Studies Toward the Total Synthesis of Amphidinolide X, Eicosanoid and Solandelactone

A THESIS

SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

TO

UNIVERSITY OF PUNE

BY

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UNDER THE GUIDANCE OF

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March 2008

DEDICATED
TO MY BELOVED
MOTHER

DECLARATION

The research work embodied in this thesis submitted for Ph. D. degree to the University of Pune has been carried out at National Chemical Laboratory, Pune under the supervision of **Dr. Mukund K. Gurjar,** Ex. Deputy Director and Head, 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 to this or any other University.

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CERTIFICATE

The research work presented in this thesis entitled "**Studies Toward the Total Synthesis of Amphidinolide X, Eicosanoid and Solandelactone**" has been carried out under my supervision and is bonafide work of **Mr. Gorakhnath S. Yellol** This work is original and has not been submitted for any other degree or diploma to this or any other University.

Pune - 411 008 **Dr. M. K. Gurjar**

Date: (Research Guide)

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Gorakhnath S. Yellol

General Remarks

- Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- 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}.
- ^{1}H Nuclear Magnetic Resonance spectra were recorded on Varian FT-200 MHz (Gemini), AC-200 MHz, MSL-300 MHz, AV-400 MHz and Bruker-500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C Nuclear Magnetic Resonance spectra were recorded on AC-50 MHz, MSL-75 MHz, AV-100 MHz and Bruker-125 MHz spectrometer.
- Mass spectra were recorded on a CEC-21-110B, AP-1 QSTAR PULSAR, Finnigan Mat 1210 or MICRO MASS 7070 spectrometer at 70 eV using a direct inlet system.
- All reactions were monitored by Thin Layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV, I_2 and anisaldehyde reagent in ethanol as development reagents.
- All evaporations (concentrations) were carried out under reduced pressure on Buchi rotary evaporator below 50 °C.
- All solvents and reagents were purified and dried according to procedures given in Vogel's Text Book of Practical Organic Chemistry.
- Silica gel (60-120) used for column chromatography was purchased from ACME Chemical Company, Mumbai, India.

Abbreviations

Ac	-	Acetyl
AcOH	-	Acetic acid
Ac_2O	-	Acetic anhydride
AIBN	-	Azoisobutyronitrile
Bn	-	Benzyl
BnBr	-	Benzyl bromide
9-BBN	-	9-Borabicyclo[3,3,1]nonane dimer
n-BuLi	-	*n*-butyl lithium
CCl_4	-	Carbontetrachloride
COSY	-	Correlation spectroscopy
DCM	-	Dichloromethane
DDQ	-	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DHP	-	dihydropyran
DIBAL-H	-	Diisobutylaluminium hydride
DMAP	-	4-*N*, *N*'-Dimethylaminopyridine
DME	-	1,2-dimethoxy ethane
DMF	-	*N*, *N*'-Dimethylformamide
DMSO	-	Dimethyl sulfoxide
DMP	-	Dess-Martin periodinane
2,2-DMP	-	2,2-Dimethoxy propane
Et	-	Ethyl
EtOAc	-	Ethyl acetate
Et_2O	-	Diethylether
EtOH	-	Ethanol
HMPA	-	Hexamethyl phosphoric acid
IBX	-	2-iodoxybenzoic acid
Im	-	Imidazole
LAH	-	Lithium aluminium hydride
LDA	-	Lithium diisopropylamide
Me	-	Methyl
MeOH	-	Methanol
MeI	-	Mehyl iodide
$NaBH_4$	-	Sodiumborohydride

NaH	-	Sodium hydride
NEt_3	-	Triethyl amine
NMR	-	Nuclear Magnetic Resonance
NOE	-	Nuclear Overhauser Effect
NOESY	-	Nuclear overhauser effect spectroscopy
Pd/C	-	Palladium on carbon
PDC	-	Pyridiniumdichromate
PMB	-	*para*-Methoxy benzyl
Ph	-	Phenyl
p-TSA	-	*para*-Toluenesulfonic acid
Py	-	Pyridine
RCM	-	Ring Closing Metathesis
TBAI	-	Tetra-n-butylammonium iodide
TBAF	-	Tetra-n-butylammonium fluoride
TBS/ TBDMS	-	*tert*-Butyldimethylsilyl
TBDPS	-	*tert*-Butyldiphenylsilyl
TFA	-	Trifluoroacetic acid
THF	-	Tetrahydrofuran
THP	-	trihydropyran
TMS	-	Trimethyl silyl
TPP	-	Triphenylphosphine
Ts	-	*p*-Toluenesulphonyl
TsCl	-	*p*-Toluenesulphonyl chloride
WHO	-	World Health Organisation

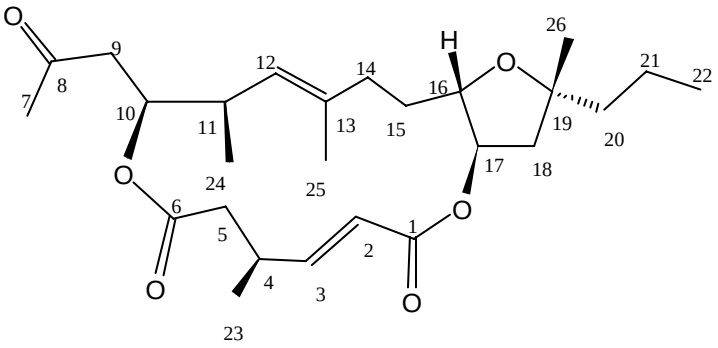
Contents

ABSTRACT

CHAPTER I: Studies Toward the Total Synthesis of Amphidinolide X

The amphidinolides are the series of chemically unique and biologically interesting secondary metabolites from marine dinoflagellates. There are 25 amphidinolides isolated from extracts of marine dinoflagellates of the genus *Amphidinium*, which are symbionts of Okinawan marine acoel flatworms, *Amphiscolops* spp. These macrolides have a variety of backbone skeletons and different sizes of macrocyclic lactone rings (12 to 29 membered). Most of the Amphidinolides exhibit potent cytotoxicity and antitumor activity. Therefore, amphidinolides have attracted great interest as challenging targets for total synthesis and biosynthetic studies.

Figure 1:



Amphidinolide X (**1**)

A novel cytotoxic 16-membered macrodiolide, amphidinolide X (**1**), has been isolated from a marine dinoflagellate *Amphidinium* sp. The gross structure of **1** was elucidated on the basis of spectroscopic data including one-bond and long-range ^{13}C-^{13}C correlations. The relative and absolute stereochemistries were also determined by combination of analysis of NOESY data with ^{1}H-^{1}H and ^{1}H-^{13}C coupling constant of **1**. Amphidinolide X shows moderate cytotoxicity against L1210 (IC_{50} : 0.6 µg/mL) and KB (IC_{50} : 7.5 µg/mL) cell lines.

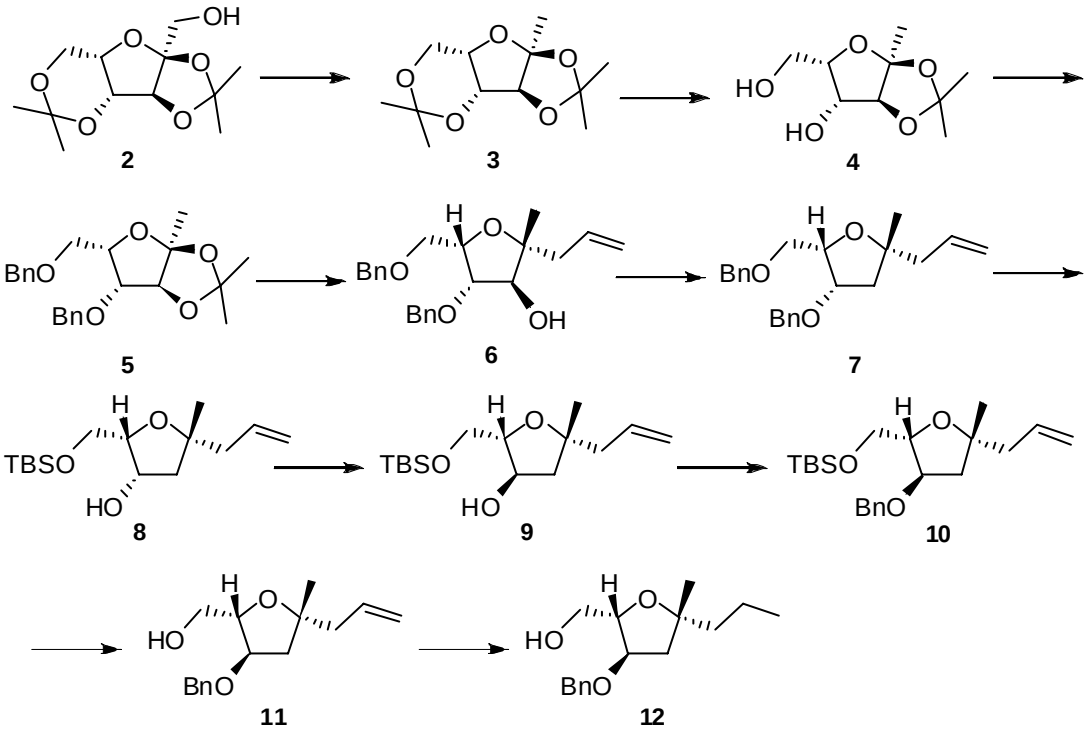
Amphidinolide X (**1**) is the only naturally occurring macrodiolide known to date that consists of a diacid and a diol unit rather than of two hydroxyacid entities. These rather unique structural features together with the promising cytotoxicity of **1**

against murine lymphoma and human epidermoid carcinoma, attracting attention as potential Cancer drug and hence prompted us to pursue its total synthesis.

As amphidinolide X consists the ester linkages forming the macrodiolide ring, these were envisaged to assemble the target molecule from three building blocks. Amphidinolide X was planned to be assembled from three building blocks namely the tetrahydrofuran fragment A, fragment B containing upper left keto moiety and lower dicarbonyl entity fragment C. Modified Julia coupling to generate the C12-C13 alkene, esterification as well as finally lactonization using Yamaguchi conditions to construct 16 member multi functionalised macrolactone ring were the key transformations. The fragment A was planned from L-Sorbose. Fragment B can be easily synthesized from ethyl acetoacetate by using Sharpless asymmetric epoxidation and regioselective epoxide opening reaction. Fragment C was planned using Evans alkylation protocol.

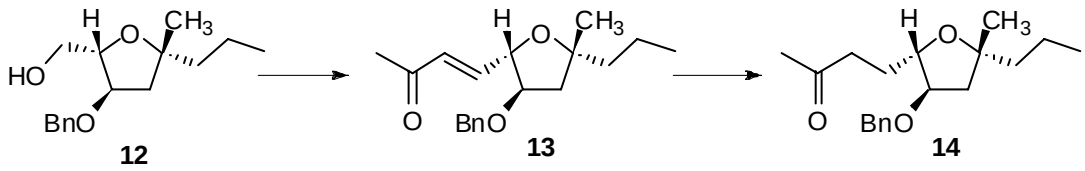
Our synthetic endeavor began with the preparation of sorbosediacetonide **2** from L-sorbose using the reported procedure (Scheme1). The primary hydroxyl from **2** was deoxygenated by iodination and subsequent displacement by tributyltin hydride to provide **3**. 4,6-acetonide of **3** was selectively hydrolyzed using 0.8% H_2SO_4 to get diol **4**, which further benzylated to its dibenzyl derivative **5**.

Scheme 1:



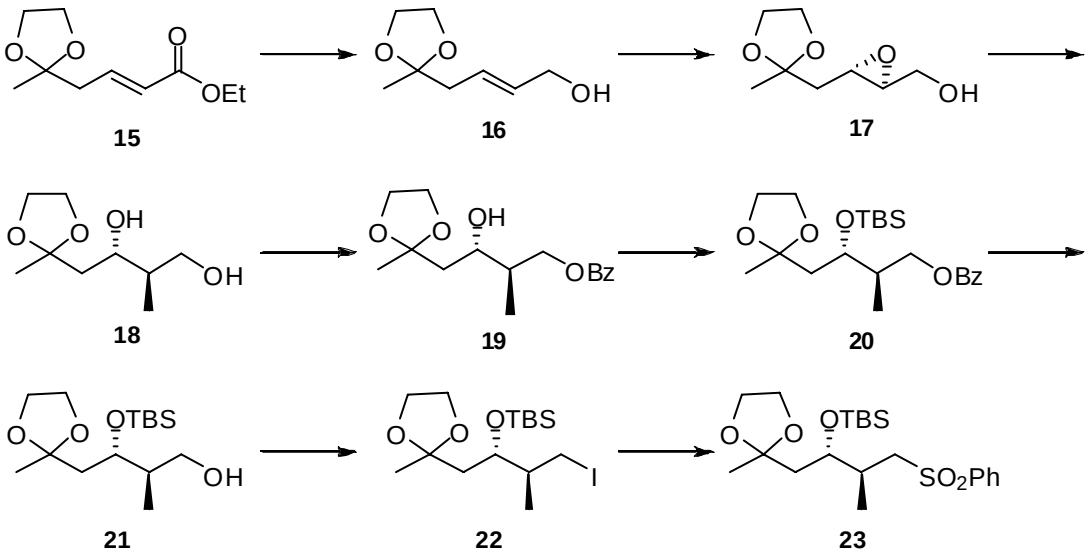
The installation of allyl group at C-2, to generate the quaternary center with desired stereochemistry, along with the deprotection of 2,3 isopropylidene group was achieved in one shot using BF_3-etherate and allyltrimethyl silane to produce **6** in high enantioselectivity. At this stage stereochemistry of newly generated center was confirmed by NOESY experiment. The compound **6** was deoxygenated by Barton-McCombie Reaction to procure the deoxy derivative **7**, which on further debenzylation and selective TBS protection of primary hydroxyl afforded alcohol **8**. Esterification of mono-TBS derivative **8** with *p*-nitrobenzoicacid under Mitsunobu conditions followed by the hydrolysis of the resultant ester gave the alcohol **9** with required stereochemistry.

Scheme 2:



Masking of the free hydroxyl as its benzyl ether was followed by the deprotection of the TBS ether to give alcohol **11**. The reduction of terminal double bond of alcohol **11** furnished alcohol **12**. Gratifyingly alcohol **12** was oxidized and resultant aldehyde was treated with wittig salt of bromoacetone to afford unsaturated ketone **13** which on mild hydrogenation furnished tetrahydrofuran segment ketone **14** (Scheme 2).

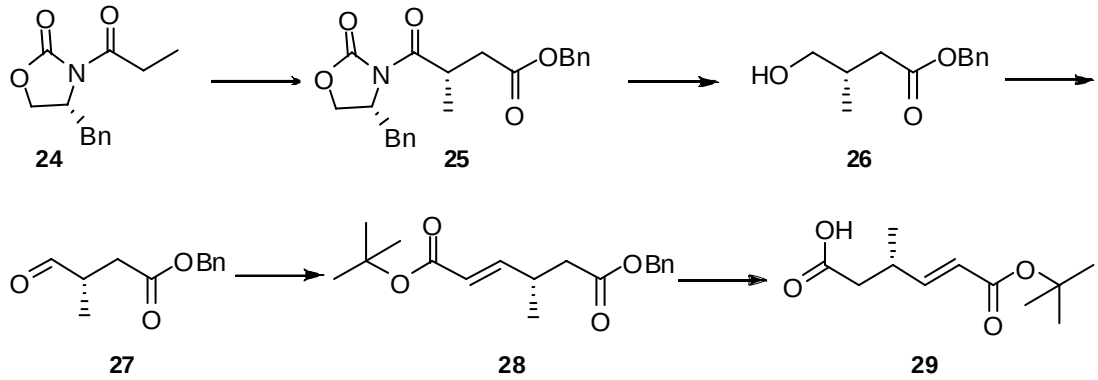
Scheme 3:



The preparation of second building block required for the total synthesis of Amphidinolide X started from **15** (Scheme 3), which was easily prepared from Ethyl acetoacetate by reported procedures. DIBAL-H reduction of the ester **15** produced allyl alcohol **16**. Epoxidation of the allylic alcohol **16** was then performed under Sharpless conditions to provide the desired epoxy alcohol **17** in decent optical purity. Opening of the epoxide in regioselective manner was achieved using MeMgCl in combination with CuCN to procure diol **18**. After establishing the stereochemistry of **18**, we proceeded further to prepare key intermediate **23**. The primary hydroxyl of **18** was selectively benzoylated and then further sillyl protection of secondary hydroxyl produced **20**, which on base treatment afforded alcohol **21**. The alcohol **21** is transformed to sulfone **23** through its iodo derivative **22** to complete the synthesis of second fragment.

The synthesis of the third lower half fragment was planned from reported *N*-propionyl oxazolidinone **24**. Compound **24** was alkylated using Evans alkylation conditions to afford compound **25** from which the oxazolidinone moiety was reductively cleaved to obtain alcohol **26**. The alcohol **26** was oxidized and resulted aldehyde **27** was subjected to two carbon Wittig homologation to produce diester **28**. The basic hydrolysis of **28** selectively hydrolyzed benzyl ester to achieve desired monoacid **29** (Scheme 4).

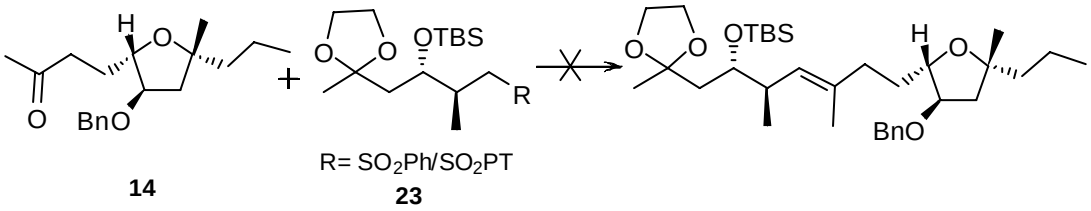
Scheme 4:



24 **25** **26** **27** **28** **29**

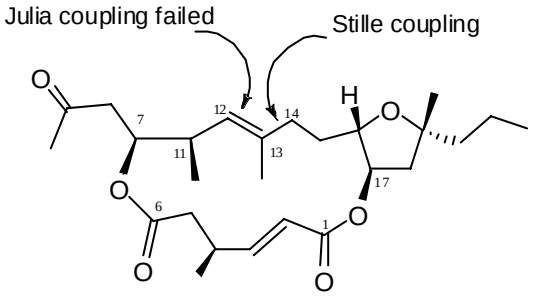
Having successfully completed the synthesis of required fragments, we focused our attention on couplings of these fragments. Even though the Julia olefination of aldehyde is well established, there are seldom reports of the same with ketones. We decided to explore the Julia olefination of ketone **14** using sulfone **23**.

Scheme 5:



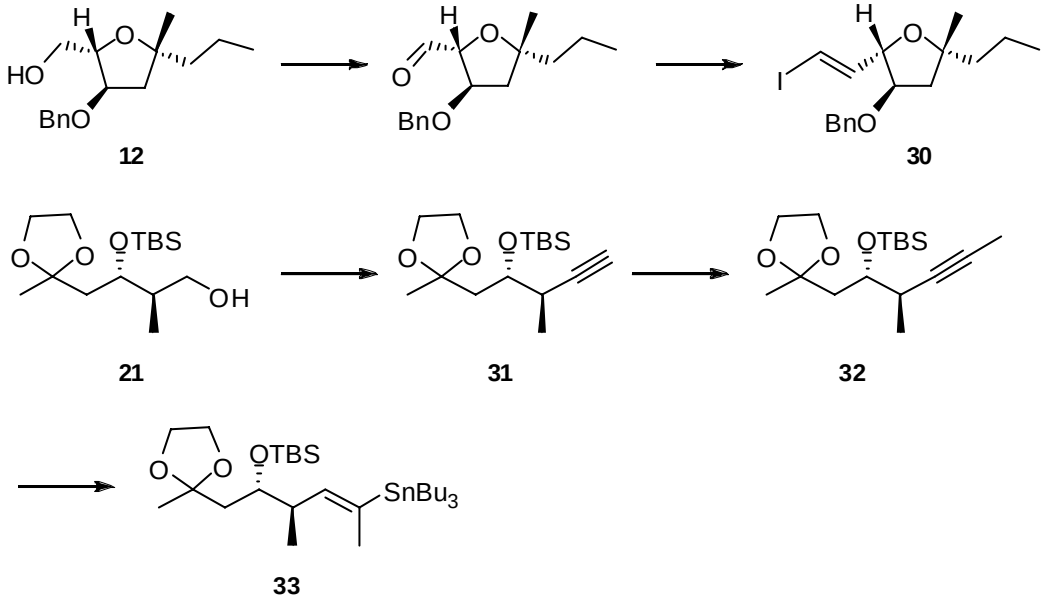
The attempts to couple these two fragments under various reaction conditions turned out to be failures (scheme-5). In view of the failures to forge the double bond between C12-C13, we planned to attempt the construction of C13-C14 bond by means of Stille reaction (Figure 2).

Figure 2:



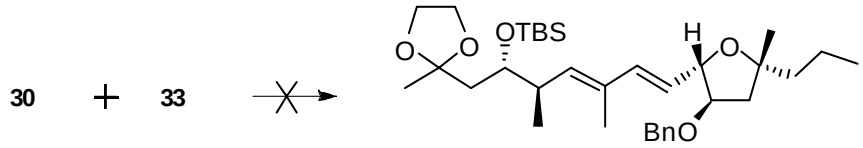
According to the redesigned synthetic strategy for well-known Stille coupling, the requisite coupling partners **30** and **33** were synthesized from intermediates **12** and **21** respectively. As depicted in Scheme 6, **12** was modified to vinyl iodo **30** by using Takai reaction conditions and **21** was converted to vinyl tin **33** over four steps.

Scheme 6:



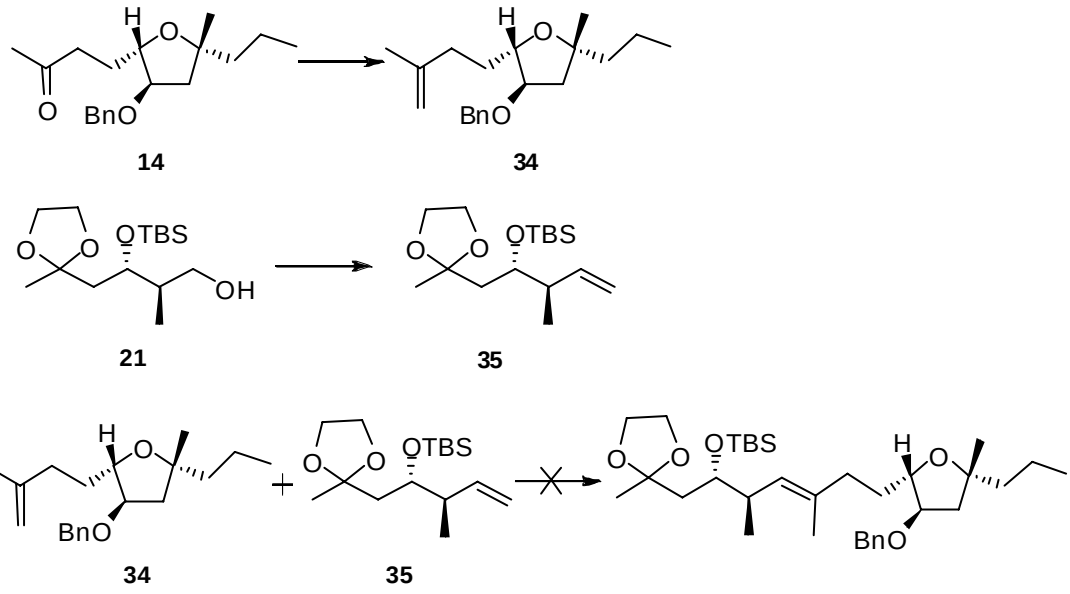
Then both fragments **30** and **33** subjected to Stille protocol, but it failed to produce required product.

Scheme 7:



As the Stille protocol also failed to couple the segments we changed our strategy towards cross metathesis to construct the C12-C13 olefin. For this purpose our strategy was modified to synthesize alkenes **34** and **35** from known intermediates **14** and **21** respectively by one carbon Wittig homologation (Scheme 8). The alkenes **34** and **35** were treated with Grubbs' second-generation catalyst with various conditions, but failed to obtain desired product.

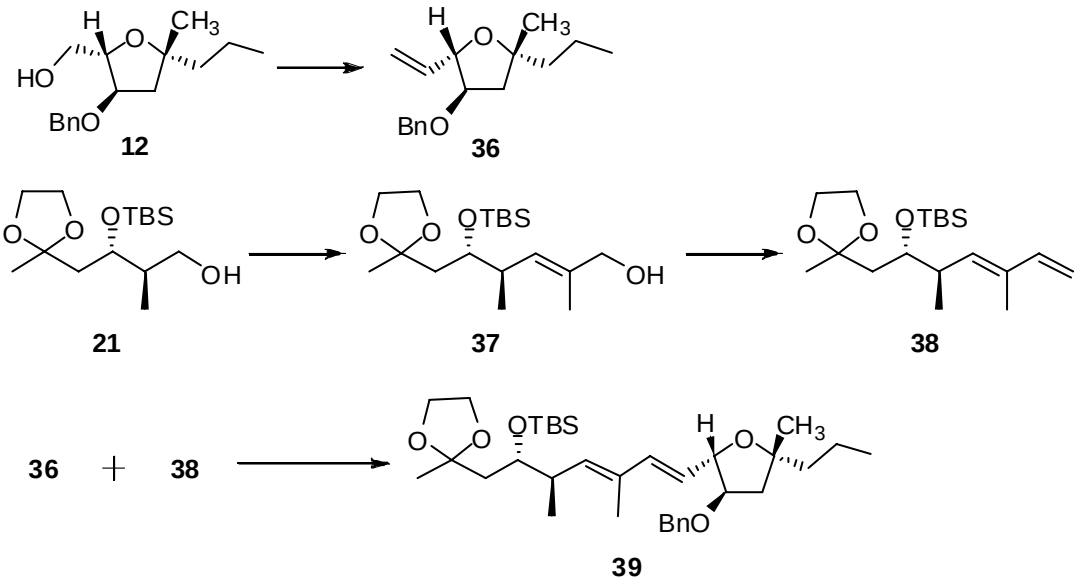
Scheme 8:



Attributing the failure in the cross metathesis for the construction of C12-C13 bond to the stearic crowding involved in the formation of trisubstituted double bond, we then focused our attention on the construction of C14-C15 double bond. The selective reduction of the disubstituted double bond in presence of trisubstituted double bond was the issue to be dealt with at latter stages. The requisite precursors for metathesis alkene **36** and diene **38** were prepared from known intermediates **12** and **21** respectively (scheme 9). These alkene **36** and diene **38** were subjected to

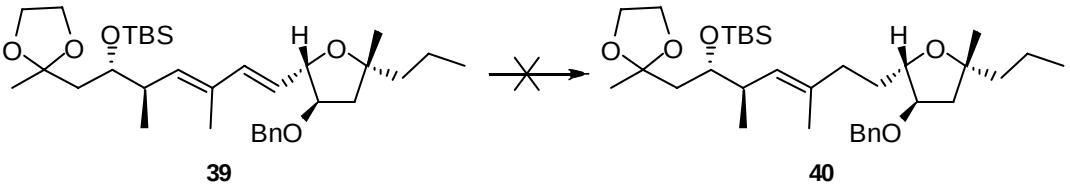
Grubbs' second-generation catalyst in refluxing DCM finally furnished desired coupled product **39**.

Scheme 9:



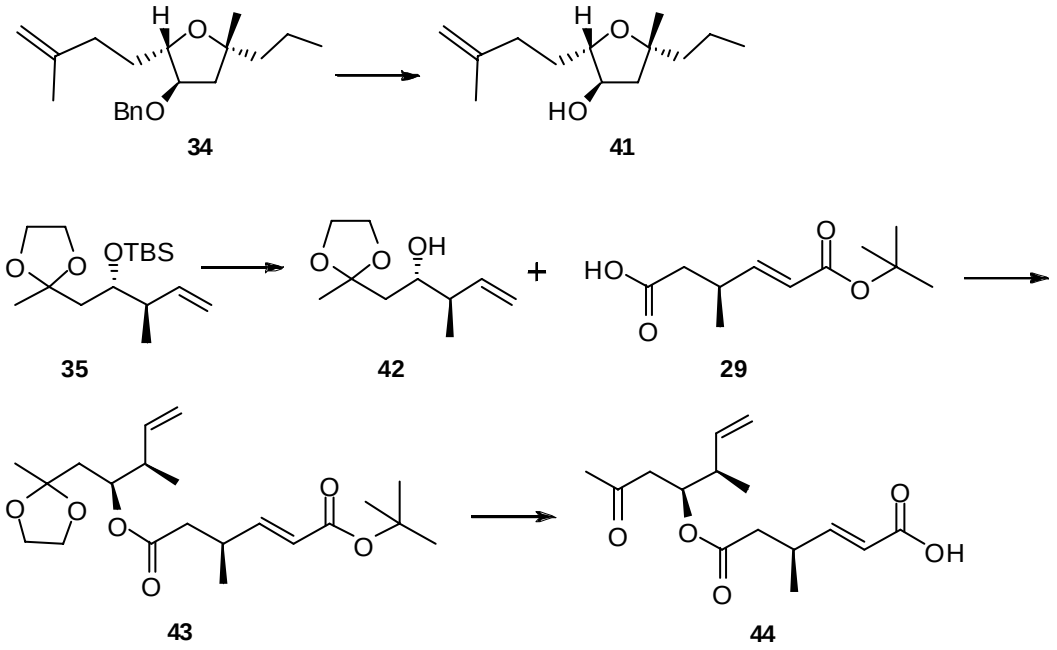
With the required compound **39** in hand, the crucial selective reduction was investigated. For the selective reduction of disubstituted double bond in presence of trisubstituted double bond, various conditions and reagents applied but unfortunately all conditions failed to give desired product **40** (Scheme 10).

Scheme 10:



Formation of carbon-carbon bond using various protocols did not work on expected line. Due to bifunctional nature of building blocks we had a choice to couple with other end first and finally construct C12-C13 bond through ring closing metathesis. Keeping this in mind, intermediate **34** was debenzylated to alcohol **41** and intermediate **35** was desilylated to alcohol **42**, which on esterification with third fragment **29** afforded ester **43**. The hydrolysis of *t*-butyl ester alongwith ketal deprotection was gave acid **44** (Scheme 11). The coupling of acid **44** with segment **41** to produce precursor of planned RCM are in progress.

Scheme-11:

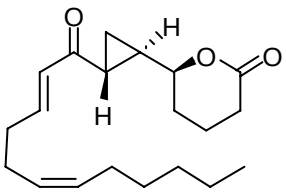


In conclusion, we have successfully accomplished the syntheses of three crucial segments with suitable protections for the projected total synthesis of Amphidinolide X. The coupling of acid **44** with segment **41** followed by ring closing metathesis in order to complete the total synthesis of Amphidinolide X is in progress in this laboratory.

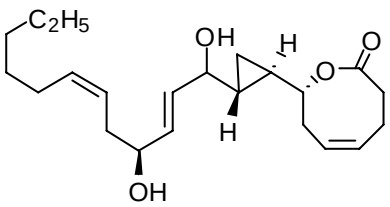
CHAPTER II: Studies Toward the Total Synthesis of Eicosanoid and Solandelactone

As a part of defense mechanism, marine organisms produce a fascinating range of secondary metabolites endowed with unusual and unexpected biological profiles. The arachidonic acid pathway in marine organisms provided a number of oxylipins containing the cyclopropyl-lactone groups.

Figure 1:



1, Eicosanoid



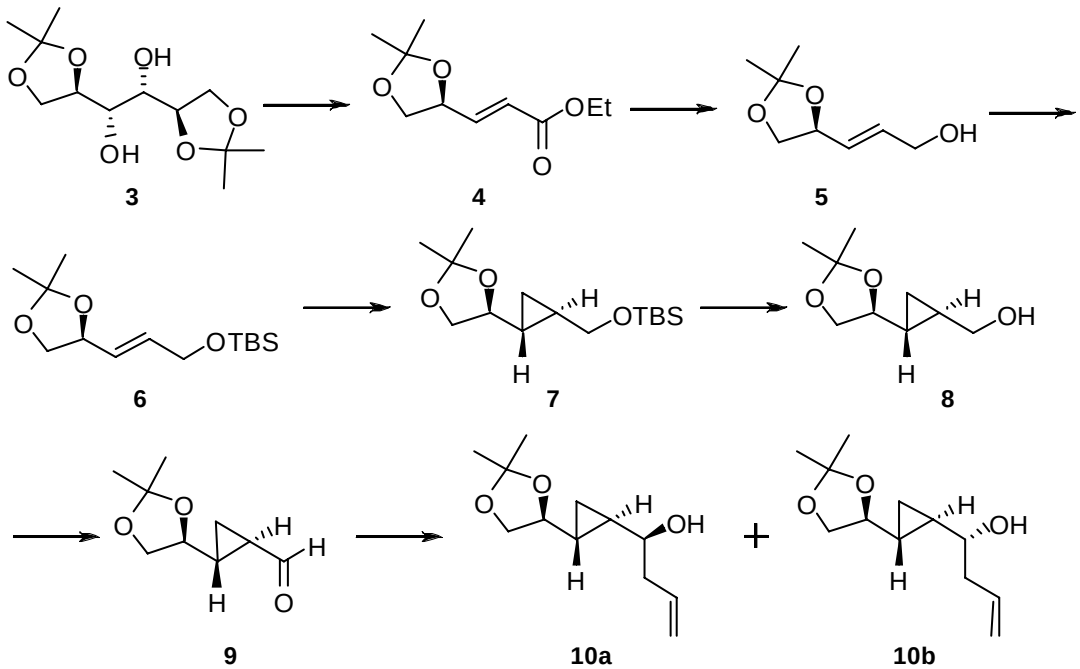
2, Solandelactones A-H

Eicosanoid **1** and Solandelactone **2** (Figure 1) are belonging to the growing class of oxylipins containing a trans-bifunctional cyclopropane ring and fatty acid lactones of marine origin. Eicosanoid **1** was isolated by the incubation of arachidonic acid with an acetone powder of the Caribbean soft coral *Plexaura homomalla*. Solandelactones (**2**) was isolated from the hydroid *Solanderia secunda* of Korean waters. In conjunction with other marine fatty acid metabolites, Eicosanoid **1** and Solandelactone **2** also incorporate a cyclopropane-lactone motif and lipoxygenase inhibiting activity and therefore provoked a considerable synthetic interest.

The retrosynthetic protocol for total synthesis of Eicosanoid and Solandelactone involved modified Simmons-Smith cyclopropanation, stereoselective reduction, ring-closing metathesis (RCM) and Nozaki-Hiyama-Kishi coupling reaction as key transformations.

The cyclopropyl alcohol **8** was prepared following reported procedure from D-mannitol with good overall yield. Oxidation of **8** and allyl Grignard reaction on the resulting aldehyde **9** afforded compound **10** as a 1:1 diastereomeric mixture of **10a** and **10b** (Scheme 1) separable with difficulty by repeated column chromatography.

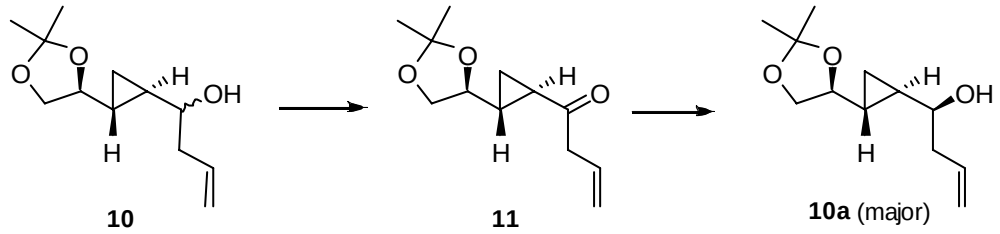
Scheme 1:



This problem was however circumvented by subjecting the homoallyl alcohol mixture to oxidation and selective reduction of the ketone compound with

K-selectride provided the diastereomers in the ratio of 9:1. The diastereomers were separated by column chromatography to provide the major homoallylic alcohol **10a**.

Scheme 2:

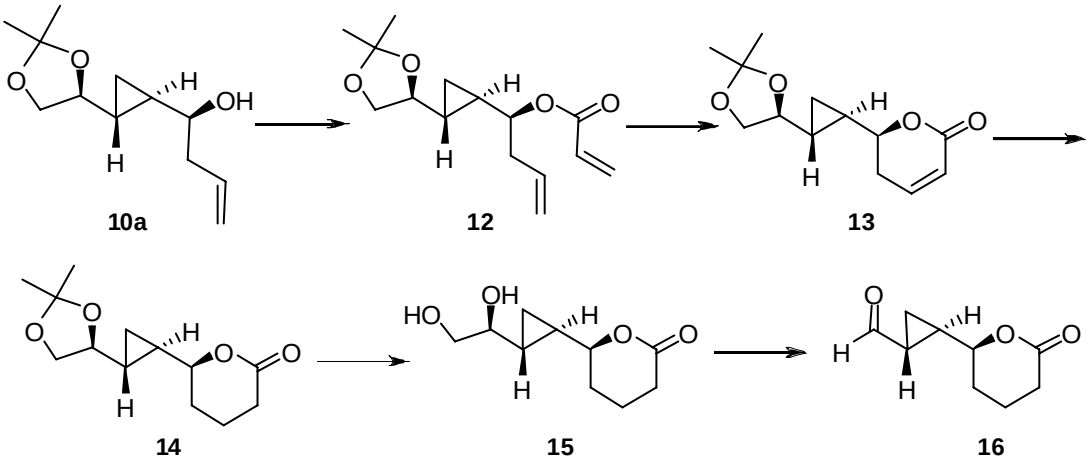


10 **11** **10a** (major)

The selectivity in reduction was rationalized on the basis of chelation controlled Cram's model. The stereochemistry as the newly created center bearing secondary hydroxyl group was assigned using modified Mosher's method. Thus alcohol **10a** was identified as the precursor of eicosanoid while alcohol **10b** was to be used for the synthesis of solandelactone.

The next job on hands was to construct the six-membered lactone ring. The (*S*)-alcohol **10a** was treated with acryloyl chloride to afford the ester **12**. Ring-closing metathesis was then attempted on **12**. Treatment of **12** with Grubbs' first generation catalyst in refluxing dichloromethane provided the desired six-membered lactone **13**. Reduction of the double bond, hydrolysis of acetonide group followed by oxidation with $NaIO_4$ afforded the aldehyde **16** (Scheme 3) in good overall yield.

Scheme 3:

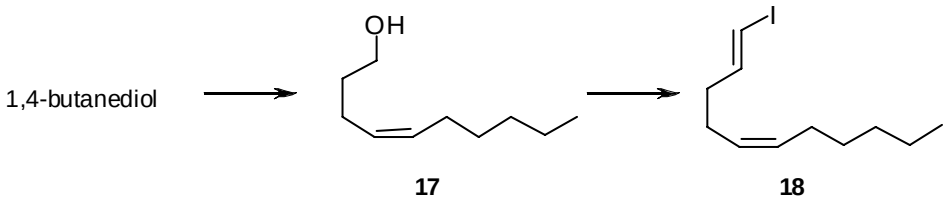


10a **12** **13**

14 **15** **16**

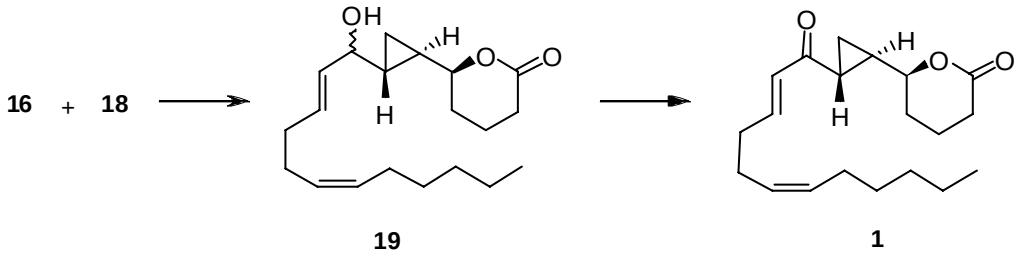
Side chain C_{10}-C_{20} of eicosanoid **1** was prepared starting from 1,4-butanediol, following standard reaction conditions. (1*E*,5*Z*)-1-iodo-1,5-undecadiene **18** was obtained in six steps as depicted in Scheme 4.

Scheme 4:



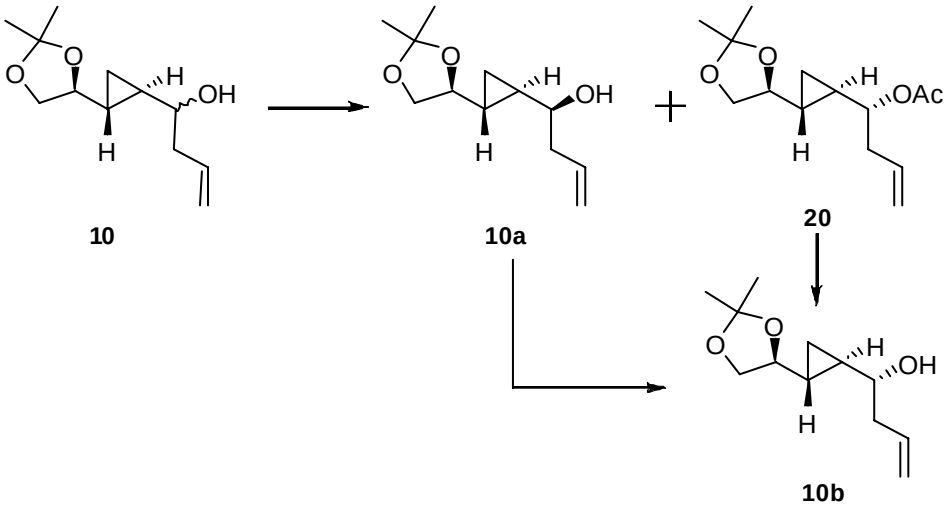
The final task was the introduction of the side chain on the cyclopropyl-lactone main core, which was achieved smoothly by subjecting compound **16** and **18** under Nozaki-Hiyama-Kishi coupling conditions to afford the corresponding allyl alcohol **19**. The total synthesis of Eicosanoid **1** was completed by oxidation of the derived hydroxyl group (Scheme 5). The spectral and analytical data of obtained product were identical in all respect to the reported data of the Eicosanoid **1**.

Scheme 5:



The next part of our endeavor was the total synthesis of Solandelactone **2**. In contradiction with earlier results for the preparation of alcohol **10a**, all our attempts to prepare alcohol **10b** in acceptable yield and chiral purity turned out to be failures. While looking for viable alternatives for the preparation of alcohol **10b**, it was decided to explore the enzymatic resolution strategy.

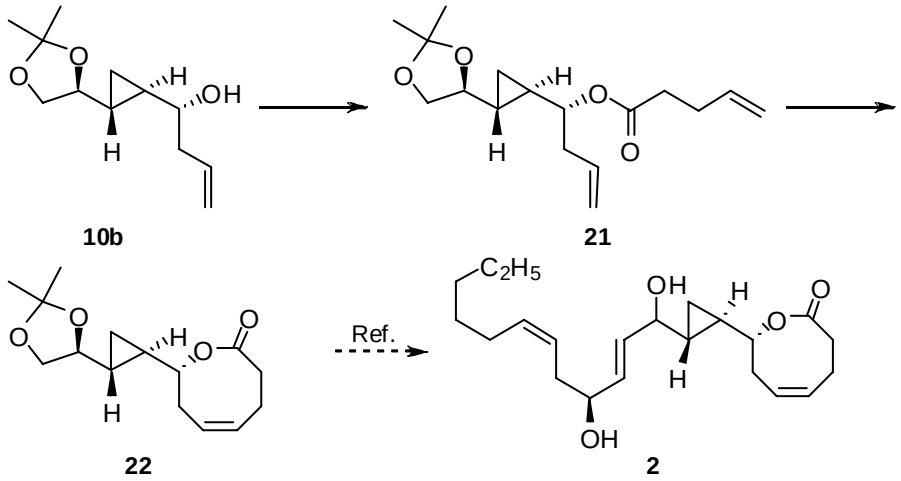
Scheme 6:



For the same when mixture of homoallylic alcohols **10a** and **10b** was subjected to Candida cylindracea lipase (CCL) which only facilitated the acylation of isomer **10b** keeping other isomer untouched, which afforded mixture of acetate **20** and homoallylic alcohol **10a** (Scheme 6). Hydrolysis of **20** afforded alcohol **10b** and alternatively alcohol **10a** converted to alcohol **10b** by Mitsunobu protocol.

Esterification of homoallyl alcohol **10b** was achieved by the treatment with 4-pentenoyl chloride. The attempts for ring-closing metathesis of compound **21** under different reaction conditions using Grubbs' first generation catalyst ended up with complete recovery of the starting material. The RCM reaction when tried with Grubbs' second generation catalyst in the presence of catalytic amount of Ti(O*i*-Pr)$_4$ under high dilution condition, the desired *Z*-isomer **22** was obtained in 71% yield (Scheme 7). The exclusive formation of the Z-isomer was confirmed by comparing the ^{1}H and ^{13}C NMR, IR value with the reported data. The total synthesis of solandelactone **2** can be achieved by introducing the side chains using the synthetic protocol published for the synthesis of constanolactones.

Scheme 7:



In conclusion, we have achieved the total synthesis of Eicosanoid and formal synthesis of Solandelactone starting from single intermediate. The strategy reported herein could be applied for getting different lactone as well as side chain motifs for a diversity oriented synthesis of the above natural products.

Chapter I

Studies Toward the Total Synthesis of Amphidinolide X

INTRODUCTION

For millions of years, humans and their ancestors suffered from diseases, of both the kinds caused by infectious pathogens (e.g., bacteria, viruses, parasites) and the kind caused by our own bodies as they age and degenerate. Over this long period, humans constantly created new ways of living and eating, and actual physical or genetic changes evolved to minimize the effects of these diseases. From the point of view of a bacteria or virus, however, any shift in the physical makeup or behavior of its human host represents not only an obstacle but also a challenge to be overcome. As a result, new diseases emerged with each major change in the human way of life. The engine that is driving the reemergence of many of the diseases is ecological change that brings humans into contact with pathogens.

Recently, much attention has been focused on the detrimental effects of industrialization on the international environment, including water, land, and atmosphere. Massive industrial production of commodities has caused pollution. Increasingly there is concern over the health implications of contaminated water supplies, over-use of pesticides in commercialized agriculture, atmospheric chemicals, and the future effects of a depleted ozone layer on human health and food production. At no other time in human history have the changes in the environment been more rapid or so extreme. Increasing incidence of cancer[1] and the increase in respiratory disease has been implicated in these environmental changes. World Health Organization (WHO) reports that 10 million people are infected with cancer in the world[2].

Cancer:

Cancer is a group of diseases in which cells are *aggressive* (grow and divide irrespective to normal limits), *invasive* (invade and destroy adjacent tissues), and sometimes *metastatic* (spread to other locations in the body). These three malignant properties of cancers differentiate them from benign tumors, which are self-limited in their growth and do not invade or metastasize (although some benign tumor types are capable of becoming malignant). Cancer may affect people at all ages, even fetuses, but risk for the more common varieties tends to increase with age. Cancer

causes about 13% of all deaths (caused by diseases).[2] Apart from humans, forms of cancer may affect other animals and plants.

John Hill first recognized[3] an environmental cause from the dangers of tobacco use in 1761 and published a book "Cautions Against the Immoderate Use of Snuff". Percivall Pott of London in 1775 described an occupational cancer of the scrotum caused by soot from chimney sweeps. This led to identification of a number of occupational carcinogenic exposures and public health measures to reduce cancer risk. This was the beginning of understanding that there may be an environmental cause to certain cancers.

Nearly all cancers are caused by abnormalities in the genetic material of the transformed cells[4]. These abnormalities may be due to the effects of carcinogens, such as tobacco smoke, radiation, chemicals, or infectious agents. Other cancer-promoting genetic abnormalities may be randomly acquired through errors in DNA replication[5], or are inherited, and thus present in all cells from birth. Complex interactions between carcinogens and the host genome may explain why only some develop cancer after exposure to a known carcinogen. New aspects of the genetics of cancer pathogenesis, such as DNA methylation, and microRNAs are increasingly being recognized as important.

Classification:

Cancers are classified[6] by the type of cell that resembles the tumor and, therefore, the tissue presumed to be the origin of the tumor. Examples of general categories include:

Carcinoma: Malignant tumors derived from epithelial cells. This group represents the most common cancers, including the common forms of breast, prostate, lung and colon cancer.

Sarcoma: Malignant tumors derived from connective tissue or mesenchymal cells.

Lymphoma and **leukemia:** Malignancies derived from hematopoetic (blood-forming) cells.

Germ cell tumor: Tumors derived from totipotent cells. In adults most often found in the testicle and ovary; in fetuses, babies, and young children most often found on the body midline, particularly at the tip of the tailbone.

Blastic tumor: A tumor (usually malignant) which resembles an immature or embryonic tissue. Many of these tumors are most common in children.

In developed and developing countries, on a yearly basis, 0.5% of the population is diagnosed with cancer. The statistics below are for perentagee of commonly occuring cancer types in recent years[2].

Table 1: *Commonly occuring cancer types*

By occurrence	By mortality
prostate cancer (33%)	lung cancer (31%)
breast cancer (32%)	breast cancer (15%)
lung cancer (13%)	prostate cancer (10%)
colorectal cancer (10%)	colorectal cancer (10%)
bladder cancer (7%)	pancreatic cancer (5%)
cutaneous melanoma (5%)	ovarian cancer (6%)
Lymphoma (4%)	Leukemia (4%)

Treatment on Cancer:

Once diagnosed, cancer is usually treated with a combination of surgery[7], chemotherapy[8] and radiotherapy[9]. The choice of therapy depends upon the location and grade of the tumor and the stage of the disease, as well as the general state of the patient (performance status). A number of experimental cancer treatments are also under development. Complete removal of the cancer without damage to the rest of the body is the goal of treatment.

Surgery:

In theory, cancers can be cured if entirely removed by surgery, but this is not always possible. When the cancer has metastasized to other sites in the body prior to surgery, complete surgical excision is usually impossible. This often limits its effectiveness.

Radiation therapy:

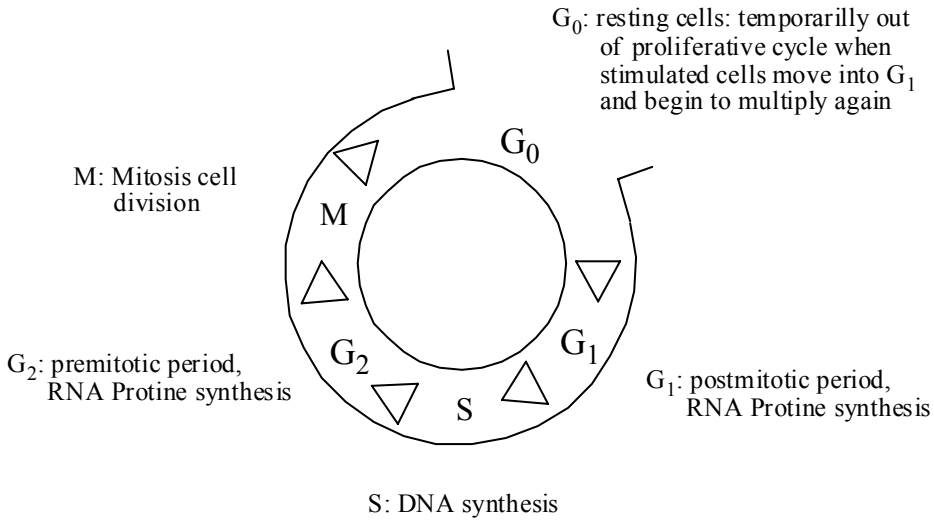
Radiation therapy (also called radiotherapy or irradiation) is the use of ionizing radiation to kill cancer cells and shrink tumors. Radiation therapy can be administered externally via external beam radiotherapy (EBRT) or internally via brachytherapy. The effects of radiation therapy are localised and confined to the region being treated. Radiation therapy injures or destroys cells in the area being treated (the "target tissue") by damaging their genetic material, making it impossible for these cells to continue to grow and divide. Radiation therapy may be used to treat

almost every type of solid tumor, including cancers of the brain, breast, cervix, larynx, lung, pancreas, prostate, skin, stomach, uterus, or soft tissue sarcomas.

Chemotherapy:

Chemotherapy is the treatment of cancer with drugs that can damage cancer cell by inhibiting biochemical reactions in cell cycle. The use of chemical agents to destroy cancer cells is a mainstay in the treatment of malignancies. The discovery of anticancer agents to treat the cancer was stated in early twentieth century during World War II and it is still continued. A major advantage of chemotherapy is its ability to treat widespread or metastatic cancer, whereas surgery and radiation therapies are limited to treating cancers that are confined to specific areas.

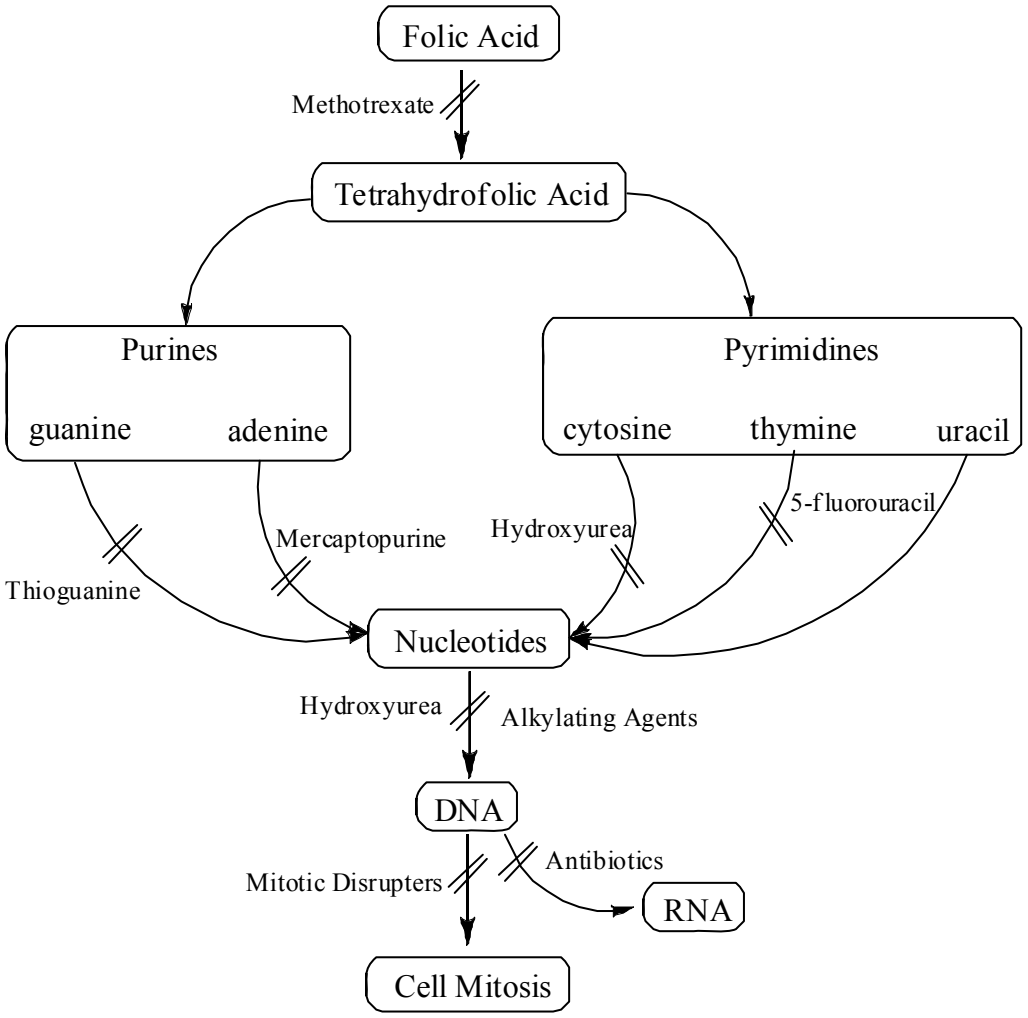
Figure 1: *Proliferative cell cycle of normal cell*



The main object of chemotherapeutic drugs is to destroy cancer cell without harming the healthy normal cells. Therefore it is necessary to understand the life cycle of cell. Normal cells divide and replicate in controlled manner (figure 1), while cancerous cells divide and replicate in uncontrolled manner. Therefore targeting some aspect of the cell growth cycle seems to be reasonable. Fast growing cells would be affected the most and slow growing cells would be least disturbed, is the basis for many chemotherapeutics.

Figure 2 represents exercise of anticancer agents, according to biochemical transformations that occur during phase cycle of the cells[10]. Thus by understanding the biochemical process of phase cycle of normal and cancer cell, type of actual treatment of cancer is manifested. Chemotherapy drugs are sometimes feared because of a patient's concern about toxic effects. Their role is to slow and hopefully halt the growth and spread of a cancer.

Figure 2: *Mechanism of chemotherapy according to cell cycle*



Chemotherapy varies with type of cancer and stage of its development and mode of action of anticancer agents. Reactions between DNA enzymes and anticancer agents are irreversible and shut down the functioning of the enzymes, leading to ultimate death of cell. In general, there are three goals associated with the use of the most commonly used anticancer agents and their mechanism of action[11].

1) Stop the synthesis of pre DNA molecule building blocks: These agents work in a number of different ways. DNA building blocks are folic acid, heterocyclic bases, and nucleotides, which are made naturally within cells. All of these agents work to block some step in the formation of nucleotides or deoxyribonucleotides (necessary for making DNA). When these steps are blocked, the nucleotides, which are the building blocks of DNA and RNA, cannot be synthesized. Thus the cells cannot replicate because they cannot make DNA without the nucleotides.

Examples: methotrexate (Abitrexate), fluorouracil (Adrucil), hydroxyurea (Hydrea), mercaptopurine (Purinethol).

2) Directly damage the DNA in the nucleus of the cell: These agents chemically damage DNA and RNA. They disrupt replication of the DNA and either totally halt replication or cause the manufacture of nonsense DNA or RNA (i.e. the new DNA or RNA does not code for anything useful).

Examples: cisplatin (Platinol), antibiotics - daunorubicin (Cerubidine).

3) Effect the synthesis or breakdown of the mitotic spindles: Mitotic spindles serve as molecular railroads with "North and South Poles" in the cell when a cell starts to divide itself into two new cells. These spindles are very important because they help to split the newly copied DNA such that a copy goes to each of the two new cells during cell division. These drugs disrupt the formation of these spindles and therefore interrupt cell division.

Examples: miotic disrupters- Vinblastine (Velban) and Pacitaxel (Taxol).

Unfortunately, the majority of drugs currently in the market are not specific, which lead to the many common side effects associated with cancer chemotherapy. Over time, cancer cells become more resistant to chemotherapy treatments. Recently, scientists have identified small pumps on the surface of cancer cells that actively move chemotherapy from inside the cell to the outside. Research on p-glycoprotein and other such chemotherapy efflux pumps, is currently ongoing. Medications to inhibit the function of p-glycoprotein are undergoing testing to enhance the efficacy of chemotherapy. On the other way it is necessary to discover and develop the new antitumor drugs to overcome this problem.

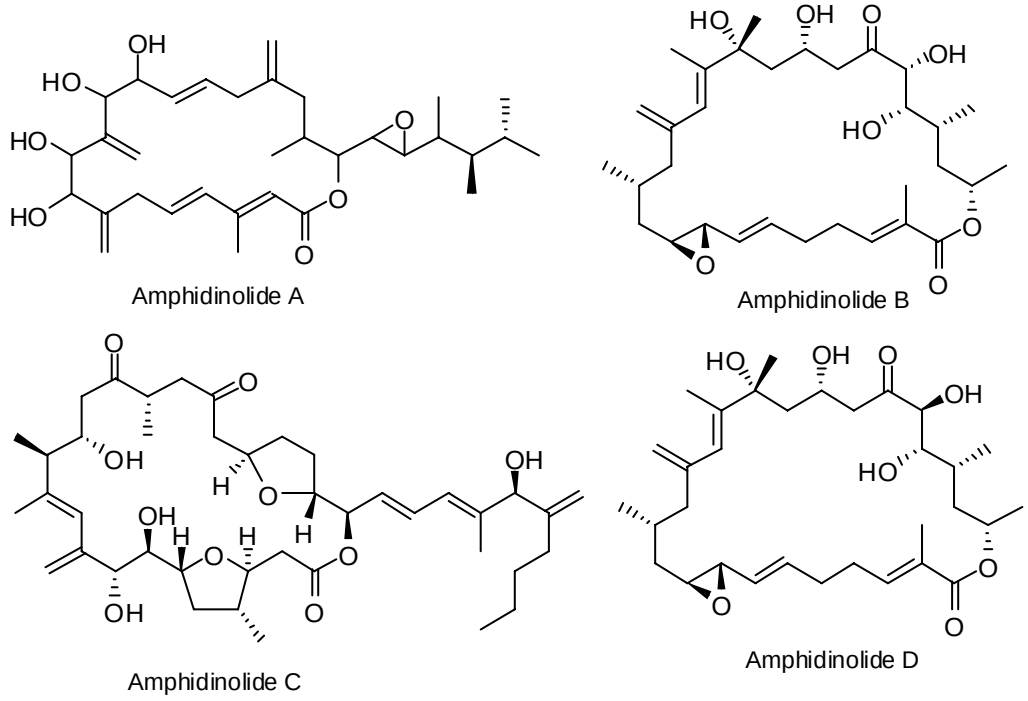
Our awareness of the importance of anticancer agents in cancer chemotherapy had been slow in early 1900. But when World declared war against cancer in 1971 the research accelarated in this area. The high level of current interest in anticancer agents is not limited to their discovery and devolopment for clinical use. Their scarcity of supply and their complex and unusual structures have offered real challenges to the biochemists, pharmacologists and organic chemists.

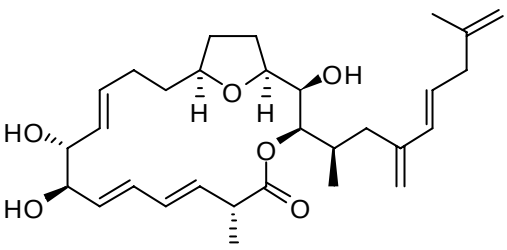
At the present time the amphidinolides[12] family has provided the most exciting news in cancer chemotherapy. Amphidinolides are showing the remarkable antitumor and cytotoxic activity as compared to other anticancer compounds. For this reasons it is clear that the study of amphidinolides is making rapid progress in a number of areas including synthesis, biochemistry and medicines.

Amphidinolides:

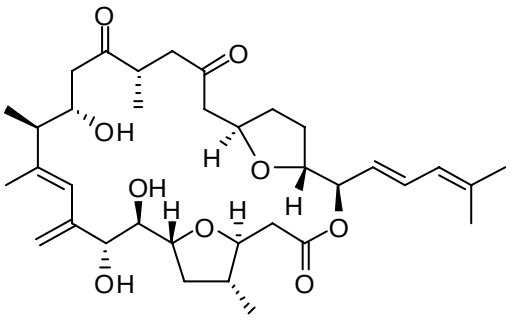
Marine microorganisms are an excellent source of bioactive natural products. A variety of structurally intriguing and biologically active secondary metabolites have served as leads for new drug discovery and developments. In search of new bioactive compounds from Okinawan marine organisms, Kobayashi and co-workers have carried out large scale cultures of symbiotic microalgae.[13] These microalgae were isolated from the marine invertebrates of the Okinawan coastal waters. One of the microalgae collected at Chatan beach is a dinoflagellate belonging to the *genus Amphidinium* (strain number Y-5), isolated[14] from the inner tissue of the host. This host was a flatworm of the genus *Amphiscolops* Graff, 1905 (green color), which was living on algae or seaweeds such as Enteromorpha and Janea app. The unialgal cultures of Amphidinium sp. (strain Y-5) led to the initial isolation of four cytotoxic macrolides, amphidinolides A, B, C and D (Figure 3). Additional species *of Amphidinium* were subjected to the extraction procedure, leading to the discovery of amphidinolides E-H. During the process of isolation, several fractions were found to exhibit cytotoxicity of greater potency than any of the amphidinolides A-H. Further investigation of these cultures led to the discovery of related macrolides, amphidinolides J-Y.

Figure 3: *Structures of some amphidinolides:*

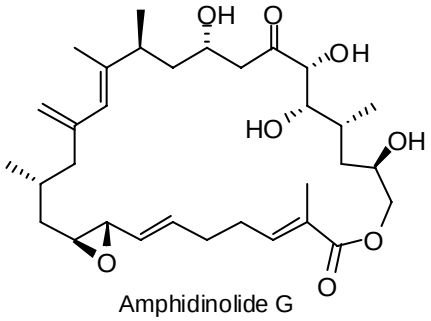




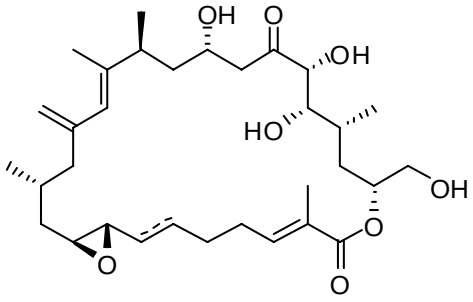
Amphidinolide E



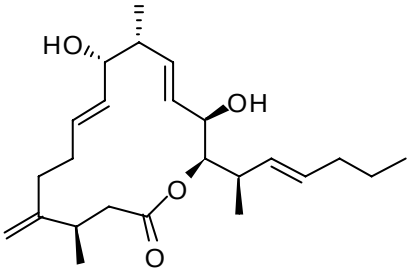
Amphidinolide F



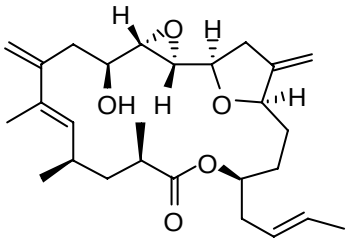
Amphidinolide G



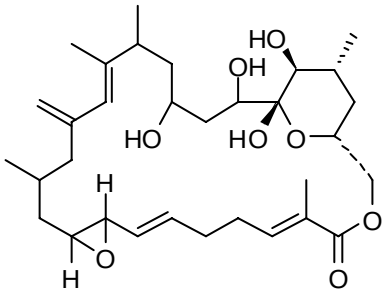
Amphidinolide H



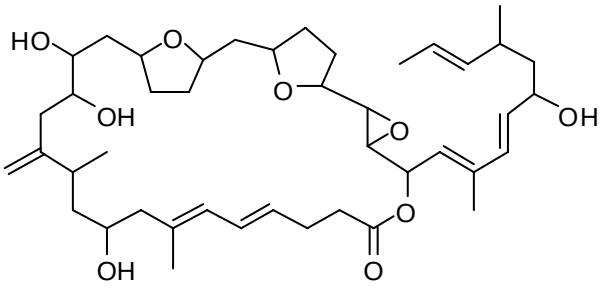
Amphidinolide J



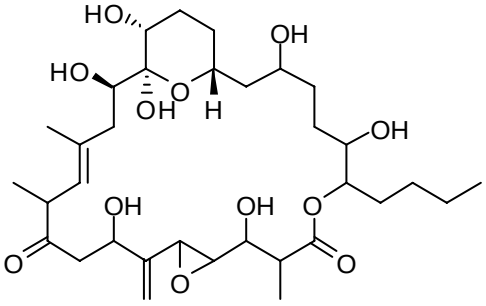
Amphidinolide K



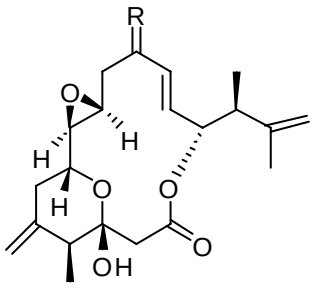
Amphidinolide L



Amphidinolide M

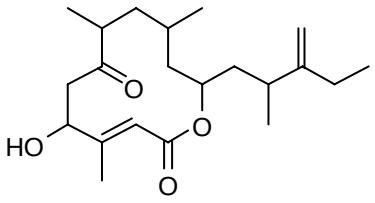


Amphidinolide N

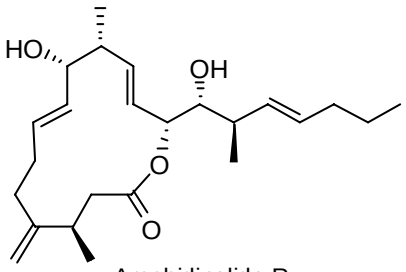


Amphidinolide O R = O

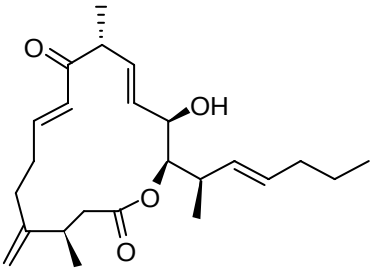
Amphidinolide P R= CH_2



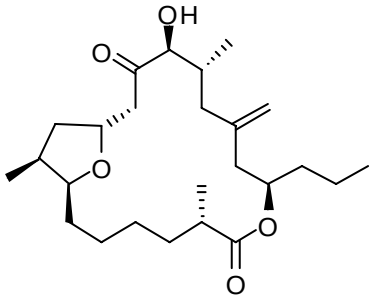
Amphidinolide Q



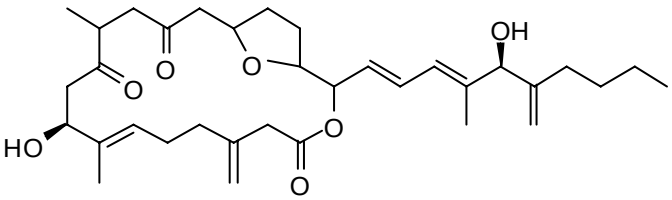
Amphidinolide R



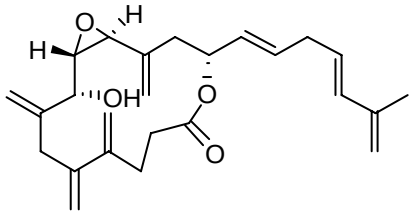
Amphidinolide S



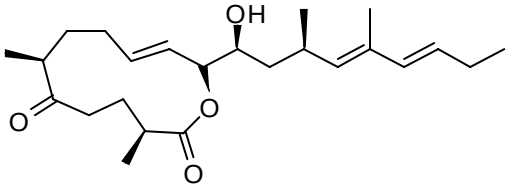
Amphidinolide T_1



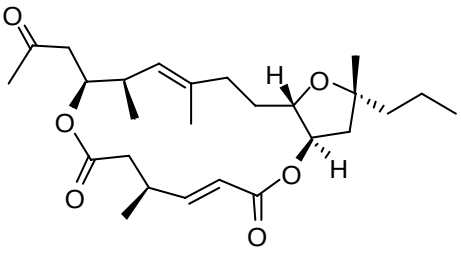
Amphidinolide U



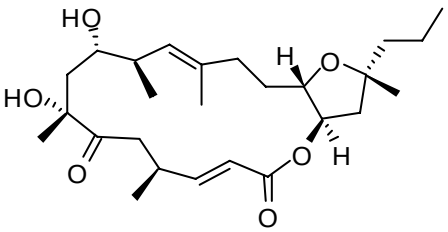
Amphidinolide V



Amphidinolide W



Amphidinolide X



Amphidinolide Y

Amphidinolides are a series of unique cytotoxic macrolides, many of which have shown significant antitumor properties against a variety of NCI tumor cell lines.[15] Table 1 summarizes the notable anticancer activity of the amphidinolides, highlighting the activity of B, C, G, H, N and X, which display the greatest potency.

Table 2: *Summary of the Cytotoxicity of the Amphidinolides.*

Amphidi-nolide	Cytotoxicity (IC_{50} μg/ml)		Amphidi -nolide	Cytotoxicity (IC_{50} μg/ml)	
	L1210	KB		L1210	KB
A	2	5.7	M	1.1	0.44
B	0.00014	0.0042	N	0.00005	0.00006
C	0.0058	0.0046	O	1.7	3.6
D	0.019	0.08	P	1.6	5.8
E	2	10	Q	6.4	>10
F	1.5	3.2	R	1.4	0.67
G1	0.0054	0.0059	S	4	6.5
G2	0.3	0.8	T1	18	35
G3	0.72	1.3	T2	10	11.5
H1	0.00048	0.00052	T3	7	10
H2	0.06	0.06	T4	11	18
H3	0.002	0.022	T5	15	20
H4	0.18	0.23	U	12	20
H5	0.2	0.6	V	3.2	7
J	2.7	3.9	W	3.9	-
K	1.65	2.9	X	0.6	7.5
L	0.092	0.1	Y	0.8	8

In addition to the striking biological activity of the amphidinolides, they possess several interesting structural features. This family of macrolides shows diversity in size, including lactones of odd-numbered ring size, and displays an abundance of stereogenic centers, exo- and endocyclic double bonds, and oxygen-containing substituents (including epoxides, THF and THP rings, hydroxyl groups, and ketones). Due to their remarkable biological activity and structural functionality, the amphidinolides are ideal and challenging synthetic targets. Since the first reports of the amphidinolide family, considerable effort has been focused on synthesizing these macrolides, resulting in several innovative and efficient total syntheses.

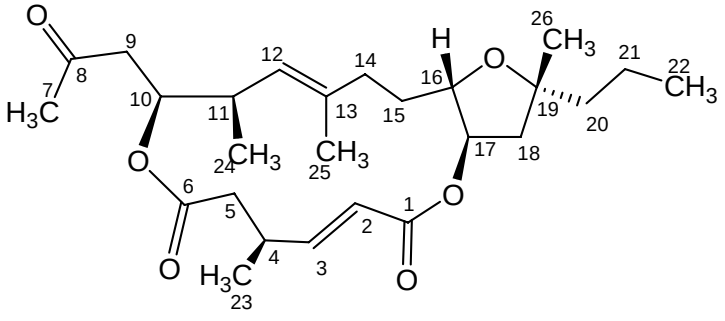
The several groups made numerous contributions in the syntheses of the amphidinolide natural products[16]. Many of them had achieved the total synthesis of some amphidinolides. Notably, Maleczka group was done total synthesis of amphidinolide A and Kobayashi group made the total synthesis of amphidinolide B and H. Williams group was succeeded in total syntheses of amphidinolide J, K and

P. Dai group and Lee group established the total synthesis of amphidinolide Y and E respectively. Furstner group had done major contribution by achieving total synthesis of T1, T3, T4, T5 and X while Ghosh group completed the total synthesis of amphidinolide T1 and W. On the other hand various groups were made contribution through the synthesis of fragments of some of the amphidinolides. All of the reported syntheses of the amphidinolide natural products are highly convergent. All syntheses highlighted the power for the stereocontrolled assembly of substituted tetrahydrofuran rings. During synthesis of amphidinolides all groups established several important methods for fragment coupling and also demonstrated a different method of macrolactone ring formation. In summary, the amphidinolide natural products present several challenges to the synthetic organic chemist.

Amphidinolide X:

Amphidinolide X (**1**), one of the more potent members was isolated[17] from a marine dinoflagellate *Amphidinium* sp. by the research group of Kobayashi in the strain Y-42. The gross structure of **1** was elucidated on the basis of spectroscopic data including one-bond and long-range ^{13}C-^{13}C correlations. The relative and absolute stereochemistries were also determined by combination of analysis of NOESY data with ^{1}H-^{1}H and ^{1}H-^{13}C coupling constant of **1**. The relative stereochemistry for C-10/C-11 was elucidated to be *erythro* by *J*-based configuration analysis, while that of the tetrahydrofuran portion was assigned on the basis of NOESY data. The absolute configurations at C-10 and C-17 were elucidated to be *S* and *R*, respectively, by application of modified Mosher's method.[18]

Figure 4: *Amphidinolide X*



1

Amphidinolide X (**1**) has neither the characteristic *exo*-methylene group, nor a vicinal one-carbon branch, nor a 1,3-diene unit found in virtually all other members of this series. Moreover, **1** is the only naturally occurring macrodiolide known to date that consists of a diacid and a diol unit rather than two hydroxyacid entities. Amphidinolide X (**1**) possesses a very unique arrangement of functionalities in its backbone. The upper half of the molecule bears one hydroxyl group in addition to a ketone carbonyl. The other half of the molecule contains tetrahydrofuran ring bearing quaternary center and two ester linkages. The molecule features a total of six stereogenic centers which include one quaternary center at C_{19} in addition to two isolated methyl bearing stereocenters at C_{11} and C_4 and three C-O centers at C_{10}, C_{16} and C_{17}. The most interesting structural features from a synthetic standpoint are the two ester linkages and two olefin moieties.

