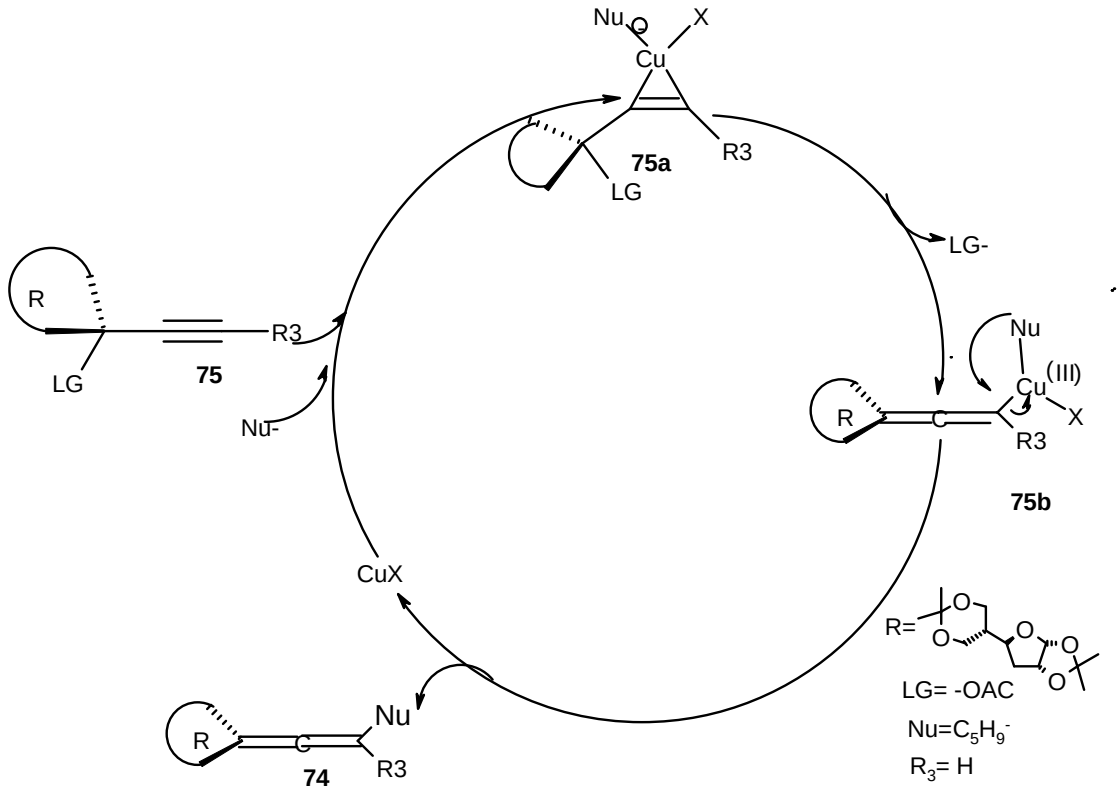
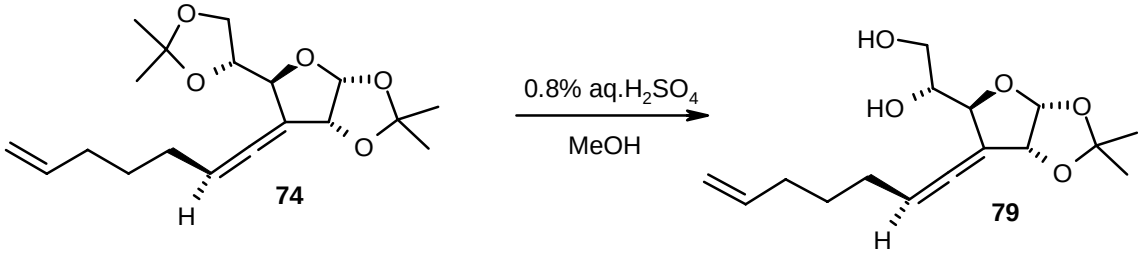


Figure 8

From the mechanistic study it was concluded that allene **74** was formed as a single product because of exclusive anti S_N2' mechanism, [48] where the pentenyl anion attacked on the β face resulting acetate departure from α face. The exclusive transannular departure was also assisted by the constrained structure of sugar substrate.

Scheme 12

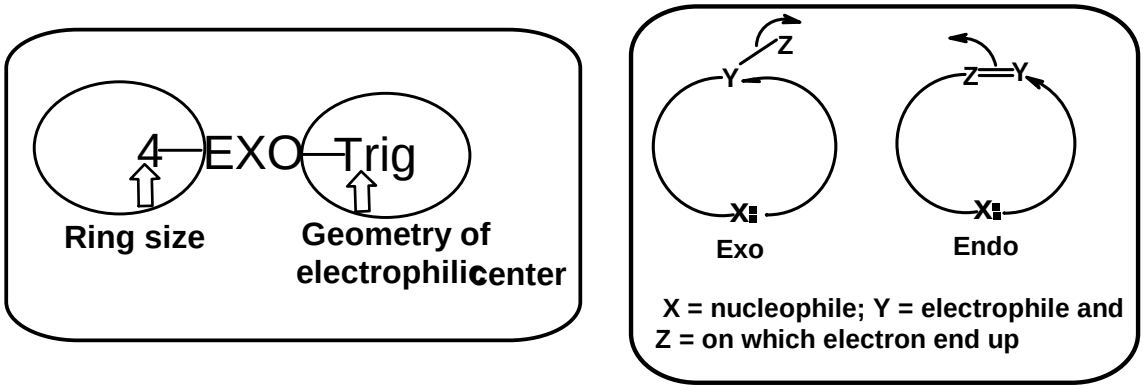


In order to continue our synthetic endeavour the 5,6-isopropylidine group of **74** was selectively cleaved using 0.8% aq. H_2SO_4 in methanol to give diol **79** as a syrup. In the ^1H NMR spectrum of compound **79**, the signals for isopropylidene protons were disappeared and the methylene protons and methine protons linked to –OH group were appeared at δ 3.74–3.67 ppm as a multiplet in addition, two hydroxyl proton signals resonated as two broad singlet at δ 2.95 (brs, 1H) and 2.60 (brs, 1H) ppm integrating for one proton each along with all other resonances according to the assigned structure. In the ^{13}C NMR spectrum the $–CH_2$ and –CH carbons linked to hydroxyl group were observed at δ 62.6 and 73.5 ppm, which were further confirmed from DEPT spectrum. IR (3600 cm^{-1}) and elemental analysis data also supported the formation of **79** (Scheme 12).

After synthesizing allenic alcohol it was worth to mention about the superb ability of allenes. Methods for transforming allenes into various other functionalities, in a stereoselective manner, have attracted more attention. Furthermore, the superb ability of allenes to transfer axial chirality to new stereogenic centers is being increasingly exploited in synthetic applications. The ability of allenic alcohols to enter into reactions in an inter or intramolecular fashion makes them valuable intermediate for the preparation of synthetically useful substances. Generally in the presence of mercury(II) or silver(I) ions, the β,γ allenic alcohol cyclizes to give six membered or seven membered cyclic ring. Here, we can also exploit allene **79** for metal mediated cycloetherification reaction for our synthesis. Before going to the synthetic point, it is very much essential to know about the mode of cyclisation and also the nomenclature of the cyclic compounds, which was well documented from Baldwin's rule.

Short account of Baldwin rules for ringclosure

Baldwin suggested a set of empirical rules for the prediction of ring closure, outcome of the intramolecular addition of nucleophiles or radicals to electrophilic center. The nomenclature of these rules is written as e.g. 4-*Exo*-Trig 4-indicate the ring size being formed. *Exo*-indicate where displaced electron end up (if it ends up out side the ring being formed; then *exo* and if it ends up within the ring being formed; then *Endo*)



Trig- indicates the geometry of electrophilic atom on which attack takes place. {if it is sp^3; then Tet (tetrahedral), if it is sp^2; then Trig (trigonal) and if it is sp: then Dig (diagonal)}.

The Baldwin rules are listed in the tabulated form below. These rules suggest wheather the ring closure is favored (√) or disfavored (x).

Ring size Being formed	***Exo***			***Endo***		
	Dig	**Trig**	**Tet**	**Dig**	**Trig**	**Tet**
3	x	√	√	√	x	√
4	x	√	√	√	x	√
5	√	√	√	√	x	x
6	√	√	√	√	√	x
7	√	√	√	√	√	√

Possible mode of cyclisation

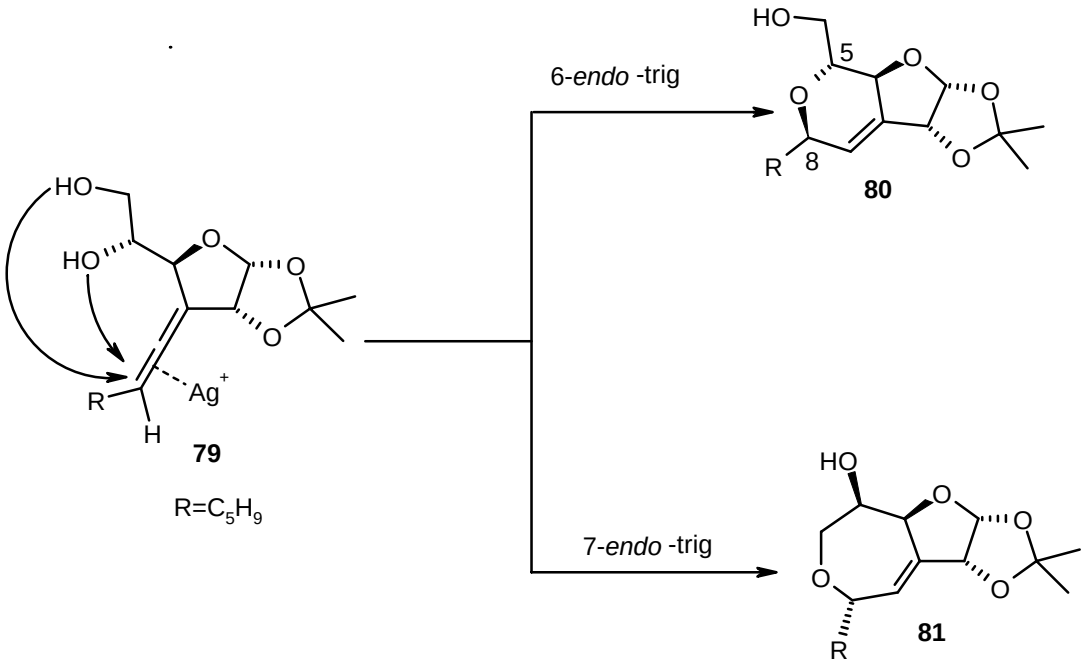
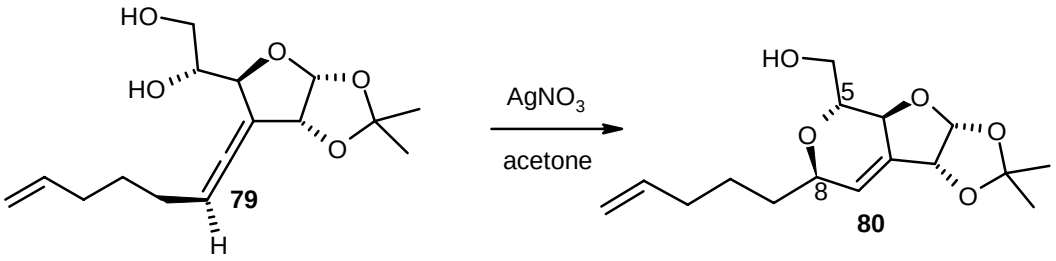


Figure 9

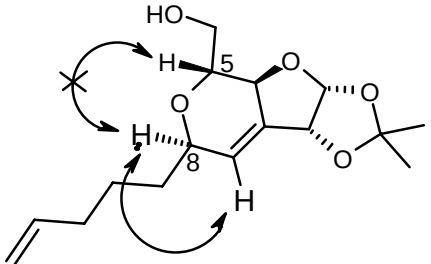
According to Baldwin's rule we can expect compound **80** and **81** will be formed from **79** by Ag(I) mediated cyclization due to 6-*endo*-trig and 7-*endo*-trig mode of cyclisation.

Scheme 13



To check the practical regioselective mode of cyclisation we planned to employ Ag(I) mediated cycloetherification reaction.[49] Accordingly allenediol **79** was treated to $AgNO_3$ in anhydrous acetone at ambient temperature in 12 h afforded cyclic ether **80** as a single product. To study the mode of cyclisation in high temperature we have carried out same sort of reaction in refluxing acetone also found product **80** exclusively. Formation of **80** as a single product, indicating 6-*endo*-trig mode of cyclisation is the favoured one, and the ring formation was independent upon kinetic and thermodynamic factor. Resulted compound was confirmed by ^{1}H, ^{13}C, DEPT and elemental analysis. In the ^{1}H NMR

spectrum of the compound **80,** the allenic proton signal was dissappeared and the resonances corresponding to ring alkene –CH signal was apparent at δ 5.86 ppm as a triplet integrating for one proton. The methine protons linked to oxygenatom of dihydropyran ring were observed at δ 3.23 (ddd, *J* = 2.8, 6.1, 8.2 Hz, 1H) and δ 4.30 (ddd, *J* = 1.8, 4.3, 8.2 Hz, 1H) ppm respectively. In the ^{13}C NMR spectrum the ring olefinic carbon signals were resonated at δ 136.4 and 126.3 ppm. In the DEPT spectrum disappearance of signal at δ 136.4 ppm indicating quaternary carbon of olefin, inaddition the negative resonances for CH_2OH carbon was observed at δ 63.2 ppm and all other carbon resonated at their expected positions assigned the structure of **80**. Elemental analysis data also supported the formation of **80** (Scheme 13).



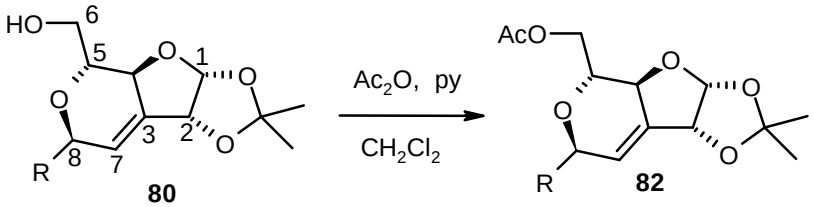
n*O*e studies of compound **80**

Figure 10

Stereochemistry of the substituted dihydro Pyran ring **80** was assigned by the help of NOESY study, where the targeted H5 and H8 protons weren't showing any n*O*e interactions assigning to *anti* conformation (Figure 10).

The presence of primary hydroxyl group in **80** was further confirmed by converting to acetate derivative **82**.

Scheme 14

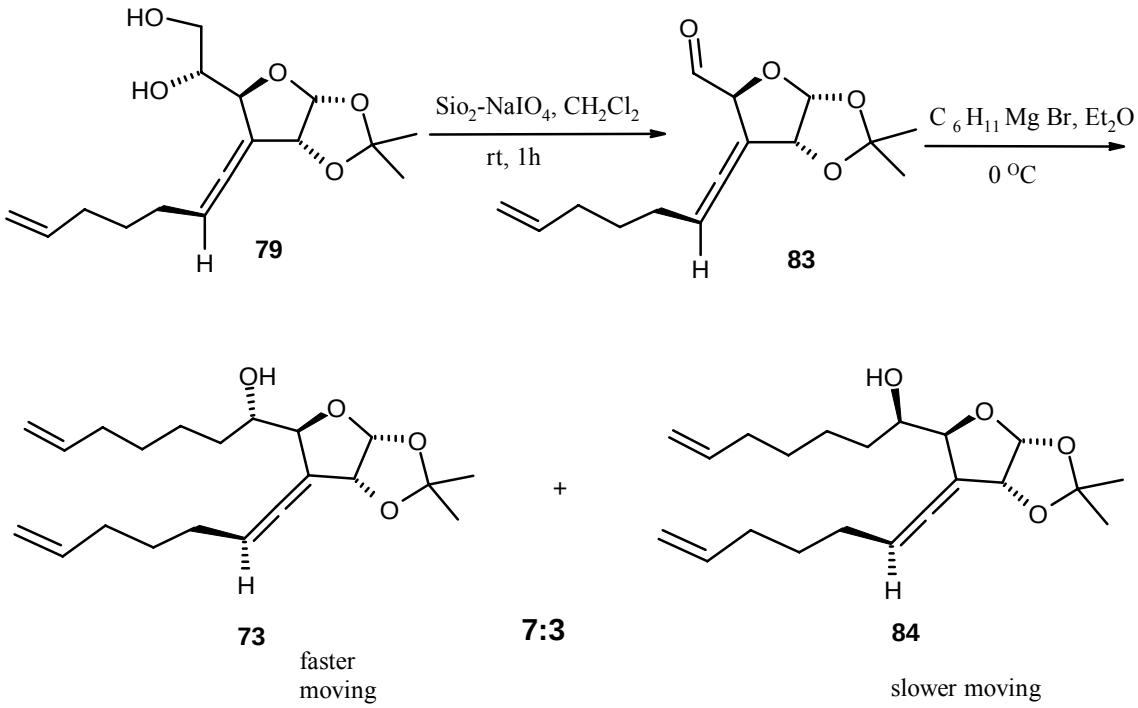


Compound **80** on treatment with Ac_2O, pyridine in dichloromethane resulted in acetate derivative **82**. In the ^1H NMR spectrum of **82** methylene protons linked to acetate group was observed at δ 4.15-4.10 (m, 2H), where as in **80** the corresponding protons appeared at δ 3.87 (dd, *J* = 2.8, 11.8Hz, 1H) and 3.70 (dd, *J* = 6.1, 11.8 Hz, 1H) ppm respectively.

Shifting of δ 0.40 ppm by acetate conversion confirmed the presence of primary hydroxyl group in **80**. This information also concluded the formation of six membered ring instead of seven membered ring in $AgNO_3$ mediated cycloetherification reaction (Scheme14).

Since our retrosynthetic approach requires a *syn*-dihydropyran-ring, the prime concern was to establish the requisite stereogenic center at C-5 position.

Scheme 15



Accordingly diol **79** was oxidatively cleaved with silicagel supported sodium metaperiodate to give aldehyde **83**, subsequent treatment with hexenyl magnesium bromide in Et_2O at 0 ^{O}C resulted in diastereomeric mixture **73** and **84** in 7:3 ratio, expected due to chelation controlled method (anti crams product, Figure 11) and the newly generated stereogenic center of major isomer was assumed as *S*, on the basis of previous report.[50]

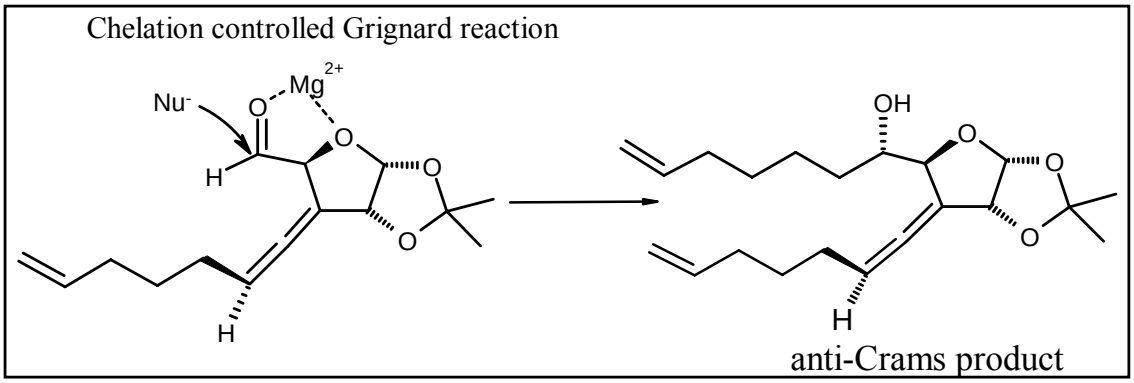
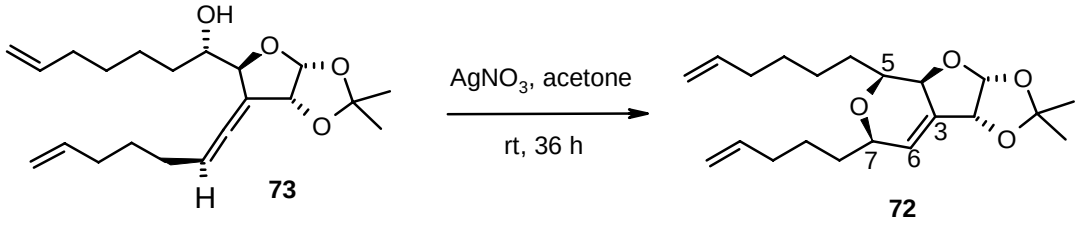


Figure 11

The diene moiety **73** and **84** were confirmed by ^{1}H, ^{13}C and DEPT NMR study.

In the ^{1}H NMR spectrum of **73,** the aldehyde proton signal of **83** was absent and new distinguished resonances were apparent at δ 5.75-5.67 and 4.95-4.84 ppm integrating to two and four protons corresponding to methine and methylene protons of two alkene groups. A similar changes was observed in the ^{1}H NMR spectrum of **84**. In addition methine proton linked to –OH group in **73** was observed at δ 3.43 (m, 1H) while the same proton in **84** was appeared at δ 3.46 (m, 1H). Additionally, appearance of five new -CH_2 signals in DEPT spectrum unambiguously determined the clean conversion of **83** to **73** (scheme-8). Compound **84** was confirmed in similar manner. Further confirmation was carried out by elemental analysis (Scheme 15).

Scheme 16

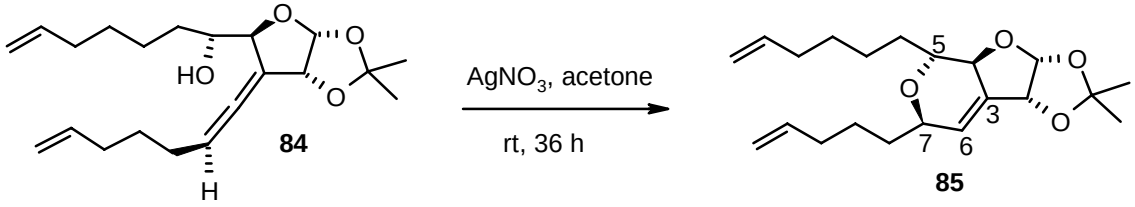


Cyclo-etherification of **73** was performed with $AgNO_3$ in dry acetone at room temperature for 36 h afforded the bicyclic derivatives **72** exclusively.The longer duration of reaction was expected due to more substituted allene. In the ^{1}H NMR spectrum of **72** the allenic proton signal was absent at δ 5.46 ppm, the–CH proton signal of ring olefin observed at δ 5.99 ppm and the methine protons linked to oxygen atom of dihydropyran ring was apparent at δ 3.63 and 3.72 ppm integrating one proton for each. In the ^{13}C NMR spectrum, the ring olefinic carbon signals were resonated at δ 136.1 and 130.6 ppm whilst the

oxymethine carbon signals of dihydropyran ring was observed at δ 73.1 and 70.6 ppm. The stereochemistry of the dihydropyran rings in **72** was assigned as *cis* with the help of ***NOESY*** studies, where the targeted H5 and H7 protons showed strong n*O*e interactions. Elemental and mass analysis data also confirmed the assigned structure (Figure 12).

After synthesizing syn dihydropyran diene we planned to synthesize anti dihydropyran diene from compound **84**. Thus, compound **84** was subjected with $AgNO_3$ in dry acetone at

Scheme 17



room temperature for 36 h afforded the bicyclic derivatives **85** exclusively. In the ^{1}H NMR spectrum of **85** the methine protons linked to oxygen atom of dihydropyran ring were identified at δ 3.00 and 4.16-4.11 ppm respectively and the corresponding carbons were resonated at δ 73.0 and 71.4 ppm in the ^{13}C NMR spectrum.The –CH carbon of ring olefin was observed at δ 126.9 ppm (Scheme 17). The stereochemistry of the dihydropyran rings in **85** was assigned as *trans* with the help of ***NOESY*** experiments, where the ringadjoined protons didn't show any n*O*e interactions (Figure 12).

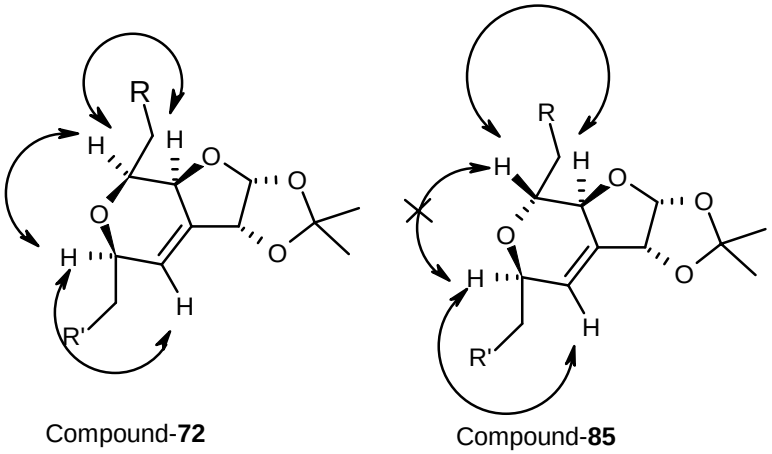
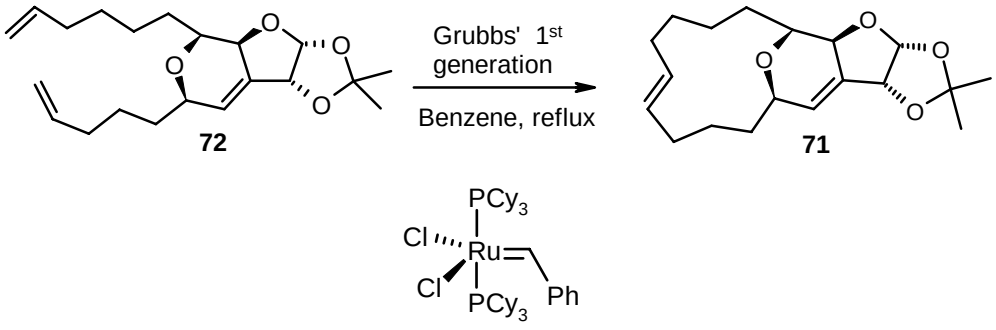


Figure 12 *nOe* studies on 72 and 85

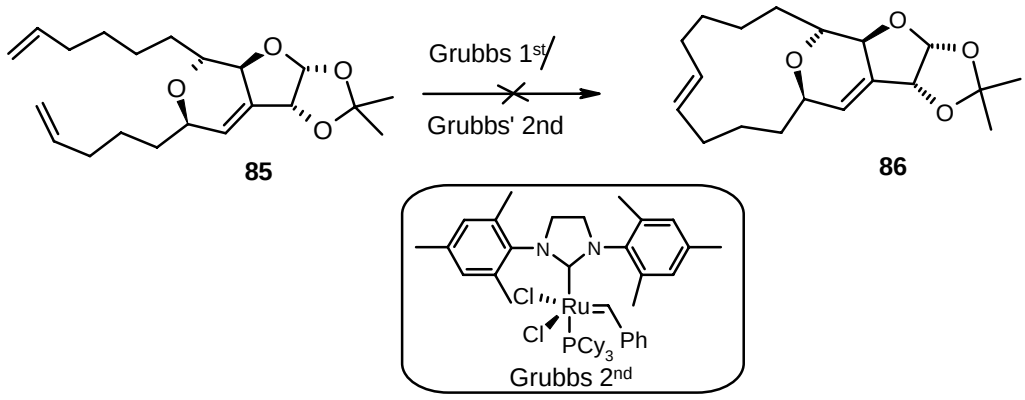
Having *syn* and *anti* dihydropyran diene we planned to do RCM reaction. The ring closing metathesis of the diene **72** was performed with 10 mol% of Grubbs'1st generation catalyst [$(Pcy)_3Cl_2Ru$=CHPh] in dichloromethane at room temperature and continued to reflux condition failed to give the desired cyclic product **71**, but resulted in noncharacterizable polymeric mixture. Where as, carrying out same reaction in refluxing benzene proceeded efficiently to give the requisite *E* isomer **71**.[51]

Scheme 18



In the ^{1}H NMR spectrum of **71** resonances due to characteristic olefinic proton appeared at δ 5.33 (dt, *J* = 7.5, 15.3 Hz, 1H) and 5.11 (dt, *J* = 6.9, 15.3 Hz, 1H) ppm. The *E*-configuration for the olefinic protons were evident from the large coupling constant (*J* = 15.3 Hz). In the ^{13}C NMR spectrum of **71** the olefinic carbon signals were resonated at δ 129.4 and 129.0 ppm, and the olefinic carbon signals of dihydropyran ring was shifted to downfield and observed at δ 135.1 and 133.7 ppm. All other carbons resonated at their expected chemical shift assigned the structure of **71** (Scheme 18).

Scheme 19



However, the RCM of **85** with Grubbs' 1st generation catalyst found to be sluggish and resulted in an intractable polymeric mixture. Further carrying out same reaction with Grubbs' 2nd generation catalyst in different solvents (dichloroethane/benzene/toluene) with different concentrations, didn't give any fruitful result, in all cases noncharacterizable polymeric mixture was obtained (Scheme 19).

The proposed mechanism for the ring closing metathesis is outlined in Figure 13.

Mechanism of ring closing metathesis

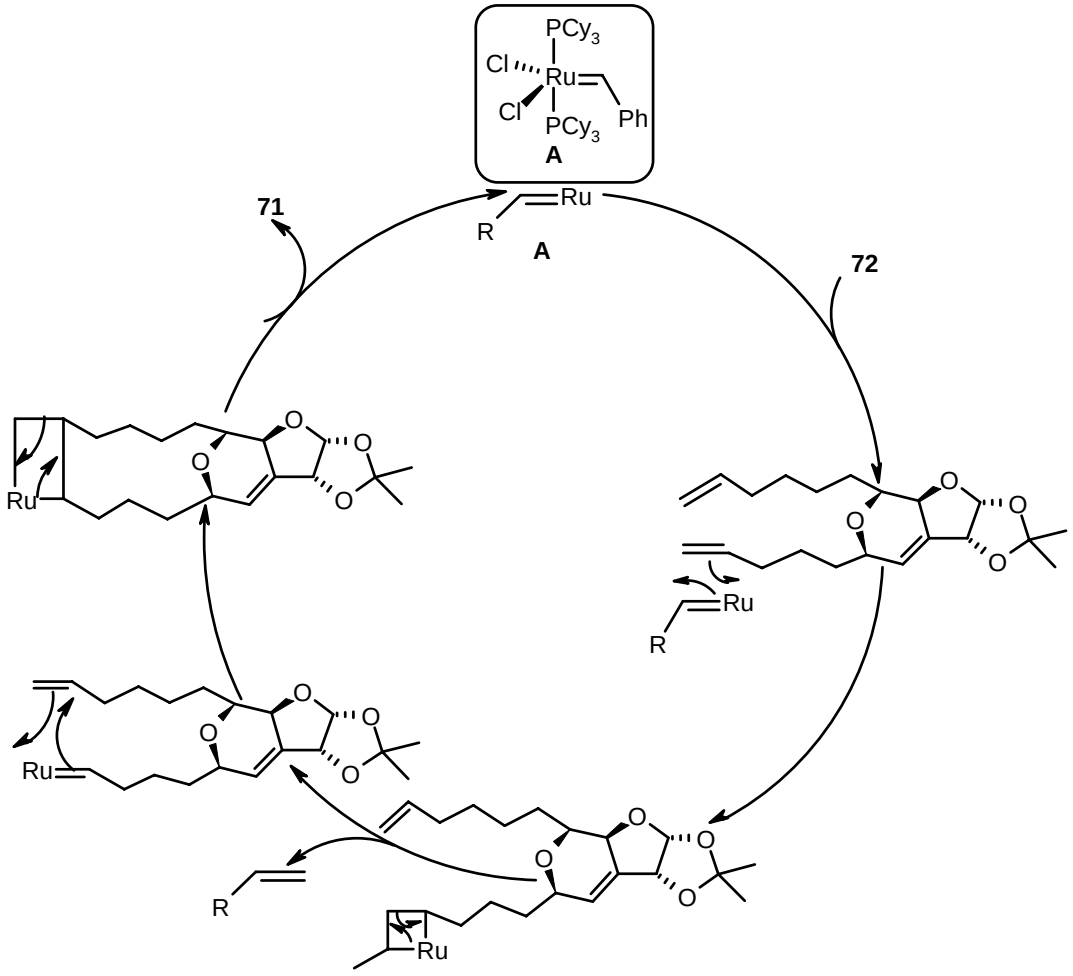
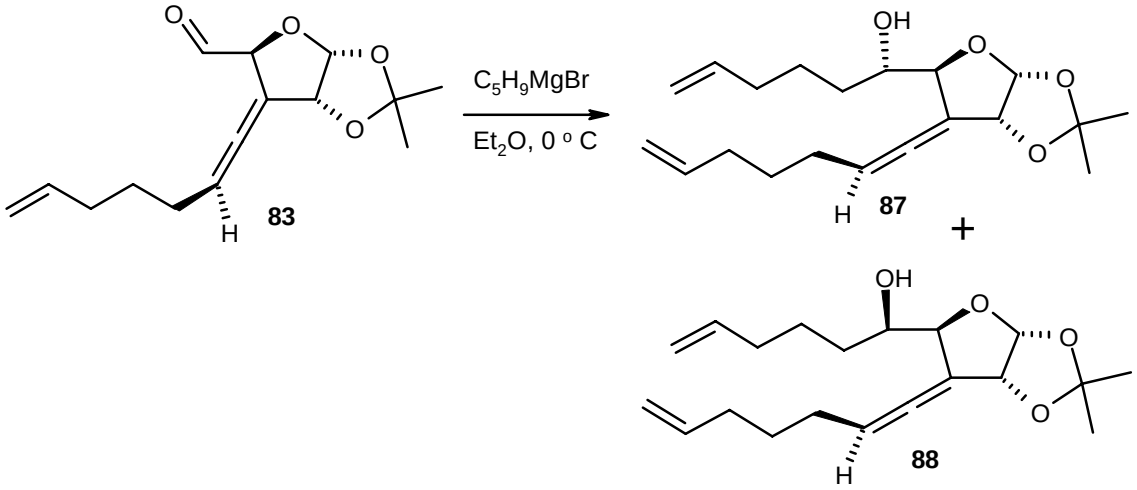


Figure 13

After establishing a strategy for the construction of twelve membered oxabridged bicyclic ring similar to the eunicin-like cembranoids, we next focussed our attention for the

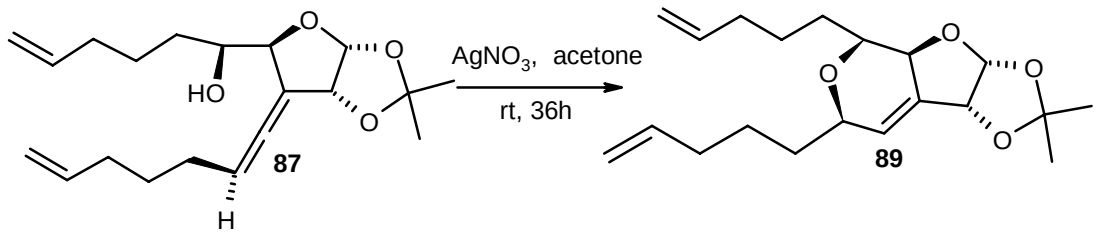
generalization of our strategies. Thus we planned to synthesize eleven membered cyclic ring.

Scheme 20

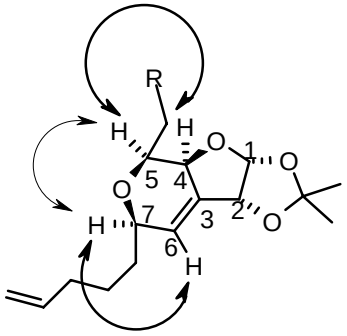


Accordingly, aldehyde **83** on treatment with pentenyl magnesium bromide in anhydrous Et_2O at 0 ^oC, resulted in diastereomeric mixture **87** and 88 in 7:3 ratio. The major isomer was fast moving and minor one slower moving in TLC. Both the compounds were seperarated by flash silica gel chromatography. The ^1H NMR spectrum of **87** showed the methine proton signal of olefin resonated at δ 5.82-5.74 ppm as a multiplet and the terminal methylene protons of olefin at δ 5.03–4.93 ppm as multiplet. Again the methine proton linked to –OH group appeared at δ 3.52 (m, 1H) ppm. Similarly in compound **88,** the olefinic methine and methylene proton signals were resonated at δ 5.81-5.74 and 5.06-5.01 ppm as multiplet respectively. The methine proton linked to –OH group was apparent at δ 3.53 (m, 1H) ppm. Further structural confirmation was carried out by ^{13}C and elemental analysis data (Scheme 20).

Scheme 21



Cycloetherification of **87** was accomplished with $AgNO_3$ in anhydrous acetone at room temperature for 36h afforded **89** in good yield. The structure of **89** was characterized by its ^1H, ^{13}C NMR and elemental analysis. In the ^1H NMR spectrum of **89** the allenic proton of **87** was absent at δ 5.55 ppm and the methine proton of ring olefin was observed at δ 6.02 ppm as a singlet The methine proton linked to oxygen atom of dihydropyran ring was apparent at δ 3.74 and 3.66 ppm. In the ^{13}C NMR spectrum the –CH carbon linked to oxygen atom of dihydropyran ring was identified at δ 73.3, 70.8 ppm while the ring olefinic carbons were observed at δ 136.3 and 130.6 ppm. In the DEPT spectrum, disappearance of signal at δ 136.3 ppm indicating to olefinic quaternary carbon. Further confirmation was carried out by elemental analysis. Stereochemistry around the dihydropyran ring was assigned as *syn* by NOESY spectrum,where the targeted protons at 5th and 7th position showed strong n*O*e interactions.

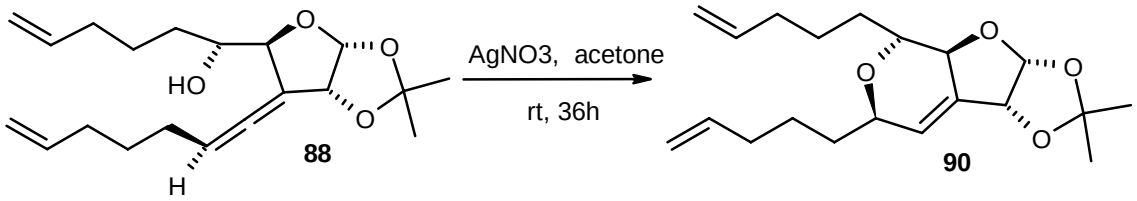


Compound-**89**

Figure 14 *nOe* studies on 89

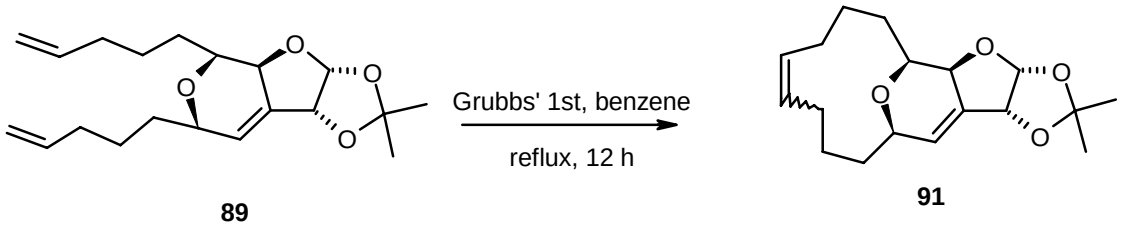
Compound **88** was exposed to $AgNO_3$ in anhydrous acetone gave dihydropyrandiene **90** exclusively. The ^1H NMR spectrum of **90** the ring olefinic methine proton signal was apparent at δ 5.83 ppm as a singlet. The allylic methine protons linked to oxygen atom of dihydropyran ring was observed at δ 4.18 ppm while other methine proton linked to ring oxygen appeared at δ 3.06 ppm. In the ^{13}C NMR spectrum the ring olefinic carbon signals observed at δ 134.1 and 126.4 ppm while –CH carbons linked to oxygen atom of dihydropyran ring was observed at δ 72.3 and 67.9 ppm respectively. Elemental analysis

Scheme 22



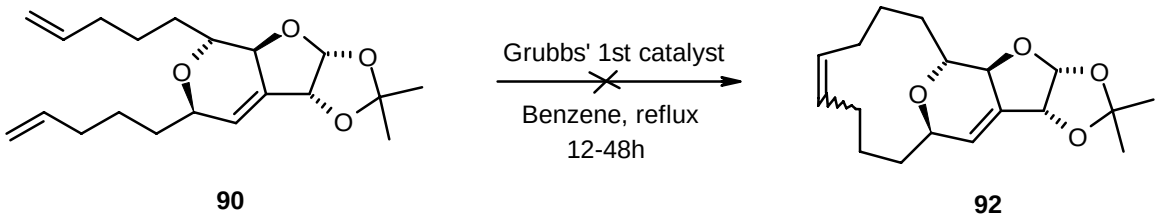
data also supported the formation of **90**. The stereochemistry around the dihydropyran ring was assigned by *NOESY* spectrum, where the H-5 proton was not showing n*O*e interaction with H-7 indicating they have anti conformation (Scheme 22).

Scheme 23



Having *syn*diene **89** in hand**,** we carried out ring closing metathesis reaction following earlier conditions. Accordingly 10 mol% of Grubbs'1st generation catalyst was treated to **89** in degassed benzene under argon atmosphere. The reaction mixture was refluxed for 12 h furnished cyclic compound **91**. In the ^{1}H NMR spectrum of **91** the characteristic olefinic protons signals were identified at δ 5.31-5.21 (m, 2H) ppm.^{13}C NMR spectrum showed a peak at δ 130.5 ppm corresponding to olefinic carbons. Although, we obtained only single isomer but the geometry wasn't determined as the olefinic protons appeared as a complex multiplet (Scheme 23).

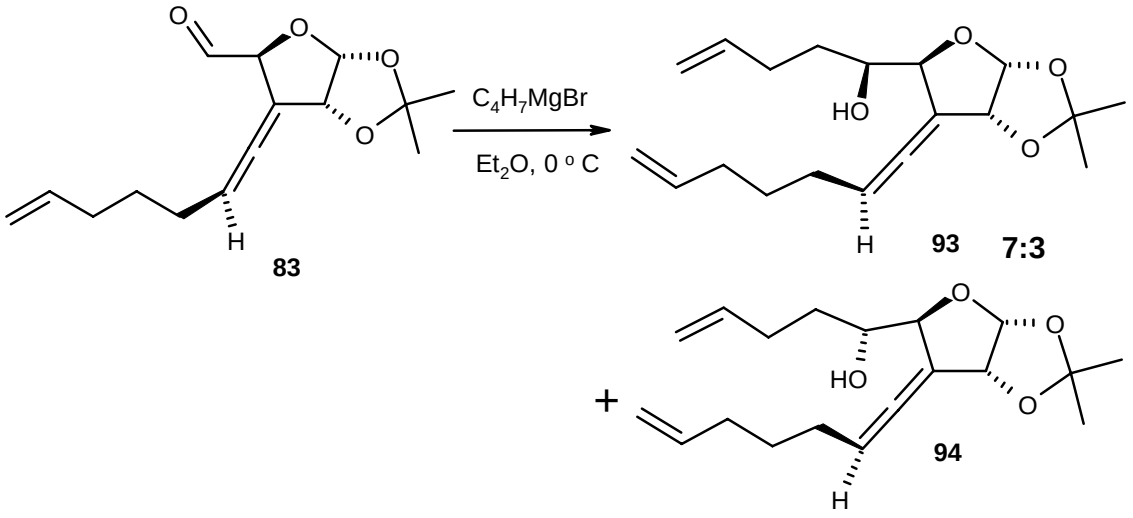
Scheme 24



Treatment of Grubbs'1st generation catalyst on anti dihydropyran diene **90** in degassed benzene under argon atmosphere refluxed for 12-48 h turned out to be unsuccessful. Here we have examined various conditions but in all cases we failed to achieve compound **92**

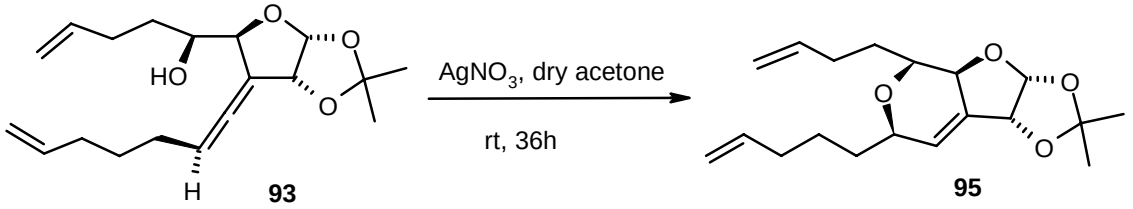
(Scheme 24). After the successful synthesis of eleven membered cyclic ring **91** we envisaged of making ten and nine membered cyclic ring following same strategies.

Scheme 25



Accordingly, treatment of butenyl magnesium bromide on aldehyde **83**, at 0 ^{o}C in anhydrous Et_2O resulted in diastereomeric mixture **93** and **94** in 7:3 ratio. The structural features of **93** and **94** were deduced from ^{1}H, ^{13}C and elemental analysis (Scheme 25).

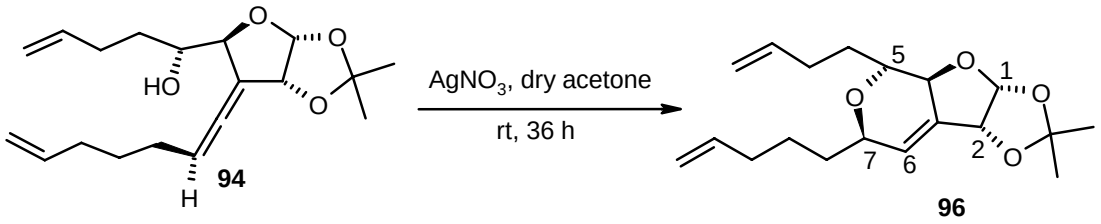
Scheme 26



The β-allenic alcohol **93** subjected with Ag(I), in anhydrous acetone at room temperature for 36 h resulted in **95**. ^{1}H NMR spectrum of compound **95** showed the methine proton signal of ring olefin at δ 6.0 ppm while the allylic methine proton linked to oxygen atom of dihydropyran ring resonated at δ 3.73 ppm and other oxymethine proton observed at δ 3.68 ppm. In the ^{13}C NMR spectrum the –CH carbon of ring olefin observed at δ130.3 ppm and the quaternary carbon of olefin observed at δ 136.3 ppm. The –CH carbons linked to oxygen atom of dihydropyran ring was resonated at δ 72.9 and 70.4 ppm. The stereochemistry around the dihydropyran ring was assigned as *syn* with respect to C5

proton by NOESY study, where the targeted oxymethine protons showed strong n*O*e interactions. The elemental analysis data also supported the formation of **95** (Scheme 26).

Scheme 27



Cycloetherification of **94** was carried out with $AgNO_3$ in anhydrous acetone at room temperature in 36 h gave **96** exclusively. In the ^{1}H NMR spectrum of **96** the methine proton of ring olefin resonated at δ 5.78-5.70 ppm while the allylic methine proton linked to oxygen atom of dihydropyran ring resonated at δ 4.20-4.15 ppm and other oxymethine proton observed at δ 3.03 ppm. In the ^{13}C NMR spectrum the –CH carbon of ring olefin observed at δ 126.7 ppm while the quaternary carbon at δ 136.2 ppm. The –CH carbons linked to oxygen atom of dihydropyran ring was resonated at δ 72.9 and 70.6 ppm (Scheme 27). As above mentioned the stereochemistry of the substituted dihydropyran ring **95** was *syn* as the oxymethine protons showed strong interactions. But in the NOESY spectrum of **96** the oxymethine protons linked to oxygen atom of dihydropyran ring wasn't

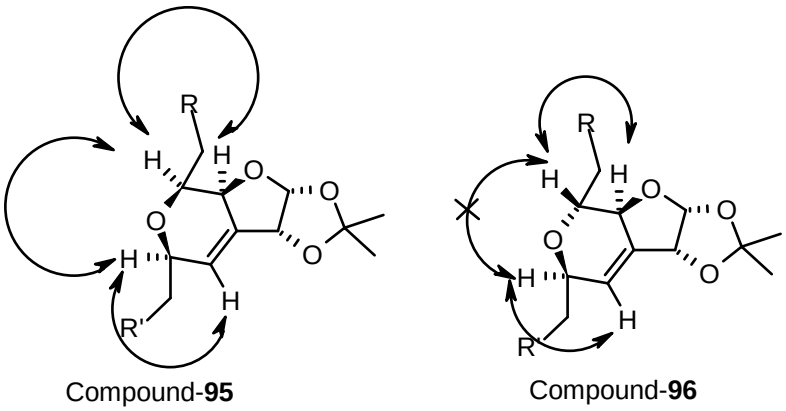
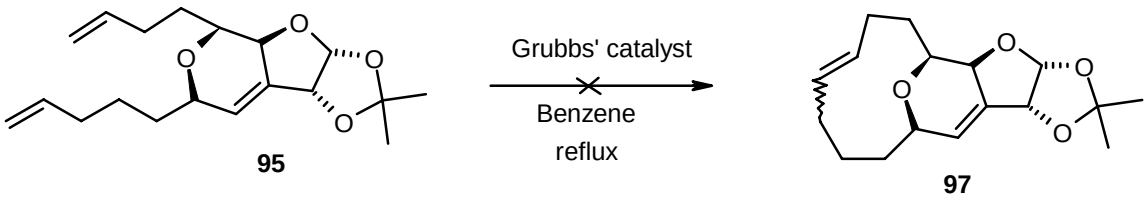


Figure 15. *nOe* studies on 95 and 96

showing any interaction assigning anti confirmation (Figure 15). Now both the diene moiety were ready for ring closing metathesis. We have first attempted on the syndiene **95**.

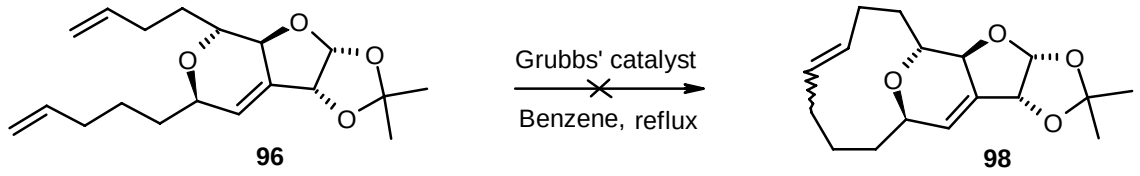
Scheme 28



95 **97**

Compound **95** was subjected with Grubbs 1st generation catalyst (20 mol %) in degassed benzene under argon atmosphere didn't give **97**. Here, we have repeated same sort of reaction by using Grubbs' 2nd generation catalyst in different solvent also failed to achieve **97** (Scheme 28).

Scheme 29



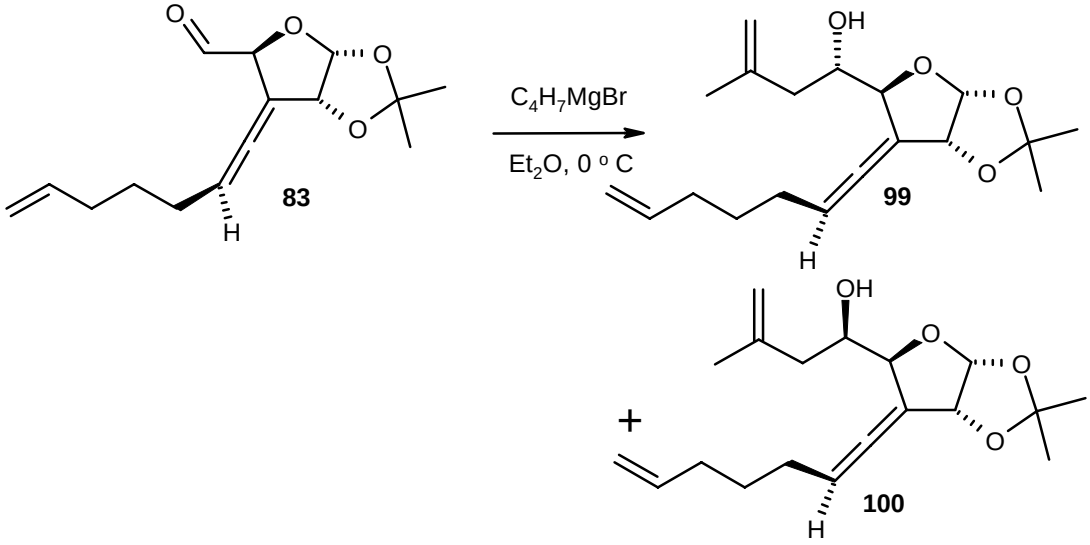
96 **98**

Being failed to achieve ten membered cyclic ring **97** from **95,** we planned to do same reaction in anti diene substrate **96** to check the feasibility of RCM reaction. Treatment of Grubbs' 1st generation/2nd catalyst on **96** in degassed benzene/CH_2Cl_2 under argon atmosphere also failed to achieve the cyclic compound **98**, but some complex reaction mixture was obtained (Scheme 29).

As we becames unsuccessful to achieve the ten-membered cyclic ring in both syn and anti dihydropyran diene, we selected a suitable substrate to examine the feasibility of 9-membered cyclic ring. Accordingly, treatment of methallyl magnesium chloride at 0 ^oC on aldehyde **83** in anhydrous Et_2O, resulted in diastereomeric mixture **99** and **100** in 7:3 ratio. Both the diastereomer were seperated by flash silica gel chromatography (Scheme-30). Newly generated stereogenic center at C5 in **99** and **100** was assumed as *S* and *R* by previous report.[50] Compound **99** and **100** were confirmed by ^1H, ^{13}C and elemental analysis. In the ^1H NMR spectrum of **99** due to methallyl group one new methyl signal appeared at δ 1.77 ppm integrating for three protons and the terminal methylene protons of olefin resonated at δ 4.86–4.82 ppm integrating to two protons. The methine proton linked to –OH group observed at δ 3.73 ppm. In the ^{13}C NMR spectrum the $–CH_2$ carbon of olefin

resonated at δ 113.2 ppm. Similarly in the ^{1}H NMR spectrum of **100** the methyl proton signals appeared at δ 1.77 ppm integrating for three protons and the methylene protons observed at

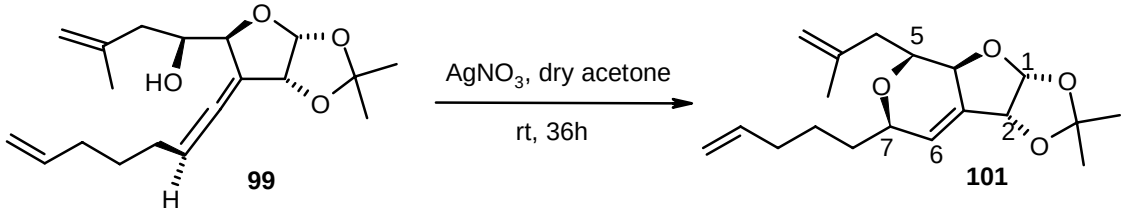
Scheme 30



δ 4.99–4.91ppm due to methallyl olefin. Elemental analysis data also supported the formation of **99** and **100** (Scheme 30).

Having β-allenic alcohols **99** and **100** we planned to carryout cycloetherification to prepare the precursor for ring closing metathesis reaction. Accordingly compound **99** was subjected with $AgNO_3$ in anhydrous acetone in room temperature stirring for 36 h resulted in **101**. ^{1}H NMR spectrum of **101** the allenic proton signal was disappeared and the ring olefinic

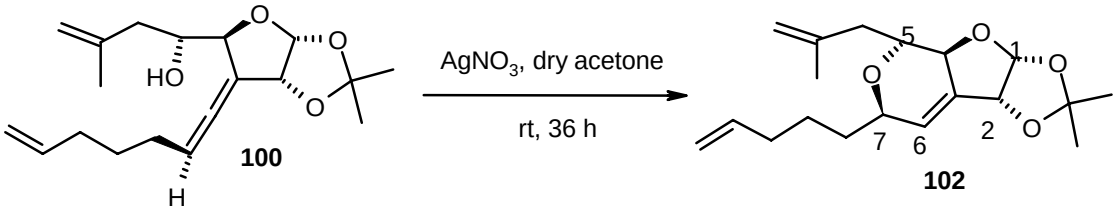
Scheme 31



proton signal was observed at δ 6.04 ppm as a triplet integrating to one proton. The allylic oxymethine proton of dihydropyran ring was identified at δ 3.85 ppm while other oxymethine proton resonated at δ 3.76 ppm. The methine proton corresponding to ring olefin was apparent at δ 6.04 ppm appeared as a triplet. In the ^{13}C NMR spectrum the –CH

carbons linked to oxygen atom of dihydropyran ring was identified at δ 73.4 and 70.8 ppm respectively while –CH and the quaternary carbon signals of ring olefin was observed at δ 130.8 and 136.2 ppm.(Scheme 31).

Scheme 32



Having *syn* dihydropyran **101** in hand, we planned to synthesize the *ant*i dihydropyran diene **102** from **100**. Accordingly, compound **100** was subjected with Ag(I) in anhydrous acetone furnished **102** in good yield. In the ^{1}H NMR spectrum of **102** the allenic proton signal was absent and the ring olefinic proton was resonated at δ 5.85 ppm. Further confirmation was carried out by ^{13}C and DEPT NMR study. The stereochemistry around the dihydropyran ring of **101** and **102** was assigned as *syn* and *anti* by NOESY studies.

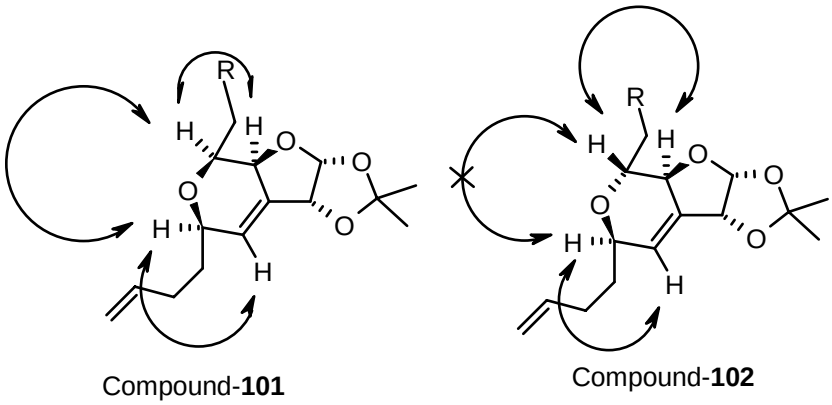
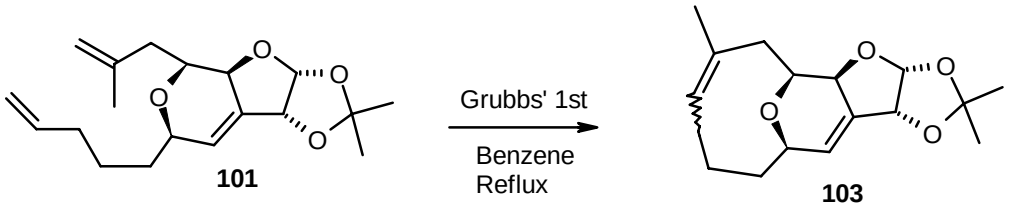


Figure 16. *nOe* studies on 101 and 102

To check the feasibility of 9-membered-cyclic-ring formation, Compound **101** was subjected with Grubbs 1st generation catalyst in degassed benzene refluxed for 12-36 h, afforded desired cyclic compound **103**. The resulted compound was confirmed by ^{1}H, ^{13}C and elemental analysis (Scheme 33).

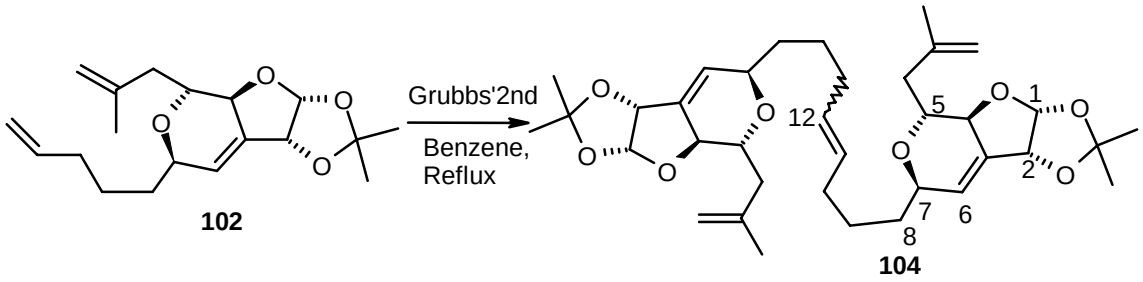
Scheme 33



101 **103**

In the ^{1}H NMR spectrum of **103** the olefinic protons of the 9-membered-ring was appeared at δ 5.53 ppm as a triplet. Similarly, in the ^{13}C NMR spectrum the –CH carbon of olefin was apparent at δ127.2 ppm while the quaternary carbon was observed at δ 135.7 ppm and all other carbons resonated at their expected position confirming the assigned structure. Although, we got only single isomer but the geometry wasn't determined as the olefinic protons were appeared as complex multiplet. In addition the elemental and mass analysis data also supported the formation of **103** (Scheme 33).

Scheme 34

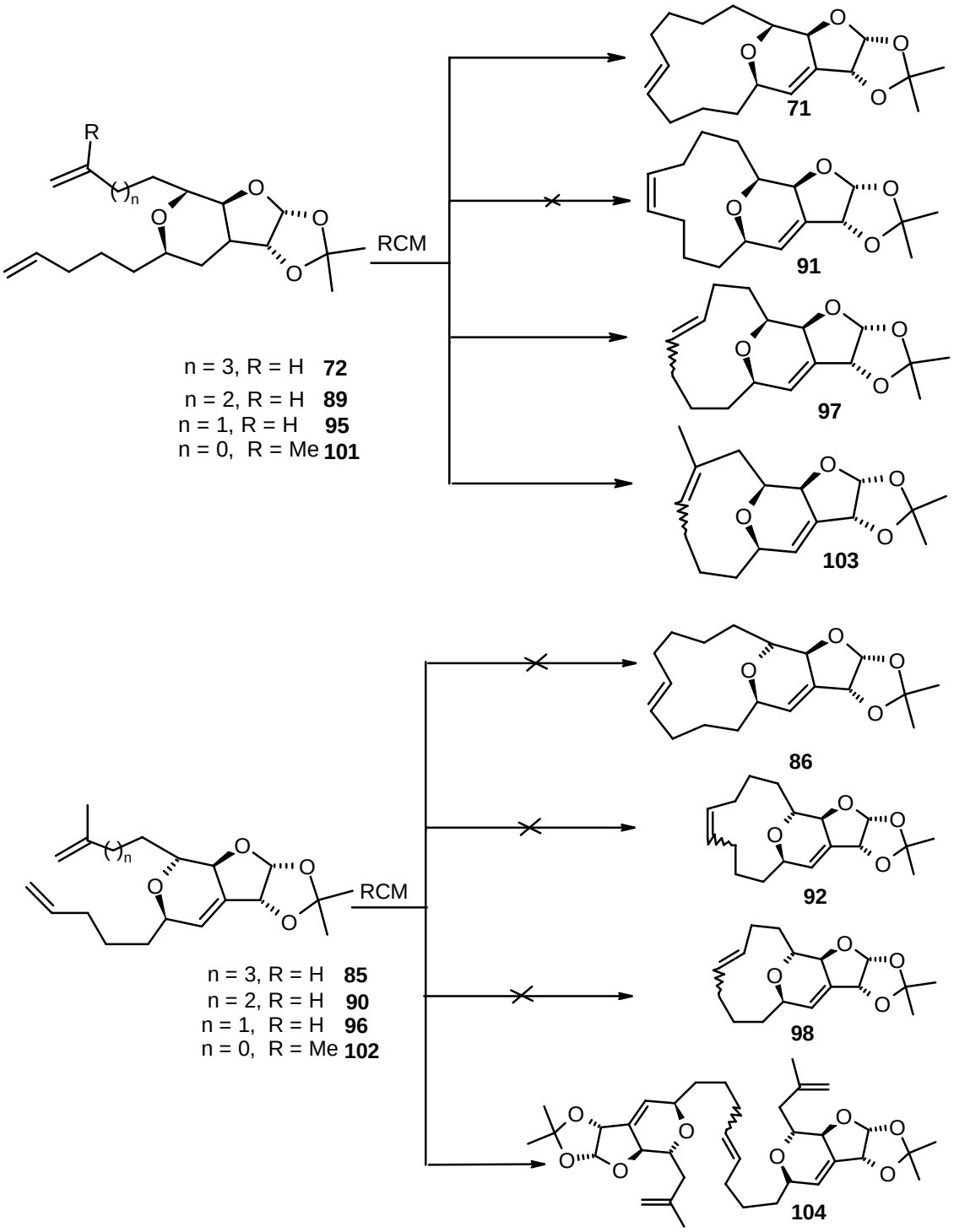


102 **104**

Successful synthesis of **103** inspired us to carryout RCM reaction on anti dihydropyran diene **102**. Accordingly, treatment of Grubbs'1st generation catalyst in degassed benzene at reflux condition afforded some polymeric mixture but failed to give desired cyclic product. But treatment of Grubbs' 2nd generation catalyst on **102** at refluxing benzene surprisingly, furnished a dimeric product **104** in 76% yield. After a thorough analysis of ^{1}H NMR spectrum of **104**, we found nine protons observed at δ 5.83 to 3.25 ppm while in the nine membered cyclic product **103** seven protons observed in that region. Presence of two additional proton signals indicating the formation of dimeric structure **104**. In the ^{13}C

NMR spectrum the C11 and C12 olefinic carbon signals were resonated at δ 130.2 and 129.7 ppm, all other signals appeared at their respective values. Elemental analysis and mass spectrometry data also supported the formation of dimeric structure of **104** (Scheme 34).

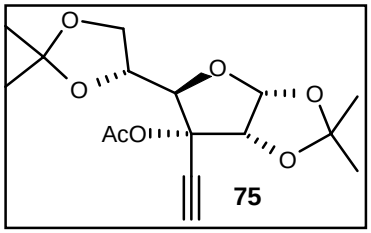
Summary:



We have synthesized stereoselectively the sugar allene and explored its synthetic potential by regioselective mode of cycloetherification. RCM approach for the synthesis of oxa-bridged-bicyclic-ring with different ring sizes was studied and observed that only *syn* diene substrates underwent ring closing metathesis whereas the *anti* dienes yielded dimeric and polymeric components.When the ring size was 12, 11, and 9 the RCM of *syn* diene gave single cyclic product.

EXPERIMENTAL

3-*C*-Ethynyl-3-*O*-acetyl-1,2:5,6-di-*O*-isopropylidene-*α*-D-allofuranose (75)

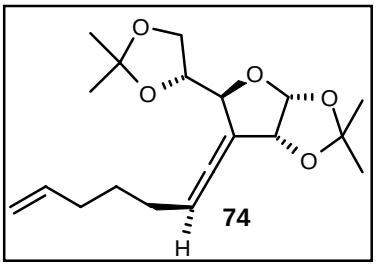


75

To a solution of compound **76** (20 g, 79.3 mmol) in anhydrous CH_2Cl_2 (200 mL), pyridine (4.5 mL, 158.6 mmol) were added Ac_2O (11.24 mL, 119.0 mmol) and cat.DMAP (0.960 g, 0.793 mmol) and stirred at room temperature for 30 min. The reaction mixture was diluted with water, extracted with CH_2Cl_2, washed with saturated aq.$NaHCO_3$, dried (Na_2SO_4) and Concentrated. The residue purified by silica gel column chromatography (30% EtOAc/light petroleum) to give **75** (19.05 g) as a yellow solid. R_f = 0.5 (60% EtOAc/light petroleum)

Yield	83%
Mol.Formula	$C_{16}H_{22}O_7$
$[\alpha]_D^{25}$	29.3 (*c* 1.1, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	3304, 3019, 2991, 2936, 2119, 1751, 1642, 1559, 1455, 1383, 1374, 1217, 1166, 1078, 668, 512
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 5.84 (d, *J* = 3.5 Hz, 1H), 5.12 (d, *J* = 3.5 Hz, 1H), 4.40 (m, 1H), 4.11–4.06 (m, 3H), 2.72 (s, 1H), 2.12. (s, 3H), 1.53 (s, 3H), 1.47 (s, 3H), 1.37 (s, 3H), 1.33 (s, 3H).
^{13}C NMR ($CDCl_3$, 50MHz)	168.4, 113.2, 109.4, 104.1, 82.8, 80.3, 77.9, 77.8, 77.7, 74.5, 66.4, 26.8, 26.7, 26.5, 25.3, 20.8
Elemental Analysis	**Calcd:** C, 58.8; H, 6.74 **Found:** C, 58.53; H, 6.87

1,2:5,6-di-*O*-isopropylidene-3-deoxy-3-*C*-(3-octa-1,7-dienylidene)-*α*-D-ribo-hexofuranose (74)

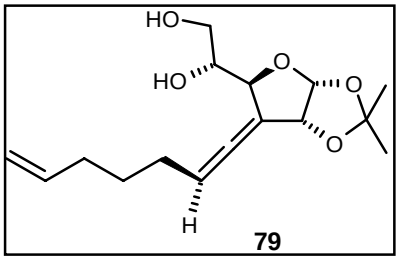


To a suspension of magnesium (4.65 g, 194 mmol) in anhydrous THF (250 mL), pentenyl bromide (19.3 mL, 129.4 mmol) was added dropwise at 0 ^{o}C and stirred for 45 min. The resulted Grignard solution was added dropwise to the premixed solution of **75** (18.2 g, 64.7 mmol) and CuBr (18.6 g, 129.4 mmol) in THF (150 mL) at -10 ^{o}C and the resulting solution was stirred for another 1h at same temperature. Reaction mixture was poured into the cold saturated solution of NH_4Cl and stirred for 30 min. The resulting suspension was filtered, and washed with ethylacetate. Organic layer was seperated and the aqueous layer was extracted with ethylacetate (5 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silicagel column chromatography (30% EtOAc:light petroleum) to afford **74** (13.31g) as a colorless liquid. $R_{f=}$ 0.5 (30% Ethylacetate/light petroleum)

Yield	71 %
Mol.Formula	$C_{19}H_{28}O_5$
$[\alpha]_D^{25}$	164.8 (*c* 2.7, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	3017, 2988, 2936, 1977, 1640, 1064, 1045
^{1}H NMR ($CDCl_3$, 500 MHz)	δ 5.84 (d, *J* = 3.9 Hz, 1H), 5.78 (m, 1H), 5.52 (m, 1H), 5.04–4.94 (m, 3H), 4.83 (t, *J* = 3.9 Hz, 1H), 4.12 (dt, *J* = 4.3, 6.6 Hz, 1H), 3.95 (ddd, *J* = 2.5, 6.8, 8.1 Hz, 1H), 3.84 (ddd, *J* = 2.4, 6.4, 8.1Hz, 1H), 2.12–2.06 (m, 4H), 1.56–1.50 (m, 2H), 1.52 (s, 3H), 1.42 (s, 3H), 1.36 (s, 3H), 1.32 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz)	198.5, 138.1, 115.1, 112.4, 109.62, 105.2, 101.9, 96.2, 82.1, 78.4, 77.5, 65.4, 33.1, 28.1, 28.0, 27.4, 26.4, 25.4.
Elemental Analysis	**Calcd:** C, 67.85; H, 8.33 **Found:** C, 67.77; H, 8.61.

1, 2-*O*-isopropylidene-3-deoxy-3-*C*-(3-octa-1,7-dienylidene)-*α*-D-ribo-hexofuranose (79)



79

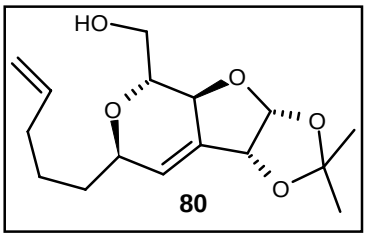
A solution of **74** (15.8 g) in MeOH (150mL) was stirred with 0.8% H_2SO_4 (75 mL) at room temperature for 8 h. Reaction mixture was neutralized by adding saturated $NaHCO_3$ solution portion wise, concentrated, diluted with water and extracted with ethylacetate (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (60% EtOAc:light petroleum) to afford **79** (10.5 g) as a colourless oil. R_f = 0.3 (50% EtOAc/ light petroleum)

Yield	76%
Mol.Formula	$C_{16}H_{24}O_5$
$[\alpha]_D^{25}$	159.2 (*c* 5.8, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	3600, 2988, 2936, 1977, 1640, 1064, 1045 cm^{-1}
^{1}H NMR ($CDCl_3$, 300 MHz)	δ 5.84 (d, *J* = 3.6 Hz, 1H), 5.76 (m, 1H), 5.56 (m, 1H), 5.06 (m, 1H), 4.96 (m, 1H), 4.83 (t, *J* = 3.6 Hz, 1H), 3.74–3.67 (m, 4H), 2.95 (brs, 1H), 2.60 (brs, 1H), 2.14–2.07 (m, 4H), 1.67–1.56 (m, 2H), 1.52 (s, 3H),

1.36 (s, 3H)

^{13}C NMR ($CDCl_3$, 75MHz)	197.9, 137.9, 114.9, 112.2, 104.8, 101.7, 96.5, 82.0, 79.6, 73.5, 62.6, 32.9, 28.1, 27.9, 27.1
Elemental Analysis	**Calcd:** C, 64.86; H, 8.10
	Found: C, 65.07; H, 8.30.

Compound 80



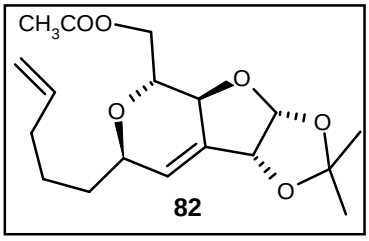
80

To a solution of β-allenic alcohol **79** (14.5 g, 48.9 mmol) in anhydrous acetone (100 mL), $AgNO_3$ (4.15 g, 24.49 mmol) was added and stirred for 12 h at rt. Reaction mixture was concentrated and purified by flash silica gel chromatography (15% EtOAc:light petroleum), to give dihydropyran **80** (11.16 g) as a colourless liquid. R_f = 0.5 (20% EtOAc/lightpetroleum)

Yield	77 %
Mol.Formula	$C_{16}H_{24}O_5$
$[\alpha]_D^{25}$	33.8 (*c* 2.4, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	3400, 2900 cm^{-1}
^{1}H NMR ($CDCl_3$, 500 MHz)	δ 5.86 (t, *J* = 1.8 Hz, 1H), 5.79 (d, *J* = 3.7 Hz, 1H), 5.78 (ddt, *J* = 6.8, 10.2, 16.9 Hz, 1H), 5.02 (ddd, *J* = 1.4, 3.2, 16.9 Hz, 1H), 4.97 (m, 1H), 4.88 (d, *J* = 3.7 Hz, 1H), 4.38 (dt, *J* = 1.8, 8.4 Hz, 1H), 4.30 (ddd, *J* = 1.8, 4.3, 8.2 Hz, 1H), 3.87 (dd, *J* = 2.8, 11.8 Hz, 1H), 3.70 (dd, *J* = 6.1, 11.8 Hz, 1H), 3.23 (ddd, *J* = 2.8, 6.1,

	8.2 Hz, 1H), 2.11 (dt, *J* = 1.8, 8.2 Hz, 2H), 1.67–1.58 (m, 3H), 1.54 (s, 3H), 1.48 (m, 1H), 1.36 (s, 3H)
^{13}C NMR ($CDCl_3$, 125 MHz)	138.1, 136.4, 126.3, 115.1, 113.0, 105.5, 79.9, 73.1, 72.0, 71.2, 63.2, 33.4, 32.5, 27.1, 26.8, 25.7.
Elemental Analysis	**Calcd:** C, 64.84; H, 8.16 **Found:** C, 65.07; H, 7.98.

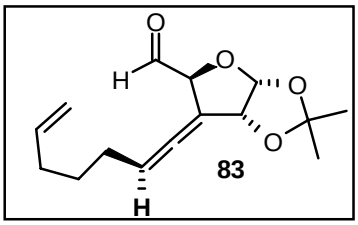
Compound-82



To a solution of **80** (100 mg, 0.41mmol) in anhydrous CH_2Cl_2 (5mL) were added pyridine (24 µL, 0.83 mmol), Ac_2O (59 µL, 0.622 mmol) at 0 ^oC and stirred for 30 min. The reaction mixture was diluted with water, extracted with CH_2Cl_2, washed with saturated aq.$NaHCO_3$, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (5 % EtOAc/lightpetroleum) to give **82** (108 mg, 95%).

Yield	95%
Mol.Formula	$C_{18}H_{26}O_6$
^{1}H NMR ($CDCl_3$, 500 MHz)	δ 5.86–5.78 (m, 3H), 5.02–4.95 (m, 2H), 4.87 (d, *J* = 3.8 Hz, 1H), 4.38–4.30 (m, 2H), 4.15–4.10 (m, 2H), 3.23 (ddd, *J* = 3.1, 6.1, 9.1 Hz, 1H), 2.11–2.07 (m, 2H), 2.1 (s, 3H), 1.66–1.58 (m, 2H), 1.54 (s, 3H), 1.51–1.43 (m, 2H), 1.36 (s, 3H)

Compound-83



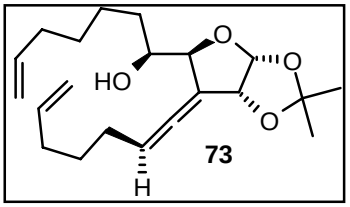
To a solution of **79** (10.2 g, 34.4 mmol) in CH_2Cl_2 (250 mL) silica gel adsorbed $NaIO_4$ (68.8 g) was added and stirred for 1 h. Reaction mixture was filtered and concentrated to give crude aldehyde **83** (6.54 g) as a yellowish liquid. R_f = 0.4 (50% EtOAc/lightpetroleum)

Yield	72%
Mol.Formula	$C_{15}H_{20}O_4$
^{1}H NMR ($CDCl_3$, 500 MHz)	δ 9.39 (s, 1H), 5.98 (d, *J* = 3.9 Hz, 1H), 5.78 (m, 1H), 5.56 (m, 1H), 5.08–5.01 (m, 3H), 4.96 (d, *J* = 10.3 Hz, 1H), 2.15–2.09 (m, 6H), 1.54 (s, 3H), 1.40 (s, 3H)

Addition of 5-hexenyl-MgBr to aldehyde 83:

Hexenylmagnesium bromide was prepared by slow addition of hexenyl bromide (19.8 mL, 0.09 mol) to the solution of magnesium turnings (4.5 g, 0.19 mol) in ether (50 mL) at 0 ^oC and was stirred for 30 min. The resulting Grignard solution was added dropwise to the solution of aldehyde **83** (6.54 g) in Et_2O (100 mL) at 0 ^oC and stirred for another 30 min. Reaction mixture was quenched by slow addition of saturated NH_4Cl and the resulting suspension stirred for another 30 min. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The crude oily material was purified by flash silica gel column chromatography (15-20% EtOAc/light petroleum), furnish **73** (4.69 g) and its diastereomer **84** (2.01 g) in 7:3 ratio as colourless liquid having 61% yield over two steps.

1,2-*O*-isopropylidene-3-deoxy-3-*C*-(3R-octa-1,7-dienylidene)-6,7,8,9, 10,11 hexadeoxy -β-L-*lyxo*-undec-10-enofuranose (73)

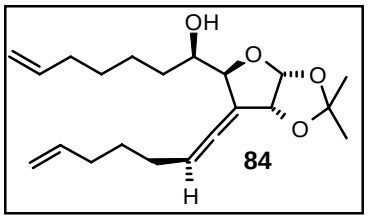


73

R_f = 0.42 (20% EtOAc/ light petroleum).

Mol.Formula	$C_{21}H_{32}O_4$
$[\alpha]_D^{25}$	145.9 (*c* 1.4, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 500 MHz)	δ 5.78 (d, *J* = 3.6 Hz, 1H), 5.75–5.67 (m, 2H), 5.46 (m, 1H), 4.99 (s, 1H), 4.95–4.84 (m, 4H), 4.56 (m, 1H), 3.43 (m, 1H), 2.05–1.93 (m, 8H), 1.59–1.47 (m, 6H), 1.45 (s, 3H), 1.30 (s, 3H)
^{13}C NMR ($CDCl_3$, 125 MHz)	198.0, 138.5, 137.9, 114.9, 114.3, 112.1, 104.8, 102.1, 96.6, 82.2, 81.0, 72.2, 33.6, 33.5, 33.0, 28.8, 28.0, 27.9, 27.2, 27.1, 25.1
Elemental Analysis	**Calcd:** C, 72.41; H,9.19
	Found: C, 72.18; H,9.32

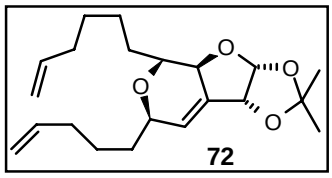
1,2-*O*-isopropylidene-3-deoxy-3-*C*-(3*R*-octa-1,7-dienylidene)-6,7,8,9,10,11hexadeoxy-β-L-*ribo*-undec-10-enofuranose (84)



84

Mol.Formula	$C_{21}H_{32}O_4$
$[\alpha]_D^{25}$	149.7 (*c* 0.8, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 500 MHz)	δ 5.78 (d, *J* = 3.8 Hz, 1H), 5.75-5.67 (m, 2H), 5.46 (m, 1H), 4.99 (d, *J* = 3.8 Hz, 1H), 4.96–4.86 (m, 4H), 4.59 (t, *J* = 3.6 Hz, 1H), 3.46 (m, 1H), 2.07–1.97 (m, 8H), 1.59–1.48 (m, 6H), 1.46 (s, 3H), 1.31 (s, 3H)
^{13}C NMR ($CDCl_3$, 200 MHz)	198.0, 138.5, 137.9, 115.0, 114.4 112.2, 105.0, 101.3, 96.2, 82.2, 81.8, 73.3, 33.6, 33.1, 31.5, 28.8, 28.2, 27.3, 25.3.
Elemental Analysis	**Calcd:** C, 72.41; H,9.19 **Found:** C, 72.14; H,9.28

Compound72



72

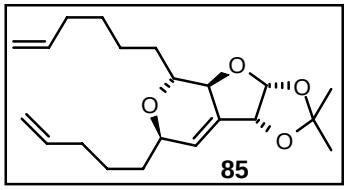
To a solution of **73** (6.0 g , 17.0 mmol) in anhydrous acetone (75 mL), $AgNO_3$ (292 mg, 1.7 mmol) was added and stirred for 36 h at rt. Reaction mixture was concentrated and purified by silica gel chromatography (15-20% EtOAc/lightpetroleum), to afford the 2,6 *syn*–dihydropyran diene **72** (5.58 g) as a colourless liquid.

$\mathbf{R}_f$ = 0.3 (20% EtOAc/ light petroleum)

Yield	93%
Mol.Formula	$C_{21}H_{32}O_4$
$[\alpha]_D^{25}$	70.0 (*c* 0.9, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 500 MHz)	δ 5.99 (t, *J* = 1.9 Hz, 1H), 5.83–5.74 (m, 2H), 5.66 (d, *J* = 3.6 Hz, 1H), 5.02–4.91 (m, 4H), 4.80 (d, *J* = 3.6 Hz, 1H), 4.18 (m, 1H), 3.72 (m, 1), 3.63 (dt, *J* = 10.2,

	5.0 Hz, 1H), 2.10–2.06 (m, 4H), 1.76–1.69 (m, 2H), 1.64–1.59 (m, 4H), 1.53 (s, 3H), 1.51–1.39 (m, 4H), 1.34 (s, 3H)
^{13}C NMR ($CDCl_3$, 50 MHz)	138.7, 138.3, 136.1, 130.6, 114.6, 114.1, 111.6, 103.3, 79.2, 76.3, 73.1, 70.6, 34.2, 33.4, 33.3, 29.9, 28.7, 26.4, 26.0, 25.3, 24.7
Elemental Analysis	**Calcd:** C, 72.41; H,9.19
	Found: C, 72.65; H, 9.34

Compound 85

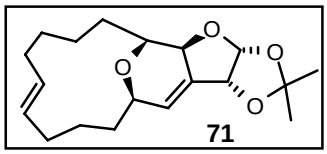


R_f = 0.3 (20% EtOAc/ light petroleum)

2,6-*anti*-dihydropyran diene **85** was prepared from compound **84** following the same procedure as that for compound **72**.

Yield	91%
Mol.Formula	$C_{21}H_{32}O_4$
$[\alpha]_D^{25}$	70.0 (*c* 0.9, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 500 MHz)	δ 5.75 (t, *J* = 1.9 Hz, 1H), 5.74–5.65 (m, 3H), 4.96–4.85 (m, 4H), 4.82 (d, *J* = 3.6 Hz, 1H), 4.16–4.11 (m, 2H), 3.0 (dt, *J* = 2.8, 11.1 Hz, 1H), 2.07–1.96 (m, 4H), 1.75 (m, 1H), 1.58–1.49 (m, 5H), 1.48 (s, 3H), 1.46–1.40 (m, 2H), 1.38–1.33 (m, 2H), 1.29 (s, 3H)
^{13}C NMR ($CDCl_3$, 125 MHz)	138.9, 138.3, 136.3, 126.9, 114.8, 114.2, 112.7, 105.1, 80.0, 75.4, 73.0, 71.4, 33.6, 33.4, 33.0, 32.4, 28.8, 27.0, 26.6, 25.7, 24.8
Elemental Analysis	**Calcd:** C, 72.41; H,9.19
	Found: C, 72.65; H, 9.34

Compound-71

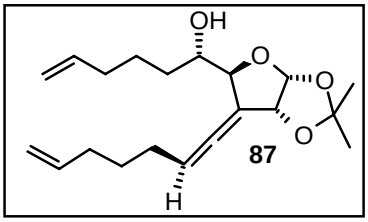


Grubbs'1st generation catalyst (0.0172 mmol, 20 mol%) was added to a solution of compound **72** (300.0 mg, 0.862 mmol) in anhydrous benzene (200 mL) and degassed under argon atmosphere and then refluxed for 12 h. The solvent was evaporated and the residue was purified by flash silica gel chromatography (10% EtOAc/lightpetroleum) furnished the compound **71** (129 mg) as a froathing solid (minor component) and the major component was the noncharacterisable polymeric mixture. $\mathbf{R}_f$ = 0.6 (20% EtOAc/ light petroleum)

Yield	47%
Mol.Formula	$C_{19}H_{28}O_4$
$[\alpha]_D^{25}$	22.6 (*c* 1, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 500 MHz)	δ 5.86 (t, *J* = 1.8 Hz, 1H), 5.67 (d, *J* = 3.7 Hz, 1H), 5.33 (dt, *J* = 7.5, 15.3 Hz, 1H), 5.11 (dt, *J* = 6.9, 15.3 Hz, 1H), 4.79 (d, *J* = 3.7 Hz, 1H), 4.40 (dt, *J* = 1.8, 5.5 Hz, 1H), 3.90 (ddd, *J* = 2.0, 4.2, 12.1Hz, 1H), 3.75 (ddd, *J* = 1.5, 5.4, 11.9 Hz, 1H), 2.03 (dt, *J* = 6.8, 12.1 Hz, 1H), 1.96–1.90 (m, 1H), 1.87–1.79 (m, 2H), 1.58–1.49 (m, 8H), 1.47 (s, 3H), 1.39–1.32 (m, 2H), 1.30 (s, 3H)
^{13}C NMR ($CDCl_3$, 125 MHz)	135.1, 133.7, 129.4, 129.0, 112.3, 104.4, 79.7, 73.0, 72.5, 71.3, 33.6, 31.5, 30.7, 28.9, 26.9, 26.6, 26.2, 25.3, 19.6
Elemental Analysis	**Calcd:** C, 71.25; H,8.75 **Found:** C, 71.55.; H,8.80

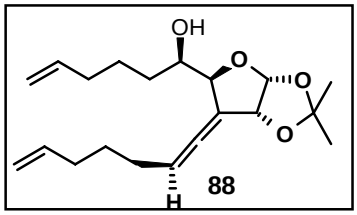
A solution of aldehyde **83** (8 g) in dry Et_2O (150 mL) was treated with 4-pentenyl magnesium bromide {prepared from pentenyl bromide (19.8 mL) and Mg (4.5 g, 190.0 mmol, Et_2O (50 mL) and stirred for 1h. Usual workup was followed and purification by chromatography (15-20% EtOAc/lightpetroleum) yielded **87**(6.8g) and **88** (2.94 g) as colourless liquid.

1,2-*O*-isopropylidene-3-deoxy-3-*C*-(3*R*-octa-1,7-dienylidene)-6,7,8,9,10,pentadeoxy-β-L-*lyxo*-deca-9-enofuranose (87)



Mol Formula	$C_{20}H_{30}O_4$
$[\alpha]_D^{25}$	158.8 (*c* 3.3, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 500 MHz)	δ 5.85 (d, *J* = 3.7 Hz, 1H), 5.82–5.74 (m, 2H), 5.55 (m, 1H), 5.07(d, *J* = 3.7 Hz, 1H), 5.03-4.93 (m, 4H), 4.65 (t, *J* = 3.6 Hz, 1H), 3.52 (m, 1H), 2.12–2.07 (m, 6H), 1.59–1.54 (m, 6H), 1.53 (s, 3H), 1.37 (s, 3H).
^{13}C NMR ($CDCl_3$, 125MHz)	198.1, 138.5, 138.1, 115.1, 114.8, 112.4, 105.0, 102.2, 96.9, 82.3, 81.1, 72.3, 33.7, 33.2, 33.1, 28.2, 28.1, 27.4, 27.3, 25.1.
Elemental Analysis	**Calcd:** C, 71.85; H,8.98 **Found:** C,71.73; H,9.12

1,2-*O*-isopropylidene-3-deoxy-3-*C*-(3*R*-octa-1,7-dienylidene)-6,7,8,9,10, pentadeoxy-β-L-*ribo*-deca-9-enofuranose (88)

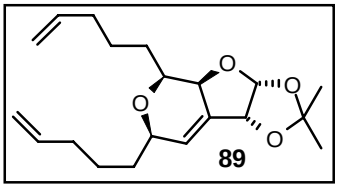


88

$\mathbf{R}_f$ = 0.4 (20% EtOAc/lightpetroleum)

Mol.Formula	$C_{20}H_{30}O_4$
$[\alpha]_D^{25}$	5.8 (*c* 1.3, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 500 MHz)	δ 5.83 (d, *J* = 3.8 Hz, 1H), 5.81–5.74 (m, 2H), 5.52 (m, 1H), 5.05 (d, *J* = 3.8 Hz, 1H), 5.06–5.01 (m, 2H), 4.99-4.93 (m, 3H), 4.66 (t, *J* = 3.6 Hz, 1H), 3.53 (m, 1H), 2.13–2.08 (m, 6H), 1.65–1.54 (m, 6H), 1.53 (s, 3H), 1.37 (s, 3H).
^{13}C NMR ($CDCl_3$, 125MHz)	198.0, 138.5, 138.1, 115.0, 114.7, 112.3, 105.0, 102.5, 96.9, 82.4, 81.0, 72.1, 33.6, 33.2, 33.1, 28.0, 27.8, 27.5, 27.4, 25.0
Elemental Analysis	**Calcd:** C, 71.85; H,8.98 **Found:** C, 71.30; H,8.63

Compound-89



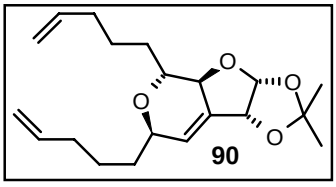
89

The 2,6 disubstituted *cis*-dihydro pyran diene **89** was prepared from compound **87** following the above mentioned procedure, as for compound **72**.

$\mathbf{R_f}$ = 0.4 (20% EtOAc/ light petroleum)

Yield	87%
Mol.Formula	$C_{20}H_{30}O_4$
$[\alpha]_D^{25}$	82.4 (*c* 0.5, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 500 MHz)	δ 6.02 (s, 1H), 5.87-5.76 (m, 2H), 5.69 (d, *J* = 3.6 Hz, 1H), 5.03–4.94 (m, 4H), 4.83 (d, *J* = 3.6 Hz, 1H), 4.22 (m, 1H), 3.74 (m, 1H), 3.66 (m, 1H), 2.13–2.04 (m, 4H), 1.79–1.73 (m, 2H), 1.64–1.56 (m, 6H), 1.54 (s, 3H), 1.35 (s, 3H)
^{13}C NMR ($CDCl_3$, 75 MHz)	138.7, 138.4, 136.3, 130.6, 114.6, 114.4, 111.8, 103.5, 79.4, 76.3, 73.3, 70.8, 34.4, 33.6, 33.4, 29.7, 26.6, 26.2, 25.3, 24.8
Elemental Analysis	**Calcd:** C, 71.85; H,8.98 **Found:** C, 71.65; H,8.59

Compound-90



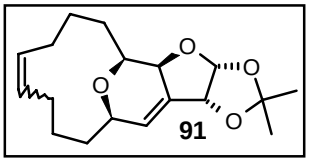
90

The 2,6 disubstituted-*trans*-dihydropyran diene **90** was prepared from compound **88** following the same procedure as that for compound **72**. R_f = 0.4 (20% EtOAc/lightpetroleum)

Yield	91%
Mol.Formula	$C_{20}H_{30}O_4$
$[\alpha]_D^{25}$	33.2 (*c* 0.7, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 500 MHz)	δ 5.83 (s, 1H), 5.81–5.73 (m, 3H), 5.02–4.82 (m, 4H), 4.86 (m, 1H), 4.23–4.22 (br d, 1H), 4.18 (d, *J* = 8.2 Hz, 1H), 3.06 (m, 1H), 2.12–2.04 (m, 4H), 1.82 (m, 1H), 1.65–1.58 (m, 4H), 1.53 (s, 3H), 1.51–1.46 (m, 2H), 1.41(m, 1H), 1.35 (s, 3H)
^{13}C NMR ($CDCl_3$, 125MHz)	138.6, 138.4, 134.1, 126.4, 114.8, 114.7, 112.7, 104.8, 79.9, 73.1, 72.3, 67.9, 34.5, 34.2, 33.7, 27.2, 26.9, 24.9, 24.4, 24.3
Elemental Analysis	**Calcd:** C, 71.85; H,8.98
	Found: C, 71.62; H,8.90

Compound-91



Compound **91** was prepared from **89** using 1st generation Grubbs'catalyst following the same procedure as that for compound **71**.

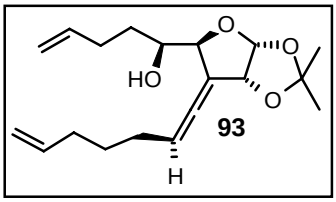
R$_f$ = 0.4 (10% EtOAc/ light petroleum)

Yield	46%
Mol.Formula	$C_{18}H_{26}O_4$
$[\alpha]_D^{25}$	25.2 (*c* 1, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 500 MHz)	δ5.89 (t, *J* = 1.9 Hz, 1H), 5.74 (d, *J* = 3.7 Hz, 1H), 5.31- 5.21 (m, 2H), 4.85 (d, *J* = 3.7 Hz, 1H), 4.34 (m, 1H), 3.89 (d, *J* = 10.8 Hz, 1H), 3.73 (t, *J* = 6.3 Hz, 1H), 2.50 (br s, 1H), 2.31 (m, 1H), 2.21–2.13 (m, 2H), 1.78–1.67 (m, 4H), 1.63–1.56 (m, 2H), 1.52 (s, 3H), 1.49–1.39 (m, 2H), 1.34 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz)	135.4, 130.5, 130.4, 112.3, 104.3, 79.8, 75.2, 74.0, 72.3, 33.8, 28.3, 27.8, 26.9, 26.6, 26.0, 25.6
Elemental Analysis	**Calcd:** C, 70.56; H,8.55
	Found: C, 70.24; H,8.75

A solution of aldehyde **83** (10 g, mmol) in dry Et_2O (250 mL) was treated with 3-butenyl-magnesiumbromide {prepared from butenyl bromide (19.8 mL, 90.0 mmol) and Mg (4.5 g, 190.0 mmol, Et_2O (50 mL)} and stirred for 1h. Usual workup was followed and purification by chromatography (15-20% EtOAc/light petroleum) yielded **93** (9.4g) and its diastereomer **94** (2.32 g) in 8:2 ratio with 71% yield from compound **79** (15.5 g).

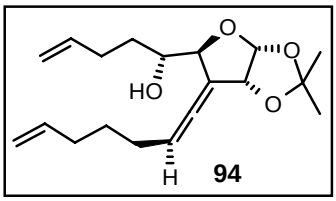
1,2-*O*-isopropylidene-3-deoxy-3-*C*-(3*R*-octa-1,7-dienylidene)-6,7,8,9-tetradeoxy-*β*-L-*lyxo*-nona-8-enofuranose (93)



$\mathbf{R}_f$ = 0.4 (15 % EtOAc/ light petroleum)

Mol.Formula	$C_{19}H_{28}O_4$
$[\alpha]_D^{25}$	18.2 (*c* 1, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 200 MHz)	5.88 (d, *J* = 3.9 Hz, 1H), 5.83–5.69 (m, 2H), 5.55 (m, 1H), 5.1–5.04 (m, 2H), 5.0–4.98 (m, 2H), 4.97–4.93 (m, 2H), 4.67 (m, 1H), 3.55 (m, 1H), 2.16–2.05 (m, 6H), 1.73–1.57 (m, 4H), 1.54 (s, 3H), 1.38 (s, 3H).
^{13}C NMR ($CDCl_3$, 75 MHz)	198.1, 138.0, 137.9, 114.8, 114.7, 104.9, 102.1, 96.7, 82.2, 81.1, 71.8, 32.9, 32.7, 29.7, 28.1, 27.9, 27.3, 27.1.
Elemental Analysis	**Calcd:** C, 71.25; H,8.75
	Found: C, 71.52; H,8.90

1,2-*O*-isopropylidene-3-deoxy-3-*C*-(3*R*-octa-1,7-dienylidene)-6,7,8,9-tetradeoxy-*β*-L-*ribo*-nona-8-enofuranose (94)

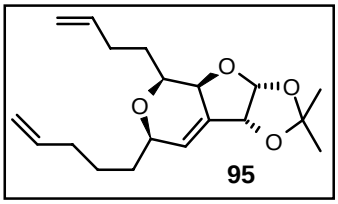


94

$\mathbf{R}_f$ = 0.5 (20% EtOAc/ light petroleum)

Mol.Formula	$C_{19}H_{28}O_4$
$[\alpha]_D^{25}$	22.1 (*c* 1, $CHCl_3$
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 5.86 (d, *J* = 3.9 Hz, 1H), 5.83–5.67 (m, 2H), 5.55 (m, 1H), 5.08–4.94 (m, 5H), 4.78 (t, *J* = 3.9 Hz, 1H), 3.72 (m, 1H), 2.35–2.01 (m, 6H), 1.65–1.58 (m, 4H), 1.53 (s, 3H), 1.38 (s, 3H)
^{13}C NMR ($CDCl_3$, 50 MHz)	198.0, 138.0, 137.9, 114.9, 112.2, 105.0, 101.3, 96.3, 82.2, 81.7, 72.7, 33.0, 30.8, 29.9, 28.1, 28.0, 27.2.
Elemental Analysis	**Calcd:** C, 71.25; H,8.75 **Found:** C, 71.32; H,8.48

Compound-95



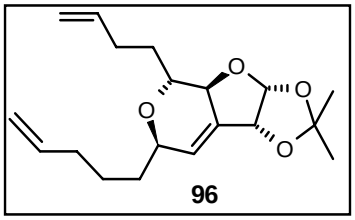
95

Syn dihydropyrandiene **95** was prepared from the β-hydroxy-allene **93** following the same procedure as that for **72**.

Yield	87%

Mol.Formula	$C_{19}H_{28}O_4$
$[\alpha]_D^{25}$	123.6 (*c* 0.5, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 500 MHz)	δ 6.0 (s, 1H), 5.87–5.75 (m, 2H), 5.67 (d, *J* = 3.6 Hz 1H), 5.05–4.94 (m, 4H), 4.80 (d, *J* = 3.6 Hz, 1H), 4.19 (m, 1H), 3.73 (m, 1H), 3.68 (dt, *J* = 10.5, 5.5Hz, 1H), 2.34–2.18 (m, 2H), 2.09 (q, *J* = 6.8, 13.7 Hz, 2H) 1.85–1.81 (m, 2H), 1.66–1.54 (m, 4H), 1.53 (s, 3H), 1.35 (s, 3H)
^{13}C NMR ($CDCl_3$, 50 MHz)	138.1, 138.0, 136.3, 130.3, 114.7, 111.5, 103.3, 95.9, 79.2, 75.2, 72.9, 70.4, 34.2, 33.3, 29.8, 29.1, 26.4, 26.0, 24.6.
Elemental Analysis	**Calcd:** C, 71.25; H, 8.75 **Found:** C, 71.62; H, 8.90

Compound-96



96

2,6 *anti* dihydropyran diene **96** was prepared from the β-hydroxy allene **94** following the same procedure as that for compound **72**.

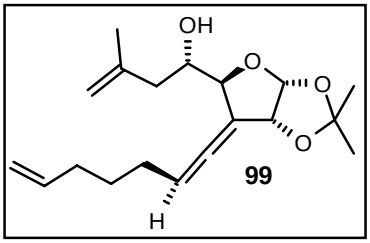
$\mathbf{R}_f$ = 0.5 (20% EtOAc/ light petroleum)

Yield	91%
Mol.Formula	$C_{19}H_{28}O_4$
$[\alpha]_D^{25}$	25.1 (*c* 1, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 500 MHz)	δ 5.78-5.70 (m, 4H), 4.98–4.89 (m, 4H), 4.82 (d, *J* = 3.6 Hz, 1H), 4.20–4.15 (m, 2H), 3.03 (m, 1H), 2.24 (m, 1H), 2.12–1.99 (m, 4H), 1.84 (m, 1H), 1.60–1.50 (m, 4H), 1.47(s, 3H), 1.29 (s, 3H)
^{13}C NMR ($CDCl_3$, 50MHz)	138.2, 136.2, 126.7, 114.9, 114.7, 112.6, 105.0, 96.0, 79.9, 75.2, 72.9, 70.6, 33.4, 32.3, 32.1, 29.4, 27.0, 26.6, 25.7.
Elemental Analysis	**Calcd:** C, 71.25; H,8.75
	Found: C, 71.62; H,8.90

Methallylmagnesiumchloride was prepared by the treatment of methallyl chloride (19.8 mL, 0.09 mol) to the solution of magnesium turnings (4.5 g, 0.19 mol) in THF (100 mL) at 0 ^oC and was stirred for 30 min. The resulting Grignard solution was added dropwise to the crude solution of aldehyde **83** (5 g) in Et_2O (250 mL) at –0 ^oC and stirred for another 30 min. Reaction mixture was quenched by slow addition of saturated NH_4Cl and the resulting suspension stirred for another 30 min. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 150 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The crude oily material was purified by flash silica gel column chromatography (15-20% EtOAc/light petroleum), furnish **99** (5.94g) and its diastereomer **100** (0.59g) in 9:1 ratio with 71% yield from compound **79** (7.75 g).

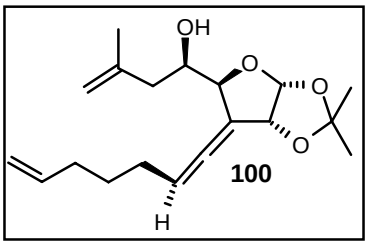
1,2-*O*-isopropylidene-3-deoxy-3-*C*-(3*R*-octa-1,7-dienylidene)-6,8-dideoxy-7-methyl-*β*-L-*lyxo*-octa-7-enofuranose (99)



99

Mol.Formula	$C_{19}H_{28}O_4$
$[\alpha]_D^{25}$	155.7 (*c* 1.1, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 5.89 (d, *J* = 3.9 Hz, 1H), 5.75 (m, 1H), 5.56 (m, 1H), 5.11–5.04 (m, 2H), 4.97-4.93 (m, 2H), 4.86–4.82 (m, 2H), 4.71 (m, 1H), 3.73 (m, 1H), 2.30 (d, *J* = 6.6 Hz, 2H), 2.25–1.96 (m, 6H), 1.77 (s, 3H), 1.53 (s, 3H), 1.38 (s, 3H).
^{13}C NMR ($CDCl_3$, 50 MHz)	197.9, 141.8, 137.9, 114.7, 113.2, 112.2, 104.9, 102.1, 96.7, 82.1, 80.4, 70.0, 41.9, 32.8, 27.9, 27.8, 27.1, 27.0, 22.3.
Elemental Analysis	**Calcd:** C,71.25; H,8.75 **Found:** C, 71.62; H,8.90

1,2-*O*-isopropylidene-3-deoxy-3-*C*-(3*R*-octa-1,7-dienylidene)-6,8-dideoxy-7-methyl-*β*-L-*ribo*-octa-7-enofuranose (100)



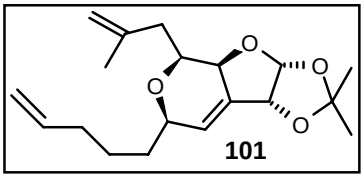
100

Yield	
Mol.Formula	$C_{19}H_{28}O_4$
$[\alpha]_D^{25}$	227.4 (*c* 1.8, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 5.88 (d, *J* = 3.9 Hz, 1H), 5.76 (m, 1H), 5.57 (m, 1H), 5.09–5.04 (m, 2H), 4.99–4.91(m, 2H), 4.88–4.81(m, 3H), 3.88 (m, 1H), 2.24 (d, *J* = 7.04 Hz, 2H), 2.17—2.06 (m, 6H), 1.77 (s, 3H), 1.53 (s, 3H), 1.38 (s, 3H).
^{13}C NMR ($CDCl_3$, 50 MHz)	198.1, 141.9, 137.9, 115.0, 113.5, 112.2, 105.0 101.3,

96.0, 82.2, 81.4, 70.8, 40.0, 33.1, 28.2, 27.3, 22.3.

Elemental Analysis **Calcd** C,71.25; H,8.75
Found: C, 71.62; H,8.90

Compound-101



101

2,6 *syn* dihydropyrandiene **101** was prepared following the same procedure as that for compound **72**.

