SYNTHESIS OF MACROLIDES BY PROTECTING GROUP DIRECTED RING-CLOSING METATHESIS (RCM) AND STUDIES ON LIPOIC ACID AND CAMINOSIDE A

A THESIS

SUBMITTED FOR THE DEGREE OF

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TO

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BY

D K RAMESH

DIVISION OF ORGANIC CHEMISTRY

NATIONAL CHEMICAL LABORATORY,

PUNE-411008, INDIA

JUNE 2008

DEDICATED

TO MY BELOVED

PARENTS

D E C L A R A T I O N

The research work embodied in this thesis has been carried out at National Chemical Laboratory, Pune under the supervision of **Dr. M. K.Gurjar**, Division of Organic Chemistry, National Chemical Laboratory, Pune- 411 008. This work is original and has not been submitted in part or full, for any degree or diploma of this or any other University.

(D. K. Ramesh)

NATIONAL CHEMICAL LABORATORY

Dr. Homi Bhabha Road, PUNE - 411 008 (INDIA)

Dr. M. K. Gurjar
Research Guide

Phone: +91-20-39821300
+91-20-25887674
E-mail:mukund.gurjar@emcure.co.in

C E R T I F I C A T E

The research work presented in thesis entitled "**Synthesis of Macrolides by protecting group directed ring-closing metathesis (RCM) and studies on Lipoic acid and Caminoside A**" has been carried out under my supervision and is a bonafide work of **Mr. D. K. Ramesh**. 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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Ramesh D K

ABBREVIATIONS

Ac	-	Acetyl
AcOH	-	Acetic acid
Ac_2O	-	Acetic anhydride
Bn	-	Benzyl
BnBr	-	Benzyl bromide
BH_3·DMS	-	Boron dimethylsulfide complex
BF_3·Et_2O	-	Boron trifluoride diethyl ether complex
Br_2	-	Bromine
CSA	-	Camphorsulphonic acid
Cl_3CCN	-	Trichloroacetonitrile
CuCl	-	Copper (I) chloride
DBU	-	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	-	2,3-Dichloro-5,6-dicyanobenzoquinone
DIBAL-H	-	Diisobutylaluminium hydride
DIPT	-	Diisopropyl tartrate
DET	-	Diethyl tartrate
DMA	-	*N*,*N*′-Dimethylacetamide
DMF	-	*N*,*N*′-Dimethylformamide
DMAP	-	*N*,*N*′-Dimethylaminopyridine
DMSO	-	Dimethyl sulfoxide
DMP	-	Dess–Martin periodinane
DMP	-	2, 2-Dimethoxy propane
EtOH	-	Ethanol
Et	-	Ethyl
EtOAc	-	Ethyl acetate
Et_3N	-	Triethyl amine
EtMgBr	-	Ethyl magnesium bromide
HBr	-	Hydrogen bromide
I_2	-	Iodine

Im	-	Imidazole
IBX	-	Iodoxybenzoic acid
K_2CO_3	-	Potassium carbonate
KHMDS	-	Potassium hexamethyldisilazide
LAH	-	Lithium aluminium hydride
MeOH	-	Methanol
Ms	-	Methanesulfonyl
MsCl	-	Methanesulfonyl chloride
Me	-	Methyl
NaOMe	-	Sodium methoxide
NaH	-	Sodium hydride
$NaBH_4$	-	Sodium borohydride
Na_2S	-	Sodium sulfide
$NaIO_4$	-	Sodium metaperiodate
n-Bu_2SnO	-	n-Dibutyl tinoxide
Oxone	-	Potassium peroxymonosulfate
Pd/C	-	Palladium on Carbon
Ph	-	Phenyl
Py	-	Pyridine
PDC	-	Pyridiniumdichromate
$PdCl_2$	-	Palladium (II) chloride
p-TSA	-	*par*a-Toluenesulfonic acid
PMB	-	*para*-methoxybenzyl
PMB-Cl	-	*para*-methoxybenzyl chloride
S	-	Sulphur
TBAF	-	Tetra-*n*-butylammonium fluoride
TBDMS-Cl	-	*tert*-Butyldimethyl silyl chloride
TBDMS	-	*tert*-Butyldimethyl silyl
TBDPS-Cl	-	*tert*-Butyldiphenyl silyl chloride
TBDPS	-	*tert*-Butyldiphenyl silyl
TBHP	-	*tert*-Butylhydroperoxide

$Ti(O^iPr)_4$	-	Titanium (IV) isopropoxide
THF	-	Tetrahydrofuran
TPP	-	Triphenyl phosphine
Ts	-	Tosyl
Zn	-	Zinc
$ZnCl_2$	-	Zinc chloride

GENERAL REMARKS

- ^{1}H NMR spectra were recorded on AC-200 MHz, MSL-300 MHz, DRX-400 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, DRX-100 and DRX-125 MHz spectrometer.
- EI Mass spectra were recorded on Finngan MAT-1020 spectrometer at 70 *eV* using a direct inlet system.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected. All reactions are monitored by Thin Layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV light, I_2 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, Bombay, India.

CONTENTS

CHAPTER - III

Synthetic studies toward Caminoside A

ABSTRACT

Abstract

The thesis entitled **"Synthesis of Macrolides by protecting group directed ring-closing metathesis (RCM) and studies on Lipoic acid and Caminoside A"** consists of three chapters and each chapter is further divided into following sections: Introduction, Present work, Experimental, Spectroscopic data and References. Chapter I, divided into three sections. Section A, describes the first total synthesis of an anti-malarial nonenolide by protecting group directed ring-closing metathesis (RCM), section B, deals with the synthesis of Decarestrictine C_2 by RCM, Section C, involves the synthesis of Macrolides by RCM. Chapter II, deals with synthesis of (±)-α-Lipoic acid and Chapter III, involves the synthetic studies toward Caminoside A.

CHAPTER I:

<u>Section A:</u> The first total synthesis of an anti-malarial nonenolide by protecting group directed ring-closing metathesis (RCM)

Cordyceps militaris, an enthomopathogenic fungus belonging to the *Ascomycetes class*, adheres to the surface of insects during the winter and then penetrates it from a fruiting body and sporangium. Reports on the isolation of biologically active secondary metabolites from *Cordyceps militaris* have been few but have received attention due to the unique structures and specific biological activities of the metabolites. Cordycepins (3'-deoxyadenosine), with antifungal, antivirus, and antitumor activities, is one of the more interesting secondary metabolites that have been previously isolated from *Cordyceps militaris*.

Nonenolide **1** was recently isolated as a white solid from *Cordyceps militaris* BCC 2816, which shows anti-malarial activity against *Plasmodium flaciparum.* The structure as assigned from spectral analysis and molecular formula, ($C_{10}H_{16}O_4$ by HRMS). It is a 10-membered macrolactone with one double bond, two hydroxyl groups, and one methyl group. The stereochemistry was confirmed by spectral data and X-ray crystallographic analysis (Figure-1).

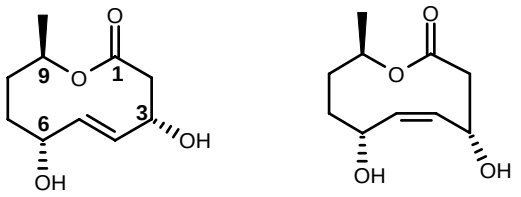
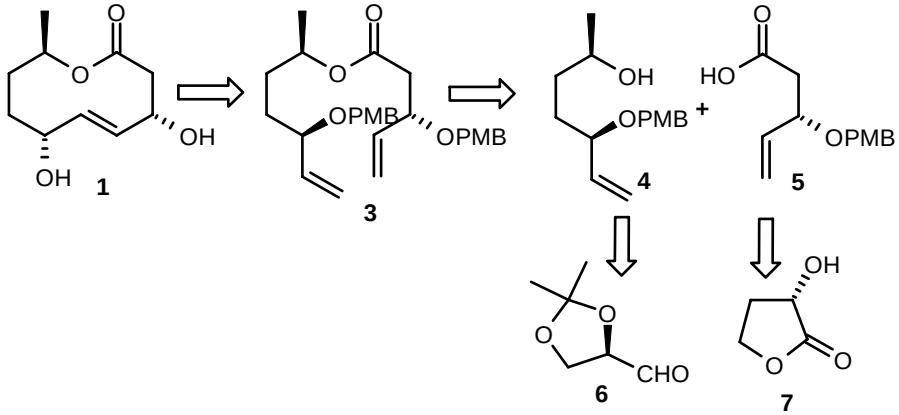


Figure-1

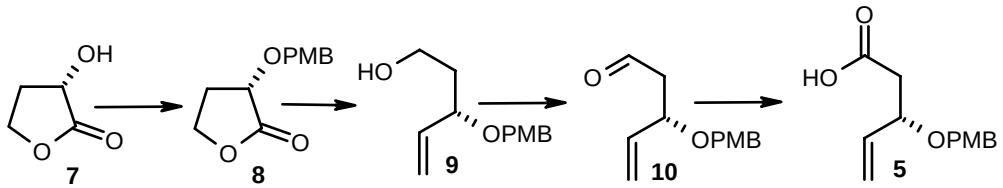
As part of our ongoing program on the synthesis of natural lactones involving ring-closing metathesis (RCM) as key step, we have devised a stereoselctive synthesis of nonenolide **1**. Despite its effectiveness in the synthesis of rings of all sizes, two factors still limit the scope of the RCM reaction; (a) in ring sizes ≥8, no control over *E*/*Z* stereochemistry of the double bond generated is possible. Stereochemical control is probably of thermodynamic origin; (b) the reports that describe application of the RCM to medium sized-particularly 10-membered rings, are still rare, especially when dense functionality close to the reaction centre is involved. There are no reports of RCM reaction on the substrate where chiral centers with protecting groups are present adjacent to both the reacting centers.

The retrosynthetic analysis is depicted in Scheme 1. The macrolactonization step relies on a RCM on a diolefinic ester. Strategic bond disconnection in ester **8** leads to chiral, nonracemic fragments acid (**5**) and alcohol (**4**) that could be derived from (*S*)-α-hydroxy-γ-butyrolactone (**7**) and 1, 2-*O*-isopropylidene (D)-glyceraldehyde (**6**), respectively.



Scheme 1

Synthesis of the acid component **5** began with **9** that was synthesized by literature procedure. The primary hydroxyl group of **9** was then oxidized with Dess-Martin periodinane (DMP) to afford the corresponding aldehyde (**10**); further treatment with $NaClO_2$ in presence of NaH_2PO_4 and 2-methyl-2-butene as a scavenger gave the required acid **5** in good yield (Scheme-2).

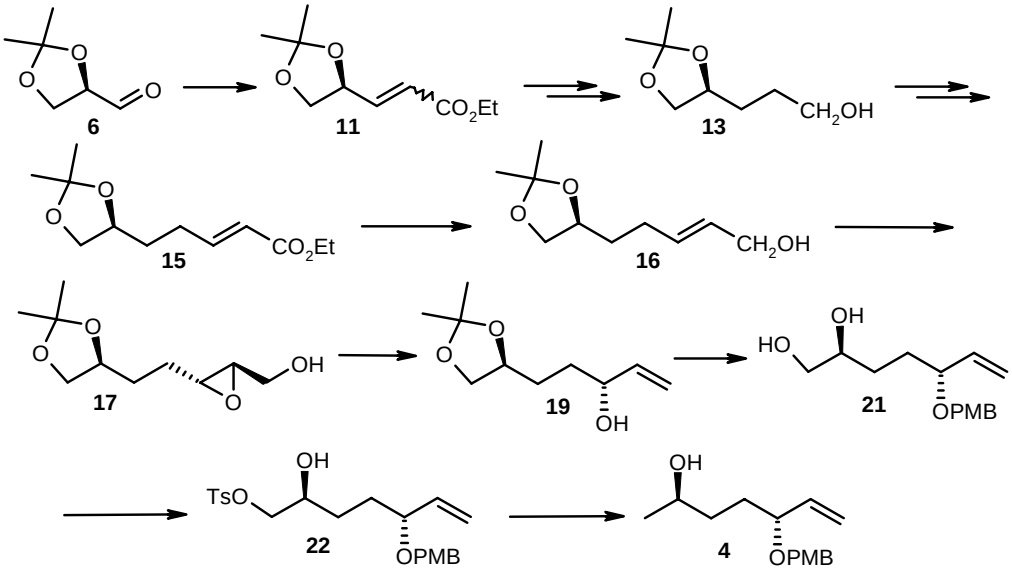


Scheme 2

The alcohol **4** was obtained in twelve steps, from 1, 2-*O*-isopropylidene (D)-glyceraldehyde (**6**) (prepared from D-mannitol), following standard protocol.

The D-glyceraldehyde derivative (**6**) when subjected to two-carbon Wittig olefination using (carbethoxymethylene)triphenylphosphorane in CH_2Cl_2, gave ester **11** as a mixture of *trans* and *cis* isomer, the mixture was carried forward for subsequent reaction. Compound **11** when subjected to catalytic hydrogenation with Pd/C afforded **12** in quantitative yield. Next, ester (**12**) was reduced with lithium aluminium hydride (LAH) in anhydrous THF to furnish the alcohol **13**. In order to secure ally alcohol (**16**), the primary hydroxyl group of **13** was oxidized with IBX to afford aldehyde **14**. It was further subjected to two carbons Wittig olefination to furnish **15**. Hydride reduction of **15** with DIBAL-H afforded the key precursor allyl alcohol **16.** Generation of the second chiral centre relevant to the target was achieved by employing Sharpless asymmetric epoxidation on **16,** in a catalytic process using (−) DET as chiral ligand, to furnish (2*R*,3*R*)-epoxide **17**. The next, epoxy alcohol was converted to epoxy iodide by iodination procedure to give **18**. Direct reduction with commercial zinc dust gave the diastereomerically pure terminal alkenic alcohol **19.** The terminal alkenic alcohol was protected as *p*-methoxybenzyl (PMB) ether **20**. The isopropylidene group of **20** was hydrolyzed under acidic conditions, to furnish diol **21**. In order to secure the alcohol fragment (**4**), we deoxygenated the primary hydroxyl group of diol. The **21** was selectively monoprotected with a tosyl group to give **22**. Then, **22** was treated with excess

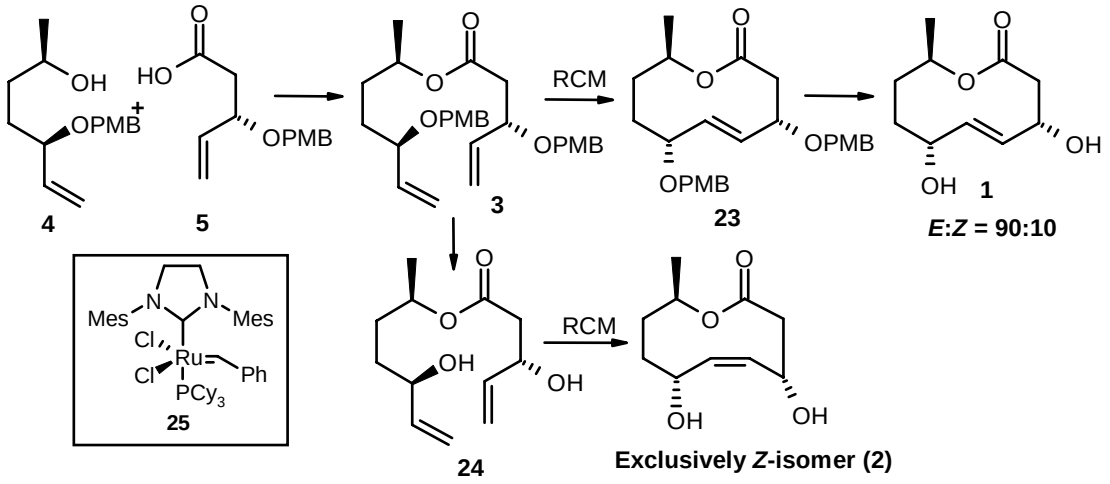
of lithium aluminium hydride (LAH) at 0 ^{o}C for 3 h in dry THF to provide requisite coupling partner alcohol **4** (scheme-3).



Scheme 3

Our next task was to couple the two fragments and conduct the critical RCM reaction. Carboxylic acid **5** was coupled with alcohol **4** under Yamaguchi conditions (2, 4, 6-trichlorobenzoyl chloride, Et_3N, DMAP) to afford the diene ester **3** (Scheme-4). This set the stage for the crucial ring-closing metathesis, which was successfully achieved with Grubbs' second generation catalyst **25**. A 0.001 M solution of **3** and 10 mol% of Grubbs' second generation catalyst **25** was heated at reflux for 8 h in dry, degassed CH_2Cl_2. This provided the desired 10-membered macrolactone (*E*)-**23** as the major product. Deprotection of the PMB groups was yielded the natural product **1** together with a small amount of the (*Z*)-isomer (**2**) (*E*/*Z* = 90:10). Constitution and configuration of the assigned compounds are unambiguous as the NMR and elemental analysis were in excellent accord with those reported values in the literature.

To verify the effect of PMB group upon the stereochemistry of the newly formed double bond, we carried out the RCM reaction with diol **24** (after deprotection of the PMB groups of **3**) afforded the 10-membered lactone **2** as the sole product. We were surprised to find the newly formed double bond to have a *Z*-conformation as evidenced by the coupling constant (11.2 Hz). No chromatographic or spectroscopic evidence for the formation of the *E* isomer was discernible (Scheme-4).



Scheme-4

In summary, a concise first total synthesis of the *E* and *Z* isomers of the potent anti-malarial nonenolide **1** and related congeners were presented. Our success was based on the synthesis of two coupling partners from inexpensive, commercially available starting materials and diastereoselective ring-closing metathesis for the formation of the 10-membered lactone ring.

Section B: Synthesis of Decarestrictine C_2 by RCM

In 1992 a joint group of Hoechst AG and the University of Gottingen reported the isolation of a family of 10-membered lactones, named decarestrictines A-M. Decarestrictines are secondary metabolites; the first representatives of a new class of fungal metabolites isolated from cultures of *Penicillium simplicissimum* and *P. corylophilum*. These metabolites revealed potent inhibitory effects on cholesterol biosynthesis in cell line tests via sodium acetate incorporation into cholesterol, with HEP-G2 liver cells. These appeared to be more selective, in that no other effects such as antibacterial, antifungal or antiviral activities were discernible.

Decarestrictines are novel 10-membered lactones structurally related to each other by their physio-chemical properties. A ten-membered lactone ring with an exocyclic methyl group constitutes the typical structural element. This interesting biological activity of decarestrictine has been responsible for stimulating synthetic activity.

We have previously published the synthesis of nonenolide **1** (*epi*-6-decarestrictine C_1) via protecting group directed ring-closing metathesis (RCM) as the key step. We undertook the task of making cyclic compounds through RCM reactions and generalizing

the observed substrate-based selectivity. We initially planned to synthesize the Decarestrictine C. Earlier reports claimed the isolated decarestrictine C to consist of an inseparable mixture of C_1 and C_2 in a 1:1 ratio. Later, Kibayashi,. *et al* reported the structure of decarestrictine C_2, based on the spectroscopic and X-ray crystallography analysis data (Figure-2).

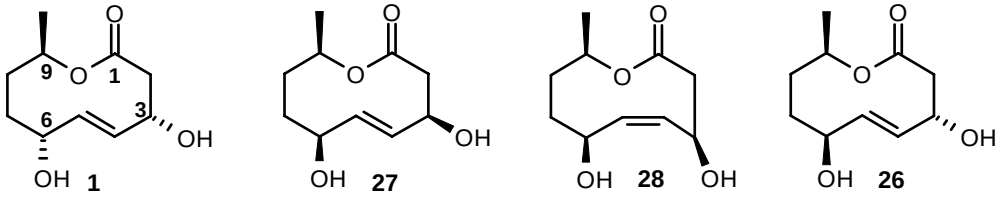
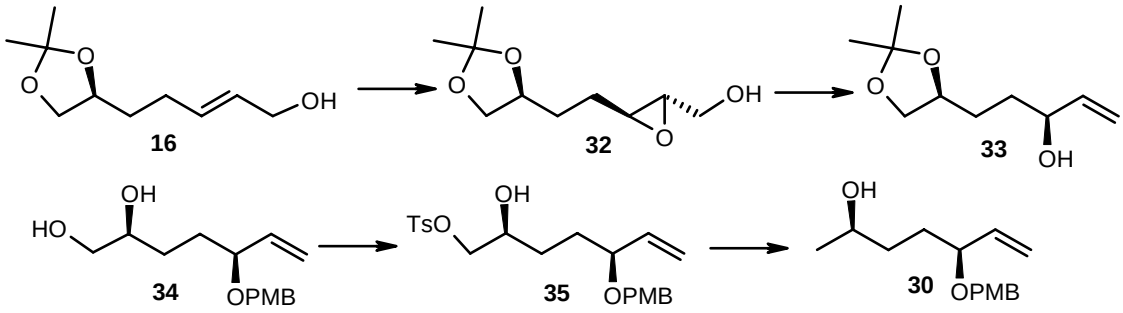


Figure-2

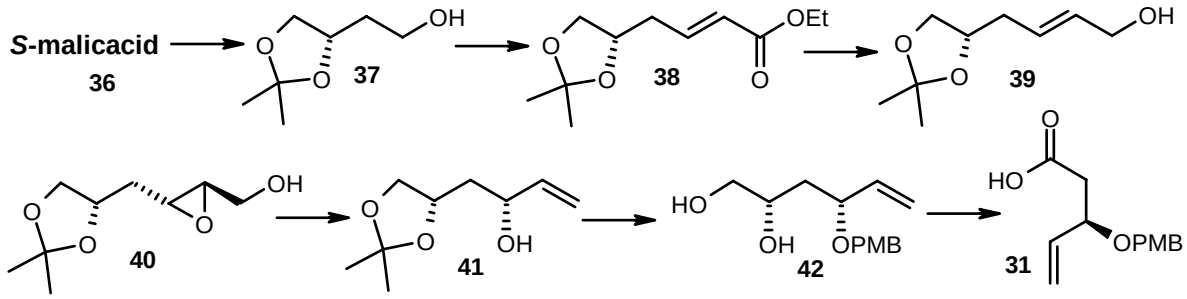
The retrosynthetic approach for decarestrictine C_2 (**27**): The macrolactonization step relies on a ring closing metathesis of a diolefinic ester that could be synthesized by Yamaguchi esterification. Strategic bond disconnection in ester (**29**) leads to alcohol (**30**) and acid (**30**) fragments.

The alcohol fragment (**30**) was prepared via epoxy alcohol derived from ally alcohol (**16**) via a Sharpless asymmetric epoxidation using (+) DET as a chiral ligand (Scheme-5).



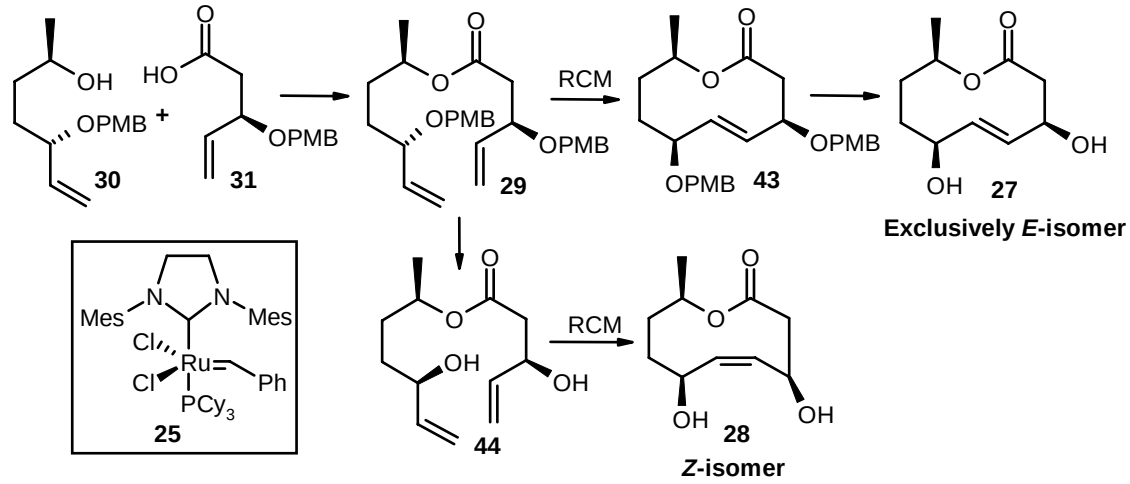
Scheme-5

The acid fragment (**31**) was synthesized from epoxide (**40**) derived from allyl alcohol (**39**) by employing Sharpless asymmetric epoxidation with (–) DET as a chiral ligand as a key step (Scheme-6).



Scheme-6

Two coupling partners in hand, our next achievement was to couple the two fragments **30** and **31** under Yamaguchi esterification conditions to furnish diolefinic ester **29.** This is the key precursor for the RCM reaction. Treatment of **29** with Grubbs second generation catalyst as before, provided the desired 10-membered lactone (**43**) *E*-isomer as the exclusively product. Deprotection of the PMB groups yielded the natural product decarestrictine C_2 (**27**). The spectroscopic and specific rotation data of the synthetic decarestrictine C_2 were in excellent accord with reported values of Kibayashi, *et al* (Scheme-7).



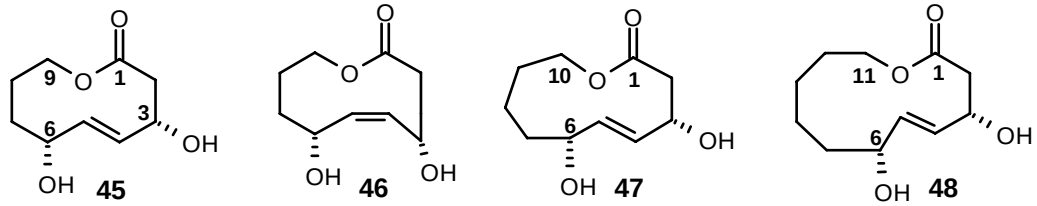
Scheme-7

We carried out the RCM reaction with diol **44** (after deprotection of the PMB groups of **29**) with Grubbs' second generation catalyst to afford the 10-membered lactone (**28**) *Z*-isomer as the product (Scheme-7).

In summary, we have successfully synthesized decarestrictine C_2 (reported by Kibayashi, *et al*) by employing RCM as the final step.

Section C: Synthesis of Macrolides by RCM

Our previous experiences in synthesis of natural lactones (Nonenolide, Decarestrictine C_2), containing chiral centers adjacent to both the reacting center, led us to the critical observation that protected diolefinic esters when subjected to RCM reaction gave *trans* selectivity, whereas unprotected diolefinic esters gave *cis* selectivity. To further exemplify the utility of these observations, we synthesized the des-methyl nonenolide, 11 and 12-memberd lactones containing dense functionality adjacent to the sterically constrained reaction centers (Figure-3).

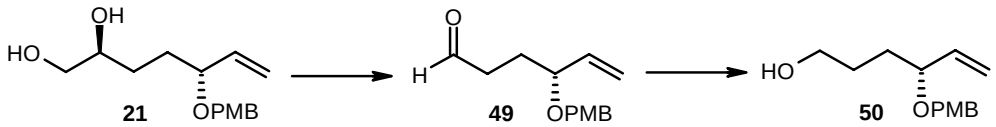


***E*-isomer desmethyl nonenolide** | ***Z*-isomer of 1** | ***E*-isomer 11-membered lactone** | ***E*-isomer 12-membered lactone**

Scheme-3

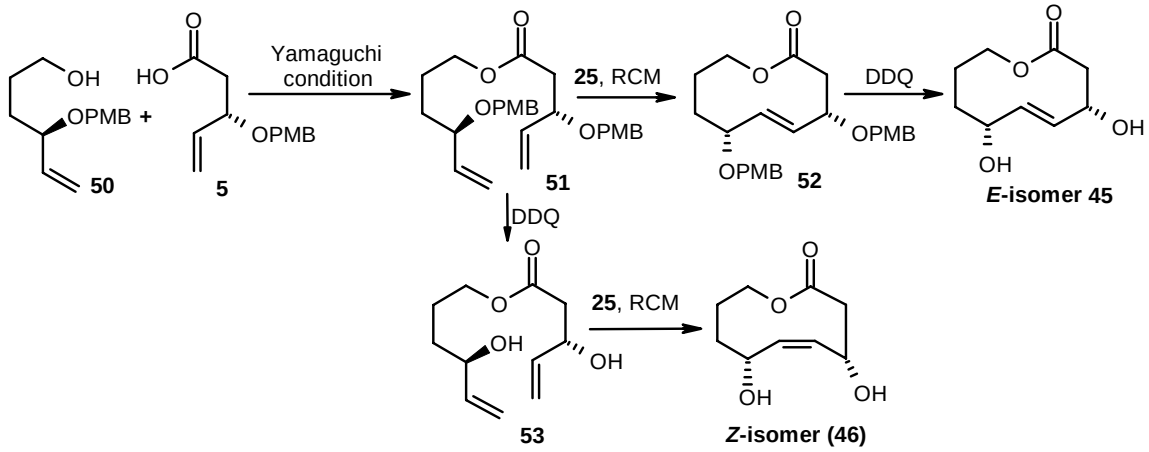
For synthesis of the RCM precursor diolefinic ester we used acid (**5**) as one of the coupling partners: it coupled with the different alcohols to give the requisite diolefinic esters.

The target alcohol fragment **50** was synthesized from diol **21** that was, in turn, prepared from D-glyceraldehyde derivative **6**. The diol **21** was oxidatively cleaved with sodium metaperiodate in dichloromethane to provide aldehyde **49.** It was subsequently reduced with sodium borohydride in absolute ethanol to furnish **50** (Scheme-8).



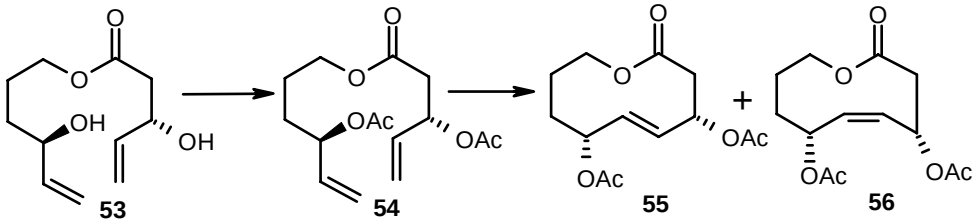
Scheme-8

The acid **5** was coupled with (*R*)-4-*p*-methoxybenzylhex-5-en-1-ol (**50**) under Yamaguchi conditions to afford ester **51**. This product was subjected to a RCM reaction to afford **52.** Deprotection of the PMB groups furnished the 10-membered lactone **45** with the *E*-isomer as the exclusive product as established by NMR analysis. Similarly, RCM reaction on diol **53** afforded exclusively the *Z*-isomer **46** (Scheme-9).



Scheme-9

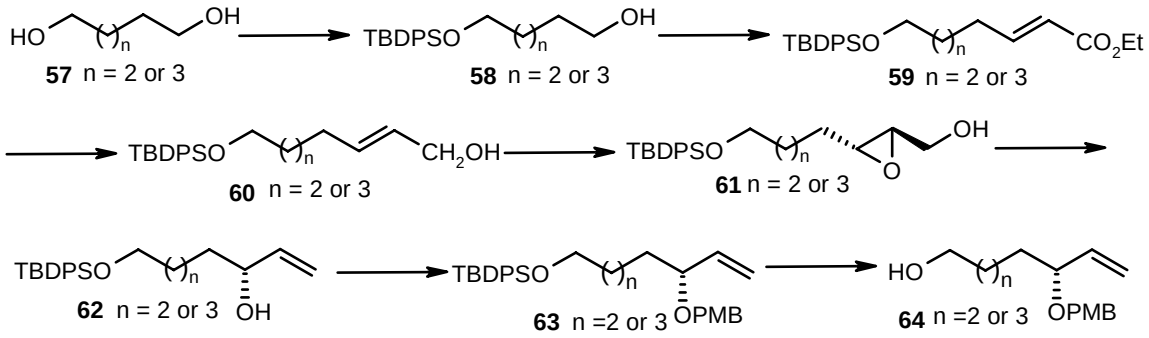
To verify the effect of protecting groups at the allylic position in controlling the stereochemical outcome of the RCM reaction in provision of olefin (*E* or *Z*), the diol **53** was acetylated using Ac_2O, to furnish **54**. The RCM reaction on **54** with Grubbs second generation catalyst afforded an isomeric mixture of 10-membered lactones in an approximately 1:1 ratio of *E*:*Z* isomers (**55:56**) (Scheme-10).



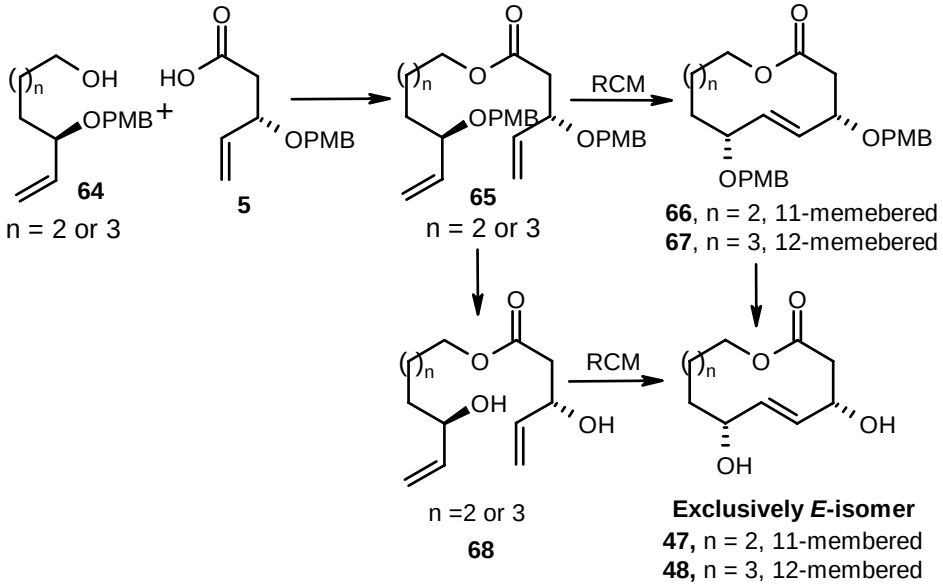
Scheme-10

The results described herein prompted us to undertake the synthesis of 11-membered and 12-membered ring lactones.

The coupling partners of alcohol fragments were synthesized from pentane-1, 5-diol (for 11-membered ring) and hexane-1, 6-diol (for 12-membered ring) (Scheme-11).



With the key intermediates **5** and **64** in hand, our next task was to couple the two fragments and conduct the RCM reaction. A 0.001 M solution of **65** and Grubbs' second-generation catalyst was heated at reflux in dry, degassed CH_2Cl_2. This provided the desired lactones (**66** or **67**) *E*-isomer as exclusive product (Scheme-12).



Scheme-12

We wish to verify the consistency of the results obtained from the RCM reactions. The diol (**68**) was subjected to RCM reaction with Grubbs' second generation catalyst to afford the lactones (**47** or **48**) *E*-isomer as the single product. No spectroscopic evidence for the formation of the *Z*-isomer was discernible.

Here, we obtained the *E*-isomer as the sole product with protected and unprotected diolefinic esters. It clearly indicates that the isomeric outcome of the olefin could not be controlled by the RCM reaction on higher than 10-membered lactones.

In conclusion, we have successfully synthesized the *E* and *Z*-isomers of the desmethyl nonenolide by employing protecting group directed RCM methodology.

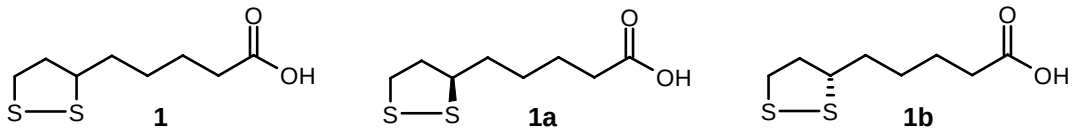
CHAPTER –II

Synthesis of (±)-α-Lipoic acid

α-Lipoic acid is an important protein-bound coenzyme and growth factor found in plant and animal tissues as well as in microorganisms. It has been recognized as a vital cofactor for the multienzyme complexes which catalyze the oxidative decarboxylation of

α-ketoacids such as pyruvate, α-ketoglutarate etc. It is known to play crucial role in photosynthesis and in tricarboxylic acid cycle. Lipoic acid exhibits beneficial effects in the treatment of diabetes. Lipoic acid and dihydrolipoic acid have been reported to be effective in preventing damage incurred by myocardial and cerebral ischemia-reperfusion injury in rats. Recently, it has also been reported that lipoic acid and their derivatives are highly active as anti-HIV and anti-tumor agents.

α-Lipoic acid was first isolated from processed liver by Reed *et al* in 1951 and was characterized as the cyclic disulfide 5-[3-(1,2-dithiolanyl)]-pentanoic acid. It is a molecule containing eight carbon atoms, a 1, 2-dithiolane ring and a carboxylic acid group. The chiral centre is embedded in the ring structure at the third position. There are two forms of lipoic acid i.e., *R* and *S*: the natural isomer *R* is pharmacologically more active than the *S*-isomer. Moreover, (±)-α-lipoic acid can be important for pharmaceutical use without resolution, since the (*S*)-enantiomer does not negatively affect the activity of the (*R*)-enantiomer (Figure-1).

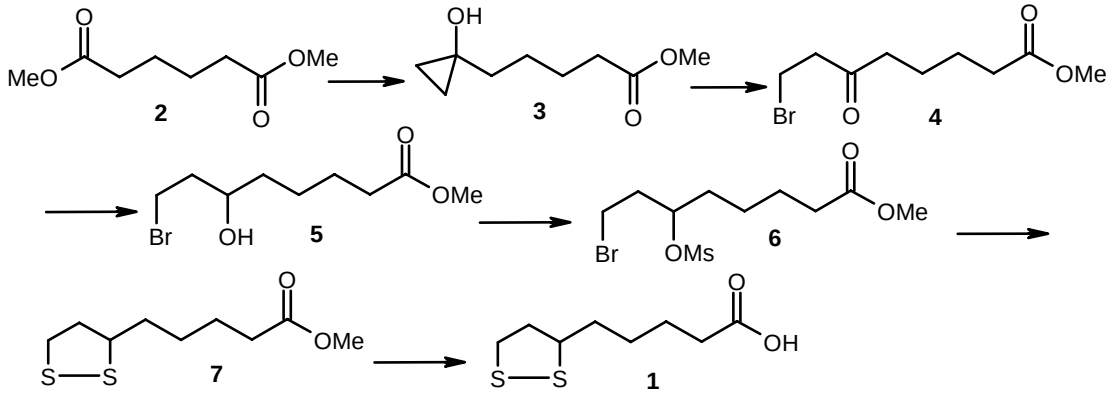


(±)-α-Lipoic acid (*R*)-α-Lipoic acid (*S*)-α-Lipoic acid

Figure-1

We planned a short, facile route for the synthesis of (±)-α-lipoic acid: our synthetic strategy suggested employing a Kulinkovich cyclopropanation for the synthesis of a key intermediate (**5**), starting from inexpensive and readily available dimethyladipate.

In order to obtain **3**, dimethyl adipate (**2**) was subjected to Kulinkovich cyclopropanation to give the cyclopropanol **3**. Electrophilic bromination of cyclopropanol proceeded by the reaction with bromine in aqueous 2-propanol afforded β-bromo ketone **4**. Next, the **4** was reduced with $NaBH_4$ to give methyl 8-bromo-6-hydroxyoctanoate (**5**). Treatment of **5** with methanesulfonyl chloride, gave the mesylate **6**. Reaction of **6** with sodium sulfide and sulfur in DMF at 90 ^{o}C afforded methyl (±)-α-Lipoate (**7**). The final conversion was achieved by the hydrolysis of **7** with 0.1M potassium hydroxide in ethanol to afford (±)-α-Lipoic acid (**1**). The spectral data and elemental data were in good agreement with the reported data (Scheme-1).



Scheme-1

In conclusion, we have accomplished the synthesis of (±)-α-Lipoic acid by deploying cheaply available starting material: Kulinkovich cyclopropanation was employed for the construction of the key precursor**.**

CHAPTER- III

Synthetic studies toward Caminoside A

Enteropathogenic *Escherichia coli* (EPEC) and enterohemorragic *E. coli* 0157:H7 (EHEC) are deadly pathogens to children and elderly. Infection by these pathogenic *E. coli* requires the bacterial secreted protein (Esps) and a type III secretory apparatus, which translocates secreted proteins across bacterial membranes, out of EPEC and EHEC, into the host epithelial cells. Remarkably, the type III secretory system, which is essential for the pathogenicity of EPEC and EHEC, is absent in nonpathogenic *E. coli.* Thus, selective inhibition of the type III secretory system might specifically attenuate pathogenic EPEC and EHEC without affecting the commensal *E. coli* flora. Recently, a high through put assay for inhibitors of the type III secretion of EPEC was developed. Activity-guided isolation of marine invertebrate extracts led to the discovery of caminoside A from the marine sponge *Caminus sphaeroconia*.

Caminoside A is an unusual marine glycolipid with non-glycerol aglycone (the C19 hydroxy ketone, **3**) that is gylcosylated at the C_{10}-OH group by a tetrasaccharide consisting of D-deoxytalose, two D-glucose units, and L-quinovose that are linked through 1, 2 and 1, 6-*O*-glycosidic bonds. The glucose residue in the middle is fully substituted. The configuration of the secondary C_{10}-OH of aglycone moiety could not be assigned at the time of synthesis (Figure-1).

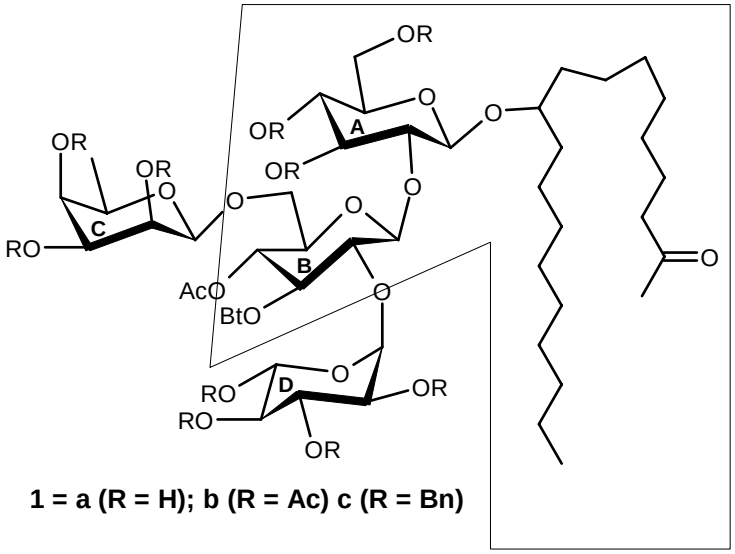
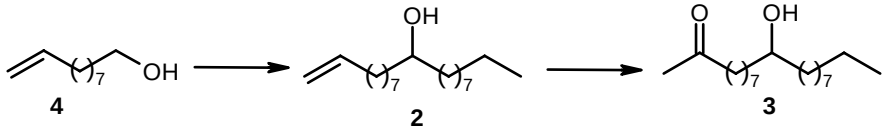


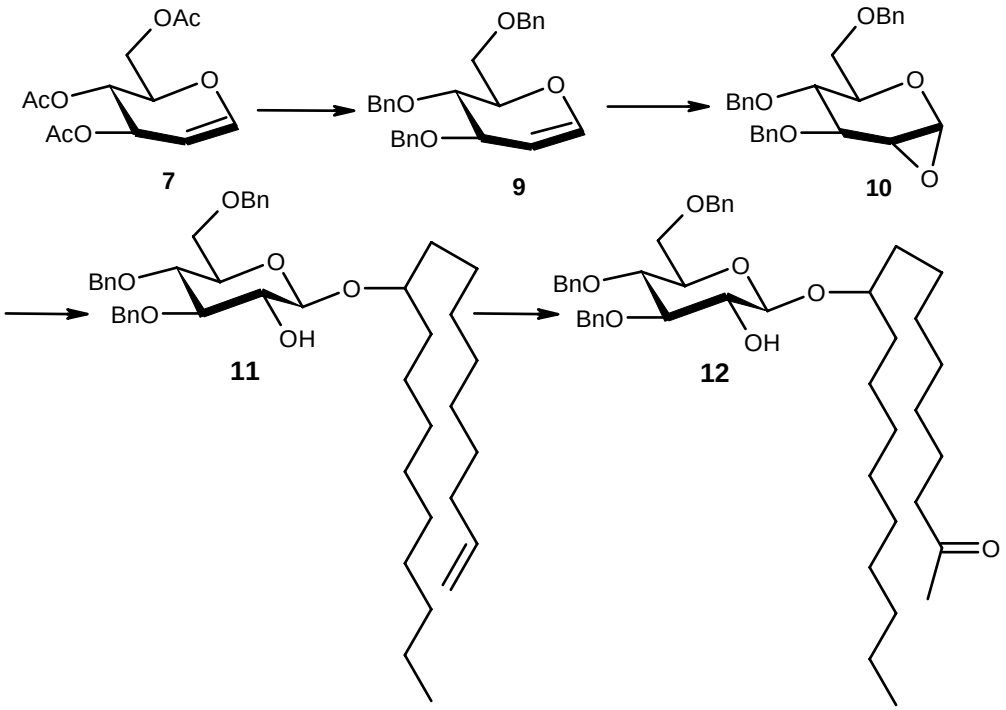
Figure-1: Caminoside A

The aglycone moiety (**2**) was prepared by oxidation of 9-decene 1-ol (**4**) with PDC in CH_2Cl_2 to afford aldehyde (**5**), which was subsequently subjected to Grignard reagent (nonanylmagnesiumbromide, **6**) to give **2.** Then, **2** was subjected to Wacker oxidation to give the aglycone moiety **3** (methyl ketone) (scheme-1).



Scheme-1

Monosaccharide (**9**) was conveniently synthesized from 3, 4, 6-tri-*O*-acetyl-D-glucal **7**. Tri-*O*-acetyl-D-glucal was converted to D-glucal (**8**) under Zemplen catalytic deacetylation conditions. Compound **8** was subjected to benzylation to afford **9.** Next, we attempted to construct the selectively β-configured glycoside **11**. This was achieved by the epoxidation of tri-*O*-benzyl-D-glucal (**9**) via reaction of DMDO (dimethyldioxirane) generated *in situ,* to obtain the glycosyl donor **10,** followed by oxirane ring opening with aglycone moiety (**2**) in the presence of anhydrous $ZnCl_2$ at -78 ^oC to provide the desired β-glucoside (**11**). The glycolipid **11** was subjected to Wacker oxidation protocol to afford methyl ketone **12**. It can serve as a glycosyl acceptor in disaccharide synthesis (Scheme-2).

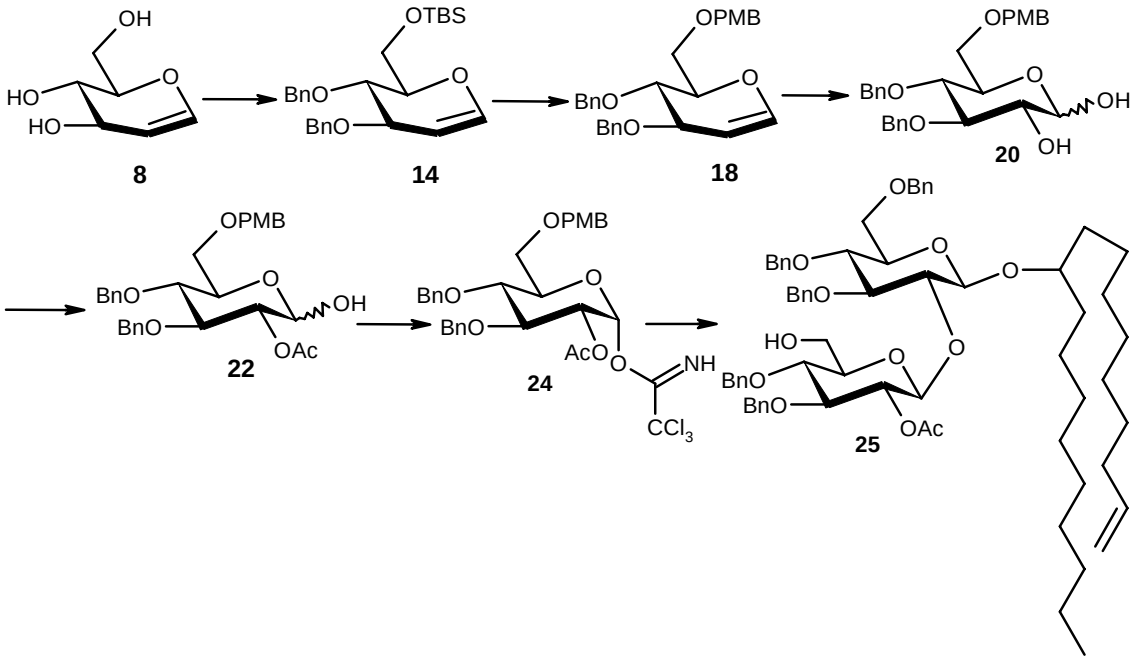


Scheme-2

The next challenge is to synthesize the glycosyl donor for the disaccharide unit. By the use of classical Hanessian silylation protocol, **8** was selectively protected at its primary C_6-OH group with TBDMS-Cl to obtain silyl ether **13.** The C(6)-*O*-silylated-D-glucal was benzylated to give the 6-*O*-silylated-3, 4-di-O-benzyl-substrate **14**.

We now wanted to achieve the disaccharide glycosylation with the uniquely installed C_2-hydroxyl on the benzyl glucose moiety **11**. Again, we hoped to use glycal epoxide methodology. Glucal derivative **14** was treated with dimethyldioxirane, to obtain the 1, 2-anhydro derivative **15**. However, all attempts to glycosylate **11** using **15** as the donor in the presence of anhydrous zinc chloride at -78 ^{o}C failed to provide the desired disaccharide **16**. A variety of attempts to bring about such glycosylation led to destruction of the glycosyl donor and recovery of the acceptor. We then investigated whether trichloroacetimidate donor would succeed where the oxirane had apparently failed. Accordingly, compound **14** was subjected to the action of TBAF to afford **17** and followed by protection with PMB ether gave **18**. Here we substituted the silyl ether with the PMB ether since silyl group could be easily deprotected during the construction of disaccharide unit in presence of Lewis acid reaction conditions. Subsequently, compound **18** was subjected to epoxidation by DMDO to provide anomeric mixture of α: β diol **20**.

Here we predicted 1, 2-anhydro derivative **19** but excess reagent and stirring for extended time, cleaved the oxirane ring and delivered the diol **20**. The diol substrate was acetylated to furnish diacetate **21**. Our choice of this protecting group for C_2 was made in order to foster β-selectivity through neighboring group participation during disaccharide formation. Next, anomeric acetyl group was selectively deprotected to afford **22**. Lactol **22** was readily converted to the corresponding trichloroacetimidate to generate the desired glycosyl donor **23**. The glycosyl donor was reacted readily and stereoselectively with glycosyl acceptor (**11**) in the presence of catalytic amount of $BF_3.Et_2O$ (-25 ^oC, MS 4 ^oA) in CH_2Cl_2 to provide the desired β-configurated disaccharide **24**. To synthesize the trisaccharide, the disaccharide **24** was treated with DDQ to selectively remove the PMB ether group to provide **25**. This compound would perform as glycosyl acceptor for the synthesis of trisaccharide (Scheme-3).



Scheme-3

In summary, we have synthesized the disaccharide unit of Caminoside A. Glycal and Schmidt methods were employed in the stereospecific construction of β-linked saccharide. Glycosyl donors (**10** and **23**) were prepared from D-glucal.

CHAPTER-I

Section A

The first total synthesis of an anti-malarial nonenolide by protecting group directed ring-closing metathesis (RCM)

INTRODUCTION

Introduction

Approximately, 40% of the world's population, mostly those living in the world's poorest countries are at risk of malaria. Every year, more than 500 million people become severely ill with malaria. Most cases and deaths are in sub-Saharan Africa. However, Asia, Latin America, the Middle East and parts of Europe are also affected. Travelers from malaria-free regions going to areas where there is malaria transmission are highly vulnerable-they have little or no immunity and are often exposed to delayed or wrong malaria diagnosis when returning to their home country.

Malaria is caused by protozoan parasites of the genus *Plasmodium*. There are four types of human malaria- *Plasmodium falciparum, P. vivax, P. malariae,* and *P. ovale*. *P. flaciparum* and *P. vivax* are the most common. *P. falciparum* is by far the most deadly type of malaria infection.

Malaria parasites are transmitted from one person to another by the female anopheline mosquito. The males do not transmit the disease as they feed only on plant juices. There are about 380 species of anopheline mosquitoes but only 60 or so are able to transmit the parasite. Like all other mosquitoes, the anophelines breed in water, each species having its preferred breeding ground, feeding patterns and resting place. Their sensitivity to insecticides is also highly variable.

Plasmodium develops in the gut of the mosquito and passed on in the saliva of an infected insect each time it takes a new blood meal. The parasites are then carried by the blood in the victim's liver where they invade the cells and multiply, after 9-16 days they return to the blood and penetrate the red cells, where they multiply again, progressively breaking down the red cells. This induces bouts of fever and anemia in the infected individual. In cerebral malaria, the infected red cells obstruct the blood vessels in the brain. Other vital organs can also be damaged often leading to the death of the patient.

Malaria is diagnosed by the clinical symptoms and microscopic examination of the blood. It can normally be cured by anti malarial drugs.[1, 2] The symptoms, fever, shivering, pain in the joints and headache, and quickly disappear once the parasite is killed. In certain regions, however, the parasites have developed resistance to certain antimalarial drugs, particularly chloroquine.

In endemic regions, where transmission is high, people are continuously infected so that they gradually develop immunity to the disease. Until they have acquired such immunity,

children remain highly vulnerable. Pregnant women are also highly susceptible since the natural defense mechanisms are reduced during pregnancy.

Malaria has been known since time immemorial, but it was centuries before the true causes were understood. Previously, it was thought that "miasma" (bad air or gas from swamps-"mal air ia") caused the disease. Surprisingly in view of this, some ancient treatments were remarkably effective. An infusion of qinghao (*Artemesia annua*) has been used for at least the last 200 years in China, its active ingredient (artemisinin) having only recently been scientifically identified. The antifebrile properties of the bitter bark of (*Cinchona ledgeriana*) were known in Peru before the 15th century. Quinine, the active ingredient of this potion was first isolated in 1820 by the pharmacist.

Systematic control of malaria started after the discovery malaria parasite by Laveran in 1889 (for which he received the Nobel Prize for medicine in 1907), and the demonstration by Ross in 1897 that the mosquito was the vector of malaria. These discoveries quickly led to control strategies and with the invention of DDT during the World War II, the notion of global eradication of the disease. Effective and inexpensive drugs of the chloroquine group were also synthesized around this time.

In recent years, the secondary metabolites from pathogenic fungi have been received great deal of attention, because of peculiar structure with specific biological activities. A long these lines, the genus *Cordyceps* are rich source of biologically active secondary metabolites. The *Cordyceps* species,[3] which are known as one of the Chinese medicinal mushrooms, are entomopathogenic fungi belonging to Clavicipitaceae and Ascomycotina. They are generally called "Tochukasa" in Japanese, meaning "winter-insect and summer-plant". It grows mushroom in summer from an insect infected by spores that hibernates during the winter. Natural Cordyceps is rather unique and rare creature that is usually found in the high lands. Some *Cordyceps* specially have long been used to promote longevity, relieve exhaustion and treat numerous illness by acting as a haemostatic, a mycolytic, an anti-asthmatic and a hypoglycemic agents in Chinese tradition medicines. They could produce many kinds of bioactive compounds such as cordycepin, ophiocordin and some polysaccharides.

There are eight different *Cordyceps* species (*CS, C. militaris, C. cicadae, C. ophioglossoides, C. heteropoda, C. pseudomilitaris, C. nipponica, C. sinclairii*). Among them *C.militatis* and *C. sinensis* are the most well known strains. *C. militaris* is one of the *Cordyceps* strains that have mushroom fruit body in orange color and silkworm pupa as host body. Recently, Rukachaisirikul *et. al.,* reported[4] that the ten-membered macrolides isolated from the

insect pathogenic fungus *Cordyceps militaris* BCC 2816 shows antimalarial activity against *Plasmodium flaciparum* (K1, multidrug resistant strain).

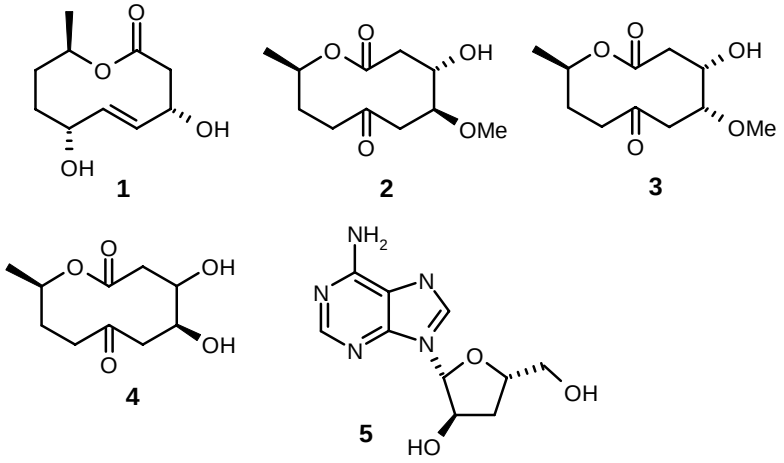


Figure-1: isolated from *C.militaris* BCC 2816

Isaka *et. al.,* reported[5] that antimalarial Cordypyridones A-D isolated from *C. nipponica* BCC 1389. Cordypyridones A and B, atropisomers of each other, exhibit potent in vitro antimalarial activity with IC_{50} values of 0.066 and 0.037 μg/mL, respectively, while their cytotoxicity was much weaker.

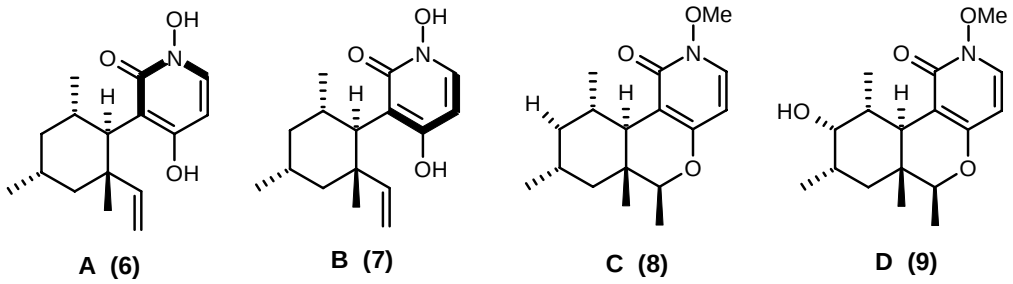


Figure-2: Structures of Cordypyridone A-D

Likewise, Kittakoop *et. al.,* reported[6] that the naphthoquinone derivatives isolated from *C. unilateralis* BCC 1869 shown antimalarial activity. The naphthoquinone with a naphthazarin nucleus can exist as an equilibrium mixture in which tautomer forms **II** and **I** are normally regarded to give major contribution in the equilibrium. While naphthaoquinones **10-14** showed antimalarial activity and cytotoxicity (against **BC, KB** and Vero cell lines), naphthoquinone **15** was active against the antimalarial parasites but not against the above cell line.

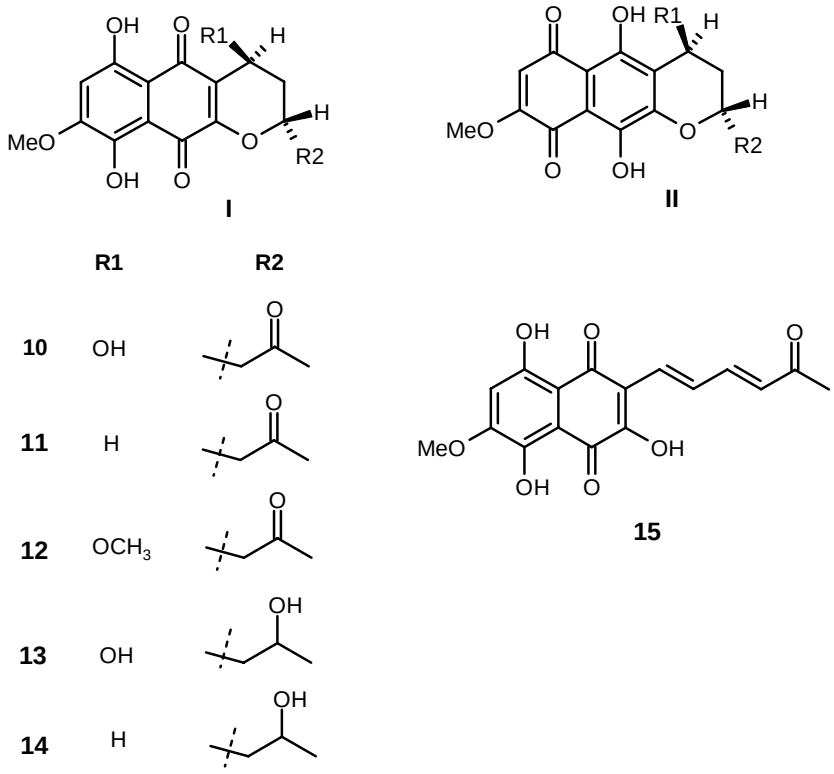


Figure-3: Structures of Erythrostominones

A short review on medium-sized ring lactones

Medium-sized[7] heterocyclic rings are becoming increasingly important in organic chemistry, as they are contained in an ever-growing number of biologically active natural products and medicinally important compounds. A numbers of methodologies have been developed for their synthesis. They are much more difficult to synthesize by cyclization methods than other cyclic compounds (ring sizes>12) because the formation of medium ring compounds is disfavored by entropy as well as enthalpy.[8]

Naturally occurring 10-membered lactones

Natural products containing ten-member framework are found in plants, insects (pheromones) and bacteria (antibiotics). They originate from terrestrial, fungal or marine sources. Jasmine is one of the oldest natural products possessing an oxecan-2-one framework isolated[9] in 1942 from essential oil of *Jasminum grandiflorium*. More recently, tuckolide was isolated as metabolite of the Canadian tuckahoe, the sclerotium of *Polyporus tuberaster* a subterranean fungus.[10] Achaetolide was isolated from the fungus of *Achaetomium cristalliferum*.[11a] Pinolidoxin, a phytotoxin was produced from the fungus of *Aschochyta pinodes*,[11b] subsequently three new metabolites of this fungus were found as epi and dihydropinolidoxins.[11c]

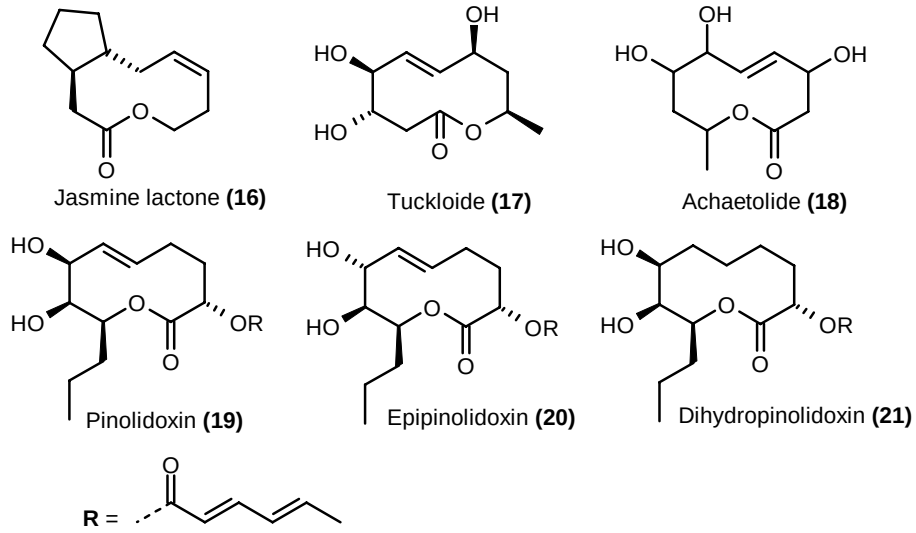


Figure-4

Diplodialides A, B, C and D four new metabolites from the culture filtrate of the plant pathogenic fungus,[12] *Diplodia pinea*. These are the first members of ten-membered lactones belonging to pentaketides. Diplodialide A, has been reported to be a steroid hydroxylase inhibitor. Pyrenolides A, B and C, which have similar structure to diplodialides isolated from pathogenic fungus, *Pyrenophora teres*.[13] These compounds show inhibitory activity against fungi.

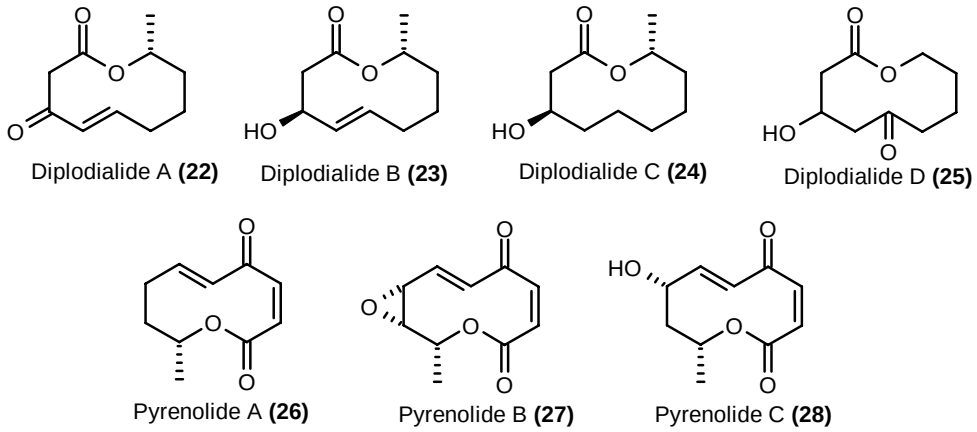


Figure-5

Cephalosporolides B and C are metabolites of fungus *Cephalosporium aphidicola*.[14a] These structures are related to the diplodialides. Another interesting metabolite, thiobiscephalosporolide A, was isolated during the fermentation of *Cephalosporium aphidicola* and found to be dimeric 10-membered lactone.[14b] On degradation, it led to a compound that is a regioisomer of diplodialide D.

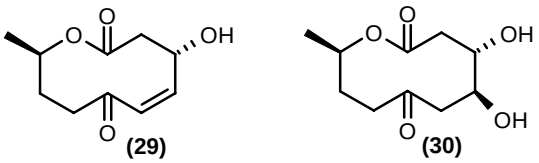


Figure-6

The metastemal gland secretion of the common eucalypt longicom, *Phoracantha semipunctata* contains two major components, phoracantholide **I** and **J**.[15]

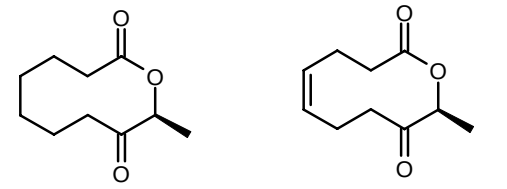


Figure-7

Metabolites of *Didenmum moseleyi* (herdman), didemnilactones A, B, and neodidemnilactone were found to be 10-membered lactones.[16] These compounds exhibit weak binding activity to leukotriene B_4 receptors in human polymorphonuclear leukocyte membrane. Ascidiatrienolides A, B and C,[17a] whose structures are recently reinvestigate,[17b] were found in marine ascidian (*Didemnum candidum*) and correspond to oxidation products of C_{20} fatty acid.

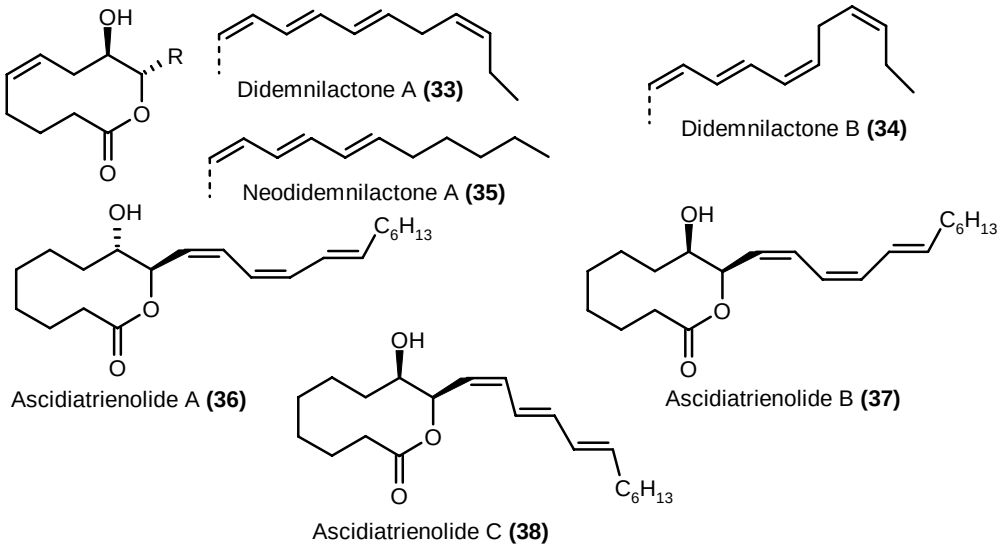


Figure-8

Trichlogoniolides that are complex lactones isolated from the aerial part of *Trichogonia* species (vide *supra*).[18]

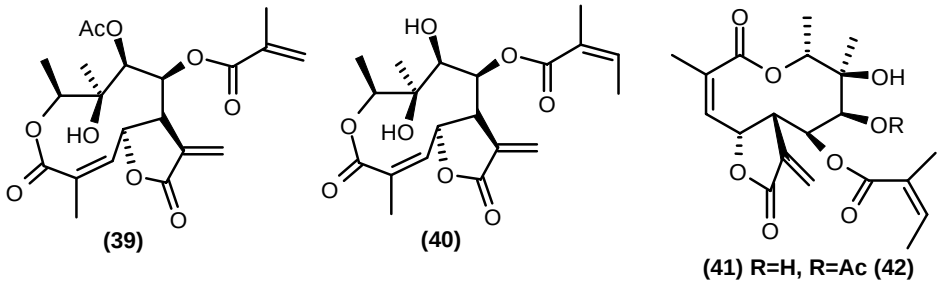


Figure-9

A new alkaloid aspidochibine was isolated from the tree bark of the *Aspidosperma quebracho blanco* Schlecht, which used for the treatment of bronchial asthma and dyspnoe in South America.[19] Nargenicin A_1[20] and nodusmicin[21] are antibiotics produced by *Nocardia argentinensis* and *Saccharopolyspora hirsuta* respectively.

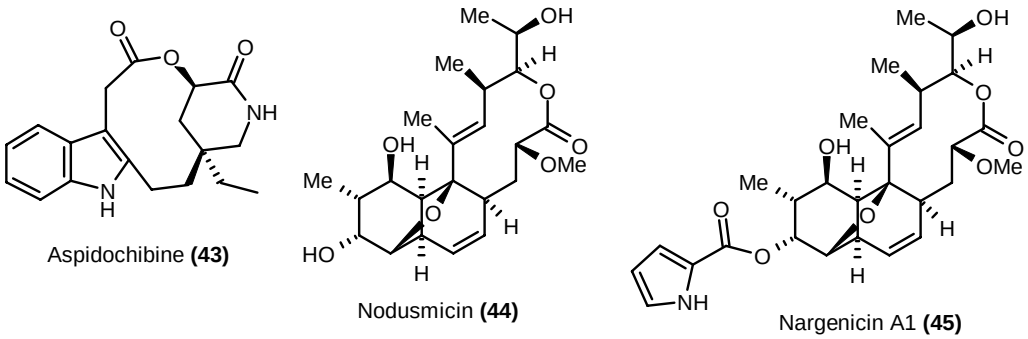


Figure-10

Flavanones, kurziflavolactones A, B, C and D, and chalcone, kurzichalcolatones are isolated from the leaves of a Malaysian plant, *Cryptocarya kurzeii* and have a weak cytotoxicity against **KB** cells.[22]

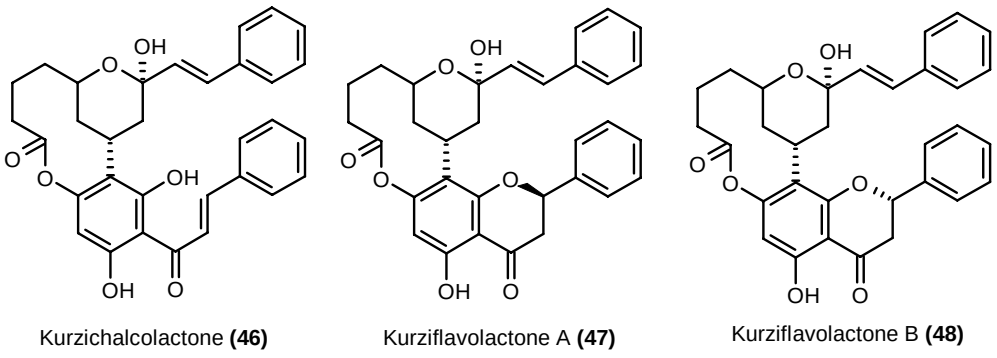


Figure-11

Microcarpalide[23] represents novel alkyl substituted nonenolide structurally related to a family of phytotoxins such as an achaetolide,[24a] pinolidoxin, putaminotoxins and herbarumins.[24b]

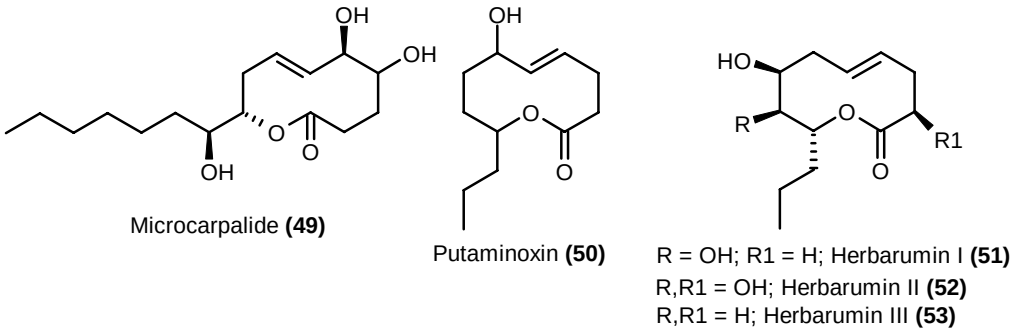


Figure-12

The decarestrictines, A-K a novel ten member lactones are secondary metabolites that were isolated from various *Pencillium* strains.[25] Among them, several members of the decarestrictine family of natural products have been shown to inhibit the biosynthesis of cholesterol.[26]

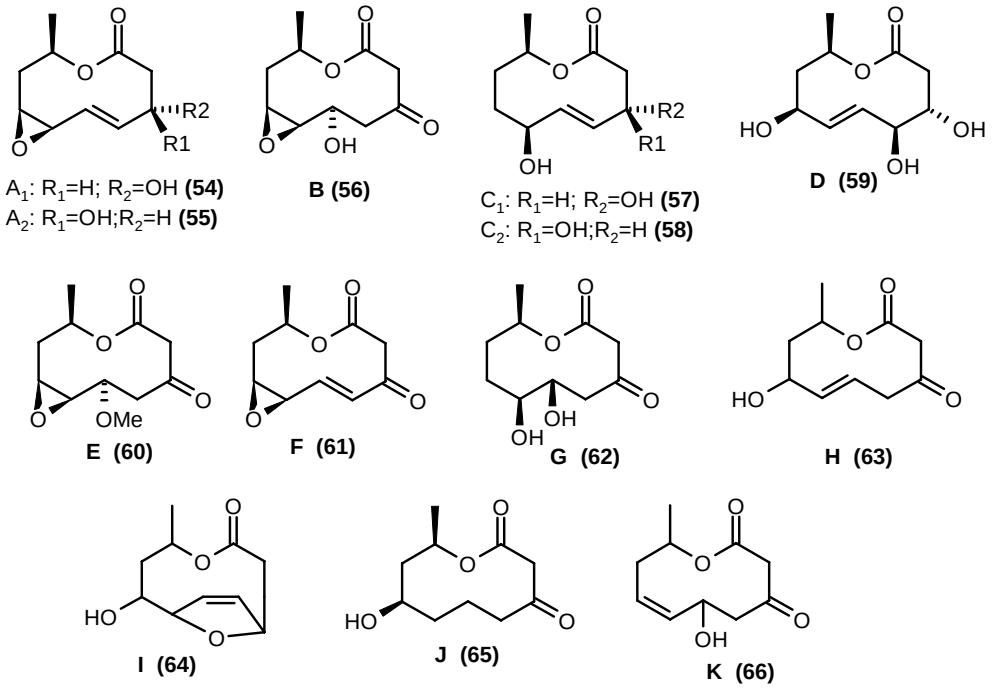


Figure-13: Decarestrictine A-K

Recently, stagonolides A-F, nonenolides produced by *Stagonospora crisii* and proposed as a potential mycoherbicide of Cirsium arvense.[27]

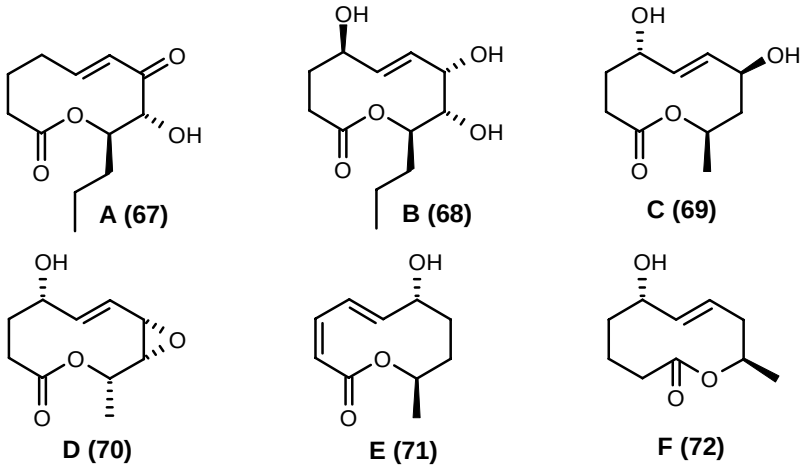


Figure-14: Stagonolides A-F

Four new decarestrictine analogues (botryolides A-D) have been isolated from cultures of fungicolous isolate of *Botryotrichum* sp.[28]

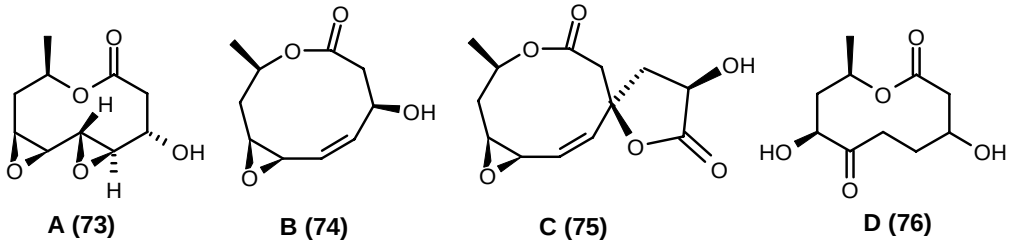


Figure-15: Botryolide A-D

Four new 10-membered lactones were isolated from the broth extract of an endophytic fungus, *Phomopsis* sp.,[29] obtained from the stem of *Azadirachta indica*. Compound 77-80 were tested for antifungal activity several plant pathogens. Compound **80** demonstrated antifungal activity in the MIC value range 31.25-500 μg/mL.

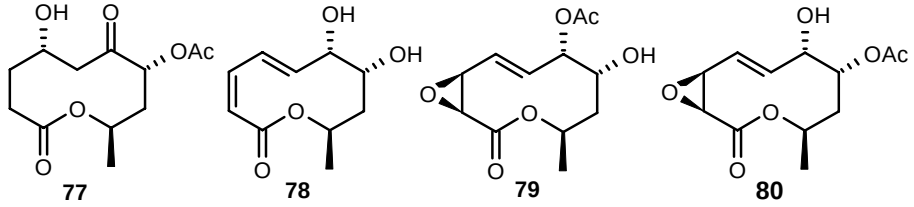


Figure-16: 10-membered lactones

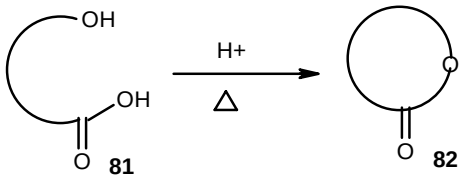
Preparation of medium ring lactones

The synthesis of the macrocyclic framework is one of the important processes for producing natural and unnatural compounds in organic chemistry. Recently, several effective C-C bond-forming reactions, such as transition metal-promoted coupling and olefin metathesis, have been widely studied for producing cyclic compounds. However, macrolactonization is

still the most popular method for producing cyclic compounds involving carboxylic ester moieties since there are some effective methods for constructing the ester linkage. Actually, the chemical synthesis of macrolactones has made great progress due to the development of efficient methods for ring closure from *ω*-hydroxycarboxylic acids (seco-acids) or their activated derivatives. There are several reactions which are widely used in the total synthesis of natural compounds as follows: the Corey-Nicolaou *S*-pyridyl ester lactonization method, the Masamune thiol ester activation method, the Mukaiyama onium salt method, the Yamaguchi mixed-anhydride method, the Keck-Steglich DCC/DMAP/HCl activation method, the Mitsunobu alcohol activation method and the Shiina benzoic anhydride method.

Lactonisation of ω-hydroxyalkanoic acids: Direct cyclisation

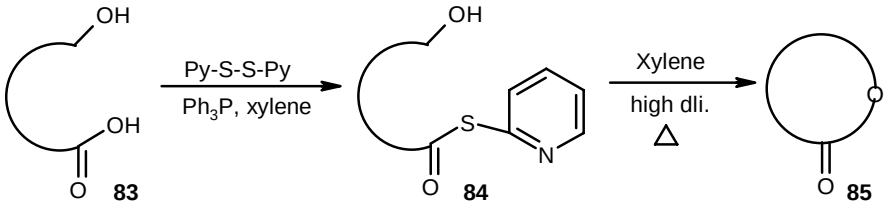
The first efforts to prepare medium ring lactones were reported by Stoll and Rouve by the cyclisation of *ω*-hydroxyalkanoic acid.[30] They showed that the major product was oligomer and the minor was monolide. An attempt to improve the yield by using boron trifluoride etherate in the presence of non-functionalized polystyrene beads as catalyst was not successful.[31] However; they synthesized successfully phoracantholide I in 60% yield by acid catalyzed lactonisation.[32]



Scheme-1

Activation methods:

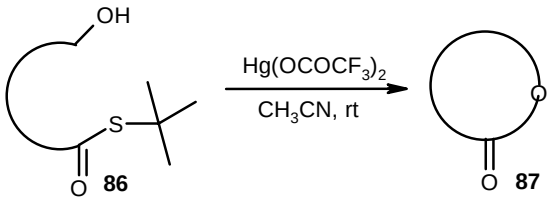
Corey-Nicolaou method (double activation method): A highly efficient method, it involves the treatment of *ω*-hydroxyalkanoic acid **83** with dipyridyl disulphide to form 2-pyridinethioester **84**, which on refluxing in xylene under high dilution to provide macrolactone **85**. [33]



Scheme-2

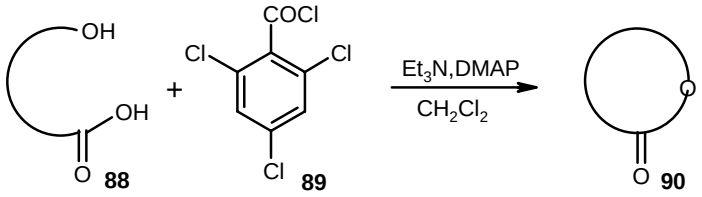
Masamune method: Masamune *et al* have developed[34] a new synthetic method for the construction of macrocyclic lactones, which is also efficient for the preparation of esters. This

procedure employs S-t-butyl thiolesters of hydroxy acids and mercuric trifluoroacetate as an activating reagent. The lactonization proceeds rapidly in dilute acetonitrile solution at room temperature.



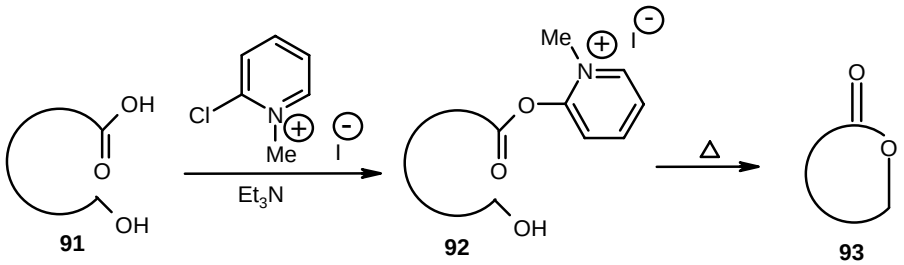
Scheme-3

Yamaghuchi methods: This method[35] involves the lactonization of mixed anhydride formed by the treatment of ω-hydroxyl acid and 2, 4, 6-trichlorobenzyol chloride in presence of a base like Et_3N.



Scheme-4

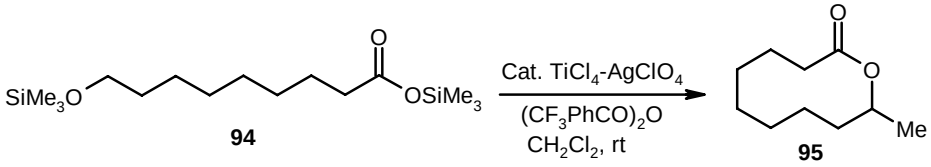
Mukaiyama method: Mukaiyama[36] developed 1-alkyl-2-halopyridinium salts which function as useful reagents for the preparation of carboxylic esters and lactones in the presence of tertiary amines. After generation of the activated onium salts from the corresponding ω-hydroxycarboxylic acids, spontaneous lactonization smoothly proceeds to produce a variety of macrolactones.



Scheme-5

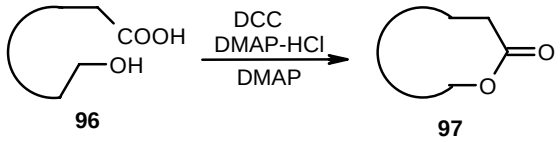
Recently, Mukaiyama and co-workers reported[37] a new method based on the lactonisation of silyl ω-siloxyalkanoate using *p*-trifluoromethylbenzoic anhydride and a catalytic mixture of $TiCl_4$ and $AgClO_4$. In specific case of medium size lactones, low yields

were obtained (0% for 8 and 9-membered lactones; 33% for decanolides) except for the formation of the undecanolide (70%).



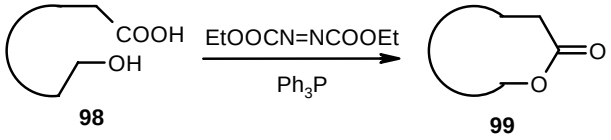
Scheme-6

Keck-Steglich method: Keck reinvestigated the ability of the DCC dehydration coupling reaction based on the Steglich's procedure.[38] In the presence of DMAP and the DMAP/HCl salt, the DCC-induced intramolecular cyclization efficiently takes place to generate macrocyclic molecules.



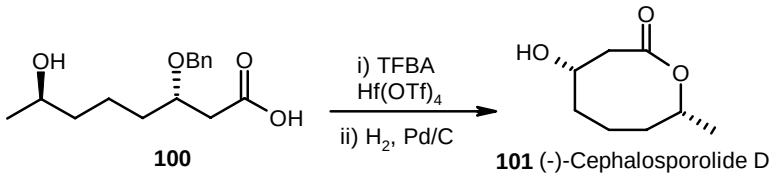
Scheme-7

Mitsunobu method: The Mitsunobu reaction,[39] an outstanding alcohol activation protocol, was used for the preparation of the macrocyclic molecules.



Scheme-8

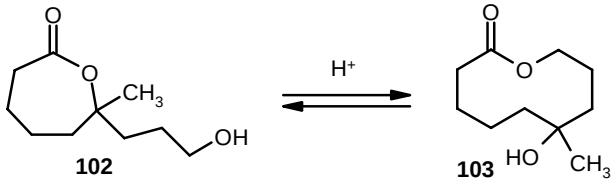
After following the developments of the lactonization methodology, **Shiina** and co-workers[40] proposed a novel mixed-anhydride method for the preparation of lactones including medium-sized ring compounds, and they applied this new technology for the preparation of several macrocyclic molecules. An acidic or basic activator such as Lewis acids, DMAP or DMAPO, could promote this reaction. The lactonization of the seco-acid was tried using the Shiina mixed-anhydride method with a catalytic amount of Lewis acids and a stoichiometric amount of TFBA. After screening several catalysts in this reaction, it was found that $Hf(OTf)_4$ was the best promoter and it effectively catalyzed the reaction to produce the desired 8-membered lactone in 81% yield.



Scheme-9

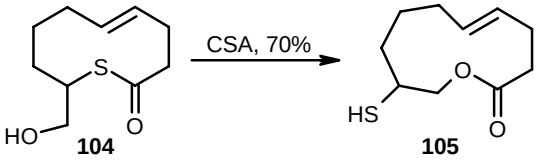
Translactonisation method:

First introduced by Corey and co-workers,[41] a hydroxyl lactone was subjected to the action of acid in catalytic to give a thermodynamically more stable hydroxylactone.



Scheme-9

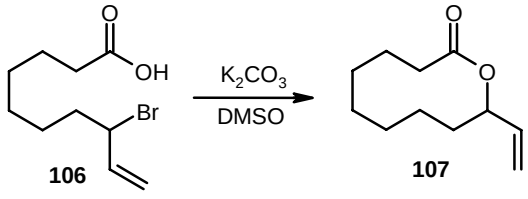
Since medium ring lactones are less stable than other lactones, it difficult to obtain by this method. Corey showed that an 8-membered ring lactone can be transformed to a 11-membered ring lactone. In a subsequent work, Vedejs and co-workers[42] have reported that rearrangement of **104** to **105** occurred upon heating in Hexane: CH_2Cl_2 + anhydrous camphorsulfonic acid in 70% yield.



Scheme-11

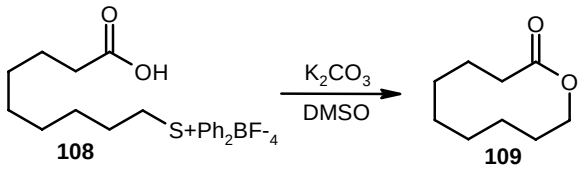
Cyclisation of *ω*-haloalkanoic acid and related compounds:

The cyclisation of *ω*-haloalkanoic acid by a base such as K_2CO_3 or NaOH is one of the oldest methods for synthesis of medium ring lactones. Hunsdiecker reported the formation of 10 and 11-membered ring lactones in good yield by the reaction of bromoalkanioc acid with potassium carbonate.[43]



Scheme-12

Kellog reported[44] that ω-halo acid, when treated with cesium carbonate to give macrolides in good yields. For 8 to 10-membered ring lactones, this cyclisation did not work as diolides were formed and only the undecalactone was obtained in 23% yield. Matsuyama and co-worker[45] studied the cyclisation of sulfonium salts by the replacement of bromo to lead in improved yields.

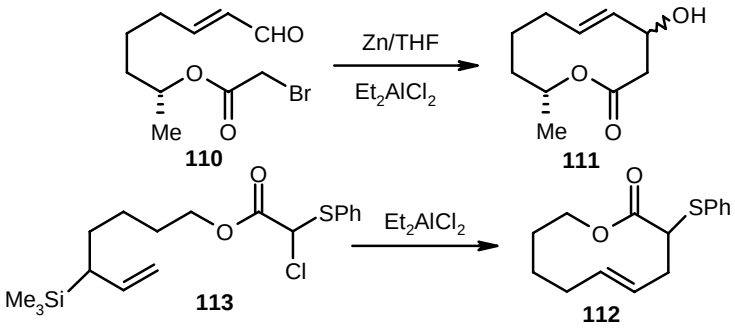


Scheme-13

Cyclisation methods:

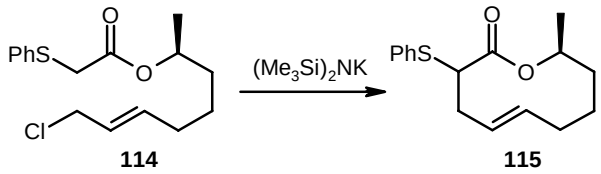
Long chain with ester linkages have been cyclized by C-C bond formation to macrocyclic lactones by a variety of techniques. The most prominent of these macrocyclic forming reaction are ring closing metathesis, electrophilic, nucleophilic and radical induced cyclization, acetylene coupling and few named reactions like Diels-Alder reaction, Dieckmann reaction etc.

Electrophile-induced cyclisation: Intramolecular Reformatsky reaction promoted by Et_2AlCl to induce the ring closure to give an unsaturated 10-membered ring lactone, of which one diastereomer was diplodialide **A**.[46] A formal synthesis of phoracantholide I was reported by this method.



Scheme-14

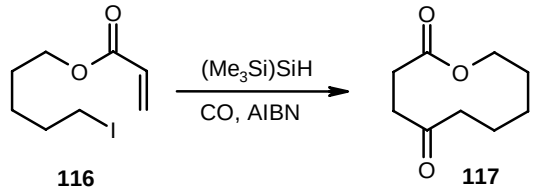
Nucleophile-induced cyclisation: Tsuji and coworkers reported the formation of lactones could be take place by the C-C bond formation via intramolecular alkylation of a carbanion generated from phenylthioacetate.[47] Ten-membered lactones were prepared successfully by this method.



114 **115**

Scheme-15

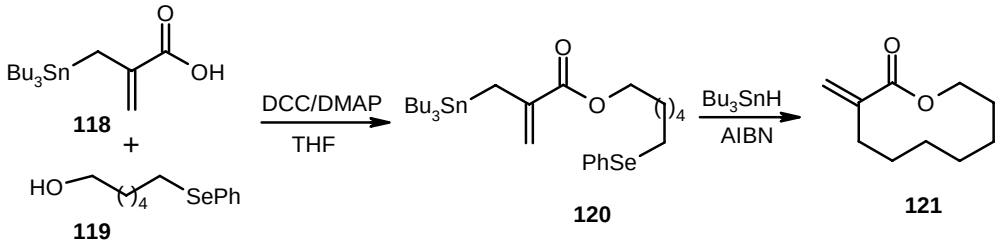
Radical-induced cyclisation: Porter reported that the treatment of 10-iodoalkylacrylate with tributyltinhydride and AIBN in benzene to provide the 11-membered lactones in low yields.[48] Subsequently it was improved by the modification of the procedure and synthesized 10-membered lactones in good yield. The Compound **116** was treated with tris(trimethylsilyl)silane and AIBN at 30 atmosphere of CO to give γ-ketolactone.[49]



116 **117**

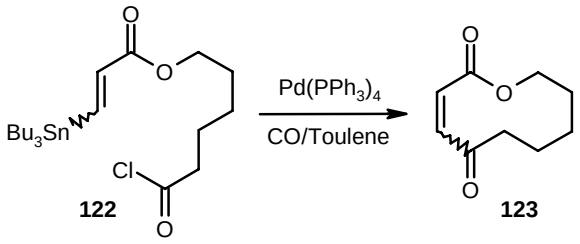
Scheme-16

Baldwin reported[50] that the radical precursors were conveniently prepared by DCC/DMAP coupling between the stannyl-acid and ω-phenylselenoalkanols following reaction with Bu_3SnH/AIBN to yield the α-methylene macrocyclic lactones. This method did not work for synthesis of the medium ring (6-9 member) lactones.



Scheme-17

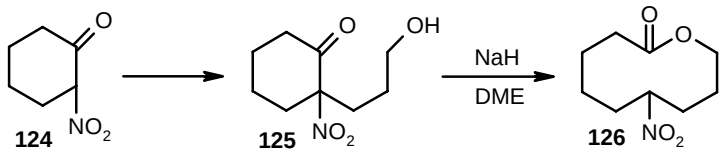
Palladium-induced reaction: Trost observed[51] that the stabilized anion react intramolecularly with acylic acetates in the presence of $Pd(PPh_3)_4$ and 1,2-diphenylphosphinoethane to give medium ring lactones. Recently, Baldwin reported the intramolecular Pd (0)-catalysed coupling of acid chloride and β-stannylalkenoate in the presence of CO as a new route to synthesize 10 to 20-membered lactones. For medium ring lactones, low yield were observed.[52]



Scheme-18

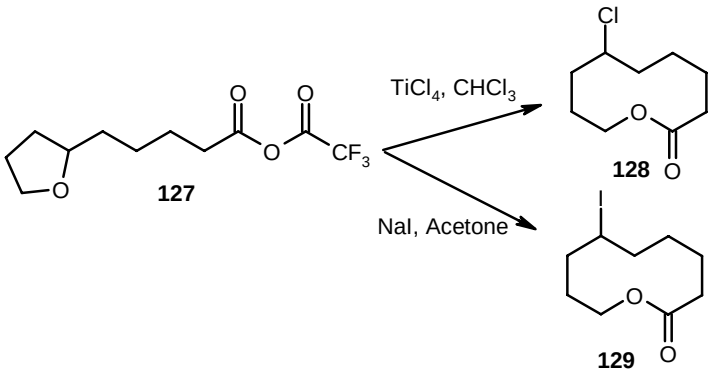
Ring Expansion Methods:

Hesse-Cookson approach: 2-(3-hydroxypropyl)-2-nitrocycloalkanones undergo base-catalysed isomerisation into nitro-lactones containing four more atoms in the ring, which can be converted to corresponding keto-lactones. Phoracantholide **I** has synthesized by this method.[53]



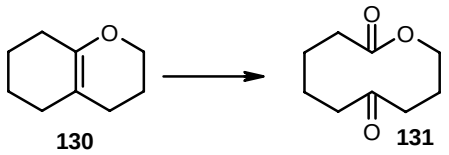
Scheme-19

Recently, Grayson and Roycroft reported that reaction of 5-(tetrahydro-2-furyl)pentanoic trifluoroacetic anhydride with Lewis acid ($TiCl_4$) or NaI in acetone leads to the formation of halolactones.[54]



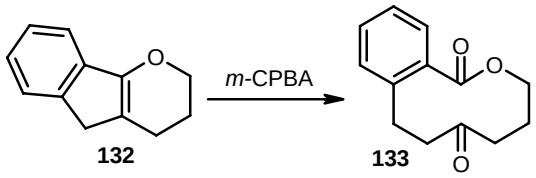
Scheme-20

Activated carbon-carbon double bond: First reported by Borowitz, 10 and 11-membered lactones are prepared by this method.[55] The mixture of ruthenium tetraoxide-sodium metaperiodate[56a] and Corey's reagents found to be effective for C-C double bond oxidative cleavage.[56b]



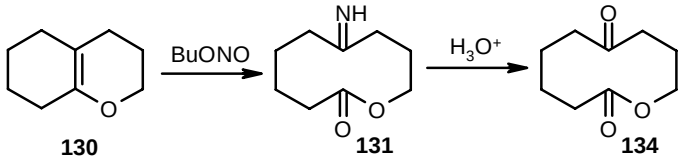
Scheme-21

m-chloroperbenzoic acid and ozone could be used for this cleavage. Benzo-mediun ring lactones have been synthesized by this method in good yield.[57a]



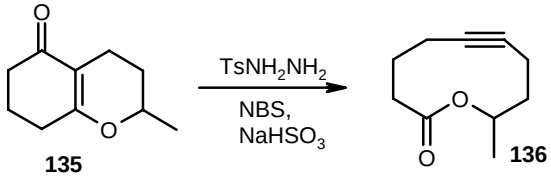
Scheme-22

Mahajan reported that n-butylnitrile was an excellent alternative reagent for this cleavage.[57b]



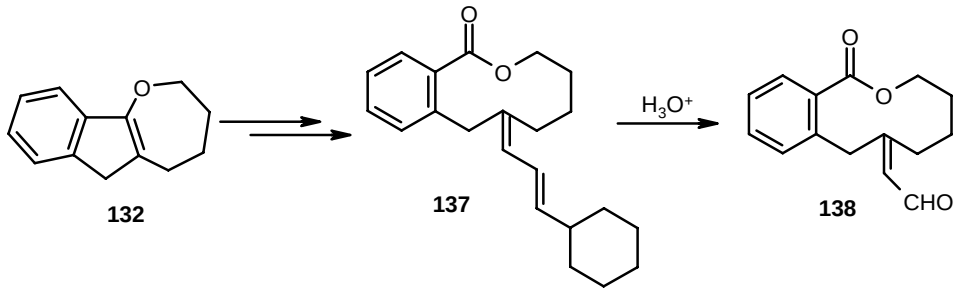
Scheme-23

Fragmentation reactions: Recently, Mahajan reported[58] that the fragmentation of keto enol ethers leads to 9 and 10-memberd ring acetylenic lactones.



Scheme-24

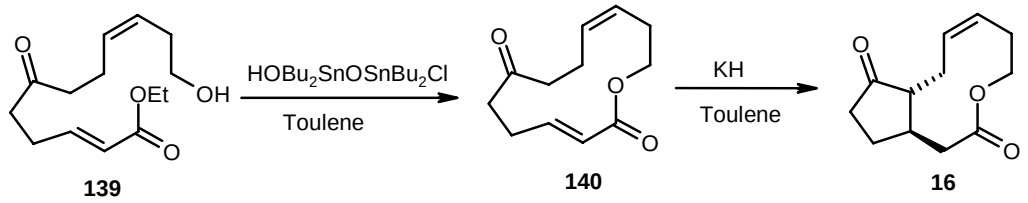
1,2-Oxazine cleavage: Shatzmiller and coworkers reported that cyclic enol ethers react with α-chloronitrone to give an adduct followed by reaction with potassium carbonate and heating to give medium ring lactones.[59]



Scheme-25

Other approaches:

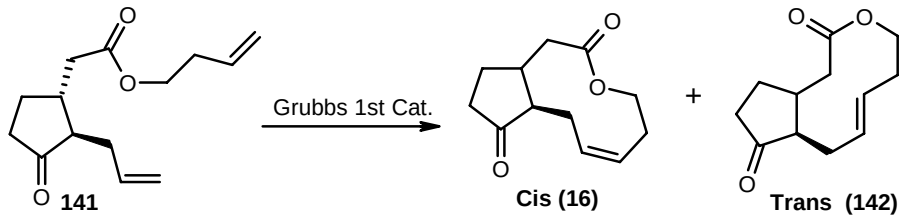
Transannular Michael reaction: Shimizu and Nakayawa reported the synthesis of (+)-jasmine lactone by an intramolecular Michael reaction.[60]



Scheme-26

Ring-closing metathesis: The ring closing metathesis has emerged as a powerful tool for organic synthesis and extensively employed in the construction of medium and large ring structures with multiple functionality. The efficiency of this method is demonstrated by the syntheses of a large number of natural products including ten-member lactones.

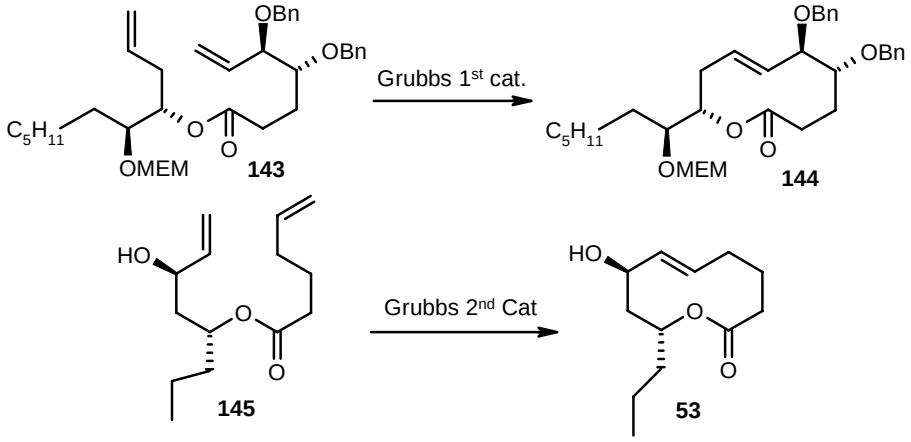
A typical example that illustrates the efficiency as well as the limitation of RCM in this arena is a synthesis of jasmine ketolactone.[61] RCM reaction on diene with high dilution by using Grubbs first-generation catalyst to afford the targeted ten-member lactones as a mixture of *cis* and *trans* isomers (2.5:1) in remarkable yield.



Scheme-27

A recent exploitation of RCM reaction reported by Gurjar *et. al.*, the total synthesis of natural products microcarpolide[62] and herbarumin III.[63] The key reaction has been carried out

by refluxing the diene with Grubbs catalyst in degassed dichloromethane to provide ten-membered lactones in predominantly *trans* configuration.



Scheme-28

PRESENT WORK

Present Work

Cordyceps is an enthomopathogenic fungus used as food and herbal medications in Asia.[64] The approximately 400 species of *Cordyceps* available so far, are distinguished from one another and classified according to the color and shape of their fruiting bodies, possession of spores, ascus shape, host insect species and by other morphological characteristics.[65]

Cordyceps militaris, an enthomopathogenic fungus belonging to the *Ascomycetes class*, adheres to the surface of insects during the winter and then penetrates it from a fruiting body and sporangium.[66] Reports on the isolation of biologically active secondary metabolites from *Cordyceps militaris*.[67] have been few but have received attention due to the unique structures and specific biological activities of the metabolites. Cordycepins (3'-deoxyadenosine), with antifungal, antivirus, and antitumor activities, is one of the more interesting secondary metabolites that have been previously isolated from *Cordyceps militaris*.[67a, 68]

Nonenolide **1** was recently isolated as a white solid from *Cordyceps militaris* BCC 2816, which shows anti-malarial activity against *Plasmodium flaciparum* (K1, multidrug resistant strain). The structure as assigned from spectral analysis and molecular formula, ($C_{10}H_{16}O_4$ by HRMS). It is a 10-membered macrolactone with one double bond, two hydroxyl groups, and one methyl group. The stereochemistry was confirmed by spectral data and X-ray crystallographic analysis (Figure-1).[4]

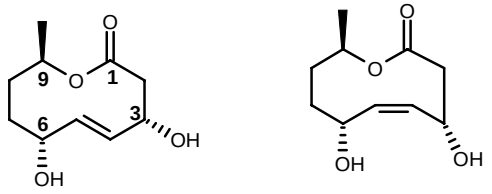


Figure-1

As part of our ongoing program on the synthesis of natural lactones[69] involving ring-closing metathesis (RCM)[70, 71] as a key step, we have devised a stereoselctive synthesis of nonenolide **1**. Despite its effectiveness in the synthesis of rings of all sizes, two factors still limit the scope of the RCM reaction; (a) in ring sizes ≥8, no control over *E*/*Z* stereochemistry of the double bond generated is possible. Stereochemical control is probably of thermodynamic origin;[72] (b) the reports that describe application of the RCM to medium sized-particularly 10-membered rings, are still rare, especially when dense functionality close to the reaction centre is involved.[73] There are no reports of RCM reaction on the substrate where chiral centers with

protecting groups are present adjacent to both the reacting centers (Figure 2): our work could be useful for the synthesis of nonenolides having chiral centers on both sides of the double bond.

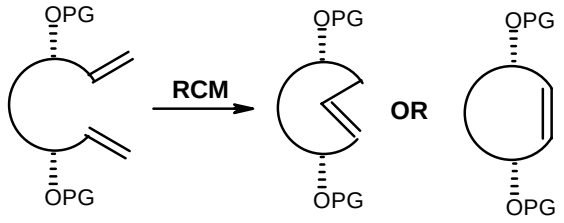
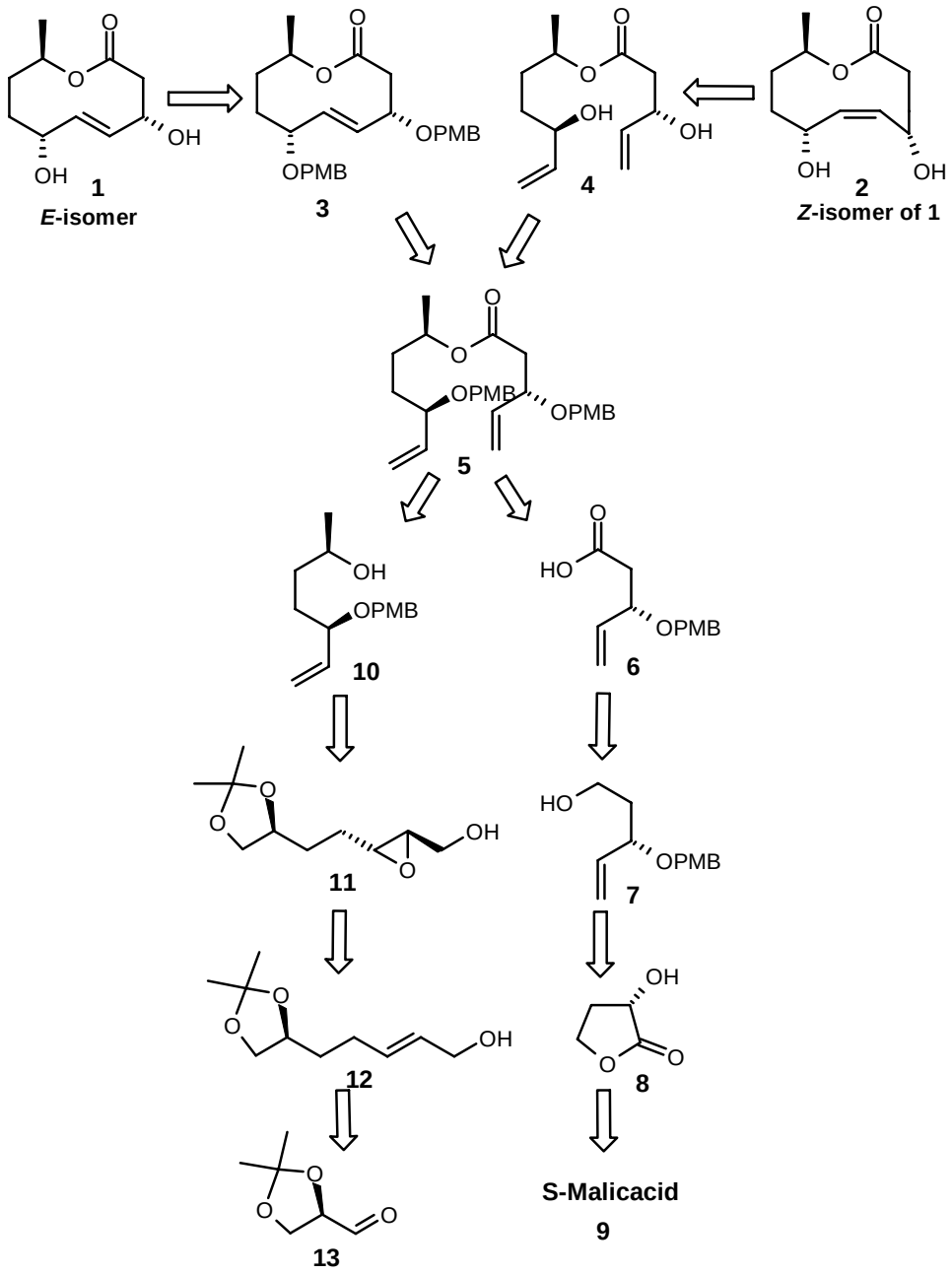


Figure-2. Outcome of the RCM reaction

The retrosynthetic analysis is depicted in Scheme 1. The macrolactonization step relies on a ring closing metathesis (RCM) on a diolefinic ester. Strategy was conceived with disconnection of the C_4-C_5 double bond (numbering based on fig.1) to reveal the diolefinic ester; it was envisaged that **5** could be synthesized by the standard protocol of Yamaguchi esterification. The strategic bond disconnection in ester (**5**) leads to chiral, nonracemic fragments acid (**6**) and alcohol (**10**).

The retrosynthetic analysis indicates that alcohol fragment could be prepared through epoxy alcohol (**11**) derived from ally alcohol (**12**); that could be generated from 1, 2-*O*-isopropylidene-(D)-glyceraldehyde (**13**). Of the two requisite stereogenic centers, one was obtained from 1, 2-*O*-isopropylidene-(D)-glyceraldehyde (synthesized from D-mannitol), while the other was introduced on the allyl alcohol (**12**) by the Sharpless asymmetric epoxidation route using (–) DET as a chiral ligand.

Retrosynthetic analysis suggested that the acid fragment could be synthesized from **7** by Pinnick oxidation of aldehyde **16**, that could be derived from commercially available (*S*)-α-hydroxy-γ-butyrolactone (**8**) (prepared from *S*-malic acid) (Scheme-1).

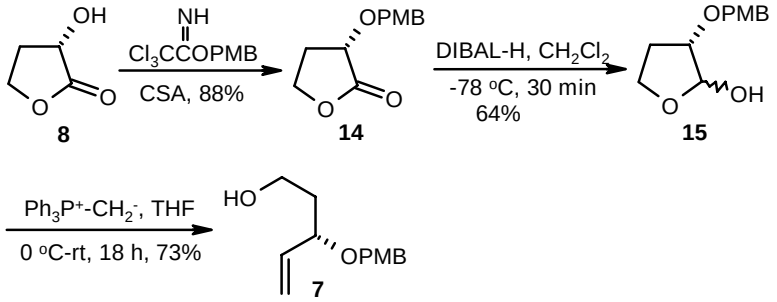


Scheme-1. Retrosynthetic analysis of nonenolide

Synthesis of Acid Fragment (6)

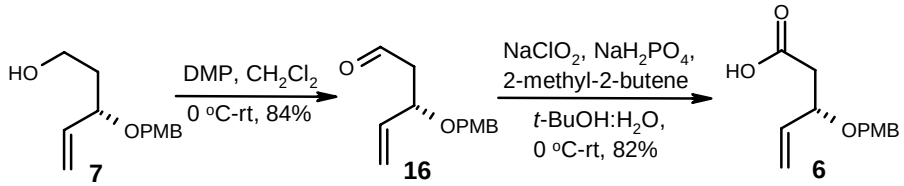
Synthesis of acid (**6**), one of the coupling partners for 10-membered macrolide (**1**) started from commercially available (*S*)-α-hydroxy-γ-butyrolactone (**8**). The hydroxyl group of **8** was protected with *p*-methoxybenzyl-2, 2, 2-trichloroacetimidate under acidic condition (camphorsulfonic acid in catalytic) in dry dichloromethane to generate the PMB ether **14** in 88% yield. The structure of **14** was confirmed by the ^{1}H NMR: CH_2 proton of PMB group resonated at 4.67 ppm (d, 1H, J = 11.4 Hz), 4.87 ppm (d, 1H, J = 11.4 Hz) and the *p*-methoxy

group at 3.81 ppm. Further, it was confirmed by elemental analysis. Lactone **14** was reduced to lactol **15**, in 64% yield, with DIBAL-H at –78 ^{o}C. Reaction with triphenylphosphonium methylide afforded the (*S*)-3-*p*-methoxybenzylpent-4-en-1-ol (**7**) in 73% yield. In proton NMR spectrum, the terminal olefin protons appeared in the region of 5.20-5.87 ppm; the ^{13}C NMR spectrum displayed olefin carbons at 117.3 and 138.2 ppm respectively. The specific rotation {$[\alpha]_D^{25}$ -54.8 (*c* 1.0, $CHCl_3$); lit.[74] $[\alpha]_D^{25}$ -56.0 (*c* 1.42, $CHCl_3$)} of **7** were in excellent agreement with that reported (Scheme-2).



Scheme-2

To get the acid fragment (**6**), the primary hydroxyl group of **7** was oxidized with Dess-Martin periodinane (DMP)[75] in CH_2Cl_2 to aldehyde **16** in 84% yield, This was subsequently transformed to carboxylic acid via Pinnick oxidation[76] ($NaClO_2$ in presence of NaH_2PO_4 and 2-methyl-2-butene as a scavenger) in 82% yield (scheme-3). In the ^{13}C NMR spectrum C=O resonances of acid appeared at 176.5 ppm. The structure was further confirmed by elemental analysis data.



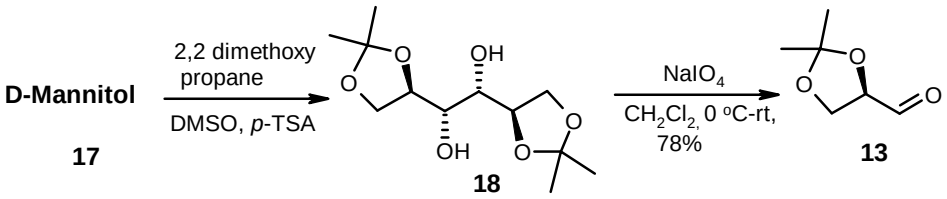
Scheme-3

<u>Synthesis of alcohol Fragment (10)</u>

Synthesis of allyl alcohol (12)

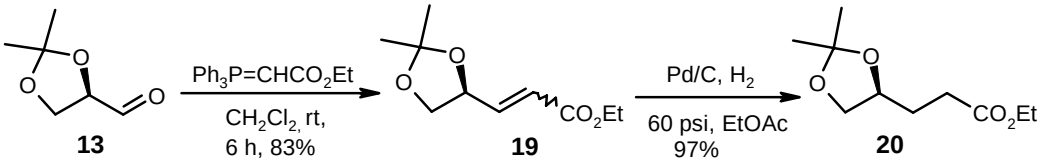
Retrosynthetic analysis outlined in (Scheme-1) suggested that **12** could be a key synthetic intermediate and objective for the construction of alcohol fragment **10**. The synthesis of **10**, commenced from commercially available D-mannitol (**17**), which was converted to 1,2: 5,6-diisopropylidene-D-mannitol (**18**) in 67% yield by treatment with 2,2-dimethoxypropane and catalytic *p*-toulenesulfonicacid in DMSO. Subsequently, the 3,4-glycol linkage of **18** was oxidatively cleaved with sodium metaperiodate ($NaIO_4$, supported on silica gel) to provide 2, 3-

O-(isopropylidene)-D-glyceraldehyde (**13**) in 78% yield. ^{1}H NMR, ^{13}C NMR, IR spectra and elemental analysis data were in good agreement with reported values[77] (Scheme-4).



