SYNTHETIC STUDIES TOWARD PROTOTYPE RENIN INHIBITORS, BASILISKAMIDES AND DECARESTRICTINE C_1

BY

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Synthetic Studies Toward Prototype Renin Inhibitors, Basiliskamides and Decarestrictine C_1

THESIS

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By

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DEDICATED
TO
MY LATE FATHER
& MY MOTHER

D E C L A R A T I O N

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

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C E R T I F I C A T E

The research work presented in thesis entitled "**Synthetic Studies Toward Prototype Renin Inhibitors, Basiliskamides and Decarestrictine C_1**" has been carried out under my supervision and is a bonafide work of **Mr. Gokarneswar Sahoo**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

Place:
Date:

(**Dr. M. K. Gurjar**)
Research Guide

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Gokarneswar Sahoo

ABBREVIATIONS

Ac	-	Acetyl
Anh.	-	Anhydrous
AIBN	-	Azoisobutyronitrile
BH_3·DMS	-	Boron dimethylsulfide complex
Bn	-	Benzyl
Boc	-	*tert*-Butoxy carbonyl
Bu	-	Butyl
CMR	-	Carbon Magnetic Resonance
COSY	-	Correlation Spectroscopy
DDQ	-	2,3-Dichloro-5,6-dicyanobenzoquinone
DEPT	-	Distorted Enhancement Polarized Transform
DIBAL-H	-	Diisobutylaluminium hydride
DET	-	Diethyl tartrate
DMF	-	*N*,*N*'-Dimethylformamide
DMAP	-	*N*,*N*'-Dimethylaminopyridine
DMSO	-	Dimethyl sulfoxide
DMP	-	Dess–Martin periodinane
DMP	-	2, 2'-Dimethoxy propane
dr	-	Diastereomeric ratio
Et	-	Ethyl
EtOAc	-	Ethyl acetate
FGT	-	Functional group transformation
GDA	-	Glucose diacetonide
HMBC	-	Heteronuclear Multiple Bond Correlation
HSQC	-	Heteronuclear Single Quantum Coherence
Im	-	Imidazole
IBX	-	Iodoxybenzoic acid
LiHMDS	-	Lithium hexamethyldisilazide
LAH	-	Lithium aluminium hydride

Me	-	Methyl
Ms	-	Methanesulfonyl
Mes	-	Mesityl
NMR	-	Nuclear Magnetic Resonance
NOESY	-	Nuclear Overhauser Enhancement Spectroscopy
ORTEP	-	Oak Ridge Thermal Ellipsoid Plot
Pd/C	-	Palladium on Carbon
Ph	-	Phenyl
PMR	-	Proton Magnetic Resonance
Pr	-	Propyl
Py	-	Pyridine
PCC	-	Pyridiniumchlorochromate
PDC	-	Pyridiniumdichromate
$PdCl_2$	-	Palladium (II) chloride
p-TSA	-	*para*-Toluenesulfonic acid
PMB	-	*para*-methoxybenzyl
TBAF	-	Tetra-*n*-butylammonium fluoride
TBDPS-Cl	-	*tert*-Butyldiphenyl silyl chloride
TBHP	-	*tert*-Butylhydroperoxide
TBTH	-	Tri n-butyltin hydride
THF	-	Tetrahydrofuran
TPP	-	Triphenyphosphine
Ts	-	Tosyl

Abbreviations used for NMR spectral informations:

br	-	Broad	q	-	Quartet
d	-	Doublet	s	-	Singlet
m	-	Multiplet	t	-	Triplet

GENERAL REMARKS

- ^{1}H NMR spectra were recorded on AC-200 MHz, MSL-300 MHz, AV-400 MHz and DRX-500 MHz spectrometers using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C NMR spectra were recorded on AC-50 MHz, MSL-75 MHz, AV-100 MHz, and DRX-125 MHz spectrometer.
- EI Mass spectra were recorded on Finngan MAT-1020 spectrometer at 70 *eV* using a direct inlet system.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected.
- The X-ray Crystal data were collected on Bruker SMART APEX CCD diffractometer using Mo K_{α} radiation with fine focus tube with 50 kV and 30 MA.
- All reactions are monitored by Thin Layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV light, I_2 and anisaldehyde in ethanol as development reagents.
- All solvents and reagents were purified and dried by according to procedures given in Vogel's Text Book of Practical Organic Chemistry. All reactions were carried out under Nitrogen or Argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 40 °C.
- Silica gel (60–120), (100-200), and (230-400) mesh were used for column chromatography and was purchased from ACME Chemical Company, Bombay, India.
- Different numbers were assigned for compounds in Abstract and each section and chapters.

CONTENTS

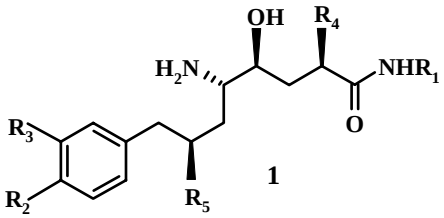
Research Student	:	Gokarneswar Sahoo
Research Guide	:	Dr. Mukund K. Gurjar
Title of Thesis	:	**Synthetic Studies Toward Prototype Renin Inhibitors, Basiliskamides and Decarestrictine C_1**
Registration No.	:	E1/123/Ph.D/2005
Date of Registartion	:	28. 06. 2004
Place of Work	:	Organic Chemistry Division, National Chemical Laboratory, Pune (INDIA)

Abstract

The thesis entitled "**Synthetic Studies Toward Prototype Renin Inhibitors, Basiliskamides and Decarestrictine C_1**" is divided into three chapters. The first chapter deliberates the total synthesis of prototype renin inhibitors. The second chapter deals with the stereoselective Simmons-Smith cyclopropanation on carbohydrate templates (Section I) and the synthetic efforts towards basiliskamides A and B (Section II). The third chapter includes the total synthesis of decarestrictine C_1.

CHAPTER I: Total Synthesis of Prototype Renin Inhibitors

Renin inhibitors are effective means of treating hypertension and cardiovascular disorders and therefore, they have attracted unprecedented attention particularly from synthetic chemists with a singular intention of preparing in respectable quantities for bioavailability and related studies. A variety of stable peptide like analogues have been developed which can inhibit the renin by intravenous administration and lower blood-pressure conditions. More recently; a new class of non-peptidic inhibitors have been classified and proven to be excellent drug candidates. Various analogues of non-peptidic renin inhibitors (**1**) carrying different substituents at the aromatic ring, the amide nitrogen and at 2,7- alkyls have been synthesized with unique binding affinities to renin.



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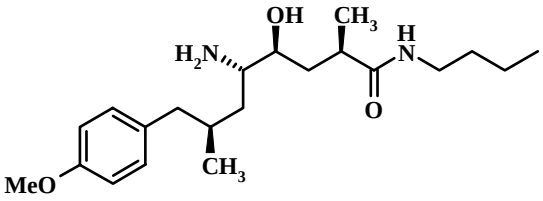


Target molecule (2)

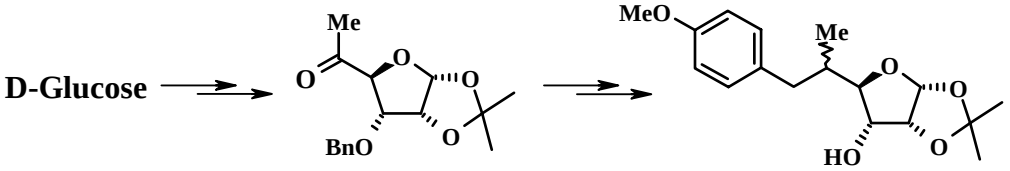
R_1 = Alkyl, amidoalkyl etc.

R_2, R_3 = Methoxy and methoxyethoxy etc.

R_4, R_5 = Isopropyl or methyl

Figure 1. General non-peptidic renin inhibitors (**1**) and our target analogue (**2**)

The synthetic effort towards prototype inhibitor **2** is based on chiral pool approach. Correlation of inherent stereochemistry at C2 and C3 of D-glucose with those at C4 and C5 of analogue **2** and off-template stereo-controlled reactions by the D(+)-glucofuranose ring system were the strong incentives for choosing D(+)-glucose to start with.

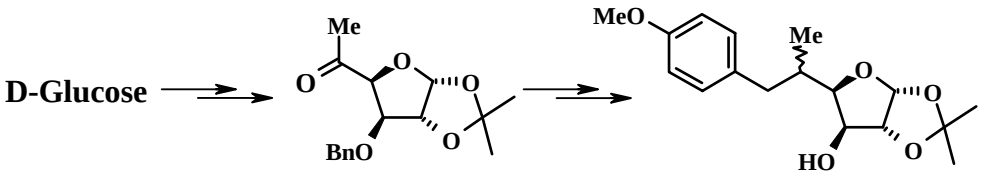


3 **4** **5**

Diastereomeric mixture (**55:45**)

Scheme 1

The known 5-ulose derivative **4** was prepared from D(+)-glucose in 7 steps (Scheme 1). The ketone **4** was next subjected to the Wittig reaction with (*p*-methoxybenzylidene) triphenylphosphorane in benzene at room temperature to provide the *E* olefin as a major product (*E*:*Z* = 92:8 from ^{1}H NMR). The geometrical isomer was confirmed by NOESY studies. The reduction of the olefin with Pd/C at 50 *psi* H_2 pressure afforded an inseparable diastereomeric mixture of alcohol **5** in ration 55:45.

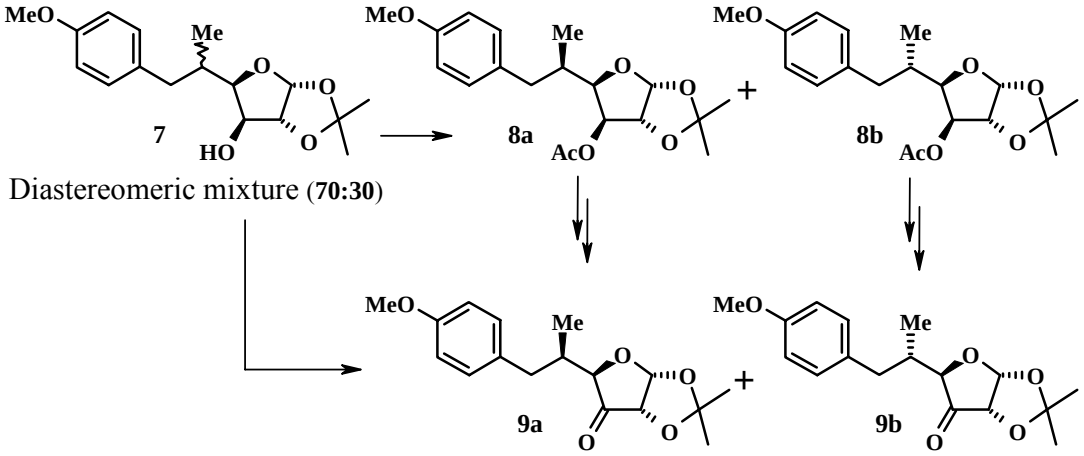


3 **6** **7**

Diastereomeric mixture (**7:3**)

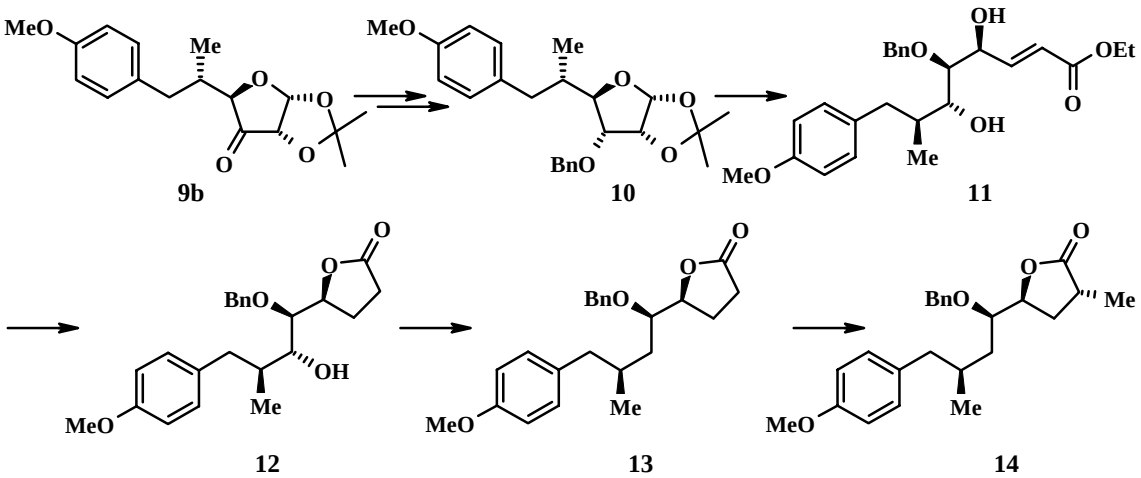
Scheme 2

Now the 5-ulose derivative **6** with the unchanged C3 stereocenter (prepared from D(+)-glucose in five steps) was subjected to the Wittig reaction with (*p*-methoxybenzylidene)triphenylphosphorane in benzene at room temperature to provide an inseparable mixture (4:1, from ^{1}H NMR) of geometrical isomers, which on hydrogenation in the presence of 10% Pd/C at 50 *psi* afforded **7**. The product **7** was a mixture of diastereomers differing in the stereocenter at C-5 in a ratio 7:3 (Scheme 2).



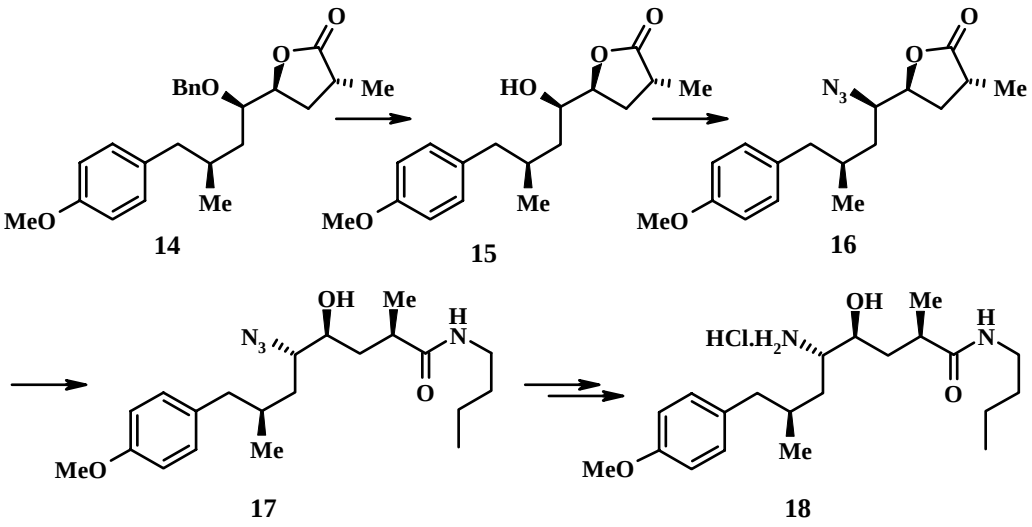
Scheme 3

Attempts to separate the diastereomers by derivatisation method were successful for the acetate compounds (**8a** and **8b**) and keto compounds (**9a** and **9b**). The structural features with stereochemistry of both the acetates were confirmed by X-ray studies. At this juncture, it was confirmed that the reduction of the olefin has resulted the required isomer as the major product (Scheme 3).



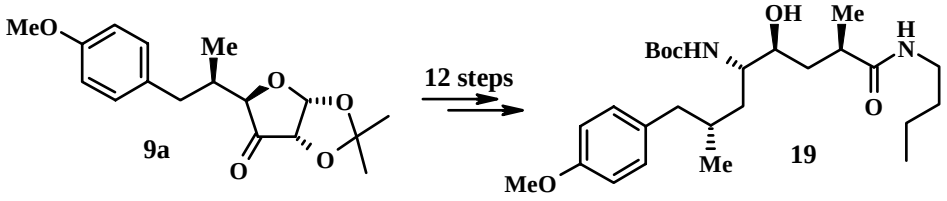
Scheme 4

The 3-ulose derivative **9b** was reduced with $NaBH_4$ in MeOH to give stereochemically inverted C_3-OH derivative and subsequent benzylation with BnBr and NaH, afforded **10**. The cleavage of the isopropylidene group followed by two-carbon homologation yielded the *E* olefin **11** as the major product. Reduction of double bond and treatment with *p*-TSA yielded the lactone derivative **12**. In order to remove the extra hydroxyl group, Barton-McCombie radical deoxygenation protocol was utilized. The C-methylation at C-2 of **13** with LiHMDS and MeI at -78 °C gave **14** as a single diastereomer (Scheme 4). NOESY studies suggested the assigned stereochemistry, and the single crystal X-ray study of its debenzylated product **15** unambiguously confirmed it.



Scheme 5

The hydroxyl compound **15** was subsequently mesylated and S_N2 displacement with LiN_3 in DMF at 60 °C gave **16**, which on treatment with *n*-$BuNH_2$ in ethanol yielded the amide **17**. Finally reduction of N_3 and Boc-protection afforded the N-Boc renin inhibitor analogue, which was later, deprotected by treatment of HCl gas to give the target molecule **18** (Scheme 5).



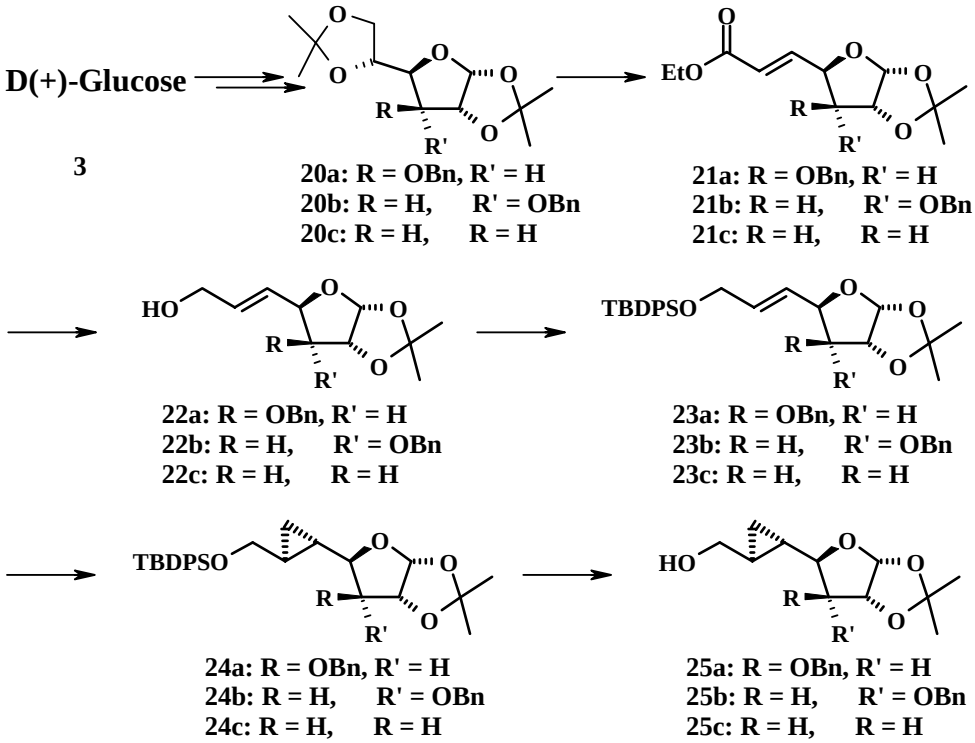
Scheme 6

The diastereomeric compound **9a** was taken through all the 12 steps as described above for **9b**, which led to the formation of 7-*epi* isomer **19** (Scheme 6). The structure and the absolute configuration of **19** were confirmed by single crystal X-ray crystallography.

CHAPTER II

Section 1: Studies Toward Stereoselective Simmons-Smith Cyclopropanation on Carbohydrate Templates

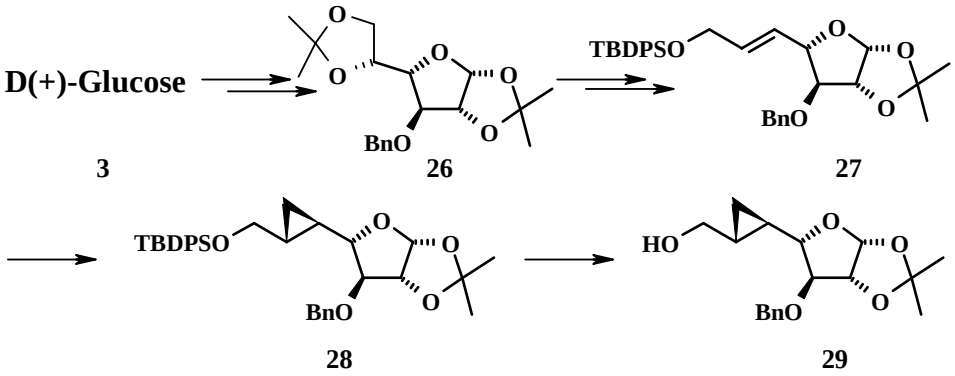
Simmons-Smith cyclopropanation is a well documented reaction and has been used for synthesizing many complex natural products. Stereoselective cyclopropanation reactions have been achieved by using some chiral catalysts and sometimes exploiting the substrate chirality by chelation control. Carbohydrates are known to behave as chiral templates for their polyhydroxyl functionalities, which specify certain orientations due to hydrogen bonding, chelation etc. In this section, we describe the off-template stereoselectivity in Simmons-Smith cyclopropanation reaction due to chelation.



Scheme 7

For this endeavor we have taken the Furanose form of glucose as the template to carry the cyclopropanation reactions. As described in scheme 7, D(+)-glucose was transformed to the corresponding 1,2,5,6-*O*-isopropylidineglucofuranose derivatives with different stereochemistry at C3 (**20a**, **20b**, **20c**). Oxidative cleavage of the 5,6-*O*-isopropylidine group independently with H_5IO_6 followed by two carbon wittig homologation in benzene under reflux condition gave selectively the *E* olefins (**21a**, **21b**, **21c**). The ester groups on selective reduction with DIBAL-H yielded the allylic alcohols (**22a**, **22b**, **22c**), of which the hydroxyl groups were protected as corresponding *t*-butyl diphenylsilyl ethers (**23a**, **23b**, **23c**). The selection of the bulky *t*-butyldiphenylsilyl group as the protecting group was to prevent the participation of the primary hydroxyl group in the complex formation. Now the substrates were ready for the cyclopropanation reaction and on reaction with Et_2Zn, CH_2I_2 in CH_2Cl_2 at -35 °C yielded exclusively single diastereomers (**24a**, **24b**, **24c**). Then the TBDPS ethers were deprotected with TBAF in THF to provide the cyclopropane methyl carbinols (**25a**, **25b**, **25c**) (Scheme 7).

Formation of single diastereomer in each case (Entries 1, 2, 3) propelled us to extend the methodology to galactofuranose derivative. Adopting a parallel reaction sequence as above, we obtained cyclopropane alcohol **29** stereoselectively (Scheme 8).



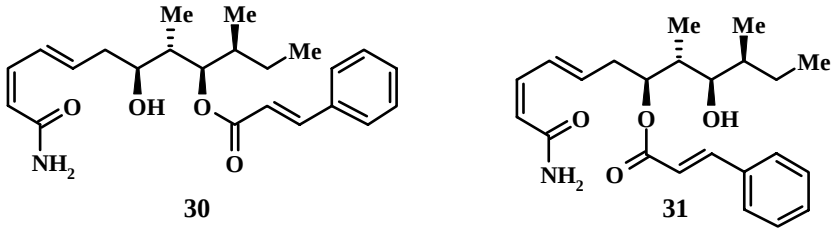
Scheme 8

CHAPTER II

Section 2: Studies Toward The Total Synthesis of Basiliskamides A and B

Novel antifungal metabolites basiliskamides A and B were isolated from the crude organic extracts from PNG-276 cultures, obtained from the tropical waters off the coast of Papua New Guinea and tentatively identified as *Bacillus laterosporus*. These

metabolites show potent inhibition of *Candida albicans* and *Escherichia coli*. Basiliskamides A and B are characterized by the unique amide functionality in conjugation with *E*, *Z* double bonds and presence of 4 contiguous stereocenters with alternative methyl and hydroxyl appendages (Figure 2).

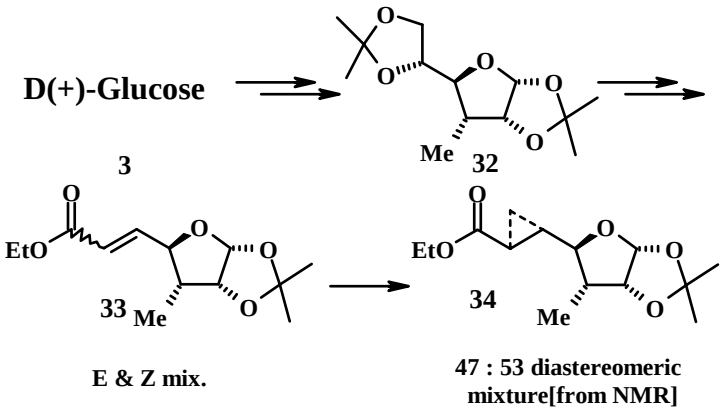


Basiliskamide A **Basiliskamide B**

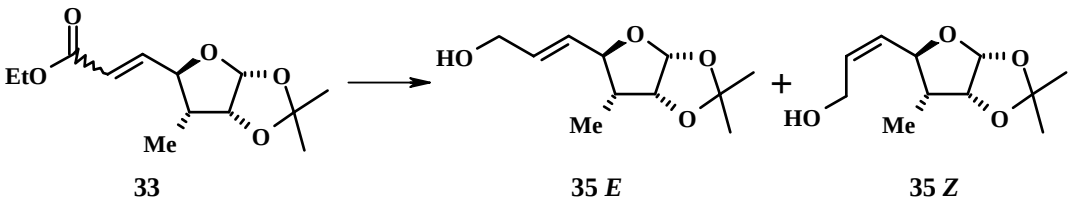
Figure 2. Novel Antifungal Metabolites

The structural feature suggests D-Glucose as an appropriate starting material, as the relative stereocenters at C2 and C4 of D-Glucose match with that of C7 and C9 stereocenters of basiliskamide A & B respectively.

