Synthetic studies toward Amphidinolide E and Acetogenins

A THESIS

SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

TO

UNIVERSITY OF PUNE

BY

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UNDER THE GUIDANCE OF

DR. M. K. GURJAR

ORGANIC CHEMISTRY: TECHNOLOGY
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PUNE-411 008, INDIA

OCTOBER 2007

DEDICATED

TO MY BELOVED

PARENTS

DECLARATION

I here by declare that the 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:Technology, 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.

(SEETARAM MOHAPATRA)

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CERTIFICATE

This is to certify that the work presented in this thesis entitled **"Synthetic studies toward Amphidinolide E and Acetogenins"** Submitted by Mr. Seetaram Mohapatra, 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.

Dr. M. K. Gurjar
(Research Guide)

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SEETARAM MOHAPATRA

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
DOS	-	Diversity oriented synthesis
EtOH	-	Ethanol
Et	-	Ethyl
Et_2O	-	Diethyl ether
EtOAc	-	Ethyl acetate
Et_3N	-	Triethylamine
HETCORE	-	Heteronuclear COrrelated SpectroscopY
HMBC	-	Heteronuclear Multiple Bond Correlation
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
nOe	-	Neuclear 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
TBDMS	-	*tert*-Butyldimethyl silyl
THF	-	Tetrahydrofuran
TPP	-	Triphenylphosphine
p-TSA	-	*p*-Toluenesulphonic acid
TON	-	Turnover number
TsCl	-	*p*-Toluenesulphonyl chloride

- ^{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_{α} 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

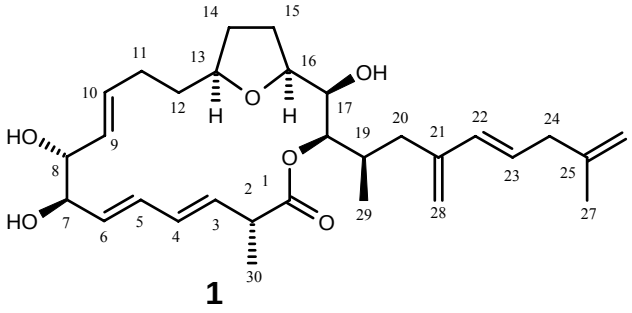
Research Student	: Seetaram Mohapatra
Research Guide	: Dr. Mukund K.Gurjar
Title of Thesis	: **"Synthetic studies toward Amphidinolide E and Acetogenins"**
Registration no.	: E1/86/Ph.D/2005
Date of registration	: 5-05-2004
Place of work	: Division of Organic Chemistry: Technology, National Chemical Laboratory, Pune

Abstract

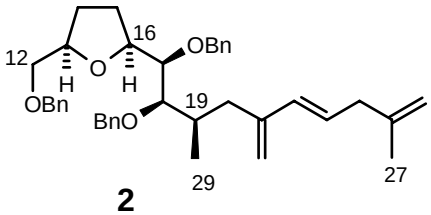
The thesis entitled **"Synthetic studies toward Amphidinolide E and Acetogenins"** has been divided into two chapters**.** The first chapter is further subdivided into two sections. The first section describes the synthesis of C12-C29 fragment of amphidinolide E and second section emphasizes on the studies toward the synthesis of macrolactone of amphidinolide E. The second chapter is also subdivided into three sections. First section deals with the synthesis of bis–THF ring cores of Annonaceous Acetogenins, second section describes the synthetic studies toward Mucoxin and the third section explains the synthesis of central core of Salzmanolin.

Chapter-1: Section 1: Synthesis of C12-C29 fragment of amphidinolide E

The family of amphidinolides, isolated from the marine dinoflagellates *Amphidinium sp*. exhibit a significant anti-tumor activity against a variety of NCI tumor cell lines. Among them, the amphidinolide E1 has a unique feature of having a 19-membered macrocyclic ring, which has been elucidated by 2D NMR. The relative stereochemistry of eight chiral centers positioned at C2, C7, C8, C13, C16, C17, C18 and C19 were confirmed by a combination of the *J*-based configuration method and detailed NOESY experiments.



1



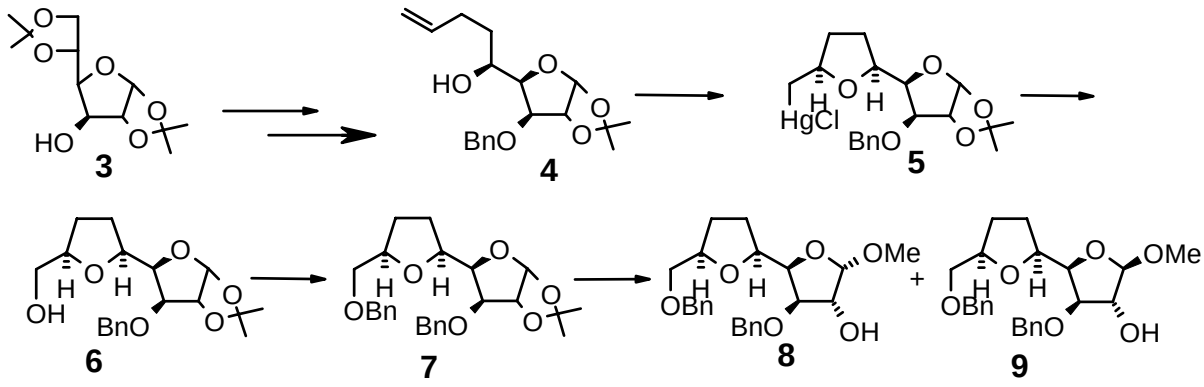
2

C12-C29 fragment

Fig. 1: Structure of amphidinolide E **1**

The absolute stereochemistry of **1** was determined by the exciton chirality method coupled with Mosher's method. Due to its unique structural features, notable biological activity, and limited availability, the amphidinolide group of molecules represents attractive targets towards their total synthesis. Herein, a synthetic approach towards C12–C29 fragment **2** of amphidinolide E starting from D-glucose is described.

Scheme 1

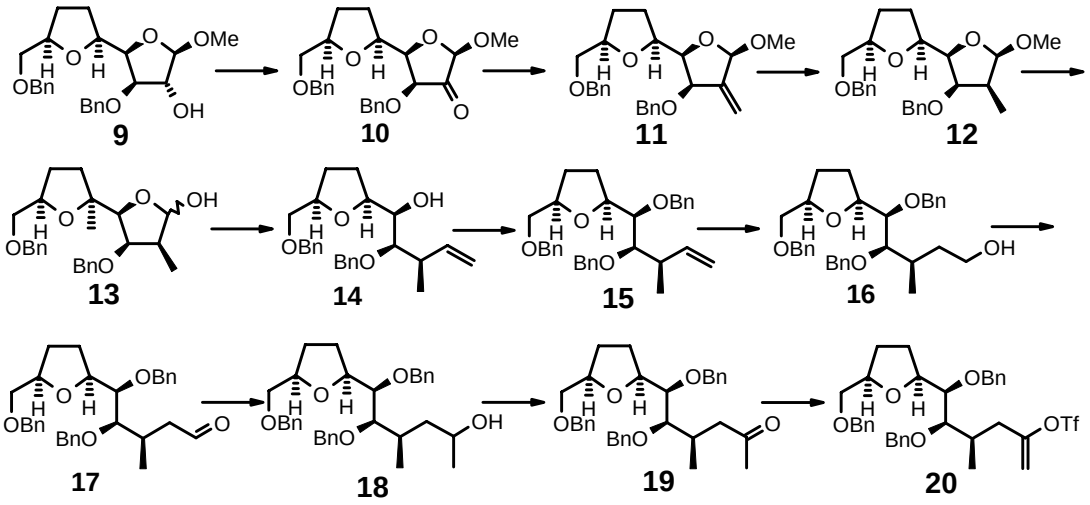


The intermediate **4** was prepared from D-glucose following the known literature procedure. The oxymercuration reaction of **4** gave a cis–trans mixture of tetrahydrofuran derivatives in the ratio of 3:1 *(cis:trans)* which were conveniently separated by flash silica gel chromatography to obtain the pure cis-tetrahydrofuran **5**. The stereochemistry of **5** was unambiguously determined by single crystal X-ray crystallography. The demercuration of **5** was carried out under a stream of oxygen in the presence of $NaBH_4$ to

give primary alcohol **6**, which was benzylated to form**7**. The compound **7** was refluxed with methanol in the presence of amberlyst IR120 to give pure ß-glycoside **9** (Scheme 1).

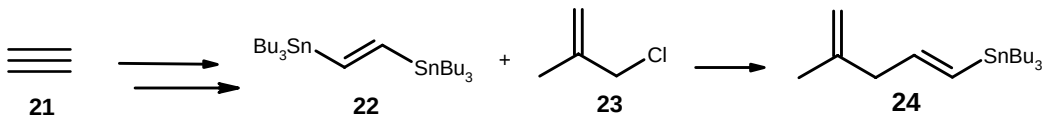
The secondary hydroxyl group present in **9** was oxidized with IBX in DMSO to get the 2-ulose derivative **10**, which was subjected to one carbon Wittig olefination to produce the olefin **11**. The hydrogenation of the double bond in presence of 10% Pd–C afforded the C_2 methyl compound **12** exclusively. The methyl glycoside **12** was

Scheme 2



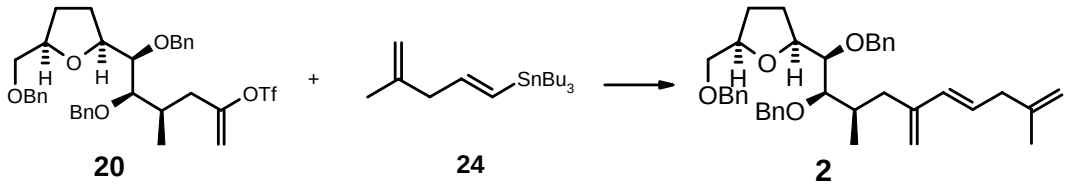
hydrolysed to form lactol **13** which on further one carbon wittig olefination gave **14**. The secondary hydroxyl group in **14** was benzylated to obtain **15** which on subsequent hydroboration – oxidation reaction yielded the primary alcohol **16**. The **c**ompound **16** on oxidation with Dess–Martin periodinane (DMP) afforded the aldehyde **17**, which on subsequent treatment with methylmagnesium bromide gave secondary alcohol **18**. The Compound **18** was further oxidized to methyl ketone **19** by using Dess Martin periodinane which was converted to triflate **20** by treatment with LDA and *N*-(2-pyridyl)-triflimide (Scheme 2).

Scheme 3



The known Bis-ethylene distannane **22** was reacted with methallyl chloride in the presence of $PdCl_2(CH_3CN)_2$ followed by distillation to give **24** (Scheme 3).

Scheme 4



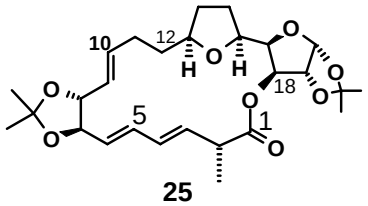
20 **24** **2**

The triflate derivative **20** was coupled with stannane **24** by the modified Stille coupling reaction to give the desired fragment **2** (Scheme 4).

In conclusion, the C_{12}–C_{29} fragment of amphidinolide E1 was synthesized successfully.

Chapter-1: Section 2: Studies toward the synthesis of macrolactone core of amphidinolide E.

After achieving the C_{12}–C_{29} fragment **2** of amphidinolide E, we next paid out attention for the synthesis of macrolactone **25**, which was found to be an important core structure of amphidinolide E.

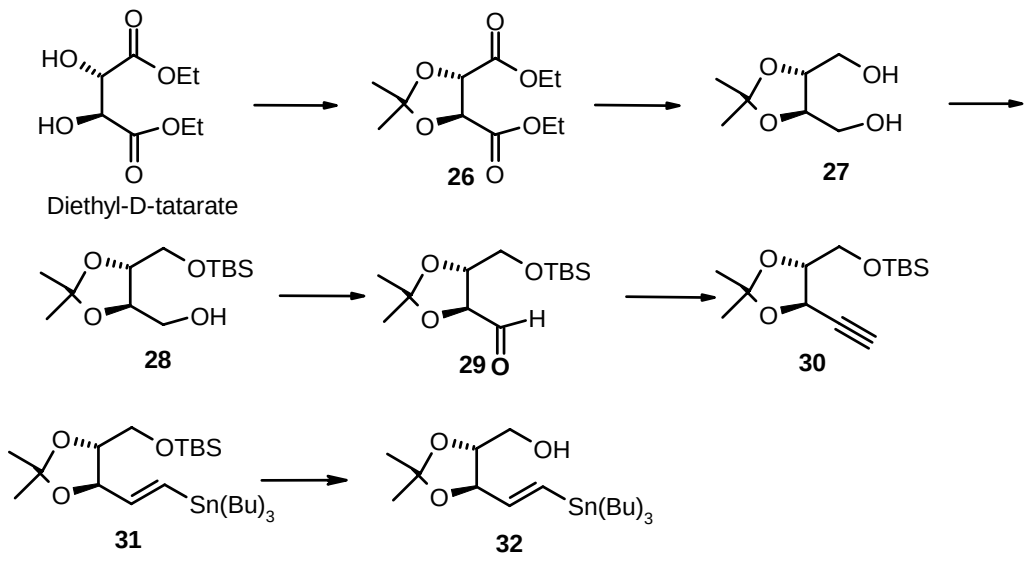


25

The synthesis of the macrolactone **25** was envisioned by esterification of C18 hydroxyl group and C1 carboxylic acid followed by ring closing metathesis as the key steps. The C1– C10 fragment of the macrolactone was obtained by using modified Stille coupling of the stannane derivative **32** and vinyl halide **37**.

Synthesis of compound (32):

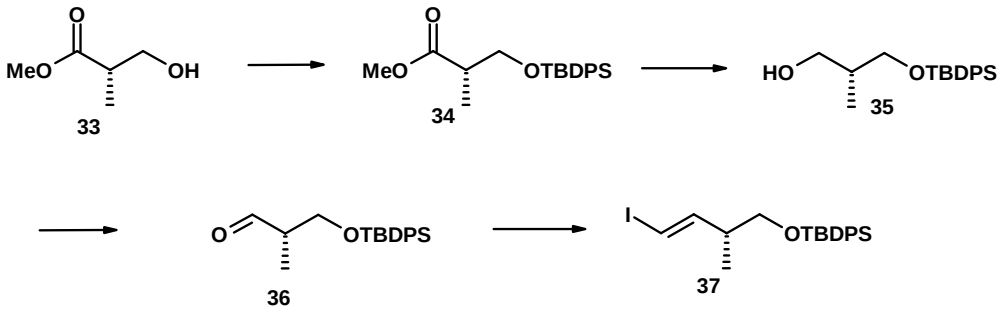
Scheme 5



The (-)-diethyl-D-tartarate was protected as its isopropylidene derivative **26** and reduced to diol **27** by using lithium alumunium hydride. The diol **27** was then mono-protected as its TBS ether **28**. The primary alcohol of **28** was oxidised to aldehyde **29** followed by treatment of Ohira-Bestmann's reagent to afford the alkyne **30**. The alkyne moiety **30** was converted to vinyltin derivative **31** by treating with tributyltin hydride and AIBN. The deprotection of TBS ether **31** by TBAF gave the alcohol **32** (Scheme 5).

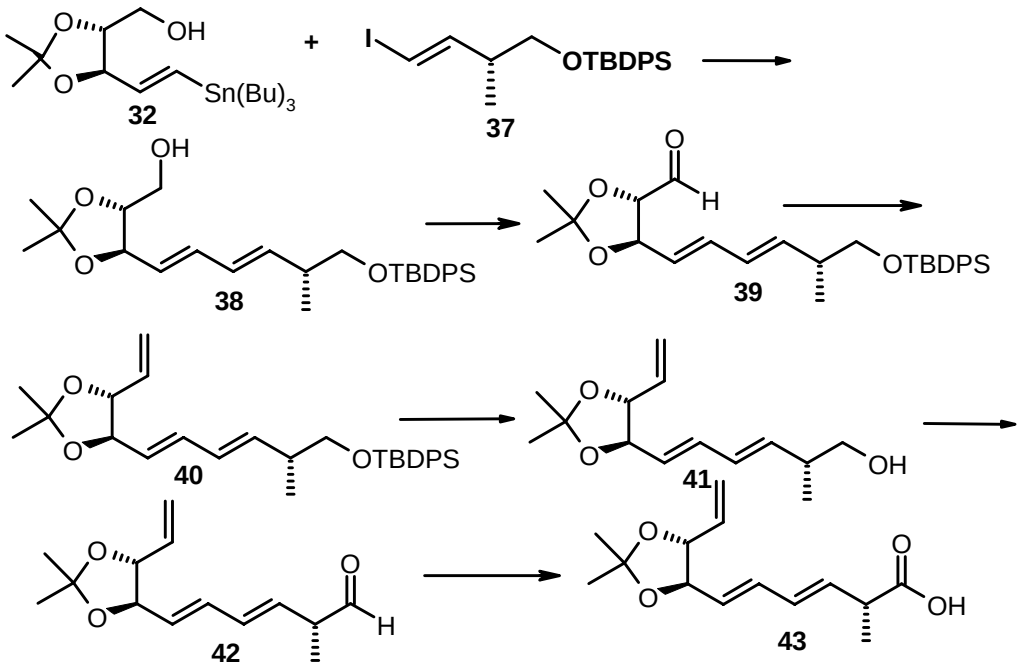
Synthesis of Vinyliodo derivative 37:

Scheme 6



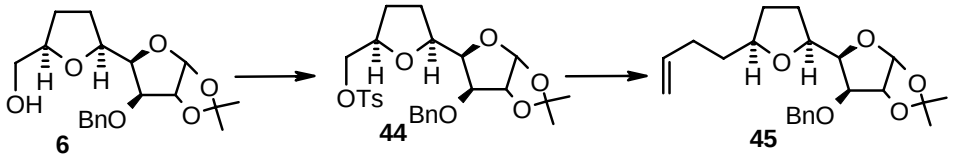
The (*S*)-3-hydroxy-2-methyl propionate **33** was protected as its TBDPS ether **34** and reduced by DIBAL-H to get the alcohol **35**, which on further oxidation with IBX followed by Takai olefination resulted in the formation of vinyl iodo compound **37** (Scheme 6).

Scheme 7



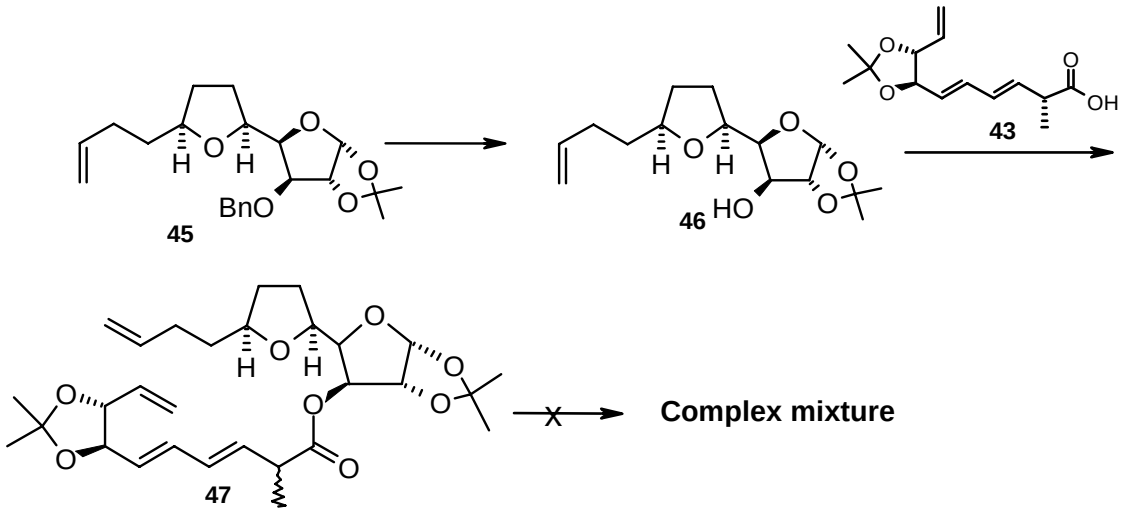
The Stille coupling of vinyl iodo derivative **37** with vinyl stannane **32** in presence of palladium(0) catalyst afforded the diene **38**. The primary hydroxyl group of **38** was oxidized to aldehyde **39** followed by one carbon Wittig olefination afforded compound **40**. The deprotection of TBDPS ether group by tetrabutyl ammonium fluoride furnished the alcohol **41**. Alcohol **41** was oxidized by IBX to give the corresponding aldehyde **42**, which was then converted to acid **43** using sodium chlorite and NaH_2PO_4(Scheme 7).

Scheme 8



The compound **45** was obtained from the substrate **6.** The primary hydroxyl **6** was converted to tosyl ether **44** which undergoes displacement reaction with diallyl lithium cuprate at -78 ºC to give **45** in good yield (Scheme 8).

Scheme 9



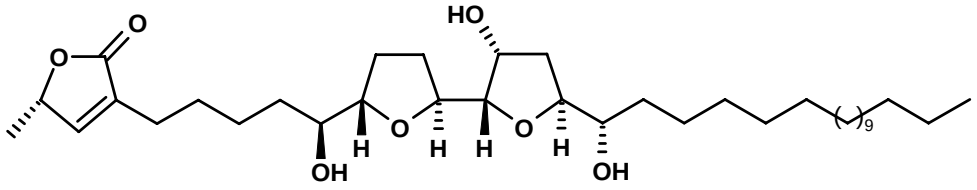
The deprotection of the benzyl ether **45** by sodium-naphthalene at 0 ^{o}C gave the secondary alcohol **46**. Esterification of acid **43** with alcohol **46** under Yamaghuchi condition afforded an epimeric mixture of compounds **47**, which was subjected to RCM reaction using Grubbs'2nd generation catalyst to obtain complex mixture of products (Scheme 9).

In conclusion we have synthesized acid component **43** sucessfully following Stille coupling as our key reaction. Studies are in progress to achieve the desired product in esterification and carrying out ring closing metathesis reaction to get the cyclic lactone in our laboratory.

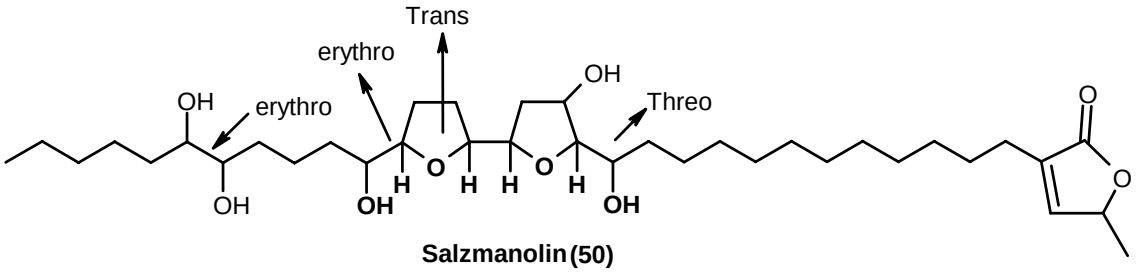
Chapter-2: Section 1: Synthesis of Bis–THF Ring cores in Annonaceous Acetogenins.

In recent years, the Annonaceous acetogenins have been in the limelight due to their remarkable range of biological properties such as antitumor, antiprotozoal, antifeedant, immunosuppressive, pesticidal, anathematic and microbial etc. In particular the 2,5-disubstituted bis-tetrahydrofuran (classical acetogenins) sub-group of this family has been found to inhibit the growth of human tumor cells at sub-micromolar levels. A large proportion of such compounds are also cytotoxic to tumor cells that are resistant to

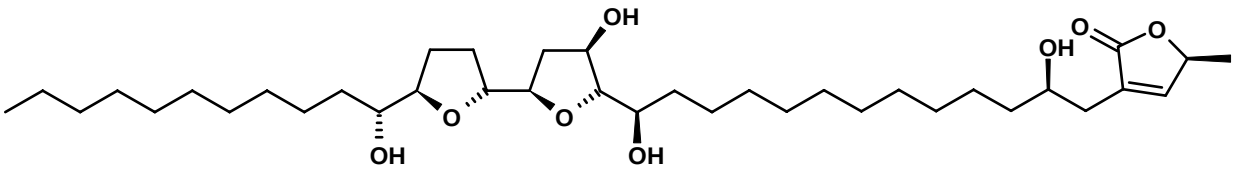
typical chemotherapeutic agents. More recently, new nonclassical acetogenins containing more complex tetrahydropyran (THP) rings and/or THF rings as the core have been isolated; examples of such are mucocin, pyragonicin, and Jimenezin, all of which are THP-containing acetogenins and have recently succumbed to total synthesis. Mucoxin, a nonclassical acetogenin, is the first of its kind found to contain a trisubstituted hydroxylated THF ring. In vitro cytotoxicity assays against a panel of six human tumor cell lines have shown mucoxin **49** to be more potent and selective against MCF-7 (breast carcinoma) cell lines than adriamycin. Mucoxin **49**, a nonclassical acetogenin, is the first of its kind found to contain a trisubstituted hydroxylated tetrahydrofuran ring. Recently, Asimitrin **51** and Salzmanolin **50** ring-hydroxylated unsymmetrical bis-tetrahydrofuran acetogenin were isolated. This class of compound showed cytotoxic selectivity with 100–10,000 times the potency compared to the classical acetogenins. These compounds have attracted the attention of synthetic organic chemists worldwide due to the diverse array of biological activities and by virtue of their extremely limited availability in nature,



Mucoxin (49)



Salzmanolin (50)



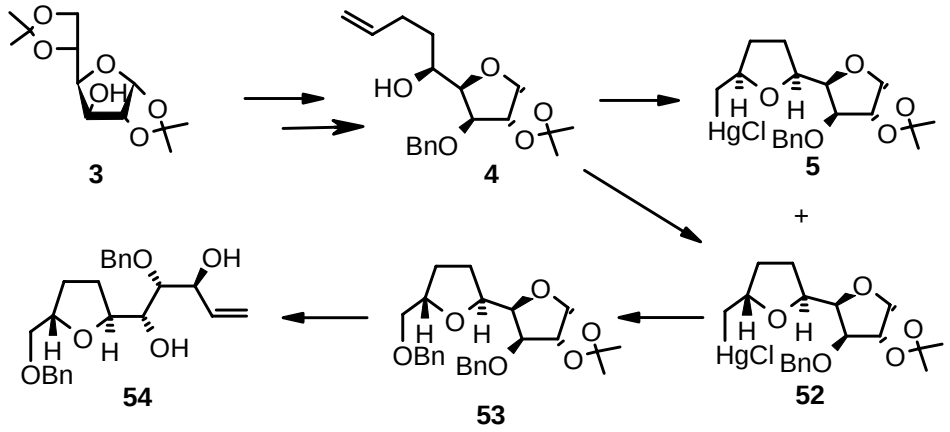
Asimitrin (51)

Stereocontrolled construction of the tetrahydrofuran unit plays a pivotal role in the total synthesis of annonaceous acetogenins. The application of an intramolecular oxymercuration strategy for an efficient synthesis of mono-and dihydroxylated bis-

tetrahydrofuran systems could be used towards building the naturally occurring acetogenins.

The stereocontrolled off-template construction of the first tetrahydrofuran ring was planned to utilize an intramolecular oxymercuration protocol on 4-alkenol derivative **4** followed by a second one on **54** to achieve to the target compound.

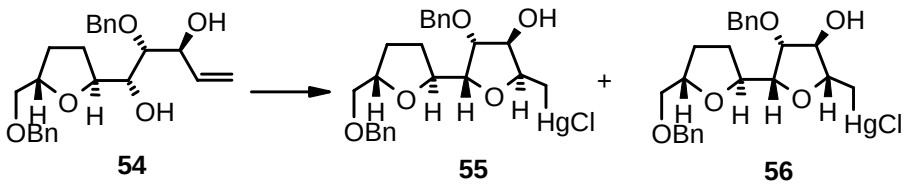
Scheme 10



The known intermediate **4** was prepared from D-glucose. The intramolecular oxymercuration reaction of **4** with mercuric chloride in water at room temperature afforded a cis–trans mixture of tetrahydrofuran derivatives with 3:1 selectivity. The mixture was conveniently separated by flash silica gel column chromatography to obtain the pure cis- and trans-tetrahydrofurans **5** and **52**. The stereochemistry of **5** was unambiguously confirmed by single-crystal X-ray crystallography. It is noteworthy that treatment of compound **4** with mercury (II) acetate in THF led to the formation of **52** exclusively. As suggested earlier, the mercurium ion formation followed by intramolecular nucleophilic attack by the C-5 hydroxyl group from the opposite face would have lead to the formation of trans-isomer as the sole product. In the presence of H_2O, the coordination is prevented and hence it leads to a mixture of cis- and trans-tetrahydrofuran products. The demercuration was then carried out by passing a stream of oxygen in the presence of sodium borohydride to obtain the primary alcohol, which on benzylation gave **53**.Our next concern was to construct the second tetrahydrofuran ring with substitution at C-3 and C-4 from the carbohydrate moiety. Thus, the compound **53** was treated with 20% acetic acid in the presence of a catalytic amount of sulfuric acid under reflux conditions to afford the hemiacetal, which was further purified by silica gel

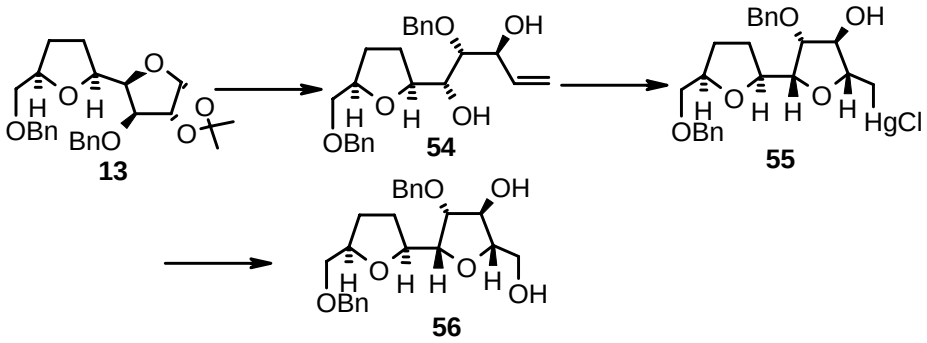
column chromatography. It was then subjected to one carbon homologation to produce the olefin **54** (Scheme 10).

Scheme 11



The treatment of compound **54** with mercury (II) acetate in dichloromethane or THF afforded **56** as the major product, while in the presence of H_2O, the compound **55** was the major product. Both the stereoisomers were separated easily by silica gel column chromatography (Scheme 11).

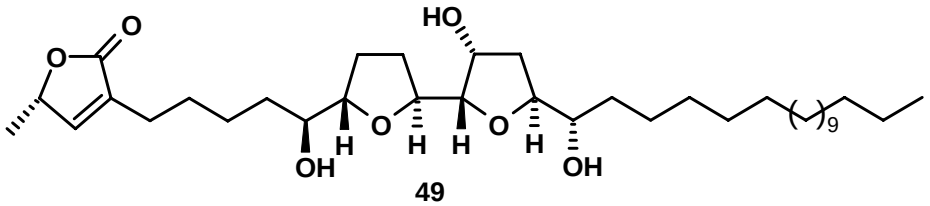
Scheme 12



Similarly mercury cyclisation on the compound **54**, gave the bis-THF compound **56** with the same stereochemistry (Scheme 12).

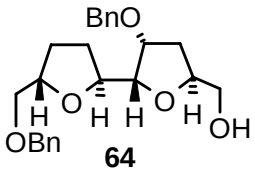
In conclusion, the stereocontrolled routes for the preparation of various functionalized bis-tetrahydrofuran derivatives which are the subunits of several polyether antibiotics and acetogenins could be easily prepared from D-glucose.

Chapter-2: Section 2. Synthetic studies toward Mucoxin.



49

Mucoxin

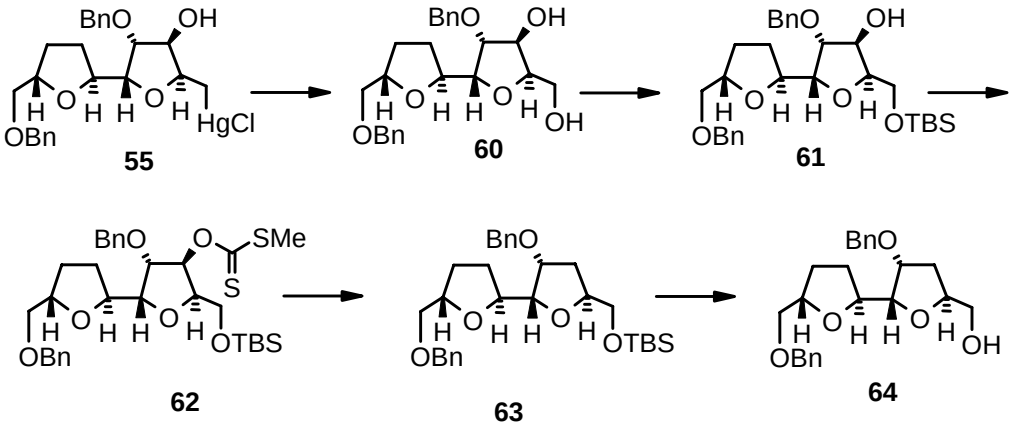


64

Mucoxin **49**, a nonclassical acetogenin, is the first of its kind found to contain a trisubstituted hydroxylated THF ring isolated by McLaughlin in 1996. In vitro cytotoxicity assays against a panel of six human tumor cell lines have shown mucoxin to be more potent and selective against MCF-7 (breast carcinoma) cell lines than adriamycin.

The mercury mediated cyclisation protocol has been applied to the synthesis of hydroxylated terahydrofuran **64** has been illustrated below.

Scheme 13

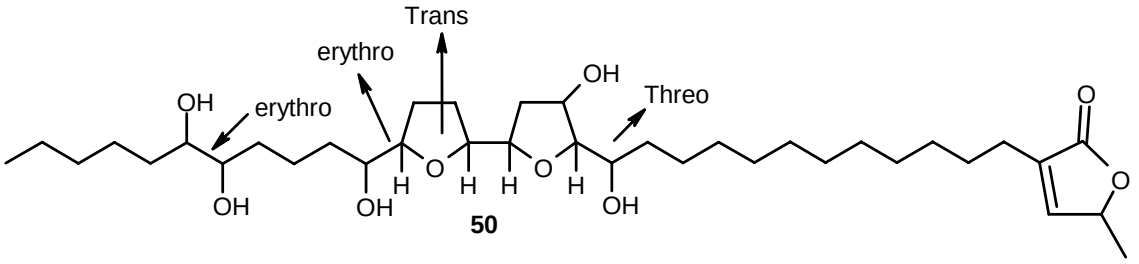


The demercuration of **55** under a stream of oxygen in the presence of sodium borohydride gave alcohol **60**, which was protected as TBS ether **61** using TBS-Cl, imidazole. The secondary hydroxyl group of **61** was removed following Barton-Mc Combie protocol via the xanthate **62** and treatment of tributylstannane to produce

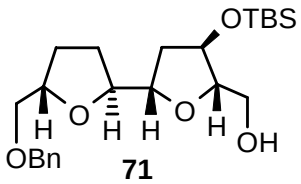
deoxygenated product **63.** Cleavage of the silyl ether using tetrabutylammonium flouride gave compound **64** (Scheme 13).

In conclusion, we have synthesized bis-THF core of mucoxin stereoselectively using mercuration reaction as key step.

Chapter-2: Section 3: Synthesis of central core of Salzmanolin



50

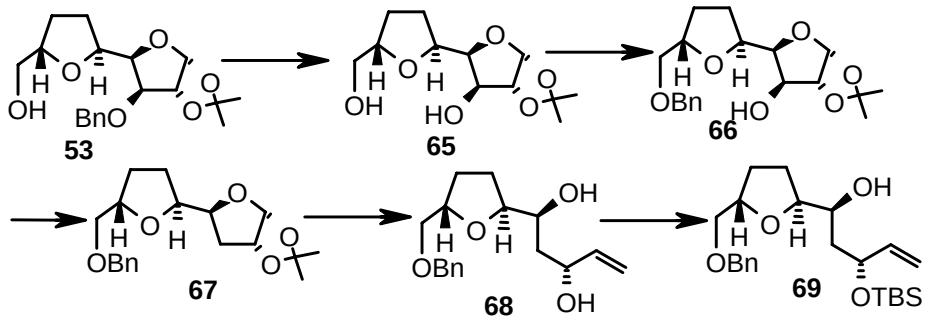


71

Recently, Salzmanolin, a ringhydroxylated unsymmetrical bis-tetrahydrofuran acetogenin was isolated by Queiroz in 2003. It displayed significant activities for a cancer cell line when compared with normal cells. The molecular weight of Salzmanolin, established by LSI MS as 654 from the [M + Na]+ ion observed at *m*/*z* 677.3, is in agreement with the molecular formula $C_{37}H_{66}O_9$. Strong absorptions at 209 nm and 1750 cm-1 in the UV and IR spectra, respectively, indicated the presence of an α, β-unsaturated γ-lactone moiety.

Application of our efficient protocol for the synthesis of the hydroxylated tetrahydrofuran skeleton of Salzmanolin has been illustrated.

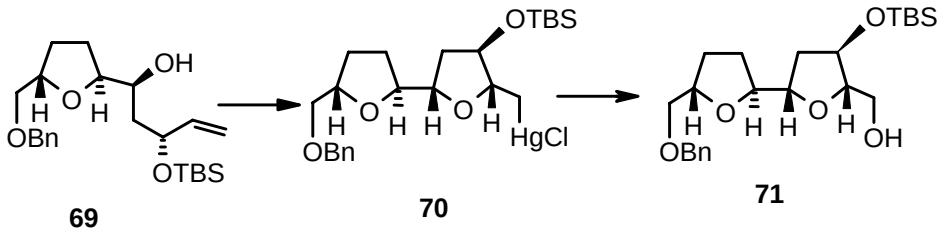
Scheme 14



53 **65** **66** **67** **68** **69**

Our synthesis started from earlier synthesized compound **53.** Debenzylation of the secondary hydroxy group in **53** gave **65** which was subjected to selective mono benzylation of the primary hydroxyl to give benzyl ether **66.** The deoxygenation of **66** using Barton–McCombie protocol via Xanthate gave **67.** The 1,2 isopropylidene of **67** was cleaved under acidic condition to give hemiacetal, which on subsequent treatment with methylenetriphenylphosphorane resulted in **68**. The allylic alcohol **68** was selectively protected as TBS ether **69** using TBSCl and imidazole in CH_2Cl_2(Scheme 14).

Scheme 15



Treatment of compound **69** with mercury (II) acetate in THF afforded **70** as a major product and demercuration of **70** with $NaBH_4$ in presence of O_2 afforded **71** in good yield (Scheme 15).

In conclusion, we have synthesized the unsymmetrical bis-tetrahydrofuran skeleton of Salzmanolin successfully.

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

CHAPTER -1

SECTION -1

Synthesis of C12-C29 fragment of amphidinolide E

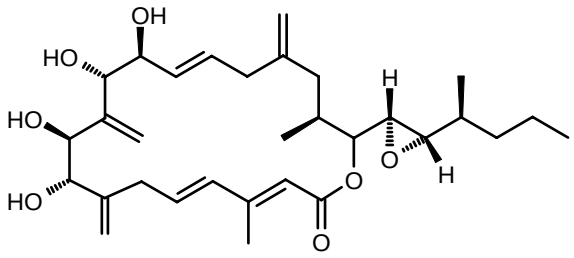
INTRODUCTION

Introduction

Marine microorganisms such as bacteria, cyanobacteria, dinoflagellates, *etc.* have attracted many natural product chemists as the real producers of marine toxins such as fish and algal poisons and bioactive substances isolated from marine invertebrates such as sponges, tunicates, and so on. Among marine microorganisms, dinoflagellates have been important sources of marine toxins, and have been investigated worldwide by natural product chemists. We have continued investigations on chemically interesting and biologically significant secondary metabolites from symbiotic marine dinoflagellates *Amphidinium* sp, which were separated from inside cells of Okinawan marine flatworms A series of cytotoxic macrolides, designated amphidinolides, and long-chain polyketides were isolated from marine symbiotic dinoflagellates *Amphidinium* sp.

In search of new bioactive substances, chemists have turned their attention to marine microorganisms that can serve as a limitless source of diverse and highly complex secondary metabolites exhibiting a wide range of biological properties like cytotoxicity, anti-viral and anti-fungal properties.[1-6] Amphidinolides A-H,[1-8] caribenolide I[9] and Amphidinolides J-V,[10-12] mentioned here broadly as amphidinolides A-V, constitute an important class of macrolides isolated mainly by Kobayashi and coworkers from the laboratory-cultured marine dinoflagellates genus *Amphidinium*, symbiotic with the Okinawan marine flatworms, *Amphiscolops* sp.[7-9] Many of these compounds have potent toxicity against various tumor cell lines and some of them are reported to be amongst the most potent of all substances tested to date in the NCI screen, thereby, attracting attention as potential cancer drugs. Structural features of the amphidinolides are unique. They show a large variation in the size of the macrocyclic lactone rings from twelve-membered to twenty-seven membered systems. They also have large number of chiral centres and many other unique structural features that make them synthetically challenging. Studies directed toward the total syntheses of many other amphidinolides are currently being pursued in many laboratories worldwide.

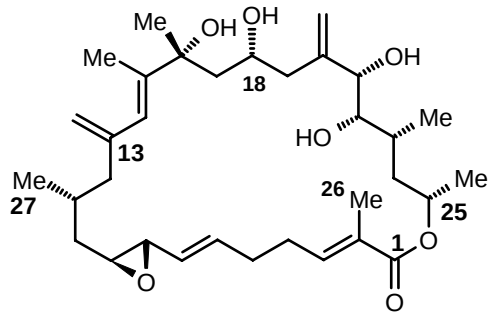
Amphidinolides :



Amphidinolide A 1

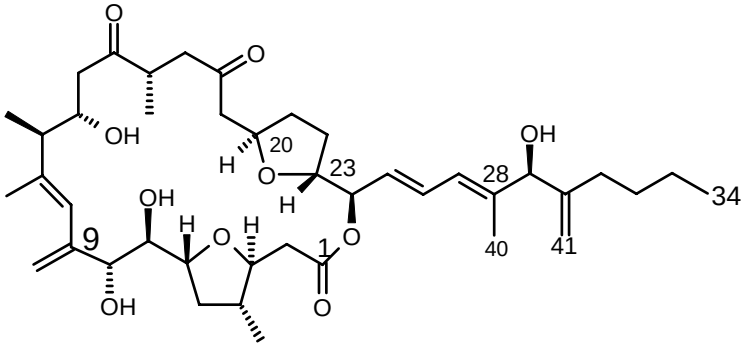
Amphidinolide A**1** is a 20-membered macrolide possessing a dienoate chromophore, three *exo*-methylenes, two 1, 2-diols, three branched methyls, an epoxide, and exhibits cytotoxicity against L1210 cells (IC_{50} 2.0 μg mL^{-1})[23] and KB cells (IC_{50} 5.7 μg mL^{-1}).[10] The stereochemistry of nine chiral centers in amphidinolide A **1** has been established on the basis of NOESY correlations and ^{1}H–^{1}H coupling constants.[24] The proposed structure was synthesized by three groups independently. Pattendent and coworkers synthesized and its epimer through inter and intramolecular *sp*2–*sp*2 Stille coupling reaction. Maleczka *et al.* have achieved the total synthesis, together with two analogues.[25] Their convergent synthesis was performed using a Stille coupling with copper thiophenecarboxylate and then a ring-closing metathesis, the latter compound being formed by Mitsunobu esterification. On the other hand, Trost and coworkers have succeeded in the total synthesis of three subunits using ruthenium catalyzed alkene–alkyne coupling.[26]

Amphidinolide B**2** is a 26-membered macrolide with an allyl epoxide and a *S-cis* diene moiety, and shows potent cytotoxicity (IC_{50} 0.00014 and 0.0042 μg mL^{-1} against L1210 and KB cells, respectively).[27,28] Amphidinolide B caused a concentration- dependent increase in the contractile force of skeletal muscle skinned fibers.[29] Shimizu and Coworkers isolated three amphidinolide B-congeners,[30] amphidinolides B**1**, B**2**, and B**3** from a free-swimming dinoflagellate *Amphidinium operculatum* ver nov *Gibbosum.* [31] The relative stereochemistry of nine chiral centers in amphidinolide B**1** was determined by X-ray analysis.



Amphidinolide B 2

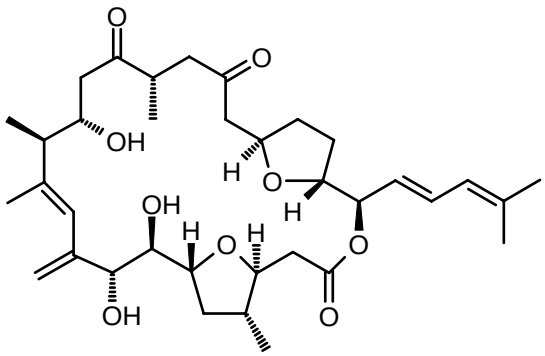
The absolute stereochemistry of B was assigned as 8*S*, 9*S*, 11*R*, 16*R*, 18*S*, 21*R*, 22*S*, 23*R*, and 25*S*.



Amphidinolide C 3

Amphidinolides C **3**[32] and F **4**[33] are 25-membered macrolides having two tetrahydrofuran rings and vicinally-located one-carbon branches. Amphidinolide C **(3)** exhibited potent cytotoxicity against tumor cells. Recently, relatively large amounts of amphidinolide C have been isolated from three strains (Y-56, Y-62, and Y-71) of the genus *Amphidinium*, which were separated from the internal cells of the marine acoel flatworm *Amphiscolops* sp. This sample was used to reinvestigate the relative stereochemistry and to determine the absolute configurations at the twelve chiral centers.[34] The relative stereochemistry of the C1–C8 and C20–C23 portions has been previously assigned tentatively by NOESY correlations.[35,36] Application of the *J*-based configuration analysis[37] revealed the *erythro*-relation for the C12–C13 bond and threo-relation for the C23–C24 bond. The absolute configurations of two oxymethine carbons at C13 and C29 were determined by the modified Mosher's method.[38] To investigate the absolute stereochemistry at C3, C4, and C5, reduction of Amphidinolide

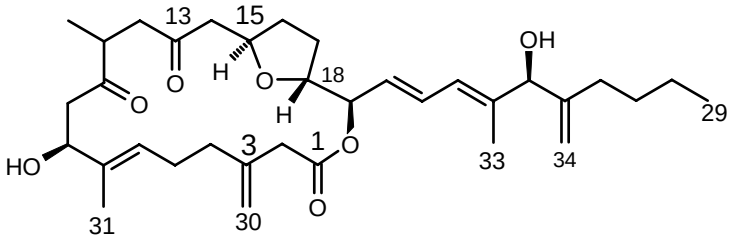
C with DIBAL, oxidative cleavage of the 7,8-diol unit with $NaIO_4$, reduction with $NaBH_4$, esterification with (*R*)-(-)-MTPACl, followed by HPLC separation furnished the bis-(*S*)-MTPA ester of the C1–C7 segment. Both bis (*S)* and (*R*) MTPA esters of the C-1–C-7 segment were prepared from D-glutamic acid. ^{1}H NMR data of the bis-(*S*)-MTPA ester derived from a natural specimen were identical with those of the synthetic bis-(*S*)-MTPA ester. Therefore, the absolute configurations at C-3, C-4, and C-6 were established to be *S*, *R*, and *R*, respectively. The absolute configurations at C-7, C-8, and C-24 were elucidated by application of modified Mosher's method for linear methyl ester of Amphidinolide C. Furthermore, from comparison of the ^{1}H NMR chemical shifts of MTPA esters of each diastereomer of the C1–C10 and C17–C29 segments with those of linear methyl ester, the absolute configurations at C-7, C-8, C-20, C-23, and C-24 in **3** were confirmed to be all *R*. To determine the absolute configuration at C-16 of amphidinolide C, a three step degradation reaction [Baeyer–Villiger oxidation using trifluoroperacetic acid (TFPA), reduction with $LiAlH_4$, and MTPA-esterification followed by HPLC separation] was applied to Amphidinolide C to afford a bis-(*R*)-MTPA ester of 1, 3-butanediol. Therefore, the absolute configurations at twelve chiral centers in amphidinolide C **3** were assigned as 3*S*, 4*R*, 6*R*, 7*R*, 8*R*, 12*R*, 13*S*, 16*S*, 20*R*, 23*R*, 24*R*, and 29*S*.



Amphidinolide F 4

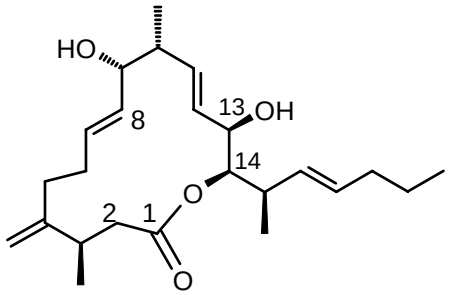
Amphidinolide F[39] **4** is a congener of amphidinolide C **3** with a shorter side chain by a C**6** unit than that of **3**. Since ^{1}H and ^{13}C chemical shifts of **4** were close to those of **3**, the relative stereochemistry of eleven chiral centers in **6** was suggested to be the same as that of amphidinolide C **3**. Amphidinolide U[40] is a novel 20-membered

macrolide possessing a tetrahydrofuran ring, two *exo*-methylenes, three branched methyls, two ketones, two hydroxyl groups, and a C_{10} linear side-chain.



Amphidinolide U 5

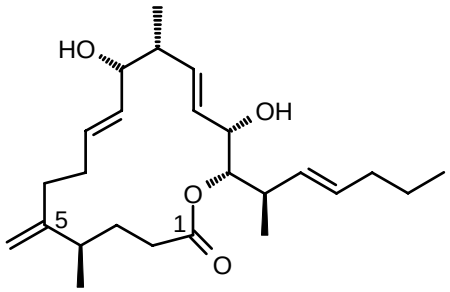
Amphidinolide U[40] **5** is a novel 20-membered macrolide possessing a tetrahydrofuran ring, two *exo*-methylenes, three branched methyls, two ketones, two hydroxyl groups, and a C10 linear side-chain. The gross structure of the C9–C29 unit in amphidinolide U **5** corresponds to that of C14–C34 of amphidinolide C[41] **3**, while the carbon skeleton of the C1–C8 unit in **5** is very close to that of C1–C8 in amphidinolide A[42] **1**. This observation suggests that amphidinolide U **5** may be biogenetically related to amphidinolides C **3** and A **1**. Amphidinolide C **3** exhibited potent cytotoxic activity against L1210 and KB cells *in vitro* with IC_{50} values of 0.0058 and 0.0046 μg mL^{-1}, respectively. Amphidinolides F and U showed only weak cytotoxicity against L1210 (IC_{50}: 1.5 and 12 μg mL^{-1}, respectively) and KB cells (IC_{50}: 3.2 and 20 μg mL^{-1}, respectively). The 25-membered macrolactone ring may be essential for cytotoxicity, and the length of side chain is considered to affect the potency of cytotoxic activity significantly.



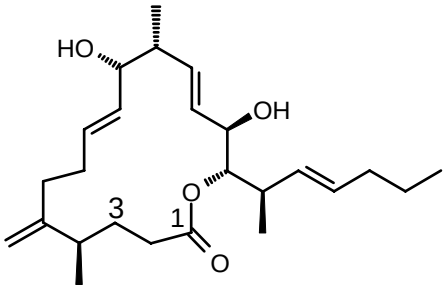
Amphidinolide J 6

Amphidinolide J[43] **6** is a 15-membered macrolide with two hydroxyl groups and four C1 branches, two of which are adjacent to each other. The absolute

stereochemistry of **6** was determined on the basis of synthesis of three segments, C1–C 7, C8–C11, and C12–C16 obtained by ozonolysis. Recently, Williams and Kissel have succeeded in the total synthesis of amphidinolide J **6** through organozinc mediated coupling between C1–C12 and C13–C20 subunits followed by macrocyclization by the Yamaguchi procedure.[44]

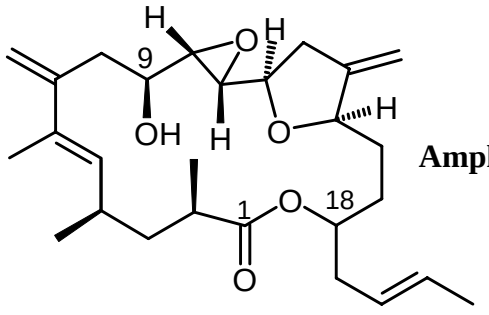


Amphidinolide R 7



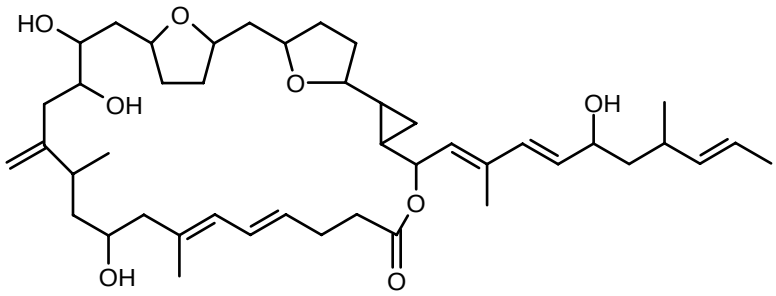
Amphidinolide S 8

Amphidinolides R **7** and S **8** are minor congeners of Amphidinolide J **6**. [45] The structure of **7** was assigned as a regioisomer of **6** having a 14-membered macrolactone ring, since treatment of **6** and **7** with sodium methoxide yielded an identical linear methyl ester. On the other hand, Amphidinolide S **8** was concluded to be the 9-dehydro form of **6** by spectroscopic data. Interestingly, treatment of amphidinolide J **6** with MnO_2 in benzene afforded the 13-keto derivative but not **8**. When oxidation of **6** with MnO_2 was carried out in DMF solution, the 9-keto form **8** was produced. No 9, 13-didehydro form was detected under either of the oxidative conditions. Since comparison of the ^{1}H NMR spectra of **6** in DMF-d_6 with those in benzene-d_6 disclosed a small difference in J(H-8,H-9) values (6.0 Hz and 8.8 Hz, respectively), the selective oxidation of the hydroxyl group at C-9 or C-13 seems to depend on these slight conformational differences around C-9 in both solvents.



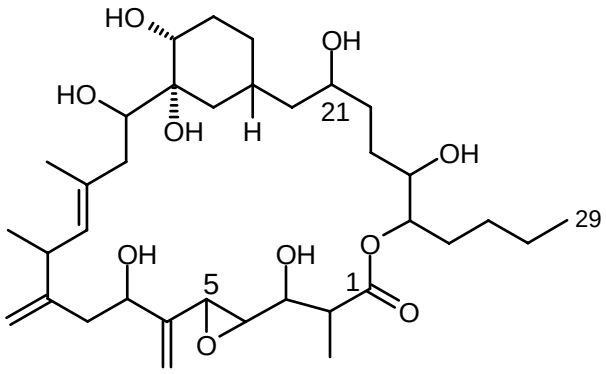
Amphidinolide K (9)

The structure of amphidinolide K **9**, [46] a 19-membered macrolide containing a tetrahydrofuran ring, an epoxide, and an *S-trans* diene, was deduced from 2D NMR data using a submilligram of sample (0.3 mg). The relative stereochemistry of the epoxide–tetrahydrofuran portion was proposed on the basis of NOESY data and coupling constants. Recently, Williams and Meyer achieved total synthesis of a stereoisomer of the proposed structure. Their convergent strategy was initialized by construction of the C7–C22 subunit *via* a coupling reaction between C7– C12 and C13–C22 segments with a chiral bromoborane. The spectral datas were identical with those of a natural specimen of amphidinolide K **9**, but the sign of the $[\alpha]_D$ value was opposite of that measured for amphidinolide K.



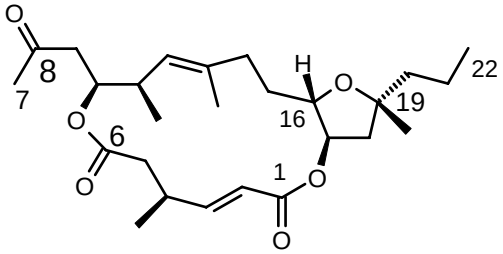
Amphidinolide M 10

Amphidinolide M[47] **10** has a 29-membered macrocyclic lactone ring with two tetrahydrofuran rings, an epoxide, two diene moieties, and two vicinally located methyl or *exo*-methylene groups. The stereochemistry of amphidinolide **M** remains undetermined though the angular hydrogens of two tetrahydrofuran portions were both implied as *trans*-relations. Amphidinolide M exhibited cytotoxicity against L1210 (IC_{50}: 1.1 μg mL^{-1}) and KB cells (IC_{50}: 0.44 μg mL^{-1}). The structure of amphidinolide N[48] was interpreted to be a 26-membered macrolide containing a 6-membered hemiacetal ring, an epoxide, a ketone carbonyl, four C branches, and seven hydroxyl groups. This compound was extremely cytotoxic against L1210 and KB cells (IC_{50}: 0.00005 and 0.00006 μg mL^{-1}, respectively). Although the relative stereochemistry of C-14, C-15, C-16, and C-19 was indicated as



Amphidinolide N 11

shown, the absolute stereochemistry of **10** was not determined. Shimizu and coworkers isolated an amphidinolide N-type macrolide, named caribenolide, from a free-swimming dinoflagellate *Amphidinium operculatum* vernov *Gibbosum*. [49] Caribenolide I was reported to show potent cytotoxicity against human colon tumor cells HCT116 and its drug-resistant strain HCT116/VM46 (IC_{50}: both 0.001 μg mL^{-1}), of which the IC_{50} value was about 100 times higher than that of amphidinolide B (IC_{50}: 0.122 μg mL^{-1}). Caribenolide I showed antitumor activity against murine leukemia P388 (T/C: 150% at a dose of 0.03 mg kg^{-1}) *in vivo*.

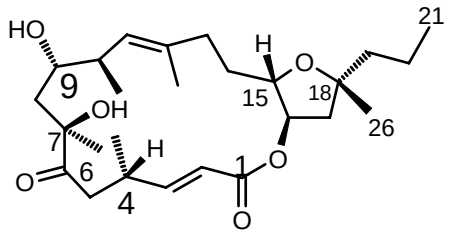


Amphidinolide X 12

A cytotoxic 16-membered macrolide, amphidinolide X, [50] has been isolated from a marine dinoflagellate *Amphidinium* sp. The gross structure of **12** was elucidated on the basis of spectroscopic data including one-bond and long-range ^{13}C-^{13}C correlations obtained from 2D DEPT C–C Relay and 2D DEPT C–C Long-Range Relay experiments. The relative stereochemistry for C-10/C-11 was elucidated to be *erythro* by *J*-based configuration analysis, while that of the tetrahydrofuran portion was assigned on the basis of NOESY data. The absolute configurations at C-10 and C-17 were elucidated to be *S* and *R*, respectively, by application of modified Mosher's method for the C8–C22 segments, which were produced together with the C1–C6

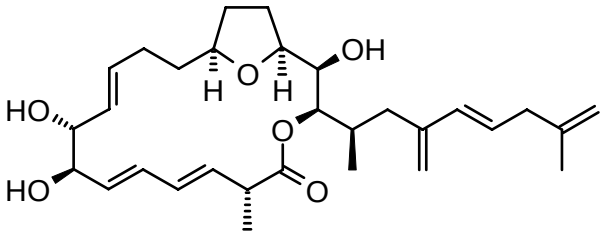
segments by reduction with $LiAlH_4$. A 4*S*-configuration was deduced from comparison of ^1H NMR data of MTPA esters of the C1–C6 segments with those of the synthetic 1, 6-bis-(*R*)-MTPA ester. Amphidinolide X is the first macrodiolide consisting of polyketide-derived diacid and diol units from natural source.

Rcently, a 17-membered macrolide, Amphidinolide Y[51], was obtained from the same strain, and it was elucidated to exist as a 9:1 equilibrium mixture of 6-keto and 6(9)-hemiacetal forms on the basis of 2D NMR data. The 6-keto form **13** were assigned on the basis of spectroscopic data and chemical conversion of **13** into amphidinolide X **12** by $Pb(OAc)_4$ oxidation. The 6-keto form of amphidinolide Y is a 17-membered macrolide possessing a tetrahydrofuran ring, five branched methyls, a ketone, and two



Amphidinolide Y 13

hydroxyl groups. Amphidinolides X and Y show cytotoxicity against L1210 (IC_{50}: 0.6 and 0.8 μg mL^{-1}, respectively) and KB cells (IC_{50}: 7.5 and 8.0 μg mL^{-1}, respectively).



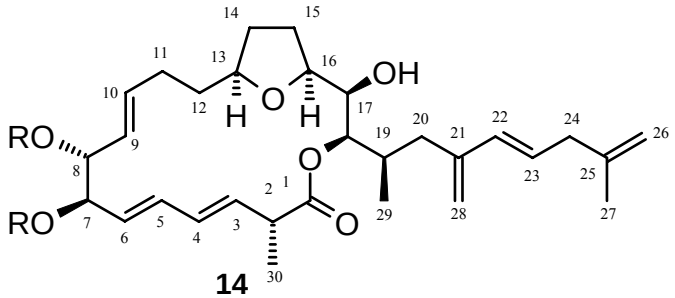
Amphidinolide E 14

Amphidinolide E[52] **14** is a 19-membered macrolide possessing a tetrahydrofuran ring, four C-C branches, and three hydroxyl groups, and exhibits cytotoxicity against L1210 cells (IC_{50}: 2.0 μg mL^{-1}). Because of unique structural features, limited availability and pronounced biological activity, we started our research work toward the synthesis of amphidinolide E.

PRESENT WORK

Present Work

Amphidinolides A-Y, constitute an important class of macrolides, isolated mainly by Kobayashi and coworkers from the laboratory-cultured marine dinoflagellates, genus *Amphidinium*, symbiotic with the Okinawan marine flatworms, *Amphiscolops* sp.[53] Many of these compounds have potent toxicity against various tumor cell lines and some of them are reported to be amongst the most potent of all substances tested to date in the NCI screen, thereby, attracting attention as potential cancer drugs. Among Amphidinolides, Amphidinolide E **14** is a unique cytotoxic 19-membered macrolide featuring an embedded *cis*-tetrahydrofuran, which has been isolated from the Y-5 strain of a dinoflagellate *Amphidinium* sp. It exhibits cytotoxic activity against L1210 (IC_{50} = 2.0 μg mL^{-1}) and L5178Y(IC50 = 4.8 μg mL^{-1}). While this structural motif is common within the amphidinolide family, the C(1)-C(6) α-chiral, β, δ, ε-dienoate moiety of amphidinolide E is not found in any of the other amphidinolides.

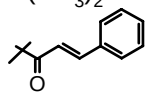


14

R = H

R = -$C(CH_3)_2$-

R =



Structure of Amphidinolide E was elucidated by 2D NMR spectral data while the relative stereochemistry of eight chiral centers positioned at C2, C7, C8, C13, C16, C17, C18 and C19 were confirmed by a combination of the *J*-based configuration method and detailed NOESY experiments. The absolute stereochemistry of **14** was determined by the exciton chirality method coupled with Moshers method. As a result of their complex structural features, promising biological activities and low availability from natural sources, the amphidinolide E has attracted considerable attention as targets for synthesis.

Retrosynthetic Analysis

A close examination of the structure of Amphidinolide E revealed that, C12-C29 fragment consists of three contigious chiral centers with stereochemistry 17R, 18R and 19R attached to a syn tetrahydrofuran ring, which could be synthesized easily from D-Glucose. Keeping this idea in mind we made a strategy which was depicted in figure-1.

The retrosynthetic analysis (figure-1) revealed that the C12-C29 fragment **15** of amphidinolide E could be assembled by employing Stille coupling between stannane **16** and triflate **17**.

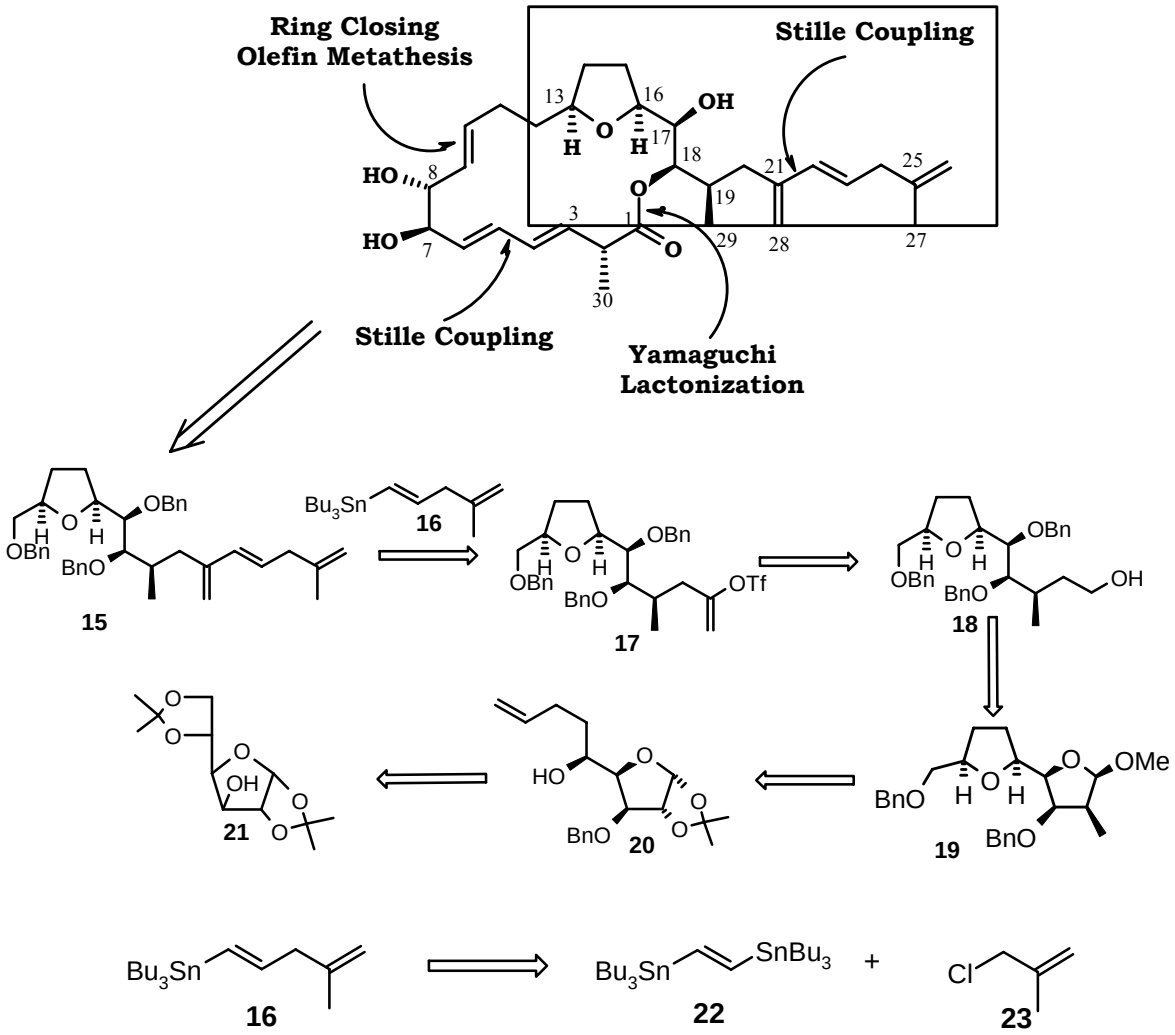


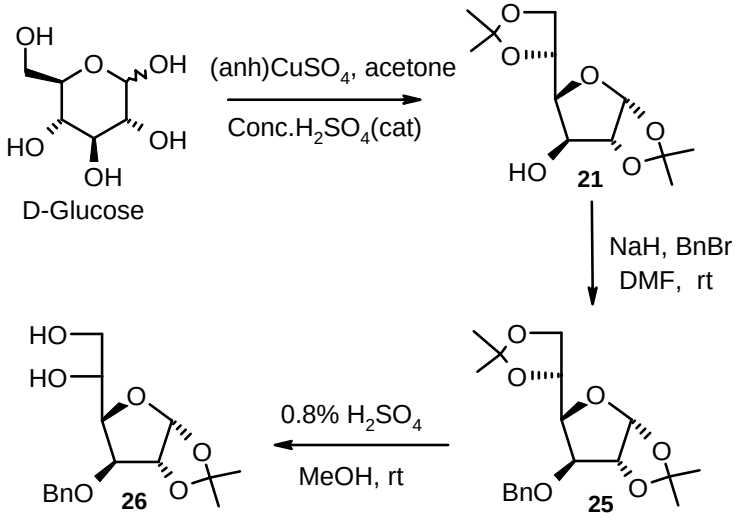
Figure 1. Retrosynthetic Analysis

Triflate **17** was envisioned to be prepared by mercuriocyclisation of known homoallylic alcohol **20** followed by simple functional group transformation. The homoallylic alcohol

20, in turn, could be obtained from 1,2-5,6 isopropylidine D-glucose **21** by known literature procedure. The vinyl stannane **16** can be prepared by Stille coupling of distannane **22** and methallyl chloride **23**.

According to retrosynthetic analysis, our synthesis started from chiral key intermediate **20,** which was prepared from commercially available β-D-glucose in a five step synthesis. D(+)glucose was converted to the glucose-diacetonide derivative **21** by treating with acetone, anhydrous $CuSO_4$ and catalytic H_2SO_4.[54] The C3-hydroxy group of **21** was protected as its benzyl ether by using sodium hydride and benzyl bromide in DMF medium.

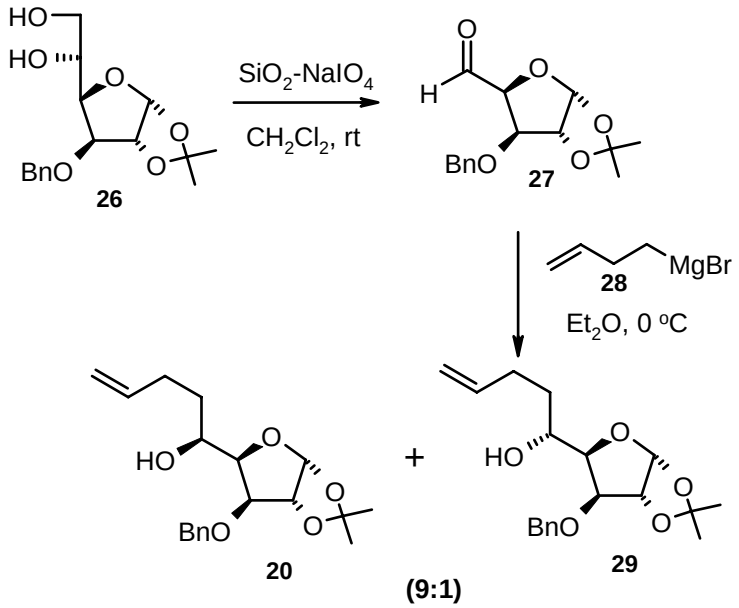
Scheme 1



Regioselective monohydrolysis of 5, 6-isopropylidene moiety of **25** with 0.8 % sulphuric acid in methanol at ambient temperature afforded diol **26** as a thick liquid (Scheme 1).

Diol **26** was subjected to oxidative cleavage with silicagel supported sodium metaperiodate[55] to yield aldehyde **27**, which was subsequently treated with butenyl magnesium bromide **28** (prepared from butenyl bromide and magnesium) in diethylether at -20 °C to form a diastereomeric mixture of alcohols **20** and **29** in 9:1 ratio.[56] Both the isomers were separated by crystallization method and characterised by ^{1}H NMR spectrum which was in good agreement with the literature data.[56] The major isomer was the desired alcohol **20** (Scheme 2).

Scheme 2

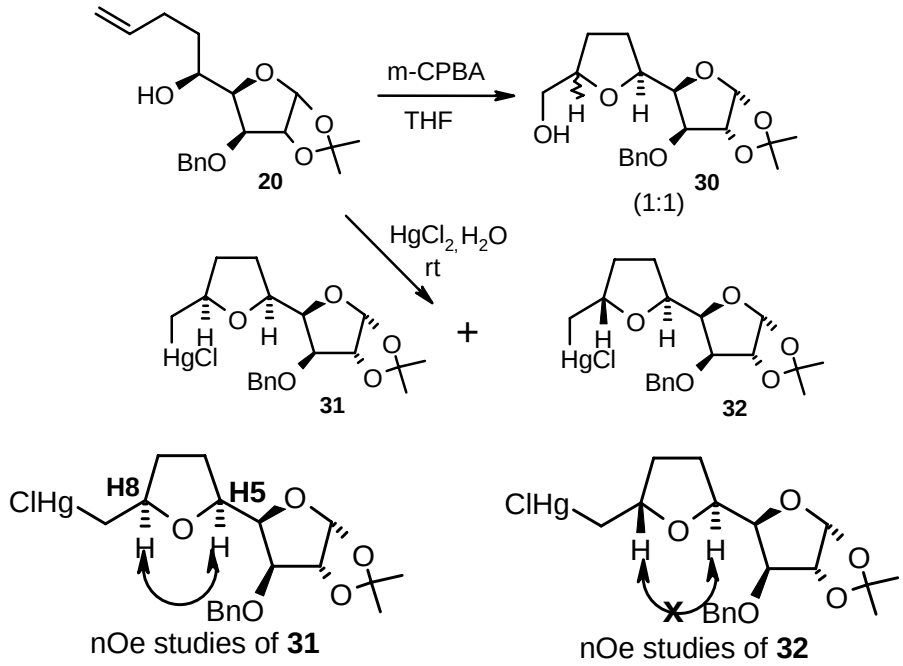


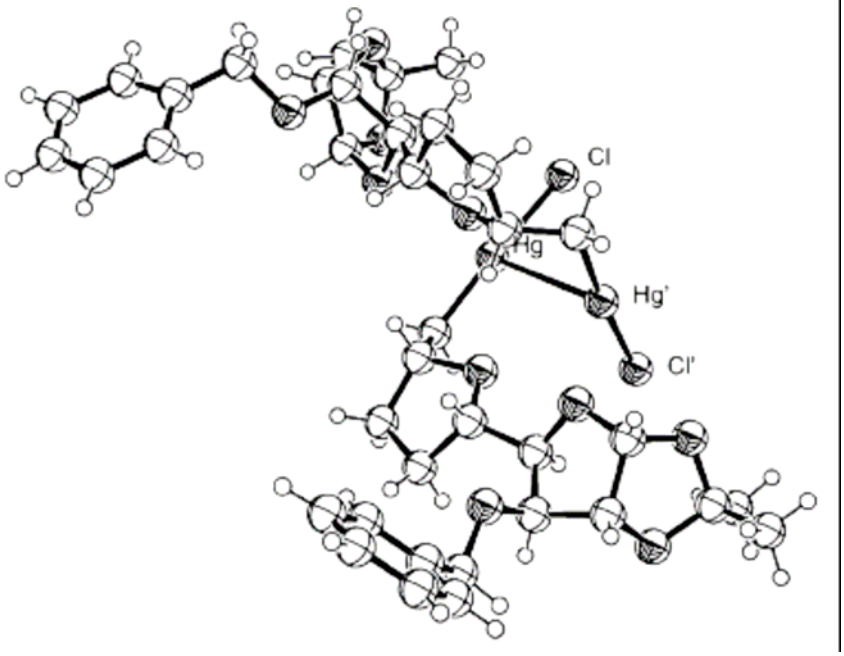
Our next concern was to make the tetrahydrofuran ring of compound **15**.

Initiallly we planned to convert the homoallylic alcohol **20** to the compound **31** through epoxidation, followed by kinetic resolution and cyclisation. Accordingly, *m*-CPBA mediated epoxidation was tried. However, to our surprise, a 1:1 mixture of cyclised furan product **30** was obtained in the reaction medium which could not be separated into individual isomers. To circumvent this problem, we employed $HgCl_2$ mediated cyclisation.[57] The homoallylic alcohol of **20** was treated with mercury chloride in H_2O provide diastereomers **31** and **32** in 3:1 ratio. Both the isomer were separated by flash silica gel chromatography and characterised by ^1H, ^{13}C NMR spectroscopy. ^1H NMR spectrum showed the oxy methine protons of THF ring at δ 4.34 (m, 1H) and 4.18 (q, 1H) ppm, while disappearance of olefinic protons in down field region confirmed the formation of **31**. But in case of **32** the oxymethine protons were resonated together at δ 4.41 ppm. Further confirmation was made by^{13}C and DEPT studies. In the ^{13}C NMR spectrum the carbons attached to the ring oxygen of tetrahydrofuran ring resonated at δ 78.7 and 77.9 ppm while disappearance of olefinic–CH_2 at δ114.6 ppm confirmed the assigned structure of **31**.Similarly in the ^{13}C NMR spectrum of **32** carbons attached to the ring oxygen of tetrahydrofuran ring resonated at δ 77.6 and 77.2 ppm respectively. The stereochemistry of tetrahydrofuran ring **31**and **32** was assigned by NOESY studies, where it was observed that in **31** there was strong nOe interactions between H5-H8 protons but in **32** there was no

such interactions. From these observations we assigned compound **31** contains *cis* tetrahydrofuran ring while compound **32** contains *trans* tetrahydrofuran ring. Further confirmation of **31** was unambiguously determined by single crystal X-ray crystallography (Scheme 3).

Scheme 3

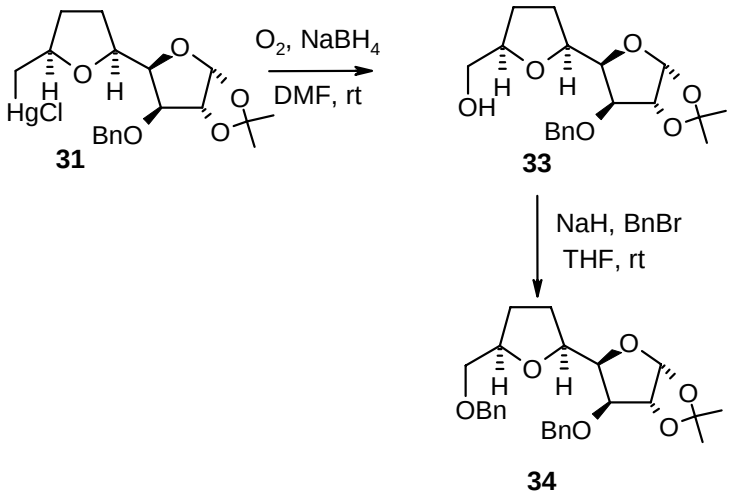




ORTEP diagram of 31

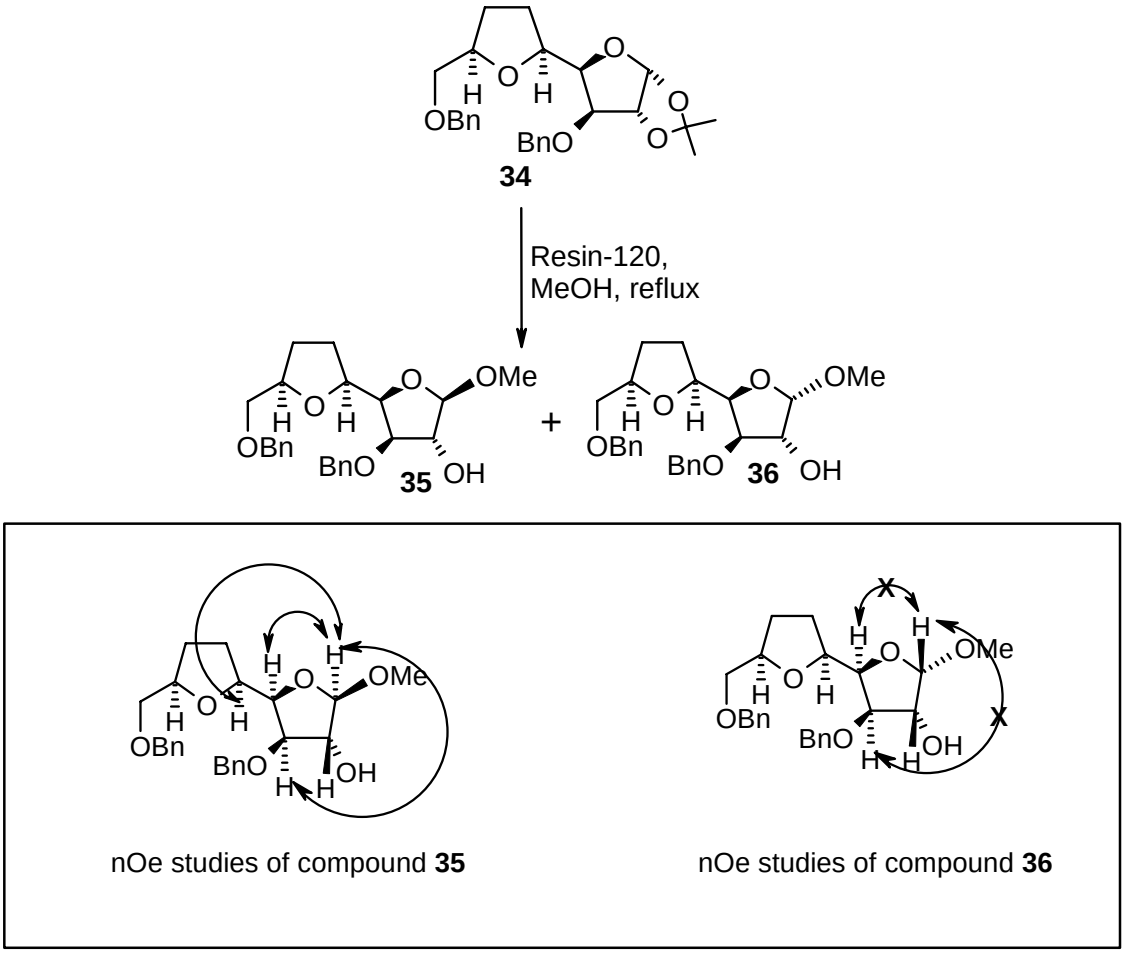
The demercuration of desired isomer **31** was carried out under a stream of oxygen in the presence of $NaBH_4$ to give alcohol **33**.[58] The structure of **33** was elucidated on the basis of ^1H NMR spectrum, where the two multiplets corresponding to CH_2-Hg group at δ 1.65 and 1.42 ppm disappeared and two new signals appeared at δ 3.68 and 3.42 ppm integrating one and one proton indicating formation of CH_2OH group. The primary hydroxyl group was protected as benzyl ether **34** by treating with sodium hydride and benzyl bromide in THF. This transformation was confirmed by ^1H and ^{13}C NMR study of compound **34**. ^1H NMR spectrum of **34** showed the signals at δ 4.58 (d, 2H), 4.54 (s, 2H) and 7.34-7.26 (m, 10H) ppm corresponding to two benzylic group. The structure was further confirmed by ^{13}C NMR and elemental analysis (Scheme 4).

Scheme 4



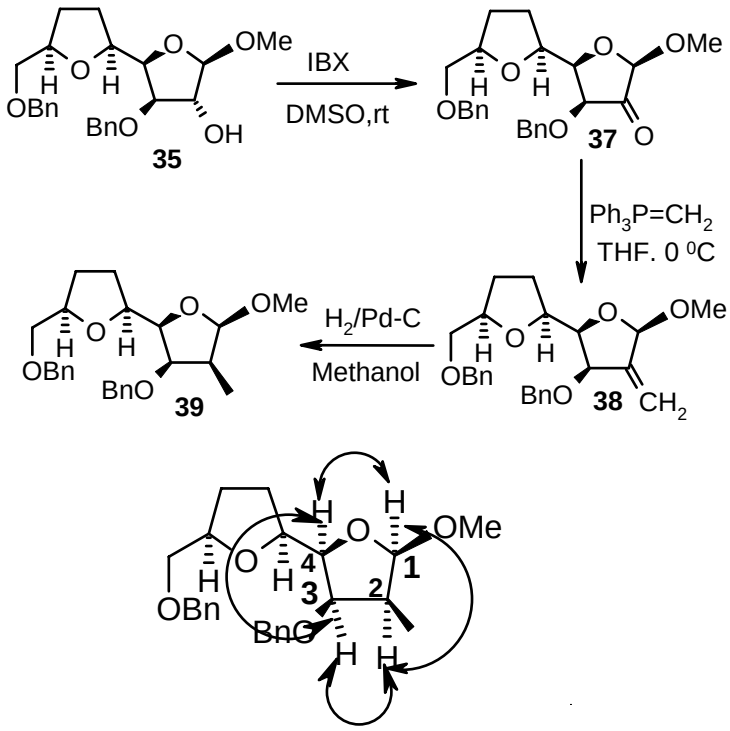
Compound **34** was refluxed with amberlite-IR 120 resin in methanol for 16 h afforded glycosides **35** and **36** in 90:10 (β:α) ratio. The structure of the β-glycoside was elucidated on the basis of ^1H NMR spectrum, in which two singlets due to isopropyldine group at δ 1.45 and δ 1.30 ppm disappeared and additionally one singlet for methoxy group appeared at δ 3.40 ppm. In the ^{13}C NMR spectrum of **35,** disappearance of carbon signals at δ 26.3, 26.7 and 111.3 ppm clearly indicates the cleavage of the isopropylidene moiety. The NOESY spectrum of **35** showed a strong nOe interactions between H1 and H4 indicating *cis* relationship. Further elemental analysis supported the assigned structure (Scheme 5).

Scheme 5



The secondary hydroxyl group present in **35** was oxidized with IBX[59] in DMSO to give the 2-ulose derivative **37** which was subsequently treated with methyl triphenylphosphonium iodide (generated by the reaction of methyl phosphonium iodide and sodamide in THF/ether) in THF at 0 °C to give the olefin **38**.

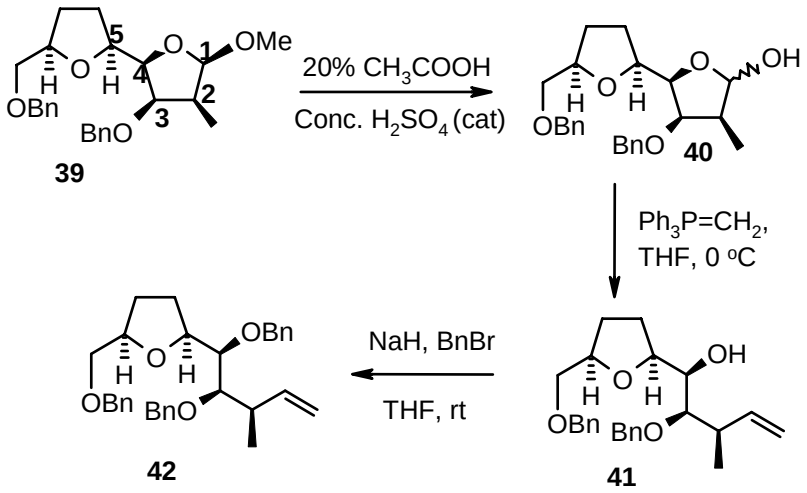
Scheme 6



nOe studies on **39**

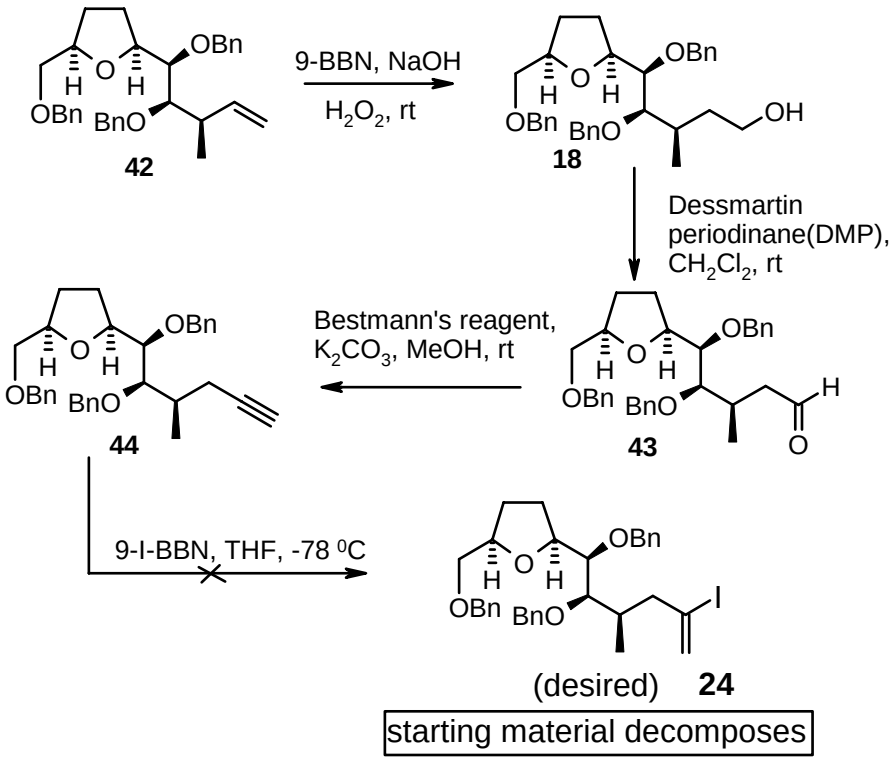
The structure **38** was deduced from ^{1}H, ^{13}C NMR spectra and confirmed by elemental analysis. In ^{1}H NMR spectrum olefinic protons appeared as doublet at δ 5.32 ppm and the chemical shift of olefinic carbon was observed at δ 113.5 ppm in its ^{13}C NMR spectrum. Olefin of **38** was reduced by using Pd/C in methanol under hydrogen atmosphere to yield saturated compound **39**, whose structure was confirmed by spectral data. In the ^{1}H NMR spectrum of **39** appearance of methine and methyl signals at δ 2.18 (m, 1H) and 1.05 (d, 3H, J = 7.1 Hz) ppm, disappearance of olefinic -CH_2 signals at δ 5.32 ppm confirmed the reduction of olefinic group. The ^{13}C NMR spectrum of **39** showed the resonances of CH_3 carbon at δ 7.8 ppm, while disappearances of –CH_2 carbon at δ 113.5 ppm completely satisfied the assigned structure. The stereochemistry at C2 in compound **39** was assigned by NOESY studies. The strong nOe interactions between H1-H2, H2-H3 and H3-H4 indicating all these protons were in the same plane, which concluded, the stereochemistry of C2 was S. (Scheme 6).