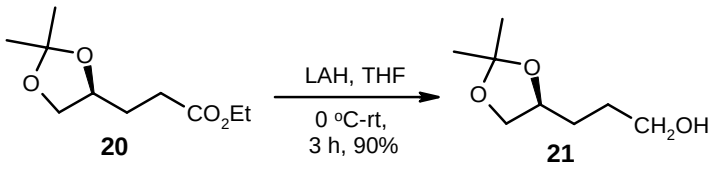
Scheme-4

The D-glyceraldehyde derivative (**13**) when subjected to two-carbon Wittig olefination using (carboethoxymethylene)triphenylphosphorane in CH_2Cl_2 at room temperature for 6 h, gave ester **19** as a mixture of *trans* and *cis* isomer in 83% yield. Since the geometry of the double bond in **19** was of no immediate consequence (it would be hydrogenated at a later stage), the mixture was carried forward for subsequent reaction. In the ^{1}H NMR spectrum the characteristic olefin signals appeared between the region of 6.05-6.85 ppm and ester group $CO_2\underline{CH_2}\underline{CH_3}$ resonated at 1.30 ppm (t, 3H) and 4.18 (m, 2H) ppm, ^{13}C spectrum showed resonances at 122.1 ppm, 144.5 ppm and 165.6 ppm. Strong IR absorption band appeared at 1722 cm^{-1} corresponding to α, β unsaturated ester. Compound **19** when subjected to catalytic hydrogenation with Palladium 10%, on activated carbon powder (Pd/C) at 60 *psi* at room temperature afforded **20** in quantitative yield (97%). The structure was assigned by ^{1}H NMR, ^{13}C NMR spectral data and confirmed by elemental analysis (Scheme-5).



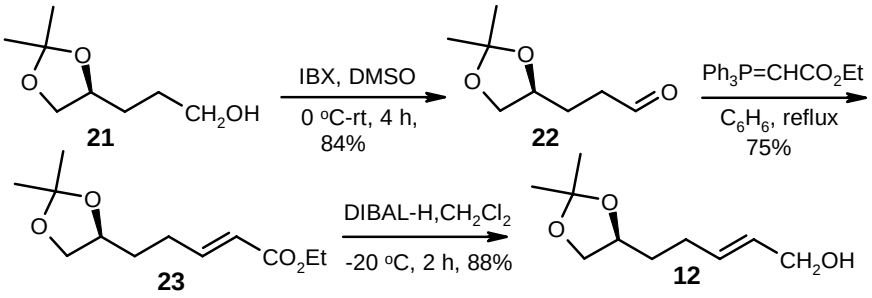
Scheme-5

Next, ester (**20**) was reduced with lithium aluminium hydride (LAH) in anhydrous THF at 0 ^{o}C for 3 h to furnish the alcohol **21** in 90% yield. Resonances specific for CO_2Et were absent in proton NMR and the CH_2 group of alcohol was localized between 4.01-4.15 ppm. Broad IR absorption at 3455 cm^{-1} corresponds to the hydroxyl group (Scheme-6).



Scheme-6

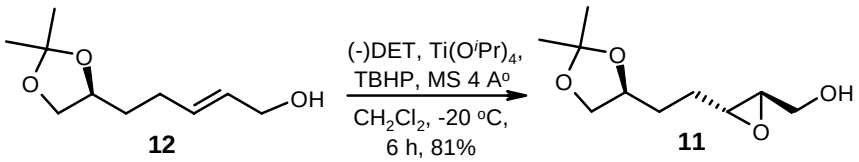
In order to secure ally alcohol (**12**), the **21** was a further subjected to two carbon Wittig homologation; the primary hydroxyl group of **21** was oxidized with IBX (2-iodoxybenzoicacid) in DMSO at 0 ^{o}C to room temperature for 4 h to afford aldehyde **22** in 84% yield. It was immediately subjected to two carbon Wittig olefination using (carboethoxymethylene)triphenylphosphorane in benzene at reflux, to furnish **23** as a mixture of *trans* and *cis* isomers in the ratio of 9:1 as judged by TLC. The minor *Z*-isomer was separated by column chromatography and the major *trans* isomer was obtained in 75% yield. ^{1}H NMR showed characteristic coupling constant (J = 15.7 Hz) for olefinic protons. The relevant resonances due to alkene appeared at 5.80 (d, 1H) and 6.89 ppm (dt, 1H) and ester group $CO_2\underline{CH_2}\underline{CH_3}$ (triplet at 1.29 and multiplet between 4.00-4.24 ppm). The ^{13}C NMR spectrum displayed olefin carbons at 121.7 ppm, 147.7 ppm and 166.1 ppm corresponding to C=O group. Hydride reduction of **23** with DIBAL-H in anhydrous CH_2Cl_2 at -78 ^{o}C for 2 h afforded the key precursor **12** in 88% yield (Scheme-7).[78] In the ^{1}H NMR spectrum, resonances due to olefinic protons moved upfield and were observed between 5.66-5.71 ppm; methylene group of ally alcohol was localized between 3.99-4.08 ppm. The ^{13}C NMR spectral signals specified for CO_2Et were absent. The IR spectrum showed a broadband absorption at 3422 cm^{-1}.



Scheme-7

Generation of the second chiral centre relevant to the target, was achieved by employing Sharpless asymmetric epoxidation in a catalytic process. Thus, **12** was treated with (−) DET as chiral ligand, Ti(O^{i}Pr)$_4$, and TBHP in anhydrous CH_2Cl_2 in presence of freshly activated 4 A^{o} MS powder at −20 ^{o}C, to furnish (2*R*,3*R*)-epoxide **11** in 81% yield. In the ^{1}H NMR spectrum, the epoxide showed absence of the resonances corresponding to the methine protons of allylic alcohol in the region of 5.66-5.71 (m, 2H) ppm. New resonances attributed to methine protons of epoxide were apparent at δ 2.87-3.02 ppm as multiplet along with other proton resonances attributable to assigned structure of **11**. ^{13}C NMR spectrum showed absence of resonances corresponding to olefinic carbons of **12** at δ 129.7 and 131.3 ppm with the appearance of bright

resonances at 55.6, and 58.7 ppm corresponding to epoxy carbons. In addition, elemental analysis data was supported the formation of **11** (scheme-8).



Scheme-8

A brief review on Sharpless Asymmetric Epoxidation[79]

Epoxides are versatile and important intermediates in organic synthesis. The strain of the three-membered heterocyclic ring makes them accessible to a large variety of reagents. This metal catalyzed epoxidation process was discovered by K. Barry Sharpless in 1980 and allows the transformation of a prochiral substrate into an optically active (or optically pure) product using a chiral catalyst. The asymmetric induction is achieved by adding an enantiomerically enriched tartrate derivative. This epoxidation is arguably one of the most important reactions discovered in the last 30 years. This has been recognized by the award of the 2001 Nobel Prize to Professor Barry Sharpless.

*In this epoxidation reaction, double bond of allylic alcohols is converted into epoxides using a transition metal catalyst ($Ti(O^{i}Pr)_4$, titanium tetra-isopropoxide) and a chiral additive (dialkyltartrate, i.e., DET or DIPT used). The oxidant for the epoxidation is tert-butylhydroperoxide. Notably, this reaction exhibits high levels of enantioselectivity (usually >90% ee) and proceeds under mild condition with good chemical yield. It is proposed that, co-ordination of the chiral ligand DET and the oxidant source TBHP to the metal center forms the catalytically active species (**24**) (Figure-3). It is generally believed that this species is dimeric, i. e. two metal centers are bridged via two oxygen ligand giving the overall shape of two edge-fused octahedral. Co-ordination of the substrate can only occur in one orientation without causing severe steric interactions (figure-3. **25**). Co-ordination in the complex on the left brings the double bond over the peroxide oxygen of the TBHP ligand. Oxidation can only occur from the bottom face, leading overall to a highly enantioselective process.*

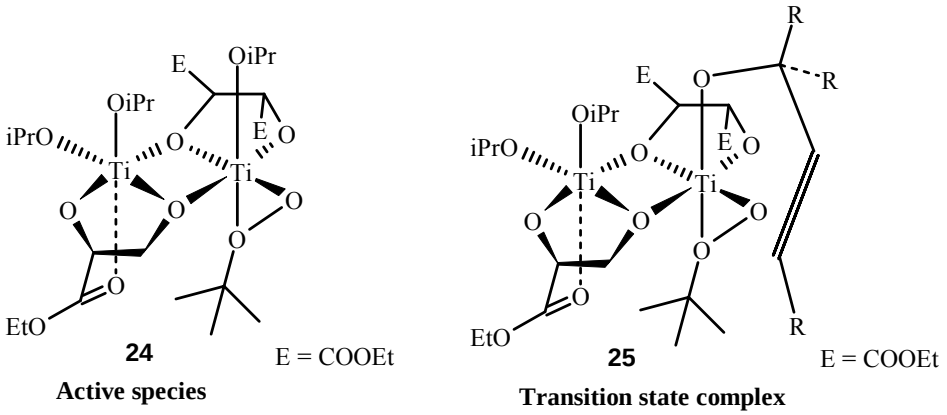


Figure 3*: Putative transition state for the Sharpless asymmetric epoxidation.*

Stereoselectivity:

The stereochemical outcome of the asymmetric epoxidation is consistent with (S,S)-(-)-DET inducing the epoxide formation on the Si face and the (R,R)-(+)-DET inducing the epoxide formation on the Re face of the allylic alcohol as illustrated in Figure-3.

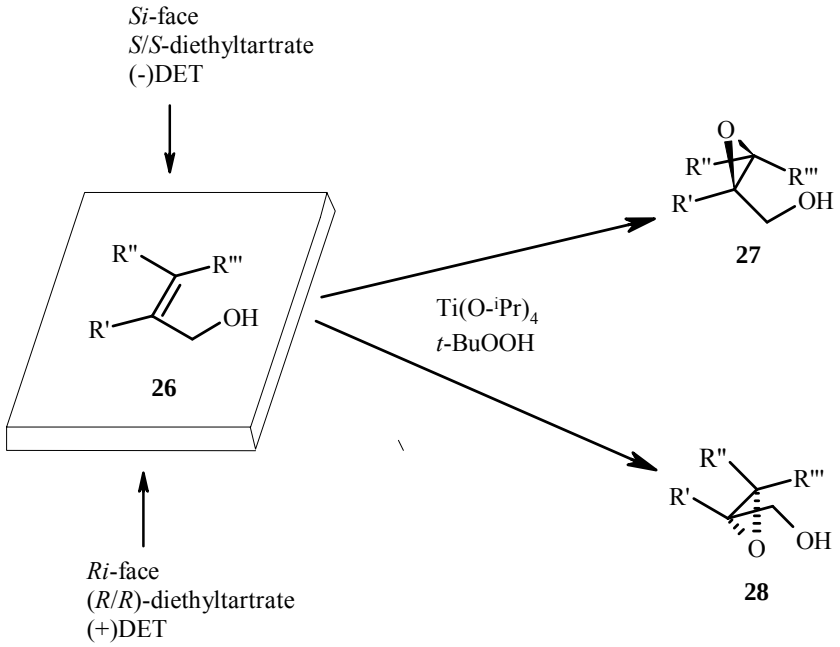


Figure 3

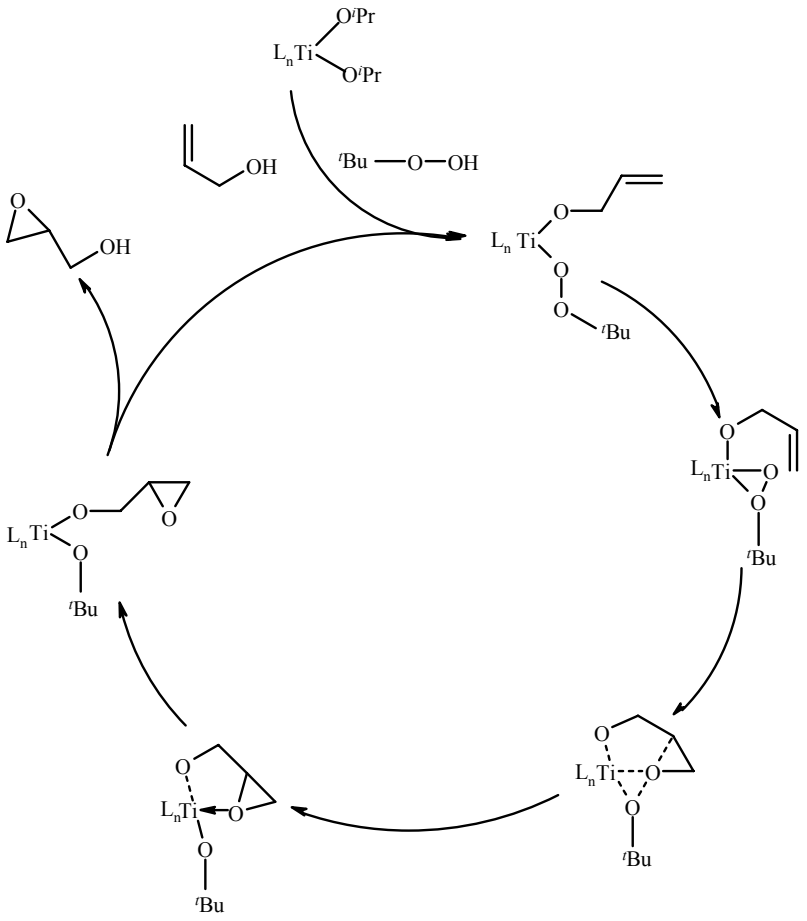
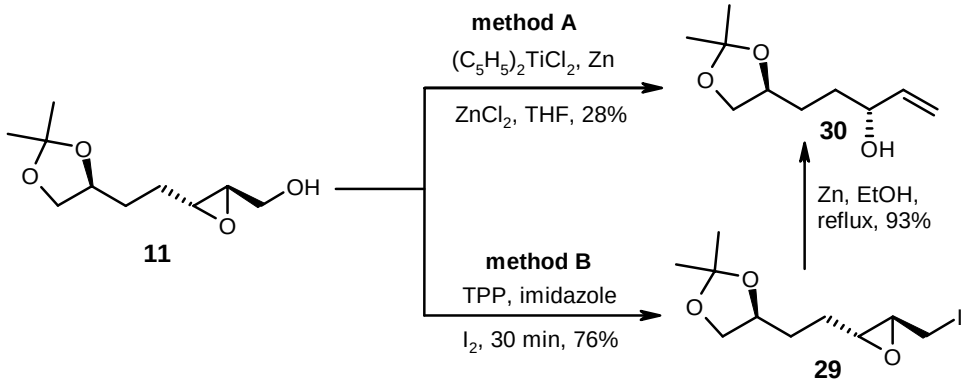


Figure 5*: The catalytic cycle for Sharpless asymmetric epoxidation.*

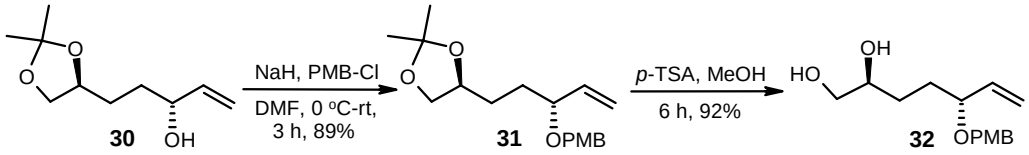
The next challenge, deoxygenation of epoxide to terminal alkenic alcohol in high regioselectivity, was achieved through two methods. In method A, epoxide (**11**) was subjected to deoxygenation with $(C_5H_5)_2TiCl$ in THF, prepared in *situ* from $(C_5H_5)_2TiCl_2$ and granulated Zinc containing $ZnCl_2$ at room temperature to obtain **30** in poor yield (28%).[80] The isopropylidene group was not stable to acidic work up.



Scheme-9

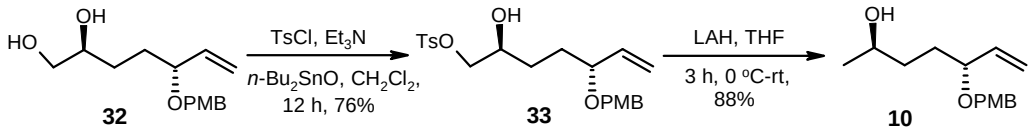
In method B, epoxy alcohol was first converted to epoxy iodide by iodination procedure using TPP, imidazole and iodine in anhydrous toluene for 30 min to give **29** in 76% yield. Direct reduction with commercial zinc dust gave the diastereomerically pure terminal alkenic alcohol **30** in 93% yield (Scheme-9).[81] In the proton spectrum, characteristic terminal olefin signals between 5.08-5.95 ppm were observed; in ^{13}C NMR spectrum olefinic carbons showed at 114.5, 140.9 ppm.

The terminal alkenic alcohol was protected as *p*-methoxybenzyl (PMB) ether **31,** using NaH, PMB-chloride in DMF, in 89% yield. In the ^{1}H NMR spectrum, CH_2 peaks appeared as doublets at 3.95 ppm, 4.29 ppm and methoxy peaks at 3.81 ppm corresponding to PMB group. The isopropylidene group of **31** was hydrolyzed under acidic conditions with *p*-TSA in methanol at room temperature, to furnish **32** in 92% yield. The structure was unambiguously corroborated from the combined spectral data of ^{1}H NMR, ^{13}C NMR and elemental analysis. In the IR spectrum broad absorption band at 3409 cm^{-1} corresponding to hydroxyl group was present (Scheme-10).



Scheme-10

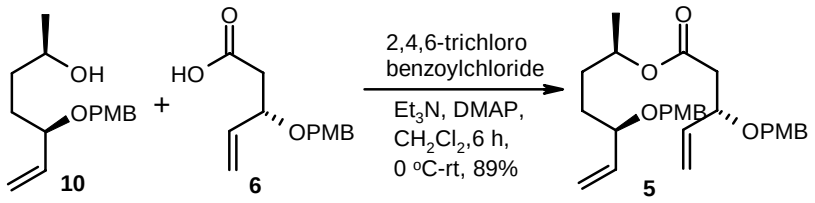
In order to secure the alcohol fragment (**10**), we deoxygenated the primary hydroxyl group of diol. The diol **32** was selectively monoprotected with a tosyl group by using TsCl, Et_3N, *n*-Bu_2SnO, in CH_2Cl_2 (0 °C to room temperature for 12 h) to give **33** in 76% yield. The structure was confirmed by the presence of additional peaks in the proton NMR spectrum due to tosylate group, i.e., a singlet at 2.45 ppm for aryl methyl and multiplet between 7.18-7.80 ppm. Then, **33** was treated with excess of lithium aluminium hydride (LAH) at 0 °C for 3 h in dry THF to provide requisite coupling partner **10** in 88% yield. New resonances due to methyl group at δ 1.15 (d, 3H, J = 6.0 Hz) in proton NMR, observance of methyl carbon at 23.3 ppm in ^{13}C NMR and confirmed by elemental and ESI mass spectral studies provided the requisite structure proof (Scheme-11).[82]



Scheme-11

Coupling reaction between Acid and Alcohol

With the two coupling fragments (**6** and **10**) in hand, our next task was to couple the two fragments and conduct the critical RCM reaction. Carboxylic acid **6** was coupled with alcohol **10** under Yamaguchi's protocol[83] (2, 4, 6-trichlorobenzoyl chloride, Et_3N, DMAP) conditions to afford the diene ester **5** in 89% yield (Scheme-12). The structure of **5** was proven by the ^1H NMR and ^{13}C NMR spectra. In the ^1H NMR spectrum, a clear cut down field shift of H-9 signals (numbering based on fig. 1) indicated ester formation. The structure was further supported by elemental analysis data (Scheme-12).



Scheme-12

A brief review on Ring-closing metathesis (RCM)

Over the past ten years, the area of olefin metathesis that has expanded most dramatically is the catalytic ring-closing metathesis (RCM). RCM has developed into a versatile synthetic tool for carbon-carbon double bond construction. In particular, medium (5-8) to large (10-13 and higher) carbo or heterocyclic rings can be very effectively constructed, and thus RCM became a reliable tool for synthesis of the natural products and spurred the synthesis of even more varied structural variants.

The word metathesis is derived from Greek word meta (change) and thesis (position). Metathesis is the exchange of parts of two substances or interchange of covalent bonds between two molecules. In the generic reaction, AB + CD → AC + BD, B has changed position with C. An example is olefin metathesis. It refers to the redistribution of alkylidene moieties between two alkenes in the presence of a catalytic amount of a metal carbene. A compound with a C=C double bond, in which the strongest bond in an alkene is broken and remade.

The 2005 Nobel Prize in Chemistry was awarded to Yves Chauvin, Robert H. Grubbs and Richard R. Schrock for development of the metathesis method in organic chemistry. History of transition metal-catalyzed olefin metathesis was discovered in the 1950's by industrial chemists at DuPont, Standard oil, and Phillips petroleum (H.S.Eleuterio, E.F.Peters, B.L. Evering, R. L. Banks, and G. C. Bailey) who reported that propene reacted to form ethylene

and 2-butenes when passed over molybdenum on alumina catalyst at high temperature. Olefin metathesis catalyzed by carbene complex has been known in polymer chemistry for 40 years. However, the reaction has been limited to simple, unfunctionalized olefin. After development of new catalyst by Schrock and Grubbs this became a very interested in organic synthesis and chemists realized the potential utility of this methodology.

Olefin metathesis has been utilized in three closely related types of reactions.

a) Ring opening metathesis polymerization (ROMP): In which a cyclic olefin is the substrate and a polymer is the product. ROMP is the thermodynamically favored for strained ring system, such as 3, 4, 8 and large-membered compound. b) Ring-closing metathesis (RCM): Acyclic diene is converted into cyclic olefin, in which a loss of ethylene takes place). c) Cross metathesis: Two different olefins react to form a new product olefin and a by-product as a volatile olefin (usually ethylene). d) Another variant of the reaction is the metathesis of an alkene and an alkyne, popularly known as enyne metathesis (EM).

Although a number of catalyst have been developed for metathesis and related reactions, the Schrock's catalyst, Hoveyda-Grubbs catalyst, Grubbs 1st and 2nd generation catalyst. The distinct catalysts shown in figure 9 and 10 have been used widely for olefin metathesis reaction.

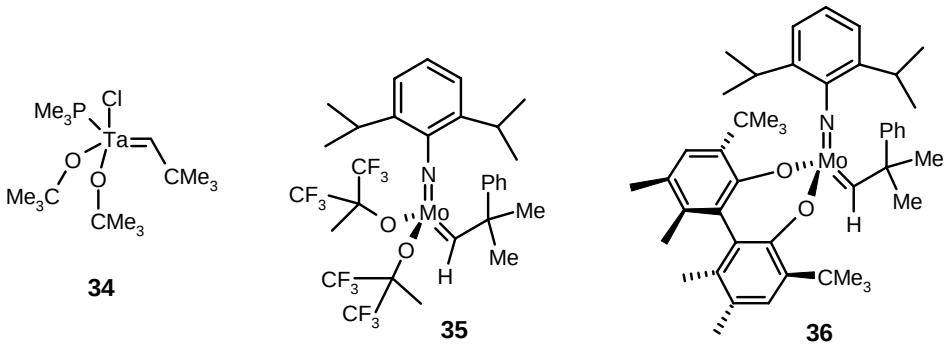


Figure-6 *Tantalum and molybdenum metathesis catalyst*

Titanium and tungsten-based catalyst have been also developed but are less used. Schrock's alkoxy imidomolybdenum (figure 6, ***35*** *and* ***36****) complex is highly reactive toward a broad range of substrate; however, this Mo-based has moderate to poor functional group tolerance, high sensitivity to air, moisture or even to trace impurities present in solvents and exhibits thermal instability.*

In particular, the ruthenium-based catalyst (Grubbs 1st and 2nd generation) have been used extensively in organic and polymeric chemistry due to its high reactivity with olefin substrate in presence of most common functional groups. Homogeneous Ruthenium catalysts

are (generally) stable, more selective and highly active at mild condition. It is superior activity over other cyclization methods like macrocyclization, Diels-alder etc., and adaptable for both solution and solid phase reactions.

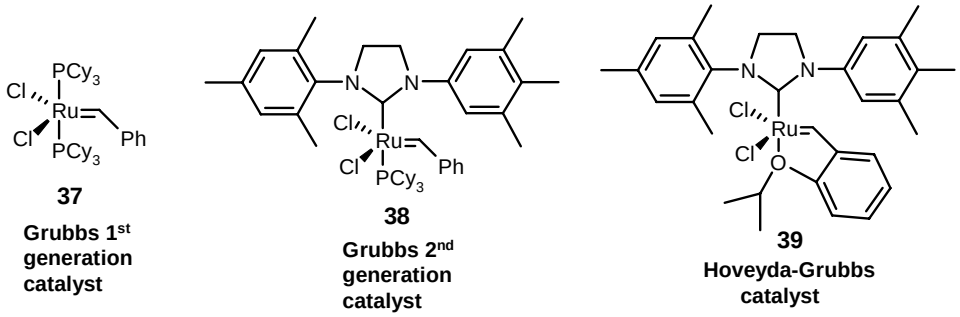


Figure-7 *Ruthenium based metathesis catalyst*

The construction of a 10-membered ring is by using RCM was first reported by Frustner and Muller in 1997 for the synthesis of Jasmine ketolactone. Frustner also synthesized herbarium I and herbarium II by RCM strategy.

RCM Mechanism:

*The mechanism of the RCM reaction has been extensively studied both experimentally and theoretically. It is now well accepted that, during the reaction the catalytically active metalacarbene complex such as [M] = CH_2 (**B**) is formed from the diene precursor (**A**) (figure-8) and the overall reaction mechanism involves, effectively, a series of alternating [2+2] cycloadditions. Metallacyclobutane intermediate such as (**C**) is formed, which opens in retro [2+2] fashion to form the carbene (**D**) as intermediate. The latter then undergoes re-cyclization to form the new metallacyclobutane (**E**), which analogously open to the product cycloalkene (**F**) and catalyst is regenerated. The mechanism is depicted schematically in figure-11. the equilibrium is continuously shifted towards the cycloalkene, due to the release of a volatile olefin (usually ethylene).*

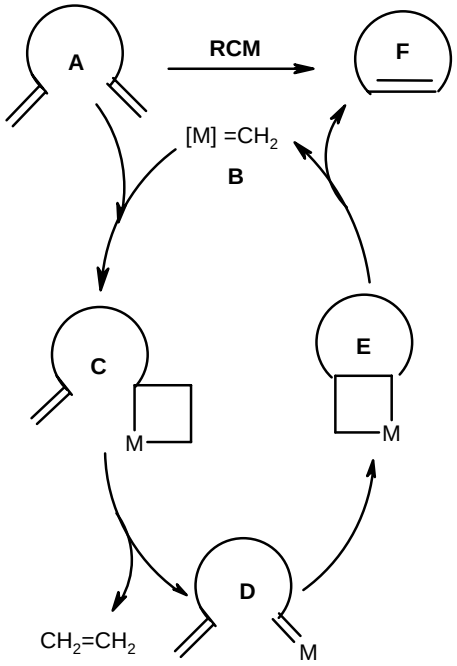
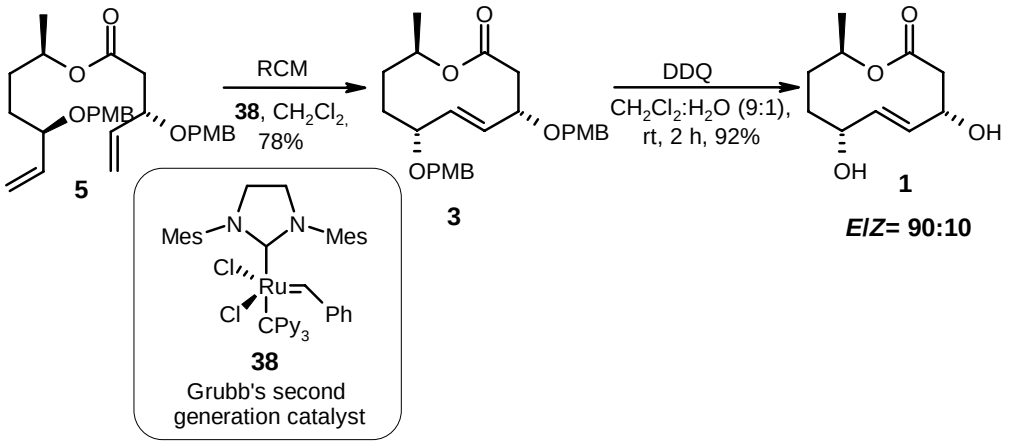


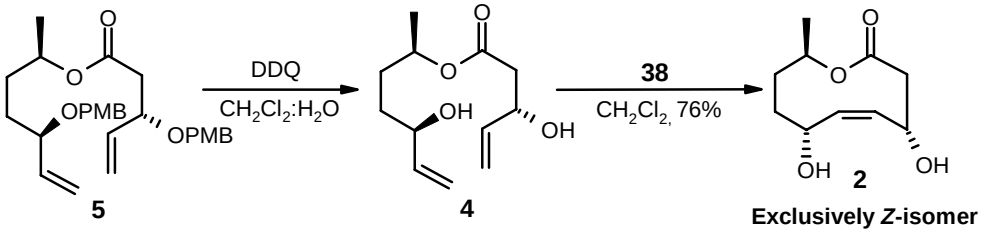
Figure-8. *RCM mechanism*

This set the stage for the crucial ring-closing metathesis, which was successfully achieved with Grubbs' second-generation catalyst **38**. The extent of bias, if any, conferred by the protecting groups on the stereochemistry of the newly formed double bond is not readily obvious and cannot be predicted with certainty. We envisaged that PMB-protecting groups around the reacting centers might act as temporary constraints to adequately shape this particular diene and simultaneously confer selectivity upon the stereochemistry of the newly formed double bond; we were pleased to observe this. A 0.001 M solution of **5** and 10 mol% of Grubbs' second generation catalyst (**38**) was heated at reflux for 8 h in dry, degassed CH_2Cl_2. This provided the desired 10-membered macrolactone (*E*)-**3** as the major product in 78% yield (Scheme-13). We were unable to ascertain the *E*/*Z* ratio. Deprotection of the PMB groups was uneventful and yielded the natural product **1** in 92% yield together with a small amount of the (*Z*)-isomer (**2**) (*E*/*Z* = 90:10). The geometry of the newly formed double bond in the major product was unequivocally assigned by detection of the olefinic J_{trans} coupling constant (15.9 Hz between the protons at δ 5.61 and 5.73 ppm, respectively). The specific rotation of the synthetic sample deviated from that of the reported one {$[\alpha]_D^{25}$ – 49.8 (*c* 0.030, MeOH); lit. $[\alpha]_D^{25}$ – 55.0 (*c* 0.036, MeOH)}; constitution and configuration of the assigned compounds are unambiguous as the NMR and IR and elemental analysis were in excellent accord with the proposed structure and perfectly matched those reported in the literature.[4]



Scheme-13

To verify the effect of PMB group upon the stereochemistry of the newly formed double bond, we carried out the RCM reaction with diol **4** after deprotection of the PMB groups of **5**. The RCM reaction on **4** (0.001 M in CH_2Cl_2) with Grubbs' second generation catalyst (10 mol%) afforded the 10-membered lactone (**2**) as the sole product in 76% yield (Scheme-14). We were surprised to find the newly formed double bond to have a *Z*- conformation as evidenced by the coupling constant of 11.2 Hz. No spectroscopic evidence for the formation of the *E* isomer was discernible.



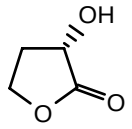
Scheme-14

Conclusion:

In summary, a concise first total synthesis of the *E* and *Z* isomers of the potent anti-malarial nonenolide **1** and related congeners was presented. Our success was based on the synthesis of two coupling partners from inexpensive, commercially available starting materials and diastereoselective ring-closing metathesis for the formation of the 10-membered lactone ring.

EXPERIMENTAL SECTION

(*S*)-3-Hydroxydihydrofuran-2(3*H*)-one (8)



Mol. Formula : $C_4H_6O_3$

$[\alpha]_D^{25}$: –69.7 (*c* 0.93, $CHCl_3$)

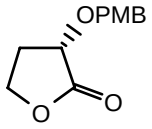
IR ($CHCl_3$) cm^{-1} : 3413, 2916, 1773, 1231, 1181, 1132, 1017.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.29 (m, 1H), 2.58 (m, 1H), 3.33 (br, s), 4.25 (m, 1H), 4.40-4.58 (m, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 30.7, 65.2, 67.16, 178.4.

Elemental Analysis : **Calcd.:** C, 47.06; H, 5.92; **Found:** C, 46.92; H, 5.78.

(*S*)-3-(4-Methoxybenzyloxy)dihydrofuran-2(3*H*)-one (14)



To a solution of **8** (0.510 g, 5.0 mmol) and *p*-methoxybenzyl 2, 2, 2-trichloroacetimidate (2.81 g, 10.0 mmol) in dry CH_2Cl_2 (20 mL) was added a camphoursulfonic acid (catalytic), and the mixture was stirred for 4 h at ambient temperature. The reaction was neutralized with solid $NaHCO_3$, the mixture was filtered, and the filtrate was concentrated under reduced pressure. Purified the residue by column chromatography (silica gel, 25% EtOAc-light Petroleum ether) to give of **14** as a colorless oil.

Yield : 0.978 g, 88%

Mol. Formula : $C_{12}H_{14}O_4$

$[\alpha]_D^{25}$: -56.3 (*c* 4.73 $CHCl_3$)

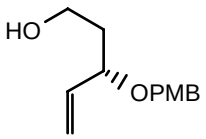
IR ($CHCl_3$) cm^{-1} : 2925, 1772, 1733, 1611, 1513, 1259, 1176, 1137, 1035.

^{1}H NMR ($CDCl_3$, 300 MHz) **:** δ 2.20-2.32 (m, 1H), 2.38-2.49 (m, 1H), 3.81 (s, 3H), 4.13-4.25 (m, 2H), 4.41 (dt, *J* = 4.0, 8.0 Hz, 1H), 4.67 (d, *J* = 11.4 Hz, 1H), 4.87 (d, 1H, *J* = 11.4 Hz), 6.89-6.92 (m, 2H), 7.30- 7.34 (m, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz) **:** δ 30.1, 55.5, 65.7, 72.0, 72.2, 113.9, 114.1, 129.1, 130.1, 159.7, 175.3.

Elemental Analysis : Calcd.: C, 64.85; H, 6.35; **Found:** C, 64.74; H, 6.22.

(*S*)-3-(4-methoxybenzyloxy)pent-4-en-1-ol (7)



To a solution of **14** (1.0 g, 4.50 mmol) in CH_2Cl_2 (40 mL) maintained at -78 °C was added a 1 M solution of DIBAL-H in hexanes (5.0 mL, 5.0 mmol), and the mixture was stirred for 30 min at -78 °C. Solid NH_4Cl and MeOH (1 mL drop) were added, and the mixture was filtered through a short column of silica gel, which was subsequently rinsed with EtOAc- MeOH (5%) mixture. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, 50% EtOAc-hexane) to afford **15** (0.645 g, 64%) as colorless oil. This compound was utilized for the subsequent step with out further purification.

To a stirred suspension of methyltriphenylphosphonium bromide (1.90 g, 5.34 mmol) in THF (40 mL) cooled to 0 °C was added a 0.91 M solution of KHMDS in THF (8.8 mL, 8.0 mmol), and stirred for 30 min at 0 °C. The solution was then cooled to -78 °C, and a solution of **15** (0.60 g, 2.67 mmol) in THF (10 mL) was added. The mixture was allowed to warm to ambient temperature, was stirred for 18 h, and then was quenched with a saturated solution of NH_4Cl (10 mL). The mixture was extracted with Et_2O (3 x 20 mL), and the combined organic extracts were washed with a saturated solution of NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography of the residue (silica gel, 30% EtOAc-light Petroleum ether) gave of **7** as a colorless oil.

Yield : 0.434 g, 73%

Mol. Formula : $C_{13}H_{18}O_3$

$[\alpha]_D^{25}$: –30.0 (*c* 0.8, $CHCl_3$)

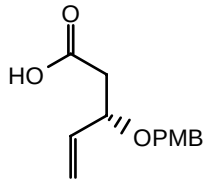
IR ($CHCl_3$) cm^{-1} : 3412, 2929, 1624, 1513, 1248, 1039, 827.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.74-1.92 (m, 2H), 2.44 (br s, 1H), 3.70-3.78 (m, 2H), 3.81 (s, 3H), 3.98 (m, 1H), 4.25 (d, *J* = 11.4 Hz, 1H), 4.53 (d, *J* = 11.4 Hz, 1H), 5.25 (m, 1H), 5.28 (m, 1H), 5.79 (m, 1H), 6.84-6.90 (m, 2H), 7.21-7.27 (m, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz) : δ 37.7, 55.1, 60.4, 69.9, 79.4, 113.8, 117.3, 128.5.0, 129.3, 130.1, 133.2, 138.2, 159.2.

Elemental Analysis : **Calcd.:** C, 70.24; H, 8.16; **Found:** C, 70.08; H, 7.96.

(*S*)-3-(4-methoxybenzyloxy)pent-4-enoic acid (6)



To a solution of alcohol **7** (0.100 g, 0.45 mmol) and PDC (0.254 g, 0.675 mmol) in dry CH_2Cl_2 was stirred at room temperature for 2 h. The reaction mixture was filtered through Celite and washed with CH_2Cl_2. The filtrate was concentrated under reduced pressure to afford **16** (0.083 g, 84%) as light yellow color oil.

To a stirred crude aldehyde **16** (0.083 g, 0.38 mmol) in *t*-butanol: water mixture (5 ml, 3:1), were added NaH_2PO_4 (0.135 g, 1.14 mmol), 2-methyl-2-butene (0.027 g, 0.38 mmol) and $NaClO_2$ (0.103 g, 1.14 mmol) at 0 ^oC and stirred for 1 h. After completion of the reaction (monitored by TLC), it was diluted with water (10 ml), separated the layers, aqueous layer was extracted with ethyl acetate (3 x 20 ml), dried over Na_2SO_4, and concentrated in vacuo. The residue purified by silica gel column chromatography (eluting in 35% EtOAc-light petroleum) to afford **6** as a colorless oil.

Yield : 0.073 g, 82%

Mol. Formula : $C_{13}H_{16}O_4$

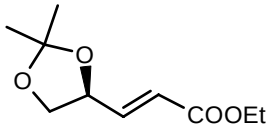
$[\alpha]_D^{25}$: –32.4 (*c* 1.1, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz) **:** δ 2.48 (dd, 1H, *J* = 5.2, 16.0 Hz), 2.63 (dd, 1H, *J* = 8.0, 16.0 Hz), 3.79 (s, 3H), 4.22 (m, 1 H), 4.30 (d, 1H, *J* = 11.2 Hz), 4.52 (d, 1H, *J* = 11.2 Hz), 5.27-5.37 (m, 2H), 5.78 (m, 1H), 6.82-6.87 (m, 2H), 7.20-7.26 (m, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz) **:** δ 40.9, 55.1, 70.2, 76.2, 113.8, 118.3, 129.4, 130.0, 136.9, 159.2, 176.5.

Elemental Analysis **:** **Calcd.:** C, 66.09; H, 6.83; **Found:** C, 65.91; H, 6.75.

(*S*,*E*)-ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (19b)



To a solution of **13** (30.0 g, 230.0 mmol) in CH_2Cl_2 (150 mL) was treated with (carboethoxymethylene)triphenyl phosphorane (104.0 g, 299 mmol) and heated at reflux for 6 h. The solvent was evaporated to give mixture of cis and trans. The residue purified by column chromatography (silica gel, 60-120 mesh, 5% EtOAc-light petroleum ether) to give **19b** as a pale yellow liquid.

Yield **:** 38.22 g, 83%

Mol. Formula **:** $C_{10}H_{16}O_4$

$[\alpha]_D^{25}$ **:** +44.0 (*c* 1.0, $CHCl_3$)

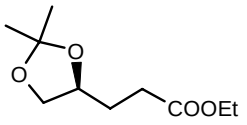
IR ($CHCl_3$) cm^{-1} **:** 2987, 2938, 2876, 1722, 1663, 1456, 1372, 1178, 1035, 758.

^{1}H NMR ($CDCl_3$, 200 MHz) **:** δ 1.30 (t, 3H, *J* = 7.1 Hz), 1.41 (s, 3H), 1.45 (s, 3H), 3.63 (dd, 1H, *J* = 7.1, 8.2 Hz), 4.14-4.26 (m, 3H), 4.65 (m, 1H), 6.05 (dd, 1H, *J* = 1.5, 15.7 Hz), 6.82 (dd, 1H, *J* = 5.5, 15.7 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz) **:** δ 14.0, 25.5, 26.3, 60.2, 68.6, 74.7, 109.9, 122.1, 144.5, 165.6.

Elemental Analysis **:** **Calcd.:** C, 59.98, H, 8.05; **Found:** C, 59.72; H, 7.80.

(*S*)-ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)propanoate (20)



To a solution of **19** (30.0 g, 149.8 mmol) in EtOAc (50 mL) was treated with Pd/C (150 mg) and K_2CO_3 (5.0 g) and subjected to hydrogenation at 60 *psi* for 4 h. The Reaction mixture was filtered through celite and the residue purified by column chromatography (silica gel, 60-120 mesh, 5% EtOAc in hexane) to give **20** as a pale yellow liquid.

Yield : 29.4 g, 97%

Mol. Formula : $C_{10}H_{18}O_4$

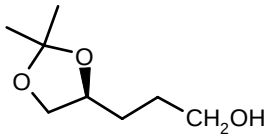
$[\alpha]_D^{25}$: +7.0 (*c* 1.0, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.27 (t, 3H, *J* = 7.1 Hz), 1.34 (s, 3H), 1.40 (s, 3H), 1.80-1.92 (m, 2H), 2.38–2.47 (m, 2H), 3.51 (dd, 1H, *J* = 6.4, 7.4 Hz), 4.0-4.19 (m, 4H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 14.1, 25.5, 26.8, 28.6, 30.3, 60.2, 68.9, 74.8, 108.8, 172.9.

Elemental Analysis : **Calcd.:** C, 59.39, H, 8.97; **Found:** C, 59.16; H, 8.82.

(*S*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)propan-1-ol (21)



To a suspension of LAH (3.79 g, 100 mmol) in THF (150 mL) at 0 ^oC was added a solution of **20** (20.2 g, 100 mmol) in THF (50 mL) drop wise in 30 min. Stirred for 3 h at same temperature, then it was quenched with saturated Na_2SO_4 solution and filtered through celite. The residue was concentrated in vacuo and purified by column chromatography (silica gel, 60-120 mesh, 20% EtOAc in hexane) to afford **21** as a pale yellow liquid.

Yield : 14.32 g, 90 %

Mol. Formula : $C_8H_{16}O_3$

$[\alpha]_D^{25}$: +14.2 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$) cm^{-1} : 3455, 3019, 2935, 1372, 1215, 1061.

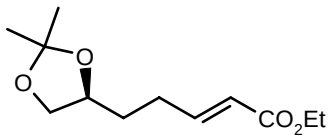
^{1}H NMR ($CDCl_3$, : δ 1.36 (s, 3H), 1.41 (s, 3H), 1.65-1.70 (m, 4H), 3.52 (t, 1H, *J* =

200 MHz) 7.3 Hz), 3.64-3.70 (m, 2H), 4.01-4.15 (m, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) **:** δ 25.7, 26.8, 29.1, 30.2, 62.3, 69.4, 75.9, 108.8.

Elemental Analysis **:** **Calcd.:** C, 59.97, H, 10.07; **Found:** C, 59.78; H, 9.95.

(*S*,*E*)-ethyl 5-(2,2-dimethyl-1,3-dioxolan-4-yl)pent-2-enoate (23)



To a stirred solution of **21** (12.08 g, 75.4 mmol) in DMSO-THF (1:1, 50 mL) at 0 ^{o}C was treated with IBX (25.4 g, 90.7 mmol) in portion wise and allowed to stir at room temperature for 4 h. The reaction mixture was treated with saturated $NaHCO_3$ solution (2 x 20 mL), filtered through celite and washed with EtOAc (3 x 50 mL) the organic layer separated and washed with water (2 x 20 mL), brine and dried over Na_2SO_4. Evaporation of the solvent gave **22** (10.02 g, 84 %) as a yellow liquid, which was used in subsequent experiments without any further purification.

To a solution of **22** (9.5 g, 60.0 mmol) in dry benzene (50 mL) was treated with (carboethoxymethylene)triphenyl phosphorane (25.0 g, 71.8 mmol) and heated at reflux for 6 h. The solvent was evaporated and the residue purified by column chromatography (silica gel, 60-120 mesh, 5% EtOAc in hexane) to afford **23** as pale yellow liquid.

Yield **:** 10.3 g, 75%

Mol. Formula **:** $C_{12}H_{20}O_4$

$[\alpha]_D^{25}$ **:** +6.0 (*c* 1.0, $CHCl_3$)

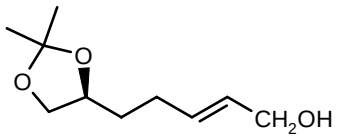
IR ($CHCl_3$) cm^{-1} **:** 2987, 2938, 2876, 1722, 1663, 1456, 1372, 1178, 1035, 758.

^{1}H NMR ($CDCl_3$, 200 MHz) **:** δ 1.29 (t, 3H, *J* = 7.2 Hz), 1.35 (s, 3H), 1.41 (s, 3H), 1.64-1.79 (m, 2H), 2.20-2.40 (m, 2H), 3.52 (t, 1H, *J* = 6.2 Hz), 4.00-4.24 (m, 4H), 5.80 (d, 1H, *J* = 15.7 Hz), 6.89 (dt, 1H, *J* = 6.8, 15.7 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz) **:** δ 14.1, 25.5, 26.8, 28.3, 31.9, 60.0, 69.0, 74.9, 108.7, 121.7, 147.7, 166.1.

Elemental Analysis **:** **Calcd.:** C, 63.14; H, 8.83; **Found:** C, 63.09; H, 8.78.

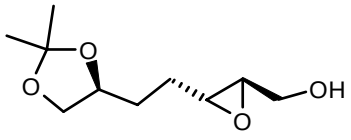
(*S*,*E*)-5-(2,2-dimethyl-1,3-dioxolan-4-yl)pent-2-en-1-ol (12)



To a stirred solution of **23** (10.0 g, 43.8 mmol) in dry CH_2Cl_2 (100 mL) at –20 ^oC was added a solution of DIBAL-H (48.3 mL, 96.5 mmol, 2M in toluene) drop wise in 30 min. After 2 h, the reaction mixture was warm to 0 ^oC and treated drop wise with MeOH (5 mL) to obtain a gelatinous cake. The mixture was diluted with CH_2Cl_2 (100 mL) and stirred for 15 min. a solution of Na-K tartarate (10 mL) was added drop wise and stirred for an additional 45 min. the reaction mixture was filtered through celite and washed with CH_2Cl_2 (2 x 50 mL). The organic layer was washed with water, brine, dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography (silica gel, 60-120 mesh, 30% EtOAc-light petroleum ether) to afford **12** as a colorless liquid**.**

Yield	**:**	7.2 g, 88%
Mol. Formula	**:**	$C_{10}H_{18}O_3$
$[\alpha]_D^{25}$	**:**	+15.6 (*c* 1.0, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	**:**	3422, 2986, 2935, 2868, 1670, 1455, 1379, 1216, 1157, 1062, 752.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ 1.35 (s, 3H), 1.40 (s, 3H), 1.62-1.72 (m, 2H), 2.07-2.21 (m, 2H), 3.51 (t, 1H, *J* = 6.6 Hz), 3.99-4.08 (m, 4H), 5.66-5.71 (m, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz)	**:**	δ 25.6, 26.8, 28.3, 32.9, 63.1, 69.1, 75.3, 108.6, 129.7, 131.3.
Elemental Analysis	**:**	**Calcd.:** C, 64.49; H, 9.74; **Found:** C, 64.26; H, 9.65.

((2*R*,3*R*)-3-(2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)oxiran-2-yl)methanol (11)



To a stirred and cooled (–20 ^oC) suspension of molecular sieves (4 A^o, 2.0 g) in CH_2Cl_2 (50 mL) under N_2 atmosphere, (–) DET (2.0 g, 9.7 mmol) in CH_2Cl_2 (25 mL),

$Ti(O\ ^{i}Pr)_4$ (2.30 g, 8.1 mmol) and TBHP (9.75 mL, 5.0-6.0 M solution in decane, 5.38 mmol) were added sequentially. After 20 min, the resulting mixture was treated with a solution of **12** (5.0 g, 26.85 mmol) in CH_2Cl_2 (25 mL). After 6 h, the reaction mixture was quenched with 10% NaOH solution in saturated with NaCl (10 mL) and filtered through celite. Evaporation of the solvent and purification of the residue by column chromatography (silica gel, 50% EtOAc in hexane) afforded **11** as a colorless liquid.

Yield : 4.4 g, 81%

Mol. Formula : $C_{10}H_{18}O_4$

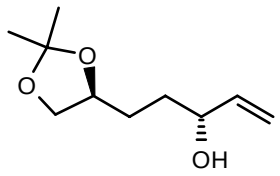
$[\alpha]_D^{25}$: +19.0 (*c* 0.4, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.34 (s, 3H), 1.40 (s, 3H), 1.55-1.80 (m, 4H), 2.1 (br, s, 1H), 2.87-3.02 (m, 2H), 3.47-3.72 (m, 2H), 3.85 (m, 1H), 4.00-4.17 (m, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 25.5, 26.8, 28.1, 29.9, 55.6, 58.7, 61.5, 69.1, 75.5, 108.6.

Elemental Analysis : **Calcd.:** C, 59.39, H, 8.97; **Found:** C, 59.12; H, 8.64.

(*R*)-5-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-1-en-3-ol (30)



To a solution of **11** (2.02 g, 10.0 mmol) in dry toluene (30 mL) were added imidazole (2.04 g, 30.0 mmol), triphenylphosphine (3.93 g, 15.0 mmol) and iodine (3.02 g, 12.0 mmol) at room temperature. Stirred for 30 min at same temperature (monitored by TLC) and quenched the reaction mixture by saturated $NaHCO_3$ solution. The aqueous layer was washed with EtOAc (2 x 30 mL), combined the EtOAc layers, dried over Na_2SO_4, evaporated the solvent in vacuo and purification of the residue by column chromatography (silica gel, 10% EtOAc-Light petroleum ether) gave **29** (2.38 g, 76%) as a light yellowish liquid.

To a solution of **29** (2.38 g, 7.62 mmol) in absolute ethanol (30 mL) added Zn dust (4.95 g, 76.2 mmol) and heated to reflux for 3 h. Evaporated the solvent and purification

of the residue by column chromatography (silica gel, 60-120 mesh, 25% EtOAc in hexane) gave **30** as a colorless liquid.

Yield : 1.32 g, 93%

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

$[\alpha]_D^{25}$: +12.0 (*c* 1.0, $CHCl_3$)

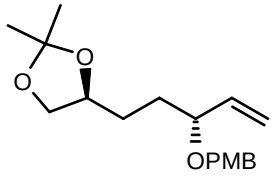
IR ($CHCl_3$) cm^{-1} : 3436, 3079, 2986, 2871, 1644, 1455, 1379, 1216, 1058, 922, 757.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.35 (s, 3H), 1.41 (s, 3H), 1.58-1.75 (m, 4H), 2.15 (br s, 1H), 3.51 (t, 1H, *J* = 6.8 Hz), 4.01-4.16 (m, 3H), 5.08-5.29 (m, 2H), 5.78-5.95 (m, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 25.7, 26.8, 29.2, 33.1, 69.4, 72.4, 76.0, 108.8, 114.6, 140.9.

Elemental Analysis : **Calcd.:** C, 64.49, H, 9.74; **Found:** C, 64.34; H, 9.60.

(*S*)-4-(*R*)-3(4-methoxybenzyloxy)pent-4-enyl)-2,2-dimethyl-1,3-dioxolane (31)



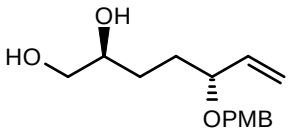
To a solution of **30** (2.5 g, 13.4 mmol) in dry DMF (40 mL) was added NaH (0.8 g, 33.5 mmol, 60% dispersion in mineral oil) at 0 ^oC, stirred for 30 min., added *p*-methoxy benzyl chloride (2.5 g, 16.0 mmol) and stirred for additional 3 h at room temperature. The reaction mixture was quenched by cold water and aqueous layer washed with EtOAc (2 x 25 mL), dried over Na_2SO_4, Evaporation of the solvent in *vacuo* and purified the residue by column chromatography (10% EtOAc-light petroleum ether) to afford **31.**

Yield : 3.65 g, 89%

Mol. Formula : $C_{18}H_{26}O_4$

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.33 (s, 3H), 1.39 (s, 3H), 1.47-1.77 (m, 4H), 3.35-3.78 (m, 3H), 3.81 (s, 3H), 3.98 (d, 1H, *J* = 11.5 Hz), 4.24 (d, 1H, *J* = 11.5 Hz), 4.55 (m, 1H), 5.18-5.28 (m, 2H), 5.64-5.84 (m, 1H), 6.84-6.89 (m, 2H), 7.22-7.27 (m, 2H).

(2*S*,5*R*)-5-(4-methoxybenzyloxy)hept-6-ene-1,2-diol (32)



To a solution of **31** (1.53 g, 5.0 mmol) in 80% AcOH (20 mL), was stirred for 6 h at room temperature and quenched the reaction mixture with saturated $NaHCO_3$ solution. The aqueous layer was washed with EtOAc (2 x 30 mL) dried over Na_2SO_4, evaporation of the solvent in *vacuo* and purified the residue by column chromatography (silica gel, 60-120 mesh, 50% EtOAc in hexane) to give **32** as a colorless liquid.

Yield : 1.22 g, 92%

Mol. Formula : $C_{15}H_{22}O_4$

$[\alpha]_D^{25}$: +17.3 (*c* 1.0, $CHCl_3$)

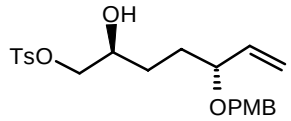
IR ($CHCl_3$) cm^{-1} : 3409, 3076, 3000, 2936, 2868, 1612, 1514, 1442, 1302, 1248, 1174, 1072, 995, 821

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.43-1.57 (m, 2H), 1.64-1.75 (m, 2H), 2.41 (br s, 2H), 3.38 (m, 1H), 3.53-3.75 (m, 3H), 3.79 (s, 3H), 4.24 (d, 1H, *J* = 11.4 Hz), 4.50 (d, 1H, *J* = 11.3 Hz), 5.16-5.29 (m, 2H), 5.66-5.84 (m, 1H), 6.83-6.87 (m, 2H), 7.19-7.26(m, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz) : δ 28.9, 31.5, 55.1, 66.5, 69.8, 71.9, 80.2, 113.7, 117.3, 129.4, 130.3, 138.6, 159.1.

Elemental Analysis : **Calcd.:** C, 67.64, H, 8.33; **Found:** C, 67.28; H, 8.12.

(2*S*,5*R*)-2-hydroxy-5-(4-methoxybenzyloxy)hept-6-enyl-4-methylbenzenesulfonate (33)



To a solution of **32** (1.0 g, 3.75 mmol), in dry CH_2Cl_2 (30 mL) were added Et_3N (0.44 g, 4.27 mmol), n-Bu_2SnO (0.47 g, 1.89 mmol), DMAP (catalytic) and Ts-Cl (0.74 g, 3.84 mmol) at 0 ^oC. Stirred for 12 h at room temperature, quenched with saturated solution of $NaHCO_3$, aqueous layer extracted with EtOAc (2 x 25 mL), combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue

purified by column chromatography (silica gel, 60-120 mesh, 15% EtOAc-light petroleum ether) to afford **33** as a colorless liquid.

Yield : 1.2 g, 76%

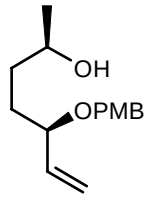
Mol. formula : $C_{22}H_{28}O_6S$

$[\alpha]_D^{25}$: +26.0 (*c* 1.2, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.43-1.71 (m, 4H), 2.45 (s, 3H), 3.66-3.78 (m, 2H), 3.80 (s, 3H), 3.85-3.98 (m, 2H), 4.21 (d, 1H, *J* = 11.5 Hz), 4.49 (d, 1H, *J* = 11.4 Hz), 5.16-5.26 (m, 2H), 5.71 (m, 1H), 6.83-6.87 (m, 2H), 7.18-7.22 (m, 2H), 7.31-7.35 (m, 2H), 7.76-7.80 (m, 2H).

Elemental Analysis : **Calcd.:** C, 62.84; H, 6.71; S, 7.63; **Found:** C, 62.74; H, 6.58.

(2*R*,5*R*)-5-(4-methoxybenzyloxy)hept-6-en-2-ol (10)



To a solution of compound **33** (0.210 g, 0.5 mmol) in dry THF (10 ml) at 0 ^oC was added LAH (0.076 g, 2.0 mmol) and stirred for 3 h. Excess of LAH was quenched by addition of a saturated Na_2SO_4 solution (1 ml). The solid formed was filtered through celite pad, washed with ethyl acetate, filtrate was concentrated in vacuo and purified by silica gel column chromatography (eluting with 20% EtOAc-light petroleum ether) to afford **10** as a colorless liquid.

Yield : 0.110 g, 88%

Mol. Formula : $C_{15}H_{22}O_3$

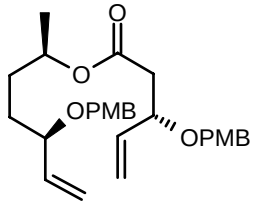
$[\alpha]_D^{25}$: +19.6 (*c* 1.1, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.15 (d, 3H, *J* = 6.0 Hz), 1.44-1.58 (m, 2H), 1.62-1.69 (m, 2H), 2.1 (br s, 1H) 3.70-3.77 (m, 2H), 3.80 (m, 3H), 4.24 (d, 1H, *J* = 11.3 Hz), 4.50 (d, 1H, *J* = 11.3 Hz), 5.16-5.26 (m, 2H), 5.76 (m, 1H), 6.84-6.88 (m, 2H), 7.21-7.27 (m, 2H);

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 23.3, 31.7, 34.9, 55.1, 67.5, 69.7, 80.2, 113.7, 117.0, 129.3, 130.4, 138.8, 159.0.

Elemental Analysis : **Calcd.:** C, 71.97; H, 8.86; **Found:** C, 71.94; H, 8.72.

(3*S*)-(2*R*,5*R*)-5-(4-methoxybenzyloxy)hept-6-en-2-yl-3-(4-methoxybenzyloxy)-pent-4-enoate (5)



To a stirred solution of **6** (0.050 g, 0.211 mmol) in dry CH_2Cl_2 (5 ml) were added Et_3N (0.042 g, 0.422 mmol) and a solution of 2, 4, 6-trichlorobenzoylchloride (0.077 g, 0.315 mmol) in dry CH_2Cl_2 (5 ml) and stirred at 0 ^oC for 20 min. A solution of **10** (0.055 g, 0.219 mmol) in dry CH_2Cl_2 (5 ml) and DMAP (catalytic) was added, stirred for 6 h at room temperature (Checked by TLC). The solvent was evaporated; the crude was purified by column chromatography (silica gel, 60-120 mesh, eluted in 10% EtOAc-light petroleum ether) to afford **5** as a colorless liquid.

Yield : 0.088 g, 89%

Mol. Formula : $C_{28}H_{36}O_6$

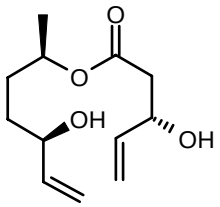
$[\alpha]_D^{25}$: + 8.5 (*c* 1.3, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.16 (d, 3H, *J* = 6.3 Hz), 1.55-1.61 (m, 4H), 2.38 (dd, 1H, *J* = 5.8, 15.0 Hz), 2.56 (dd, 1H, *J* = 8.0, 15.0 Hz), 3.64 (m, 1H), 3.78 (s, 3H), 3.79 (s, 3H), 4.20 (m, 1H), 4.28 (d, 2H, *J* = 11.3 Hz), 4.46 (d, 2H, *J* = 11.3 Hz), 4.89 (m, 1H), 5.13-5.33 (m, 4H), 5.59-5.85 (m, 2H), 6.81-6.87 (m, 4H), 7.19-7.27 (m, 4H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 19.96, 31.3, 31.7, 41.3, 55.0, 69.7, 70.1, 71.0, 76.7, 79.8, 113.6, 117.1, 117.7, 129.2, 130.3, 130.6, 137.4, 138.9, 159.0, 170.2.

Elemental Analysis : **Calcd.:** C, 71.77; H, 7.74; **Found:** C, 71.68; H, 7.64.

(*S*)-((2R,5R)-5-hydroxyhept-6-en-2-yl)-3-hydroxypent-4-enoate (4)



To a solution of **5** (0.200 g, 0.427 mmol) and DDQ (0.203 g, 0.896 mmol) in CH_2Cl_2:H_2O mixture (20:1) was stirred at room temperature for 2 h. The reaction mixture was quenched with saturated solution of $NaHCO_3$, separated the organic layer, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 60-120 mesh, eluted in 40% EtOAc-light petroleum ether) to afford **4** as a colorless liquid.

Yield **:** 0.076 g, 78%

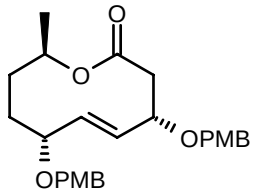
Mol. Formula **:** $C_{12}H_{20}O_4$

IR ($CHCl_3$) cm^{-1} **:** 3417, 3083, 2980, 2927, 1714, 1645, 1426, 1378, 1277, 1178, 1032.

^{1}H NMR ($CDCl_3$, 200 MHz) **:** δ 1.23 (d, 3H, *J* = 6.3 Hz), 1.51-1.69 (m, 4H), 1.90 (br s, 1H), 2.49-2.54 (m, 2H), 3.15 (br s, 1H), 4.10 (m, 1H), 4.53 (m, 1H), 5.00 (m, 1H), 5.09-5.36 (m, 4H), 5.76-5.96 (m, 2H).

Elemental Analysis **:** **Calcd.:** C, 63.14; H, 8.83; **Found:** C, 62.94; H, 8.72.

(4*S*,5*E*,7*R*,10*R*)-4,7-bis(4-methoxybenzyloxy)-3,4,7,8,9,10-hexahydro-10-methyl oxecin-2-one (3)



To a solution of **5** (0.050 g, 0.107 mmol, 0.001M) in freshly distilled degassed anhydrous CH_2Cl_2 (110 ml) was added Grubb's second generation catalyst (**38**) (0.009 g, 0.010 mmol) and heated at reflux for 8 h under an argon atmosphere until the complete consumption of starting material (monitored by TLC). The solvent was evaporated to a brown residue, which was purified by column chromatography (silica gel, 60-120 mesh, 10% ethyl acetate- light petroleum) to afford **3** as a colorless liquid.

Yield **:** 0.037 g, 78%

Mol. Formula **:** $C_{26}H_{32}O_6$

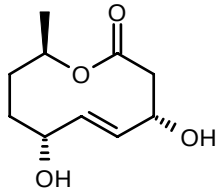
$[\alpha]_D^{25}$ **:** -18.3 (*c* 0.7, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 500 MHz) **:** δ 1.16 (d, 3H, *J* = 6.4 Hz), 1.54 (m, 1H), 1.72-1.80 (m, 2H), 2.02 (m, 1H), 2.39 (dd, 1H, *J* = 4.0, 12.0 Hz), 2.68 (dd, 1H, *J* = 3.0, 12.0 Hz), 3.80 (2 x s, 6H), 3.84 (m, 1H), 4.30 (m, 2H), 4.44 (d, 1H, *J* = 11.9 Hz), 4.49 (d, 1H, *J* = 11.6 Hz), 4.60 (d, 1H, *J* = 11.9 Hz), 4.86 (m, 1H), 5.61 (dd, 1H, *J* = 2.7, 15.9 Hz), 5.74 (m, 1H), 6.85-6.89 (m, 4H), 7.23-7.31 (m, 4H).

^{13}C NMR ($CDCl_3$, 125 MHz) **:** δ 21.8, 29.7, 42.5, 55.3, 69.5, 70.2, 72.9, 74.7, 81.1, 113.8, 126.9, 128.7, 129.2, 130.2, 130.8, 131.2, 132.3, 137.3, 159.2, 169.2.

Elemental Analysis **:** **Calcd.:** C, 70.89; H, 7.32; **Found:** C, 70.72; H, 7.28.

(4*S*,5*E*,7*R*,10*R*)-3,4,7,8,9,10-hexahydro-4,7-dihydroxy-10-methyloxecin-2-one (1)



To a solution of **3** (0.025 g, 0.0567 mmol) and DDQ (0.029 g, 0.13 mmol) in CH_2Cl_2:H_2O mixture (20:1) was stirred at room temperature for 2 h. The reaction mixture was quenched with saturated solution of $NaHCO_3$, organic layer was separated, washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (silica gel, 60-120 mesh, 10% MeOH-$CHCl_3$) to give **1** (*E*/*Z* = 90:10) as semisolid mass.

Yield **:** 0.010 g, 92%

Mol. Formula **:** $C_{10}H_{16}O_4$

$[\alpha]_D^{25}$ **:** Found: -49 (*c* 0.3, MeOH); lit: -55 (*c* 0.036, MeOH)

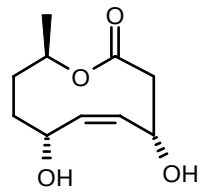
^{1}H NMR (CD_3OD, 400 MHz) **:** δ 1.14 (d, 2.7H, *J* = 6.5 Hz), 1.18(d, 0.3H, *J* = 6.8 Hz, cis), 1.57-1.64 (m, 2H), 1.77 (m, 1H), 1.95 (m, 1H), 2.30 (dd, 0.1H, *J* = 6.4, 13.8 Hz, cis), 2.46 (dd, 0.9H, *J* = 3.5, 11.9 Hz), 2.51 (dd, 0.9H, *J* = 3.7, 11.9 Hz), 2.93 (dd, 0.1H, *J* = 7.6, 13.8 Hz, cis), 4.11 (m, 1H), 4.63 (m, 1H), 4.78 (m, 1H), 5.61 (ddd, 1H, *J* = 1.3, 8.4, 15.9 Hz), 5.73 (dd, 1H, *J* = 3.0, 15.9 Hz).

^{13}C NMR (CD_3OD, 100 MHz) : δ 20.6, 29.4 (cis), 31.3, 31.7 (cis), 36.9, 44.0, 66.8, 70.7 (cis), 72.9, 74.3, 130.4, 133.0, 170.3.

Elemental Analysis : **Calcd.:** C, 59.98; H, 8.05; **Found:** C, 59.87; H, 8.02.

MS (ESI) *m/z* 223.22 (M^+ + Na).

(4*S*,5*Z*,7*R*,10*R*)-3,4,7,8,9,10-hexahydro-4,7-dihydroxy-10-methyloxecin-2-one (2)



To a stirred solution of **4** (0.04 g, 0.175 mmol, 0.001M) in freshly distilled degassed anhydrous CH_2Cl_2 (175 ml) was added Grubb's second generation catalyst (**38**) (0.015 g, 0.0176 mmol) and heated at reflux for 8 h under an argon atmosphere until the complete consumption of starting material (monitored by TLC). The solvent was evaporated to a brown residue, which was purified by column chromatography (silica gel, 60-120 mesh, 10% MeOH-$CHCl_3$) to afford **2** as light yellowish oil.

Yield : 0.026 g, 76%

Mol. Formula : $C_{10}H_{16}H_4$

$[\alpha]_D^{25}$: -28 (*c* 0.5, MeOH)

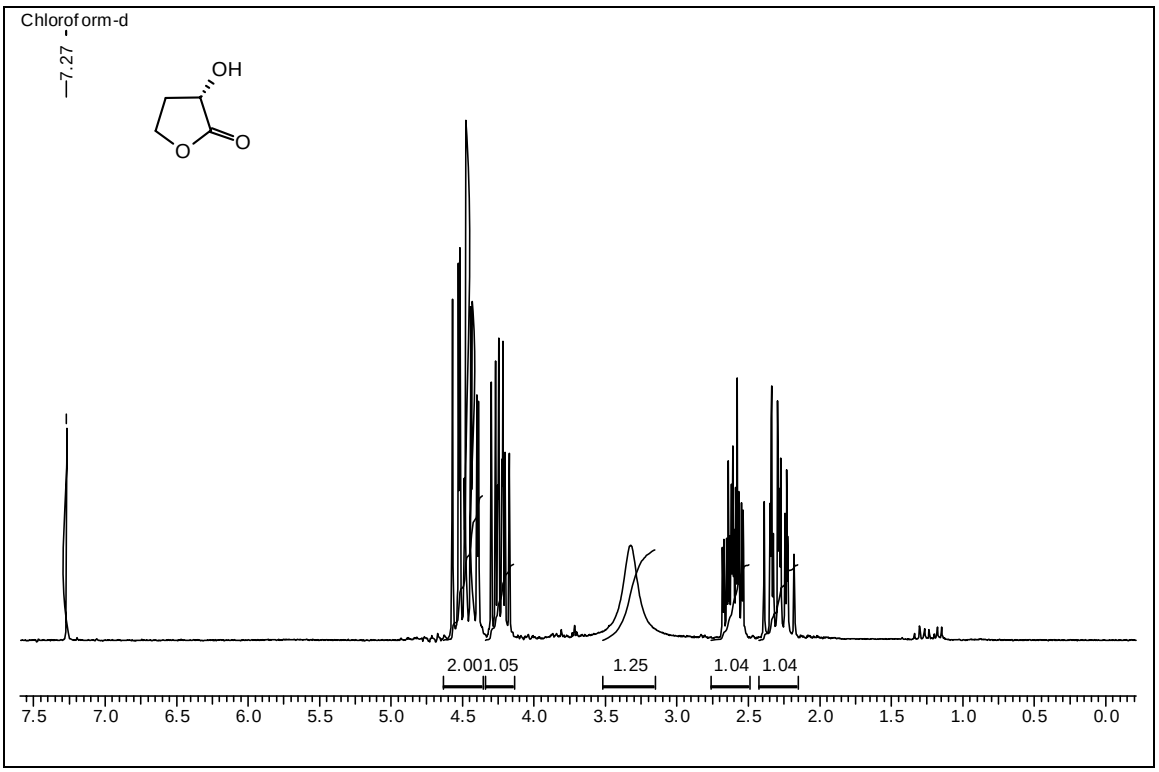
^{1}H NMR (CD_3OD, 500 MHz) : δ 1.22 (d, 3H, *J* = 3.1 Hz), 1.35-1.43 (m, 2H), 1.71 (m, 1H), 2.0 (m, 1H), 2.08 (dd, 1H, *J* = 11.0, 14.2 Hz), 2.83 (dd, 1H, *J* = 5.9, 14.2 Hz), 4.67 (m, 1H), 4.84 (m, 1H), 4.98 (m, 1H), 5.24 (m, 1H), 5.35 (dd, 1H, *J* = 9.3, 11.2 Hz)

^{13}C NMR (CD_3OD, 125 MHz) : δ 17.1, 29.7, 30.7, 43.8, 65.2, 67.0, 71.7, 133.4, 134.3, 170.9.

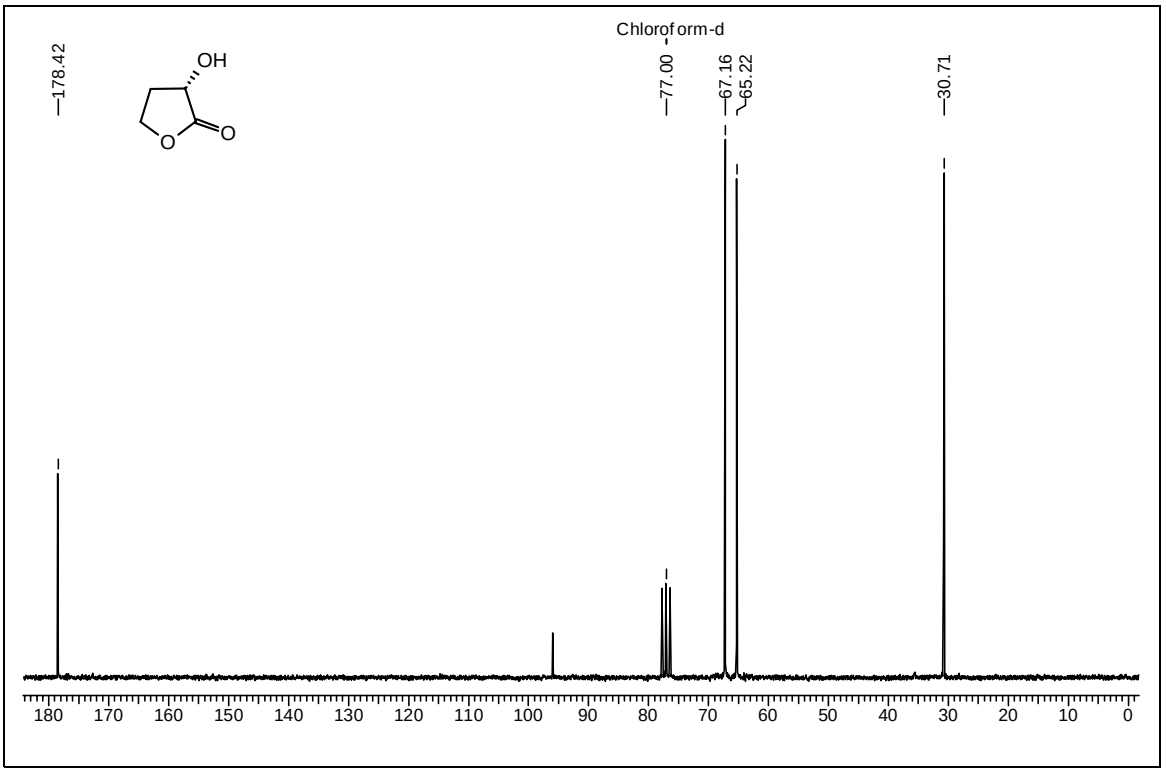
Elemental Analysis : **Calcd.:** C, 59.98; H, 8.05; **Found:** C, 59.79; H, 8.12.

MS (ESI) *m/z* : 223.22 (M^+ + Na).

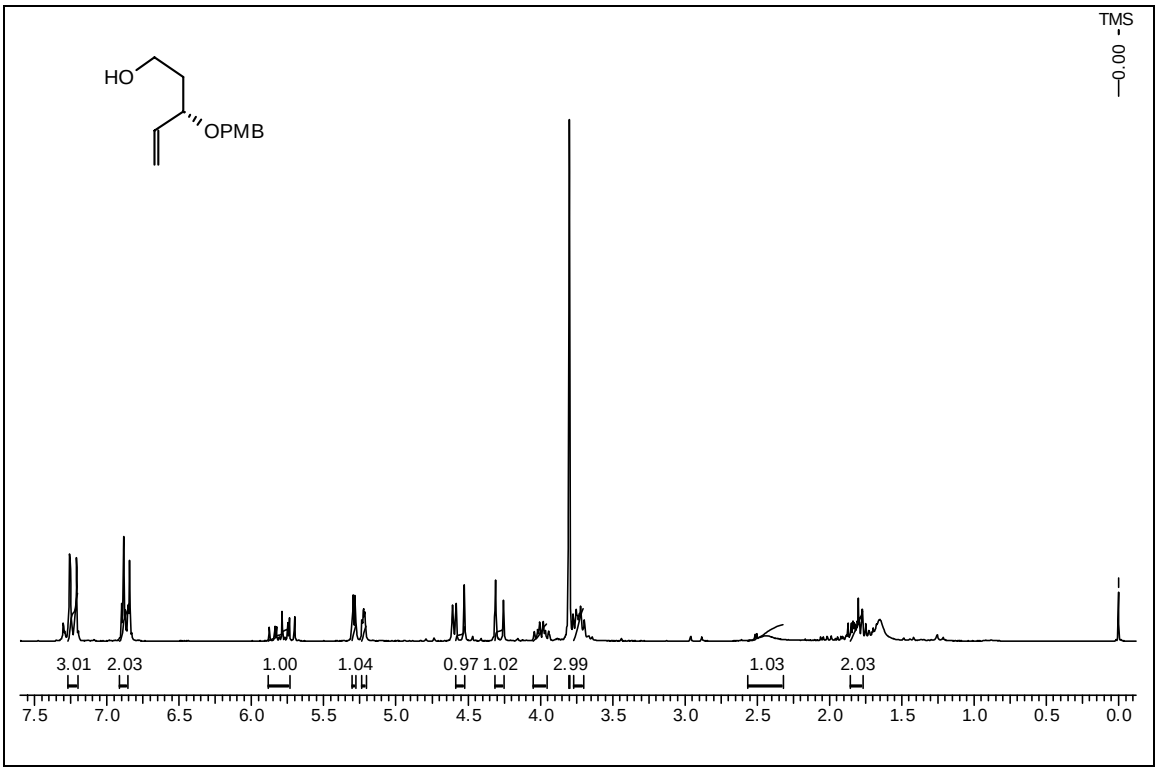
SPECTRA



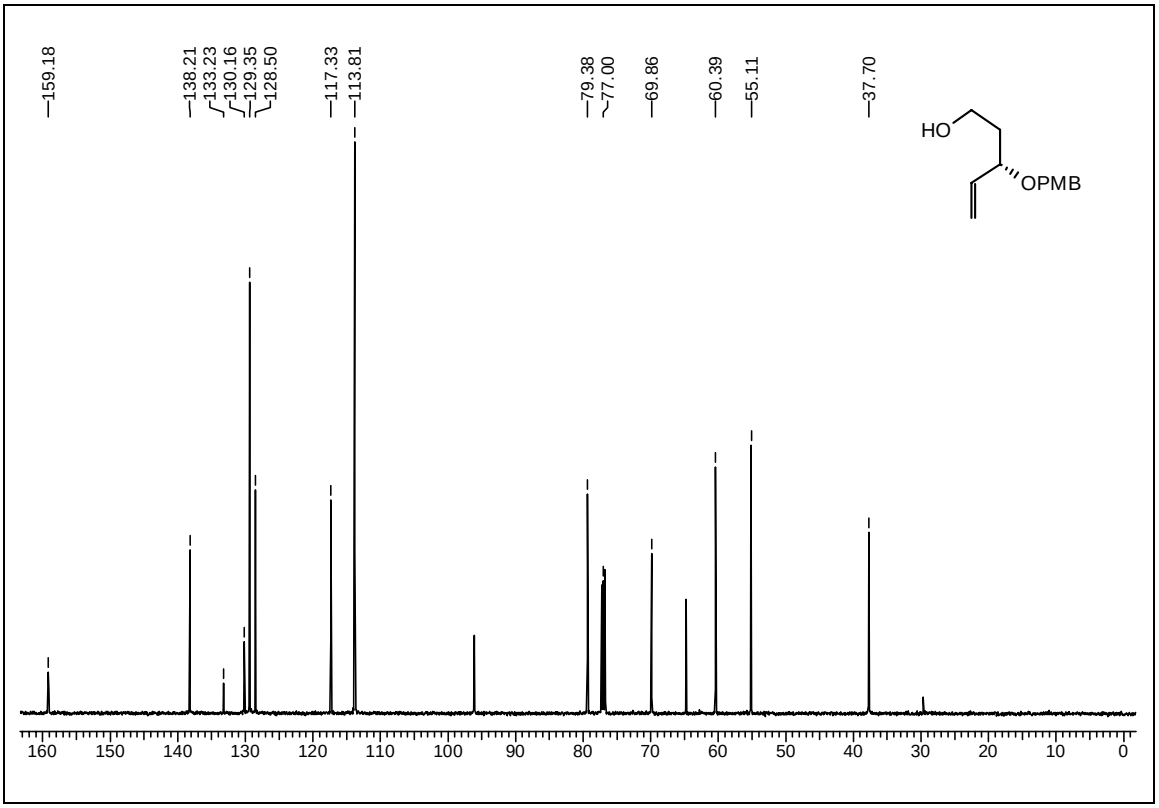
^{1}H NMR spectrum of compound 8 in $CDCl_3$



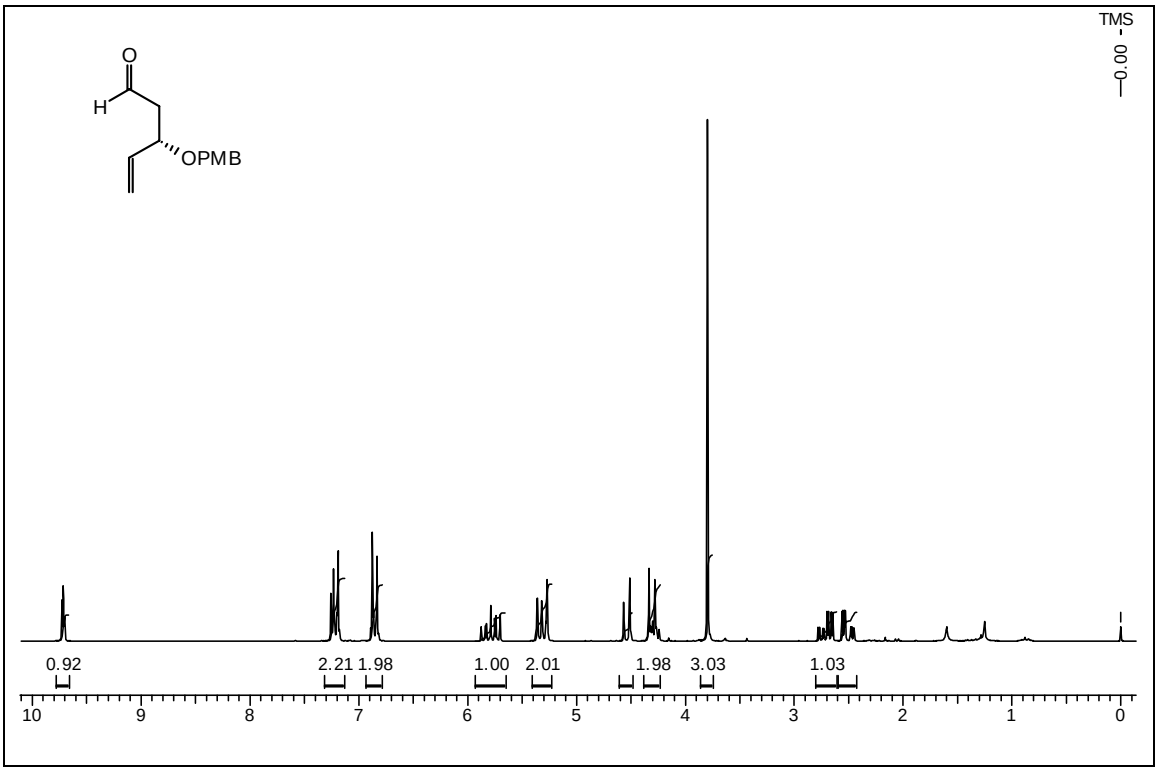
^{13}C NMR spectrum of compound 8 in $CDCl_3$



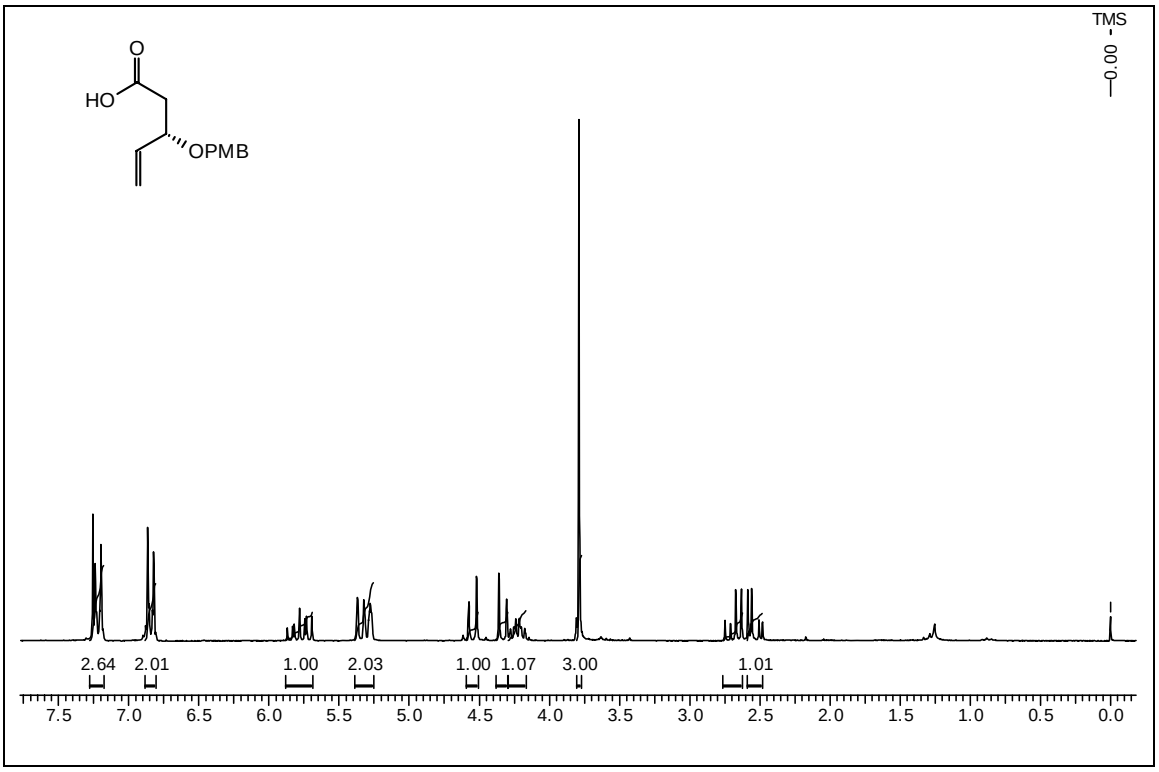
^{1}H NMR spectrum of compound 7 in $CDCl_3$



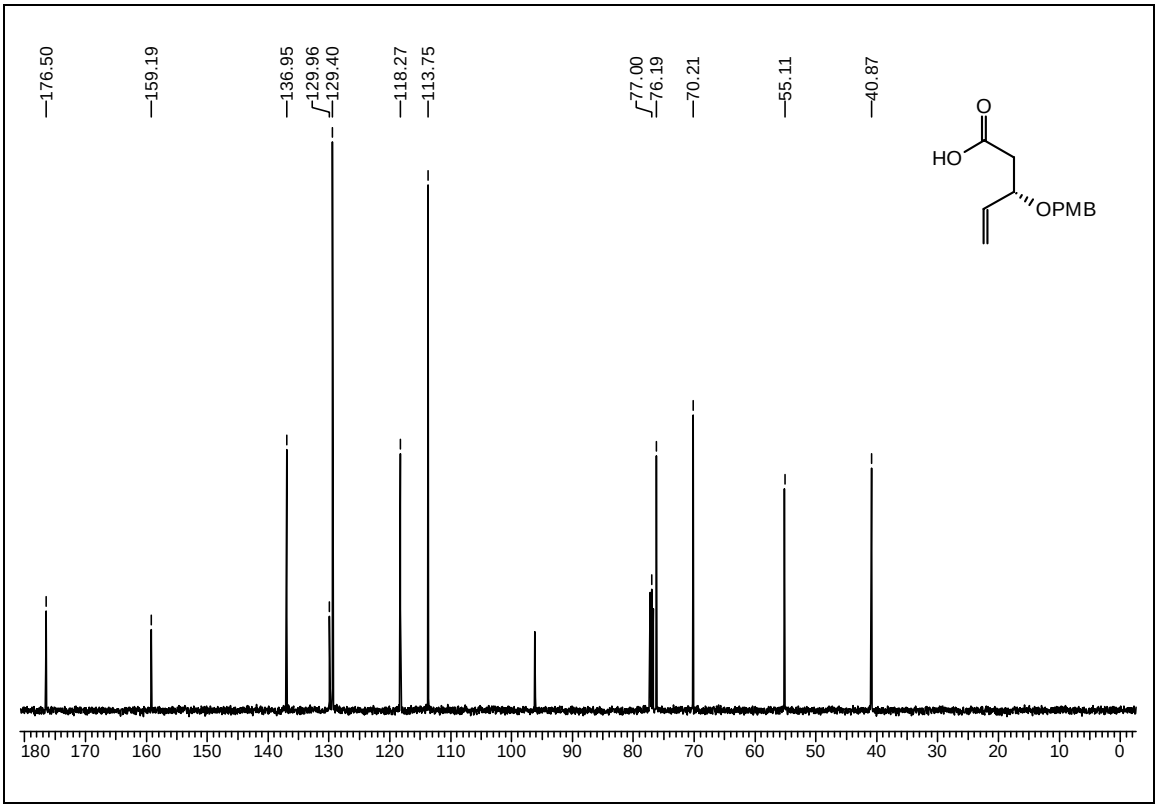
^{13}C NMR spectrum of compound 7 in $CDCl_3$



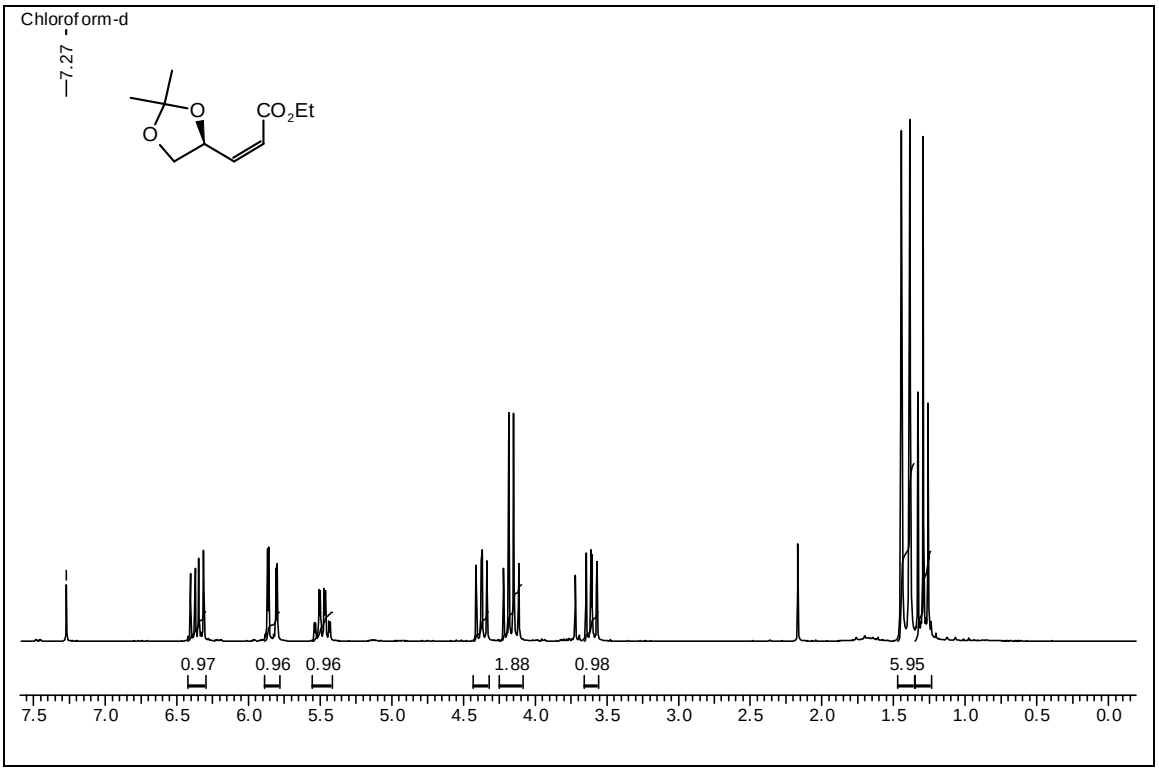
^{1}H NMR spectrum of compound 16 in $CDCl_3$



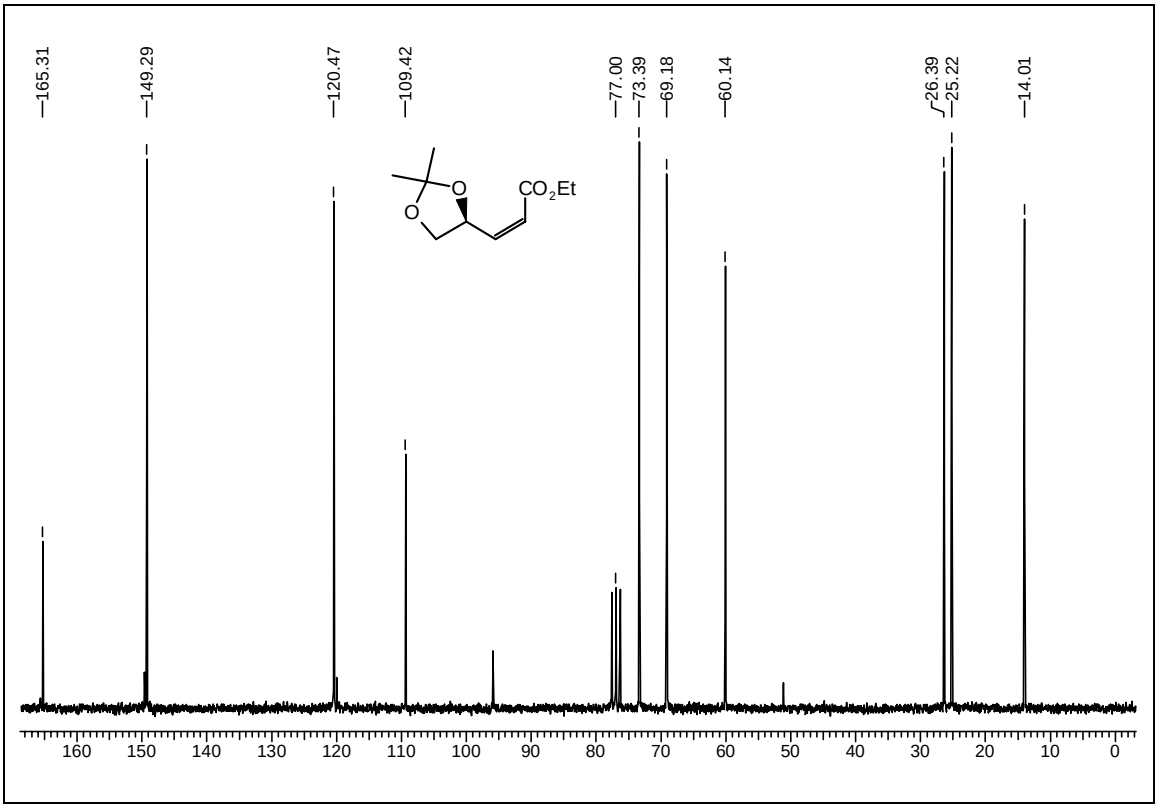
^{1}H NMR spectrum of compound 6 in $CDCl_3$



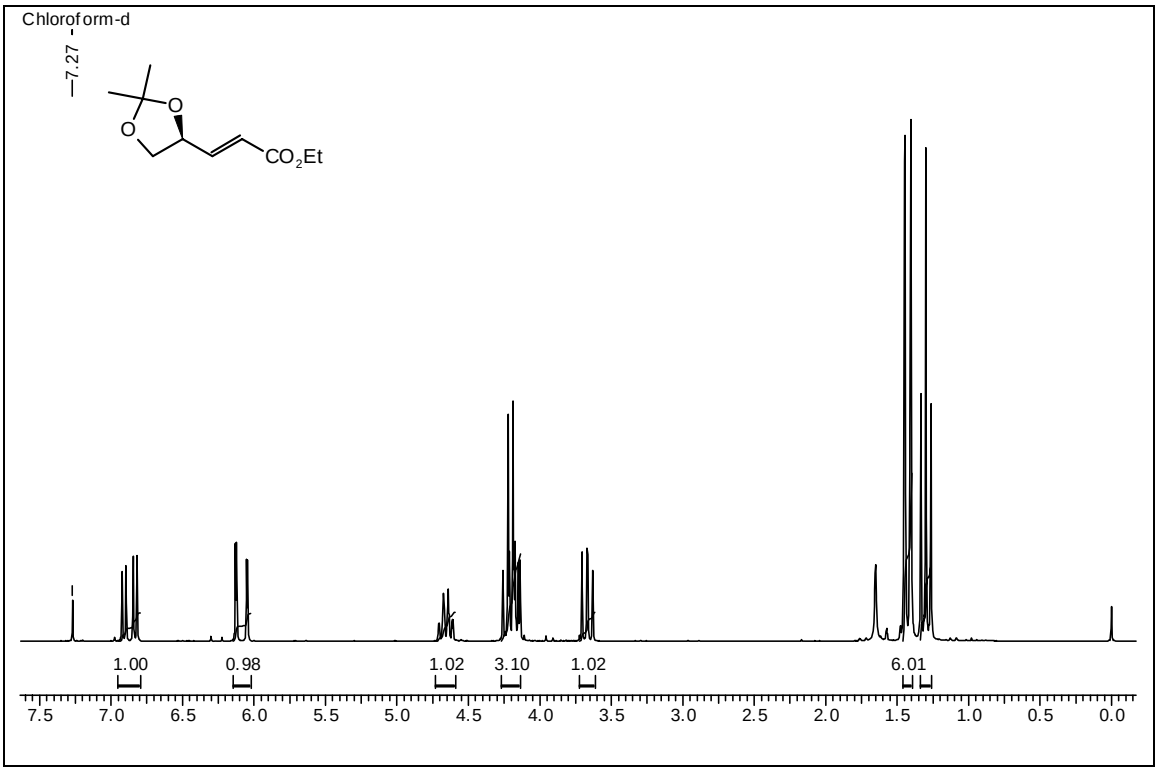
^{13}C NMR spectrum of compound 6 in $CDCl_3$



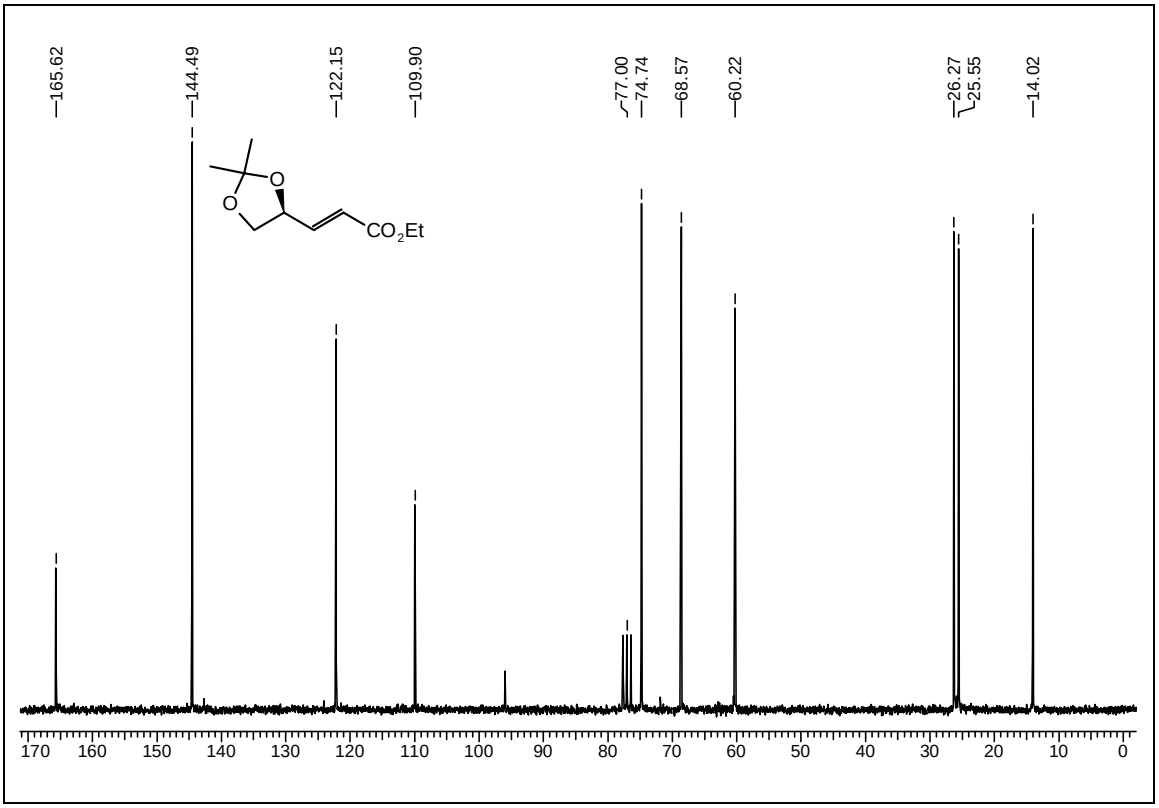
^{1}H NMR spectrum of compound 19a in $CDCl_3$



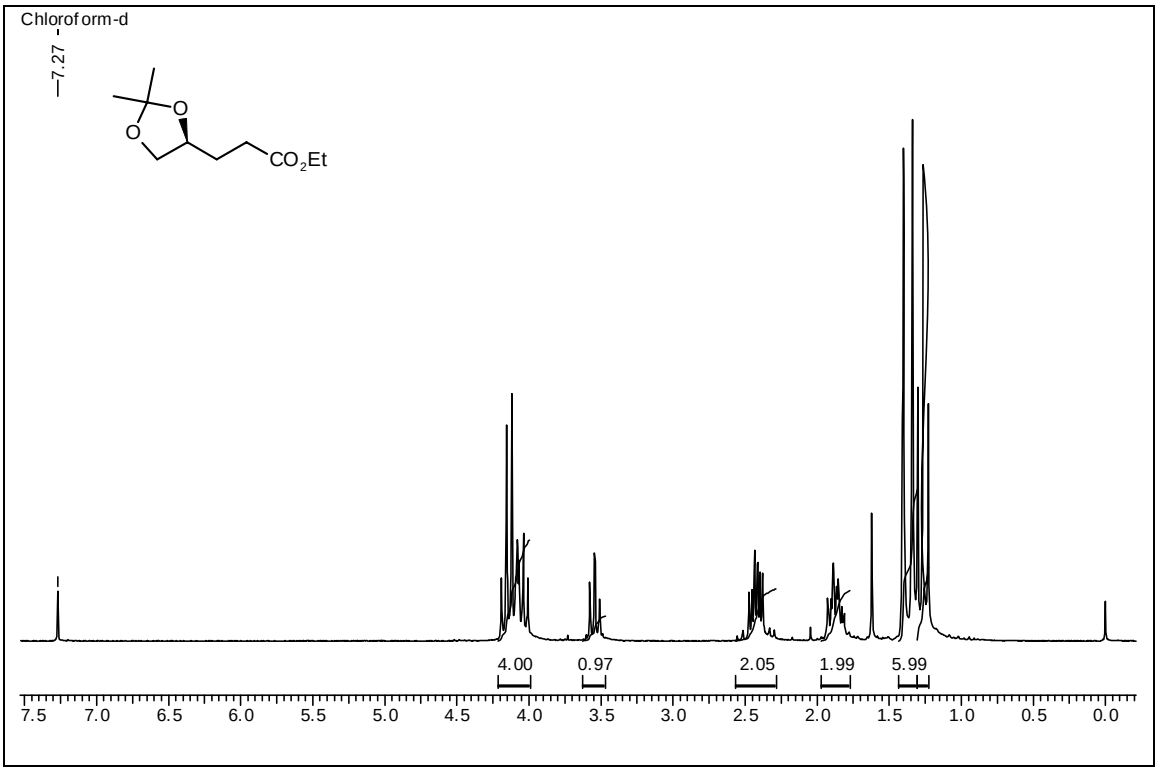
^{13}C NMR spectrum of compound 19a in $CDCl_3$



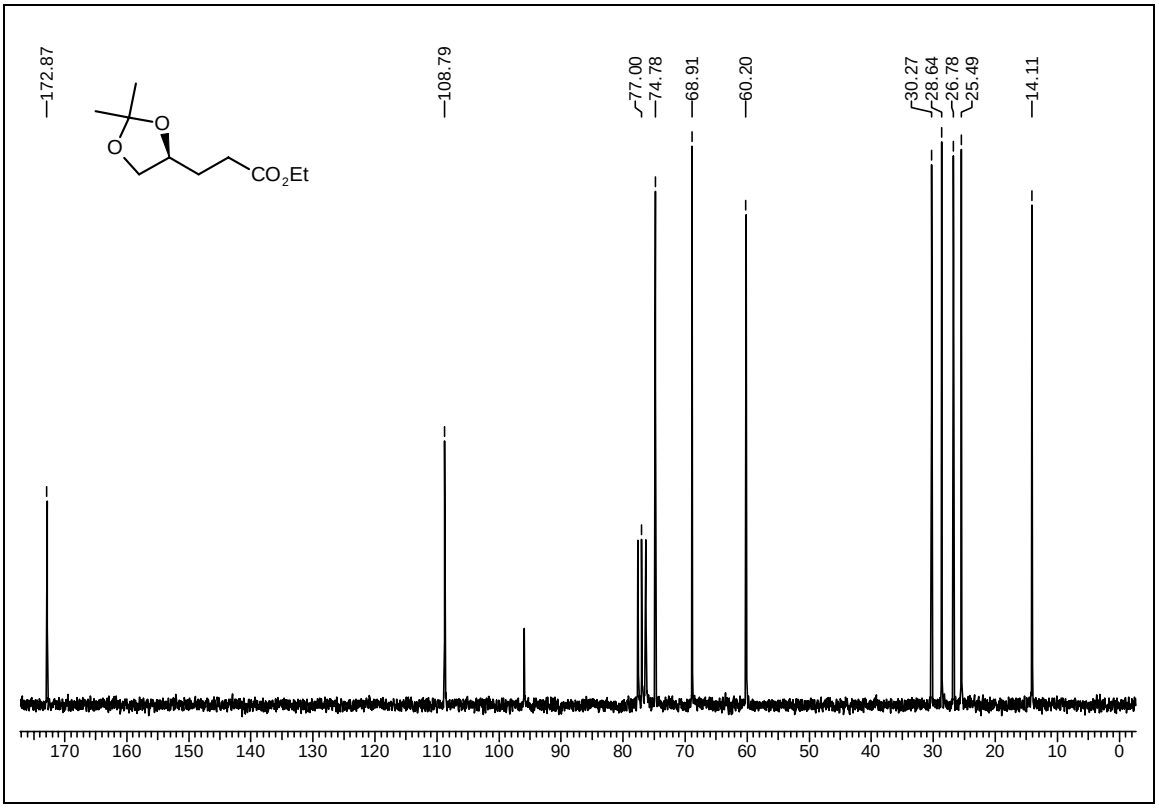
^{1}H NMR spectrum of compound 19b in $CDCl_3$



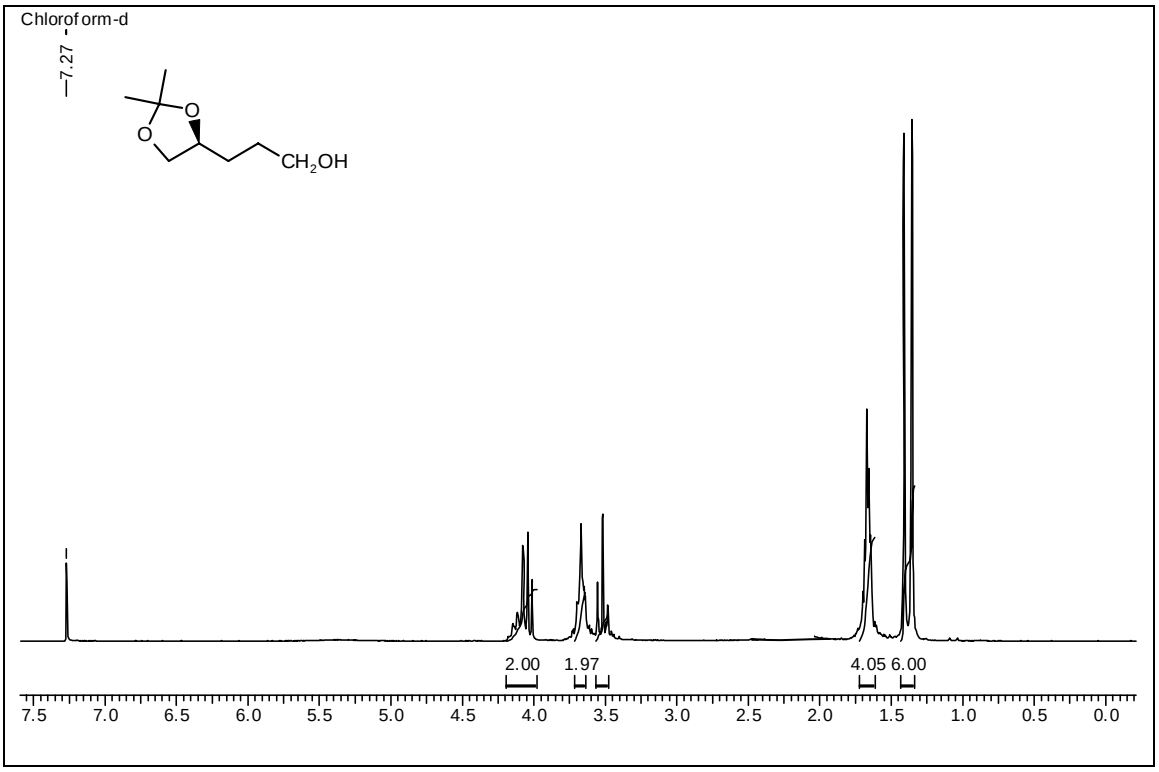
^{13}C NMR spectrum of compound 19b in $CDCl_3$



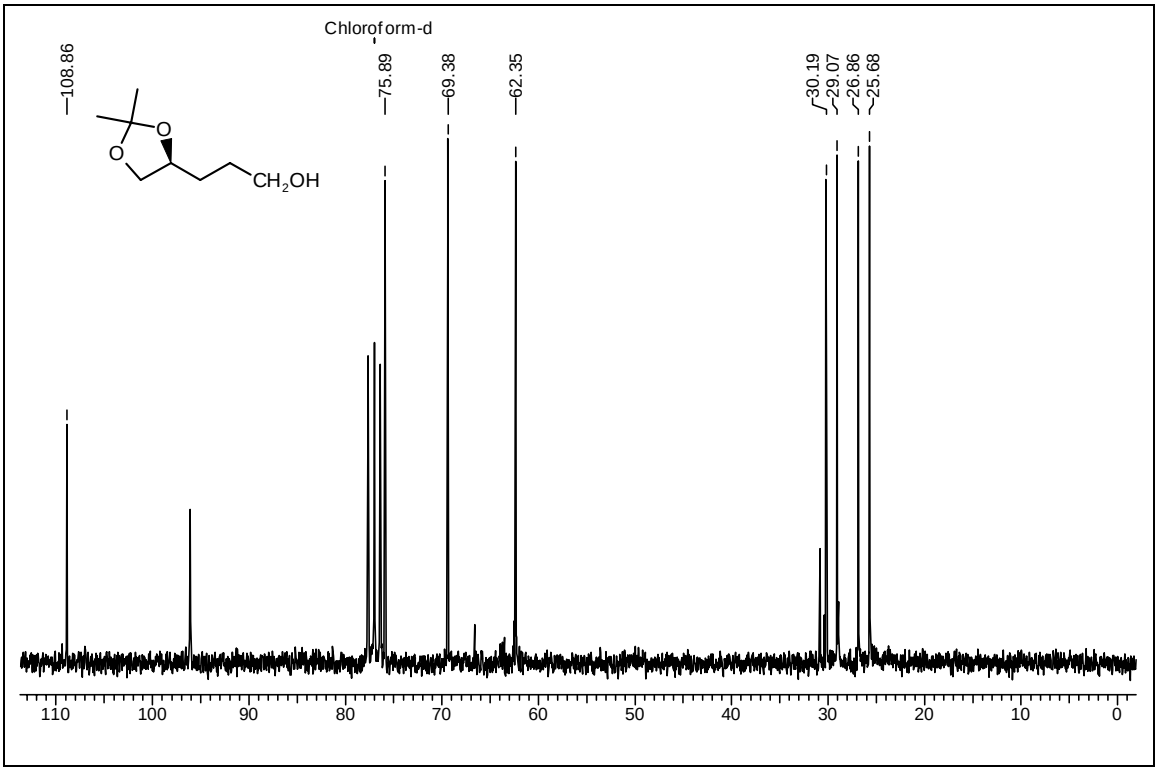
^{1}H NMR spectrum of compound 20 in $CDCl_3$



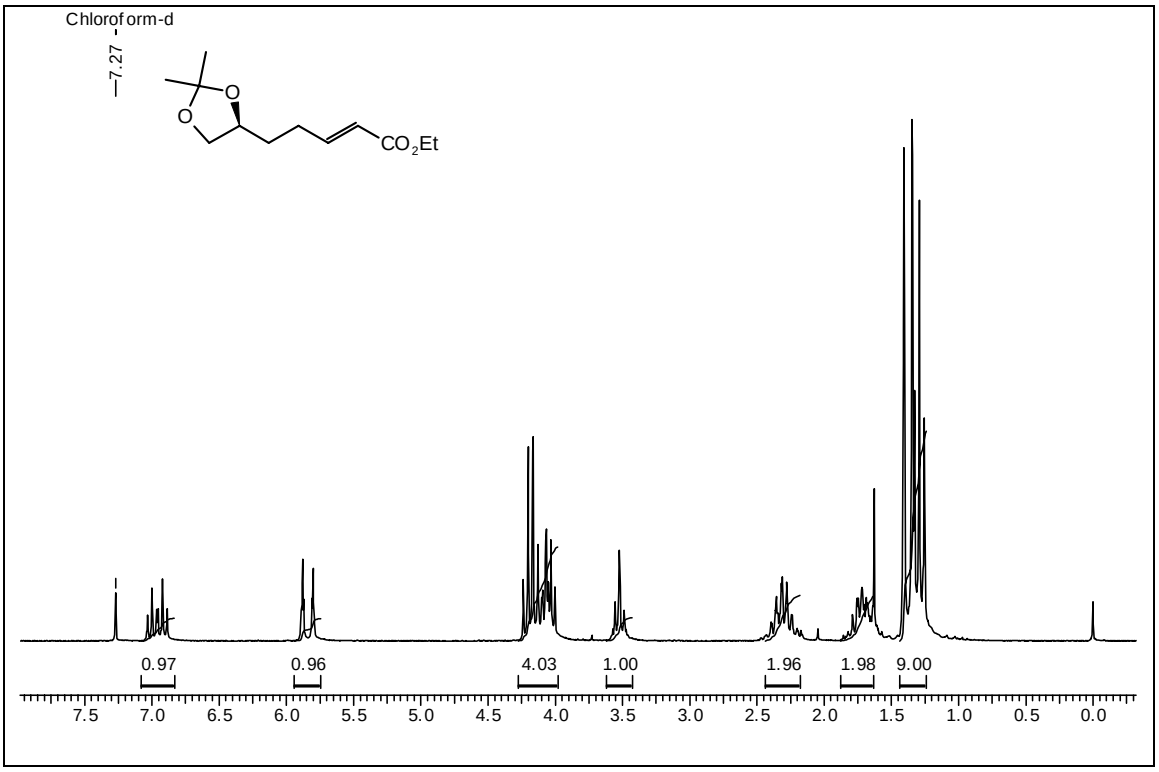
^{13}C NMR spectrum of compound 20 in $CDCl_3$