Yield 78%

Mol.Formula $C_{19}H_{28}O_4$

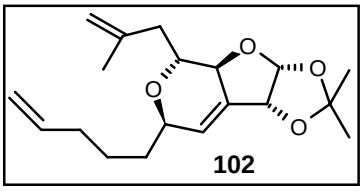
$[\alpha]_D^{25}$ 82.1 (*c* 1, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.04 (t, *J* = 2.03 Hz, 1H), 5.80 (m, 1H), 5.71 (d, *J* = 3.6 Hz, 1H), 5.02–4.94 (m, 2H), 4.84 (d, *J* = 3.6 Hz, 1H), 4.83 (br s, 2H), 4.25 (m, 1H), 3.85 (quin, *J* = 4.5 Hz, 1H), 3.76 (m, 1H), 2.47–2.44 (m, 2H), 2.07 (q, *J* = 6.8 Hz, 2H), 1.81 (s, 3H), 1.65-1.57 (m, 4H), 1.55 (s, 3H), 1.36 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz) 142.7, 138.5, 136.2, 130.8, 114.6, 111.9, 103.5, 79.4, 75.2, 73.4, 70.8, 38.0, 34.3, 33.4, 26.5, 26.2, 24.8, 23.0.

Elemental Analysis **Calcd:** C, 71.85; H,8.98
Found: C, 71.62; H,8.90

Compound-102

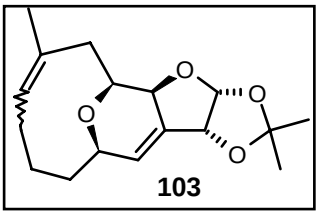


102

2,6 *anti* dihydropyran diene **102** was prepared from the β-alleneic alcohol **100** following the same procedure as that for compound **72**.

Yield	75%
Mol.Formula	$C_{19}H_{28}O_4$
$[\alpha]_D^{25}$	17.1 (*c* 1.2, $CHCl_3$)
^{1} NMR ($CDCl_3$, 200 MHz)	δ 5.85 (t, *J* = 1.9 Hz, 1H), 5.80 (d, *J* = 3.9Hz, 1H), 5.70 (m, 1H), 5.03 (q, *J* = 1.56 Hz, 1H), 4.99–4.91(m, 2H), 4.89 (d, *J* = 3.9 Hz, 1H), 4.81 (br s, 1H), 4.30–4.21 (m, 2H), 3.26 (m, 1H), 2.55 (m, 1H), 2.26–1.96 (m, 4H), 1.77 (s, 3H), 1.66–1.56 (m, 3H), 1.54 (s, 3H), 1.36 (s, 3H).
13C NMR ($CDCl_3$, 50 MHz)	142.0, 138.2, 136.2, 126.6, 114.7, 112.6, 112.3, 104.9 79.9, 74.9, 72.9, 70.3, 40.9, 33.4, 32.3, 27.0, 26.6, 25.5, 22.8
Elemental Analysis	**Calcd:** C, 71.85; H,8.98 **Found:** C, 71.62; H,8.90

Compound-103

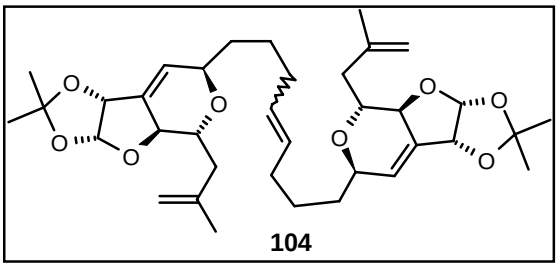


103

Compound **103** was prepared from 2,5 *syn* dihydro pyran diene **101** using Grubbs2nd generation catalyst, following the same procedure as that for compound **71**.

Yield	48%
Mol.Formula	$C_{17}H_{24}O_4$
$[\alpha]_D^{25}$	– 8.9 (*c* 1, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 500 MHz)	δ 5.94 (t, *J* = 1.9 Hz, 1H), 5.84 (d, *J* = 3.7 Hz, 1H), 5.58 (t, *J* = 7.7 Hz, 1H), 4.97 (t, *J* = 3.7 Hz, 1H), 4.90 (m, 1H), 4.47 (m, 1H), 4.32 (ddd, *J* = 4.7, 6.4,12.2 Hz, 1H), 2.22 (t, *J* = 13.0 Hz, 1H), 2.04 (dt, *J* = 7.6, 13.8 Hz, 1H), 1.93–1.85 (m, 4H), 1.72 (s, 3H), 1.66–1.61 (m, 2H), 1.54 (s, 3H), 1.38 (s, 3H)
^{13}C NMR ($CDCl_3$, 75MHz)	135.7, 133.6, 127.2, 127.0, 112.7, 105.2, 79.9, 76.6, 73.1, 71.9, 34.2, 32.4, 29.7, 27.3, 26.9, 23.6, 23.0.
Elemental Analysis	**Calcd:** C, 69.84; H,8.27 **Found:** C, 69.65; H,8.14

Compound-104

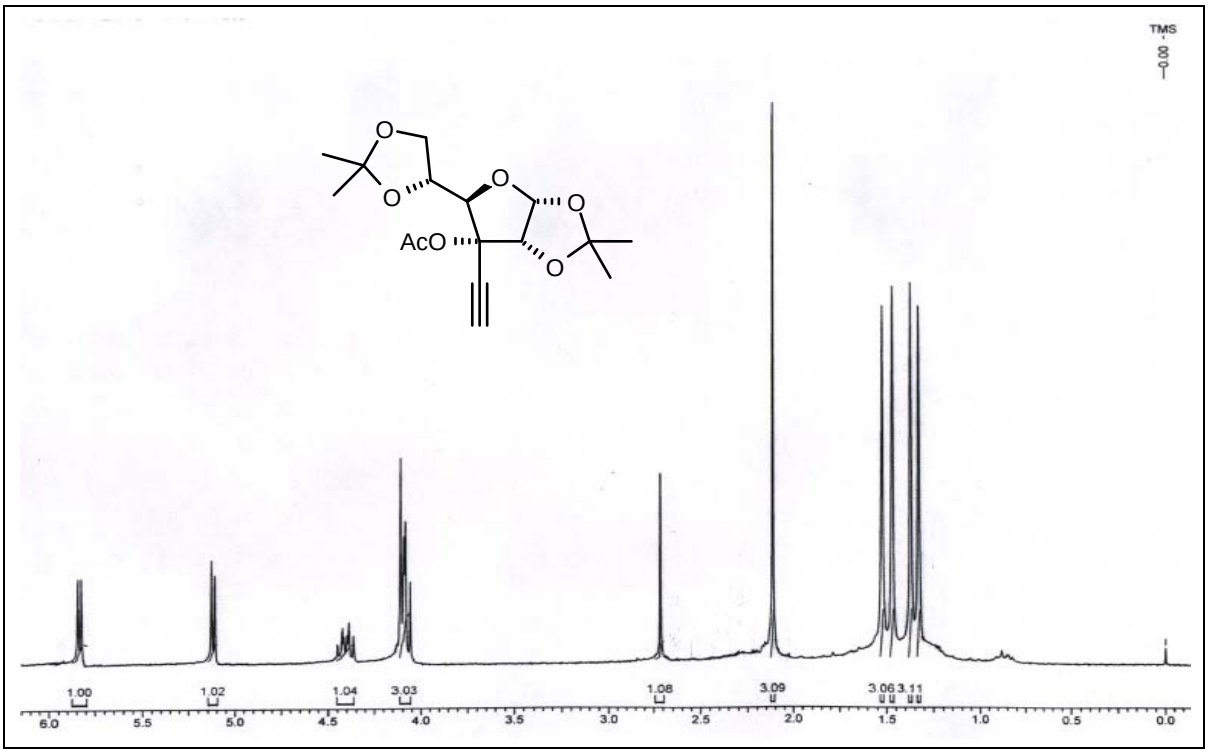


104

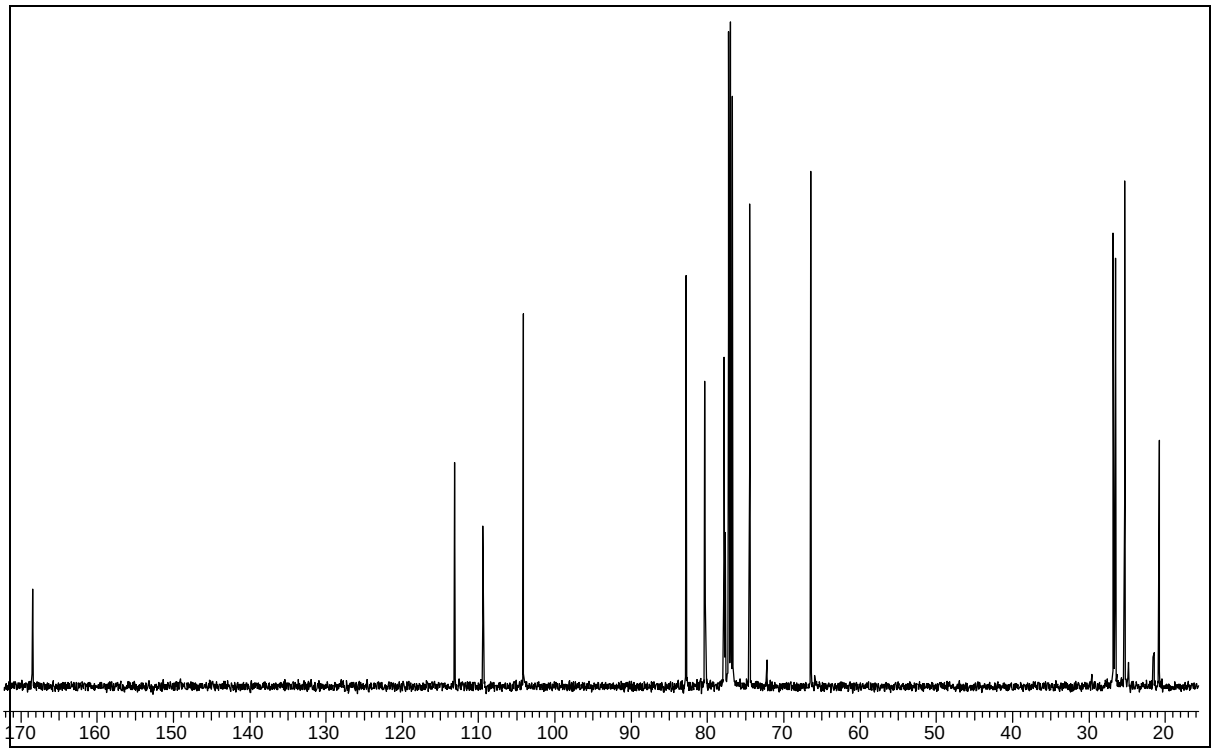
Dimeric compound **104** was prepared from compound **102** using Grubbs 2nd generation catalyst following same procedure as that for compound **71**.

Yield	
Mol.Formula	$C_{36}H_{52}O_8$
$[\alpha]_D^{25}$	15.9 (*c* 3, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 5.83 (s, 1H), 5.79 (d, *J* = 3.9 Hz, 1H), 5.34 (m, 1H), 4.88 (d, *J* = 3.9 Hz, 1H), 4.79 (br s, 2H), 4.22 (d, *J* = 7.8 Hz, 2H), 3.25 (m, 1H), 2.53 (d, *J* = 14.3 Hz, 1H), 2.24–2.12 (m, 2H), 2.05–1.89 (m, 3H), 1.74 (s, 3H), 1.64–1.62 (m, 2H), 1.52 (s, 3H), 1.34 (s, 3H).
^{13}C NMR ($CDCl_3$, 75MHz)	142.1, 136.5, 130.2, 129.7, 126.7, 126.6, 112.8, 112.4, 105.1, 80.1, 75.1, 73.0, 70.7, 41.1, 32.7, 32.6, 32.2, 29.6, 27.1, 26.9, 26.8, 26.4, 26.3, 23.0.
Elemental Analysis	**Calcd:** C, 70.58; H,8.49 **Found:** C, 70.62; H,8.69

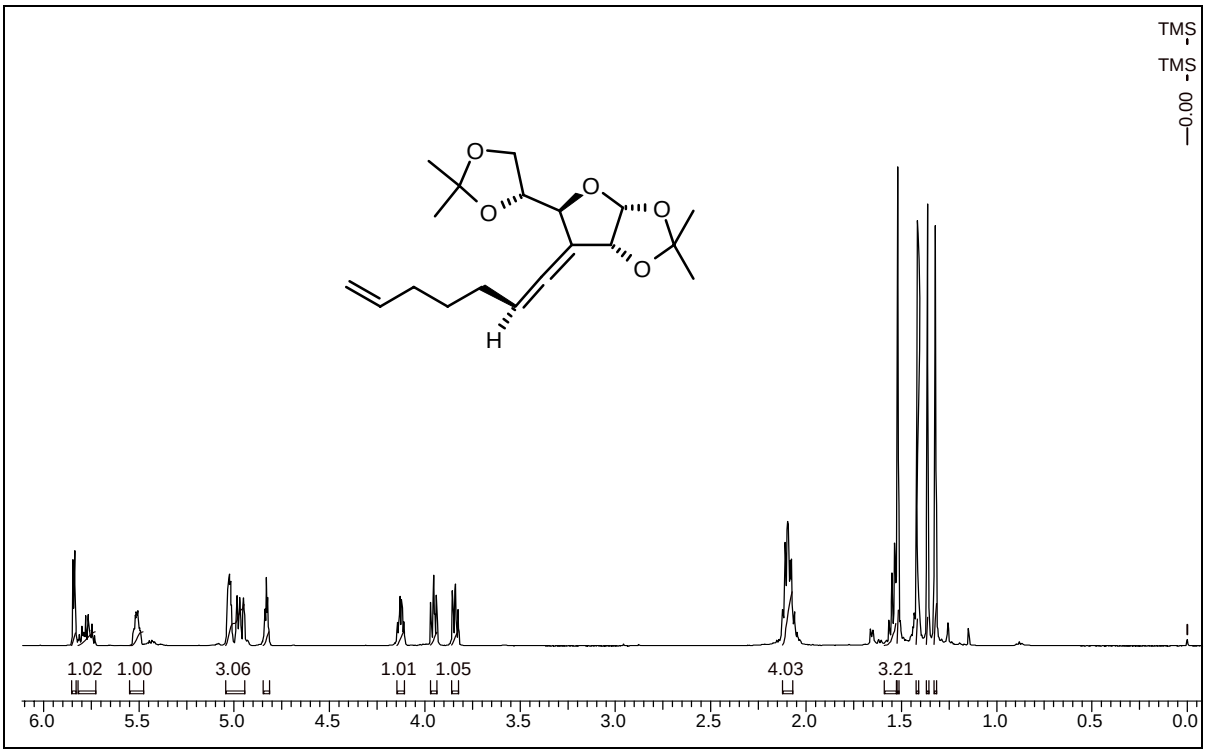
SPECTRA



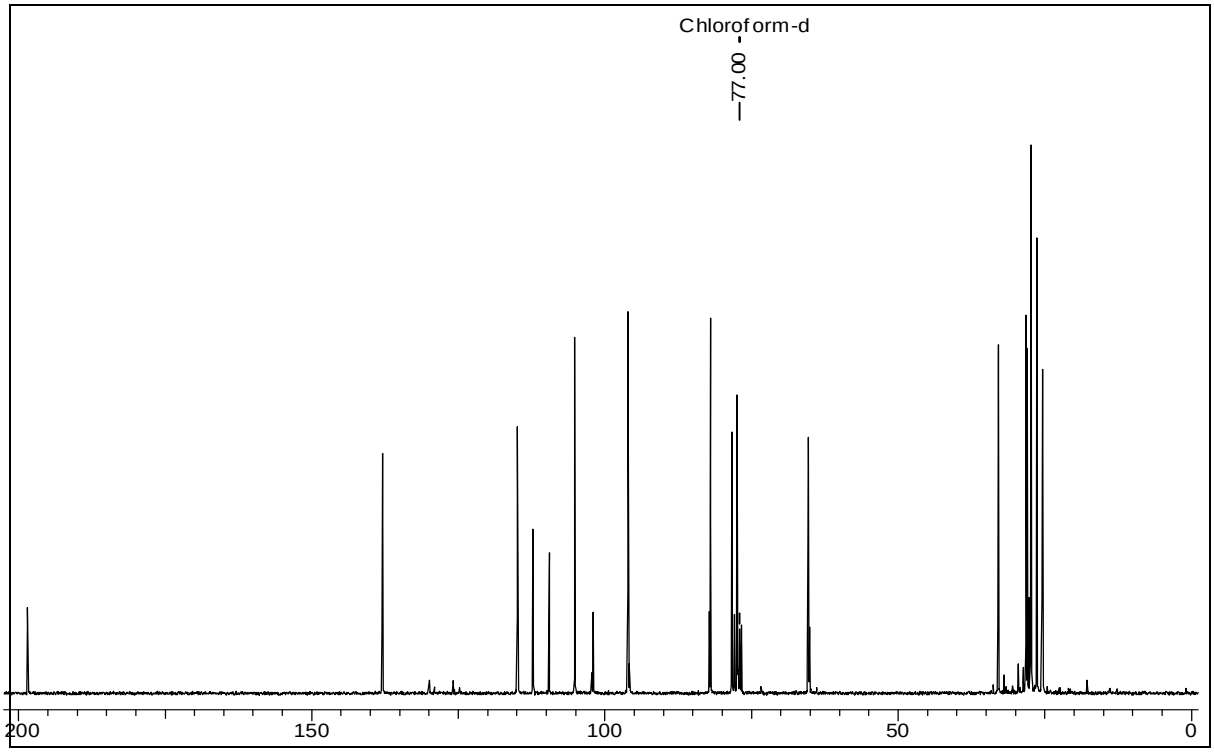
^{1}H NMR spectrum of compound 75 in $CDCl_3$



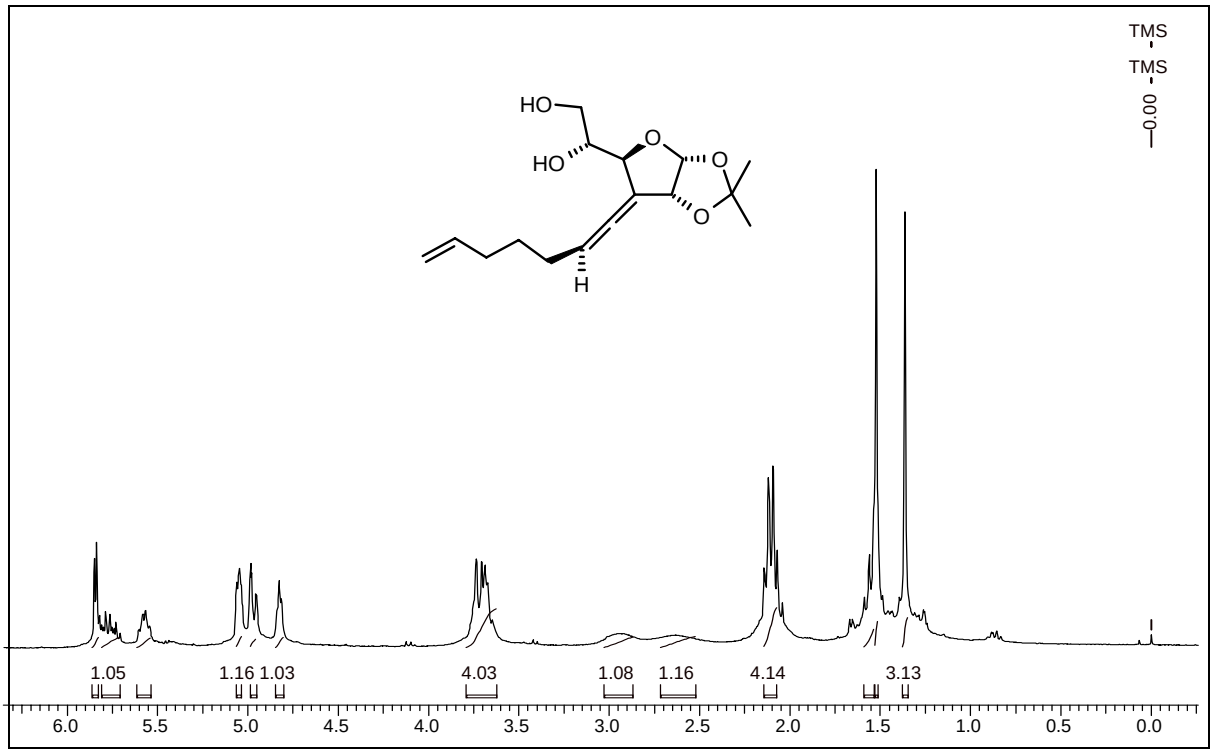
^{13}C NMR spectrum of compound 75 in $CDCl_3$



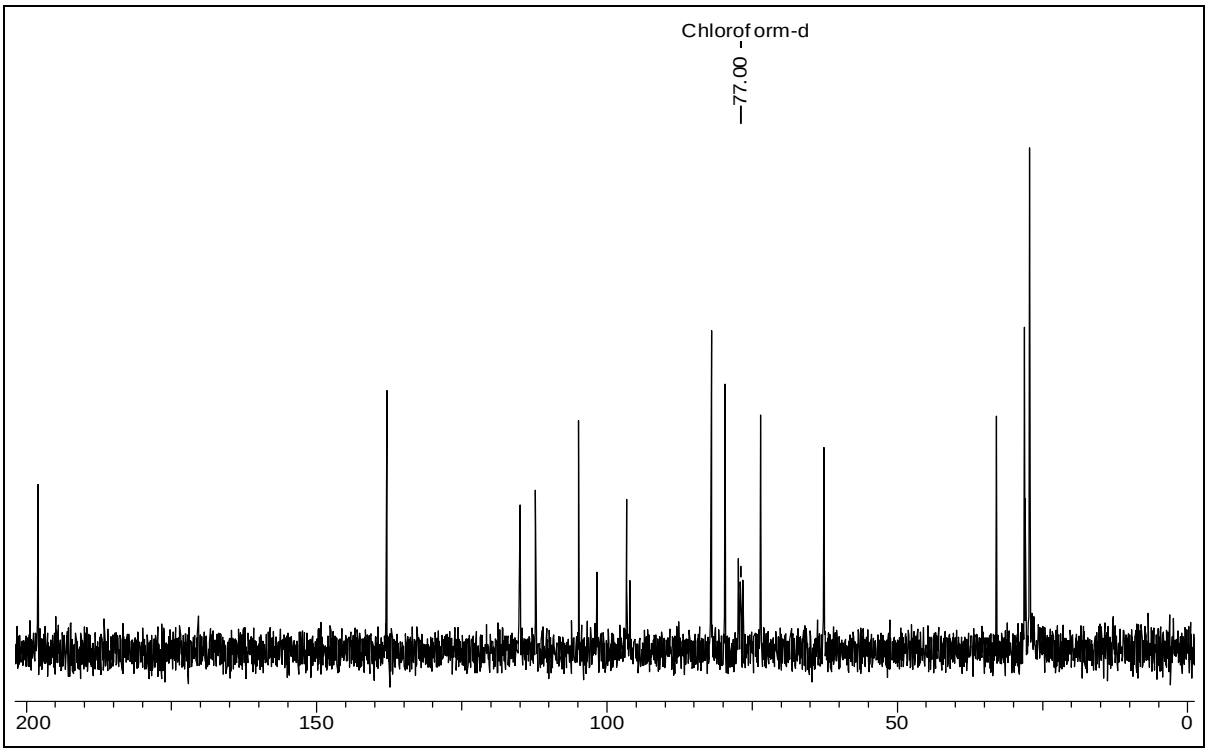
^{1}H NMR spectrum of compound 74 in $CDCl_3$



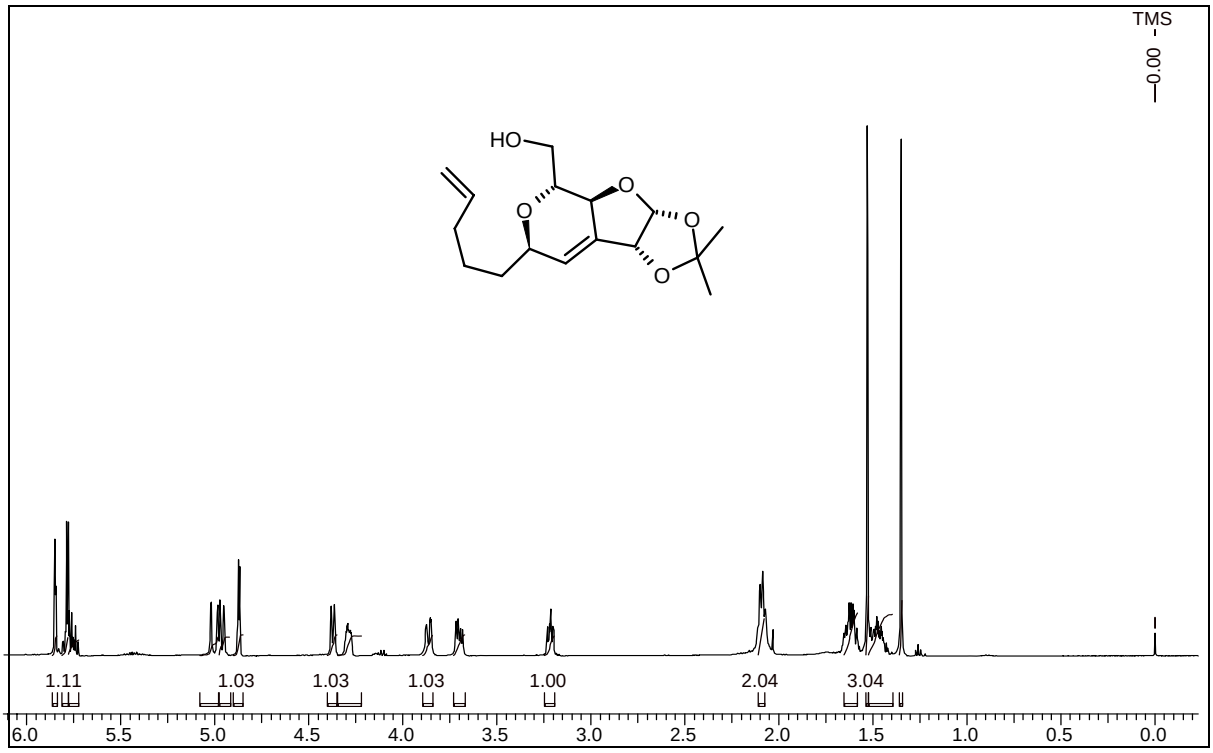
^{13}C NMR spectrum of compound 74 in $CDCl_3$



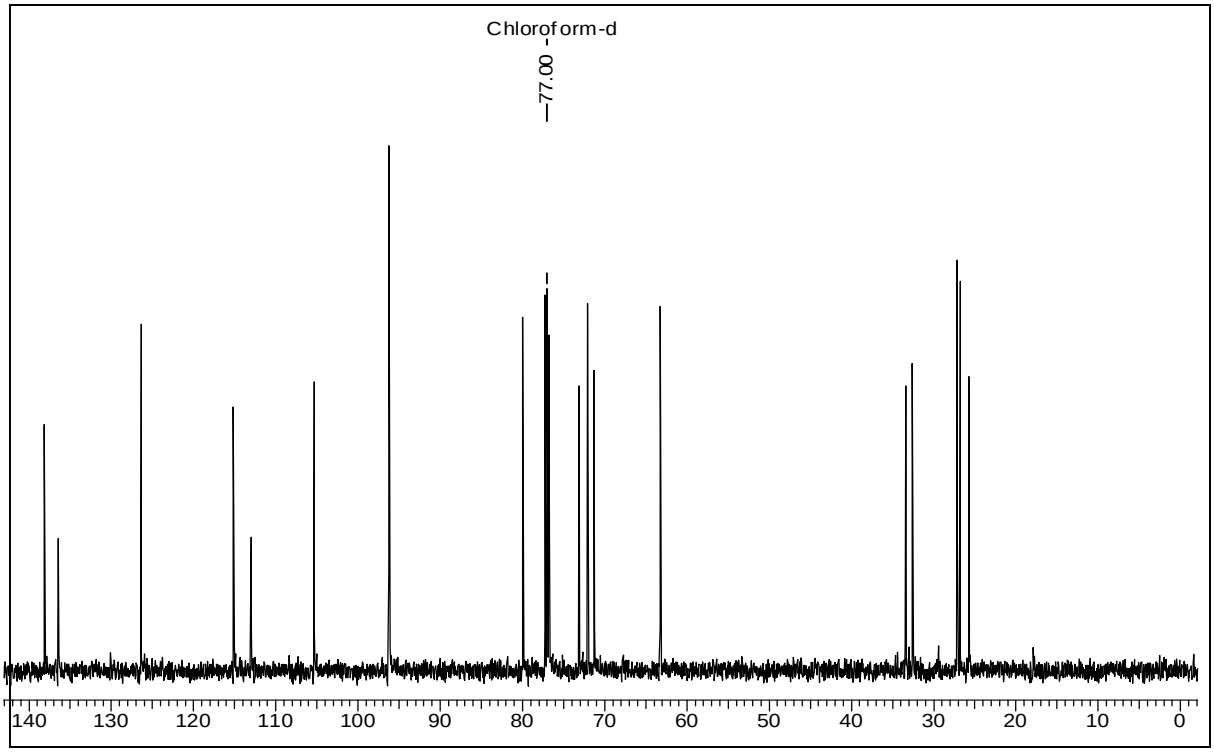
^{1}H NMR spectrum of compound 79 in $CDCl_3$



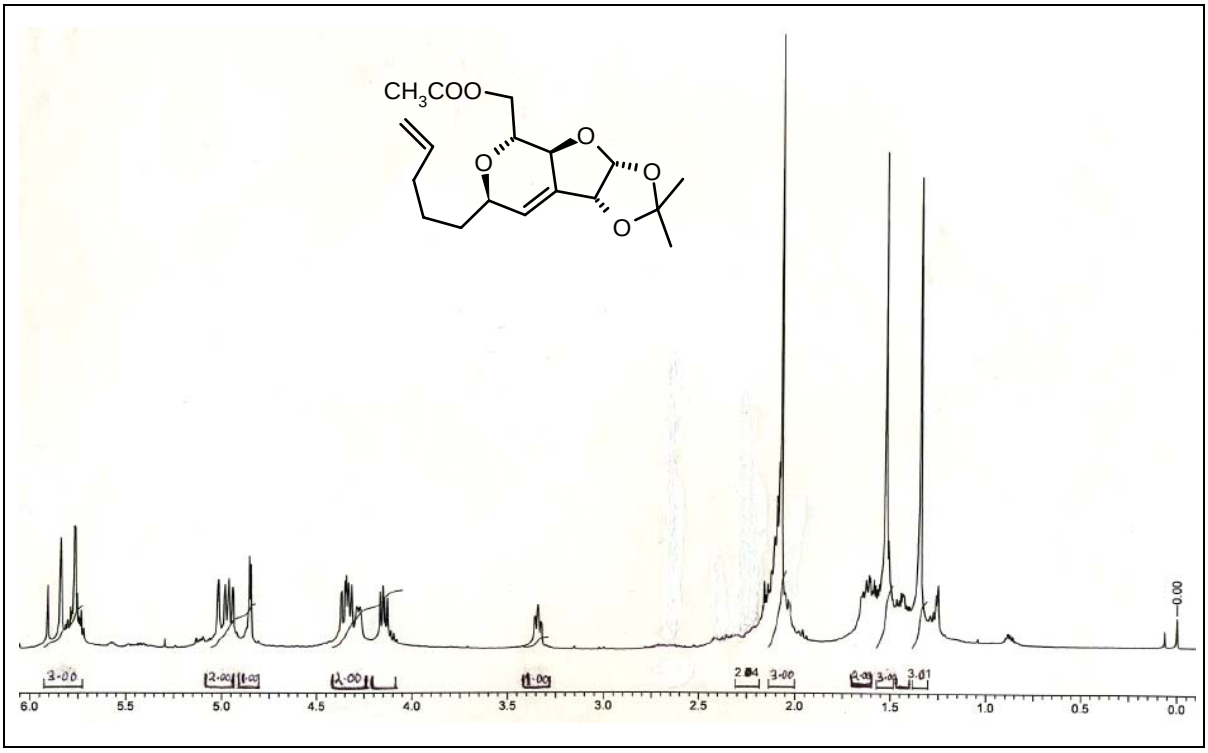
^{13}C NMR spectrum of compound 79 in $CDCl_3$



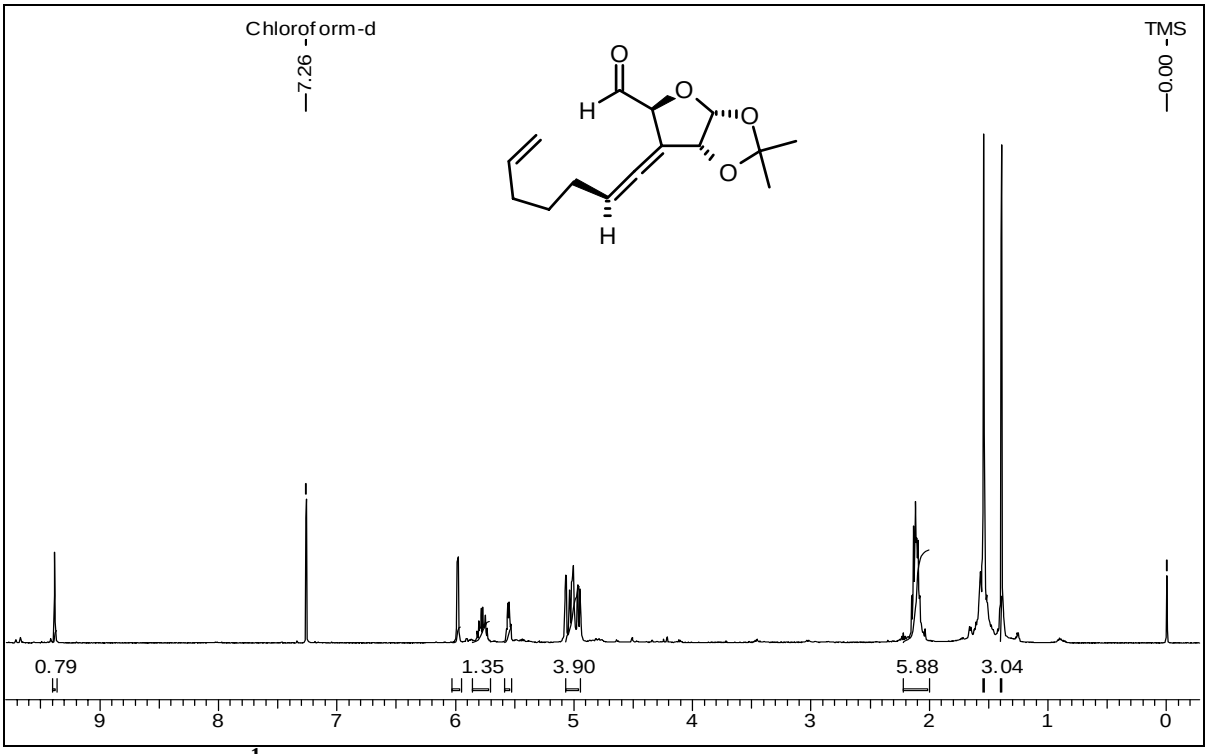
^{1}H NMR spectrum of compound 80 in $CDCl_3$



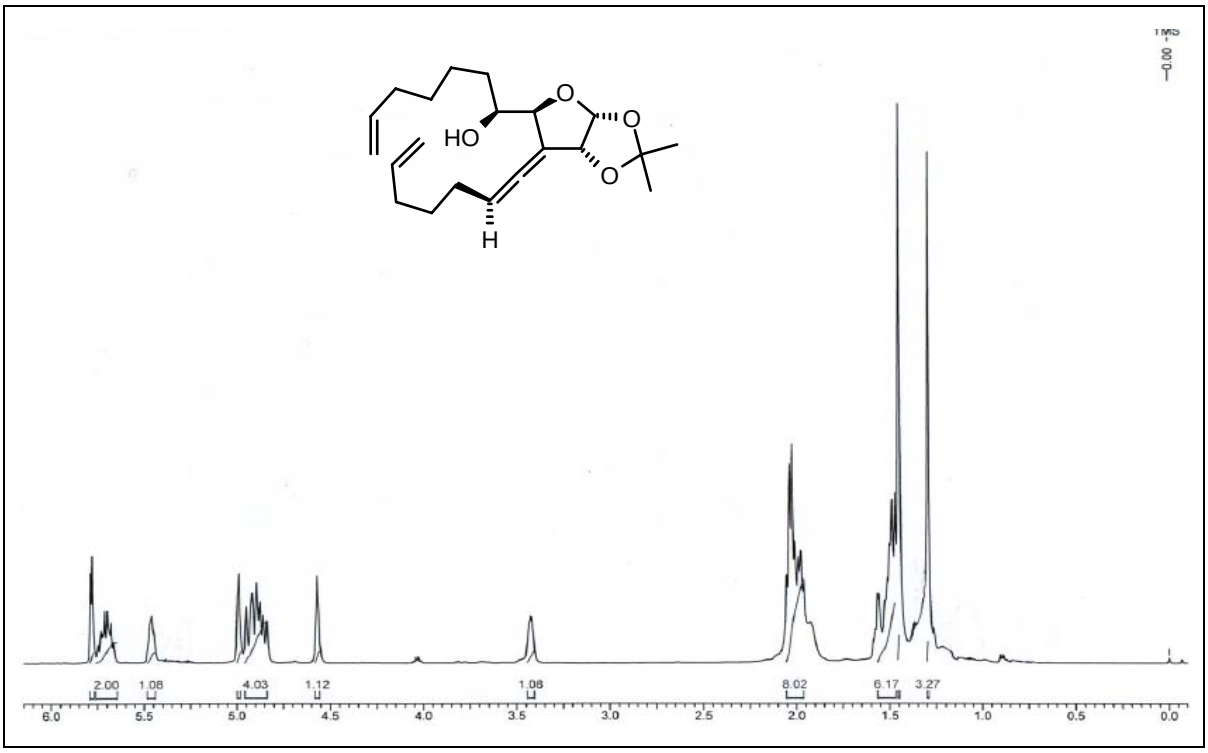
^{13}C NMR spectrum of compound 80 in $CDCl_3$



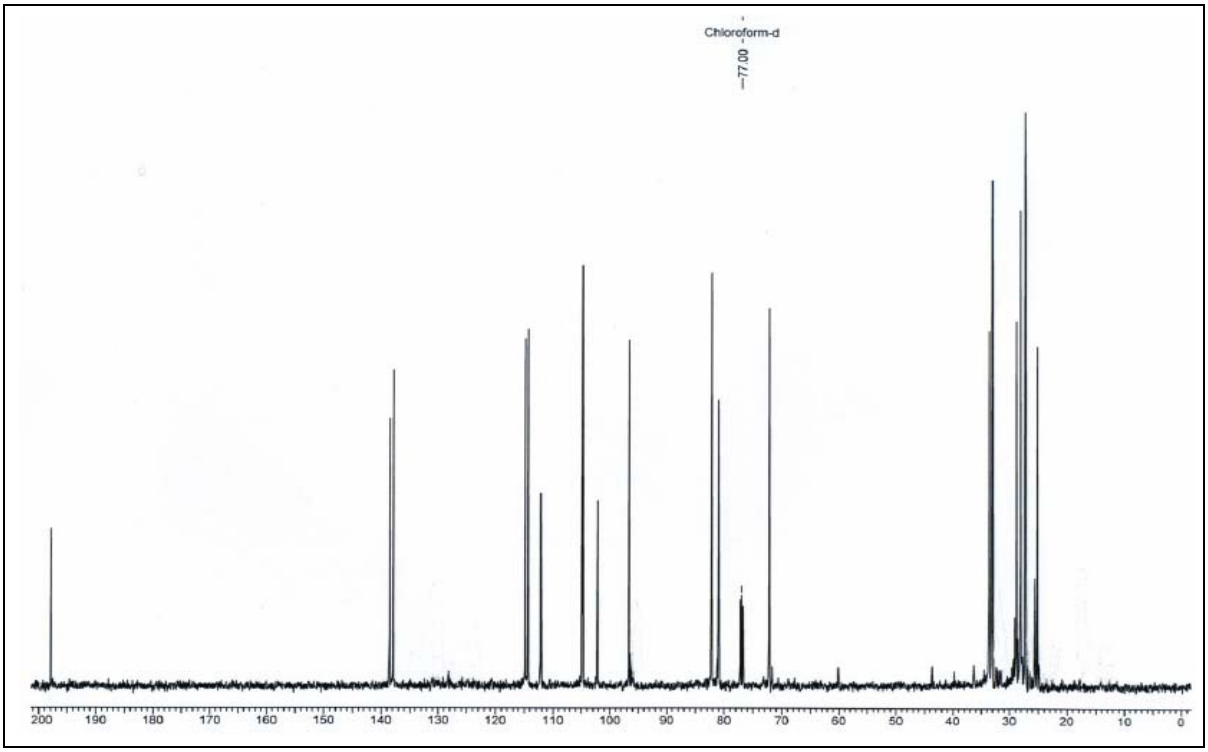
^{1}H NMR spectrum of compound 82 in $CDCl_3$



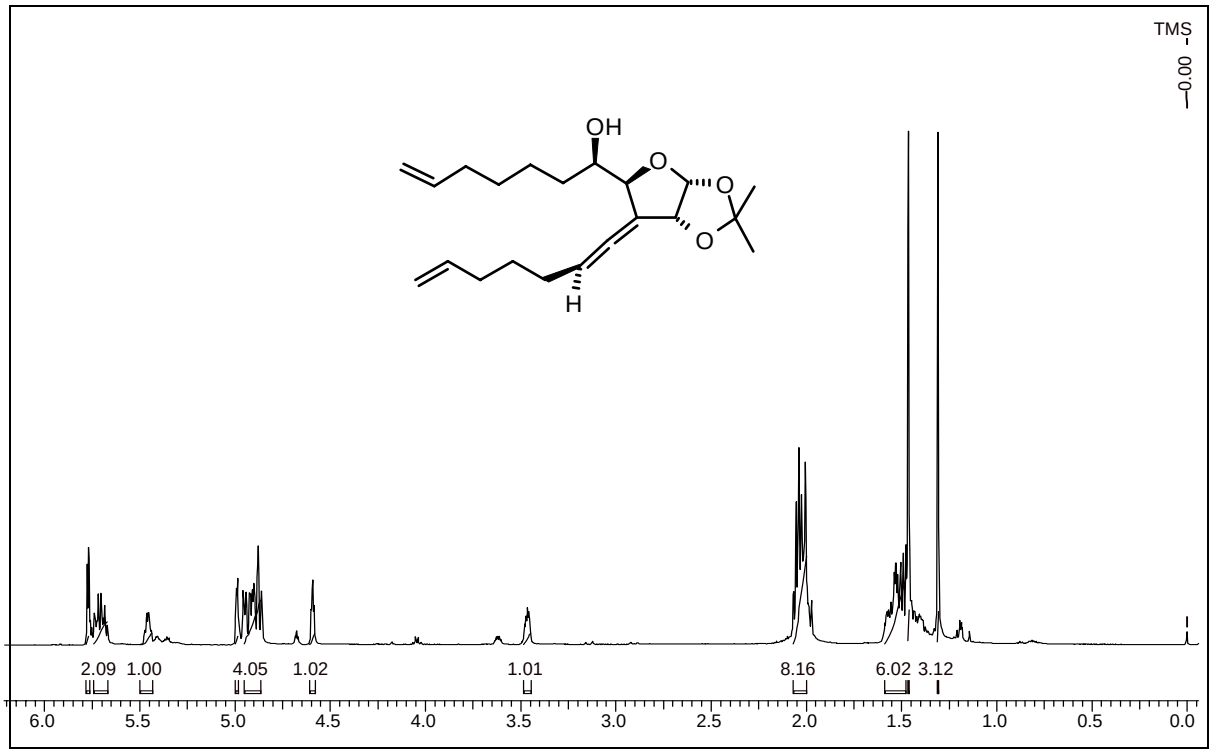
^{1}H NMR spectrum of compound 83 in $CDCl_3$



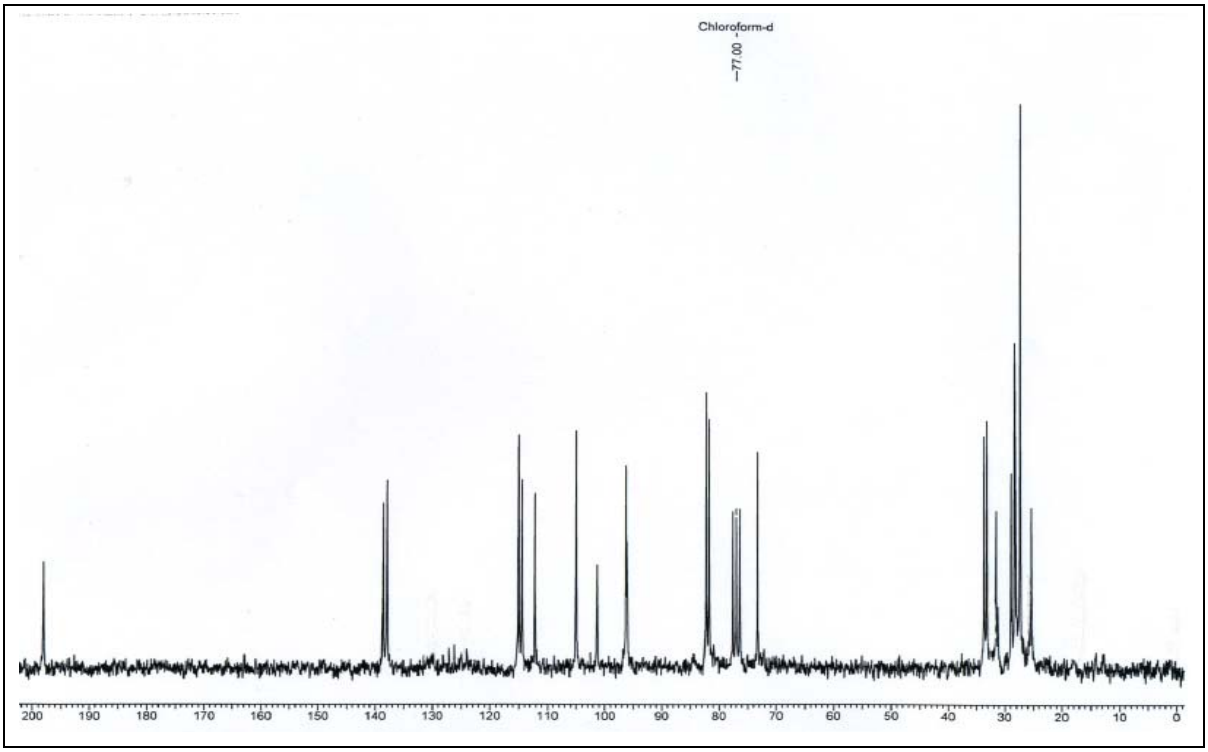
^{1}H NMR spectrum of compound 73 in $CDCl_3$



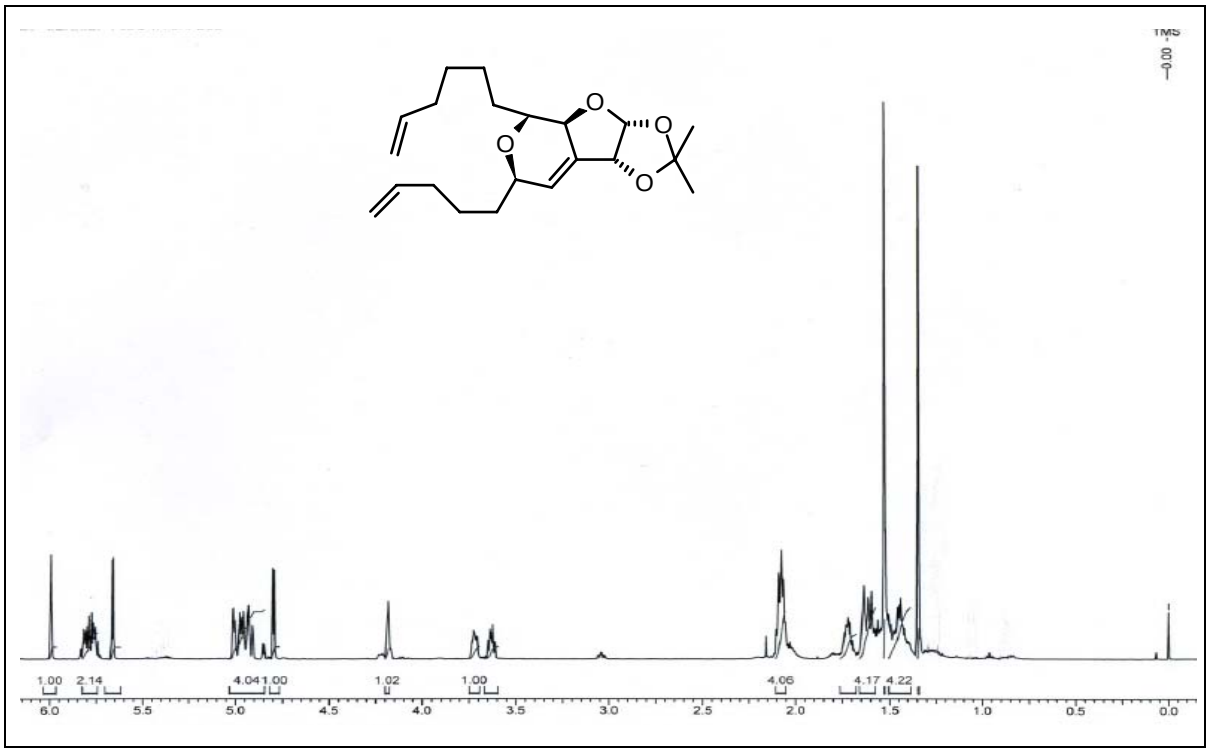
^{13}C NMR spectrum of compound 73 in $CDCl_3$



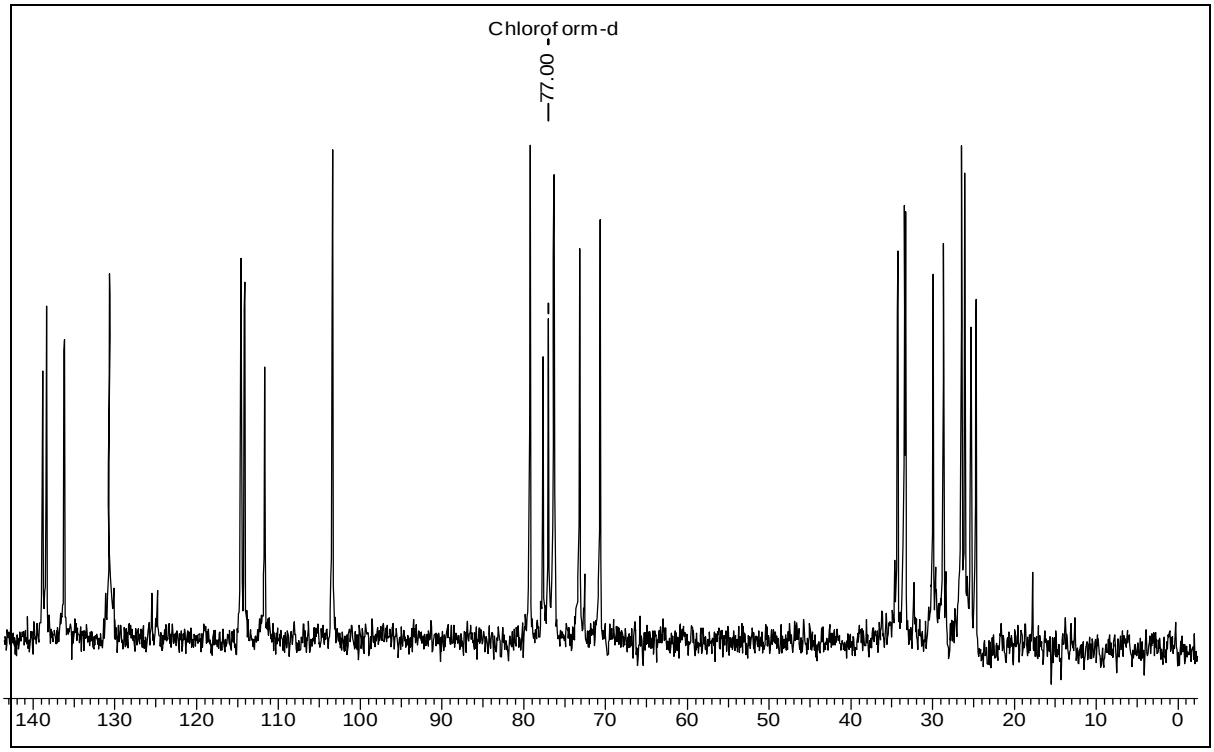
^{1}H NMR spectrum of compound 84 in $CDCl_3$



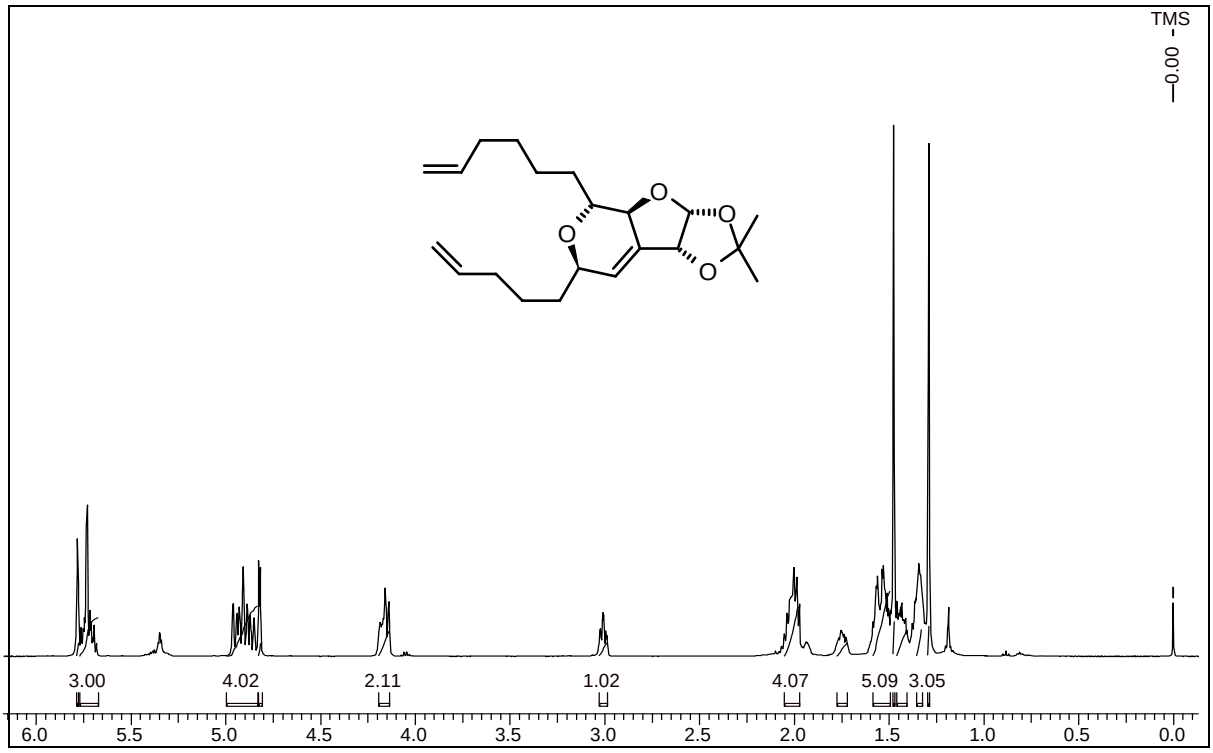
^{13}C NMR spectrum of compound 84 in $CDCl_3$



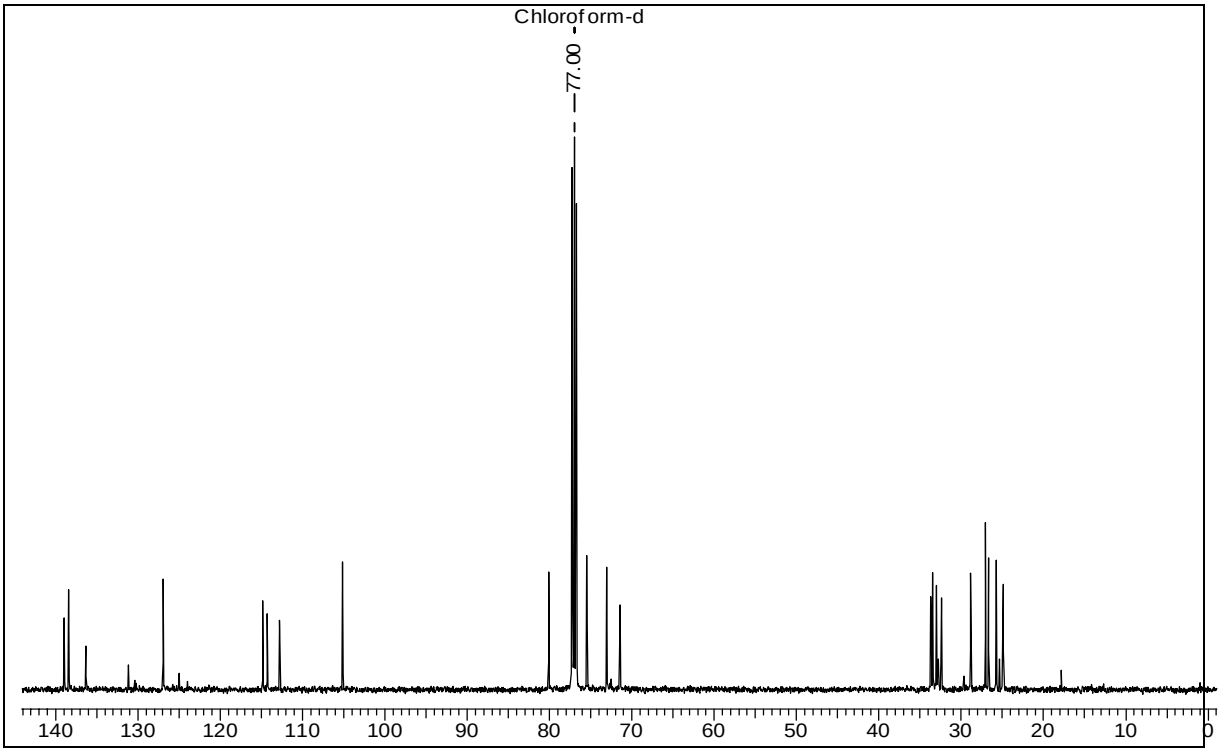
^{1}H NMR spectrum of compound 72 in $CDCl_3$



^{13}C NMR spectrum of compound 72 in $CDCl_3$



^{1}H NMR spectrum of compound 85 in $CDCl_3$



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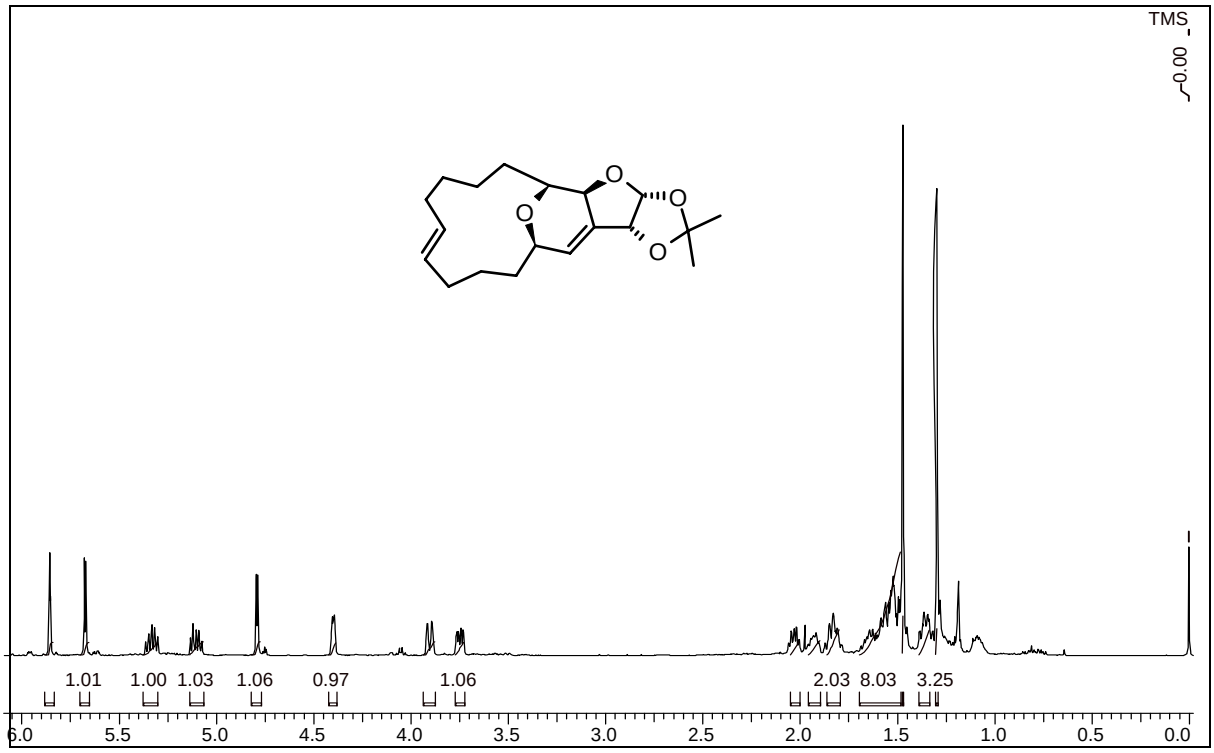
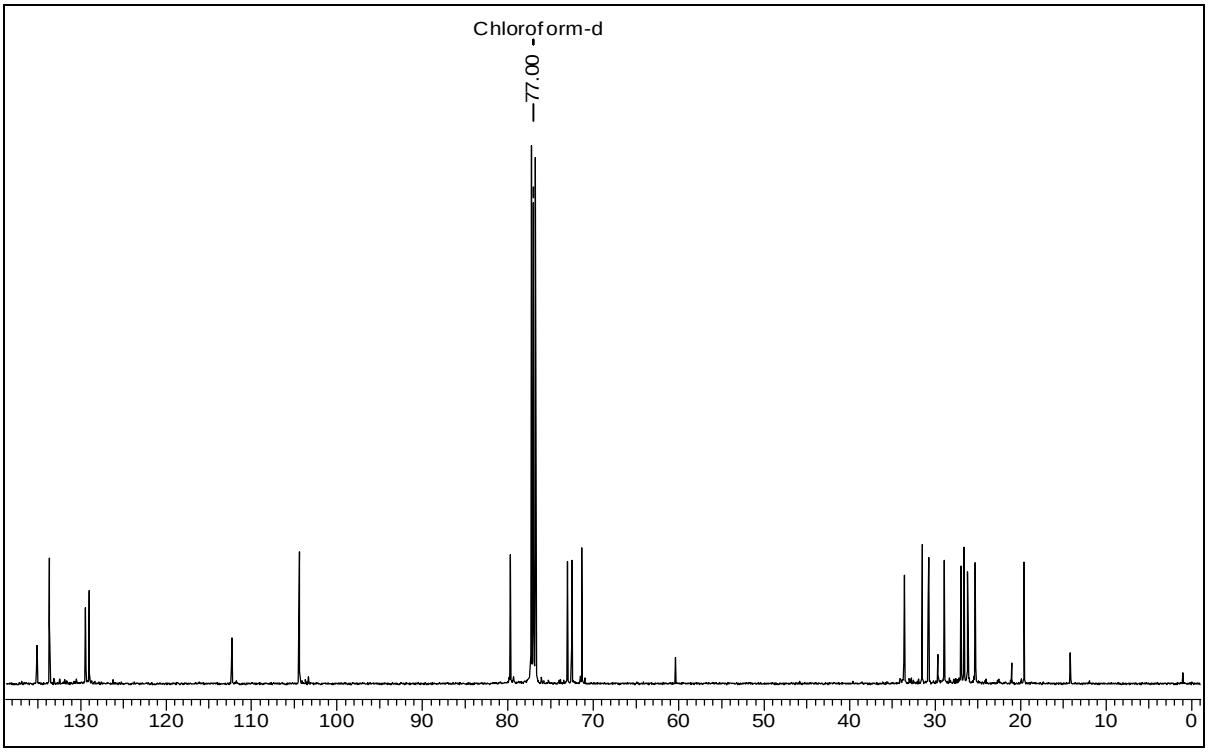
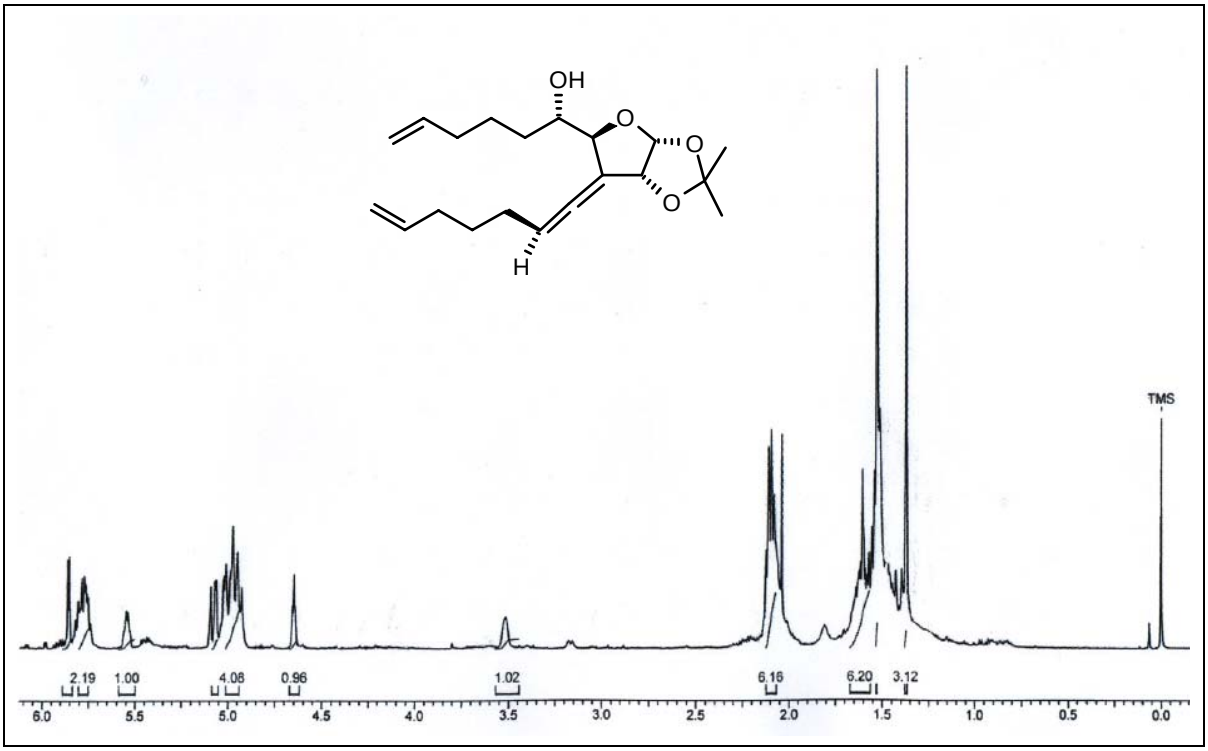


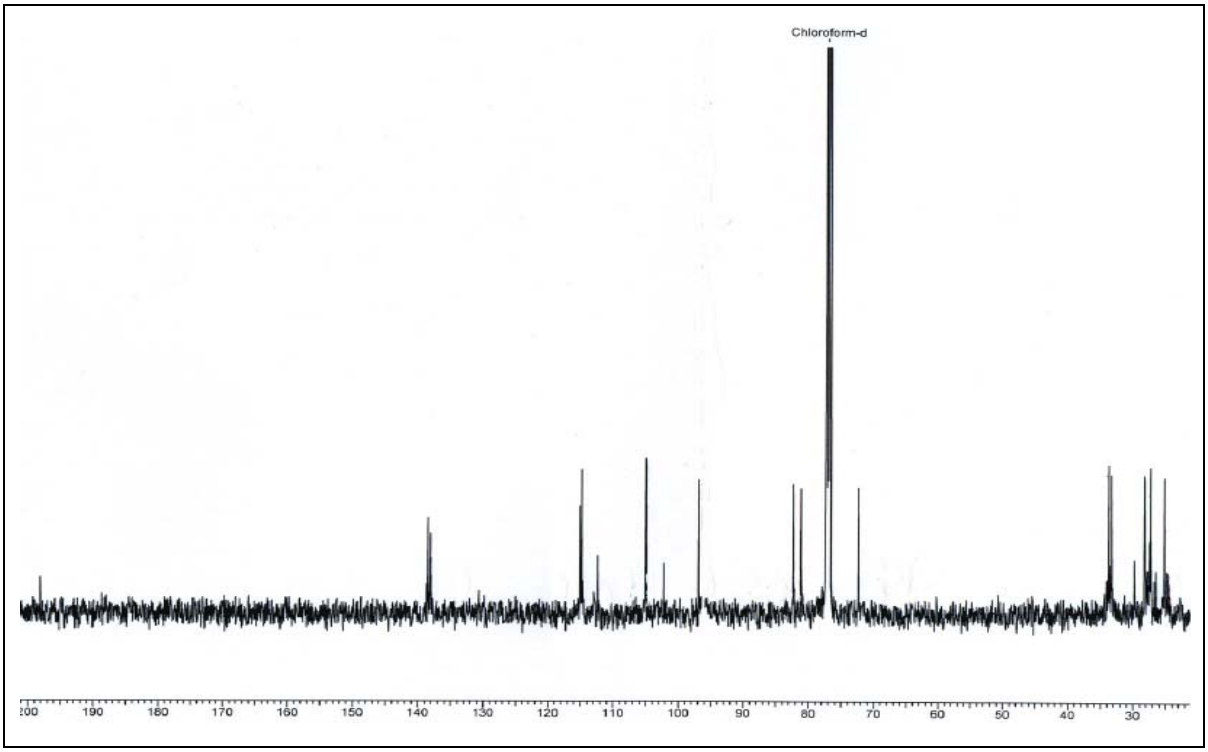
^{1}H NMR spectrum of compound 71 in $CDCl_3$



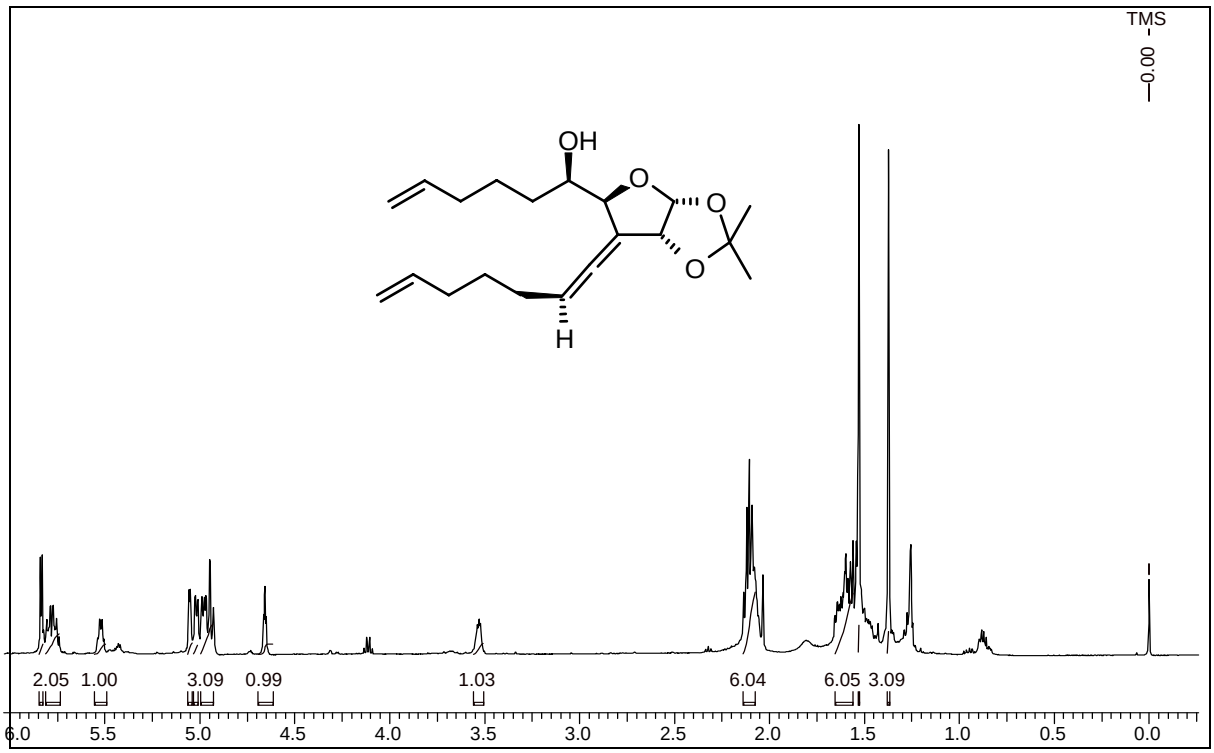
^{13}C NMR spectrum of compound 71 in $CDCl_3$



^{1}H NMR spectrum of compound 87 in $CDCl_3$



^{13}C NMR spectrum of compound 87 in $CDCl_3$



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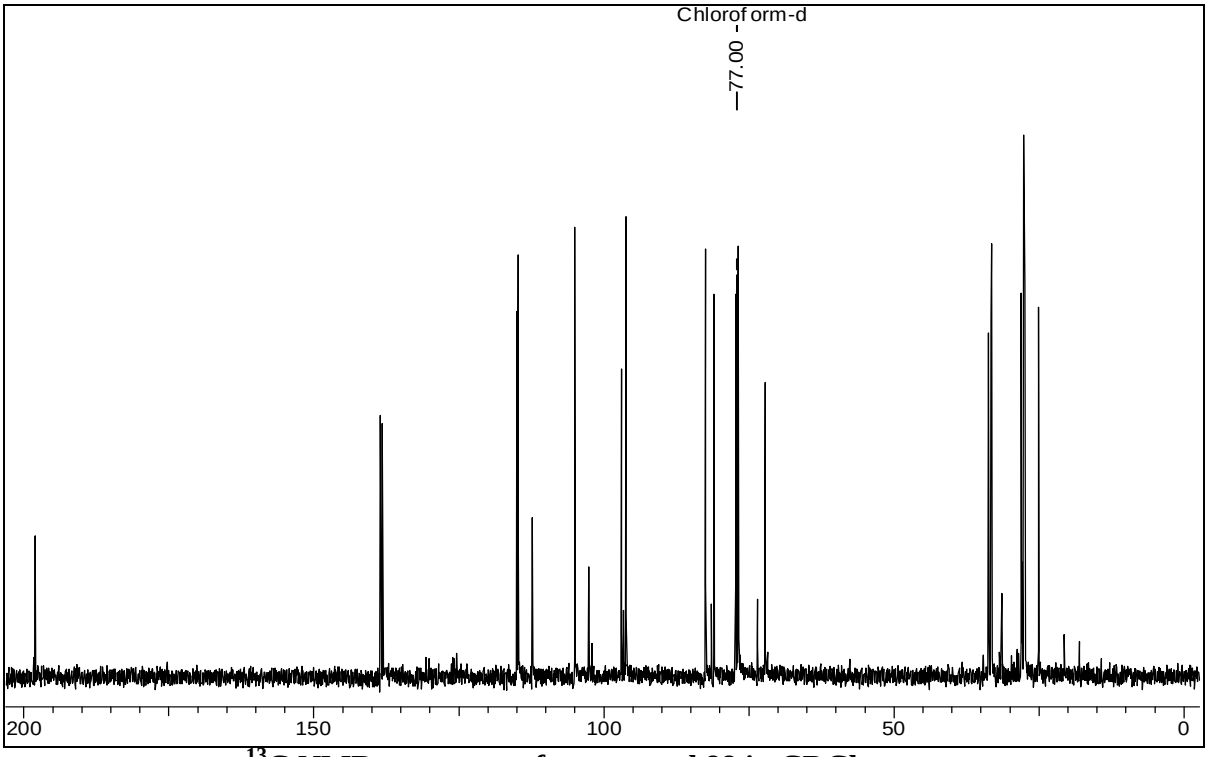
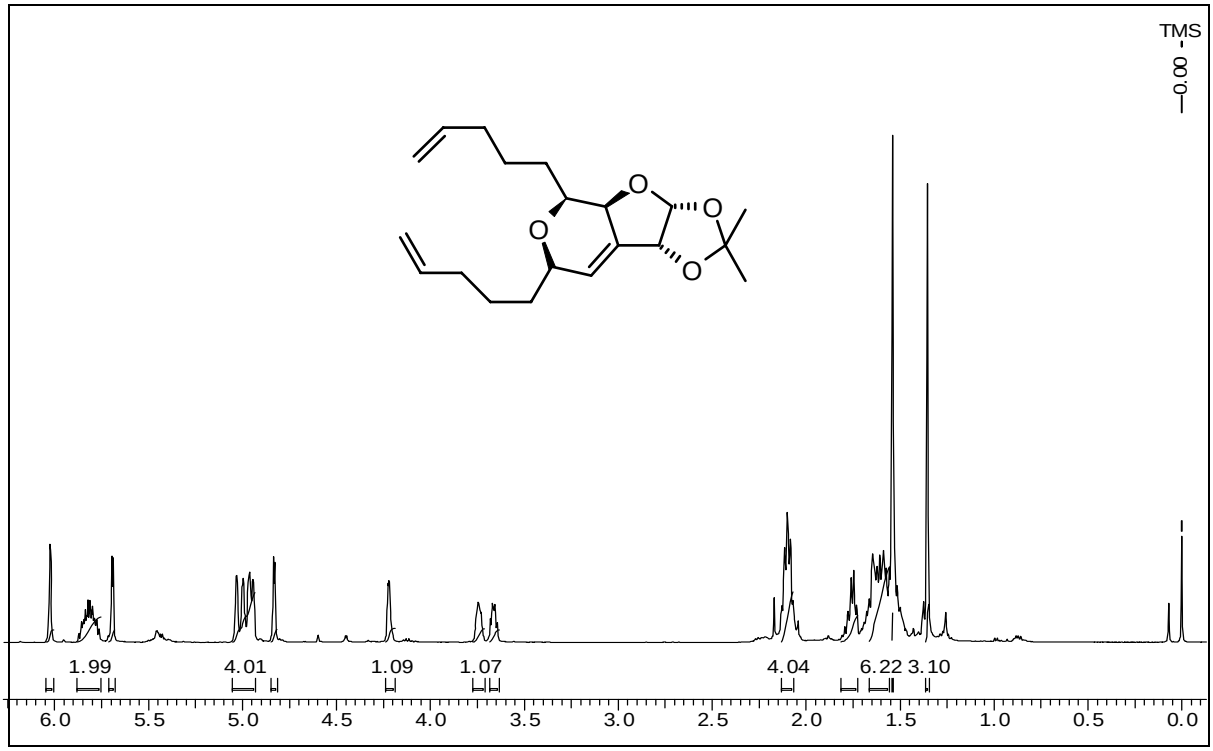
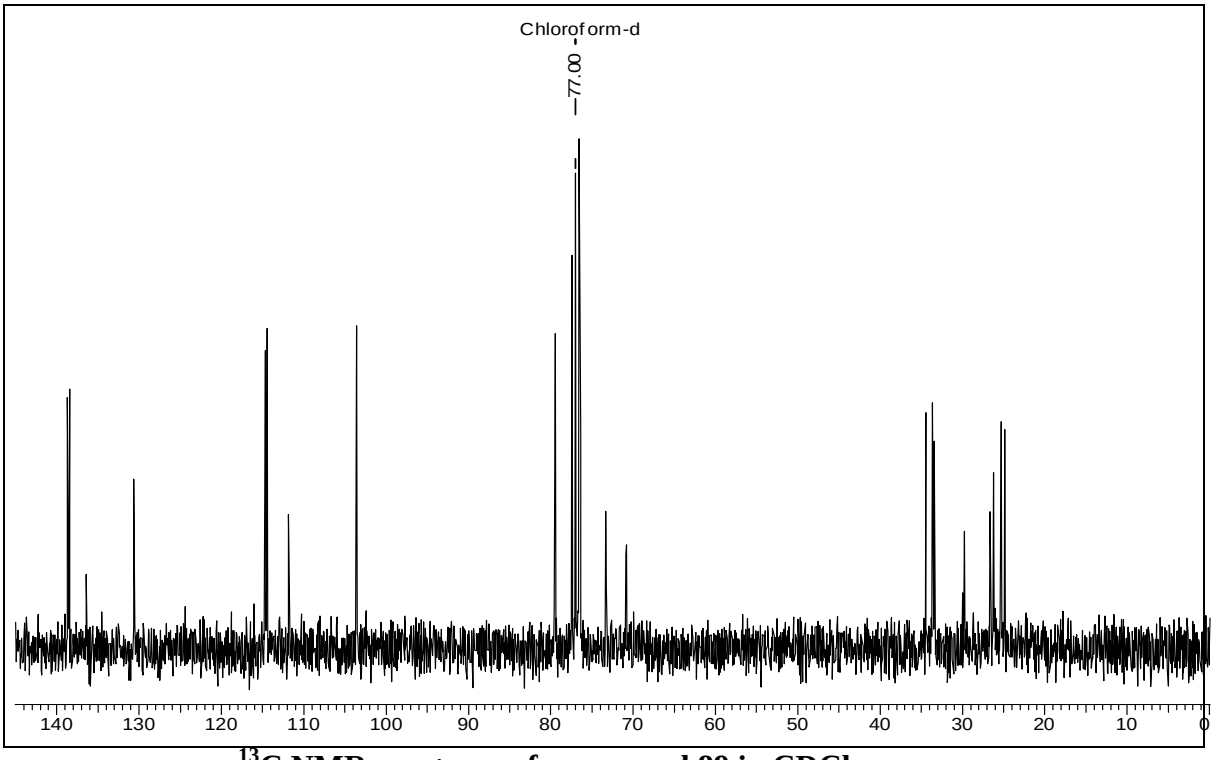


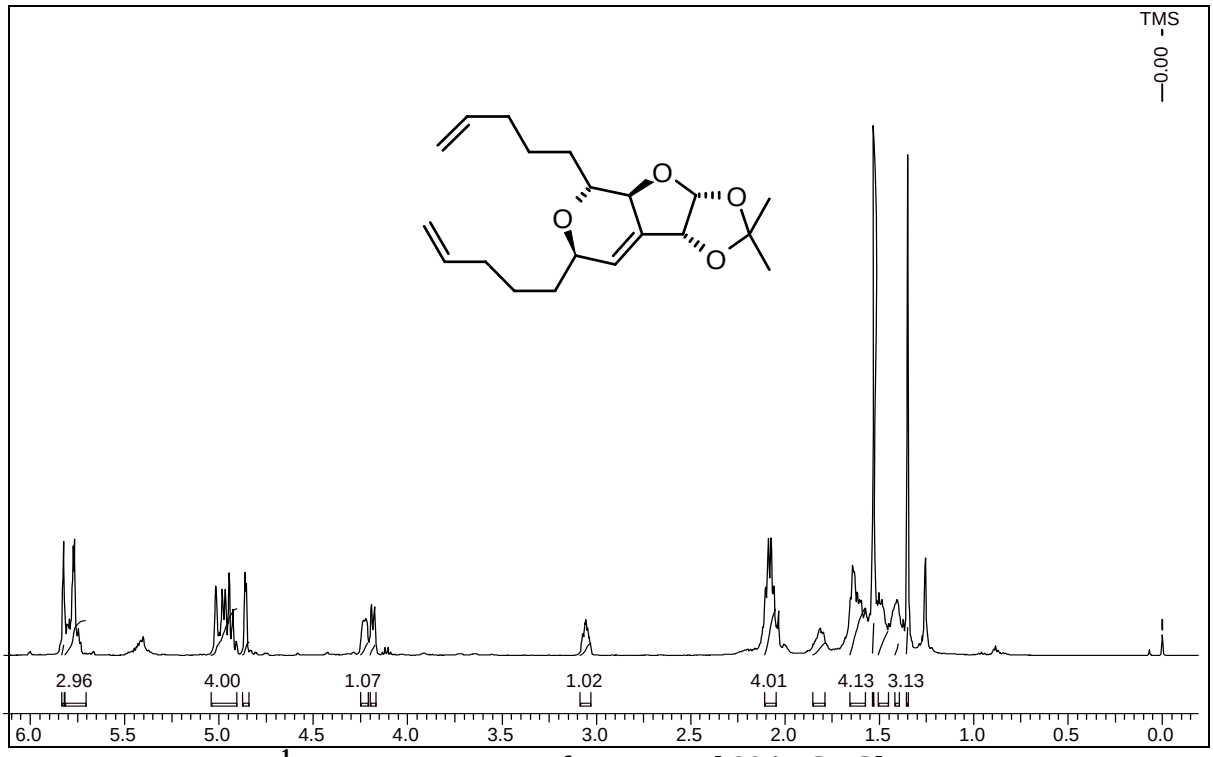
^{13}C NMR spectrum of compound 88 in $CDCl_3$



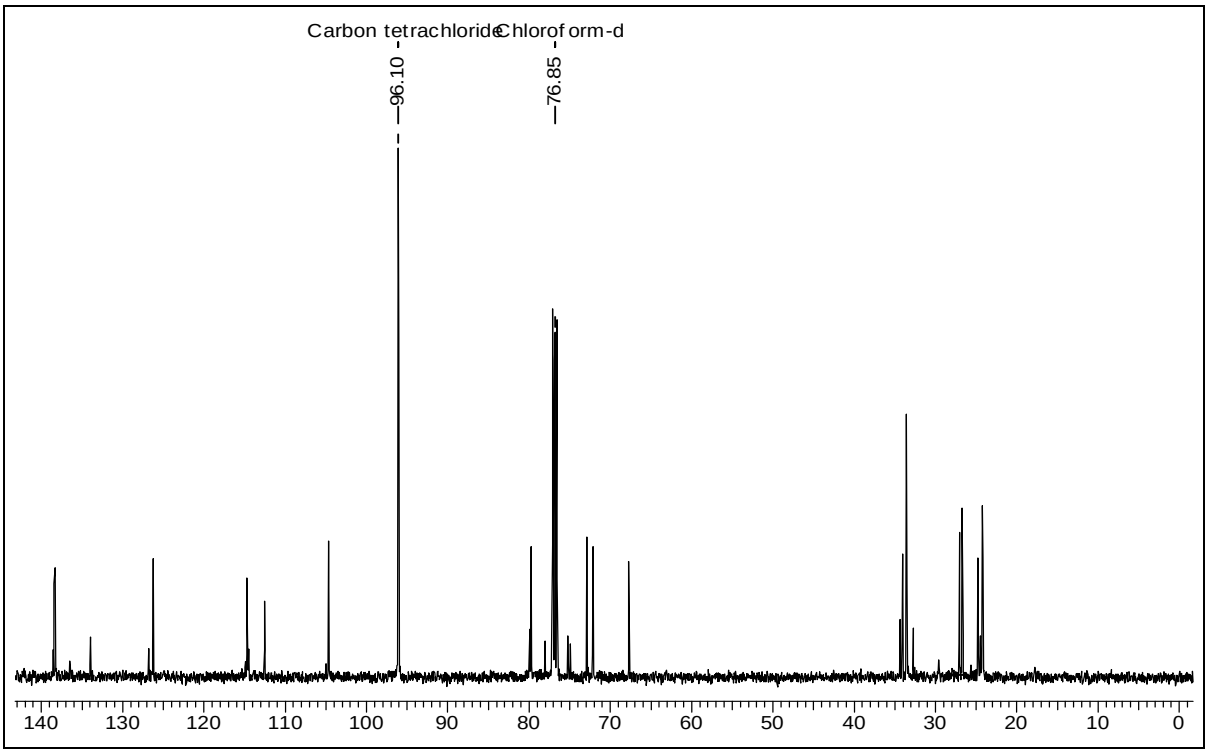
^{1}H NMR spectrum of compound 89 in $CDCl_3$



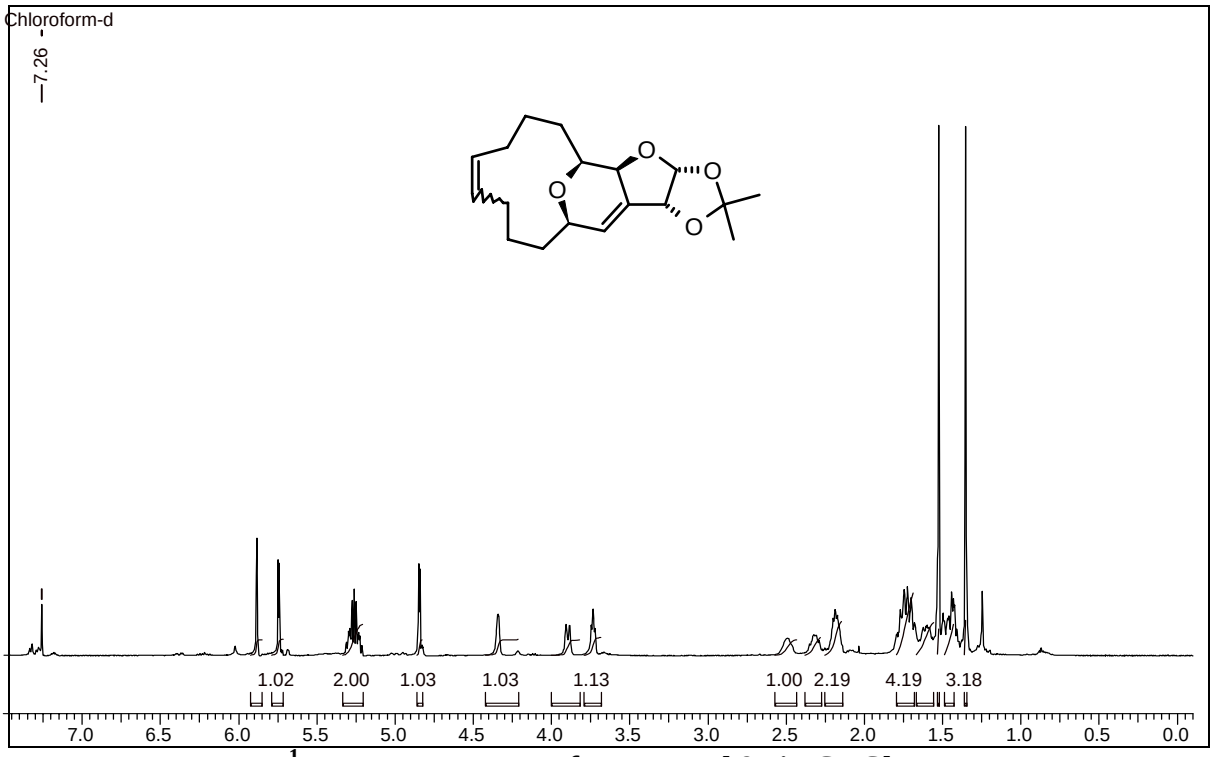
^{13}C NMR spectrum of compound 89 in $CDCl_3$



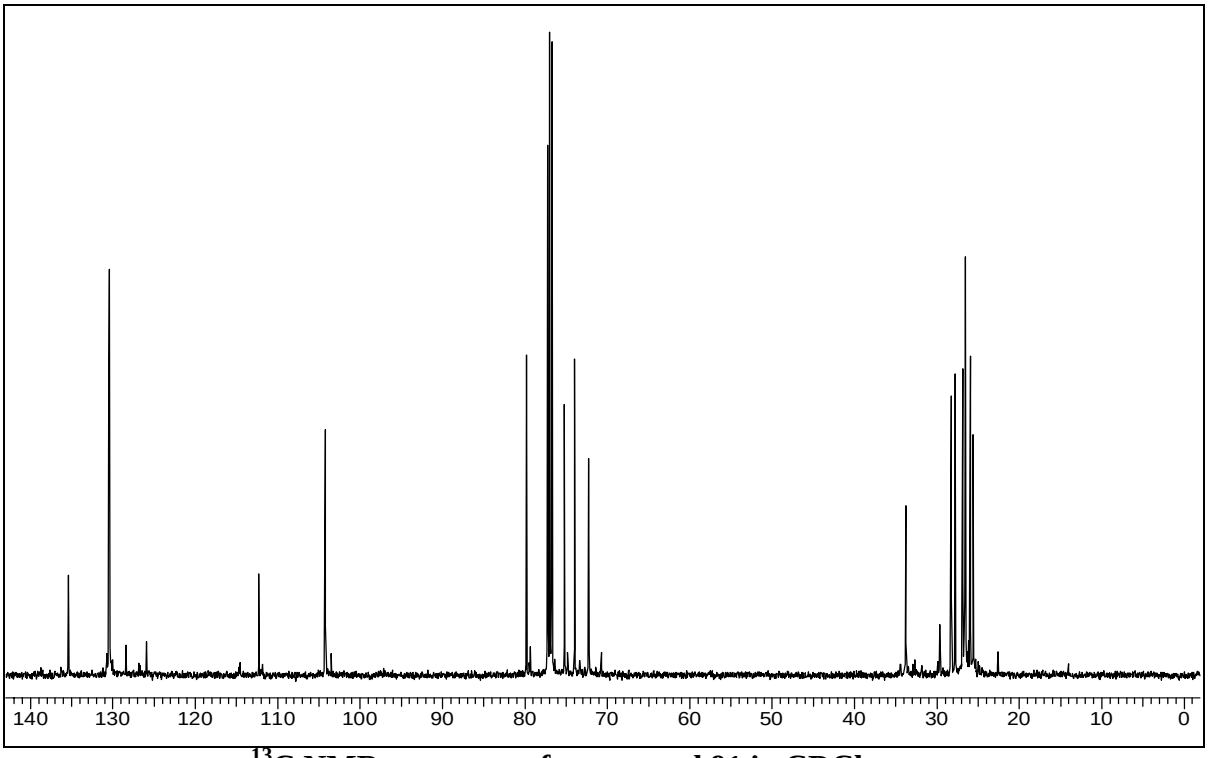
^{1}H NMR spectrum of compound 90 in $CDCl_3$



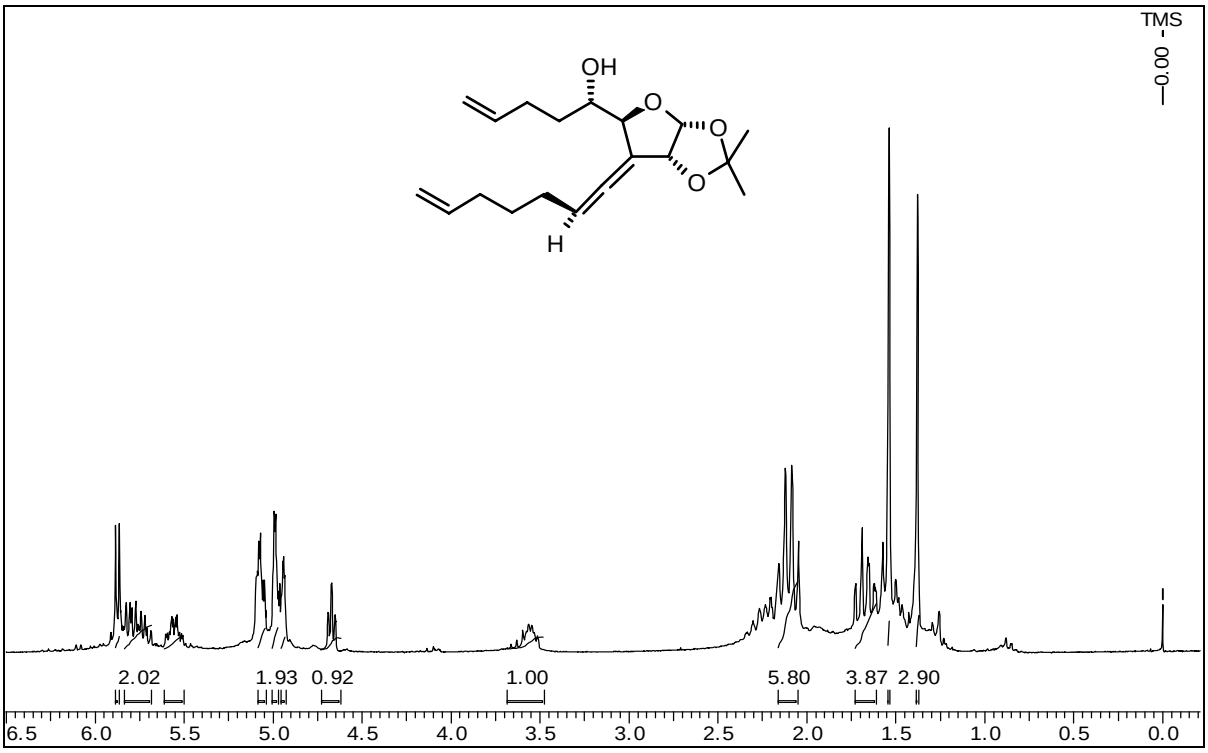
^{13}C NMR spectrum of compound 90 in $CDCl_3$



^{1}H NMR spectrum of compound 91 in $CDCl_3$



^{13}C NMR spectrum of compound 91 in $CDCl_3$



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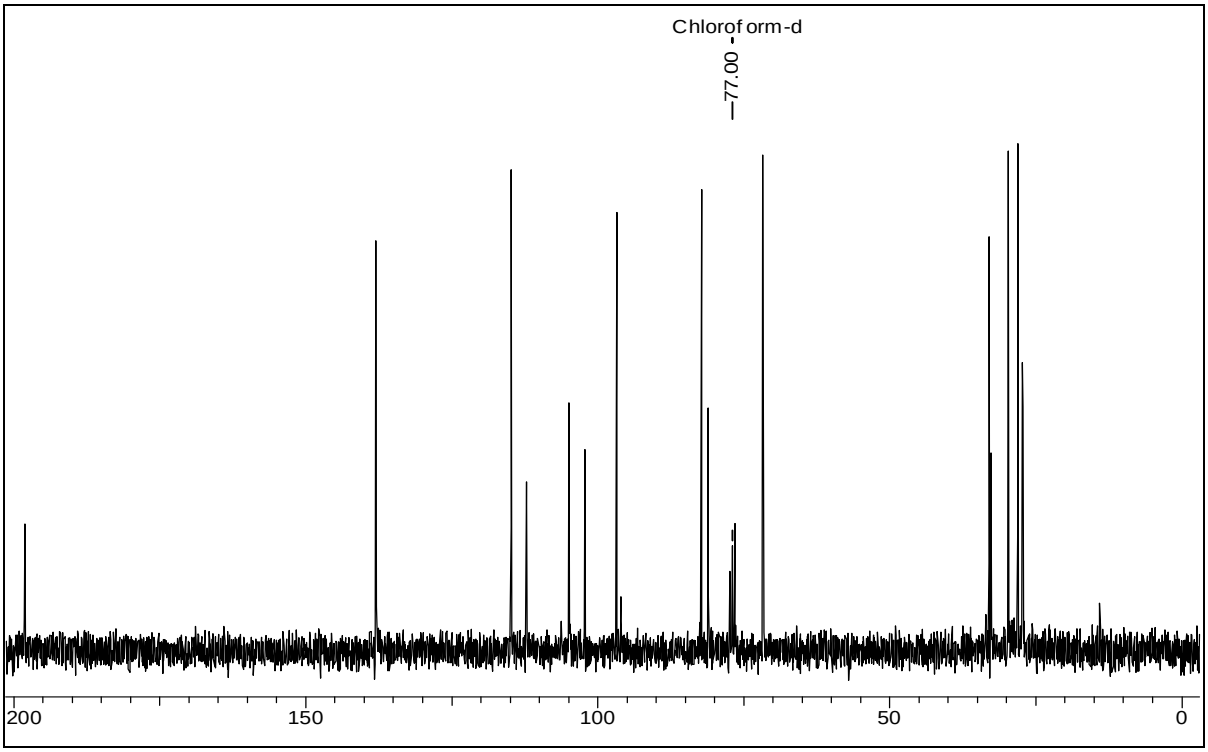
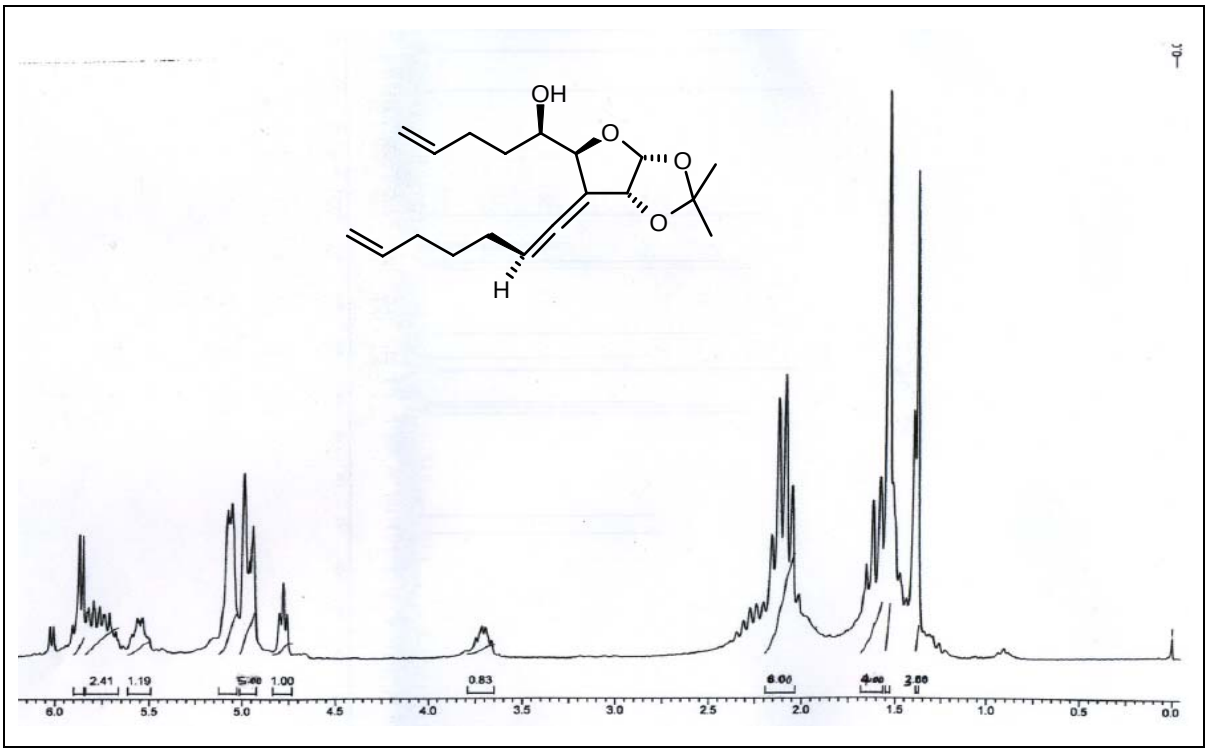
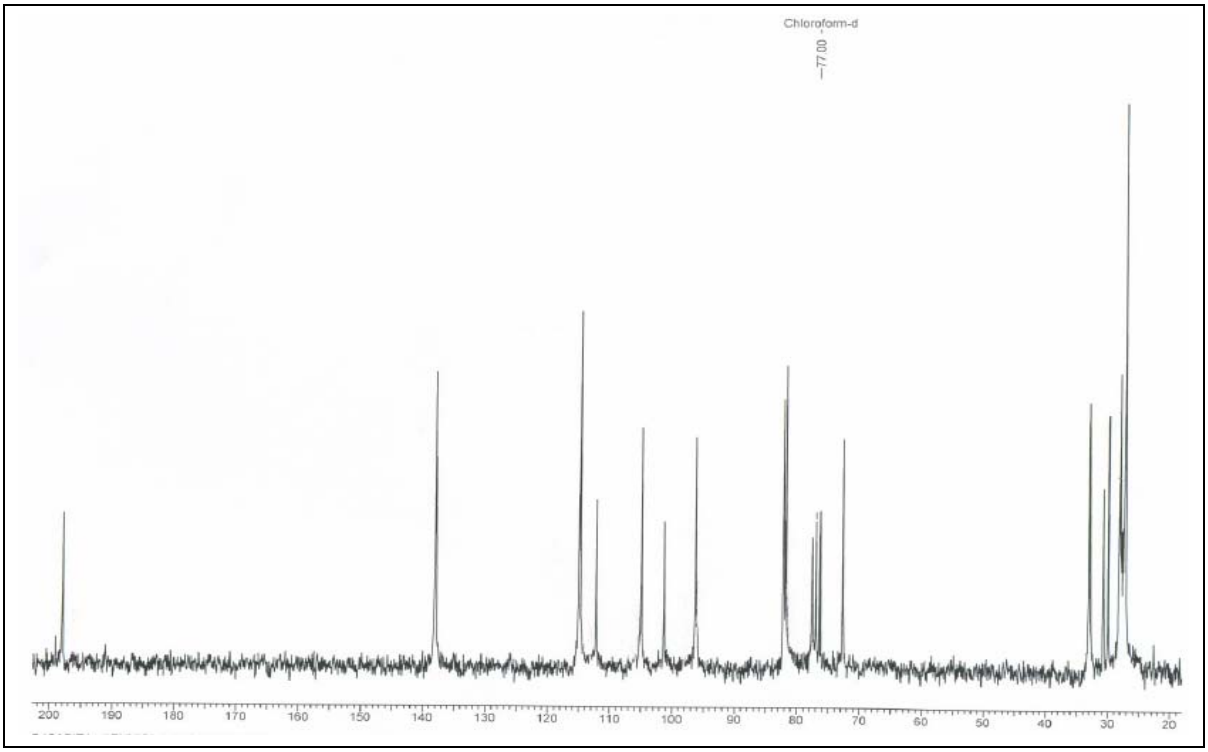