Scheme 7



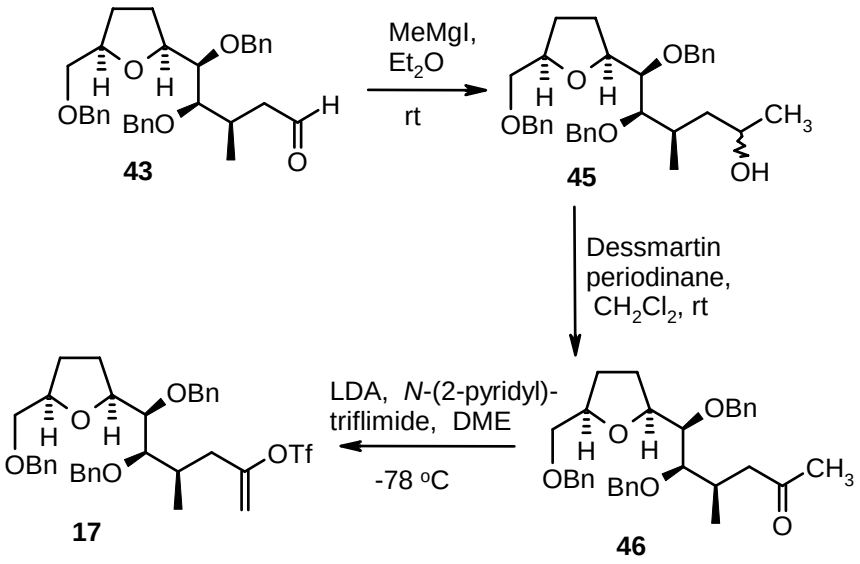
Hydrolysis[60] of methyl acetal group of **39** was accomplished with 20% acetic acid and catalytic amount of H_2SO_4 under refluxing conditions afforded hemiacetal **40** in good yield; subsequent treatment of **40** with methyl triphenylphosphonium iodide in THF at -20 °C gave olefin **41**. The structure of **41** was characterized by it's ^1H, ^{13}C NMR spectra and elemental analysis. The ^1H NMR spectrum displayed characterstic vinylic protons at δ 5.89 (m, 1H) and δ 5.10-4.98 (m, 2H) ppm indicating internal and terminal olefinic protons. The resonances due to rest of the protons were in conformity with the proposed structure of **41**. ^{13}C NMR spectrum of **41** showed the peaks due to vinyl carbons at δ 115.0 (terminal olefin carbon) and δ 140.4 (internal olefin carbon) ppm.The secondary hydroxyl group of **41** was protected as benzyl ether by treatment with sodium hydride and benzyl bromide in THF afforded **42** in good yield. The structural features of **42** was deduced from the analysis of ^1H and ^{13}C NMR spectrum. ^1H NMR spectrum of **42** showed signals at δ 4.80-4.54 (2H) due to benzylic protons and a multiplet between δ 7.24-7.31(5H) due to aromatic ring protons. The structure of **42** was further confirmed by ^{13}C NMR spectrum together with elemental analysis (scheme 7)**.**

Scheme 8



The terminal olefin of **42** was subjected to hydroboration–oxidation condition with 9-BBN followed by alkaline hydrogenperoxide to give regiospecifically primary alcohol **18**.[61] The ^{1}H NMR spectrum showed a signal at δ 3.54 (dd, 1H) and 3.45 (dd, 1H) ppm for CH_2OH protons. The primary alcohol **18** was oxidised to corresponding aldehyde **43** using Dess-Martin periodinane[62] which was converted to alkyne **44** by using Bestman's reagent. Getting alkyne **44** in hand, we planned to make vinyliodo moiety **24** by treatment with 9-I-BBN in THF medium, but unfortunately this reaction failed. In stead of giving vinyliodo compound the starting material itself was decomposed in the reaction medium (scheme 8).

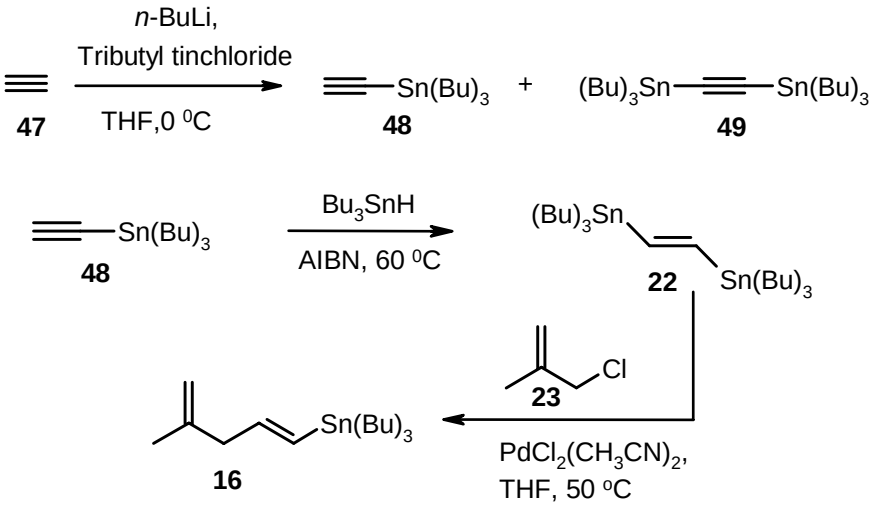
Scheme 9



Due to failure of this transformation, we have adopted an alternative method to make the corresponding vinyl triflate. Accordingly the aldehyde **43** was treated with MeMgI in diethylether to obtain distereomeric mixture of secondary alcohols **45**. Which was subsequently oxidized with Dess Martin periodinane[62] to obtain the ketone **46** whose structure was confirmed by ^{1}H and ^{13}C NMR spectroscopies studies. In the ^{13}C NMR spectrum of **46** the distinguished carbonyl carbon resonated at δ 209.0 (Scheme 9). Treatment of LDA on keto comound generated enolate which was quenched with *N*-(2-pyridyl)-trifliimide gave trifilate **17**.[63] The structure of **17** was confirmed by ^{1}H, ^{13}C and elemental analysis data (Scheme 9). As the triflate derivative **17** was ready, our next concern was to synthesize the stannane counterpart **16** for carrying out the Stille coupling to get the desired compound **15.**

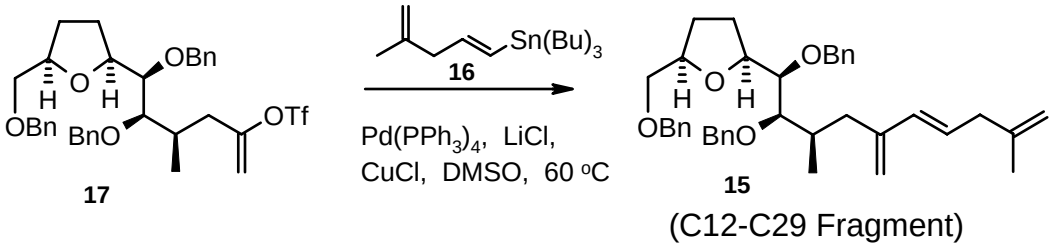
As the stannane derivative **16** wasn't known so designing it's synthetic path way became our first priority**.** Amongst several protocols that could be envisaged, a Pd-catalyzed C–C bond forming approach was chosen for its simplicity. Accordingly acetylene gas was passed through the solution of *n*-BuLi and THF, to it tributyltin chloride was added dropwise to give acetylene tributytin **48** and bis acetylene tributytin **49** ^{1}H, ^{13}C NMR data and boiling point of compound **48** matched with the reported values. The tributytin acetylene **48** was reacted with tributytinhydride, in presence of AIBN to furnish

Scheme 10



bis-ethylene di-stannane derivative **22** whose structure was confirmed by ^{1}H, ^{13}C NMR and boiling point measurement which was identical with the reported values. The bisstannane derivative **22** underwent Stille coupling with methallyl chloride **23** in presence of $PdCl_2(CH_3CN)_2$ to give stannane derivative **16**. In the ^{1}H NMR spectrum of **16** signals appeared at δ 5.95 (m, 2H) and 4.74 (m, 2H) ppm corresponding to internal and terminal olefinic protons. ^{13}C NMR spectrum of **16** showed the internal and terminal olefinic carbons resonated at δ 146.7, 129.5 and 110.9 ppm while rest of the carbons resonated at their appropriate positions confirming the structure (Scheme 10). As both the coupling partner i,e triflate and stannane were ready, we are very nearer to achieve the desired fragment **15**.

Scheme 11



(C12-C29 Fragment)

The triflate **17** was reacted with vinyl stannane derivative **16** in presence of CuCl, LiCl, and $Pd(PPh_3)_4$[64] to afford targeted C12-C29 fragment **15**.[65] The structure of **15** was confirmed by its ^{1}H, ^{13}C NMR spectra and elemental analysis. ^{1}H NMR spectrum of **15** showed the olefinic protons of two exo double bond at δ 4.95 (s, 1H), 4.83 (s,1H), 4.77 (d, 2H) ppm and the internal olefinic protons resonated at δ 6.04 (d, 1H, J = 15.6 Hz) and

5.78 (m, 1H) ppm. In the ^{13}C NMR spectrum the olefinic carbons of two exo double bond resonated at δ 115.0 and 110.7 ppm and the carbons of internal olefin resonated at δ133.6 and inbetween δ 128.0-127.0 ppm. Finally the product was confirmed by mass spectrometric analysis (ESIMS-$[M+Na]^+$= 604) (scheme 11).

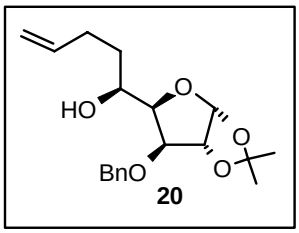
Conclusions:

In conclusion we have synthesized the *cis*-tetrahydrofuran ring of C12-C29 fragment following intramolecularmercurio cyclisation and the structure was unambiguously determined by X-ray crystallographic study. C-2 Me group was installed by stereoselective reduction of olefin **38.** Synthesis of vinyltriflate **17** was carried out successfully. We have first reported the vinylstannane fragment **16** following a novel strategy. We have successfully achieved the C12-C29 fragment of Amphidinolide E following mercuriocyclisation, Wittig olefination and Stille coupling as our key reactions.

EXPERIMENTAL

3-*O*-benzyl-1,2-*O*-isopropylidene-6,7,8,9-tetradeoxy-ß-L-ido-non-8-enofuranose furanose (20) and 3-*O*-benzyl-1,2-*O*-isopropylidene-6,7,8,9-tetradeoxy-α-D-gluco-non-8-enofuranose furanose (29):

To a suspension of magnesium (12.3 g, 512 mmol) in anhydrous Et_2O (100 mL) was added 3-bromobut-1-ene **28** (36.4 mL, 358 mmol) dropwise at rt and stirred for 1h to give butylmagnesium bromide, which was added dropwise to the solution of aldehyde (28.5 gm, 0.102 mole) **27** in diethylether (300mL) at -20 ºC and stirred for 1h. Reaction mixture was poured into sat. NH_4Cl solution and extracted with Et_2O. The organic layer was dried (Na_2SO_4), concentrated to give crude product, which on flash column chromatography (silica gel, 10-15% EtOAc/petroleum ether) afforded homoallylic alcohol **20** as a white powder (24.7 g) and **29** as an oily liquid (2.7 g) in a 9:1 ratio (80% yield).



20

Compound 20

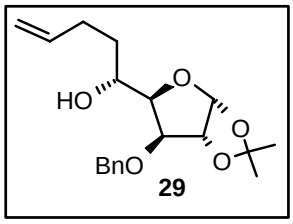
$[\alpha]_D$ **:** – 54.3 (*c* 1.1, CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39–7.28 (m, 5H), 5.99 (d, 1H, *J* = 3.6 Hz), 5.79 (m, 1H), 5.03 (d, 1H, *J* = 17.1 Hz), 4.96 (d, 1H, *J* = 10.3 Hz), 4.73 (d, 1H, *J* = 11.5 Hz), 4.60 (d, 1H, *J* = 3.9 Hz), 4.47 (d, 1H, *J* = 11.5 Hz), 4.02 (m, 1H), 3.99-3.94 (m, 2H), 2.71 (brs, 1H), 2.29 (m, 1H), 2.15 (m, 1H), 1.61 (m, 1H), 1.5 (s, 3H), 1.44 (m, 1H), 1.35 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 138.1, 136.1, 128.4, 128.0, 127.8, 114.6, 111.6, 104.6, 82.8, 82.2, 82.1, 71.6, 68.9, 31.8, 29.5, 26.7, 26.2.

Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 67.95; H, 7.66.

Compound 29



29

$[\alpha]_D$ **:** –72 .0 (*c* 0.16, $CHCl_3$)

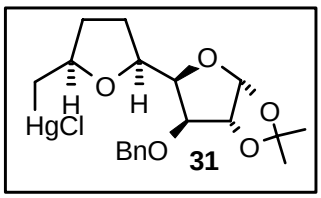
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.33 (m, 5H), 5.92 (d, 1H, *J* = 3.8 Hz), 5.81 (m, 1H), 5.04 (d,1H, *J* = 17.3 Hz), 4.92 (d, 1H, *J* = 9.8 Hz), 4.69 (d,1H, *J* = 11.9 Hz), 4.59 (d, 1H, *J* = 3.8 Hz), 4.47 (d, 1H, *J* = 11.9 Hz), 4.05 (d, 1H, *J* = 2.8 Hz), 3.99-3.89 (m, 2H), 2.37-2.10 (m, 3H), 1.73 (m, 1H),1.47 (s, 3H), 1.31 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 138.3, 136.9, 128.6, 128.2, 127.8, 114.6, 111.4, 104.9, 82.2, 81.9 81.8, 71.7, 68.7, 33.4, 29.6, 26.7, 26.7, 26.2.

Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 67.90; H, 7.82

5,8 -Anhydro-3-*O*-benzyl-9-chloromercuryl -6,7,9-trideoxy-1,2-*O*-isopropylidene-L-*glycero*- ß-L-*ido*-nonanofuranose (31) and 5,8 –Anhydro-3-*O*-benzyl-9-chloromercuryl-6,7,9- trideoxy-1,2-*O*-isopropylidene- D - *glycero*- ß-L-*ido*-nonanofuranose (32)

To a solution of alcohol **20** (2 g, 5.98 mmol) in H_2O (10 mL), was added mercury(II) chloride (1.95 g, 7.17 mmol) and allowed to stir for 1 h at rt. Brine solution (5 mL) was added and the solution stirred for a further 0.5 h. The reaction mixture was diluted with CH_2Cl_2. The organic layer was separated, aqueous layer further extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), concentrated to give residue which on Flash column chromatography (silica gel, 15-20% EtOAc/petroleum ether) afforded **31** as white solid (2.3 g) and **32** as thick liquid (0.8 g) in a 3:1 ratio (yield 90%).



31

Compound 31

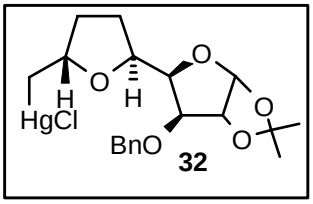
$[\alpha]_D$ **:** – 29.3 (*c* 3.55, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.26 (m, 5H), 6.02 (d,1H, *J* = 3.8 Hz), 4.67 (d, 1H, *J* = 11.9 Hz), 4.58 (d, 1H, *J* = 3.8 Hz), 4.45 (d, 1H, *J* = 11.9 Hz), 4.34 (m, 1H), 4.18 (q, 1H, *J* = 7.4 Hz), 4.02 (dd, 1H, *J* = 3.3, 6.5 Hz), 3.86 (d, 1H, *J* = 3.3 Hz), 2.34 (dd, 1H, *J* = 5.3, 12.5 Hz), 2.13 (m, 1H), 2.05 (m, 1H), 1.96 (m, 1H), 1.65 (m, 1H), 1.49 (s, 3H), 1.42 (m, 1H), 1.31 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 137.5, 128.5, 128.0, 127.9, 111.7, 105.3, 83.2, 83.0, 82.0, 78.7, 77.9, 71.8, 38.3, 35.3, 28.8, 27.0, 26.5.

Anal. Calcd for $C_{19}H_{25}O_5HgCl$: C, 40.07; H, 4.42. Found: C, 40.32; H, 4.78.

Compound 32



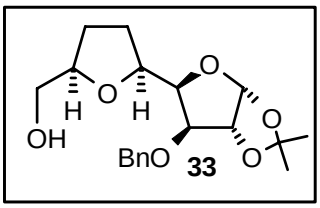
$[\alpha]_D$ **:** – 40.0 (*c* 2.8, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.26 (m, 5H), 5.94 (d, 1H, *J* = 3.7 Hz), 4.67 (d ,1H, *J* = 11.9 Hz), 4.58 (d, 1H, *J* = 3.7 Hz), 4.41– 4.35 (m, 3H), 4.03 (dd, 1H, *J* = 3.7, 8.24 Hz), 3.83 (d, 1H, *J* = 3.7 Hz), 2.35 (dd, 1H, *J* = 5.5, 11.9 Hz), 2.17 (dd, 1H, *J* = 5.5, 11.92 Hz), 2.10-1.99 (m, 2H), 1.48 (s, 3H), 1.38 (s, 3H), 1.52 (m,1H), 1.40 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 138.9, 128.3, 127.8, 127.6, 111.3, 105.1, 82.8, 82.0, 81.5, 77.6, 77.2, 71.4, 37.4, 36.0, 28.5, 26.6, 26.1.

Anal. Calcd for $C_{19}H_{25}O_5HgCl$: C, 40.07; H, 4.42. Found: C, 40.03; H, 4.35.

5,8-Anhydro-3-*O*-benzyl-6,7-dideoxy-1,2-*O*-isopropylidene-L-*glycero*-ß-L-*ido*-nonanofuranose (33):



A solution of compound **31** (1.8 g, 3.16 mmol) in DMF (22.5 mL), was bubbled with O_2 for 10 min. To a suspension of $NaBH_4$ (143 mg, 3.79 mmol) in DMF (11.6 mL), O_2 was

passed in a fast rate. To it mercurated compound was added dropwise. Reaction mixture was diluted with EtOAc, filtered and concentrated to give residue, which was purified by flash coloum chromatography (40-50% EtOAc/petroleum ether) to afford alcohol **33** as a colourless liquid (0.9 g, 81%).

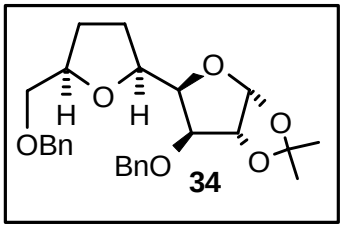
$[\alpha]_D$: – 56.2 (*c* 6.9, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (m, 5H), 5.93 (d, 1H, *J* = 3.7 Hz), 4.61 (d, 1H, *J* = 11.9 HZ), 4.55 (d, 1H, *J* = 3.7 Hz), 4.37 (d, 1H, *J* = 11.9 Hz), 4.13 (q, 1H, *J* = 6.4 Hz), 4.00 (dd, 2H, *J* = 3.6, 8.3 Hz), 3.83 (d, 1H, *J* = 3.6 Hz), 3.68 (dd,1H, *J* = 3.2, 11.9 Hz), 3.42 (dd, 1H, *J* = 4.77, 11.9 Hz), 1.86-1.79 (m, 2H), 1.68 (m, 1H), 1.43 (s, 3H), 1.40 (m, 1H), 1.26 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 138.4, 137.8, 128.2, 128.1, 127.6, 127.5, 127.4, 127.3, 101.9, 83.5, 80.7, 78.3, 78.1, 76.2, 73.2, 72.4, 71.5, 55.6, 28.1, 27.5.

Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.12; H, 7.47. Found: C, 65.10; H, 7.43.

5,8-Anhydro-3,9-di-*O*-benzyl-6,7-dideoxy-1,2-*O*-isopropylidene-L-*glycero*- ß-L-*ido*-nonanofuranose (34):



34

Compound **33** (4.4 g, 12.5 mmol) in DMF (40 mL) was added to a stirred suspension of NaH (0.601 g, 60% dispersion in oil, 15.0 mmol) in DMF (20 mL) at 0 °C. The resulting solution was stirred at RT for 30 min, BnBr (1.6 mL, 13.7 mmol) was added. After 1 h, the reaction mixture was quenched by ice-cold water and extracted with EtOAc. The combined organic layers were washed with H_2O, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel chromatography (10-12 % EtOAc/light petroleum ether) to obtain **34** (5.09g, 94%).

$[\alpha]_D$ **:** – 45.1 (*c* 4.4, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (m, 10H), 5.96 (d, 1H, *J* = 3.5 Hz), 4.65 (d, 1H, *J* = 11.4 Hz), 4.58 (d, 1H, *J* = 3.5 Hz), 4.54 (s, 2H), 4.41 (d, 1H, *J* = 11.4 Hz), 4.12 (m, 2H), 4.06 (dd, 1H, *J* = 3.2, 6.9 Hz), 3.85 (d, 1H, *J* = 3.4 Hz), 3.54 (dd, 1H, *J* = 4.4, 9.3 Hz), 3.46

(dd, 1H, *J* = 4.4, 9.3 Hz), 1.94 (m, 1H), 1.81 (m, 2H), 1.50 (m, 1H),1.45 (s, 3H), 1.30 (s, 3H).

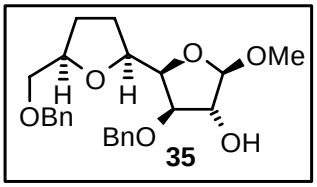
^{13}C NMR (125 MHz, $CDCl_3$): δ 138.3, 137.1, 128.2, 128.0, 127.7, 127.5, 127.3, 127.2, 111.3,105.31, 83.3, 82.5, 81.7, 78.3, 78.0, 73.0, 72.4, 71.4, 28.0, 27.2, 26.7, 26.3.

Anal. Calcd for $C_{26}H_{32}O_6$: C, 70.88; H, 7.32. Found: C, 71.12; H, 7.14.

Methyl-5,8-anhydro-3,9-di-*O*-benzyl-6,7-dideoxy-L-*glycero*-α-L-*ido*-nonanofuranoside (35) and methyl-5,8-anhydro–3,9–di-*O*-benzyl-6,7-dideoxy-L-*glycero*–β–L–*ido*-nonanofuranoside (36):

To a solution of **34** (4.4 g, 10 mmol) in anhydrous MeOH (60 mL) was added Amberlyst-120 (12 g) and refluxed for 16 h. The resin was filtered off through a plug of cotton and the filtrate concentrated. The residue was purified on silica gel with 50-60% EtOAc /petroleum ether to give β-isomer **35** (3.2 g) and α-isomer **36** (0.36 g) in the ratio 9:1 (86% yield) as colourless liquid.

Compound 35



35

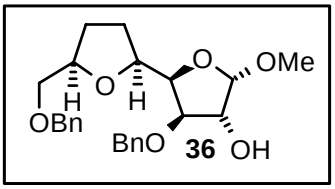
$[\alpha]_D$: –38.0 (*c* 2.2, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34–7.32 (m, 10H), 4.78 (s,1H), 4.65 (d, 1H, *J* = 11.9 Hz), 4.53 (brs, 2H), 4.46 (d, 1H, *J* = 11.9 Hz), 4.24 (brs, 1H), 4.12 (m, 2H), 4.06 (t, 1H, *J* = 6.3 Hz), 3.84 (dd, 1H, *J* = 3.0, 6.3 Hz), 3.56 (dd, 1H, *J* = 4.8, 9.8 Hz), 3.45 (dd, 1H, *J* = 4.8, 9.8 Hz), 3.40 (s, 3H),1.94 (m, 2H), 1.75 (m, 1H), 1.53 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 138.6, 137.8, 128.4, 128.3, 127.9, 127.8, 127.7, 127.5, 109.6, 83.8, 83.4, 79.3, 78.6, 78.4, 73.4, 72.9, 72.1, 55.7, 28.6, 27.6.

Anal. Calcd for $C_{24}H_{30}O_6$: C, 69.54; H, 7.29; Found: C, 69.43; H, 7.42.

Compound 36



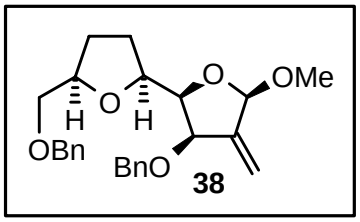
$[\alpha]_D$: + 41.6 (*c* 0.7, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.25 (m, 10H), 4.95 (d, 1H, *J* = 4.7 Hz), 4.77 (d, 1H, *J* = 11.9 Hz), 4.56 (brs, 2H), 4.55 (d, 1H, *J* = 11.9 Hz), 4.32 (t, 1H, *J* = 4.4 Hz), 4.17-4.11 (m, 2H), 4.02 (t, 1H, *J* = 5.9 Hz), 3.91 (dd, 1H, *J* = 4.4, 5.9 Hz), 3.54 (dd, 1H, *J* = 4.8, 9.9 Hz), 3.47 (s, 3H), 3.45 (dd, 1H, *J* = 5.6, 9.9 Hz), 1.96 (m, 2H), 1.81 (m, 1H), 1.65 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 138.4, 137.8, 128.2, 128.1, 127.6, 127.5, 127.4, 127.3, 101.8, 83.6, 80.7, 78.3, 78.1, 76.2, 73.2, 72.5, 71.5, 55.6, 28.1, 27.5.

Anal. Calcd for $C_{24}H_{30}O_6$: C, 69.54; H, 7.29; Found: C, 69.48; H, 7.45.

Methyl-5,8- anhydro- 3,9-di-*O*- benzyl–2,6,7-trideoxy -2-*C*-methylene –α-L-gluco-nonanofuranoside (38):



IBX (1.35 g, 4.83 mmol) was dissolved in DMSO (3 mL) and stirred at rt for 20 min, the opaque solution turned clear. To the solution, alcohol **35** (1.337g, 3.22 mmol) in THF (5 mL) was added dropwise. After 3 h stirring, the reaction mixture was quenched by sat. $Na_2S_2O_3$ solution (6 mL) and extracted with Et_2O (100 mL × 2). The organic phase was washed with sat. $NaHCO_3$ solution (10 mL × 2) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated to give keto compound **37** (1.2 g, 92%), which was used for next reaction without purification.

Compound **37** (1.2 g) was dissolved in anhydrous THF (30 mL) and cooled to –15 ºC. Methylene triphenylphosphorane [prepared from $P^+Ph_3CH_3I^-$ (3.52 g, 8.72 mmol) and $NaNH_2$ (351 mg, 9.01 mmol)] in THF was added and stirred for 30min. The reaction mixture was quenched by addition of saturated NH_4Cl solution. The two layers were separated, the organic layer dried (Na_2SO_4) and concentrated to form a residue which was

purified on silica gel chromarography using 12% EtOAc/light petroleum ether to furnish **38** (0.95 g, 78%) as a colorless oil.

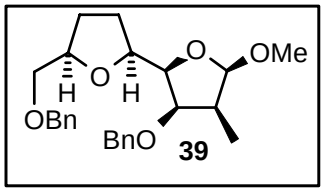
$[\alpha]_D$ **:** + 85.5 (*c* 3.5, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28-7.14 (m, 10H), 5.32 (d, 2H, *J* = 20.6 Hz), 5.13 (s, 1H), 4.65 (d, 1H, *J* = 11.9 Hz), 4.50 (d, 1H, *J* = 11.9 Hz), 4.51 (2H, s), 4.24 (m, 1H), 4.09-4.05 (m,2H), 3.6 (m, 1H), 3.42- 3.37(m, 2H), 3.34 (s, 3H), 1.90-1.80 (m, 3H), 1.73 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 146.8, 138.2, 137.9, 128.0, 127.5, 127.3, 127.2, 113.5, 104.1, 83.6, 79.4, 78.6, 78.5, 73, 72.5, 70.1, 54.1, 28.1, 26.9.

Anal. Calcd for $C_{25}H_{30}O_6$: C, 73.14; H, 7.36. Found: C, 73.05; H, 7.31.

Methyl-5,8-anhydro- 3,9-di-*O*-benzyl-2,6,7-trideoxy-2-*C*-methyl-L-*glycero*-α-L gulo-nonanofuranoside (39):



39

To the solution of **38** (0.6 g, 1.46 mmol) in MeOH (10 mL), 20% Pd/C (0.030 g) was added, and the mixture was degassed with argon and flushed with with H_2 for 5 min. Reaction mixture was stirred under H_2 atmosphere for 15 min, then the mixture was filtered through a pad of celite and concentrated. The residue was purified on silicagel using 12-15% EtOAC/light petroleum ether to afford **39** as a thick syrup (0.554 g, 92%).

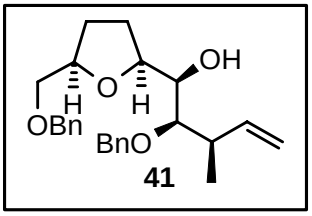
$[\alpha]_D$ **:** + 33.2 (*c* 5.6, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30–7.23 (m, 10H), 4.70 (d, 1H, *J* = 5.4 Hz), 4.56 (m, 2H), 4.51 (m, 2H), 4.08 (m, 1H), 4.04 (t, 1H, *J* = 3.7 Hz), 3.85 (m, 1H), 3.80 (dd, 1H, *J* = 2.2, 6.7 Hz), 3.38 (m, 2H), 3.37 (s, 3H), 2.18 (m, 1H),1.90–1.71 (m, 4H), 1.05 (d, 3H, *J* = 7.1 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ 138.7, 138.5, 128.3, 127.8, 127.7, 127.6, 107.1, 85.6, 80.7, 80.4, 78.6, 73.4, 73.0, 72.2, 55.5, 42.1, 28.5, 27.4, 7.8.

Anal. Calcd for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 72.52; H, 7.64.

(1*R*, 2*R*, 3*R*)-2-(benzyloxy)-1-((2*S*, 5*R*)-5-(benzoyloxymethyl)-tetrahydrofuran-2-yl)-3-methylpent-4-en-1-ol (41):



41

To the solution of compund **39** (330 mg, 0.79 mmol) in 20% acetic acid in H_2O (10 mL) with catalytic amount of H_2SO_4 was added and heated at 70 °C for 3 h. The reaction mixture was neutralized by addition of solid $NaHCO_3$, filtered and concentrated. The residue was partitioned between EtOAc-water, the organic layer was separated, washed with water, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel using 18-20% EtOAc/light petroleum ether to obtain the aldehyde **40** (242 mg), which was dissolved in THF (10 mL) and methylene triphynylphosphorane was added [prepared from PPh_3CH_3I (1.5 g) and *n*-BuLi (1.6 M, 1.9 mL)] at –20 ºC. After 3 h stirring at rt, it was worked up in an usual manner and the residue was purified on a silica gel column chromatography using 13% EtOAc/light petroleum ether to furnish **41** (0.207 g, 86%) as a oily liquid.

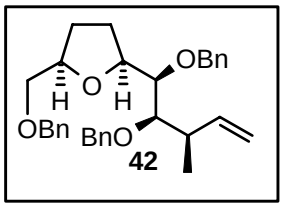
$[\alpha]_D$: + 54.44 (*c* 1.2, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (m, 10H), 5.89 (m, 1H), 5.10-4.98 (m, 2H), 4.65 (d, 2H, *J* = 4.3 Hz), 4.57 (d, 2H, *J* = 2.4 Hz), 4.29 (m, 1H), 4.15 (m, 1H), 3.68 (dd, 1H, *J* = 3.5, 10.2 Hz), 3.41 (dd, 1H, *J* = 3.5, 10.2 Hz), 3.36 (brs, 2H), 2.71 (q, 1H, *J* = 7.4 Hz), 1.99 (m, 4H), 1.13 (d, 3H, *J* = 7.4 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 140.4, 139.0, 137.9, 128.4, 128.2, 127.8, 127.5, 127.3, 115.0, 84.3, 78.7, 78.5, 74.4, 73.6, 73.4, 72.1, 39.9, 28.4, 28.1, 17.7.

Anal. Calcd for $C_{25}H_{32}O4$: C, 75.53; H, 8.36. Found: C, 75.65; H, 8.29.

(2*R*, 5*S*)-2-(benzyloxymethyl)-5-((1*R*, 2*R*, 3*R*)-1,2-bis(benzyloxy)-3-methylpent-4-enyl)-terahydrofuran (42):



Compound **41** (50 mg, 10.1 mmol) in THF (2 mL) was added to the stirred suspension of NaH (6 mg, 60% dispersion in oil, 0.15 mmol) in THF (2 mL) at 0 ºC. The resulting solution was stirred at rt for 30 min, then BnBr (0.2 mL, 0.13 mmol) was added. After 1 h, the reaction mixture was quenched by ice-cold water and extracted with EtOAc. The combined organic layers were washed with water, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel chromatography using 10% EtOAc-light petroleum ether to obtain **42** (53 mg, 93%).

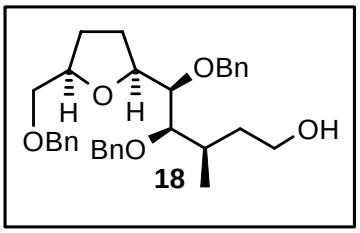
$[\alpha]_D$: + 14.0 (*c* 1.3, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30–7.15 (m, 15H), 5.90 (m, 1H), 5.04 (m, 2H), 4.80-4.61 (m, 4H), 4.54 (s, 2H), 4.20 (brs, 2H), 3.60-3.37 (m, 4H), 2.75-2.59 (m, 1H), 2.66 (m, 4H), 1.13 (d, 3H, *J* = 6.1 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 141, 138.9, 138.8, 138.6, 128.2, 128.1, 127.5, 127.4, 127.3,115.1, 83.4,81.3 , 79.7, 77.8, 74.4, 74.1, 73.2, 73.0, 40.0, 28.6, 27.3, 18.8.

Anal. Calcd for $C_{32}H_{38}O_4$: C, 78.97; H, 7.86. Found: C, 78.90; H, 7.79.

(3*R*, 4*R*, 5*R*)-4, 5-bis(benzyloxy)-5-((2*S*, 5*R*)-5-(benzyloxymethyl)-tetrahydrofuran-2-yl)-3-methylpentan-1-ol (18):



To a solution of **42** (83 mg, 0.17 mmol) in anhydrous THF (1.3 mL) was added 9-BBN (42 mg, 0.34 mmol) at 0 °C. After stirring for 4 h, saturated aq NaOAc solution was introduced followed by the addition of 30% H_2O_2 (0.5 mL). The reaction mixture was further stirred at

rt for 1 h, diluted with EtOAc. The combined organic layers were washed with water, dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography using 20-23% EtOAc/light petroleum ether to provide alcohol **18** (83 mg, 90%).

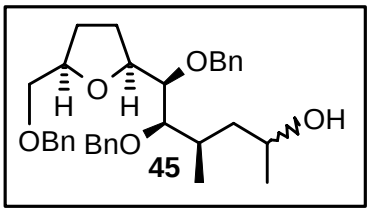
$[\alpha]_D$: + 14.6 (*c* 1.3, $CHCl_3$)

^1H NMR (300 MHz, $CDCl_3$): δ 7.30–7.15 (m, 15H), 4.71 (m, 3H), 4.56 (m, 3H), 4.14 (m, 2H), 3.69 (m, 1H), 3.54 (dd, 1H, *J* = 3.2, 7.7 Hz), 3.52 (m, 3H), 3.45 (dd, 1H, *J* = 3.2, 7.7 Hz), 2.09 (brs, 1H), 1.92 (m, 3H), 1.78 (m, 3H), 1.61 (m, 1H), 1.00 (d, 3H, *J* = 3.9 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6, 138.4, 128.3, 128.2, 127.8, 127.6, 127.5, 84.0, 81.0, 80.2, 77.8, 74.2, 73.3, 73.0, 60.2, 34.3, 31.5, 28.5, 27.6, 18.0.

Anal. Calcd for $C_{25}H_{40}O_5$: C, 76.15; H, 7.98. Found: C, 76.04; H, 7.85.

(4*R*, 5*R*, 6*R*)-5, 6-bis (benzyloxy)-6-((2*S*, 5*R*)-5-(benzyloxymethyl)-tetrahydrofuran-2-yl)-4-methylhexan-2-ol (45):



To the solution of alcohol **18** (55 mg, 0.11 mmol) in anhydrous CH_2Cl_2 (4 mL) was added Dess-Martin periodinane (67 mg, 0.16 mmol) and stirred at rt for 3 h.The reaction mixture was diluted with Et_2O (10 mL), and neutralized by saturated aqueous $NaHCO_3$ (10 mL), $Na_2S_2O_3$ (10 mL). The organic layer was separated and washed second times with $NaHCO_3$ and $Na_2S_2O_3$.The organic layer was separated, dried over Na_2SO_4, and carefully concentrated. The crude product was quickly passed through a plug of silica gel with CH_2Cl_2 as the eluent. The filtrate was carefully concentrated to give the desired compound aldehyde **43** as a clear oil (53 mg, 96%).

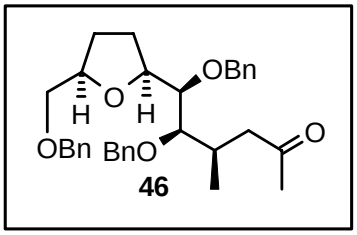
Compound **43** (53 mg, 0.10 mmol) was dissolved in anhydrous THF (5 mL) and cooled to 0 ºC. A 2 M solution of MeMgI in THF (0.2 mL, 0.32 mmol) was added. After 2 h stirring at rt, it was quenched by saturated NH_4Cl solution (5 mL). The two layers were separated, the organic layer was dried (Na_2SO_4) and concentrated to form a residue which was purified on silica gel using 18% EtOAc/light petroleum ether to furnish a 1: 1 mixture of product **45** (48 mg, 87%).

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.32-7.25 (m, 15H), 4.80-4.71 (m, 3H), 4.58-4.48 (m, 3H), 4.18-4.11 (m, 2H), 3.90 (m,1H), 3.63-3.41 (m, 4H), 2.13 (m, 1H), 2.0-1.7 (m, 6H), 1.12 (t, 3H, *J* = 5.5 Hz), 1.0 (t, 3H, *J* = 7.4 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 138.7, 138.3, 128.4, 128.3, 128,127.9, 127.7, 127.6, 127.5, 84.7, 84.3, 81.6, 81.2, 80.7, 80.4, 78, 77.4, 74.4, 74.2, 73.8, ,73.4, 73.2, 66.3, 64.8, 41.5, 41.4, 31.6, 29.7, 28.5, 27.8, 25, 23.6, 18.9, 18.6.

Anal. Calcd for $C_{33}H_{42}O_5$: C, 76.41; H, 8.16. Found: C, 76.24; H, 7.46.

(4*R*, 5*R*, 6*R*)-5,6-bis(benzyloxy)-6-((2*S*, 5*R*)-5-(benzyloxymethyl)- tetrahydrofuran-2-yl)-4-methylhexane-2-one (46):



46

To a solution of alcohol **45** (48 mg, 0.09 mmol) in anhydrous CH_2Cl_2 (4 mL) was added Dess-Martin periodinane and stirred at room temperature for 3 h. The reaction mixture was diluted by Et_2O (5 mL), followed by addition of saturated $NaHCO_3$ (5 mL), and $Na_2S_2O_3$ (5 mL) solution. The organic layer was separated and washed again with $NaHCO_3$ and $Na_2S_2O_3$.The organic layer was separated, dried over Na_2SO_4, and carefully concentrated. The crude product was quickly passed through a plug of silica gel with CH_2Cl_2 as the eluent. The filtrate was carefully concentrated to give the desired compound as a clear oil **46** (46 mg, 95%).

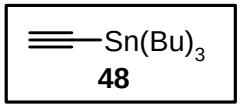
$[\alpha]_D$ **:** + 15.8 (*c* 0.9, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.25 (m, 15H), 4.71(m, 3H), 4.55 (s, 2H), 4.43 (d, 1H, *J* = 11.6 Hz), 4.14 (m, 2H), 3.54 (m, 3H), 3.39 (m, 1H), 2.87 (dd, 1H, *J* = 3.6, 16.9 Hz), 2.46 (m, 1H), 2.27 (m, 1H), 1.99 (s, 3H), 1.89-1.66 (m, 4H), 0.94 (d, 3H, *J* = 6.9 Hz).

^{13}C NMR (50 MHz, $CDCl_3$)**:** δ 209.0, 138.9, 138.7, 128.3, 128.2,128.0, 127.8, 127.6, 127.5, 127.4, 83.9, 82.0, 81.0, 77.9,74.2, 73.4, 73.2,46.5, 30.7, 30.3, 29.7, 28.4, 18.8.

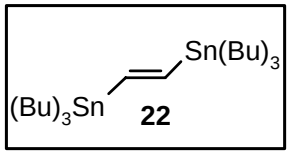
Anal. Calcd for $C_{33}H_{40}O_5$: C, 76.71; H, 7.80. Found: C, 76.41; H, 7.52

Tributyl (ethynyl) stannane (48):



n-Butyl lithium (74 mL, 119 mmol, 1.6 M in hexane) in dry THF (84 mL) was stirred under acetylene atmosphere at 0 ºC stir for 1 h, then tributyltin chloride (30g, 92 mmol) was added dropwise over a period of 30 min. The reaction mixture was warmed to rt and stored under a close acetylene atmosphere for 12 h. Water (5 mL) was added and reaction mixture was concentrated in vacuum. Heptane (125 mL) was added and the reaction mixture was washed with one portion of water (500 mL), dried over Na_2SO_4 and concentrates in vaccum to furnish an oil. Distilation of crude liquid (b.p = 200 ºC, 2 mm) afforded tri-n-butyl stannane **48** (22.5g, 75%).

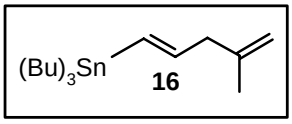
(*E*) Bis-ethylene distannane (22):



A mixture of tri-*n*-butylstannane (2.5 mL, 9.4 mmol) and tri-n-butyl ethynyl stannane **48** (2.9g, 9.4) was heated for 10 h at 90 ºC under the argon atmosphere. Distillation of the reaction mixture yielded **22** (5.02 gm, 92%) fraction with b.p = 177-178/2 mm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 153, 29.3, 27.4, 14.0, 9.7.

(*E*)-tributyl(4-methylpent-1,4-dienyl)stannane (16):



To a suspension of bis(aceto-nitrile)palladiumchloride (11mg, 0.04 mmol), triphenyl phosphine (5.5 mg, 0.02 mmol) in THF (10 mL) was introduced distannane **22** (1.3 g, 2.13 mmol) followed by methallyl chloride **23** (0.2 mL, 2.09 mmol). The resulting yellow solution was degassed with Ar and heated at 50 ºC for 3 h. It was concentreated in vacuum and purified by distillation to give **16** (12.2 gm, 84%, b.p = 120-125º C/1mm).

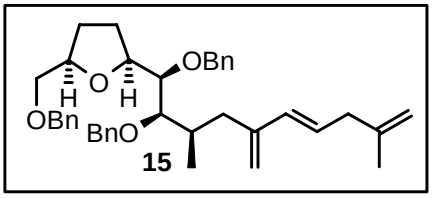
^{1}H NMR (300 MHz, $CDCl_3$): δ 5.95 (t, 2H, *J* = 8.3 Hz), 4.74 (m, 2H), 2.85 (s, 2H), 1.74 (s, 3H), 1.49 (m, 6H), 1.34 (m, 6H), 0.92 (m, 15H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 146.7, 144.0, 129.5, 110.9, 46.9, 29.3, 27.4, 22.2, 13.7, 9.48.

IR ($CHCl_3$, cm^{-1}): 2957, 2925, 2872, 1649, 1595, 1463, 1376, 1292, 1220, 1181, 1071, 989, 888, 689.

Anal.Calcd for $C_{18}H_{36}Sn$: C, 58.24; H, 9.78. Found: C, 58.46; H, 9.84.

(2*R*, 5*S*)-2-(benzyloxymethyl)-5-((1*R*, 2*R*, 3*R*, *E*) -1, 2-bis (benzyloxy)-3,9-dimethyl-5-methylenedeca-6,9-dienyl)-tetrahydrofuran (15):



15

To a solution of ketone **46** (33 mg, 0.06 mmol) in anahydrous dimethoxyethane (2 mL) was added LDA (0.07 mL, 1M soln in THF, 0.07 mmol) at -78 ºC and stirred for 1 h at same temperature then, *N*-(2-Pyridyl)-triflimide (25 mg, 0.07 mmol) in DME (2 mL) was added and continued 2 h at -78 ºC. Reaction mixture was quenched with ice water, extracted with ethyl acetate. The combined organic layers was washed with water, dried (Na_2SO_4) and concentrated. The crude product was quickly passed through the plug of silica gel and eluted with 20% EtOAc/light petroleum ether to afford **17** (33 mg, 81%).

LiCl (9 mg, 0.2 mmol) was dried under high vaccum. Upon cooling, $Pd(PPh_3)_4$ (4 mg, 0.003 mmol) and CuCl (18 mg, 0.2 mmol) were added, and the mixture was degassed under high vacuum with an Ar purge. DMSO (2.0 mL) was introduced with concomitant stirring, followed by the addition of an triflate **17** (24 mg, 0.04 mmol) in DMSO (2 mL) and vinyltin **16** (16 mg, 0.04 mmol) in DMSO (2 mL). The resulting mixture was rigorously degassed by the freeze-thaw process. The reaction mixture was stirred at room temperature for 1 h, then heated to 60 °C. The reaction mixture was cooled, diluted with Et_2O (30 mL), and washed with a mixture of brine (20 mL) and 5% aqueous NH_4OH (4 mL). The aqueous layer was further extracted with Et_2O (2 X 15 mL), and the combined organic layers were washed with water (2 X 20 mL) then brine (2 X 20 mL),

dried over Na_2SO_4, and concentrated to a residue that was purified on silica gel using 8% EtOAc-light petroleum ether to furnish clean oil **15** (19 mg, 92%).

$[\alpha]_D$ **:** + 11.2 (*c* 0.3, $CHCl_3$)

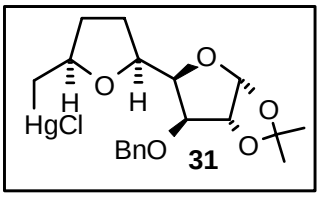
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.26 (m, 15H), 6.04 (d, 1H, *J* = 15.6 Hz), 5.78 (m, 1H), 4.95 (s, 1H), 4.83 (s, 1H), 4.77 (d, 2H, *J* = 12.8 Hz), 4.73 (s, 1H), 4.70 (d, 1H, *J* = 2.8 Hz), 4.66 (s, 1H), 4.54 (m, 3H), 4.15 (m, 2H), 3.59 (t, 1H, *J* = 4.8 Hz), 3.54 (dd, 1H, *J* = 4.8, 9.5 Hz), 3.46 (m, 2H), 2.71 (d, 2H, *J* = 7.1 Hz), 2.31 (m,1H), 1.91 (m, 3H), 1.72 (s, 3H), 1.66 (s, 3H), 0.87 (d, 3H, *J* = 7.1 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ 145.1, 144.6,139.0, 138.9, 138.6, 133.6, 128.3, 128.2, 128.0, 127.8, 127.7,127.6, 127.5, 127.4, 127.3, 127.2, 115.0, 110.7, 84.8, 82.0, 80.1, 77.6, 73.8, 73.7, 73.3, 73.1, 41.4, 34.4, 33.4, 28.4, 27.9, 22.4, 17.3.

MS (ESI) *m/z*: [M+Na] = 604.

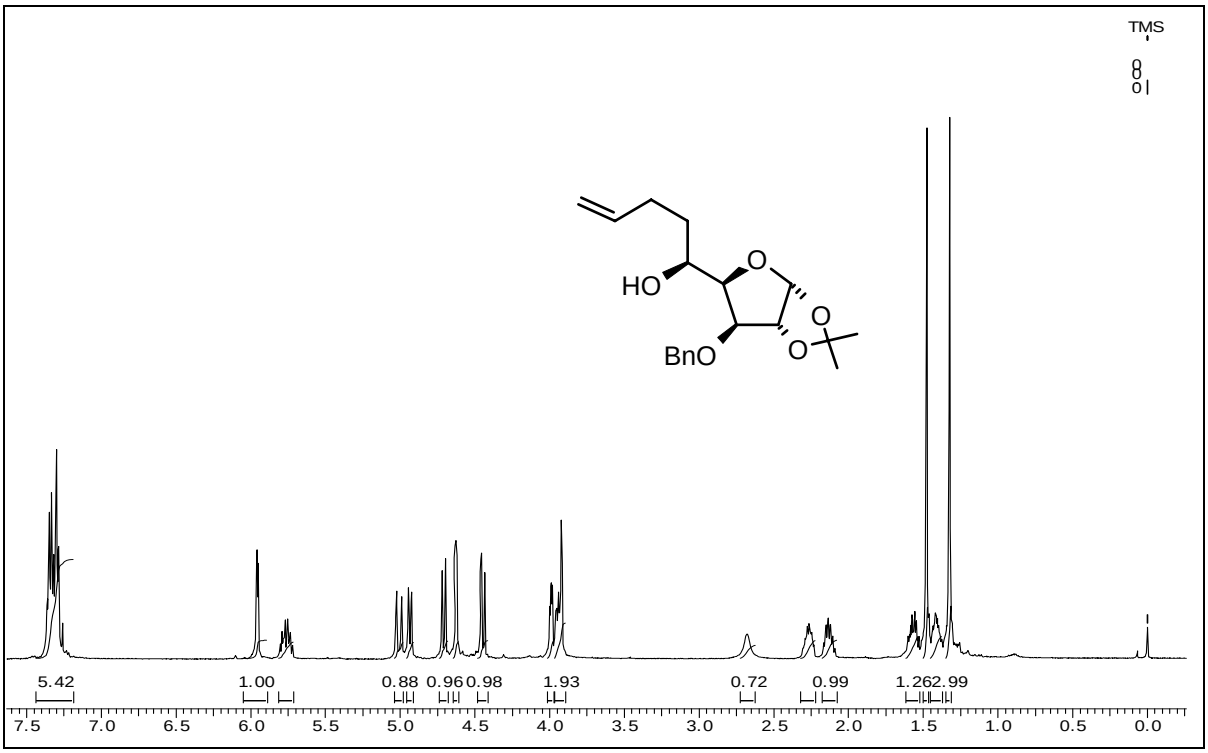
Anal. Calcd for $C_{39}H_{48}O_4$: C, 80.65; H, 8.33.Found: C, 80.51; H, 8.42.

X-ray Crystal data of 31

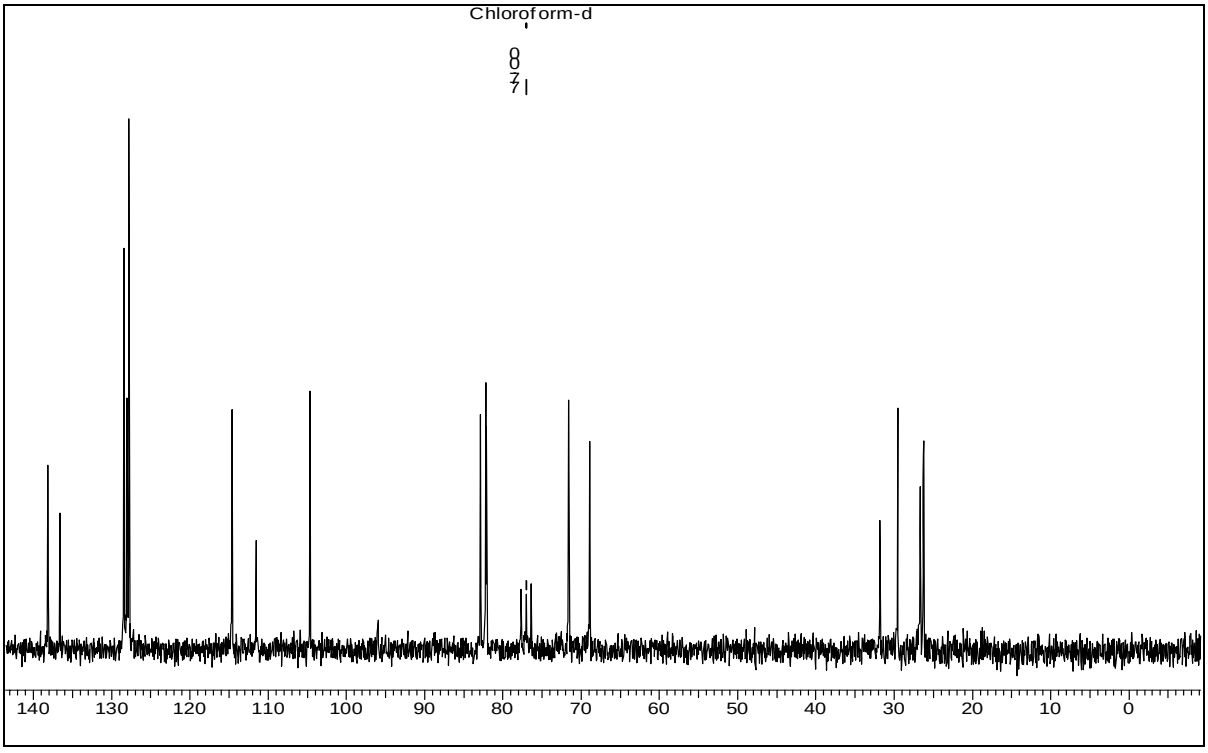


CCDC 244671, X-ray crystal data: Single crystals of the complex were grown by slow evaporation of the solution in dichloromethane. Colorless needle of approximate size 0.37x0.18x0.08mm, was used for data collection on Bruker SMART APEX CCD diffractometer using Mo Kα radiation with fine focus tube with 50kV and 30mA. Crystal to detector distance 6.05cm, 512 · 512pixels/ frame, Quadrant data acquisition. Total scans = 4, total frames = 2424, oscillation/frame -0.3º, exposure/frame = 20.0 s/frame, maximum detector swing angle = 30.0º, beam center = (260.2, 252.5), in plane spot width = 1.24, SAINT integration, θ range = 2.13 to 28.31º, completeness to h of 28.31º is 94.9%. SADABS correction applied, 2(C19H25O5HgCl). 0.5 H2O, M = 1156.88. Crystals belong to orthorhombic, space group P21, a = 10.987(2), b = 20.206(3), c = 11.125(2)A ˚ , V = 2414.0(6)A ˚ 3, Z = 2, Dc = 1.592mgm^{-3}, l (MoKa) = 6.511mm^{-}1, T = 295(2)K, 27,288 reflections measured, 11,013 unique [I > 2r(I)], R value 0.0373, wR2 = 0.0865. All the data were corrected for Lorentzian, polarization, and absorption effects. SHELX-97 (ShelxTL) was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model. Compound crystallizes with half molecules of water as solvent of crystallization (Sheldrick, G. M. SHELX- 97 Program for Crystal Structure Solution and Refinement, University of Gottingen, Germany, 1997).

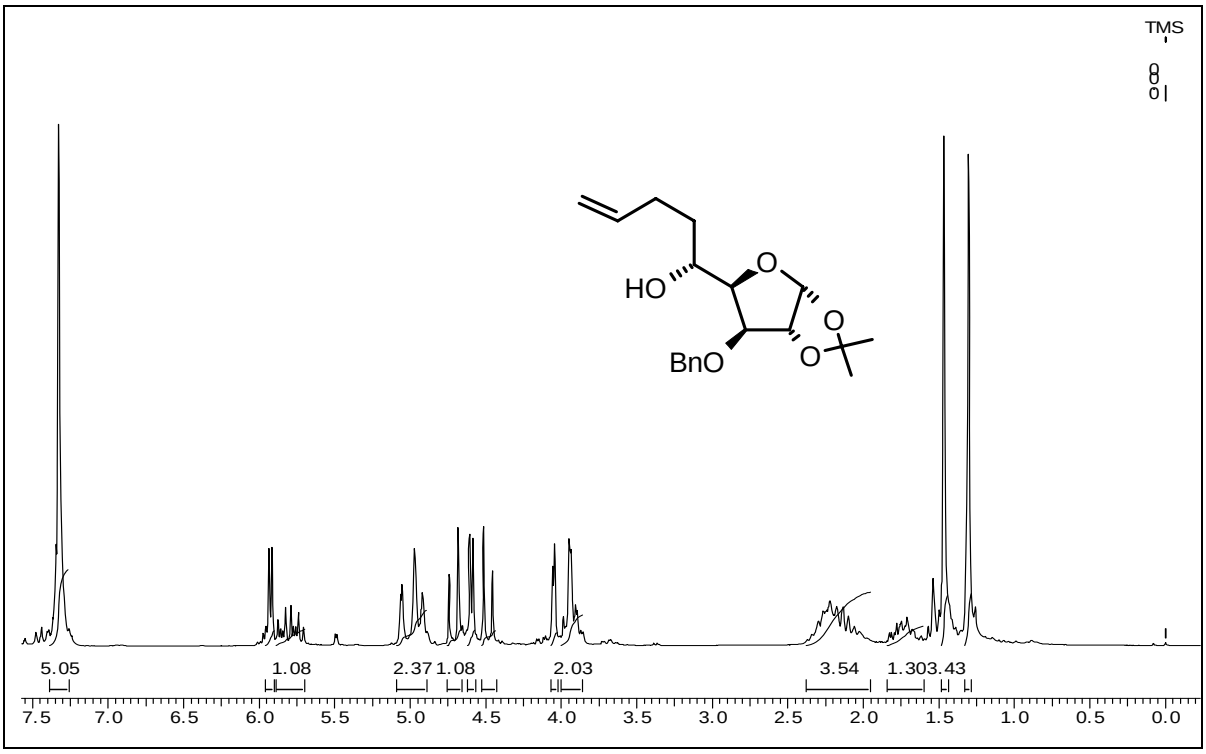
SPECTRA



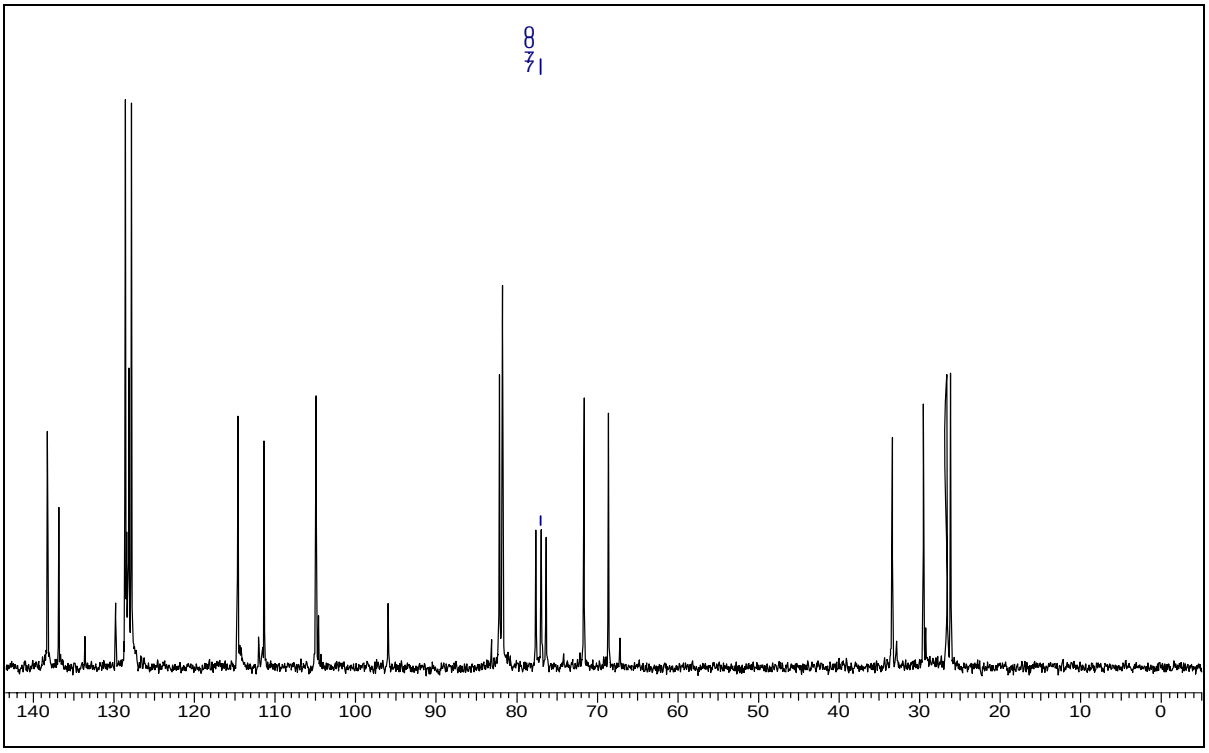
^{1}H NMR spectrum of compound 20 in $CDCl_3$



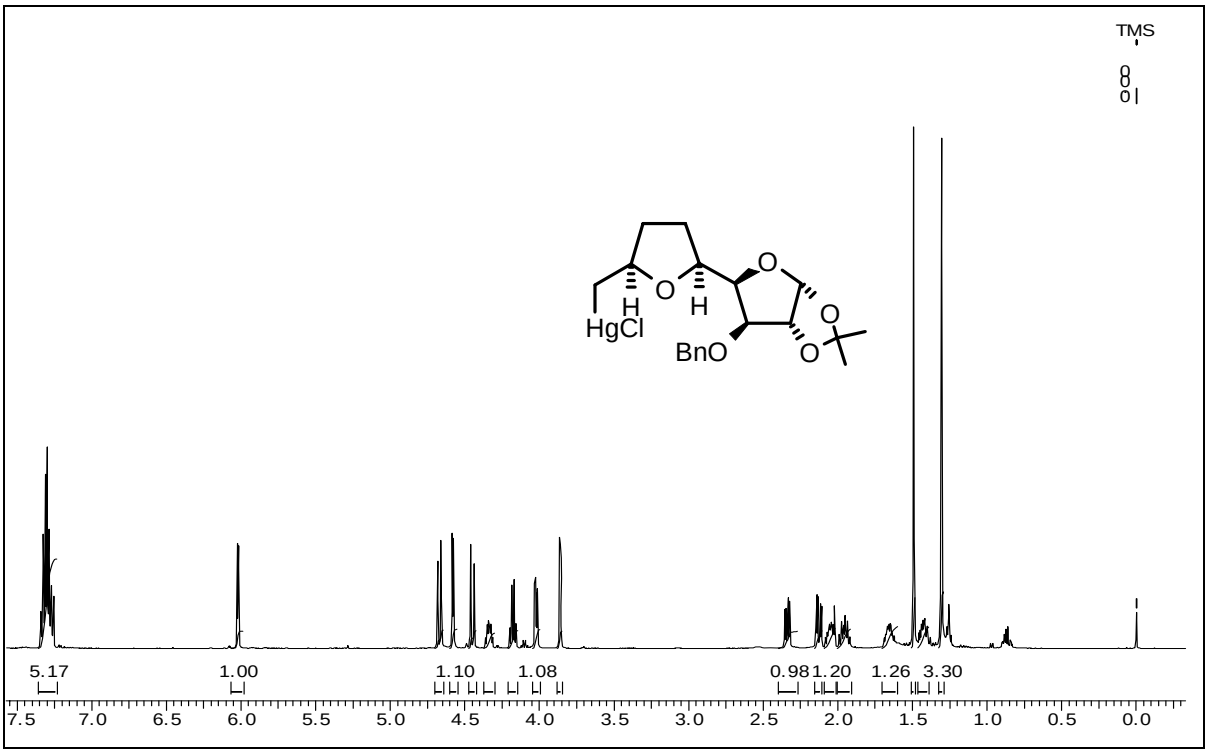
^{13}C NMR spectrum of compound 20 in $CDCl_3$



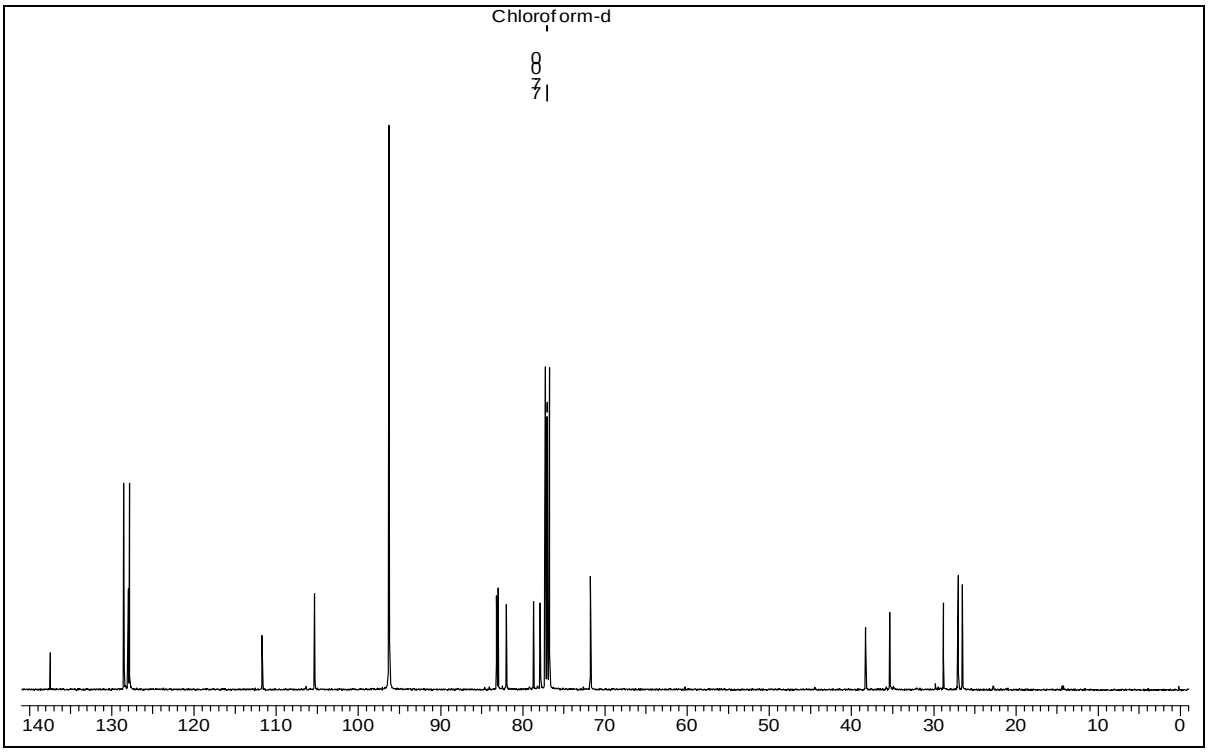
^{1}H NMR spectrum of compound 29 in $CDCl_3$



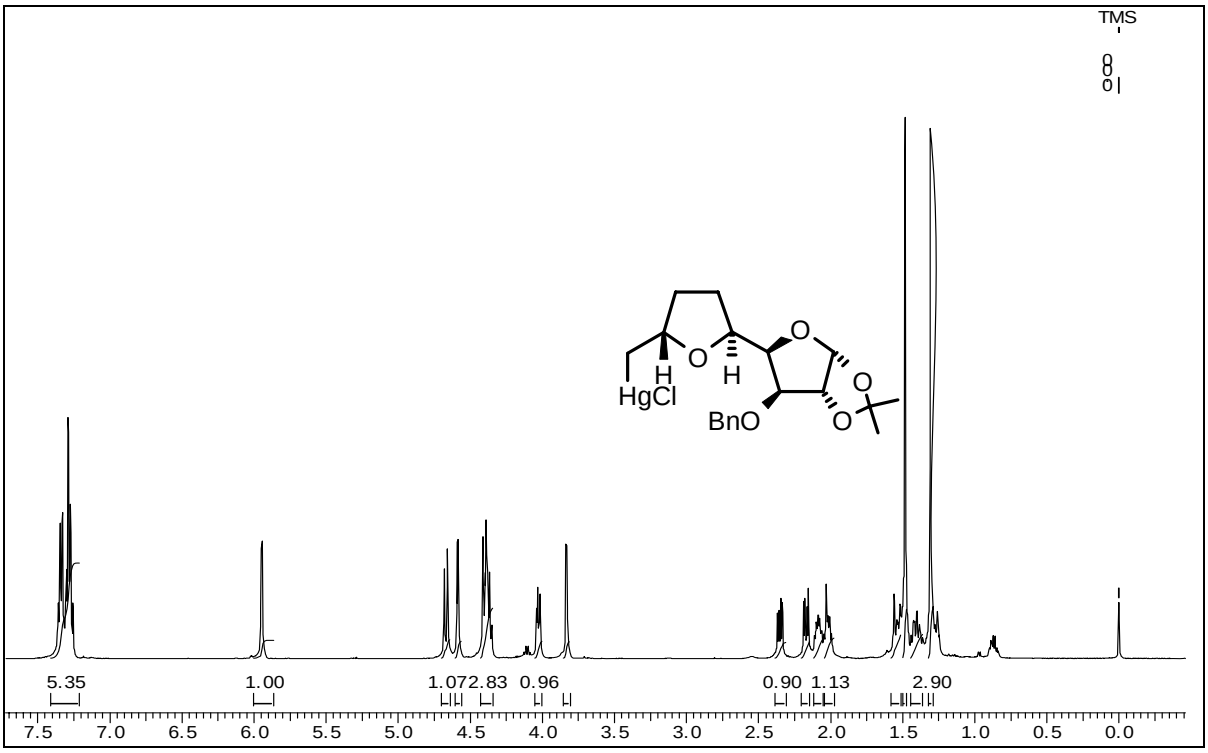
^{13}C NMR spectrum of compound 29 in $CDCl_3$



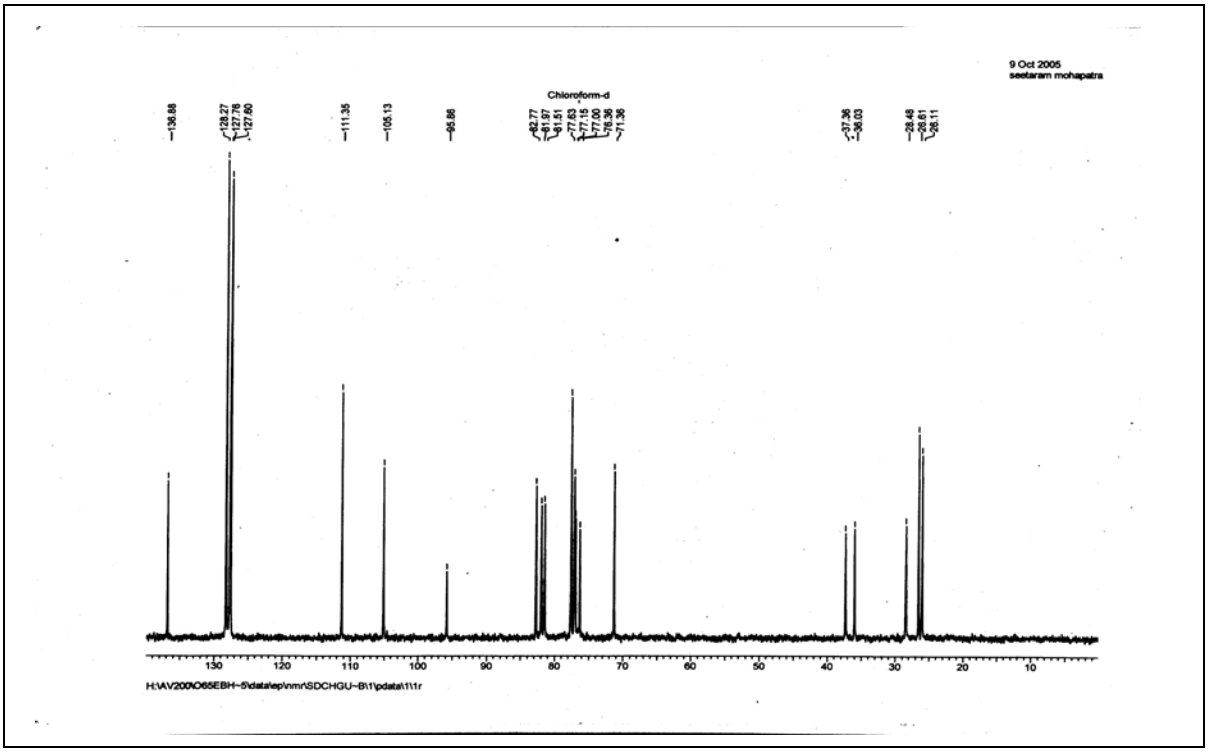
^{1}H NMR spectrum of compound 31 in $CDCl_3$



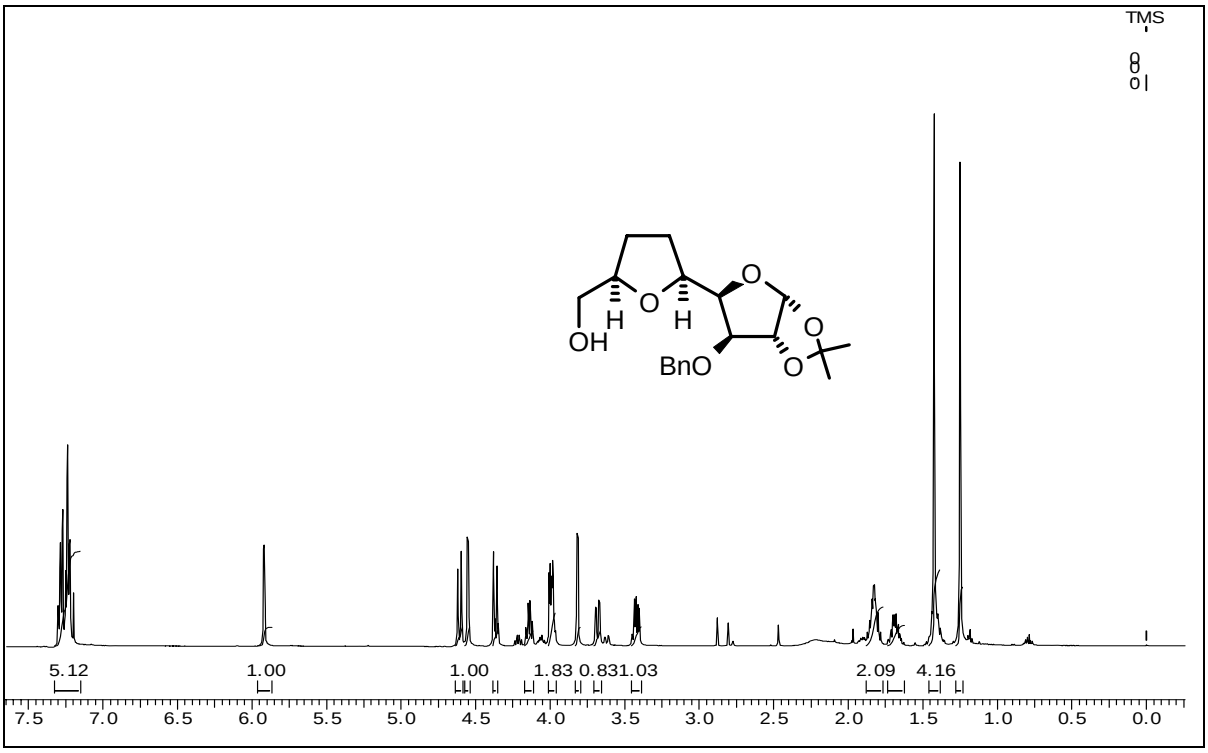
^{13}C NMR spectrum of compound 31 in $CDCl_3$



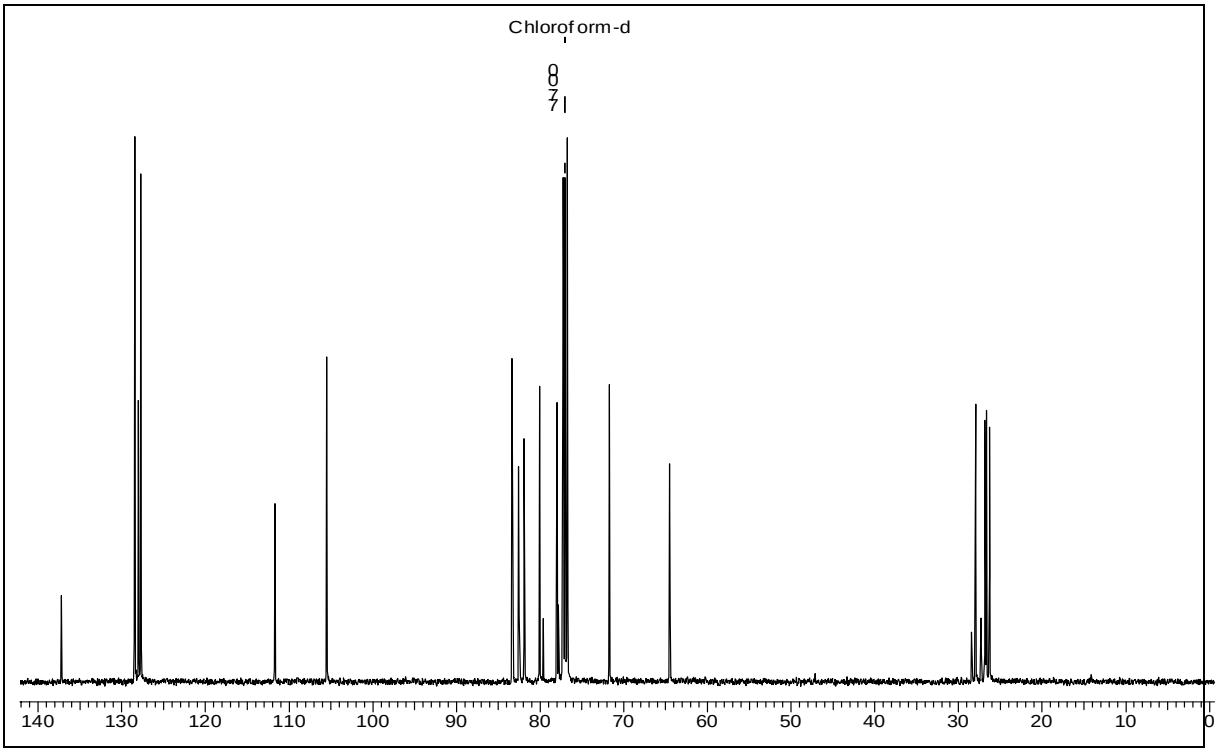
^{1}H NMR spectrum of compound 32 in $CDCl_3$



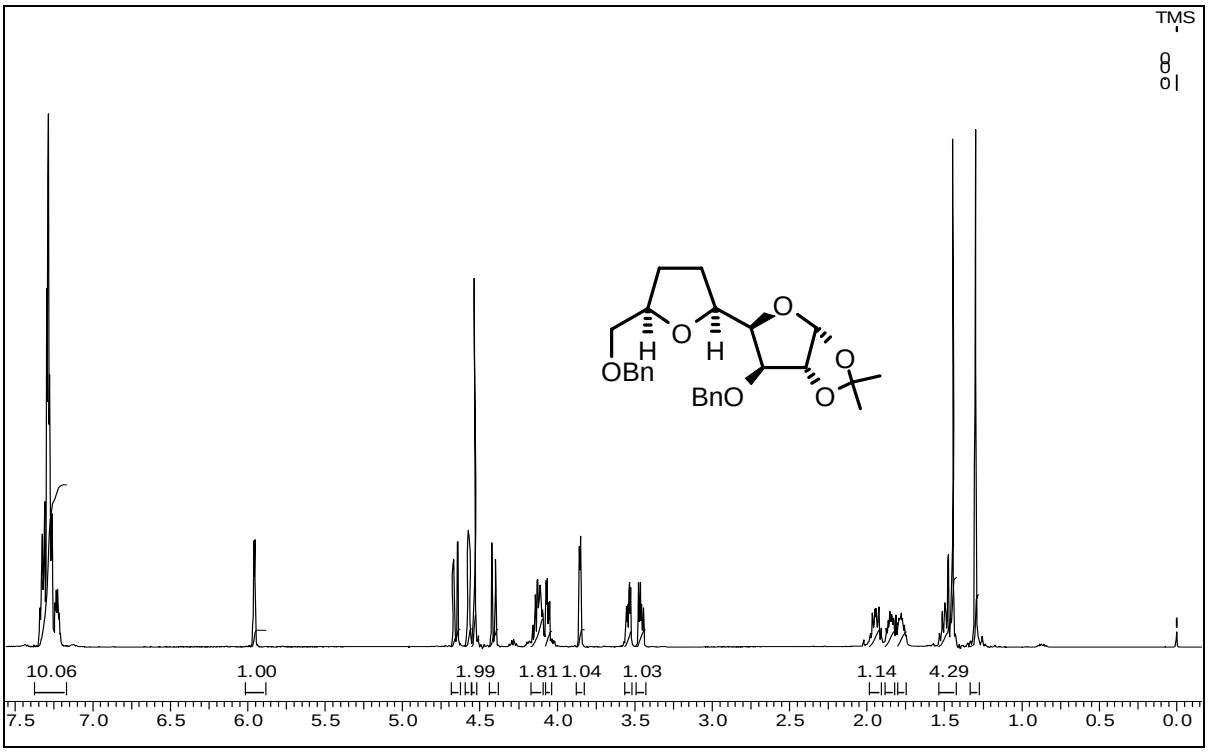
^{1}H NMR spectrum of compound 32 in $CDCl_3$



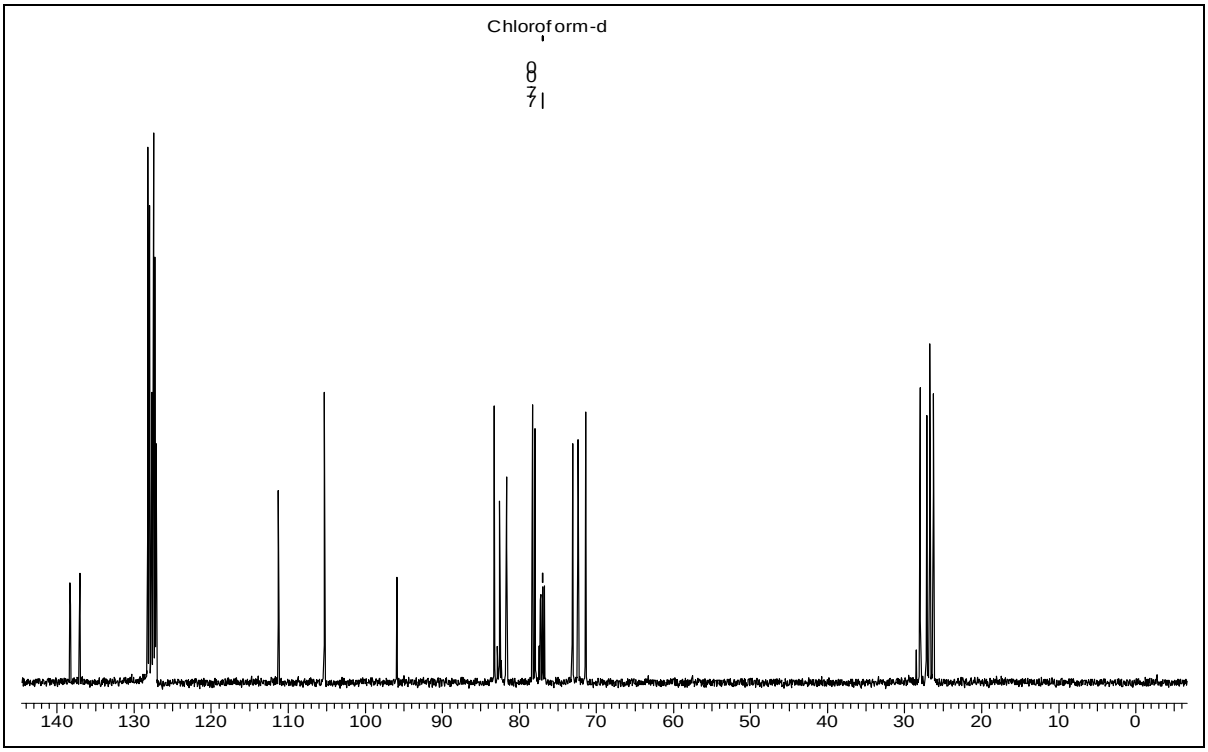
^{13}C NMR spectrum of compound 33 in $CDCl_3$



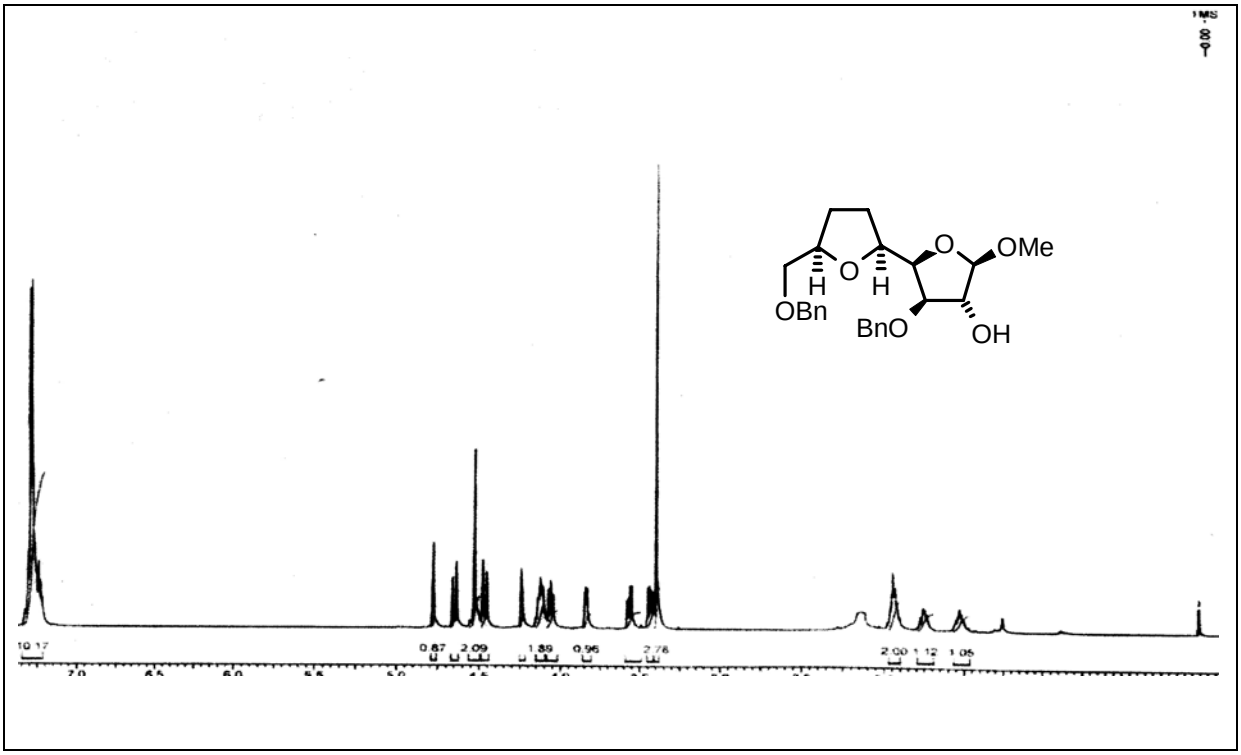
^{1}H NMR spectrum of compound 33 in $CDCl_3$