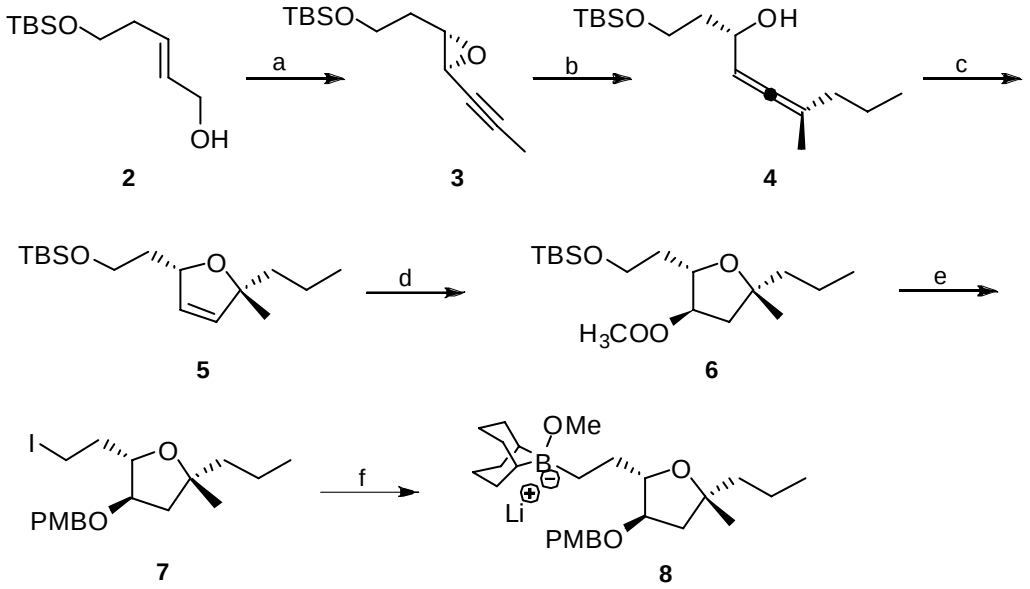
Biological assays have placed amphidinolide X as among of the most cytotoxic in the family of amphidinolides. It shows moderate cytotoxicity against L1210 (IC_{50} 0.6 μg/mL) and KB (IC_{50} 7.5 μg/mL) cell lines.[15] Although assays have been performed to determine its biological activity, there have been no reports about the mechanism of action of amphidinolide X. Sparse amounts available from natural sources and the lack of a total synthesis of the compound have severely hindered such studies. The synthetic community at large has been interested in achieving a total synthesis of this molecule. These rather unique structural features together with the promising cytotoxicity of **1** against murine lymphoma and human epidermoid carcinoma prompted us to pursue a total synthesis of this scarce compound. Herein we describe the chronology of events that led to the total effective synthesis of the synthones of **1** along with efficient assembly of these fragments.

Previous Approaches for the Total Synthesis of Amphidinolide X:

During our synthetic studies the first total synthesis of **1** was reported. Fürstner and co-workers recently reported[19] the first total synthesis of amphidinolide X (**1**) via construction of C13-C14 bond between tetrahydrofuran fragment (C14–C22) and a keto-alkene (C1–C13) by metal catalyzed cross coupling and finally formation of macrolactone ring using Yamaguchi lactonization. The tetrahydrofuran fragment was synthesized starting with a Sharpless asymmetric epoxidation of allyl alcohol **2** to corresponding epoxide, which was further transformed to propargyl epoxide **3**. Treatment of this propargyl epoxide and *n*-PrMgCl under iron-catalyzed

reaction conditions led to a chiral allene **4**. This was latter cyclized to the tetrahydrofuran ring **5** fixing the stereochemistry of quaternary center (at C19). The hydroxyl center at C-17 was installed via bromoesterification-dehalogenation sequence of reactions to get compound **6**. It was transformed to corresponding borate **8** through its iodo derivative **7** and with some protecting group manipulations (Scheme 1).

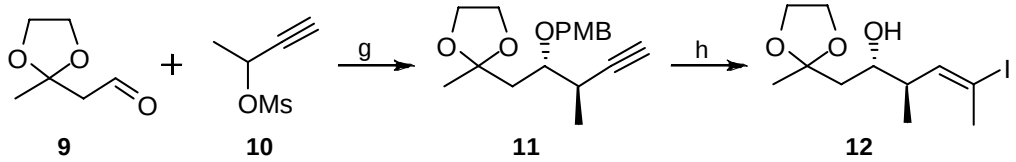
Scheme 1:



Reagents and conditions: [a] (i) $Ti(OiPr)_4$, (+) DET, *t*BuOOH, MS 4Å, CH_2Cl_2. (ii) oxalylchloride, DMSO, Et_3N, CH_2Cl_2; (iii) $(MeO)_2P(O)C(N_2)COMe$, K_2CO_3, MeOH; (iv) LiHMDS, MeOTf, THF; [b] PrMgCl, $Fe(acac)_3$, toluene; [c] $AgNO_3$, $CaCO_3$, aq. acetone; [d] (i) NBS, DMF/H_2O (15/1); (ii) AIBN, $(TMS)_3SiH$, toluene; [e] (i) $NaHCO_3$, MeOH; (ii) $PMBOC(dNH)CCl_3$, PPTS, CH_2Cl_2/C_6H_{12}; (iii) TBAF, THF; (iv) PPh_3, imidazole, I_2, MeCN/Et_2O; [f] *t*BuLi, 9-MeO-9-BBN, Et_2O/THF.

The other fragment (C1-C13) was prepared starting from the zinc mediated palladium catalyzed reaction of acetal **9** with propargyl mesylate **10** to obtain desired anti configurated product **11** which was further converted to vinyl iodo derivative **12** (Scheme 2).

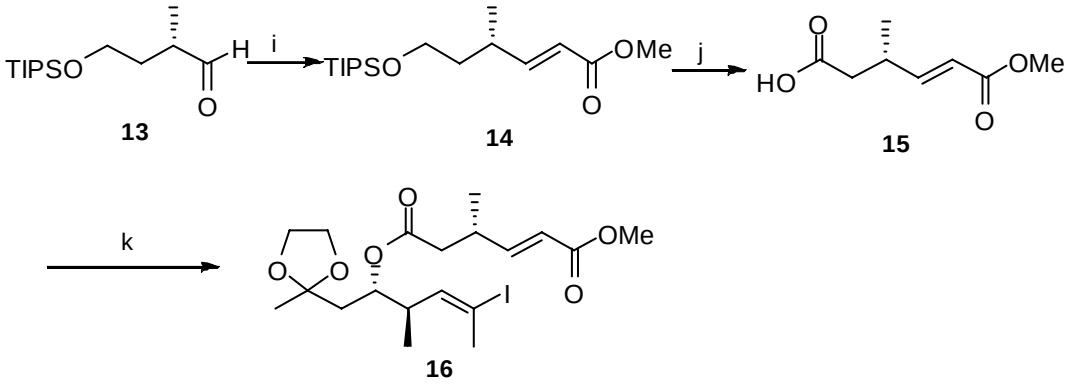
Scheme 2:



Reagents and conditions: [g] (i) Et_2Zn, $Pd(OAc)_2$, PPh_3, THF; (ii) PMBCl, NaH, TBAI, DMF; [h] (i) LiHMDS, MeI, THF; (ii) Cp_2ZrHCl, C_6H_6; (iii) I_2, CH_2Cl_2; (iv) DDQ, CH_2Cl_2, *p*H 7 buffer;

The third side chain **15** was easily prepared from **13** and further esterification with alcohol **12** furnished second coupling partner **16** (Scheme 3).

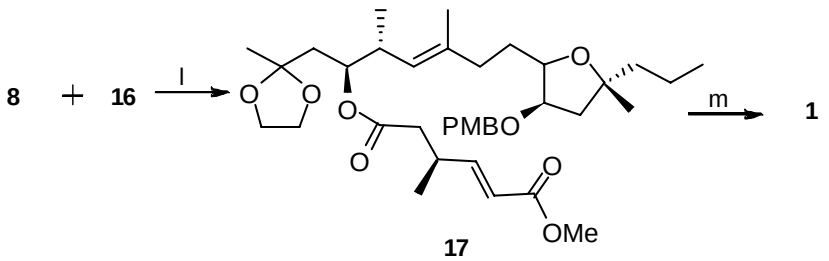
Scheme 3:



Reagents and conditions: [i] (i) $(EtO)_2P(O)CH_2COOMe$, LiCl, DBU, MeCN; [j] (i) HF-pyridine, MeCN; (ii) oxalylchloride, DMSO, Et_3N, CH_2Cl_2; (iii) $NaClO_2$, NaH_2PO_4, $(CH_3)_2C{=}CHCH_3$, *t*BuOH; [k] **12**, 2,4,6-trichlorobenzoyl chloride, DMAP, Et_3N, toluene.

Both the coupling partners **8** and **16** were coupled by employing Suzuki cross coupling condition to form ester **17** which further cyclized under Yamaguchi's conditions to achieve the total synthesis amphidinolide X (**1**).

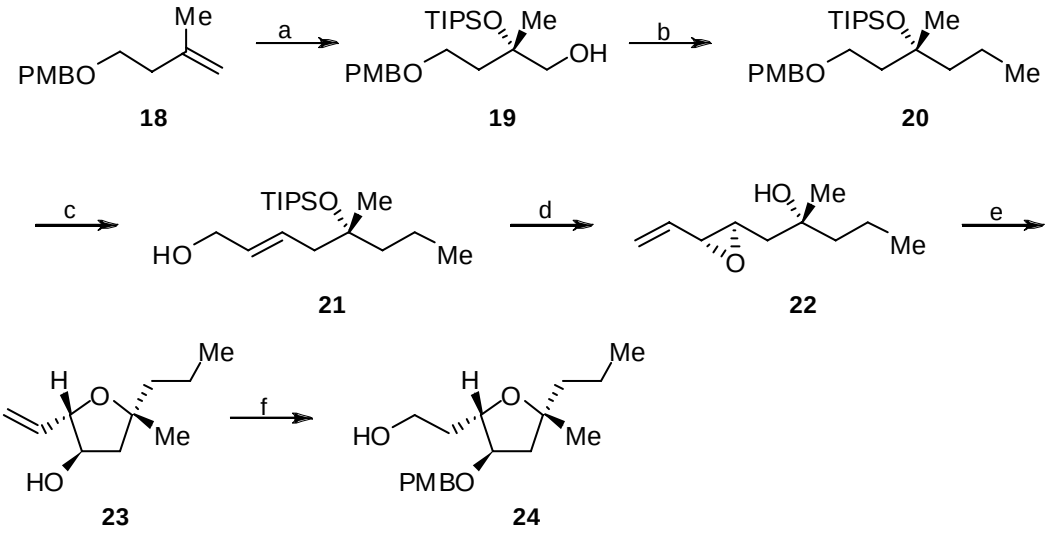
Scheme 4:



Reagents and conditions: [l] (i) *t*BuLi, Et_2O/THF, 9-MeO-9-BBN; [m] (i) $(dppf)PdCl_2$, Ph_3As, K_3PO_4, aq. DMF; (ii) LiI, pyridine, 125 °C; (iii) aq. AcOH; (iv) DDQ, CH_2Cl_2, *p*H 7 buffer; (v) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, DMAP.

In parallel with our studies, Wei-Min Dai and co-workers reported[20] the synthesis of the tetrahydrofuran fragment of Amphidinolide X. They assembled oxygenated chiral quaternary center by asymmetric dihydroxylation in high enantioselectivity and the tetrahydrofuran ring was constructed by an acid-catalyzed 5-*endo* ring-opening cyclization of the epoxide (**22**) possessing a vinyl moiety as depicted in Scheme 5.

Scheme 5:



Reagents and conditions: a) (i) AD-mix-α, *t*-BuOH–H_2O (1:1), 0 °C, 2h; (ii) Piv.Cl, DMAP, Et_3N, CH_2Cl_2, rt., 6h; (iii) TIPSOTf, 2,6-lutidine, CH_2Cl_2, rt., 24h; (iv) DIBAL-H, PhMe, –78 °C to 0 °C, 2h; b) (i) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, Et_3N, –78 °C to rt.; (ii) $Ph_3P^+EtBr^-$, *n*-BuLi, THF, –10 °C, 3h; (iii) Pd/C, H_2, EtOH–EtOAc (1:1), rt., 6h; c) (i) CAN, MeCN–H_2O (3:2), 0 °C, 10 min; (ii) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 2h, Et_3N, –78 °C to rt.; (iii) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, rt., 24h; (iv) DIBAL-H, PhMe, –78 °C to 0 °C, 3h; d) (i) $Ti(O\textit{i}\text{-}Pr)_4$, D(–)DET, *t*-BuOOH, 4 Å MS, CH_2Cl_2, –20 °C, 24h; (ii) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 2h, Et_3N, –78 °C to rt.; e) (i) $Ph_3P^+MeBr^-$, KHMDS, THF, –10 °C, 3h; (ii) $n Bu_4NF$, THF, reflux, 0.5h f) (i) CSA, CH_2Cl_2, –40 °C to rt., 6h; (ii) NaH, PMBCl, MeCN, rt., 32h; (iii) $BH_3{\cdot}SMe_2$, THF, 0 °C, 2h; then aq. NaOH, H_2O_2, 0 °C to rt., 2h.

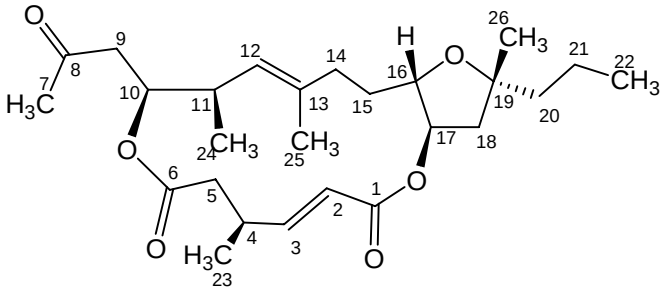
Since from isolation of amphidinolide X, there has been renewed interest in the synthetic community in realizing the goal of a total synthesis of this molecule. Only Fürstner and co-workers achieved total synthesis of this molecule. Our synthetic strategy represents a novel approach towards total synthesis of

amphidinolide X. Our longstanding interest in the chemistry of carbohydrates and their use in total synthesis of natural products inspired us to synthesize amphidinolide X using suitable carbohydrate precursor. From the inception of our investigations, we planned to synthesize the 16-membered macrocycle using the modified Julia olefination reaction and Yamaguchi lactonization. Additionally, we intended to utilize a one-shot allyl substitution and acetonide deprotection to install a required stereochemistry at quaternary center. We contemplated to synthesize amphidinolide X using chiron approach, beginning from L-sorbose.

PRESENT WORK

The amphidinolides are the series of chemically unique and biologically interesting secondary metabolites from marine dinoflagellates. There are 25 amphidinolides isolated from extracts of marine dinoflagellates[21] of the genus *Amphidinium*, which are symbionts of Okinawan marine acoel flatworms, *Amphiscolops* spp. These macrolides have a variety of backbone skeletons and different sizes of macrocyclic lactone rings (12 to 29 membered). Most of the amphidinolides exhibit potent cytotoxicity and antitumor activity and have attracted great interest as challenging targets for total synthesis and biosynthetic studies.

Figure 1: *Amphidinolide* X



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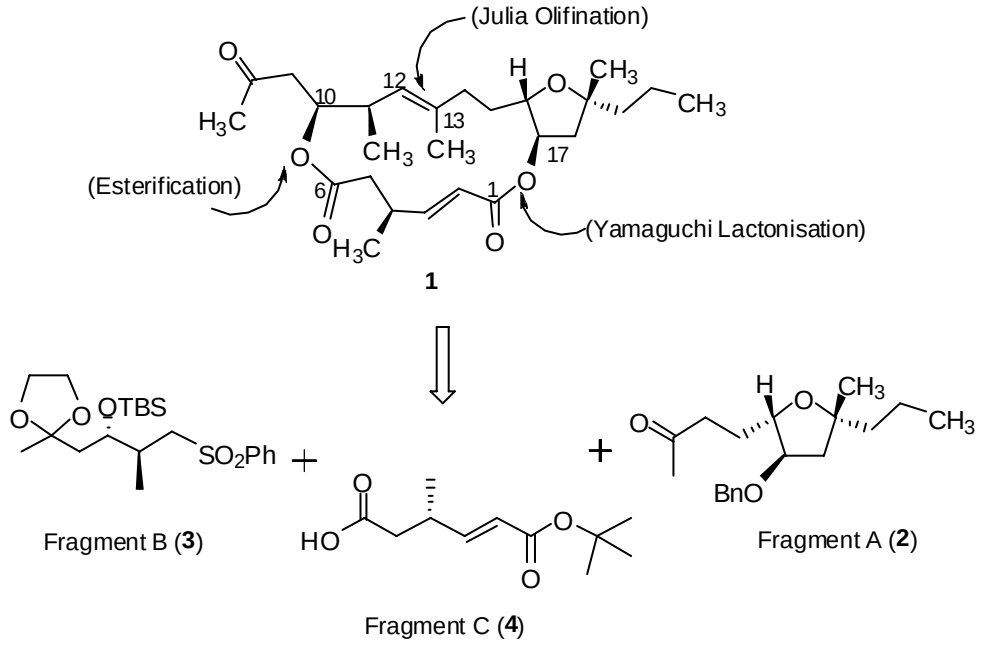
Amphidinolide X (**1**), a 16-membered macrodiolide, has been recently isolated[18] from a marine dinoflagellate *Amphidinium* sp. The gross structure of **1** was elucidated on the basis of spectroscopic data including one-bond and long-range ^{13}C-^{13}C correlations. The relative and absolute stereochemistries were also determined by analysis of NOESY data in combination with ^{1}H-^{1}H and ^{1}H-^{13}C coupling constant of **1**. Amphidinolide X shows moderate cytotoxicity against L1210 (IC_{50} 0.6 µg/mL) and KB (IC_{50} 7.5 µg/mL) cell lines.

Amphidinolide X, however, has neither the characteristic *exo*-methylene group nor a 1,3-diene unit found in virtually all other members of this series. Moreover, **1** is the only naturally occurring macrodiolide known to date that consists of a diacid and a diol unit rather than of two hydroxyacid entities. These rather unique structural features together with the promising cytotoxicity of **1** against murine lymphoma and human epidermoid carcinoma, attracting attention as potential cancer drug and henceforth prompted us to pursue its total synthesis.

Retrosynthetic Analysis:

As amphidinolide X consists the ester linkages forming the macrodiolide ring, these were envisaged as obvious sites of disconnection. Amphidinolide X was planned to be assembled from three building blocks namely the tetrahydrofuran fragment A (**2**), upper left keto moiety containing fragment B (**3**) and lower dicarbonyl entity fragment C (**4**) (Figure 2). The major disconnections are at the C12-C13, C6-O and C1-O bonds. The critical carbon-carbon bond formation (C12-C13) between fragment A and B was planned using modified Julia coupling[22]. The ester linkage between C6-O can be built by the coupling of the requisite acid and alcohol under suitable conditions. The final lactonization at C1-O bond employing Yamaguchi conditions[23] to construct 16 membered multi-functionalised macrolactone ring was the another key transformation.

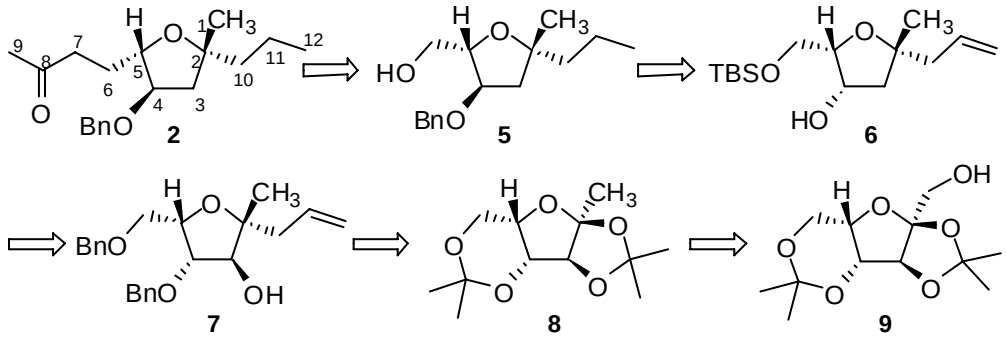
Figure 2: *Retrosynthetic Analysis of Amphidinolide X*



Fragment A was planned to be synthesized from L-sorbose using a tactical combination of transformations, as outlined in Scheme 1. The extended ketone chain of **2** could be easily prepared from alcohol **5** by means of corresponding Wittig reaction and subsequent reduction of resultant double bond. Synthesis of compound **5** would be planned from **6** by the inversion of stereochemistry at C4 using Mitsunobu protocol[24] along with reduction of terminal double bond. Compound **6** was to be prepared from **7** by deoxygenation at C3 followed by some protecting group manipulations. Installation of the quaternary center in compound **7** with desired stereochemistry was the critical transformation and was contemplated

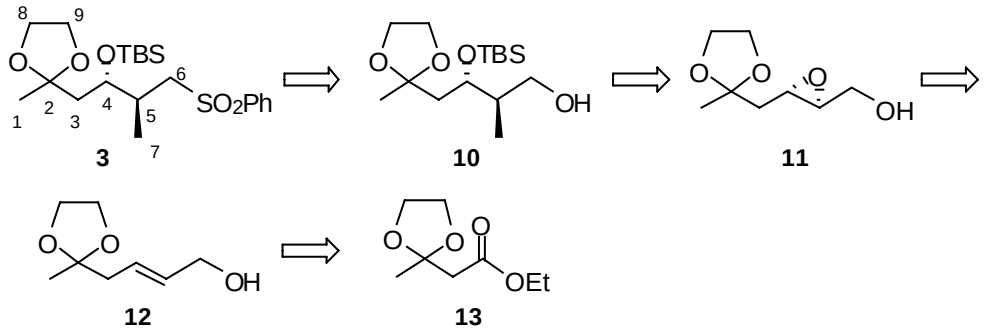
employing allylation and isopropylidene deprotection in one shot. The compound **8** was to be procured from L-sorbose through isopropylidine protection followed by deoxyganation.

Scheme 1:



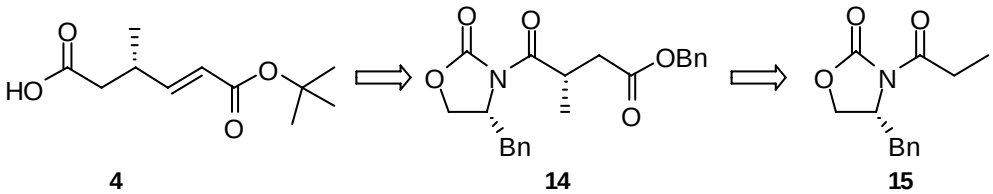
Fragment B (**3**) was visualized from ethyl acetoacetate by using Sharpless asymmetric epoxidation[25] and regioselective epoxide opening as key steps (Scheme 2). Sulfone **3** was planned from corresponding alcohol **10**. The alcohol **10** bearing methyl and hydroxyl centers could be prepared by stereoselective and regioselective opening of 2(*S*), 3(*S*)-epoxide **11** using methyl magnesium chloride. The 2(*S*),3(*S*)-epoxide **11** was to be prepared using Sharpless asymmetric epoxidation of allyl alcohol **12**, which in turn was to be synthesized from protected ethyl acetoacetate **13**.

Scheme 2:



Fragment C was planned using Evans' alkylation protocol[26] (Scheme 3). The acid **4** would be obtained from alkyl oxazolidinone **14** over three steps namely oxazolidinone cleavage, oxidation followed by corresponding two carbon Wittig reaction. Compound **14** being a product of Evans' alkylation of **15**.

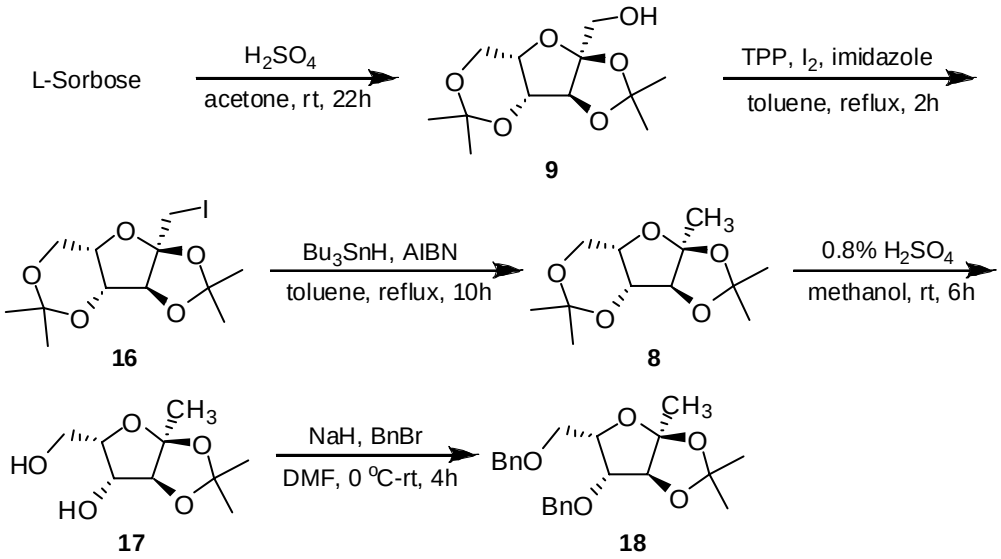
Scheme 3:



Synthesis of Fragment A:

Our synthesis of fragment A began with the preparation of 2,3:4,6-di-*O*-isopropylidene-L-sorbose (**9**) employing literature procedure[27] (Scheme 4). The spectroscopic and other analytical data of **9** were in agreement with the reported[27] data. The primary hydroxyl group at C1 of **9** was converted to its iodo derivative **16** by treating with triphenyl phosphine, imidazole and iodine in refluxing toluene. Compound **16** was treated with tributyltin hydride in presence of catalytic AIBN in toluene under reflux conditions to provide corresponding deoxy derivative **8**. The signal integrating for three protons appeared at δ 1.72 in the ^{1}H NMR spectrum and the carbon resonated at 18.5 ppm in the ^{13}C NMR spectrum indicating presence of methyl group. The structure was further supported by the mass spectrum with the highest molecular ion peak at *m/z* 267 $[M+Na]^{+}$. The next job was to remove 4,6-isopropylidene protection selectively keeping the other 2,3-isopropylidene protection intact. This was achieved by using 0.8% H_2SO_4 in MeOH at room temperature to get diol **17**. The selective mono acetonide deprotection was evident from the ^{1}H NMR spectrum where signals due to one of the isopropylidene groups were absent.

Scheme 4:



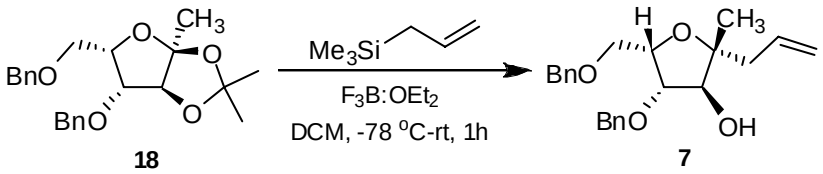
Both the free hydroxyl groups in **17** were masked as their benzyl ethers by treatment with sodium hydride followed by benzyl bromide in DMF at ambient tempareture to furnish its dibenzyl derivative **18**. The presence of the benzyl groups was evident from the ^{1}H NMR spectrum where signals due to benzylic protons at δ 4.50 and 4.64 integrating for four protons and aromatic protons at δ 7.31 integrating

for ten protons were observed. Moreover in the ^{13}C NMR spectrum the bezylic carbons were seen at δ 71.8 and 73.4 alongwith the signals for aromatic carbons present in the molecule. In the mass spectrum the molecular ion peak was seen at *m/z* 407 $[M+Na]^+$ which further supported the structure. The elemental analysis was also found to match with the calculated values for **18**.

The next task was installation of allyl group at C2 of tetrahydrofuran moiety and to generate the quaternary centre with the desired stereochemistry. After extensive literature investigations,[28] it was thought that allylation and 2,3-isopropylidene deprotection when carried out in one shot should provide the required result. This conjecture was based on the possible mechanism of the transformation.

Thus the dibenzyl derivative **18** on treatment with allyl trimethylsilane and BF_3-etherate in DCM at -78 ^oC to room temperature afforded allyl derivative **7** with high stereoselectivity (Scheme 5). The deprotection of isopropylidene group and installation of allyl group was evident from the ^1H NMR spectrum of **7**. Signals due to allyl group appeared at δ 2.38 (d, 2H), 5.02-5.10 (m, 2H) and 5.73-5.94 (m, 1H). In the ^{13}C NMR spectrum, allyl group carbons were resonated at δ 44.8, 118.0 and 134.2 while newly generated quaternary carbon (C2) resonated at 82.4 ppm. Other analytical data also supported the structure of **7** beyond any doubt. The stereochemistry of newly generated stereocentre was confirmed by COSY and NOESY experiments.

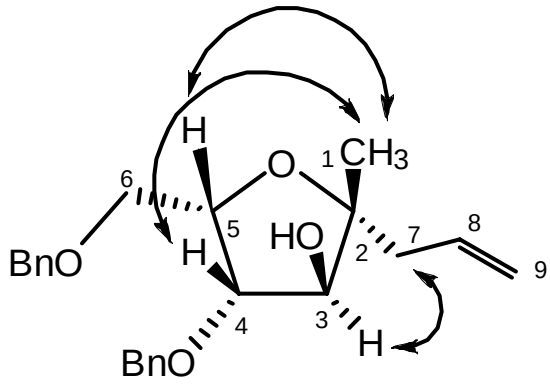
Scheme 5:



18 **7**

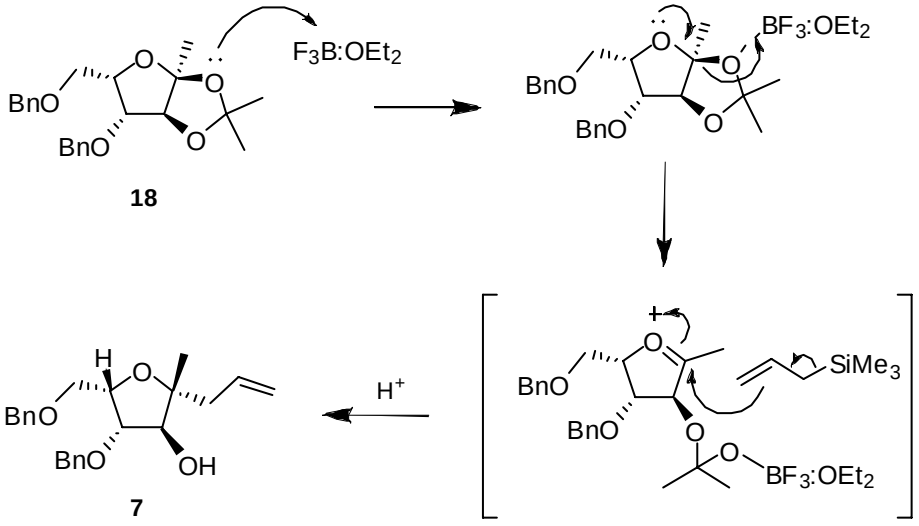
The NOESY analysis of **7** showed a strong NOE between C1-Me and C5-H as well as C1-Me and C4-H indicating their *cis*-relationship whereas C3-H showed NOE signals with C7 methylenic proton and confirmed *cis*-relationship between C3-H and C7 methylenic protons. The fact that there was no NOE observed between C1-Me and C3-H indicated their *trans* relationship. These observations evidently confirmed the stereochemical assignment of **7** (Figure 3).

Figure 3: *Key NOE interactions of 7*



The observed outcome of the allylation reaction can be explained on the basis of the plausible mechanism depicted in figure 4. The isopropylidine oxygen at C2 chelats with lewis acid and cleavage of C2-O bond is assisted due to electron donation from furan ring oxygen. The C2 carbon bears hybridization at its transition state in which all groups on C2 are in plane. The allyl group attacks on C2 from opposite side of hydroxyl group of C3 because of steric hindrance. This results the C1-methyl and hydroxyl group at C3 fixing in syn conformation resulting into desired stereochemistry at C2 quaternary center.

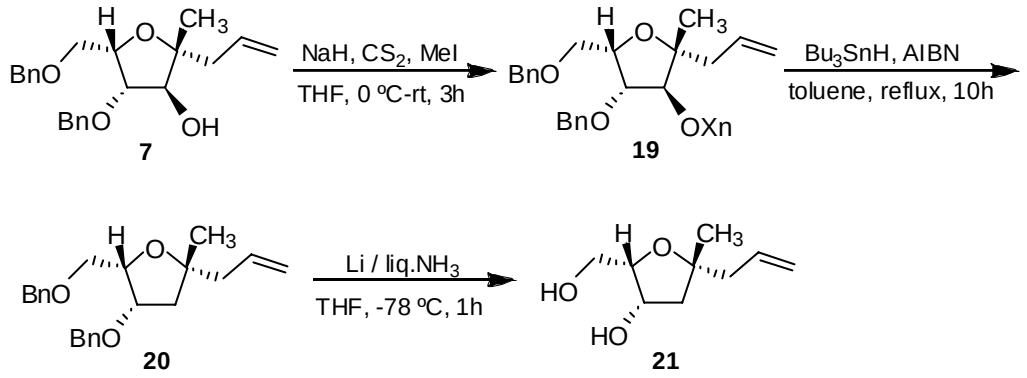
Figure 4: *Plausible mechanism for creation of quaternary center.*



The free hydroxyl at C3 on tetrahydrofuran ring of **7** was deoxygenated using the Barton McCombie's protocol.[29] The xanthate derivative **19** was prepared by treating **7** with NaH, CS_2 and MeI. Subsequently, the xanthate derivative **19** was treated with *n*-Bu_3SnH and catalytic AIBN in refluxing toluene to obtain the deoxy derivative **20** (Scheme 6). The structure **20** was well supported by ^1H NMR, ^{13}C NMR, mass spectrum and elemental analysis. In the ^1H NMR spectrum of **20**, two signals for C3 methylene protons were located in the upfield region (1.75 and 2.11

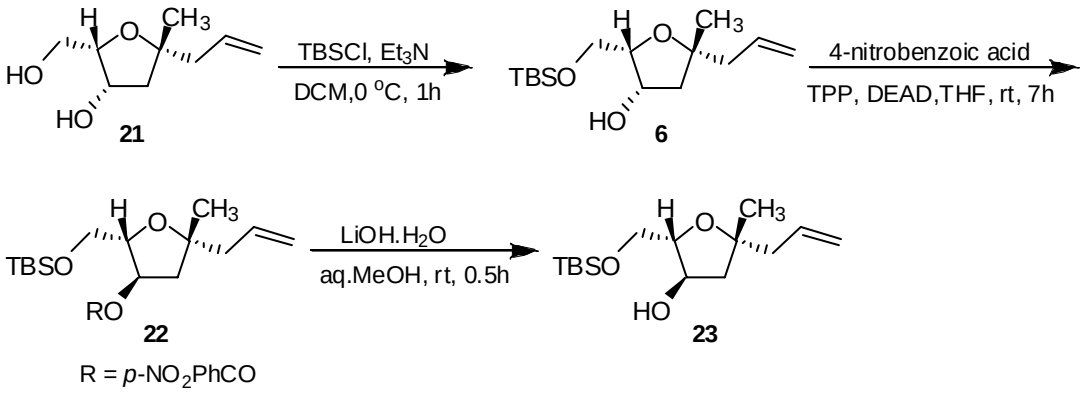
ppm as dd's). In the partially decoupled ^{13}C NMR spectrum, C3 resonated at δ 41.3 as a triplet confirming the presence of methylene group. Treatment of **20** with two equivalents of lithium in liquid ammonia gave a product with the highest mass peak at *m/z* 195 $[M+Na]^+$ in the mass spectrum suggesting the debenzylated product **21**.

Scheme 6:



The next critical transformation was the inversion of stereochemistry at C3 by Mitsunobu protocol.[24] For this purpose, it was necessary to protect the primary alcohol. The primary hydroxyl group of the diol **21** was selectively protected as its silyl ether using TBSCl and triethyl amine in DCM at 0 ^oC to afford compound **6** (Scheme 7). In the ^1H NMR spectrum of **6**, peaks due to TBS-group were observed at δ 0.10 (2s, 6H) and 0.91 (s, 9H). The structure was further supported by the mass spectrum with the highest mass peak at *m/z* 309 $[M+Na]^+$. Treatment of the mono-TBS derivative **6** with 4-nitrobenzoic acid in presence of TPP and DEAD afforded the benzoate ester **22** (Scheme 7). Presence of benzoate ester was visible in the ^1H NMR spectrum by the appearance of additional signals at δ 8.21-8.36 (m, 4H) in aromatic region whereas the C4 proton appeared as a multiplet in the downfield region at 5.00-5.55 ppm.

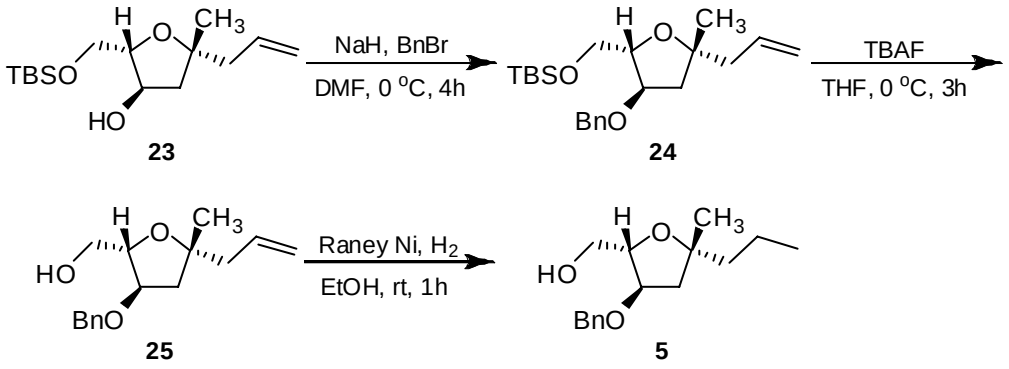
Scheme 7:



The hydrolysis of the benzoate ester **22** was achieved by treatment with lithium hydroxide monohydrate in aqueous methanol to yield alcohol derivative **23**. The structure of **23** was confirmed by spectral and analytical data. In the ^{1}H NMR spectrum the peak due to C4-proton observed at δ 4.48-4.58 in **6** was shifted to δ 5.50-5.55 in benzoate ester **22** that latter shifted to δ 4.21-4.31 in compound **23** confirmed the inversion in stereochemistry at C4 centre. It was also supported by ^{13}C NMR spectrum, where C4 carbon of **6** resonated at 83.5 ppm while C4 carbon of **23** was resonated at 83.7 ppm. The inversion of stereochemistry at C3 was also supported by the comparison of R_f values on TLC and the optical rotation values of compound **6** and **23**.

The masking of the free hydroxyl of **23** as its benzyl ether was achieved using NaH and benzyl bromide in DMF at 0 ^{o}C, to afford compound **24**. The silyl ether in **24** was subsequently removed by the action of TBAF in THF to afford compound **25**. In the ^{1}H and ^{13}C NMR spectra of **25**, the peaks due to TBS group were absent. The presence of the benzyl group was evident from the ^{1}H NMR spectrum where signals due to benzylic protons appeared at δ 4.50 integrating for two protons and aromatic protons were seen at δ 7.31 as a multiplet.

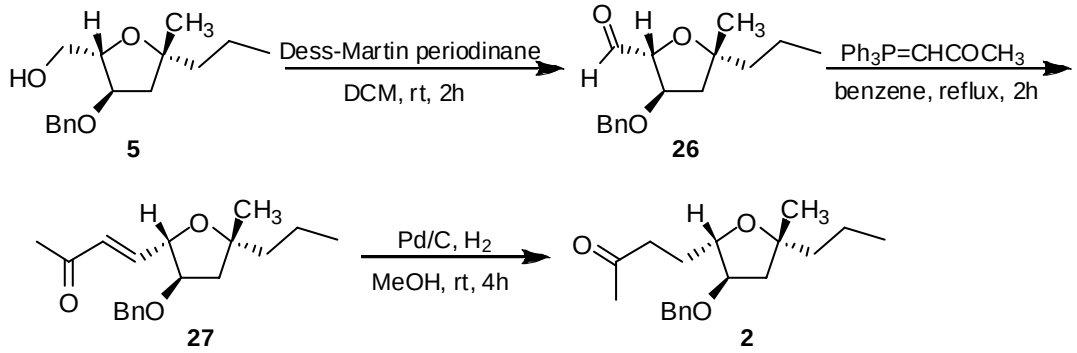
Scheme 8:



The reduction of terminal double bond of alcohol **25** on treatment with catalytic Raney nickel in ethanol under hydrogen atmosphere furnished alcohol derivative **5** (Scheme 8). In the ^{1}H NMR spectrum of **5,** the peaks due to olefinic protons were absent and signal at δ 0.92 (t) integrating for three protons and at δ 1.29-1.37 (m) integrating for two protons confirmed the reduction of double bond. The ^{13}C NMR spectrum and elemental analysis were found to be in accordance with the structure of **5**.

Finally alcohol **5** was oxidized using Dess-Martin periodinane[30] in DCM and resultant aldehyde **26** was treated with methylcarbonylmethylene triphenylphosphorane to provide unsaturated ketone derivative **27**. In the ^{1}H NMR spectrum of **27** the olefinic protons appeared at δ 5.60 and δ 6.80 integrating for one proton each.

Scheme 9:



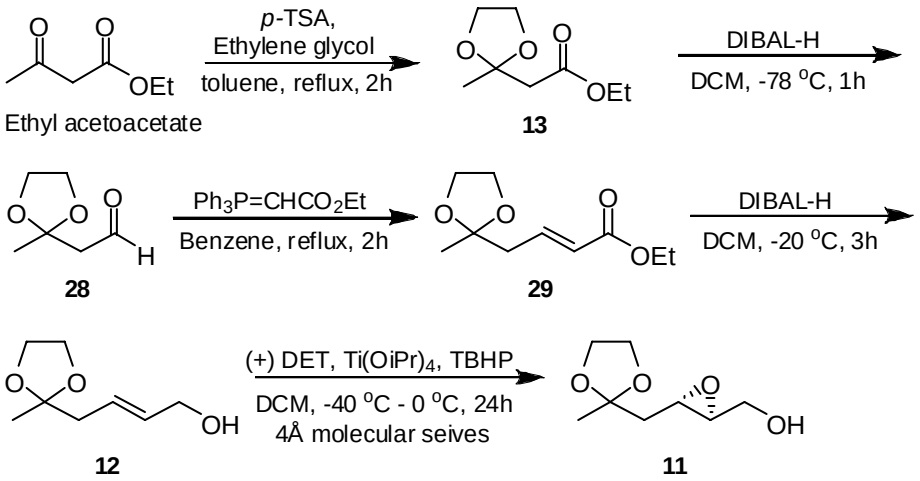
The compound **27** on mild hydrogenation using 10% palladium on charcoal in methanol furnished saturated ketone **2** (Scheme 9). The ^{1}H NMR and ^{13}C NMR spectral data of the product **2** was found to be in excellent agreement with the proposed structure. The absence of the signals due to olefinic protons and the presence of peaks due to benzyl group at δ 4.43 (d, 1H), 4.51 (d, 1H) and 7.29-7.32 (m, 5H) from the ^{1}H NMR spectrum of **2** were the evident for reduction of olefin keeping 3-*O*-benzyl group intact. In the ^{13}C NMR spectrum, carbonyl carbon resonated at 208.7 ppm while in IR spectrum carbonyl frequency appeared at 1741 cm^{-1}. Mass spectrum of the product exhibited peak at *m/z* 327 $[M+Na]^+$, suggesting the successful conversion into desired product. Elemental analysis for **2** was found in well agreement with the structure. In this way the synthesis of tetrahydrofuran segment **2** was completed.

Synthesis of Fragment B:

The synthetic endeavor for requisite sulfone fragment **3** began with the preparation of the allyl derivative **12** from cheaply available ethyl acetoacetate in four steps (Scheme 10). The ketone group from ethyl acetoacetate was protected as its ketal derivative **13** by treatment with ethylene glycol in the presence of catalytic *p*-TSA in refluxing toluene. The ester group in **13** was reduced to produce aldehyde **28** by treatment with DIBAL-H in DCM at –78 ^{o}C. Aldehyde **28** was refluxed with

ethoxycarbonylmethylenetriphenylphosphorane in benzene to provide corresponding Wittig product **29**. The ester derivative **29** was again treated with DIBAL-H in DCM at –20 ^{o}C to procure the allyl derivative **12** in 50% overall yield. The ^{1}H and ^{13}C NMR spectra and other analytical data of **12** were in agreement with that of expected structure.

Scheme 10:

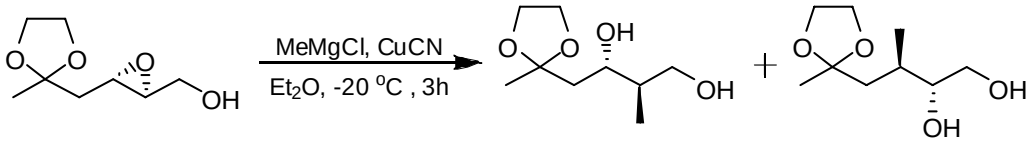


The next job was the synthesis of 2(*S*), 3(*S*)-epoxide derivative **11** by using Sharpless asymmetric epoxidation of **12**. Taking into account the literature precedence's for closely related substrates[31] it was concluded that natural diethyl tartarate should provide the epoxide with required stereochemistry. Alcohol **12** was treated with (+) diethyl tartarate, titanium(IV) isopropoxide and *ter*-butyl hydrogen peroxide in DCM at -40 ^{o}C to provide epoxide derivative **11**. The presence of the characteristic peaks in the ^{1}H NMR spectrum at δ 2.95 (dt, J = 2.3, 4.3 Hz) and 3.12 (ddd, J = 2.3, 5.9, 11.7 Hz) integrating for one proton each indicated the presence of epoxide group in **11**. In the ^{13}C NMR spectrum carbonyl carbons from epoxide group resonated at 55.2 and 61.7 ppm. In the mass spectrum, the highest molecular ion peak at *m/z* 197 due to $[M+Na]^{+}$ further supported the structure of **11**. Other analytical data was also found in accordance with the epoxide derivative **11**.

Our next concern was the opening of the epoxide in regio and stereo-selective manner. The epoxide **11** was treated with the mixture of methyl magnesium chloride and copper cyanide in diethyl ether at -20 ^{o}C procured 1,3 diol **30** (>90%) contaminated by 1,2 diol **31** (<10%). The aforementioned ratios were calculated from the relative integrations of the signals in the ^{1}H NMR spectrum of the mixture. It is pertinent to mention that the mixture of **30** and **31** was inseparable

on TLC as well as by column chromatography. For purification we used a conventional chemical method, where we took the advantage of the fact that sodium metaperiodate can cleave only 1,2 diols and not the 1,3 diols. The mixture of **30** and **31** was subjected to cleavage using $NaIO_4$ supported on silica gel[32] in DCM at ambient temperature which enabled chopping of only 1,2 diol **31** to corresponding aldehyde keeping 1,3 diol (**30**) intact. Resultant mixture of aldehyde (from **31**) and diol **30** was easily separated by column chromatography to give pure diol **30**.

Scheme 11:

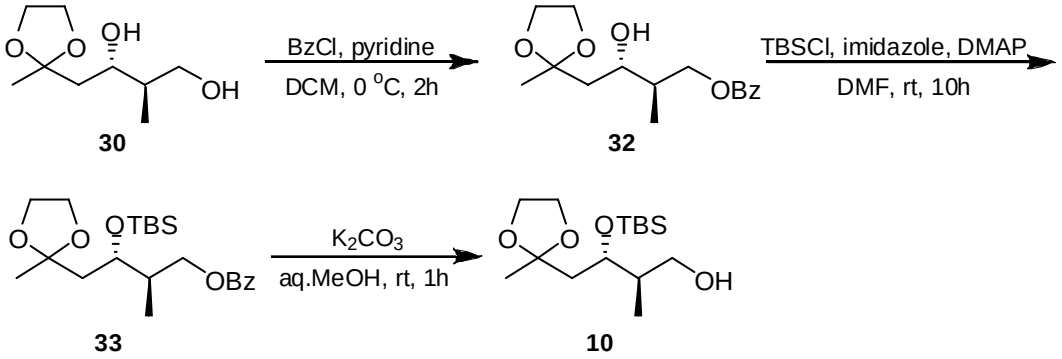


11 **30** major (>90%) **31** minor (<10%)

In the ^{1}H NMR spectrum of **30**, the characteristic peaks due to epoxide group were disappeared and the presence of the peak at δ 0.88 (d, J = 7.0) integrating for three protons indicated methyl group, while the rest of the spectrum was also in complete agreement with the assigned structure. Further support for structure of **30** came from its ^{13}C NMR and DEPT spectral data. Other analytical data were in agreement with the structure of **30**.

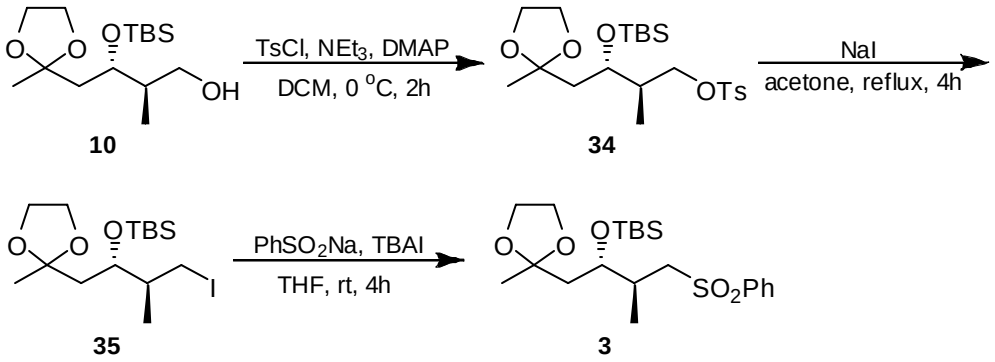
The temporary masking of the primary hydroxyl group of **30** as its benzoate derivative using benzoyl chloride and pyridine in DCM at 0 ^{o}C led to **32** (Scheme 12). The presence of the characteristic peaks due to the phenyl group in the aromatic region and shifting of methylene protons from δ 3.60-3.72 (m, 2H) to 4.15-4.39 (m, 2H) in the ^{1}H NMR spectrum of **32** indicated the selective protection of primary hydroxyl group. The secondary hydroxyl functionality of **32** was converted to its silyl ether derivative **33** on treatment with imidazole and DMAP followed by TBSCl in DMF at room temparature for 10 h. Subsequently the benzoyl protection of crude **33** was removed using K_2CO_3 in aqueous MeOH at room temperature to furnish alcohol **10** in overall 64% yield. Signals due to benzoyl group were absent in the ^{1}H NMR and the ^{13}C NMR spectra while the presence of the characteristic peaks of TBS-group in the ^{1}H NMR spectrum [δ 0.09 (s, 3H), 0.10 (s, 3H) and 0.89 (s, 9H)] confirmed the structure **10**. This was further supported by the mass spectrum with the highest mass peak at *m/z* 327 $[M+Na]^+$. Other analytical data were also found in accordance with the structure of **10**.

Scheme 12:



In order to incorporate sulfone functionality at C6 carbon, the hydroxyl group was first converted into its tosyl derivative **34** on treatment with tosyl chloride, triethyl amine and catalytic DMAP in DCM at 0 ^{o}C (Scheme 13). The tosyl derivative **34** was further transformed to its iodo derivative **35** by treating contents with sodium iodide in refluxing acetone for 4 h. Subsequently, crude iodo derivative **35** was stirred with $PhSO_2Na$ and TBAI in THF at room temperature for 4 h to furnish sulfone **3** in 61% overall yield after three steps.

Scheme 13:

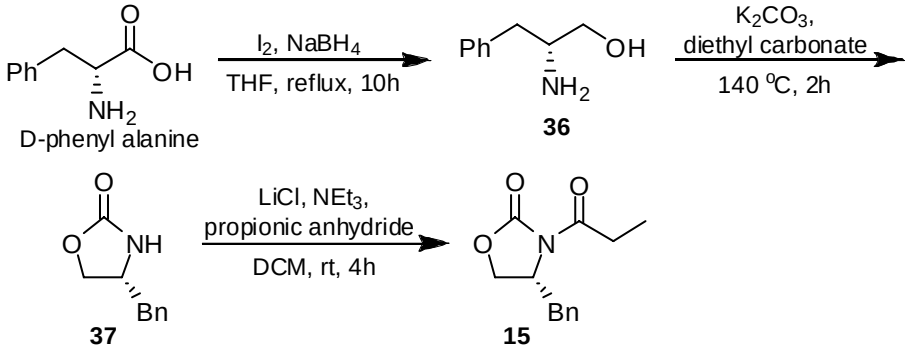


The structure of **3** was confirmed by ^{1}H NMR and ^{13}C NMR spectra. In the ^{1}H NMR spectrum, the characteristic multiplet at δ 7.54-7.58 due to phenyl protons was observed. The peaks due to methylene protons were shifted little upfield from 3.50 (dd, *J* = 5.6, 11.3 Hz, 1H) and 3.88 (dd, *J* = 3.5, 11.3 Hz, 1H) to 3.21 (dd, *J* = 8.0, 13.2 Hz, 1H) and 3.62 (dd, *J* = 4.4, 13.2 Hz, 1H) indicating the change in the electronic environment due to conversion of alcohol to sulfone. In the ^{13}C NMR spectrum, the peaks due to methylene carbon shifted from 64.2 to 35.1 ppm. The structure of **3** was further confirmed by observing its mass spectrum (the peak located at *m/z*: 451 corresponding to $[M+Na]^{+}$) and satisfactory elemental analysis. This completed the synthesis of fragment B.

Synthesis of Fragment C:

According to the projected plan for the synthesis of fragment C, Evans alkylation was employed using chiral imide enolate derived from chiral oxazolidinone **15**, which in turn was prepared from D-phenylalanine. D-phenylalanine was reduced to D-phenylalaninol (**36**) using sodium borohydride and iodine in THF and then the amino alcohol was protected as a cyclic carbamate **37** using diethyl carbonate and K_2CO_3 at 140 ^oC. The imide **15** was prepared by N-acylation of oxazolidinone using propionic anhydride, lithium chloride and triethyl amine as a base. The presence of lithium chloride was essential for the acylation, possibly due to the chelation of lithium ion, which results in the activation of the propionic anhydride. The ^1H NMR spectral data revealed that the methyl and methylene protons of propionyl group resonated at δ 1.20 (t) and 2.95 (m) respectively. The two-diastereotopic protons were appeared as doublets at δ 3.30 and 2.75 (Scheme 14).

Scheme 14:

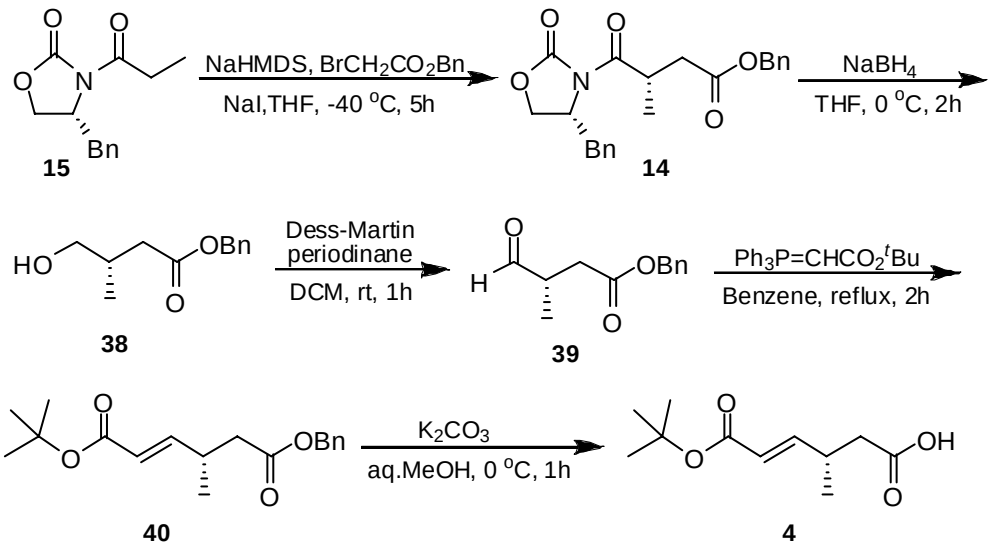


Our first concern was the Evans' alkylation reaction between the (*R*)-oxazolidinone derivative **15** and benzyl bromoacetate. It was reported[33] that this type of alkylation ensures higher diastereomeric excess. The alkylation reaction was carried out in the presence of NaHMDS at -40 ^oC to give **14** as the sole product (Scheme 15). The ^1H NMR spectrum of compound **14** showed characteristic methyl signal at δ 1.22 as a doublet (J = 7.1 Hz) along with the additional signals in aromatic region (7.26-7.34 ppm) due to phenyl protons and in the ^{13}C NMR spectrum methyl carbon resonated at 17.0 ppm. In addition, the mass spectral analysis showed a base peak at *m/z*: 404 due to $[M+Na]^+$ and elemental analysis was also in full agreement. Our next objective was the nondestructive removal of the chiral oxazolidinone moiety. Reports[34] indicate that the reductive cleavage of *N*-acyl

groups using sodium borohydride at low temperature can work successfully, keeping intact the ester moiety. The treatment of compound **14** with sodium borohydride in THF at 0 ^{o}C for 2 h led to the compound **38** in 80% yield. This compound was characterized by spectral as well as by other analytical data. In the ^{1}H NMR spectrum, the characteristic peaks due to oxazolidinone group were absent and methylene protons were resonated at δ 3.44 (dd, *J* = 6.6, 10.7 Hz, 1H), 3.56 (dd, *J* = 5.0, 10.7 Hz, 1H). Other analytical data was also in accordance with the structure.

Oxidation of the **38** with Dess-Martin periodinane in DCM at ambient temperature led to the aldehyde **39**. Subsequently the crude aldehyde **39** was refluxed with *tert*-butoxycarbonylmethylenetriphenylphosphorane in benzene afforded diester derivative **40** in 80% yield. Two carbon Wittig reagent containing *tert*-butyl ester moiety was chosen so as to offer selective hydrolysis of either of the ester linkages at latter stages. The presence of the characteristic peak in the ^{1}H NMR spectrum at δ 1.48 (s) integrating for nine protons indicated the presence of *tert*-butyl functionality in **40** and also the two signals appeared at δ 5.73 (dd) and 6.78 (dd) integrating for one proton each indicated the olefinic protons. The presence of two olefinic carbons at 122.1 and 150.3 ppm in the ^{13}C NMR spectrum along with other analytical data such as mass spectrum, elemental analysis and IR spectrum supported the required structure **40**.

Scheme 15:



The final task of this endeavor was the selective hydrolysis of **40**. The hydrolysis of benzyl ester can be achieved in present of *tert*-butyl ester because of the fact that the benzyl ester could be selectively hydrolyzed in mild basic conditions

while *ter*-butyl ester in mild acidic conditions. The diester **40** was subjected to K_2CO_3 in aqueous methanol at 0 ^oC for 1 h to procure acid **4** (Scheme 15). The signal due to the *tert*-butyl group integrating for nine protons appeared at δ 1.48 in the ^1H NMR spectrum while signals due to benzyl group were missing, clearly indicating selective hydrolysis of benzyl ester. The molecular ion peak observed at *m/z* 237 $[M+Na]^+$ in the mass spectrum and the elemental analysis supported the structure **4**. This completed the synthesis of fragment C.

Coupling of Fragments A and B:

Having successfully completed the synthesis of required fragments A, B and C; we next focused our attention on assembling these fragments as per our retrosynthetic plan. We recognized that coupling of fragments A and B through Julia-Lythgoe olefination reaction was potentially a challenging task. Needless to say, the formation of carbon-carbon double bonds is one of the most important reactions in organic synthesis.[35] Especially, the methods including carbon-carbon coupling are of high value. The Wittig and related reactions, Peterson-type reactions, McMurry coupling, Ramberg-Backlund reaction, and Julia Lythgoe olefination are well-known methods for the formation of olefinic compounds with carbon-carbon coupling.[36] These methods allow for regiospecificity and in some cases provide excellent stereoselectivity.

Coupling by using Julia-Lythgoe olefination:

The Julia-Lythgoe coupling[37] procedure has the benefits of tendency to produce predominantly *E* olefins (depending on conditions and substitution pattern), a long proven history as an important tool in organic synthesis. This procedure is particularly prominent in convergent approaches to complex structures. The formation of olefins from sulfones and carbonyl compounds via reductive elimination of β-hydroxy sulfones or their derivatives has been known as the Julia-Lythgoe olefination. Originally, the reductive elimination was carried out with Na-Hg. Later, because of the high toxicity of Hg, this step was improved by replacing Na-Hg with other reducing agents, such as SmI or Mg.[38]

As the Julia olefination reaction was successfully used in our group for the preparation of disubstituted olefins, we thought of employing this tool for the formation of trisubstituted olefin. Examination of the literature[37] revealed that the

preparation of trisubstituted olefins employing the Julia-Lythgoe protocol was not much explored. Here we decided to investigate the Julia-Lythgoe olefination of ketone **2** using sulfone **3**.

In the first attempt, the compound **2** was added in the mixture of sulfone **3** and KHMDS in DME at –60 ^{o}C and the reaction mixture was allowed to attain the room temperature. However the desired coupling reaction did not take place under these conditions and the ketone **2** was recovered (Scheme 16). A careful survey of other conditions for the crucial fragment coupling was conducted (Table 1). Unfortunately, it was found that all the attempts to couple ketone **2** and sulfone **3** fragments by Julia olefination procedures under various reaction conditions turned out to be failures.

Scheme 16:

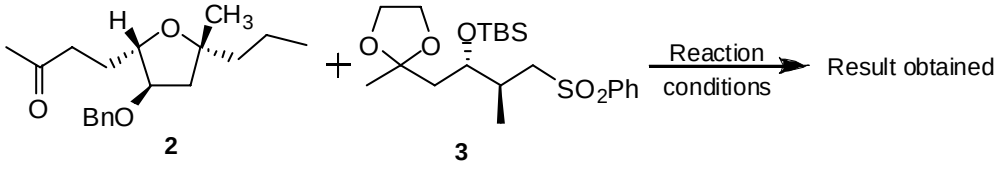
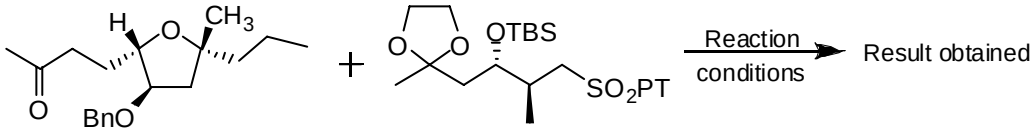


Table 1: *Conditions applied and results obtained in Julia olefination*

Entry	Reaction conditions	Results obtained
1	KHMDS, DME, -60 ^{o}C to rt	No reaction, Ketone **2** recovered.
2	*n*BuLi, THF, -78 ^{o}C to rt	No reaction, Ketone **2** recovered.
3	*n*BuLi, BF_3-etherate, THF, -78 ^{o}C to rt	Complex mixture.
4	*n*BuLi, HMPA, THF, -78 ^{o}C - rt	Sulfone decomposed.
5	LDA, THF, -78 ^{o}C to rt	Sulfone decomposed.

Scheme 17:



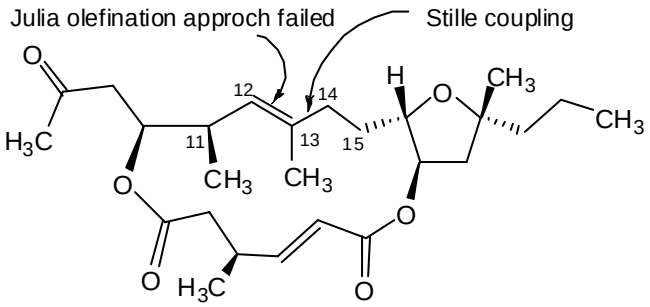
2 **41**

There are some reports that the modified Julia olefination[39] involving use of 1-phenyl-1*H*-tetrazol-5-yl sulfone instead of simple phenyl sulfone which is more convenient and higher yielding than the classical Julia olefination reaction. The modified Julia olefination also offers slightly better stereoselectivity. The sulfone **41** was prepared from **10** over two steps. However the coupling of **41** and **2** under the conditions summarized in table 1 (provided same results) was also not successful.

Coupling by using Stille Reaction:

Having met with failures to forge the double bond between C12-C13 using Julia protocol, we redesigned our retrosynthetic strategy and it was decided to attempt the construction of C13-C14 bond instead of C12-C13 bond (Figure 5). It was planned to attempt installation of C13-C14 bond by means of Stille coupling reaction between vinyl iodo **42** and vinyl stannane **45**. Selective reduction of C14-C15 double bond formed in this process was contemplated at latter stages.

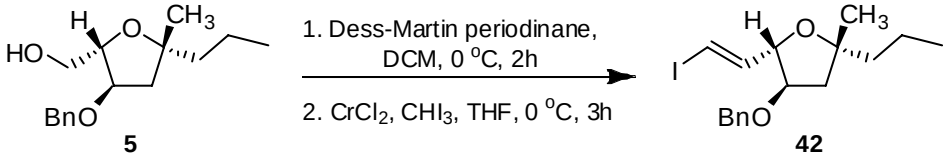
Figure 5: *Redesigned retrosynthetic strategy*



According to the redesigned synthetic strategy focused on Stille coupling, requisite coupling partners **42** and **45** were planned from intermediates **5** and **10** respectively. As depicted in Scheme 20, compound **5** was modified to vinyl iodo derivative **42** by oxidation with Dess-Martin periodinane in DCM followed by subsequent Takai reaction[40] of resulted aldehyde using $CrCl_2$, CHI_3 in THF at 0 ^oC. In the ^1H NMR spectrum of **42** olefinic protons resonated at δ 6.40 (d, J = 14.4 Hz, 1H) and 6.56 (dd, J = 6.0, 14.4 Hz, 1H) . Moreover the mass analysis supported the

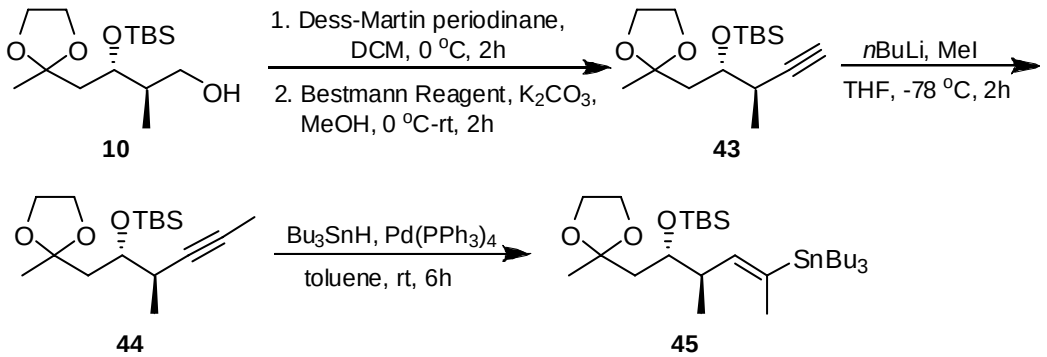
structure of vinyl iodo derivative with the highest molecular ion peak at *m/z*: 409 $[M+Na]^+$.

Scheme 18:



The vinyl stannane **45**, second coupling partner for Stille reaction, was synthesized from key intermediate **10** over four steps (Scheme 19). The alcohol **10** was subjected to Dess-Martin periodinane oxidation to give aldehyde which was subsequently treated with Bestmann reagent[41] and K_2CO_3 in methanol at ambient temperature for 2 h to afford alkyne derivative **43** in 71% overall yield from **10**. In the ^{1}H NMR spectrum of **43**, the characteristic peak at δ 2.03 (d, *J* = 2.5 Hz) integrating for one proton indicated the alkyne proton. The other analytical data was in accordance with the structure. Alkyne derivative **43** was stirred with *n*BuLi in THF and then treated with methyl iodide at -78 °C to furnish methyl alkyne derivative **44**. The alkynyl methyl protons were resonated at δ 1.78 (d, *J* = 2.4 Hz, 3H) in the ^{1}H NMR spectrum while the rest of the spectrum was in complete agreement with the assigned structure. In the ^{13}C NMR spectrum the peak appeared at 3.6 ppm was indicated the alkynyl methyl carbon while alkyne carbons were resonated at 71.2 and 80.9 ppm. Further confirmation of the structure of **44** came from its and DEPT spectral data. In addition, ESI-MS analysis indicated peaks at m/z: 313 $[M+H]^+$ and 335 accounting for $[M+Na]^+$, supported the structure. The elemental analysis of **44** was satisfactory.

Scheme 19:

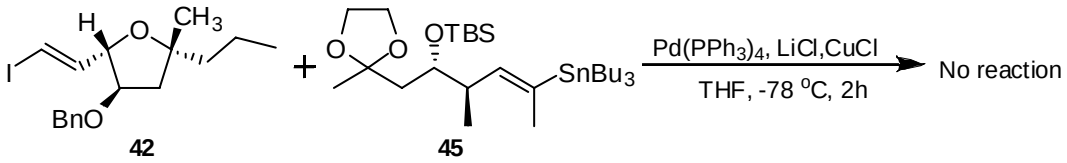


When compound **44** was subjected to tributyltinhydride in presence of catalytic $Pd[PPh_3]_4$ in toluene at room temperature afforded requisite coupling

partner, vinyl stannane derivative **45** (Scheme 19). In the ^{1}H NMR spectrum of **45**, the olefinic proton was resonated at δ 5.90-5.92 (m, 1H) and peak due to methyl protons shifted from δ 1.78 (d, J = 2.4 Hz, 3H) to 1.53 (s, 3H). The ESI-MS showed peak at *m/z*: 626 accounting for $[M+Na]^+$. Other analytical data was in well agreement with the structure.

The vinyl iodo derivative **42** and vinyl stannane derivative **45** were treated with LiCl, CuCl and catalyst $Pd[PPh_3]_4$ at –78 ^oC and subsequently warmed to room temperature (Scheme 20). The coupling of fragments **42** and **45** under these and various other conditions reported for Stille reaction turned out to be failures.

Scheme 20:



Having met with failures in the C13-C14 bond formation using palladium under Stille protocol, we thought of exploring the possibilities using another transition metal, Ruthenium this time, for our purpose.

Coupling by using Cross Metathesis Reaction:

Among the many types of transition-metal-catalyzed C-C bond forming reactions, olefin metathesis has come to the fore in recent years owing to the wide range of transformations that are possible with commercially available and easily handled catalysts. Consequently, olefin metathesis is now widely considered as one of the most powerful synthetic tools in organic chemistry. Until recently the intermolecular variant of this reaction, cross-metathesis, had been neglected despite its potential. With the evolution of new catalysts, the selectivity, efficiency, and functional-group compatibility of this reaction have improved to a level that was unimaginable just a few years ago. These advances, together with a better understanding of the mechanism and catalyst–substrate interactions, have brought us to a stage where we thought employing cross-metathesis[42] in our synthesis.

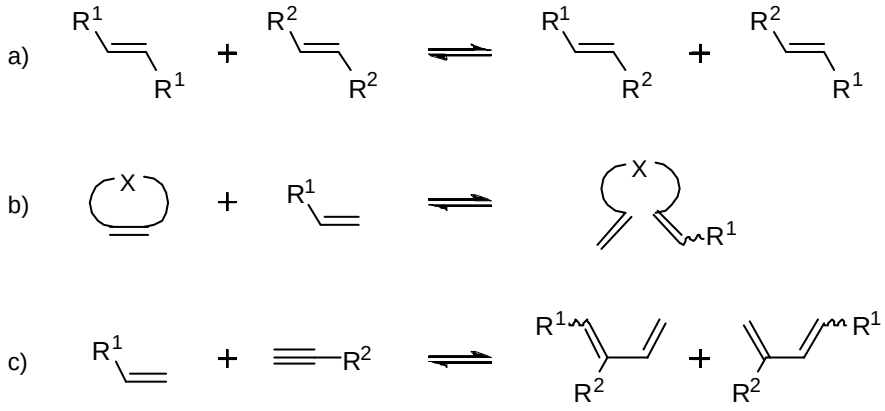
A brief review on Cross Metathesis:

Over the last 10 years, CM has begun to emerge from the shadow of RCM and ROMP to take its place as a powerful and mild method for the formation of C-C bonds.

This is in no small part a consequence of the advent of highly active ruthenium alkylidene catalysts, which allow the use of previously incompatible substrates with high chemo- and stereoselectivity.

Olefin cross-metathesis can be formally described as the intermolecular mutual exchange of alkylidene (or carbene) fragments between two olefins promoted by metal-carbene complexes. There are three main variations on this theme (Figure 6): a) cross-metathesis, b) ring-opening cross-metathesis, and c) intermolecular enyne metathesis

Figure 6: *Main variation of cross metathesis*



As an acyclic carbon–carbon bond-forming tool, cross metathesis has numerous advantages typical of modern olefin-metathesis reactions:

1) The process is catalytic typically 1–5 mol% of catalyst required.

2) High yields can be obtained under mild conditions in relatively short reaction times.

3) A wide range of functional groups are tolerated, with minimal substrate protection necessary.

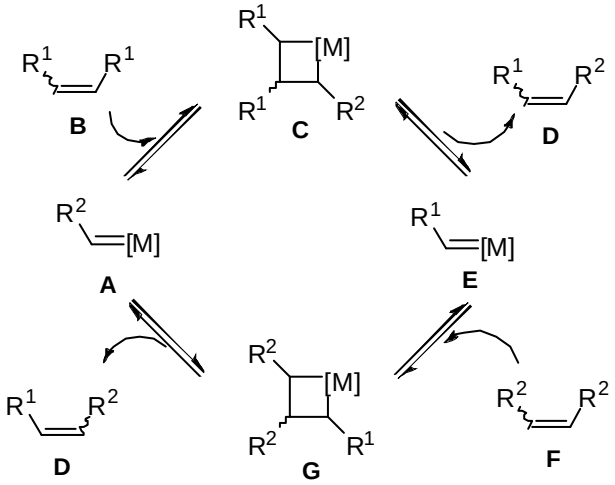
4) The reaction is reversible, relatively atom-economic, and gaseous ethylene is usually the only by-product, which is an important consideration in industrial applications.

5) The olefin substrates are generally easier and less expensive to prepare than those associated with other common catalytic C-C bond-forming reactions (e.g. unsaturated boranes, stannanes, halides, triflates).

A general mechanistic scheme for the CM of two symmetrically substituted olefins is presented in Figure 7. The first step in the catalytic cycle (after the first catalyst turnover to produce A) is a cycloaddition reaction between olefin B and a transition metal carbene A to give a metallacyclobutane C. The latter undergoes subsequent collapse

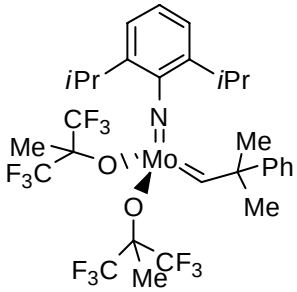
in a productive fashion to afford a new olefin product D and a new metal carbene (alkylidene) E, which carries the alkylidene fragment R¹. Similarly, E can react with a molecule of F via G to yield D and A, which then re-enters the catalytic cycle. The net result is that D is formed from B and F with A and E as catalytic intermediates.

Figure 7: *Mechanism of cross metathesis*

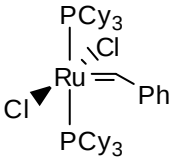


The success of the alkene-metathesis reaction and the many stunning and ingenious situations in which it has been applied are largely due to the advent of todays readily available catalyst systems that display high activity and excellent functional-group tolerance. The four such catalysts most routinely used by organic chemists are shown in Figure 8.

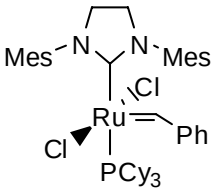
Figure 8: *Commonly used cross metathesis catalysts*



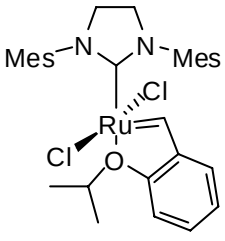
Schrock's catalyst



Grubb's 1st generation catalyst



Grubb's 2nd generation catalyst



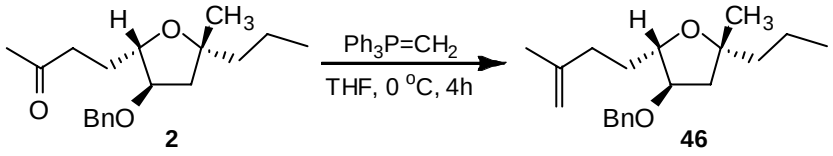
Hoveyda Grubb's catalyst

Alkene cross-metathesis has long been of great commercial importance to the industrial sector, but its transition to synthetically viable methodology in total synthesis has been a much more recent affair. Alkene cross-metathesis represents a particularly appealing alternative to other transition metal- mediated cross-coupling processes (e.g. the Stille or Suzuki reaction) in that readily available alkenes are employed, and no synthetic investment in the preparation of elaborated coupling partners (e.g. vinyl

stannanes, vinyl halides, etc.) is required. Furthermore, the mild reaction conditions and functional-group tolerance of modern cross metathesis often complements the more traditional olefination methods (e.g. the Wittig reaction). Despite its enormous potential for carbon–carbon bond formation, the widespread uptake of alkene cross-metathesis by synthetic chemists has lagged far behind that of the corresponding ring-closing processes. Indeed, until recently, many chemists_ experience of cross-metathesis merely involved the unwanted formation of dimeric products arising from a disappointing ring-closing metathesis event. The biggest challenge in cross-metathesis is the chemo-and stereoselective formation of the desired compound from amongst the myriad of potential reaction products. In this regard, it has been the recent advances in catalyst design, coupled with the development of empirical models for predicting the outcome of cross-metathesis reactions (largely due to the pioneering work of the Grubbs group), that have emboldened chemists with the courage to commit their valuable intermediates to these processes. In return, they have been rewarded with new synthetic avenues and opportunities that were unthinkable even just a few years ago.

The coupling partners **46** and **47** required for cross metathesis were prepared from ketone **2** and alcohol **10** respectively. One carbon Wittig homologation of **2** by treatment with methyltriphenylphosphorane in THF furnished the required alkene fragment **46** (Scheme 21).

Scheme 21:

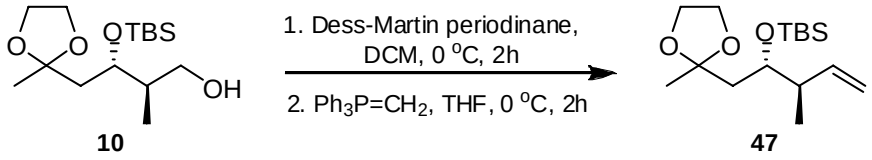


The signals for the olefinic protons integrating for two protons appeared as a broad singlet at δ 4.67 in the ^{1}H NMR spectrum. The presence of two olefinic carbons at δ 109.8 and 146.0 in the ^{13}C NMR spectrum along with other analytical data such as mass spectrum, elemental analysis and IR spectrum supported the structure **46**.