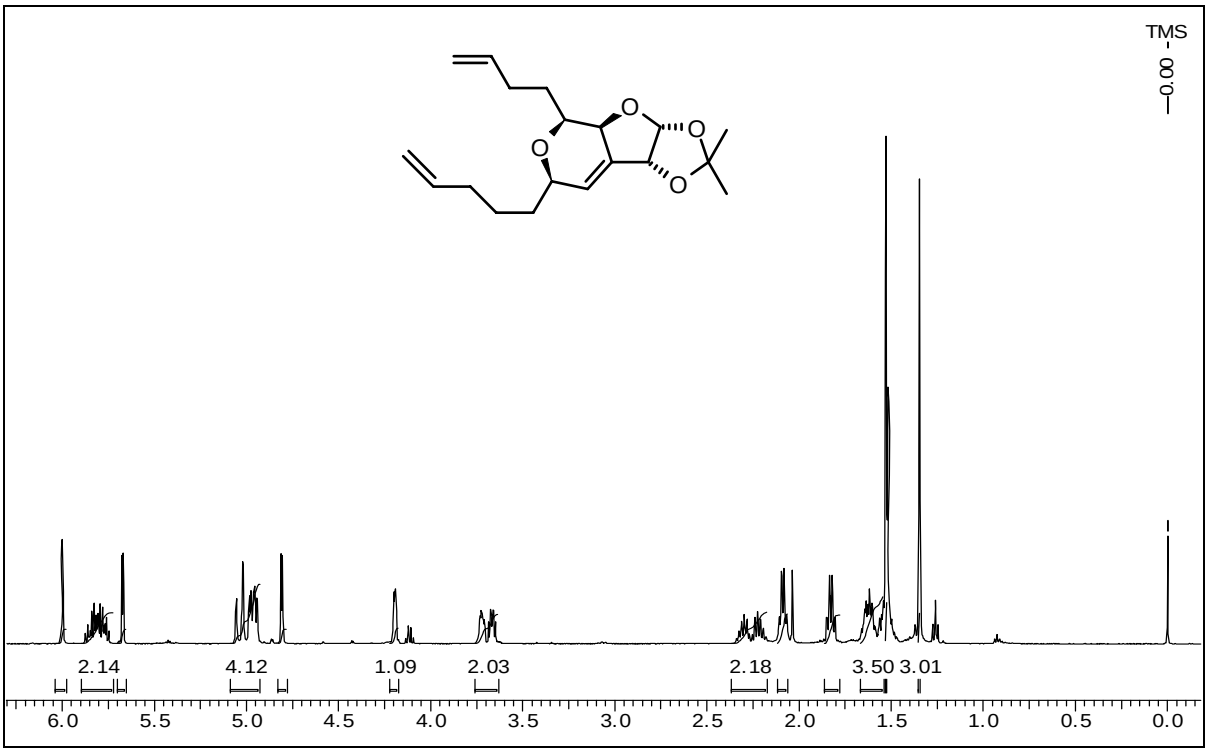
^{13}C NMR spectrum of compound 93 in $CDCl_3$



^{1}H NMR spectrum of compound 94 in $CDCl_3$



^{13}C NMR spectrum of compound 94 in $CDCl_3$



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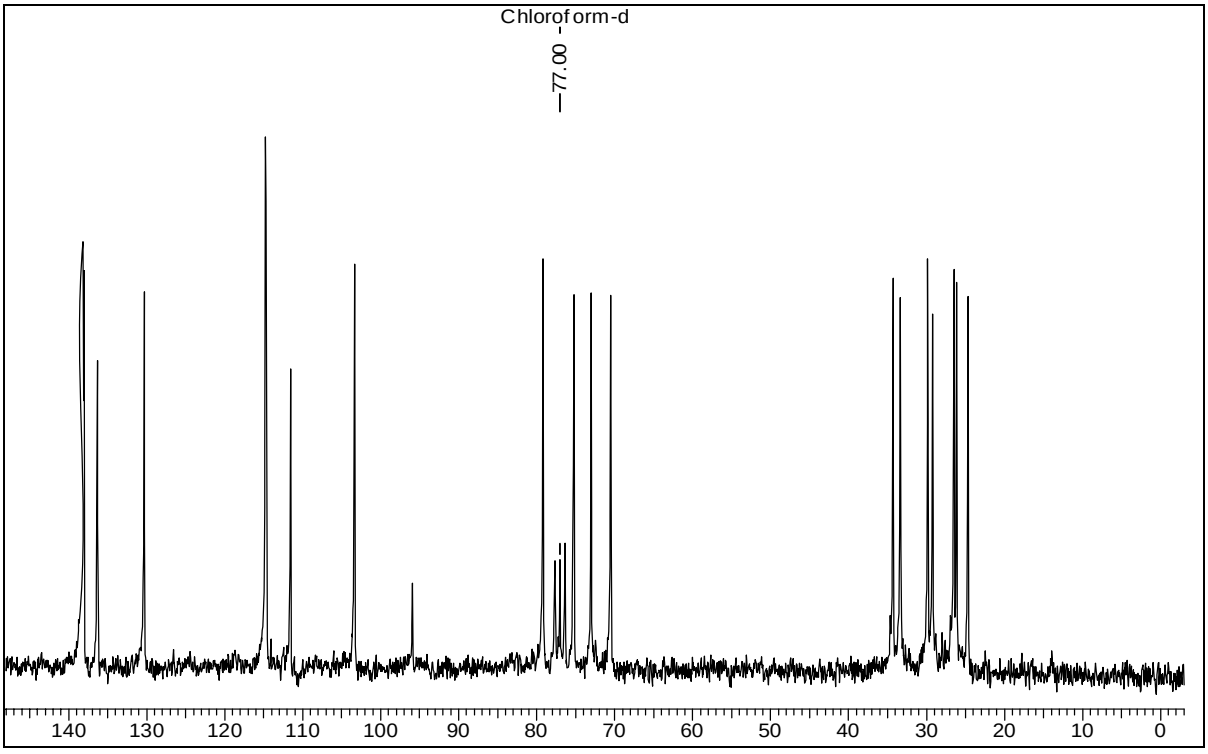

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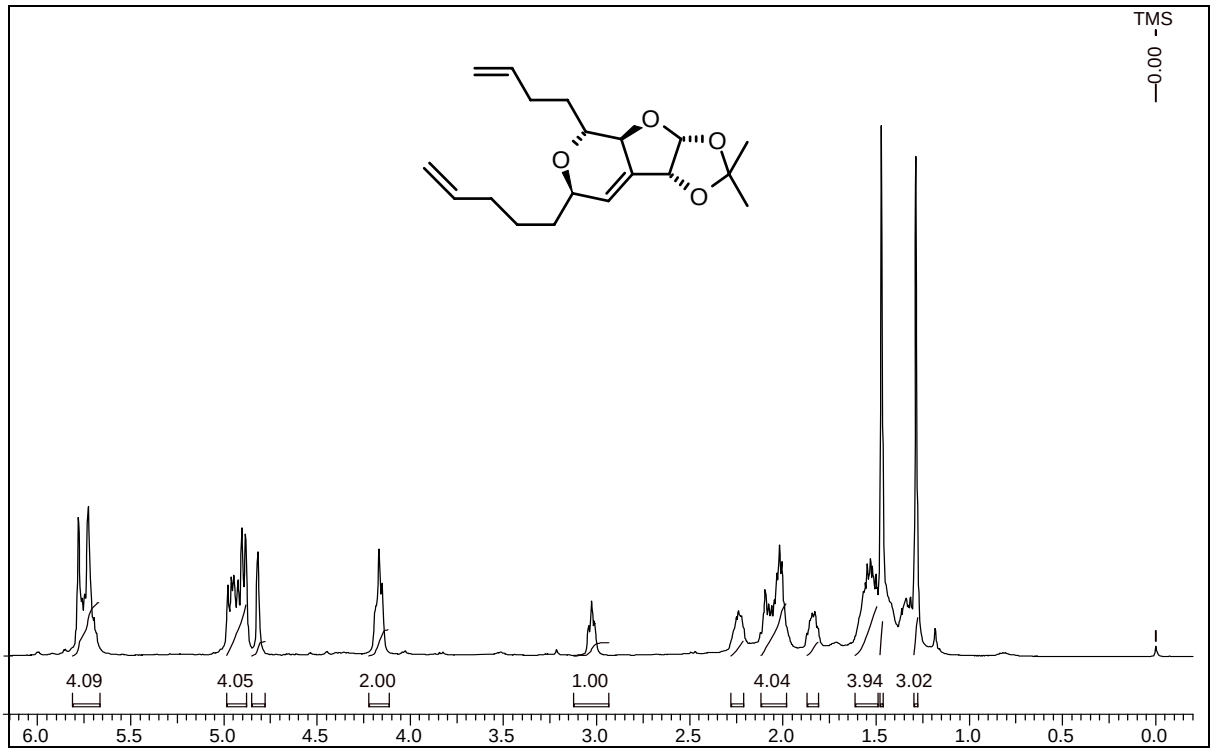

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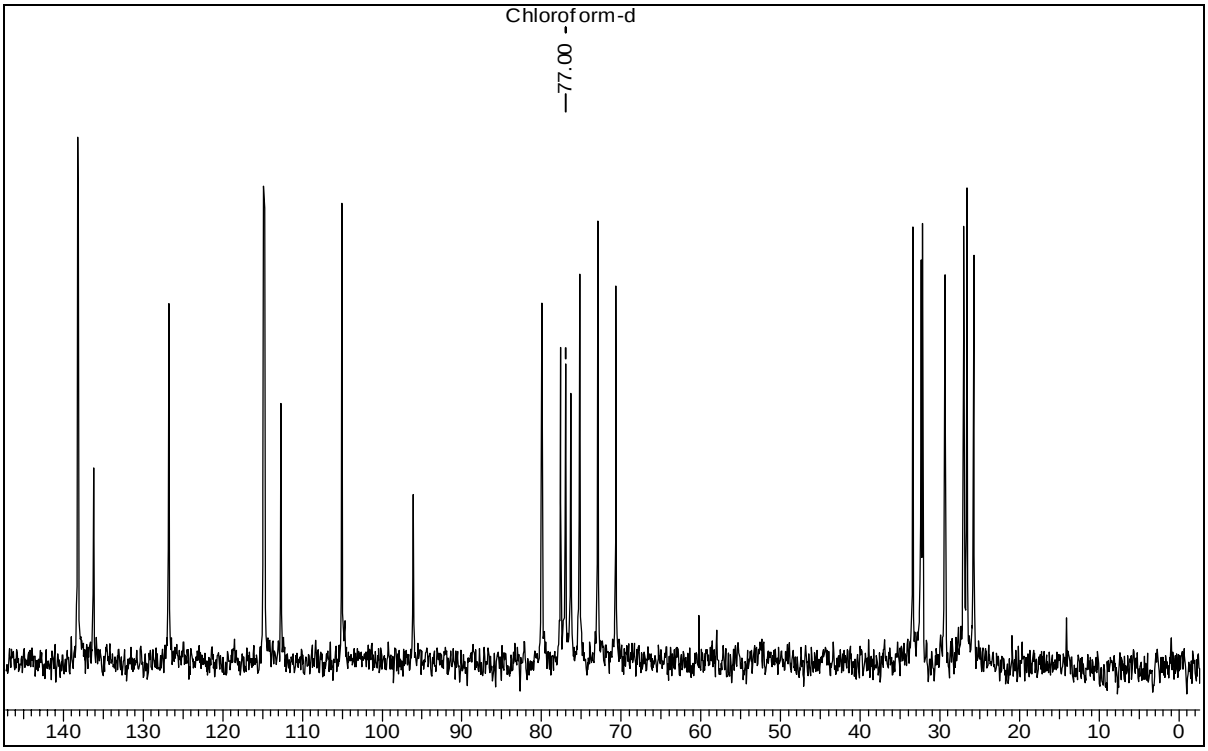

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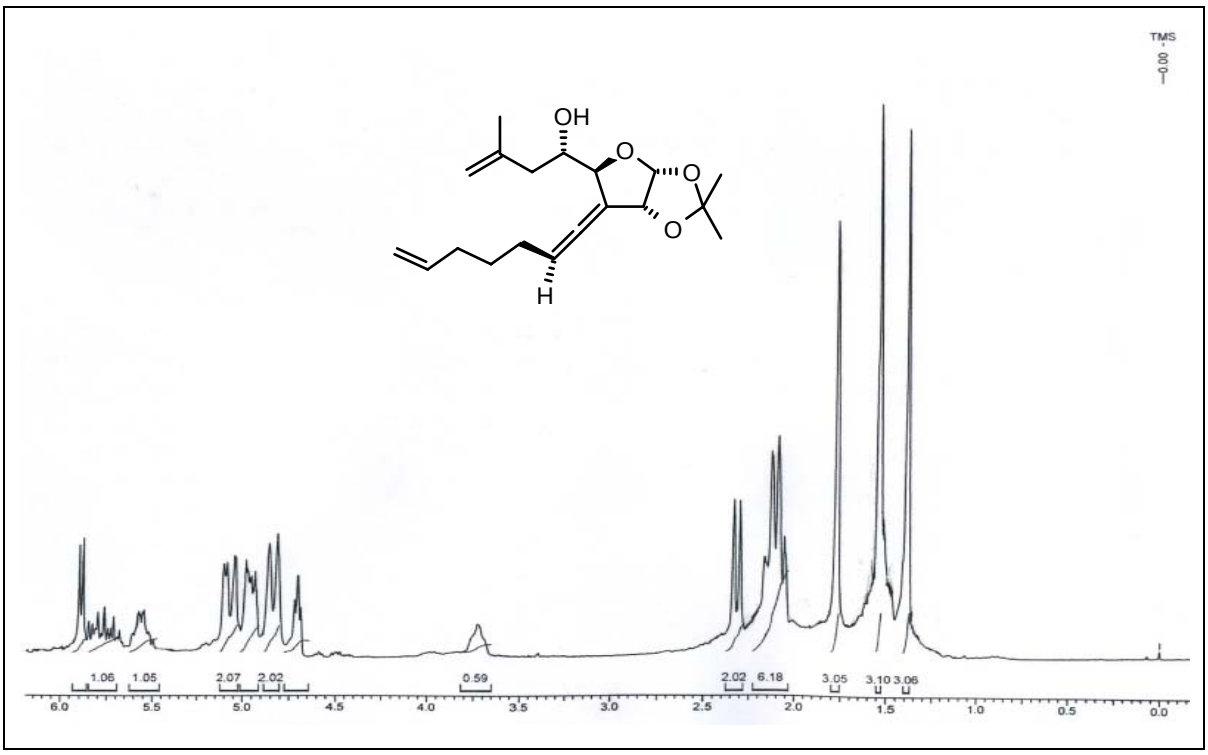
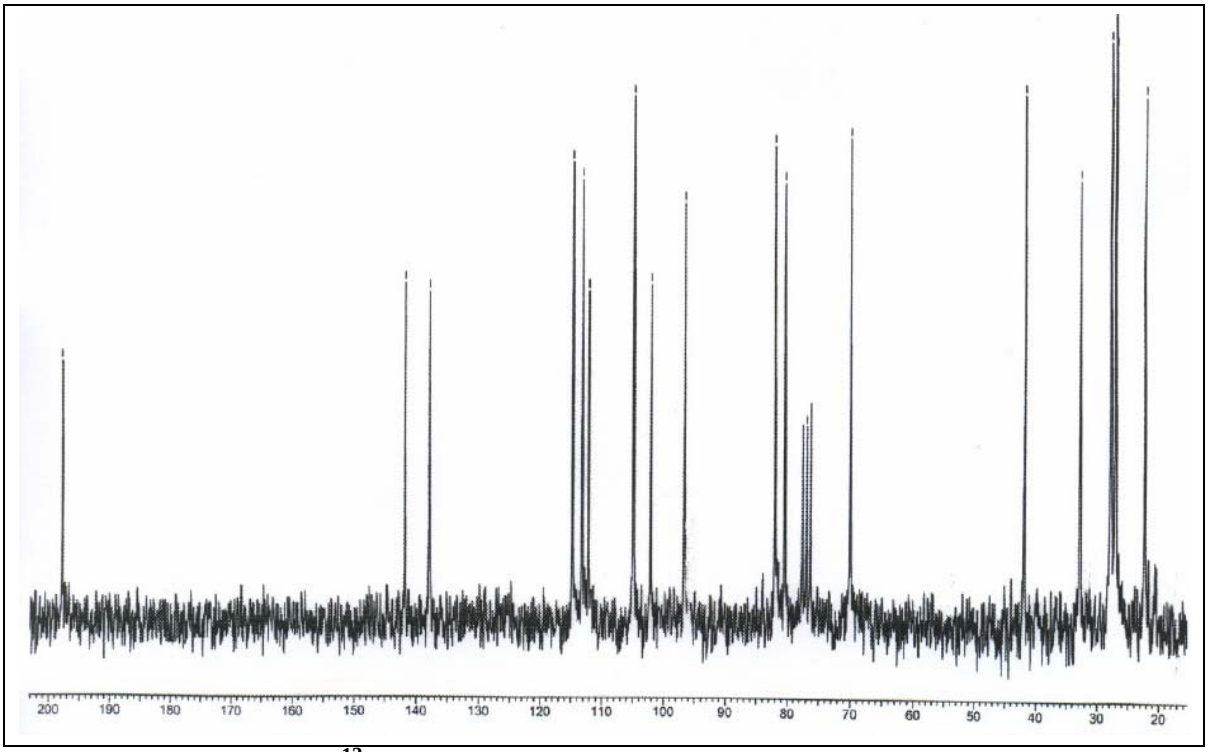
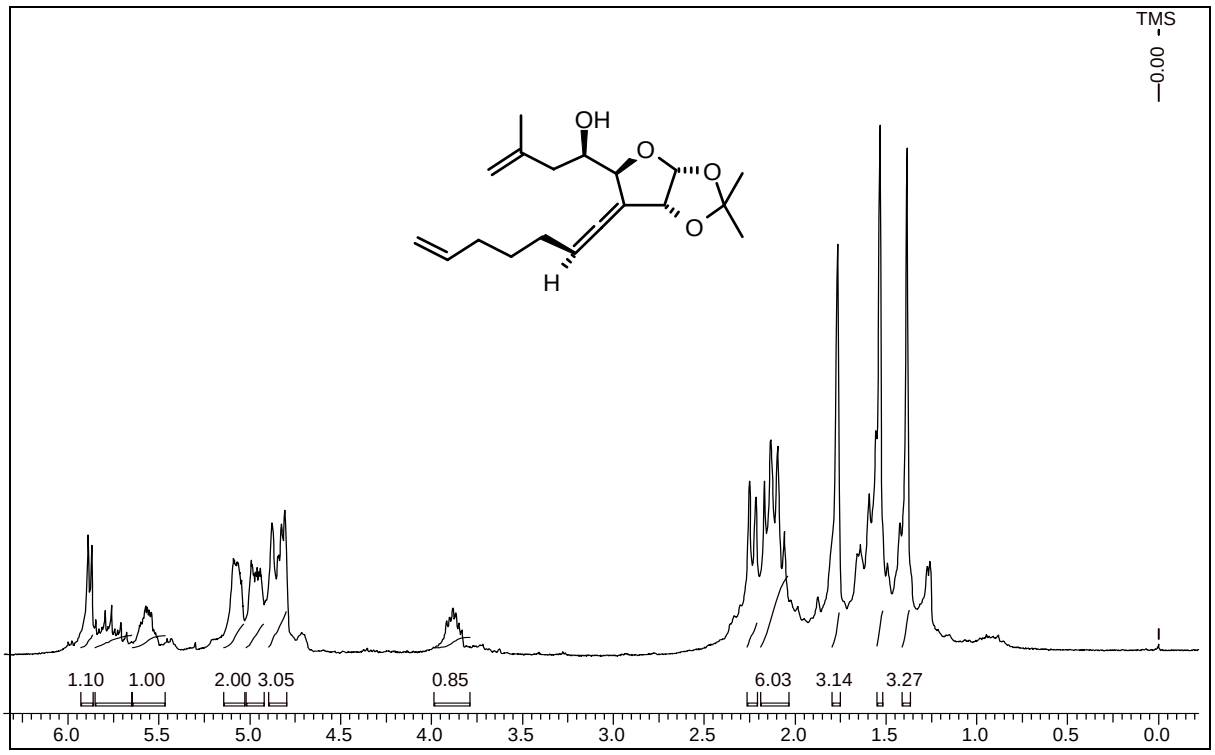


^{1}H NMR spectrum of compound 99 in $CDCl_3$



^{13}C NMR spectrum of compound 99 in $CDCl_3$



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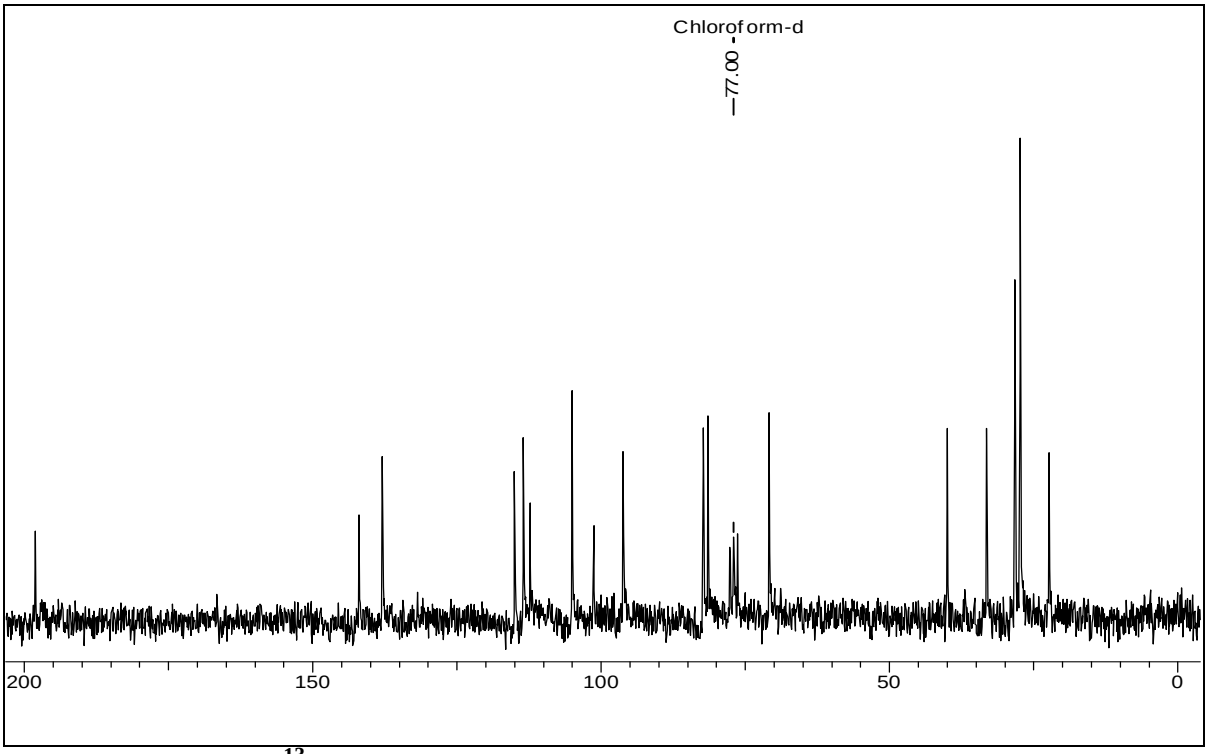

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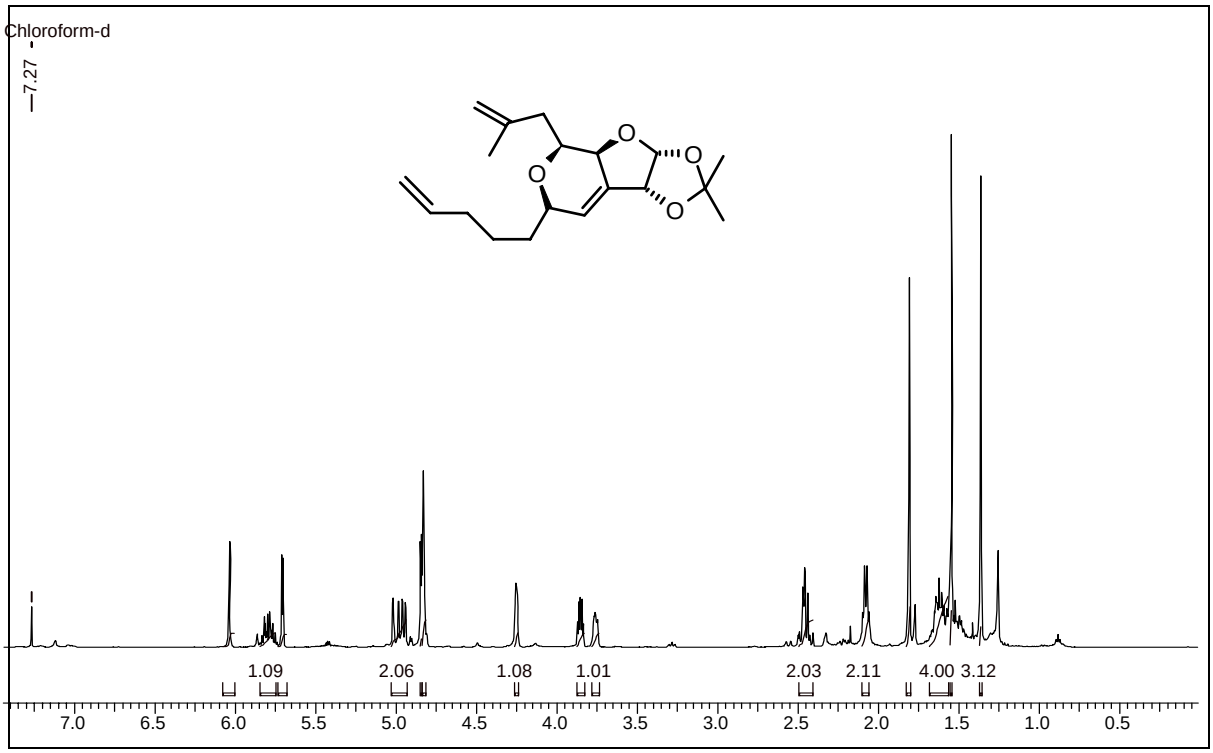

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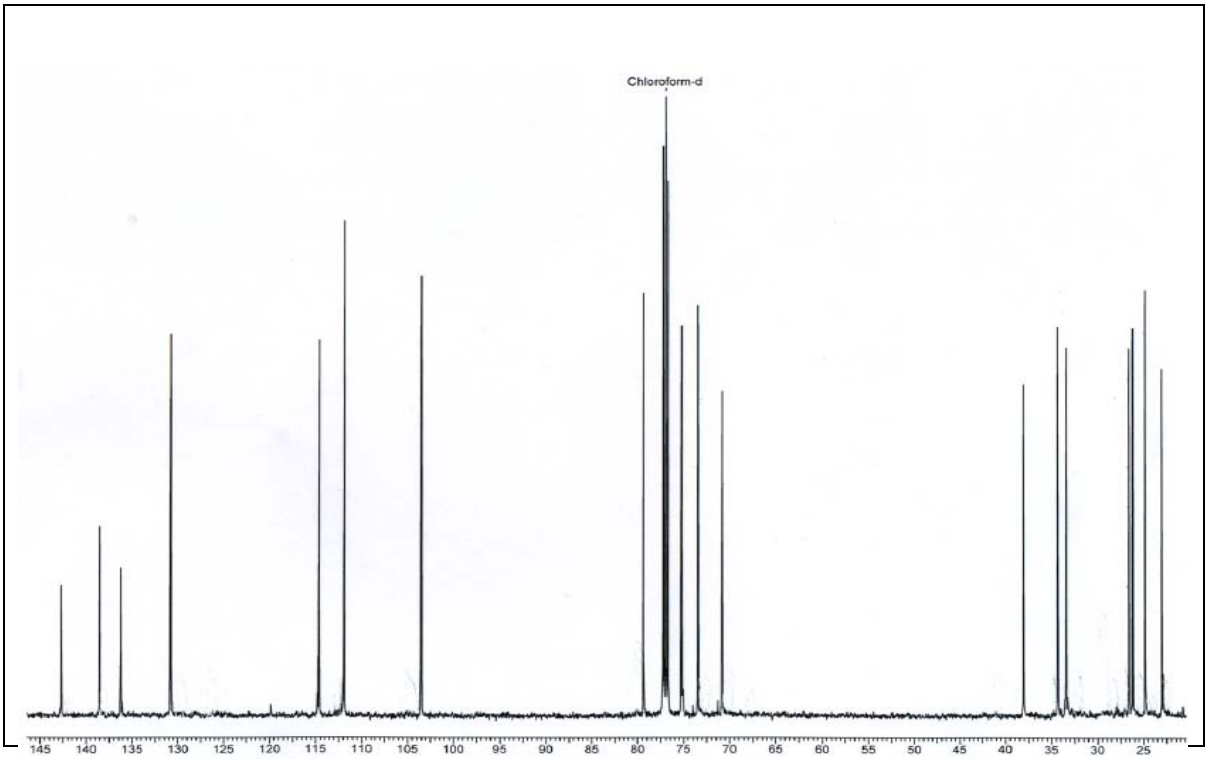

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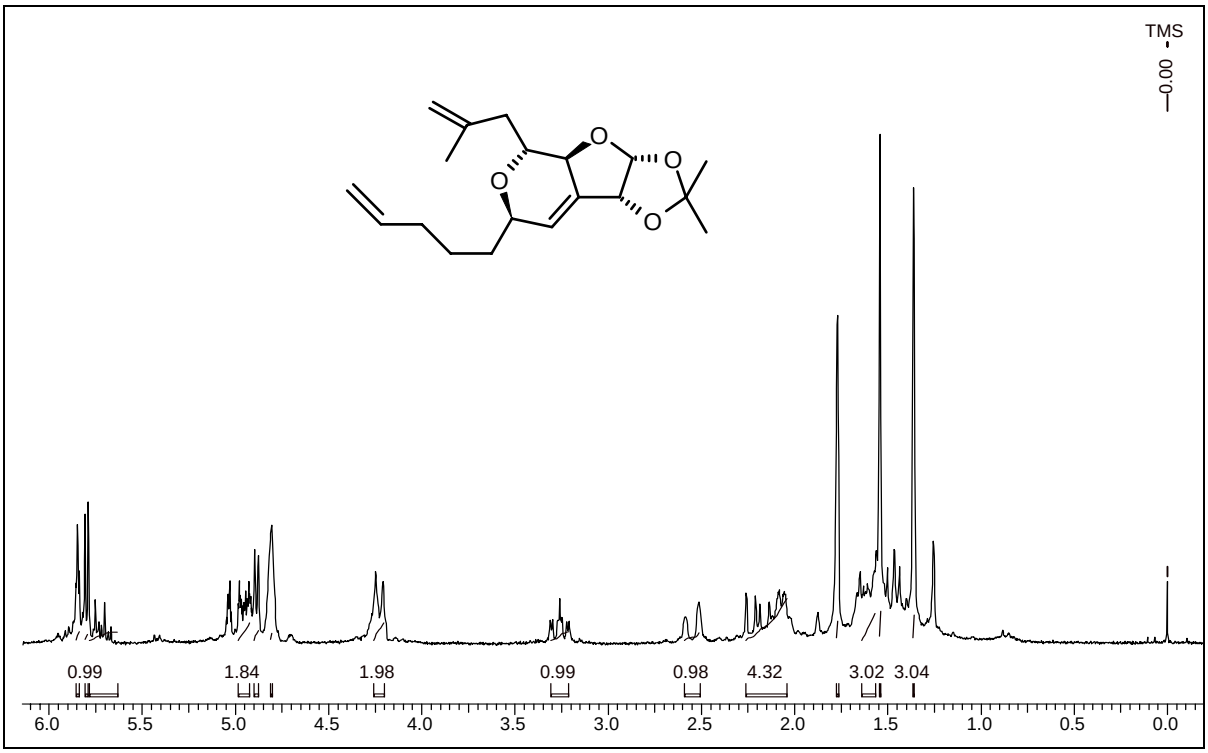
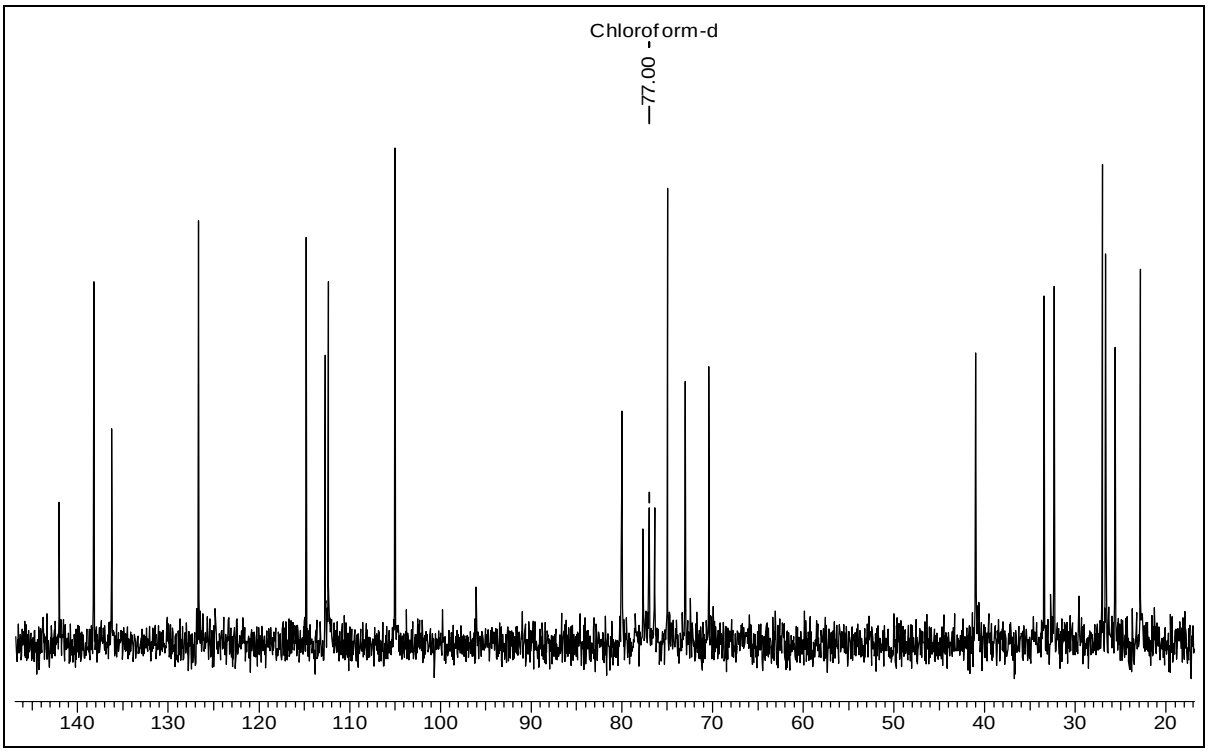
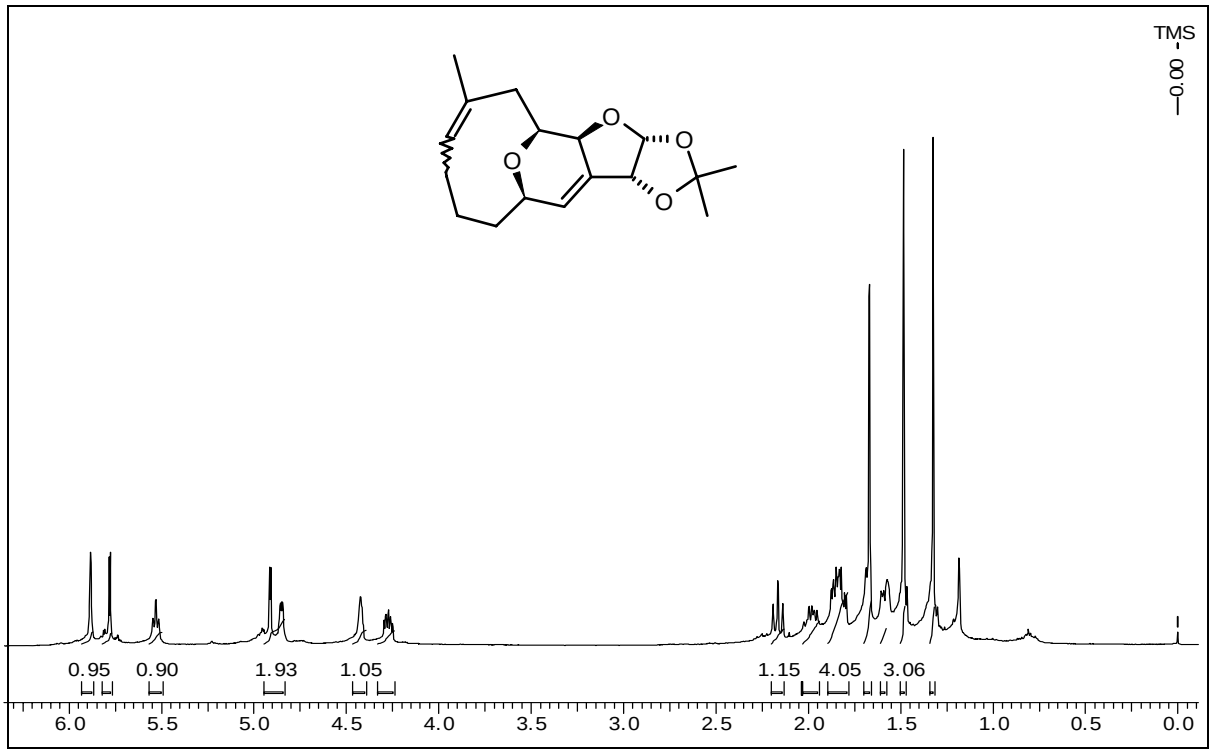


^{1}H NMR spectrum of compound 102 in $CDCl_3$



^{13}C NMR spectrum of compound 102 in $CDCl_3$



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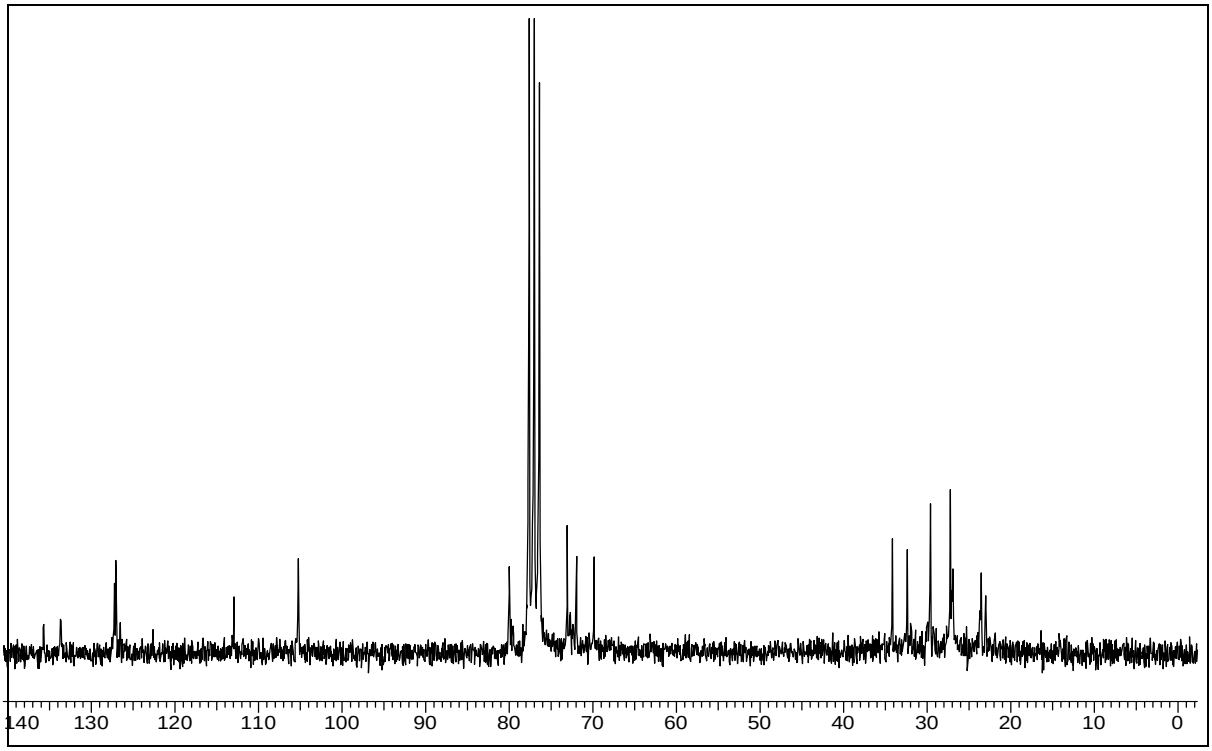
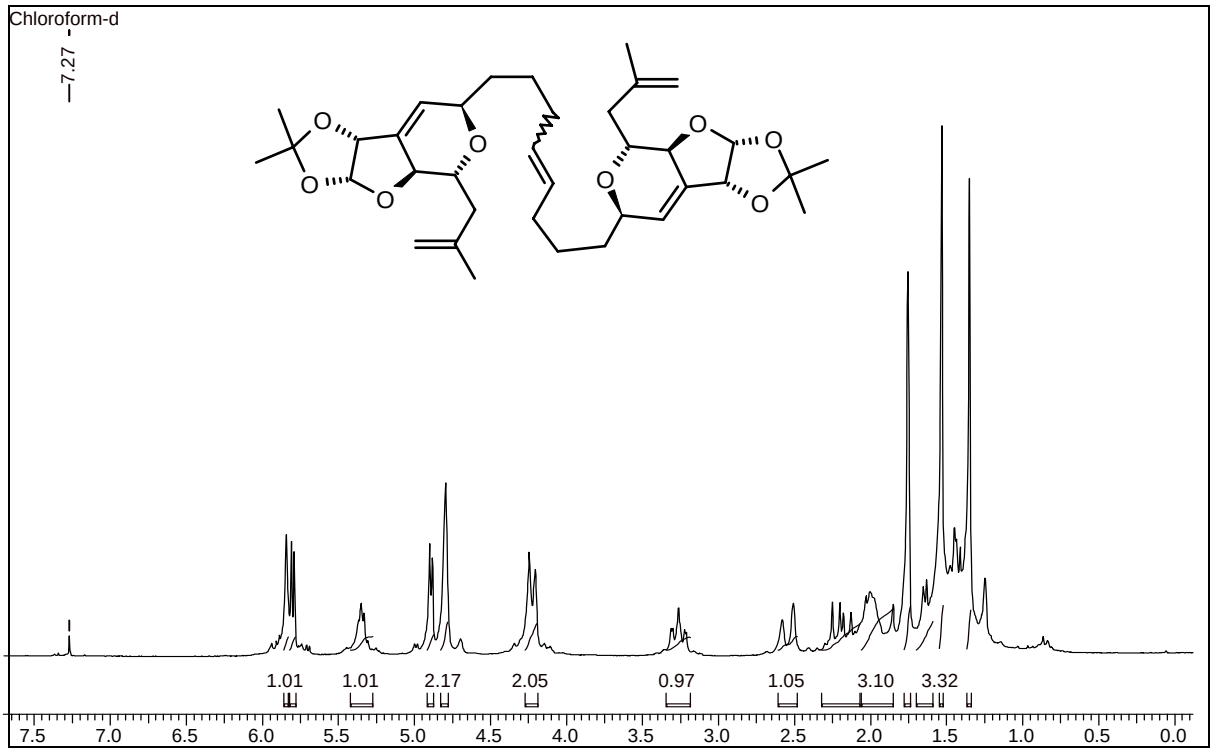
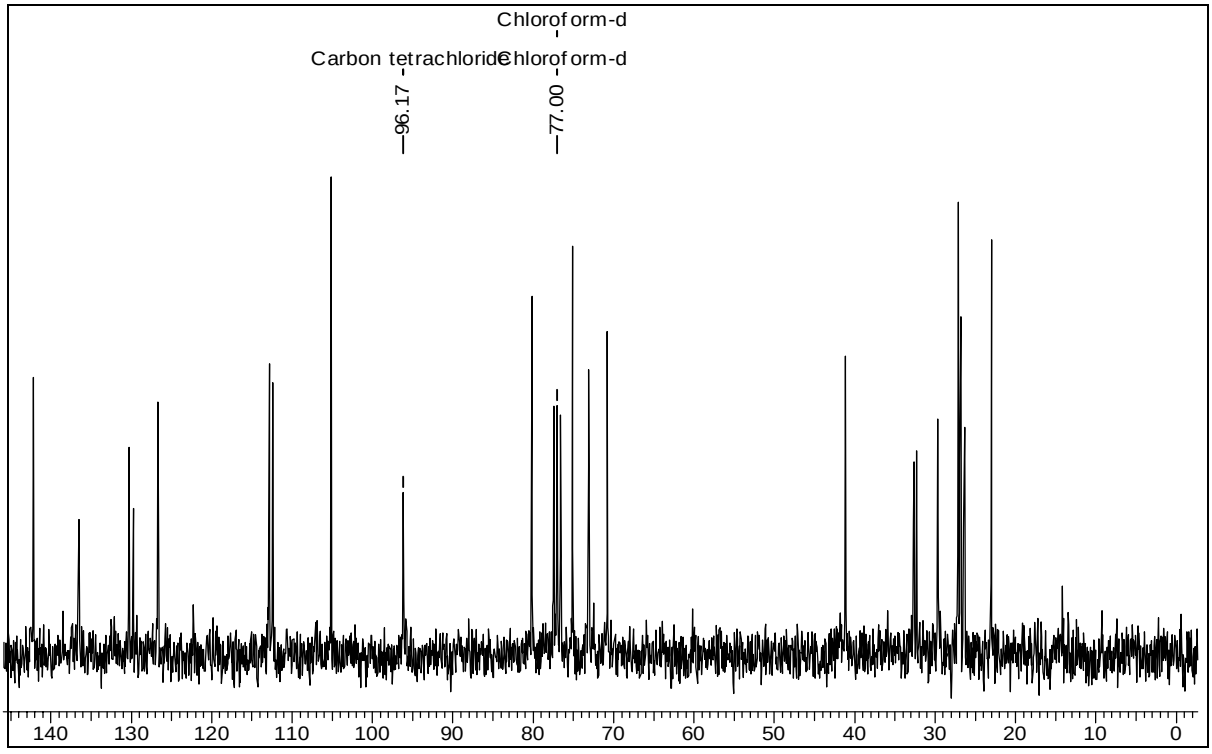


^{13}C NMR spectrum of compound 103 in $CDCl_3$



^{1}H NMR spectrum of compound 104 in $CDCl_3$



^{13}C NMR spectrum of compound 104 in $CDCl_3$

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CHAPTER –II

Synthetic studies toward Palau'amide

INTRODUCTION

INTRODUCTION

Introduction

The marine environment has been shown to provide a source of great diversity of chemical structures with promising biological activities. Among them nitrogen containing secondary metabolites are distinctly visible. Marine organism like cyanobacteria, molluskas and sponges are the largest producer of peptides, alkaloids, terpenoids, fatty acids, lipids and steroids. Current review study revealed that till date a total of 128 nitrogen-containing secondary metabolites, belonging mainly to the mixed PKS-NRPS structural class, isolated from filamentous marine cyanobacteria.

Cyanobacteria are an ancient and diverse group of microorganisms. They are able to inhabit and thrive in an incredible variety of environments because of their ability to produce a rich range of secondary metabolites. These metabolites have already been shown to display a wide spectrum of biological activities ranging from antibacterial[1] to immunosuppressive.[2] This diversity has generated considerable interest in cyanobacteria, since over half of the new drugs approved from 1983 to 1994 and 60% of the drugs currently approved for the treatment of cancer are still of natural origin[3] and basically consists of peptides, cyclic peptides and depsipeptides. One compound already in clinical trials for the treatment of cancer is based on the cryptophycins[4] isolated from terrestrial cyanobacteria. Dolastatin 10,[5] a modified pentapeptide isolated originally from the sea hare *Dolabella auricularia* and more recently from a marine cyanobacterium,[6] is another anti tumor agent being clinically evaluated.[7]

A number of highly potent cyanobacterial natural products have been discovered as potential lead compounds for further drug development basically consists of cyclic peptides and depsipeptides. Cyclic structures reduce peptide conformational freedom and often result in high receptor binding affinities by reducing unfavorable entropic effects. For this reasons the cyclic peptides often make promising lead compounds in drug discovery.[8]

Today, a vast number of challenging complex peptide molecules have been isolated and fully characterized from marine cyanobacteria and this is possible because of the advancement of reverse phase HPLC, chiral chromatography and development of characterization techniques by spectroscopy especially 2D NMR and FAB mass.

Bioactive cyclic depsipeptide

Depsides and depsipeptides are two classes of natural products that have recently received much attention. These polymeric compounds are analogous to peptides. Peptides are composed of amino acids linked by amide bonds; depsides are composed of hydroxy acids linked by ester bonds; and depsipeptides are composed of both hydroxy and amino acids linked by ester and amide bonds. Many depsipeptides exhibit special biological activities.

There are several prominent and important depsipeptides that have been extensively well known. These include vancomycin,[9] valinomycin,[10] actinomycins,[11] destruxins, [12] didemnins, [13,14] discodermins, discokiolides, theonellapeptolides, polydiscamides,[15a] dolastatins,[15b] FR901228,[16] arenastatin A,[17] quinoxaline,[18] micropeptins, oscillapeptin, microviridin, cryptophycins, and aeruginosins. [19, 20]

Depsipeptides have shown the greatest therapeutic potential as anticancer agents. Four depsipeptides have entered clinical trials for cancer treatment. These are didemnin B, dehydrodidemnin B (DDB, aplidine), dolastatin 10, and FR901228. Didemnin B entered Phase II trials where it demonstrated its efficacy against cancer.

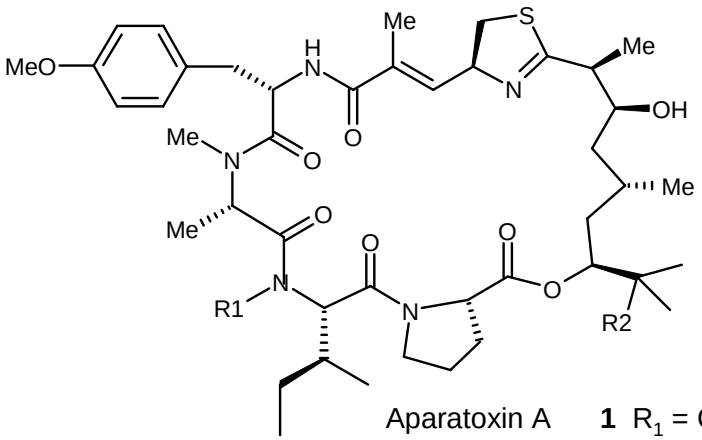
Among the antiviral compounds discovered, the callipeltins[21,22] and quinoxapeptins are particularly promising due to their inhibitory activities against HIV. Possibly these compounds can be developed as anti AIDS drugs. If not possibly synthetic analogs based on their pharmacophores can be developed into clinically useful compounds. Sansalvamide[23] also shows activity against the poxvirus molluscum contagious virus (MCV) linked with AIDS opportunistic infections.

Antifungal compounds includes jaspamides,[24] cyclolithistideA,[25] LI-F antibiotics,[26] and viscosinamide.[27]

Several depsipeptides, including WAP-8294A2,[28,29] theonellapeptolides,[30] fusaricidins,[31,32] and vinylamycin,[33] inhibit the growth of several bacteria.

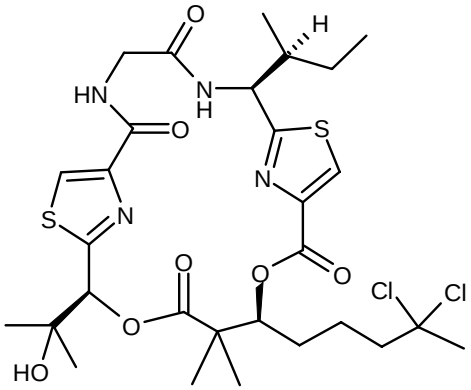
Depsipeptides from cyanobacterial *Lyngbya*

Apratoxins A-C (**1-3**) are intriguing marine natural products of mixed biogenetic origin. Isolated from cyanobacterial *Lyngbya spp.* collected in Guam[34] and Palau[35] by Moore, Paul, and co-workers.

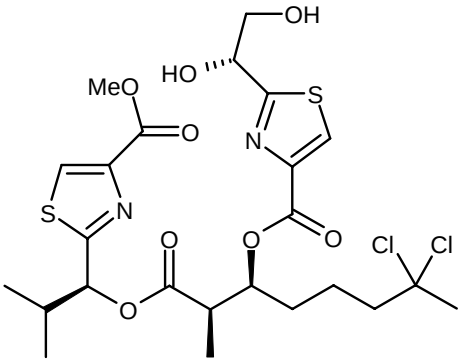


Aparatoxin A **1** $R_1 = CH_3$, $R_2 = CH_3$
Aparatoxin B **2** $R_1 = H$, $R_2 = CH_3$
Aparatoxin C **3** $R_1 = H$, $R_2 = H$

1-3 are cyclodepsipeptides that embody both polypeptide and polyketide domains. These include highly methylated amino acids joined via proline ester and thiazoline moieties to a novel 3,7-dihydroxy-2, 5, 8, 8-tetramethylnonanoic acid. The unique structural features of **1** are accompanied by high levels of cytotoxicity against KB and LoVo cancer cells, with *in vitro* IC_{50} values of 0.52 and 0.36 nM, respectively. However, **1** was poorly tolerated *in vivo* in mice. Although the mode of action of **1** remains unknown, it appears to effect neither microtubule polymerization dynamics nor topoisomerase I. Apratoxin C displayed an *in vitro* cytotoxicity profile similar to that of **1**. These results suggest that *in vitro* cytotoxicity of the apratoxins is closely related to subtle primary structural variations that are manifested in larger tertiary changes in molecular conformation. The small amounts of the apratoxins available via isolation from natural sources presently limit more in-depth biological studies.

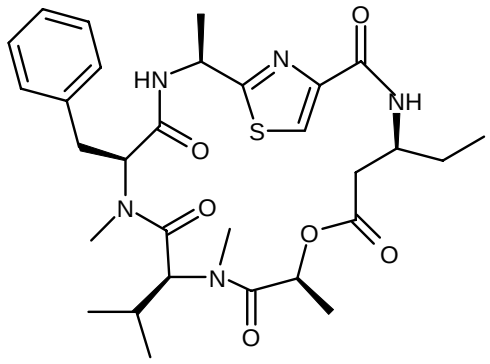


Lyngbyabellin (**4**)



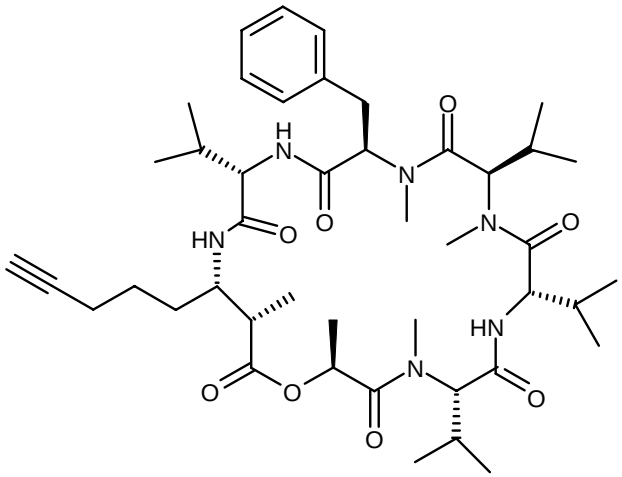
Dolabellin (**5**)

LyngbyabellinA (**4**), a new cytotoxin that is closely related to another compound originally isolated from *D. auricularia*, dolabellin (**5**).[36] Cyanobacterium VP417 was collected at Finger's Reef, Apra Harbor, Guam, and identified as a strain of *L. majuscule*,[37] which was first collected on August 4, 1997, and a specimen was preserved in formalin has been deposited at the University of Hawaii. The freeze-dried VP 417, was extracted with CH_2Cl_2-EtOAc-MeOH (1:1:1). This lipophilic extract (6.31 g) was partitioned between hexane and 80% aqueous MeOH. The solvent-evaporated methanolic phase (1.73 g) was chromatographed on Si gel, eluting initially with CH_2Cl_2, followed by CH_2Cl_2 solutions containing progressively increasing amounts of *i*-PrOH, and finally with MeOH. The fraction eluting with 8% *i*-PrOH (14.3 mg) was subjected to semipreparative reversed-phase HPLC (flow rate, 2 mL/min) to afford **4** (5.6 mg, *t*R 14.0 min). Compound **4** exhibits moderate cytotoxicity against KB cells (a human nasopharyngeal carcinoma cell line) and LoVo cells (a human colon adenocarcinoma cell line), with IC_{50} values of 0.03 μg/mL and 0.50 μg/mL, respectively. *In vivo* trials revealed that **4** is toxic to mice. The lethal dose varied from 2.4 to 8.0 mg/kg. At sublethal doses (i.e., 1.2-1.5 mg/ kg), there was no antitumor activity against the murine colon adenocarcinoma C38 or the mammary adenocarcinoma M16.



Obyanamide (**6**)

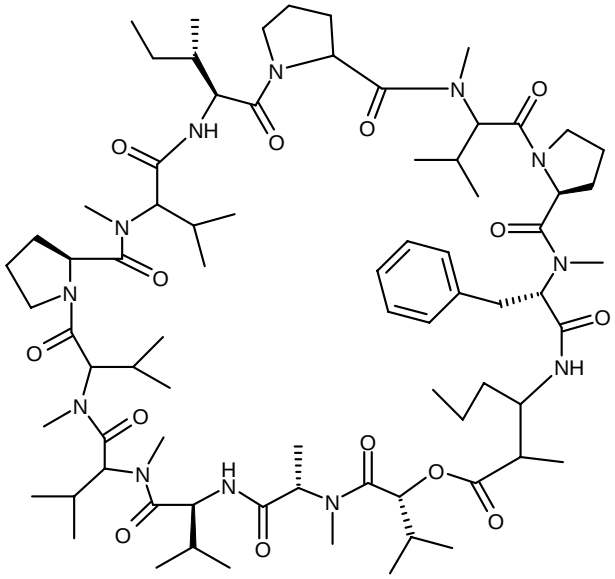
Obyanamide (**6**) was isolated from a variety of the marine cyanobacterium *Lyngbya confervoides* collected in Saipan, Commonwealth of the Northern Mariana Islands.[38] HRFABMS analysis established the molecular formula for **6** as $C_{30}H_{41}N_5O_6S$. Gross structural elucidation of this novel cyclic depsipeptide relied on extensive application of 2D NMR techniques. Compound **6** exhibited moderate cytotoxicity against KB and LoVo cells with IC_{50} values of 0.58 and 3.14 μg/mL, respectively.



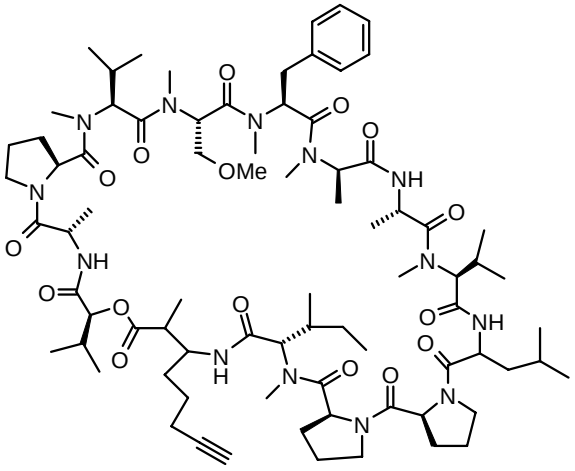
Ulangapeptin (**7**)

Ulongapeptin (**7**), a cyclic depsipeptide, was isolated from a Palauan marine cyanobacterium *Lyngbya* sp.[39] The gross structure was elucidated through one-dimensional TOCSY experiments and other spectroscopic techniques. The absolute and relative stereochemistry of the α-amino acid, 3-amino-2-methyl-7-octynoic acid (AMO), in **7** was determined by synthesis of the saturated α-alkyl-β-amino acid and Marfey's analysis of the acid hydrolysate of tetrahydro-**1**. Ulongapeptin (**7**) was cytotoxic against KB cells at an IC_{50} value of 0.63 μM.

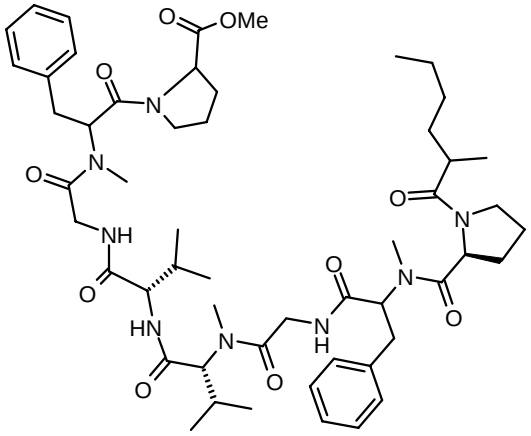
The malevamides A-C (**8**-**10**),[40] are three structurally unrelated depsipeptides isolated from the cytotoxic extracts of the cyanobacterium *Symploca laete-viridis.* The organisms were collected off Oahu. The malevamides contain some unusual amino and hydroxy acids,



Malevamide B (**9**)



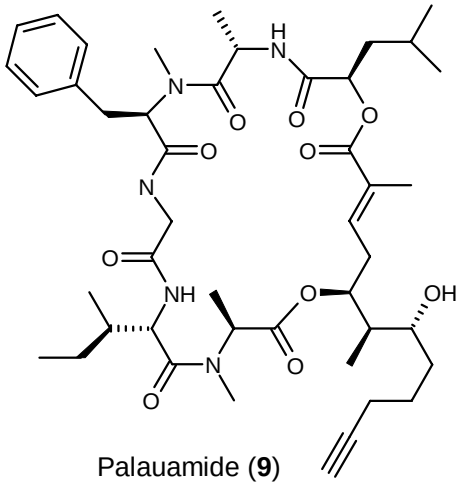
Malevamide C (**10**)



Malevamide A (**8**)

including several methylated and dimethylated residues. Other unusual moieties include 3-amino-2-methylhexanoic acid (Amh) and 3-amino-2-methyl-7-octynoic acid (Amo). Configurations of most of the residues could be determined by chiral HPLC analysis. However, the stereochemistries of 2-methylhexanoic acid, Amh, Amo, and several

N-methyl amino acids were not determined. The pure malevamides A-C were inactive against P388, A-549, and HT-29 cell lines at concentrations up to 2 mg/mL (2 mM). In the spring of 2000, Moore and co-workers collected a strain of cyanobacterium from Ulong Channel, palau, belonging to the genus *Lyngbya*. Bioassay-guided fractionation of the lipophilic extract of the species of *Lyngbya* from Palau has yielded 24-membered cyclic depsipeptide Palau'amide (**9**), which had an IC_{50} value of 13 nM against KB cells.[41]



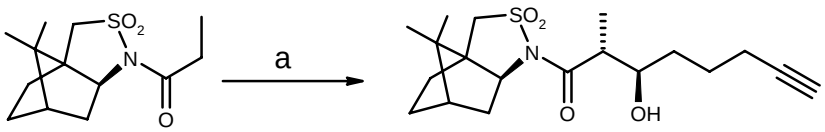
Palauamide (**9**)

The molecular formula of Palauamide (**9**) was determined by high-resolution mass spectrometry which produced a $[M+Na]^+$ ion at *m/z* 874.5003 afforded a molecular formula of $C_{46}H_{69}O_{10}N_5$ (0.1 mDa error).The gross structure analysis was carried out by ^1H, ^{13}C, COSY, HMBC and TOCSY experiments.The complex structural feature and interesting biological profile prompted us to undertake its synthesis. Only one synthesis of **9** has been reported by Ma et al. It is worth to mention their synthetic protocol here.

Previous Work

Ma approach:[42]

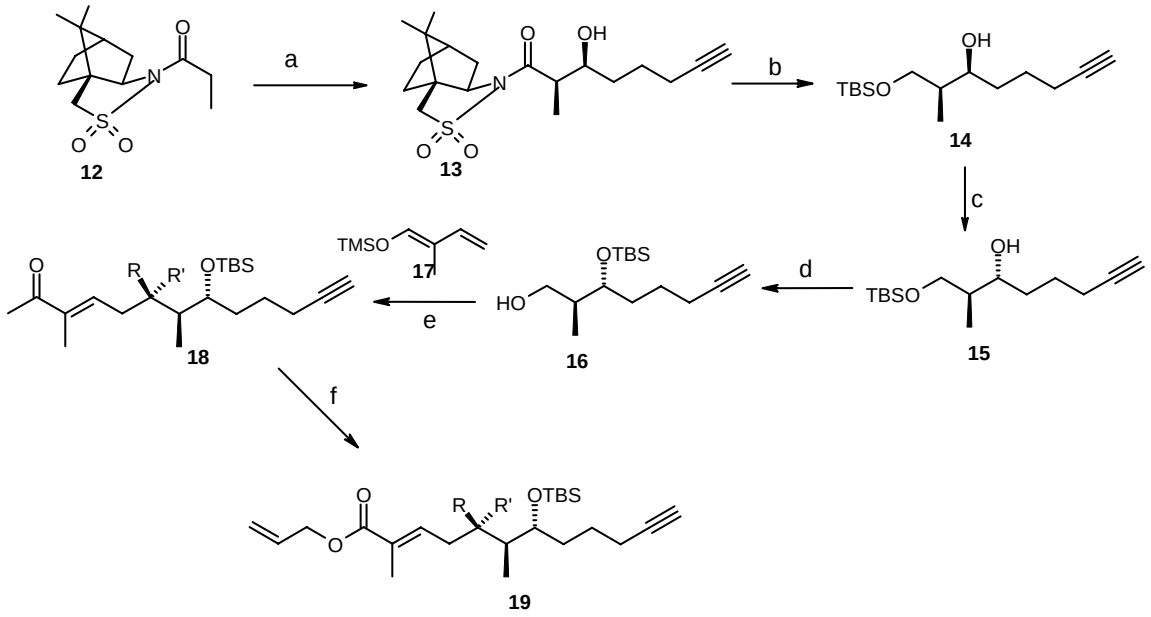
Scheme 1 Synthesis of Polyketide alcohol following *Syn* aldolization strategy



10 **11**

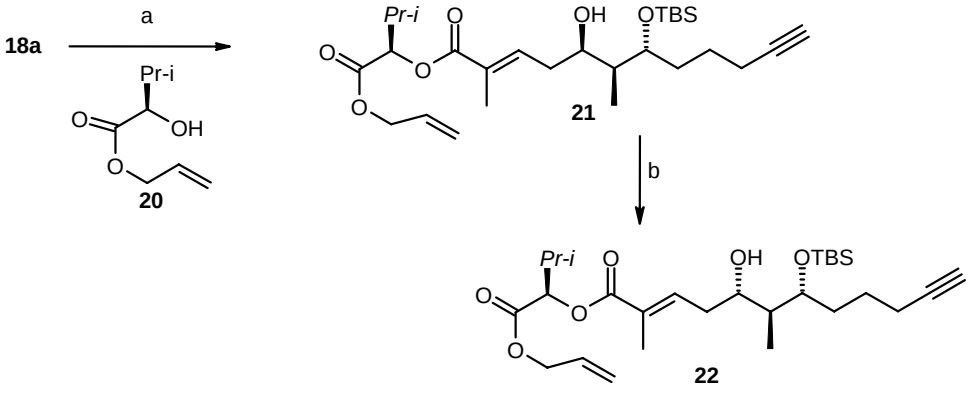
Reagent and conditions: a) Et_2BOTf/DIPEA, CH_2Cl_2, -15 ^oC, 5-hexynal, $TiCl_4$, -78 ^oC

Scheme 2: Synthesis of Polyketide Chain



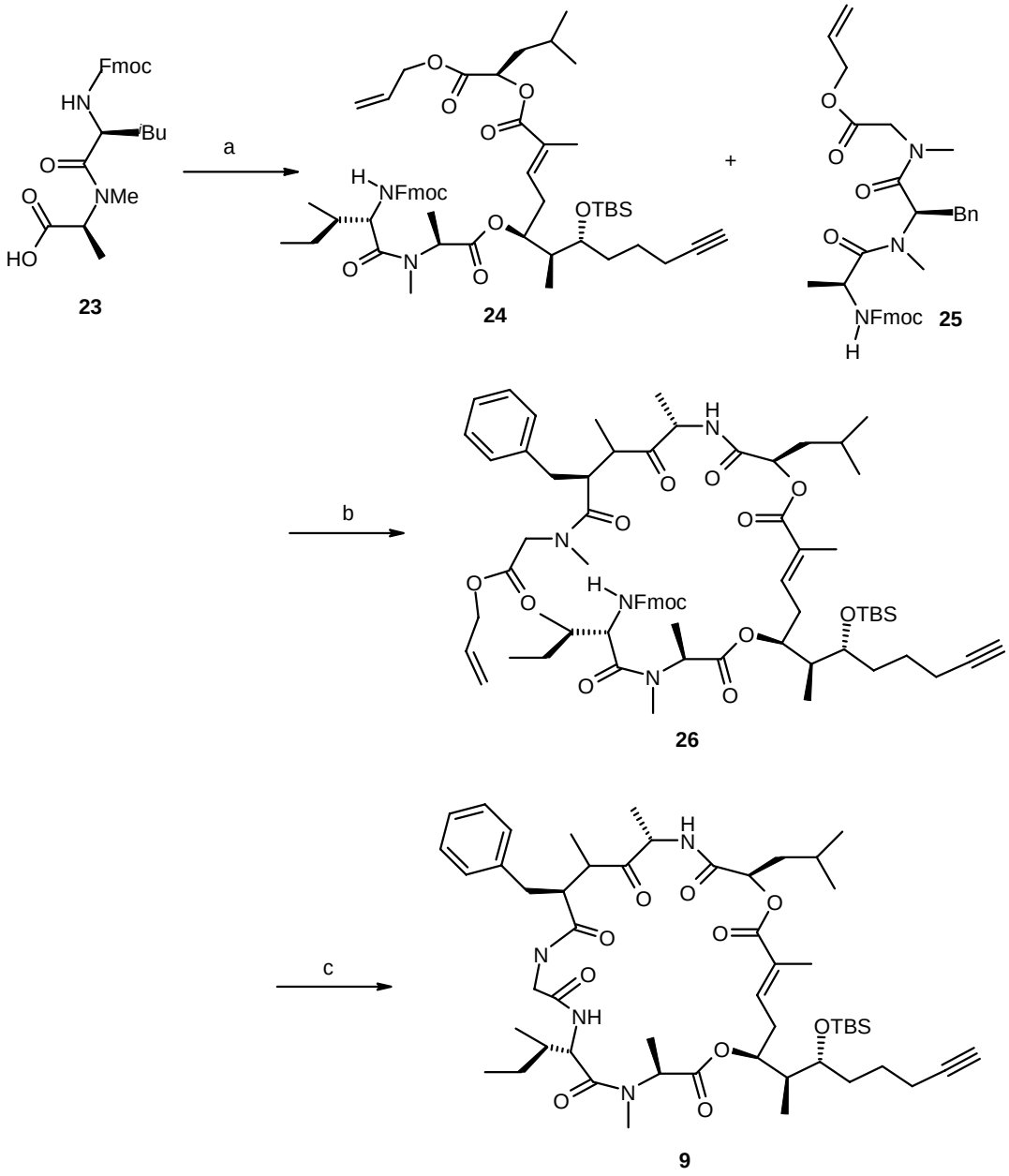
Reagent and conditions: a) Et_2BOTf, DIPEA, DCM, -15 ^oC, 5-hexynal, -78 ^oC b) i.LAH, THF; ii. TBSCl, imidazole; c) i. Ph_3P, DEAD, p-nitrobenzoic acid; ii.KOH d) i. TBSCl, imidazole; ii.pyridine hydrofluoric salt e) Swern oxidation, **17**, BF_3:Et_2O, 9:1 DCM:Et_2O, -78 ^oC f) i. $NaClO_2$, NaH_2PO_4, *t*-BuOH, 2-methyl-2-butene; ii. Allylbromide, $KHCO_3$, DMF

Scheme 3 Synthesis of 29



Reagent and conditions: a) **18a**, $NaClO_2$, NaH_2PO_4, **20**, EDC; b) i. Dess-martin periodinane, DCM, ; ii. $NaBH_4$, MeOH, -50 ^oC

Scheme 4 Synthesis of the proposed structure of Palau'amide (9)



Reagent and conditions: a) 2,4,6-trichloro-benzoyl chloride, DIPEA, **22**, DMAP; b) i. Pd $(PPh_3)_4$, NMA, THF; ii. Et_2NH, CH_3CN; iii. HATU, DIPEA; c) i. $Pd(PPh_3)_4$, NMA; ii. Et_2NH, CH_3CN; iii. HATU, DIPEA; iv. 5% HF, CH_3CN.

PRESENT WORK

In 2003, Moore and co-workers reported the isolation, structure elucidation, and biological activity (cytotoxicity to KB cells, IC_{50} = 13 nm) of palauamide (**9**), an architecturally novel cyclic depsipeptide from the bioassay-guided fractionation of the extract species of lyngbya from Palau.[41] Key structural elements include a five aminoacids backbone fused together in a macrocycle and a novel polyketide chain incorporated into the molecule. The molecular architecture of the polyketide comprises three contigious chiral centers having 1,3-syn diol flanked by a methyl group anti to each other, a terminus containing an alkyne moiety and an α,β unsaturated carboxylic acid at the other end. Potent biological activity coupled with unique structural features and limited availability prompted us to explore the synthesis of Palau'amide (**9**).

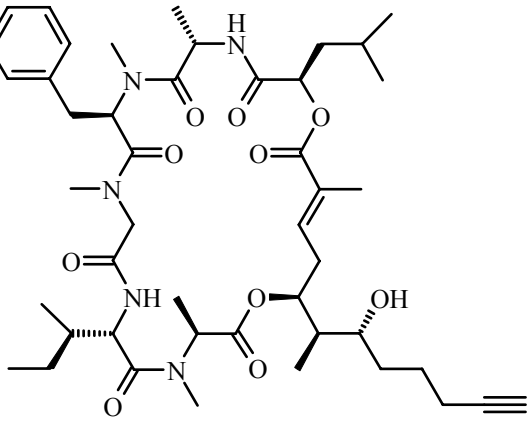


Figure 1. Palau'amide (**9**)

The first total synthesis of Palau'amide has been reported by Dawei Ma and co-workers in 2005[42]: the polyketide chain was synthesized by following Oppolzers protocol and utilizing a vinylogous Mukaiyama aldol reaction as the key reactions. The aldolization strategy to build the C38 and C39 stereocentre wasn't successful. "*Syn*" aldolization and Mitsonobue inversion were required to obtain the requisite stereochemistry. The analytical data of synthesized Palau'amide didn't matched with the natural one. In this context, we planned to synthesize the Palau'amide molecule following an alternative path to correlate the data with the natural one.

Here, we envisaged a retrosynthetic path for the synthesis of Palau'amide **9** keeping in mind Yamaguchi Lactonisation and esterification as our key reactions. According to retrosynthetic analysis (Figure 2) cyclic depsipeptide **9** could be obtained from **27** by Yamaguchi lactonisation which in turn can be synthesized by Yamaguchi esterification of pentapeptide acid **28** and polyketide alcohol **29**.

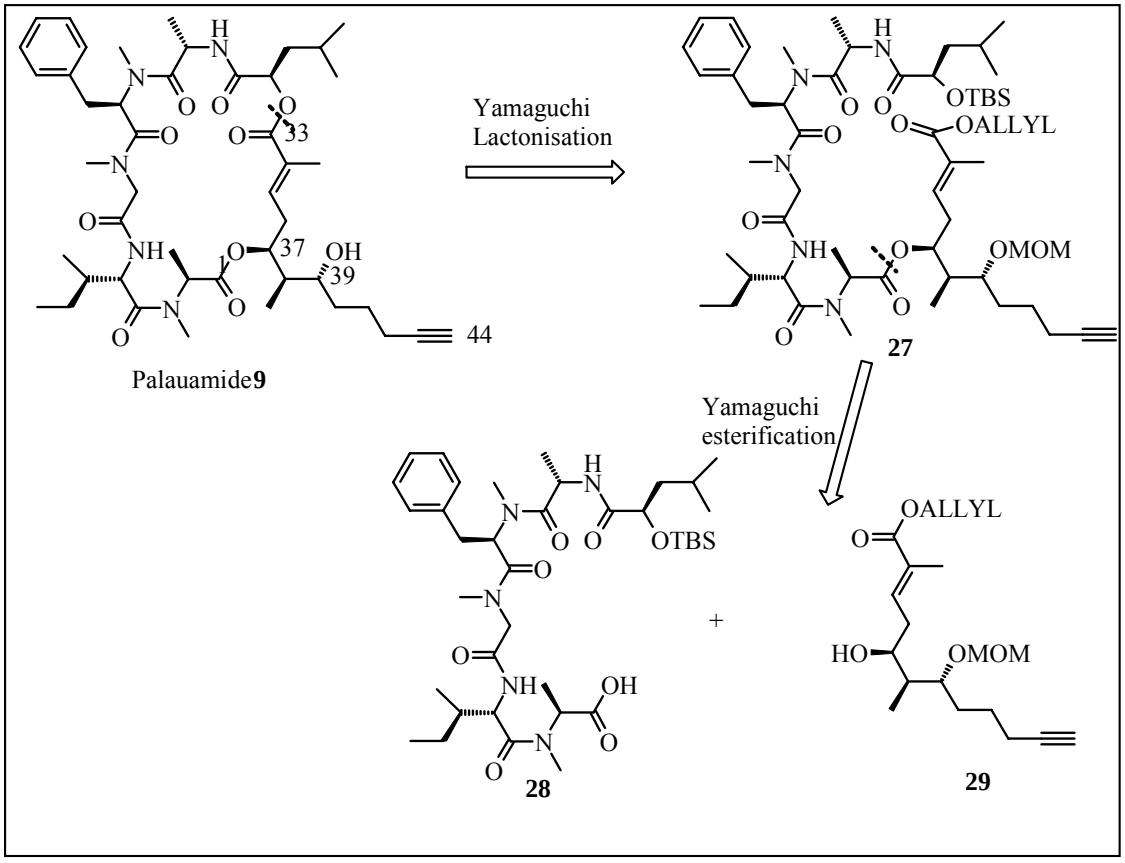


Figure 2. Retrosynthetic analysis of Palau'amide **9**

Our initial goal was to achieve a convergent protocol for the synthesis of the polyketide alcohol 29 and its retrosynthetic analysis is depicted in Figure 3.

Retrosynthetic analysis of Polyketide alcohol 29 [C33 to C44 fragment of Palauamide]

Retrosynthetic analysis revealed that olefinic double bond present in alcohol **29** could be synthesized by Wittig reaction of aldehyde **31** with allyloxycarbonylethyledene triphenylphosphorane **30**. The ylide **30** can be prepared from commercially available 2-bromopropionic acid **32** in two steps synthesis. Aldehyde **31** can be synthesized from **33** by two step synthesis i.e. deprotection of PMB-ether, followed by IBX oxidation.

The alkyne motif **33** was planned to be prepared by displacement of bromo of **34** with lithiumacetylide. Compound **34** can be synthesized from allylderivative **35** in a two step synthesis. Compound **35** can be synthesized from **36** following sequence of simple transformations. 1,3-dihydroxy-2-methyl motif present in **36** was envisaged to be prepared from epoxide **37** by regioselective ring opening using $Me_2CuCNLi_2$, whereby the methyl group can be selectively introduced at C38 stereogenic centre.

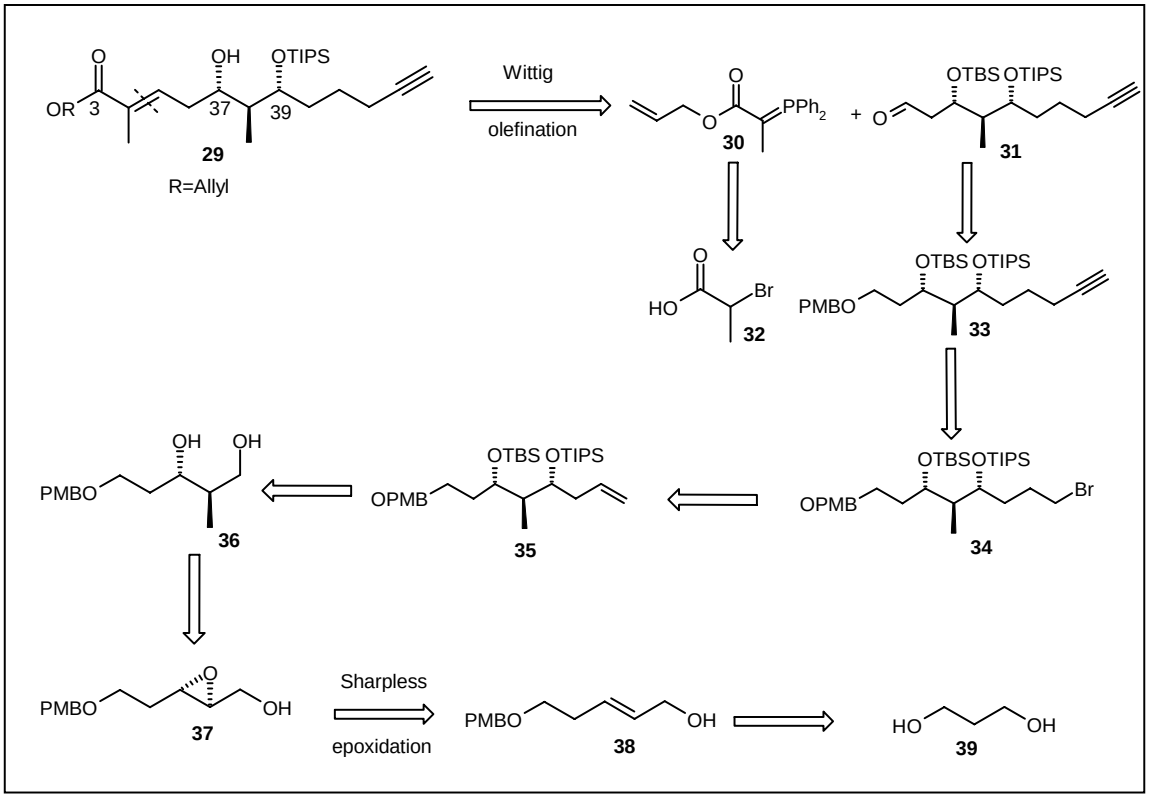
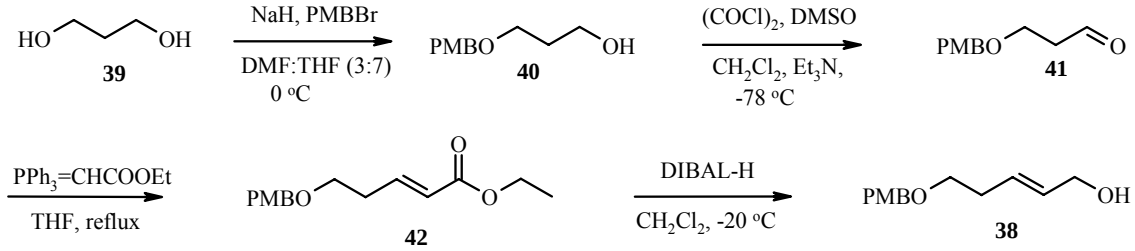


Figure 3. Retrosynthetic analysis of C33-C44 fragment **29**

The epoxide **37** can be synthesized by Sharpless asymmetric epoxidation of allylic alcohol **38,** which in turn, could be obtained from commercially available1,3 propane diol **39** by general functional group transformations.

Based on the retrosynthetic analysis, we intended to prepare the chiral key intermediate (2*S*, 3*S*) epoxyalcohol **37**, from commercially available 1,3 propane diol **39** by a five step synthesis.

Scheme 5



1,3 propanediol **39** was treated with NaH, paramethoxy benzylbromide in THF:DMF mixtures (7:3) at 0 ^{o}C resulted in 3–PMB–1–propanol **40** in 80% yield. The primary alcohol of **40** was oxidised by Swern oxidation condition using oxallyl chloride, DMSO in CH_2Cl_2 at –78 ^{o}C resulted in aldehyde **41**, which on subsequent treatment with ethoxycarbonyl methyledenetriphenylphosphorane in THF at refluxing condition furnished the required *trans*–α,β–unsaturated ester **42** in good yield. Reduction of α,β-unsaturated ester **42** was carried out by DIBAL-H at –20 ^{o}C to room temperature in 1 h resulted in allylic alcohol **38** in quantitative yield. The ^{1}H and ^{13}C NMR spectral data of **38** was in good agreement with the reported values (Scheme 5).[43]

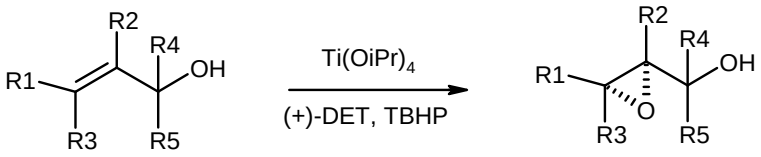
A Short Aaccount on Sharpless Asymmetric Epoxidation

Asymmetry is ubiquitous in every part of nature and has a great impact in many field, not only in chemistry but also even in arts. In the pharmaceuticals area and drug discovery process, asymmetry plays an important role, since both enantiomers of a determinate drug do not necessarily have the same activity. Enantioselective synthesis is defined as the transformation of an achiral substrate into only one of the two possible product enantiomers, mainly through the use of a chiral catalyst, solvents, etc, and avoiding the annoying attachment and detachment of chiral auxiliaries, typical of the related diastereoselective approaches. The last three decades have witnessed tremendious increase in the research in enantioselective synthesis and have undergone a true revolution and one process resulted in the award of the 2001 Nobel prize in chemistry, to professors Sharpless, Knowles and Noyori for their work on enantioselective synthesis. Titanium is seventh most aboundant metal on earth and one of the chiepest transition metal and nontoxic compare to other transition metal such as Pb, Hg, Cr, Ni, Mn etc. Its nontoxic and environment friendly nature has permitted its use in medicinal sciences, such as sunscreens, removal of

toxic metals, prostheses and its relative inertness toward the redox processes and the possibility of adjusting its reactivity and selectivity by different ligands make it a preferred candidate for any enantioselective reaction, even employing stoichiometric amount of titanium component. In 1980 a major shift occurred with the introduction of the enantioselective epoxidation of allylic alcohols. Without any doubt this reaction has changed the dimensions of the enantioselective synthesis.[44]

In general, enantioselective epoxidation of allylic alcohols was accomplished by reaction of an alkylhydroperoxide in the presence of Titanium alkoxide and a chiral tartarate ester. The enantioselectivity depends strongly on different variables such as, chiral tartrates, ratio of titanium to tartarate, ratio of catalyst (titanium-tartrate complex) to allylic alcohol etc.

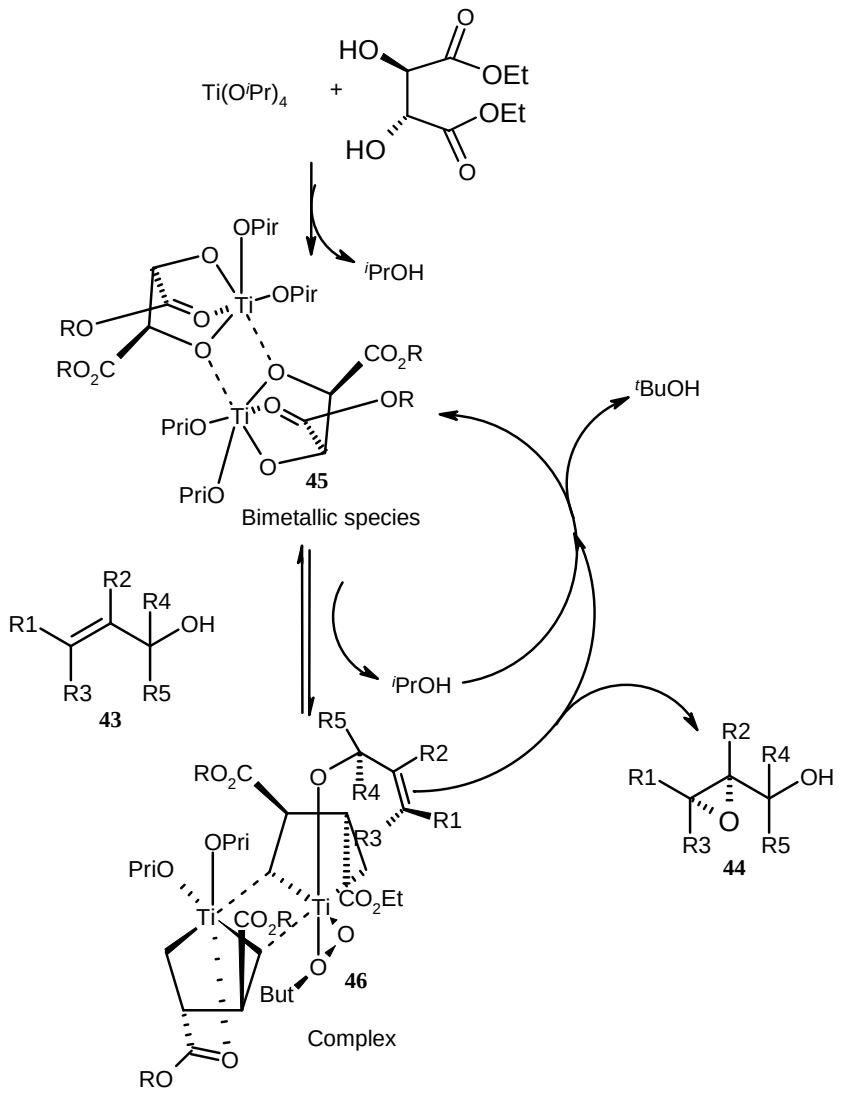
Scheme 6: Sharpless Asymmetric Epoxidation



Mechanism

There are so many reports for the mechanism of SAE reaction, but after so many studies, the mechanism given in Figure 4 is finally accepted. The X-ray crystallography studies revealed that the reaction goes through a bimetallic species which, after a double exchange between two isopropoxide ligands and both the hydroperoxide and the starting olefin gave the real catalytic species denoted as complex. The hydroperoxide must occupy both the equatorial site and one of the two available axial co-ordination site with the allylalcohol in the remaining axial site. To achieve the necessary proximity for transferring the oxygen atom to the olefin, the distal oxygen is placed in the equatorial position. The axial site of lower face of the complex is chosen for the most sterically demanding tertiary butyl moiety, with the allylic alcohol binding to the remaining axial co-ordination site. The enantioselective epoxidation takes place on this intermediate, in which olefin co-ordinates in an appropriate space.

Figure 4. Proposed catalytic cycle for the Sharpless Epoxidation



Stereoselectivity

The stereochemical outcome of the asymmetric epoxidation is consistent with (*S,S*)-(-)-DET inducing the epoxide formation on the *Si* face and the (*R,R*)-(+)-DET inducing the epoxide formation on the *Re* face of the allylic alcohol as illustrated in Figure-5. For a given tartrate or tatramide, the system delivers the epoxide oxygen from the same enantioface of the olefin regardless of the olefinic substitution pattern.

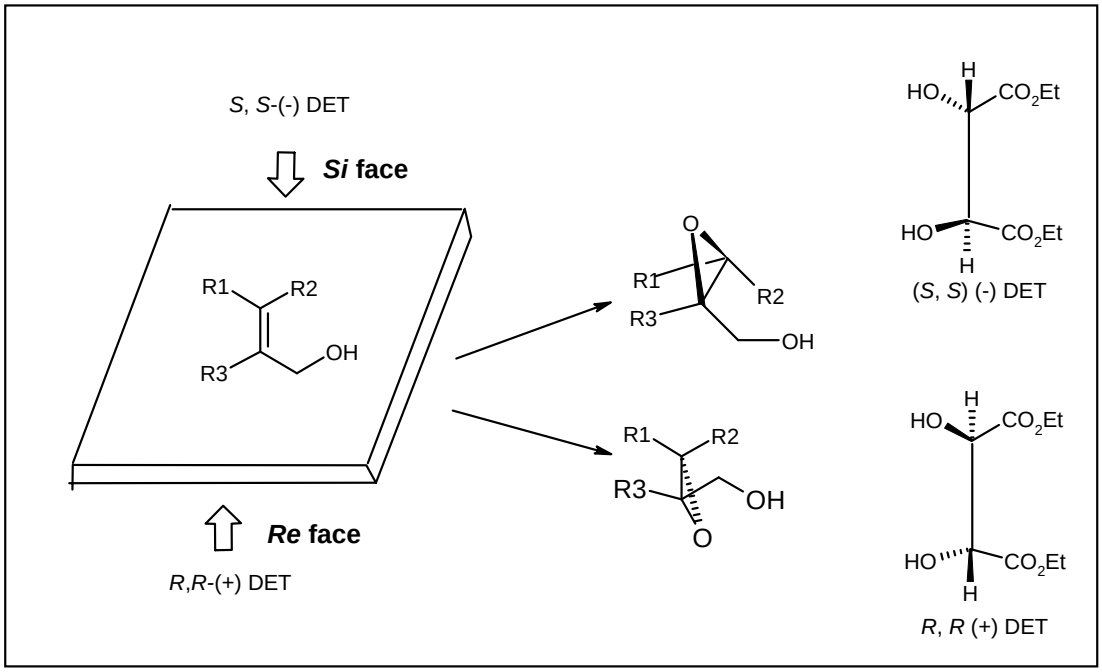


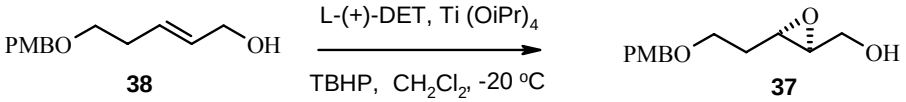
Figure 5.Asymmetric epoxidation of primary allylic alcohol

For most allylic alcohols the asymmetric induction is generally high (>90% ee) but there have been instances in which this is not the case.

Sharpless Asymmetric Epoxidation on (38)

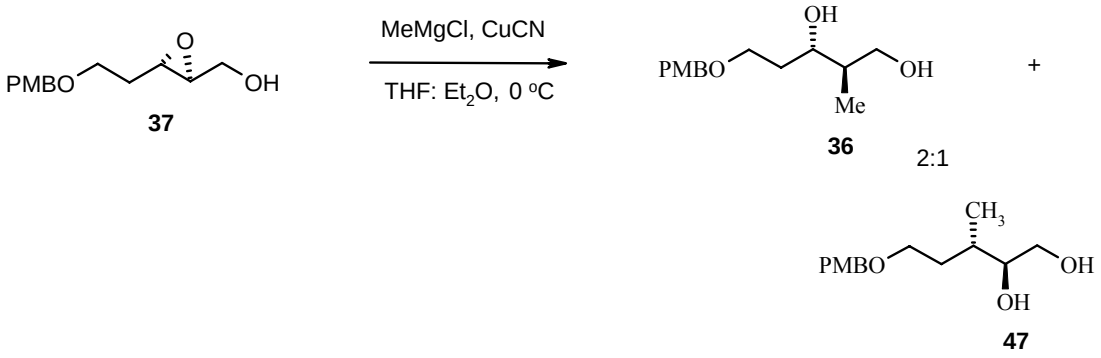
Allyl alcohol **38** was subjected to Sharpless asymmetric epoxidation reaction using $Ti(O^iPr)_4$, L-(+)-diethyltartrate and *t*-butylhydrogenperoxide in anhydrous CH_2Cl_2 inpresence of freshly activated $4A^o$ MS powder to obtain epoxide **37.**[45] The ^1H NMR spectrum of the epoxide **37** showed absence of the resonances corresponding to the methine protons of allylic alcohol at δ 5.71-5.67 (m, 2H) ppm where as new resonances attributed to methine protons of epoxide were apparent at δ 3.08 and 2.95 ppm as two multiplates along with other proton resonances according to assigned structure of epoxide **37**. ^{13}C NMR spectrum showed absence of resonances corresponding to alkene carbons of **38** at δ 131.0, 130.2 ppm with the appearance of two new resonances at δ 58.3 and 54.8 ppm corresponding to epoxycarbons. In addition the IR (3016, 1270, 840 cm^{-1}) spectrum and elemental analysis data also supported the formation of **37**. The enantioselectivity was determined by HPLC on a CHIRALCEL OJ-H column to be 95% (Scheme 7).

Scheme 7



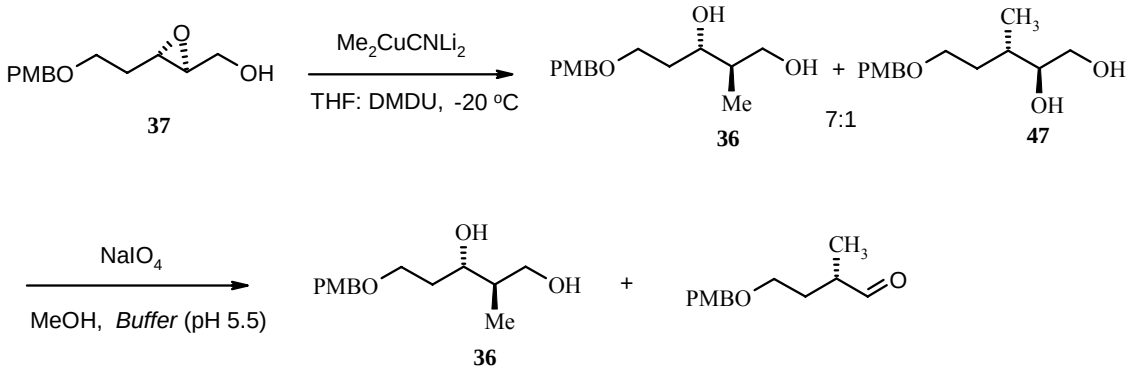
Our next concern was the nucleophilic epoxide opening by Grignard reagent to introduce methyl group regioselectively in 2-position, which correlated with the C38 stereogenic center of polyketide alcohol .

Scheme 8



Accordingly Nucleophilic opening of epoxide **37** with MeMgCl inpresence of CuCN afforded a mixture of desired 1,3 diol **36** and the corresponding 1,2-diol **47** in 2:1 ratio (Scheme 8)**.**[46]

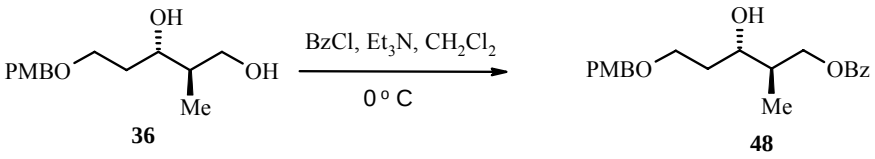
Scheme.9



Where as using $Me_2CuCNLi_2$ in THF: DMDU (4:1) mixture at –20 ^oC, the ratio of **36** and **47** was improved to 7:1.[47] Since 1, 2 diol **47** was of no consequences to us, was easily removed by treatment of sodiummetaperiodate.[48] In the ^1H NMR spectrum of **36**, the signal due to methyl (CH_3) group was observed at δ 0.85 (d, J = 6.9 Hz, 3H) ppm. In the ^{13}C NMR spectrum the –CH_3 carbon resonated at δ 13.8 ppm and the –CH carbon linked to

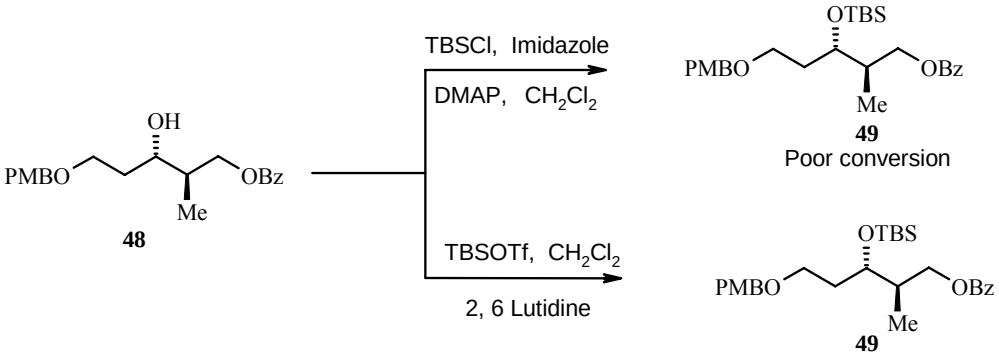
–OH group observed at δ 73.1 ppm. The IR (3430, 2935cm^{-1}) and elemental analysis data also supported the formation of compound **36** (Scheme 9).

Scheme 10



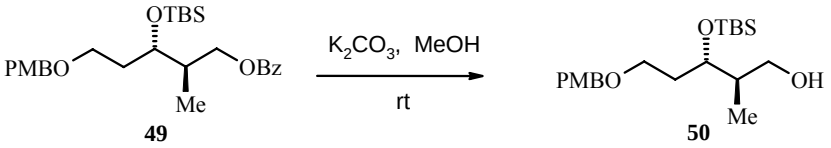
Selective benzoylation of alcohol **36** with BzCl, Et_3N in dichloromethane at 0 ^oC afforded monobenzoate **48**. The structure of **48** was elucidated from the ^1H and ^{13}C NMR spectral data. The ^1H NMR spectrum displayed three signals at δ 8.06-8.01 (m, 2H), 7.54 (m, 1H) and 7.50-7.42 (m, 2H) due to phenyl ring protons. The methylene protons linked to –OBz group appeared at δ 4.39 (dd, J = 1.5, 5.3 Hz, 2H) ppm, which was earlier appeared at δ 3.76-3.55 ppm in compound **36**. In the ^{13}C NMR spectrum the diagnostic carbonyl carbon of benzoate group was identified at δ 166.5 ppm along with all other carbon resonances at their respective position. The IR (1715 cm^{-1}) and elemental analysis data also supported the formation of **48** (Scheme 10).

Scheme 11



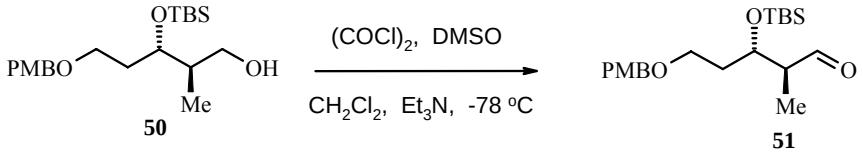
The secondary hydroxyl of **48** was protected as TBS ether by using TBSCl, Imidazole and catalytic DMAP in CH_2Cl_2 suffers from low conversions even after prolonged reaction times (48 h).[49] However treatment of TBSOTf, 2,6 Lutidine in CH_2Cl_2 at 0 ^oC on **48** resulted quick and clean conversion to **49** with good yield (90%).[50] In the ^1H NMR spectrum of **49** two singlets appeared in the upfield region at δ 0.8 and 0.9 ppm integrating for six and nine protons were assigned to TBS group. All other protons resonated at their respective values assigned the structure of **49**. Elemental analysis data also supported the assigned structure (Scheme 11).

Scheme 12



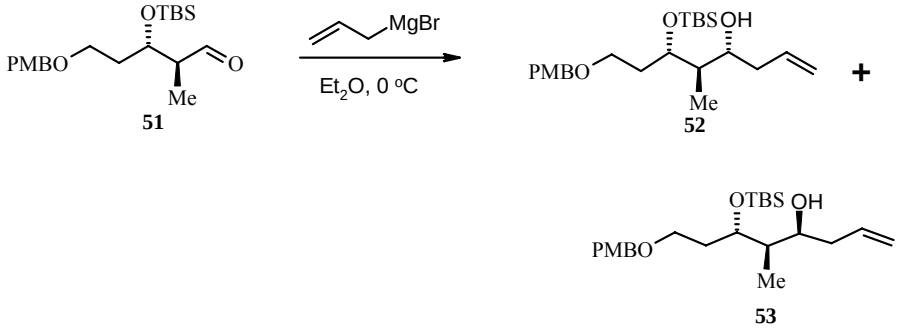
The benzoate group of **49** was hydrolysed to alcohol **50** by the combined action of K_2CO_3 and MeOH.[51] Structure of **50** was deduced from ^1H, ^{13}C NMR and elemental analysis data. In the ^1H NMR spectrum of **50** disappearance of signals in the down field region at δ 8.06-8.01 (m, 2H), 7.54 (m, 1H) and 7.50-7.42 (m, 2H) ppm indicates the deprotection of benzoate group and appearance of a triplet at δ 3.50 ppm integrating for three protons indicates the presence of CH_2OH group as well as of a oxymethine proton. In addition the ^{13}C NMR spectrum showed a signal at δ 66.4 ppm corresponding to CH_2OH group, which was unambiguously confirmed from DEPT spectrum. All other carbon resonances at their expected chemical shift confirmed the structure of **50** (Scheme 2).

Scheme 13



The primary alcohol of **50** was oxidised by Swern oxidation[52] condition using oxalylchloride, DMSO, CH_2Cl_2 and Et_3N at –78 ^oC furnished aldehyde **51** in quantitative yield. In the ^1H NMR spectrum the diagnostic aldehydic proton signal was observed at δ 9.16 ppm. All other protons resonated at their expected chemical shift assigned the structure of **51** (Scheme 13).

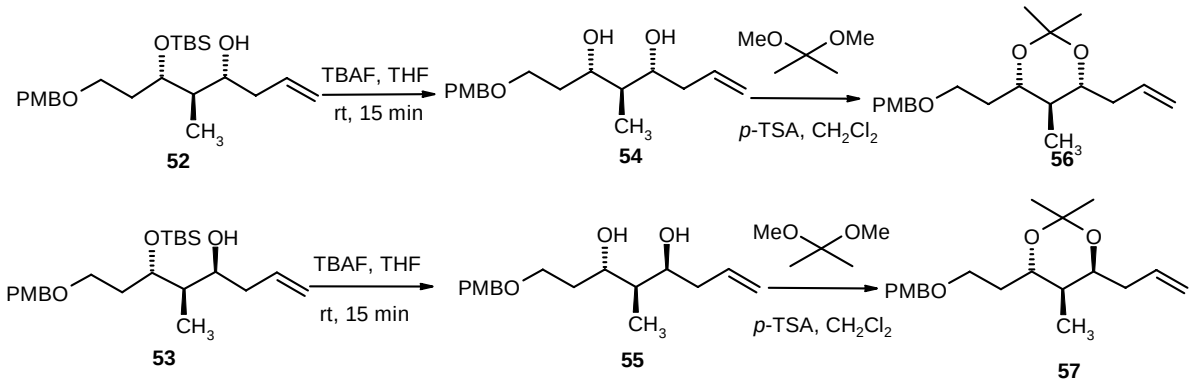
Scheme 14



Aldehyde **51** was subjected to Grignard reaction by treatment with allylmagnesiumbromide at 0 ^{o}C furnished the diastereomeric mixture of **52** and **53** in 1:1.5 ratio.[53] Both the diastereomer were separated by flash silicagel chromatography. In the ^{1}H NMR spectrum of **52** the aldehydic proton signal of was vanished and the methine proton of alkene appeared as multiplet at δ 5.85 ppm integrating to one proton, whilest the methylene protons of alkene was observed at δ 5.16 and 5.09 ppm integrating to one proton each. In the ^{13}C NMR spectrum the olefinic carbons were identified at δ 135.1 and 117.8 ppm.IR and elemental analysis data also supported the formation of **52**. In the ^{1}H NMR spectrum of **53**, the methine and methylene protons of alkene resonated at δ 5.70 (m, 1H) and 5.12-4.99 (m, 2H) ppm. In the ^{13}C NMR spectrum the olefinic carbons were observed at δ 135.3 and 116.8 ppm. All other carbon resonances observed at their expected positions confirmed the structure of **53** (Scheme 14).