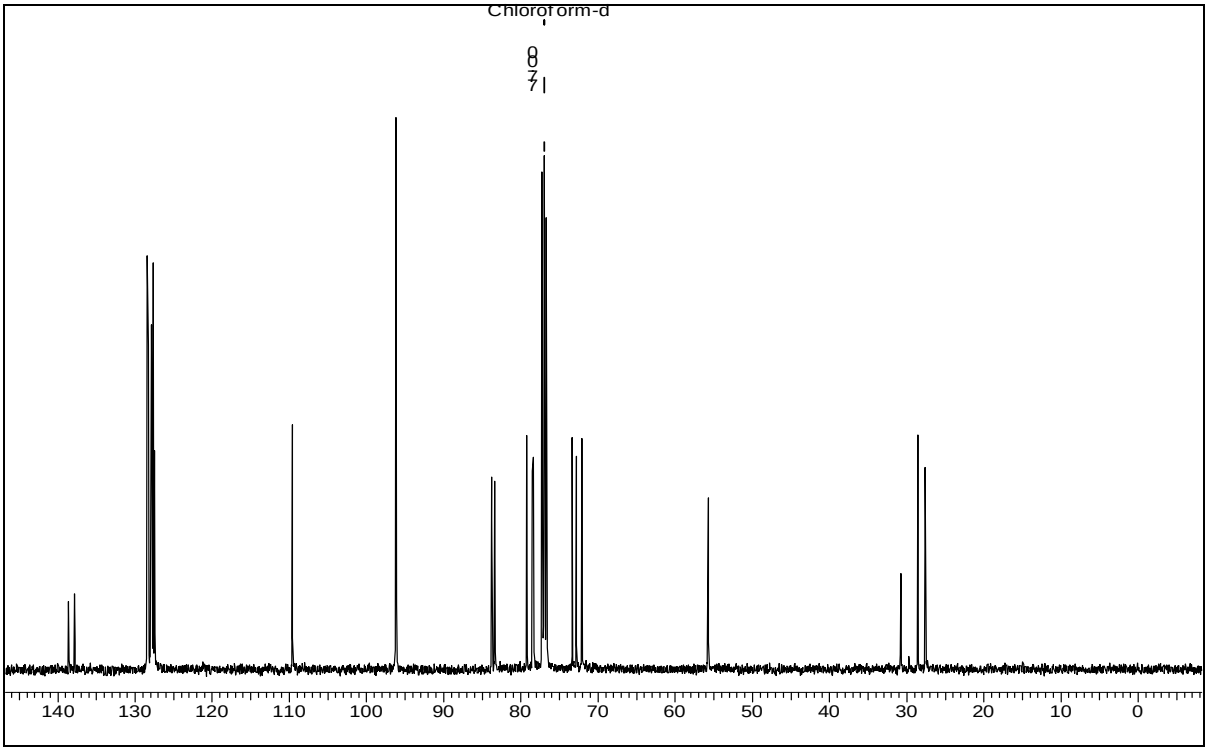
^{1}H NMR spectrum of compound 34 in $CDCl_3$



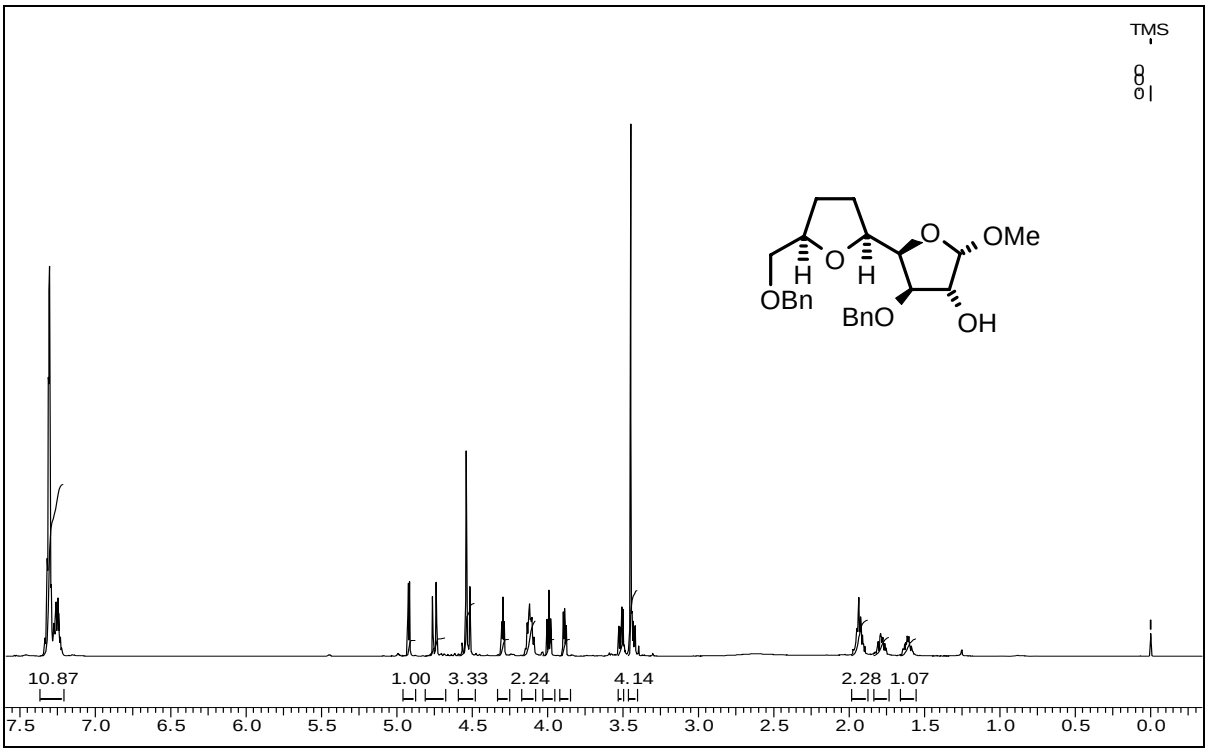
^{13}C NMR spectrum of compound 34 in $CDCl_3$



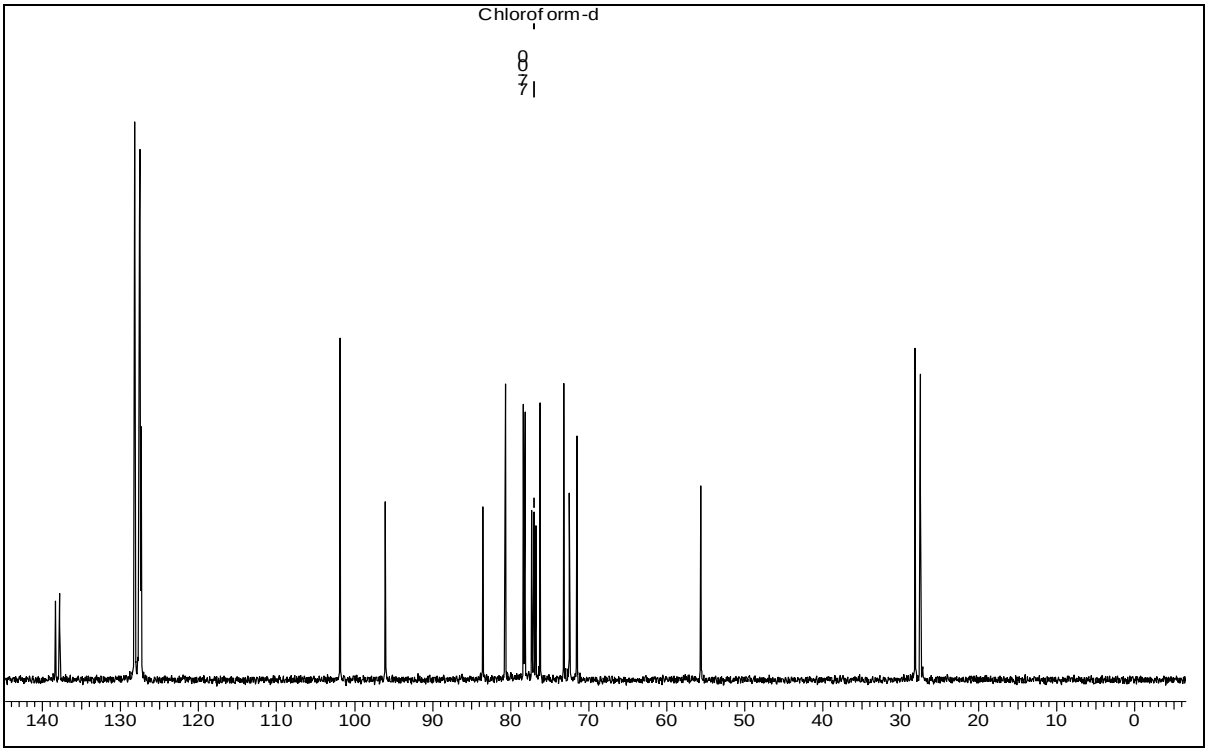
^{1}H NMR spectrum of compound 35 in $CDCl_3$



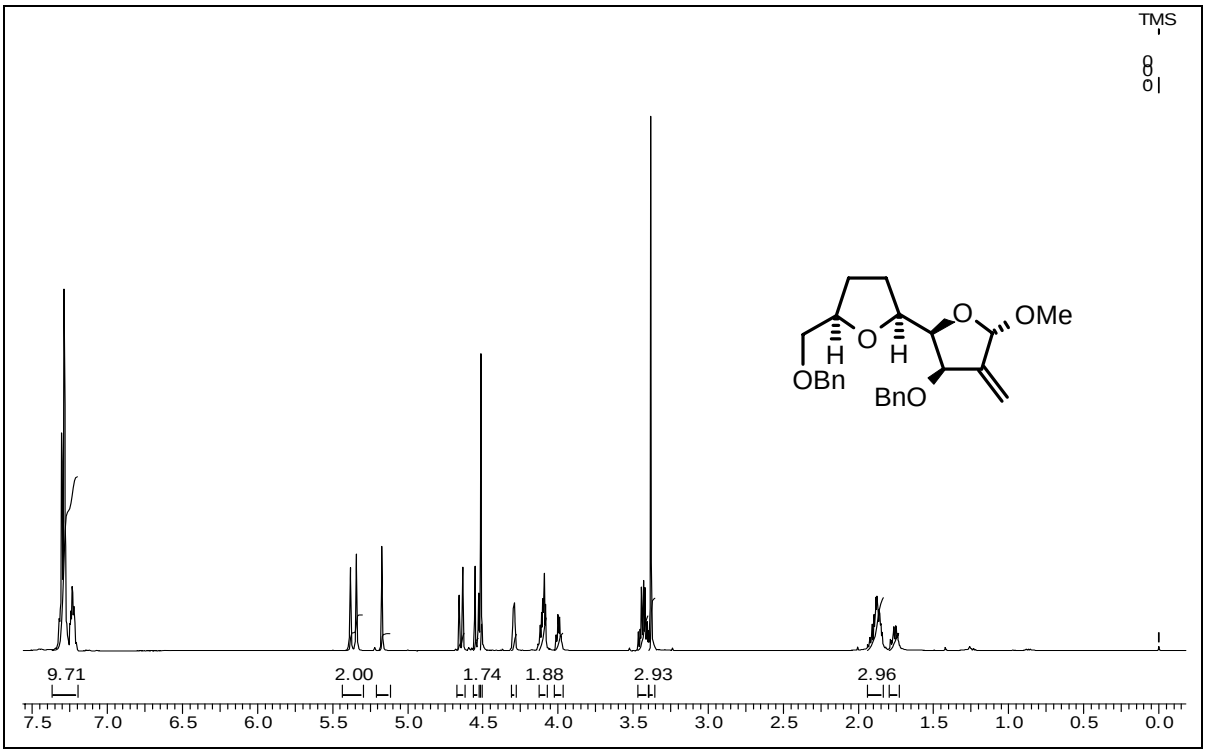
^{13}C NMR spectrum of compound 35 in $CDCl_3$



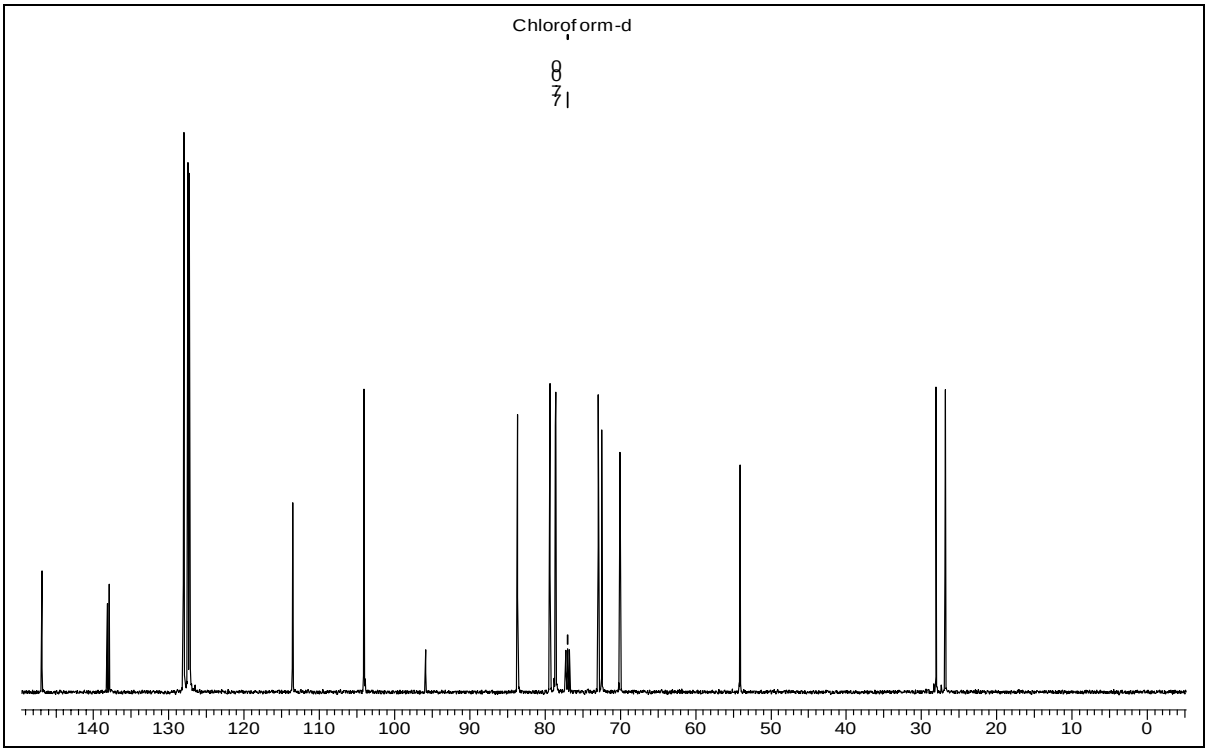
^{1}H NMR spectrum of compound 36 in $CDCl_3$



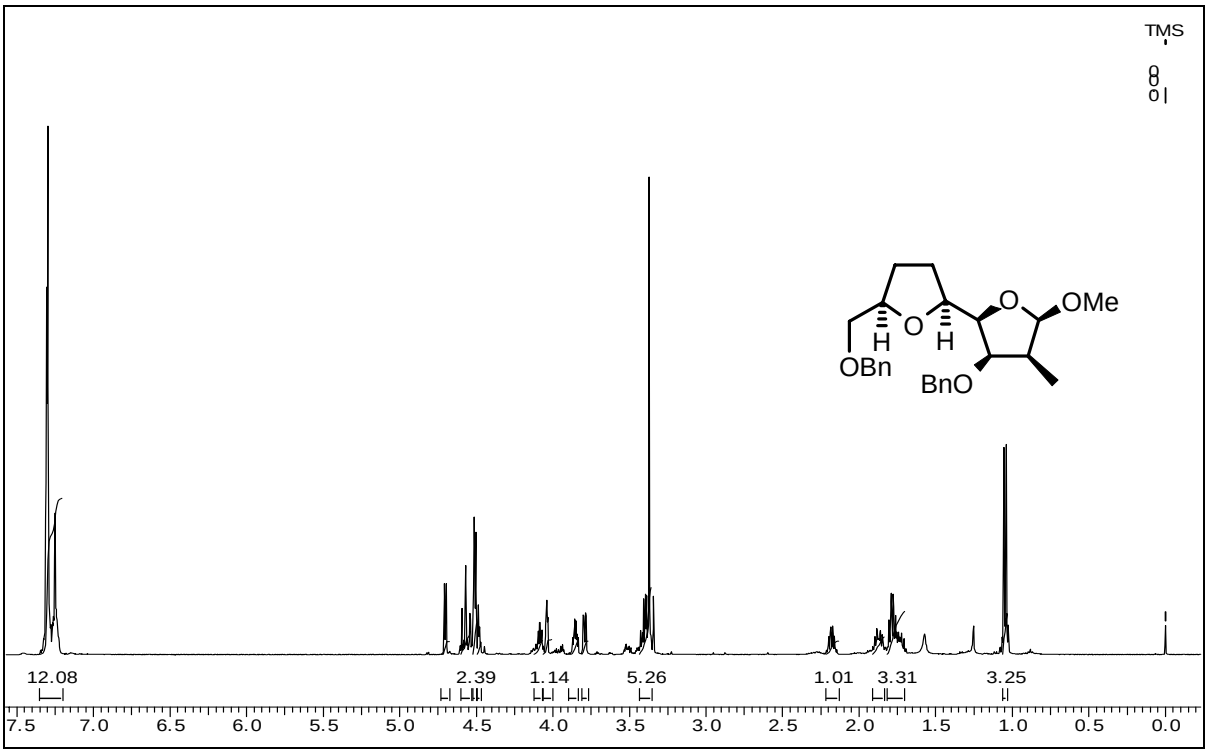
^{13}C NMR spectrum of compound 36 in $CDCl_3$



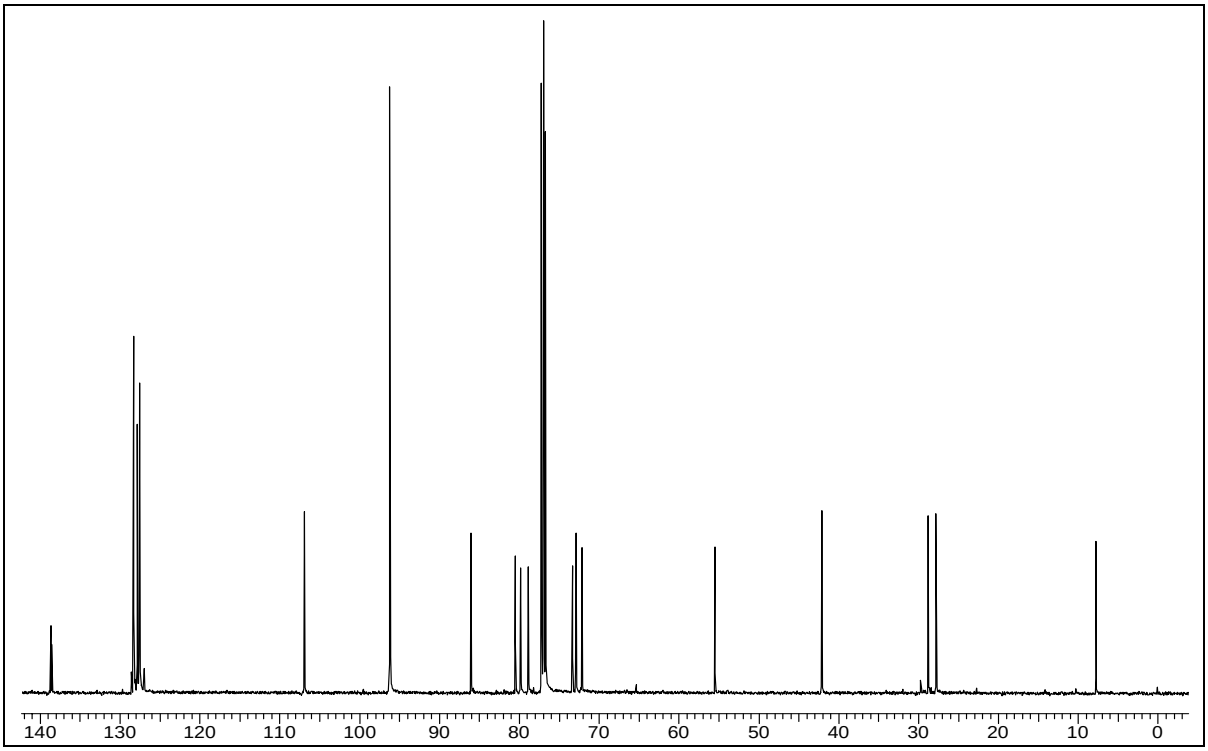
^{1}H NMR spectrum of compound 38 in $CDCl_3$



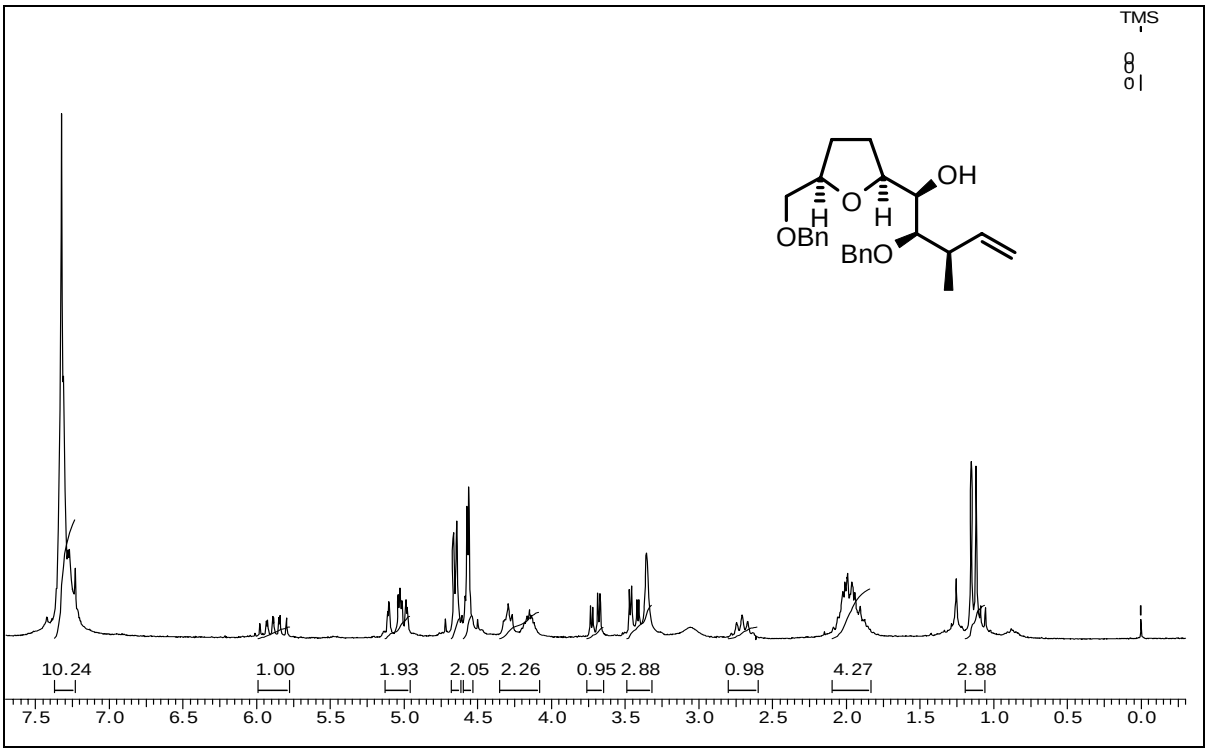
^{13}C NMR spectrum of compound 38 in $CDCl_3$



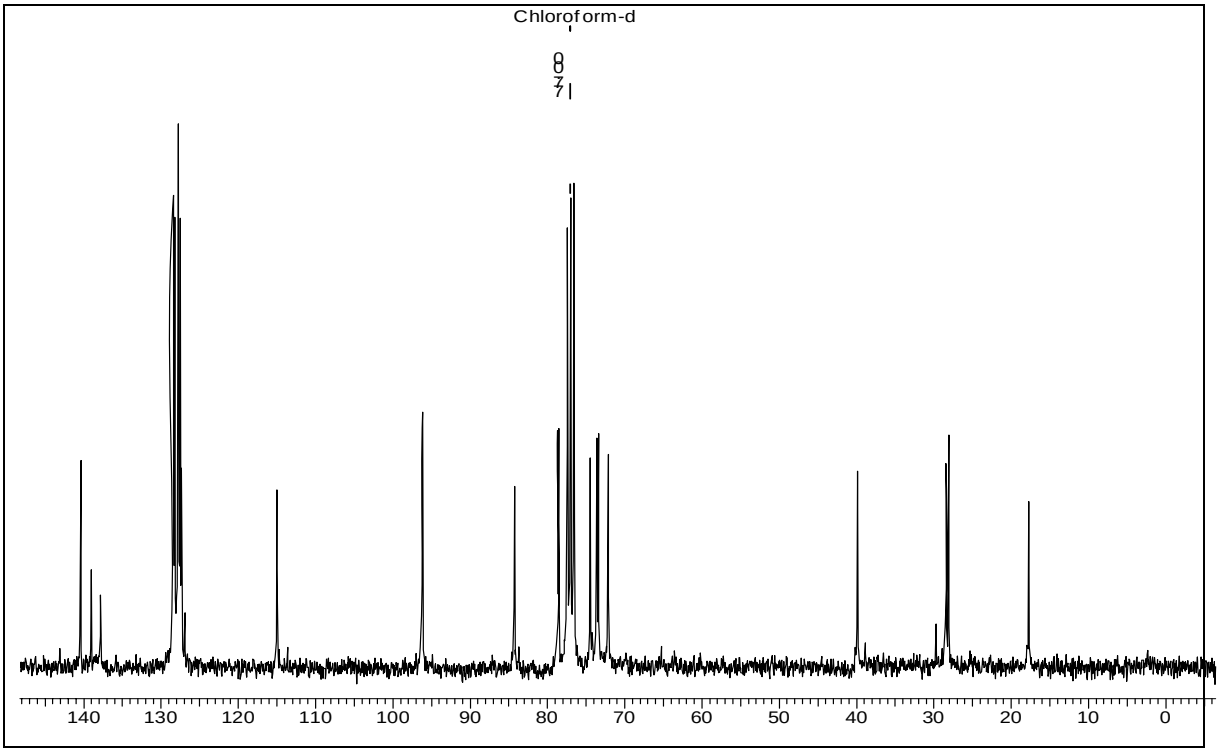
^{1}H NMR spectrum of compound 39 in $CDCl_3$



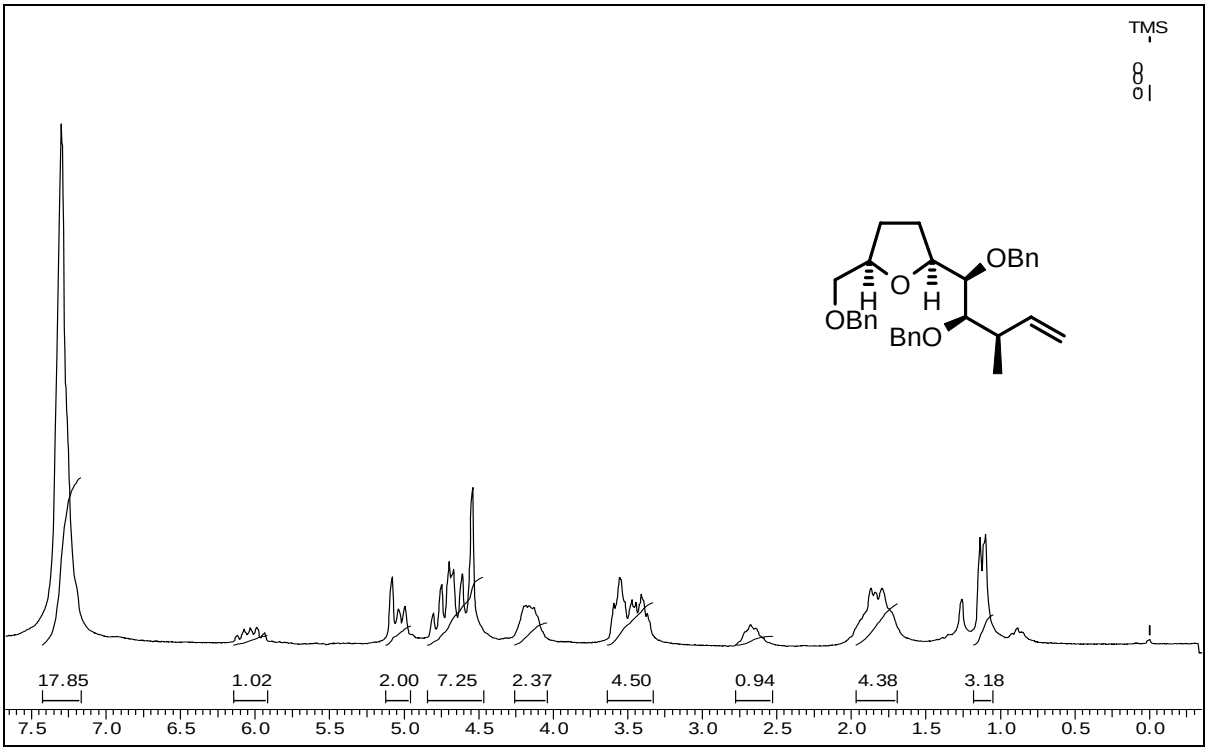
^{13}C NMR spectrum of compound 39 in $CDCl_3$



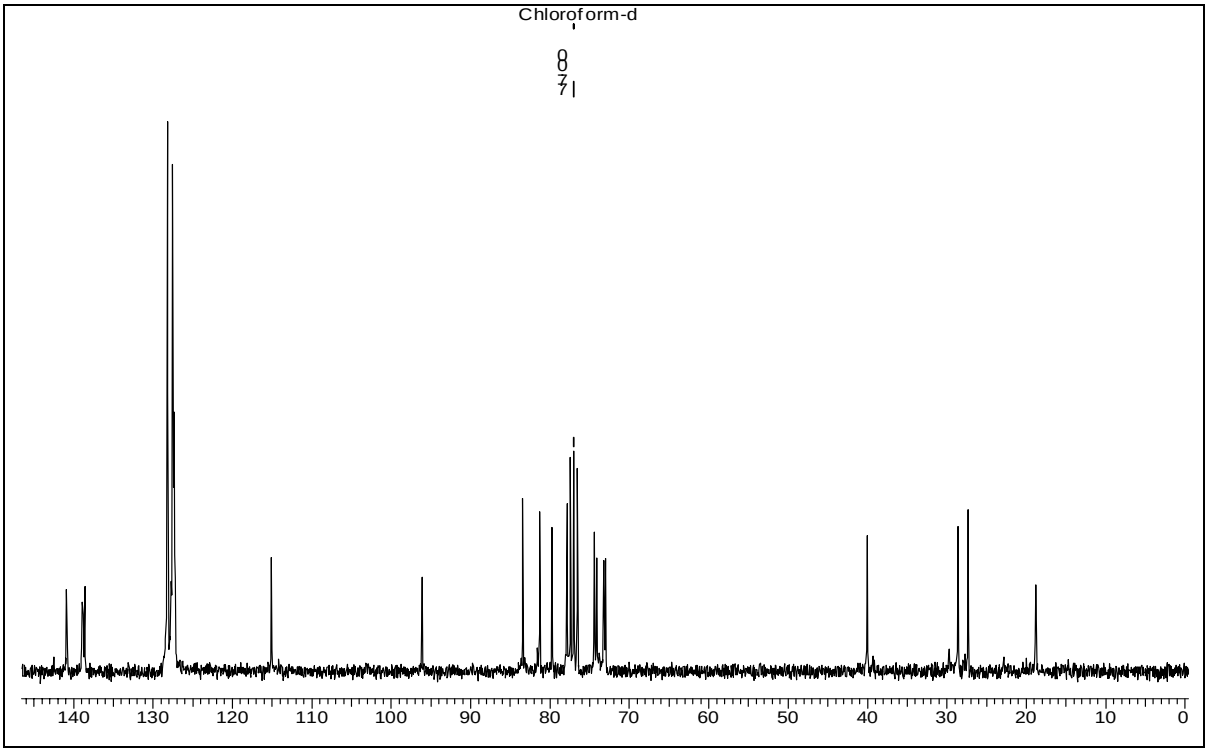
^{1}H NMR spectrum of compound 41 in $CDCl_3$



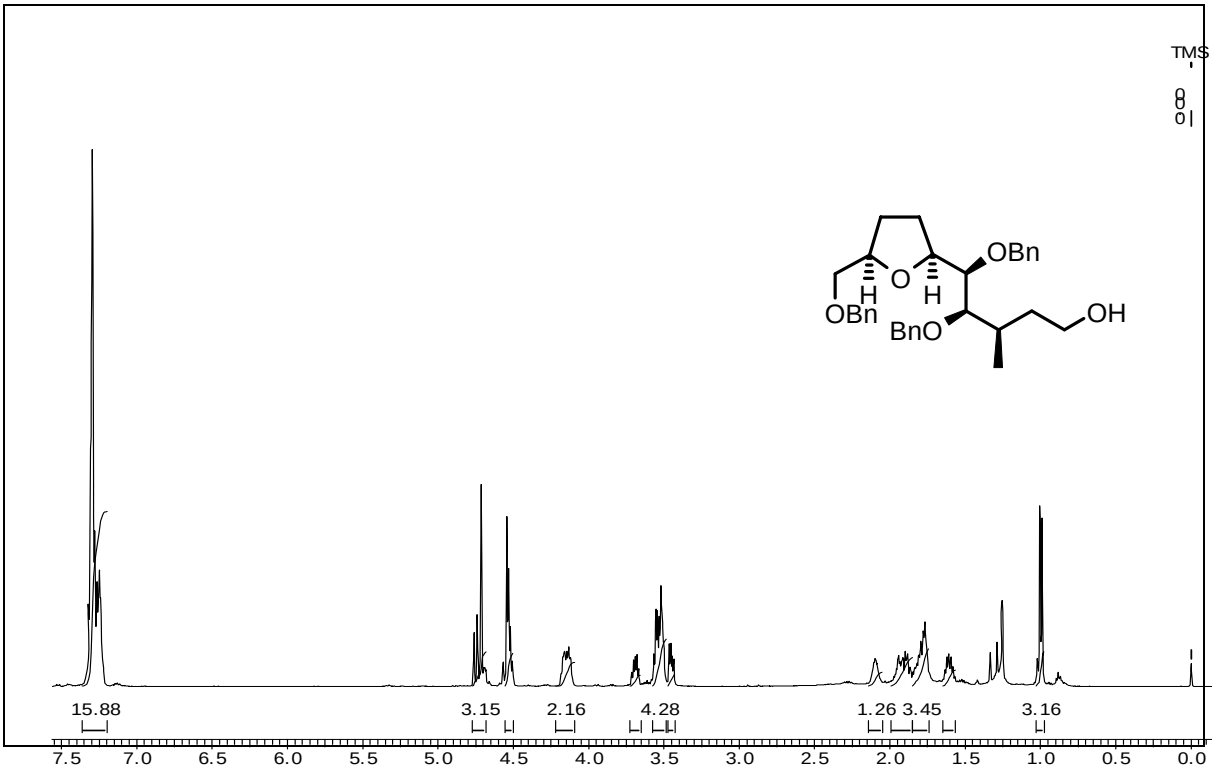
^{13}C NMR spectrum of compound 41 in $CDCl_3$



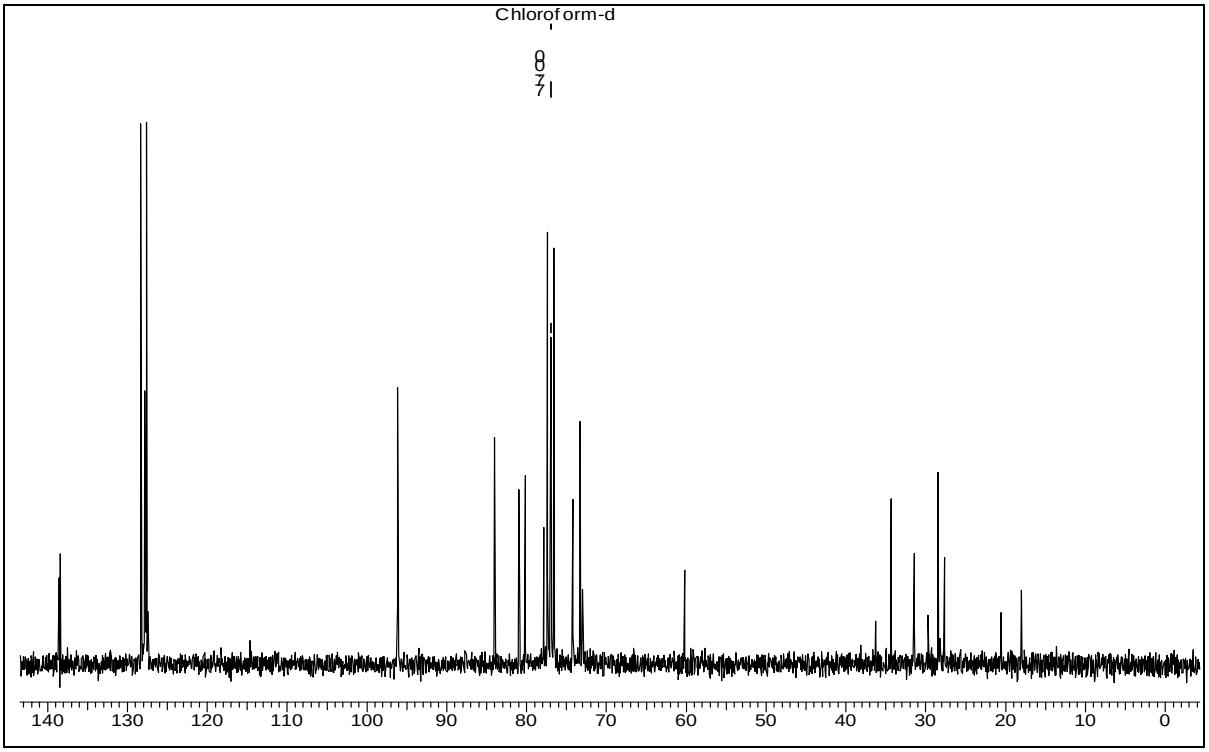
^{1}H NMR spectrum of compound 42 in $CDCl_3$



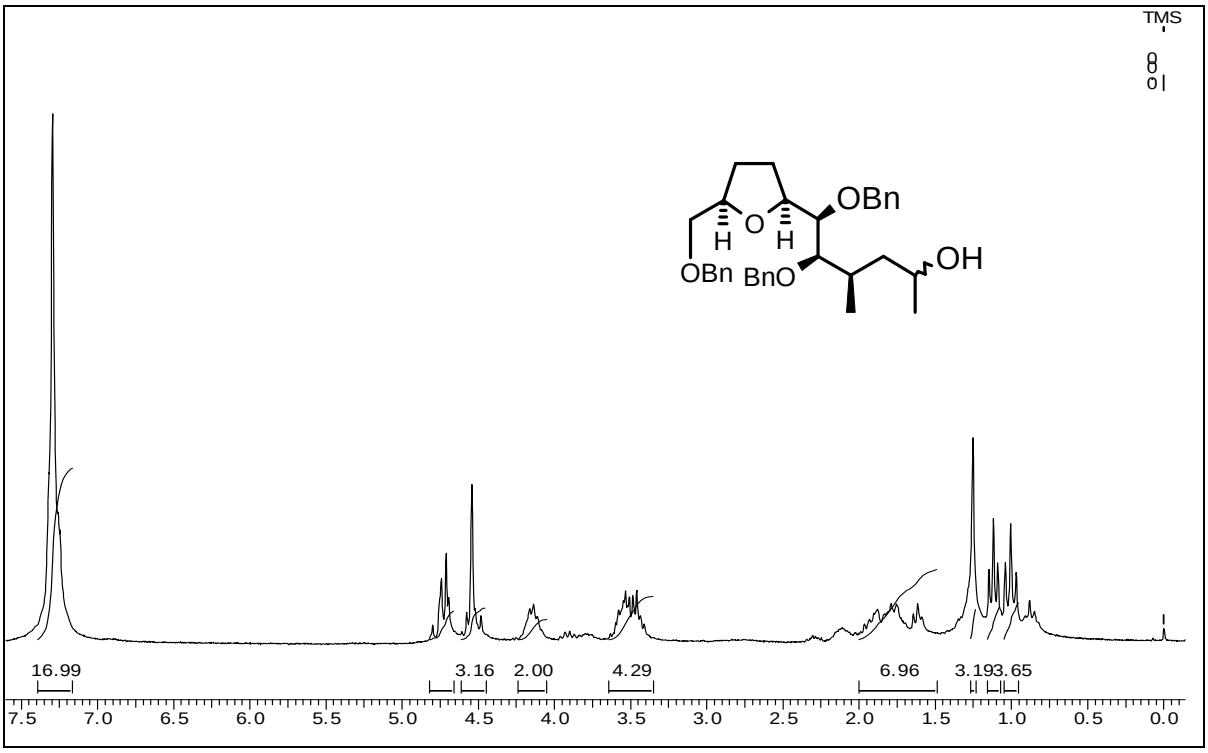
^{13}C NMR spectrum of compound 42 in $CDCl_3$



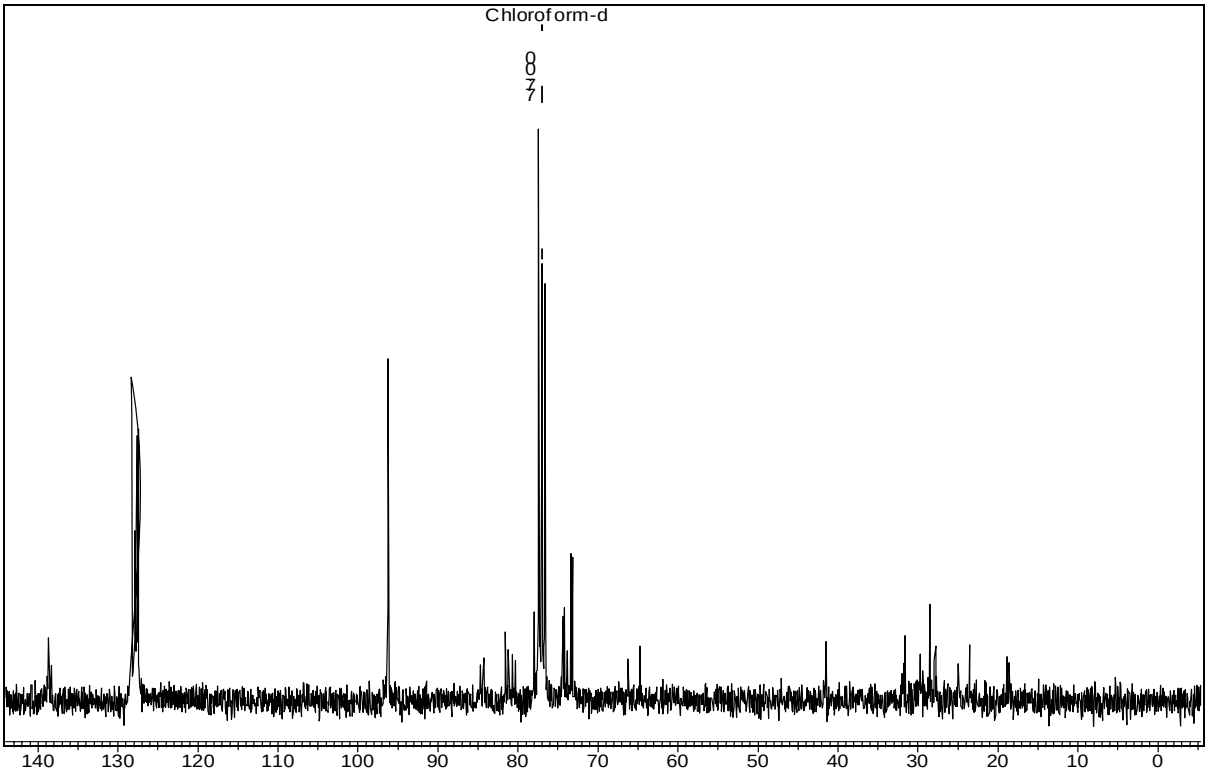
^{1}H NMR spectrum of compound 18 in $CDCl_3$



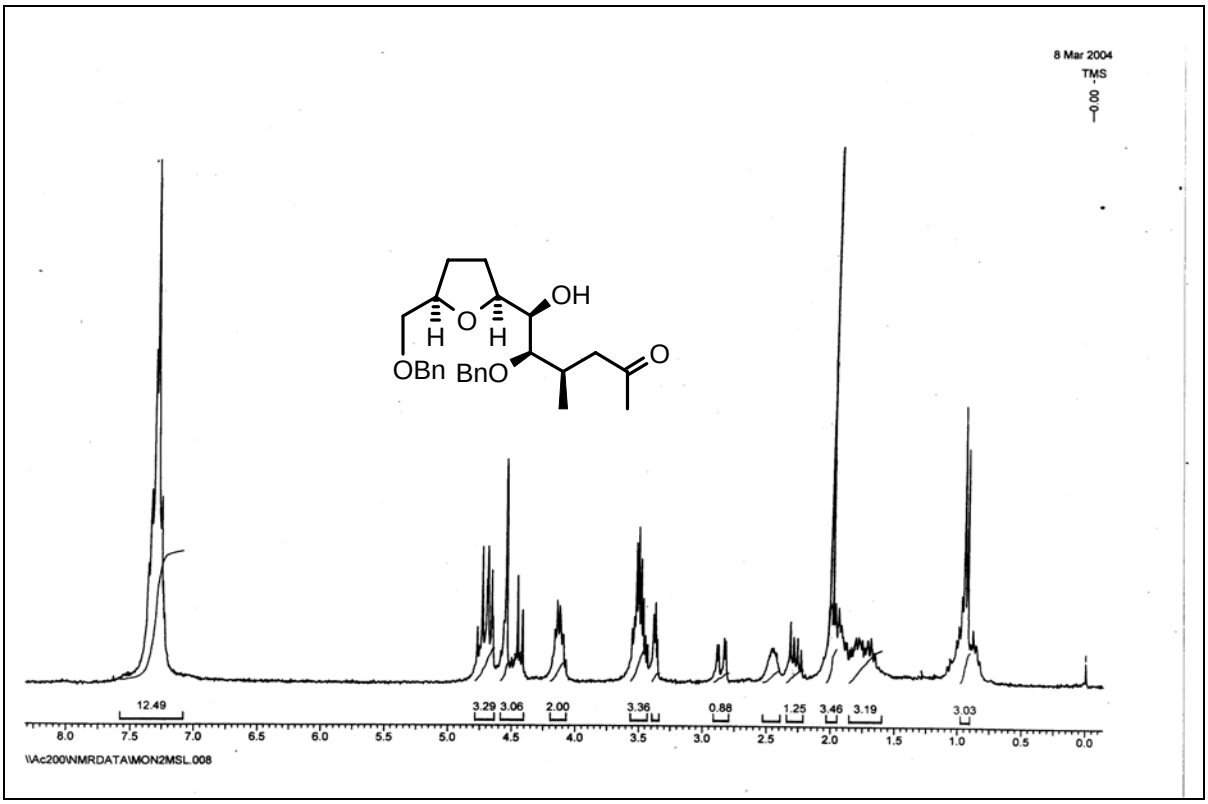
^{13}C NMR spectrum of compound 18 in $CDCl_3$



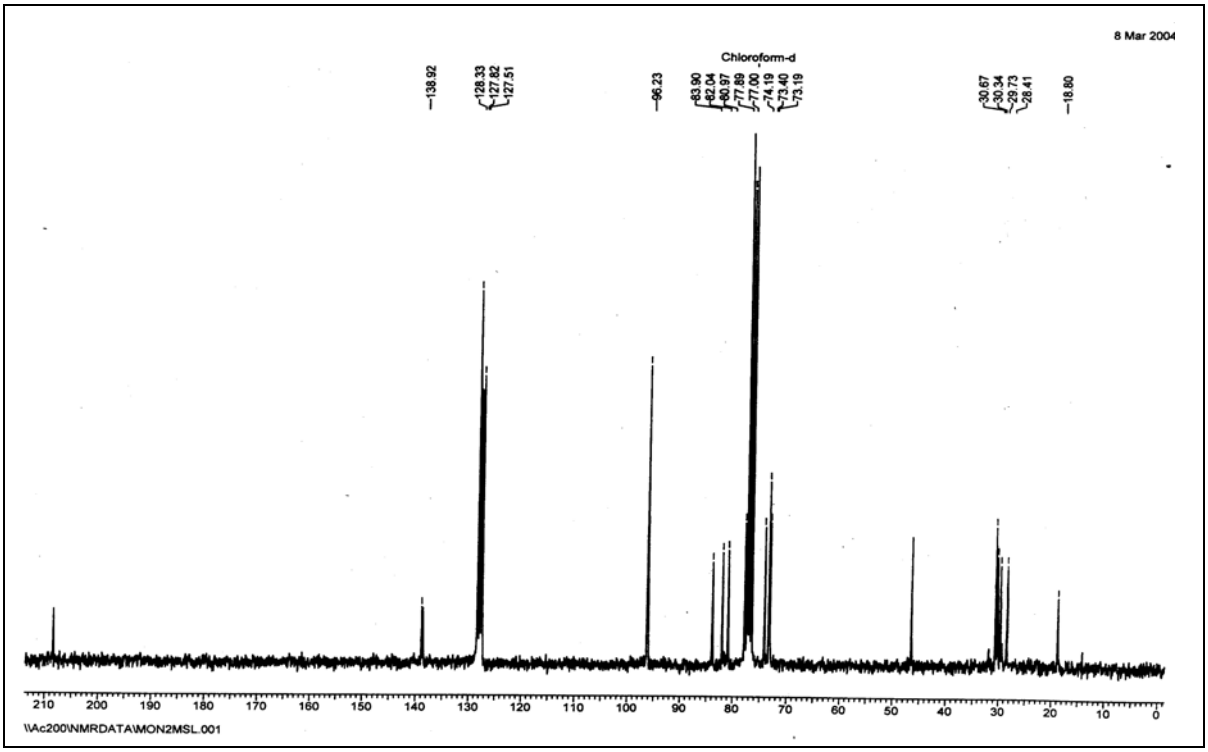
^{1}H NMR spectrum of compound 45 in $CDCl_3$



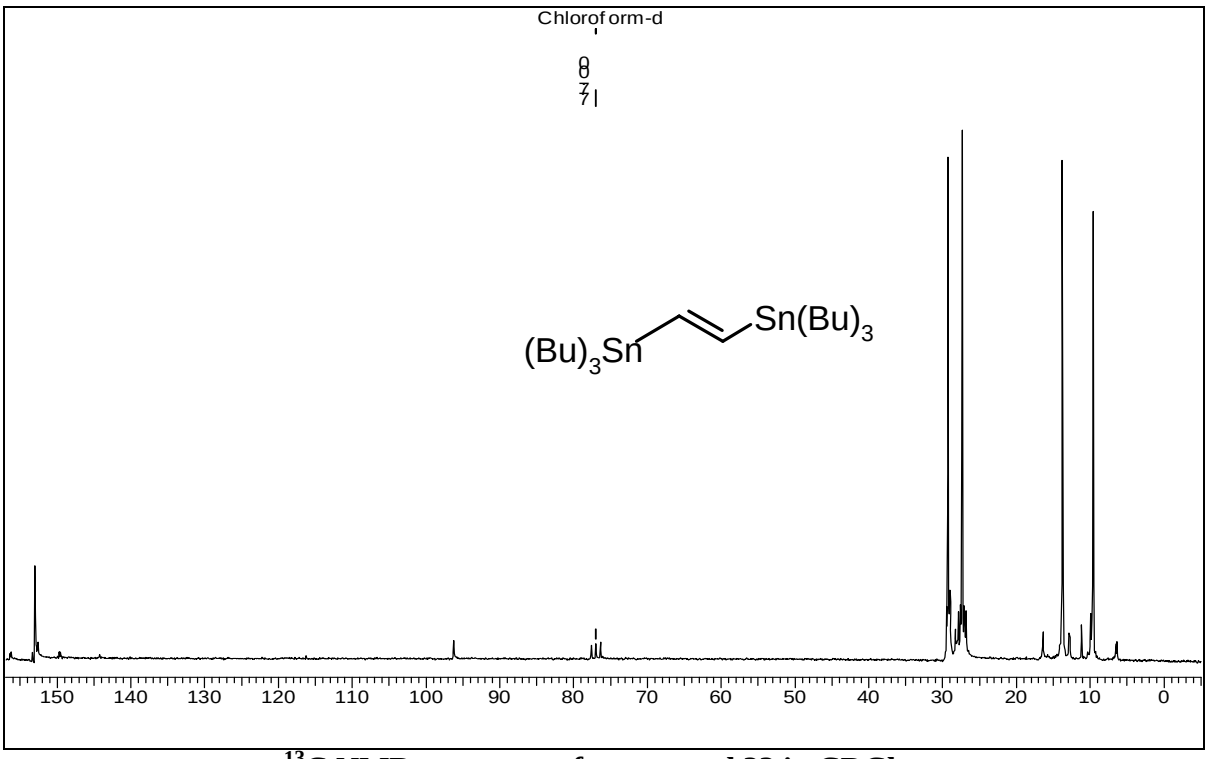
^{13}C NMR spectrum of compound 45 in $CDCl_3$



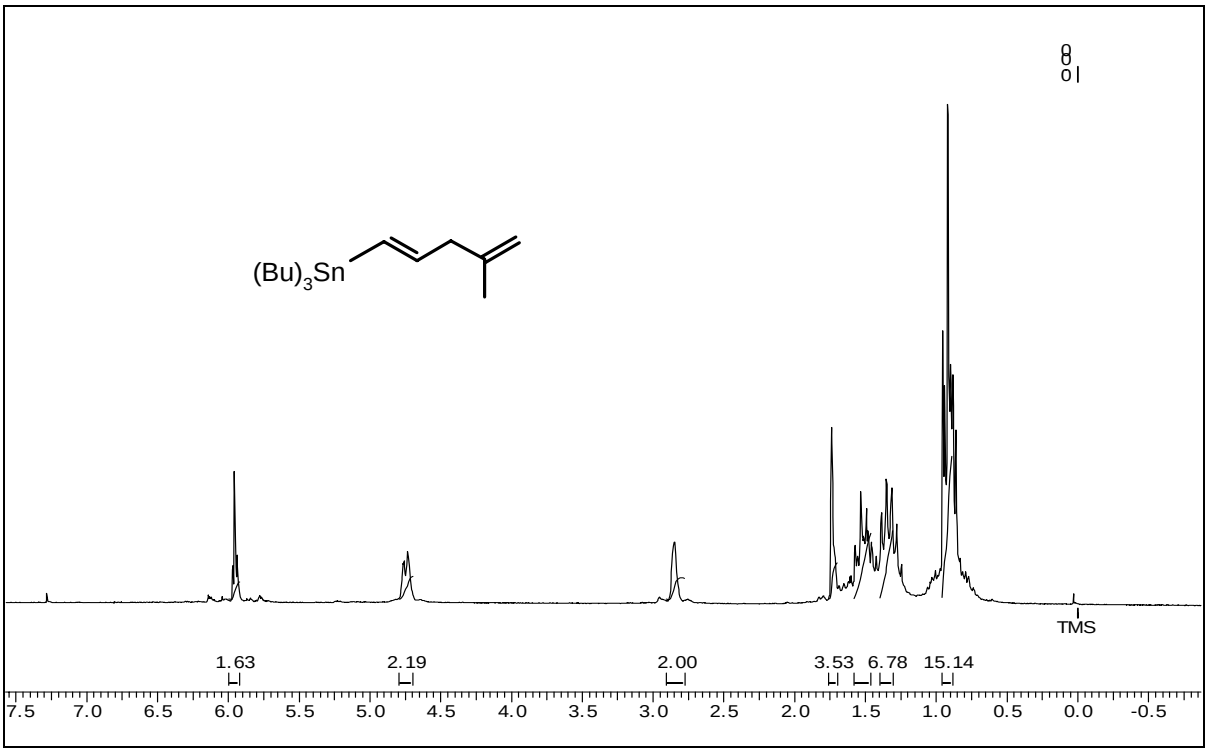
^{1}H NMR spectrum of compound 46 in $CDCl_3$



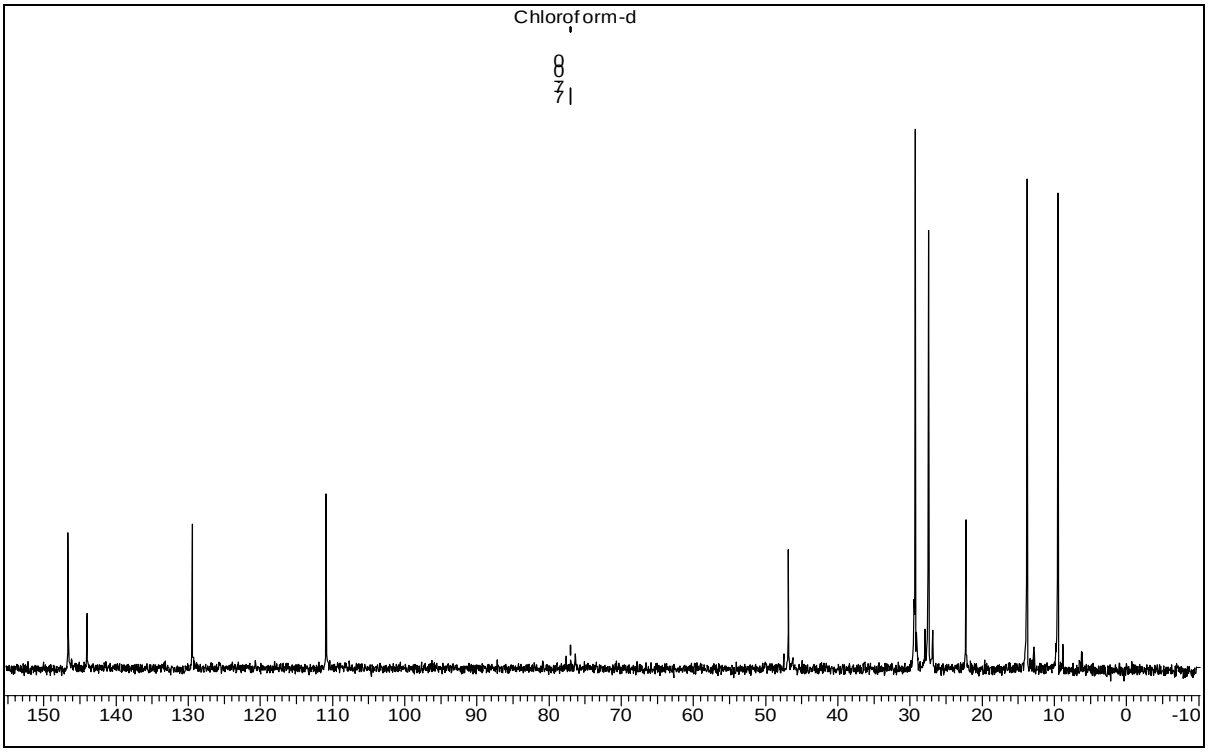
^{13}C NMR spectrum of compound 46 in $CDCl_3$



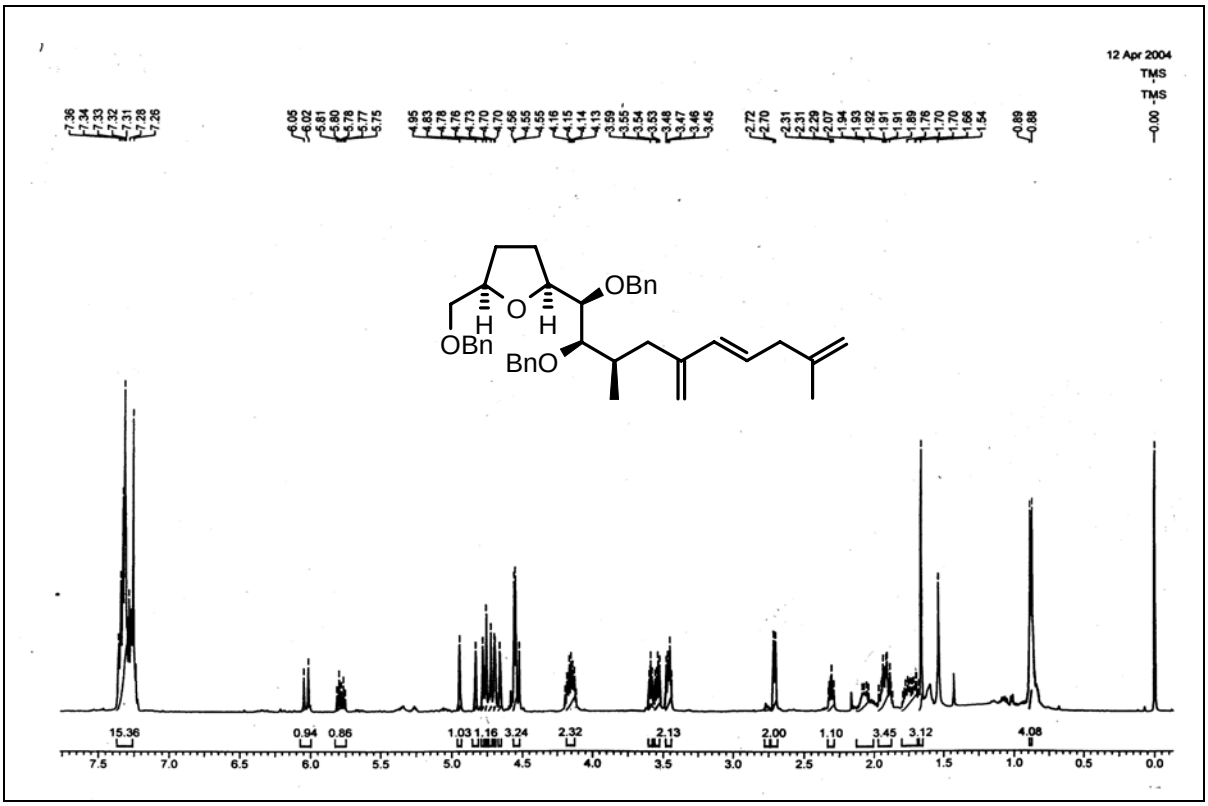
^{13}C NMR spectrum of compound 22 in $CDCl_3$



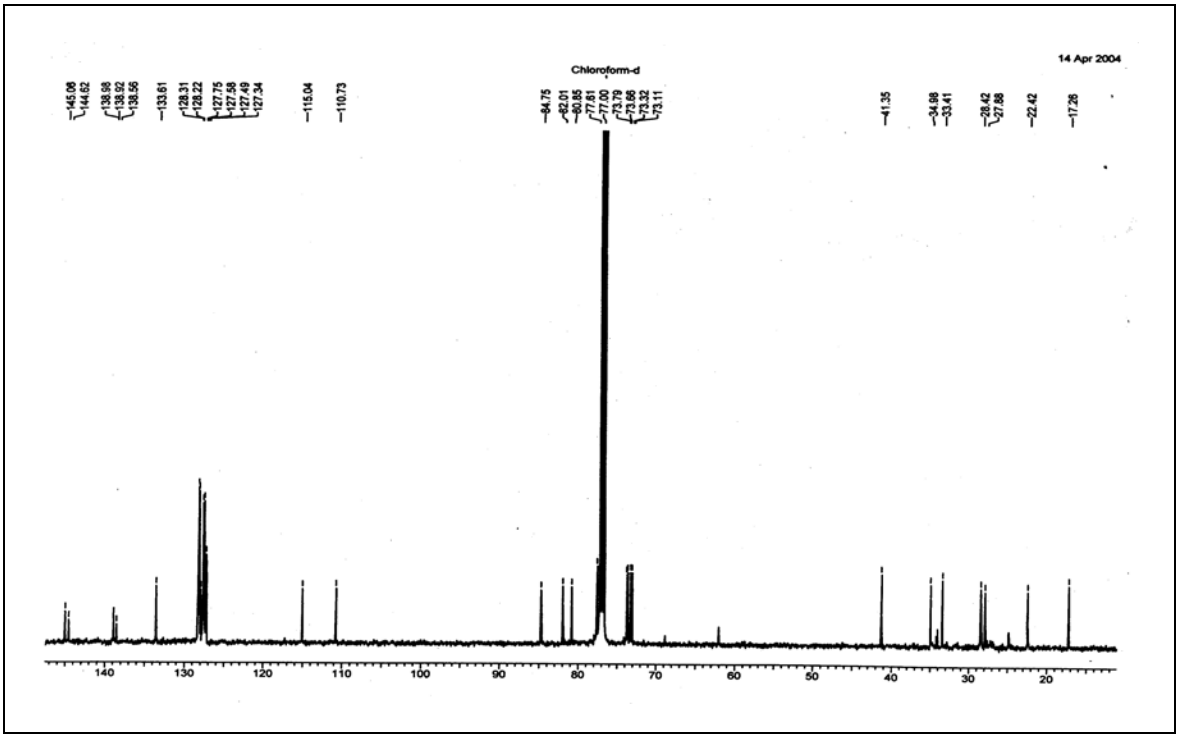
^{1}H NMR spectrum of compound 16 in $CDCl_3$



^{13}C NMR spectrum of compound 16 in $CDCl_3$



^{1}H NMR spectrum of compound 15 in $CDCl_3$



^{13}C NMR spectrum of compound 15 in $CDCl_3$

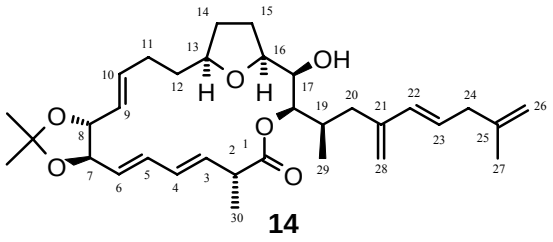
CHAPTER-1

SECTION - 2

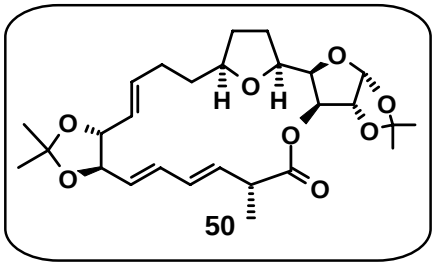
Studies toward the synthesis of macrolactone core of amphidinolide E

PRESENT WORK

Achieving C12-C29 fragment of amphidinolide E successfully, we next turned our attention for the synthesis of macrolactone **50** which consists of a major core structure of Amphidinolide E.

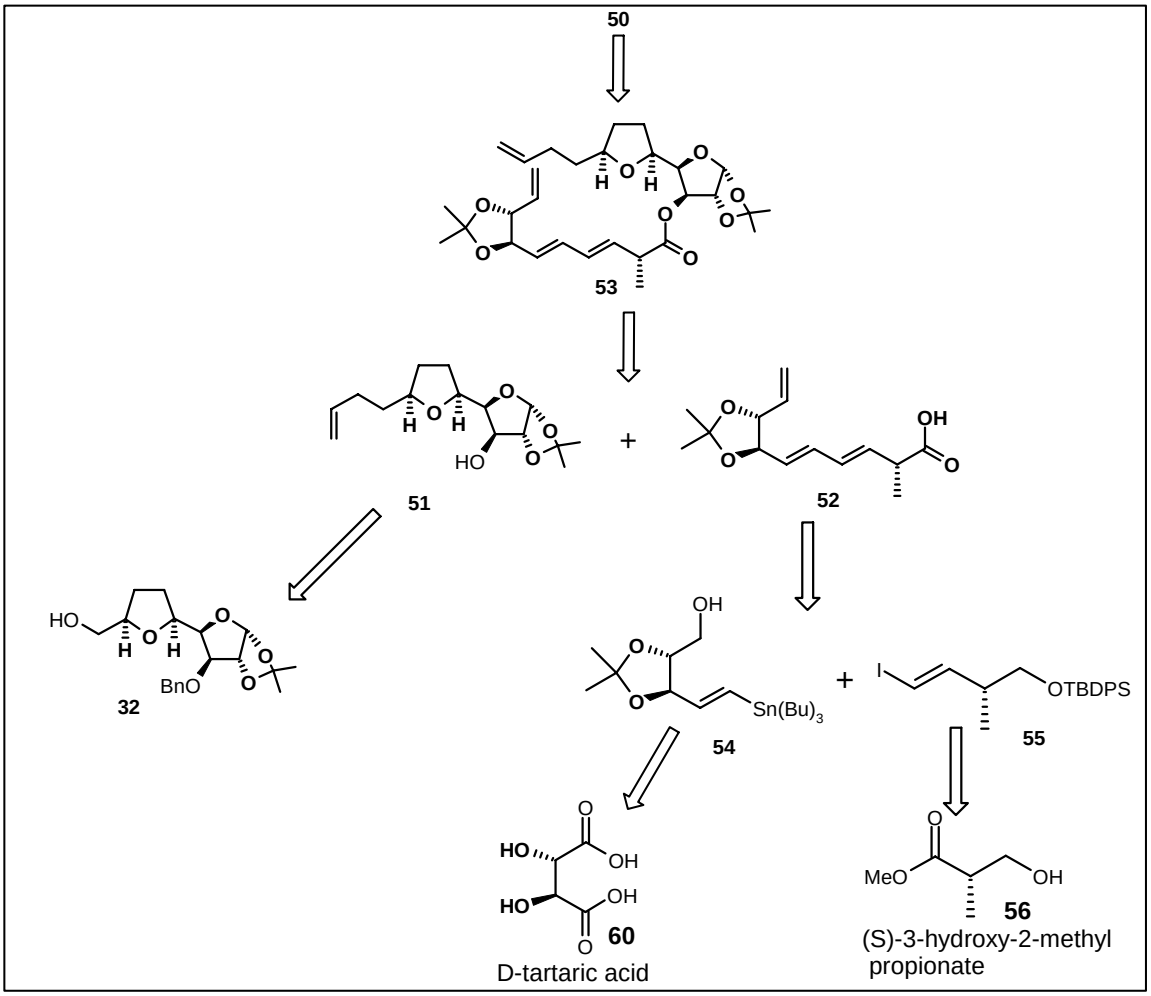


14



50

Figure 2: Retrosynthetic analysis of **50**:



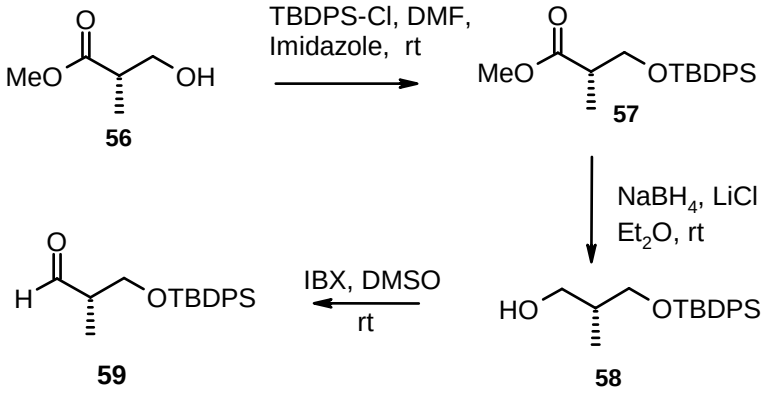
After a close examination of macrolactone, we noticed that half part of it was occupied by earlier synthesized fragment (**15**) and other untouched half contains a methyl center, conjugated doublebond, two chiral hydroxyl group and a lactone moiety. After a thorough study we planned a strategy for the synthesis of macrolactone (**50**), whose retrosynthetic analysis was depicted in figure-2.

The retrosynthetic analysis revealed that macrolactone **50** could be synthesized from **53** by employing ringclosing metathesis. The esterfunctionality of **53** can be assembled by Yamaguchi esterification of alcohol **51** and acid **52.** The alcoholic component **51** can be synthesized from **32,** whose synthesis was already explained in chapter-**1**, section-**1**. The acid component **52** was envisioned to be prepared by Stille coupling of vinylstannane **54** and vinyliodo **55.** The vinyliodo **55** was inturn, could be synthesized from commercially available methyl (S)-3-hydroxy-2-methyl propionate **56** and the vinylstannane **54** can be synthesized from D-tartaric acid **60**.

Synthesis of vinyliodo **55:**

According to retrosynthetic analysis synthesis of fragment **55** commenced from chiral precursor **56**, which was converted to it's silylether derivative using TBDPSCl, imidazole in DMF to give **57**. The methylester of **57** was reduced by $NaBH_4$, LiCl resulting in alcoholic moiety[66] **58**. In the ^1H NMR spectrum disappearance of signals at δ 3.65 ppm (OMe-group) and appearance of signal at δ 3.76 ppm indicates the formation of CH_2OH group.

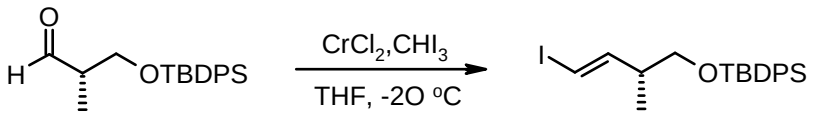
Scheme 12



The primary hydroxyl of **58** was oxidised by IBX in DMSO to result in aldehyde **59**, whose structure was confirmed by ^{1}H, ^{13}C NMR spectroscopy. In the ^{1}H NMR spectrum a signal appeared at δ 9.73 ppm characteristic of aldehydic proton (scheme-12).

Aldehyde **59** was subjected to Takai condensation[67] with $CrCl_2$ and CHI_3 at -20 ^{o}C to afford (E)-vinyl iodide **55**. Compound **55** was confirmed by ^{1}H, ^{13}C NMR spectroscopy followed by elemental analysis. In the ^{1}H NMR spectrum vinyl protons resonated at δ 6.48 (dd, *J* = 6.31, 14.5 Hz) and 6.04 (d, 1H, *J* = 14.5 Hz) ppm. The coupling constant *J* = 14.5 Hz clearly indicates the formation of E-isomer.^{13}C NMR spectrum of **55** showed that the olefinic carbons resonated at δ 149.0 and δ 75.4 ppm confirming the formation of **55** (Scheme 13).

Scheme 13



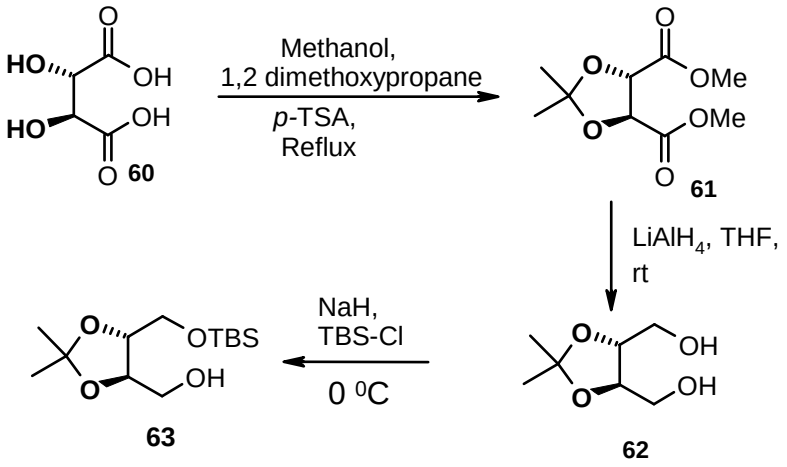
59 **55**

Getting **55** in hand we thought of synthesizing vinylstannane component **54.**

Synthesis of vinylstannane **54**:

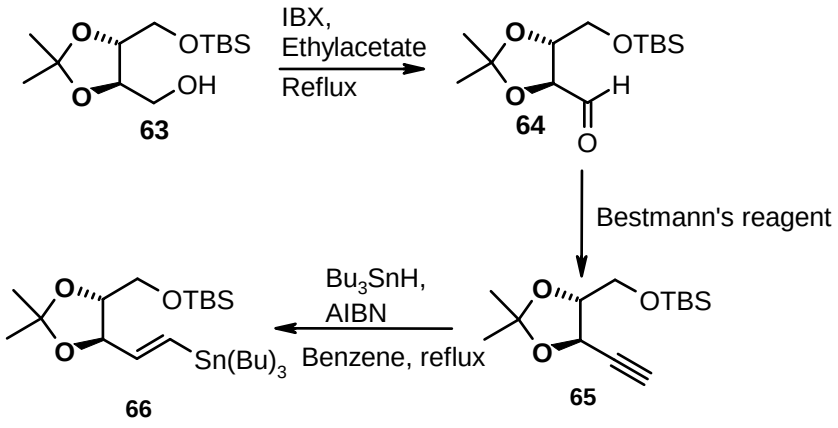
The synthesis of **54** commenced from D-tartaric acid. One pot acetonide protection and esterification of *D*-tartaric acid **60** was carried out by refluxing with methanol, 2,2-dimethoxypropane in presence of *p*-TSA and removing methanol azeotropically to obtain **61**. $LiAlH_4$ reduction of diester **61** resulted in corresponding diol **62.**[68] Here monosilylether protection of the diol **62** was chosen as it can be easily removed in later stages. The selective monosilylation of diol **62,** was carried out by treating with with NaH, TBSCl in THF at rt gave **63**. The structure was elucidated on the basis of ^{1}H and ^{13}C NMR spectroscopy which were in good agreement with literature data (Scheme 14).[69]

Scheme 14



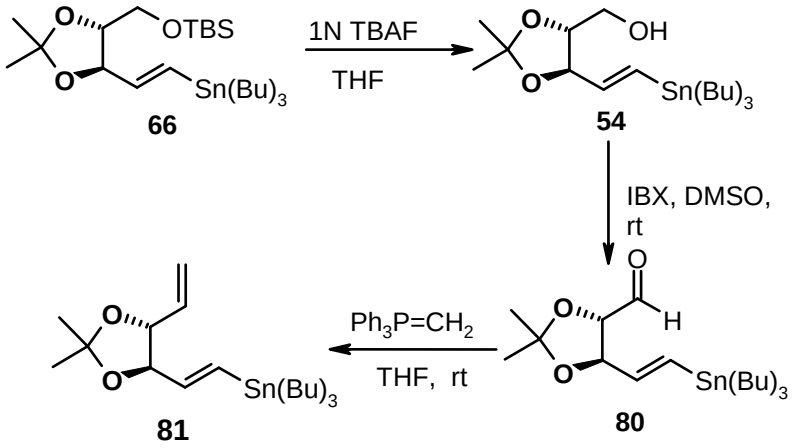
The primary alcohol **63** was oxidised with IBX to give aldehyde **64**, which on subsequent treatment with Bestmann's reagent[70] resulted alkyne **65** in good yield. The alkyne moiety **65** on treatment with tributyltin hydride and catalytic AIBN resulted in **66** in 95:5 ratio. The product was confirmed by ^{1}H, ^{13}C NMR spectroscopic studies. In the ^{1}H NMR spectrum disappearance of acetylenic proton at δ 2.49 ppm and appearance of olefinic protons at δ 6.36 (d, J =19.1 Hz) and 6.01 (dd, J = 6.4, 19.1 Hz) ppm indicating formation of **66.** The large coupling constant J =19.1Hz, indicates the formation of E-isomer. ^{13}C NMR spectrum showed that olefinic carbons resonated at δ 145.5 and δ 133.0 ppm. Mass spectrum along with elemental analysis also supported the formation of **66** (Scheme 15).

Scheme 15



The deprotection of silyl ether **66** by using TBAF in THF gave alcohol **54**. Oxidation of alcohol **54** with IBX gave the aldehyde **80** which on treatment with one cabon Wittig ylide in THF furnished the olefin **81 (**Scheme 16).

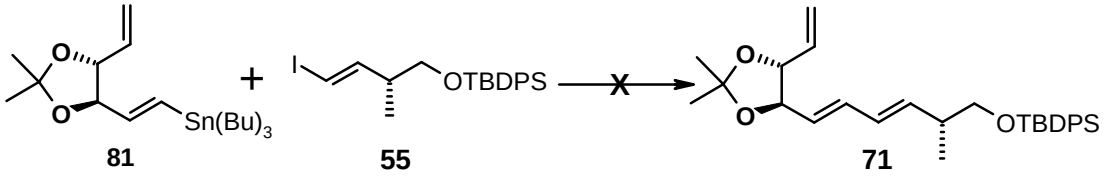
Scheme 16



Coupling of Vinyl iodo 55 and stannane 54 :

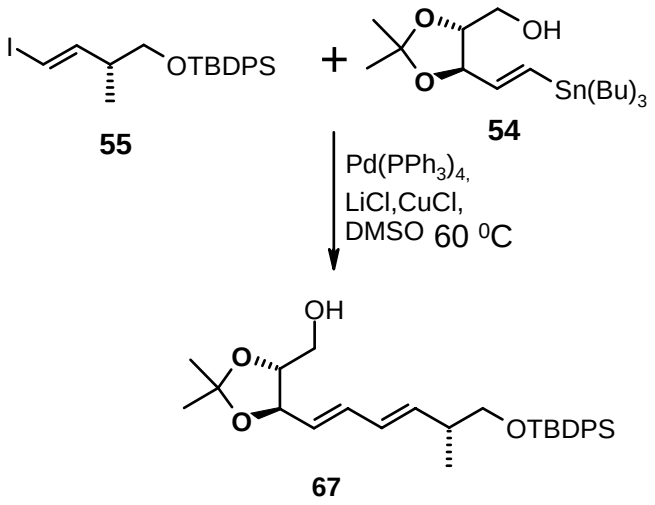
Since both the coupling partner were ready now the stage is set for carrying out Stille coupling. Unfortunately Pd(0) mediated Stille[71] coupling of **81** with **55** failed to give **71** but resulted in complex mixture of products **(**Scheme 17).

Scheme 17



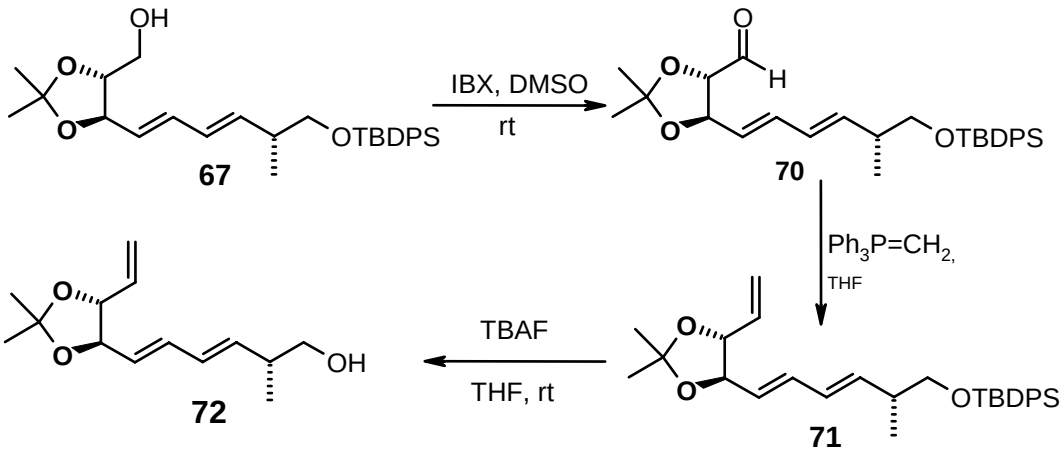
Being unsuccessful in synthesizing **71,** we planned to do Stille[71] coupling with free alcoholic stannane **54** instead of **81.** Accordingly coupling of **54** with **55** gave **67** exclusively. In the ^{1}H NMR spectrum of **67** olefinic protons resonated at δ 6.28 (dd, 1H, *J* =10.4, 15.2 Hz), 6.06 (dd, 1H, *J* =10.4, 15.2 Hz), 5.75-5.47 (m, 2H) ppm and in ^{13}C NMR spectrum four olefinic carbons resonated at δ 138.6, 134.5, 128.8 and 127.4 ppm clearly indicates the presence of diene moiety. Elemental analysis and mass spectrometric data also supported the formation of **67** (Scheme 18).

Scheme 18



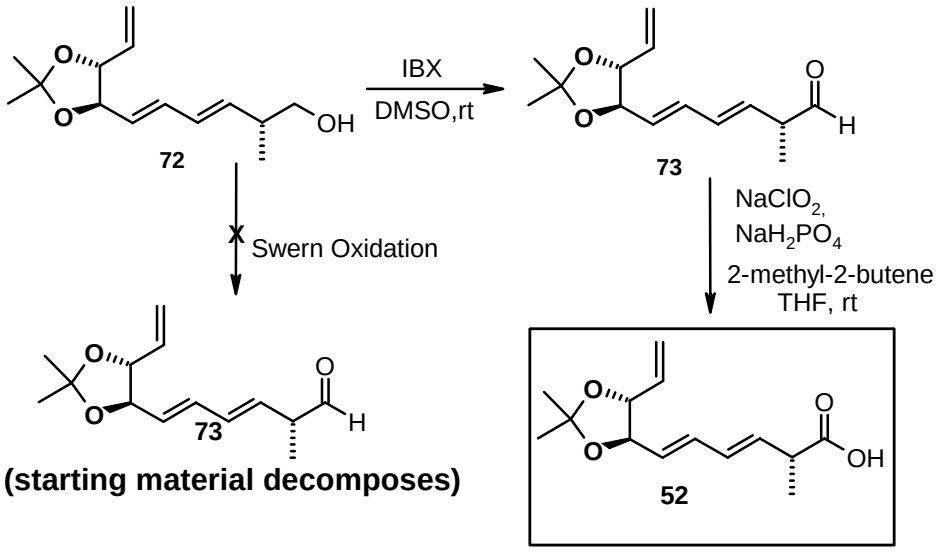
The alcohol **67** on oxidation with IBX gave corresponding aldehyde **70**, which on subsequent treatment with one carbon Wittig ylide $Ph_3P{=}CH_2$ at – 20 °C resulted in olefin **71** in good yield. The structure of **71** was deduced from ^1H, ^{13}C NMR spectra and elemental analysis. ^1H NMR spectrum of **71** showed that the six olefinic protons resonated at δ 6.26 (dd, *J* =10.4, 14.9Hz, 1H), 6.05 (dd, *J* =10.4, 14.9Hz, 1H.), 5.89-5.46 (m, 3H), 5.34 (d, 1H, *J* = 17.1 Hz), 5.27 (d, 1H, *J* = 11.4 Hz) ppm and disappearance of aldehyde proton in down field region confirmed the conversion of aldehyde to olefin. The cleavage of silyl ether of **71** was accomplished with TBAF in THF at 0 °C to result an alcohol **72**. The ^1H, ^{13}C, NMR spectra and elemental analysis of **72** were in good agreement with assigned structure (Scheme 19).

Scheme 19



The next step in our ordeal, the oxidative conversion of the primary hydroxyl group **72** into carboxylicacid group **52** proved painfully difficult. For example Dess-Martin periodinane oxidation resulted in a scrambling of NMR spectroscopy signals from the side chain region. In Swern oxidation the starting material was decomposed. Eventually it was found that the treatment of the primary alcohol **72** with IBX[72] furnished aldehyde **73** cleanly. The aldehyde was then converted into carboxylic acid **52** by oxidation with sodium chlorite and sodium hydrogen phosphate. The acid **52** was confirmed by ^{1}H, ^{13}C, NMR spectroscopy and elemental analysis. ^{1}H NMR spectrum of **52** showed α proton appeared at δ 3.24 ppm and in ^{13}C NMR spectrum carbonyl carbon of acid group was resonated at δ 179.7. IR spectrum showed a peak at 1712 cm^{-1} corresponding to the –COOH carbonyl group (Scheme 20).

Scheme 20

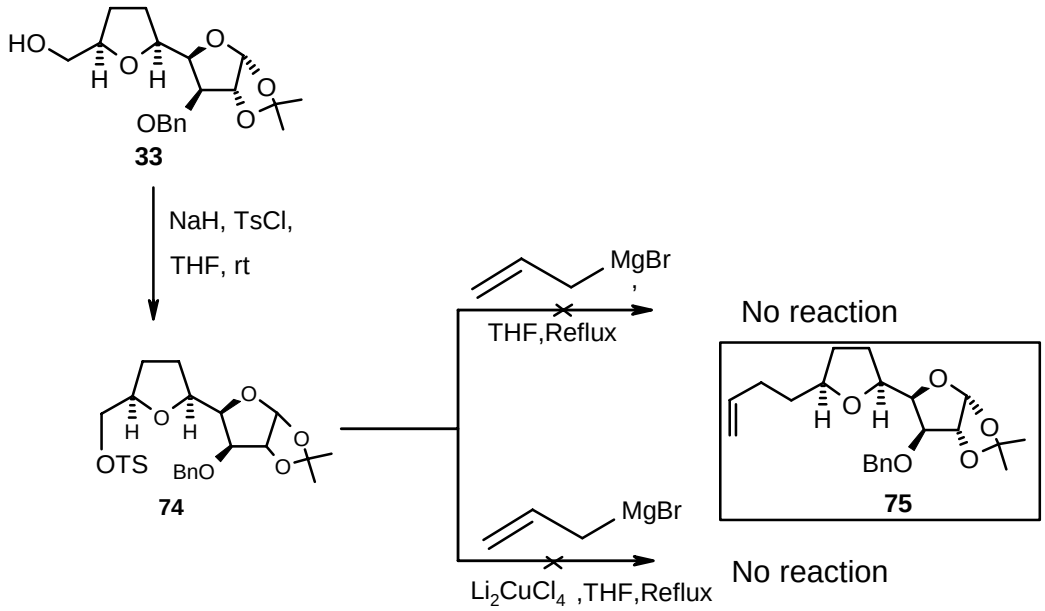


After successful synthesis of acid component **52**, we thought of synthesizing alcoholic component **51** to carryout Yamaguchi esterification.