D(+)-Glucose was transformed to the known compound **32** through reported literature. The 5,6-acetonide was oxidatively cleaved by periodic acid to yield the aldehyde, which on two carbon Wittig homologation yielded a mixture of geometrical isomers **33**. The diastereomeric compound **33** was cyclopropanated using Corey-Chaykovsky protocol. The reaction yielded a mixture of cyclopropanated products **34** (dr = 47:53 from ^{1}H NMR) (Scheme 9). So there was need for other methods to get rid of the poor selectivity.



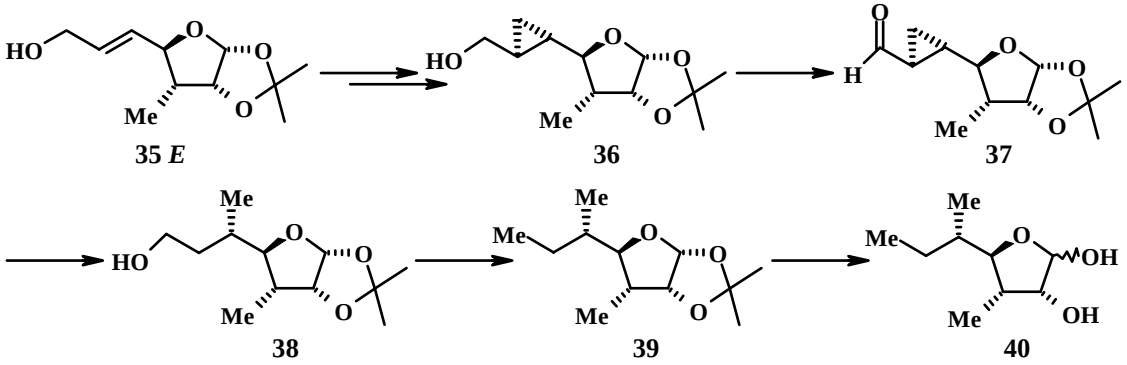
Scheme 9



33 **35 *E*** **35 *Z***

Scheme 10

To circumvent the loss of stereoselectivity, we planned for Simmons-Smith cyclopropanation as detailed in previous section. DIBAL reduction was next performed on **33** and chromatographically both **35*E*** and **35*Z*** isomers were separated (Scheme 10). Following our generalized Simmons-Smith cyclopropanation methodology, the cyclopropane methyl alcohol **36** was obtained as a single diastereomer. The alcohol group was oxidized with IBX in DMSO and subsequent hydrogenation of the aldehyde with Pd/C in *i*-PrOH at 80 *psi* yielded **38**. The primary hydroxyl group was converted to its *p*-toluenesulphonate derivative, which on treatment with $LiAlH_4$, furnished the deoxy compound **39**. For extrapolation of the furanose moiety, the 1,2-*O*-isopropylidine ring was opened with 6N HCl to yield the lactol **40** (Scheme 11).

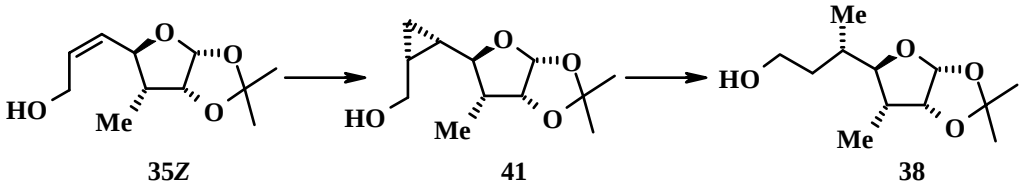


35 *E* **36** **37**

38 **39** **40**

Scheme 11

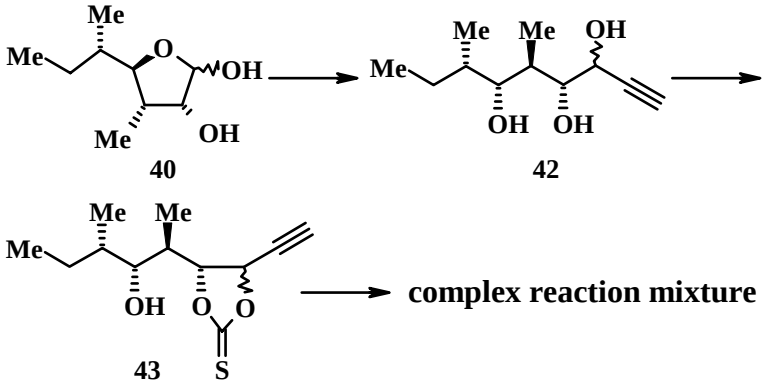
The same sequence of reactions was performed on **35*Z*** to achieve the primary alcohol **38**. This reaction sequence confirmed same facial selectivity for both geometrical isomers (Scheme12).



35*Z* **41** **38**

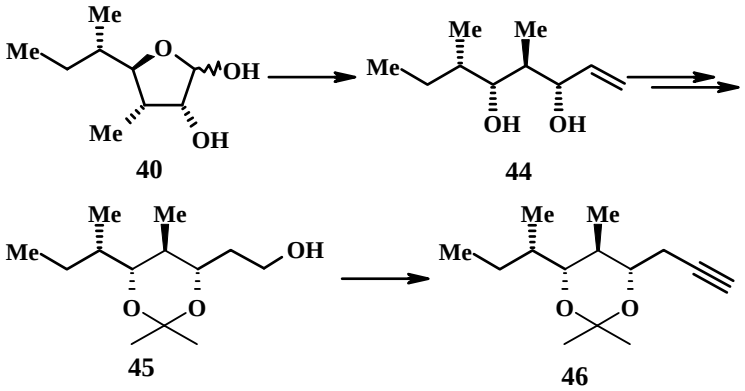
Scheme 12

The lactol **40** was treated with lithium acetylide:EDTA complex in DMSO to yield a diastereomeric mixture **42**. We proceeded with the mixture, as in next step the epimeric stereocenter would be destroyed. Treatment of **42** with TCDI yielded the 5-membered thiocarbonate **43** selectively. But the assumed deoxygenation and stannylation of the alkyne with TBTH, AIBN in one pot, yielded a complex reaction mixture (Scheme 13).



Scheme 13

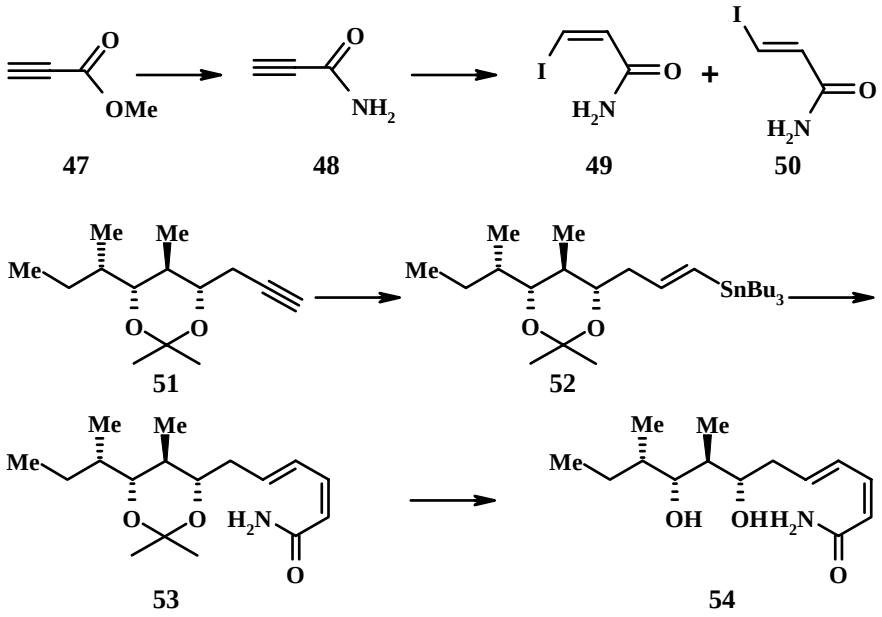
Failing at this point, we planned a sequential conversion strategy. First one carbon extension was achieved by employing Wittig reaction of the lactol. The 1,3 diol thus formed, was protected as its isopropylidine derivative with dimethoxypropane in acetone and catalytic amount of *p*-TSA. Then the olefin **63** was converted to the primary alcohol **45** by hydroboration-oxidation approach. The primary hydroxyl group thus formed was oxidized to the corresponding aldehyde, which on treatment with Ohira-Bestmann reagent in MeOH yielded the terminal alkyne **46** (Scheme 14).



Scheme 14

The Stille coupling partner **49** was synthesized from methyl propiolate in two steps. First treatment with aqueous ammonia gave propionamide (**48**), followed by

reaction with LiI in CH_3CN and AcOH at reflux condition yielded the vinyl iodo compound (***E***:***Z*** = 10:90). The other Stille coupling fragment, vinyl stannane was achieved by radical addition of TBTH to the terminal alkyne, which was used for Stille reaction without Silica gel purification. The coupling of fragments **49** and **52** in DMF with $Pd(CH_3CN)_2Cl_2$ yielded the diene **53**, which on deketalization in acidic medium resulted the common intermediate **54** for both basiliskamide (Scheme 15).



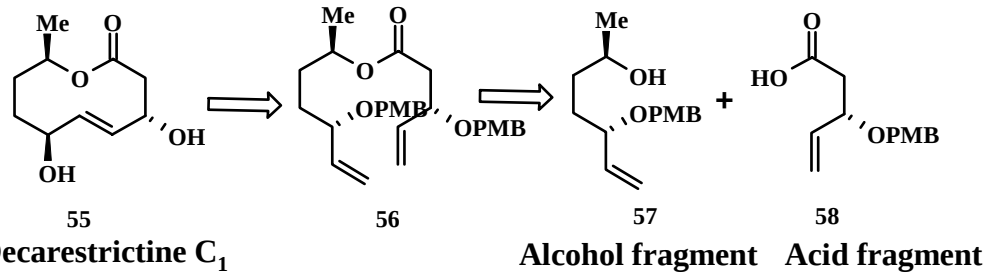
Scheme 15

CHAPTER III: **Total Synthesis of Decarestrictine C_1**

Isolated from *Pencillium simplicissium* and *Pencillium corylophilum*, decarestrictines represent a class of fungal metabolites. Tested via sodium acetate incorporation into cholesterol, the decarestrictines have shown more or less potent inhibitory effects on cholesterol biosynthesis in cell line tests with HEP-G2 liver cells and hence yield favorable effects on *in vivo* lipid metabolism. These are appeared to be more selective in that it exhibits no significant antibacterial, antifungal, antiprotozal or antiviral activity. The decarestrictines represent a family of novel class of 10 membered lactones, which are structurally related to each other based on their physio-chemical properties. In continuation of our long standing interest in exploiting Ring Closing Metathesis for making cyclic compounds and generalizing its substrate based selectivity, we planned to synthesize decarestrictine C_1.

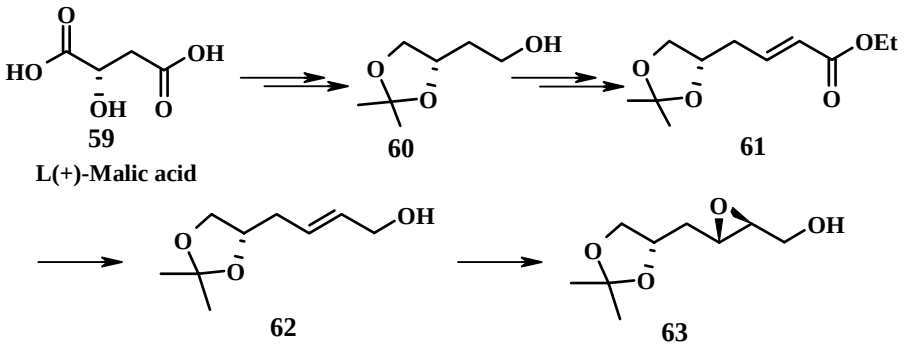
The synthetic strategy involves a convergent approach, using esterification and ring closing metathesis as the uniting factor of acid and alcohol fragments. The similarity in the backbone of the two fragments (presence of allylic secondary hydroxyl functionality) suggests a flexible yet stereochemically unambiguous approach (Scheme 16).

Retrosynthetic approach:



Scheme 16

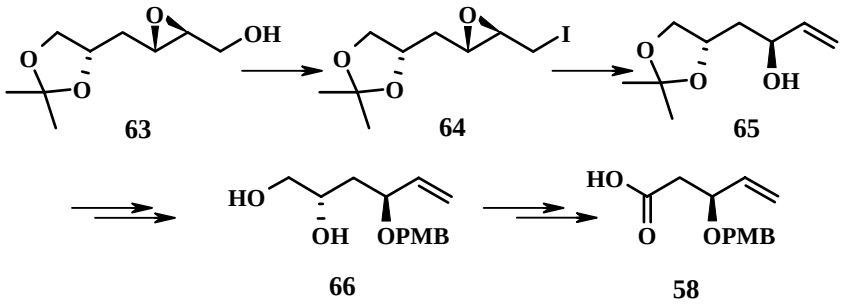
Synthesis of the acid fragment: Our endeavor started with the conversion of L(+) malic acid to the known primary alcohol **60**. One pot conversion of the alcohol to the *E* α, β-unsaturated ester **61** was achieved by IBX oxidation in DMSO followed by treating the same reaction mixture with (ethoxycarbonylmethylene)triphenylphosphorane. The ester was selectively reduced to the Allylic alcohol **62** by DIBAL-H in CH_2Cl_2 at -78 °C. Now the incorporation of the required chirality was achieved by well documented Sharpless asymmetric epoxidation. The allylic alcohol **62** was treated with $Ti(O^iPr)_4$, (+)DET and *t*-BuOOH to get the (*S*,*S*) epoxide **63** (Scheme 17).



Scheme 17

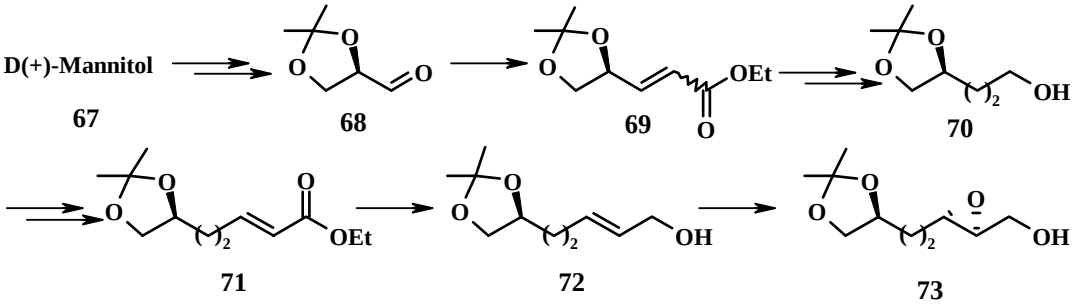
The primary hydroxyl group of the epoxide **63** was transformed to its iodo derivative **64**. Opening of the epoxide of the iodo compound was achieved with Zn in refluxing EtOH. The secondary allylic alcohol **65** was protected as its *p*-methoxybenzyl

ether by reaction with NaH, PMBCl in DMF at room temperature. Then the isopropylidine group was deprotected by treatment with *p*-TSA in MeOH. The resulted diol was cleaved by silica gel supported $NaIO_4$ followed by oxidation with $NaClO_2$ to give the acid coupling partner **58** (Scheme 18).



Scheme 18

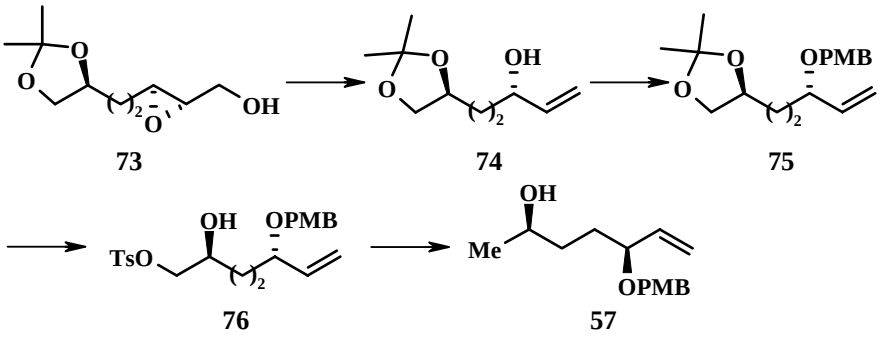
Synthesis of the alcohol fragment for the decarestrictine C_1: The known aldehyde was synthesized from D(+)-mannitol and was subjected to two carbon Wittig homologation to result a mixture of geometrical isomers **69**. The olefins were sequentially reduced with Pd/C, H_2 first and then with $LiAlH_4$ to get the saturated alcohol **70**. Further two carbon extensions were achieved by oxidation of the primary alcohol and Wittig reaction with (carboethoxymethylene)triphenylphosphorane in benzene under reflux condition. The α, β-unsaturated ester **71** was selectively reduced by DIBAL-H to furnish the allylic alcohol **72**, which on Sharpless asymmetric epoxidation with $Ti(O^iPr)_4$, (+)DET and *t*-BuOOH to get the (*S*,*S*) epoxide **73** (Scheme 19).



Scheme 19

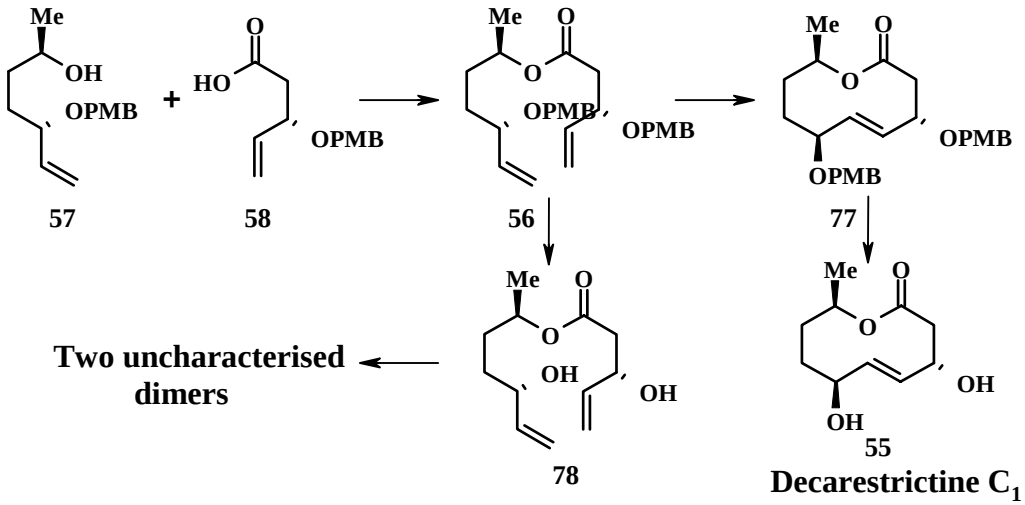
The primary hydroxyl group of the epoxide compound **73** was transformed to its iodo derivative. The epoxide ring opening was achieved by reaction with Zn in refluxing EtOH. The secondary alcohol **74** thus formed, was protected as its *p*-methoxybenzyl

ether. Then the isopropylidine group was deprotected by treatment with catalytic amount of *p*-TSA in MeOH. Selectively the primary hydroxyl group of the diol was converted to its tosyl derivative **76** by treating with TsCl, Et_3N and catalytic amount of *n*-Bu_2SnO. Further the tosyl compound was reacted with $LiAlH_4$ to get the required alcohol fragment **57** (Scheme 20).



Scheme 20

Synthesis of decarestrictine C_1: The alcohol and the acid fragment was coupled using 2,4,6-trichlorobenzoyl chloride to furnish the ester **56**. The ester under ring closing metathesis condition using Grubb's 2nd generation catalyst in CH_2Cl_2 and refluxing condition yielded the single trans diastereomer **77**, which was characterized by ^1H, ^{13}C NMR, mass, IR and analytical values. The mass deprotection of the *p*-methoxybenzyl ethers was carried out by DDQ in CH_2Cl_2:H_2O mixture to get the natural product decarestrictine C_1 (Scheme 21).



Scheme 21

But the free diol **78**, obtained by deprotection of the PMB groups of the ester compound **56**, gave uncharacterized dimers with Grubbs 2nd generation catalyst at both room temperature and reflux condition (Scheme 21).

To our revelation, we found the previous reports on isolation and synthesis of these metabolites dubious. Earlier reports claim the isolated decarestrictine C to be an inseparable diastereomeric mixture of decarestrictine C_1 and decarestrictine C_2. The ^{1}H NMR data of our synthesized decarestrictine C_1 completely agrees with that of the isolated decarestrictine C, showing a mixture of two isomers at room temperature. As we went for high temperature NMR spectroscopy, at 110 °C the rotameric mixture showed a single compound and again after cooling to room temperature, the NMR showed isomeric mixtures. From this fact, we have proved that decarestrictine C_1 exits in two different conformations in solution at room temperature.

Chapter I:

Total synthesis of prototype renin inhibitors

Introduction

Even today, in the 21st century, when science and technology have reached a great height hand in hand, some diseases like hypertension, diabetes, depression, cardiovascular events such as stroke, heart attack, heart failure etc. remain a big concern for the human being. The search for new drugs, their mimetics are in up rise.

Cardiovascular disease refers to the class of diseases that involve the heart or blood vessels (arteries and veins). While the term technically means any disease that affects the cardiovascular system, it is usually used to refer to those related to atherosclerosis (arterial disease). Among the various types of cardiovascular diseases, the most common and important one is high blood pressure (hypertension). In this prologue we would focus mainly on the pros and cons of this particular cause.

Hypertension, most commonly referred to as "high blood pressure", is a medical condition in which the blood pressure is chronically elevated. It was previously referred as nonarterial hypertension, but in current usage, the word "*hypertension*" without a qualifier normally refers to arterial hypertension (high blood pressure of the arteries).[1] Persistent hypertension is one of the risk factors for strokes, heart attacks, heart failure and arterial aneurysm, and is a leading cause of chronic renal failure. Even moderate elevation of arterial blood pressure leads to shortened life expectancy. At severely high pressures, defined as mean arterial pressures 50% or more above average, a person can expect to live no more than a few years unless appropriately treated.[2] Hypertension is considered to be present when a person's systolic blood pressure is consistently 140 mmHg or greater, and/or their diastolic blood pressure is consistently 90 mmHg or greater. Recently, as of 2003, the *Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure*[3] has defined blood pressure 120/80 mmHg to 139/89 mmHg as "prehypertension". Prehypertension is not a disease category; rather, it is a designation chosen to identify individuals at high risk of developing hypertension. The Mayo Clinic website specifies blood pressure is "normal if it's below 120/80" but that "some data indicate that 115/75 mm Hg should be the gold standard." Studies have shown that in patients with diabetes mellitus or kidney

disease, blood pressure over 130/80 mmHg should be considered high and warrants further treatment.

Based on the nature and symptoms of a patient, hypertension can be classified as follow:

1) Primary or essential hypertension
2) Secondary hypertension

1) Primary hypertension: Nearly 95 per cent of all hypertensives suffer from this type of hypertension. In these cases, despite all investigations, one cannot attribute any direct cause for the problem of hypertension. There could be a whole lot of contributory factors, like the patient's lifestyle or various hereditary factors.

2) Secondary hypertension: This type of hypertension afflicts about 4-5 per cent of all hypertensives. Secondary hypertension indicates that the high blood pressure is a result of (*i.e.*, secondary to) another condition, such as kidney disease or tumors (pheochromocytoma and paraganglioma). This means raised blood pressure is caused due to some basic disease, leading to high blood pressure.

Factors of primary/essential hypertension: Although no specific medical cause can be determined in essential hypertension, the most common form has several contributing factors. These include salt sensitivity, renin homeostasis, insulin resistance, genetics, and age to name a few**.** Following are the details of some interesting factors responsible for this essential hypertension.

1. Liquorice: Consumption of liquorice (which can be of *potent* strength in liquorice candy) can lead to a surge in blood pressure. People with hypertension or history of cardio-vascular disease should avoid liquorice to prevent raising their blood pressure to risky levels. Frequently, if liquorice is the cause of the high blood pressure, a low blood level of potassium will also be present.

2. Sodium sensitivity: Sodium is an environmental factor that has received the greatest attention. Approximately one third of the essential hypertensive population is responsive to sodium intake. This is due to the fact that increasing amounts of salt in a person's bloodstream causes cells to release water (due to osmotic pressure) to equilibrate concentration gradient of salt between the cells and the bloodstream; increasing the

pressure on the blood vessel walls. The effects of excess amounts of salt in the body depend on how much excess salt (or salty food) is eaten in a specific time versus how well the kidneys function. When the salt content of the blood elevates, water is attracted from around the cells (in muscles and organs) into the blood, in order to dilute blood salinity. There is salt as sodium outside every cell in the body. When the salt content of the fluid around the cells goes up, it attracts water from the blood and swelling occurs. The kidneys are responsible for regulating salt and water levels in the body. When salt and water levels increase around cells, the excess is drawn into the blood, which is filtered by the kidneys. The kidneys remove excess salt and water from the blood, both of which are excreted as urine. When the kidneys do not work well, fluid builds up around cells and in the blood. The heart is the pump that pushes the blood around. If there is more fluid in the blood, the heart has to work harder and the blood pressure can go up because there is more pressure on the walls of the blood vessels. The heart can get weaker or worn out from the extra work leading to heart diseases. Salt has been blamed in the past for causing high blood pressure. New research suggests that too little calcium or potassium also has an impact on blood pressure. Some authorities believe that potassium might both prevent and treat hypertension. It goes on to advise that salt avoidance may assist in lowering blood pressure in two ways, one of which is by replacing highly processed (salted foods) with natural foods which contain higher levels of potassium, and the other is by reducing salt intake.