As our synthetic strategy required *syn* 1,3 diol here it was necessary to prove the newly generated stereogenic centre of **52** and **53**.

Scheme15



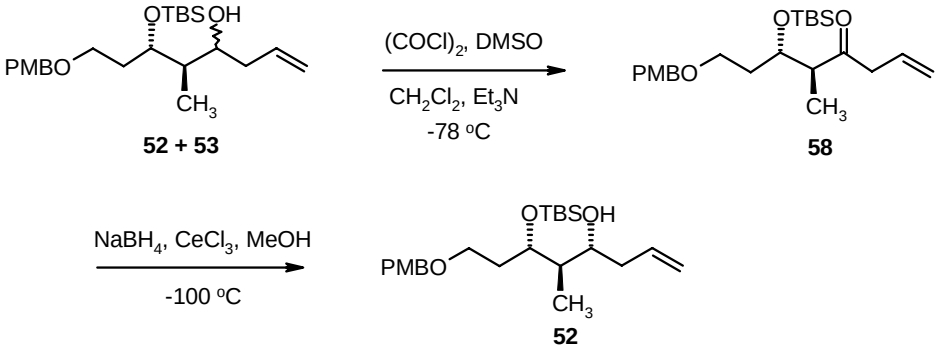
Rychnovsky[54] has shown that the acetonides of syn and anti 1, 3 diols can be unambiguously distinguished by the ^{13}C chemical shifts of the acetonide methyl groups

and the acetal carbon atom. The ^{13}C NMR spectra of *syn* 1, 3 diol acetonides show an axial methyl group carbon at δc 19.6 and the corresponding equatorial one at δc 30.0. This is in contrast to the spectra of the *anti* 1,3 diol acetonides, which shows the methyl resonances at δc 24.7. The acetal carbon chemical shifts are also indicative of the stereochemistry δc 98.5 for the *syn* 1,3 diol acetonides and δc 100.4 for the *anti* stereoisomer.

Accordingly TBS ether of **52** and **53** were deprotected using TBAF[55] in THF resulted 1,3 diol **54** and **55,** which were protected as their dioxalone derivative using dimethoxypropane, catalytic *p*-TSA in CH_2Cl_2 furnished **56** and **57** respectively. The ^{13}C chemical shifts observed for the methyl groups of **56** at δc 30.0 and 19.5 ppm and the acetal carbon at δ 97.7 ppm confirmed the *syn* relationship for the C-4 and C-6 oxygen atoms in **54** whereas in **57** the corresponding carbons resonated at δ 24.7, 23.6 and 100.3 respectively confirmed the anti relationship for the C-4 and C-6 oxygen atoms in **55** (Scheme 15).

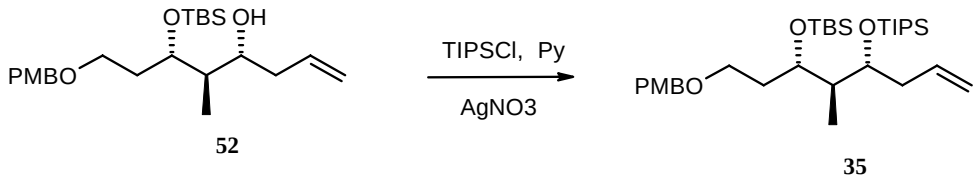
Our next task was to get the 1,3-*syn* diol **52**, exclusively. For that we followed known oxidation and reduction strategy.

Scheme 16



Accordingly we oxidized the mixture of products **52** and **53** to the keto compound **58**, which was stereoselectively reduced by Luche's condition using $NaBH_4$ and $CeCl_3$ at low temperature (-100 ^oC) resulted in exclusive formation of compound **52** (Scheme 16).[56]

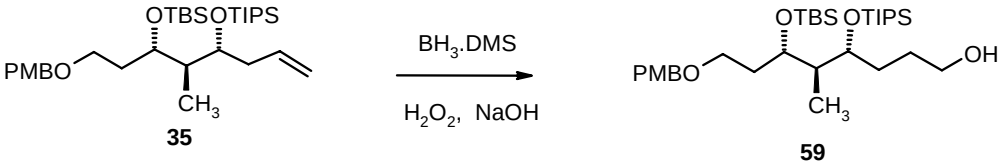
Scheme 17



52 **35**

The secondary hydroxy group of **52** was protected as TIPS ether using TIPSCl, Py in CH_2Cl_2 didn't produced the desired TIPS ether **35** even after prolonged reaction time (24 h), but further addition of pyridine and catalytic amount of silvernitrate [57] to the same reaction mixture complete conversion occurs within 6h. In the ^{1}H NMR spectrum the signal for three isopropyl group resonated at δ 0.95 (21H, s) ppm confirmed the formation of TIPS ether **35** (Scheme 17).

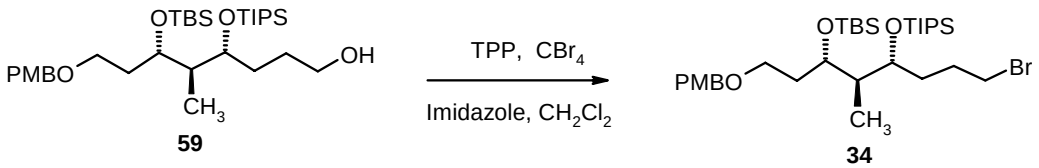
Scheme 18



35 **59**

With a views to transform allyl group into corresponding pentynyl, the allylic double bond of **35** was exposed to BH_3:DMS in THF followed by oxidative work up with H_2O_2 and NaOH produced the desired primary alcohol **59**. In the ^{1}H NMR spectrum of **59** the olefinic protons signals of **35** were absent and the methylene protons linked to hydroxyl group was observed at δ 3.55–3.40 ppm. In the ^{13}C NMR spectrum the –CH_2OH carbon resonated at δ 63.3 ppm, which was further confirmed by DEPT spectrum. IR and elemental analysis data also confirmed the structure of **59** (Scheme 18).

Scheme 19

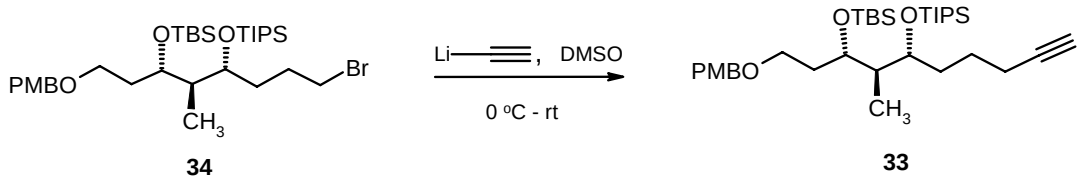


59 **34**

Compound **59** on treatment with triphenylphosphine, tetrabromomethane[58] and imidazole in CH_2Cl_2 resulted in the formation of corresponding bromide **34**. Transformation of

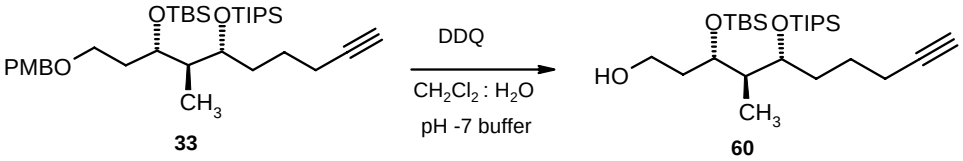
hydroxyl to bromo was noticed by TLC, which was further confirmed by ^{1}H and mass spectrometric study (Scheme 19).

Scheme 20



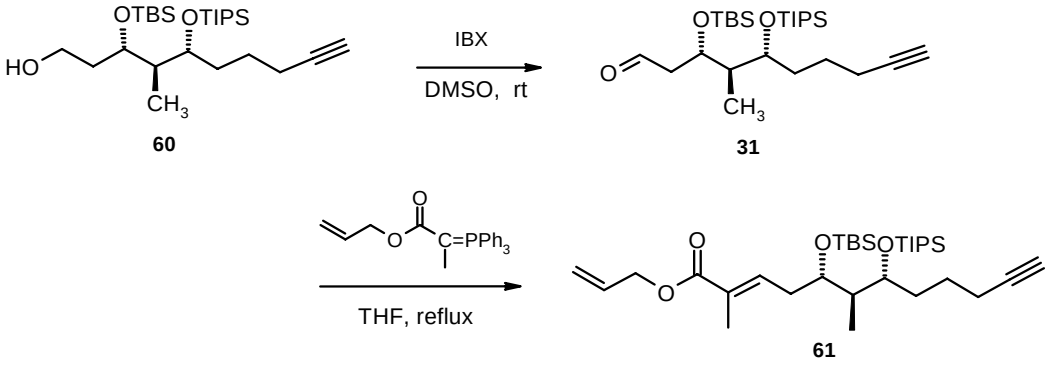
Nucleophilic displacement of bromo group of **34** by lithium acetylide in DMSO at 0 ^{o}C–room temperature giving rise to alkyne motif **33**.[59] ^{1}H NMR spectrum of **33** displayed a signal at δ 1.87 (1H) ppm characteristic of acetylinic proton. In the ^{13}C NMR spectrum the acetylinic carbons resonated at δ 84.3, 68.4 ppm and rest of the carbons appeared in their conformity. The IR (3313, 2171cm^{-1}) and elemental analysis data also supported the formation of **33** (Scheme 20).

Scheme 21



After successful installation of all the required stereocentres and pentynyl chain, our next objective was the introduction of *E*-enoate moiety. Accordingly paramethoxybenzyl ether was deprotected by using DDQ in CH_2Cl_2:H_2O (12:1) mixtures in presence of pH –7 buffer yielded primaryalcohol **60**.[60] In the ^{1}H NMR spectrum disappearance of aromatic signals at δ 7.24 and 6.86 ppm confirmed the assigned structure (Scheme 21).

Scheme 22



Primary alcohol of **60** was oxidized to the corresponding aldehyde **31** using iodoxybenzoic acid in DMSO, [61] followed by addition of allyloxyethyledenetriphenylphosphorane in refluxing THF afforded the α,β unsaturated allyl ester **61**.[62] In the ^{1}H NMR spectrum the trisubstituted olefinic methine signals appeared at δ 6.85 (m,1H) ppm and the terminal olefinic methine and methylene proton signals were observed at 5.80 (m,1H) and 5.24-5.07 (m, 2H) ppm indicating the presence of α,β-unsaturated-allylester. All other protons resonated at their respective values, confirming the structure of **61**. In addition the elemental analysis data and mass spectrometry value also confirmed the structure of **61** (Scheme 22).

Having made the compound **61**, with all the required stereocentres and '*E*' geometry of the double bond, the only task remained to be done was the selective deprotection of TBS ether in presence of TIPS ether.[63] Surprisingly all attempts made to transfer compound **61** to **29** failed and in all cases only 1,3 diol **62** was formed (Table-1).

Scheme 23

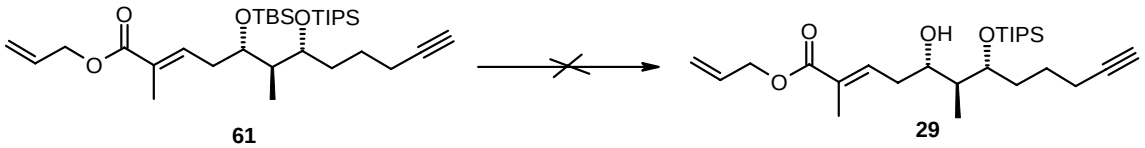


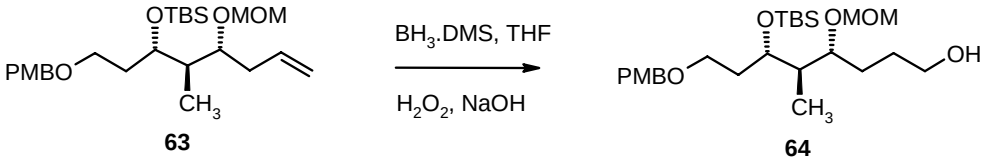
Table 1**.** Over view of reaction condition that failed to transform **61** to **62**

Solvent	Reagent	Temperature	Time
MeOH	PPTS	0 ^{o}C-rt	1 h
MeOH	HCl	0 ^{o}C-rt	30 min
	Acetic acid	0 ^{o}C-rt	3 h
CH_3CN	HF, Pyridine	0 ^{o}C-rt	30 min
THF	TBAF	0 ^{o}C-rt	1 h

Being unsuccessful in selective TBS ether deprotection to achieve the required mono hydroxy compound **29**, we intended to change the protecting group from TIPS to MOM to

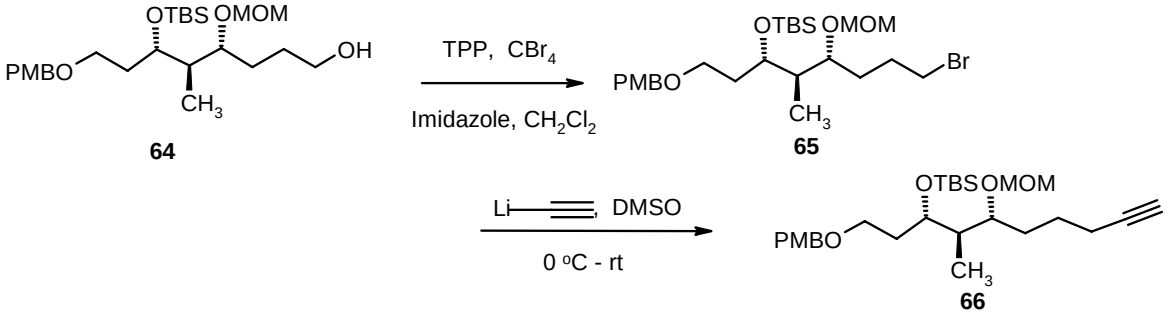
satisfy our purpose. Accordingly treatment of MOMCl, diisopropylethylamine (Hunigbase) on **52** in dichloromethane was found very slow conversion to **63** even after prolonged reaction time (36 h).[64] However addition of catalytic amount of silvernitrate, reaction proceeded to completion within 6 h. ^{1}H NMR spectrum of **63** showed the signals at δ 4.39 (s, 2H), 3.30 (s, 3H) corresponding to OCH_2 and OCH_3 group of methoxymethylether. In the ^{13}C NMR spectrum the $–OCH_2$ carbon was appeared at δ 95.8 ppm, whilst the $–OCH_3$ carbon signal observed at δ 55.1 ppm. All other carbons were resonated at their expected chemical shifts (Scheme 23).

Scheme 24



Hydroboration oxidation of olefin **63** using BH_3.DMS resulted primary alcohol **64**. ^{1}H NMR spectrum of **64** showed a signal at δ 3.65 (t, J = 5.6 Hz, 2H) indicating the formation of $–CH_2OH$ group. In the ^{13}C NMR spectrum the $–CH_2OH$ carbon was resonated at δ 62.9 ppm which was unambiguously determined by DEPT spectrum. IR (3444 cm^{-1}) and ESI-MS $(M)^+$ = 470.96, $(M + Na)^+$ = 493.04 data also supported the formation of **64** (Scheme 24).

Scheme 25

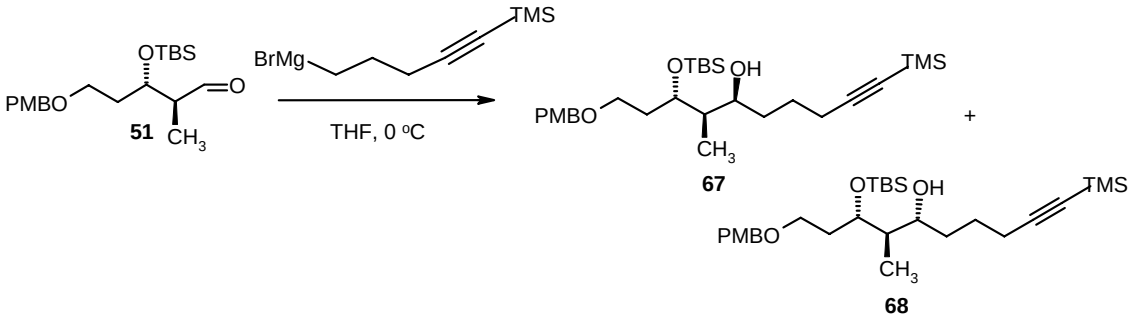


The primaryalcohol **64** was subjected with TPP, CBr_4 and imidazole (catalytic) in CH_2Cl_2 resulted in bromo compound **65**, which on subsequent treatment with Lithium acetylide in DMSO at 0 ^{o}C-room temperature furnished the alkyne moiety **66**. The ^{1}H NMR spectrum showed a signal at δ 1.93 ppm as a triplet integrating for one proton characterstics of alkyne proton. ^{13}C NMR spectrum showed the alkyne carbons at δ 84.3 and 68.4 ppm and

rest other carbons resonated at their conformity indicating the formation of **66** (Scheme 25).

As the synthesis of **66** from **51** required multistep synthesis, so we encounter the stability issues while scaling up the reaction. This warranted an alternative approach; a shorter step introduction of pentynylchain by Grignard reaction.

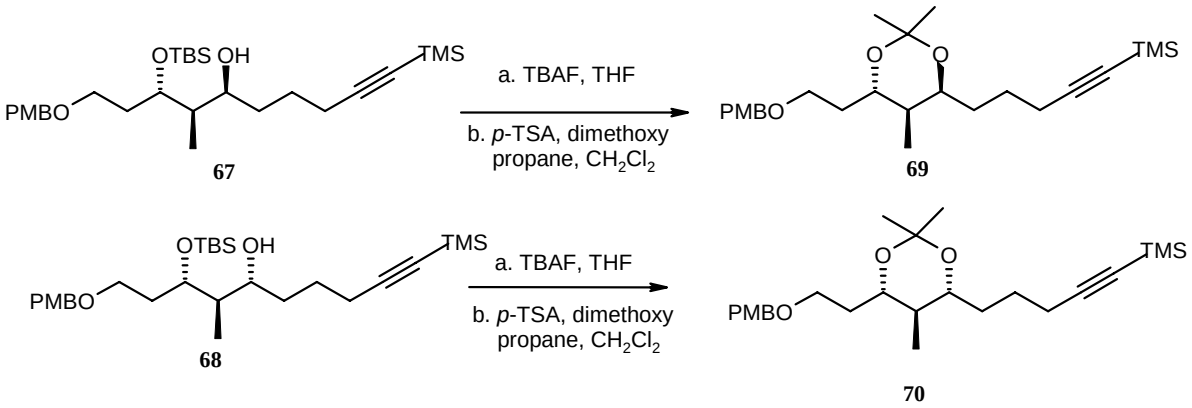
Scheme 26



Thus, 1-TMS-Pentynylbromide was prepared from 4-pentynyl-1-alcohol following known literature procedure.[65] which was distilled off in pure form without contamination with alcoholic counterpart. Grignard reaction of pentynylmagnesiumbromide with aldehyde **51** resulted in diastereomeric mixture of **67** and **68** in good yield. Both were seperated by flash silicagel chromatography. In the ^{1}H NMR spectrum of **67,** the aldehydic proton was absent and the signal for –TMS group observed at δ 0.88 ppm as a singlet integrating for nine protons. In the ^{13}C NMR spectrum the alkyne carbons were resonated at δ 107.1 and 84.5 ppm, whilest the –CH carbon linked to –OH group appeared at δ 76.0 ppm . In the DEPT spectrum absence of alkyne carbons and appearance of three additional –CH_2 carbons in δ 35.0, 33.5 and 16.6 ppm confirmed the incorporation of pentynyl chain. In the ^{1}H NMR spectrum of **68**, similar chemical shift was observed. Additionally elemental and MASS spectrometric data also supported the assigned structure (Scheme 26).

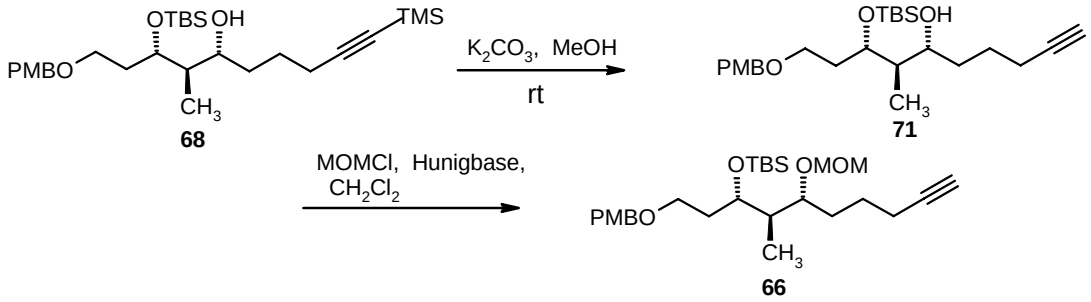
To confirm the newly generated stereocenter of **67** and **68,** TBS ether was deprotected using TBAF in THF resulted 1,3 diol, which was protected to their oxalone derivatives by using cat *p*-TSA, dimethoxypropane in dichloromethane produced **69** and **70.** Comparison of ^{13}C data confirmed the oxymethine protons of **69** were *anti* and in **70** *syn* in nature (Scheme 27).

Scheme 27



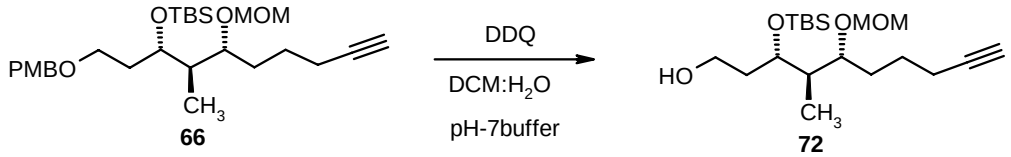
Since compound **68** was required exclusively, here we followed known oxidation-reduction method as mentioned earlier. Latter on deprotection of TMS group was carried out by K_2CO_3, MeOH resulted in compound **71**, which was protected as MOM ether using MOMCl, Diisopropylethylamine, $AgNO_3$ (catalytic) in dichloromethane resulted in compound **66** in good yield.

Scheme 28



The ^{1}H, ^{13}C, IR and ESI-MS data of **66** was tallied with the data reported earlier (Scheme 28).

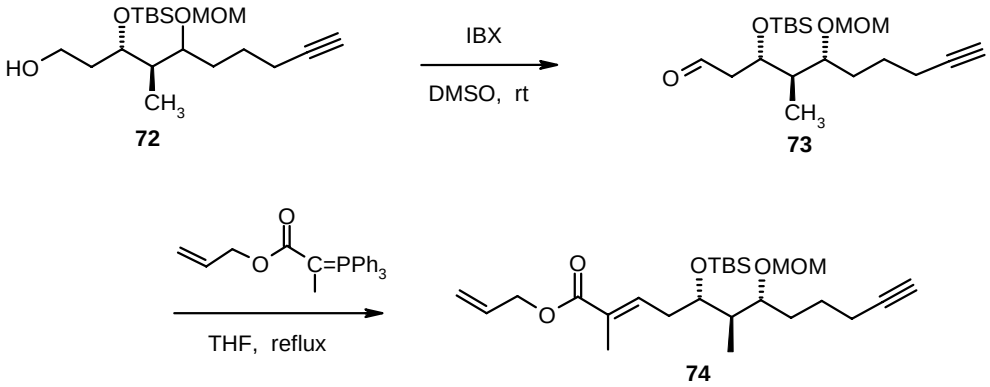
Scheme 29



PMB-ether of **66** was deprotected using DDQ, CH_2Cl_2:H_2O (12:1) mixtures in pH-7 buffer resulted in **72** with good yield. ^{1}H NMR spectrum of **72** showed the disappearance of signals in the down field region and appearance of a triplet at δ 3.74 ppm integrating for

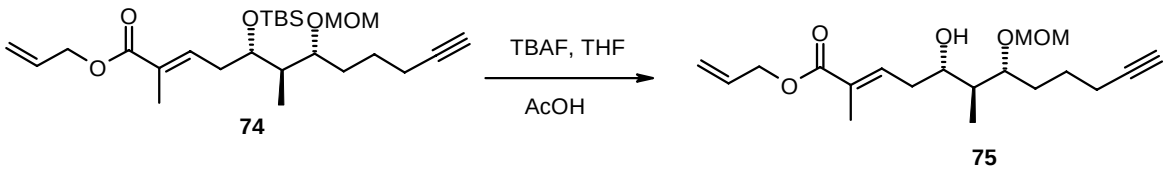
two protons indicates the methylene protons linked to –OH group. In the ^{13}C NMR spectrum the $-CH_2OH$ carbon was appeared at δ 60.3 ppm, which was further confirmed from DEPT spectrum. IR and elemental analysis data also supported the formation of **72** (Scheme 29).

Scheme 30



Oxidation of **72** using IBX in DMSO resulted aldehyde **73**, which on subsequent treatment with allyloxyethyledenetriphenylphosphorane in refluxing THF yielded α,β-unsaturated-ester **74** in good yield. In the ^1H NMR spectrum the methine proton of trisubstituted olefin was observed at δ 6.90 ppm and the substituted methyl proton was at δ1.84 ppm, whilest the terminal olefinic protons were observed at δ 5.92 and 5.27 ppm. In the ^{13}C NMR spectrum the diagnostic carbonyl carbon was observed at δ167.8 ppm. Additionally, IR and mass spectrometric data also supported the formation of **74** (Scheme 30).

Scheme 31

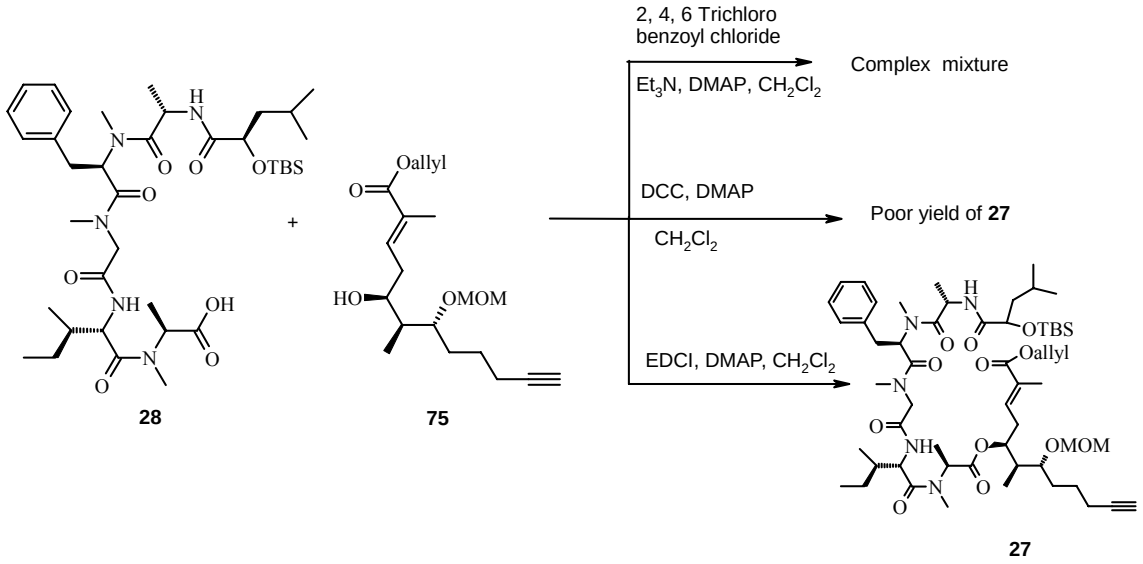


TBS-ether of **74** was deprotected using TBAF, THF and catalytic AcOH resulted in mono-hydroxyl compound **75** in good yield. In the ^1H NMR spectrum the signal for TBS-group was disappeared, indicating the formation of **75**. ESI-MS data also supported the formation of **75** (Scheme 31).

Coupling of pentapeptide acid with polyketide alcohol

Getting free hydroxy polyketide **75** in hand, we focused our attention for coupling with the necessary pentapeptide acid **28** usingYamaguchi esterification method (2,4,6 trichlorobenzoyl chloride, Et_3N),[66] but reaction failed to give the desired product **27.** However, following standard DCC, DMAP conditions[67] poor yield (20%) of desired esterified compound **27** was isolated. In contrast, esterification of **75** and **28** using EDCI, DMAP (catalytic) in dichloromethane resulted in ester **27** with good yield.[68]

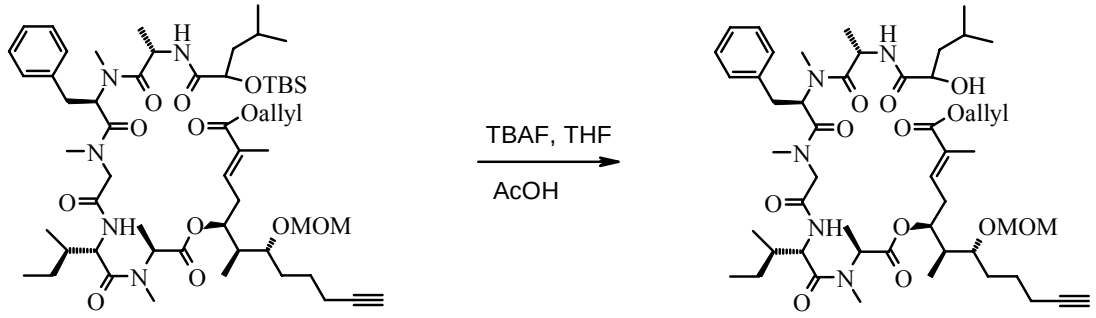
Scheme 32



^{1}H NMR spectrum of **27** showed the signals at δ 0.05 (s, 3H) and 0.02 (s, 3H) ppm indicating the presence of *t*-butyldimethylsilyl group. The signal for methoxymethylether group was observed at δ 4.62-4.59 ppm. All other protons appeared in their respective positions. ESI-MS of **27** showed a signal at 1089.1 corresponding to $(M + Na)^+$ confirmed the assigned structure (Scheme32).

The TBS ether in **27** was deprotected easily using TBAF, AcOH (catalytic) in THF resulted alcohol **76** in good yield. In the ^{1}H NMR spectrum the signal for TBS group was absent indicating formation of **76**.ESI-MS specrum showed the peaks at 976.83 $(M+ Na)^+$ and 992.7 $(M + K)^+$ confirmed the structure of **76** (Scheme 33).

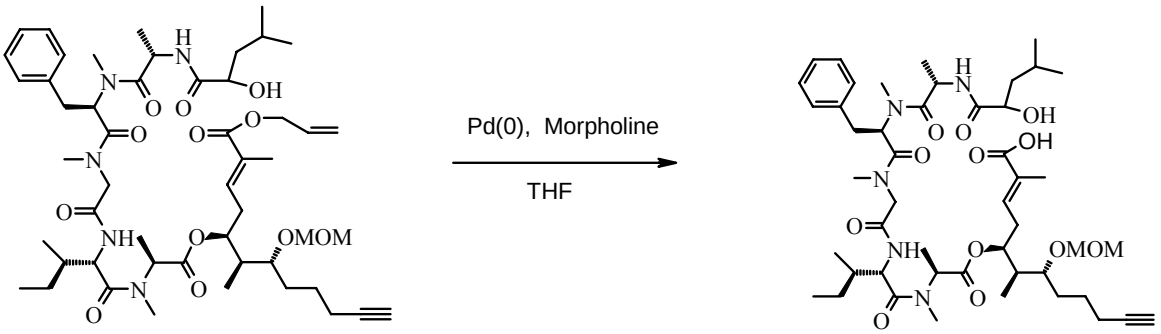
Scheme 33



27 76

Getting free hydroxyl compound **76**, we planned to cleave the allyl ester to get the acid component **77**. Several standard reaction conditions has been tried which was mentioned in Table-2. Though here we faced lot of problem in allyl ester deprotection but finally using Pd (0), Morpholine in THF, allylester[69] was cleaved to give the desired acid **77** in moderate yield (Scheme 34).

Scheme 34



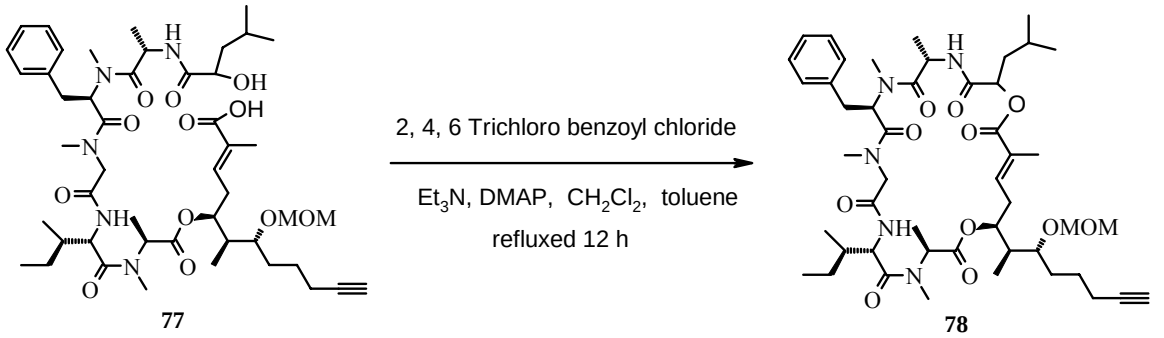
76 **77**

Table 2. Catalyst and base used for the transformation of **76** to **77**

Solvent + Base	Catalyst	Temperature	Product
CH_2Cl_2, Et_3N	Pd(0)	0 ^oC-rt	Complex mixtures
NMA	Pd(0)	0 ^oC-rt	Complex mixtures
$(Et)_2NH$	Pd(0)	0 ^oC-rt	Complex mixtures
Na-salt of ethylhexanoate	Pd(0)	0 ^oC-rt	Complex mixtures
Morpholine	Pd(0)	0 ^oC-rt	**77**

In the ^{1}H NMR spectrum the olefinic methine signals for allyl group at δ 5.95 (m, 1H) ppm was vanished away and the mass spectrometric data confirmed the formation of **77** (Scheme 34).

Scheme 35



77 **78**

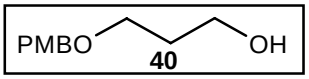
Next, intramolecular macrocyclization of **77** was carried out by using 2,4,6-trichlorobenzoyl chloride, diisopropylethylamine and DMAP in benzene produced a cyclic peptide **78** in 15% yield.[70] ESI-MS of **78** showed a peaks at 919 $(M + Na)^+$ and 935 $(M + K)^+$ indicates the formation of lactone ring but the ^{1}H NMR spectrum was so complex it was very difficult to assign. LCMS spectrum of **78** showed two peaks corresponding to same mass, indicating there was racemisation. It was assumed the racemisation might be happened in esterification step, rather than lactonisation step. So further synthesis of **78**, seperation of each components present there and further characterization is going on in our laboratory (Scheme 35).

Conclusion:

Stereoselective synthesis of polyketide chain was carried out by employing Sharpless Asymmetric Epoxidation, regeioselective epoxide opening by $Me_2CuCNLi_2$ and installation of pentyne unit following Grignard reaction as our key reactions.We have studied the coupling of -OH (polyketide) and –COOH (Pentapeptide) groups with different coupling reagents and found that EDCI was the best coupling reagent for this reaction. Deproection of allyl ester with various base and Pd(0) catalyst was studied and finally the allylester was successfully cleaved by using Pd(0), Morpholine in THF. Intramolecular lactonization was successfully achieved following Yamaguchi Lactonisation.

EXPERIMENTAL

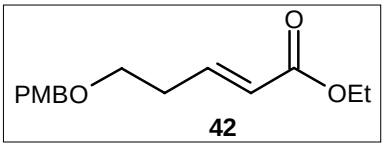
3-(4-methoxybenzyloxy)propan-1-ol



A solution of 1, 3 propanediol (50.0 g, 0.657 mol) in THF (400 mL) was added to a suspension of NaH (31.5 g, 0.789 mol, 60%) in DMF (100 mL) at 0 ^{o}C. After stirring for 30 min, paramethoxybenzyl bromide (110.1 mL, 0.657 mol) was added over a period of 1h and further stirred for 1 h. Then the reaction mixture was quenched by water, organic layer was seperated and the aqueous layer was extracted with ethylacetate (3 x 100 mL).Combined organic layers were dried over Na_2SO_4 and concentrated. Purification of the residue by silica gel chromatography (40 % EtOAc/light petroleum) resulted 3-O-PMB-1-propanol **40** (103.0 g) as a colorless liquid.

Yield	80%
Mol.Formula	$C_{11}H_{16}O_3$
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 7.25 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.44 (s, 2H), 3.79 (s, 3H), 3.75 (t, *J* = 5.6 Hz, 2H), 3.62 (t, *J* = 5.8 Hz, 2H), 2.58 (br s, 1H), 1.84 (quin, *J* = 5.6 Hz, 2H).
^{13}C NMR ($CDCl_3$, 50MHz)	159.1, 130.0, 129.1, 113.7, 72.7, 68.6, 61.3, 55.0, 32.0.
Elemental Analysis	**Calcd:** C, 67.32; H, 8.22 **Found:** C, 67.24; H, 8.37

(*E*)-ethyl 5-(4-methoxybenzyloxy)pent-2-enoate



42

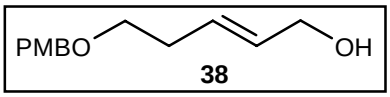
A solution of DMSO (58 mL, 0.765 mol) in CH_2Cl_2 (70 mL) was added dropwise to a solution of oxalyl chloride (22.08 mL, 0.255 mol) in CH_2Cl_2 (100 mL) at -78 ^oC. After 30 min, a solution of alcohol **40** (50.0 g, 0.255 mol) in CH_2Cl_2 (50 mL) was added to the reaction mixture at same temperature and stirred for additional 30 min. Triethyl amine (154.53 mL,1.53 mol) was added and the reaction mixture was allowed to warm to room temperature. Reaction mixture was diluted with water and extracted with CH_2Cl_2 (2 x 100 mL). The organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give crude aldehyde **41** (49.7 g), which was used for next reaction without purification.

Compound **41**(49.7 g, 0.256 mol) was dissolved in anhydrous THF (150 mL) and was added to the refluxing solution of carboethoxy methylidenetriphenylphosphorane (266.0 g, 0.764 mol) in THF (400 mL) and refluxed for 45 min. The THF was removed by rotavapour under vaccum and the residue was purified by silica gel chromatography (15 % Ethylacetate/light petroleum), provided α,β unsaturated ester **42** (53.8 g) as a colourless liquid.

Yield	80%
Mol.Formula	$C_{15}H_{20}O_4$
IR ($CHCl_3$) cm^{-1}	1751
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 7.22 (d, *J* = 8.7 Hz, 2H), 6.96 (m, 1H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.86 (dt, *J* = 15.6, 1.6 Hz, 1H), 4.43 (s, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.79 (s, 3H), 3.53 (t, *J* = 6.4 Hz, 2H), 2.53-2.42 (dq, *J* = 1.5, 6.5 Hz, 2H), 1.28 (t, *J* = 7.0 Hz, 3H).
^{13}C NMR ($CDCl_3$, 50MHz)	166.1, 159.1, 145.4, 130.0, 129.1, 122.8, 113.7, 72.6,

	67.8, 60.0, 55.0, 32.5, 14.2.
Elemental Analysis	**Calcd:** C, 68.18; H, 7.63
	Found: C, 68.20; H, 7.45

(*E*)-5-(4-methoxybenzyloxy)pent-2-en-1-ol

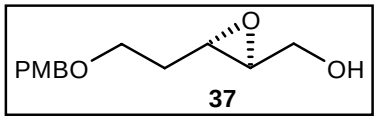


38

To a solution of α, β unsaturated ester **42** (100.3 g, 0.379 mol) in CH_2Cl_2 (500 mL), 2.5 M solution of DIBAL-H (404.6 mL, 1.139 mol) in toluene was added at –20 ^oC over a period of 30 mins and stirred for another 30 min. Excess DIBAL-H was quenched at same temperature by saturated aq.Na-Ktartrate solution. The heterogeneous mixture was stirred vigorously till both the layer clearly separates. The CH_2Cl_2 layer was separated, dried over Na_2SO_4 and concentrated.The crude compound was purified by silicagel chromatography (25% EtOAc/light petroleum) resulting in allylic alcohol **38** (75.9 g) as a colourless liquid.

Yield	90%
Mol.Formula	$C_{13}H_{18}O_3$
IR ($CHCl_3$) cm^{-1}	3304, 3019, 2991, 2936
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 7.23 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.71–5.67 (m, 2H), 4.42 (s, 2H), 4.09–4.01 (m, 2H), 3.79 (s, 3H), 3.47 (t, *J* = 6.6 Hz, 2H), 2.38–2.30 (m, 3H).
^{13}C NMR ($CDCl_3$, 50MHz)	159.0, 131.0, 130.2, 129.2, 128.8, 113.6, 72.4, 69.1, 63.2, 55.0, 32.5
Elemental Analysis	**Calcd:** C, 70.24; H, 8.16
	Found: C, 70.38; H, 8.29

(2*S*,3*S*)-5-(4-methoxybenzyloxy)-2,3-Oxiranyl-pentanol

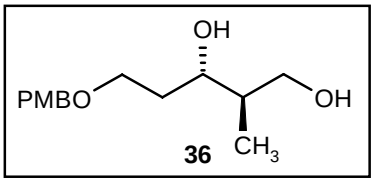


37

To a stirred and cooled (-20 ^{o}C) solution of (+)- DET (12.3 g, 72.0 mmol) and powdered molecular sieves (40 g) in dry CH_2Cl_2 (100 mL) under nitrogen was added titaniumtetraisopropoxide (21.3 g, 72.0 mmoL) and stirred for 15 min. A solution of allylic alcohol **38** (20 g, 90.0 mmol) in CH_2Cl_2 (200 mL) was introduced and after 45 min TBHP (81mL, 270 mmol) was added slowly maintaining the temperature at –20 ^{o}C. The reaction mixture was stored at –20 ^{o}C for 24 h, then brought to 0 ^{o}C. The tartrate was hydrolysed by adding 1mL of 30% aq NaOH solution saturated with NaCl and stirred for 30 min. This was filtered through a bed of celite, aq layer was seperated and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) concentrated and the residue was purified by silicagel column chromatography (35 % EtOAc/light petroleum) afforded epoxy alcohol **37** (12.1 g) as an oil.

Yield	70%
Mol.Formula	$C_{13}H_{18}O_4$
$[\alpha]_D^{25}$	-20.34 (*c* 1.7, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	3016, 1270, 840
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 7.24 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.44 (s, 2H), 3.82 (m, 1H), 3.80 (s, 3H), 3.64 –3.53 (m, 3H), 3.08 (m, 1H), 2.95 (m, 1H), 2.00 –1.74 (m, 3H).
^{13}C NMR ($CDCl_3$, 50MHz)	158.9, 129.9, 128.9, 113.5, 72.3, 66.2, 61.5, 58.3, 54.8, 53.4, 31.7.
Elemental Analysis	**Calcd:** C, 65.53; H, 7.61 **Found:** C, 65.35; H, 7.66

(2*R*,3*S*)-5-(4-methoxybenzyloxy)-2-methylpentane-1,3-diol

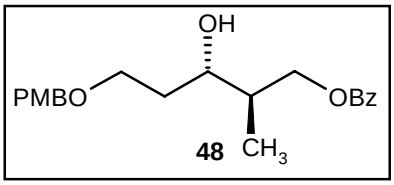


36

To a stirred solution of CuCN (18 g, 103 mmol) in THF-DMDU (4:1, 250mL), MeLi (1.5 M, 136.3 mL, 206.0 mmol) was added at –20 ^{o}C and stirred for 1 h. The epoxyalcohol (10.0 g, 51.5 mmol) was added in THF and temperature was maintained for 1 h, then the temperature was raised to 0 ^{o}C in 1h. The reaction mixture was quenched by saturated NH_4Cl. The organic layer was separated and the aqueous layer was extracted with ethylacetate (3 x 100 mL). The combined organic layers were concentrated and the residue obtained was dissolved in CH_2Cl_2 (200 mL) and silicagel adsorbed $NaIO_4$ (45 g) was added, stirred for 2 h. Reaction mixture was filtered and concentrated. The residue was purified by silicagel column chromatography (40% EtOAc/light petroleum) to afford compound **36** (7.5g) as a colorless liquid.

Yield	70%
Mol.Formula	$C_{14}H_{22}O_4$
$[\alpha]_D^{25}$	–0.95 (*c* 4.2, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	3430
^{1}H NMR ($CDCl_3$, 200 MHz)	δ7.22 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 4.45 (s, 2H), 4.10 (brs, 2H), 3.80 (s, 3H), 3.76 –3.58 (m, 5H), 1.84 –1.65 (m, 3H), 0.85 (d, *J* = 6.9 Hz, 3H).
^{13}C NMR ($CDCl_3$, 50MHz)	159.3, 129.6, 129.3, 113.8, 77.6, 73.1, 69.1, 67.5, 55.1, 40.0, 34.2, 13.8.
Elemental Analysis	**Calcd:** C, 66.14; H,8.72
	Found: C, 66.34; H, 8.53

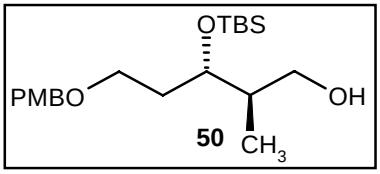
(2*R*,3*S*)-3-hydroxy-5-(4-methoxybenzyloxy)-2-methylpentyl benzoate



To a stirred solution of compound **36** (8.0 g, 38.0 mmol) in CH_2Cl_2 (75 mL) Et_3N (8.6 mL, 76.0 mmol), were added benzoylchloride (5.0 mL, 41.9 mmol) at 0 ^oC and stirred for 30 min. Reaction mixture was diluted with water and extracted with CH_2Cl_2 (100 mL) .The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL).The combined organic layers were concentrated and purified by silicagel column chromatography (25% EtOAc/light petroleum) afforded monobenzoate compound **48** (11.60 g) as a colorless liquid.

Yield	97 %
Mol.Formula	$C_{21}H_{26}O_5$
$[\alpha]_D^{25}$	71.64 (*c* 0.41, CH_2Cl_2)
IR ($CHCl_3$) cm^{-1}	1715
^{1}H NMR ($CDCl_3$, 200 MHz)	δ8.06–8.01 (m, 2H), 7.54 (m, 1H), 7.50–7.42 (m, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 4.44 (s, 2H), 4.39 (dd, *J* = 1.5, 5.3 Hz, 2H), 3.77 (s, 3H), 3.74–3.58 (m, 3H), 2.01 (m, 1H), 1.86–1.76 (m, 2H), 1.04 (d, *J* = 6.9 Hz, 3H).
^{13}C NMR ($CDCl_3$, 50MHz)	166.5, 159.1, 132.7, 130.2, 129.7, 129.4, 129.1, 128.2, 113.6, 72.8, 72.5, 68.7, 66.5, 55.0, 38.7, 33.2, 13.5.
Elemental Analysis	**Calcd:** C, 70.37; H, 7.31
	Found: C, 70.54; H, 7.60

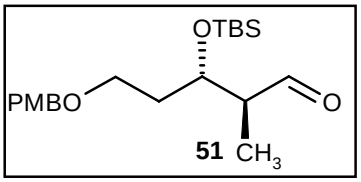
(2*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)-2-methylpentan-1-ol



Compound **48** (11.0 g, 35.03 mmol) was dissolved in CH_2Cl_2 (100 mL), 2, 6 lutidine (12.2 mL, 105.2 mmol) and TBSOTf (9.6 mL, 42.0 mmol) was added at 0 ^oC and stirred for 30 min. Reaction mixture was diluted with water and CH_2Cl_2 layer was separated and concentrated. The residue was purified by silicagel column chromatography (15% EtOAc/light petroleum) to give compound **49** (11.9 g, 80%), which was dissolved in methanol (120 mL) and K_2CO_3 (11.5 g, 83.4 mmol) was added and stirred for 3 h. The reaction mixture was filtered and concentrated. The crude product was purified by silicagel chromatography (20% EtOAc/lightpetroleum) afforded compound **50** (7.83 g) in excellent yield.

Yield	98 %
Mol.Formula	$C_{20}H_{36}O_4Si$
$[\alpha]_D^{25}$	–1.32 (*c* 1.7, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 7.24 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.41 (AB q, *J* = 11.6, 13.1 Hz, 2H), 3.89 (q, *J* = 5.9 Hz, 1H), 3.81 (s, 3H), 3.69 (dd, *J* = 3.9, 10.9 Hz, 1H), 3.50 (t, *J* = 6.5 Hz, 3H), 2.69 (brs, 1H), 1.88 –1.74 (m, 3H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H)
^{13}C NMR ($CDCl_3$, 50MHz)	159.1, 130.3, 129.2, 113.7, 73.6, 72.7, 66.4, 65.1, 55.1, 39.1, 34.2, 25.8, 18.0, 13.7, – 4.4, – 4.6
Elemental Analysis	**Calcd:** C, 65.17; H, 9.84 **Found:** C, 65.24; H, 9.69

(2*S*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)-2-methylpentanal



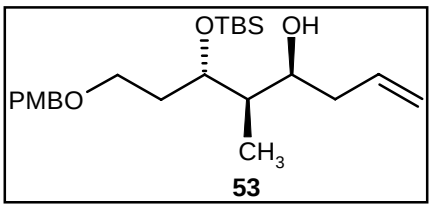
A solution of DMSO (5.50 mL, 72.2 mol) in CH_2Cl_2 (70 mL) was added dropwise to a solution of oxalyl chloride (2.07 mL, 24.0 mol) in CH_2Cl_2 (100 mL) at – 78 ^oC. After 30 min, a solution of alcohol **50** (7.8 g, 24.0 mol) in CH_2Cl_2 (50 mL) was added to the reaction mixture at same temperature and stirred for an additional 30 min. Triethyl amine (15.39 mL, 144.0 mol) was added and reaction mixture was allowed to come to room temperature. Water was added to the reaction mixture and extracted with CH_2Cl_2 (2 x 100 mL). The organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give crude aldehyde **51** (6.9 g), which was immediatedly used for next reaction without further purification.

^{1}H NMR (200 MHz, $CDCl_3$): 9.16 (d, *J* =2.1 Hz,1H) 6.68 (d, *J* = 8.7 Hz, 2H), 6.32 (d, *J* = 8.7 Hz, 2H), 3.85 (s, 2H), 3.60 (m, 1H), 3.26 (s, 3H), 2.97 (t, *J* = 6.0 Hz, 2H), 1.98-1.95 (m, 2H), 1.23 (m, 1H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), –0.09 (s, 6H).

To a stirred solution of aldehydic compound **51** (6.9 g, 21.3 mmol) in diethylether (60 mL) under nitrogen at 0 ^oC was added a solution of allylmagnesium bromide [prepared from Mg (2.5g, 106.8mmol) and allylbromide (5.42 mL, 64.08 mmol) in 100 mL Et_2O] and stirred for 1h.The reaction mixture was quenched by sat aq NH_4Cl. The ethereal layer was seperated and the aqueous layer was extracted thrice with (3 x 50 mL) Et_2O. The combined ethereal layer was washed with brine, dried over Na_2SO_4 and concentrated on rotavapour. The residue was purified by silicagel chromatography (15%

EtOAc/light petroleum) afforded alcohol **53** (3.2 g) and it's diastereomer **52** (2.2 g) in 1.5:1 ratio in 70 % yield as colourless liquid.

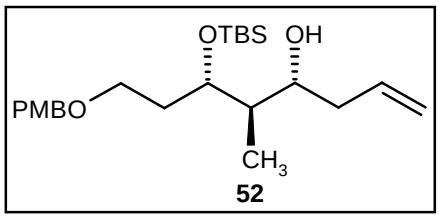
(4*S*,5*R*,6*S*)-6-(*tert*-butyldimethylsilyloxy)-8-(4-methoxybenzyloxy)-5-methyloct-1-en-4-ol



53

Mol.Formula	$C_{23}H_{40}O_4Si$
$[\alpha]_D^{25}$	–10.87 (*c* 1.4, CH_3COCH_3)
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 7.21 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.70 (m, 1H), 5.12–4.99 (m, 2H), 4.38 (ABq, *J* = 11.6, 17.1 Hz, 2H), 4.06-3.90 (m, 2H), 3.80 (s, 3H), 3.45 – 3.34 (m, 2H), 2.28 (m, 1H), 2.07 (m, 1H), 1.92 (q, *J* = 6.6 Hz, 2H), 1.50 (m, 1H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.09 (s, 6H)
^{13}C NMR ($CDCl_3$, 50MHz)	159.2, 135.3, 130.2, 129.1, 116.8, 113.7, 75.9, 72.6, 69.9, 66.2, 55.1, 39.2, 38.2, 34.9, 25.8, 17.9, 10.9, – 4.4, – 4.6
Elemental Analysis	**Calcd:** C, 67.64; H, 9.85 **Found:** C, 67.54; H, 9.73

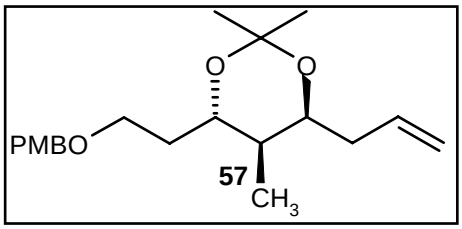
(4*R*,5*R*,6*S*)-6-(*tert*-butyldimethylsilyloxy)-8-(4-methoxybenzyloxy)-5-methyloct-1-en-4-ol



52

Mol.Formula	$C_{23}H_{40}O_4Si$
$[\alpha]_D^{25}$	–10.33 (*c* 1.3, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 7.23 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.85 (m, 1H), 5.16-5.09 (m, 2H), 4.42 (s, 2H), 4.06 (quin, *J* = 4.0 Hz, 1H), 3.79 (s, 3H), 3.55–3.41 (m, 3H), 2.45–2.33 (m, 2H), 2.06 (m, 1H), 1.81–1.60 (m, 3H), 0.87 (s, 9H), 0.83 (d, *J* = 6.9 Hz, 3H), 0.05 (s, 3H), 0.02 (s, 3H).
^{13}C NMR ($CDCl_3$, 125MHz)	159.1, 135.1, 130.3, 129.2, 117.8, 113.7, 72.6, 72.3, 70.8, 67.0, 55.1, 43.9, 39.3, 32.6, 25.8, 18.0, 10.9, –4.4, – 4.6
Elemental Analysis	**Calcd:** C, 67.64; H, 9.85
	Found: C, 67.54; H, 9.73

(4*S*,5*R*,6*S*)-4-allyl-6-(2-(4-methoxybenzyloxy)ethyl)-2,2,5-trimethyl-1,3-dioxane

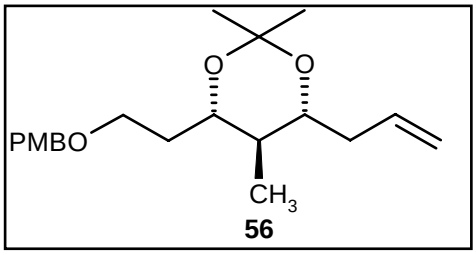


To a methanolic (5mL) solution of compound **53** (0.1 g, 0.27 mmol)**,** *p*-TSA (4 mg, 0.02 mmol) was added at room temperature and stirred for 30 min. The reaction mixture was neutralized with Et_3N (1mL), concentrated and purified by silicagel chromatography afforded diol **55** (73.0 mg, 90%) in very good yield.

Compound **55** was dissolved in CH_2Cl_2 (5 mL)**,** 2,2-dimethoxypropane (0.3 mL, 0.36 mmol) and *p*-TSA (4.2 mg, 0.024 mmol) were added and stirred at room temperature for 30 min, neutralized with Et_3N (1mL), concentrated and purified by silicagel chromatography to afford acetonide **57** (57.0 mg) in good yield.

Yield	70%
Mol.Formula	$C_{20}H_{30}O_4$
^{1}H NMR ($CDCl_3$, 200 MHz)	δ7.22 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 5.79 (m, 1H), 5.12–4.98 (m, 2H), 4.41 (s, 2H), 3.86 (m, 1H), 3.75 (s, 3H), 3.54–3.47 (m, 2H), 3.38 (dd, *J* = 3.0, 8.2 Hz, 1H), 2.28–1.99 (m, 2H), 1.89–1.58 (m, 3H), 1.29 (s, 6H), 0.84 (d, *J* = 6.8 Hz, 3H)
^{13}C NMR ($CDCl_3$, 50MHz)	158.9, 135.1, 130.4, 129.0, 116.2, 113.5, 100.3, 72.5, 71.4, 68.6, 66.4, 54.9, 39.6, 34.9, 34.6, 24.7, 23.6, 11.4
Elemental Analysis	**Calcd:** C, 71.85; H, 8.98 **Found:** C, 71.74; H, 8.53

(4*R*,5*R*,6*S*)-4-allyl-6-(2-(4-methoxybenzyloxy)ethyl)-2,2,5-trimethyl-1,3-dioxane

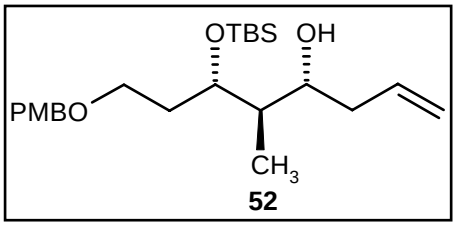


56

Compound **56** was prepared following same procedure as that for compound **54**.

Yield	70%
Mol.Formula	$C_{20}H_{30}O_4$
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 7.25 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 5.87 (m, 1H), 5.14–5.01 (m, 2H), 4.42-4.38 (m, 2H), 3.79 (s, 3H), 3.67–3.48 (m, 4H), 2.38–1.48 (m, 4H), 1.40 (s, 3H), 1.35 (s, 3H), 1.32 (s, 1H), 0.79 (d, *J* = 6.6 Hz, 3H).
^{13}C NMR ($CDCl_3$, 50MHz)	159.0, 134.9, 130.6, 129.1, 116.2, 113.6, 97.7, 73.9, 72.5, 71.0, 66.2, 55.1, 37.8, 37.3, 33.3, 30.0, 19.5, 12.0.
Elemental Analysis	**Calcd:** C, 71.85; H, 8.98 **Found:** C, 71.74; H, 8.53

(4*R*,5*R*,6*S*)-6-(*tert*-butyldimethylsilyloxy)-8-(4-methoxybenzyloxy)-5-methyloct-1-en-4-ol

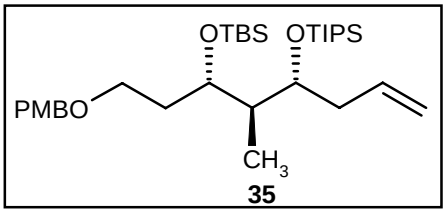


52

A solution of DMSO (8.0 mL, 105 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a solution of oxalyl chloride (3.03 mL, 35.0 mmol) in CH_2Cl_2 (30 mL) at -78 ^oC. After 30 min, a solution of mixture of alcohol **52** and **53** (14.3 g, 35.0 mmol) in CH_2Cl_2 (50 mL) was added at same temperature and stirred for additional 30 min. Triethyl amine (23.5 mL, 210.0 mmol) was added to the reaction mixture and allowed to come to room temperature. Water was added to the reaction mixture and extracted with CH_2Cl_2 (2 x 100 mL). The organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give crude ketone **58** (13.3 g), which was immediatedly used for next reaction without further purification.

To a solution of ketone **58** (13.3 g, 32.7 mmol) in methanol (75 mL), $NaBH_4$ (2.42 g, 65.5 mmol) and $CeCl_2$ (5.5 g, 16.3 mmol) was added at –100 ^oC under nitrogen. The solution was stirred for 1 h, quenched with saturated NH_4Cl and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silicagel chromatography (15% EtOAc/light petroleum) to give **52** (12.8 g) in 90% yield over 2 steps.

(4*R*, 5*R*, 6*S*)- 6-(*tert*-butyldimethylsilyloxy)-8-(4-methoxybenzyloxy)- 5-methy-4-(tri-*iso*propylsilyloxy)- oct-1en

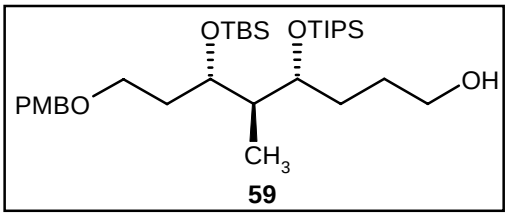


35

To a solution of alcohol **52** (8.0 g, 21.9 mmol) in CH_2Cl_2 (100 mL) pyridine (3.54 mL, 43.8 mmol), were added triisopropylsilyl chloride (6.36 g, 32.9 mmol) and cat$AgNO_3$ (1.11 g, 6.57 mmol) under nitrogen atmosphere and stirred 6h. Reaction mixture was diluted with water and the organic layer was separated and washed thrice with brine solution, dried over Na_2SO_4 and concentrated. The residue was purified by silicagel chromatography (10% EtOAc /light petroleum) to give **35** (8.67 g) as colorless oil.

Yield	70%
Mol.Formula	$C_{32}H_{60}O_4Si_2$
$[\alpha]_D^{25}$	–10.68 (*c* 1.2, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 7.13 (d, *J* = 8.5 Hz, 2H), 6.74 (d, *J* = 8.5 Hz, 2H), 5.81(m, 1H), 4.98–4.90 (m, 2H), 4.30 (s, 2H), 3.94–3.76 (m, 2H), 3.69 (s, 3H), 3.50–3.34 (m, 2H), 2.12 (m, 1H), 1.79–1.60 (m, 4H), 0.95 (s, 24H), 0.76 (s, 9H), –0.07 (s, 6H)
^{13}C NMR ($CDCl_3$, 50MHz)	159.0, 135.5, 130.6, 129.2, 116.5, 113.6, 72.6, 70.4, 70.1, 66.3, 55.1, 43.8, 37.6, 32.9, 25.8, 18.3, 17.7, 12.9, 12.3, –4.3, –4.5
Elemental Analysis	**Calcd:** C, 68.03; H,10.73 **Found:** C, 68.24; H, 11.32

(4*R*,5*R*,6*S*)-6-(*tert*-butyldimethylsilyloxy)-8-(4-methoxybenzyloxy)-5-methyl-4-(triisopropylsilyloxy)octan-1-ol

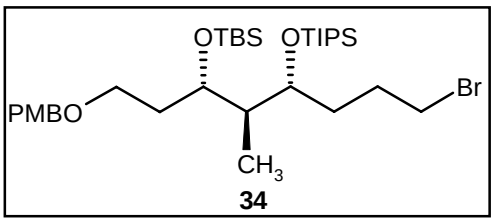


59

To a solution of **35** (3.2 g, 5.3 mmol) in anhydrous THF (100 mL) at 0 ^{o}C, $H_3B{:}SMe_2$ (2.1 mL, 21.2 mmol) was added slowly over a period of 10 min. After stirring for 2 h, 3N aq. NaOH solution (30 mL) and 30% H_2O_2 solution (30 mL) were introduced in succession at the same temperature. The reaction mixture was diluted with EtOAc, washed with saturated aq. Na_2SO_3, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel chromatography (30% EtOAc/light petroleum) to provide **59** (2.34 g) as a liquid.

Yield	76%
Mol.Formula	$C_{32}H_{62}O_5Si_2$
$[\alpha]_D^{25}$	2.31 (*c* 1.2, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 200 MHz)	δ7.14 (d, *J* = 8.5 Hz, 2H), 6.76 (d, *J* = 8.5 Hz, 2H), 4.31 (s, 2H), 3.91 (q, *J* = 5.3 Hz, 1H), 3.76 (m, 1H), 3.71 (s, 3H), 3.55–3.40 (m, 4H), 1.85–1.46 (m, 5H), 1.42–1.17 (m, 2H), 0.97 (s, 21H), 0.78 (s, 9H), 0.74 (d, *J* = 7.0 Hz, 3H), –0.06 (s, 6H).
^{13}C NMR ($CDCl_3$, 50MHz)	159.0, 130.6, 129.2, 113.6, 72.7, 72.6, 70.8, 66.1, 63.3, 55.1, 43.6, 33.0, 28.5, 25.8, 18.3, 18.0, 17.9, 13.0, 9.8, –4.4
Elemental Analysis	**Calcd:** C, 65.92; H,10.72 **Found:** C, 65.64; H, 10.53

(4*R*, 5*R*, 6*S*)- 6-(*tert*-butyldimethylsilyloxy)-8-(4-methoxybenzyloxy)- 5-methy-4-(tri-*iso*propylsilyloxy)- 1-bromo-octane

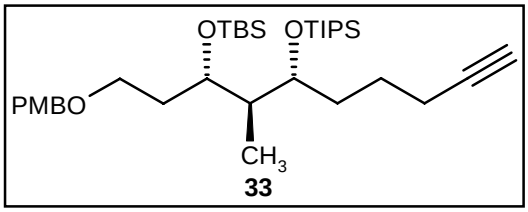


34

To a solution of alcohol **59** (5.6 g, 9.6 mmol) in CH_2Cl_2 (75 mL) imidazole (55 mg, 0.96 mmol) was added and cooled to 0 ^oC. Triphenylphosphine (5.04 g, 19.24 mmol) was added under nitrogen, followed by addition of CBr_4 (4.79 g, 14.4 mmol) in CH_2Cl_2 and stirred at room temperature for 1 h. The CH_2Cl_2 layer was washed with water dried (Na_2SO_4) and concentrated. The residue was purified quickly by passing through a short bed of silicagel with 6% EtOAc/light petroleum to produce the bromo compound **34** (5.28 g, 85%).

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 4.37 (s, 2H), 3.99 (m, 1H), 3.83 (m, 1H), 3.77 (s, 3H), 3.49 (t, *J* = 7.0 Hz, 2H), 3.38 (t, *J* = 5.8 Hz, 2H), 2.14 (s, 1H), 1.94–1. 51(m, 4H), 1.49–1.40 (m, 2H), 1.01 (s, 21H), 0.83 (s, 12H), 0.00 (s, 6H)

(6*R*, 7*R*, 8*S*)- 8-(*tert*-butyldimethylsilyloxy)-10-(4-methoxybenzyloxy)- 7-methy-6-(tri-*iso*propylsilyloxy)- 1-ynyl-decane

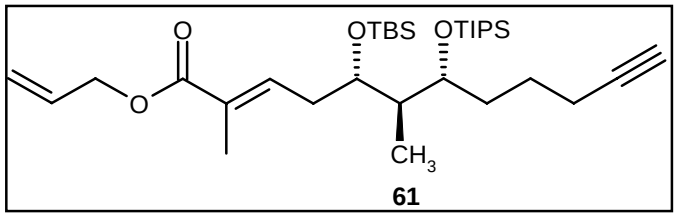


33

To a solution of bromo compound **34** (5 g, 7.73 mmol) in DMSO (30 mL), Lithium acetylide:EDTA complex (1.42 g, 15.4 mmol) was added at 4 ^{o}C and stirred for 30 min. Reaction mixture was diluted with water and extracted with EtOAc. The organic layer was separated, dried over Na_2SO_4 and concentrated on rotavapour. The residue was purified by silicagel chromatography (5% EtOAc/light petroleum) afforded alkyne compound **33** (3.2 g) as a brownish liquid.

Yield	73%
Mol.Formula	$C_{34}H_{62}O_4Si_2$
$[\alpha]_D^{25}$	2.62 (*c* 1.0, CH_2Cl_2)
IR ($CHCl_3$) cm^{-1}	3313, 2955, 2927, 2171, 1743
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 7.20 (d, *J* = 8.4 Hz, 2H), 6.81 (d, *J* = 8.4 Hz, 2H), 4.37 (s, 2H), 4.0 (m, 1H), 3.82 (m, 1H), 3.76 (s, 3H), 3.49 (t, *J* = 7.0 Hz, 2H), 2.20–2.10 (m, 2H), 1.87 (t, *J* = 2.4 Hz, 1H), 1.82–1.70 (m, 3H), 1.52–1.41 (m, 4H), 1.02 (s, 21H), 0.84 (s, 9H), 0.77 (d, *J* = 7.0 Hz, 3H), 0.00 (s, 6H)
^{13}C NMR ($CDCl_3$, 50MHz)	δ159.1, 130.7, 129.2, 113.7, 84.3, 72.7, 70.9, 68.4, 66.1, 55.1, 43.7, 33.1, 31.6, 25.9, 24.3, 18.9, 18.3, 18.0, 17.9, 17.9, 17.2, 13.0, 9.9, 9.0, –4.3, –4.4
Elemental Analysis	**Calcd:** C, 69.15; H,10.84 **Found:** C, 69.34; H, 10.43

(5*S*,6*R*,7*R*,*E*)-allyl 5-(*tert*-butyldimethylsilyloxy)-2,6-dimethyl-7-(triisopropylsilyloxy)dodec-2-en-11-ynoate



61

To a solution of compound **33** (3.2 g, 5.4 mmol) in CH_2Cl_2: H_2O (48:12 mL), pH 7 buffer solution (0.08 mL) was added and stirred in room temperature. DDQ (1.84 g, 8.1 mmol) was added and the resulting mixture was stirred at rt for 2 h. The mixture was diluted with CH_2Cl_2 and washed with aq. $NaHCO_3$ (4 x 15 mL), dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography (20% EtOAc/lightpetroleum) provided alcohol **60** as a colourless liquid (2.04 g, 91%).

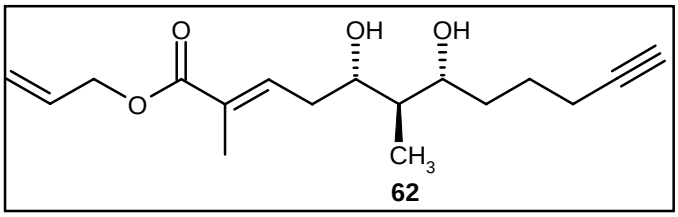
The alcohol **60** was dissolved in DMSO (15 mL) to it iodoxybenzoic acid (4.1 g, 14.7 mmol) was added at room temperature and stirred for 1h. Reaction mixture was diluted with 5 mL ice cold water, a white precipitate was formed and filtered. The filtrate was collected and extracted with ether. The ether layer was washed twice with water, dried over Na_2SO_4 and concentrated. The crude aldehyde **31**(1.6 g, 3.8 mmol) was dissolved in anhydrous THF (20 mL) and allyloxyethyledenetriphenyl phosphorane (4.3 g, 11.6 mmol) was added and stirred in reflux condition for 1h. THF was removed by rotavapour under vacuum and the residue was purified by column chromatography with 5% EtOAc in light petroleum to give the compound **61** (2.17g).

Yield	80%
Mol.Formula	$C_{32}H_{60}O_4Si_2$
$[\alpha]_D^{25}$	2.62 (*c* 1.0, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 6.85 (m, 1H), 5.80 (m, 1H), 5.24–5.07 (m, 2H), 4.51 (d, *J* = 1.3 Hz, 2H), 3.94-3.69 (m, 2H), 2.32-2.00 (m, 4H), 1.71 (m, 1H), 1.70 (s, 3H), 1.50–1.12 (m, 4H), 1.14 (s, 1H), 0.93 (s, 21H), 0.76 (s, 9H), 0.68 (d, *J* =

7.0 Hz, 3H), 0.07 (s, 6H)

Elemental Analysis **Calcd:** C, 69.15; H,10.84
Found: C, 69.34; H, 10.43

(5*S*,6*R*,7*R*,*E*)-allyl 5,7-dihydroxy-2,6-dimethyldodec-2-en-11-ynoate



62

Compound **61** (0.2 g, 0.337 mmol) was dissolved in methanol (5 mL) and PPTS (16 mg, 0.067 mmol) was added at 0 ^{o}C and stirred for 30 min. The reaction temperature was increased from 0 ^{o}C–rt and stirred for 30 min. Reaction mixture was quenched by Et_3N, concentrated and purified by 20% EtOAc/light petroleum provided diol **62** (36 mg) as a single product.

Yield 90%

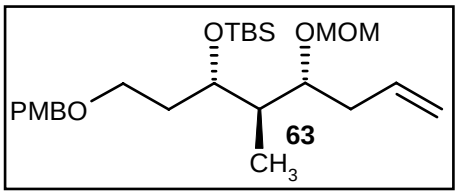
Mol.Formula $C_{17}H_{26}O_4$

$[\alpha]_D^{25}$ 4.32 (*c* 1.0, CH_2Cl_2)

^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.94 (dt, *J* = 1.3, 6.5 Hz, 1H), 5.97 (m, 1H), 5.39-5.21 (m, 2H), 4.68-4.66 (m, 2H), 4.64 (t, *J* = 1.2 Hz, 2H), 3.79-3.65 (m, 2H), 2.78 (br s, 1H), 2.48-2.30 (m, 2H), 2.26-2.20 (m, 2H), 1.97 (t, *J* = 2.6 Hz, 1H), 1.89 (s, 3 H), 1.76-1.52 (m, 3H), 0.89 (d, *J* = 6.9 Hz, 3H)

Elemental Analysis **Calcd:** C, 69.38; H**,** 8.84
Found: C, 69.34; H, 8.53

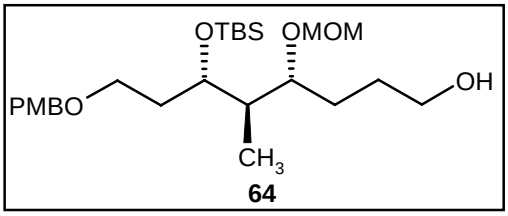
(4*R*, 5*R*, 6*S*)- 6-(*tert*-butyldimethylsilyloxy)-8-(4-methoxybenzyloxy)- 5-methy-4-(methoxymethyl)- 1-octene



To a solution of alcohol **52** (0.8 g, 1.96 mmol) in CH_2Cl_2 (3 mL) were added diisopropylethylamine (0.7 mL, 5.8 mmol), methoxymethyl chloride (0.3 mL, 2.9 mmol) and $AgNO_3$ (6 mg, 0.392 mmol) in 0 ^oC under nitrogen. The resulting solution was stirred for 6 h in rt Reaction mixture was diluted with water and the organic layer was separated and washed with brine solution, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography eluting with 15% EtOAc/light petroleum to give **63** (0.779 g) as colorless oil.

Yield	88%
Mol.Formula	$C_{25}H_{44}O_5Si$
$[\alpha]_D^{25}$	-30.77 (*c* 1.0, CH_2Cl_2)
IR ($CHCl_3$) cm^{-1}	3436, 3075, 2931, 1614
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 7.23 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 5.83 (m, 1H), 5.11–5.02 (m, 2H), 4.58 (AB q, J = 6.8, 7.8 Hz, 2H), 4.39 (s, 2H), 4.00 (m, 1H), 3.77 (s, 3H), 3.55–3.47 (m, 3H), 3.30 (s, 3H), 2.38 (s, 1H), 2.17 (s, 1H), 1.92-1.62 (m, 3H), 0.86 (s, 9H), 0.83 (d, *J* = 7.0 Hz, 3H), 0.02 (s, 6H).
^{13}C NMR ($CDCl_3$, 125 MHz)	159.0, 134.7, 130.7, 129.1, 116.8, 113.6, 95.8, 78.2, 72.5, 69.5, 67.1, 55.7, 55.1, 41.8, 35.6, 32.2, 25.8, 17.9, 9.8, –4.4, –4.6.
Elemental Analysis	**Calcd:** C, 66.50, H, 9.70
	Found: C, 66.54; H 9.63

(4*R*,5*R*,6*S*)-6-(*tert*-butyldimethylsilyloxy)-8-(4-methoxybenzyloxy)-4-(methoxymethoxy)-5-methyloctan-1-ol

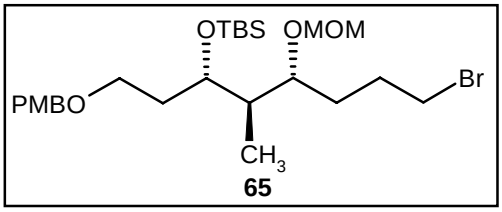


64

Compound **63** was prepared following same procedure as that for compound **64**.

Yield	76%
Mol.Formula	$C_{25}H_{46}O_6Si$
$[\alpha]_D^{25}$	–7.42 (*c* 12.1, CH_2Cl_2)
IR ($CHCl_3$) cm^{-1}	3444, 2930, 2063, 1727, 1614, 1470
^1H NMR ($CDCl_3$, 200 MHz)	δ 7.24 (d, *J* = 7.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.60 (s, 2H), 4.41 (s, 2H), 3.97 (quin, *J* = 4.1 Hz, 1H), 3.80 (s, 3H), 3.65 (t, *J* = 5.6 Hz, 2H), 3.58–3.48 (m, 3H), 3.33 (s, 3H), 1.96–1.66 (m, 7H), 0.87 (s, 9H), 0.83 (d, *J* = 7.0 Hz, 3H), 0.03 (s, 6H)
^{13}C NMR ($CDCl_3$, 125 MHz)	159.0, 130.6, 129.1, 113.6, 95.9, 78.7, 72.5, 69.7, 66.9, 62.9, 55.7, 55.1, 41.5, 32.3, 27.7, 27.1, 25.8, 17.9, 9.9, –4.5, –4.6
Elemental Analysis	**Calcd:** C, 63.8; H, 9.78 **Found:** C, 63.74; H 9.53

(4*R*,5*R*,6*S*)-6-(*tert*-butyldimethylsiloxy)-8-(4-methoxybenzyloxy)-4-(methoxymethyloxy)-5-methyl-1-bromo-octane

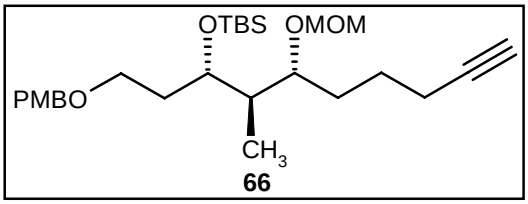


65

Compound **65**was prepared following the same procedure as that for compound **64**.

Yield	72 %
Mol.Formula	$C_{25}H_{45}O_5SiBr$
$[\alpha]_D^{25}$	–3.42 (*c* 2.1, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 7.23 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.55 (s, 2H), 4.39 (s, 2H), 3.93 (m, 1H), 3.78 (s, 3H), 3.56–3.44 (m, 3H), 3.41 (t, *J* = 6.5 Hz, 2H), 3.30 (s, 3H), 1.97-1.41 (m, 7H), 0.86 (s, 9H), 0.82 (d, *J* = 7.0 Hz, 3H), 0.02 (s, 6H).
Elemental Analysis	**Calcd:** C, 56.28; H, 8.44 **Found:** C, 56.54; H 8.78

(4*R*,5*R*,6*S*)-6-(*tert*-butyldimethylsiloxy)-8-(4-methoxybenzyloxy)-4-(methoxymethyloxy)-5-methyl-1-alkynyl-decane



66

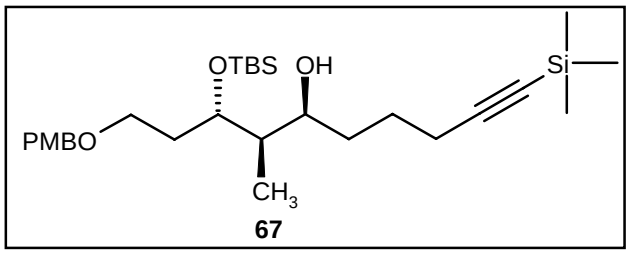
Compound **66** was prepared from bromo compound **65** using litium acetylide:EDTA complex following the procedure as that for compound **33**.

Yield	74%
Mol.Formula	$C_{27}H_{46}O_5Si$
$[\alpha]_D^{25}$	–7.49 (*c* 3.4, CH_2Cl_2)
IR ($CHCl_3$) cm^{-1}	3309, 3013, 2955, 2857, 2117, 1724
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 7.24 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.58 (s, 2H), 4.41 (s, 2H), 3.94 (m, 1H), 3.80 (s, 3H), 3.56–3.48 (m, 3H), 3.32 (s, 3H), 2.26–2.14 (m, 2H), 1.93 (t, *J* = 2.6 Hz, 1H), 1.89–1.60 (m, 7H), 0.87 (s, 9H), 0.83 (d, *J* = 7.2 Hz, 3H), 0.03 (d, *J* = 1.6 Hz, 6H)
^{13}C NMR ($CDCl_3$, 50 MHz)	159.0, 130.7, 129.1, 113.6, 95.8, 84.3, 78.3, 72.5, 69.9, 68.4, 66.9, 55.7, 55.2, 41.6, 32.5, 29.8, 25.8, 23.6, 18.6, 18.0, 10.0, –4.5, –4.5
Elemental Analysis	**Calcd:** C, 67.92; H, 9.64
	Found: C, 67.64; H, 9.54

To a stirred solution of aldehydic compound **51** (6.9 g, 18.8 mmol) in THF (60 mL) under nitrogen at 0 ^oC was added a solution of pentynylmagnesium bromide [prepared from Mg (2.25 g, 94.0 mmol) and TMS-pentynylbromide (8.2 g, 37.6 mmol) in 60 mL THF] and stirred for 1h.The reaction mixture was quenched by sat NH_4Cl. The THF layer was seperated and the aqueous layer was extracted thrice with (3 x 50 mL) EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and

concentrated on rotavapour.The residue was purified by silicagel chromatography afforded alcohol **67** (4.8 g) and it's diastereomer **68** (3.2 g) in 1. :1.5 ratio in 84% yield over two steps as colourless liquid.

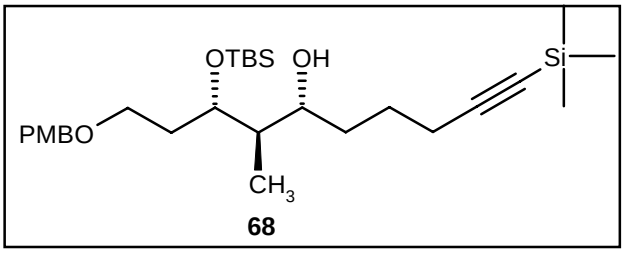
(3*S*,4*R*,5*S*)- 10-(trimethylsilyl)- 4-methyl-3-(*tert*-butyldimethylsilyloxy)-1-(4-methoxybenzyloxy)-dec-9-yn-5-ol



67

Mol.Formula	$C_{28}H_{50}Si_2O_4$
$[\alpha]_D^{25}$	–2.85 (*c* 0.7, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 7.22 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 4.39 (AB q, *J* = 11.6, 19.4 Hz, 2H), 4.12 (m, 1H), 3.95 (dt, *J* = 2.4, 6.8 Hz, 1H), 3.80 (s, 3H), 3.54 (m, 1H), 3.46–3.38 (m, 2H), 2.26 (t, *J* = 6.9 Hz, 2H), 1.94 (q, *J* = 6.7 Hz, 2H), 1.81–1.63 (m, 2H), 1.55–1.25 (m, 3H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.13(s, 9H), 0.09 (s, 6H)
^{13}C NMR ($CDCl_3$, 50 MHz)	159.1, 130.2, 129.2, 113.7, 107.1, 84.5, 76.0, 72.6, 69.1, 66.2, 55.1, 38.6, 35.0, 33.5, 25.8, 17.9, 16.6, 11.3, 0.19, –4.4, –4.7.
Elemental Analysis	**Calcd:** C, 66.40; H, 9.88 **Found:** C, 66.32; H,10.14

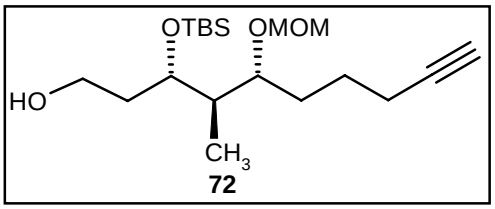
(3*S*,4*R*,5*R*)- 10-(trimethylsilyl)- 4-methyl-3-(*tert*-butyldimethylsilyloxy)-1-(4-methoxybenzyloxy)-dec-9-yn-5-ol



68

Mol.Formula	$C_{28}H_{50}Si_2O_4$
$[\alpha]_D^{25}$	3.05 (*c* 1.3, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 7.22 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 4.40 (s, 2H), 4.02 (m, 1H), 3.78 (s, 3H), 3.53–3.44 (m, 3H), 2.33 (dt, *J* = 2.02, 7.0 Hz, 2H), 2.20 (m, 1H), 1.94–1.44 (m, 7H), 0.86 (s, 9H), 0.82 (d, *J* = 6.9 Hz, 3H), 0.12 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H).
^{13}C NMR ($CDCl_3$, 50 MHz)	159.1, 130.2, 129.3, 113.7, 107.5, 84.7, 72.8, 72.7, 71.5 67.0, 55.1, 44.2, 33.6, 33.3, 25.8, 18.0, 16.2, 11.6, 0.18, –4.4, –4.5
Elemental Analysis	**Calcd:** C, 66.40; H,9.88
	Found: C, 66.32; H,10.14

(3*S*,4*R*,5*R*)-3-(*tert*-butyldimethylsilyloxy)-5-(methoxymethoxy)-4-methyldec-9-yn-1-ol

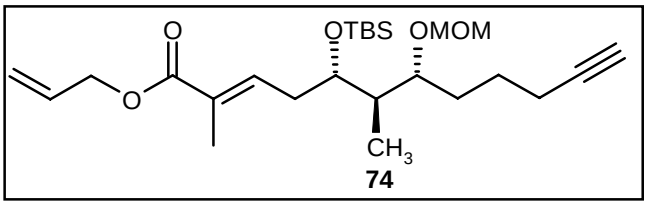


72

Paramethoxybenzyl ether of compound **66** was deprotected by DDQ following same procedure as that for compound **70** resulted in compound **72**.

Yield	91%
Mol.Formula	$C_{19}H_{38}O_4Si$
$[\alpha]_D^{25}$	–15.73 (*c* 2.6, CH_2Cl_2)
IR ($CHCl_3$) cm^{-1}	3447, 3312, 2953, 2887, 2857, 1472
^1H NMR ($CDCl_3$, 200 MHz)	δ 4.60 (s, 2H), 4.06 (m, 1H), 3.74 (t, *J* = 5.9 Hz, 2H), 3.49 (m, 1H), 3.36 (s, 3H), 2.29 (br s, 1H), 2.25–2.14 (m, 2H), 1.94 (t, *J* = 2.5 Hz, 1H), 1.74–1.69 (m, 2H), 1.64 (d, *J* = 5.3 Hz, 2H), 1.58–1.47 (m, 2H) 0.89 (s, 9H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.09 (s, 3H), 0.07(s, 3H)
^{13}C NMR ($CDCl_3$, 50 MHz)	95.9, 84.1, 78.8, 71.3, 68.4, 60.3, 55.7, 41.5, 33.9, 29.9, 25.7, 23.3, 18.5, 17.8, 9.9, –4.5, –4.5
Elemental Analysis	**Calcd:** C, 63.68; H,10.60 **Found:** C, 63.54; H, 10.43

(5*S*,6*R*,7*R*,*E*)-allyl 5-(*tert*-butyldimethylsilyloxy)-7-(methoxymethoxy)-2,6-dimethyldodec-2-en-11-ynoate

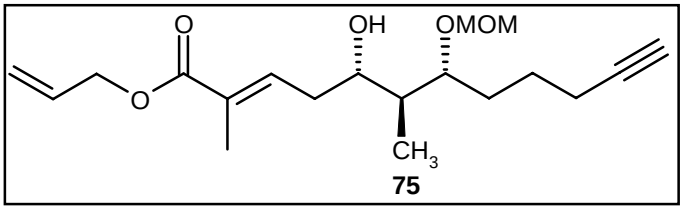


74

Compound **74** was prepared from **73** following same procedure as that for compound **23**.

Yield	80%
Mol.Formula	$C_{25}H_{44}O_5Si$
$[\alpha]_D^{25}$	3.63 (*c* 5.4, CH_2Cl_2)
IR ($CHCl_3$) cm^{-1}	3309, 3018, 2857, 2401, 2117, 1707, 1648, 1462, 1379, 1362, 1252, 1097, 936, 837
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 6.90 (dt, *J* = 1.3, 7.3 Hz, 1H), 5.92 (m, 1H), 5.27 (ddd, *J* = 1.3, 10.3 Hz, 2H), 4.62 (dt, *J* = 1.3, 5.5 Hz, 2H), 4.59 (s, 2H), 3.90 (q, *J* = 5.5 Hz, 1H), 3.59 (m, 1H), 3.34 (s, 3H), 2.33 (t, *J* = 6.3 Hz, 2H), 2.25–2.16 (m, 2H), 2.00-1.94 (m, 2H), 1.84 (s, 3H), 1.70-1.48 (m, 4H), 0.87 (s, 9H), 0.83 (d, *J* = 6.9 Hz, 3H), 0.04 (s, 3H), 0.02 (s, 3H)
^{13}C NMR ($CDCl_3$, 50 MHz)	167.8, 140.1, 132.8, 128.7, 117.8, 96.1, 84.5, 78.6, 72.3, 68.7, 65.2, 56.0, 42.0, 32.7, 30.0, 26.0, 24.1, 18.8, 18.2, 12.8, 10.5, –4.1, –4.3
Elemental Analysis	**Calcd:** C, 66.37; H, 9.70. **Found:** C, 66.54; H, 10.10

(5*S*,6*S*,7*R*,*E*)-allyl 5-hydroxy-7-(methoxymethoxy)-2,6-dimethyldodec-2-en-11-ynoate

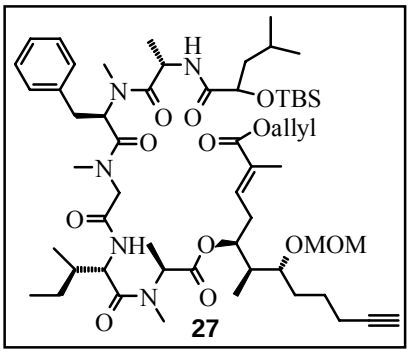


75

To a solution of compound **74** (0.1g, 0.221mmol) in THF (2 mL), TBAF in THF (2.21 mL, 0.221mmol) was added at 0 ^{o}C and catalytic amount of AcOH (0.1 mL) was added and stirred for 2 h. Reaction mixture was concentrated and purified by silicagel chromatography (15% EtOAc/light petroleum) to give compound **75** (0.06 g) as colourless liquid.

Yield	86%
Mol.Formula	$C_{19}H_{30}O_5$
$[\alpha]_D^{25}$	–16.71 (*c* 1.0, CH_2Cl_2)
IR ($CHCl_3$) cm^{-1}	3470, 3308, 3019, 2958, 2401, 1706
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 6.94 (m, 1H), 5.97 (m, 1H), 5.39–5.20 (m, 2H), 4.68–4.66 (m, 3H), 4.64 (t, *J* = 1.3 Hz, 1H), 3.81–3.63 (m, 2H), 3.40 (s, 3H), 2.30 (m, 1H), 2.19-2.14 (m, 2H), 1.97 (t, *J* = 2.6 Hz, 1H), 1.89 (s, 3H), 1.76–1.55 (m, 5H), 1.20 (s, 1H), 0.88 (d, *J* = 6.9 Hz, 3H)
^{13}C NMR ($CDCl_3$, 125 MHz)	167.5, 138.9, 132.4, 129.5, 117.7, 95.7, 84.1, 79.7, 73.2, 68.5, 65.1, 55.9, 41.5, 34.1, 29.3, 23.6, 18.3, 12.6, 12.0.
Elemental Analysis	**Calcd:** C, 67.40; H, 8.87 **Found:** C, 67.54; H, 8.53

Compound-27

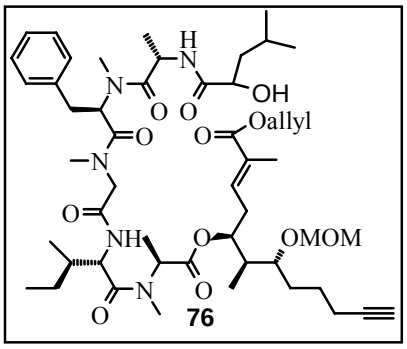


27

To a solution of acid **28** (0.165 g, 0.221 mmol) in CH_2Cl_2 (5 mL) were added EDCI (56 mg, 0.295 mmol) and DMAP (0.8 mg, 0.0073 mmol). Alcohol **75** (0.025g, 0.0739 mmol) in CH_2Cl_2 (2 mL) was added and stirred for 7 h. Reaction mixture was concentrated and purified by silicagel chromatography (60% EtOAc/light petroleum) afforded compound **27** (63 mg) as a liquid.

Yield	80 %
Mol.Formula	$C_{57}O_{12}H_{93}N_5Si$
$[\alpha]_D^{25}$	28.17 (*c* 0.5, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 7.22 (d, *J* = 4.1 Hz, 2H), 7.19-7.13 (m, 3H), 6.71(m, 1H), 6.53 (m, 1H), 5.90 (m, 1H), 5.30 (d, *J* = 17.4 Hz, 1H), 5.23-5.18 (m, 2H), 5.09 (m, 1H), 4.86-4.76 (m, 2H), 4.68 (t, *J* = 7.34 Hz, 1H), 4.62-4.59 (m, 4H), 4.12-4.03 (m, 3H), 3.50 (brs, 1H), 3.35 (d, *J* = 6.4 Hz, 3H), 3.25-3.17 (m, 2H), 3.07-2.91(m, 14H), 2.54 (m, 1H), 2.42 (m, 1H), 2.21-2.16 (m, 2H), 2.09(m, 1H), 2.02 (s, 1H),1.95 (m, 1H), 1.84 (s, 4H), 1.81(s, 2H), 1.64-1.58 (m, 3H), 1.57-1.51 (m, 3H), 1.49-1.47 (m, 3H), 1.43-1.40 (m, 2H), 1.36 (dd, *J* = 7.3, 14.2 Hz, 4H), 1.25-1.22 (m, 2H), 0.90 (s, 9H), 0.86-0.82 (m, 4H), 0.80 (d, *J* = 6.8 Hz, 2H), 0.05 (s, 3H), 0.02 (s, 3H)
ESI Mass(m/e)	$[M^+ + Na] = 1090.66$, $[M^+ + K] = 1106.66$

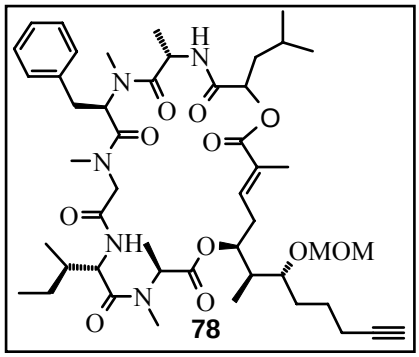
Compound-76



To a solution of compound **27** (0.1g, 0.093mmol) in THF (5 mL), TBAF in THF (0.02 mL, 0.102 mmol) was added at 0 ^{o}C and catalytic amount of AcOH was added and stirred for 2 h. Reaction mixture was concentrated and purified by silicagel chromatography (70% EtOAc/light petroleum) afforded compound **76** (0.06 g) as colourless liquid.