Synthesis of alcohol **51:**

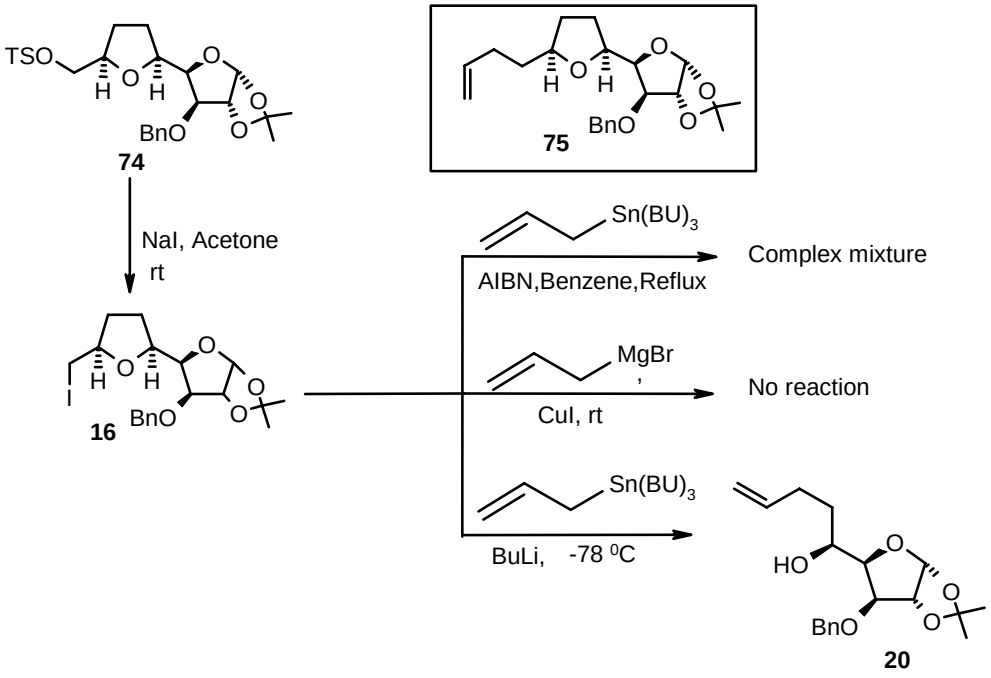
The known alcohol **33** was treated with sodium hydride, tosyl chloride in THF to yield **74**. The displacement of tosyl ether by allyl anion was carried out using several allylreagent (scheme 21).

Scheme 21



For synthesis of **75** from **74,** several attempts have been made which were shown in scheme **21**. The **74** on treatment with allyl magnesium bromide didn't give **75.** Similarly **74** was subjected with allyl magnesium bromide in the presence of Li_2CuCl_4 also failed to give **75.** Having failed in displacement of tosyl to allyl group, we thought of converting tosyl to iodo and again trying some allyl displacement conditions.

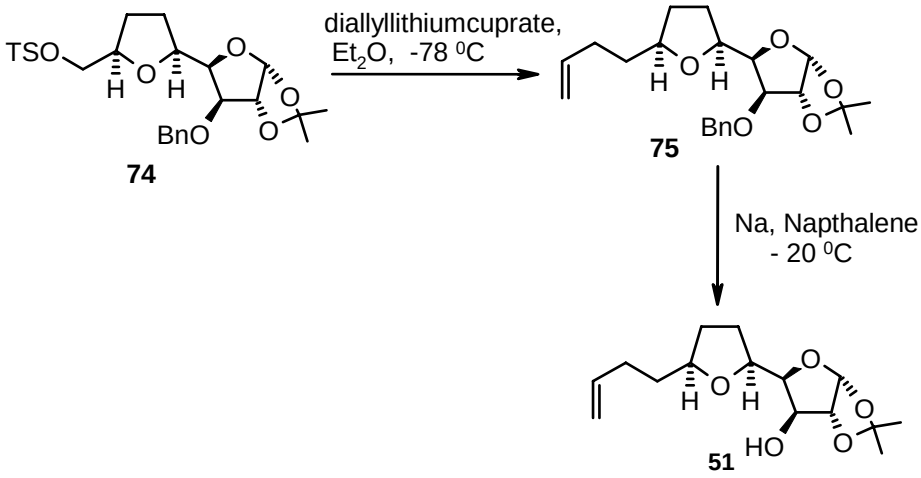
Scheme 22



Accordingly we converted the tosyl to iodo derivative **16** by using sodium iodide in acetone. Compound **16** upon refluxing with allyl tributyltin resulted in decomposition of starting material instead of giving **75**. Treatment of allyl magnesiumbromide in presence of Li_2CuCl_4 on **16** failed to give **75**. However treatment of allyl lithium (prepared by mixing allyl tributyltin and butyllithium) on **16** resulted opening of tetrahydrofuran ring to give undesired product **20** (Scheme 22).

Again we tried displacement reaction on tosyl substrate **74**.Finally we succeeded to displace tosyl group by using diallyl lithium cuprate[73] at -78 ^oC furnished **75** in excellent yield. The structure of **75** was confirmed by ^1H, ^{13}C NMR spectrum and elemental analysis. In the ^1H NMR spectrum of compound **75**, olefinic protons resonated at δ 5.82 and δ 5.02-4.94 but simultaneously disappearance of aromatic protons confirmed formation of **75**. Deprotection of benzylether by sodium-napthalene at 0 °C gave the alcohol **51** in good yield. The product was elucidated by ^1H and ^{13}C NMR spectroscopy. In the ^1H NMR spectrum absence of aromatic protons at δ 7.3 ppm indicates the formation of **51**. Finally the product was confirmed by mass spectral analysis (Scheme 23).

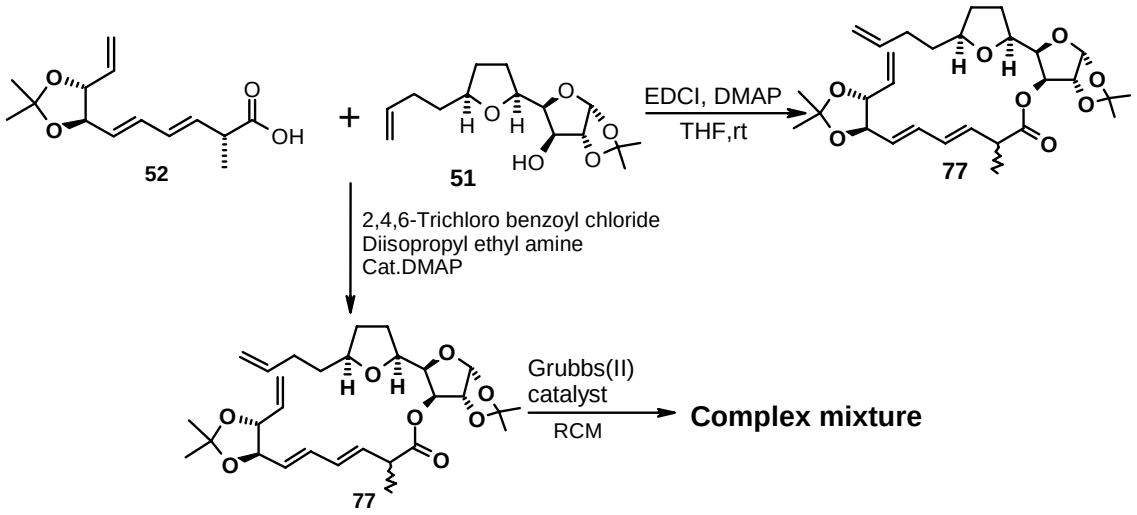
Scheme 23



As the acid component **52** and alcohol **51** was ready**,** they underwent Yamaguchi esterification[74] using 2,4,6 trichlorobenzoylchloride and cat.DMAP to give epimeric mixture of products **77**. The product was confirmed by ^1H, ^{13}C NMR and mass spectrometric study. The mixture was not separated in conventional silicagel chromatography or by HPLC method. Esterification of **52** with **51** using EDCI, DMAP also gave epimeric mixture of **77**, which were not possible to separate by general silicagel

chromatography as well as by HPLC. Next we pcoceeded further to check the feasibility of ongoing reactions. Accordingly epimeric ester **77** underwent RCM reaction[75] by using Grubbs' 2nd generation catalyst gave a complex mixture of products (Scheme 24). Getting complex mixture in RCM reaction we concluded it was very difficult to proceed further without separation of **77** into individual pure isomers.

Scheme 24



Now studies are in progress in our laboratory to get the desired product in esterification reaction and carrying out RCM reaction to achieve the macrolactone **50**.

Conclusion:

In conclusion we have synthesized acid component **52** sucessfully following Stille coupling as our key reaction. Here we have studied the free alcoholic component **54** in Stille coupling gave the desired product while the olefin component **81** didn't give the desired product **67**. Alcoholic component **51** was synthesized successfully from the known precursor **31**. Here, we have studied the action of various allylic reagent for tosyl displacement reaction. Alcohol **51** and acid **52** underwent Yamaguchi esterification gave epimeric mixture of **77.**

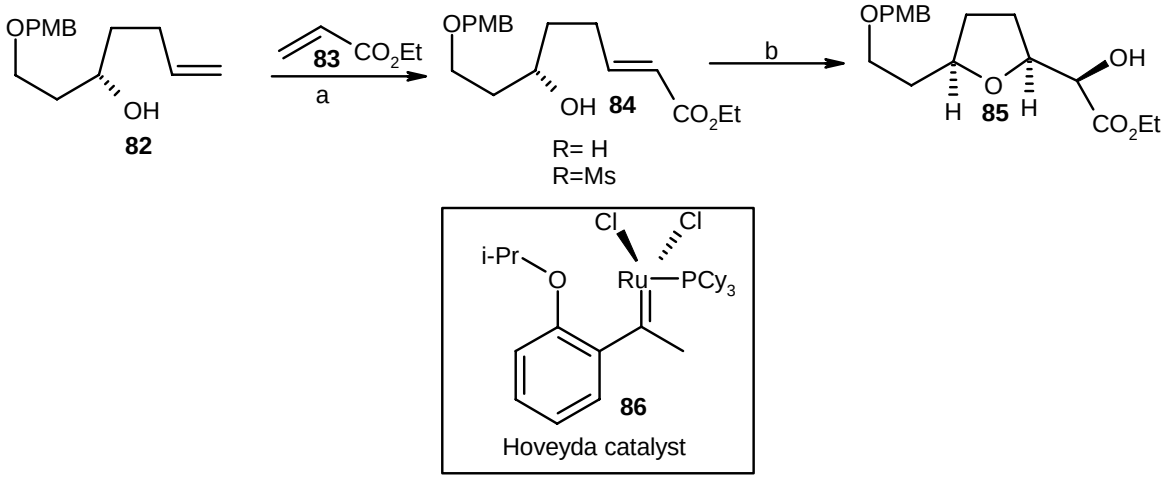
POST WORK

Post work

It is worth to mention here that after publishing our work of amphidinolide E, three reports came.

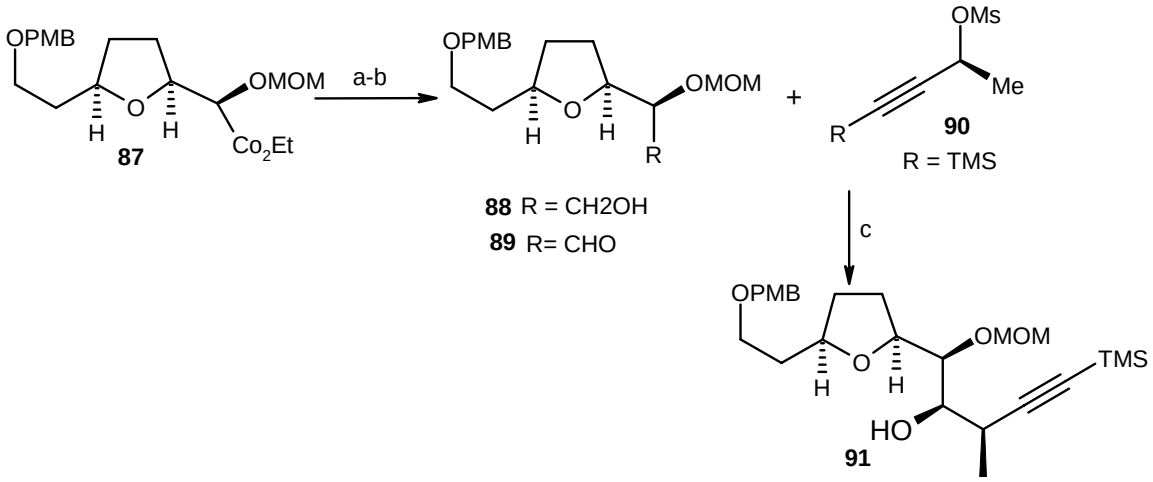
Marshall approach:[76] Synthesis of the C6-C21 Segment of Amphidinolide E

Scheme 25: Synthesis of tetrahydrofuran



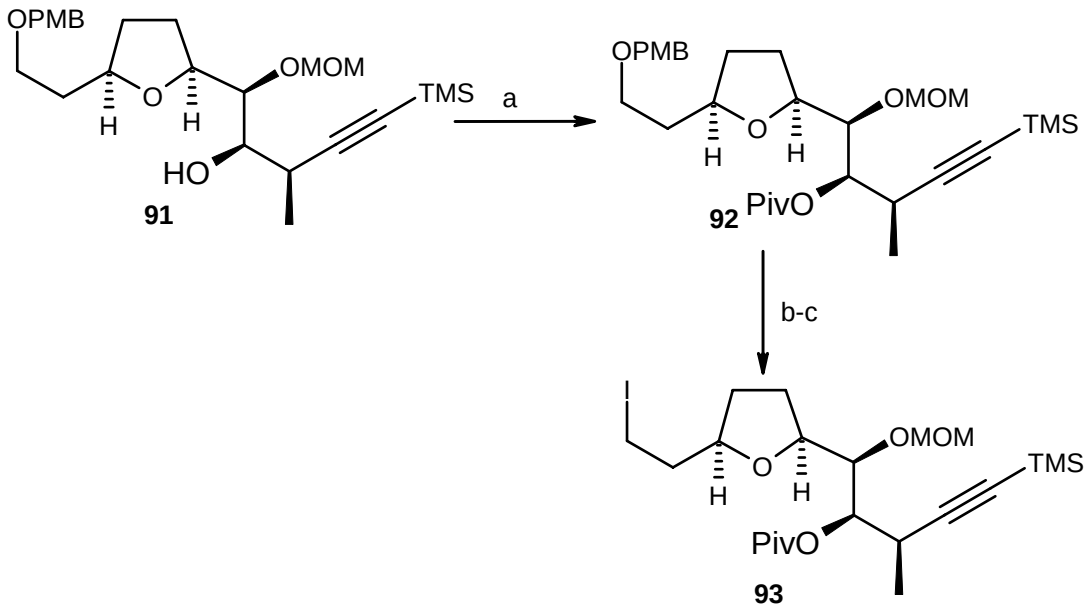
Reagents and conditions: (a) Hoveyda catalyst, ethylacrylate; (b) AD- mix α.

Scheme 26: Synthesis of alkyne



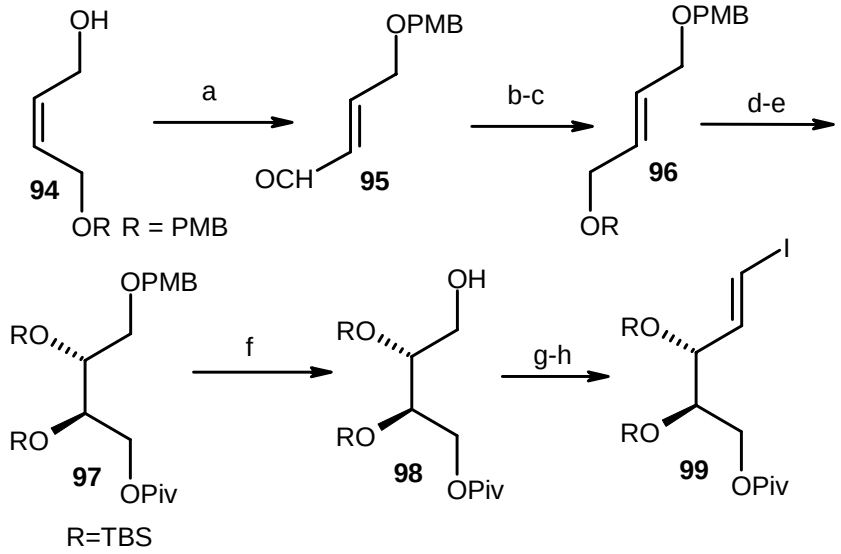
Reagents and conditions: (a) $LiALH_4$, THF; (b) Dess-Martin periodinane; (c) $Pd(OAC)_2.PPh_3$, THF, InI.

Scheme 27: Synthesis of iodo compound



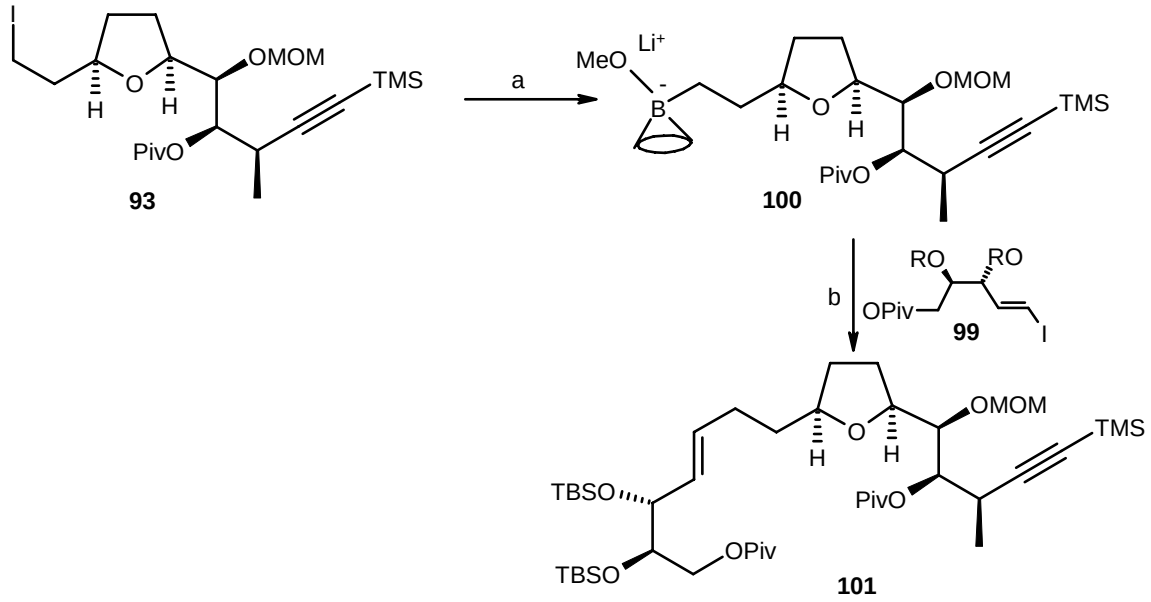
Reagents and conditions: (a) PivCl, DMAP; (b) DDQ; (C) I_2, Ph_3P, Im.

Scheme 28: Synthesis of vinyl iodo



Reagents and conditions: (a) PCC, CH_2Cl_2 ; (b) (1) DIBAL-H; (c) $(t\text{-}BuCO)_2O$; (d) AD-mix-β; (e) TBSOTf, TEA; (f) DDQ, DCM, H_2O; (g) Dess-Martin; (h) CHI_3, $CrCl_3$, Zn, NaI.

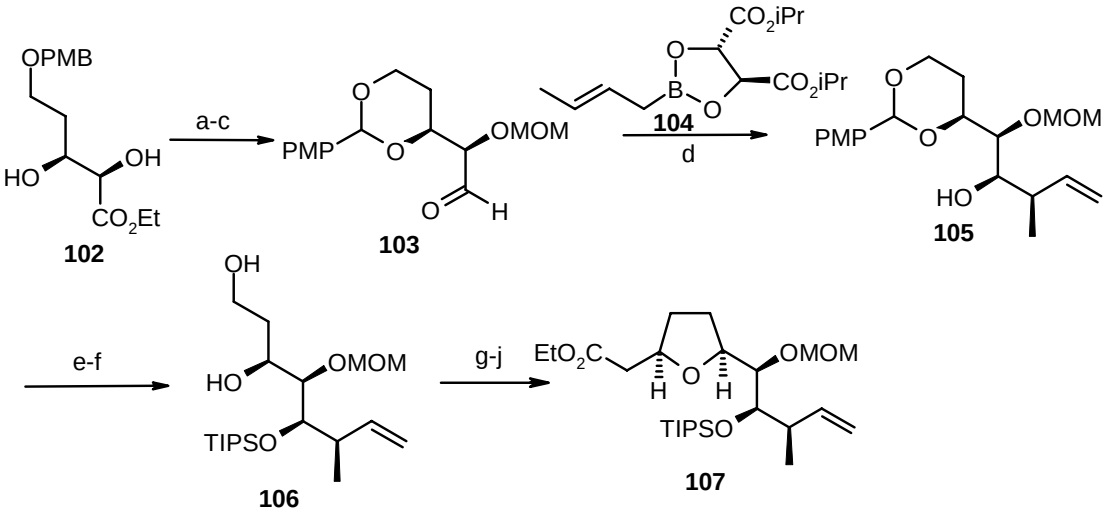
Scheme 29: Coupling reaction



Reagents and conditions: (a) Tert-Buli, 9-MeO-9-BBN; (b) $Pd(dppf)Cl_2$, DMF, K_3PO_4.

Eun Lee Approach:[77] Total Synthesis of (-)-Amphidinolide E

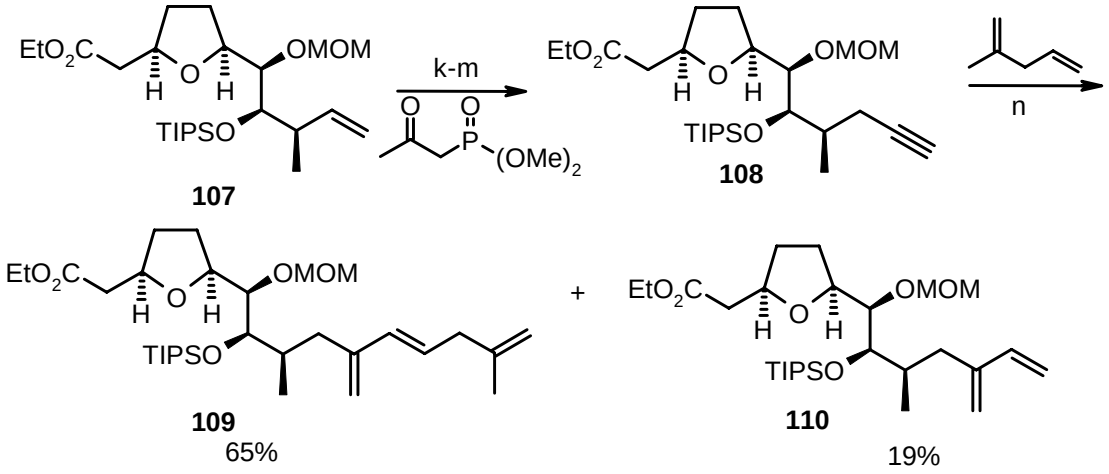
Scheme 30: Synthesis of tetrahydro furan ring using radical cyclisation



Reagents and conditions: (a) DDQ, 3-Å MS, CH_2Cl_2, 0 °C; (b) MOMCl, DIPEA, DMAP, CH_2Cl_2, reflux; (c) DIBAL, CH_2Cl_2, -78 °C; (d) 104, 4- Å MS, toluene, -78 °C; (e) TIPSOTf, collidine, CH_2Cl_2; (f) CAN, MeCN/H_2O (9:1), 0 °C; (g) TsCl, Et_3N, CH_2Cl_2, 0

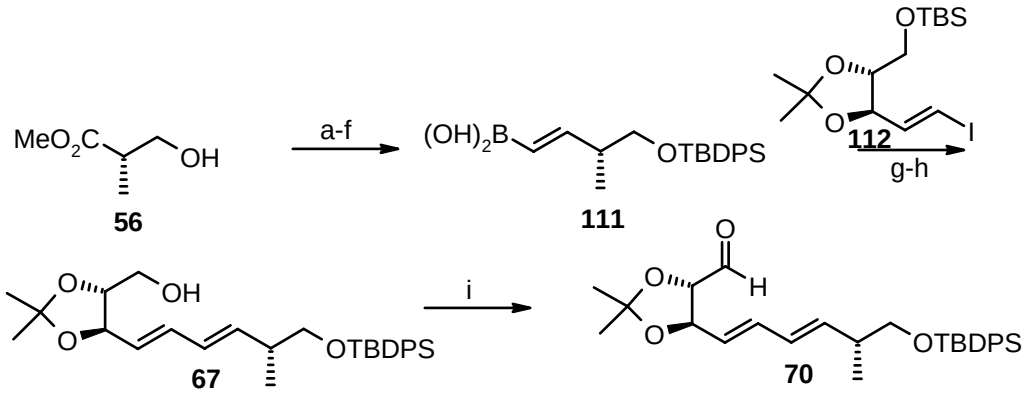
°C; (h) $CHCCO_2Et$, NMM, CH_2Cl_2; (i) NaI, acetone, reflux; (j) $(TMS)_3SiH$, Et_3B, toluene, -20 °C.

Scheme 31: Synthesis of trine using cross enyne metathesis reaction



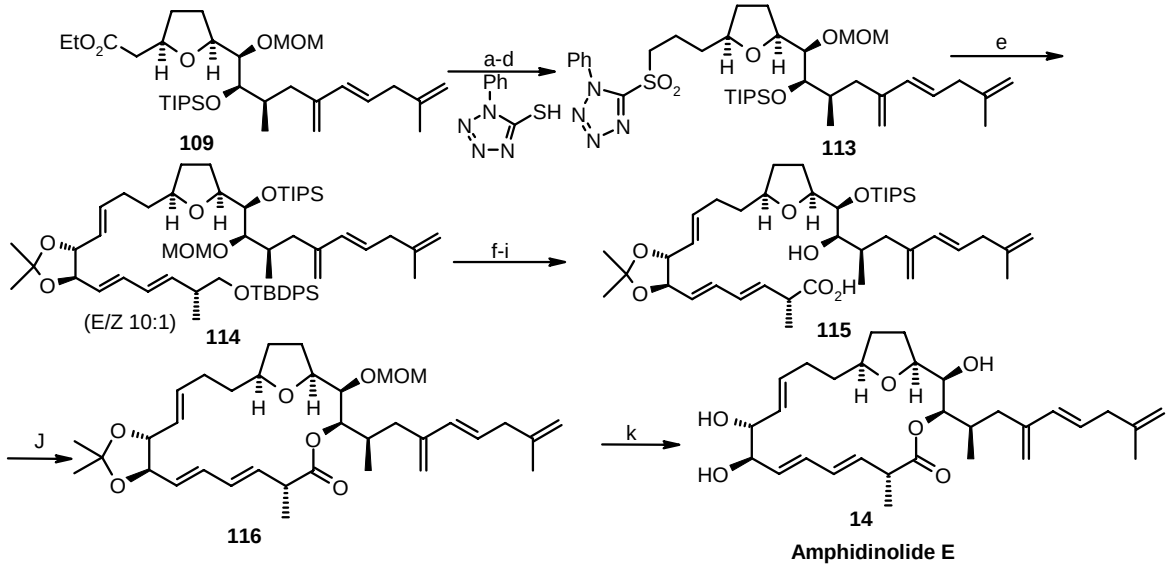
Reagents and conditions: (k) $(Sia)_2BH$, THF, 0 °C; $NaBO_3{\cdot}4H_2O$, H_2O; (l) Dess–Martin periodinane, pyridine, CH_2Cl_2, 0 °C→ RT; (m) Cs_2CO_3, EtOH, 0 °C→ RT; (n) $[(H_2IMes_2)RuCl_2(P(c\text{-}Hex)_3)]$, CH_2Cl_2.

Scheme 32: Synthesis of aldehyde using Suzuki coupling



Reagents and conditions: (a) TBDPSCl, imidazole, CH_2Cl_2, 0°C→ RT; (b) $LiBH_4$, Et_2O; (c) $SO_3{\cdot}$pyridine, Et_3N, DMSO/CH_2Cl_2 (1:1), 0°C→ RT; (d) CBr_4, Ph_3P, Zn, CH_2Cl_2, 0 °C→RT; (e) *n*BuLi, THF,-78 °C; (f) $BHBr_2{\cdot}SMe_2$, CH_2Cl_2, 0°C → RT; H_2O/Et_2O (1:3), 0 °C→RT; (g) $[Pd(PPh_3)_4]$, TlOEt, THF/H_2O (4:1); (h) PPTS, EtOH; (i) $SO_3{\cdot}$pyridine, Et_3N, DMSO/CH_2Cl_2 (1:1), 0 °C→RT.

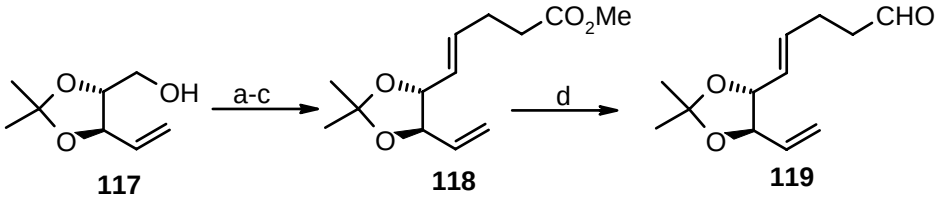
Scheme 33: Synthesis of Amphidinolide E



Reagents and conditions: (a) DIBAL, THF, -78 °C; (b) $(Ph_3P^+CH_2OMe)Cl^-$, tBuOK, THF, 0°C→RT; $Hg(OAc)_2$, THF/H_2O (10:1), 0 °C; (c) $NaBH_4$, MeOH; (d) 18, PPh_3, DIAD, THF; H_2O_2, $(NH_4)_6[Mo_7O_{24}]\cdot 4H_2O$, EtOH; (e) LiHMDS, THF, -78 °C → - 40 °C; DMF/DMPU (3:1),-78 °C→RT; (f) 15% NaOH/DMPU (1:10); (g) IBX, DMSO/THF (1:1); (h) $NaClO_2$, NaH_2PO_4, tBuOH/2-methyl-2-butene/ H_2O (1:1:1); (i) TBAF, THF; (j) EtOCCH, [{$RuCl_2$(p-cymene)}$_2$], toluene, 0°C→RT; CSA, RT→50°C; (k) 4N HCl, MeOH.

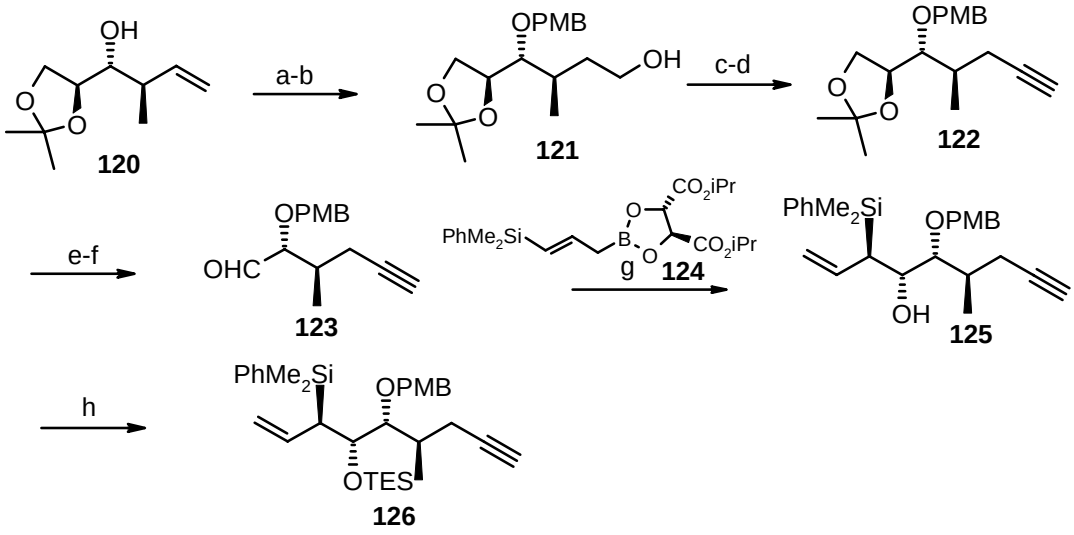
Willam R. Roush approach:[78] Total Synthesis of Amphidinolide E

Scheme 34: Synthesis of aldehyde



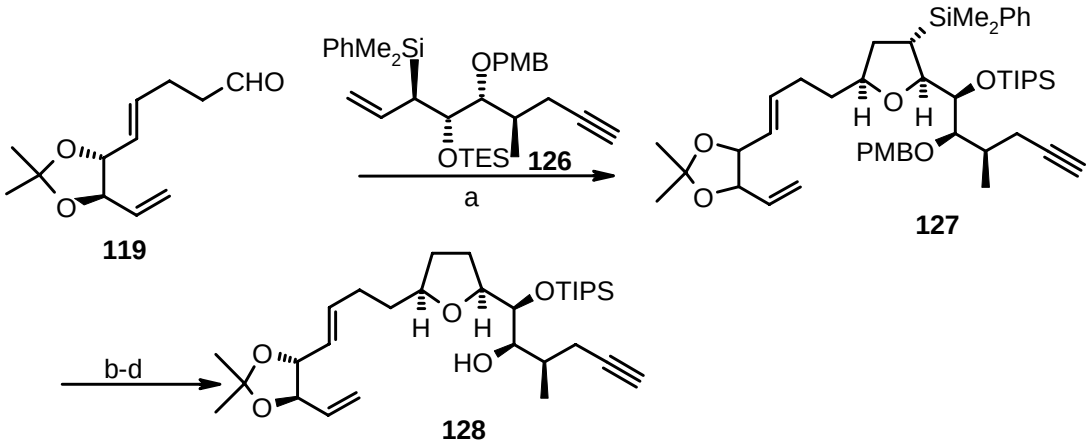
Reagents and conditions: (a) (1) $(COCl_2)$, DMSO, Et_3N; (b) vinyl magnesium bromide, THF, 0 °C; (c) $(MeO)_3CMe$, $EtCO_2H$, PhMe, 110 °C; (d) DIBAL, PhMe, -78 °C.

Scheme 35: Synthesis of allylsilane



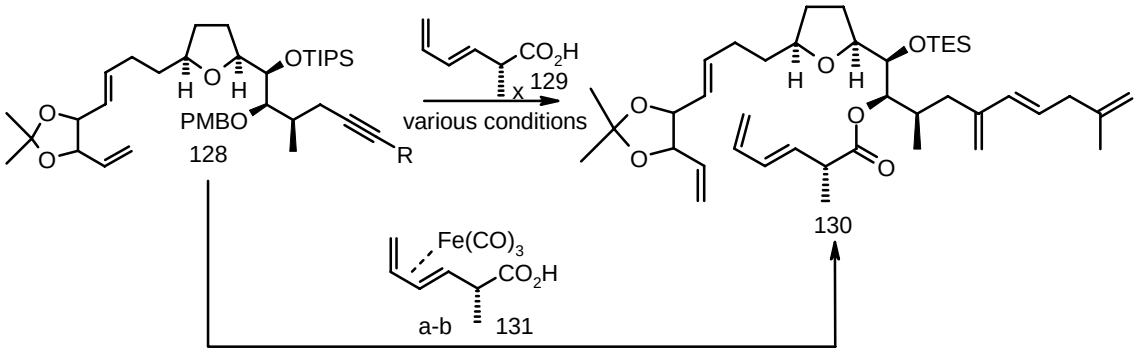
Reagents and conditions: (a) PMBCl, NaH, $(Bu)_4NI$; (b) 9-BBN:H_2O_2, NaOH; (c) SO_3-Py, DMSO, $EtN(i\text{-}Pr)_2$; (d) PPh_3, CBr_4, n-BuLi, -78 °C; (e) AcOH, H_2O, 40 °C; (f) $NaIO_4$, DCM; (g) PhMe, 4A MS, -78 °C; (h) TESCl, Imidazole, DMF, 45 °C.

Scheme 36: [3+2] anulation reaction



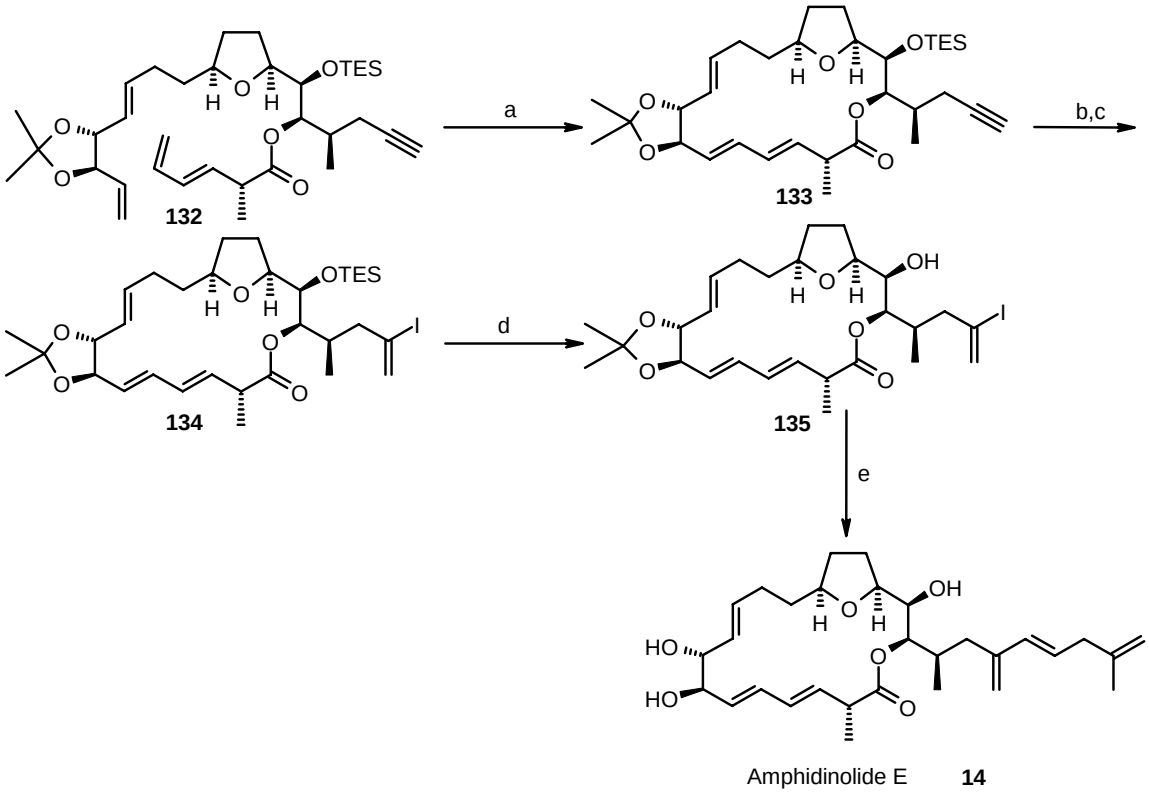
Reagents and conditions: (a) $BF_3.OEt_2$ (1equiv), CH_2Cl_2, -78 °C, 4 A MS, 48%, (b) TBAF.$3H_2O$, DMF, 90 °C (c) TESOTf, Et_3N (d) DDQ, 76 %.

Scheme 37: Esterification



Reagents and conditions: (a) 2, 4, 6-Trichlorobenzoyl chloride, Et_3N, DMAP, THF, 25 °C ; (b) CAN, Acetone, 0 °C, 94 %.

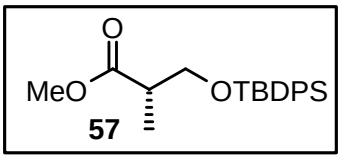
Scheme 38: Completion of the total synthesis of Amphidinolide E



Reagents and conditions: (a) Grubbs(II) catalyst, CH_2Cl_2, reflux; (b) Bu_3Sn-$AlEt_2$, CuCN, THF, -30 °C; (c) NIS, CH_2Cl_2, -45 °C; (d) AcOH, H_2O, THF, 40 °C; (e) $Pd(PPh_3)_4$, CuCl, THF.

EXPERIMENTAL

(*S*)-3-hydroxy-2-methylpropionate (57):



To a solution of (*S*)-(+)-3-hydroxy-2-methylpropionate **56** (5.3 g, 44.9 mmol) in DMF (80 mL), imidazole (8.6 g, 125.7 mmol) was added and stirred. To it added TBDPSCl (12.8 g, 46.6 mmol) in portion wise. The mixture was stirred for 5 h, poured into a dilute solution of $NaHCO_3$, and extracted with ether (3x100 mL). The combined organic extracts were washed successively with a dilute solution of $NaHCO_3$ and brine followed by drying over Na_2SO_4. Following filtration, the solvent was removed in vacuum to give crude product that was purified by chromatography on silica gel (hexane/ethyl acetate 15:1) to give **57** as a colorless liquid (22.3 g, 86%).

$[\alpha]_D$ **:** + 18.54 (*c* 7.2, $CHCl_3$)

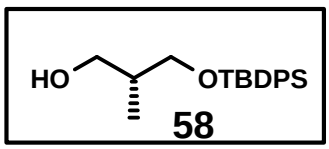
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.69-7.63 (m, 4H), 7.42-7.29 (m, 6H), 3.86-3.70 (m, 2H), 3.65 (s, 3H), 2.75-2.61 (q, 1H, *J* = 7.0 Hz), 1.14 (d, 3H, *J* = 7.0 Hz), 1.02 (s, 9H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 175.0, 135.4, 133.3, 133.2, 129.6, 127.6, 65.8, 51.3, 42.2, 26.6, 19.1, 13.4.

IR ($CHCl_3$, cm^{-1}): 2952, 2933, 1742, 1462, 1472, 1428, 1176, 1199, 1112, 823, 702, 613, 506.

Anal. Calcd for $C_{21}H_{28}O_3$ Si: C, 70.74; H, 7.92. Found: C, 70.70; H, 7.89.

(*R*)-3-(*tert*-butyldiphenylsiloxy)-2-methylpropan-1-ol (58):



$LiBH_4$ (2.0 M in THF, 27 mL, 54 mmol) was added to the solution of ester **57** (9.65 g, 27.1 mmol) in Et_2O (270 mL) at 0 °C and the reaction mixture was allowed to warm to rt. After 24 h, the reaction mixture was quenched by addition of sat. NH_4Cl solution (100 mL). The

reaction mixture was extracted with Et_2O (2x 100 mL) and the organic phase was dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Light Petroleumether-EtOAc, 4:1) gave alcohol **58** (8.6 g, 97%).

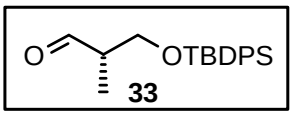
$[\alpha]_D$: + **7.**00 (*c* 3.3, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69-7.65 (m, 4H), 7.43-7.35 (m, 6H), 3.76-3.50 (m, 4H), 2.64 (brs, 1H), 2.10-1.87 (m, 1H), 1.06 (s, 9H), 0.82 (d, 3H, *J* = 0.82 Hz)

^{13}C NMR (50 MHz, $CDCl_3$): δ 135.4, 133.3, 129.5, 127.5, 67.5, 66.1, 37.6, 26.8, 19.0, 13.2.

Anal. Calcd for $C_{20}H_{28}O_2Si$: C, 72.87; H, 8.56. Found: C, 72.80; H, 8.53.

(*S*)-3-(*tert*-butyldiphenylsiloxy)-2-methylpropanal (33):



33

IBX (3.237 mg, 11.56 mmol) was dissolved in DMSO (7 mL) and stirried at rt. for 20 min, the opaque solution turned clear. To the solution, alcohol **58** (2.54 g, 7.71 mmol) in THF (7 mL) was added dropwise. After 3 hr stirring, the reaction mixture was quenched by sat. $Na_2S_2O_3$ solution (10 mL) and extracted with Et_2O (2 x100 mL).The organic phase was washed with sat. $NaHCO_3$ solution (2 x 50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated to give (1.97 g, 78%) which was used in the next step without further purification.

$[\alpha]_D$: +12.7 (*c* 0.4, $CHCl_3$)

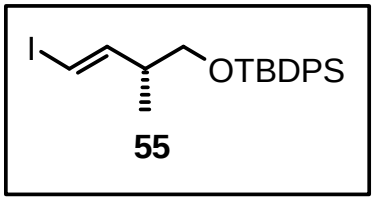
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.7 (d, 1H, *J* = 1.7 Hz), 7.63 (m, 4H), 7.39 (m, 6H), 3.86 (m, 2H), 2.55 (m, 1H), 1.08 (d, 3H, *J* = 7.1 Hz), 1.04 (s, 9H).

^{13}C NMR (200 MHz, $CDCl_3$): δ 204, 135.5, 135.3, 134.8, 129.8, 129.5, 127.7, 127.6, 64.1, 48.7, 26.8, 26.6, 19.2, 10.3.

IR ($CHCl_3$, cm^{-1}): 3072, 2931, 2858, 2717, 1738, 1589, 1472, 1428, 1390, 1113, 1036, 823, 740, 608, 504.

Anal. Calcd for $C_{20}H_{26}O_2Si$: C, 73.32; H, 8.00. Found: C, 73.54; H, 8.05.

(*R*, *E*)-*tert*-butyl(4-iodo-2-methylbut-3-enyloxy)diphynylsilane (55):



55

Anhydrous $CrCl_2$ (5.51 g**,** 44.8 mmol) was suspended in THF (25 mL) under an argon atmosphere. A solution of aldehyde **59** (2.45 g**,** 7.5 mmol) and iodoform (5.9 g, 14.9 mmol) in THF (40 mL) was added dropwise to the suspension at 0 °C**.** After stirring at 0 °C for 3 h, the reaction mixture is poured into water (50 mL) and extracted with ether (3 X 500 mL). The combined extracts were dried over Na_2SO_4 and concentrated. Purification by column chromatography on silica gel with Pet ether affords **55** as colorless oil (2.63 g, 78%).

$[\alpha]_D$: +10.0 (*c* 4.4, $CHCl_3$**)**

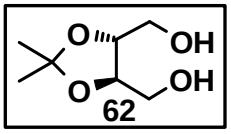
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65-7.61 (m, 4H), 7.40-7.38 (m, 6H), 6.48 (dd, 1H, *J* = 6.3, 14.5 Hz), 6.04 (d, 1H, *J* = 14.5 Hz), 3.50 (d, 2H, *J* = 6.3 Hz), 2.41 (m, 1H), 1.05 (s, 9H), 1.01 (d, 3H, *J* = 6.8 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 149, 135.6, 133.6, 133.5, 129.7, 127.7, 75.4, 67.5, 43.1, 27, 19.3, 15.7.

IR ($CHCl_3$, cm^{-1}): 3054, 3070, 2960, 2930, 2858, 1590, 1472, 1428, 1386, 1256, 1217, 1187, 1113, 1023, 948, 823, 740, 759, 701, 505.

Anal. Calcd for $C_{21}H_{27}OSiI$: C, 55.99; H, 6.04. Found: C, 55.91; H, 6.01.

((4*R*, 5*R*)-2, 2-dimethyl-1, 3-dioxolane-4, 5-diyl) dimethanol (62):



62

In a 1-L, one-necked, round-bottom flask fitted with a reflux condenser, a large magnetic stirrer under the argon atmosphere, a mixture of *D*(-)tartaric acid **60** (101 g, 0.673 mol), 2,2-dimethoxypropane (190 mL, 161 g, 1.54 mol), dry methanol (40 mL) and *p*-toluenesulfonic acid monohydrate (0.4 g, 2.1 mmol) was charged and the whole contents were warmed for about 2 h on an oil bath at 60 °C with stirring until a dark-red homogeneous solution was obtained. Additional amounts of 2, 2-dimethoxypropane (95

mL, 80.5 g, 0.77 mol) and cyclohexane (450 mL) were added and the reflux condenser was replaced with a 30-cm Vigreux column and distillation head. The mixture was heated to reflux and the azeotrope of the methanol-cyclohexane (53 °C) and acetone-cyclohexane (54.5 °C) were slowly removed over a period of 48 h (10-15ml/hr). After approximately 600 mL of distillate was collected, additional amount of 2, 2-dimethoxypropane (6 mL, 5.1 g, 49 mmol) was added and the mixture was heated under reflux for 15 min. The reaction mixture was cooled to rt, anhydrous potassium carbonate (1 g, 7.2 mmol) was added and the mixture was stirred until the reddish color had disappeared. Volatile material was removed under reduced pressure and the residue was fractionally distilled under vacuum to afford **61** (135 g, 95% yield) as a pale-yellow oil, bp = 90–101 °C (0.6 mm).

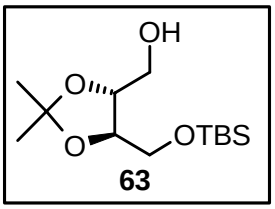
In a dry 500 mL two-neck round-bottom flask, equipped with a 250-mL pressure-equalized addition funnel, a reflux condenser and a magnetic stirring bar, was added lithium aluminum hydride (6 g, 158.1 mmol) in THF (100 mL) under argon. To this mixture a solution of (34 g, 156 mmol) in THF (150 mL) was added drop-wise over a period of 2 h and then refluxed for 6 h. The mixture was cooled to 0–5 °C and *cautiously* treated with water (6 mL) followed by 2N sodium hydroxide solution (12 mL) and water (12-18 mL). The mixture was then stirred at rt until the gray color of unquenched lithium aluminum hydride has completely disappeared. To the resulting white suspension was added anhydrous sodium sulphate. The slurry was filtered on a Büchner funnel and the inorganic precipitate was given a wash with (5 x 200 ml) THF. The combined filtrate was dried over anhydrous sodium sulphate. The filtrate was concentrated under reduced pressure. This crude mixture was fractionally distilled under vacuum to afford **62** as a colorless to pale-yellow oil, (bp 96-108 °C, 0.6 mm); (23 g 90% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.95 (brs, 1H), 3.81-3.61 (m, 6H), 1.30 (s, 6H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 109, 78.3, 62.1, 26.7

IR ($CHCl_3$, cm^{-1}): 2992, 2956, 1759, 1438, 1384, 1213, 1111.

(4*R*, 5*R*)-5-((*tert*-butyldimethylsiloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (63):



63

To the solution of NaH (1.48 g, 61.7 mmol; 60% in mineral oil) in THF (50 mL), a solution of diol (10 g, 61.7 mmol) in THF (40 mL) was added at rt and stirred for 45 min until a large quantity of a white solid has been formed. TBSCl (9.3 g, 61.7 mmol) was added and vigorous stirring was continued for 45 min. The mixture was diluted with Et_2O (150 mL) and successively treated with 10% aqueous K_2CO_3 (120 mL), brine (100 mL), dried over Na_2SO_4 and concentrated, Purification by column chromatography on silica gel with (1:9) ethylacetate/pet ether furnished the monoprotected diol **63** as a colorless oil (14.2 g, 83%).

$[\alpha]_D$: –5.5 (*c* 2, MeOH), lit, -5.4(*c* 5, MeOH)

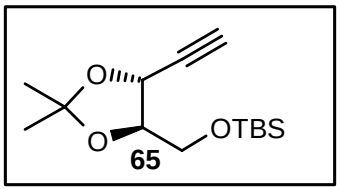
^{1}H NMR (300 MHz, $CDCl_3$): δ 3.99-3.63 (m, 6H), 2.50 (s, 1H), 1.42 (s, 3H), 1.40 (s, 3H), 0.91(s, 9H), 0.09 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 108.6, 79.4, 77.6, 63.4, 62.3, 26.7, 26.6, 25.5, 17.9, -5.80

IR ($CHCl_3$, cm^{-1}): 3469, 2987, 2885, 2859, 2955, 2931, 1749, 1463, 1371, 1254, 1083, 838, 778.

Anal. Calcd for $C_{13}H_{28}O_4Si$: C, 56.48; H, 10.20. Found: C, 56.42; H, 10.10.

***Tert*-butyl (((4*R*, 5*R*)-5-ethynyl-2, 2-dimethyl-1, 3-dioxolan-4-yl)methoxy)dimethylsilane (65):**



65

To a solution of alcohol **63** (20.0 g, 72.46 mmol) in ethyl acetate (250 mL), was added IBX (34.5 g, 123 mmol). The resulting suspension was immersed in an oil bath set at 80 °C and stirred vigorously open to the atmosphere. After 9 h, the reaction was cooled to rt and

filtered. The filter cake was washed with ethyl acetate (3 x 100 mL) and the combined filtrates were concentrated to yield **64 (**19. 5 g, 98 % yield).

To a solution of aldehyde **64** (2.5 gm, 9.11 mmol) and K_2CO_3 (2.51 gm, 18.2 mmol) in MeOH (30 mL) at 0°C, dimethyl 1-diazo-2-oxopropylphosphonate (2.1 gm, 10.9 mmol) in MeOH (20 mL) was added slowly. The reaction mixture was stirred for 1 h at rt. and diluted with Et_2O (25 mL) and quenched by sat. NH_4Cl solution (15 mL). The mixture was extracted with Et_2O (2x50 mL), washed with brine (10 mL) and dried over Na_2SO_4. After filtration and evaporation, flash column chromatography (3% EtOAc/Petether) provided alkyne **65** (1.7 gm, 95%).

$[\alpha]_D$: + 12.64 (*c* 1.6, $CHCl_3$)

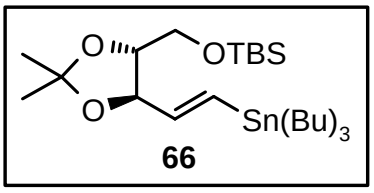
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.56 (dd, 1H, *J* = 2.4, 7.4 Hz), 4.10 (m, 1H), 3.75 (d, 2H, *J* = 3.9 Hz), 2.49 (d, 1H, *J* = 2.0 Hz), 1.47 (s, 3H), 1.39 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 110, 81.8, 81.1, 74.1, 66.5, 61.7, 26.6, 25.9, 25.5, 17.9, -5.65, -5.76.

IR ($CHCl_3$, cm^{-1}): 3313, 2989, 2859, 2955, 2931, 1473, 1382, 1256, 1148, 1086, 836, 778.

Anal. Calcd for $C_{14}H_{26}O_3Si$: C, 62.17; H, 9.69. Found: C, 62.13; H, 9.60.

***Tert*-butyl(4R,5R)-2,2-dimethyl-5-(E)-2-(tributylstannyl)vinyl)-1,3-dioxalan-4-yl)methoxy)dimethylsilane (66):**



66

The alkyne **65** (7.16 g, 26.4 mmol) was dissolved in benzene, and tributyltin hydride (8.6 mL, 29.1 mmol) and AIBN (10 mg) were added at rt. The reaction mixture was refluxed for 20 min and concentrated, and then the residual oil was purified by silica gel chromatography with pet ether to give **66** (14.9 g, 78% yield).

Optical Rotation: + 6.38 (c 3.41, $CHCl_3$)

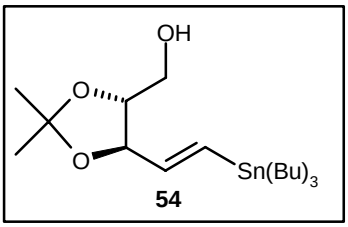
^{1}H NMR (200MHz, $CDCl_3$): δ 6.36 (d, 1H, *J* = 19.1 Hz), 6.01 (dd, 1H, *J* = 6.4, 19.1 Hz), 4.29 (m, 1H), 3.78–3.64 (m, 3H), 1.60 -1.19 (m, 21H), 0.97-0.84 (m, 21H), 0.05 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 145.3, 133.0, 109.0, 81.6, 81.4, 62.6, 29.1, 27.3, 27.1, 26.0, 13.8, 9.5, -5.3, -5.4.

IR ($CHCl_3$, cm^{-1}): 2956, 2857, 1463, 1378, 1253, 1145, 1085, 989, 838, 778, 673, 596, 512

Anal. Calcd for $C_{26}H_{54}O_3SnSi$: C, 55.61; H, 9.69. Found: C, 55.58; H, 9.60.

(4*R*,5*R*)-2,2–dimethyl–5-((E)–2-(tributylstannyl)vinyl)-1,3–dioxolan–4-yl)methanol (54):



54

To a solution of **66** (6.2 g, 11.04 mmol) in THF (40 mL) at rt was added a solution of TBAF (16.5 mL, 16.5 mmol, 1.0 M in THF). The mixture was stirred for 20 h and water (40 mL) was added. The mixture was extracted with ether (3x200 mL) and the combined organic extracts were washed successively with a saturated solution of NH_4Cl and brine. After drying over Na_2SO_4, the suspension was filtered and the solvent removed in vacuum. The crude product was purified by chromatography on silica gel with 5 % ethyl acetate/ hexane to afford **54** as a yellow oil (4.54 g, 92%).

$[\alpha]_D$: + 7.9 (*c* 4.3, $CHCl_3$)

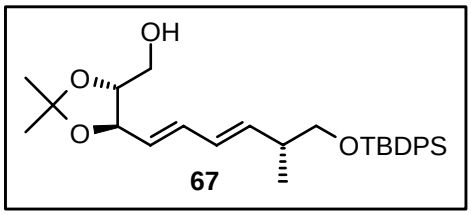
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.27 (d, 1H, *J* = 19.1 Hz), 5.87 (dd, 1H, *J* = 6.7, 19.1 Hz), 4.18 (t, 1H, *J* = 7.6 Hz), 3.78-3.66 (m, 2H), 3.48 (m,1H), 2.38 (brs,1H), 1.38 (m, 12H), 1.27-1.13 (m, 6H), 0.91-0.69 (m, 15H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 144.8, 133.1, 108.8, 81.2, 80.6, 60.7, 28.8, 26.7, 26.6, 13.3, 9.2.

IR ($CHCl_3$, cm^{-1}): 3446, 3019, 2958, 2400, 1598, 1464, 1382, 1047, 856, 758, 669.

Anal. Calcd for $C_{20}H_{40}O_3Sn$: C, 53.70; H, 9.01. Found: C, 53.63; H, 9.04.

((4*R*, 5*R*)–5-((*R*, 1*E*, 3*E*)-6-(*tert*-butyldiphenylsilyloxy)–5–methylhexa-1,3-dienyl)-2, 2–dinethyl-1,3–dioxolan–4-yl)methanol(67):



67

LiCl (1.4 mg, 34.01 mmol) was dried on flame under vacuum. Upon cooling, $Pd(PPh_3)_4$ (589 mg, 0.09 mmol) and CuCl (2.8 g, 28.34 mmol) were added, and the mixture was degassed with an Ar. DMSO (10 mL) was introduced with concomitant stirring, followed by the addition of **55** (2.5 gm, 5.67 mmol) and a vinyltin compound **54** (2.54 gm, 5.7 mmol). The resulting mixture was rigorously degassed. The reaction mixture was stirred at rt for 1 h, then heated to 60 °C for 1h. Then reaction mixture was cooled, diluted with Et_2O (30 mL), and washed with a mixture of brine (40 mL) and 5% aqueous NH_4OH (8 mL). The aqueous layer was further extracted with Et_2O (2 x 15 mL), and the combined organic layers were washed with water (2 x 40 mL) then brine solution, dried over Na_2SO_4, and concentrated to give the residue, which was purified with 8-10 % ethylacetate/pet ether gave compound **67** (2.37g, 86%).

Compound 67

$[\alpha]_D$: + 6.36 (*c* 3.9, $CHCl_3$)

^1H NMR (300 MHz, $CDCl_3$): δ 7.67-7.63 (m, 4H), 7.46-7.37 (m, 6H), 6.28 (dd, 1H, *J* = 10.4, 15.2 Hz), 6.06 (dd, 1H, *J* = 10.4, 15.2 Hz), 5.75-5.47 (m, 2H), 4.35 (t, 1H, *J* = 7.8 Hz), 3.87-3.71 (m, 2H), 3.62 – 3.49 (m, 3H), 2.43 (m,1H), 1.45 (s, 6H), 1.06 (s, 12H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 138.6, 135.5, 134.5, 133.8, 129.5, 28.8, 127.5, 127.4, 108.9, 81.4, 77.9, 68.4, 60.1, 39.3, 26.7, 26.9, 19.3, 16.4.

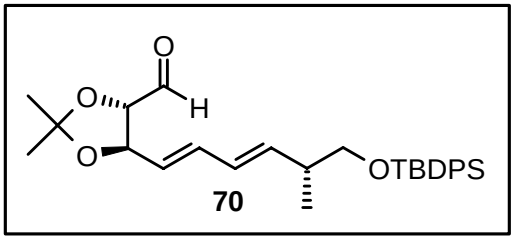
IR ($CHCl_3$, cm^{-1}): 3446, 3019, 2929, 2857, 1724, 1482, 1382, 1112, 704, 669, 505.

Anal. Calcd for $C_{29}H_{40}O_4Si$: C, 72.45; H, 8.38. Found: C, 72.40; H, 8.35.

IR ($CHCl_3$, cm^{-1}): 3452, 3072, 2960, 2931, 1729, 1428, 1383, 1217, 1112, 823, 703, 668, 614, 505, 489.

Anal. Calcd for $C_{29}H_{40}O_4Si$: C, 72.45; H, 8.38. Found: C, 72.40; H, 8.33.

(4*S*,5*R*)-(*R*,1*E*,3*E*)–6-(tert-butyldiphenylsiloxy)–5–methylhexa-1,3-dienyl)-2,2–dimethyl-1, 3–dioxalane–4-carbaldehyde (70):



70

IBX (.91 g, 3.24 mmol) was dissolved in DMSO (2 mL). Upon stirring at rt. for 20 min, the opaque solution turned to clear. To the solution, alcohol **67** (1.3 mg, 2.7 mmol) in THF (2.5 mL) was added dropwise. After 3 h stirring, the reaction was quenched by sat.$Na_2S_2O_3$ solution (3 mL) and extracted with Et_2O (10 mL × 2). The organic phase was washed with sat. $NaHCO_3$ solution (2x 5 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated gave **70** (0.98 gm, 76%).

$[\alpha]_D$: + 5.0 (*c* 1.9, $CHCl_3$)

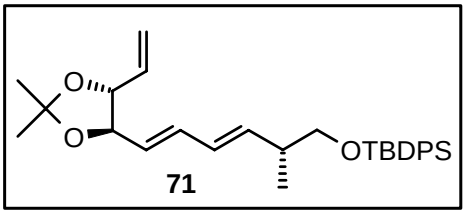
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (d, 1H, *J* = 2.0 Hz), 7.67 (d, 4H, *J* = 6.5 Hz), 7.45 – 7.27 (m, 6H), 6.29 (dd, 1H, *J* = 15.3, 10.3 Hz), 6.06 (dd, 1H, *J* = 10.3, 15.3 Hz), 5.72 (dd, 1H, *J* = 7.3, 15.3 Hz), 5.59 (dd, 1H, *J* = 15.3, 7.3 Hz), 4.52 (t, 1H, *J* = 7.3 Hz), 4.06 (dd, 1H, *J* = 7.3, 2.0 Hz), 3.59 – 3.50 (m, 2H), 2.46 (m, 1H), 1.52 (s, 3H), 1.48 (s, 3H), 1.08 (s, 12H).

^{13}C NMR (100MHz, $CDCl_3$): δ 199.5, 139.7, 135.7, 134.9, 133.8, 129.6, 128.6, 128.5, 127.6, 126, 111.3, 84.7, 77.8, 68.3, 39.4, 26.9, 26.3, 19.3, 16.4.

IR ($CHCl_3$, cm^{-}1): 3136, 3072, 2956, 2931, 2715, 1889, 1824, 1749, 1658, 1589, 1463, 1381, 1111, 991.

Anal Calcd for $C_{29}H_{38}O_4Si$: C, 72.76; H, 8.00. Found: C, 72.72; H, 8.03.

***Tert*-butyl (((*R*, 3*E*, 5*E*)-6-((4*R*, 5*R*)-2, 2dimethyl-5-vinyl-1, 3-dioxolan-4-yl)-2-methylhexa-3, 5-dienyloxy) diphnylsilane (71):**



71

A solution of aldehyde **70** (0.28 g, 0.58 mmol) in THF (20 mL) at –10 °C was treated with methylene triphenyl Phosphorane [generated from PPh_3CH_2I(0.71 g, 1.8 mmol) and $NaNH_2$ (71 mg,1.8 mmol) in dry Et_2O:THF] and contents were stirred at rt for 10 h. The reaction mixture was quenched with saturated NH_4Cl solution, partioned between ethyl acetate-water. The combine ethyl acetate layer was dried (over Na_2SO_4), concentrated and residue was purified over silica gel chromatography with eluent 2% ethylacetate/petether to furnish **71** as a colourless oil (0.23 gm, 76%).

$[\alpha]_D$: – 25.6 (*c*, 8 $CHCl_3$)

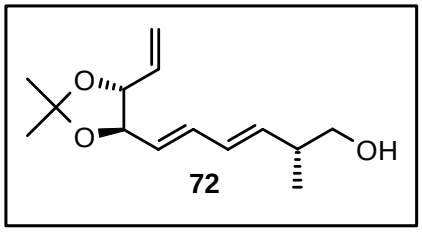
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.71 –7.58 (m, 4H), 7.46-7.26 (m, 6H), 6.26 (dd, 1H, *J* = 10.4, 14.9 Hz), 6.05 (dd, 1H, *J* = 10.4, 14.9 Hz), 5.89 –5.46 (m, 3H), 5.34 (d, 1H, *J* = 17.1 Hz), 5.24 (d, 1H, *J* = 11.4 Hz), 4.16-4.03 (m, 2H), 3.51 (dd, 2H, *J* = 1.0, 7.2 Hz), 2.43 (q, 1H, *J* = 7.2 Hz), 1.45 (s, 6H), 1.04 (s, 9H), 1.02 (d, 3H, *J* = 7.2 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 138.6, 134.5, 134.3, 133.8, 129.5, 129, 127.6, 126.5, 118.6, 109, 82.4, 81.9, 68.4, 39.4, 27.1, 27.0, 19.3, 16.4.

IR ($CHCl_3$, cm^{-1}): 3050, 3072, 3014, 2986, 2960, 2859, 2932, 1734, 1659, 1590, 1472, 1482, 1380, 1172, 1113, 1053, 989, 931, 883, 824, 759, 703.

Anal. Calcd for $C_{30}H_{40}O_3Si$: C, 70.96; H, 7.94. Found: C, 70.96; H, 7.94.

(*R*, 3*E*, 5*E*)-6-((4*R*, 5*R*)-2, 2 dimethylhexa-3,5-dien-1-ol (72):



72

To a solution of **70** (0.2 g, 0.40 mmol) in THF (5 mL) at rt was added a solution of TBAF (0.5 mL, 0.50 mmol, 1.0 M in THF). The mixture was stirred for 5 h. Water (10 mL) was added, extracted with ether (3x10 mL) and the combined organic extracts were washed successively with a saturated solution of NH_4Cl and brine. After drying (over Na_2SO_4), the suspension was filtered and the solvent removed in vaccum. The crude product was purified by chromatography on silica gel with 10 % ethyl acetate/Petether to afford **72** as a yellow oil (77 mg, 82%).

Optical Rotation: + 6.4 (*c* 3.9, $CHCl_3$)

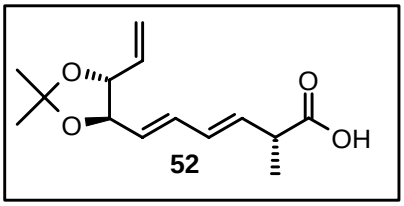
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.27 (dd, 1H, *J* = 10.9, 15.12 Hz), 6.12 (dd, 1H, *J* =10.9, 15.1 Hz), 5.80 (m, 1H), 5.59 (m, 2H), 5.35 (d,1H, *J* = 16.9 Hz), 5.24 (d, 1H, *J* =10.9 Hz), 4.08 (m, 2H), 3.47 (m, 2H), 2.40 (m, 1H), 1.97 (brs, 1H), 1.44 (s, 6H), 1.03 (d, 3H, *J* = 6.41).

^{13}C NMR (125 MHz, $CDCl_3$): δ 137.8, 134.2, 134.0, 130.0, 127.2, 118.8, 109.1, 82.3, 81.7, 67.2, 39.6, 27.1, 27.0, 16.3.

IR ($CHCl_3$, cm^{-1}): 3440, 2961, 2933, 1732, 1462, 1382, 1113, 1054, 757.

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.30. Found: C, 70.50; H, 9.25.

(*R*, 3*E*, 5*E*)-6-((4*R*, 5*R*)-2, 2-dimethyl-5-vinyl-1, 3-dioxolan-4-yl)-2-methylhexa-3, 5-dienoic acid (52):



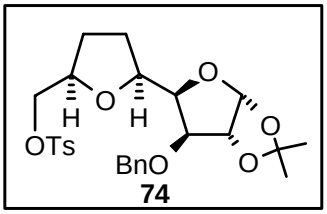
52

IBX (70 mg, 0.25 mmol) was dissolved in DMSO (1 mL). Upon stirring at rt. for 20 min, the opaque solution turned to clear. To the solution, alcohol **72** (50 mg, 0.21 mmol) in THF (1 mL) was added dropwise. After 3 h stirring, the reaction mixture was quenched by sat. $Na_2S_2O_3$ solution (3 mL) and extracted with Et_2O (2 x 10 mL).The organic phase was washed with sat. $NaHCO_3$ solution (5 mL × 2) and brine (5 mL), dried over $NaSO_4$, filtered, and concentrated. This crude aldehyde **73** (36 mg, 0.15 mmol) was directly dissolved in *t*-BuOH (3.3 mL) and 2-methyl-2-butene (3.3 mL). After cooling to 0 °C, $NaClO_2$ (41 mg, 0.46 mmol) and NaH_2PO_4 (54 mg, 0.46 mmol) in water (3.3mL) was added to the solution. The reaction mixture was stirred vigorously for 5 h at rt, diluted with EtOAc (30 mL), and quenched by water (10 mL). The aqueous phase was extracted with EtOAc (10 mL × 2) and the combined organic phase was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography by 30% (ethylacetate/petether) provided acid **52** (33 mg, 86%).

$[\alpha]_D$: –60.23, (*c* 1.3, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.27 (dd, 1H, *J* = 15.1,10.5 Hz), 6.16 (dd,1H, *J* = 15.1, 10.5 Hz), 5.83 – 5.76 (m, 2H), 5.61 (dd, 1H, *J* = 6.4, 15.1 Hz), 5.35 (d, 1H, *J* = 17.4), 5.25 (d, 1H, *J* = 9.6 Hz), 4.13 – 4.09 (m, 2H), 3.24 (m, 1H), 1.4 (s, 6H),1.30 (d, 3H, *J* = 7.2 Hz).
^{13}C NMR (125MHz, $CDCl_3$): δ 179.7, 134.1, 133.2, 132.9, 130.8, 128.7, 118.9, 109.8, 82.4, 81.6, 42.5, 27.0, 17.0.
IR ($CHCl_3$, cm^{-1}): 3407, 3020, 2400, 1712, 1653, 1519, 1424, 1215, 1048, 929,755, 669.
Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.98. Found: C, 66.60; H, 7.93

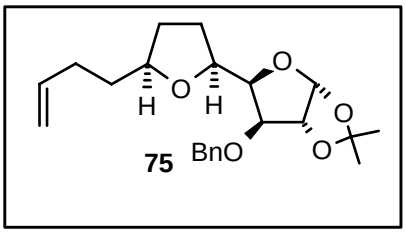
5,8-Anhydro-3-*O*-benzyl-6,7-dideoxy- 1,2- *O*-isopropylidine-9-*O*- tosyl-1-*glycero*-β-L-*ido*-nonanofuranose (74):



74

An ice cold solution of alcohol (0.37 gm, 1.04 mmol) in dry DMF (5ml) was treated with NaH (41 mg, 1.04 mmol, 60 % dispersion in oil) and stirred for 30 min. Then the reaction mixture was treated with tosyl chloride (0.2 gm, 1.04 mmol) at 0 ^oC and the stirring was continued for an additional 4 h at rt. The reaction mixture was quenched with ice water and portioned between ethyl acetate. The combined ethyl acetate layer was dried (Na_2SO_4), concentrated and residue was purified over silica gel chromatography with 18% ethyl acetate/ light petroleum ether as an eluent to furnish **74** as a colourless oil (0.46 gm, 93%).
$[\alpha]_D$: – 61.3 (*c* 1.5, $CHCl_3$)
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, 2H, *J* = 8.3 Hz), 7.35–7.25 (m, 7H), 5.97 (t, 1H, *J* = 3.9Hz), 4.67 (dd, 1H, *J* = 2.9, 11.8 Hz), 4.61 (dd, 1H, *J* = 1.8, 3.8 Hz), 4.41 (dd, 1H, *J* = 2.9, 11.8 Hz), 4.25-3.86 (m, 6H), 2.14 (s, 3H), 1.95-1.81 (m, 3H), 1.53-1.49 (s, 1H), 1.50 (s, 3H), 1.32 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ 144.6, 137.0, 132.8, 129.8, 128.6, 128, 127.7, 111.6, 105.5, 96.1, 83.2, 82.5, 81.8, 78.6, 76.4, 71.6, 71.12, 27.7, 27.2, 26.8, 26.4, 21.6.
IR ($CHCl_3$, cm^{-1}): 3020, 2401, 1732, 1374, 1216, 1176, 1076, 757, 668.
Anal. Calcd for $C_{26}H_{32}O_8S$: C, 66.08; H, 6.82. Found: C, 66.05; H, 6.80

9-*C*-Allyl-5,8-anhydro-3-*O*-benzyl-6,7,9-trideoxy-1,2-*O*-isopropylidene-L-*glycero*-β-L-*ido* furanose (75):



75

To an ether soln. of diallyl cuprate (0.5 ml, 0.5 mmol, 1M solution in THF) at – 78 °C was added an ether solution of tosyl compound **74** (.2 gm, 0.4 mmol). The reaction was allowed to run for 6 h and then quenched with sat NH_4Cl and extracted with ethyl acetate. The combined ethyl acetate layer was dried (Na_2SO_4), concentrated and residue was purified over silica gel chromatography with 12% ethyl acetate/light petroleum ether as an elutent to furnish **75** (106 mg, 67%) as a colourless oil.

$[\alpha]_D$: –54.6 (*c* .9, $CHCl_3$)

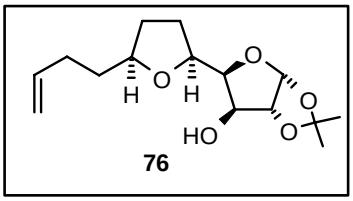
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.36-7.26 (m, 5H), 6.0 (d, 1H, *J* = 3.8 Hz), 5.82 (m, 1H), 5.02 (m, 1H), 4.94 (m, 1H), 4.68 (d, 1H, *J* = 11.9 Hz), 3.92 (d, 1H, *J* = 3.9 Hz), 4.43 (d, 1H, *J* = 11.7 Hz), 4.21–4.04 (m, 2H), 3.86 (m, 1H), 2.16 –2.09 (m, 2H), 1.96-1.73 (m, 3H), 1.64 –1.50 (m, 3H),1.49 (s, 3H), 1.44 (m, 1H), 1.33 (s, 3H).

^{13}C NMR (125MHz, $CDCl_3$): δ 138.6, 137.3, 128.4, 127.9, 127.7, 114.3, 111.6, 105.6, 83.7, 82.8, 82.7, 81.9, 79.4, 71.7, 34.8, 30.7, 30.2, 27.4, 26.9, 26.3.

IR ($CHCl_3$, cm^{-1}): 3019, 1726, 1375, 1265, 1074, 1023, 757, 668

Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.07. Found: C, 70.52; H, 8.04

9-*C*-Allyl-5,8-anhydro- 6,7,9-trideoxy-1,2-*O*-isopropylidene-L-*glycero*-β-L- ido furanose (76):



76

A solution of **75** (0.2g, 0.539 mmol) in anhydrous THF (10 mL) was added to a solution of sodium (37mg, 1.6 mmol) in napthalene (207 mg, 1.618 mmol) maintained at –20 ºC. The reaction mixture was stirred for 1 h and quenched with saturated NH_4Cl solution. Then the

reaction mixture was diluted with ethyl acetate and washed with water, brine, dried (Na_2SO_4) and evaporated. The residue was purified on silica gel by using 20% EtOAc/Petether to obtain **51** (103 mg, 67%).

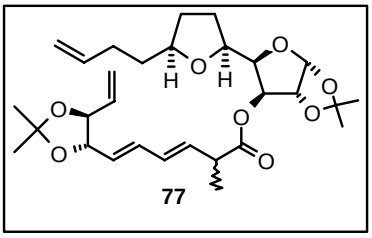
$[\alpha]_D$: – 8.2 (*c* 2, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.91 (d, 1H, *J* = 3.55 Hz), 5.79 (m,1H), 5.00 (m, 1H, *J* =1.7 HZ), 4.93 (m, 1H), 4.83 (brs, 1H), 4.47 (d, 1H, *J* = 2.5 Hz), 4.34 (m, 1H), 4.23 (m, 1H), 4.05 (m, 1H), 4.97 (m, 1H), 2.8 (m, 3H), 1.89 (m, 1H), 1.77-1.52 (m, 4H),1.46 (s, 3H), 1.30 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 138.2, 114.7, 111.4, 104.8, 85.5, 81.0, 79.7, 78.2, 77.0 34.3, 30.5, 30.4, 29.1, 26.8, 26.2.

Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.35; H, 8.50. Found: C, 63.32; H, 8.47.

Diene compound (77):

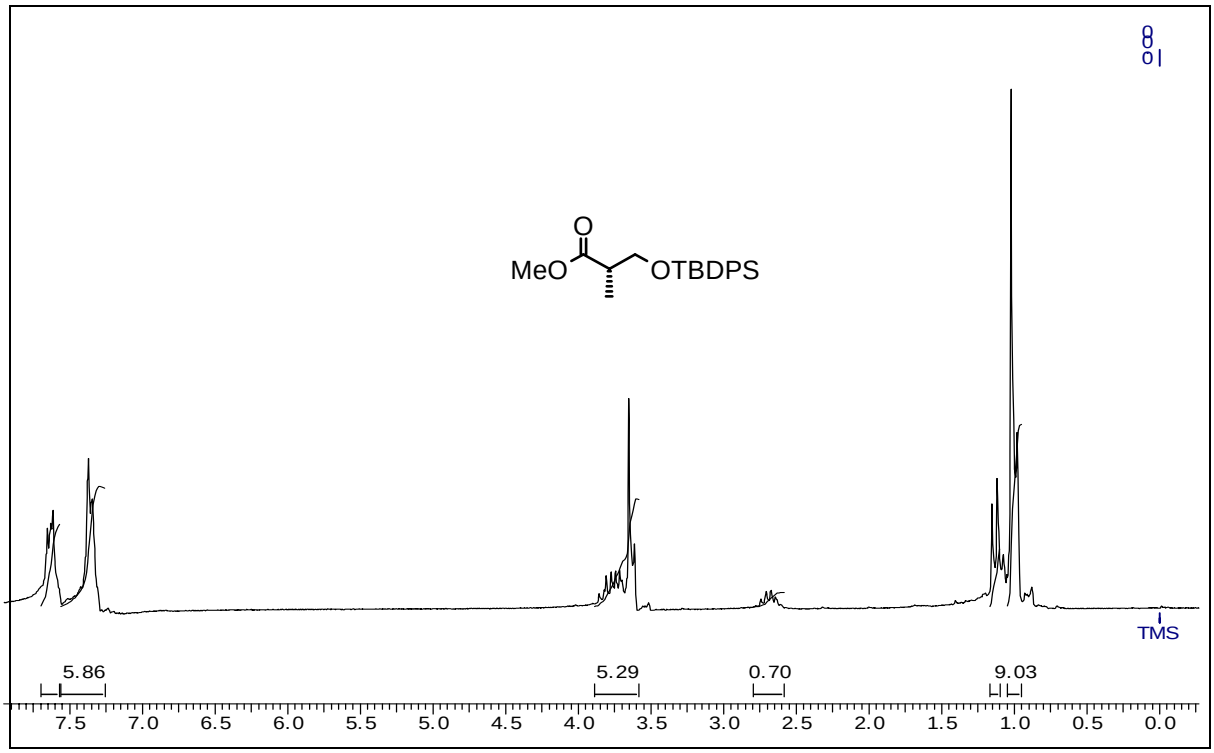


77

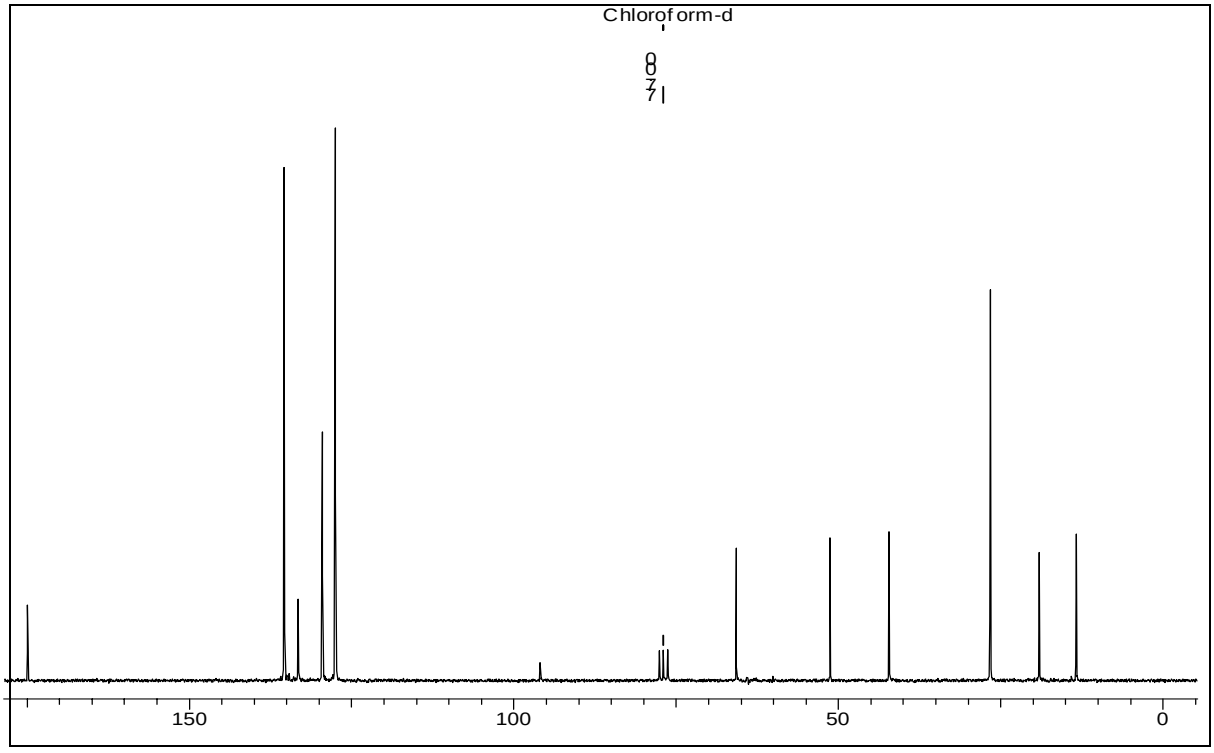
To a solution of acid (31mg, 0.12 mmol) in dry THF (2 mL), triethylamine (0.03 ml, 0.24 mmol) was added under N_2.The reaction mixture was cooled to 0 °C 2, 4, 6 –trichloro benzoyl chloride (0.03 mL, 0.18 mmol) was added slowly and allowed to stirrered for 1h. To it alcohol (26mg, 0.09 mmol) in THF and catalytic amount of DMAP (5 mg, 0.04 mmol) was added to this reaction mixture at 0 °C and stirring continued for four hours more and to this cold water was added, extracted with ethylacetate. The combine organic layer was thoroughly washed with saturated $NaHCO_3$ solution (5 mL) and (5mL).The aqueous phase was extracted with ethylacetate. The organic phase was washed with sat aq NH_4Cl, brine, dried over anahydrous Na_2SO_4, and concentrated.Purification of the crude product by flash column chromatography using 14% ethylacetate/Petether afforded **77** (24 mg, 52%) as a mixture of colourless oil.