3. Role of renin: Renin is an enzyme secreted by the juxtaglomerular apparatus of the kidney and linked with aldosterone in a negative feedback loop. The range of renin activity observed in hypertensive subjects tends to be broader than in normotensive individuals. In consequence, some hypertensive patients have been defined as having low-renin and others as having essential hypertension. Low-renin hypertension is more common in African Americans than white Americans, and may explain why they tend to respond better to diuretic therapy than drugs that interfere with the renin-angiotensin system. High renin levels predispose to hypertension as the channel given below:

Increased Renin → Increased Angiotensin II → Increased Vasoconstriction, Thirst/ADH and Aldosterone → Increased Sodium Resorption in the Kidneys (DCT and CD) → Increased Blood Pressure.

4. Insulin resistance: Insulin is a polypeptide hormone secreted by cells in the islets of langerhans, which are contained throughout the pancreas. Its main purpose is to regulate the levels of glucose in the body antagonistically with glucagon through negative feedback loops. Insulin also exhibits vasodilatory properties. In normotensive individuals, insulin may stimulate sympathetic activity without elevating mean arterial pressure. However, in more extreme conditions such as that of the metabolic syndrome, the increased sympathetic neural activity may over-ride the vasodilatory effects of insulin. Insulin resistance and/or hyperinsulinemia have been suggested as being responsible for the increased arterial pressure in some patients with hypertension. This feature is now widely recognized as part of syndrome X, or the metabolic syndrome.

5. Sleep apnea: Sleep apnea is a common, under-recognized cause of hypertension.[4] It is often best treated with nocturnal nasal continuous positive airway pressure, but other approaches include the Mandibular advancement splint (MAS), UPPP, tonsilectomy, adenoidectomy, sinus surgery, or weight loss.

6. Genetics: Hypertension is one of the most common complex disorders, with genetic heritability averaging 30%. Data supporting this view emerge from animal studies as well as in population studies in humans. Most of these studies support the concept that the inheritance is probably multifactorial or that a number of different genetic defects each have an elevated blood pressure as one of their phenotypic expressions.

7. Age: Over time, the number of collagen fibers in artery and arteriole walls increases, making blood vessels stiffer. With the reduced elasticity comes a smaller cross-sectional area in systole, and so a raised mean arterial blood pressure. Blood pressure readings vary with age and sex. In most big cities, where there is relative affluence with little physical activity, younger and younger boys and girls are reported to be suffering from this problem. The readings for age-sex blood pressure ratio should be as follows:

Age (in years)	Girls	Boys		Age (in years)	Girls	Boys
1	86/40	85/37		10	102/60	102/61
2	88/45	88/42		11	103/61	104/61
3	89/49	91/46		12	105/62	106/62
4	91/52	93/50		13	107/63	108/62
5	93/54	95/53		14	109/64	111/63
6	94/56	96/55		15	110/65	113/64

7	96/57	97/57		16	111/66	116/65
8	98/58	99/59		17	111/66	118/67
9	100/59	100/60				

Table 1: Age-sex blood pressure ratio

Etiology of secondary hypertension: Only in a small minority of patients with elevated arterial pressure, can a specific cause be identified. This is probably due to an endocrine or renal defect that, if corrected, could bring blood pressure back to normal values.

1. Renal hypertension (Hypertension produced by diseases of the kidney): This includes diseases such as polycystic kidney disease or chronic glomerulonephritis. Hypertension can also be produced by diseases of the renal arteries supplying the kidney. This is known as renovascular hypertension; it is thought that decreased perfusion of renal tissue due to stenosis of a main or branch renal artery activates the renin-angiotensin system.

2. Adrenal hypertension: Hypertension is a feature of a variety of adrenal cortical abnormalities. In primary aldosteronism there is a clear relationship between the aldosterone-induced sodium retention and the hypertension.

3. Cushing's syndrome (hypersecretion of cortisol): Both adrenal glands can overproduce the hormone cortisol or it can arise in a benign or malignant tumor. Hypertension results from the interplay of several pathophysiological mechanisms regulating plasma volume, peripheral vascular resistance and cardiac output, all of which may be increased. More than 80% of patients with Cushing's syndrome have hypertension. In patients with pheochromocytoma increased secretion of catecholamines such as epinephrine and norepinephrine by a tumor (most often located in the adrenal medulla) causes excessive stimulation of [adrenergic receptors], which results in peripheral vasoconstriction and cardiac stimulation. This diagnosis is confirmed by demonstrating increased urinary excretion of epinephrine and norepinephrine and/or their metabolites (vanillylmandelic acid).

4. Genetic causes: Hypertension can be caused by mutations in single genes, inherited on a Mendelian basis.

5. Coarctation of the aorta: Aortic coarctation is narrowing of the aorta in the area where the ductus arteriosus (ligamentum arteriosum after regression) inserts. Depending

of the occurrence of narrowing to the insertion of the ductus arteriosus, this has been classified as preductal, ductal and post ductal coarctation.

6. Drugs: Certain medications, especially NSAIDS (Motrin/Ibuprofen) and steroids can cause hypertension. Licorice (*Glycyrrhiza glabra*) inhibits the 11-hydroxysteroid hydrogenase enzyme (catalyzes the reaction of cortisol to cortison) which allows cortisol to stimulate the Mineralocorticoid Receptor (MR) which will lead to effects similar to hyperaldosteronism, which itself is a cause of hypertension.

7. Spinal misalignment: A 2007 chiropractic pilot study indicated that some cases of hypertension may be caused by a misalignment of the atlas vertebra.[5]

8. Rebound hypertension: High blood pressure that is associated with the sudden withdrawal of various antihypertensive medications. The increases in blood pressure may result in blood pressures greater than when the medication was initiated. Depending on the severity of the increase in blood pressure, rebound hypertension may result in a hypertensive emergency. Rebound hypertension is avoided by gradually reducing the dose (also known as "dose tapering"), thereby giving the body enough time to adjust to reduction in dose. Medications commonly associated with rebound hypertension include centrally-acting antihypertensive agents, such as clonidine and beta-blockers.

Treatment

Lifestyle modification (nonpharmacologic treatment)

i) Weight reduction and regular aerobic exercise (*e.g.*, jogging) are recommended as the first steps in treating mild to moderate hypertension. Regular mild exercise improves blood flow and helps to reduce resting heart rate and blood pressure.

ii) Reducing sodium (salt) diet is proven very effective: it decreases blood pressure in about 60% of people.

iii) Additional dietary changes beneficial to reducing blood pressure includes the DASH diet (Dietary Approaches to Stop Hypertension), which is rich in fruits and vegetables and low fat or fat-free dairy foods. This diet is shown effective based on National Institutes of Health sponsored research. In addition, an increase in daily calcium intake has the benefit of increasing dietary potassium, which theoretically can offset the effect

of sodium and act on the kidney to decrease blood pressure. This has also been shown to be highly effective in reducing blood pressure.

iv) Discontinuing tobacco use and alcohol consumption has been shown to lower blood pressure (especially systolic). The exact mechanisms are not fully understood, but blood pressure (especially systolic) always transiently increases following alcohol and/or nicotine consumption. Besides, abstention from cigarette smoking is important for people with hypertension because it reduces the risk of many dangerous outcomes of hypertension, such as stroke and heart attack. Note that coffee drinking (caffeine ingestion) also increases blood pressure transiently, but does *not* produce chronic hypertension.

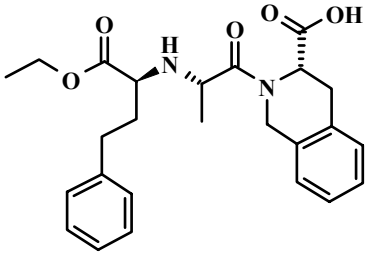
v) Relaxation therapy, such as meditation, that reduces environmental stress, reducing high sound levels and over-illumination can be an additional method of ameliorating hypertension.

vi) Jacobson's Progressive Muscle Relaxation and biofeedback are also used particularly device guided paced breathing.

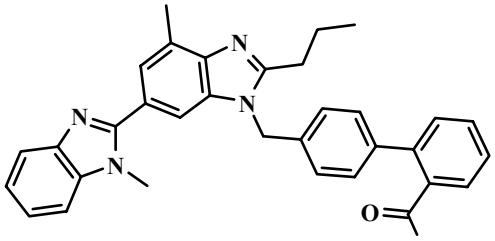
Medications (pharmacologic treatment)

There are many classes of medications for treating hypertension, together called antihypertensives, which act by lowering blood pressure. Evidence suggests that reduction of the blood pressure by 5-6 mmHg can decrease the risk of stroke by 40%, of coronary heart disease by 15-20%, and reduces the likelihood of dementia, heart failure, and mortality from vascular disease. Commonly used drugs include:

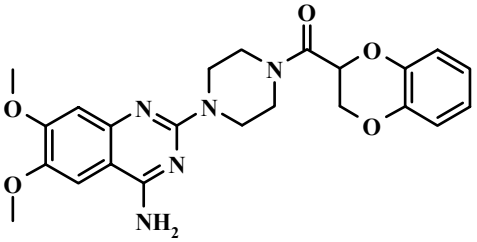
i) ACE inhibitors: ACE inhibitors lower arteriolar resistance and increase venous capacity; increase cardiac output and cardiac index, stroke work and volume, lower renovascular resistance, and lead to increased natriuresis (excretion of sodium in the urine). These include creatine captopril, enalapril, fosinopril (Monopril), lisinopril (Zestril), quinapril (**1a**), and ramipril (Altace).



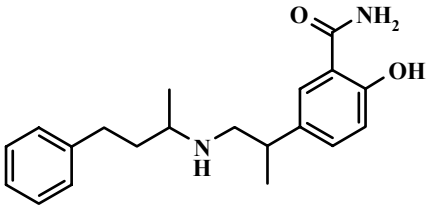
ACE inhibitors: Quinapril (1a)



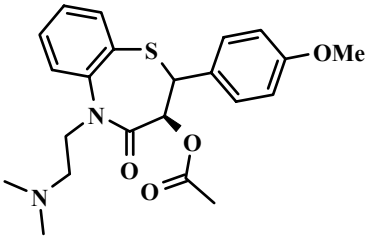
Angiotensin II receptor antagonists: Telmisartan (1b)



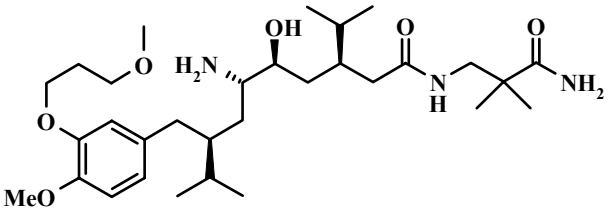
Alpha blockers:Doxazosin (1c)



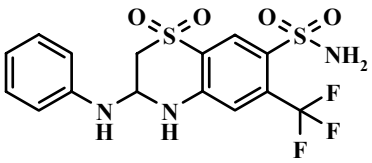
Beta blockers: Labetalol (1d)



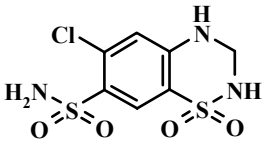
Calcium channel blockes: Diltiazem (1e)



Direct renin inhibitors: Aliskiren (1f)



Diuretics: Bendroflumethiazide (1g)



Combination product: Hydrochlorothiazide + another drug (1h)

Figure 1: Anti-hypertensive drugs

ii) Angiotensin II receptor antagonists: These substances are AT_1-receptor antagonists i.e. they block the activation of angiotensin II AT_1 receptors. Blockage of AT_1 receptors directly causes vasodilation, reduces secretion of vasopressin, reduces production and secretion of aldosterone, amongst other actions – the combined effect of which is reduction of blood pressure. e.g. telmisartan (**1b**) (Micardis, Pritor), irbesartan (Avapro), losartan (Cozaar), valsartan (Diovan), and candesartan (Amias).

iii) Alpha blockers: Alpha blockers (also called alpha-adrenergic blocking agents) constitute a variety of drugs which block α_1-adrenergic receptors in arteries and smooth muscles. These include doxazosin (**1c**), prazosin, or terazosin.

iv) Beta blockers: Beta blockers block the action of endogenous catecholamines {epinephrine (adrenaline) and norepinephrine (noradrenaline) in particular}, on β-adrenergic receptors, part of the sympathetic nervous system which mediates the fight or flight response. There are three known types of beta receptor, designated β_1, β_2 and β_3. β_1-Adrenergic receptors are located mainly in the heart and in the kidneys. β_2-Adrenergic receptors are located mainly in the lungs, gastrointestinal tract, liver, uterus, vascular smooth muscle, and skeletal muscle. β_3-receptors are located in fat cells. Some examples of beta blockers are atenolol, labetalol (**1d**), and metoprolol (Lopressor, Toprol-XL).

v) Calcium channel blockers: Calcium channel blockers work by blocking voltage-gated calcium channels (VGCCs) in muscle cells of the heart and blood vessels. This prevents calcium levels from increasing as much in the cells when stimulated, leading to less muscle contraction. In the heart, a decrease in calcium available for each beat results in a decrease in cardiac contractility. In blood vessels, a decrease in calcium results in less contraction of the vascular smooth muscle and therefore an increase in blood vessel diameter, a phenomenon called vasodilation. Vasodilation decreases total peripheral resistance, while a decrease in cardiac contractility decreases cardiac output. Since blood pressure is in part determined by cardiac output and peripheral resistance, blood pressure drops. Some of these drugs are named as nifedipine (Adalat) amlodipine (Norvasc), diltiazem (**1e**), and verapamil.

vi) Direct renin inhibitors: This type is the key concern of the work embodied in this chapter and will be detailed in following write ups. One example of this type of drug is aliskiren (**1f**) (Tekturna).

vii) Diuretics: A **diuretic** is any drug that elevates the rate of urination (diuresis). These include bendroflumethiazide (**1g**), chlortalidone, and hydrochlorothiazide (also called HCTZ).

Renin-angiotensin system:

Renin-angiotensin system plays an important role in regulating cardiovascular and renal function and in maintaining the electrolyte balance of the body.[6] Renin, an enzyme secreted by kidney, is a member of the well-studied family of aspartic proteinase.[7] Renin controls the first and rate-limiting step of the renin–angiotensin system catalysing the cleavage of the Leu10–Val11 peptide bond of angiotensinogen and releasing the decapeptide angiotensin I (Figure 2). Angiotensinogen is the only known physiological substrate for renin; therefore renin is an absolutely essential and extremely specific enzyme, in contrast to the angiotensin-converting enzyme (ACE), which can be bypassed by the serine proteinase chymase and is also active against other peptides such as bradykinin.

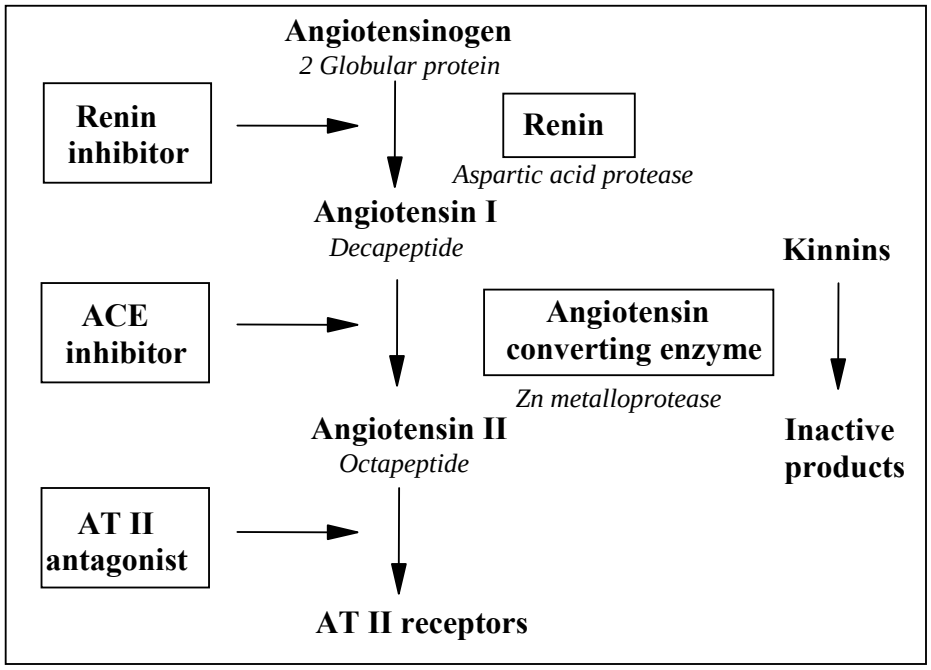


Figure 2: Various stages of renin-angiotensin system

Peptidic renin inhibitors: Renin inhibitors are effective means of treating hypertension and cardiovascular disorders, and therefore, they have attracted unprecedented attention particularly from synthetic chemists with a singular intention of preparing in respectable quantities for bioavailability and related studies. A large variety of peptide inhibitors of human renin with different stable transition-state analogues of the scissile peptide bond

have been developed. These analogues can inhibit the renin by intravenous administration and lower blood-pressure conditions. Moreover, these renin inhibitors possess good pharmacokinetic and antihypertensive activities in experimental animals but oral absorption in human is far from satisfactory. Moreover as none of these compounds survived all stages of drug development, new classes of nonpeptide renin inhibitors were discovered that fulfill all criteria for becoming successful drugs.

Inhibitor design concept: Crystal structures of human renin show that the enzyme consists of two mainly β-sheet domains related by an approximately twofold axis. The active-site cleft is located between the two domains and extends over eight residues of the respective substrate. Each domain provides one of the catalytically essential aspartic acid carboxylates. The initial substrate-based design of inhibitors of renin provided peptide analogues of the amino-terminal part of the substrate angiotensinogen, in which the amino acids flanking the cleavage site were modified.[8] An instrumental approach towards the development of nonsubstrate based renin inhibitors was the replacement of the scissile Leu10–Val11 dipeptide moiety according to the transition state analogue concept,[9] which led to a vast number of *in vitro* highly potent peptide-like (classified recently as type-I inhibitors[10]) renin inhibitors.

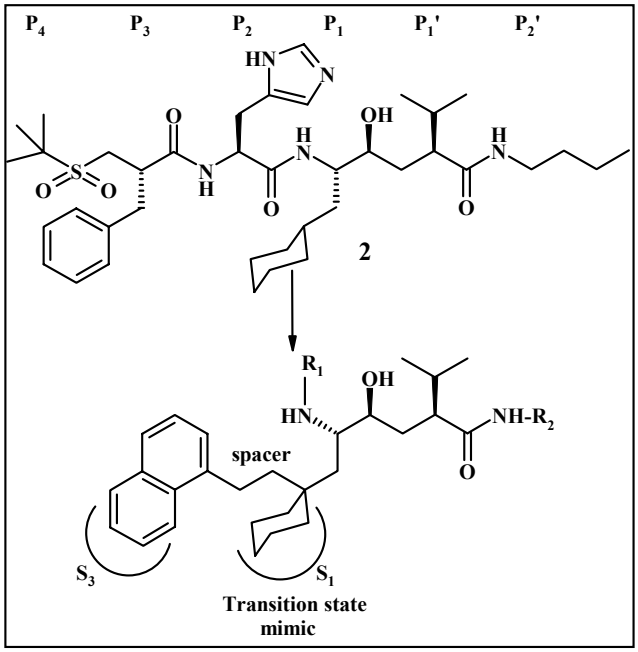
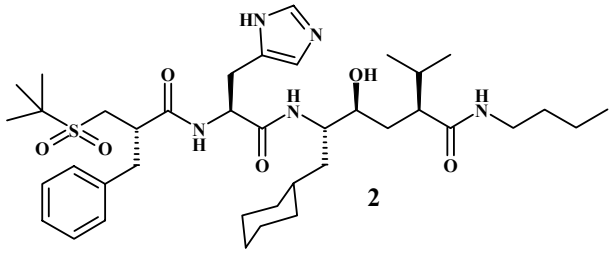
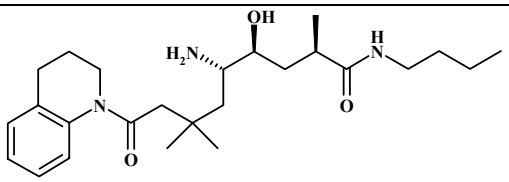


Figure 3: Representation of the P_3-P_1 structural design approach towards novel nonpeptide renin inhibitors.

Poor oral absorption and rapid biliary uptake, resulting from unfavorable lipophilicity and molecular size, are major reasons for the limited bioavailability of most peptide-like renin inhibitors. For example the renin inhibitor **CGP 38560** (**2**)[11]a representative of such type-I inhibitors contains the dipeptide isostere (2*S*,4*S*,5*S*)-5-amino-4-hydroxy-2-isopropyl-6- cyclohexyl-hexanoic acid at the P_1–P_1' position and mimics the substrate angiotensinogen from residue P_3 to P_1' (Figure 3), according to the Schechter and Berger nomenclature.[12]The compound is a potent and specific inhibitor with an IC_{50} value of 0.7 x 10^{-9} M for human rennin,[13] but it has only a weak blood-pressure lowering effect in salt depleted marmosets after oral dosing, mainly as a result of very limited overall bioavailability.

Non-peptidic renin inhibitors: The above figure showing the transition state mimic of **2** triggers the search for nonpeptide inhibitors of lower molecular weight with good oral bioavailability and efficacy in animal models and stablility against metabolic degradation.[14] After analyzing the shape and chemical properties of the active site of human renin initially using a homology model structure,[15] it became apparent that the S_1 and S_3 pockets form a contiguous and large hydrophobic cavity.[16] Applying molecular modelling methods, compounds were designed (Table 2) that would optimally exploit the extended hydrophobic surface corresponding to the large S_3–S_1 cavity and therefore might lead to a sufficient increase in free binding energy through improved van der Waals contacts. At the same time this would allow the elimination of the peptide main chain from P_1 to P_4 leading to the nonpeptidic inhibitors as shown in Figure 3.

S. No.	Formula	IC_{50} (μM)
1	 **2**	0.001
2		0.052

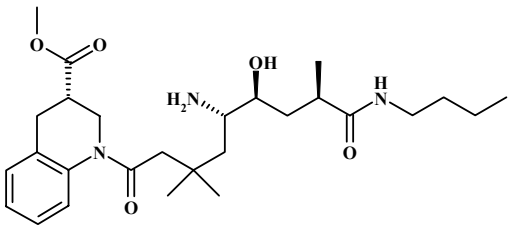
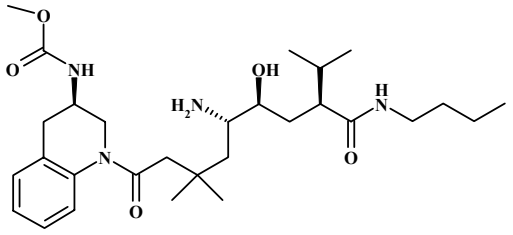
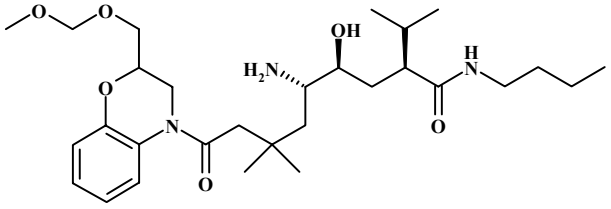
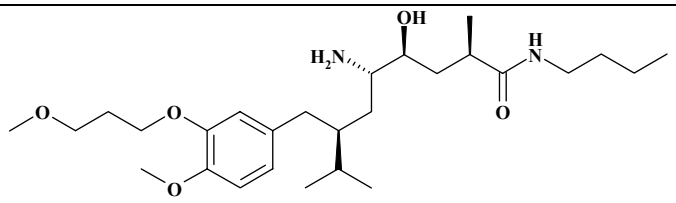
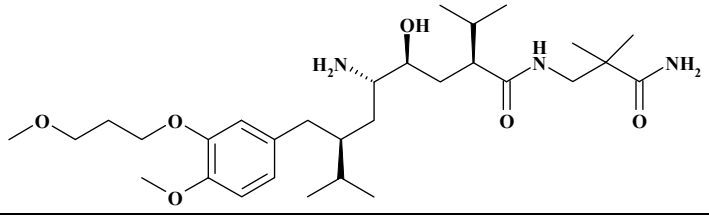
3		0.0008
4		0.0005
5		0.0001
6		0.0004
7		0.0006

Table 2: Biological activity of selected inhibitors of rennin[17] (Purified human rennin).

To summarize, designing of non-peptidic analogues of the natural peptidic renin inhibitors and their successful renin inhibition *in vivo* with good to excellent IC_{50} values, has eradicated the much tension of hypertension and cardiovascular diseases. It is therefore desirable to synthesize these new mimetics for medication purposes.

The challenge of ameliorating hypertension and cardiovascular diseases continued unabated in the last couple of decades. The natural peptidic renin inhibitors (*in vitro*) are being replaced by their non-peptidic mimics with potent *in vivo* activity.[18]Recently Maibaum *et al.* from Novartis have reported[19] the design of non-peptidic renin inhibitor.

The gist of the report has been shown in figure 4. Intrigued by the close spatial proximity of both the P_1 cyclohexyl and P_3 phenyl side chains in its predicted binding mode within the S_3/S_1 site, the possibility of extending P_1 by annulating a phenyl ring was examined, for tethering P_3, to the C3'-C4' bond of the cyclohexyl, which was predicted to be distal to the surface of the S_1 site (Structure A). Modeling of such a tetrahydronaphthalene substituted dipeptide isostere, as well as its 'ring-opened' congener (structure B) with R_1 = H, R_2 = Et) suggested that in both cases the rigid phenyl spacer would direct a hydrophobic substituent R_3, such as aryl or bulky alkyl, towards the S_3 pocket, and that the P_1 alkyl group would be well accomodated by the S_1 site. Furthermore, these initial design considerations predicted the β-configuration at P_1 (B, R_1 = H, R_2 = alkyl) to be preferred over the α-configuration (B, R_1 = alkyl, R_2 = H) with respect to a better fit in the S_3/S_1 pocket.