Yield	71%
Mol.Formula	$C_{51}O_{12}H_{79}N_5$
$[\alpha]_D^{25}$	-16.71 (*c* 1.0, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 7.64 (m, 1H), 7.23-7.16 (m, 5H), 6.72 (m, 1H), 5.93 (m, 1H), 5.50 (m, 1H), 5.32(d, *J* = 17.3 Hz, 1H), 5.24 (m, 1H), 5.14 (m, 1H), 4.90-4.71(m, 2H), 4.63 (s, 3H), 4.52 (t, *J* = 17.5Hz, 1H), 4.11(q, *J* = 7.2 Hz, 4H), 4.06 (brs, 1H), 3.46 (m, 1H), 3.37 (s, 3H), 3.20-2.99 (m, 12H), 2.88 (d, *J* = 8.0 Hz, 1H), 2.80 (t, *J* = 8.5 Hz, 3H), 2.43 (m, 1H), 2.25-2.16 (m, 2H), 2.09(m, 1H), 2.04 (s, 3H), 1.99-1.93 (m, 2H), 1.86 (s, 4H), 1.65-1.50 (m, 9H), 1.34 (d, *J* = 7.2 Hz, 4H), 1.26 (s, 4H), 0.93 (s, 6H)
ESI Mass (m/e)	[M^++Na] = 976.83, [M^++K] = 992.79

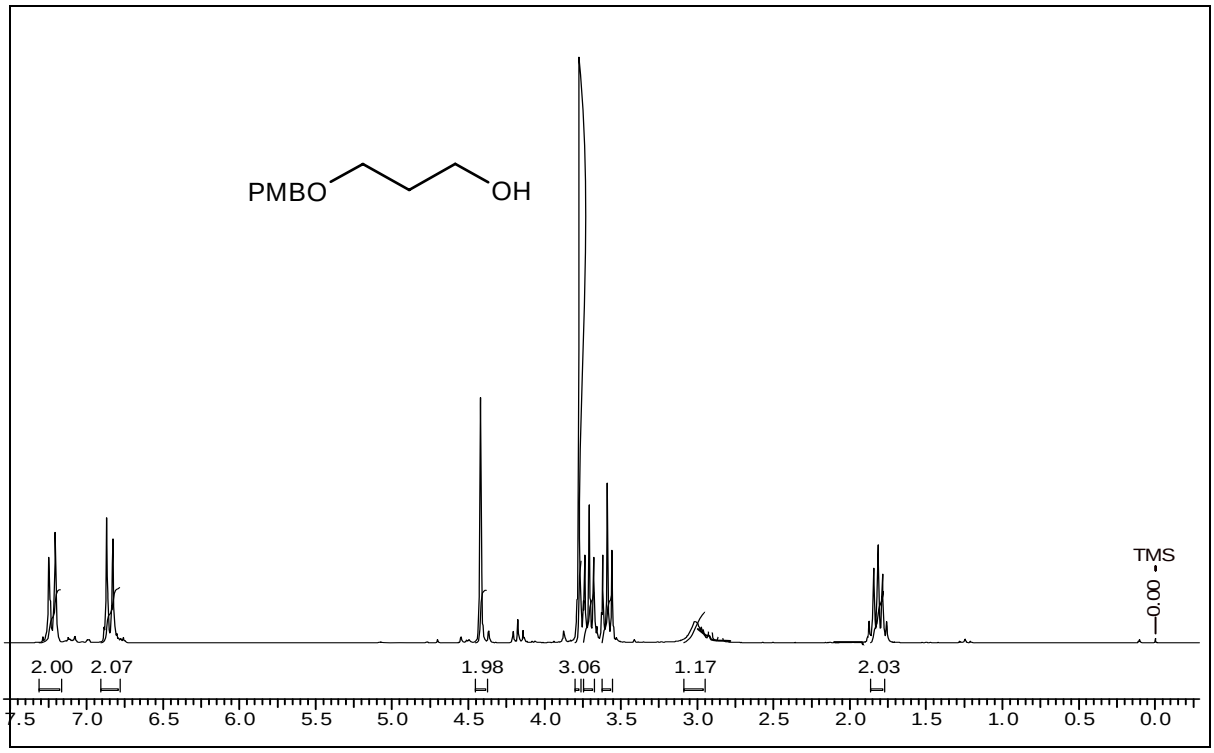
Compound-78



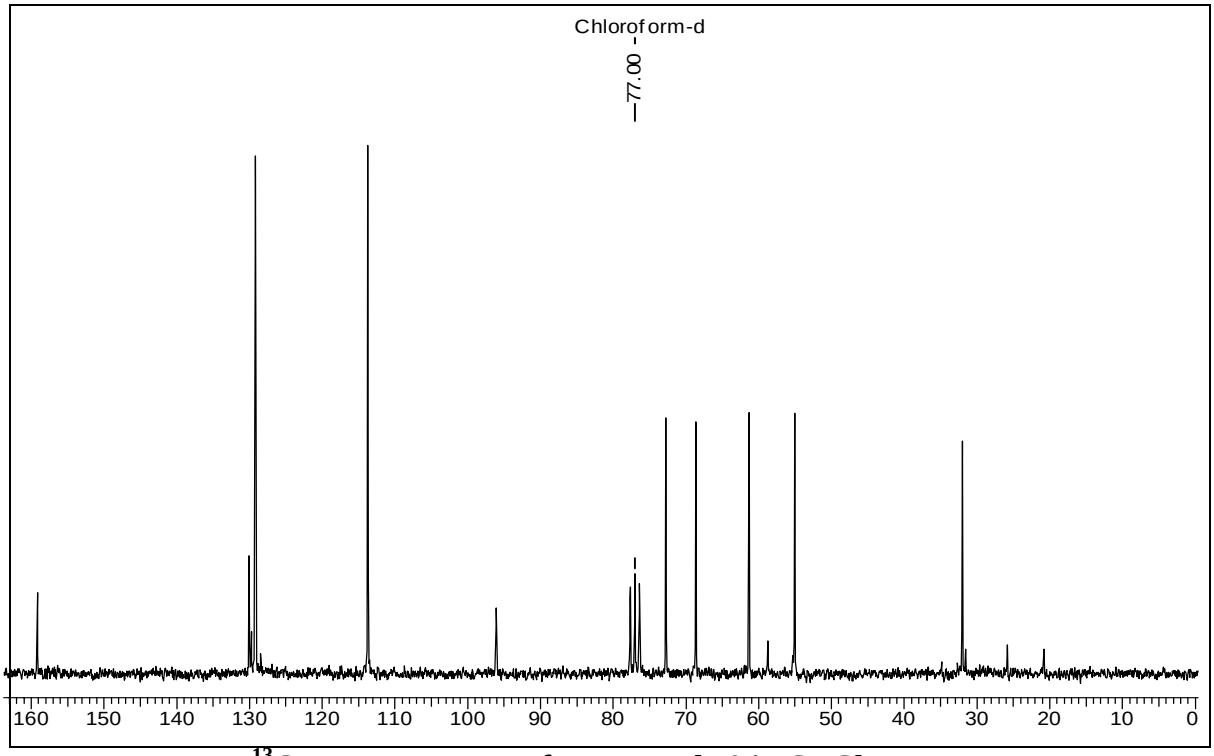
78

Yield	15%
Mol.Formula	$C_{48}H_{73}O_{11}N_5$
$[\alpha]_D^{25}$	-1.53 (*c* 0.8, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 200 MHz)	7.60 (m, 1H), 7.27-7.15 (m, 5H), 6.78 (m, 1H), 5.48-5.22 (m, 2H), 4.98-4.61 (m, 5H), 4.28-4.04 (m, 2H), 3.88 (m, 1H), 3.75-3.63 (m, 3H), 3.41-3.33 (m, 3H), 3.11-2.94 (m, 13H), 2.46-2.06 (m, 4H), 1.96(m, 1H), 1.88-1.76 (m, 5H), 1.72-1.46 (m, 14H), 1.26 (s, 6H), 0.90 (s, 8H).
ESI Mass (m/e)	[M^++Na] = 919, [M^++K] = 935

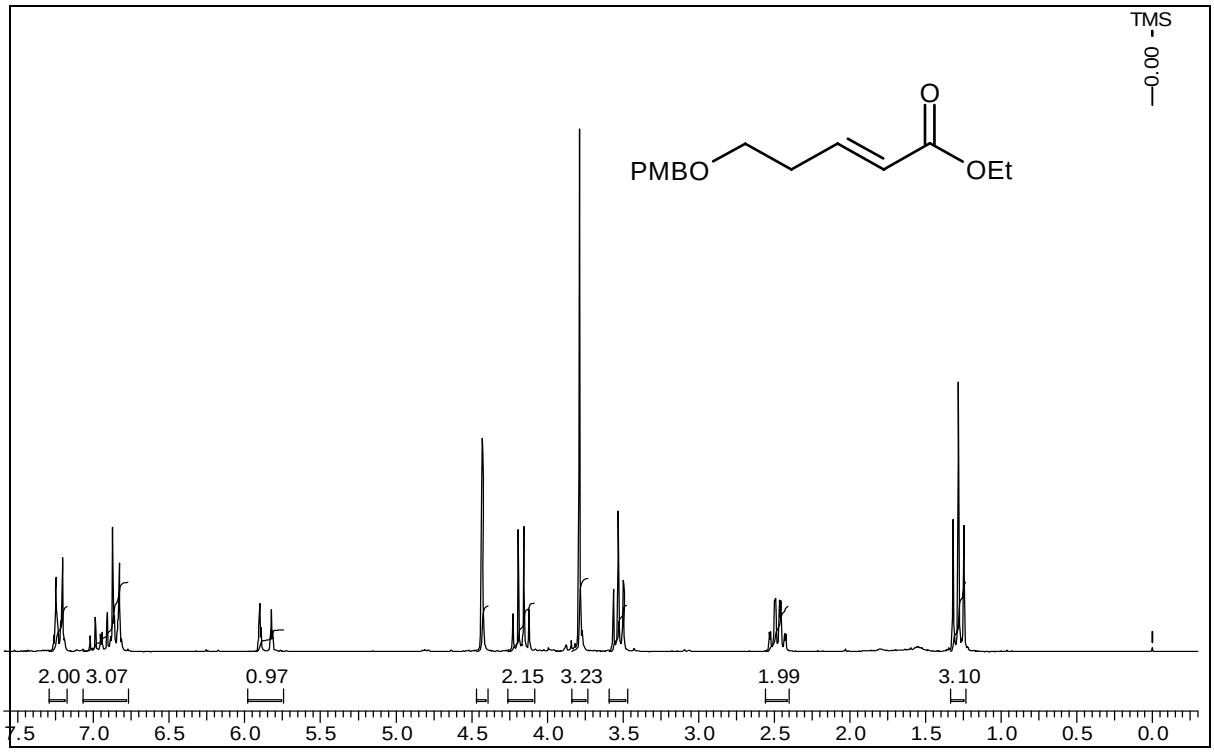
SPECTRA



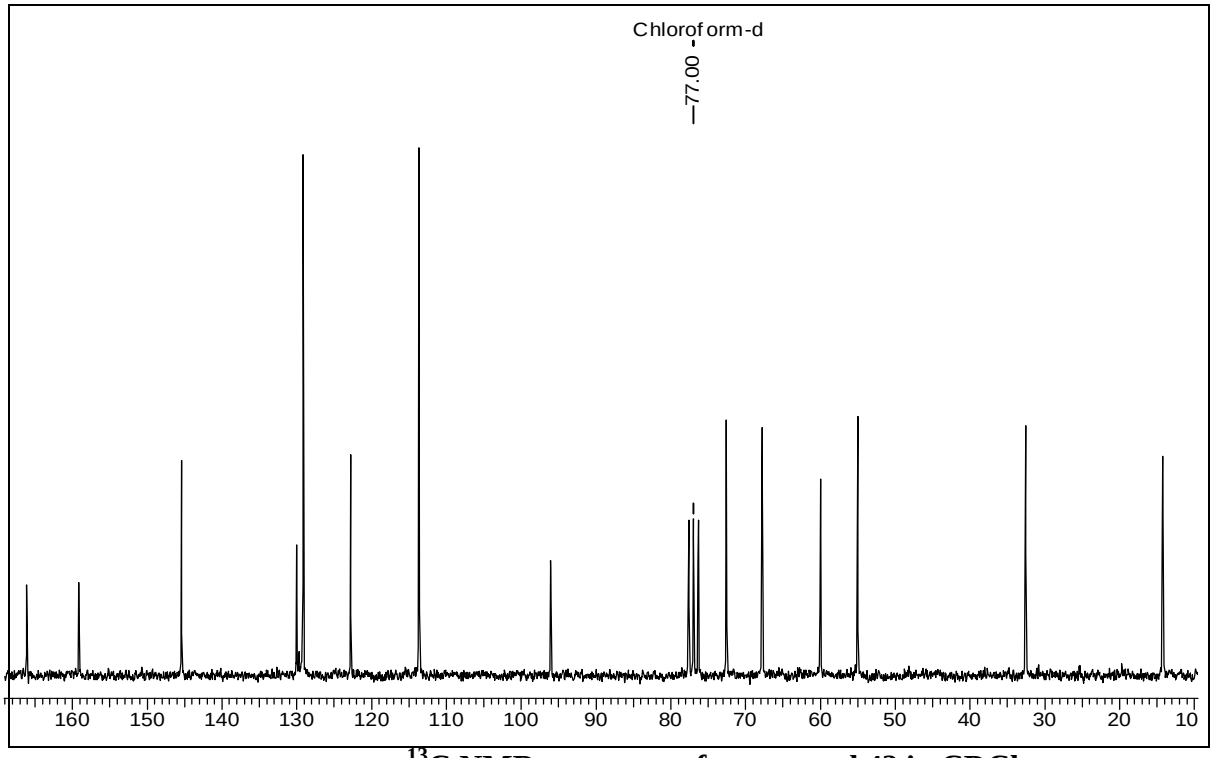
^{1}H NMR spectrum of compound 40 in $CDCl_3$



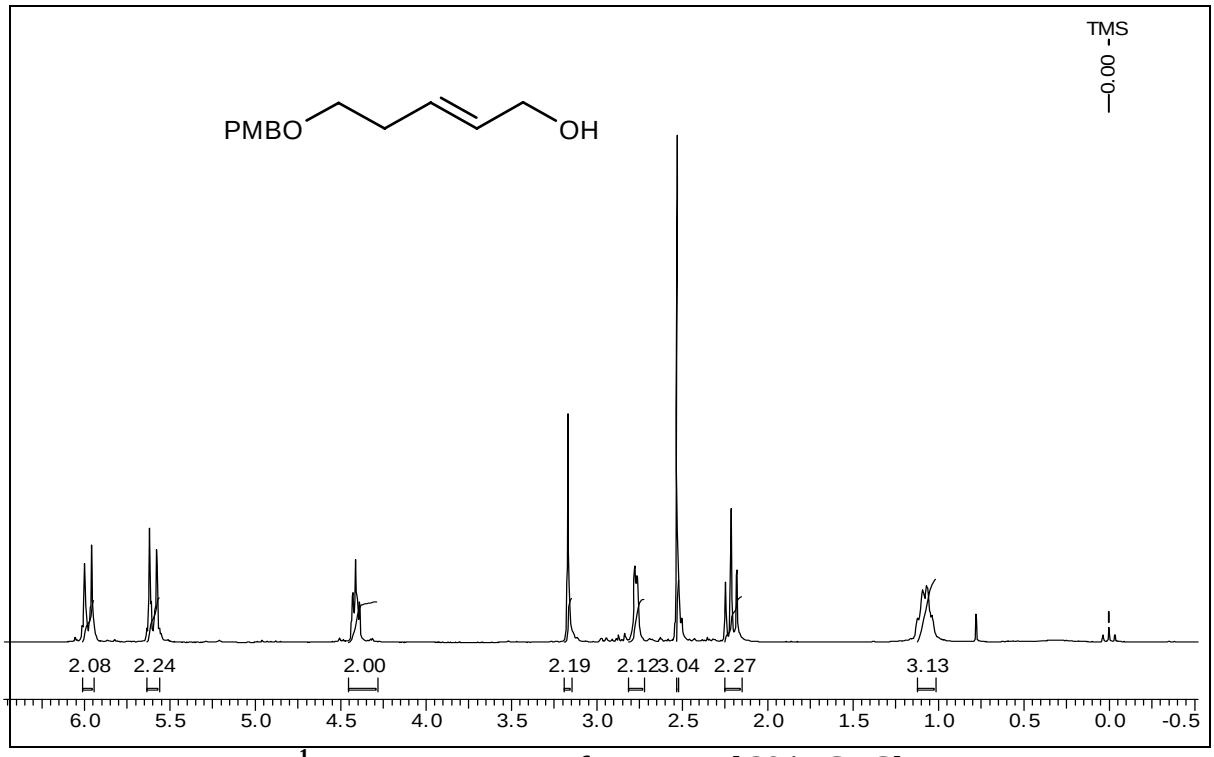
^{13}C NMR spectrum of compound 40 in $CDCl_3$



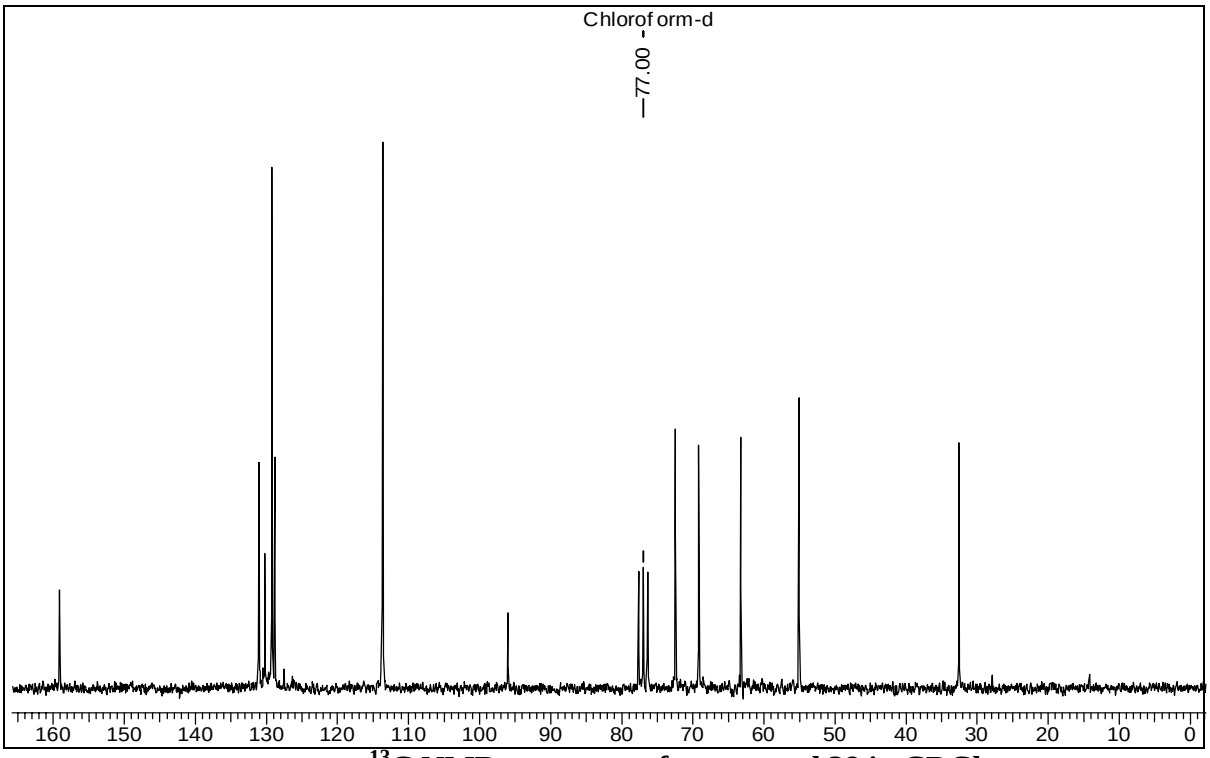
^{1}H NMR spectrum of compound 42 in $CDCl_3$



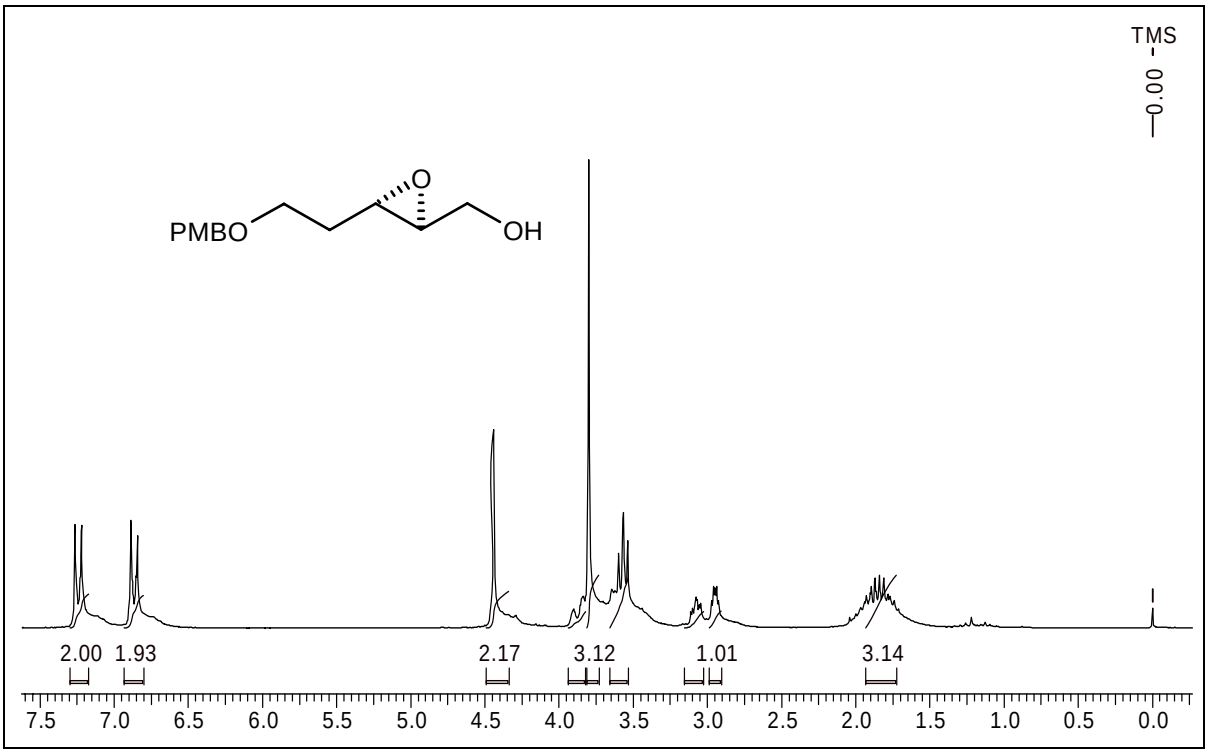
^{13}C NMR spectrum of compound 42 in $CDCl_3$



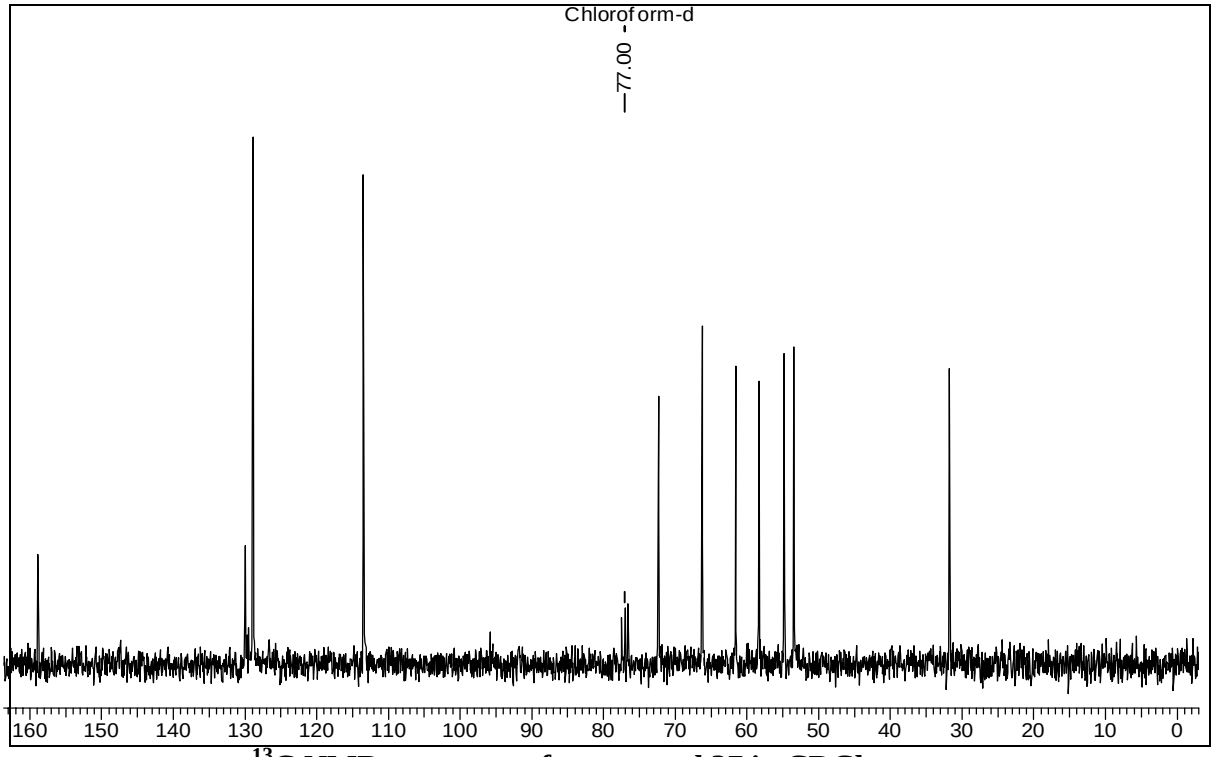
^{1}H NMR spectrum of compound 38 in $CDCl_3$



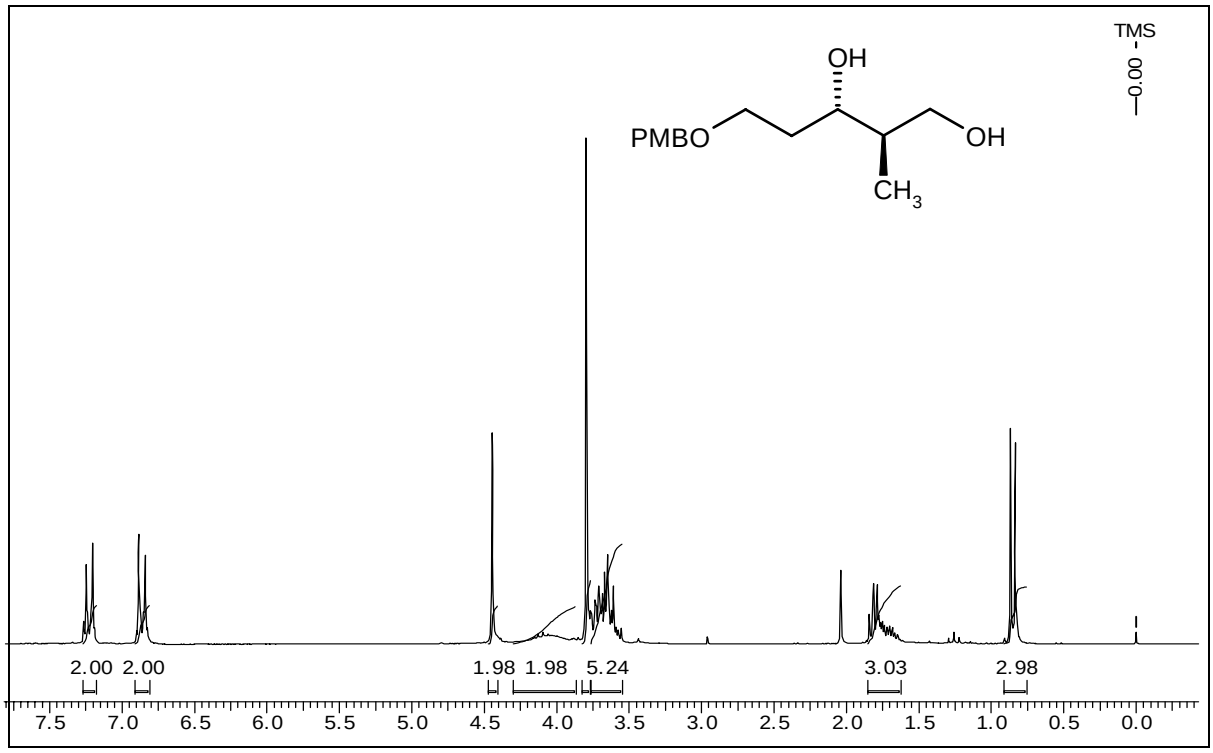
^{13}C NMR spectrum of compound 38 in $CDCl_3$



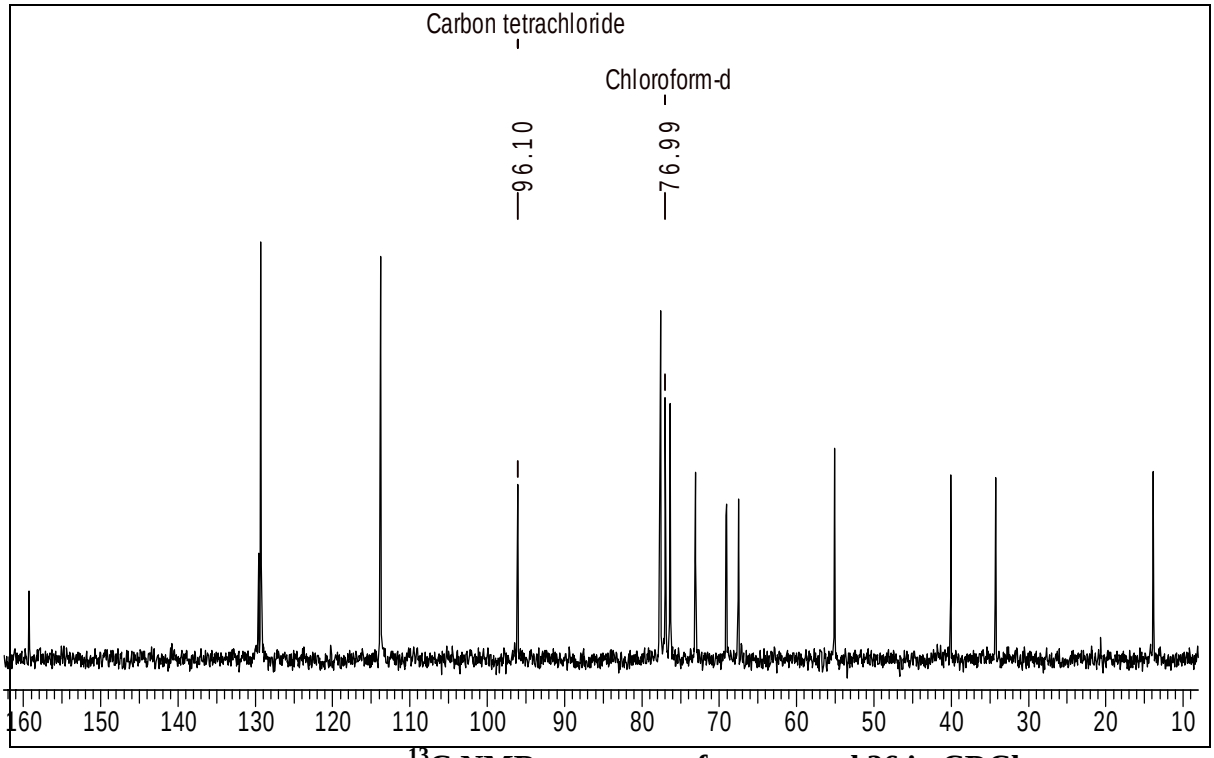
^{1}H NMR spectrum of compound 37 in $CDCl_3$



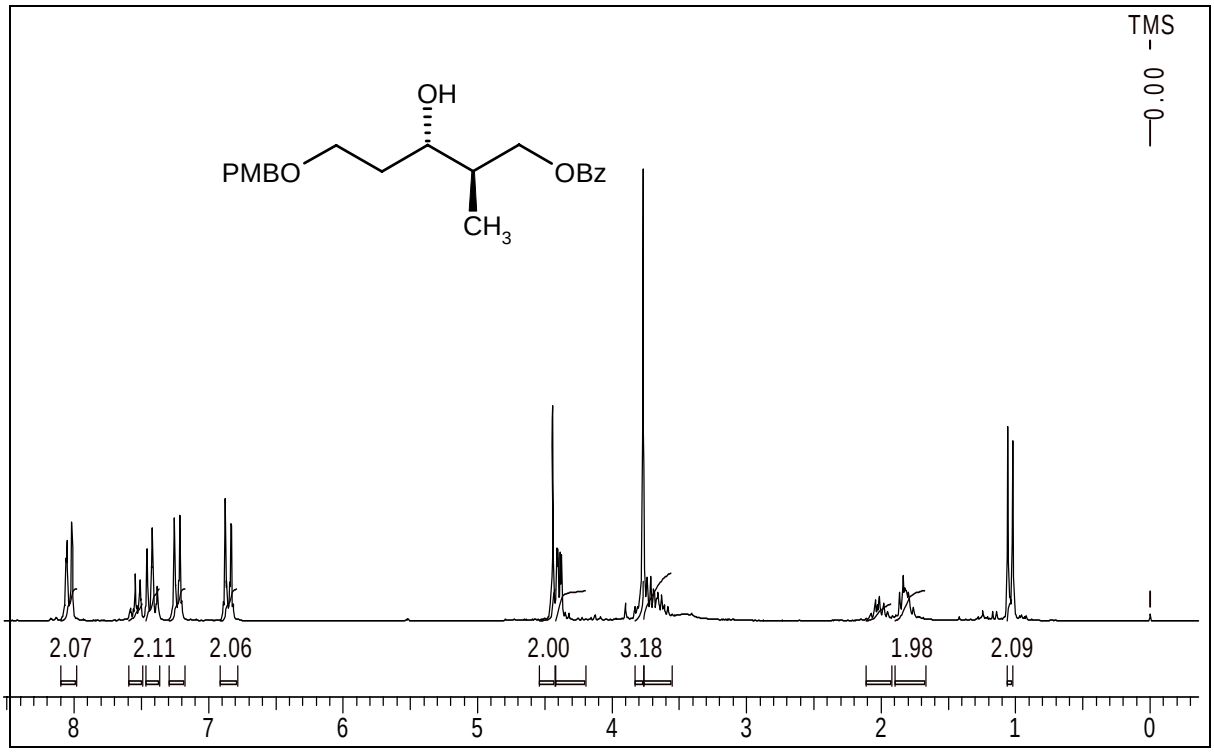
^{13}C NMR spectrum of compound 37 in $CDCl_3$



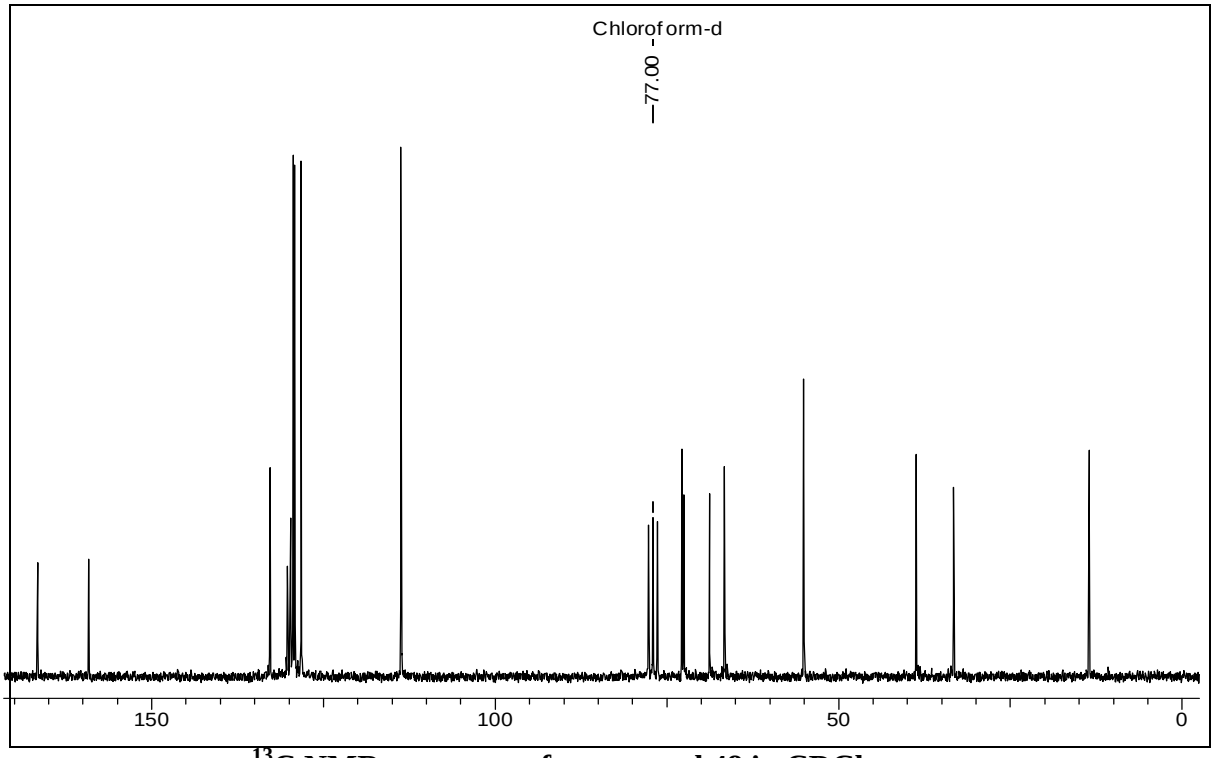
^{1}H NMR spectrum of compound 36 in $CDCl_3$



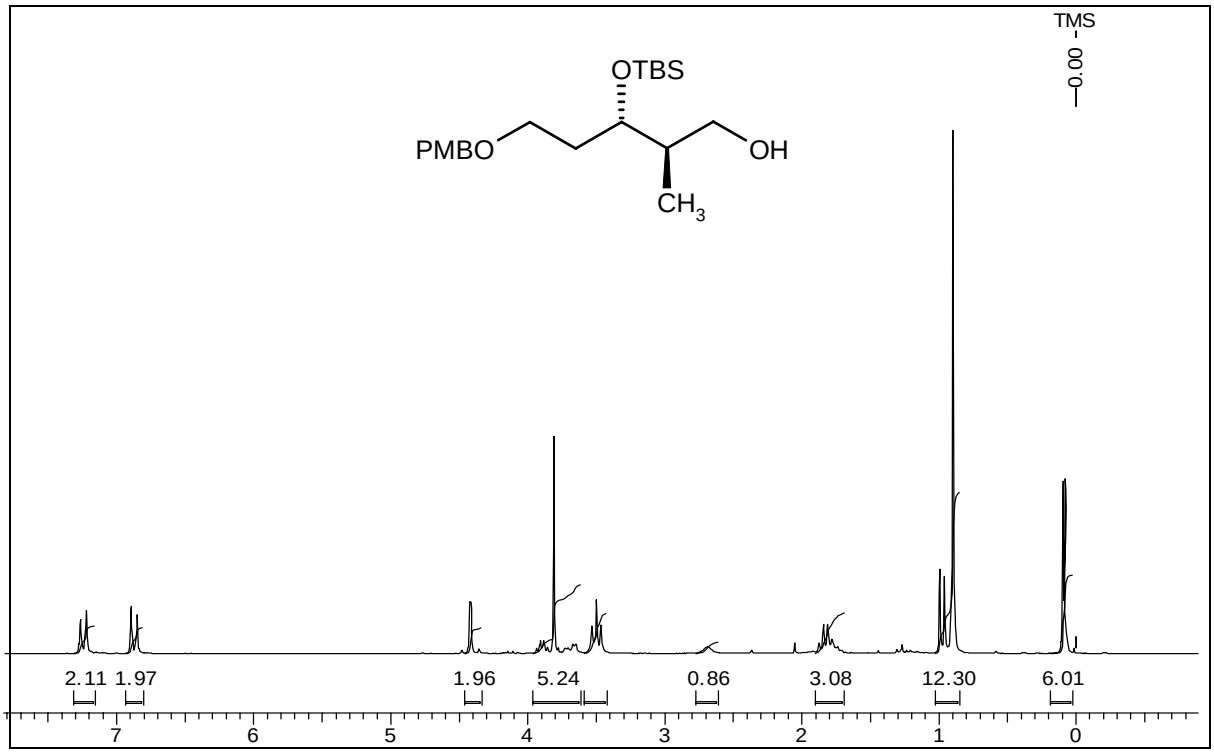
^{13}C NMR spectrum of compound 36 in $CDCl_3$



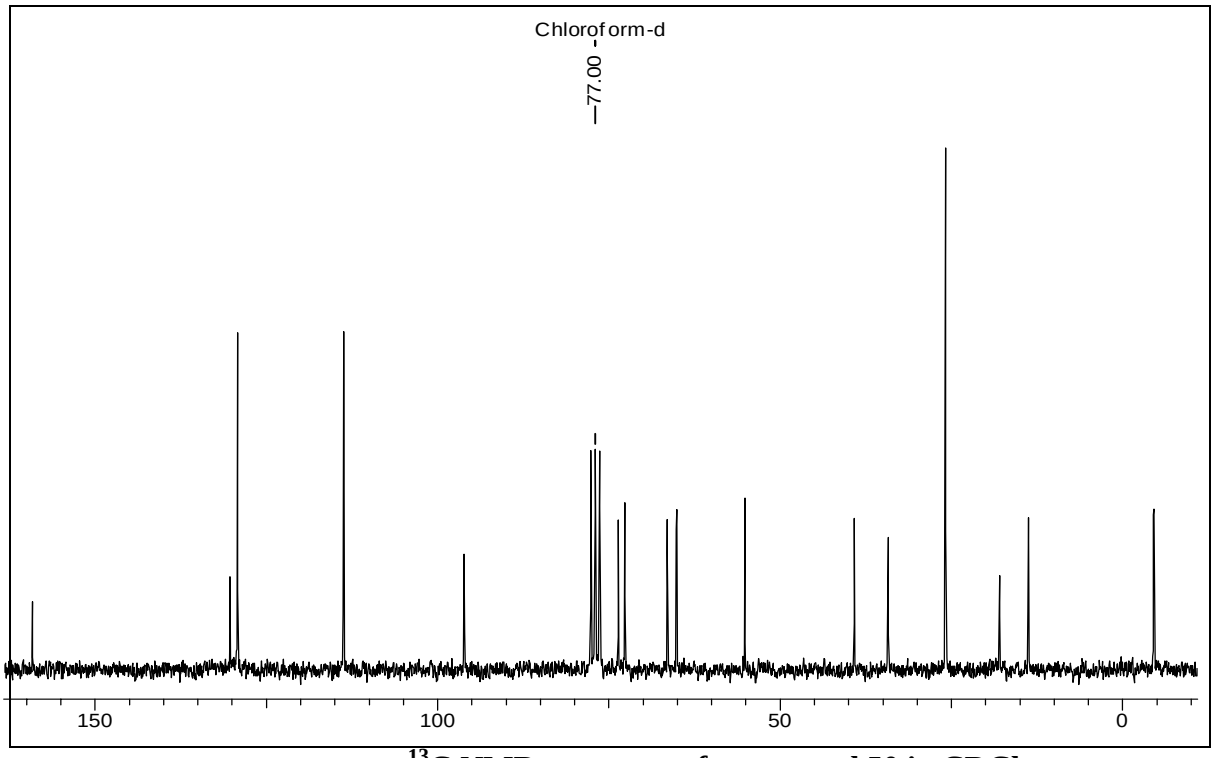
^{1}H NMR spectrum of compound 48 in $CDCl_3$



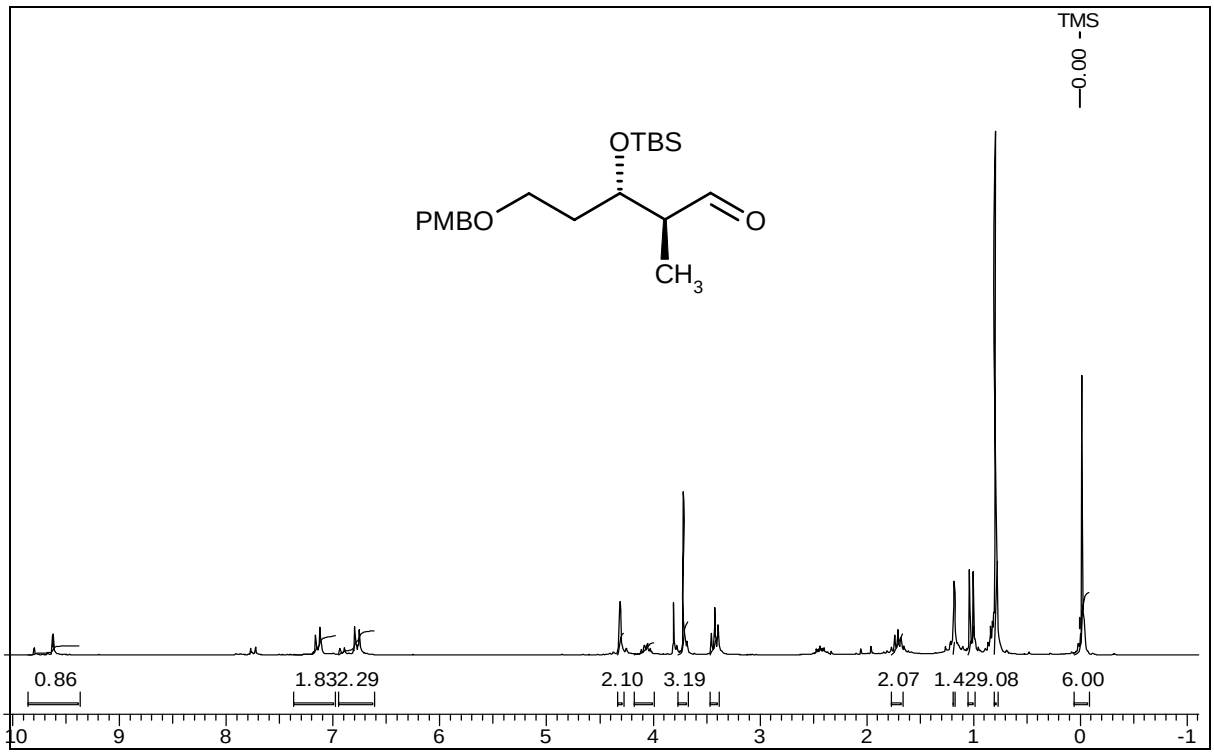
^{13}C NMR spectrum of compound 48 in $CDCl_3$



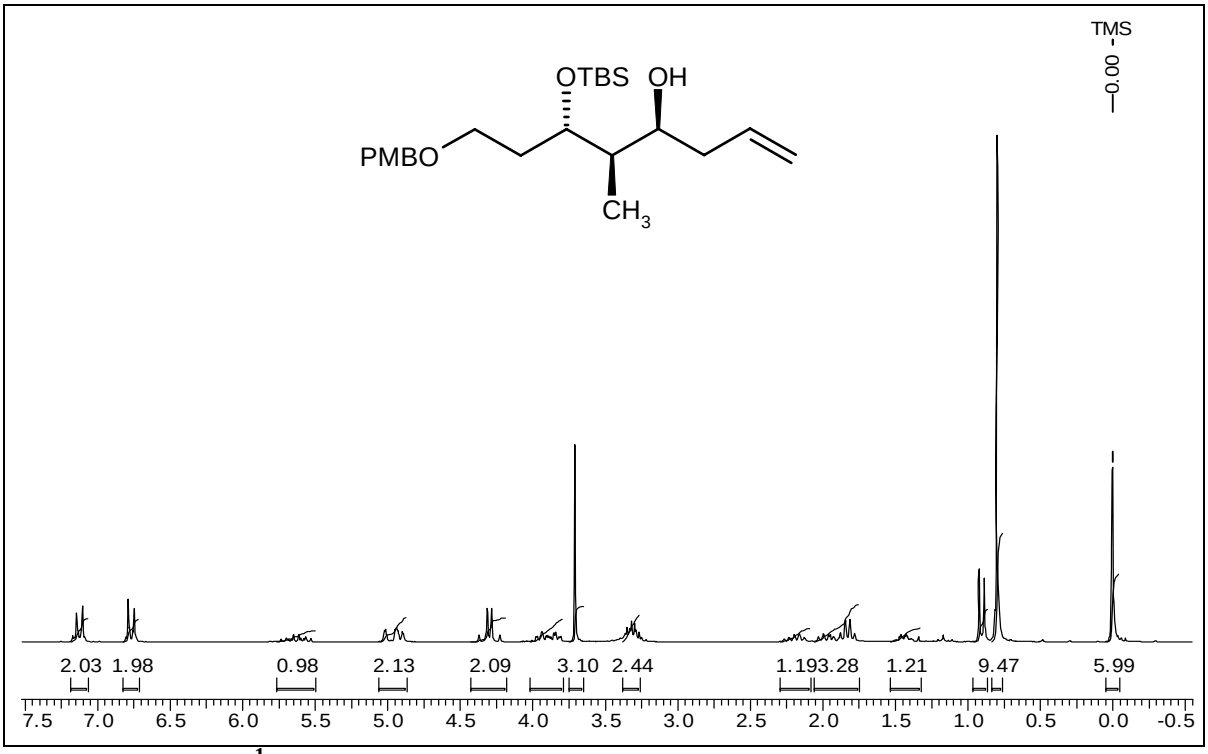
^{1}H NMR spectrum of compound 50 in $CDCl_3$



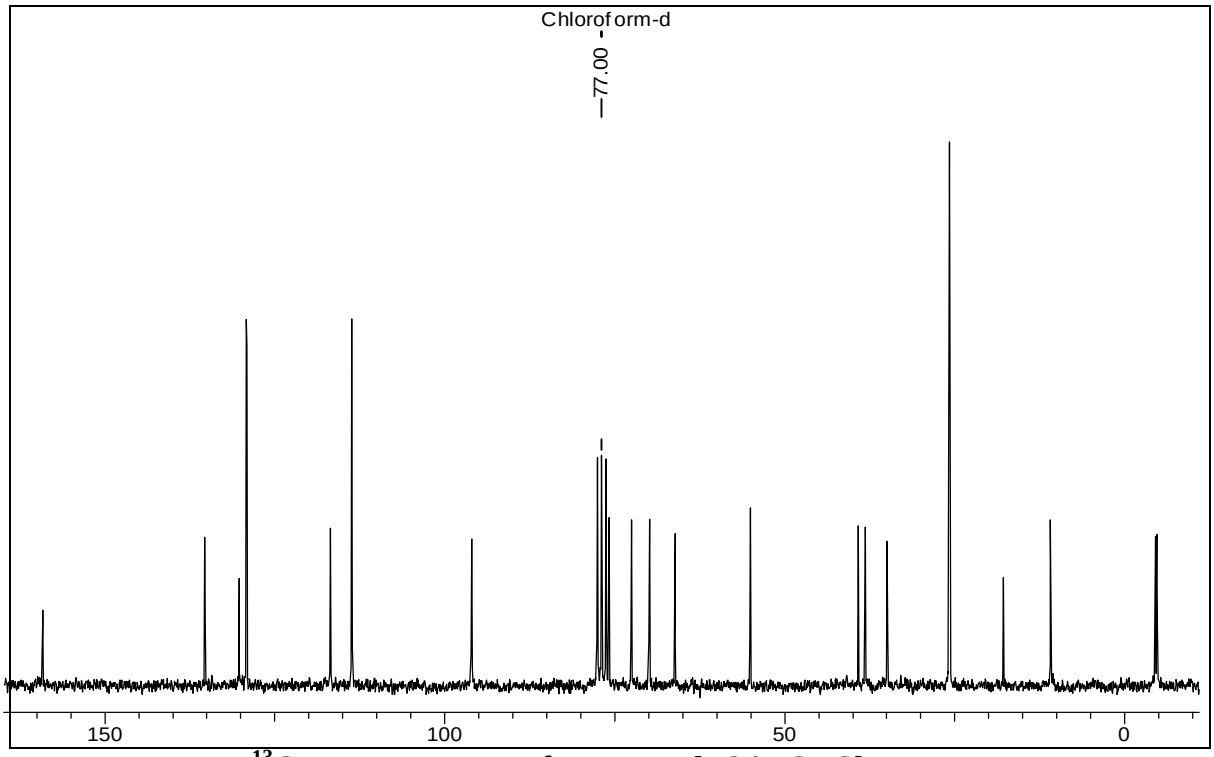
^{13}C NMR spectrum of compound 50 in $CDCl_3$



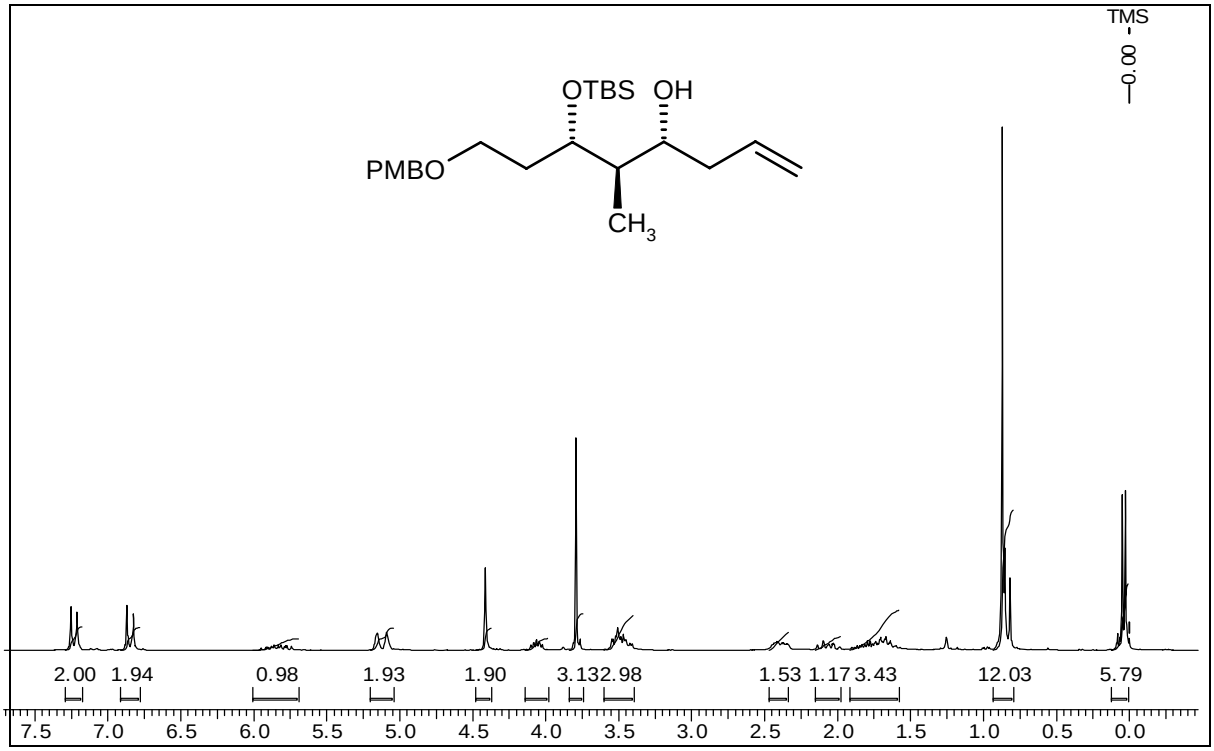
^{1}H NMR spectrum of compound 51 in $CDCl_3$



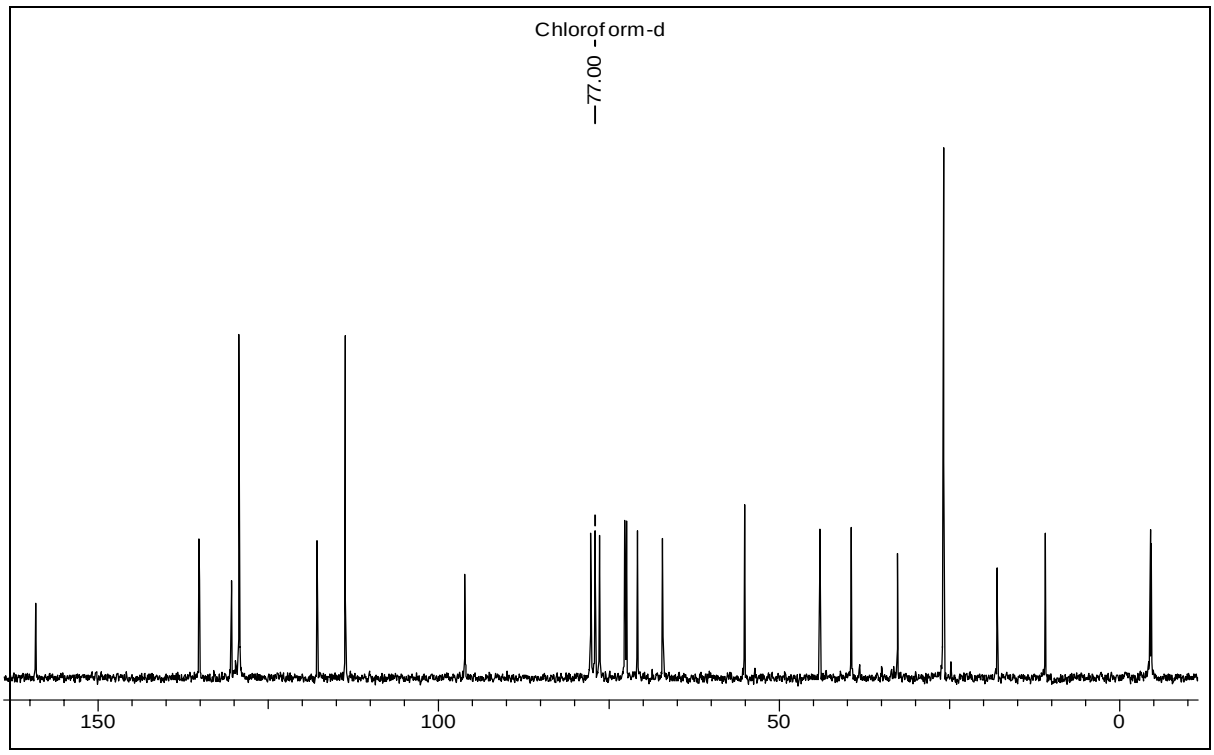
^{1}HNMR spectrum of compound 53 in $CDCl_3$



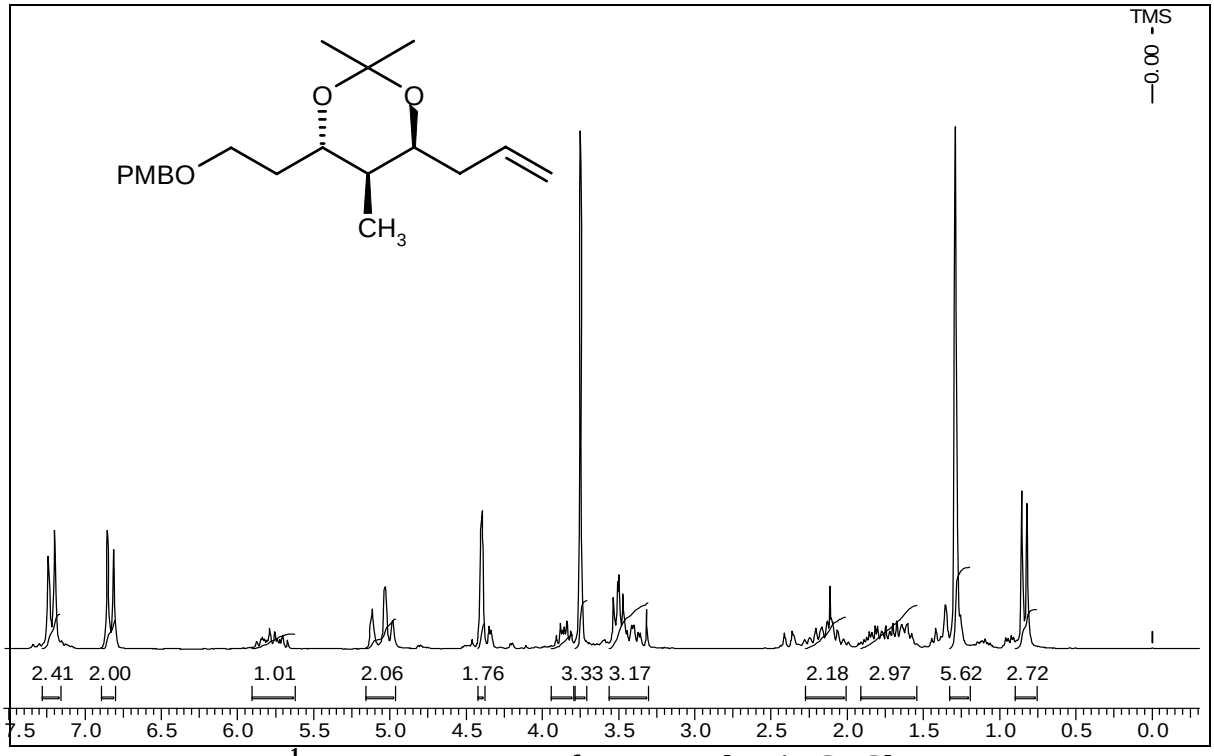
^{13}C NMR spectrum of compound 53 in $CDCl_3$



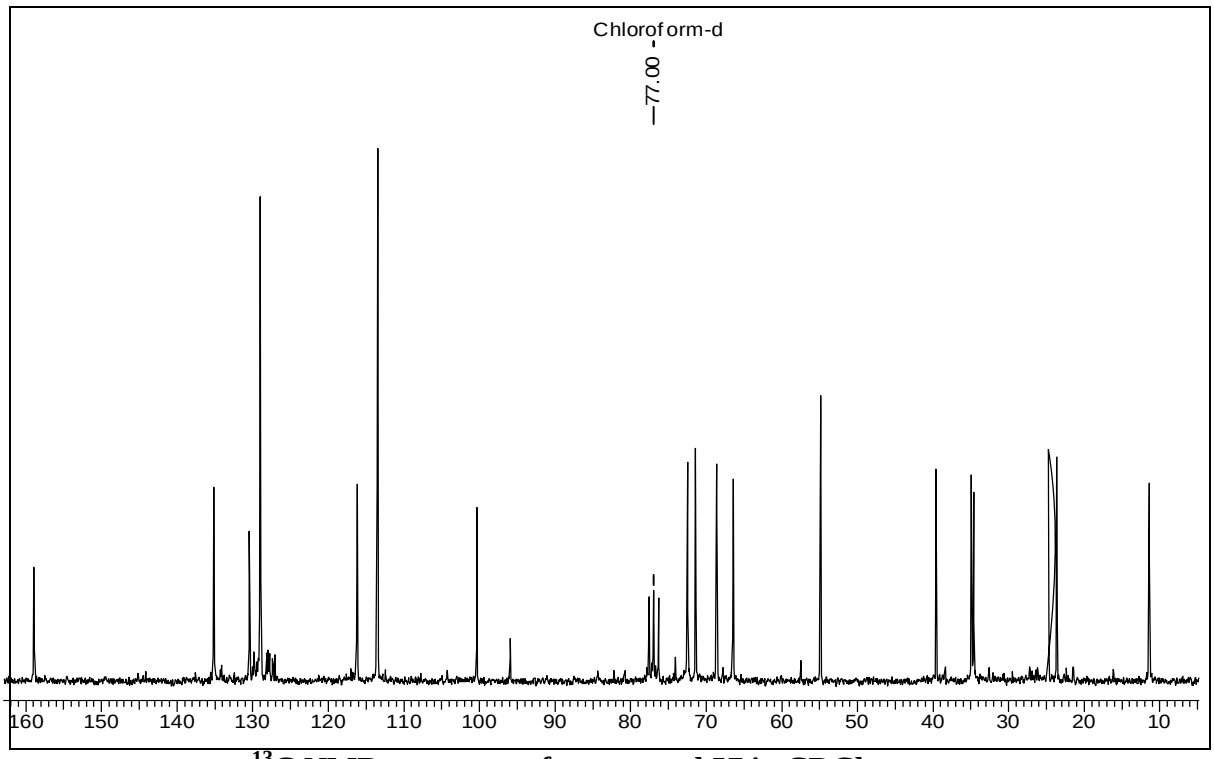
^{1}H NMR spectrum of compound 52 in $CDCl_3$



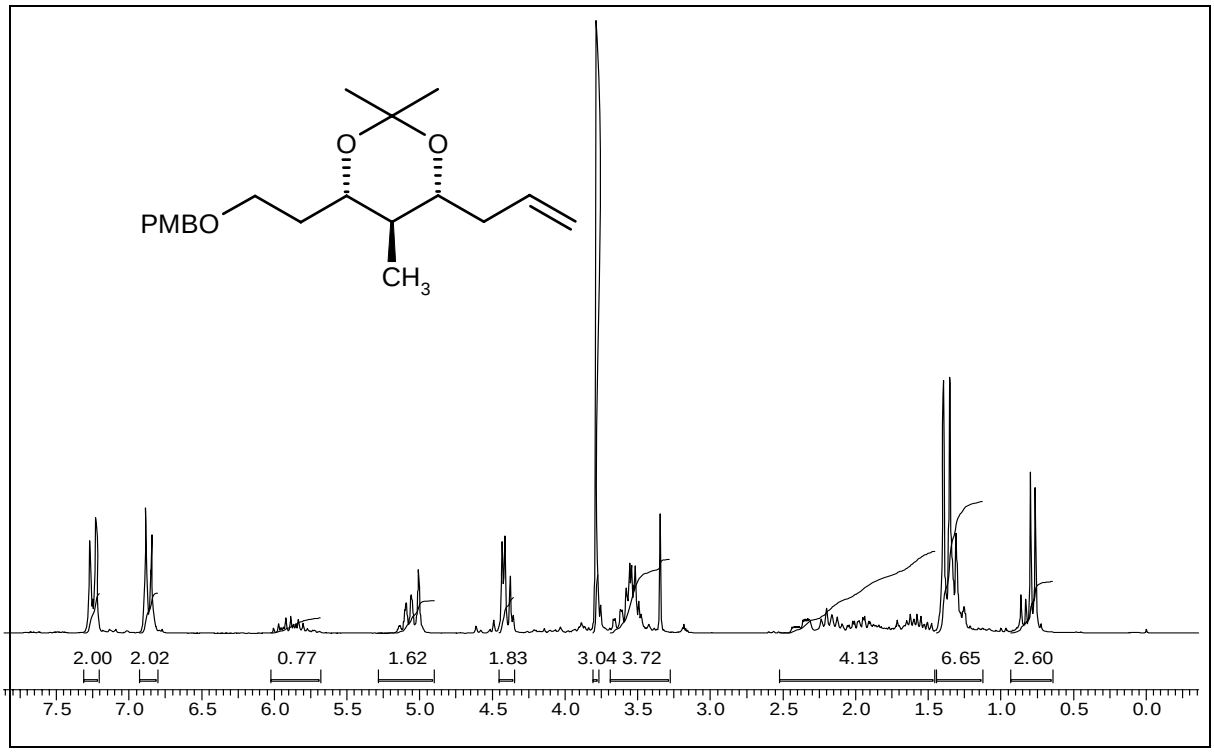
^{13}C NMR spectrum of compound 52 in $CDCl_3$



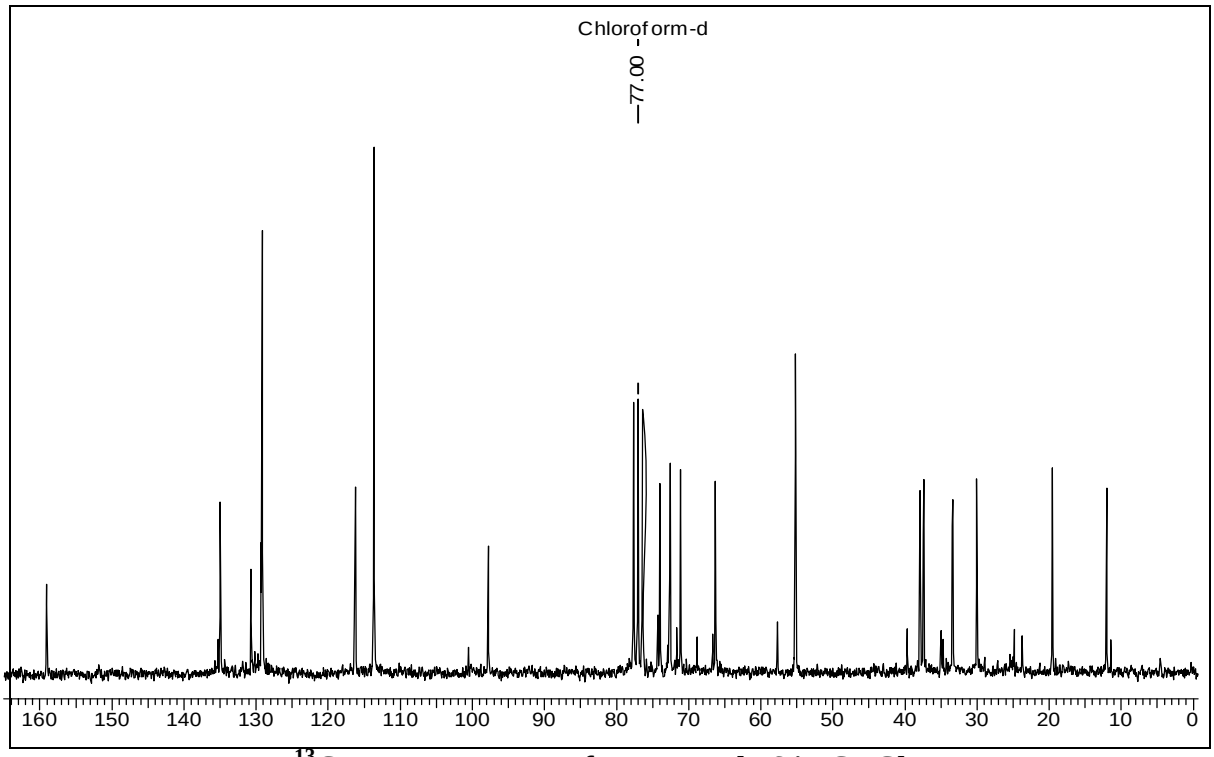
^{1}H NMR spectrum of compound 57 in $CDCl_3$



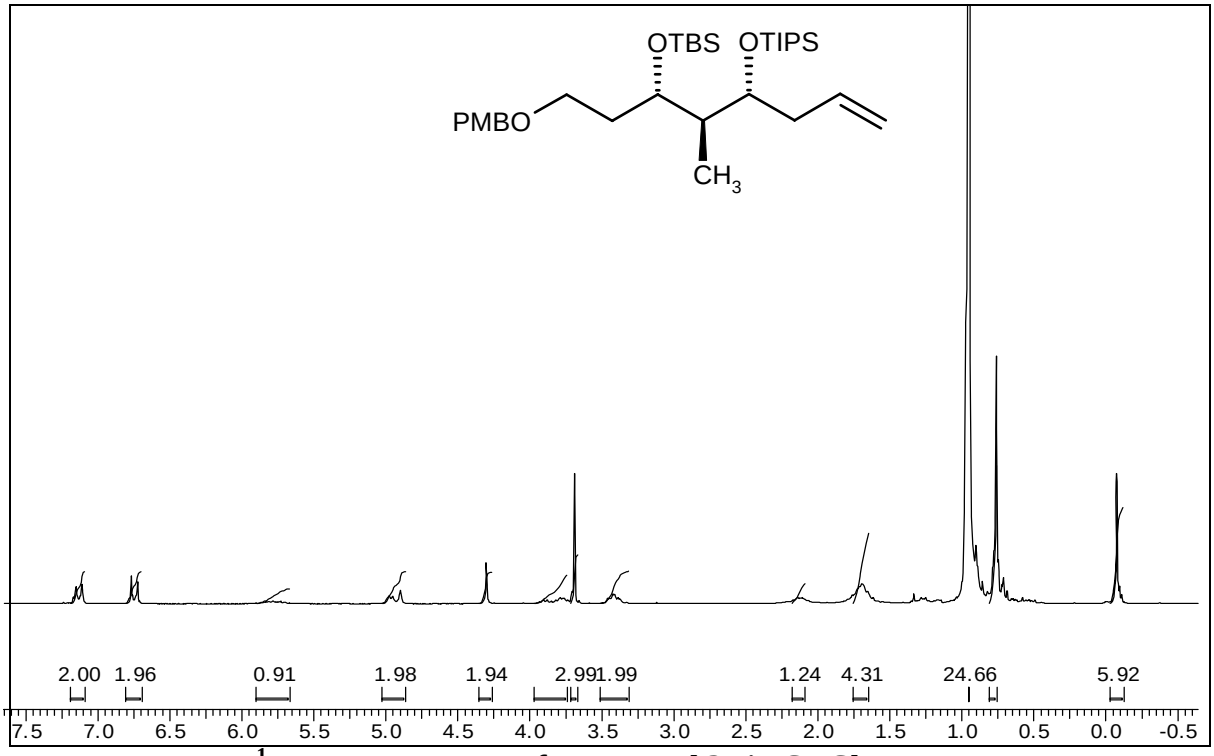
^{13}C NMR spectrum of compound 57 in $CDCl_3$



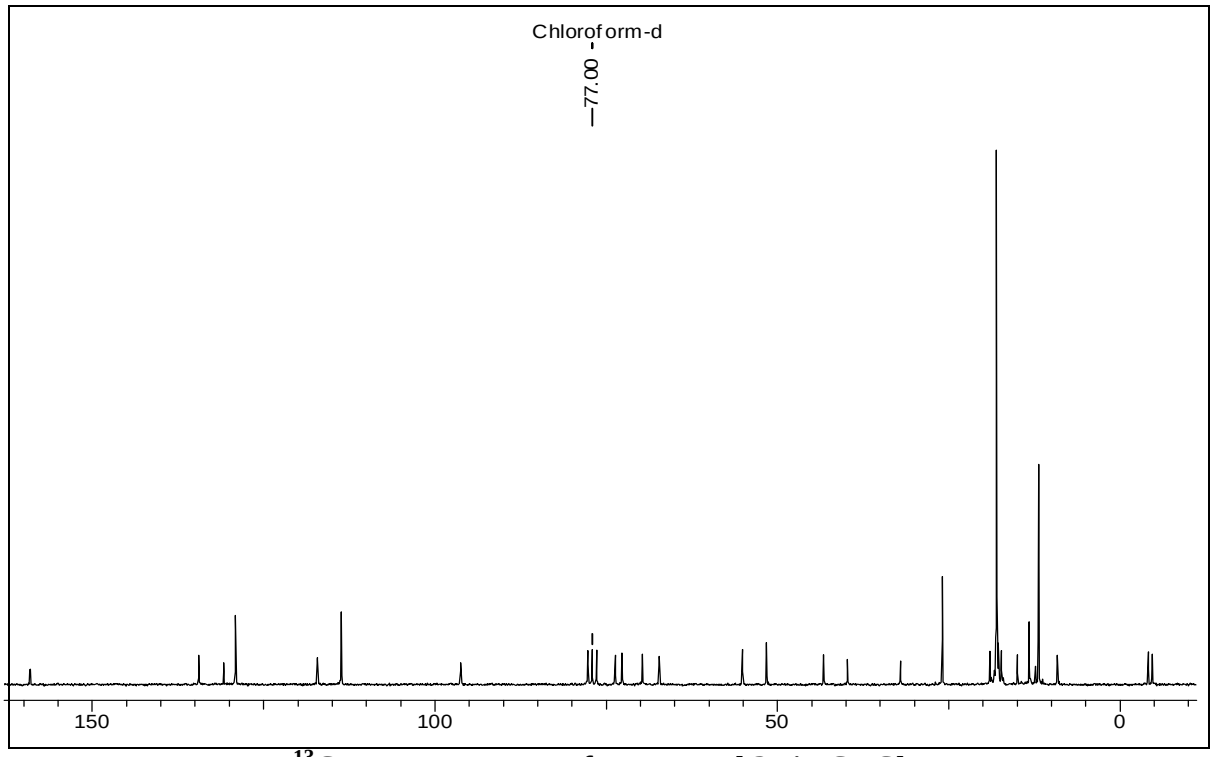
^{1}H NMR spectrum of compound 56 in $CDCl_3$



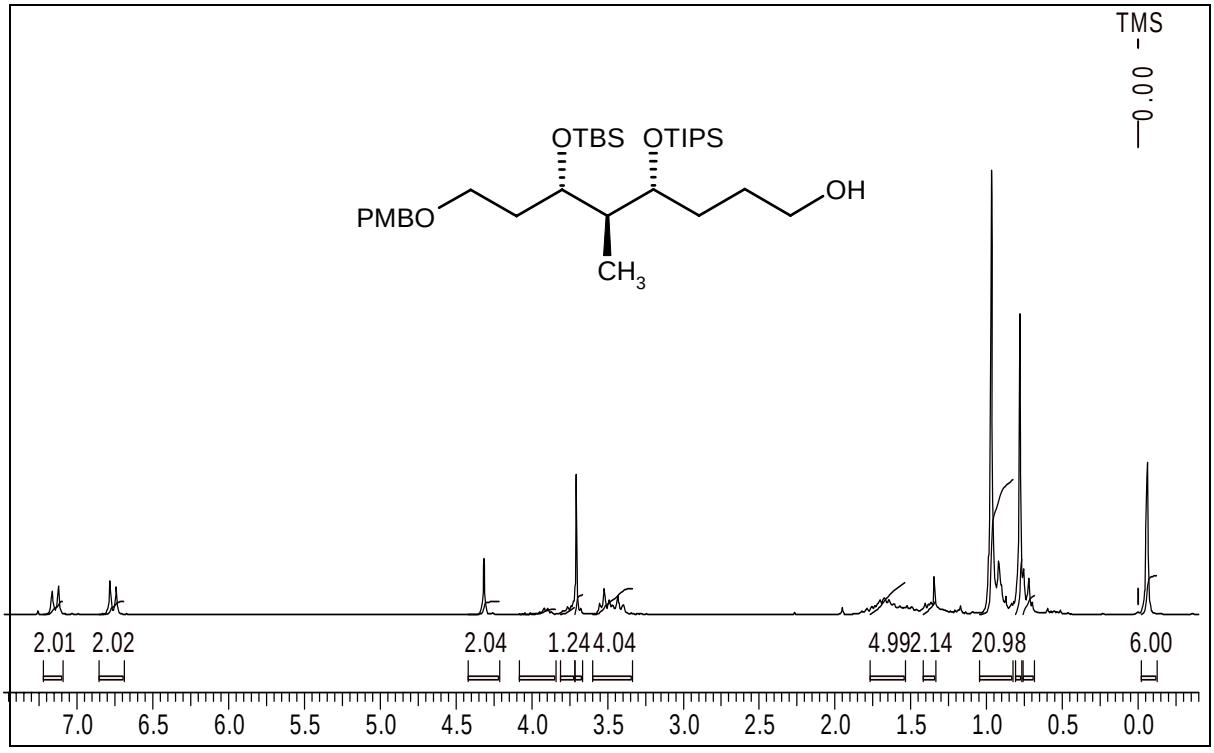
^{13}C NMR spectrum of compound 56 in $CDCl_3$



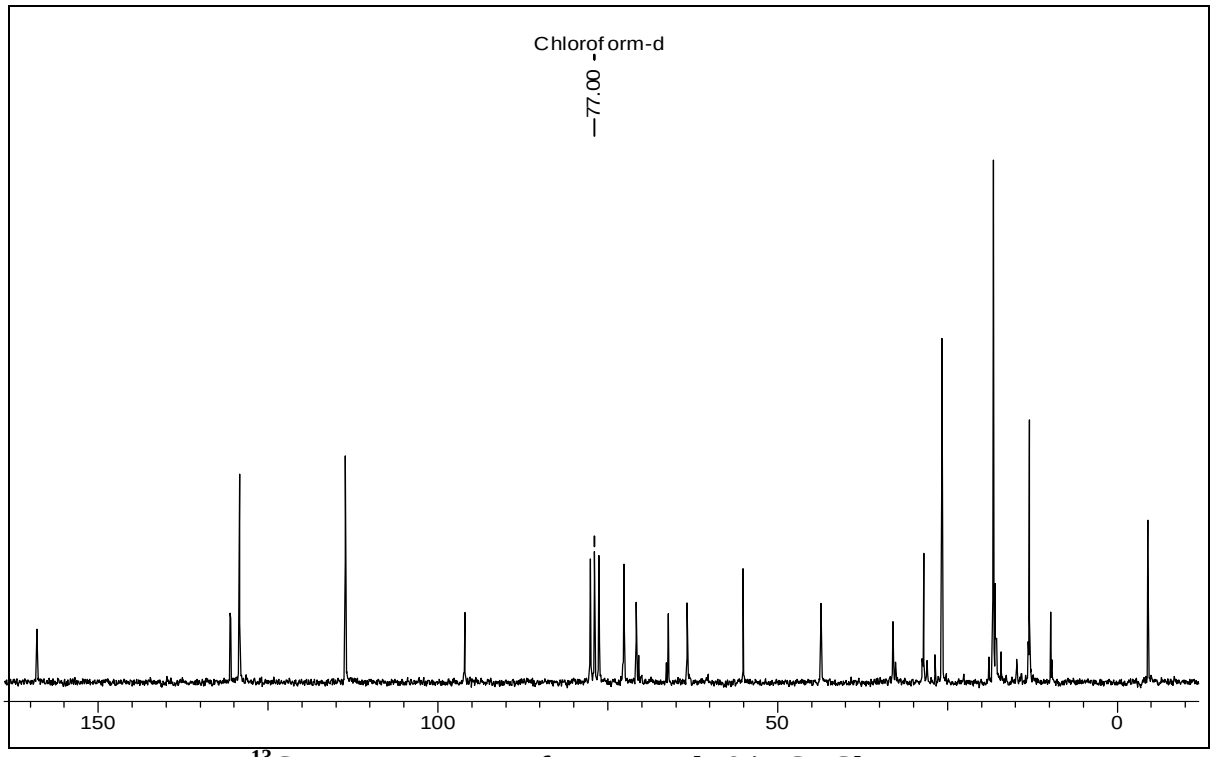
^{1}H NMR spectrum of compound 35 in $CDCl_3$



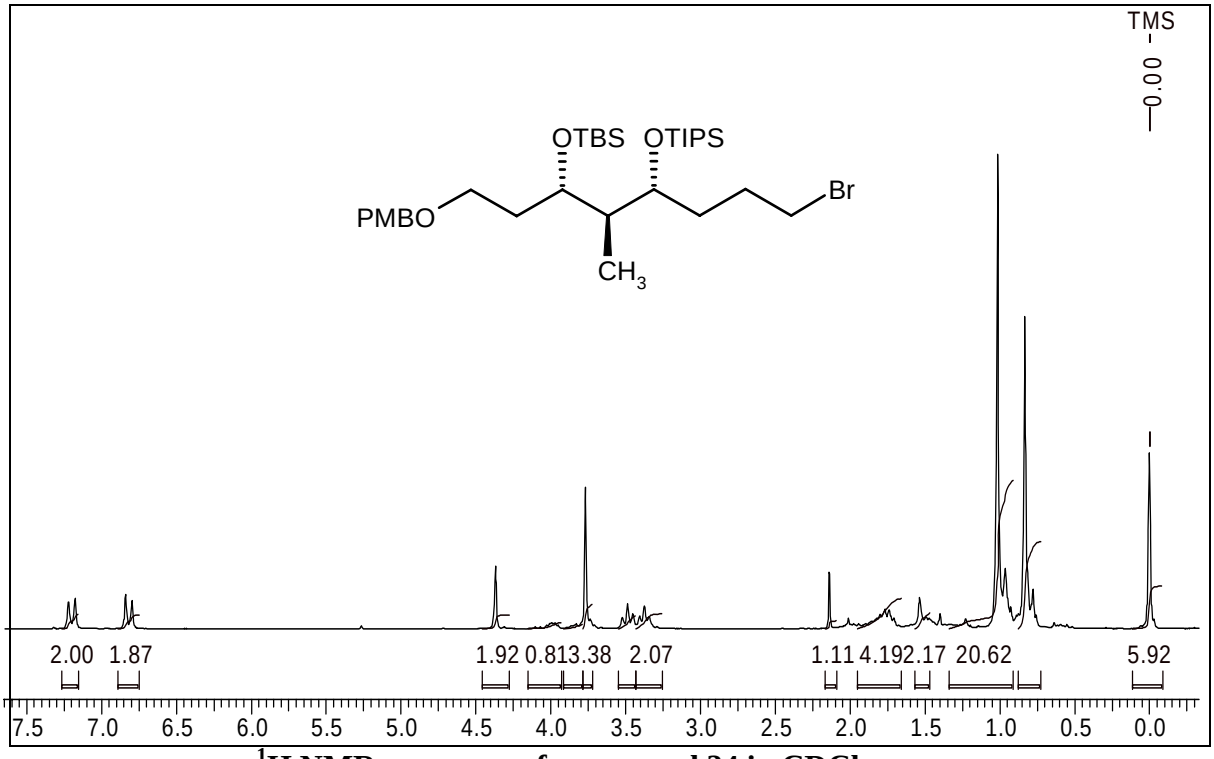
^{13}C NMR spectrum of compound 35 in $CDCl_3$



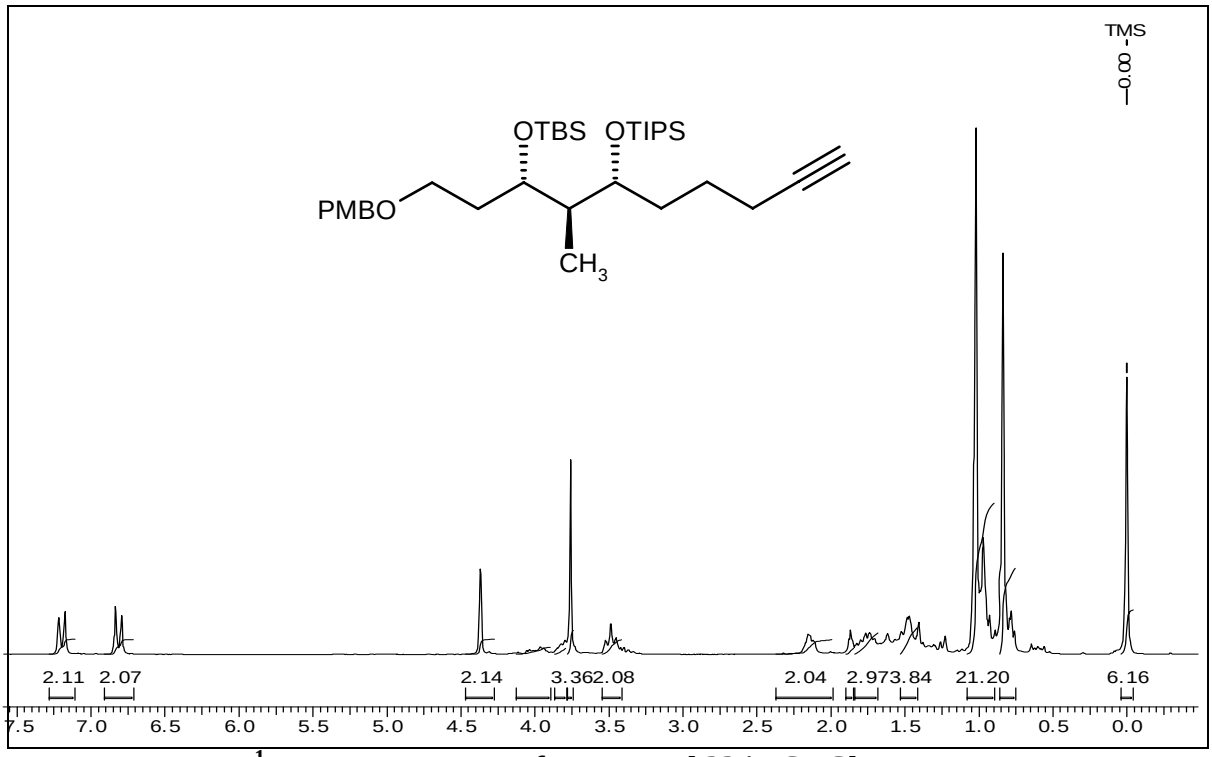
^{1}H NMR spectrum of compound 59 in $CDCl_3$



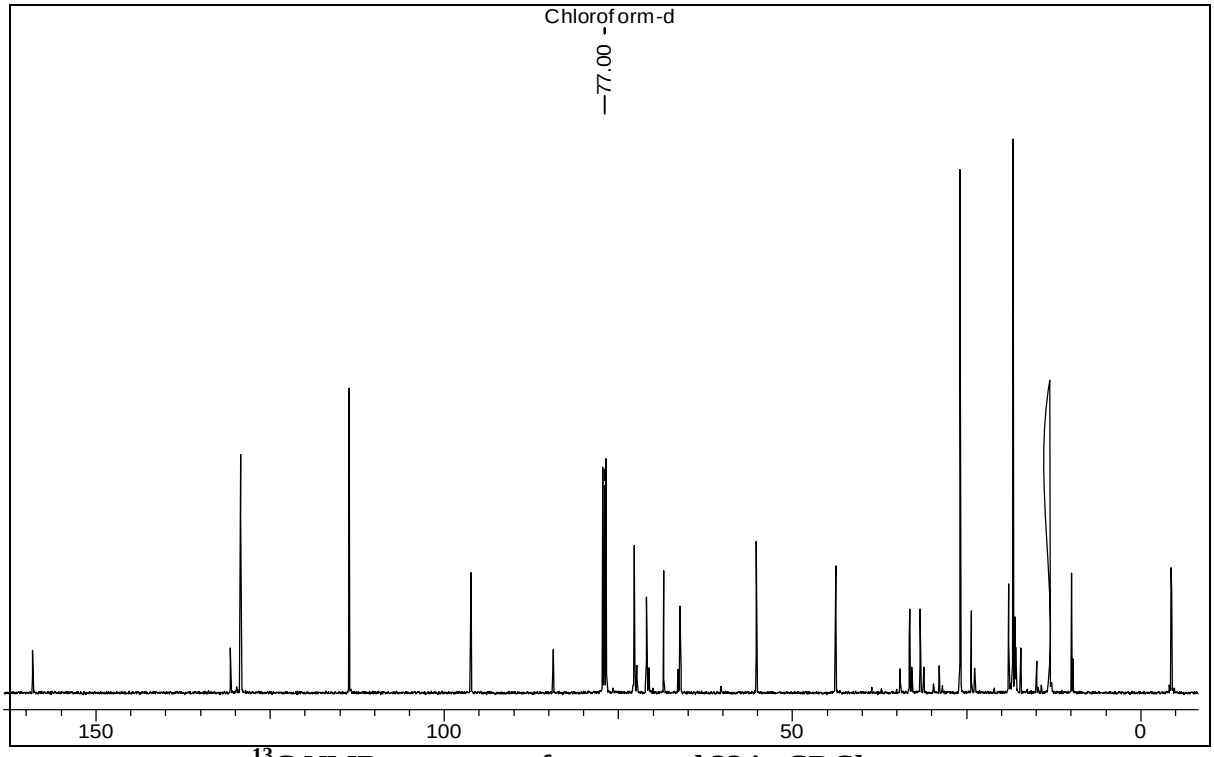
^{13}C NMR spectrum of compound 59 in $CDCl_3$



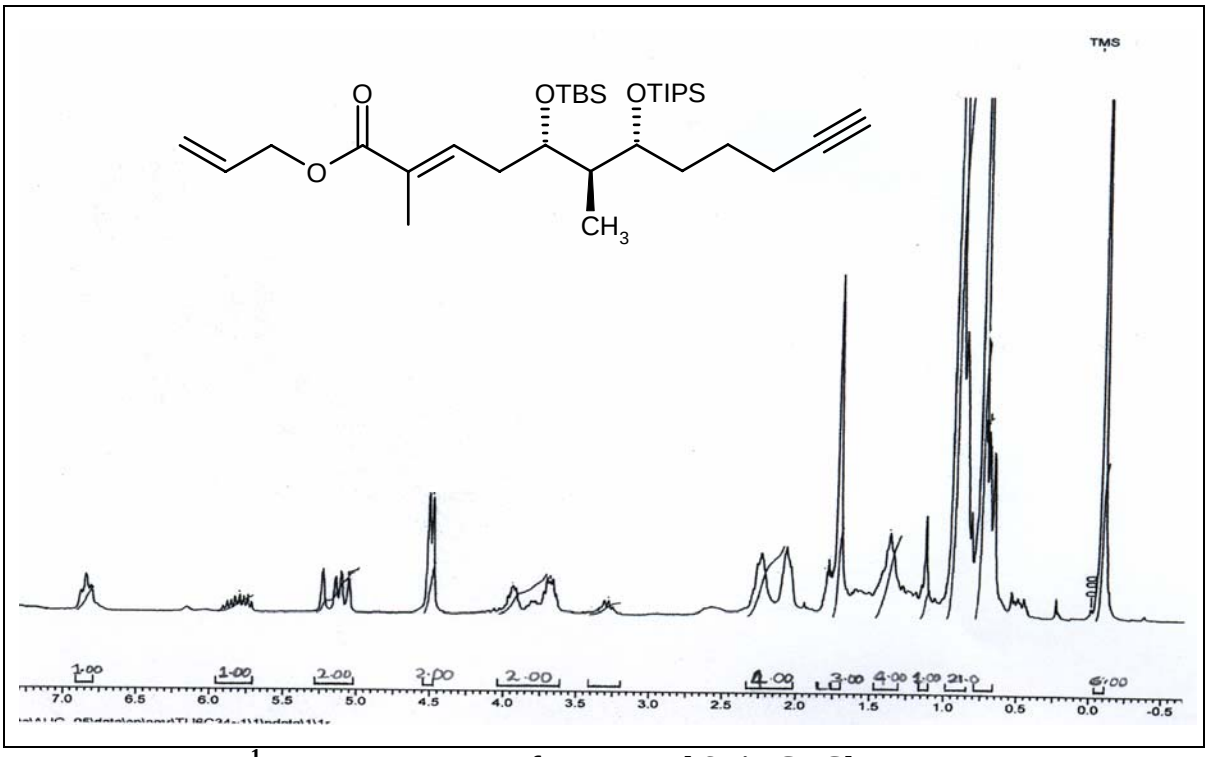
^{1}H NMR spectrum of compound 34 in $CDCl_3$



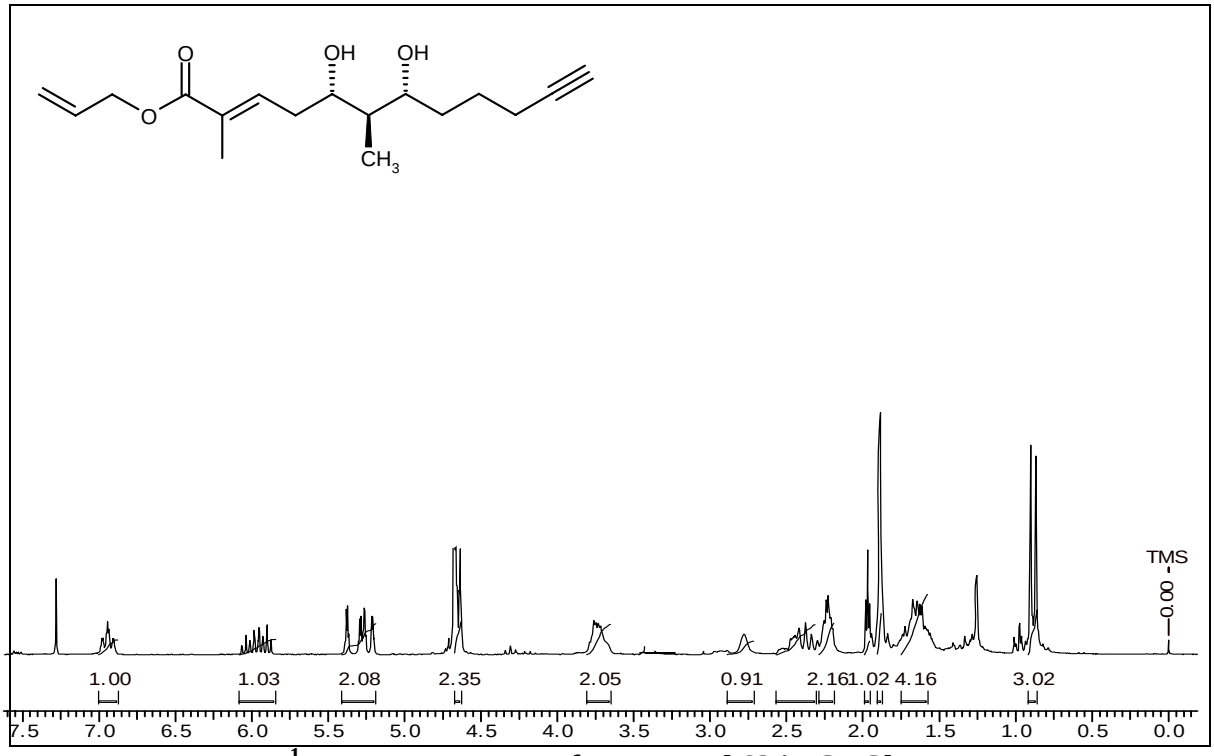
^{1}H NMR spectrum of compound 33 in $CDCl_3$



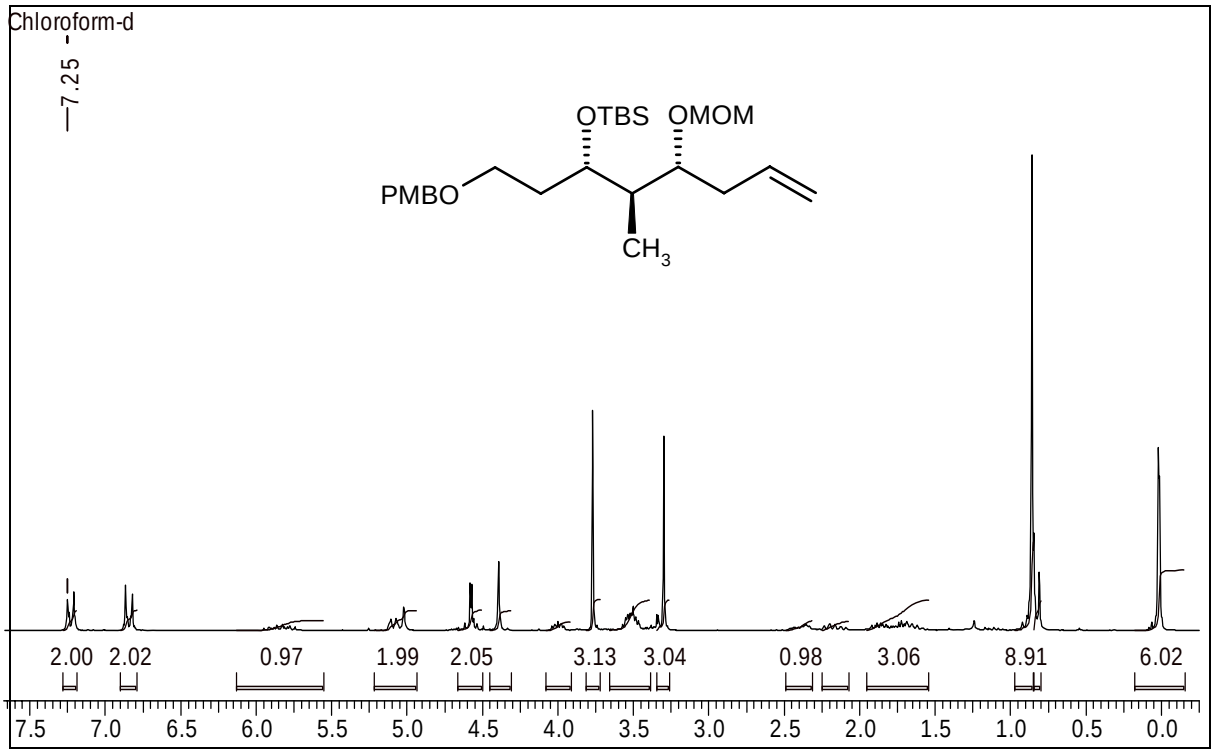
^{13}C NMR spectrum of compound 33 in $CDCl_3$



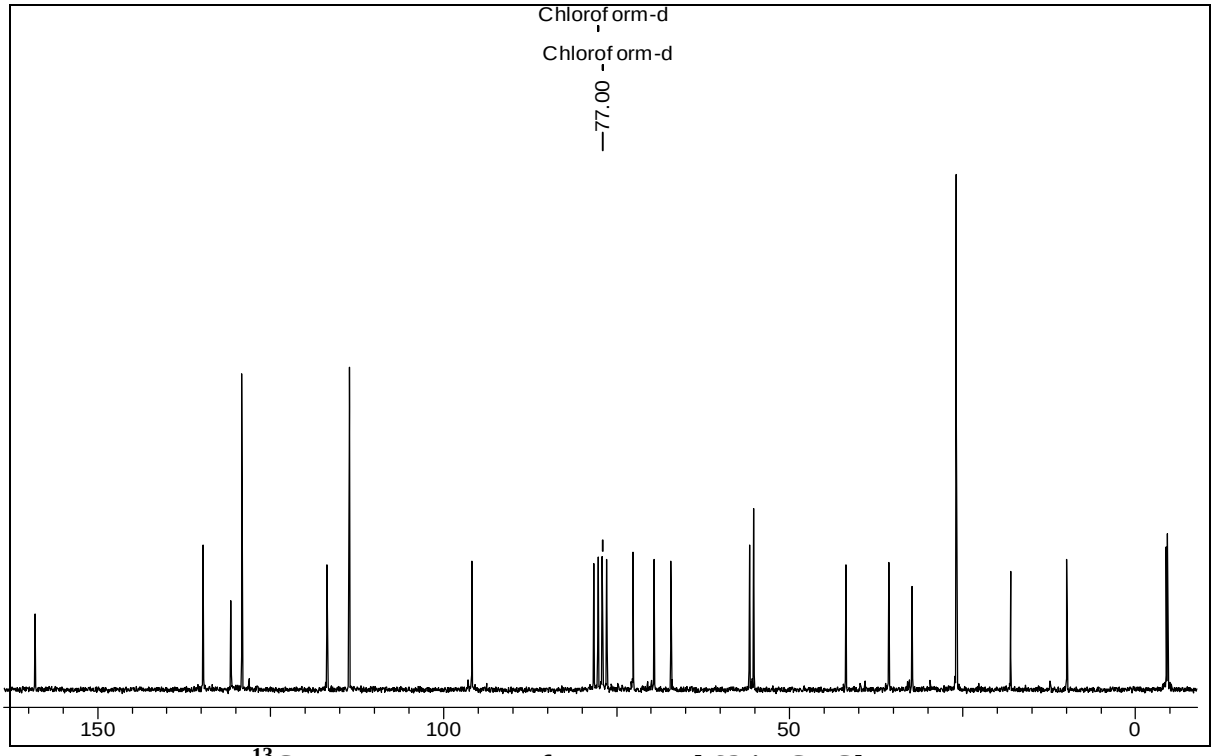
^{1}H NMR spectrum of compound 61 in $CDCl_3$



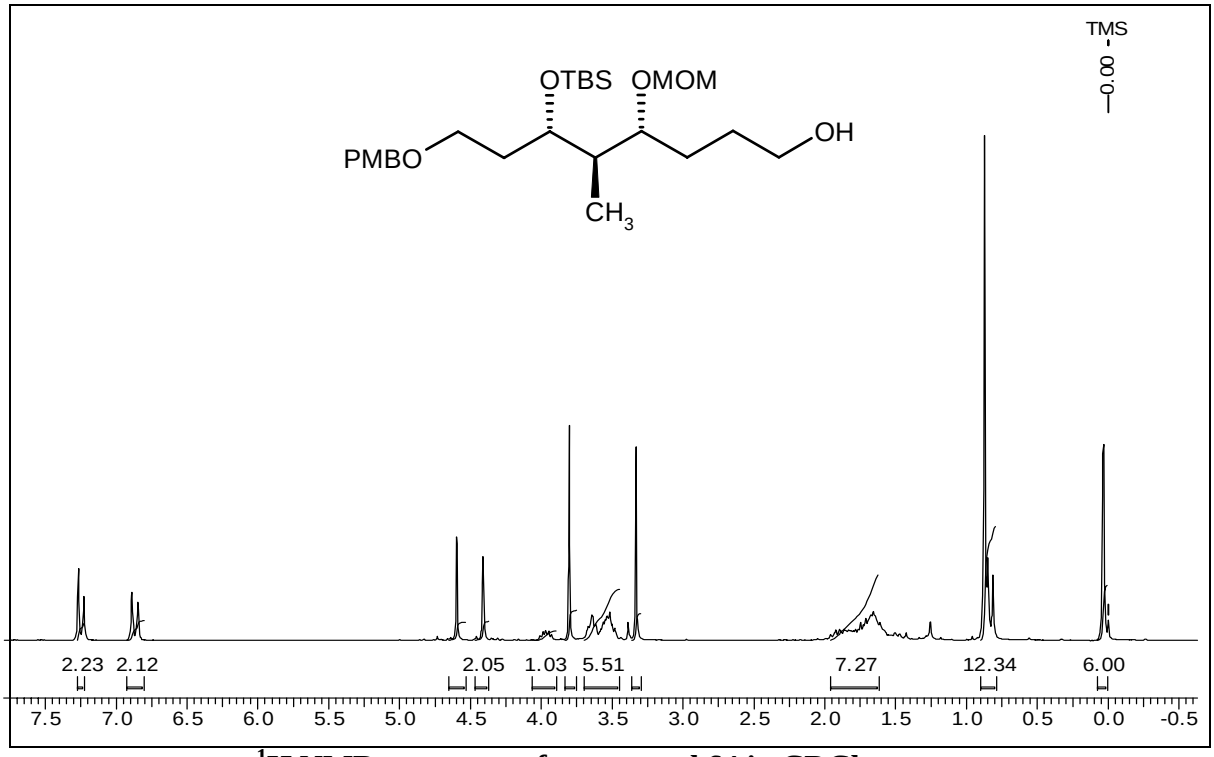
^{1}H NMR spectrum of compound 62 in $CDCl_3$



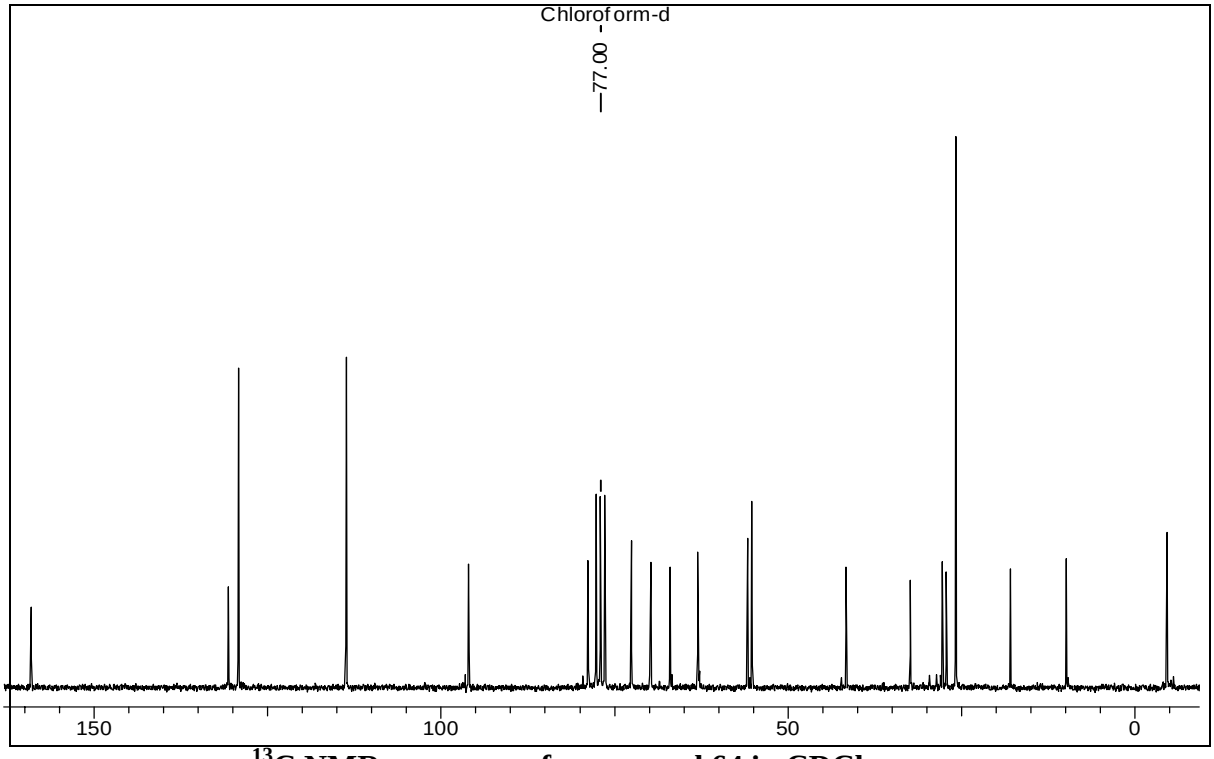
^{1}H NMR spectrum of compound 63 in $CDCl_3$



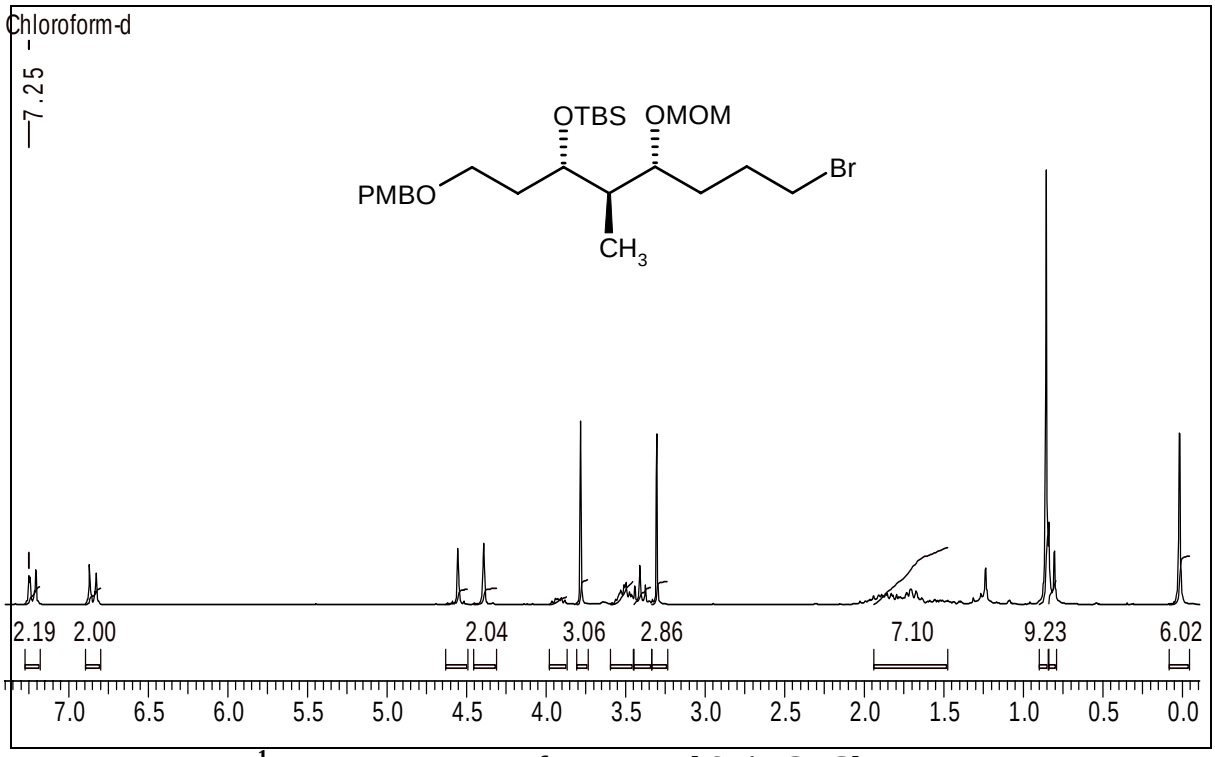
^{13}C NMR spectrum of compound 63 in $CDCl_3$



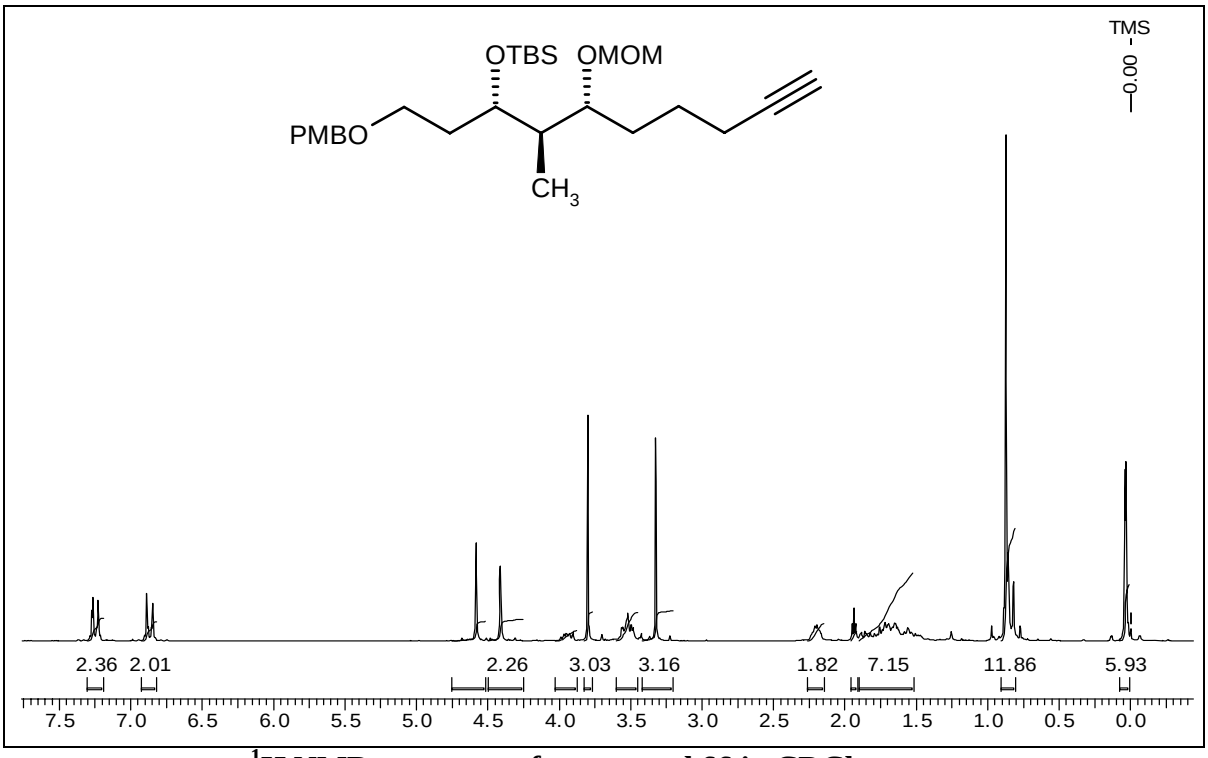
^{1}H NMR spectrum of compound 64 in $CDCl_3$



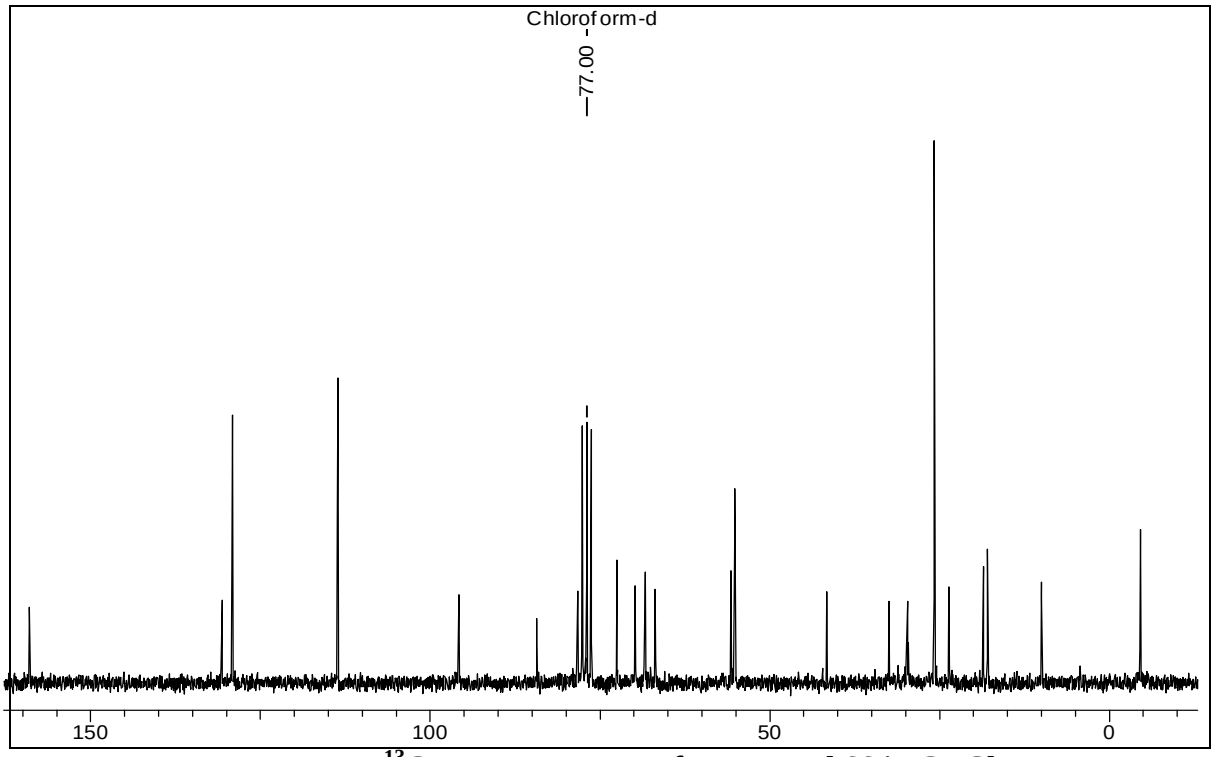
^{13}C NMR spectrum of compound 64 in $CDCl_3$