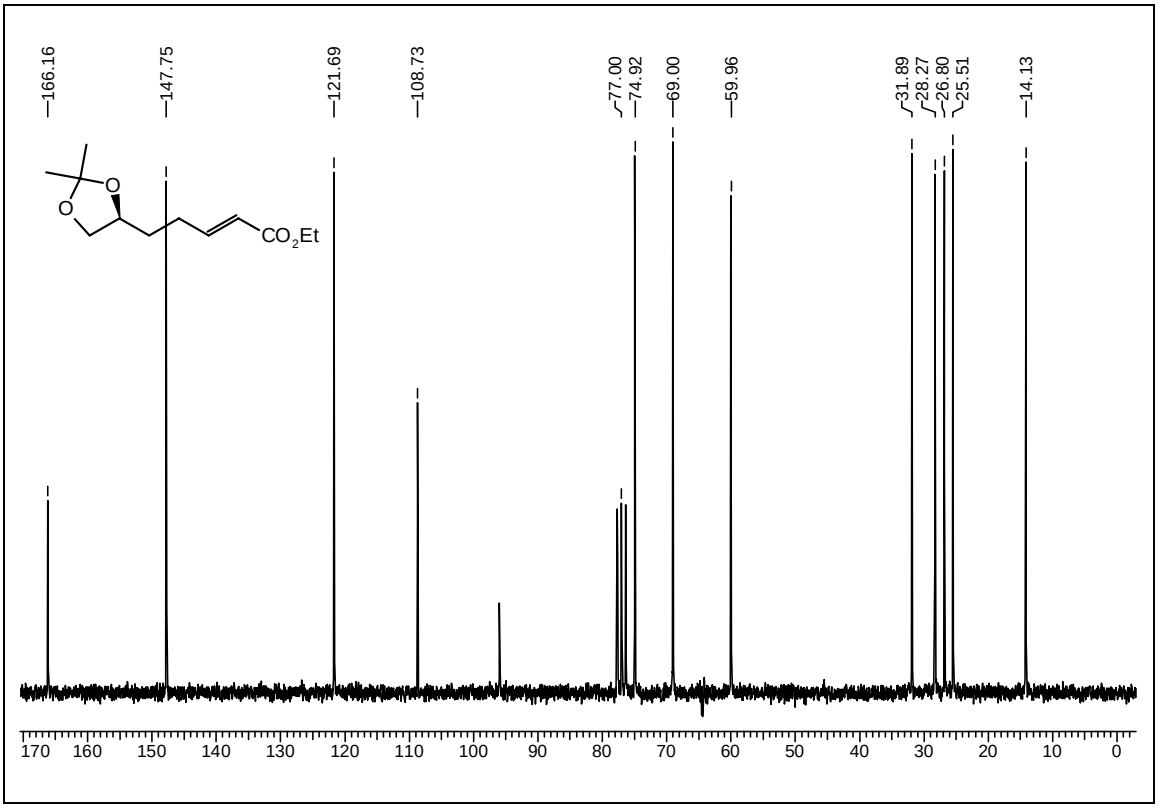
^{1}H NMR spectrum of compound 21 in $CDCl_3$



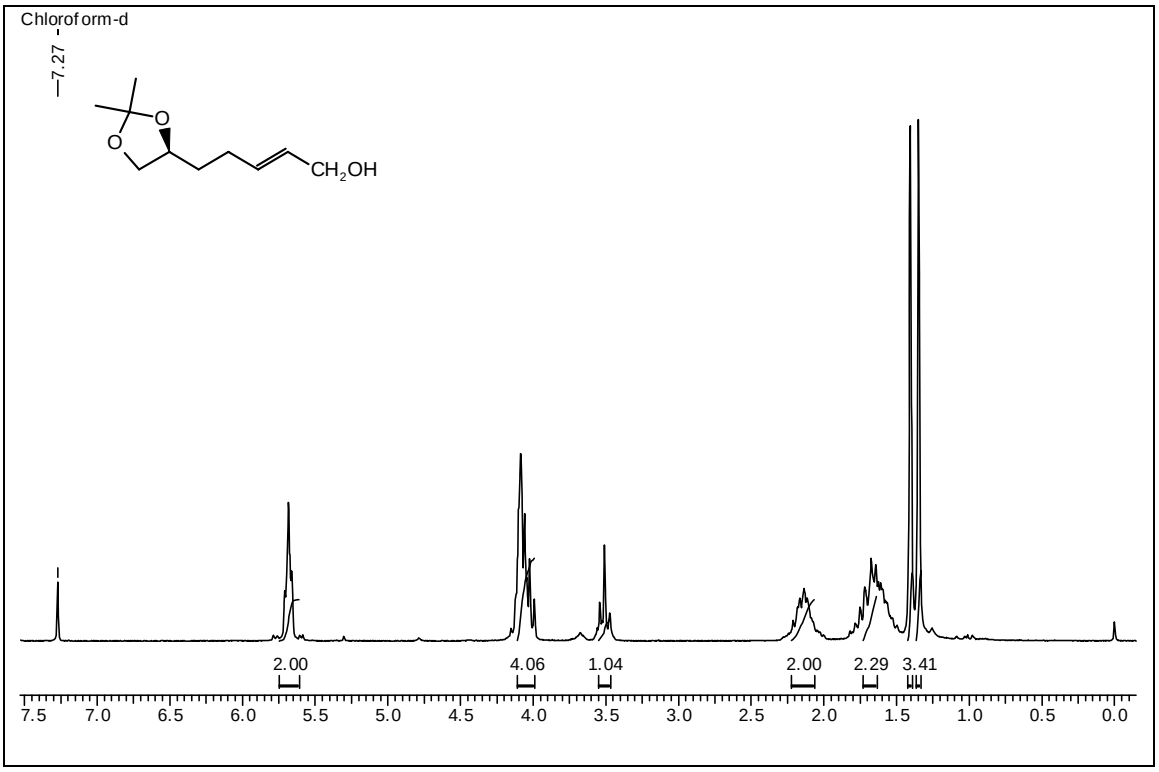
^{13}C NMR spectrum of compound 21 in $CDCl_3$



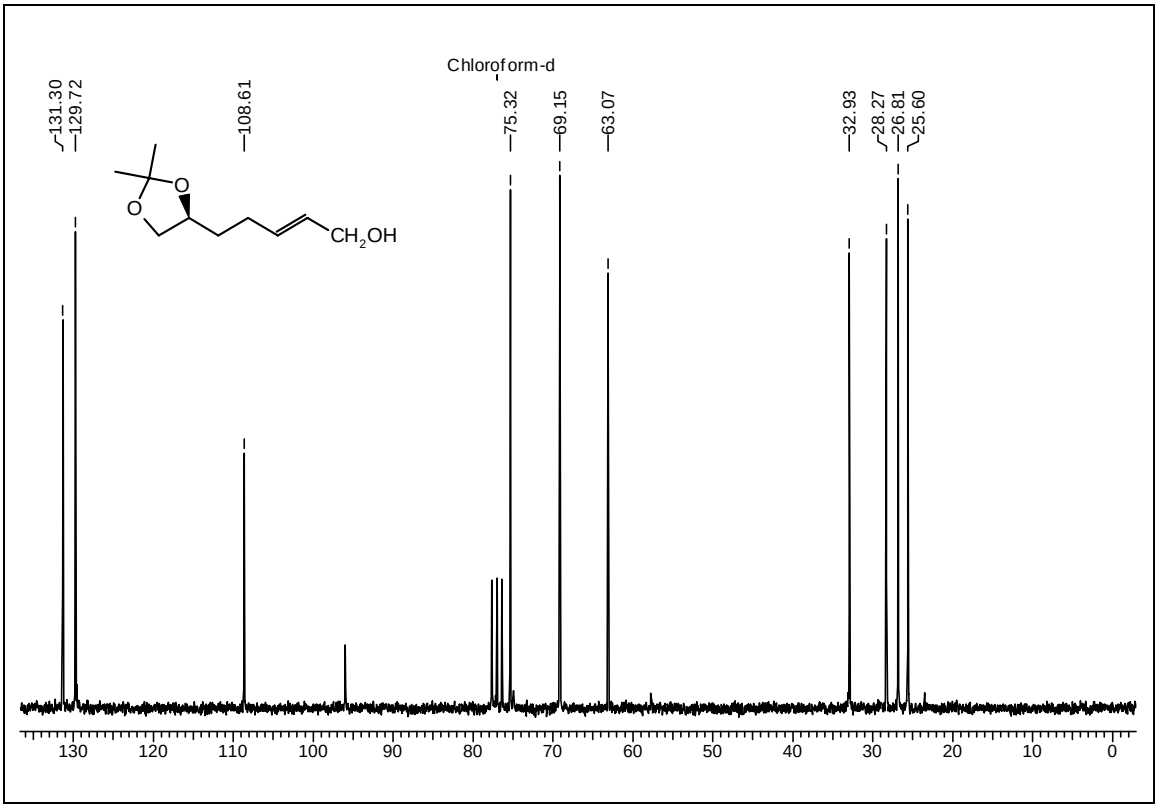
^{1}H NMR spectrum of compound 23 in $CDCl_3$



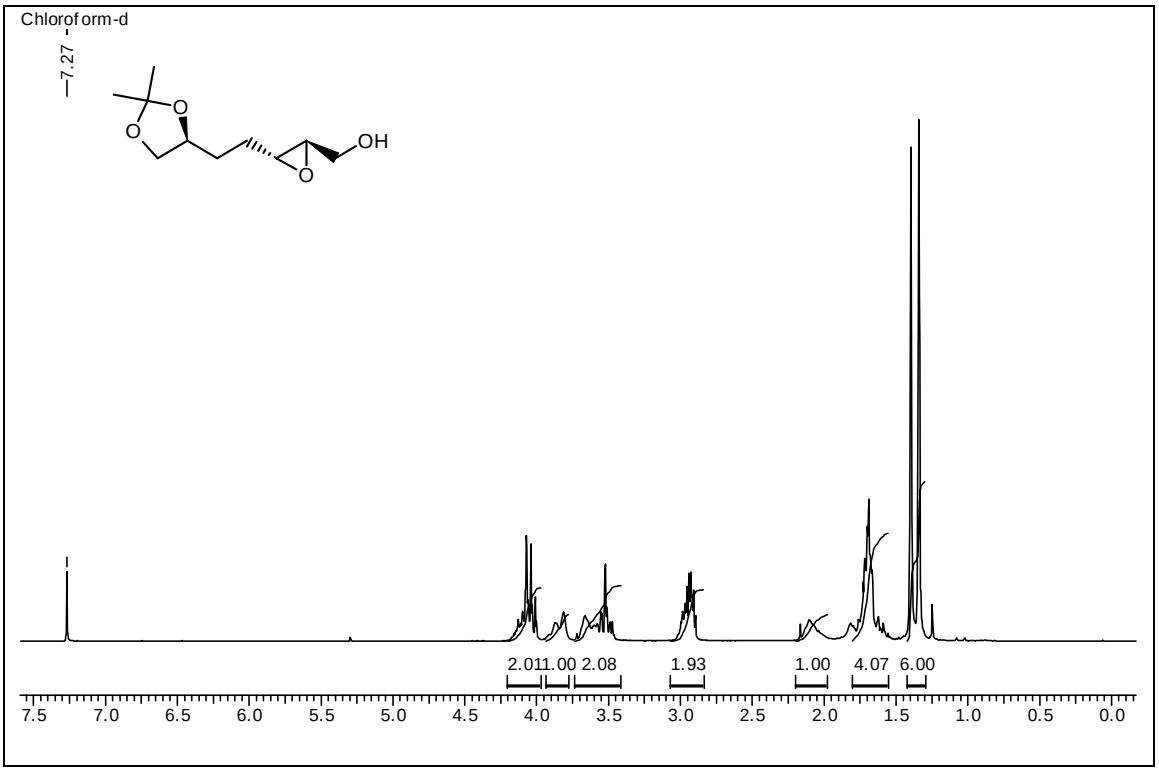
^{13}C NMR spectrum of compound 23 in $CDCl_3$



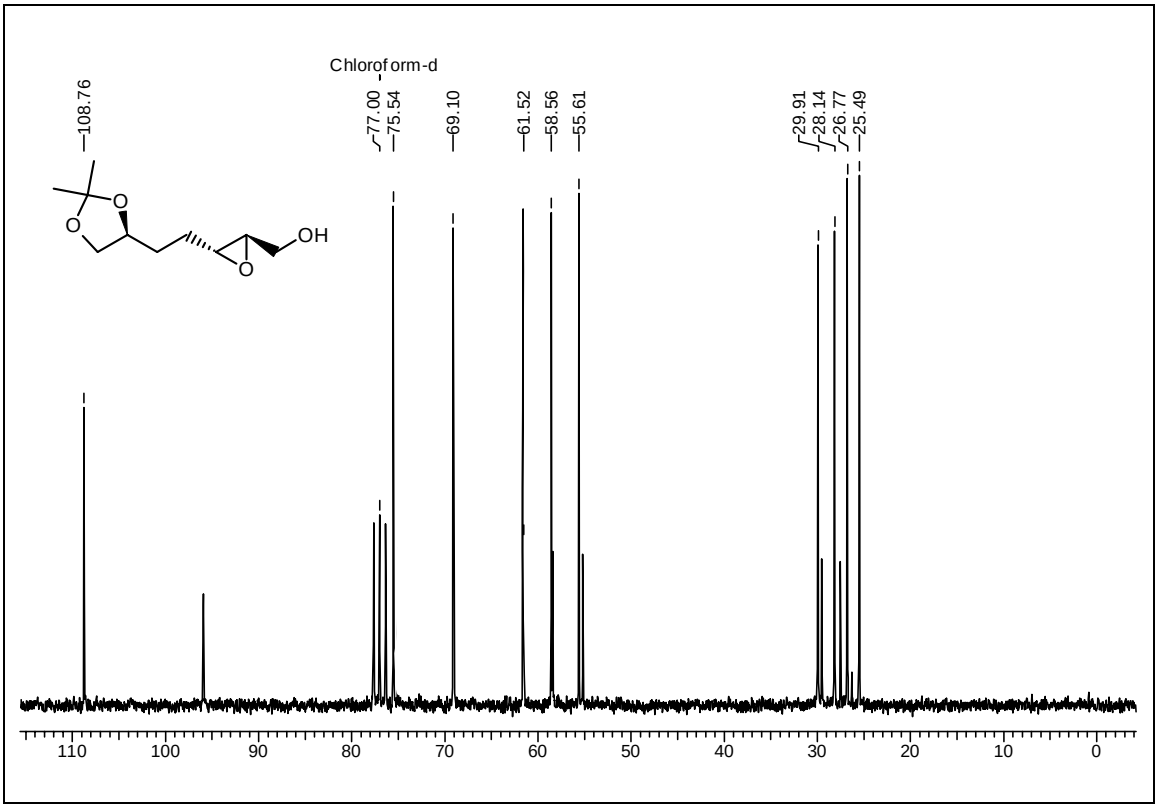
^{1}H NMR spectrum of compound 12 in $CDCl_3$



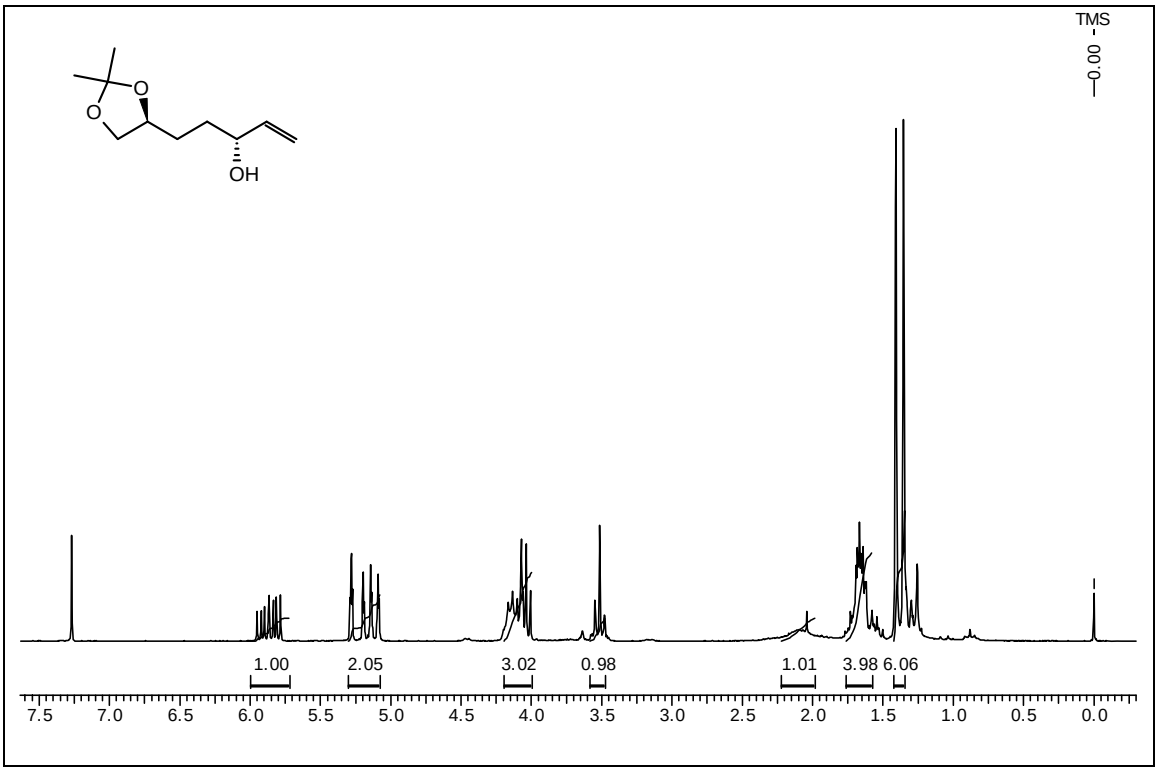
^{13}C NMR spectrum of compound 12 in $CDCl_3$



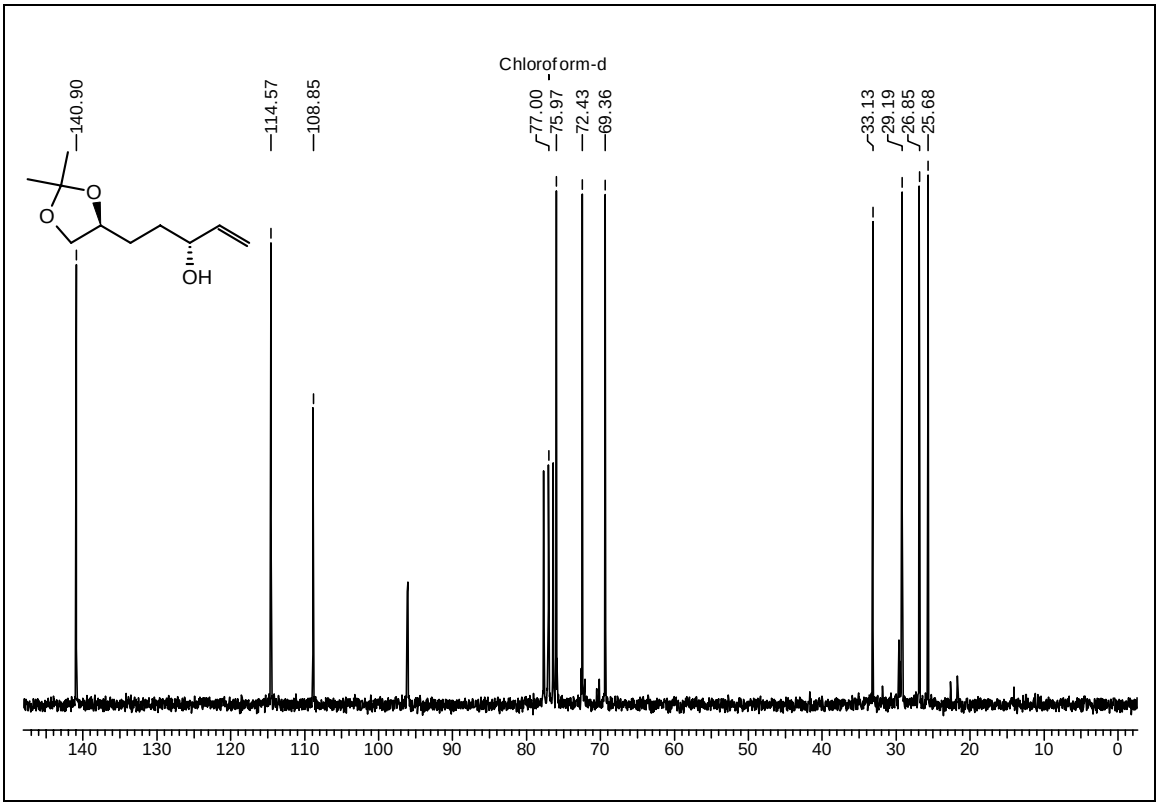
^{1}H NMR spectrum of compound 11 in $CDCl_3$



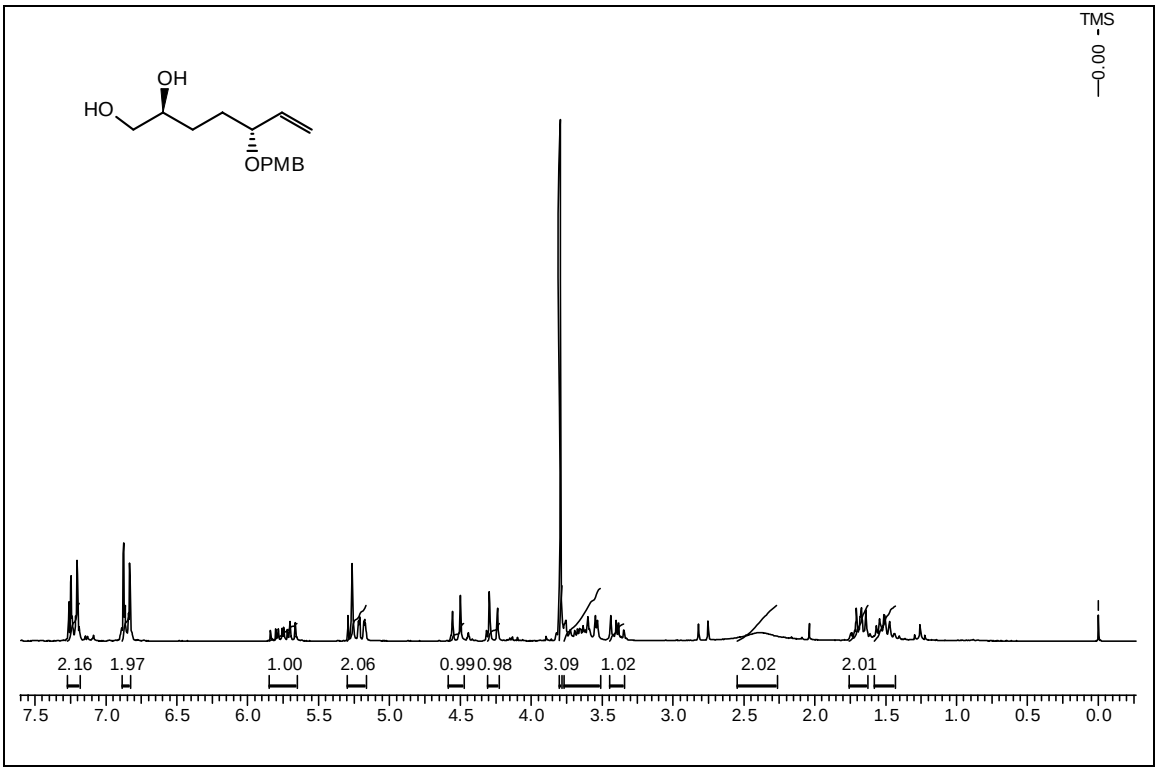
^{13}C NMR spectrum of compound 11 in $CDCl_3$



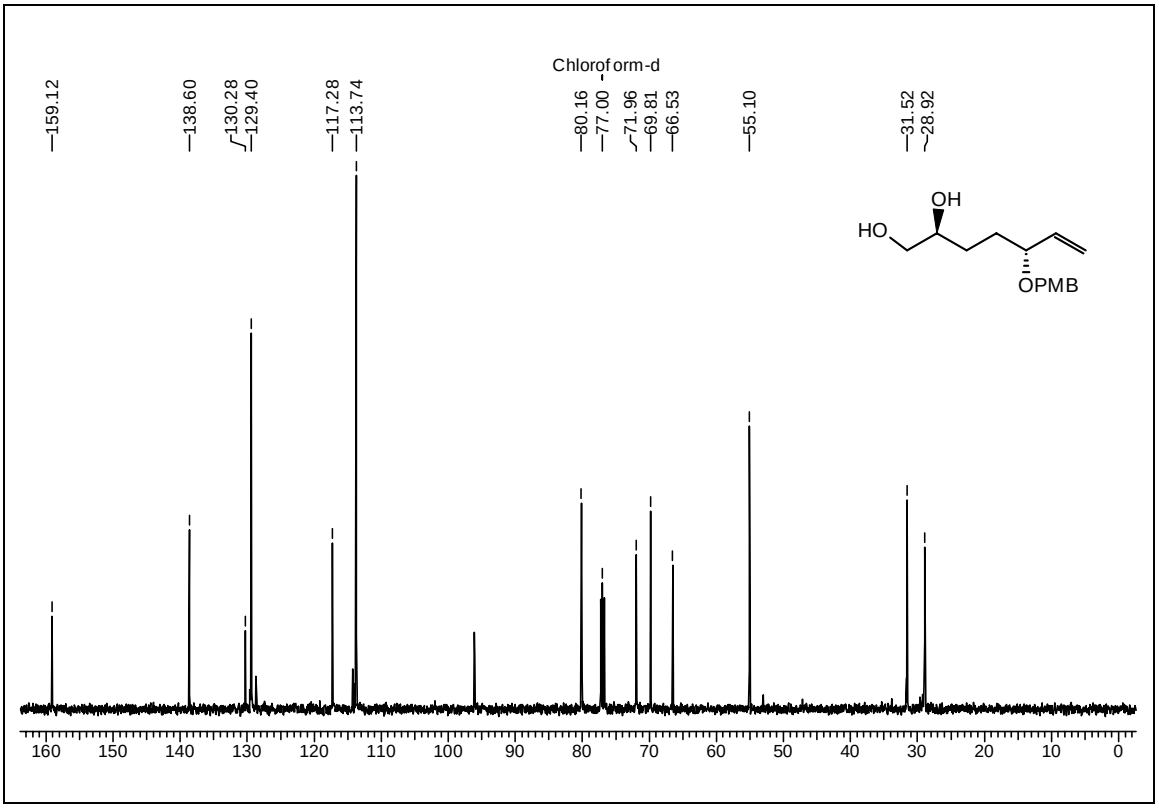
^{1}H NMR spectrum of compound 30 in $CDCl_3$



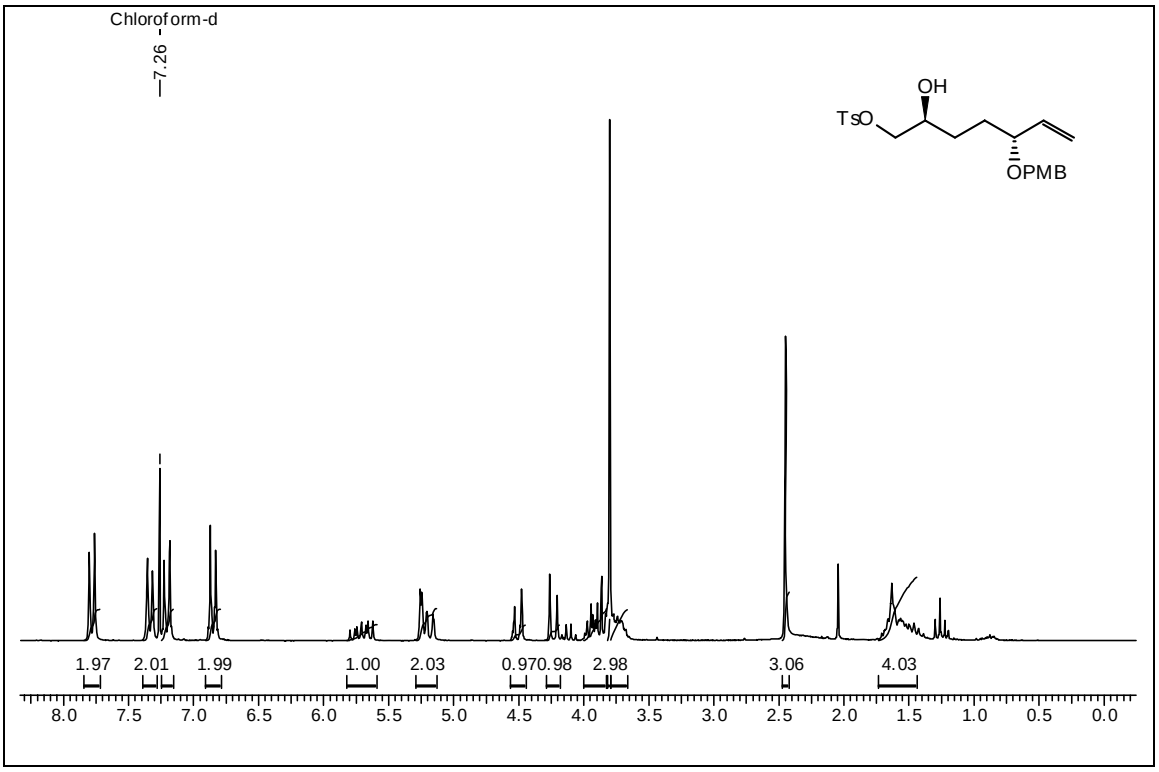
^{13}C NMR spectrum of compound 30 in $CDCl_3$



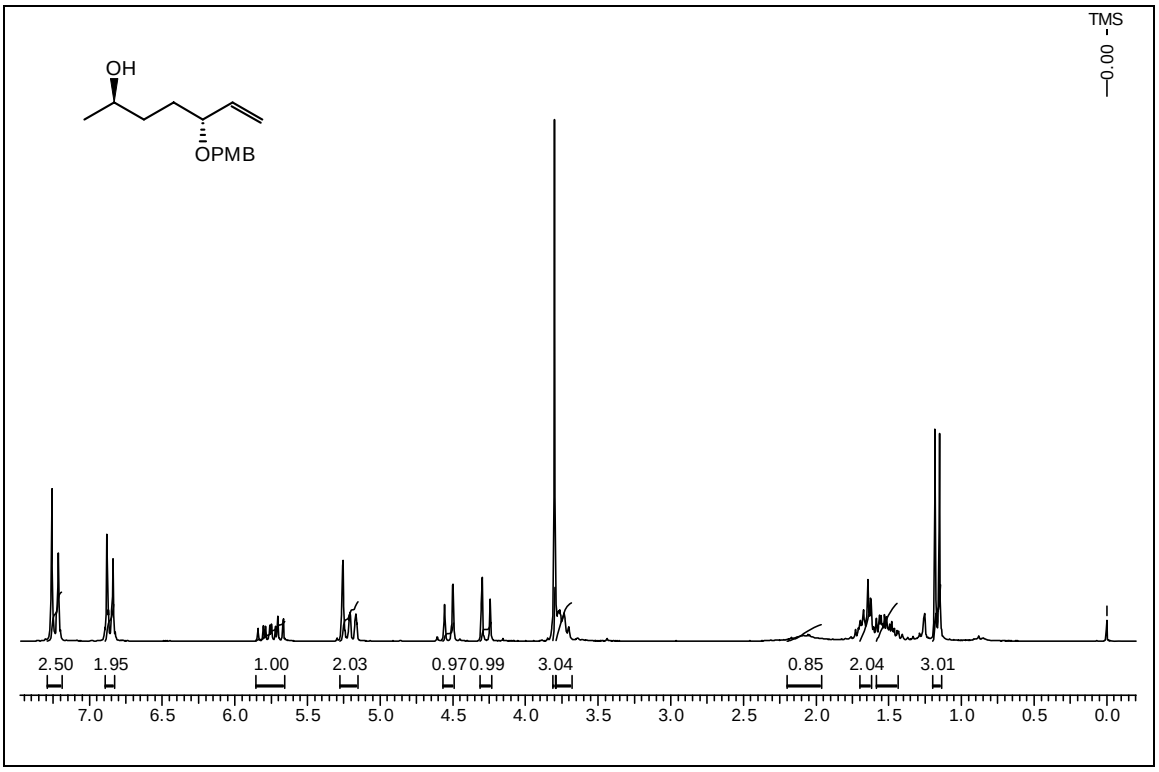
^{1}H NMR spectrum of compound 32 in $CDCl_3$



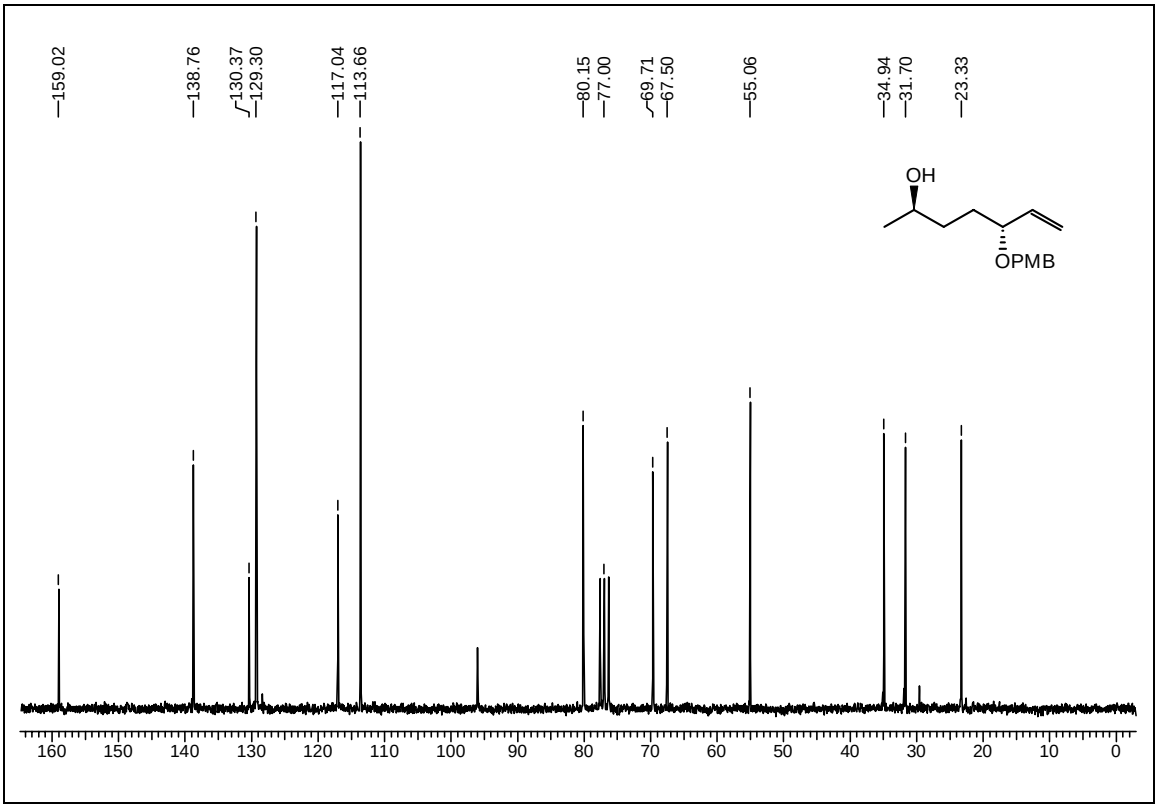
^{13}C NMR spectrum of compound 32 in $CDCl_3$



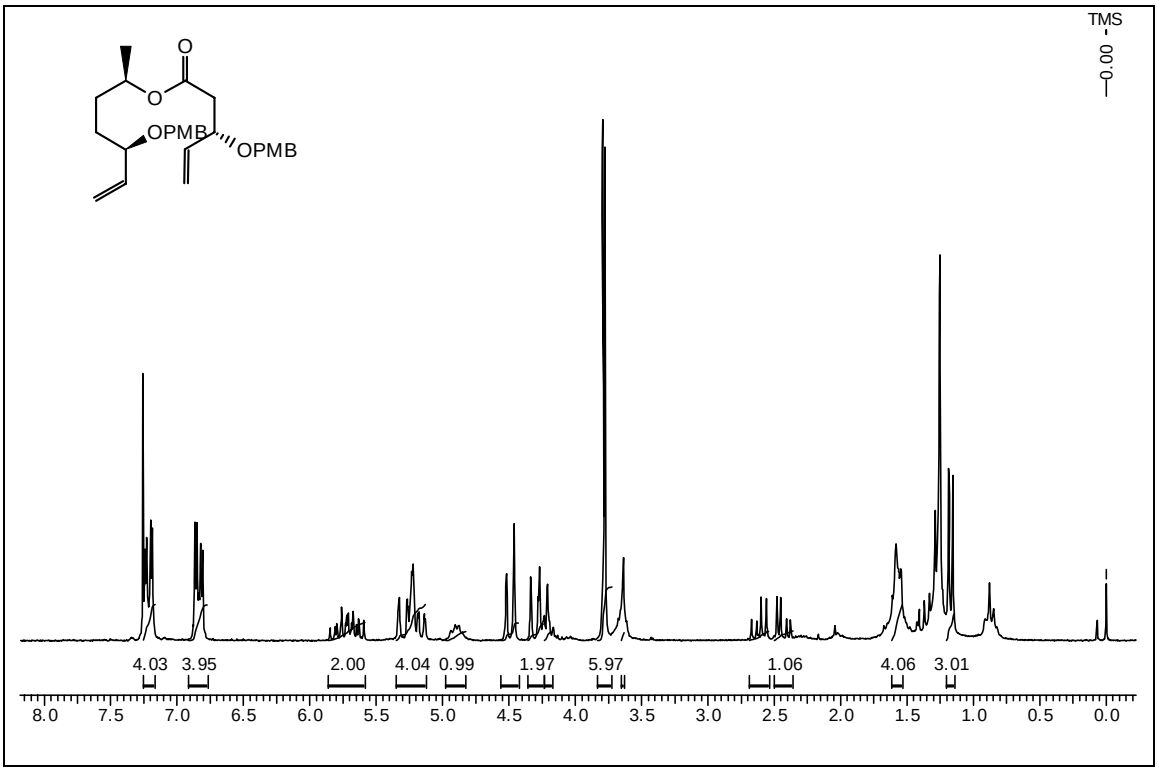
^{1}H NMR spectrum of compound 33 in $CDCl_3$



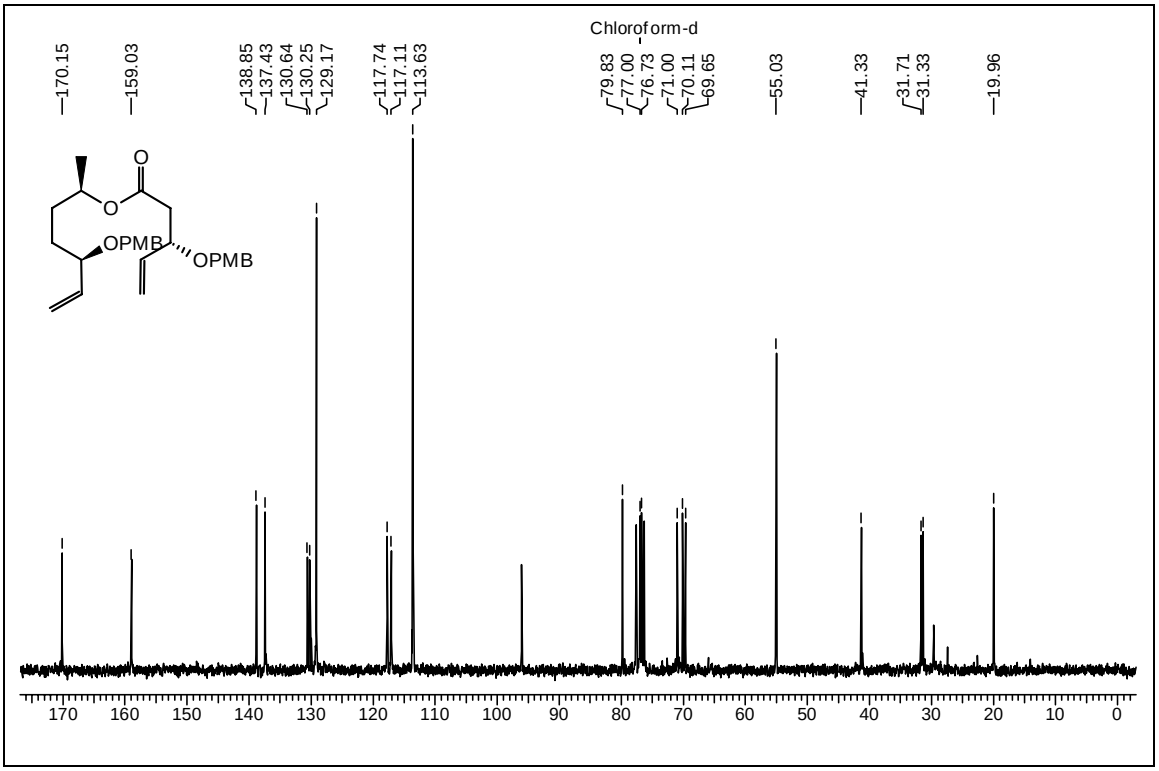
^{1}H NMR spectrum of compound 10 in $CDCl_3$



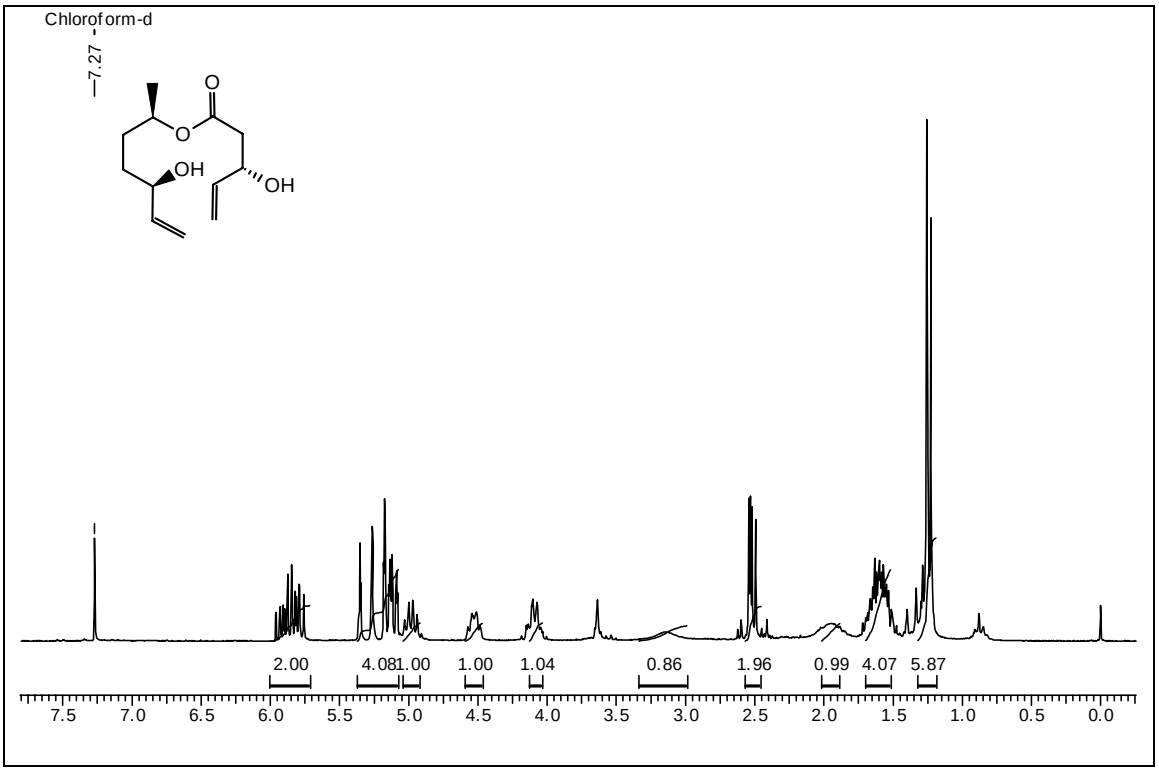
^{13}C NMR spectrum of compound 10 in $CDCl_3$



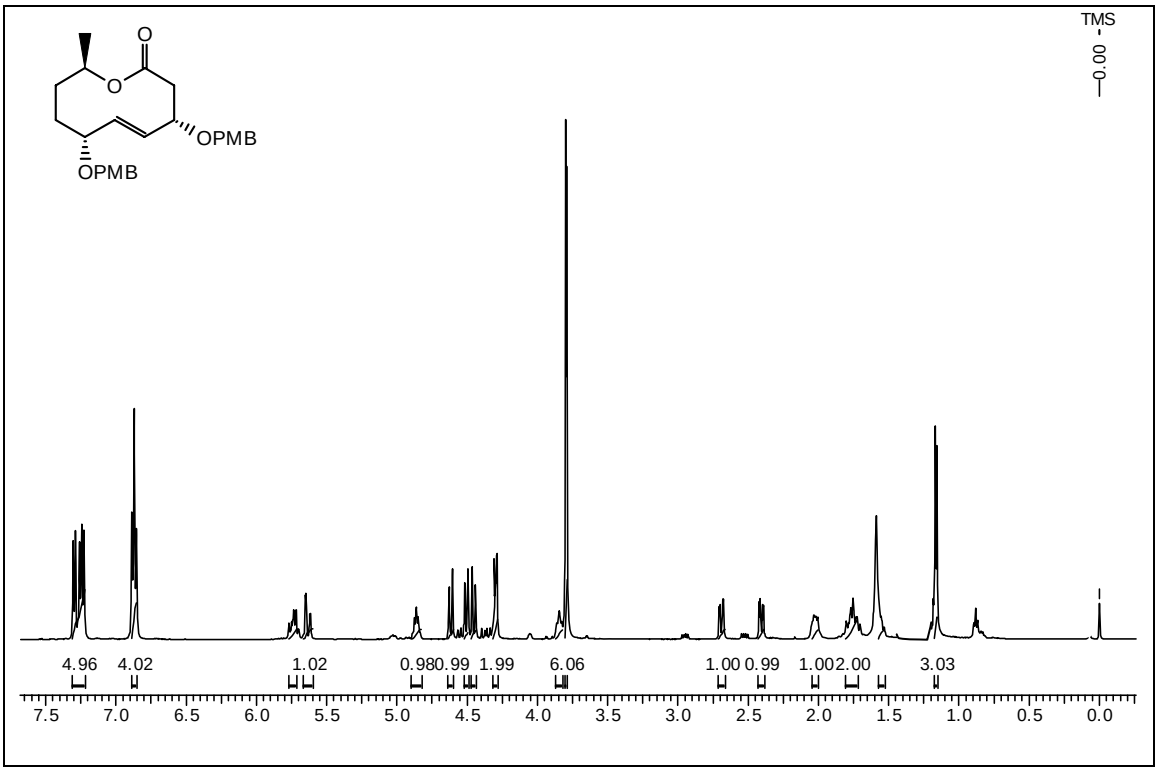
^{1}H NMR spectrum of compound 5 in $CDCl_3$



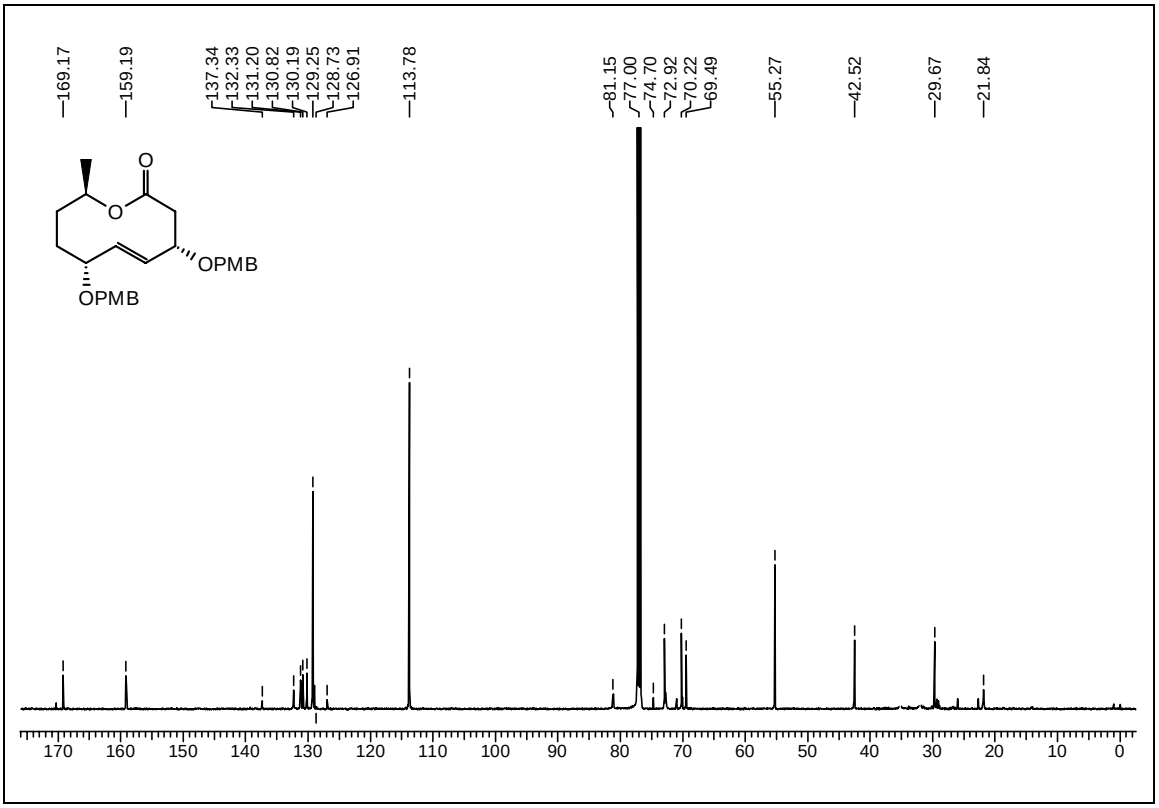
^{13}C NMR spectrum of compound 5 in $CDCl_3$



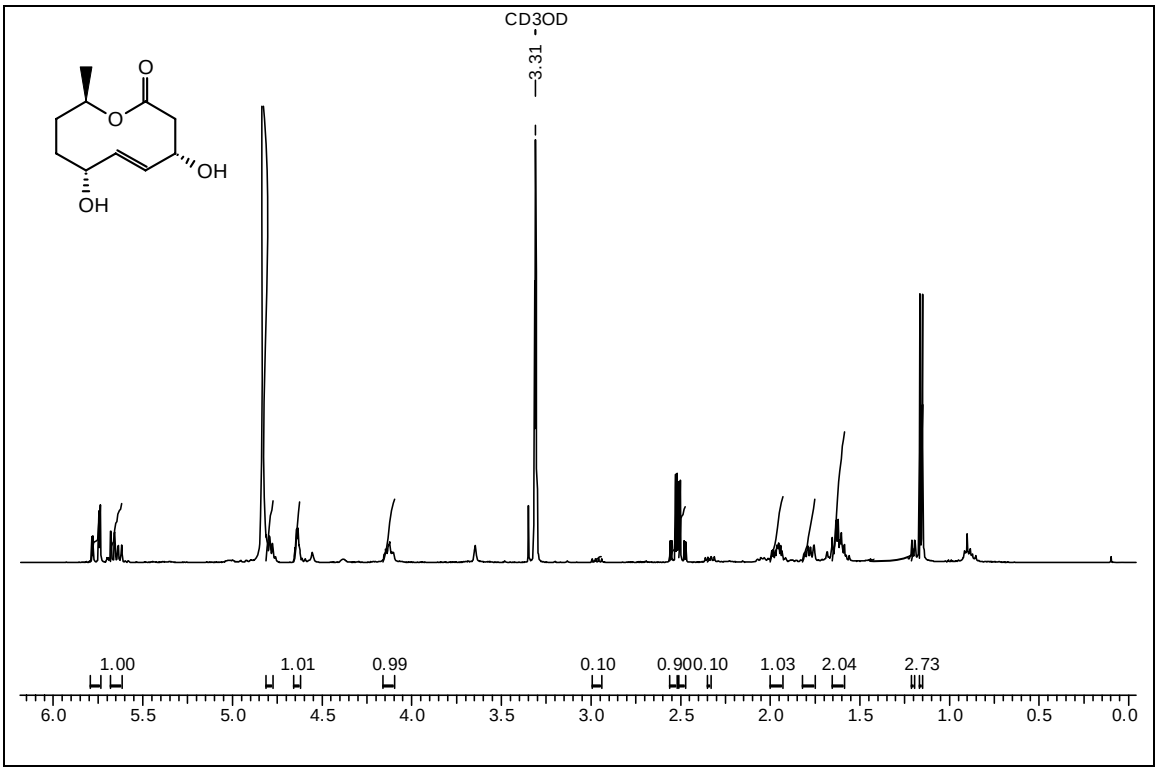
^{1}H NMR spectrum of compound 4 in $CDCl_3$



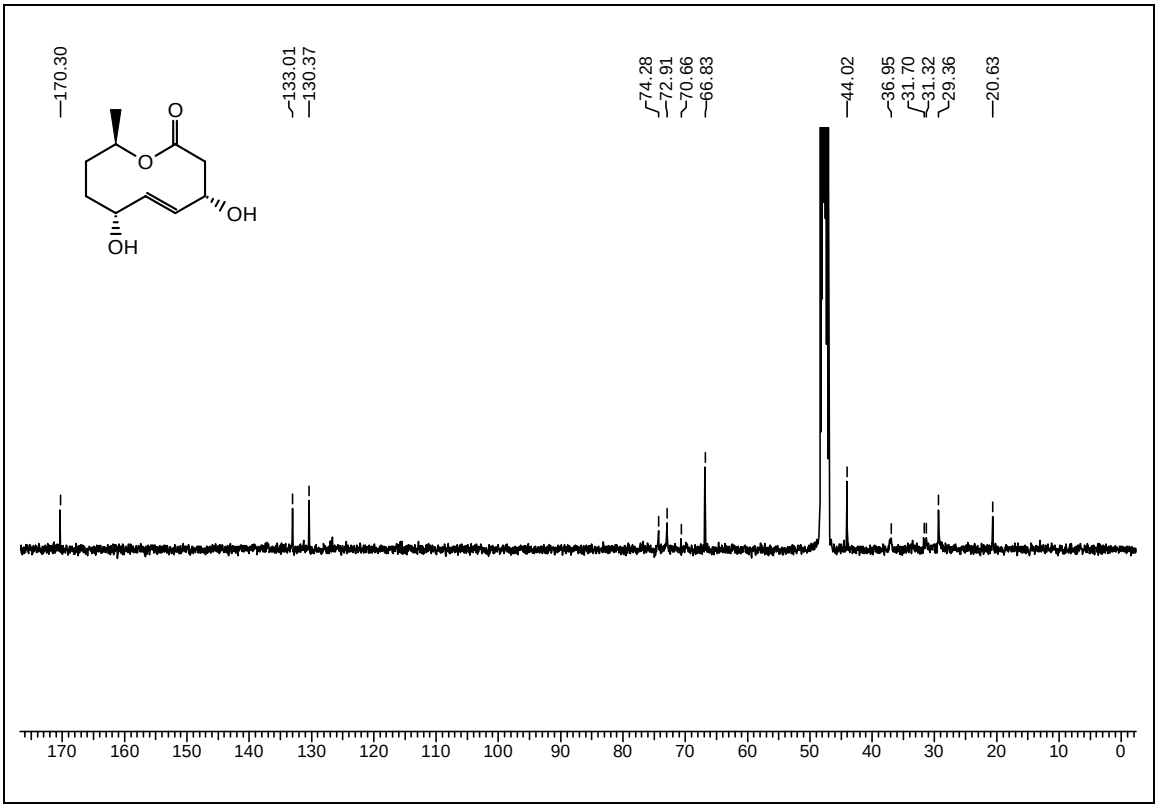
^{1}H NMR spectrum of compound 3 in $CDCl_3$



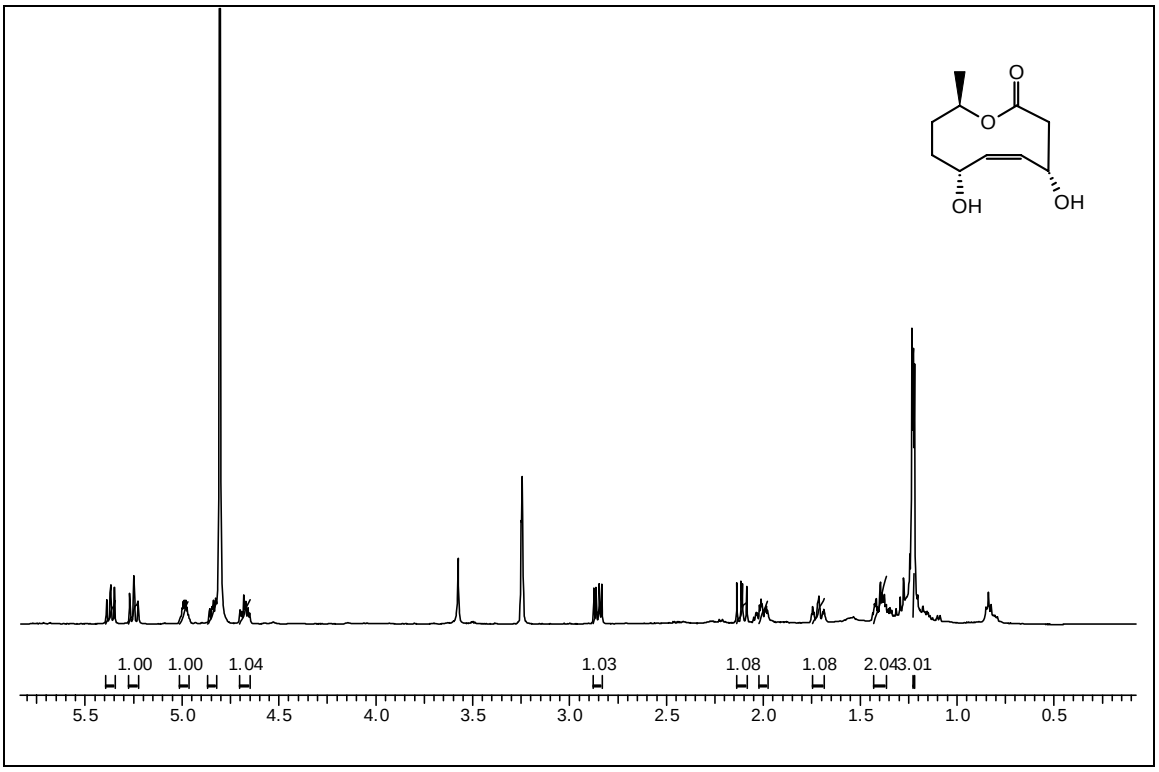
^{13}C NMR spectrum of compound 3 in $CDCl_3$



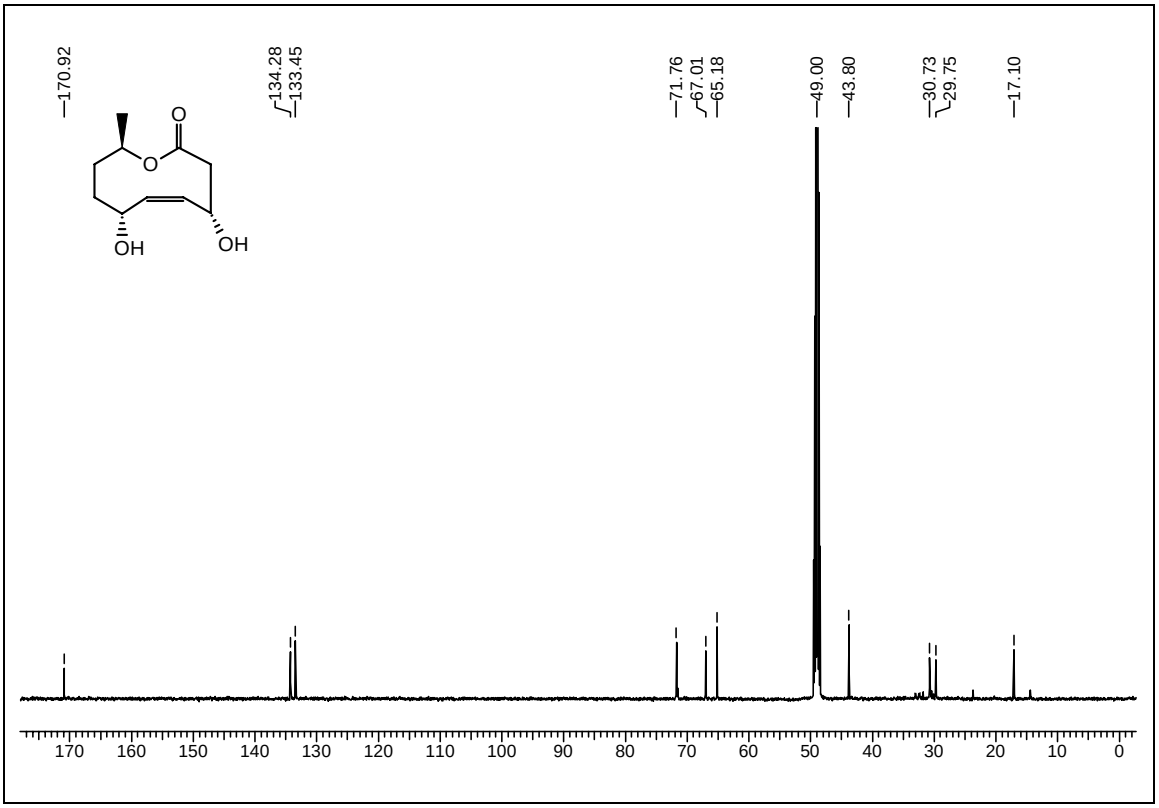
^{1}H NMR spectrum of compound 1 in CD_3OD



^{13}C NMR spectrum of compound 1 in CD_3OD



^{1}H NMR spectrum of compound 2 in CD_3OD



^{13}C NMR spectrum of compound 2 in CD_3OD

CHAPTER-I

Section B

Synthesis of Decarestrictine C_2 by RCM

PRESENT WORK

Present Work

In 1992 a joint group of Hoechst AG and the University of Gottingen reported[84] the isolation of a family of 10-membered lactones, named decarestrictines A-D. Decarestrictines are secondary metabolites; the first representatives of a new class of fungal metabolites isolated from cultures of *Penicillium simplicissimum* and *P. corylophilum*. Subsequent research by the same group on these cultures led to the further discovery of decarestrictine E-M as minor component of this class of fungal metabolites.[85] These metabolites revealed potent inhibitory effects on cholesterol biosynthesis in cell line tests, via sodium acetate incorporation into cholesterol, with HEP-G2 liver cells. These appeared to be more selective, in that no other effects such as antibacterial, antifungal or antiviral activities were discernible.

Decarestrictines are novel 10-membered lactones structurally related to each other by their physio-chemical properties. A ten-membered lactone ring with an exocyclic methyl group constitutes the typical structural element. This interesting biological activity of decarestrictine has been responsible for stimulating synthetic activity.

We have previously published the synthesis of nonenolide **1** (*epi*-6-decarestrictine C_1) via protecting group directed ring-closing metathesis (RCM) as the key step.[86] We undertook the task of making cyclic compounds through RCM reactions and generalizing the observed substrate-based selectivity. We initially planned to synthesize the Decarestrictine C. Earlier reports claimed the isolated decarestrictine C to consist of an inseparable mixture of C_1 and C_2 in a 1:1 ratio. Later, Kibayashi,. *et al* reported[87] the structure of decarestrictine C_2, based on the spectroscopic and X-ray crystallography analysis data (Figure-1).

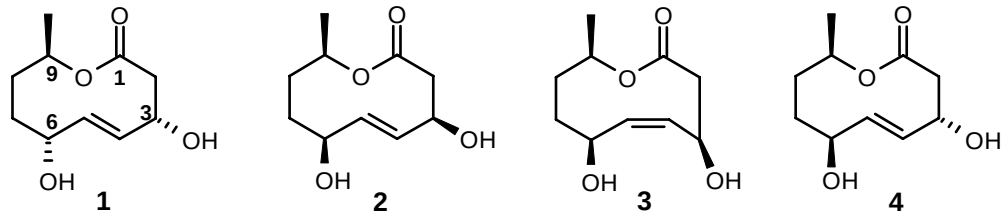
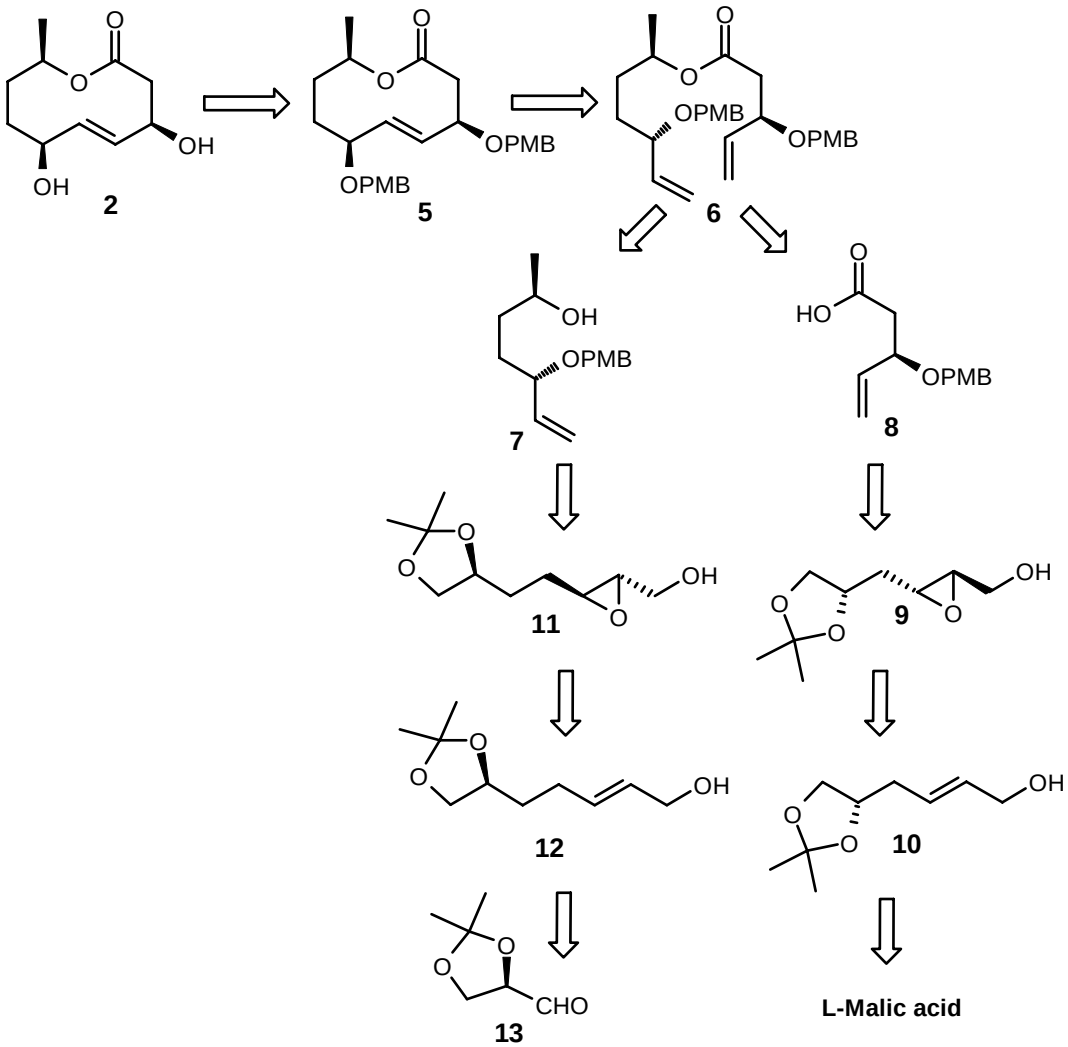


Figure-1

The retrosynthetic approach for decarestrictine C_2 (**2**) is outlined in Scheme-1**.** The macrolactonization step relies on a ring closing metathesis of a diolefinic ester that could be synthesized by Yamaguchi esterification. Strategic bond disconnection in ester (**6**) leads to alcohol (**7**) and acid (**8)** fragments.

The alcohol fragment (**7**) could be prepared via epoxy alcohol derived from ally alcohol (**12**) via a Sharpless Asymmetric Epoxidation using (+) DET as a chiral ligand.

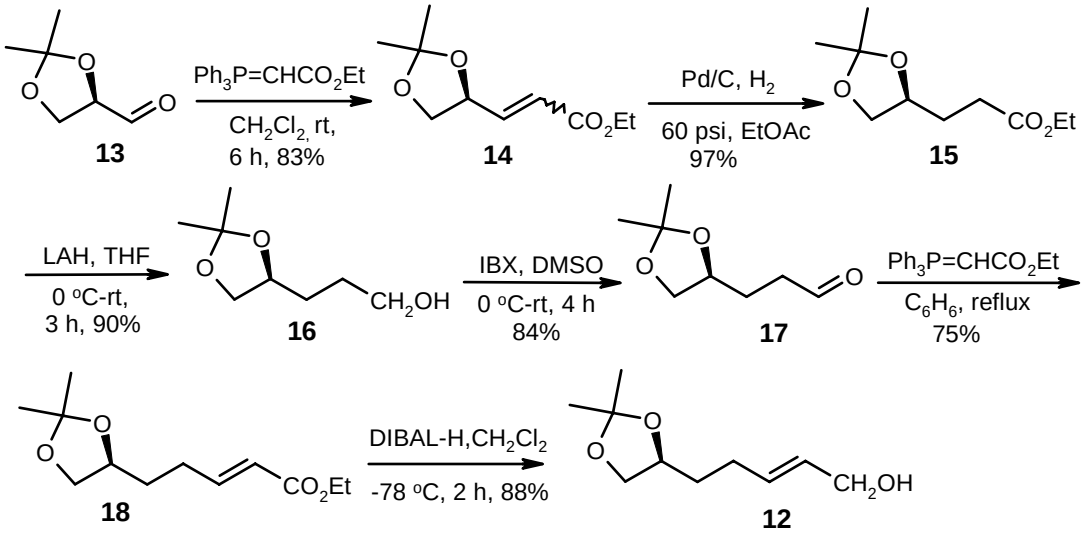
The acid fragment could be synthesized from epoxide (**9**) derived from allyl alcohol (**10**) by employing Sharpless asymmetric epoxidation with (–) DET as a chiral ligand as a key step (Scheme-1).



Scheme-1 Retrosynthesis of Decarestrictine C_2

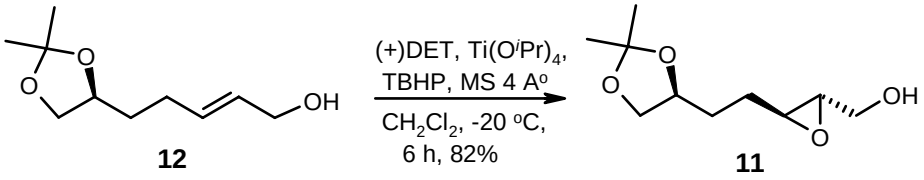
Synthesis of alcohol Fragment (7)

D-glyceraldehyde derivative **13** (synthesized from D-mannitol) was converted into allyl alcohol **12** in six steps by two carbons Wittig homologation (Scheme-2).



Scheme-2

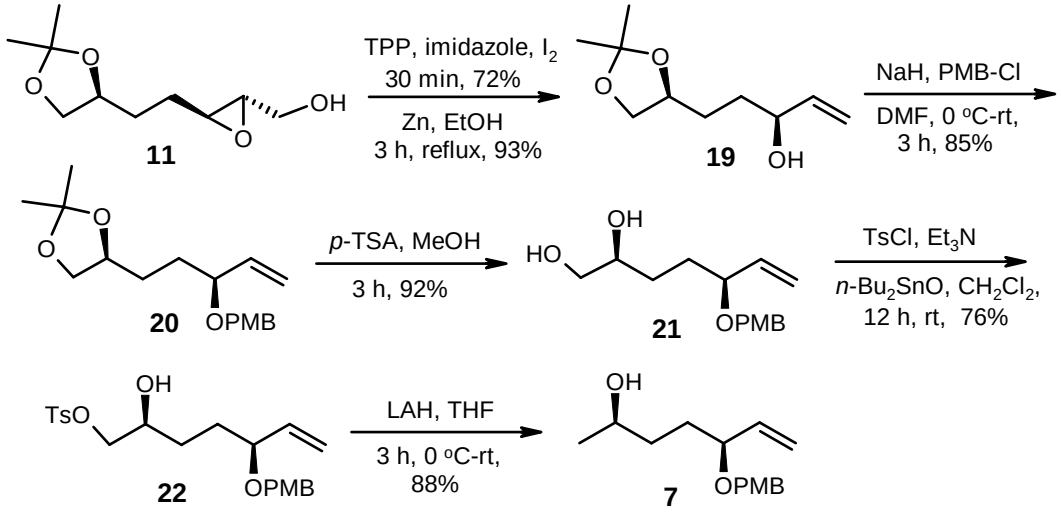
Generation of the chiral centre relevant to the target was achieved by employing Sharpless asymmetric epoxidation in a catalytic procedure. Thus, **12** was treated with (+) DET as chiral ligand, $Ti(O^iPr)_4$ and TBHP at −20 ^oC, in anhydrous CH_2Cl_2 in presence of freshly activated $4A^o$ MS powder to furnish (2*S*,3*S*)-epoxide **11** in 82% yield. The NMR spectrum, elemental analysis and specific rotation data were in good agreement with the reported values (Scheme-3).



Scheme-3

Next, epoxide (**11**) was converted to alcohol (**7**) sequentially in six-steps. Deoxygenation of epoxide **11** to terminal alkenic alcohol **19** in high regioselectivity was achieved in two steps via epoxy iodide. The terminal alkenic alcohol was protected by *p*-methoxy benzyl (PMB) ether to obtain **20** in 85% yield. Then, isopropylidene group of **20** was hydrolyzed with *p*-TSA in methanol to furnish diol **21** in 92% yield. To secure the alcohol fragment **7**, we selectively mono protected the primary hydroxyl group in **21** with

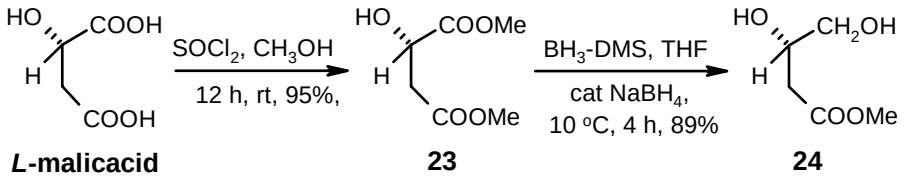
a tosyl group to give **22** in 76% yield and subsequently treated **22** with excess LAH to provide requisite alcohol **7** in 88% yield. The specific rotation {$[\alpha]_D^{25}$ –43.8 (*c* 1.2, $CHCl_3$)}, NMR spectrum and elemental analysis data of **6** were in good agreement with reported values (scheme-4).



Scheme-4

Syntheses of Acid fragment (8)

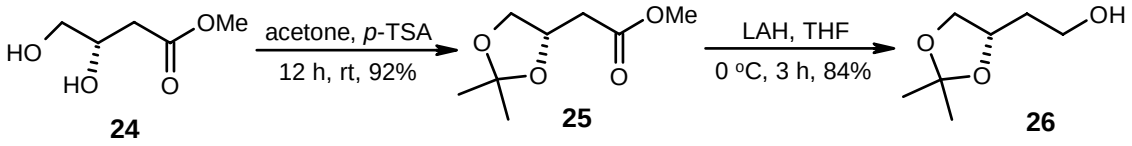
Our first objective was to obtain the key intermediate allyl alcohol **10**. L-malic acid was converted to dimethyl malate **(23)** by treatment with $SOCl_2$ in methanol for 24 h, at room temperature. ^{1}H NMR spectrum showed resonances at 3.71 ppm (s, 3H) and 3.81 ppm (s, 3H) corresponding to ester. The ester group adjacent to the hydroxyl group was reduced with borane-dimethyl sulfide complex (BH_3-DMS) and catalytic sodium borohydride ($NaBH_4$) in anhydrous THF to furnish diol **24** in 89% yield (scheme-5).



Scheme-5

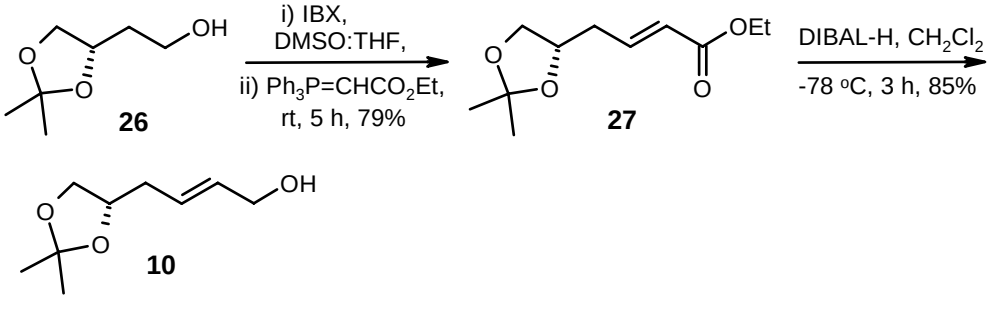
Next, the ketalization of diol **24** in acidic medium was achieved **25** in 92% yield by the reaction with acetone and *p*-toulenesulfonic acid. ^{1}H NMR spectrum showed resonances at δ 1.35 ppm (s, 3H) and 1.40 ppm (s, 3H)) due to -CH_3 groups of

isopropylidene moiety; corresponding ^{13}C NMR spectrum showed resonances at 25.24 ppm, and 26.62 ppm. The ester **25** was reduced with lithium aluminium hydride (LAH) in dry THF at 0 ^{o}C to room temperature for 3 h to give alcohol **26** in 84% yield. Broad IR absorption at 3455 cm^{-1} corresponds to hydroxyl group (Scheme-6).



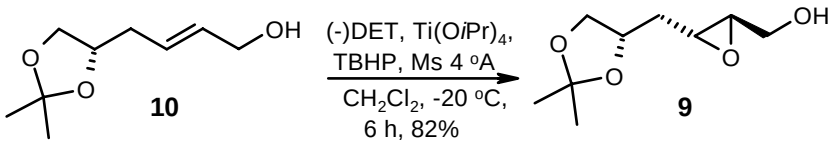
Scheme-6

To synthesize the key intermediate ally alcohol **10**, the primary hydroxyl group of **26** was oxidized with IBX in DMSO/THF mixture and the mixture was stirred for 4 h to afford aldehyde. The reaction mixture was treated with (carboethoxymethylene) triphenylphosphorane for 5 h, at room temperature to furnish **27** as a mixture of *cis* and *trans* isomers in ratio of 1:9 as judged by TLC. They were separated by column chromatography and the major *trans* isomer was obtained in 79% yield. The proton NMR spectrum showed new resonances of olefinic protons at 5.90 ppm and 6.90 ppm and showed characteristic coupling constant (J = 15.7 Hz) for trans olefin. The ^{13}C NMR spectrum displayed olefin carbons at 123.9 ppm, 143.63 ppm and 166.0 ppm corresponding to ester groups. The structure of **27** was further conformed by IR spectrum and elemental analysis data. Hydride reduction of **27** with DIBAL-H in anhydrous dichloromethane at -78 ^{o}C for 3 h afforded allyl alcohol **10** in 85% yield. In proton NMR spectrum, resonances of olefinic protons moved upfield and were observed between the regions at 5.55-5.77 ppm as a multiplet. IR spectrum showed the broad band at 3455 cm^{-1} corresponding to hydroxyl group (scheme-7).



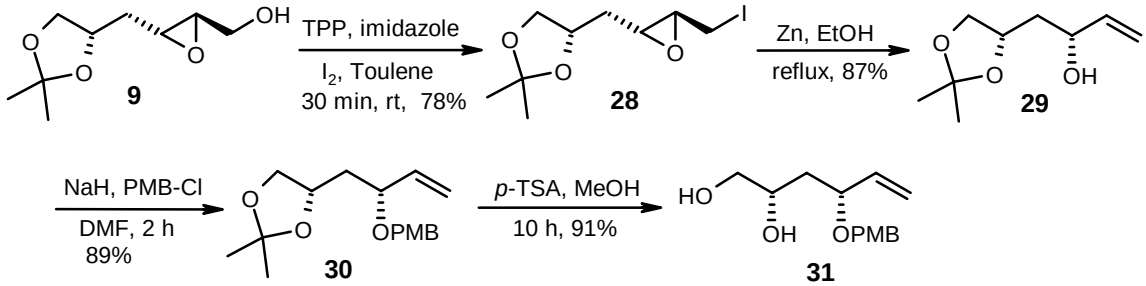
Scheme-7

Generation of chiral centre relevant to target, was obtained by employing Sharpless asymmetric epoxidation in a catalytic method. Thus, **10** was treated with $Ti(O^iPr)_4$, D-(–)-DET as a chiral ligand and *t*-butyl hydrogen peroxide (TBHP) in anhydrous CH_2Cl_2 in presence of freshly activated 4A^o MS powder to afford (2*R*, 3*R*)-epoxide **9** in 82% yield. The ^{1}H NMR spectrum of **9** showed new resonances attributed to methine protons of epoxide at δ 3.01-3.65 (2H) ppm as a multiplet. The ^{13}C NMR spectrum showed the appearance of new resonances at δ 52.52 and 57.75 ppm corresponding to epoxy carbons. In addition, the elemental analysis data also supported the formation of **9** (scheme-8).



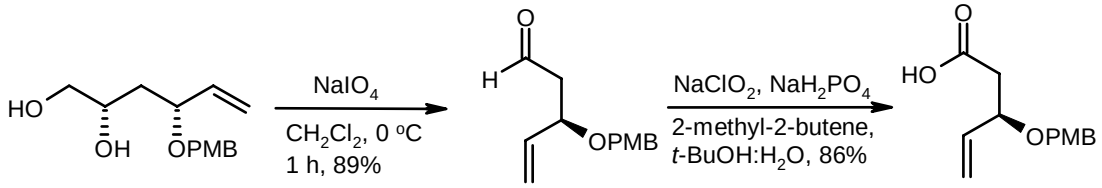
Scheme-8

Next, the epoxide **9** was converted to diol **31** sequentially in four steps in 55% overall yield (scheme-9).



Scheme-9

In order to secure the acid fragment **8**, the diol **31** was oxidatively cleaved using $NaIO_4$ support on silica gel to afford aldehyde **32** in 89% yield; this was subsequently

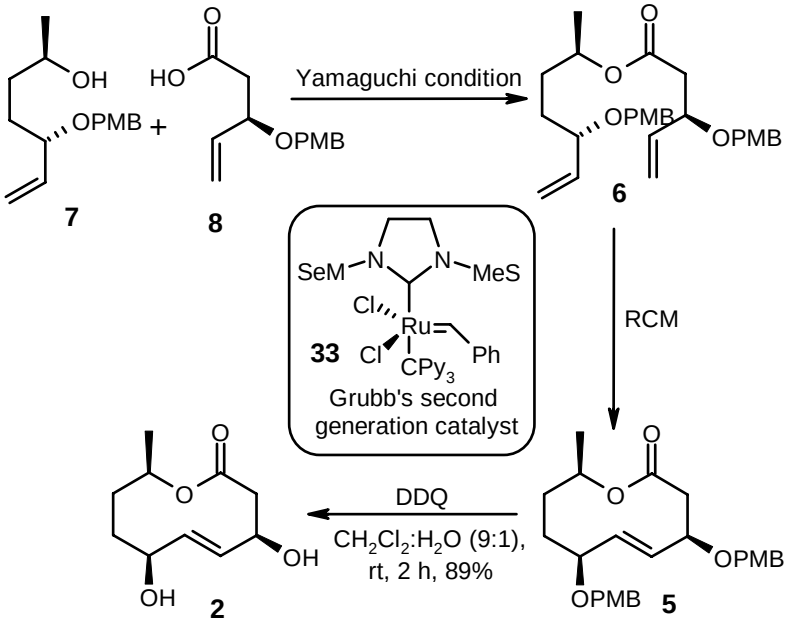


Scheme-10

transformed to carboxylic acid via Pinnick oxidation ($NaClO_2$ in presence of NaH_2PO_4 and 2-methyl-2-butene as a scavenger) in 86% yield. In proton NMR spectrum, resonances of -CH_2 group protons attached to acid showed at δ 2.62 ppm correspondingly; the ^{13}C NMR spectrum of **8** displayed carbon of acid at 176.2 ppm (scheme-10).

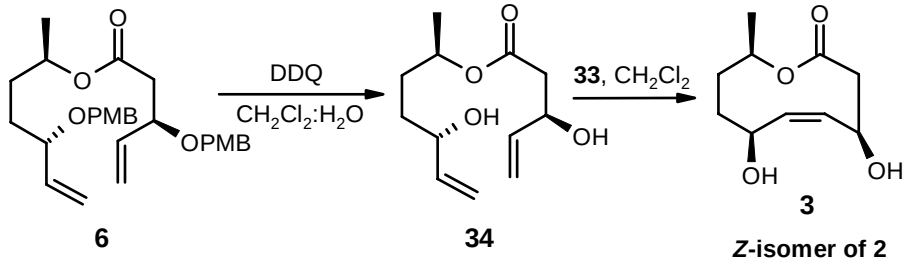
Coupling between acid and alcohol

Two coupling partners in hand, our next achievement was to couple the two fragments **7** and **8** under Yamaguchi esterification conditions to furnish diolefinic ester **6** in 84% yield. This is the key precursor for the RCM reaction. Treatment of **5** with Grubbs second generation catalyst as before in dry, degassed CH_2Cl_2 under reflux for 8 h provided the desired 10-membered lactone (**5**) *E*-isomer as the exclusively product in 78% yield. Deprotection of the PMB groups was uneventful and yielded the natural product decarestrictine C_2 (**2**) in 89% yield. The geometry of the formed double bond in the product was unambiguously assigned by detection of the olefinic J_{trans} coupling constant (15.9 Hz, between the protons at δ 5.45 and 5.73 ppm, respectively). The spectroscopic and specific rotation data of the synthetic decarestrictine C_2 were in excellent accord with reported values of Kibayashi, *et al.* {$[\alpha]_D^{27}$ –35.0 (*c* 0.66, MeOH); lit. $[\alpha]_D^{27}$ –38.0 (*c* 0.66, MeOH)} (Scheme-11).



Scheme-11

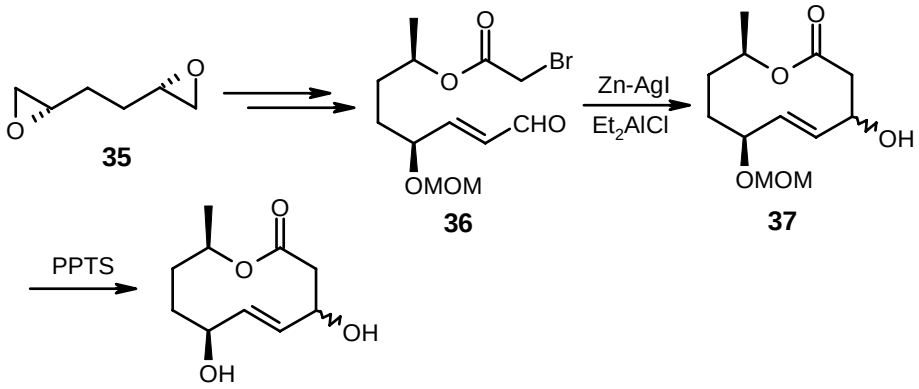
We carried out the RCM reaction with diol **34** (after deprotection of the PMB groups of **6)** with Grubbs' second generation catalyst (10 mol%) to afford the 10-membered lactone (**3**) *Z*-isomer as the product in 74% yield. The geometry of the double bond in the major product was unequivocally assigned by detection of the olefinic protons at δ 5.38 ppm and 5.47 ppm (J_{cis} = 11.25 Hz) (Scheme-12).



Scheme-12

Kibayashi Approach:

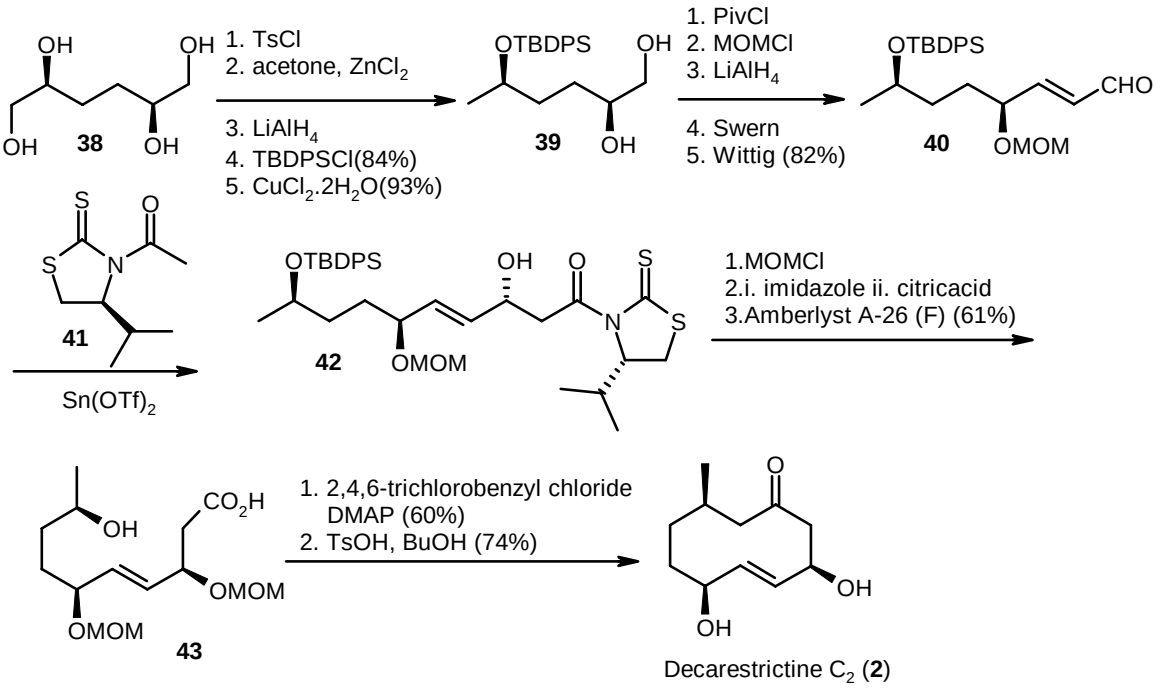
In 1993 Kibayashi reported the synthesis of decarestrictine C_1/C_2 (**4/2**) as an inseparable 1:1 epimeric mixture at C-3 starting with (*S*,*S*)-diepoxide **35** (Scheme-13). The synthetic material was found to be identical with a diastereomeric mixture of natural decarestrictine C_1/C_2 (**4/2**).



Scheme-13

In 2000 Kibayashi published the enantioselective synthesis of the proposed structure of (–)-decarestrictine C_2 (**2**) using (2*S*,5*S*)-1,2,5,6-hexanetetrol (**38**) as a C_2-symmetric chiral synthon, in which the diastereoselective aldol–type reaction of a tin(II) enolate of 3-acetyl-(4*S*)-isopropyl-1,3-thiazolidine-2-thione with α,β-unsaturated aldehyde **40** was used as a key step. Removal of the chiral auxiliary and deprotection of

the TBDPS group afforded the **43**. Subsequent lactonization of **43** by the Yamaguchi method afforded 10-membered lactone in 60% yield. Deprotection of the MOM group furnished decarestrictine C_2 (**2**) (Scheme-14).



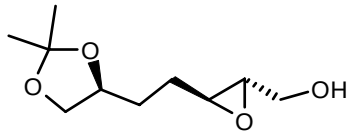
Scheme-14

Conclusion:

We have successfully synthesized decarestrictine C_2 (reported by Kibayashi, *et al*) by employing RCM as the final step.

EXPERIMENTAL SECTION

((2*S*,3*S*)-3-(2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)oxiran-2-yl)methanol (11)



To a stirred and cooled (–20 ^{o}C) suspension of molecular sieves (4 A^{o}, 2.0 g) in CH_2Cl_2 (50 mL) under N_2 atmosphere, (+) DET (2.0 g, 9.7 mmol) in CH_2Cl_2 (25 mL), $Ti(O^iPr)_4$ (2.30 g, 8.1 mmol) and TBHP (9.75 mL, 5.0-6.0 M solution in decane, 5.38 mmol) were added sequentially. After 20 min, the resulting mixture was treated with a solution of **12** (5.0 g, 26.85 mmol) in CH_2Cl_2 (25 mL). After 6 h, the reaction mixture was quenched with 10% NaOH solution in saturated with NaCl (10 mL) and filtered through celite. Evaporation of the solvent and purification of the residue by column chromatography (silica gel, 50% EtOAc in hexane) afforded **11** as a colorless liquid.

Yield : 4.45 g, 82%

Mol. Formula : $C_{10}H_{18}O_4$

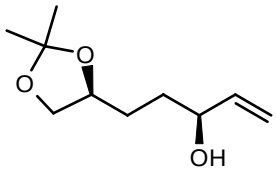
$[\alpha]_D^{25}$: –22.6 (*c* 1.0, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.34 (s, 3H), 1.40 (s, 3H), 1.67-1.83 (m, 4H), 2.06 (br, s, 1H), 2.91-3.02 (m, 2H), 3.52 (t, 1H, *J* = 6.8 Hz), 3.65 (m, 1H), 3.86 (m, 1H), 4.00-4.18 (m, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 25.4, 26.7, 27.4, 29.4, 55.1, 58.4, 61.5, 68.9, 74.9, 108.6.

Elemental Analysis : **Calcd.:** C, 59.39, H, 8.97; **Found:** C, 59.35; H, 8.79.

(*S*)-5-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-1-en-3-ol (19)



To a solution of **11** (2.02 g, 10.0 mmol) in dry toluene (30 mL) were added imidazole (2.04 g, 30.0 mmol), triphenylphosphine (3.93 g, 15.0 mmol) and iodine (3.02 g, 12.0 mmol) at room temperature. Stirred for 30 min at same temperature (monitored by

TLC) and quenched the reaction mixture by saturated $NaHCO_3$ solution. The aqueous layer was washed with EtOAc (2 x 20 mL), combined the EtOAc layers, dried over Na_2SO_4, and evaporated the solvent in vacuo. Purification of the residue by column chromatography (silica gel, 10% EtOAc-Light petroleum ether) afforded iodo compound (2.23 g, 72%) as a light yellowish liquid.

To a solution of iodo compound (2.23 g, 7.13 mmol) and Zn dust (4.64 g, 71.3 mmol) in absolute EtOH (30 mL) was heated to reflux for 3 h., evaporated the solvent and purification of the residue by column chromatography (silica gel, 60-120 mesh, 25% EtOAc in hexane) afforded **19** as a colorless liquid.

Yield : 1.24 g, 93%

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

$[\alpha]_D^{25}$: +22.0 (*c* 1.0, $CHCl_3$)

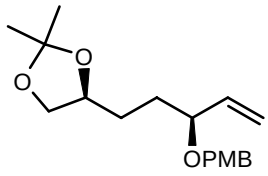
IR ($CHCl_3$) cm^{-1} : 3436, 3079, 2986, 2871, 1644, 1455, 1379, 1216, 1058, 922, 757.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.35 (s, 3H), 1.41 (s, 3H), 1.61-1.69 (m, 4H), 2.68 (br s, 1H), 3.52 (t, 1H, *J* = 7.2 Hz), 4.01-4.18 (m, 3H), 5.08-5.28 (m, 2H), 5.78-5.95 (m, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 25.6, 26.8, 29.4, 33.1, 69.2, 72.5, 75.8, 108.8, 114.5, 140.9.

Elemental Analysis : **Calcd.:** C, 64.49, H, 9.74; **Found:** C, 64.41; H, 9.62.

(*S*)-4-((*S*)-3(4-methoxybenzyloxy)pent-4-enyl)-2,2-dimethyl-1,3-dioxolane (20)



To a solution of **19** (2.5 g, 13.4 mmol) in dry DMF (40 mL) was added NaH (0.80 g, 33.5 mmol, 60% dispersion in mineral oil) at 0 ^oC, stirred for 30 min. added *p*-methoxy benzyl chloride (2.5 g, 16.0 mmol) and stirred for additional 3 h at room temperature. The reaction mixture was quenched by cold water and aqueous layer washed with EtOAc (2 x 25 mL), dried over Na_2SO_4, Evaporation of the solvent in vacuo and purified the residue by column chromatography (10% EtOAc-light petroleum ether) to afford **20.**

Yield : 3.5 g, 85%

Mol. Formula : $C_{18}H_{26}O_4$

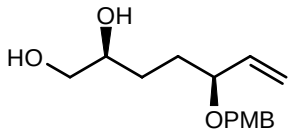
$[\alpha]_D^{25}$: –23.3 (*c* 0.8, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.33 (s, 3H), 1.39 (s, 3H), 1.47-1.77 (m, 4H), 3.35-3.78 (m, 3H), 3.81 (s, 3H), 3.98 (d, 1H, *J* = 11.5 Hz), 4.24 (d, 1H, *J* = 11.5 Hz), 4.55 (m, 1H), 5.18-5.28 (m, 2H), 5.74 (m, 1H), 6.84-6.89 (m, 2H), 7.22-7.27 (m, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 25.7, 26.9, 29.1, 31.3, 55.1, 69.2, 69.6, 75.7, 79.5, 108.6, 113.6, 117.3, 129.2, 130.6, 138.7, 159.0.

Elemental Analysis : **Calcd.:** C, 70.56, H, 8.55; **Found:** C, 70.48; H, 8.56.

(2*S*,5*S*)-5-(4-methoxybenzyloxy)hept-6-ene-1,2-diol (21)



To a solution of **20** (1.53 g, 5.0 mmol) in 80% AcOH (20 mL), was stirred for 2 h at room temperature and quenched the reaction mixture with saturated $NaHCO_3$ solution. The aqueous layer was washed with EtOAc (2 x 30 mL) dried over Na_2SO_4 and evaporation of the solvent in vacuo. Purified the residue by column chromatography (silica gel, 60-120 mesh, 50% EtOAc in hexane) to afford **21** as a colorless liquid.

Yield : 1.22 g, 92%

Mol. Formula : $C_{15}H_{22}O_4$

$[\alpha]_D^{25}$: –37.5 (*c* 1.2, $CHCl_3$)

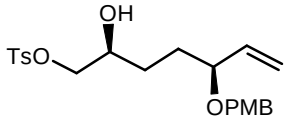
IR ($CHCl_3$) cm^{-1} : 3409, 3076, 3000, 2936, 2868, 1612, 1514, 1442, 1302, 1248, 1174, 1072, 995, 821.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.44-1.56 (m, 2H), 1.61-1.76 (m, 2H), 2.34 (br s, 2H), 3.36 (m, 1H), 3.53-3.77 (m, 3H), 3.80 (s, 3H), 4.23 (d, 1H, *J* = 11.4 Hz), 4.51 (d, 1H, *J* = 11.4 Hz), 5.18-5.27 (m, 2H), 5.75 (m, 1H), 6.84-6.89 (m, 2H), 7.19-7.25 (m, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 28.9, 31.6, 55.1, 66.5, 69.7, 71.9, 80.0, 113.7, 117.3, 129.4, 130.2, 138.6, 159.1**.**

Elemental Analysis : **Calcd.:** C, 67.64; H, 8.33; **Found:** C, 67.62; H, 8.22.

(2*S*,5*S*)-2-hydroxy-5-(4-methoxybenzyloxy)hept-6-enyl 4-methylbenzenesulfonate (22)



To a solution of **21** (1.0 g, 3.75 mmol), in dry CH_2Cl_2 (30 mL) added Et_3N (0.44 g, 4.27 mmol), n-Bu_2SnO (0.47 g, 1.89 mmol), DMAP (catalytic) and Ts-Cl (0.74 g, 3.84 mmol) at 0 ^oC. Stirred for 12 h at room temperature, quenched with saturated solution of $NaHCO_3$, aqueous layer extracted with EtOAc (2 x 25 mL), organic layer washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 60-120 mesh, 15% EtOAc-light petroleum ether) to afford **22** as a colorless liquid.

Yield : 1.2 g, 76%

Mol. Formula : $C_{22}H_{28}O_6S$

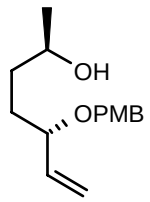
$[\alpha]_D^{25}$: –29.20 (*c* 1.0, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.43-1.71 (m, 4H), 2.45 (s, 3H), 3.66-3.78 (m, 2H), 3.80 (s, 3H), 3.85-3.98 (m, 2H), 4.21 (d, 1H, *J* =11.5 Hz), 4.49 (d, 1H, *J* =11.4 Hz), 5.16-5.26 (m, 2H), 5.71 (m, 1H), 6.83-6.87 (m, 2H), 7.18-7.22 (m, 2H), 7.31-7.35 (m, 2H), 7.76-7.80 (m, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 21.4, 28.6, 31.0, 55.0, 68.7, 69.6, 73.5, 79.3, 113.6, 117.3, 127.8, 129.3, 129.9, 132.6, 138.2, 144.6, 159.0.

Elemental Analysis : **Calcd.:** C, 62.84; H, 6.71; S, 7.63; **Found.** C, 62.74; H, 6.58.

(2*R*,5*S*)-5-(4-methoxybenzyloxy)hept-6-en-2-ol (7)



To a solution of compound **22** (0.210 g, 0.5 mmol) in dry THF (10 ml) at 0 ^oC was added LAH (0.076 g, 2.0 mmol) and stirred for 3 h. Excess of LAH was quenched by addition of a saturated Na_2SO_4 solution (1 ml). The solid formed was filtered, washed

with ethyl acetate (2 x 25 mL) and the combined filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with 20% EtOAc-light petroleum ether to afford **7** as a colorless liquid.

Yield : 0.110 g, 88%

Mol. Formula : $C_{15}H_{22}O_3$

$[\alpha]_D^{25}$: –61.4 (*c* 1.2, $CHCl_3$)

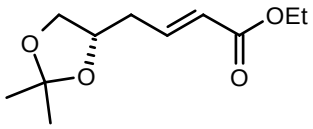
IR ($CHCl_3$) cm^{-1} : 3409, 3076, 3006, 2966, 2934, 1613, 1513, 1248, 1173, 1036, 994, 756.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.15 (d, 3H, *J* = 6.2 Hz), 1.47-1.74 (m, 4H), 2.02 (br s, 1H) 3.69-3.77 (m, 2H), 3.81 (s, 3H), 4.25 (d, 1H, *J* = 11.4 Hz), 4.51 (d, 1H, *J* = 11.4 Hz), 5.17-5.26 (m, 2H), 5.75 (m, 1H), 6.85-6.89 (m, 2H), 7.23-7.27 (m, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 23.2, 31.8, 35.0, 55.0, 67.5, 69.6, 80.0, 113.6, 117.1, 129.3, 130.3, 138.7, 158.9.

Elemental Analysis : **Calcd.:** C, 71.97; H, 8.86; **Found:** C, 71.94; H, 8.72.

(*S*,*E*)-ethyl 4-(2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enoate (27)



The alcohol **26** (7.3 g, 50.0 mmol) was dissolved in DMSO (80 mL) and added IBX (18.2 g, 65.0 mmol) slowly while cooling the reaction mixture in cold water. It was stirred at room temperature for 2h. After completion of the oxidation reaction, two carbon Wittig ylide (26.1 g, 75.0 mmol, in 75 mL DMSO) was added and the reaction mixture was stirred for 5h at room temperature. Then the reaction mixture was quenched with aqueous $NaHCO_3$ solution and filtered through celite pad. The filtrate was extracted with ethyl acetate. The combined organic layer was washed with water, brine solution and dried over Na_2SO_4. Evaporated the solvent in vacuum pressure and purified by column chromatography (eluted in 5% EtOAc-light petroleum ether) to afford trans olefin **27**.

Yield : 8.46 g, 79 %

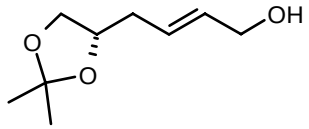
Mol. Formula : $C_{11}H_{18}O_4$

^{1}H NMR ($CDCl_3$, 200 MHz) **:** δ 1.29 (t, 3H, *J* = 7.20 Hz), 1.35 (s, 3H), 1.40 (s, 3H), 2.36-2.51 (m, 2H), 3.52 (dd, 1H, *J* = 6.6, 8.1 Hz), 4.0 (dd, 1H, *J* = 6.0, 8.1 Hz), 4.11-4.20 (m, 3H), 5.90 (dt, 1H, *J* = 1.5, 15.7 Hz), 6.90 (dt, 1H, *J* = 7.2, 15.7 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz) **:** δ 14.28, 25.57, 26.88, 36.48, 60.25, 68.80, 74.20, 109.31, 123.91, 143.63, 166.00.

Elemental Analysis **:** **Calcd.:** C, 61.66; H, 8.47%; **Found:** C, 61.55; H, 8.43%.

(*S*,*E*)-4-(2,2-dimethyl-1,3-dioxolan-4-yl)but-2-en-1-ol (10)



The ester **27** (10.0 g, 46.71 mmol) was dissolved in CH_2Cl_2 (100 mL) and cooled to -78 ^oC. To this DIBAL-H (108 mL, 1M in toluene) was added dropwise and stirred at -78 ^oC for 2h. After the completion of the reaction, quenched with aqueous sodium potassium tartarate solution and stirred at room temperature for 30 min. The two layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over Na_2SO_4, concentrated and purified by column chromatography to yield the allylic alcohol **10** as a colorless liquid.

Yield **:** 6.83 g, 85 %

Mol. Formula **:** $C_9H_{16}O_3$

$[\alpha]_D^{25}$ **:** + 8.17 (*c* 1, MeOH)

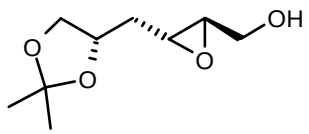
IR ($CHCl_3$) cm^{-1} **:** 3413, 2987, 2935, 2874, 1671, 1456, 1372, 1157, 1062, 973, 851, 757, 514.

^{1}H NMR ($CDCl_3$, 200 MHz) **:** δ 1.31 (s, 3H), 1.38 (s, 3H), 2.24-2.39 (m, 3H), 3.50 (dd, 1H, *J* = 6.7, 7.8 Hz), 3.95-4.15 (m, 4H), 5.55-5.77 (m, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) **:** δ 25.52, 26.80, 36.45, 63.09, 68.73, 5.18, 108.94, 127.01, 132.23.

Elemental Analysis **:** **Calcd.:** C, 62.77; H, 9.36%; **Found:** C, 62.78; H, 9.16%.

((2*R*,3*R*)-3-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)oxiran-2-yl)methanol (9)



Flame dried powdered 4 ^{o}A molecular sieves (5 g) were taken with dry CH_2Cl_2 (50 mL) in a two neck round bottomed flask and cooled to -20 ^{o}C. To this (–) DET (1.8 g, 8.73 mmol) was added, followed by $Ti(O^{i}Pr)_4$ (2.06 g, 7.2 mmol). After 10 min, TBHP (10.5 mL, 5.5 M in decane) was added and stirred at same temperature for 30 min. Then a solution of the allylic alcohol **10** (5.0 g, 29.0 mmol in 15 mL CH_2Cl_2) was added slowly and stirred for 12 h. and after completion of the reaction, quenched with saturated solution of 10%NaCl and NaOH. The mixture was filtered through a celite pad and concentrated in vacuo. The crude product was purified by column chromatography to afford the epoxide **9** as a colorless liquid.

Yield : 4.48 g, 82 %

Mol. Formula : $C_9H_{16}O_4$

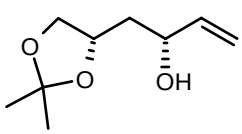
$[\alpha]_D^{25}$: +23.75 (*c* 1.6, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.36 (s, 3H), 1.43 (s, 3H), 1.90 (t, 2H, *J* = 5.56 Hz), 2.08 (br s, 1H), 3.01 (m, 1H), 3.10 (m, 1H), 3.58 (dd, 2H, *J* = 7.1, 7.7 Hz), 3.90 (dd, 1H, *J* = 2.02, 12.55 Hz), 4.08 (dd, 1H, *J* = 6.07, 7.96 Hz), 4.17-4.37 (m, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 25.57, 26.75, 34.86, 52.52, 57.75, 61.50, 68.75, 72.88, 109.07.

Elemental Analysis : **Calcd.:** C, 57.43; H, 8.57%; **Found:** C, 57.31; H, 8.46%.

(*R*)-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-2-ol (29)



To a solution of **9** (3.21 g, 17.0 mmol) in toluene (30 mL) added imidazole (3.47 g, 50.97 mmol), triphenyl phosphine (6.7 g, 75.57 mmol) and iodine (4.5 g, 17.86 mmol)

sequentially keeping the reaction temperature at 25 ^{o}C and the reaction mixture was stirred at room temperature for 15min. Monitored by TLC, the reaction mixture was quenched by solid $NaHCO_3$ and filtered. Evaporated the solvent in *vacuo* and purified by column chromatography to give the iodo compound **28** (3.95 g, 78 %).

The iodo compound **28** (3.95 g, 13.24 mmol) and activated Zn dust (6.02 g, 92.6 mmol) in absolute ethanol (40 mL) was refluxed for 2 h. The suspension was filtered through a pad of celite and the filtrate was concentrated and purified by column chromatography to afford **29** as a colorless liquid.

Yield **:** 2.00 g, 87 %

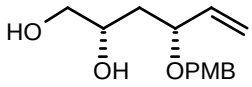
Mol. Formula **:** $C_9H_{16}O_3$

^{1}H NMR ($CDCl_3$, 200 MHz) **:** δ 1.36 (s, 3H), 1.42 (s, 3H), 1.73-1.80 (m, 2H), 2.70 (br s, 1H), 3.57 (dd, 1H, *J* = 7.32, 7.95 Hz), 4.08 (dd, 1H, *J* = 5.9, 8.02 Hz), 4.19-4.37 (m, 2H), 5.12 (dt, 1H, *J* = 1.5, 10.36 Hz), 5.27 (dt, 1H, *J* = 1.5, 17.71 Hz), 5.86 (m, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) **:** δ 25.78, 26.89, 40.47, 69.62, 71.67, 75.00, 109.27, 114.78, 140.18.

Elemental Analysis **:** **Calcd.:** C, 62.77; H, 9.36%; **Found:** C, 62.55; H, 9.28%.

(2*S*,4*R*)-4-(4-methoxybenzyloxy)hex-5-ene-1,2-diol (31)



To a solution of **29** (0.9 g, 5.23 mmol) in anhydrous THF was added NaH (419 mg of 60 % suspension in paraffin oil, 10.47 mmol) at 0 ^{o}C. After stirring the reaction mixture for 15 min, PMB-Cl (1.42 mL, 10.47 mmol) was added and stirred at room temperature for 2 h. It was quenched by cold water and the layers were separated. The aqueous layer was washed with ethyl acetate (2 x 25 mL) and the combined organic layer was dried over Na_2SO_4, concentrated and purified by column chromatography. The resulted compound **30** was dissolved in MeOH (8 mL) and added catalytic *p*-TSA The mixture was stirred at room temperature for 10 h. and quenched with Et_3N. The reaction mixture was concentrated and purified by column chromatography to afford the diol **31** as a colorless liquid.

Yield : 1.12 g, 85 % over two steps

Mol. Formula : $C_{14}H_{20}O_4$

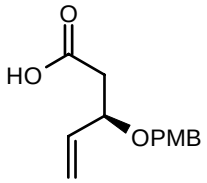
$[\alpha]_D^{25}$: +51.11 (*c* 1.8, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.60 (m, 1H), 1.83 (dt, 1H, *J* = 9.35, 14.53 Hz), 2,42 (br s, 1H), 3.40-3.60 (m, 2H), 3.76 (m, 1H), 3.80 (s, 3H), 3.89 (m, 1H), 4.40 (m, 1H), 4.26 (d, 1H, *J* = 11.20 Hz), 4.54 (d, 1H, *J* = 11.20) Hz, 5.24 (m, 1H), 5.30 (m, 1H), 5.75 (ddd, 1H, *J* = 7.83, 9.85, 17.68 Hz), 6.86-6.90 (m, 2H), 7.22-7.26 (m, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 38.58, 55.21, 66.59, 69.87, 71.32, 80.16, 113.92, 117.87, 129.56, 137.88, 159.30.

Elemental Analysis : **Calcd.:** C, 66.65; H, 7.99%; **Found :** C, 66.48; H, 8.02%.

(*R*)-3-(4-methoxybenzyloxy)pent-4-enoic acid (8)



The Diol **31** (1.05 g, 4.17 mmol) was dissolved in CH_2Cl_2 (15 mL) and added silica supported $NaIO_4$ (1.34 g, 6.25 mmol). The reaction mixture was stirred at room temperature for 30 min. The suspension was then filtered and concentrated to give the crude aldehyde **32**. It was taken for subsequent step with out further purification.

The crude aldehyde **32** and 2-methyl-2-butene (0.8 mL, 8.33 mmol) was dissolved in t-BuOH: H_2O (9:3 mL) solvent mixture. To this NaH_2PO_4 (1.0 g, 8.33 mmol) was added followed by $NaClO_2$ (753 mg, 8.33 mmol). The reaction mixture was stirred at room temperature for 2 h., concentrated in vacuo and partitioned between ethyl acetate/water. The aqueous layer was washed with ethyl acetate (2 x 25 mL). The combined organic layer was dried over Na_2SO_4, concentrated and purified by flash column chromatography to afford the acid **8** as light yellowish oil.

Yield : 849 mg, 86 %

Mol. Formula : $C_{13}H_{16}O_4$

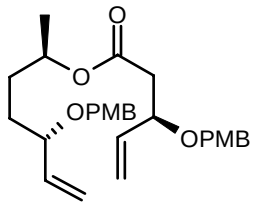
$[\alpha]_D^{25}$: +29.14 (*c* 1, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz) **:** δ 2.48 (dd, 1H, *J* = 5.27, 15.41 Hz), 2.64 (dd, 1H, *J* = 8.08, 15.41 Hz) 3.80 (s, 3H), 4.24 (m, 1H), 4.32 (d, 1H, *J* = 11.24 Hz), 4.52 (d, 1H, *J* = 11.24 Hz), 5.26-5.38 (m, 2H), 5.76 (m, 1H), 6.83-6.87 (m, 2H), 7.21-7.26 (m, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) **:** δ 41.0, 55.17, 70.22, 76.20, 113.76, 118.30, 130.0, 137.0, 159.20, 176.17.

Elemental Analysis **:** **Calcd.:** C, 66.09%; H, 6.83%; **Found :** C, 65.89; H, 6.69%.

(3*R*)-(2*R*,5*S*)-5-(4-methoxybenzyloxy)hept-6-en-2-yl-3-(4-methoxybenzyloxy)-pent-4-enoate (6)



To a stirred solution of **8** (0.050 g, 0.211 mmol) in dry CH_2Cl_2 (5 ml) were added Et_3N (0.042 g, 0.422 mmol) and a solution of 2, 4, 6-trichlorobenzoylchloride (0.077 g, 0.315 mmol) in dry CH_2Cl_2 (5 ml) and stirred at 0 ^oC for 20 min. A solution of **7** (0.055 g, 0.219 mmol) in dry CH_2Cl_2 (5 ml) and DMAP (catalytic) was added, stirred for 6 h at room temperature (Checked by TLC). The solvent was evaporated, the crude was purified by column chromatography (silica gel, 60-120 mesh, eluted in 10% EtOAc-light petroleum ether) to afford **6** as a colorless liquid.

Yield **:** 0.083 g, 84%

Mol. Formula **:** $C_{28}H_{36}O_6$

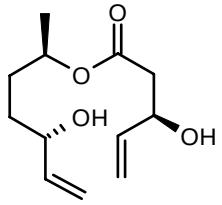
$[\alpha]_D^{25}$ **:** –9.8 (*c* 1.0, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz) **:** δ 1.17 (d, 3H, *J* = 6.2 Hz), 1.47-1.72 (m, 4H), 2.40 (dd, 1H, *J* = 5.7, 14.9 Hz), 2.58 (dd, 1H, *J* = 8.0, 14.9 Hz), 3.68 (m, 1H), 3.80 (s, 3H), 3.81 (s, 3H), 4.20 (m, 1H), 4.29 (d, 2H, *J* = 11.5 Hz), 4.48 (d, 2H, *J* = 11.5 Hz), 4.90 (m, 1H), 5.15-5.35 (m, 4H), 5.61-5.86 (m, 2H), 6.84-6.90 (m, 4H), 7.22-7.26 (m, 4H).

^{13}C NMR ($CDCl_3$, 50 MHz) **:** δ 19.9, 31.1, 31.4, 41.3, 55.0, 69.6, 70.1, 70.7, 76.9, 79.5, 113.6, 117.2, 117.8, 129.1, 130.0, 130.2, 130.5, 137.3, 138.7, 159.0, 170.2.

Elemental Analysis : **Calcd.:** C, 71.77; H, 7.74; **Found:** C, 71.68; H, 7.64.

(*R*)-((2*R*,5*S*)-5-hydroxyhept-6-en-2-yl) 3-hydroxypent-4-enoate (34)



To a solution of **6** (0.200 g, 0.427 mmol) and DDQ (0.203 g, 0.896 mmol) in CH_2Cl_2:H_2O mixture (20:1) was stirred at room temperature for 2 h. The reaction mixture was quenched with saturated solution of $NaHCO_3$, separated the organic layer, washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (silica gel, 60-120 mesh, 40% EtOAc-light petroleum ether) to afford **34** as a colorless liquid.

Yield : 0.076 g, 78%

Mol. Formula : $C_{12}H_{20}O_4$

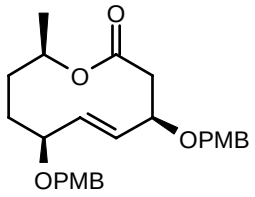
IR ($CHCl_3$) cm^{-1} : 3417, 3083, 2980, 2927, 1714, 1645, 1426, 1378, 1277, 1178, 1032.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.23 (d, 3H, *J* = 6.3 Hz), 1.52-1.76 (m, 4H), 2.03 (br s, 2H), 2.50-2.56 (m, 2H), 4.14 (m, 1H), 4.54 (m, 1H), 5.00 (m, 1H), 5.10-5.36 (m, 4H), 5.77-5.97 (m, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 20.0, 31.4, 32.3, 41.6, 68.9, 71.3, 72.5, 114.9, 115.2, 138.9, 140.8, 171.7.

Elemental Analysis : **Calcd.:** C, 63.14; H, 8.83; **Found:** C, 62.94; H, 8.72.