The other coupling partner was prepared from the intermediate alcohol derivative **10**. Oxidation of **10** with Dess-Martin periodinane in DCM led to the corresponding aldehyde, which was subsequently treated with methyl-

triphenylphosphorane in THF afforded alkene **47** in 79% yield (Scheme 22). The presence of the typical terminal olefinic pattern of three protons in the ^{1}H NMR spectrum appeared at δ 4.97-5.07 (m, 2H) and 5.71-5.89 (m, 1H) suggested the compound **47**. The presence of two olefinic carbons at δ 115.0 and 140.4 in the ^{13}C NMR and DEPT spectra also supported the structure. Other analytical data such as mass spectrum, elemental analysis and IR spectrum were in well agreement with structure of compound **47**.

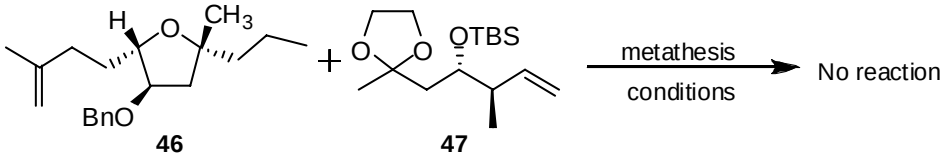
Scheme 22:



10 **47**

The next critical step was the cross metathesis reaction to construct the C12-C13 olefin. However several attempts for coupling of alkenes **46** and **47** employing various cross metathesis conditions turned out to be failures to obtain the desired product.

Scheme 23:



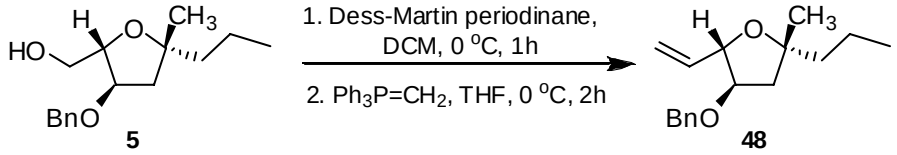
46 **47**

Attributing the failure in the cross metathesis for the construction of C12-C13 bond to the stearic crowding involved in the formation of trisubstituted double bone, we then focused our attention on the construction of C14-C15 double bond. The selective reduction of the disubstituted double bond in presence of trisubstituted double bond was the issue to be dealt with at latter stages.

The required precursors for modified cross metathesis, alkene **48** and diene **51** were prepared from intermediates **5** and **10** respectively. The intermediate **5** was oxidized using Dess-Martin periodinane in DCM at 0 ^{o}C to obtain corresponding aldehyde in 1h, the resultant aldehyde was treated with methyltriphenylphosphorane in THF which furnished required alkene derivative **48** (Scheme 24). The signals for the olefinic protons appeared at δ 5.15 (ddd, J = 1.4, 1.7, 10.2 Hz), 5.35 (ddd, J = 1.3, 1.7, 17.2 Hz) and 5.87 (ddd, J = 6.5, 10.2, 17.2 Hz) integrating for one proton each in the ^{1}H NMR spectrum. The presence of two olefinic carbons at 116.3 and

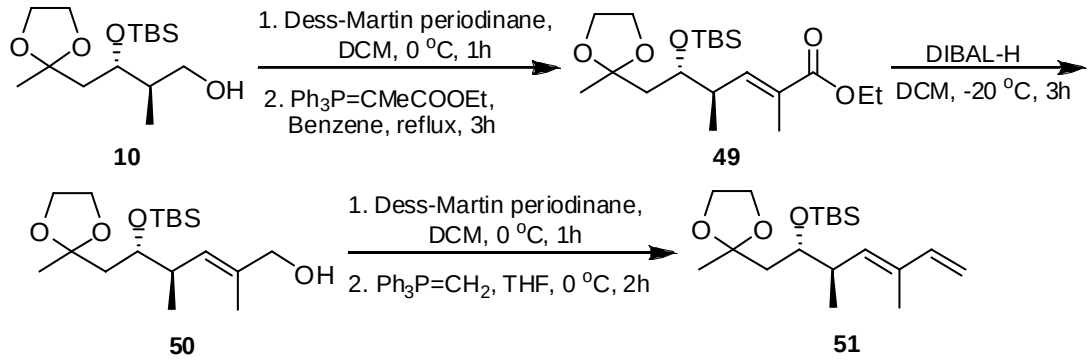
137.8 ppm in the ^{13}C NMR spectrum along with other analytical data such as mass spectrum, elemental analysis and IR spectrum supported the proposed structure **48**.

Scheme 24:



For the preparation of another segment, intermediate alcohol derivative **10** was oxidized by Dess-Martin periodinane and resulting aldehyde was refluxed with Ph_3P=CMeCOOEt in benzene to afford corresponding Wittig product **49**. The ester functionality in compound **49** was reduced to alcohol by treatment with DIBAL-H in DCM at –20 ^oC to produce **50**. The characteristic ethyl ester group peaks were disappeared in ^1H NMR spectrum and peak at δ 4.2 integrating for two protons appeared which indicated the desired product.

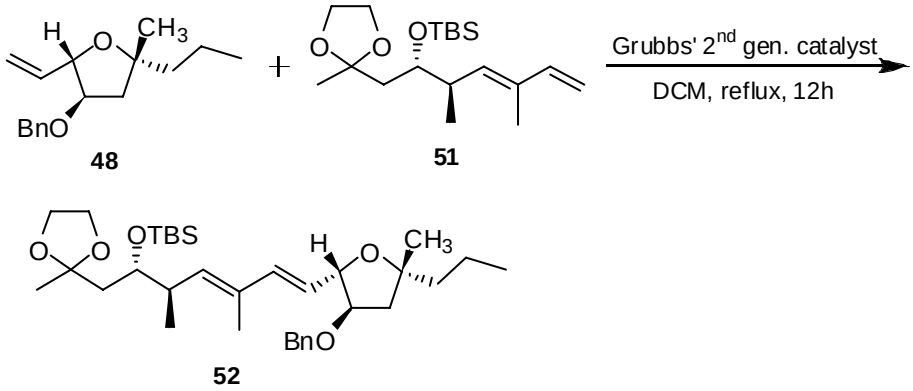
Scheme 25:



One carbon Wittig homologation of **50** using Dess-martin periodinane oxidation followed by treatment with methyltriphenylphosphorane led to the requisite diene **51** (Scheme 25). The signals for the olefinic protons of diene appeared at δ 4.93 (d, J = 10.7 Hz, 1H), 5.08 (d, J = 17.4 Hz, 1H), 5.51 (d, J = 9.5 Hz, 1H) and 6.40 (dd, J = 10.7, 17.4 Hz, 1H) in the ^1H NMR spectrum. The peaks at 110.4, 134.0, 134.9 and 142.1 ppm in the ^{13}C NMR spectrum represented the four olefinic carbons of diene. The mass spectrum, elemental analysis and IR spectrum were also in well agreement with the diene structure.

Having the requisite partners in hand a stage was set for the critical cross metathesis reaction. The cross metathesis of alkene **48** and diene **51** employing Grubbs' second-generation catalyst in refluxing DCM was eventually successful and furnished desired coupled product **52** (Scheme 26).

Scheme 26:



The signals for olefinic protons were observed as multiplets at δ 5.39 (dd), 5.49 (ddd) and 6.31 (d) integrating for one proton each in the ^{1}H NMR spectrum. In the ^{13}C NMR spectrum the peaks due to olefinic carbons were observed in olefinic/aromatic region along with the peaks for aromatic carbons of benzyl group. In the mass spectrum the peak was observed at *m/z* 595 corresponding to $[M+Na]^{+}$. Elemental analysis was also found matching with the calculated values.

Scheme 27:

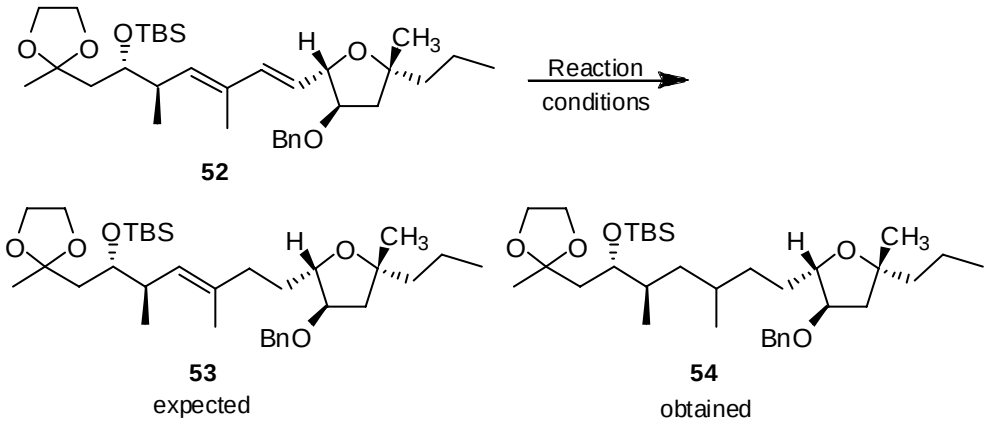


Table 2: *Conditions applied and results obtained in selective reduction*

No	Reaction conditions	Results
1	Raney Ni (W4)-H_2, RT, atmospheric pressure	Compound **54**
2	Pd/C- H_2, RT, atmospheric pressure	Compound **54**
3	Raney Ni (W4)-H_2, 0^{o}C, atmospheric pressure	Compound **54**
4	Raney Ni (W2)-H_2, RT, atmospheric pressure	Compound **54**
5	Wilkinsons' Catalyst-H_2, atmospheric pressure	No Reaction

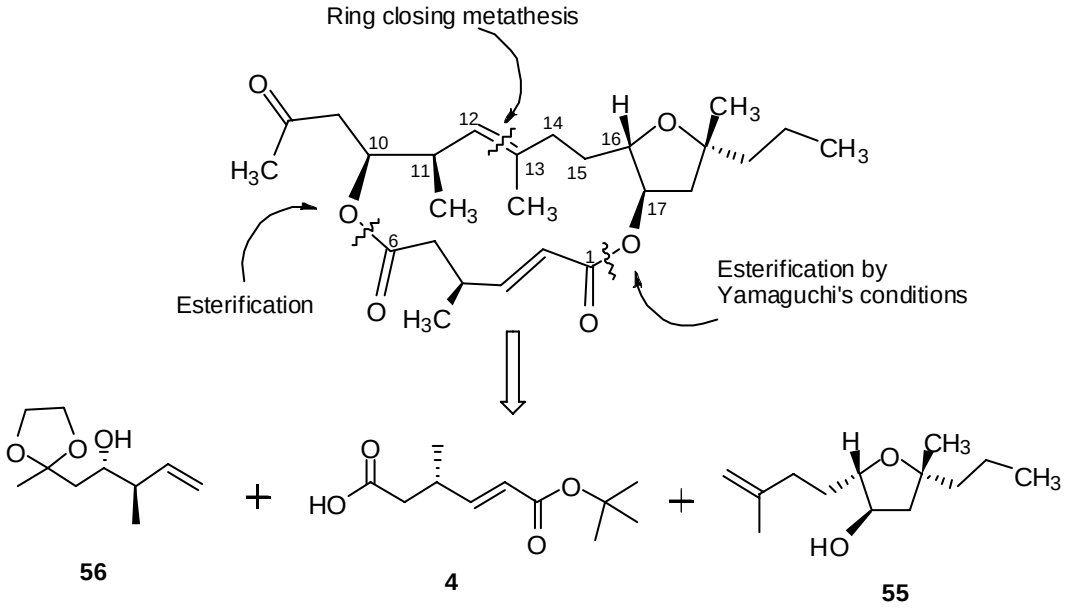
With the required coupled compound **52** in hand, the crucial selective reduction was investigated.[43] For the selective reduction of a disubstituted double bond in presence of a trisubstituted double bond, various conditions and reagents were applied and the results are summarized in table 2. But unfortunately all the conditions failed to give the desired product **53** (Scheme 27). In most of the cases compound **54,** with the both the double bonds reduced, was the major product

As the formation of carbon-carbon double bond between C12-C13 did not work on expected lines at earlier stages of synthesis the only choice left was to try and construct it using ring closing metathesis at the final stages of the assembly of all the three building blocks.

Coupling by using Ring Closing Metathesis:

Due to bifunctional nature of building blocks we had a choice to couple other ends first and finally to construct macrocyclic framework through ring closing metathesis (Figure 9). Thus, we thought to couple fragments **56** and **4** first by esterification to form C10-O bond. And C1-O bond was also planned to be construct latter by means of esterification using anyone of the reported conditions with fragment **55**. The final macrolactonisation ring formation can be achieved using ring closing metathesis reaction.

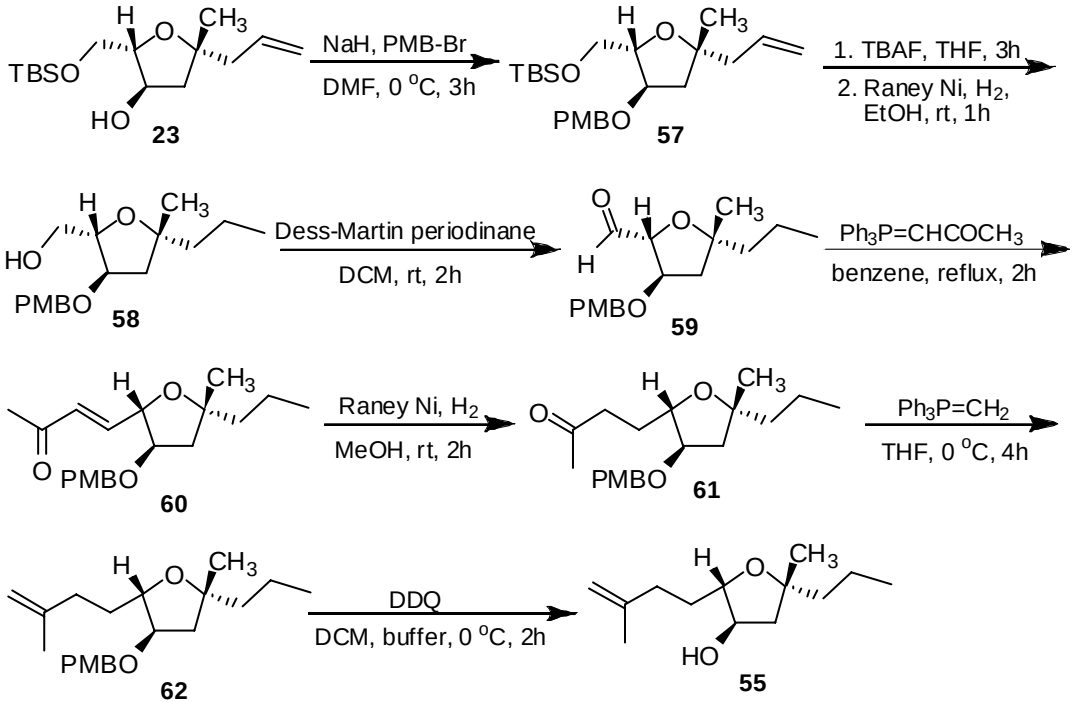
Figure 9: *Revised retrosynthetic strategy of Amphidinolide X*



According to our revised synthetic strategy, the requisite coupling partners **55** and **56** were planned from intermediates **46** and **47** respectively. For the

preparation of fragment **55**, we tried debenzylation of intermediate **46**, but the removal of benzyl group in presence of terminal double bond from **41** was difficult. To circumvent this problem, an alternative approach was followed for the synthesis of requisite modified fragment **55**. Here it was decided to change the hydroxyl protection to *para*-methoxybenzyl ether. The PMB ether protection instead of benzyl ether protection was preferred because it can be easily removed keeping olefin intact. Keeping this in mind, synthesis of fragment **55** was started from intermediate **23**. The compound **23** was treated with NaH and PMB-Br in DMF at 0 ^{o}C to get PMB alcohol derivative **57** in good yield. The reaction of **57** with TBAF in THF at ambient temperature led to the corresponding deprotected alcohol, which on reduction with raney nickel catalyst in ethanol furnished PMB alcohol derivative **58**. The NMR spectral data of **58** was in full agreement with the assigned structure. Moreover the mass analysis suggested the structure of PMB alcohol derivative by showing the molecular ion peak at *m/z*: 317 $[M+H]^{+}$.

Scheme 28:

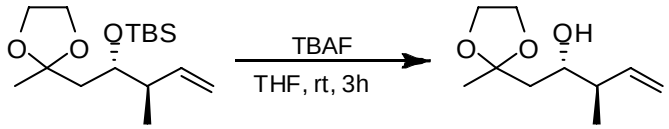


As depicted in scheme 28, the PMB alcohol derivative **58** was transformed to PMB alkene derivative **62** following the same protocol used earlier for the preparation of intermediate **46** from compound **5**. The compound **62** was characterized by using ^{1}H NMR, ^{13}C NMR and elemental analysis. The ^{1}H NMR spectrum revealed the presence of two olefinic protons appeared at δ 4.68 as a broad

singlet whereas in ^{13}C NMR spectrum the signals due to olefinic carbons appeared at 109.6 and 145.8 ppm. The elemental analysis was in well agreement with that of the calculated values for **62**. The removal of PMB ether was carried out by treating **62** with the mixture of DDQ in DCM and NaH_2PO_4-Na_2HPO_4 (*p*H 7) buffer at 0 ^oC to furnish **55**. The all the spectral and analytical data of **55** was in excellent agreement with the reported data.[44] The IR spectrum revealed the presence of free hydroxyl group attributable to absorption at 3417 cm^{-1}. The optical rotation of **55** ($[\alpha]_D$ –24.4) was also found to be in agreement with reported value ($[\alpha]_D$ −25.8).

The second requisite fragment was easily prepared from intermediate **47**. The silyl ether protection of **47** was removed by TBAF solution in THF at ambient temperature in 3 h to furnish alkene derivative **56** (Scheme 29). In the ^1H NMR spectrum of **56** the characteristic peaks due to TBS group disappeared. The ^{13}C NMR spectral data and other analytical data also supported the structure of **56**.

Scheme 29:

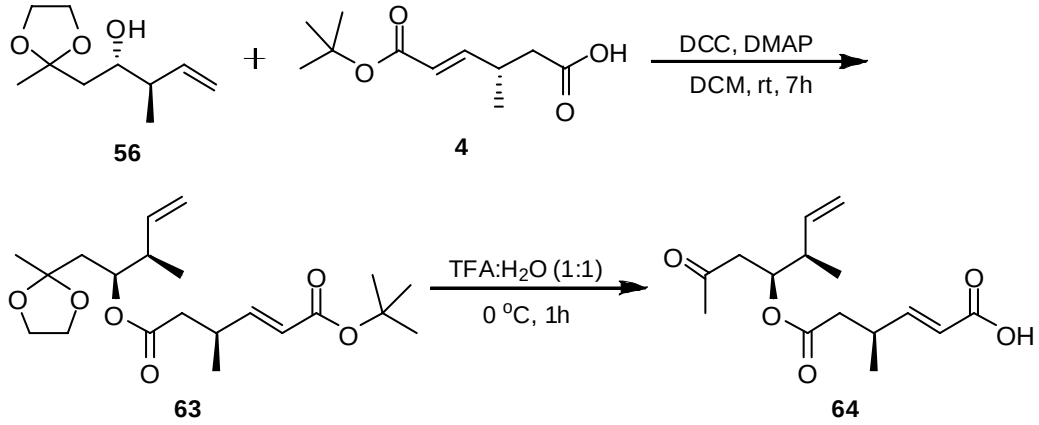


47 **56**

With fragments **4, 55** and **56** in hand, we next focused our attention to assemble them. According to our redesigned synthetic strategy, we first decided to couple fragments **4** and **56** first, which was to be followed by coupling with fragment **55**. Coupling of fragments **56** with acid derivative **4** was carried out by means of a DCC-mediated esterification. In the mixture of **4**, **56** and DMAP in DCM was added DCC at 0 ^oC and the reaction mixture was allowed to attain the room temperature to afford diester derivative **63** in good yield (Scheme 30).

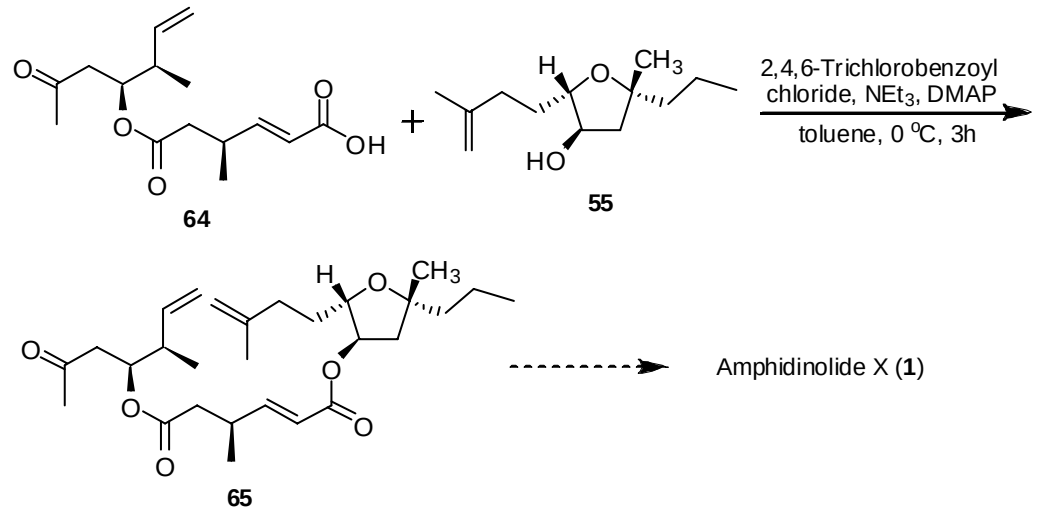
The olefinic protons resonated at δ 5.01-5.18 (m, 2H), 5.64-5.79 (m, 2H) and 6.82 (dd, 1H) in the ^1H NMR spectrum while the rest of the spectrum was in complete agreement with the assigned structure. Further confirmation of the structure of **63** came from its ^{13}C NMR and DEPT spectral data. For example, in the ^{13}C NMR spectrum, olefinic carbons were identified at 114.8, 128.4, 140.2 and 153.8 ppm. In addition, ESI-MS analysis indicated peaks at *m/z*: 383 $[M+H]^+$ and 405 accounting for $[M+Na]^+$. The elemental analysis of **63** was satisfactory (Calcd. for $C_{26}H_{27}NO_4$: C, 65.94; H, 8.96% Found: C, 66.47; H, 9.29%).

Scheme 30:



The selective hydrolysis of *ter*-butyl ester and removal of ketal protection, both were achieved in one shot by treating the diester derivative **63** with the mixture of trifloroacetic acid and water (1:1) at 0 ^{o}C for 1 h to get acid **64** (Scheme 30). As acid **64** was found to be unstable, it was taken for next reaction characterizing only by ^{1}H NMR and mass spectrum analysis. In the ^{1}H NMR spectrum, characteristic peaks due to *ter*-butyl group were missing and also the peaks due to ketal protection were absent. Moreover the mass analysis suggested the structure **64** by showing the highest mass peak at *m/z*: 305 $[M+Na]^{+}$.

Scheme 31:



The coupling of the acid derivative **64** with the alcohol **55** to furnish the ring closing metathesis precursor **65** was unsuccessful using DCC and EDCI. Attempts for the coupling through esterification employing the Yamaguichi's reaction conditions are in progress in our laboratory, which are to be followed by the final ring closing metathesis in order to achieve the total synthesis of amphidinolide X.

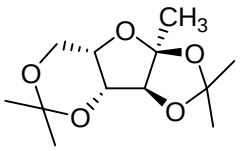
Conclusion:

In fact, the amphidinolide X natural products present several challenges to the synthetic organic chemist some of them were solved. Finally, in contrast, that different solutions were devised for some of the problems demonstrates that natural products often stimulate the development of and provide a proving ground for new strategies and methods of organic synthesis.

In summary, we have successfully accomplished the syntheses of three crucial segments with suitable protections for the projected total synthesis of Amphidinolide X. Our strategy presents a very different approach from the previous syntheses of tetrahydrofuran fragment. The allylation and simultaneous installation of the quaternary centre with correct stereochemistry of tetrahydrofuran fragment was achieved with excellent disastereocontrol.

EXPERIMENTAL

1-deoxy-2,3:4,6-di-*O*-isopropylidene-L-sorbofuranos (8):



2,3:4,6-di-*O*-isopropylidene-L-sorbofuranose (**9**) (20.0 g, 0.077 mol), TPP (40.3 g, 153.8 mmol), I_2 (39.0 g, 0.154 mol) and imidazole (15.7 g, 0.231 mol) in toluene (300 mL) were refluxed for 2 h. Toluene was removed, the residue partitioned between water and ethyl acetate. The organic phase was washed with $NaHCO_3$, $Na_2S_2O_3$ and brine, dried and concentrated. The residue was purified on silica gel by using ethyl acetate/light petroleum ether (1:3) to afford compound **16** (24.0 g, 85%) as pale yellow syrup. This iodo derivative **16** (24.0 g, 0.065 mol) was dissolved in toluene (200 mL), the solution was degassed with Argon and AIBN (100 mg) and tri-*n*-butyltinhydride (26.0 mL, 0.098 mol) were added. The contents were heated under reflux for 10 h and concentrated. The residue was purified on silica gel by eluting with ethyl acetate/light petroleum ether (1:9) to afford **8** (13.7 g, 87%) as colorless oil.

Mol. Formula : $C_{12}H_{20}O_5$

Mol. Weight : 244

ESI-MS *m/z* : 267 $[M+Na]^+$

Elemental Analysis : Calcd: C, 59.00; H, 8.25%

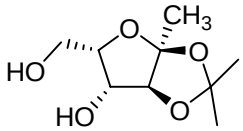
Found: C, 58.79; H, 8.67%

$[\alpha]_D^{25}$: -15.1 (*c* 1.25, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.36 (s, 3H), 1.39 (s, 3H), 1.44 (s, 3H), 1.48 (s, 3H), 1.72 (s, 3H), 4.05 (m, 3H), 4.22 (s, 1H), 4.28 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 18.5, 24.5, 26.2, 27.1, 28.9, 60.2, 71.9, 73.6, 87.2, 97.2, 110.8, 113.5

1-deoxy-2,3 -*O*-isopropylidene-L-sorbofuranos (17):



A solution of compound **8** (15.0 g, 61.4 mmol) and 0.8% aqueous H_2SO_4 (1 mL) in MeOH (150 mL) was stirred at room temperature for 6 h. Neutralization of the reaction mixture with aqueous $NaHCO_3$, concentration, extraction with ethyl acetate and purification over a silica gel column (ethyl acetate/light petroleum 1:1) gave the diol **17** (10.3 g, 82%) as a colorless oil.

Mol. Formula : $C_9H_{16}O_5$

Mol. Weight : 204

ESI-MS *m/z* : 227 $[M+Na]^+$

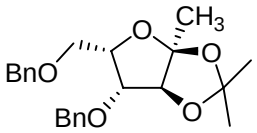
Elemental Analysis : Calcd: C, 52.93; H, 7.90%

Found: C, 53.42; H, 8.34%

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.35 (s, 3H), 1.48 (s, 3H), 1.71 (s, 3H), 1.90 (s, 1H), 4.08-4.12 (m, 1H), 4.18 (dd, *J* = 2.8, 4.0 Hz, 2H), 4.25 (s, 1H), 4.32 (t, *J* = 2.8 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 24.4, 25.8, 26.8, 60.7, 76.1, 78.9, 87.8, 110.5, 112.9

1-deoxy-4-benzyloxy-5-(benzyloxymethyl)-2,3 -*O*-isopropylidene-L-sorbofuranos (18):



To a solution of **17** (10 g, 0.049 mol) in DMF (100 mL) was added NaH (60% w/w dispersion in paraffin oil, 4.9 g, 0.123 mol) portion wise over a period of 30 min at 0 °C and then BnBr (14.5 mL, 0.123 mol) was introduced into reaction mixture. After stirring for 4 h, the reaction mixture was quenched with ice-cold water and extracted with Et_2O. Combined organic layer was washed with water,

brine, dried (Na_2SO_4), concentrated and the residue was purified on silica gel using ethyl acetate /light petroleum ether (1:9) as an eluent to give **18** (17.0 g, 91%) as a colorless liquid.

Mol. Formula : $C_{23}H_{28}O_5$

Mol. Weight : 384

ESI-MS *m/z* : 407 $[M+Na]^+$

Elemental Analysis : Calcd: C, 71.85; H, 7.34%

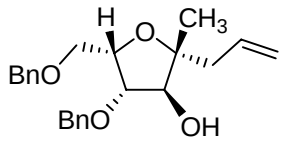
Found: C, 71.57; H, 7.39%

$[\alpha]_D^{25}$: +41.1 (*c* 1.10, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.34 (s, 3H), 1.47 (s, 3H), 1.65 (s, 3H), 3.74 (dd, *J* = 3.7, 6.5 Hz, 2H), 3.95 (d, *J* = 3.0 Hz, 1H), 4.30 (s, 1H), 4.42 (dd, *J* = 3.0, 6.2 Hz, 1H), 4.50 (dd, *J* = 2.4, 12.3 Hz, 2H), 4.64 (dd, *J* = 10.1, 12.0 Hz, 2H), 7.28-7.33 (m, 10H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 24.7, 26.3, 27.2, 67.5, 71.8, 73.4, 79.5, 82.1, 84.9, 110.8, 113.2, 127.3(2C), 127.5, 127.6, 127.7(2C), 128.2(2C), 128.3(2C), 137.7, 138.0

(2R,3S,4S,5S)-2-allyl-4-(benzyloxy)-5-(benzyloxymethyl)-2-methyltetrahydro-furan-3-ol(7):



A solution of **18** (5.0 g, 13 mmol) and allyltrimethylsilane (12.4 mL, 78 mmol) in 20 mL DCM was cooled to -78 °C. Freshly distilled boron trifluoride diethyl etherate was added in drop wise manner (2.5 mL, 20 mmol), and the solution was allowed to attain the ambient temperature. After 1 h. saturated $NaHCO_3$ and H_2O were added (5 mL each), the layers were separated, and the organic phase was extracted with DCM. The combined organic layers were dried (Na_2SO_4), filtered and

concentrated. The crude residue purified on silica gel using ethyl acetate /light petroleum ether (2:9) as an eluent to afford **7** (3.3 g, 68%) as colorless oil.

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

Mol. Weight : 368

ESI-MS *m/z* : 391 $[M+Na]^+$

Elemental Analysis : Calcd: C, 74.97; H, 7.66%

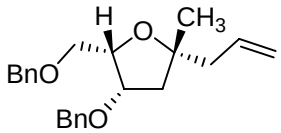
Found: C, 74.56; H, 8.26%

$[\alpha]_D^{25}$: -4.5 (*c* 1.0, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.18 (s, 3H), 1.70 (br s, 1H), 2.38 (d, *J* = 7.3 Hz, 2H), 3.57 (dd, *J* = 6.5, 10.1 Hz, 1H), 3.71 (dd, *J* = 4.7, 10.1 Hz, 1H), 4.05 (d, *J* = 4.4 Hz, 1H), 4.06 (s, 1H), 4.31-4.34 (m, 1H), 4.58 (dd, *J* = 12.3, 17.2 Hz, 2H), 4.61 (dd, *J* = 11.7, 15.9 Hz, 2H), 5.02-5.10 (m, 2H), 5.73-5.94 (m, 1H), 7.30-7.32 (m, 10H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 19.9, 44.8, 69.5, 72.4, 73.3, 75.9, 79.4, 82.4, 85.3, 118.0, 127.4(2C), 127.5, 127.6, 127.7(2C), 128.2(2C), 128.4(2C), 134.2, 138.0, 138.2

(2R,4S,5S)-2-allyl-4-(benzyloxy)-5-(benzyloxymethyl)-2-methyltetrahydrofuran (20):



To a solution of **7** (5.0 g, 13.5 mmol) in dry THF (50 mL) at 0 °C was added NaH (60% w/w dispersion in mineral oil, 0.8 g, 20.4 mmol) followed by carbon disulfide (1.6 mL, 20.4 mmol) after 20 min. After 20 min at the same temperature methyl iodide (1.3 mL, 20.4 mmol) was introduced. After 2 h, reaction mixture was quenched by the addition of ice water and repeatedly extracted with ethyl acetate.

The combined organic extract was washed with water, dried (Na_2SO_4) and concentrated. The crude xanthate derivative **19** (5.2 g, 11.4 mmol) was dissolved in toluene (55 mL), the solution was degassed with Argon. AIBN (50 mg) and tri-*n*-butyltinhydride (4.6 mL, 17.1 mmol) were added in reaction mixture. The contents were heated under reflux for 10 h and concentrated. The residue was purified on silica gel by eluting with ethyl acetate/light petroleum (1:9) to afford **20** (2.9 g, 68%) as colorless oil.

Mol. Formula : $C_{23}H_{28}O_3$

Mol. Weight : 352

ESI-MS *m/z* : 375 $[M+Na]^+$

Elemental Analysis : Calcd: C, 78.38; H, 8.01%

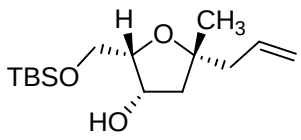
Found: C, 78.58; H, 8.49%

$[\alpha]_D^{25}$: +41.9 (*c* 1.20, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.21 (s, 3H), 1.75 (dd, *J* = 5.8, 13.2 Hz, 1H), 2.11 (dd, *J* = 2.2, 13.2 Hz, 1H), 2.40 (d, *J* = 6.6, Hz, 2H), 3.66 (dd, *J* = 5.1, 9.5 Hz, 1H), 3.78 (dd, *J* = 5.1, 9.5 Hz, 1H), 4.11-4.21 (m, 2H), 4.35-4.64 (m, 4H), 5.00-5.08 (m, 2H), 5.78-5.87 (m, 1H), 7.27-7.32 (m, 10H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 26.5, 41.3, 46.6, 69.1, 70.8, 73.1, 79.7, 79.9, 81.8, 117.2, 127.0(2C), 127.2(2C), 127.5(2C), 128.0(2C), 128.1(2C), 134.9, 138.1, 138.2

(2S,3S,5R)-5-allyl-2-((tert-butyldimethylsilyloxy)methyl)-5-methyltetrahydro-furan-3-ol (6):



A solution of **20** (4.5 g, 12.8 mmol) in anhydrous THF (20 mL) was added to a solution of lithium (0.76 g, 128.0 mmol) in liquid NH_3 (50 mL) maintained at –78 °C. The reaction mixture was stirred for 1 h and quenched with solid NH_4Cl. The excess ammonia gas was allowed to evaporate and then the resulting residue was taken in ethyl acetate washed with water, brine, dried (Na_2SO_4) and evaporated. The residue was purified on silica gel by using ethyl acetate/light petroleum (4:1) to obtain diol **21** (1.8 g, 81%), which was used for next step without purification.

TBDMSCl (1.7 g, 11.5 mmol) was added to a solution of diol **21** (1.8 g, 10.5 mmol) and triethylamine (2.2 mL, 15.7 mmol) in DCM (30 mL) at 0 °C and stirred for 1 h. The reaction mixture was quenched with saturated aq. $NaHCO_3$ solution (5 mL) and extracted with DCM. The combined organic layer was washed with brine, dried (Na_2SO_4), concentrated and the residue was purified on silica gel column chromatography using ethyl acetate/light petroleum (1:4) as an eluent to afford **6** (2.8 g, 92%) as colorless liquid.

Mol. Formula : $C_{15}H_{30}O_3Si$

Mol. Weight : 286

ESI-MS *m/z* : 309 $[M+Na]^+$

Elemental Analysis : Calcd: C, 62.89; H, 10.55%

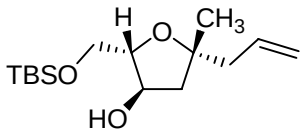
Found: C, 62.19; H, 11.34%

$[\alpha]_D^{25}$: +17.1 (*c* 1.10, $CHCl_3$)

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.10 (2s, 6H), 0.91 (s, 9H), 0.92 (s, 1H), 1.18 (s, 3H), 1.93-2.05 (m, 2H), 2.41 (d, *J* = 7.3 Hz, 2H), 3.40 (d, *J* = 5.6 Hz, 1H), 3.92-3.95 (m, 2H), 4.48-4.58 (m, 1H), 5.06-5.12 (m, 2H), 5.73-5.94 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ -5.5(2C), 18.3, 25.9(3C), 27.2, 44.2, 47.0, 64.6, 75.0, 82.5, 83.5, 117.8, 134.5

(2S,3R,5R)-5-allyl-2-((tert-butyldimethylsilyloxy)methyl)-5-methyltetrahydro-furan-3-ol (23):



To a solution of **6** (2.0 g, 7.0 mmol), TPP (3.7 g, 14.0 mmol) and *p*-nitro benzoic acid (2.4 g, 14.0 mmol) in THF (23 mL) at 0 °C was added DEAD (2.5 mL, 17.5 mmol) in dropwise manner. Stirring was continued at 0 ^{o}C for 1 h and then at room temperature for next 6 h. The solvent was removed under reduced pressure and the crude residue was purified on silica gel by eluting with ethyl acetate/light petroleum (1:9) to afford ester **22** (2.7 g, 88%). To a solution of **22** (2.7 g, 6.2 mmol) in moist MeOH (27 mL) was added $LiOH.H_2O$ (945mg, 24.8 mmol) and the reaction mixture was stirred at room temperature for 0.5 h and concentrated. The residue was purified on silica gel by eluting with ethyl acetate/light petroleum (1:5) to furnish **23** (1.4 g, 78%) as colorless oil.

Mol. Formula : $C_{15}H_{30}O_3Si$

Mol. Weight : 286

ESI-MS *m/z* : 309 $[M+Na]^+$

Elemental Analysis : Calcd: C, 62.89; H, 10.55%

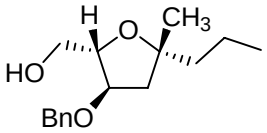
Found: C, 62.82; H, 11.18%

$[\alpha]_D^{25}$: -6.5 (*c* 1.35, $CHCl_3$)

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.08 (2s, 6H), 0.90 (s, 9H), 1.34 (s, 3H), 1.65 (s, 1H), 1.72 (dd, *J* = 6.3, 12.9 Hz, 1H), 2.14-2.25 (m, 3H), 3.58 (dd, *J* = 2.7, 8.7 Hz, 1H), 3.77-3.89 (m, 2H), 4.21-4.31 (m, 1H), 5.02-5.10 (m, 2H), 5.70-5.91 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ -5.4(2C), 18.0, 25.9(3C), 27.2, 44.3, 47.0, 64.6, 74.9, 82.4, 83.7, 117.7, 134.5

((2S,3R,5R)-3-(benzyloxy)-5-methyl-5-propyltetrahydrofuran-2-yl)methanol(5):



To an ice-cooled solution of **23** (1.4 g, 4.9 mmol), in anhydrous DMF (12 mL) was added NaH (60% w/w dispersion in mineral oil, 295 mg, 7.4 mmol) in portion-wise manner. Stirring was continued at the same temperature for 1 h. In this reaction mixture BnBr (0.7 mL, 5.9 mmol) was added in drop-wise manner at 0 ^{o}C. Reaction was stirred at the same temperature for 3 h. Reaction mixture was quenched by addition of ice, diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated to afford **24**. The compound **24** (1.8 g, 4.8 mmol) was taken in THF (15 mL) and treated with TBAF (1M solution in THF, 7.2 mL, 7.2 mmol). The reaction mixture was stirred for 3 h at 0 ^{o}C and then concentrated. The residue was chromatographed on silica gel by eluting with ethyl acetate/light petroleum (1:3) to afford alcohol **25** (0.9 g, 71%).

To a suspension of catalytic Raney nickel in EtOH (10 mL) was added solution of **25** (0.9 g, 3.4 mmol) in EtOH (10 mL) and stirred for 1 h under hydrogen atmosphere. The reaction mixture was filtered through a plug of celite, concentrated and the residue was purified by silica gel column chromatography using ethyl acetate/light petroleum (1:9) as an eluent to afford **5** (0.94 g, 93%) as colorless liquid.

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

Mol. Weight : 264

ESI-MS *m/z* : 287 $[M+Na]^+$

Elemental Analysis : Calcd: C, 72.69; H, 9.15%

Found: C, 71.98; H, 9.21%

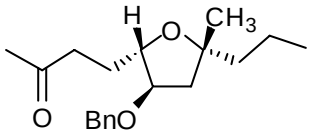
$[\alpha]_D^{25}$: -34.4 (*c* 0.95, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.92 (t, *J* = 7.3 Hz, 3H), 1.29-1.37 (m, 2H) 1.33 (s, 3H), 1.46-1.52 (m, 2H), 1.85 (dd, *J* = 3.8, 13.2 Hz, 1H), 1.95

(dd, *J* = 7.3, 13.2 Hz, 1H), 2.30 (s, 1H), 3.55 (dd, *J* = 4.5, 11.5 Hz, 1H), 3.71 (dd, *J* = 3.3, 11.5 Hz, 1H), 3.98-4.02 (m, 1H), 4.04-4.07 (m, 1H), 4.45 (d, *J* = 11.5 Hz, 1H), 4.51 (d, *J* = 11.5 Hz, 1H), 7.32-7.34 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$) **:** δ 14.5, 17.8, 25.6, 42.8, 44.7, 63.1, 71.5, 80.6, 83.1, 83.6, 126.7, 127.3(2C), 128.2(2C), 138.1

4-((2S,3R,5R)-3-(benzyloxy)-5-methyl-5-propyltetrahydrofuran-2-yl)butan-2-one (2):



To a solution of **5** (1.0 g, 3.8 mmol) in dry DCM (20 mL), was added Dess Martin periodinane reagent (3.2 g, 7.6 mmol) and stirred for 2 h. Water was added and extracted with DCM (3x20 mL), concentrated to obtain aldehyde **26** (0.89 g, 90%). A mixture of **26** (0.89 g, 3.4 mmol) and methylcarbonylmethylene triphenylphosphorane (2.2 g, 6.8 mmol) was refluxed in benzene for 2 h. Solvent was evaporated to leave the residue, which was purified on silica gel column with ethyl acetate/light petroleum (1:4) to afford **27** (0.92 g, 90%) as a thick liquid.

To a solution of **27** (920 mg, 3.2 mmol) in MeOH (4 mL) was added 10% Pd/C (10 mg) and stirred under H_2 atmosphere at room temperature for 4 h. The reaction mixture was filtered through a pad of celite, concentrated and the residue was purified on silica gel using ethyl acetate/light petroleum (1:5) as an eluent to give **2** (860 mg, 93%) as a colorless liquid.

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

Mol. Weight **:** 304

ESI-MS *m/z* **:** 327 $[M+Na]^+$

Elemental Analysis **:** Calcd: C, 74.96; H, 9.27%

Found: C, 75.23; H, 8.87%

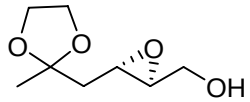
$[\alpha]_D^{25}$: -42.9 (*c* 0.80, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 1047, 1242, 1373, 1741, 2983 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.91 (t, *J* = 7.0 Hz, 3H), 1.25-1.36 (m, 2H), 1.28 (s, 3H), 1.40-1.49 (m, 2H), 1.64-1.82 (m, 2H), 1.87-2.02 (m, 2H), 2.12 (s, 3H), 2.52 (dd, *J* = 6.2, 17.8 Hz, 1H), 2.53 (d, *J* = 6.2 Hz, 1H), 3.66-3.79 (m, 1H), 3.90 (dt, *J* = 4.6, 8.5 Hz, 1H), 4.43 (d, *J* = 11.8 Hz, 1H), 4.51 (d, *J* = 11.8 Hz, 1H), 7.29-7.32 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 14.6, 17.8, 26.3, 28.4, 29.9, 40.1, 42.4, 45.2, 71.6, 81.4, 82.9, 84.0, 127.6(3C), 128.4(2C), 138.2, 208.7

((2S,3S)-3-((2-methyl-1,3-dioxolan-2-yl)methyl)oxiran-2-yl)methanol (11):



To a mixture of D(+)DET (7.8 g, 3.8 mmol) and 4Å molecular sieves powder (5.0 g) in DCM (50 mL) were added titanium(IV) isopropoxide (9.4 mL, 3.2 mmol) at -40 °C. After 15 minutes, a solution of allylic alcohol **12** (5.0 g, 3.2 mmol) in DCM (10 mL) was introduced and stirred for 45 min. The reaction mixture was then charged with TBHP (3.3 M solution in toluene, 19 mL, 6.3 mmol) slowly over a period of 15 min. at the same temperature. After 24 h, the reaction mixture was quenched with 10% aq. tartaric acid and extracted with DCM. Combined organic layer was dried (Na_2SO_4), concentrated and the residue was purified on silica gel using ethyl acetate/light petroleum (1:1) as an eluent to obtain epoxide **11** (6.5 g, 76% yield) as a colorless syrup.

Mol. Formula : $C_8H_{14}O_4$

Mol. Weight : 174

ESI-MS *m/z* : 197 $[M+Na]^+$

Elemental Analysis : Calcd: C, 55.16; H, 8.10%

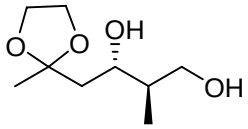
Found: C, 54.54; H, 8.97%

$[\alpha]_D^{25}$: -11.2 (*c* 1.10, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.40 (s, 3H), 1.89-1.92 (m, 2H), 2.95 (dt, *J* = 2.3, 4.3 Hz, 1H), 3.12 (ddd, *J* = 2.3, 5.9, 11.7 Hz, 1H), 3.64 (dd, *J* = 4.3, 12.5 Hz, 1H), 3.91 (dd, *J* = 4.3, 12.5 Hz, 1H), 3.95-4.00 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 21.8, 32.1, 55.2, 61.7, 66.5, 70.1, 72.3, 113.8

(2R,3S)-2-methyl-4-(2-methyl-1,3-dioxolan-2-yl)butane-1,3-diol (30):



To a strried suspension of cuprous cyanide (2.7 g, 3.0 mmol) in 30 mL of anhydrous diethylether under N_2 at -10 ^oC was added a solution of methyl magnesium chloride (3M solution in THF, 27 mL, 8.0 mmol). The light yellow suspension was then immediately cooled to -20 ^oC and epoxy alcohol **11** (3.5 g, 2.0 mol) in 5 mL of diethylether was added slowly *via* cannula. The yellow heterogeneous mixture was stirred at -20 ^oC for 3 h. The reaction mixture was partitioned between diethylether and saturated aq. NH_4Cl that had been basified to *p*H 8 by addition of conc. NH_4OH. The etheral extract was washed with brine, dried (Na_2SO_4), filtered, concentrated and purified by silica gel chromatography using ethyl acetate/light petroleum ether (7:3) as an eluent to obtain diol **30** (2.4 gm, 62%) as thick syrup.

Mol. Formula : $C_9H_{18}O_4$

Mol. Weight : 190

ESI-MS *m/z* : 213 $[M+Na]^+$

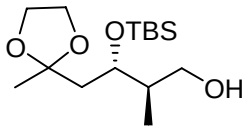
Elemental Analysis : Calcd: C, 56.82; H, 9.54%

Found: C, 57.34; H, 10.43%

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.88 (d, *J* = 7.0 Hz, 3H), 1.37 (s, 3H), 1.80-2.04 (m, 3H), 3.37 (s, 1H), 3.60-3.72 (m, 2H), 3.77-3.86 (m, 1H), 3.99-4.03 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 13.9, 24.1, 40.2, 43.0, 64.2, 64.6, 67.3, 73.8, 110.5

(2R,3S)-3-(tert-butyldimethylsilyloxy)-2-methyl-4-(2-methyl-1,3-dioxolan-2-yl)butan-1-ol (10):



To a solution of **30** (3.0 g, 1.6 mmol) and pyridine (1.8 mL, 2.1 mmol) in DCM (30 mL) at 0 ºC was added benzoyl chloride (2.1 mL, 1.6 mmol). After 2 h, the reaction mixture was extracted with ethyl acetate and the combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel by eluting with ethyl acetate/light petroleum (3:7) to give benzoylate derivative **32** (4.2 g, 90%).

A solution of **32** (4.2 g, 1.4 mmol), TBDMSCl (5.9 g, 2.1 mmol), imidazole (2.0 g, 2.9 mmol) and catalytic DMAP in DMF (40 mL) was stirred for 10 h at room temperature. The reaction mixture was diluted with diethyl ether and washed with water. The organic layer was dried (Na_2SO_4), concentrated to afford **33** (6.8 g, 90 %). The crude **33** (6.8 g, 1.3 mmol) was dissolved in MeOH (70 mL) and K_2CO_3 (3.5 g, 2.6 mmol) was added. The mixture was stirred at room temperature for 1 h. and concentrated. The residue was dissolved in water and extracted with EtOAc, washed with water, dried (Na_2SO_4) and evaporated. Purification of the residue on silica gel using ethyl acetate/light petroleum (2:3) as an eluent afforded pure alcohol **10** (3.0 g, 80%) as a colorless liquid.

Mol. Formula : $C_{15}H_{32}O_4Si$

Mol. Weight : 304

ESI-MS *m/z* : 327 $[M+Na]^+$

Elemental Analysis : Calcd: C, 59.17; H, 10.59%

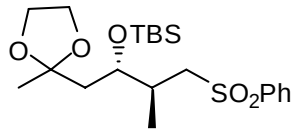
Found: C, 60.55; H, 11.20%

$[\alpha]_D^{25}$: -43.0 (*c* 0.80, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.09 (s, 3H), 0.10 (s, 3H), 0.89 (s, 9H), 1.02 (d, *J* = 7.0 Hz, 3H), 1.32 (s, 3H), 1.84 (dd, *J* = 3.4, 14.9 Hz, 1H) 1.91-2.02 (m, 1H), 2.18 (dd, *J* = 8.2, 14.9 Hz, 1H), 3.50 (dd, *J* = 5.6, 11.3 Hz, 1H), 3.88 (dd, *J* = 3.5, 11.3 Hz, 1H), 3.92-3.94 (m, 4H), 3.96-4.00 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ -4.9, -4.7, 14.0, 17.7, 24.2, 25.7(3C), 38.7, 43.0, 64.0, 64.2, 64.3, 72.7, 109.0

tert-butyldimethyl((2S,3S)-3-methyl-1-(2-methyl-1,3-dioxolan-2-yl)-4-(phenylsulfonyl)butan-2-yloxy)silane (3):



Compound **10** (1.0 g, 3.3 mmol), TsCl (1.0 g, 5.0 mmol), triethylamine (1mL, 6.6 mmol) and catalytic DMAP were stirred in DCM (10 mL) at 0 ºC for 2 h. The solvent was removed under reduced pressure and the residue obtained was extracted with EtOAc, washed with water, brine, dried (Na_2SO_4) and evaporated to obtain tosylate **34**. A solution of **34** (1.3 g, 3.0 mmol) and anhydrous sodium iodide (0.9 g, 6.0 mmol) in acetone (15 mL) was heated under reflux for 4 h. The solvent was removed under reduced pressure. The residue was chromatographed on silica gel by eluting with ethyl acetate/light petroleum (1:9) to get **35** (1.0 g, 81%) as syrup. A mixture of **35** (1.0 g, 2.4 mmol), $PhSO_2Na$ (0.6 g, 3.6 mmol) and catalytic TBAI were stirred in anhydrous THF (10 mL) at room temperature for 4 h. The

solvent was removed under reduced pressure. The residue was purified on silica gel by eluting with ethyl acetate/light petroleum (4:1) to give **3** (0.8 g, 78%) as thick oil.

Mol. Formula : $C_{21}H_{36}O_5SSi$

Mol. Weight : 428

ESI-MS *m/z* : 451 $[M+Na]^+$

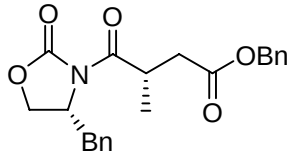
Elemental Analysis : Calcd: C, 58.84; H, 8.46%

Found: C, 59.22; H, 7.73%

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.03 (s, 3H), 0.07 (s, 3H), 0.87 (s, 9H), 1.07 (d, *J* = 7.3 Hz, 3H), 1.32 (s, 3H), 1.79 (dd, *J* = 3.7, 14.7 Hz, 1H), 2.11 (dd, *J* = 8.0, 14.7 Hz, 1H), 2.22-2.29 (m, 1H), 3.21 (dd, *J* = 8.0, 13.2 Hz, 1H), 3.62 (dd, *J* = 4.4, 13.2 Hz, 1H), 3.85-3.88 (m, 1H), 3.91-3.93 (m, 4H), 7.54-7.58 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ -4.9, -4.6, 16.1, 17.8, 24.3, 25.7(3C), 35.1, 37.7, 42.8, 64.0, 64.4, 71.7, 108.7, 123.6(2C), 129.5(2C), 129.7, 154.7

(S)-benzyl 4-((R)-4-benzyl-2-oxooxazolidin-3-yl)-3-methyl-4-oxobutanoate (14):



20 mL of sodium hexamethyldisilazide (1 M in THF, 20.0 mmol) was added dropwise to a stirring solution of *N*-propyl oxazolidinone (3.0 g, 12.8 mmol) in 22 mL of THF at –40 °C. After 1 h, solution of benzyl bromoacetate (5.8 g, 25.6 mmol) and NaI (2.0 g, 12.8 mmol) in THF (18mL) was added into reaction mixture in a dropwise manner. The solution was stirred at -40 °C for 4 h. Extraction and concentration yielded a liquid residue. Which was purified on silica gel using ethyl acetate/light petroleum (1:4) as an eluent to afford **14** (4.1 g, 84%) as a pale yellow liquid.

Mol. Formula : $C_{22}H_{23}NO_5$

Mol. Weight : 381

ESI-MS *m/z* : 404 $[M+Na]^+$

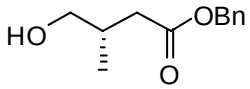
Elemental Analysis : Calcd: C, 69.28; H, 6.08, N, 3.67%

Found: C, 68.57; H, 6.67, N, 4.07%

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.22 (d, *J* = 7.1 Hz, 3H), 2.45-2.56 (m, 2H), 3.02 (dd, *J* = 10.0, 16.9 Hz, 1H), 3.21 (dd, *J* = 3.2, 13.5 Hz, 1H), 4.08-4.21 (m, 3H), 4.55-4.65 (m, 1H), 5.10 (s, 2H), 7.26-7.34 (m, 10H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 17.0, 28.9, 34.2, 37.1, 37.5, 54.9, 66.2, 126.7, 128.0(2C), 128.1(4C), 128.4, 128.6(2C), 129.2, 135.4, 152.8, 170.4, 175.8

(S)-benzyl 4-hydroxy-3-methylbutanoate (38):



To a solution of **14** (2.0 g, 5.2 mmol) in THF/H_2O (3:1 v/v, 20 mL) at 0 ^oC was added $NaBH_4$ (0.2 g, 5.2 mmol) in portions. After 2 h, saturated aq. NH_4Cl was added to the reaction mixture and it was extracted with EtOAc. The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified on silica gel using ethyl acetate/light petroleum (1:3) to afford **38** (1.0 g, 80%) as a colorless liquid.

Mol. Formula : $C_{12}H_{16}O_3$

Mol. Weight : 208

ESI-MS *m/z* : 231 $[M+Na]^+$

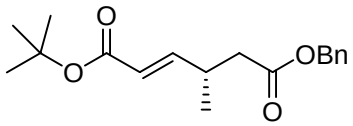
Elemental Analysis : Calcd: C, 69.21; H, 7.74%

Found: C, 70.11; H, 8.82%

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 0.96 (d, *J* = 6.6 Hz, 3H), 1.76 (br.s, 1H), 2.13-2.32 (m, 2H), 2.50 (dd, *J* = 6.4, 14.7 Hz, 1H), 3.44 (dd, *J* = 6.6, 10.7 Hz, 1H), 3.56 (dd, *J* = 5.0, 10.7 Hz, 1H), 5.11 (s, 2H), 7.32-7.35 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$) **:** δ 16.7, 29.7, 38.8, 56.2, 67.5, 128.4(3C), 128.9(2C), 135.3, 168.3

(S,E)-6-benzyl 1-tert-butyl 4-methylhex-2-enedioate (40):



To a solution of **38** (1.6 g, 7.7 mmol) in DCM (20 mL) was added freshly prepared Dess-Martin periodinane (4.9 g, 11.5 mmol) at room temperature. After stirring for 1 h, the reaction mixture was filtered through a plug of celite and concentrated. The resulting aldehyde (1.4 g, 6.8 mmol) and Ph_3P=CHCOO*t*Bu (5.1 g, 13.6 mmol) in benzene (15 mL) were heated under reflux for 2 h. Solvent was evaporated and residue was purified on silica gel with ethyl acetate/light petroleum (1:9) as an eluent to afford diester **40** (1.6 g, 80%) as a colorless liquid.

Mol. Formula **:** $C_{18}H_{24}O_4$

Mol. Weight **:** 304

ESI-MS *m/z* **:** 327 $[M+Na]^+$

Elemental Analysis **:** Calcd: C, 71.03; H, 7.95%

Found: C, 70.23; H, 8.47%

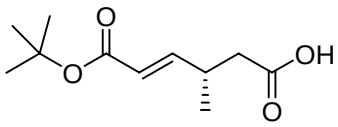
$[\alpha]_D^{25}$ **:** +12.6 (*c* 1.0, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 1.11 (d, *J* = 6.7 Hz, 3H), 1.48 (s, 9H), 2.35 (dd, *J* = 7.6, 15.3 Hz, 1H), 2.49 (dd, *J* = 6.8, 15.3 Hz, 1H), 2.78-2.92 (m, 1H), 5.11 (s, 2H), 5.73 (dd, *J* = 1.4, 15.7 Hz, 1H), 6.78

(dd, *J* = 7.0, 15.7 Hz, 1H), 7.34(s, 5H).

^{13}C NMR (50 MHz, $CDCl_3$) **:** δ 19.1, 28.1(3C), 32.8, 40.3, 66.3, 80.1, 122.1, 128.2(3C), 128.5(2C), 135.7, 150.3, 165.7, 171.4

(S,E)-6-tert-butoxy-3-methyl-6-oxohex-4-enoic acid (4):



The compound **40** (500 mg, 1.6 mmol) was dissolved in MeOH (7 mL) and K_2CO_3 (450 mg, 3.3 mmol) was added. The mixture was stirred at 0 ^oC for 1 h. and concentrated. The residue was dissolved in water and extracted with ethyl acetate, organic layer was washed with water, dried (Na_2SO_4) and evaporated. Purification of the residue on silica gel using ethyl acetate/light petroleum (1:3) as an eluent afforded pure acid **4** (265 mg, 75%) as a thick syrup.

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

Mol. Weight **:** 214

ESI-MS *m/z* **:** 237 $[M+Na]^+$

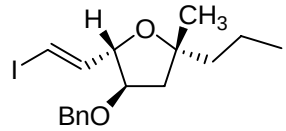
Elemental Analysis **:** Calcd: C, 61.66; H, 8.47%

Found: C, 61.12; H, 9.25%

$[\alpha]_D^{25}$ **:** +21.8 (*c* 0.9, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 1.14 (d, *J* = 6.7 Hz, 3H), 1.48 (s, 9H), 2.34 (dd, *J* = 7.7, 15.8 Hz, 1H), 2.50 (dd, *J* = 6.6, 15.8 Hz, 1H), 2.77-2.90 (m, 1H), 5.76 (dd, *J* = 1.3, 15.7 Hz, 1H), 6.80 (dd, *J* = 7.0, 15.7 Hz, 1H).

(2R,4R,5S)-4-(benzyloxy)-5-((E)-2-iodovinyl)-2-methyl-2-propyltetrahydrofuran (42):



To a solution of **5** (150 mg, 0.6 mmol) in dry DCM (5 mL) at 0 ^{o}C, was added Dess-Martin periodinane (362 mg, 0.9 mmol) and stirred for 2 h. Water was added to the reaction mixture and it was extracted with DCM. The combined extracts were dried (Na_2SO_4) and concentrated to obtain aldehyde **26** (126 mg, 85% crude yield), which was used for next step without purification.

Anhydrous $CrCl_2$ (338 mg**,** 2.8 mmol) was suspended in THF (8 mL) under Argon atmosphere. A solution of aldehyde **26** (120 mg**,** 0.6 mmol) and iodoform (361 mg, 0.9 mmol) in THF (7 mL) was added in dropwise manner to the suspension at 0 °C. After stirring at 0 °C for 3 h, the reaction mixture is poured into water and extracted with diethylether. The combined extracts were dried (Na_2SO_4) and concentrated. Purification by column chromatography on silica gel by eluting with ethyl acetate/light petroleum (1:6) afforded **42** (138 mg, 78%) as a colorless oil. (As compound **42** was unstable, it was characterized only by ^{1}H NMR and mass analysis and taken for the next reaction)

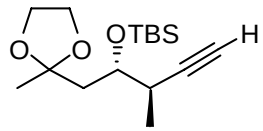
Mol. Formula : $C_{17}H_{23}IO_2$

Mol. Weight : 386

ESI-MS *m/z* : 409 $[M+Na]^+$

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.92 (t, *J* = 7.1 Hz, 3H), 1.31 (s, 3H), 1.33-1.36 (m, 2H), 1.42-1.50 (m, 2H), 1.82 (dd, *J* = 4.8, 13.0 Hz, 1H), 2.04 (dd, *J* = 7.5, 13.0 Hz, 1H), 3.81-3.93 (m, 1H), 4.31-4.37 (m, 1H), 4.51 (s, 2H), 6.40 (d, *J* = 14.4 Hz, 1H), 6.56 (dd, *J* = 6.0, 14.4 Hz, 1H), 7.30-7.36 (m, 5H).

Tert-butyldimethyl((2S,3R)-3-methyl-1-(2-methyl-1,3-dioxolan-2-yl)pent-4-yn-2-yloxy)silane (43):



To a solution of **10** (500 mg, 1.6 mmol) in DCM (10 mL) was added Dess-Martin periodinane (1.1 g, 2.5 mmol) and the reaction mixture was stirred for 2 h and then diluted with DCM and quenched with ice water. The aqueous layer was extracted with DCM. Combined organic extract was dried (Na_2SO_4) and concentrated to obtain crude aldehyde. To a solution of resultant aldehyde (450 mg, 1.5 mmol) and K_2CO_3 (412 mg, 3.0 mmol) in MeOH (5 mL) at 0 °C, dimethyl 1-diazo-2-oxopropylphosphonate (572 mg, 3.0 mmol) in MeOH (5 mL) was added slowly. The reaction mixture was stirred for 2 h at room temperature and diluted with Et_2O and quenched by sat. NH_4Cl solution. The mixture was extracted with Et_2O, washed with brine and dried (Na_2SO_4). After filtration and evaporation, flash column chromatography on silica gel using ethyl acetate/light petroleum (1:9) provided alkyne **43** (400 mg, 79%) as colorless liquid.

Mol. Formula **:** $C_{16}H_{30}O_3Si$

Mol. Weight **:** 298

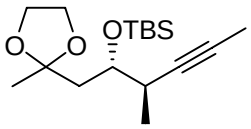
ESI-MS *m/z* **:** 321 $[M+Na]^+$

Elemental Analysis **:** Calcd: C, 64.38; H, 10.13%

Found: C, 63.79; H, 11.02%

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 0.07 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 1.16 (d, *J* = 7.1 Hz, 3H), 1.36 (s, 3H), 1.74 (dd, *J* = 5.7, 14.6 Hz, 1H), 2.03 (d, *J* = 2.5 Hz, 1H), 2.18 (dd, *J* = 5.2, 14.6 Hz, 1H), 2.72-2.79 (m, 1H), 3.83-3.88 (m, 1H), 3.92-3.94 (m, 4H).

Tert-butyldimethyl((2S,3R)-3-methyl-1-(2-methyl-1,3-dioxolan-2-yl)hex-4-yn-2-yloxy)silane (44):



1.6 M solution of *n*BuLi (0.8 mL 15% solution in hexane, 1.8 mmol) was added to a solution of alkyne **43** (400 mg, 1.2 mmol) in THF (8 mL) at –78 ^{o}C. The reaction was stirred for 1 h at same temperature and for 30 min at –20 ^{o}C. The mixture was cooled to –78 ^{o}C, before MeI (0.3 mL, 2.4 mmol) was introduced, and stirring was continued for 2 h. An aq. saturated NH_4Cl was added, the aqueous layer was extracted with ethyl acetate, the combined organic layer was dried (Na_2SO_4), filtered, evaporated and the residue was purified by flash chromatography on silica gel using ethyl acetate/light petroleum (1:19) to afford methyl alkyne derivative **44** (395 mg, 94%) as a colorless syrup.

Mol. Formula : $C_{17}H_{32}O_3Si$

Mol. Weight : 312

ESI-MS *m/z* : 313 $[M+H]^+$, 335 $[M+Na]^+$

Elemental Analysis : Calcd: C, 65.33; H, 10.32%

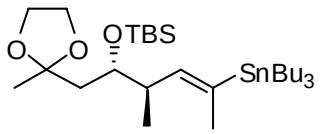
Found: C, 66.08; H, 9.57%

$[\alpha]_D^{25}$: -11.7 (*c* 1.0, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.06 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 1.08 (d, *J* = 6.9 Hz, 3H), 1.37 (s, 3H), 1.69 (dd, *J* = 6.5, 14.5 Hz, 1H), 1.78 (d, *J* = 2.4 Hz, 3H), 2.12 (dd, *J* = 4.0, 14.5 Hz, 1H), 2.59-2.65 (m, 1H), 3.82-3.89 (m, 1H), 3.92-3.94 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ -4.6, -4.5, 3.6, 14.4, 18.0, 24.5, 25.8(3C), 32.9, 41.5, 62.2, 64.1, 64.3, 71.2, 80.9, 109.3

tert-butyldimethyl((2S,3R,E)-3-methyl-1-(2-methyl-1,3-dioxolan-2-yl)-5-(tributylstannyl)hex-4-en-2-yloxy)silane (45):



Preparation of Pd (0):

A mixture of $PdCl_2$ (50 mg, 0.3 mmol) and PPh_3 (370 mg, 1.5 mmol) in DMSO (5 mL) was heated to 140 ^oC till a clear solution was obtained. The oil bath was removed and the solution stirred for 15 min. Hydrazine hydrate was then added rapidly (57 mg, 1.2 mmol) and the mixture was immediately cooled with water bath. Crystallization begins at 125 ^oC. At this point, the mixture was allowed to cool without external cooling. The crystals of $Pd[PPh_3]_4$ were filtered under nitrogen, washed successively with ethanol and ether, dried, stored under nitrogen and protected from light.

To a stirred solution of **44** (100 mg, 0.3 mmol) in toluene (3 mL) were added *n*-Bu_3SnH (0.2 mL, 0.6 mmol) and $Pd[PPh_3]_4$ (34 mg, 5 mol %) at room temperature. The reaction mixture was degassed with Argon and stirred for 6 h. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography using ethyl acetate/light petroleum (1:4) to give **45** (150 mg, 86%) as a colorless liquid.

Mol. Formula : $C_{29}H_{60}O_3SnSi$

Mol. Weight : 603

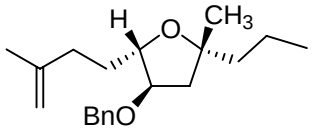
ESI-MS *m/z* : 626 $[M+Na]^+$

Elemental Analysis : Calcd: C, 57.71; H, 10.02%

Found: C, 56.83; H, 11.14%

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.07 (2s, 6H), 0.85-0.92 (m, 15H), 0.89 (s, 9H), 1.00 (d, *J* = 7.0 Hz, 3H), 1.28-1.35 (m, 6H), 1.33 (s, 3H), 1.41-1.50 (m, 6H), 1.53 (s, 3H), 1.61 (dd, *J* = 5.0, 14.4 Hz, 1H), 1.87 (dd, *J* = 4.5, 14.4 Hz, 1H), 2.40-2.48 (m, 1H), 3.83-3.92 (m, 5H), 5.90-5.92 (m, 1H).

(2R,4R,5S)-4-(benzyloxy)-2-methyl-5-(3-methylbut-3-enyl)-2-propyltetrahydrofuran (46):



To a solution of **2** (200 mg, 0.7 mmol) in THF (5 mL) at 0 ^{o}C was added methyltriphenylphosphorane ylide [generated by the action of *n*-BuLi (0.7 mL 3.0 M solution in hexane, 2.0 mmol) on $Ph_3P^+CH_3I^-$ (800 mg, 2.0 mmol) in anhydrous THF (5 mL) at 0 ^{o}C]. The reaction mixture was stirred at 0 ^{o}C for 4 h, quenched with saturated NH_4Cl and filtered. The organic layer was separated and aqueous layer extracted with ethyl acetate. The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The residue thus obtained was purified on silica gel by eluting with ethyl acetate/light petroleum (1:19) to furnish **46** (173 mg, 87%) as a colorless liquid.

Mol. Formula : $C_{20}H_{30}O_2$

Mol. Weight : 302

ESI-MS *m/z* : 325 $[M+Na]^+$

Elemental Analysis : Calcd: C, 79.42; H, 10.00%

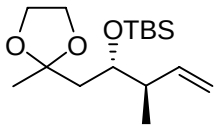
Found: C, 78.91; H, 9.32%

$[\alpha]_D^{25}$: -21.3 (*c* 1.2, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.91 (t, *J* = 7.0 Hz, 3H), 1.30 (s, 3H), 1.35-1.43 (m, 2H), 1.46-1.59 (m, 2H), 1.62-1.69 (m, 2H), 1.72 (s, 3H), 1.80 (dd, *J* = 3.9, 13.2 Hz, 1H), 1.94 (dd, *J* = 6.8, 13.2 Hz, 1H), 2.02-2.14 (m, 2H), 3.71-3.80 (m, 1H), 3.95 (ddd, *J* = 4.8, 6.3, 12.5 Hz, 1H), 4.44 (d, *J* = 11.9 Hz, 1H), 4.53 (d, *J* = 11.9 Hz, 1H), 4.67 (br.s, 2H), 7.24-7.33 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 14.8, 18.0, 22.8, 26.5, 32.9, 34.0, 42.6, 45.4, 71.4, 82.2, 82.8, 83.9, 109.8, 127.8(2C), 128.0, 129.4(2C), 130.6, 146.0

Tert-butyldimethyl((2S,3R)-3-methyl-1-(2-methyl-1,3-dioxolan-2-yl)pent-4-en-2-yloxy)silane (47):



To a solution of **10** (500 mg, 1.6 mmol) in DCM (10 mL) was added Dess-Martin periodinane (1.0 g, 2.5 mmol) at 0 ^{o}C and the reaction mixture was stirred for 2 h and then diluted with DCM and quenched with ice water. The aqueous layer was extracted with DCM. Combined organic extract was dried (Na_2SO_4) and concentrated to get a crude aldehyde. To a solution of resultant aldehyde (450 mg, 1.5 mmol) in anhydrous THF (25 mL), methylenetriphenylphosphorane [prepared from $Ph_3P^+CH_3I^-$ (1.8 g, 4.5 mmol) and *n*BuLi (1.6 M in hexane 2.8 mL, 4.5 mmol)] was added in dropwise manner at 0 ^{o}C. After 2 h, reaction mixture was quenched by addition of saturated aqueous solution of NH_4Cl. The two layers were separated, the organic layer was dried (Na_2SO_4) and concentrated to get a residue, which was purified on silica gel using ethyl acetate/light petroleum (1:9) to furnish **47** (350 mg, 79%) as a colorless oil.

Mol. Formula : $C_{16}H_{32}O_3Si$

Mol. Weight : 300

ESI-MS *m/z* : 323 $[M+Na]^+$

Elemental Analysis : Calcd: C, 63.95; H, 10.73%

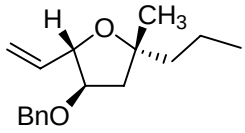
Found: C, 64.78; H, 11.46%

$[\alpha]_D^{25}$: -14.7 (*c* 1.1, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.07 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 1.02 (d, *J* = 6.8 Hz, 3H), 1.34 (s, 3H), 1.64 (dd, *J* = 5.1, 14.7 Hz, 1H), 1.88 (dd, *J* = 6.1, 14.7 Hz, 1H), 2.41-2.49 (m, 1H), 3.79-3.84 (m, 1H), 3.88-3.94 (m, 4H), 4.97-5.07 (m, 2H), 5.71-5.89 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ -4.5, -4.4, 15.7, 18.1, 24.6, 25.9(3C), 42.4, 43.5, 64.1, 64.3, 72.1, 109.3, 115.0,140.4

(2R,4R,5S)-4-(benzyloxy)-2-methyl-2-propyl-5-vinyltetrahydrofuran (48):



To a solution of **26** (120 mg, 0.5 mmol) in anhydrous THF (5 mL), methylenetriphenylphosphorane [prepared from $Ph_3P^+CH_3I^-$ (740 mg, 1.8 mmol) and *n*BuLi (1.6 M solution in hexane, 1.2 mL, 1.8 mmol) at -78 ^oC] was added in dropwise manner at 0 ^oC. After 2 h, reaction mixture was quenched by addition of saturated aqueous solution of NH_4Cl. The reaction mixture was extracted with ethyl acetate, the combined organic layer was dried (Na_2SO_4) and concentrated to give a residue, which was purified on silica gel using ethyl acetate/light petroleum (1:20) to furnish **48** (100 mg, 84%) as colorless oil.

Mol. Formula : $C_{17}H_{24}O_2$

Mol. Weight : 260

ESI-MS *m/z* : 283 $[M+Na]^+$

Elemental Analysis : Calcd: C, 78.42; H, 9.29%

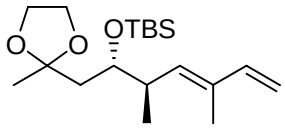
Found: C, 79.17; H, 8.69%

$[\alpha]_D^{25}$: -22.8 (*c* 1.4, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.92 (t, *J* = 7.1 Hz, 3H), 1.21-1.25 (m, 2H) 1.33 (s, 3H), 1.36-1.48 (m, 2H), 1.82 (dd, *J* = 4.8, 13.0 Hz, 1H), 2.04 (dd, *J* = 7.5, 13.0 Hz, 1H), 3.80-3.88 (m, 1H), 4.36-4.42 (m, 1H), 4.51 (s, 2H), 5.15 (ddd, *J* = 1.4, 1.7, 10.2 Hz, 1H), 5.35 (ddd, *J* = 1.3, 1.7, 17.2 Hz, 1H), 5.87 (ddd, *J* = 6.5, 10.2, 17.2 Hz, 1H), 7.30-7.33 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$) **:** δ 14.6, 17.8, 26.3, 42.7, 45.0, 71.7, 83.2, 83.6, 84.3, 116.3, 127.5(2C), 127.6, 128.4(2C), 137.8, 138.2

tert-butyl((2S,3R,E)-3,5-dimethyl-1-(2-methyl-1,3-dioxolan-2-yl)hepta-4,6-dien-2-yloxy)dimethylsilane (51):



To a solution of **10** (304 mg, 1.0 mmol) in DCM (5 mL) was added Dess-Martin Periodinane (502 mg, 1.2 mmol) at room temperature. After stirring for 1 h, the reaction mixture was filtered through a plug of celite and concentrated. The resulting aldehyde (300 mg, 1.0 mmol) and Ph_3P=C(Me)COOEt (720 mg, 2.0 mmol) in benzene (10 mL) were heated under reflux for 3 h. Solvent was evaporated and residue was purified on silica gel with ethyl acetate/light petroleum (20:1) as an eluent to afford ester **49** (300 mg, 79%).

To a solution of **49** (300 mg, 0.8 mmol) in DCM (10 mL) at -20 °C was added DIBAL-H (2.0 M solution in toluene, 1 mL, 2.0 mmol) dropwise over a period of 5 min. After 3 h, the reaction mixture was quenched with saturated sodium potassium tartarate solution, filtered through a pad of silica gel and concentrated. The residue was purified on silica gel using ethyl acetate/light petroleum (1:3) as an eluent to afford **50** (208 mg, 78%) as thick syrup.

Oxidation and one carbon wittig homologation of **50** (200 mg, 0.6 mmol) was performed as described earlier for the preparation of **46**, using Dess Martin periodinane in DCM and methylenetriphenylphosphorane in THF to give **51** (160 mg, 81%) as thick syrup after silica gel column purification using ethyl acetate/light petroleum (1:19).

Mol. Formula **:** $C_{19}H_{36}O_3Si$

Mol. Weight **:** 340

ESI-MS *m/z* **:** 363 $[M+Na]^+$

Elemental Analysis **:** Calcd: C, 67.01; H, 10.65%

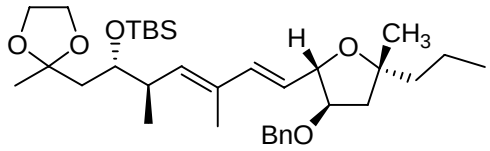
Found: C, 67.34; H, 11.19%

$[\alpha]_D^{25}$: -9.4 (*c* 1.0, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.07 (2s, 6H), 0.90 (s, 9H), 0.97 (d, *J* = 6.8 Hz, 3H), 1.32 (s, 3H), 1.69-1.84 (m, 2H), 1.76 (d, *J* = 1.3 Hz, 3H), 2.75-2.85 (m, 1H), 3.76-3.82 (m, 1H), 3.86-3.92 (m, 4H), 4.93 (d, *J* = 10.7 Hz, 1H), 5.08 (d, *J* = 17.4 Hz, 1H), 5.51 (d, *J* = 9.5 Hz, 1H), 6.40 (dd, *J* = 10.7, 17.4 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ -4.6, -4.4, 12.0, 17.3, 18.1, 24.6, 25.9(3C), 38.2, 43.7, 64.2, 64.4, 72.3, 109.0, 110.4, 134.0, 134.9, 142.1

((2S,3R,4E,6E)-7-((2S,3R,5R)-3-(benzyloxy)-5-methyl-5-propyltetrahydrofuran-2-yl)-3,5-dimethyl-1-(2-methyl-1,3-dioxolan-2-yl)hepta-4,6-dien-2-yloxy)(tert-butyl)dimethylsilane (52):



A degassed solution of **48** (52 mg, 0.2 mmol), **51** (68 mg, 0.2 mmol) and Grubbs' 2nd generation catalyst (9 mg, 10 μmol) in freshly distilled DCM (2 mL) was heated to reflux under Argon atmosphere for 12 h and then concentrated. The residue was purified on silica gel by eluting with ethyl acetate/light petroleum (1:9) to furnish coupled compound **52** (67 mg, 60%) as a thick colorless liquid.