Mass: EI-MS M/Z $[M+Na]^+$ = 541

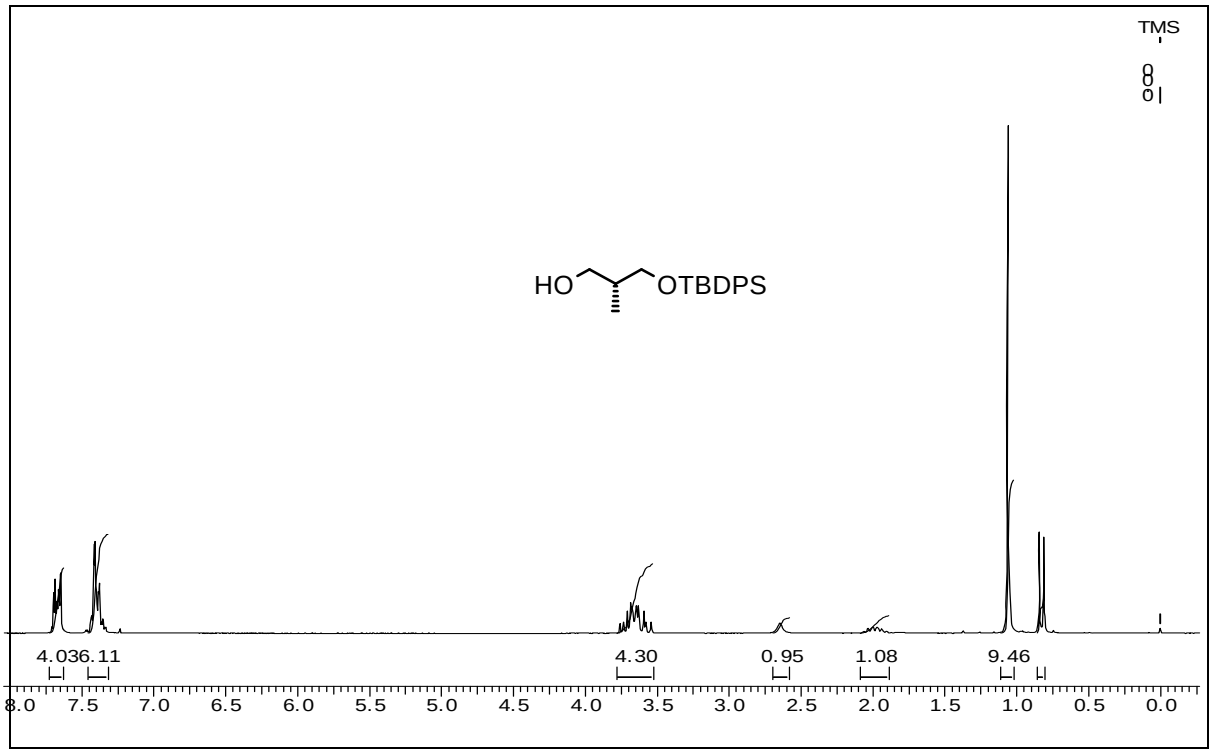
SPECTRA



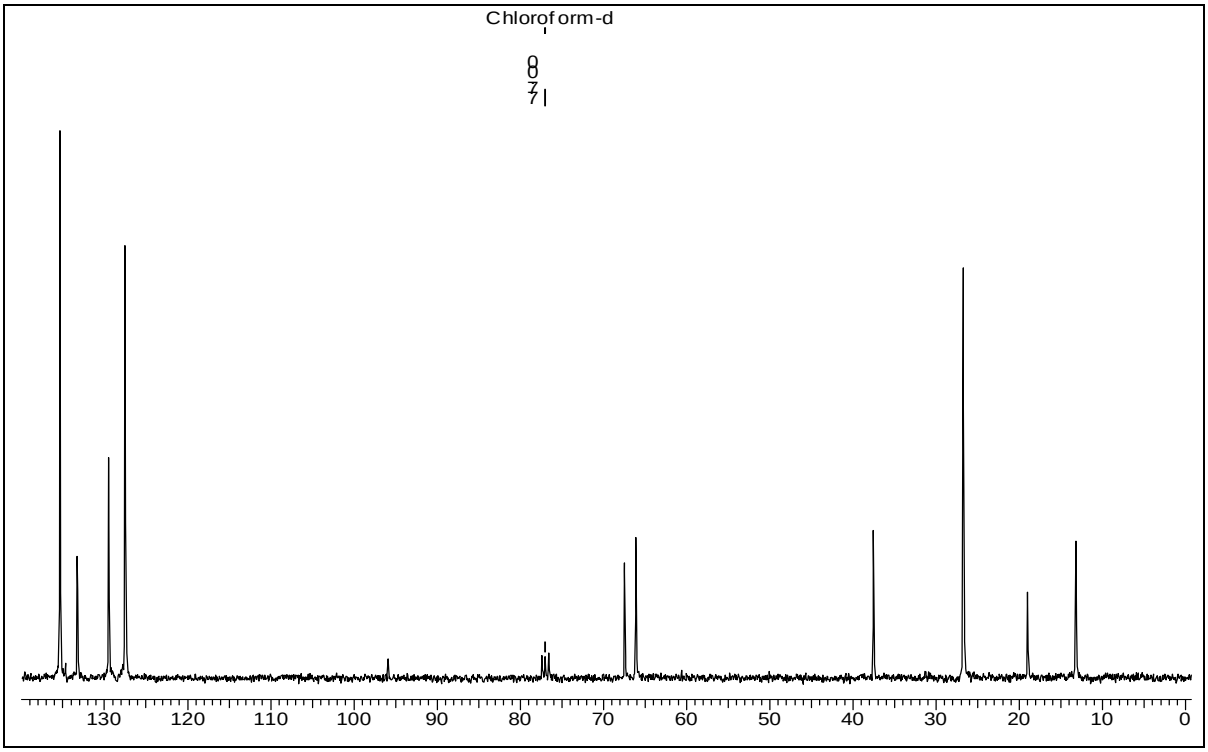
^{1}H NMR spectrum of compound 57 in $CDCl_3$



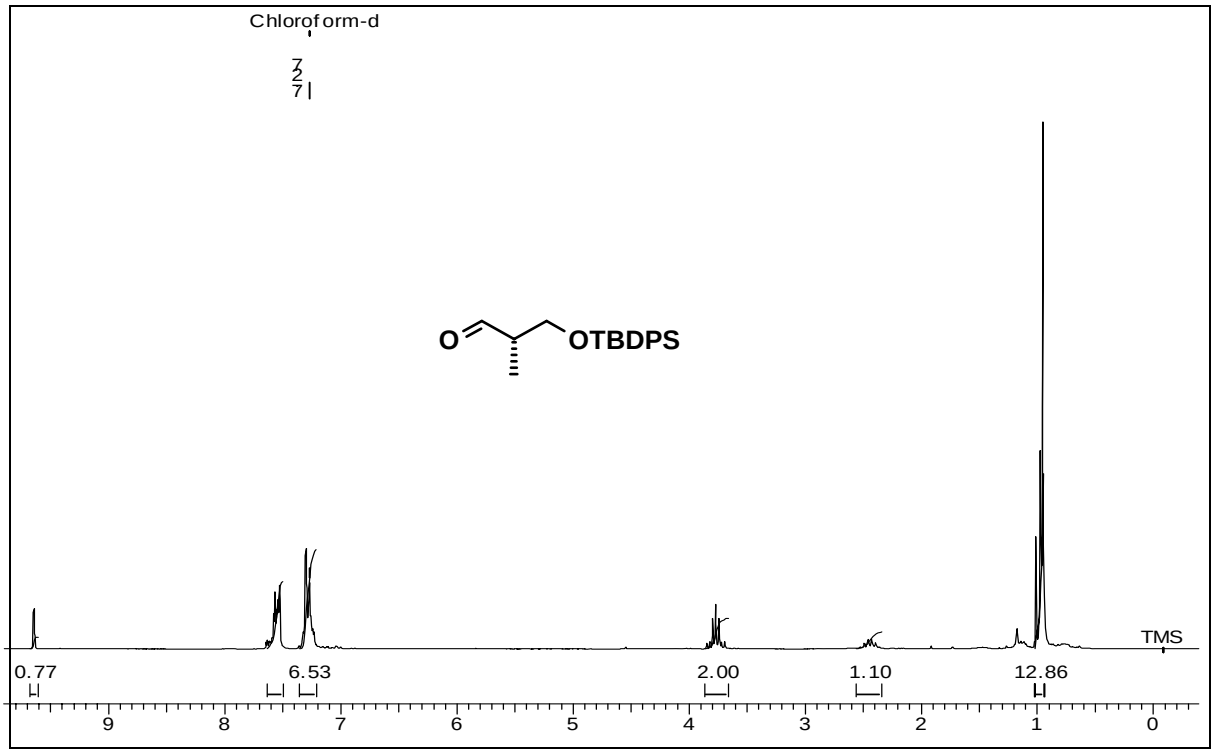
^{13}C NMR spectrum of compound 57 in $CDCl_3$



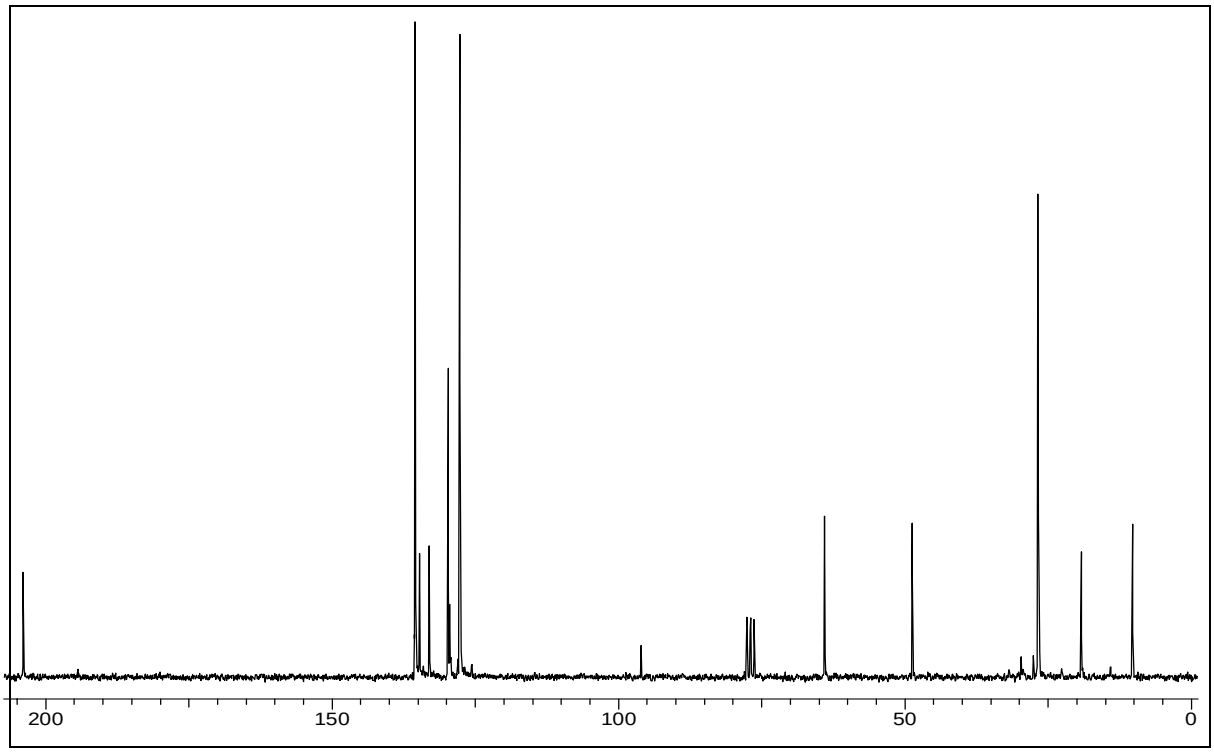
^{1}H NMR spectrum of compound 58 in $CDCl_3$



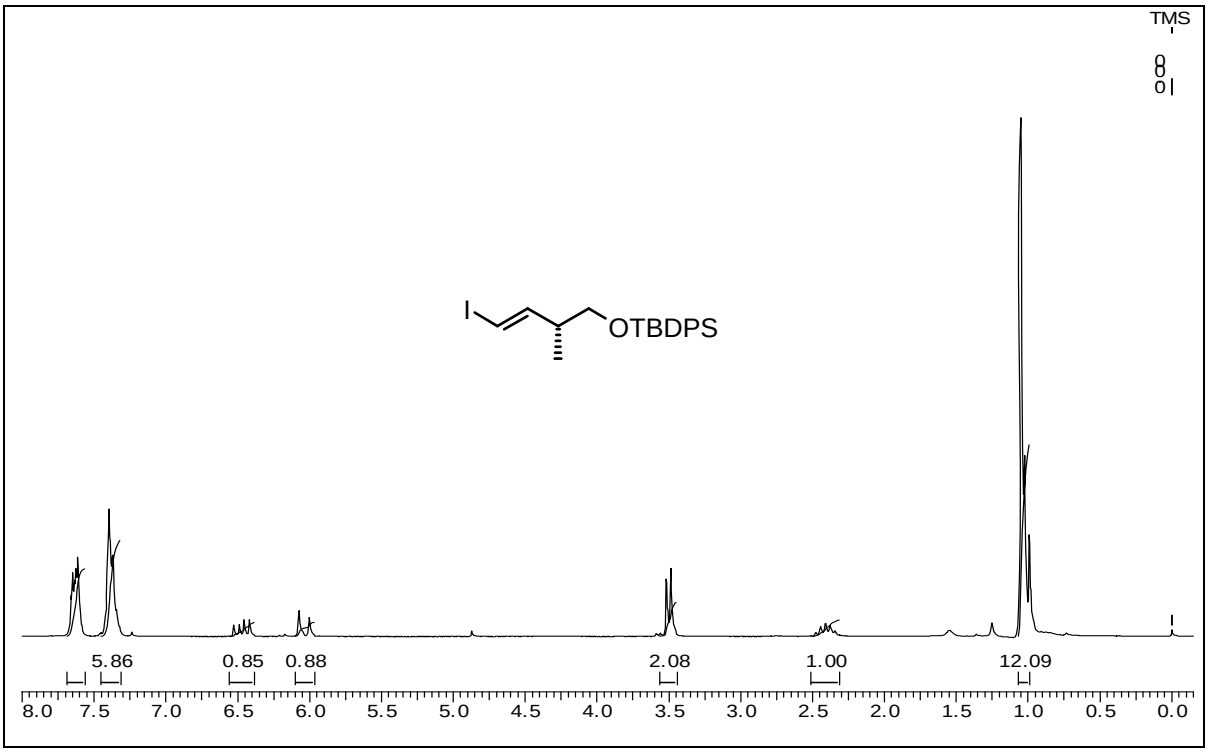
^{13}C NMR spectrum of compound 58 in $CDCl_3$



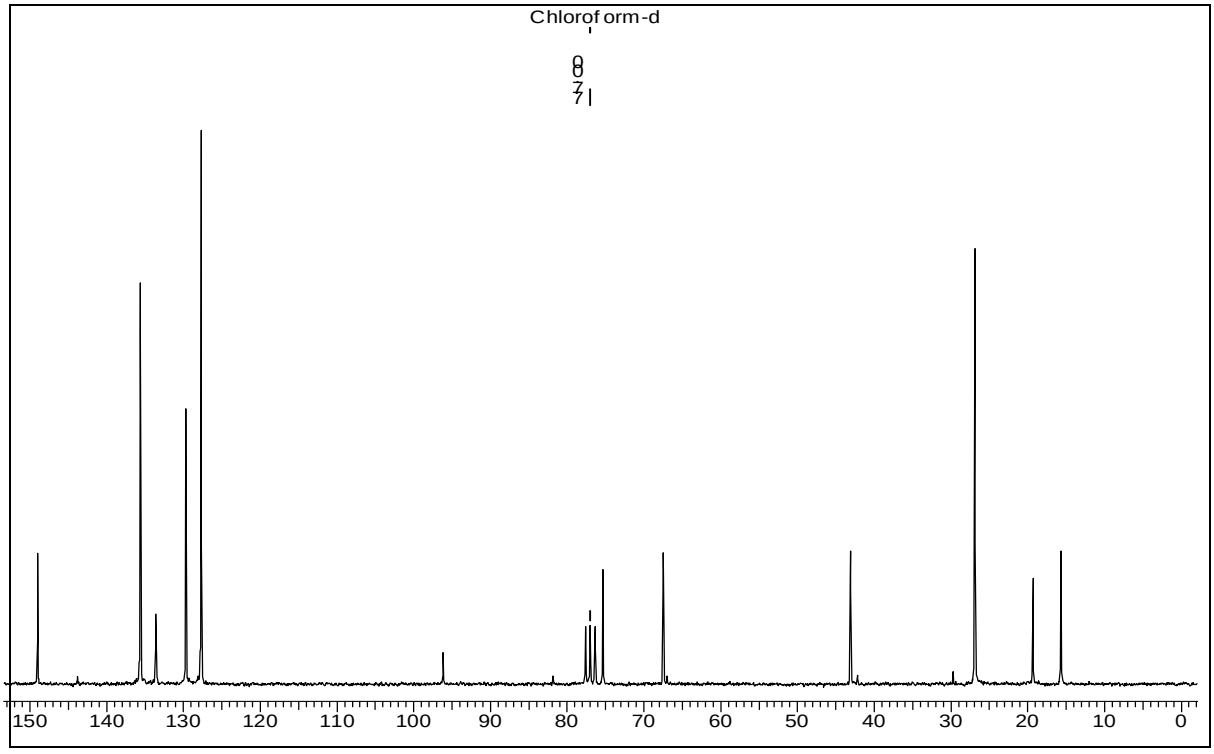
^{1}H NMR spectrum of compound 59 in $CDCl_3$



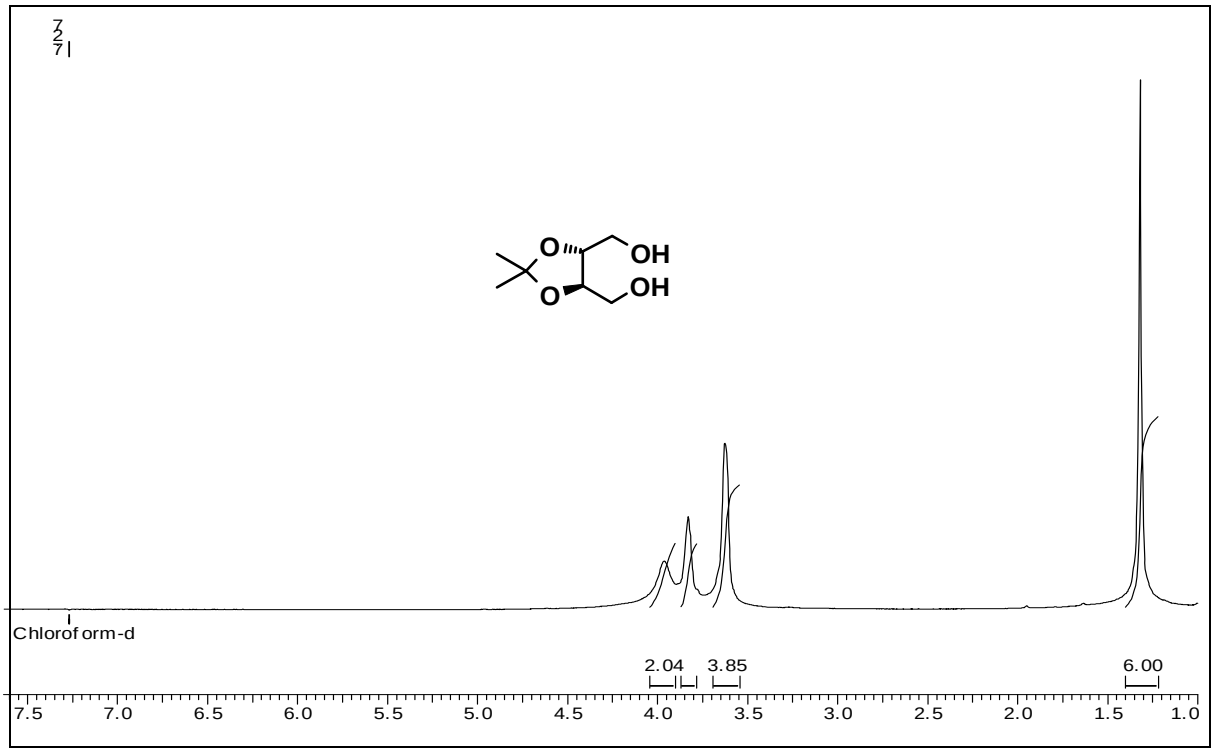
^{13}C NMR spectrum of compound 59 in $CDCl_3$



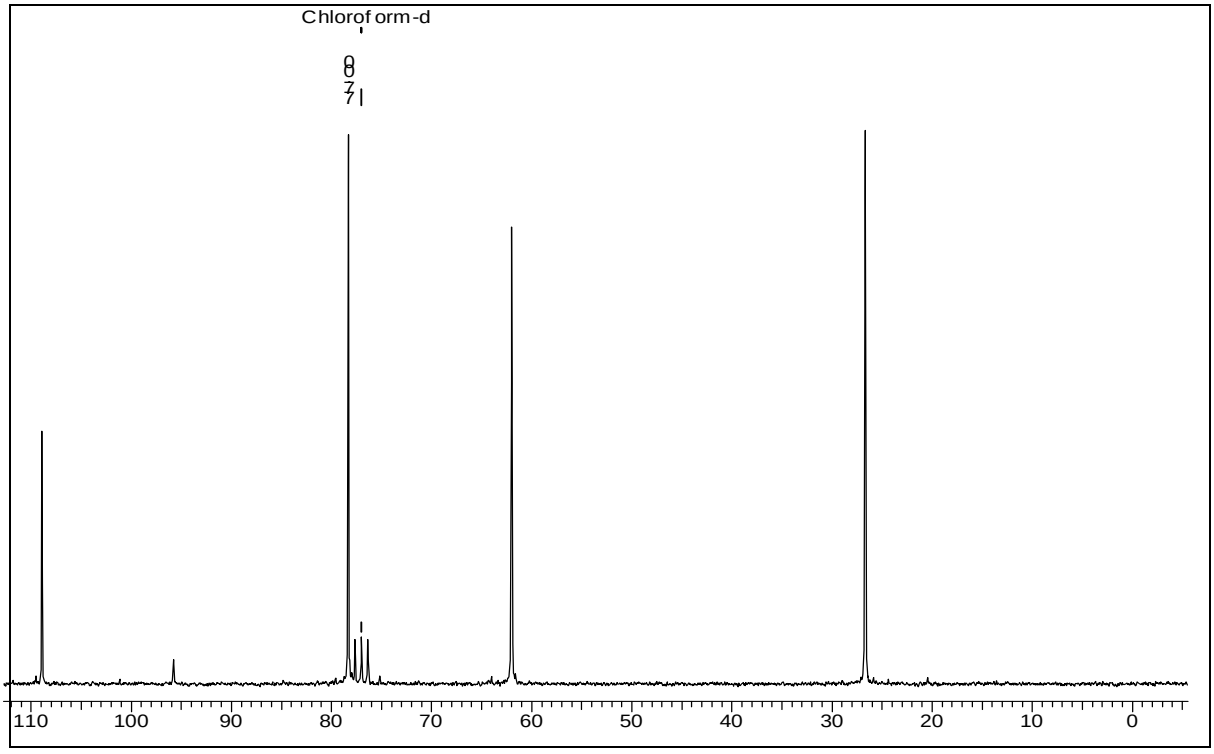
^{1}H NMR spectrum of compound 55 in $CDCl_3$



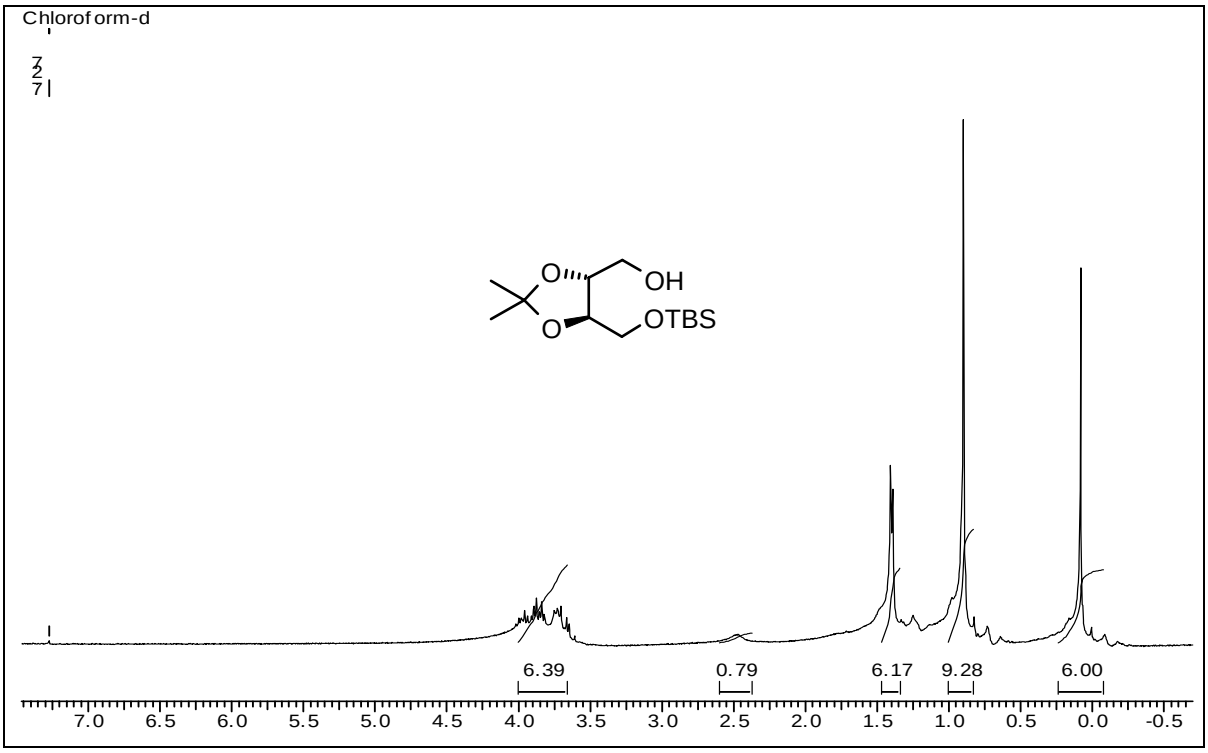
^{1}H NMR spectrum of compound 55 in $CDCl_3$



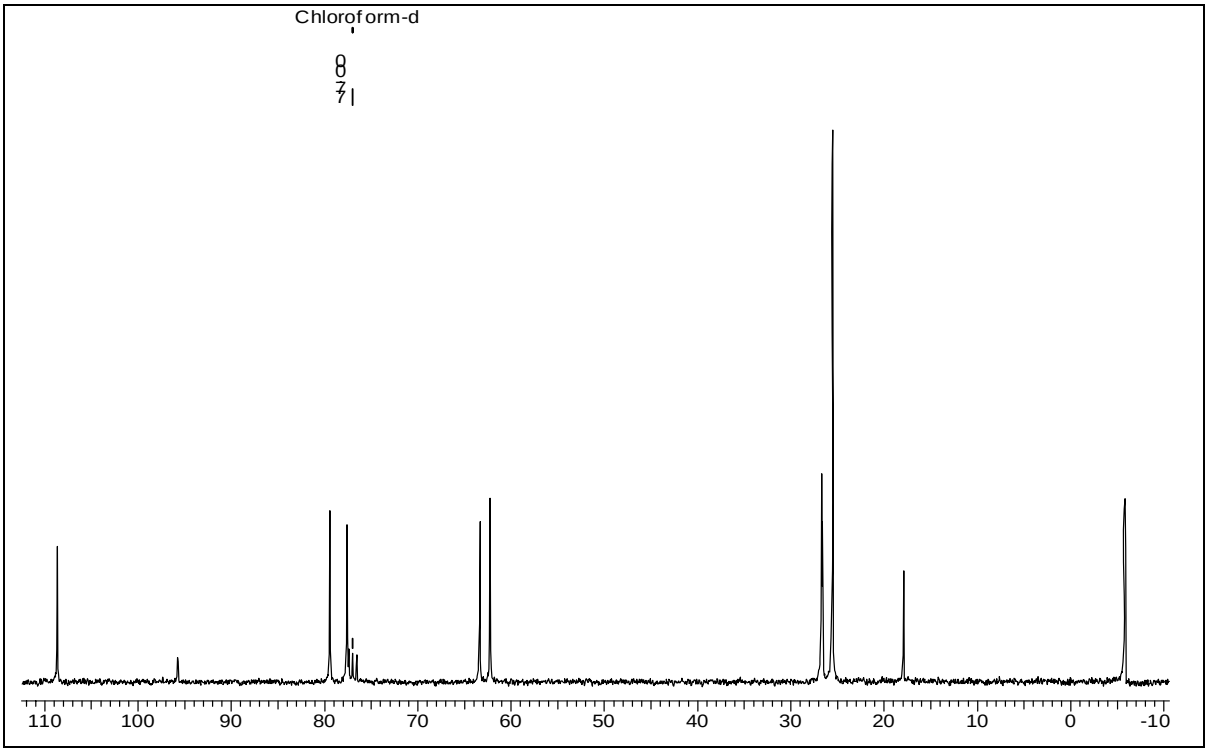
^{13}C NMR spectrum of compound 60 in $CDCl_3$



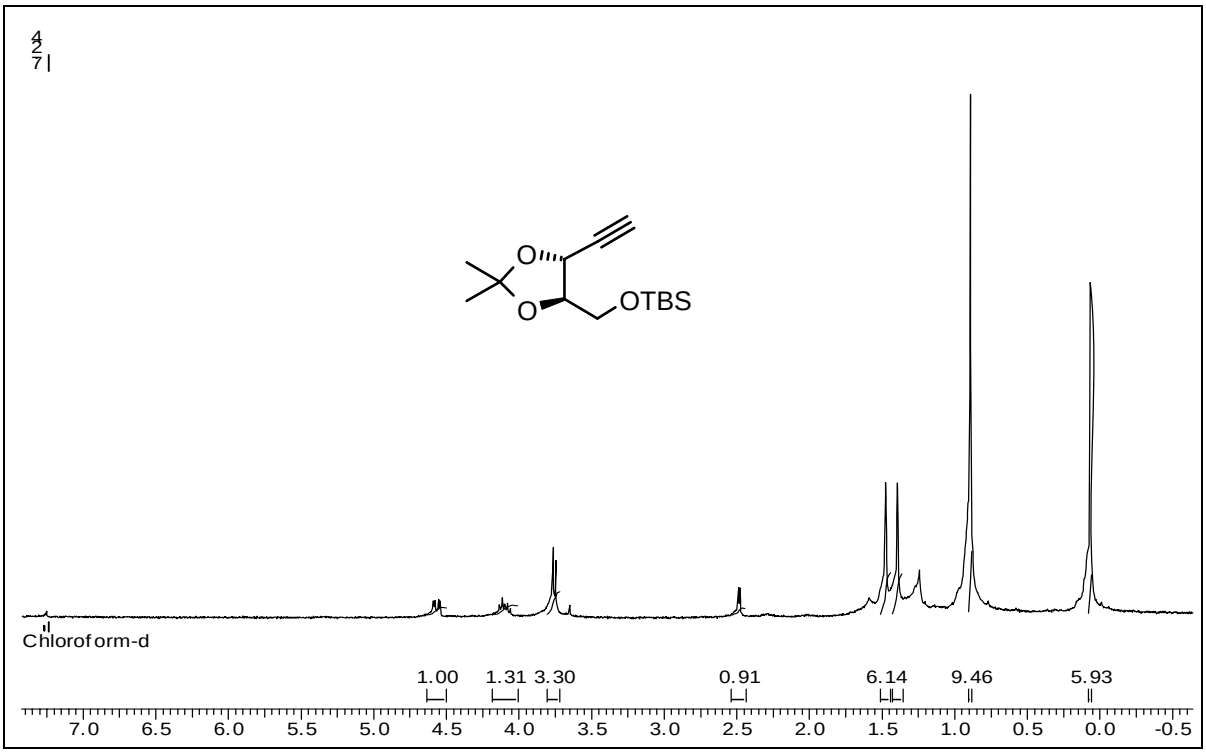
^{1}H NMR spectrum of compound 60 in $CDCl_3$



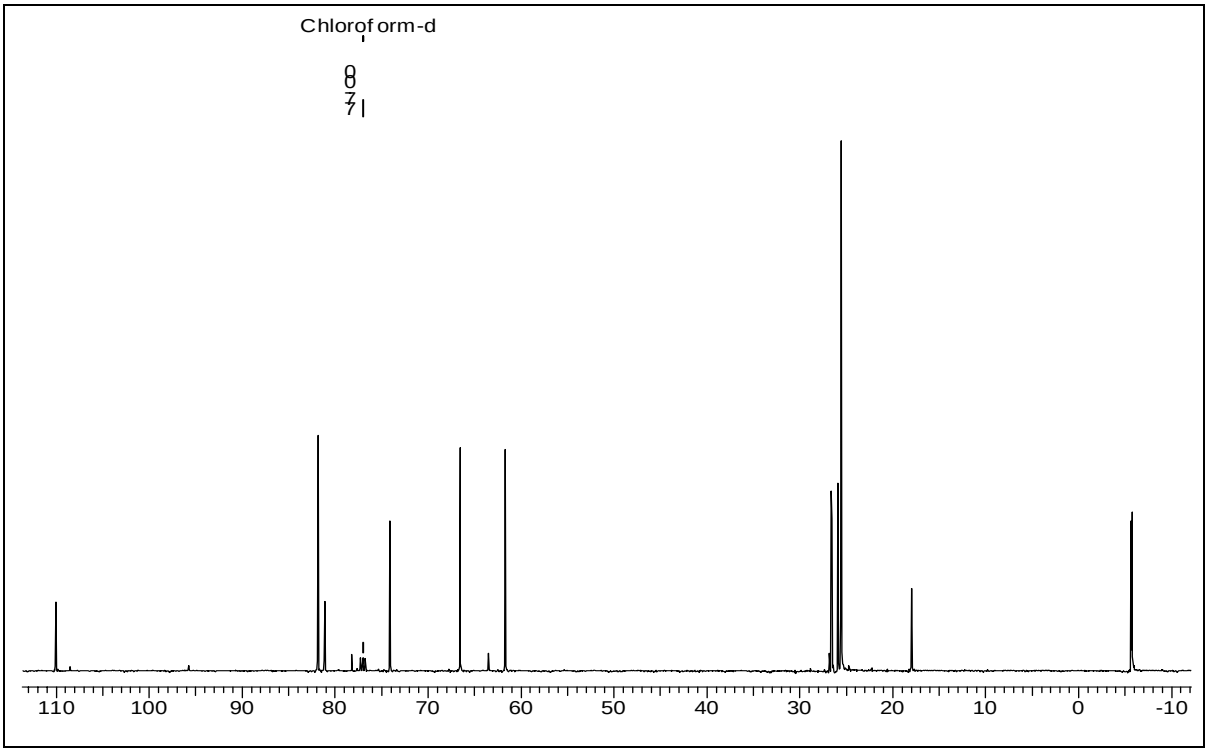
^{1}H NMR spectrum of compound 63 in $CDCl_3$



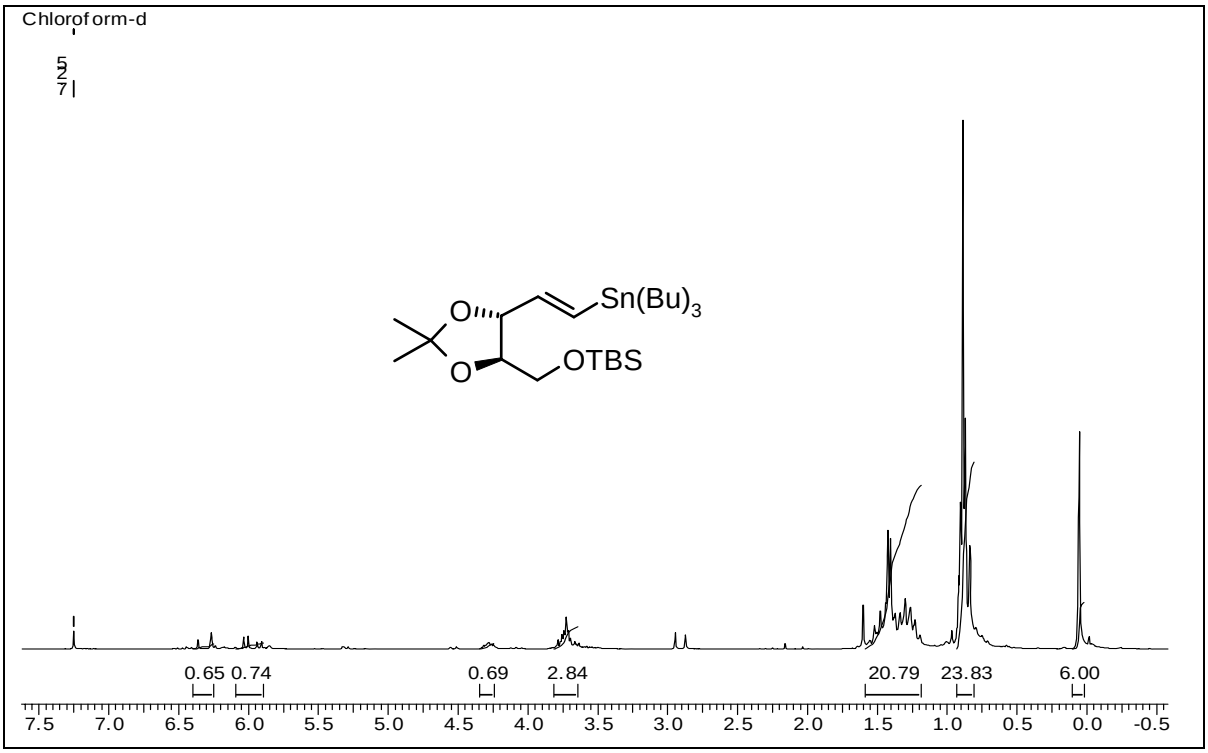
^{13}C NMR spectrum of compound 63 in $CDCl_3$



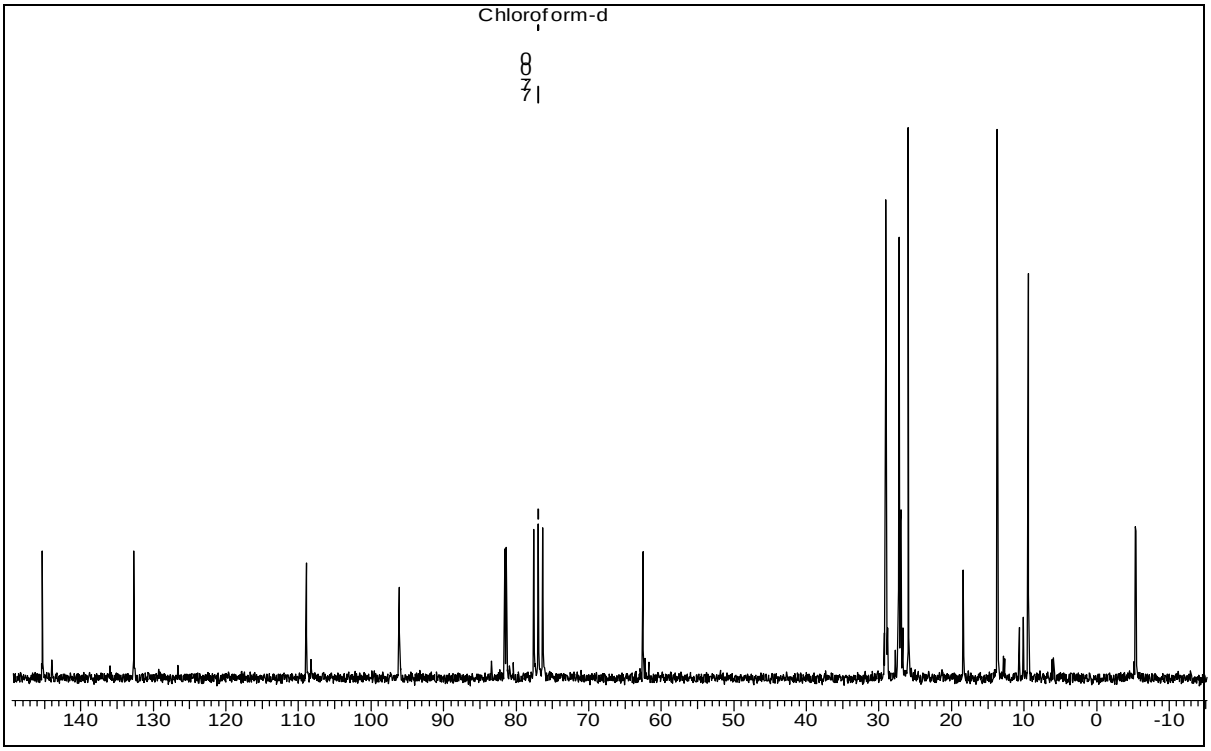
^{1}H NMR spectrum of compound 65 in $CDCl_3$



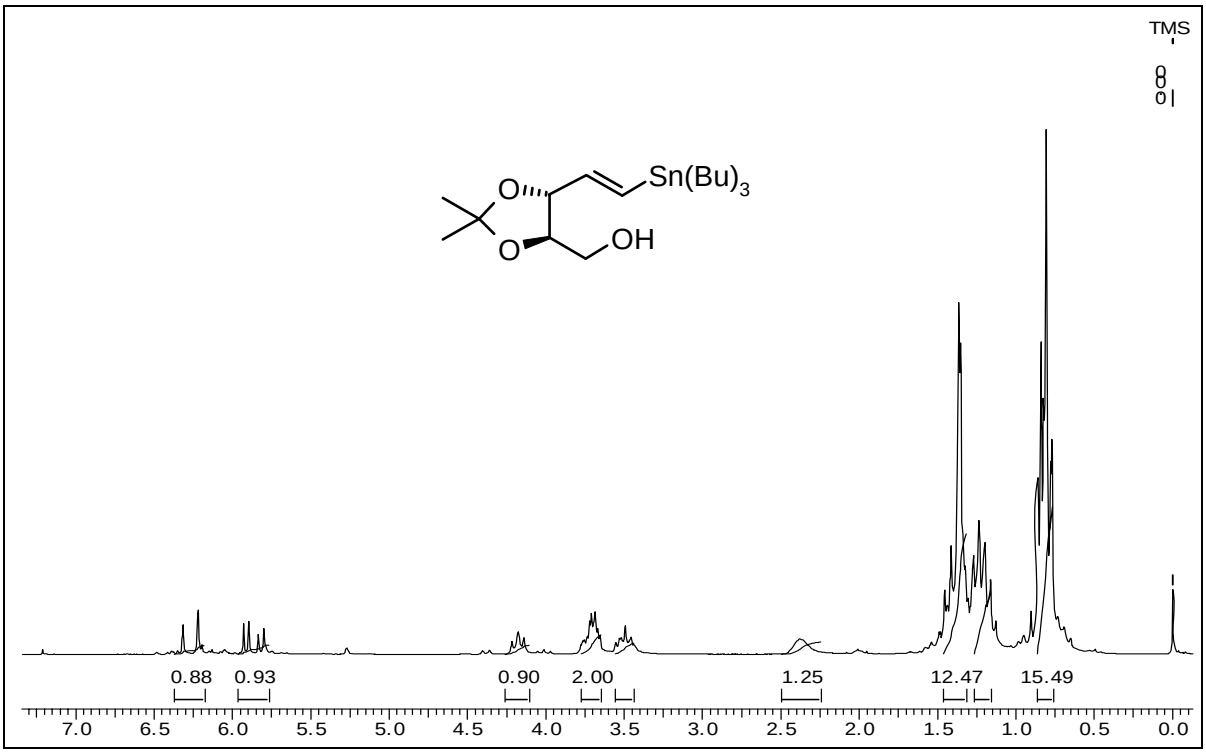
^{13}C NMR spectrum of compound 65 in $CDCl_3$



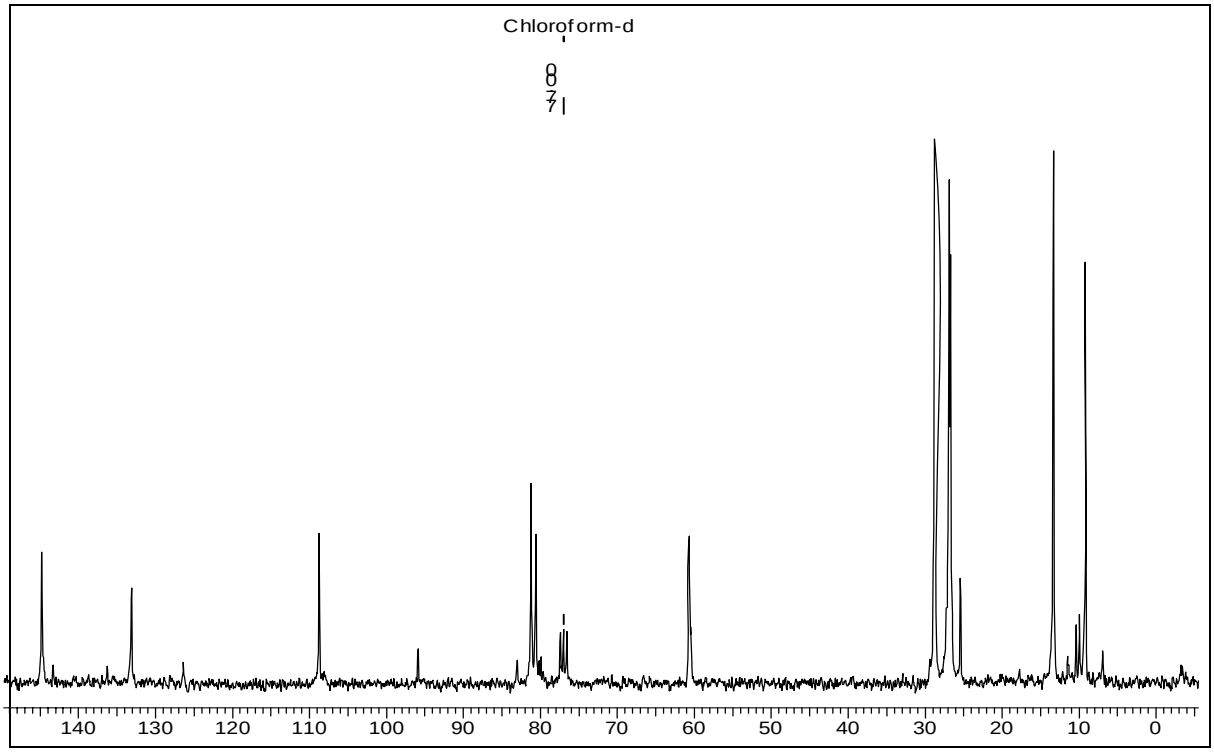
^{1}H NMR spectrum of compound 66 in $CDCl_3$



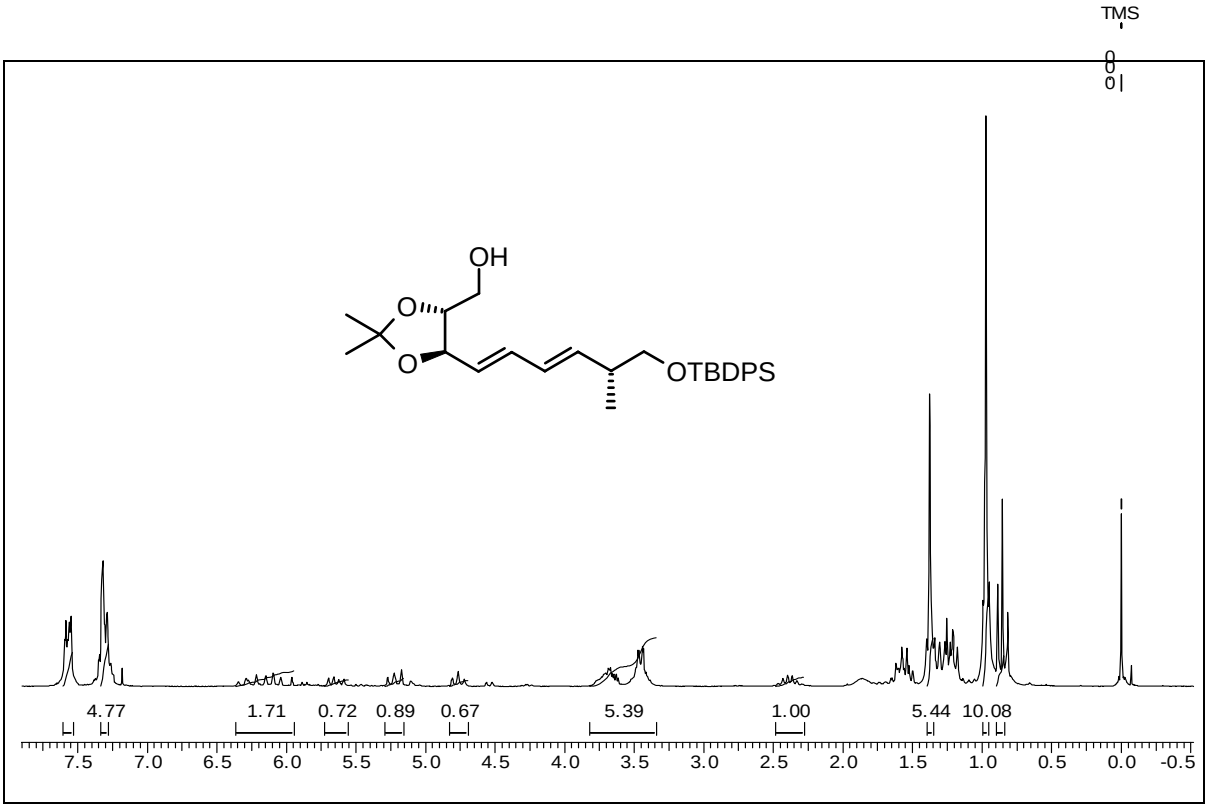
^{13}C NMR spectrum of compound 66 in $CDCl_3$



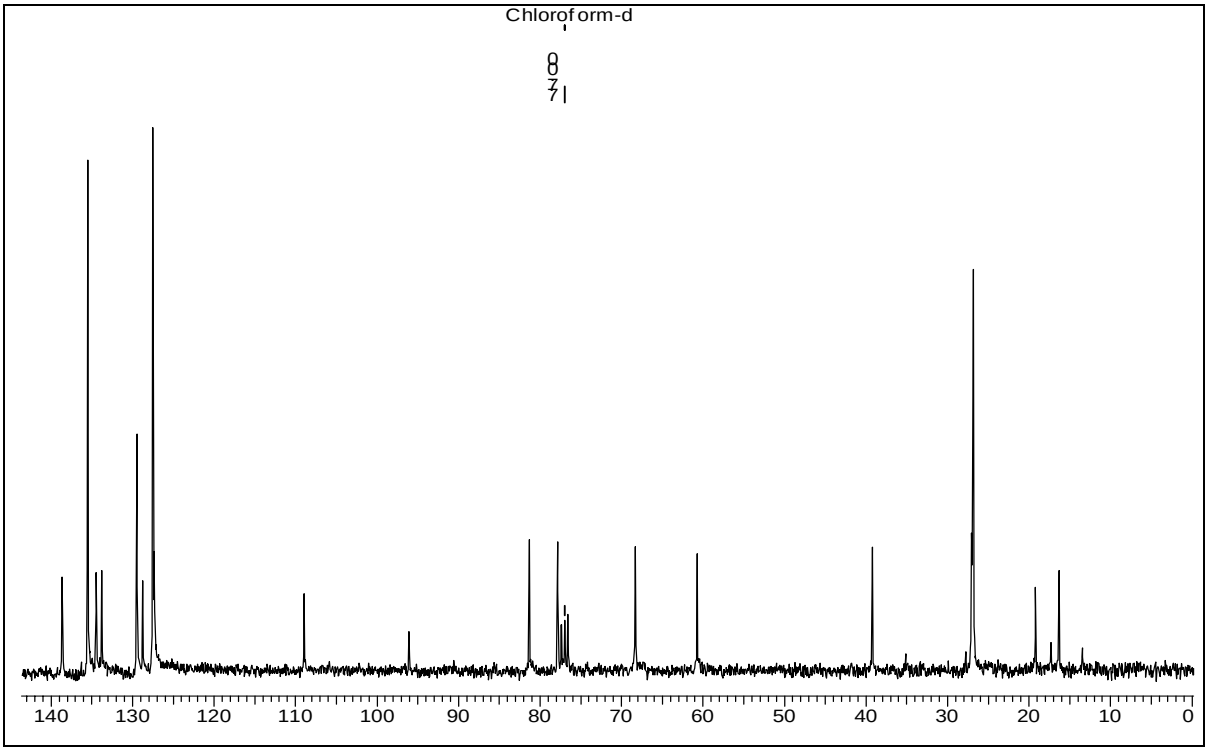
^{1}H NMR spectrum of compound 54 in $CDCl_3$



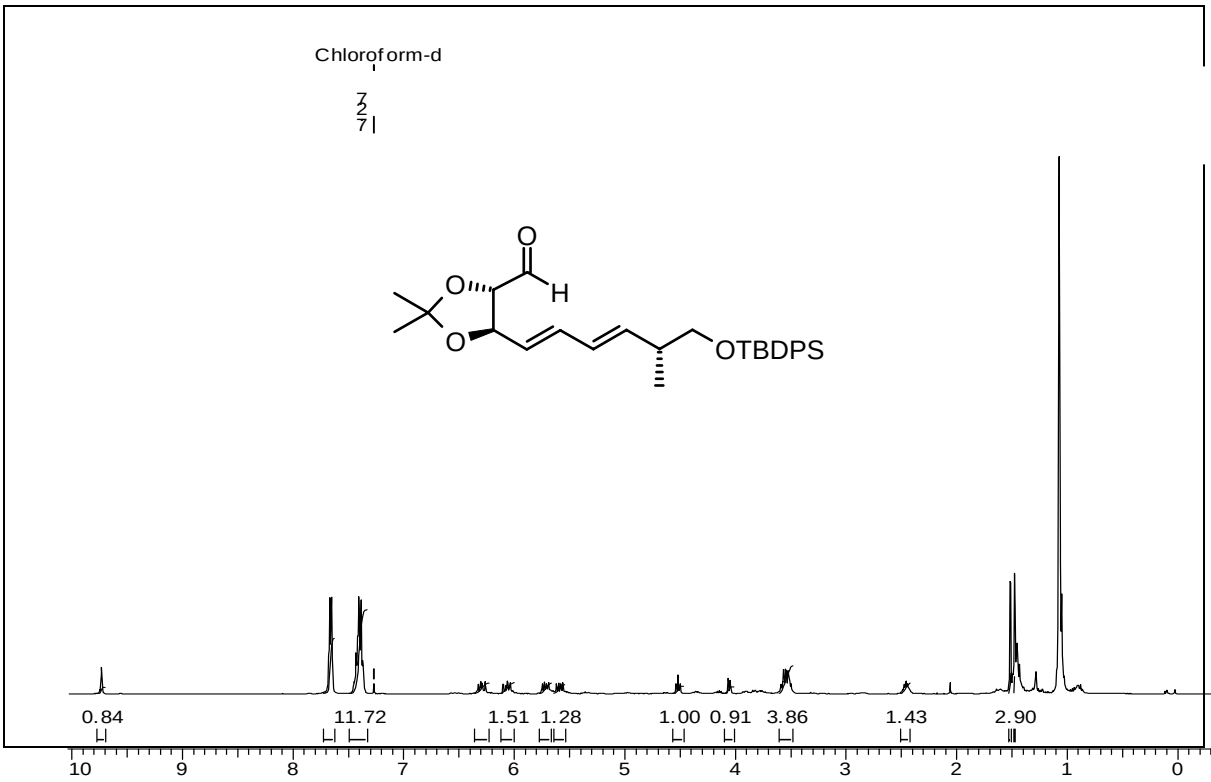
^{13}C NMR spectrum of compound 54 in $CDCl_3$



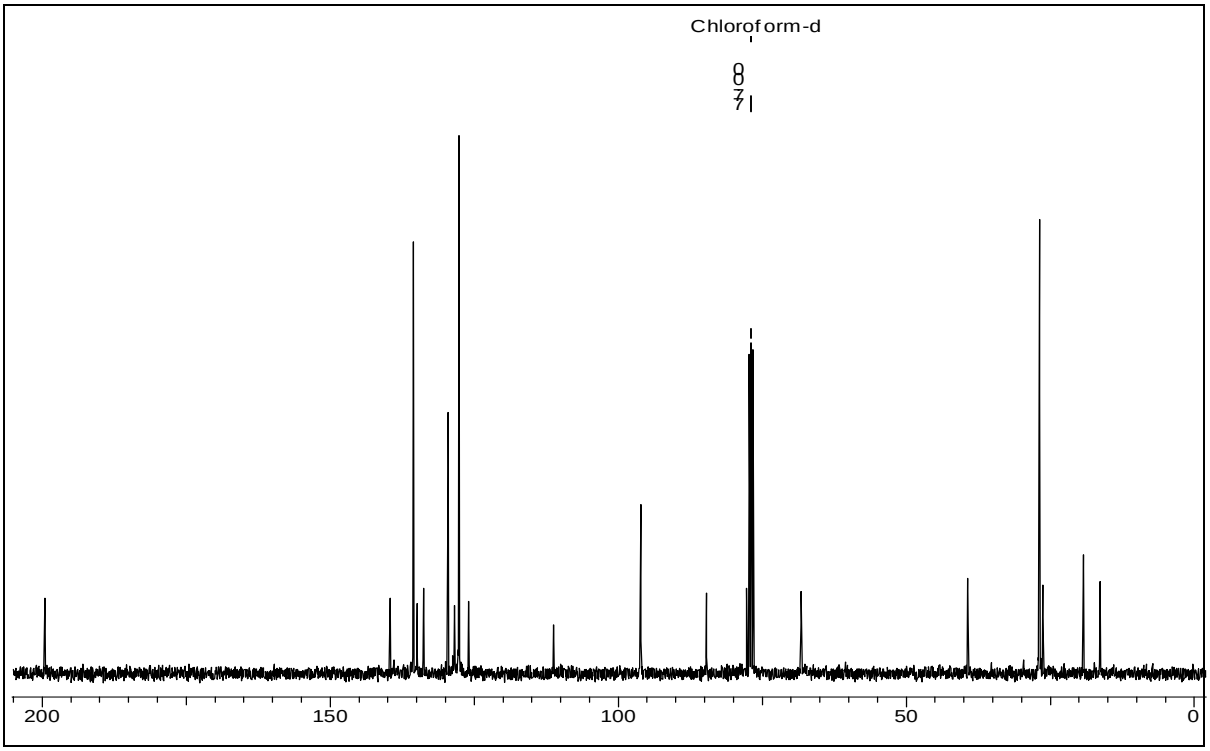
^{1}H NMR spectrum of compound 67 in $CDCl_3$



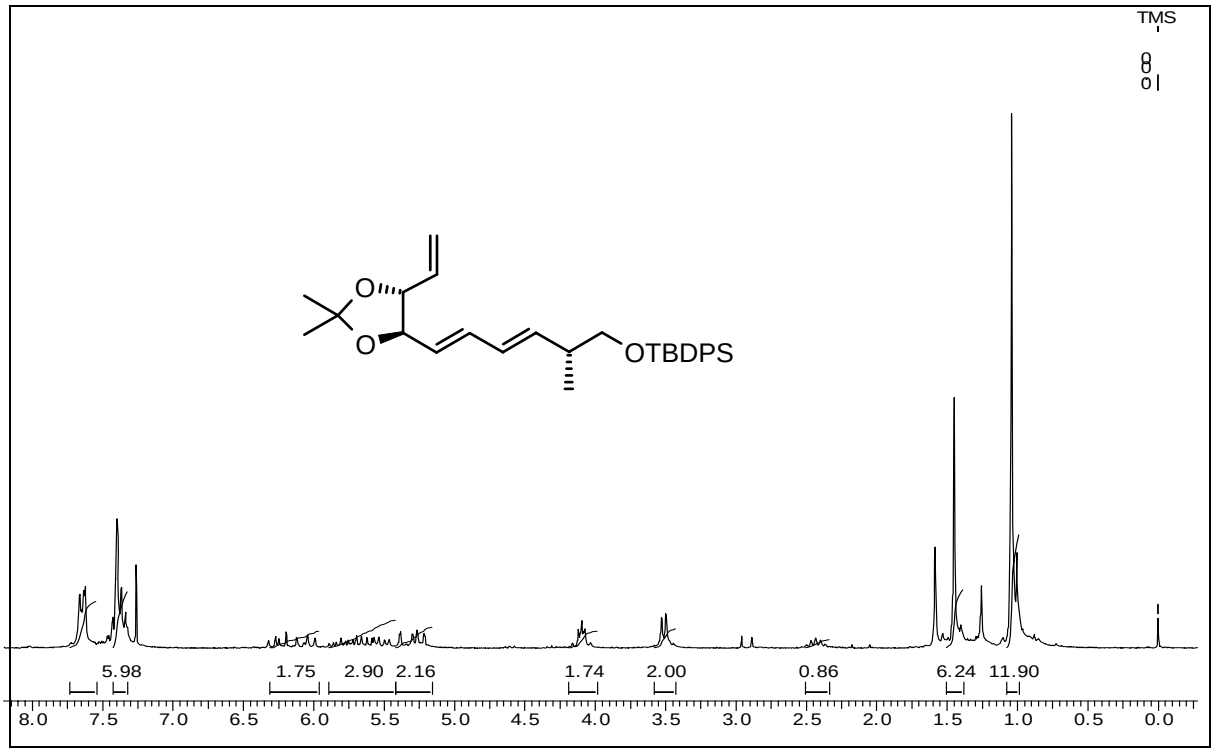
^{13}C NMR spectrum of compound 112 in $CDCl_3$



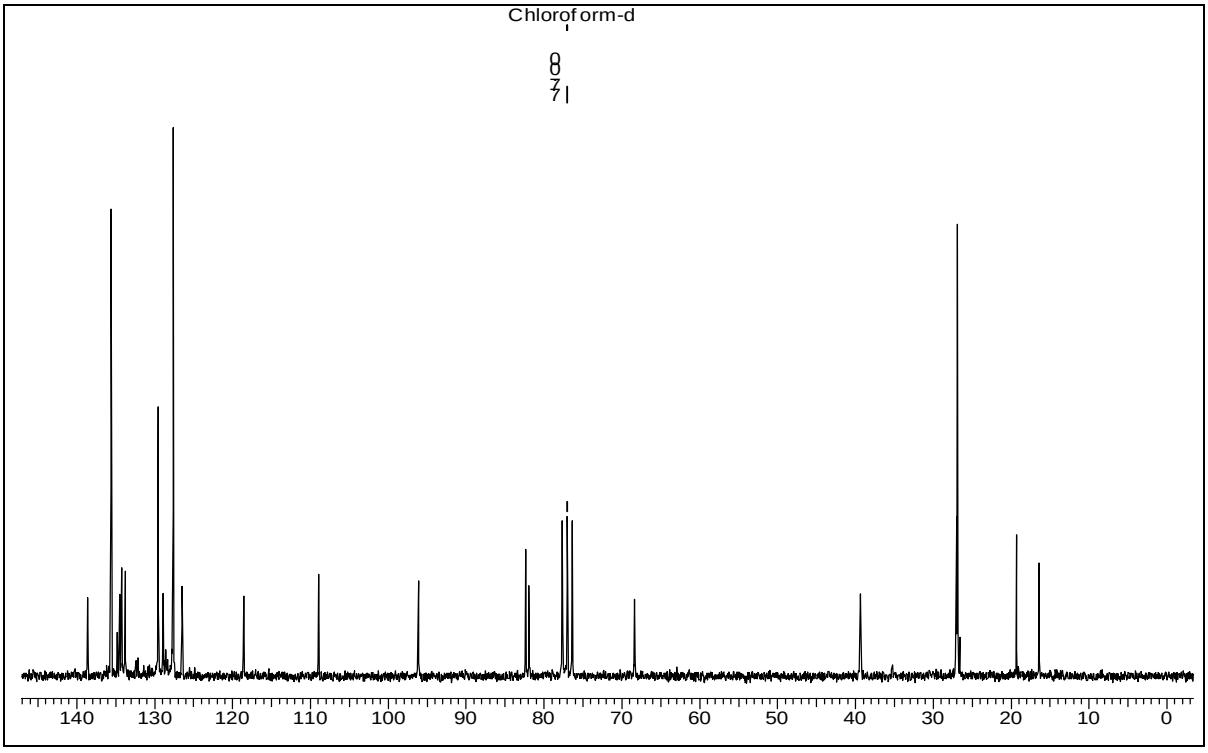
^{1}H NMR spectrum of compound 70 in $CDCl_3$



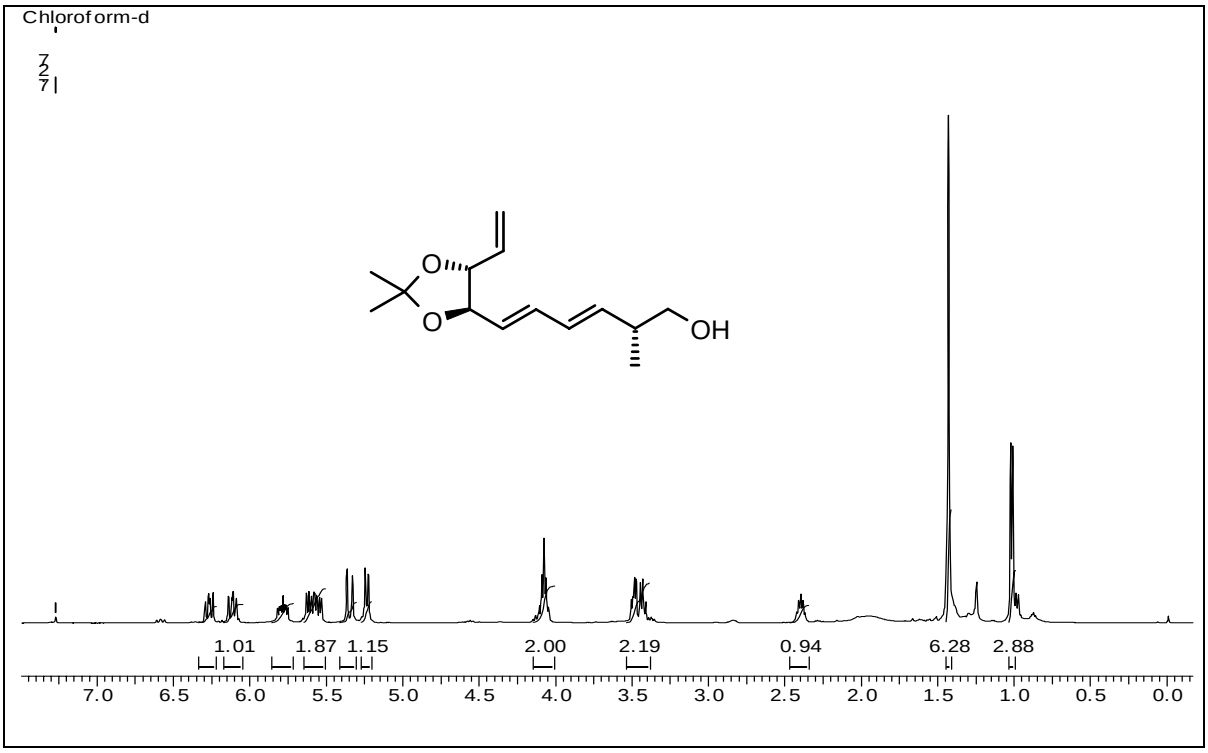
^{13}C NMR spectrum of compound 70 in $CDCl_3$



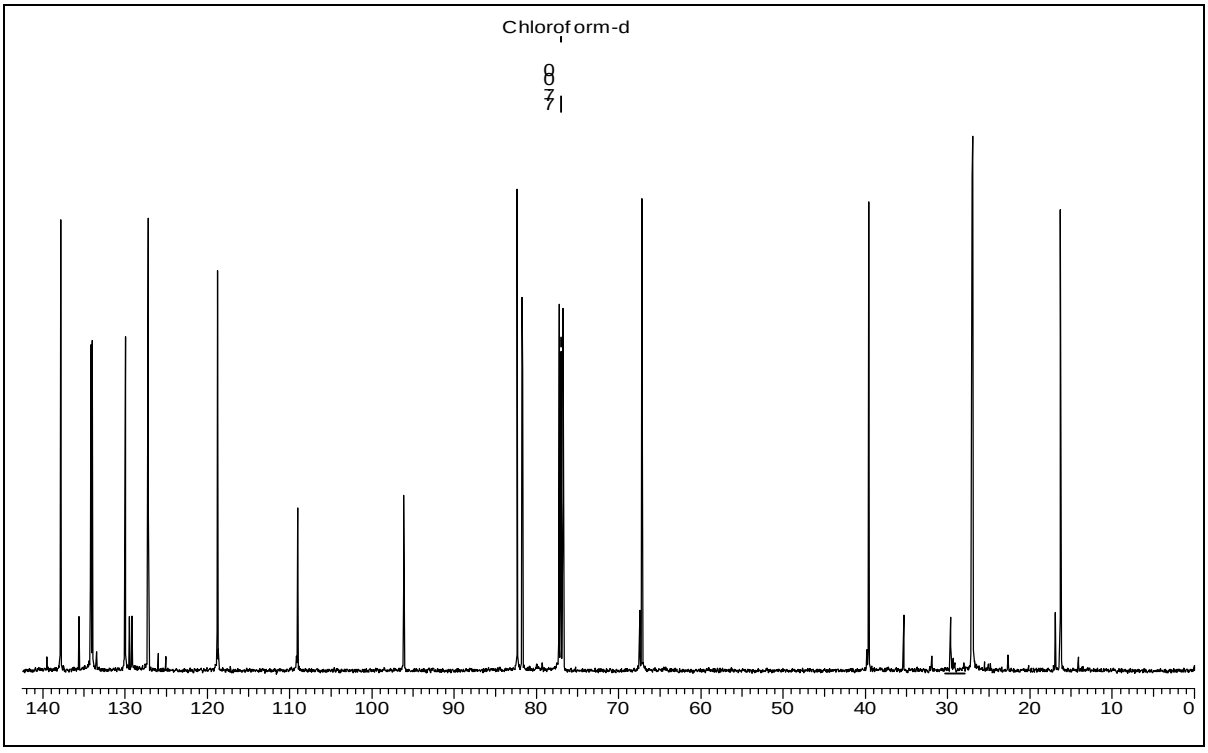
^{1}H NMR spectrum of compound 71 in $CDCl_3$



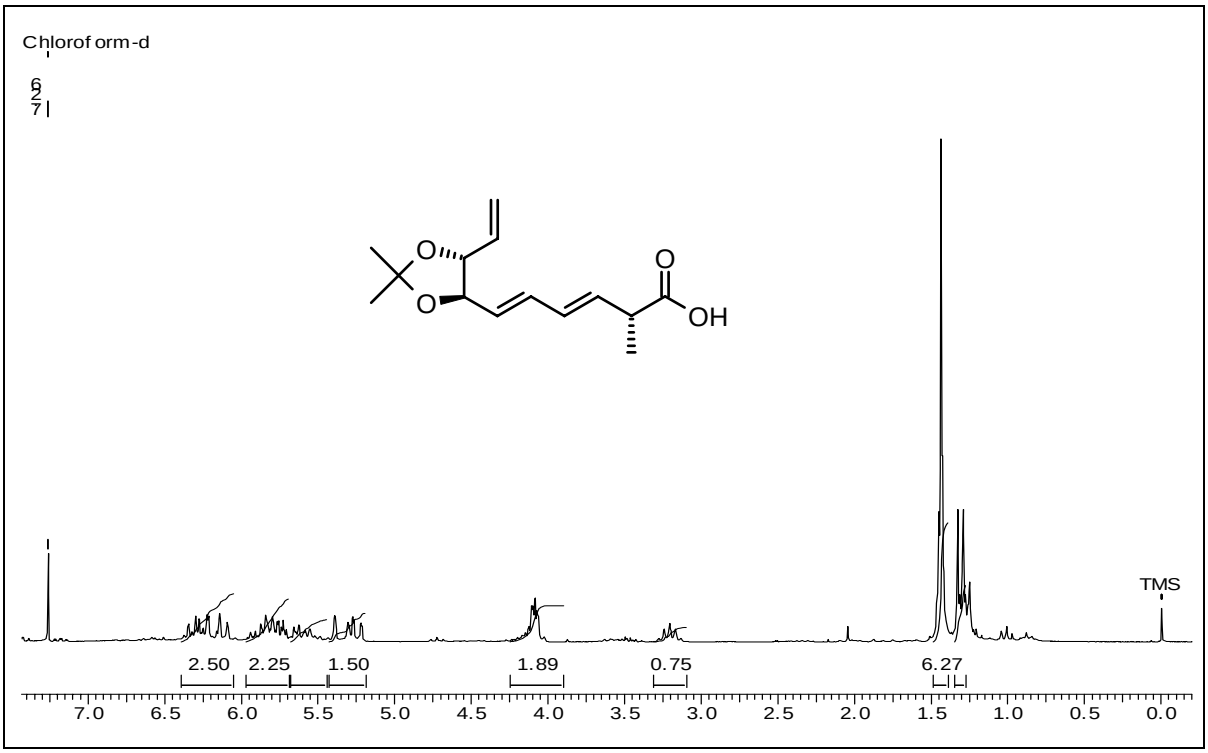
^{13}C NMR spectrum of compound 71 in $CDCl_3$



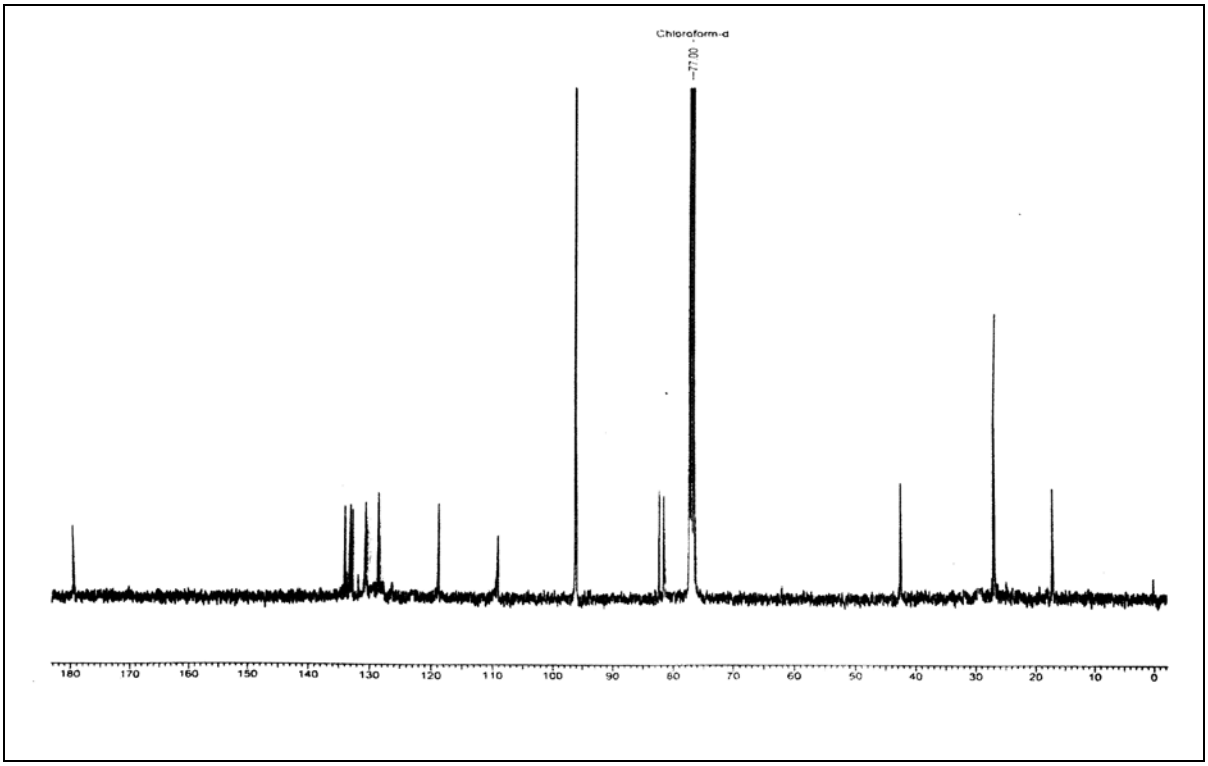
^{1}H NMR spectrum of compound 72 in $CDCl_3$



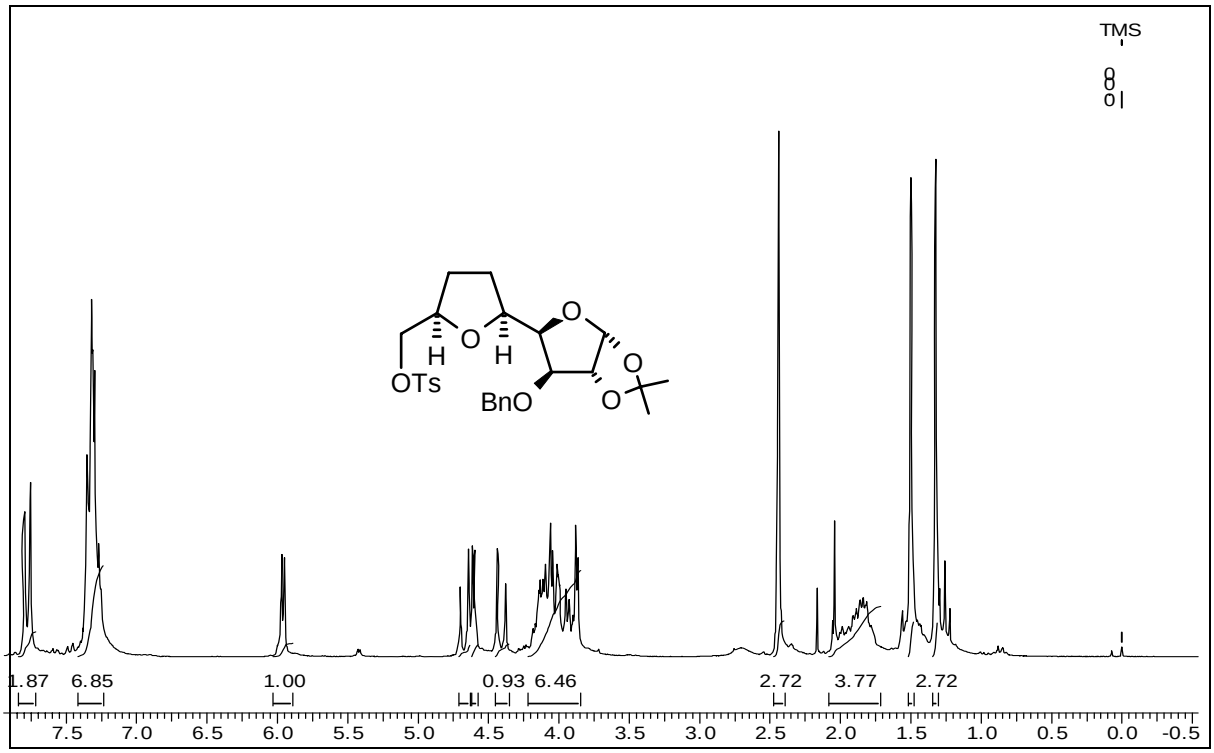
^{13}C NMR spectrum of compound 72 in $CDCl_3$



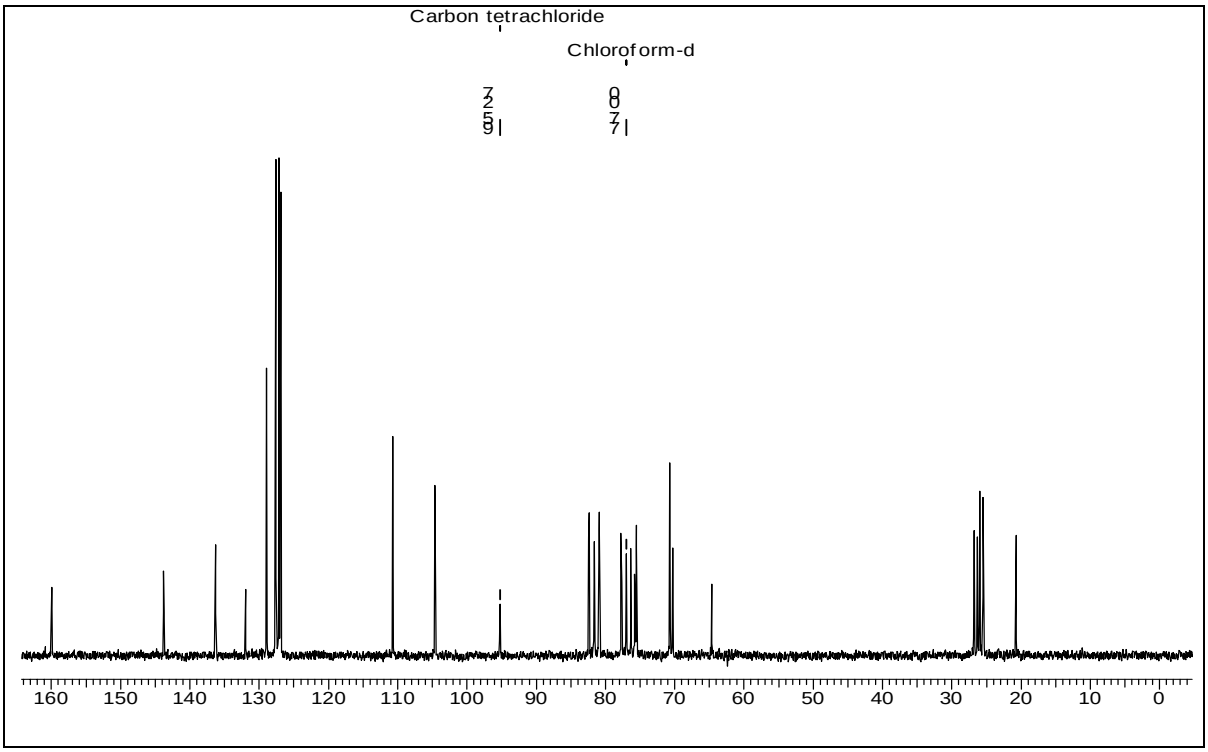
^{1}H NMR spectrum of compound 52 in $CDCl_3$



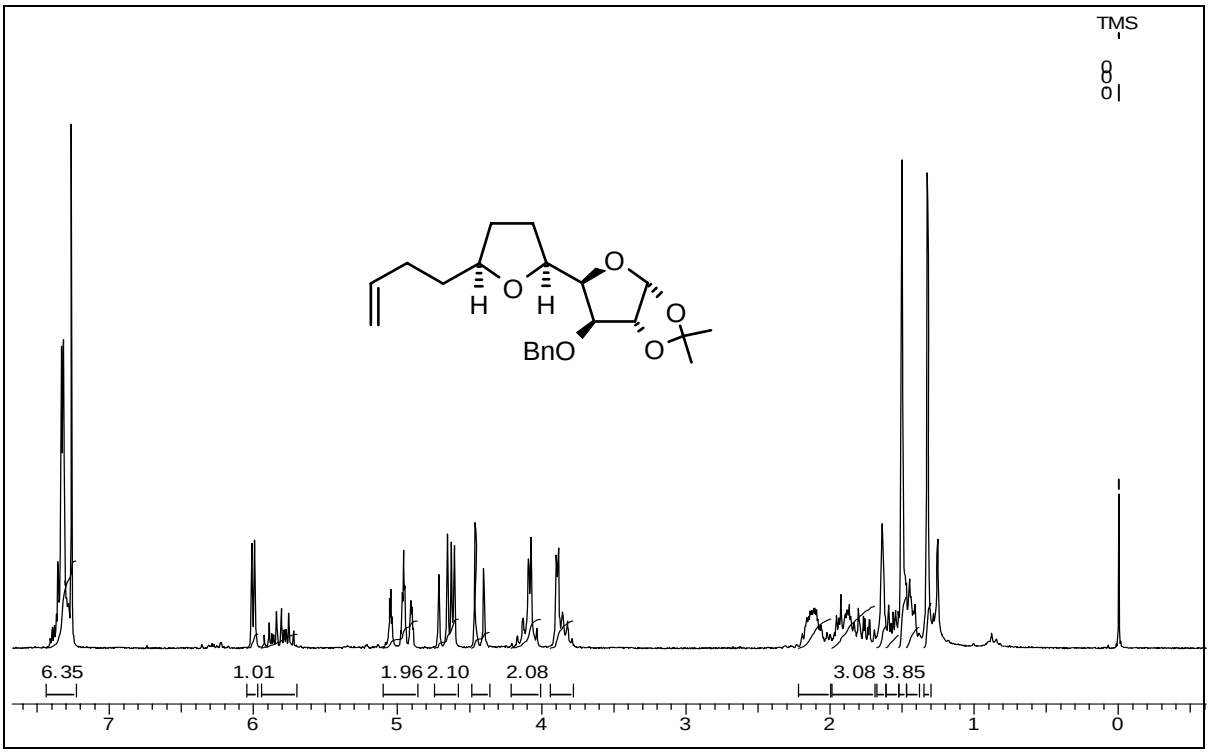
^{13}C NMR spectrum of compound 52 in $CDCl_3$



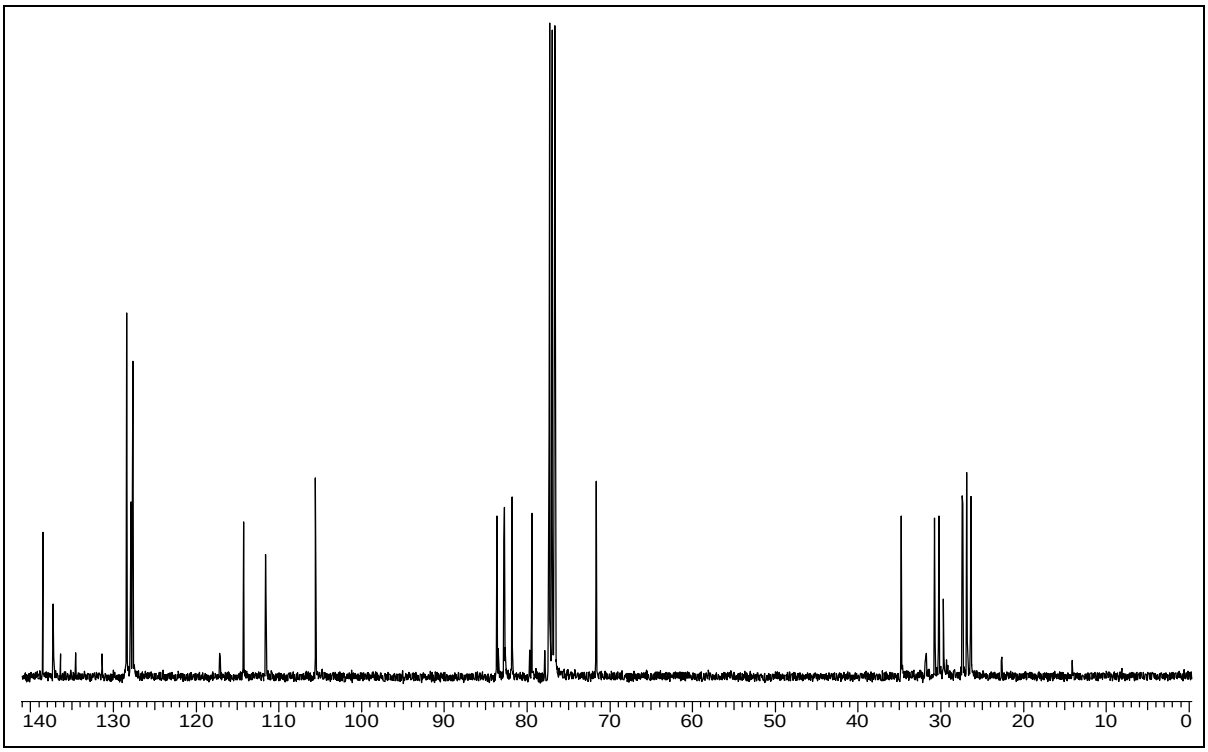
^{1}H NMR spectrum of compound 74 in $CDCl_3$



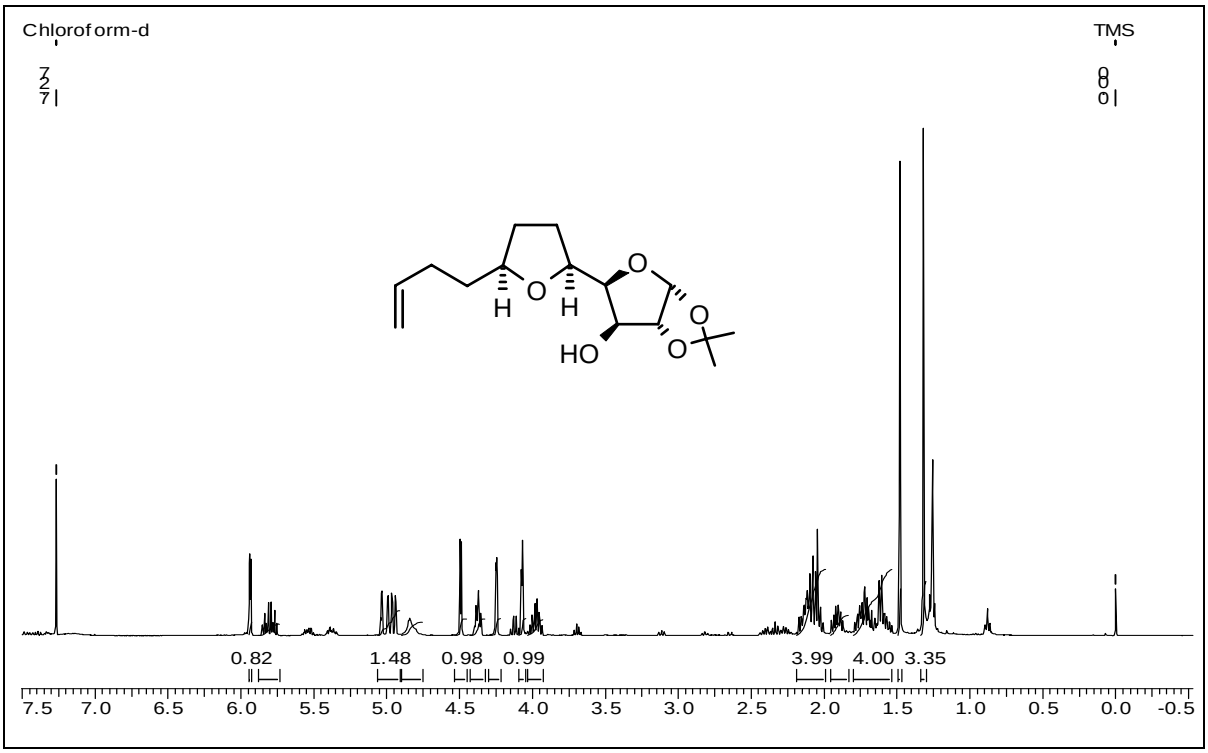
^{13}C NMR spectrum of compound 74 in $CDCl_3$



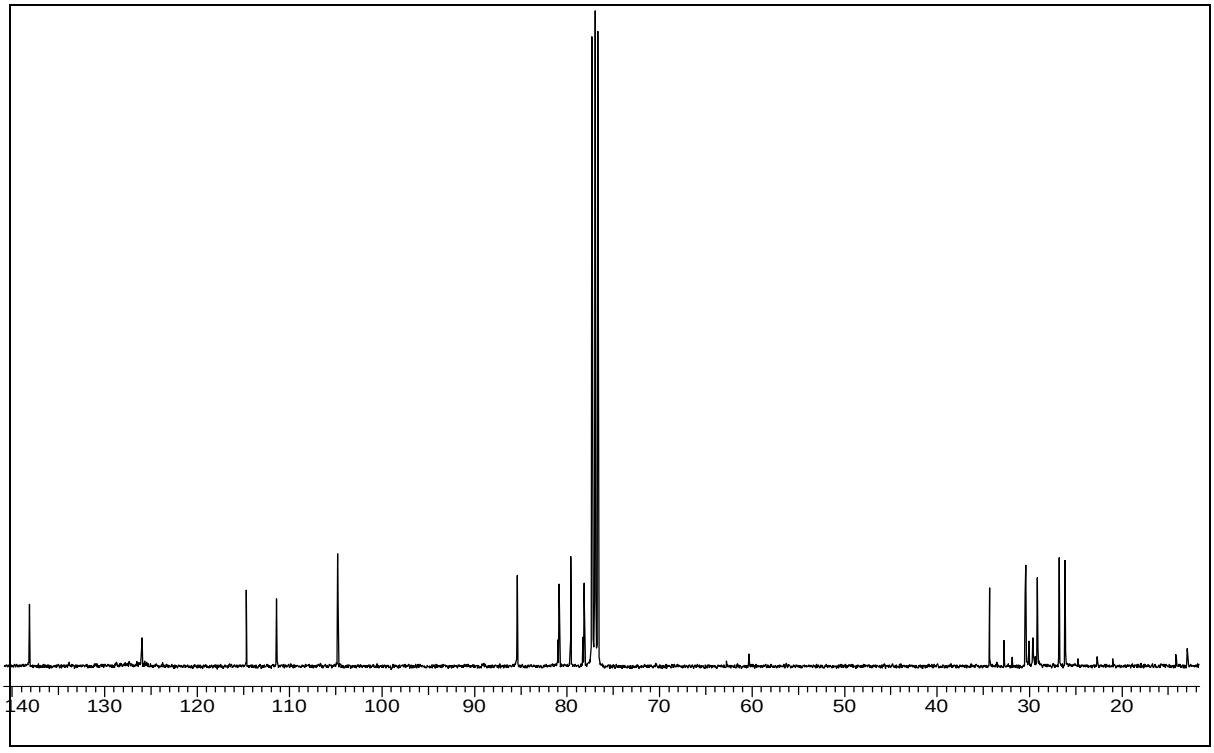
^{1}H NMR spectrum of compound 75 in $CDCl_3$



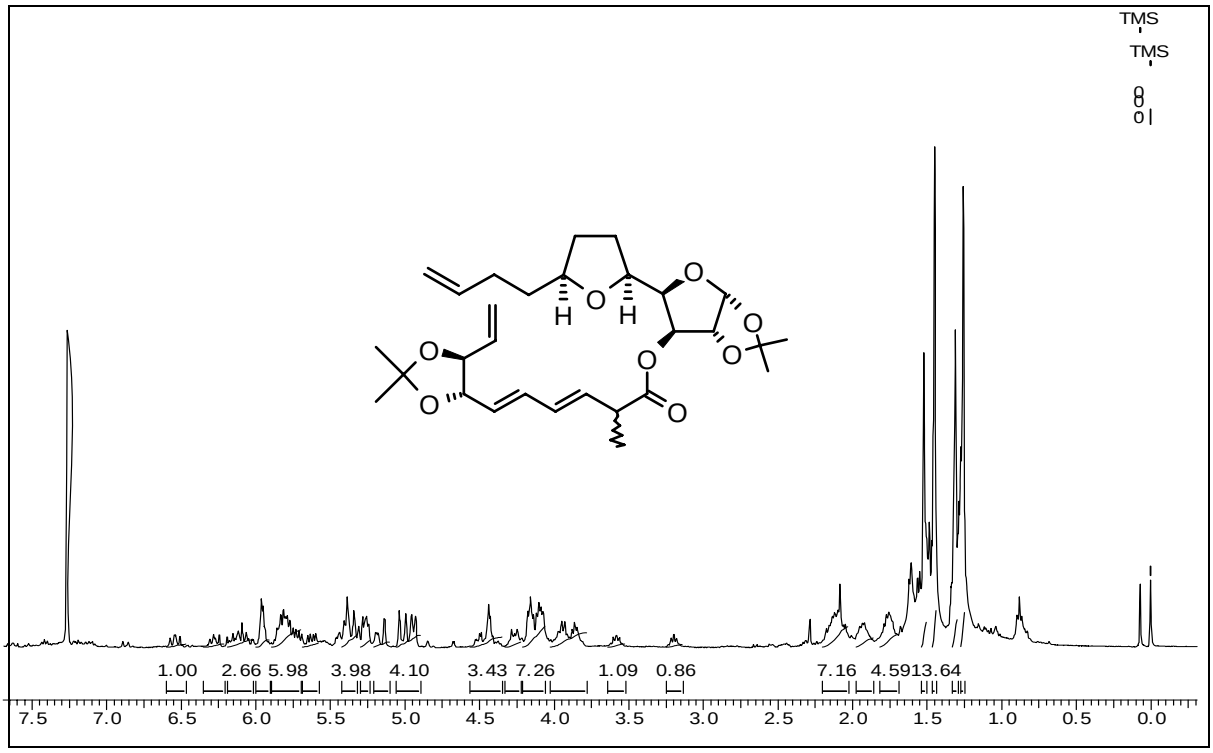
^{13}C NMR spectrum of compound 75 in $CDCl_3$



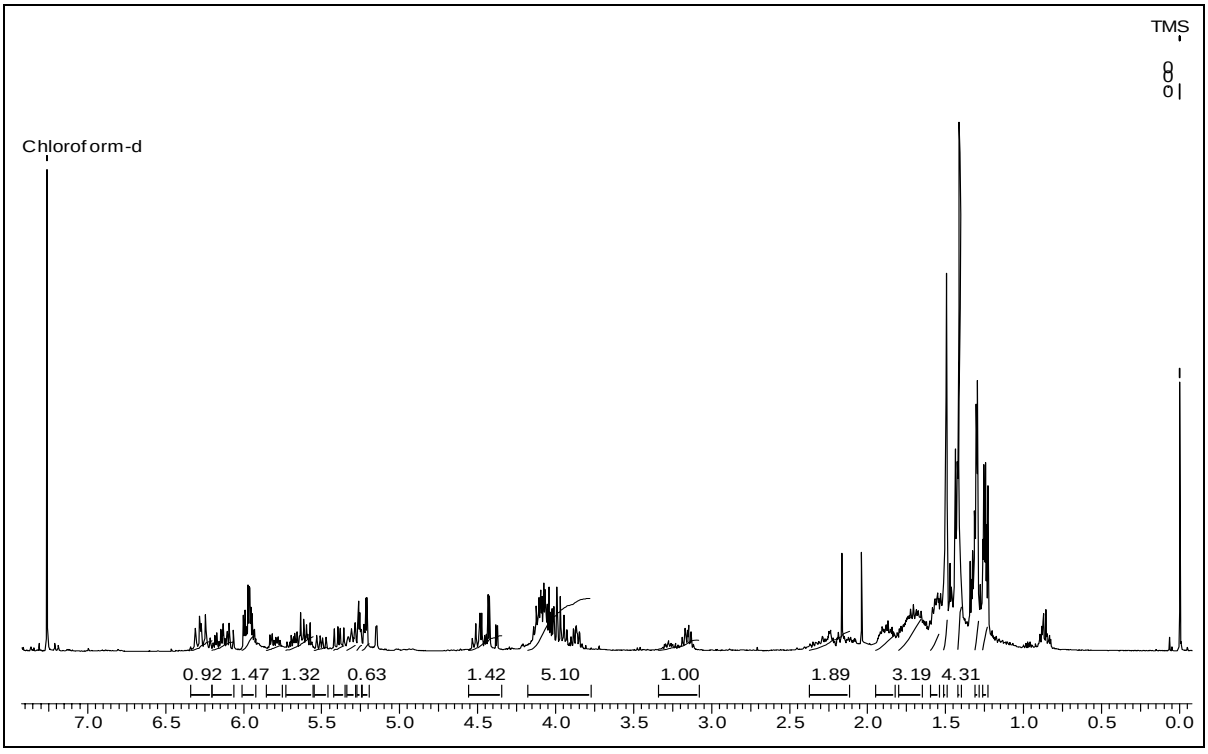
^{1}H NMR spectrum of compound 51 in $CDCl_3$



^{13}C NMR spectrum of compound 51 in $CDCl_3$



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



^{1}H NMR spectrum of complex mixture in $CDCl_3$

REFERENCES

References

1. Poore, G.C.B.; Wilson, G.D.F. *Nature*, **1993**, *361*, 597.
2. Vries, D.J.; Hall, M.R. *Drug. Dev. Res*., **1994**, *33*, 161.
3. Cowan, D.A. *Trends Biotechnol*., **1997**, *15*, 129.
4. Jaspers, M. In *Drug Discovery Techniques*, Harvey, A.L., Ed.; Wiley, **1998**, pp. 65-84.
5. Staley, J.T.; Gosink, J.J. *Annu. Rev. Microbiol*., **1999**, *53*, 189.
6. Harvey, A. *Drug Discovery Today*, **2000**, *5*, 294.
7. Kobayashi, J.; Ishibashi, M. *Chem. Rev*., **1993**, *93*, 1753.
8. Ishibashi, M.; Kobayashi, J. *Heterocycles*, **1997**, *44*, 543.
9. Kobayashi, J.; Ishibashi, M. In *Comprehensive Natural Products Chemistry*, Mori, K., Ed.; Elsevier; New York, **1999**; Vol. 8, pp 619-649.
10. An review on the synthetic studies toward amphidinolides see: Norcross, R.D.; Paterson, I. *Chem.Rev*., **1995**, *95*, 2041.
11. 11. Kobayashi, J.; Ishibashi, M.; Nakamura, H.; Ohizumi, Y.; Yamasu, T.; Sasaki, T.; Hirata, Y. *Tetrahedron Lett*., **1986**, *27*, 5755.
12. 12. Kobayashi, J.; Ishibashi, M.; Hirota, H. *J. Nat. Prod*., **1991**, *54*, 1435.
13. 13. Ishibashi, M.; Ohizumi, Y.; Hamashima, M.; Nakamura, H.; Hirata, Y.; Sasaki, T.; Kobayashi, J. *J. Chem. Soc., Chem.Commun*., **1987**, 1127.
14. 14. Kobayashi, J.; Ishibashi, M.; Nakamura, H.; Ohizumi, Y.; Yamasu, T.; Hirata, Y.; Sasaki, T.; Ohta, T.; Nozoe, S. *J.Nat. Prod*., **1989**, *52*, 1036.
15. 15. Bauer, I.; Maranda, L.; Shimizu, Y.; Peterson, R.W.; Cornell, L.; Steiner, J.R.; Clardy, J. *J. Am. Chem. Soc*.,**1994**, *116*, 2657.
16. 16. Ishibashi, M.; Ishiyama, H.; Kobayashi, J. *Tetrahedron Lett*., **1994**, *35*, 8241.
17. Kobayashi, J.; Ishibashi, M.; Wälchli, M.R.; Nakamura, H.; Hirata, Y.; Sasaki, T.; Ohizumi, Y. *J. Am. Chem. Soc*.,**1988**, *110*, 490.
18. Ishiyama, H.; Ishibashi, M.; Kobayashi, J. *Chem. Pharm.Bull*., **1996**, *44*, 1819.
19. Kobayashi, J.; Ishibashi, M.; Murayama, T.; Takamatsu, M.; Iwamura, M.; Ohizumi, Y.; Sasaki, T. *J. Org. Chem*., **1990**, *55*, 3421.