(4*R*,5*E*,7*S*,10*R*)-4,7-bis(4-methoxybenzyloxy)-3,4,7,8,9,10-hexahydro-10-methyl oxecin-2-one (5)



To a solution of **6** (0.094 g, 0.20 mmol, 0.001M) in freshly distilled degassed anhydrous CH_2Cl_2 (200 ml) was added Grubb's second generation catalyst (**33**) (0.017 g, 0.02 mmol) and heated at reflux for 8 h under an argon atmosphere until the complete

consumption of starting material (monitored by TLC). The solvent was evaporated to a brown residue, which was purified by column chromatography (silica gel, 60-120 mesh, 10% ethyl acetate- light petroleum) to afford **5** as a colorless liquid.

Yield : 0.069 g, 78%

Mol. Formula : $C_{26}H_{32}O_6$

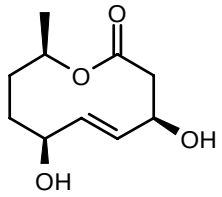
$[\alpha]_D^{25}$: –3.0 (*c* 1.5, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 1.16 (d, 3H, *J* = 6.5 Hz), 1.49 (m, 1H), 1.64 (m, 1H), 1.80 (m, 1H), 1.95 (m, 1H), 2.44 (t, 1H, *J* = 10.8 Hz), 2.73 (dd, 1H, *J* = 5.5, 10.3 Hz), 3.79 (m, 3H), 3.80 (s, 3H), 3.98 (m, 1H), 4.22 (m, 1H), 4.36 (t, 2H, *J* = 12.8 Hz), 4.51 (dd, 2H, *J* = 6.0, 11.3 Hz), 4.83 (m, 1H), 5.48 (dd, 1H, *J* = 2.6, 16.0 Hz), 5.87 (dd, 1H, *J* = 9.0, 16.0 Hz), 6.84-6.88 (m, 4H), 7.22-7.27 (m, 4H).

^{13}C NMR ($CDCl_3$, 100 MHz) : δ 21.1, 27.6, 29.7, 43.6, 55.2, 70.3, 70.7, 74.3, 78.6, 113.8, 129.1, 129.4, 130.1, 130.7, 132.8, 159.1, 170.5.

Elemental Analysis : **Calcd.:** C, 70.89; H, 7.32; **Found:** C, 70.72; H, 7.28.

(4*R*,5*E*,7*S*,10*R*)-3,4,7,8,9,10-hexahydro-4,7-dihydroxy-10-methyloxecin-2-one (2)



To a solution of **5** (0.05 g, 0.113 mmol) and DDQ (0.057 g, 0.25 mmol) in CH_2Cl_2:H_2O mixture (20:1) was stirred at room temperature for 2 h. The reaction mixture was quenched with saturated solution of $NaHCO_3$; organic layer was separated, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 60-120 mesh, 10% MeOH-$CHCl_3$) to afford **2** as a white solid.

Yield : 0.020 g, 89%

Mol. formula : $C_{10}H_{16}O_4$

$[\alpha]_D^{25}$: –38.0 (*c* 0.66, MeOH)

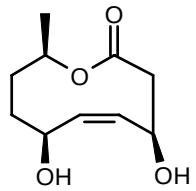
^{1}H NMR (CD_3OD, 500 MHz) **:** δ 1.16 (d, 3H, *J* = 6.5 Hz), 1.44 (d, 1H, *J* = 7.0, 15.9 Hz), 1.67 (br t, 1H, *J* = 12.3 Hz), 1.83-1.95 (m, 2H), 2.32 (t, 1H, *J* = 10.4 Hz), 2.61 (dd, 1H, *J* = 5.2, 10.1 Hz), 4.32 (m, 1H), 4.35 (ddd, 1H, *J* = 5.2, 8.6, 10.6 Hz), 4.77 (m, 1H), 5.45 (br d, 1H, *J* = 15.9 Hz), 5.73 (ddd, 1H, *J* = 1.6, 8.6, 15.9 Hz).

^{13}C NMR (CD_3OD, 125 MHz) **:** δ 22.46, 29.53, 36.54, 47.92, 69.15, 74.26, 74.87, 131.89, 134.78, 173.0.

Elemental Analysis **:** **Calcd.:** C, 59.98; H, 8.05; **Found:** C, 59.87; H, 8.02.

MS (ESI) m/z 223.22 (M^+ + Na).

(4*R*,5*Z*,7*S*,10*R*)-3,4,7,8,9,10-hexahydro-4,7-dihydroxy-10-methyloxecin-2-one (3)



To a stirred solution of **34** (0.04 g, 0.175 mmol, 0.001M) in freshly distilled degassed anhydrous CH_2Cl_2 (175 ml) was added Grubb's second generation catalyst (**33**) (0.015 g, 0.0176 mmol) and heated at reflux for 8 h under an argon atmosphere until the complete consumption of starting material (monitored by TLC). The solvent was evaporated to a brown residue, which was purified by column chromatography (silica gel, 60-120 mesh, 10% MeOH-$CHCl_3$) to afford **3** as light yellow oil.

Yield **:** 0.026 g, 74%

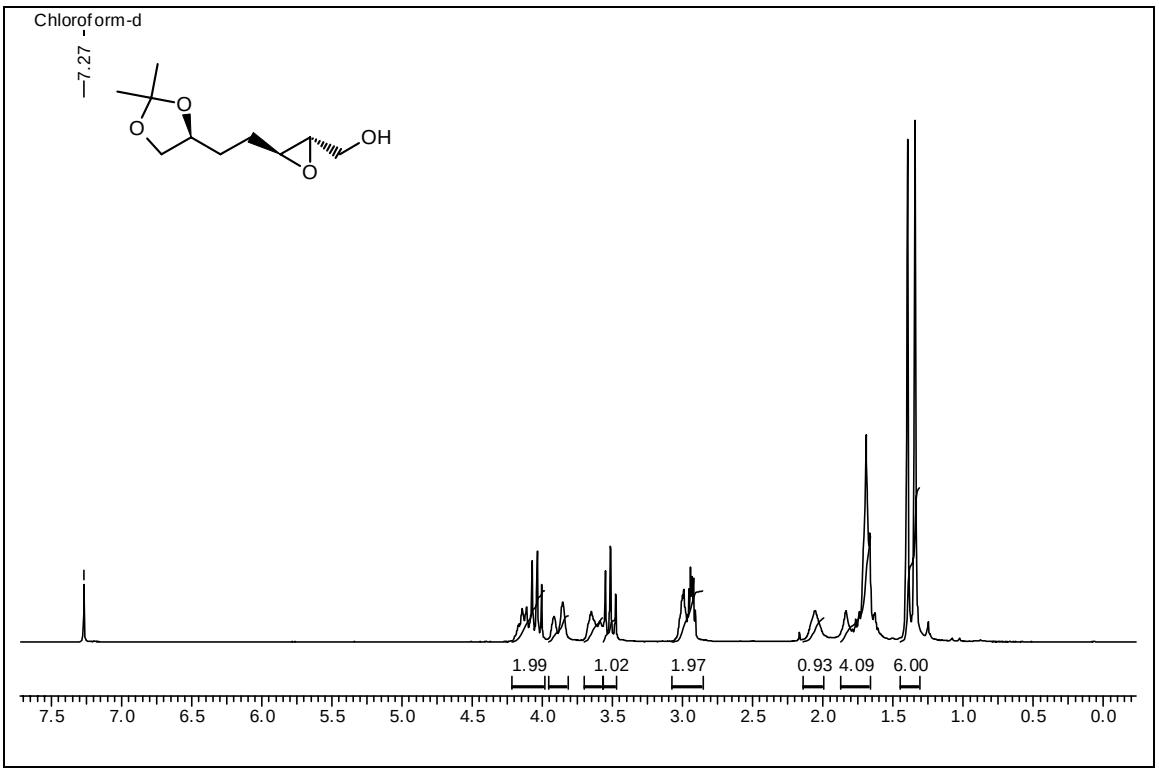
Mol. Formula **:** $C_{10}H_{16}O_4$

^{1}H NMR (CD_3OD, 500 MHz) **:** δ 1.30 (d, 3H, *J* = 6.6 Hz), 1.58 (m, 1H), 1.62 (m, 1H), 1.80 (m, 1H), 1.90 (m, 1H), 2.28 (t, 1H, *J* = 11.57 Hz), 2.60 (dd, 1H, *J* = 4.1, 11.57 Hz), 4.28 (m, 1H), 4.72-4.77 (m, 2H), 5.38 (dd, 1H, *J* = 1.25, 11.26 Hz), 5.47 (dd, 1H, *J* = 7.82, 11.26 Hz).

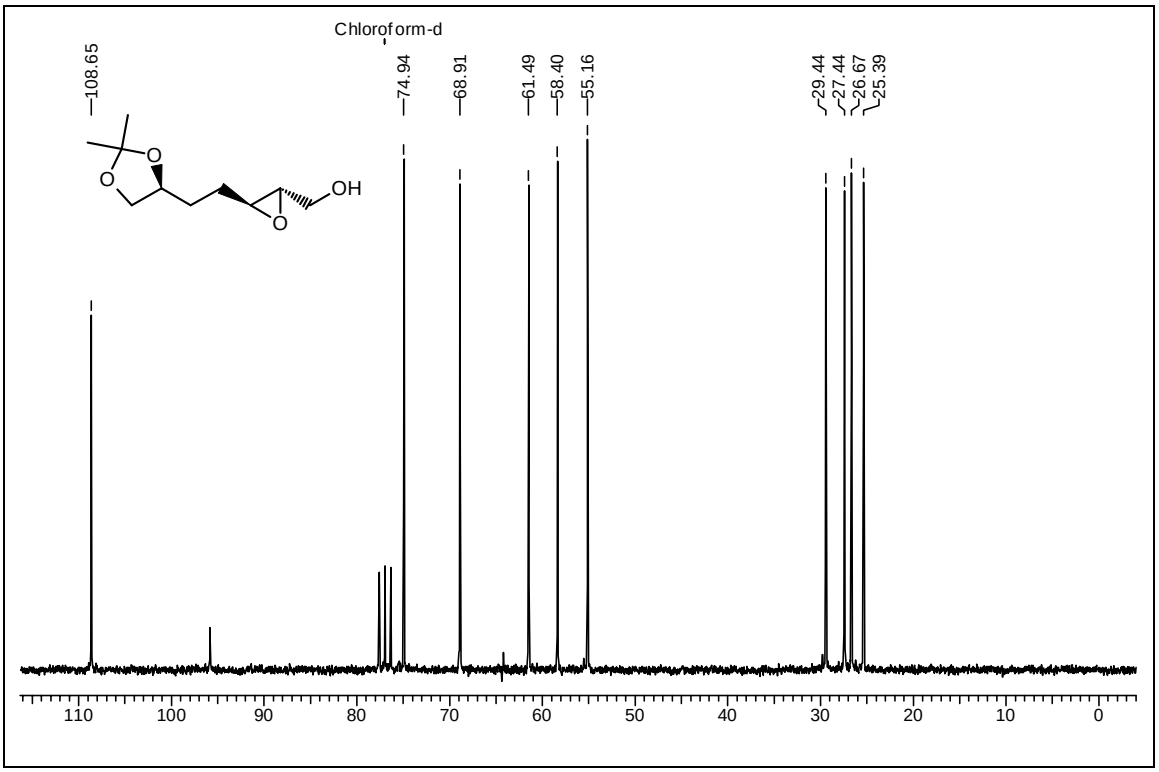
^{13}C NMR (CD_3OD, 125 MHz) **:** δ 21.6, 32.0, 36.2, 44.9, 66.7, 75.5, 78.9, 133.6, 134.7, 171.6.

Elemental Analysis **:** **Calcd.:** C, 59.98; H, 8.05; **Found:** C, 59.92; H, 8.02.

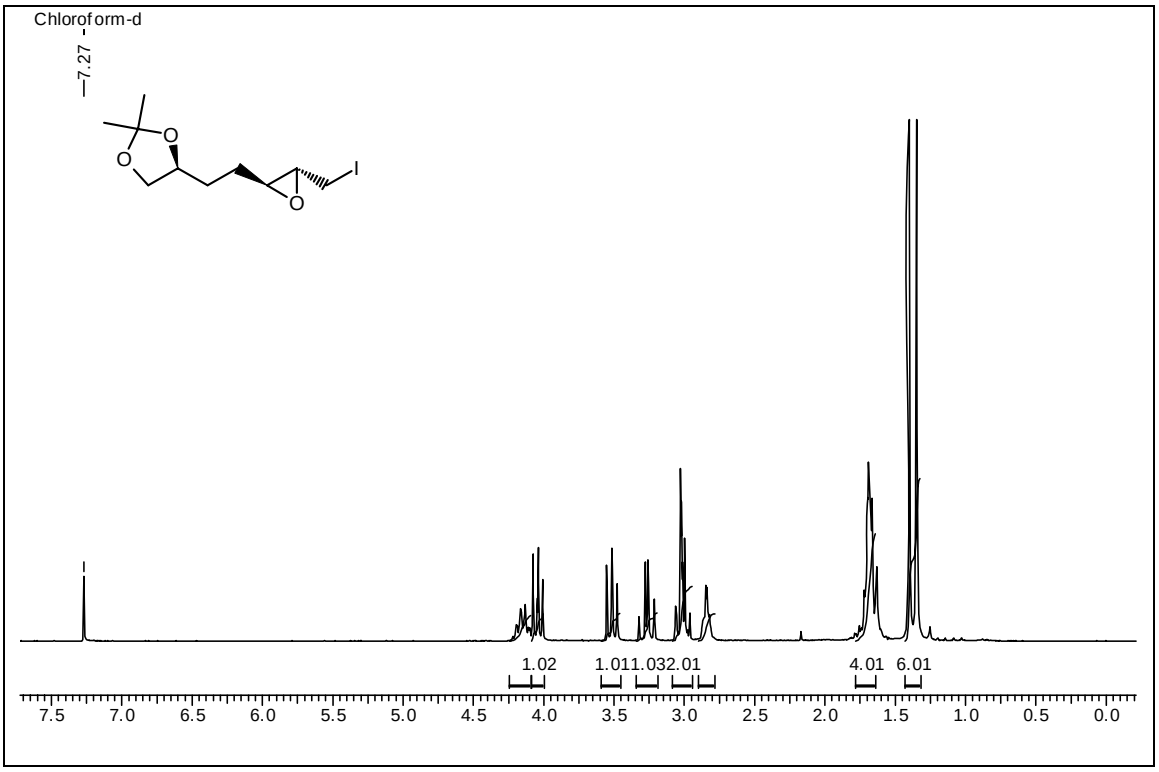
SPECTRA



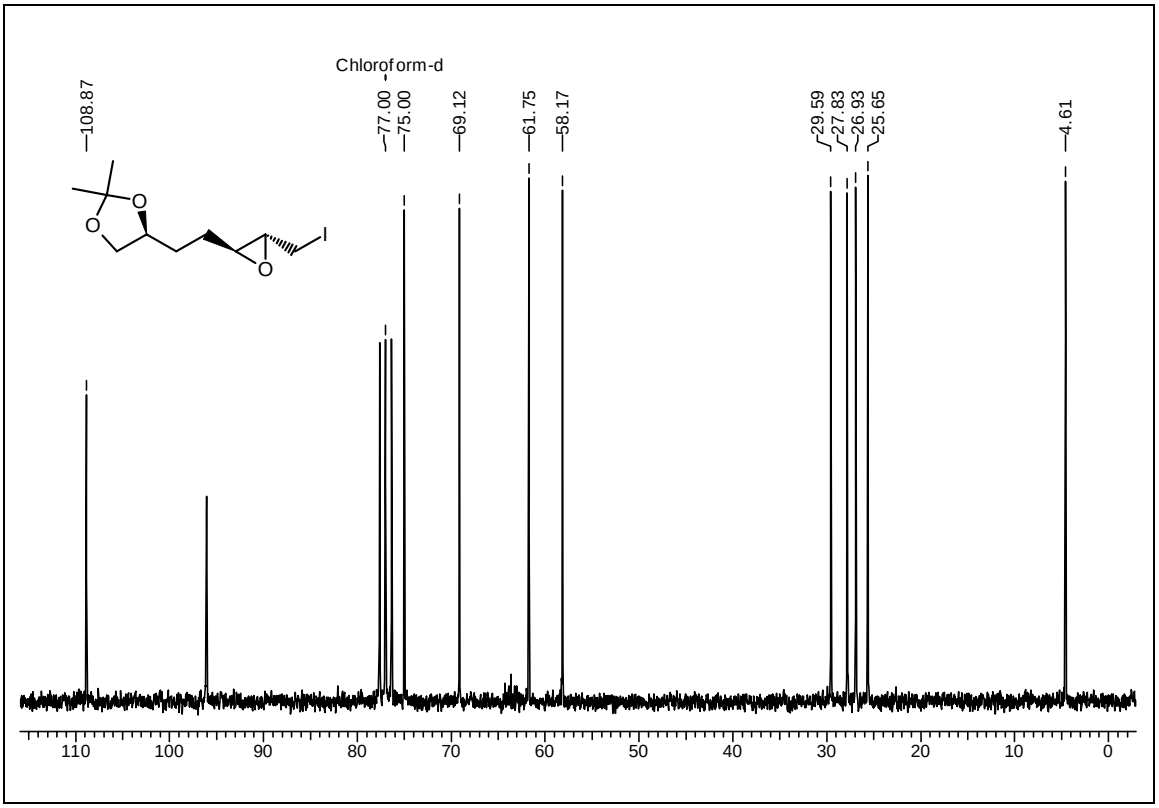
^{1}H NMR spectrum of compound 11 in $CDCl_3$



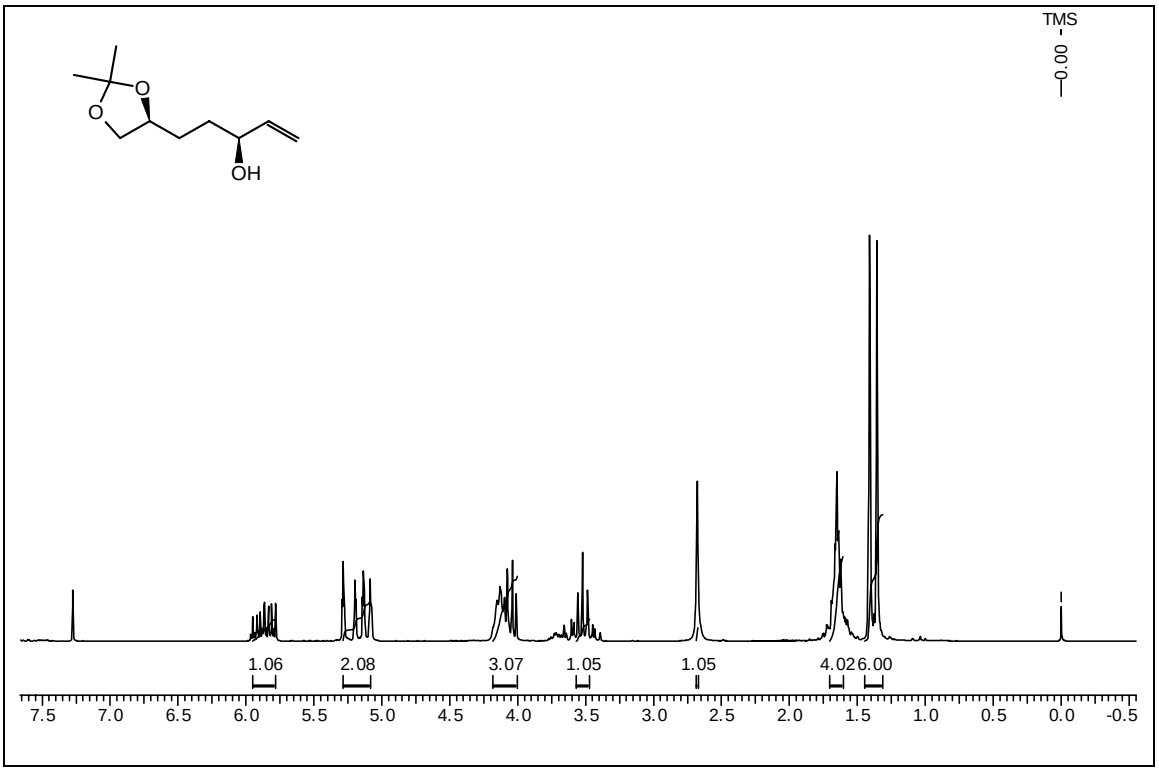
^{13}C NMR spectrum of compound 11 in $CDCl_3$



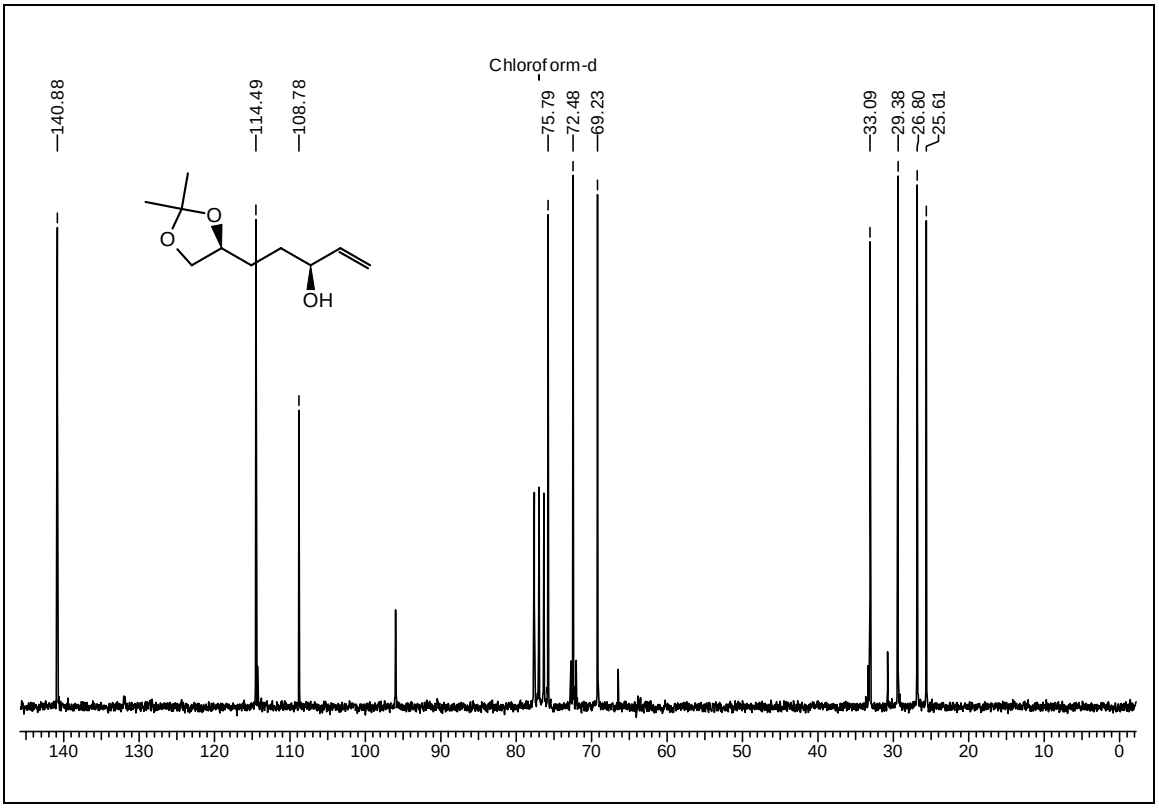
^{1}H NMR spectrum of compound 11a in $CDCl_3$



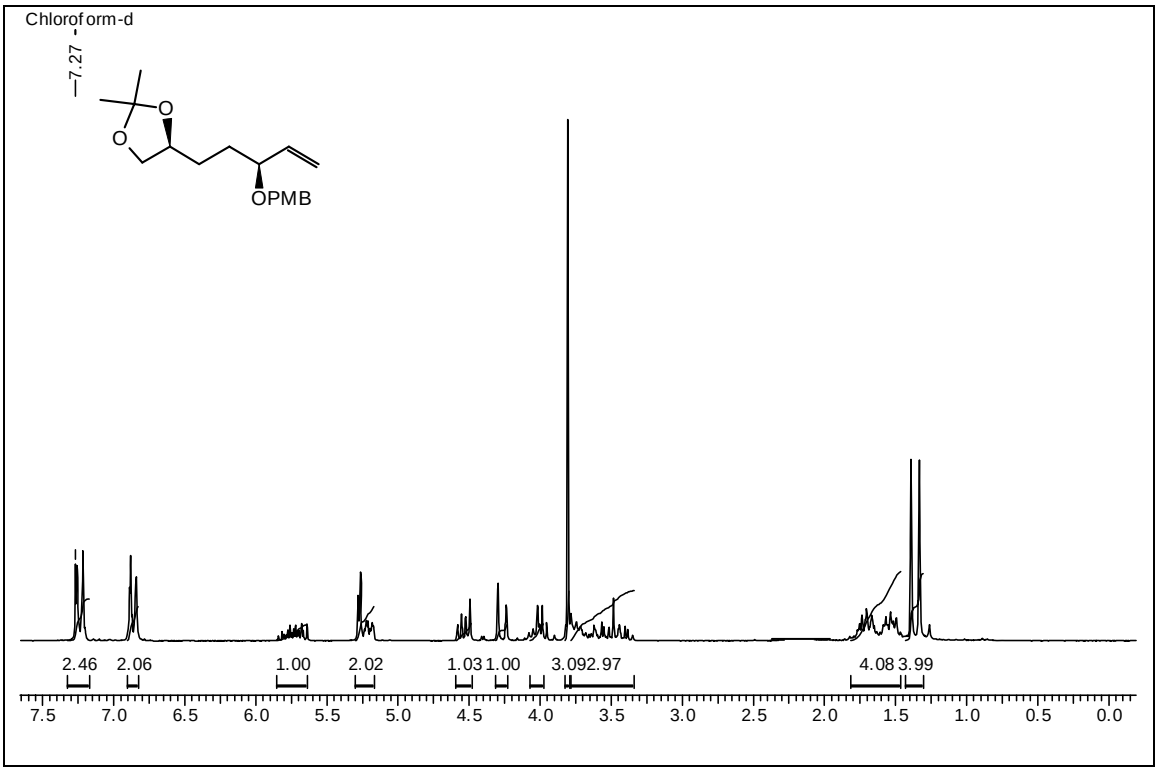
^{13}C NMR spectrum of compound 11a in $CDCl_3$



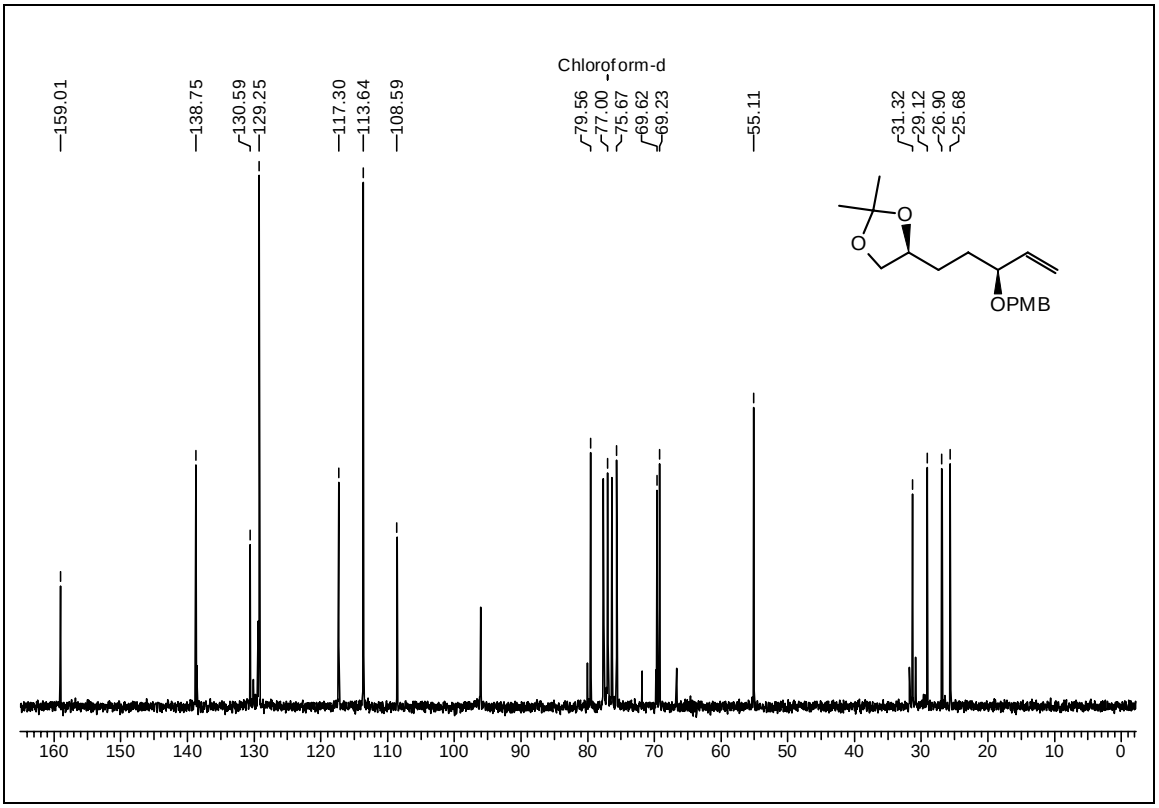
^{1}H NMR spectrum of compound 19 in $CDCl_3$



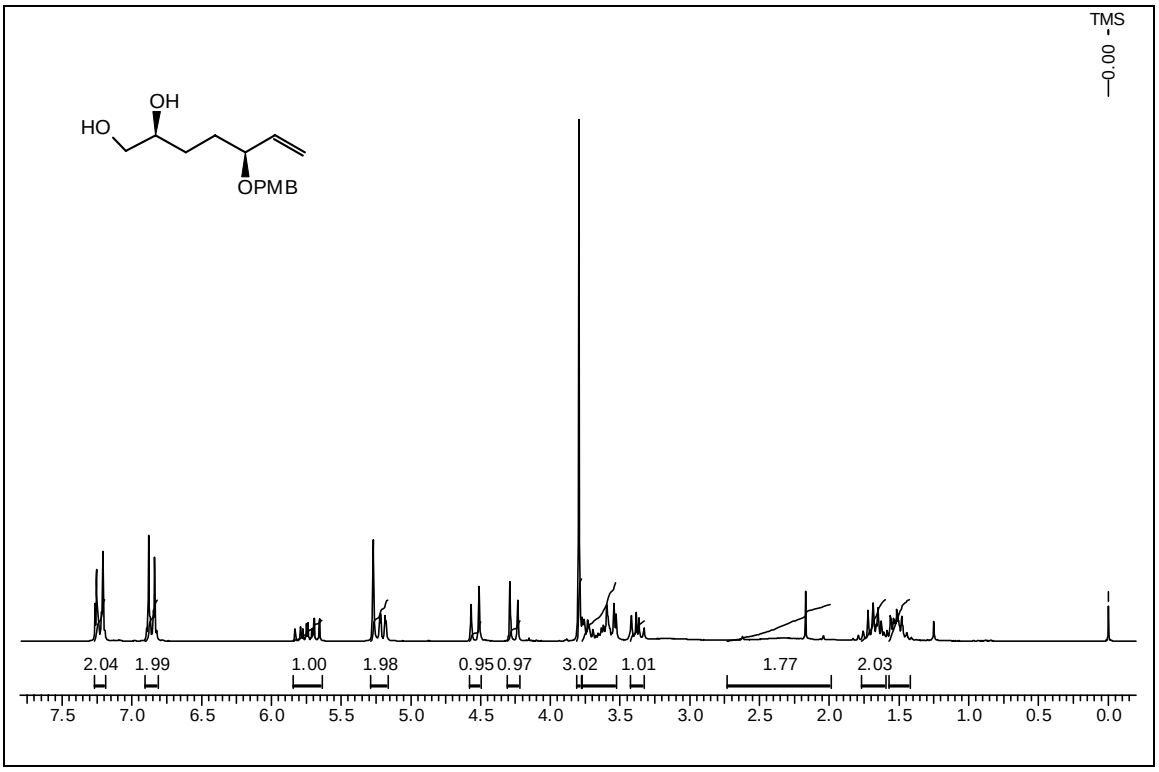
^{13}C NMR spectrum of compound 19 in $CDCl_3$



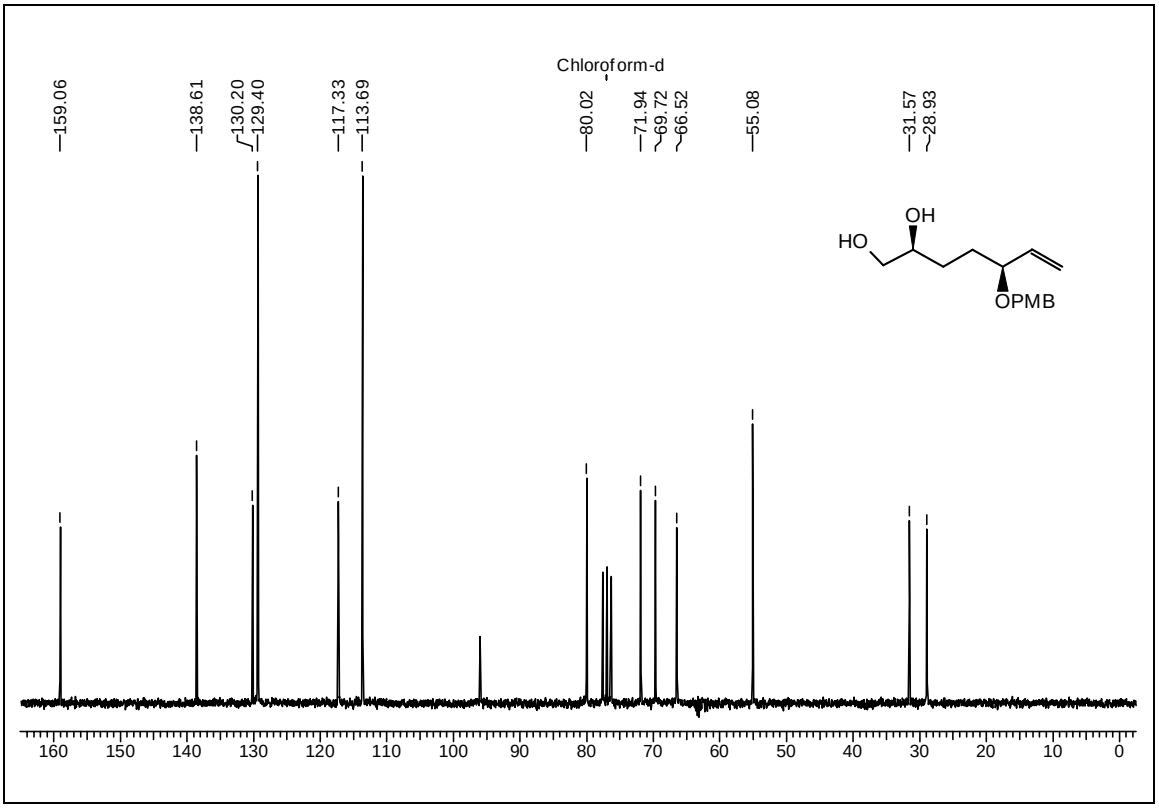
^{1}H NMR spectrum of compound 20 in $CDCl_3$



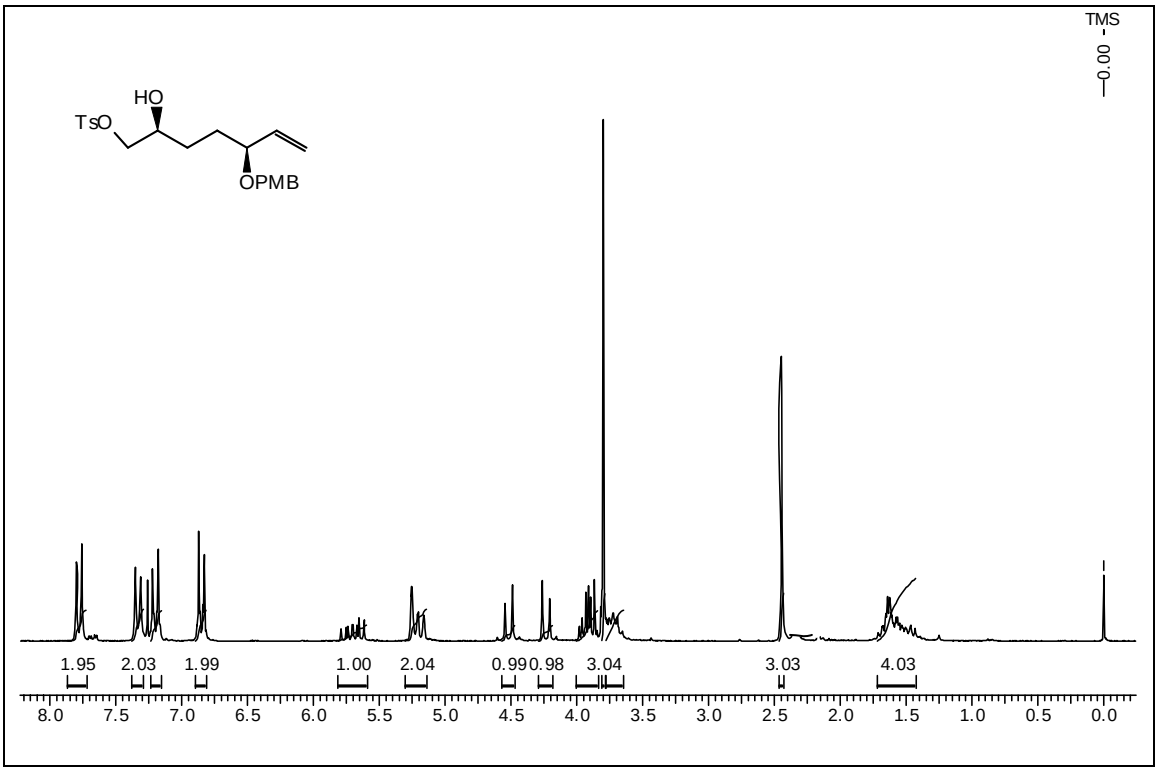
^{13}C NMR spectrum of compound 20 in $CDCl_3$



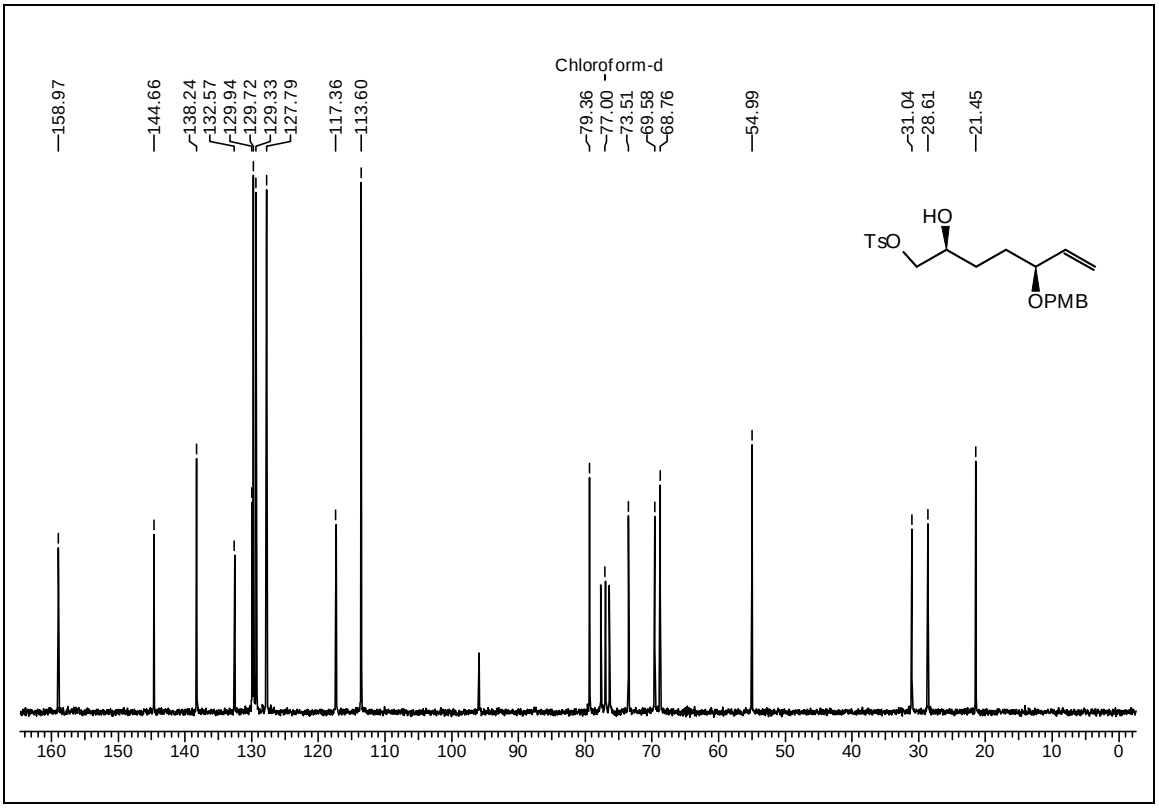
^{1}H NMR spectrum of compound 21 in $CDCl_3$



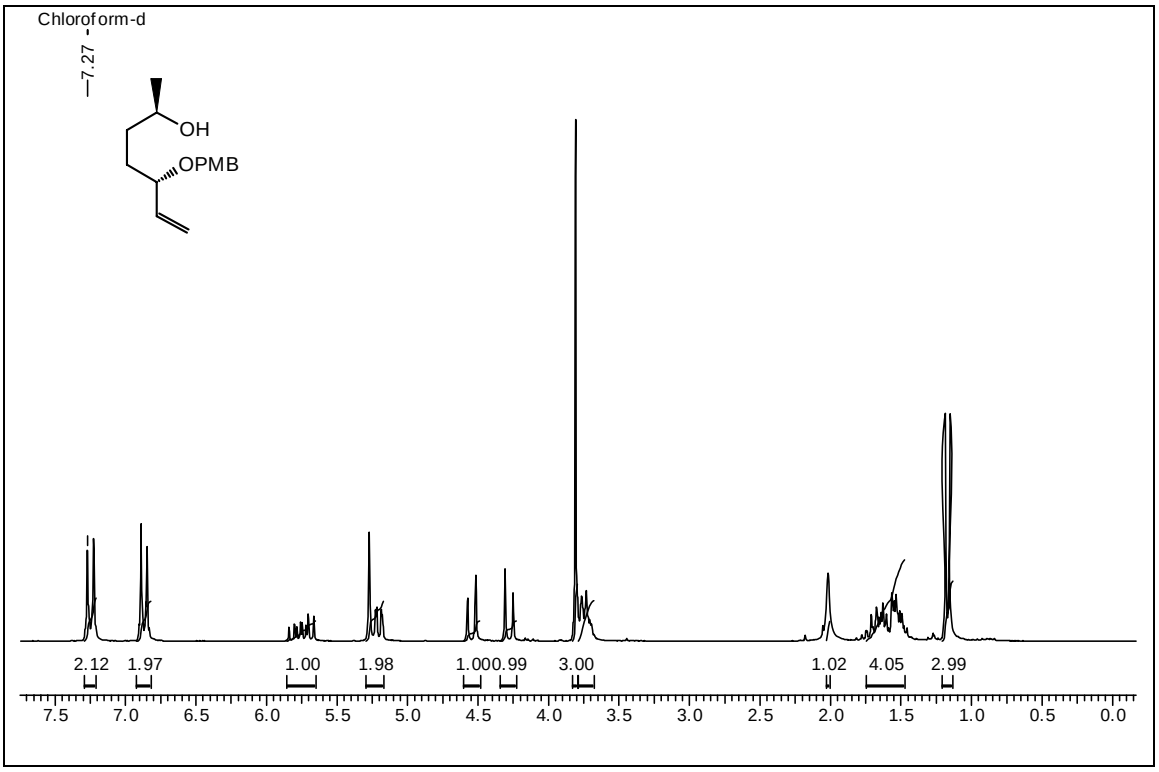
^{13}C NMR spectrum of compound 21 in $CDCl_3$



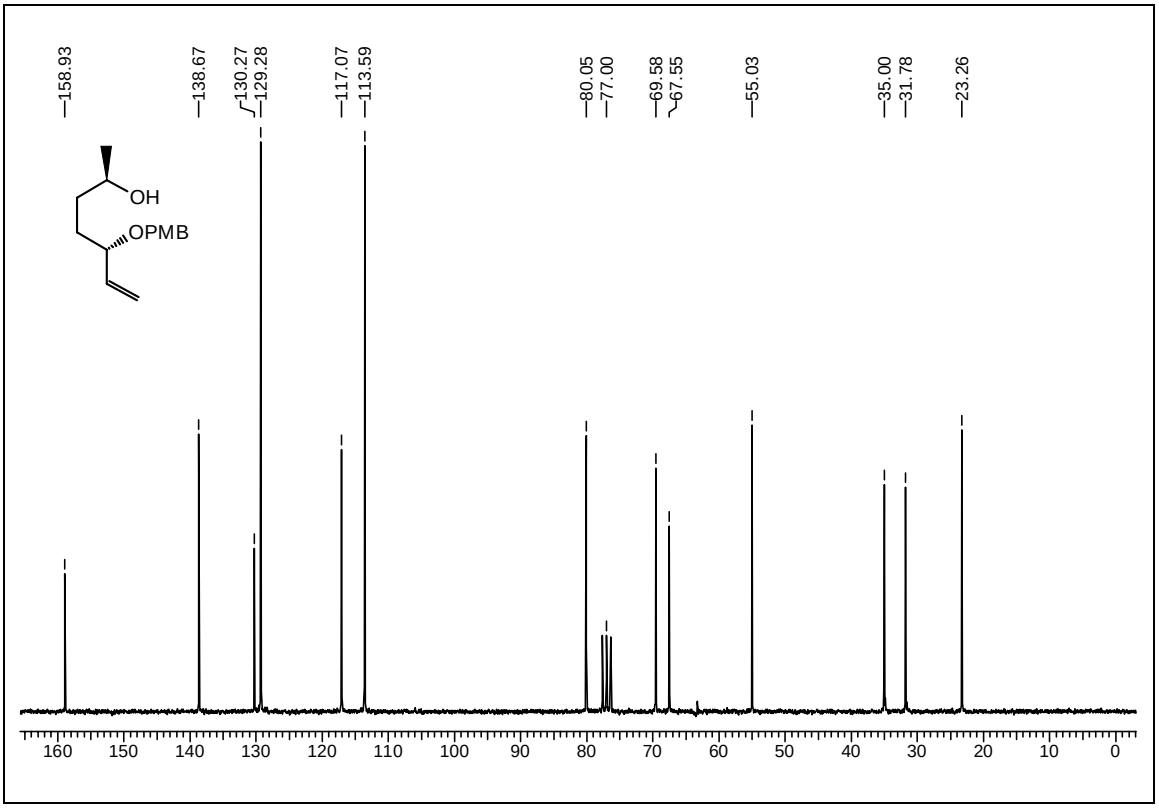
^{1}H NMR spectrum of compound 22 in $CDCl_3$



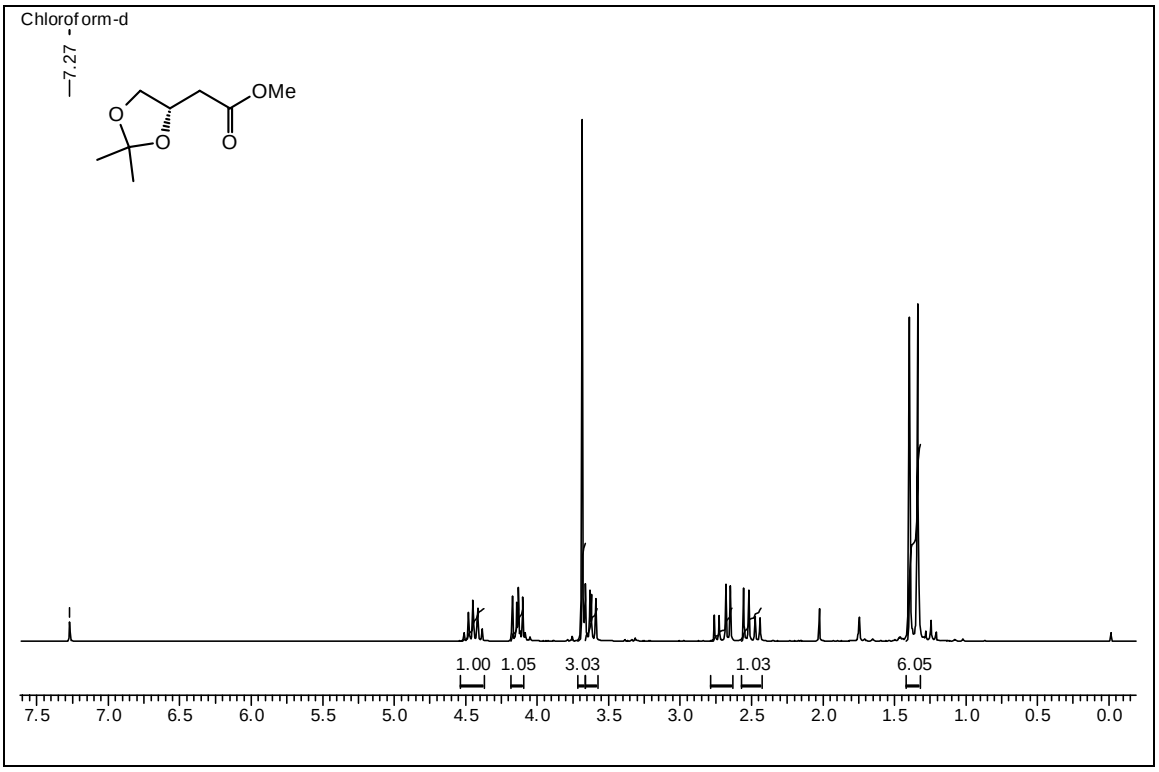
^{13}C NMR spectrum of compound 22 in $CDCl_3$



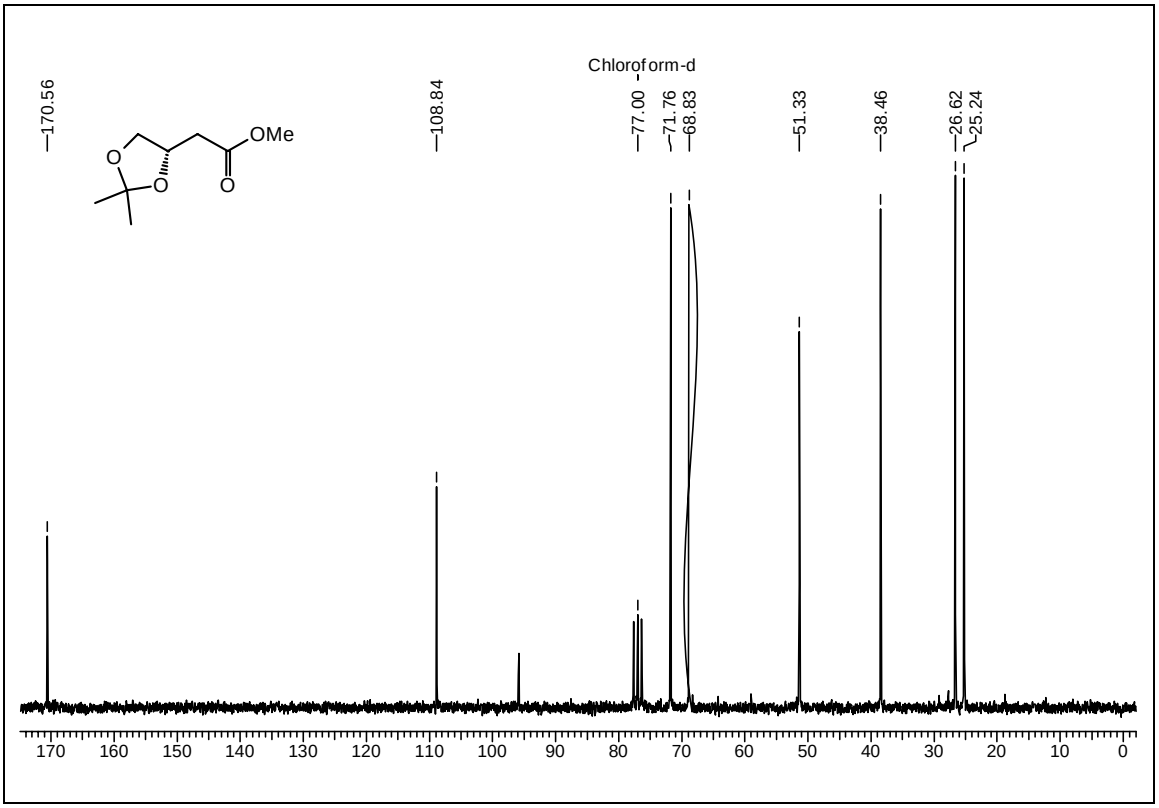
^{1}H NMR spectrum of compound 7 in $CDCl_3$



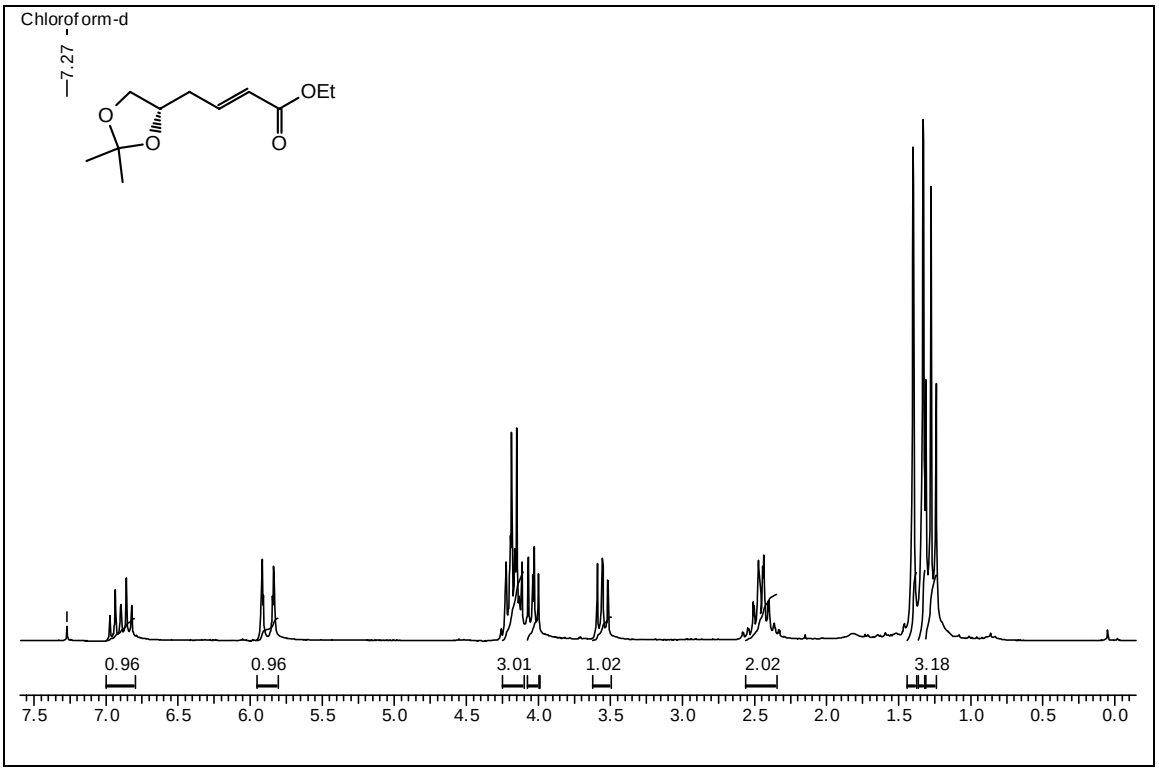
^{13}C NMR spectrum of compound 7 in $CDCl_3$



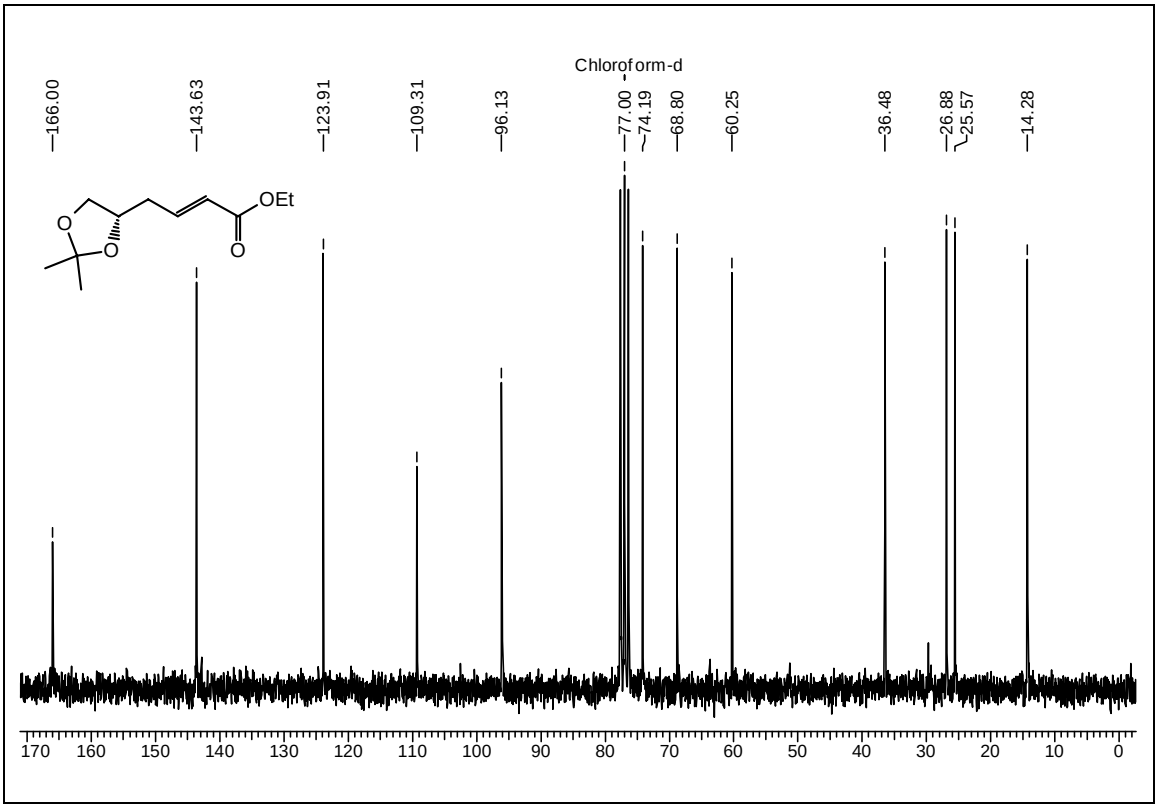
^{1}H NMR spectrum of compound 25 in $CDCl_3$



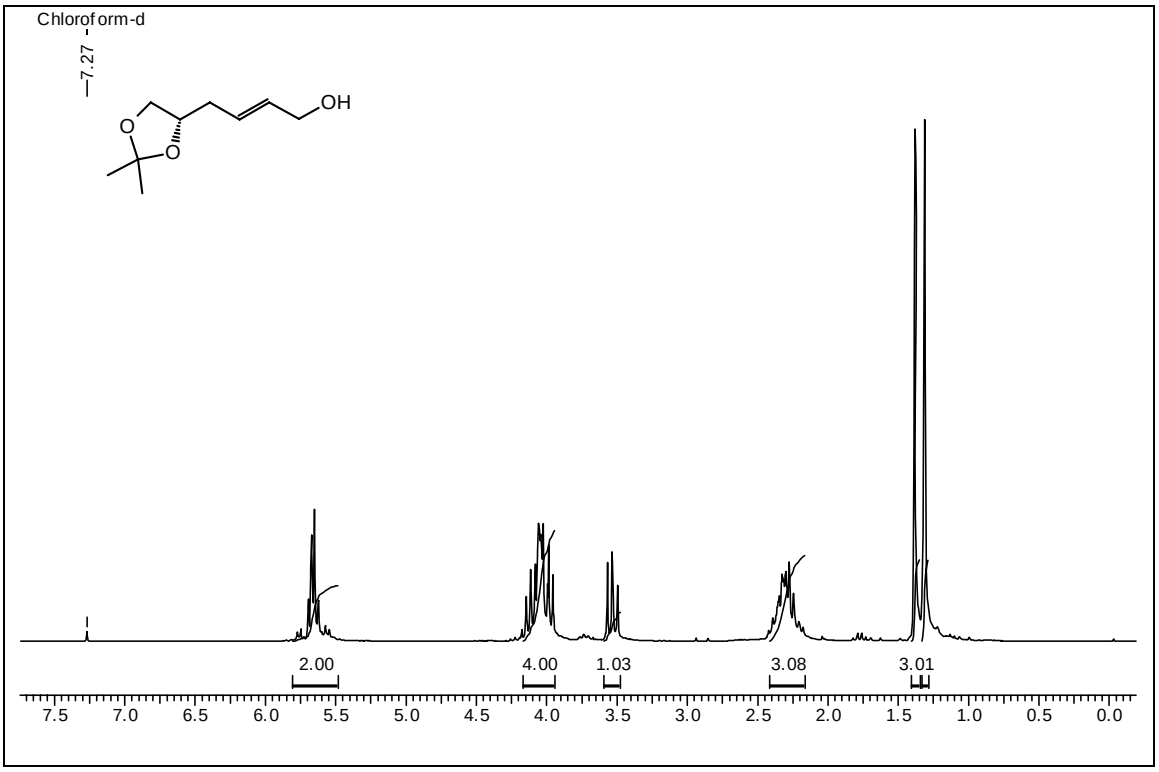
^{13}C NMR spectrum of compound 25 in $CDCl_3$



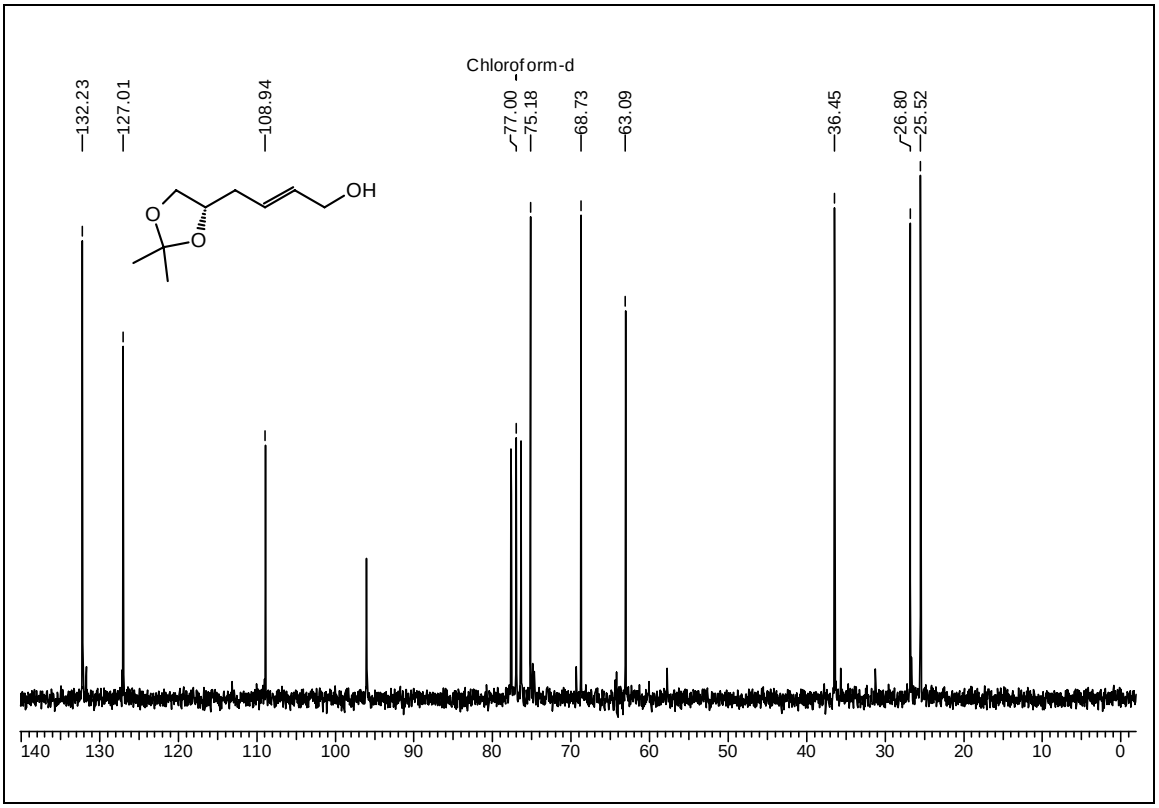
^{1}H NMR spectrum of compound 27 in $CDCl_3$



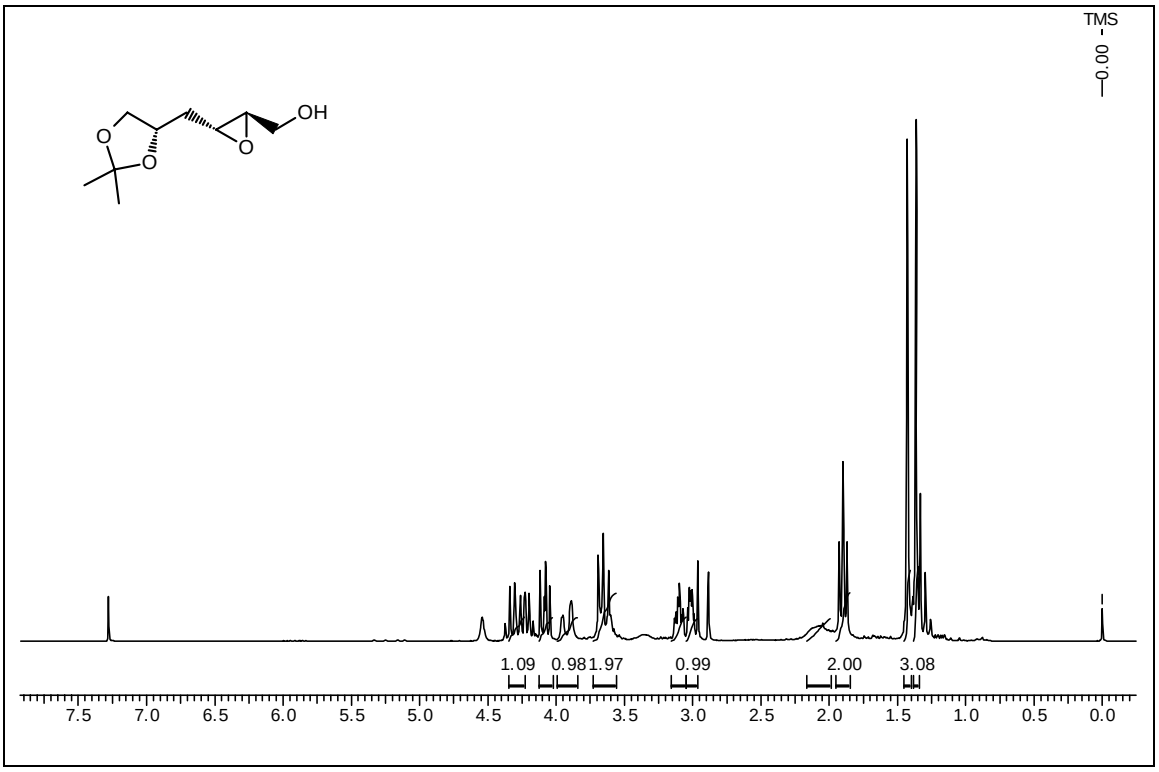
^{13}C NMR spectrum of compound 27 in $CDCl_3$



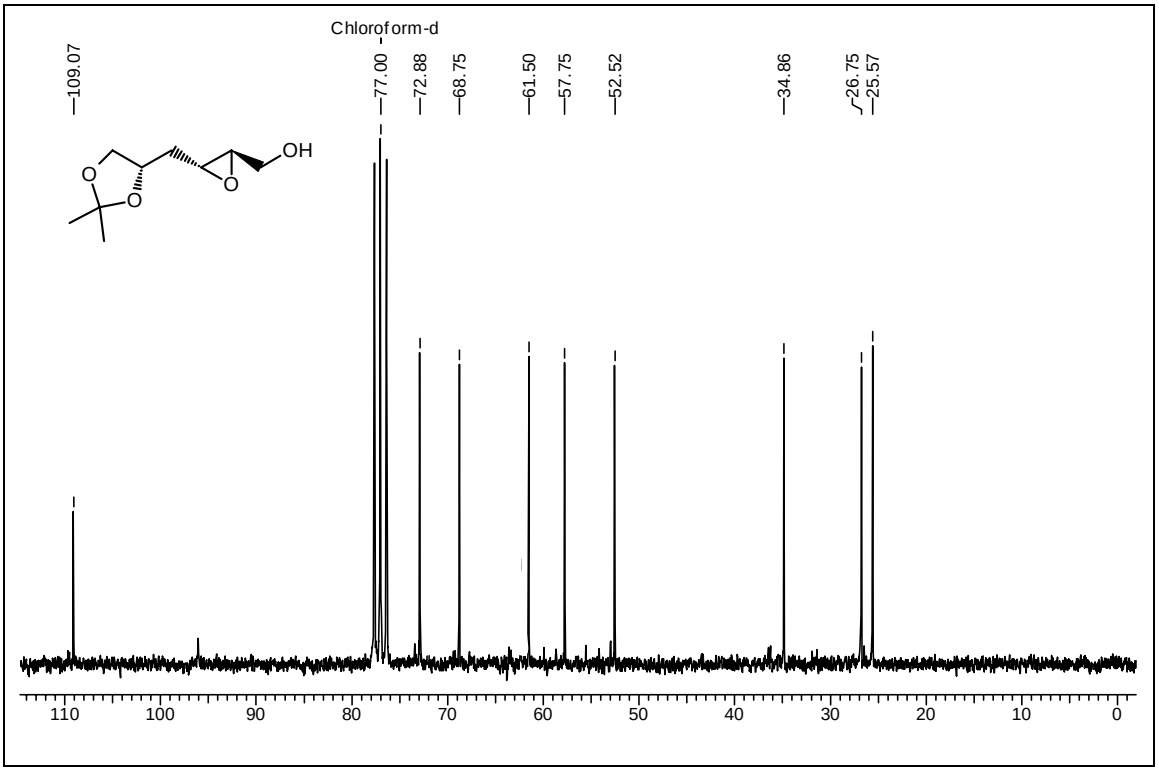
^{1}H NMR spectrum of compound 10 in $CDCl_3$



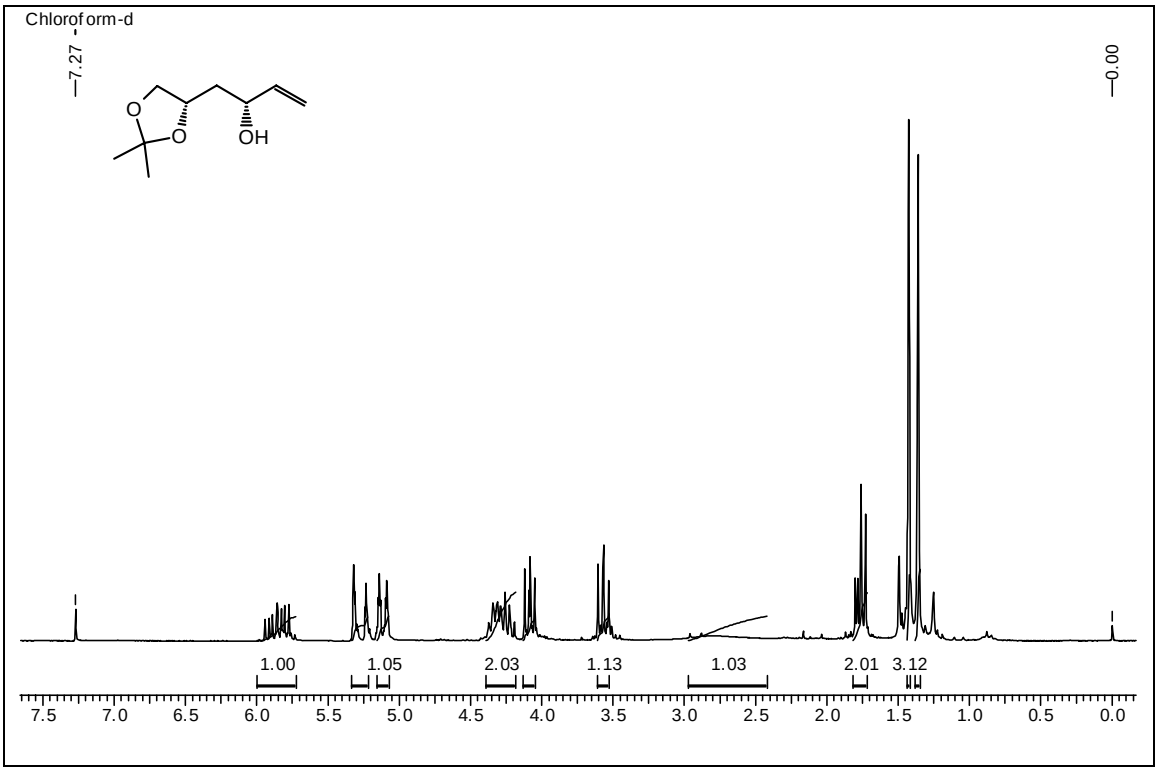
^{13}C NMR spectrum of compound 10 in $CDCl_3$



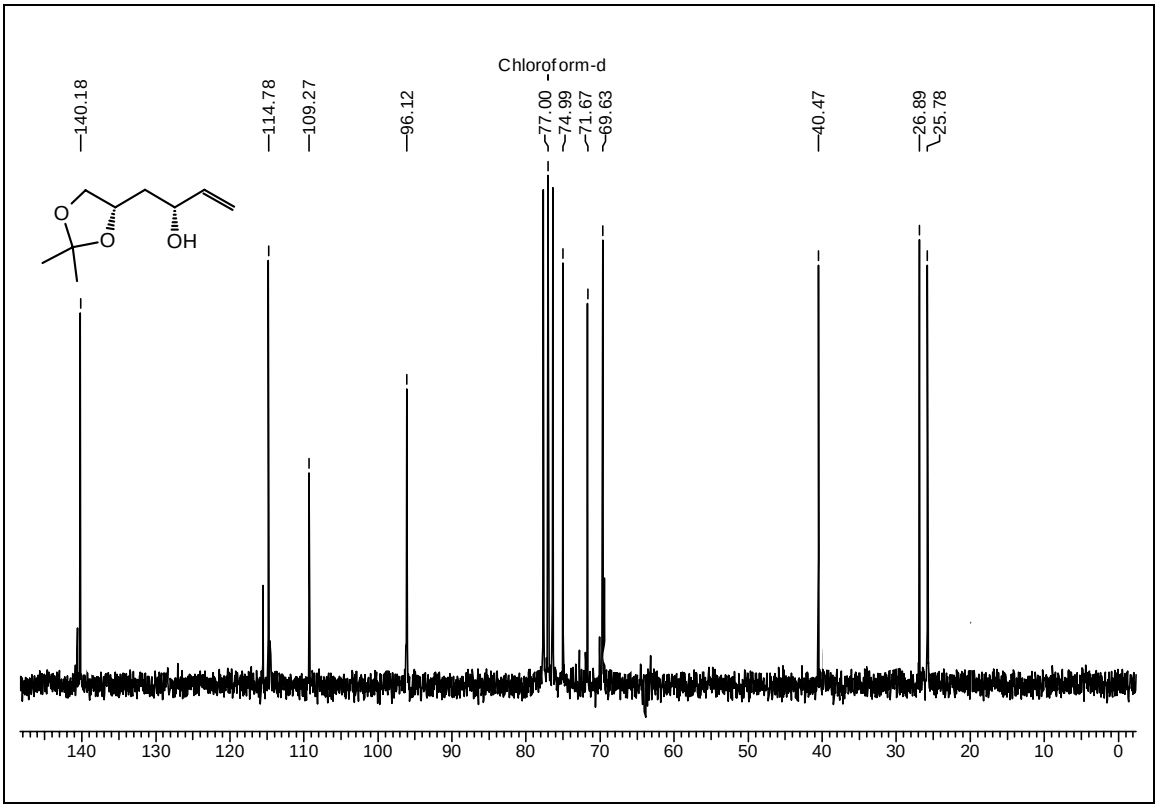
^{1}H NMR spectrum of compound 9 in $CDCl_3$



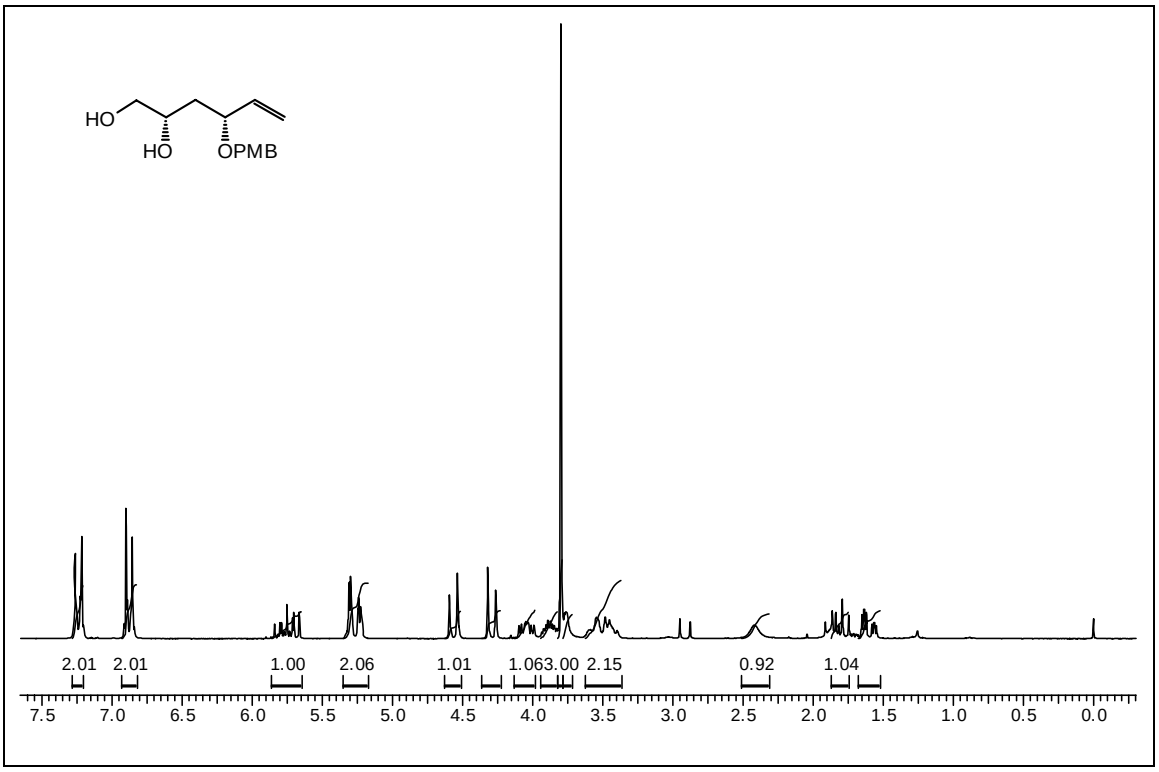
^{13}C NMR spectrum of compound 9 in $CDCl_3$



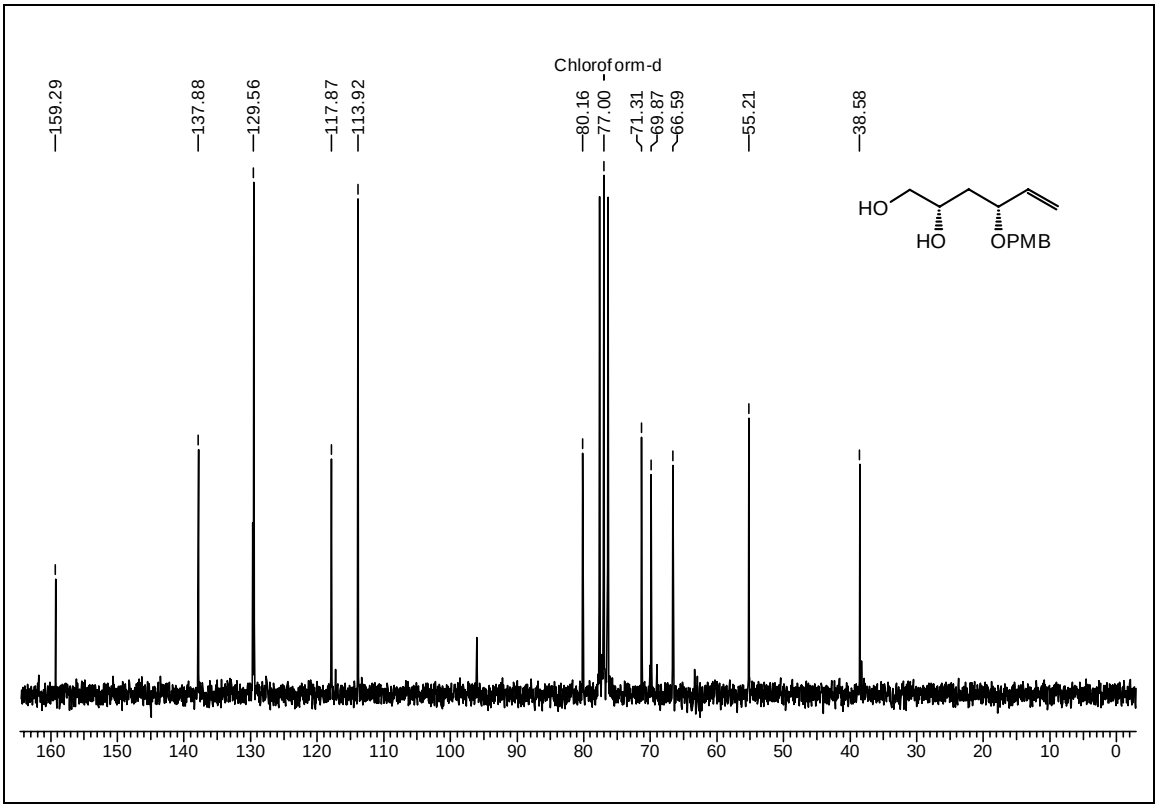
^{1}H NMR spectrum of compound 29 in $CDCl_3$



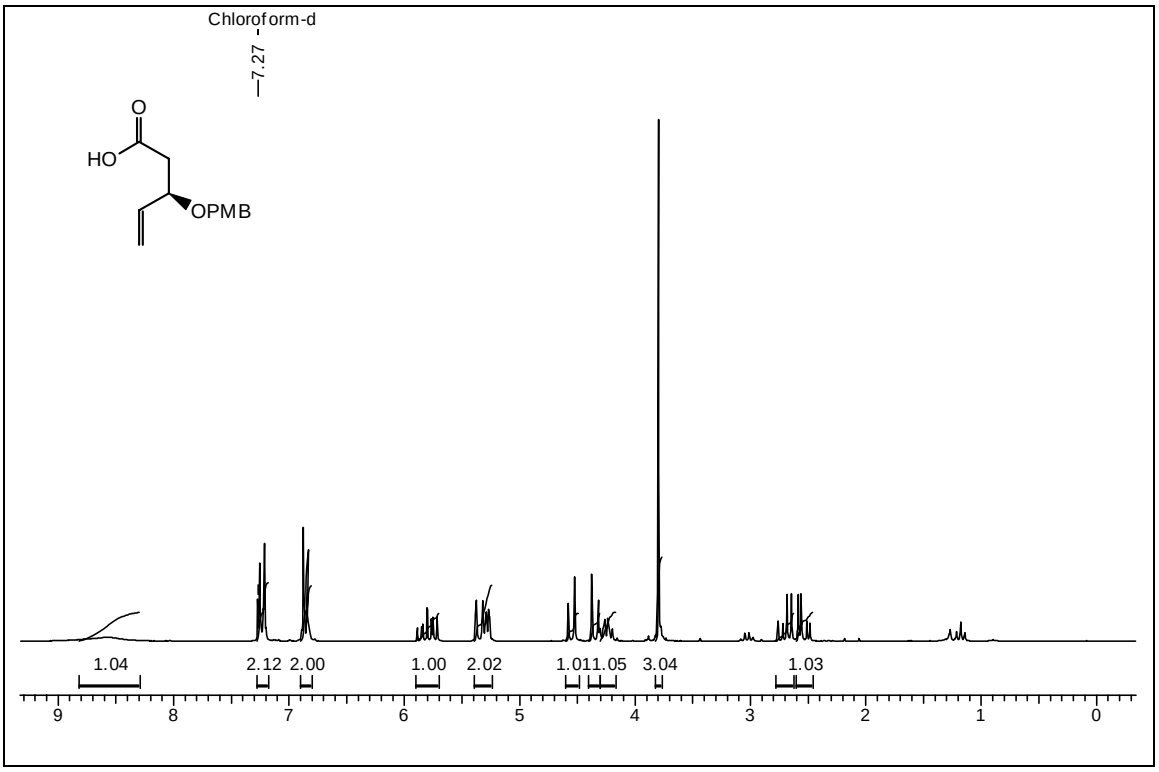
^{13}C NMR spectrum of compound 29 in $CDCl_3$



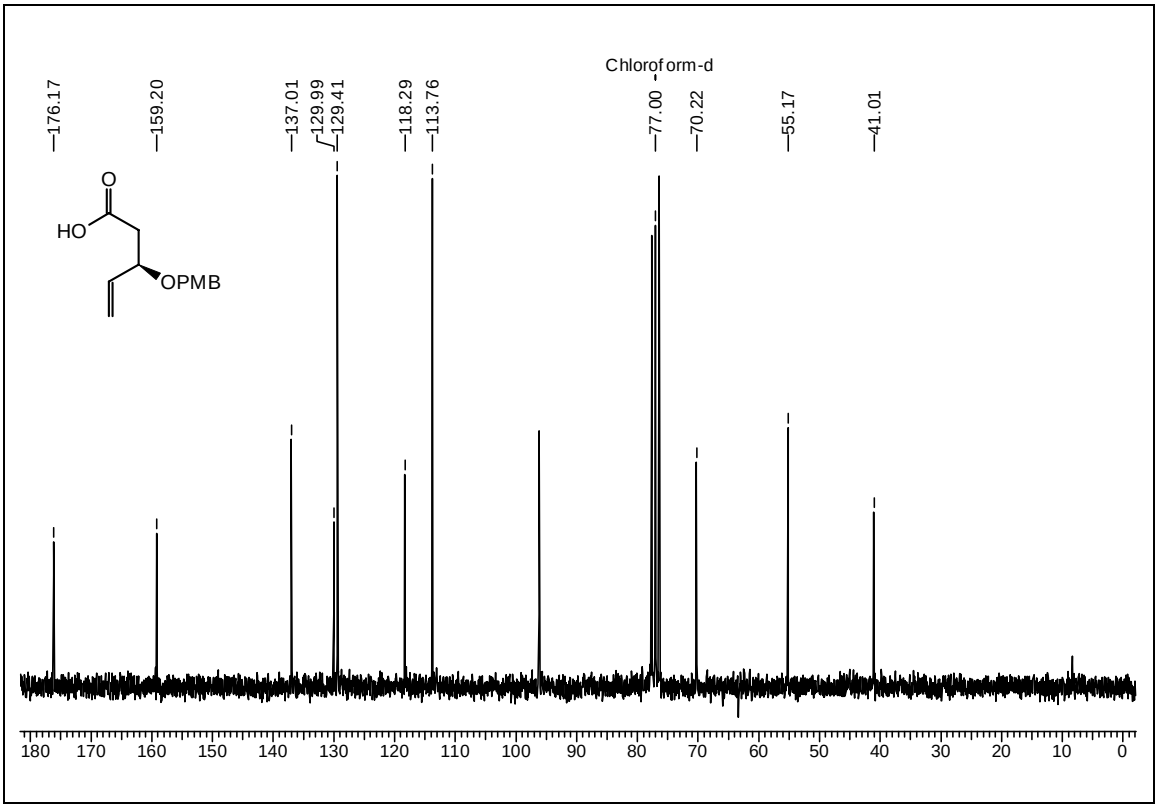
^{1}H NMR spectrum of compound 31 in $CDCl_3$



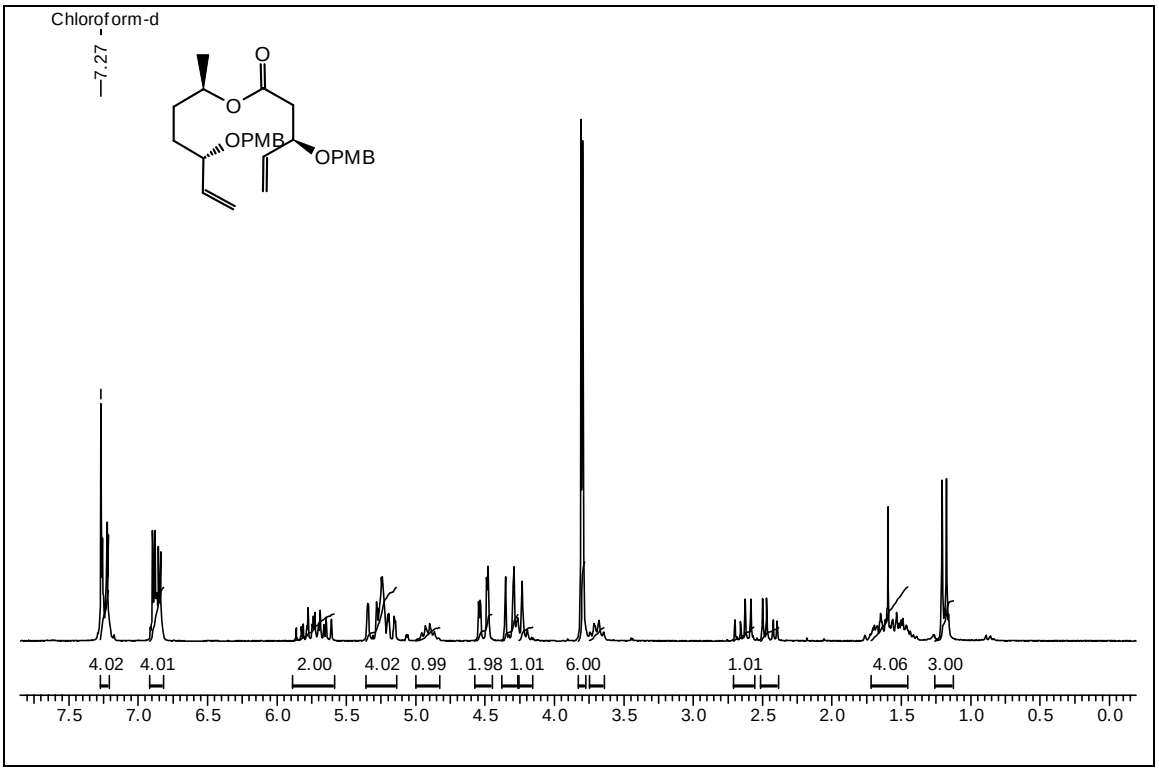
^{13}C NMR spectrum of compound 31 in $CDCl_3$



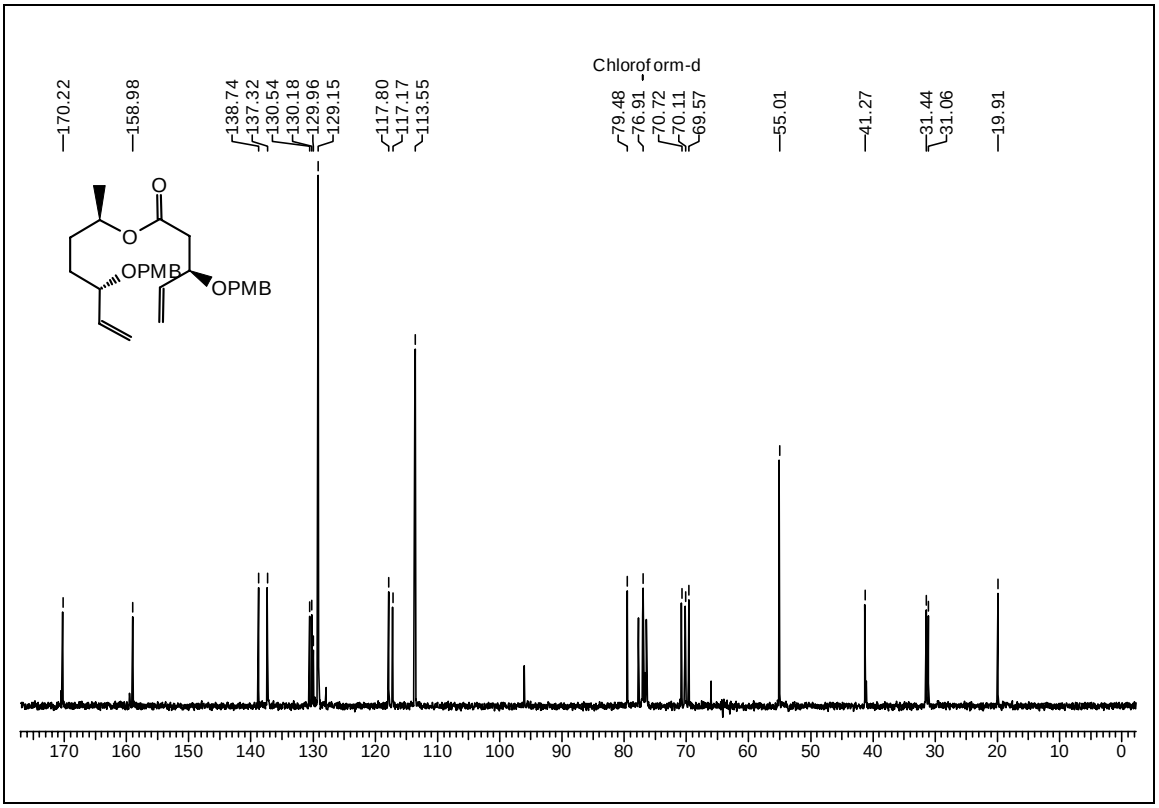
^{1}H NMR spectrum of compound 8 in $CDCl_3$



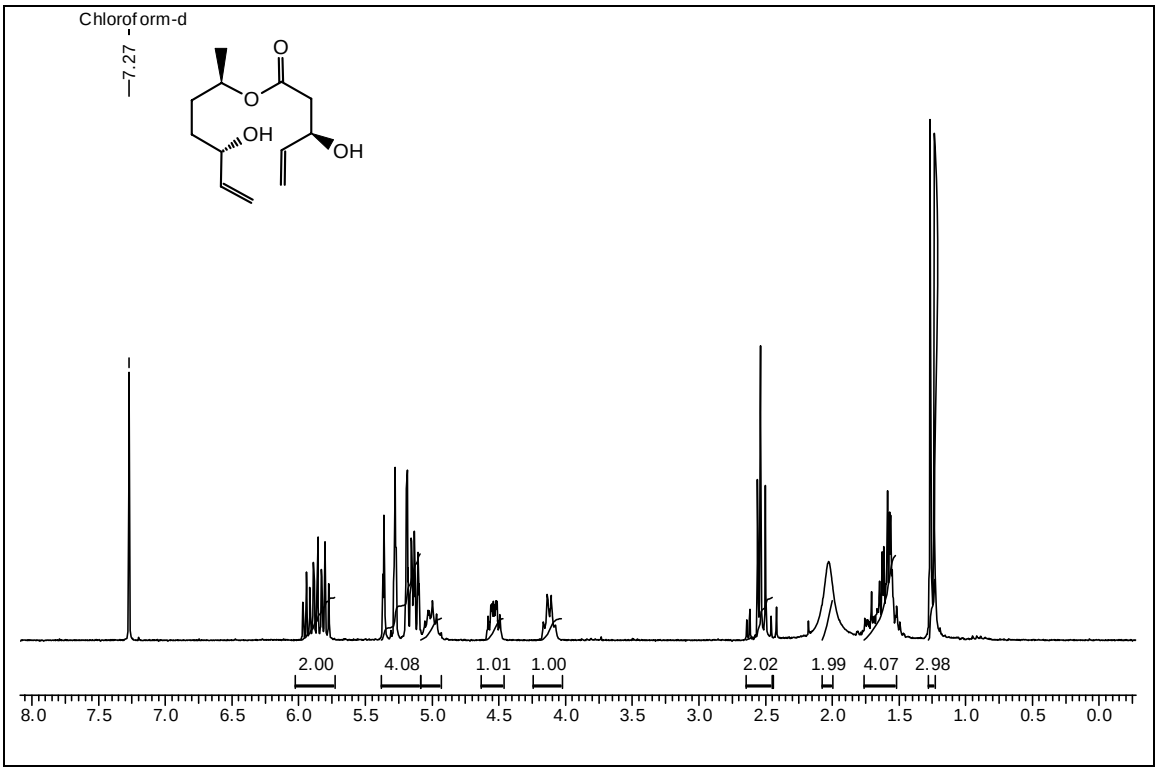
^{13}C NMR spectrum of compound 8 in $CDCl_3$



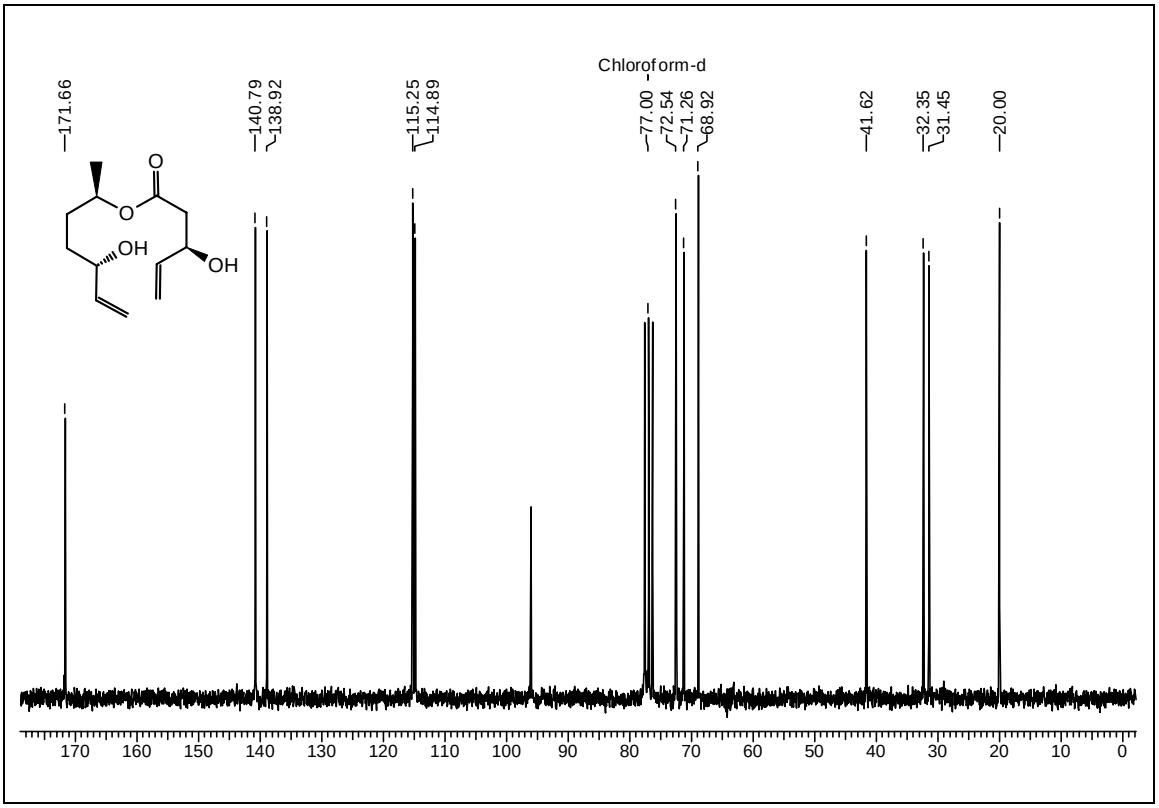
^{1}H NMR spectrum of compound 6 in $CDCl_3$



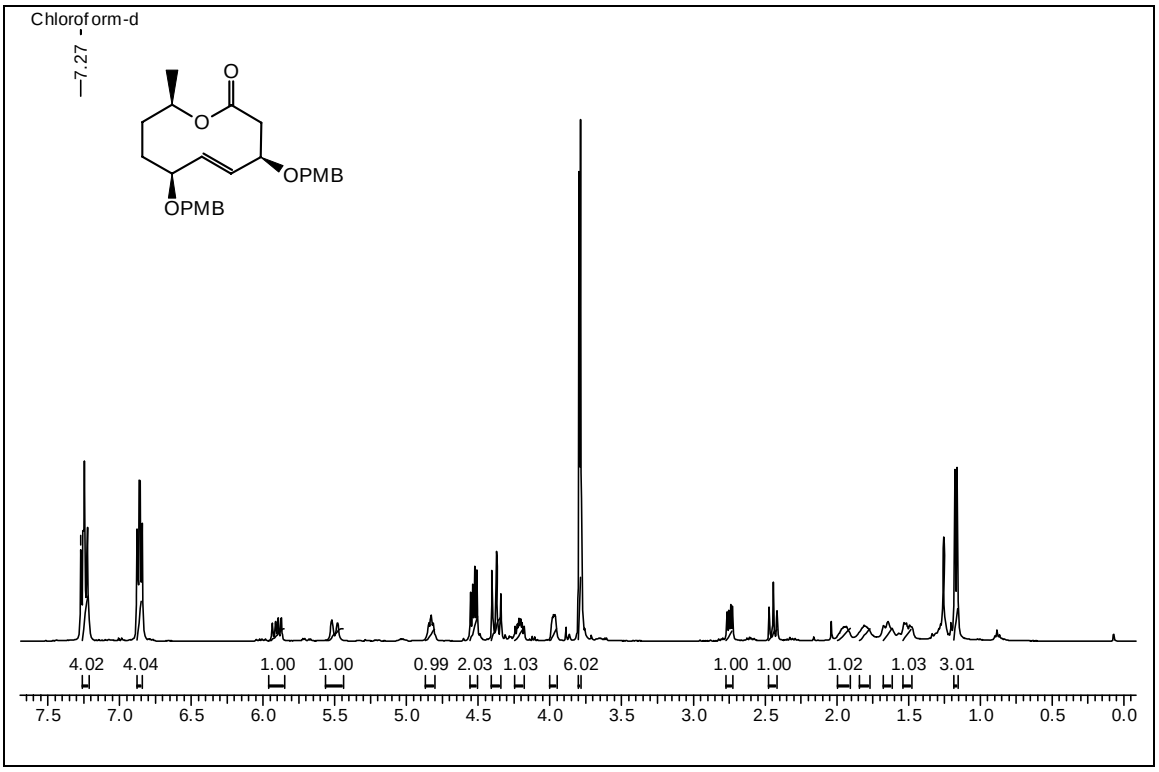
^{13}C NMR spectrum of compound 6 in $CDCl_3$



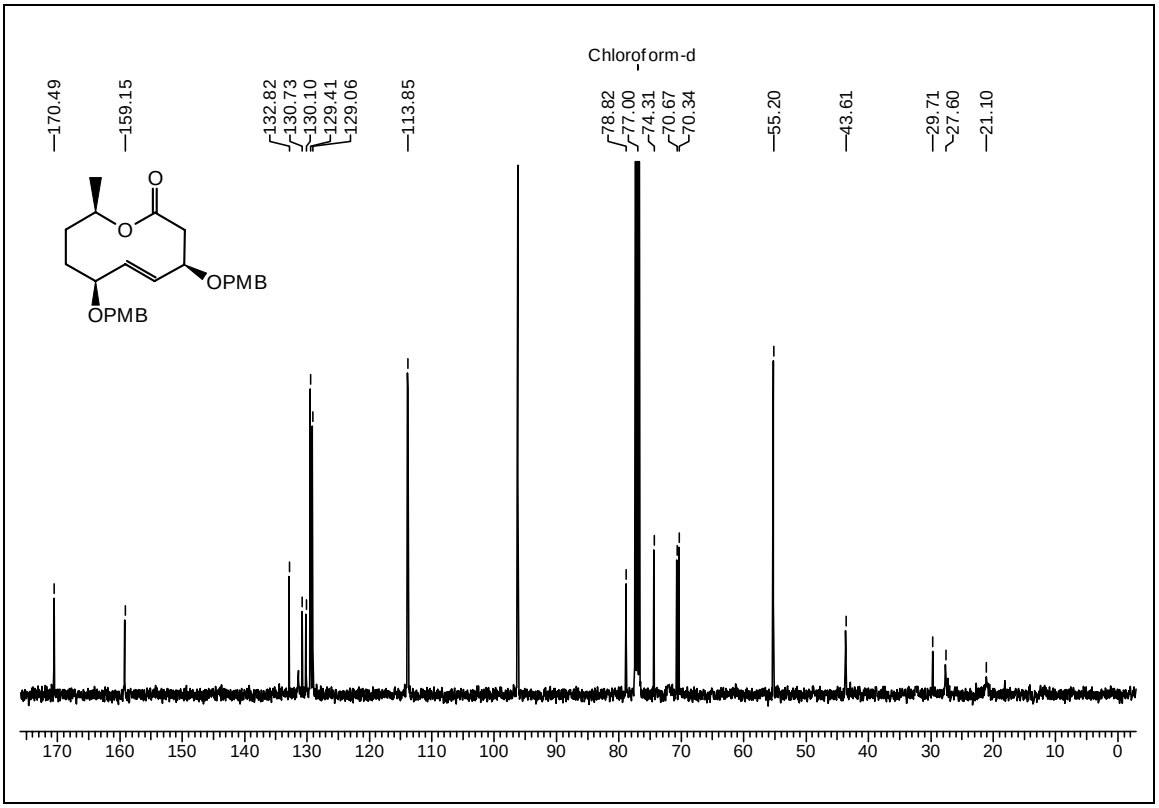
^{1}H NMR spectrum of compound 34 in $CDCl_3$



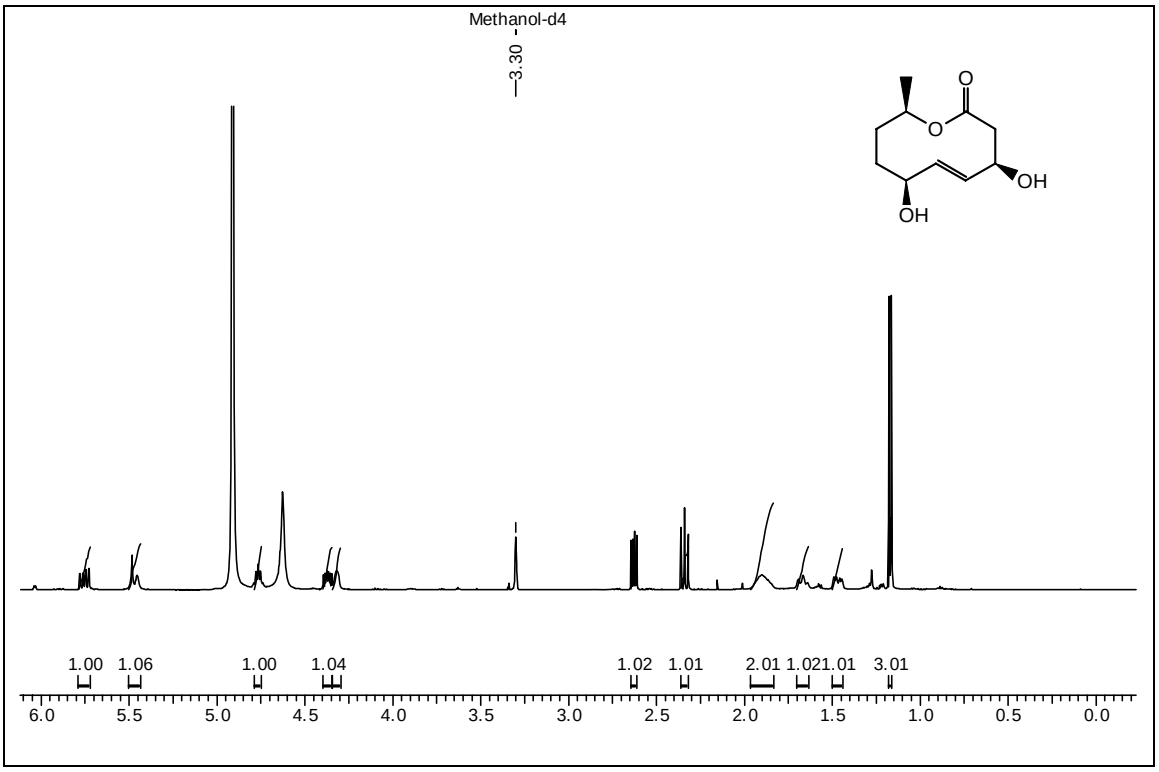
^{13}C NMR spectrum of compound 34 in $CDCl_3$



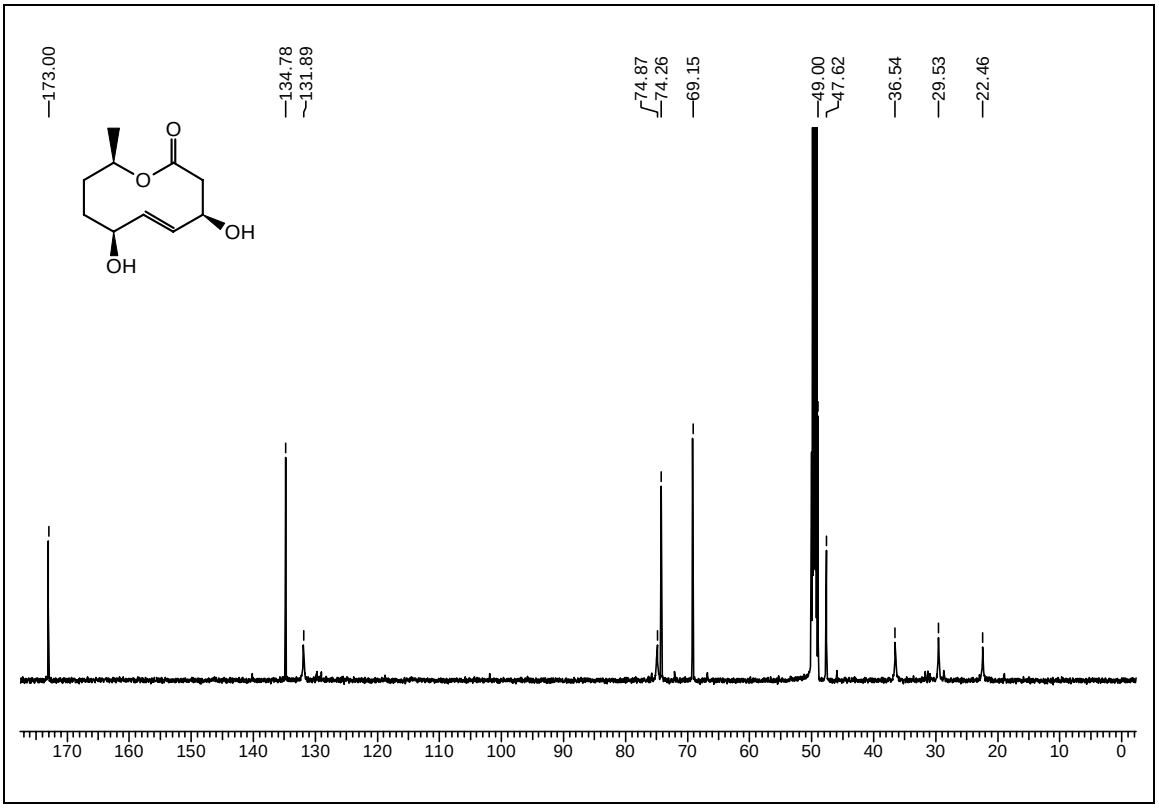
^{1}H NMR spectrum of compound 5 in $CDCl_3$



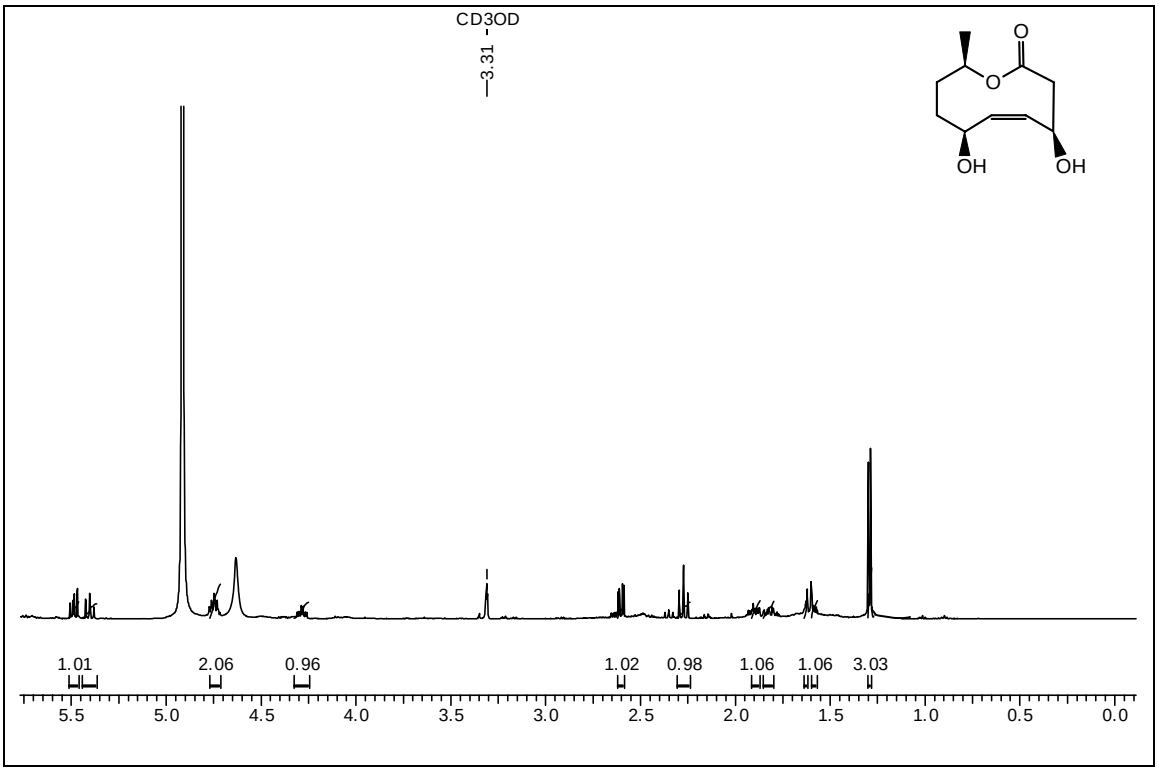
^{13}C NMR spectrum of compound 5 in $CDCl_3$



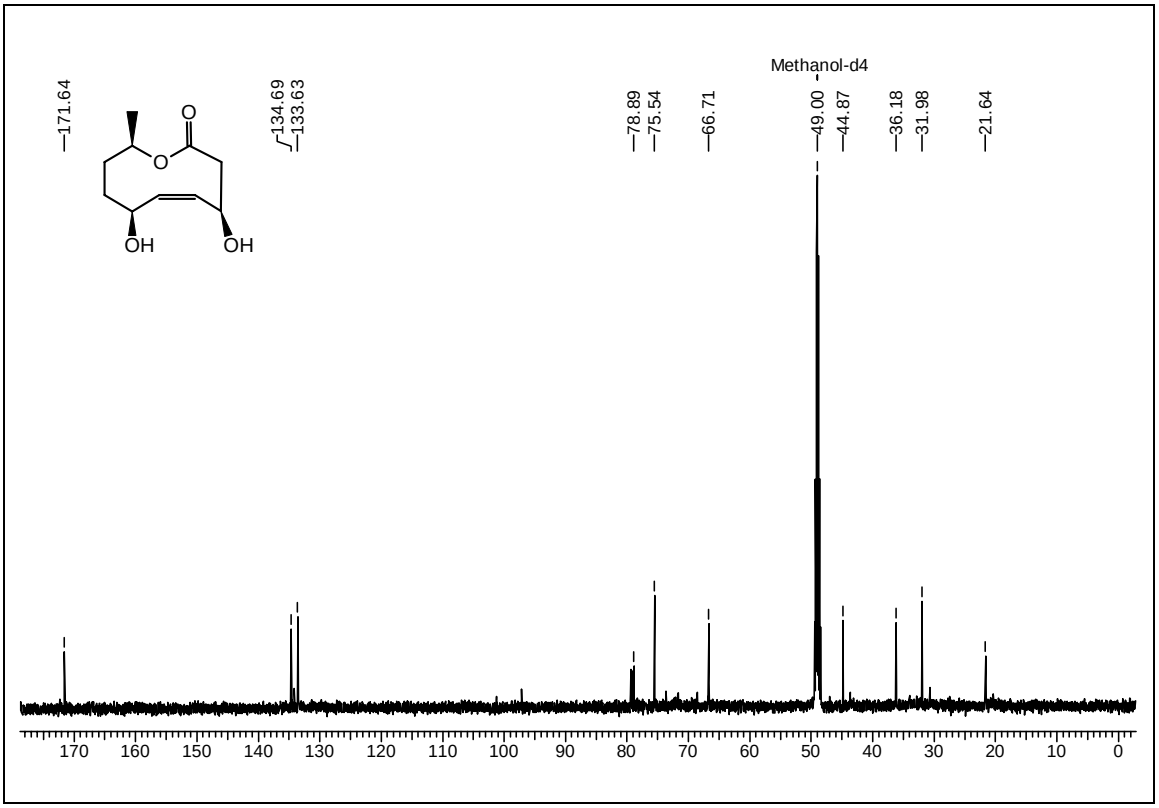
^{1}H NMR spectrum of compound 2 in CD_3OD



^{13}C NMR spectrum of compound 2 in CD_3OD



^{1}H NMR spectrum of compound 3 in CD_3OD



^{13}C NMR spectrum of compound 3 in CD_3OD

CHAPTER-I

Section C

Synthesis of Macrolides by RCM

PRESENT WORK

Present Work

Our previous experiences in synthesis of natural lactones (Nonenolide, Decarestrictine C_2), containing chiral centers adjacent to both the reacting centers, led us to the critical observation that protected diolefinic esters when subjected to RCM reaction gave *trans* selectivity, whereas unprotected diolefinic esters gave *cis* selectivity. To further exemplify the utility of these observations, we synthesized the des- methyl nonenolide, 11 and 12-memberd lactones containing dense functionality adjacent to the sterically constrained reaction centers (Figure-1).