Mol. Formula : $C_{34}H_{56}O_5Si$

Mol. Weight : 572

ESI-MS *m/z* : 595 $[M+Na]^+$

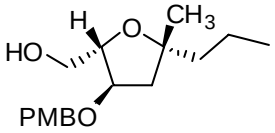
Elemental Analysis : Calcd: C, 71.28; H, 9.85%

Found: C, 70.55; H, 10.42%

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 0.05 (s, 3H), 0.06 (s, 3H), 0.88-0.92 (m, 12H), 0.97 (d, *J* = 4.8 Hz, 3H), 1.29 (s, 3H), 1.32 (s, 3H), 1.37-1.55 (m, 4H), 1.67-1.85 (m, 2H), 1.79 (s, 3H), 1.93-2.11 (m, 2H), 2.57-2.70 (m, 1H), 3.34-3.44 (m, 1H), 3.55-3.67 (m, 4H), 3.77-3.87 (m, 1H), 4.39 (dd, *J* = 6.0, 7.3 Hz, 1H), 4.50 (s, 2H), 5.39 (dd, *J* = 2.8, 10.3 Hz, 1H), 5.49 (ddd, *J* = 2.8, 7.5,15.5 Hz, 1H), 6.31 (d, *J* = 15.5 Hz, 1H), 7.25-7.30 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$) **:** δ -4.4(2C), 12.8, 14.6, 17.9, 19.8, 25.9(3C), 26.5, 29.7, 37.8, 38.5, 41.4, 43.0, 45.1, 62.1, 69.1, 71.8, 73.2, 82.6, 83.6, 84.5, 96.1, 125.8, 127.6(3C), 128.3(2C), 132.8, 135.3, 137.7, 138.3

((2S,3R,5R)-3-(4-methoxybenzyloxy)-5-methyl-5-propyltetrahydrofuran-2-yl)methanol (58):



To an ice-cooled solution of **23** (3.0 g, 10.4 mmol), in anhydrous DMF (35 mL) was added NaH (60% w/w dispersion in mineral oil, 545 mg, 13.6 mmol) in portion-wise manner. Stirring was continued at the same temperature for 1 h and then 4-methoxybenzyl bromide (1.6 g, 15.6 mmol) was added in drop-wise manner. Reaction mixture was allowed to attain room temperature and was stirred for 2 h. After completion, the reaction mixture was quenched by addition of ice, diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated to obtain **57**. The crude **57** (1.5 g, 3.7 mmol) was taken in THF (15 mL) and treated with TBAF (1.0 M solution in THF, 5.5 mL, 5.5 mmol). The reaction mixture was stirred for 3 h at room temperature and then concentrated under reduced pressure. The residue was chromatographed on silica gel by eluting with ethyl acetate/light petroleum (1:3) to afford PMB alcohol derivative, which was characterized, and used for the next reaction (Yield: 825 mg, 76%)

To a suspension of catalytic Raney nickel in EtOH (5 mL) was added PMB alcohol derivative (825 mg, 2.8 mmol) in EtOH (5 mL) and the reaction mixture was stirred under hydrogen atmosphere for 1 h. The reaction mixture was filtered through a plug of celite, concentrated and the residue was purified by silica gel column chromatography using ethyl acetate/light petroleum (1:20) as an eluent to afford **58** (780 mg, 94%) as a colorless liquid.

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

Mol. Weight : 294

ESI-MS *m/z* : 317 $[M+Na]^+$

Elemental Analysis : Calcd: C, 69.36; H, 8.90%

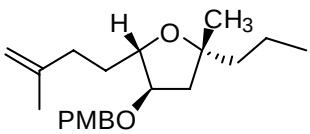
Found: C, 68.88; H, 9.26%

$[\alpha]_D^{25}$: -28.8 (*c* 0.95, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.92 (t, *J* = 7.0 Hz, 3H), 1.20-1.51 (m, 4H), 1.32 (s, 3H), 1.84-1.93 (m, 2H), 3.55 (d, *J* = 12.0 Hz, 1H), 3.74 (d, *J* = 12.0 Hz, 1H), 3.80 (s, 3H), 3.94-4.04 (m, 2H), 4.42 (d, *J* = 6.8 Hz, 2H), 6.86 (d, *J* = 9.0 Hz, 2H), 7.23 (d, *J* = 9.0 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 14.9, 17.7, 26.6, 42.2, 46.5, 55.2, 63.2, 64.9, 71.4, 80.0, 83.2, 113.8(2C), 128.6, 129.2(2C), 159.2

(2R,4R,5S)-4-(4-methoxybenzyloxy)-2-methyl-5-(3-methylbut-3-enyl)-2-propyltetrahydrofuran (62):



The PMB alcohol derivative **58** was transformed to compound **61** using the same procedures used for the preparation of **2** from **5**.

To a solution of **61** (150 mg, 0.5 mmol) in THF (5 mL) at 0 ^{o}C was added methyltriphenylphosphorane ylide [generated by the action of *n*BuLi (1.6 M solution in hexane, 1.2 mL, 1.8 mmol) with $Ph_3P^+CH_3I^-$ (730 mg, 1.8 mmol) in anhydrous THF (5 mL) at 0 ^{o}C]. The reaction mixture was stirred at 0 ^{o}C for 4 h, quenched with saturated NH_4Cl and filtered. The organic layer was separated and aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel by eluting with ethyl acetate/light petroleum (1:19) to furnish **62** (130 mg, 88%) as a colorless liquid.

Mol. Formula : $C_{21}H_{32}O_3$

Mol. Weight : 332

ESI-MS *m/z* : 355 $[M+Na]^+$

Elemental Analysis : Calcd: C, 75.86; H, 9.70%

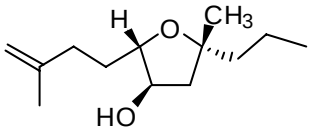
Found: C, 76.08; H, 9.83%

$[\alpha]_D^{25}$: -16.5 (*c* 1.0, $CHCl_3$); Lit. $[\alpha]_D = -17.8$ (*c* 1.9, $CHCl_3$)

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.91 (t, *J* = 7.0 Hz, 3H), 1.30 (s, 3H), 1.32-1.50 (m, 6H), 1.58-1.66 (m, 2H), 1.72 (s, 3H), 1.93-2.10 (m, 2H), 3.70-3.78 (m, 1H), 3.80 (s, 3H), 3.90-3.99 (m, 1H), 4.38 (d, *J* = 11.4 Hz, 1H), 4.47 (d, *J* = 11.4 Hz, 1H), 4.68 (br.s, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 8.7 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 14.6, 17.8, 22.6, 26.3, 32.7, 33.8, 42.4, 45.2, 55.2, 71.2, 81.9, 82.6, 83.7, 109.6, 113.8(2C), 129.2(2C), 130.4, 145.8, 159.2

(2S,3R,5R)-5-methyl-2-(3-methylbut-3-enyl)-5-propyltetrahydrofuran-3-ol (55):



To a solution of **62** (100 mg, 0.3 mmol) in DCM (5 mL) at 0 °C was added aqueous NaH_2PO_4/Na_2HPO_4 (*p*H 7) buffer (2 mL) and DDQ (82 mg, 0.4 mmol). The reaction mixture was stirred at 0 °C for 2 h, then filtered through a celite pad and layers were separated. The aqueous layer was extracted with DCM and the combined organic layer was dried (Na_2SO_4) and concentrated. The residue was purified on silica gel by eluting with ethyl acetate/light petroleum (1:6) to afford **55** (56 mg, 87%) as a thick liquid.

Mol. Formula : $C_{13}H_{24}O_2$

Mol. Weight : 212

ESI-MS *m/z* : 235 $[M+Na]^+$.

Elemental Analysis : Calcd: C, 73.54; H, 11.39%

Found: C, 73.87; H, 10.96%

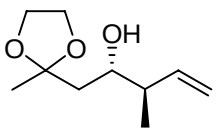
$[\alpha]_D^{25}$: −24.4 (*c* 1.2, $CHCl_3$); Lit. $[\alpha]_D$ = −25.8 (*c* 1.9, $CHCl_3$)

IR ($CHCl_3$) $\tilde{\nu}$: 3417 (br), 2961, 2933, 1650, 1454, 1374, 1081 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.92 (t, *J* = 7.0 Hz, 3H), 1.31 (s, 3H), 1.33-1.36 (m, 2H), 1.43-1.49 (m, 2H), 1.66-1.71 (m, 3H), 1.74 (s, 3H), 2.09-2.19 (m, 3H), 3.74-3.79 (m, 1H), 4.00-4.05 (m, 1H), 4.72 (br.s, 2H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 14.6, 17.8, 22.6, 26.9, 32.0, 33.8, 45.3, 45.7, 76.9, 82.2, 84.0, 109.8, 145.8

(2S,3R)-3-methyl-1-(2-methyl-1,3-dioxolan-2-yl)pent-4-en-2-ol (56):



A solution of **47** (200 mg, 0.7 mmol) and 1M solution of TBAF (1.4 mL, 1.4 mmol) in THF were stirred at an ambient temperature for 3 h. After completion of reaction, solvent was removed under reduced pressure. The crude residue was

chromatographed on silica gel using ethyl acetate/light petroleum (3:7) to give **56** (110 mg, 89%) as colorless thick syrup.

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

Mol. Weight : 186

ESI-MS *m/z* : 209 $[M+Na]^+$

Elemental Analysis : Calcd: C, 64.49; H, 9.74%

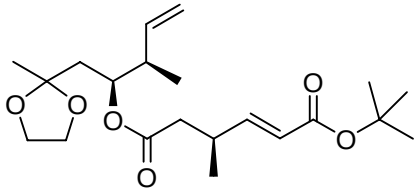
Found: C, 65.18; H, 10.23%

$[\alpha]_D^{25}$: -8.6 (*c* 0.7, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.04 (d, *J* = 6.9 Hz, 3H), 1.35 (s, 3H), 1.73-1.77 (m, 2H), 2.18-2.28 (m, 1H), 3.49 (br.s, 1H), 3.78-3.86 (m, 1H), 3.98-3.99 (m, 4H), 5.00-5.08 (m, 2H), 5.74-5.92 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 15.7, 24.6, 42.4, 43.5, 64.1, 64.3, 72.1, 109.3, 115.0, 140.4.

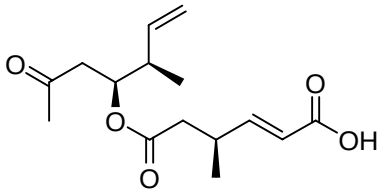
(S,E)-1-tert-butyl 6-((2S,3R)-3-methyl-1-(2-methyl-1,3-dioxolan-2-yl)pent-4-en-2-yl) 4-methylhex-2-enedioate (63):



To a mixture of **56** (100 mg, 0.5 mmol) and **4** (140 mg, 0.7 mmol) in dry DCM (5 ml), was successively added DMAP (122 gm, 0.8 mmol) and DCC (166 mg, 0.8 mmol) at 0 °C and stirred at room temperature for 7 h. The by-product was removed by filtration on celite pad. The combined filtrate was washed with 0.5N HCl, saturated $NaHCO_3$ and brine successively. The organic layer was dried (Na_2SO_4), concentrated and the residue was chromatographed on silica gel by eluting with ethyl acetate/light petroleum (1:4) to afford **63** (250 mg, 67%) as colorless liquid

Mol. Formula	**:**	$C_{21}H_{34}O_6$
Mol. Weight	**:**	382
ESI-MS *m/z*	**:**	405 $[M+Na]^+$, 383 $[M+H]^+$
Elemental Analysis	**:**	Calcd: C, 65.94; H, 8.96% Found: C, 66.47; H, 9.29%
$[\alpha]_D^{25}$	**:**	+12.9 (*c* 1.0, $CHCl_3$).
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 0.99 (d, *J* = 6.8 Hz, 3H), 1.11 (d, *J* = 6.8 Hz, 3H), 1.30 (s, 3H), 1.47 (s, 9H), 1.82-1.88 (m, 2H), 2.26-2.45 (m, 3H), 2.78-2.91 (m, 1H), 3.88-3.93 (m, 4H), 5.01-5.18 (m, 3H), 5.64-5.79 (m, 2H), 6.82 (dd, *J* = 7.0, 15.7 Hz, 1H).
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ 15.3, 18.8, 24.0, 26.1(3C), 32.5, 40.0, 41.7, 43.4, 64.1, 64.6, 70.9, 72.4, 110.3, 114.8, 128.4, 140.2, 153.8, 166.0, 172.0

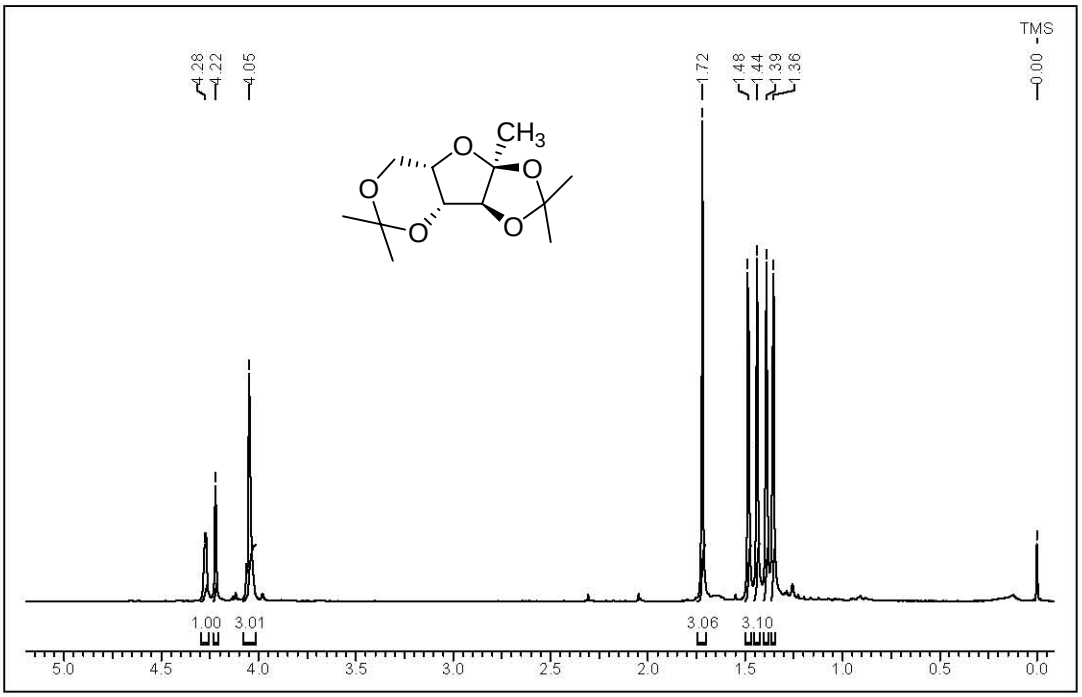
(S,E)-4-methyl-6-((3R,4S)-3-methyl-6-oxohept-1-en-4-yloxy)-6-oxohex-2-enoic acid (64):



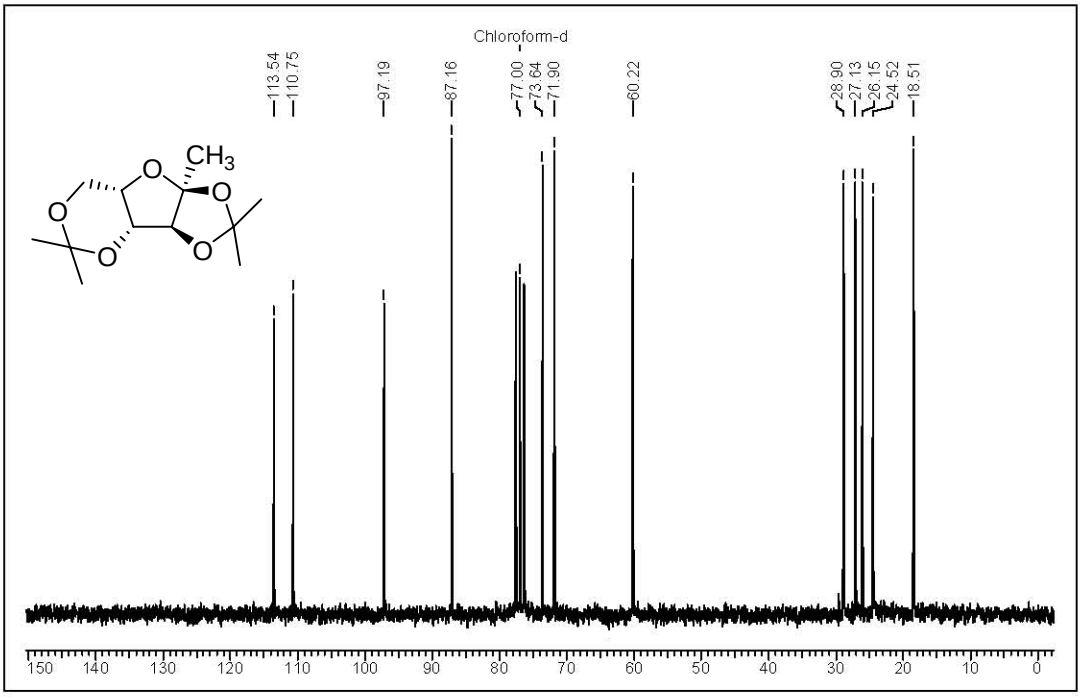
A solution of compound **63** (76 mg, 0.2 mmol) in TFA: H_2O (1:1, 4 mL) was stirred at 0 °C for 1 h, solvent was removed under reduced pressure and the resulting residue partitioned between EtOAc and water. Organic layer was washed with saturated aq. Na_2CO_3, brine, dried (Na_2SO_4), concentrated and the residue purified on silica gel using ethyl acetate/light petroleum (2:3) as an eluent to give **64** (34 mg, 60%) as thick colorless syrup.

Mol. Formula	**:**	$C_{15}H_{22}O_5$
Mol. Weight	**:**	282
ESI-MS *m/z*	**:**	305 $[M+Na]^+$
Elemental Analysis	**:**	Calcd: C, 63.81; H, 7.85% Found: C, 64.56; H, 8.49%
IR ($CHCl_3$) $\tilde{\nu}$	**:**	2937, 1718, 1648, 1153, 1027 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 1.02 (d, *J* = 6.8 Hz, 3H), 1.13 (d, *J* = 6.8 Hz, 3H), 2.14 (s, 3H), 2.33-2.49 (m, 3H), 2.61-2.66 (m, 2H), 2.83-2.93 (m, 1H), 5.01-5.11 (m, 2H), 5.23-5.34 (m, 1H), 5.62-5.90 (m, 2H), 7.01 (dd, *J* = 7.0, 15.7 Hz, 1H).

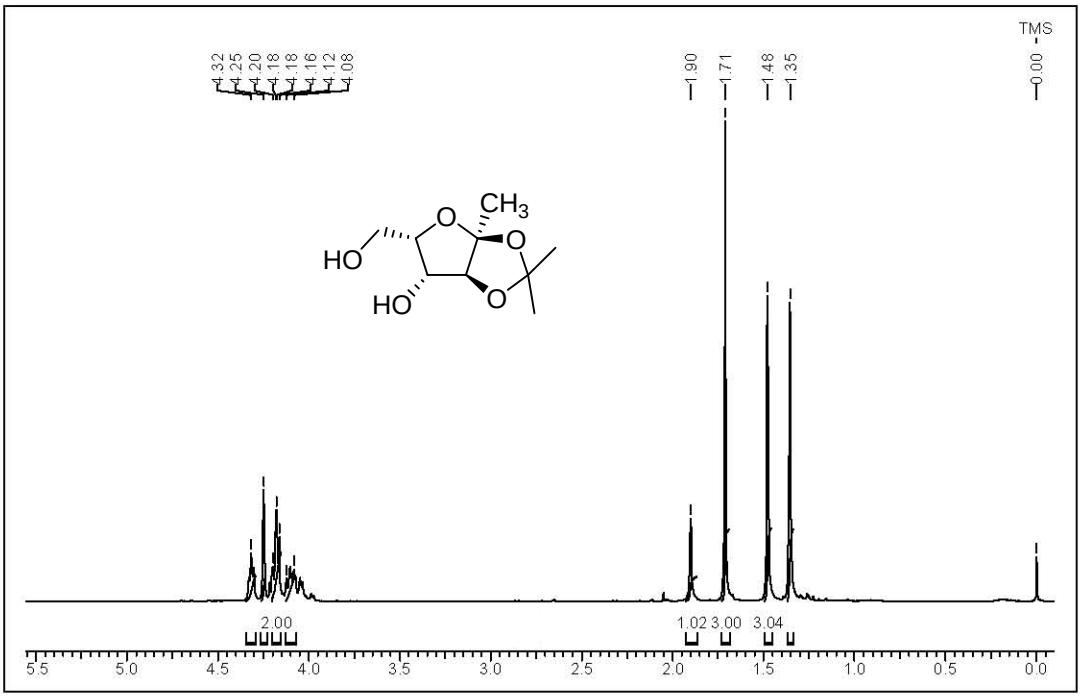
SPECTROSCOPIC DATA



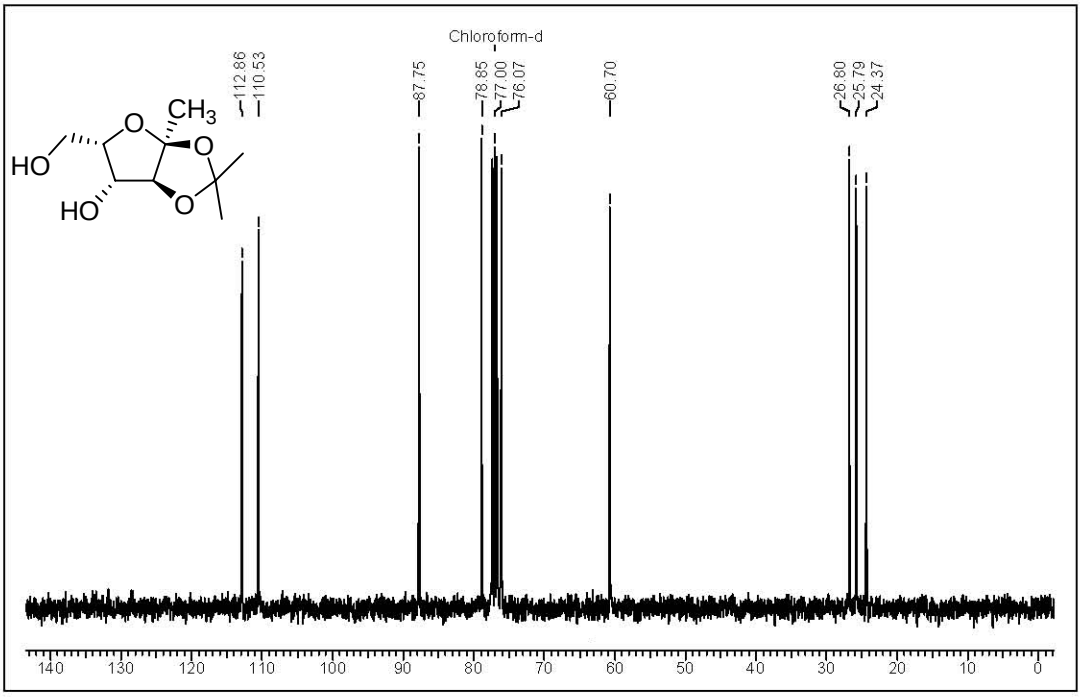
^{1}H NMR spectra of compound 8 in $CDCl_3$



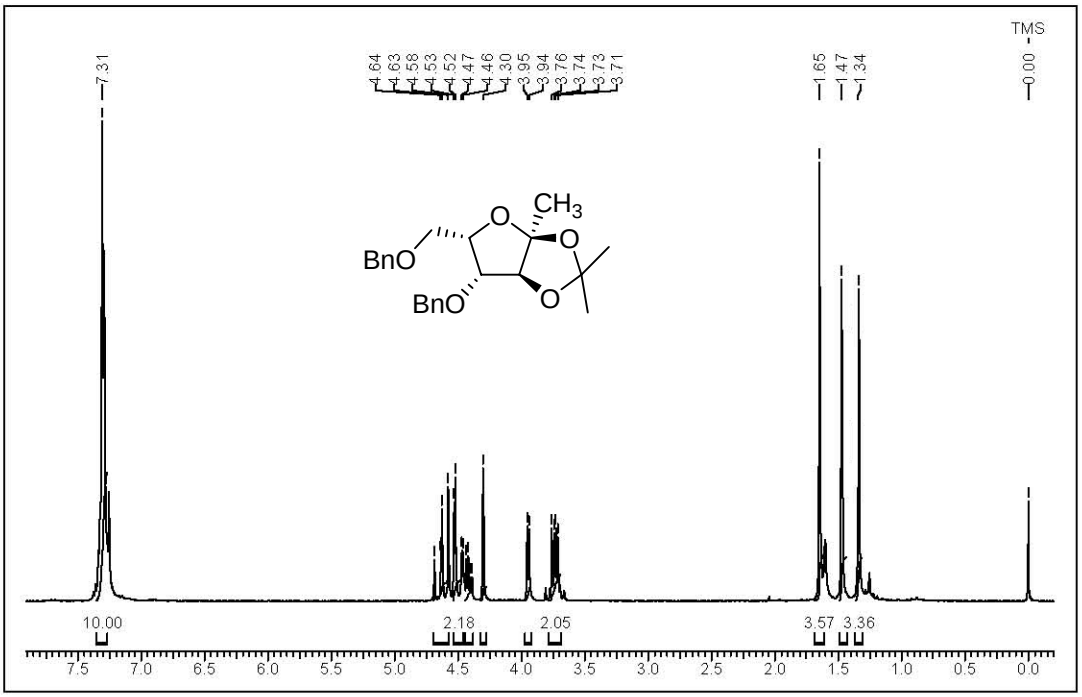
^{13}C NMR spectra of compound 8 in $CDCl_3$



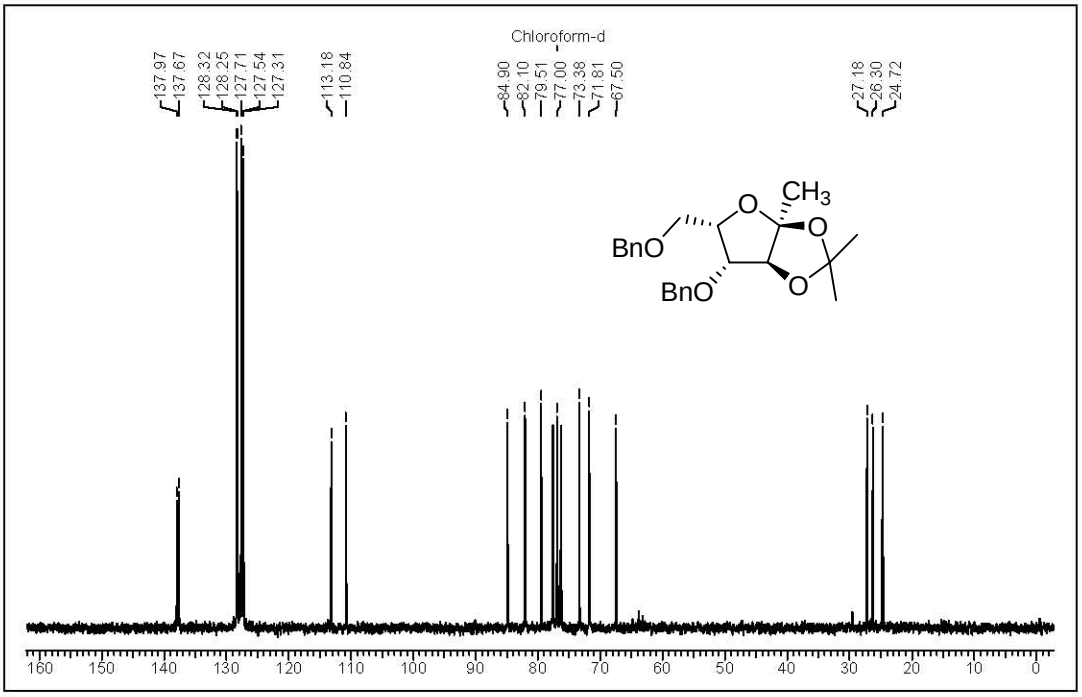
^{1}H NMR spectra of compound 17 in $CDCl_3$



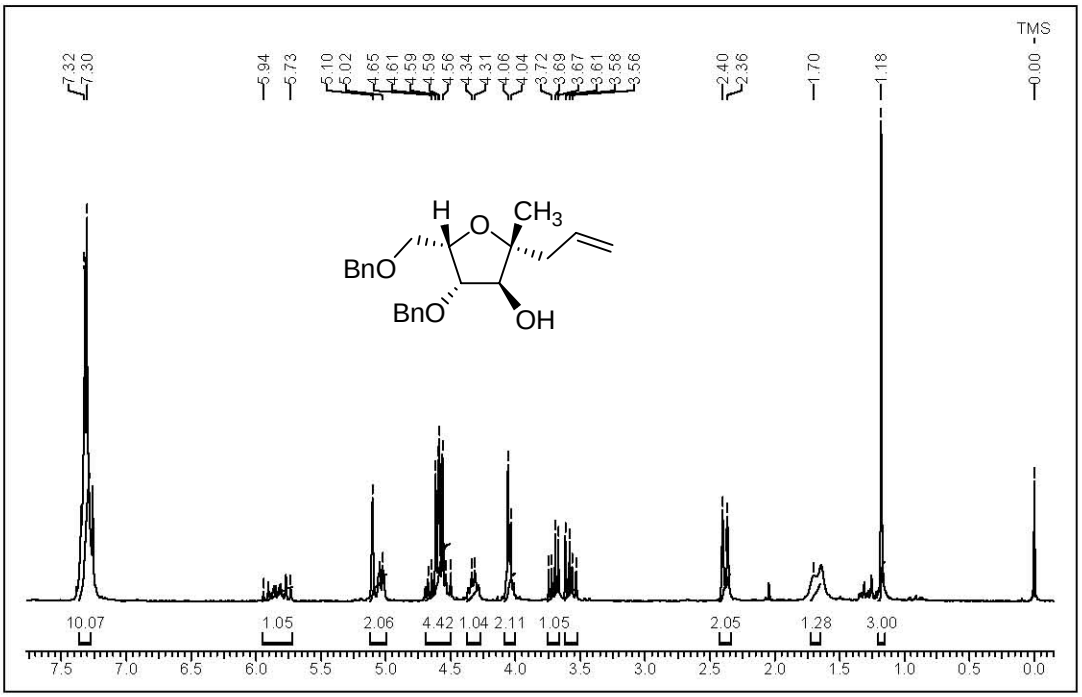
^{13}C NMR spectra of compound 17 in $CDCl_3$



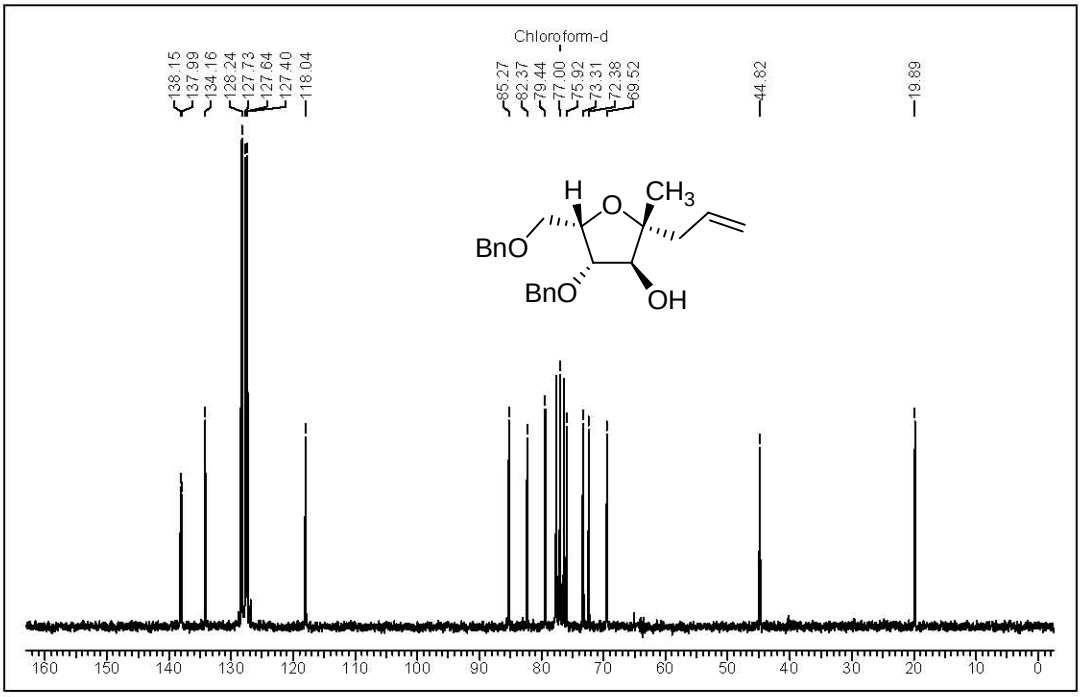
^{1}H NMR spectra of compound 18 in $CDCl_3$



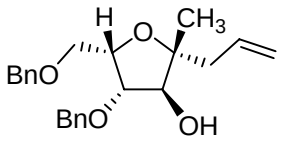
^{13}C NMR spectra of compound 18 in $CDCl_3$

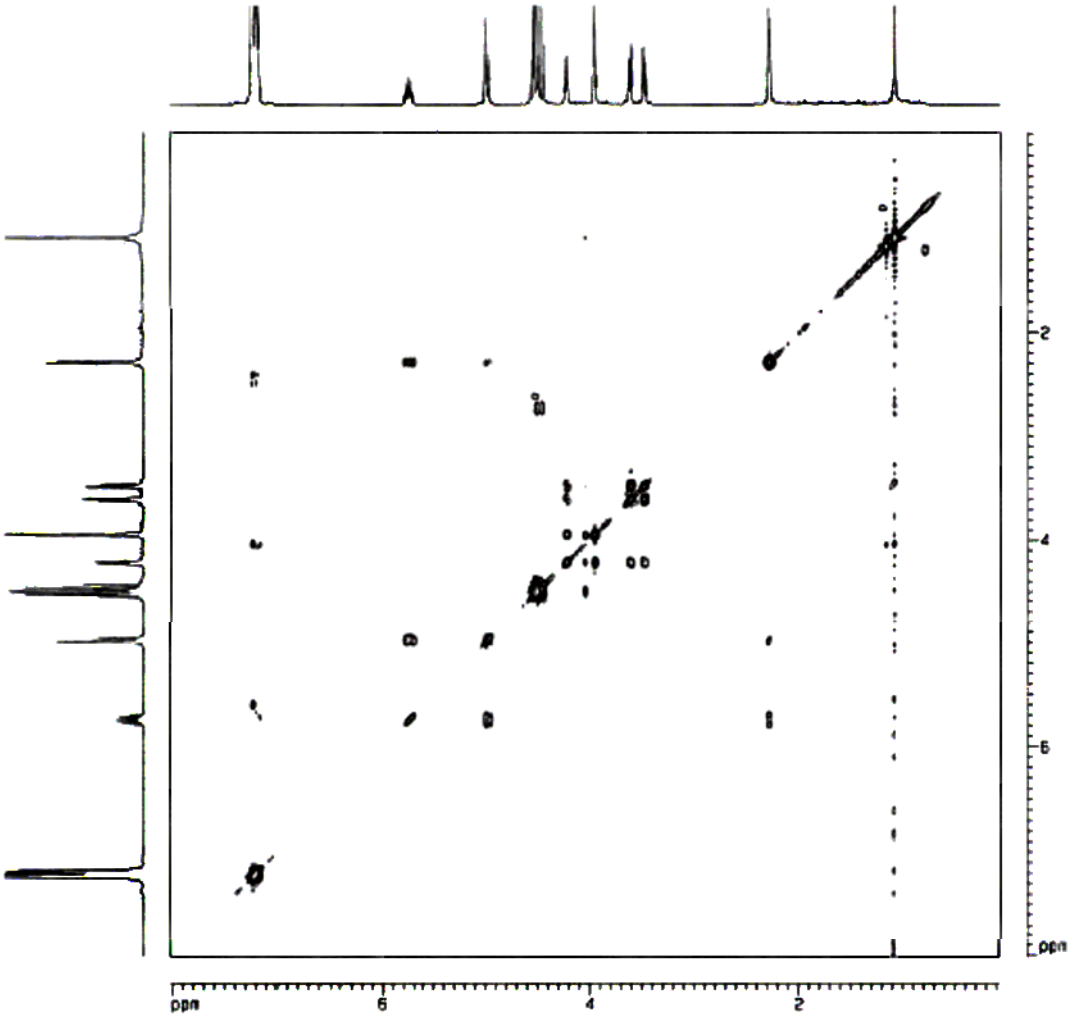


^{1}H NMR spectra of compound 7 in $CDCl_3$

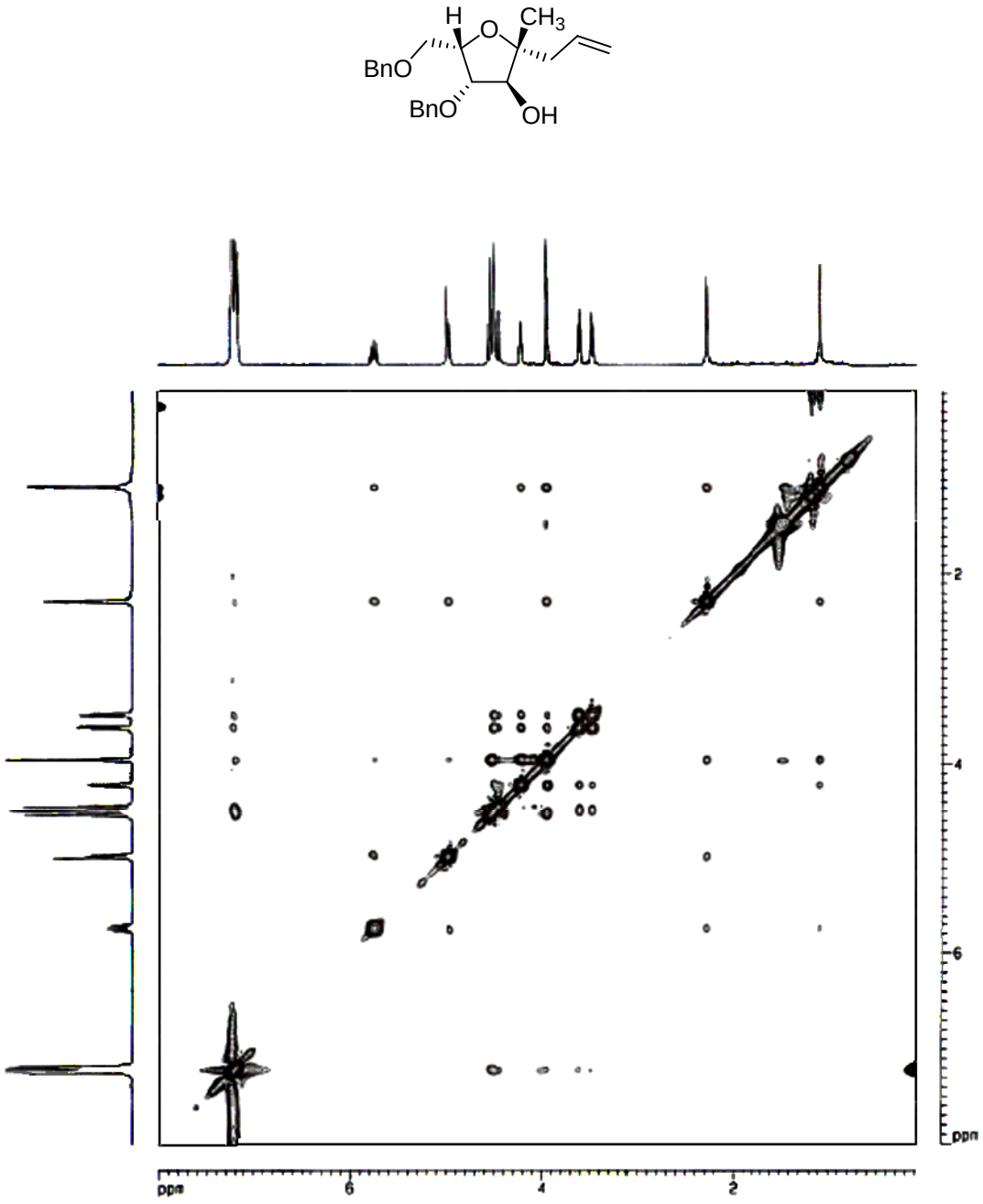


^{13}C NMR spectra of compound 7 in $CDCl_3$

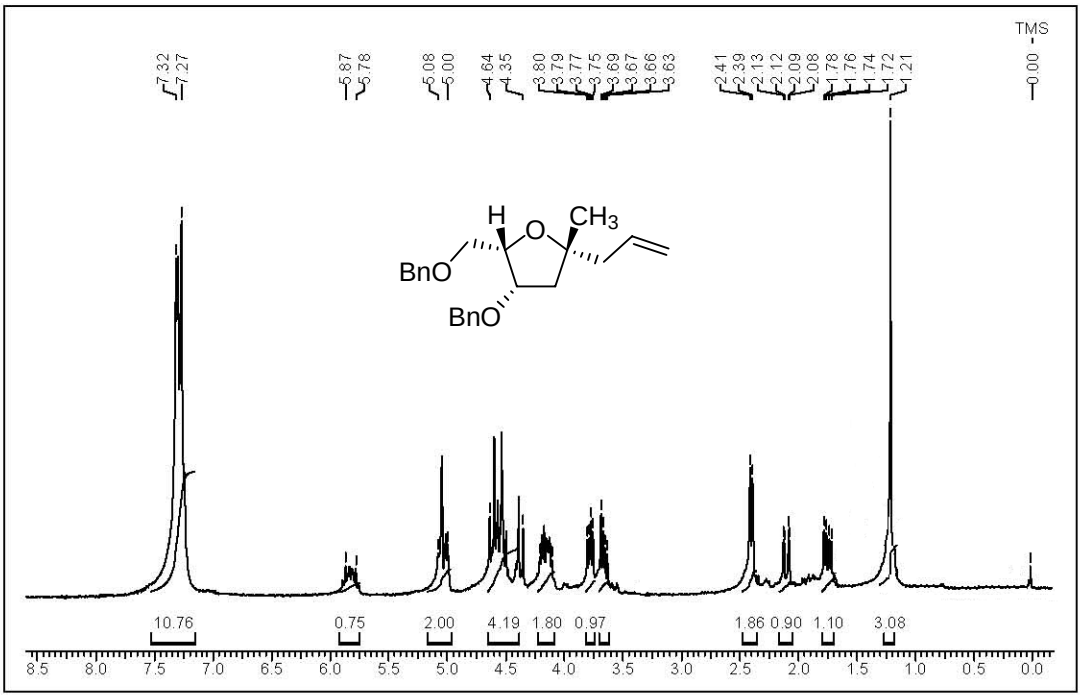




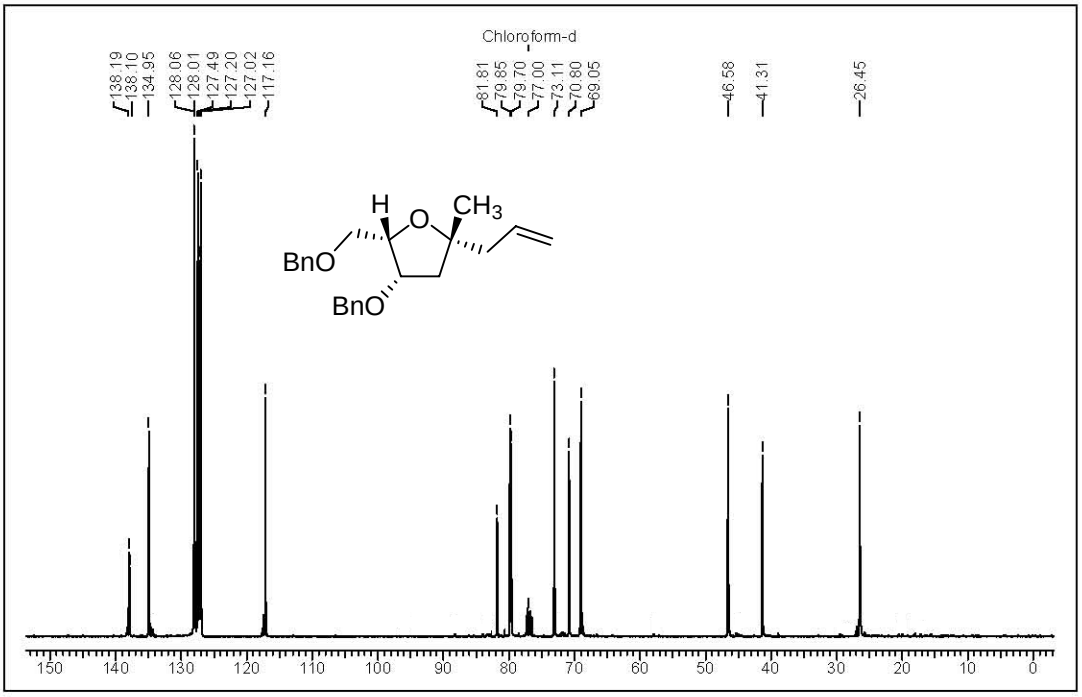
COSY spectra of compound 7 in $CDCl_3$



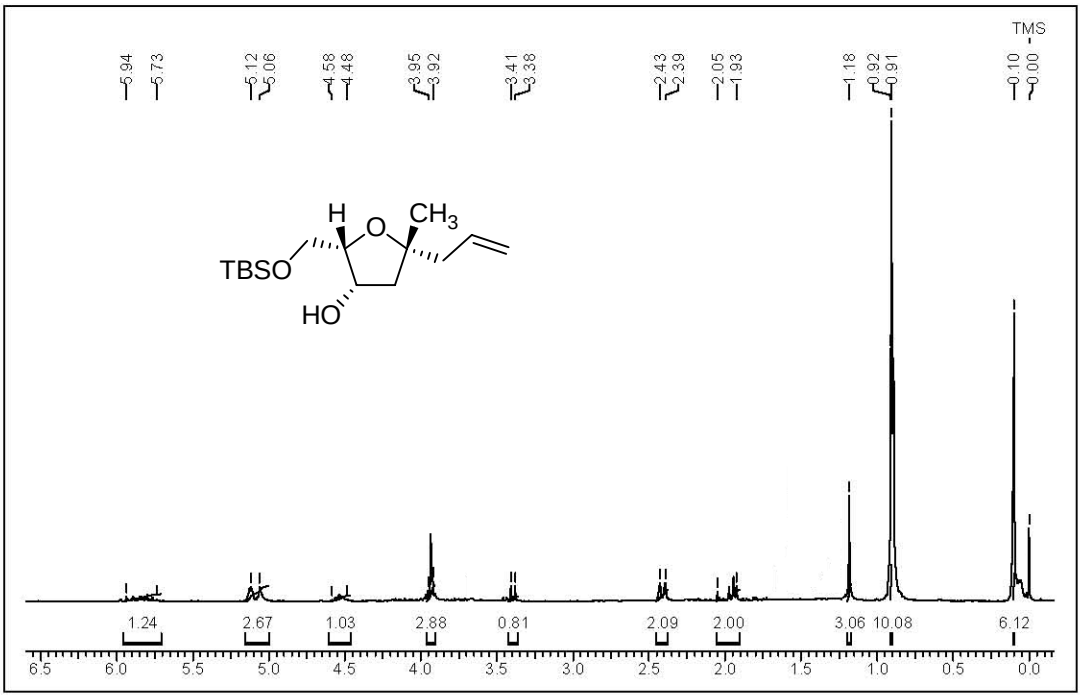
NOESY spectra of compound 7 in $CDCl_3$



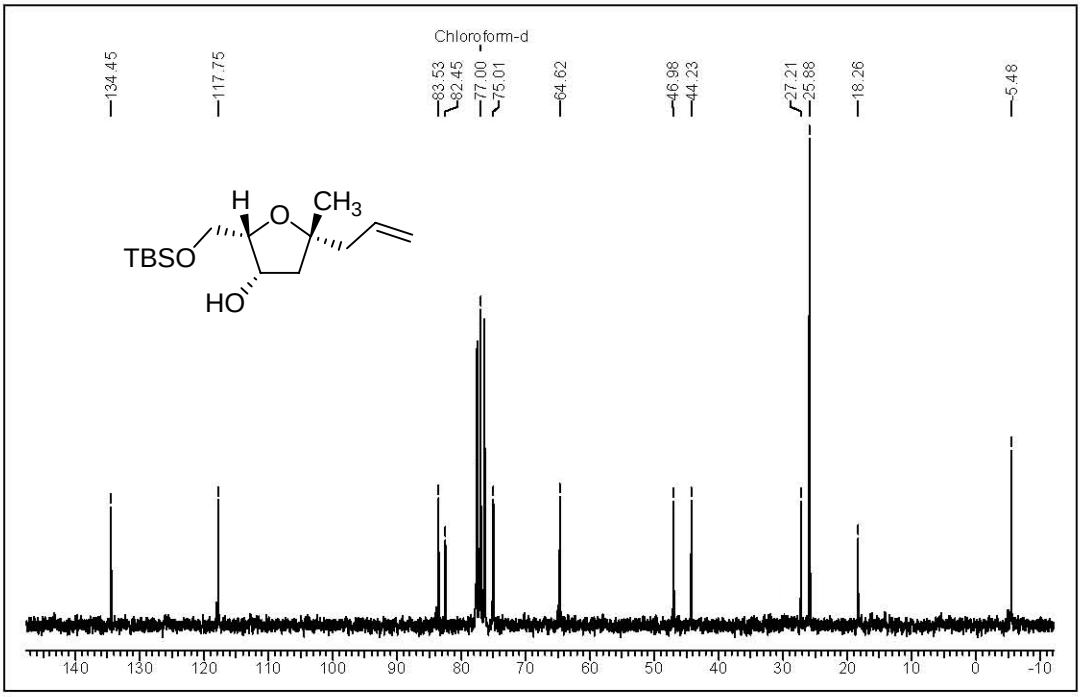
^{1}H NMR spectra of compound 20 in $CDCl_3$



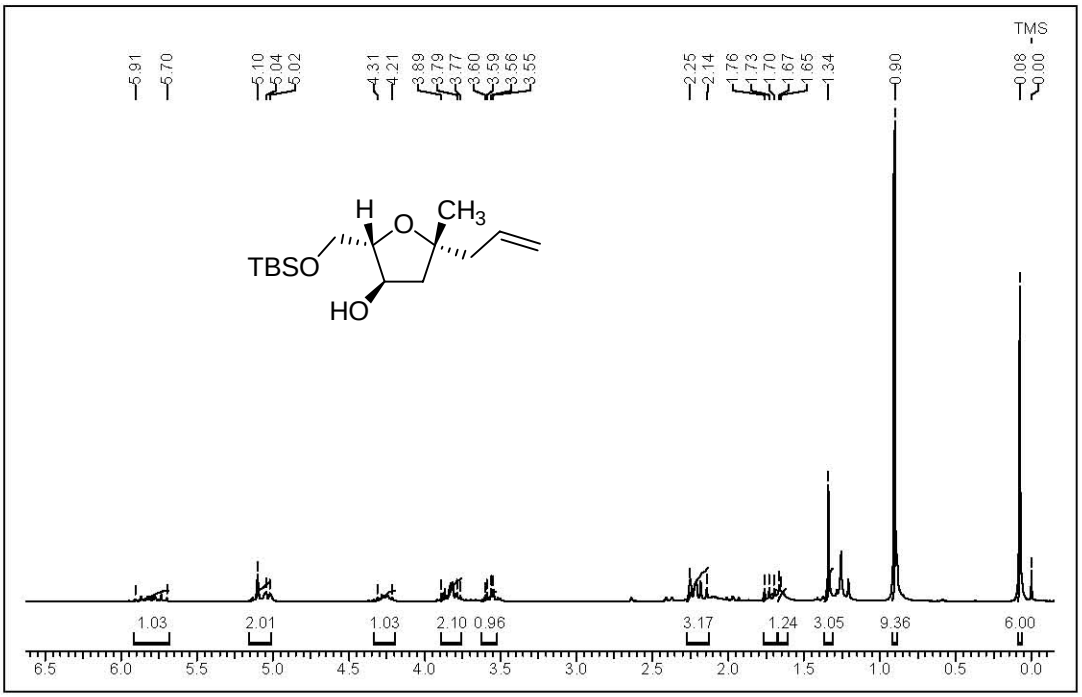
^{13}C NMR spectra of compound 20 in $CDCl_3$



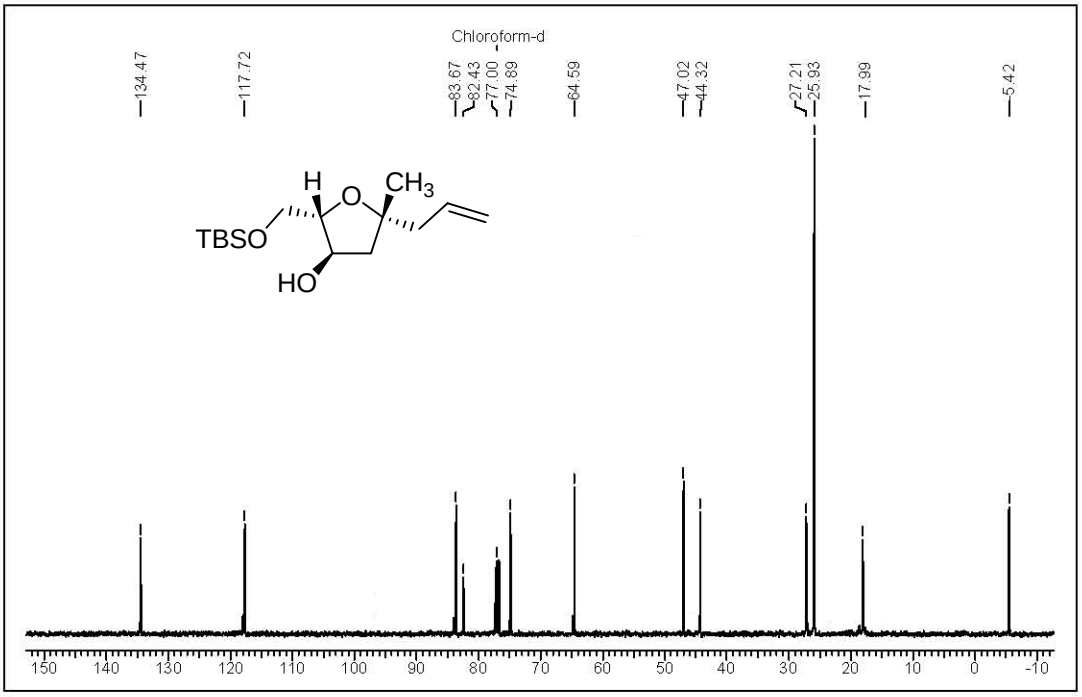
^{1}H NMR spectra of compound 6 in $CDCl_3$



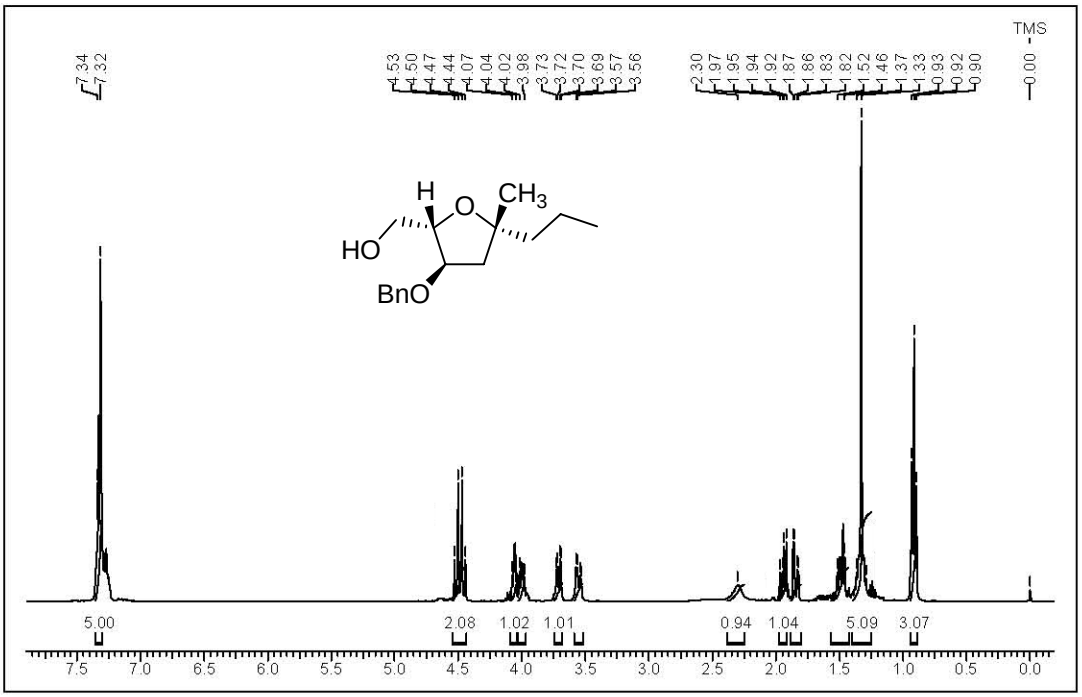
^{13}C NMR spectra of compound 6 in $CDCl_3$



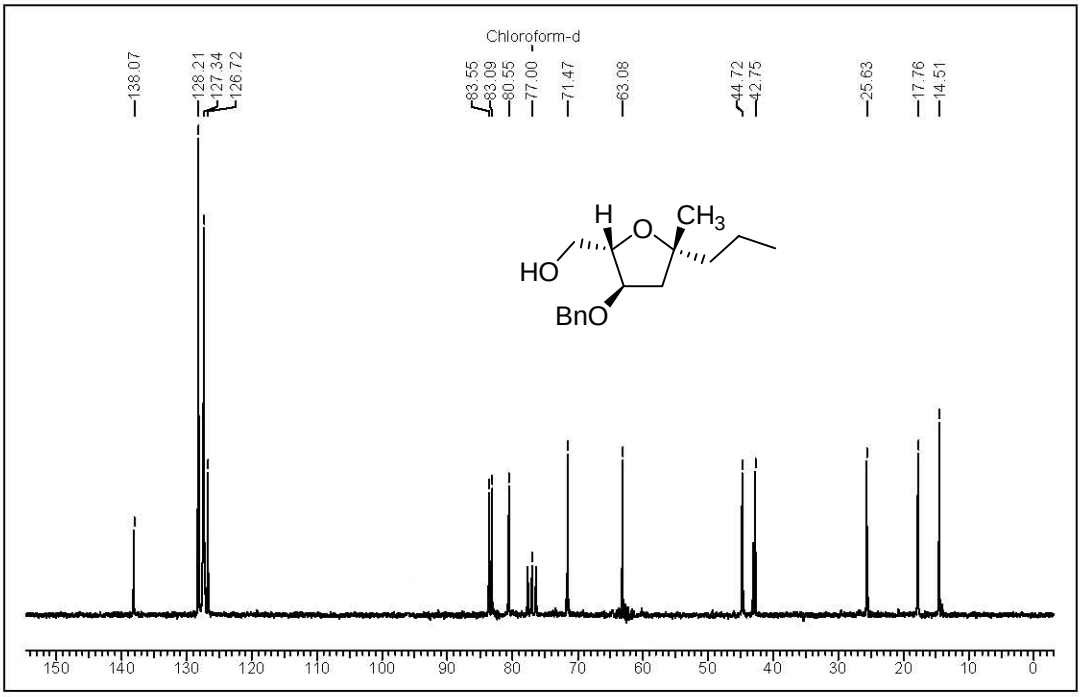
^{1}H NMR spectra of compound 23 in $CDCl_3$



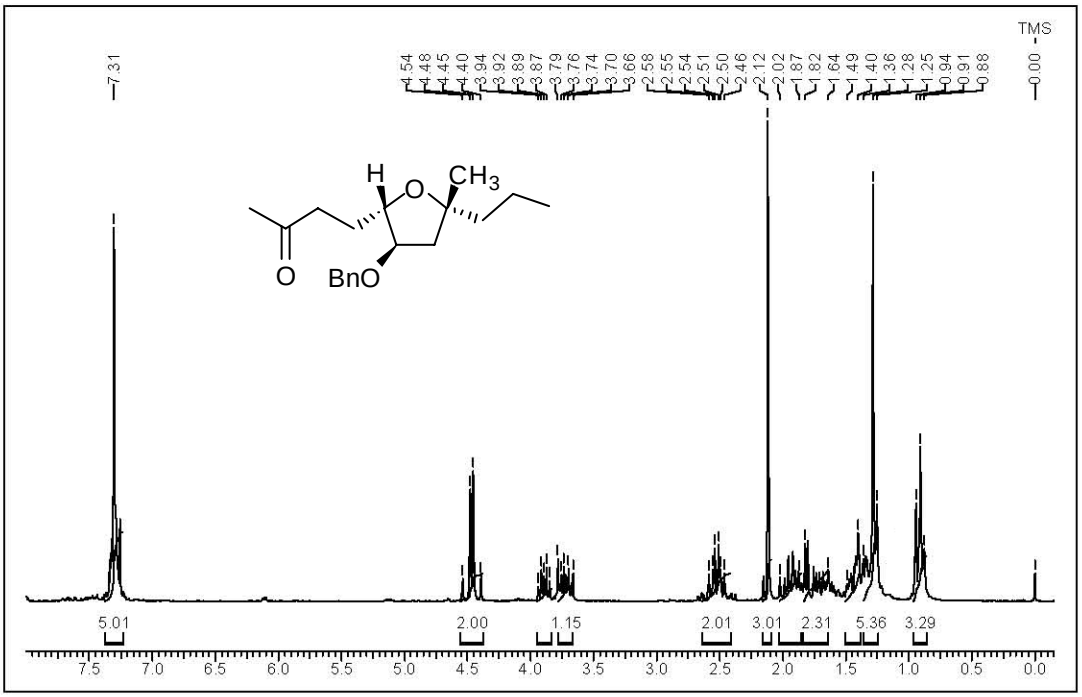
^{13}C NMR spectra of compound 23 in $CDCl_3$



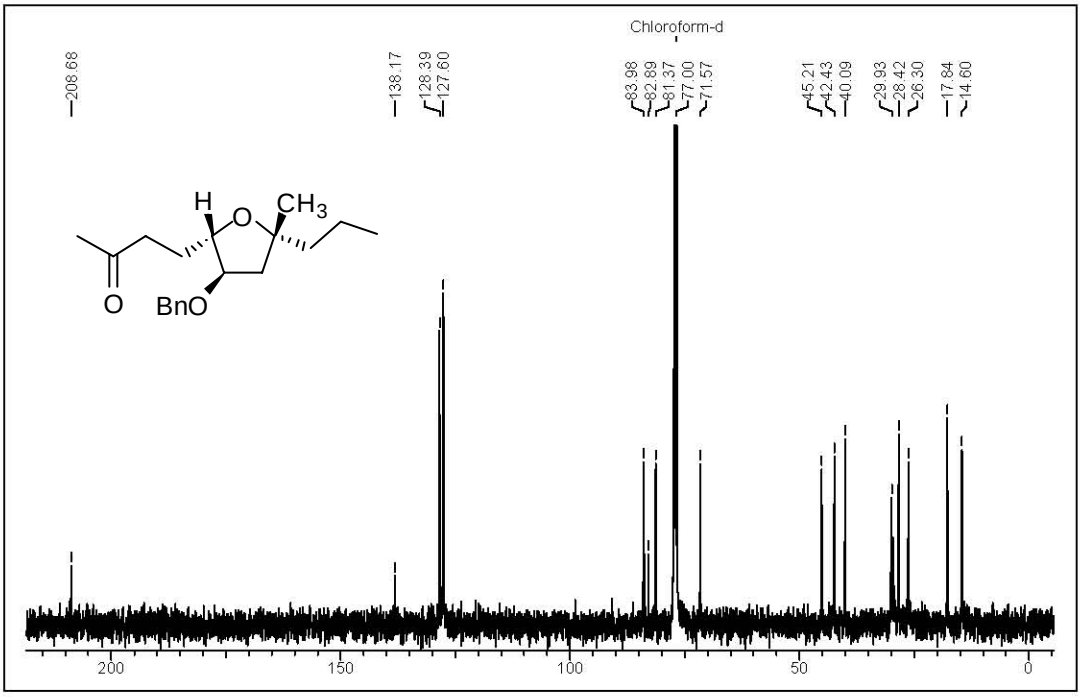
^{1}H NMR spectra of compound 5 in $CDCl_3$



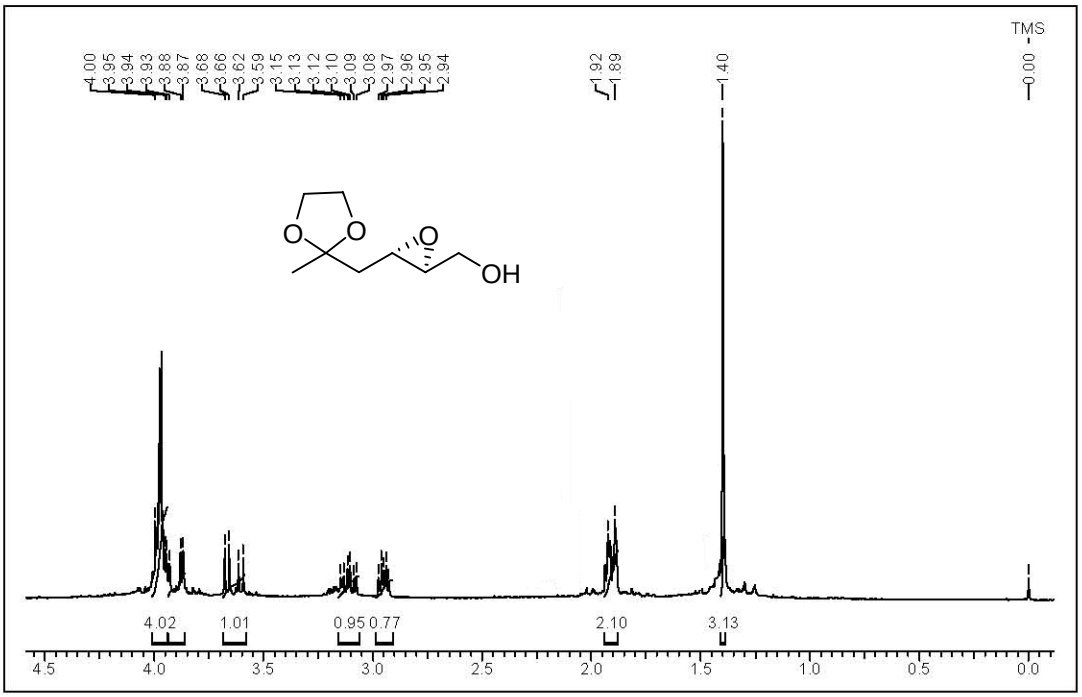
^{13}C NMR spectra of compound 5 in $CDCl_3$



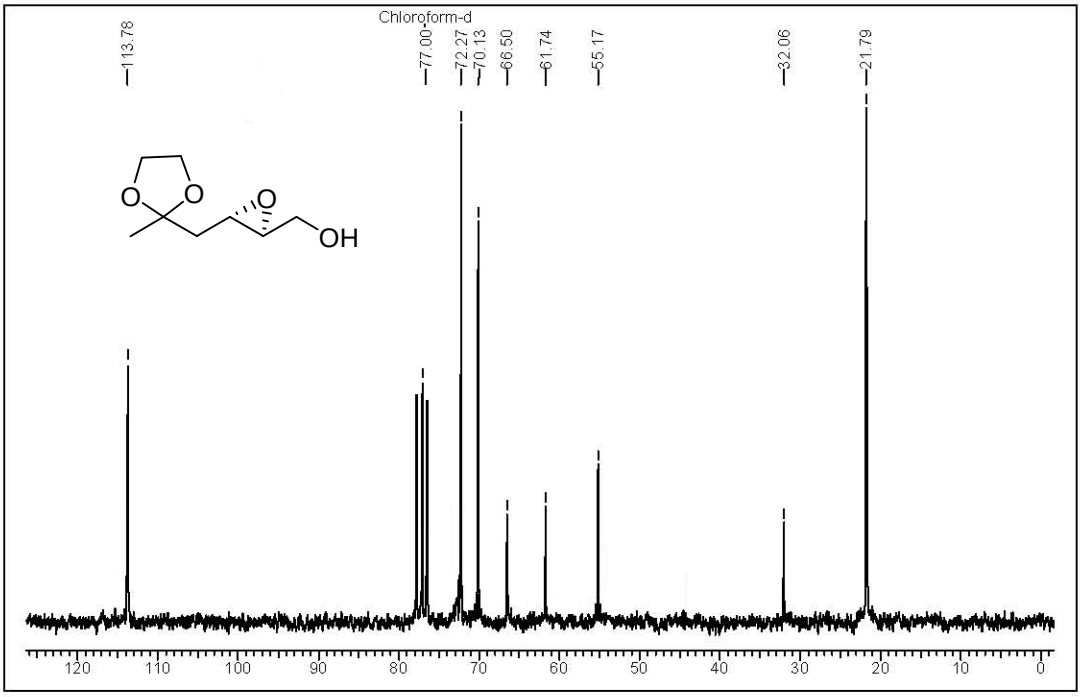
^{1}H NMR spectra of compound 2 in $CDCl_3$



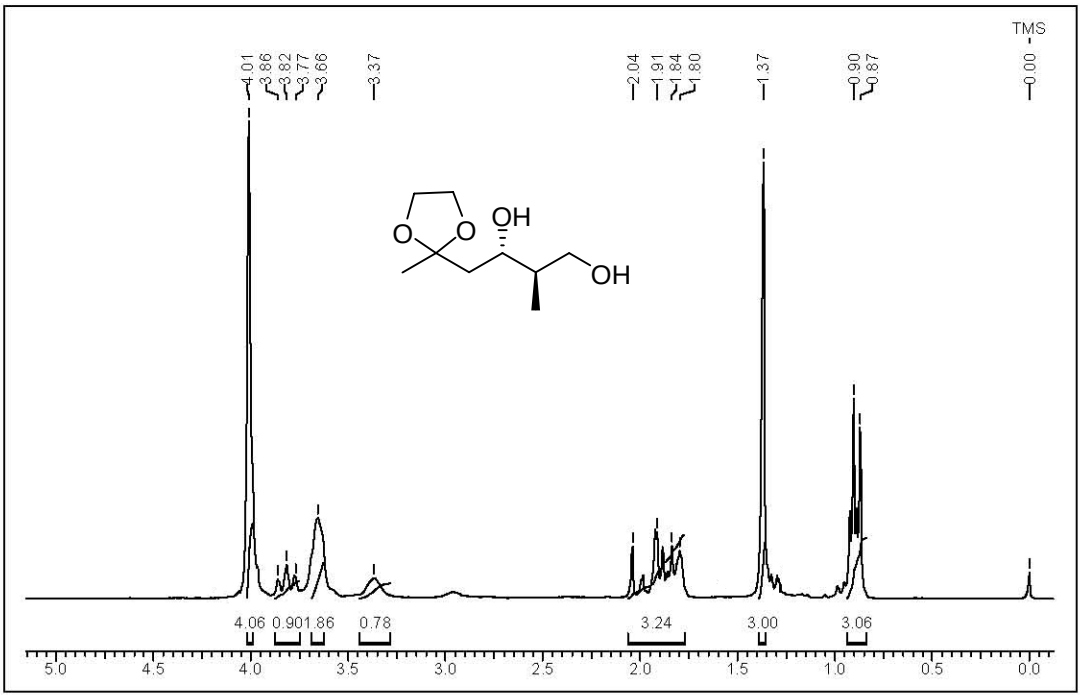
^{13}C NMR spectra of compound 2 in $CDCl_3$



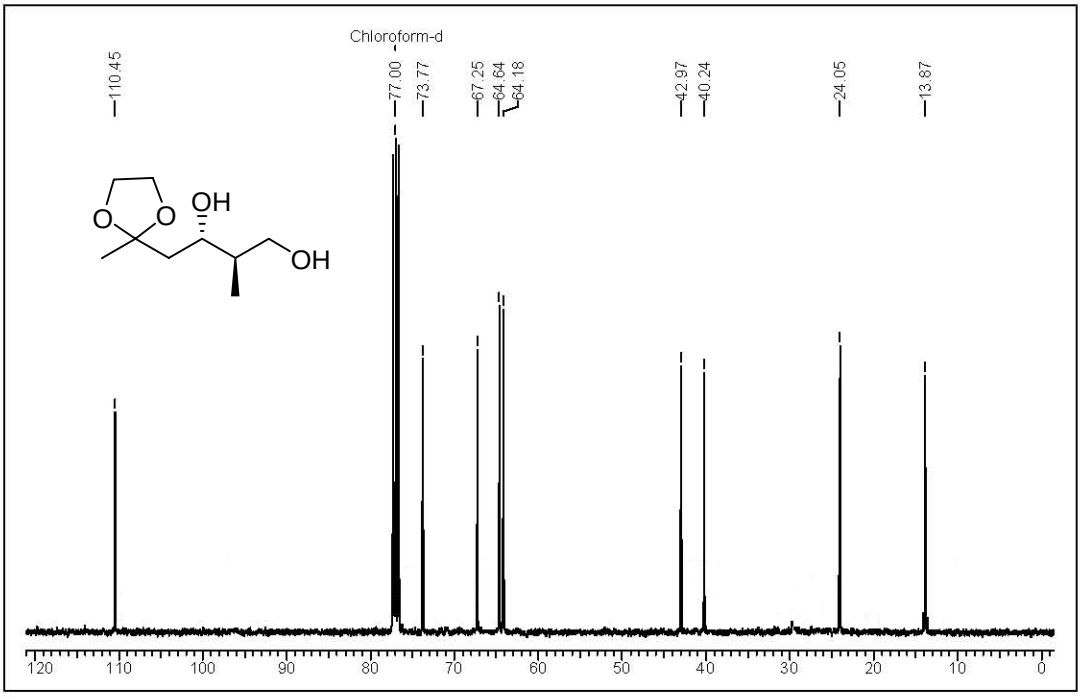
^{1}H NMR spectra of compound 11 in $CDCl_3$



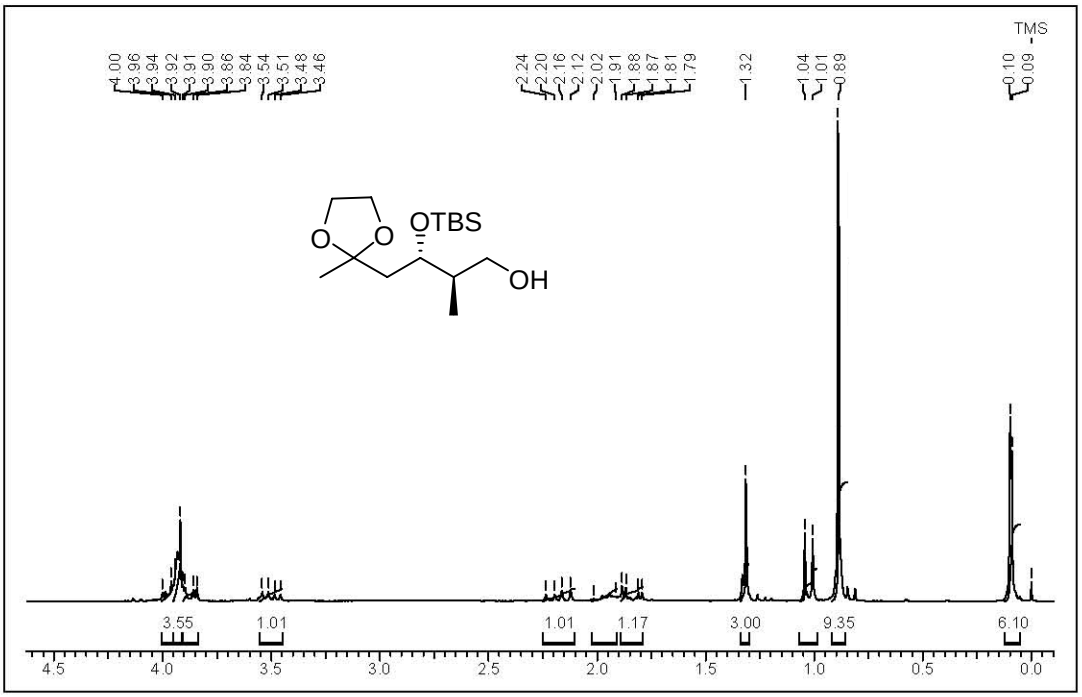
^{13}C NMR spectra of compound 11 in $CDCl_3$