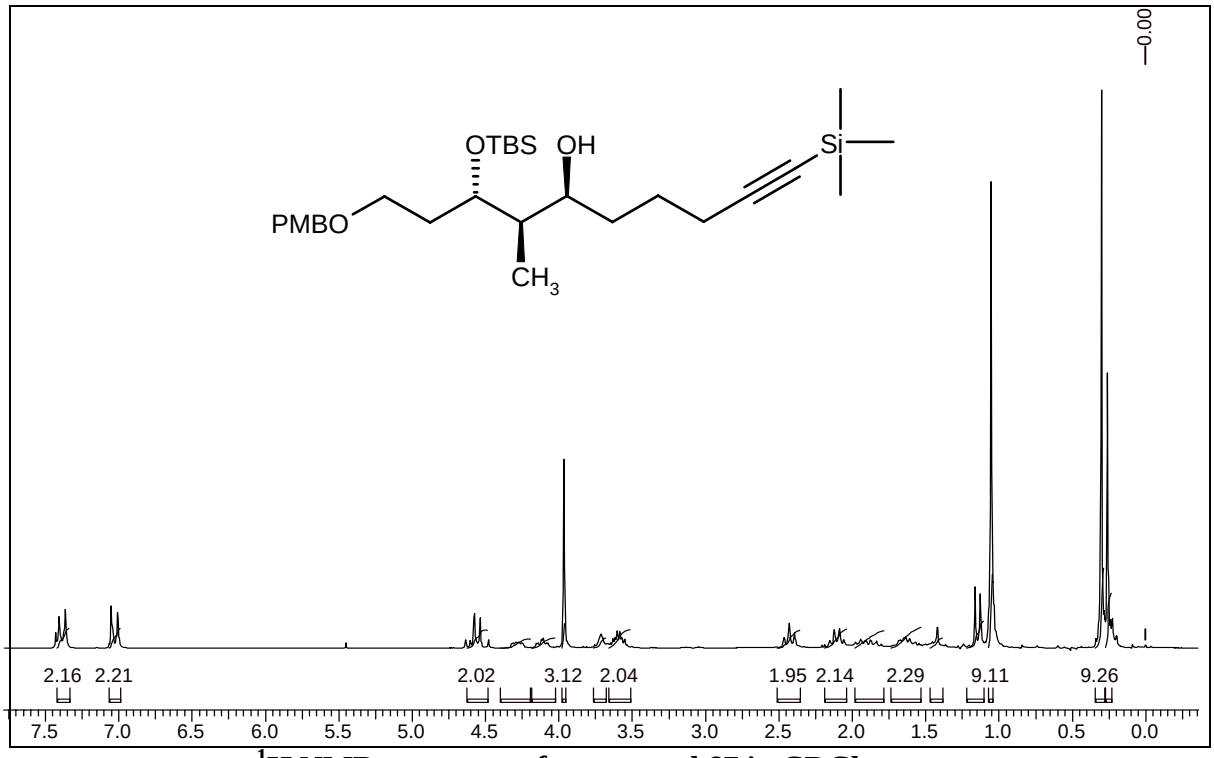
^{1}H NMR spectrum of compound 65 in $CDCl_3$



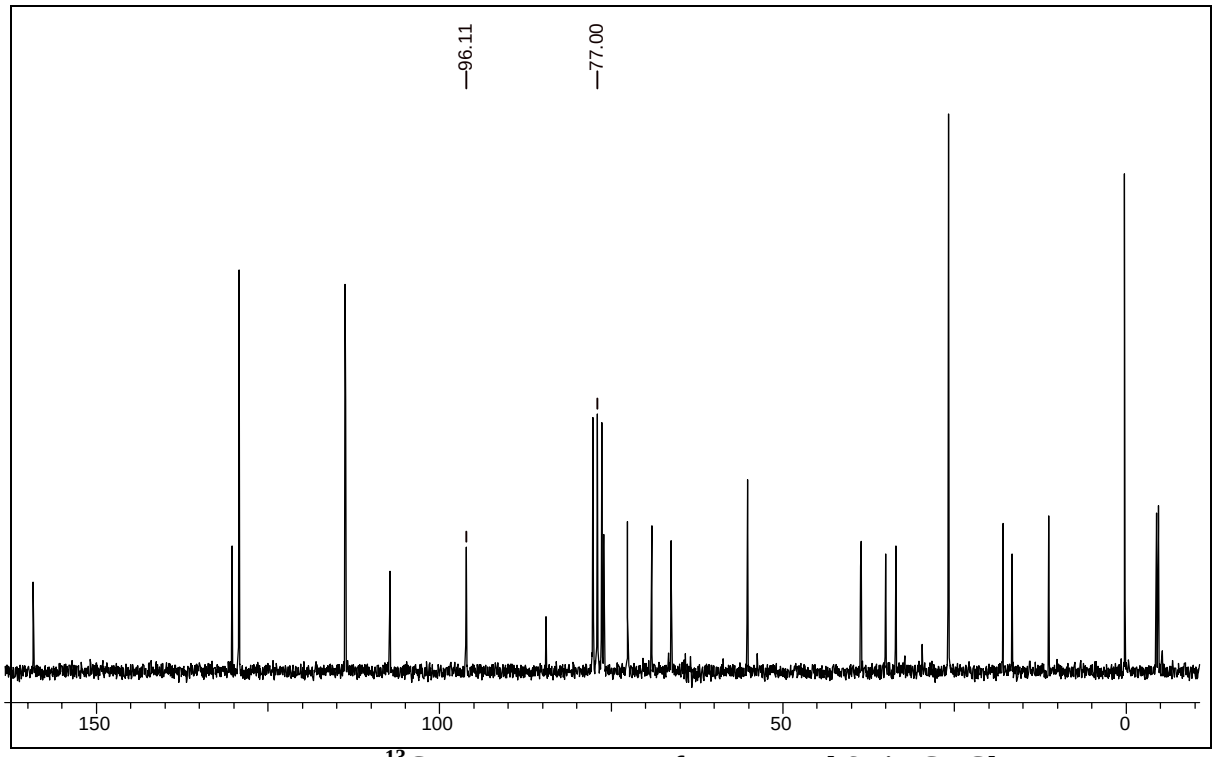
^{1}H NMR spectrum of compound 66 in $CDCl_3$



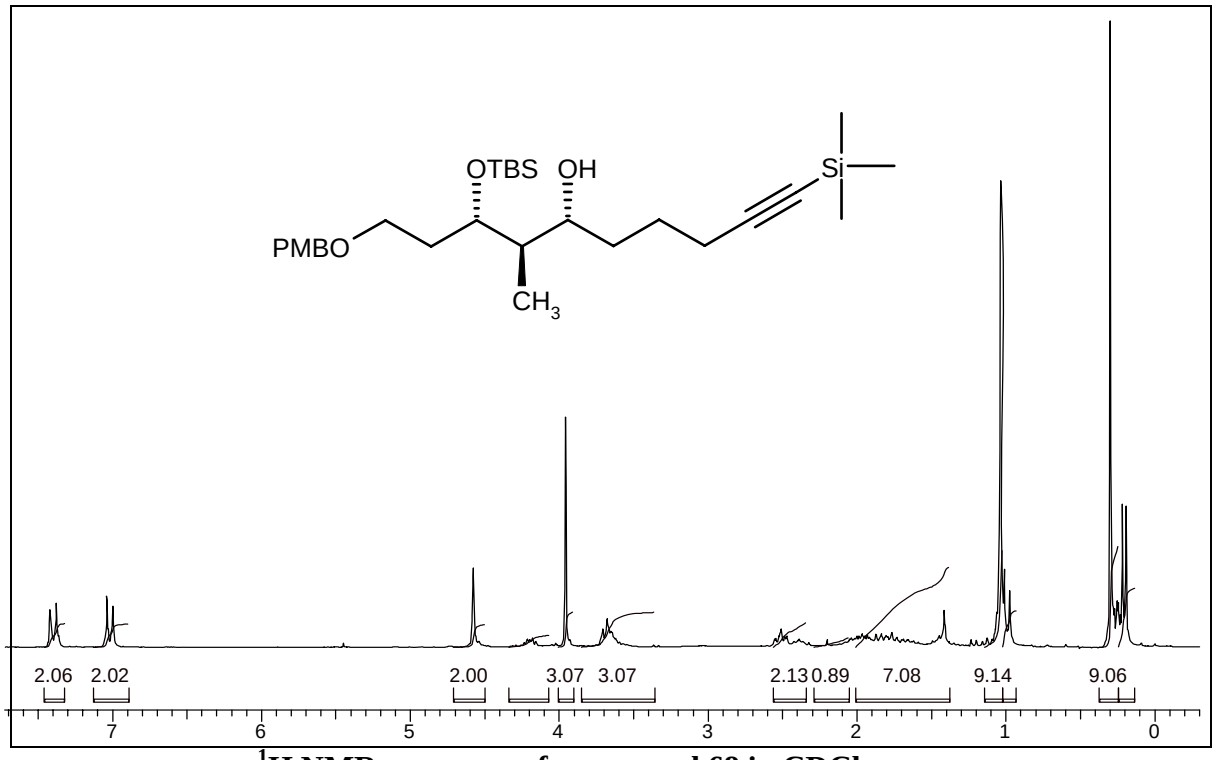
^{13}C NMR spectrum of compound 66 in $CDCl_3$



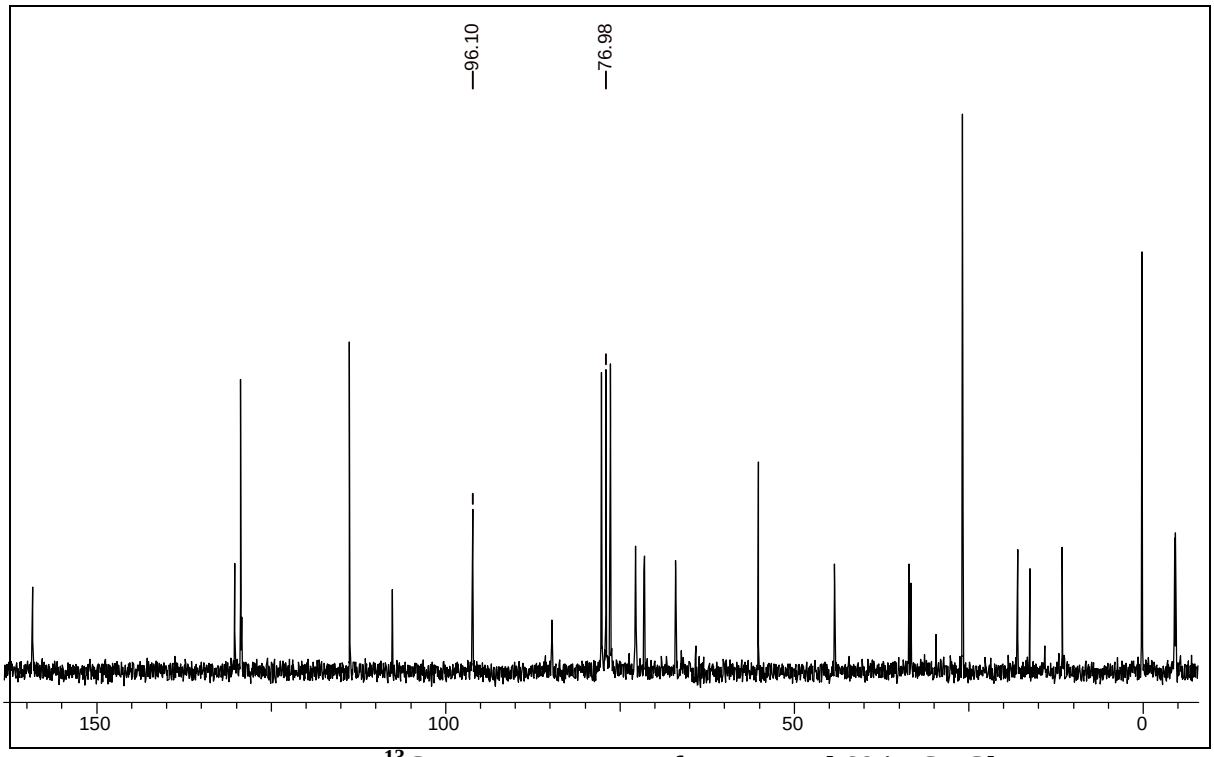
^{1}H NMR spectrum of compound 67 in $CDCl_3$



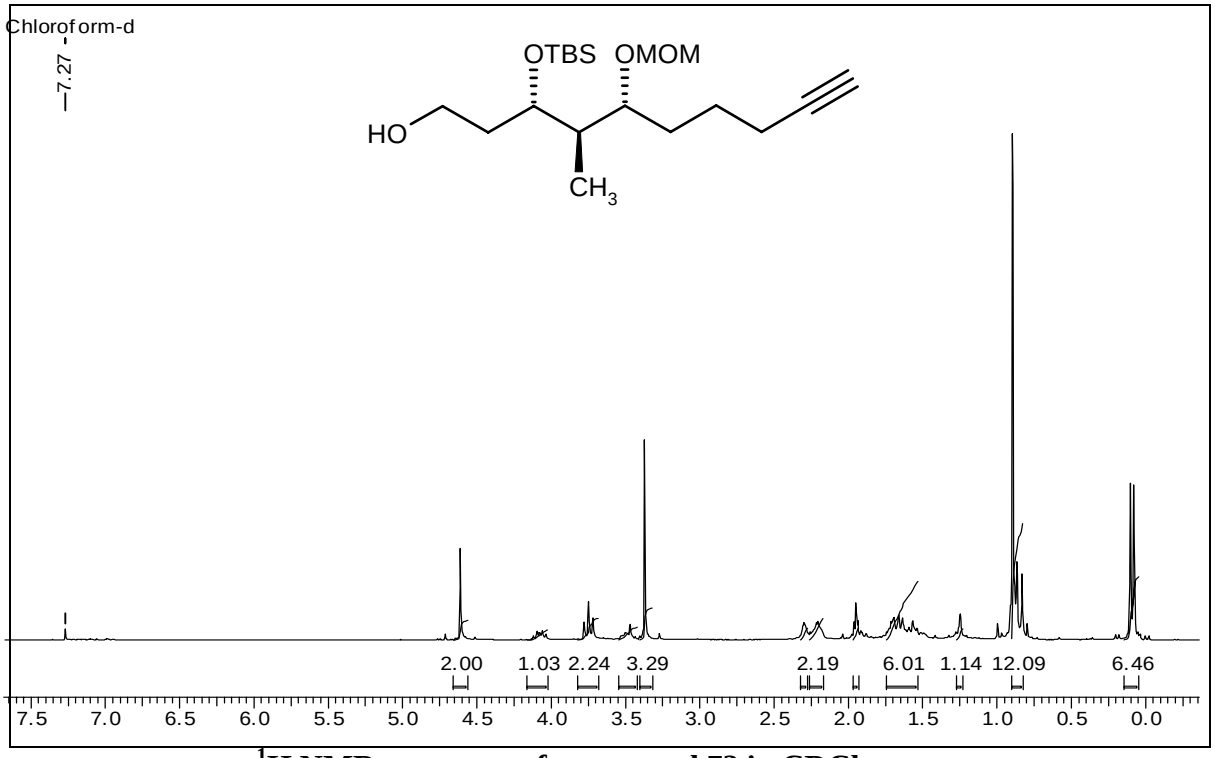
^{13}C NMR spectrum of compound 67 in $CDCl_3$



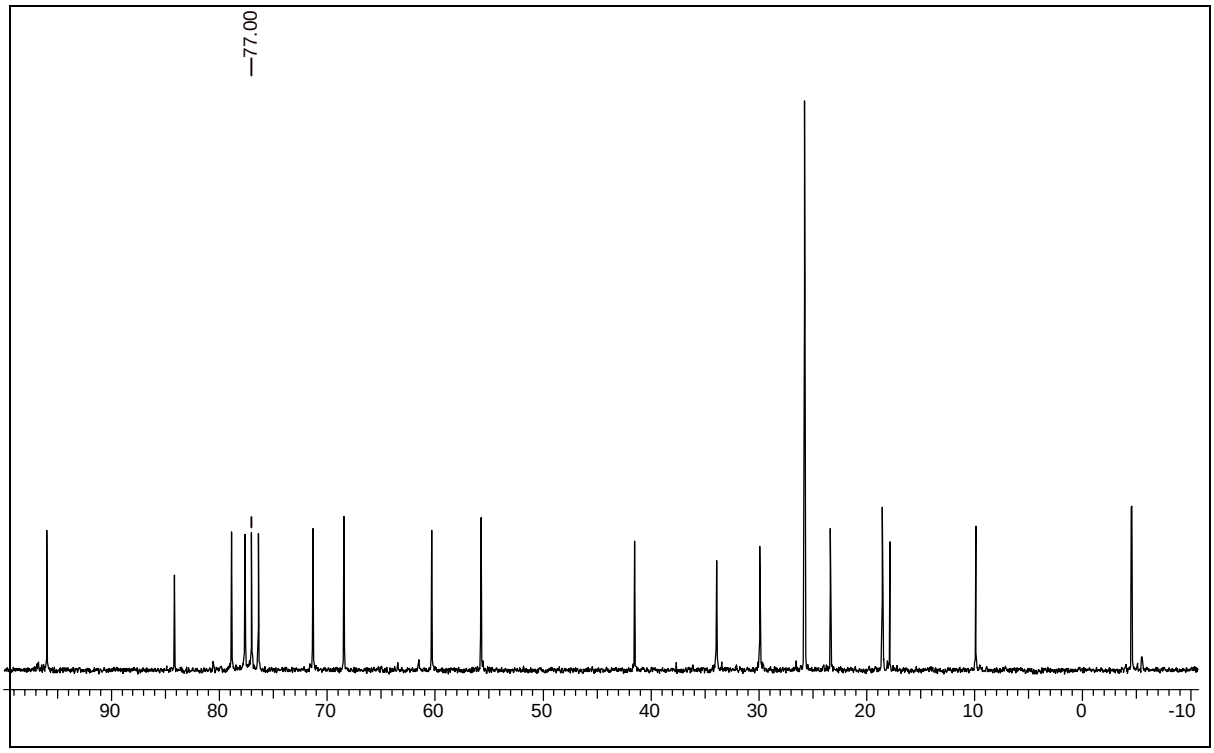
^{1}H NMR spectrum of compound 68 in $CDCl_3$



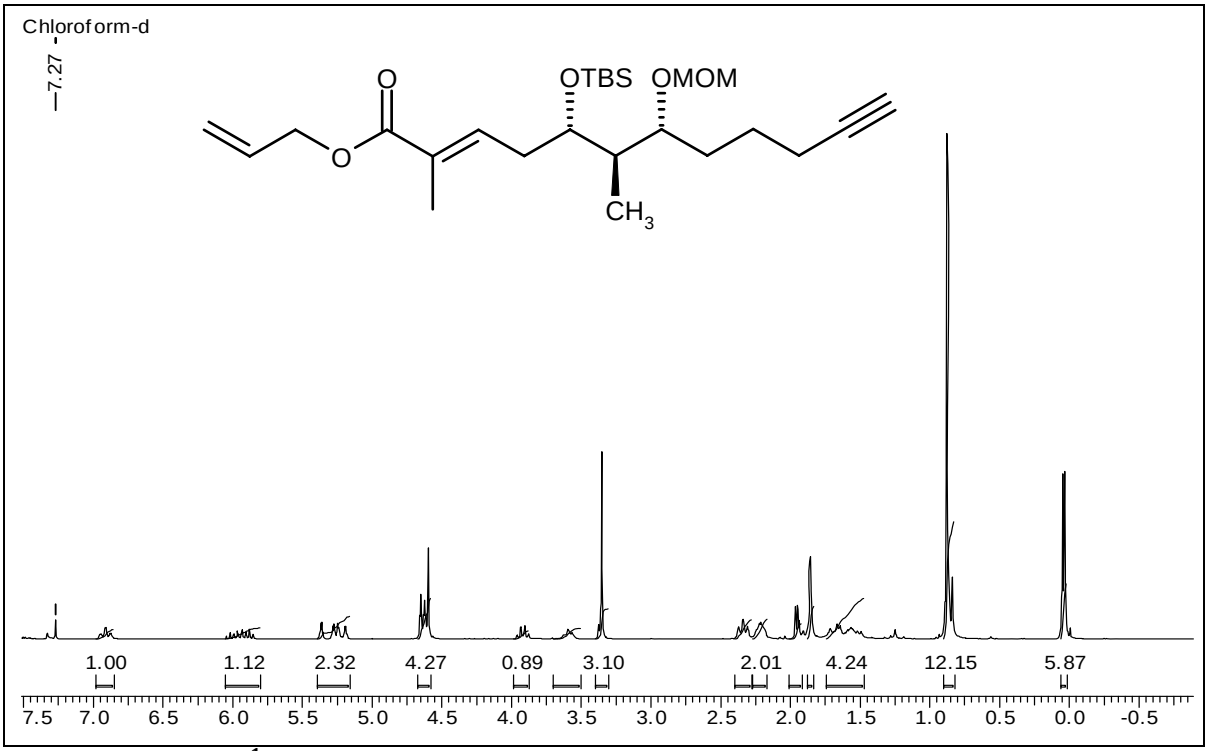
^{13}C NMR spectrum of compound 68 in $CDCl_3$



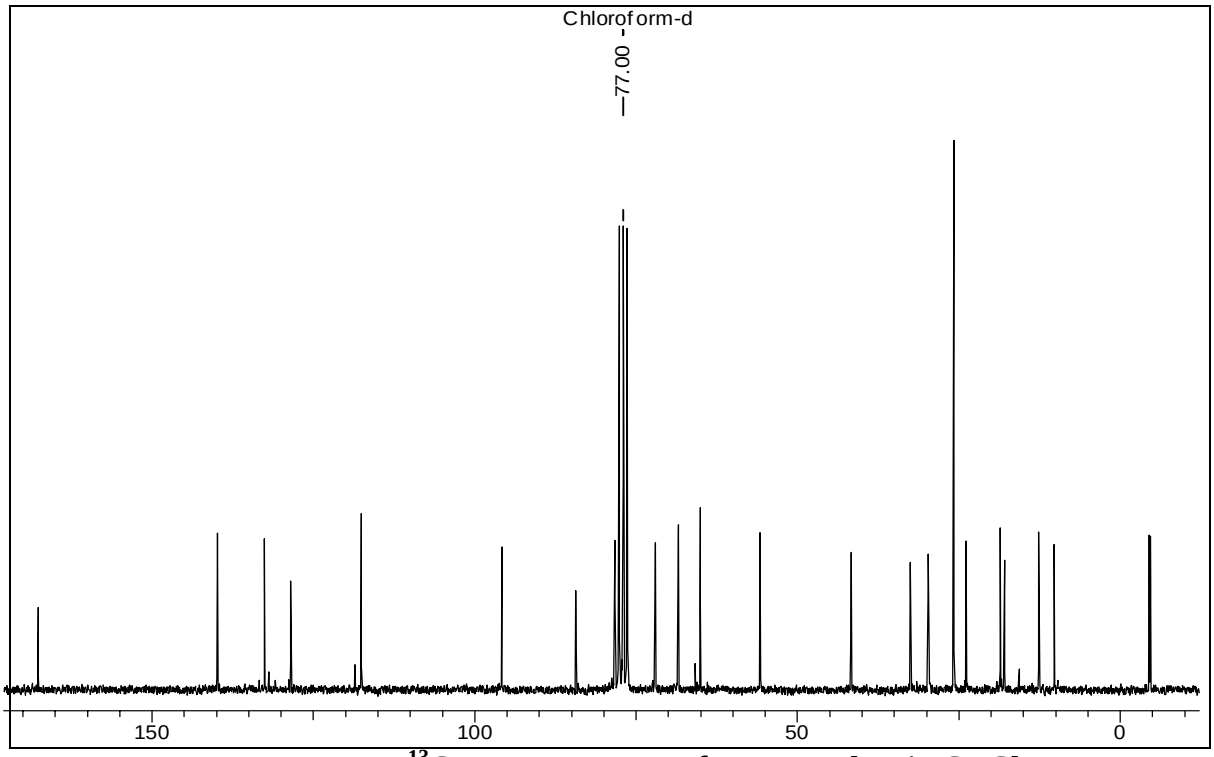
^{1}H NMR spectrum of compound 72 in $CDCl_3$



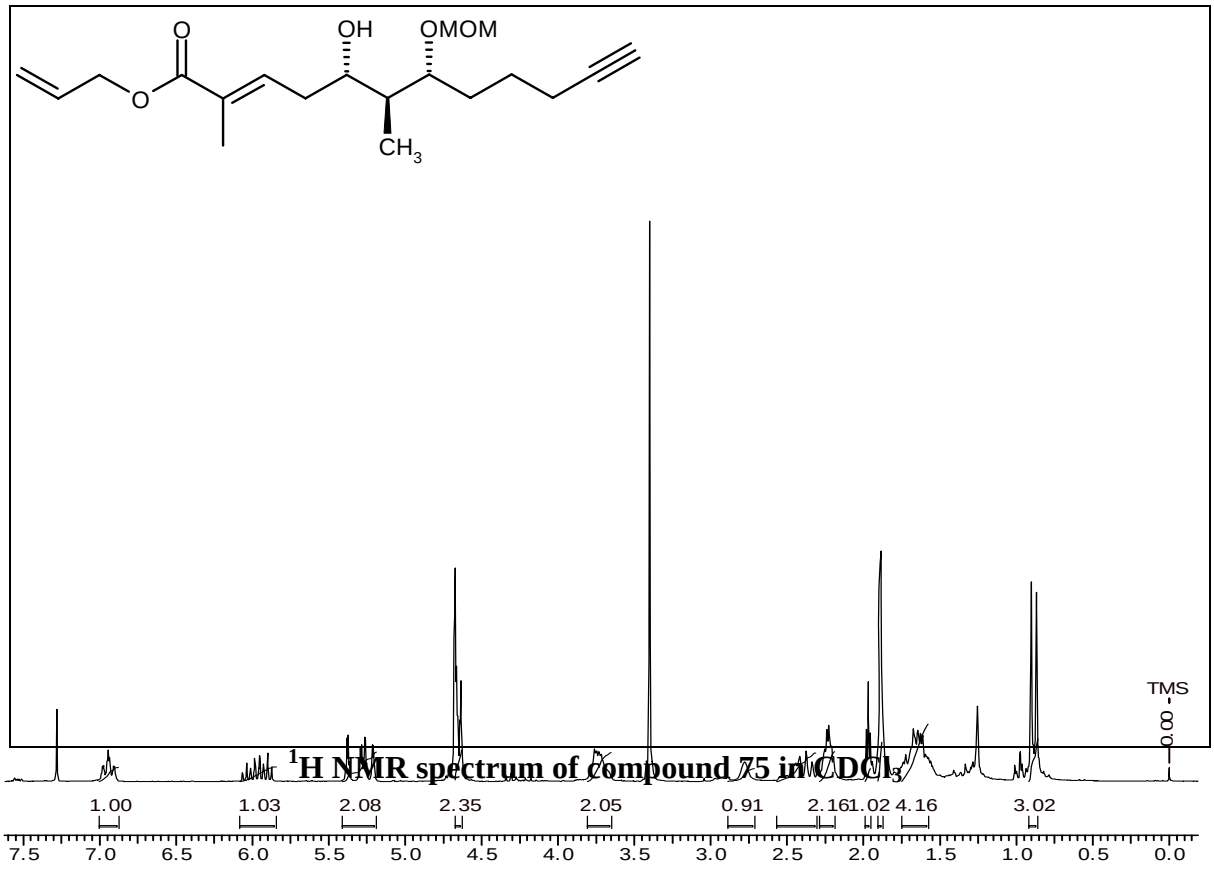
^{13}C NMR spectrum of compound 72 in $CDCl_3$



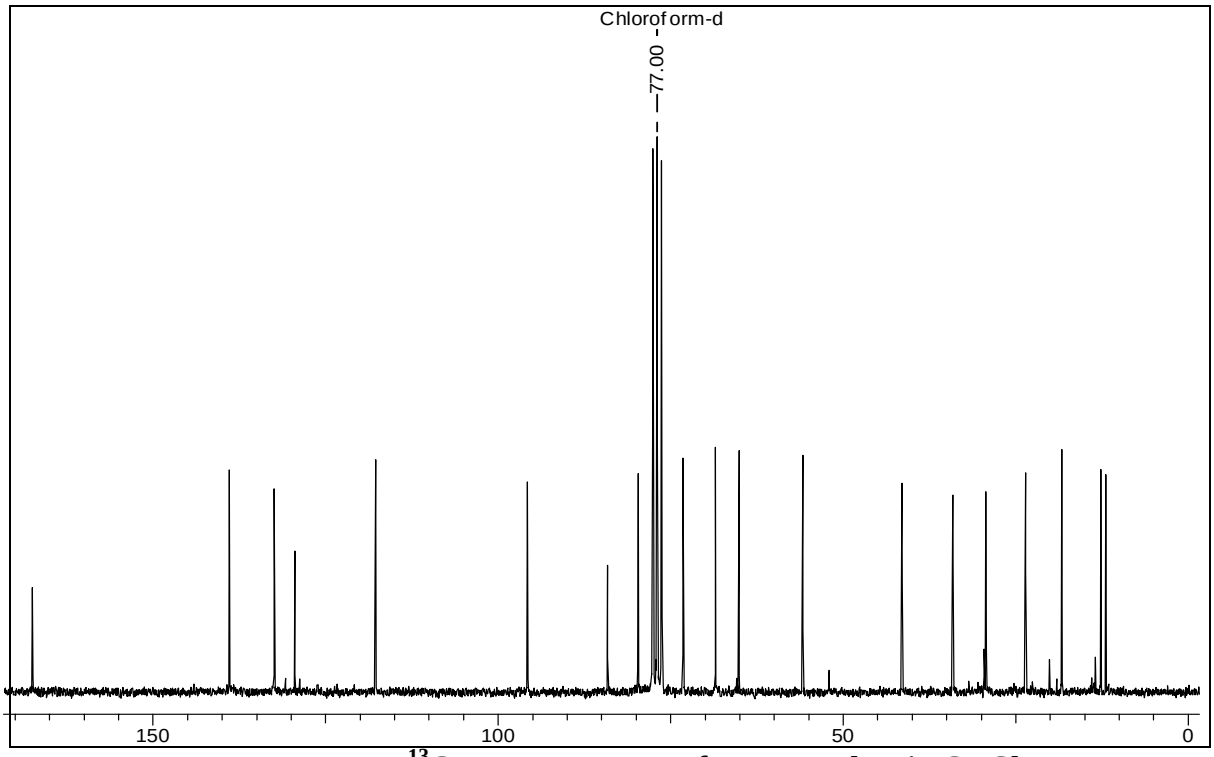
^{1}H NMR spectrum of compound 74 in $CDCl_3$



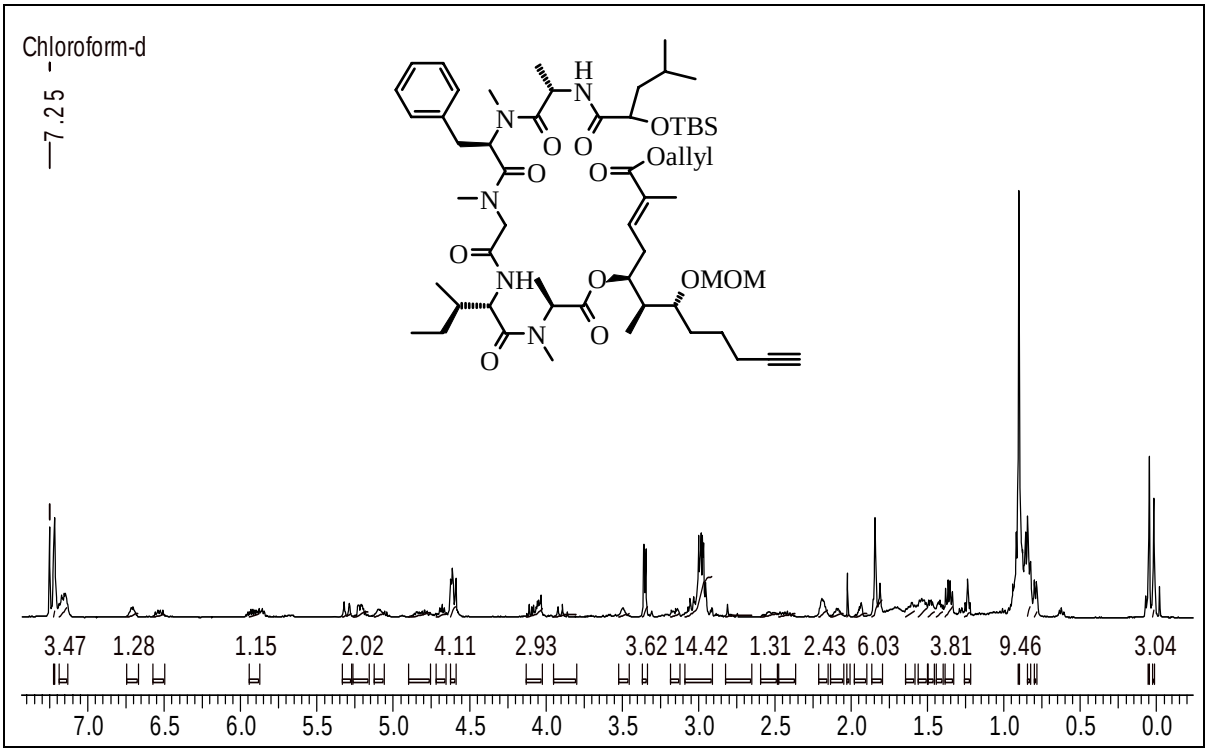
^{13}C NMR spectrum of compound 74 in $CDCl_3$



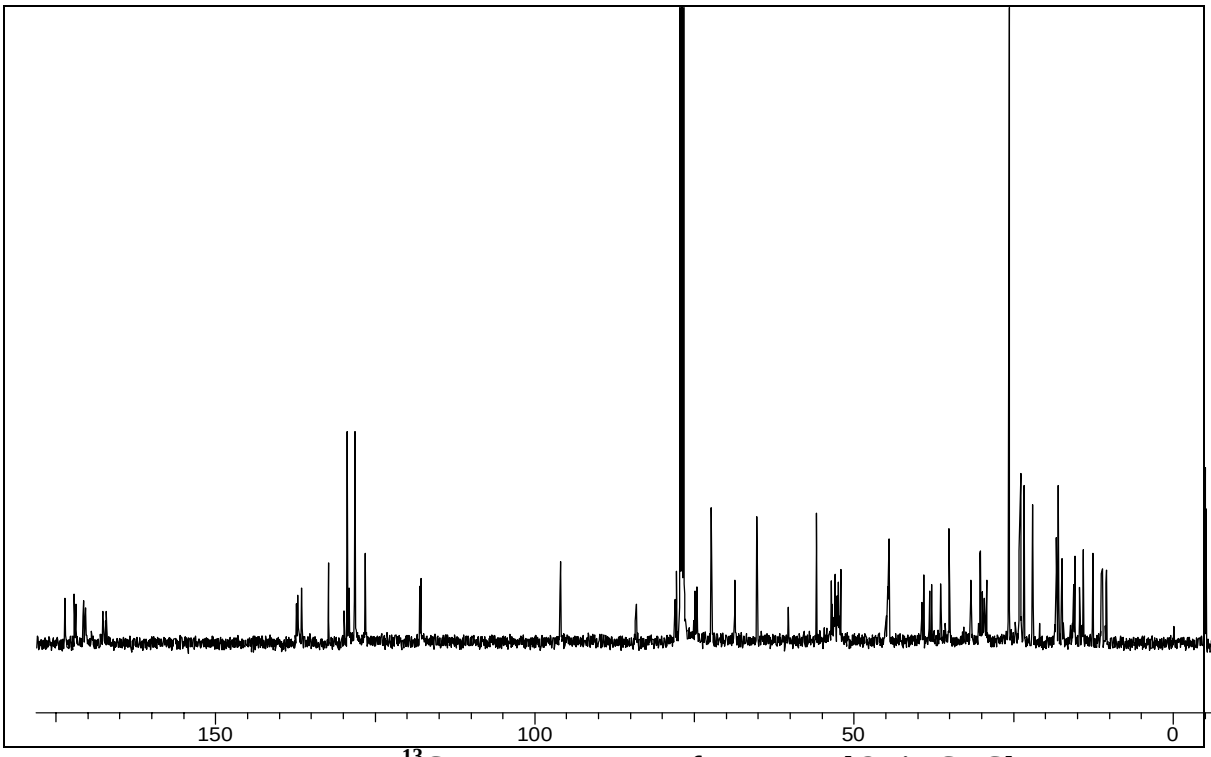
^{1}H NMR spectrum of compound 75 in $CDCl_3$



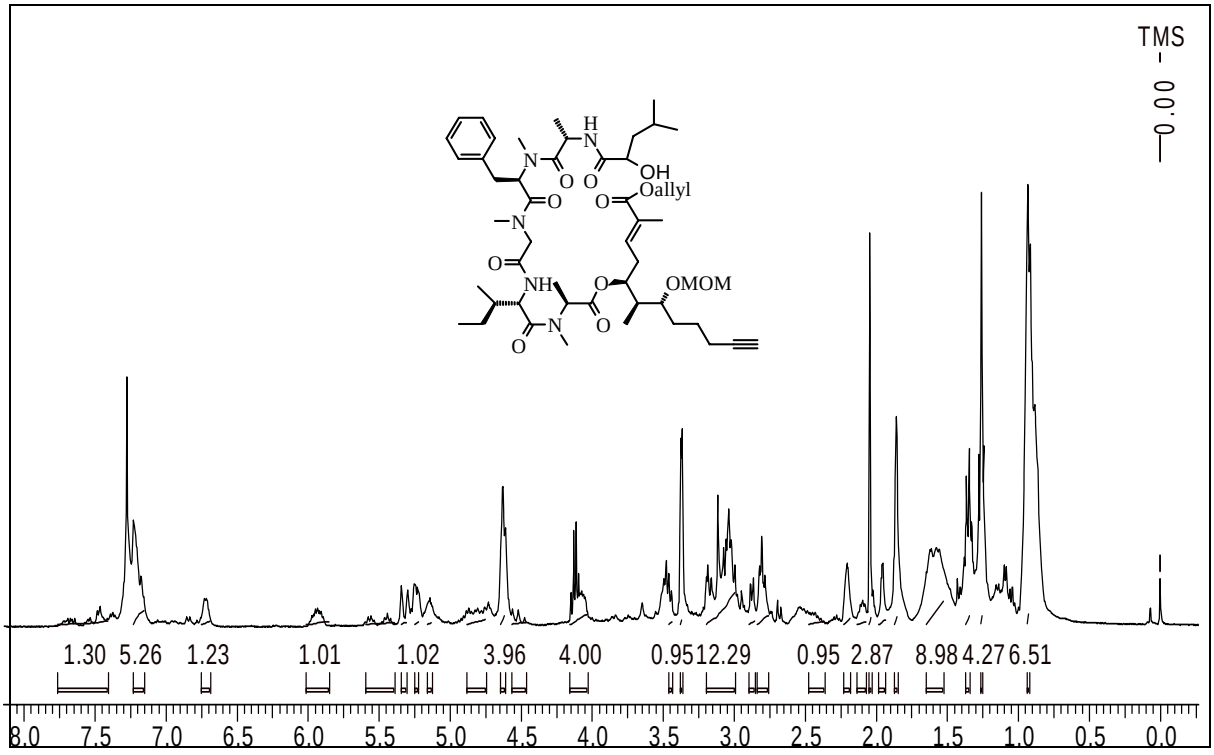
^{13}C NMR spectrum of compound 75 in $CDCl_3$



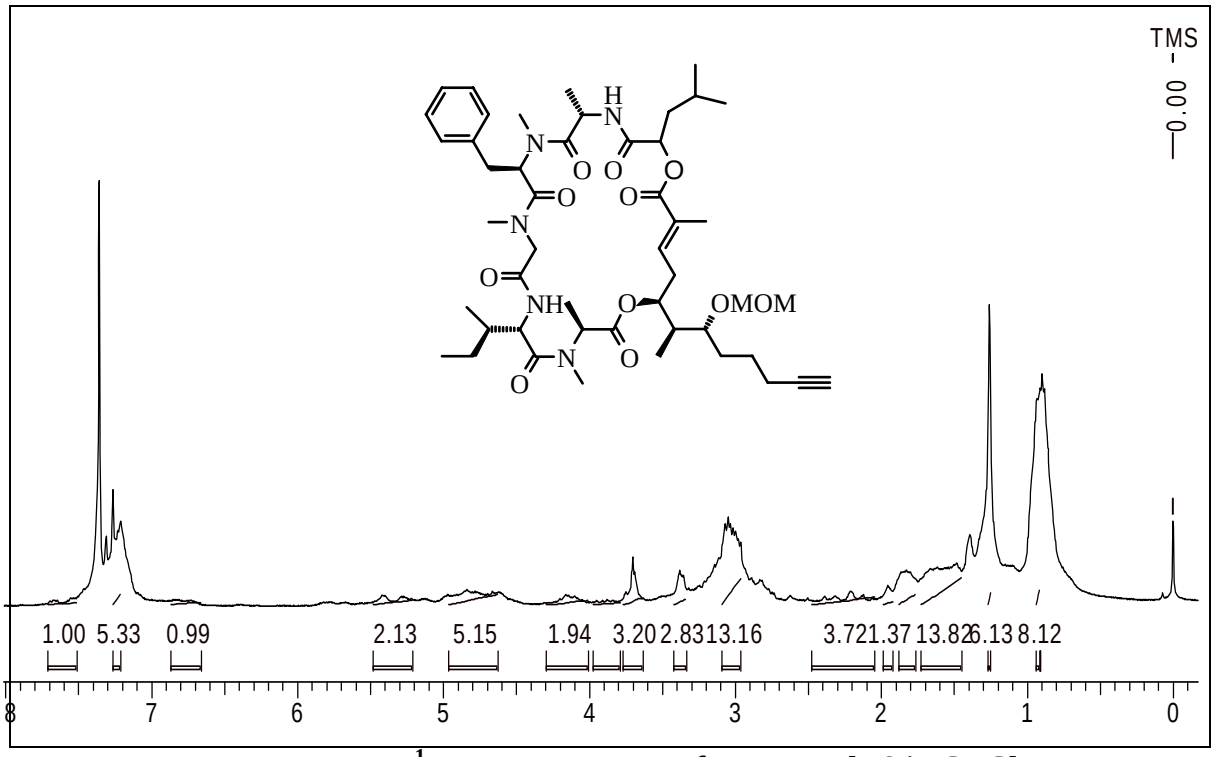
^{1}H NMR spectrum of compound 27 in $CDCl_3$



^{13}C NMR spectrum of compound 27 in $CDCl_3$



^{1}H NMR spectrum of compound 76 in $CDCl_3$



^{1}H NMR spectrum of compound 78 in $CDCl_3$

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CHAPTER –III

Synthetic studies toward Asimitrin

INTRODUCTION

Cancer is a devastating disease for which there is yet no absolute cure. Genetic predisposition and mutations (abnormal changes in the nuclei of cells) caused by chemicals, radiation, hormones, and viruses account 90-95% of all cancers. Cancer afflicts almost every part of the human body from the skin to the marrows and is indiscriminate of age.

Tumor cells grow and replicate more rapidly than normal cells as they are better equipped to receive glucose, a good source of energy for fast replication. Also, cancer cells quickly develop a network of blood vessels (angiogenesis) to ensure an efficient supply of nutrients and oxygen.

Different approaches are employed in the treatment of cancer among them chemotherapy and radiation therapy are well known. In chemotherapy normally anticancer drugs used to destroy cancer cells by damaging their genetic material, thus stopping their proleferation. Some drugs work better together than alone, hence two or more drugs are often given at the same time. Unfortunately, most anticancer drugs are not selective, thus healthy cells can also be harmed and cancer cells also develop resistance to the drugs, rendering chemotherapy inactive and futile after a period of remmision. The organisms and cancer cells smartly find a way of protecting themselves from damaging effects of drugs. They generate the ABC transporter superfamily, which transports a variety of substrates including aminoacids, sugars, inorganic ions, polysaccharides, peptides, and the multidrug resistant (MDR) proteins, which is overexpressed and helps to pump drugs out of the cancer cells, making the cancer cells simultaneously resistant to a variety of drugs. In radiation therapy, the ionizing radiation especially used for localized solid tumors, such as cancers of the skin, tongue, brain, breast, or uterine cervix. It can also be used to treat leukemia and lymphoma (cancers of the blood-forming cells and lymphatic system) but the ionizing radiation destroys cells in the area being treated by damaging their genetic material, making it impossible for these cells to continue to grow. Newer forms of treatment involve angiogenesis inhibition, stimulating the immune system to fight cancer, bone marrow, and peripheral stem cell transplantation, gene and photodynamic therapy. Possible side effects of cancer treatment include loss of hair, skin irritation,

Transportation and metastasizing of cancer cells in other parts of the body.It restricts abnormal cell division by depleting the DNA and RNA blocks of the cells, and this has been found to be particularly effective against human CEM leukemia cells. The bark of this tree also used for folk medicine because it contains useful alkaloids.

Annonaceous acetogenins:

Studies on several types of annonaceous acetogenins have been compiled since the 1980's. These acetogenins were believed to have characteristics capable of halting the growth of cancerous tumors in animals and humans.

The Annonaceae (custard-apple family), considering its large size (130 genera and 2300 species), is chemically one of the least known of the tropical plant families.[4] Phytochemical studies and, to a lesser extent, pharmacological studies on Annonaceous species have intensified in the last 15 years; this is largely due to the discovery of the Annonaceous acetogenins, a class of natural compounds with a wide variety of biological activities.[5-6] Before 1982, most investigations centered upon the many isoquinoline alkaloids in this family. About 320 secondary natural products from 150 species belonging to 41 genera were summarized from 288 publications in 1982 by the group of Professor Andre´ Cave´ in France. The discovery of uvaricin in 1982,[7] the first of the Annonaceous acetogenins, as an in vivo active antileukemic (P-388) agent, invigorated wide interest in this family. The Annonaceous acetogenins are now one of the most rapidly growing classes of new natural products and offer exciting anthelminitic, in vivo and cytotoxic antitumor, antimalarial, antimicrobial, antiprotozoal, and pesticidal activities and special promise of becoming new chemotypes for antitumor and pesticidal agents. Structurally, the Annonaceous acetogenins are a series of C35/C37 natural products derived from C32/C34 fatty acids that are combined with a 2-propanol unit. They are usually characterized by a long aliphatic chain bearing a terminal methyl-substituted α,β-unsaturated-γ-lactone ring (sometimes rearranged to a ketolactone), with one, two, or three tetrahydrofuran (THF) rings located along the hydrocarbon chain and a number of oxygenated moieties (hydroxyls, acetoxyls, ketones, epoxides) and/or double bonds being present. To a lesser extent,

tetrahydropyran (THP) ring compounds and acyclic compounds are also found.[8-12] The Annonaceous acetogenins are the most powerful of the known inhibitors of complex I (NADH:ubiquinone oxidoreductase) in mammalian and insect mitochondrial electron transport systems;[13-16] in addition,they are potent inhibitors of NADH oxidase of the plasma membranes of cancer cells;[17] these actions decrease oxidative, as well as, cytosolic ATP production. The consequence of such ATP deprivation is apoptosis (programmed celldeath).[18] Recently, we have shown that the acetogenins also inhibit cancer cells that are multidrug resistant (MDR),[19-21]and in addition, they combat pesticide-resistant German cockroaches effectively.[22] Thus, they thwart biological resistance.

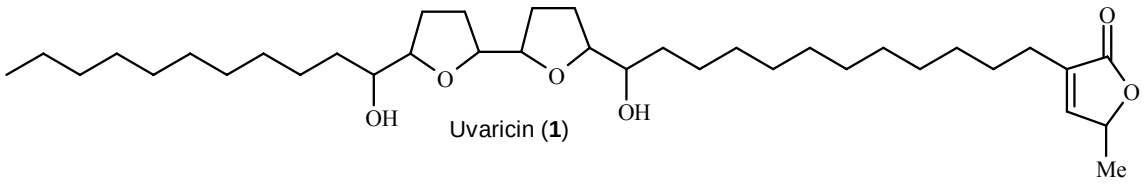
Types of acetogenins

Acetogenins are broadly classified into two categories these are

(i) Classical acetogenins

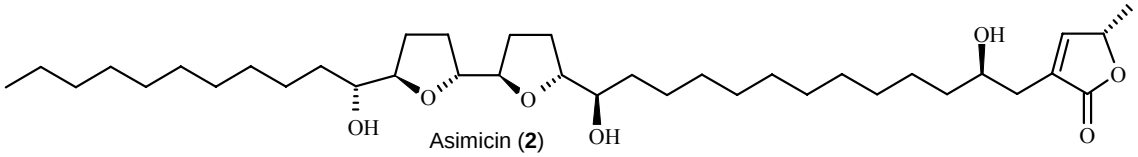
(ii) **Non classical acetogenins**

Classical acetogenins Structurally, classical acetogenins contain an array of 2, 5-disubstituted tetrahydrofuran (THF) rings. Examples of such are uvaricin, bullatacin, asimicin, annonisim, guanaconne, and rollidecin.



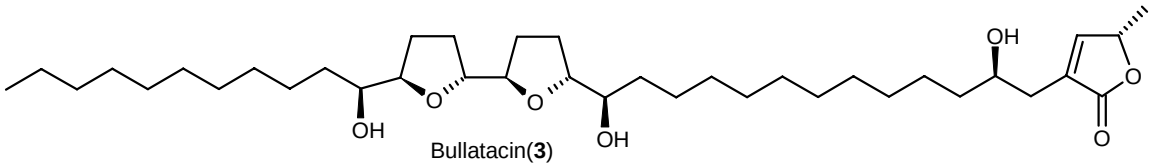
Uvaricin (**1**)

The novel antitumor agent uvaricin (**l**), a bis(tetrahydrofuranoid) fatty acid lactone isolated from the roots of *Uuan'a accuminuta* (Annonaceae).[8]



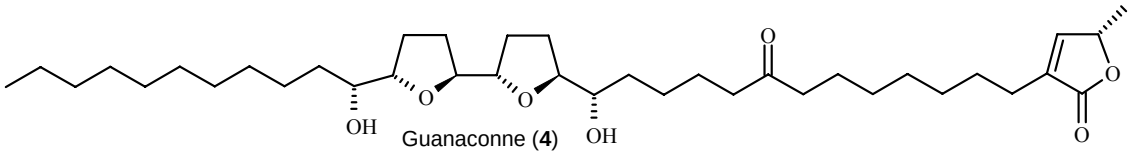
Asimicin (**2**)

Asimicin(**2**),[23] and bullatacin(**3**)[24] are two diastereomeric members of the Annonaceous acetogenins, a rapidly growing family of natural products, that are known not only for their antitumor activity but also for being potent antimalarial, immunosuppressive, pesticidal, and antifeedant agents.[25]



Bullatacin(**3**)

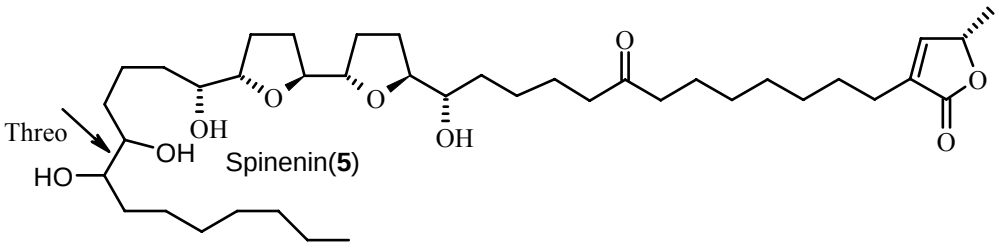
Asimicin was isolated from *Asimina triloba* Dunal, and bullatacene was discovered in *Annona bullata* using the brine shrimp lethality assay for activity-directed fractionation. High cytotoxicity was exhibited by asimicin in cell lines of human nasophyraneal carcinoma (9KB, ED50, 10-5 *m*g/mL) and murine lymphocyte leukemia (9BS, ED50, 10-7 mg/mL). Similarly, bullatacene and its analogues have shown potential in vivo antitumor activity with normal mice bearing L1210 murine leukemia and with mice bearing A2780 conventional ovarian cancer xenografts.[25] The cytotoxicity of Bullatacene was found to be higher than that of other chemotherapeutic agents in a variety of cancer cell lines, [26] particularly in HL-60 cells that are resistant to adriamycin.[27] The structure of **2** and **3** was assigned mainly on the basis of ^{1}H and ^{13}C NMR and MS data. Their absolute configurations were determined using ^{1}H and ^{19}F NMR spectral data of both their (*R*) and (*S*) Mosher esters in comparison with model compounds.[28, 29] These structures were confirmed via the total syntheses of both **2** and **3**,[30] by the Hoye,[31]Marshall,[32] and Sasaki groups.[33]



Guanaconne (**4**)

From a Colombian tree known as “guanacona” or “tiotio” an unusual 10-keto bis-tetrahydrofuran (THF) acetogenin, guanacone **4**, was isolated from the EtOAc extract as a colorless wax. Its molecular weight was determined by peaks at *m*/*z* 643 $[M + Na]^{+}$ and *m*/*z* 621 $[MH]^{+}$ in the FABMS, corresponding to the molecular formula $C_{37}H_{64}O_7$. The existence of α,β-unsaturated γ-lactone in **4**was first suggested by a positive Kedde reaction and by a 1751 cm^{-1} carbonyl absorption band in the IR spectrum and was confirmed by the characteristic signals in the ^{1}H and ^{13}C NMR spectrum, which proved the absence of an OH at the C-4 position typically found in most acetogenins.[34] The presence of a keto group in **4** was suggested by the existence of a triplet at δ 2.39 (H-9, 11) in the ^{1}H NMR spectrum and ^{13}C NMR resonances at δ 211.46 (C-10) and δ 42.70 (C-9,11) due to

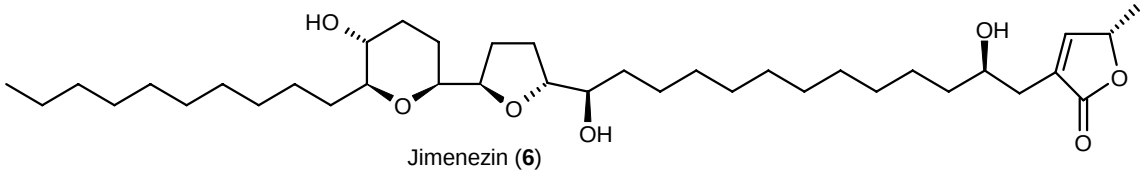
the keto-bearing carbon and the two flanked methylene carbons, respectively. The location of the keto group was confirmed by the fragments at *m/z* 223 and *m/z* 195 in the EIMS Moreover, two OH groups in **4** could be proposed from the prominent IR absorption at 3416 cm^{-1}, two successive losses of H_2O from the $[MH]^+$ in the FABMS, and the preparation of diacetate and di-TMS derivatives. An adjacent bis-THF system in **4** could be unambiguously assigned by 1D (^1H, ^{13}C, and DEPT) and 2D (COSY and HMQC) NMR experiments, and its placement in the alkyl chain was deduced by the EIMS. The relative stereochemistry across this R, R'-dihydroxylated bis-THF system, was deduced as *threo*/*trans*/*threo*/*trans*/*erythro* based on the ^1H and ^{13}C NMR data, which were consistent with those of model compounds.[35]



The present study has led to the isolation and structure elucidation of spinencin (**5)**, a new C37 bis-tetrahydrofuran acetogenin, together with the known almunequin,[36] bullatanocin,[37] isodesacetyluvaricin,[38] atemoyin or squamocin K[39,40]desacetyluvaricin,[41] and neoannonin.[42] The structures were determined by ^1H and ^{13}C NMR (COSY, HMBC, and HMQC) and MS (ESI-MS/MS) on the native compounds and on the acetonide derivative of spinencin **5** was isolated as a transparent oil from the MeOH extract of the seeds by the usual chromatographic methods followed by preparative HPLC. The electrospray-ionization (ESI) mass spectrum of compound **5** showed only two main ions, corresponding to the cationized species $[M + Li]^+$ and $[M + Na]^+$ (*m/z* 645.6 and 661.6, respectively). The molecular weight of 638.6 was also confirmed by the presence of two weak ion peaks appearing at *m/z* 1284.2 and 1300.2, which were attributed to the dimeric ion species $[2M + Li]^+$ and $[2M + Na]^+$. Such a molecular weight is in agreement with a C37 acetogenin ($C_{37}H_{66}O_8$) containing two tetrahydrofuran rings and four hydroxy groups.[43]

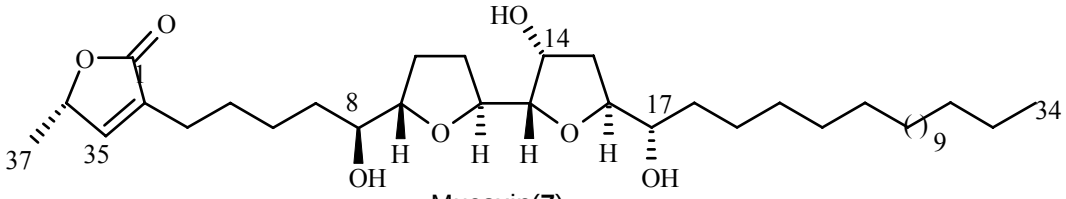
Non classical acetogenins: More recently, new nonclassical acetogenins containing more complex tetrahydropyran (THP) rings and/or THF rings as the core have been isolated;

examples of such are mucoxin, muconin, pyragonicin, and Jimenezin, all of which are THP-containing acetongenins and have recently succumbed to total synthesis. Mucoxin, a nonclassical acetogenin, is the first of its kind found to contain a trisubstituted hydroxylated THF ring. After isolation of mucoxin, recently two other potent nonclassical acetogenin has been isolated named as salzmanolin and asimitrin, which contains trisubstituted hydroxylated THFring. These acetogenins have strong biological activity than classical acetogenins.[44]



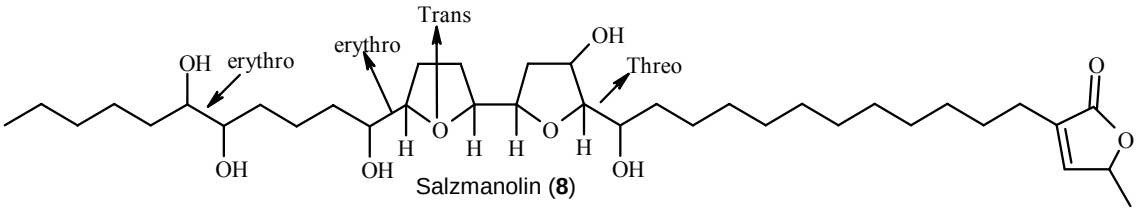
Jimenezin (**6**)

Jimenezin (**6)** was isolated from seeds of *Rollinia mucosa* in 1998.[45] Its structure consisting of a tetrahydropyran (THP) ring adjacent to a tetrahydrofuran (THF) ring was proposed by spectroscopic techniques and its structure was revised after a total synthesis by Takahashi.[46] Although most annonaceous acetogenins contain one to three THF rings in the polyether part, jimenezin belongs to the small subgroup with an additional THP ring and is structurally related to mucocin.[47,48] The stereocontrolled synthesis of this THP ring represents one of the challenges of a total synthesis of jimenezin. Takahashi used a chiral pool approach from galactono-1,5-lactone to solve the THP problem, whereas Lee[49]applied a Samarium iodide-mediated radical cyclization in his synthesis.



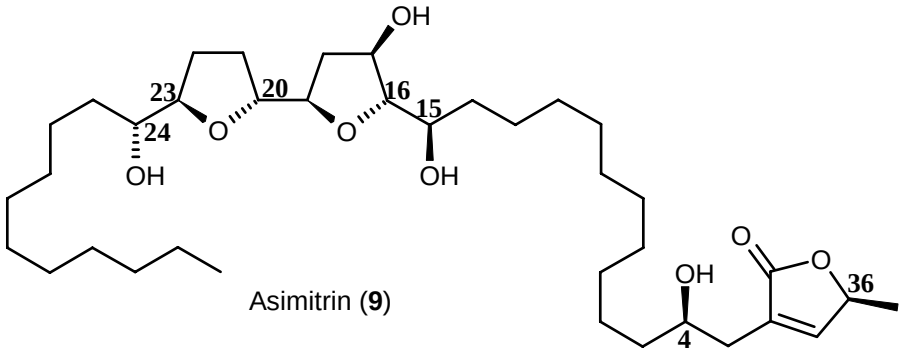
Mucoxin(**7**)

Mucoxin (**7)** a nonclassical acetogenin, is the first of its kind found to contain a trisubstituted hydroxylated THF ring.[50] In vitro cytotoxicity assays against a panel of six human tumor cell lines have shown mucoxin to be more potent and selectiveagainst MCF-7 (breast carcinoma) cell lines than adriamycin.



Salzmanolin (**8**)

Salzmanolin (**8)**, were isolated from a MeOH extract of the roots of *Annona salzmani* by Emerson F. Queiroz in 2003.[51] The structure of **8** was elucidated by spectroscopic methods including LSIMS/MS, on both the natural compounds and their acetonide derivatives. Compounds **8** showed significant activity against the KB and Vero cell lines.



Asimitrin (**9**)

Asimitrin (**9)** a ringhydroxylated unsymmetrical bis-tetrahydrofuran acetogenin was isolated from the seeds of *Asimina triloba* by Mi Hee Woo in 2005.[52] This novel type of acetogenin was found to be cytotoxic selectively against prostate carcinoma (PC-3) at about 10,000 times and colon adrenocarcinoma (HT-29) at about 100 times the potency of adriamycin.Compound **9** was isolated by the fractionation of chromatographic treatment of the aqueous MeOH partition (F005) [53] showed $[\alpha]^{23}_{D}$ +20.0° (*c* 0.01, CH_2Cl_2), was isolated as a white wax. Its molecular weight was suggested by the mass peak at *m*/*z* 639 $[M + H]^+$ in the FABMS. The HRFABMS gave *m*/*z* 639.4821 for the $[M + H]^+$ ion (calcd 639.4836), corresponding to the molecular formula $C_{37}H_{67}O_8$. Compound **9** showed an IR carbonyl absorption at 1763 cm-1, a UV *v*max (MeOH) at 228 nm (log _ 3.06), 1H NMR resonances at δ 7.19, 5.06, 3.84, 2.53, and 2.40, and ^{13}C NMR resonances at δ 174.6, 151.7, 131.2, 78.0, 70.0, and 19.1, all of which provided characteristic spectroscopic features for an α, β unsaturated γ-lactone fragment with an OH-4 group.[54-56] The presence of four hydroxyl functionalities in **9** was evident from the IR absorption at 3367 cm-1 and four successive losses (*m*/*z* 926, 836, 746, and 656) of TMSiOH (*m*/*z* 90) from the $[M]^+$ in the EIMS.

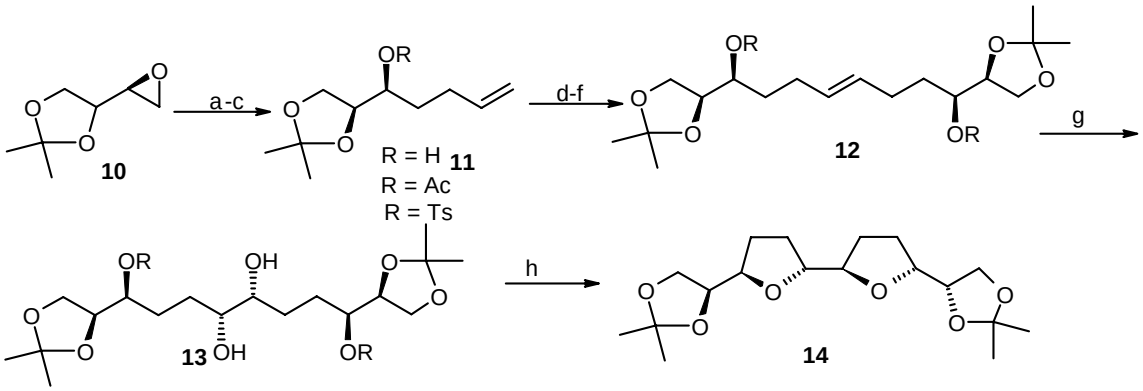
Furthermore, the ^{13}C NMR spectrum of **9** showed four resonances due to oxygen-bearing carbons at δ 70.0, 72.0, 73.4, and 73.4, confirming the presence of four hydroxyl groups. The positions of the unusual adjacent ring-hydroxylated bis-THF and hydroxyl groups on the hydrocarbon chain were determined by careful analysis of the ^{1}H NMR, COSY, ^{13}C NMR, HMQC, and HMBC spectra. The OH-17 position was proposed on a rigid ring system rather than an open-ended hydrocarbon chain because of the large δ value difference of its neighboring methylene protons (δ1.94 for H-18a and 2.36 for H-18b). In turn, H-19, a methine proton at δ 4.14, was identified by tracing its COSY cross-peaks to both H-18a and H-18b. At this point, a hydroxylated THF ring across C-16/19 was established.This inference was supported by the three new peaks at C-19/H-17, C-17/H-15, and C-16/H-18ab in the HMBC spectrum. In addition, the ^{13}C NMR chemical shift of **9** for C-16 shifted downfield to δ 91.4 and C-19 was shifted upfield to δ 79.9 and was also supported by the α,β-effect and a γ-gauche effect [57] due to the hydroxyl group at C-17. The assignment of the second THF ring at C-20/23 was made possible by the H-20/23 cross-peak (δ 4.00/3.91) in the double-relayed COSY spectrum. In the 1H-1H COSY spectrum of **9**, the correlations observed at H-23/24 (δ 3.91/3.43) confirmed the placement of the hydroxyl flanking the adjacent bis-THF rings.

Several approaches for the synthesis of bis-THF core of acetogenins:

B.V Rao approach: [58]

Synthesis of Bis-THF ring using cross metathesis

Scheme 1. **C**ross RCM reaction



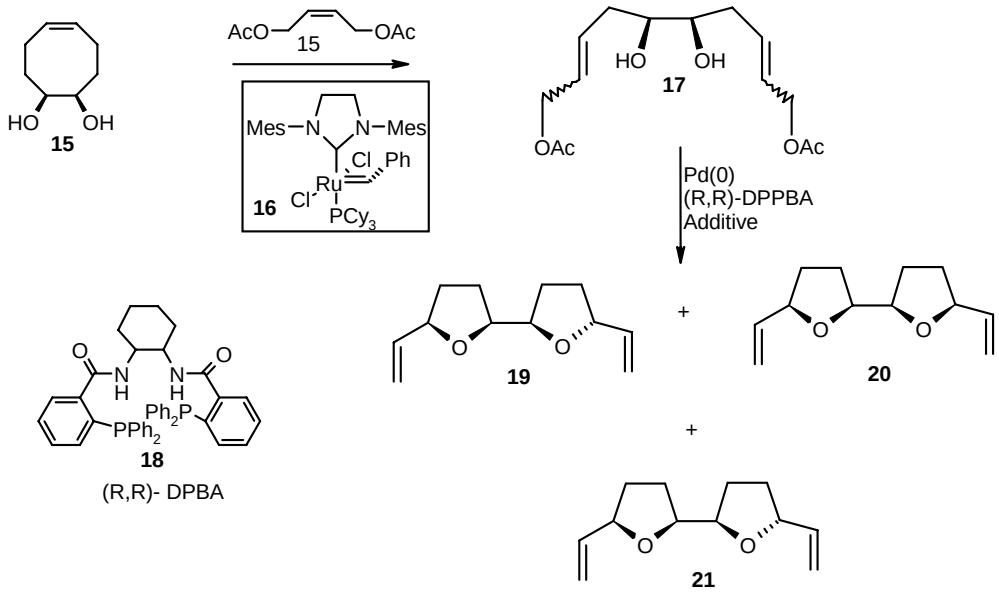
***Reagents and conditions*:** (a) CH_2=CH-CH_2MgBr, CuI, ether, -20 ºC, 12 h, 85%; (b) $(CH_3CO)_2O$, TEA,DMAP, DCM, 0 ºC-rt, 3 h, 90%; (c) *p*-TsCl, TEA, DMAP, DCM, 0 ºC

to rt, 24 h, 87%; (d) 10 mol% Grubbs' 1st generation catalyst, DCM, 40 ºC 12 h; (e) K_2CO_3, methanol, ºC to rt, 2 h, 85%; (f) *p*-TsCl, TEA, DMAP, DCM, 0 ºC to rt, 36 h, 87%; (g) AD mix-β, H_2O: *t*-BuOH (1:1) 0 ºC, 12 h, 85%; (h) NaH, THF, 0 ºC-rt, 6 h, 80%.

Steven D. Burke approach:[59]

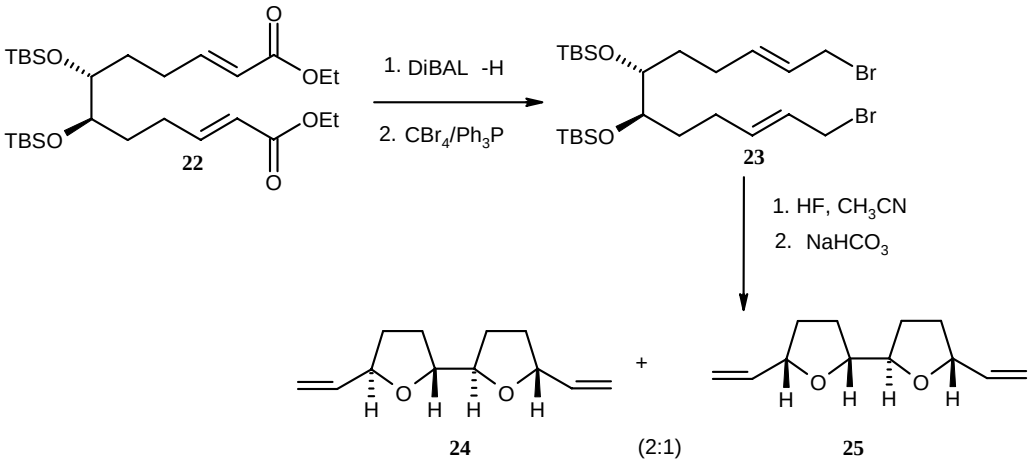
Stereochemical General Approach to Adjacent Bis(tetrahydrofuran) Cores of Annonaceous Acetogenins

Scheme 1: Double etherification



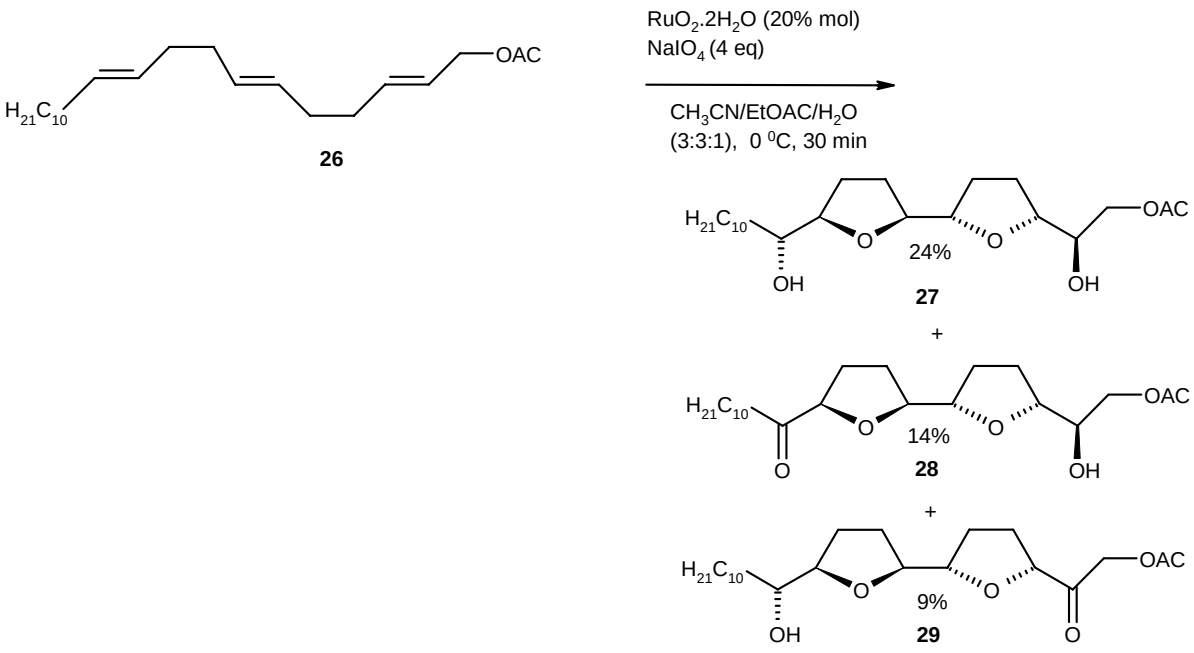
Kang Zhao Approach:[60]

Scheme 2: SN Cyclization of E-Olefin



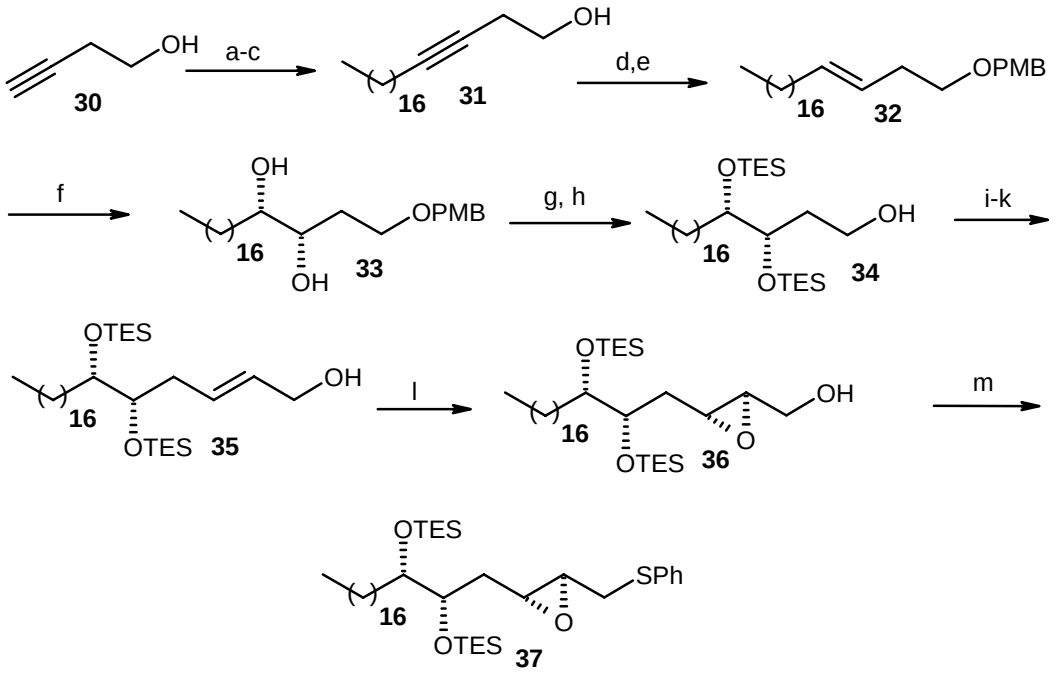
Vincenzo Piccialli approach:[61]

Scheme 3: RuO4-mediated oxidative bis-cyclization of (E,E,E)-acetic acid henicosa-2,6,10-trienyl ester



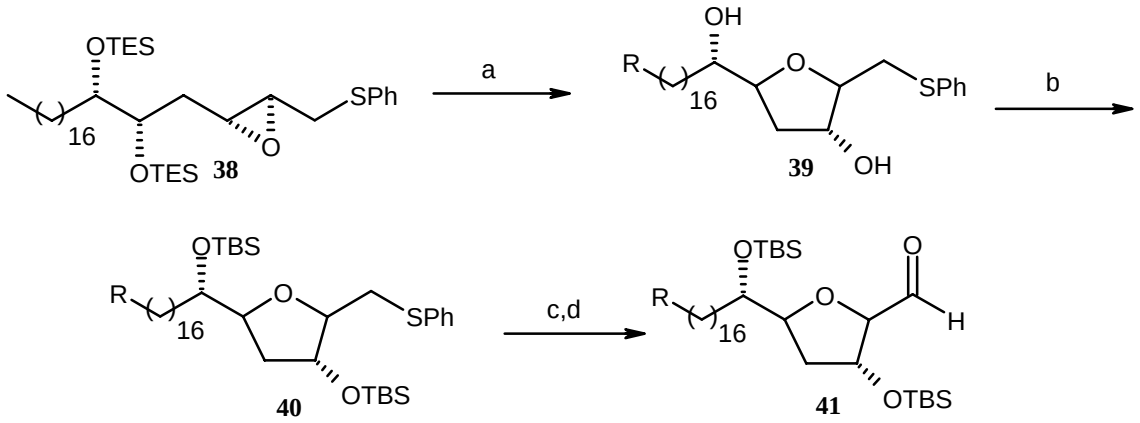
Babak Borhan approach:[62] Synthesis of bis-THF core of Mucoxin

Scheme 4: Synthesis of epoxysulfide:



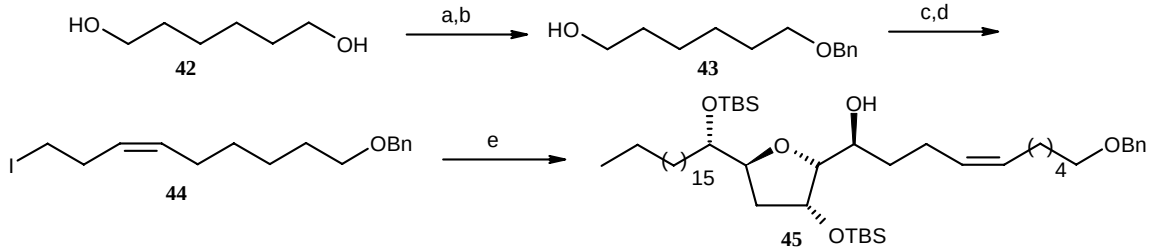
***Reagent and conditions*:** (a) TBSCl, imid., DMF, room temperature (73%); (b) *n*-BuLi, $CH_3(CH_2)_{16}I$, THF/HMPA (3:1), 0 °C (80%); (c) TBAF, THF, -10 °C (90%); (d) LAH, diglyme, 125 °C (87%); (e) NaH, PMBCl, TBAI, THF, 60 °C (91%); (f) AD-mix-R, $MeSO_2NH_2$, $K_2OsO_4{\cdot}2H_2O$, *t*-BuOH/H_2O (1:1), 0 °C (92%); (g) TESCl, Et_3N, DMAP, THF, rt, (quantitative); (h) DDQ, CH_2Cl_2/pH 7 phosphate buffer (10:1), 0 °C(78%); (i) $PhI(OAc)_2$, TEMPO, CH_2Cl_2, room temperature (96%); (j) $Ph_3PdCHCO_2Et$, THF, reflux (91%); (k) DIBALH, Et_2O, 0 °C (89%); (l) (D)-DIPT/Ti ($OiPr)_4$ (1.2:1.0), *t*-BuOOH, MS 4 Å, CH_2Cl_2, -20 °C (73%); (m) $(PhS)_2$, Bu_3P, TEA, 0 °C to room temperature (94%).

Scheme 5: Synthesis of Aldehyde (**41**)



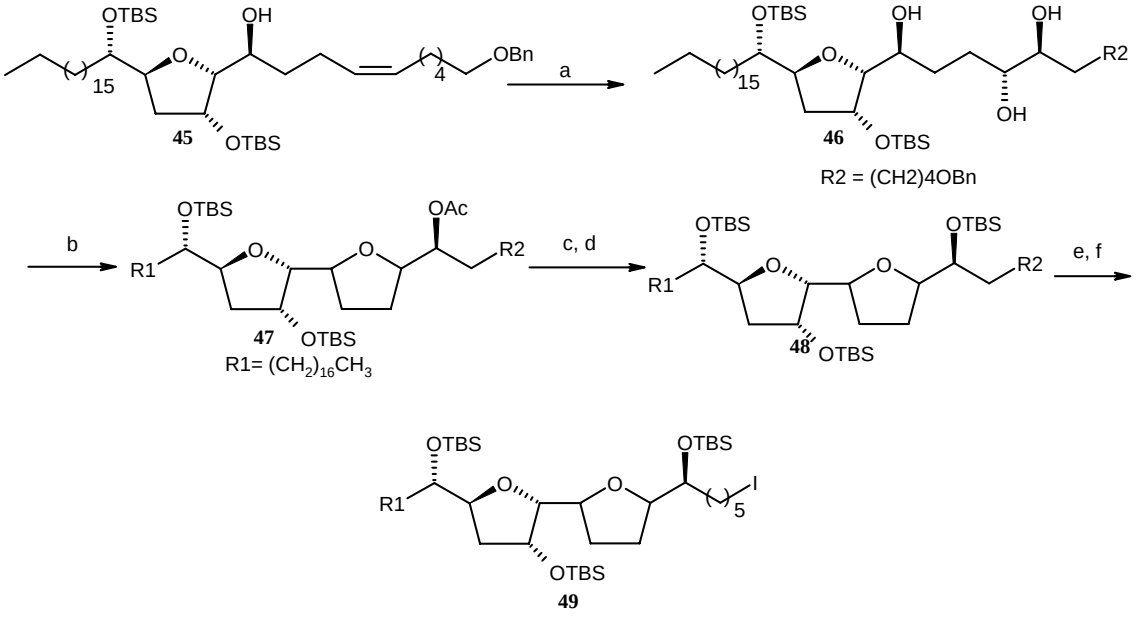
Reagents and conditions: (a) BF_3:OEt_2 (6 equiv), Et_2O (0.04 M), 0 °C to room temperature (56%); (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C (91%); (c) *m*-CPBA, CH_2Cl_2, 0 °C (quantitative); (d) (i) TFAA, 2,6-lutidine, CH_2Cl_2, 0 °C; (ii) $NaHCO_3$ (solid), CH_3CN (63% over two steps).

Scheme 6: Synthesis of Hydroxyene (**45**)



***Reagent and conditions*:** (a) NaH, BnBr, TBAI, THF, 60 °C (78%); (b) PCC, CH_2Cl_2, rt (82%); (c) $Ph_3P(CH_2)_3OHBr$, KHMDS, TMSCl, then AcOH/THF/H_2O (6:3:1), 0 °C (83%); (d) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C; (ii) NaI, acetone, reflux, 77%; (e) *t*-BuLi, -100 °C, $MgBr_2$:OEt_2, Et_2O, -95 °C, then **41**, $MgBr_2$:OEt_2, -40 °C (88%).

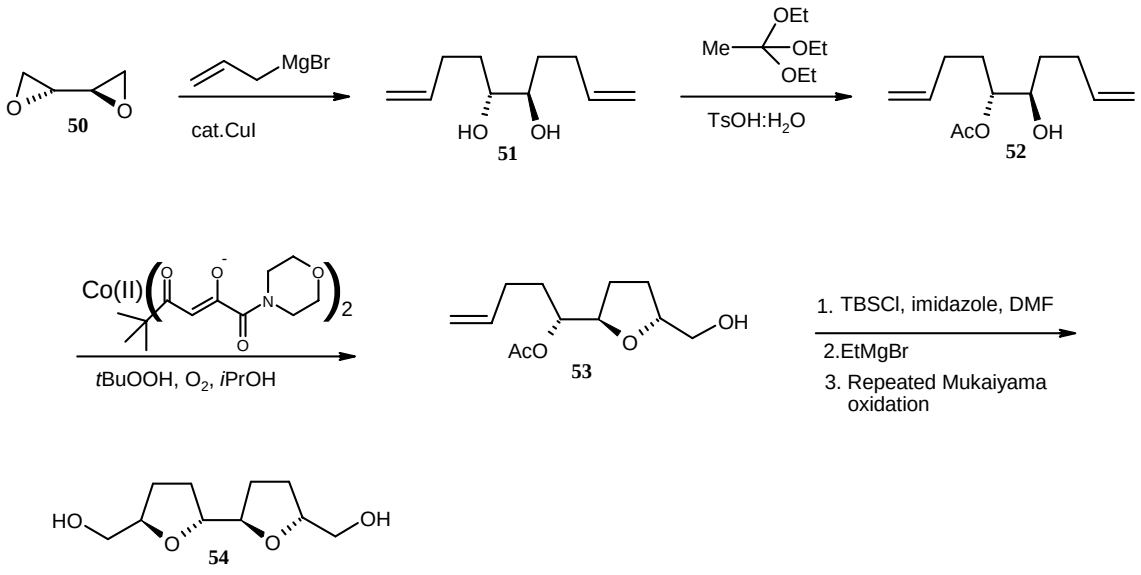
Scheme 7: Synthesis of Bistetrahydrofuran[63]



Reagent and conditions: (a) AD-mix-R, $MeSO_2NH_2$, K_2OsO_4:$2H_2O$, 0 °C (88% yield, dr) 5:1); (b) $MeC(OMe)_3$, PPTS (10 mol %), CH_2Cl_2, room temperature, then BF_3:OEt_2 (25 mol %); (c) K_2CO_3, MeOH, room temperature; (d) TBSOTf, 2,6-lutidine, 0 °C (90%, 3 steps); (e) H_2, Pd/C, EtOAc/*i*-PrOH (1:1), rt (92%); (f) PPh_3, imid., I_2, toluene, rt (87%).

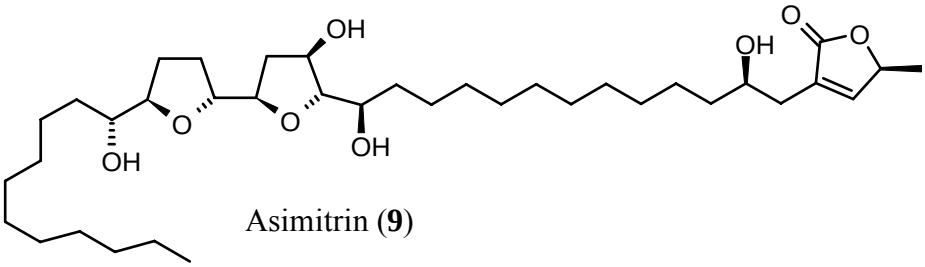
Brian L. Pagenkopf approach: [63] Synthesis of bis-THF core of Bullatacin

Scheme 8: Synthesis of Bistetrahydrofuran



PRESENT WORK

In recent years the Annonaceous acetogenins have been the focus of extensive synthetic efforts as a result of their remarkable range of biological activities such as antitumor, antifeedant, immunosuppressive, pesticidal, anthelmintic and microbial. Particularly, after identification of Uvaricin,[7] as an *in vivo* active antitumor agent, there has been significant interest arises in the isolation and biological evaluation of acetogenins derived from Annonaceous family.[63] Annonaceous acetogenins are known to be highly potent and selective antitumor agents. More interestingly, some members of this family have been shown to possess the ability to combat resistance in multi drug-resistant cancerous cells.[64,65] The origin of the selective cytotoxicity of acetogenins is believed to result from their complexation with ubiquinone-linked NADH oxidase present in the plasma membrane of tumor cells. Acetogenins also bind NADH-ubiquinone oxidoreductase (Complex I), which is a membrane protein present in the mitochondrial electron-transport system.[66–70] Complex I has been implicated in several diseases including idiopathic Parkinson's disease, maturity onset diabetes, stroke-like episodes, and Huntington's disease.[71] However, the precise mode of complexation of acetogenins with the target proteins has not been delineated. Important characteristic structural features of Annonaceous acetogenins include a butenolide segment, one or more tetrahydrofuran rings, and alkyl chain residues on either side.



Asimitrin (**9**)

Asimitrin (**9)** a ringhydroxylated unsymmetrical bis-tetrahydrofuran acetogenin was isolated from the seeds of Asimina triloba by Mi Hee Woo in 2005.[52] This novel type of acetogenin was found to be cytotoxic selectively against prostate (PC-3) at about 10,000 times and colon adrenocarcinoma (HT-29) at about 100 times the potency of adriamycin. Such powerful antitumor activity and the unique structure of **9** attracted us to undertake its total synthesis.

A close examination of the structure of Asimitrin **9** revealed that the artechitectural feature contains nine chiral centres, among them eight stereocentres have '*R*' stereochemistry and only one contains '*S*' stereochemistry. After a through literature study we realized a chiral pool approach will be the suitable one to fix the desired stereocentres and 3-deoxy-1,2:5,6-di-*O*-isopropylidene-xylofuranose was considered as a suitable precursor. On this background we envisaged a retrosynthetic analysis for the synthesis of **9**, which was illustrated in Figure 1.

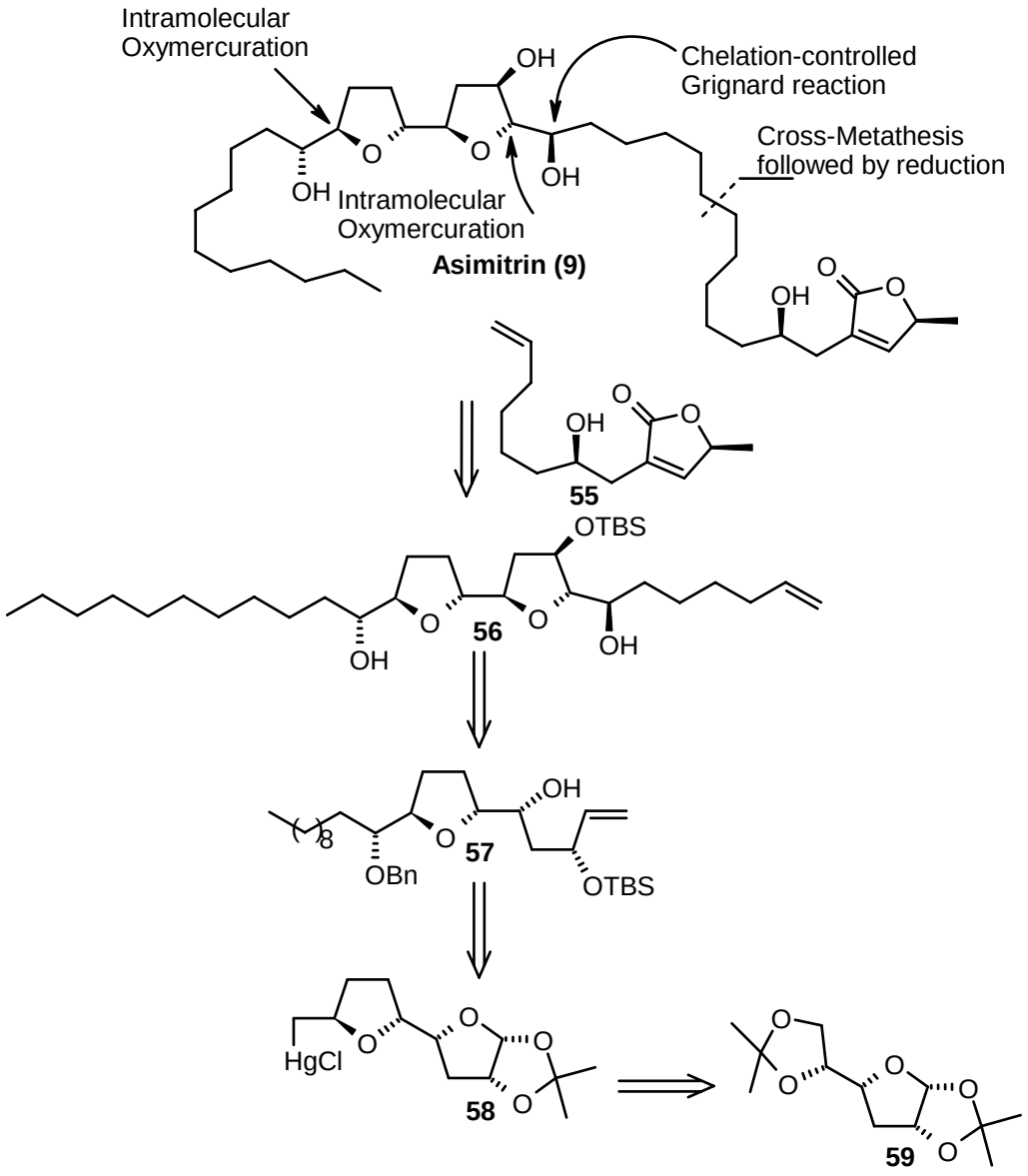
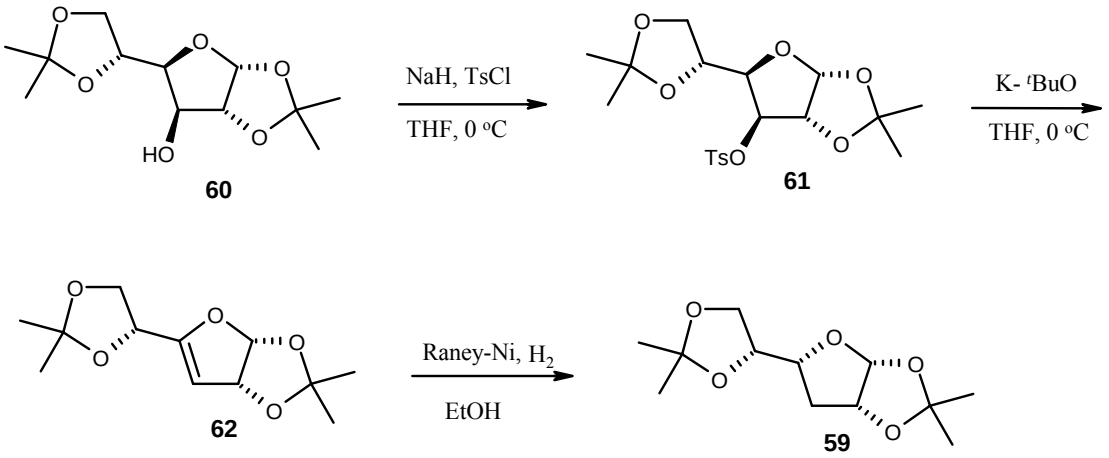


Figure1. Retrosynthetic analysis of (**9**)

Our retrosynthetic strategy towards **9** was based on a convergent approach involving a cross metathesis for coupling the bis-THF core **56** with γ-lactone segment **55**. The bis-THF core would be prepared from 1,2:5,6-di-*O*-isopropylidene-3-deoxy-α-D-xylofuranose **59**, which plays a central role, serving not only as the source of the C17, C19, and C20 stereocenters, but also setting the stage for introducing the C16 and C23 stereocenters through stereoselective intramolecular oxymercuration and chelation–controlled Grignard reactions.

In the beginning of our synthetic approach we planned to synthesize C10-C34 fragment **56** of Asimitrin. According to retrosynthetic analysis our synthetic endeavor commenced from 1,2:5,6-di-*O*-isopropylidene-3-deoxy-α-D-xylofuranose **59**, which was synthesized from commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **60** in a three step synthesis following known literature procedure.[72] Thus, the secondary hydroxyl group of **60** was protected as tosyl ether by using NaH, TsCl in THF at 0 ^{o}C furnished **61** in 90% yield.

Scheme 1



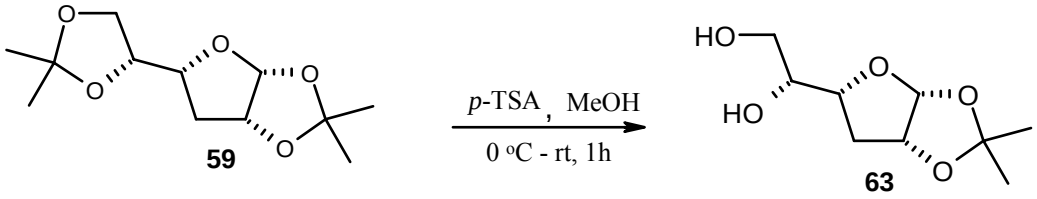
60 **61** **62** **59**

Elimination of tosyl ether was carried out by treatment of potassium *tert*-butoxide, in THF at 0 ^{o}C resulted in 3, 4 alkene **62**. The double bond was reduced by Raney-Ni in ethanol at 60 psi H_2 pressure afforded 3-deoxy xylofuranose **59** in good yield. The ^{1}H, ^{13}C NMR and elemental analysis data of **59** was in good agreement with the reported values (Scheme 1).

Selective cleavage of the 5, 6-isopropylidene group in **59** was accomplished with cat *p*-TSA in MeOH to give 5,6 diol **63**. Structure of **63** was assigned from the relevant chemical shift observed in the ^{1}H NMR spectrum. Dissappearance of 5,6 isopropylidene signals and

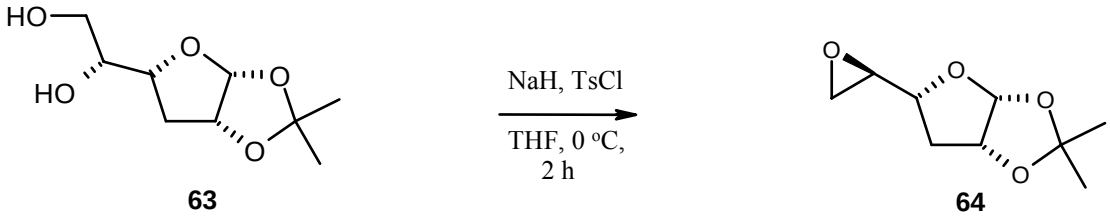
appearance of methine and methylene protons linked to hydroxyl group at δ 3.87(m, 1H), 3.75 (dd, 1H) and 3.55(dd, 1H) ppm indicating the conversion of **59** to **63**.

Scheme 2



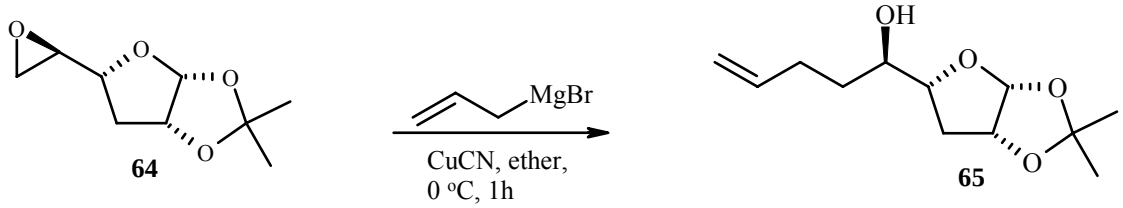
In the ^{13}C NMR spectrum the $-CH_2OH$ carbon was identified at δ 63.2 ppm, which was unambiguously confirmed from DEPT spectrum. IR (3402 cm^{-1}) and elemental analysis data also supported the formation of **63** (Scheme 2).

Scheme 3



The epoxide **64** was generated *in situ* by exposure of 2eq NaH and 1eq TsCl in THF on **63**.[73] The structure of **64** was confirmed by ^1H, ^{13}C, IR and elemental analysis data.In the ^1H NMR spectrum the signal due to methine proton of epoxide was identified at δ 3.35 (m, 1H) ppm whilst the methylene proton was observed at δ 2.81 (t, J = 4.0 Hz, 1H) and 2.58 (dd, J = 2.6, 4.8 Hz, 1H) ppm. In the ^{13}C NMR spectrum the epoxy carbons were resonated at δ 53.5, 44.5 ppm and all other carbons observed at their expected chemical shift. Additionally, IR (1597, 1495 and 1454 cm^{-1}) and elemental analysis data also supported the formation of **64** (Scheme 3).

Scheme 4

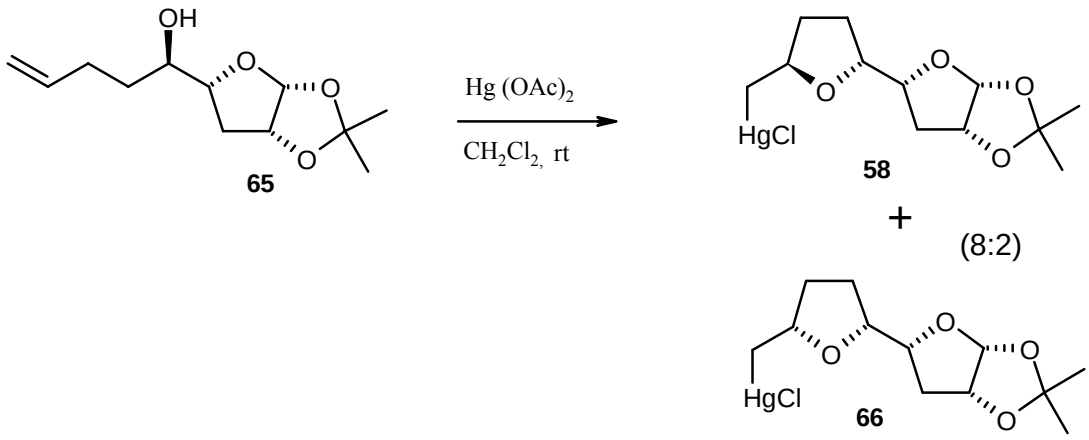


After synthesizing epoxide **64** successfully, we planned to open it regioselectively. Treatment of allylcuprousmagnesiumbromide in ether on epoxide **64** furnished **65** as the single product.[74] In the ^1H NMR spectrum the olefinic methine proton signal was observed

at δ 5.91-5.71 ppm whilst the methylene protons were resonated at δ 5.04-4.87 (m, 2H) ppm. In the ^{13}C NMR spectrum the diagnostic olefinic carbons were identified at δ138.2 and 114.7 ppm. EI mass spectrum showed two peaks at 251 and 267 corresponding to $(M + Na)^+$ and $(M + K)^+$ confirming the structure of **65** (Scheme 4).

Synthesizing suitably substituted olefinic alcohol **65**, we turned our attention towards the diastereoselective synthesis of 5,8 *anti*-tetrahydrofuran ring. The conversion of suitably–posed alkenyl alcohols into diastereoselective tetrahydro-furanyl and pyranyl ethers via mercurium ion of alkenes and subsequent capture by the adventurous nucleophile in an intramolecular fashion has been earmarked as one of the main synthetic strategies in the construction of cyclic, polycyclic and fused ether.[75]We envisaged that the mercurium ion of terminal alkene and *in situ* ring closure by intramolecular oxygen nucleophile would be the ideal approach for our purpose since the resulting chloromercurated methyl tetrahydrofuran can be further elaborated to our required destiny following demercuration reaction.

Scheme 5



Accordingly, **65** was exposed to $Hg(OAc)_2$ in CH_2Cl_2 at room temperature for 2 h, followed by further stirring with aq NaCl for 30 min to provide the monoTHF product **58** and **66** in 8:2 ratio. The isomers were separated by flash silicagel chromatography and characterized by ^1H, ^{13}C NMR and elemental analysis. In the ^1H NMR spectrum of **58** the ring junctioned methine protons of tetrahydro furan ring were appeared at δ 4.40 (m, 1H) and 4.32 (q, J = 7.7 Hz, 1H) ppm. The methylene proton linked to HgCl was noticed at δ 2.39 (1H) and 2.23-2.07 (1H) ppm. In the ^{13}C NMR spectrum 5th and 8th positional carbons

of THF ring resonated at single position and found at δ 80.6 ppm, whilst the CH_2HgCl carbon was observed at δ 38.0 ppm, was further confirmed from DEPT spectrum.

In the ^1H NMR spectrum of **66** the ring junctioned methine proton signals of tetrahydro furan ring were appeared at δ 4.37 and 4.12 ppm integrating one proton each. ^{13}C NMR spectrum showed two signals at δ 81.4 and 80.4 ppm corresponding to ring junctioned carbons of THF ring. The carbon linked to –HgCl was identified at δ 38.5 ppm (Scheme-5).

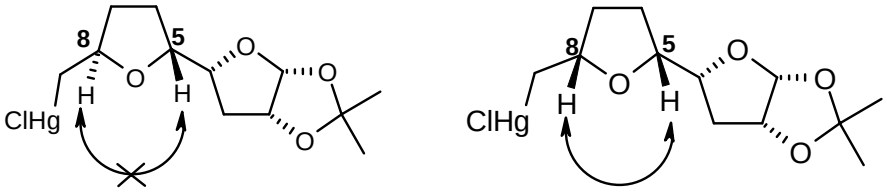
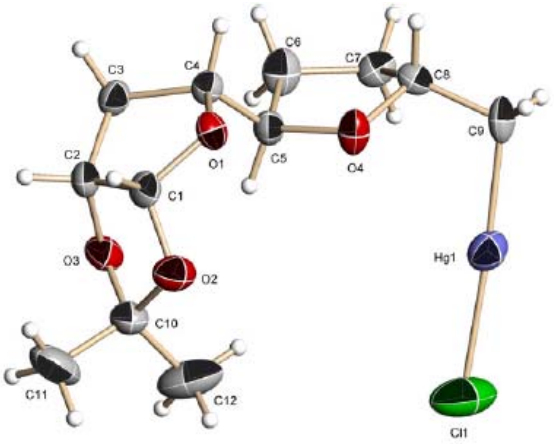


Figure 2 n*O*e study of compound **58** and **66**

The relative stereochemistry around the THF ring of **58** and **66** was assigned by NOESY studies. In the NOESY spectrum of **58**, the 5th positional β-hydrogen wasn't showing any interaction with 8th positional proton indicating there was α-hydrogen, whilst in **66** the 5th positional β-hydrogen was showing strong n*O*e interaction with 8th positional hydrogen indicating there was a β-hydrogen.



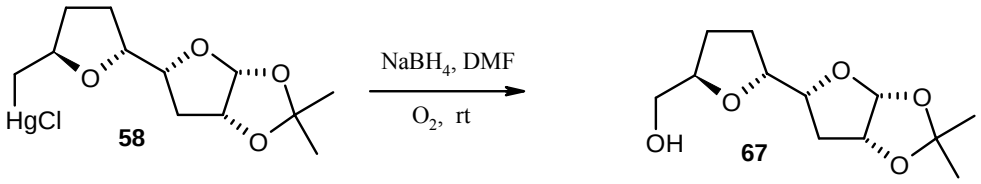
ORTEP diagram of **58**

Further, the relative stereochemistry around the THF ring was unambiguously confirmed by single crystal X-ray crystallographic study.

Assigning *syn* and *anti* stereochemistry of tetrahydrofuran ring, the required chloromercurated compound **58** was demercurated using $NaBH_4$ in DMF at high O_2

pressure resulted in **67** with good yield. The product **67** was confirmed for its structure by the ^{1}H, ^{13}C NMR, IR, EI-MS and elemental analysis data.