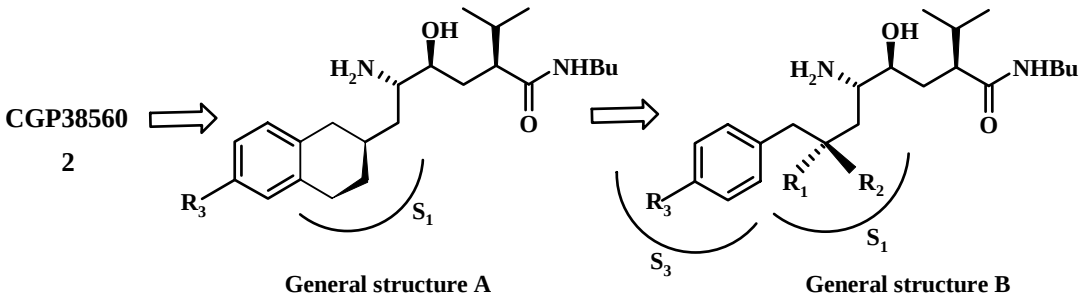


Figure 4

As described above, the finds and facts culminate in the 8-aryl octanoic amide backbone constituting the scaffold for a prolific drug candidate. Extensive search and re-search into the substituents on the backbone revealed differences in activity summarized in table 3.

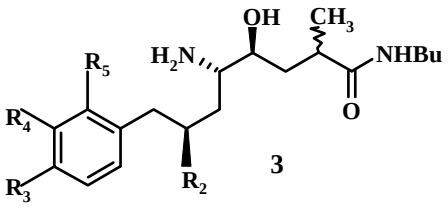
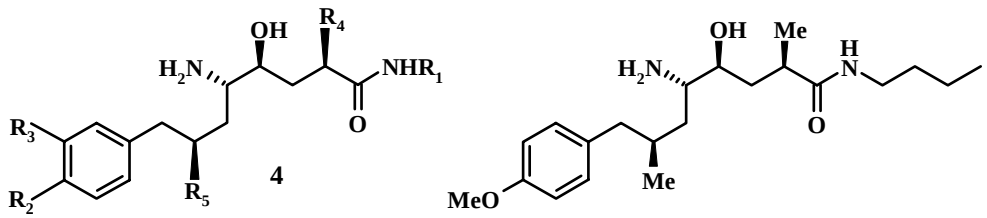


Figure 5: General structure for entries of table 3

S. No.[a]	R_2	R_3	R_4	R_5	IC_{50} (μM)
1	CH_3	Phenyl	H	H	3
2	CH_3	*tert*-butyl	H	H	2
3	C_2H_5	*tert*-butyl	H	H	0.8
4	C_2H_5[a]	*tert*-butyl	H	H	3
5	$CH(CH_3)_2$	*tert*-butyl	H	H	0.1
6	$CH_2CH(CH_3)_2$	*tert*-butyl	H	H	4
7	$C(CH_3)_3$	*tert*-butyl	H	H	1.5
8	Phenyl[c]	*tert*-butyl	H	H	39
9[b]	$CH(CH_3)_2$	*tert*-butyl	OH	H	0.13
10	C_2H_5	*tert*-butyl	OC_4H_9	H	0.24
11[b]	$CH(CH_3)_2$	*tert*-butyl	$OCH_2CH=CH_2$	H	0.11
12	$CH(CH_3)_2$	*tert*-butyl	$OCH_2CO_2CH_3$	H	0.006
13	$CH(CH_3)_2$	*tert*-butyl	H	$OCH_2CO_2C_2H_5$	0.29
14[b]	$CH(CH_3)_2$	H	$OCH_2CO_2CH_3$	H	0.037
15	$CH(CH_3)_2$	*tert*-butyl	OCH_2COOH	H	0.120
16	$CH(CH_3)_2$	*tert*-butyl	OCH_2CONH_2	H	0.020
17	$CH(CH_3)_2$	*tert*-butyl	$OCH_2SO_2CH_3$	H	0.013

Table 3: IC_{50}sof 5(*S*)-amino-4(*S*)-hydroxy-8-phenyl-octanecarboxamides against purified human renin; a) Tested as 1:1-mixtures of C2(*R*,*S*)-diastereomers, b) (*R*) configured at C7; b) Pure diastereomer of 2(*R*),4(*S*),5(*S*),7(*S*) absolute configuration; c) (*R*,*S*)-configured at C7.

All the above studies summarize a new class of non-peptidic inhibitors having a general structure of **3** and are proven drug candidates (Figure 6). Various analogues of **4** carrying different substituents at the aromatic ring and the amide nitrogen have been synthesized with unique binding affinities to renin.[20,21] These informations attracted us to devise a divergent synthesis of an analogue **5**, which will be compatible and informative for synthesis of a pool of analogues of varying diversity by incorporating appropriate changes to the intermediates in the main strategy.



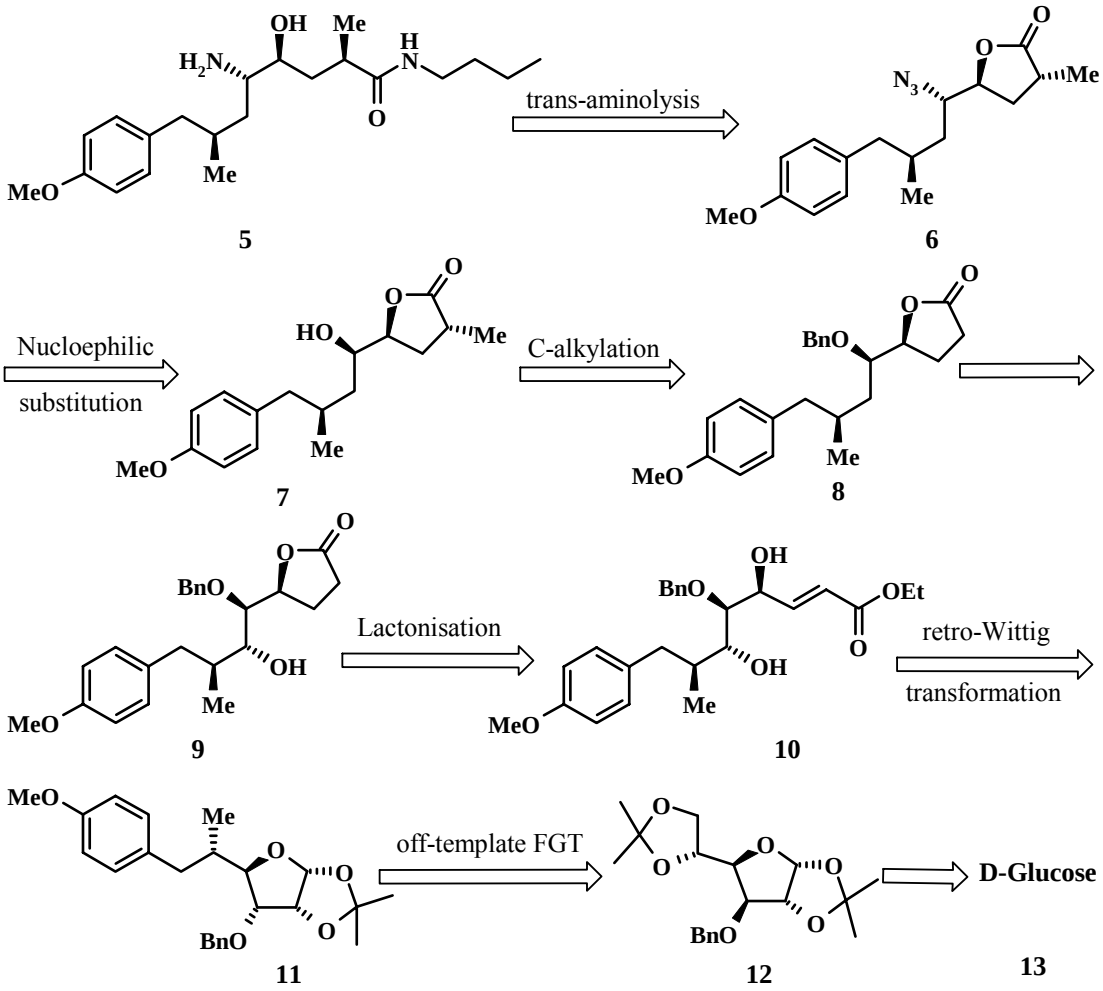
R_1 = Alkyl, amidoalkyl etc.

R_2, R_3 = Methoxy and methoxyethoxy etc.

R_4, R_5 = Isopropyl or methyl

Figure 6: General structure of potent renin inhibitor and our targeted analogue

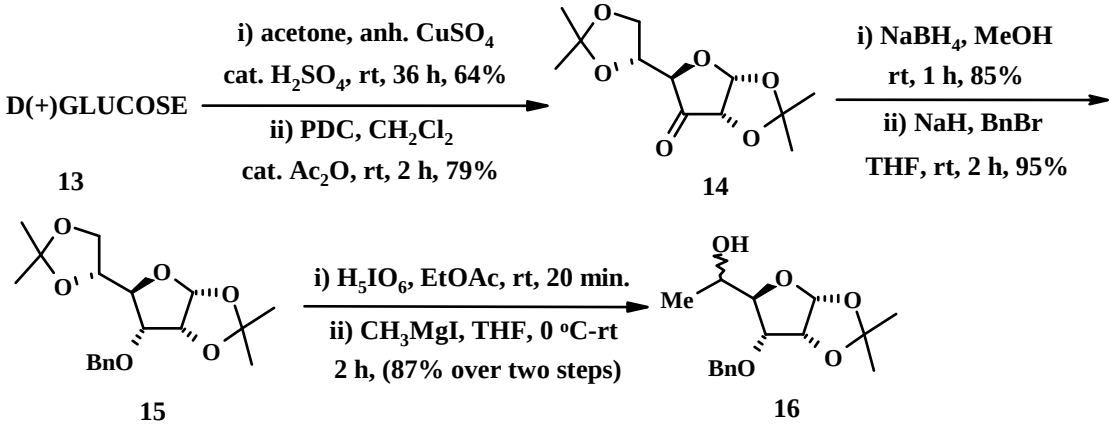
Retrosynthetic Strategy: The retrosynthetic path is a 'tactical combination of transforms' putting onus on chiral pool approach. As outlined in Scheme 1, the retrosynthesis of the target molecule **5** envisaged D(+)-glucose as an appropriate starting precursor. The cheap and easy availability, high enantiomeric purity and similarity in inherent stereo-chemical centers at C2 and C3 of D(+)-glucose to those at C4 and C5 of our target molecule **5** were the strong incentives for our interest to start with D(+)-glucose. In addition, the D(+)-glucofuranose ring system was expected to provide necessary off-template stereo-controlled[22,23] reactions particularly in present case at C-5. At the beginning, trans aminolysis of the target molecule describes the lactone **6** as its precursor, while the introduction of the second N atom could be achieved by double S_N2 reaction, thus retaining the same stereocenter as of D(+)-Glucose. Stereoselective C-methylation of the butenolide **8** would provide the alkyl appendage at C2 of the target molecule **5**. The butenolide **8**, which sets the tone for incorporation of the new stereocenter, could be synthesized by some functional group transformations, important among them was a two carbon wittig homologation. The left half of the target molecule was thought to be achieved by off-template stereoselection. The aromatic segment was introduced via Wittig reaction. In this synthetic sequence, Wittig reaction and the aminolysis of the butenolide are the diversity points, where different aromatic moieties and amines can be introduced so as to furnish a library of renin inhibitor analogues for the ever growing efforts in biological studies.



Scheme 1: Retrosynthetic analysis

Accordingly the synthesis began with the conversion of D(+)-Glucose (**13**) to 1,2:5,6-di-*O*-isopropylidine-(D)-glucofuranose by treating with acetone, anh. $CuSO_4$ as the dehydrating agent and conc. H_2SO_4 as catalyst. The more stable 5 membered dimethyl ketals and appropriate vicinal hydroxyl stereocenters of glucose intimidate more favorism for the furanose isomer to react than the pyranose. This single step diacetonide protection differentiates the reactivity of the five hydroxyl groups of glucose, which can be reacted at will. As our plan, we thought of introducing the amine functionality in the later stage of our synthesis. To retain the stereocenter for the amine substituent, double inversion of present stereocenter was intended. The hydroxyl group was first inverted by sequential oxidation and reduction path. For that 1,2:5,6-di-*O*-isopropylidineglucofuranose was subjected to PDC in CH_2Cl_2 with anhydrous 4 A^o

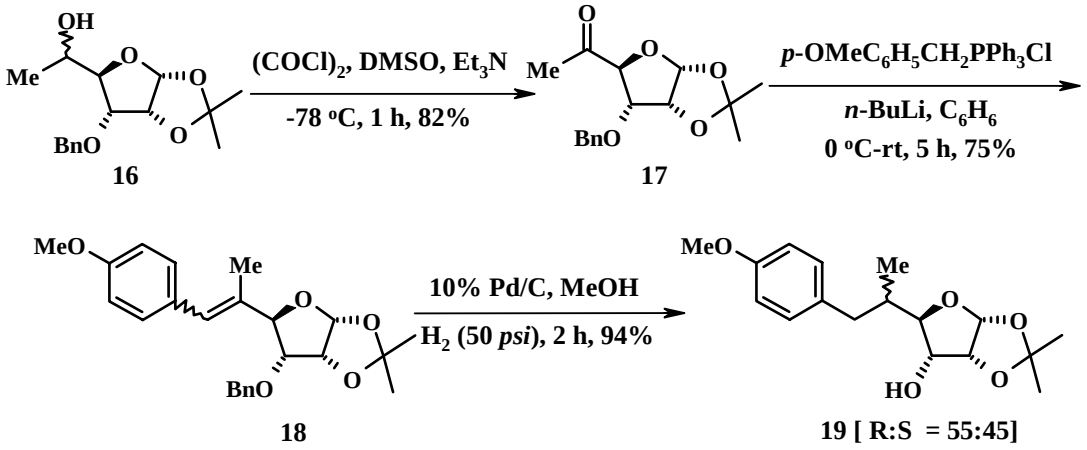
molecular sieves powder, and catalytic Ac_2O to yield the 3-ulose derivative **14**, which on subsequent reduction with $NaBH_4$ in MeOH provided the secondary alcohol with stereo inversion. As expected the hydride ion attacks from the face opposite to the fused 1,2-*O*-isopropylidine ring. The hydroxyl group was next protected as its benzyl ether by reacting with NaH, BnBr in THF at room temperature in quantitative yield. Now the 5,6-*O*-isopropylidine ring was oxidatively cleaved to the aldehyde with H_5IO_6 in EtOAc at room temperature.[24] The aldehyde thus obtained was treated with CH_3MgI (generated in situ by reaction of CH_3I with Mg in THF being activated by I_2) at room temperature, yielding an inseparable diastereomeric mixture of secondary alcohols **16** (Scheme 2).



Scheme 2

The stereocenter of the hydroxyl center was of no significance, as it was oxidized next in Swern condition[25] to yield the methyl keto compound **17**. The spectral data were in full accordance to the structural feature of **17**. In ^1H NMR spectrum, the emergence of a peak at 2.20 ppm (s, 3H) due to the acetyl group approved the product. Also in ^{13}C NMR the carbonyl carbon appears at 204.9 ppm, which substantially follows the ^1H NMR. The methyl keto compound **17** on reaction with *p*-methoxybenzylidine triphenylphosphorane[26] (generated in situ by reaction of the *p*-methoxybenzyl triphenylphosphonium chloride with *n*-BuLi in benzene) at ambient temperature selectively gave the *E* isomer **18** with trace amount of *Z* olefin (92:8). The upfield shifting of the singlet from 2.20 ppm to 1.72 ppm for the vinyl CH_3 group was attributed to the change of carbonyl moiety (C=O) to olefin functionality (C=C) at α-position. Other protons resonated at their routine positions; for example, the single olefin proton

resonated at 6.60 ppm, a singlet at 3.81 ppm appeared due to the anisole OC<u>H</u>$_3$, two doublets at 6.86, 7.21 ppm accounting for the aromatic protons.



Scheme 3

The *E* geometry of the olefin was confirmed from NOESY study (Figure 7)**.** A strong n*O*e interaction was well observed between the aromatic ortho-hydrogen (7.21 ppm) and the vinyl methyl protons (1.72 ppm) showing their close proximity. No n*O*e interaction was visible for the olefinic proton (6.60 ppm) and the vinyl methyl protons (1.72 ppm) indicating their *trans* relation. The heterogeneous reduction of the olefin **18** by Pd/C with H_2 at 50 *psi* pressure yielded a mixture of the diastereomers in dr 55:45. The structural feature of the reduced product was codified from the ^{1}H NMR spectral data. In ^{1}H NMR spectrum, the peaks for olefinic proton at 6.60 ppm, and vinyl methyl at 1.72 ppm were disappeared and two doublets at 0.91 ppm in ratio 55:45 for the C-methyl protons were seen. The poor selectivity could be attributed to the anti nature of the C3 and C4 centers of the Furanose ring (Scheme 3).

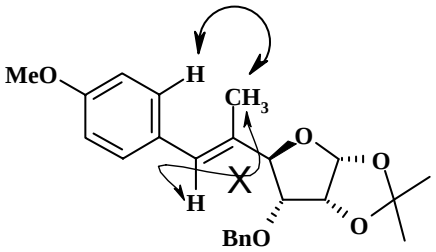
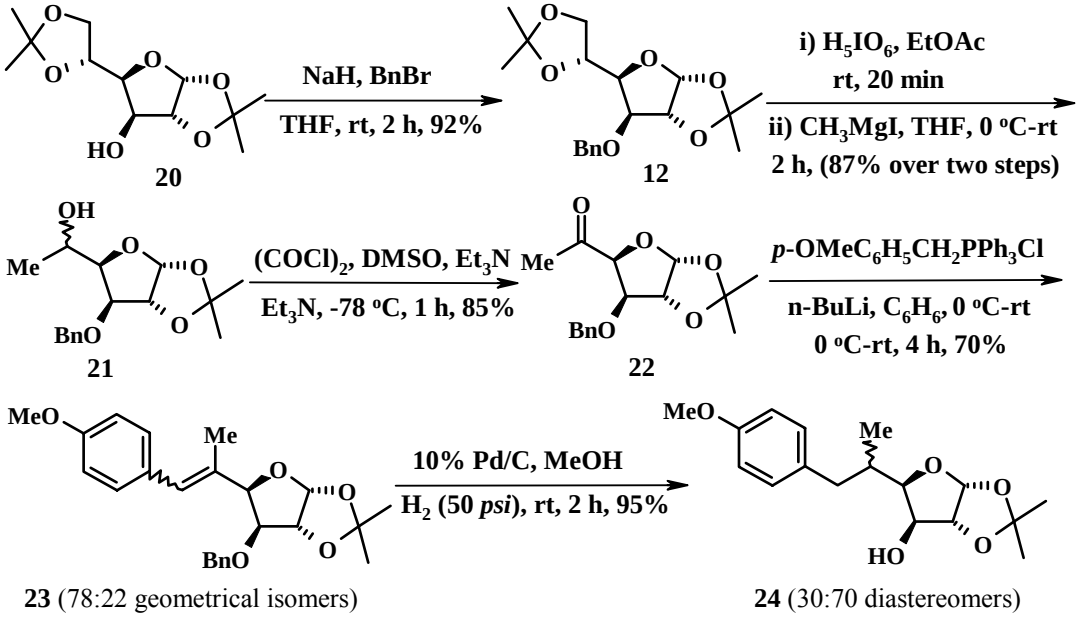


Figure 7: n*O*e interactions in the olefin **18**

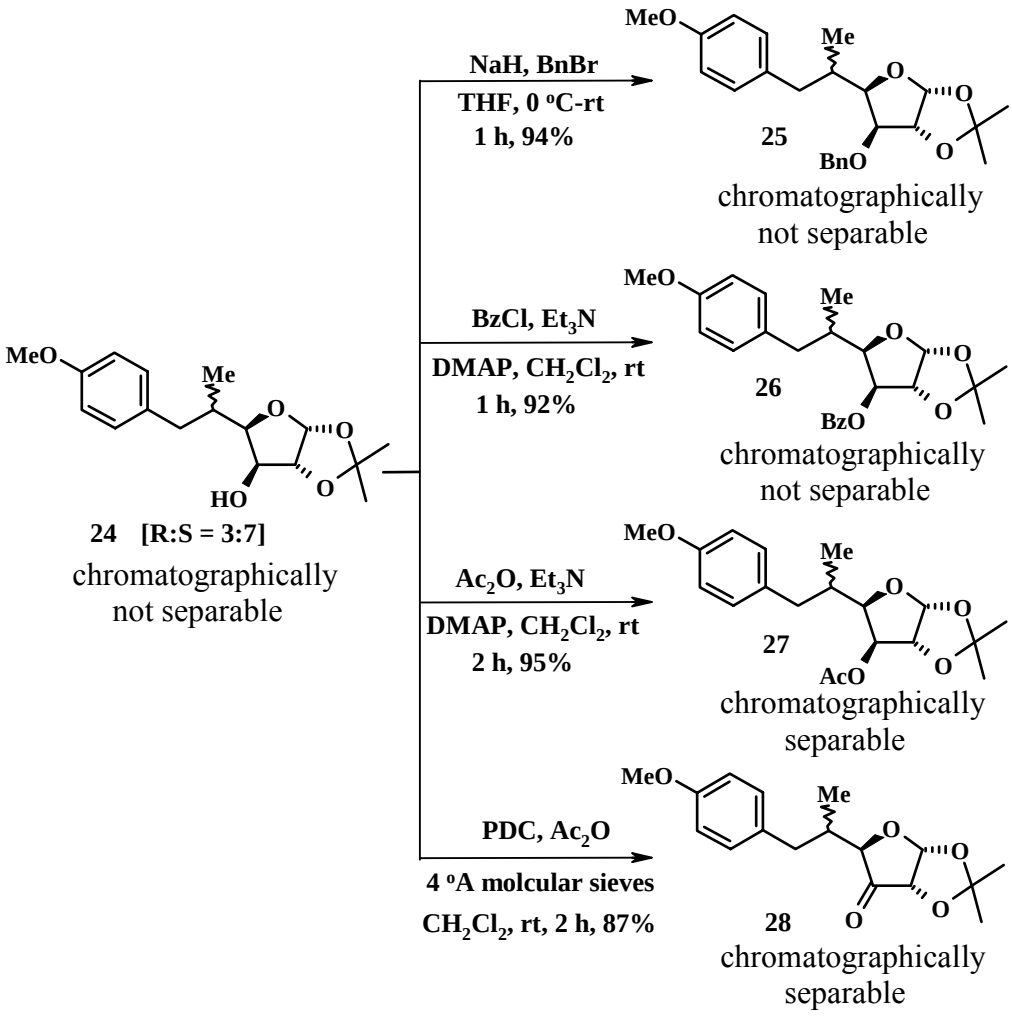
The hindsight gained out of the above failure indicated that the position of the OBn group above the plane might fetch some facial selection for the olefin reduction.[27] So, the hydroxyl group of 1,2:5,6-di-*O*-isopropylidineglucofuranose (**20**) was protected as its benzyl ether **12** and the oxidative cleavage of the 5,6-*O*-isopropylidine group with H_5IO_6 followed by Grignard reaction[28] with methyl magnesium chloride yielded diastereomeric mixture of the secondary alcohols **21** in 80:20 ratio. Both secondary alcohols on oxidation in Swern condition[25] yielded the same methyl keto compound **22**, which was proved by the presence of a peak at 2.23 ppm (s, 3H) due to the ($C\underline{H}_3CO$) in ^1H NMR spectrum and a singlet at 205.7 ppm for the carbonyl carbon in ^{13}C NMR spectrum. The carbonyl compound was next exposed to Wittig reaction with highly active *p*-methoxybenzylidine triphenylphosphorane[26] in benzene at room temperature to yield a 78:22 mixture of geometrical isomers **23**. Unlike the previous case, following the same procedure, Wittig olefination resulted a geometrical mixture, which may be attributed to the steric presence of the OBn group at the C3 position. The PMR spectrum highlighted the major structural features along with the dr value efficiently. Presence of the vinyl CH_3 group at 1.82 and 2.02 ppm; olefin proton singlets at 6.49 and 6.63 ppm confirmed the product and their corresponding ratios gave the dr value.



Scheme 4

As in the next step, the chirality at C6 differentiating the geometrical isomers was to be destroyed we carried forward with the mixture. The olefin **23** on hydrogenation yielded an inseparable mixture of diastereomers **24** in 3:7 ratio. The diastreomeric product **24** was reliably confirmed by the analysis of the ^{1}H NMR spectrum. The upfield shift of the methyl peak from 2.08 ppm to 1.03 ppm was noticed along with the disappearance of the olefin proton at 6.49 ppm (Scheme 4).

Attempts to separate the diastereomers by derivatisation method:



Scheme 5

Further proceeding in the synthetic sequence needed diastereomeric pure product with assigned stereochemistry. So we adopt the derivatisation method for this purpose expecting that the derivatisation of the hydroxy group may lead to the change in physical properties like adsorption to silica gel (for diastereomeric separation), crystalline solid

nature (for stereochemistry determination) to our favor. Thus the diastereomeric mixture of alcohols was converted to respective benzyl ethers **25**, benzoate esters **26**, acetate esters **27**, and keto derivatives **28** by standard procedures (Scheme 5). The diastereomeric benzyl ethers **25** and the benzoate esters **26** were not chromatographically separable, where as the acetate compounds **27** and the keto compounds **28** could be separated chromatographically. The structural features of pure diastereomers were unambiguously corroborated from the combined spectral studies (PMR, CMR spectroscopy).