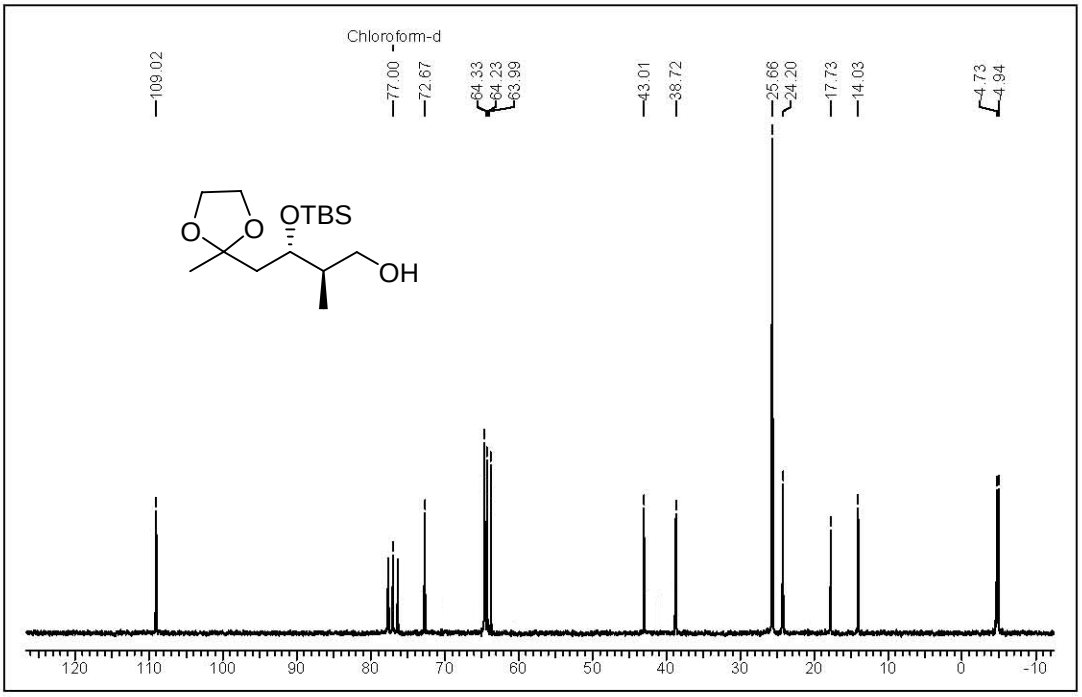
^{1}H NMR spectra of compound 30 in $CDCl_3$



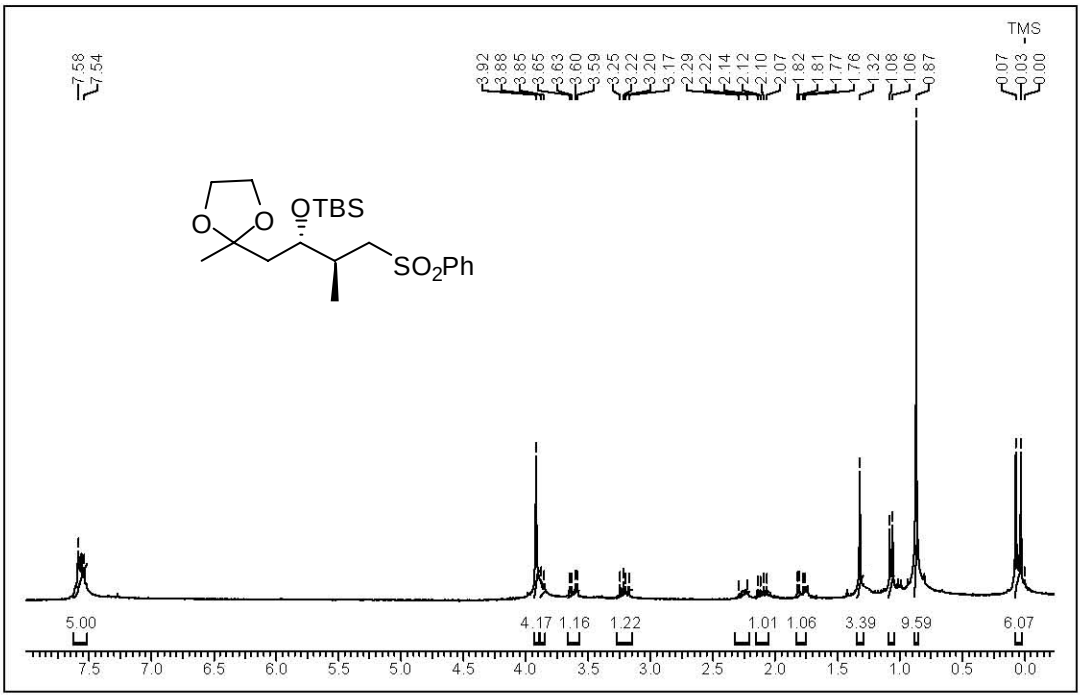
^{13}C NMR spectra of compound 30 in $CDCl_3$



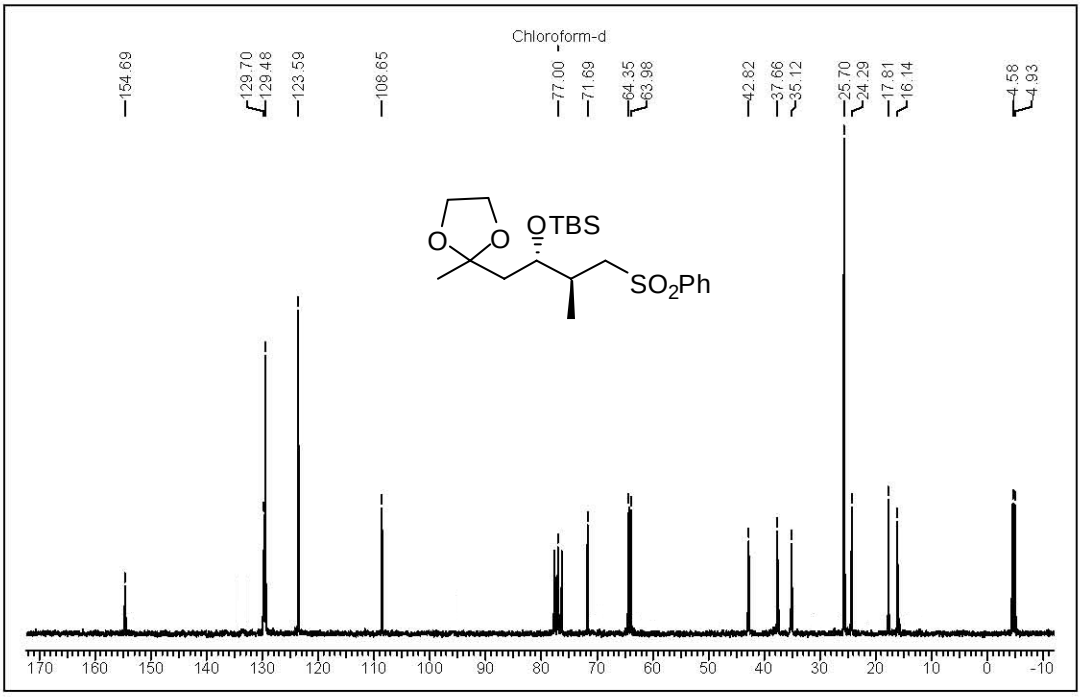
^{1}H NMR spectra of compound 10 in $CDCl_3$



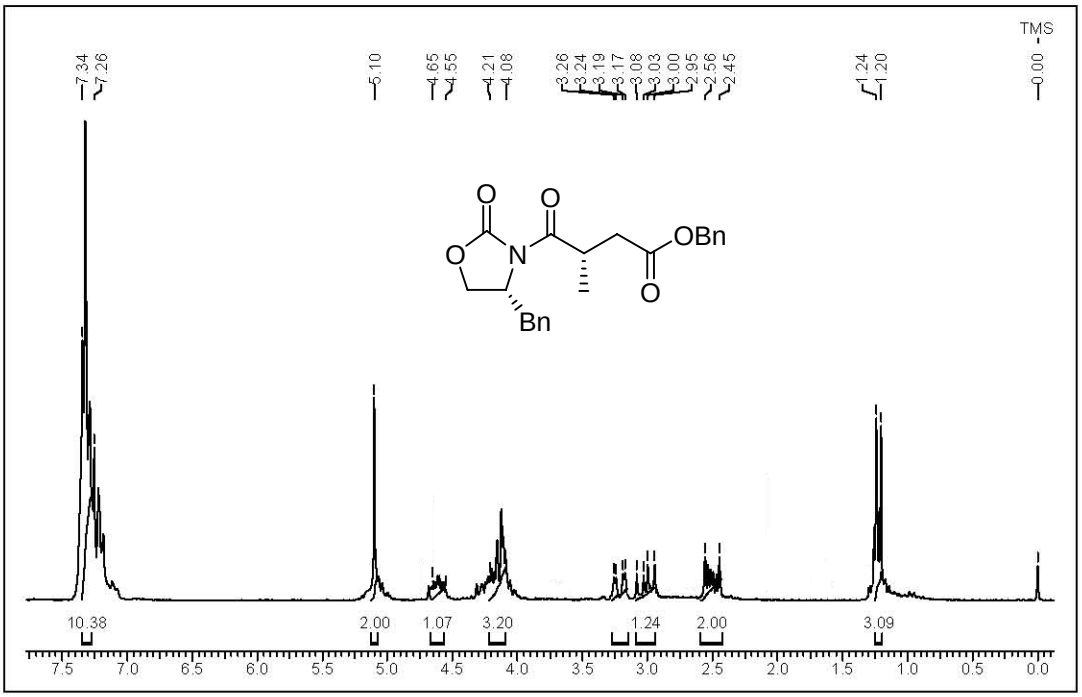
^{13}C NMR spectra of compound 10 in $CDCl_3$



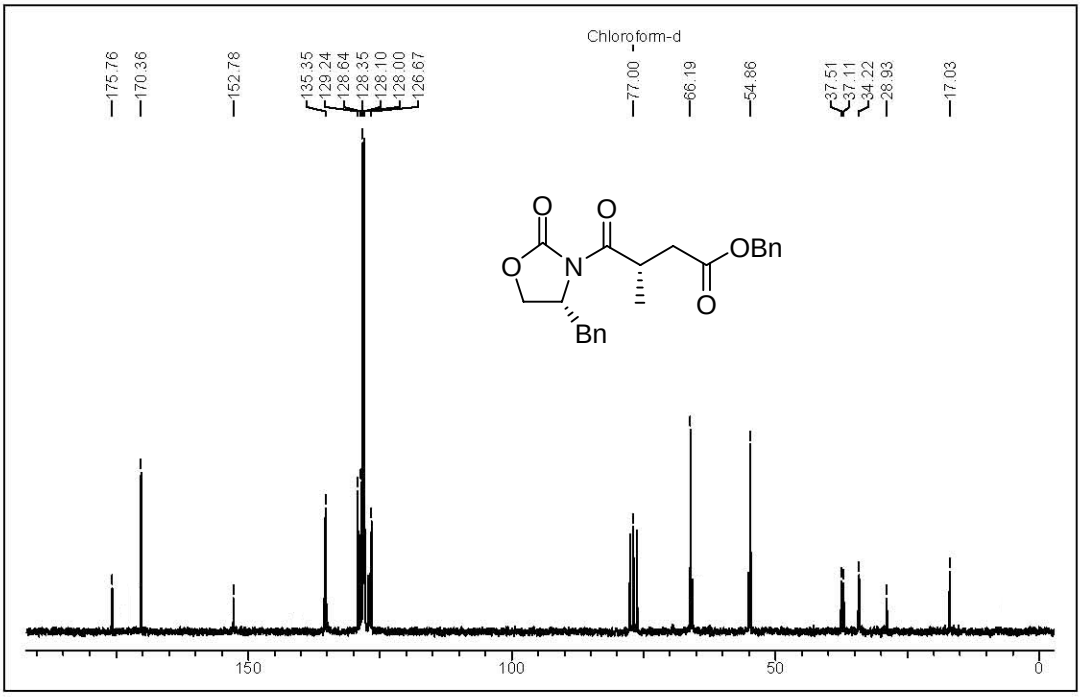
^{1}H NMR spectra of compound 3 in $CDCl_3$



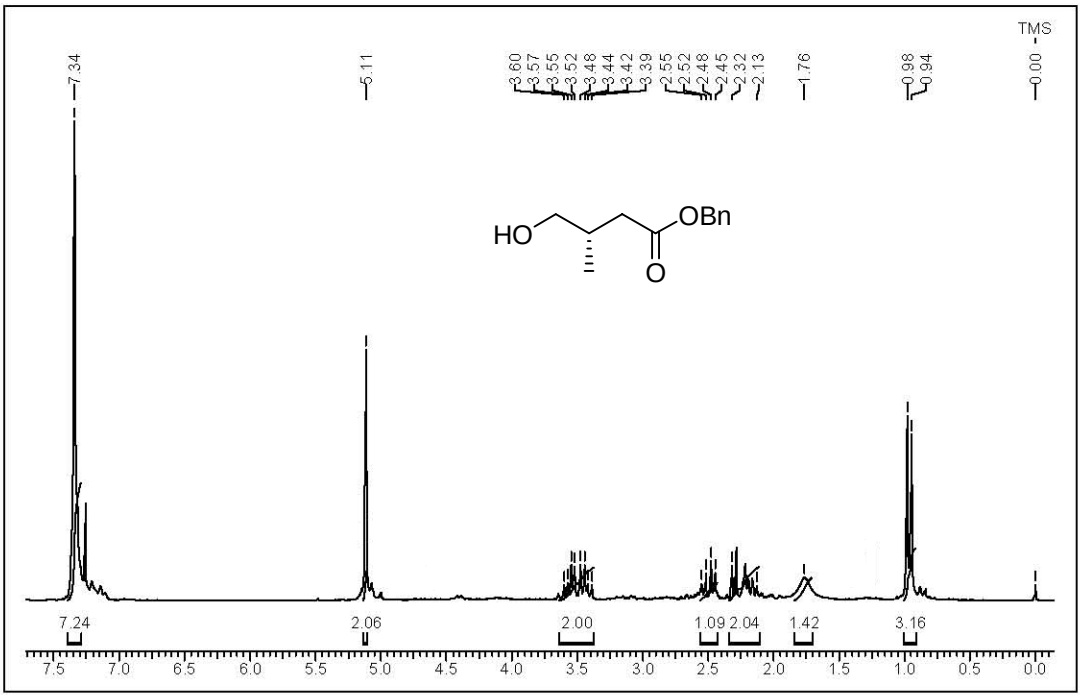
^{13}C NMR spectra of compound 3 in $CDCl_3$



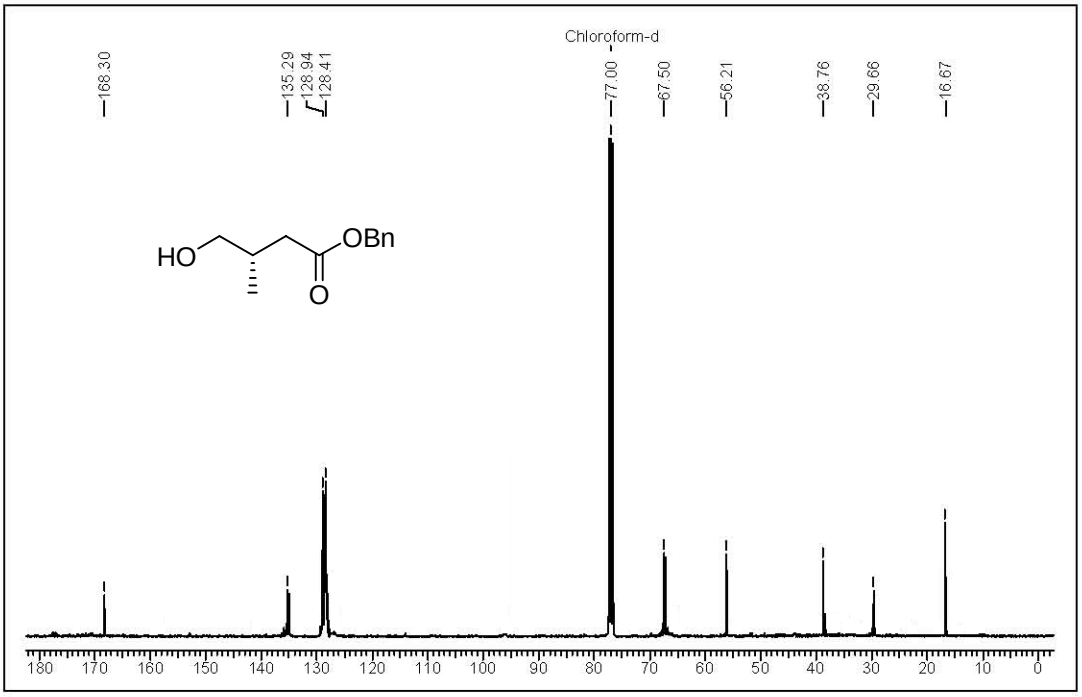
^{1}H NMR spectra of compound 14 in $CDCl_3$



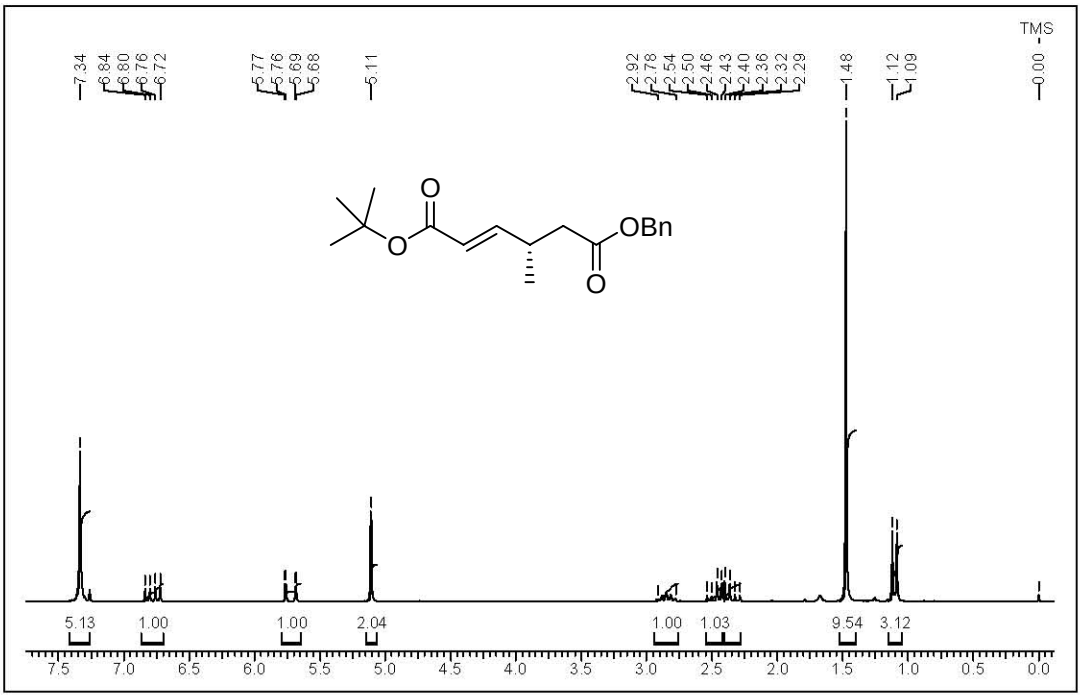
^{13}C NMR spectra of compound 14 in $CDCl_3$



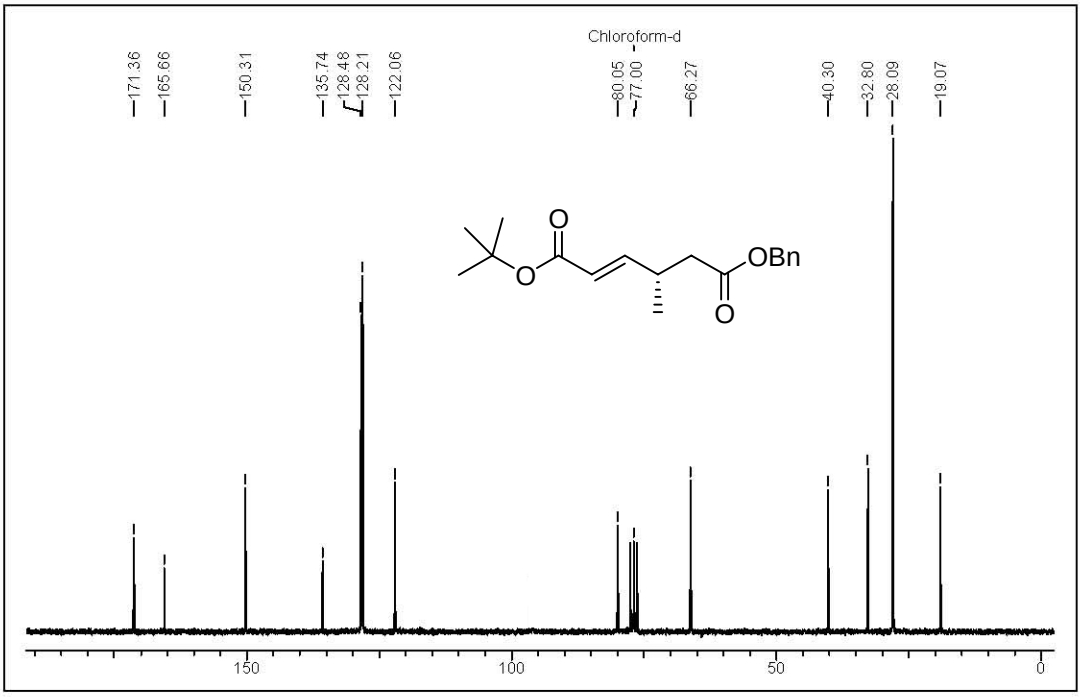
^{1}H NMR spectra of compound 38 in $CDCl_3$



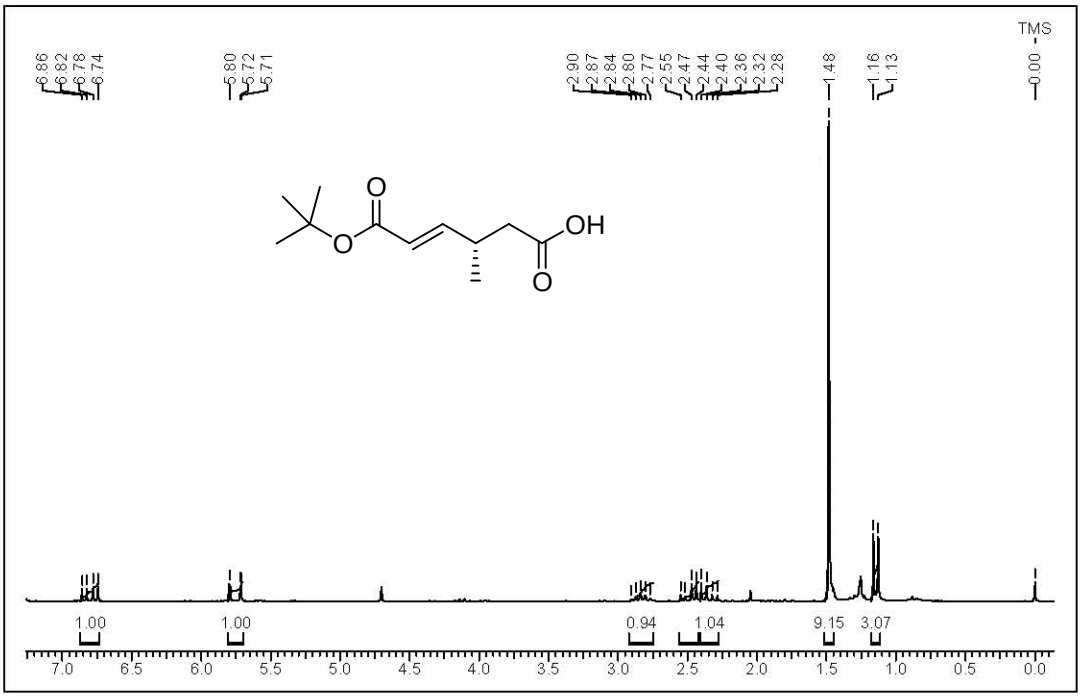
^{13}C NMR spectra of compound 38 in $CDCl_3$



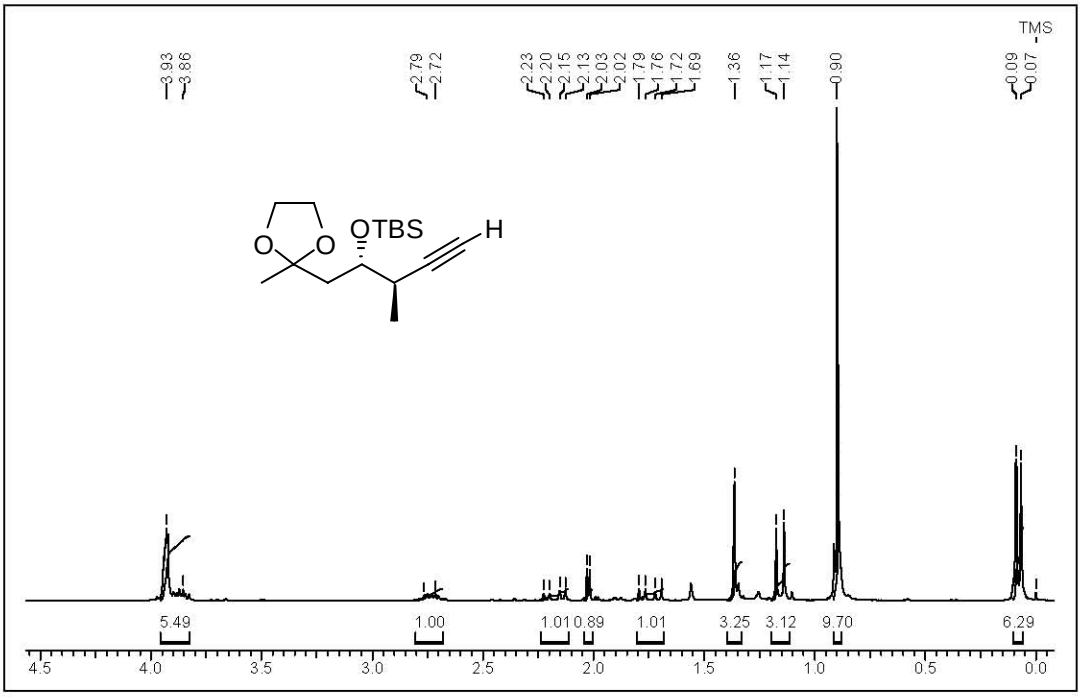
^{1}H NMR spectra of compound 40 in $CDCl_3$



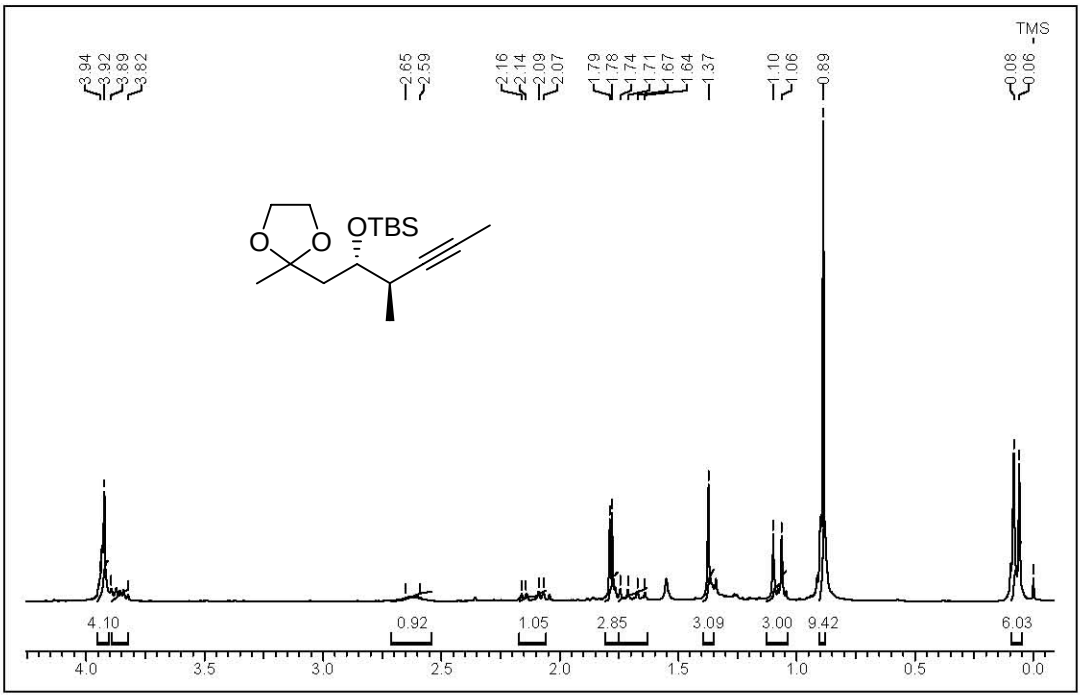
^{13}C NMR spectra of compound 40 in $CDCl_3$



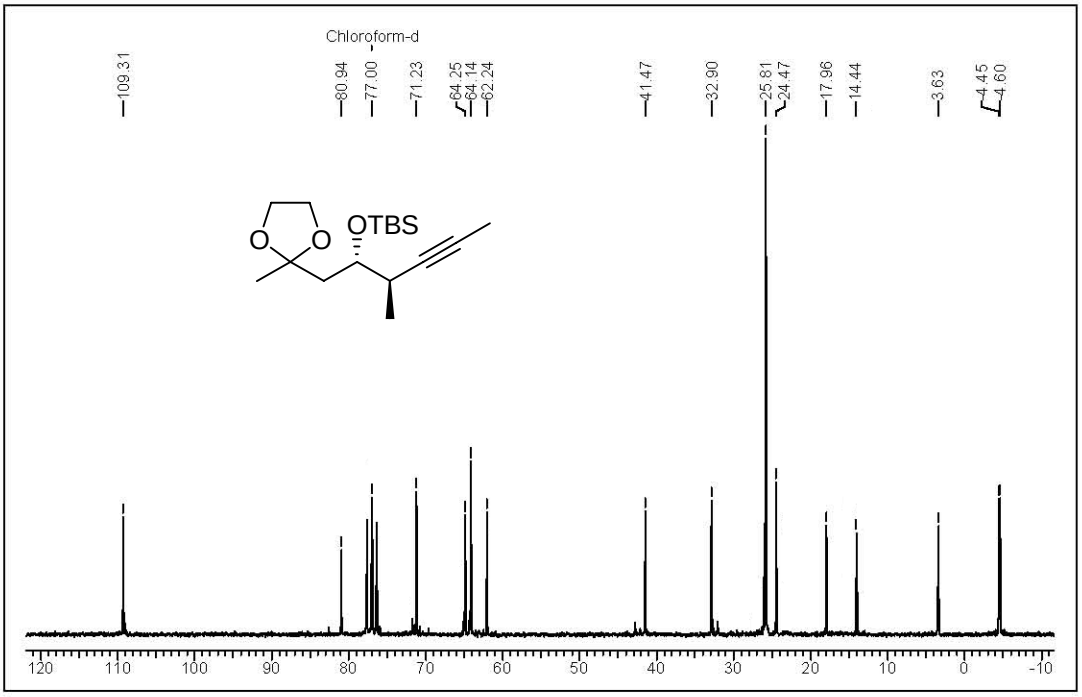
^{1}H NMR spectra of compound 4 in $CDCl_3$



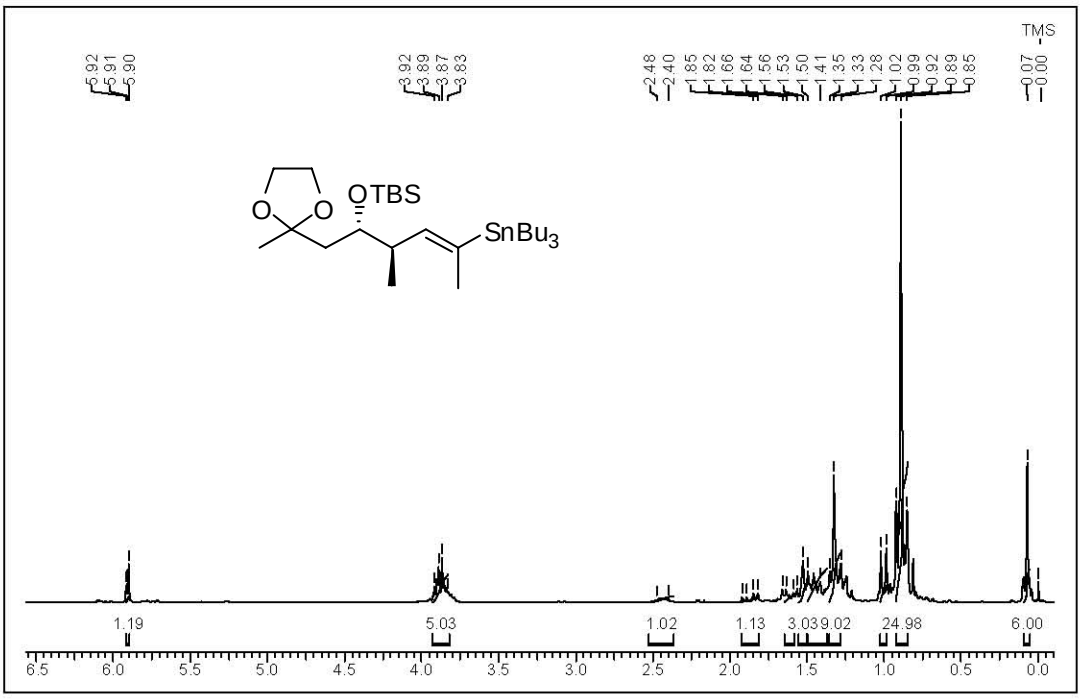
^{1}H NMR spectra of compound 43 in $CDCl_3$



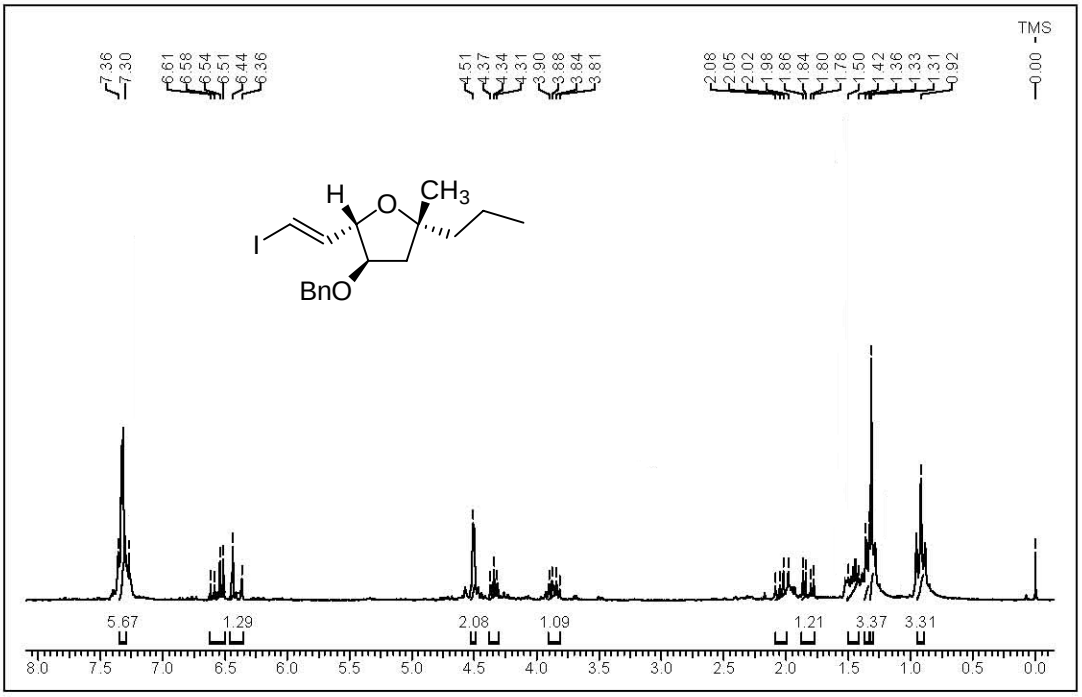
^{1}H NMR spectra of compound 44 in $CDCl_3$



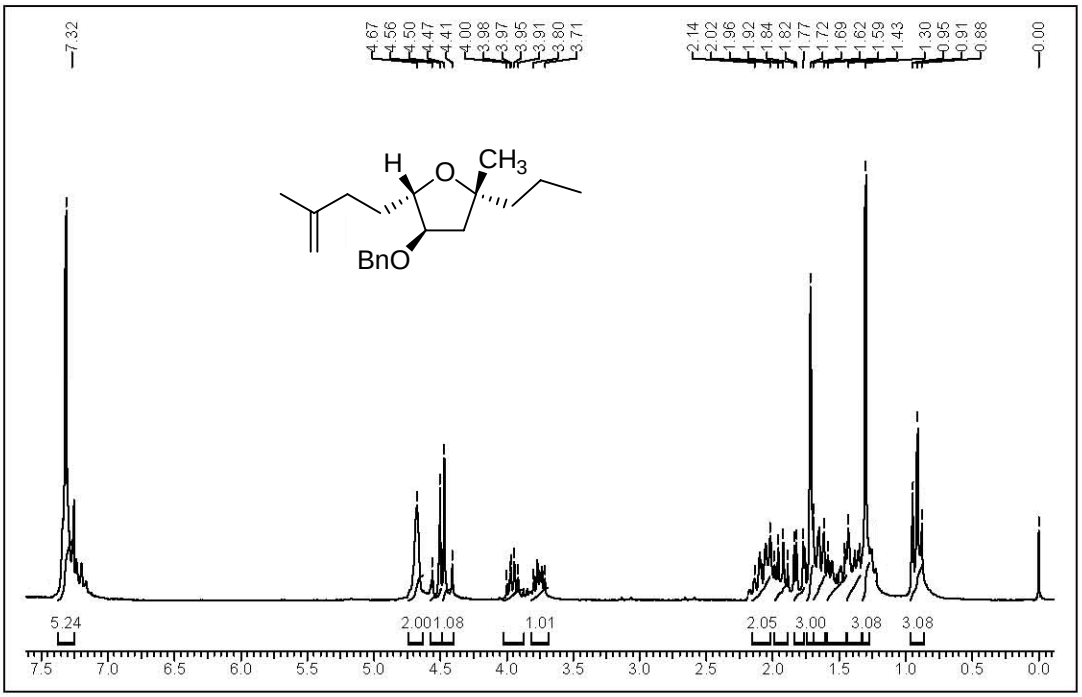
^{13}C NMR spectra of compound 44 in $CDCl_3$



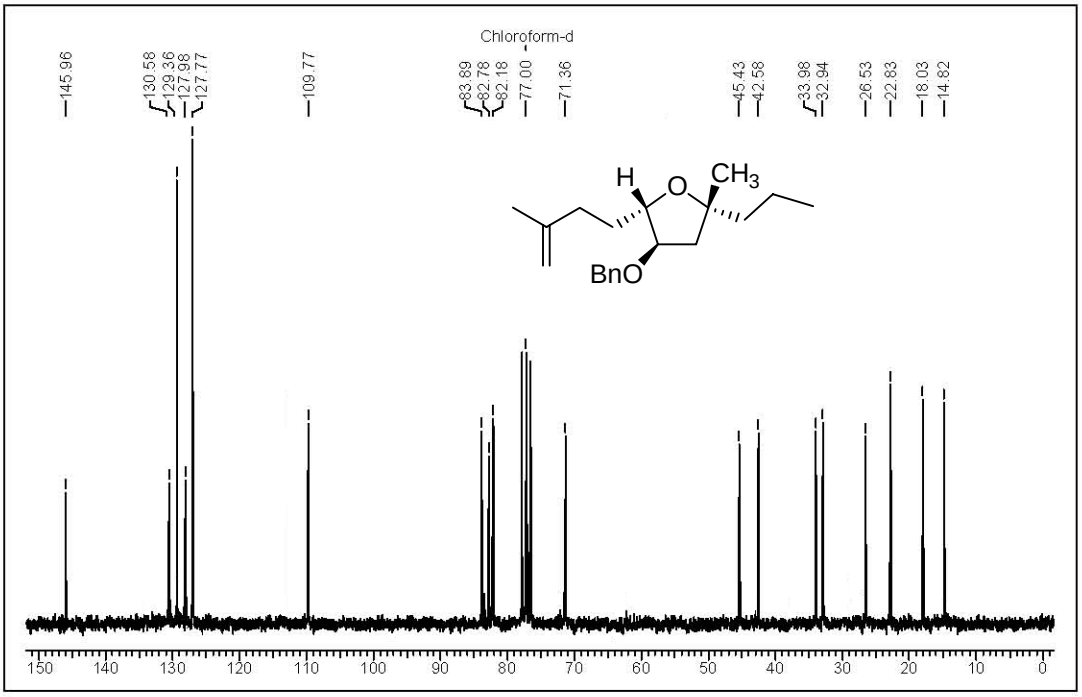
^{13}C NMR spectra of compound 45 in $CDCl_3$



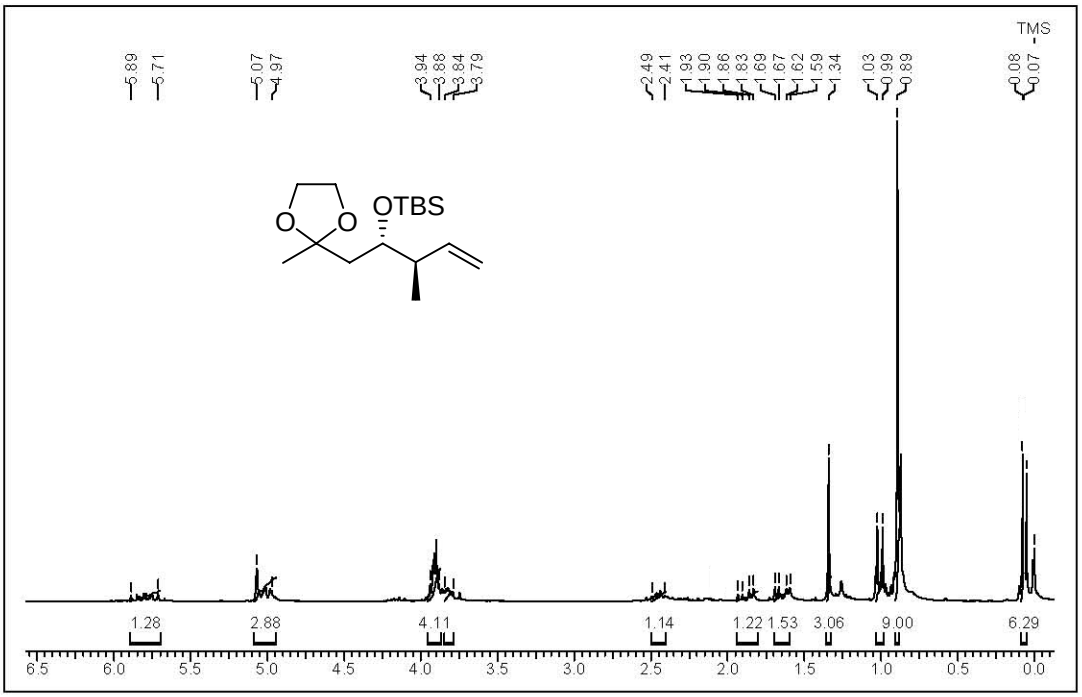
^{13}C NMR spectra of compound 42 in $CDCl_3$



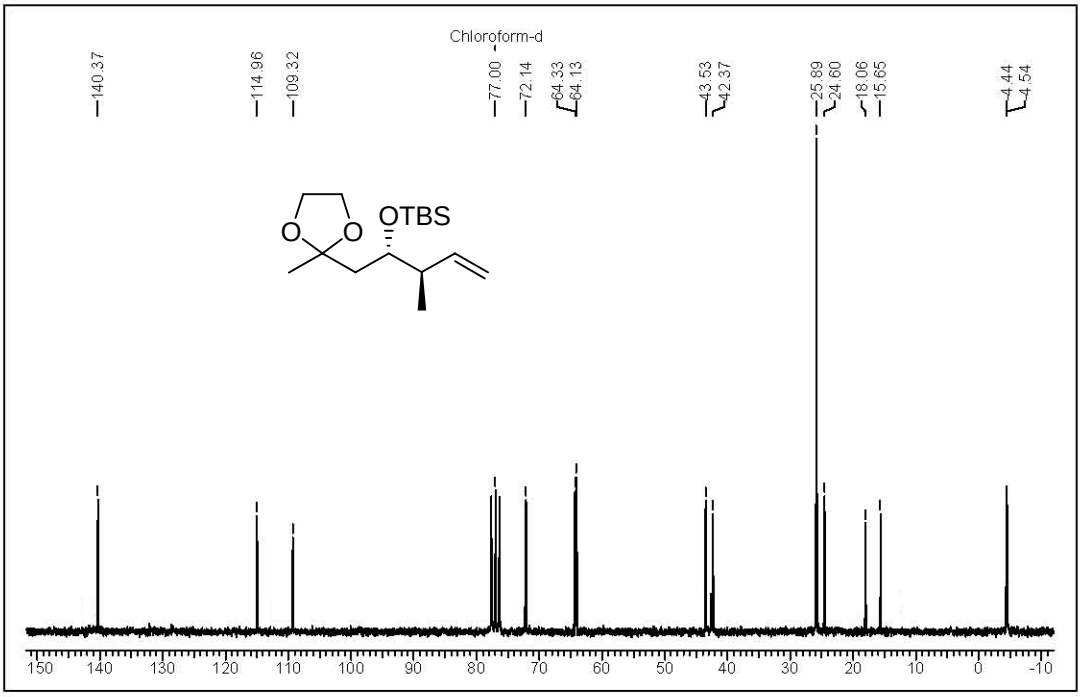
^{1}H NMR spectra of compound 46 in $CDCl_3$



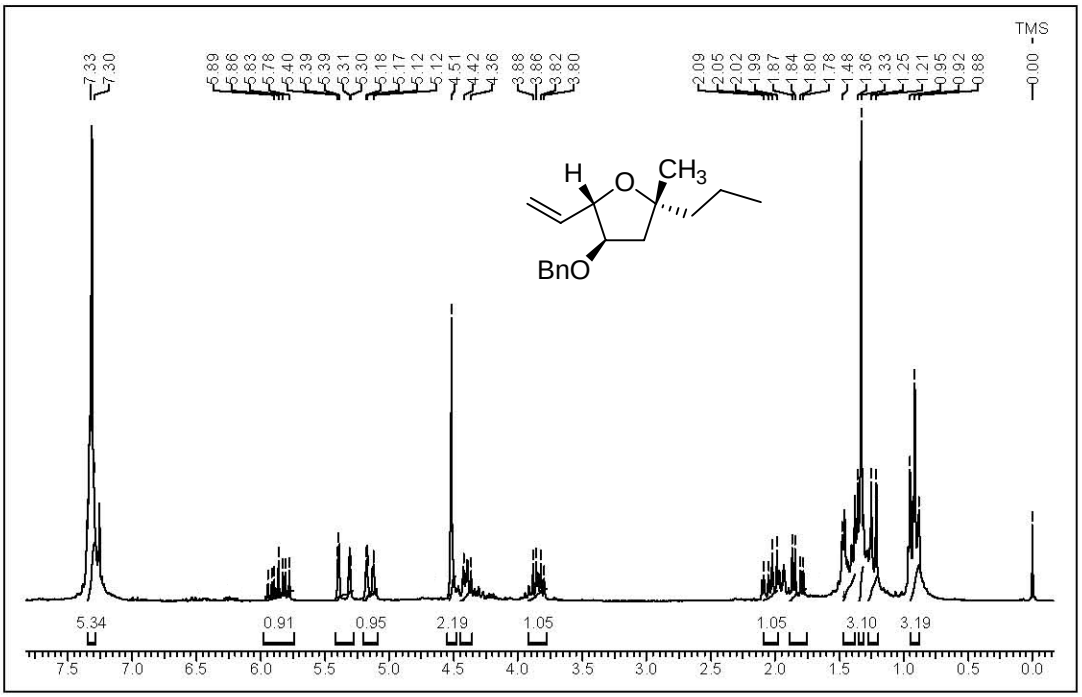
^{13}C NMR spectra of compound 46 in $CDCl_3$



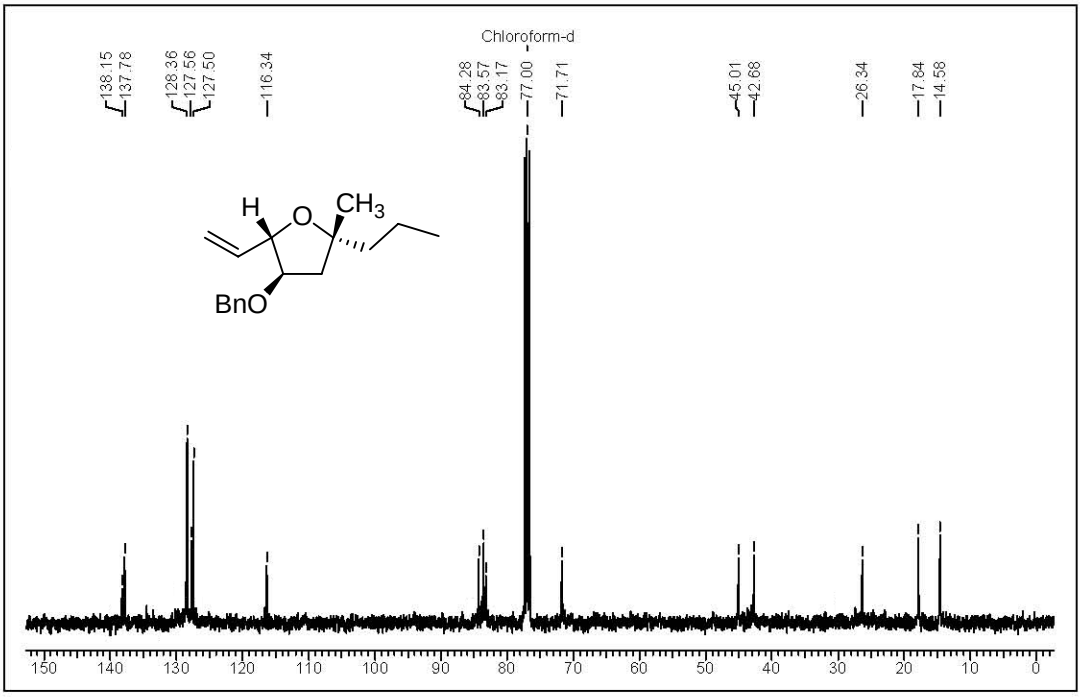
^{1}H NMR spectra of compound 47 in $CDCl_3$



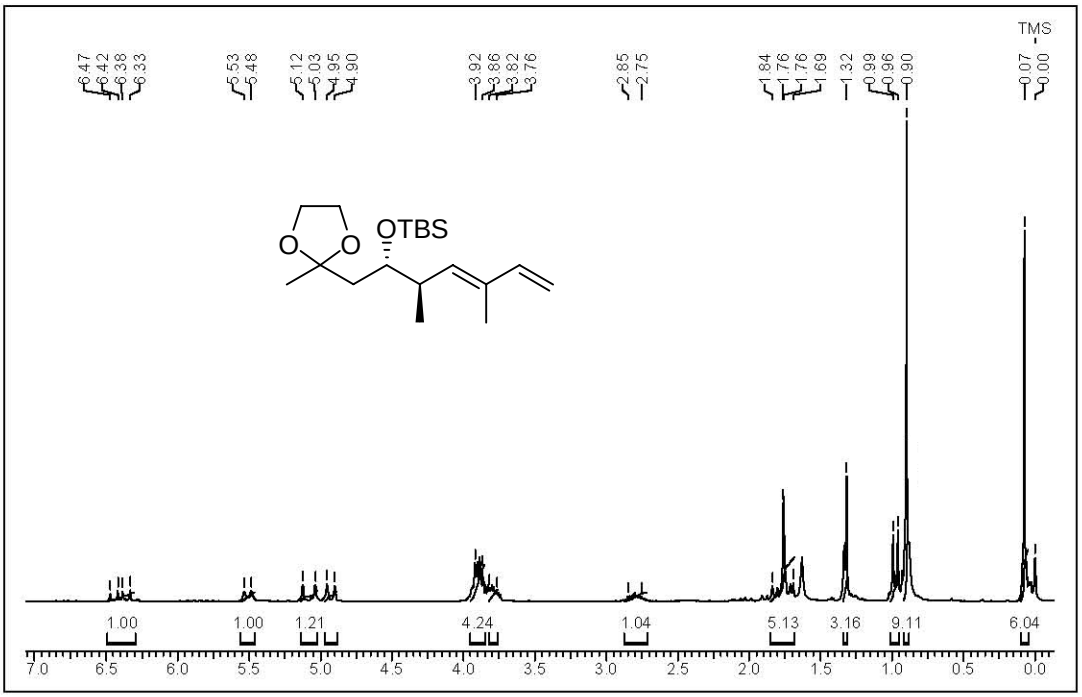
^{13}C NMR spectra of compound 47 in $CDCl_3$



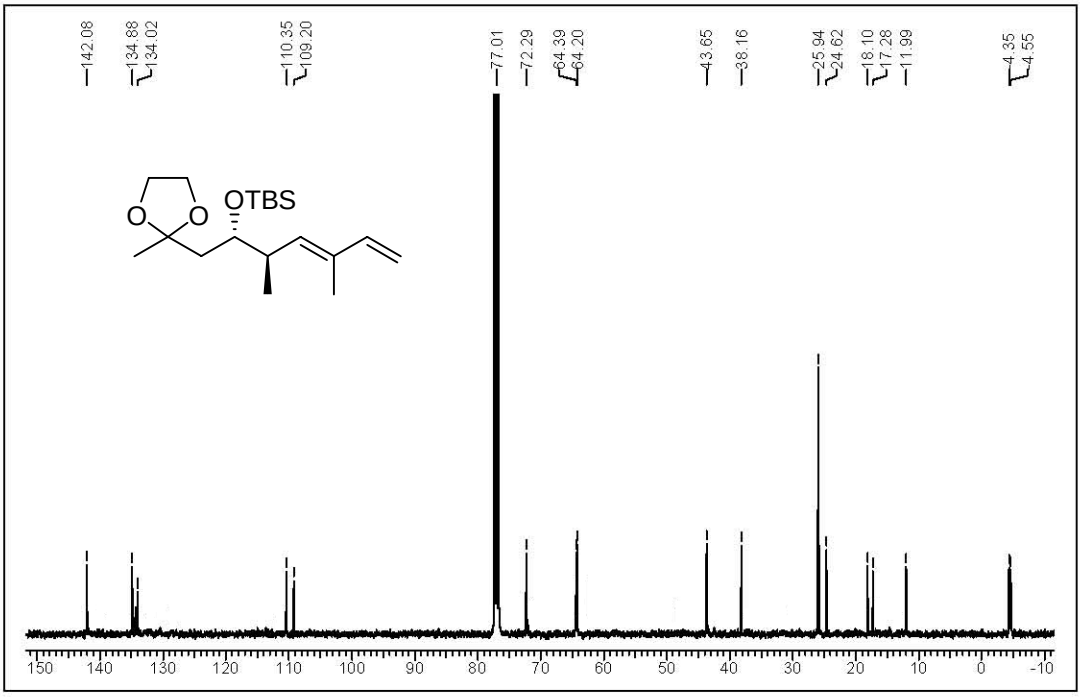
^{1}H NMR spectra of compound 48 in $CDCl_3$



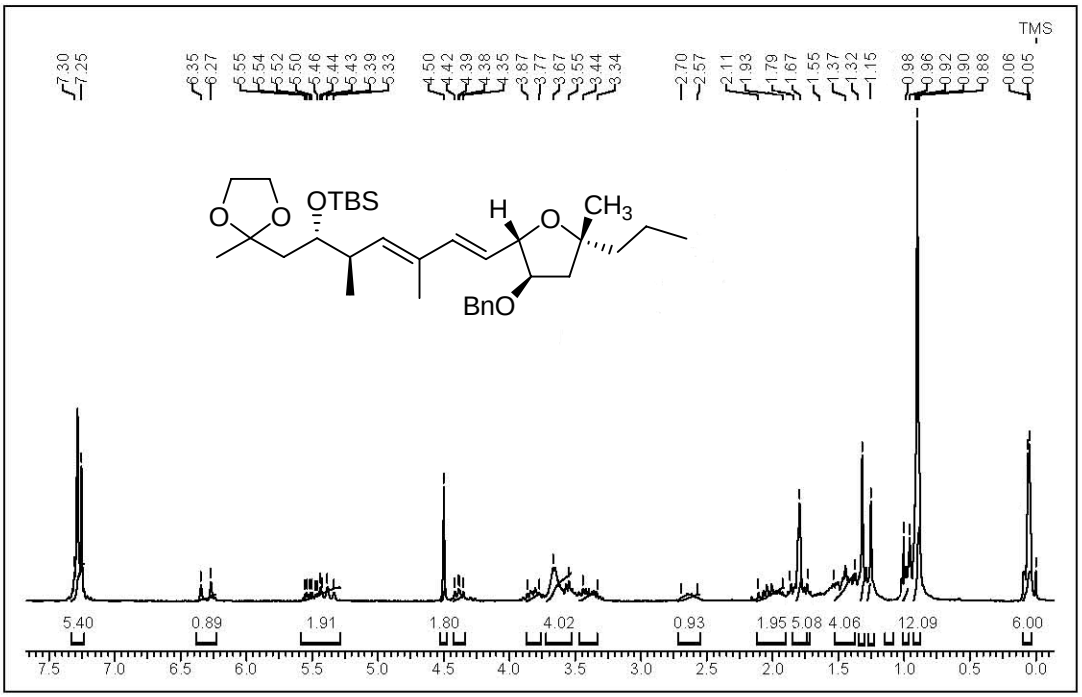
^{13}C NMR spectra of compound 48 in $CDCl_3$



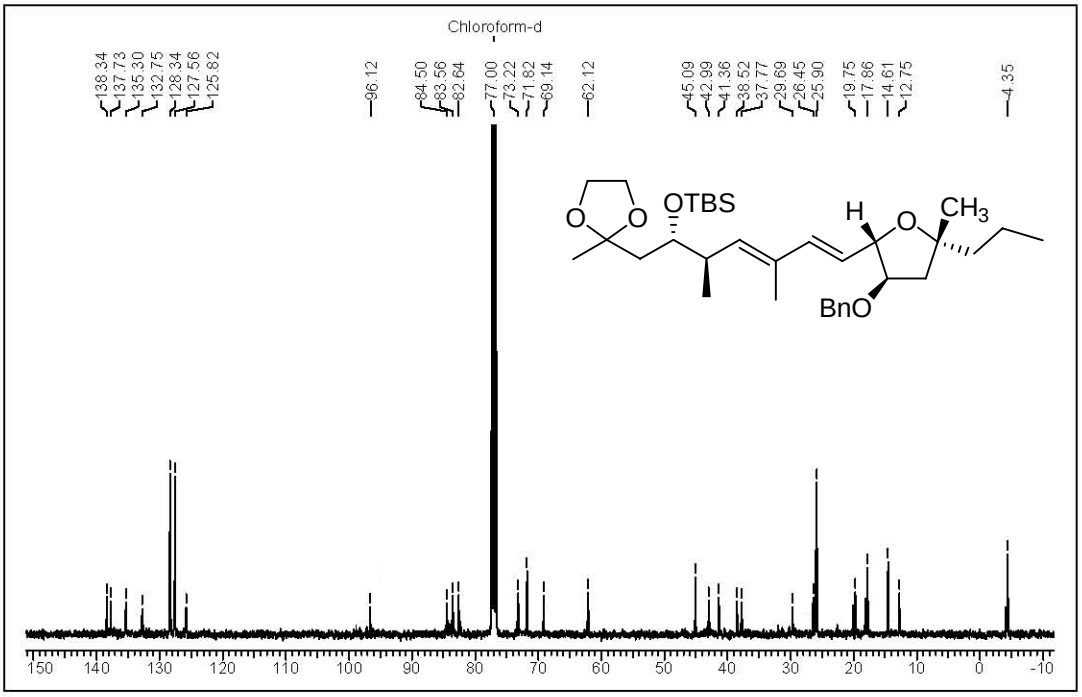
^{1}H NMR spectra of compound 51 in $CDCl_3$



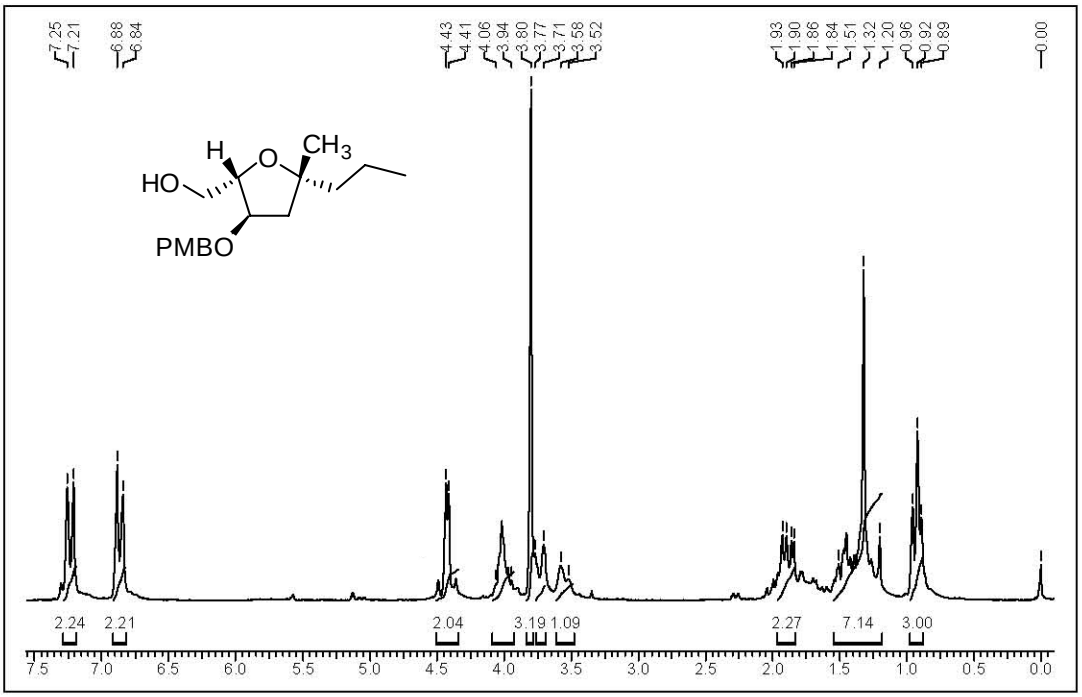
^{13}C NMR spectra of compound 51 in $CDCl_3$



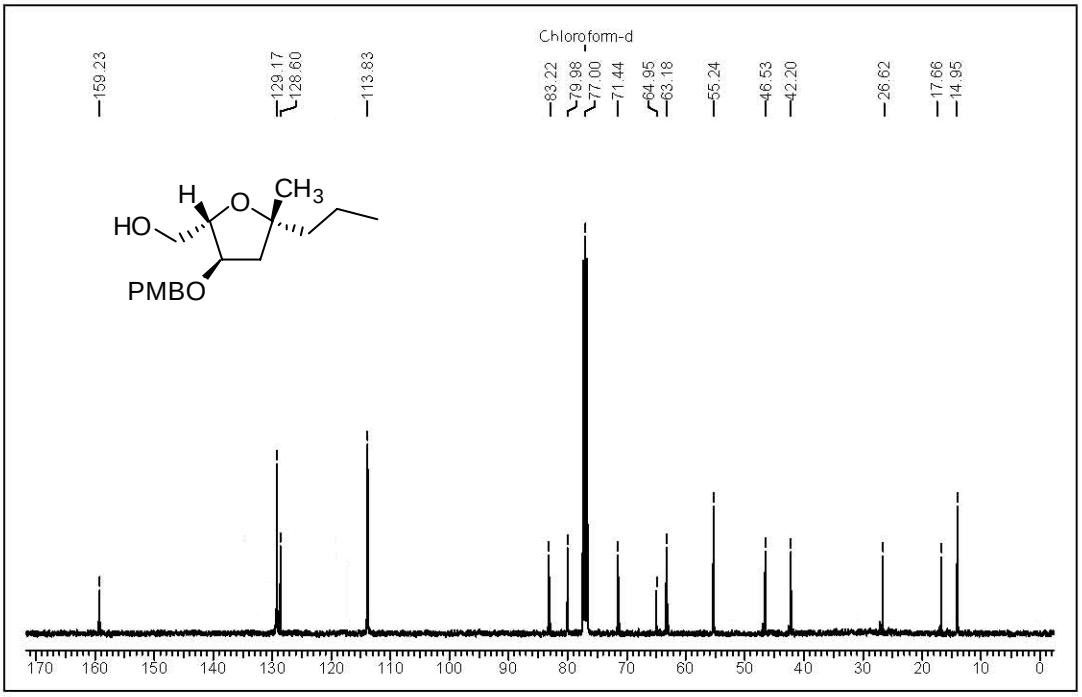
^{1}H NMR spectra of compound 52 in $CDCl_3$



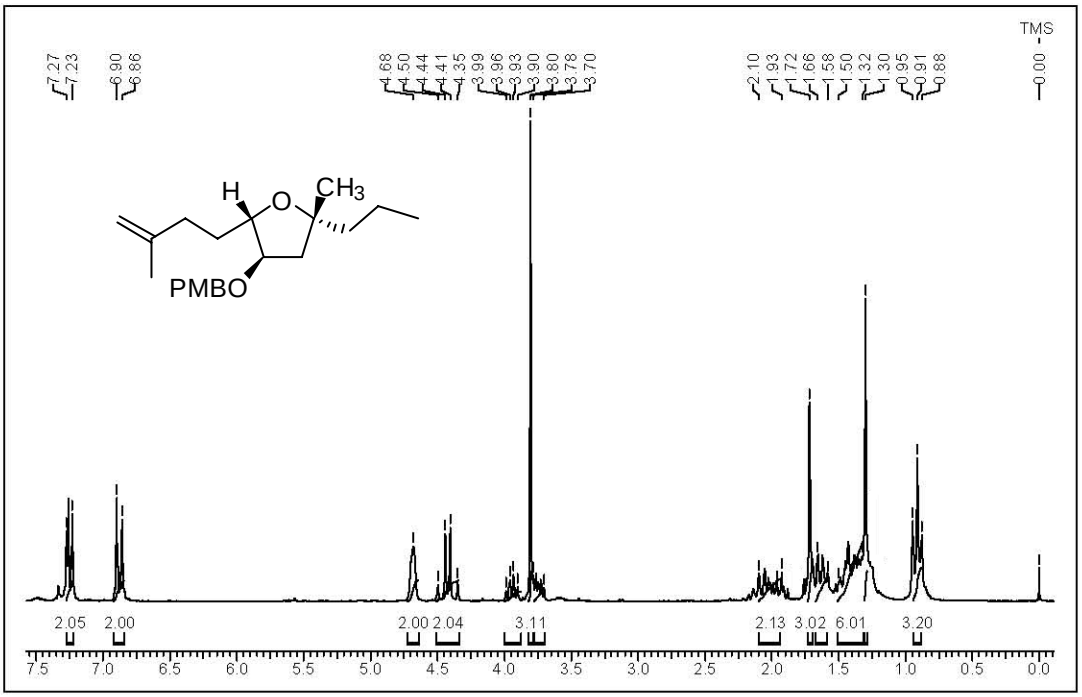
^{13}C NMR spectra of compound 52 in $CDCl_3$



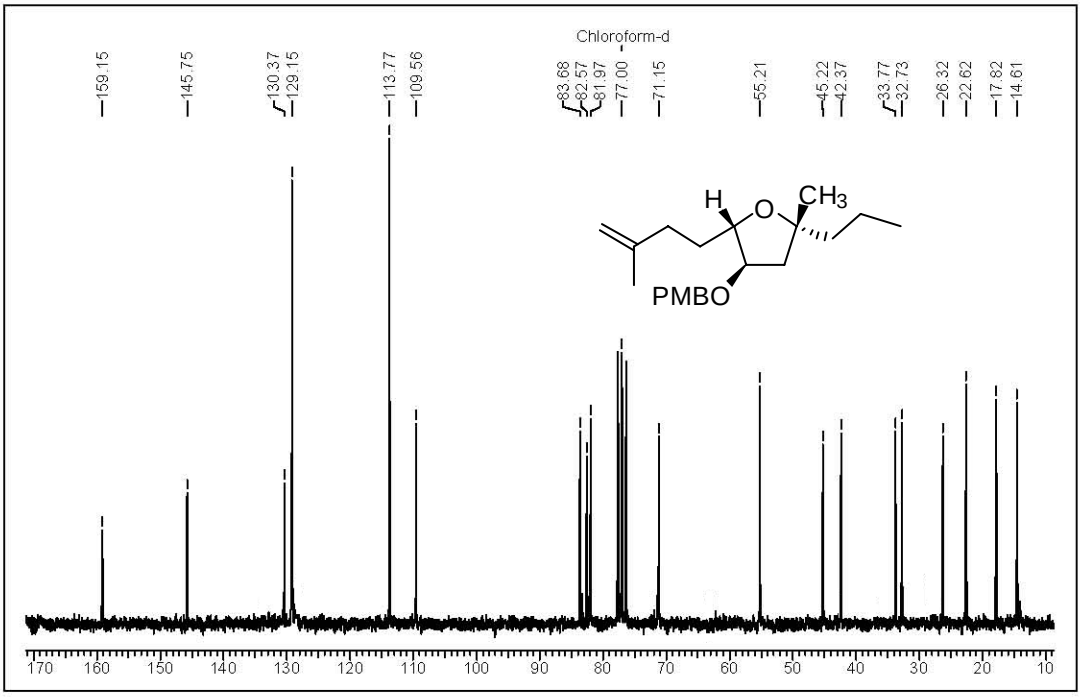
^{1}H NMR spectra of compound 58 in $CDCl_3$



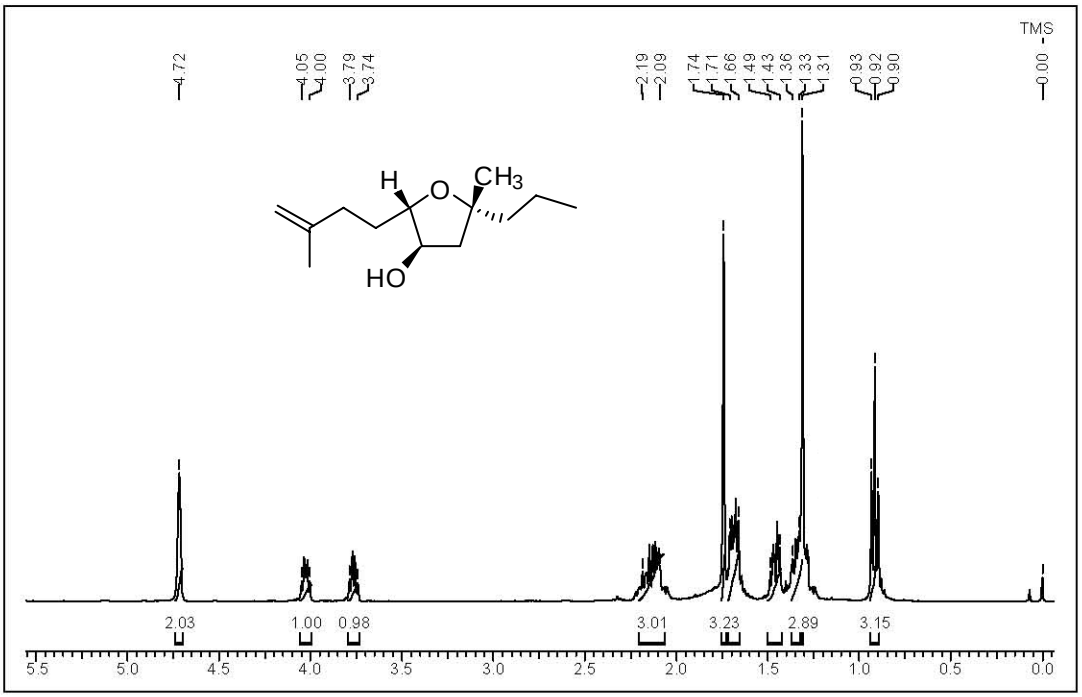
^{13}C NMR spectra of compound 58 in $CDCl_3$



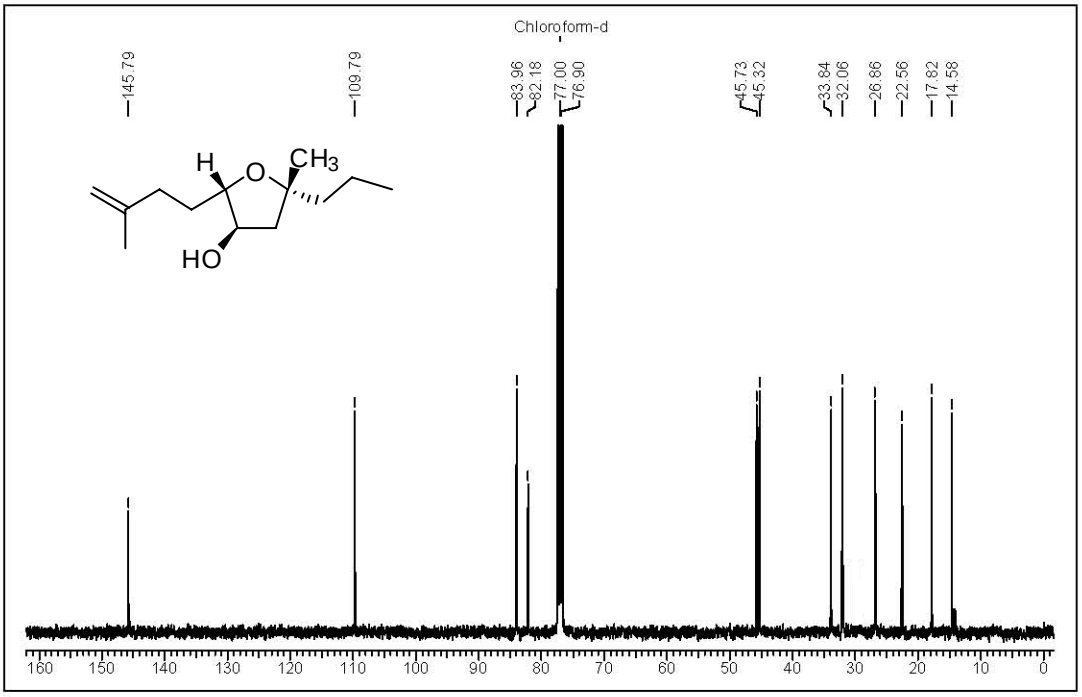
^{1}H NMR spectra of compound 62 in $CDCl_3$



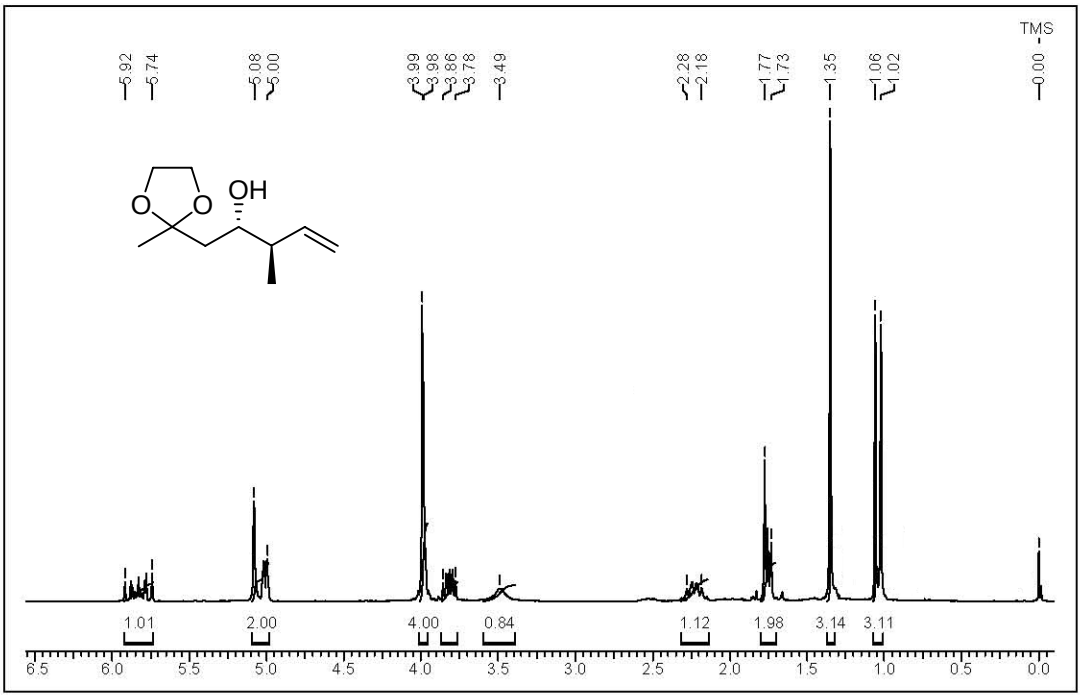
^{13}C NMR spectra of compound 62 in $CDCl_3$



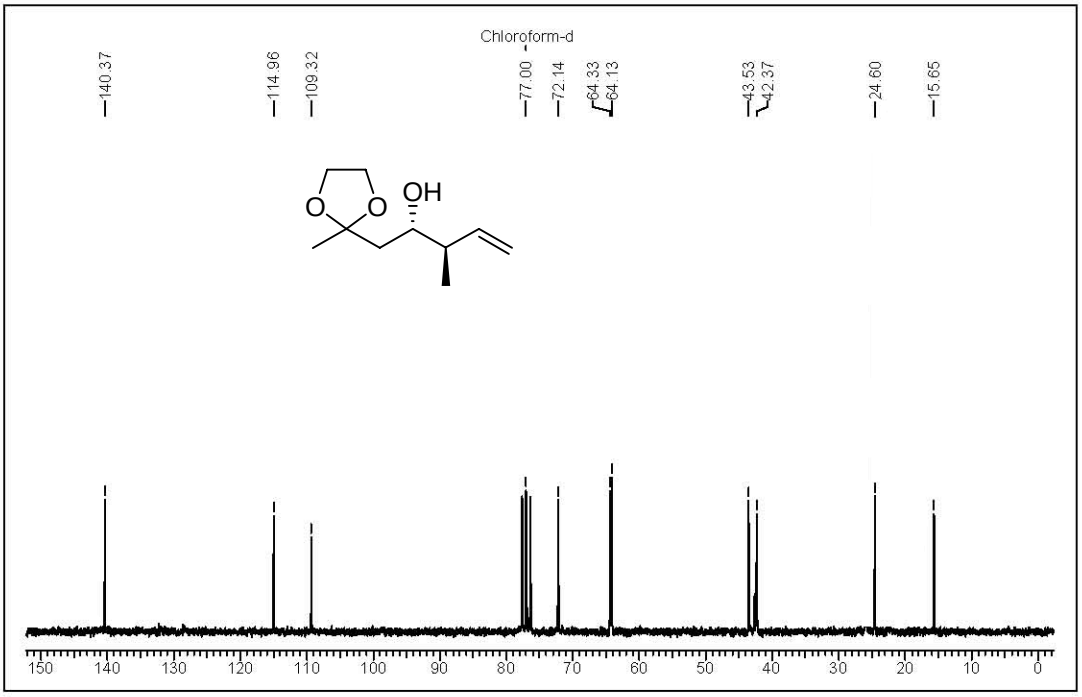
^{1}H NMR spectra of compound 55 in $CDCl_3$



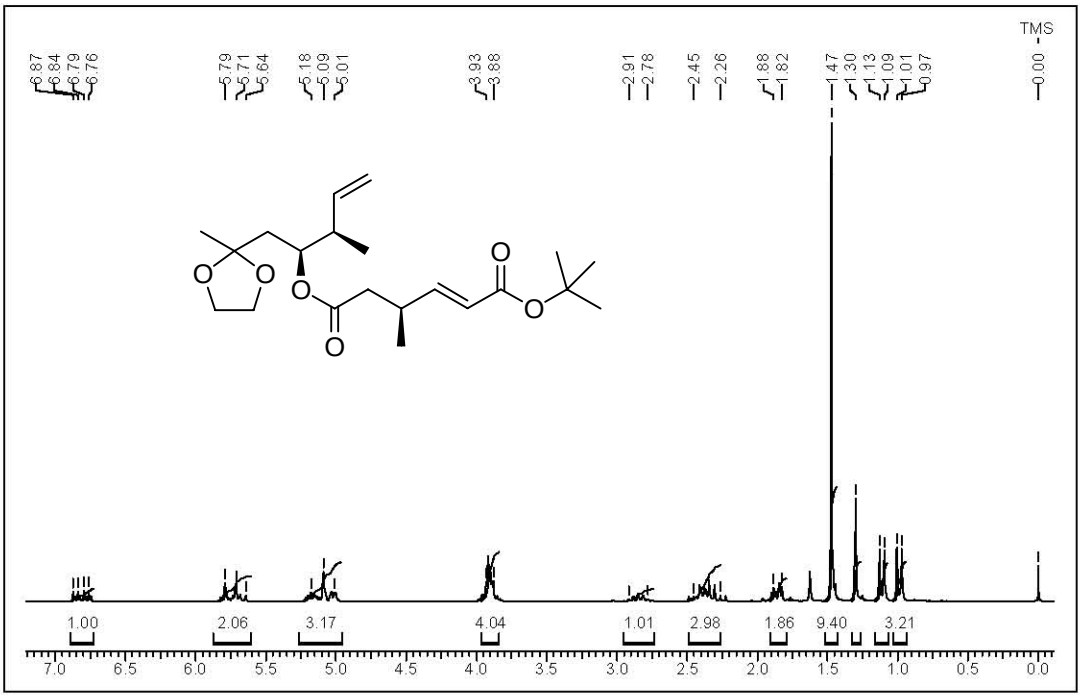
^{13}C NMR spectra of compound 55 in $CDCl_3$



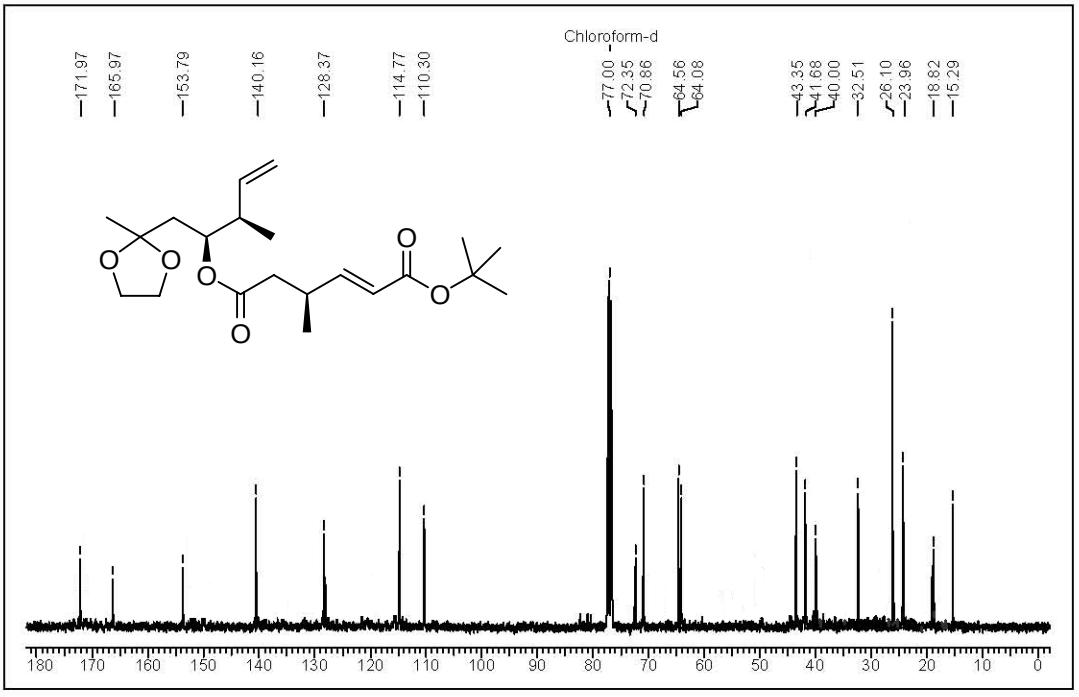
^{1}H NMR spectra of compound 56 in $CDCl_3$



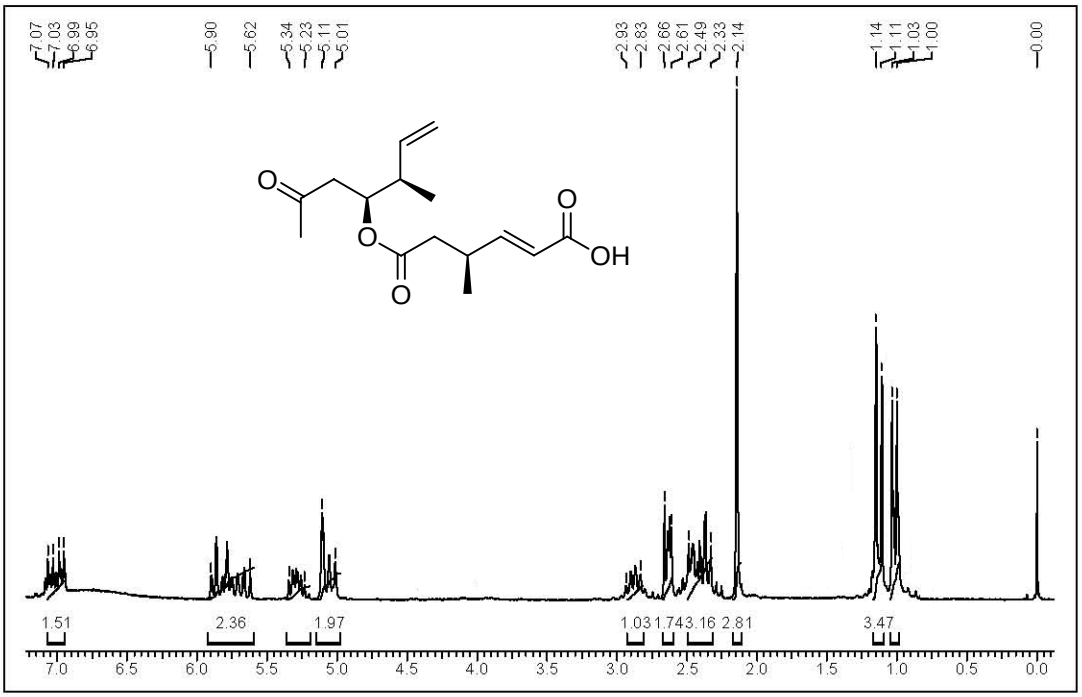
^{13}C NMR spectra of compound 56 in $CDCl_3$



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



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



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

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Chapter II

Studies Toward the Total Synthesis of Eicosanoid and Solandelactone

INTRODUCTION

Eicosanoids:

Eicosanoids are signaling molecules made by oxygenation of twenty-carbon essential fatty acids (EFAs). They exert complex control over many bodily systems, mainly in inflammation or immunity and as messengers in the central nervous system.[1] The networks of controls that depend upon eicosanoids are among the most complex in the human body.