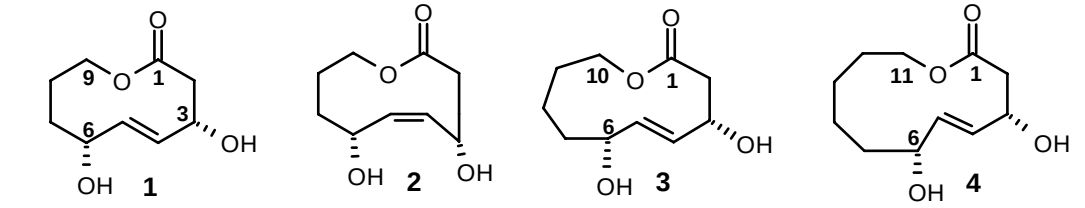
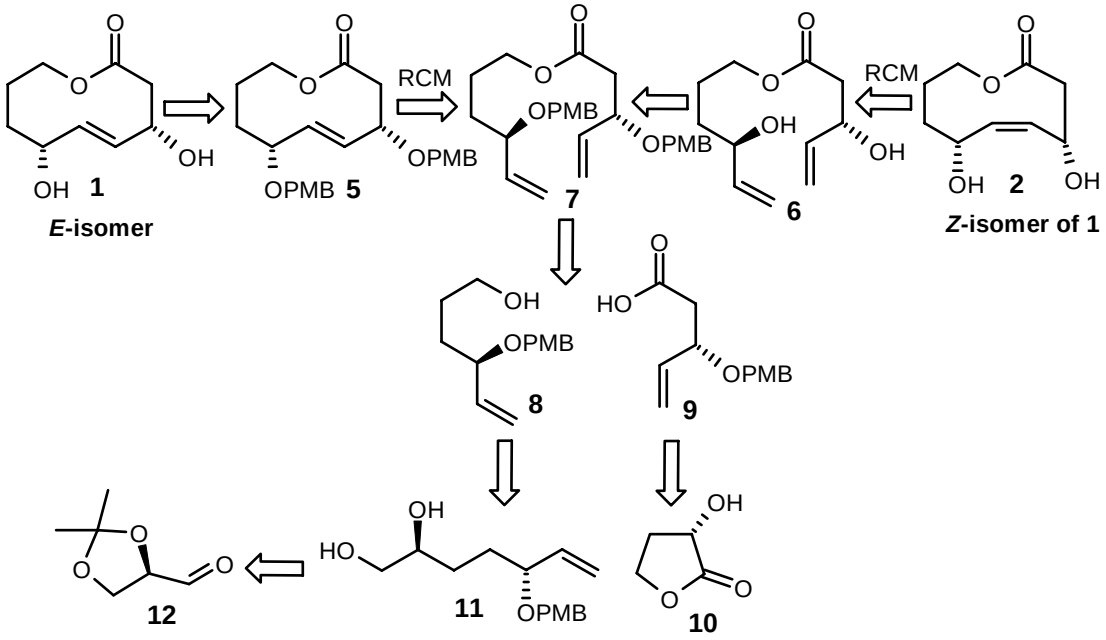


Figure-1

For synthesis of the RCM precursor diolefinic ester we used acid (**9**) as one of the coupling partners: it coupled with the different alcohols to give the requisite diolefinic esters.

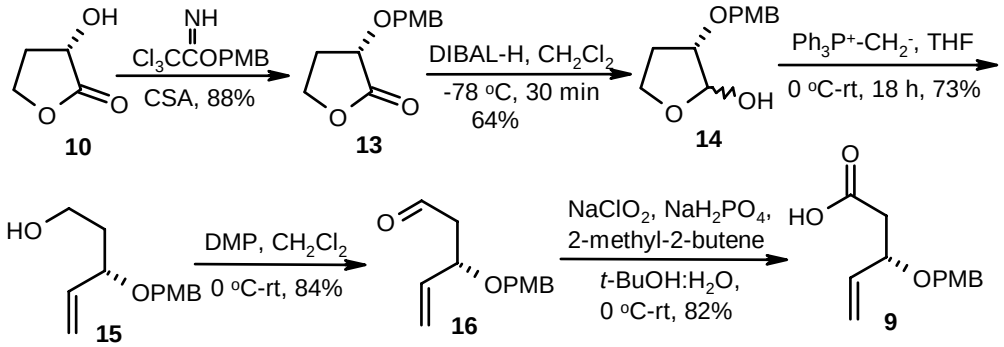


Scheme-1: Retrosynthesis

Retrosynthesis of Desmethyl Nonenolide

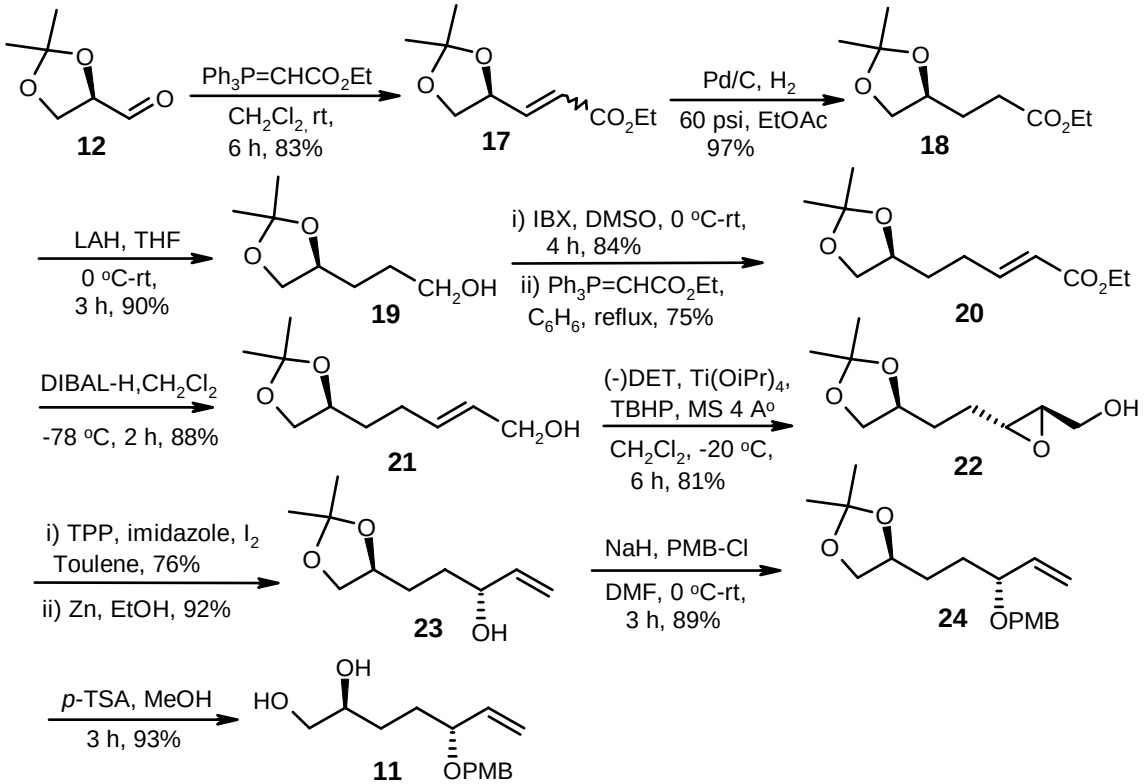
The retrosynthetic analysis is depicted in Scheme-1. The macrolactonization step relies on a RCM on a diolefinic ester. Strategic bond disconnection in ester **7** leads to chiral fragments **8** and **9** that could be derived from D-glyceraldehyde derivative (**12**) and (*S*)-α-hydroxy-γ-butyrolactone (**10**) respectively.

Synthesis of Acid Fragment (9): As given in Chapter-I, section-I



Scheme-2

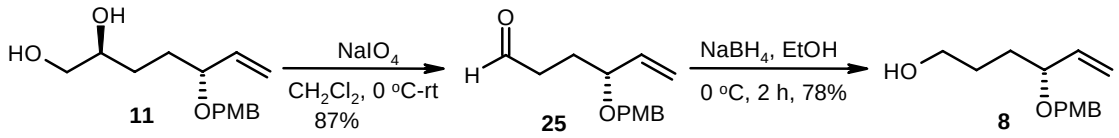
Synthesis of Alcohol fragment (8):



Scheme-3

The target alcohol fragment **8** was synthesized from diol **11** that was, in turn, prepared from D-glyceraldehyde derivative **12** (Scheme-3).

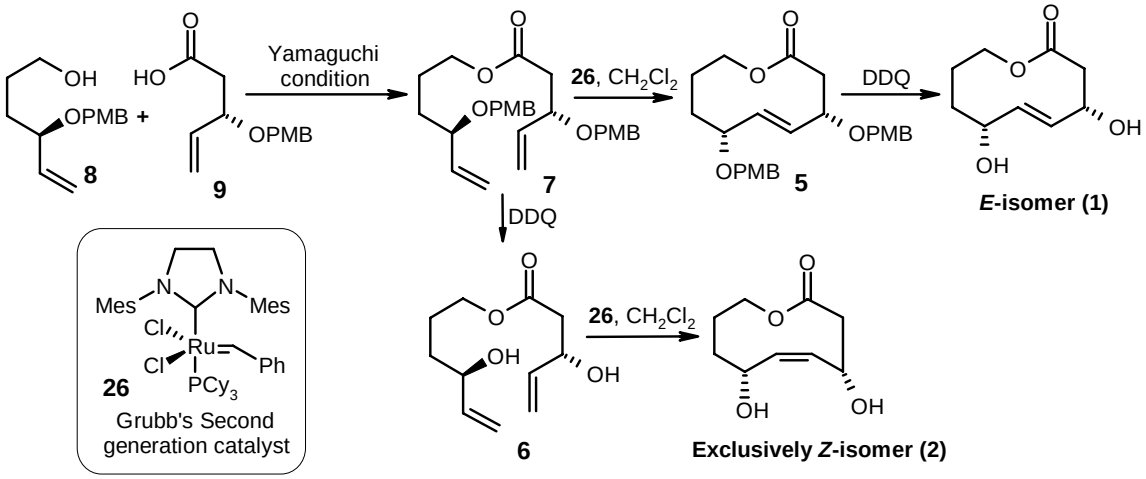
The diol **11** was oxidatively cleaved with sodium metaperiodate (supported on silica gel) in dichloromethane to provide aldehyde **25** in 87% yield. It was subsequently reduced with sodium borohydride ($NaBH_4$) in absolute ethanol to furnish **8** in 78% yield. The structure of **8** was confirmed by NMR studies and elemental analysis (Scheme-4).



Scheme-4

Coupling of Acid and alcohol

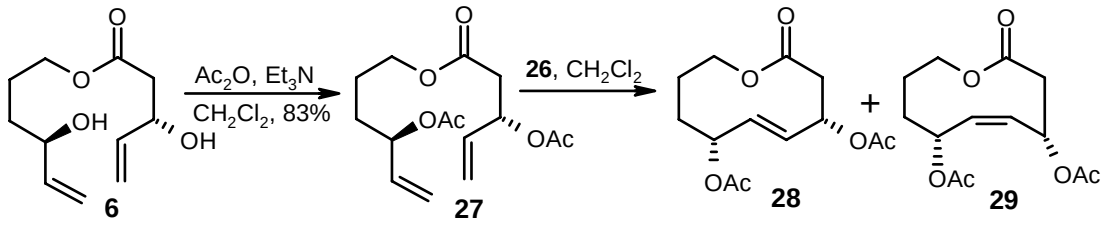
The acid **9** was coupled with (*R*)-4-*p*-methoxybenzylhex-5-en-1-ol (**8**) under Yamaguchi conditions to afford ester **7** in 88% yield. This product was subjected to a RCM reaction to afford **5.** Deprotection of the PMB groups furnished the 10-membered lactone **1** with the *E*-isomer as the exclusive product as established by ^{1}H and ^{13}C NMR analysis. Similarly, RCM reaction on diol **6** (after deprotection of the PMB ether groups of diolefinic ester) afforded exclusively the *Z*-isomer **2** in 75% yield (Scheme-5).



Scheme-5

To verify the effect of protecting groups at the allylic position in controlling the stereochemical outcome of the RCM reaction in provision of olefin (*E* or *Z*), the diol **6** was acetylated using Ac_2O, triethylamine in dichloromethane to furnish **27** in 83% yield.

The RCM reaction on **27** with Grubbs second generation catalyst (10 mol%) afforded an isomeric mixture of 10-membered lactones in an approximately 1:1 ratio of *E*:*Z* isomers (Scheme-6).



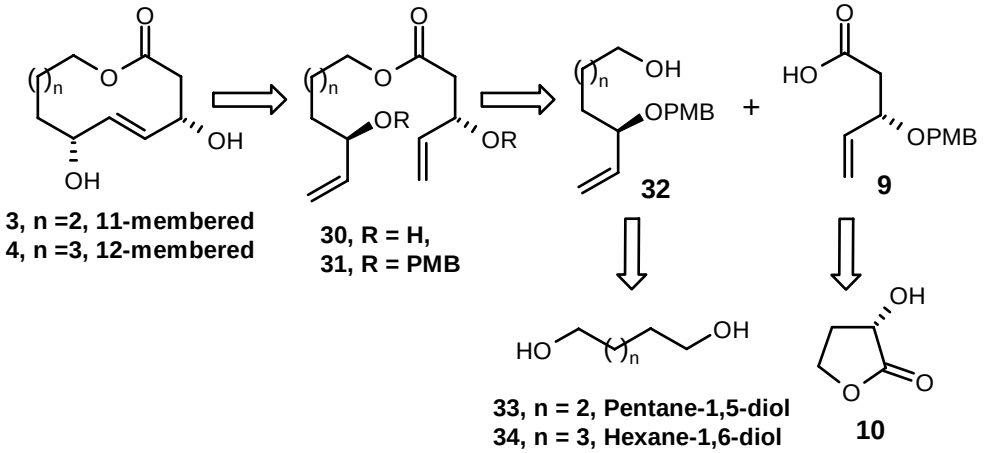
Scheme-6

Synthesis of 11 and 12-membered lactones

The results described herein prompted us to undertake the synthesis of 11-membered and 12-membered ring lactones.

Retro synthetic analysis for 11 and 12-membered lactones

Retrosynthetic analysis indicates that coupling partners of acid (**9**) could be synthesized from (*S*)-α-hydroxy-γ-butyrolactone (**10**) and the alcohol fragments from pentane-1,5-diol (for 11-membered ring) and hexane-1,6-diol (for 12-membered ring).

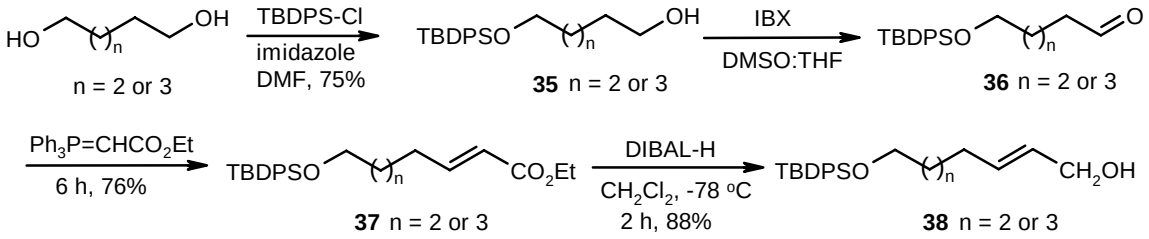


Scheme-7: Retrosynthesis

Synthesis of alcohol fragments (for 11 and 12-members)

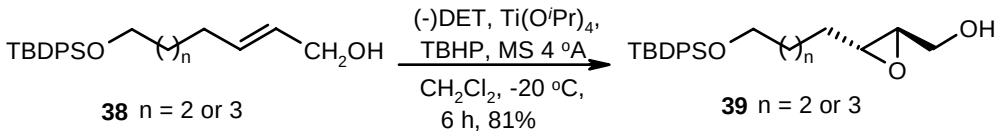
Monoprotection of diol was achieved in 75% yield on treatment with TBDPS-Cl, imidazole in DMF. Proton NMR spectrum showed resonances at 1.06 ppm (9H) as a singlet and between the regions of 7.35-7.69 ppm (10H) as a multiplet corresponds to the silyl ether groups. For homologation of **35**, the primary hydroxyl group was oxidized

with IBX, in DMSO:THF to afford aldehyde **36**, that was subsequently treated with (carboethoxymethylene)triphenylphosphorane to furnish a mixture of *trans* and *cis* products. The minor *cis* compound was separated by silica gel column chromatography and the major *trans* isomer was obtained in 76% yield. The structure of **37** was confirmed by NMR, and by IR and elemental analysis. Hydride reduction of **37** with DIBAL-H yielded the allyl alcohol **38** in 88% yield. The structure of **38** was confirmed by spectroscopic data and by elemental analysis (Scheme-8).



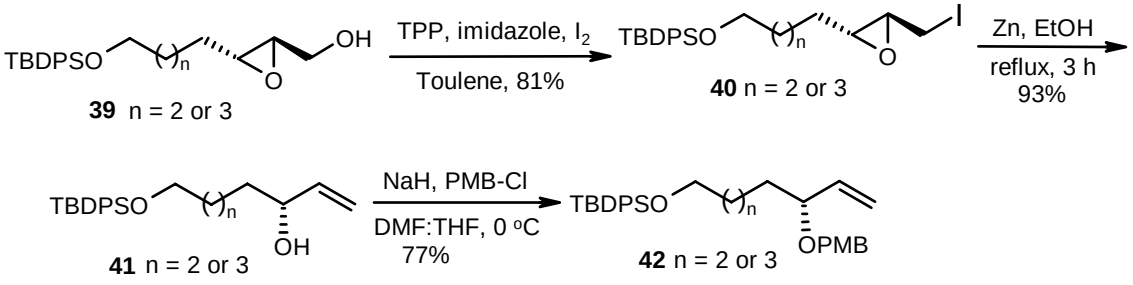
Scheme-8

Generation of the chiral centre was achieved by employing Sharpless asymmetric epoxidation procedure. Thus, compound **38** was treated with (−) DET as a chiral ligand, $Ti(O^iPr)_4$ and TBHP at −20 °C to furnish (2*R*,3*R*)-epoxide **39** in 81% yield (Scheme-9).



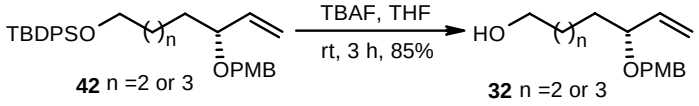
Scheme-9

Next, the compound **39** was converted to **42** in three steps in 58% overall yield. In proton NMR spectrum, the characteristic terminal olefinic signals between the regions of 5.08-5.95 ppm and resonances due to PMB group were observed at 3.80 ppm and between the regions of 6.84-7.27 ppm (Scheme-10).



Scheme-10

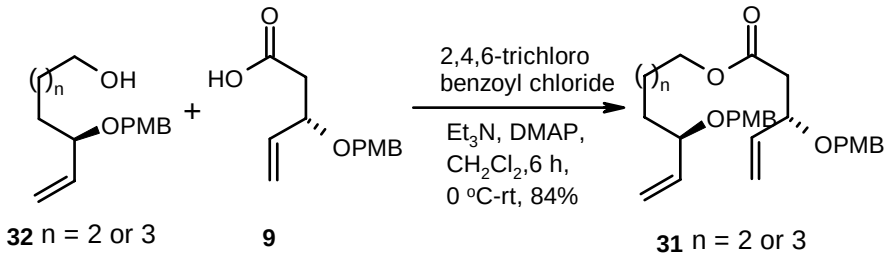
To secure the target fragment, compound **42** was treated with 1.0 M tetra butyl ammonium fluoride (TBAF) in THF to obtain the requisite alcohol **32** in 85% yield. The structure of **32** was established by NMR studies and elemental analysis data (Scheme-11).



Scheme-11

Coupling reaction between Acid (9) and alcohol (32)

With the key intermediates **9** and **32** in hand, our next task was to couple the two fragments and conduct the RCM reaction. The acid **9** coupled with alcohol **32** under Yamaguchi conditions to afford **31** in 84% yield. Proton NMR spectrum clearly showed the down field shift of signals (H-10 for 11-member and H-11 for 12-member) indicated ester formation (Scheme-12).

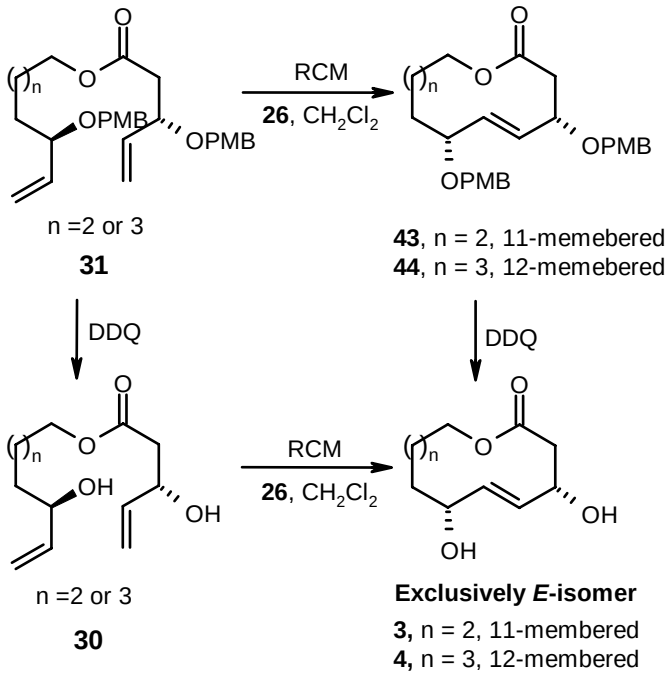


Scheme-12

This set the stage for the crucial ring-closing metathesis: it was successfully achieved with Grubbs' second-generation catalyst. A 0.001 M solution of **31** and 10-mol% of Grubbs' second-generation catalyst **26** was heated at reflux for 8 h in dry, degassed CH_2Cl_2. This provided the desired lactones (**43** or **44**) *E*-isomer as exclusive product in 75% yield. Deprotections of the PMB groups afforded the desired lactones (**3** or **4**). The geometry of the newly formed double bond was clearly assigned by detection of the olefinic J_{trans} coupling constant (15.56 Hz) (Scheme-13).

We wished to verify the consistency of the results obtained from the RCM reactions. The diol (**30**) was subjected to RCM reaction with Grubbs' second generation catalyst (10 mol%) to afford the lactones (11 or 12-membered) *E*-isomer as the single

product in 76% yield. No spectroscopic evidence for the formation of the *Z*-isomer was discernible (Scheme-13).



Scheme-13

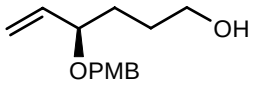
Here, we obtained the *E*-isomer as the sole product with protected and unprotected diolefinic esters. It clearly indicates that the isomeric outcome of the olefin could not be controlled by the RCM reaction on higher than 10-membered lactones.

Conclusion:

We have successfully synthesized the *E* and *Z*-isomers of the desmethyl nonenolide by employing protecting group directed RCM methodology.

EXPERIMENTAL SECTION

(*R*)-4-(4-methoxybenzyloxy)hex-5-en-1-ol (8)

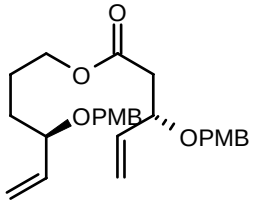


To a solution of **11** (0.266 g, 1.0 mmol) and $NaIO_4$ (0.277 g, 1.3 mmol) in CH_2Cl_2 (20 mL), was stirred at room temperature for 3 h. The reaction mixture filtered through the pad of celite, dried over Na_2SO_4 and concentrated under pressure to afford aldehyde **25** in 87% yield.

The crude aldehyde (0.204 g, 0.870 mmol) was treated with $NaBH_4$ (0.035 g, 0.925 mmol) at 0 ^oC, in absolute EtOH (10 mL) and stirred for 2 h at same temperature. The reaction mixture was quenched with 1% AcOH, filtered, dried over Na_2SO_4 and evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (eluted in 35% EtOAc: light petroleum ether) to give **8** as colorless oil.

Yield	**:**	0.160 g, 78%
Mol. Formula	**:**	$C_{14}H_{20}O_3$
$[\alpha]_D^{25}$	**:**	+27.8 (*c* 1.0, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	**:**	3425, 3018, 2937, 1513, 1216, 1036, 758.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ 1.62-1.68 (m, 4H), 1.93 (br s, 1H), 3.57-3.64 (m, 2H), 3.75 (m, 1H), 3.80 (s, 3H), 4.25 (d, 1H, *J* = 11.37 Hz), 4.51 (d, 1H, *J* = 11.37 Hz), 5.17-5.26 (m, 2H), 5.75 (m, 1H), 6.84-6.90 (m, 2H), 7.23-7.27 (m, 2H).
^{13}C NMR ($CDCl_3$, 100 MHz)	**:**	δ 28.8, 32.3, 55.2, 62.7, 69.8, 80.0, 113.8, 117.2, 129.4, 130.4, 138.8, 159.2.
Elemental Analysis	**:**	**Calcd.:** C, 71.16; H, 8.53; **Found:** C, 70.95; H, 8.48.

(*S*)-((*R*)-4-(4-methoxybenzyloxy)hex-5-enyl)-3-(4-methoxybenzyloxy)pent-4-enoate (7)



To a stirred solution of **9** (0.150 g, 0.635 mmol) in dry CH_2Cl_2 (15 ml) were added Et_3N (0.126 g, 1.25 mmol) and a solution of 2, 4, 6-trichlorobenzoylchloride (0.231 g, 0.950 mmol) in dry CH_2Cl_2 (10 ml) and stirred at 0 ^oC for 20 min. The solution of **8** (0.150 g, 0.635 mmol) in dry CH_2Cl_2 (10 ml) and DMAP (catalytic) was added and stirred for 6 h at room temperature (Checked by TLC). The solvent was evaporated, the crude was purified by silica gel column chromatography (eluted in 12% EtOAc:light petroleum ether) to afford **7** as a colorless liquid.

Yield : 0.254 g, 88%

Mol. Formula : $C_{27}H_{34}O_6$

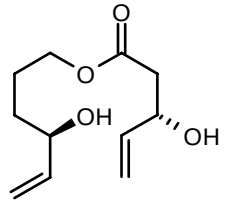
$[\alpha]_D^{25}$: +4.6 (*c*, 1.0, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.54-1.69 (m, 4H), 2.39 (dd, 1H, *J* = 5.56, 15.04 Hz), 2.57 (dd, 1H, *J* = 7.96, 15.04 Hz), 3.68 (m, 1H), 3.79 (2 x s, 6H), 4.05 (t, 2H, *J* = 6.3 Hz), 4.19 (m, 1H), 4.27 (d, 2H, *J* = 11.60 Hz), 4.47 (d, 2H, *J* = 11.60 Hz), 5.14-5.33 (m, 4H), 5.61-5.85 (m, 2H), 6.81-6.86 (m, 4H), 7.18-7.25 (m, 4H).

^{13}C NMR ($CDCl_3$, 100 MHz) : δ 24.7, 31.9, 41.1, 55.2, 64.4, 69.7, 70.2, 76.7, 79.6, 113.7, 113.8, 117.2, 117.8, 129.2, 129.3, 130.3, 130.7, 137.4, 138.8, 159.1, 170.7.

Elemental Analysis : **Calcd.:** C, 71.34; H, 7.54; **Found:** C, 71.12; H, 7.48.

(*S*)-((*R*)-4-hydroxyhex-5-enyl)-3-hydroxypent-4-enoate (6)



To a solution of compound **7** (0.100 g, 0.220 mmol) in CH_2Cl_2:H_2O mixture (9:1, 10 mL) was added DDQ (0.110 g, 0.484 mmol) and stirred at room temperature for 2 h. The reaction mixture was quenched with saturated solution of $NaHCO_3$, organic layer was separated, washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (silica gel, 60-120 mesh, 40% EtOAc in light petroleum ether) to afford **6** as a colorless liquid.

Yield : 0.036 g, 77%

Mol. Formula : $C_{11}H_{18}O_4$

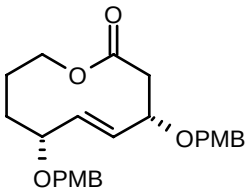
$[\alpha]_D^{25}$: –5.7 (*c*, 0.8, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 3417, 3083, 2980, 1714, 1645, 1277, 1032, 993, 752.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.58-1.64 (m, 2H), 1.68-1.77 (m, 2H), 2.52-2.57 (m, 2H), 4.08 (m, 1H), 4.15 (t, 2H, *J* = 6.2 Hz), 4.54 (m, 1H), 5.10-5.37 (m, 4H), 5.78-5.97 (m, 2H).

Elemental Analysis : **Calcd.:** C, 61.66; H, 8.47; **Found:** C, 61.58; H, 8.41.

(4*S*,7*R*,*E*)-4,7-bis(4-methoxybenzyloxy)-3,4,7,8,9,10-hexahydrooxecin-2-one (5)



To a stirred solution of **7** (0.05 g, 0.11 mmol, 0.001M) in freshly distilled degassed anhydrous CH_2Cl_2 (110 ml) was added Grubb's second generation catalyst (0.010 g, 0.011 mmol) and heated at reflux for 8 h under an argon atmosphere until the complete consumption of starting material (monitored by TLC). The solvent was evaporated to a brown residue, which was purified by silica gel column chromatography (eluted in 12% EtOAc:light petroleum) to afford **5**.

Yield : 0.035 g, 74%

Mol. Formula : $C_{25}H_{30}O_6$

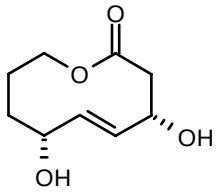
$[\alpha]_D^{25}$: –19.6 (*c*, 0.5, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 1.60 (m, 1H), 1.74 (m, 1H), 1.88 (m, 1H), 1.98 (m, 1H), 2.53 (t, 1H, *J* = 10.8 Hz), 2.81 (dd, 1H, *J* = 5.78, 10.8 Hz), 3.75 (m, 1H), 3.82 (2 x s, 6H), 4.03 (m, 1H), 4.24-4.44 (m, 4H), 4.55-4.65 (m, 2H), 5.54 (dd, 1H, *J* = 3.27, 16.08 Hz), 5.92 (dd, 1H, *J* = 9.04, 16.08 Hz), 6.89-6.92 (m, 4H), 7.26-7.31 (m, 4H).

^{13}C NMR ($CDCl_3$, 100 MHz) : δ 21.2, 33.8, 43.3, 55.2, 65.2, 70.2, 70.6, 74.1, 78.5, 113.8, 129.0, 129.3, 129.4, 130.7, 130.8, 133.3, 159.2, 170.8.

Elemental Analysis : **Calcd.:** C, 70.40; H, 7.09; **Found:** C, 70.22; H, 69.95.

(4*S*,7*R*,*E*)-4,7-dihydroxy-3,4,7,8,9,10-hexahydrooxecin-2-one (1)



To a solution of **5** (0.035 g, 0.082 mmol) in CH_2Cl_2:H_2O mixture (9:1, 8 mL) was added DDQ (0.041 g, 0.18 mmol) and stirred at room temperature for 2 h. The reaction mixture was quenched with saturated solution of $NaHCO_3$, organic layer was separated, washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (silica gel, 60-120 mesh, 10% MeOH:$CHCl_3$) to afford **1**.

Yield : 0.013 g, 86%

Mol. Formula : $C_9H_{14}O_4$

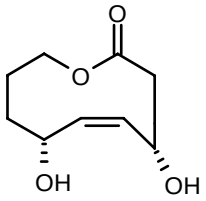
$[\alpha]_D^{25}$: +7.0 (*c*, 0.4, $CHCl_3$)

^{1}H NMR (CD_3OD, 400 MHz) : δ 1.57-1.72 (m, 2H), 1.85-1.98 (m, 2H), 2.38 (t, 1H, *J* = 10.5 Hz), 2.68 (dd, 1H, *J* = 5.52, 10.54 Hz), 3.82 (m, 1H), 4.33-4.43 (m, 3H), 5.49 (dd, 1H, *J* = 3.01, 15.81 Hz), 5.74 (dd, 1H, *J* = 7.28, 15.81 Hz).

^{13}C NMR (CD_3OD, 100 MHz) : δ 22.2, 37.06, 46.8, 66.7, 73.4, 75.2, 131.0, 134.9, 172.8.

Elemental Analysis : **Calcd.:** C, 58.05; H, 7.58; **Found:** C, 57.89; H, 7.50.

(4*S*,5*Z*,7*R*,)-4-7-dihydroxy-3,4,7,8,9,10-hexahydrooxecin-2-one (2)



To a stirred solution of **6** (0.035 g, 0.163 mmol, 0.001 M) in freshly distilled degassed anhydrous CH_2Cl_2 (165 ml) was added Grubb's second generation catalyst (0.014 g, 0.016 mmol) and heated at reflux for 8 h under an argon atmosphere until the complete consumption of starting material (monitored by TLC). The solvent was

evaporated to a brown residue, which was purified by column chromatography (silica gel 60-120 mesh, 10% MeOH-$CHCl_3$) to afford **2** as light yellowish oil.

Yield : 0.023 g, 75%

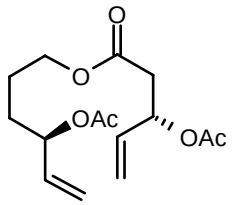
Mol. Formula : $C_9H_{14}O_4$

^{1}H NMR (CD_3OD, 400 MHz) : δ 1.53-1.64, (m, 3H), 1.91 (m, 1H), 2.13 (dd, 1H, *J* = 3.2, 11.2 Hz), 2.89 (dd, 1H, *J* = 6.0, 14.2 Hz), 3.66 (dt, 1H, *J* = 1.4, 11.2 Hz), 4.75 (m, 1H), 4.89 (m, 2H), 5.29 (m, 1H), 5.40 (dd, 1H, *J* = 9.2, 11.2 Hz).

^{13}C NMR (CD_3OD, 100 MHz) : δ 25.5, 37.1, 43.2, 65.3, 66.6, 67.3, 133.6, 134.1, 171.3.

Elemental Analysis : **Calcd.:** C, 58.05; H, 7.58; **Found:** C, 57.94; H, 7.51.

(S)-((*R*)-4-acetoxyhex-5enyl)3-acetoxypent-4-enoate (27)



To a solution of **6** (0.025 g, 0.117 mmol) in CH_2Cl_2 were added Et_3N (0.030 g, 0.295 mmol), DMAP (catalytic) and AC_2O (0.027 g, 0.265 mmol) and stirred for 12 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 and organic layer was washed with water, brine and concentrated under reduced pressure. The residue was purified by column chromatography (eluted in 10% EtOAc-light petroleum ether) to afford **27**.

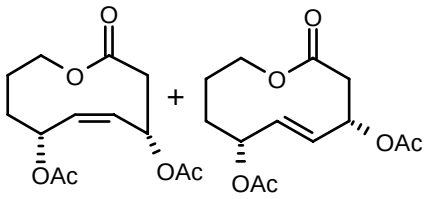
Yield : 0.029 g, 83%

Mol. Formula : $C_{15}H_{22}O_6$

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.64-1.68 (m, 4H), 2.06 (s, 3H), 2.07 (s, 3H), 2.64 (t, 2H, *J* = 7.7 Hz), 4.06-4.12 (m, 2H), 5.16 (m, 1H), 5.18-5.35 (m, 4H), 5.60 (m, 1H), 5.70-5.92 (m, 2H).

Elemental Analysis : **Calcd.:** C, 61.66; H, 8.47; **Found:** C, 61.58; H, 8.41.

(4S,7R)-2-oxo-3,4,7,8,9,10-hexahydro-2H-oxecine-4,7-diyl diacetate (28 and 29)



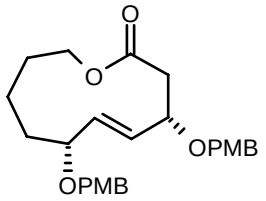
To a stirred solution of **27** (0.025 g, 0.083 mmol, 0.001M) in freshly distilled degassed anhydrous CH_2Cl_2 (85 ml) was added Grubb's second generation catalyst (0.008 g, 0.009 mmol) and heated at reflux for 8 h under an argon atmosphere until the complete consumption of starting material (monitored by TLC). The solvent was evaporated to a brown residue, which was purified by silica gel column chromatography (eluted in 12% EtOAc:light petroleum) to afford mixture of cis (**29**) and trans (**28**) in a 1:1 ratio.

Yield **:** 0.016 g, 70%

^{1}H NMR ($CDCl_3$, 400 MHz) **:** δ 1.60-1.72 (m, 4H), 1.78-1.95 (m, 4H), 2.04 (s, 3H), 2.07 (s, 3H), 2.12 (s, 3H), 2.15 (s, 3H), 2.46 (dd, 1H, *J* = 9.8, 11.05 Hz), 2.61 (dd, 1H, *J* = 4.3, 12.55 Hz), 2.70 (dd, 1H, *J* = 3.51, 12.55 Hz), 2.92 (dd, 1H, *J* = 6.02, 11.05 Hz), 3.85 (m, 1H), 3.98 (m, 1H), 4.36 (m, 1H), 4.48 (m, 1H), 5.22 (ddd, 1H, *J* = 3.26, 8.53, 11.8 Hz), 5.40 (m, 1H), 5.46-5.52 (m, 1H), 5.60 (m, 1H), 5.62 (dd, 1H, *J* = 2.8, 16.05 Hz), 5.67 (dd, 1H, *J* = 8.56, 12.30 Hz), 5.71 (dd, 1H, *J* = 7.9, 12.30 Hz), 5.81 (dd, 1H, *J* = 3.5, 16.05 Hz).

Elemental Analysis **:** **Calcd.:** C, 61.66; H, 8.47; **Found:** C, 61.58; H, 8.41.

(4*S*,7*R*,*E*)-4,7-bis(4-methoxybenzyloxy)oxacycloundec-5-en-2-one (43)



Procedure same as described to **5**

Yield : 71%

Mol. Formula : $C_{26}H_{32}O_6$

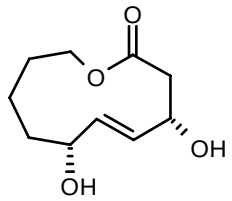
IR ($CHCl_3$) cm^{-1} : 2929, 2857, 1729, 1612, 1514, 1248, 1036, 821, 769.

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 1.33-1.42 (m, 3H), 1.56-1.75 (m, 3H), 2.57 (t, 1H, *J* = 10.08 Hz), 2.68 (dd, 1H, *J* = 4.27, 11.04 Hz), 3.81 (2 x s, 6H), 4.05 (m, 1H), 4.21 (m, 1H), 4.35-4.58 (m, 6H), 5.49 (dd, 1H, *J* = 4.26, 15.8 Hz), 5.76 (dd, 1H, *J* = 7.78, 15.8 Hz), 6.86-6.88 (m, 4H), 7.25-7.27 (m, 4H).

^{13}C NMR ($CDCl_3$, 100 MHz) : δ 16.4, 29.1, 30.8, 41.5, 55.2, 63.8, 70.0, 70.1, 75.3, 77.1, 113.7, 113.8, 129.0, 130.2, 130.6, 130.8, 132.2, 159.1, 159.2, 170.7.

Elemental Analysis : **Calcd.:** C, 70.89; H, 7.32; **Found:** C, 70.85; H, 7.25.

(4*S*,7*R*,*E*)-4,7-dihydroxyoxacycloundec-5-ene-2-one (3)



Procedure same as given to **2**.

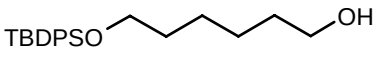
Yield : 73%

Mol. Formula : $C_{10}H_{16}O_4$

^{1}H NMR ($CDCl_3$, 200 MHz + a drop of CD_3OD) : δ 1.35-1.70 (m, 6H), 2.47 (dd, 1H, *J* = 8.03, 11.54 Hz), 2.57 (dd, 1H, *J* = 4.01, 11.54 Hz), 4.03-4.10 (m, 2H), 4.21 (m, 1H), 4.48 (m, 1H), 5.49 (dd, 1H, *J* = 5.77, 15.56 Hz), 5.67 (dd, 1H, *J* = 6.27, 15.56 Hz).

Elemental Analysis : **Calcd.:** C, 59.98; H, 8.05; **Found:** C, 59.78; H, 7.89.

6-(*tert*-butyldiphenylsilyloxy) hexan-1-ol (35)



To a solution **34** (5.0 g, 42.3 mmol) in dry DMF (75 mL) was added imidazole (5.75 g, 84.6 mmol) and TBDPS-Cl (12.20 g, 44.38 mmol) at room temperature under

nitrogen atmosphere. After 12 h, added cold water and extracted with CH_2Cl_2 (3 x 50 ML). The combined extracts were washed with water, brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluted in 40% EtOAc: light petroleum ether) to afford **35** as colorless liquid.

Yield : 11.31 g, 75%.

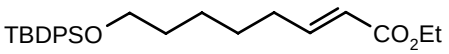
Mol. Formula : $C_{22}H_{32}O_2Si$

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.06 (s, 9H), 1.30-1.41 (m, 4H), 1.49-1.63 (m, 4H), 3.60-3.70 (m, 4H), 7.35-7.44 (m, 6H), 7.65-7.69 (m, 4H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 19.2, 25.4, 25.5, 26.8, 32.4, 32.6, 62.7, 63.7, 127.5, 129.4, 134.0, 135.5.

Elemental Analysis : **Calcd.:** C, 74.10; H, 9.05; **Found:** C, 73.85; H, 8.79.

(*E*)-Ethyl-8-(*tert*-butyldiphenylsilyloxy)oct-2-enoate (37)



To a stirred solution of **35** (10.0 g, 28.0 mmol) in DMSO:THF (75:25, 10 mL) at 0 ^oC was treated with IBX (10.2 g, 36.4 mmol) in portion wise and allowed to stir at room temperature for 4 h. The reaction mixture was treated with saturated $NaHCO_3$ solution (20 mL), filtered through celite and washed with EtOAc (3 x 50 mL). The organic layer separated, washed with water (2 x 20 mL), brine and dried over Na_2SO_4. Evaporation of the solvent gave **36** (8.15 g, 82 %) as light yellowish liquid, which was used in subsequent experiments without further purifications.

To a solution of **36** (8.15 g, 23.0 mmol) and (carboethoxymethylene)triphenyl phosphorane (9.8 g, 28.4 mmol) in dry benzene (75 mL) was heated at reflux for 6 h. The solvent was evaporated and the residue purified by column chromatography (silica gel, 60-120 mesh, 5% EtOAc in hexane) to afford **37** as pale yellow liquid.

Yield : 7.42 g, 76%

Mol. Formula : $C_{26}H_{36}O_3Si$

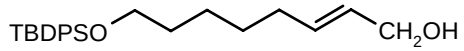
IR ($CHCl_3$) cm^{-1} : 2932, 2852, 1720, 1654, 1428, 1112, 1044, 760.

^{1}H NMR ($CDCl_3$, 200 MHz) **:** δ 1.06 (s, 9H), 1.30 (t, 3H, *J* = 7.2 Hz), 1.41-1.45 (m, 3H), 1.52-1.61 (m, 3H), 2.14-2.25 (m, 2H), 3.68 (t, 2H, *J* = 6.1 Hz), 4.14 (q, 2H, *J* = 7.20, 14.28 Hz), 5.75 (dt, 1H, *J* =1.52, 15.66), 6.87 (dt, 1H, *J* = 6.95, 15.67), 7.35-7.43 (m, 6H), 7.64-7.69 (m, 4H).

^{13}C NMR ($CDCl_3$, 50 MHz) **:** δ 14.3, 19.2, 25.3, 26.9, 27.7, 32.1, 32.2, 60.0, 63.6, 121.4, 127.6, 129.5, 134.0, 135.5, 149.1, 166.5.

Elemental Analysis **:** **Calcd.:** C, 73.54; H, 8.54; **Found:** C, 73.22; H, 8.37.

(*E*)-8-(*tert*-butyldiphenylsilyloxy)oct-2-en-1-ol (38)



To a stirred solution of **37** (5.0 g, 11.77 mmol) in dry CH_2Cl_2 (100 mL) at –78 ^oC was added a solution of DIBAL-H (14.8 mL, 2M in toluene) drop wise. After 2 h, the reaction mixture was warmed to 0 ^oC and treated dropwise with MeOH (5 mL) to furnish a gelatinous cake. The mixture was diluted with CH_2Cl_2 (100 mL) and stirred for 15 min. The solution of Na-K tartrate (10 mL) was added drop wise and stirred for an additional 45 min., the reaction mixture was filtered through celite and washed with CH_2Cl_2 (2 x 50 mL). The organic layer was washed with water, brine, dried over Na_2SO_4 and the solvent was evaporated. The residue was purified by column chromatography (silica gel, 60-120 mesh, 25% EtOAc: light petroleum ether) to afford **38** as a colorless liquid**.**

Yield **:** 3.96 g, 88%

Mol. Formula **:** $C_{24}H_{34}O_2Si$

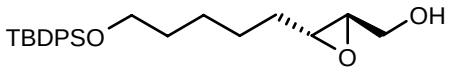
IR ($CHCl_3$) cm^{-1} **:** 3352, 2931, 2857, 1427, 1112, 760

^{1}H NMR ($CDCl_3$, 200 MHz) **:** δ 1.06 (s, 9H), 1.34-1.41 (m, 4H), 1.44 (br s, 1H), 1.54-1.60 (m, 2H), 2.00-2.08 (m, 2H), 3.66 (t, 2H, *J* = 6.2 Hz), 4.08 (m, 2H), 5.62-5.68 (m, 2H), 7.36-7.44 (m, 6H), 7.65-7.69 (m, 4H).

^{13}C NMR ($CDCl_3$, 50 MHz) **:** δ 19.2, 25.3, 26.9, 28.8, 32.1, 32.3, 63.6, 63.8, 127.5, 129.0, 129.5, 133.0, 134.0, 135.5.

Elemental Analysis **:** **Calcd.:** C, 75.34; H, 8.96; **Found:** C, 75.25; H, 8.77.

(2*R*, 3*R*)-8-(*tert*-butyldiphenylsilyloxy) 2,3-oxiranyl-octanol (39)



To a stirred and cooled (–20 ^{o}C) suspension of molecular sieves (4 A^{o}, 2.0 g) in CH_2Cl_2 (25 mL) under N_2 atmosphere, (–) DET (0.484 g, 2.35 mmol) in CH_2Cl_2 (25 mL), Ti($O^{i}Pr$)$_4$ (0.623 g, 2.19 mmol) and TBHP (2.85 mL, 5.5 M solution in decane) were added sequentially. After 20 min, the resulting mixture was treated with a solution of **38** (3.0 g, 7.84 mmol) in CH_2Cl_2 (25 mL). The reaction mixture, after 6 h, was quenched with 10% NaOH solution, saturated with NaCl (10 mL) and filtered through celite. Evaporation of the solvent and purification of the residue by column chromatography (silica gel, 60-120 mesh, 50% EtOAc: light petroleum ether) gave **39** as a colorless liquid.

Yield : 2.53 g, 81%

Mol. Formula : $C_{24}H_{34}O_3Si$

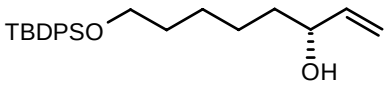
$[\alpha]_D^{25}$: +14.0 (*c*, 1.0, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.06 (s, 9H), 1.40-1.46 (m, 3H), 1.55-1.63 (m, 5H), 1.74 (m, 1H), 2.88-2.97 (m, 2H), 3.57 (m, 1H), 3.67 (t, 2H, *J* = 6.2 Hz), 3.90 (m, 1H), 7.32-7.44 (m, 6H), 7.64-7.69 (m, 4H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 19.1, 25.6, 26.8, 31.4, 32.3, 55.8, 58.5, 61.6, 63.6, 127.5, 129.4, 133.9, 135.4.

Elemental Analysis : **Calcd.:** C, 73.32; H, 8.60; **Found:** C, 75.30; H, 8.55.

(*R*)-8-(*tert*-butyldiphenylsilyloxy)oct-1-en-3-ol (41)



To a solution of **39** (2.0 g, 5.0 mmol) in dry toluene (30 mL) were added imidazole (1.02 g, 15.0 mmol), triphenylphosphine (1.96 g, 7.5 mmol) and iodine (1.56 g, 6.0 mmol) at room temperature. The reaction mixture stirred for 30 min. (monitored by TLC), quenched the reaction mixture by saturated $NaHCO_3$ solution and aqueous layer washed with EtOAc (2 x 20 mL), combined the EtOAc layers, dried over Na_2SO_4, and evaporated the solvent in vacuo. The residue was purified by column chromatography

(silica gel, 60-120 mesh, 10% EtOAc in hexane) to afford **40** (2.54 g, 81%) as light yellowish liquid.

To a solution of **40** (2.54 g, 5.0 mmol) in absolute EtOH (30 mL) added Zn dust (2.1 g, 32.4 mmol) and heated to reflux for 3 h. Evaporated the solvent and purification of the residue by column chromatography (silica gel, 60-120 mesh, 25% EtOAc: light petroleum ether) afforded **41** as a colorless liquid.

Yield : 1.78 g, 93%

Mol. Formula : $C_{24}H_{34}O_2Si$

$[\alpha]_D^{25}$: +16.0 (*c*, 2.1, $CHCl_3$)

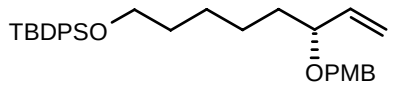
IR ($CHCl_3$) cm^{-1} : 3401, 3070, 2932, 2858, 1428, 1112, 702

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.06 (s, 9H), 1.30-1.42 (m, 4H), 1.50-1.61 (m, 4H), 3.66 (t, 2H, *J* = 6.2 Hz), 4.07 (m , 1H), 5.08-5.26 (m, 2H), 5.80 (m, 1H), 7.35-7.42 (m, 6H), 7.65-7.69 (m, 4H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 19.2, 25.0, 25.7, 26.9, 32.5, 37.0, 64.0, 73.1, 114.5, 127.6, 129.5, 134.0, 135.5, 141.3.

Elemental Analysis : **Calcd.:** C, 75.34; H, 8.96; **Found:** C, 75.14; H, 8.78.

(*R*)-*tert*-butyl(6-(4-methoxybenzyloxy)oct-7-enyloxy)diphenylsilane (42)



To a solution of **41** (1.1 g, 2.87 mmol) in dry DMF:THF (1:1, 30 mL) added NaH (0.171 g, 4.3 mmol, 60% dispersion in mineral oil) at 0 ^oC, stirred for 30 min., added *p*-methoxy benzyl chloride (0.593 g, 3.73 mmol) and stirred for additional 5 h at same temperature. Monitored by TLC, quenched the reaction mixture by cold water and aqueous layer washed with EtOAc (2 x 20 mL), dried over Na_2SO_4, Evaporation of the solvent in *vacuo* and purified the residue by column chromatography (silica gel, 60-120 mesh, 10% EtOAc-light petroleum ether) to give **42** as a colorless liquid.

Yield : 1.11 g, 77%

Mol. Formula : $C_{32}H_{42}O_3Si$

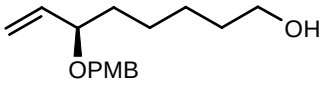
$[\alpha]_D^{25}$: +20.0 (*c*, 1.0, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz) **:** δ 1.05 (s, 9H), 1.32-1.40 (m, 4H), 1.52-1.61 (m, 4H), 3.64 (t, 2H, *J* = 6.4 Hz), 3.69 (m, 1H), 3.80 (s, 3H), 4.24 (d, 1H, *J* = 11.5 Hz), 4.50 (d, 1H, *J* = 11.5 Hz), 5.14-5.24 (m, 2H), 5.71 (m, 1H), 6.84-6.88 (m, 2H), 7.22-7.27 (m, 2H), 7.37-7.40 (m, 6H), 7.64-7.69 (m, 4H).

^{13}C NMR ($CDCl_3$, 50 MHz) **:** δ 19.2, 25.1, 25.7, 26.9, 32.5, 35.5, 55.1, 63.9, 69.6, 80.1, 113.7, 116.9, 127.6, 129.2, 129.5, 130.8, 134.1, 135.5, 139.3, 159.0.

Elemental Analysis **:** **Calcd.:** C, 76.45; H, 8.42; **Found:** C, 76.44; H, 8.36.

(*R*)-6-(4-methoxybenzyloxy)oct-7-en-1-ol (32)



To a solution of **42** (1.2 g, 2.38 mmol) and TBAF (3.6 mL, 1M solution in THF) in anhydrous THF (20 mL) was stirred for 3 h at room temperature. Evaporated the THF under reduced pressure. The residue was purified by silica gel column chromatography (eluted in 25% EtOAc-light petroleum ether) to obtain **32**.

Yield **:** 0.535 g, 85%

Mol. Formula **:** $C_{16}H_{24}O_3$

$[\alpha]_D^{25}$ **:** +40.0 (*c*, 1.0, $CHCl_3$)

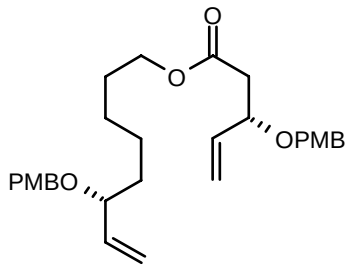
IR ($CHCl_3$) cm^{-1} **:** 3392, 2934, 2860, 1613, 1514, 1248, 1036, 821, 757.

^{1}H NMR ($CDCl_3$, 200 MHz) **:** δ 1.27-1.55 (m, 8H), 3.61 (t, 2H, *J* = 6.5 Hz), 3.71 (m, 1H), 3.81 (s, 3H), 4.24 (d, 1H, *J* = 11.55 Hz), 4.50 (d, 1H, *J* = 11.55 Hz), 5.15-5.25 (m, 2H), 5.72 (m, 1H), 6.85-6.89 (m, 2H), 7.23-7.27 (m, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) **:** δ 25.0, 25.6, 30.7, 32.5, 35.3, 55.1, 62.6, 64.6, 69.5, 79.9, 113.6, 116.9, 128.4, 129.2, 130.7, 139.1, 158.9.

Elemental Analysis **:** **Calcd.:** C, 72.69; H, 9.15; **Found:** C, 72.58; H, 9.04.

(*S*)-((*R*)-6-(4-methoxybenzyloxy)oct-7-enyl)-3-(4-methoxybenzyloxy)pent-4-enoate (31)



To a stirred solution of **9** (0.150 g, 0.634 mmol) in dry CH_2Cl_2 (10 ml) were added Et_3N (0.126 g, 1.25 mmol) and a solution of 2, 4, 6-trichlorobenzoylchloride (0.231 g, 0.950 mmol) in dry CH_2Cl_2 (10 ml) and stirred at 0 ^oC for 20 min. A solution of **32** (0.167 g, 0.632 mmol) in dry CH_2Cl_2 (10 ml) and DMAP (catalytic) was added, stirred for 6 h at room temperature (Checked by TLC). The solvent was evaporated, the crude was purified by column chromatography (silica gel, 60-120 mesh, 10% EtOAc in hexane) to afford **31** as a colorless liquid.

Yield **:** 0.258 g, 84%

Mol. Formula **:** $C_{29}H_{38}O_6$

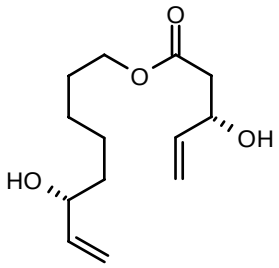
$[\alpha]_D^{25}$ **:** +10.0 (*c*, 1.0, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz) **:** δ 1.27-1.40 (m, 4H), 1.48-1.60 (m, 4H), 2.42(dd, 1H, *J* = 5.56, 15.03 Hz), 2.59 (dd, 1H, *J* = 8.08, 150.3 Hz), 3.68 (m, 1H), 3.79 (2 x s, 6H), 4.05 (t, 2H, *J* = 6.57 Hz), 4.20-4.35 (m, 3H), 4.49 (d, 2H, *J* = 11.40 Hz), 5.05-5.35 (m, 4H), 5.63-5.87 (m, 2H), 6.83-6.89 (m, 4H), 7.20-7.27 (m, 4H).

^{13}C NMR ($CDCl_3$, 50 MHz) **:** δ 24.9, 25.7, 28.4, 35.2, 41.0, 55.1, 64.4, 69.5, 70.1, 76.6, 79.9, 113.6, 116.9, 117.8, 129.2, 130.2, 130.7, 137.2, 139.0, 159.0, 170.7.

Elemental Analysis **:** **Calcd.:** C, 72.71; H, 7.94; **Found:** C, 72.58; H, 7.82.

(*S*)-((*R*)-6-hydroxyoct-7-enyl)3-hydroxypent-4-enoate (30)



Procedure same as described to **6.**

Yield : 80%

Mol. Formula : $C_{13}H_{22}O_4$

$[\alpha]_D^{25}$: –6.0 (*c*, 1.5, $CHCl_3$)

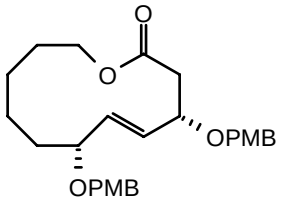
IR ($CHCl_3$) cm^{-1} : 3401, 2938, 1734, 1514, 1248, 1036, 757.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.30-1.46 (m, 4H), 1.50-1.68 (m, 4H), 2.18 (br s, 2H), 2.47-2.63 (m, 2H), 4.05-4.54 (m, 3H), 4.54 (m, 1H), 5.08-5.36 (m, 4H), 5.78-5.97 (m, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 24.8, 25.8, 28.4, 36.7, 41.2, 64.7, 68.8, 72.9, 114.6, 115.3, 138.8, 141.2, 172.2.

Elemental Analysis : **Calcd.:** C, 64.44; H, 9.15; **Found:** C, 64.30; H, 9.02.

(4*S*,7*R*,*E*)-4,7-bis(4-methoxybenzyloxy)oxacyclododec-5-en-2-one (44)



Procedure same as described to **5.**

Yield : 0.035 g, 75%

Mol. Formula : $C_{27}H_{34}O_6$

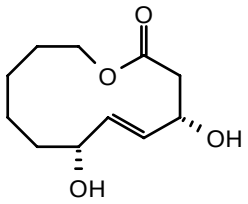
$[\alpha]_D^{25}$: +4.0 (*c*, 1.2, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 1.30-1.50 (m, 4H), 1.61-1.76 (m, 4H), 2.62-2.69 (m, 2H), 3.81 (s, 6H), 3.96-4.04 (m, 2H), 4.24-4.32 (m, 2H), 4.36 (d, 1H, *J* = 11.85 Hz), 4.46 (d, 1H, *J* = 11.55 Hz), 4.50 (d, 1H, *J* = 11.55 Hz), 4.55 (d, 1H, *J* = 11.85 Hz), 5.62 (dd, 1H, *J* = 5.52, 15.81 Hz), 5.69 (dd, 1H, *J* = 5.52, 15.81 Hz), 6.86-6.88 (m, 4H), 7.25-7.29 (m, 4H).

^{13}C NMR ($CDCl_3$, 100 MHz) **:** δ 21.9, 23.3, 26.2, 31.5, 41.1, 55.2, 62.9, 70.1, 75.6, 77.7, 113.7, 113.8, 128.9, 129.3, 130.2, 130.7, 130.9, 132.6, 159.0, 159.2, 170.4.

Elemental Analysis **:** **Calcd.:** C, 71.34; H, 7.54; **Found:** C, 71.18; H, 7.48.

(4*S*,7*R*,*E*)-4,7-dihydroxyoxacyclododec-5-en-2-one (4)



Procedure same as described to **2**.

Yield **:** 0.034 g, 76%

Mol. Formula **:** $C_{11}H_{18}O_4$

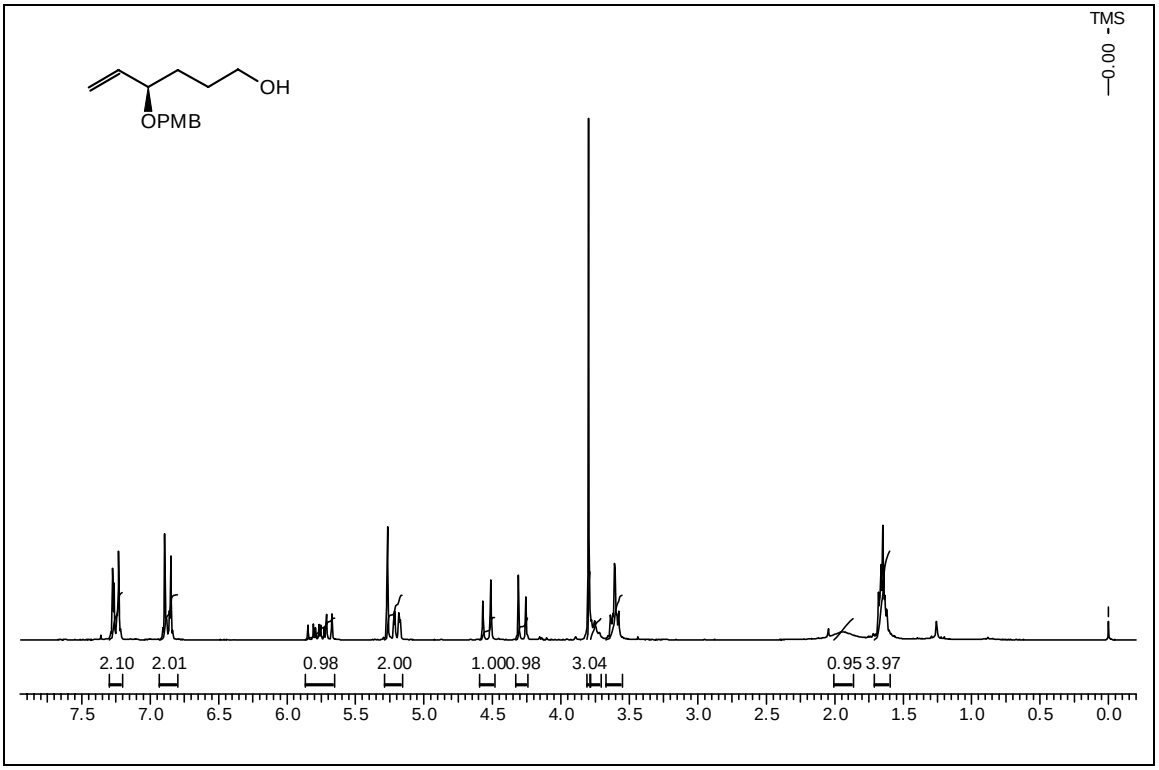
$[\alpha]_D^{25}$ **:** –6.0 (*c*, 1.0, MeOH)

^{1}H NMR ($CDCl_3$, 400 MHz + a drop of CD_3OD) **:** δ 1.14-1.41 (m, 4H), 1.45-1.56 (m, 2H), 1.64-1.75 (m, 2H), 2.55-2.63 (m, 2H), 3.04 (br s, 2H), 3.88 (dt, 1H, *J* = 5.02, 11.3 Hz), 4.20 (m, 1H), 4.34 (ddd, 1H, *J* = 3.54, 10.54, 13.81 Hz), 4.51 (m, 1H), 5.58 (dd, 1H, *J* = 7.53, 15.56 Hz), 5.67 (dd, 1H, *J* = 3.76, 15.56 Hz).

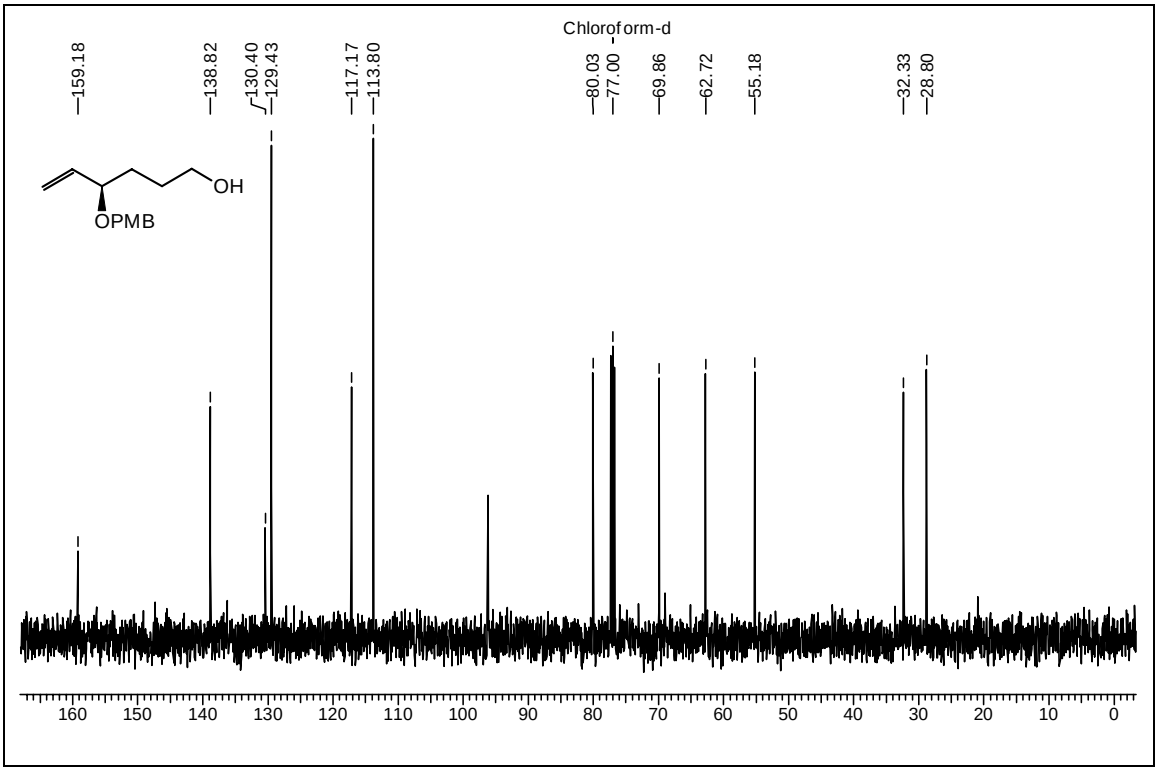
^{13}C NMR ($CDCl_3$, 100 MHz + a drop of CD_3OD) **:** δ 21.9, 26.1, 33.5, 41.9, 62.3, 68.1, 71.7, 131.6, 132.3, 171.6.

Elemental Analysis **:** **Calcd.:** C, 61.66; H, 8.47; **Found:** C, 61.54; H, 8.38.

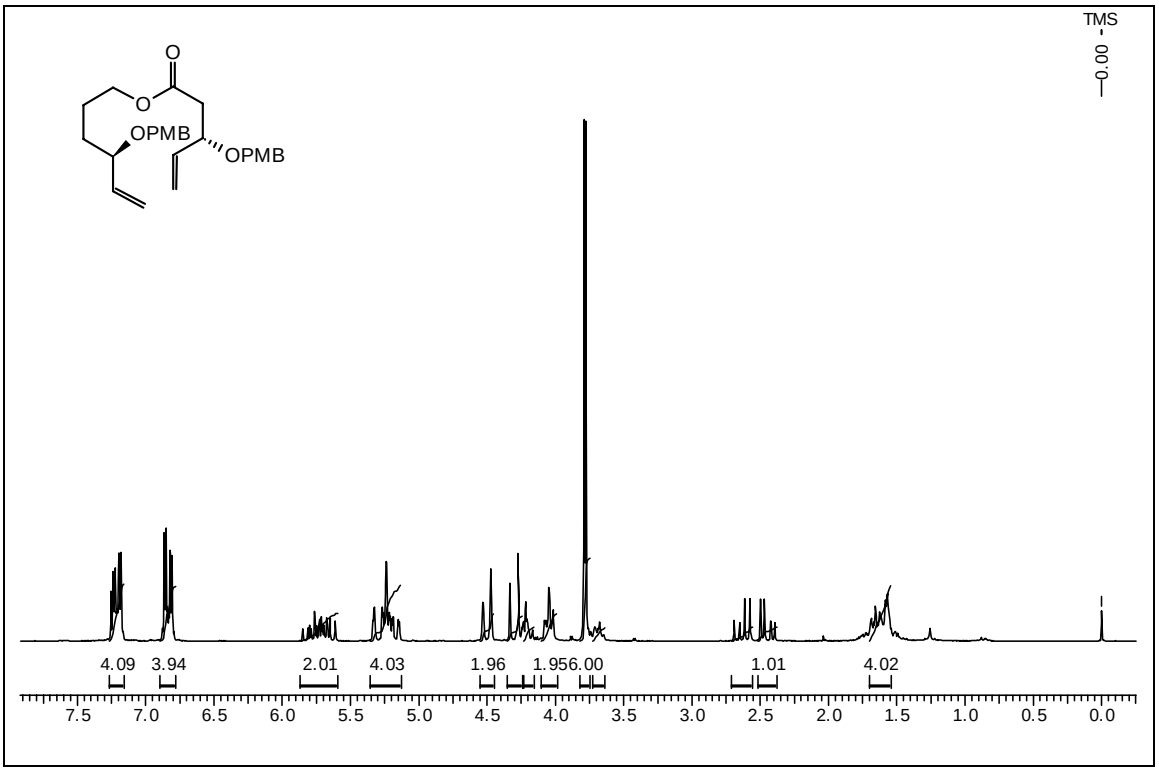
SPECTRA



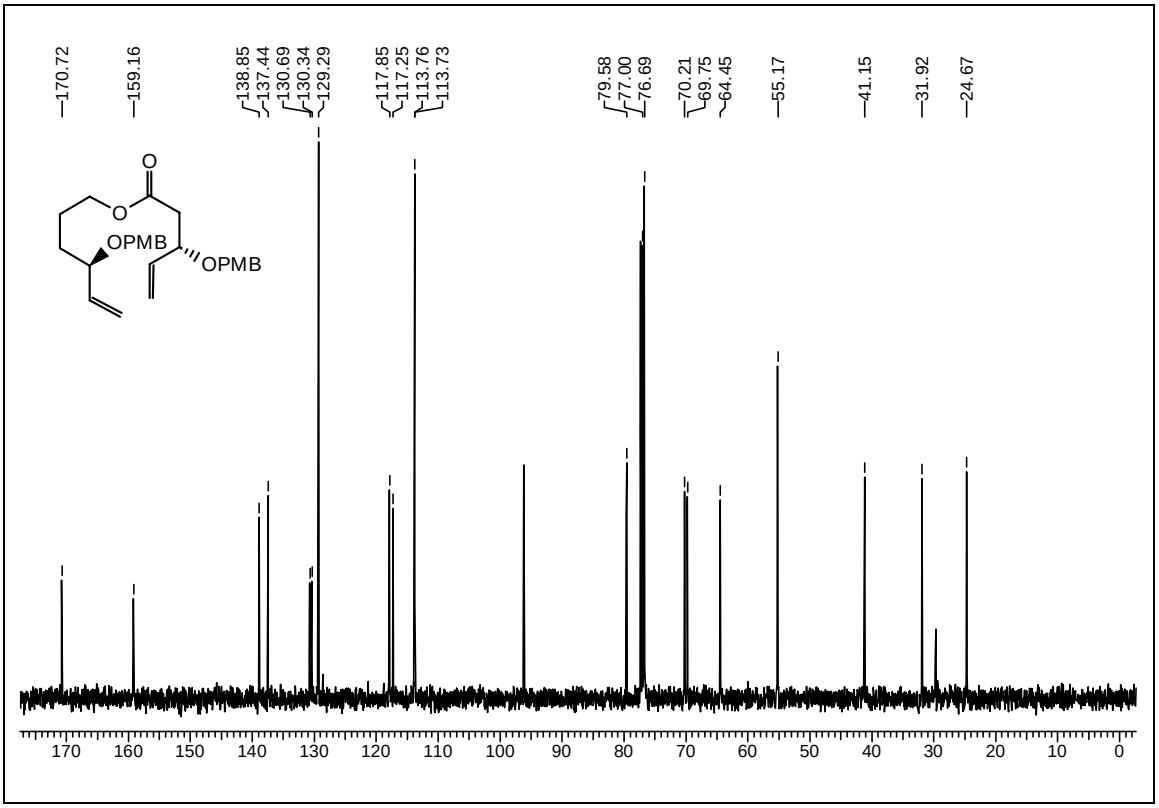
^{1}H NMR spectrum of compound 8 in $CDCl_3$



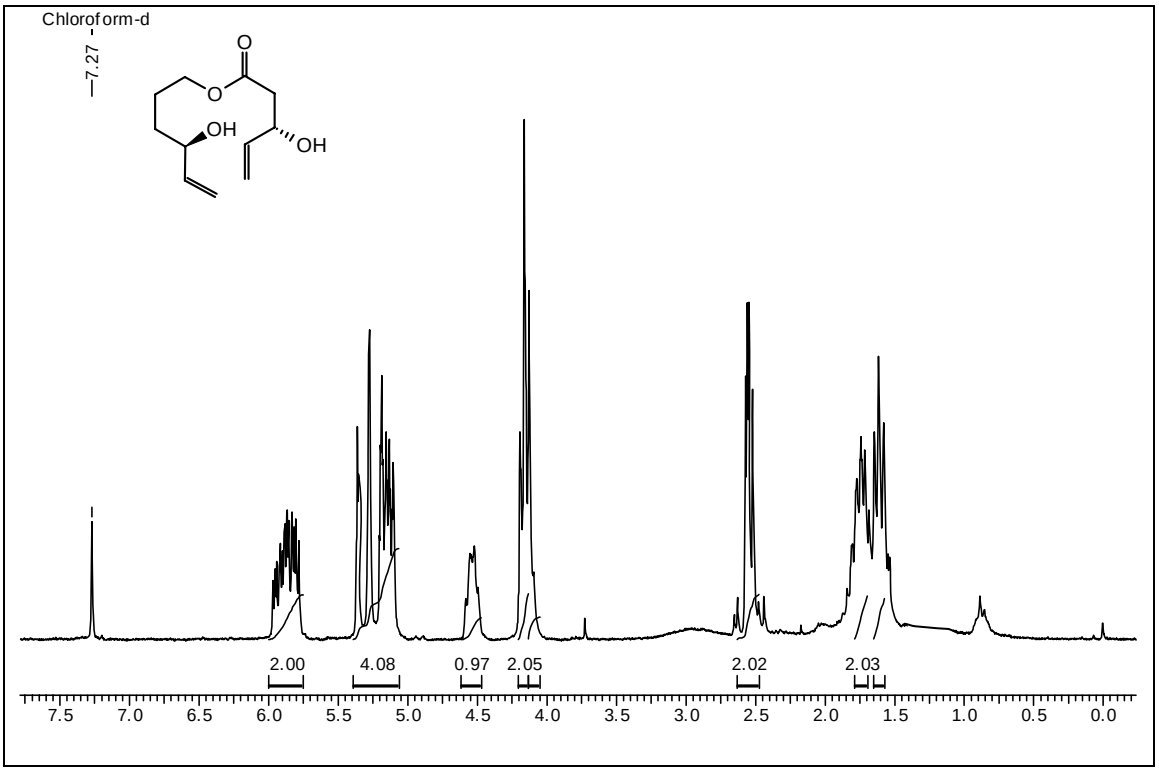
^{13}C NMR spectrum of compound 8 in $CDCl_3$



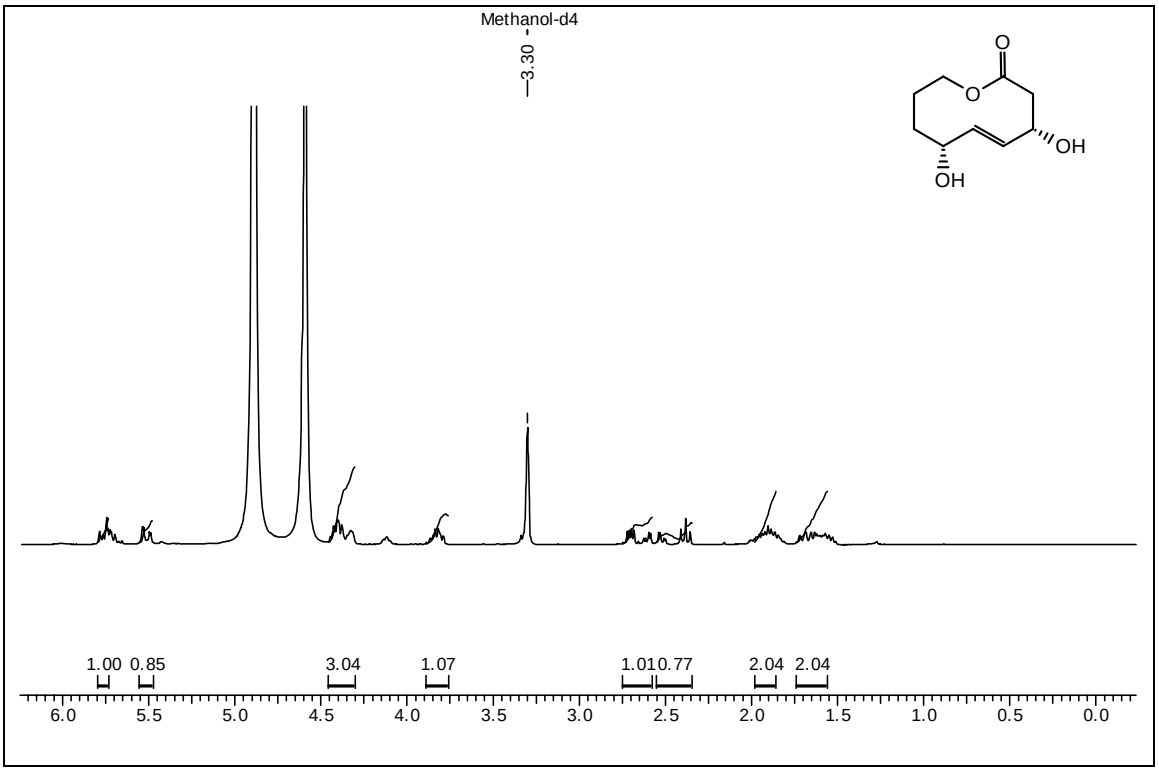
^{1}H NMR spectrum of compound 7 in $CDCl_3$



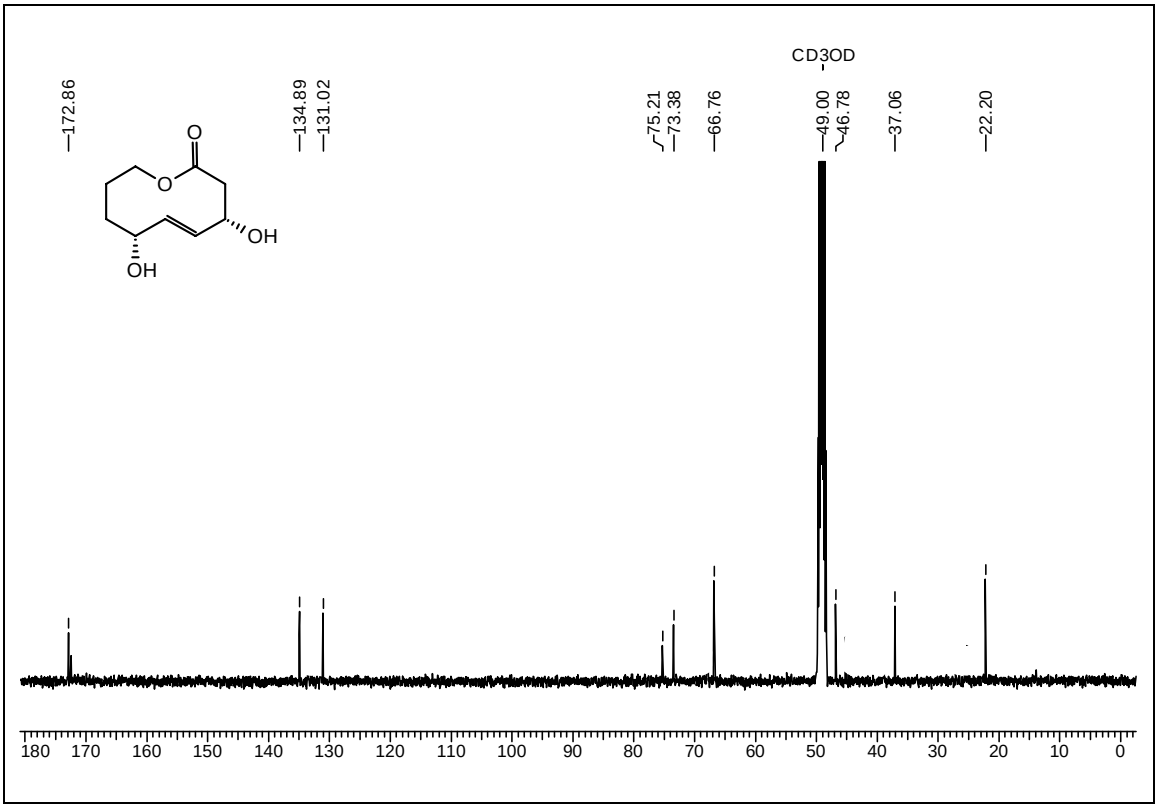
^{13}C NMR spectrum of compound 7 in $CDCl_3$



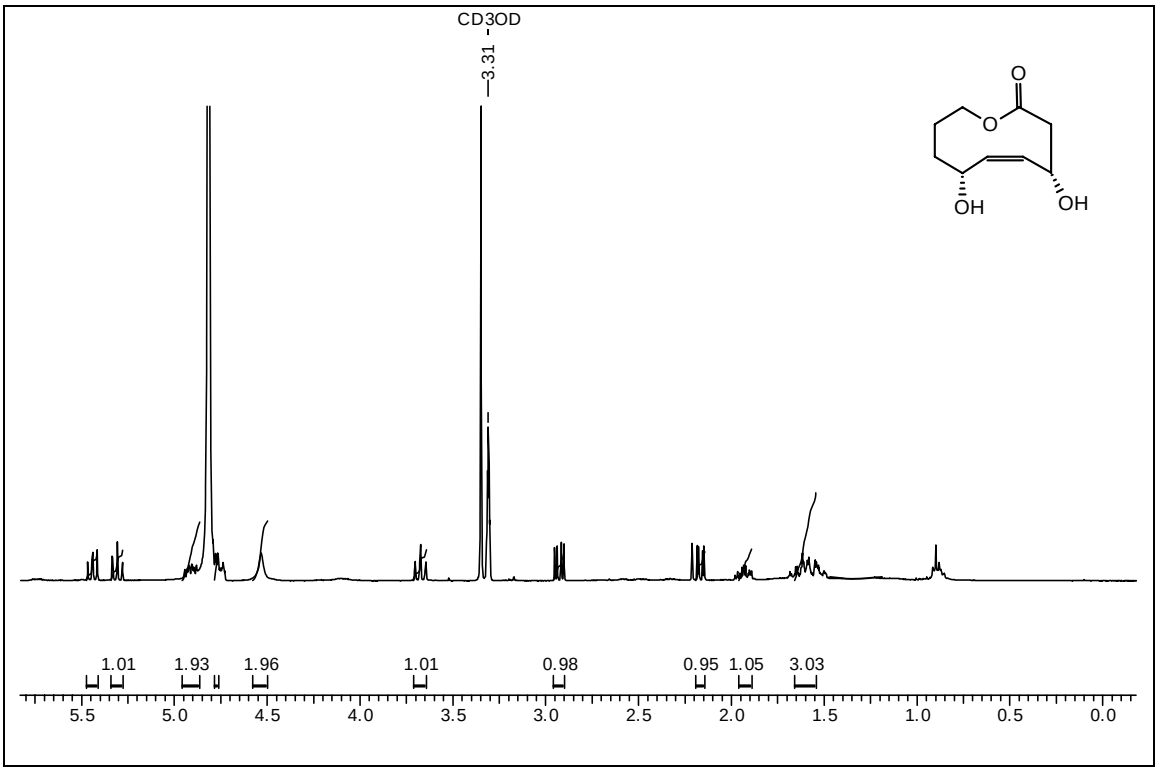
^{1}H NMR spectrum of compound 6 in $CDCl_3$



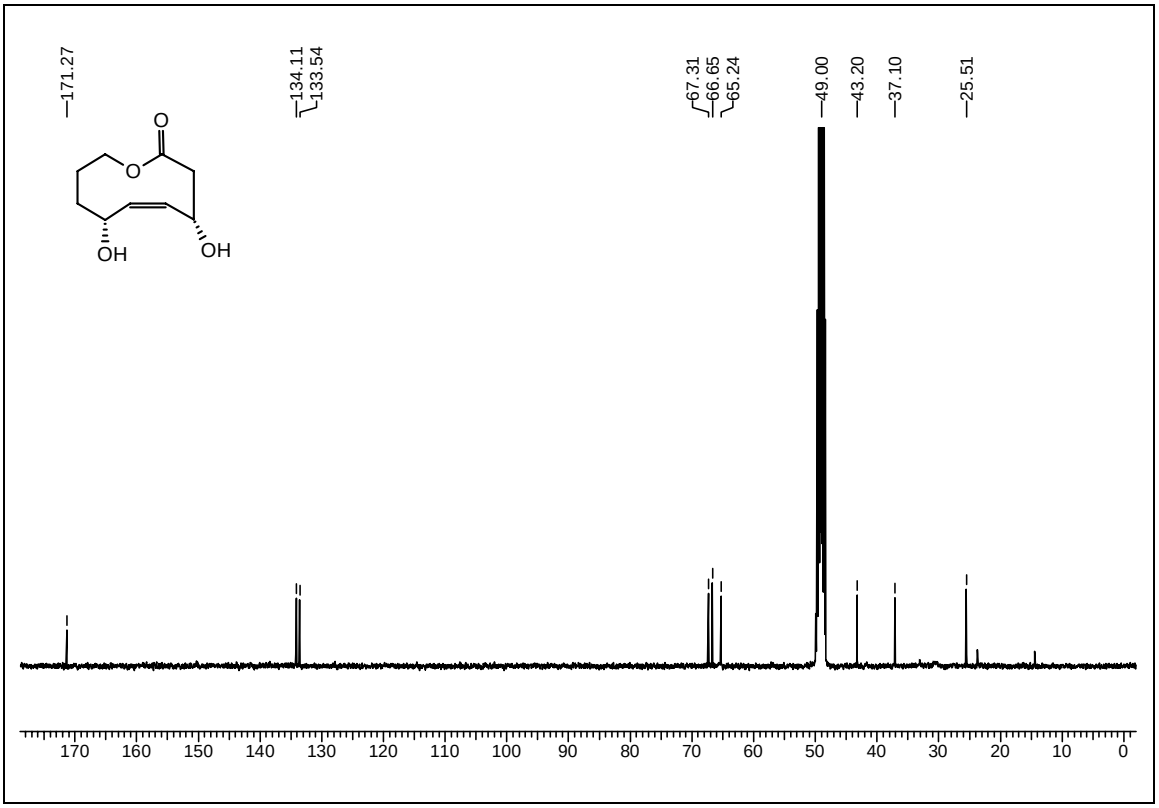
^{1}H NMR spectrum of compound 1 in CD_3OD



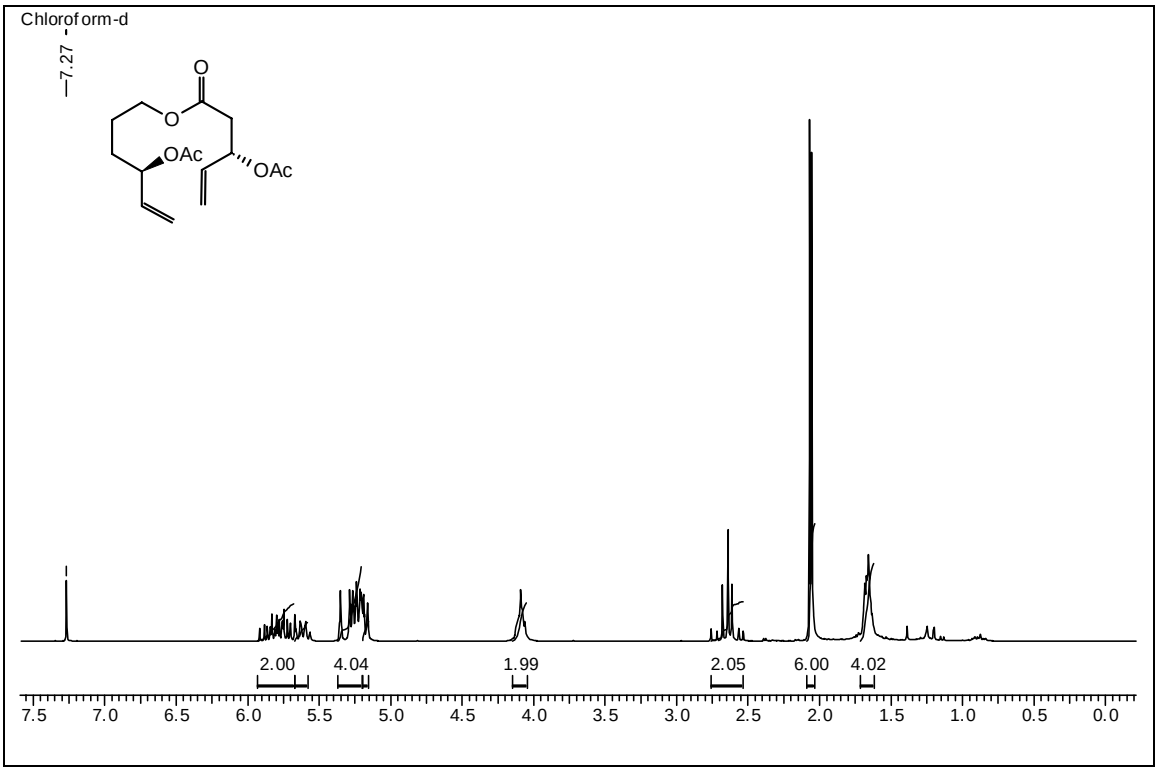
^{13}C NMR spectrum of compound 1 in CD_3OD



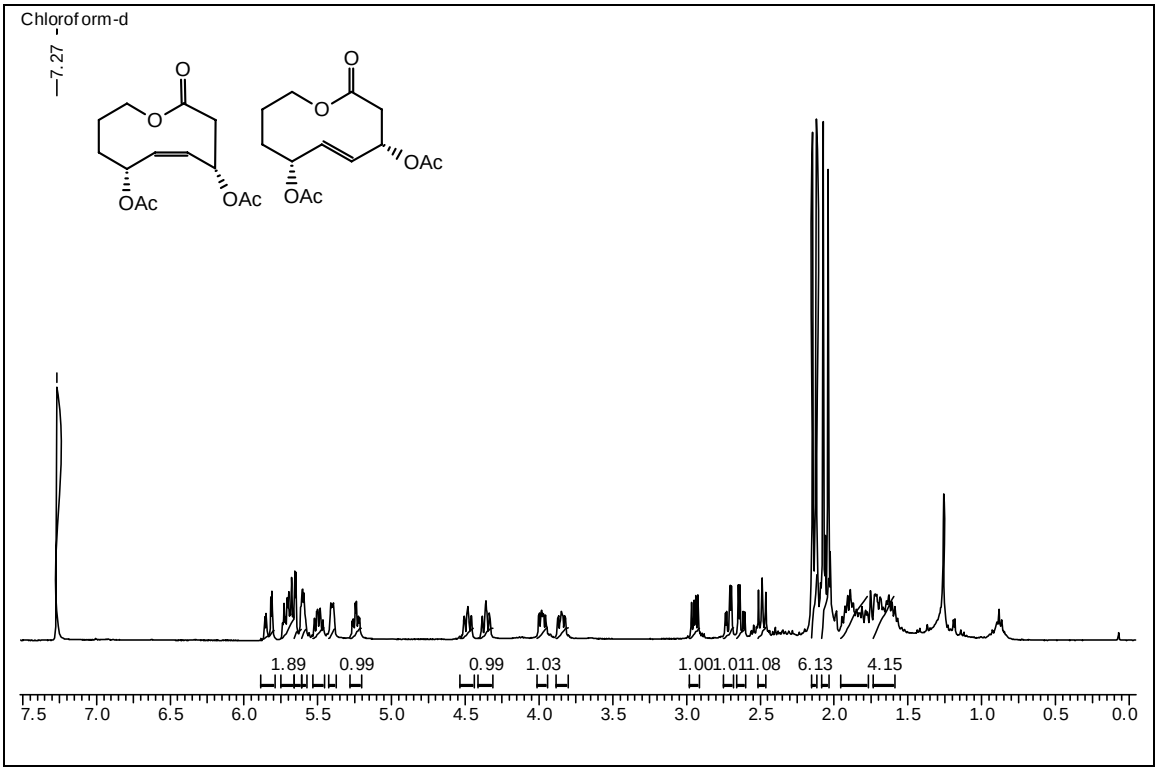
^{1}H NMR spectrum of compound 2 in CD_3OD



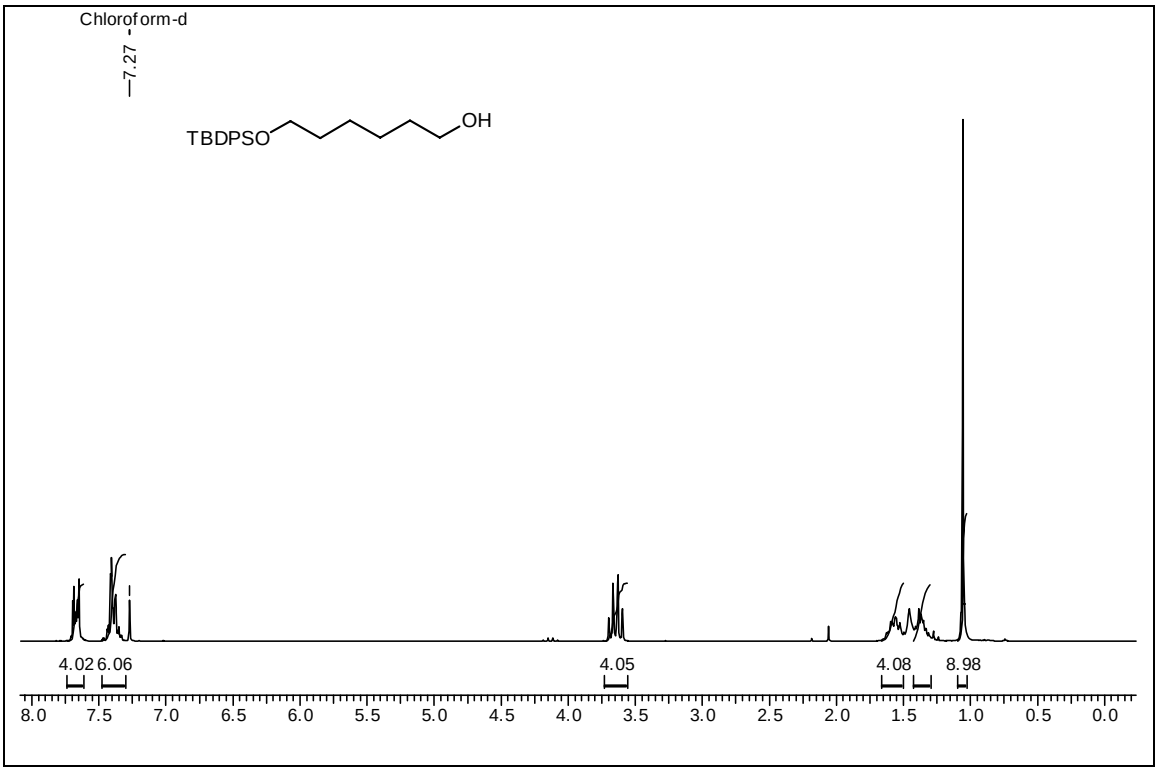
^{13}C NMR spectrum of compound 2 in CD_3OD



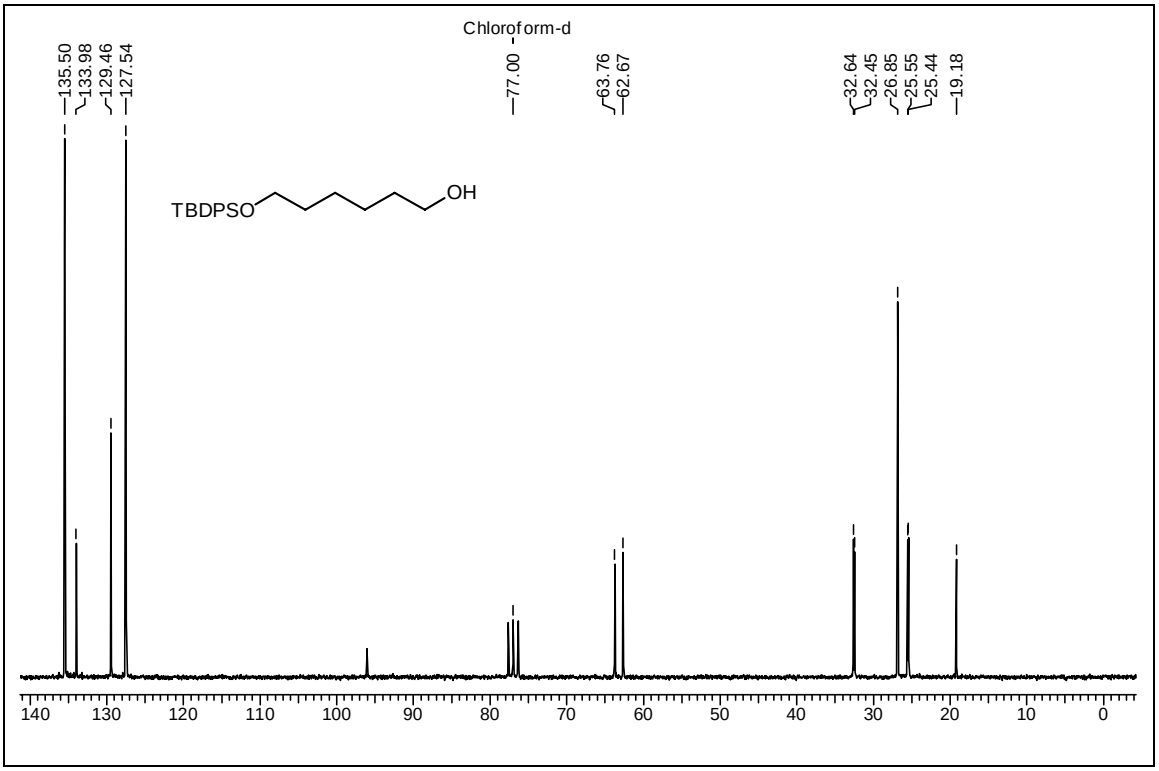
^{1}H NMR spectrum of compound 27 in $CDCl_3$



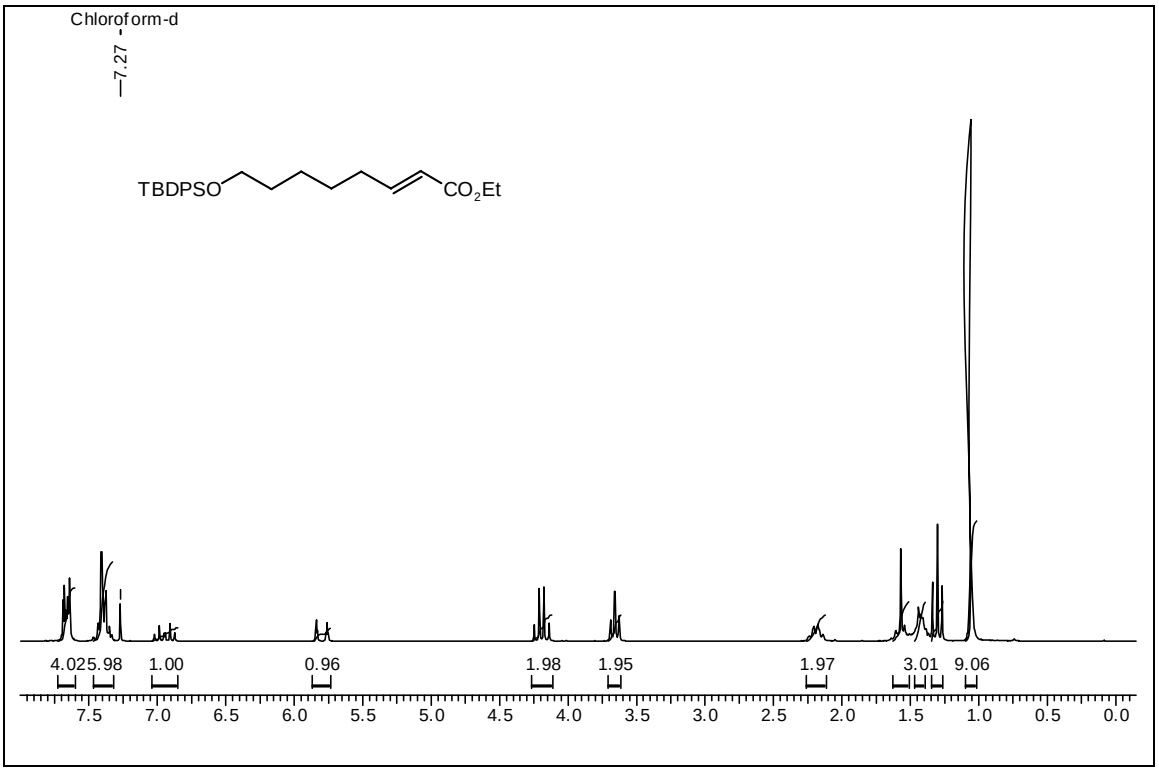
^{1}H NMR spectrum of mixture of compound 28 and 29 in $CDCl_3$



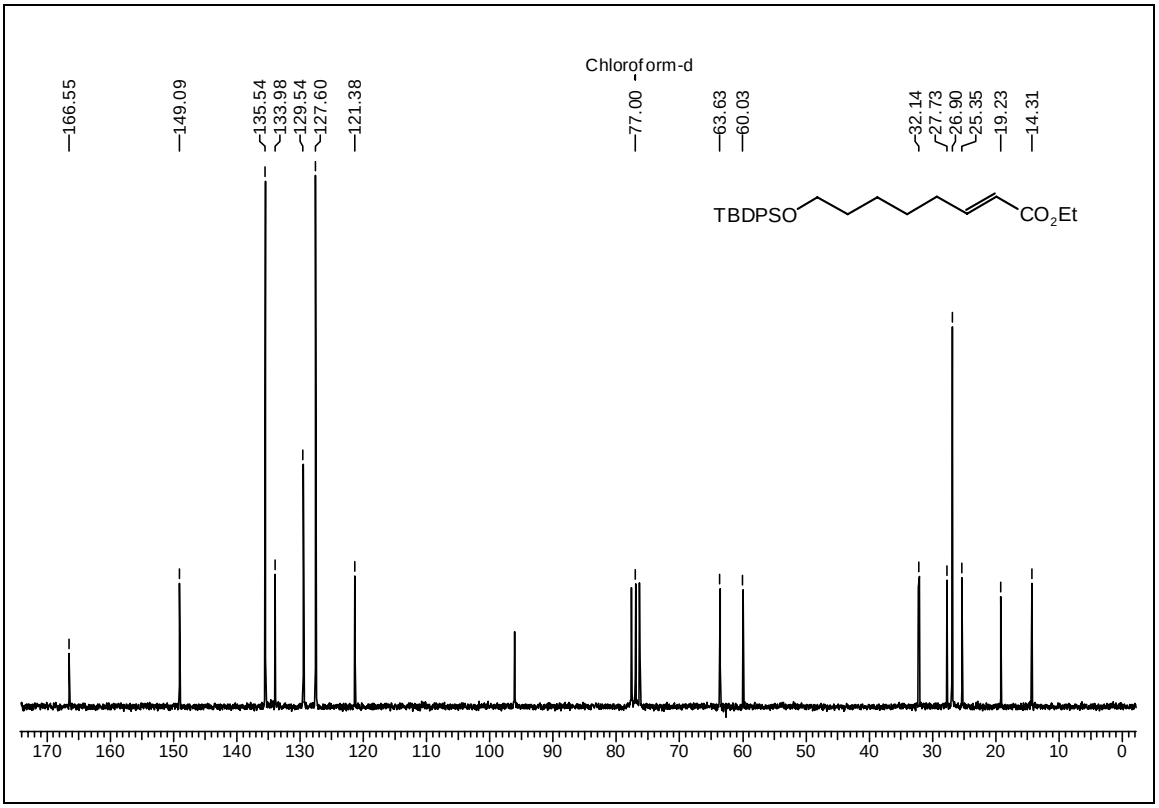
^{1}H NMR spectrum of compound 35 in $CDCl_3$



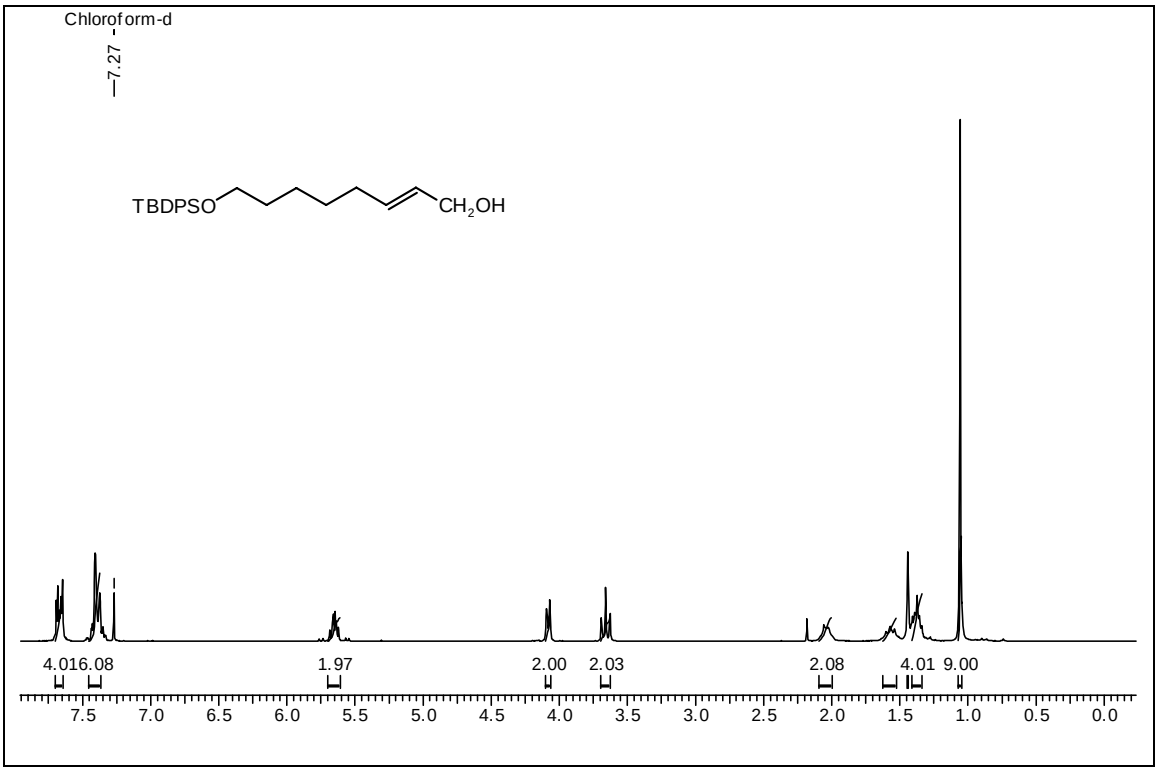
^{13}C NMR spectrum of compound 35 in $CDCl_3$



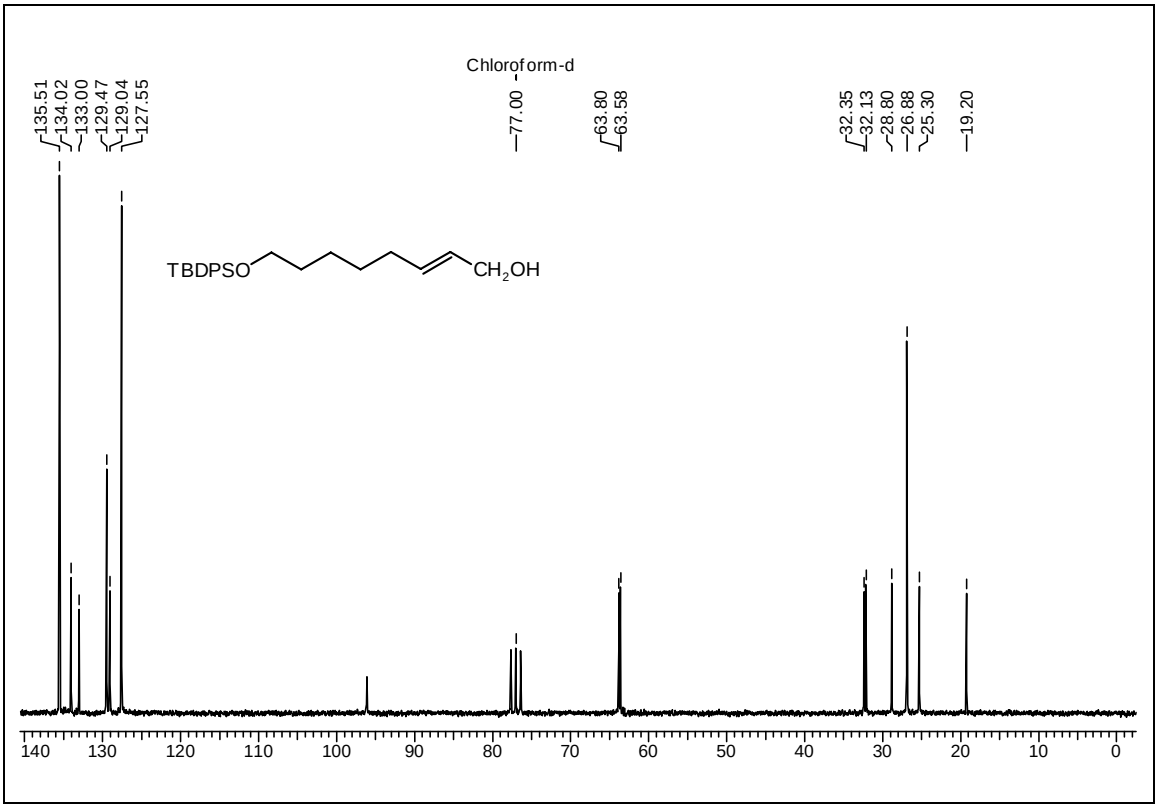
^{1}H NMR spectrum of compound 37 in $CDCl_3$



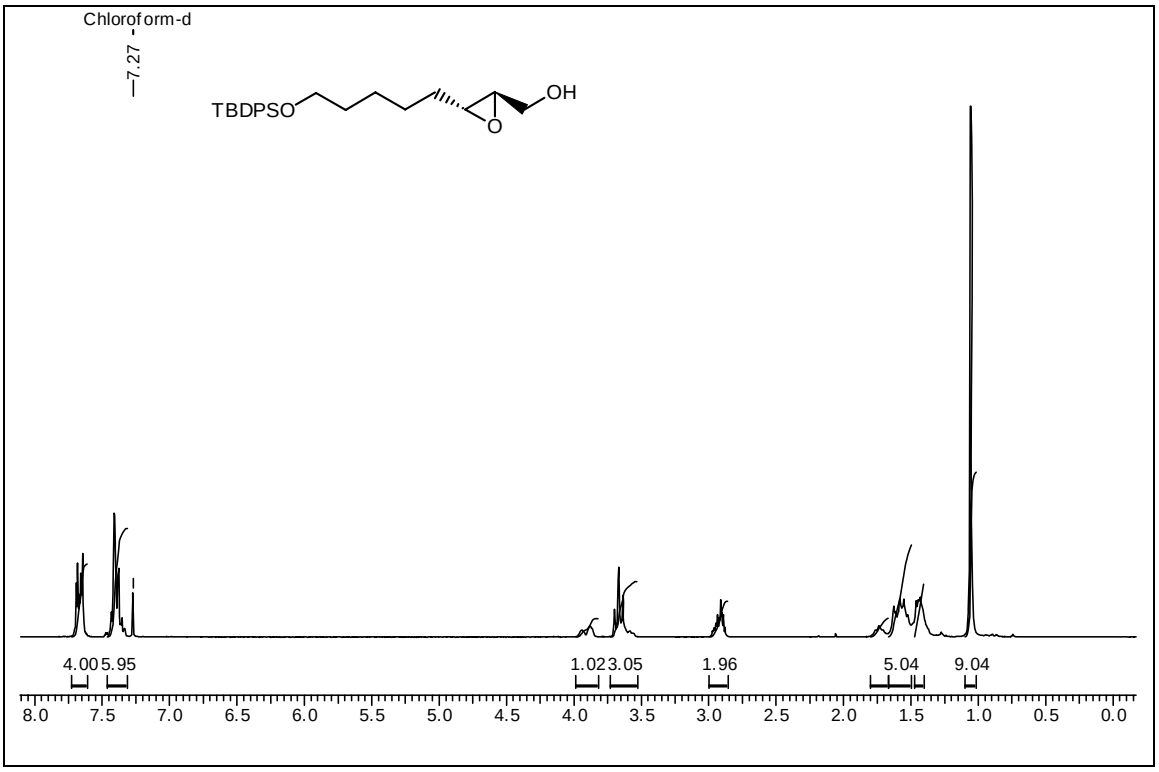
^{13}C NMR spectrum of compound 37 in $CDCl_3$



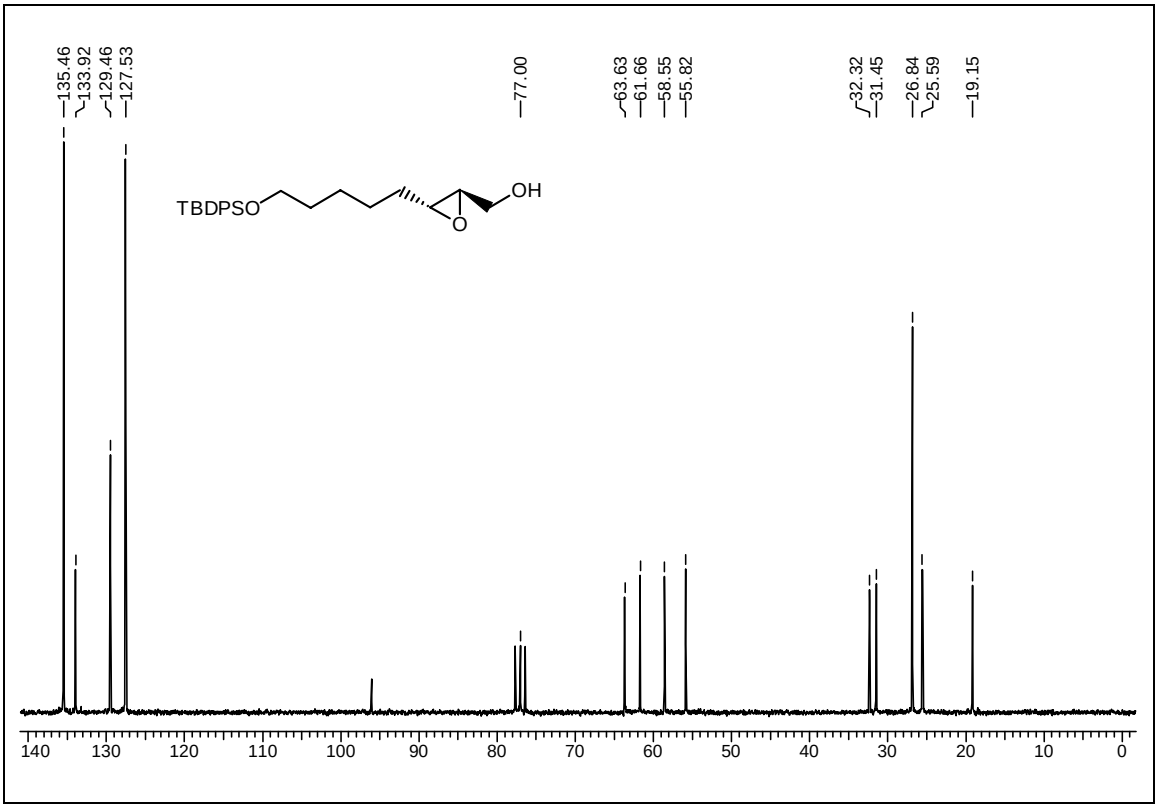
^{1}H NMR spectrum of compound 38 in $CDCl_3$