Scheme 6

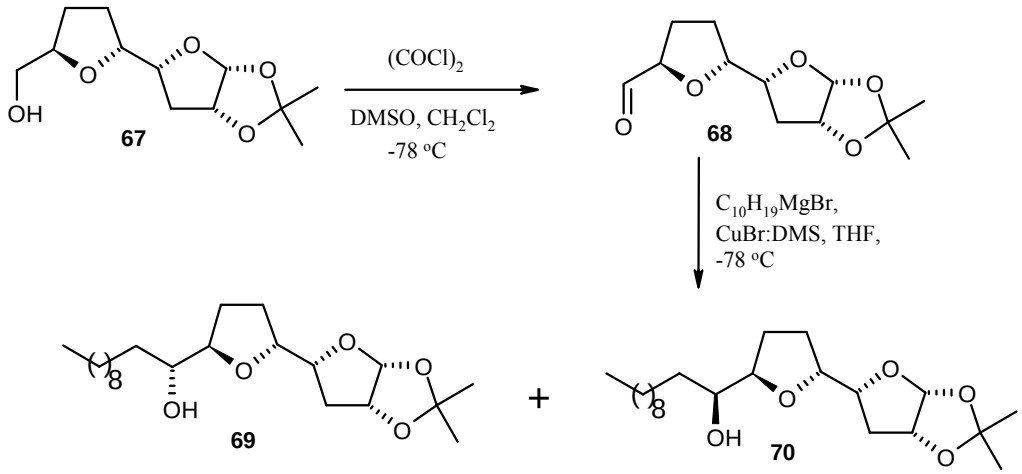


The chemical shift of methylene protons linked to –OH group shifted downfield and appeared at δ 3.71 (m, 1H) and 3.48 (dd, J = 5.1, 11.7 Hz, 1H) ppm. ^{13}C NMR spectrum showed the $–CH_2OH$ carbon at δ 64.3 ppm, which was further confirmed by DEPT spectrum. In the IR spectrum, one broad peak at 3384 cm^{-1} characteristic of hydroxyl group was observed. The EI-MS spectrum two ion peaks at 267 and 283 appeared corresponding to $(M+Na)^{+}$ and $(M + K)^{+}$ ion (Scheme 6).

Getting primary alcohol **67** in hand we planned to carry out oxidation and grignard reaction to incorporate ten carbon chain.

Thus, the primary hydroxyl group of **67** was oxidized employing swern oxidation condition furnished aldehyde **68**, which on subsequent treatment with decylmagnesiumbromide and CuBr.DMS in Et_2O at -78 ^{o}C resulted in **69** and **70** with 7:3 ratio.[76]

Scheme 7



Both the diastereomers were were separated by flash silicagel chromatography and thoroughly characterized by ^{1}H, ^{13}C, IR, EImass spectrum. In the ^{1}H NMR spectrum of **69**

the aldehydic proton signal was absent and the terminal methyl proton of decyl chain was observed at δ 0.90 ppm as a triplet integrating to three protons and at δ 1.27 ppm a singlet observed integrating for 18H. In addition, DEPT spectrum showed the twelve $-CH_2$ carbons signals at δ 33.9 to 14.0 ppm indicating incorporation of decyl chain. Similarly in the ^{1}H NMR spectrum of **70** the terminal methyl proton of decyl chain was observed at δ 0.84 ppm. IR, Mass and Elemental analysis data also supported the formation of **69** and **70** (Scheme 7). The newly generated stereocentre at C9-OH in **69** was confirmed by modified Mosher ester analysis of derived MTPA esters.[77]

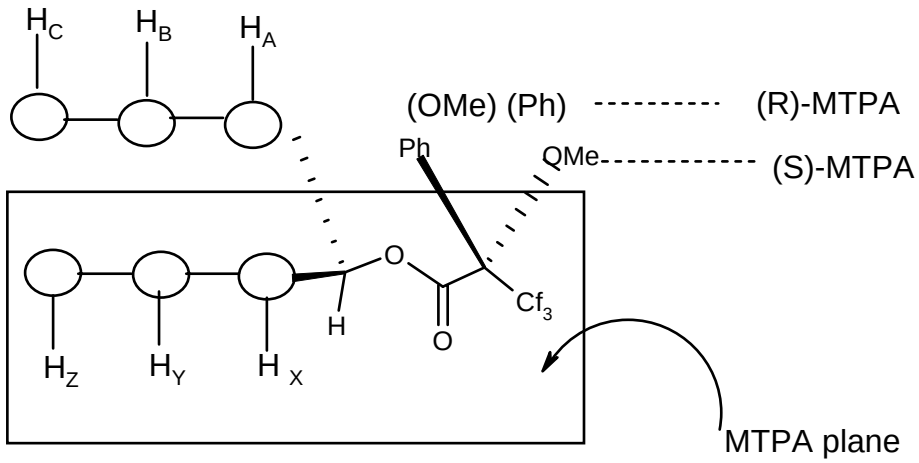
Modified Mosher's ester method: Application for stereochemical assignment of C_9-OH of (69)

Determination of the absolute stereochemistry of organic compounds has become an important aspect for natural product chemistry.The limitations involved in physical methods such as *Exciton* chirality method and X-ray crystallography method forced synthetic chemists to look for a more reliable alternative.Although there are several chemical methods used to predict the absolute configuration of organic substances, Mosher's method using 2-methoxy-2-phenyl-2-(trifluoromethyl) acetic acid (MTPA) esters has been used most frequently. Mosher proposed that, in solution, the β C-H bond, ester carbonyl, and trifluoromethyl group of the MTPA derivative lie in the same plane (Figure 3).When the MTPA group is in the hypothesized conformation, Mosher pointed out that the ^{1}H NMR signal of L_2 of the (*R*)-MTPA ester will appear upfield relative to that of the (*S*)-MTPA ester due to the diamagnetic effect of the benzene ring. The lack of reliability associated with Mosher's ^{19}F method using ^{19}F NMR motivated Kakisawa *et al*.to elaborate this concept for more accuracy. The modified Mosher's ester method is one of the simple and efficient methods to determine the absolute stereochemistry of the secondary alcohols.

The basic concept of the modified Mosher's ester method is essentially the same as Mosher proposed. The idealized conformation is depicted in Figure 3 . The plane with the hypothesized conformation of MTPA group is as the MTPA plane with ideal conformation.Due to the diamagnetic effect of the benzene ring, the H_A, H_B, H_C…signals of (*R*)-MTPA ester in the ^{1}H NMR spectrum should appear upfield to those of the (*S*)-MTPA ester. The reverse should hold true for protons, H_X, H_Y, H_Z……Hence, when $\Delta\delta$ =

(ΔS – ΔR)x1000 protons on the right side of the MTPA plane must have positive values (Δδ >0), and the protons on the left side of the MTPA plane must have negative values (Δδ < 0) as illustrated in simpler model A (Figure 3).

Figure 3 MTPA plane of a MTPA ester



Thus, modified Mosher's method can be used following the 4 steps:

(i) Assign as many proton signal as possible with respect to each of the (*R*)-and (*S*) –MTPA esters

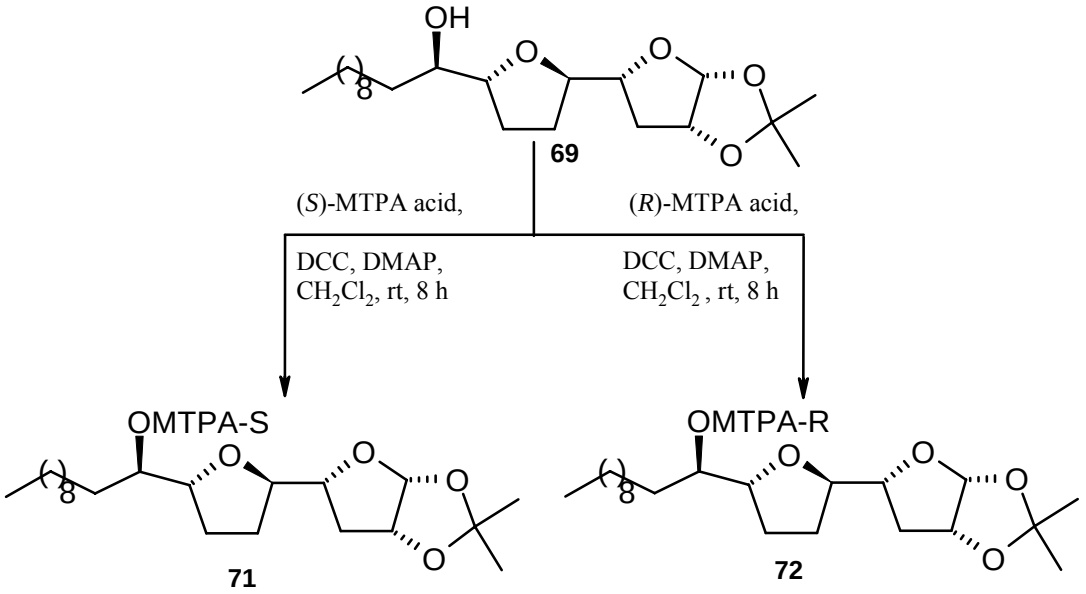
(ii) Obtain Δδ values for the protons

(iii) Arrange the protons with positive Δδ values right side and those with negative Δδ values on the left side of the model

(iv) Construct a molecular model of the compound in question and confirm that all the assigned protons with positive and negative Δδ values are actually found on the right and left sides of the MTPA plane respectively.

In order to assign the absolute stereochemistry of C9-OH in **69**, the *S*-MTPA ester**71** and *R*-MTPA ester **72** were independently prepared from **69** by using corresponding *S*-MTPA acid and *R*-MTPA acid in presence of coupling agent DCC and DMAP (cat) in anhydrous CH_2Cl_2 at room temperature (Scheme 8).

Scheme 8



The Δδ = (ΔS- ΔR) x 1000values were calculated for as many protons as possible from the ^{1}H NMR spectrum of *S*-MTPA ester **71** and *R*-MTPA ester **72** (Table-1) The Δδ = (ΔS - ΔR) x 1000 values were arranged as shown in Table-1. On the basis of the model, (Figure 3) we have assigned the absolute stereochemistry at C-9 of **69** with *R* configuration

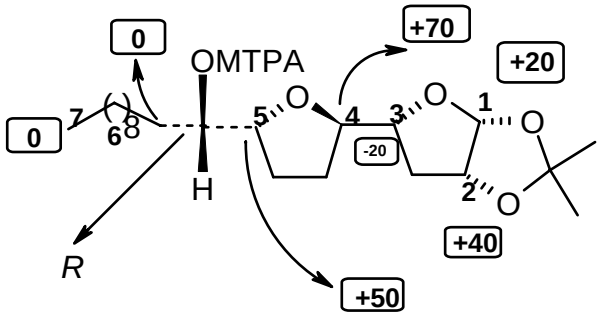


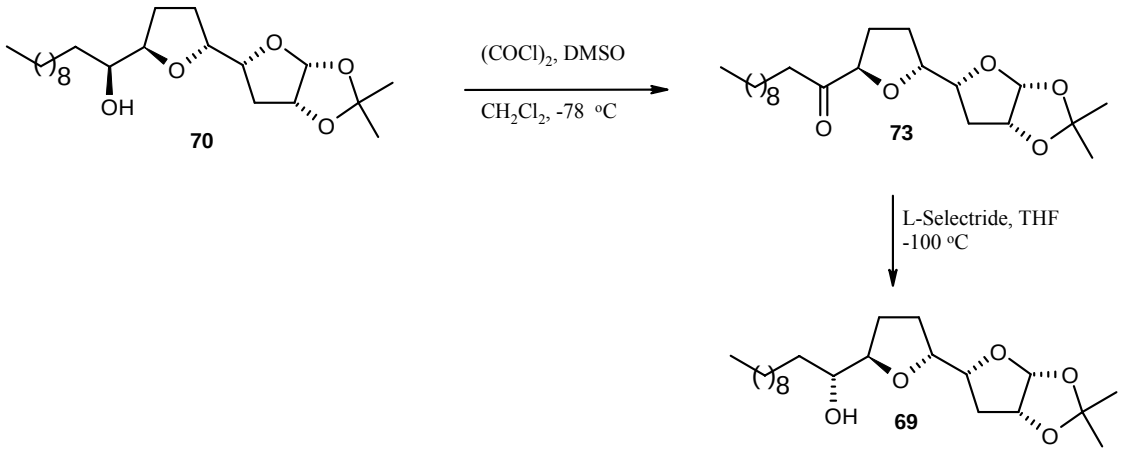
Figure 4

Table-1

Protons	1	2	3	4	5	6	7
Δs	5.73	5.26	4.72	4.11	3.90	1.25	0.88
ΔR	5.71	5.22	4.70	4.04	3.85	1.25	0.88
Δδ	+20	+40	+20	+70	+50	0	0

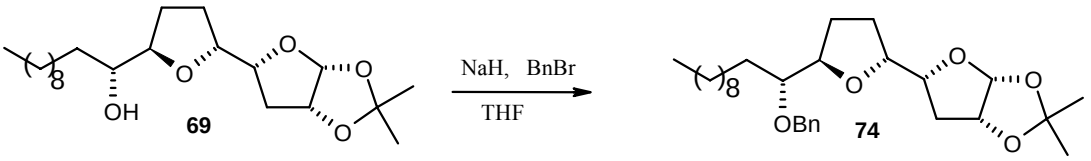
After assigning stereochemistry at C-9, we planned to convert the minor product **70** into our required isomer **69**. Accordingly we oxidised **70** following Swern oxidation condition to give keto compound**73**, which was reduced by L-Selectride[78] at -100 ^{o}C furnished **69** and **70** in **9**:**1** ratio (Scheme 9).

Scheme 9



The secondary hydroxyl group of **69** was protected as benzylether, as it could withstand in the isopropylidine cleavage condition. Thus **69** was subjected with NaH, BnBr in THF at 0 ^{o}C resulted in **74**.

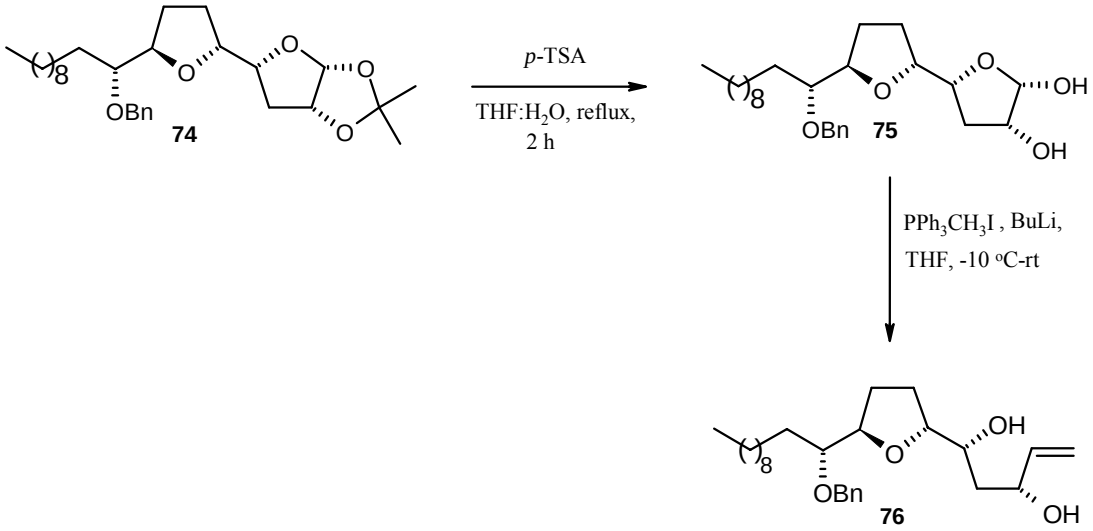
Scheme 10



In the ^{1}H NMR spectrum two new signals observed at δ 7.36-7.22 and 4.79-4.56 ppm integrating five and two protons indicating the formation of benzyl ether.^{13}C NMR spectrum showed the signals at δ139.4, 128.1, 127.6, 127.2 and 73.3 ppm confirmed the formation of **74**. In addition IR, mass and elemental analysis data also supported the formation of **74** (Scheme 10).

Now the stage is set for making second tetrahydrofuran ring. Thus 1,2 isopropylidene of **74** was cleaved by treatment of cat *p*-TSA, THF:H_2O (7:3) in refluxing condition for 1 h afforded diol **75** in good yield (Scheme 11).

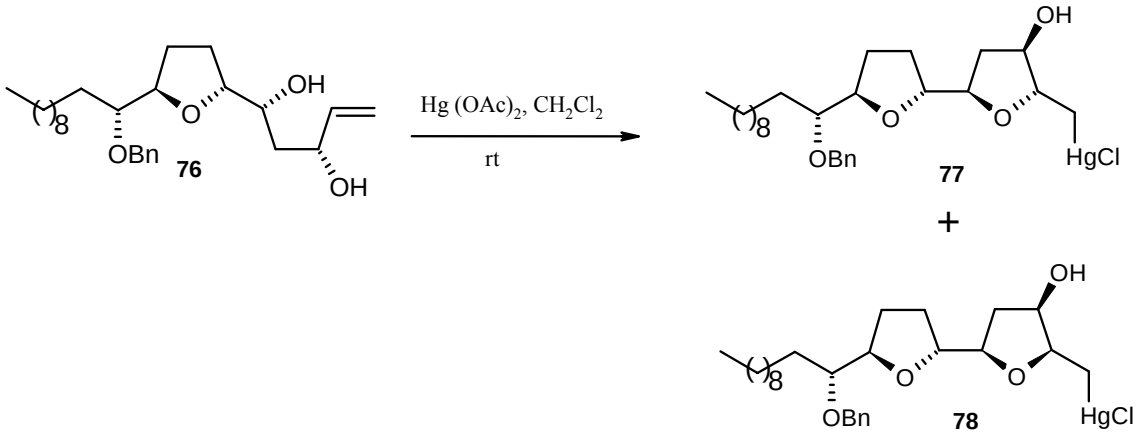
Scheme 11



In the ^{1}H NMR spectrum of **75** the signal for isopropylidene group was disappeared indicating the formation of hemiacetal. The acetal **75** was subjected to one carbon wittig olefination at -10 ^{o}C to room temperature furnished **76**.[79] The structure of **76** was assigned by ^{1}H, ^{13}C, IR and EI spectrum.The olefinic proton signals were observed at δ 5.91 (m, 1H) and 5.35-5.09 (m, 2H) ppm. In the ^{13}C NMR spectrum the olefinic –CH carbon was resonated at δ 138.9 ppm whilst the methylene carbon was observed at δ 114.1 ppm. IR, mass and elemental analysis data also assisted the formation of **76** (Scheme 11).

The next phase of endeavour was chelation controlled intramolecular oxymercuration reaction of α, γ-dihydroxy alkene **76**. Here we can generate the second stereogenic center via diastereoselective substrate bias, taking advantage of α-hydroxyl group.The mercuration reaction was performed with $Hg(OAc)_2$, CH_2Cl_2 resulted in the formation of chloromercurated bis-tetrahydrofuran ring **77** and **78** in 8:2 ratio (scheme-12). Both the diastereomers were separated by flash silicagel chromatography and structural identity was secured from the interpretation of ^{1}H, ^{13}C NMR, IR and EI-MS spectral data. In the ^{1}H NMR spectrum of **77** the olefinic signals were dissappeared and two new signals observed at δ 2.16 (dd) and 2.05-1.93 (m) ppm consisting methylenechlomercurated protons. The carbon linked to –HgCl appeared at δ 38.4 ppm.

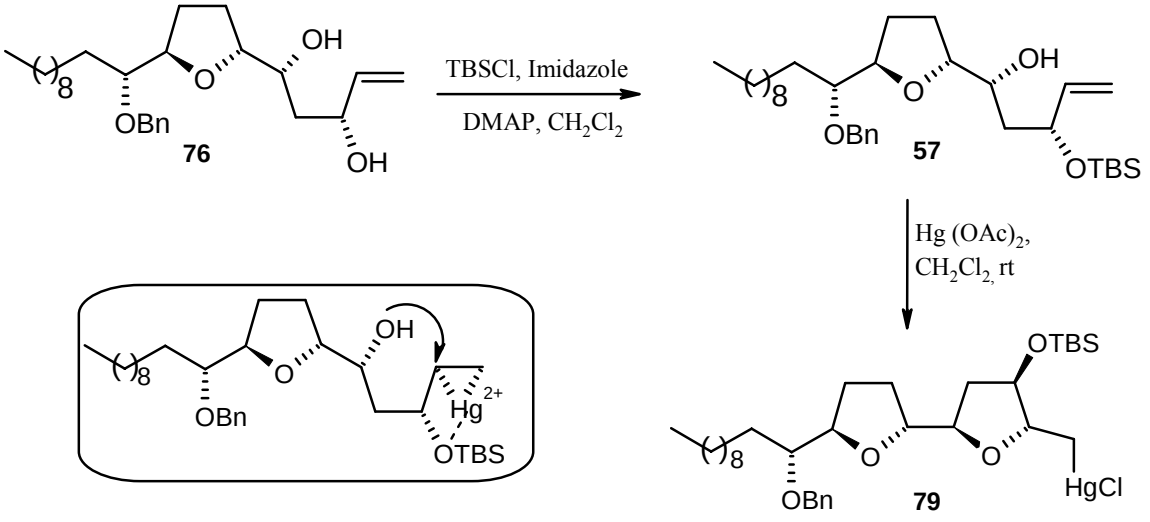
Scheme 12



In the ^{1}H NMR spectrum of **78** the methylene protons linked to –HgCl was resonated at δ 2.13 (m, 1H) and 2.05-1.87 (m, 1H) ppm, whilest the carbon linked to –HgCl was identified at δ 37.0 ppm in the ^{13}C NMR spectrum. MASS spectrometric data also supported the formation of **77** and **78** (Scheme 12).

As the α-hydroxyl chelated oxymercuration reaction didn't give exclusive desired product, we planned to protect the α-hydroxyl group as TBS ether and then carrying out oxymercuration to get the desired diastereomer exclusively.

Scheme 13



Thus, vinylic alcohol was selectively protected as TBS-ether **57** by the treatment of TBSCl, imidazole and cat DMAP in CH_2Cl_2 at ambient temperature. Appearance of three new singlet at δ 0.91, 0.10 and 0.05 ppm integrating to nine, three and three protons assigned to TBS group. Intramolecular oxymercuration reaction of **57** was accomplished

on treatment with $Hg(OAc)_2$ in CH_2Cl_2 to afford single diastereomer **79** in excellent yield. The product was confirmed by the relevant signals in the ^1H, ^{13}C NMR spectrum. and the relative stereochemistry around the second THF ring was assigned by NOESY studies, where the H_2 proton wasn't showing any n*O*e interaction with H-5 proton indicating *anti* relationship (Scheme 13).

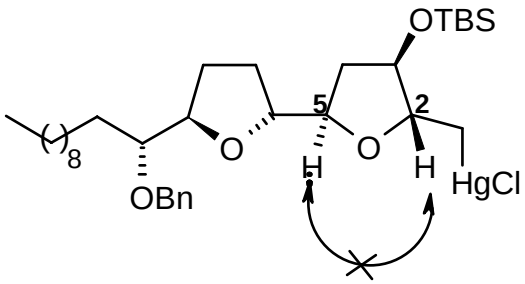
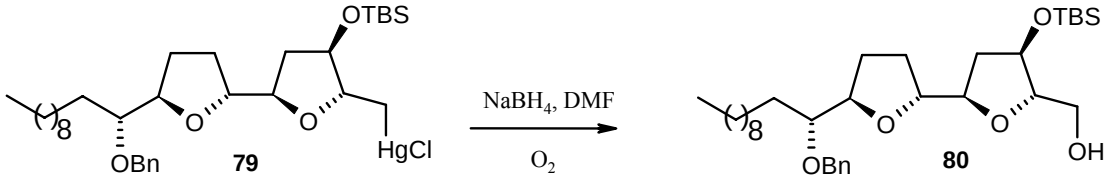


Figure 5. n*O*e study of compound **79**

Demercuration of **79** was conveniently accomplished with $NaBH_4$ in DMF at high O_2 pressure to obtain bis-tetrahydrofuran methylalcohol **80**. Compound **80** was characterized by ^1H, ^{13}C NMR and elemental analysis (Scheme 14).

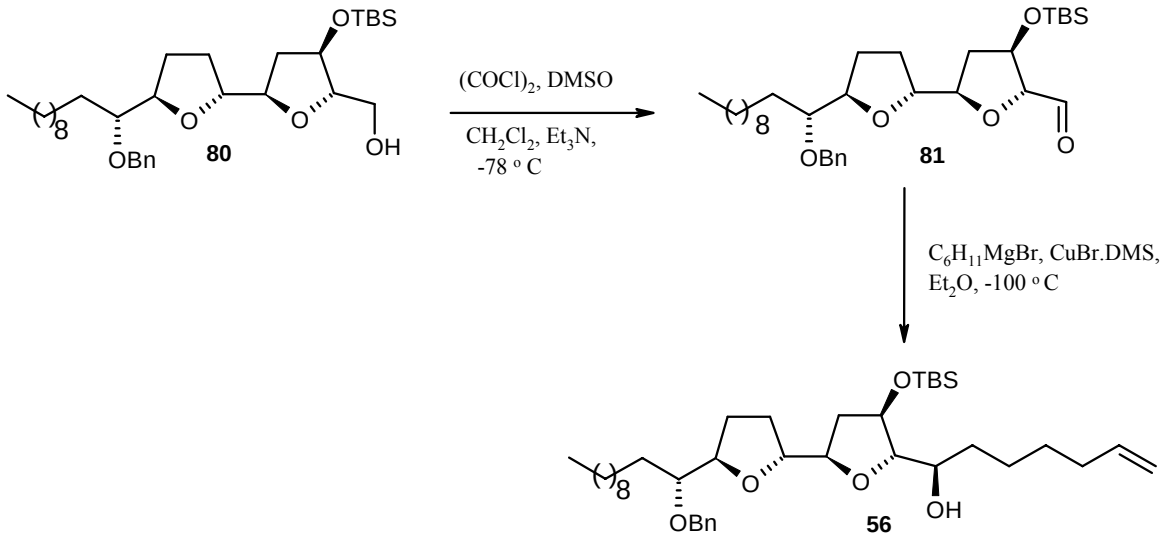
Scheme 14



The methylene protons linked to –OH group was resonated at δ 4.17-3.91 ppm and the same carbon was observed at δ 62.7 ppm in ^{13}C NMR spectrum, which was further confirmed from DEPT spectrum. IR and elemental analysis data also supported the conversion of **79** to **80**.

Having compound **80** in hand, we were very nearer to achieve our targeted compound **2**, which can be made by two step synthesis following Swern oxidation and Cu^{2+}mediated grignard reaction. Accordingly, primary hydroxyl group was subjected to $(COCl)_2$, DMSO in CH_2Cl_2 at -78 ^oC furnished aldehyde **81,** which on subsequent Grignard reaction with hexenylmagnesiumbromide in presence of catalytic CuBr.DMS in Et_2O at –100 ^oC to give single isomer **56** with good yield. The exclusive formation of **56** was expected due to chelation controlled grignard reaction (Scheme 15).[80, 81]

Scheme 15



The salient features of structure **56** was clearly corborated from the spectral data in ^{1}H, ^{13}C NMR, IR and EI-MS.

The olefinic protons were resonated at δ 5.79 (m, 1H), 4.97 (m, 1H) and 4.90 (m, 1H) ppm. ^{13}C NMR spectrum showed the olefinic carbons at δ 139.0 and 114.2 ppm and DEPT spectrum showed the presence of twelve $-CH_2$ carbons. In addition the mass spectrum also confirmed the assigned structure of **56**.

The absolute stereochemistry of the newly generated stereogenic centre was assigned by modified Mosher's ester method. The alcohol functionality in **56** was independently coupled with *R* and *S* Mosher's acid using DCC, cat DMAP in anhydrous DCM to afford the respective Mosher esters **82** and **83** in 80%yields.^{1}H NMR spectrum was recorded for the esters **82** and **83** and all possible protons were assigned. The difference $\Delta\delta = (\delta S - \delta R) \times 1000$ was calculated, and it was found that the molecule exactly fits into the Mosher's model satisfying all the conditions (Scheme 16).

Scheme 16

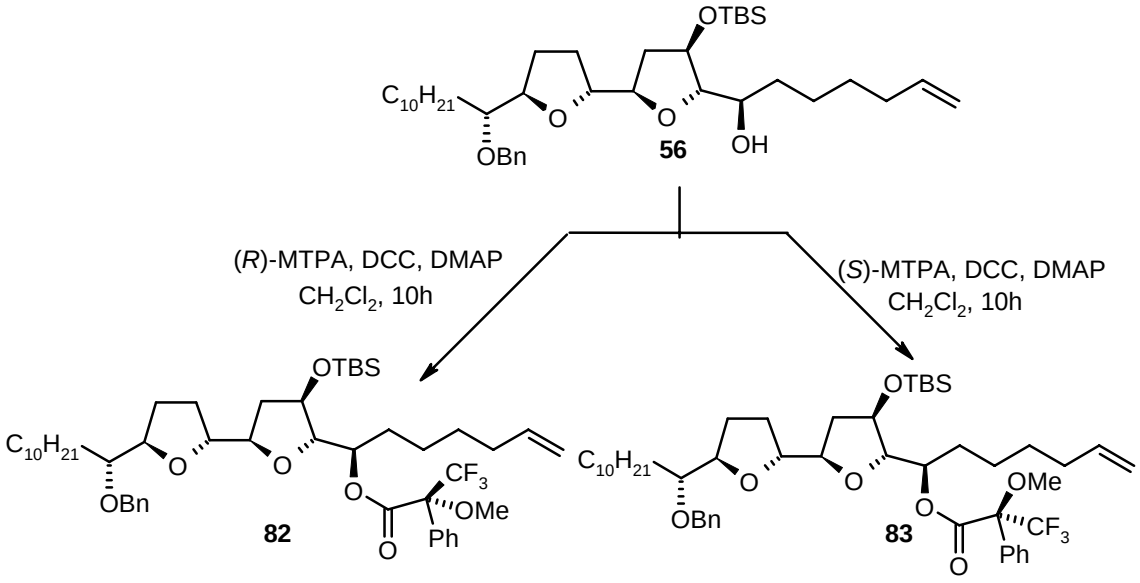
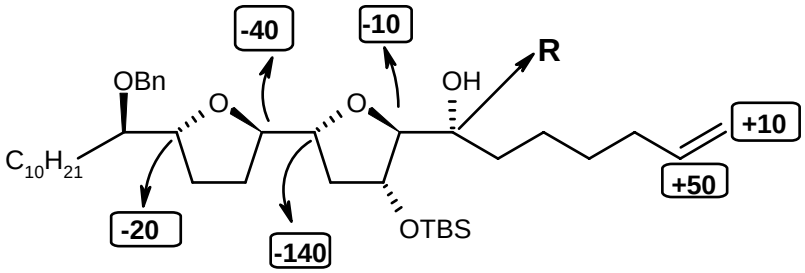


Table-2

Proton	1	2	3	5	6	7
S-MTPA	4.95	5.76	3.82	5.29	4.32	3.98
R-MTPA	4.94	5.71	3.83	5.43	4.36	3.96
Δδ x 1000	+10	+50	-10	-140	-40	-20

From the Mosher's model, the absolute stereochemistry of the hydroxyl centre was found to be (*R*).

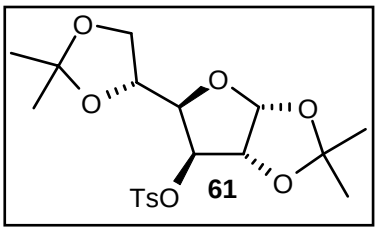


Summary:

Commercially available 1,2:5,6-di-*O*-isopropylidene-3-deoxy-α-D-xylosefuranose was elaborated via a double stereoselective intramolecular oxymercuration reaction sequence developed in our laboratories, to the C10–C34 fragment of Asimitrin in a simple and efficient stereocontrolled manner. Total synthesis of the target molecule is going on in our laboratory.

EXPERIMENTAL

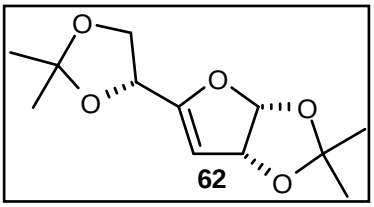
1,2,5,6-di-*O*- isopropylidene-3-tosyl-α-D-*gluco*-furanose (61)



To a suspension of NaH (3.6 g, 60%) in THF (150mL) was added 1,2-5,6-di-*O*-isopropylidene-α-D-glucofuranose **60** (20 g, 0.076mol) at 0 ^{o}C and stirred for 30 min then tosyl chloride (17.5 g, 0.092mol) in THF (100mL) was added to it over a period of 30 min and stirred for another 30 min. Reaction mixture was quenched by slow addition of water, the organic layer was separated and the aqueous layer was extracted with ethylacetate (3 x 100mL). The combined organic layer were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silicagel column chromatography (25% EtOAc/light petroleum) to afford **61** (28.6g) as a solid.

Yield	90%
Mol.Formula	$C_{19}H_{26}O_8S$
$[\alpha]_D^{25}$	+28.8 (c 1.3, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	3389, 2990, 1598 cm^{-1}
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 7.83 (d, *J* = 7.5Hz, 2H), 7.34(d, *J* = 8.2 Hz, 2H), 5.91(d, *J* = 3.5Hz, 1H), 4.82(d, *J* = 3.5Hz, 1H), 4.05-3.97(m, 3H), 3.90 (dd, *J* =3.7, 9.0Hz, 1H), 2.15(s, 3H), 1.47(s, 3H), 1.31(s, 3H), 1.20(s, 3H), 1.15 (s, 3H)
^{13}C NMR ($CDCl_3$, 50MHz)	144.8, 132.4, 129.4, 128.1, 112.1, 108.7, 104.8, 83.0, 81.7, 79.6, 71.5, 66.7, 26.2, 25.8, 24.5, 21.2
Elemental Analysis	**Calcd:** C,55.06; H, 6.32 **Found:** C,55.32; H, 6.54

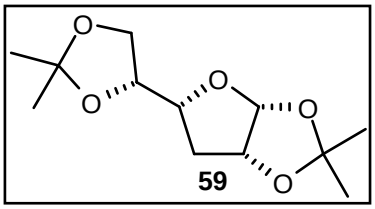
1,2,5,6-di-*O*- isopropylidene-3-deoxy-α-D- erythro-hex-3-enofuranose (62)



To the solution of compound **61** (10g, 0.024mol) in THF (300 mL) at 0 ^{o}C, K-*tert*-butoxide (3.2g, 0.028 mol) was added portion wise in 1h and further stirred for another 1h. Then reaction mixture was quenched with water and the organic layer was separated and the aqueous layer was extracted with hexane (3 x 100 mL), combined organic layers were washed with 5%H_2SO_4, saturated $NaHCO_3$, and saturated NaCl and then dried. Purification of the residue by 10 % EtOAc/light petroleum to give **62** (4.8 g) as a white solid (mp 48-50 ^{o}C).

Yield	84%
Mol. Formula	$C_{12}H_{18}O_5$
$[\alpha]_D^{25}$	+25.4 (c 1.5, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 200 MHz)	δ ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.00 (d, *J* = 5.1 Hz, 1H), 5.23 (m, 1H), 5.17(dd, *J* = 1.1, 2.4 Hz, 1H), 4.51(m, 1H), 4.07 (dd, *J* = 6.7, 8.3 Hz, 1H), 3.89(dd, J = 5.8, 8.3 Hz, 1H), 1.40 (s, 6H), 138 (s, 3H), 1.32(s, 3H)
Elemental Analysis	**Calcd:** C,59.49; H,7.49 **Found:** C, 59.63 ; H,7.49

Compound 59

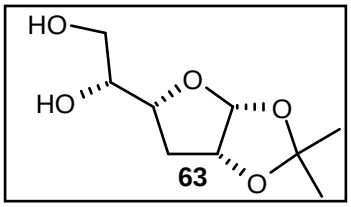


59

The olefinic compound **62** (5.0g) in ethanol (60 mL) was exposed to raney Ni (1g) in 60 psi hydrogen pressure for 12 h. Reaction mixture was filtered over a celite bed and the filtrate was concentrated and purified by silica gel chromatography resulted in **59** (4.5g) as a solid.

Yield	90%
Mol.Formula	$C_{12}H_{20}O_5$
$[\alpha]_D^{25}$	-28.39 (c 0.9,CH_2Cl_2)
IR ($CHCl_3$) cm^{-1}	3360, 2989, 1655 cm^{-1}
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 5.80 (d, *J* = 3.7 Hz, 1H), 4.73 (m, 1H), 4.43(m, 1H), 4.16-4.01(m, 2H), 3.61 (dd, *J* = 6.8, 8.2 Hz, 1H), 2.21(ddd, *J* = 6.1, 8.3,14.2 Hz, 1H), 1.82 (ddd, *J* = 1.0, 3.9,14.2 Hz, 1H), 157 (s, 3H), 1.45 (s, 3H), 1.37(s, 3H), 1.33(s, 3H).
^{13}C NMR ($CDCl_3$, 50MHz)	112.7, 109.8, 106.4, 81.4, 80.4, 77.5, 66.0, 33.5, 27.2, 26.6, 26.2, 25.2
Elemental Analysis	**Calcd:** C,59.0; H, 8.25
	Found: C,59.34; H, 8.10

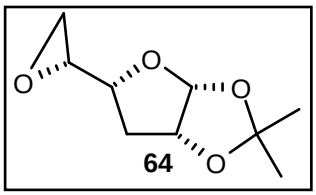
Compound 63



Compound **59** (7.0 g, mmol) was dissolved in MeOH (mL) and catalytic *p*-TSA(10mg) was added and stirred in 0 ^{o}C for 1h then quenched by Et_3N (1 mL). The reaction mixture was concentrated and purified by silica gel chromatography (60% Ethylacetate/light petroleum) provided diol compound **63** (5.3 g) as a syrup.

Yield	84%
Mol.Formula	$C_9H_{16}O_5$
$[\alpha]_D^{25}$	-22.3 (c 1, CH_2Cl_2)
IR ($CHCl_3$) cm^{-1}	3402 cm^{-1}
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 5.81 (d, *J* = 4.0 Hz, 1H), 4.77 (m, 1H), 4.23 (m, 1H), 3.87 (m, 1H), 3.75 (dd, *J* = 3.2, 11.7 Hz, 1H), 3.55 (dd, *J* = 4.6, 11.7Hz, 1H), 1.01 (brs, 1H), 2.40 (brs, 1H), 2.23 (ddd, *J* = 6.0, 8.2, 14.2 Hz, 1H), 2.10-2.01(m, 1H), 1.55 (s, 3H), 1.32 (s, 3H)
^{13}C NMR ($CDCl_3$, 50MHz)	112.4, 106.1, 81.1, 80.6, 72.9, 63.2, 33.4, 26.8, 25.8
Elemental Analysis	**Calcd:** C, 52.93; H, 7.90
	Found: C, 52.78; H, 7.67

5,6-Anhydro-3-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose (64)

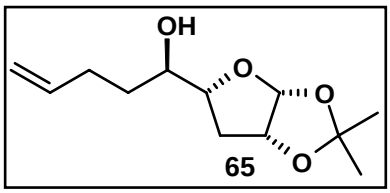


To a slurry of NaH (15.6 g, 392.1 mmol) in THF (200 mL) was added 3-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranoside **63** (40.0 g, 196.0 mmol) in THF (100

mL) at 0 °C. After 15 min, tosyl chloride (37.2 g, 196.0 mmol) in THF (100 mL) was added and stirred at 0 °C. After completion of reaction, checked by TLC, reaction mixture was quenched by slow addition of water. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silicagel column chromatography (15% EtOAc/light petroleum) to afford epoxide **64** (29.0 g, 80%) as a colorless liquid. R_f = 0.4 (30% Ethylacetate/light petroleum)

Yield	90%
Mol. Formula	$C_9H_{14}O_4$
$[\alpha]_D^{25}$	-37.7 (*c* 1.0, CH_2Cl_2)
IR ($CHCl_3$) cm^{-1}	1597, 1495, 1454cm^{-1}
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 5.83 (d, *J* = 3.7 Hz, 1H), 4.75(ddd, *J* = 1.2, 3.7, 5.3 Hz, 1H), 3.82 (ddd, *J* = 3.0, 7.3, 10.3 Hz, 1H), 3.35 (m, 1H), 2.81 (t, *J* = 4.0 Hz, 1H), 2.58 (dd, *J* = 2.6, 4.8 Hz, 1H), 2.22 (dd, *J* = 5.6, 8.5 Hz, 1H), 2.14 (m, 1H), 1.57 (s, 3H), 1.34 (s, 3H)
^{13}C NMR ($CDCl_3$, 50MHz)	112.3, 106.7, 82.3, 80.3, 53.5, 44.5, 34.0, 27.0, 25.9
Elemental Analysis	**Calcd:** C, 58.06; H, 7.58
	Found: C, 58.32; H, 7.74

3-Deoxy-1,2-*O*-isopropylidene-6,7,8,9- tetradeoxy-α-D-*xylo*-non-8-enofuranose (65)



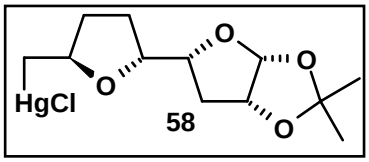
A solution of allyl bromide (26.4 mL, 311.8 mmol) in ether (50 mL) was added dropwise to a mixture of magnesium (14.9 g, 639.2 mmol) and iodine (catalytic amount) in ether (100 mL) and stirred for 30 min at room temperature. Cuprous cyanide (1.3 g, 15.5 mmol) was added at once, resulting in immediate colour change to a dark

brown color. After cooling to –20 ^{o}C, epoxide **64** (29.0 g, 155.9 mmol) in ether (100 mL) was added dropwise. The reaction mixture was stirred for 30 min at –20 ^{o}C, quenched by slow addition of saturated NH_4Cl solution and the resulting suspension stirred for another 30 min. Inorganic solid materials were filtered off and washed with ether. Organic layer was seperated and the aqueous layer extracted with ethylacetate (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude brown colored oily material was purified by flash column chromatography (10% Ethylacetate-light petroleum) to afford homoallylic alcohol **65** as a colorless liquid (28.9 g).

Yield	81%
Mol.Formula	$C_{12}H_{20}O_4$
$[\alpha]_D^{25}$	–2.02 (*c* 1.3, CH_2Cl_2)
IR ($CHCl_3$) cm^{-1}	3488, 2986, 2940, 1640, 1598 cm^{-1}
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 5.91–5.71 (m, 2H), 5.04–4.87 (m, 2H), 4.69 (ddd, *J* = 1.3, 4.0, 6.0 Hz, 1H), 3.89 (dt, *J* = 3.0, 8.2 Hz, 1H), 3.71 (dt, *J* = 4.0, 8.2 Hz, 1H), 2.69 (br s, 1H), 2.30–1.60 (m, 6H), 1.47 (s, 3H), 1.24 (s, 3H)
^{13}C NMR ($CDCl_3$, 50MHz)	138.2, 114.7, 112.3, 106.1, 84.6, 80.7, 71.9, 33.5, 32.4, 29.7, 26.8, 25.9
Elemental Analysis	**Calcd:** C, 63.15; H, 8.70 **Found:** C, 63.34; H, 8.58.

To a solution of homoallylic alcohol **65** (25.0 g, 109.6 mmol) in CH_2Cl_2 (200 mL), $Hg(OAc)_2$ (26.1 g, 153.5 mmol) was added at room temperature. After 2h stirring, reaction mixture was quenched with brine solution (25 mL) and stirred for 30 min. Organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 x 100 mL). Combined organic layers were dried over Na_2SO_4 and concentrated. Purification of the crude compound by flash silica gel column chromatography (20% Ethylacetate/light petroleum) provided the chloromercurated compound **58** as a major diastereomer (32.6 g) and further elution afforded the minor cis-isomer **66** (8g) in 84%yield

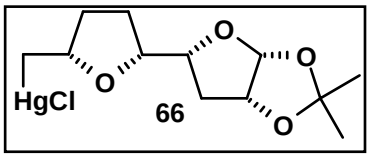
5,8-Anhydro-3,6,7,9-tetradeoxy-9-chloromercuryl-1,2-*O*-isopropylidene-D-glycero-α-D-*xylo*-nonanofuranose (58)



R_f = 0.4 (60% Ethylacetate-light petroleum)

Mol.Formula	$C_{12}H_{19}O_4HgCl$
$[\alpha]_D^{25}$	-16.5 (*c* 0.6, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 5.75 (d, *J* = 3.91 Hz, 1H), 4.71 (m, 1H), 4.40 (m, 1H), 4.32 (q, *J* = 7.7 Hz, 1H), 3.95 (m, 1H), 2.39 (dd, *J* = 5.5, 12.0 Hz, 1H), 2.23-2.07 (m, 5H), 1.88 (m, 1H), 1.71 (s, 1H), 1.56 (s, 3H), 1.32 (s, 3H)
^{13}C NMR ($CDCl_3$, 50MHz)	112.8, 106.2, 82.5, 80.6, 77.8, 38.0, 36.6, 33.6, 29.1, 27.6, 26.5
Elemental Analysis	**Calcd:** C, 31.16; H, 4.11
	Found: C, 31.38; H, 4.25

Compound-66



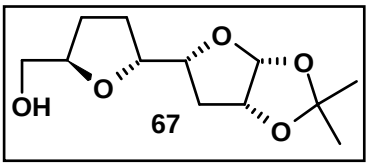
R_f = 0.45 (60% Ethylacetate-light petroleum)

Mol.Formula	$C_{12}H_{19}O_4HgCl$
$[\alpha]_D^{25}$	-27.13 (*c* 0.9, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 5.77 (d, *J* = 4.0 Hz, 1H), 4.70 (m, 1H), 4.37 (m, 1H), 4.12 (q, *J* = 7.5 Hz, 1H), 3.98 (m, 1H), 2.39 (m, 1H), 2.25-2.06 (m, 4H), 1.98 (m, 1H), 1.86 (dd, *J* = 4.7,

14.3 Hz, 1H), 1.62 (m, 1H), 1.55 (s, 3H), 1.31 (s, 3H)

^{13}C NMR ($CDCl_3$, 50MHz)	112.6, 106.3, 83.0, 81.4, 80.4, 78.5, 38.5, 34.8, 34.0, 28.2, 27.4, 26.3
Elemental Analysis	**Calcd:** C, 31.16; H, 4.11
	Found: C, 31.38; H, 4.25

5,8-Anhydro-3,6,7-trideoxy- 1,2-*O*-isopropylidene-D-glycero-α-D-*xylo*-nonanofuranose (67)



To a stirred solution of compound **58** (32.0 g, 69.2 mmol) in DMF (492mL), O_2 was bubbled through a long syringe needle for 10 min. In an another flask, a suspension of $NaBH_4$ (3.4 g, 90.0 mmol) in DMF (275mL) was prepared and O_2 was passed for 20 min, to it the reaction mixture was added dropwise via cannula in 3 h. Reaction mixture was diluted with ethylacetate, filtered and concentrated. DMF was removed under reduced pressure and the crude brown colored oily material was purified by silica gel column chromatography (80% Ethylacetate/lightpetroleum) to afford primary alcohol **67** (14.4 g, 86 %) as a colorless liquid .

Mol.Formula	$C_{12}H_{20}O_5$
$[\alpha]_D^{25}$	- 42.98 (*c* 0.6, CH_2Cl_2)
IR ($CHCl_3$) cm^{-1}	3384, 3019 cm^{-1}
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 5.78 (d, *J* = 3.9 Hz, 1H), 4.73 (m, 1H), 4.45-4.10 (m, 2H), 3.98 (m, 1H), 3.71 (dd, *J* = 3.0, 11.7 Hz, 1H), 3.48 (dd, *J* = 5.1, 11.7 Hz, 1H), 2.30 (brs, 1H), 2.28(m, 1H), 2.10-1.58 (m, 5H), 1.56 (s, 3H), 1.33 (s, 3H)
^{13}C NMR ($CDCl_3$, 50MHz)	112.7, 106.4, 83.0, 80.9, 80.6, 79.9, 64.3, 33.9, 29.0,

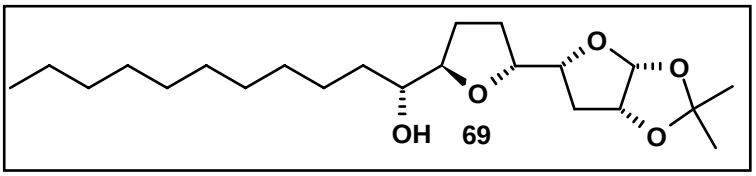
27.3, 26.3

Elemental Analysis **Calcd:** C, 59.01; H, 8.10

Found: C, 59.24; H, 8.10

A solution of DMSO (25.1 mL, 329.5 mmol) in CH_2Cl_2 (40 mL) was added dropwise to a solution of oxalyl chloride (14.3 mL, 164.7 mmol) in CH_2Cl_2 (40 mL) at -78 ^oC . After 30 min, a solution of alcohol **67** (13.4 g, 54.9 mmol) in CH_2Cl_2 (50 mL), was added dropwise to the reaction mixture at same temperature and stirred for additional 30 min. Triethyl amine (49.0 mL, 490.1 mmol) was added to the reaction mixture and allowed to warm to room temperature. Water was added to the reaction mixture and extracted with CH_2Cl_2 (2 x 100 mL). The organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude oil by silica gel column chromatography (60% Ethylacetate/light petroleum) provided the aldehyde **68** as ayellowish oil (9.3 g, 70.32%). Decylmagnesiumbromide in THF was {prepared from decyl bromide (16.9 mL, 76.5 mmol), magnesium turnings (4.5 g, 191.3 mmol) in THF (50 mL, refluxed for 2 h} added to the precooled solution of aldehyde **68** (9.3 g, 38.2 mmol) and CuBr.DMS (0.7 g, 3.1 mmol) in ether (50 mL) at –78 ^oC and stirred for 1h. The reaction mixture was then quenched by slow addition of saturated NH_4Cl and the resulting suspension stirred for another 30 min. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The crude oily material was purified by flash silica gel chromatography (20% Ethylacetate/light petroleum), provided compound **69** (7.2 g) and **70** (3.0 g) in 7:3 ratio.

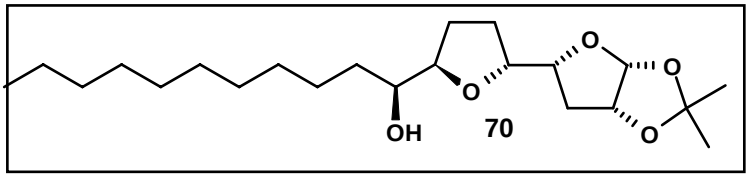
Compound-69



R_f = 0.5 (40% Ethylacetate/light petroleum)

Mol.Formula	$C_{22}H_{40}O_5$
$[\alpha]_D^{25}$	- 31.2 (*c* 0.5, CH_2Cl_2)
IR ($CHCl_3$) cm^{-1}	3471, 2925, 2854 cm^{-1}
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 5.79 (d, *J* = 3.9 Hz, 1H), 4.74 (ddd, *J* = 1.7, 3.9, 6.1 Hz, 1H), 4.26 (m, 1H), 4.03-3.86 (m, 3H), 2.33-1.74 (m, 6H), 1.57 (s, 3H), 1.34 (s, 3H), 1.27 (s, 18H), 0.90 (t, *J* = 6.1 Hz, 3H)
^{13}C NMR ($CDCl_3$, 50MHz)	112.6, 106.3, 83.0, 82.4, 81.2, 80.5, 71.0, 33.9, 32.2, 31.8, 29.6, 29.5, 29.4, 29.2, 29.0, 27.3, 26.4, 25.9, 24.4, 22.5, 14.0
Elemental Analysis	**Calcd:** C, 68.75; H, 10.41
	Found: C, 68.53, H, 10.68

Compound-70



70

R_f = 0.45 (40% Ethylacetate/light petroleum)

Mol. Formula	$C_{22}H_{40}O_5$
$[\alpha]_D^{25}$	- 23.82 (*c* 2.7, CH_2Cl_2)
IR ($CHCl_3$) cm^{-1}	3486, 2925, 2854
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 5.72 (d, *J* = 3.9 Hz, 1H), 4.6 (m, 1H), 4.13 (m, 1H), 3.97-3.76 (m, 2H), 3.33 (m, 1H), 2.58 (brs, 1H), 2.23-2.09 (m, 2H), 2.01-1.81 (m, 3H), 1.60 (m, 1H),1.52 (s,

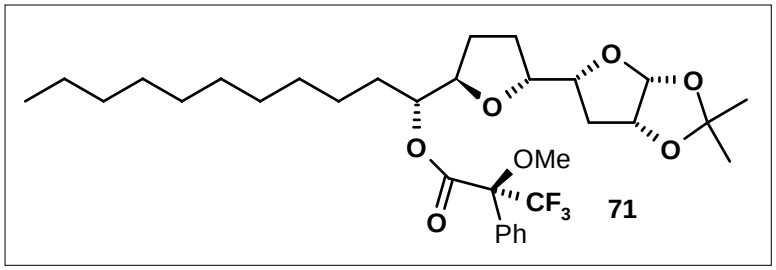
3H),1.29 (s, 3H), 1.22 (s, 18 H), 0.84 (t, *J* = 6.7 Hz, 3H)

^{13}C NMR ($CDCl_3$, 50MHz) 112.8, 106.3, 83.0, 82.5, 80.6, 73.8, 34.1, 33.3, 31.8, 29.6, 29.5, 29.2, 28.2, 27.4, 26.5, 25.6, 22.6, 14.0

Elemental Analysis **Calcd:** C, 68.75; H, 10.41

Found: C, 68.53, H, 10.68

Compound71



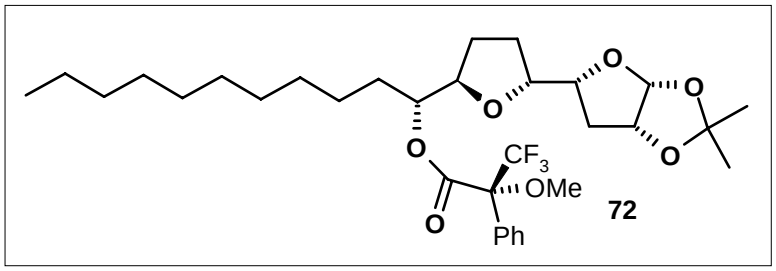
To a solution of alcohol **69 (**10mg**,** 0.026mmol**)** in dry CH_2Cl_2 (2 mL) was added *S*-(-)-MTPA (6mg, 0.0312) and the reaction mixture was cooled to 0 ^oC. To this, DCC (6 mg, 0.031mmo) was added in one portion followed by catalytic amount of DMAP and stirred at rt for 12 h. The reaction mixture was quenched with ice the organic phase was separated, washed with water (3 x 5 mL), brine (1 x 5 mL), dried over Na_2SO_4, filtered and concentrated. The residue obtained was purified by column chromatography (7% Ethylacetate/light petroleum) to give ester **71** (12mg, 85%) as colorless liquid.

Mol.Formula $C_{32}H_{47}F3O_7$

^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.58-7.50 (m, 2H), 7.43-7.37 (m, 3H), 5.73 (d, *J* = 4.0 Hz, 1H), 5.26 (m, 1H), 4.72 (m, 1H), 4.18-4.06 (m, 2H), 3.90 (m, 1H), 3.55(s, 3H), 2.17 (m, 1H), 2.04-1.83 (m, 4H), 1.68-1.56 (m, 3H), 1.52 (s, 3H), 1.34 (s,

3H), 1.25 (s, 16H), 0.88(s, 3H)

Compound72

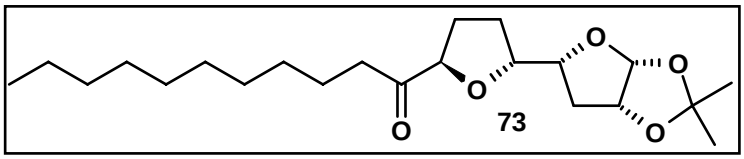


To a solution of alcohol **69 (**10mg**,** 0.026mmol**)** in dry CH_2Cl_2 (2 mL) was added *R*-(-)-MTPA (6mg, 0.0312) and the reaction mixture was cooled to 0 ^oC. To this, DCC (6 mg, 0.031mmo) was added in one portion followed by catalytic amount of DMAP and stirred at rt for 12 h. The reaction mixture was quenched with ice the organic phase was separated, washed with water (3x5 mL), brine (1x5 mL), dried over Na_2SO_4, filtered and concentrated. The residue obtained was purified by column chromatography (5% Ethylacetate/lightpetroleum) to give ester **72** (10 mg, 84%) as colorless liquid.

Mol. Formula $C_{32}H_{47}F3O_7$

^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.66-7.51(m, 2H), 7.40-7.36(m, 3H), 5.71(d, *J* = 4.0 Hz, 1H), 5.22 (m, 1H), 4.70 (m, 1H), 4.04 (q, J = 5.4 Hz, 2H), 3.85 (m, 1H), 3.55(s, 3H), 2.13(m, 1H), 1.94-1.80 (m, 3H), 1.70-1.59 (m, 4H), 1.55 (s, 3H), 1.38 (s, 3H), 1.25 (s, 16H), 0.88(s, 3H)

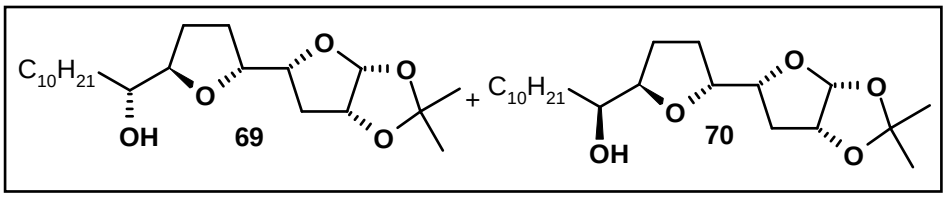
Compound-73



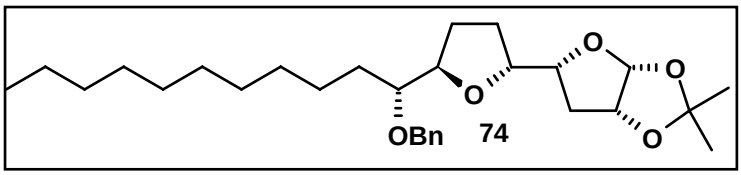
To a slurry of IBX (14.5 g, 52.08 mmol) in DMSO (30 mL), diastereomeric mixture of compound **69** and **70** (10.0 g, 26.04 mmol), in THF (40mL) was added slowly at 0 ^{o}C and stirred for 1h. Reaction mixture was quenched by saturated $NaHCO_3$ and diluted with ether. Reaction mixture was filtered over a celite bed, the organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The crude oily material was purified by flash silica gel chromatography (20% Ethylacetate/light petroleum), provided the keto compound **73** (9.0 g, 92%) as an oily liquid. R_f = 0.6 (40% Ethylacetate/light petroleum

Mol.Formula	$C_{22}H_{37}O_5$
$[\alpha]_D^{25}$	- 5.87 (*c* 1, CH_2Cl_2)
IR ($CHCl_3$) cm^{-1}	1774, 1730, 1585 cm^{-1}
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 5.81 (d, *J* = 3.9 Hz, 1H), 4.75 (m, 1H), 4.39 (m, 1H), 4.01 (m, 1H), 2.75-2.48 (m, 2H), 2.30-2.14 (m, 2H), 2.05-1.84 (m, 2H), 1.58 (s, 3H),1.35(s, 3H), 1.25(s, 18H), 0.88 (t, *J* = 6.8Hz, 3H)
^{13}C NMR ($CDCl_3$, 50MHz)	213.0, 112.8, 83.8, 82.5, 81.8, 80.0, 38.0, 34.0, 31.8, 29.5, 29.4, 29.4, 29.2, 29.2, 28.8, 28.3, 27.3, 26.4, 22.9, 22.6, 14.0
Elemental Analysis	**Calcd:** C, 69.22; H, 9.71 **Found:** C, 69.42, H, 9.93

To a solution of **73** (6.9 g, 18.10 mmol) in THF (50 mL) at -100 ^{o}C was added L-Selectride (27.16mL, 27.16 mmol, 1.0M THF solution) and stirred for 2h., than 2M NaOH (25 mL) and 30% H_2O_2 (18mL) were added successively via syringe, and the reaction was warmed to room temperature. The resulting mixture was diluted with ether (150 mL)and the organic layer was separated and washed twice with saturated aqueous NH_4Cl (25mL), dried (Na_2SO_4) and concentrated. The crude reaction mixture was purified by silicagel column chromatography (20% Ethylacetate/lightpetroleum) afforded **69** (8.05 g) and **70** (0.9 g) in 9:1 ratio with 89% yield.



Compound74

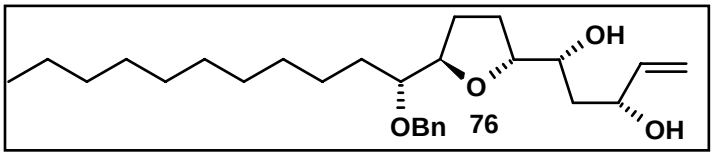


A solution of alcohol **69** (7.2 g, 18.7mmol) in THF (40 mL) was added to a suspension of NaH (0.9 g, 24.3mmol, 60%) in THF (20 mL) at 0 ^{o}C and stirred for 30 min. Benzyl bromide (2.4 mL, 20.6 mmol) was added slowly and stirred for 2 h. The reaction mixture was quenched by water and diluted with Et_2O. The oraganic layer was separated and the aqueous layer was extracted with ether (3 x 100 mL). Combined organic layers ware dried over Na_2SO_4 and concentrated. Purification of the residue by flash silica gel chromatography (20-30% Ethylacetate/light petroleum) provided the benzyl ether **74** (8.1 g, 91%) as a colorless liquid . R_f = 0.3 (50% Ethylacetate-lightpetroleum)

Mol.Formula	$C_{29}H_{46}O_5$
$[\alpha]_D^{25}$	- 14.37 (*c* 0.5, CH_2Cl_2)
IR ($CHCl_3$) cm^{-1}	3019, 2400, 1215, 1045, 757 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz)	δ 7.36-7.22 (m, 5H), 5.76 (d, *J* = 3.9 Hz, 1H), 4.79-4.56 (m, 3H), 4.26 (m, 1H), 4.11-3.88 (m, 2H), 3.65 (m, 1H), 2.35-1.81(m, 6H), 1.50 (s, 3H), 1.31 (s, 3H), 1.24 (s, 18H), 0.88 (t, *J* = 6.6 Hz, 3H)
^{13}C NMR ($CDCl_3$, 50MHz)	139.4, 128.1, 127.6, 127.2, 112.8, 106.4, 82.8, 80.8, 80.8, 73.3, 34.1, 32.1, 31.9, 29.6, 29.3, 29.1, 27.5, 26.6, 25.8, 22.7, 14.1
Elemental Analysis	**Calcd:** C, 73.41; H, 9.70
	Found: C, 73.68; H, 9.89

(1*R*)-1-((2*R*,5*R*)-5-((*R*)-1-(benzyloxy)undecyl)-tetrahydrofuran-2-yl)pent-4-ene-1,3-diol (76)



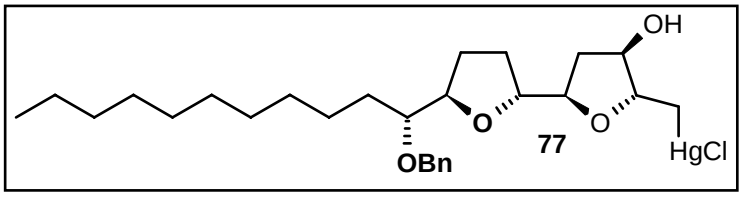
The benzyl ether**74** (7.0 g, 18.7mmol) was dissolved in THF: H_2O (85:15 mL) and catalytic *p*-TSA (10mg) was added and refluxed for 2 h at 60 ^oC and then cooled to 0 ^oC, quenched by Et_3N (1 mL). The reaction mixture was concentrated and purified by silica gel chromatography (60% Ethylacetate/light petroleum) provided lactol compound **75** (5.3 g, 84%) as a colorless oil, which was subsequently treated with $PPh_3^+CH_3I^-$ (28.4 g, 70.6mmol) and *n*-BuLi (1.6 M, 36.8 mL, 58.8 mmol) in THF (50 mL) at -10 ^oC and stirred for 10 h in room temperature. Reaction mixture was quenched by water and the organic layer was separated and the aqueous layer was extracted with ethylacetate (2 x 50mL). Combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by flash silica gel chromatography (20% Ethylacetate/lightpetroleum) afforded **76** (3.6 g, 72%) as a colorless liquid. $R_f = 0.3$ (50% Ethylacetate/lightpetroleum)

Mol.Formula	$C_{27}H_{44}O_4$
$[\alpha]_D^{25}$	- 2.11 (*c* 0.3, CH_2Cl_2)
IR ($CHCl_3$) cm^{-1}	3425, 3030,1650 , 1720, 1455, 994, 666 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz)	δ 7.31–7.26 (m, 5H), 5.91 (m, 1H), 5.35-5.09 (m, 2H), 4.62 (ABq, *J* = 11.4, 19.0Hz, 2H), 4.46 (br s, 1H), 4.01 (m, 1H), 3.90-3.66 (m, 2H), 3.54 (m, 1H), 1.99-1.90 (m, 3H), 1.79-1.53 (m, 3H), 1.49-1.36 (m, 3H), 1.25 (s, 16H), 0.88 (t, *J* = 6.06 Hz, 3H)
^{13}C NMR ($CDCl_3$, 50MHz)	140.7, 138.9, 128.2, 127.8, 127.4, 114.1, 82.4, 82.0, 82.3, 73.1, 71.3, 69.3., 39.8, 31.6, 29.5, 29.3, 28.3, 26.8, 25.6, 22.6, 14.1
Elemental Analysis	**Calcd:** C, 75.00; H, 10.18
	Found: C, 75.18; H, 10.24

To a solution of **76** (5.0 g, 11.5 mmol) in CH_2Cl_2 (100 mL), $Hg(OAc)_2$ (7.3g, 23.0 mmol) was added at room temperature and stirred for 2h. The reaction mixture was quenched with brine solution (25 mL) and stirred for 30 min. Organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 x 50 mL). Combined organic layers were dried over Na_2SO_4 and concentrated. Purification of the crude compound by flash silica gel column chromatography (40% Ethylacetate/lightpetroleum) provided the chloromercurated compound **77**(4.9g) and **78** (1.23g) in 8:2 ratio with 80% yield.

(((2*R*,2'*R*,4*R*,5*R*,5'*R*)-5'-((*R*)-1-(benzyloxy)undecyl)-4-hydroxy-octahydro-2,2'-bifuran-5-yl)methyl) mercury(II) chloride (77)

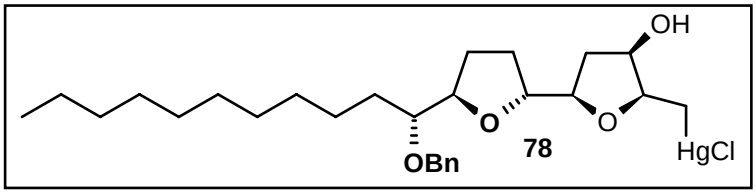


R_f = 0.5 (40% Ethylacetate/light petroleum)

Mol. Formula	$C_{27}H_{43}O_4HgCl$
$[\alpha]_D^{25}$	- 6.11 (*c* 0.3, CH_2Cl_2)

^{1}H NMR ($CDCl_3$, 200 MHz)	δ 7.40–7.26 (m, 5H), 4.62 (ABq, *J*=11.6, 16.8 Hz, 2H), 4.42 (m, 1H), 4.25-4.14 (m, 2H), 3.85-3.78 (m, 2H), 3.65(m, 1H), 2.41 (m, 1H), 2.16 (dd, *J* = 5.1, 12.5 Hz, 1H), 2.05-1.93 (m, 6H), 1.25 (s, 18H), 0.88 (t, *J* = 6.7 Hz, 3H)
^{13}C NMR ($CDCl_3$, 50MHz)	139.1,128.2, 127.7, 127.4, 83.0, 81.9, 81.4, 80.4, 77.4, 73.5, 71.0, 38.4, 31.9, 31.5, 29.7, 29.6, 29.4, 27.8, 27.5, 26.1, 25.9, 22.7, 14.2
Elemental Analysis	**Calcd:** C, 48.60; H, 6.40
	Found: C, 48.58; H, 6.24

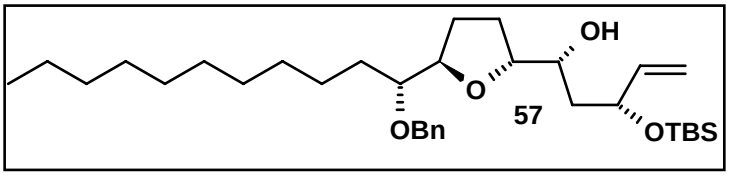
(((2*R*,2'*R*,4*R*,5*R*,5'*R*)-5'-((*R*)-1-(benzyloxy)undecyl)-4-hydroxy-octahydro-2,2'-bifuran-5-yl)methyl)mercury(II) chloride (78)



R_f = 0.45 (40% Ethylacetate/light petroleum)

Mol.Formula	$C_{27}H_{43}O_4HgCl$
$[\alpha]_D^{25}$	- 4.11 (*c* 0.6, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 7.36–7.24 (m, 5H), 4.61(ABq, *J* =11.5, 29.8 Hz, 2H), 4.20 (ddd, *J* = 2.0, 6.2, 8.2 Hz, 1H), 4.14 (m, 1H), 4.09-4.04 (m, 2H), 3.84 (br s, 1H), 3.51 (m, 1H), 2.45 (m, 1H), 2.13 (m, 1H), 2.05-1.87 (m, 4H), 1.85-1.79 (m, 2H), 1.25 (s, 19H), 0.88 (t, *J* = 6.5Hz, 3H)
^{13}C NMR ($CDCl_3$, 50MHz)	139.0, 128.3, 127.7, 127.4, 86.4, 83.0, 81.8, 80.2, 78.9, 77.6, 73.3, 37.0, 36.6, 31.9, 31.7, 29.8, 29.7, 29.7, 29.6, 29.3, 28.0, 26.6, 25.7, 22.7, 14.1
Elemental Analysis	**Calcd:** C, 48.60; H, 6.40
	Found: C, 48.58; H, 6.24

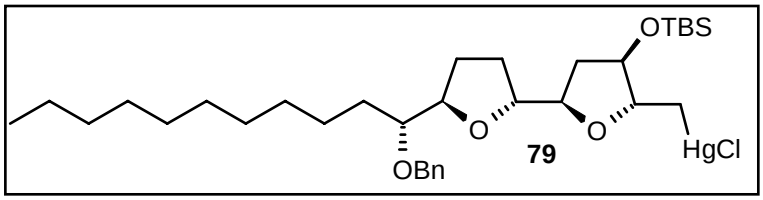
(1*R*)-1-((2*R*,5*R*)-5-((*R*)-1-(benzyloxy)undecyl)-tetrahydrofuran-2-yl)-3-(*tert*-butyldimethylsilyloxy)pent-4-en-1-ol (57)



To a solution of alcohol **76** (0.9 g, 2.0 mmol) in CH_2Cl_2 was added imidazole (0.4 g, 6.2 mmol), TBSCl (0.3 g, 2.4 mmol) and DMAP (cat) at 0 ^oC and stirred for 4 h, the reaction mixture was quenched with saturated $NaHCO_3$ solution and the organic layer was separated. Aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL), combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude compound by flash silica gel chromatography (10% Ethylacetate/ light petroleum) furnished **57** as a colorless oil (1.1 g, 94 %).R_f = 0.6 (20% Ethylacetate-light petroleum)

Yield	94%
Mol. Formula	$C_{33}H_{58}O_4Si$
$[\alpha]_D^{25}$	+5.94 (*c* 0.9, CH_2Cl_2)
IR ($CHCl_3$) cm^{-1}	3584, 2923, 1731, 1644, 1463, 1403, 926, 758, 667 cm^{-1}
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 7.33-7.24 (m, 5H), 5.84 (m, 1H), 5.20-5.05 (m, 2H), 4.68 (ABq, *J* = 11.6, 16.9 Hz, 2H), 4.44 (m, 1H), 4.04 (ddd, *J* = 3.7, 6.8, 10.7 Hz, 1H), 3.80 (m, 1H), 3.72-3.52 (m, 2H), 2.00-1.88 (m, 3H), 1.70-1.38 (m, 6H), 1.25 (s, 15H), 0.91(s, 9H), 0.88 (t, *J* = 2.0 Hz, 3H), 0.10 (s, 3H), 0.05 (s, 3H)
^{13}C NMR ($CDCl_3$, 50MHz)	141.4, 139.1, 128.2, 127.8, 127.4, 113.8, 82.7, 82.1, 80.3, 73.1, 70.8, 70.5, 41.3,31.9, 31.8, 29.7, 29.6, 29.3, 28.3, 26.7, 25.9, 25.7, 22.7, 18.2, 14.1,-4.3, -4.9
Elemental Analysis	**Calcd:** C, 72.52; H, 10.62 **Found:** C, 72.32; H, 10.68.

(((2*R*,2'*R*,4*R*,5*R*,5'*R*)-5'-((*R*)-1-(benzyloxy)undecyl)-4-(*tert*-butyldimethylsilyloxy)-octahydro-2,2'-bifuran-5-yl)methyl) mercury(II)chloride (79)

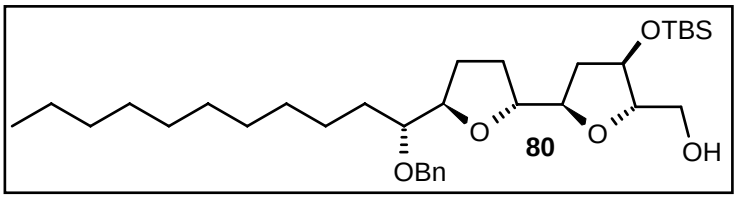


To a solution of TBS ether **57** (1.0 g, 1.8 mmol) in CH_2Cl_2 (20 mL), $Hg(OAc)_2$ (0.4 g, 2.5 mmol) was added at room temperature. After 1 h stirring, reaction mixture was quenched with brine solution. Organic layer was seperated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). Combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude compound by silica gel chromatography (25% Ethylacetate/light petroleum) resulted in compound **79** (single isomer) as a colorless oil (1.05 g). $R_f = 0.5$ (50% Ethylacetate/light petroleum)

Yield	82%
Mol.Formula	$C_{33}H_{57}O_4SiHgCl$
$[\alpha]_D^{25}$	-8.86, (*c* 1.3, CH_2Cl_2)
IR ($CHCl_3$) cm^{-1}	3059, 3025, , 1869, 1802, 1747, 1668, 1601, 1583, 1492, 979, 964, 748
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 7.25-7.14 (m, 5H), 4.65 (d, *J* = 11.6 Hz, 1H), 4.49 (d, *J* = 11.6 Hz, 1H), 4.22-4.13 (m, 2H), 4.05-3.89 (m, 2H), 3.74 (m, 1H), 3.54 (m, 1H), 2.24-2.03 (m, 2H), 1.94-1.77 (m, 3H), 1.72-1.51 (m, 3H), 1.27 (brs, 1H), 1.15 (s, 17H), 0.85 (s, 9H), 0.79 (t, *J* = 5.5 Hz, 3H), 0.03 (s, 6H)
^{13}C NMR ($CDCl_3$, 50MHz)	139.3, 128.2, 127.9, 127.3, 82.8, 81.1, 80.8, 80.5, 80.4, 73.6, 73.5, 38.7, 31.9, 29.7, 29.6, 29.4, 28.7, 26.3, 25.9, 25.9, 22.7, 18.5, 14.2, -4.4
Elemental Analysis	**Calcd:** C, 50.76; H, 7.30

Found: C, 50.82; H, 7.48.

((2*R*,2'*R*,4*R*,5*S*,5'*R*)-5'-((*R*)-1-(benzyloxy)undecyl)-4-(*tert*-butyldimethylsilyloxy)-octahydro-2,2'-bifuran-5-yl)methanol (80)



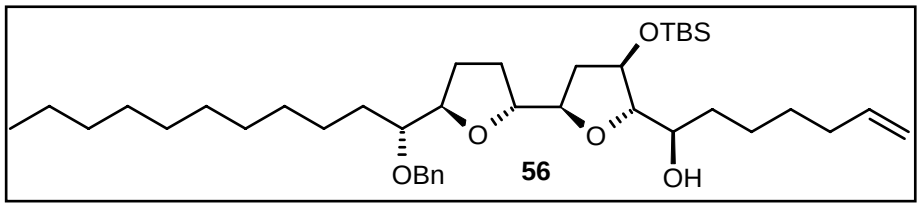
80

To a stirred solution of mercurated compound **79 (**0.9 g, 1.2 mmol**)** in DMF (10 mL), O_2 was bubbled through a long syringe needle for 10 min. Latter on O_2 was passed to the suspension of $NaBH_4$ (0.06 g, 1.5 mmol) in DMF (5 mL) for 20 min, to it O_2 dissolved mercurated compound 19 was added dropwise in 30 min with high flow rate of O_2. Reaction mixture was diluted with Ethylacetate, filtered and concentrated. DMF was removed by rotavapour in reduced pressure. The crude brown coloured oily material was purified by silica gel column chromatography (30% Ethylacetate/light petroleum) to afford primary alcohol **80** as a colorless liquid (0.8 g). R_f = 0.4 (60% Ethylacetate/lightpetroleum)

Yield	81%
Mol.Formula	$C_{33}H_{58}O_5Si$
$[\alpha]_D^{25}$	-6.05 (*c* 0.3, CH_2Cl_2)
IR ($CHCl_3$) cm^{-1}	3017, 2400, 1672, 1548
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 7.37-7.26 (m, 5H), 4.72-4.49 (m, 3H), 4.17-3.91 (m, 3H), 3.83 (ddd, *J* = 2.7, 6.5, 12.7 Hz, 1H), 3.77 (dd, *J* = 7.4, 12.1 Hz, 2H), 3.64 (m, 1H), 2.15 (m, 1H), 2.04-1.87 (m, 3H), 1.73 (m, 1H), 1.23 (brs, 1H), 1.25 (s, 18H), 0.90 (s, 9H), 0.88 (t, *J* = 7.0 Hz, 3H), 0.09 (s, 6H)
^{13}C NMR ($CDCl_3$, 50MHz)	139.3, 128.2, 127.8, 127.3, 82.8, 81.4, 81.1, 80.4, 79.8, 73.4, 62.7, 37.7, 32.0, 31.9, 29.7, 29.6, 29.3, 28.7,

	25.9, 25.8, 25.7, 22.6, 17.9, 14.1, -4.6, -5.1
Elemental Analysis	**Calcd:** C, 70.46; H, 10.32
	Found: C, 70.42; H, 10.59.

(*R*)-1-((2*R*,2'*R*,4*R*,5*S*,5'*R*)-5'-((*R*)-1-(benzyloxy)undecyl)-4-(*tert*-butyldimethyl silyloxy)-octahydro-2,2'-bifuran-5-yl)hept-6-en-1-ol (56)



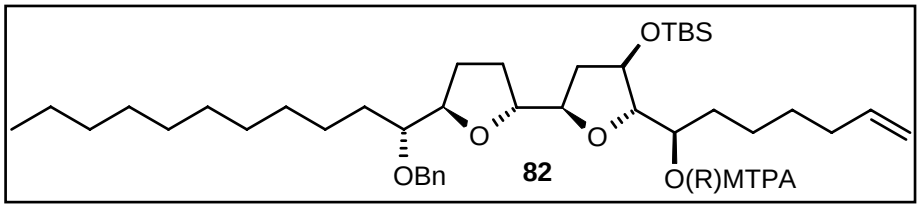
The aldehyde compound **81** was prepared from compound **80** (0.5g) following the same procedure mentioned for **69** (0.4 g, 79%). Hexenyl magnesium bromide was prepared by slow addition of hexenylbromide (0.19 mL, 1.1 mmol) to the mixture of magnesium (0.6 g, 2.3 mmol) in ether (5mL) and stirred for 30 min. A solution of aldehyde (0.3 g, 0.59 mmol) in ether (5 mL) was cooled to –78 ^{o}C, CuBr.DMS (0.012 g, 0.06 mmol) was added to it and stirred for 10 min. To this precomplexed aldehyde, a solution of the above mentioned Grignard reagent was cannulated at –100 ^{o}C and the mixture was further stirred for 30 min at same temperature. The reaction mixture was then quenched by slow addition of saturated NH_4Cl solution and the resulting suspension stirred for additional 30 min. The organic layer was separated and the aqueous layer was extracted with ethylacetate (2 x 50 mL). Combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude brown colored oily material was purified by flash column chromatography (15% Ethylacetate-light petroleum) to afford the title compound **56** as a colorless liquid (0.26 g). R_f = 0.5 (30% Ethylacetate-light petroleum)

Yield	76%
Mol.Formula	$C_{39}H_{68}O_5Si$
$[\alpha]_D^{25}$	-10.94 (*c* 0.4, CH_2Cl_2)
IR ($CHCl_3$) cm^{-1}	3480, 2976, 2940,1640, 1598

^{1}H NMR ($CDCl_3$, 200 MHz)	δ 7.35-7.29 (m, 4H), 7.23 (m, 1H), 5.79 (m, 1H), 4.97 (m, 1H), 4.90 (m, 1H), 4.72 (d, *J* = 11.6 Hz, 1H), 4.58 (d, *J* = 11.6 Hz, 1H), 4.43(q, *J* = 6.2 Hz, 1H), 4.09-4.04 (m, 2H), 3.82(m, 1H), 3.75(m, 1H), 3.62 (ddd, *J* = 3.6, 6.8, 11.0 Hz, 2H), 2.15 (m, 1H), 2.07-2.03 (m, 2H), 2.0-1.87 (m, 3H), 1.82 (m, 1H), 1.68 (m, 1H), 1.52-1.37 (m, 7H), 1.30-1.22 (m, 17H), 0.90 (s, 9H), 0.88 (t, *J* = 6.8 Hz, 3H), 0.08 (s, 6H)
^{13}C NMR ($CDCl_3$, 50MHz)	139.3, 139.0, 128.2, 127.8, 127.3, 114.2, 83.7, 82.9, 81.1, 80.3, 79.5, 73.4, 73.2, 70.4, 38.0, 33.9, 33.5, 32.0, 31.9, 29.7, 29.6, 29.4, 29.2, 28.8, 26.0, 25.9, 25.8, 25.5, 22.7, 18.0, 14.1, -4.3, -5.0
Elemental Analysis	**Calcd:** C, 72.67; H, 10.55 **Found:** C, 72.83; H, 10.37.

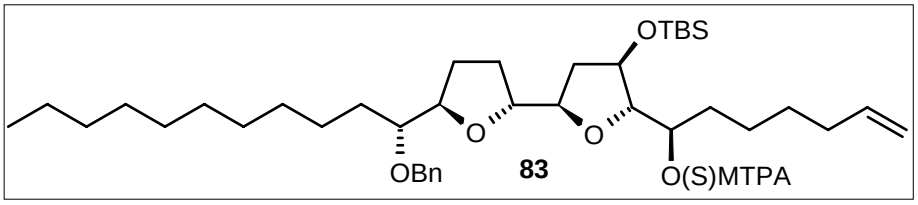
The Mosher ester **82** and **83** were prepared following same procedure as that for **71** and **72**.

Compound 82



Mol.Formula	$C_{49}H_{75}F3O_7Si$
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 7.69-7.60 (m, 3H), 7.44-7.31 (m, 7H), 5.71(m, 1H), 5.43 (m, 1H), 5.03-4.90 (m, 2H), 4.69 (d, *J* = 11.7Hz, 1H), 4.53 (d, *J* = 11.7 Hz, 1H), 4.36 (m, 1H), 4.00 (m, 1H), 3.87-3.71(m, 2H), 3.60 (s, 3H), 3.52 (m, 1H), 2.08-1.82 (m, 6H), 1.75-1.60(m, 5H), 1.47-1.34 (m, 3H), 1.25 (s, 18H), 0.88 (s, 12H), 0.07 (s, 6H)

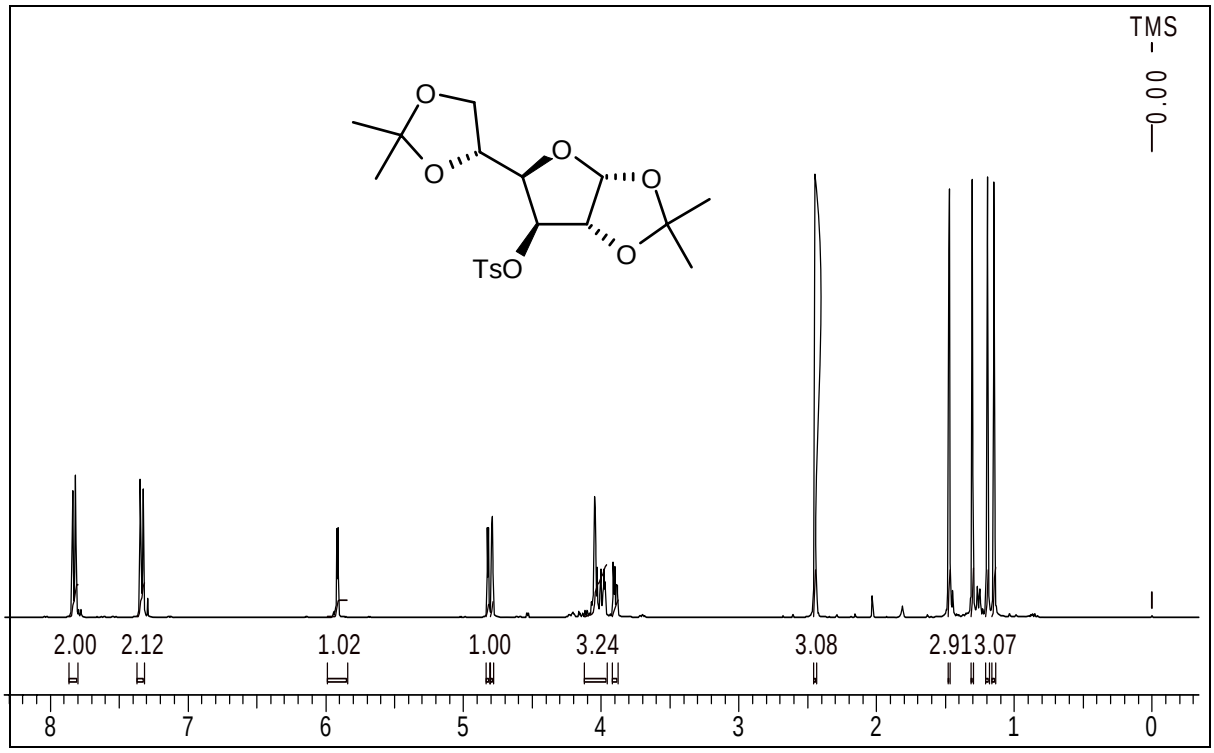
Compound 83



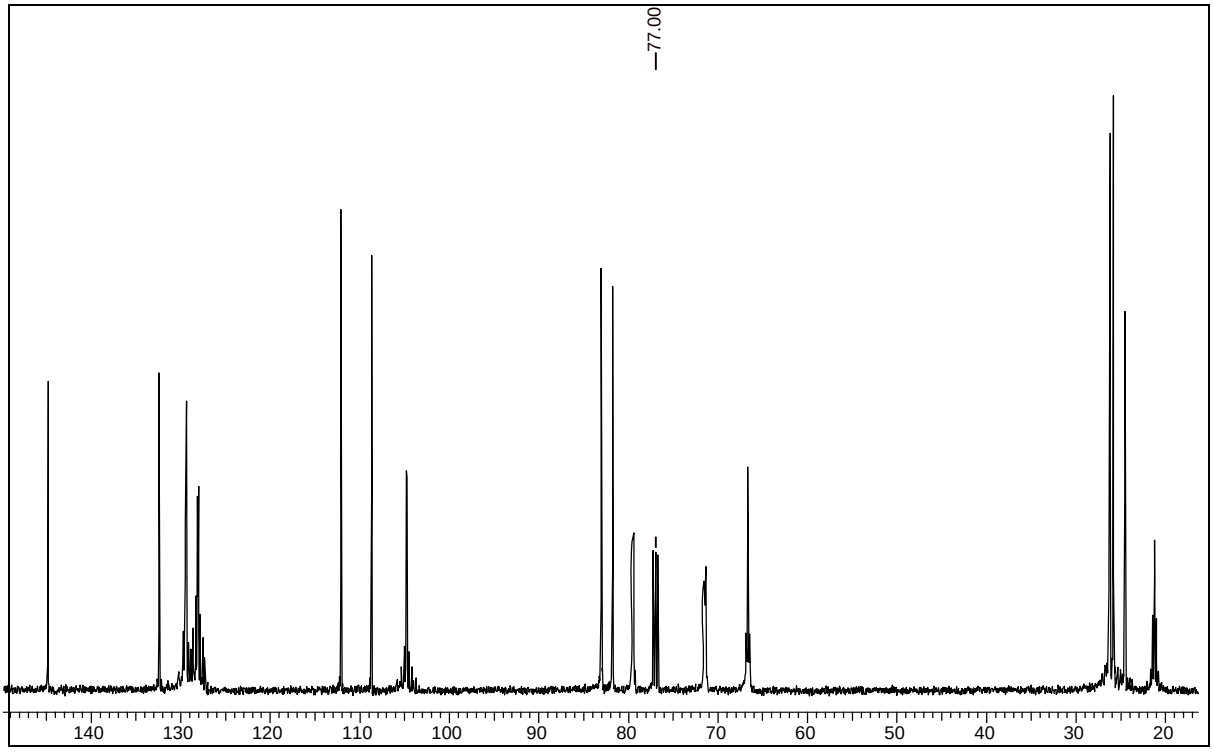
Mol. Formula $C_{49}H_{75}F3O_7Si$

^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.66-7.52 (m, 3H), 7.38-7.28 (m, 7H), 5.76 (m, 1H), 5.29 (m, 1H), 5.02-4.90 (m, 2H), 4.71 (d, *J* = 11.7Hz, 1H), 4.57 (d, *J* = 11.7 Hz, 1H), 4.32 (m, 1H), 4.00-3.93 (m, 2H), 3.82 (m, 1H), 3.71-3.59 (m, 2H), 3.53 (m, 1H), 2.01-1.92 (m, 2H), 1.87-1.73 (m, 5H), 1.46-1.33 (m, 6H), 1.24 (s, 19H), 0.88 (s, 12H), 0.07 (s, 6H)

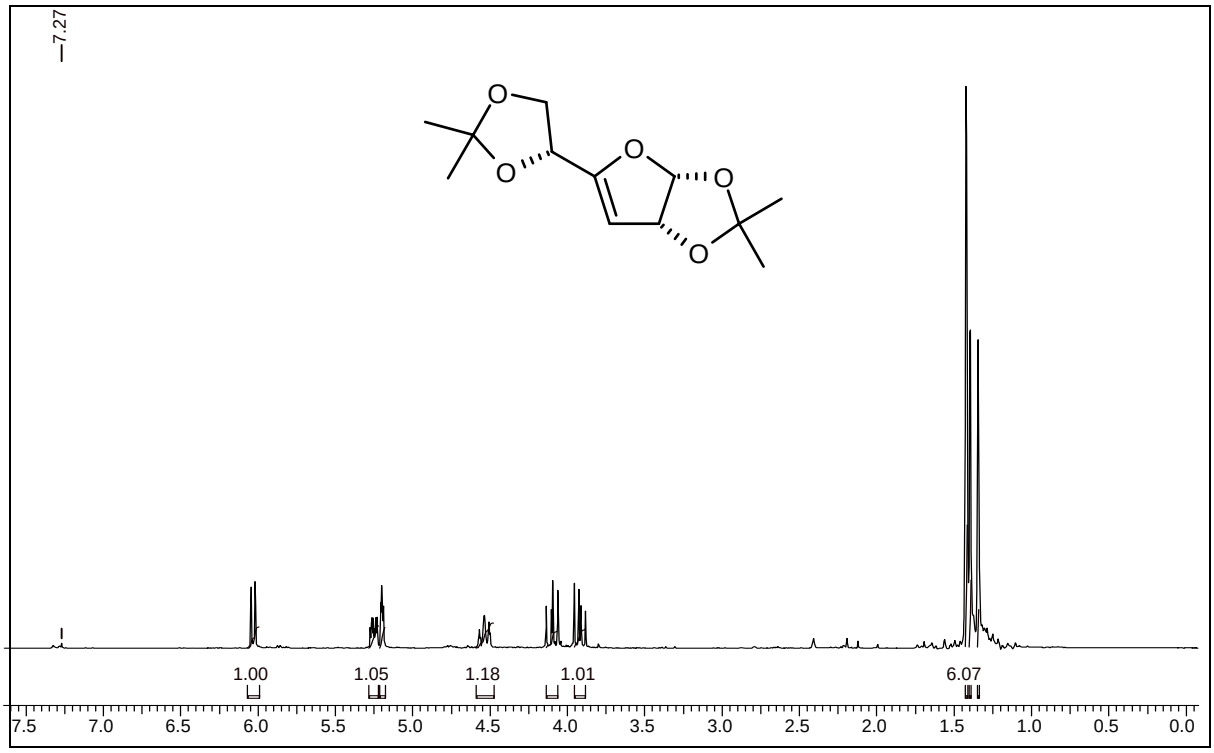
SPECTRA



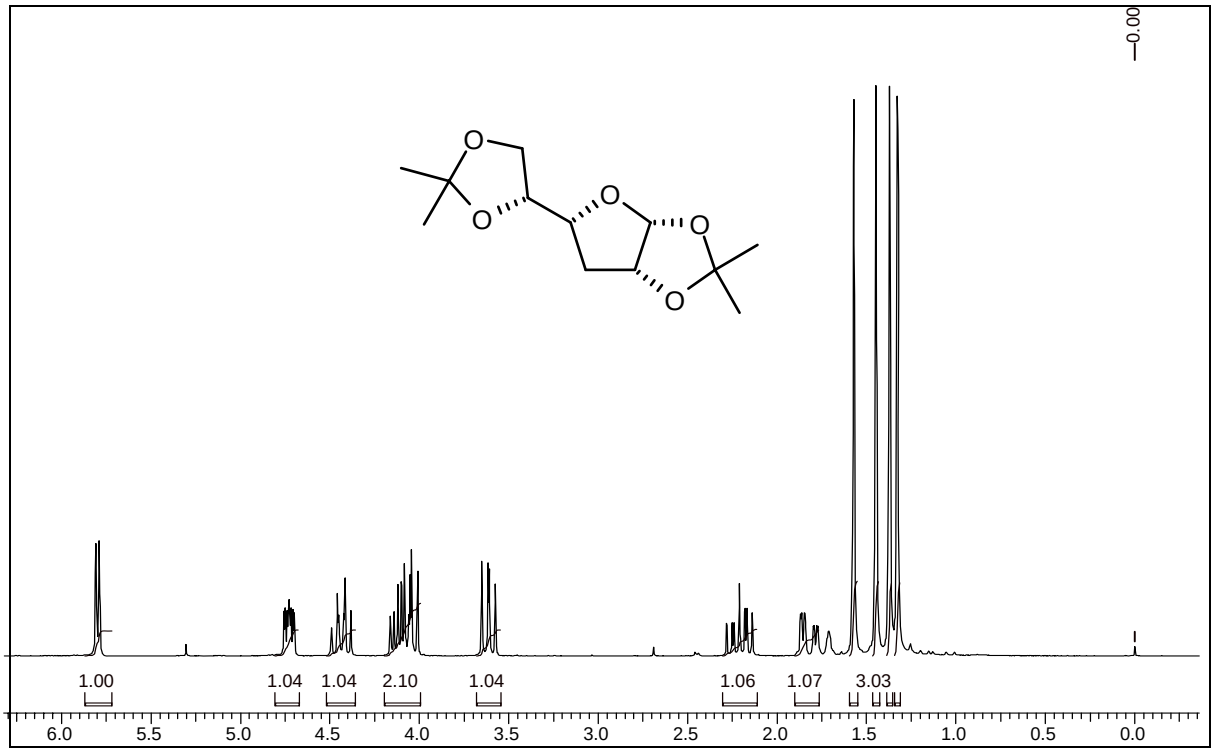
^{1}H NMR spectrum of compound 61 in $CDCl_3$



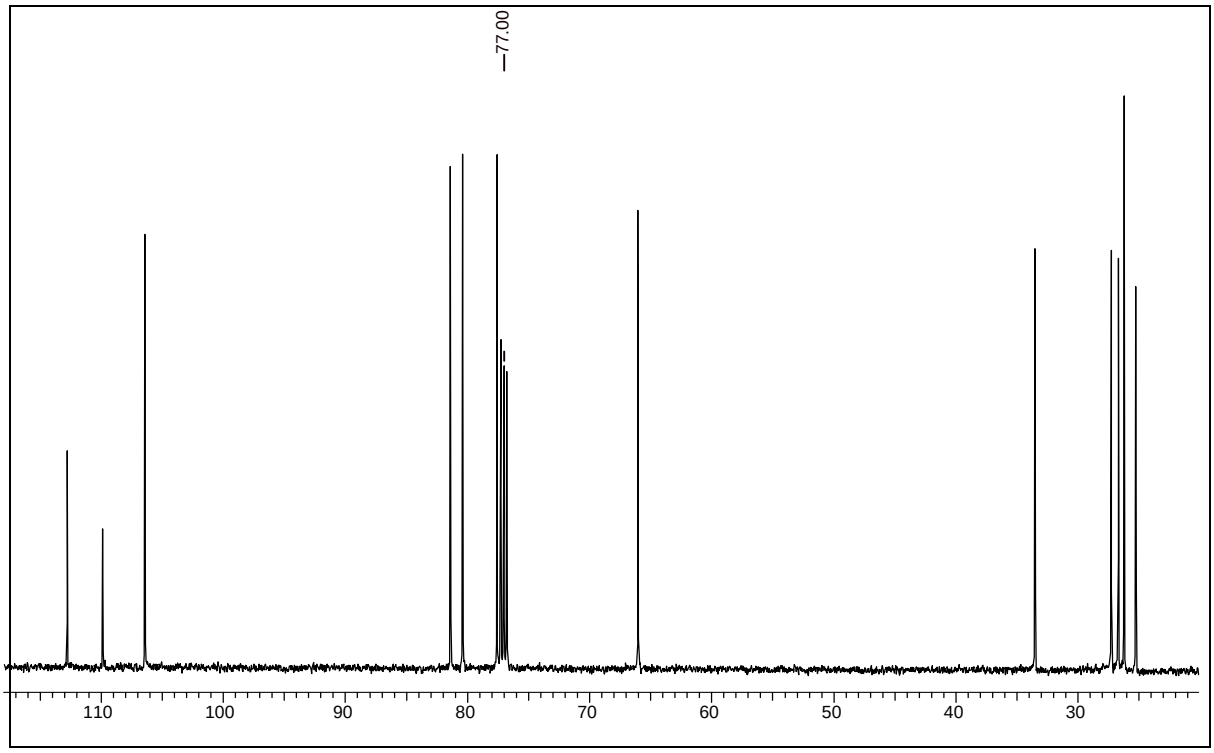
^{13}C NMR spectrum of compound 61 in $CDCl_3$



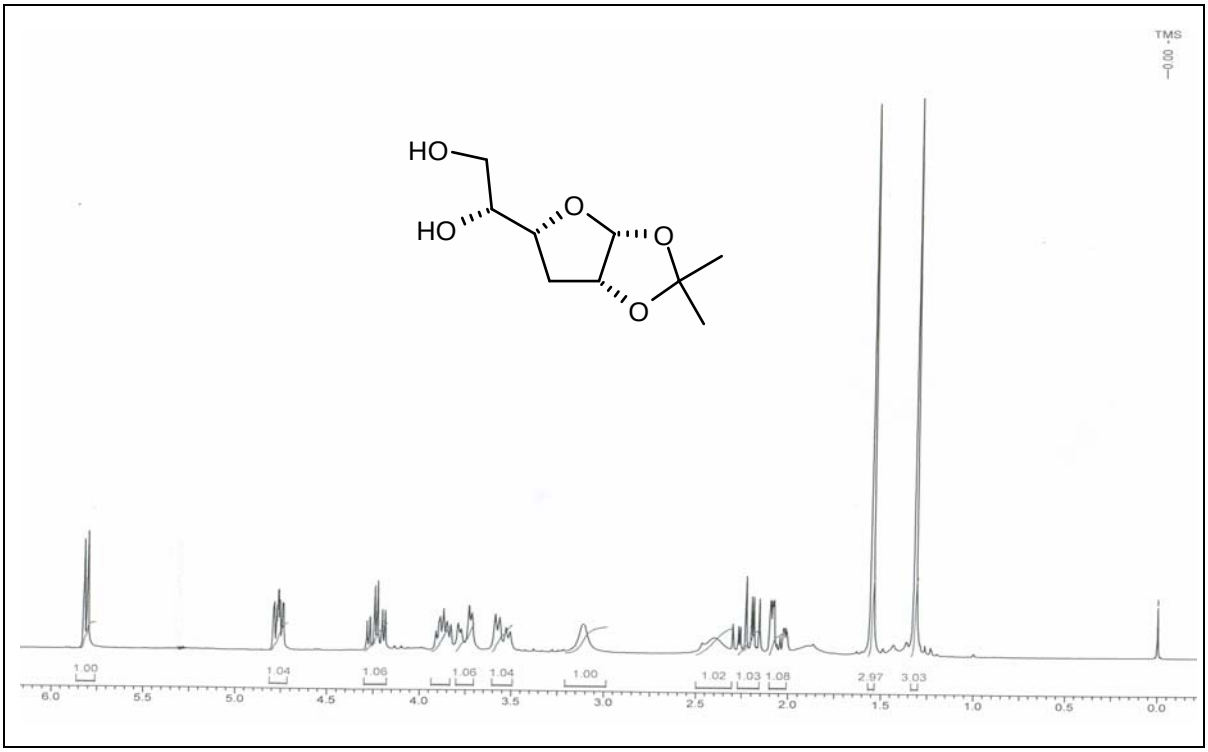
^{1}H NMR spectrum of compound 62 in $CDCl_3$



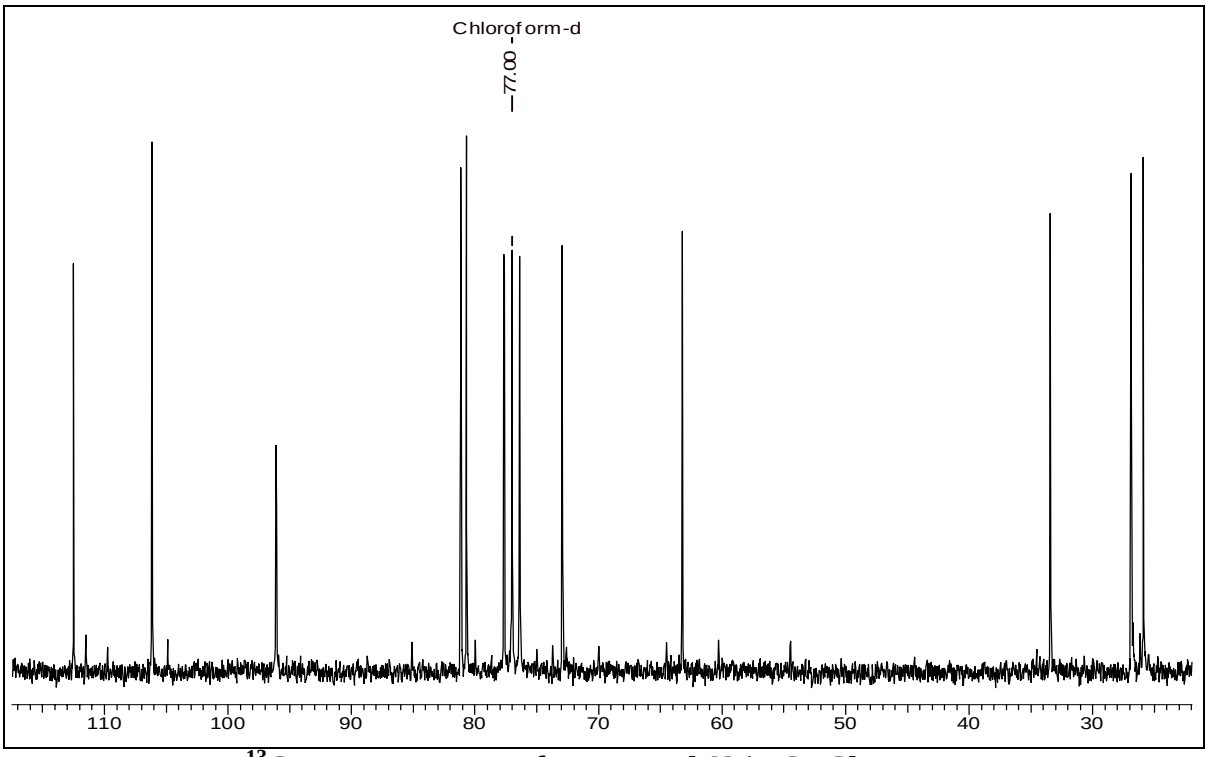
^{1}H NMR spectrum of compound 59 in $CDCl_3$



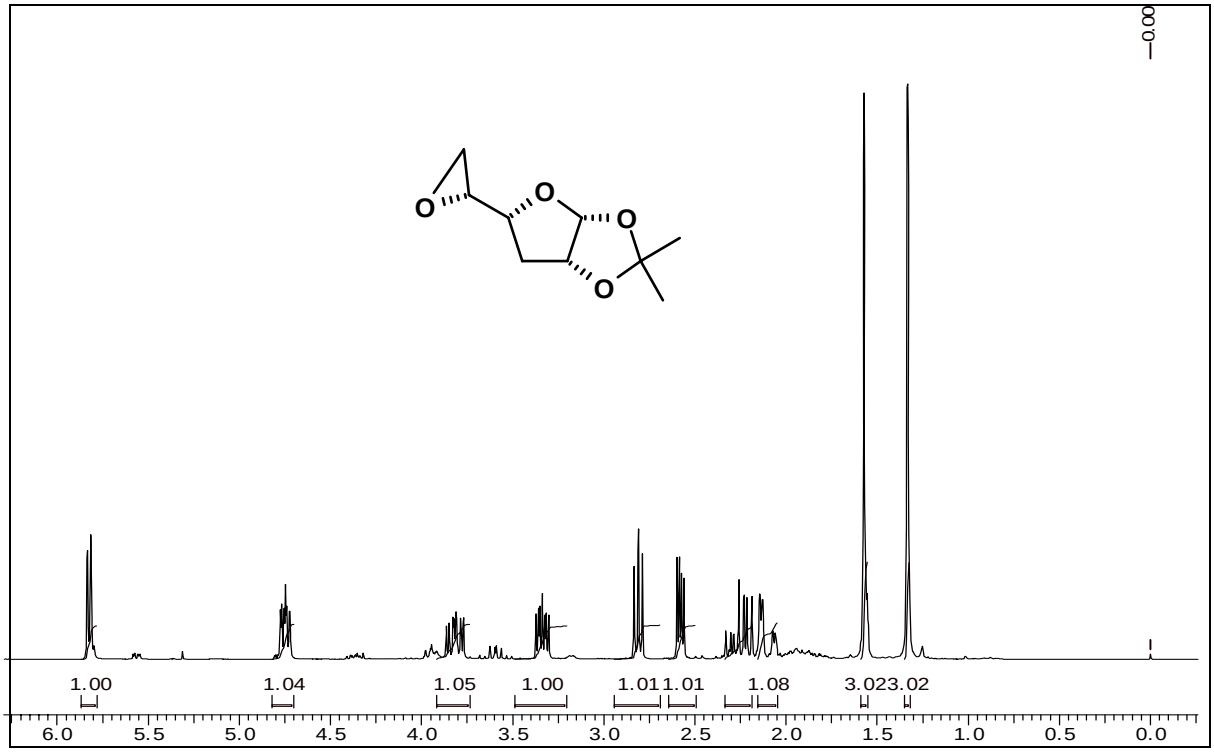
^{13}C NMR spectrum of compound 59 in $CDCl_3$