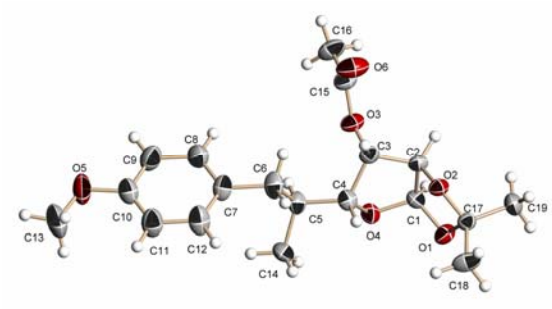


Figure 8: Ortep diagram of **27a**

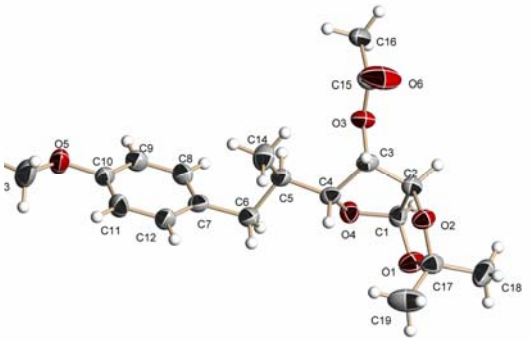
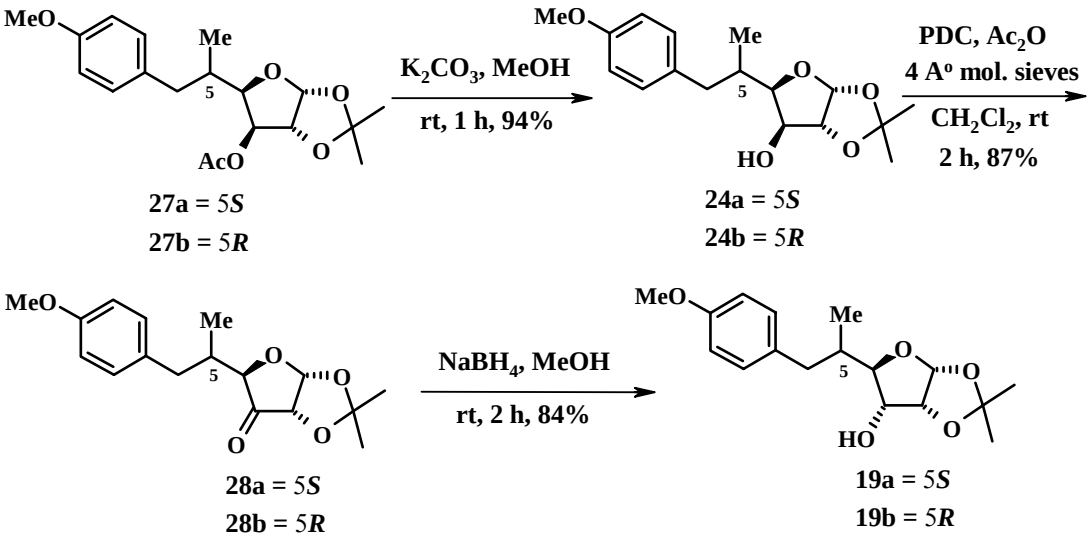


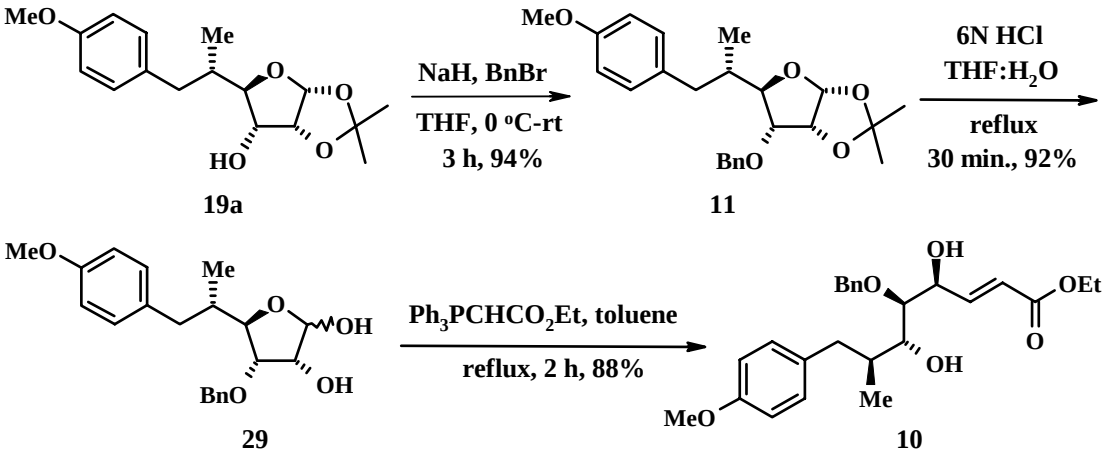
Figure 9: Ortep diagram of **27b**

To our desire, interestingly both acetate esters **27a** and **27b** were crystalline solids, and hence the absolute stereochemistry at C5 position was determined beyond doubt by single crystal X-ray crystallographic study (Figure 8 and 9). At this point, we confirmed that the reduction of the olefin **23** has yielded the required product **24a** as the major product.



Scheme 6

Then the corresponding acetate esters (**27a** and **27b**) were converted separately to the alcohols (**24a** and **24b**) quantitatively by treatment with anh. K_2CO_3 in MeOH. The structures of the alcohols **24a** and **24b** were confirmed by their ^{1}H NMR spectra with evidences from ^{13}C NMR, and analytical studies. The alcohols were next oxidized to corresponding keto compounds **28a** and **28b** by PDC oxidation procedure.[29] It is noteworthy to mention that these keto compounds could directly be obtained by the oxidation of the diastereomeric alcohol **24** (PDC oxidation) and chromatographic separation of the ketone mixture. The manifestation of singlet carbons at 211.4 and 211.1 for the carbonyl carbons of ketone **28a** and **28b** respectively and other peaks at expected chemical shifts assigned the structures. For introducing the amine functionality at C3 with retention of chirality, the keto compound **28a** was first reduced with $NaBH_4$ in MeOH at ambient temperature to obtain the inverted secondary alcohol **19a** in 84% yield. A triplet at 4.51 (J = 4.6 Hz) for the C2 proton in ^{1}H NMR spectrum indicated the syn nature of the C1, C2 and C3 methine protons of the furanose ring. The single crystal X-ray crystallography of compound **19a** (Figure 10) assigned the stereocenters with aplomb. Similarly the minor keto compound **28b** was reduced to the inverted alcohol **19b**, which was structurally consistent with the spectral and analytical informations (Scheme 6).



Scheme 7

The inverted secondary hydroxyl group **19a** was next protected as its benzyl ether **11** by reaction with NaH, BnBr in THF at room temperature. The surge in the integration values in the aromatic region at 7.35 ppm (5H) in ^{1}H NMR assigned the structure of **11**. Now we shifted our attention to the right half of the target molecule **5**.

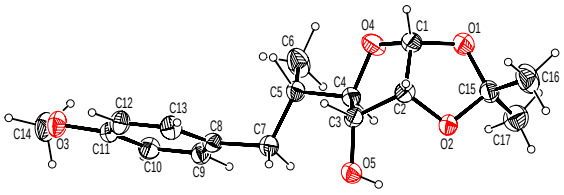
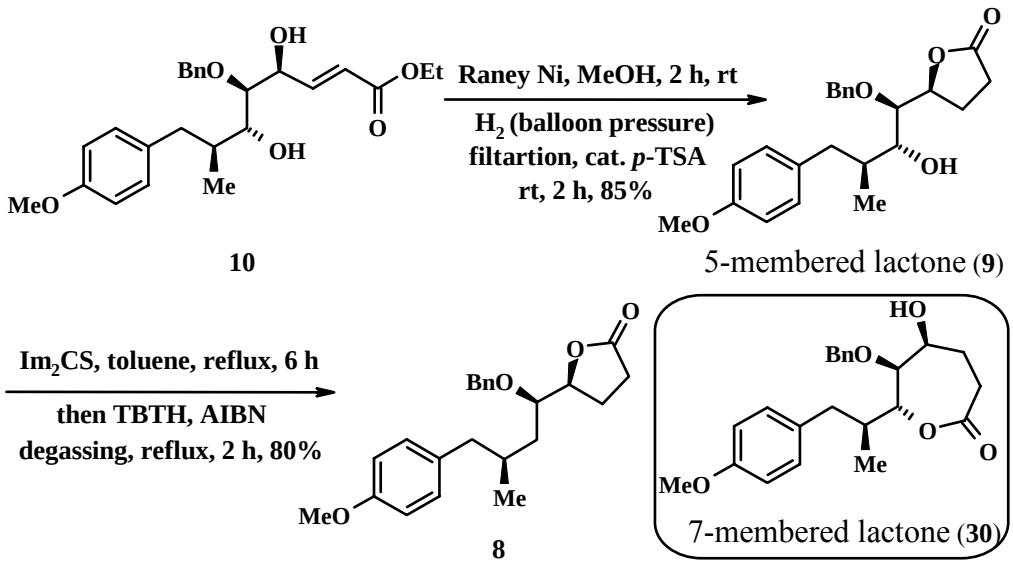


Figure 10: Ortep diagram of **19a**

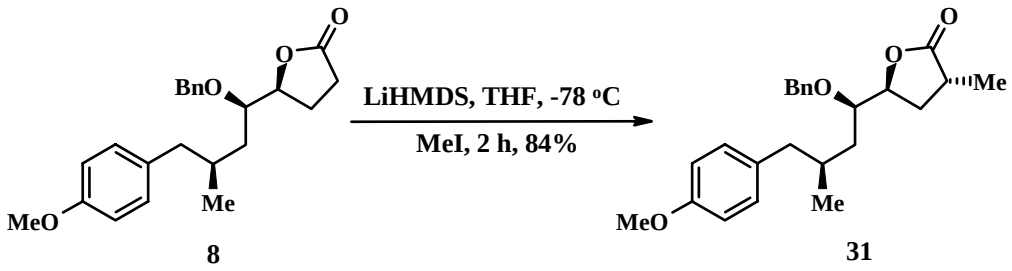
Deketalisation of the compound **11** with 6N HCl in THF:H_2O at reflux condition opened the floodgate for extrapolation of glucofuranose moiety. The lactol **29** on two carbon Wittig elongation with (ethoxycarbonylmethylene)triphenylphosphorane in toluene under reflux condition yielded the *E* isomer **10** as the major product. Disappearance of singlets at 1.35 and 1.54 ppm due to the isopropylidine methyl protons alongwith the emergence of olefin protons at 6.13 ppm (dd, J = 15.8, 1.9 Hz) and 7.08 ppm (dd, J = 15.8, 4.4 Hz) clearly indicated the structural change and (*E*) nature of the α, β-unsaturated ester compound **10**. In ^{13}C NMR spectrum the carbonyl carbon resonated at 166.5 ppm (Scheme 7).



Scheme 8

Selective double bond reduction with Raney Nickel[30] in hydrogen atmosphere followed by treatment of the filtrate with catalytic amount of *p*-TSA at ambient temperature yielded the γ-butyrolactone derivative **9** in preference to the 7-membered

lactone **30**. This step served many purposes as the regioselective formation of the 5-membered lactone ensures the protection of the γ- hydroxyl group, leaving the other hydroxyl group unaffected without necessitating any further protecting group manipulation. It is useful to mention that addition of *p*-TSA without filtering the Raney Nickel conferred the debenzylation reaction to some extent. So the reaction mixture was filtered prior to the addition of *p*-TSA. The integrity of the product **9** was confirmed by spectral analysis. In ^{1}H NMR spectrum, disappearance of double bond protons at 6.13 and 7.08 ppm iterates the reduction of the double bond. The lactonisation process was reiterated by the absence of the characteristic ethoxy protons at 1.28 and 4.59 ppm in ^{1}H NMR spectrum and the presence of a sharp peak at 1771 cm^{-1} in IR spectroscopy. The unwanted hydroxyl group in compound **9** was removed using sequential one pot Barton-McCombie radical deoxygenation protocol.[31]The hydroxyl compound **9** was treated with 1,1'-thiocarbonyldiimidazole in benzene under reflux condition for the formation of thioester, followed by addition of AIBN, TBTH with degassing under reflux condition furnished the deoxy compound **8**. This transformation was confirmed by the conspicuous disappearance of the signal for the methine proton at 3.51 ppm (Scheme 8).



Scheme 9

The introduction of the second methyl appendage with the required chirality was investigated next. For that the enolate derived from compound **8** by treatment with LiHMDS was quenched with MeI at -78 ºC (Scheme 9). The kinetic controlled C-alkylation reaction yielded a single diastereomer as was evident from the ^{1}H NMR and ^{13}C NMR spectrum. Exclusive formation of compound **31** was established by n*O*e studies. As depicted in figure 11, H_{3a} (1.80 ppm) shows strong n*O*e interactions with both H_4 (4.40 ppm) and the 2a-methyl protons (1.22 ppm). Also relevant n*O*e interactions were observed between H_{2b} (2.72 ppm) and H_{3b} (2.43 ppm) confirming the *syn*

relationship of the methyl group with H_4. The single diastereomer formation could be explained by the anti approach of the incoming methyl group to that of γ-hydroxyl group of the butenolide ring for minimizing the steric repulsion.

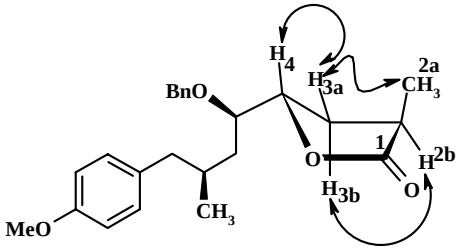
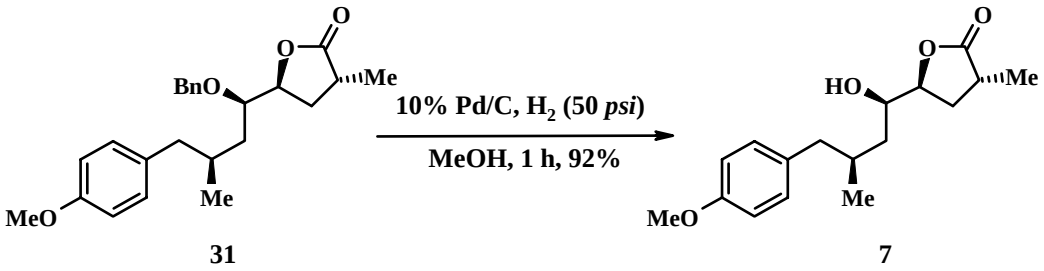


Figure 11: n*O*e interactions for the compound **31**

To introduce the amine functionality at C5, the benzyl ether of compound **31** was cleaved by catalytic heterogeneous hydrogenation in H_2 atmosphere over 10% Pd/C at room temperature (Scheme 10). The secondary alcohol **7** thus formed was characterized fully by spectral studies and adequately supported by X-ray crystallographic study. In ^1H NMR spectrum, the absence of the multiplet at 7.3 ppm for aromatic protons explained the deprotection of the benzyl ether. Although the n*O*e studies on **31** suggested the assigned stereochemistry (Figure 11), the single crystal X-ray crystallography of the debenzylated product **7** (Figure 12), unambiguously confirmed it.



Scheme 10

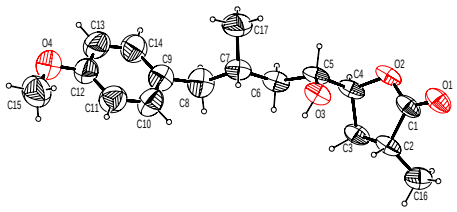
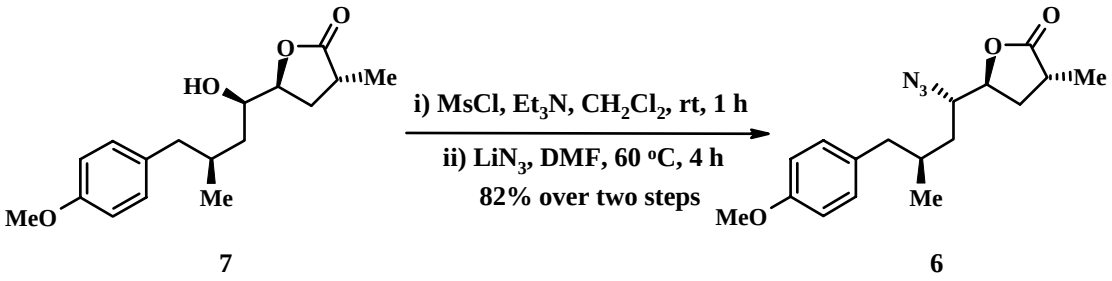


Figure 12: Ortep diagram of compound **7**

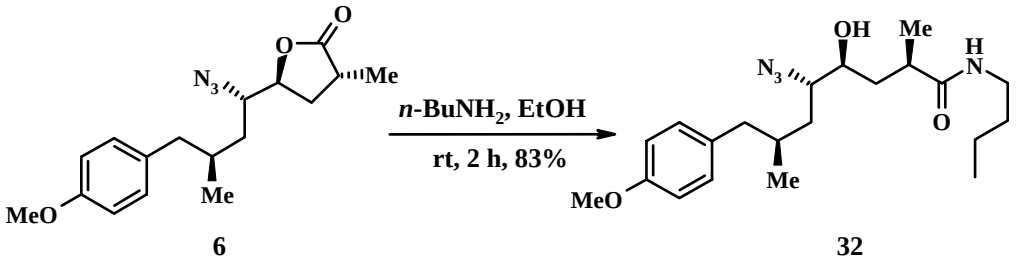
Compound **7** was subsequently mesylated with MsCl, Et_3N at room temperature in quantitative yield. Nucleophilic substitution of the super leaving mesylate functionality by azide nucleophile was achieved by treating the mesylate compound with LiN_3[32] in DMF at 60 °C. The conversion was approved by the characteristic peak at 2108 cm^{-1} in IR spectroscopy for azide group. In ^1H NMR spectrum, upfield shift of the peak (from 4.00 ppm to 3.33 ppm) belonging to methine proton (-C<u>H</u>N_3) compared to that of **7** (-C<u>H</u>OH) was noticed.



7 **6**

Scheme 11

At this juncture, the intermediate **6** could serve as the point for divergent synthesis of different renin inhibitor analogues differing in their amide fragment. As our target molecule demands, aminolysis of the lactone by nucleophilic opening with *n*-$BuNH_2$ in ethanol[33] at room temperature yielded the amide **32**, which forms the backbone 8-aryl octanoic acid amide of the target molecule. The additional peaks at higher magnetic field value and the broad peak at 5.91 ppm (N<u>H</u>) collectively assured the addition of the *n*-$BuNH_2$ to the lactone. In IR spectra the shift of peak from 1612 $cm^{-1}$to 1634 cm^{-1} confirmed the conversion of lactone to amide functionality (Scheme 12).

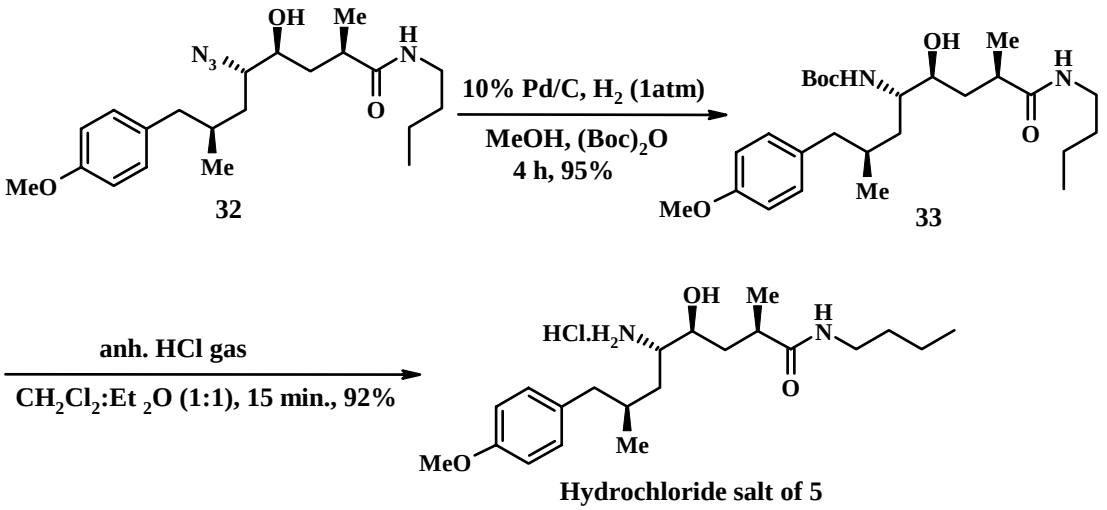


6 **32**

Scheme 12

Finally reduction of the azide group and *in situ* Boc-protection of the amine was achieved by treatment with 10% Pd/C, $(Boc)_2O$ in MeOH and subjecting the reaction

mixture to H_2 at balloon pressure. The structural feature of the product **33** was corroborated from the combined spectral data from ^{1}H NMR, ^{13}C NMR, IR and elemental analysis. The spectral studies revealed that the protected renin analogue **33** exists in rotameric isomers in solution. In ^{1}H NMR spectrum, the representative $(Boc)_2O$ protons appeared as a singlet at 1.39 ppm and the characteristic peak at 2108 cm^{-1} (for the azide group) in IR spectroscopy was disappeared. The total synthesis of the target molecule in hydrophilic mode was culminated by converting the hydrophobic organic compound **33** into the hydrochloride salt of **5** with dry HCl gas in ether/CH_2Cl_2 (1:1) solvent mixture. The product was reliably confirmed by the analysis of ^{1}H NMR, ^{13}C NMR spectrum in D_2O. The absence of characteristic $(Boc)_2O$ peaks in both PMR and CMR spectrum confirmed the conversion (Scheme 13).

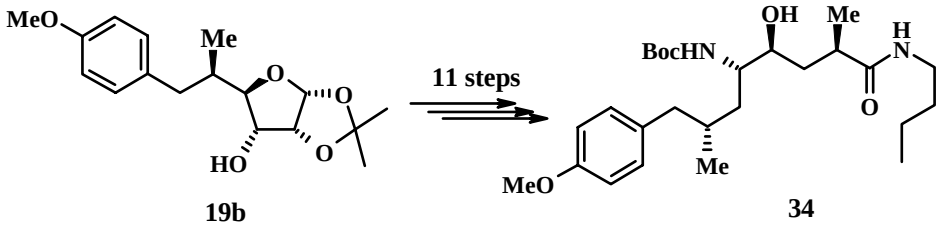


Scheme 13

Synthesis of the 7-*epi* analogue:

In a quest for renin inhibitor analogues, we launched the synthesis of the 7-*epi* analogue, starting from the minor isomer obtained in the hydrogenation reaction of **23**. So the diastereomer **19b** was taken through a parallel reaction sequence as described above for **19a**, which led to the formation of the epimer **34** (Scheme 14). The noticeable and advantageous fact is that, the structure and the absolute configuration of the epimer **34** could be confirmed by single crystal X-ray crystallographic study (Figure 13), which

could also assure the structural feature of our target molecule **5** by method of contradiction.



Scheme 14: Synthesis of the 7-*epi* analogue of our target molecule

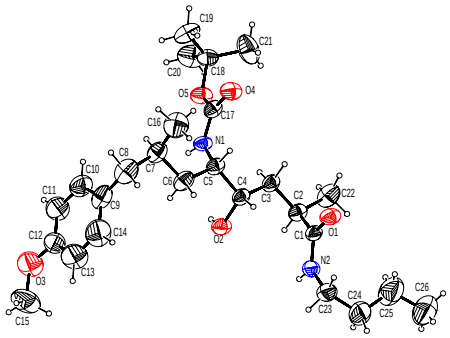
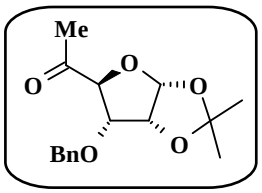


Figure 13: Ortep diagram of **34**

Epilogue:

In thumbnail, we accomplished the synthesis of a prototype renin inhibitor in a divergent synthesis sequence starting from D(+)-glucose. We anticipate that the stereoselective strategy, detailed above, could be extended to prepare the corresponding analogues through incorporating appropriate changes in the main strategy for diversity oriented synthesis.

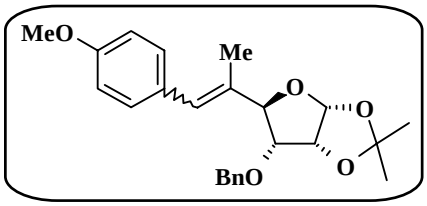
1-((3a*R*,5*S*,6*S*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl) (17):



The compound **17** was prepared from D(+)-glucose (**13**) in 7 steps (29% overall yield) as a yellow liquid.

Mol. Formula	:	$C_{16}H_{20}O_5$
Mol. Weight	:	292.33
ESI-MS *m/z*	:	315.38 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 65.74; H, 6.90 Found: C, 65.55; H, 7.03
^{1}H NMR (500 MHz, $CDCl_3$)	:	δ 1.38 (s, 3H), 1.61 (s, 3H), 2.20 (s, 3H), 3.76 (dd, 1H, *J* = 4.7, 9.2 Hz), 4.50 (d, 1H, *J* = 8.8 Hz), 4.56 (t, 1H, *J* = 4.7 Hz), 4.62 (d, 1H, *J* = 11.3 Hz), 4.76 (d, 1H, *J* = 11.3 Hz), 5.81 (d, 1H, *J* = 3.9 Hz), 7.33 (m, 5H)
^{13}C NMR ($CDCl_3$)	:	δ 26.7 (q), 26.9 (2q), 72.2 (t), 77.7 (d), 79.2 (d), 82.4 (d), 104.4 (d), 113.3 (s), 128.0 (d), 128.2 (d), 128.4 (d), 137.1 (s), 204.9 (s)

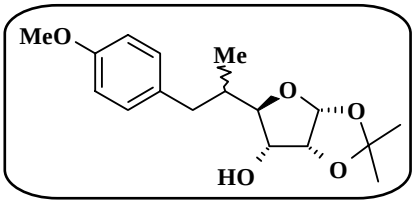
(3a*R*,5*R*,6*R*,6a*R*)-6-(benzyloxy)-5-(1-(4-methoxyphenyl)prop-1-en-2-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole (18):



To a suspension of *p*-methoxybenzyl triphenylphosphonium chloride (2.87 g, 6.85 mmol) in dry benzene (30 mL) was added *n*-BuLi (3.2 mL, 1.6 M in hexane, 5.15 mmol) drop wise at 0 °C under argon atmosphere. The reaction was warmed to room temperature and after 4 h the supernatant was slowly cannulated to a solution of ketone **17** (1.0 g, 3.45 mmol) in dry benzene (5 mL) under argon atmosphere. The suspension was stirred for 5 h at room temperature and quenched with saturated aqueous ammonium chloride solution and the organic layer was separated. The organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated to give the crude product which on purification by silica gel column chromatography using ethyl acetate: light petroleum (1:19) afforded **18** (1.02 g, 75%) as a liquid.