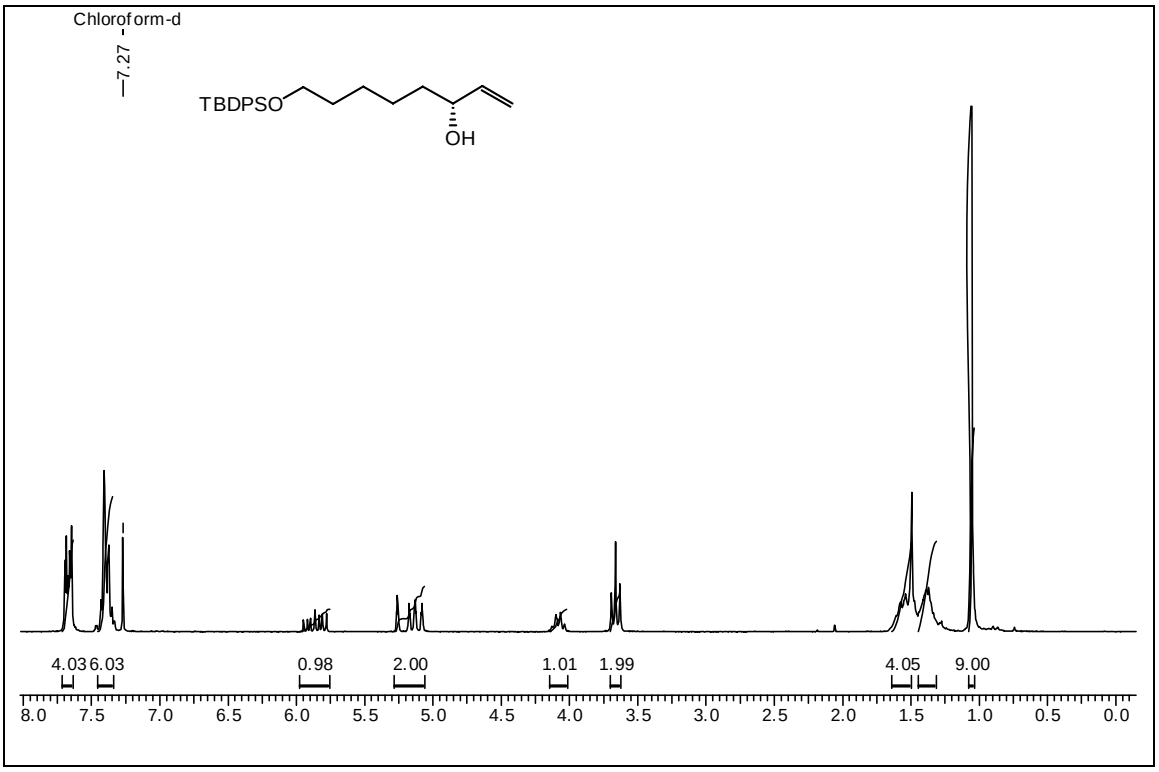
^{13}C NMR spectrum of compound 38 in $CDCl_3$



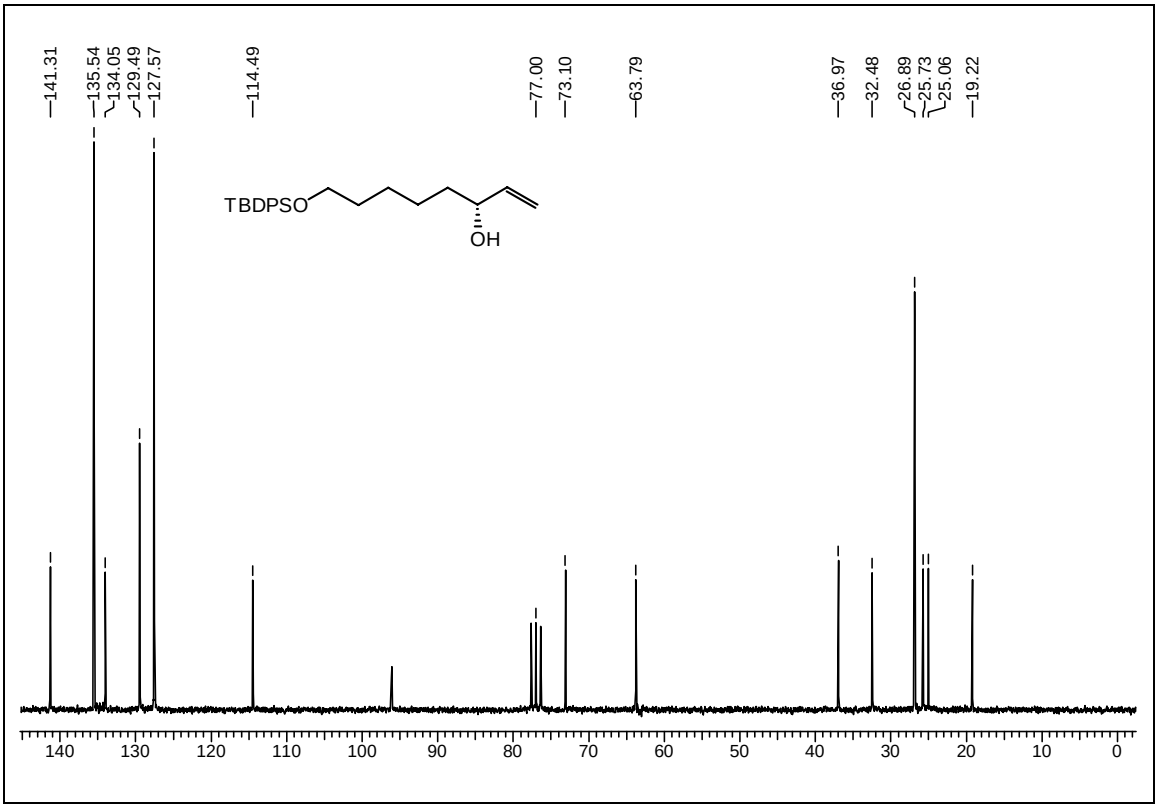
^{1}H NMR spectrum of compound 39 in $CDCl_3$



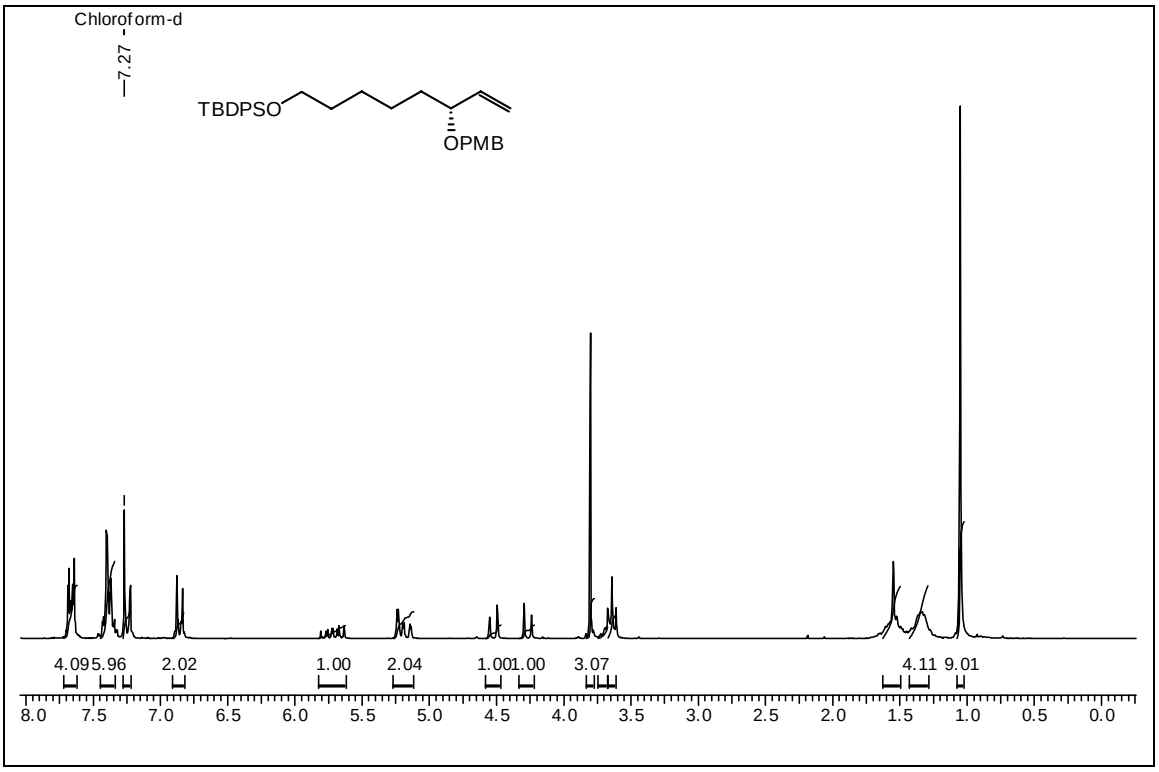
^{13}C NMR spectrum of compound 39 in $CDCl_3$



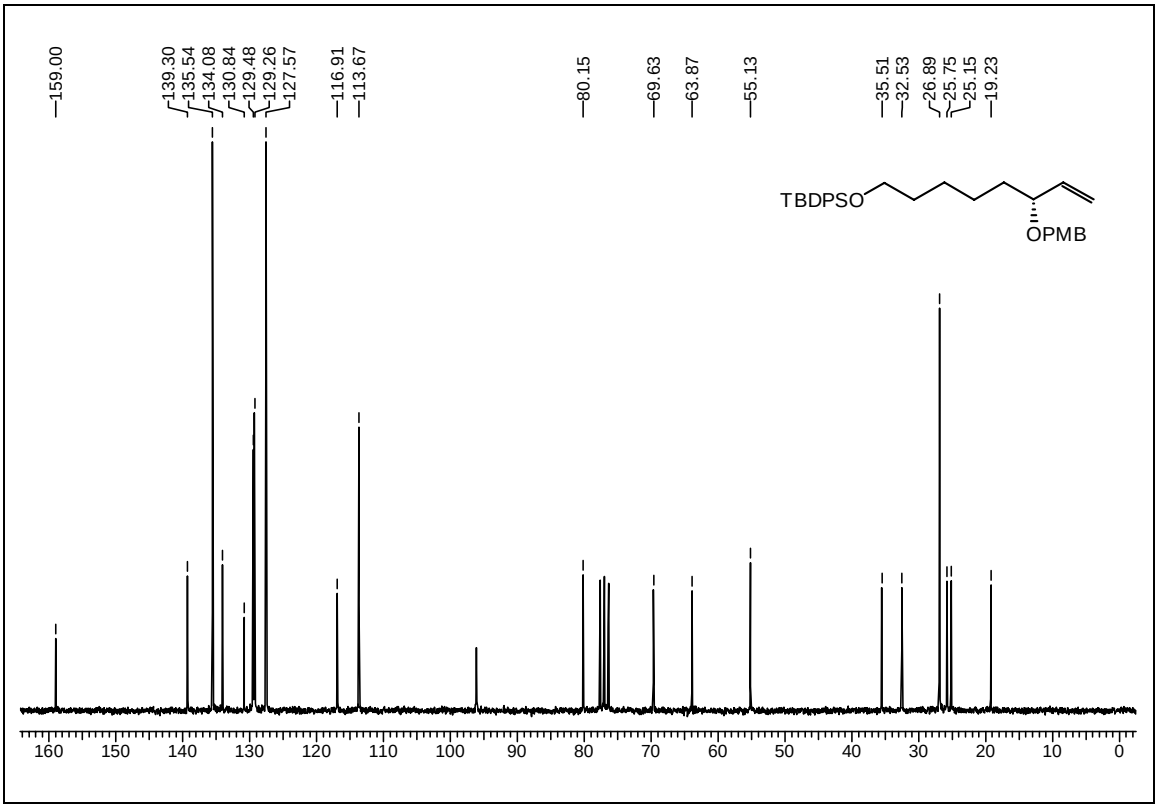
^{1}H NMR spectrum of compound 41 in $CDCl_3$



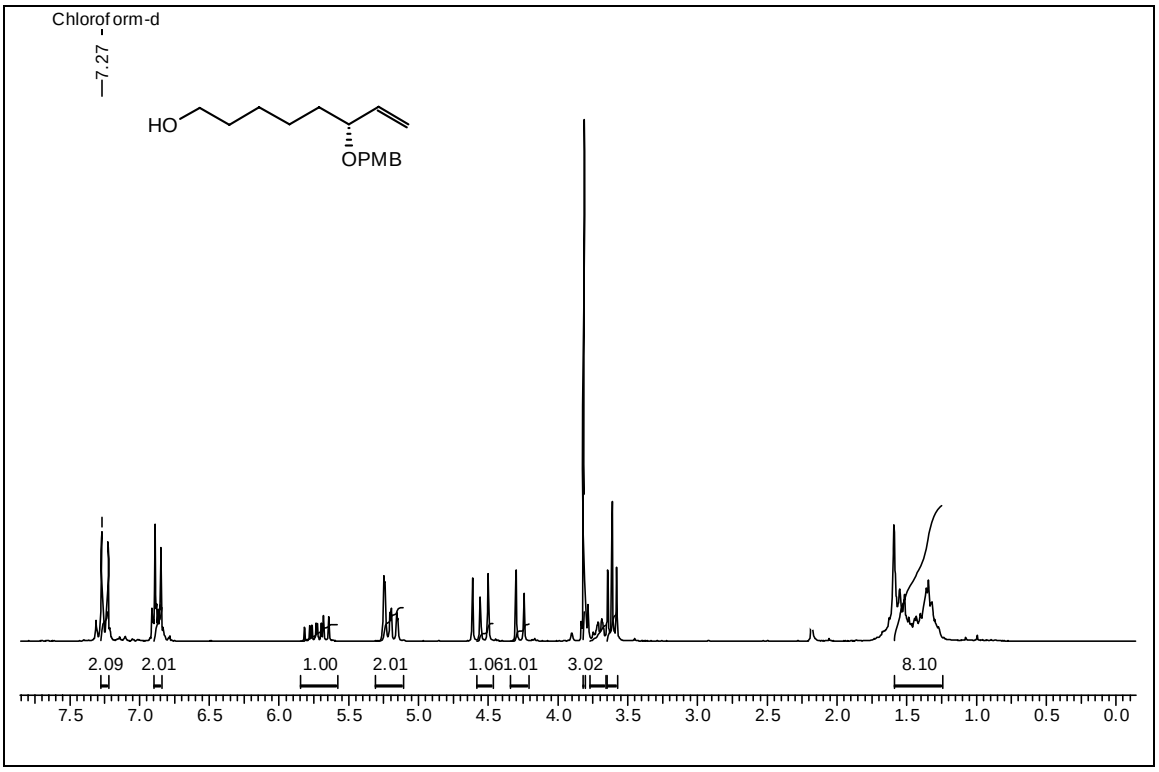
^{13}C NMR spectrum of compound 41 in $CDCl_3$



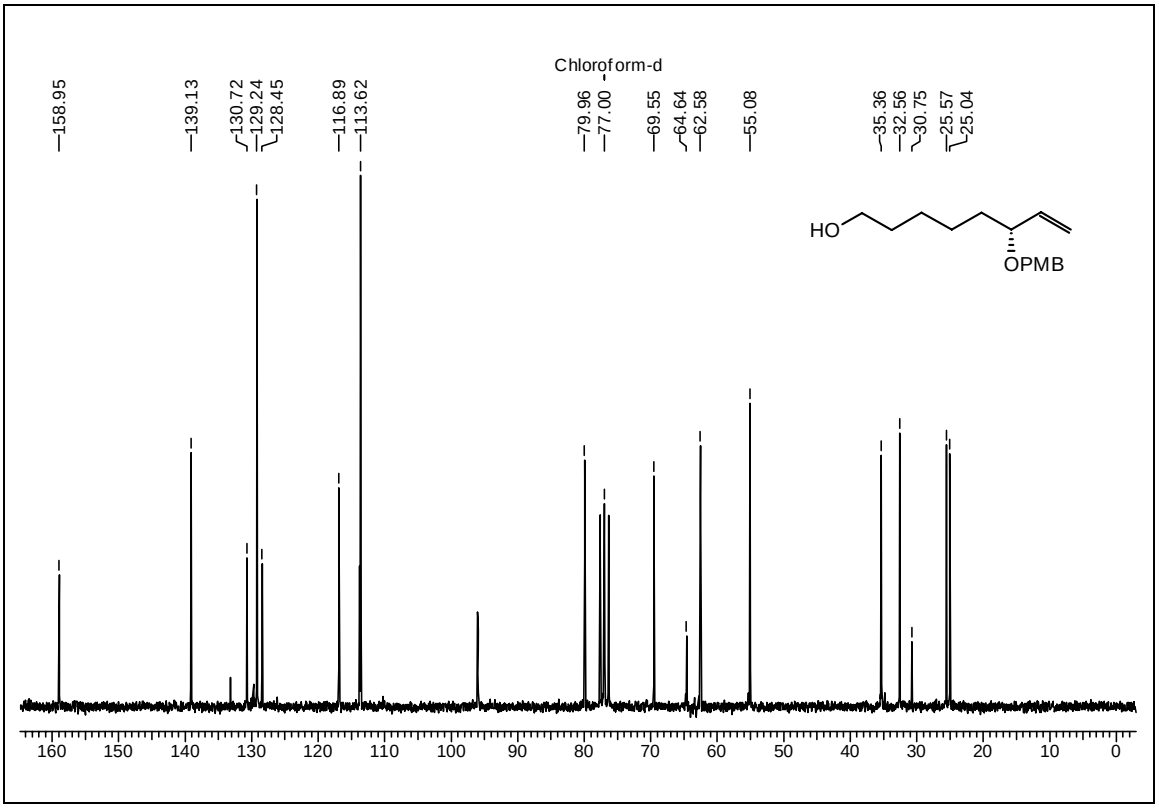
^{1}H NMR spectrum of compound 42 in $CDCl_3$



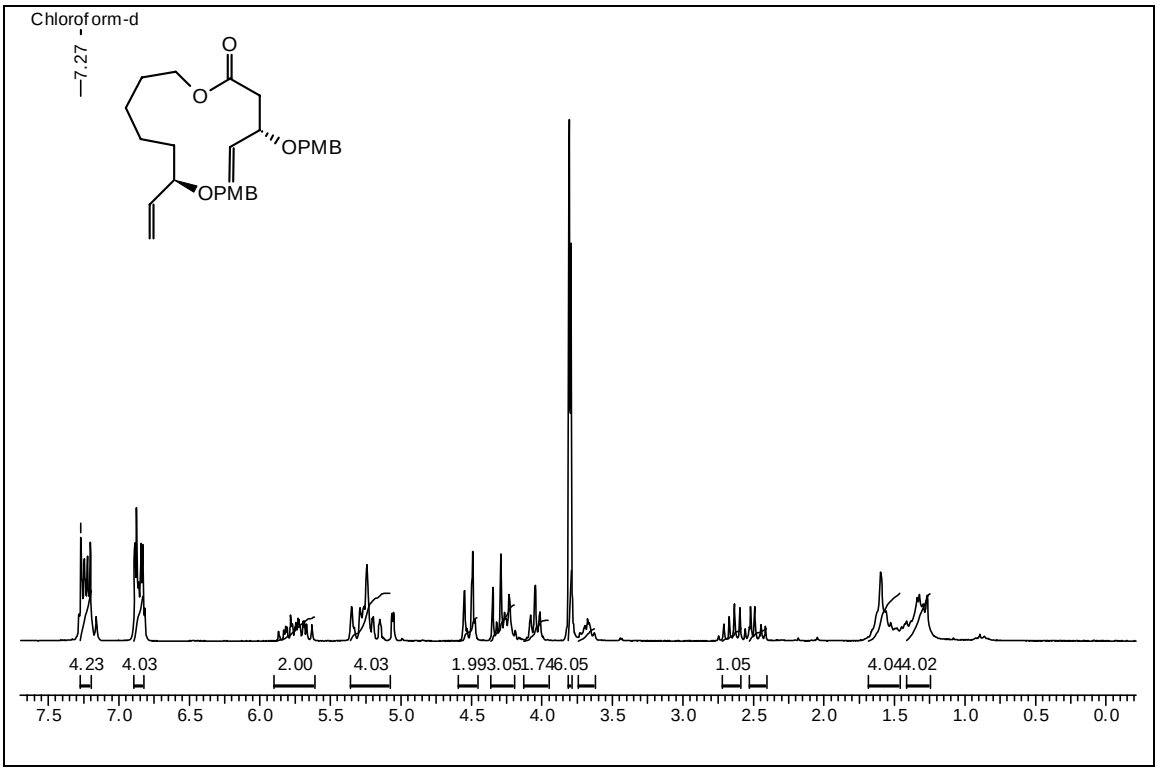
^{13}C NMR spectrum of compound 42 in $CDCl_3$



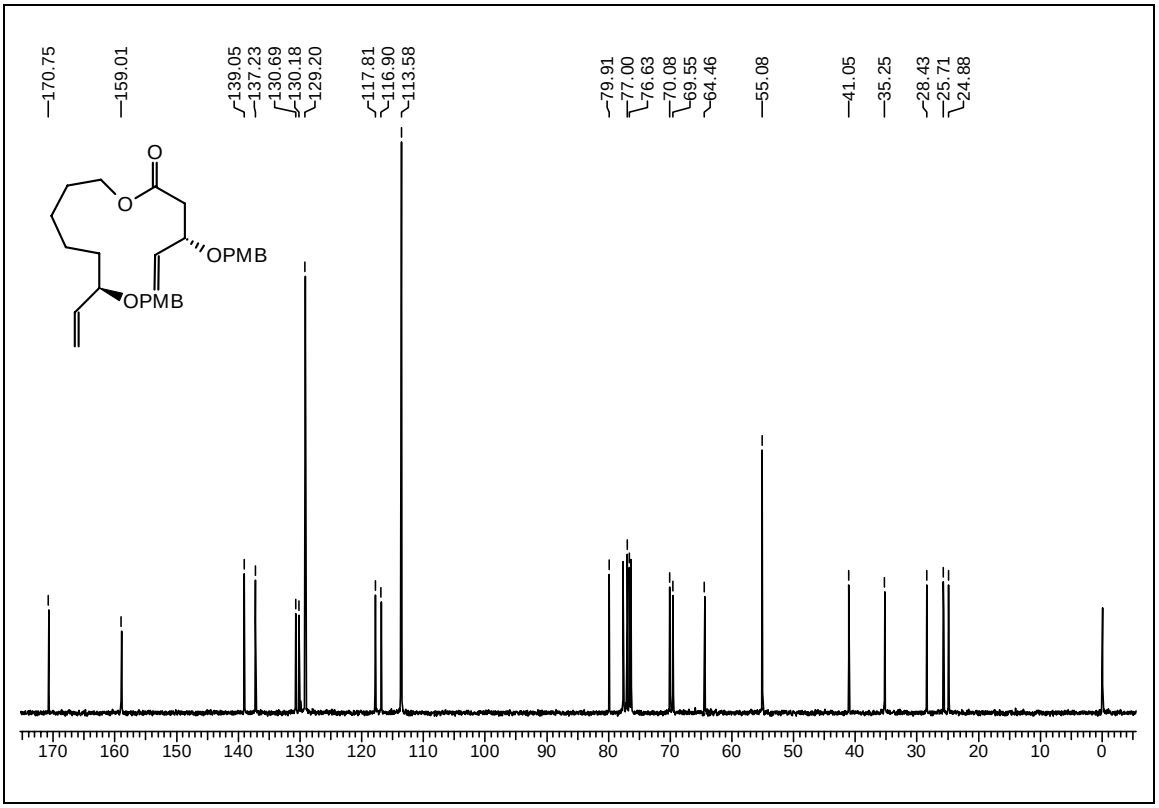
^{1}H NMR spectrum of compound 32 in $CDCl_3$



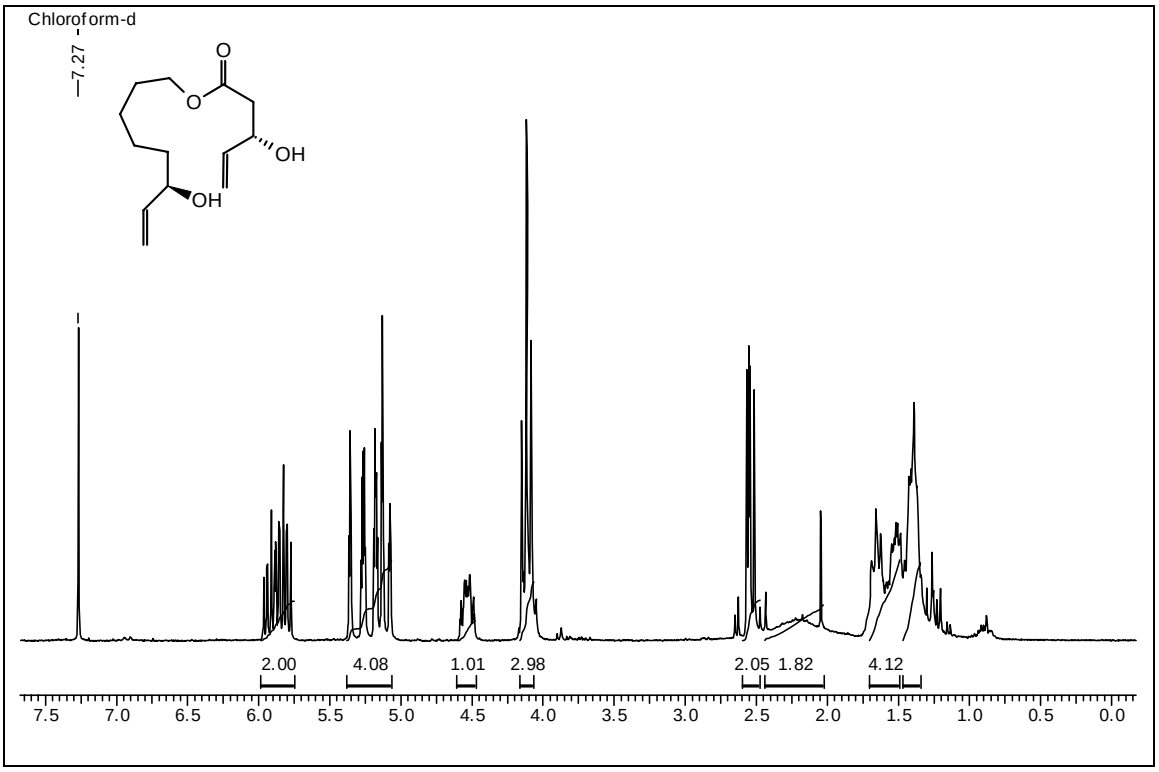
^{13}C NMR spectrum of compound 32 in $CDCl_3$



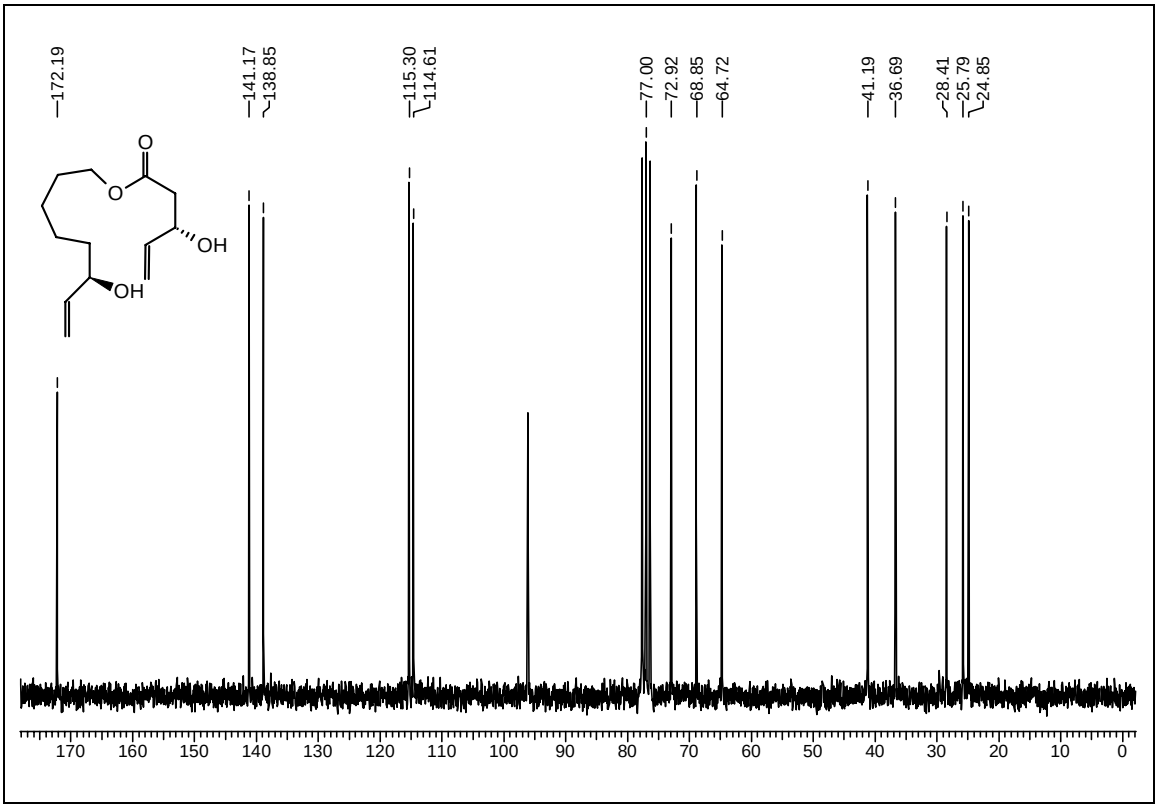
^{1}H NMR spectrum of compound 31 in $CDCl_3$



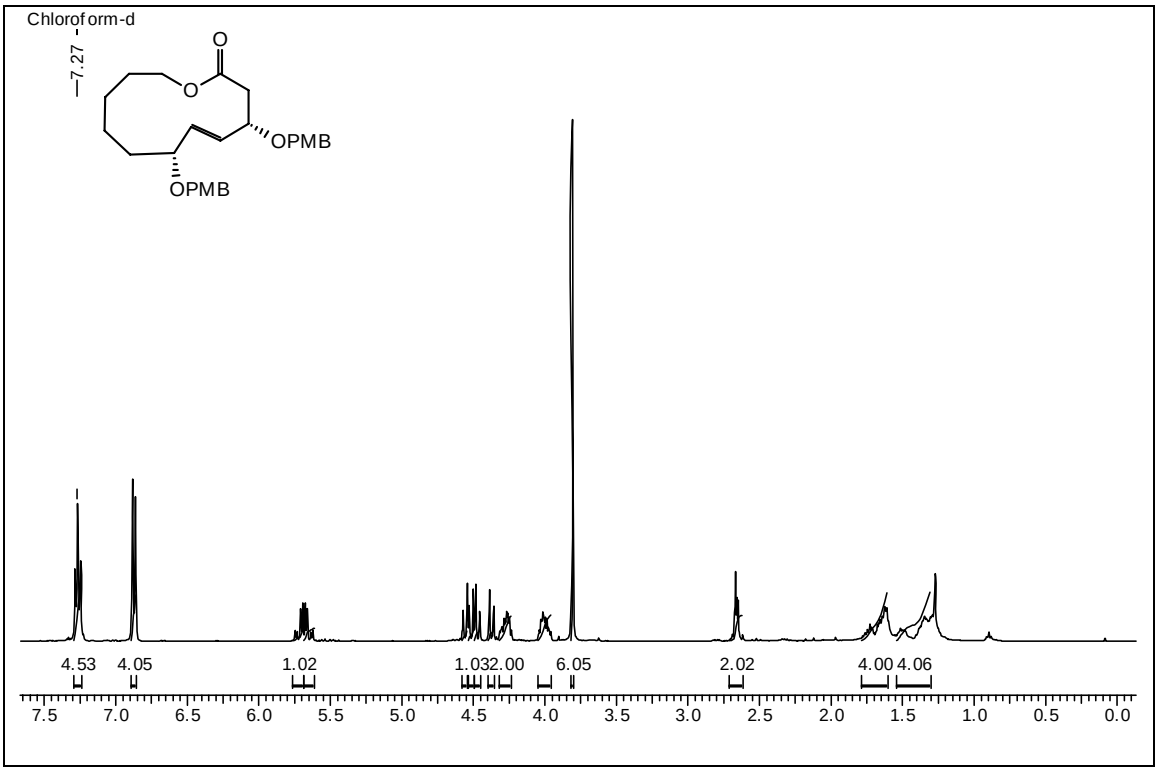
^{13}C NMR spectrum of compound 31 in $CDCl_3$



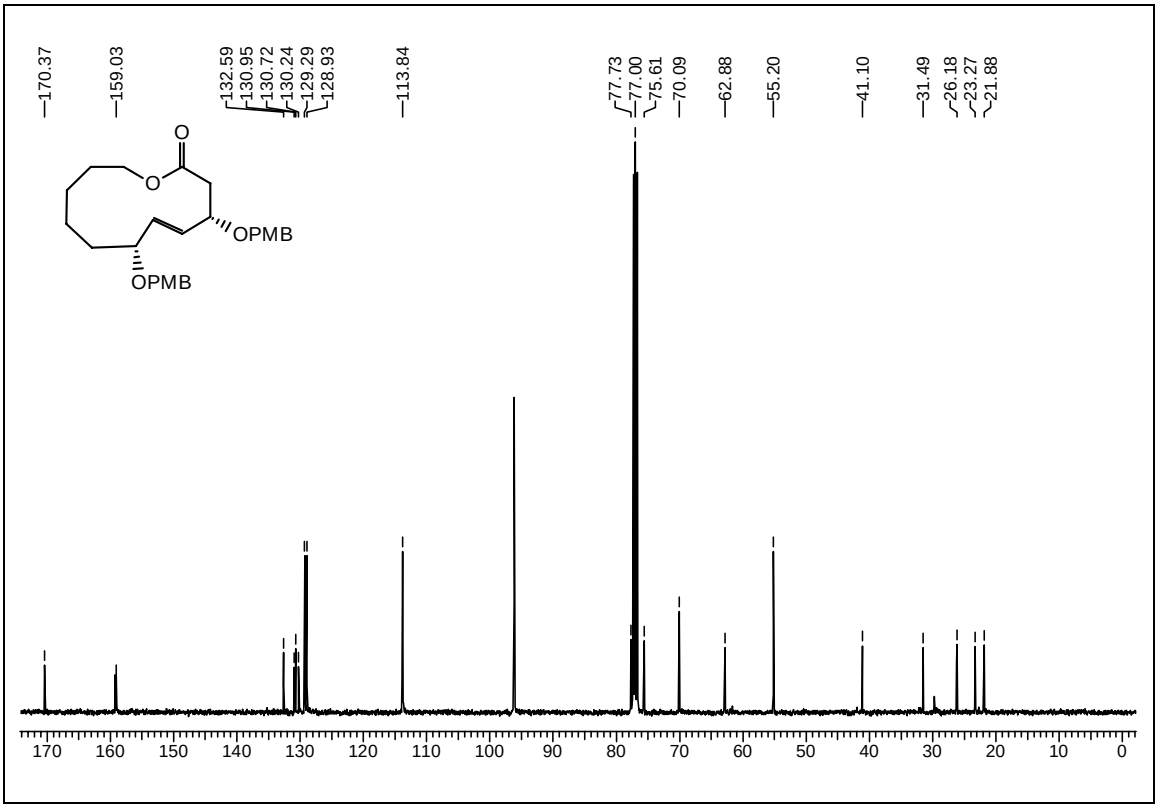
^{1}H NMR spectrum of compound 30 in $CDCl_3$



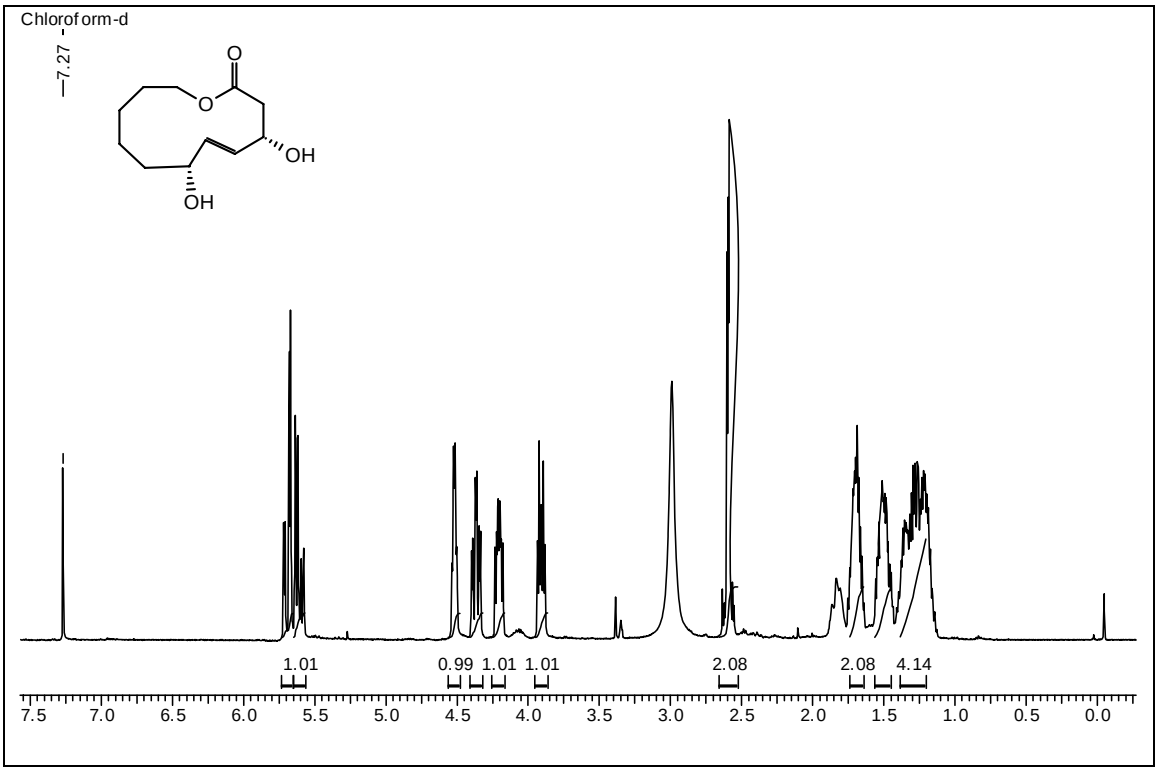
^{13}C NMR spectrum of compound 30 in $CDCl_3$



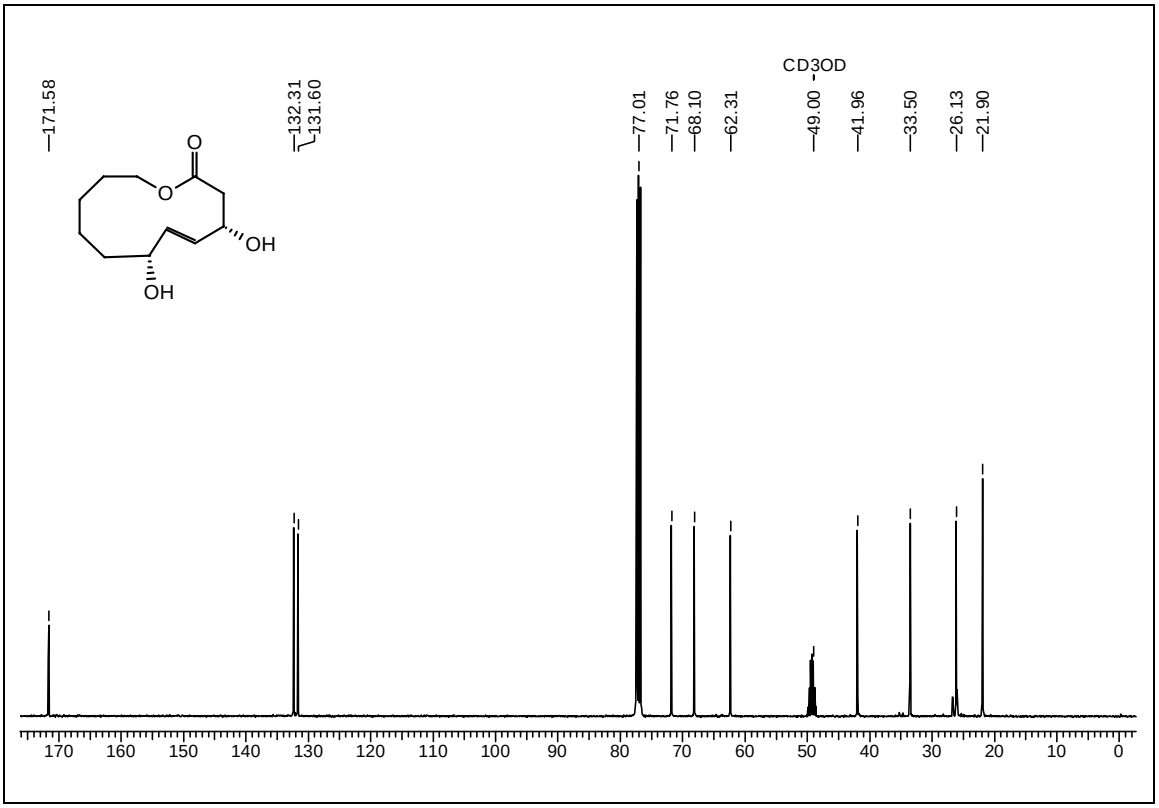
^{1}H NMR spectrum of compound 44 in $CDCl_3$



^{13}C NMR spectrum of compound 44 in $CDCl_3$



^{1}H NMR spectrum of compound 4 in $CDCl_3$ + a drop of CD_3OD



^{13}C NMR spectrum of compound 4 in $CDCl_3$ + a drop of CD_3OD

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CHAPTER-II

Synthesis of (±)-α-Lipoic acid

INTRODUCTION

Introduction

α-Lipoic acid is an important protein-bound coenzyme and growth factor found in plant and animal tissues and in microorganisms.[1,2] It has been recognized as a vital cofactor for the multienzyme complexes which catalyze the oxidative decarboxylation of α-ketoacids such as pyruvate, α-ketoglutarate etc.[3] It is known to play a crucial role in photosynthesis and in tricarboxylic acid cycle.

Lipoic acid (**1**) was first isolated in 1951 by Reed and his co-workers [4] at the University of Texas in Austin. The first purified sample of lipoic acid was 30 mg of yellow crystals that were extracted from 100 kg of liver residue. The substance was known as α-lipoic acid (or) ALA. Some scientists believed the substance should be named thioctic acid because it contained two sulfur atoms (theion in Greek) and eight carbon atoms (octo in Greek). Ultimately, it was given the name lipoic acid because of its ability to dissolve in lipids.

Alpha lipoic acid is not considered a vitamin because the body in small amounts from essential fatty acids can synthesize it. Alpha lipioc acid is found in variety of foods, notably kidney, heart and liver meats as well as spinach, broccoli and potatoes.

Lipoic acid works at the cellular level to help essential substances for metabolism to enter the mitochondria. Lipoic acid is an antioxidant. An increase in the amount of lipoic acid increases the amount of cellular fuel that is burned. This generates a greater energy reserve for the body that is available for growth, tissue repair and muscle development. Lipoic acid has been proposed as preventive against a variety of disease including aging, diabetes, cancer and cardiovascular disease.

Alpha lipoic acid does not accumulate in tissues and therefore does not have any toxicity in the amounts usually taken. Because it is distributed through the tissues, it is useful in a wide variety of conditions. It is particularly protective of the brain, which is the most sensitive of organs to free radical damage and the eye. However, animal experiments have shown that this protective effect is highly dependent upon the timing and the form of administration.

As part of the glycolytic pathway, alpha lipoic acid stimulates insulin activity and reduces insulin resistance. It has been shown to enhance the burning of glucose. Alpha

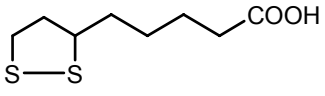
lipoic acid is a key part of the metabolic machinery that turns glucose (blood sugar) into energy for the body's need. One study of adult diabetic patients showed that alpha lipoic acid increased the cellular uptake and oxidation of glucose by about 50%. This is important for athletes and for the overweight persons. The efficient burning of glucose is essential for the normal production of energy in the muscles, and impaired muscle metabolism have been found in the brain.

The reduction of alpha lipoic acid (**1**) into dihydrolipoic acid (**2**) and the role of alpha lipoic acid in the production of glutathione appeal to be normal functions of alpha lipoic acid in the body. These are two of its several vitamins like physiologic functions. Alpha lipoic acid is unique in that, like vitamin C, it is effective as an antioxidant in water based tissues such as the blood, and yet as dihydro lipoic acid also is effective in protecting non-water based tissues like fatty tissues and membranes, a role it shares with vitamin E.

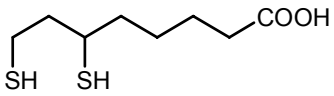
The alpha lipoic acid and dihydrolipoic acid together function as a universal anti oxidants, i.e., quenches free radicals in both lipid and water-soluble positions of tissues and cells. Lipoic acid and dihydrolipoic acids are extremely powerful quenchers of hydroxyl, singlet-oxygen, peroxy nitrite and other free radicals. We could also call lipoic acid a "broad spectrum" antioxidant because of its activity in aqueous and lipid phases.

Free radicals are associated with the development of artherosclerosis, lung disease and neurological disorders as well as being implicated in chronic inflammation, such as that found with rheumatoid arthritis and inflammatory bowel disease. Smog and many other sources of environmental toxins either are themselves (or) lead to the creation of free radicals in the body.

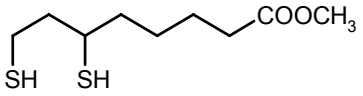
A healthy body makes enough lipoic acid to supply its requirements; external sources are not necessary. However, several medical conditions appear to be accompanied by low level of lipoic acid specific diabetes, liver cirrhosis and atherosclerosis, which suggests supplementation, would be helpful.



α-Lipoic acid (**1**)



Dihydrolipoic acid (**2**)



Methyl lipoate (**3**)

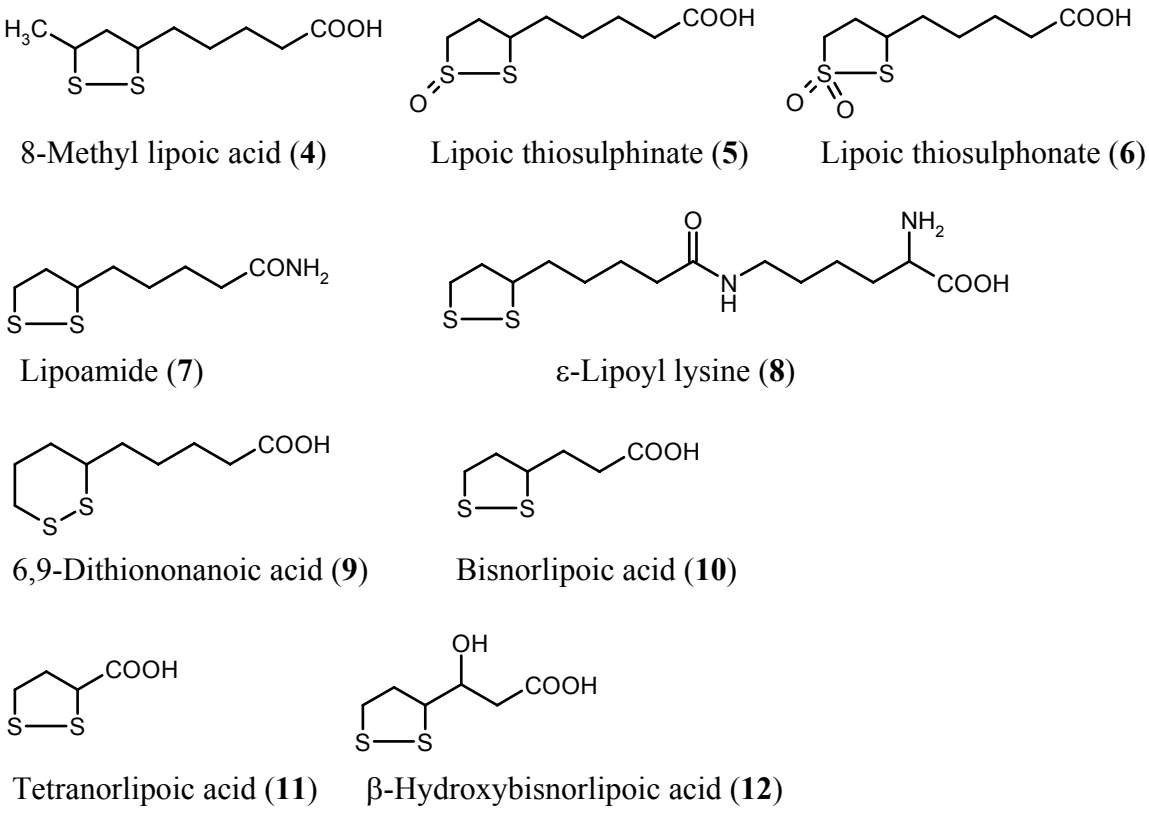
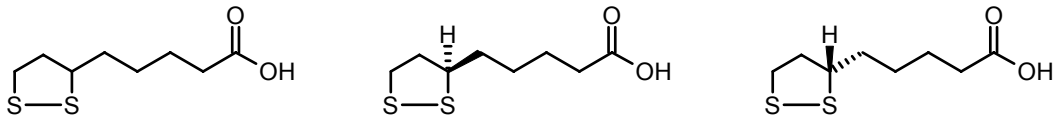


Figure-1 The structure of α-Lipoic acid and some of its related products.

Structure:

Lipoic acid is known by a variety of different names. Officially, it is known as lipoic acid (or) 1, 2-dithiolane-3-pentanoic acid. Unofficially, it has been known as α-lipoic acid, 6, 8-thiooctic acid, 5-(1, 2-dithiolan-3-yl)-valeric acid (or) 5, 3-(1, 2-dithiolanyl)-pentatonic acid.

It is a molecule containing eight carbon atoms, a 1, 2-dithiolane ring and a carboxylic acid group. The chiral centre is embedded in the ring structure at the third position. There are two forms of lipoic acid i.e., *R* and *S*: the natural isomer *R* is pharmacologically more active than that the *S*-isomer. Moreover, (±)-α-lipoic acid can be important for pharmaceutical use without resolution, since the (*S*)-enantiomer does not negatively affect the activity of the (*R*)-enantiomer.



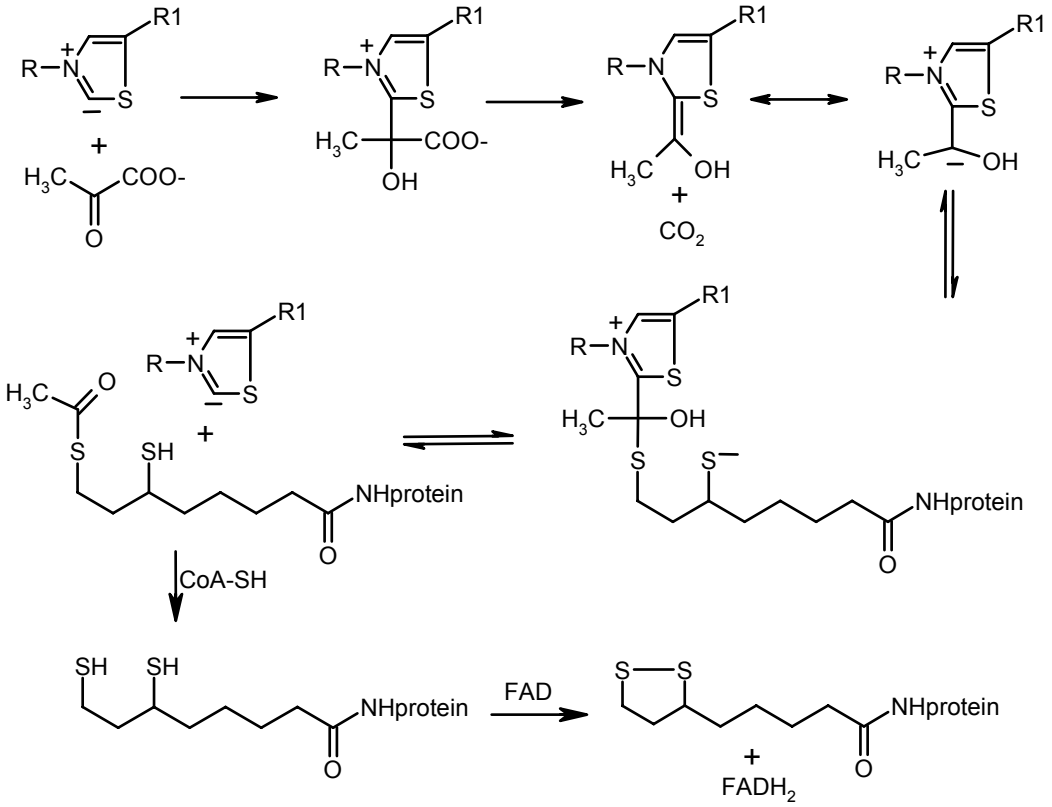
α-Lipoic acid (**1**) *R*-(+)-α-Lipoic acid (**1a**) *S*-(+)-α-Lipoic acid (**1b**)

Figure 2

Biological Action of α-Lipoic Acid:

The complete oxidation of pyruvate during aerobic glycolysis takes place by tricarboxylic acid (TCA) cycle. Pyruvate undergoes oxidative decarboxylation before it enters TCA cycle.

The coenzymes required for the overall oxidative decarboxylation of pyruvate are thiamine pyrophosphate (TPP), nicotinamide adenine dinucleotide (NAD), α-lipoic acid, coenzyme A and flavin adenine dinucleotide (FAD). [5] The stages involved in this complex process are shown in scheme-1.



Scheme-1

Thiamine pyrophosphate interacts with lipoic acid to form an addition complex which subsequently gets cleaved to form acyl lipoic acid complex and TPP is regenerated. The acetyl group, now present as a thioester, is then transferred from acyl

lipoic acid to coenzyme-A to form acyl-CoA by the acetyl-transfer enzyme system. Finally, the reduced lipoic acid moiety is reoxidised by the interaction with FAD and the cycle is completed. The acyl-CoA then enters the TCA cycle. FAD is regenerated by interaction with NAD+ in the electron transport system.

The hydrophobic interaction and the metal ion coordinating ability[6] of the molecule which helps the free passage of the compound in various tissues are the factors which are responsible for the high biological activity of lipoic acid. α-Lipoic acid offers metal ions two different binding sites, the carboxylate group and the disulfide linkage. The carboxylate group dominates the coordinating properties of this ligand towards metal ions but a disulfide-metal ion interaction is still possible, and under sterically favored conditions, may become very important. This could be true under enzymic conditions when the carbonyl group is no longer free but in the form of amide-linked to the protein. Further, the lipoyl moiety is ideally suited to undergo hydrophobic ligand-ligand interaction in the mixed ligand complexes due to the presence of valeric acid side chain.

Biological and Pharmacological Importance of α-Lipoic acid:

- α-lipoic acid functions as a universal antioxidant and free radical scavenger.[7]
- α-lipoic acid is a co-enzyme associated with a-keto acid dehydrogenation. [8,9]
- Recycles both Fat and Water-soluble antioxidant vitamins.[10]
- Improves sugar metabolism and energy production. (i. e. controls diabetes).[11]
- α-lipoic acid has been used as a therapeutic agent in a number of conditions related to liver.[12]
- α-lipoic acid appears to have the potential to slow the process of aging.[13]
- α-lipoic acid significantly reduces inflammation and it also acts as an antitumour agent.[14]
- α-lipoic acid is an effective inhibitor of human immuno deficiency virus (HIV) replication.[15]
- α-lipoic acid has been found beneficial against radiation injury, smoking, heavy metal poisoning and chagas disease.[16]

Apart from the pharmacological importance, α-lipoic acid also finds its use in cosmetic preparations. α-Lipoic acid and its derivatives are used in skin lotions,

ointments and creams as skin-whitening cosmetics.[17].Also, α-lipoic acid and its derivatives are used in hair tonics to control dandruff and stimulate hair growth.

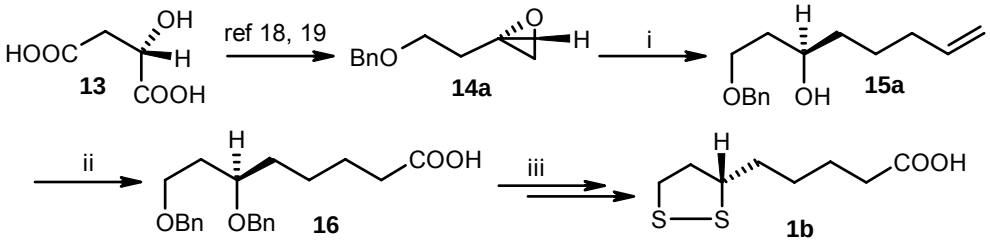
Finally, it is truly amazing how a relatively small and simple molecule like lipoic acid could have such a profound effect on so many diverse systems and functions in our body. It is thus becomes readily apparent that maintaining adequate alpha lipoic acid status is crucial for our long-term health and well being.

Literature Review:

Reed and co-workers reported the isolation of α-lipoic acid in 1951 from liver residue. The chemical structure of α-lipoic acid was determined in the early 1950's and its absolute configuration was confirmed to be *R* in 1983, when Golding synthesized the complementary enantiomer from *S*-malic acid. It clearly indicates that scientists considered lipoic acid as small molecule and after knowing the biological activity and pharmaceutical importance the scientific community was attracted by its synthesis as a result a number of (±)-α-lipoic acid and optically active lipoic acids have been documented in the literature.[18]

Golding *et al* (1983, Scheme-2, 1988, Scheme-3) [18,19]

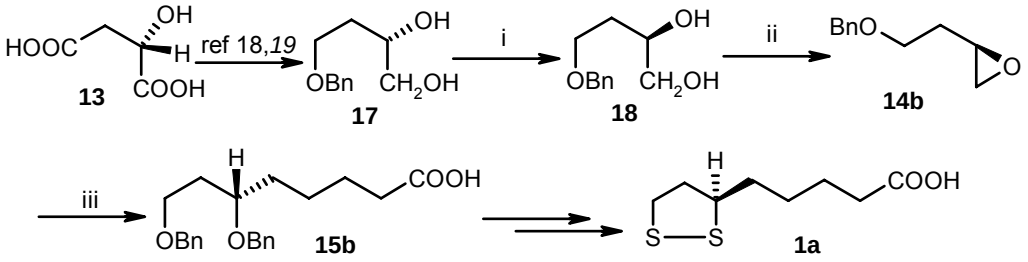
Golding and co-workers have utilized epoxide **14a** as the chiral precursor, which was prepared by known procedure from *S*-malic acid. Opening of epoxide with but-3-enyl magnesium chloride catalysed by lithium chloro cuprate furnished the compound **15a**. The hydroxyl groups were protected with benzyl ether, followed by hydroboration and oxidation to give the acid **16**. Esterification of acid **16** and deprotection of benzyl ether gave diol ester, which was mesylated and converted to methyl lipoate by treatment with Na_2S, sulfur in DMF and final hydrolysis of ester furnished the (*S*)-α-Lipoic aicd.



Scheme-2

Reagents and conditions: (i) (a) CH_2=$CHCH_2CH_2MgCl$, Li_2CuCl_4 (catalytic), THF; ii) $PhCH_2Br$, NaH, THF; iii) (a) $HBSia_2$, THF, alkaline H_2O_2; (b) PDC, DMF; (c) i. MeOH-HCl; ii. Pd/C, H_2; (d) i. $MeSO_2Cl$, Et_3N; ii. Na_2S, S, DMF; (e) aq. NaOH

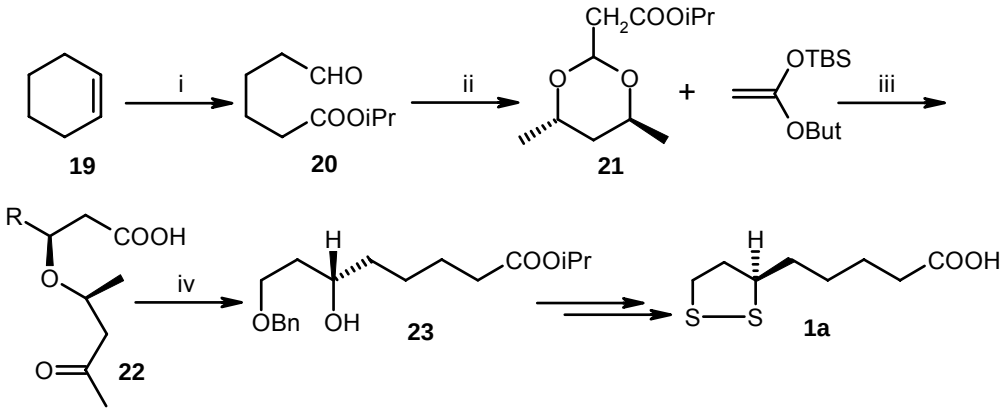
In another approach Golding and Brookes synthesized enantiomer of epoxide **14a** for the synthesis of *R*-Lipoic acid. They used the same starting material i.e., *S*- malic acid but inverted the configuration of hydroxyl group to prepare the epoxide **14b**. Epoxide **14b** was converted in to *R*-Lipoic acid following the same sequence of reactions used in the earlier approach.



Scheme-3

Reagents and conditions: (i) (a) $MeSO_2Cl$, Et_3N; (b) KOAc, Ac_2O; (c) K_2CO_3, MeOH; (ii) (a) PhCHO, H^+; (b) NBS, $ClF_2CCCl_2F_2$; (c) NaOH, $HOCH_2CH_2OH$; (iii) (a) $HBSia_2$, THF, alkaline H_2O_2; (b) PDC, DMF; (c) i. MeOH-HCl; ii. Pd/C, H_2; (d) i. $MeSO_2Cl$, Et_3N; ii. Na_2S, S, DMF; (e) aq. NaOH.

Elliott *et al* (1985, Scheme-4) [20]



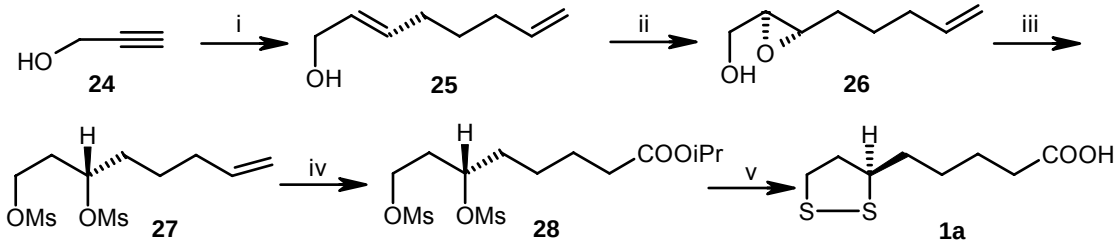
Scheme-4

Reagents and conditions: (i) (a) O_3, iPrOH, -78 ^oC, Ac_2O, Et_3N; (ii) (2*S*, 4*S*)- pentane-2, 4-diol, *p*-TSA, Benzene; (iii) (a) TiCl4, CH_2Cl_2, -78 ^oC; (b) TFA, H_2O; (c) Jones oxidation; (iv) Piperidinium acetate, benzene, reflux, 97 %; (b) BH_3.THF, then 4 M aq. KOH, 82 %.

Elliott and co-workers have reported the first synthesis of *R*-(+)-lipoic acid using highly diastereoselective $TiCl_4$ catalyzed aldol-type coupling of chiral acetal **21** with 1-*t*-butyldimethyl silyloxy ethane. The coupling product on hydrolysis followed by oxidation with Jones reagent gave acid **22**. Removal of the chiral auxiliary by b-elimination followed by hydroboration delivered the diol ester **23**. The diol ester was converted to *R*-(+)-lipoic acid by using Golding's Procedure.

Sutherland *et al* (1986, Scheme 5)[21]

Sutherland and co-workers employed the alkylation of lithiodianion of propargyl alcohol in liquid ammonia solution with 6-bromohex-1-ene followed by dissolving metal reduction to deliver the allyl alcohol **25**. Sharpless asymmetric epoxidation of allyl alcohol **25** gave the (2*S*, 3*S*)-epoxy alcohol **26**. Reduction of **26** with Red-Al and mesylation of the diol to give the dimesylate **27**. Ruthenium tetroxide oxidation of the terminal double bond of **27** and final disulfide displacement of acid **28** delivered the *R*-(+)-Lipoic acid.

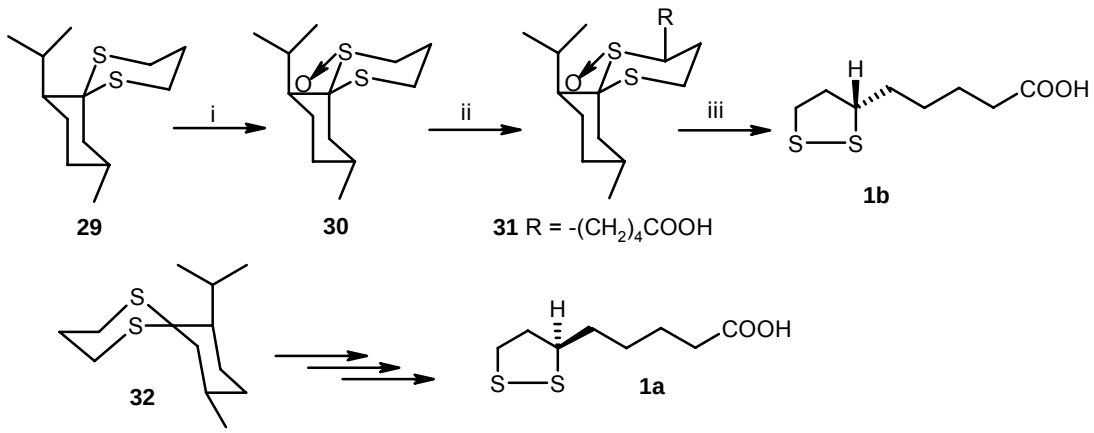


Scheme-5

Reagents and conditions: (i) Na, liq. NH_3,$Br(CH_2)_3CH=CH_2$; (ii) L-(+)-diisopropyl tartarate, $Ti(OPri)_4$, TBHP, CH_2Cl_2, -20 ^oC; (iii)(a) Red-Al, THF; (b) $MeSO_2Cl$, Et_3N, CH_2Cl_2; (iv) RuO_4 (v) Na_2S, S, DMF, then 4 M aq. KOH.

Ravindranathan *et al* (1987, Scheme 6) [22]

Ravindranathan's approach involves the formation of 1, 3-dithiane **29** from 1, 3-propane dithiol and L-menthone. Regioselective oxidation of dithiane **29** afforded sulfoxide **30**. Stereo selective alkylation of **30** followed by hydrolytic cyclization afforded *R*-(+)-lipoic acid. In the similar manner *S*-lipoic acid prepared by using D-menthone. In their approach they recovered the starting menthones in almost quantitative yield. This is the shortest and probably the best synthesis for both the enantiomers of lipoic acid.

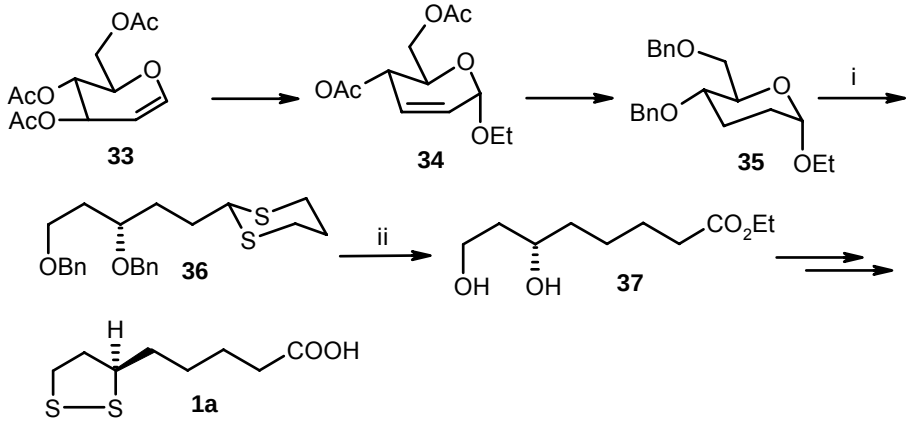


Scheme-6

Reagents and conditions: (i) $NaIO_4$, MeOH, 0 ^oC; (ii) LDA, TMEDA, THF, $Br(CH_2)_4CO_2Li$, -78 ^oC; (iii) aq. HCl, benzene.

Rama Rao *et al* (1986, 1987, 1987, 1987) [23]

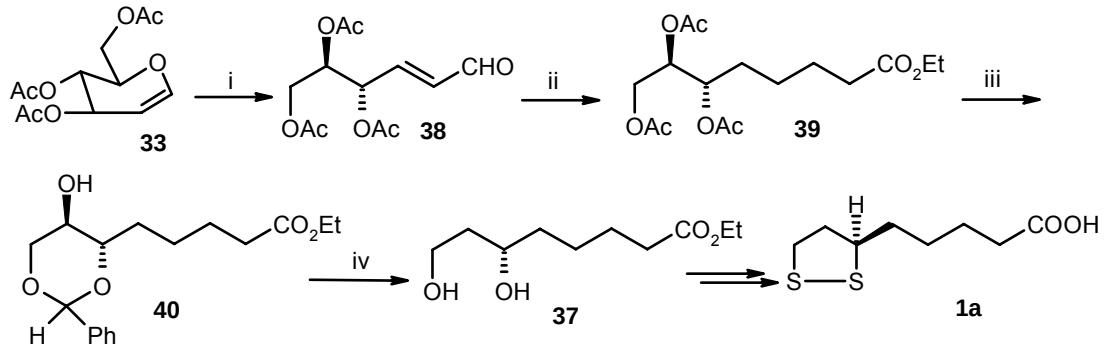
Rama Rao and co-workers have reported four different routes for the synthesis of lipoic acid. Rama Rao's first synthesized from D-glucose, which was converted to 4, 6-di-o-benzyl derivative through 3, 4, 6-tri-o-acetyl-D-glucal by known procedure. Treatment of **35** with propane dithiol followed by xanthate formation and tri-n-butyl tin hydride mediated reductive removal afforded dithiane derivative **36**. Sequential dithiane deprotection, two carbon Wittig olefination, hydrogenation using Raney nickel delivered the diol **37**. The diol **37** was converted to lipoic acid by the known procedure.



Scheme-7

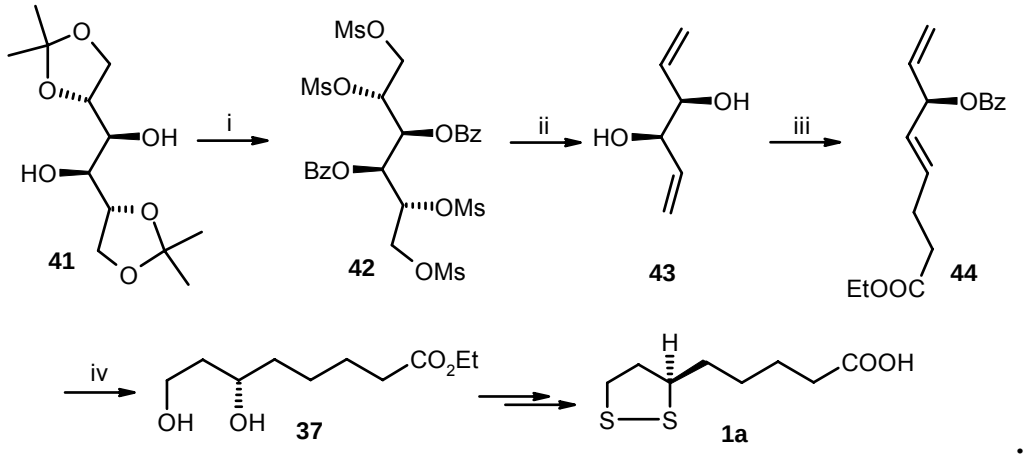
Reagents and conditions: (i) (a) 1, 3-propane dithiol, $BF_3.Et_2O$, CH_2Cl_2; (b) NaH, CS_2, MeI; (c) n-Bu_3SnH, AIBN; (ii) (a) HgO, $BF_3.OEt_2$; (b) Ph_3P=CHCOOEt (c) H_2, Raney Ni.

In Rama Rao's second approach: tri-o-acetyl-D-glucal was converted to unsaturated aldehyde **38** using mercurous ion catalyzed ring opening. Sequential hydroxyl group protection, two carbon Wittig homologation and hydrogenation gave the tri acetate **39**. Deacetylation and protection of 6, 8-hydroxyl groups with benzaldehyde dimethyl acetal gave the benzylidene protected compound **40**. Deoxygenation of the free hydroxyl group followed by removal of benzylidene protection gave the diol **37**, which was converted to lipoic acid (Scheme-8).



Scheme-8

Reagents and conditions: (i) (a) $HgSO_4$, H^+, Dioxane; (b) Ac_2O, Pyridine; (ii) (a)Ph_3P=CHCOOEt; (b) H_2, Raney Ni; (iii) (a) NaOEt, EtOH; (b) $PhCH(OMe)_2$, H^+; (iv) (a) Thiocarbonyl diimidazole, THF; (b) n-Bu_3SnH, AIBN; (c) H_2, Pd/C.

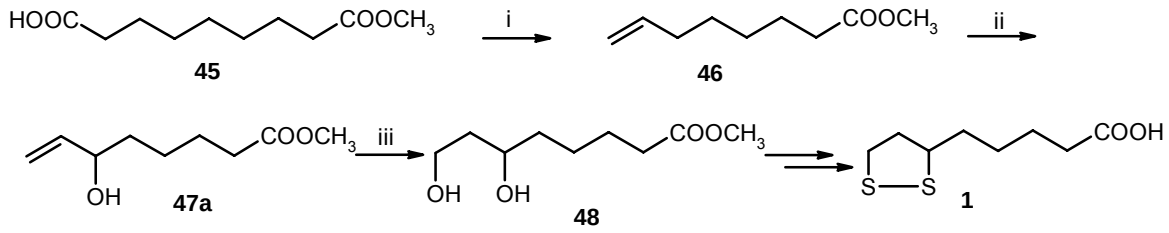


Scheme-9

Reagents and conditions: (i) (a) PhCOCl, Pyridine; (b) 50 % aq. AcOH (c) $MeSO_2Cl$, Et_3N, CH_2Cl_2; (ii) (a) NaI, Zn, DMF, Reflux; (b) NaOMe (iii) (a) Bu_2SnO, Toluene, Reflux; (b) 1.2 eq $PhCH_2Br$, DMF, 100 ^oC; (c) $CH_3CH(OEt)_3$, Propionic acid (cat), 145 ^oC; (iv) (a) 9-BBN, OH-/H_2O_2; (b) H_2, Pd/C.

Third approach involves the utilization of mannitol diacetonide as a chiral precursor. Benzoyl protection of the hydroxyl groups followed by isopropylidene group deprotection and mesylation gave the tetra mesylate **42**. Treatment of **42** with sodium Iodide and Zinc dust followed by debenzoylation gave (3*R*, 4*R*)-1, 2-divinyl glycol **43**. Selective protection of hydroxyl group and claisen-ester rearrangement of the resultant monoprotected benzyl ether delivered the compound **44**. Sequential hydroboration, oxidation and reduction of the double bond gave the known diol **37** which was converted in to *R*-(+)-lipoic acid (Scheme-9).

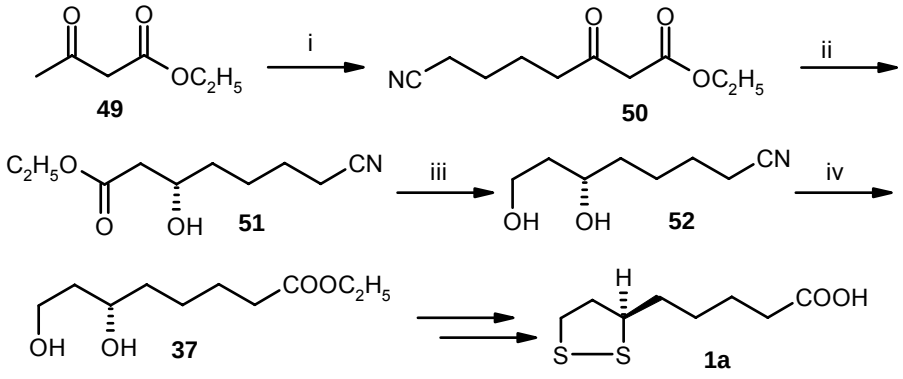
Fourth approach, Rama Rao employed highly regioselective Sharpless allylic oxidation of the olefin **46** with TBHP and SeO_2 to deliver the compound **47a**. Hydroboration, oxidation of olefinic compound **47a** delivered the known diol **48** which by a series of known reactions converted to (±)-α-lipoic acid (Scheme-10).



Scheme-10

Reagents and conditions: (i) $Pb(OAc)_4$, $CuSO_4$, Benzene; (ii) TBHP, SeO_2, CH_2Cl_2; (iii) B_2H_6-THF, NaOOH.

Gopalan and Jacobs (1989, Scheme 11) [24]



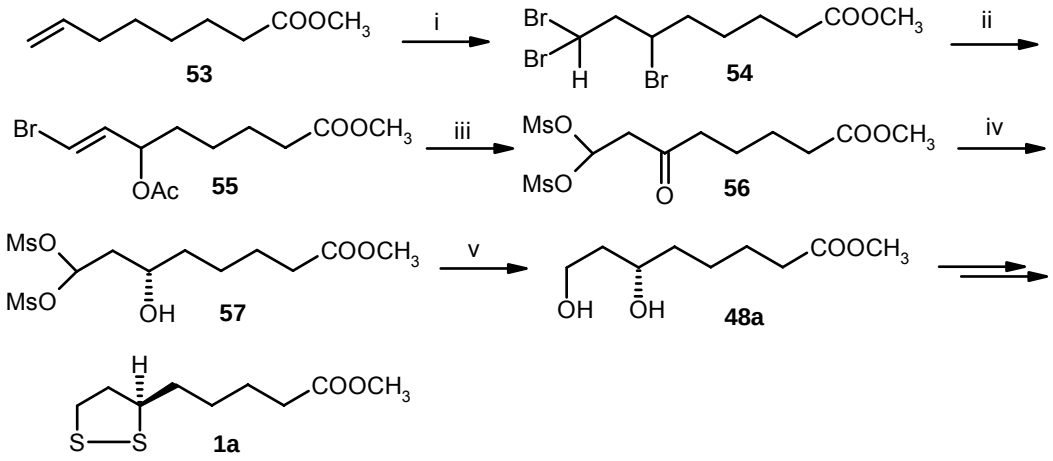
Scheme-11

Reagents and conditions: (i) (a) NaH, THF, HMPA, 0 ^oC; (b) nBuLi, $I(CH_2)_3CN$; (ii) Baker's Yeast (iii) $LiBH_4$, THF, 0 ^oC; (iv) EtOH, H^+, Reflux.

Gopalan and Jacobs have utilized highly enantioselective yeast reduction of β-keto ester **50** as the key step to deliver the compound **51**. Reduction of ester **51** with $LiBH_4$ in THF at room temperature gave the diol **52**. The diol was converted in to diol ester **36** by using ethanol in presence of acid. Diol ester **37** was converted to *R*-(+)-lipoic acid by a series of known reactions.

Bhalerao *et al* (1990, Scheme 12) [25]

Bhalerao and co-workers have used copper catalyzed bromoform addition to alkene **53** to give methyl-6, 8, 8-tribromooctonoate **54**, which on treatment with potassium acetate and 18-crown-6 in DMF gave compound **55**. Hydrolysis, Oxidation and followed by treatment with triton-B gave the keto acetal **56**. The keto acetal **55** was reduced enantioselectively by baker's yeast to give compound **57**, which on treatment with H_3PO_4 in acetone followed by $NaBH_4$ reduction resulted in the formation of diol **37**. The diol was converted to *R*-(+)-lipoic acid in a similar fashion reported earlier.



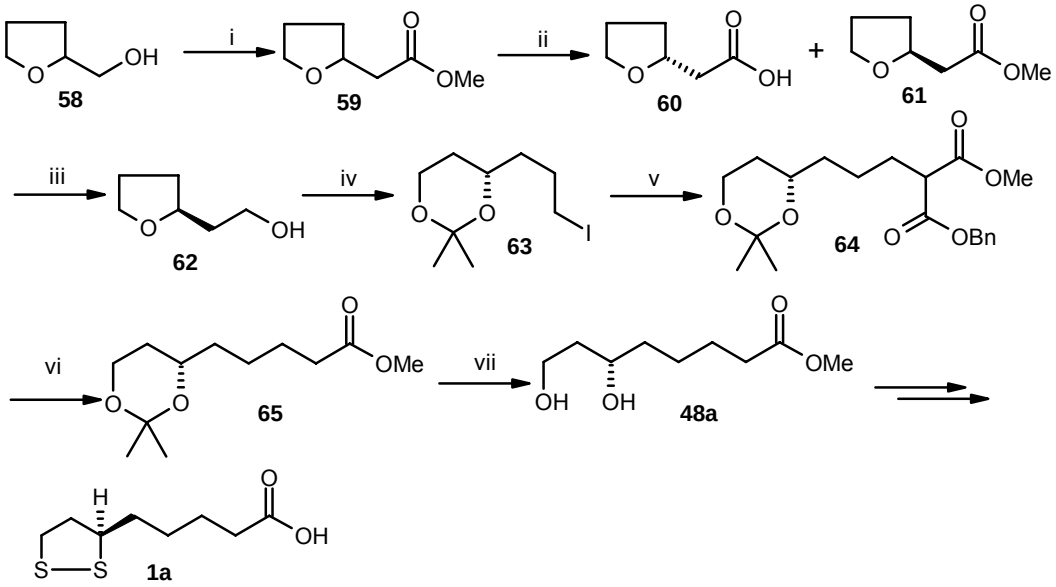
Scheme-12

Reagents and conditions: (i) Cu, $CHBr_3$, 80 %; (ii) KOAc, 18-crown-6, DMF; (iii) (a) K_2CO_3, MeOH then PCC, 68 %; (b) Triton B, MeOH; (iv) Baker's Yeast, pH 4.5-5; (v) H_3PO_4, Acetone then $NaBH_4$.

Iyengar's approach (1996, Scheme 13) [26]

Iyengar and Laxmi have employed selective hydrolysis of methyl 2-(tetrahydro-2-furyl) acetate **59** using lipase as the key step. On lipase hydrolysis, *R*-isomer undergoes hydrolysis but *S*-isomer did not under go hydrolysis. So the *S*-ester was then reduced with $LiAlH_4$ to give the compound **62**. Regioselective opening of **62** with TMSCl, NaI in

acetone gave iodo acetonide **63**. Alkylation of **63** with benzyl methyl malonate gave the compound **64**. Compound **64** on debenzylation, decarboxylation followed by hydrolysis in acidic condition furnished the diol ester **48a**. Following the same procedure reported earlier the diol ester was converted to *R*-(+)-lipoic acid.

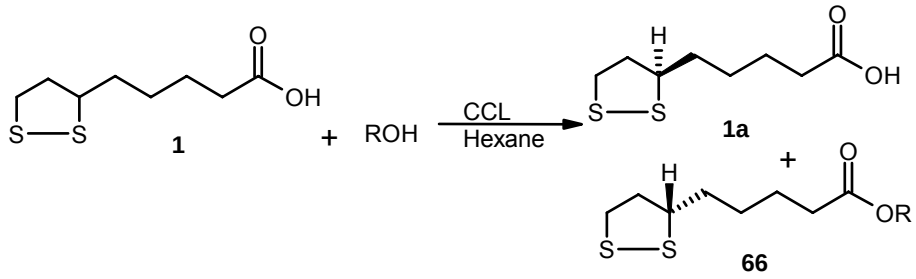


Scheme-13

Reagents and conditions: (i) (a) TsCl, KOH, 93 %; (b) KCN, 74 %; (c) KOH, 93 %; (d) MeOH, H^+; (ii) Liphase/Phosphate buffer (iii) $LiAlH_4$, ether, 84 % (iv) TMSCl, NaI, acetone; (v) Benzyl methyl malonate, NaH, THF, 25 %; (vi) (a) Pd/C, H_2, 98 % (b) 160 ^oC, 95%; (vii) MeOH, H^+, 98 %.

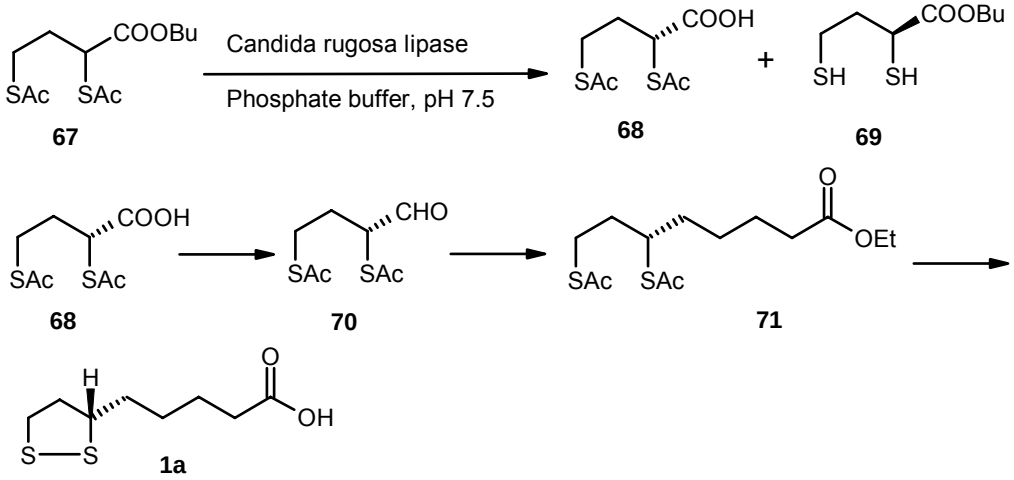
Fadnavis *et al* (1997, Scheme 14, 1998, Scheme 15)[27]

Fadnavis and Koteshwar have utilized lipase catalyzed enantioselective esterification of racemic α-lipoic acid to deliver the *R*-(+)-lipoic acid. In presence of lipase of candida rugosa *S*-isomer is converted to its corresponding ester.



Scheme-14

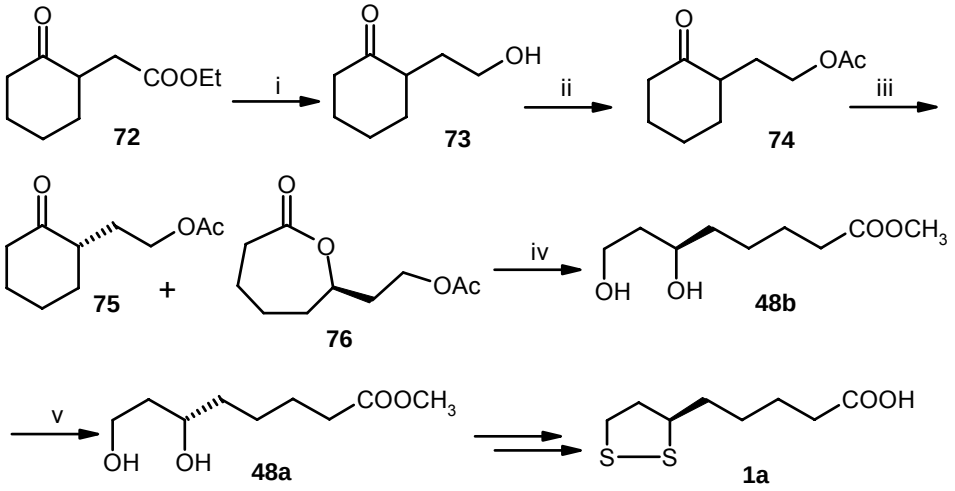
In an another approach Fadnavis and co-workers have synthesized *R* and *S* isomers of lipoic acid using lipase catalyzed regio and stereospecific hydrolysis of *n*-butyl ester of 2, 4- dithioacetyl butanoic acid **67**. Hydroboration **68** followed by PCC oxidation resulted in the formation of aldehyde **70**. Aldehyde on four carbon Wittig homologation and subsequent hydrogenation with Wilkinson's catalyst gave the ethyl ester **71**. Hydrolysis of **71** with wheat germ lipase followed by treatment with oxidative enzyme mushroom tyrosinase gave *S*-(-)-lipoic acid. Similar *R*-(+)-lipoic acid was prepared starting with **69**.



Scheme-15

Reagents and conditions:(i) (a) BH_3.DMS, 0 ^oC; (b) PCC (ii) (a) Br^- $^+PPh_3$ $(CH_2)_3COOEt$, NaHMDS, -78 ^oC; (b) $(PPh_3)_3RhCl$, H_2; (iii) (a) Wheat germ Lipase, pH 7.0; (b) Tyrosinase.

Adger *et al* (1997, Scheme 16)[28]



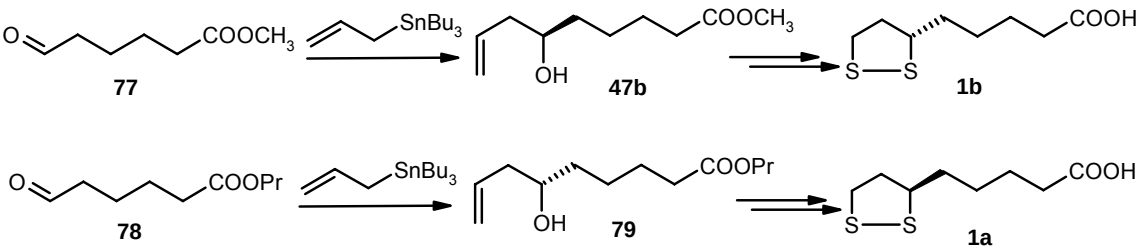
Scheme-16

Reagents and conditions: (i) (a) Ethylene glycol, *p*-TSA, Toluene; (b) $LiAlH_4$, Ether, 0-25 ^oC; (ii) Ac_2O, Pyridine, DMAP then HCl, MeOH; (iii) 2-Oxo-3-4, 5, 5-trimethyl cyclopentenyl acetyl-CoA. Monooxegenase, NADPH, G-6-P, G-6-PDH; (iv) NaOMe, MeOH; (v)(a) p-$NO_2C_6H_4COOH$, PPh_3, DEAD, THF; (b) K_2CO_3, MeOH.

Adger and co-workers, regio and enantioselectively converted 2-(2-acetoxy ethyl) cyclohexanone **74** in to the lactone **76**, using monooxygenase enzyme. The lactone was converted to diol **48b** using sodium methoxide in methanol. The stereochemistry at C-6 was inverted by using Mitsunobu reaction. Hydrolysis of benzoate ester delivered the known diol ester **48a,** which was converted to *R*-(+)-lipoic acid by a series of known reactions.

Zimmer *et al* (2000, Scheme 17)[29]

Zimmer and co-workers have employed catalytic asymmetric allyl stannation reaction as the key step to deliver the required stereochemistry. In the presence of 0.2 equivalents of (*S*)-BINOL, 0.2 eq. of $Ti(O_iPr)_4$ and 4 A^o molecular sieves the aldehyde **77** and allyl tributyl stannane provided *R*-alcohol **47b** with 98 % enantiomeric excess. The homoallylic alcohols could be converted to lipoic acid by known methods.

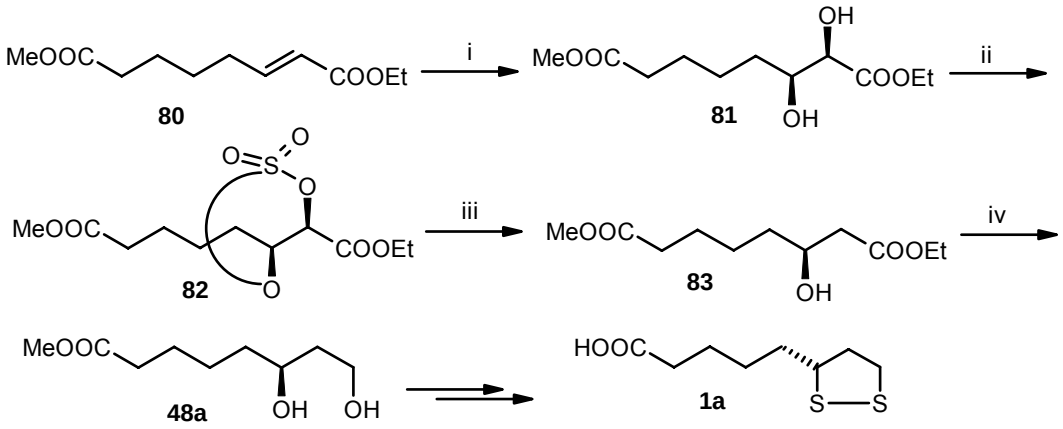


Scheme-17

Reagents and conditions: (i) (*S*)-BINOL (0.2 eq), $Ti(OiPr)_4$ (0.2 eq), CH_2Cl_2, 2 days, 75 %, 98 % ee. (ii) (*R*)-BINOL (0.2 eq), $Ti(OPri)_4$ (0.1 eq), CH_2Cl_2, 6 days, 89 %, 98% ee.

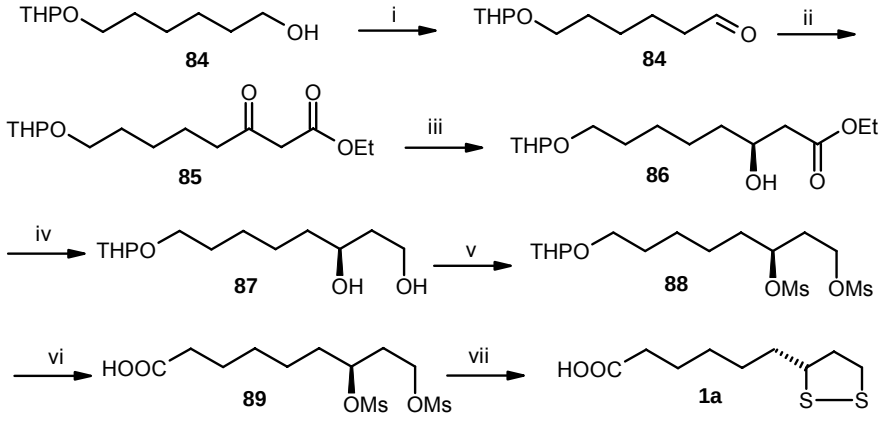
Sudalai *et al* (2001, Scheme 18 &19) [30]

Sudalai and co-workers employed Sharpless asymmetric dihydroxylation and Ruthenium catalyzed asymmetric hydrogenation reactions to get the β-hydroxy esters **83** and **87** respectively. The esters are the key precursors for the synthesis of *R*-(+)-lipoic acid.



Scheme-18

Reagents and conditions: (i) OsO_4, $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, 0 ^oC, 95 %; (ii) (a) $SOCl_2$, Et_3N, CH_2Cl_2, 0 ^oC, 9 h; (b) $RuCl_3$ (cat), $NaIO_4$, 85 %; (iii) $NaBH_4$, DMAC, 20 % H_2SO_4, 63 %; (iv) $NaBH_4$, Et_3N, MeOH:DMF (2:1), AcOH, 0 ^oC, 5h.



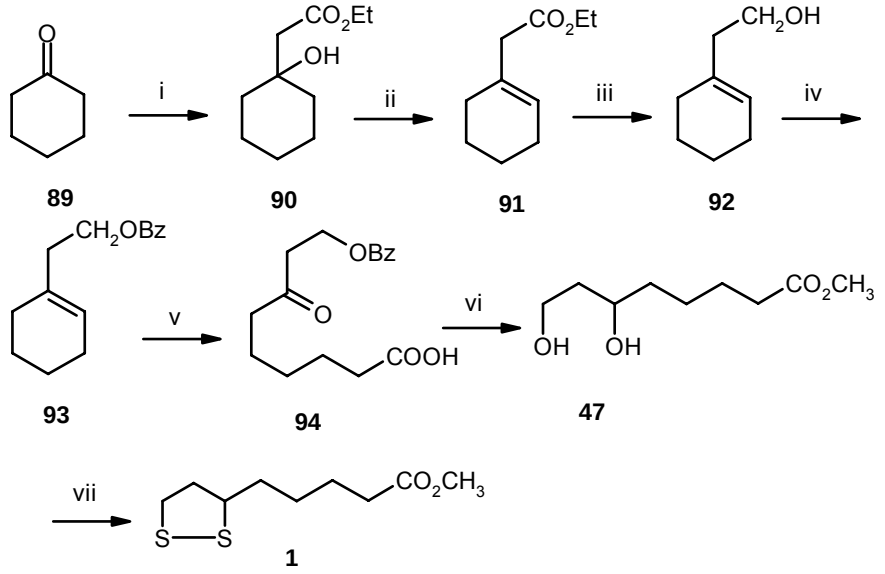
Scheme-19

*Reagents and conditions***:** (i) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, 75 %; (ii) (a) N_2CHCO_2Et, CH_2Cl_2, $SnCl_2$, 1 h, 85 %; (or) Zn, $BrCH_2CO_2Et$, Benzene, 4 h then PCC, CH_3CO_2Na, CH_2Cl_2, 4 h, 65 %; (iii) H_2 (400 Psi), MeOH, (S)-BINAP-Ru; (II), 6h, 90 %; (iv) $NaBH_4$, $CuSO_4$, EtOH, 7h; (v) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 ^oC, 6 h; (vi) *p*-TSA, MeOH, 10 h; (b) PCC, CH_2Cl_2, 3 h and then Ag_2O, NaOH, 1 h, 62 %; (vii) $Na_2S.9H_2O$, DMF, HCl, 28 h, 45 %.

Chavan's synthesis (Schemes 20, 21, 22) [31]

Chavan *et al* the synthesis of lipoic acid has been achieved by using modified Reformatsky reaction. The elimination of the alcohol to furnish selectively the β, γ-unsaturated ester is another feature of this synthesis. Reformatsky reaction with chloroester was carried out on cyclohexanone to furnish alcohol ester **90**, which was then

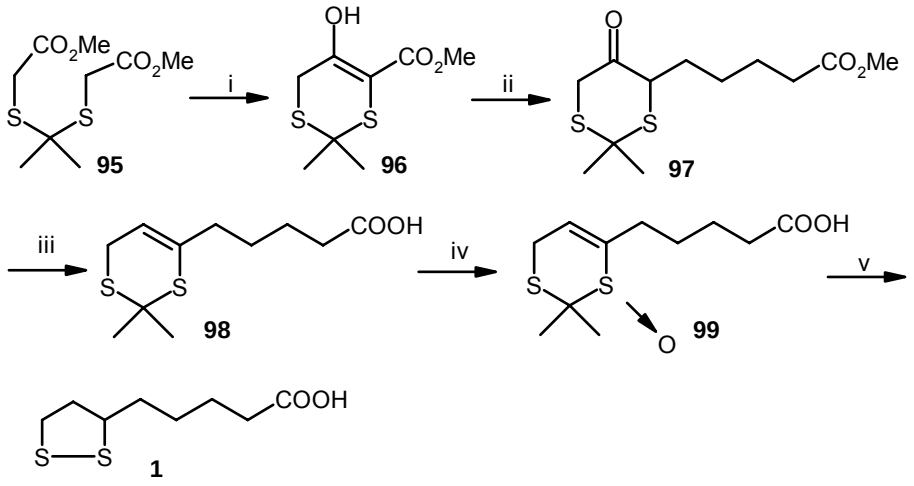
set for elimination using thionyl chloride and pyridine. The β, γ-ester thus obtained was then reduced using DIBAL-H. The alcohol **92** formed, was then protected using benzoyl chloride to give benzoate ester **93**, which was then subjected to ozonolysis followed by Jones oxidation to furnish ketoacid **94**. The reduction of ketoacid **94**, followed by esterification, furnished diol ester **47.** The diol ester **47** was then converted to methyl lipoate by known protocol (Scheme-20).



Scheme-20

Reagents and conditions: (i) Zinc, $ClCH_2COOEt$, benzene-ether (1:1), reflux, 65%; (ii) $SOCl_2$, pyridine, DCM, 86 %; (iii) DIBAL-H, DCM, -78 ^oC, 65 % ; (iv) BzCl, Et_3N, DCM, 92%; (v) (a) O_3, DCM; (b) Jones reagent, 85 %; (vi) (a) $NaBH_4$, MeOH, 90 %; (b) CH_2N_2, ether; (c) NaOMe, MeOH, 91 %; (vii) (a) $MeSO_2Cl$, Et_3N, (b) Na_2S, S, DMF, 60 % for 2 steps.

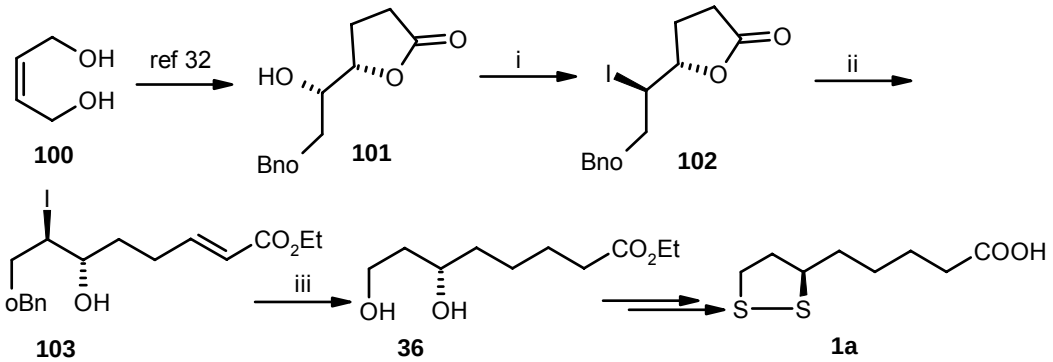
In another approach Chavan *et al* accomplished (±)-lipoic acid synthesis by using diester **95**, which was readily prepared in two steps from thioglycolic acid. Subjection of diester **95** to Dieckmann condensation delivered the β-keto ester **96** which exists in enolic form. Phase transfer catalyzed alkylation of **96** followed by decarboxylation gave the ester **97**. The keto ester was converted into olefin acid **98** by treating with tosyl hydrazone followed by refluxing in presence of NaOH. Sequential reduction of double bond, oxidation to mono sulfoxide and final hydrolytic cyclization of **99** afforded (±)-lipoic acid (Scheme-21).

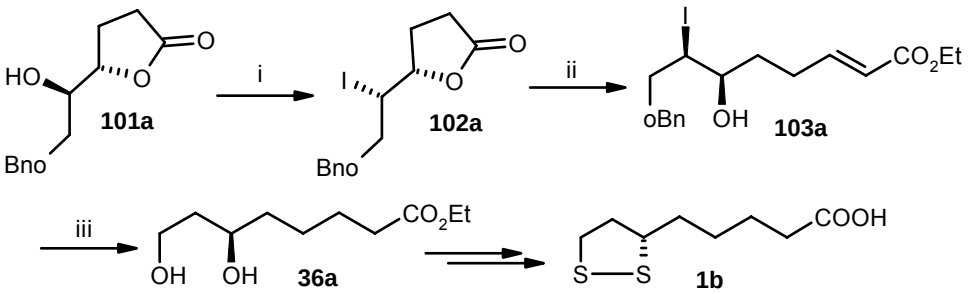


Scheme-21

Reagents and conditions: (i) NaH, THF, 60 ^{o}C, 3 h, 86 %; (ii) (a) K_2CO_3, $Br(CH_2)_4COOCH_3$, Bu_4NHSO_4, THF, rt; (b) DMSO, NaCl, H_2O, 140 ^{o}C; (iii) (a) $TsNHNH_2$, MeOH, rt, 67 %; (b) NaOH (2 equiv), iPrOH, Reflux, 84 %; (iv) (a) Et_3SiH, TFA, 0 ^{o}C, rt, 73 %; (b) $NaIO_4$, MeOH, 0 ^{o}C, 2 h, 68 %; (v) aq. HCl:Benzene (1:1), 50 ^{o}C, 7 h, 69 %.

In third approach enantiomerically pure hydroxy lactone **(101)**, the versatile intermediate for synthesis, obtained in four steps from cis-2-butene-1,4-diol **(100)**, was treated with triphenylphosphine, iodine and imidazole to give the iodo lactone **(102)**. Reduction of the lactone using DIBAL-H at 78 ^{o}C followed by an insitu two-carbon Wittig reaction gave the unsaturated ester **(103)**. Removal of the benzyl protection, removal of iodine and reduction of the double bond was achieved in one pot using W2 Raney nickel in the presence of hydrogen at room temperature and pressure for 24 h to give the diol **(36)**. The diol **(36)**, a well known intermediate for the synthesis of (+)-lipoic acid.



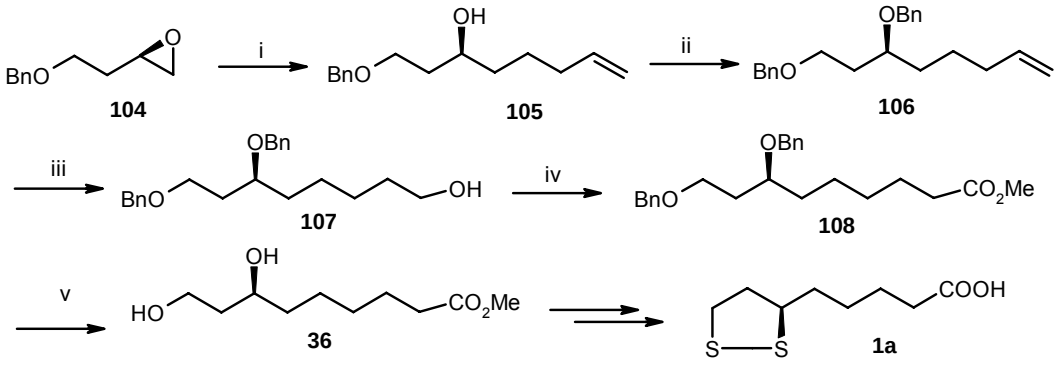


Scheme-22

Reagents and conditions: (i) PPh_3, I_2, imidazole, 70 ^oC, 3 h, 94%; (ii) DIBAL-H, DCM, 78 ^oC, 1 h, $Ph_3PCHCOOC_2H_5$, 24 h; rt, 96%; (iii) W2 Raney nickel, H_2, rt, 24 h, 84%.

Subhas Bose syntheses (Scheme 23) [33]

The regiospecific opening of epoxide (*R*)-**104** with but-3-enylmagnesium bromide (3 equiv) in THF containing 10 mol% lithium tetrachlorocuprate15 at –78 °C furnished 1-enzyloxyoct-7-en-3-ol (**105**) in 90% yield. The hydroxy group in **105** was protected as benzyl ether by reaction with benzyl bromide in the presence of sodium hydride and TBAI in DMF. The next step was to elaborate the terminal olefin into the corresponding acid function. Thus, compound **106** was subjected to hydroboration–oxidation, using borane- DMS–hydrogen peroxide in THF to afford the primary alcohol **107** in 88% yields. Oxidation of the primary alcohol to the carboxylic acid was achieved with a mixture of sodium chlorite and bleach, catalyzed by TEMPO and followed by esterification with diazomethane to afford the ester **108**. Removal of the benzyl group by hydrogenolysis gave the diol **36**, which was converted to a-(*R*)-α-lipoic acid **1a**, by the standard sequence of reactions.



Scheme-23

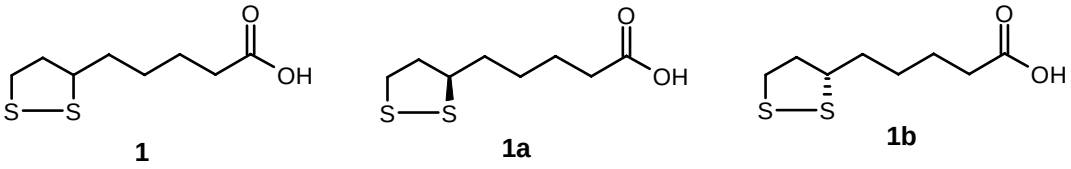
Reagents and conditions: (i) CH_2=$CHCH_2CH_2MgBr$, Li_2CuCl_4 (cat.), THF, –78 °C to r.t.; (ii) NaH, BnBr, DBAI, DMF, 85%; (iii) BH_3·DMS, $MeCO_2Na$, H_2O_2, THF, 88%; (iv) (i) $NaClO_2$, TEMPO, NaOCl; (ii) CH_2N_2, Et_2O; (v) H_2, Pd/C, EtOH.

PRESENT WORK

Present Work

α-Lipoic acid is an important protein-bound coenzyme and growth factor found in plant and animal tissues as well as in microorganisms. It has been recognized as a vital cofactor for the multienzyme complexes which catalyze the oxidative decarboxylation of α-ketoacids such as pyruvate, α-ketoglutarate etc. It is known to play a crucial role in photosynthesis and in the tricarboxylic acid cycle. Lipoic acid exhibits beneficial effects in the treatment of diabetes. Lipoic acid and dihydrolipoic acid have been reported to be effective in preventing damage incurred by myocardial and cerebral ischemia-reperfusion injury in rats. Recently, it has also been reported that lipoic acid and their derivatives are highly active as anti-HIV and anti-tumor agents.

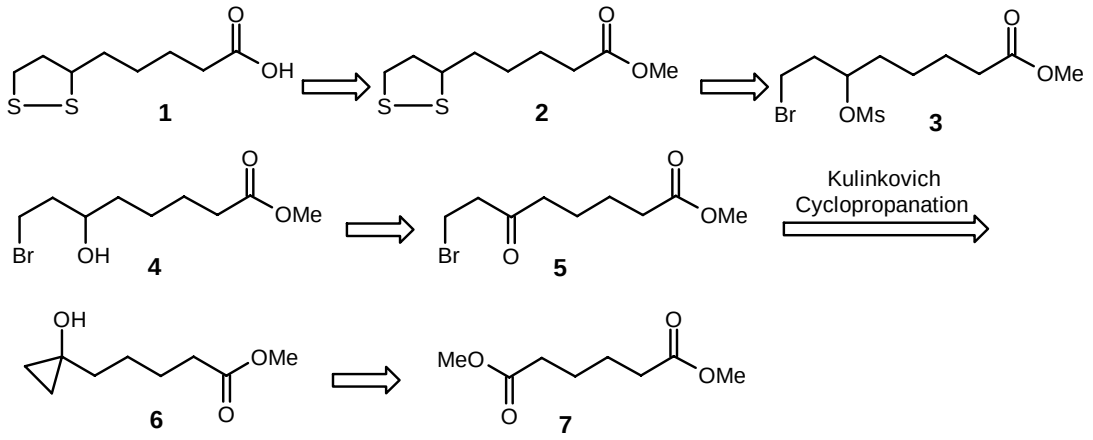
α-Lipoic acid was first isolated from processed liver by Reed *et al* in 1951 and was characterized as the cyclic disulfide 5-[3-(1,2-dithiolanyl)]-pentanoic acid. It is a molecule containing eight carbon atoms, a 1, 2-dithiolane ring and a carboxylic acid group. The chiral centre is embedded in the ring structure at the third position. There are two forms of lipoic acid i.e., *R* and *S*: the natural isomer *R* is pharmacologically more active than the *S*-isomer. Moreover, (±)-α-lipoic acid can be important for pharmaceutical use without resolution, since the (*S*)-enantiomer does not negatively affect the activity of the (*R*)-enantiomer (Figure-1).



(±)-α-Lipoic acid (*R*)-α-Lipoic acid (*S*)-α-Lipoic acid

Figure-1

We planned a short, facile route for the synthesis of (±)-α-lipoic acid: our retrosynthesis suggested employing a Kulinkovich cyclopropanation for the synthesis of a key intermediate, starting from inexpensive and readily available dimethyladipate (Schem-1).



Scheme-1. Retrosynthesis of (±)-α-Lipoic acid

We envisaged that methyl-8-bromo-6-hydroxooctanoate (**4**) could serve as a key precursor: the requisite fragment **4** could be built up by Kulinkovich cyclopropanation reaction.

A brief review on Kulinkovich[34a] cyclopropanation:

Cyclopropanes and their hydroxyl-substituted analogues are among the most reactive and versatile hydrocarbon frameworks. The use of cyclopropanols in synthetic methodology has increased since the invention of the Kulinkovich reaction, which was first described in the late 1980's. Ethylmagnesium bromide in presence of catalytic amount of titanium tetraisopropoxide, when added to simple carboxylic ester **9**, furnished cyclopropanol **11** in a one pot operation (figure-2). The ethyl group of the Grignard reagent serves as the synthetic equivalent of a two-carbon dianion synthon **12**, representing an unusual reactivity pattern (figure-3).

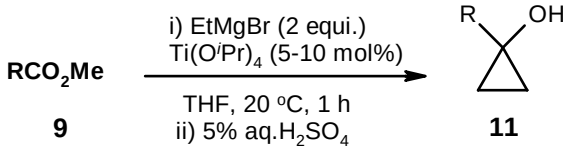


Figure-2. EtMgBr/Ti(O^iPr)$_4$- the Kulinkovich reagent

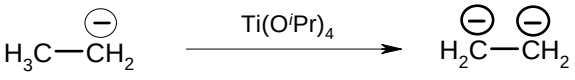
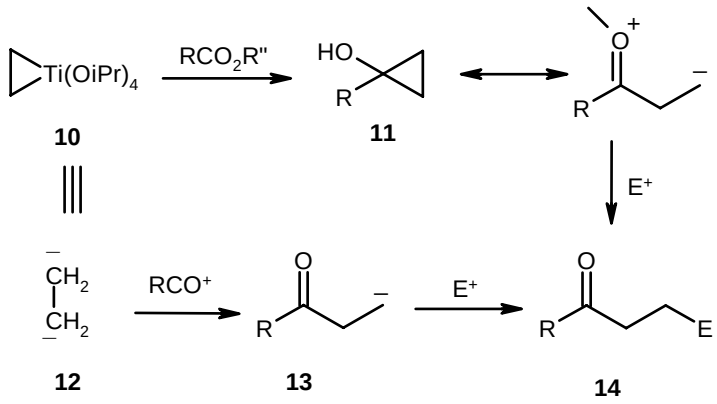


Figure-3. Synthetic equivalent of a two carbon-1, 2-dianion synthon

The synthetic value of this reaction is not limited only to the convenient preparation of cyclopropane derivatives because cyclopropanol **11** can easily be converted into certain classes of organic compound via ring opening reaction.[34b] For example, heterolytic C1-C2 ring cleavage of substituted cyclopropanol is strongly facilitated by the Л-electron donor oxygen atom. As a result, cyclopropanols readily react with electrophiles to give carbonyl compound **14** (figure-4). In these transformations, the cyclopropanols formally act as equivalents of β-oxocarbanions (homoenolate anions) **13**, and for the two-stage conversion of esters into ketones. The cyclopropane ring-closing step in the titanium-mediated cyclopropanation reaction could be considered as a peculiar protection of the carbanionic center in ethylene-1,2-dicarbanion **12**. Such methodology for connecting the RCO^+ and E^+ reactive groups by the dimethylene unit, with the help of titanacyclopropanols reagent **10** has good preparative value.



10 **11** **12** **13** **14**

Figure-4

Mechanism: Kulinkovich cyclopropanation[34c]

The catalytic cycle proposed for the above transformation (figure-2) is depicted in figure-5. A first step ligand exchange reaction between titaniumtetraalkoxide and ethyl magnesium bromide provides the diethyl titanium intermediate **15**, which immediately undergoes β-elimination with formation of the titanacyclopropane **16**. Next, a nucleophilic attack at the ester carbonyl furnishes the titanoxacyclopentane **17**. Rearrangement to the homoenolate **18** with concomitant activation of the carbonyl group allows for an intramolecular attack of the titanium-carbon bond to the carbonyl function to give the titanium cyclopropane alkoxide **19**. Metal exchange reaction with excess of

Grignard reagent liberates the product as the magnesium alkoxide **20** and regenerates the catalytically active species **15**.