20. Kobayashi, J.; Tsuda, M.; Ishibashi, M.; Shigemori, H.;Yamasu, T.; Hirota, H.; Sasaki, T. *J. Antibiot*., **1991**, *44*, 1259.
21. Kobayashi, J.; Shigemori, H.; Ishibashi, M.; Yamasu, T.; Hirota, H.; Sasaki, T. *J. Org. Chem*., **1991**, *56*, 5221.
22. Sato, M.; Shimbo, K.; Tsuda, M.; Kobayashi, J.*Tetrahedron Lett*., **2000**, *41*, 503.
23. J. Kobayashi, M. Ishibashi, H. Nakamura, Y. Ohizumi, T. Yamasu, T. Sasaki and Y. Hirata, *Tetrahedron Lett.*, **1986**, *27*, 5755.
24. J. Kobayashi, M. Ishibashi and H. Hirota, *J. Nat. Prod.*, **1991**, *54*, 1435.
25. 25.. Maleczka, R.E.; Terrell, L.R.; Geng, F.; Ward, J. S. III, *Org.Chem.*, **2002**, *4*, 2841.
26. 26.. Trost, B.M.; Chisholm, J.D.; Wrobleski, S.T.; Jung, M. *J. Am.Chem. Soc*., **2002**, *124*, 12421.
27. Ishibashi, M.; Ohizumi, Y.; Hamashima, M.; Nakamura, H.; Hirata, Y.; Sasaki, T.; Kobayashi, J.; *J. Chem. Soc., Chem. Commun.*, **1987**, 1127.
28. Kobayashi, J., Ishibashi, M.; Nakamura, H.; Ohizumi, Y.; Yamasu, T.; Hirata, Y.; Sasaki, T.; Ohta, T.; Nozoe, S. *J. Nat. Prod.*, **1989**, *52*, 1036.
29. Matsunaga, K.; Nakatani, K.; Ishibashi, M.; Kobayashi, J.; Ohizumi, Y. *Biochim. Biophys. Acta*, **1999**, *24*,1427.
30. Bauer, I.; Maranda, L.; Shimizu, Y.; Peterson, R.W.; Cornell, L. *J. Am. Chem. Soc.*, **1994**, *116*, 2657.
31. Maranda, L.; Shimizu, Y. *J. Phycol.*, **1996**, *32*, 873.
32. Kobayashi, J.; Ishibashi, M.;. Walchli, M. R.; Nakamura, H.; Hirata, Y.; Sasaki, T.; Ohizumi, Y. *J. Am. Chem. Soc.*, **1988**, *110*, 490.
33. Tsuda, M.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.*, **1994**, *59*, 3734.
34. Kubota, T.; Tsuda, M.; Kobayashi, J. *Org. Lett.*, **2001**, *3*, 1363.
35. Kobayashi, J.; Ishibashi, M. *Chem. Rev.*, **1993**, *93*, 1753
36. Ishiyama, H.; Ishibashi, M.; Kobayashi, J. *Chem. Pharm. Bull.*, **1996**, *44*, 1819
37. Matsumori, N.; Kaneno, D.; Murata, M.; Nakamura, H,; Tachibana, K. *J. Org.Chem.*, **1999**, *64*, 866.

38. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.*, **1991**, *113*, 4092.

39. Kobayashi, J.; Tsuda, M.; Ishibashi, M.; Shigemori, H.; Yamasu, T.; Hirota, H.; Sasaki, T. *J. Antibiot.*, **1991**, *44*, 1259.

40. Tsuda, M.; Endo, T.; Kobayashi, J.; *Tetrahedron*, **1999**, *55*, 14565.

41. Ishibashi, M.; Ohizumi, Y.; Hamashima, M.; Nakamura, H.; Hirata, Y.; Sasaki, T.; Kobayashi, J. *J. Chem. Soc., Chem.Commun.*, **1987**, 1127.

42. Kobayashi, J.; Ishibashi, M.; Nakamura, H.; Ohizumi, Y.; Yamasu, T.; Sasaki, T.; Hirata, Y. *Tetrahedron Lett.*, **1986**, *27*, 5755.

43. Kobayashi, J.; Sato, M.; Ishibashi, M. *J. Org. Chem.*, **1993**, *58*, 2645.

44. Williams, D. R.; Kissel, W. S. *J. Am. Chem. Soc.*, **1998**, *120*, 11198.

45. Ishibashi, M.; Takahashi, M.; Kobayashi, J. *Tetrahedron*, **1997**, *53*, 7827.

46. Ishibashi, M.; Sato, M.; Kobayashi J. *J. Org. Chem.*, **1993**, *58*, 6928.

47. Kobayashi, J.; Yamaguchi, N.; Ishibashi, M. *J. Org. Chem.*, **1994**, *59*, 4698.

48. Ishibashi, M.; Yamaguchi, N.; Sasaki, T.; Kobayashi, J. *J. Chem. Soc., Chem. Commun.*, **1994**, 1445.

49. Bauer, I.; Maranda, L.; Young, K.A.; Shimizu, Y.; Fairchild, C.; Cornell, L.; MacBeth, J.; Huang, S. *J. Org. Chem.*, **1995**, *60*, 1084.

50. Tsuda, M.; Izui, N.; Shimbo, K.; Sato, M.; Fukushi, E.; Kawabata, J.; Katsumata, K.; Horiguchi, T.; Kobayashi, J. *J. Org. Chem.*, **2003**, *68*, 5339.

51. Tsuda, M.; Izui, N.; Shimbo, K.; Sato, M.; Fukushi, E.; Kawabata, J.; Kobayashi, J. *J. Org. Chem.*, **2003**, *68*, 9109.

52. Kobayashi, J.; Ishibashi, M.; Murayama, T.; Takamatsu, M.; Iwamura, M.; Ohizumi, Y.; Sasaki, T. *J. Org. Chem.*, **1990**, *55*, 3421.

53. a. Kobayashi, J.; Ishibashi, M.; Murayama, T.; Takamatsu, M.; Iwamura, M.; Ohizumi, Y.; Sasaki, T. *J. Org. Chem.* 1990, *55*, 3421 – 3423; b. Kubota, T.; Tsuda, M.; Kobayashi, J.; *J. Org. Chem*. **2002**, *67*, 1651 – 1656.

54. Schmidt, O. T.; In. *Methods in Carbohydrate Chemistry*, Whistler, R. L., Wolfrom, M. L. Ed.; *Academic; New York*, **1963**, Vol 2, pp 318-325

55. Zhong, Y. L.; Shing, T. K. M. *J. Org. Chem*. **1997**, *62*, 2622–2624.

56. Bertrand, P.; Sukkari, H. E.; Gesson, J. P.; Renoux, B. *Synthesis* **1999**, *2*, 330-335

57. (a) Speziale, V.; Roussel, J.; Lattes, A. *J. Heterocycl.Chem*. **1974**, *11*, 771; (b) Vincens, M.; Dumont, C.; Vidal, M. *Can. J. Chem*., **1979**, *57*, 2314.

58. Sih, J. C.; Graber, D. R. *J. Org. Chem.* **1982**, *47*, 4919–4927.

59. Frigeno, M.; Santagostino, M. *Tetrahedron Lett*. **1994**, *35*, 8019–8022

60. Kruse, C. G.; Jonkers, F. L.; Dert, V.; Gen, A. V. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 371.

61. Brown, H. C.; Knights, E. F.; Scouten, C. G. *J. Am. Chem. Soc.* **1974**, *96*, 7765–7770

62. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc*. **1991**, 113, 7277–7287.

63. Comins, D. L.; Dehghani, A. *Tetrahedron Lett*. **1992**, *33*, 6299–6301.

64. (a) Bottaro, J. C.; Hanson, R. N.; Seitz, D. E. *J. Org. Chem*. **1981**, *46*, 5221–5222. (b) Naruse, Y.; Esaki, T.; Yamamoto, H. *Tetrahedron* **1988**, *44*, 4747–4756. (c) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc*. **1999**, *121*, 7600–7605.

65. Gurjar, M. K.; Mohapatra S; Phalgune U. D.; Puranik V. G.; Mohapatra D. K. *Tetrahedron Letters* **2004**, *45*, 7899–7902

66. (a)Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348. (b) Burke, S. D.; Cobb, J. E.; Takeuchi, K. *J. Org. Chem.* **1990**, *55*, 2138. (c) Trost, B.M.; Papillon, J.P.N. *J. Am. Chem. Soc* **2004**, *126*, 13618-13619

67. Takai, K; Nitta, K; Utimoto, K. *J. Am. Chem. SOC.* **1986,** *108*, 7408-7410

68. (a) Mash, E.A.; Nelson, K.A.; Deusen s.v.; Hempenly, S.B. Org. Synth. 68, *92*, **1989** (b) Feit, P.W. *J.med. Chem*. 7, *14*, **1964**. (c) Carmack M.; Kelley, C.J. *J. Org. Chem.* **1968**, *33*, 2171.

69. Pilli R.A.; Victor M.M. *J. Braz. Chem. Soc.,* Vol. 12, No. 3, 373-385, **2001.**

70. (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561. (b) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H.J. *Synlett* **1996**, 521.(c) Roth, G. J.; Liepold, B.; Müller, S. G.; Bestmann, H.J. *Synthesis* **2004**, 59.

71. (a) Stille, J.K; Tanaka, M. *J. Am. Chem. SOC.* **1987,** *109*, 3785-3786. (b) Collins, P.W.; Gasiecki, A.F.; Perkins, W.E.; Gullikson, G.W.; Bianchi R.G.; Kramer, S.W.; Ng, J. S.; Yonan, E.E.; Swenton, L.; Jones, P.H.; Bauer, R.F. *J. Med. Chem.*, **1990**, *33*, 2784.

72. Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem*. **1999**, *64*, 4537 – 4538.

73. Hanessian, S.; Thavonekham, B**.;** DeHoff, B. *J. Org. Chem.* **1989**, *64*, 5830 – 5833.

74. Ghosh, A. K.; Liu, C. *J. Am. Chem. Soc***. 2003**, 125, 2374-2375

75. Louis, I.; Hungerford, N. L.; Humphries, E. J.; Mcleod, M. D.; *Org. Lett.* **2006**, *8*, 1117 -1120.

76. Marshall, J. A.; Schaaf, G.; Nolting, A. *Org. Lett*. **2005**, *7*, 5331.

77. Kim, C. H.; An, H. J.; Shin, W. K.; Yu, W.; Woo, S. K.; Jung, S. K.; Lee, E. *Angew. Chem. Int. Ed.* **2006**, *45*, 8019-8021

78**.** (a) Va, P.; Roush, W. R. *J. Am. Chem. So*c. **2006**, *128*, 15960. (b) Va, P.; Roush, W. R. *Org. Lett*. **2007**, *9*, 307. (C) Va, P.; Roush, W. R. *Tetrahedron* **2007**, *63*, 5768-5796.

CHAPTER -2

SECTION-1

Synthesis of Bis–THF Ring cores in Annonaceous Acetogenins

INTRODUCTION

Introduction

The multiplication of cells is carefully regulated and responsive to specific needs of the body. Normally body cells grow, divide and die in an orderly fashion. During the early years of life normal cells divide more rapidly until the person becomes an adult. After that, normal cells of most tissues divide only to replace worn-out or dying cells and to repair injuries.

Very occasionally, the control that regulates the cell multiplication brakes down and cells continue to grow and divide with out responding to regulation. These cells accumulate and forms a mass called tumor that may compress, invade and destroy normal tissues. If cells break away from such a tumor, they can travel through the blood stream or the lymph system to other areas of the body. There they may settle and form colony of tumors. In the new location, the cancer cells continue growing. The spread of a tumor to a new site is called metastasis. When cancer spreads, though, it is still named after the part of the body where it started. For example, if prostate cancer spreads to the bones, it is still prostate cancer, and if breast cancer spreads to the lungs, it is still called breast cancer. Leukemia, a form of cancer, does not usually form a tumor. Instead, these cancer cells involve the blood and blood-forming organs (bone marrow, lymphatic system, and spleen), and circulate through other tissues where they can accumulate. It is important to realize that not all tumors are cancerous. *Benign* (noncancerous) tumors do not metastasize and, with very rare exceptions, are not life threatening.[1]

Cancer is a disease that has created panic in patients and frustration in doctors for several decades. The incidence of bronchogenic carcinoma has reached epidemic proportions in the developed world. The disease is the most common malignancy and leading cause of death from cancer among men in many countries. Cigarette smoking is the single major contributing factor.[2]

Though there are many methods are available today to cure the cancer, chemotherapy is the best and can be used at any stage of the disease.Though several antineoplastic drugs have been prescribed but they are always associated with high degree of myclotoxicity, nephrotoxicity, and other adverse side effects. Therefore, development of

new agents is essential in order to prolong overall survival with minimized side effects of patients.[3] In search of new antitumor agents from different natural sources, every year thousands of natural products are isolated and screened by natural product chemists and phytochemists and new compounds of promising therapeutic value have been discovered.[4]

More recently Annonaceous acetogenins a class of compounds belongs to the family Annonacia came to the lime light because of their potent cytotoxic activity.[5-10] The discovery of uvaricin[11] in 1982, the first of the Annonaceous acetogenins, as an in vivo active antileukemic agent, invigorated wide interest in this family. These class compounds are most powerful of the known inhibitors of complex I (NADH: ubiquinone oxidoreductase) in mammalian and insect mitochondrial electron transport systems; in addition, they are potent inhibitors of NADH oxidase of the plasma membranes of cancer cells; these actions decrease oxidative, as well as, cytosolic ATP production.

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.[12]

Structurally, the Annonaceous acetogenins are a series of C-35/C-37 natural products derived from C-32/C-34 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.

Structural elucidation:

Synthetic models of known stereochemistry are used routinely to predict the relative stereochemistry of both the THF and the γ-lactone ring systems bearing the nearby 4-hydroxyl of the acetogenins. The locations of the THF ring and/or the free hydroxyls continue to be determined by careful analysis of mass spectral fragments. No significant changes have been introduced in the methods for structural elucidation of Annonaceous acetogenins in the last two years. Nevertheless, the following three contributions merit

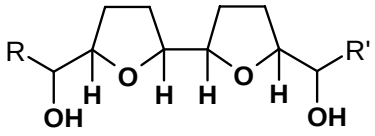
discussion. This consists of analysis of the mass spectra to determine the exact molecular formula, followed by EI-MS and FAB-MS, which allow one to determine the position of the functional groups on the alkyl chain. Elucidation of the relative stereochemistry of the stereogenic centres by careful analysis of the ^{1}H and ^{13}C-NMR spectra is now straightforward, due to the possible comparisons of the spectra between those of the natural products and synthetic models. For the determination of the absolute configurations, the advanced Mosher ester methodology has allowed several authors to determine unambiguously the absolute configuration of the carbinols present in the vicinity of the THF rings, and thus to assign the whole configuration of the THF units. For isolated carbinols, the use of 2-NMA (2-napthylmethoxy acetic acid) esters is of great interest, since the influence of the aromatic rings can extend to five carbon–carbon bonds.[13]

Classification of Acetogenins:

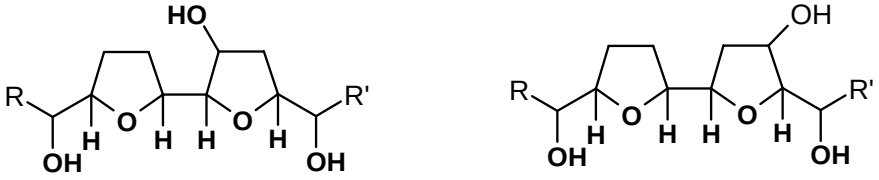
Annonaceous acetogenins were classified according to their relative stereo structures across the THF rings; Classical acetogenin and Non classical acetogenin, but it leads to a plethora of subclasses. The Annonaceous acetogenins seem to be best classified into mono-THF, adjacent bis-THF, nonadjacent bis-THF, non-THF ring, tri- THF, and nonclassical acetogenins (THP and ring-hydroxylatedTHF compounds), followed by subclassification of the γ-lactone, substituted γ-lactone, or ketolactone.

(i) **Classical acetogenins**

(ii) **Non classical acetogenins**



(Clacssical Acetogenins)

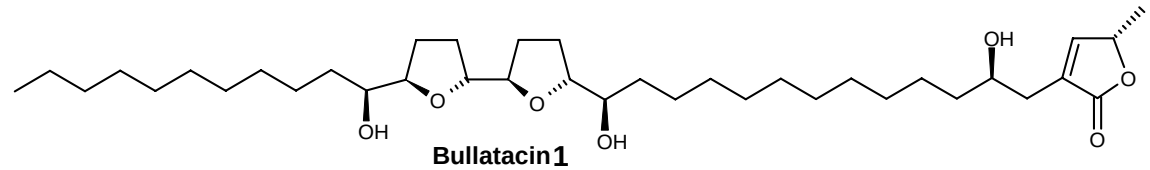


(Non -Classical Acetogenins)
R = Alkyl side chain
R'= Butenolide chain

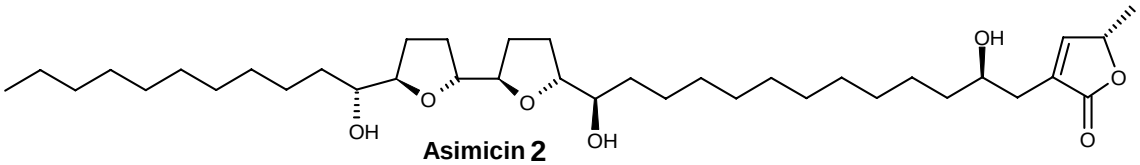
Figure - 1

Structural differentition of Classical and non classical acetogenins have been presented in figure-**1**.

Classical acetogenins: Structurally, classical acetogenins belongs to adjacent bis-THF acetogenins contain an array of 2, 5- disubstituted tetrahydrofuran (THF) rings. Examples of are Bullatacin, Asimicin, Annonisim, Guanaconne, and Rollidecin etc.

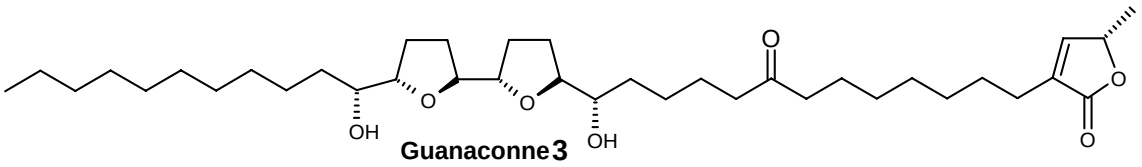


Bullatacin 1



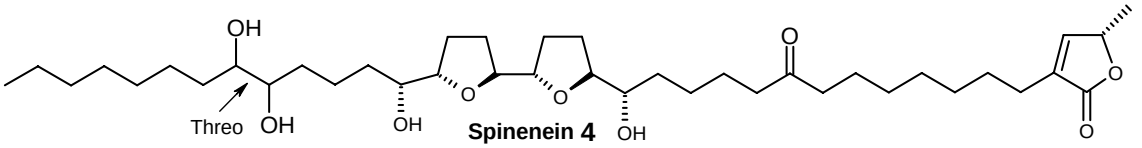
Asimicin 2

Bullatacin**1**[14] and asimicin **2**,[15] 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.[16] Compound **2** was isolated from *Asimina triloba*, 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 *í*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.[16] The cytotoxicity of Bullatacene was found to be higher than that of other chemotherapeutic agents in a variety of cancer cell lines, [17] particularly in HL-60 cells that are resistant to adriamycin.[18] The structure of **1** and **2** 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.[19,20] These structures were confirmed via the total syntheses of both **1** and **2**,[21] by the Hoye,[22] Marshall,[23] and Sasaki groups.[24]



Guanaconne 3

From a Colombian tree known as "guanacona" or "tiotio" an unusual 10-keto bis-tetrahydrofuran (THF) acetogenin, guanacone **3**, 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 in **3** of and α,β-unsaturated γ-lactone 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 ^1H and ^{13}C NMR spectrum, which proved the absence of an OH at the C-4 position typically found in most acetogenins[25]. The presence of a keto group in **3** was suggested by the existence of a triplet at δ 2.39 (H-9, 11) in the ^1H 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 **3** 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 **1** 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.[26]

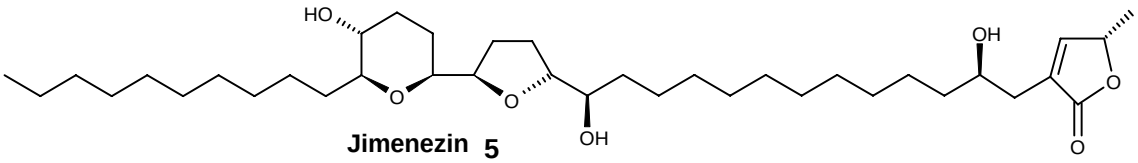


Spinenein 4

The present study has led to the isolation and structure elucidation of spinencin **4**, a new C37 bis-tetrahydrofuran acetogenin, together with the known almunequin,[27] bullatanocin,[28] , isodesacetyluvaricin,[29] atemoyin or squamocin K[30, 31] desacetyluvaricin,[32] and neoannonin.[33] All these acetogenins are reported for the first time from this plant. The

structures were determined by ^{1}H- and ^{13}CNMR (COSY, HOHAHA, HMBC, and HMQC) and MS (ESI-MS/MS) on the native compounds and on the acetonide derivative of spinencin **4** 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 **4** 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.[34]

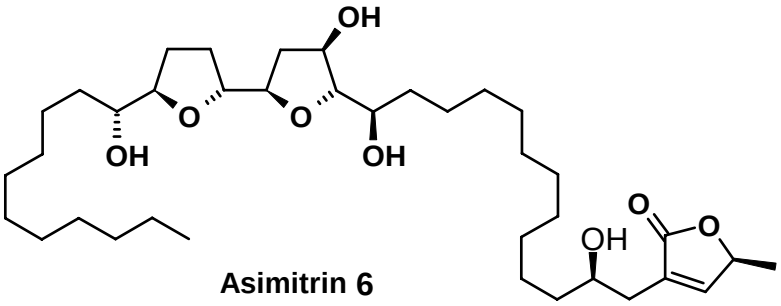
Non classical acetogenins: More recently, new nonclassical acetogenins containing more complex tetrahydropyran (THP) rings and/or THF rings as the core have been isolated; examples of such are mucocin, pyragonicin, and Jimenezin, all of which are THP-containing acetongenins and have recently succumbed to total synthesis. Mucoxin, a nonclassical acetogenin, is the first of its kind found to contain a trisubstituted hydroxylated bis-THF ring. After isolation of mucoxin, recently two other potent nonclassical acetogenin has been isolated named as salzmanolin and asimitrin, which also contains trisubstituted hydroxylated adjacent bis-THF ring. These acetogenins are showing strong biological activity than classical acetogenins.[35]



Jimenezin 5

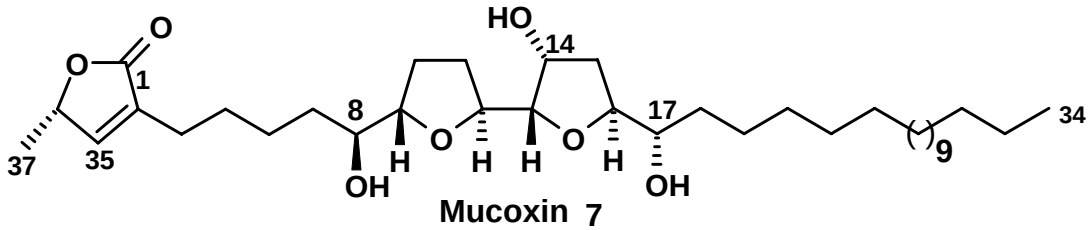
Jimenezin **5** was isolated from seeds of *Rollinia mucosa* in 1998.[36] Structurally it consists of a tetrahydropyran (THP) ring adjacent to a tetrahydrofuran (THF) ring was proposed by spectroscopic techniques[36] and its structure was revised after a total synthesis by Takahashi.[37] Although most 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.[38, 39] 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[40] applied a Samarium iodide-mediated radical cyclization in his synthesis.



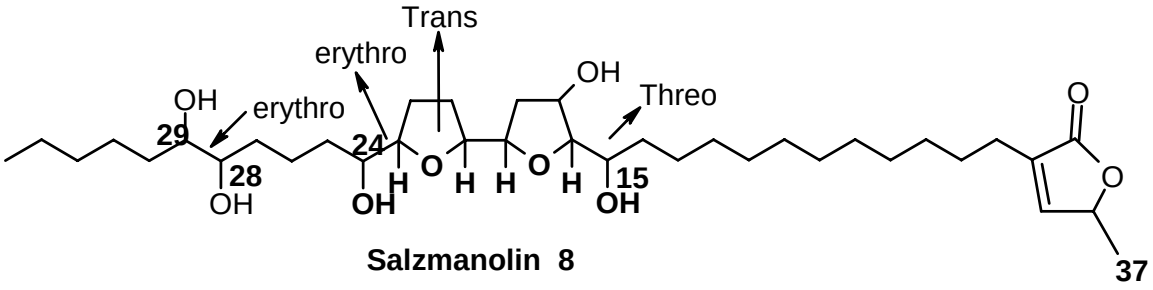
Asimitrin 6

Recently, asimitrin **6** a ringhydroxylated unsymmetrical bis-tetrahydrofuran acetogenin was isolated from the seeds of *Asimina triloba* by Mi Hee Woo in 2005.[41] 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.



Mucoxin 7

Mucoxin, **7** a nonclassical acetogenin, is the first of its kind found to contain a trisubstituted hydroxylated adjacent bis-THF ring.[41] In vitro cytotoxicity assays against a panel of six human tumor cell lines have shown mucoxin to be more potent and selective against 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.[42] 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

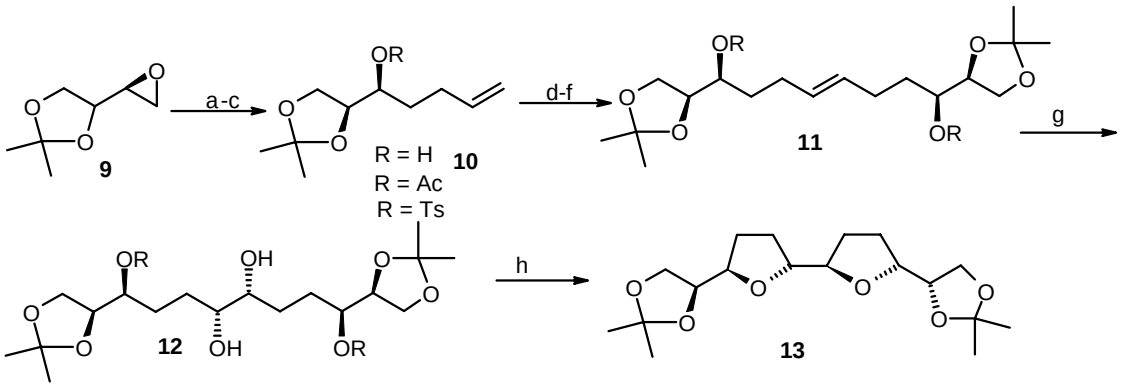
cell lines. The molecular weight of **8**, established by LSIMS as 654 from the $[M + Na]^+$ ion observed at *m*/*z* 677.3, is in agreement with the molecular formula $C_{37}H_{66}O_9$. Strong absorptions at 209 nm and 1750 cm^{-1} in the UV and IR spectrum, respectively, indicated the presence of an α, β-unsaturated γ-lactone moiety, characteristic of acetogenins. The typical resonances observed in the ^1H and ^{13}C NMR spectra, also indicating the absence of an -OH group at C4. The presence of an adjacent bis-THF system was deduced from the ^{13}C NMR signals at δ 83.0 (1C), 82.7 (1C), 82.1 (1C), and 81.9 (1C) ppm.

Several approaches for the synthesis of bis-THF ring of classical acetogenins:

B.V Rao approach: [43]

Synthesis of Bis-THF core using cross metathesis

Scheme 1: **C**ross RCM reaction

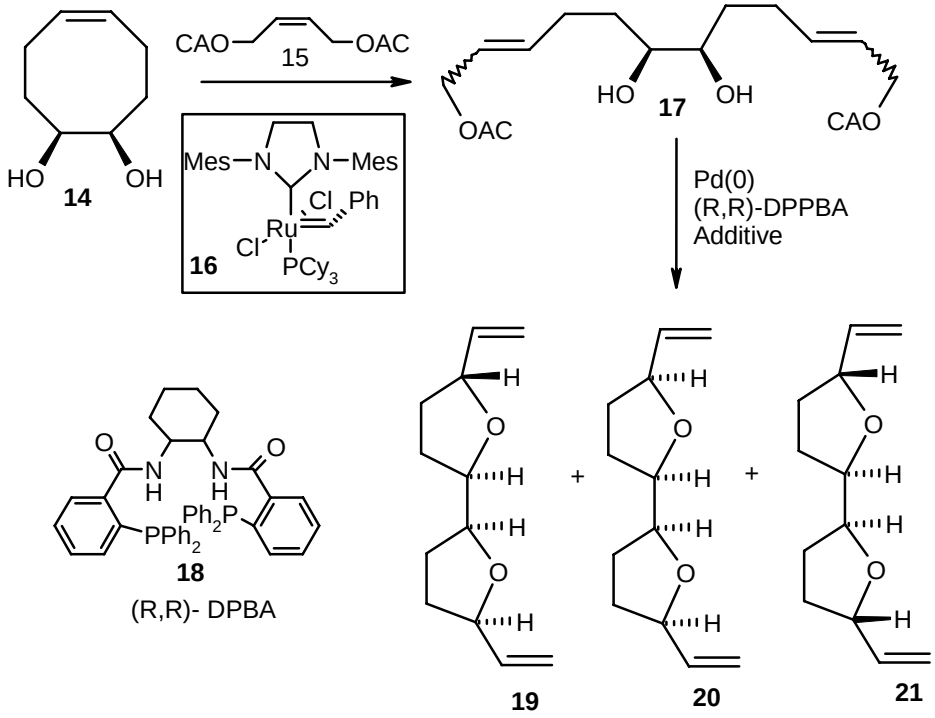


***Reagents and conditions*:** (a) CH_2=CH-CH_2MgBr, CuI, ether, -20 ºC, 12 h, 85%; (b) $(CH_3CO)_2O$, TEA,DMAP, DCM, 0 ºC-rt, 3 h, 90%; (c) *p*-TsCl, TEA, DMAP, DCM, 0 ºC to rt, 24 h, 87%; (d) 10 mol% Grubbs' 1st generation catalyst, DCM, 40 ºC 12 h; (e) K_2CO_3, methanol, ºC to rt, 2 h, 85%; (f) *p*-TsCl, 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:[44]

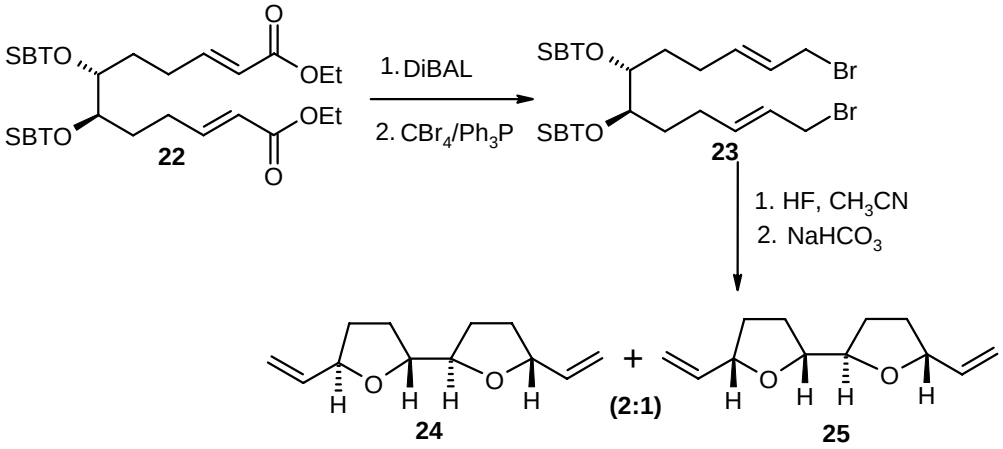
Stereochemical General Approach to Adjacent Bis(tetrahydrofuran) Cores of Annonaceous Acetogenins

Scheme 1A: Double etherification



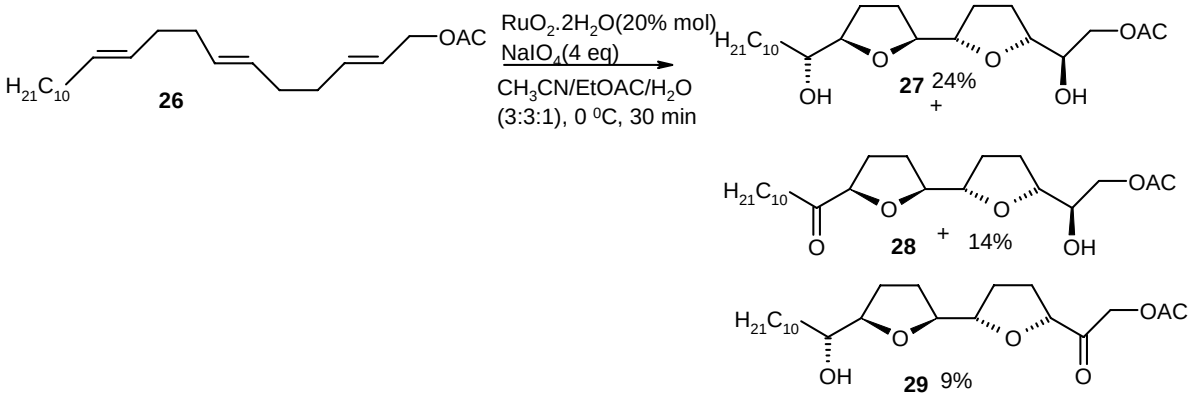
Kang Zhao Approach:[45]

Scheme 2: SN Cyclization of E-Olefin



Vincenzo Piccialli approach:[46]

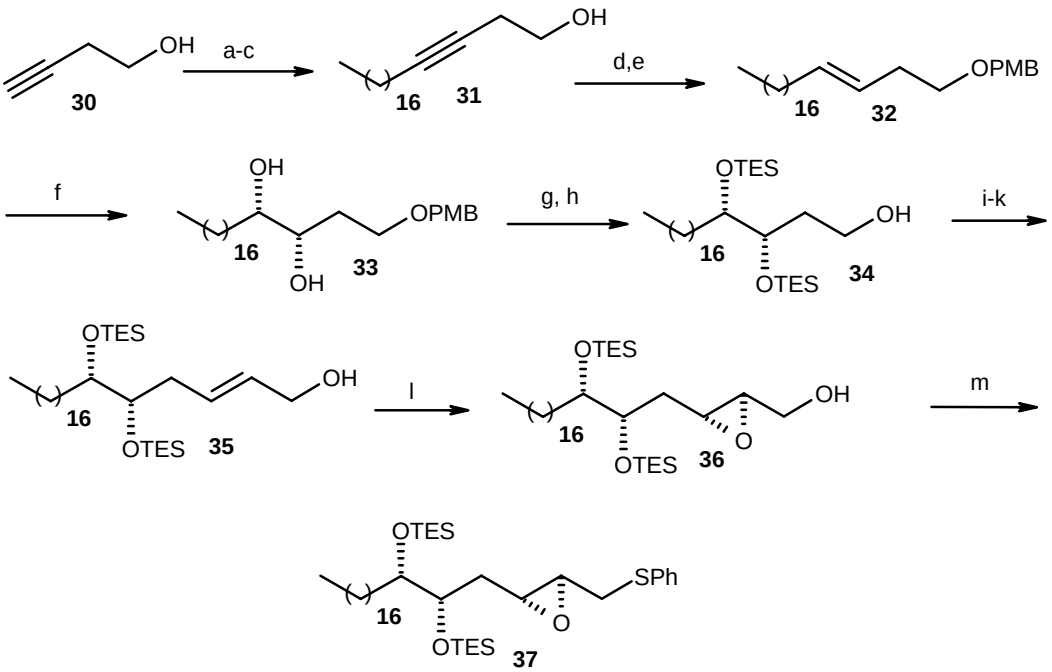
Scheme 3: RuO4-mediated oxidative bis-cyclization of (E,E,E)-acetic acid henicosa-2,6,10-trienyl ester



Past work of Mucoxin:[47]

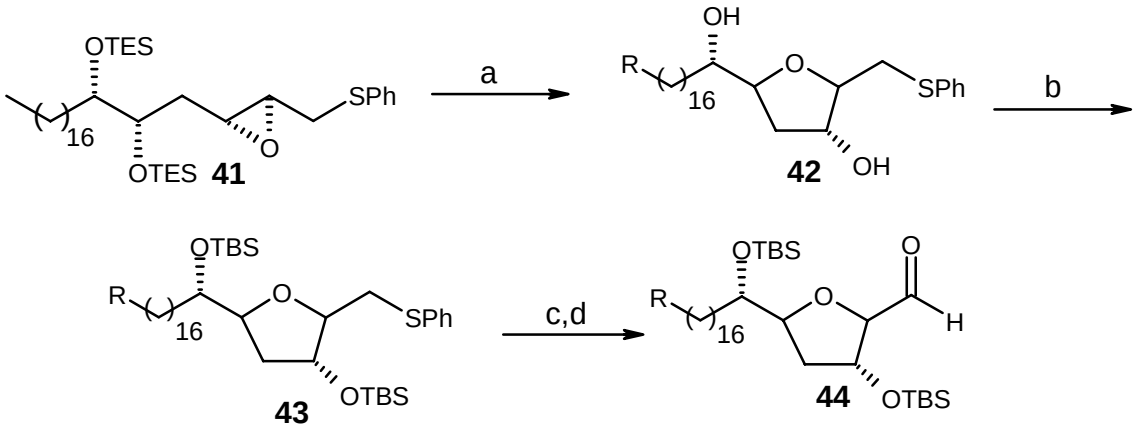
Babak Borhan approach: Synthesis of the Proposed Structure of Mucoxin via Regio- and Stereoselective Tetrahydrofuran Ring-Forming strategies.

Scheme 4: Synthesis of epoxysulfide:



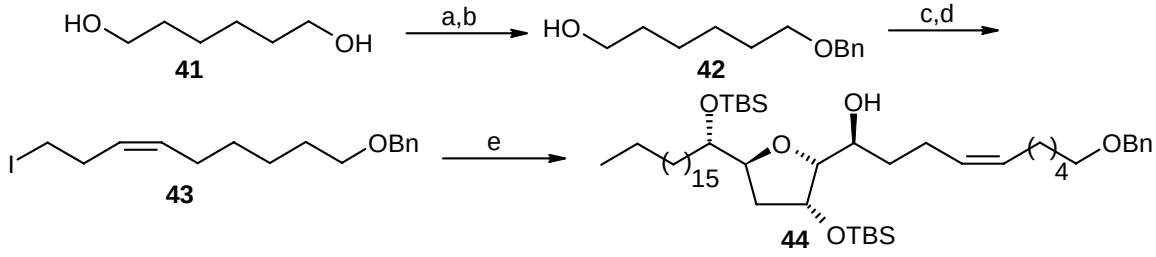
***Reagent and conditions*:** (a) TBSCl, imid., DMF, room temperature (73%); (b) *n*-BuLi, $CH_3(CH_2)_{16}I$, THF/HMPA (3:1), 0 °C (80%); (c) TBAF, THF, -10 °C (90%); (d) LAH, diglyme, 125 °C (87%); (e) NaH, PMBCl, TBAI, THF, 60 °C (91%); (f) AD-mix-R, $MeSO_2NH_2$, $K_2OsO_4{\cdot}2H_2O$, *t*-BuOH/H_2O (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



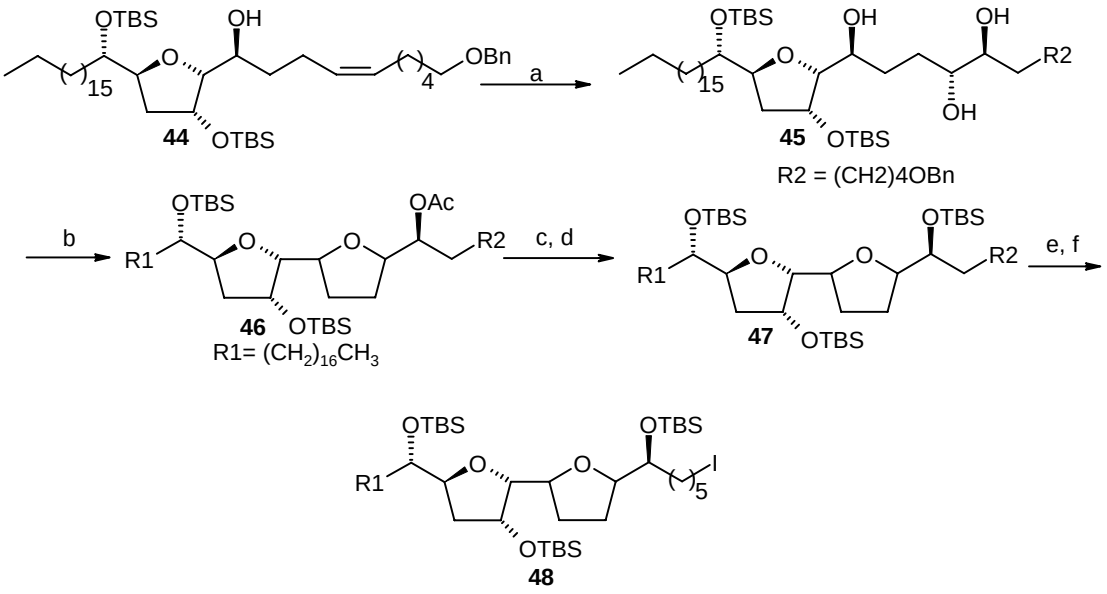
***Reagents and conditions*:**(a) BF_3:OEt_2 (6 equiv), Et_2O (0.04 M), 0 °C to room temperature (56%); (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C (91%); (c) *m*-CPBA, CH_2Cl_2, 0 °C (quantitative); (d) (i) TFAA, 2,6-lutidine, CH_2Cl_2, 0 °C; (ii) $NaHCO_3$ (solid), CH_3CN (63% over two steps).

Scheme 6: Synthesis of Hydroxyene



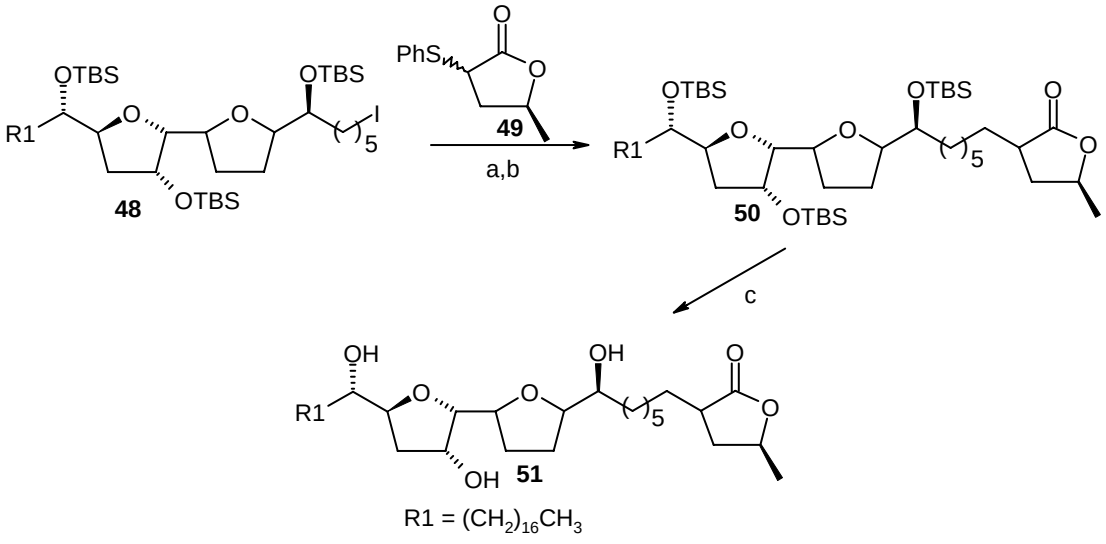
***Reagent and conditions*:** (a) NaH, BnBr, TBAI, THF, 60 °C (78%); (b) PCC, CH_2Cl_2, rt (82%); (c) $Ph_3P(CH_2)_3OHBr$, KHMDS, TMSCl, then AcOH/THF/H_2O (6:3:1), 0 °C (83%); (d) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C; (ii) NaI, acetone, reflux, 77%; (e) *t*-BuLi, -100 °C, $MgBr_2$:OEt_2, Et_2O, -95 °C, then **44**, $MgBr_2$:OEt_2, -40 °C (88%).

Scheme 7: Synthesis of Bistetrahydrofuran



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%).

Scheme 8: **Completion of the synthesis of proposed structure of Mucoxin**



Reagents and conditions: (a) LDA, **49**, THF/HMPA (4:1), 0 °C-rt (87%); (b) (i) *m*-CPBA, CH_2Cl_2, 0 °C; (ii) toluene, reflux (84% over two steps); (c) HF:Py, THF, rt (80%).

As an application of mercury mediated cyclization strategy for the construction of adjacent bis-tetrahydrofuran ring hasn't been established so we were intrigued with the possibility of using this strategy for the efficient preparation of bistetrahydrofuran systems which could be used to synthesize a sufficient amount of the naturally occurring acetogenins and/or the isomers with various side chains for the evaluation of biological activity.

PRESENT WORK

Present Work

The relevance of nonclassical acetogenins class of compounds has been well elaborated in the introduction part of this chapter. Ring hydroxylated bis-THF core is an essential feature of the nonclassical acetogenins. It is an intriguing unit present in many natural products and have attracted immense attention of organic chemists. There are several protocols available in literature for the synthesis of bis-THF ring, like tandem Sharpless epoxidation and dihydroxylation followed by cyclization,[48] addition of chiral allenyltin reagents to aldehydes,[49] and elaboration of natural enantiopure materials,[50] but very few synthesis has been reported for the ring hydroxylated adjacent bis-THF core structure. Literature report revealed that synthesis of hydroxylated bis-THF core of acetogenins starting from carbohydrate precursor wasn't reported till date.

As a part of our ongoing efforts directed towards the synthesis of natural products containing ring hydroxylated bis-THF ring systems, we envisioned that a homoallylic alcohol substituted carbohydrate backbone would be a potential precursor. As in our earlier synthesis we have employed oxymercuration protocols for the diastereoselective synthesis of monoTHF ring (compound **33,** 1st chapter, page-**15**), so here, using same strategies we envisioned to synthesize the bis-THF core of various nonclassical acetogenins and their analogues stereoselectively.

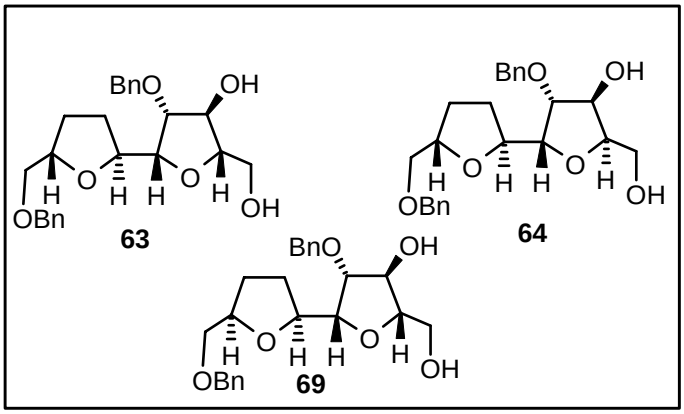


Figure-2

Prompted by the hydroxylated tetrahydrofuran core present in non-classical acetogenins as well as their pronounced activity, we became intrigued with the possibility of using an intramolecular oxymercuration strategies for an efficient preparation of mono

and dihydroxylated bis-tetrahydrofuran systems **63**, **64**, and **69** which could be used to synthesize sufficient amounts of naturally occurring acetogenins and/or their derivatives and congeners with various side-chains, for the evaluation of biological activity.

Here, we have elaborated only the synthetic strategies of bis-THF alcohols **63**, **64** and **69** etc. The retrosynthetic analysis for the hydroxylated bis tetrahydrofuran ring system was illustrated in figure-**3**. The stereo controlled off-template construction of the first tetrahydrofuran ring was planned to synthesize **58** and **65** employing an intramolecular oxymercuration protocol on 4-alkenol derivative **55**, followed by second intramolecular oxymercuration led to the formation of desired Bis-THF alcohol **63**, **64** and **69** respectively(Figure-3).

Retrosynthetic Analysis:

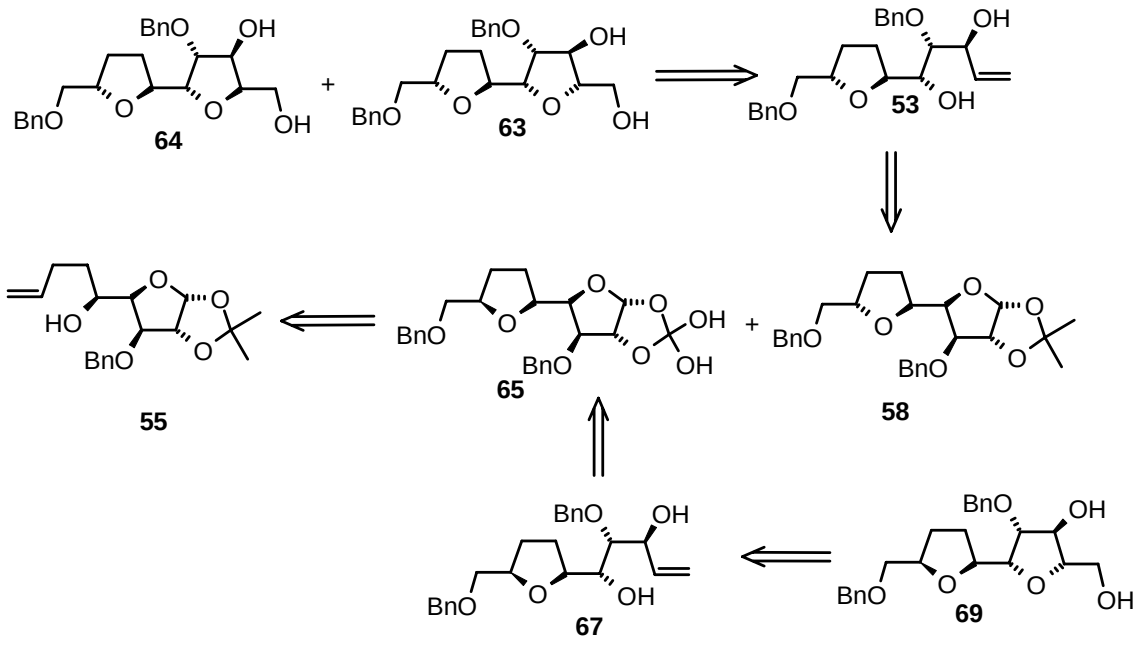
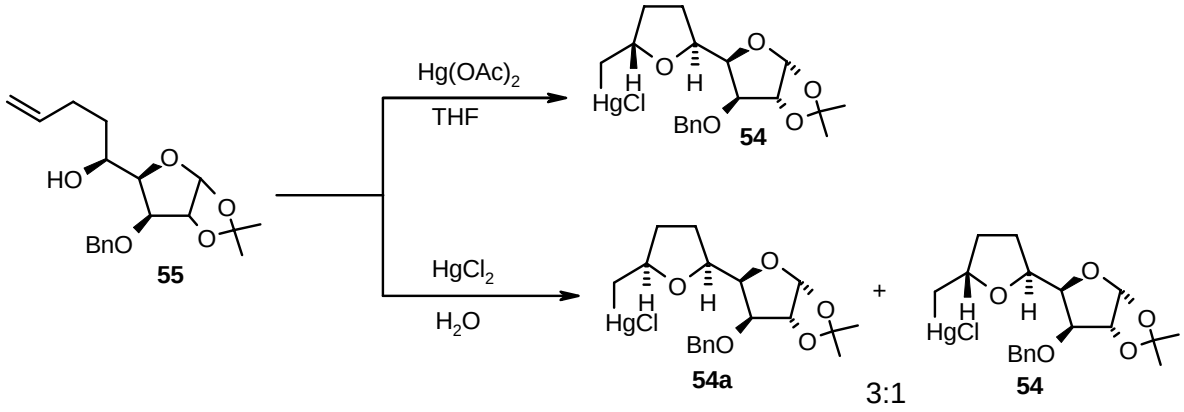


Figure-3

Our synthesis started from known chiral intermediate **55,** [51] which was prepared easily from D-glucose by known literature procedure. Compound **55** upon treatment with mercury (II) acetate in THF led to the formation of **54**, exclusively. As previously suggested, in THF, coordination-controlled mercurium ion formation followed by intramolecular[52] nucleophilic attack by the C-5 hydroxyl group from the opposite face

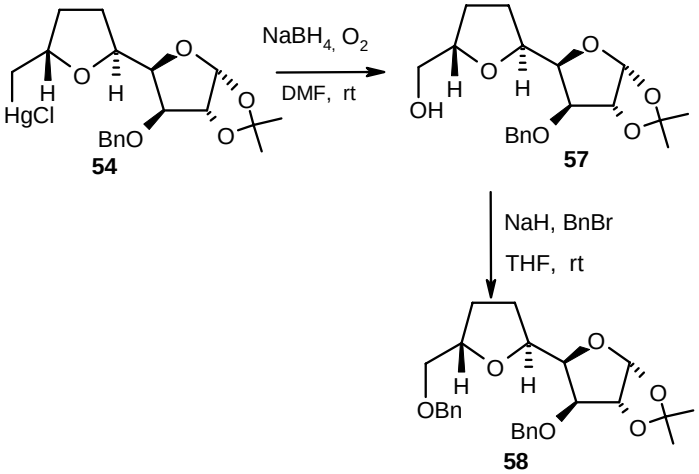
would lead to the formation of the *trans*-isomer as the sole product. Whereas, treatment of $HgCl_2$ and H_2O on **55** resulted in a 3:1 mixture of **54a** and **54** respectively. Both the isomer were separated by flashsilicagel chromatography. The compound **54** and **54a** was confirmed by ^1H, ^{13}C and elemental analysis (Scheme 9).

Scheme 9



The demercuration[53] of **54** was carried out under a stream of oxygen in the presence of $NaBH_4$ to give the primary alcohol **57**. The structure of **57** was elucidated on the basis of ^1H NMR spectroscopy, where the methylene protons at δ 1.65 and δ 1.42 ppm corresponding to CH_2Hg group disappeared and two new signals appeared at δ 3.63 (dd, 1H, *J* = 5.30, 11.8 Hz) and δ 3.49 (dd, 1H, *J* = 5.30, 11.8 Hz) ppm confirming the transformation of **54** to **57**(scheme-9).

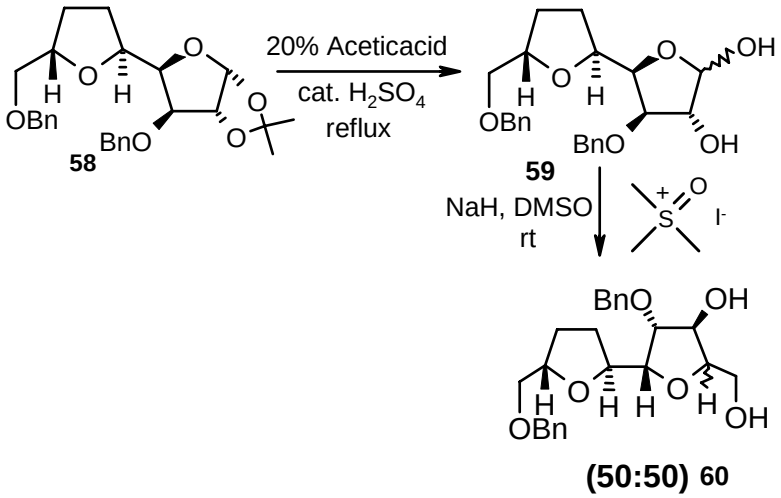
Scheme 10



Next the primary hydroxyl group of **57** was protected as its benzyl ether **58** by treatment with sodium hydride and benzyl bromide in THF. This transformation was apparent from the ^{1}H and ^{13}C NMR spectrum of compound **58**. In the ^{1}H NMR spectrum signals appeared at δ 7.32-7.35 (m, 10H), 4.66 (d, *J* =11.9Hz, 1H), 4.54 (s, 2H) and 4.41(d, *J* = 11.9Hz, 1H) ppm indicating the presence of two benzylic group. The structure was further confirmed by ^{13}C NMR spectrum together with elemental analysis (Scheme 10).

Our next concern was to construct the second tetrahydrofuran ring stereoselectively. Thus hydrolysis of isopropylidene group of **58** was accomplished with 20% acetic acid and catalytic amount of H_2SO_4 under refluxing conditions to give acetal **59**. The acetal immediatedly reacted with trimethyl sulfoxonium iodide[54] in presence of sodium hydride in DMSO to give inseparable mixture of alcohol **60** (Scheme 11).

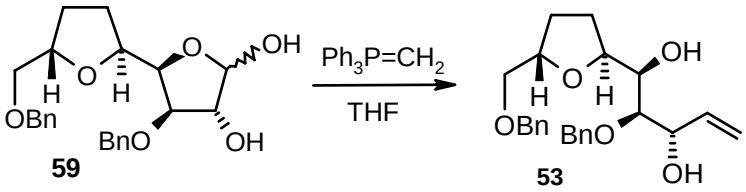
Scheme 11:



Being unsuccessful in synthesizing diastereomerically pure components of **60** in a single step synthesis, we planned a multistep strategies. Accordingly compound **59** was subjected with one carbon Wittig ylide [55] in THF at -20 °C to afford compound **53**.The structure of **53** was characterized by its ^{1}H, ^{13}C NMR study and elemental analysis. The ^{1}H NMR spectrum showed the methine signals of olefin at δ 6.01ppm, where as the methylene protons of the olefin resonated at δ 5.40 (dt, *J* = 17.2, 1.64 Hz) and 5.22 (dt, *J* = 10.5, 1.64 Hz) ppm confirmed the conversion of **59** to **53**. The resonances due to rest of the protons were in conformity with the proposed structure **53**. The structure of **53** was further confirmed by its ^{13}C NMR spectrum in which resonances due to vinylic carbons were

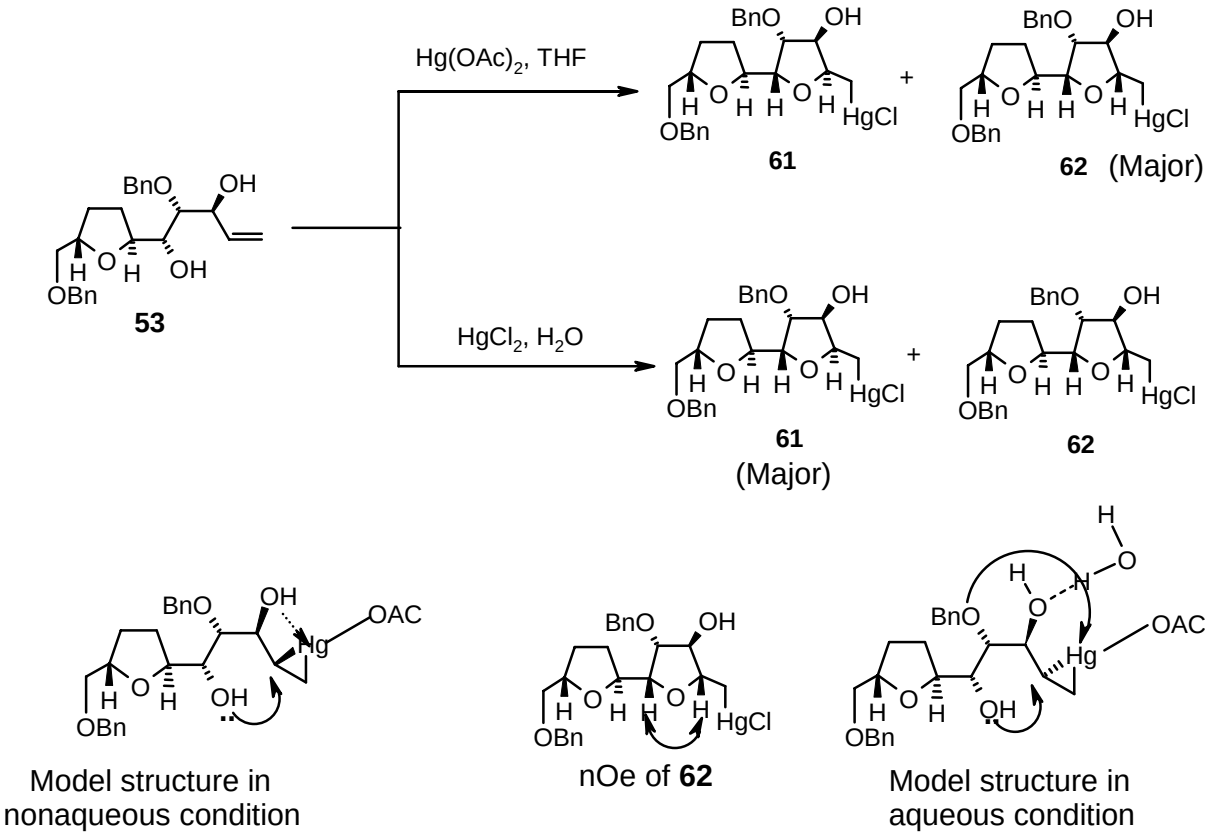
identified at δ 116.2 (terminal olefin carbon) and δ 138.1 (internal olefin carbon) ppm (Scheme 12).

Scheme 12



Now, the requisite structural skeleton was set for the second intramolecular oxymercuration. Treatment of compound **53** with mercury (II) acetate in dichloromethane or THF afforded **62** as the major product, whereas in the presence of H_2O, compound **61** formed as the major product.

Scheme 13



Structure of **61** and **62** was confirmed by ^1H, ^{13}C NMR and elemental analysis. ^1H NMR spectrum of **61** showed the methylene signals at δ 2.19 (dd, J = 6.8, 11.9Hz, 1H), 2.10 (dd,

J = 3.2, 11.9Hz, 1H) ppm due to –CH_2Hg group and disappearance of olefinic signals at δ 6.01(m, 1H), 5.40 (dt, *J* =17.2, 1.6 Hz, 1H) and 5.22 (dt, *J* =10.5, 1.6Hz, 1H) ppm indicating the transformation of **53** to **61**. Similarly in the ^{1}H NMR spectrum of **62** the methylene signals corresponding to -CH_2Hg- group appeared at δ 2.05 (dd, *J* = 7.0, 12.0 Hz, 1H) and 2.02 (m, 1H) ppm. Further confirmation was carried out by ^{13}C NMR spectroscopy. The relative stereochemistry was ascertained by using NOESY spectrum, where the targeted oxymethine protons of **62** showed (scheme-13) strong nOe interactions confirming the assigned structure.

As **61** and **62** obtained stereoselectively by simple alternation, we becames curious to check the selectivity in various conditions. Accordingly several parameters have been changed and the results observed in oxymercuration reaction were presented in the Table-**1**.

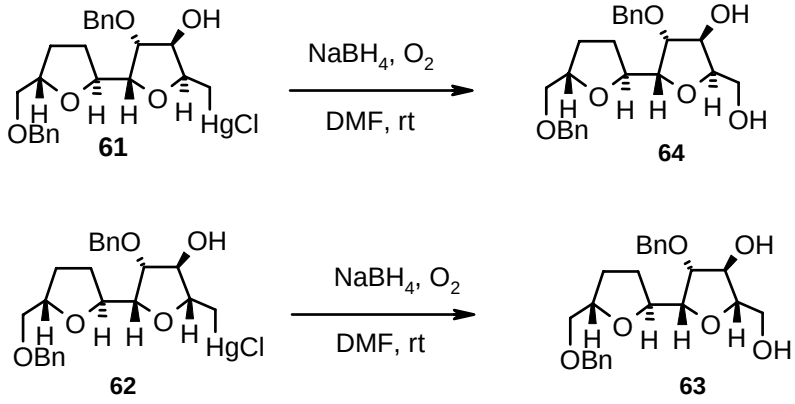
Table 1 Conversion of **53** to **61** and **62** under various conditions

Entry	Equivalents of **53**	Conditions	Ratio **61**:**62**	Yield
1	1.0	$Hg(OAc)_2$(1.5 equiv), CH_2Cl_2, rt, 3 h	5:95	92
2	1.0	$Hg(OAc)_2$(1.5 equiv), THF, rt, 3 h	5:95	89
3	1.0	$Hg(OAc)_2$(1.5 equiv), H_2O:THF, (2:1) rt, 3 h	85:15	90
4	1.0	HgCl2(1.5 equiv), H2O-THF(2:1), rt, 2 h	87:13	87
5	1.0	$HgCl_2$(1.5 equiv), H_2O, rt, 2 h	95:5	92
6	1.0	$HgCl_2$(1.5 equiv), THF, rt, 2 h	14:86	91

From these studies we concluded that in $HgCl_2$, H_2O condition **61** and **62** obtained in high yield with 95:5 ratio, whereas using $Hg(OAC)_2$, CH_2Cl_2 **61** and **62** obtained in high yield with 5:95 ratios.

Next, demercuration of **61** and **62** under the stream of oxygen in the presence of sodium borohydride to give alcohols **64** and **63** respectively. Compound **64** and **63** were confirmed by ^1H, ^{13}C NMR and elemental analysis (Scheme 14). In the ^1H NMR spectrum of **64** methylene signals appeared at δ 3.78 (dd, *J* = 3.7, 11.6Hz, 1H) and 3.71 (dd, *J* = 3.7, 11.6 Hz, 1H) ppm corresponding to -CH_2OH group. In the ^{13}C NMR spectrum the characteristic primary hydroxylic carbon resonated at δ 62.6 ppm confirming the assigned structure. Elemental analysis data also supported the formation of **64**. Similarly ^1H NMR spectrum of **63** showed the methylene signals at δ 3.91 (d, *J* = 12.3 Hz, 1H) and 4.22 (m, 1H) ppm indicating formation of CH_2OH group. All other protons resonated at their expected values. ^{13}C NMR spectrum of **63** showed a signal at δ 62.3 ppm corresponding to CH_2OH group, which was further confirmed by DEPT spectrum.

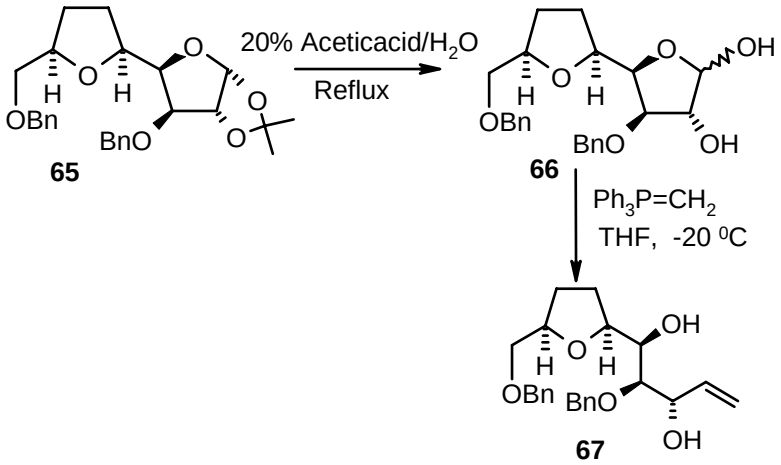
Scheme 14



After getting bisTHF alcohol **63** and **64** in hand, we intended to synthesize various bis-THF alcohols with varying stereochemistry using same mercuriocyclisation protocol starting from **65** (Its synthesis was already mentioned in chapter-**1**). We performed the same set of reactions as described in scheme-**15** and scheme-**16** respectively. The hydrolysis of compound **65** was accomplished in the presence of 20% acetic acid and catalytic amount of H_2SO_4 under refluxing conditions to give hemiacetal

66. The compound **66** was treated with one carbon Wittig ylide $Ph_3P=CH_2$ (generated in situ by the reaction of methylenetriphenyl phosphonium iodide and *n*-Buli in THF) in THF at -20 °C to afford compound **67**. The structure of **67** was characterized by its ^1H, ^{13}C NMR study and elemental analysis. The ^1H NMR spectrum displayed characterstic peaks due to methine protons of olefin at δ 5.94 (m, 1H) and the methylene protons of olefin at δ 5.39 (dt, 1H, *J* = 17.31, 1.7 Hz) and 5.18 (dt, 1H, *J* = 10.5, 1.7 Hz) ppm. The resonances due to rest of the protons were in conformity with the proposed structure of **67**. The structure of **67** was further analysed from its ^{13}C NMR spectrum, where CH_2 carbon of olefin identified at δ 115.8 (terminal olefin carbon) ppm and the internal –CH carbon resonated at δ 137.7 ppm (internal olefin carbon) (Scheme 15).

Scheme 15



Now, the requisite structural skeleton was set for the second intramolecular oxymercuration. Treatment of compound **67** with mercury (II) acetate in dichloromethane or THF afforded **68** as the major product. Demercuration of **68** under a stream of oxygen in the presence of sodium borohydride to give alcohol **69**. ^1H NMR spectrum showed the methylene signal at δ 3.50 ppm integrating two protons corresponding to $–CH_2OH$ group. In the ^{13}C NMR spectrum the distinguished $–CH_2OH$ carbon resonated at δ 62.0 ppm, which was further confirmed by DEPT spectrum. In addition to it elemental analysis data also supported the formation of **69** (Scheme 16).

Scheme 16

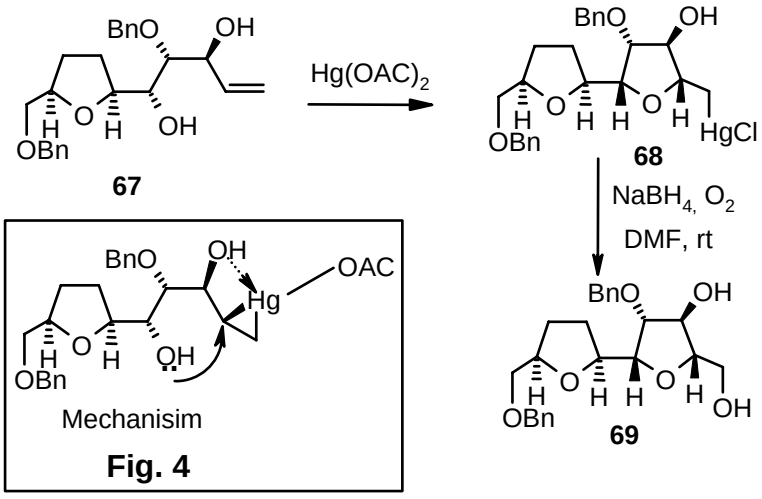


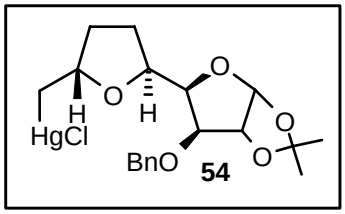
Fig. 4

Conclusion:

In conclusion bis-THF alcohols **63**, **64** and **69** of nonclassical acetogenins has been synthesized stereoselectively employing intramolecular mercurio cyclisation as the key reaction. The influence of H_2O in mercury mediated cyclisation has been studied. All of our synthesis was commenced from chiral precursor **55**, which was easily prepared from D-Glucose.

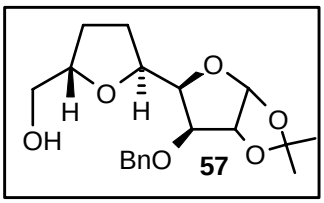
EXPERIMENTAL

5,8- Anhydro-3-*O*-benzyl-6,7,9-trideoxy-9-chloromercuryl-1,2-*O*-isopropylidene-D-*glycero*-β-L-*ido*-nonano furanose (54)



To a solution of homoallylic alcohol 55 (5.2 g, 15.5 mmol) in CH_2Cl_2 (50 mL), $Hg(OAc)_2$ (5.8 g, 18.6 mmol) was added at room temperature. After 2h stirring, reaction mixture was quenched with brine solution (20 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, concentrated under reduced pressure. Purification of the crude compound by flash silica gel column chromatography (20%Ethylacetate/light petroleum) provided the title compound as a single diastereomer 54 (7.97 g, 90%).

5,8- Anhydro-3-*O*-benzyl-6,7-dideoxy-1,2-*O*-isoprropylidene-D-*glycero*-β-L-*ido* nonanofuranose (57)



To a stirred solution of compound 32 (5.2 g, 9 mmol) in DMF (50 mL), O_2 was bubbled through a long syringe needle for 10 min. In an another flask, a suspension of $NaBH_4$ (414mg, 10 mmol) in DMF (10mL) 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 flash silica gel column chromatography (80% ethylacetate/light petroleum ether) to afford primary alcohol 57 (2.8 g, 87%) as a colorless liquid.

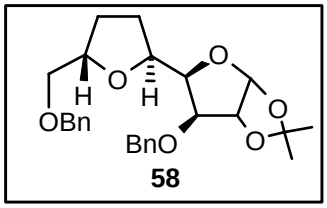
$[\alpha]_D$: –54.0 (c 2.4, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 – 7.26 (m, 5H), 5.95 (d, 1H, *J* = 3.7 Hz), 4.66 (d,1 H, *J* = 11.8 Hz), 4.41 (d,1H, *J* = 11.8 Hz), 4.26 (m, 1H), 4.08 (m, 2H), 3.86 (d, 1H, *J* = 3.4 Hz), 3.63 (dd, 1H, *J* = 3.7, 11.8 Hz), 3.49 (dd , 1H, *J* = 5.30, 11.8 Hz), 3.20 (brs, 1H), 2 .00 –1.71 (m, 3H), 1.49 (m, 1H), 1.48 (s, 3H), 1.30 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 137.1, 128.5, 128.0, 127.8, 111.6, 105.4, 83 .2, 82.4, 81.8, 79.7, 77.6, 71. 6, 64.4, 28.3, 27.4, 26.9, 26.4

Anal. Calcd for $C_{19}H_{25}O_5HgCl$: C, 40.07; H, 4.42. Found: C, 40.32; H, 4.78.

5,8-Anhydro-3,9-di-*O*-benzyl-6,7-dideoxy-1,2-*O*-isopropylidene-D-glycero-β-L-*ido*-nonanofuranose (58)



58

Compound **57** (3.6 g, 10 mmol) in DMF (20 mL) was added to a stirred suspension of NaH (0.493 g, 60% dispersion in oil, 15.0 mmol) in DMF (20 mL) at 0 °C. The resulting solution was stirred at rt for 30 min, BnBr (1.3 mL, 11 mmol) was added. After 1 h, the reaction was quenched by ice-cold water and extracted with EtOAc. The combined organic layers were washed with H_2O, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel using 10-15% EtOAc/light petroleum ether to obtain **58** (4.2 g, 94%).

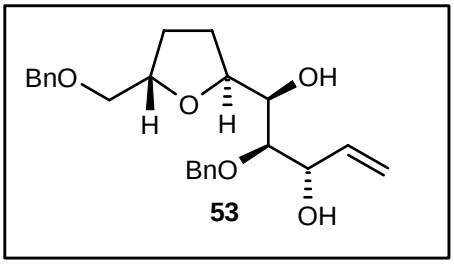
$[\alpha]_D$ **:** –50.13 (*c* 3.1, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.35 (m, 10H), 5.96 (d, 1H , *J* = 3.9 Hz), 4.66 (d , 1H, *J* = 11.9 Hz), 4.59 (d, 1H , *J* = 3.9 Hz), 4.54 (s, 2H), 4.41 (d ,1H, *J* = 11.9 Hz), 4.31-4.10 (m, 2H), 4.06 (dd ,1H, *J* = 3.53, 8.08 Hz), 3.85 (d, 1H, *J* = 3.54 Hz), 3.60-3.42 (ddd, 2H, *J* = 4.7, 10.0 Hz), 2.05-1.66 (m, 3H), 1.48 (s, 3H), 1.48 (m,1H), 1.30 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 138.1, 136.8, 127.9, 127.8, 127.4, 127.2, 127.1, 126.9, 110.9, 105.0, 82.6, 82.0, 81.4, 77.6, 77.3, 72.7, 72.2, 71.1, 28.2, 27 .7, 26.4, 25.9.

Anal. Calcd for $C_{26}H_{32}O_6$: C, 40.07; H, 4.42. Found: C, 40.32; H, 4.78.

(1*R*,2*R*,3*S*)-2-(benzyloxy)-1-((2*S*,5*S*)-5-(benzyloxymethyl)-tetrahydrofuran-2yl) Pent-4-ene-1, 3-diol (53)



53

The benzyl ether **58** (2.4 g, 5.4 mmol) was dissolved in THF:H_2O (18:5 mL) and catalytic amount of *p*-TSA was added. The reaction mixture was 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 **59** (1.7 g, 78%) as a colorless oil which was converted to olefin 53 via Wittig reaction using PPh3+CH3I- (9.692 g, 24 mmol) and n-BuLi (1.6 M, 13 mL, 21 mmol) in 100 mL THF at 0 °C. To THF (200 mL) solution of the lactol, the ylide was added and stirred for 10 h at room temperature and the reaction mixture was quenched by water. 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/light petroleum) afforded **53** (1.5 g, 88 %) as a colorless oil over two steps.

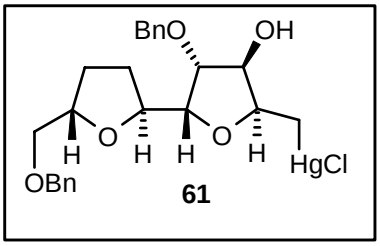
$[\alpha]_D$: –10.7 (*c* 2.4, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (m, 10H), 6.01 (m, 1H), 5.40 (dt, 1H, *J* = 17.2, 1.64 Hz), 5.22 (dt, 1H, *J* = 10.5, 1.64 Hz), 4.69 (s, 2H), 4.54 (s, 2H), 4.37 (m, 3H), 4.18 (m, 2H), 3.59 (t, 1H, *J* = 3.8 Hz), 3.45 (m, 3H), 2.07-1.65 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 138.1, 137.9, 128.3, 128.2, 128.0, 127.7, 127.6, 127.5, 127.4, 116.2, 82.2, 78.9, 78.4, 74.3, 73.2, 72.6, 72.5, 72.1, 28.4, 28.0.