Mol. Formula	:	$C_{24}H_{28}O_5$
Mol. Weight	:	396.49
ESI-MS *m/z*	:	419.47 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 72.71; H, 7.12
		Found: C, 72.88; H, 7.37
^{1}H NMR	:	δ 1.38 (s, 3H), 1.65 (s, 3H), 1.72 (s, 3H), 3.65 (dd, 1H, *J* =
(500 MHz, $CDCl_3$)		4.4, 8.9 Hz), 3.81 (s, 3H), 4.53 (d, 1H, *J* = 8.9 Hz), 4.59
		(t, 1H, *J* = 4.2 Hz), 4.60 (d, 1H, *J* = 12.3 Hz), 4.75 (d, 1H,
		J = 12.3 Hz), 5.71 (d, 0.08H, *J* = 3.7 Hz), 5.76 (d, 0.92H,
		J = 3.7 Hz), 6.60 (s, 1H), 6.86 (d, 2H, *J* = 8.5 Hz), 7.21
		(d, 2H, *J* = 8.5 Hz), 7.29 (m, 5H)

(3a*R*,5*R*,6*R*,6a*R*)-5-(1-(4-methoxyphenyl)propan-2-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-ol (19):

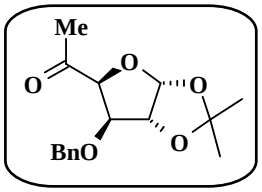


A suspension of **18** (0.56 g, 1.4 mmol) and 10% Pd/C (20 mg) in methanol (5 mL) was hydrogenated at 50 *psi* for 2 h. The reaction mixture was filtered through a bed of

Celite and the clear filtrate was evaporated. The residue was purified on silica gel column chromatography by using ethyl acetate: light petroleum (1:6) to obtain **19** (0.41 g, 94%) as a solid.

Mol. Formula	:	$C_{17}H_{24}O_5$
Mol. Weight	:	308.38
ESI-MS *m/z*	:	331.24 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 66.21; H, 7.84 Found: C, 66.35; H, 8.03
^{1}H NMR (500 MHz, $CDCl_3$)	:	δ 0.91 (ovlp doublets, 3H, *J* = 6.9 Hz), 1.35 and 1.37 (2s, 3H), 1.48 and 1.54 (2s, 3H), 1.96 (m, 1H), 2.21 (d, 0.45H, *J* = 11.0 Hz), 2.31 (d, 0.55H, *J* = 11.0 Hz), 2.42 (ovlp triplets, 1H, *J* = 13.3 Hz), 2.82 (dd, 0.45H, *J* = 6.6, 13.5 Hz), 2.88 (dd, 0.55H, *J* = 4.1, 13.5 Hz), 3.52 (dd, 0.55H, *J* = 6.6, 9.1 Hz), 3.58 (dd, 0.45H, *J* = 3.9, 9.1 Hz), 3.75 (m, 1H), 3.77 (s, 3H), 4.51 (t, 0.45H, *J* = 4.7 Hz), 4.53 (t, 0.55H, *J* = 4.7 Hz), 5.77 (d, 0.45H, *J* = 3.9 Hz), 5.79 (d, 0.55H, *J* = 3.9 Hz), 6.79 (2d, 2H, *J* = 8.4 Hz), 7.08 (2d, 2H, *J* = 8.4 Hz)

1-((3a*R*,5*S*,6*R*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)ethanone (22):



Compound **22** was prepared from D(+)-glucose (**13**) in 5 steps (44% overall yield).

Mol. Formula	:	$C_{16}H_{20}O_5$
Mol. Weight	:	292.33
ESI-MS *m/z*	:	315.11 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 65.74; H, 6.90

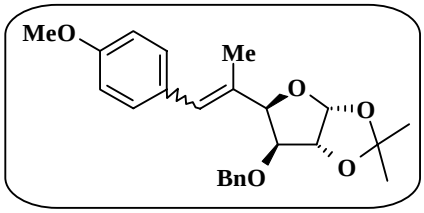
Found: C, 65.55; H, 7.03

$[\alpha]^{25}_{D}$: -81.3 (*c* 1, $CHCl_3$)

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.33 (s, 3H), 1.48 (s, 3H), 2.23 (s, 3H), 4.27 (d, 1H, *J* = 3.7 Hz), 4.47 (d, 1H, *J* = 11.8 Hz), 4.60 (d, 1H, *J* = 11.8 Hz), 4.63 (t, 2H, *J* = 3.9 Hz), 6.09 (d, 1H, *J* = 3.7 Hz), 7.32 (m, 5H)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 25.8 (q), 26.4 (q), 27.7(q), 71.8 (t), 81.3 (d), 83.2 (d), 84.9 (d), 105.4 (d), 111.6 (s), 127.1 (d), 127.5 (d), 128.0 (d), 136.5 (s), 205.7 (s)

(3a*R*,5*R*,6*S*,6a*R*)-6-(benzyloxy)-5-(1-(4-methoxyphenyl)prop-1-en-2-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole (23):



To a suspension of *p*-methoxybenzyl triphenylphosphonium chloride (5.74 g, 13.7 mmol) in dry benzene (50 mL) was added *n*-BuLi (6.4 mL, 1.6 M in hexane, 10.3 mmol) drop wise at 0 ^oC under argon atmosphere. After 4 h at room temperature, the supernatant was then slowly cannulated to a solution of ketone **22** (2.0 g, 6.9 mmol) in dry benzene (10 mL) under argon atmosphere. The reaction mixture was stirred for 5 h at room temperature and quenched with saturated aqueous ammonium chloride solution and the organic layer separated. The organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated to give the crude product which on purification by silica gel column chromatography using ethyl acetate: light petroleum (1:19) afforded **23** (1.9 g, 70%) as a yellow liquid.

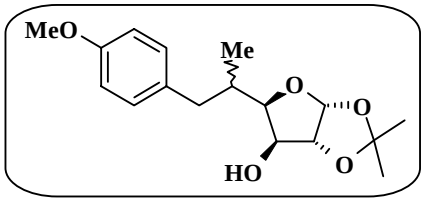
Mol. Formula : $C_{24}H_{28}O_5$

Mol. Weight : 396.49

ESI-MS *m/z* : 419.31 $[M+Na]^+$

Elemental Analysis	:	Calcd: C, 72.71; H, 7.12
		Found: C, 72.51; H, 7.40
^{1}H NMR	:	δ 1.28 (s, 3H), 1.33 (s, 3H), 1.82 (d, 0.7H, *J* = 1.0 Hz),
(200 MHz, $CDCl_3$)		2.08 (d, 2.3H, *J* = 1.4 Hz), 3.77 (s, 2.3H), 3.8 (s, 0.7H), 3.95 (d, 1H, *J* = 3.4 Hz), 4.58 (m, 3H), 5.05 (d, 1H, *J* = 3.4 Hz), 5.89 (d, 0.78H, *J* = 4.1 Hz), 5.97 (d, 0.22H, *J* = 4.1 Hz), 6.49 (s, 0.78H), 6.63 (s, 0.22H), 6.78, (d, 2H, *J* = 8.8 Hz), 6.96 (d, 2H, *J* = 8.8 Hz), 7.30 (m, 5 H)

(3a*R*,5*R*,6*S*,6a*R*)-5-(1-(4-methoxyphenyl)propan-2-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-ol (24):



A solution of **23** (5.6 g, 14.3 mmol) and 10% Pd/C (100 mg) in methanol (20 mL) was hydrogenated at 50 *psi* for 2 h. The reaction mixture was filtered through a small pad of Celite and the clear filtrate was evaporated. The residue was purified on silica gel column chromatography by using ethyl acetate: light petroleum (1:6) to obtain **24** (4.1 g, 95%) as a colorless liquid

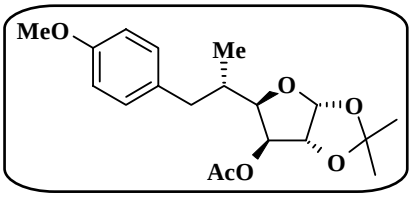
Mol. Formula	:	$C_{17}H_{24}O_5$
Mol. Weight	:	308.38
ESI-MS *m/z*	:	331.22 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 66.21; H, 7.84
		Found: C, 66.05; H, 8.01
^{1}H NMR	:	δ 0.82 (d, 0.9H, *J* = 6.8 Hz), 1.03 (d, 2.1H, *J* = 6.5 Hz),
(200 MHz, $CDCl_3$)		1.29-1.30 (2s, 3H), 1.47-1.49 (2s, 3H), 2.09 (m, 1H), 2.32 (dd, 0.7H, *J* = 8.4, 13.5 Hz), 2.50 (dd, 0.3H, *J* = 8.6, 13.5 Hz), 2.70 (dd, 0.7H, *J* = 5.4, 13.5 Hz), 2.97 (dd, 0.3H, *J* = 3.3, 13.5 Hz), 3.72 (m, 1H), 3.77 (s, 3H), 4.03 (d, 1H, *J* =

1.9 Hz), 4.45-4.48 (2d, 1H, *J* = 3.9 Hz), 5.84 (d, 0.7H, *J* = 3.9 Hz), 5.92 (d, 0.3H, *J* = 3.9 Hz), 6.79 (2d, 2H, *J* = 8.8 Hz), 7.10 (2d, 2H, *J* = 8.8 Hz)

Preparation of compounds 27a and **27b**:

The CH_2Cl_2 solution of the alcohol **24** (2.3 g, 7.5 mmol) was treated with Ac_2O (0.85 mL, 9.0 mmol), Et_3N (1.6 mL, 11.2 mmol), and DMAP (0.09 g, 0.75 mmol) for 2 h at room temperature. The reaction mixture was then concentrated and the diastereomeric acetate compounds were purified through flash column chromatography by using ethyl acetate: light petroleum (1:9) to obtain **27a** (1.75 g, 67%) and **27b** (0.73 g, 28%) as crystalline solids.

(3a*R*,5*R*,6*S*,6a*R*)-5-((*S*)-1-(4-methoxyphenyl)propan-2-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl acetate (27a):



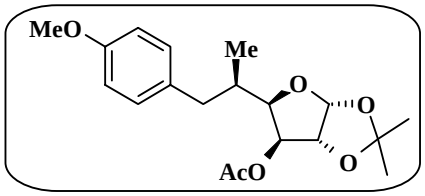
Mol. Formula	:	$C_{19}H_{26}O_6$
Mol. Weight	:	350.42
ESI-MS *m/z*	:	373.44 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 65.13; H, 7.48 Found: C, 65.29; H, 7.57
$[\alpha]_D^{25}$	:	-3.3 (*c* 1, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.99 (d, 3H, *J* = 6.6 Hz), 1.30 (s, 3H), 1.51 (s, 3H), 2.08 (m, 1H), 2.11 (s, 3H), 2.22 (dd, 1H, *J* = 9.6, 13.1 Hz), 2.60 (dd, 1H, *J* = 3.9, 13.1), 3.77 (s, 3 H), 3.94 (dd, 1H, *J* = 2.4, 9.4 Hz), 4.47 (d, 1H, *J* = 3.8 Hz), 5.18 (d, 1H, *J* = 2.4 Hz), 5.86 (d, 1H, *J* = 3.8 Hz), 6.79 (d, 2H, *J* = 8.3 Hz), 6.99 (d, 2 H, *J* = 8.3 Hz)
^{13}C NMR	:	δ 16.4 (q), 20.4 (q), 25.8 (q), 26.2 (q), 33.9 (d), 38.2 (t),

(50 MHz, $CDCl_3$)	54.7 (q), 75.6 (d), 82.8 (d), 83.3 (d), 103.7 (d), 111.1 (s), 113.4 (d), 129.6 (d), 131.3 (s), 157.7 (s), 169.1 (s)

Table 4. Crystal data and structure refinement for compound 27a:

Identification code	Data_**27a**
Empirical formula	C19 H26 O6
Formula weight	350.40
Temperature	297(2) K
Wavelength	0.71073 A
Crystal system, space group	Orthorhombic, P 212121
Unit cell dimensions	a = 5.408(3) A alpha = 90 deg. b = 9.450(5) A beta = 90 deg. c = 36.895(19) A gamma = 90 deg.
Volume	1885.6(17) A^3
Z, Calculated density	4, 1.234 Mg/m^3
Absorption coefficient	0.091 mm^-1
F(000)	752
Crystal size	0.78 x 0.07 x 0.04 mm
Theta range for data collection	2.21 to 25.00 deg.
Limiting indices	-6<=h<=6, -9<=k<=11, -38<=l<=43
Reflections collected / unique	9451 / 3318 [R(int) = 0.1365]
Completeness to theta = 25.00	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9964 and 0.9323
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3318 / 0 / 231
Goodness-of-fit on F^2	0.927
Final R indices [I>2sigma(I)]	R1 = 0.0635, wR2 = 0.0738
R indices (all data)	R1 = 0.2210, wR2 = 0.0978
Absolute structure parameter	0.5(18)
Largest diff. peak and hole	0.160 and -0.136 e.A^-3

(3a*R*,5*R*,6*S*,6a*R*)-5-((*R*)-1-(4-methoxyphenyl)propan-2-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl acetate (27b):



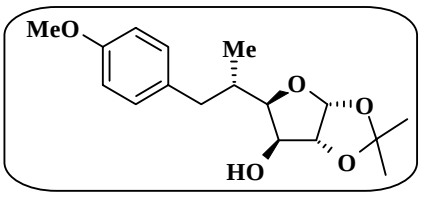
Mol. Formula	:	$C_{19}H_{26}O_6$
Mol. Weight	:	350.42
ESI-MS *m/z*	:	373.38 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 65.13; H, 7.48
		Found: C, 65.35; H, 7.33
$[\alpha]_D^{25}$	:	-14.7 (*c* 1, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.71 (d, 3H, *J* = 6.8 Hz), 1.31 (s, 3H), 1.49 (s, 3H), 2.02 (m, 1H), 2.09 (s, 3H), 2.48 (dd, 1H, *J* = 8.7, 13.5 Hz), 2.98 (dd, 1H, *J* = 3.3, 13.5), 3.78 (s, 3 H), 3.87 (dd, 1H, *J* = 2.6, 10.3), 4.46 (d, 1H, *J* = 3.9 Hz), 5.11 (d, 1H, *J* = 2.7 Hz), 5.91 (d, 1H, *J* = 3.9 Hz), 6.80 (d, 2H, *J* = 8.6 Hz), 7.12 (d, 2 H, *J* = 8.9 Hz).
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 14.5 (q), 20.6 (q), 26.1 (q), 26.4 (q), 33.2 (d), 38.4 (t), 54.91 (q), 75.9 (d), 81.9 (d), 83.3 (d), 104.2 (d), 111.5 (s), 113.3 (d), 130.6 (d), 131.0 (s), 157.8 (s), 169. 5 (s).

Table 5. Crystal data and structure refinement for compound 27b:

Identification code	Data_ **27b**
Empirical formula	C19 H26 O6
Formula weight	350.40
Temperature	297(2) K
Wavelength	0.71073 A
Crystal system, space group	Orthorhombic, P 212121
Unit cell dimensions	a = 5.523(5) A alpha = 90 deg.
	b = 15.129(15) A beta = 90 deg.

	c = 22.78(2) A gamma = 90 deg.
Volume	1903(3) A^3
Z, Calculated density	4, 1.223 Mg/m^3
Absorption coefficient	0.090 mm^-1
F(000)	752
Crystal size	0.76 x 0.12 x 0.03 mm
Theta range for data collection	1.62 to 25.00 deg.
Limiting indices	-6<=h<=5, -17<=k<=16, -26<=l<=26
Reflections collected / unique	8458 / 3332 [R(int) = 0.0633]
Completeness to theta = 25.00	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9973 and 0.9345
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3332 / 0 / 231
Goodness-of-fit on F^2	1.000
Final R indices [I>2sigma(I)]	R1 = 0.0642, wR2 = 0.1327
R indices (all data)	R1 = 0.1322, wR2 = 0.1565
Absolute structure parameter	1(2)
Largest diff. peak and hole	0.127 and -0.143 e.A^-3

(3a*R*,5*R*,6*S*,6a*R*)-5-((*S*)-1-(4-methoxyphenyl)propan-2-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-ol (24a):



The acetate compound **27a** (1.4 g, 4.0 mmol) was dissolved in MeOH (12 mL), and the solution was treated with anh. K_2CO_3 (0.66 g, 4.8 mmol) After stirring the reaction mixture for 1 h at room temperature, the solvent was removed in vacuo. The crude remaining was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc and the combined organic layer was dried over Na_2SO_4,

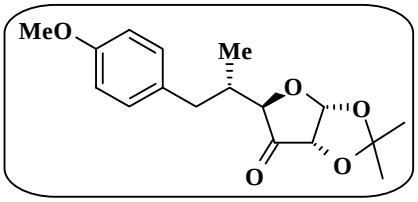
concentrated and purified through silica gel column chromatography by using ethyl acetate: light petroleum (1:4) to obtain **24a** (1.16 g, 94%) as a colorless liquid.

Mol. Formula	:	$C_{17}H_{24}O_5$
Mol. Weight	:	308.38
ESI-MS *m/z*	:	331.31 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 66.21; H, 7.84 Found: C, 66.35; H, 8.11
$[\alpha]_D^{25}$	:	+18.0 (*c* 1, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 1.03 (d, 3H, *J* = 6.5 Hz), 1.29 (s, 3H), 1.49 (s, 3H), 2.11 (m, 1H), 2.32 (dd, 1H, *J* = 8.4, 13.5 Hz), 2.70 (dd, 1H, *J* = 5.4, 13.5 Hz), 3.74 (dd, 1H, *J* = 2.6, 9.7 Hz), 3.78 (s, 3H), 4.03 (d, 1H, *J* = 1.9 Hz), 4.45 (d, 1H, *J* = 3.9 Hz), 5.84 (d, 1H, *J* = 3.9 Hz), 6.80 (d, 2H, *J* = 8.8 Hz), 7.09 (d, 2H, *J* = 8.8 Hz)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 16.8 (q), 25.9 (q), 26.4 (q), 33.9 (d), 38.2 (t), 54.8 (q), 74.1 (d), 85.0 (d), 85.2 (d), 103.8 (d), 111.0 (s), 113.5 (d), 129.8 (d), 131.9 (s), 157.7 (s)

Preparation of compounds 28a and 28b:

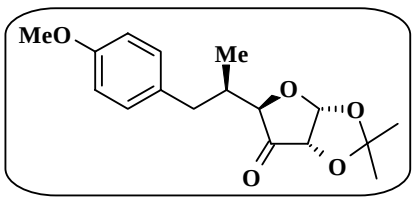
The suspension of **24** (3.0 g, 9.7 mmol), 4 A^o molecular sieves (7.5 g), PDC (4.4 g, 11.7 mmol), Ac_2O (0.5 mL) in dichloromethane (60 mL) was stirred for 2 h at room temperature. It was filtered through a pad of Celite, concentrated and purified on silica gel using ethyl acetate: light petroleum (1:19) to afford **28a** (1.8 g, 61%) as a light yellow liquid, followed by compound **28b** (0.78 g, 26%) as a light yellow liquid.

(3a*R*,5*R*,6a*S*)-5-((*S*)-1-(4-methoxyphenyl)propan-2-yl)-2,2-dimethyldihydrofuro[2,3-*d*][1,3]dioxol-6(3aH)-one (28a):



Mol. Formula	:	$C_{17}H_{22}O_5$
Mol. Weight	:	306.36
ESI-MS *m/z*	:	329.24 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 66.65; H, 7.24
		Found: C, 66.49; H, 7.37
$[\alpha]_D^{25}$	:	+153.3 (*c* 1, $CHCl_3$)
^{1}H NMR	:	δ 0.82 (d, 3H, *J* = 6.7 Hz), 1.40 (s, 3H), 1.42 (s, 3H), 2.14
(200 MHz, $CDCl_3$)		(m, 1H), 2.52 (dd, 1H, *J* = 7.5, 13.5 Hz), 2.72 (dd, 1H, *J* =
		8.2, 13.5 Hz), 3.78 (s, 3H), 4.22 (m, 2H), 6.03 (d, 1H, *J* =
		4.3 Hz), 6.80 (d, 2H, *J* = 8.7 Hz), 7.08 (d, 2H, *J* = 8.7 Hz)
^{13}C NMR	:	δ 14.1 (q), 27.2 (q), 27.3 (q), 37.6 (d), 38.6 (t), 55.1 (q),
(50 MHz, $CDCl_3$)		76.7 (d), 80.4 (d), 102.6 (d), 113.7 (s), 113.8 (d), 130.1
		(d), 131.5 (s), 158.1 (s), 211.4 (s)

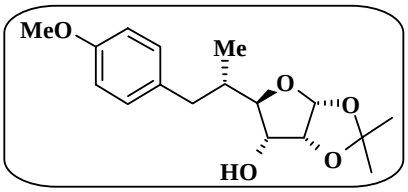
(3a*R*,5*R*,6a*S*)-5-((*R*)-1-(4-methoxyphenyl)propan-2-yl)-2,2-dimethyldihydrofuro[2,3-*d*][1,3]dioxol-6(3aH)-one (28b):



Mol. Formula	:	$C_{17}H_{22}O_5$
Mol. Weight	:	306.36
ESI-MS *m/z*	:	329.26 $[M+Na]^+$

Elemental Analysis	:	Calcd: C, 66.65; H, 7.24 Found: C, 66.84; H, 7.12
$[\alpha]_D$ [25]	:	+109.9 (*c* 1.8, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 1.02 (d, 3H, *J* = 6.83 Hz), 1.38 (s, 3H), 1.42 (s, 3H), 2.31 (ddd, 1H, *J* = 3.4, 7.1, 14.1 Hz), 2.52 (dd, 1H, *J* = 7.4, 13.5), 2.62 (dd, 1H, *J* =7.7, 13.5 Hz), 3.77 (s, 3H), 3.93 (dd, 1H, *J* = 0.9, 4.6 Hz), 4.18 (d, 1H, *J* = 3.4 Hz), 5.98 (d, 1H, *J* = 4.6 Hz), 6.78 (d, 2H, *J* = 8.5 Hz), 7.03 (d, 2H, *J* = 8.5 Hz)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 16.7 (q), 27.2 (q), 27.3 (q), 36.9 (t), 37.7 (d), 55.1 (q), 76.4 (d), 81.5 (d), 102.5 (d), 113.3 (s), 113.7 (d), 130.5 (d), 131.1 (s), 158.2 (s), 211.1 (s)

(3a*R*,5*R*,6*R*,6a*R*)-5-((*S*)-1-(4-methoxyphenyl)propan-2-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-ol (19a):



A solution of **28a** (4.2 g, 13.7 mmol) and $NaBH_4$ (0.62 g, 16.5 mmol) in MeOH (30 mL) at 0 ^oC was stirred for 2 h. The reaction mixture was then quenched with water and methanol was removed. The aqueous phase was extracted with ethyl acetate thrice. The organic layer was washed with water, brine, dried over Na_2SO_4, concentrated and purified on silica gel column chromatography by using ethyl acetate: light petroleum (1:6) to give **19a** (3.55 g, 84%) as a white solid.

Mol. Formula	:	$C_{17}H_{24}O_5$
Mol. Weight	:	308.38
Mp (^{o}C)	:	94.5 °C
ESI-MS *m/z*	:	331.37 $[M+Na]^+$

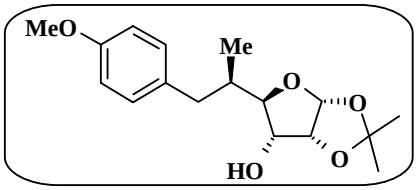
Elemental Analysis	:	Calcd: C, 66.21; H, 7.84 Found: C, 65.97; H, 8.03
$[\alpha]_D^{25}$	:	+48.4 (*c* 1, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.91 (d, 3H, *J* = 6.8 Hz), 1.35 (s, 3H), 1.48 (s, 3H), 1.99 (m, 1H), 2.21 (d, 1H, *J* = 10.2 Hz), 2.43 (dd, 1H, *J* = 8.6, 13.4 Hz), 2.82 (dd, 1H, *J* = 6.6, 13.4 Hz), 3.57 (dd, 1H, *J* = 3.9, 8.9 Hz), 3.77 (s, 3H), 3.77 (ovlp m, 1H), 4.51 (t, 1H, *J* = 4.6 Hz), 5.77 (d, 1H, *J* = 3.9 Hz), 6.79 (d, 2H, *J* = 8.5 Hz), 7.09 (d, 2H, *J* = 8.5 Hz)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 14.0 (q), 26.4 (q), 26.8 (q), 35.9 (d), 38.8 (t), 55.1 (q), 72.7 (d), 78.7 (d), 81.8 (d), 103.6 (d), 112.2 (s), 113.6 (d), 130.1 (d), 132.5 (s), 157.8 (s)

Table 6: **Crystal data and structure refinement for compound 19a**:

Identification code	Data_**19a**
Empirical formula	C17 H24 O5
Formula weight	308.36
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P2(1)
Unit cell dimensions	a = 10.2759(19) Å alpha = 90º. b = 5.7656(11) Å beta = 97.622(3)º. c = 14.152(3) Å gamma = 90º.
Volume	831.0(3) $Å^3$
Z, Calculated density	2, 1.232 Mg/m^3
Absorption coefficient	0.090 mm^{-1}
F(000)	332
Crystal size	0.82 x 0.26 x 0.08 mm
Theta range for data collection	2.00 to 25.50º.
Limiting indices	-12<=h<=12, -6<=k<=6, -17<=l<=16
Reflections collected / unique	4337 / 2635 [R(int) = 0.0266]

Completeness to theta = 25.50	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9931 and 0.9299
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2635 / 1 / 295
Goodness-of-fit on F^2	1.050
Final R indices [I>2sigma(I)]	R1 = 0.0380, wR2 = 0.0926
R indices (all data)	R1 = 0.0411, wR2 = 0.0944
Absolute structure parameter	-0.9(11)
Largest diff. peak and hole	0.172 and -0.123 e. $Å^{-3}$

(3a*R*,5*R*,6*R*,6a*R*)-5-((*R*)-1-(4-methoxyphenyl)propan-2-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-ol (19b):

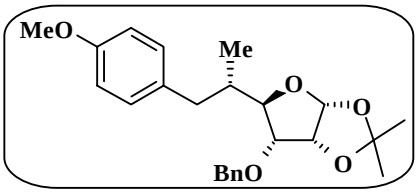


Following the above procedure, **28b** (3.7 g, 12.1 mmol) was reduced with $NaBH_4$ (0.54 g, 14.6 mmol) in MeOH (30 mL) to the corresponding alcohol **19b** (3.13 g, 84%) as a white solid.