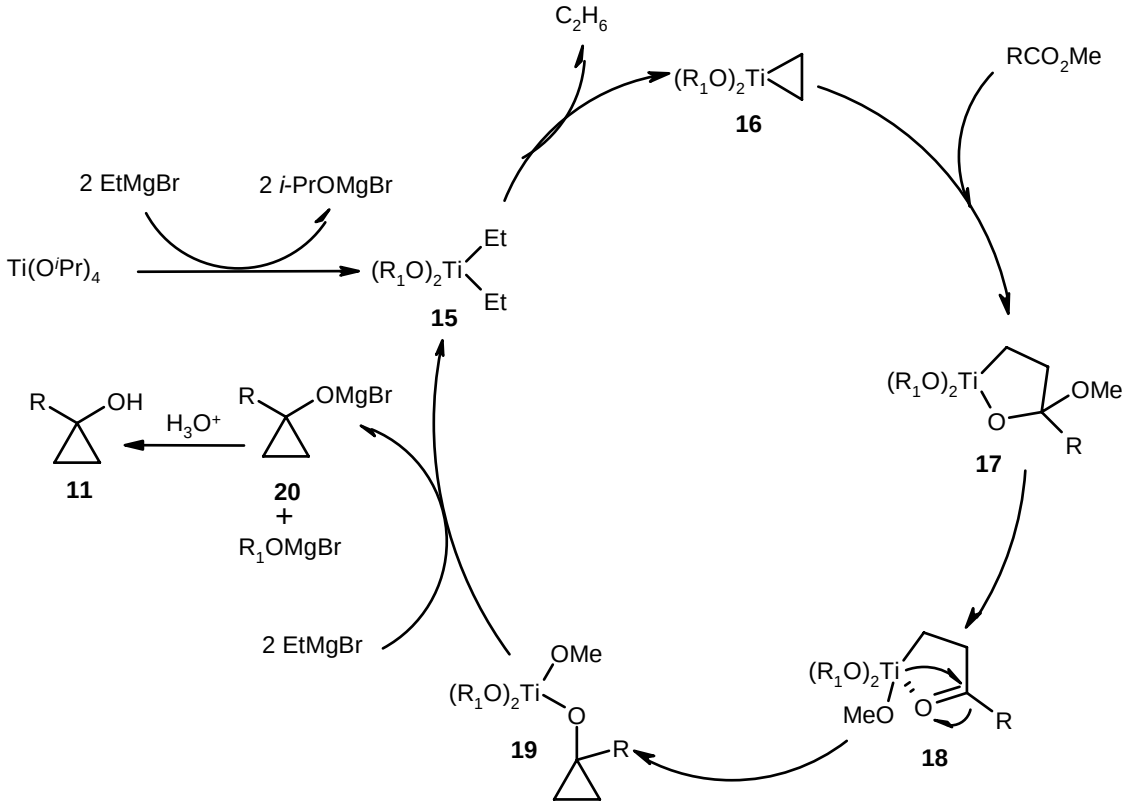
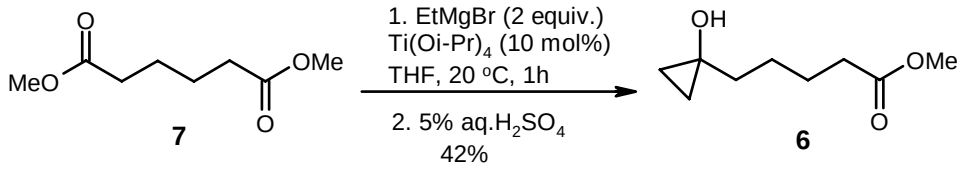


Figure-5. Mechanism of the Kulinkovich reaction

In order to obtain **6**, dimethyl adipate (**7**) was subjected to Kulinkovich cyclopropanation using ethylmagnesiumbromide (2 equivalent) in presence of catalytic $Ti(O^iPr)_4$ (titanium (IV) isopropoxide) to give the cyclopropanol **6** in 42% yield (Scheme-2). In the proton NMR spectra resonance due to cyclopropane ring showed at 0.40 ppm and 0.71 ppm as a double doublet; in ^{13}C NMR spectra carbon peaks of cyclopropane showed at 13.5 ppm. In additional, the structure was supported by elemental analysis data.



Scheme-2

The next challenge faced was the ring opening of cyclopropanol. The presence of an oxygen atom attached to a cyclopropane ring creates favorable possibilities for cyclopropannols in ring-opening or ring-expansion reactions. Such transformations are facilitated or initiated by i) Л-electron-donor effect of the oxygen due to stabilization of transition state in which electron deficiency is generated at the adjacent carbon atom, ii) removal of one electron from the lone electron pair of oxygen with formation of unstable oxycyclopropyl cation radical, or iii) heterolytic cleavage of the carbon-oxygen covalent bond, bond which promotes cleavage of the opposite carbon-carbon bond of the cyclopropane ring. Such reactions often proceed with high selectivity; in our case, heterolytic cleavage of cyclopropane ring was favorable. Cyclopropanols readily rearrange into the corresponding carbonyl compound by C1-C2 ring-cleavage reactions, especially under basic or acidic conditions. The hydroxyl group strongly activates the reaction and directs the ring opening so that electron-deficient center is formed upon heterolytic C1-C2 ring cleavage attached to the Л-electron-donor oxygen atom (as in the conjugate acid), the carbanion center located at the β-position to the carbonyl group (as in the conjugate base) act as homoenolate anion equivalent (figure-6).

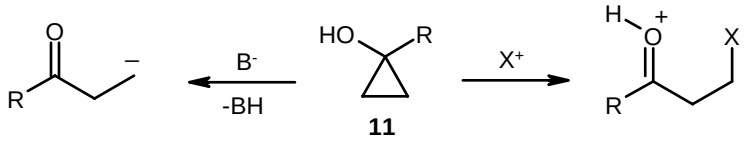
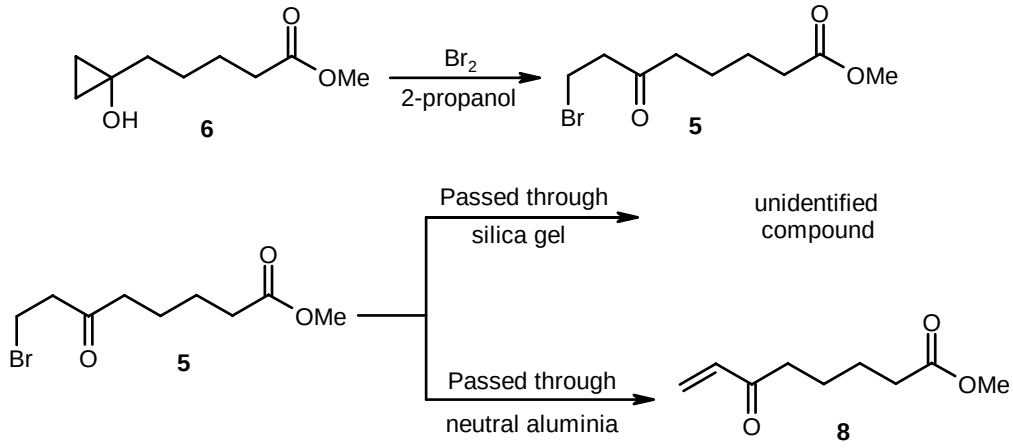


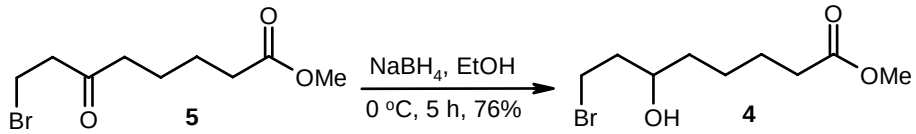
Figure-6

Electrophilic bromination of cyclopropanol[35] (**6**) proceeded by the reaction with bromine in aqueous 2-propanol afforded β-bromo ketone (methyl 8-bromo-6-oxooctanoate), **5**. Attempted purification by silica gel column chromatography resulted in decomposition to an unidentified compound. Passage of **5** through neutral alumina resulted in the bromo-elimination product **8** (Scheme-3).[36] ^{1}H NMR spectrum showed the terminal olefinic peaks between the regions of 5.79-6.28 ppm. The proton spectrum of **5** clearly showed the CH_2 attached to bromo group at 3.54 ppm and CH_2 attached to keto group at 3.00 ppm. Therefore, the subsequent reaction was carried out without further purification.



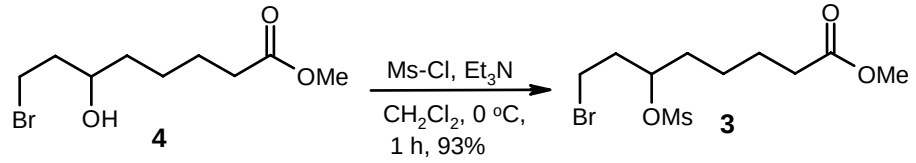
Scheme-3

Next, the **5** was reduced with $NaBH_4$ in absolute EtOH at 0 ^oC in 5 h to give methyl 8-bromo-6-hydroxyoctanoate (**4**) in 76% yield (Scheme-4). Proton NMR spectrum showed a methine attached to hydroxyl group at 3.84 ppm and further studied by elemental analysis data.



Scheme-4

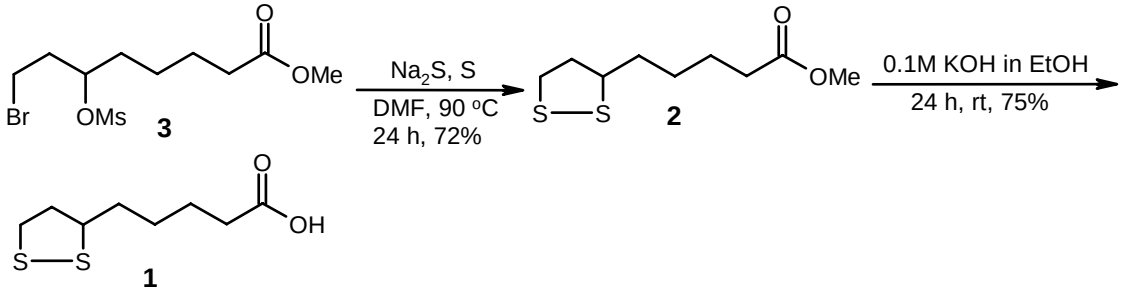
The **4** was key intermediate for the synthesis of α-Lipoic acid. Treatment of **4** with methanesulfonyl chloride, triethylamine in dichloromethane gave the mesylate **3** in almost quantitative yield. The ^1H NMR spectrum contained a singlet for the mesyl group and a signal at 3.06 ppm (scheme-5).



Scheme-5

Reaction of **3** with sodium sulfide and sulfur in *N*,*N*-dimethylformamide at 90 ^oC afforded 72% of the expected methyl (±)-α-Lipoate (**2**), It was confirmed by NMR signals at 3.04-3.22 (m, 2H) ppm and 3.56 (m, 1H) ppm for H-8,8' and H-6, respectively. The upfield shifts of the signals for these protons were expected because of the shielding effect of the sulfur atom. In the ^{13}C spectra, disappearance of mesyl group indicates the

formation of methyl lipoate. The final conversion was achieved by the hydrolysis of **2** with 0.1M potassium hydroxide in ethanol at room temperature to afford 75% of (±)-α-Lipoic acid (**1**). The spectral data and elemental data were in good agreement with the reported data (Scheme-6).



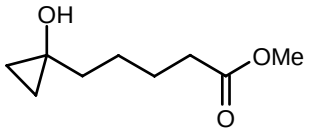
Scheme-6

Conclusion:

Accomplished the synthesis of α-Lipoic acid by deploying cheaply available starting material: Kulinkovich cyclopropanation was employed for the construction of key precursor**.**

EXPERIMENTAL SECTION

Methyl 5-(1-hydroxycyclopropyl)pentanoate (6)



To a stirred solution of dimethyladipate (**7**) (1.74 g, 10.0 mmol) in dry THF (15 mL) was added $Ti(O^iPr)_4$ (0.284g, 1.0 mmol) at 0 ^oC, followed by addition of readily prepared ethyl magnesium bromide (1 M, 20.0 mL, 20.0 mmol) in dry THF. The reaction mixture was left for stirring to attain the room temperature (2 h) (Monitored by TLC). After completion of the reaction, quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (3 x 20 ml). The organic layer was combined, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by the column chromatography (silica gel, 60-120 mesh, 25% EtOAc-light petroleum ether) to afford **6** as colorless oil.

Yield : 0.722 g, 42%

Mol. formula : $C_9H_{16}O_3$

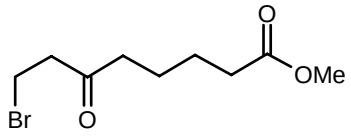
IR ($CHCl_3$) cm^{-1} : 3378, 2950, 2868, 1735, 1438, 1250, 1010.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.40 (dd, 2H, *J* = 5.06, 6.95 Hz), 0.71 (dd, 2H, *J* = 4.80, 6.95 Hz), 1.53-1.57 (m, 4H), 1.64-1.76 (m, 2H) 2.16 (br s, 1H), 2.34 (t, 2H, *J*= 7.20 Hz), 3.67 (s, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 13.5, 24.7, 25.5, 34.0, 37.8, 51.5, 55.3, 174.2.

Elemental Analysis : **Calcd.:** C, 62.77; H, 9.36; **Found:** C, 62.49; H, 9.12.

Methyl-8-bromo-6-oxooctnoate (5)



To a solution of **6** (0.345 g, 2.0 mmol) and bromine (0.384 g, 2.4 mmol) in 2-propanol (10 mL) at 0 ^oC was stirred for 1 h. After consumption of the starting material, quenched with saturated solution of Sodium thiosulphate (5 mL) and extracted with $CHCl_3$ (2 x 25 mL). The combined extract was washed with satd. solution of $NaHCO_3$,

water, brine and dried over Na_2SO_4 and concentrated under reduced pressure. Utilized for subsequent reaction without further purification.

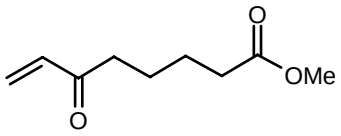
Yield : 0.467 g, 93%

Mol. Formula : $C_9H_{15}BrO_3$

IR ($CHCl_3$) cm^{-1} : 2951, 1735, 1718, 1172.

^{1}H NMR ($CDCl_3$, 500 MHz) : δ 1.62 (m, 4H), 2.32 (m, 2H), 2.46 (m, 2H), 2.99 (t, 2H, *J* = 6.6 Hz), 3.54 (t, 2H, *J* = 6.6 Hz), 3.66 (s, 3H).

Methyl-6-oxooct-7-enoate (8)



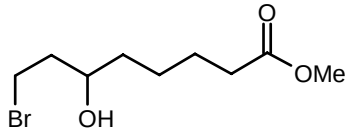
Compound **5** was passed through the neutral alumina.

Mol. Formula : $C_9H_{14}O_3$

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.61-1.68 (m, 4H), 2.33 (t, 2H, *J* = 7.1 Hz), 2.60 (t, 2H, *J* = 6.95 Hz), 3.65 (s, 3H), 5.79 (dd, 1H, *J* = 1.90, 9.7 Hz), 6.14 (dd, 1H, *J* = 2.02, 17.68 Hz), 6.28 (dd, 1H, *J* = 9.7, 17.68 Hz).

Elemental Analysis : **Calcd.:** C, 63.51; H, 8.29; **Found:** C, 63.48; H, 8.30.

Methyl 8-bromo-6-hydroxyoctanoate (4)



To a solution of **5** (1.26 g, 5.0 mmol) and $NaBH_4$ (0.210 g, 5.52 mmol) in absolute ethanol (15 mL) at 0 ^oC, was stirred at same temperature for 5 h (monitored by TLC). The reaction mixture was quenched with dilute acetic acid and extracted with EtOAc (2 x 25 mL), organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by column chromatography (neutral alumina, eluting in 25% of EtOAc-light petroleum ether) to afford **4** as a colorless liquid.

Yield : 0.962 g, 76%

Mol. formula : $C_9H_{17}BrO_3$

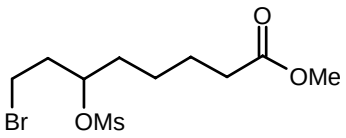
IR ($CHCl_3$) cm^{-1} : 3378, 2950, 2868.

^{1}H NMR ($CDCl_3$, 200 MHz) **:** δ 1.40-1.55 (m, 4H), 1.61-1.71 (m, 2H), 1.78 (br s, 1H), 1.90-2.00 (m, 2H), 2.34 (t, 2H, *J* = 7.2 Hz), 3.51-3.59 (m, 2H), 3.68 (s, 3H), 3.84 (m, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) **:** δ 24.6, 24.9, 30.4, 33.8, 36.8, 39.9, 51.5, 69.1, 174.1.

Elemental Analysis **:** **Calcd.:** C, 42.70; H, 6.77; Br, 31.57; **Found:** C, 42.65; H, 6.76.

Methyl 8-bromo 6-(methylsulfonylloxy)octanoate (3)



To a stirred solution of **4** (1.0 g, 3.95 mmol) in dry CH_2Cl_2 (15 mL) were added Et_3N (0.479 g, 4.74 mmol), DMAP (catalytic) and methane sulfonyl chloride (0.497g, 4.34 mmol) in order at 0 ^oC. Stirred the reaction mixture at same temperature for 1 h and quenched by water. The aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL), combined the organic layer, dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by column chromatography (neutral alumina, eluting in 25% of EtOAc-light petroleum ether) to afford **3** as colorless liquid.

Yield **:** 1.22 g, 93%

Mol. Formula **:** $C_{10}H_{19}BrO_5S$

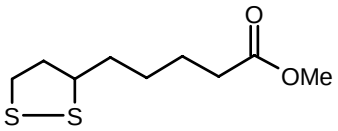
IR ($CHCl_3$) cm^{-1} **:** 3030, 1735, 1170.

^{1}H NMR ($CDCl_3$, 200 MHz) **:** δ 1.40-1.52 (m, 2H), 1.67-184 (m, 4H), 2.06-2.26 (m, 2H), 2.34 (t, 2H, *J* = 7.1 Hz), 3.06 (s, 3H), 3.43-3.51 (m, 2H), 3.67 (s, 3H), 4.87 (m, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) **:** δ 24.0, 24.3, 28.0, 33.5, 34.1, 37.2, 38.4, 51.4, 80.5, 173.5.

Elemental Analysis **:** **Calcd.:** C, 36.26; H, 5.78; Br, 24.12; S, 9.68; **Found:** C, 36.14; H, 5.62; S, 9.48.

Methyl 5-(1,2-dithiolan-3-yl)pentanoate (2)



To a stirred solution of **3** (1.0 g, 3.0 mmol) in dry DMF (15 ml) was added Na_2S (0.725 g, 3.0 mmol) and Sulphur (0.096 g, 3.0 mmol) and stirred at 90 ^oC for 24 h. The reaction mixture was quenched by cold water and extracted with EtOAc (2 x 25 mL), combine the organic layer, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude residue was purified by column chromatography (silica gel, 60-120 mesh, eluting in 20% of EtOAc-light petroleum ether) to afford **2** as colorless liquid.

Yield : 0.475 g, 72%

Mol. Formula : $C_9H_{16}O_2S_2$

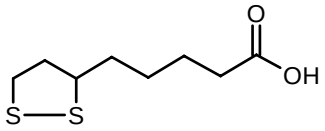
IR ($CHCl_3$) cm^{-1} : 3020, 2400, 1731, 757

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.45-1.53 (m, 2H), 1.63-175 (m, 4H), 1.89 (m, 1H), 2.34 (t, 2H, *J* = 7.1 Hz), 2.44 (m, 1H), 3.04-3.22 (m, 2H), 3.56 (m, 1H), 3.67 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) : δ 24.5, 28.6, 33.7, 34.5, 38.3, 40.1, 51.3, 56.1, 173.6.

Elemental Analysis : **Calcd.:** C, 49.06; H, 7.32; S, 29.10; **Found:** C, 48.90; H, 7.05; S, 28.90.

5-(1,2-dithiolan-3-yl)pentanoic acid (1)

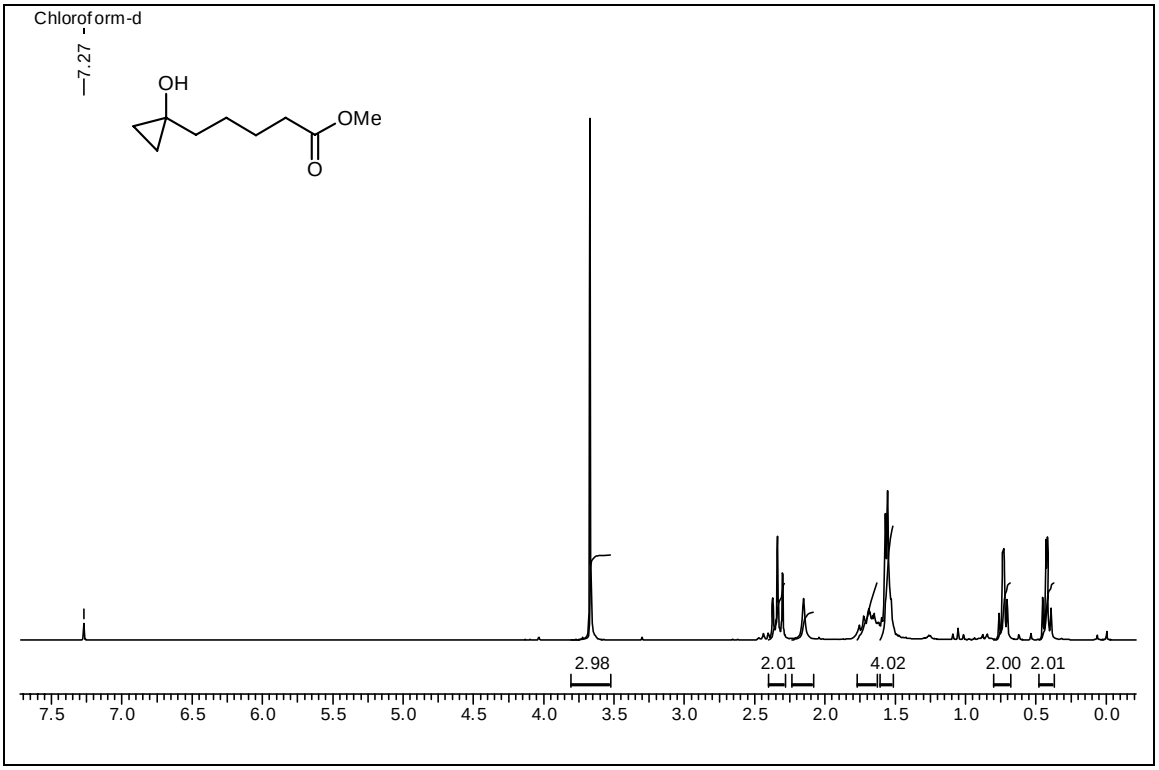


To a solution of **2** (0.440 g, 2.0 mol) in absolute ethanol (10 mL) was added 0.1 M ethanolic KOH (8 mL) in the dark and under nitrogen atmosphere. After stirring for 24 h, ethanol was evaporated and the aqueous solution was washed with light petroleum to remove the impurities. The aqueous layer was acidified to pH 1 by the addition of 2 N HCl and then extracted with ether (3 x 12 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The

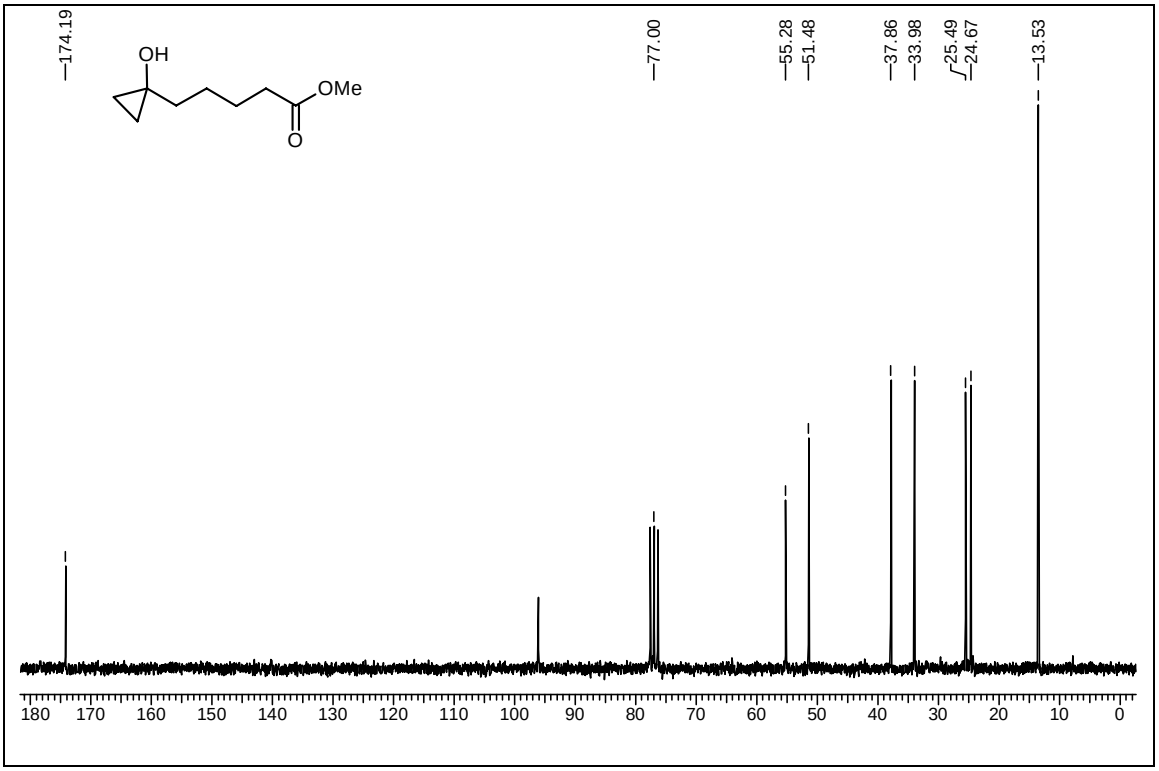
residue was purified by column chromatography (silica gel, 60-120 mesh, 30% EtOAc-light petroleum) to afford α-lipoic acid **1.**

Yield	**:**	0.310 g, 75%
Mol. Formula	**:**	$C_8H_{14}O_2S_2$
IR ($CHCl_3$) cm^{-1}	**:**	3018, 2934, 1701.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ 1.52-1.62 (m, 2H), 1.65-1.76 (m, 4H), 1.91 (m, 1H), 2.37 (t, 2H, *J* = 7.2 Hz), 2.50 (m, 1H), 3.08-3.20 (m, 2H), 3.55 (m, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	**:**	δ 24.4, 28.7, 33.9, 34.6, 38.5, 40.2, 56.2, 179.8
Elemental Analysis	**:**	**Calcd.:** C, 46.57; H, 6.84, S, 31.08; **Found:** C, 46.62; H, 6.91, S, 30.23.

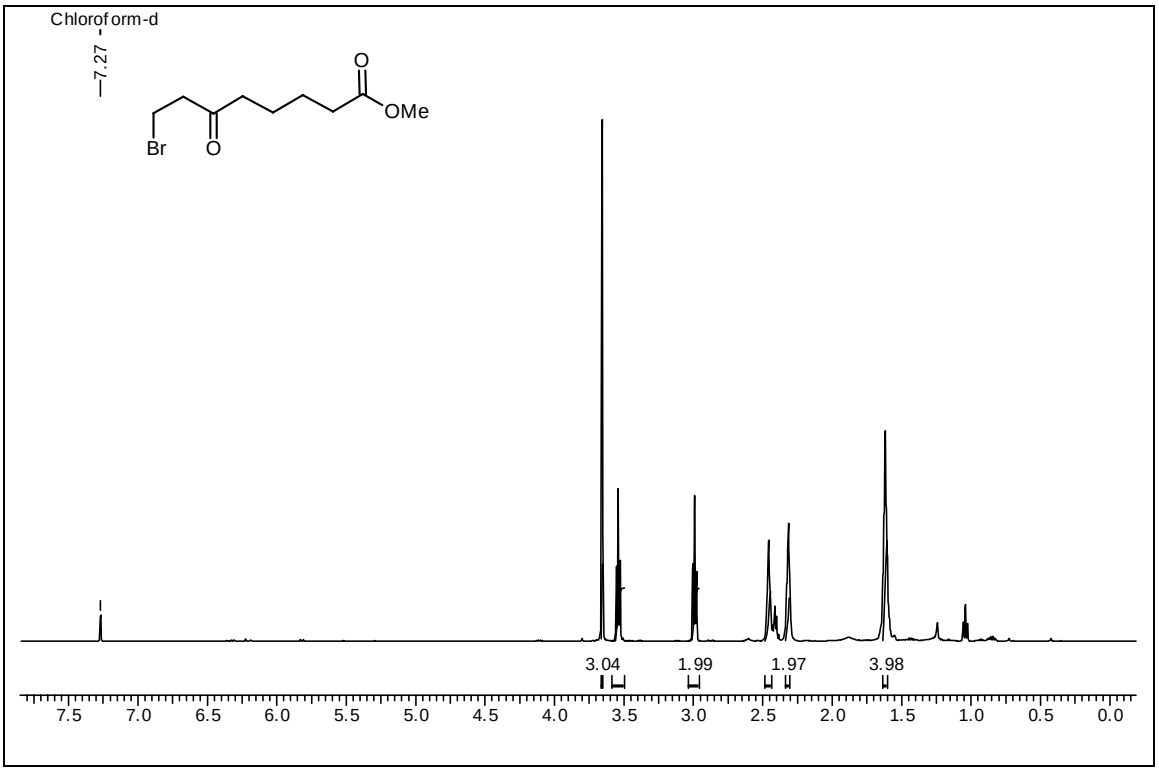
SPECTRA



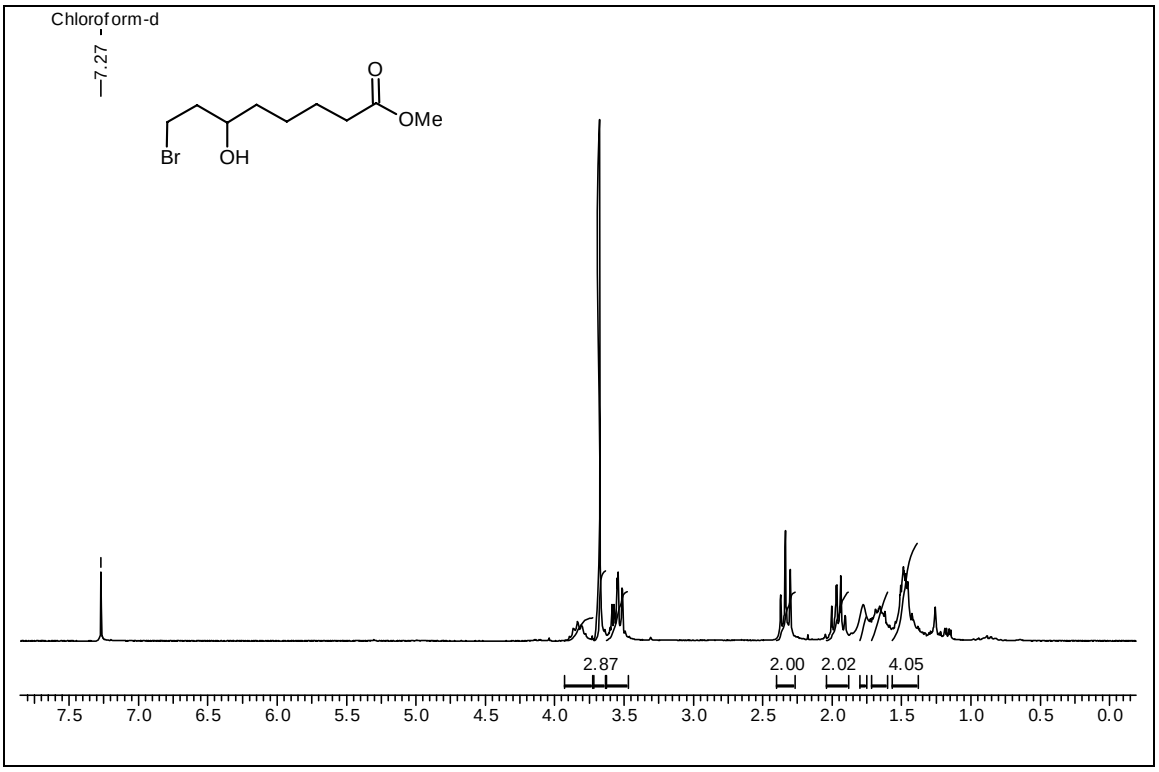
^{1}H NMR spectrum of compound 6 in $CDCl_3$



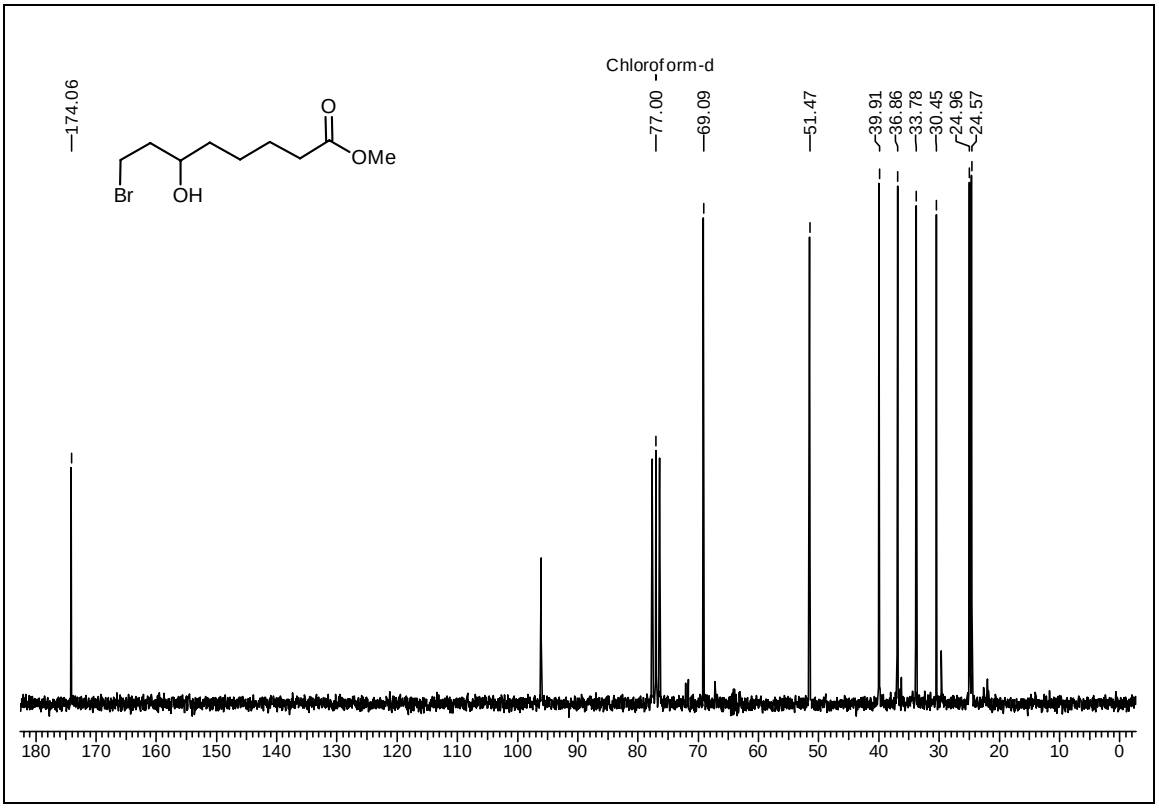
^{13}C NMR spectrum of compound 6 in $CDCl_3$



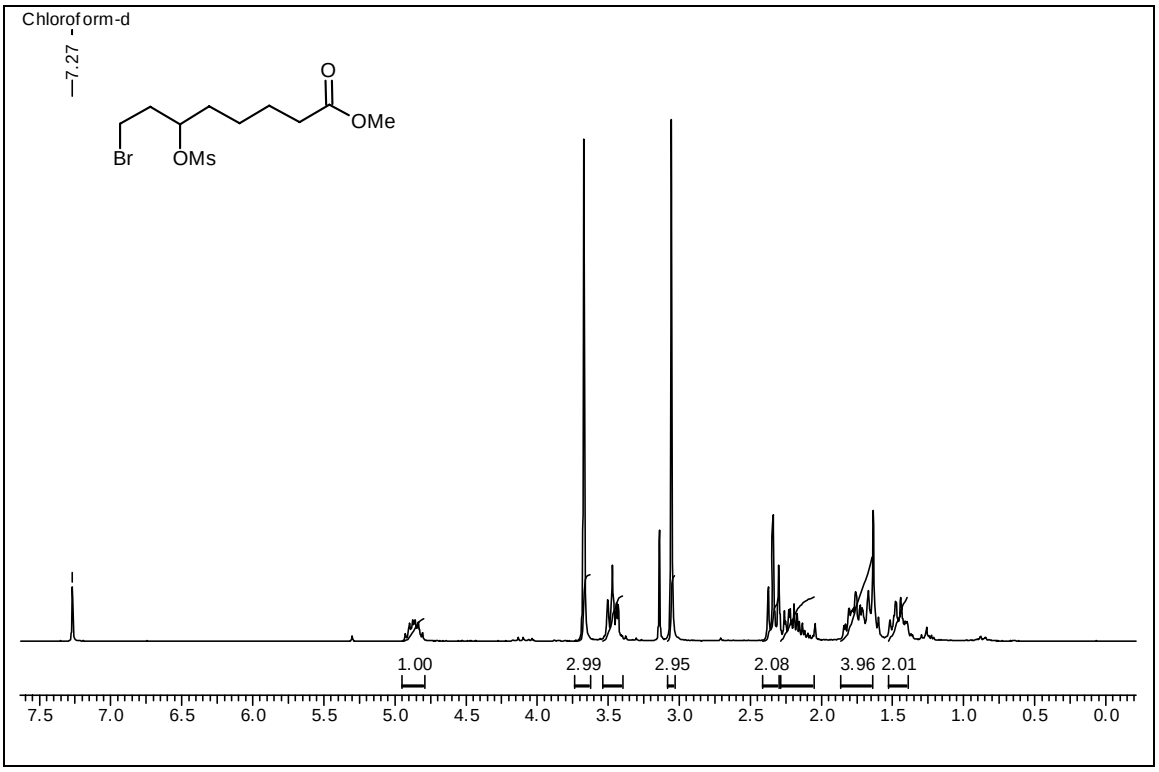
^{1}H NMR spectrum of compound 5 in $CDCl_3$



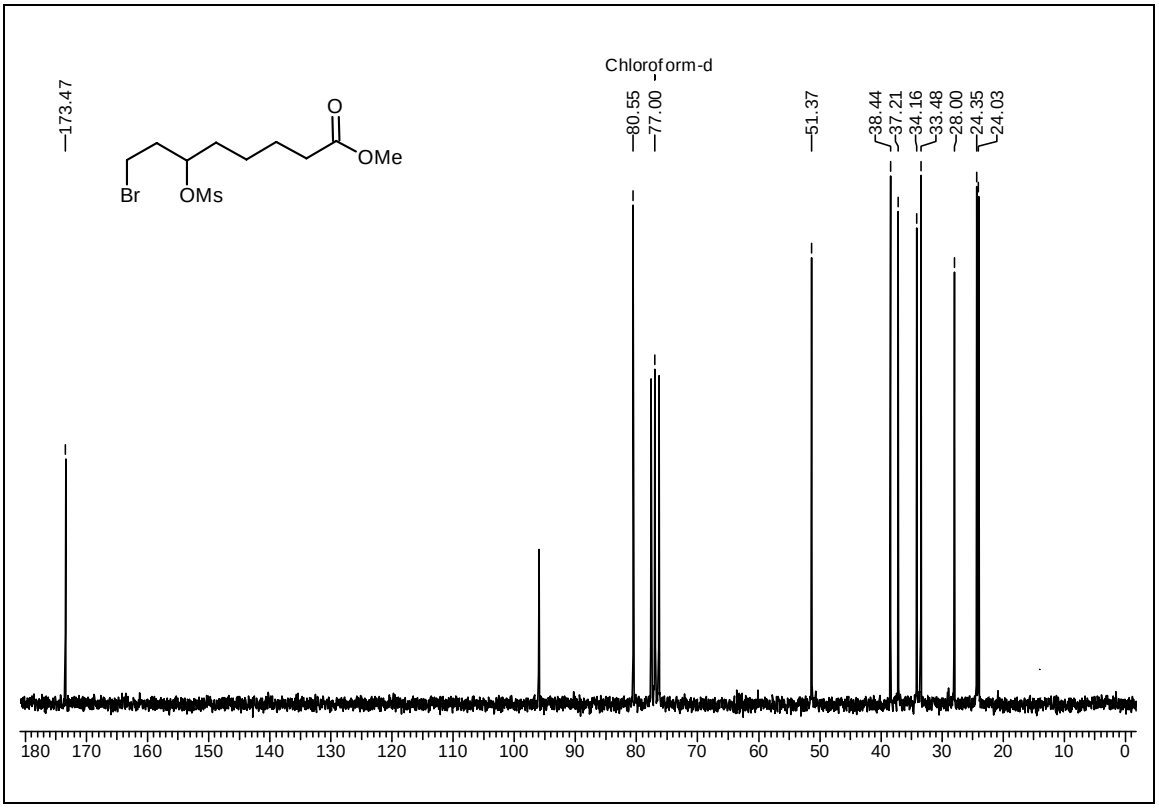
^{1}H NMR spectrum of compound 4 in $CDCl_3$



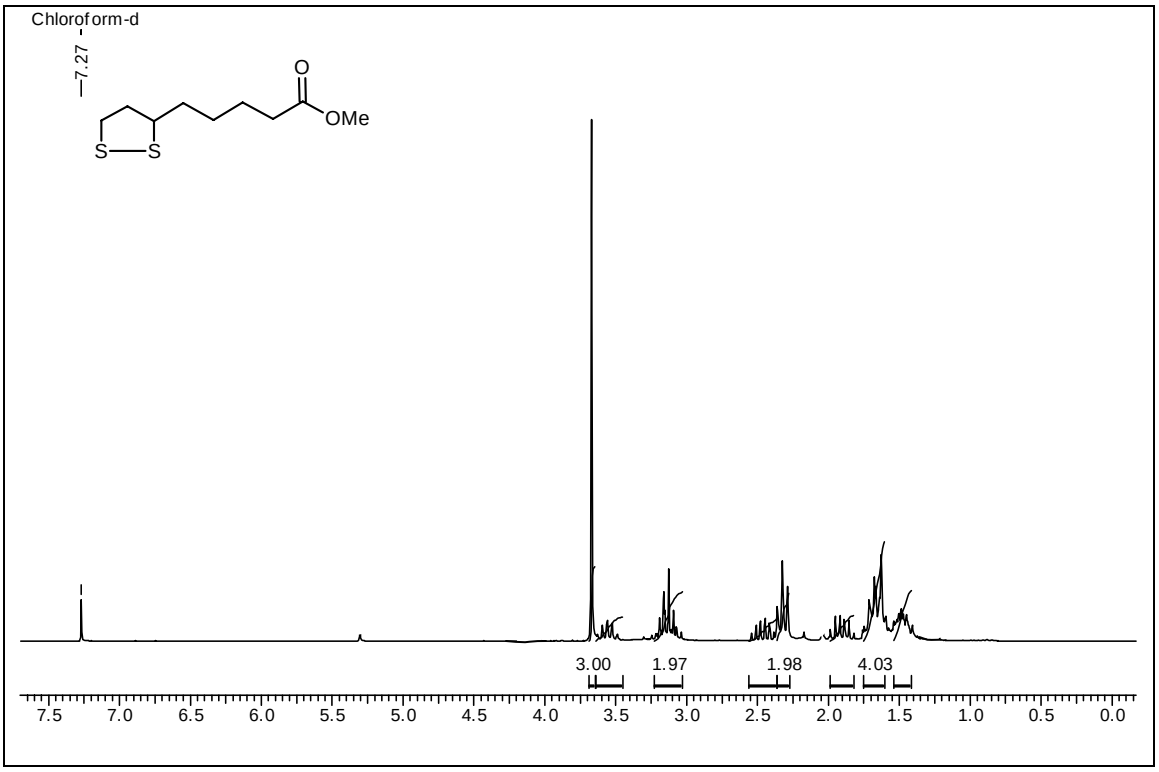
^{13}C NMR spectrum of compound 4 in $CDCl_3$



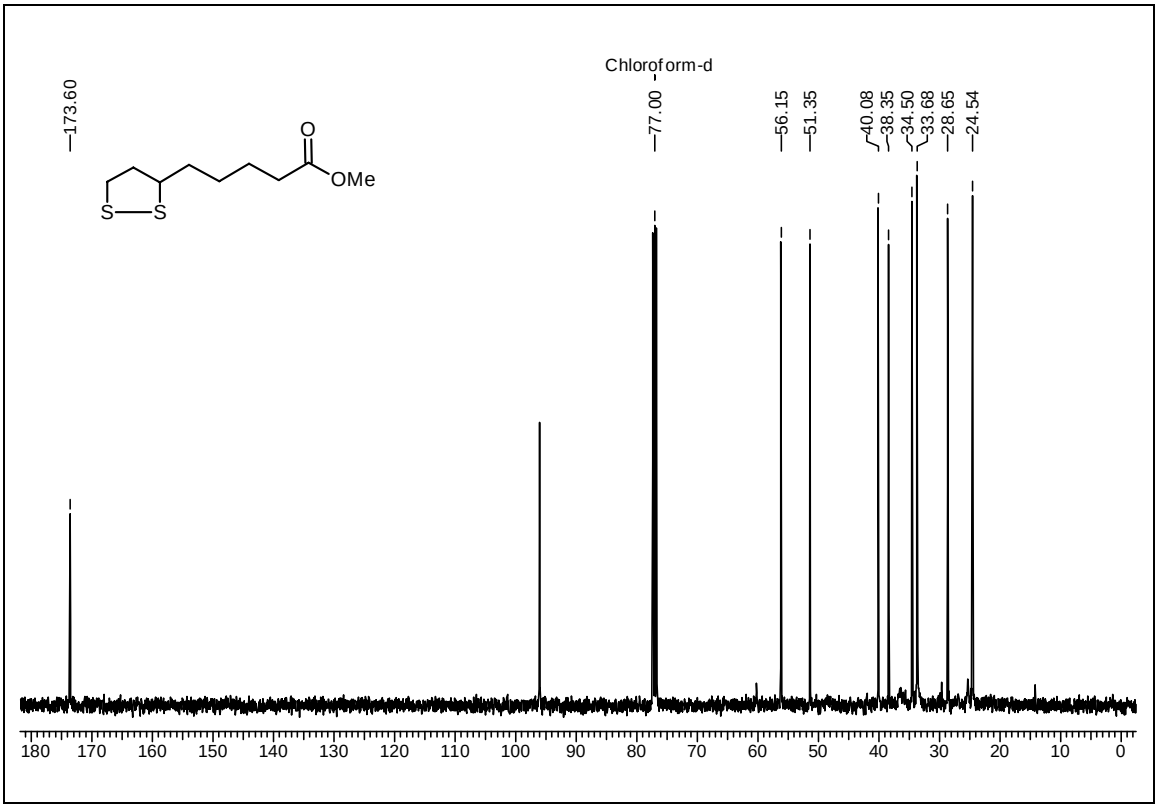
^{1}H NMR spectrum of compound 3 in $CDCl_3$



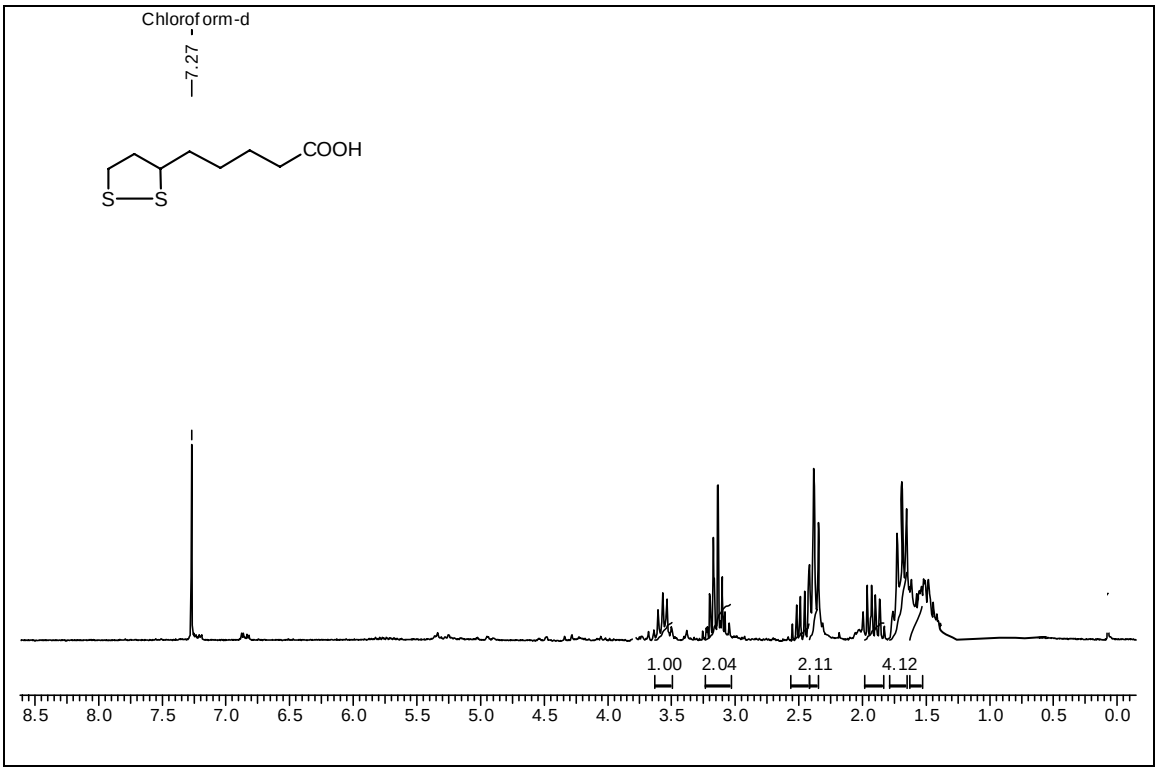
^{13}C NMR spectrum of compound 3 in $CDCl_3$



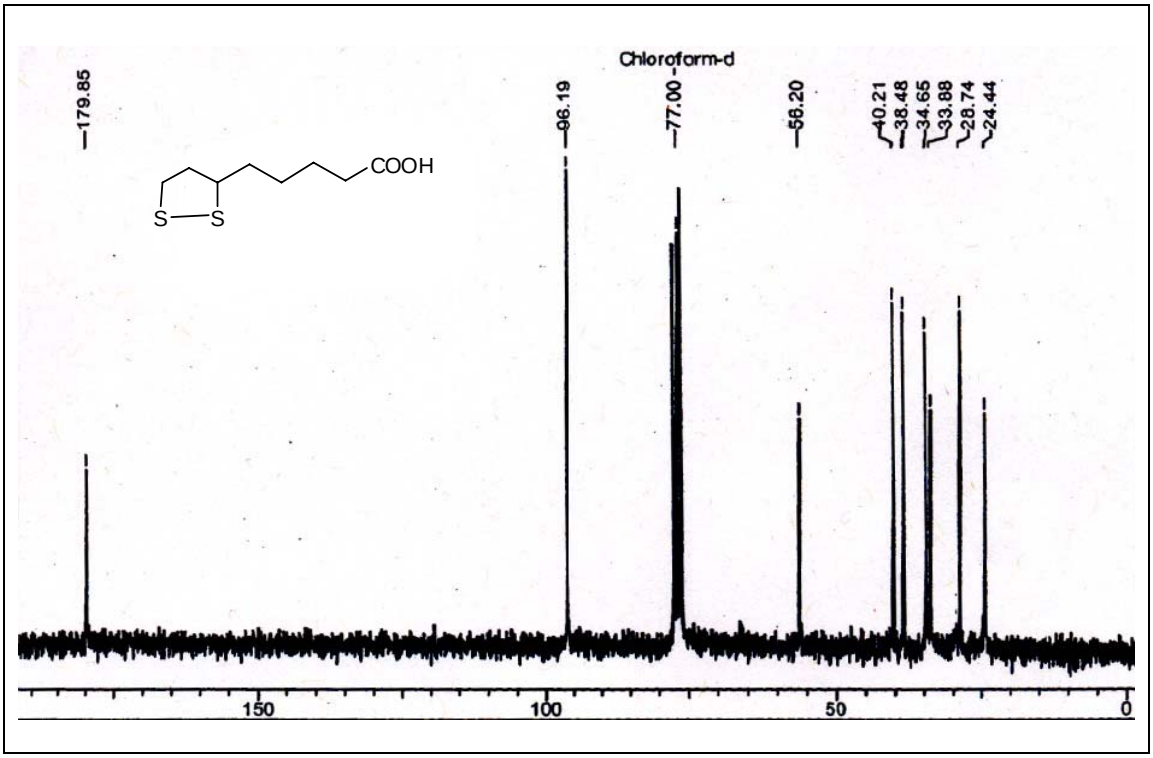
^{1}H NMR spectrum of compound 2 in $CDCl_3$



^{13}C NMR spectrum of compound 2 in $CDCl_3$



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



^{13}C NMR spectrum of compound 1 in $CDCl_3$

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CHAPTER-III

Synthetic studies toward Caminoside A

INTRODUCTION

Introduction

Marine biotechnology is the science that studies which marine organisms are used full or partially to make or modify products, to improve plants or animals or to develop microorganisms for specific uses. With the help of different molecular and biotechnological techniques, scientists have been able to design many biological methods and elucidate mechanisms applicable to both aquatic and terrestrial organisms. Approximately[1] 10% of over 25,000 plants have been investigated for biological activity. The marine environment may contain over 80% of the world's plant and animal species[2]. In recent years, many bioactive compounds have been extracted from various marine animals like tunicates, sponges, soft corals, sea hares, node branches, bryozoans, sea slugs and marine organisms. [3, 4] The search for new metabolites from marine organisms has resulted in the isolation of nearly 10,000 metabolites[5], many of which are endowed with pharmaceutical relevance.

Recently, Linington *et al.* (2002) developed[6] a high throughput assay to screen marine compounds for their ability to inhibit a type III secretory system which is an essential component of the pathogenicity of enteropathogenic and enterohermorragic *E. coli*. Their efforts resulted in the isolation of a novel antimicrobial glycolipid caminoside A from the marine sponge *Caminus spaeroconia*. Caminoside A was ''reasonably potent'' against methicillinresistant *S. aureus* (MIC=12 Ag/mL) and vancomycinresistant enterococcal strains (MIC=12 Ag/mL).

Escherichia coli

Escherich first described *E. coli* in 1885, as *Bacterium coli commune,* isolated from the feces of newborns. It was later renamed *Escherichia coli,* and for many years the bacterium was simply considered to be an organism persistent in the large intestine. It was not until 1935 that a strain of *E. coli* was shown to be the cause of an outbreak of diarrhea among infants. The GI tract of most warm-blooded animals is colonized by *E. coli* within hours or a few days after birth. The bacterium is ingested via foods or water or obtained directly from other individuals handling the infant. *E. coli* can adhere to the mucus overlying the large intestine. Once established, an *E. coli* strain may persist for

months or years. The entire DNA base sequence of the *E. coli* genome has been known since 1997.

E. coli is the head of the large bacterial family, ***Enterobacteriaceae***, the **enteric bacteria**, which are facultative anaerobic Gram-negative rods that live in the intestinal tracts of animals in health and disease. The *Enterobacteriaceae* are among the most important bacteria medically. A number of genera within the family are human intestinal pathogens (e.g. *Salmonella*, *Shigella*, *Yersinia*). Several others are normal colonists of the human gastrointestinal tract (e.g. *Escherichia*, *Enterobacter*, *Klebsiella*), but these bacteria, as well, may occasionally be associated with diseases of humans.

Enteropathogenic *Escherichia coli* (EPEC) is a leading cause of infantile diarrhea in developing countries. In industrialized countries, the frequency of these organisms has decreased, but they continue to be an important cause of diarrhea.[7] The central mechanism of EPEC pathogenesis is a lesion called attaching and effacing (A/E), which is characterized by microvillus destruction, intimate adherence of bacteria to the intestinal epithelium, pedestal formation, and aggregation of polarized actin and other elements of the cytoskeleton at sites of bacterial attachment. The fluorescent actin staining test allows the identification of strains that produce A/E lesions, through detection of aggregated actin filaments beneath the attached bacteria.[8] Ability to produce A/E lesion has also been detected in strains of Shiga toxin–producing *E. coli* (enterohemorrhagic *E. coli* [EHEC]) and in strains of other bacterial species.

The genetic determinants for the production of A/E lesions are located on the locus of enterocyte effacement (LEE),[9] a pathogenicity island that contains the genes encoding intimin, a type III secretion system, a number of secreted (Esp) proteins, and the translocated intimin receptor named Tir. Two LEE insertion sites have been described on the *E. coli* chromosome, and a third unidentified insertion site has been reported.[10]

Methods of Glycosylation

Glycoconjugates are biopolymers formed by an oligosaccharide moiety joined to a protein (glycoproteins) or to a lipid moiety (glycolipids). These biopolymers together with proteins and nucleic acids are mainly responsible of information transfer between cells, which is a fundamental process of life and central to all cellular systems.

Complex oligosaccharides in the form of glycolipids and glycoprotein are present in the membranes of cells and can mediate a large number of diverse and important biological functions. Oligosaccharides play a major role in inflammation, immune response, metastasis, fertilization and many other important biomedical processes. Specific carbohydrates cover different kinds of functions. They could act as markers of certain types of tumors, others act as signal molecules of symbiotic processes such as the symbiosis between *Rhizobium* bacteria and legume plants; others are binding sites for bacterial and viral pathogens.

Glycobiology deals with the study, preparation and biological role of sugars, from monosaccharides to complex oligosaccharides and their analogues.

The important role of carbohydrates in biology and biomedicine has been a major incentive for devising new methods for the chemical and enzymatic synthesis of this class of molecules.

1. General Aspects of Glycosidic Bond Formation

1) Formation of a glycosidic bond

2) General mechanistic pathway for glycosidic bond formation

3) Choices, challenges and problems of the glycosidic bond

4) Structure and reactivity of glycosyl donors and of glycosyl acceptors

5) Promoters, solvents and experimental conditions

6) Anomeric control in chemical glycosylations.

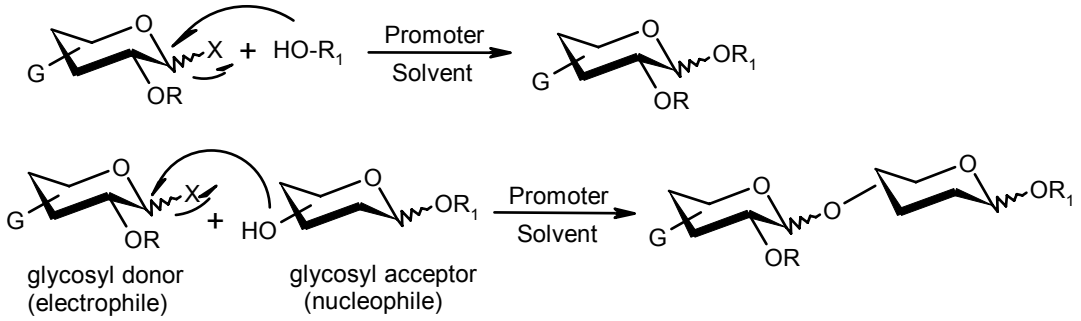
Methods for stereoselective formation of glycosidic linkages.

1. Preparation of 1,2-*trans*-glycosides by neighboring group participation
2. *In situ* anomerization for the synthesis of α-glycosides (**Lemieux**)
3. Stereo selective preparation of α- and β-glycosides by participation of the solvent
4. Heterogeneous catalysis (**Paulsen**).
5. Intramolecular aglycone delivery approach

1. Formation of a glycosidic bond:

Glycosidic bond is formed by a nucleophilic displacement of a leaving group (X) attached to the anomeric carbon of a sugar moiety by an alcohol ROH, or by the OH group of a partially protected sugar moiety. The compound that "gives" the glycosyl moiety is called the *glycosyl donor*, and the alcohol that receives it, is known as *glycosyl*

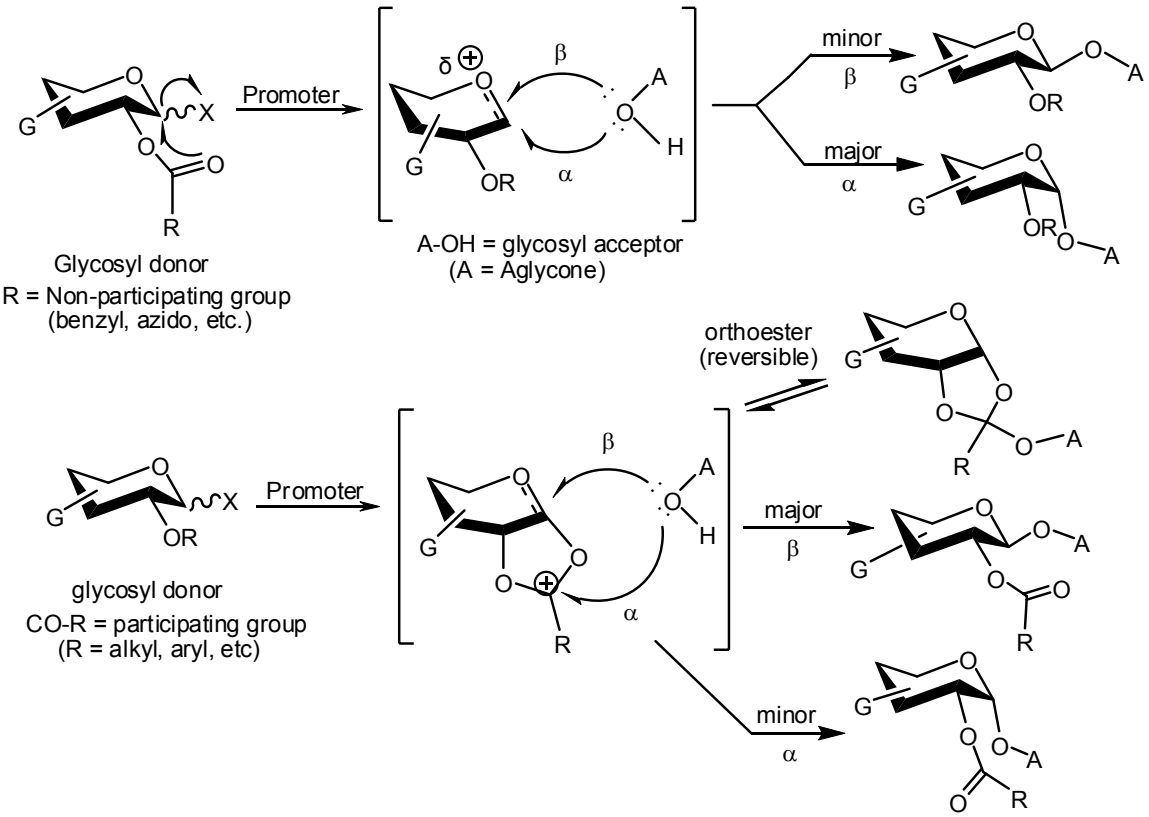
acceptor. The reaction generally is performed in the presence of an activator called "promoter". The role of the promoter is to assist the departure of the leaving group.



Scheme-1

Promoters are used in catalytic amounts, although in some instances they are used stoichiometrically. In some cases, other additives such as molecular sieves or any base that may act as acid scavenger are used. There are many methods available for glycosidic bond formation.

2. General mechanistic pathway for glycosidic bond formation1[11]



Scheme-2

The general mechanistic pathway for glycosidic bond formation is represented in Scheme 2. Over 90% of all the glycosylations reported, formally proceed *via* this general mechanistic pathway. There are some exceptions such as *in situ* anomerization, intramolecular aglycon delivery and the use of additives such as acetonitrile, which appears to react at the anomeric center itself. The timing of events heavily depends on the structures of the glycosyl donors, acceptors and promoters.

3. Choices, challenges and problems inherent in forming of the glycosidic bond

The success of a coupling reaction between two sugars depends on the reactivity of the donor and acceptor, on the promoter, on the kind of substituents on both saccharide units and, of course, on the preferred selectivity of the reaction towards the α- or the β-anomeric form.

Choices

1) Leaving group and participating or non-participating group in the donor
2) Potential leaving group and participating or non-participating group in the acceptor
3) Promoter or catalyst
4) Solvent and temperature
5) Protecting groups

Challenges and problems

1) Anomeric selectivity for 1, 2-*cis* or 1, 2-*trans* linkages.
2) Site selectivity and reactivity of acceptor OH groups (e.g. axial, equatorial, primary)
3) Configuration, substituent, steric and electronic effect in the donor and acceptor
4) Stoichiometry relative to the ratio donor: acceptor equivalents
5) Selective activation of anomeric groups
6) Alterative glycosylation in a stepwise manner
7) Minimum manipulation of protecting groups

4. Structures and reactivity of glycosyl donors and of glycosyl acceptors used in oligosaccharide synthesis

Structures and reactivity of glycosyl donors

There are numerous glycosylation methods involving different glycosyl donors. The name of the glycosylation method generally reflects the functionality of the glycosyl

donor except for the Fischer glycosylation that uses reducing sugars and the Köening-Knorr procedures that use glycosyl halides as donors.

The reactivity at the anomeric center depends to a large degree on the choice of the protecting groups specially those on C-2. Glycosyl donors are then classified into two main groups: armed donors (with an ether group on C-2) more reactive than disarmed donors (with esters, amides on C-2).

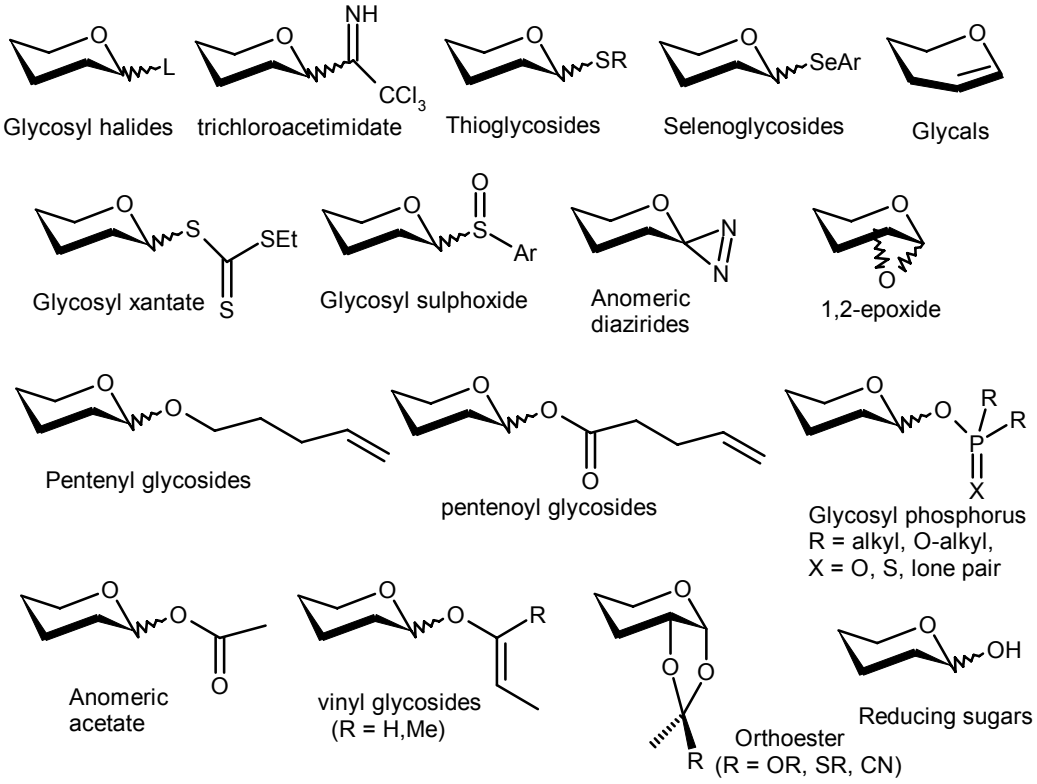
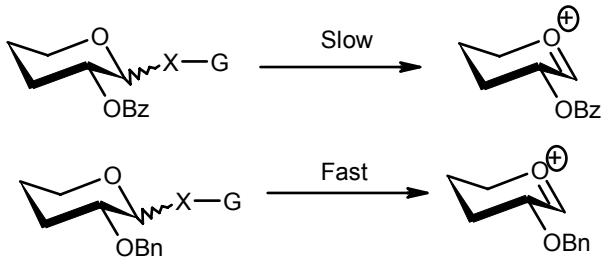


Figure-1: structures of glycosyl donors

Ester groups induce some positive charge at the anomeric center making the formation of the oxonium ion a slower process. When identical protecting group's patterns are desired, different leaving groups may control reactivity. Both the nature of the heteroatom **X** and substituent **G** of the leaving group affect the reactivity. The configuration of the glycoside also influences its reactivity. Another element of control occurs *via* the use of different promoters **P** for leaving groups activation. Finally, sterical/torsional factors also have an influence. Fused rings resist flattening of the pyranose ring during oxonium ion formation.



Scheme-3

Reactivity of Glycosyl Acceptors

The reactivity of the acceptor depends on the nucleophilicity of the hydroxyl groups[12] in partially protected carbohydrates that in turn depends on their nature (1º more reactive than 2º), their spatial orientation (equatorial more reactive than axial), the conformation of the sugar ring and the presence of other protecting groups in the molecule. It can be generalized that electron-withdrawing groups diminish the reactivity of the acceptor. In addition, the steric hindrance of the groups has an influence.

5) Promoters, Solvents and Experimental Conditions

The nature of the promoter, generally a Lewis acid, has an influence in the sense that it favors the departure of the leaving group. Reactions can be homogenous and heterogeneous with profound implications for the stereochemistry.

The solvent also impacts the overall rate of the process and on the stereochemistry, especially in the case of non-participating glycosyl donors. Anhydrous solvents are required to avoid competition from water. Solvents of low polarity, such as dichloromethane or ether are frequently used. Sometimes polar aprotic solvents such as acetonitrile or nitromethane are used.

The experimental conditions are very critical for the success of the reaction. Generally, the uses of extremely dry solvents, inert atmosphere and molecular sieves that can act as acid scavenger are needed. Sometimes a non-nucleophilic base is also needed. The order in which the reagents are added is also important in some cases. The normal procedure of adding reagents (NP) is appropriate for less reactive disarmed donors. The promoter (P) is added over a mixture of acceptor (A) and donor (D). For highly reactive armed donors, the inverse procedure (IP) in which the donor is added over a mixture of acceptor and promoter is the most convenient.[13]

6) Anomeric control in chemical glycosylation:

Methods for stereoselective formation of glycosidic linkages

Types of anomeric linkages

The stereoselective introduction of the glycosidic linkage is one of the most challenging problems in chemical oligosaccharide synthesis. The anomeric linkages can be classified according to the relative and absolute configuration at C-1 and C-2.

The 1,2-*cis*- and 1,2-*trans*-2-D-*glycero* series (allo-, gluco-, gulo- and galactopyranosides) and the 1,2-*cis* and 1,2-*trans*-2-L-*glycero* series (altro-, manno-, ido- and talopyranosides). In addition, some miscellaneous glycosidic linkages can be identified, including 2-deoxyglycosides and 3-deoxy-2-keto-ulo(pyranosylic) acids.

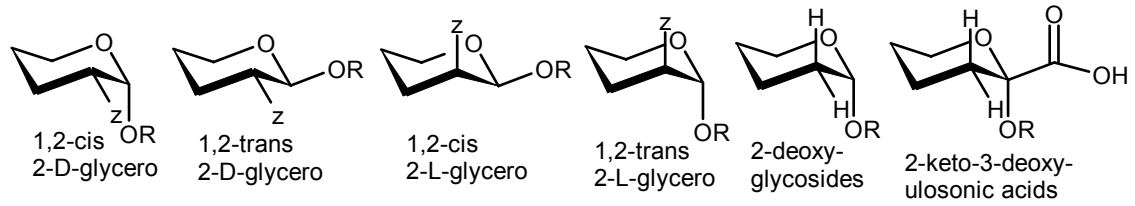
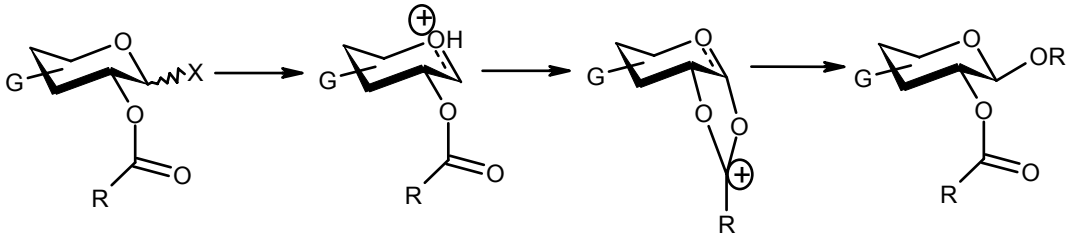


Figure-2

Preparation of 1, 2-trans-glycosides by neighboring group participation

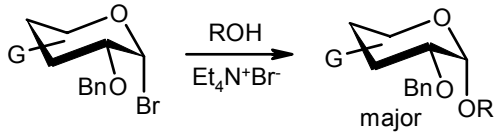
The nature of the protecting group at C-2 of the glycosyl donor is a major determinant of the anomeric selectivity. A protecting group at C-2 that can provide anchimeric assistance via neighboring group participation (disarmed donors) during glycosylation will give 1, 2-*trans* glycosidic linkages. Nucleophilic attack of the alcohol at the anomeric center of the more stable oxonium cation **3** originating from participation of the neighboring after departure of the leaving group X, results in the formation of a 1, 2-*trans*-glycoside **4**. Glucosyl type donors will give β-linked products while mannosides will give α-glycosides.



Scheme-4

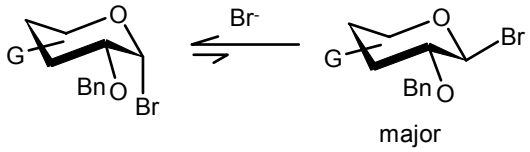
In situ anomerization for the synthesis of α-glycosides (Lemieux)

Lemieux and co-workers introduced this procedure in 1975 as a way of controlling the anomeric selectivity in armed donors with non-assisting functionality at C-2. The reaction conditions (e.g. solvent, temperature, and promoter) will determine the anomeric selectivity. The *in situ anomerization procedure* results mainly in the formation of α-glycosides.



Scheme-5

Lemieux discovered that the α-haloglucopyranoside is in equilibrium with the more reactive β-halide and that the equilibrium is catalyzed by halide ions derived from tetraalkylammonium halides, and the reaction proceeds with inversion of a highly reactive β-halide with the alcohol component via nucleophilic substitution.

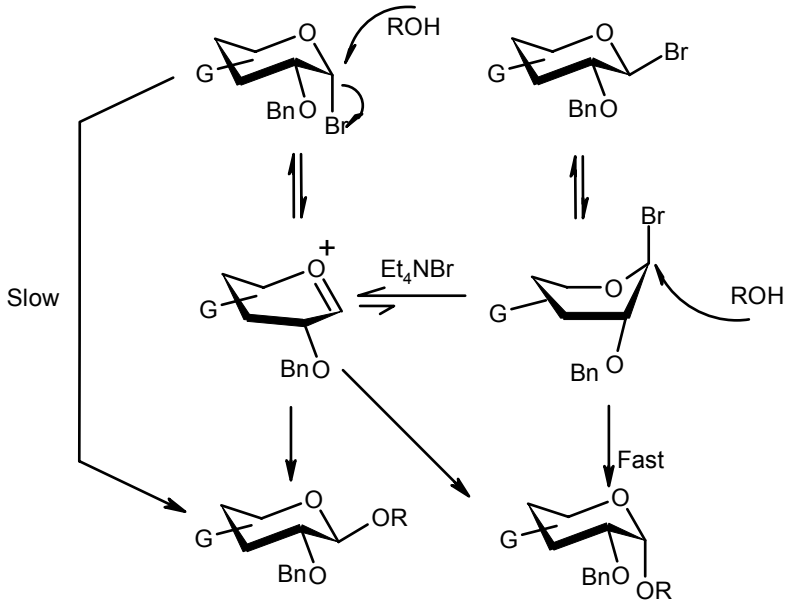


Scheme-6

This reaction is thought to proceed through several intermediates (Scheme 9). At equilibrium, the proportion of the α-halide is relatively high. The β-halide is less stable because of the de-stabilization as a result of the anomeric effect but reacts more rapidly than the α-halide with an *O*-nucleophile.

To allow substitution of the β-halide, the C-1-halide bond, in order to be broken, must be anti-periplanar to the electron lone pair of the ring oxygen.[14] To establish such an arrangement, a conformational change to the highly reactive boat-like intermediate is required. This makes reaction of the β-halide fast. In the case of the α-halide, a conformational change is not required since the C-1 halide bond is already anti-periplanar to the ring oxygen lone pair and the substitution of the α-halide is slow. It is clear that the equilibrium rate must be fast enough to ensure that sufficient β-halide is continuously present. If the difference in reaction rate between the α- and β-halides with the alcohol is large enough, α-linked *O*-glycosides are obtained as major compounds or exclusively.

The reaction requires very reactive glycosyl halides (armed) and long reaction times, in particular when the originally tetra-alkyl ammonium bromides are used as catalysts.

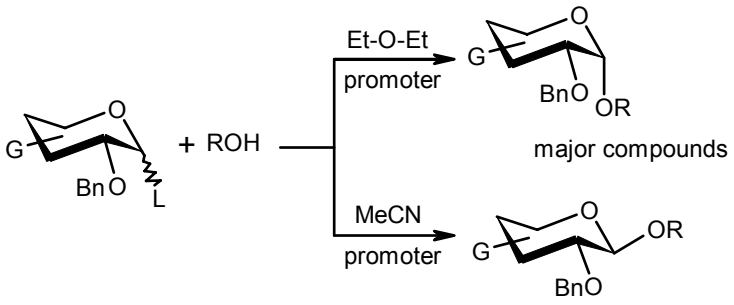


Scheme-7 Preparation of α-glycosides by *in situ* anomerization

The *in situ anomerization* procedure has proven to be very useful. The use of other promoters such as mercuric bromide, silver perchlorate and silver triflate make it possible to carry out the reaction with even less reactive halides. However, the stereoselective outcome of the glycosylations is very dependent not only on the reactivity of the catalyst, but also on the reactivity of both the halide and the acceptor.

Stereoselective preparation of α- and β-glycosides by participation of the solvent

The choice of the combination promoter/solvent plays a crucial role for the anomeric stereocontrol of a glycosylation, especially when a non-participating group is at C-2 position. In general, if any participating group is present at C-2, the glycosylation reaction follows a S_N2 pathway in non-polar solvents. The influence of the solvent under S_N1-type conditions has been extensively studied for ethers and nitriles.[15] Ethers such as diethyl ether or THF favor the α-linkage while with acetonitrile; β-glycosides are commonly obtained.



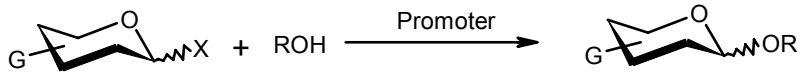
Scheme-8

Different procedures of glycosylation reactions by direct activation

1. Köenings-Knorr method and related Glycosyl Fluorides (**Mukaiyama**)
2. *O*-Alkylation and the trichloroacetimidate method (**Schmidt**)
3. Glycosylation with glycals (**Lemieux, Thiem, Danishefsky**)
4. *n*-Pentenyl glycoside method (**Fraser-Reid**)
5. *S*-Glycoside methods (**Lönn, Garegg, van Boom**)
6. Phenylselenoglycosides

1. Köenings-Knorr and related methods[16]

This reaction reported in 1901 is still one of the most useful reactions for preparing a wide variety of *O*-glycosides. It is useful for coupling reactions with either alkyl or



X = Br, Cl

Promoter	Conditions
Ag_2CO_3	PhH, drierite (drying agent), I_2
Ag_2O	s-collidine (acid scavenger)
$AgNO_3$	HgO (acid scavenger)
$AgClO_4$	Ag_2ClO_3 (acid scavenger), THF or toulene, rt
AgOTf	CH_2Cl_2, rt

Scheme-9

aromatic alcohols as well as for coupling between sugars. The methodology requires silver salts as catalyst and among them the oxide, carbonate, nitrate, and triflate silver salts are the most commonly employed (scheme-9). In addition, a drying agent such as calcium sulfate, calcium chloride, or molecular sieves is recommended. Improved yields are obtained with iodide, vigorous stirring, and protection against light during the course of the reaction.

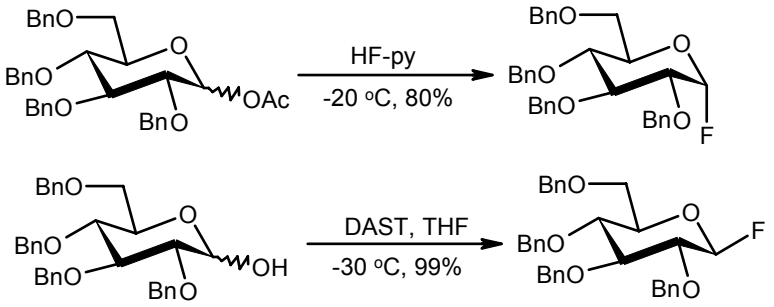
The stereochemistry observed is 1, 2-trans type in most of the cases reported, as a consequence of neighboring group participation. When the protecting group is acetate at C (2), there is an intramolecular nucleophilic displacement of the leaving group; generating an orthoester. This intermediate is responsible for the incorporation of the alcohol on the β-position. Only until recently a method for preparing 1, 2-cis glycosides has been developed involving the use of (1S)-phenyl-2- phenylsulfonyl) ethyl moiety at C-2 of a glycosyl donor to give a quasi-stable anomeric sulfonium ion. The sulfonium ion is formed as a trans decalin ring system. Displacement of the sulfonium ion by a hydroxyl leads to the stereoselective formation of α-glycosides.

In spite of the generality of the method, several inconveniences have limited its use. The intrinsic instability of glycosyl halides, the requirement of at least an equimolar amount (often up to 4 eq) of metal salts as promoters (frequently incorrectly termed as "catalyst").

Glycosyl fluorides (Mukaiyama)[17]

In 1981, Mukaiyama and co-workers introduced anomeric fluorides for the preparation of *O*-glycosides. The use of fluorine as leaving group is a good alternative to the Köenings-Knorr method due to the stability of the C-F bond. Fluorides are typically prepared from the anomeric acetates by reaction with HF/py, from hemiacetals by reaction with DAST or from thioglycosides by reaction with NBS/DAST. Because of the difference in halophilicity of this element compared with bromine and chlorine, the glycosylation reactions require the use of other promoter systems besides silver salts.

Glycosylations with anomeric fluorides follow the general principles described for bromides and chlorides. Apart from their enhanced stability, anomeric fluorides have not proven to be superior to bromides or chlorides in terms of glycosylation efficiency.



Scheme-10

2. O-Alkylation and the trichloroacetimidate method (Schmidt)

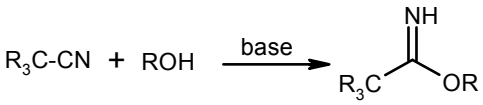
O-Alkylation method[18]

The anomeric oxygen of a sugar can be activated for a glycosylation by acids (Fischer glycosylation) and by bases. Upon treatment of a hemiacetalic sugar with a base, the generated anomeric oxide can be alkylated leading directly and irreversibly to a glycoside. This process is called anomeric *O*-alkylation.

In this procedure, some inconveniences are evident: The equilibrium between the two anomeric forms and the open-chain form gives three sides of attack and also, a base catalysed elimination in the open chain form could become an important side reaction. Therefore, the yield, the regioselectivity and the stereoselectivity of the anomeric *O*-alkylation was not expected to be outstanding. However, Schmidt and co-workers have described several good examples of this method including glycosylation of unprotected sugars.

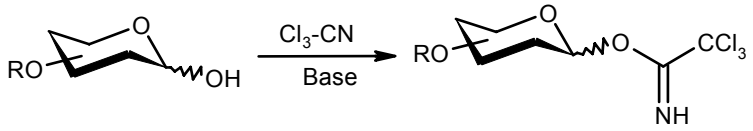
The trichloroacetimidate method[19]

Electron deficient nitriles are known to undergo direct and reversible base-catalysed addition of alcohols to the triple bond system, providing *O*-alkyl imidates. The free imidates can be directly isolated as stable adducts.



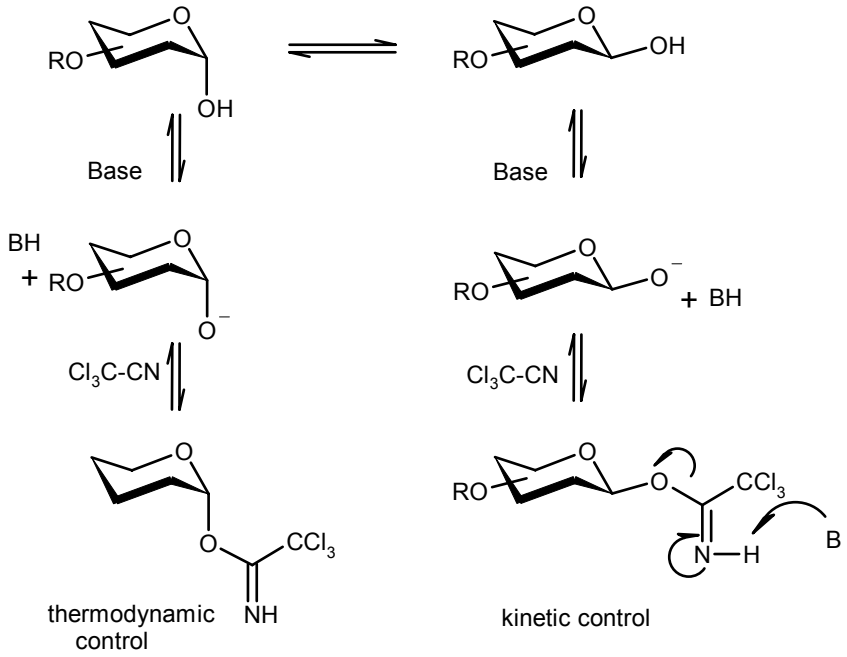
Scheme-11

The reaction of hemiacetalic sugars in the presence of a base with trichloroacetonitrile gives the anomeric trichloroacetimidates. In this way, the anomeric oxygen atom has been transformed into a good leaving group.



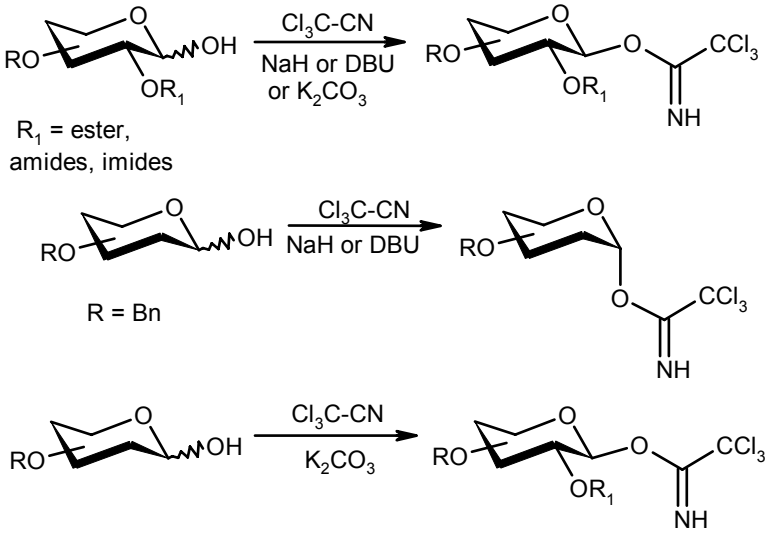
Scheme-12

Taking into account the equilibrium between both anomers and the enhanced nucleophilicity of equatorial oxygen atoms (owing to steric effects and to the stereoelectronic kinetic anomeric affect), the equatorial (β)-trichloroacetimidate is generated with preference or even exclusively in a very rapid and reversible reaction. However, this product anomerizes in a slow base catalyzed reaction through retro-anomerization of the 1-oxide anion. Through a novel trichloroacetonitrile addition, the thermodynamically more stable axial (α)-trichloroacetimidate is formed (thermodynamic anomeric effect).



Scheme-13

Stronger bases can speed up the equilibration between the two trichloroacetimidates. Thus, with different bases both *O*-activated anomers can be obtained in pure form and high yield. NaH is appropriate for axial trichloroacetimidates while weaker bases such as K_2CO_3 is appropriate for equatorial trichloroacetimidates.



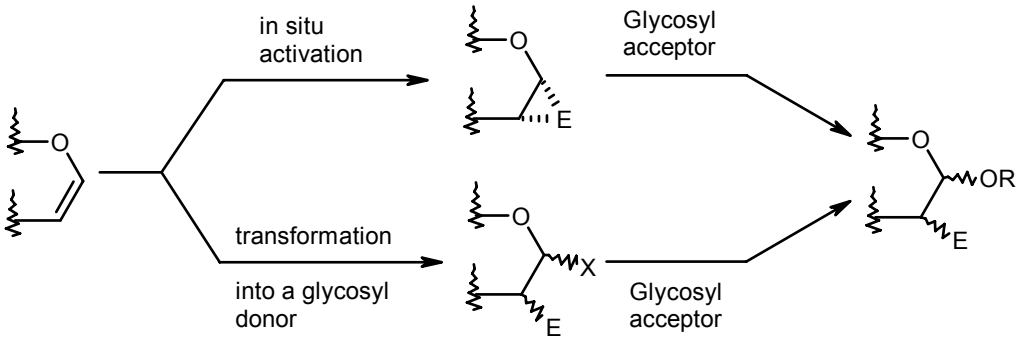
Scheme-14

Concerning the glycosylation step, reaction of donor and acceptor under very mild acid conditions leads to the corresponding glycoside in an irreversible manner. Acids, such as $BF_3.OEt_2$ or TMSOTf are used in catalytic amounts. The proton liberated on the glycoside bond formation reacts with the forming leaving group. This leads to a stable, non-basic trichloroacetamide that provides the driving force of the reaction.

The outstanding significance of the trichloroacetimidate method lies in the ability of glycosyl trichloroacetimidates to act as strong glycosyl donors under relatively mild acid catalysis. This method has not only been used in oligosaccharide synthesis, but also in the chemistry of natural products where sugars are glycosylated to different moieties.

Glycosylation with glycals (Lemieux, Thiem, Danishefsky)

Glycals in oligosaccharide synthesis were first used by Lemieux in 1960s, by Thiem in 1980s and since then, by Danishefsky and co-workers. Glycals can be used as glycosyl donors in two modalities. In the first motif, *in situ* activation makes the glycal act as glycosyl donor by forming a non-isolable intermediate. In the second motif, the glycal is first converted into a glycosyl donor through different types of reactions (epoxidation, azidonitration or sulfonamide glycosylation). That is, the glycal is precursor of a defined glycosyl donor.



Scheme-15

Lemieux and Thiem, who used halonium-mediated coupling to suitable acceptors, did pioneering experiments that used glycals as glycosyl donors. This particular reaction has a tendency to trans-diaxial addition and provides a crucial route to α-linked disaccharides having an axial 2-iodo function at the non-reducing end. Because the displacement of an axial iodine atom has proven to be very difficult, azaglycosylation of glycals has been investigated with the idea of preparing glycosides of 2-acylaminosugars.

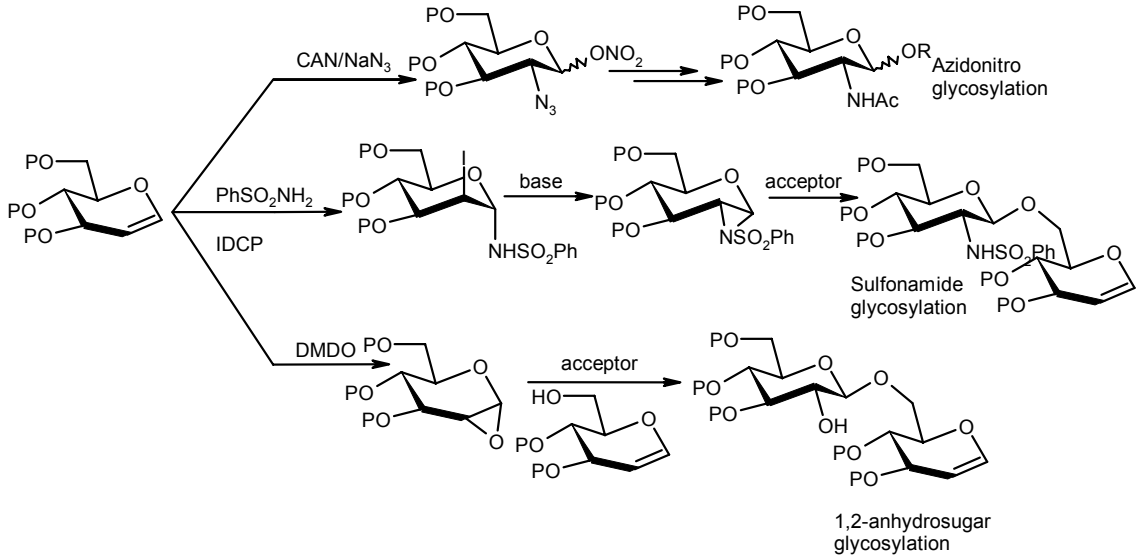
Azidonitration with CAN/NaN_3 was studied by Lemieux and constituted an important advance at the time, nevertheless the conversion of the nitro-azido compounds into oligosaccharides has not been fully optimized with regards to the yield and stereoselectivity.

Other procedures, such as iodo-sulfonamidation developed by Danishefsky,[20] have been used with more success for the synthesis of 2-acylamino oligosaccharides.

This method implies a *trans*-diaxial addition of an *N*-halobenzene sulfonamide to a glycal followed by a base treatment that gives an intermediate that reacts with any acceptor, for instance, another glycal, furnishing glycosides of benzenesulfonyl glucosamine derivatives: sulfonamido-glycosylation.

While iodo-glycosylation and sulfonamido-glycosylation are rather good methods for the conversion of glycals in various glycosides, the 1,2-anhydro sugar glycosylation provides a general method for converting glycals into common oligosaccharides of glucose, mannose and galactose in a high stereocontrolled manner. Once the glycal is converted into the 1, 2-oxirane, it may react with several acceptors leading to

disaccharides. This method has been the most widely used for the rapid assembly of oligosaccharides, and is appropriate for solid-phase synthesis.



Scheme-16

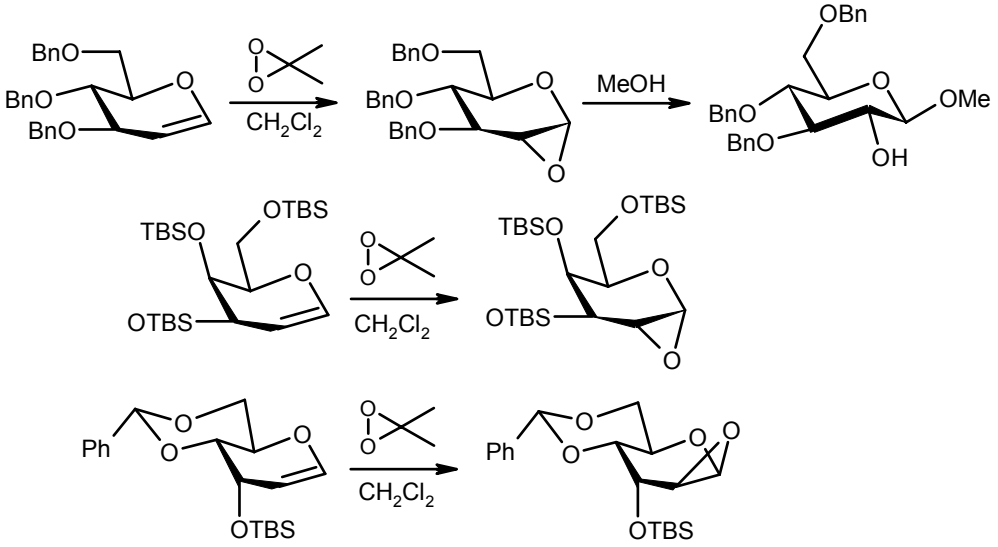
Protecting groups influence the reactivity of glycals as donors. The armed-disarmed concept that prevails in pentenyl glycosides and thioglycosides is also applied here. When a benzylated glycal is made to react with benzoylated glycal no self-condensation is observed and only one product is obtained derived from the more reactive glycal acting as donor.

With regards to 1, 2-anhydro sugars,[21] the method was able to be applied when it was discovered that glycals react smoothly with 2,2-dimethyldioxirane prepared as a solution in dichloromethane, giving 1,2-anhydro sugars in good yields. The stereoselectivity of the epoxidation highly depends on the type of protecting groups and on the steric hindrance of the substituents.

The 3, 4, 6-tri-*O*-benzyl-D-glucal gives the epoxide in quantitative yield. Its solvolysis gave the corresponding methyl glycoside with a stereoselectivity of 20:1 in favor of the α-isomer. With resident acetyl protecting groups, the stereoselectivity of the epoxidation is much reduced.

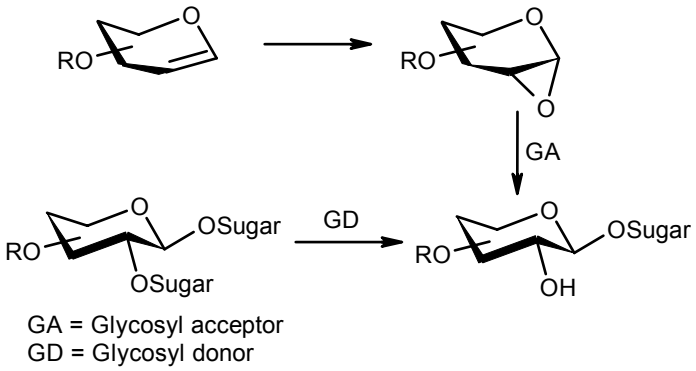
TBS protecting groups or acetals also give high stereoselective epoxidations. Steric hindrance also has an influence. Reaction of TBS-protected galactal gives stereoselectively the α-epoxide, while the presence of an axial substituent at C-3 on the

glycal promotes a quite selective epoxidation from its β-face. On the other hand, the gulal configurated glycal with hindering substituents on both faces of the double bond gave a 1:1 mixture of epoxides.



Scheme-17

The strategy consists on the preparation of a glycal epoxide that reacts as donor with a glycosyl acceptor leading to a C(1)-O-sugar, with one hydroxyl group at C-2. This derivative acts as glycosyl acceptor when it reacts with a glycosyl donor furnishing a branched trisaccharide.

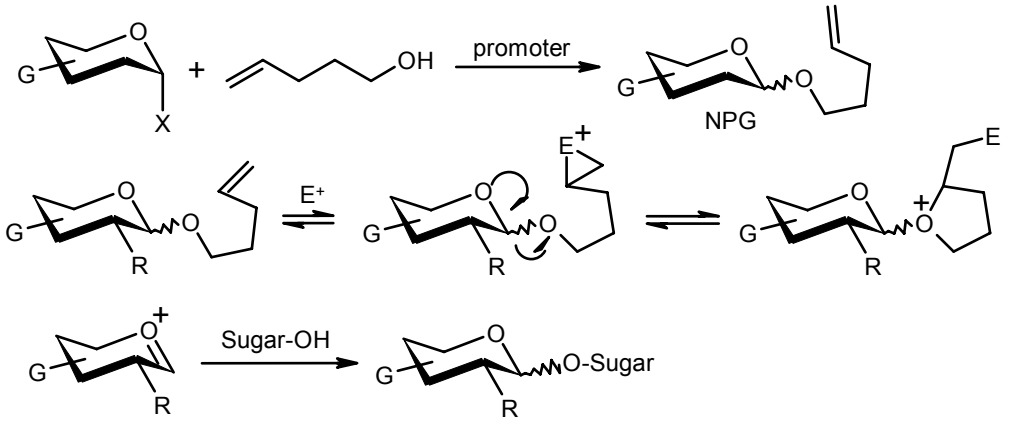


Scheme-18

n-Pentenyl glycoside method[22]

This method using pentenyl glycosides as glycosyl donors was introduced by Fraser-Reid in 1988. The activation of the leaving group is based on an electrophilic addition to the double bond of the aglycone, followed by an intramolecular displacement

by the ring oxygen and eventual expulsion of the pentenyl chain to form oxonium specie. Trapping with aglycosyl acceptor, then leads to the desired glycoside.



Scheme-19

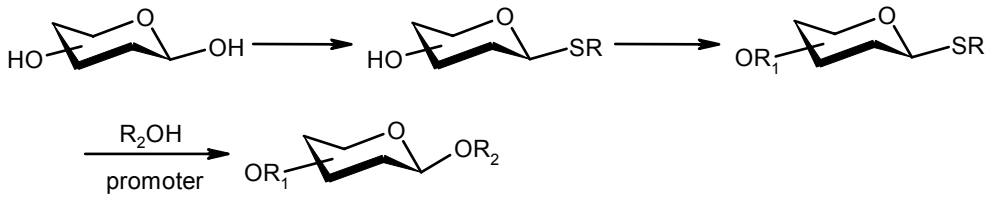
The promoter of choice is any source of halonium ion. NBS or NIS alone or activated by Lewis acid. NIS/Et_3SiOTf is commonly used. Sometimes TfOH is also used. When using halosuccinimides alone, the reaction is very slow, and often requires hours or days for completion. A promoter of intermediate potency is IDCP (iodonium dicollidone perchlorate).

S-Glycoside methods

There are several methods in which, the anomeric carbon is activated by groups having sulphur in place of the exocyclic hemiacetal oxygen. The best known example of this type of protection/activation group is the alkyl/aryl/thio group (thioglycosides). Oxidized forms of thioglycosides, such as sulfoxides can act as glycosyl donors as well as other derivatives like *S*-xantates.

Thioglycosides[23]

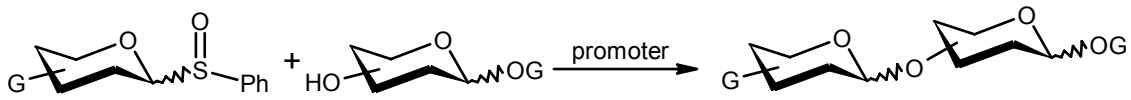
The sulfur atom in a thioglycoside is a soft nucleophile and is able to react selectively with soft electrophiles such as heavy metal cations, halogens, and alkylating or acylating reagents. These facts make thioglycosides very versatile agents in carbohydrate chemistry. Additionally, the hydroxy and ring oxygen atoms of carbohydrates are hard nucleophiles, which can be functionalized with "hard" reagents, without affecting alkyl (aryl) thio function. An electrophile activates the thioglycoside by producing intermediate sulfonium ions, which then give rise to glycosylating carbocationic intermediates that react with the alcohol giving the glycoside.



Scheme-20

Sulfinil glycosides: the sulfoxide method[24]

The use of glycosyl sulfoxides as glycosyl donors provides a new and powerful method for chemical glycosylations, where a glycosyl sulfoxide (also called sulfinil glycosides) reacts with a glycosyl acceptor in the presence of a promoter, to give a di- tri- or oligosaccharide.



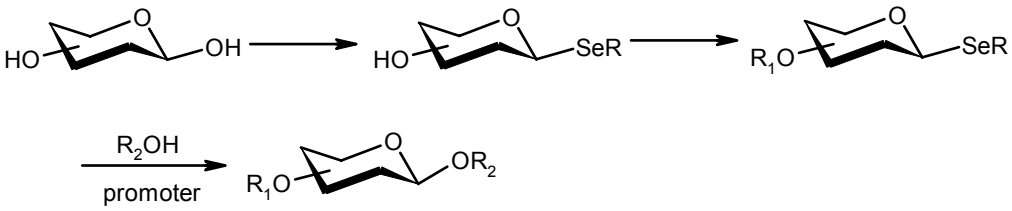
promoter: Tf_2O, TMSOTf, TfOH
acid Acavenger: DTBMP

Scheme-21

The promoter systems for these sulfinil glycosides are triflic anhydride (Tf_2O) or trimethylsilyl triflates in stoichiometric amount or triflic acid in catalytic amount. The reaction is always carried out in the presence of an acid scavenger (di*terc*-butyl methyl pyridine).

Phenylseleno glycosides[25]

Anomeric phenylselenides are interesting glycosyl donors. The phenylseleno substituent behaves largely like thioglycosides with respect to stability towards protecting group manipulations and lability towards electrophilic reagents. Phenylseleno glycosides are more reactive than thioglycosides allowing chemoselective glycosylations.



Scheme-22

PRESENT WORK

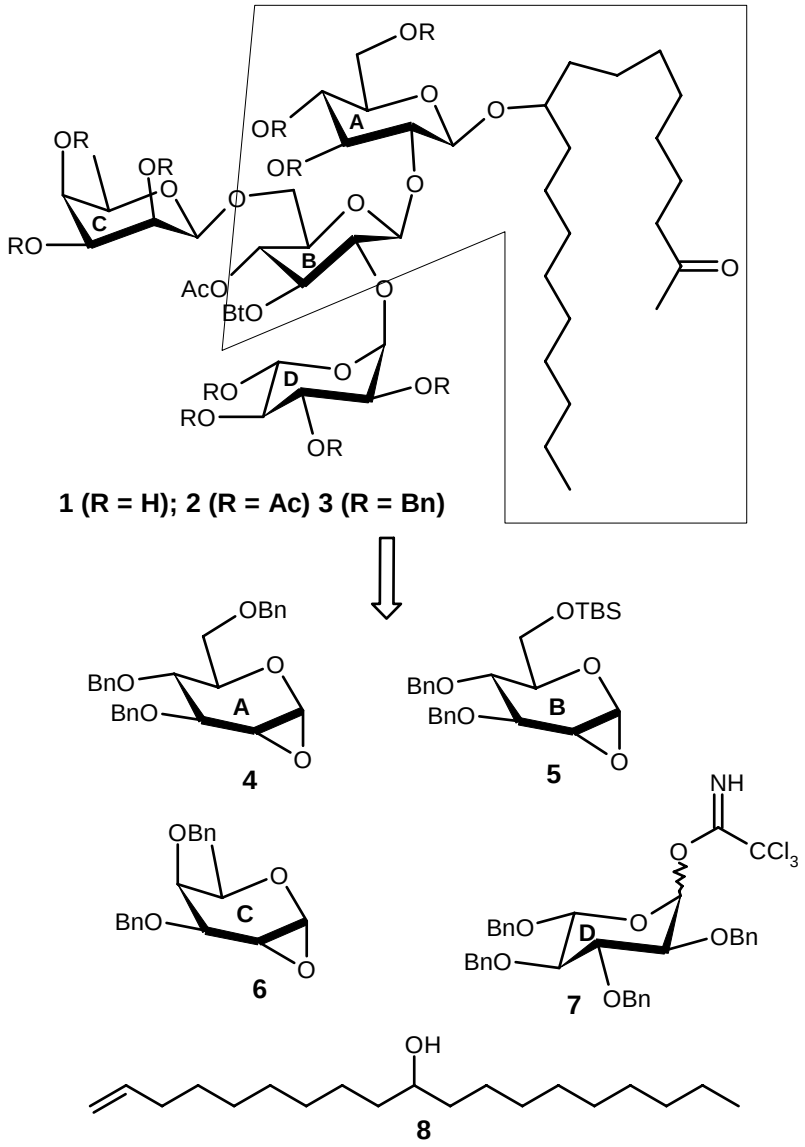
Present Work

Enteropathogenic *Escherichia coli* (EPEC) and enterohemorragic *E. coli* 0157:H7 (EHEC) are pathogens that are deadly to children and the elderly. Infection by these pathogenic *E. coli* requires the bacterial secreted protein (Esps) and a type III secretory apparatus, which translocates secreted proteins across bacterial membranes, out of EPEC and EHEC, into the host epithelial cells. Remarkably, the type III secretory system, which is essential for the pathogenicity of EPEC and EHEC, is absent in nonpathogenic *E. coli.* Thus, selective inhibition of the type III secretory system might specifically attenuate pathogenic EPEC and EHEC without affecting the commensal *E. coli* flora. Recently, a high throughput assay for inhibitors of the type III secretion of EPEC was developed. Activity-guided isolation of marine invertebrate extracts led to the discovery of caminoside A from the marine sponge *Caminus sphaeroconia*.[6,26] This type III secretion inhibitor (IC 50 = 20 μm) also displayed reasonably potent in vitro inhibition against the growth of methicillin resistant *Staphylococcus aureus* (MIC=12 μg/mL) and vancomycin resistant *Enterococcus* (MIC = 12 μg/mL).

Caminoside A is an unusual marine glycolipid with a non-glycerol aglycone (the C19 hydroxy ketone, **9**) that is gylcosylated at the C_{10}-OH group by a tetrasaccharide consisting of D-deoxytalose, two D-glucose units, and L-quinovose that are linked through 1, 2 and 1, 6-*O*-glycosidic bonds. The glucose residue in the middle is fully substituted. The configuration of the secondary C_{10}-OH of aglycone moiety could not be assigned at the time of synthesis.

We planned removal of the benzyl protective group (**3**) as the final step in the elaboration of the target molecule Caminoside A (**1**). In assembling **3**, stereocontrolled construction of the four glycosidic linkages is of paramount importance. Formation of 1, 2-*trans*-β-glucopyranoside linkages (of sugar **A** and **B**, sugar **A** and aglycone moiety **8**) would be ensured by glycosylation with donors i.e., 1, 2-anhydro-substrates **5** and **4** respectively. Glycosylation with the L-glucopyranose donor **7**, which bears a non-participating 2-*O*-Bn group, would produce the desired thermodynamically favored 1, 2-*cis*-α-quinovopyranoside linkage (sugar **D**) predominantly. Construction of the 6-deoxy-talose (sugar **C**) is not an insignificant problem; an indirect approach was planned:

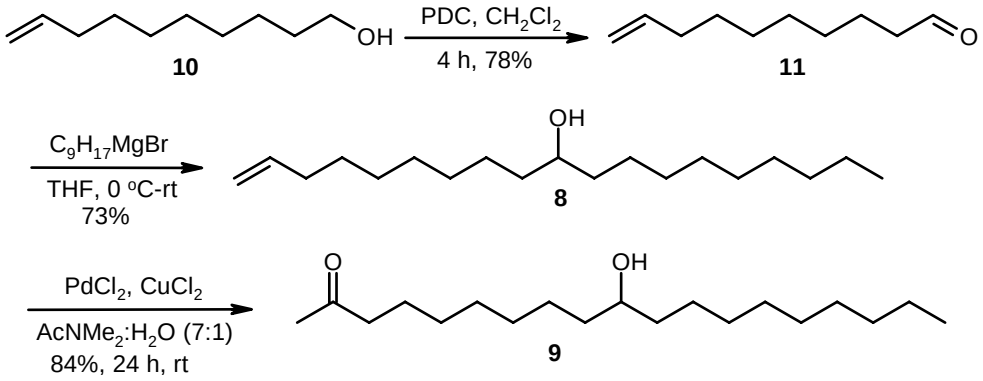
Glycosylation with 1, 2-anhydro substrate **6** to afford the β-glycosidic linkage stereoselectively with a 2-OH group, followed by an inversion of the 2-OH configuration would furnish the desired 6-deoxy-1, 2-*cis*-β-talopyranosidic linkage (Scheme-1).



Scheme-1: Caminoside A; retrosynthesis

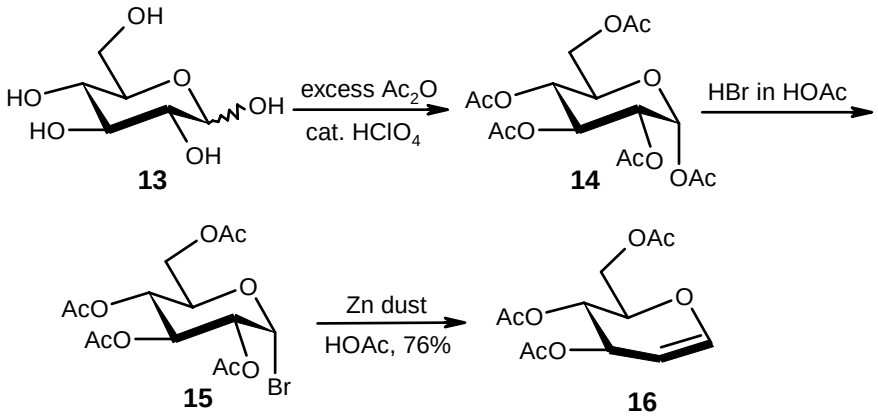
The aglycone moiety (**9)** was prepared by oxidation of 9-decene 1-ol (**10)** with PDC in CH_2Cl_2 to afford aldehyde (**11)** in 78% yield, which was subsequently subjected to reaction with Grignard reagent (nonanylmagnesiumbromide, **12**) to give **8** in 73% yield.[27] The structure was unambiguously assigned by NMR data. The proton NMR spectrum clearly showed the methine (hydroxyl attached to C_{10}) as a multiplet at δ 3.58 ppm and other relevant peaks at appropriate positions. The IR spectrum showed a broad band at

3345 cm^{-1} and in the structure assignment was additionally confirmed by the elemental analysis data. Then, **8** was subjected to Wacker oxidation[28] to give the aglycone moiety **9** (methyl ketone) in 84% yield. The proton spectrum illustrated the disappearance of olefin between the region of δ 4.91-5.79 ppm and new resonances due to methyl ketone as a singlet at δ 2.13 ppm. The corresponding ^{13}C NMR spectrum was appropriate. Further support for the structure was provided by the appearance of a IR absorption band at 1709 cm^{-1} for the C=O (scheme-2).



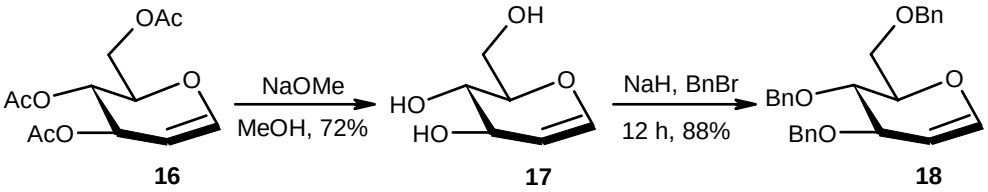
Scheme-2

Preparations of the designed monosaccharide building blocks (**4** and **5**) were straightforward. Monosaccharide (**20)** was conveniently synthesized from **16.** Tri-*O*-acetyl-D-glucal (**16**) was prepared by standard procedure[29] by the reaction of penta-*O*-acetyl-D-glucopyranose (**14**) with HBr in HOAc to give the tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**15**) that was subsequently reduced with Zn dust in acetic acid to afford **16** in 76% yield. The NMR spectrum of **16** and elemental analysis data were in good agreement with those of reported values (scheme-3).



Scheme-3

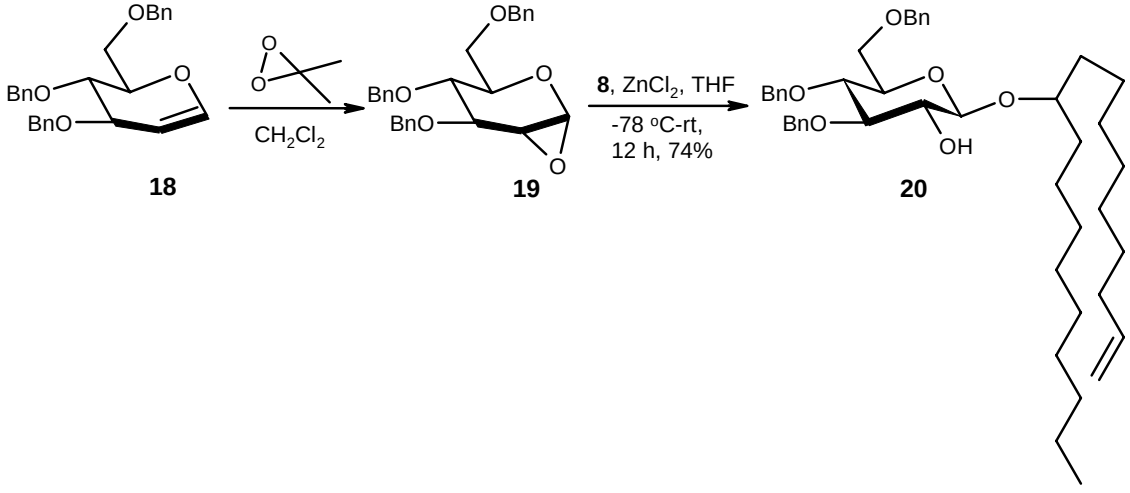
Tri-*O*-acetyl-D-glucal (**16**) was converted to D-glucal[29d] (**17**) in 72% yield under Zemplen catalytic deacetylation conditions by treatment with sodium methoxide in methanol. Compound **17** was subjected to benzylation using excess of both sodium hydride and benzyl bromide in dry DMF (at 0 ^{o}C to room temperature for 12 h) to afford **18** in 88% yield (scheme-4).



16 **17** **18**

Scheme-4

Next, we attempted to construct the selectively β-configured glycoside **20**. This was achieved by the epoxidation of tri-*O*-benzyl-D-glucal (**18)** via reaction of DMDO[30] (dimethyldioxirane), generated *in situ,* in DCM to obtain the glycosyl donor **19** followed by oxirane ring opening with aglycone moiety (**8)** in the presence of anhydrous $ZnCl_2$ at -78 ^{o}C to provide the desired β-glucoside (**20)** in 74% yield[31] (scheme-5). The proton NMR spectrum of **20** showed the resonances of anomeric proton at δ 4.27 ppm, (d, J = 7.53 Hz), correspondingly the ^{13}C NMR spectrum revealed the anomeric carbon at δ 100.75 ppm indicating the β-configured glucoside.