Eicosanoids are derived from either omega-3 (ω-3) or omega-6 (ω-6) EFAs. The ω-6 eicosanoids are generally pro-inflammatory; ω-3's are much less so. The amounts and balance of these fats in a person's diet will affect the body's eicosanoid-controlled functions, with effects on cardiovascular disease, triglycerides, blood pressure, and arthritis.[2] Anti-inflammatory drugs such as aspirin and other NSAIDs (non-steroidal anti-inflammatory drugs) act by downregulating eicosanoid synthesis.

There are four families of eicosanoids-the prostaglandins, prostacyclins, the thromboxanes and the leukotrienes. For each, there are two or three separate series, derived either from an ω-3 or ω-6 EFAs. These series with different activities largely explain the health effects of ω-3 and ω-6 fats.[3]

Nomenclature:

"Eicosanoid" (*eicosa-*, Greek for "twenty") is the collective term for oxygenated derivatives of three different 20-carbon essential fatty acids:

- Eicosapentaenoic acid (EPA), an ω-3 fatty acid with 5 double bonds;
- Arachidonic acid (AA), an ω-6 fatty acid, with 4 double bonds;
- Dihomo-gamma-linolenic acid (DGLA), an ω-6, with 3 double bonds.

Current usage limits the term to the leukotrienes[4] (LT) and three types of prostanoids[5] namly prostaglandins (PG), prostacyclins (PGI), and thromboxanes (TX). However, several other classes can technically be termed eicosanoid, including the hepoxilins, resolvins, isofurans, isoprostanes, lipoxins, epi-lipoxins, epoxyeicosatrienoic acids (EETs) and endocannabinoids. Leukotrienes and prostanoids are sometimes termed ‘classic eicosanoids’[6] in contrast to the 'novel', 'eicosanoid-like' or ‘nonclassic eicosanoids’.[7]

A particular eicosanoid is denoted by a four-character abbreviation,[8] composed of:

- Its two letter abbreviation (eg. PG, LT, EP),
- One A-B-C sequence-letter (eg. TXA, LTB, EPA) and
- A subscript indicating the number of double bonds (e.g. PGH_3, PGI_3, TXA_3).

Biosynthesis:

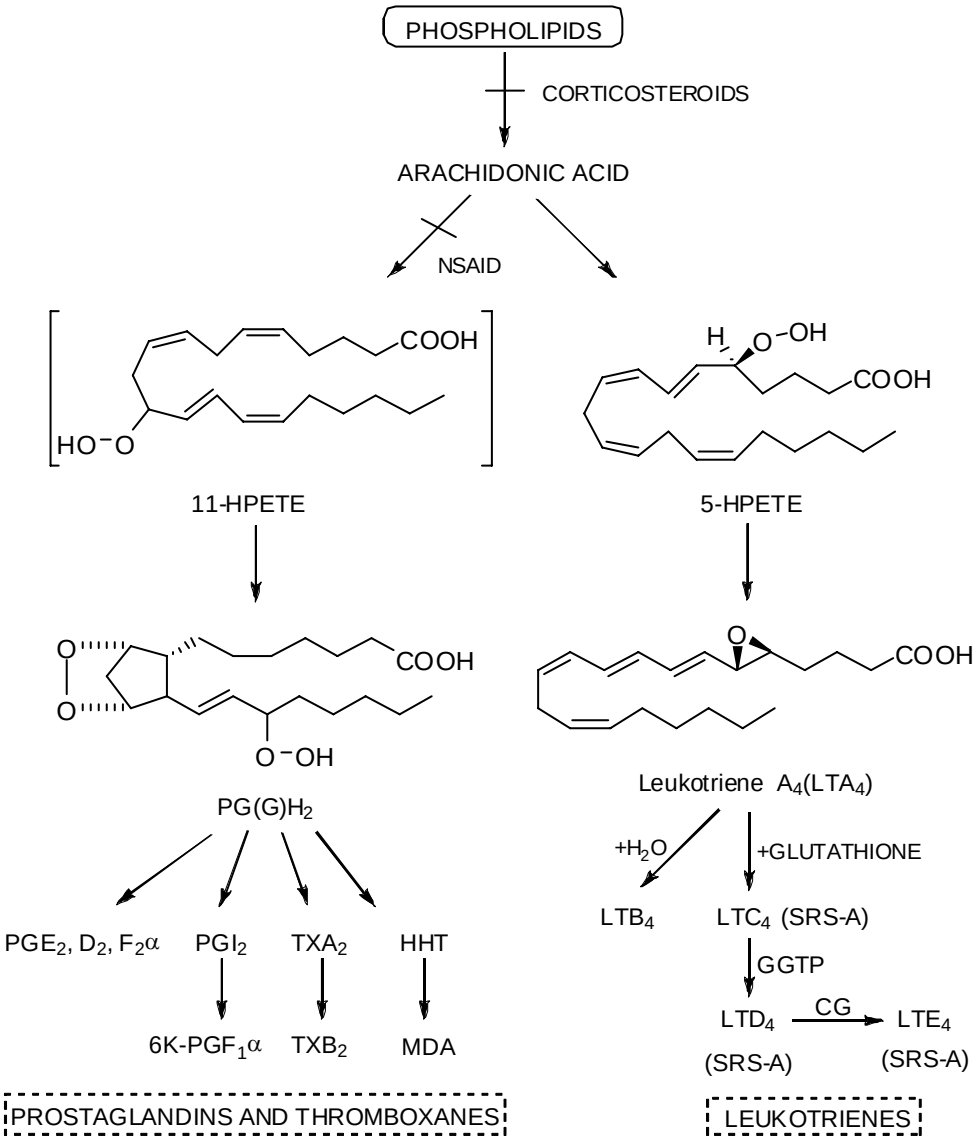
Although eicosanoid formation is seemingly ubiquitous in mammalian tissues, their precise physiological role cannot as yet be defined. They can be classified as autacoids, i.e., substances which are evanescent and exert their effects locally in the microenvironment of the tissues where they were generated. Such effects might include regulation of vascular tone and permeability of capillaries and venues, contraction or relaxation of muscle, stimulation or inhibition of platelet function, activation of leukocytes, regulation of renal blood flow and mineral metabolism, and possible control of growth and/or spread of malignant cells.[2]

Eicosanoids are not stored in cells and must always be newly synthesized in response to perturbation. The precursor, arachidonic acid, is present only in esterified form and must be hydrolyzed prior to utilization for eicosanoid synthesis. The exact mechanisms governing release of arachidonic acid upon cell stimulation are incompletely understood at present. Released arachidonate can be processed in several ways. It may leave the cell and become available for metabolism by another cell or it may be bound by plasma albumin. Most importantly, arachidonate can be enzymatically oxygenated by a particulate cyclooxygenase and/or a cytoplasmic lipoxygenase with the formation of unstable intermediate compounds. These include endoperoxides (PGG_2/PGH_2) for prostaglandin formation and hydroperoxides and epoxides (LTA_4) for hydroxy acid and leukotriene production.[4] Ultimately, the derivatives formed will depend on the type of converting enzymes present in a tissue. Pathways of formation of prostaglandins, thromboxanes, and leukotrienes from arachidonic acid are summarized in Figure 1.

Figure 1 shows the summary of biochemical reactions involved in the formation of prostaglandins, thromboxanes, and leukotrienes from arachidonic acid.[9] Hydrolysis of esterified arachidonic acid from cellular phospholipid is the first rate-limiting step in the eicosanoid pathway. It can be blocked by corticosteroids. The cyclooxygenation step (blocked by NSAIDs) shown on the left, results in formation

of the first oxygenation products-the endoperoxides. Further conversion of endoperoxides to other metabolites is cell and tissue-specific. Formation of $PGF_{2\alpha}$ may be nonenzymatic and PGD_2 may be produced in the presence of serum albumin. TXA_2 and PGI_2 are formed enzymatically and are measured as their end products TXB_2 and 6-keto-$PGF_{1\alpha}$. The 5-lipoxygenase pathway, shown on the right, is found mainly in cells involved in the inflammatory response. Platelets contain a 12-lipoxygenase and interestingly, ecosinophils can carry out 15-lipoxygenation. Leukotriene A_4 can give rise to LTB_4 or, in the presence of glutathione-S-transferase, become metabolized to SRS-A (LTC_4, LTD_4, LTE_4).

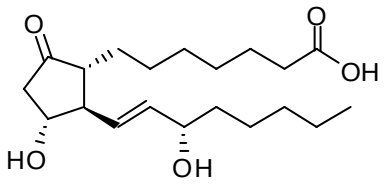
Figure 1: *Summary of biochemical reactions involved in the formation of eicosanoids (prostaglandins, thromboxanes and leukotrienes) from arachidonic acid*



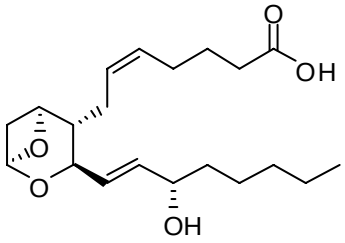
It is of great interest that arachidonic acid, originally thought to be solely a structural component of cell membranes, can be transformed into such a large number of metabolic derivatives with diverse and potent biological activities.

All three classes of prostanoids originate from prostaglandine hydroxide (PGH). All have distinctive rings in the center of the molecule. They differ in their structures. The PGH compounds (parents to all the rest) have a 5-carbon ring, bridged by two oxygens (a peroxide). The derived prostaglandins contain a single, unsaturated 5-carbon ring. In prostacyclins, this ring is conjoined to another oxygen-containing ring. In thromboxanes the ring becomes a 6-member ring with one oxygen. The leukotrienes do not have rings. As an example, figure 2 shows structures of selected eicosanoids.

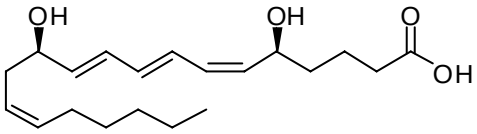
Figure 2: *Structures of Selected Eicosanoids*



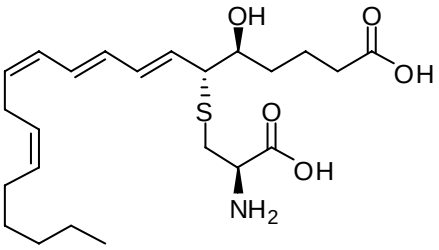
Prostaglandin E_1. The 5-member ring is characteristic of the class



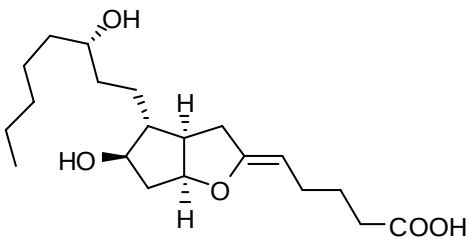
Thromboxane A_2. Oxygens have moved into the ring



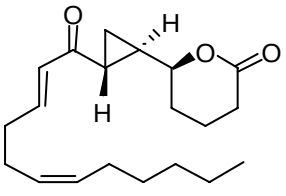
Leukotriene B_4. Note the 3 conjugated double bonds



Prostacyclin I_2. The second ring distinguishes it from the prostaglandins



Leukotriene E_4, an example of a cysteinyl leukotriene.



Eicosanoid δ-lactone, containing a chiral cyclopropane ring

Function and pharmacology:

Eicosanoids exert complex control over many bodily systems, mainly in inflammation or immunity, and as messengers in the central nervous system.[10] Eicosanoids are found in most living things. In humans, eicosanoids are local hormones that are released by most cells, act on that same cell or nearby cells and then are rapidly inactivated. The table 1 shows the Metabolic actions of selected prostanoids and leukotrienes.

Table 1: *Metabolic actions of selected eicosanoids (prostanoids and leukotrienes)*

PGD_2	Promotion of sleep	TXA_2	Stimulation of platelet aggregation; vasoconstriction
PGE_2	Smooth muscle contraction; inducing pain, heat, fever.	15d-PGJ_2	Adipocyte differentiation
$PGF_{2\alpha}$	Uterine contraction	LTB_4	Leukocyte chemotaxis
PGI_2	Inhibition of platelet aggregation; vasodilation; embryo implantation	Cysteinyl-LTs	Anaphylaxis; bronchial smooth muscle contraction.

Eicosanoids have a short half-life, ranging from seconds to minutes. Dietary antioxidants inhibit the generation of some inflammatory eicosanoids, e.g. trans-resveratrol against thromboxane and some leukotrienes.[11] There are specific receptors for all eicosanoids.

Arachidonic acid (AA; ω-6) sits at the head of the 'arachidonic acid cascade,' more than twenty different eicosanoid-mediated signaling paths controlling a wide array of cellular functions, especially those regulating inflammation, immunity and the central nervous system.[3] Low dietary intake of these less-inflammatory essential fatty acids, especially the ω-3s, has been linked to several inflammation-related diseases and perhaps some mental illnesses.

Since antiquity, the cardinal signs of inflammation have been known as: calor (warmth), dolor (pain), tumor (swelling) and rubor (redness). The eicosanoids are involved with each of these signs.

- **Redness**: An insect's sting will trigger the classic inflammatory response. Short acting vasoconstrictors (TXA_2) are released quickly after the injury. The site may momentarily turn pale. Then TXA_2 mediates the release of the

vasodilators PGE_2 and LTB_4. The blood vessels engorge and the injury reddens.

- **Swelling**: LTB_4 makes the blood vessels more permeable. Plasma leaks out into the connective tissues, and they swell.
- **Pain**: The cytokines increase COX-2 activity. This elevates levels of PGE_2, sensitizing pain neurons.
- **Heat**: PGE_2 is also a potent pyretic agent. Aspirin and other NSAID drugs that block the COX pathways and stop prostanoid synthesis, limit fever or the heat of localized inflammation.

Table 2: *Eicosanoid, eicosanoid analogs used as medicines*

Medicine	Type	Medical condition or use
Alprostadil	PGI_1	Erectile dysfunction, maintaining a patent ductus arteriosus in the fetus
Beraprost	PGI_1 analog	Pulmonary hypertension, avoiding reperfusion injury
Bimatoprost	PG analog	Glaucoma, ocular hypertension
Carboprost	PG analog	Labor induction, abortifacient in early pregnancy
Iloprost	PGI_2 analog	Pulmonary arterial hypertension
Misoprostol	PGE_1 analog	Stomach ulcers, labor induction, abortifacient
Montelukast	LT receptor antagonist	Asthma, seasonal allergies
Travoprost	PG analog	Glaucoma, ocular hypertension
Treprostinil	PGI analog	Pulmonary hypertension

Prostanoids mediate local symptoms of inflammation, vasoconstriction or vasodilation, coagulation, pain and fever. Leukotrienes play an important role in

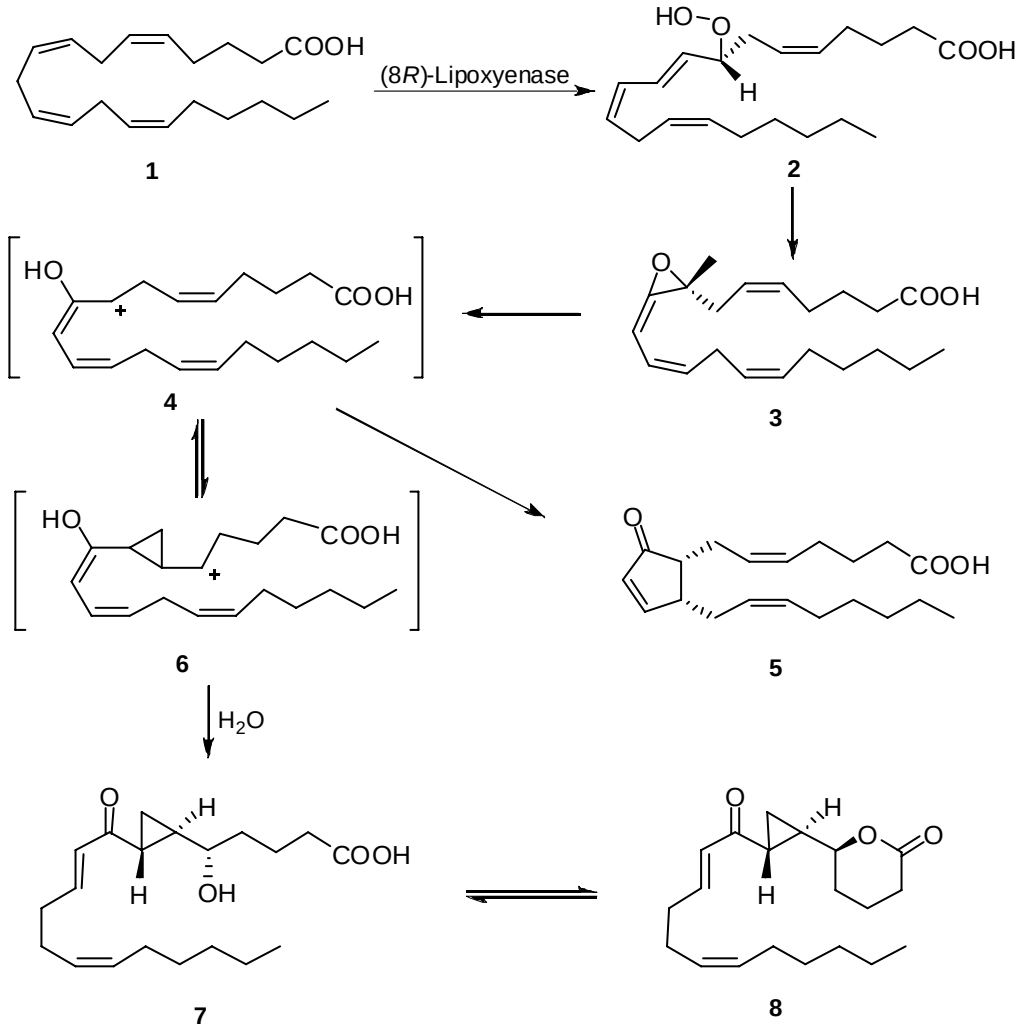
inflammation. Inhibition of cyclooxygenase is the hallmark of NSAIDs, such as aspirin. Blocking leukotriene receptors can play a role in the management of inflammatory diseases such as asthma (by the drugs montelukast and zafirlukast), nasal allergies, psoriasis, and rheumatoid arthritis. Some of the medical uses of eicosanoids[12] and their analogs are summerized in table 2.

As eicosanoids exibits lipoxygenase inhibiting activity and hence attracted the attention of a number of organic chemists worldwide.

Corey's pathway for biosynthesis of Eicosanoids:

In 1987 Corey put forward a general pathway for marine prostanoid biosynthesis[13] (Figure 3) in which arachidonic acid (**1**) is oxidized by a lipoxygenase enzyme to (8*R*)-8-hydroperoxyeicosatetraenoic acid (8*R*-HPETE, **2**). The latter is then converted enzymatically to the allene oxide **3**.

Figure 3:



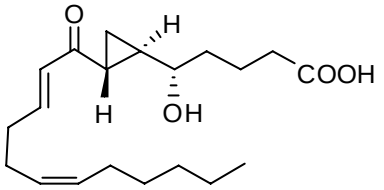
It was suggested that prostanoids, such as preclavulone (**5**), originate by closure of the derived cation **4** at C12 of the eicosanoid. Subsequently, Brash was isolated and characterized Corey's proposed allene oxide by incubation of **2** with an acetone powder from the coral *Plexaura homomalla*. Similar incubation of arachidonic acid itself was found to give, in addition to **5**, a novel eicosanoid **7** containing a cyclopropane. This finding has led to an extension of Corey's biogenetic hypothesis that includes an alternative pathway from cation **4** involving participation by the δ-bond (Figure 5). Rearrangement of **4** to the cyclopropyl carbocation **6** followed by hydrolysis and relocation of the bond into conjugation with the C9 ketone would lead to **7.** This δ-hydroxy acid was found to undergo facile lactonization to **8**[15] in which the cyclopropane substituents were shown to be *trans*.

White's Biomimetic Synthesis of Eicosanoid (8):

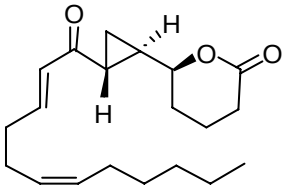
The arachidonic acid (AA) pathway in marine organisms has been found to produce, in addition to metabolites of the prostanoid family, C20 cyclopropanes which invariably contain sites of oxygenation adjacent to the three-membered rings.[14] A singular example is **7**, isolated from incubation of AA with an acetone powder of the Caribbean soft coral *Plexaura homomalla*[16] and characterized as the δ-lactone **8**. The latter is clearly related to the constanalactones, e.g., **9**, which occur in the *red alga Constantinea simplex*. A unifying biogenetic hypothesis accommodating **7** and the 5,6-trans prostanoids present in *Plexaura homomalla* has been proposed on the basis of the allene oxide **10**. This epoxide, presumably formed via an (8*R*)-lipoxygenase pathway, was originally put forward by Corey as a key intermediate in the biosynthesis of preclavulone-A from 8-(*R*)-HPETE in *Plexaura homomalla* and has been isolated by Brash from an acetone powder of the coral.[17]

The biogenetic pathway from **10** to **7** postulates that epoxide opening triggers carbocyclization to a cyclopropyl carbinyl cation, which is followed by trapping of the carbocation by the terminal carboxyl group or water. White has describe on the basis of this precept a synthesis of **7** via **8** which features construction of the cyclopropyl lactone moiety and which unambiguously defines its relative configuration.[18]

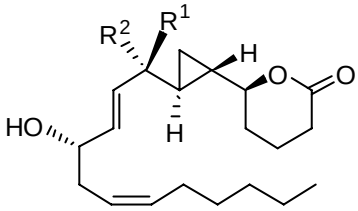
Figure 4: *Eicosanoid (**8**) and related compounds*



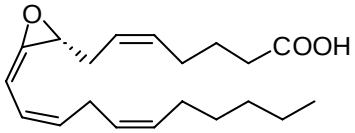
Eicosanoic acid (**7**)



Eicosanoid (**8**)



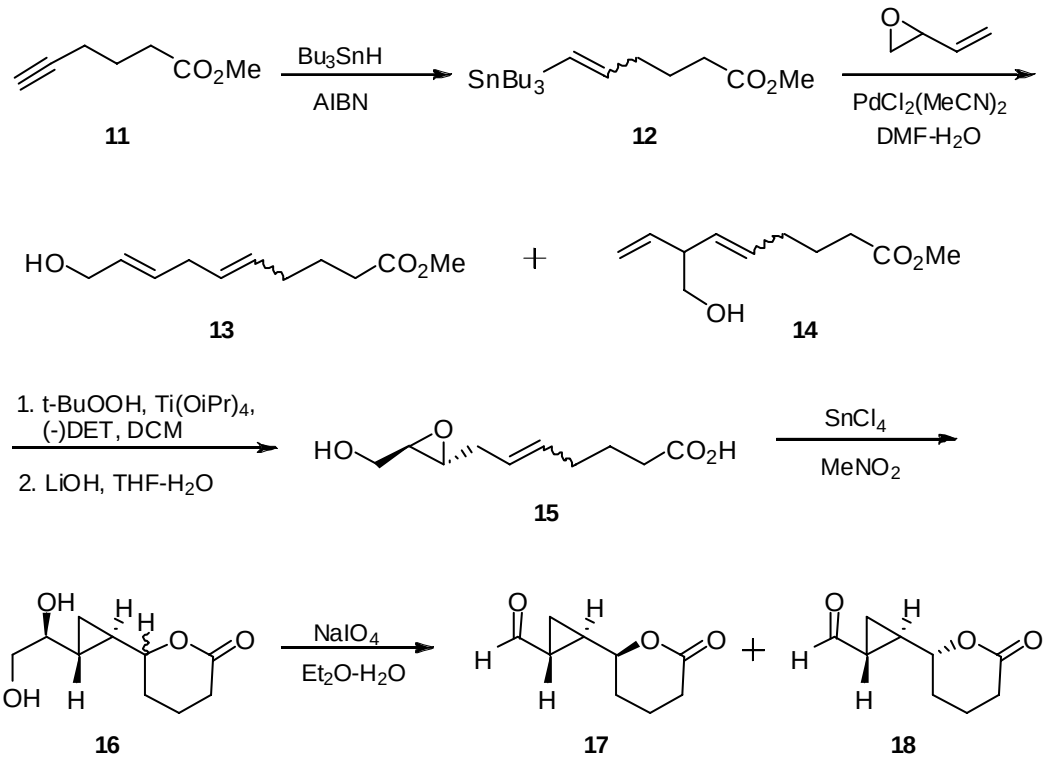
R^1= H, R^2= OH; R^1= OH, R^2= H
Constanolactones (**9**)



Allene oxide (**10**)

Hydrostannylation of methyl 5-hexynoate (**11**) afforded a mixture of *(E)* and (Z) stannanes **12**. These isomers were difficult to separate, and the mixture of isomers was therefore subjected to reaction with butadiene monoepoxide in the presence of a catalytic bis(acetonitri1e) complex of palladium(II) chloride. A mixture of 1,4- and 1,2-addition products **13** and **14** respectively was obtained, each as a *(5E,Z)* mixture of olefin isomers.

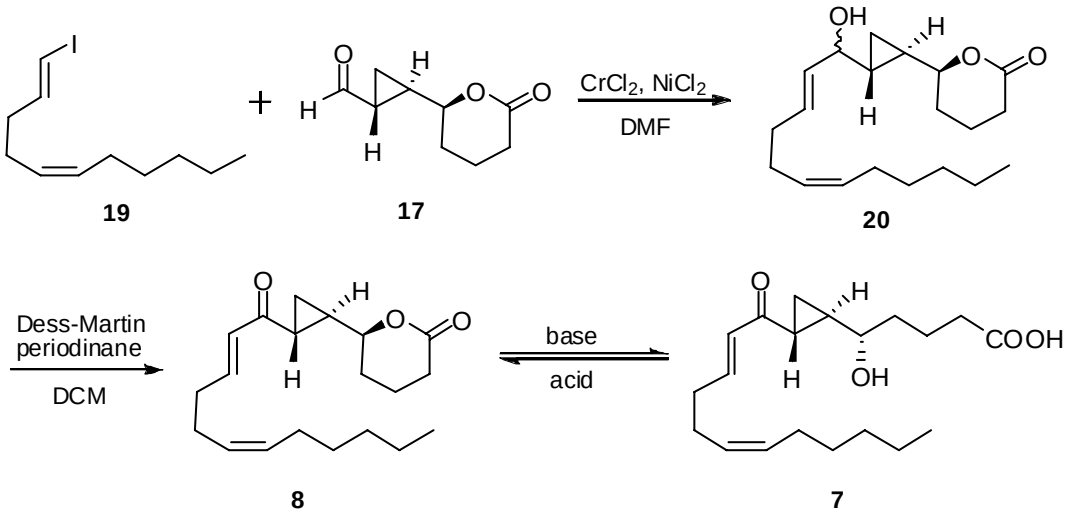
Scheme 1:



11 **12** **13** **14** **15** **16** **17** **18**

The allylic alcohol **13** in this mixture underwent asymmetric epoxidation to furnish epoxide. Further saponification gave carboxylic acids **15**. The carboxylic acid **15** when treated with stannic chloride in cold nitromethane furnished the mixture of stereoisomeric lactone **16**. The lactone **16** was oxidized with sodium periodate to afford aldehydes **17** and **18**. Both aldehydes readily formed (2,4-dinitrophenyl)-hydrazones, which were then separated by medium-pressure liquid chromatography.

Scheme 2:



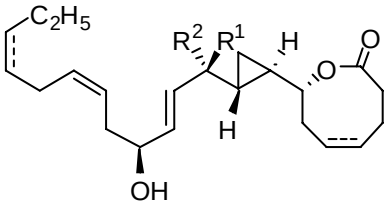
The coupling partner for **17**, (1*E*,5*Z*)-l-iodo-1,5-undecadiene (**19**), was prepared from (4*Z*)-4-decenal using the homologation method of Takai. Treatment of **19** with $CrCl_2$ and $NiCl_2$ followed by addition of **17**, afforded a 1:l mixture of stereoisomeric alcohols **20**, which was directly oxidized with Dess-Martin periodinane to furnish eicosanoid **8**. Saponification of synthetic eicosanoid **8** afforded the hydroxy acid **7**, which rapidly relactonized to **8** in presence of mineral acid.

Solandelactone:

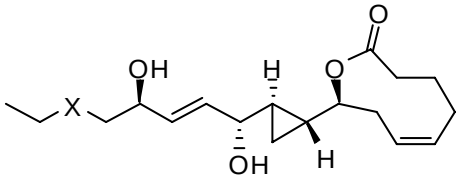
Solandelactones A-H (**21**), belonging to a growing class of cyclopropane ring containing fatty acid lactones of marine origin, were isolated from the hydroid *Solanderia secunda* of the Korean coast.[19] The structures of this compound and their absolute stereochemistry have been determined by exhaustive spectral and chemical studies. Thus, solandelactones, having a central *trans*-substituted cyclopropane unit with an eight-membered lactone ring to the right hand side and hydroxy group containing alkenyl chain on the left were found to be structurally similar to some of

the other marine derived oxylipins, *viz,* constanolactones (**9**), halicholactone (**22**) and neohalicholactone (**23**).

Figure 5: *Solandelactones and related compounds*



R^1= H, R^2= OH; R^1= OH, R^2= H
Solandelactones A-H (**21**)



X= -CH_2-CH_2- ; Halicholactone(**22**)
X= -CH_2=CH_2- ; Neohalicholactone(**23**)

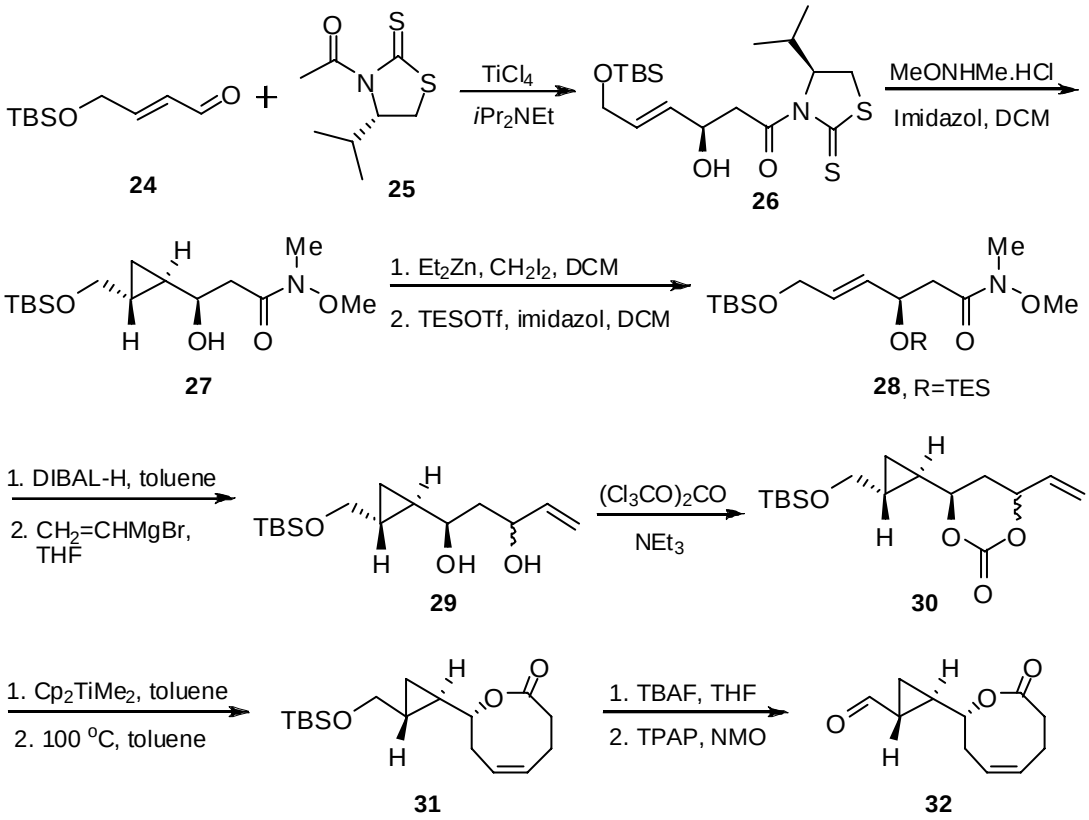
However, while the above compounds are of eicosanoid origin containing a six or nine-membered lactone ring respectively, solandelactones with an eight-membered lactone ring and of C22 skeletal framework are thought to be derived from docosanoid precursors. Another notable difference is the opposite absolute stereochemistry across the cyclopropane ring in solandelactones compared to the other oxylipins.

White's Approach for synthesis of Solandelactones:

In 2007, White accomplished the asymmetric total synthesis of solandelactone E and F for the confirmation of stereochemistry of solandelactones.[20] In their total synthesis the key steps involved a Nagao asymmetric acetate aldol reaction, Simmons-Smith cyclopropanation, a Holmes-Claisen rearrangement to establish the unsaturated octalactone, and a Nozaki-Hiyama-Kishi coupling to connect two major fragments.

Treatment of aldehyde **24**, prepared from *cis*-2-butene-1,4-diol, with the enolate from thionothiazolidine **25** gave (*R*)-hydroxy amide **26**. Exposure of **26** to *N*,*O*-dimethylhydroxylamine cleaved the auxiliary and led to Weinreb amide **27**. When **27** was subjected to Simmons-Smith cyclopropanation followed by TES protection, **28** was produced as a single isomer. Amide **28** was reduced to aldehyde, which was reacted with vinylmagnesium bromide to yield allylic alcohol **29** as 1:1 mixture of stereoisomers. Compound **29** was first converted to cyclic carbonate **30** with triphosgene followed by Claisen rearrangement with Petasis' reagent in hot toluene to produce lactone **31**. Cleavage of the silyl ether from **31** and oxidation of the resultant alcohol gave aldehyde **32**.

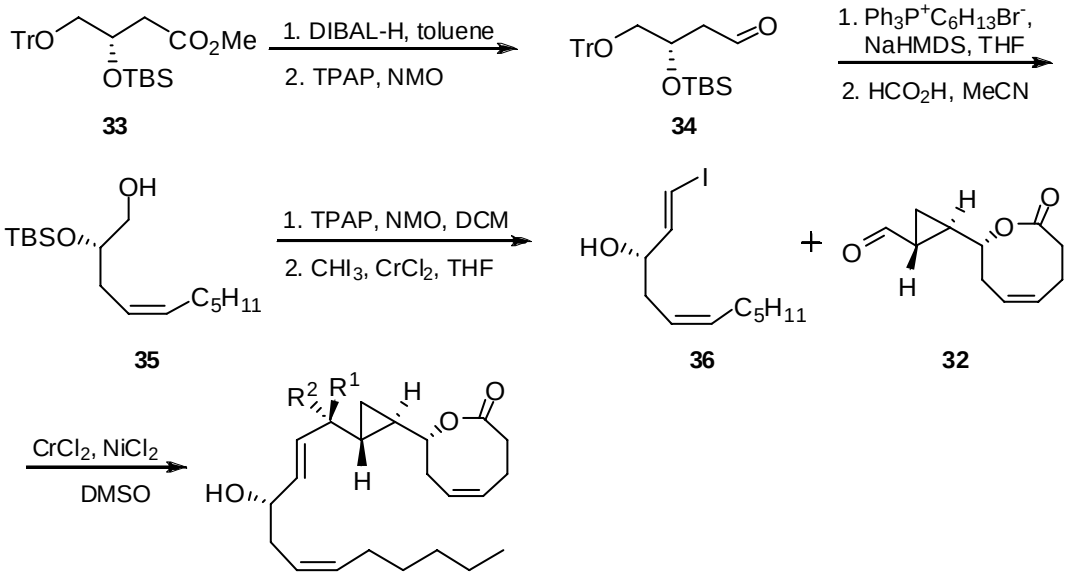
Scheme 3:



Synthesis of the acyclic segment of the solandelactones commenced from compound **33**, which was reduced to alcohol by using DIBAL-H (Scheme 4). Subsequent oxidation yielded an unstable aldehyde **34** that underwent Wittig olefination with hexyltriphenylphosphonium bromide followed by removal of the trityl protection to furnish alcohol **35**. The oxidation of resultant alcohol **35** gave an aldehyde, which upon Takai-Utimoto reaction with iodoform led to iodoalkene that on subsequent removal of silyl ether yielded vinyliodo derivative **36** as the coupling partner for **32**.

The reaction of **36** with **32** under Nozaki-Hiyama-Kishi conditions led to a 3.5:1 mixture of isomeric alcohol **21e** and **21f**. The major *R*-alcohol **21e** is the solandelactone-E. Similarly; the minor *S*-alcohol **21f** was identified as solandelactone-F.

Scheme 4:



21e. R^1= H, R^2= OH; Solandelactone E
21f. R^1= OH, R^2= H; Solandelactone F

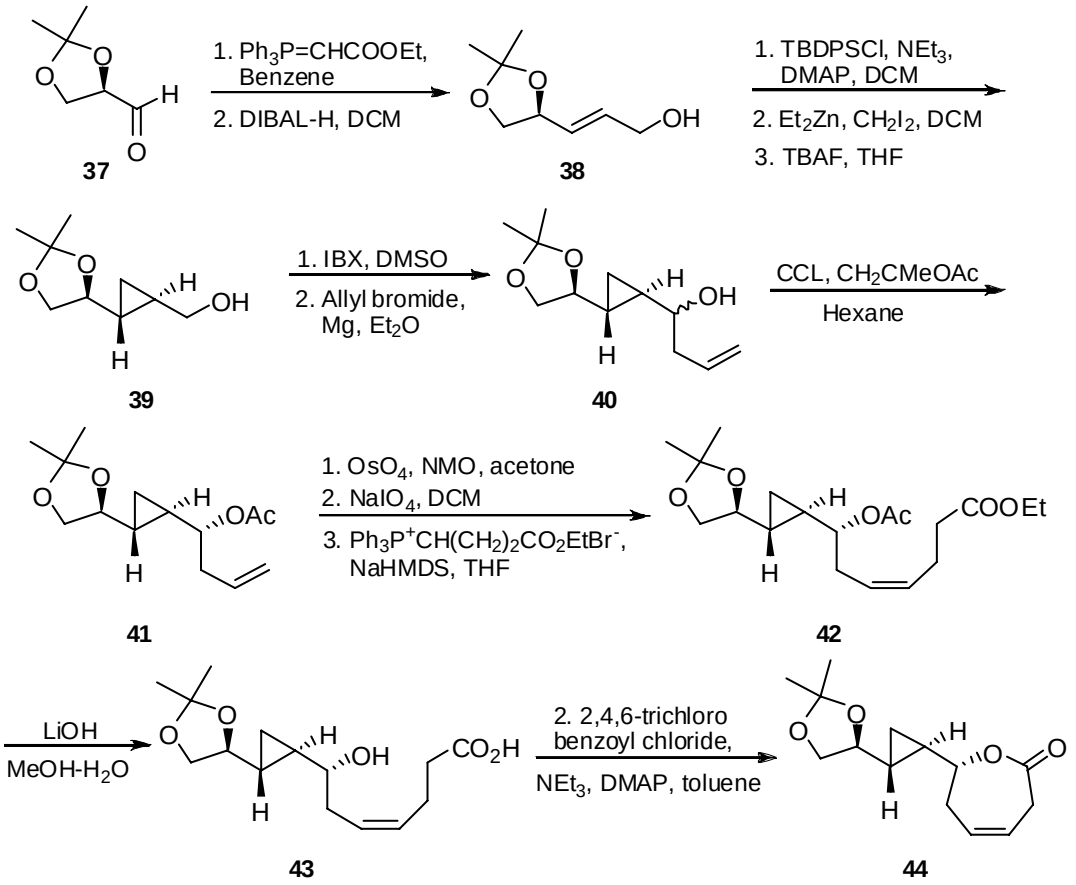
Datta's Approach for synthesis of C1-C11 fragment of Solandelactone:

Datta's group has developed a stereoselective route to the right hand fragment of solandelactones[21] starting from an easily available (*R*)-glyceraldehyde derivative. Their strategy involved i) initial stereodefined synthesis of a pivotal bifunctional cyclopropane moiety and ii) construction of the required lactone ring on the preformed cyclopropane unit.

The (*R*) –glyceraldehyde acetonide **37** was first converted to allyl alcohol **38** by two carbon Wittig reaction followed by reduction. Protection of the hydroxy group in **38** as its TBDPS ether and modified Simmons- Smith cyclopropanation followed by deprotection of the silyl ether gave the cyclopropane derivative **39**. Oxidation by IBX of the primary alcohol in **39** and reaction of the resultant aldehyde with allylmagnesium bromide afforded the alcohol **40** as a diastereomeric mixture, which are difficult to separate by column chromatography. Hence the isomeric mixture of alcohols **40** was subjected to *Candida cylindracea lipase* (CCL) catalyzed enzymatic resolutions, which provided the corresponding acetate **41** while other unreacted isomer of alcohol was removed by column chromatography. Degradative oxidation of the olefin from **41** to aldehyde followed by a *cis*-selective Wittig reaction with the reagent derived from 4-carboethoxybutyltriphenylphosphonium bromide in presence of NaHMDS at –78 °C

yielded the corresponding ester **42**. Simultaneous deprotection of the ester functionalities gave the lactone precursor seco-acid **43**.

Scheme 5:



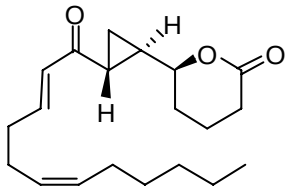
Finally, lactonization of the compound **43** under Yamaguchi conditions afforded the eight-membered lactone **44**, thereby culminating in an efficient synthesis of the targeted right hand fragment of solandelactones.

The interesting structural features and potent biological activity of this class of compounds have attracted the attention of a number of organic chemists worldwide. Presence of cyclopropyl group bearing two stereocenters linked to lactones of varying ring sizes is one of the prominent structural features of this class of oxylipins. To expedite current pharmaceutical evaluations of eicosanoid family, we initiate studies toward the synthesis of these eicosanoids and here we describe the designed general synthetic strategy for the synthetic studies toward total synthesis of the eicosanoid **8** and solandelactone **21**.

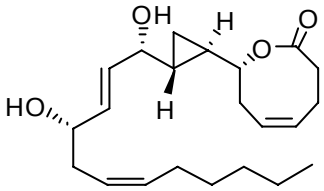
PRESENT WORK

As a part of defense mechanism, marine organisms produce a fascinating range of secondary metabolites endowed with unusual and unexpected biological profiles. The arachidonic acid pathway in marine organisms provided a number of oxylipins[22] such as eicosanoid (**1**), solandelactone (**2**), Constanolactones (**3**), Halicolactone (**4a**) and Neohalicolactone (**4b**) containing the cyclopropyl-lactone groups (Figure 1). These are belonging to the growing class of oxylipins containing a *trans*-bifunctional cyclopropane ring and fatty acid lactones of marine origin.[23]

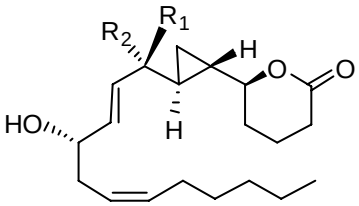
Figure 1: *Structures of some cyclopropane ring containing oxylipins*.



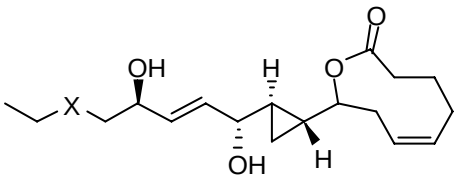
Eicosanoid (**1**)



Solandelactone (**2**)



R^1= H, R^2= OH; Constanolactone A(**3a**)
R^1= OH, R^2= H; Constanolactone B(**3b**)



X= $-CH_2-CH_2-$ Halicolactone (**4a**)
X= -CH=CH- Neohalicolactone(**4b**)

Taking into consideration the similarity in the structures of various cyclopropyl oxylipins of eicosanoid family, it was thought to design a general synthetic strategy, which would be useful to synthesize cyclopropyl oxylipin member of this family by making subtle changes in the substrates. Presence of cyclopropyl group bearing two stereocenters linked to lactones of varying ring sizes is one of the prominent structural features of this class of oxylipins.

Since the stereo-control in the installation of cyclopropyl group using Simmons-Smith cyclopropanation method was well established[24] on the closely related substrates, it was thought to exploit the same method. The lactone ring in the molecule was envisaged by employing the ring closing metathesis (RCM) reaction

of suitable diene ester. Variation in the number of carbons in diene ester would enable us to synthesize different ring sizes of lactones by ring closing metathesis reaction. Taking into account the biological activities of cyclopropyl oxylipins, it was decided to undertake the total synthesis of eicosanoid and formal total synthesis of solandelactone to evaluate the proposed synthetic strategy.

Eicosanoid (**1**) was isolated[25] by the incubation of arachidonic acid with an acetone powder of the Caribbean soft coral *Plexaura homomalla*. Structure and absolute configuration of eicosanoid (**1**) was determined on the basis of extensive spectroscopic analysis and degradation studies, and were later confirmed by its total synthesis.

Solandelactone (**2**) was isolated[26] from the hydroid *Solanderia secunda* of Korean waters and their structures were elucidated by exhaustive spectroscopic and chemical methods. The solandelactones have an eight-membered lactone, saturated or unsaturated, linked to a cyclopropane moiety. A noteworthy difference between solandelactone (**2**) and eicosanoids (**1**) is that the latter is C20 presumably derived from arachidonic acid, whereas all of the solandelactones contain 22 carbons. In conjunction with other marine fatty acid metabolites,[27] eicosanoid (**1**) and solandelactone (**2**) also incorporate a cyclopropane-lactone motif and exhibit lipoxygenase inhibiting activity and therefore provoked a considerable synthetic interest.[28] To expedite current pharmaceutical evaluations of this family, we attempted a synthetic study towards total synthesis of Eicosanoid (**1**) and Solandelactone (**2**).

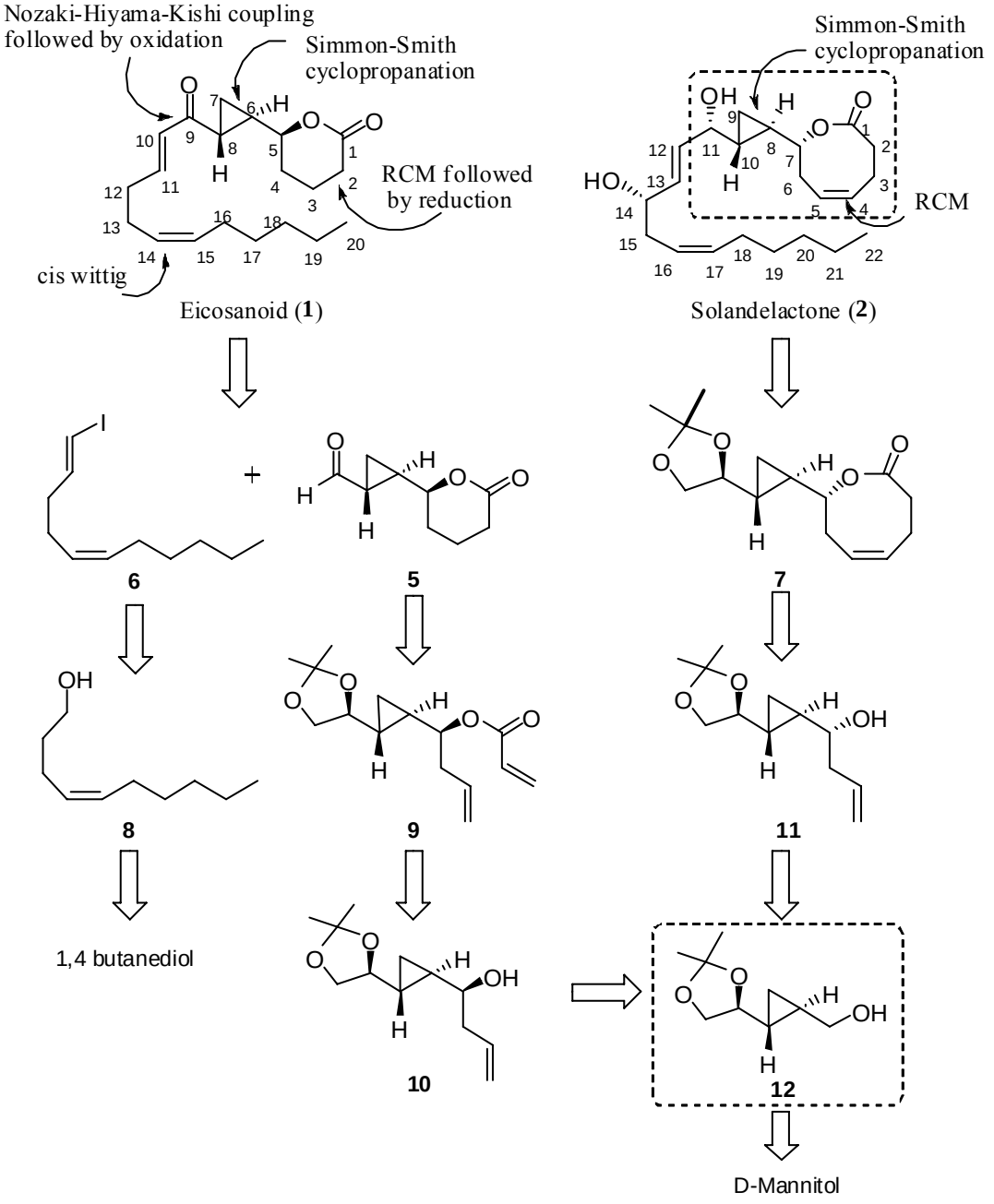
Retrosynthetic Analysis:

The salient feature of the structures of eicosanoid (**1**) and solandelactone (**2**) is the presence of a cyclopropyl ring linked with lactone moiety along with three stereogenic centers. The two carbons of cyclopropane ring constituted the two of the three stereo-centers present in the molecule. Thus it was planned to synthesize both, eicosanoid (**1**) and solandelactone (**2**), from a common intermediate. The basic strategy for the synthesis of eicosanoid (**1**) and solandelactone (**2**) is delineated in the retrosynthetic analysis (Figure 2).

An appealing strategy for the synthesis of eicosanoid was envisaged by the installation of C10-C20 side chain using Nozaki-Hiyama-Kishi coupling reaction[29] between aldehyde **5** and vinyl iodide **6** followed by oxidation. Six-membered

lactone ring of **5** could be installed using ring closing metathesis[30] approach followed by reduction from diene **9**. In the synthetic direction, it was anticipated that the diene precursor **9** required for RCM could be obtained from homoallylic alcohol **10** by *O*-acylation. Side chain **6** could be derived from alcohol **8** by oxidation followed by Takai reaction, which in turn could be prepared from 1,4-butanediol.

Figure 2: *Retrosynthetic strategy for eicosanoid and solandelactone*



Similarly, solandelactone (**2**) was envisaged from coupling of C12-C22 side chain with the C1-C11 fragment. Towards the total synthesis of solandelactone, the synthesis of crucial intermediate **7** was our immediate target. Its retrosynthetic

analysis was proposed along with eicosanoid as depicted in Figure 2. In line with the proposed general strategy, intermediate **7** could be synthesized from homoallylic alcohol **11** using tactical combination of reactions like acylation and ring closing metathesis.

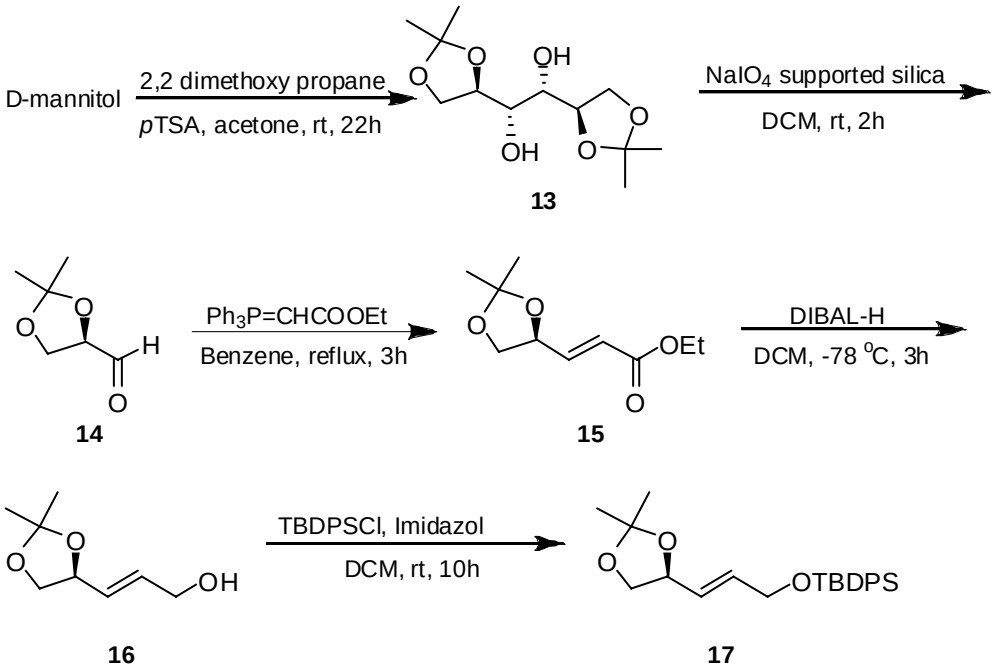
The epimeric homoallylic alcohols **10** and **11** would result from allyl Grignard reaction on corresponding aldehyde, which would be procured by oxidation of cyclopropyl alcohol **12**. The retrosynthetic analysis outlined in Figure 2 identified compound **12** as a potential synthetic intermediate and its synthesis would be the first milestone of the synthetic objective in the total synthesis of eicosanoid (**1**) as well as solandelactone (**2**). Cyclopropyl ring with appropriate stereochemistry in **12** could be installed using Simmons-Smith cyclopropanation.[3] For that task, (*R*)-glyceraldehyde acetonide was chosen as an appropriate precursor, which could be easily obtained from D-mannitol in two steps.

Synthesis of homoallylic alcohol 10:

Our synthetic endeavor began with the preparation of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**13**) from cheaply available D-mannitol employing literature procedure[31] (Scheme 1). The spectroscopic and other analytical data of **13** was found in accordance with the reported data.[31] Compound **13** was subjected to cleavage using $NaIO_4$ supported on silica gel in DCM at an ambient temperature to afford corresponding aldehyde **14**. Subsequently the crude aldehyde **14** was refluxed with ethoxycarbonylmethylenetriphenylphosphorane in benzene to afford unsaturated ester derivative **15**. In the ^{1}H NMR spectrum of **15** the two signals appearrd at δ 6.08 (d) and 6.86 (dd) integrating for one proton each indicated the olefinic protons. In the ^{13}C NMR spectrum, the two olefinic carbons resonated at δ 122.1 and 150.1 while carbonyl carbon resonated at 170.2 ppm. The other analytical data such as mass spectrum, elemental analysis and IR spectrum supported the structure **15**. The ester functionality in compound **15** was reduced to alcohol by treatment with DIBAL-H in DCM at −78 ^{o}C within 3 h to procure allylic alcohol **16**. The peaks due to ethyl ester group were found to be absent in the ^{1}H NMR spectrum of **16** and the peak at δ 4.12 integrating for two protons accounting for newly generated methylene group appeared which indicated the desired product. The

highest molecular ion peak at *m/z* 181 for $[M+Na]^+$ and satisfactory elemental analysis also supported the structure of **16**.

Scheme 1:

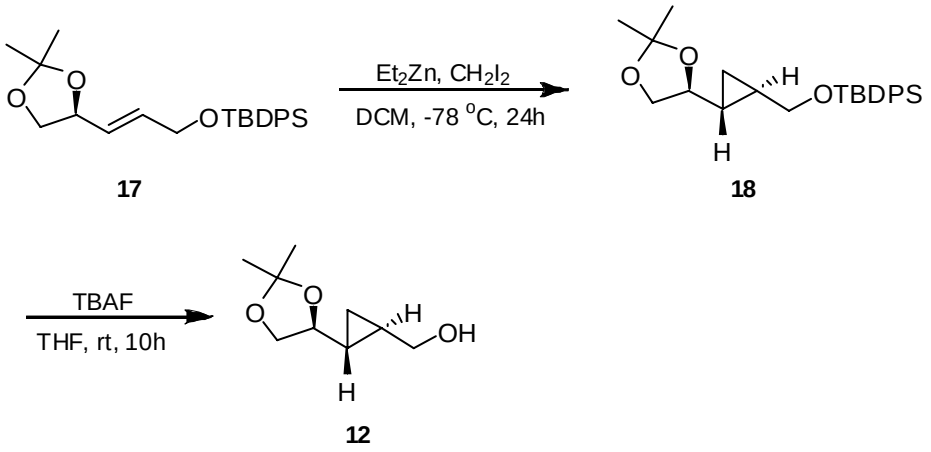


The next step in the synthesis was the stereoselective cyclopropanation. The Simmons-Smith reaction is the most widely used method for the stereoselective cyclopropanation of olefins. The diastereoselectivity of cyclopropyl product was dependent on the protecting group on the terminal allylic oxygen (TBDPS > MOM > Bn) and on the stereochemistry of the double bond (*Z*>*E*). Examination of the literature[32] revealed that when the TBDPS group was used to protect the hydroxyl group, cyclopropyl product was obtained as a single diastereomer. Accordingly, the free hydroxyl group of **16** was protected as its TBDPS-ether using TBDPSCl and imidazole in DCM at room temperature to afford compound **17** (Scheme 1). In the ^{1}H NMR spectrum of **17** signals due to TBDPS-group were observed at δ 0.98 (s, 9H) and 7.30-7.54 (m, 10H). The structure was further supported by the mass spectrum with the highest mass peak at *m/z* 419 $[M+Na]^+$. Other analytical data was also found in accordance with the proposed structure.

Gratifyingly, cyclopropanation of compound **17** was accomplished by employing modified Simmons-Smith cyclopropanation. Reaction of **17** with Et_2Zn and diiodomethane in DCM at -78 °C to -10 °C for 24 h furnished cyclopropane derivative **18** in quantitative yields and with >98% de (Scheme 2). In the ^{1}H NMR spectrum of **18**, the signals due to cyclopropane protons resonated at δ 0.54 (m, 2H)

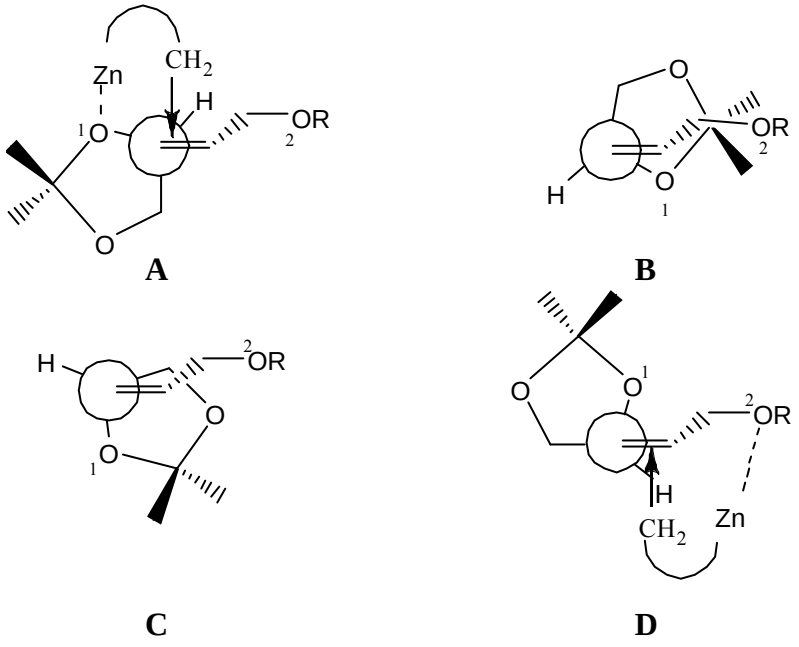
and 0.82 (m, 2H) while in the ^{13}C NMR spectrum cyclopropyl carbons appeared at δ 7.6, 17.5 and 19.8 ppm. The absolute stereochemistry of **18** was assigned as 1*R*, 2*S* on the basis of a comparison of its specific rotation value ($[\alpha]_D$ −7.7) with that in the literature[33] ($[\alpha]_D$ −7.9). Other analytical data was also in accordance with the structure.

Scheme 2:



The selectivity in cyclopropanation was elucidated on the basis of the possible conformers in transition state of **17** (Figure 3). Chelation-controlled positioning of the reagent[34] has been proposed to account for the diastereoselectivity of the Simmons-Smith cyclopropanation reaction of allyl alcohols and ethers.

Figure 3: *Possible conformers in transition state models of cyclopropanation of **17**.*

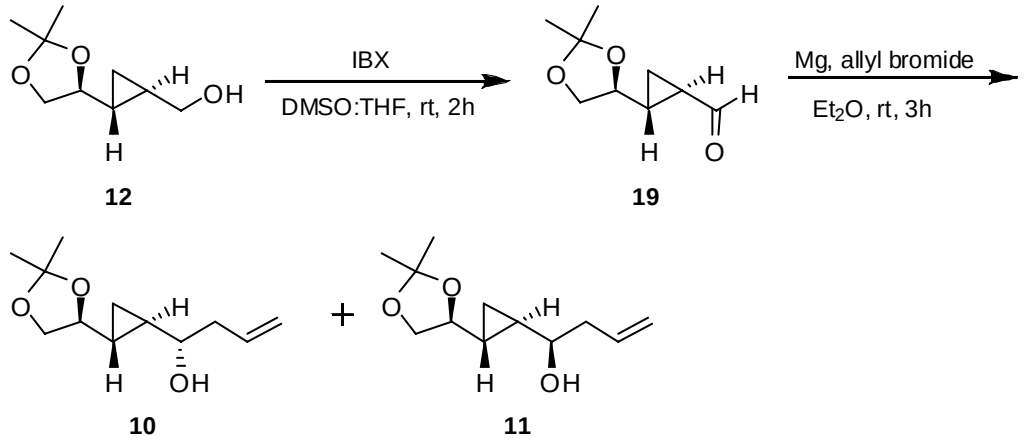


Four conformers, **A-D**, are considered as possible transition state models for **17** (Figure 3). Conformers **A** and **D** are considered to be more favorable than conformers **B** and **C** because of steric repulsion between the dioxolane ring and TBDPS group. In conformer **A**, coordination of the reagent to the allylic oxygen (*O*-1) of the dioxolane ring and methylene (carbene) transfer from the less-hindered face (top face, 1*Re*-2*Si*) of the double bond would provide the major cyclopropane product. The reduction in the diastereoselectivity may be ascribed to reaction through conformer **D** *via* coordination of the reagent to *O*-2 but bulky TBDPS ethers rule out coordination of the reagent to *O*-2 and henceforth lessen the possibility of decease in diastereoselectivity. As expected, the cyclopropanation of TBDPS-protected **17** proceeded through conformer **A** and results with high diastereoselectivity to give cyclopropane product **18** (>98% de).

The silyl ether in **18** was deprotected by using TBAF in THF at room temperature to afford the cyclopropyl alcohol **12**. In the ^{1}H NMR spectrum of **12** the characteristic peaks due to TBDPS group were absent and cyclopropyl protons resonated at δ 0.63 (m, 2H), 0.87 (m, 1H) and 1.01 (m, 1H). The ^{13}C NMR spectrum was in accordance with the expected structure. In addition, elemental analysis was in agreement with the calculated values. The optical rotation of compound **12** was found to be in agreement with the reported[12] value $[\alpha]_D$ +16.5 (*c* 1.25, $CHCl_3$); lit. $[\alpha]_D$ +16.7 (*c* 1.25, $CHCl_3$), which confirmed the stereochemistry of cyclopropyl alcohol **12**.

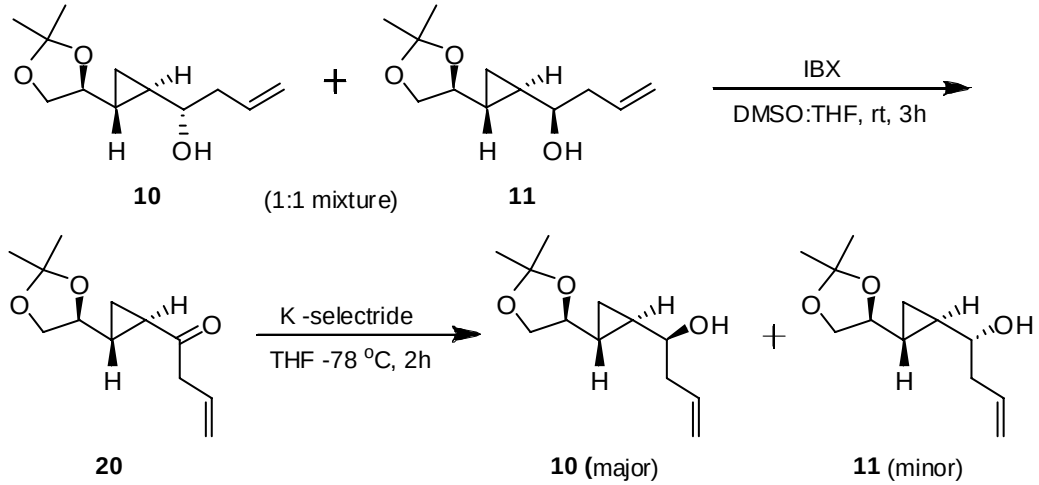
Compound **12** was then subjected to mild oxidation condition using 2-Iodoxybenzoic acid (IBX)[35] to afford the aldehyde **19** (Scheme 3). In the ^{1}H NMR spectrum of **19** the aldehyde proton resonated at δ 9.18 (d) while in the ^{13}C NMR spectrum aldehyde carbonyl carbon appeared at 194.9 ppm. Addition of aldehyde **19** to allylmagnesium bromide in diethyl ether provided the homoallyl alcohols **10** and **11** as 1:1 diastereomeric mixture in 87% yield, separable with difficulty by repeated column chromatography. The problem in the separation of alcohols **10** and **11** by column chromatography prompted us to look for other methods as **10** and **11** were the key intermediates for the syntheses of eicosanoid and solandelactone. For this task it was decided to obtain one of the homoallylic alcohol selectively by subjecting the mixture of homoallylic alcohols to oxidation followed by selective reduction using chiral reagents.[36]

Scheme 3:



Hence, the mixture of homoallyl alcohols **10** and **11** was oxidized using IBX in DMSO:THF at room temperature to provide keto compound **20** (Scheme 4). In the ^{1}H NMR spectrum of **20**, the peaks due to cyclopropyl group shifted downfield indicating the change in electronic environment in the vicinity of cyclopropyl group by the presence of ketone functionality while signals due to allyl group were observed at δ 3.32 (dd, *J* = 1.5, 6.2 Hz, 2H), 5.19 (m, 2H) and 5.93 (m, 1H). In the ^{13}C NMR spectrum of **20**, the signal due to carbonyl carbon was observed at 206.7 ppm. The structure of keto compound was also supported by mass spectrum accounting highest molecular ion peak at 233 for $[M+Na]^{+}$.

Scheme 4:

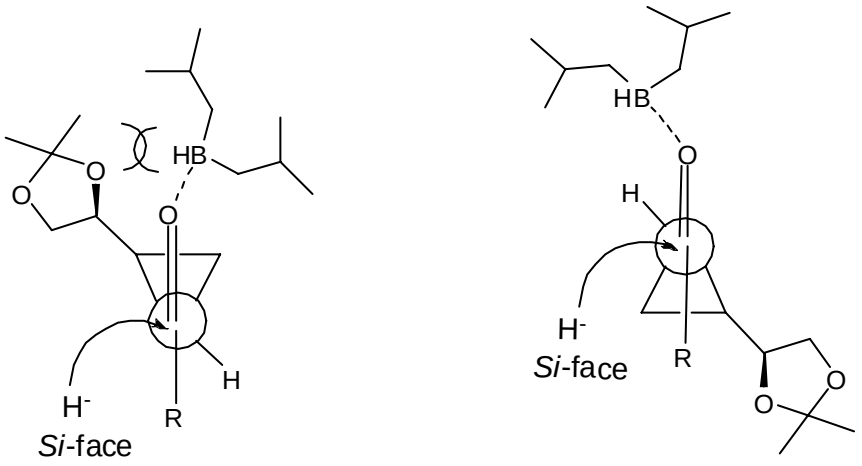


Further, when the keto compound **20** was subjected to selective reduction with K-selectride provided the major homoallyl alcohol isomer **10** (>90%) along with isomer **11** (<10%). These diastereomers were separated by column chromatography to afford pure homoallylic alcohols **10** and **11** (Scheme 4). Both the isomers were characterized by the spectral as well as other analytical methods. In the

^{1}H NMR spectrum of **10**, signals due to allyl group appeared at δ 2.32 (m, 2H), 5.13 (m, 2H) and 5.86 (m, 1H). In the ^{13}C NMR spectrum signals due to allyl group carbons resonated at δ 41.7, 118.0 and 134.3 ppm while newly generated hydroxyl bearing carbon (C-2) resonated at 79.1 ppm. Other analytical data also supported the structure of **10** beyond any doubt. Similarly, the minor isomer **11** was also characterized using the ^{1}H and ^{13}C NMR spectral data. In the ^{1}H NMR spectrum of **11** signals due to allyl group appeared at δ 2.33 (m, 2H), 5.15 (m, 2H) and 5.84 (m, 1H). Also in the ^{13}C NMR spectrum signals due to allyl group carbons resonated at 41.7, 117.9 and 134.4 ppm while newly generated hydroxyl bearing carbon (C-2) resonated at 79.1 ppm. Other analytical data also supported the structure of **11**.