Mol. Formula	:	$C_{17}H_{24}O_5$
Mol. Weight	:	308.38
Mp (^{o}C)	:	117.1 ^{o}C
ESI-MS *m/z*	:	331.32 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 66.21; H, 7.84
		Found: C, 66.04; H, 7.97
$[\alpha]_D^{25}$	:	+37.7 (*c* 1.1, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.92 (d, 3H, *J* = 6.9 Hz), 1.37 (s, 3H), 1.54 (s, 3H), 1.99 (m, 1H), 2.34 (d, 1H, *J* = 10.4 Hz), 2.43 (dd, 1H, *J* = 9.2, 13.6 Hz), 2.89 (dd, 1H, *J* = 4.1, 13.6 Hz), 3.52 (m, 1H),

		3.72 (m, 1H), 3.78 (s, 3H), 4.55 (t, 1H, *J* = 4.8 Hz), 5.81 (d, 1H, *J* = 4.0 Hz), 6.80 (d, 2H, *J* = 8.5 Hz), 7.10 (d, 2H, *J* = 8.5 Hz)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 14.4 (q), 26.4 (q), 26.7 (q), 37.6 (d), 38.2 (t), 55.1 (q), 73.7 (d), 78.9 (d), 83.0 (d), 103.4 (d), 112.2 (s), 113.5 (d), 130.3 (d), 132.1 (s), 157.8 (s)

(3a*R*,5*R*,6*R*,6a*R*)-6-(benzyloxy)-5-((*S*)-1-(4-methoxyphenyl)propan-2-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole (11):



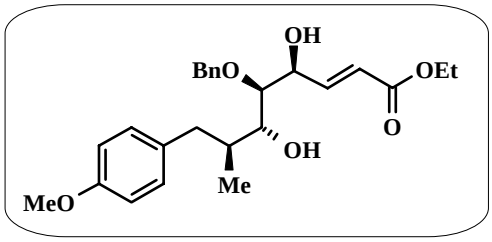
Sodium hydride (0.74 g, 60% in mineral oil, 18.7 mmol) was added to a stirred solution of **19a** (4.8 g, 15.6 mmol) in THF (40 mL) at 0 ^{o}C under nitrogen. After 1 h, BnBr (4.32 mL, 17.0 mmol) was introduced and stirring continued at room temperature for an additional 2 h, at which time cold water was added and layers were separated. The organic layer was dried over Na_2SO_4, concentrated and the crude product was purified on silica gel by using ethyl acetate: light petroleum (1:9) to afford **11** (5.83 g, 94%) as a colorless liquid.

Mol. Formula	:	$C_{24}H_{30}O_5$
Mol. Weight	:	398.50
ESI-MS *m/z*	:	421.41 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 72.34; H, 7.59
		Found: C, 72.38; H, 7.77
$[\alpha]_D^{25}$	:	+72.4 (*c* 1, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.74 (d, 3H, *J* = 6.8 Hz), 1.35 (s, 3H), 1.54 (s, 3H), 1.91 (m, 1H), 2.39 (dd, 1H, *J* = 9.0, 13.6 Hz), 2.76 (dd, 1H, *J* = 6.4, 13.6 Hz), 3.57 (dd, 1H, *J* = 4.4, 9.1 Hz), 3.78 (s, 3H), 3.97 (dd, 1H, *J* = 3.5, 9.1 Hz), 4.51 (d, 1H, *J* = 12.2 Hz),

4.54 (t, 1H, *J* = 4.0 Hz), 4.78 (d, 1H, *J* = 12.2 Hz), 5.69 (d, 1H, *J* = 4.0 Hz), 6.80 (d, 2H, *J* = 8.4 Hz), 7.07 (d, 2H, *J* = 8.4 Hz), 7.35 (m, 5H)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 13.4 (q), 26.7 (q), 35.7 (d), 39.0 (t), 55.0 (q), 71.6 (t), 77.2 (d), 78.2 (d), 79.5 (d), 103.6 (d), 112.5 (s), 113.5 (d), 127.9 (d), 128.3 (d), 130.0 (d), 132.5 (s), 137.5 (s), 157.7 (s)

(4*S*,5*R*,6*R*,7*S*,*E*)-ethyl 5-(benzyloxy)-4,6-dihydroxy-8-(4-methoxyphenyl)-7-methyloct-2-enoate (10):



A stirred solution of **11** (2.0 g, 5.03 mmol) in THF-H_2O (3:1, 20 mL), 6 N HCl (15 mL), and catalytic amount of H_2SO_4 (2 drops) was heated under reflux for 30 min. Solid $NaHCO_3$ was added to quench the reaction. THF was removed, the crude reaction mixture was partitioned between ethyl acetate (70 mL) and water (30 mL). The organic layer was separated, washed with water, brine, dried over Na_2SO_4, and concentrated to give the lactol **29** as colorless viscous liquid (1.66 g, 92%), which was used as such for the next reaction. The crude lactol **29** (1.66 g, 4.2 mmol) was dissolved in anhydrous toluene (30 mL) and to it, was added (ethoxycarbonylmethylene)triphenylphosphorane (2.77 g, 5.57 mmol) in toluene (25 mL). The reaction mixture was refluxed for 2 h. Solvent was evaporated and purified on silica gel by using ethyl acetate: light petroleum (1:4) to get **10** (1.74 g, 88%) as a viscous liquid.

Mol. Formula : $C_{25}H_{32}O_6$

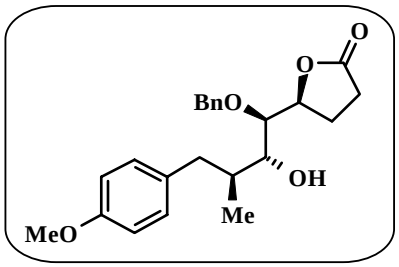
Mol. Weight : 428.53

ESI-MS *m/z* : 451.41 $[M+Na]^+$

IR ($CHCl_3$, cm^{-1}) : 3449, 3064, 3030, 2964, 2934, 1782, 1717, 1655, 1611,

		1583, 1512, 1456, 1247, 1178, 1037, 755, 699
Elemental Analysis	:	Calcd: C, 70.07; H, 7.53 Found: C, 69.88; H, 7.67
$[\alpha]_D^{25}$	:	+14.9 (*c* 3.3, MeOH)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.83 (d, 3H, *J* = 6.7 Hz), 1.28 (t, 3H, *J* = 7.1 Hz), 2.17 (m, 1H), 2.49 (m, 1H), 2.64 (m, 1H), 3.00 (b, 1H), 3.45 (dd, 1H, *J* = 5.1, 8.2 Hz), 3.71 (m, 1H), 3.78 (s, 3H), 4.18 (q, 2H, *J* = 7.2 Hz), 4.59 (d, 1H, *J* = 11.1 Hz), 4.60 (d, 1H, *J* = 11.1 Hz), 4.54 (ovlp m, 1H), 6.13 (dd, 1H, *J* = 1.8, 15.8 Hz), 6.78 (d, 2H, *J* = 8.6 Hz), 7.04 (d, 2H, *J* = 8.6 Hz), 7.08 (dd, 1H, *J* = 15.8, 4.4 Hz), 7.30 (m, 5H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 12.4 (q), 14.0 (q), 35.9 (d), 39.4 (t), 54.9 (q), 60.2 (t), 72.6 (d), 73.5 (t), 74.7 (d), 81.9 (d), 113.6 (d), 120.8 (d), 127.7 (d), 127.9 (d), 128.1 (d), 128.2 (d), 129.8 (d), 132.6 (s), 137.6 (s), 147.5 (d), 157.7 (s), 166.5 (s)

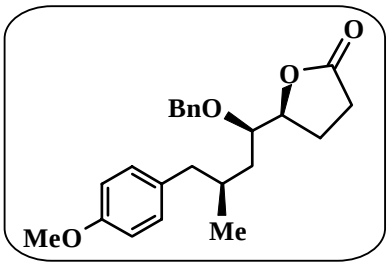
(*S*)-5-((1*R*,2*R*,3*S*)-1-(benzyloxy)-2-hydroxy-4-(4-methoxyphenyl)-3-methylbutyl)-dihydrofuran-2(3*H*)-one (9):



Compound **10** (1.6 g, 3.7 mmol) in MeOH (15 mL) was hydrogenated at balloon pressure using Raney Ni. After 2 h, the reaction mixture was filtered through a short bed of Celite and treated with catalytic amount of *p*-TSA (0.05 g). After 2 h, the reaction mixture was neutralized with solid $NaHCO_3$, concentrated and partitioned between ethyl acetate (70 mL) and water (30 mL). The organic layer was separated, dried over Na_2SO_4, concentrated and purified on silica gel column chromatography using ethyl acetate: light petroleum (1:6) to afford **9** (1.22 g, 85%) as a colorless liquid.

Mol. Formula	:	$C_{23}H_{28}O_5$
Mol. Weight	:	384.48
ESI-MS (*m/z*)	:	407.41 $[M+Na]^+$
IR ($CHCl_3$,)	:	3480, 3032, 2962, 2934, 2837, 1771, 1611, 1584, 1512, 1456, 1247, 1179, 1036, 752, 700, 682 cm^{-1}
Elemental Analysis	:	Calcd: C, 71.85; H, 7.34 Found: C, 71.83; H, 7.39
$[\alpha]_D^{25}$	:	-4.8 (*c* 3.6, MeOH)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.84 (d, 3H, *J* = 6.8 Hz), 1.85 (m, 1H), 2.14 (m, 2H), 2.31 (m, 1H), 2.46 (m, 3H), 2.62 (dd, 1H, *J* = 6.7, 13.7 Hz), 3.52 (m, 1H), 3.77 (s, 3H), 3.84 (m, 1H), 4.52 (d, 1H, *J* = 10.9 Hz), 4.68 (d, 1H, *J* = 10.9 Hz), 4.92 (ddd, 1H, *J* = 2.4, 6.7, 8.2 Hz), 6.80 (d, 2H, *J* = 8.6 Hz), 7.04 (d, 2H, *J* = 8.6 Hz), 7.30 (m, 5H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 12.5 (q), 21.2 (t), 28.4 (t), 35.8 (d), 39.3 (t), 54.9 (q), 72.7 (d), 74.5 (t), 79.4 (d), 81.5 (d), 113.7 (d), 127.7 (d), 127.9 (d), 128.2 (d), 129.7 (d), 132.2 (s), 137.6 (s), 157.8 (s), 177.6 (s)

(*S*)-5-((1*R*,3*S*)-1-(benzyloxy)-4-(4-methoxyphenyl)-3-methylbutyl)-dihydrofuran-2(3*H*)-one (8):

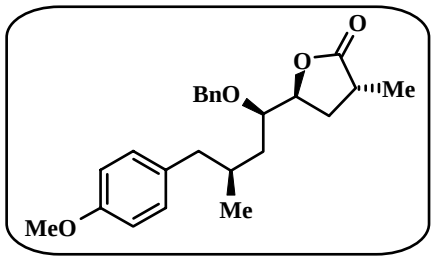


A solution of **9** (1.1 g, 2.9 mmol) and 1,1'-thiocarbonyl diimidazole (0.62 g, 3.4 mmol) in toluene (20 mL) was heated under reflux for 6 h. After completion of the reaction, the reaction mixture was brought to room temperature and degassed with argon. TBTH (1 mL, 3.4 mmol) and catalytic amount of AIBN (0.02 g) was added to the

reaction mixture and heated under reflux again for 2 h. The reaction mixture was concentrated and partitioned between ethyl acetate (50 mL) and water (20 mL). The organic layer was separated, washed with water, brine, dried over Na_2SO_4, concentrated and purified on silica gel by using ethyl acetate: light petroleum (1:9) to give **8** (0.84 g, 80%) as a colorless liquid.

Mol. Formula	:	$C_{23}H_{28}O_4$
Mol. Weight	:	368.48
ESI-MS (*m/z*)	:	391.43 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	3064, 3018, 2956, 2929, 2871, 1774, 1612, 1583, 1512, 1456, 1248, 1276, 1179, 1036, 756, 698, 667
Elemental Analysis	:	Calcd: C, 74.97; H, 7.66 Found: C, 74.86; H, 7.68
$[\alpha]_D^{25}$	:	+7.5 (*c* 1.25, MeOH)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.83 (d, 3H, *J* = 6.5 Hz), 1.09 (ddd, 1H, *J* = 3.8, 9.3, 13.5 Hz), 1.59 (ddd, 1H, *J* = 4.0, 9.3, 13.5 Hz), 1.89 (m, 1H), 2.17 (m, 2H), 2.38-2.59 (m, 4H), 3.77 (s, 3H), 3.84 (m, 1H), 4.45 (m, 1H), 4.50 (d, 1H, *J* = 11.2 Hz), 4.62 (d, 1H, *J* = 11.2 Hz), 6.79 (d, 2H, *J* = 8.6 Hz), 7.10 (d, 2H, *J* = 8.6 Hz), 7.3 (m, 5H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 19.3 (q), 21.5 (t), 28.2 (t), 31.2 (d), 37.9 (t), 43.0 (t), 54.9 (q), 73.7 (t), 77.4 (d), 82.6 (d), 113.6 (d), 127.6 (d), 127.8 (d), 128.2 (d), 129.8 (d), 132.3 (s), 138.1 (s), 157.8 (s), 176.6 (s)

(3*R*,5*S*)-5-((1*R*,3*S*)-1-(benzyloxy)-4-(4-methoxyphenyl)-3-methylbutyl)-3-methyl-dihydrofuran-2(3*H*)-one (31):

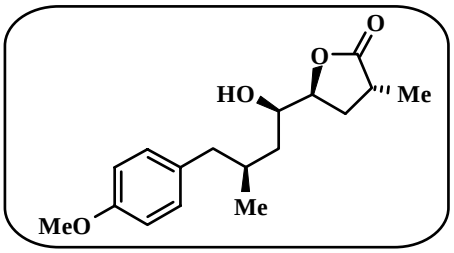


To a stirred solution of **8** (0.76 g, 2.06 mmol) in THF (20 mL) at -78 ^{o}C, was added LiHMDS (2.06 mL, 1 M solution in THF, 2.06 mmol). After 1 h, MeI (0.13 mL, 2.06 mmol) was added and the reaction mixture stirred for an additional 1 h. The reaction was quenched by saturated aqueous NH_4Cl solution (5 mL) and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, concentrated and the crude product was purified on silica gel using ethyl acetate: light petroleum (1:9) to afford **31** (0.66 g, 84%) as a colorless liquid.

Mol. Formula	:	$C_{24}H_{30}O_4$
Mol. Weight	:	382.50
ESI-MS *m/z*	:	405.41 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 75.36; H, 7.91 Found: C, 75.48; H, 8.02
$[\alpha]_D^{25}$	:	+13.3 (*c* 1, MeOH)
^{1}H NMR (500 MHz, $CDCl_3$)	:	δ 0.85 (d, 3H, *J* = 6.57 Hz), 1.09 (ddd, 1H, *J* = 3.9, 9.4, 13.4 Hz), 1.23 (d, 3H, *J* = 7.4 Hz), 1.60 (ddd, 1H, *J* = 4.1, 9.0, 13.4 Hz), 1.80 (ddd, 1H, *J* = 8.6, 12.8, 17.2 Hz), 1.88 (m, 1H), 2.38 (dd, 1H, *J* = 7.9, 13.5 Hz), 2.43 (ddd, 1H, *J* = 3.8, 9.6, 12.9 Hz), 2.53 (dd, 1H, *J* = 6.4, 13.5 Hz), 2.72 (m, 1H), 3.77 (s, 3H), 3.81 (dt, 1H, *J* = 3.4, 6.6, 9.0 Hz), 4.40 (dt, 1H, *J* = 3.4, 6.4, 8.6 Hz), 4.47 (d, 1H, *J* = 11.2 Hz), 4.58 (d, 1H, *J* = 11.2 Hz), 6.79 (d, 2H, *J* = 8.5 Hz), 7.00 (d, 2H, *J* = 8.5 Hz), 7.3 (m, 5H)
^{13}C NMR	:	δ 16.5 (q), 19.5 (q), 30.0 (t), 31.4 (d), 34.2 (d), 38.2 (t),

(125 MHz, $CDCl_3$)	43.2 (t), 55.1 (q), 74.1 (t), 77.8 (d), 80.5 (d), 113.6 (d), 127.8 (d), 128.1 (d), 128.4 (d), 129.9 (d), 132.4 (s), 138.0 (s), 157.9 (s), 180.0 (s)

(3*R*,5*S*)-5-((1*R*,3*S*)-1-hydroxy-4-(4-methoxyphenyl)-3-methylbutyl)-3-methyl-dihydrofuran-2(3*H*)-one (7):



Compound **31** (0.6 g, 1.57 mmol) in MeOH (10 mL) was hydrogenated by catalytic amount of 10% Pd/C (0.03 g) at 50 *psi*. After 1 h, the reaction mixture was filtered through a small bed of Celite, concentrated, and purified on silica gel column chromatography using ethyl acetate: light petroleum (1:4) to obtain **7** (0.42 g, 92%) as white solid which on recrystallization (ethyl acetate/light petroleum) gave good crystalline solid.

Mol. Formula	:	$C_{17}H_{24}O_4$
Mol. Weight	:	292.38
Mp (^{o}C)	:	80.5 ^{o}C
ESI-MS *m/z*	:	315.31 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 69.84; H, 8.27 Found: C, 69.75; H, 8.15
$[\alpha]^{25}_D$	:	+38.0 (*c* 1.1, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.88 (d, 3H, *J* = 6.6 Hz), 1.07 (ddd, 1H, *J* = 2.7, 10.2, 13.2 Hz), 1.23 (d, 3H, *J* = 7.3 Hz), 1.48 (ddd, 1H, *J* = 3.7, 10.6, 13.2 Hz), 1.78 (ddd, 1H, *J* = 8.2, 12.8, 16.2 Hz), 2.00 (m, 1H), 2.34-2.62 (m, 3H), 2.75 (m, 1H), 3.04 (bs, 1H), 3.77 (s, 3H), 4.00 (d, 1H, *J* = 10.5 Hz), 4.31 (m, 1H), 6.79 (d, 2H, *J* = 8.7 Hz), 7.04 (d, 2H, *J* = 8.7 Hz)

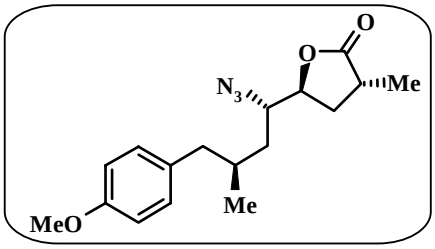
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 16.3 (q), 18.8 (q), 29.6 (t), 31.0 (d), 34.4 (d), 38.9 (t), 43.3 (t), 55.0 (q), 69.4 (d), 81.2(d), 113.6 (d), 129.9 (d), 132.6 (s), 157.8 (s), 180.6 (s)

Table 7: **Crystal data and structure refinement for compound 7**:

Identification code	Data_**7**
Empirical formula	C17 H24 O4
Formula weight	292.36
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions	a = 5.5146(12) Å alpha = 90 deg. b = 9.2177(19) Å beta = 90 deg. c = 33.537(7) Å gamma = 90 deg.
Volume	1704.8(6) $Å^3$
Z, Calculated density	4, 1.139 Mg/m^3
Absorption coefficient	0.080 mm^{-1}
F(000)	632
Crystal size	0.67 x 0.60 x 0.10 mm
Theta range for data collection	2.29 to 25.50º.
Limiting indices	-6<=h<=6, -7<=k<=11, -40<=l<=40
Reflections collected / unique	8848 / 3165 [R(int) = 0.0295]
Completeness to theta = 25.50	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9917 and 0.9481
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3165 / 0 / 194
Goodness-of-fit on F^2	1.044
Final R indices [I>2sigma(I)]	R1 = 0.0502, wR2 = 0.1294
R indices (all data)	R1 = 0.0887, wR2 = 0.1453
Absolute structure parameter	-1(2)

Largest diff. peak and hole 0.127 and -0.119 e. $Å^{-3}$

(3*R*,5*S*)-5-((1*S*,3*S*)-1-azido-4-(4-methoxyphenyl)-3-methylbutyl)-3-methyl-dihydrofuran-2(3*H*)-one (6):

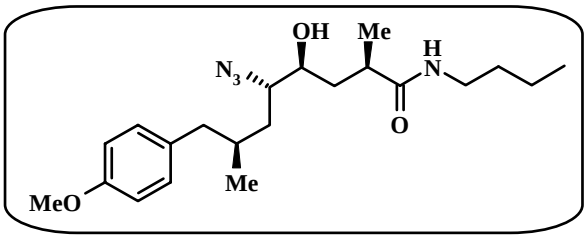


A solution of **7** (0.4 g, 1.4 mmol), Et_3N (0.23 mL, 1.6 mmol), and MsCl (0.13 mL, 1.6 mmol) in CH_2Cl_2 (10 mL) was stirred under nitrogen at 0 ^oC. After 1 h, the reaction mixture was partitioned between CH_2Cl_2 and water. The organic layer was separated, washed with water, brine, dried over Na_2SO_4, concentrated to afford the mesylated product as a brownish liquid. The crude compound was taken with LiN_3 (0.27 g, 5.6 mmol) in DMF (5 mL) and the reaction mixture was heated at 60 ^oC for 4 h. After completion of the reaction, the reaction mixture was partitioned between diethyl ether and water. The organic layer was separated, washed with water, brine, dried over Na_2SO_4, concentrated, and purified on silica gel using ethyl acetate: light petroleum (1:9) to get **6** (0.36 g, 82%) as a light yellow liquid.

Mol. Formula	:	$C_{17}H_{23}N_3O_3$
Mol. Weight	:	317.39
ESI-MS *m/z*	:	340.35 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	2932, 2851, 2108, 1778, 1612, 1583, 1513, 1457, 1380, 1248, 1178, 1034, 920, 807, 754
Elemental Analysis	:	Calcd: C, 64.33; H, 7.30; N, 13.24 Found: C, 64.52; H, 7.57; N, 13.20
$[\alpha]_D^{25}$	:	+53.6 (*c* 1, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.92 (d, 3H, *J* = 6.6 Hz), 1.27 (d, 3H, *J* = 7.4 Hz), 1.61 (m, 2H), 1.94 (m, 2H), 2.28 (m, 2H), 2.75 (m, 2H), 3.32 (m, 1H), 3.78 (s, 3H), 4.42 (p, 1H, *J* = 4.3, 4.0, 8.3 Hz),

		6.80 (d, 2H, *J* = 8.6 Hz), 7.04 (d, 2H, *J* = 8.6 Hz)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 16.4 (q), 20.0 (q), 32.1 (d), 32.8 (t), 33.7 (d), 37.2 (t), 42.2 (t), 55.1 (q), 63.0 (d), 78.5 (d), 113.8 (d), 130.0 (d), 132.0 (s), 158.1 (s), 179.0 (s)

(2*R*,4*S*,5*S*,7*S*)-5-azido-N-butyl-4-hydroxy-8-(4-methoxyphenyl)-2,7-dimethyloctanamide (32):



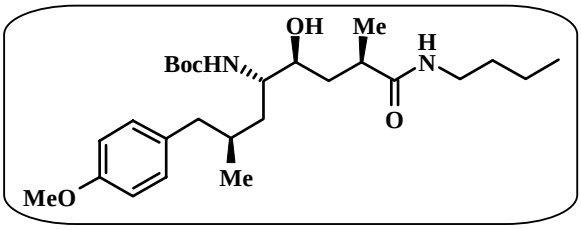
Compound **6** (0.15 g, 0.47 mmol) was treated with a 33% w/v solution of *n*-$BuNH_2$ in dry ethanol (1.7 g. *n*-$BuNH_2$ in 5 mL dry ethanol) under nitrogen. After 2 h, the reaction mixture was concentrated, partitioned between ethyl acetate and water. The organic layer was washed with water, brine, dried over Na_2SO_4, concentrated and purified on silica gel column by using ethyl acetate: light petroleum (1:6) to afford **32** (0.153 g, 83%) as a colorless liquid.

Mol. Formula	:	$C_{21}H_{34}N_4O_3$
Mol. Weight	:	390.53
ESI-MS *m/z*	:	413.41 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	3316, 2931, 2873, 2108, 1634, 1549, 1512, 1463, 1376, 1247, 1178, 1037, 850, 805, 754
Elemental Analysis	:	Calcd: C, 64.59; H, 8.78; N, 14.35 Found: C, 64.46; H, 8.95; N, 14.19
$[\alpha]_D^{25}$	:	-10.5 (*c* 1, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.89 (d, 3H, *J* = 6.6 Hz), 0.92 (t, 3H, *J* = 7.0 Hz), 1.19 (d, 3H, *J* = 6.9 Hz), 1.32 (m, 4H), 1.58 (m, 4H), 1.91 (m, 1H), 2.28 (dd, 1H, *J* = 8.6, 13.4 Hz), 2.57 (m, 1H), 2.70 (dd, 1H, *J* = 5.3, 13.4 Hz), 3.23 (m, 3H), 3.55 (m, 1H),

3.79 (s, 3H), 5.91 (bs, 1H), 6.83 (d, 2H, *J* = 8.6 Hz), 7.07 (d, 2H, *J* = 8.6 Hz)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 13.7 (q), 18.1 (q), 20.0 (t), 20.1 (q), 31.6 (t), 32.2 (d), 37.7 (d), 37.8 (t), 38.3 (t), 39.2 (t), 41.9 (t), 55.2 (q), 65.4 (d), 71.1 (d), 113.7 (d), 130.0 (d), 132.6 (s), 157.8 (s), 176.4 (s)

***tert*-butyl (2*S*,4*S*,5*S*,7*R*)-8-(butylamino)-5-hydroxy-1-(4-methoxyphenyl)-2,7-dimethyl-8-oxooctan-4-ylcarbamate (33):**



Compound **32** (0.065 g, 0.17 mmol) in methanol (5 mL), was hydrogenated by catalytic amount of 10% Pd/C (0.01 g) at 1 atmosphere for 3 h. After completion of the reaction, Boc_2O (0.05 mL, 0.2 mmol) was added to the reaction mixture and stirred at room temperature for 1 h. The reaction mixture was passed through a short Celite plug, concentrated and purified on silica gel column chromatography (1:9) to give **33** (0.073 g, 95%) as a foam solid.