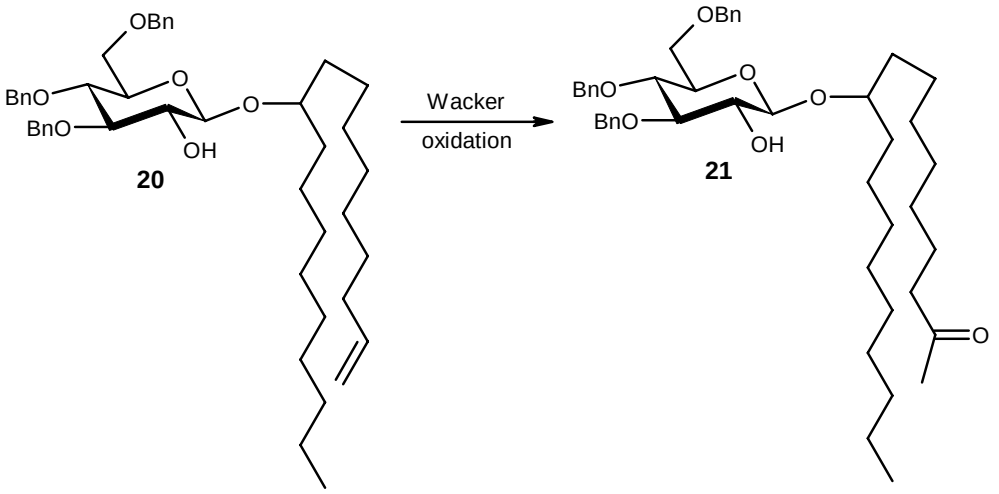


18 **19** **20**

Scheme-5

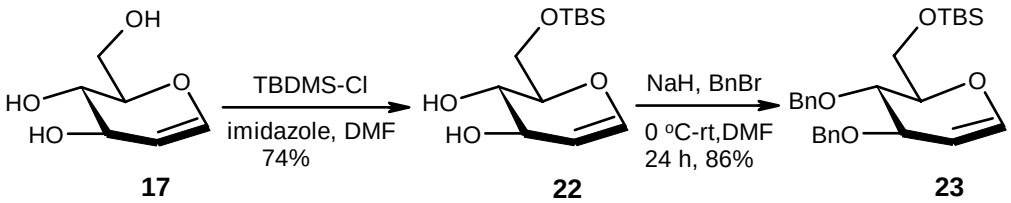
The glycolipid **20** was subjected to Wacker oxidation protocol, using 10 mol% $PdCl_2$, 2 equiv CuCl, and O_2 in $AcNMe_2$: H_2O (7:1) to afford methyl ketone **21** in 84% yield. The glycolipid **21** can serve as a glycosyl acceptor in disaccharide synthesis. The

proton NMR spectrum showed new resonances at δ 2.07 ppm for a singlet due to a methyl ketone (scheme-6).



Scheme-6

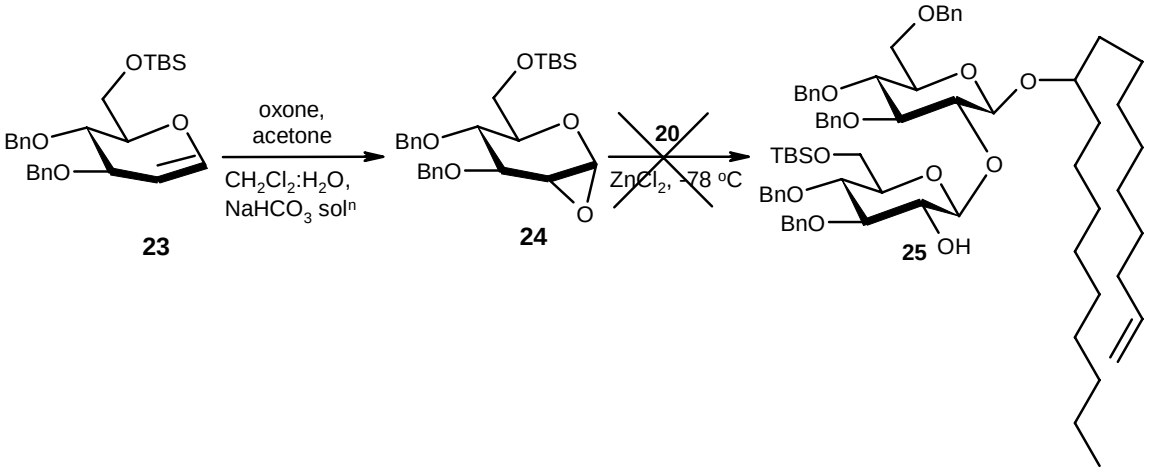
The next challenge is to synthesize the glycosyl donor for the disaccharide unit. D-glucal (**17**) had been used as a common precursor to construct the both the saccharide units (mono and disachharide). By the use of classical Hanessian silylation protocol, **17** was selectively protected at its primary C_6-OH group with TBDMS-Cl to obtain silyl ether **22** in 74% yield.[32] The silyl ether **22** was assigned by NMR spectrum and elemental analysis data. The C(6)-*O*-silylated-D-glucal was benzylated[33] to give the 6-*O*-silylated-3,4-di-O-benzyl-substrate **23** using NaH, anhydrous THF, BnBr, and catalytic nBu_4NI at 0 ^oC-rt, 24 h in 86% yield. The proton NMR spectrum showed peaks between δ 7.20-7.30 ppm as multiplets due to resonances of benzyl group: silyl ether peaks were at δ 0.02 ppm (s, 6H) and δ 0.85 ppm (s, 9H) and structure was further confirmed by elemental analysis data (scheme-7).



Scheme-7

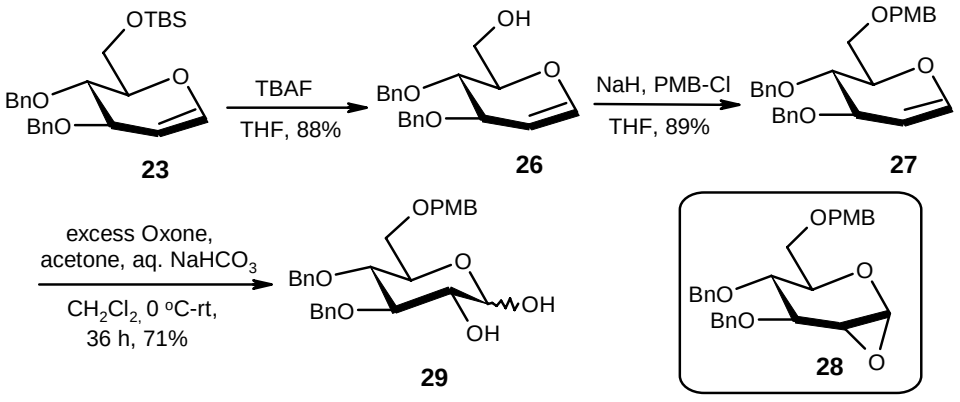
We now wanted to achieve the disaccharide glycosylation with the uniquely installed C_2-hydroxyl on the benzyl glucose moiety **20**. Again, we hoped to use glycal

epoxide methodology. Glucal derivative **23** was treated with 3, 3-dimethyldioxirane, to furnish the 1, 2-anhydro derivative **24**. However, all attempts to glycosylate **20** using **24** as the donor in the presence of anhydrous zinc chloride at -78 ^{o}C failed to provide the desired disaccharide.[34] A variety of attempts to bring about such glycosylation led to destruction of the glycosyl donor and recovery of the acceptor (scheme-8).



Scheme-8

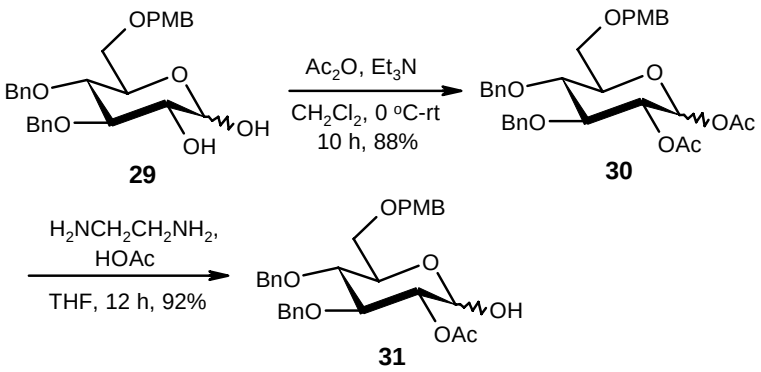
We then investigated whether trichloroacetimidate donor would succeed where the oxirane had apparently failed. Accordingly, compound **23** was subjected to the action of TBAF to afford **26** and followed by protection with PMB ether gave **27** in 89% yield. Here we substituted the silyl ether with the PMB ether since silyl group could be easily deprotected during the construction of disaccharide unit in presence of Lewis acid (e.g., $BF_3.Et_2O$) reaction conditions. Subsequently, compound **27** was subjected to epoxidation by DMDO, generated *in situ,* with excess of Oxone, acetone and $NaHCO_3$ solution



Scheme-9

in CH_2Cl_2: H_2O (1:1), for 36 h at room temperature to provide anomeric mixture of α: β diol **29** in 71% yield. Here we predicted 1, 2-anhydro derivative **28** but excess reagent and stirring for extended time, cleaved the oxirane ring and delivered the diol **29** (Scheme-9).

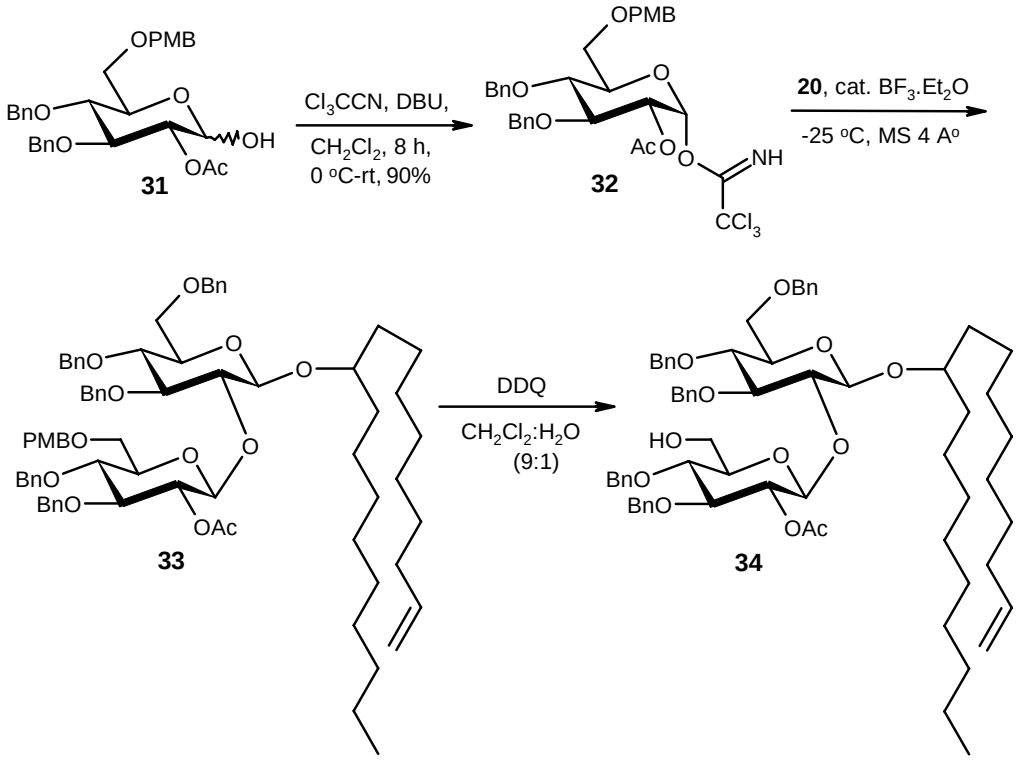
The diol substrate **29** was acetylated using Ac_2O and Et_3N in CH_2Cl_2 to furnish diacetate **30** in 88% yield. Our choice of this protecting group for C_2 was made in order to foster β-selectivity through neighboring group participation during disaccharide formation. Next, anomeric acetyl group was selectively deprotected using ethylenediamine and acetic acid in anhydrous THF to afford **31** in 92% yields.[35] NMR, IR spectrum and elemental analysis confirmed the structure of **31**. No attempt was made to separate the α: β mixture of **31** (Scheme-10).



Scheme-10

Lactol **31** was readily converted to the corresponding trichloroacetimidate by treatment with trichloroacetonitrile and DBU in CH_2Cl_2 for 8 h at 0 ^oC to room temperature to generate the desired glycosyl donor **32** as the only product. The glycosyl donor **32** was reacted readily and stereoselectively with glycosyl acceptor (**20**) in the presence of catalytic amount of $BF_3.Et_2O$ (-25 ^oC, MS 4 ^oA) in CH_2Cl_2 to provide the desired β-configurated disaccharide[36] **33** in 71% yield. The proton NMR spectrum of **33** revealed resonances corresponding to anomeric protons at δ 4.36 ppm (d, J = 7.58 Hz) and δ 5.40 ppm (d, J = 7.58 Hz): the ^{13}C NMR spectrum showed resonances of the anomeric carbons at δ 102.42 ppm and δ 97.72 ppm respectively. There by confirming the β-configuration of the disaccharide (Scheme-11). To synthesize the trisaccharide, the disaccharide **33** was treated with DDQ to selectively remove the PMB ether group to

provide **34** in 78% yield. This compound would perform as glycosyl acceptor for the synthesis of trisaccharide.

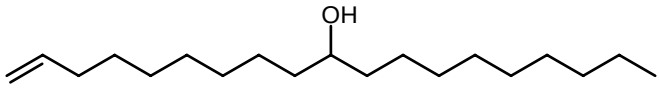


Scheme-11

In summary, we have synthesized the disaccharide unit of Caminoside A. Glycal and Schmidt (trichloroacetimidate) methods were employed in the stereospecific construction of β-linked saccharide. Glycosyl donors (**19** and **32**) were prepared from D-glucal.

EXPERIMENTAL SECTION

Nonadec-1-en-10-ol (8)



To a solution of **10** (1.56 g, 10.0 mmol) and PDC (5.64 g, 15.0 mmol) in dry CH_2Cl_2, under argon atmosphere was stirred for 6 h at room temperature. The reaction mixture was filtered through a pad of celite and concentrated in vacuo. The crude residue was subsequently treated with nonylmagnesiumbromide **12** (4.6 g in 1M THF, 20.0 mmol) in anhydrous THF at 0 ^oC and stirred for 2 h at same temperature (monitored by TLC). Quenched the reaction mixture with saturated solution of NH_4Cl, separated the layers, organic phase dried over Na_2SO_4 and concentrated in vacuo. The residue was purified on silica gel (eluted in 5% EtOAc-light petroleum ether) to provide **8** as a colorless solid.

Yield : 2.06 g, 73%

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

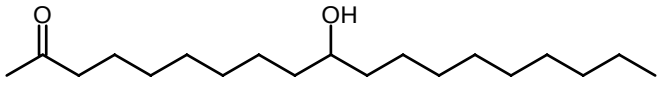
IR ($CHCl_3$) cm^{-1} : 3345, 2917, 2850, 1466, 1255, 1132, 911, 758.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.89 (t, 3H, *J* = 6.7 Hz), 1.28-1.32 (m, 20H), 1.38-1.42 (m, 8H), 1.99-2.09 (m, 2H), 3.58 (m, 1H), 4.91-5.03 (m, 2H), 5.79 (m, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 14.1, 22.7, 25.7, 28.9, 29.1, 29.3, 29.5, 29.6, 29.7, 29.8, 31.9, 33.8, 37.5, 71.76, 114.2, 138.9.

Elemental Analysis : **Calcd.:** C, 80.78; H, 13.56; **Found:** C, 80.54, H, 13.24.

10-Hydroxynonadecan-2-one (9)



A suspension of **8** (1.41 g, 5.0 mmol), $PdCl_2$ (0.089 g, 0.5 mmol) and CuCl (0.99 g, 10.0 mmol) in $AcNMe_2/H_2O$ (7:1, 15 mL) were placed under oxygen (1 atm) and stirred for 24 h at room temperature. The reaction mixture was diluted with ether (10 mL),

filtered through a pad of celite employing ether (3 x 10 mL) to wash the filter cake, poured into water (20 mL), and extracted with ether (3 x 10 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purified the residue by silica gel column chromatography (eluted in 20% EtOAc-light petroleum ether) to afford **9** as a colorless solid.

Yield : 1.25 g, 84%

Mol. Formula : $C_{19}H_{38}O_2$

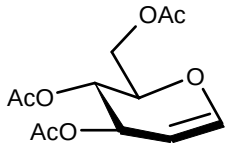
IR ($CHCl_3$) cm^{-1} : 3301, 2917, 2849, 1709, 1467, 1130, 757.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.88 (t, 3H, *J* = 6.7 Hz), 1.25-1.33 (m, 20H), 1.37-1.44 (m, 6H), 1.53-1.60 (m, 2H), 2.13 (s, 3H), 2.42 (t, 2H, *J* = 7.4 Hz), 3.57 (m, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 14.0, 22.56, 23.66, 25.47, 25.58, 29.0, 29.25, 29.4, 29.5, 29.6, 31.8, 37.3, 37.4, 43.6, 71.63, 208.8.

Elemental Analysis : **Calcd.:** C, 76.45, H, 12.83; **Found:** C, 76.22; H, 12.44.

Tri-*O*-acetyl-D-glucal (16)



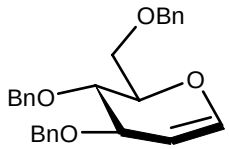
Mol. Formula : $C_{12}H_{16}O_7$

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.03 (3 x s, 9H), 4.12-4.26 (m, 2H), 4.35 (m, 1H), 4.80 (dd, 1H, *J* = 3.15, 6.18 Hz), 5.15 (dd, 1H, J = 5.81, 7.45 Hz), 5.30 (m, 1H), 6.42 (dd, 1H, *J* = 1.25, 6.19 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 20.23, 20.33, 20.51, 61.01, 66.96, 67.11, 73.70, 98.73, 145.33, 168.99, 169.75, 169.90.

Elemental Analysis : **Calcd.:** C, 52.94, H, 5.92; **Found:** C, 52.50; H, 5.75.

Tri-*O*-benzyl-D-glucal (18)



Tri-*O*-acetyl–D-glucal (12.0 g, 44.0 mmol) and sodium (0.102 g, 4.4 mmol) in dry methanol (150 mL) was stirred for 24 h at room temperature and quenched with dry ice (solid CO_2). The residue was extracted with hot ethyl acetate (3 x 75 mL), combined the extract and concentrated in vacuo to afford a crystalline D-glucal (4.64 g, 72% yield).

To a suspension of **17** (4.64 g, 31.7 mmol) and NaH (4.20 g, 60% dispersion in oil, 104.5 mmol) in dry DMF (75 mL) under argon atmosphere at 0 ^oC was added benzyl bromide (13.2 mL, 110.9 mmol) and stirred for 3 h at room temperature. The reaction was quenched with ice-cold water and extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with water, dried over Na_2SO_4 and evaporated. The crude residue was purified by silica gel column chromatography (eluted in 5% EtOAc-light petroleum ether) to afford **18** as a light yellowish solid.

Yield : 11.62 g, 88%

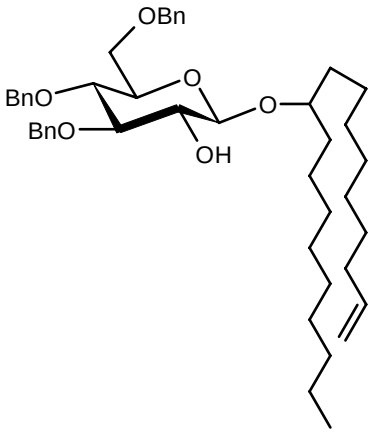
Mol. Formula : $C_{27}H_{28}O_4$

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.72-3.82 (m, 2H), 3.83 (dd, 1H, *J* = 6.2, 8.7 Hz), 4.02-4.10 (m, 1H),4.21 (m,, 1H), 4.53-4.59 (m, 3H), 4.63 (d, 2H, *J* = 11.12 Hz), 4.82-4.90 (m, 2H), 6.41 (dd, 1H, *J* = 1.26, 6.06 Hz), 7.25-7.36 (m, 15H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 68.37, 70.30, 73.37, 73.63, 74.25, 75.70, 76.66, 99.85, 127.53, 127.60, 27.65, 127.78, 128.27, 137.89, 138.13, 138.26, 144.60.

Elemental Analysis : **Calcd.:** C, 77.86, H, 6.78; **Found:** C, 77.52; H, 6.70.

1-(nonadec-1-en-10-yloxy)-3,4,6-tri-*O*-benzyl-β-D-glucopyranoside (20)



To a vigorously stirred, cooled (ice bath) biphasic solution of **18** (1.0 g, 2.40 mmol) in CH_2Cl_2: H_2O (1:1, 40 mL), acetone (1.5 mL) and saturated aq $NaHCO_3$ (1.00 g, 11.90 mmol). A solution of Oxone (2.9 g, 4.8 mmol) in H_2O (10 mL) was added drop wise over 15 min. The mixture was vigorously stirred at 0 ^oC for 2 h at room temperature and separated the aqueous layer and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phase were dried over Na_2SO_4 and concentrated to afford epoxide **19** (0.475 g, 78% yield).

To a solution of crude epoxide **19** (0.475 g, 1.1 mmol) and alcohol **8** (0.310 g, 1.1 mmol) in anhydrous THF was added anhydrous $ZnCl_2$ (0.15 g, 1M solution in THF) at -78 ^oC and stirred at room temperature for 12 h. The reaction mixture was quenched with water, extracted with CH_2Cl_2 (3 x 25 mL), combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluted in 5% EtOAc-light petroleum ether) to afford β-configured monosaccharide **20** as a light yellowish solid.

Yield : 0.582 g, 74%

Mol. Formula : $C_{46}H_{66}O_6$

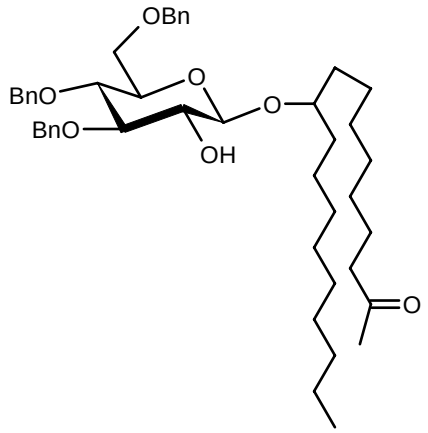
IR ($CHCl_3$) cm^{-1} : 3468, 3064, 3030, 2917, 1454, 1112, 910, 755, 698.

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 0.87 (t, 3H, *J* = 6.78 Hz), 1.24-1.40 (m, 24H), 1.48-1.58 (m, 4H), 1.98-2.06 (m, 2H), 2.30 (br s, 1H), 3.45-3.55 (m, 2H), 3.58-3.65 (m, 3H), 3.68-3.72 (m, 2H), 4.27 (d, 1H, *J* = 7.53 Hz), 4.53 (d, 1H, *J* = 9.03 Hz), 4.56 (d, 1H, *J* = 7.53 Hz), 4.60 (d, 1H, *J* = 12.05 Hz), 4.81 (d, 1H, *J* = 5.52 Hz), 4.84 (d, 1H, *J* = 5.02 Hz), 4.90-5.00 (m, 3H), 5.80 (m, 1H), 7.19-7.38 (m, 15H).

^{13}C NMR ($CDCl_3$, 100 MHz) : δ 14.09, 20.90, 22.65, 24.98, 25.29, 28.89, 29.29, 29.34, 29.48, 29.66, 31.87, 33.78, 34.13, 34.87, 69.01, 73.49, 73.61, 74.91, 75.10, 78.13, 80.73, 83.15, 100.75, 114.16, 127.55, 127.63, 127.79, 128.01, 128.37, 137.96, 138.26, 139.06, 139.15, 169.28.

Elemental Analysis : **Calcd.:** C, 77.27, H, 9.30; **Found:** C, 77.02; H, 9.24

1-(nonadec-2-one-10-yloxy)-3,4,6-tri-*O*-benzyl-β-D-glucopyranoside (21)



A suspension of **20** (0.50 g, 0.69 mmol), $PdCl_2$ (0.013 g, 0.073 mmol) and CuCl (0.138 g, 1.39 mmol) in $AcNMe_2/H_2O$ (7:1, 10 mL) was placed under oxygen (1 atm) and stirred for 24 h at room temperature. The reaction mixture was diluted with ether (10 mL), filtered through celite employing ether (3 x 10 mL) to wash the filter cake, poured into water (20 mL), and extracted with ether (3 x 10 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purified the residue by silica gel column chromatography (eluted in 20% EtOAc-light petroleum ether) to afford **21**.

Yield **:** 0.43 g, 84%

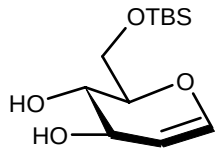
Mol. Formula **:** $C_{46}H_{66}O_7$

IR ($CHCl_3$) cm^{-1} **:** 3468, 3064, 3030, 2917, 1709, 1454, 1112, 910, 755, 698;

^{1}H NMR ($CDCl_3$, 200 MHz) **:** δ 0.84 (t, 3H, *J* = 6.78 Hz), 1.20-1.34 (m, 22H), 1.48-1.54 (m, 6H), 2.07 (s, 3H), 2.28-2.40 (m, 2H), 3.38-3.66 (m, 7H), 4.22 (d, 1H, *J* = 6.82 Hz), 4.48-4.62 (m, 3H), 4.75 (d, 1H, *J* = 4.68 Hz), 4.81 (d, 1H, *J* = 4.30 Hz), 4.90 (d, 1H, *J* = 11.36 Hz), 7.12-7.36 (m, 15H).

Elemental Analysis **:** **Calcd.:** C, 75.58, H, 9.10; **Found:** C, 75.50; H, 9.02.

6-*O*-*(tert*-Butyldimethylsilyl)-D-glucal (22)



To a solution of **17** (2.92 g, 20.0 mmol) in dry DMF (45 mL), imidazole (2.73 g, 40.0 mmol) and TBS-Cl (3.31 g, 22.0 mmol) were added at 10 ^{o}C under nitrogen atmosphere. The reaction was stirred for overnight (12 h) at room temperature, poured into water and extracted with ether (3 x 50 mL). The combined organic layer was washed with water, dried over Na_2SO_4, filtered and evaporated. The crude residue was purified by silica gel column chromatography (eluted in 50% EtOAc-light petroleum ether) to give **22** as a colorless liquid.

Yield : 3.85 g, 74%

Mol. Formula : $C_{12}H_{24}O_4Si$

$[\alpha]_D^{25}$: + 20.0 (*c* 1.0, $CHCl_3$).

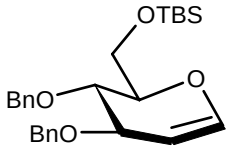
IR ($CHCl_3$) cm^{-1} : 3389, 1651, 1253, 837.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.11 (s, 6H), 0.91 (s, 9H), 3.35 (br s, 1H), 3.77-4.02 (m, 4H), 4.25 (m, 1H), 4.70 (dd, 1H, *J* = 2.4, 6.2 Hz), 6.29 (dd, 1H, *J* = 1.77, 6.06 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ -5.26, 18.35, 25.89, 63.05, 69.48, 70.59, 77.60, 102.58, 144.0.

Elemental Analysis : **Calcd.:** C, 55.35, H, 9.29, Si, 10.79; **Found:** C, 55.18; H, 9.05.

3,4-Di-*O*-Benzyl-6-*O*-(*tert*-butyldimethylsilyl)-D-glucal (23)



To a solution of **22** (3.5 g, 13.4 mmol) in Dry DMF was added NaH (1.18 g, 60% dispersion in oil, 29.5 mmol) at 0 ^{o}C under nitrogen. After 30 min added *n*-Bu_4NI (catalytic) and benzyl bromide (4.0 mL, 33.5 mmol) and stirred for 12 h at room temperature. The reaction was quenched with ice-cold water and extracted with ether (3 x 50 mL). The combined organic layer was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. The crude was purified by silica gel column chromatography (eluted in 15% EtOAc: light petroleum ether) to give **23** as a colorless liquid.

Yield : 5.08 g, 86%

Mol. Formula : $C_{26}H_{36}O_4Si$

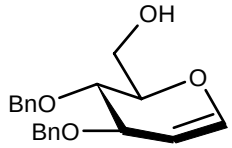
IR ($CHCl_3$) cm^{-1} : 1650, 1232, 1106, 753, 710.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.02 (s, 6H), 0.85 (s, 9H), 3.80-3.94 (m, 4H), 4.15 (m, 1H), 4.48 (d, 1H, *J* = 11.75 Hz), 4.57 (d, 1H, *J* = 11.75 Hz), 4.65 (d, 1H, *J* = 11.25 Hz), 4.75 (dd, 1H, *J* = 2.53, 6.06 Hz), 4.78 (d, 1H, *J* = 11.25 Hz), 6.30 (dd, 1H, *J* = 1.52, 6.32 Hz), 7.20-7.30 (m, 10H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ -5.34, -5.13, 18.35, 25.94, 61.66, 70.59, 73.88, 74.17, 75.88, 78.03, 99.77, 127.55, 127.63, 127.69, 127.87, 128.33, 138.39, 138.44, 144.66.

Elemental Analysis : **Calcd.:** C, 70.87, H, 8.23, Si, 6.37; **Found:** C, 70.45; H, 8.05.

3,4-Di-*O*-benzyl-D-glucal (26)



To a solution of **23** (2.0 g, 4.5 mmol) and TBAF (5.4 mL, 1M solution in THF) in anhydrous THF (20 mL) was stirred for 2 h at room temperature. Evaporated the THF under reduced pressure. The residue was purified by silica gel column chromatography (eluted in 25% EtOAc-light petroleum ether) to afford **26**.

Yield : 1.3 g, 88%

Mol. Formula : $C_{20}H_{22}O_4$

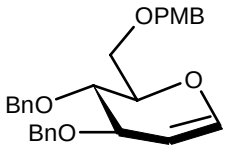
IR ($CHCl_3$) cm^{-1} : 3440, 1648, 1237, 1099, 753, 698.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.09 (br s, 1H), 3.75 (dd, 2H, *J* = 6.06, 8.59 Hz), 3.85 (m, 2H), 4.20 (m, 1H), 4.52 (d, 1H, *J* = 11.75 Hz), 4.61-4.83 (m, 3H), 4.85 (dd, 1H, *J* = 2.66, 6.32 Hz), 6.37 (d, 1H, *J* = 6.06 Hz), 7.23-7.35 (m, 10H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 61.46, 70.41, 73.59, 74.38, 75.44, 77.28, 100.02, 127.61, 127.61, 127.85, 128.32, 137.91, 138.02, 144.40.

Elemental Analysis : **Calcd.:** C, 73.60, H, 6.79; **Found:** C, 73.48; H, 6.64

3,4-Di-*O*-Benzyl-6-*O*-(*p*-methoxybenzyl)-D-glucal (27)



To a suspension of **26** (1.2 g, 3.68 mmol) and NaH (0.191 g, 60% dispersion in oil, 4.78 mmol) in anhydrous THF at 0 ^{o}C was added PMB-Cl (0.878 g, 5.52 mmol). Stirred for 3 h at room temperature, quenched the reaction mixture with ice-cold water and extracted with ethyl acetate (2 x 30 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Purified the residue on silica gel (eluted in 5% EtOAc-light petroleum ether) to afford **27** as a light yellowish liquid.

Yield : 1.46 g, 89%

Mol. Formula : $C_{28}H_{30}O_5$

$[\alpha]_D^{25}$: +10.0 (*c* 1.0, $CHCl_3$)

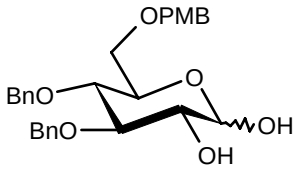
IR ($CHCl_3$) cm^{-1} : 1648, 1454, 1248, 1036, 821, 737, 698.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.70-3.85 (m, 6H), 4.00 (m, 1H), 4.16 (m, 1H), 4.41 (d, 1H, *J* = 11.75 Hz), 4.49-4.55 (m, 2H), 4.56-4.65 (m, 2H), 4.77-4.86 (m, 2H), 6.37 (d, 1H, *J* = 6.06 Hz), 6.79-6.89 (m, 2H), 7.18-7.31 (m, 12H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 55.33, 68.30, 70.59, 73.3, 73.92, 74.63, 76.06, 77.95, 100.17, 113.96, 127.80, 127.87, 128.05, 128.53, 129.64, 130.25, 138.48, 138.61, 144.92, 159.44.

Elemental Analysis : **Calcd.:** C, 75.31, H, 6.77; **Found:** C, 75.08; H, 6.54.

3,4,-Di-*O*-benzyl-6-*O*-(p-methoxybenzyl)-α-β-D-glucopyranose (29)



To a vigorously stirred, cooled (ice bath) biphasic solution of **27** (1.2 g, 2.69 mmol) in CH_2Cl_2: H_2O (1:1, 40 mL), acetone (1.5 mL) and saturated solution of $NaHCO_3$ (1.13 g, 13.45 mmol). A solution of Oxone (3.3 g, 5.38 mmol) in H_2O was added drop wise

over 15 min. The mixture was vigorously stirred at 0 ^{o}C for 36 h at room temperature and separated the aqueous layer and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (eluted in 55% EtOAc-light petroleum ether) to afford diol **29** as a colorless solid.

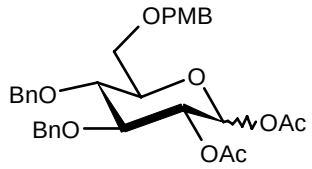
Yield : 0.918 g, 71%

Mol. Formula : $C_{28}H_{32}O_7$

IR ($CHCl_3$) cm^{-1} : 3400, 1248, 1056, 820, 752, 698.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.81 (br s, 2H), 3.44-3.53 (m, 2H), 3.56-3.66 (m, 3H), 3.73-3.82 (m, 2H), 3.90-4.06 (m, 1H), 4.11 (d, 0.2H, *J* = 7.20 Hz) 4.38-4.50 (m, 3H), 4.52 (m, 0.4H), 4.76-4.88 (m, 3H), 4.91 (d, 0.15H, *J* = 4.7 Hz), 5.21 (d, 0.8H, *J* = 3.54 Hz), 6.80-6.86 (m, 2H), 7.10-7.36 (m, 14H).

1,2-di-*O*-acetyl-3,4,-di-*O*-benzyl-6-*O*-(*p*-methoxybenzyl)-α-β-D-glucopyranose (30)



To a solution of **29** (0.800 g, 1.66 mmol) in dry CH_2Cl_2 (20 mL) was added triethylamine (0.420 g, 4.16 mmol), DMAP (catalytic) and acetic anhydride (0.390 g, 3.82 mmol) under nitrogen. Stirred for 12 h, quenched the reaction mass with water and extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (eluted in 15% EtOAc-light petroleum ether) to afford **30**.

Yield : 0.825 g, 88%

Mol. Formula : $C_{32}H_{36}O_9$

IR ($CHCl_3$) cm^{-1} : 1741, 1246, 1039, 820, 751, 698.

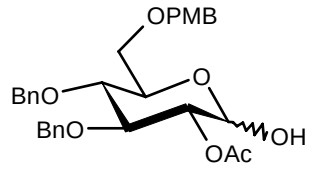
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.94 (s, 0.6H), 1.97 (s, 2.4H), 2.10 (s, 0.6H), 2.12 (s, 2.4H), 3.60 (dd, 1H, *J* = 1.8, 11.0 Hz), 3.70-3.82 (m, 5H), 3.84-4.02 (m, 2H), 4.08 (dd, 1H, *J* = 7.2, 14.3 Hz), 4.40 (dd, 1H, *J* = 4.0,

11.9 Hz), 4.48 (d, 1H, *J* = 10.6 Hz), 4.56 (dd, 1H, *J* = 2.3, 11.75 Hz), 4.68-4.87 (m, 3H), 5.02 (dd, 0.8H, *J* = 3.6, 9.85 Hz), 5.11 (d, 0.15H, *J* = 8.96 Hz), 5.58 (d, 0.15H, *J* = 8.21 Hz), 6.30 (d, 0.75H, *J* = 3.54 Hz), 6.83-6.88 (m, 2H), 7.11-7.16 (m, 2H), 7.24-7.32 (m, 10H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 20.55, 20.65, 20.80, 20.85, 55.05, 67.43, 71.78, 72.00, 73.09, 73.60, 74.90, 75.03, 75.20, 75.26, 75.67, 77.19, 79.81, 82.66, 89.86, 92.14, 113.66, 113.73, 127.41, 127.62, 127.79, 127.84, 127.90, 128.03, 128.25, 128.32, 129.14, 129.55, 129.73, 137.79, 137.79, 137.96, 138.10, 138.29, 159.16, 159.29, 168.83, 169.18, 169.61, 169.89.

Elemental Analysis : **Calcd.:** C, 68.07, H, 6.43; **Found:** C, 67.92; H, 6.35.

2-*O*-acetyl-3,4,-di-*O*-benzyl-6-*O*-(*p*-methoxybenzyl)-α-β-D-glucopyranose (31)



To a solution of **30** (0.80 g, 1.41 mmol) in anhydrous THF was treated with glacial acetic acid (0.102 g, 1.70 mmol) and ethylenediamine (0.102 g, 1.70 mmol) at 0 ^{o}C under nitrogen atmosphere. Stirred for 12 h at room temperature, the reaction was quenched with 2M HCL and extracted with chloroform (3 x 30 mL). The combined organic layer was washed with saturated $NaHCO_3$, water, brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified on silica gel (eluted in 25% EtOAc-light petroleum ether) to afford **31** as a light yellowish solid.

Yield : 0.681 g, 92%

Mol. Formula : $C_{30}H_{34}O_8$

IR ($CHCl_3$) cm^{-1} : 3378, 1741, 1246, 1039, 820, 751, 698

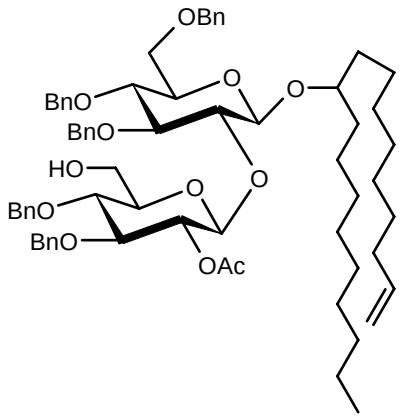
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.00 (s, 2.2H), 2.13 (s, 0.8H), 3.38-3.65 (m, 3.4H), 3.73 (s, 3H), 3.90-4.25 (m, 2.3H), 4.30-4.55 (m, 3.75H), 4.60-4.90 (m, 3.8H), 5.14 (m, 0.25H), 5.34 (br s, 0.75H, *J* = 3.4 Hz), 6.79-

6.83 (m, 2H), 7.12-7.27 (m, 12H).

^{13}C NMR ($CDCl_3$, 50 MHz) **:** δ 20.78, 21.00, 55.00, 67.87, 68.18, 69.12, 69.88, 70.70, 72.82, 73.66, 74.87, 75.28, 78.09, 79.79, 82.56, 90.17, 92.23, 113.69, 127.47, 127.59, 127.73, 127.81, 128.0, 128.21, 128.25, 129.17, 129.57, 137.75, 137.94, 138.10, 138.48, 159.09, 159.18, 170.16, 170.61.

Elemental Analysis **:** **Calcd.:** C, 68.95, H, 6.56; **Found:** C, 68.92; H, 6.48.

Disaccharide (34)

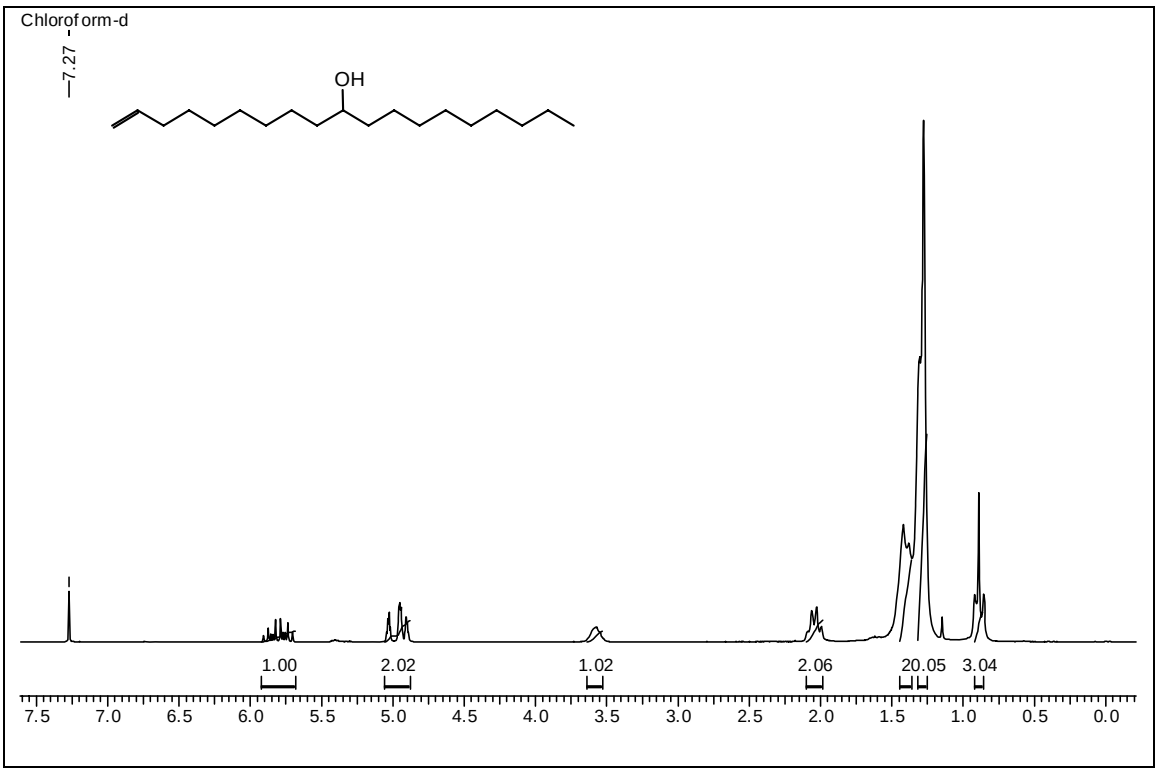


To a cooled suspension of **32** (0.170 g, 0.258 mmol), MS 4 ^{o}A (powdered) and alcohol **20** (0.166 g, 0.232 mmol) in anhydrous CH_2Cl_2 (20 mL) was added BF_3OEt_2 (0.011 g, 0.077 mmol). After stirring the reaction mixture at the same temperature until TLC indicates complete conversion (1 h), insoluble residue was filtered through a pad of celite and rinsed with CH_2Cl_2. the combined filtrate was concentrated and purified by silica gel column chromatography (eluted in 25% EtOAc-light petroleum ether) to afford **33** as a colorless liquid in 71% yield.

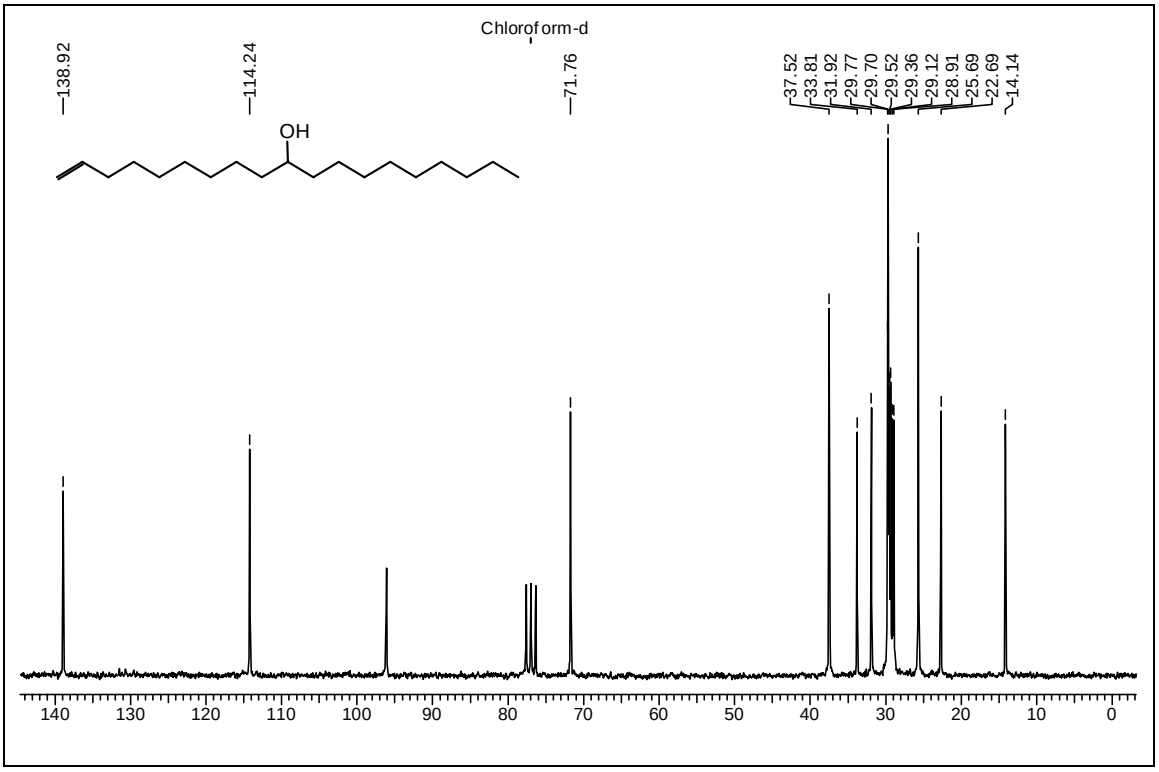
To a solution of **33** (0.100 g, 0.082 mmol) in CH_2Cl_2-H_2O (9:1, 5 mL) was added DDQ (0.02 g, 0.088 mmol) and stirred for 2 h at room temperature (monitored by TLC). The reaction mixture was quenched by saturated solution of $NaHCO_3$, extracted the aqueous layer with CH_2Cl_2 (2 x 15 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (eluted in 30% EtOAc-Hexane) to afford the disaccharide **34** as a colorless liquid.

Yield	**:**	0.07 g, 78%
Mol. Formula	**:**	$C_{68}H_{90}O_{12}$
IR ($CHCl_3$) cm^{-1}	**:**	3438, 2997, 2920, 2860, 1752, 1615, 1586, 1462, 1442, 1382, 1249, 1171, 1066, 1035, 820.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ 0.87 (d, 3H, *J* = 6.58 Hz), 1.22-132 (m, 24H), 1.48-1.57 (m, 4H), 1.98-2.04 (m, 2H), 2.12 (s, 3H), 3.36-3.74 (m, 11H), 3.86-3.94 (m, 2H), 4.36 (d, 1H, *J* = 7.58 Hz), 4.48 (d, 1H, *J* = 5.05 Hz), 4.52 (d, 1H, *J* = 8.08 Hz), 4.56-4.62 (m, 3H), 4.66-4.82 (m, 4H), 4.84-5.04 (m, 3H), 5.40 (d, 1H, *J* = 7.58 Hz), 5.80 (m, 1H), 7.04-7.16 (m, 5H), 7.20-7.30 (m, 20H).
^{13}C NMR ($CDCl_3$, 75 MHz)	**:**	δ 14.56, 21.39, 23.13, 25.64, 26.00, 29.45, 29.66, 30.18, 32.38, 34.27, 35.10, 62.71, 68.76, 69.43, 71.96, 72.12, 74.13, 74.59, 75.35, 75.69, 76.27, 76.51, 78.40, 79.26, 79.47, 83.96, 97.72, 102.42, 114.63, 128.03, 128.21, 128.76, 138.28, 138.53, 138.80, 139.29, 139.50, 169.96.

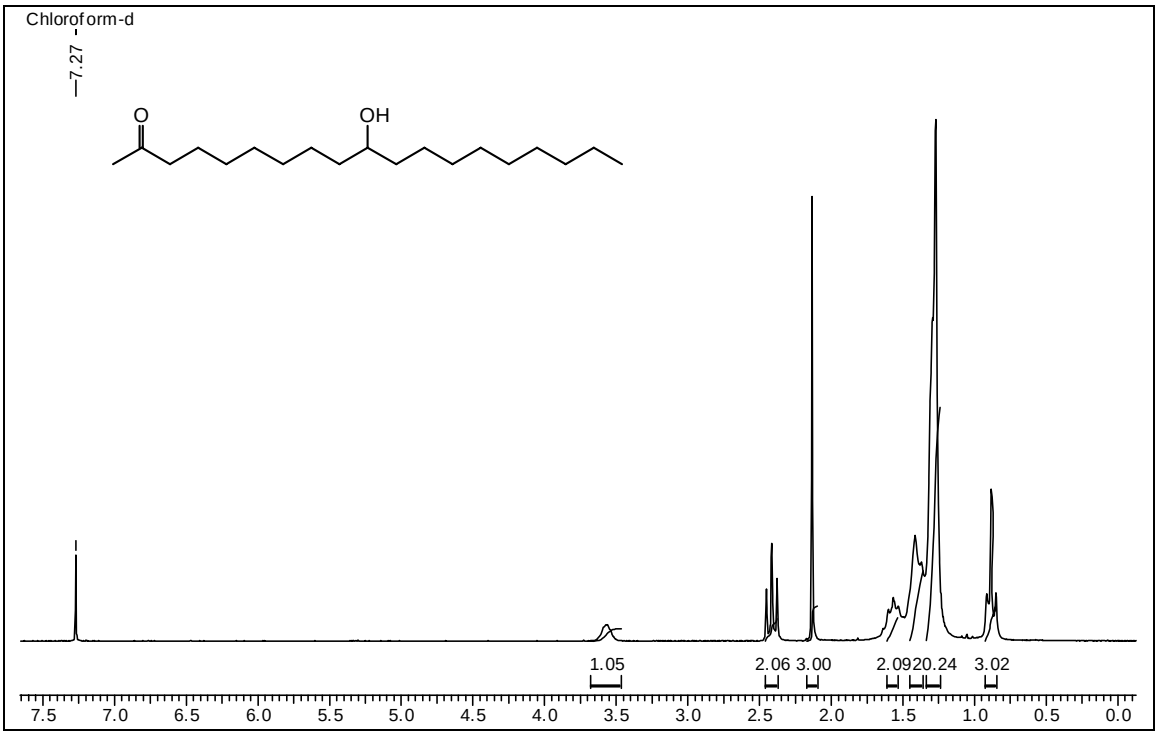
SPECTRA



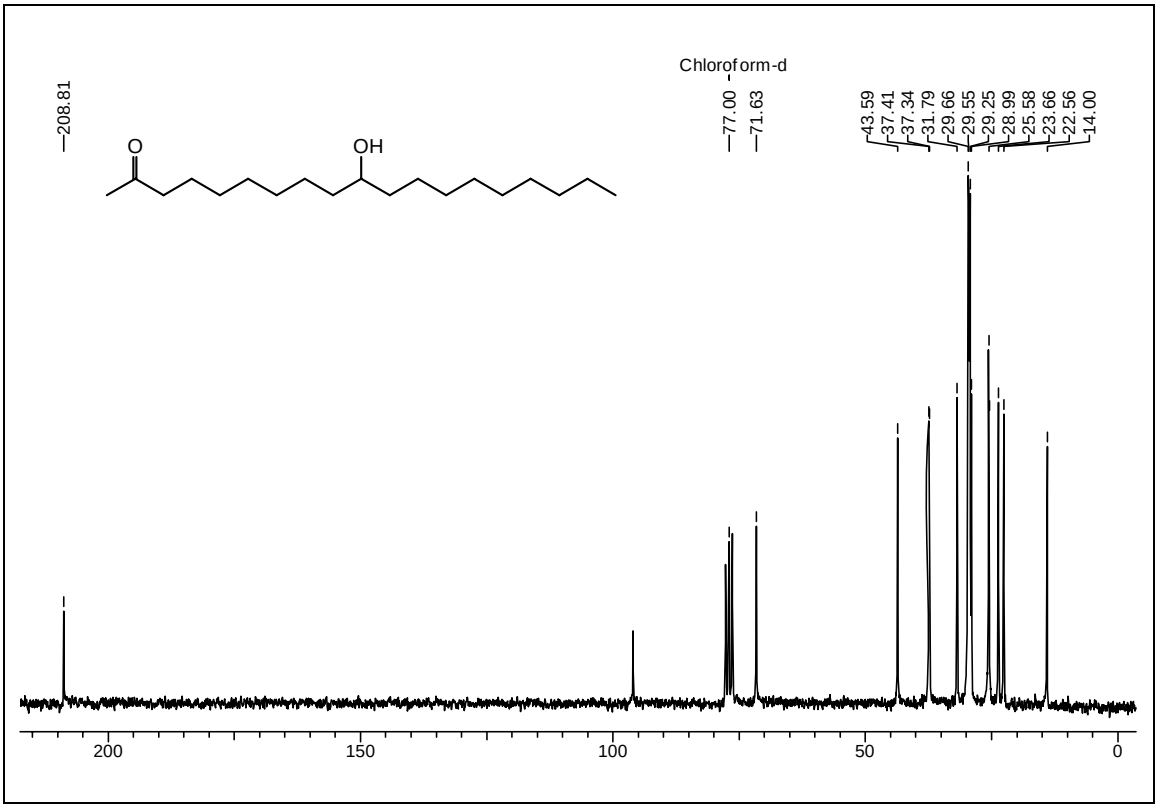
^{1}H NMR spectrum of compound 8 in $CDCl_3$



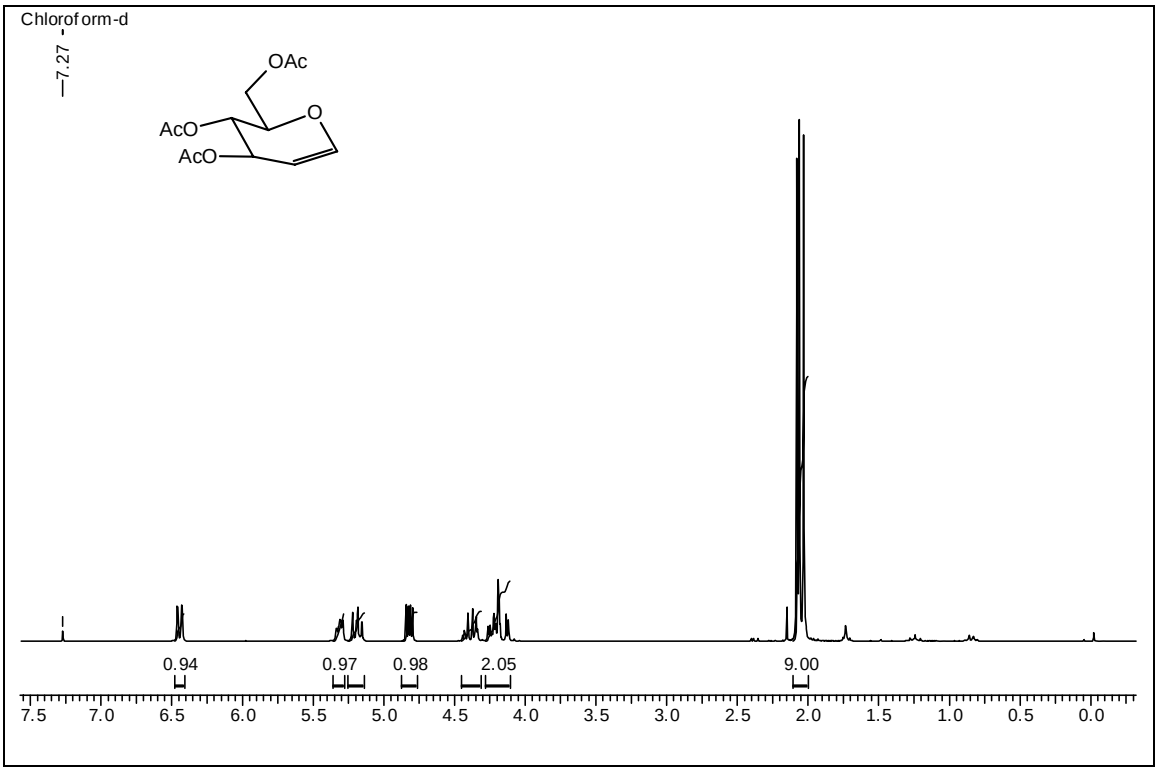
^{13}C NMR spectrum of compound 8 in $CDCl_3$



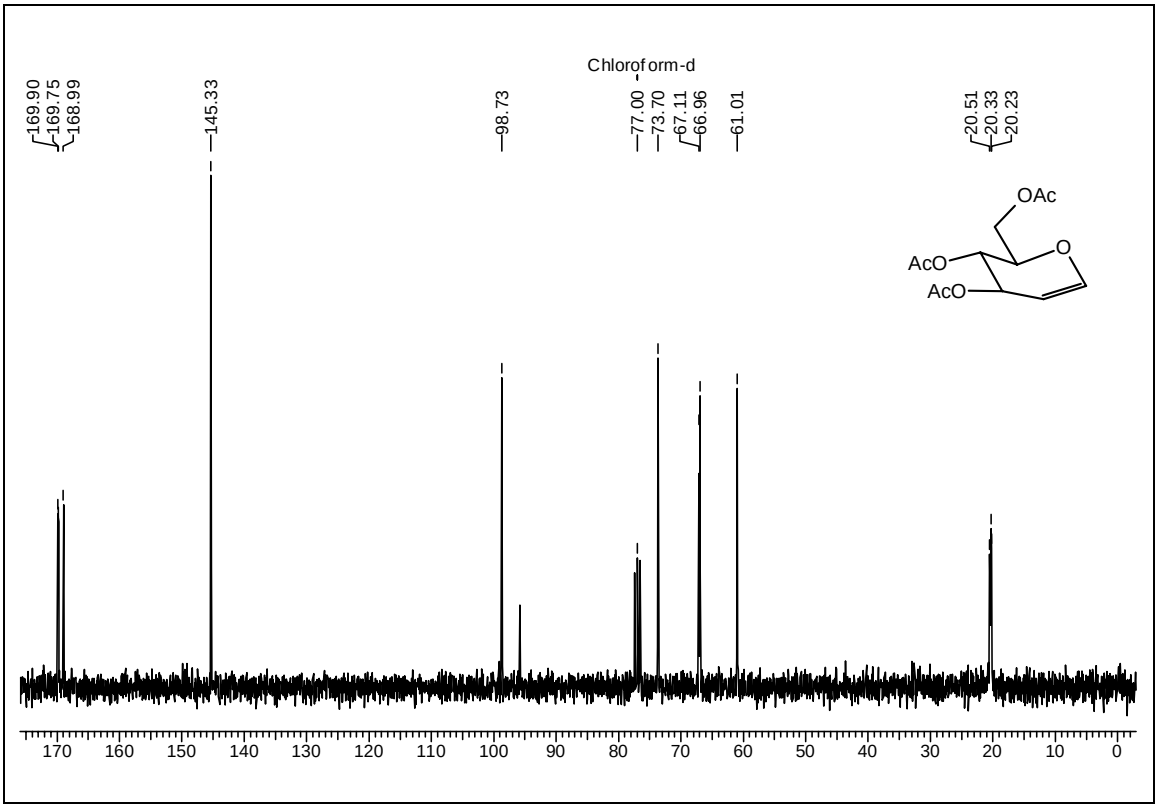
^{1}H NMR spectrum of compound 9 in $CDCl_3$



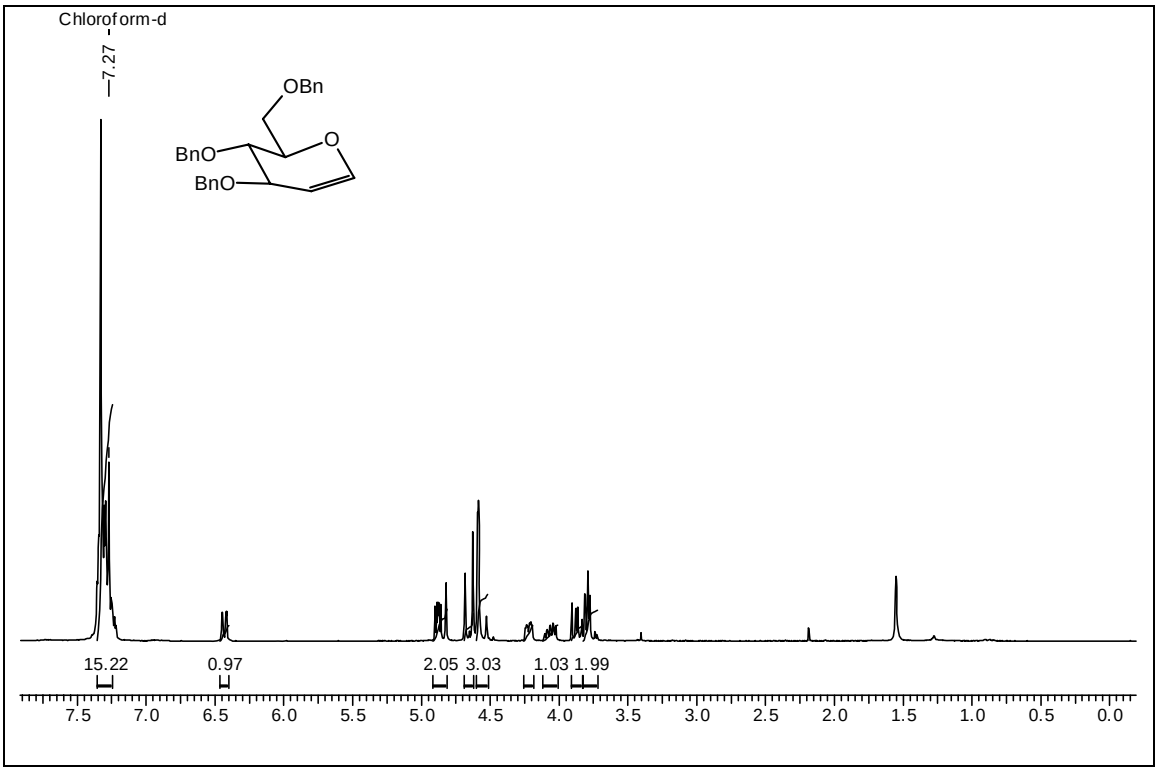
^{13}C NMR spectrum of compound 9 in $CDCl_3$



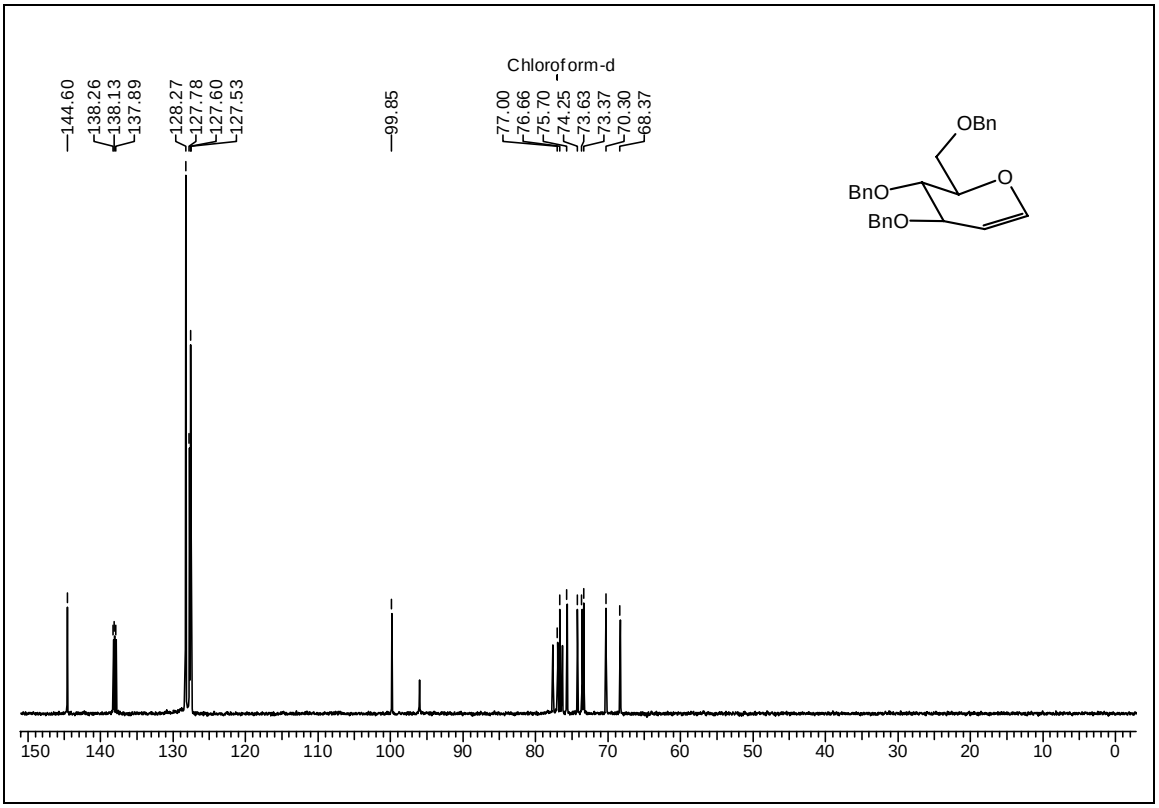
^{1}H NMR spectrum of compound 16 in $CDCl_3$



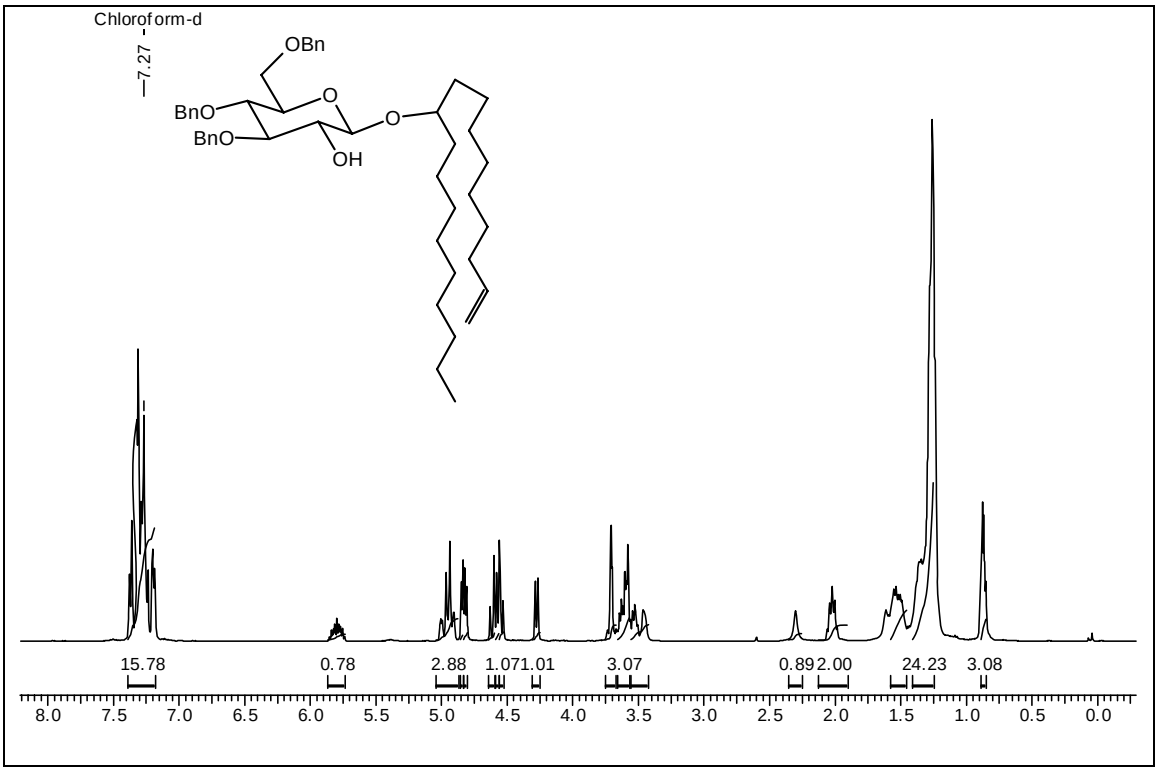
^{13}C NMR spectrum of compound 16 in $CDCl_3$



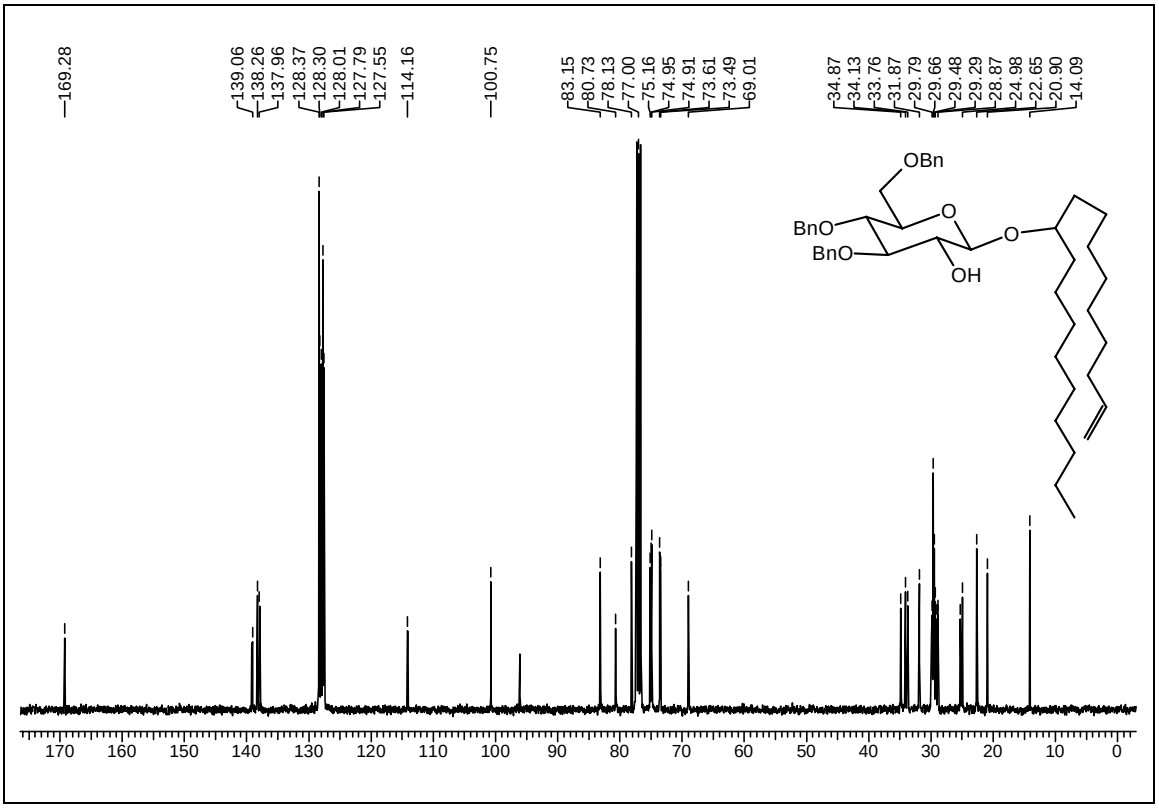
^{1}H NMR spectrum of compound 18 in $CDCl_3$



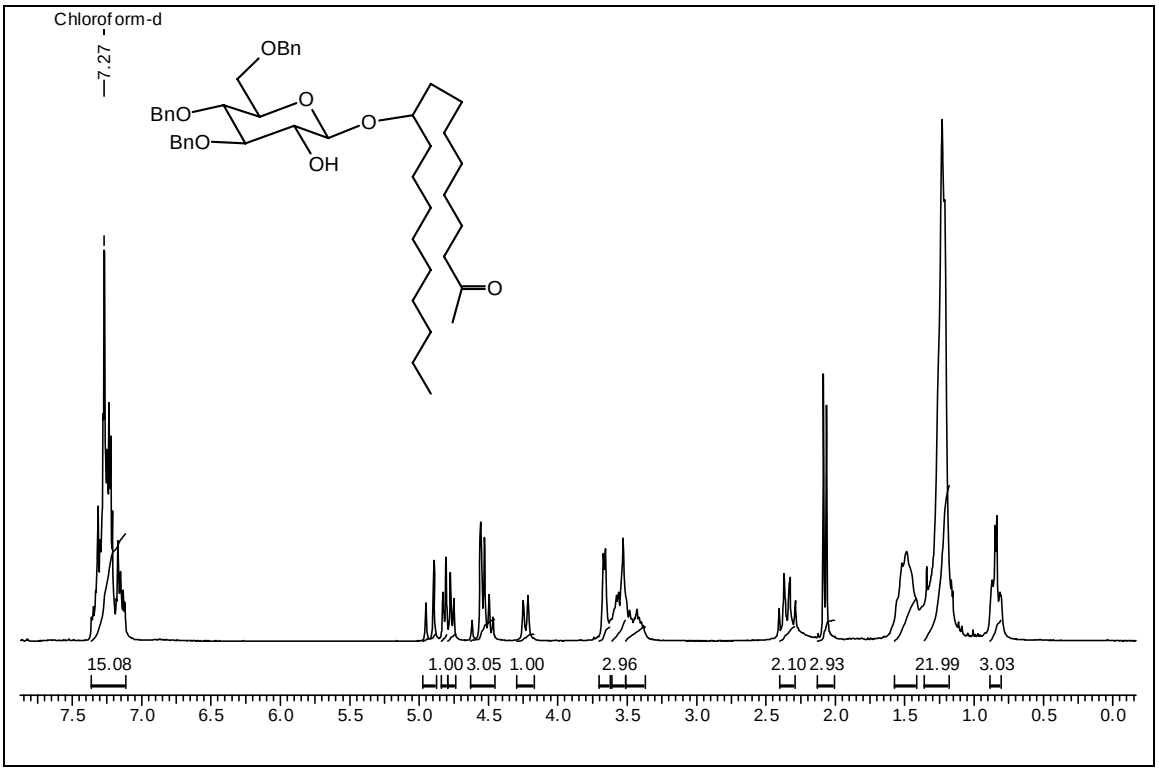
^{13}C NMR spectrum of compound 18 in $CDCl_3$



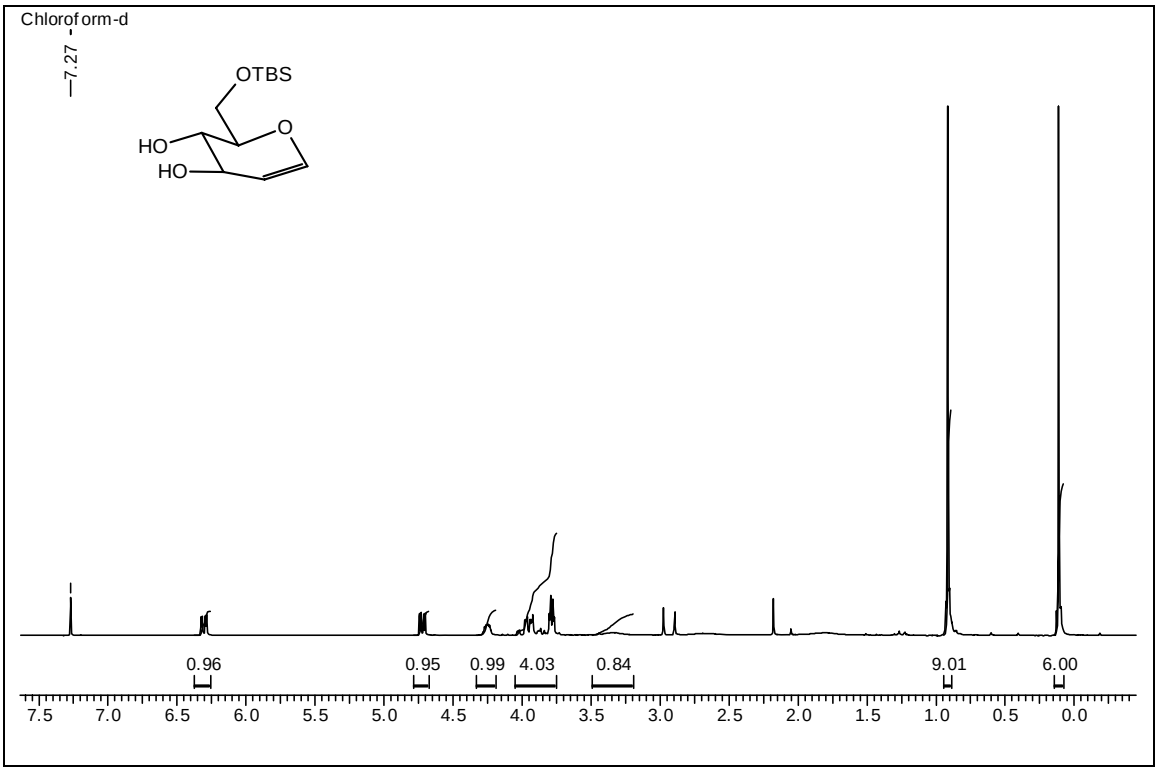
^{1}H NMR spectrum of compound 20 in $CDCl_3$



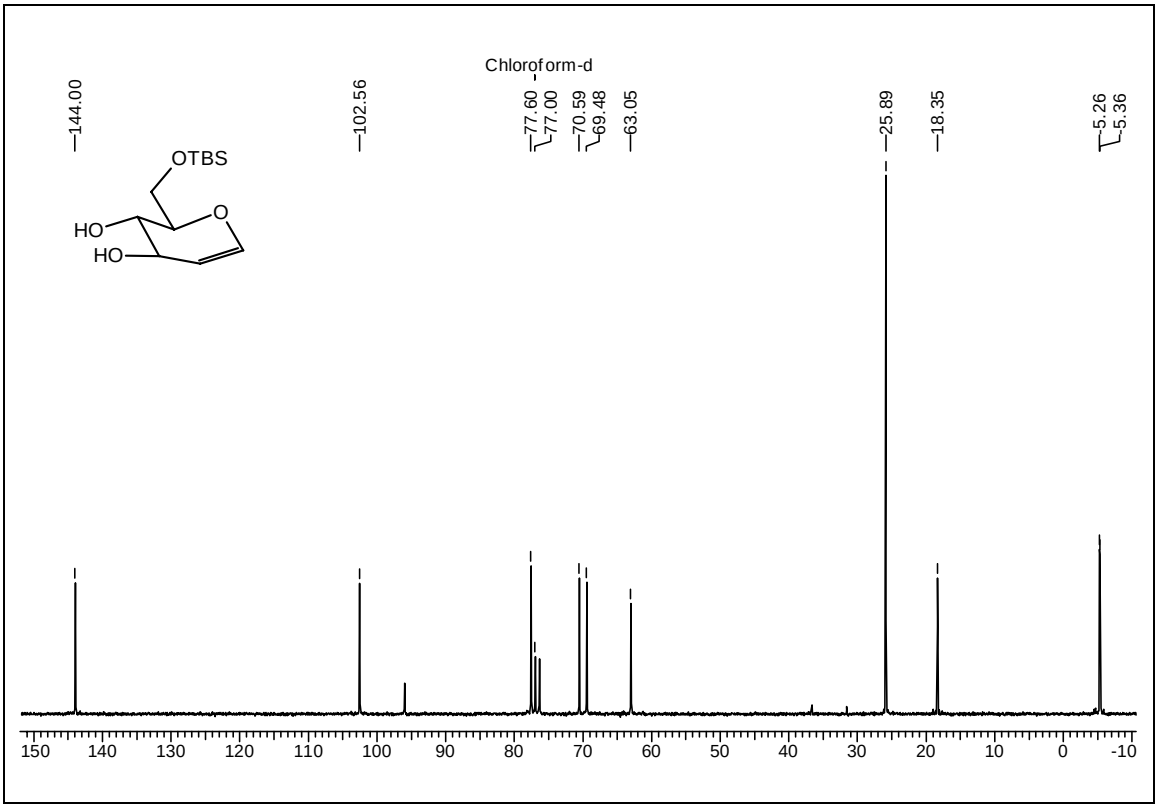
^{13}C NMR spectrum of compound 20 in $CDCl_3$



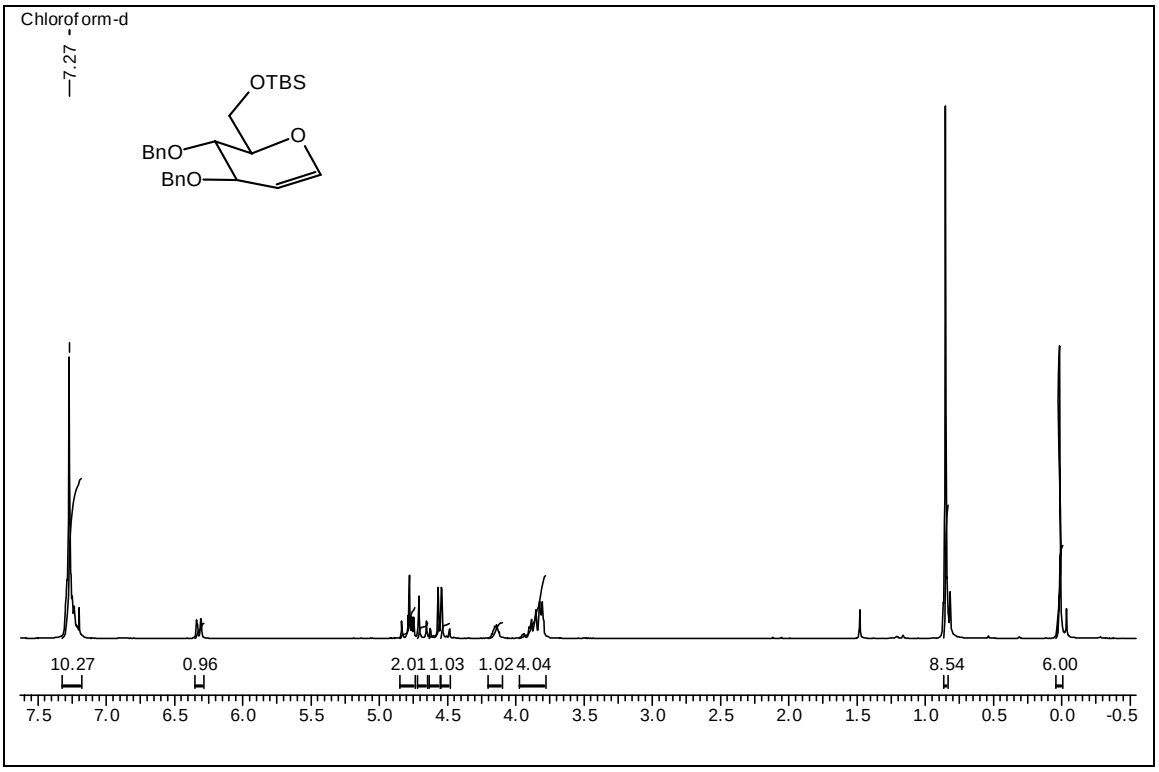
^{1}H NMR spectrum of compound 21 in $CDCl_3$



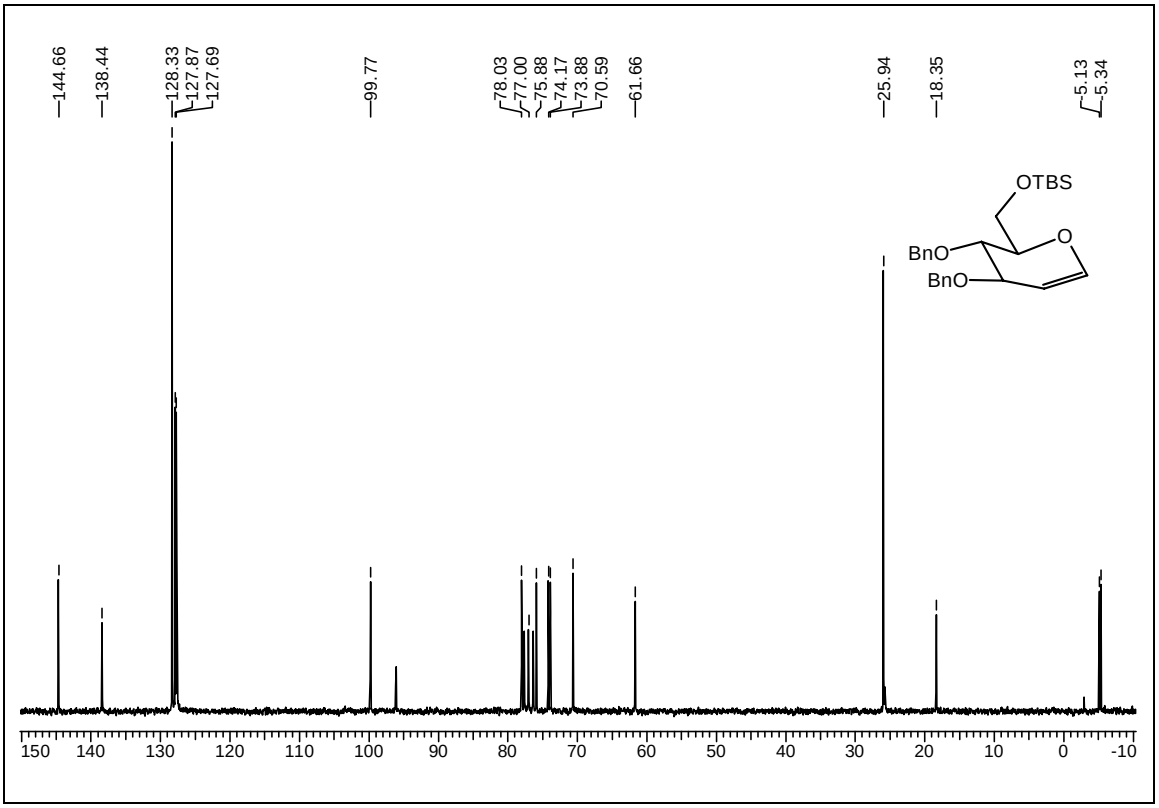
^{1}H NMR spectrum of compound 22 in $CDCl_3$



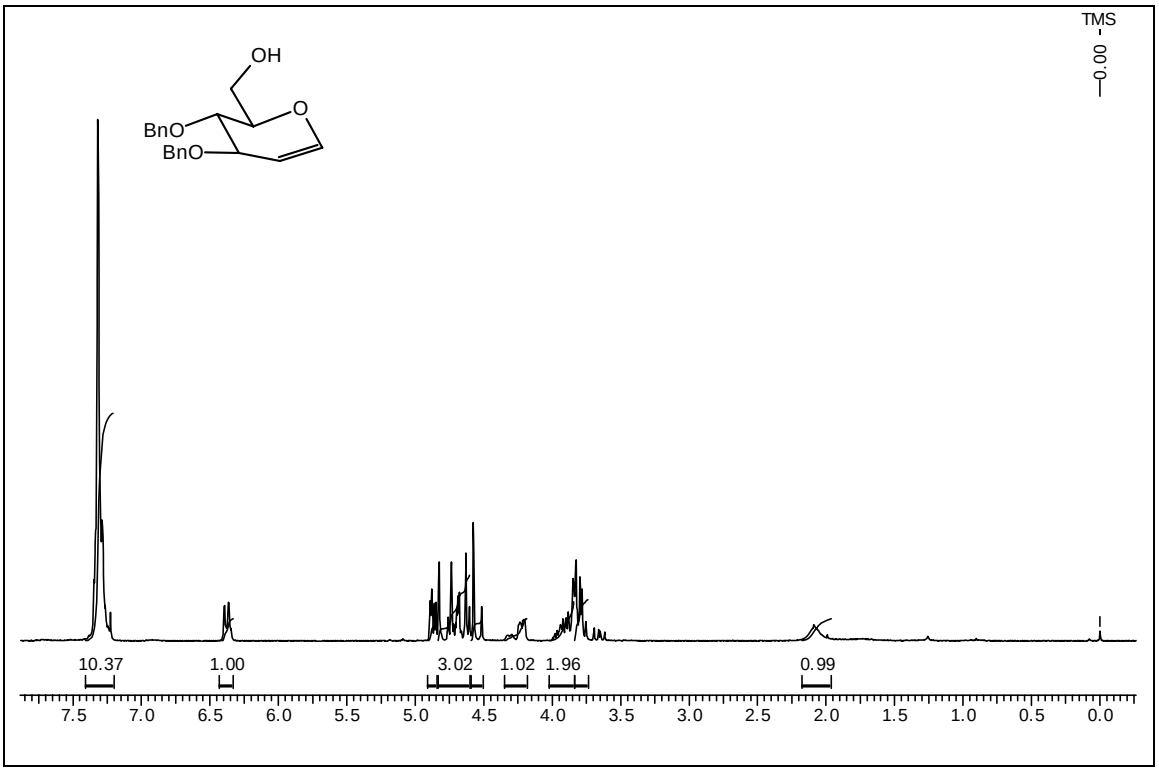
^{13}C NMR spectrum of compound 22 in $CDCl_3$



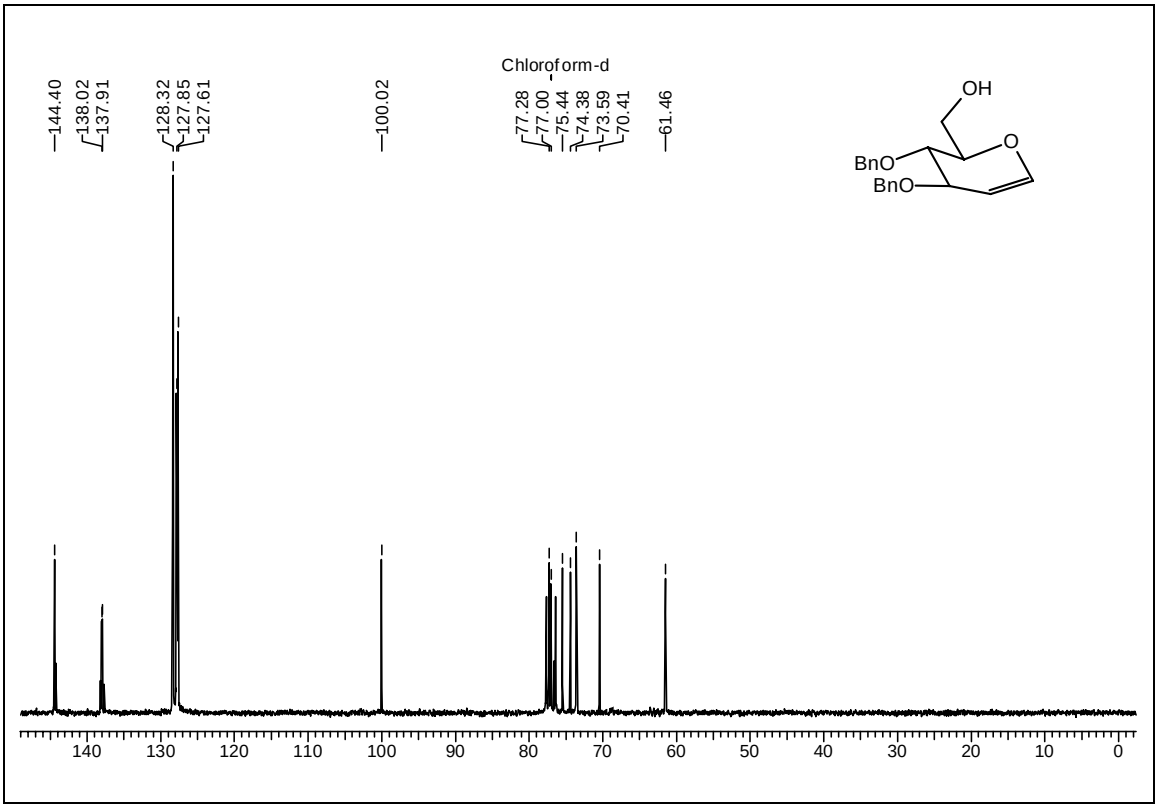
^{1}H NMR spectrum of compound 23 in $CDCl_3$



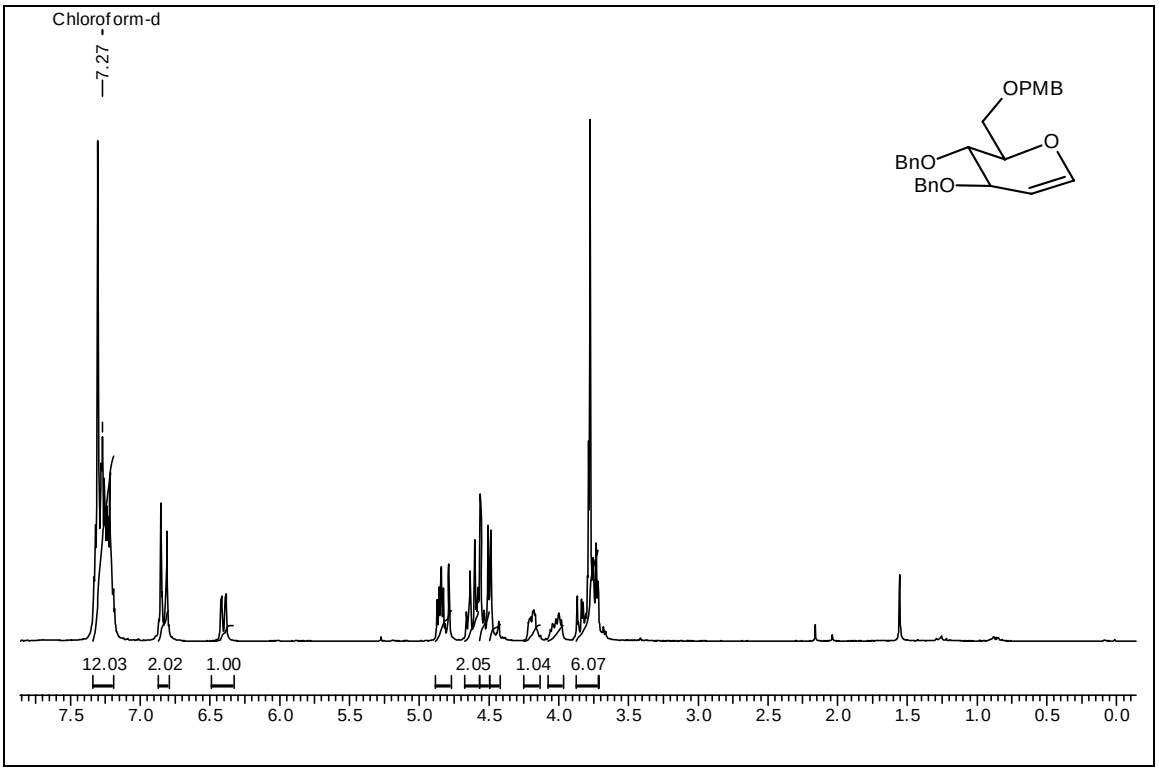
^{13}C NMR spectrum of compound 23 in $CDCl_3$



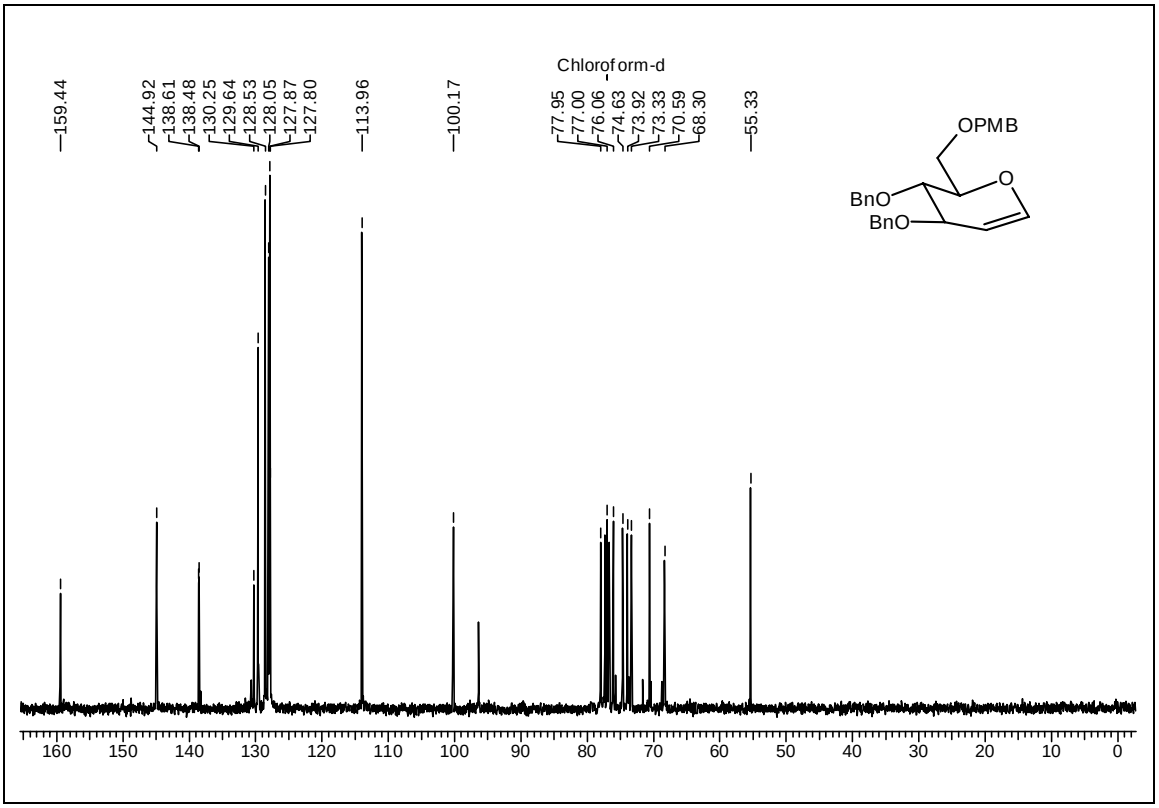
^{1}H NMR spectrum of compound 26 in $CDCl_3$



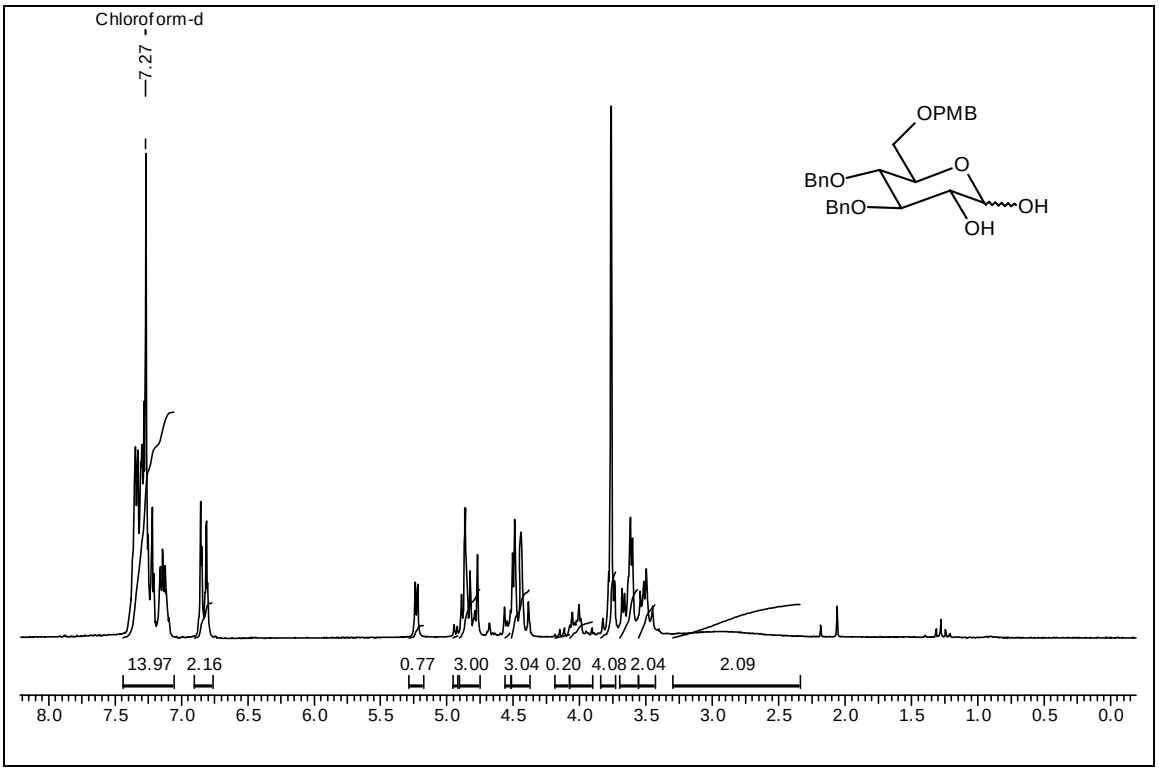
^{13}C NMR spectrum of compound 26 in $CDCl_3$



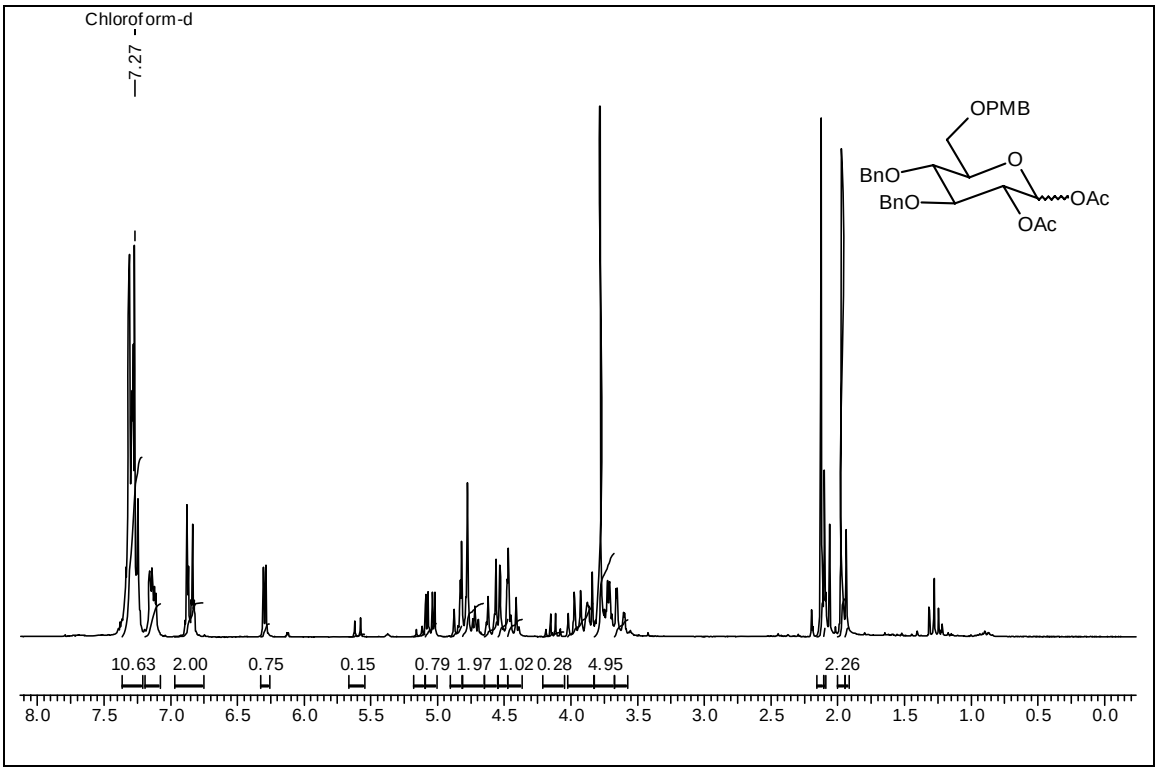
^{1}H NMR spectrum of compound 27 in $CDCl_3$



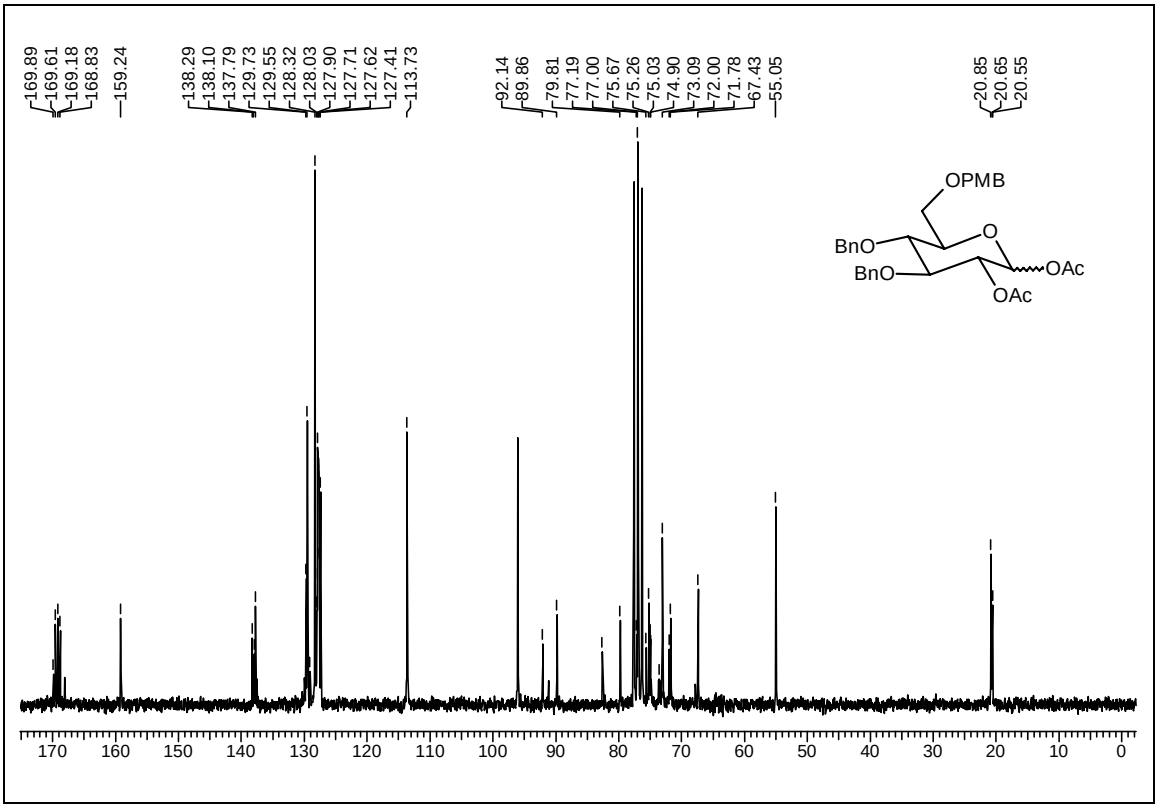
^{13}C NMR spectrum of compound 27 in $CDCl_3$



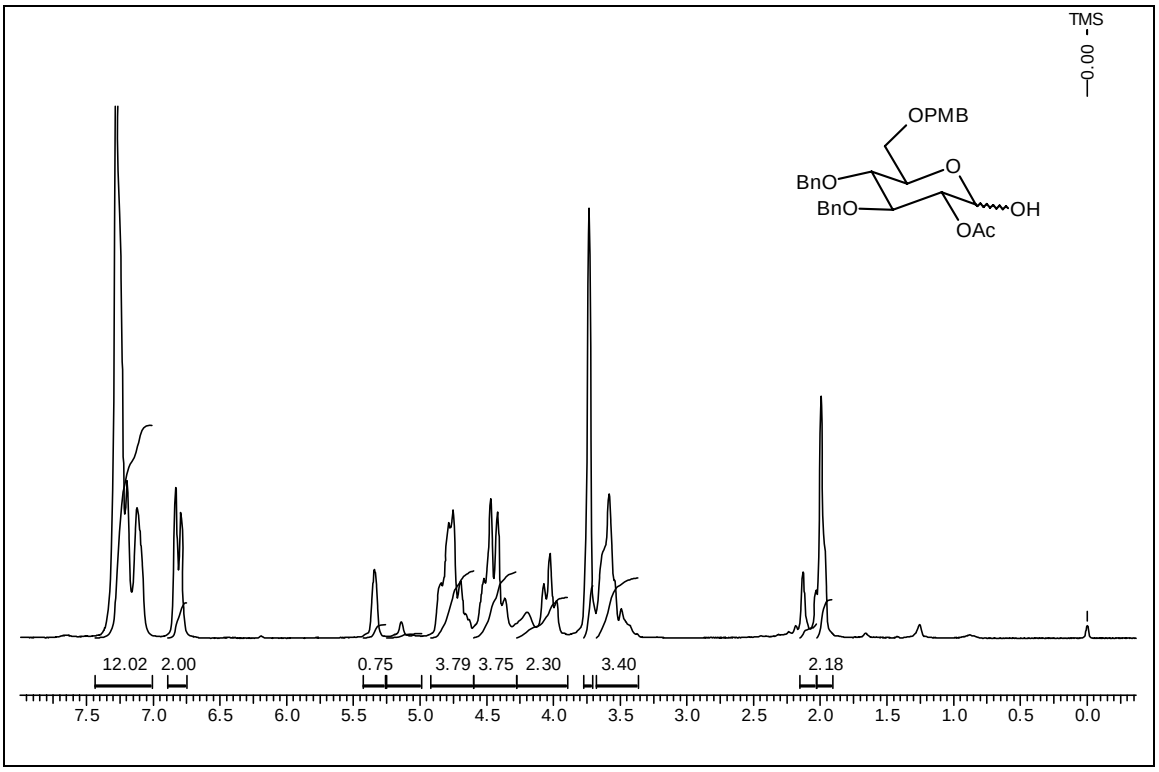
^{1}H NMR spectrum of compound 29 (α:β mixture) in $CDCl_3$



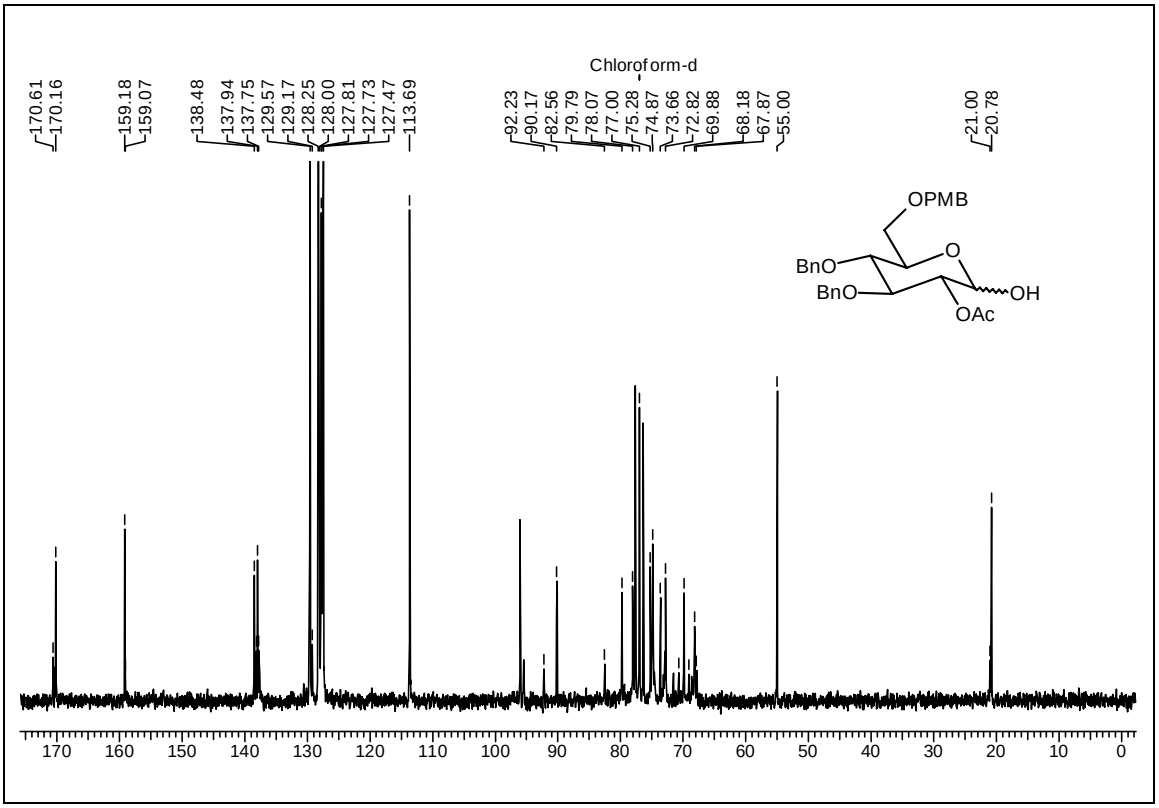
^{1}H NMR spectrum of compound 30 in $CDCl_3$



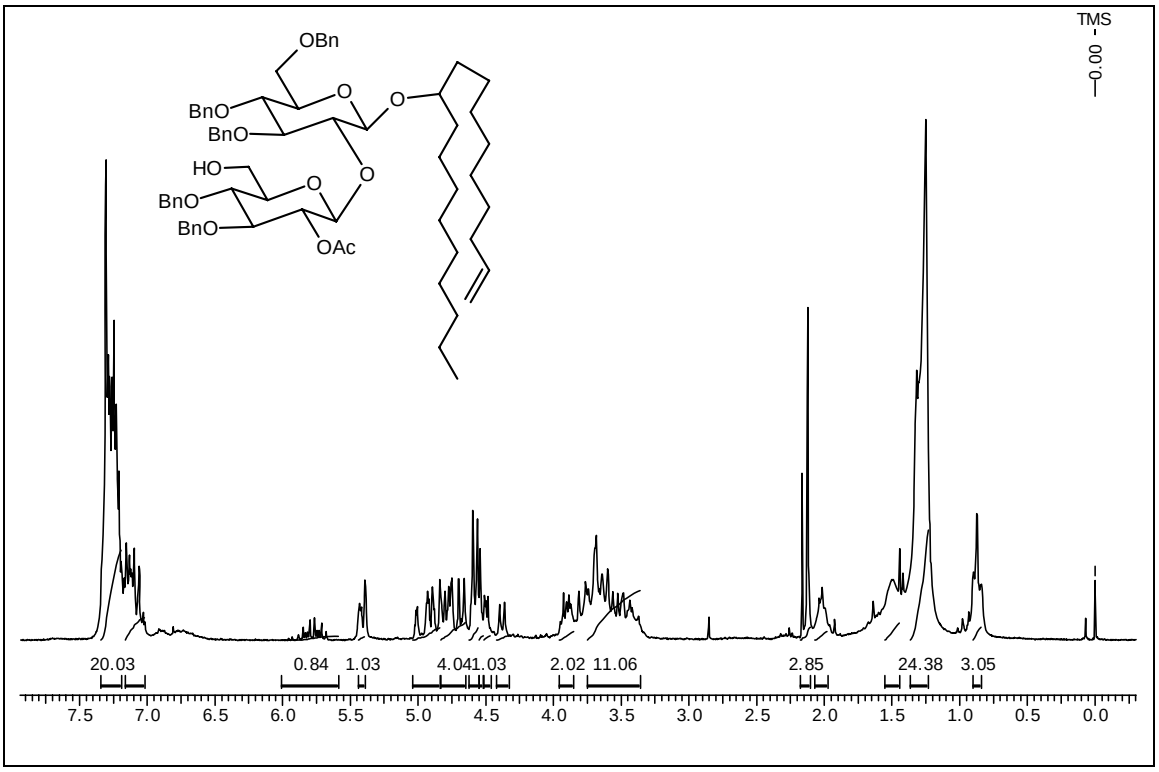
^{13}C NMR spectrum of compound 30 in $CDCl_3$



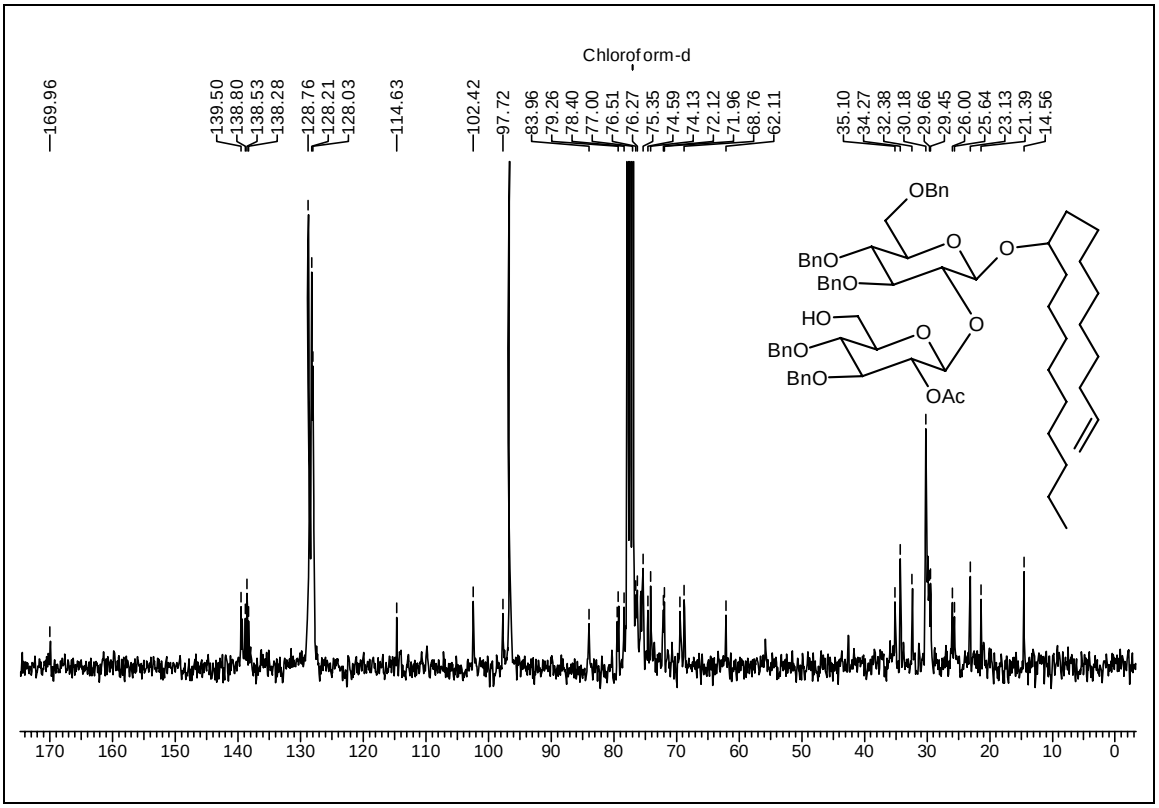
^{1}H NMR spectrum of compound 31 in $CDCl_3$



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



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



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

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LIST OF PUBLICATIONS

1. Protecting group directed ring-closing metathesis (RCM): the first total synthesis of an anti-malarial nonenolide. Mohapatra, D. K.; **Ramesh, D. K.**; Giardello, M. A.; Chorghade, M. K.; Gurjar, M. K.; Grubbs R. H. *Tetrahedron Lett.* **2007,** *48,* 2621-2625.