The selectivity in reduction was rationalized on the basis of chelation controlled Cram's model[36] (Figure 4).

Figure 4: *Conceivable transition states of the hydride reduction of cyclopropyl ketones*



S-(*cis*) *S*-(*trans*)

Interaction between cyclopropyl C-C bonds and carbonyl π orbitals is maximized when the cyclopropyl and carbonyl groups are oriented orthogonally. Both the bisect (*S*)-(*cis*) and (*S*)- (*trans*) conformations are able to provide maximum stabilization. Mark Lautens *et al*. reported[36] that treatment of tributylsilyl cyclopropyl ketone with $LiBH_4$ resulted in a diastereomeric mixture of 2.5:1 and explained the stereoselectivity by proposing the following (*S*)-(*cis*) model. But S. Shuto and co-workers reported[36] the reverse stereoselectivity with DIBAL-H and it was explained by (*S*)-(*trans*) model. When DIBAL-H is coordinated to the carbonyl group, due to stearic repulsion between the two bulky isobutyl group and the substituent in the cyclopropyl group, (*S*)-(*trans*) conformation is preferred. The same

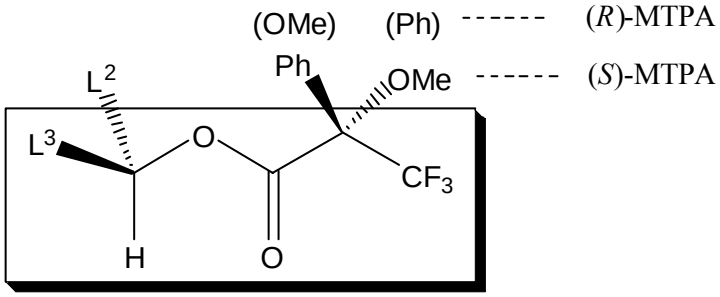
argument holds true in the case of K-selectride, which demands a lot of steric repulsion due to its three *sec*-butyl groups. The major *S*-isomer (**10**) was the result of the hydride attack from the less hindered *Re*-face in the (*S*)-(*trans*) conformation.

The stereochemistry at newly created chiral center was assigned following modified Mosher's method.[37] For this purpose we used the minor isomer **11** for Mosher's study. It is obvious that the establishment of the stereochemistry of minor isomer would ultimately prove the stereochemistry of major isomer **10**.

A brief review on Modified Mosher's ester method:

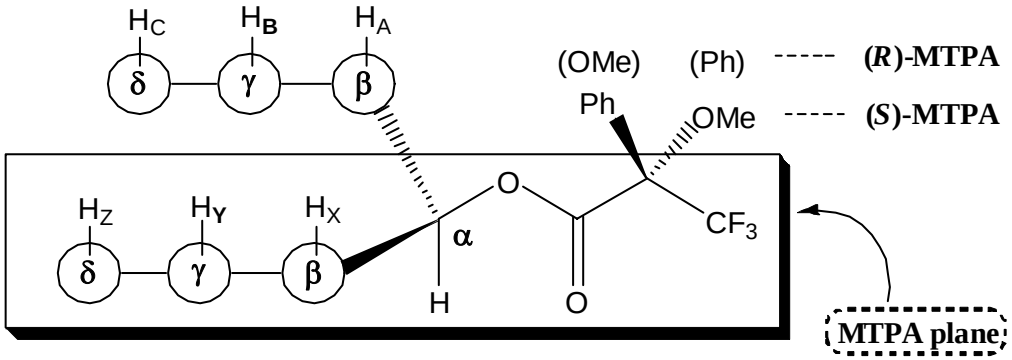
Determination of the absolute stereochemistry of organic compounds has become an important aspect for natural product chemists as well as synthetic chemists. The limitations involved in physical methods such as exciton chirality method and X-ray crystallography forced synthetic chemists for a more reliable alternative. Although there are several chemical methods used to predict the absolute configuration of organic substances, Mosher's method using 2-methoxy-2-phenyl-2-(trifluoromethyl)acetic acid (MTPA) esters has been most frequently used. Mosher proposed that, in solution, the carbinyl proton, ester carbonyl and trifluoromethyl group of the MTPA moiety lie in the same plane (Figure 5).[38]

Figure 5: *Configurational correlation model for (R)–MTPA and (S)–MTPA derivatives proposed by Mosher.*



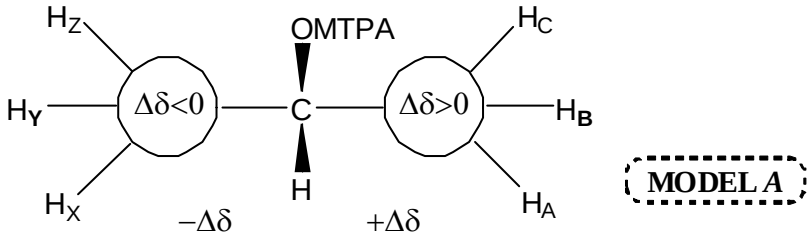
When the MTPA group is in the hypothesized conformation, Mosher pointed out that the ^1H NMR signal of L^2 of the (R)-MTPA ester will appear upfield relative to that of the (S)- MTPA ester due to the diamagnetic effect of the benzene ring. The lack of reliability associated with Mosher's ^{19}F method using ^{19}F NMR motivated Kakisawa et al. to elaborate this concept for more accuracy.[39] *The modified Mosher's ester method is one of the simple and efficient ways to determine the absolute stereochemistry of the secondary alcohols and amine stereo centers in organic molecules.*

Figure 6: *MTPA plane of an MTPA ester is shown. $H_{A,B,C,....}$ and $H_{X,Y,Z,....}$ are on the right and left side of the plane respectively.*



The basic concept of the modified Mosher's ester method is essentially the same as Mosher proposed. The idealized conformation is depicted in Figure 6. The plane and the conformation of MTPA group will be called as the MTPA plane and ideal conformation respectively. Due to the diamagnetic effect of the benzene ring, the $H_{A,B,C...}$ signals of (R)-MTPA ester in the ^1H NMR spectrum should appear upfield to those of the (S)-MTPA ester. The reverse should hold true for $H_{X,Y,Z.....}$ Hence, when $\Delta\delta = (\delta S - \delta R) \times 1000$ protons on the right side of the MTPA plane must have positive values ($\Delta\delta > 0$), and the protons on the left side of the MTPA plane must have negative values ($\Delta\delta < 0$). This is illustrated in model A (Figure 7).

Figure 7: *A view of MTPA ester drawn in Figure 6 from the direction indicated by outlined arrow to determine the absolute configuration of secondary alcohol.*

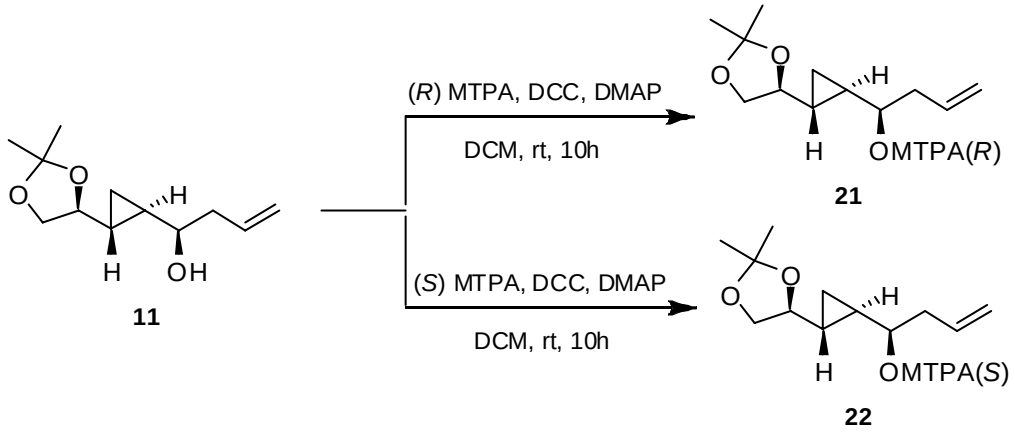


According to Kakisawa and coworkers,[39] the Mosher's method can be extended as follows: (i) assign as many proton signals as possible with respect to each of the (R)- and (S)- MTPA esters (ii) obtain $\Delta\delta$ values for the protons (iii) arrange the protons with positive $\Delta\delta$ values right side and those with negative $\Delta\delta$ values on the left side of the model (iv) construct a molecular model of the compound in question and confirm that all the assigned protons with positive and negative $\Delta\delta$ values are actually found on the right and left sides of the MTPA plane respectively. When these conditions are all satisfied, model A will represent the correct absolute configuration of the compound.

Application of Mosher's method for stereochemical assignment of C_6-OH of 11:

According to the Mosher's method, in order to assign the absolute stereochemistry of the homoallyl alcohol **11** at C-6, the (*R*)- MTPA ester **21** and (*S*)-MTPA ester **22** were independently prepared from **11** by using corresponding (*R*)-MTPA and (*S*)-MTPA in presence of coupling agent DCC and DMAP (cat.) in anhydrous DCM at room temperature (Scheme 5).

Scheme 5:

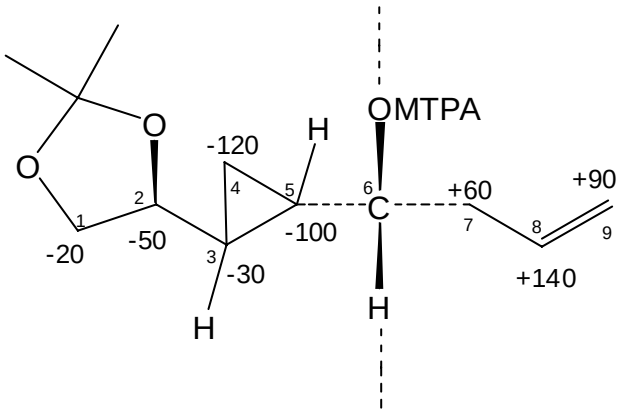


The $\Delta\delta = (\delta S - \delta R)$ x 1000 values were calculated for as many protons as possible from the ^{1}H NMR spectrum of (*R*)-MTPA ester **21** and (*S*)-MTPA ester **22** (Table 1). Then, a molecular model of the compound was constructed and the $\Delta\delta = (\delta S - \delta R)$ x 1000 values were uniformly arranged as shown in Figure 8.

Table 1: *δS, δR and Δδ values of (R)-MTPA ester **21** and (S)-MTPA ester **22***

Protons	H-1	H-2	H-3	H-4	H-5	H-6	H-7	H-8	H-9
δS	3.59	3.98	0.77	0.94	0.64	4.67	2.50	5.75	5.15
δR	3.61	4.03	0.80	1.06	0.74	4.60	2.44	5.61	5.06
$\Delta\delta$	-20	-50	-30	-120	-100	+70	+60	+140	+90

Figure 8: $\Delta\delta = (\delta S - \delta R) \times 10^3$ *for (R) - and (S)-MTPA esters of compound **11**.*

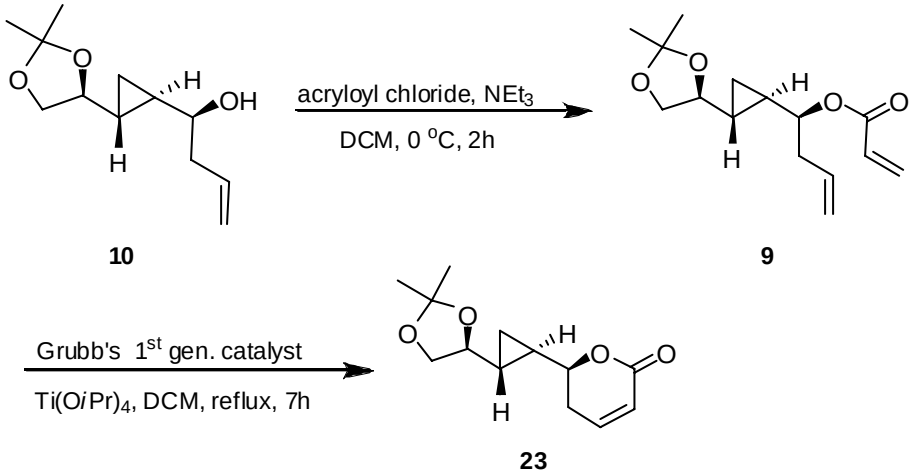


The analysis of the ^{1}H NMR spectral data of both the compound **21** and **22** showed negative chemical shift differences ($\Delta\delta = \delta S - \delta R$) for the protons at C1 to C5 while protons at C7 to C9 showed positive chemical shifts differences. According to Mosher's method we arranged alcohol **11** as shown in figure 8. On the basis of the model (Figure 8) we have assigned the absolute stereochemistry of homoallyl alcohol **11** at C-6 as (*R*)-configuration. This ultimately proved that homoallyl alcohol **10** possesses the (*S*)-configuration. Thus, alcohol **10** was identified as the precursor of eicosanoid while alcohol **11** was to be used for the synthesis of solandelactone.

Synthesis of C1-C9 segment of Eicosanoid (1):

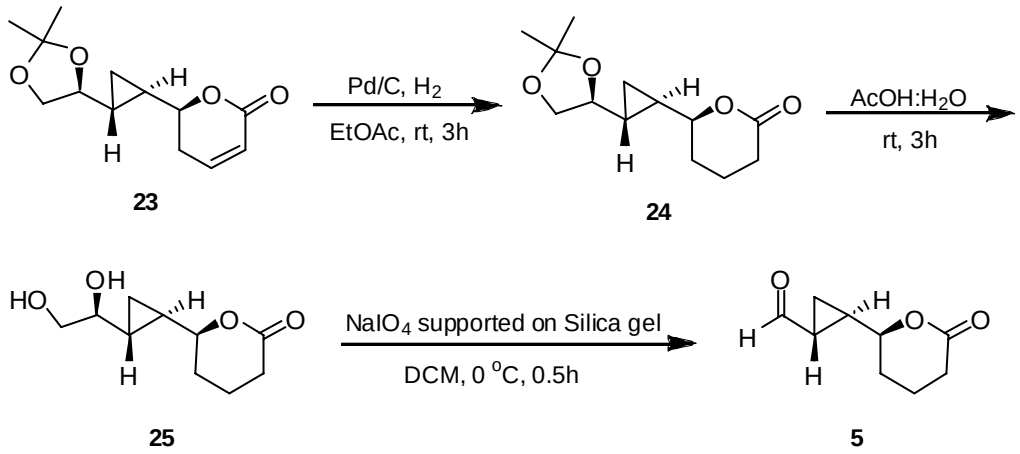
Having secured the absolute configuration of homoallyl alcohol **10** at C6 beyond doubt, we focused our attention on the building of the C1-C9 segment through construction of six membered lactone ring. The homoallyl alcohol **10** was then treated with acryloyl chloride in DCM in presence of triethyl amine at 0 ^{o}C to afford the diene **9** (Scheme 6). In the ^{1}H NMR spectrum of diene **9** the olefinic protons resonated at δ 5.09 (m, 2H), 5.80 (m, 2H), 6.10 (dd, 1H) and 6.39 (d, 1H), which confirmed the presence of two terminal olefin groups and hence the structure of **9**. In the ^{13}C NMR spectrum the four olefinic carbons resonated at δ 117.4, 128.5, 131.0 and 133.3 while carbonyl carbon appeared at 165.6 ppm. The structure of **9** was further supported by accounting the highest molecular ion peak at *m/z* 289 for $[M+Na]^+$ in mass spectrum. Other analytical data was in accordance with the proposed structure **9**.

Scheme 6:



With the diene **9** in hand, a stage was set for the application of ring closing metathesis reaction to obtain the lactone core, which would be a landmark towards the synthesis of eicosanoid. The attempts for ring-closing metathesis of diene derivative **9** under different reaction conditions using Grubbs' first generation catalyst ended up with poor yields of cyclized product **23** and recovery of the starting material. When the RCM reaction was tried with Grubbs' first generation catalyst in the presence of catalytic amount of titanium(IV) isopropoxide in refluxing dichloromethane under high dilution condition[40] furnished the lactone derivative **23** in good yield (Scheme 6). In the ^{1}H NMR spectrum of compound **23**, the frequency corresponding to olefinic protons appeared at δ 6.02 (d, J = 9.5 Hz), 6.87 (dt, J = 4.4, 9.5 Hz) integrating for one proton each. In the ^{13}C NMR spectrum the olefinic carbons resonated at δ 121.3 and 144.5 ppm while carbonyl appeared at 163.5 ppm. The elemental analysis substantiated the proposed structure. In the mass spectrum the peak was observed at *m/z* 261 corresponding to $[M+Na]^{+}$ of compound **23**.

Scheme 7:



23 **24** **25** **5**

The compound **23** on mild hydrogenation using 10% palladium on charcoal in ethyl acetate furnished saturated lactone **24** in 94% yield (Scheme 7). The ^{1}H NMR and ^{13}C NMR spectral data of the product was found to be in excellent agreement with the proposed structure. The absence of the signals due to olefinic protons in the ^{1}H NMR spectrum of **24** was the evident for reduction of olefin. Mass spectrum of the product exhibited peak at *m/z* 263 $[M+Na]^{+}$. The ^{13}C NMR spectral data and elemental analysis also suggested the desired structure **24**.

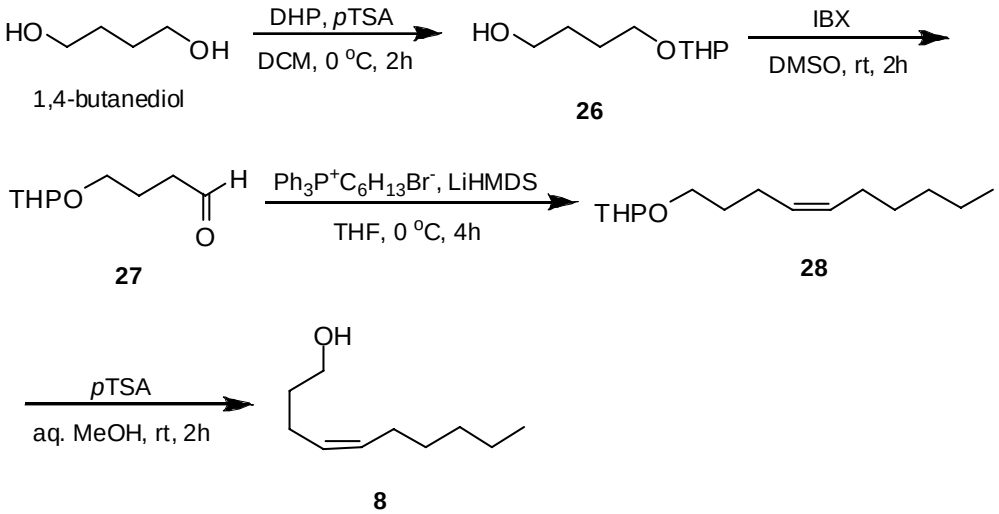
The next job was to remove isopropylidine protection selectively keeping the lactone ring intact. This was achieved by using 50% aqueous AcOH at room temperature to get diol **25**. The removal of the isopropylidine group was evident

from the ^{1}H NMR spectrum where signals due to the isopropylidine group were absent. The mass spectral data and elemental analysis also supported the structure of **25**. The diol **25** was cleaved using $NaIO_4$ supported on silica gel in DCM at 0 ^{o}C to furnish corresponding aldehyde **5** in 94% yield. In the ^{1}H NMR spectrum of **5**, the aldehyde proton resonated at δ 9.10 while in the ^{13}C NMR spectrum the carbonyl carbons resonated at 199.8 ppm. In the IR spectrum of **5** the carbonyl frequency appeared at 1732 cm^{-1}. Other analytical data was in accordance with the structure. This completes the synthesis of main core of eicosanoid.

Synthesis of C10-C20 side chain of Eicosanoid (6):

According to our retrosynthetic plan for the synthesis of C10-C20 side chain **6**, Takai reaction[41] conditions were to be employed on aldehyde derived from alcohol **8**, which in turn was to be prepared from 1,4-butanediol. In that direction, one of the hydroxyl groups of 1,4-butanediol was selectively protected as its THP-ether using DHP and catalytic *p*TSA in DCM at 0 ^{o}C to afford mono protected compound **26** (Scheme 8).

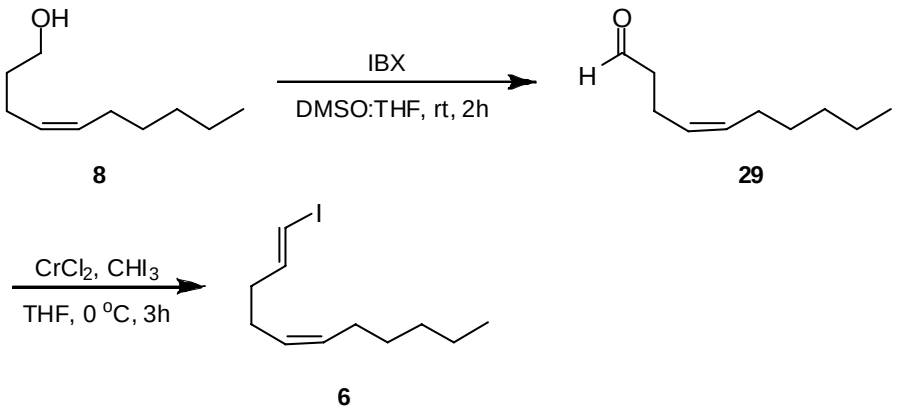
Scheme 8:



The free hydroxyl group of **26** was oxidized using IBX in DMSO at ambient temperature to provide aldehyde **27**. The aldehyde **27** treated with well stirred mixture of hexyltriphenylphosphonium bromide and LiHMDS in THF at 0 ^{o}C to afford the mixture of *cis* and *trans* isomers (85:15) of **28**. This mixture was separated by column chromatography and major *cis* isomer of compound **28** was taken for the next reaction. The THP ether in **28** was subsequently removed by the

action of *p*TSA in aqueous methanol to furnish alcohol **8**. The ^{1}H NMR and the ^{13}C NMR spectral data of **8** was in well agreement with the reported data.[41]

Scheme 9:

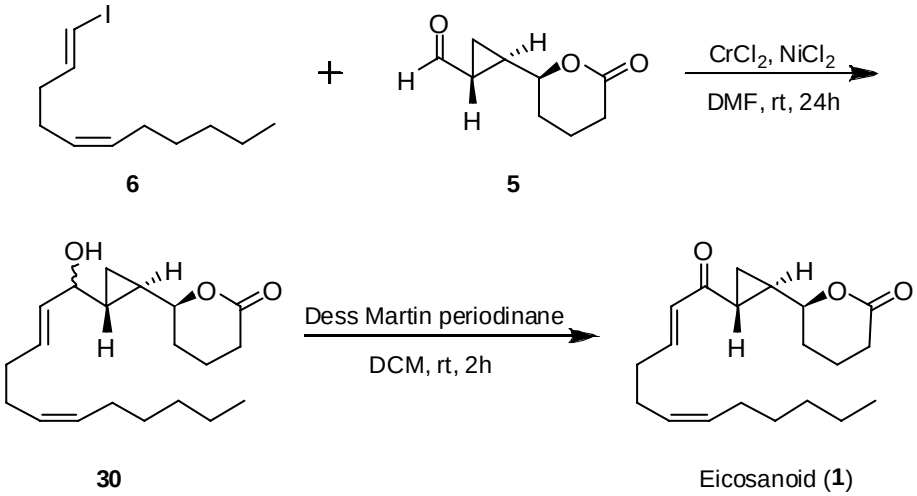


Our next concern was the synthesis of vinyl iodide using aldehyde **29** by employing Takai reaction conditions. Thus, oxidation of alcohol **8** with IBX in DMSO:THF at ambient temperature procured aldehyde **29**. The aldehyde **29** was treated with $CrCl_2$, CHI_3 in THF at 0 ^{o}C to furnish vinyl iodide **6**. In the ^{1}H NMR spectrum of **6**, the four olefinic protons resonated at δ 5.35 (m, 2H), 6.06 (d, J = 14.4 Hz, 1H) and 6.48 (m, 1H). In the ^{13}C NMR spectrum the olefinic carbons resonated at 75.0, 127.8, 131.4 and 145.8 ppm. Moreover the mass analysis supported the structure of **6** with the molecular ion peaks at *m/z* 279 for $[M+H]^{+}$ and 301 for $[M+Na]^{+}$. The elemental analysis and IR spectrum were in accordance with the structure. This completed the synthesis of C10-C20 side chain of eicosanoid.

Synthesis of Eicosanoid:

Having successfully achieved the synthesis of cyclopropyl-lactone main core **5** and side chain **6**, the final job of our endeavor was the introduction of the side chain on the cyclopropyl-lactone main core by employing Nozaki-Hiyama-Kishi reaction conditions as per our retrosynthetic plan. This was achieved smoothly by subjecting aldehyde **5** and vinyl iodo derivative **6** to $CrCl_2$ and catalytic $NiCl_2$ in DMF at room temperature to afford the coupled allylic alcohol **30**. The allylic alcohol **30** was found to be unstable and was used directly for the next reaction without purification. The total synthesis of eicosanoid (**1**) was completed by oxidation of the derived hydroxyl group in **30** by Dess-Martin periodinane[42] in DCM at an ambient temperature for 2 h (Scheme 10). The ^{1}H NMR and ^{13}C NMR spectral data of eicosanoid (**1**) were compatible with the reported data[43] (Table 2).

Scheme 10:



In addition, ESI-MS analysis indicated peaks at *m/z*: 319 and 341 accounting for $[M+H]^+$ and $[M+Na]^+$ respectively. The elemental analysis of **1** was satisfactory (Calcd. C, 75.43; H, 9.50% Found: C, 75.12; H, 9.83%). The optical rotation of **1** ($[\alpha]_D$ -25.8) was also found to be in agreement with reported value[43] ($[\alpha]_D$ -27.4).

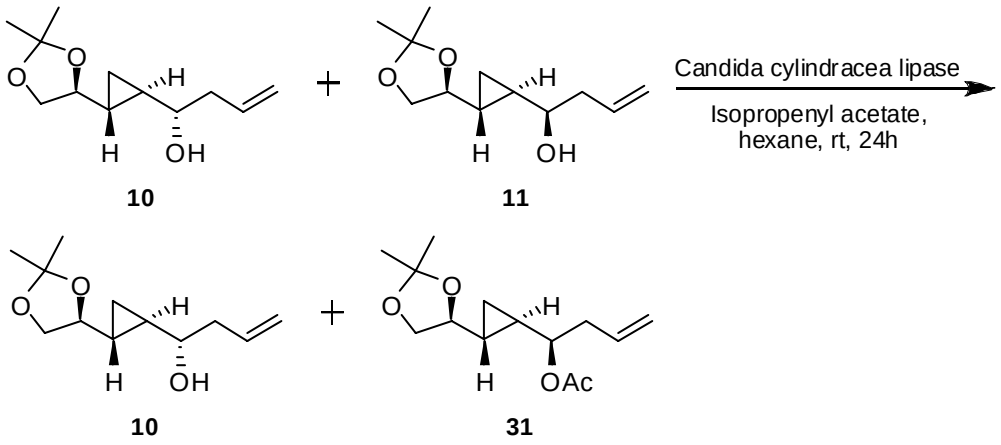
Table 2: *Comparison of ^{1}H NMR data of Eicosanoid (**1**) with the reported data*

Observed ^{1}H NMR δ values for Eicosanoid (**1**) (200 MHz, $CDCl_3$)	Reported[43] ^{1}H NMR δ values for Eicosanoid (500 MHz, $CDCl_3$)
0.89 (t, *J* = 6.5 Hz, 3H)	0.89 (t, *J* = 7 Hz, 3H)
0.97 (m, 1H)	0.98 (ddd, *J* = 8, 6, 4 Hz, 1H)
1.29 (m, 7H)	1.29 (m, 7H)
1.71 (m, 2H)	1.73 (m, 2H)
1.83 (m, 1H)	1.83 (m, 1H)
1.95 (m, 1H)	1.95 (m, 1H)
2.03 (m, 3H)	2.02 (m, 3H)
2.26 (m, 5H)	2.24 (m, 2H); 2.29 (m, 3H)
2.48 (m, 1H)	2.47 (m, 1H)
2.55 (m, 1H)	2.57 (m, 1H)
3.88 (m, 1H)	3.88 (ddd, *J* = 10, 8, 3 Hz, 1H)
5.33 (m, 1H)	5.35 (dt, *J* = 11, 7 Hz, 1H)
5.43 (m, 1H)	5.43 (dt, *J* = 11, 7 Hz, 1H)
6.25 (d, *J* = 16.0 Hz, 1H)	6.25 (dt, *J* = 16, 1 Hz, 1H)
6.94 (dt, *J* = 15.6, 6.9 Hz, 1H)	6.94 (dt, *J* = 16, 7 Hz, 1H)

Synthesis of homoallylic alcohol 11:

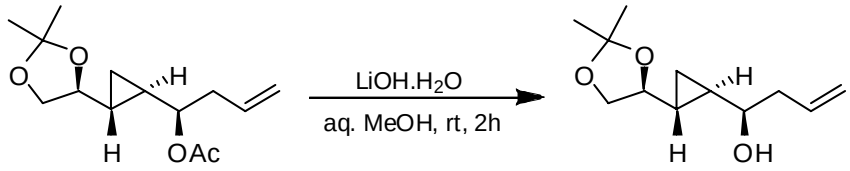
As described earlier in Scheme 3, the allyl Grignard reaction on aldehyde derived from cyclopropyl alcohol **12** afforded the distereomeric mixture of homoallylic alcohols **10** and **11** and the separation was difficult by column chromatography. In contradiction with earlier results for the preparation of alcohol **10**, all our attempts to prepare alcohol **11** in acceptable yields and chiral purity turned out to be failures using selective reduction approach in ketone **20**. While looking for viable alternatives for the preparation of alcohol **11**, it was decided to explore the enzymatic resolution strategy.[44] For the same, when mixture of homoallylic alcohols **10** and **11** was subjected to Candida cylindracea lipase (CCL) and isopropenyl acetate in hexane, CCL only facilitated the acylation of isomer **11** keeping other isomer **10** untouched, which afforded mixture of acetate **31** and homoallylic alcohol **10** (Scheme 11). The resolution was remarkably high and did not acylate the (*S*)-alcohol **10** even after prolonged exposure under same reaction conditions. Resultant mixture of acetate **31** and homoallylic alcohol **10** was easily separated by column chromatography to give pure acetate **31**. In the ^{1}H NMR spectrum of **31** characteristic signal due to acetate group appeared at δ 2.04 (s, 3H). In the ^{13}C NMR spectrum, signals due to acetate group carbons resonated at δ 39.0 and 170.3 ppm. Other analytical data also supported the structure of **31**.

Scheme 11:



Hydrolysis of acetate **31** using lithium hydroxide monohydrate in aqueous methanol at an ambient temperature furnished the requisite homoallylic alcohol **11** in good yields (Scheme 12).

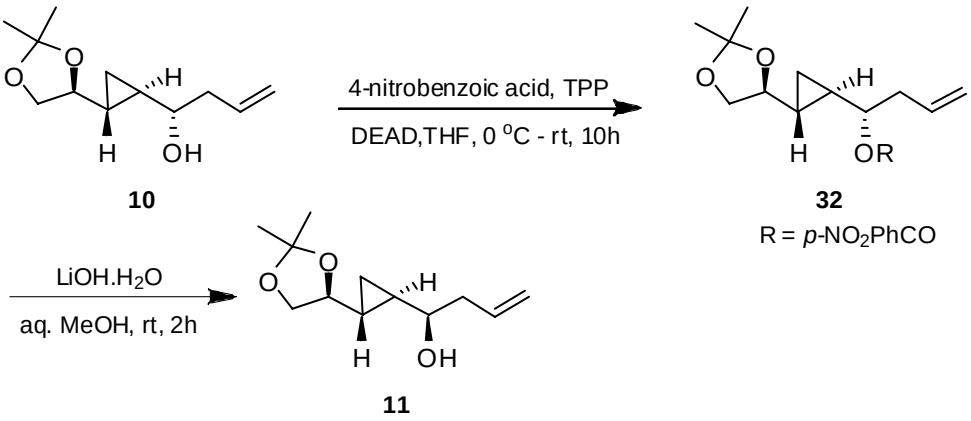
Scheme 12:



31 **11**

Also the homoallylic alcohol **10** could be easily converted to homoallylic alcohol **11** over two steps *via* standard Mitsunobu protocol[45] (Scheme 13). Treatment of the homoallylic alcohol **10** with 4-nitrobenzoic acid in presence of TPP and DEAD afforded the benzoate ester **32** (Scheme 13). Subsequent hydrolysis of the benzoate ester derivative **32** was achieved by treatment with lithium hydroxide monohydrate in aqueous methanol to furnish inverted alcohol **11** in 76% overall yield.

Scheme 13:



10 **32**

R = *p*-NO_2PhCO

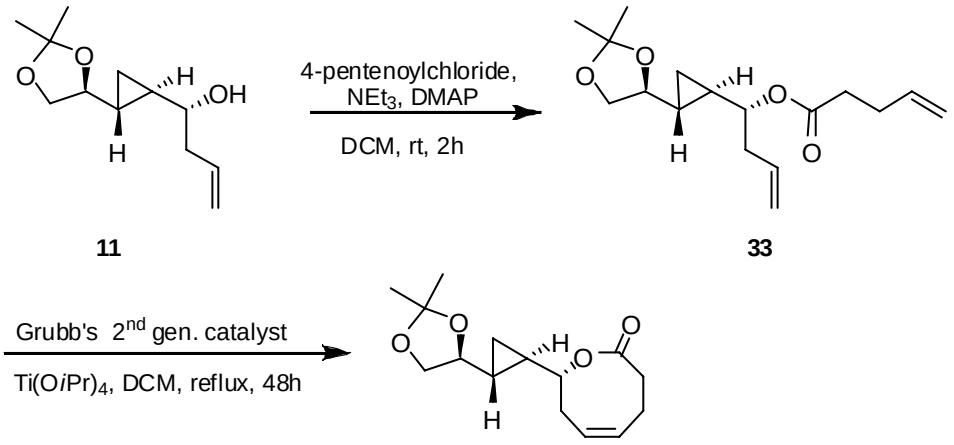
11

Synthesis of Solandelactone:

The next part of our effort was the synthesis of C1-C11 segment (**7**) of solandelactone (**2**). Here it was decided to examine the proposed general strategy for the synthesis of solandelactone (**2**), which was successfully used for the synthesis of eicosanoid (**1**). Accordingly, the requisite homoallyl alcohol **11** was treated with the mixture of 4-pentenoyl chloride, DMAP and triethylamine in DCM at an ambient temperature to furnish corresponding ester **33** (Scheme 14). In the ^{1}H NMR spectrum of **33** olefinic protons resonated at δ 5.07 (m, 4H) and 5.77 (m, 2H) while the rest of the spectrum was in complete agreement with the assigned structure. Further confirmation of the structure of **33** came from its ^{13}C NMR and DEPT spectral data. For example, in the ^{13}C NMR spectrum, olefinic carbons were identified at 115.4,

117.6, 133.4 and 136.5 ppm while carbonyl carbon resonated at 172.0 ppm. In the IR spectrum of **33** the ester carbonyl appeared at 1738 cm^{-1}. In addition, ESI-MS analysis indicated peaks at *m/z*: 317 accounting for $[M+Na]^+$. The elemental analysis of **33** was satisfactory.

Scheme 14:



The foremost mission of our endeavor was establishment of eight membered lactone ring with *Z*-stereochemistry of olefin by means of ring closing metathesis reaction. The attempts for ring-closing metathesis of compound **33** under different reaction conditions using Grubbs' first generation catalyst ended up with complete recovery of the starting material. The RCM reaction when tried with Grubbs' second generation catalyst[46] in the presence of catalytic amount of titanium(IV) isopropoxide in DCM under high dilution condition, the desired *Z*-isomer product **7** was isolated in 71% yield. The exclusive formation of the *Z*-isomer was confirmed by comparing the ^1H and ^{13}C NMR, IR value with the reported[41] data. In the ^1H NMR of compound **7**, the frequency corresponding to olefinic protons resonated at δ 5.10 (m) integrating for two protons. In the ^{13}C NMR spectrum the olefinic carbons resonated at 127.6 and 129.0 ppm while lactone carbonyl resonated at 172.7 ppm, which was reported for *Z*-isomer. The elemental analysis substantiated the proposed structure. The mass spectrum also supported the required structure of lactone derivative **7** by the highest molecular ion peak at *m/z* 289 accounting for $[M+Na]^+$.

Scheme 15:

7

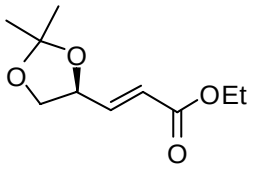
The total synthesis of solandelactone (**2**) could be achieved by introducing the requisite side chains on the cyclopropyl-lactone main core by using the synthetic protocol published for the synthesis of constanolactones[47] (Scheme 15). Since the compound **7** has already been transformed[20] into the solandelactone (**2**) in two steps the present synthesis of compound **7** constitutes a formal total synthesis of solandelactone (**2**).

Conclusion:

In conclusion, we have achieved the total synthesis of Eicosanoid and formal synthesis of Solandelactone starting from a common intermediate. We have successfully developed a general strategy for the synthesis of cyclopropyl oxylipins of eicosanoid family. Modified Simmons-Smith cyclopropanation, stereoselective reduction, ring-closing metathesis and Nozaki-Hiyama-Kishi reactions have been used successfully to construct the core cyclopropyl-lactone moieties. The strategy reported herein could be applied for the synthesis of different lactone motifs for a diversity-oriented synthesis of the cyclopropane ring containing oxylipins natural products.

EXPERIMENTAL

(*S*,*E*)-ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (**15**)



1,2:5,6-di-*O*-isopropylidene-D-mannitol (**13**) (5.0 g, 19.0 mmol) was dissolved in DCM (75 mL) and $NaIO_4$ supported silica gel (50 g) was added in the reaction mixture at room temperature and reaction mixture was stirred for 2 h. The reaction mixture was filtered and the filtrate was concentrated to get (*R*)-glyceraldehyde acetonide as a colorless liquid. The crude (*R*)-glyceraldehyde acetonide (**14**) (5.0 g, 38.5 mmol) and ethoxycarbonylmethylenetriphenyl-phosphorane (26.8 g, 77.0 mmol) in benzene (250 mL) were heated under reflux for 3 h. Solvent was evaporated and residue was purified on silica gel with ethyl acetate/light petroleum (1:9) as an eluent to afford ester **15** (6.0 g, 80%) as a colorless liquid.

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

Mol. Weight : 200

ESI-MS *m/z* : 223 $[M+Na]^+$

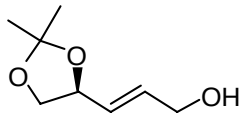
Elemental Analysis : Calcd: C, 59.98; H, 8.05%

Found: C, 60.43; H, 8.76%

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.30 (t, *J* = 7.2 Hz, 3H), 1.40 (s, 3H), 1.44 (s, 3H), 3.66 (dd, *J* = 7.4, 8.0 Hz, 1H), 4.17 (dd, *J* = 6.4, 8.0 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.65 (m, 1H), 6.08 (d, *J* = 15.5 Hz, 1H), 6.86 (dd, *J* = 5.6, 15.5 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 15.6, 25.1, 26.2, 64.6, 68.6, 78.5, 108.2, 122.1, 150.1, 170.2

3-[2,2-Dimethyl-(4*S*)-1,3-dioxolan-4-yl]-(*E*)-2-propen-1-ol (16)



To a solution of (*S*,*E*)-ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (**15**) (8.0 g, 40.0 mmol) in DCM was added DIBAL-H (40.84 mL, 1M solution in toluene) at -78 ^{o}C. The solution was stirred for 1 h at the same temperature and then allowed to warm to 0 ^{o}C slowly and stirred for next 2 h. After completion of the reaction, MeOH (20 mL) was added slowly followed by the addition of cold aqueous saturated sodium potassium tartarate (50 mL). The biphasic mixture was stirred for further 2 h and then partitioned. Aqueous layer was extracted with DCM. Combined organic extract was dried (Na_2SO_4) and purified by silica gel column chromatography using ethyl acetate/petroleum ether (1:4) to obtain pure **16** (5.43 g, 86%) as colorless viscous liquid.

Mol. Formula : $C_8H_{14}O_3$

Mol. Weight : 158

ESI-MS *m/z* : 181 $[M+Na]^+$

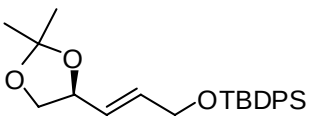
Elemental Analysis : Calcd: C, 60.74; H, 8.92%

Found: C, 60.24; H, 8.96%

$[\alpha]_D^{25}$: +32.5 (*c* 3.5, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.35 (s, 3H), 1.40 (s, 3H), 2.80 (br.s, 1H), 3.56 (t, *J* = 6.2 Hz, 1H), 4.12 (m, 3H), 4.52 (m, 1H), 5.65 (m, 1H), 5.88 (m, 1H).

(1*E*,4*S*)-*tert*-Butyl[3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-propenyl]oxydiphenyl silane (17)



To a solution of allylic alcohol **16** (5.0 g, 31.6 mmol) in DCM (40 mL) was added imidazole (6.45 g, 94.9 mmol) at 0 ^{o}C. The reaction mixture was then stirred for 15 min at the same temperature and *tert*-butyldiphenylchlorosilane (TBDPSCl) (9.65 mL, 38.0 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 10 h. After completion of the reaction, water was added to the reaction mixture. Organic layer was separated and aqueous layer was extracted with DCM. Combined organic extract was washed successively with water and brine, dried (Na_2SO_4) and purified by silica gel column chromatography using ethyl acetate/petroleum ether (1:19) to afford pure silyl ether **17** (10.0 g, 80%) as colorless liquid.

Mol. Formula : $C_{24}H_{32}O_3Si$

Mol. Weight : 396

ESI-MS *m/z* : 419 $[M+Na]^+$

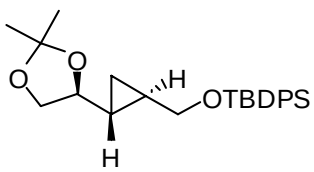
Elemental Analysis : Calcd: C, 72.68; H, 8.13%

Found: C, 72.94; H, 8.42%

$[\alpha]_D^{25}$: +22.4 (*c* 1.2, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.98 (s, 9H), 1.25 (s, 3H), 1.34 (s, 3H), 3.46 (t, *J* = 6.7 Hz, 1H), 3.98 (m, 1H), 4.12 (d, *J* = 5.7 Hz, 2H), 4.30 (q, *J* = 6.6 Hz, 1H), 5.67 (m, 2H), 7.30 (m, 6H), 7.54 (m, 4H)

(1*R*,2*R*,4*S*)-*tert*-Butyl[2-(2,2-dimethyl-1,3-dioxolan-4-yl)cyclopropyl] methoxydiphenylsilane (18)



Et_2Zn (142.5 mL, 115.9 mmol, 1M solution in hexane) was added dropwise to a clear solution of **17** (9.5 g, 23.2 mmol) in DCM (200 mL) at -78 ^{o}C. After 10

min. CH_2I_2 (9.3 mL, 115.9 mmol) was added in to the reaction mixture. The reaction mixture was stirred at the same temperature for 4 h and then at -10 ^oC for 20 h. The reaction mixture was poured into a saturated solution of NH_4Cl. Organic layer was separated and aqueous layer was extracted with DCM. Combined organic extract was washed successively with water, brine, dried (Na_2SO_4) and purified by silica gel column chromatography using ethyl acetate/petroleum ether (1:24) to give pure compound **18** (9.34 g, 95%) as colorless liquid.

Mol. Formula : $C_{25}H_{34}O_3Si$

Mol. Weight : 410

ESI-MS *m/z* : 433 $[M+Na]^+$

Elemental Analysis : Calcd: C, 73.13; H, 8.34%

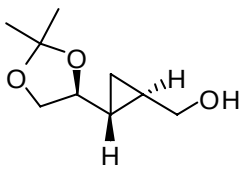
Found: C, 72.94; H, 8.76%

$[\alpha]_D^{25}$: -7.7 (*c* 1.4, $CHCl_3$); literature $[\alpha]_D$ = -7.9 (*c* 1.15, $CHCl_3$)

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.54 (m, 2H), 0.82 (m, 2H), 1.05 (s, 9H), 1.35 (s, 3H), 1.44 (s, 3H), 3.46 (m, 2H), 3.68 (m, 2H), 4.05 (m, 1H), 7.41 (m, 5H), 7.72 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 7.6, 17.5, 18.9, 19.8, 25.4, 26.6, 28.4(3C), 65.0, 68.9, 78.6, 108.7, 128.0(4C), 129.6(6C), 134.0(2C)

[2-(2,2-Dimethyl-(4*S*)-1,3-dioxolan-4-yl)-(1*R*,2*R*)-cyclopropyl]methanol (12)



To a stirred solution of **18** (9.0 g, 22.0 mmol) in THF (50 mL) at 0 ^oC, was added TBAF (32.9 mL, 32.9 mmol, 1M solution in THF) dropwise and stirring was continued for 1 h at 0 ^oC. The reaction mixture was then brought to room temperature and stirred overnight. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography using ethyl

acetate/petroleum ether (1:4) to afford pure compound **12** (3.25g, 86%) as colorless viscous liquid.

Mol. Formula : $C_9H_{16}O_3$

Mol. Weight : 172

ESI-MS *m/z* : 195 $[M+Na]^+$

Elemental Analysis : Calcd: C, 62.77; H, 9.36%

Found: C, 62.84; H, 9.72%

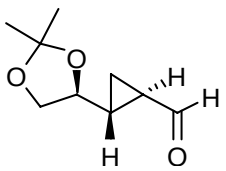
$[\alpha]_D^{25}$: +16.5 (*c* 1.25, $CHCl_3$); lit. $[\alpha]_D$ = +16.7 (*c* 1.25, $CHCl_3$)

IR ($CHCl_3$) $\tilde{\nu}$: 3598, 1676, 1245 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.63 (m, 2H), 0.87 (m, 1H), 1.01 (m, 1H), 1.33 (s, 3H), 1.42 (s, 3H), 2.68 (br.s, 1H), 3.38 (dd, *J* = 7.3, 11.2 Hz, 1H), 3.52 (dd, *J* = 6.4, 11.2 Hz, 1H), 3.65 (m, 2H), 4.07 (dt, *J* = 2.0, 5.4 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 7.4, 17.4, 18.7, 25.3, 26.4, 64.9, 68.7, 78.5, 108.5

2-[2,2-Dimethyl-(4*S*)-1,3-dioxolan-4-yl]-(1*R*,2*R*)-cyclopropanecarbaldehyde (19)



To a stirred solution of 2-iodoxybenzoic acid (IBX) (7.81 g, 27.9 mmol) in DMSO (20 mL), was added a solution of **12** (3.2 g, 18.6 mmol) in THF (10 mL) at room temperature and stirring was continued for further 2 h. After completion of the reaction, cold water was added to the reaction mixture, precipitate was filtered off and the filtrate was diluted with water and extracted with ether. The combined organic layer was washed successively with aqueous $NaHCO_3$, water, brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography using ethyl

acetate/petroleum ether (1:6) to afford pure aldehyde **19** (2.97 g, 94%) as colorless liquid.

Mol. Formula : $C_9H_{14}O_3$

Mol. Weight : 170

ESI-MS *m/z* : 171 $[M+H]^+$

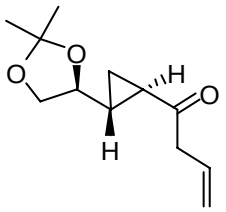
Elemental Analysis : Calcd: C, 63.50; H, 8.28%

Found: C, 62.94; H, 8.36%

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.25 (m, 2H), 1.35 (s, 3H), 1.40 (s, 3H), 1.65 (m, 1H), 1.87 (m, 1H), 3.68 (t, *J* = 6.2 Hz, 1H), 3.84 (m, 1H), 4.10 (m, 1H), 9.18 (d, *J* = 6.2 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 13.4, 24.1, 25.5(2C), 27.3, 69.0, 76.7, 109.5, 194.9

1-{2-[2,2-Dimethyl-(4*S*)-1,3-dioxolan-4-yl]-(1*R*,2*R*)-cyclopropyl}-3-buten-1-one (20)



To an ice cooled solution of aldehyde **19** (2.9 g, 17.0 mmol) in ether (20 mL) was added an ethereal solution of allyl magnesium bromide [prepared from allyl bromide (2.94 mL, 34.0 mmol) in dropwise manner and Mg (1.22 g, 51.0 mmol) in ether (50 mL)] and stirring was continued for 3 h at room temperature. The reaction mixture was then quenched with 5% HCl (20 mL) and extracted with ethyl acetate. The combined organic layer was washed successively with aqueous $NaHCO_3$, water, brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography using ethyl acetate/petroleum ether (1:4) to afford 1:1 mixture of homoallyl alcohol diastereomers **10** and **11** (3.14 g, 87%).

To a stirred solution of IBX (4.95 g, 17.7 mmol) in DMSO (30 mL), was added a solution of homoallylic alcohols **10** and **11** (2.50 g, 11.8 mmol) in THF (20 mL) at room temperature and stirring was continued for further 3 h. After completion of the reaction, water was added to the reaction mixture, precipitate was filtered off and the filtrate was diluted with water and extracted with ether. The combined organic layer was washed successively with aqueous $NaHCO_3$, water, brine, and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography using ethyl acetate/petroleum ether (1:9) to afford pure cyclopropyl ketone **20** (2.23 g, 90%) as colorless liquid.

Mol. Formula : $C_{12}H_{18}O_3$

Mol. Weight : 210

ESI-MS *m/z* : 233 $[M+Na]^+$

Elemental Analysis : Calcd: C, 68.54; H, 8.63%

Found: C, 69.22; H, 8.45%

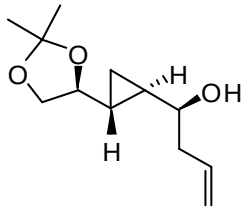
$[\alpha]_D^{25}$: - 59.7 (*c* 1.30, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3079, 1718, 1621 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.08 (m, 1H), 1.26 (m, 1H), 1.34 (s, 3H), 1.40 (s, 3H), 1.63 (m, 1H), 1.98 (m, 1H), 3.32 (dd, *J* = 1.5, 6.2 Hz, 2H), 3.66 (t, *J* = 7.4 Hz, 1H), 3.87 (dd, *J* = 6.6, 8.1 Hz, 1H), 4.08 (dd, *J* = 6.6, 8.1 Hz, 1H), 5.19 (m, 2H), 5.93 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 14.2, 24.2, 25.6, 26.5, 26.6, 48.5, 69.1, 76.2, 109.3, 118.9, 130.5, 206.7

1-{2-[(2,2)-Dimethyl-(4*S*)-1,3-dioxolan-4-yl]-(1*R*,2*R*)-cyclopropyl}-3-buten-1-ol (10)



To a stirred solution of **20** (1.0 g, 4.8 mmol) in THF (30 mL), was added K-selectride (7.42 mL, 7.4 mmol, 1M solution in THF) at -78 ^{o}C, and stirred for 2 h at the same temperature. Methanol was added and the reaction mixture was brought to room temperature. After removal of the solvent at reduced pressure, the residue was treated with 2M NaOH solution (15 mL) and extracted with ethyl acetate. Combined organic layer was dried (Na_2SO_4) and concentrated to afford the crude product, which on flash chromatographic separation using ethyl acetate/petroleum ether (1:4) afforded major isomer **10** (855 mg, 78%) and minor isomer **11** (74 mg, 7%) as a colorless liquids.

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

Mol. Weight : 212

ESI-MS *m/z* : 235 $[M+Na]^+$

Elemental Analysis : Calcd: C, 67.89; H, 9.49%

Found: C, 67.92; H, 10.06%

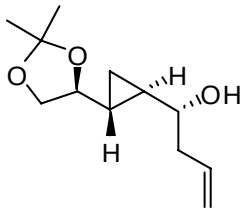
$[\alpha]_D^{25}$: -17.3 (*c* 0.97, $CHCl_3$)

IR ($CHCl_3$) $\tilde{\nu}$: 3550, 3108, 2980, 1653 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.65 (m, 2H), 0.85 (m, 2H), 1.33 (s, 3H), 1.42 (s, 3H), 2.18 (br.s, 1H), 2.32 (m, 2H), 3.07 (dt, *J* = 4.8, 7.3 Hz, 1H), 3.60 (dd, *J* = 7.8, 16.6 Hz, 1H), 3.68 (m, 1H), 4.04 (dd, *J* = 5.8, 7.8 Hz, 1H), 5.13 (m, 2H), 5.86 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 7.9, 18.7, 21.6, 25.6, 26.7, 41.7, 69.2, 73.8, 79.1, 108.9, 118.0, 134.3.

1-{2-[(2,2)-Dimethyl-(4*S*)-1,3-dioxolan-4-yl]-(1*R*,2*R*)-cyclopropyl}-(1*R*)-3-buten-1-ol (11)



The acetate derivative **31** (1.5 g, 5.9 mmol) was dissolved in aqueous MeOH and treated with lithium hydroxide monohydrate (0.3 g) for 2 h. The solid was then filtered off, filtrate was concentrated and the residue was purified by silica gel column chromatography using ethyl acetate/petroleum ether (1:5) to afford **11** (1.15 g, 92%) as colorless oil.

Mitsunobu Reaction:

To a solution of **10** (1.2 g, 5.66 mmol) in THF (30 mL) was added PPh_3 (4.45 g, 17.0 mmol) and *p*-nitrobenzoic acid (2.84 g, 17.0 mmol) and the resultant mixture was cooled to 0 ^oC. A solution of diethyl azodicarboxylate (DEAD) (3.13 mL, 19.8 mmol) in THF (5 mL) was added in dropwise manner to the reaction mixture. The reaction mixture was then brought to room temperature and stirred overnight. After removal of the solvent, the residue was taken in DCM and was washed successively with aqueous $NaHCO_3$, water, brine, and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product **32** was dissolved in aqueous MeOH and treated with lithium hydroxide monohydrate (0.3 g) for 1 h. The solid was then filtered off, filtrate was concentrated and the residue was purified by silica gel column chromatography using ethyl acetate/petroleum ether (1:5) to afford **11** (0.91g, 76%) as colorless oil.

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

Mol. Weight : 212

ESI-MS *m/z* : 235 $[M+Na]^+$

Elemental Analysis : Calcd: C, 67.89; H, 9.49%

Found: C, 67.55; H, 9.26%

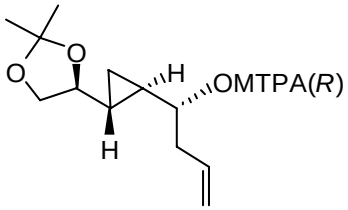
$[\alpha]_D^{25}$: +48.10 (*c* 1.20, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$ **:** 3558, 3120, 2968, 1598 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 0.66 (m, 2H), 0.86 (m, 2H), 1.32 (s, 3H), 1.41 (s, 3H), 1.89 (br.s, 1H), 2.33 (m, 2H), 3.08 (dt, *J* = 4.9, 7.3 Hz, 1H), 3.55 (dd, *J* = 5.4, 7.3 Hz, 1H), 3.63 (dd, *J* = 7.3, 14.8 Hz, 1H), 4.04 (dd, *J* = 5.4, 7.3 Hz, 1H), 5.15 (m, 2H), 5.84 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) **:** δ 7.5, 18.6, 21.3, 25.6, 26.7, 41.7, 69.1, 73.5, 79.1, 108.9, 117.9, 134.4.

(*R*)-2-Methoxy-2-(trifluoromethyl)-2-phenylacetic acid (MTPA) ester(21)



To a solution of **11** (20 mg, 0.1 mmol) in DCM (2 mL) was added (*R*)-2-methoxy-2-(trifluoromethyl)-2-phenylacetic acid (*R*-MTPA) (35 mg, 0.16 mmol), DCC (30 mg, 0.17 mmol) and catalytic amount of DMAP. The reaction mixture was stirred overnight at room temperature. The solid was filtered off, filtrate was concentrated and the residue was purified by silica gel column chromatography using ethyl acetate/petroleum ether (1:19) to afford pure (*R*)-MTPA ester **21** (35 mg, 80%) as a colorless liquid.

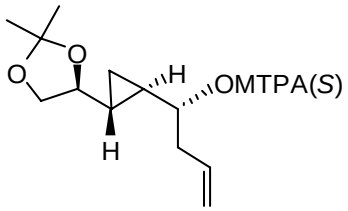
Mol. Formula **:** $C_{22}H_{27}F_3O_5$

Mol. Weight **:** 428

ESI-MS *m/z* **:** 451 $[M+Na]^+$

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 0.74 (m, 1H), 0.80 (m, 1H), 1.06 (m, 2H), 1.32 (s, 3H), 1.41 (s, 3H), 2.44 (m, 2H), 3.61 (m, 5H), 4.03 (m, 1H), 4.60 (m, 1H), 5.06 (m, 2H), 5.61 (m, 1H), 7.40 (m, 3H), 7.54 (m, 2H).

(*S*)-2-Methoxy-2-(trifluoromethyl)-2-phenylacetic acid (MTPA) ester(22).



To a solution of **11** (20 mg, 0.1 mmol) in DCM (2 mL) was added (*S*)-2-methoxy-2-(trifluoromethyl)-2-phenylacetic acid (*S*-MTPA) (35 mg, 0.16 mmol), DCC (30 mg, 0.17 mmol) and catalytic amount of DMAP. The reaction mixture was stirred overnight at room temperature. The solid was filtered off, filtrate was concentrated and the residue was purified by silica gel column chromatography using ethyl acetate/petroleum ether (1:19) to afford pure (*S*)-MTPA ester **22** (34 mg, 78%) as a colorless liquid.

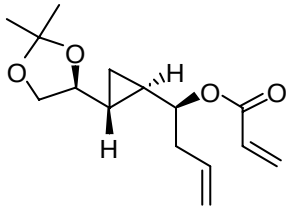
Mol. Formula : $C_{22}H_{27}F_3O_5$

Mol. Weight : 428

ESI-MS *m/z* : 451 $[M+Na]^+$

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.64 (m, 1H), 0.77 (m, 1H), 0.94 (m, 2H), 1.31 (s, 3H), 1.39 (s, 3H), 2.50 (m, 2H), 3.59 (m, 5H), 3.98 (m, 1H), 4.67 (m, 1H), 5.15 (m, 2H), 5.75 (m, 1H), 7.40 (m, 3H), 7.53 (m, 2H).

1[2-(2,2-Dimethyl-1, 3-dioxolan-4-yl)cyclopropyl]-3-butenyl acrylate (9)



Acryloyl chloride (0.12 mL, 1.4 mmol) was added in dropwise manner to a solution of alcohol **10** (0.2 g, 0.9 mmol) and triethylamine (0.4 mL, 2.8 mmol) in DCM (15 mL) at 0 ^oC. After stirring for 2 h at 0 ^oC, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL), poured into brine and extracted with DCM. The combined organic extract was dried (Na_2SO_4), concentrated and the

residue was purified over neutral alumina using ethyl acetate/petroleum ether (1:19) to furnish **9** (0.196 g, 92%) as colorless oil.

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

Mol. Weight : 266

ESI-MS *m/z* : 289 $[M+Na]^+$

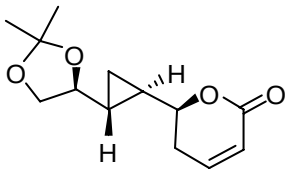
Elemental Analysis : Calcd: C, 67.64; H, 8.33%

Found: C 68.13; H, 7.56%

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.63 (m, 1H), 0.74 (m, 1H), 0.93 (m, 2H), 1.31 (s, 3H), 1.40 (s, 3H), 2.44 (m, 2H), 3.61 (m, 2H), 4.02 (m, 1H), 4.47 (m, 1H), 5.09 (m, 2H), 5.80 (m, 2H), 6.10 (dd, *J* = 10.2, 16.8 Hz, 1H), 6.39 (d, *J* = 17.5 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 7.9, 18.9, 19.3, 25.4, 26.5, 38.9, 68.8, 75.4, 78.0, 108.5, 117.4, 128.5, 131.0, 133.3, 165.6

6-[2-(2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopropyl]-5,6-dihydro-2*H*-pyran-2-one (23)



To a stirred solution of **9** (0.17 g, 0.6 mmol) in freshly distilled anhydrous DCM (80 mL) was added Ti(O*i*Pr)$_4$ (0.3 mL, 0.3 mmol) and refluxed for 1 h. Then the temperature of the reaction mixture was brought to room temperature and a solution of *bis*-(tricyclohexylphosphine)[benzylidene]ruthenium(IV) dichloride (18 mg, 0.06 mmol) in dichloromethane was added to the reaction mixture and reaction mixture was degassed with Argon. After refluxing for 6 h, the solvent was removed under vacuum and the residue was purified by silica gel column chromatography using ethyl acetate/petroleum ether (1:9) to afford **23** (0.136 g, 90%) as colorless liquid.

Mol. Formula : $C_{13}H_{18}O_4$

Mol. Weight : 238

ESI-MS *m/z* : 261 $[M+Na]^+$

Elemental Analysis : Calcd: C, 65.53; H, 7.61%

Found: C, 65.32; H, 8.07%

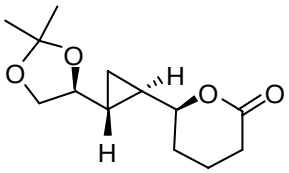
$[\alpha]_D^{25}$: - 55.0 (*c* 0.95, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3318, 2986, 1668 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.62 (m, 1H), 0.78 (m, 1H), 1.12 (m, 2H), 1.33 (s, 3H), 1.41 (s, 3H), 2.47 (m, 2H), 3.68 (m, 1H), 3.78 (m, 2H), 4.10 (dd, *J* = 5.9, 8.0 Hz, 1H), 6.02 (d, *J* = 9.5 Hz, 1H), 6.87 (dt, *J* = 4.4, 9.5 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 6.7, 18.8, 19.2, 25.4, 26.5, 29.2, 69.0, 77.7, 80.6, 108.6, 121.3, 144.5, 163.5.

6-[2-(2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopropyl]tetrahydro-2*H*-pyran-2-one (24)



Palladium on charcoal (20 mg) was added to a stirred solution of **23** (0.2 g, 0.84 mmol) in ethyl acetate (15 mL) under hydrogen atmosphere at room temperature for 3 h. After completion of the reaction, the reaction mixture was filtered through a pad of celite and the solvent was remover under reduced pressure and residue was purified by silica gel column chromatography using ethyl acetate/petroleum ether (1:9) to afford **24** (0.19 g, 94%) as colorless oil.

Mol. Formula : $C_{13}H_{20}O_4$

Mol. Weight : 240

ESI-MS *m/z* : 263 $[M+Na]^+$

Elemental Analysis : Calcd: C, 64.98; H, 8.39%

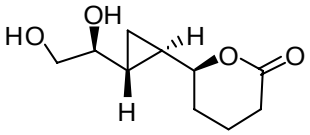
Found: C, 64.63; H, 8.48%

$[\alpha]_D^{25}$: +8.5 (*c* 1.15, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.60 (dt, *J* = 5.0, 8.2 Hz, 1H), 0.74 (dt, *J* = 5.5, 8.7 Hz, 1H), 0.99 (m, 1H), 1.08 (m, 1H), 1.32 (s, 3H), 1.40 (s, 3H), 1.67 (m, 1H), 1.81 (m, 1H), 1.94 (m, 1H), 2.02 (m, 1H), 2.44 (ddd, *J* = 6.9, 8.7, 1.8 Hz, 1H), 2.55 (dt, *J* = 17.4, 6.9 Hz, 1H), 3.66 (m, 2H), 3.75 (t, *J* = 7.8 Hz, 1H), 4.09 (dd, *J* = 6.4, 8.3 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) : δ 6.6, 18.2, 19.2, 19.7, 25.4, 26.5, 27.7, 29.2, 69.0, 77.8, 83.0, 108.6, 170.6.

6-[2-(1,2)-Dihydroxyethyl)cyclopropyl]tetrahydro-2*H*-pyran-2-one(25).



A solution of **24** (0.25 g, 1.0 mmol) in 50% aqueous AcOH (5 mL) was stirred at room temperature for 3 h. The reaction mixture was then diluted with DCM (20 mL) cooled to 0 ^oC and neutralized to *p*H 7 by adding solid $NaHCO_3$ in small portions. The layer was then separated; aqueous layer extracted with DCM and the combined organic extract was washed sequentially with water and brine. After drying over Na_2SO_4 and removal of solvent under reduced pressure, the residue was column chromatographed using ethyl acetate/petroleum ether (1:1) to furnish **25** (0.16 g, 75%) as a colorless viscous liquid.

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

Mol. Weight : 200

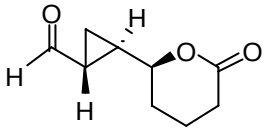
ESI-MS *m/z* : 223 $[M+Na]^+$

Elemental Analysis : Calcd: C, 59.98; H, 8.05%

Found: C, 60.46; H, 8.23%

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.59 (dt, *J* = 5.0, 8.2 Hz, 1H), 0.75 (dt, *J* = 5.5, 8.7 Hz, 1H), 1.08 (m, 2H), 1.67 (m, 1H), 1.79 (m, 1H), 1.98 (m, 2H), 2.45 (ddd, *J* = 6.8, 8.8, 17.6 Hz, 1H), 2.55 (dt, *J* = 17.6, 5.8 Hz, 1H), 3.22 (m, 1H), 3.64 (m, 2H), 3.77 (dd, *J* = 4.0, 11.2 Hz, 1H), 5.23 (br.s, 2H).

2-(6-Oxotetrahydro-2*H*-pyran-2-yl)cyclopropanecarbaldehyde (5)



To a vigorously stirred solution of **25** (0.1 g, 0.5 mmol) in DCM (10 mL), $NaIO_4$ supported on silica gel (1.5 g) was added at 0 ^oC. After stirring at the same temperature for 0.5 h, the solid was removed by filtration, washed with DCM, combined filtrate was concentrated under vacuum and the residue was column chromatographed using ethyl acetate/petroleum ether (1:3) to afford the aldehyde **5** (0.08 g, 94%) as a colorless liquid.

Mol. Formula : $C_9H_{12}O_3$

Mol. Weight : 168

ESI-MS *m/z* : 191 $[M+Na]^+$

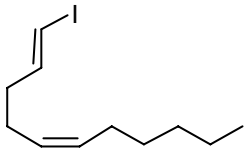
$[\alpha]_D^{25}$: -39.3 (*c* 1.10, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3001, 1732, 1698, 1245 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 1.12 (ddd, *J* = 4.5, 8.2, 11.4 Hz, 1H), 1.35 (dt, *J* = 4.5, 8.7 Hz, 1H), 1.80 (m, 6H), 2.38 (m, 2H), 3.84 (m, 1H), 9.10 (s, 1H)

^{13}C NMR (50 MHz, $CDCl_3$) **:** δ 11.8, 18.5, 26.5, 26.8, 28.0, 29.5, 81.2, 170.7, 199.8

(1*E*,5*Z*)-1-iodoundeca-1,5-diene (6)



To a stirred solution of IBX (4.95 g, 17.7 mmol) in DMSO (30 mL), was added a solution of (*Z*)-dec-4-en-1-ol (**8**) (2.50 g, 11.8 mmol) in THF (20 mL) at room temperature and stirring was continued for further 2 h. After completion of the reaction, water was added to the reaction mixture, precipitate was filtered off and the filtrate was diluted with water and extracted with ether. The combined organic layer was washed successively with aqueous $NaHCO_3$, water, brine, and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford aldehyde **29**, which was taken for next reaction without further purification.

Anhydrous $CrCl_2$ (338 mg**,** 2.8 mmol) was suspended in THF (8 mL) under Argon atmosphere. A solution of aldehyde **29** (120 mg**,** 0.6 mmol) and iodoform (361 mg, 0.9 mmol) in THF (7 mL) was added dropwise to the suspension at 0 °C. After stirring at 0 °C for 3 h, the reaction mixture was poured into water and extracted with diethylether. The combined extract was dried (Na_2SO_4) and concentrated. Purification by column chromatography on silica gel by eluting with ethyl acetate/light petroleum ether (1:6) afforded **6** (138 mg, 78%) as a colorless oil.

Mol. Formula **:** $C_{11}H_{19}I$

Mol. Weight **:** 278

ESI-MS *m/z* **:** 301 $[M+Na]^+$, 279 $[M+H]^+$

Elemental Analysis : Calcd: C, 47.49; H, 6.88%

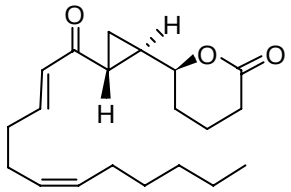
Found: C, 48.05; H, 7.43%

IR ($CHCl_3$) $\tilde{\nu}$: 1468, 2852, 2930, 2958, 3010 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.89 (t, *J* = 7.0 Hz, 3H), 1.29 (m, 6H), 2.01 (m, 4H), 2.25 (m, 2H), 5.35 (m, 2H), 6.06 (d, *J* = 14.4 Hz, 1H), 6.48 (m, 1H)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 14.2, 22.7, 26.7, 27.3, 29.2, 31.5, 36.2, 75.0, 127.8, 131.4, 145.8

6-[2-(2,6-dodecadienoyl)cyclopropyl]tetrahydro-2*H*-pyran-2-one(1)



To a mixture of **5** (0.04 g, 0.2 mmol) and **6** (0.4 g, 1.4 mmol), were added degassed DMF (10 mL), chromium(II) chloride (0.18 g, 1.4 mmol), and nickel(II) chloride (catalytic). The green colored solution was stirred at room temperature for 24 h and was poured into saturated NH_4Cl. Ether was then added to the resulting mixture and extracted with diethylether, the combined organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure. Compound **30** was taken for the next reaction immediately without further purification.

To a stirred solution of **30** (0.09 g, 0.28 mmol) in DCM (10 mL) was added Dess-Martin periodinane (0.24 g, 0.56 mmol) at 0 ^oC and the suspension was stirred at room temperature for 2 h. The reaction mixture was quenched with water and filtered through a pad of celite. The residue was washed with DCM. The organic layer was separated and aqueous layer was extracted with DCM. The combined extract was dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography using ethyl acetate/petroleum ether (1:9) to afford **1** (0.078 g, 89%) as a colorless liquid.

Mol. Formula : $C_{20}H_{30}O_3$

Mol. Weight : 318

ESI-MS *m/z* : 341 $[M+Na]^+$, 319 $[M+H]^+$.

Elemental Analysis : Calcd: C, 75.43; H, 9.50%

Found: C, 75.12; H, 9.83%

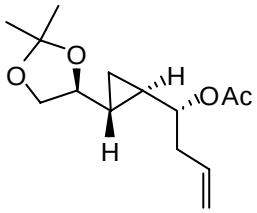
$[\alpha]_D^{25}$: -25.8 (*c* 0.60, $CHCl_3$); lit. $[\alpha]_D$ = -27.4 (*c* 0.46, $CHCl_3$)

IR ($CHCl_3$) $\tilde{\nu}$: 3005, 2930, 2893, 2875, 1737, 1683, 1660 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.89 (t, *J* = 6.5 Hz, 3H), 0.97 (m, 1H), 1.29 (m, 7H), 1.71 (m, 2H), 1.83 (m, 1H), 1.95 (m, 1H), 2.03 (m, 3H), 2.26 (m, 5H), 2.48 (m, 1H), 2.55 (m, 1H), 3.88 (m, 1H), 5.33 (m, 1H), 5.43 (m, 1H), 6.25 (d, *J* = 16.0 Hz, 1H), 6.94 (dt, *J* = 15.6, 6.9 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) : δ 13.9, 14.1, 18.5, 22.6, 23.5, 25.9, 27.3, 28.2, 28.3, 29.5, 29.6, 31.6, 32.7, 81.5, 127.8, 130.8, 131.5, 147.5, 170.5, 197.8.

4-[2-[(2,2)-dimethyl-(4S)-1,3-dioxalan-4-yl]-(1R,2R)-cyclopropyl]-4-methyl carbonyloxy buten-1-ol (31)



To a stirred solution of homoallylic alcohols **10** and **11** (1:1 diastereomeric mixture, 3.0 g, 14.2 mmol) in anhydrous hexane (20 mL) was added isopropenyl acetate (9.46 mL, 85.2 mmol) followed by Candida Cylindracea Lipase (CCL) (0.5 g). The reaction mixture was stirred for 24 h. The solid was then filtered through pad

of celite and solvent was removed under reduced pressure. The crude residue was purified by silica gel column chromatography using ethyl acetate/light petroleum ether (1:19) to provide **31** (1.65 g, 46%) and of alcohol **10** (1.2 g, 43%) as colorless liquids.

Mol. Formula : $C_{14}H_{22}O_4$

Mol. Weight : 254

ESI-MS *m/z* : 277 $[M+Na]^+$

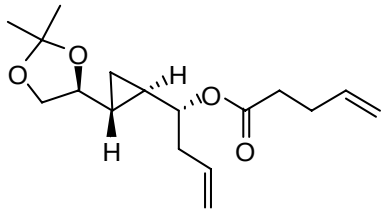
Elemental Analysis : Calcd: C, 66.12; H, 8.72%

Found: C 66.23, H, 7.90%

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.62 (m, 2H), 0.88 (m, 2H), 1.28 (s, 3H), 1.42 (s, 3H), 2.04 (s, 3H), 2.36 (m, 2H), 3.57 (m, 2H), 4.04 (m, 1H), 4.38 (m, 1H), 5.15 (m, 2H), 5.78 (m, 1H).

^{13}C NMR (50MHz, $CDCl_3$) : δ 8.3, 19.1, 19.4, 21.0, 26.6, 26.7, 39.0, 69.1, 75.7, 78.6, 108.9, 117.8, 133.4, 170.3.

Pent-4-enoic acid-1-[2-(2,2-dimethyl-[1,3]dioxalan-4-yl)-cyclopropyl]-but-3-enyl ester (33)



To a solution of **11** (0.2 g, 0.94 mmol) in anhydrous DCM (10 mL) was added Et_3N (9 mL, 1.41 mmol) and catalytic DMAP at 0 ^oC and stirred for 10 min at the same temperature. In the reaction mixture, 4-pentenoylchloride (0.1 mL, 1.12 mmol) was added in dropwise manner. The reaction mixture was then brought to room temperature and stirred for 2 h. After completion of the reaction, the solid was filtered off, filtrate was concentrated and the residue was purified by silica gel column chromatography using ethyl acetate/light petroleum ether (1:19) to afford **33** (0.255 g, 92%) as a colorless liquid.

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

Mol. Weight : 294

ESI-MS *m/z* : 317 $[M+Na]^+$.