Anal. Calcd for $C_{24}H_{30}O_5$: C, 72.33; H, 7.58. Found: C, 72.30; H, 7.53.

(2*R*,2'*S*,3*R*,4*R*,5*S*,5'*S*)-3-(benzyloxy)-5'-(benzyloxymethyl)-4-hydroxy-octahydro-2,2'-bifuran-5-yl)methyl)mercury(II)chloride (61)



61

To a solution of homoallylic alcohol **53** (34 g, 85 mmol) in H_2O (10 mL), $Hg(OAc)_2$ (350 mg, 1.12 mmol) was added at room temperature. After 2h stirring, reaction mixture was quenched with brine solution (15 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, concentrated under reduced pressure. Purification of the crude compound by flash silica gel column chromatography (20% Ethylacetate/light petroleum) provided the title compound as a major *trans* diastereomer **61** (471 mg) and further elution afforded the minor *cis*-isomer (25 mg) as a colorless thick liquid.

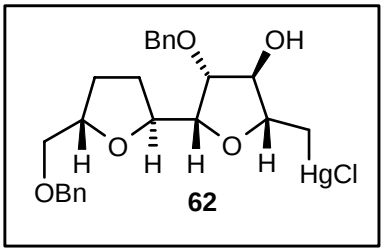
$[\alpha]_D$ **:** –23.1 (*c* 2.3, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35–7.26 (m, 10H), 4.67 (d, 1H, *J* = 12.4 Hz), 4.53 (d, 2H, *J* = 2.3 Hz), 4.45 (d, 1H, *J* = 12.4 Hz), 4.27 (q, 1H, *J* = 7.8 Hz), 4.23–418. (m, 2H), 3.85 (dd, 1H, *J* = 4.1,7.8 Hz), 3.76–3.71 (m, 2H), 3.57 (dd, 1H, *J* = 5.9, 10.1 Hz), 3.46 (dd, 1H, *J* = 4.6, 10.1 Hz), 2.19 (dd, 1H, *J* = 6.8, 11.9 Hz), 2.10 (dd, 1H, *J* = 3.2, 11.9 Hz), 1.94 (m, 1H), 1.79 (m, 1H), 1.64 (m, 1H), 1.37 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 138.1, 137.1, 128.7, 128.6, 128.4, 128.3, 127.9, 127.7, 85.1, 84.7, 83.1, 81.6, 78.2, 78.0, 73.4, 72.7, 71.6, 29.7, 28.6, 28.0.

Anal. Calcd for $C_{24}H_{29}O_5HgCl$: C, 45.50; H, 4.61. Found: C, 45.38; H, 4.73.

(2*R*,2'*S*,3*R*,4*R*,5*R*,5'*S*)-3-(benzyloxy)-5'-(benzyloxymethyl)-4-hydroxy-octahydro-2,2'-bifuran-5-yl)methyl)mercury(II)chloride (62)



62

To a solution of homoallylic alcohol **53** (.3 g, .75 mmol) in CH_2Cl_2 (20 mL), $Hg(OAc)_2$ (350 mg, 1.12 mmol) was added at room temperature. After 2h stirring, reaction mixture was quenched with brine solution (15 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, concentrated under reduced pressure. Purification of the crude compound by flash silica gel column chromatography (20% Ethylacetate/light petroleum) provided the title compound as a major *cis* diastereomer **62** (414 mg, 92%) and further elution afforded the minor *trans*-isomer (22 mg) as a colorless thick liquid.

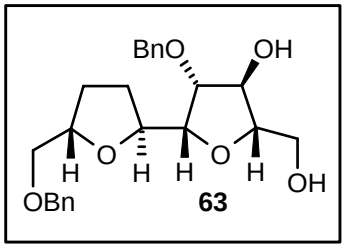
$[\alpha]_D$: –19.27 (*c* 1.7, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.24 (m, 10H), 4.61–4.55 (m, 2H), 4.52 (s, 2H), 4.43 (d, 1H, *J* = 11.9 Hz), 4.28 (q, 1H, *J* = 7.6 Hz), 4.24–4.17 (m, 1H), 4.13–4.07 (m, 2H), 3.87 (d, 1H, *J* = 4.0 Hz), 3.55 (dd, 1H, *J* = 5.8, 10.1 Hz), 3.46 (dd, 1H, *J* = 4.27, 10.1 Hz), 3.12 (brs, 1H), 2.05 (dd, 1H, *J* = 7.0, 12.0 Hz), 2.02 (m, 1H), 1.78 (dd, 1H, *J* = 3.7,12.0 Hz), 1.74–1.62 (m, 2H), 1.47 (m, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 138.1, 137.7, 128.5, 128.4, 128.0, 127.9, 127.7, 127.5, 85.3, 82.7, 79.4, 78.6, 77.9, 74.2, 73.4, 72.8, 72.3, 28.7, 28.0, 27.9.

Anal. Calcd for $C_{24}H_{29}O_5HgCl$: C, 45.50; H, 4.61 Found: C, 45.32; H, 4.52.

(2*R*,2'*S*,3*R*,4*S*,5*S*,5'*S*)-3-(benzyloxy)-5'-(benzyloxymethyl)-5-hydroxymethyl-octahydro-2,2'-bifuran-4-ol (63)



To a stirred solution of compound **62** (200 mg, .32 mmol) in DMF (8 mL), O_2 was bubbled through a long syringe needle for 10 min. In an another flask, a suspension of $NaBH_4$ (15 mg, 0.4 mmol) in DMF (7 mL) 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 flash silica gel column chromatography (80% Ethylacetate/light petroleum) to afford primary alcohol **63** (.168 mg, 86 %) as a colorless liquid.

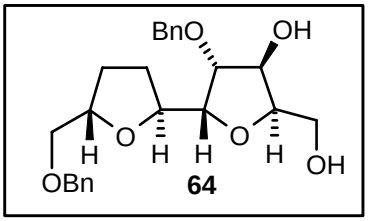
$[\alpha]_D$: -20.41 (c 0.5, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.26 (m, 10H), 4.64 (d, 1H, *J* = 11.8 Hz), 4.55 (s, 2H), 4.46 (d, 1H, *J* = 11.8 Hz), 4.44 (brs, 1H), 4.31 (q, 1h, *J* = 8.03 Hz), 4.22-4.14 (m, 4H), 3.97 (d, 1H, *J* =12.3Hz), 3.90 (d, 1H, *J* = 3.8 Hz), 3.57 (dd, 1H, *J* = 5.02, 9.79 Hz), 3.48 (dd, 1H, *J* = 5.27, 10.04 Hz), 2.84 (brs, 1H), 2.00 (m, 2H), 1.51 (m, 1H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 138.2, 137.6, 128.4, 128.3, 127.8, 127.7, 127.5, 85.3, 84.0, 78.9, 78.8, 78.1, 77.2, 73.4, 72.7, 72.2, 62.1, 28.8, 28.04.

Anal. Calcd for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30 Found: C, 69.52; H, 7.24.

(2*R*,2'*S*,3*R*,4*S*,5*R*,5'*S*)-3-(benzyloxy)-5'-(benzyloxymethyl)-5-(hydroxymethyl)-octahydro-2,2'-bifuran-4-ol (64)



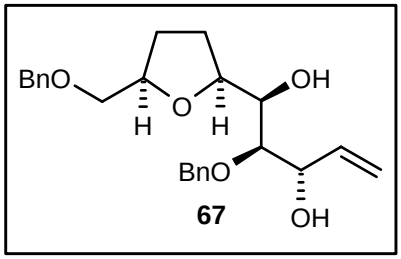
$[\alpha]_D$ **:** –13.6 (*c* 2.4, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31–7.26 (m, 10H), 4.65 (d, 1H, *J* = 11.9 Hz), 4.53 (s, 2H), 4.41 (d, 1H, *J* = 11.9 Hz), 4.32 (brs, 1H), 4.29 (q, 1H, *J* = 8.3 Hz), 4.19 (m, 1H), 3.92 (dd, 1H, *J* = 4.6, 7.8 Hz), 3.89 (q, 1H, *J* = 4.1 Hz), 3.83 (dd, 1H, *J* = 1.8, 4.1 Hz), 3.78 (dd, 1H, *J* = 3.7, 12.0 Hz), 3.71 (dd, 1H, *J* = 4.1, 11.6 Hz), 3.53 (dd, 1H, *J* = 5.0, 10.1 Hz), 3.46 (dd, 1H, *J* = 5.0, 10.1 Hz), 3.25 (brs, 1H), 3.06 (brs, 1H), 2.04–1.95 (m, 2H), 1.76–1.68 (m, 1H), 1.56–1.49 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 138.2, 137.5, 128.4, 128.3, 127.9, 127.8, 127.6, 127.5, 86.2, 85.2, 83.0, 78.1, 75.4, 73.3, 72.5, 71.4, 62.6, 28.6, 28.2.

Anal. Calcd for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30 Found: C, 69.52; H, 7.24.

(1*R*, 2*R*, 3*S*)-2-(benzyloxy)-1-(2*S*, 5*R*)-5-(benzyloxymethyl)-tetrahydrofuran-2-yl)pent-4-ene-1,3-diol (67)



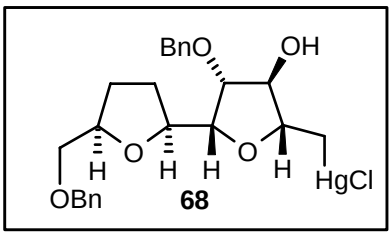
67

Compound **65** (1.3 g, 2.26 mmol) was taken in 20% acetic acid (20 mL) and catalytic amount of H_2SO_4 was added and heated at 70 °C for 3 h. The reaction mixture was neutralized by addition of solid $NaHCO_3$, filtered and concentrated. The residue was partitioned between EtOAc-water, the organic layer separated, washed with water, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel using 18-20% EtOAc/light petroleum ether to obtain **96** (807 mg) which was dissolved in THF (10 mL) and CH_2=PPh_3 [prepared from PPh_3CH_3I (4.9 g) and *n*-BuLi (1.6 M, 6.3 mL) at –20 ºC was added. After 3 h stirring at rt, it was worked up was done as usual and the residue purified on silica gel column using 17% EtOAc/light petroleum ether to furnish **67** (532 mg, 66%) as a thick oil.

$[\alpha]_D$ **:** + 2.6 (*c* 3.1, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–7.24 (m, 10H), 5.94 (m, 1H), 5.39 (dt, 1H, *J* = 17.31 Hz), 5.18 (dt, 1H, *J* = 10.5 Hz), 4.65 (s, 2H), 4.53 (d, 2H, *J* = 2.53 Hz), 4.40–4.10 (m, 3H), 3.63 (dd, 2H, *J* = 3.67, 10.11 Hz), 3.50–3.40 (m, 2H), 3.20 (brs, 1H), 1.93–1.92 (m, 4H)
^{13}C NMR (50 MHz, $CDCl_3$): δ 138.5, 138.3, 137.7, 128.4, 128.3, 128.1, 128.7, 127.7, 115.8, 82.8, 79.1, 78.8, 78.7, 74.4, 73.4, 72.2, 71.5, 28.4, 27.9.
Anal. Calcd for $C_{24}H_{30}O_5$: C, 72.33; H, 7.58. Found: C, 72.30; H, 7.51.

(2*R*,2'*S*,3*R*,4*R*,5*R*,5'*R*)-3-(benzyloxy)-5'-(benzyloxymethyl)-4-hydroxy-octahydro-2,2'-bifuran-5-yl)methyl)mercury(II)chloride (68)

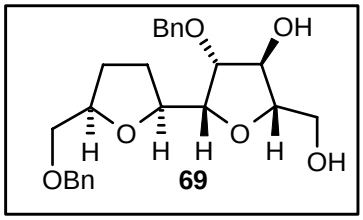


To a solution of homoallylic alcohol **67** (472 mg, 1.178 mmol) in CH_2Cl_2 (8 mL), $Hg(OAc)_2$ (552 mg, 1.767 mmol) was added at room temperature. After 2h stirring, reaction mixture was quenched with brine solution (25 mL) and stirred for 30 min. Organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 x 100 mL). Combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure. Purification of the crude compound by flash silica gel column chromatography (20% Ethylacetate/light petroleum ether) provided the compound **68** as a single diastereomer (642 mg, 86%) as a colorless thin liquid.

$[\alpha]_D$ **:** +12.32 (*c* 2.1, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.22 (m, 10H), 4.59 (d, 2H, *J* = 11.8 Hz), 4.52 (s, 2H), 4.44 (d, 1H, *J* = 11.5 Hz), 4.13 (m, 4H), 3.87 (brs, 1H), 3.01 (brs, 1H), 2.03 (dd, 1H, *J* = 7.2, 12.4 Hz), 3.54 (dd, 1H, *J* = 5.27, 9.79 Hz), 3.44 (dd, 1H, *J* = 5.02, 10.0 Hz), 1.98 – 1.84 (m, 2H), 1.74(m, 2H), 1.47 (m, 1H)
^{13}C NMR (50 MHz, $CDCl_3$): 138.2, 137.6, 128.5, 128.4, 127.0, 127.9, 127.7, 127.5, 85.5, 83.1, 79.3, 79.2, 78.3, 74.2, 73.4, 72.9, 72.3, 28.25, 27.89, 27.25.
Anal. Calcd for $C_{24}H_{29}O_5HgCl$: C, 48.19; H, 4.88. Found: C, 48.16; H, 4.82.

(2*R*,2'*S*,3*R*,4*S*,5*R*,5'*R*)-3-(benzyloxy)-5'-(benzyloxymethyl)-5-(hydroxymethyl)-octahydro-2,2'-bifuran-4-ol (69)



To a stirred solution of compound **68** (462 mg, 0.72 mmol) in DMF (10 mL), O_2 was bubbled through a long syringe needle for 10 min. In an another flask, a suspension of $NaBH_4$ (33mg, 0.87 mmol) in DMF (7 mL) 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 flash silica gel column chromatography (80% Ethylacetate/light petroleum) to afford primary alcohol **69** (251mg, 83 %) as a colorless liquid.

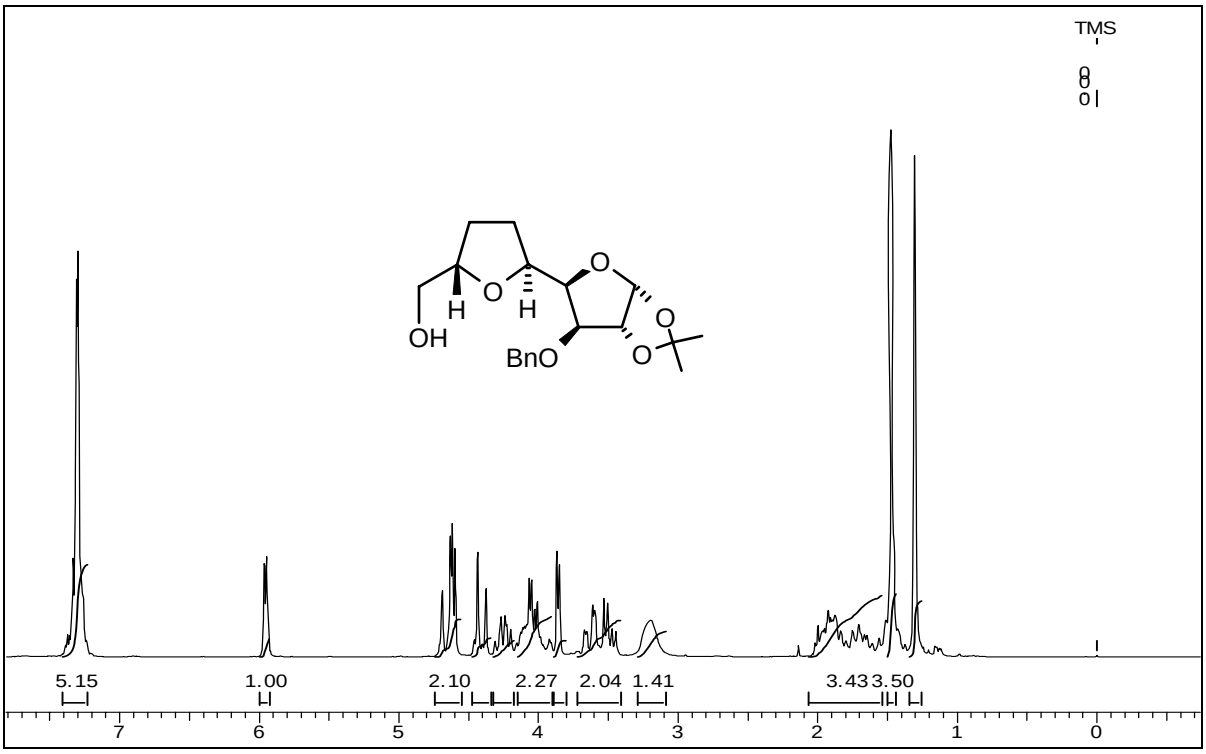
$[\alpha]_D$: –13.87 (*c* 1.4, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.26 (m, 10H), 4.64 (d, 1H, *J* = 11. 7 Hz), 4.54 (s, 2H), 4.42 (d, 1H, *J* = 11.7 Hz), 4.30 (s ,1H), 4.16–4.12 (m, 4H), 3.94 (d, 1H, *J* = 13.5 Hz), 3.90 (s , 1H), 3.6 (s, 1H), 3.50 (dd, 2H, *J* = 4.7, 7.3 Hz), 2.06-1.94 (m, 4H)

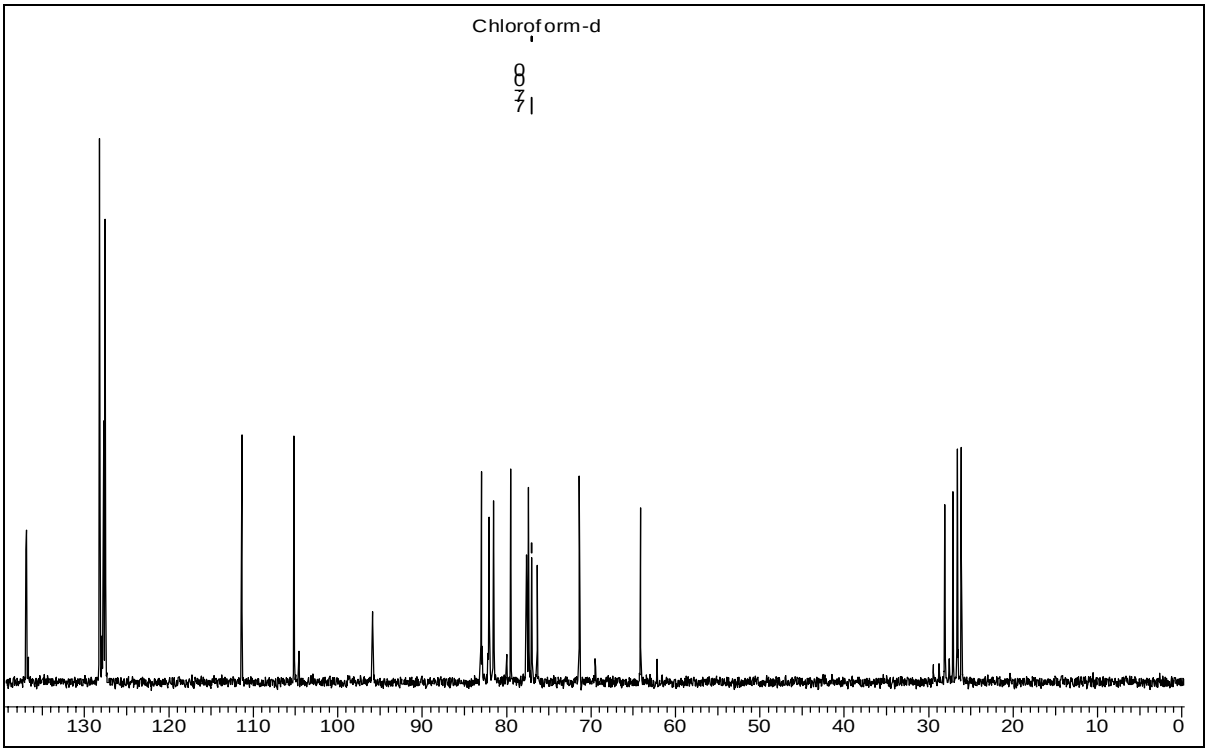
^{13}C NMR (50 MHz, $CDCl_3$): 1383, 137.7, 128.5, 128.5, 127.9, 127.6, 127.6, 127.6, 85.5, 84.1, 79.4, 78.9, 78.3, 76.5, 73.3, 72.6, 72.2, 62.0, 28.2, 27.2.

Anal. Calcd for $C_{24}H_{30}O_6$: C, 48.19; H, 4.88. Found: C, 48.16; H, 4.82.

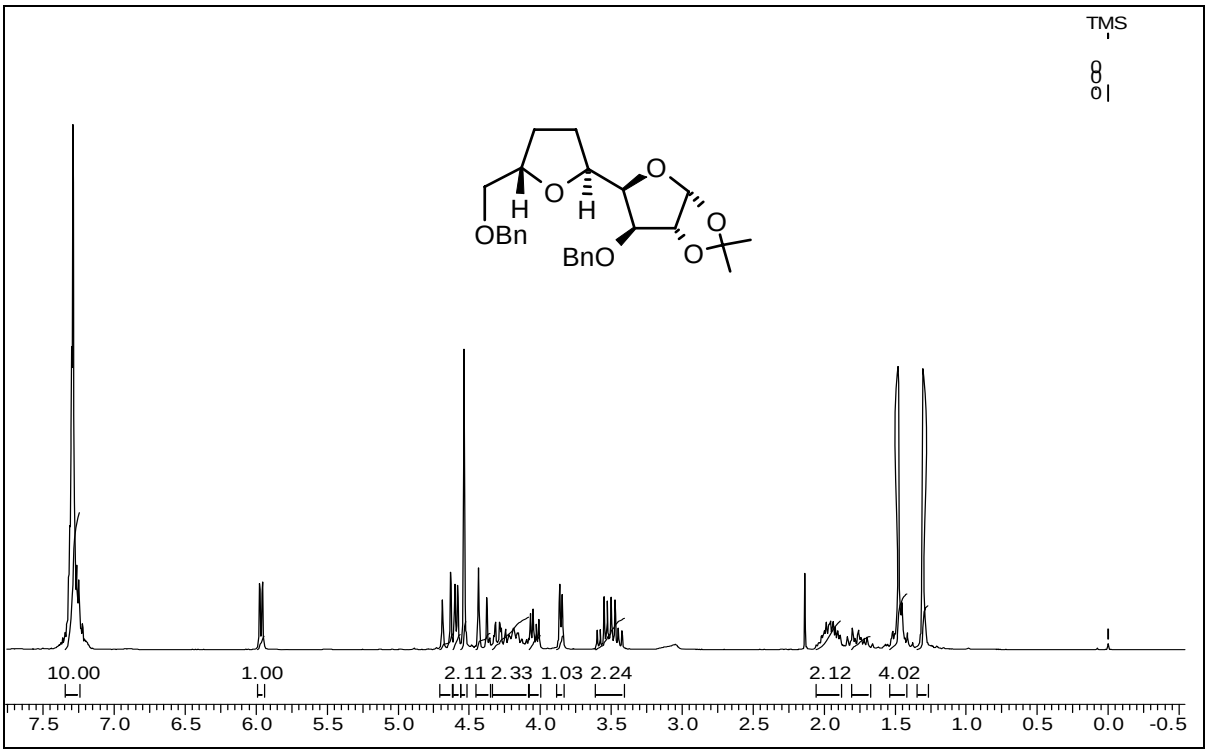
SPECTRA



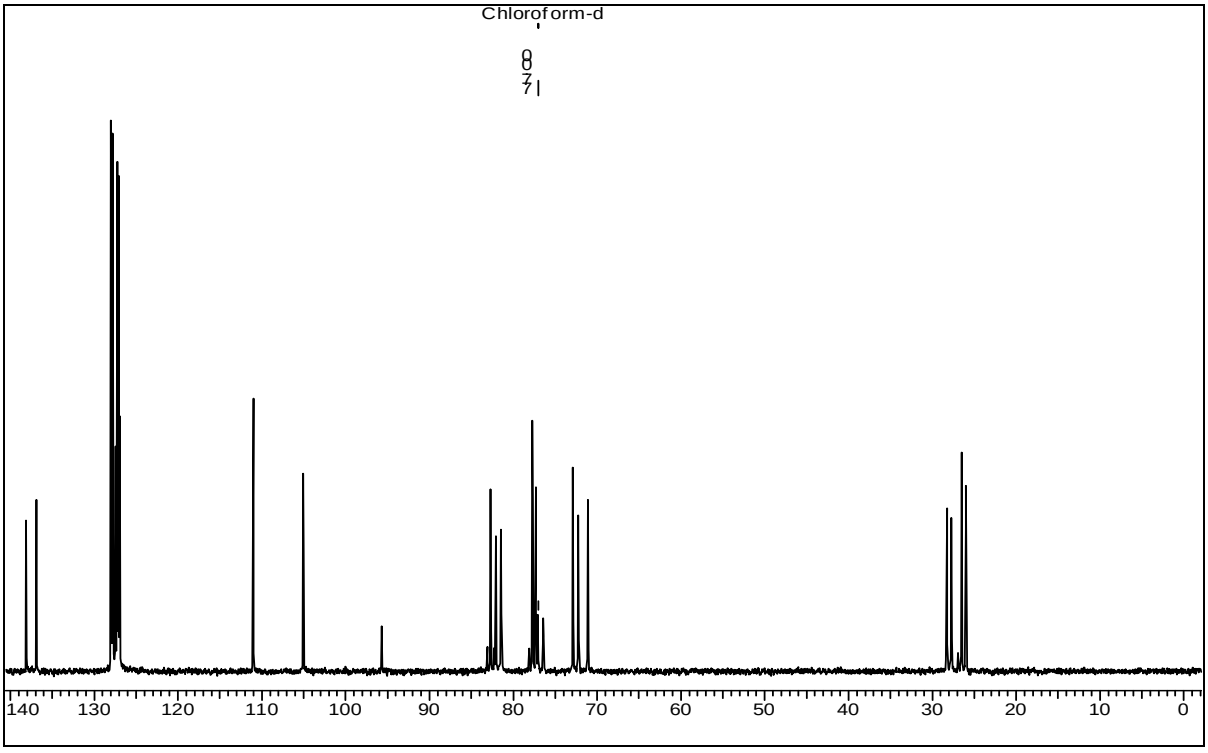
^{1}H NMR spectrum of compound 57 in $CDCl_3$



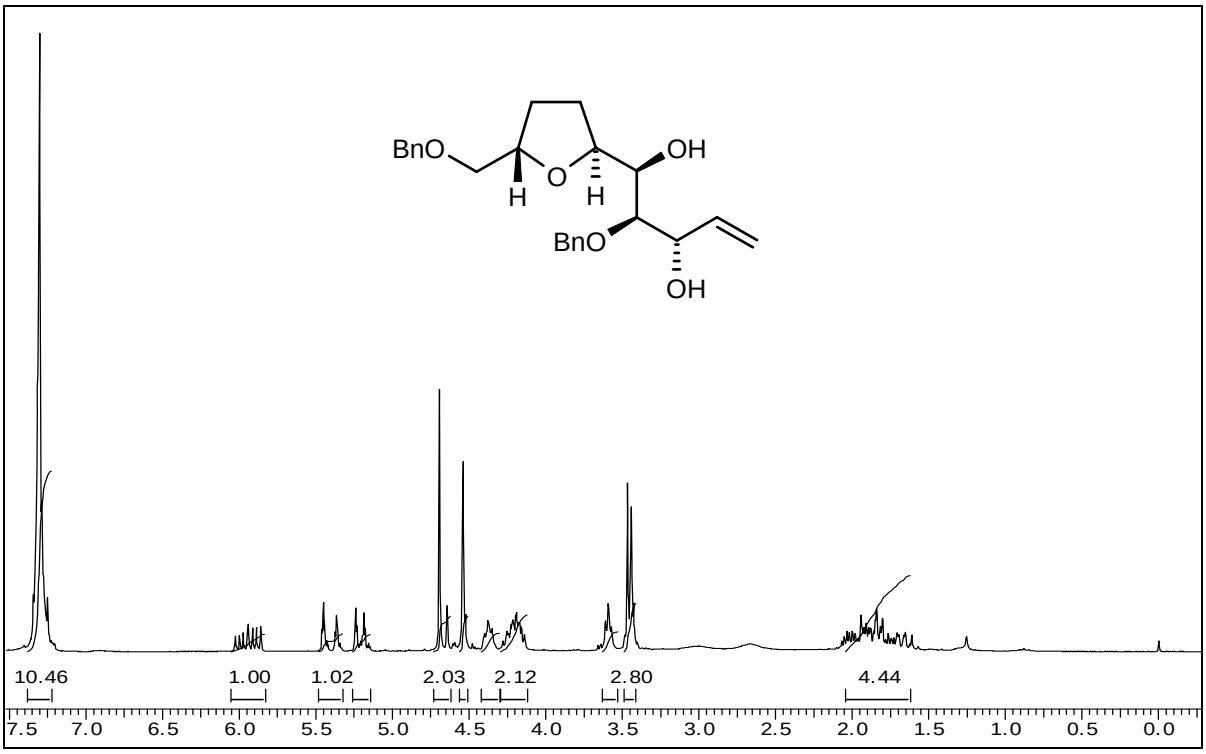
^{13}C NMR spectrum of compound 57 in $CDCl_3$



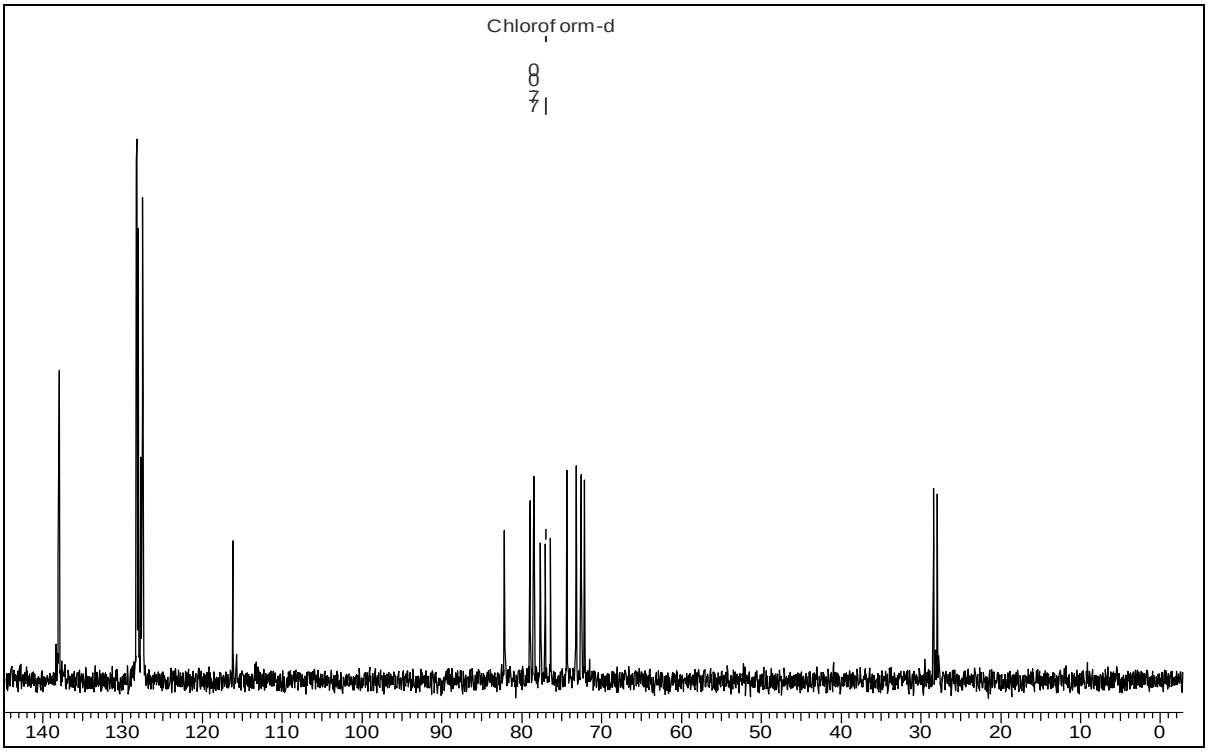
^{1}H NMR spectrum of compound 58 in $CDCl_3$



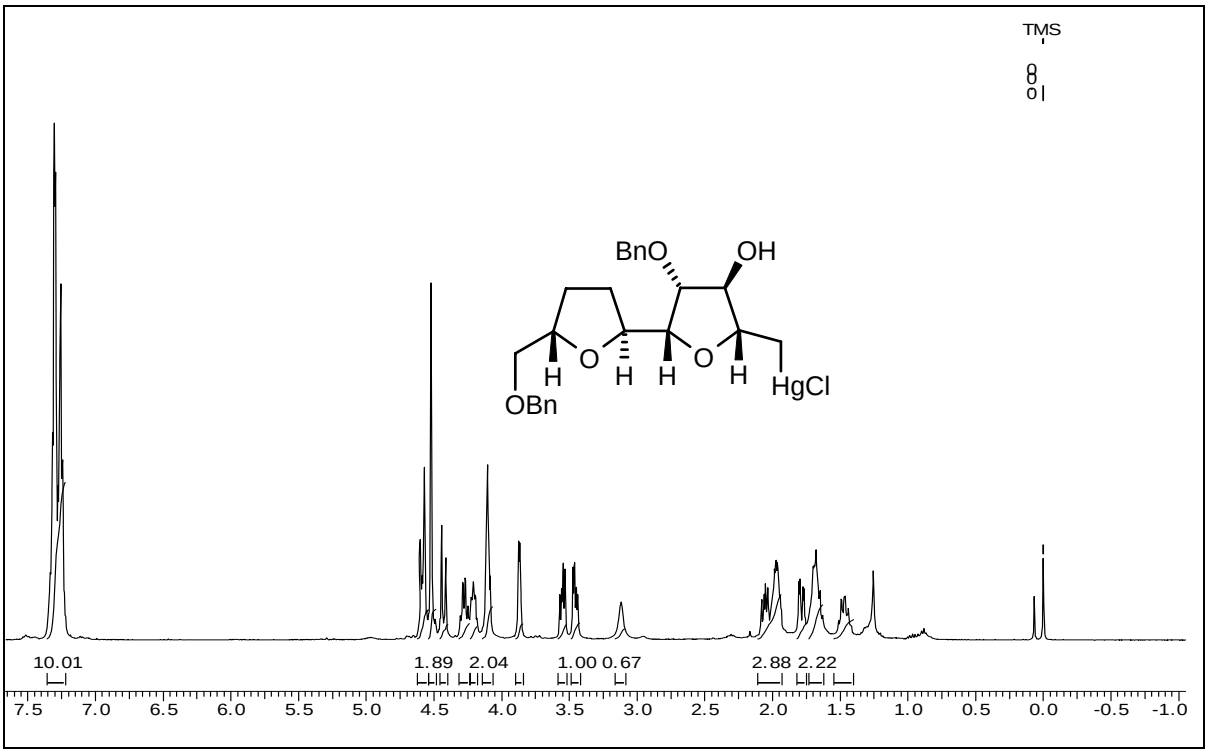
^{13}C NMR spectrum of compound 58 in $CDCl_3$



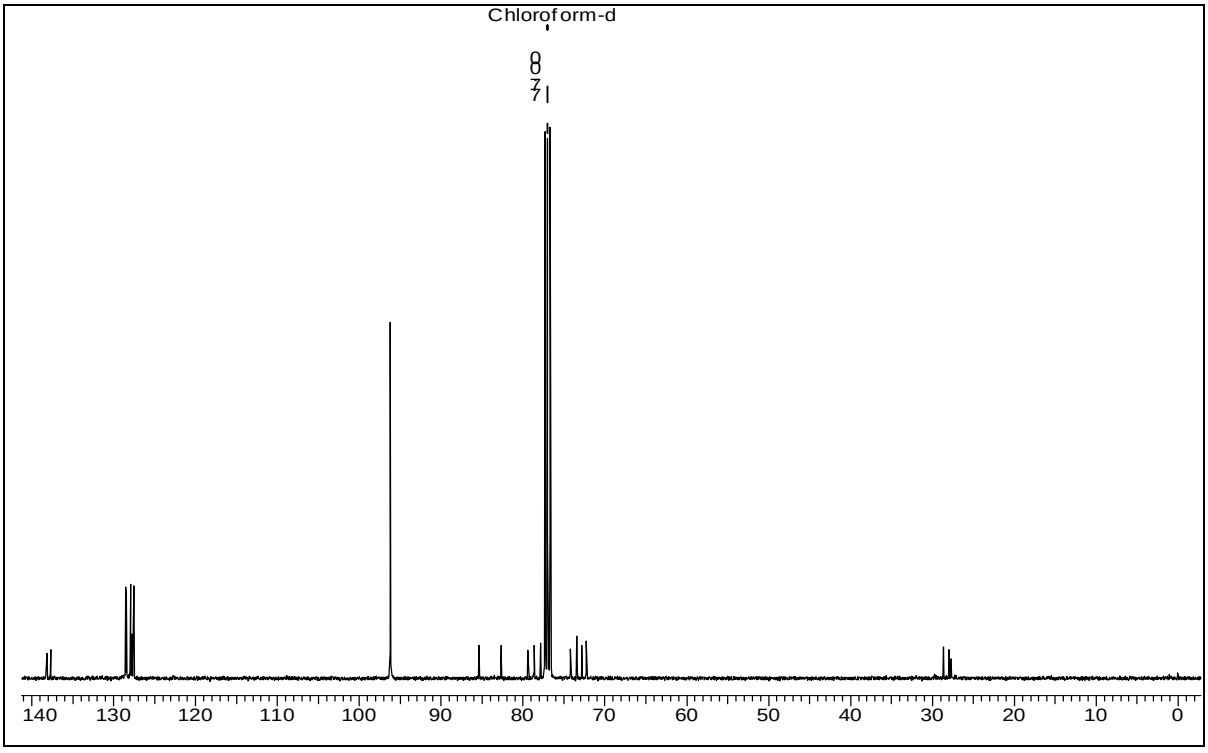
^{1}H NMR spectrum of compound 53 in $CDCl_3$



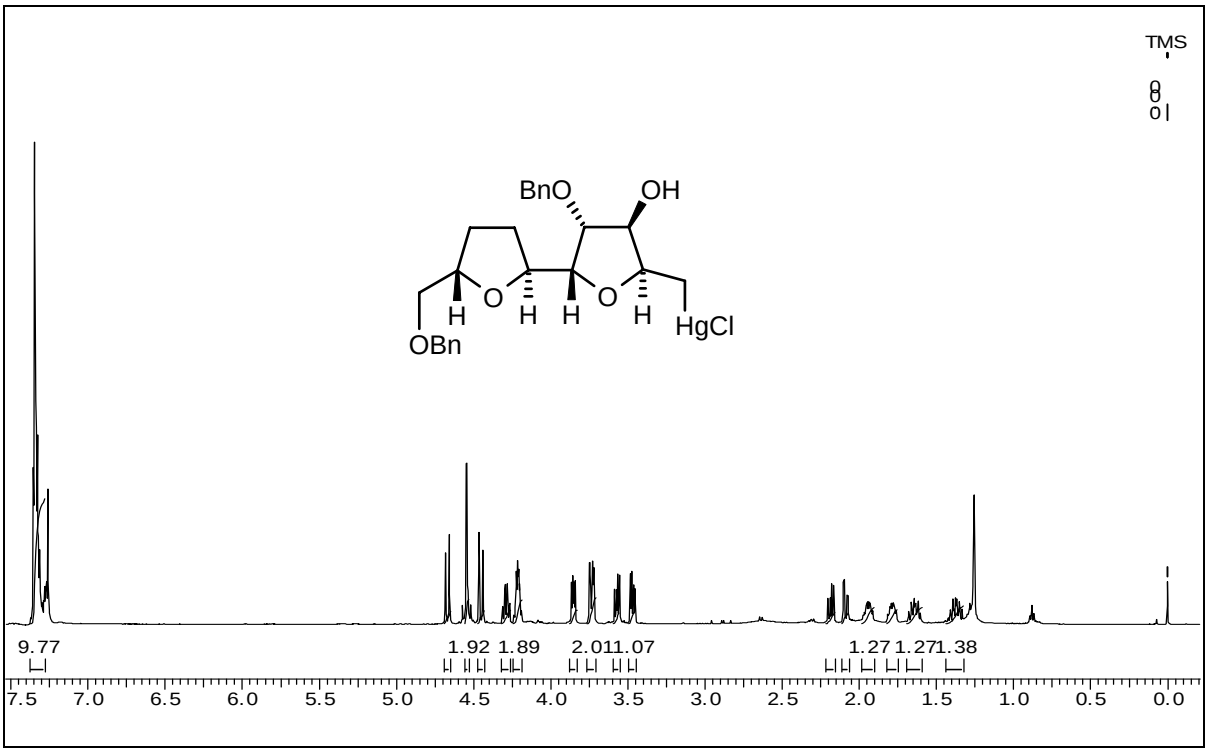
^{13}C NMR spectrum of compound 53 in $CDCl_3$



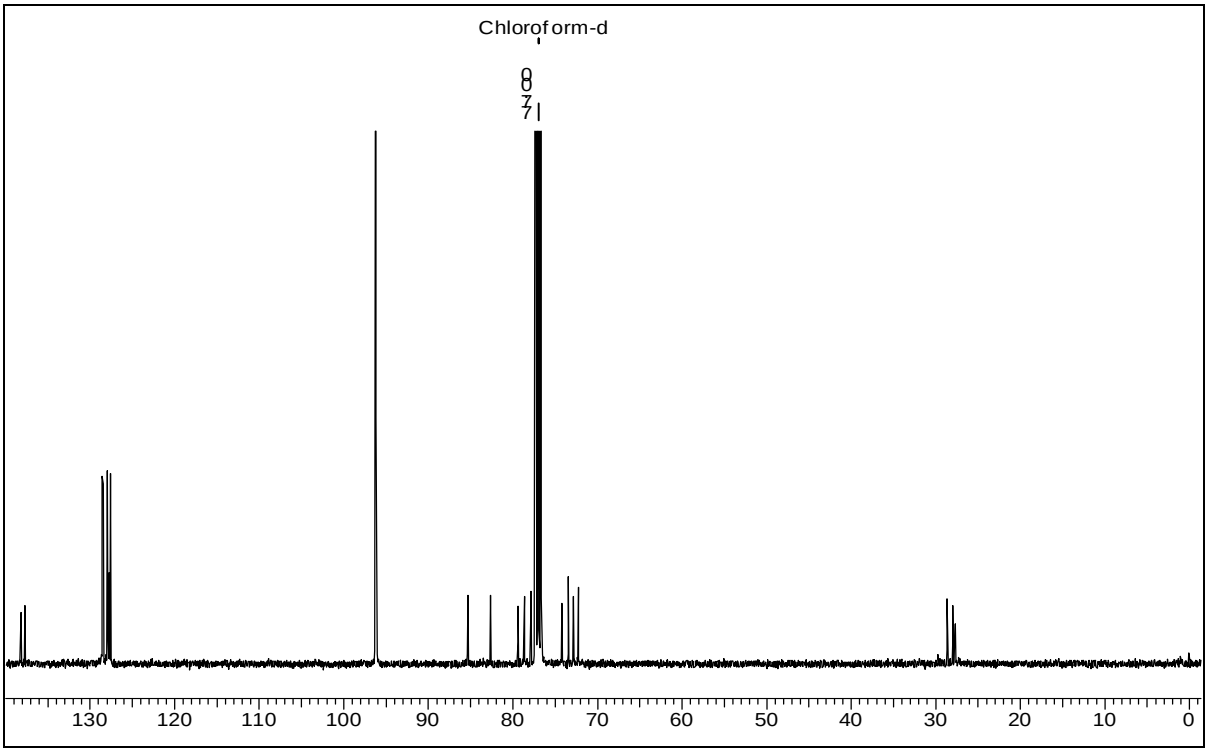
^{1}H NMR spectrum of compound 62 in $CDCl_3$



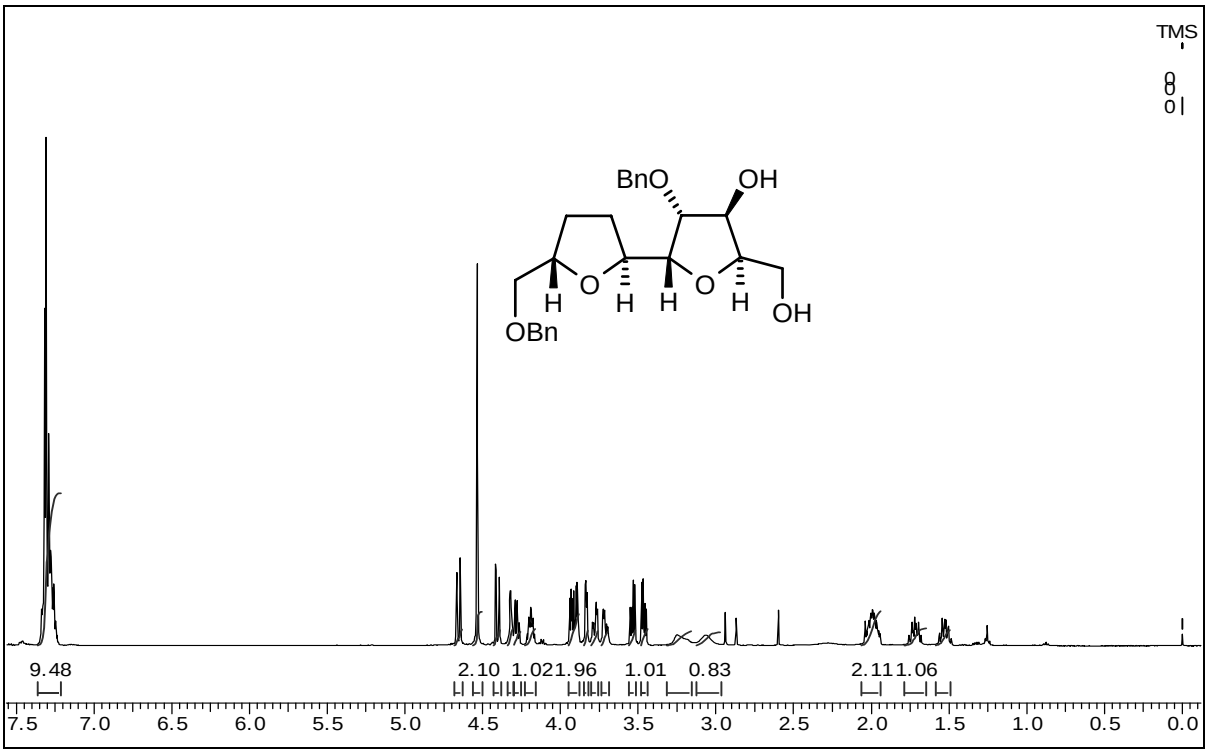
^{13}C NMR spectrum of compound 62 in $CDCl_3$



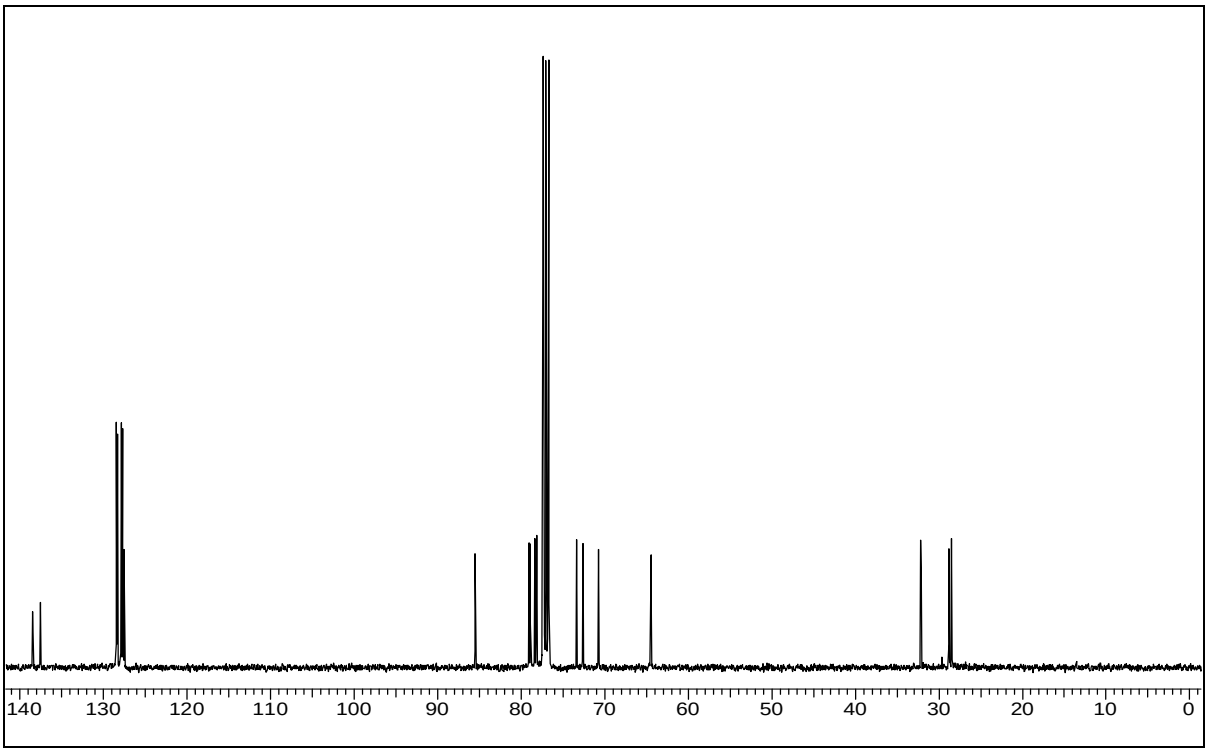
^{1}H NMR spectrum of compound 61 in $CDCl_3$



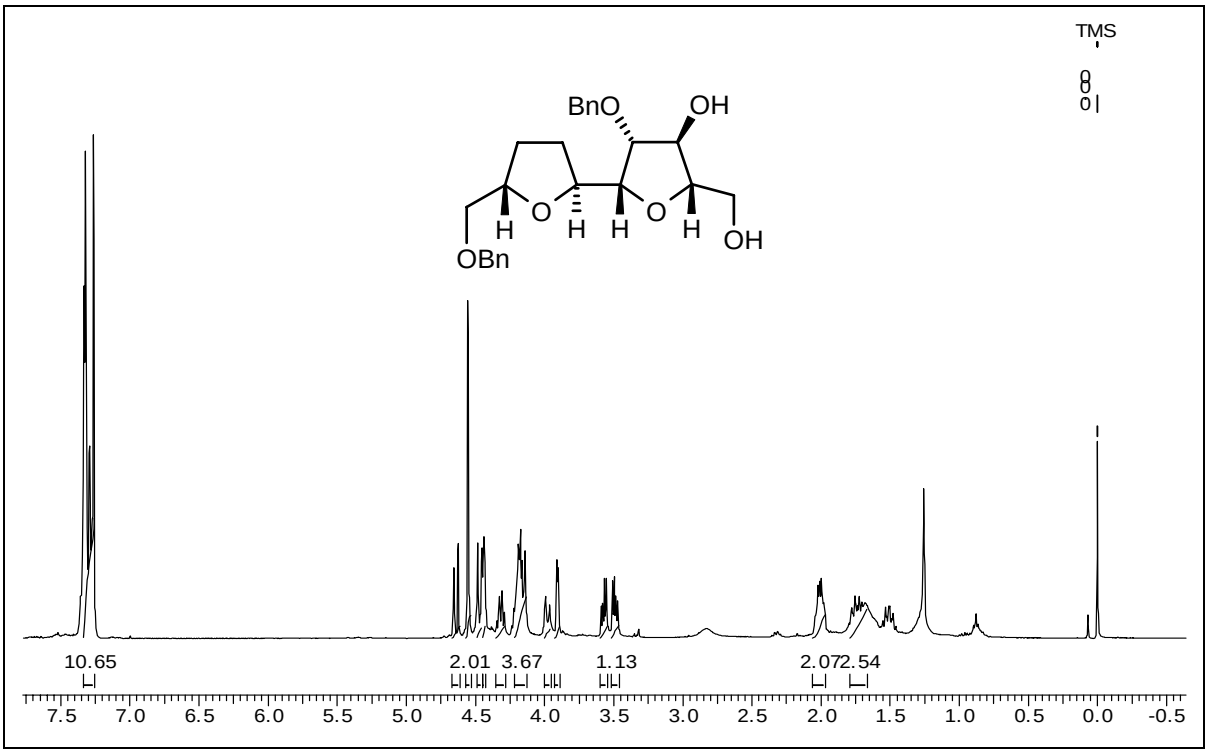
^{13}C NMR spectrum of compound 61 in $CDCl_3$



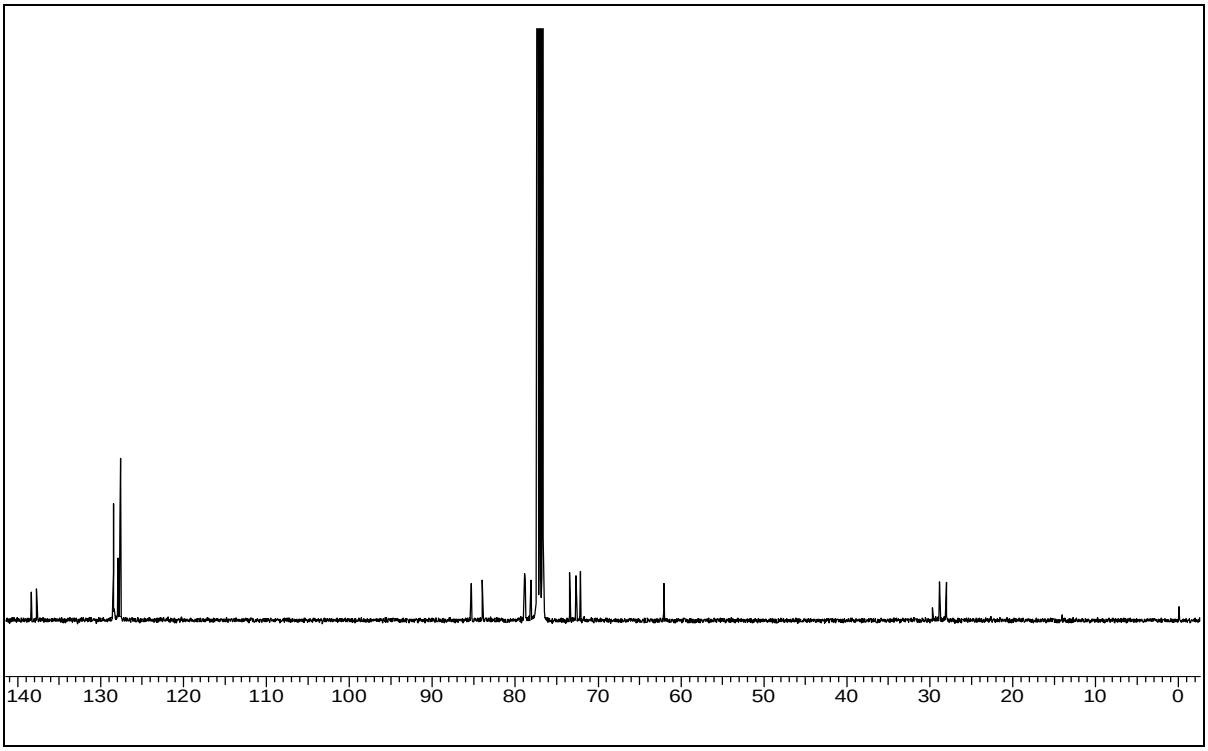
^{1}H NMR spectrum of compound 64 in $CDCl_3$



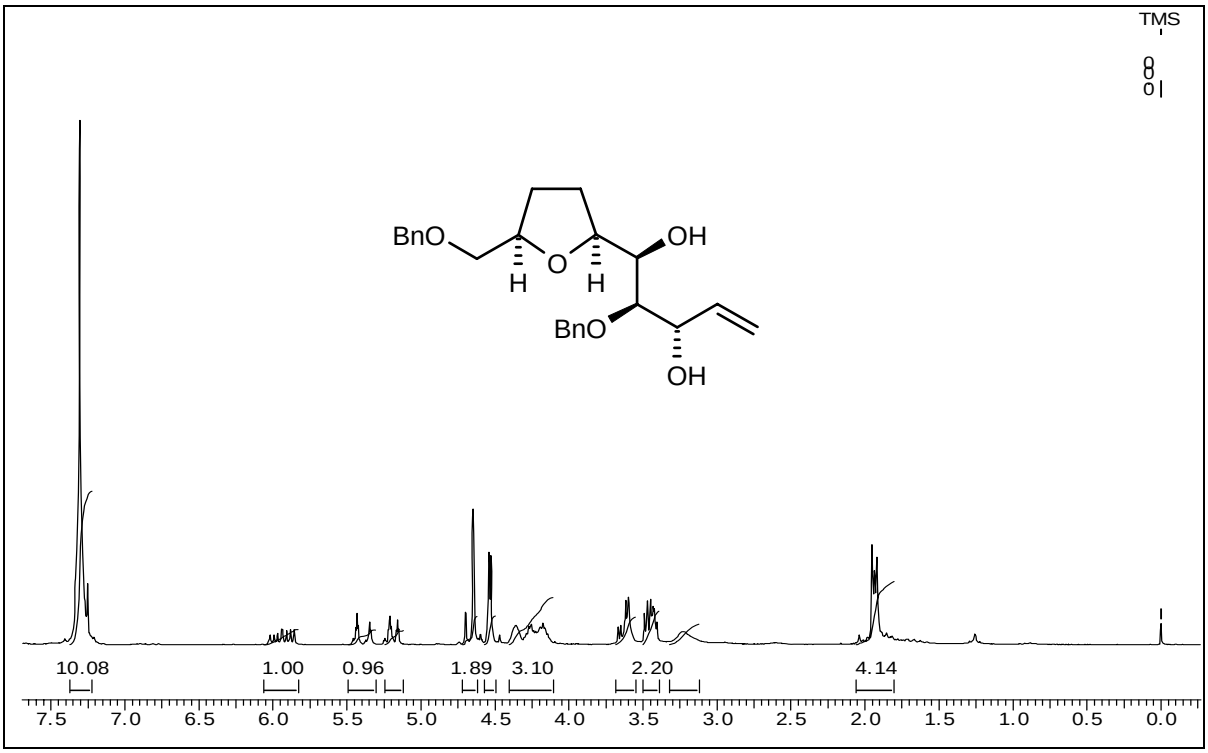
^{13}C NMR spectrum of compound 64 in $CDCl_3$



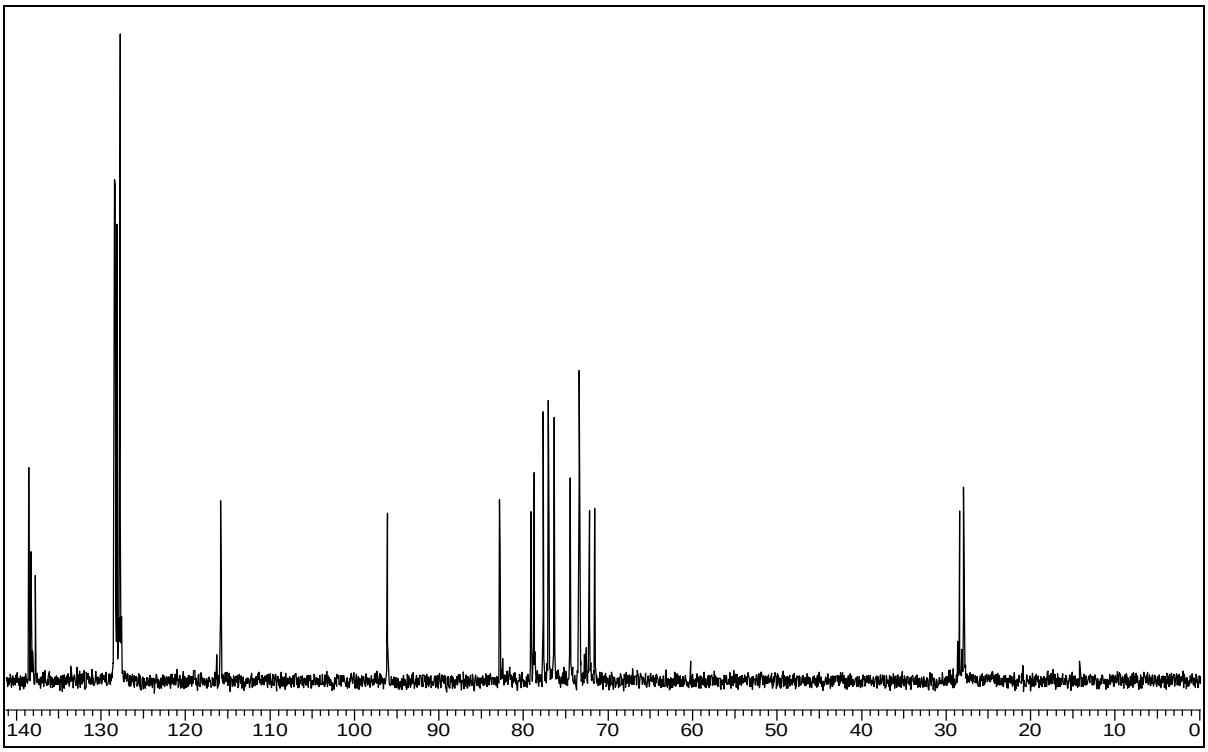
^{1}H NMR spectrum of compound 63 in $CDCl_3$



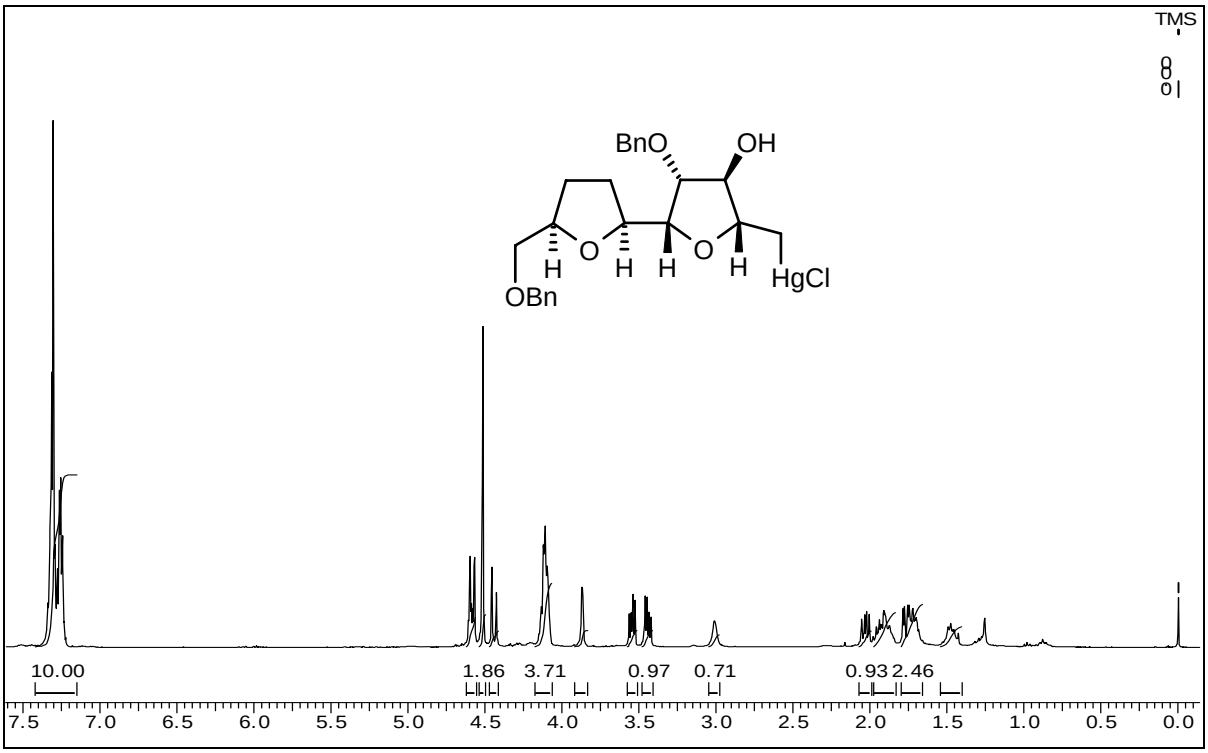
^{13}C NMR spectrum of compound 63 in $CDCl_3$



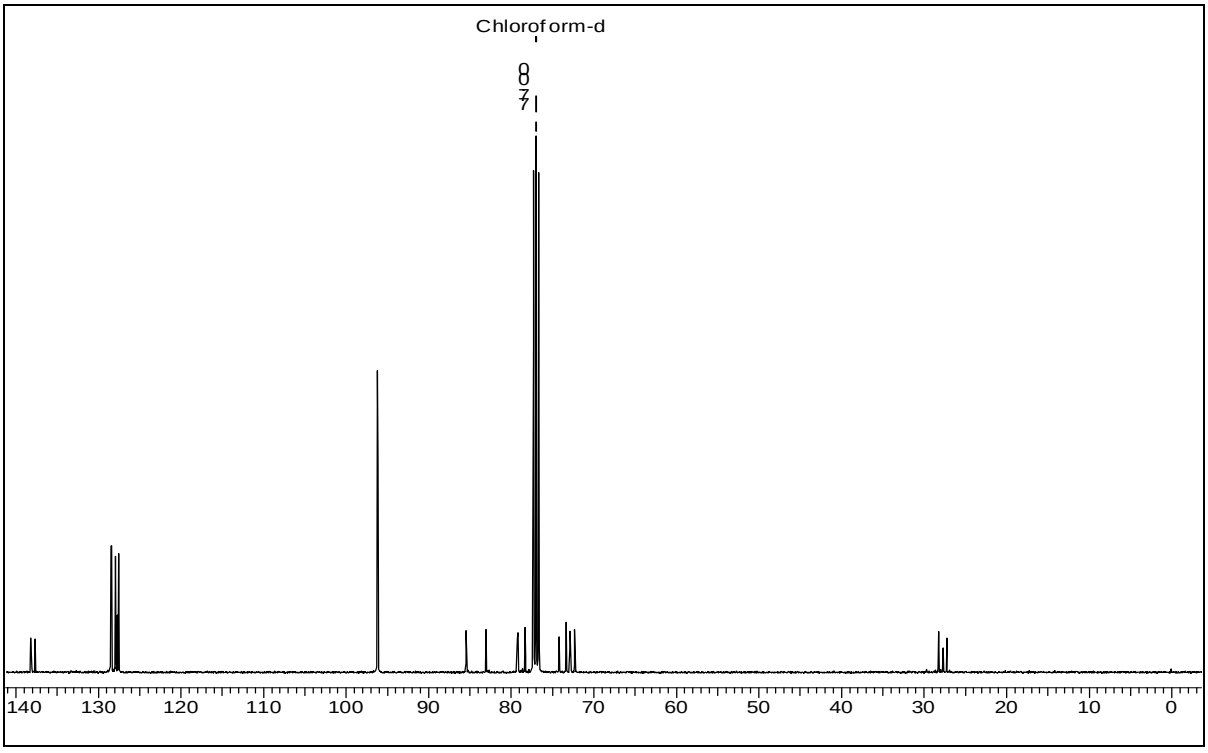
^{1}H NMR spectrum of compound 67 in $CDCl_3$



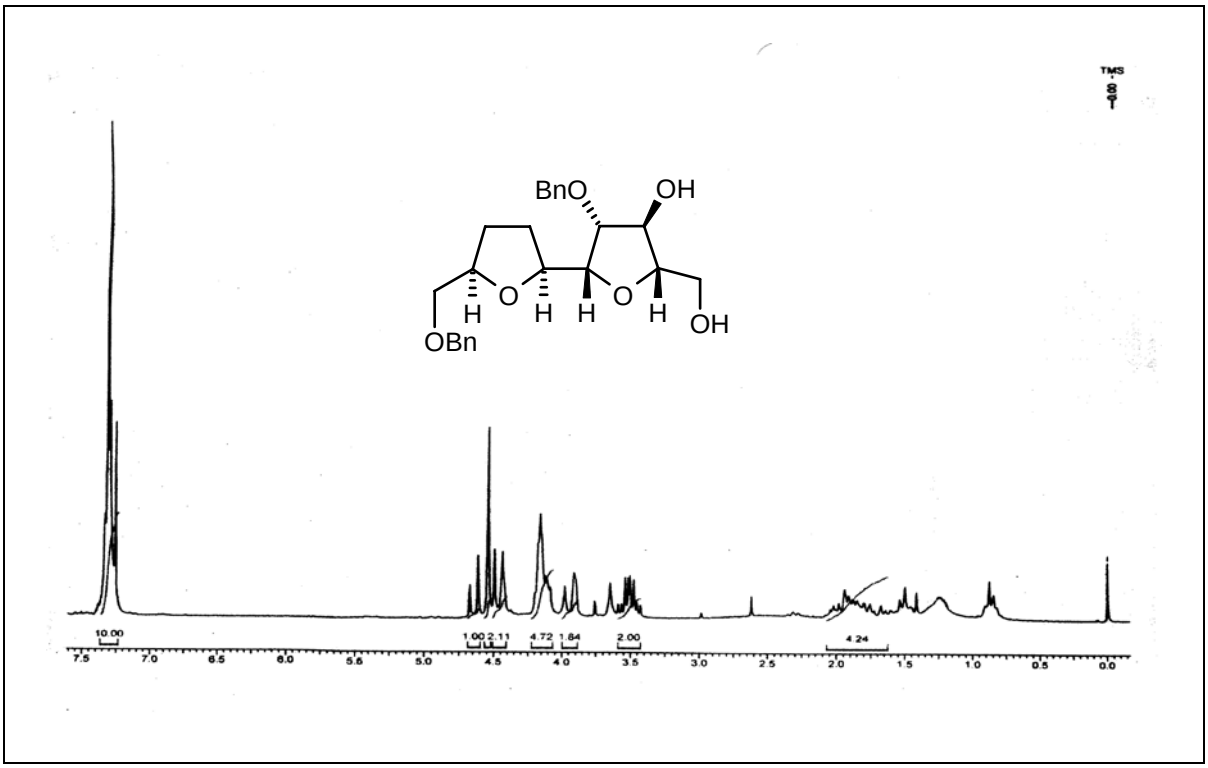
^{1}H NMR spectrum of compound 67 in $CDCl_3$



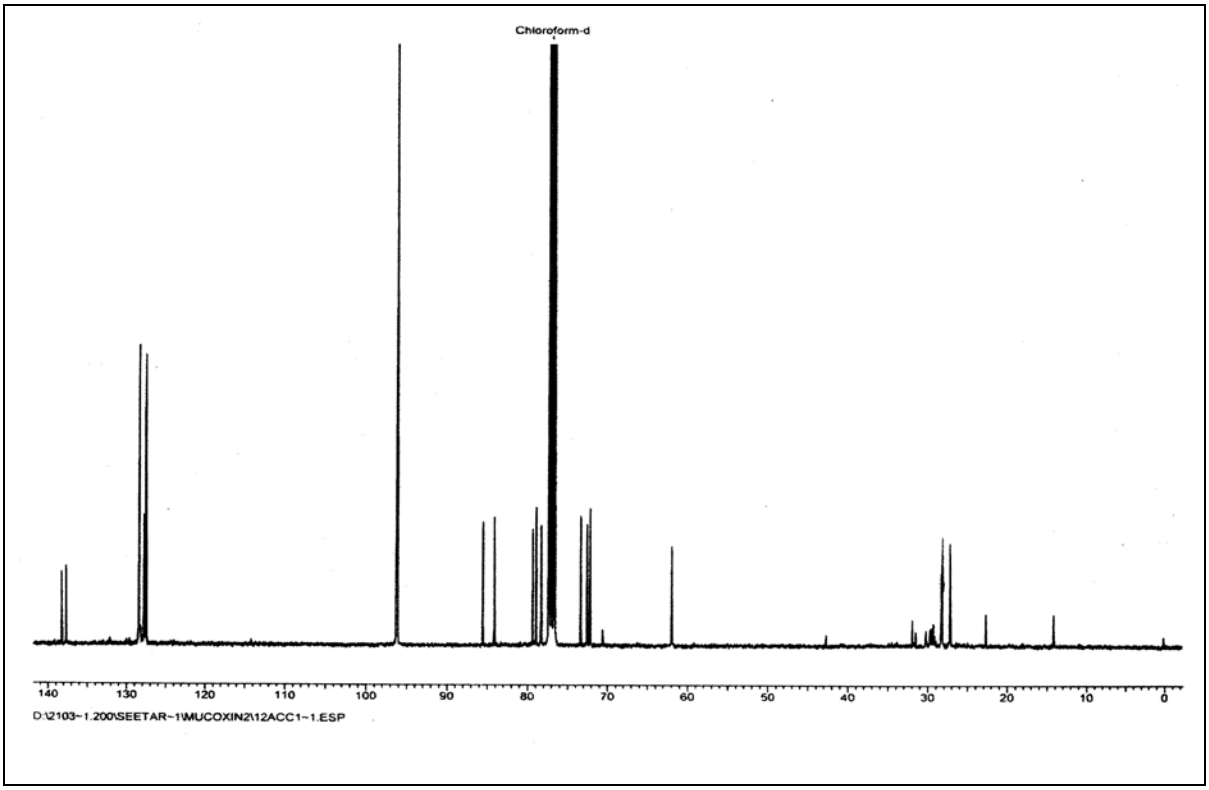
^{13}C NMR spectrum of compound 68 in $CDCl_3$



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



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



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

CHAPTER -2

SECTION -2

Synthetic studies toward Mucoxin

PRESENT WORK

Present WorK

Mucoxin **7** (Figure 5) as the first acetogenin(nonclassical) that bears a hydroxylated THF ring was isolated by McLaughlin et al.[56]In vitro cytotoxicity assays against a panel of six human tumor cell lines have shown mucoxin to be more potent and selective against MCF-**7** (breast carcinoma) cell lines than adriamycin. In the structural analysis part only the relative configuration of the bistetrahydrofuran core (C8-C17) of mucoxin has been established but the absolute configuration of C36 was assigned as *S*. Prompted by its novel hydroxyl THF core as well as by the biological activity (although limited information is available because of lack of material), we interested to synthesize mucoxin.

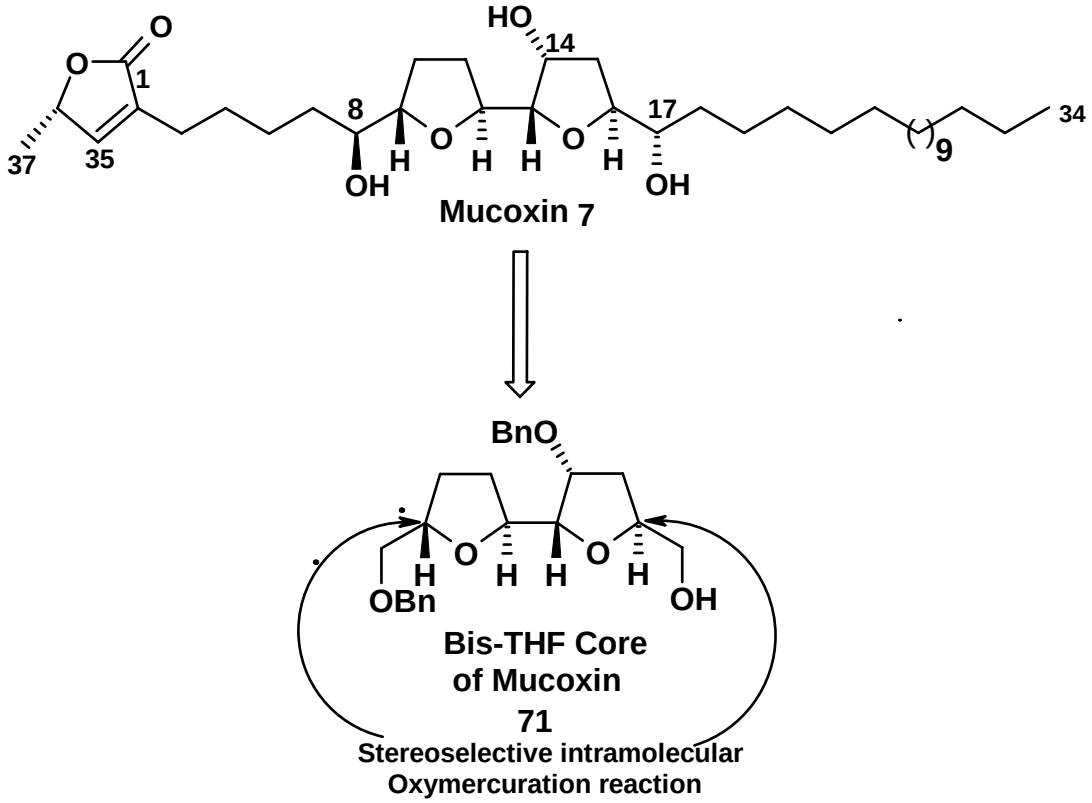


Figure 5

In our synthetic approach towards **7**, first, we planned to synthesize the novel bis-THF core of mucoxin. In the first section of this chapter we have elaborated the synthesis of various core structures of non classical acetogenins using mercuriocyclization reaction, and, here it was planned to implement the same protocol for the synthesis of **71**.

For the synthesis of **71**, we designed a retrosynthetic plan, which was depicted in figure **6**.

Retrosynthetic analysis:

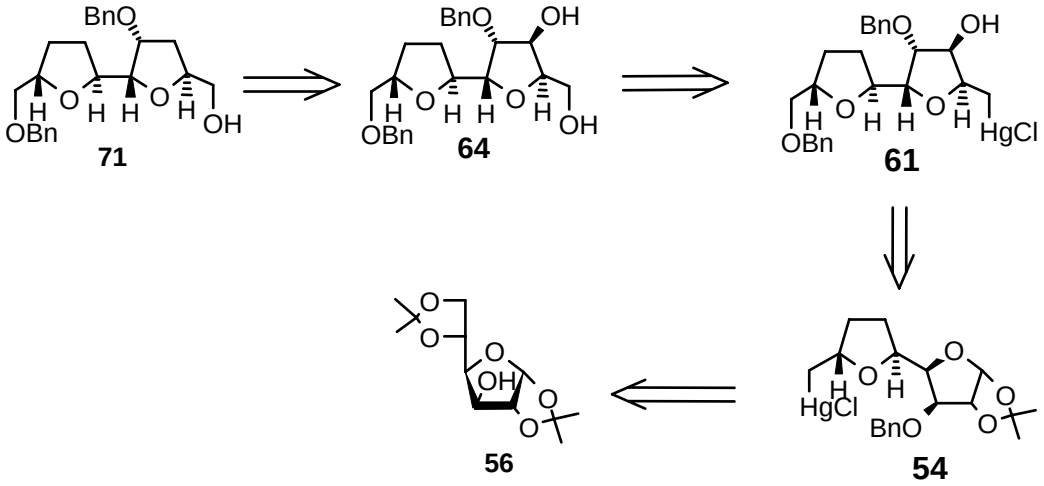
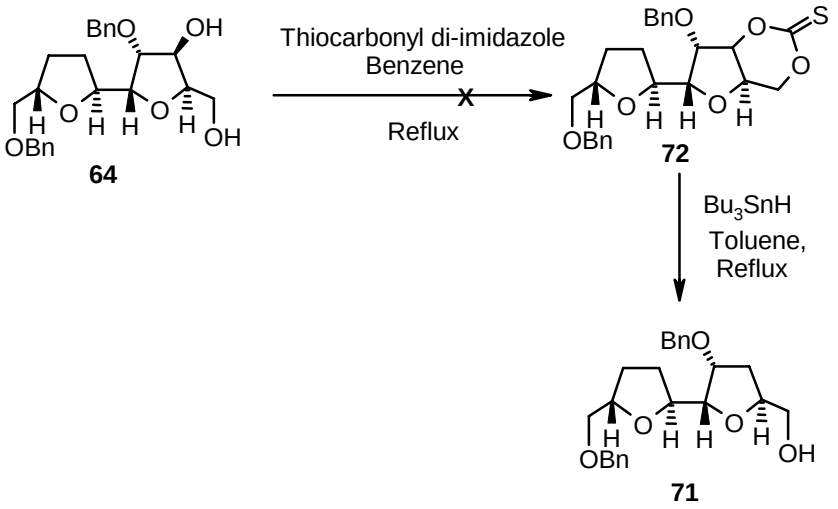


Fig 6

According to the retrosynthetic analysis compound **71** could be obtained from **64** by deoxygenation of secondary hydroxyl group of benzylated THF ring, Where as compound **64** can be synthesized from **61** following demercuration conditions. Compound **61** in turn could be prepared from **54**.

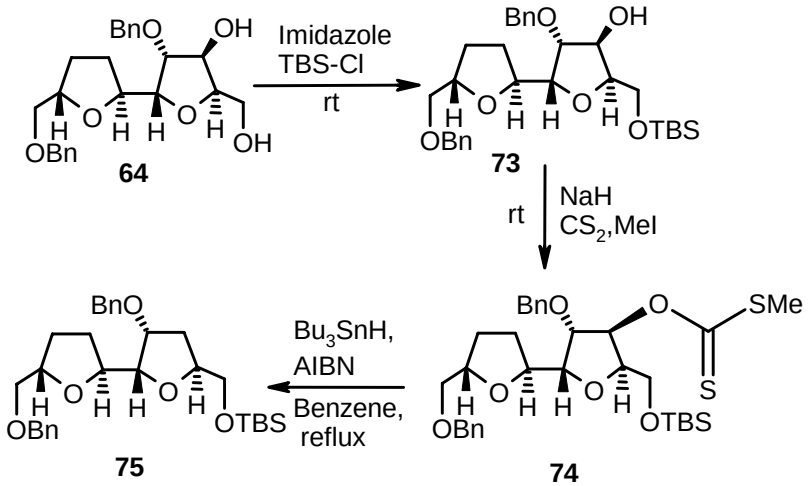
Here, our synthesis was commenced from chiral intermediate **64**, whose synthesis was already mentioned in section-**1** of chapter-**2**. As the compound **64** was in our hand, we planned to deoxygenate the secondary hydroxyl group via the thiocarbonate derivative. Accordingly treatment of thiocarbonyl di-imidazole on **64** in refluxing benzene failed to give **72**. (Scheme 17). Having failed to get **72** we planned to synthesize it in an alternative way.

Scheme 17



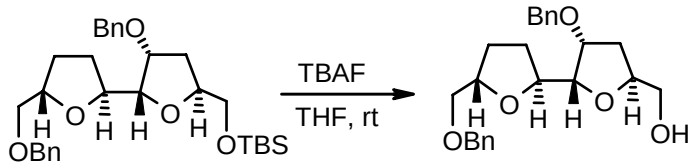
Accordingly primary hydroxyl of **64** was selectively monoprotected as its silyl ether **73** using TBS-Cl and imidazole in room temperature. Compound **73** was confirmed by ^{1}H, ^{13}C NMR study. The 2^{o} alcohol of **73** was converted to xanthate derivative **74** by using NaH, CS_2 and MeI, which on subsequent treatment with tributyltin hydride and AIBN to give required deoxy compound **75**. The product **75** was confirmed by ^{1}H and ^{13}C NMR study. The ^{1}H NMR spectrum of **75** showed a signal at δ 2.12-1.90 (m, 2H) ppm corresponding to the ring methylene protons of the benzylated THF ring and in the ^{13}C NMR spectrum, the -CH_2- carbon signal resonated at δ 33.7 ppm, which was further confirmed by DEPT spectrum. Elemental analysis data also supported the formation of **75** (Scheme 18).

Scheme 18



Ultimately, the central core of Mucoxin **71** was obtained by desilylation of **75** using tetrabutylammonium fluoride. Formation of **71** was apparent from it's ^{1}H and ^{13}C NMR spectrum. The ^{1}H NMR spectrum showed the absence of methyl and tertiary butyl proton signals at δ 0.82 and -0.02, also in ^{13}C NMR spectrum there was absence of tertiary butyl carbon and methyl carbon at δ 26.02 and -5.17 was observed. In addition to it elementalanalysis data also supported the formation of **71** (Scheme 19).

Scheme 19



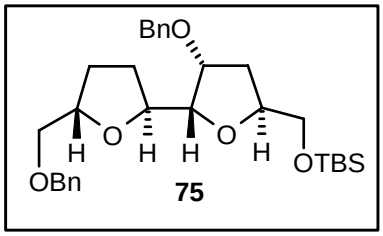
75 **71**

Central core of Mucoxin

In conclusion, we have synthesized bis-THF core of mucoxin stereoselectively using the chiral intermediate **64**, following deoxygenation and desilylation reactions.

EXPERIMENTAL

(2*S*,2'*S*,3*R*,5*S*,5'*S*)-3-(benzyloxy)-5'-(benzyloxymethyl)-octahydro-2,2'-bifuran-5-yl)methoxy)(*tert*-butyl) dimethylsilane (75)



75

Compound **64** (50 mg, 0.12 mmol), imidazole (16 mg, 0.24 mmol) and TBSCl (18 mg, 0.12 mmol) in CH_2Cl_2 (4 mL) were stirred at rt for 1 h, washed with water and concentrated. The residue was purified on silica gel using EtOAc-light petroleum (1:49) to furnish **73** (58 mg, 92%) as a colorless liquid.

To a solution of alcohol **73** (51 mg, 0.09 mmol) in dry THF (4 mL) at 0 °C, was added NaH (5 mg, 0.12 mmol) (60% percent dispersion in oil). After being stirred for 30 min, carbon disulphide (.1 mL) was added. After another interval of 30 min, methyl iodide (.1 mL) was added. The reaction mixture was stirred for 1h, and then quenched with ice cold water and solvent was evaporated to leave the residue, which was taken in ethylacetate. The organic layer was washed with water and brine, dried Na_2SO_4 and concentrated to afford crude product, which on purification over silicagel coloumn with 16% ethylacetate: petroleum ether as eluent gave **74** (54 mg, 93%) as alight yellow oil.

The above product **74**, *n*Bu_3SnH (0.03 mL, 0.12 mmol) and AIBN (5 mg) in toluene (5 mL) under argon were heated under reflux for 7 h, concentrated and chromatographed on silica gel using 18% EtOAc-light petroleum ether (3:97) to afford **75** (0.78 g, 73%) as a clear liquid.

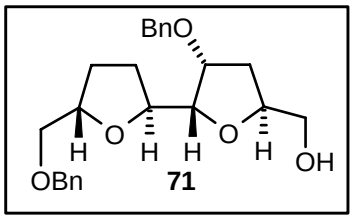
$[\alpha]_D$ **:** +18.54 (*c* 7.2, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 –7.20 (m, 10H), 4.52 (d, 1H, *J* = 11.9 Hz), 4.50 (s, 2H), 4.23 (m, 2H), 4.12 (m, 1H), 3.99 (m, 2H), 3.79 (dd, 1H, *J* = 4.9, 9.7 Hz), 3.62 (dd, 1H, *J* = 4.3, 8.0 Hz), 3.52 (m, 2H), 3.40 (dd, 1H, *J* = 5.7, 15.7 Hz), 2.12 - 1.90 (m, 4H), 1.71 (m, 1H), 1.47 (m, 1H), 0.82 (s, 9H), - 0.02 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ138.6, 138.0, 128.4, 128.3, 127.7, 127.6, 127.5, 85.6, 79.2, 79.0, 78.7, 78.1, 73.4, 72.7, 70.7, 66.0, 33.7, 29.0, 28.5, 26.02, 18.4, -5.17, -5.25.

Anal. Calcd for $C_{30}H_{44}O_5Si$: C, 72.68; H, 11.18. Found: C, 72.61; H, 11.13.

(2*S*,2'*S*,3*R*,5*S*,5'*S*)-3-(benzyloxy)-5'-(benzyloxymethyl)-octahydro-2,2'-bifuran-5-yl)methanol (71)



A solution of **75** (59 mg, 0.12 mmol) and 1M solution of *n*-Bu_4NF (0.13 mL, 0.13 mmol) in THF were stirred for1 h and concentrated. The crude was extracted with EtOAc, washed with water, dried (Na_2SO_4), concentrated. The residue was chromatographed on silica gel using (3:7) EtOAc-light petroleum ether to give **71** (34 mg, 76 %) as colorless thick syrup.