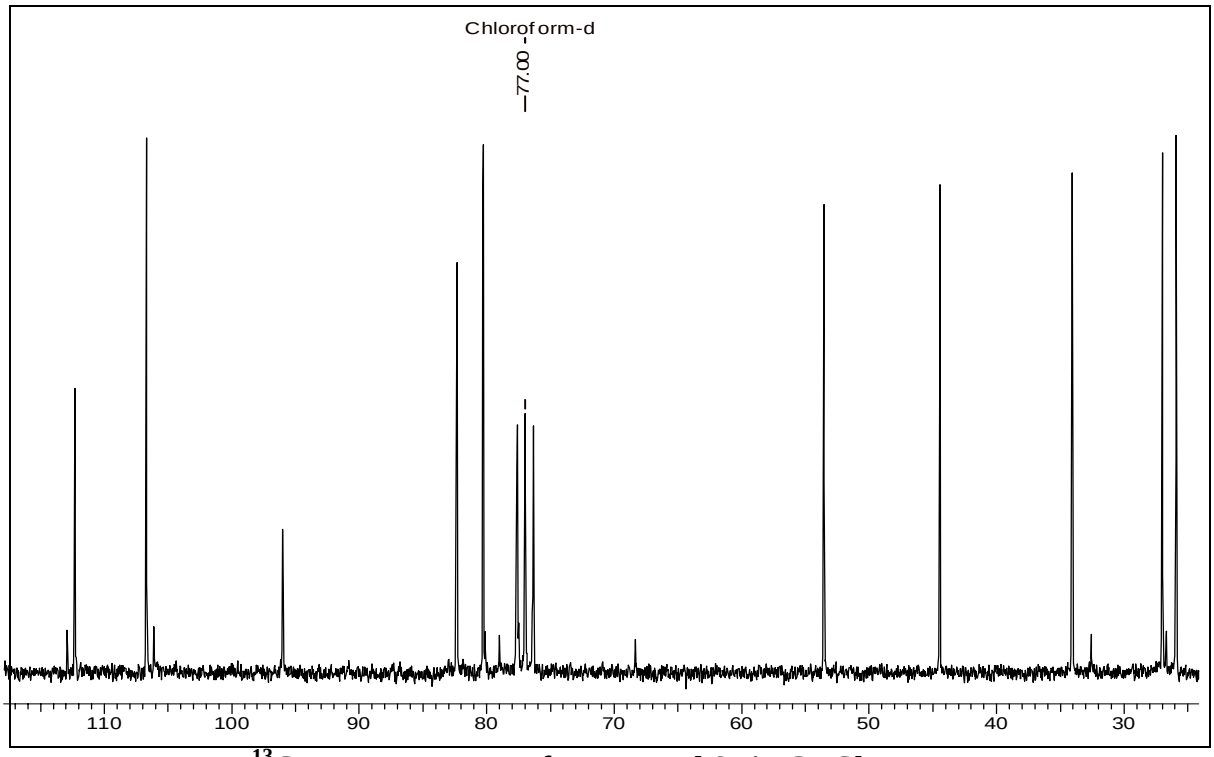
^{1}H NMR spectrum of compound 63 in $CDCl_3$



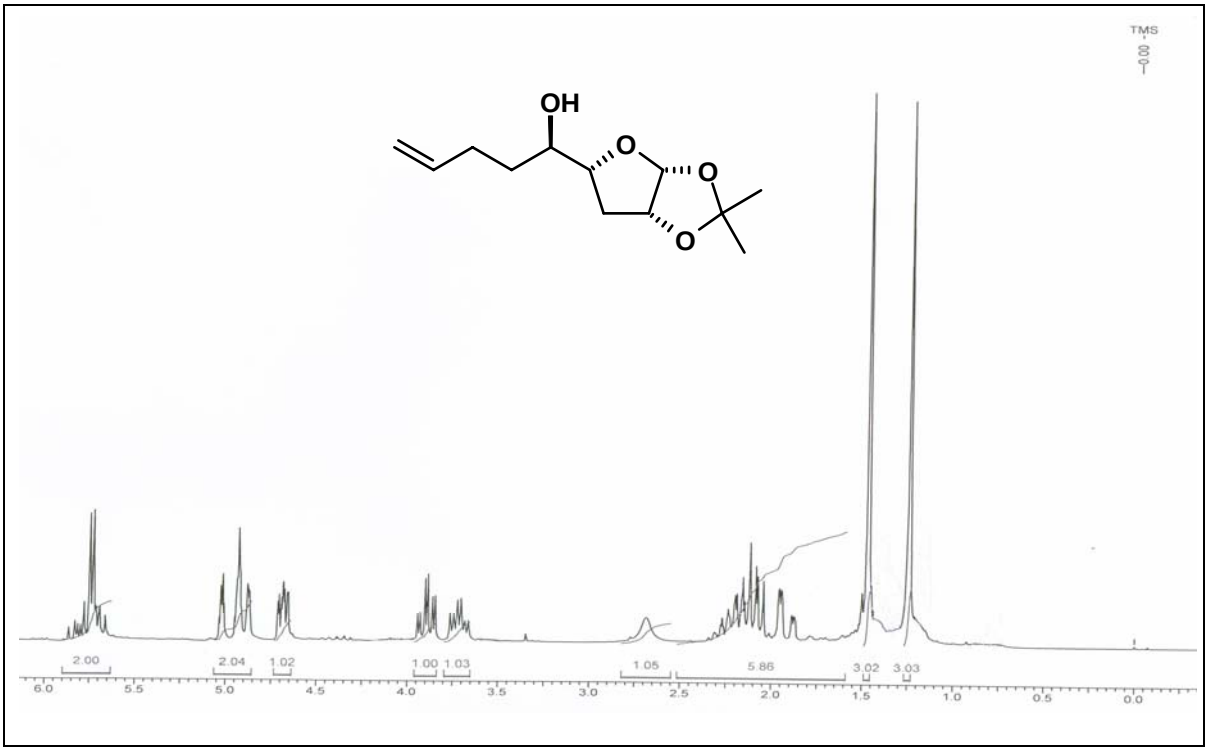
^{13}C NMR spectrum of compound 63 in $CDCl_3$



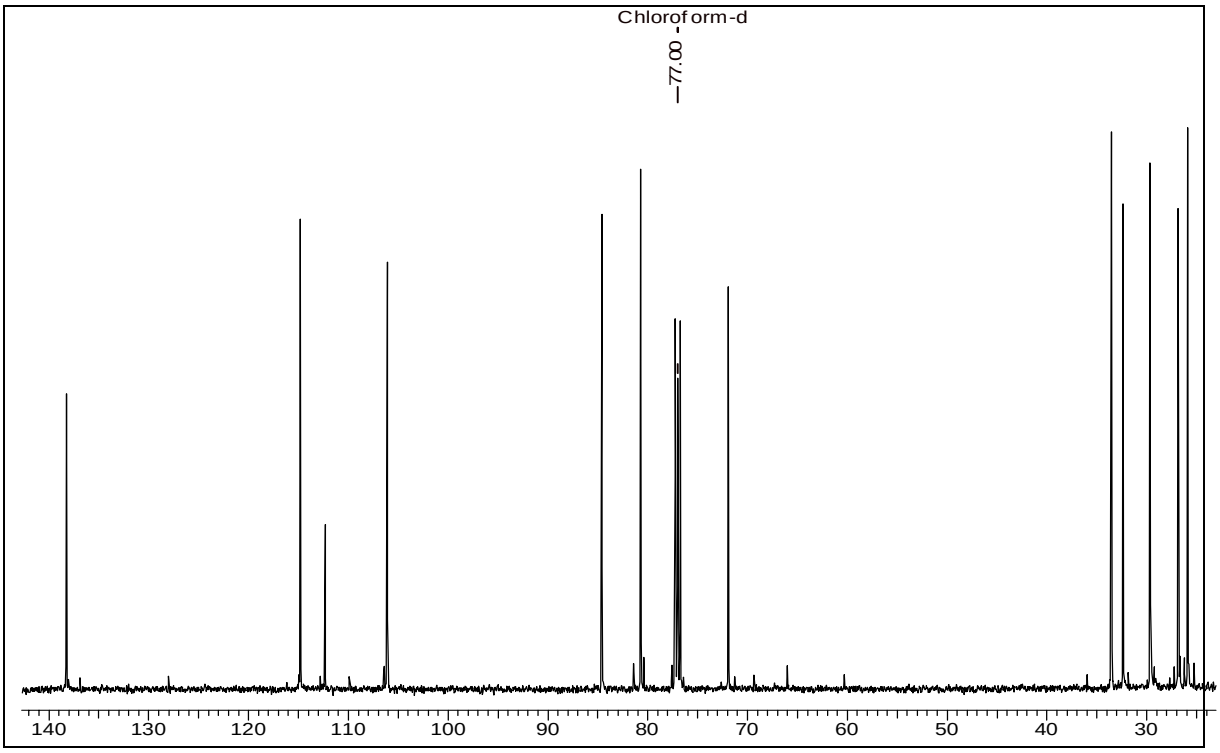
^{1}H NMR spectrum of compound 64 in $CDCl_3$



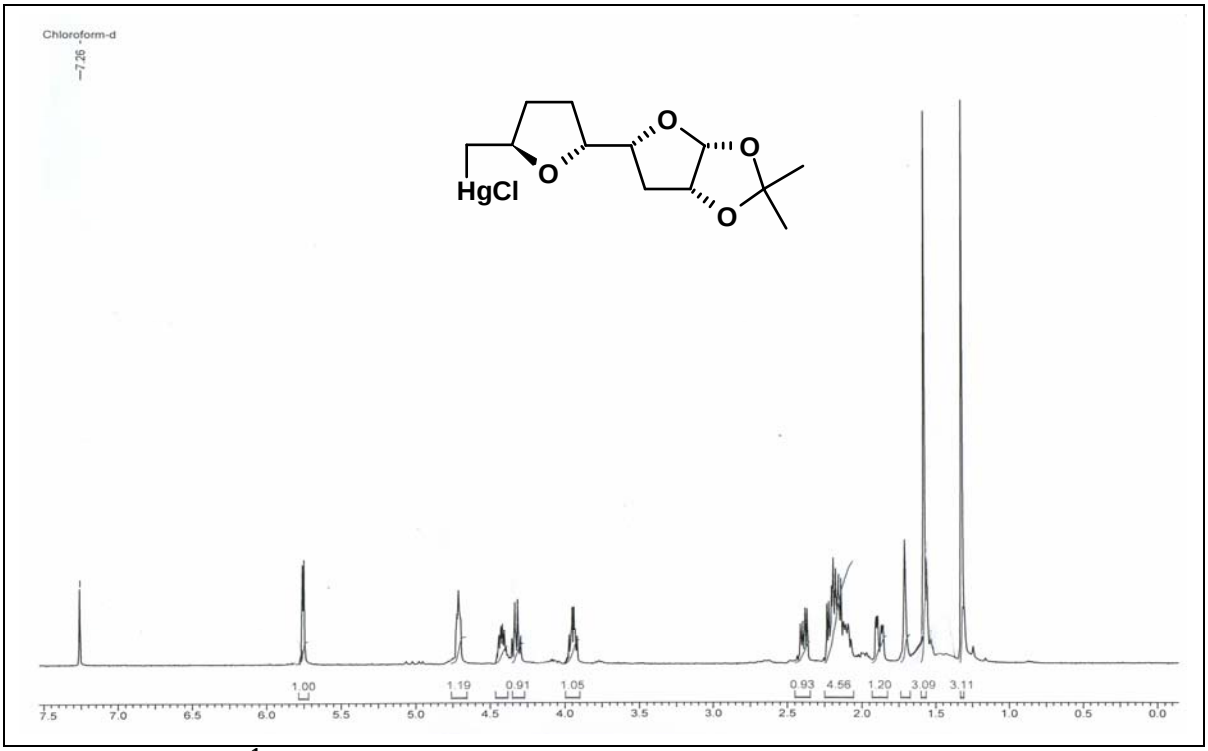
^{13}C NMR spectrum of compound 64 in $CDCl_3$



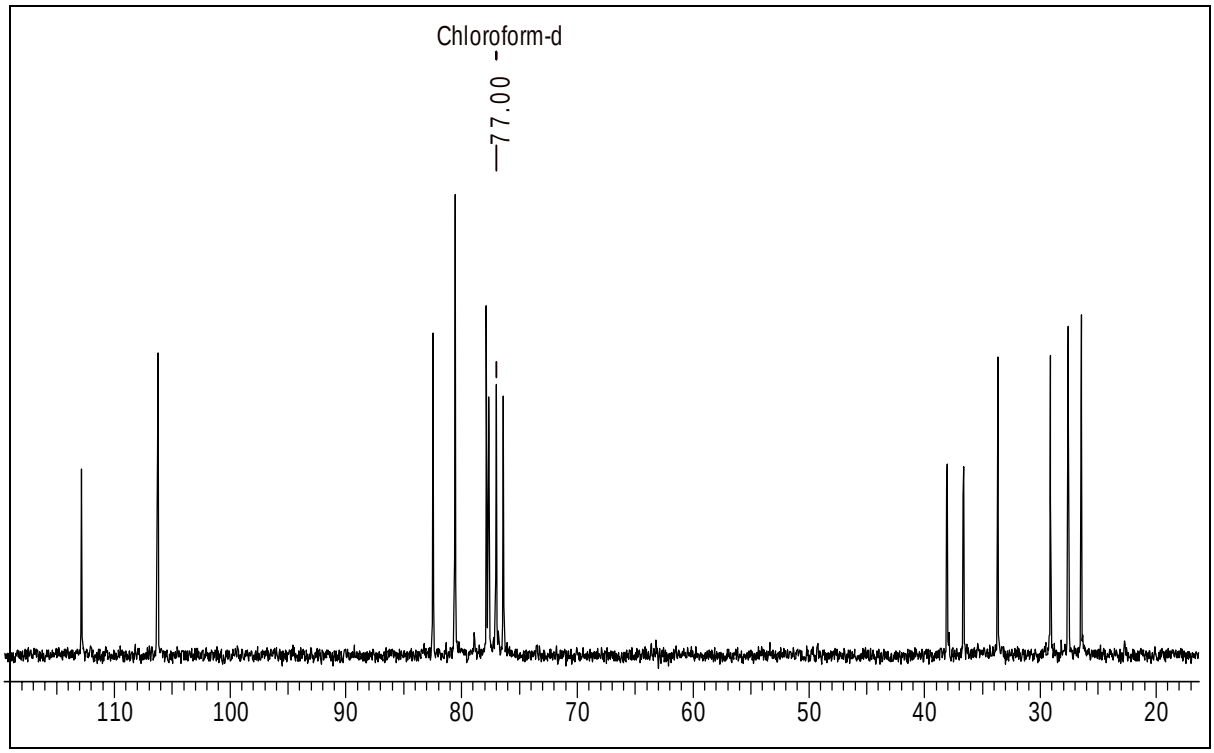
^{1}H NMR spectrum of compound 65 in $CDCl_3$



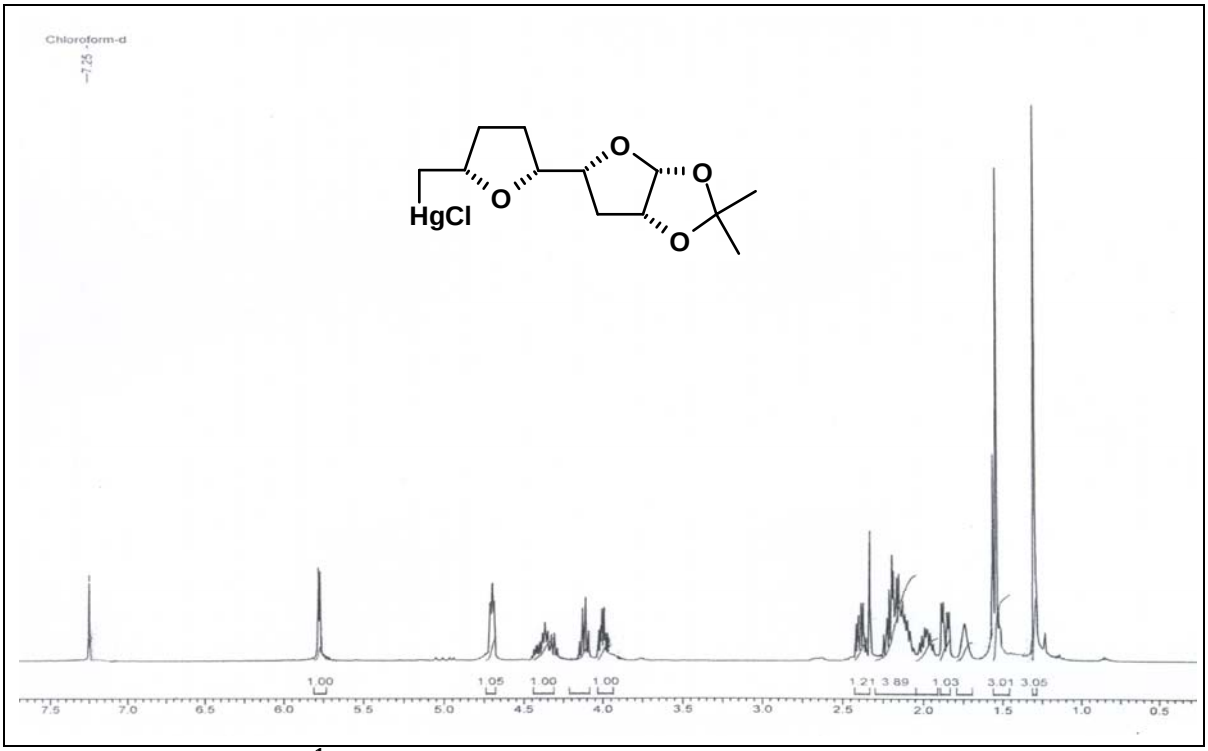
^{13}C NMR spectrum of compound 65 in $CDCl_3$



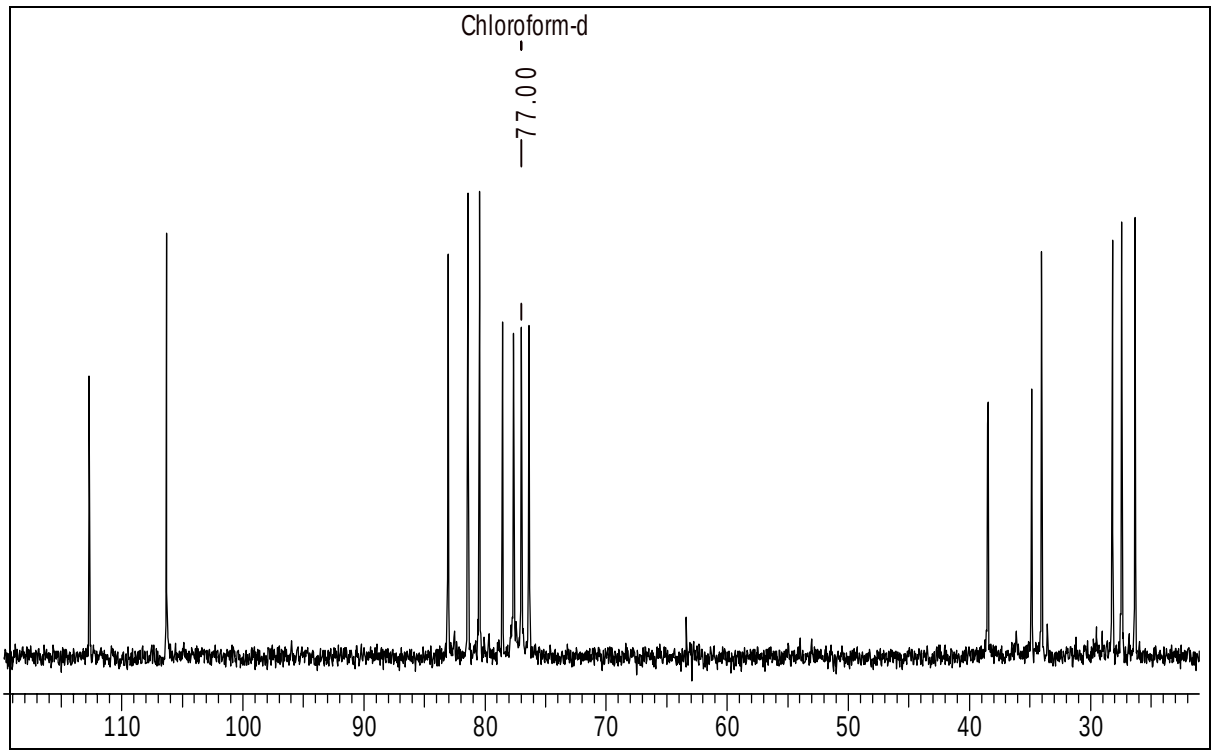
^{1}H NMR spectrum of compound 58 in $CDCl_3$



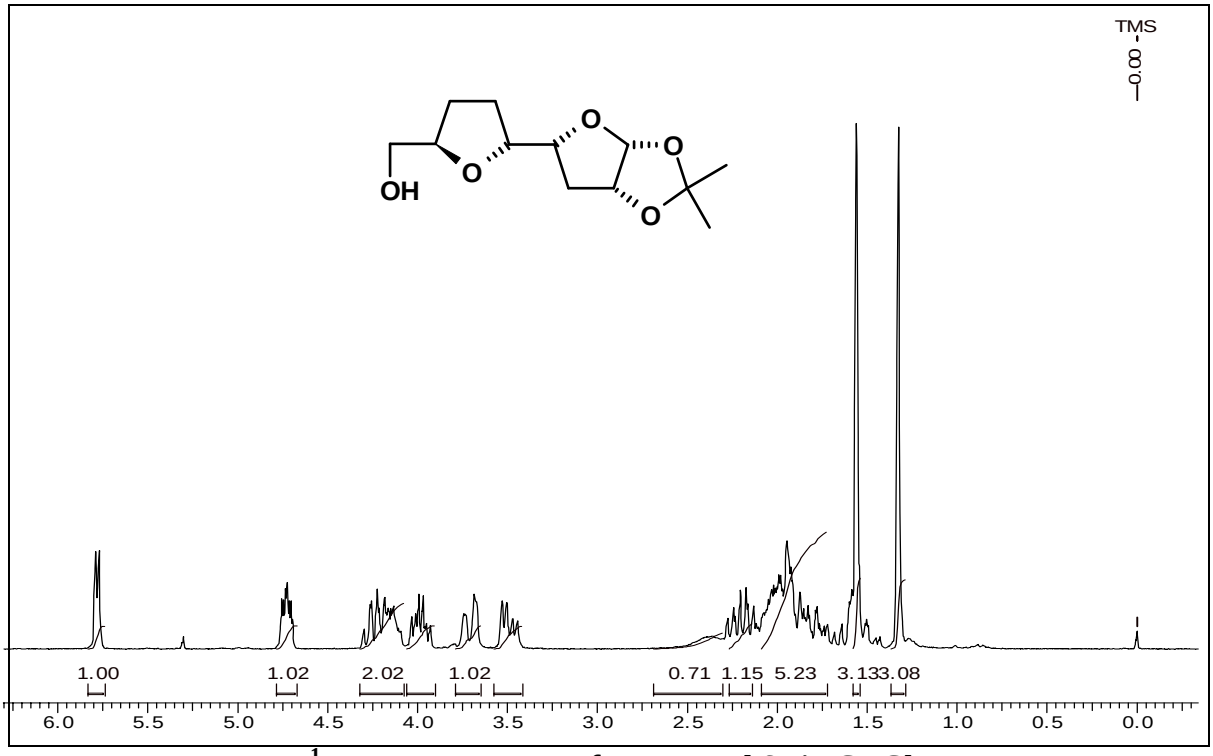
^{13}C NMR spectrum of compound 58 in $CDCl_3$



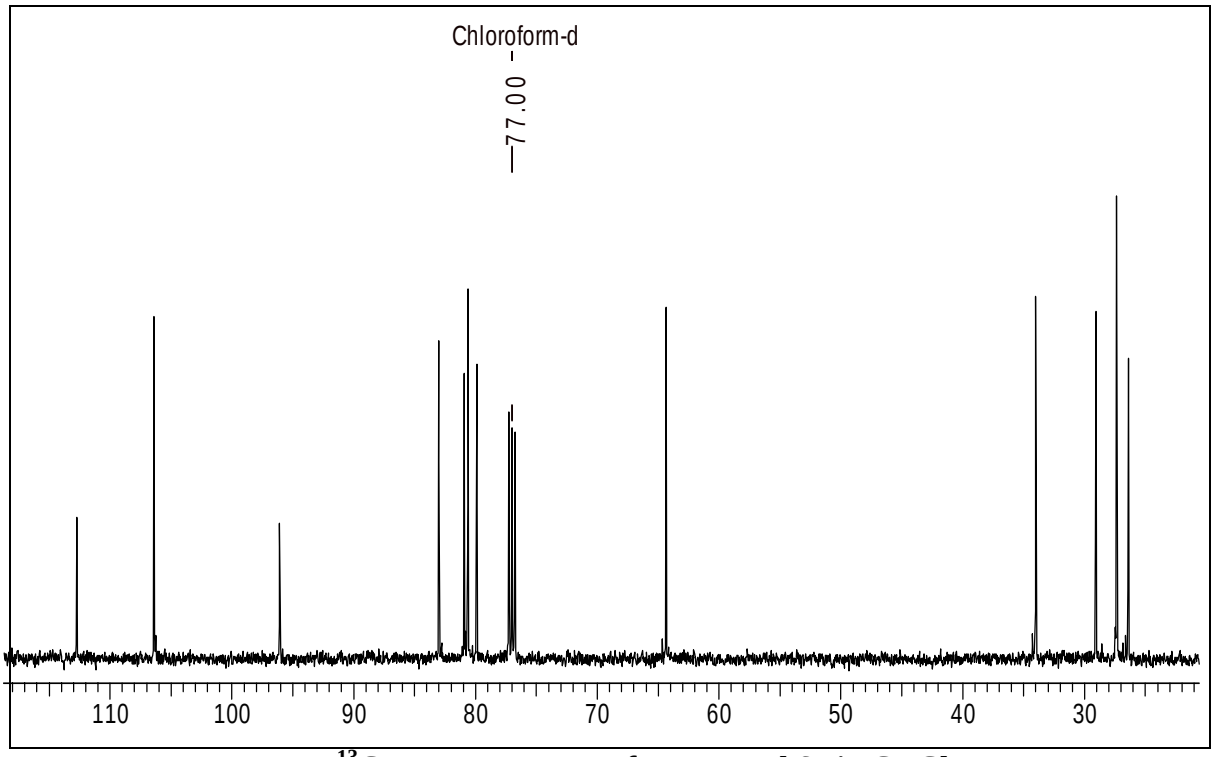
^{1}H NMR spectrum of compound 66 in $CDCl_3$



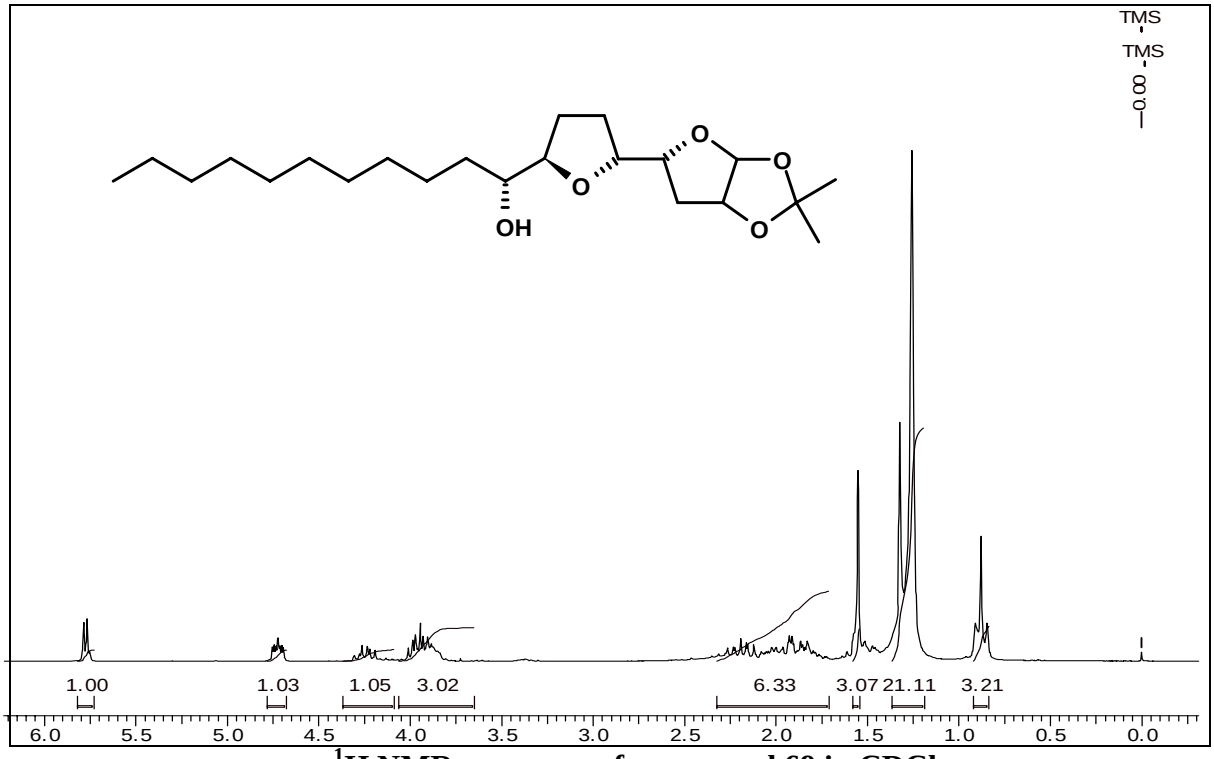
^{13}C NMR spectrum of compound 66 in $CDCl_3$



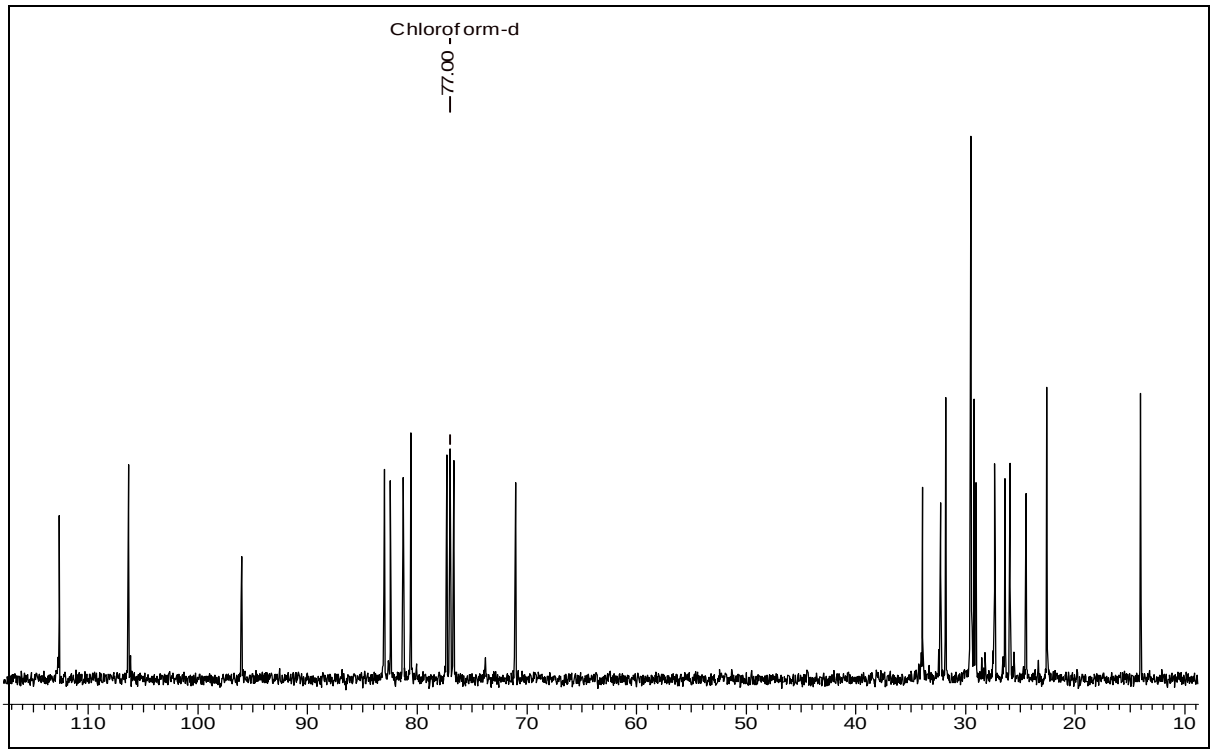
^{1}H NMR spectrum of compound 67 in $CDCl_3$



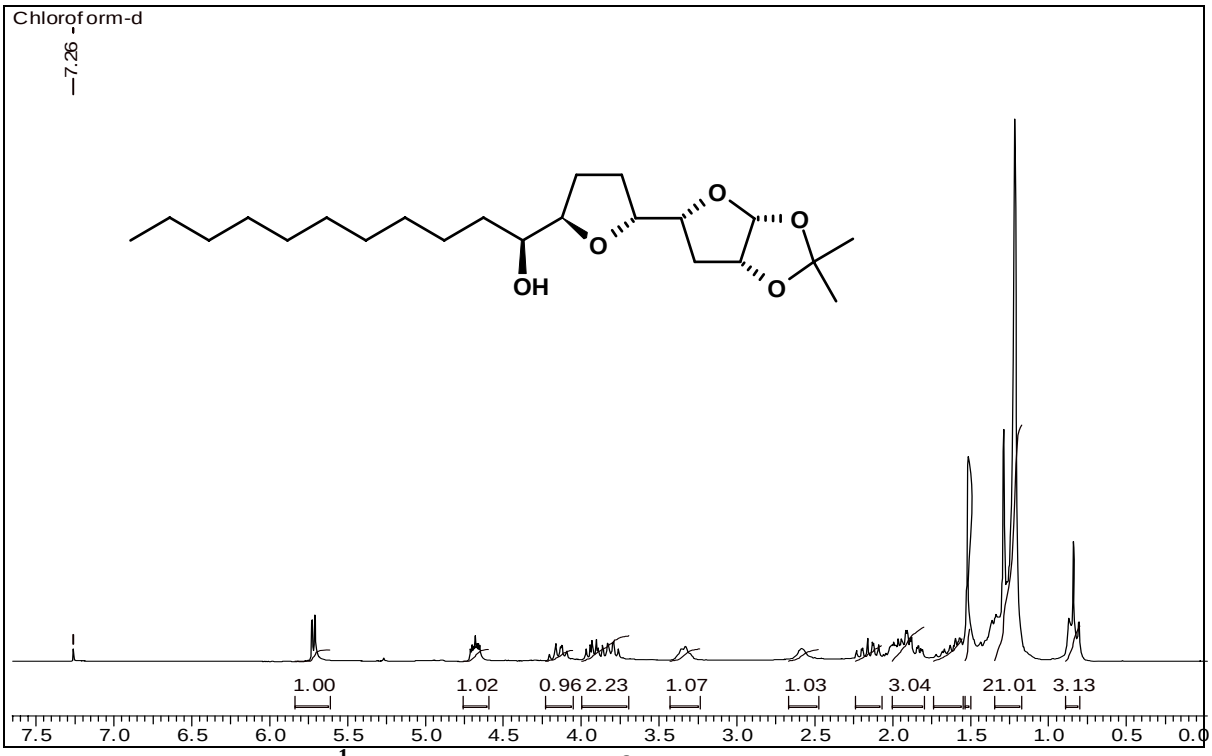
^{13}C NMR spectrum of compound 67 in $CDCl_3$



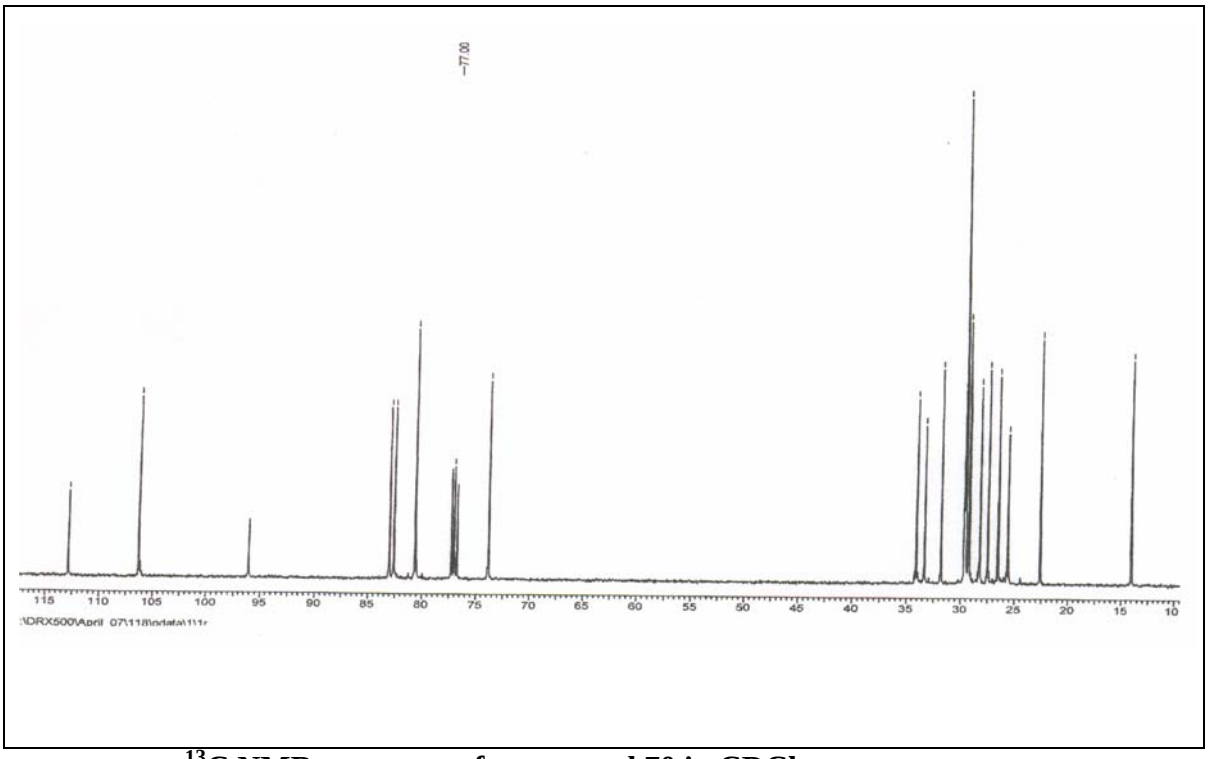
^{1}H NMR spectrum of compound 69 in $CDCl_3$



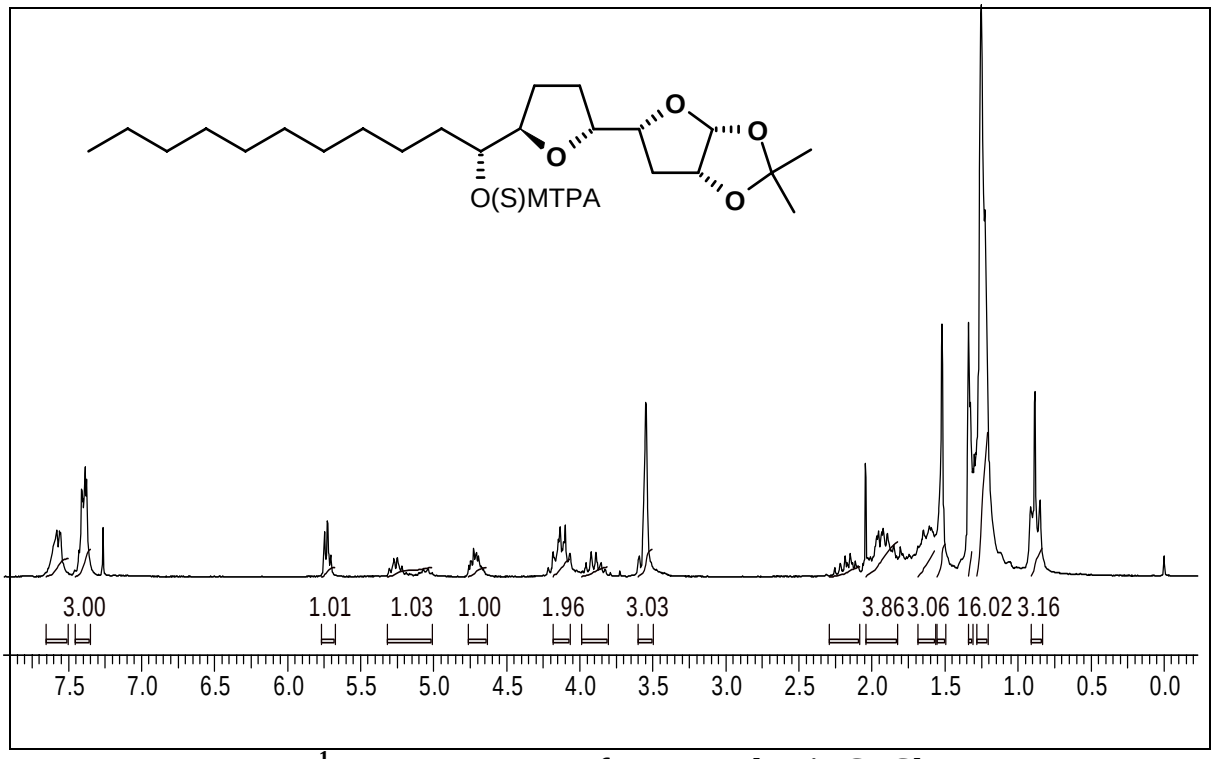
^{13}C NMR spectrum of compound 69 in $CDCl_3$



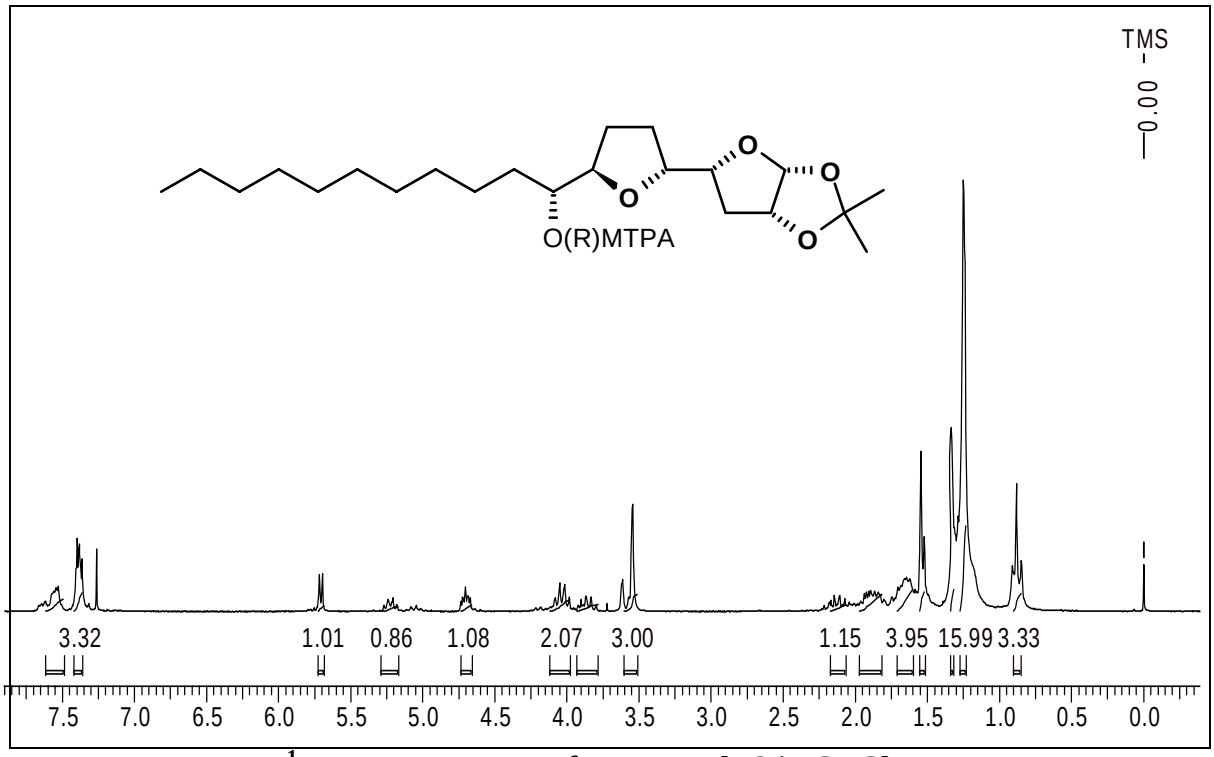
^{1}H NMR spectrum of compound 70 in $CDCl_3$



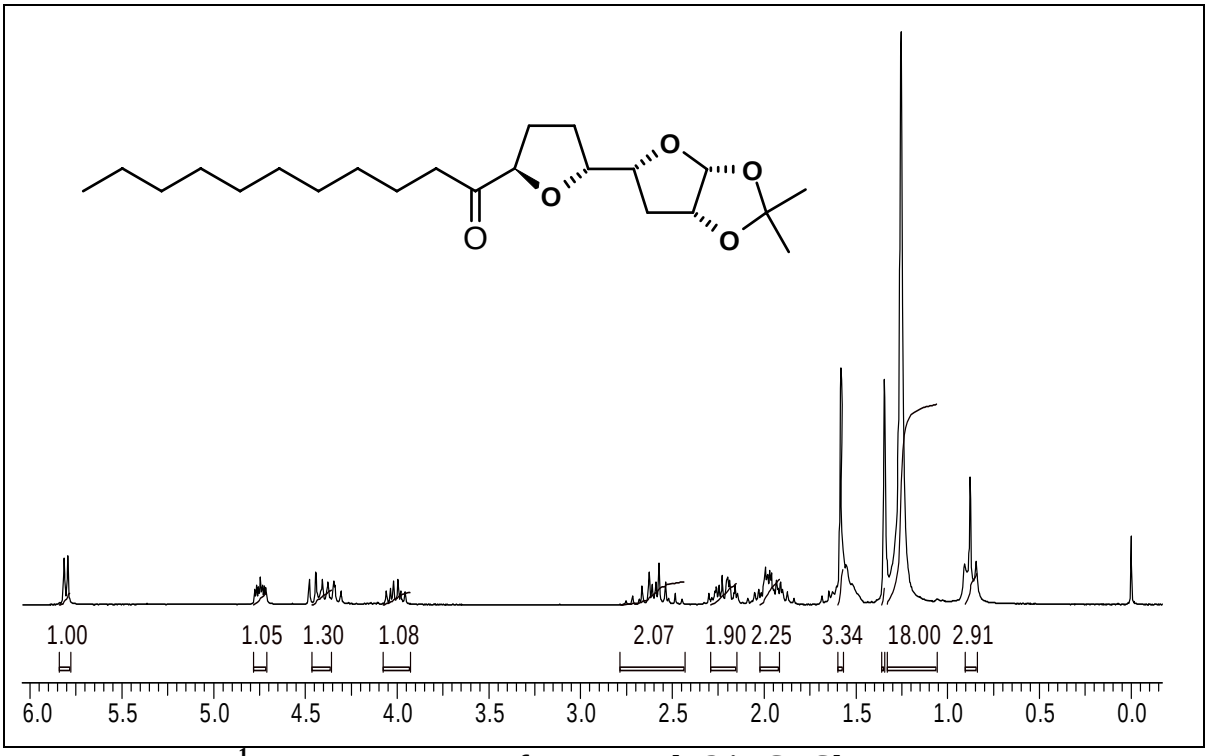
^{13}C NMR spectrum of compound 70 in $CDCl_3$



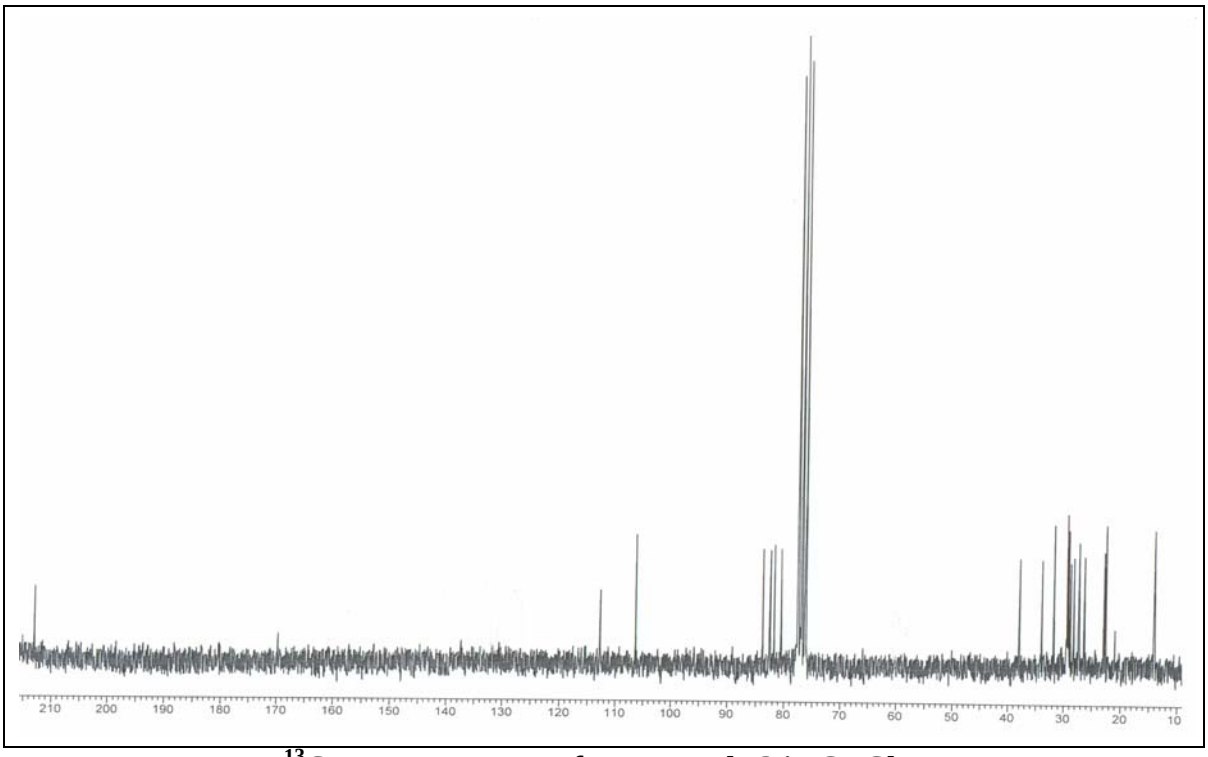
^{1}H NMR spectrum of compound 71 in $CDCl_3$



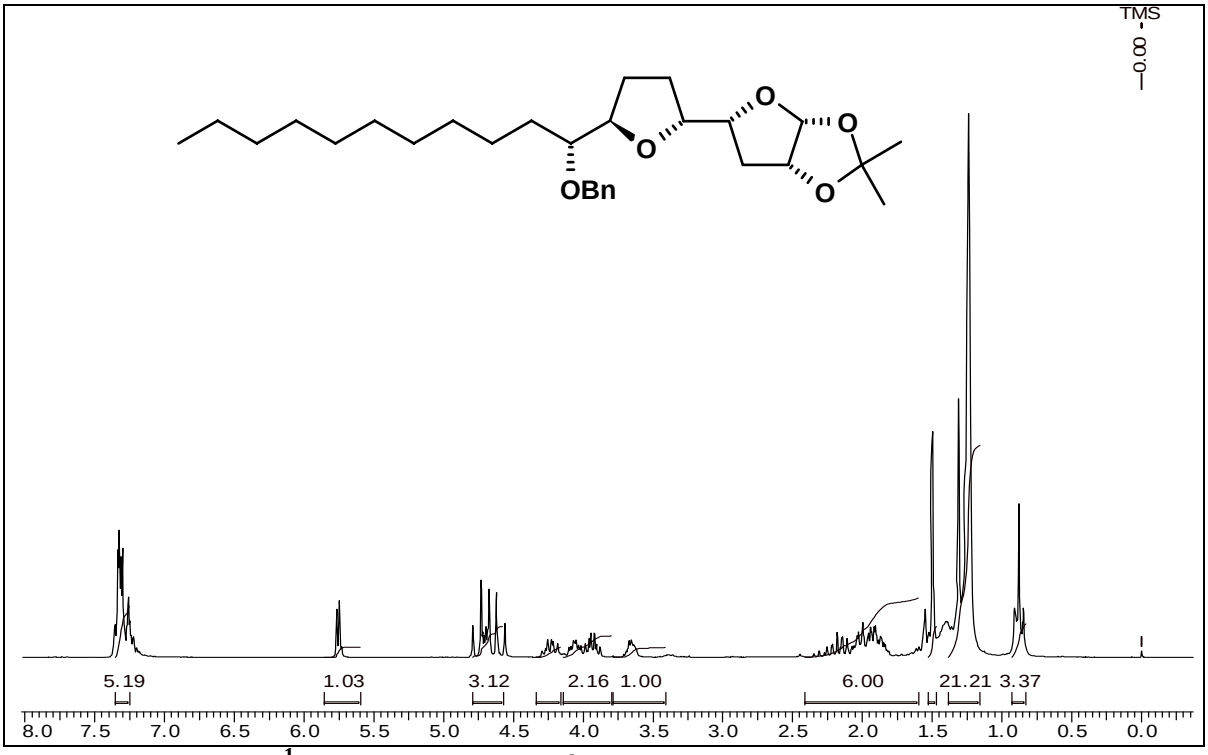
^{1}H NMR spectrum of compound 72 in $CDCl_3$



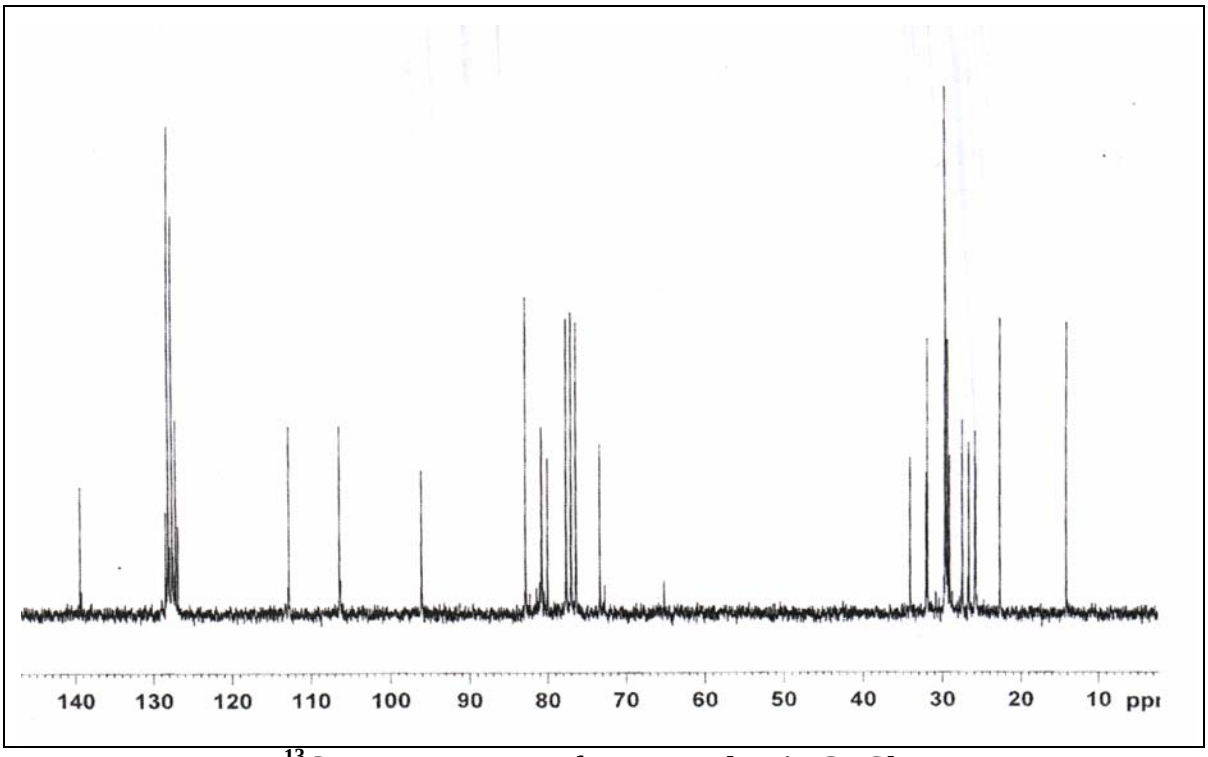
^{1}H NMR spectrum of compound 73 in $CDCl_3$



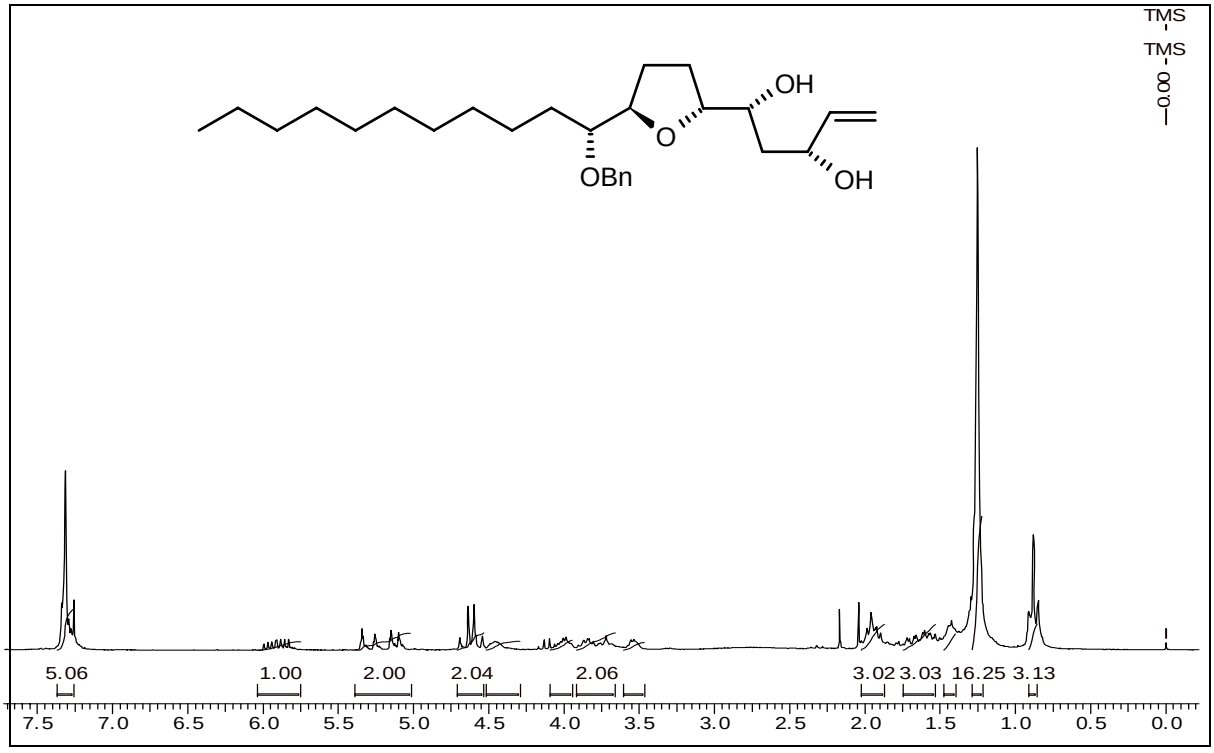
^{13}C NMR spectrum of compound 73 in $CDCl_3$



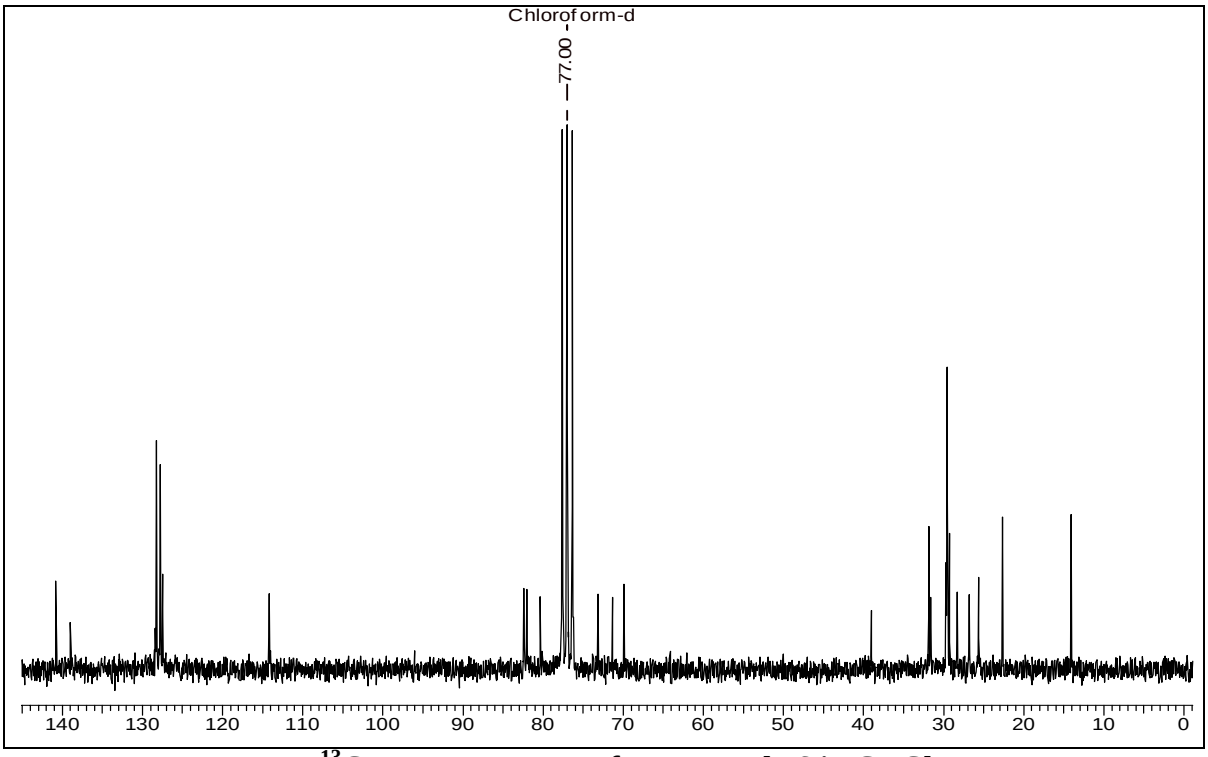
^{1}H NMR spectrum of compound 74 in $CDCl_3$



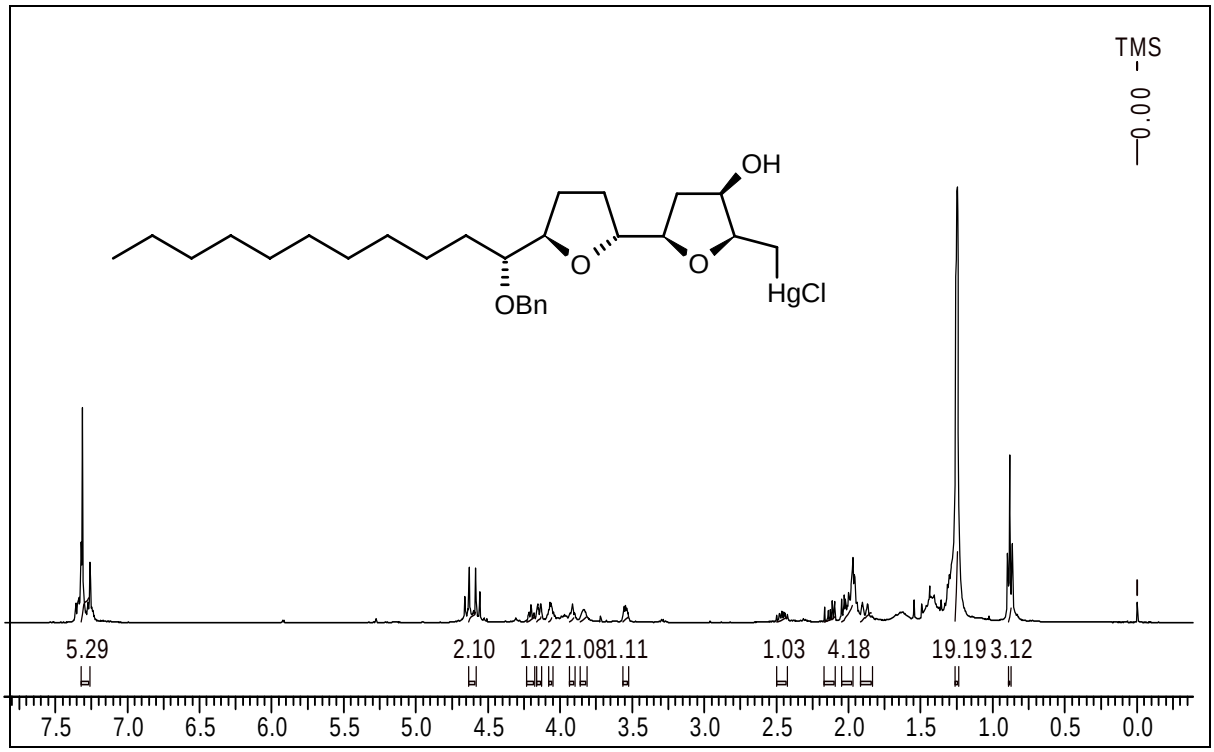
^{13}C NMR spectrum of compound 74 in $CDCl_3$



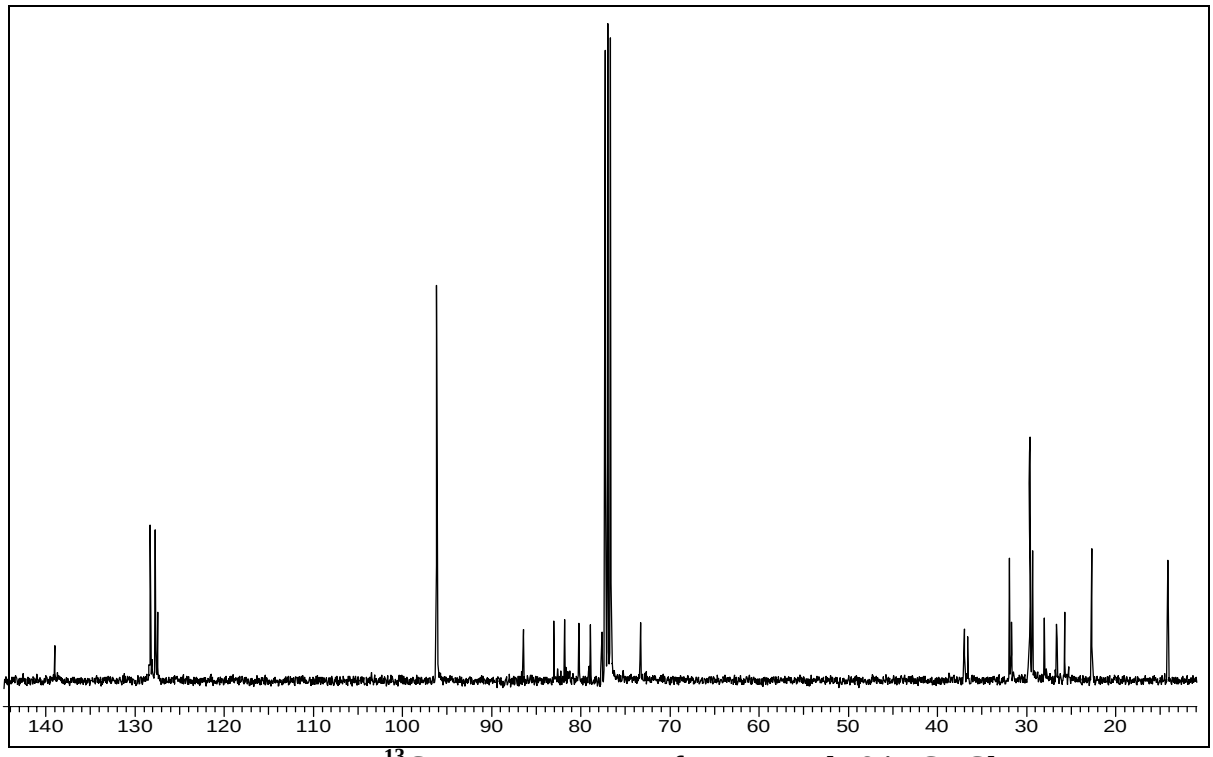
^{1}H NMR spectrum of compound 76 in $CDCl_3$



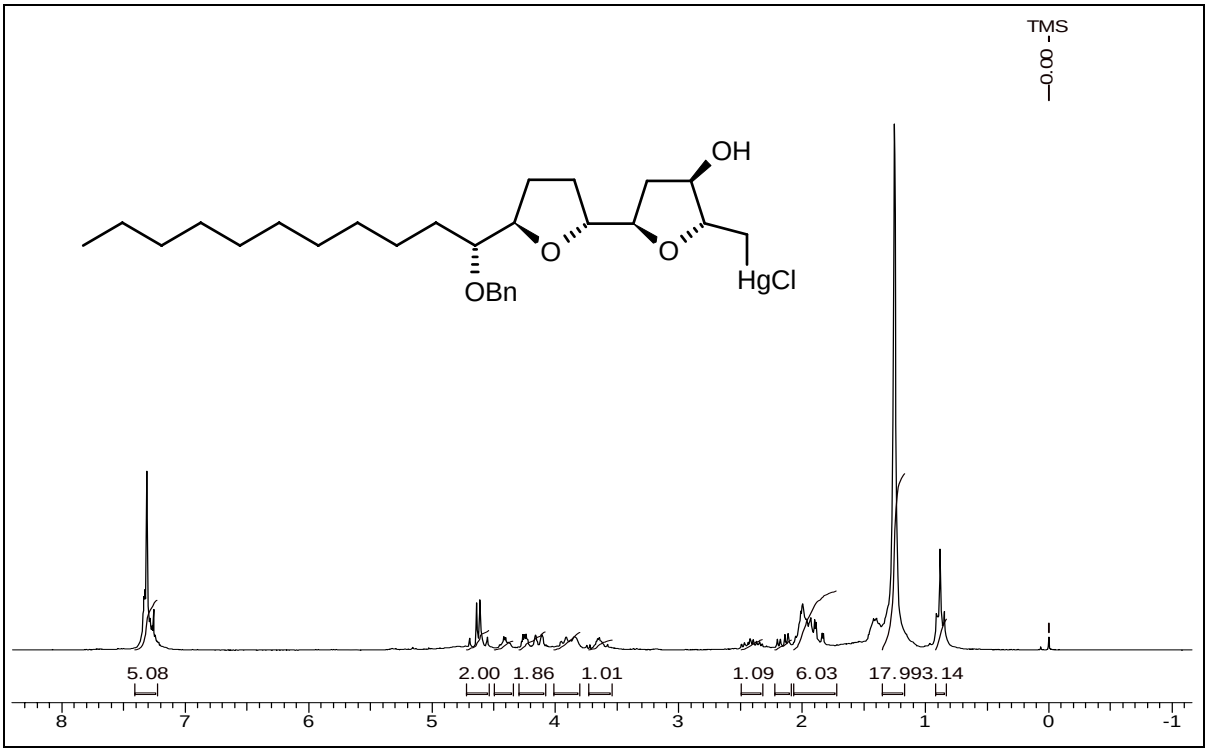
^{13}C NMR spectrum of compound 76 in $CDCl_3$



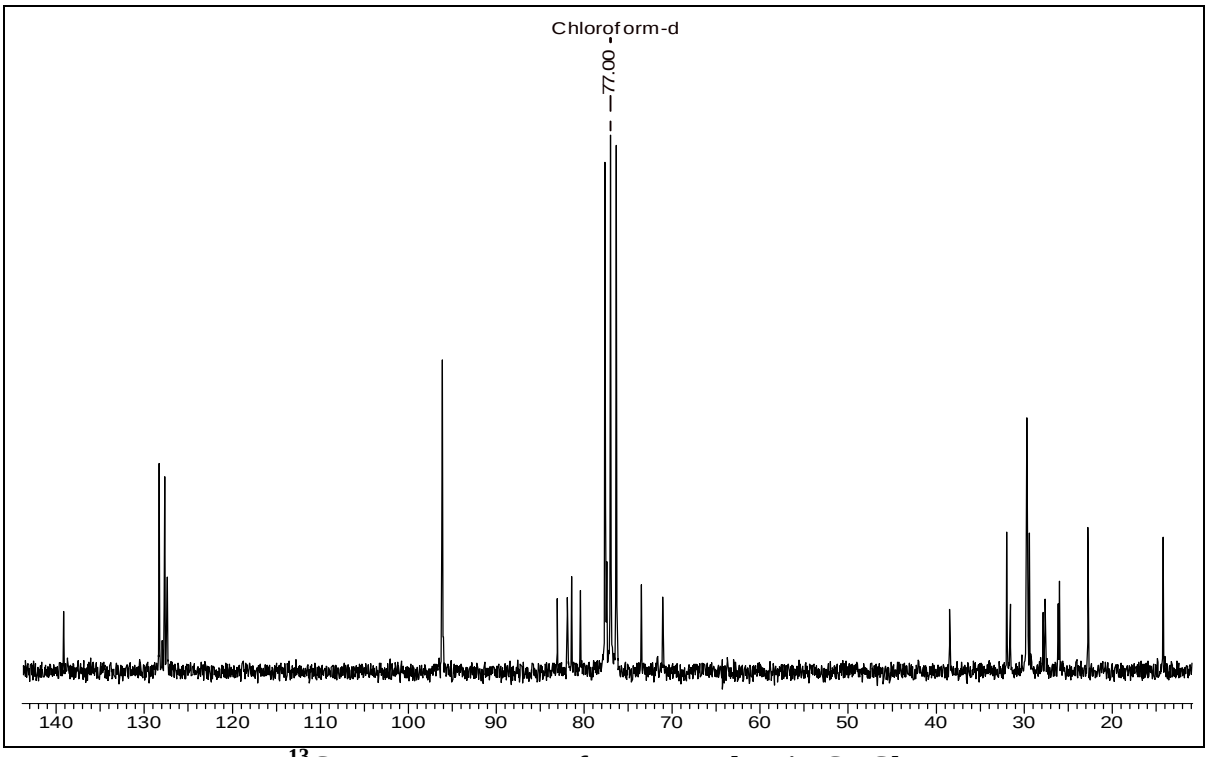
^{1}H NMR spectrum of compound 78 in $CDCl_3$



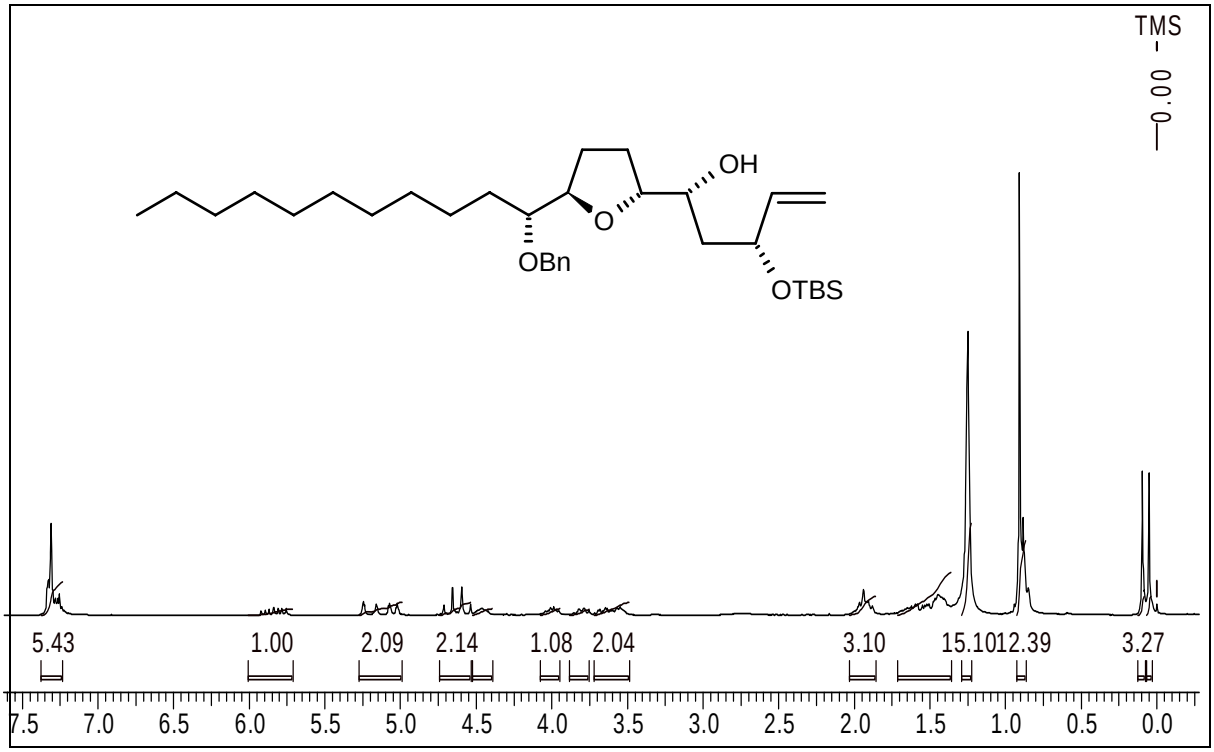
^{13}C NMR spectrum of compound 78 in $CDCl_3$



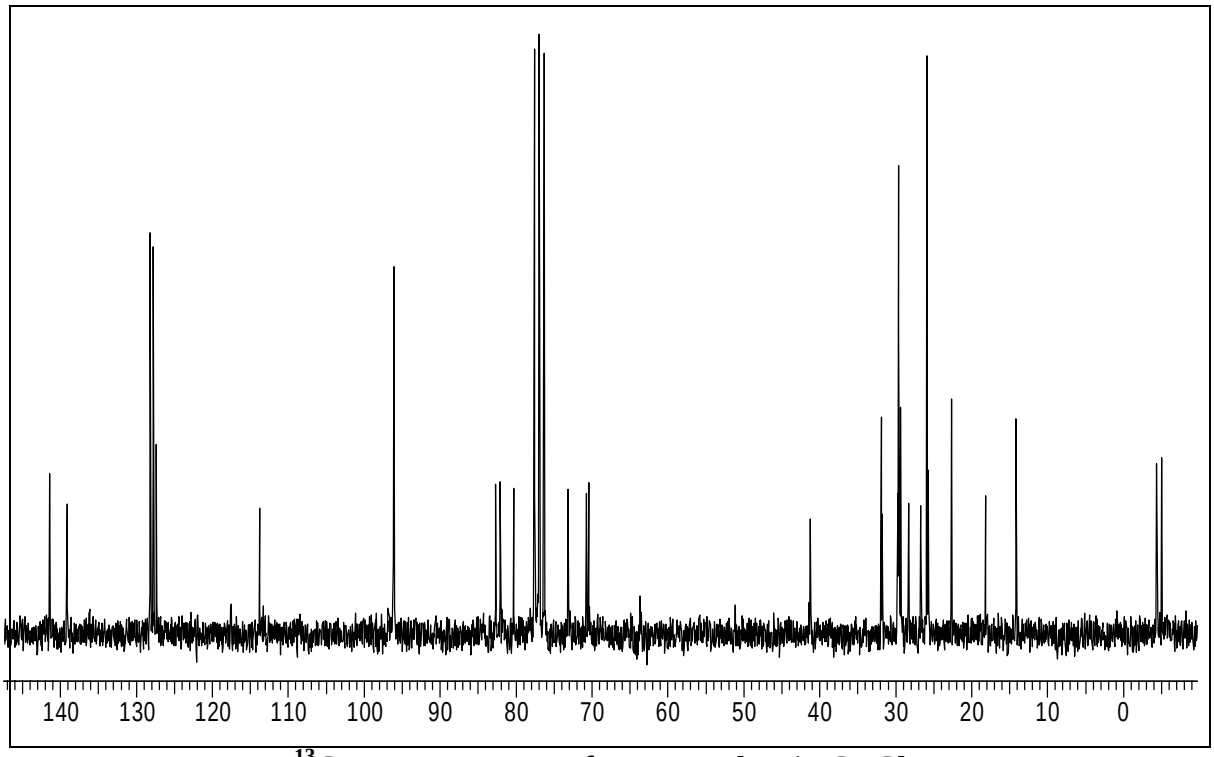
^{1}H NMR spectrum of compound 77 in $CDCl_3$



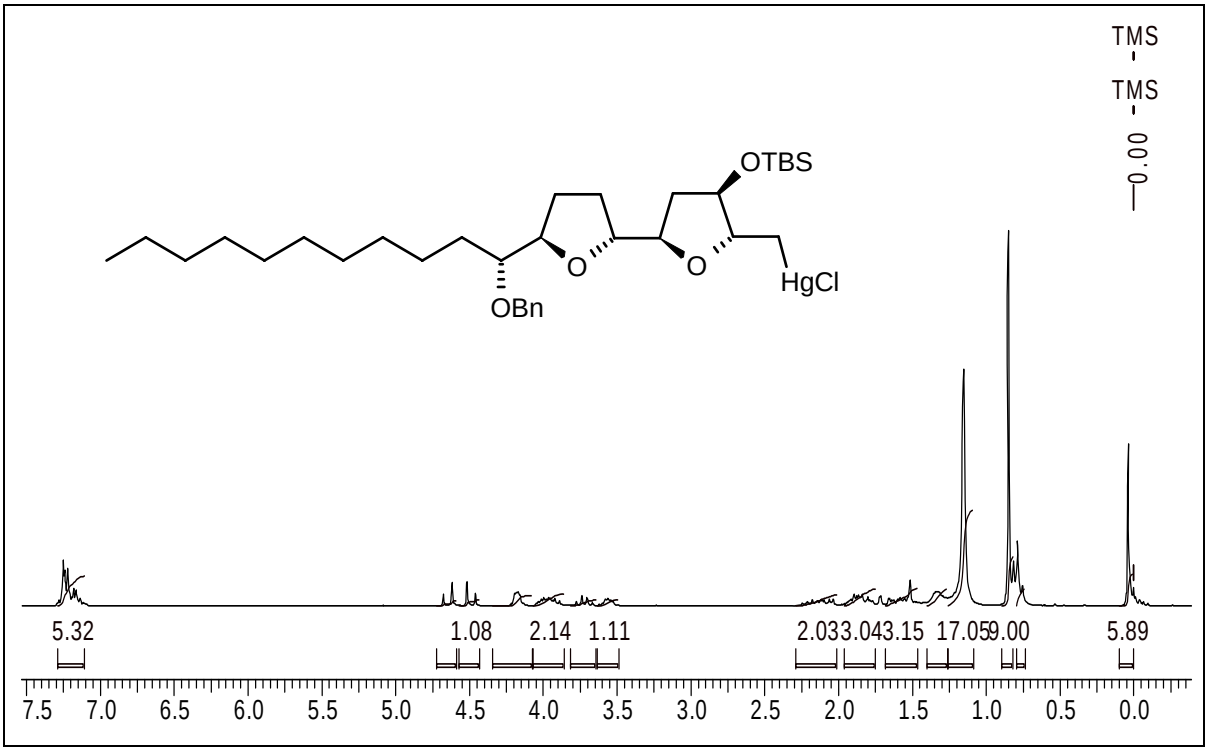
^{13}C NMR spectrum of compound 77 in $CDCl_3$



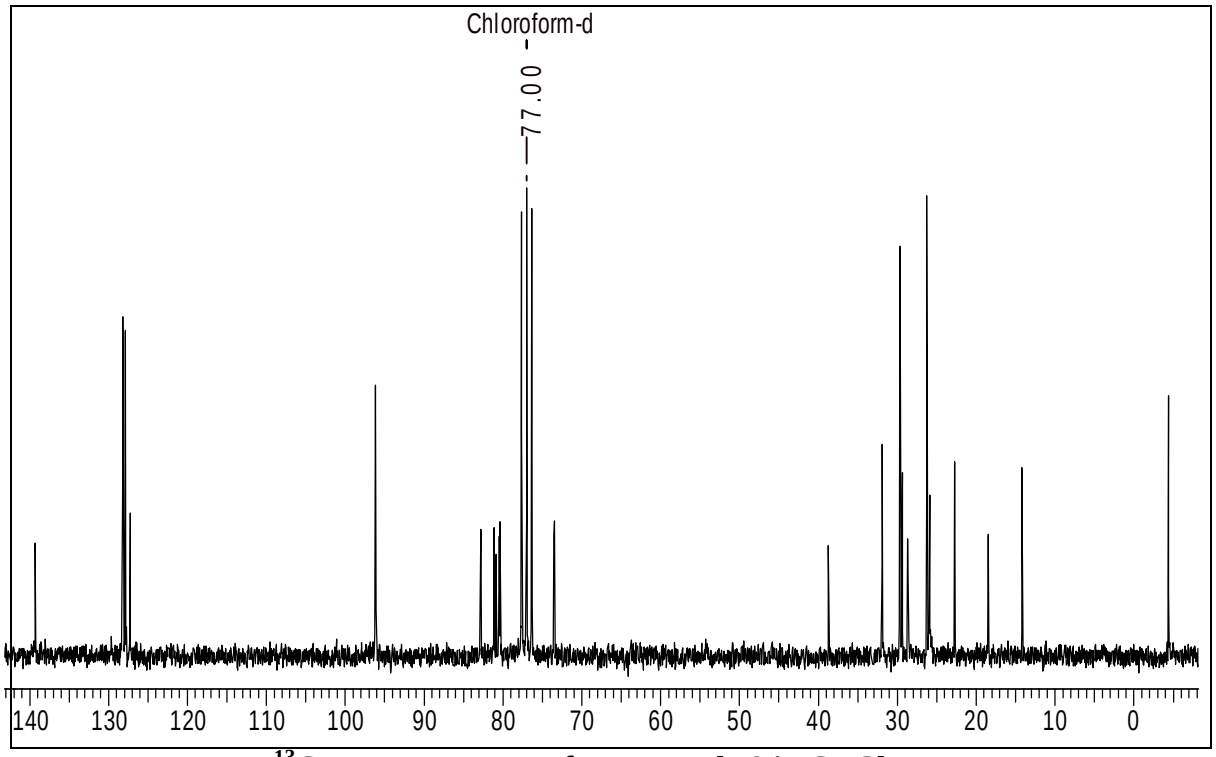
^{1}H NMR spectrum of compound 57 in $CDCl_3$



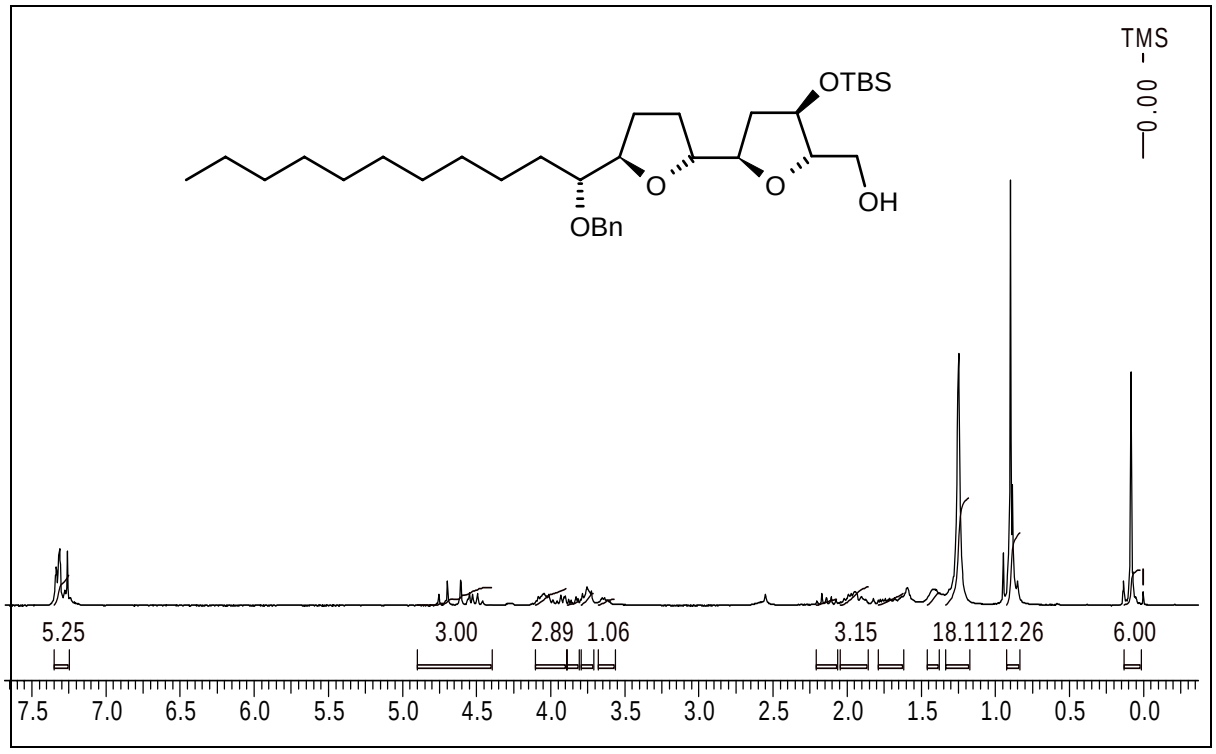
^{13}C NMR spectrum of compound 57 in $CDCl_3$



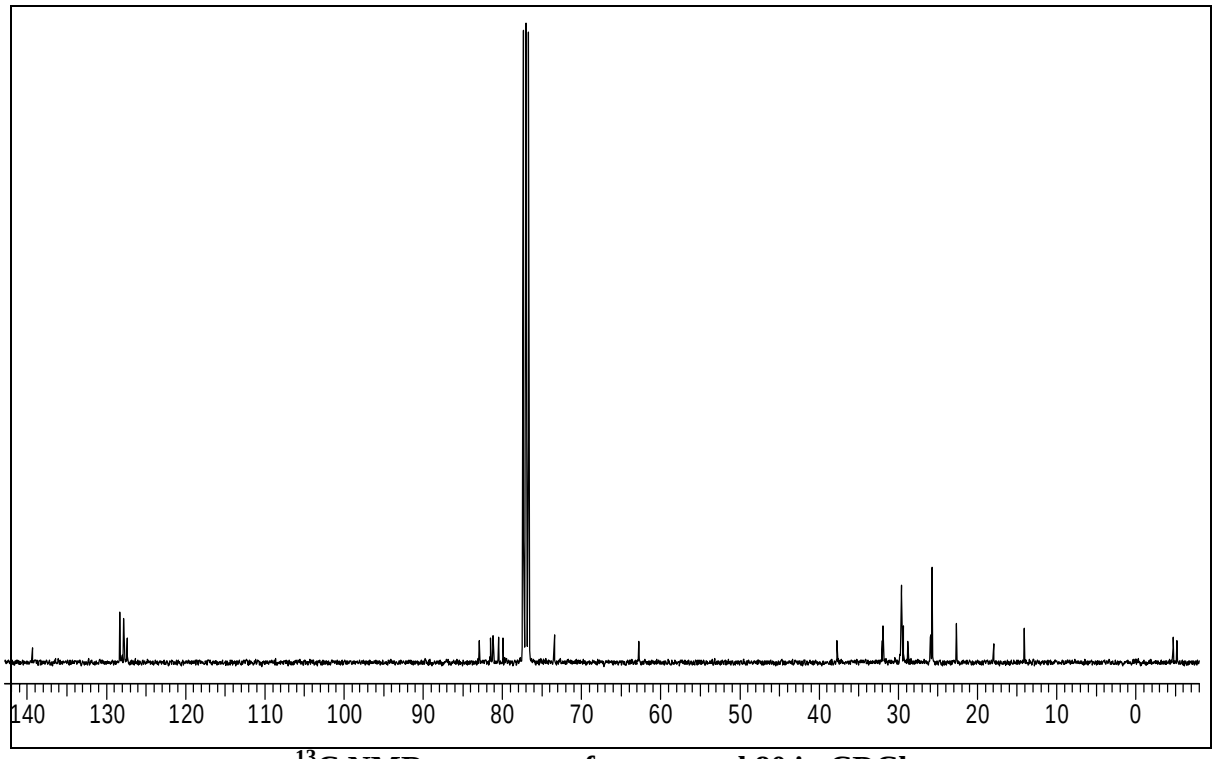
^{1}H NMR spectrum of compound 79 in $CDCl_3$



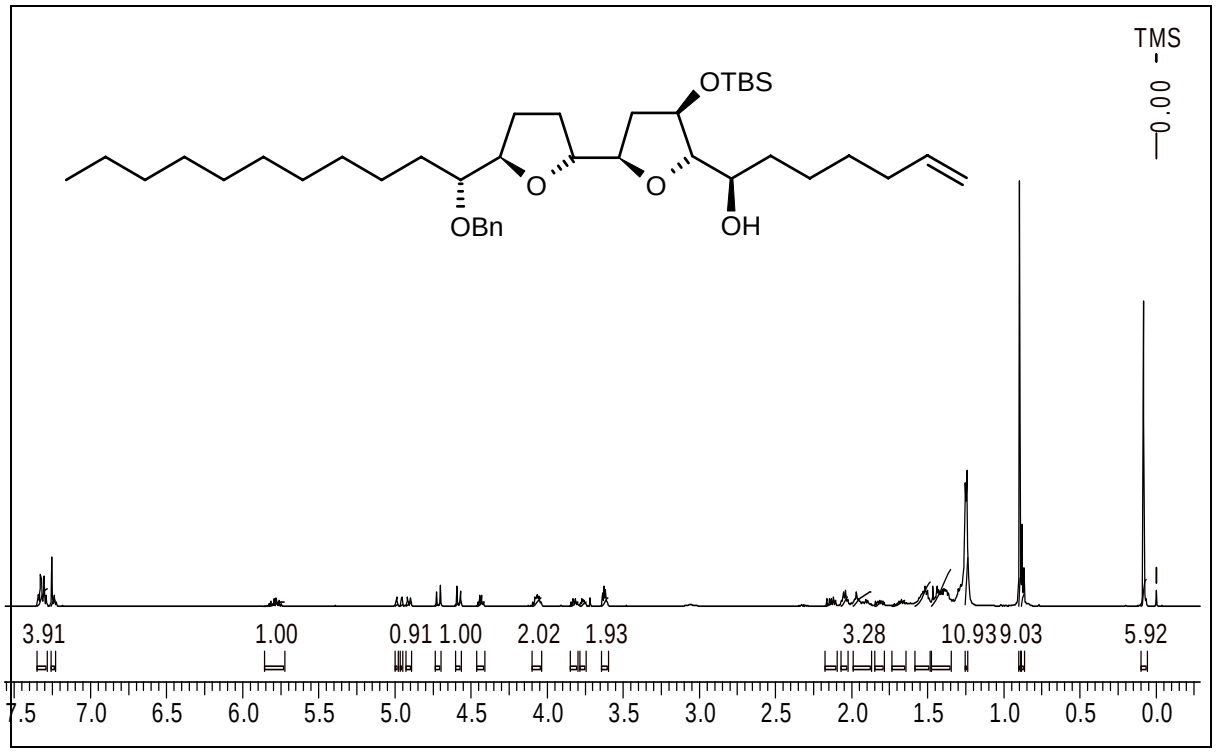
^{13}C NMR spectrum of compound 79 in $CDCl_3$



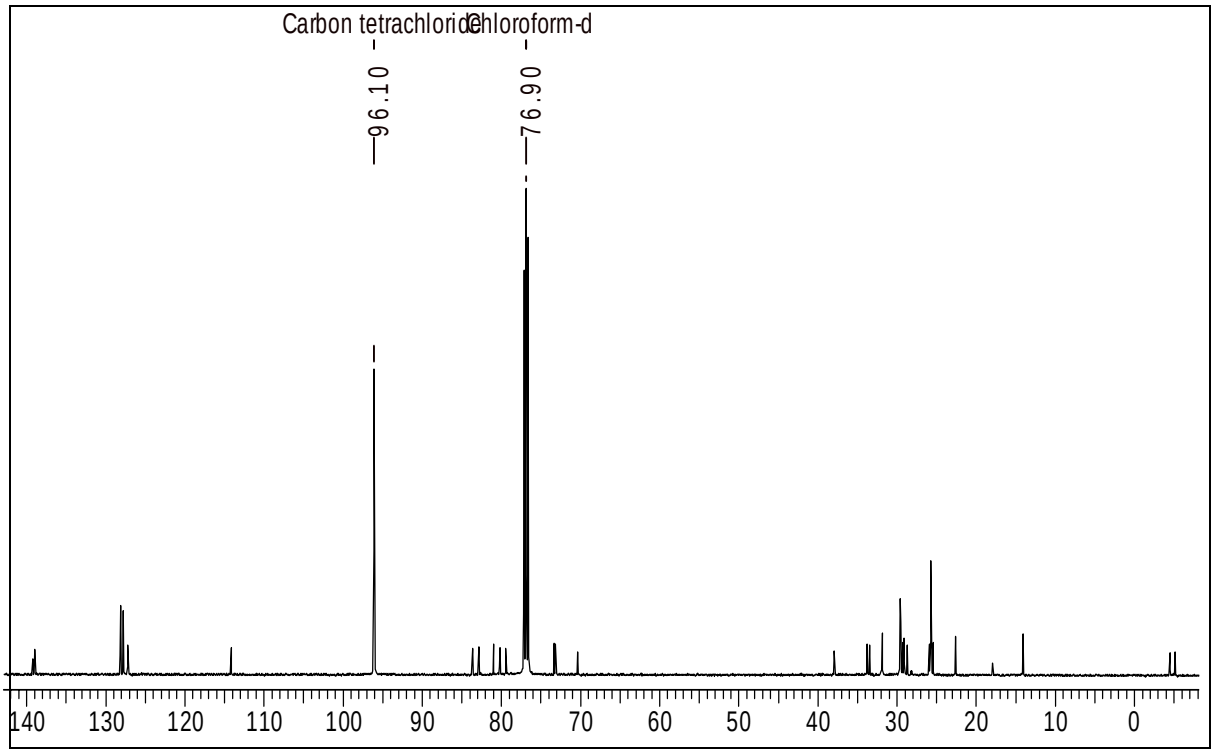
^{1}H NMR spectrum of compound 80 in $CDCl_3$



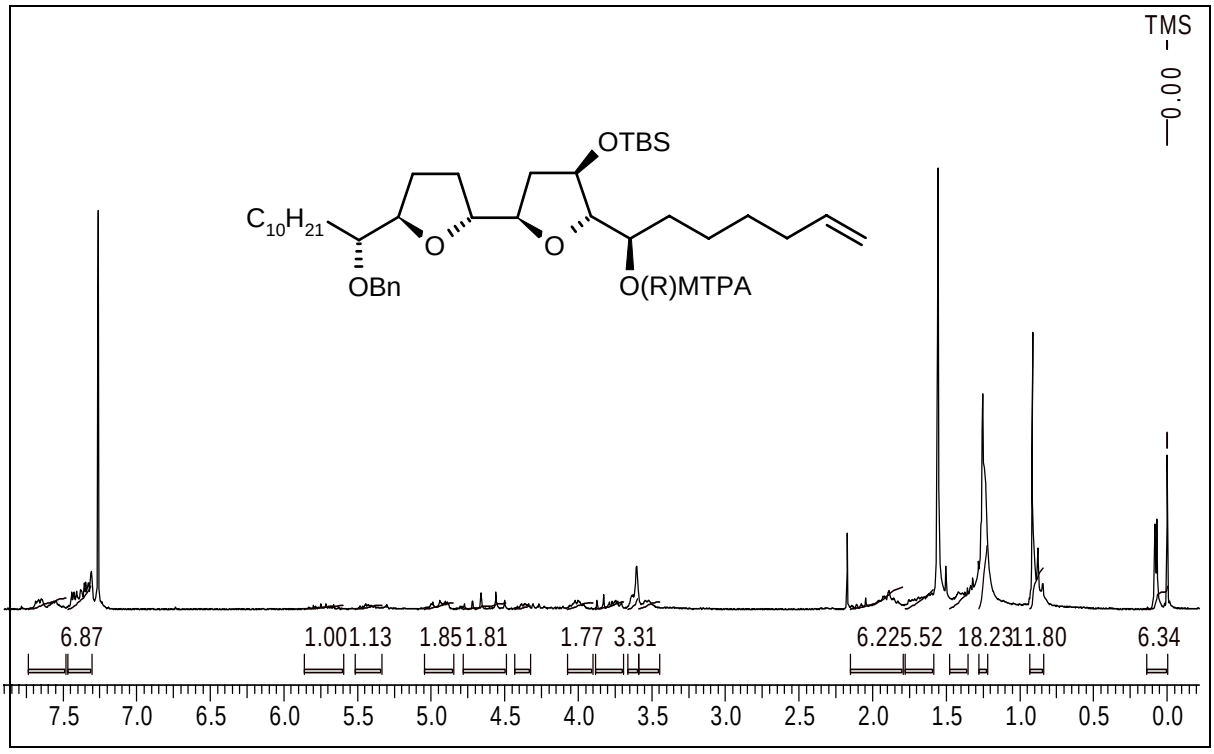
^{13}C NMR spectrum of compound 80 in $CDCl_3$



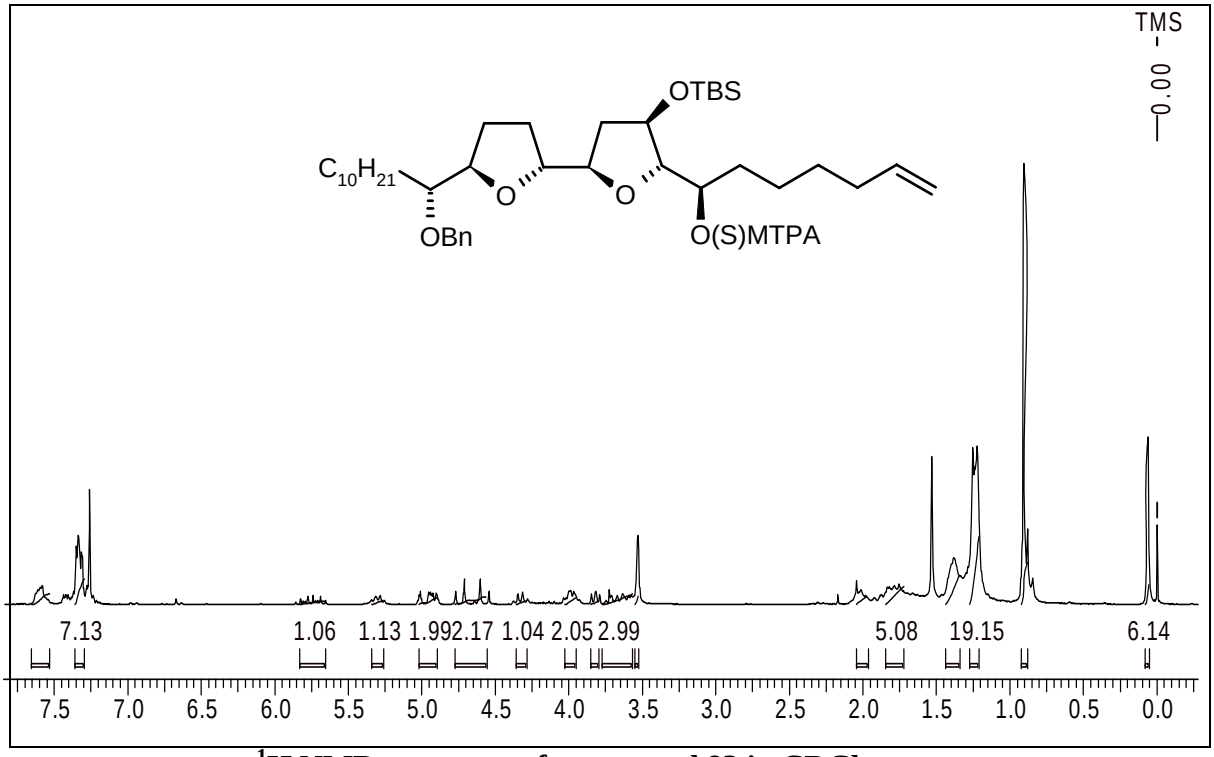
^{1}H NMR spectrum of compound 56 in $CDCl_3$



^{13}C NMR spectrum of compound 56 in $CDCl_3$



^{1}H NMR spectrum of compound 82 in $CDCl_3$



^{1}H NMR spectrum of compound 83 in $CDCl_3$

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List of publication

1. 1.Synthetic Studies toward Tricyclic Cembranoids: A modular approach for the construction of the tricyclic frame work of Eunicin": Gurjar, M. K.; **Nayak, S**; Ramana C.V. *Tetrahedron Letters* **2005**,46, 1881-1884.
2. 2.Double intramolecular oxymercuration: the first stereoslective synthesis of C10-C34 segment of Asimitrin: Mohapatra D. K.; **Nayak S**.: Mohapatra S.; Chorghade M.S. and Gurjar M. K *Tetrahedron Letter* **2007**, *48,* 5197-5200.
3. 3.Stereoselective synthesis of C-28 to C-33 Fragment of Palau'amide: **Nayak, S.** ; Mohapatra D. K. *Tetrahedron* Letter **2007**(In press)
4. 4. Synthetic studies towards Salzmanolin Gurjar, M.K.; **Nayak S.**; Mohapatra, S .; Mohapatra, D. K. (to be Comunicated).
5. one-pot synthesis of unsymmetrical bis-THF ring of nonclassical acetogenins employing intramolecular oxymercuration Gurjar, M.K.; **Nayak S.**; Mohapatra, S .; Mohapatra, D. K. (to be Comunicated).
6. Synthetic studies towards Palau'amide: Gurjar, M.K.; **Nayak S**.; Maity, P.; Mohapatra D. K :*Tetrahedron* **2007**(communicated)