Elemental Analysis : Calcd: C, 69.36; H, 8.90%

Found: C, 69.51; H, 9.49%

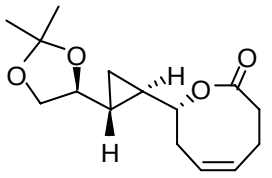
$[\alpha]_D^{25}$: -12.9 (*c* 1.05, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3348, 2985, 1738, 1608 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.63 (m, 1H), 0.72 (m, 1H), 0.92 (m, 2H), 1.32 (s, 3H), 1.40 (s, 3H), 2.37 (m, 6H), 3.61 (m, 2H), 4.03 (m, 1H), 4.43 (m, 1H), 5.07 (m, 4H), 5.77 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 8.1, 19.1(2C), 25.6, 26.6, 28.8, 33.6, 39.0, 68.9, 75.5, 78.2, 108.7, 115.4, 117.6, 133.4, 136.5, 172 .0

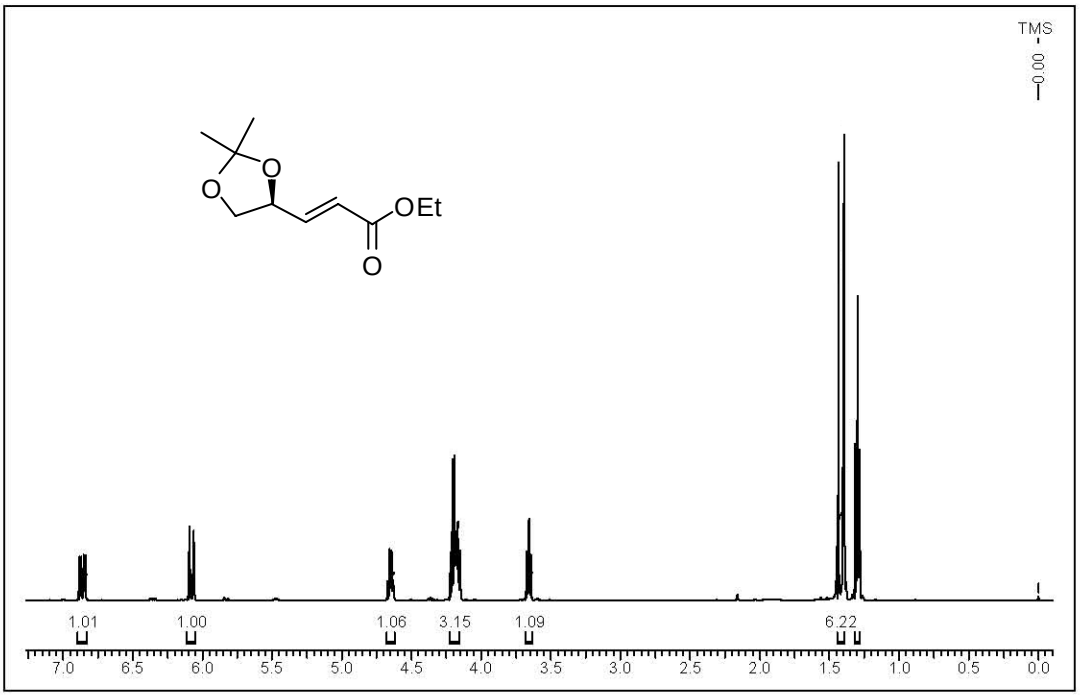
8-[2(2,2-Dimethyl-[1,3]dioxalan-4-yl)-cyclopropyl]-3,4,7,8-tetrahydro-oxacin-2-one (7)



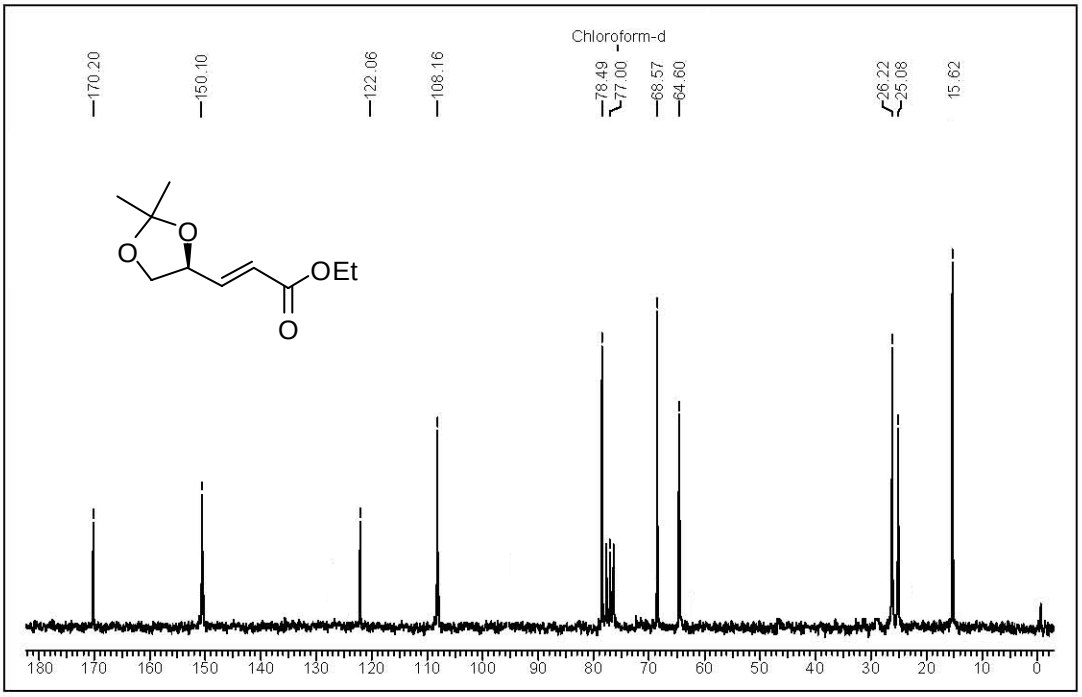
A solution of **33** (0.1 g, 0.34 mmol) and freshly distilled $Ti(OiPr)_4$ (0.01 mL, 0.03 mmol) in anhydrous DCM (200 mL) was refluxed for 1 h under an Argon atmosphere. Grubbs' second-generation catalyst (20 mg) in dry DCM (5 mL) was added to the reaction mixture. The reaction mixture was then refluxed for 48 h. After completion of the reaction, the reaction mixture was filtered through a pad of celite. The organic solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography using ethyl acetate/light petroleum ether (1:9) to afford pure compound **7** (64 mg, 71%) as a colorless viscous liquid.

Mol. Formula	:	$C_{15}H_{22}O_4$
Mol. Weight	:	266
ESI-MS *m/z*	:	289 $[M+Na]^+$.
Elemental Analysis	:	Calcd: C, 67.65; H, 8.33% Found: C, 68.28; H, 7.83%
$[\alpha]_D^{25}$	:	– 4.6 (*c* 0.4, $CHCl_3$), lit. $[\alpha]_D$ = – 4.7 (*c* 0.9, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	:	3267, 3008, 1746, 1620 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.63 (m, 1H), 0.71 (m, 1H), 0.96 (m, 2H), 1.31 (s, 3H), 1.40 (s, 3H), 2.35 (m, 6H), 3.61 (m, 2H), 4.02 (m, 1H), 4.40 (m, 1H), 5.10 (m, 2H).
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 9.5, 18.9, 19.0, 25.7, 26.7, 27.3, 33.9, 36.9, 69.0, 76.3, 78.9, 109.1, 127.6, 129.0, 172.7

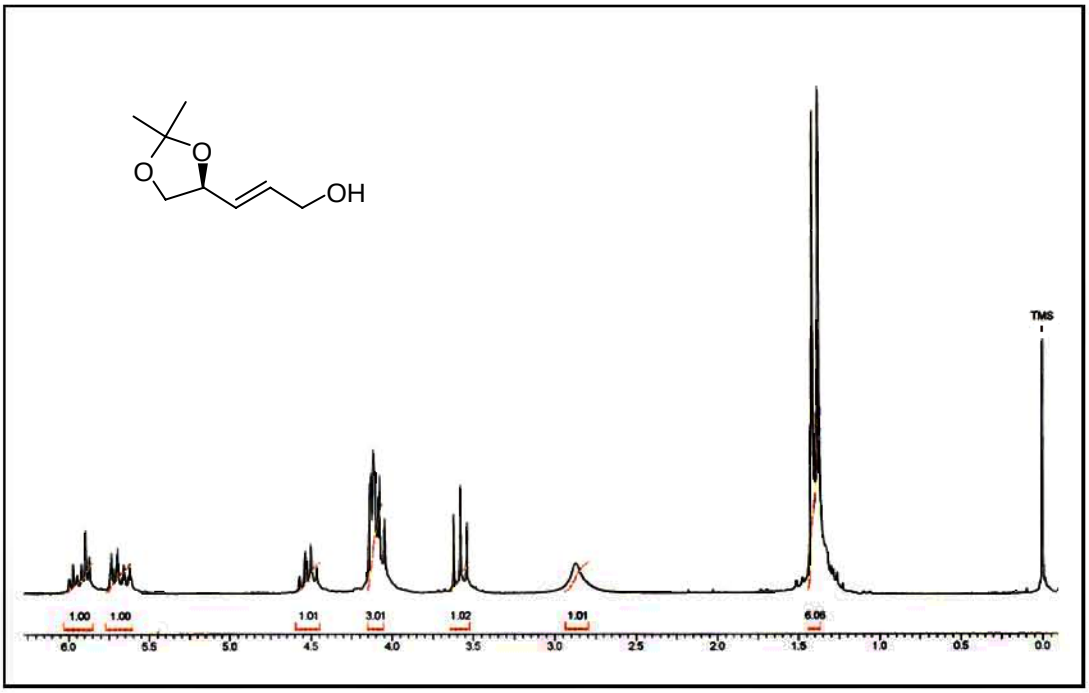
SPECTROSCOPIC DATA



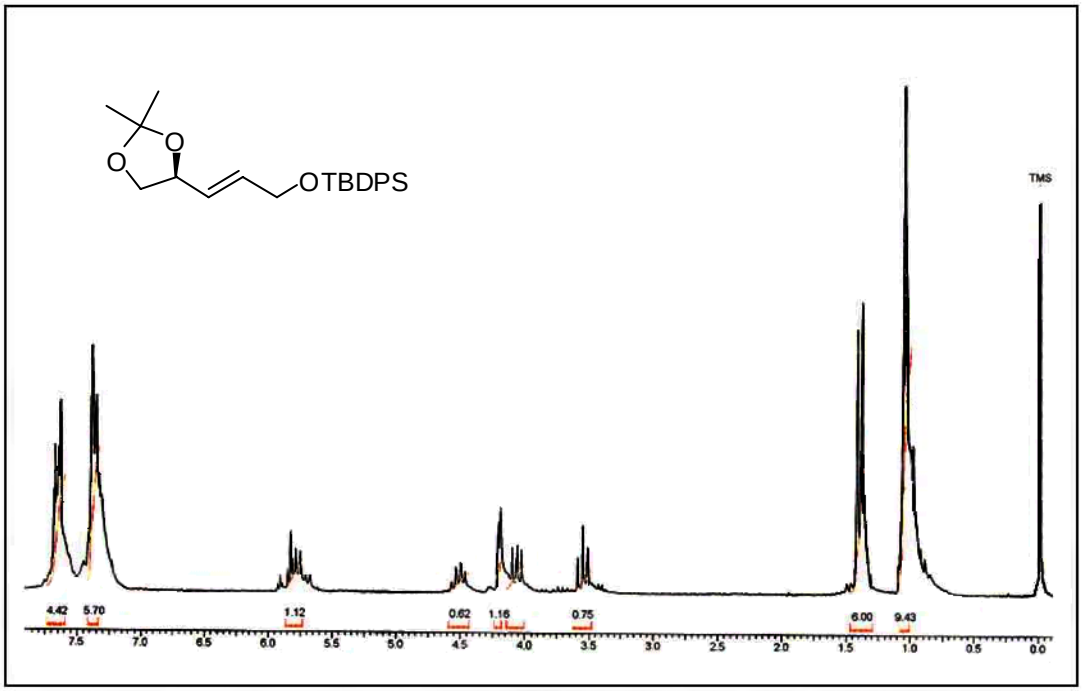
^{1}H NMR spectra of compound 15 in $CDCl_3$



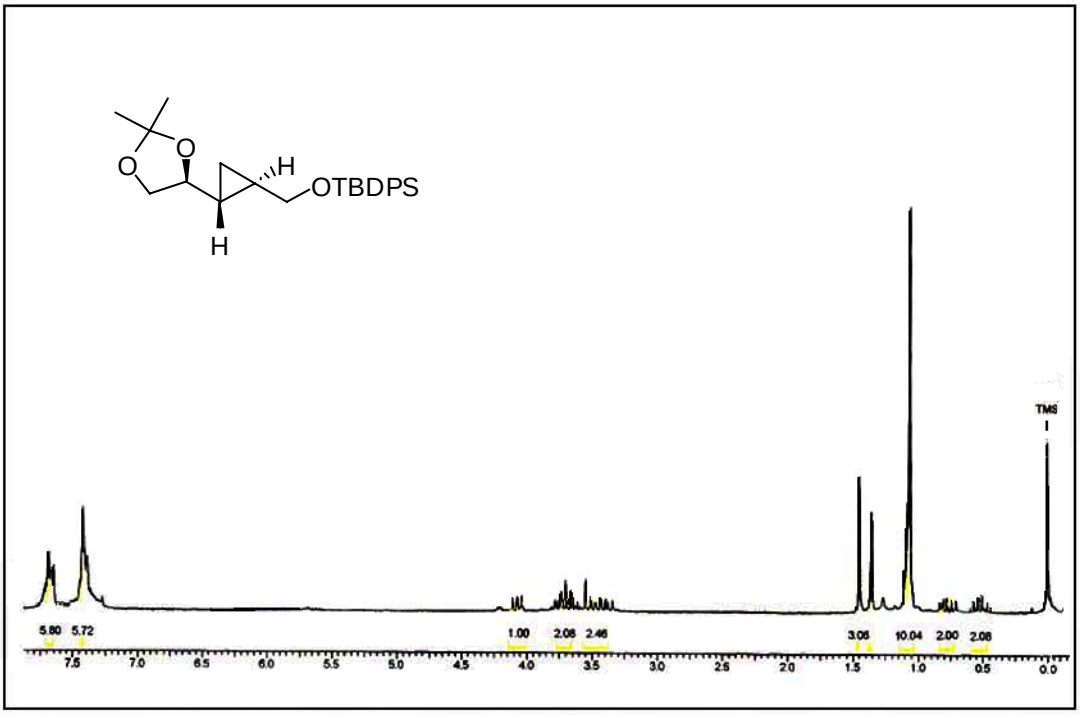
^{13}C NMR spectra of compound 15 in $CDCl_3$



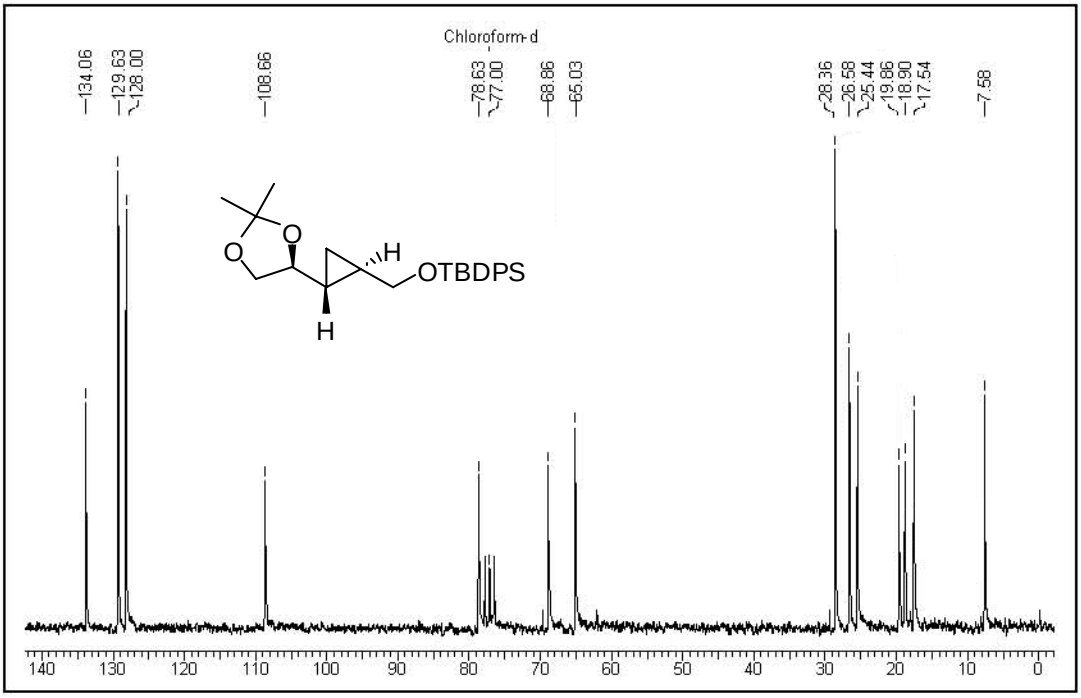
^{1}H NMR spectra of compound 16 in $CDCl_3$



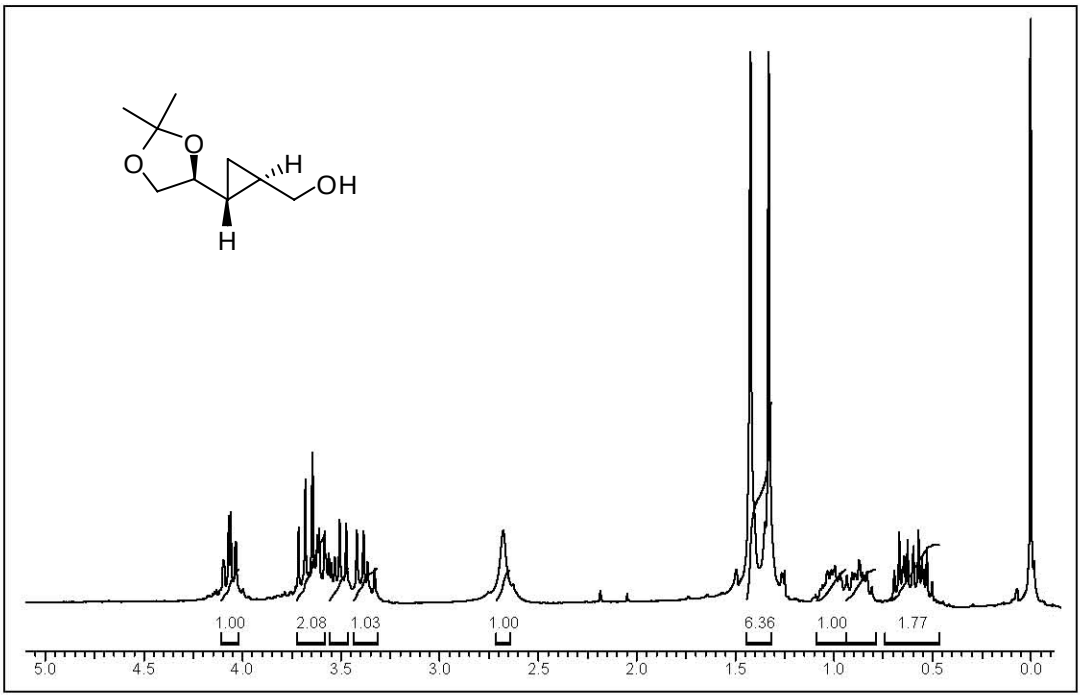
^{1}H NMR spectra of compound 17 in $CDCl_3$



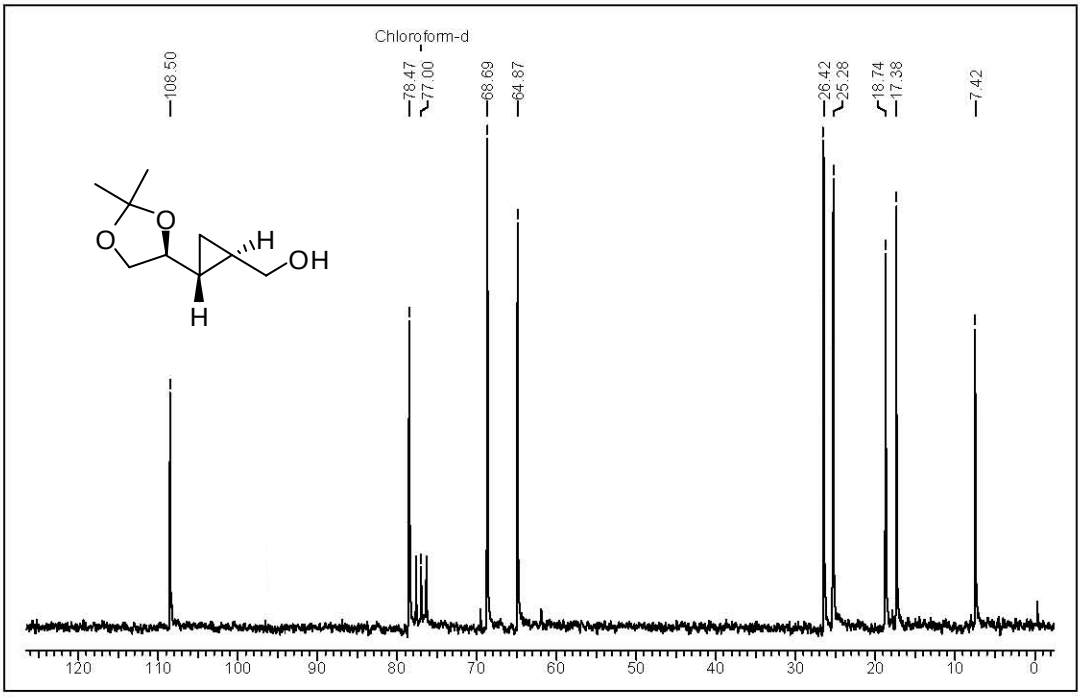
^{1}H NMR spectra of compound 18 in $CDCl_3$



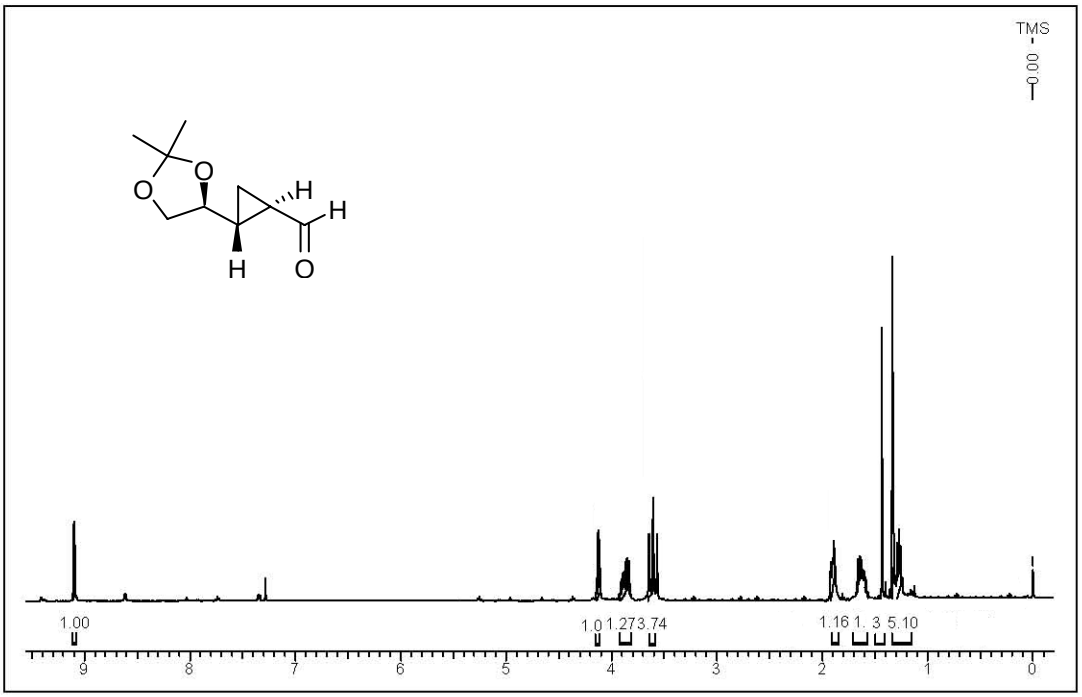
^{13}C NMR spectra of compound 18 in $CDCl_3$



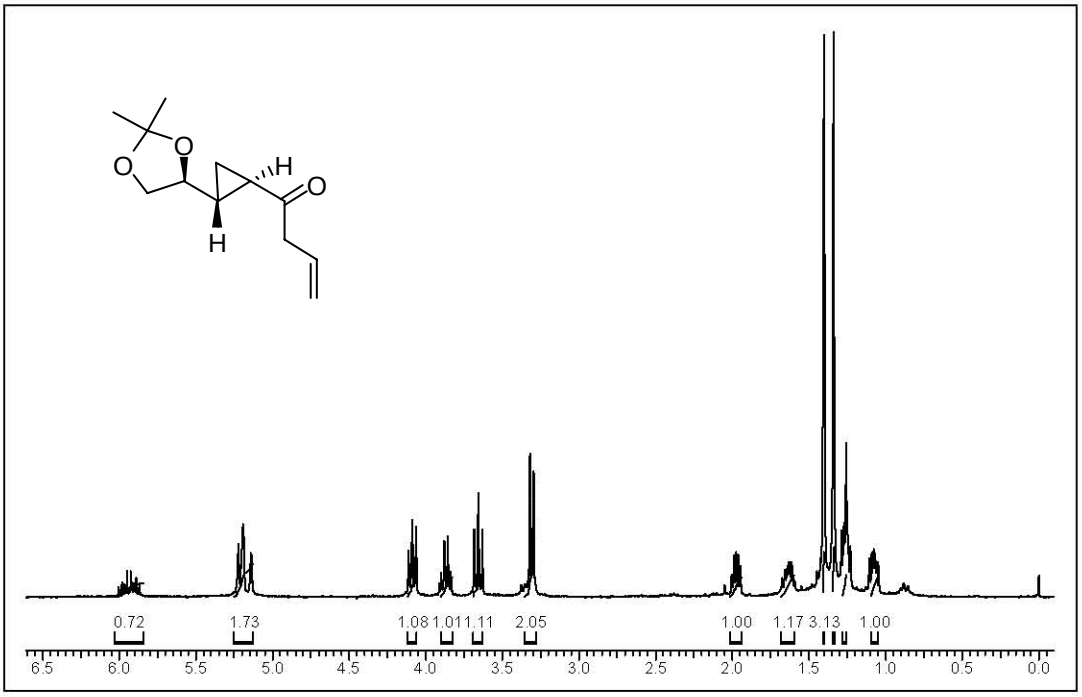
^{1}H NMR spectra of compound 12 in $CDCl_3$



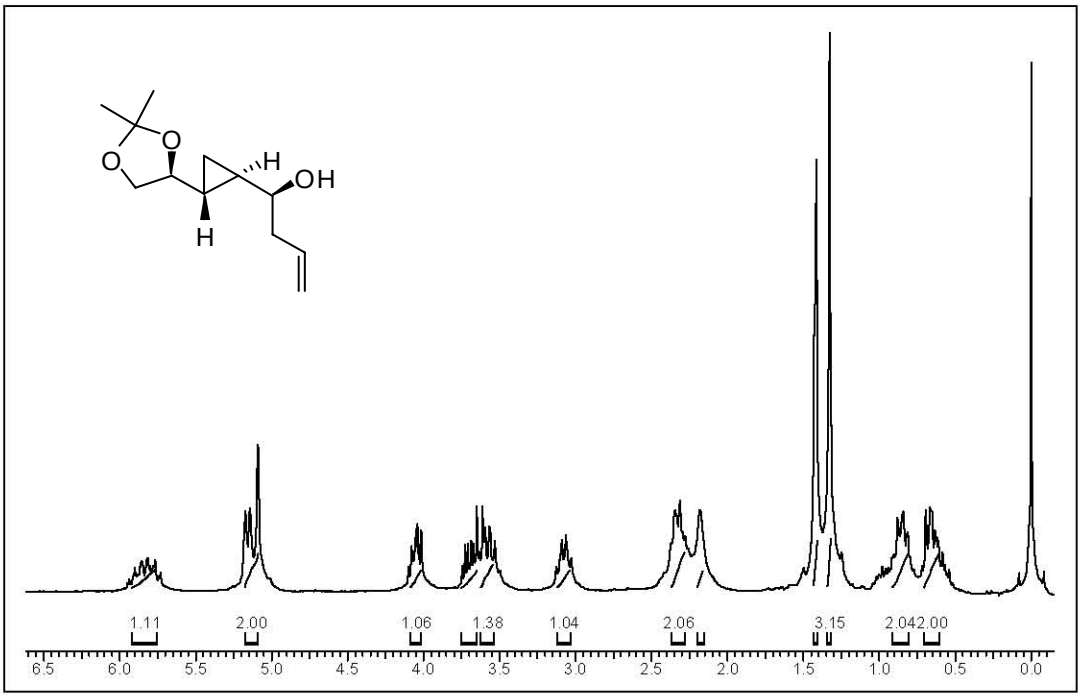
^{13}C NMR spectra of compound 12 in $CDCl_3$



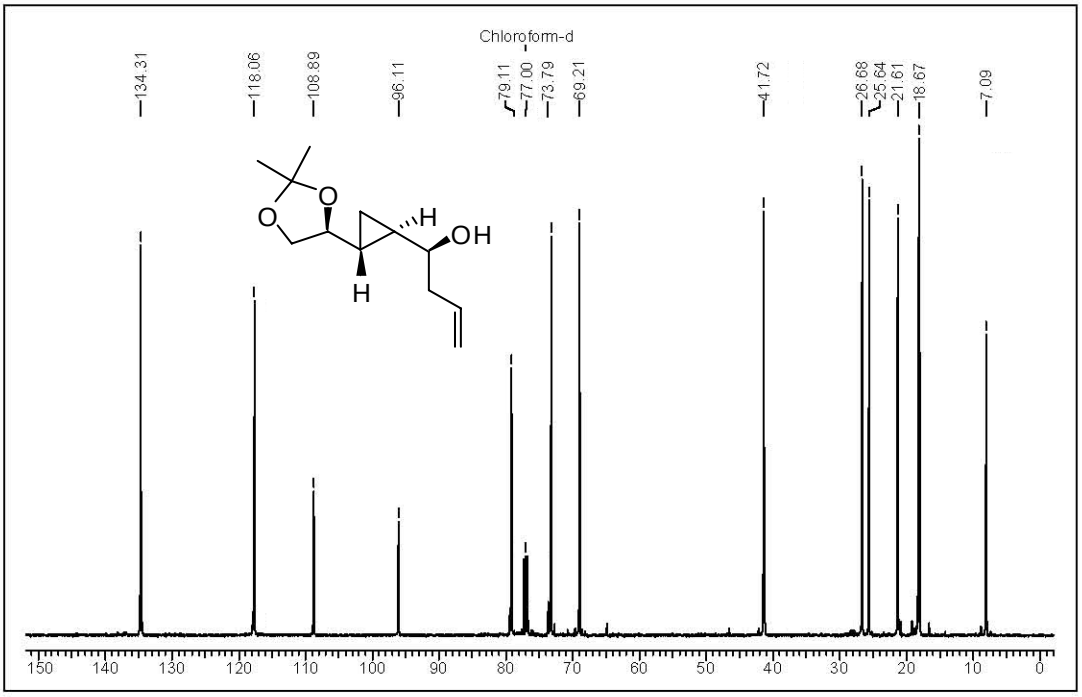
^{1}H NMR spectra of compound 19 in $CDCl_3$



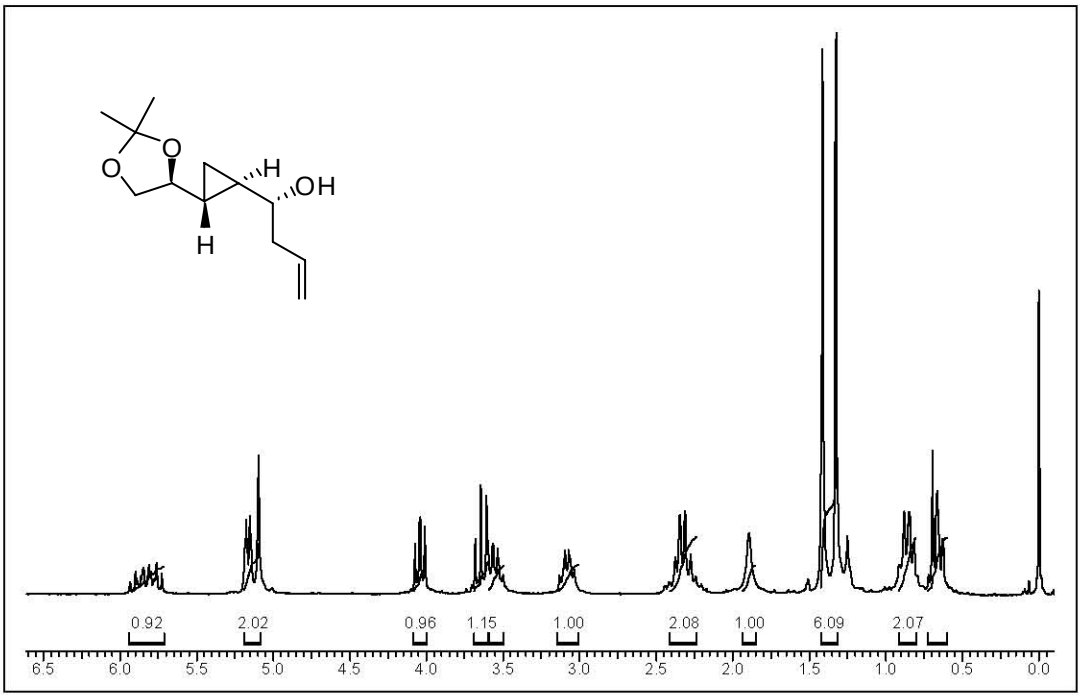
^{1}H NMR spectra of compound 20 in $CDCl_3$



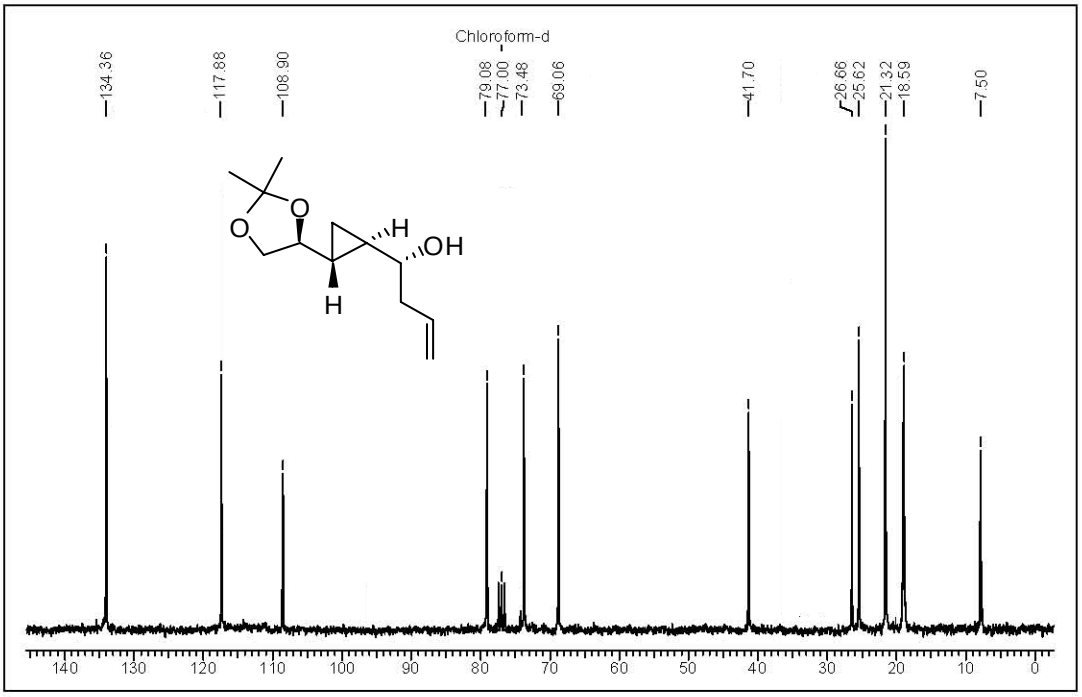
^{1}H NMR spectra of compound 10 in $CDCl_3$



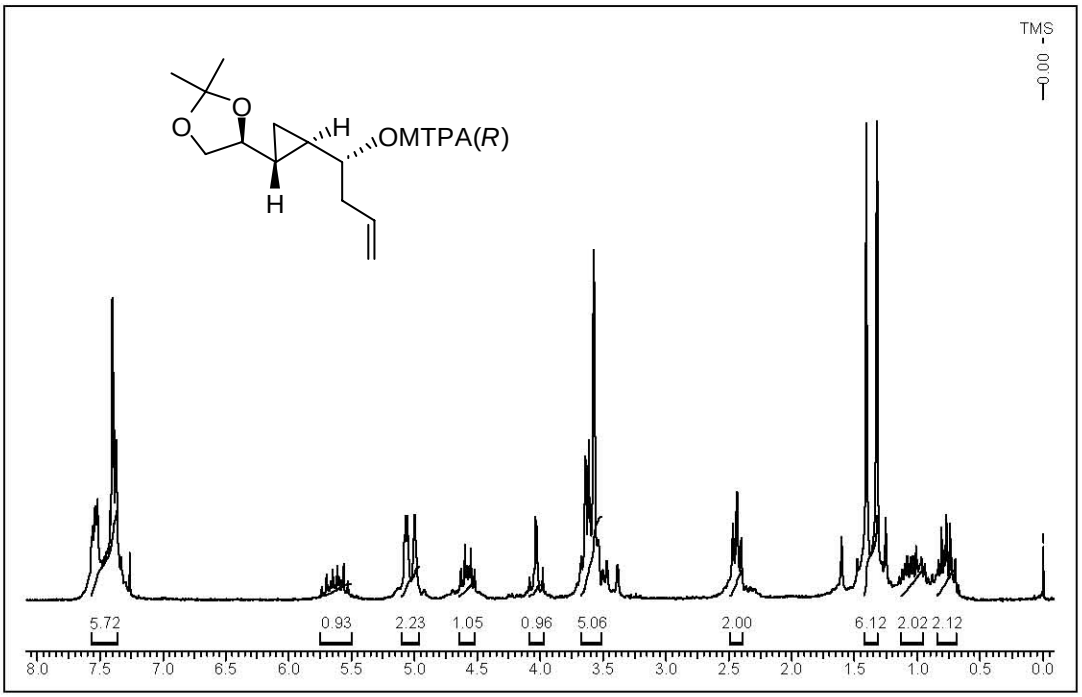
^{13}C NMR spectra of compound 10 in $CDCl_3$



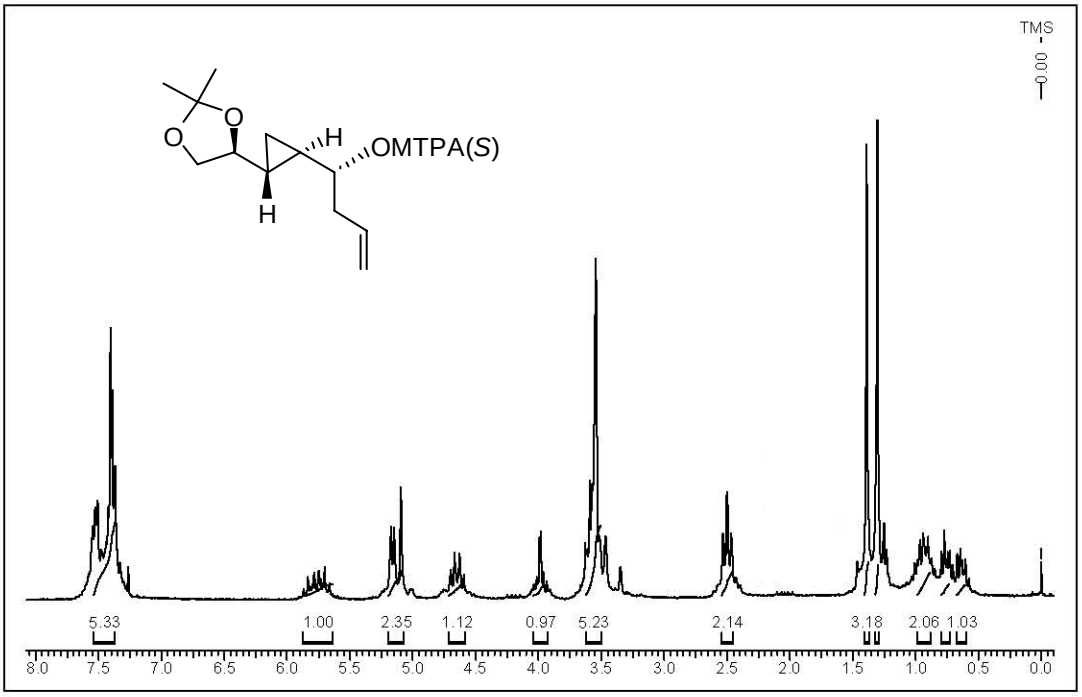
^{1}H NMR spectra of compound 11 in $CDCl_3$



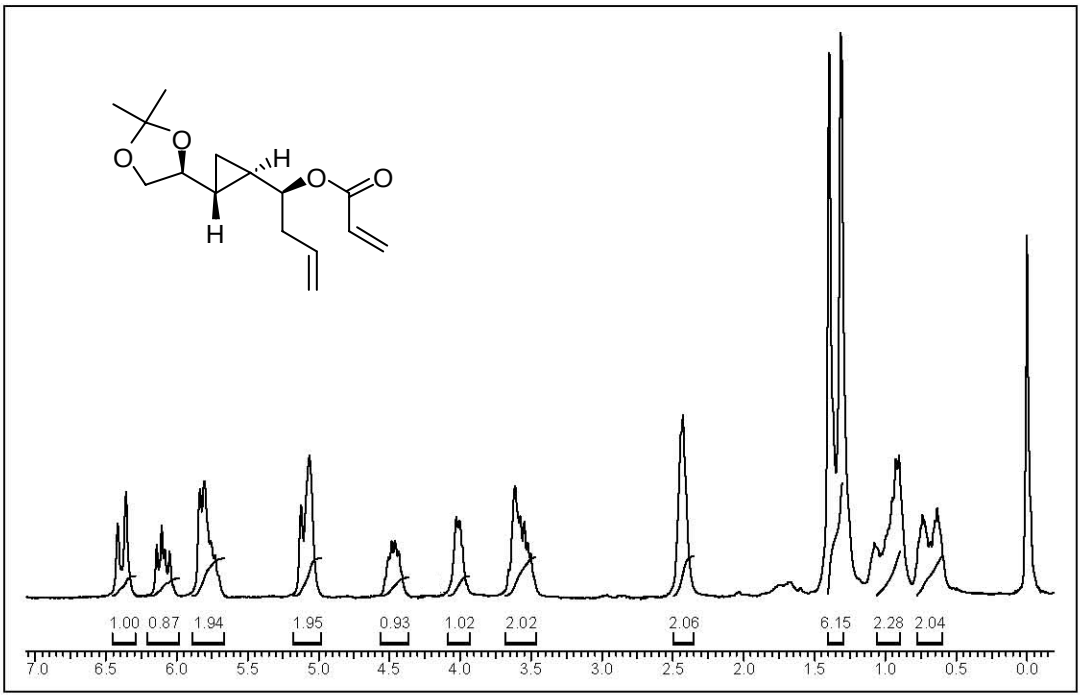
^{13}C NMR spectra of compound 11 in $CDCl_3$



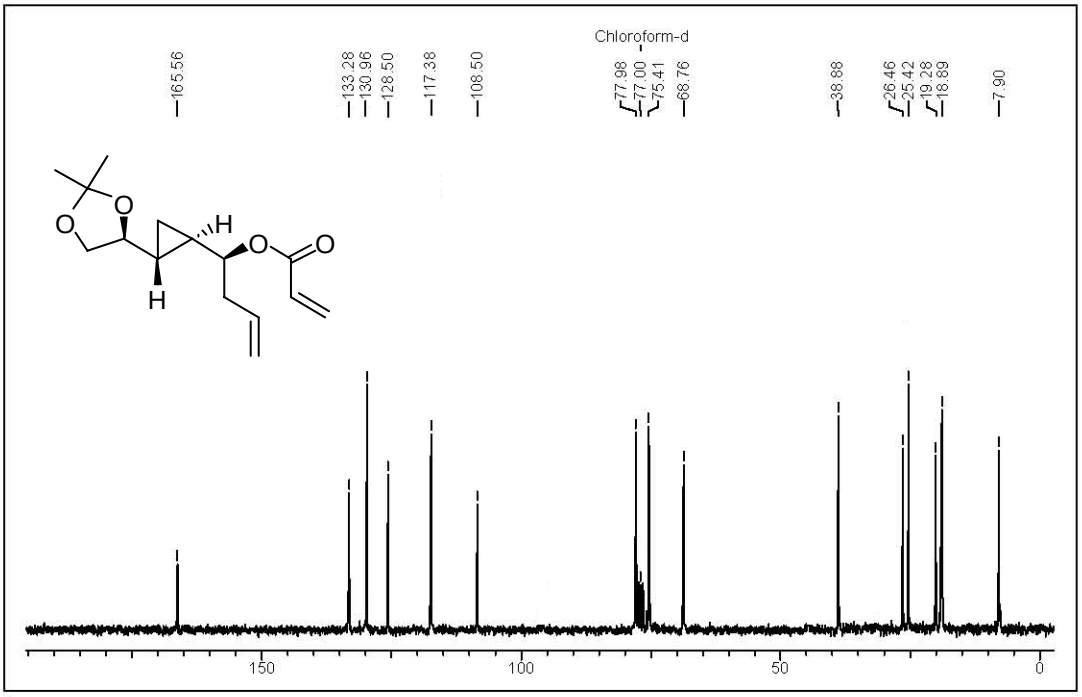
^{1}H NMR spectra of compound 21 in $CDCl_3$



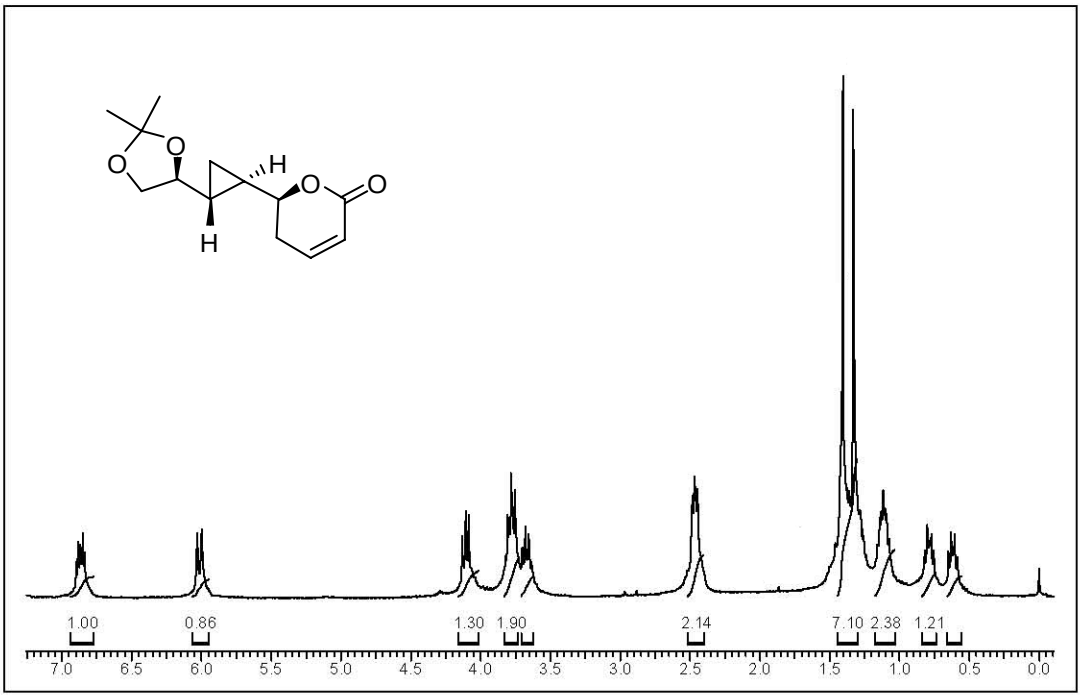
^{1}H NMR spectra of compound 22 in $CDCl_3$



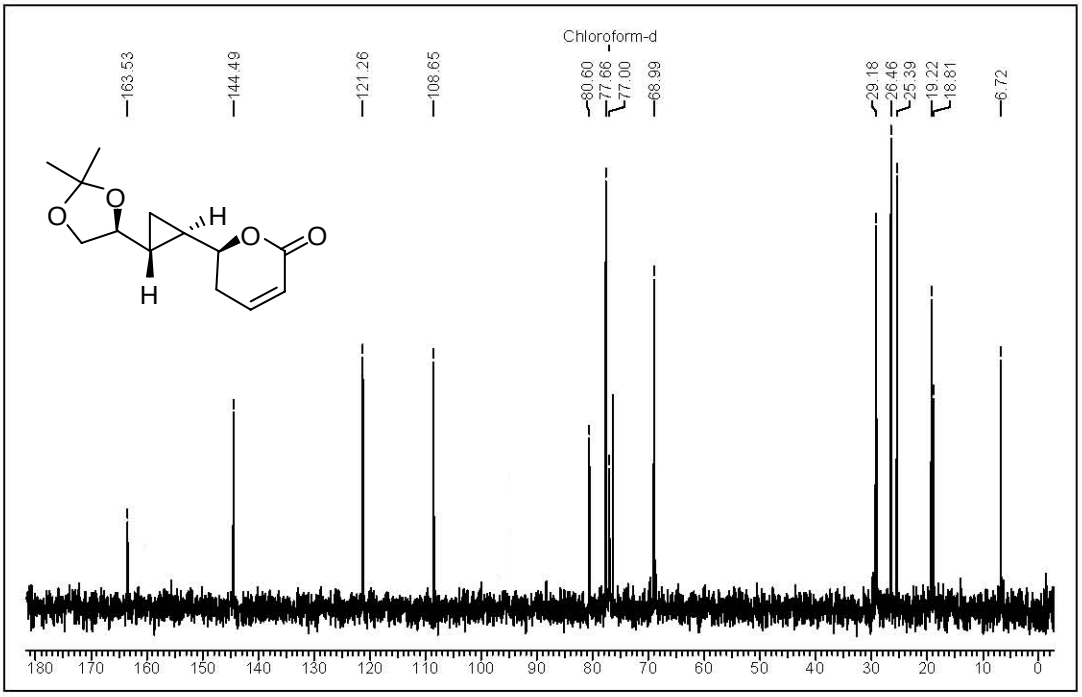
^{1}H NMR spectra of compound 9 in $CDCl_3$



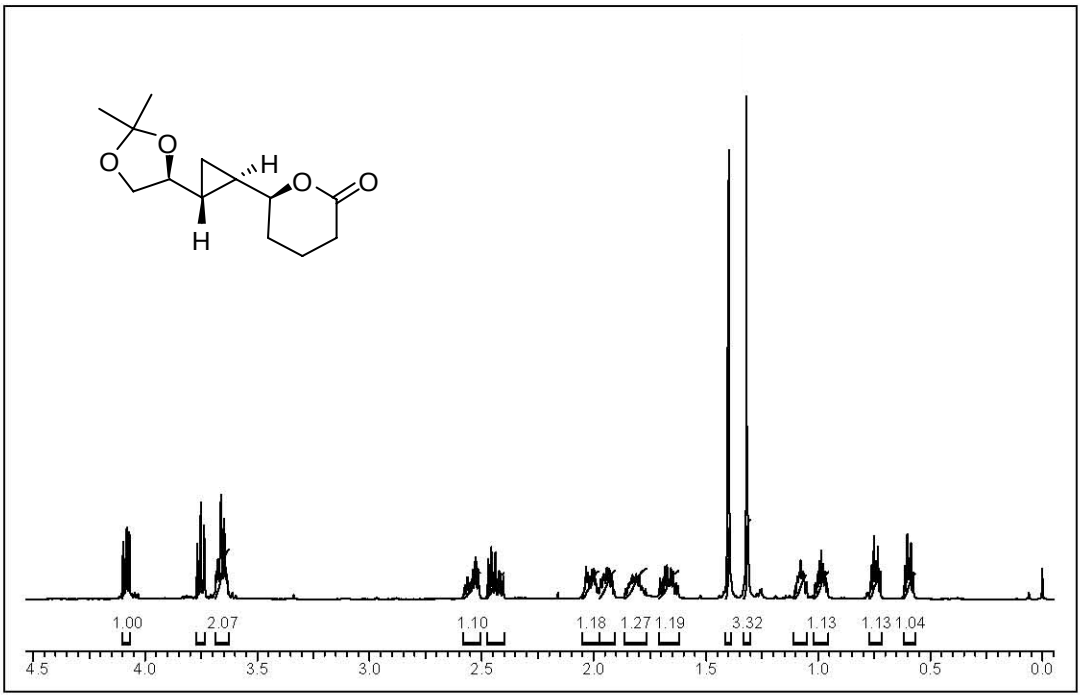
^{13}C NMR spectra of compound 9 in $CDCl_3$



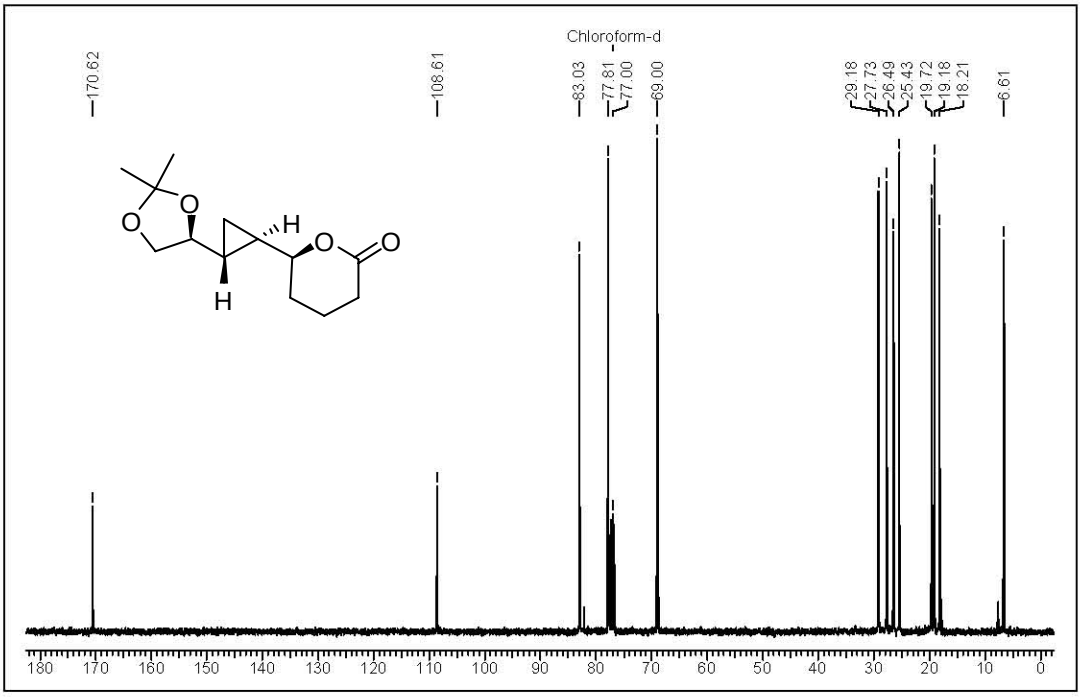
^{1}H NMR spectra of compound 23 in $CDCl_3$



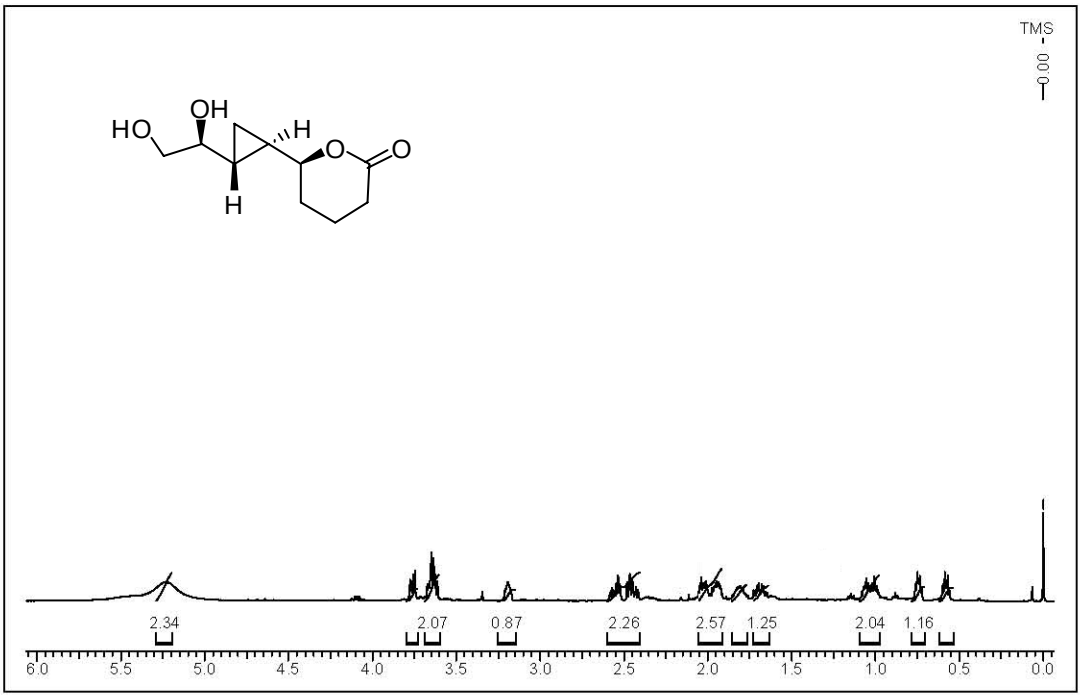
^{13}C NMR spectra of compound 23 in $CDCl_3$



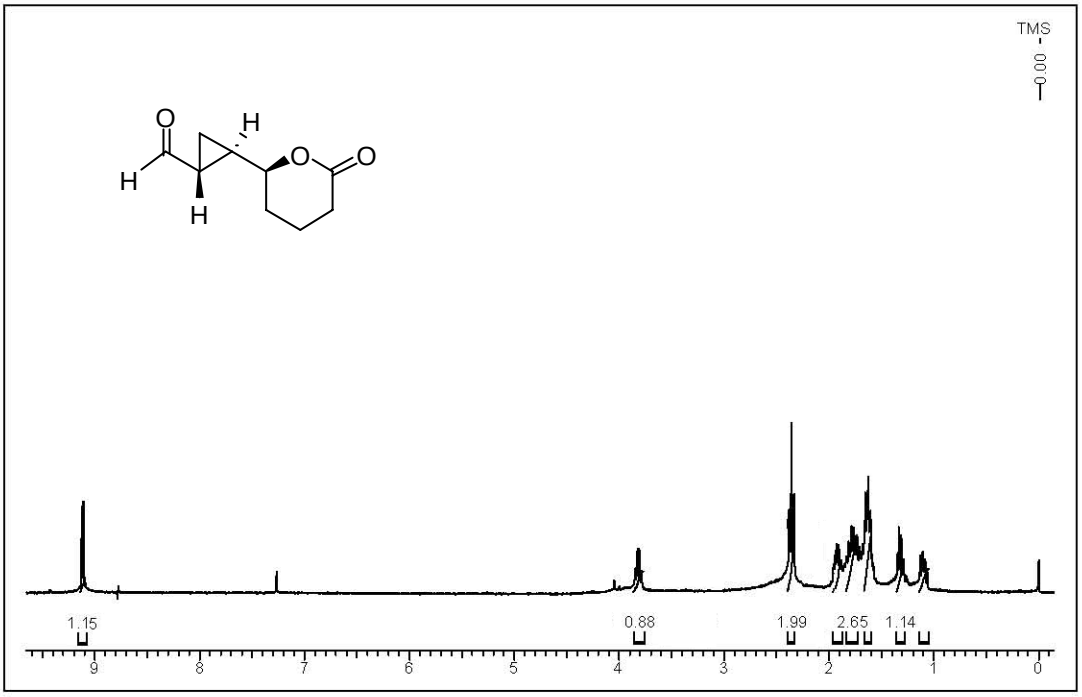
^{1}H NMR spectra of compound 24 in $CDCl_3$



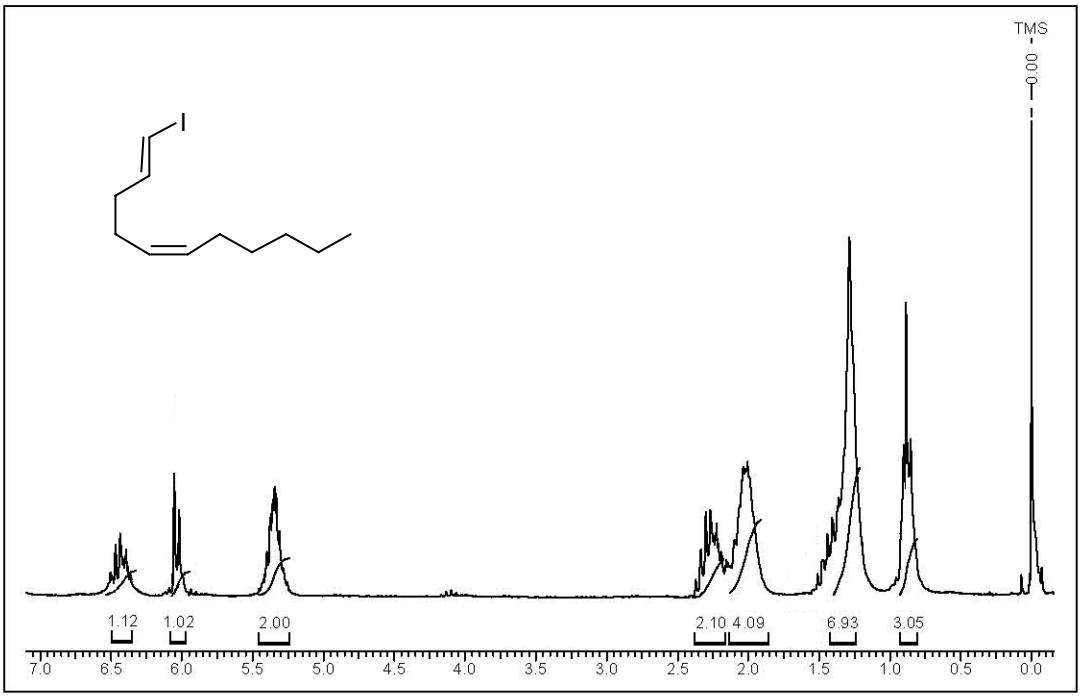
^{13}C NMR spectra of compound 24 in $CDCl_3$



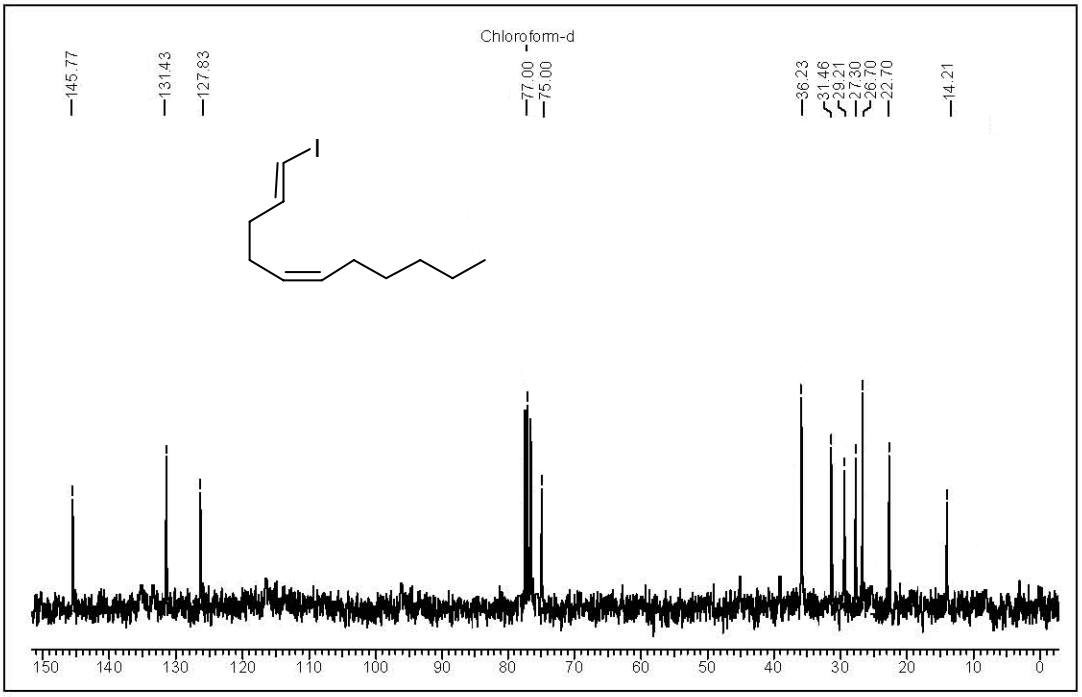
^{1}H NMR spectra of compound 25 in $CDCl_3$



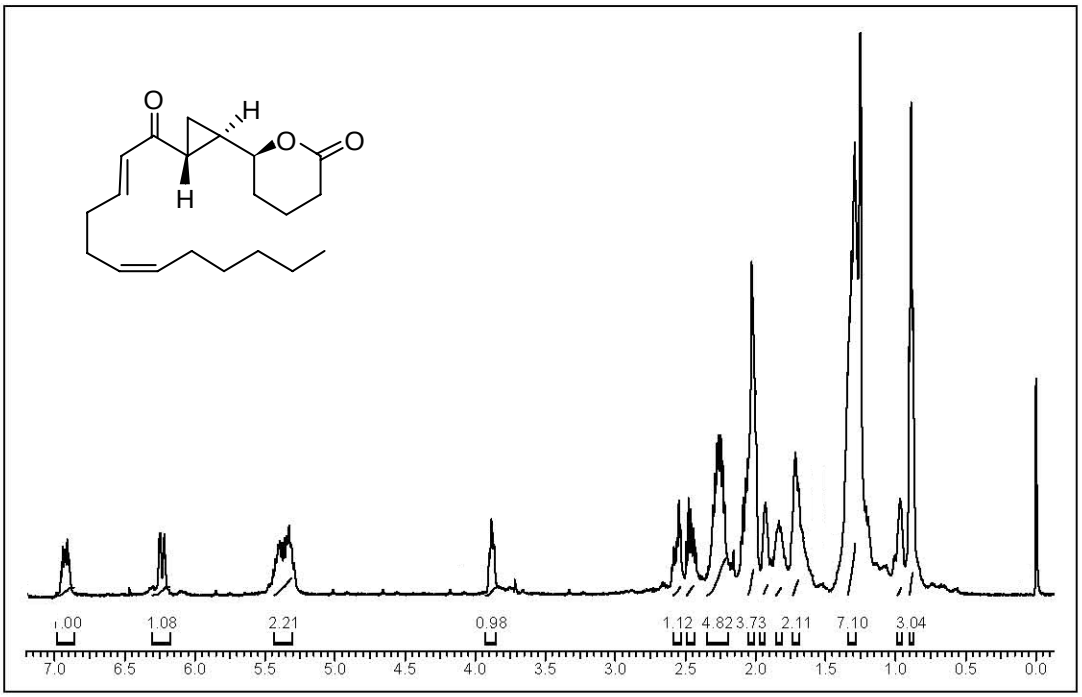
^{1}H NMR spectra of compound 5 in $CDCl_3$



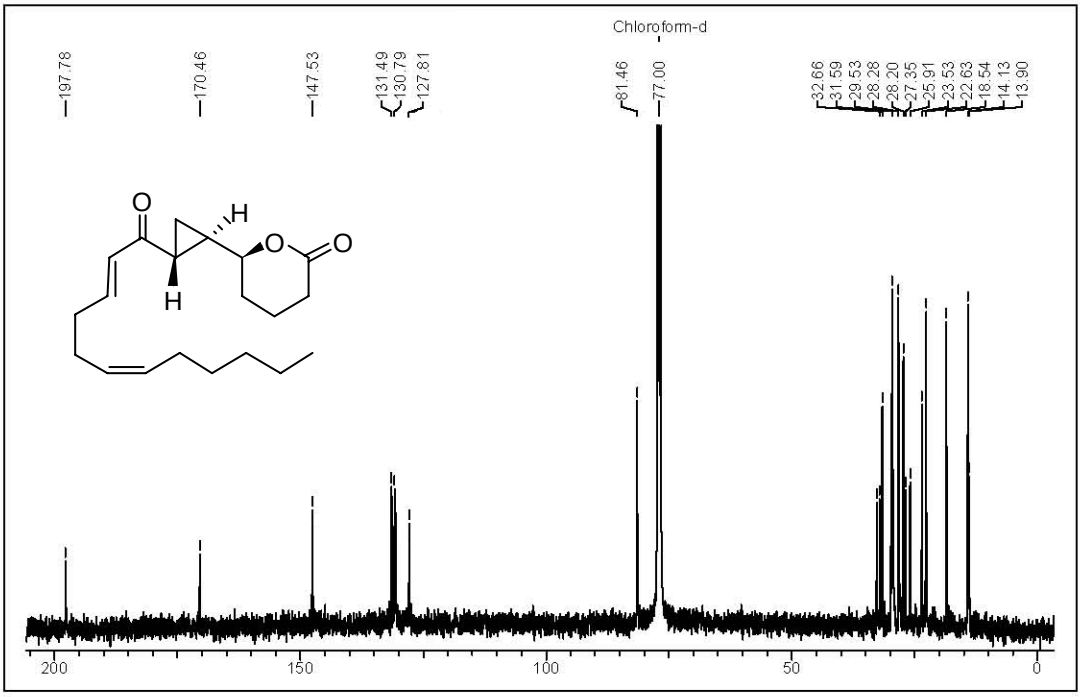
^{1}H NMR spectra of compound 6 in $CDCl_3$



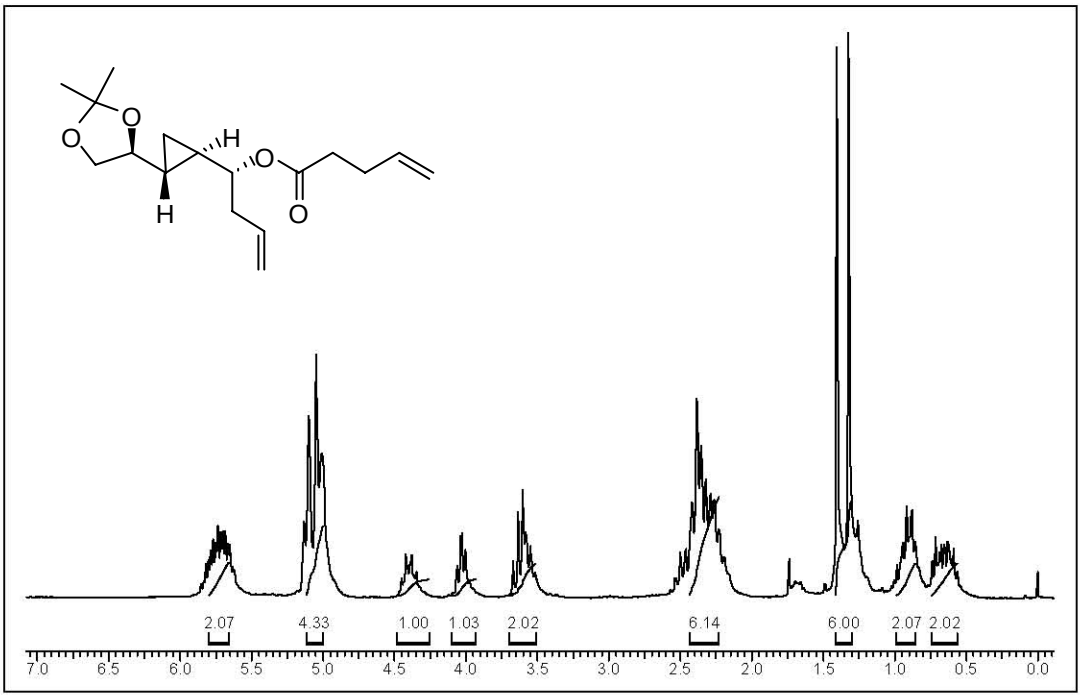
^{13}C NMR spectra of compound 6 in $CDCl_3$



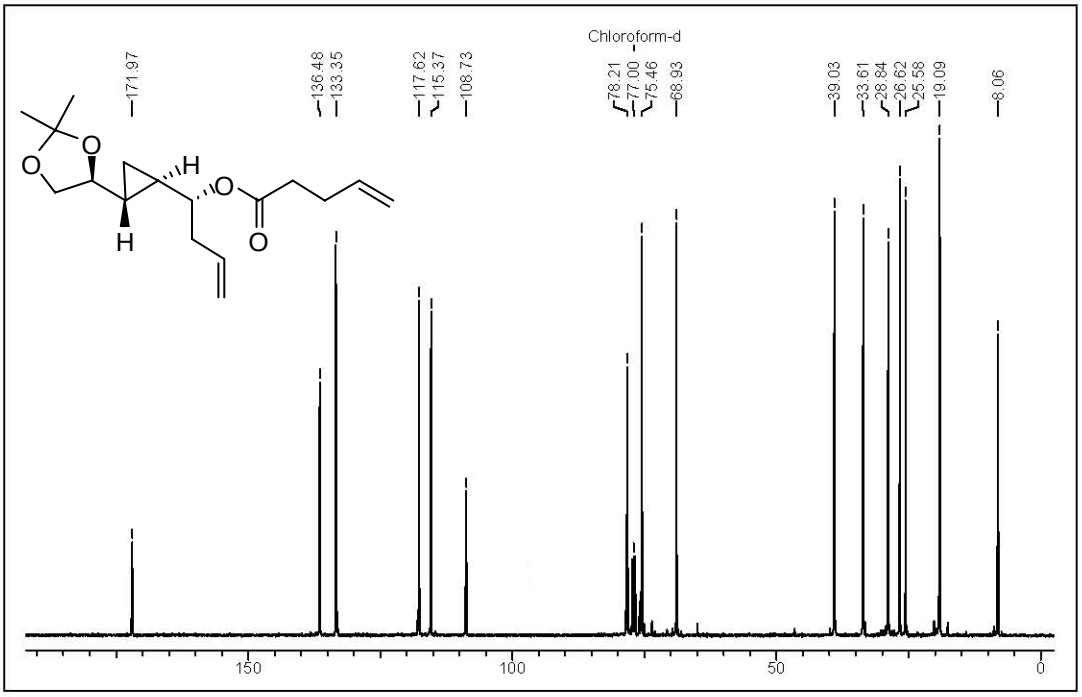
^{1}H NMR spectra of compound 1 in $CDCl_3$



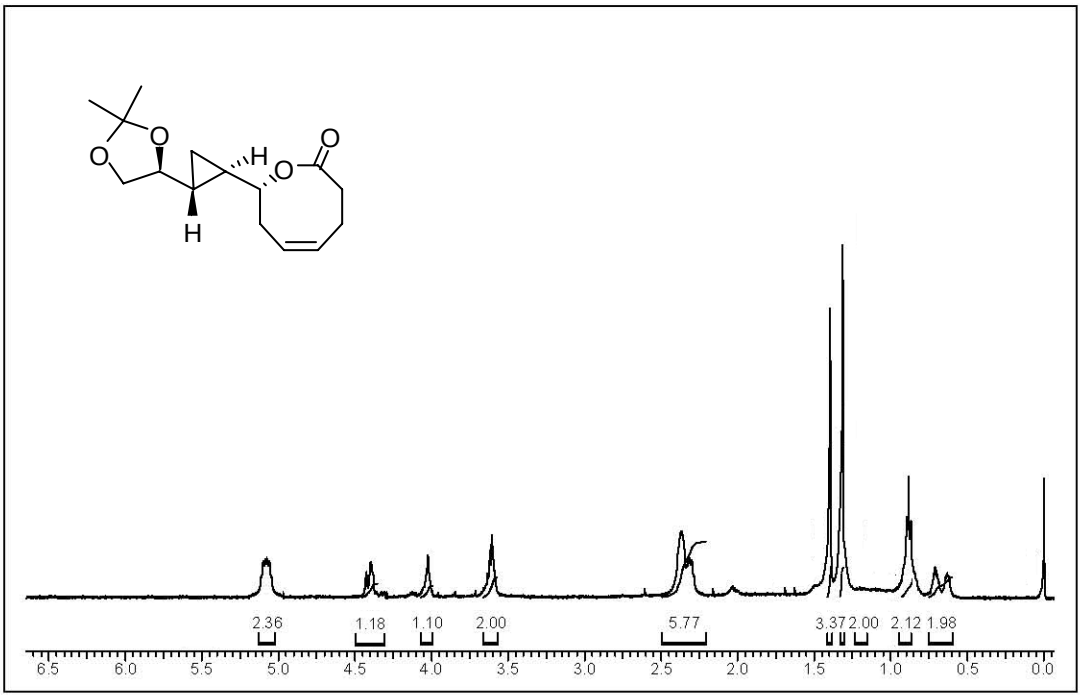
^{13}C NMR spectra of compound 1 in $CDCl_3$



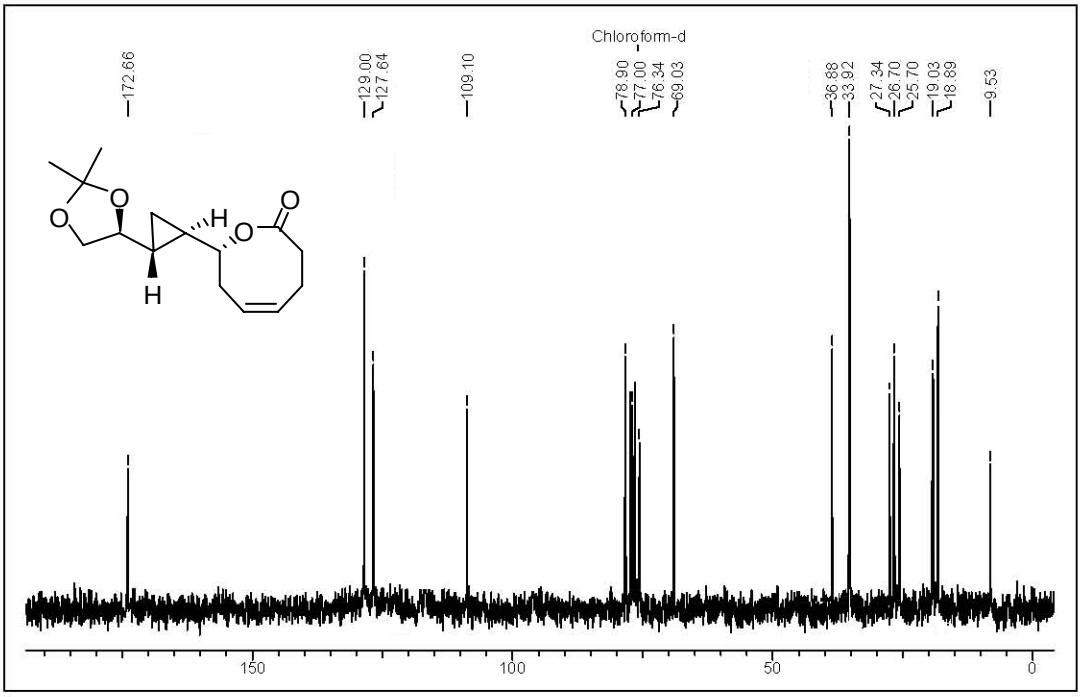
^{1}H NMR spectra of compound 33 in $CDCl_3$



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



^{1}H NMR spectra of compound 2 in $CDCl_3$



^{13}C NMR spectra of compound 2 in $CDCl_3$

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Publications

1. D. K. Mohapatra and **Gorakhanath S. Yellol** *ARKIVOC* **2003** *(ix)* 21-33 "Ring-closing metathesis (RCM) reaction: application in the synthesis of cyclopropyl-lactone segment of solandelactones "

2. D. K. Mohapatra and **Gorakhanath S. Yellol** *ARKIVOC* **2005** *(iii)* 144-155 "Asymmetric total synthesis of eicosanoid "

3. M. K. Gurjar, **G. S. Yellol**, C. V. Ramanna, D. K. Mohapatra "Towards the total synthesis of Amphidinolides X" (manuscript under preparation)