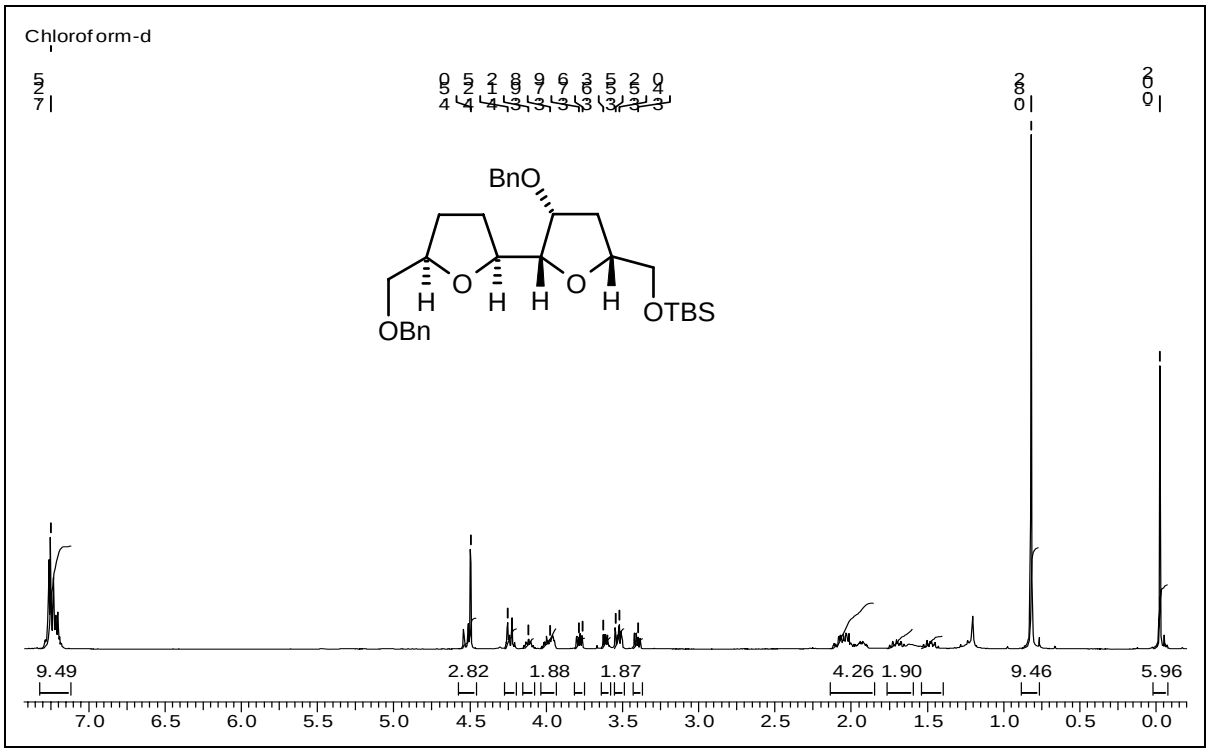
$[\alpha]_D$: – 45.9 (*c* 7.2, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 –7.25 (m, 10H), 4.59 (d, 1H, *J* = 11.6 Hz), 4.55 (s, 2H), 4.36 (dt, 1H, *J* = 6.5, 9.8 Hz), 4.29 (d, 1H, *J* = 11.6 Hz), 4.26–4.16 (m, 2H), 4.02 (m,1H), 3.84 (dd, 1H, *J* = 2.5, 11.6 Hz), 3.67 (dd, 1H, *J* = 4.0, 7.8 Hz), 3.60–3.54 (m, 2H), 3.48 (dd, 1H, *J* =5.3, 9.8 Hz), 2.54 (brs, 1H), 2.20–2.07 (m, 3H), 2.03–1.96 (m, 1H), 1.82–1.73 (m, 1H), 1.59–1.48 (m, 1H).

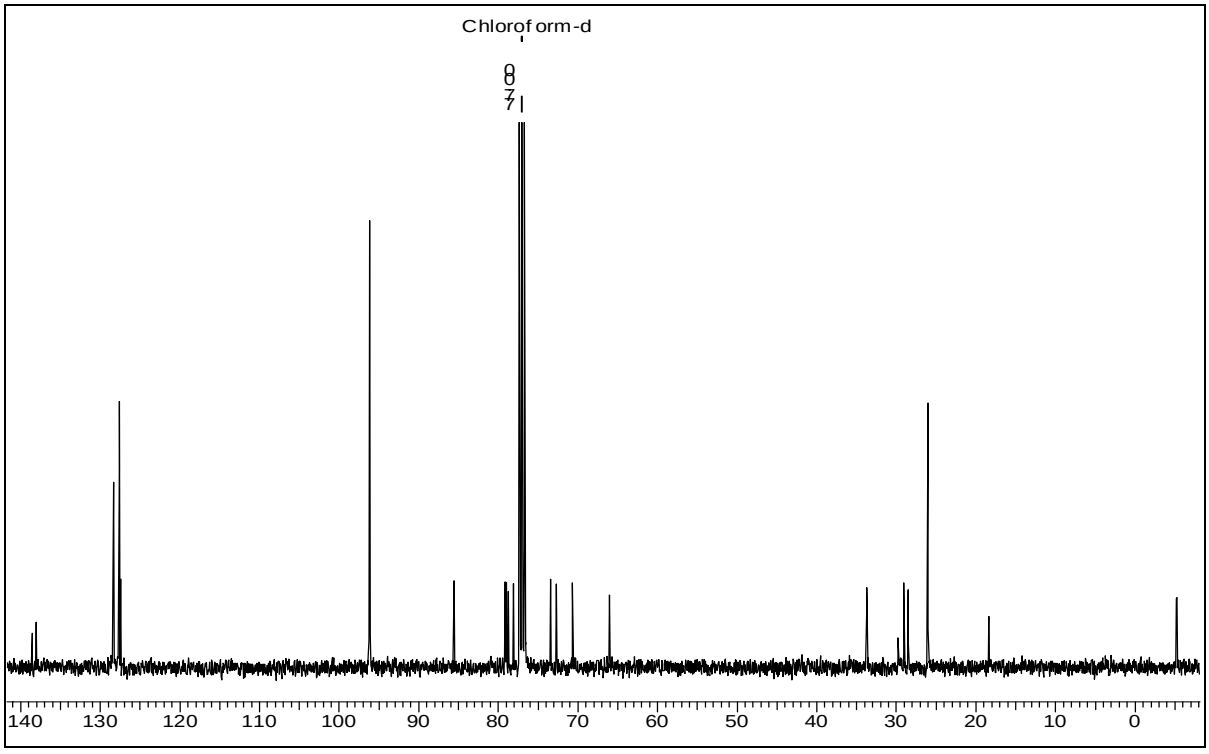
^{13}C NMR (50 MHz, $CDCl_3$): δ 138.4, 137.5, 128.4, 128.3, 127.8, 127.7, 127.6, 127.5, 85.5, 79.1, 78.9, 78.4, 78.1, 73.4, 72.6, 70.7, 64.4, 32.2, 28.8, 28.5.

Anal. Calcd for $C_{24}H_{30}O_5$: C, 72.34; H, 7.59%. Found: C, 72.30; H, 7.66%.

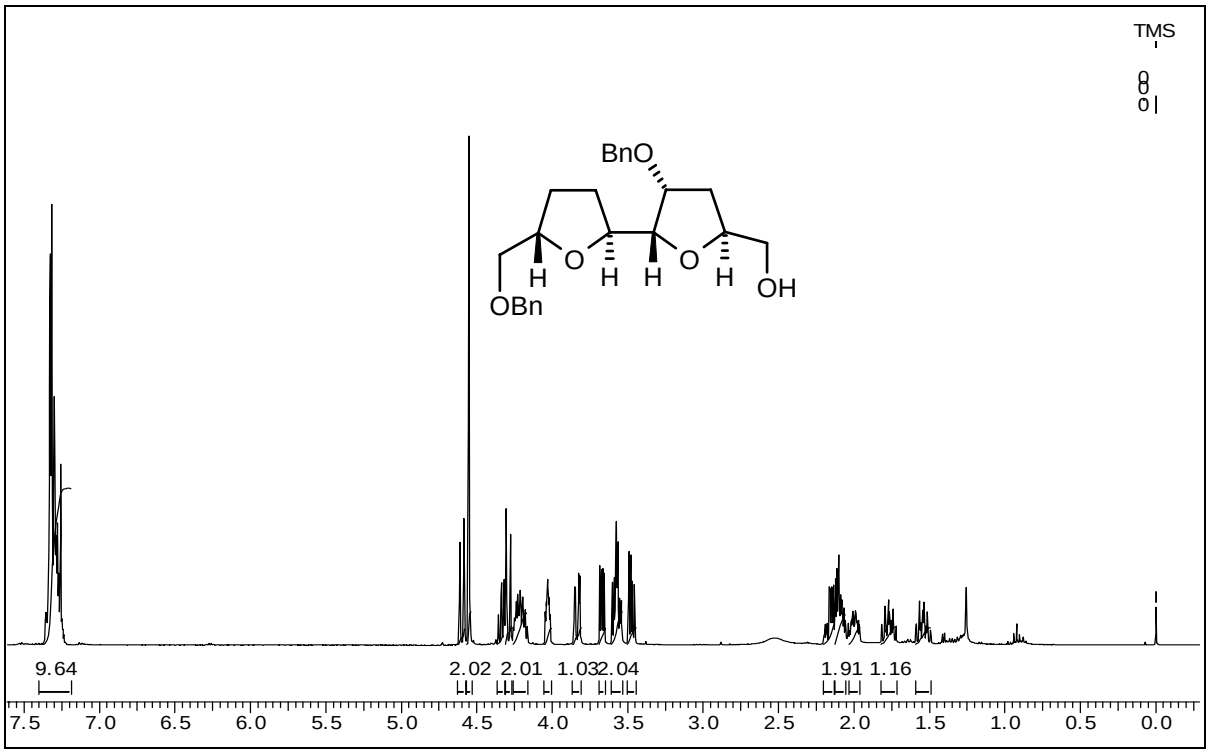
SPECTRA



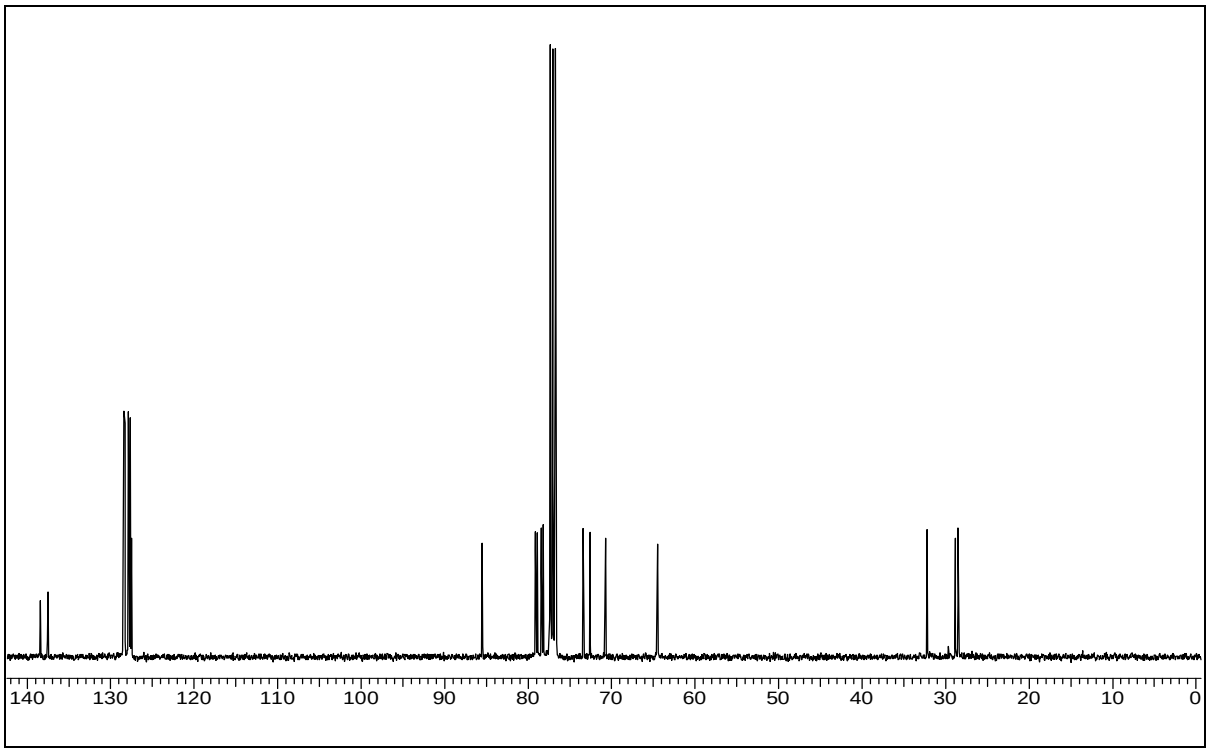
^{1}H NMR spectrum of compound 75 in $CDCl_3$



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



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



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

CHAPTER-2

SECTION - 3

Synthesis of central core of Salzmanolin

PRESENT WORK

Present work

Recently, Salzmanolin **8**, a ringhydroxylated unsymmetrical bis-tetrahydrofuran acetogenin was isolated by Queiroz in 2003,[42] and displayed significant activities for a cancer cell line when compared with normal cells (Vero, ED_{50} >1x 10-2 μg/mL).

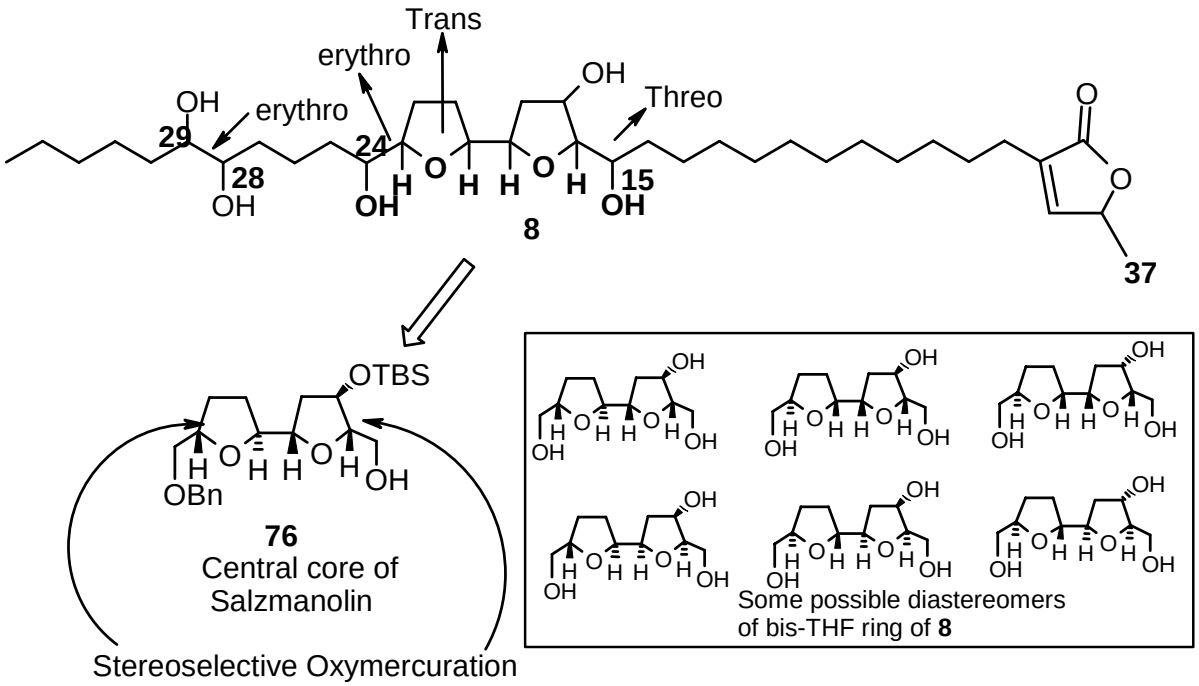


Figure 7

The novel bis-THF core as well promising biological activity (although limited information is available because of lack of material), prompted us to undertake its synthesis.

After a close examination of the structure **8,** we noticed that only the relative stereochemistry was described. On that basis few possible diastereomers has been calculated and, among them we took one diastereomer related to our previous synthetic background. In the first section, we have accessed three bis-THF alcohols stereoselectively employing mercury mediated cyclisation. Here, we applied the same protocol for the synthesis of the hydroxylated bis-tetrahydrofuran skeleton present in **8** from the known compound **57** will be illustrated.

The retrosynthetic analysis of **76** was depicted in figure **8.** Compound **76** could be synthesized from hydroxylated olefinic compound **77,** which inturn could be synthesized from **78**. The benzylated compound **78** can be synthesized easily from the alcoholic counterpart **57** in a two steps synthesis following regular transformations. Compound **57** can be synthesized easily following earlier synthetic route.

Retrosynthetic analysis:

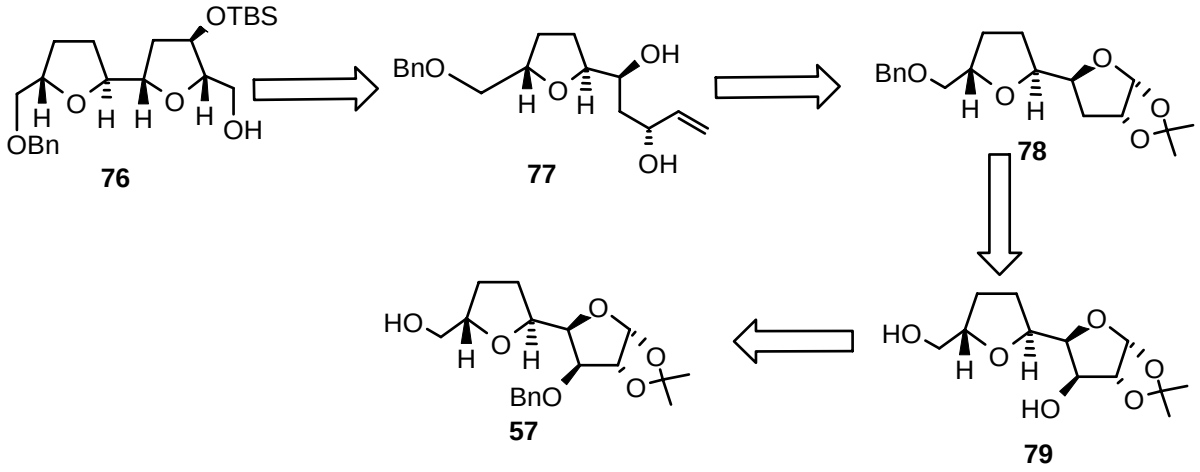
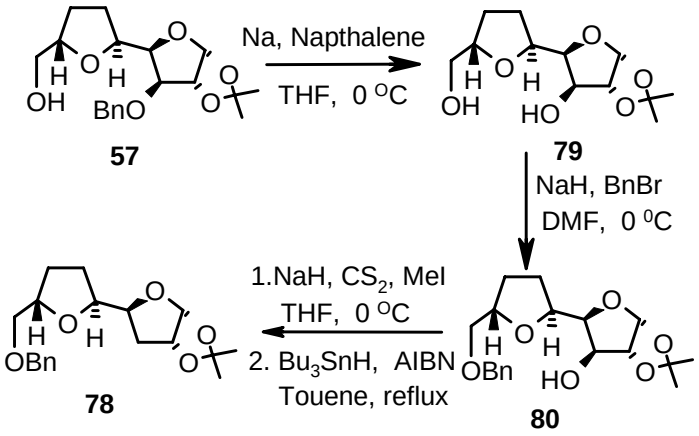


Figure 8

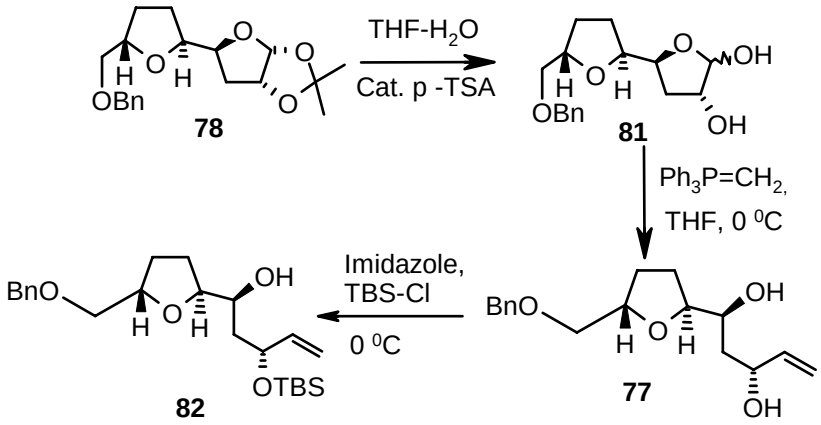
According to the retrosynthetic analysis deprotection of benzylether in compound **57** was carried out by using sodium and naphthalene in THF medium gave diol **79**.The conversion was clearly apparent in its ^{1}H NMR spectrum, which showed the absence of aromatic ring protons at δ 7.30 ppm indicating the cleavage of benzyl ether. Further confirmation was carried out by ^{13}C and mass spectral analysis. Next, selective benzylation of the primary hydroxyl group in **79** was accomplished with sodium hydride and benzyl bromide in DMF at 0 ºC to give benzyl ether **80**. The secondary-OH group of **80** was treated with NaH, CS_2, and MeI at 0 ^{o}C resulted xanthate derivative, which was subsequently, treated to deoxygenation reaction using Barton–McCombie protocol to give **78**. The ^{1}H NMR spectrum showed a signal at δ 1.86-1.68 ppm integrating two protons due to C3 methylene protons. ^{13}C NMR spectrum of **78** showed a new signal at δ 34.9 ppm corresponding to the $–CH_2-$ carbon of C3 position. Elemental analysis data also supported the formation of **78** (scheme 20).

Scheme 20



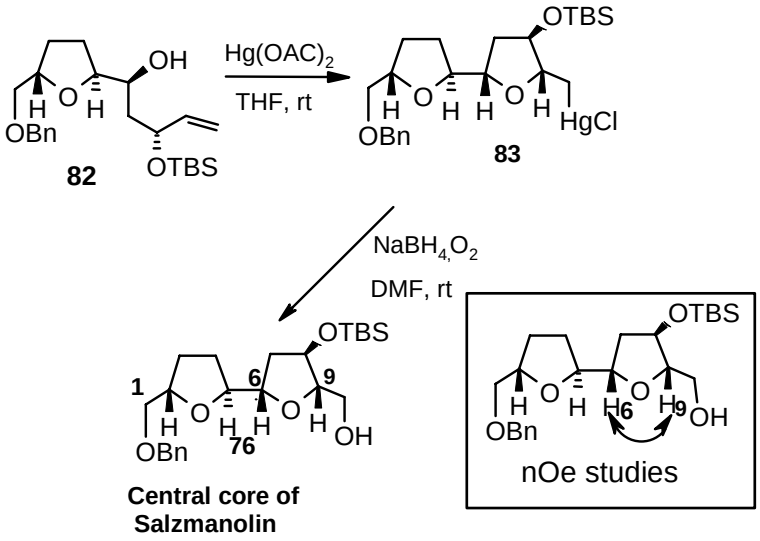
The precursor of **83** was planned to synthesize from **78**. Accordingly, cleavage of isopropylidene group of **78** was carried out by using *p*-TSA, THF-H_2O (7:3) under reflux condition to afford hemiacetals **81**, which was subjected to one carbon homologation by using one carbon wittig ylide[81] to produce olefin **77**. In ^{1}H NMR spectrum of **77** characteristics peaks due to the vinyl olefinic protons appeared at δ 5.84 (m, 1H), δ 5.25 (d, 1H, *J* = 17.2 Hz), and δ 5.09 (d, 1H, *J* = 10.5 Hz) ppm. The resonances due to rest of the protons were in conformity with the proposed structure of **77**. ^{13}C NMR spectrum showed the resonances of olefinic carbons at δ 114.4 (terminal olefin carbon) and δ 140.6 ppm (internal olefin carbon) respectively. Our next attempt was to selectively protect the more reactive secondary allylic hydroxyl group. Accordingly **77** was treated with TBS-Cl, imidazole in CH_2Cl_2 at 0 ˚C furnished **82** in good yield. The structure of **82** was confirmed by the assistance of the ^{1}H, ^{13} C NMR study. In the ^{1}H NMR spectrum of **82** signal appeared at δ 0.90, 0.09 and 0.06 ppm integrating to nine, three and three protons corresponding to TBS group. Elemental analysis data also supported the formation of **82** (Scheme 21).

Scheme 21:



The requisite skeleton was now set for the second intramolecular oxymercuration reaction. Treatment of mercury (II) acetate on the compound **82** in dichloromethane afforded **83** as a single diastereomer. The structure of compound **83** was confirmed by ^{1}H, ^{13}C NMR studies. In the ^{1}H NMR spectrum dissappearance of olefinic protons at δ 5.78 (m, 1H), 5.14 (d, 1H) and 5.04 (d, 1H) ppm regions and appearance of methylene protons at δ 1.82 ppm integrating two protons corresponding to $–CH_2Hg$ group indicating there was cyclisation. The ^{13}C NMR spectrum showed the resonances of $–CH_2Hg$ carbon at δ 28.7 ppm, which was further confirmed from DEPT spectrum. Demercuration of **83** was carried out under the fast flow of oxygen in the presence of sodium borohydride to obtain **76**. In the ^{1}H NMR spectrum of **76**, the methylene protons of CH_2OH group resonated at δ 3.99 and 3.76 ppm which was earlier appeared at δ 1.82 ppm in compound **83.** The presence of an adjacent bis-THF ring was deduced from the ^{13}C NMR spectrum, where the five oxymethine carbons resonated at δ 82.4, 81.2, 80.1, 78.6 and 72.8 ppm regions, and in the DEPT spectrum three CH_2 carbons of the bis-THF ring appeared at δ 38.5, 28.1, and 25.8 ppm respectively. Stereochemistry around the tetrahydrofuran ring was assigned by nOe experiments. There was strong nOe interactions observed between H6 and H9 protons in compound **76,** assigned the syn stereochemistry. Further conformation was carried out by mass spectrum analysis (Scheme 22).

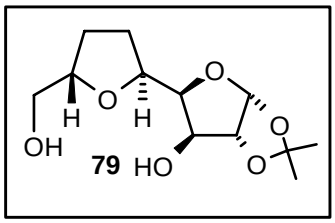
Scheme 22:



In conclusion, we have synthesized the unsymmetrical bis-tetrahydrofuran skeleton of Salzmanolin stereoselectively employing mercuriocyclization reaction starting from chiral precursor **57**.

EXPERIMENTAL

5,8-Anhydro-3-*O*-benzyl-6,7-dideoxy-1,2-*O*-isopropylidene-L-*glycero*-ß-L-*ido*-nonanofuranose (79)



$[\alpha]_D = -7.27$ (*c* 1.6, $CHCl_3$)

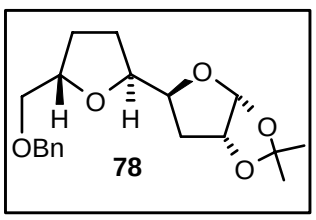
A solution of **57**(1.3 g, 3.7 mmol) in anhydrous THF (20 mL) was added to a solution of sodium (255 mg, 11.1 mmol) in napthalene (1.4 g, 11.1 mmol) maintained at –20 °C. The reaction mixture was stirred for 1 h and quenched with saturated NH_4Cl solution. Then the reaction mixture was taken in ethyl acetate and washed with water, brine, dried (Na_2SO_4) and evaporated. The residue was purified on silica gel by using 60% EtOAc/Petether to obtain **79** (705 mg, 73%).

^1H NMR (300 MHz, $CDCl_3$): δ (d, 1H, *J* = 3.2 Hz), 4.50 (d, 1H, *J* = 3.7 Hz), 4.40 (dd, 1H, *J* = 2.9, 7.2 Hz), 4.30-4.21 (m, 2H), 4.05 (t, 1H, *J* = 2.8), 3.70 (dd, 1H, *J* = 3.2, 12.0 Hz), 3.50 (dd, 1H, *J* = 5.3, 12.0 Hz), 2.19-1.97 (m, 3H), 1.82-1.63 (m, 1H), 1.48 (s, 3H), 1.31 (s, 3H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 111.5, 104.7, 85.4, 81.5, 80.4, 78.5, 76.8, 64.4, 29.4, 26.8, 26.7, 26.2.

Anal. Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74. Found: C, 55.32; H, 7.75.

5,8-Anhydro-9-*O*-benzyl-3,6,7-trideoxy-1,2-*O*-isopropylidene-L-*glycero*-ß-L-*ido*-nonanofuranose (78)



$[\alpha]_D = -12.23$ (*c* 2.1, $CHCl_3$)

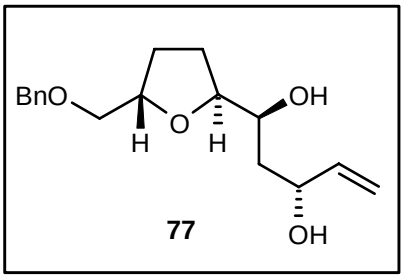
To a solution of alcohol **80** (742 mg, 2.853 mmol) in dry THF (10 mL) at 0 °C, was added NaH (60% percent dispersion in oil, 137 mg, 3.42 mmol). After being stirred for 30 min, carbon disulphide (0.2 mL, 2.8 mmol), another interval of 30 min, methyl iodide (0.2ml, 2.8 mmol) was added. The reaction mixture was stirred for 1h then quenched with ice cold water and solvent was evaporated to leave the residue, which was taken in ethylacetate. The organic layer was washed with water and brine, dried $NaSO_4$ and concentrated to afford crude product, which on purification over silicagel coloumn with 8% ethylacetate: petroleum ether as eluent gave a light yellow oil (764 mg, 82%). The above product, *n*Bu_3SnH (0.5 mL, 1.9 mmol) and AIBN (5 mg) in toluene (10 mL) under argon were heated under reflux for 7 h, concentrated and chromatographed on silica gel using(10:90) EtOAc-light petroleum ether to afford **78** (402 mg, 72%).

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.32 (m, 5H), 5.82 (d, 1H, *J* = 3.8 Hz), 4.71 (t, 1H, *J* = 4.42 Hz), 4.56 (s, 2H), 4.26-4.12 (m, 2H), 3.99 (m, 1H), 3.49 (dd, 2H, *J* = 1.3, 4.8 Hz), 2.09-1.97 (m, 3H), 1.86-1.68 (m, 3H), 1.51 (s, 3H), 1.31 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$):138.4, 128.2, 127.5, 110.9, 105.6, 80.4, 80.3, 79.7, 78.6, 73.3, 72.7, 34.9, 28.6, 28.2, 26.8, 26.21

Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.83. Found: C, 68.20; H, 7.78.

(1*S*,3*R*)-1-((2*S*, 5*S*)-5-(benzoyloxy) methyl)-tetrahydrofuran-2-yl)pent-4-ene-1,3-diol (77)



77

$[\alpha]_D = -10.0$ (*c* 1.5, $CHCl_3$)

The benzyl ether **78**(532 mg, 1.65 mmol) was dissolved in THF: H_2O (14:6 mL) and catalytic amount of *p*-TSA was added. The reaction mixture was refluxed for 2 h at 60 ^oC and then cooled to 0 ^oC, quenched by Et_3N (1 mL).Then the reaction mixture was concentrated and purified by silica gel chromatography (60% Ethylacetate/light petroleum) provided lactol compound **81** (0.199 g, 68 %) as a colorless oil which was converted to

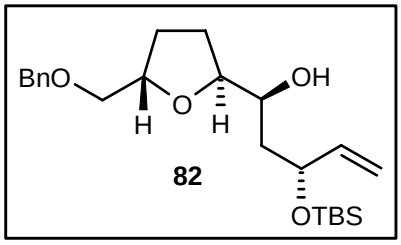
olefin **77** via Wittig reaction using $PPh_3^+CH_3I^-$ (1.64 g, 4.05 mmol) and *n*-BuLi (1.6 M, 2.1 mL, 3.38 mmol). The ylide in THF (10 mL) was added at 0 ^oC to the lactol compound and stirred for 10 h at room temperature and the reaction mixture was quenched by water. The organic layer was separated 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 (35% Ethylacetate/light petroleum) afforded **77** (122 mg, 62%) as a colorless oil over two steps.

^1H NMR (300 MHz, $CDCl_3$): δ 7.32 (m, 5H), 5.84 (m, 1H), 5.25 (d, 1H, *J* = 17.2 Hz), 5.09 (d, 1H, *J* = 10.5 Hz), 4.56 (s, 2H), 4.38 (m, 1H), 4.18 (m, 1H), 3.87 (q, 1H, *J* = 6.7 Hz), 3.68 (m, 1H), 3.47 (d, 2H, *J* = 5.1 Hz), 2.04-1.91 (m, 3H), 1.62 (m, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 140.6, 138.1, 128.4, 127.7, 114.4, 82.5, 78.4, 74.3, 73.4, 72.7, 72.2, 39.7, 28.9, 27.9.

Anal Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 69.78; H, 8.20

(1*S*,3*R*)-1-((2*S*,5*S*)-5-(benzyloxymethyl)-tetrahydrofuran-2-yl)-3-*tert*-butyldimethylsilyloxy)pent-4-en-1-ol(82)



82

$[\alpha]_D = -11.39$ (*c* 1.1, $CHCl_3$)

To a solution of alcohol **77** (200 g, 0.68 mmol) in (2 mL) CH_2Cl_2 was added imidazole (93 mg, 1.4 mmol), TBSCl (103 mg, 0.68 mmol) and catalytic amount of DMAP at room temperature. After 3 h stirring, 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 **82** as a colorless oil (228 mg, 82 %).

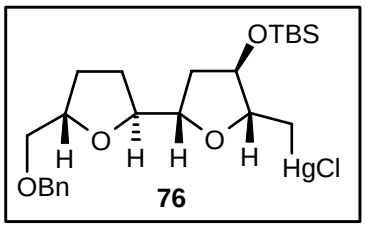
^1H NMR (300 MHz, $CDCl_3$): δ 7.27 (m, 5H), 5.78 (m, 1H), 5.14 (d, 1H, *J* = 17.2 Hz), 5.04 (d, 1H, *J* = 12 Hz), 4.58 (brs, 2H), 4.39 (q, 1H, *J* = 6.82 Hz), 4.14 (m, 1H), 3.91(dd, 1H, *J*

= 6.1, 7.3 Hz), 3.65 (m, 1H), 3.48 (d, 2H, *J* = 4.8 Hz), 2.81 (brs, 1H), 1.97 (2H, m), 1.67 (m, 2H), 1.58 (m, 2H), 0.90 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 141.1, 138.3, 128.3, 127.6, 114.6, 82.5, 78.3, 73.4, 72.9, 72.8, 71.7, 41.3, 28.9, 27.7, 25.9, 18.2, -4.2, -4.8.

Anal. Calcd for $C_{23}H_{38}O_4Si$: C, 67.93; H, 9.41. Found: C, 67.92; H, 9.38.

(2*S*,2*S'*,4*R*,5*R*,5'*S*)-5'-(benzyloxymethyl)-4-(*tert*-butyldimethylsiloxy)-octahydro-2,2'-bifuran-5-yl)methyl)mercury(II) chloride(83)



76

To a solution of allylic alcohol **82** (88 mg, 0.216 mmol) in (2 mL) CH_2Cl_2, $Hg(OAc)_2$ (88 mg,0.28 mmol 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, concentrated under reduced pressure. Purification of the crude compound by flash silica gel column chromatography (20% Ethylacetate/light petroleum) provided the compound as a single diastereomer **83** (100 mg, 76%).

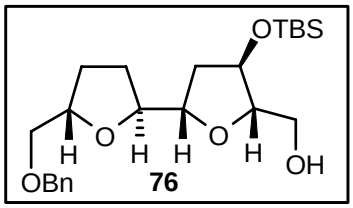
$[\alpha]_D$ = –8.98 (*c* 1.3, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (m, 5H), 4.57 (s, 2H), 4.40 (m, 1H), 4.20 (m, 3H), 3.90 (q, 1H, *J* = 6.8 Hz), 3.49 (d, 2H, *J* = 4.9 Hz), 2.28 (m, 2H), 1.93 (m, 3H), 1.82-1.65 (m, 3H), 1.26 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 138.4, 128.3, 127.6, 127.5, 81.5, 80.6, 79.8, 78.6, 74.6, 73.3, 72.8, 38.8, 28.7, 28.1, 26.4, 18.5, 14.2, -4.1, -4.4.

Anal. Calcd for $C_{23}H_{37}O_4HgCl$: C, 43.05; H, 5.81 Found: C, 43.02; H, 5.75

(2*S*,2*S*',4*R*,5*S*,5'*S*)-5'-(benzyloxymethyl)-4-(*tert*-butyldimethylsiloxy)-octahydro-2,2'-bifuran-5-yl)methanol (76)



To a stirred solution of compound **83** (60mg, 0.097 mmol) in DMF (1mL), O_2 was bubbled through a long syringe needle for 10 min. In an another flask, a suspension of $NaBH_4$ (5 mg, 0.12 mmol) in DMF (0.5 mL) 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 flash silica gel column chromatography (80% Ethylacetate/light petroleum) to afford primary alcohol **76** (28 mg, 74%) as a colorless liquid .

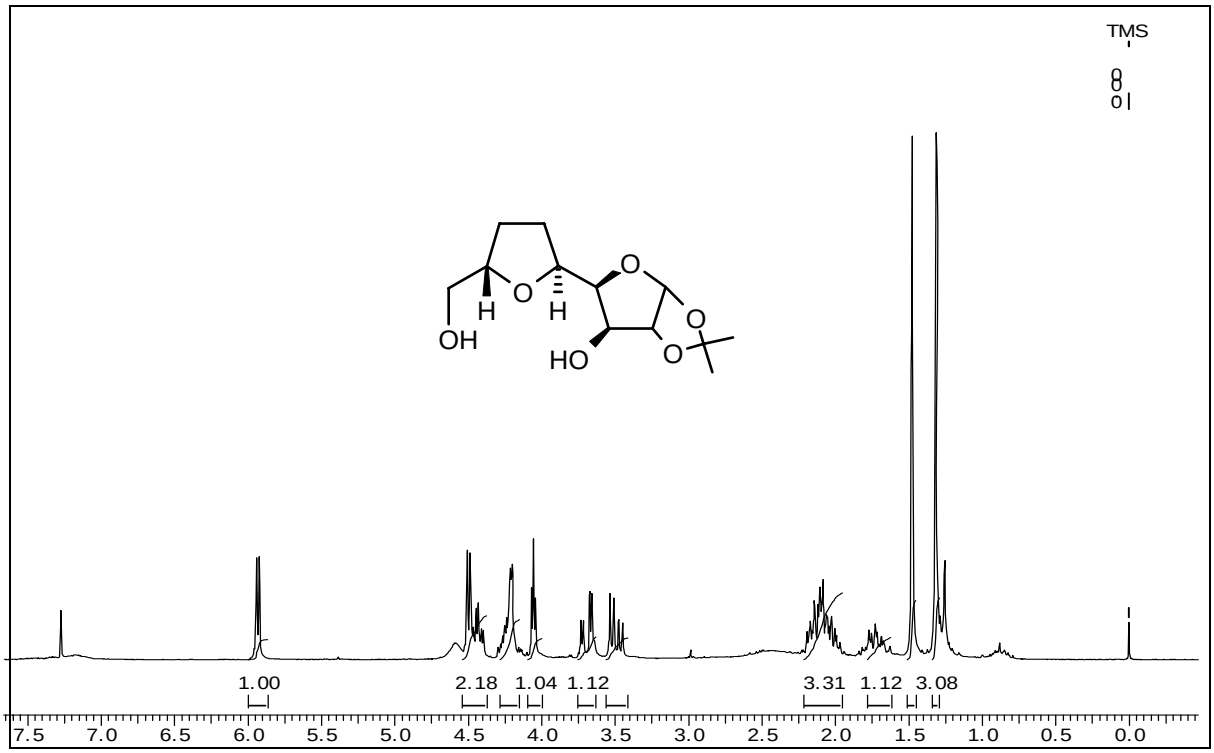
$[\alpha]_D = -16.24$ (*c* .9, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.24 (m, 5H), 4.56 (s, 2H), 4.52 (m, 1H), 4.18 (m, 2H) 3.99 (m, 2H), 3.76 (dd, 1H, *J* = 5.5, 11.8 Hz), 3.50 (m, 2H), 2.10-1.94 (m, 3H), 1.90-1.68 (m, 3H), 0.90 (s, 9H), 0.09 (s, 6H).

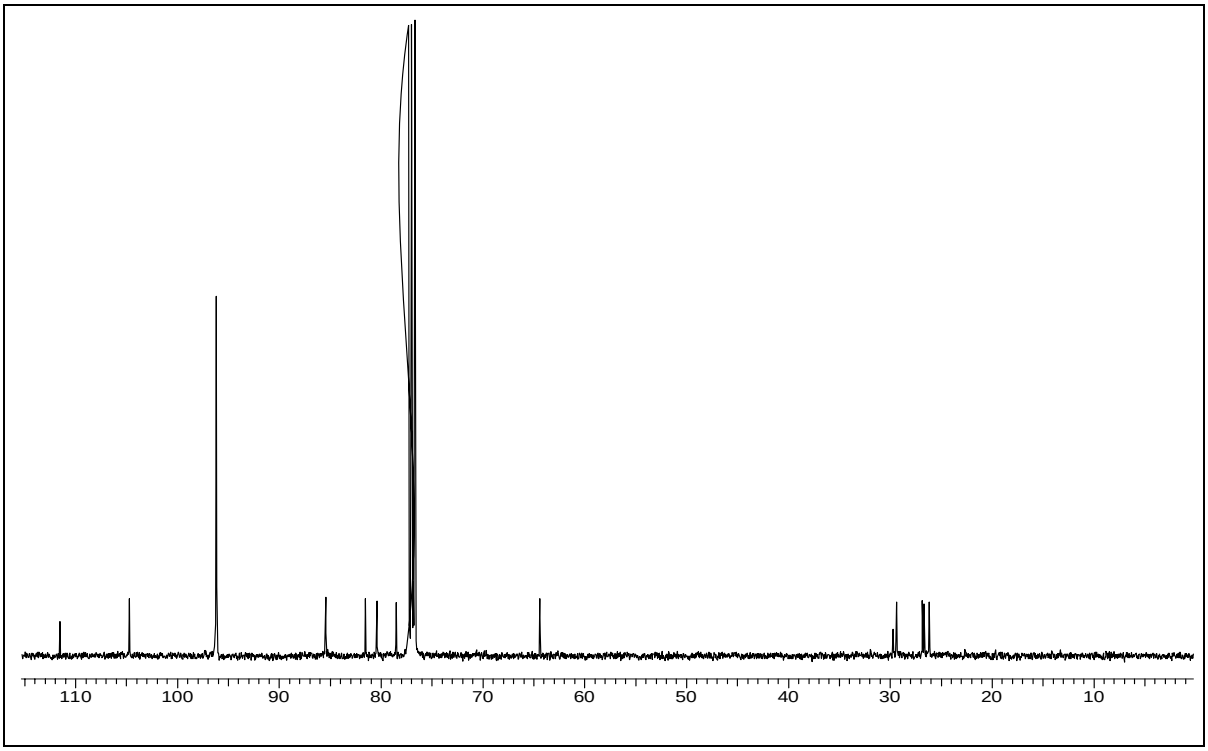
^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4, 128.3, 127.6, 82.4, 81.2, 80.1, 78.6, 74.0, 73.3, 72.9, 62.6, 38.5, 28.9, 28.1, 25.8, 18.0, -4.6, -5.1.

Anal. Calcd for $C_{23}H_{38}O_5Si$: C, 65.40; H, 8.99. Found: C, 65.35; H, 8.83

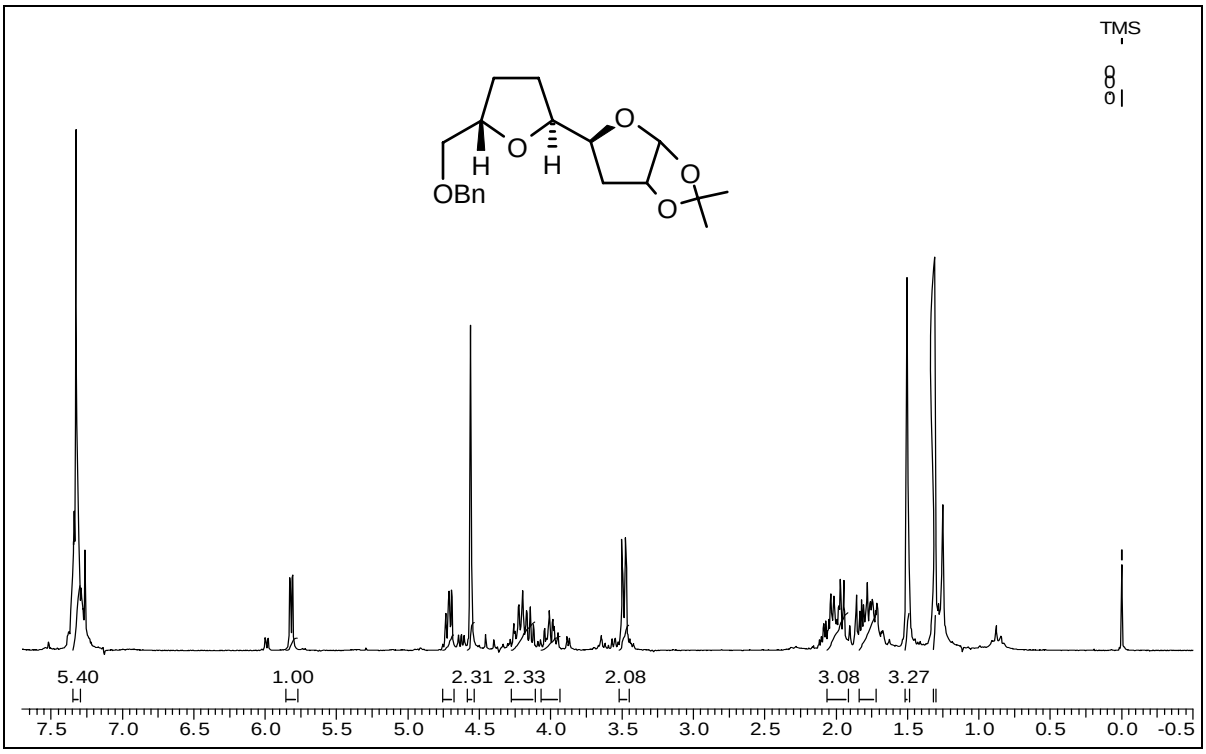
SPECTRA



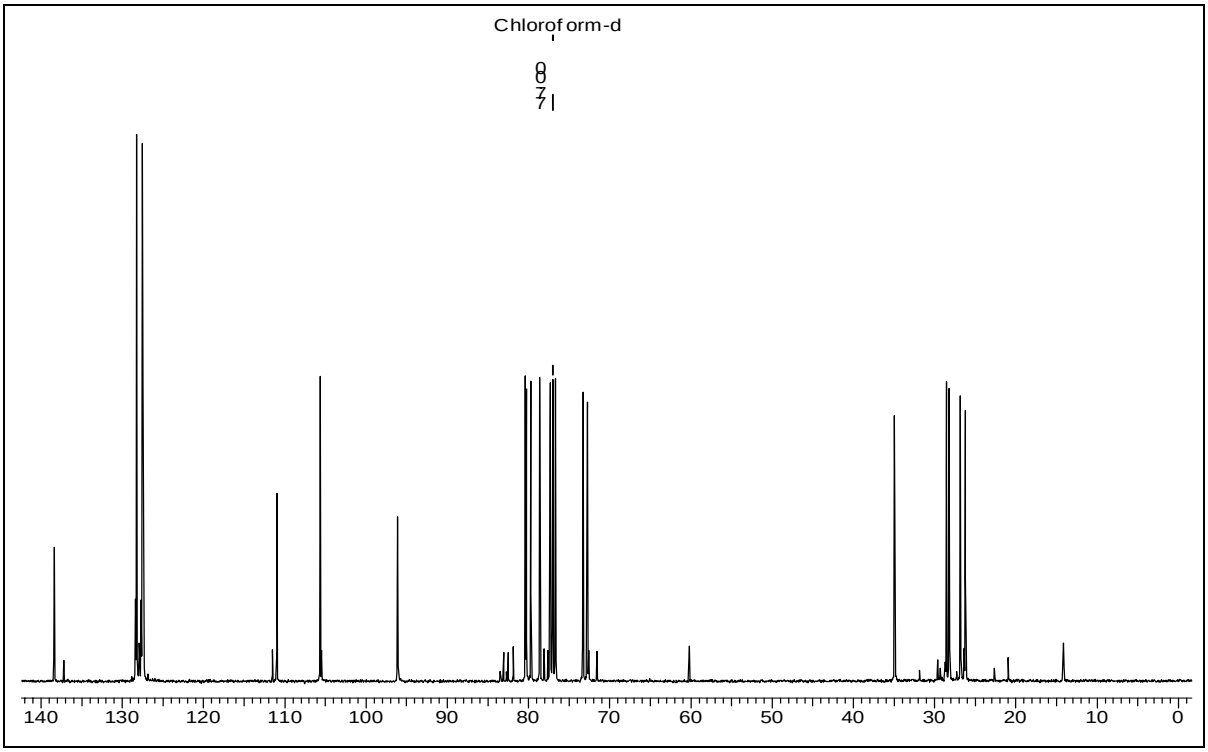
^{1}H NMR spectrum of compound 79 in $CDCl_3$



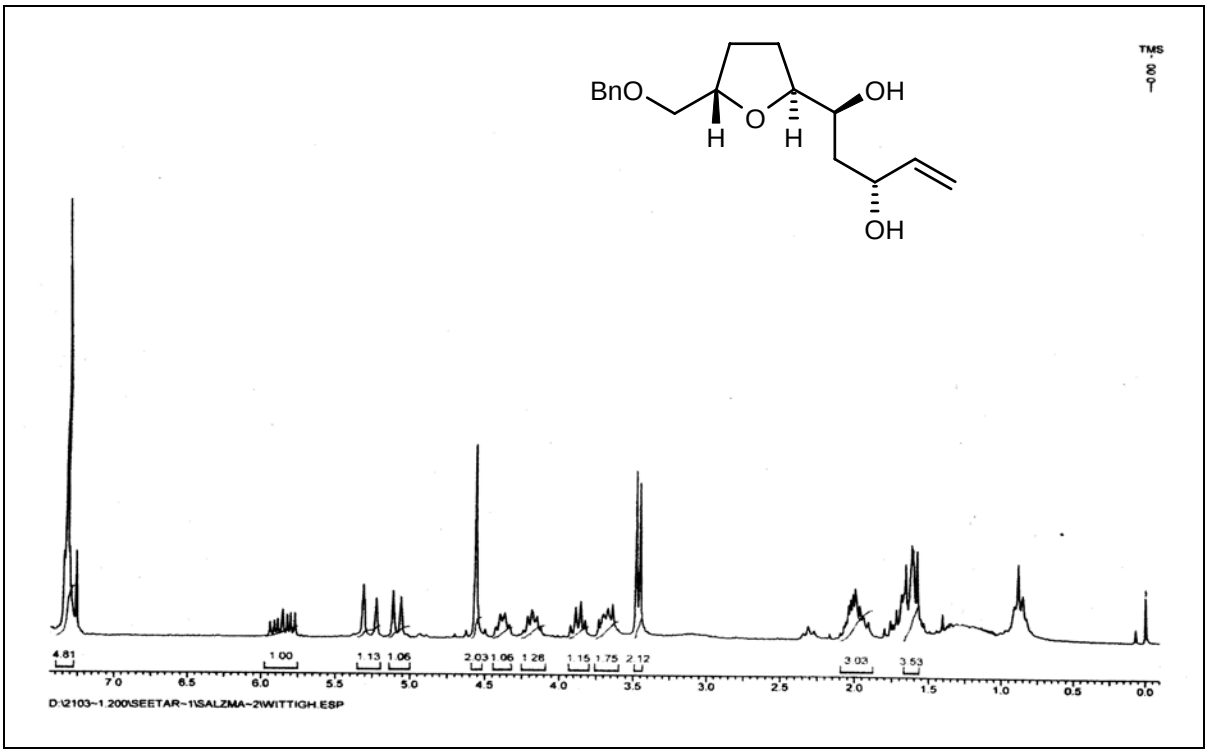
^{13}C NMR spectrum of compound 79 in $CDCl_3$



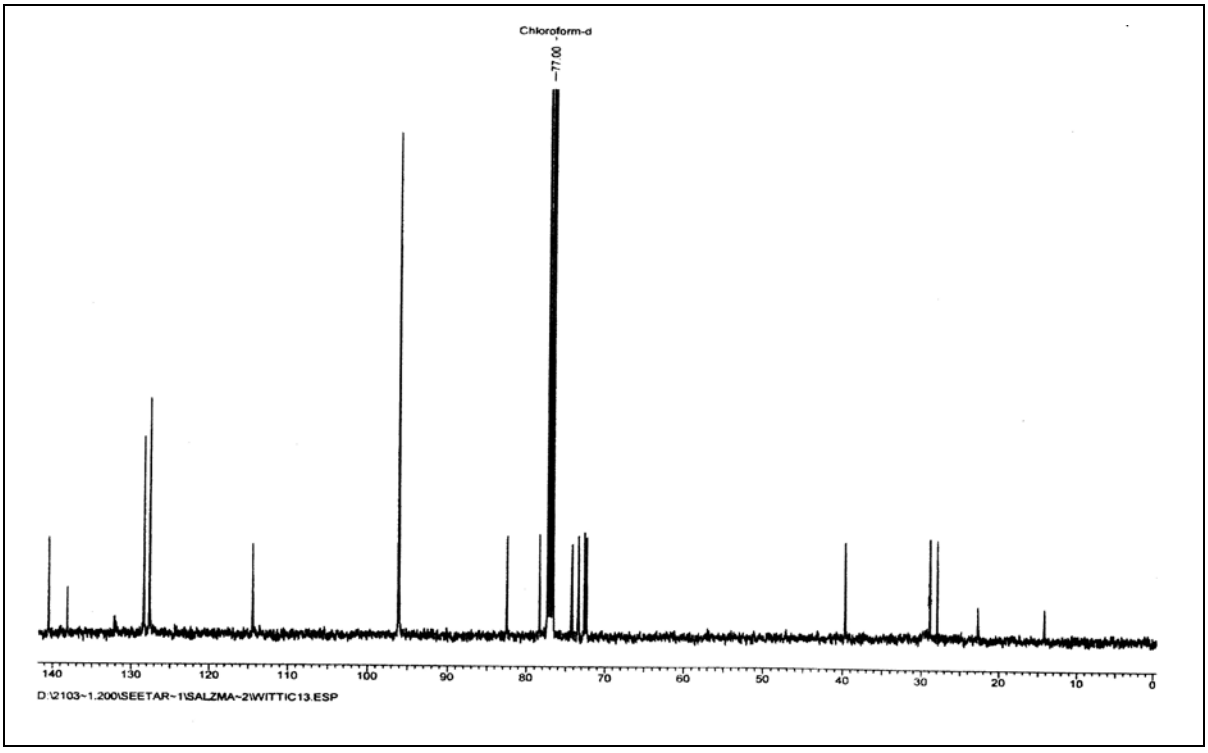
^{1}H NMR spectrum of compound 78 in $CDCl_3$



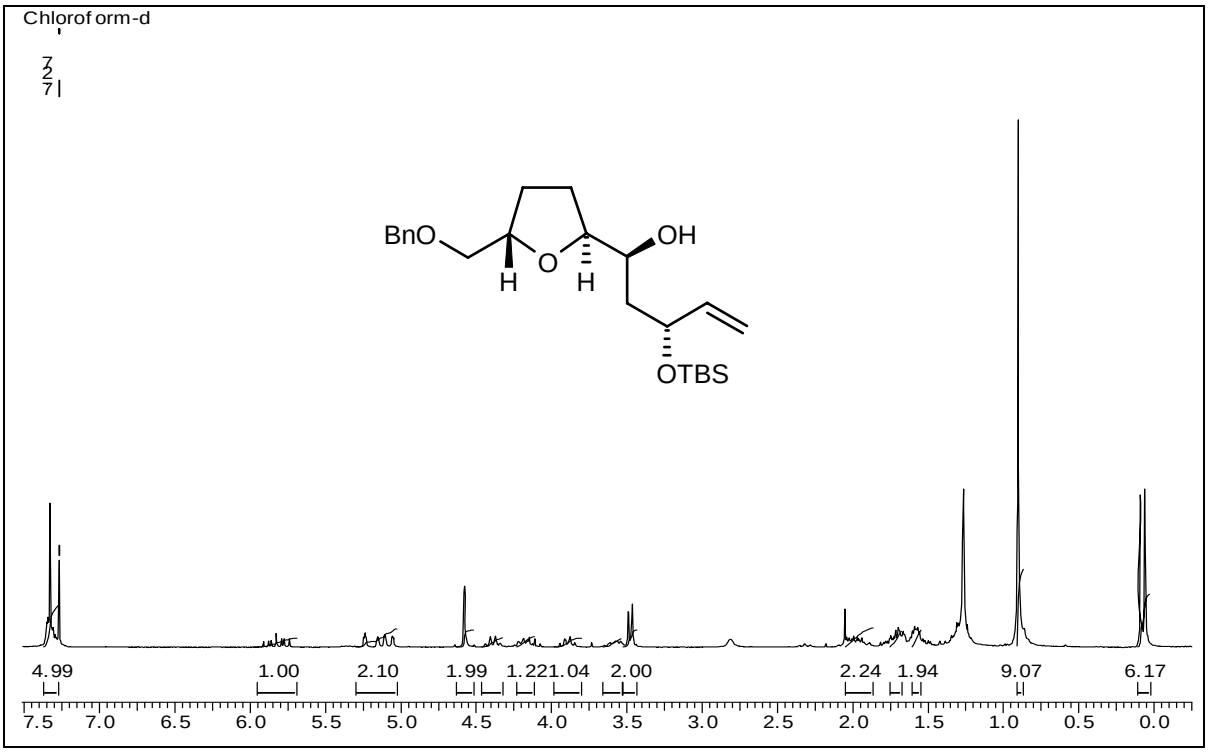
^{13}C NMR spectrum of compound 78 in $CDCl_3$



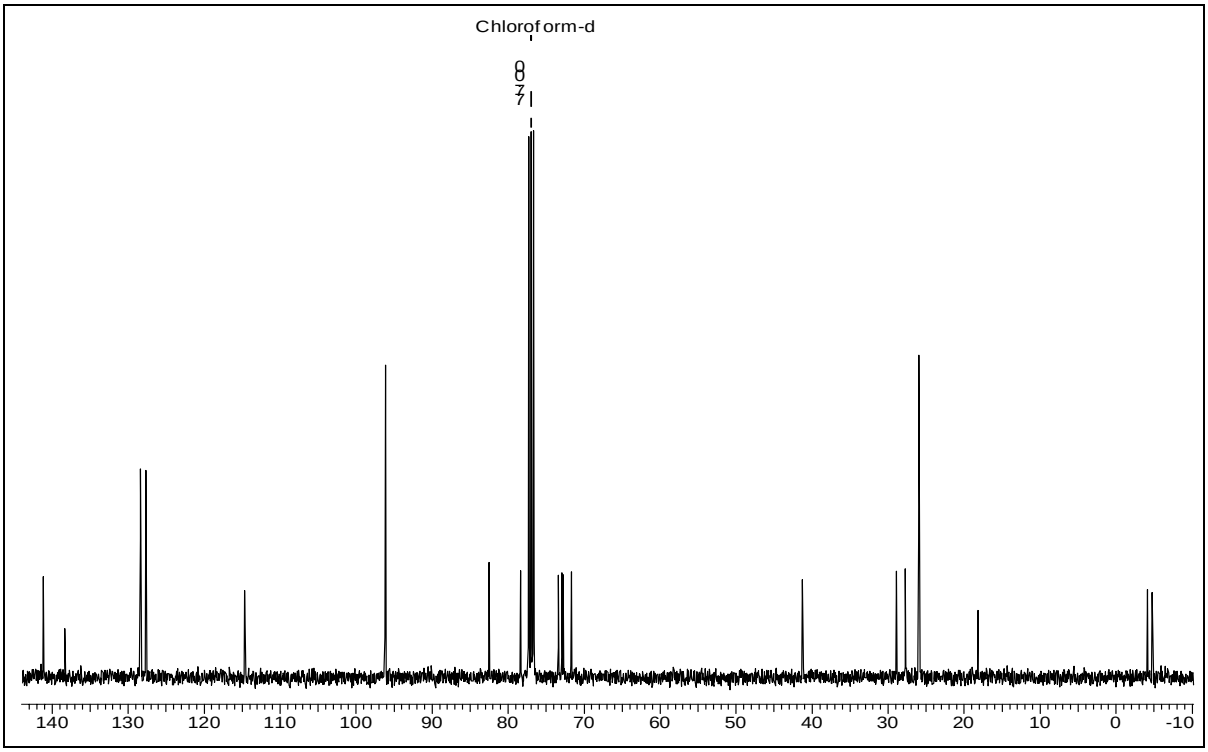
^{1}H NMR spectrum of compound 77 in $CDCl_3$



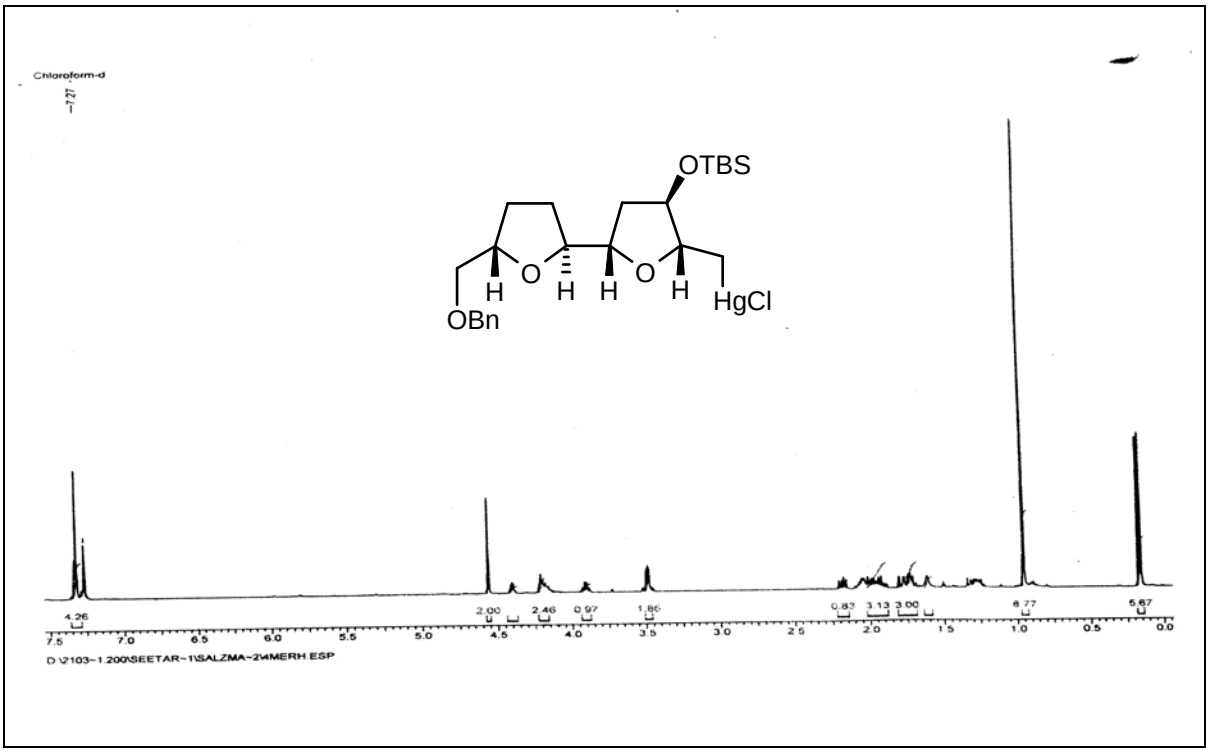
^{13}C NMR spectrum of compound 77 in $CDCl_3$



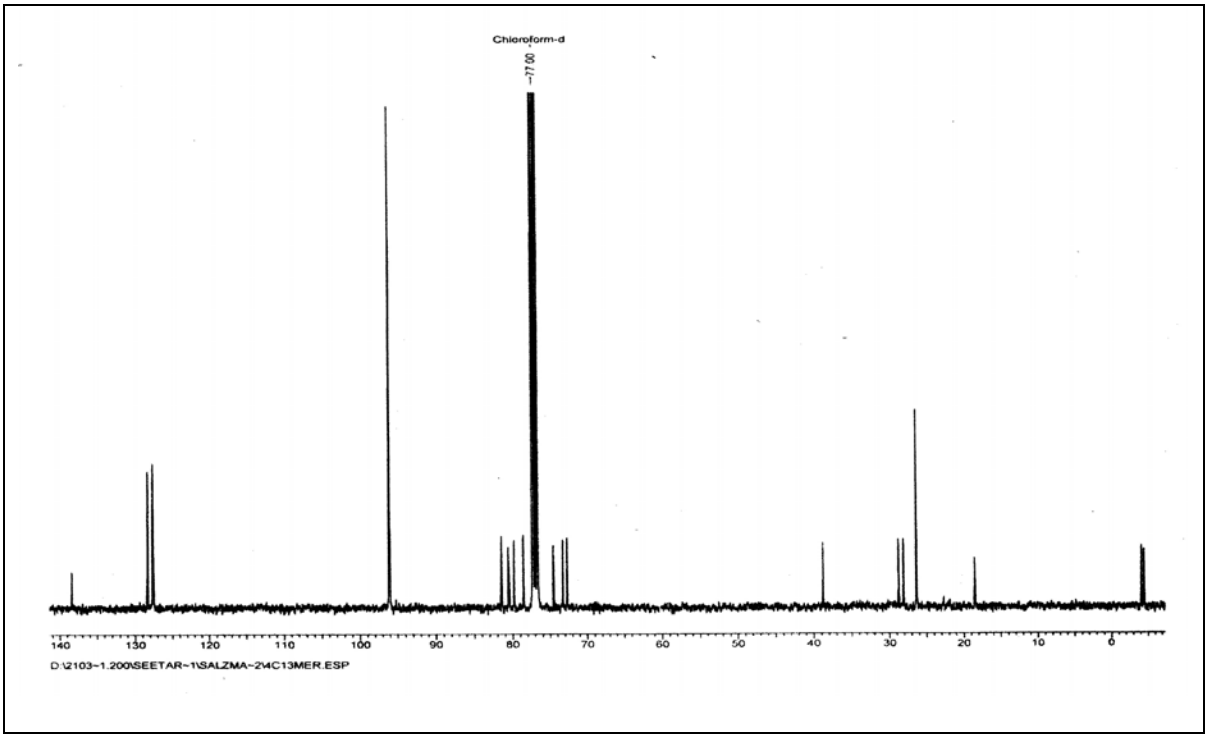
^{1}H NMR spectrum of compound 82 in $CDCl_3$



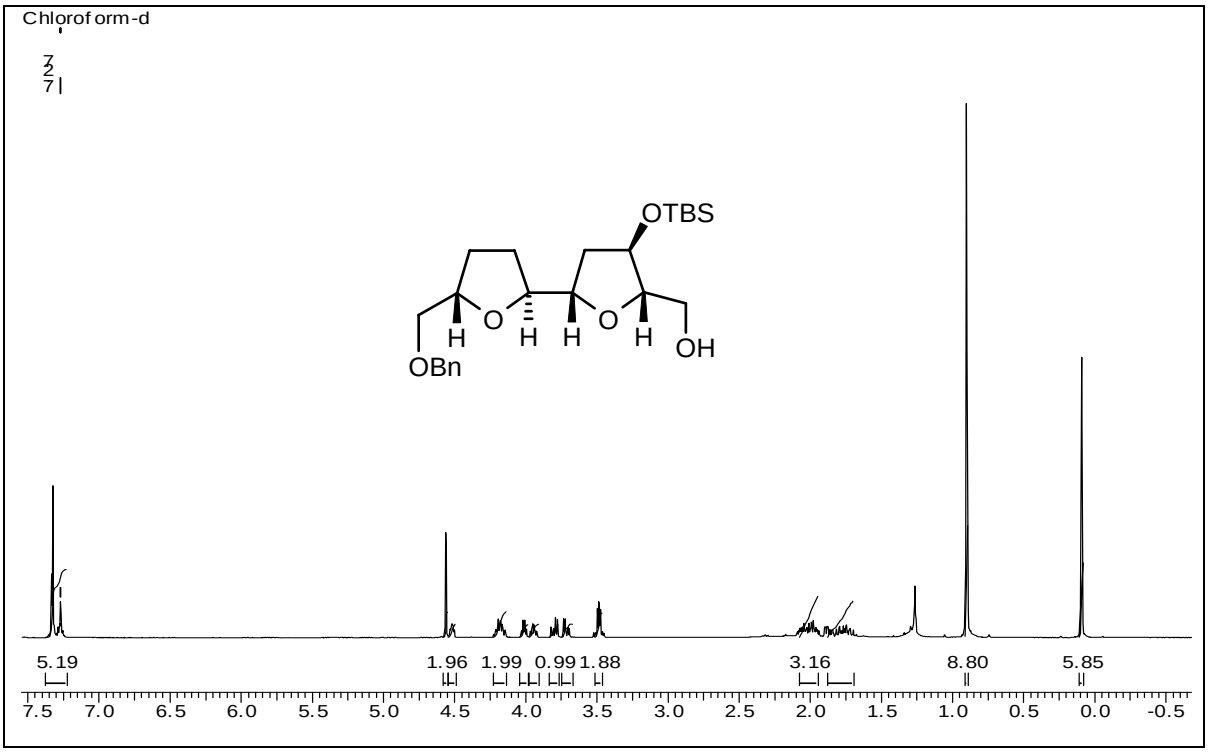
^{1}H NMR spectrum of compound 82 in $CDCl_3$



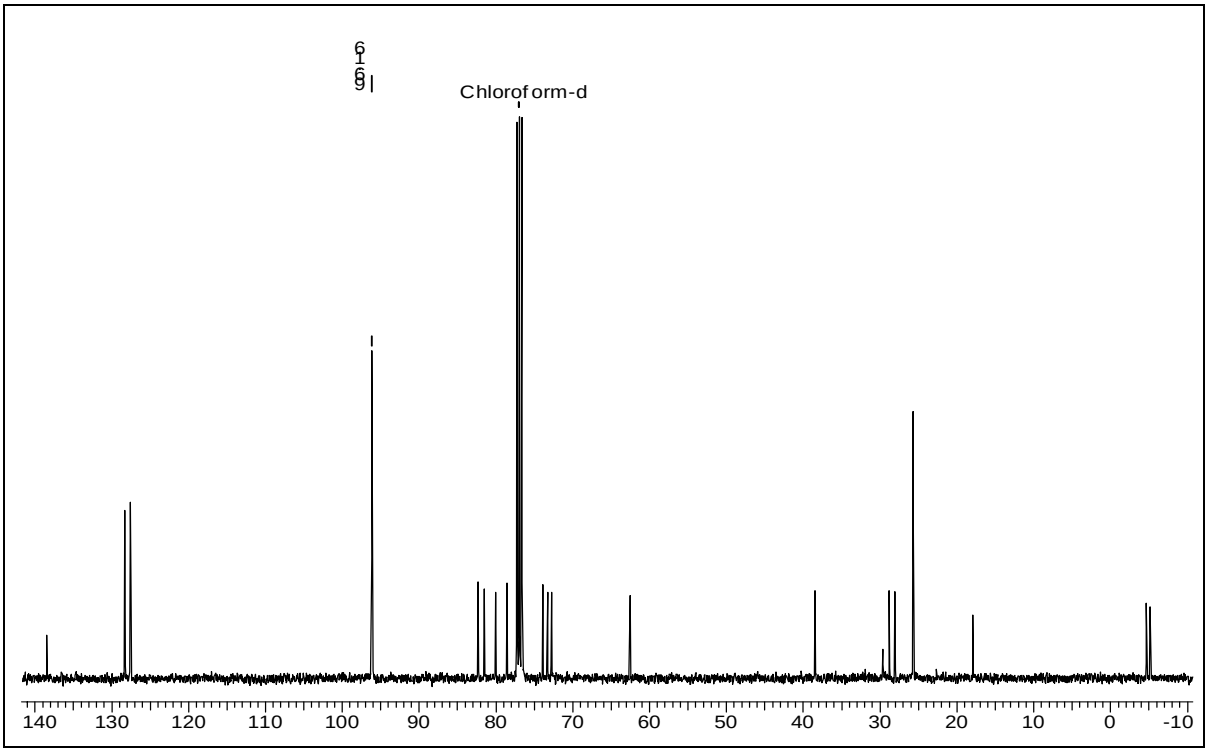
^{13}C NMR spectrum of compound 83 in $CDCl_3$



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



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



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

REFERENCES

References

1. Darnell, J.; Loddish, H.; Baltimre, D. *Molecular Cell Biology*; Scientific American Books.
2. George, G. I.; Thomas, T.; Chem. Iowa; Oima; Dolatrai; Vyas, M. *ACS Symposium series 583*. 3.
3. Remers, N. A. *Antineoplastic agents,* 1984.
4. (a) Gunasekhara, S. P.; Gunasekhara, M.; Longley, R. E. *J. Org. Chem.* **1950**, *55*, 4912. (b) Gunasekhara, S. P.; Gunasekhara, M.; Longley, R. E. *ibid* **1991**, *56*, 1346. (c) Hofle, G.; Bedorf, N.; Steinmetz, H.; Schomburg, D.; Gurth, K.; Reichenback, H. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1567. (d) Horton, P. A.; Kohen, F. E.; Longley, R. E.; Mc Connel, O. J. *J. Am. Chem. Soc.* **1994**, *116*, 6015.
5. M. C. Zafra-Polo, M. C. Gonz´alez, E. Estornell, S. Sahpaz and D.Cortes, Acetogenins fromAnnonaceae, Inhibitors of Mitochondrial Complex I, *Phytochemistry*, **1996**, *42*, 253–271.
6. M. C. Zafra-Polo, B. Figad`ere, T. Gallardo, J. R. Tormo and D. Cortes, Natural Acetogenins from Annonaceae, synthesis and mechanisms of action, *Phytochemistry*, **1998,** *48*, 1087–1117.
7. L. Zeng, Q. Ye, N. H. Oberlies, G. Shi, Z.-M. Gu, K. He and J. L. McLaughlin, Recent Advances in Annonaceous Acetogenins, *Nat.Prod. Rep.*, **1996**, *13*, 275–306.
8. A. Cav´e, B. Figad`ere, A. Laurens and D. Cortes. Acetogenins from Annonaceae, in *Progess in the Chemistry of Organic NaturalProducts*, eds. W. Herz, G. W. Kirby, R. E. Moore, W. Seglich and Ch. Tamm, Springer-Verlag,Wien, **1997**, *70*, 81–288.
9. F. Q. Alali, X.-X. Liu and J. L. McLaughlin, Annonaceous Acetogenins: Recent Progress, *J. Nat. Prod.*, **1999**, *62*, 504–540.
10. J. R. Tormo, T. Gallardo, M. C. Gonz´alez, A. Bermejo, N. Cabedo, I. Andreu and E. Estornell, Annonaceous acetogenins as inhibitors of mitochondrial complex I,*Curr. Top. Phytochem.*, **1999**, *2*, 69–90.
11. Jolad, S. D.; Hoffman, J. J.; Schram, K.H.; Cole, J.R.; Tempesta, M.S.; Kriek, G.R.; Bates, R.B. *J. Org. Chem.* **1982**, *47*, 3151-3153.

12. Zeng, L.; Ye, Q.; Oberlies. H. N.; Shi, G; Gu, Z.M.; He, K.; Mclaughlin, J.L. *Nat. Prod. Rep.* **1996**, *29*, 249-310.
13. P. Duret, A. I. Waechter, B. Figad`ere, R. Hocquemiller and A. Cav´e, Determination of absolute configurations of carbinols of Annonaceous acetogenins with 2-naphthylmethoxyacetic acid esters (2-NMA esters), *J. Org. Chem.*, **1998**, *63*, 4717–4720.
14. (a) Hui, Y. H.; Rupprecht, J. K.; Liu, Y. M.; Anderson, J. E.; Smith, D. L.; Chang, C.-J.; McLaughlin, J. L. *J. Nat. Prod.* **1989**, *52*, 463. (b) Li, X. H.; Hui, Y. H.; Rupprecht, J. K.; Liu, Y. M.; Wood, K. V.; Smith, D. L.; Chang, C. J.; McLaughlin, J. L. *J. Nat. Prod.* **1990**, *53*, 81. (c) Rieser, M. J.; Hui, Y.-H.; Rupprecht, J. K.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L.; Hanson, P. R.; Zhuang, Z.; Hoye, T. R. J. *Am. Chem. Soc.* **1992**, *114*, 10203
15. (a) Rupprecht, J. K.; Chang, C.-J.; Cassady, M. J.; McLaughlin, J. L. *Heterocyclic* **1986**, *24*, 1197. (b) Lewis M. A.; Arnason, J. T.; Philogene, B. J. R.; Rupprecht, J. K.; Mclaughlin J. L. *PesticideBiochem. Physiol.* **1993**, *45*, 15. (c) Zhao, G. X.; Miesbauer, L. R.; Smith, D. L.; Mclaughlin J. L. *J. Med. Chem.* **1994**, *37*, 1971.
16. Ahmadsahib K. I.; Hollingworth R. M.; McGovren J. P.; Hui Y.- H.; McLaughlin J. L. *Life Sci.* **1993**, *53*, 1113-1120.
17. Chrestine, H.; Johnson, H. M.; Knox, R. M.; Rezai, A.; Ryan, W. J.; Montz F. J. *Cancer Chemother. Pharmacol*. **1994**, *34*, 166-170.
18. Morre, D. J.; Cabo, R. D.; Farley, C.; Oberlies, H. N.; McLaughlin, J. L. *Life Sci.* **1995**, *56*, 343-348.
19. (1) (a) Rupprecht, J. K.; Chang, C.-J.; Cassady, M. J.; McLaughlin, J. L. *Heterocyclic* **1986**, *24*, 1197. (b) Lewis M. A.; Arnason, J. T.; Philogene, B. J. R.; Rupprecht, J. K.; Mclaughlin J. L. *PesticideBiochem. Physiol.* **1993**, *45*, 15. (c) Zhao, G. X.; Miesbauer, L. R.; Smith,D. L.; Mclaughlin J. L. *J. Med. Chem.* **1994**, *37*, 1971.
20. (a) Hui, Y. H.; Rupprecht, J. K.; Liu, Y. M.; Anderson, J. E.;Smith, D. L.; Chang, C.-J.; McLaughlin, J. L. *J. Nat. Prod.* **1989**, *52*, 463. (b) Li, X. H.; Hui, Y. H.; Rupprecht, J. K.; Liu, Y. M.; Wood, K.V.; Smith, D. L.; Chang, C. J.; McLaughlin, J. L. *J. Nat. Prod.* **1990**, *53*, 81. (c) Rieser, M. J.; Hui, Y.-H.; Rupprecht, J. K.;

Kozlowski, J. F.;Wood, K. V.; McLaughlin, J. L.; Hanson, P. R.; Zhuang, Z.; Hoye, T.R. J. *Am. Chem. Soc.* **1992**, *114*, 10203.

21. For a preliminary version of this work, see: Sinha, S. C.; Sinha-Bagchi, A.; Yazbak, A.; Keinan, E. *Tetrahedron Lett.* **1995**, *36*, 9257.
22. (a) Hoye, T. R.; Tan, L. *Tetrahedron Lett*. **1995**, 1981. (b) For the synthesis of (-)-bullatacin, see: Hoye, T. R.; Hanson, P. R. *Tetrahedron Lett.* **1993**, *34*, 5043.
23. For the synthesis of asimicin, see: Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1997**, *62*, 5989.
24. For the synthesis of bullatacin, see: Naito, H.; Kawahara, E.;Maruta, K.; Maeda, M.; Sasaki, S. *J. Org. Chem.* **1995**, *60*, 4419.
25. (a) Zafra-Polo, M. C.; Gonza´ lez, M. C.; Estornell, E.; Sahpaz, S.; Cortes, D. *Phytochemistry* **1996**, *42*, 253-271.(b) Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z. M.; He, K.;McLaughlin, J. L. *Nat. Prod. Rep*. **1996**, *13*, 275-306.
26. Hoye, T.R.; Zhuang, Z.P. *J. Org. Chem*. **1988**, *53*, 5578-5580.
27. Cortes, D.; Myint, S. H.; Dupont, B.; Davoust, D. *Phytochemistry* **1993**, *32*, 1475-1482.
28. Gu, Z. M.; Fang, M. P.; Rieser, M. J.; Huy, Y. H.; Miesbauer, L.R.; Smith, D. L.; Wood, K. V.; McLaughlin, J. L. *Tetrahedron* **1993**, *49*, 747-754.
29. Hisham, A.; Pieters, L. A. C.; Claeys, M.; van den Heuvel, H.; Esmans, E.; Dommisse, R.; Vlietinck, A. J. *Phytochemistry* **1991**, *30*, 2373-2377.
30. Duret, P.; Hocquemiller, R.; Laurens, A.; Cave´, A. *Nat. Prod. Lett*. **1995**, *5*, 295-302.
31. Sahai, M.; Singh, S.; Singh, M.; Gupta, Y. K.; Akashi, S.; Yuji, R.; Hirayama, K.; Asaki, H.; Araya, H.; Hara, N.; Eguchi, T.;Kakinuma, K.; Fujimoto, Y. *Chem. Pharm. Bull.* **1994**, *42*, 1163-1174.
32. Jolad, S. D.; Hoffmann, J. J.; Cole, J. R.; Barry, C. E.; Bates, R.B.; Linz, G. S.; Konig, W. A. *J. Nat. Prod*. **1985**, *48*, 644-645.
33. Kawazu, K.; Alcantara, J. P.; Kobayashi, A. *Agric. Biol. Chem.* **1989**, *53*, 2719-2722.
34. Tomer, K. B.; Crow, F. W.; Gross, M. L. *J. Am. Chem. Soc.* **1983**, *105*, 5487-5488.

35. (a)Bermejo, A.; Figade`re, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269. (b) Allali, F. Q. Allali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504.(c) Jolad, S. D.; Hoffman, J. J.; Schram, K.H.; Cole, J.R.; Tempesta, M.S.; Kriek, G.R.; Bates, R.B. *J. Org. Chem.* **1982**, *47*, 3151-3153.
36. Chavez, D.; Acevedo, L. A.; Mata, R. *J. Nat. Prod.* **1998**, *61*, 419.
37. Takahashi, S.; Maeda, K.; Hirota, S.; Nakata, T. *Org. Lett.* **1999**, *1*, 2025.
38. For mucocin syntheses, see: (a) Neogi, P.; Doundoulakis, T.; Yazbak, A.; Sinha, Sa. C.; Sinha, Su. C.; Keinan, E. *J. Am. Chem. Soc.* **1998**, *120*, 11279. (b) Ba¨urle, S.; Hoppen, S.; Koert, U. *Angew. Chem., Int. Ed.* **1999**, *38*, 1263. (c) Takahashi, S.; Nakata, T. *J. Org. Chem.* **2002**, *67*, 5739 and references therein. (d) Takahashi, S.; Kubota, A.; Nakata, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 4751. (e) Evans, P. A.; Cui, J.; Gharpure, S. J.; Polosukhin, A.; Zhang, H. *J. Am. Chem. Soc.* **2003**, *125*, 14702. (f) Zhu, L.; Mootoo,D. R. *Org. Biomol. Chem.* **2005**, *3*, 2750 (g) Crimmins, M. T.; Zhang, Y.; Diaz, F. A. *Org. Lett.* **2006**, *8*, 2369.
39. Hoppen, S.; Ba¨urle, S.; Koert, U. *Chem.-Eur. J.* **2000**, *6*, 2382.
40. Hwang, C. H.; Keum, G.; Sohn, K. I.; Lee, D. H.; Lee, E. *Tetrahedron Lett.* **2005**, *46*, 6621.
41. Kim, E. J.; Suh, K. M.; Kim, D. H.; Jung, E. J.; Seo, C. S.; Son, J. K.; Woo, M. H.; McLaughlin, J. L. *J. Nat. Prod*. **2005**, *68*, 194–197.
42. Queiroz, F.E.; Roblot, F.R.; Vote, L.O.; Paulo, M.D.;Hocquemiller, R. *J. Nat. Prod.* **2003,** *66*, 755-758
43. Ramu. E.; Bhaskar. G.; Rao B.V.; Ramanjaneyulu. G.S.*Tetrahedron Letters*, **2006**, *47*, 3401–3403.
44. Wysocki M.L.; Dodge W.M.; Voight E.A.; Burke S.D. Organic Letter, **2006**, *8*, 5637-5640.
45. Li pan.; Yang. J.; Zhao. Kang. *J. Org. Chem.* **1999,** *64*, 2259-2263
46. Piccialli. V.; Caserta. T.; Caruso. L.; , Paloma. G.L Bifulco. G. Tetrahedron 2006, *62*, 10989–11007.
47. Narayan S.R.; Borhan B. *J. Org. Chem.* **2006**, *71*, 1416-1429.

48. THF's via Williamson type etherification: (a) Yazbak, A.; Sinha, S. C.; Keinan, E. J. Org. Chem. 1998, 63, 5863–5868; (b) Emde, U.; Koert, U. Eur. *J. Org. Chem.* **2000**, 889–1904.
49. Recent reviews on the synthesis of THF acetogenins: (a) Figadere, B. *Acc. Chem. Res*. **1995**, *28*, 359–365; (b) Koert, U. *Synthesis* **1995**, *115–132*; (c) Hoppe, R.; Scharf, H.-D. *Synthesis* **1995**, 1447–1464; (d) Casiraghi, G.; Zanardi, F.; Battistini, L.; Rassu, G.; Appendino, G. Chemtracts: *Org. Chem*. **1998**, *11*, 803–827.
50. Marshall, J. A.; Jiang, H. *J. Org. Chem.* **1999,** *64*, 971–975.
51. (a) Hanessian, S.; Cooke, N. G.; Dettoff, B.; Sakito, Y. *J. Am. Chem. Soc.* **1990**, *112*, 5276–5290; (b) Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am.Chem. Soc*. **1990**, *112*, 5290–5313. (c) Bertrand, P.; Sukkari, H. E.; Gesson, J. P.; Renoux, B. Synthesis **1999,** 330–335.
52. (a) Thaisrivongs, S.; Seebach, D. *J. Am. Chem. Soc.* **1983,** *105*, 7407–7413; (b) Giese, B.; Bartmann, D. *Tetrahedron Lett*. **1985,** *26*, 1197–1200; (c) Garavelas, A.; Mavropoulos, I.; Perlmutter, P.; Westman, G. *Tetrahedron Lett.***1995**, *36*, 463–466; (d) Bratt, K.; Garavelas, A.; Perlmutter, P.; Westmann, G. *J. Org. Chem.* **1996**, *61*, 2109–2117.
53. Sih, J. C.; Graber, D. R. *J. Org. Chem*. **1982,** *47*, 4919–4927.
54. Okuma, K.; Tanaka, Y.; Kaji, S.; Ohta, H. *J. Org. Chem.* **1983**, *48*, 5133.
55. Freeman, F.; Robarge, K. D. *Carbohydr. Res*. **1986**, *154*, 270–274.
56. Shi, G.; Kozlowski, J. F.; Schwedler, J. T.; Wood, K. V.; MacDougal, J. M.; McLaughlin, J. L. *J. Org. Chem.* **1996**, *61*, 7988-7989.

PUBLICATIONS

List of Publication

1. Towards the total synthesis of amphidinolide E: an enantioselective synthesis of C12–C29 fragment: Gurjar, M. K.; **Mohapatra S**; Phalgune U. D.; Puranik V. G.; Mohapatra D. K. *Tetrahedron Letters* **2004**, *45*, 7899–7902
2. Double intramolecular oxymercuration: stereoselective synthesis of highly substituted bis-tetrahydrofuran: Mohapatra D. K.; **Mohapatra S**.; Gurjar M. K. *Tetrahedron Letter* **2006**, *47*, 5943–5947.
3. Synthetic studies towards Central core of Mucoxin, Salzmanolin and Asimitrin: Mohapatra, D. K.; Gurjar, M.K.; **Mohapatra, S**.; Nayak, S.; Gurjar, M.K. (to be communicated)
4. Synthetic studies toward the macrolactone core of amphidinolide E: Gurjar, M. K.; **Mohapatra S**; Mohapatra D. K. (to be communicated)
5. Double intramolecular oxymercuration: the frist 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.