Mol. Formula : $C_{26}H_{44}N_2O_5$

Mol. Weight : 464.64

ESI-MS *m/z* : 487.59 $[M+Na]^+$

IR ($CHCl_3$, cm^{-1}) : 3438, 3346, 3017, 2964, 2933, 1696, 1646, 1512, 1456, 1367, 1247, 1176, 1039, 756, 668

Elemental Analysis : Calcd: C, 67.21; H, 9.54; N, 6.03
Found: C, 67.14; H, 9.59; N, 6.10

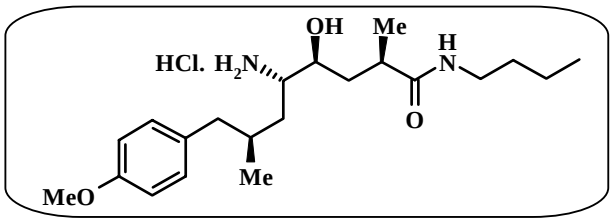
$[\alpha]_D^{25}$: -17.6 (*c* 1, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) : δ 0.78 (2d, 3H, *J* = 6.8 Hz), 0.86 (2t, 3H, *J* = 7.3 Hz), 1.10 (d, 3H, *J* = 6.9 Hz), 1.2 (m, 2H), 1.27 (m, 2H), 1.39 (s,

9H), 1.42 (m, 4H), 1.59 (m, 2H), 1.68 (b, 1H), 2.10 (dd, 0.8H, *J* = 9.3, 13.4 Hz), 2.24 (m, 0.2H), 2.33 (m, 0.2H), 2.48 (m, 0.8H), 2.63 (m, 0.2H), 2.70 (dd, 0.8H, *J* = 4.5, 13.4 Hz), 2.92 (m, 0.2H), 3.10 (m, 0.8H), 3.19 (m, 1 H), 3.55 (m, 0.8H), 3.60 (m, 0.8H), 3.70 (2s, 3H), 3.78 (m, 0.2H), 3.88 (m, 0.2H), 4.43 (d, 0.2H, *J* = 9.6 Hz), 4.78 (d, 0.8H, *J* = 9.6 Hz), 6.03 (bs, 1H), 6.72 (d, 2H, *J* = 8.1 Hz), 6.98 (d, 2H, *J* = 8.1 Hz)

^{13}C NMR (125 MHz, $CDCl_3$) : **Major Rotamer**: δ 13.7 (q), 17.1 (q), 19.8 (q), 20.0 (t), 28.4 (q), 31.6 (t), 32.1 (d), 37.6 (d), 38.5 (t), 39.2 (t), 40.0 (t), 41.7 (t), 52.0 (d), 55.1 (q), 70.2 (d), 79.2 (d), 113.4 (d), 130.1 (d), 133.2 (s), 156.5 (s), 157.6 (s), 176.9(s); **Minor Rotamer:** δ 13.4 (q), 16.6 (q), 19.7 (q), 19.9 (t), 28.3 (q), 32.4 (t), 34.3 (d), 37.0 (d), 38.7 (t), 39.4 (t), 40.1(t), 41.5 (t), 51.3 (d), 58.9 (q), 70.5 (d), 80.0 (s), 113.5 (d), 130.0 (d), 132.7 (s), 156.0 (s), 157.7 (s), 174.6 (s)

Hydrochloride Salt of (2*R*,4*S*,5*S*,7*S*)-5-amino-*N*-butyl-4-hydroxy-8-(4-methoxyphenyl)-2,7-dimethyloctanamide (5):



To a stirred solution of **33** (0.028 g, 0.07 mmol) in CH_2Cl_2:Et_2O (2:2 mL) at room temperature, dry HCl gas was passed for 15 min. The suspension was filtered and the residue was washed with CH_2Cl_2. The compound was dried to get hydrochloride salt of compound **5** as white solid (0.022 g, 92%).

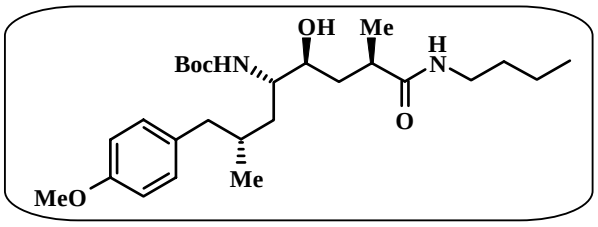
Mol. Formula : $C_{21}H_{37}N_2O_3Cl$

Mol. Weight : 400.99

ESI-MS *m/z* : 424.01 $[M+Na]^+$

Elemental Analysis	:	Calcd: C, 62.90; H, 9.30, N, 6.99, Cl, 8.84 Found: C, 62.76; H, 9.59, N, 7.16, Cl, 8.69
$[\alpha]_D^{25}$	:	+6.2 (*c* 0.5, H_2O)
^{1}H NMR (400 MHz, H_2O)	:	δ 0.89 (t, 3H, *J* = 7.4 Hz), 0.93 (d, 3H, *J* = 6.5 Hz), 1.18 (d, 3H, *J* = 7.0 Hz), 1.33 (m, 2H), 1.48 (m, 4H), 1.79 (m, 2H), 2.52 (dd, 1H, *J* = 7.5, 13.6 Hz), 2.64 (m, 2H), 3.21 (m, 3H), 3.52 (dq, 1H, *J* = 2.3, 4.5, 10.54 Hz), 3.86 (s, 3H), 7.00 (d, 2H, *J* = 8.8 Hz), 7.25 (d, 2H, *J* = 8.8 Hz)
^{13}C NMR (100 MHz, H_2O)	:	δ 14.7 (q), 19.7 (q), 20.3 (q), 21.1 (t), 32.3 (t), 32.9 (d), 37.9 (t), 39.2 (t), 39.3 (d), 40.6 (t), 43.2 (t), 56.1 (d), 57.1 (q), 69.4 (d), 115.7 (d), 132.3 (d), 134.9 (s), 158.9 (s), 179.9 (s)

***tert*-butyl (2*S*,4*S*,5*S*,7*S*)-8-(butylamino)-5-hydroxy-1-(4-methoxyphenyl)-2,7-dimethyl-8-oxooctan-4-ylcarbamate (34):**



Following the same sequence of reaction procedures as of **19a**, 7-*epi* isomer of **2** was obtained from **19b** in 11 steps (22% overall yield).

Mol. Formula	:	$C_{26}H_{44}N_2O_5$
Mol. Weight	:	464.64
ESI-MS *m/z*	:	487.65 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 67.21; H, 9.54; N, 6.03 Found: C, 67.15; H, 9.65; N, 6.12
$[\alpha]_D^{25}$	:	–17.9 (*c* 0.3, $CHCl_3$)

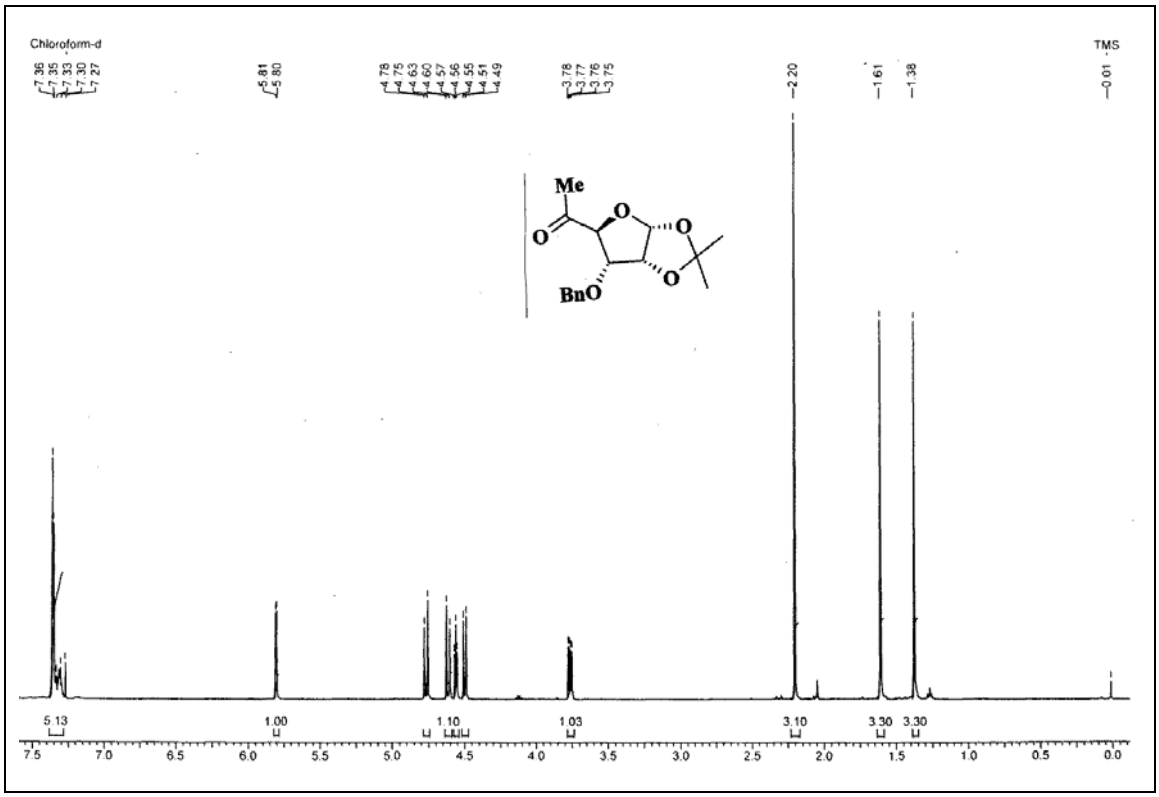
^{1}H NMR (500 MHz, $CDCl_3$)	:	δ 0.90 (d, 3H, *J* = 6.4 Hz), 0.91 (t, 3H, *J* = 7.3 Hz), 1.17 (d, 3H, *J* = 6.9 Hz), 1.26 (m, 1H), 1.32 (m, 2H), 1.43 (s, 9H), 1.47 (m, 2H), 1.65 (m, 3H), 1.76 (m, 1H), 2.39 (dd, 1H, *J* = 7.7, 13.3 Hz), 2.53 (dd, 1H, *J* = 6.3, 13.3 Hz), 3.17 (m, 1H), 3.26 (m, 1H), 3.57 (m, 2H), 3.79 (s, 3H), 4.64 (d, 1H, *J* = 9.5 Hz), 6.01 (b, 1H), 6.80 (d, 2H, *J* = 8.4 Hz), 7.06 (d, 2H, *J* = 8.4 Hz)
^{13}C NMR (125 MHz, $CDCl_3$)	:	δ 13.7(q), 17.2 (q), 19.1 (q), 20.0 (t), 28.3 (q), 31.6 (t), 31.8 (d), 37.6 (d), 38.5 (t), 39.2 (t), 39.4 (t), 43.0 (t), 52.4 (d), 55.2 (q), 71.3 (d), 79.2 (d), 113.6 (d), 130.2 (d), 133.0 (s), 156.7 (s), 157.7 (s), 176.9 (s)

Table 8: **Crystal data and structure refinement for compound 34**:

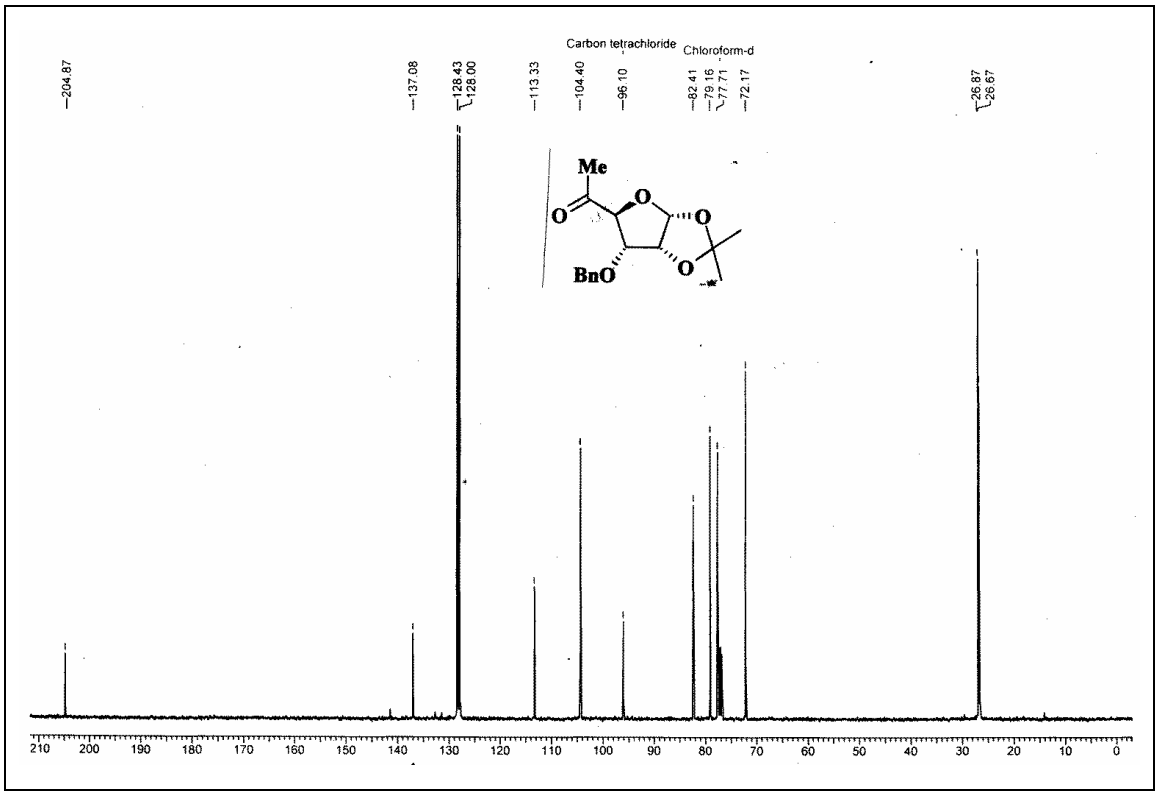
Identification code	Data_**34**
Empirical formula	C26 H44 N2 O5
Formula weight	464.63
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions	a = 9.474(4) Å alpha = 90º. b = 10.893(5) Å beta = 90º. c = 27.787(12) Å gamma = 90º.
Volume	2867(2) $Å^3$
Z, Calculated density	4, 1.076 Mg/m^3
Absorption coefficient	0.074 mm^{-1}
F(000)	1016
Crystal size	0.87 x 0.09 x 0.08 mm
Theta range for data collection	2.01 to 25.00º
Limiting indices	-10<=h<=11, -12<=k<=7, -32<=l<=32
Reflections collected / unique	12036 / 5031 [R(int) = 0.0762]
Completeness to theta = 25.00	99.8 %

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9943 and 0.9389
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5031 / 0 / 306
Goodness-of-fit on F^2	0.957
Final R indices [I>2sigma(I)]	R1 = 0.0670, wR2 = 0.1246
R indices (all data)	R1 = 0.1948, wR2 = 0.1575
Absolute structure parameter	2(2)
Largest diff. peak and hole	0.190 and -0.126 e. $Å^{-3}$

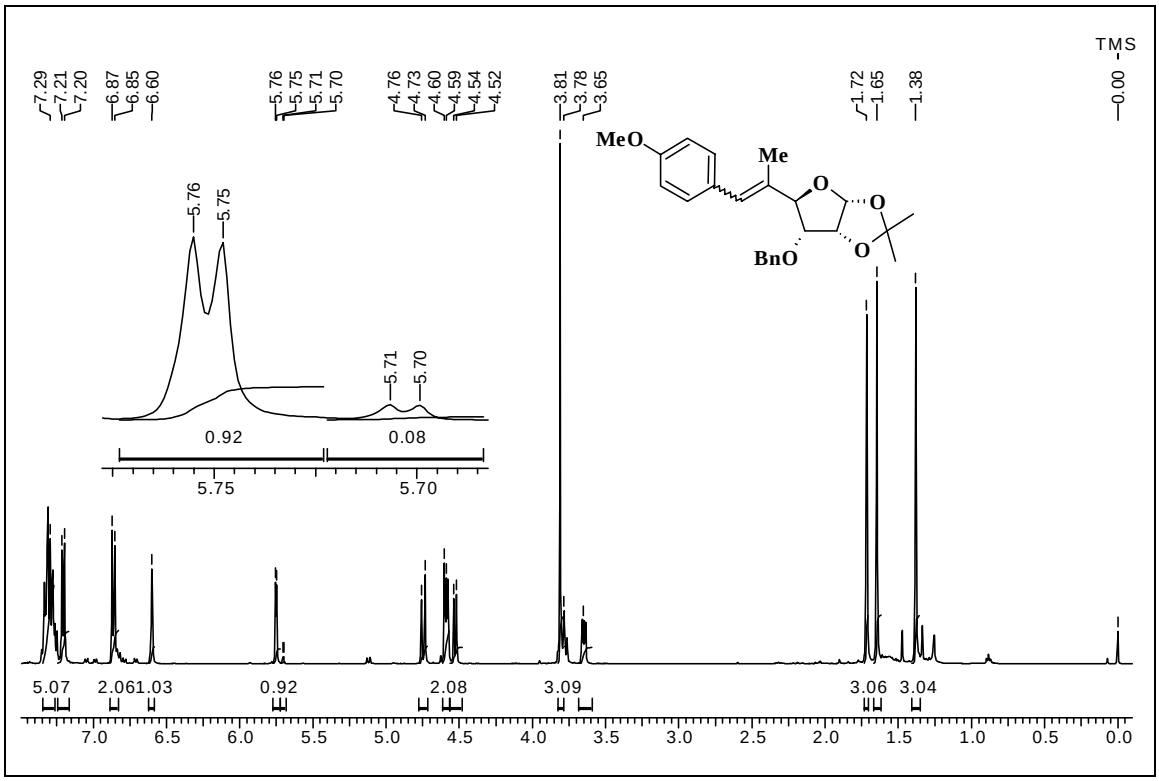
Spectra



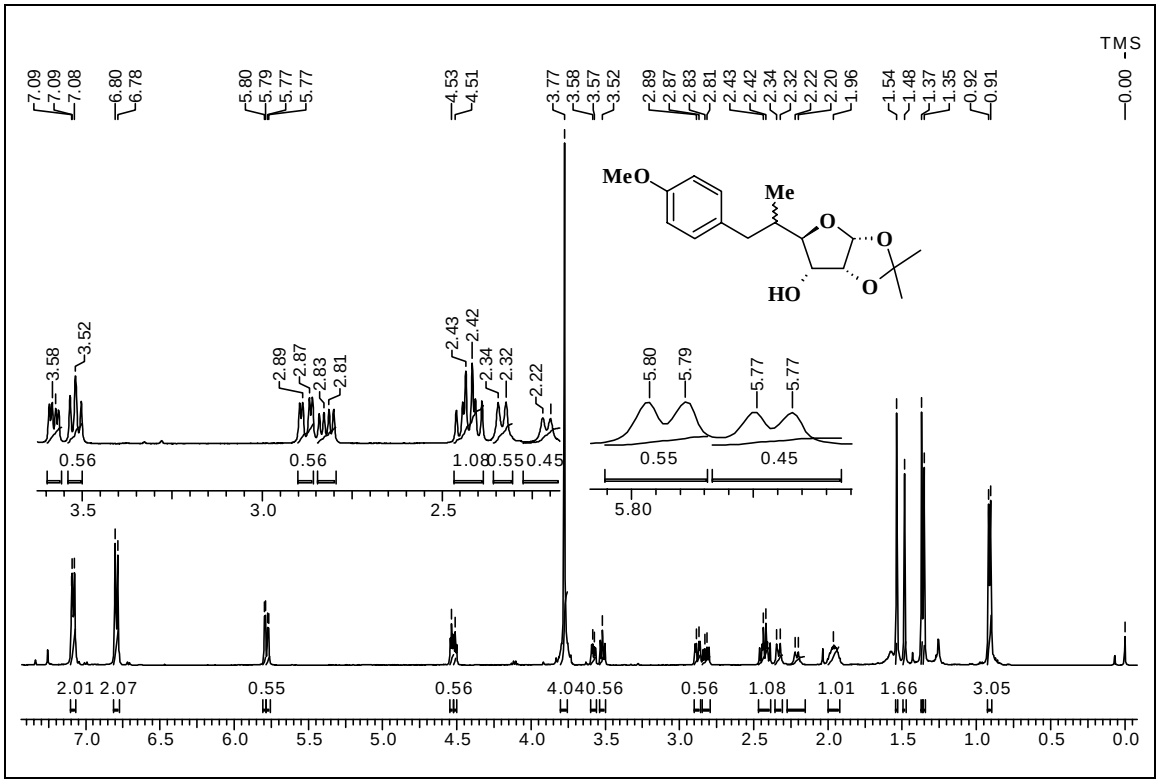
^{1}H NMR spectrum of compound 17 in $CDCl_3$



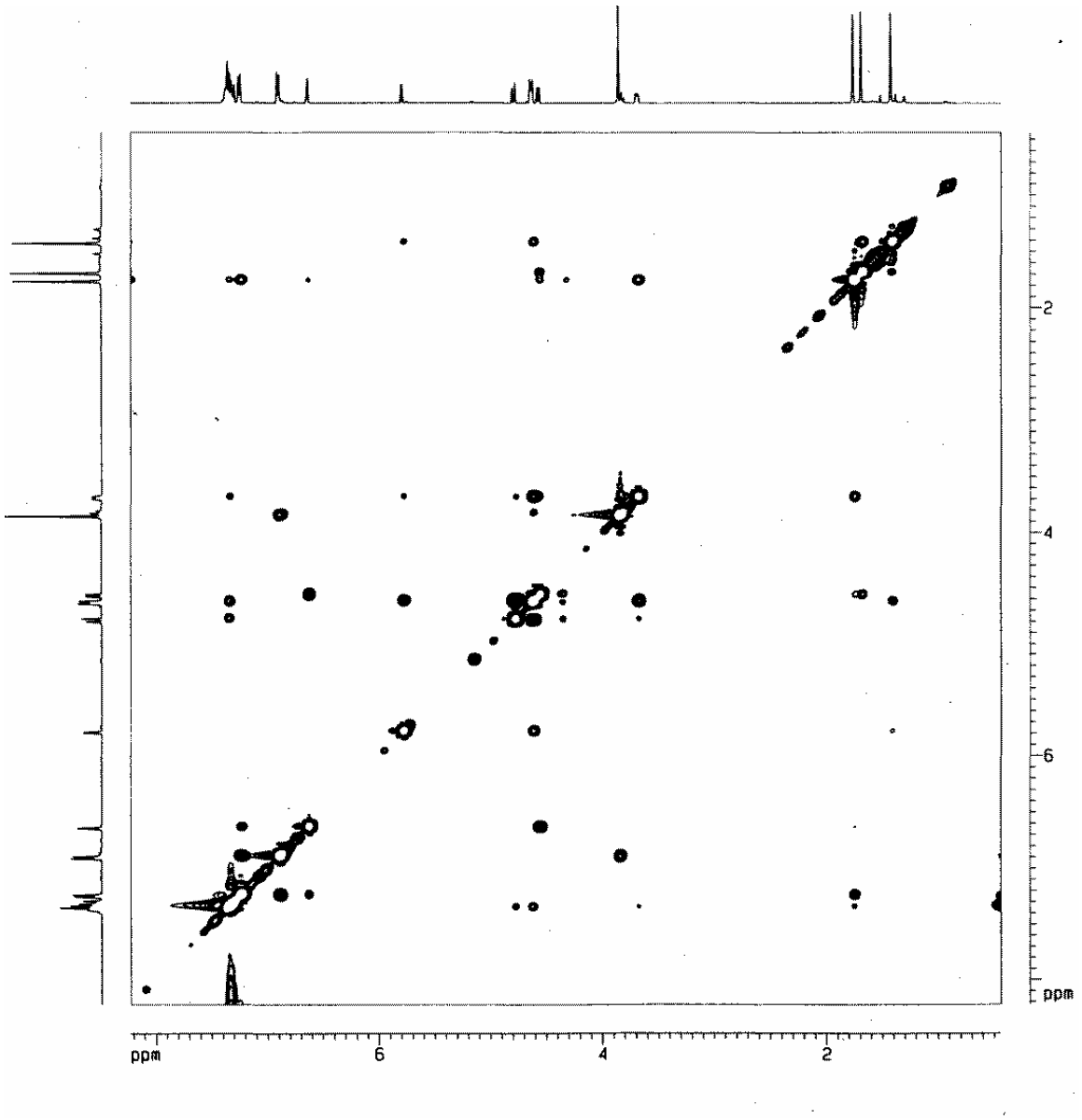
^{13}C NMR spectrum of compound 17 in $CDCl_3$

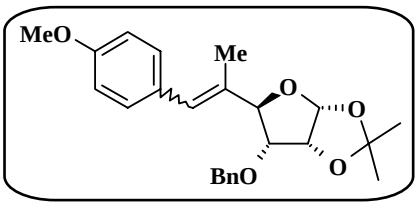


^{1}H NMR spectrum of compound 18 in $CDCl_3$

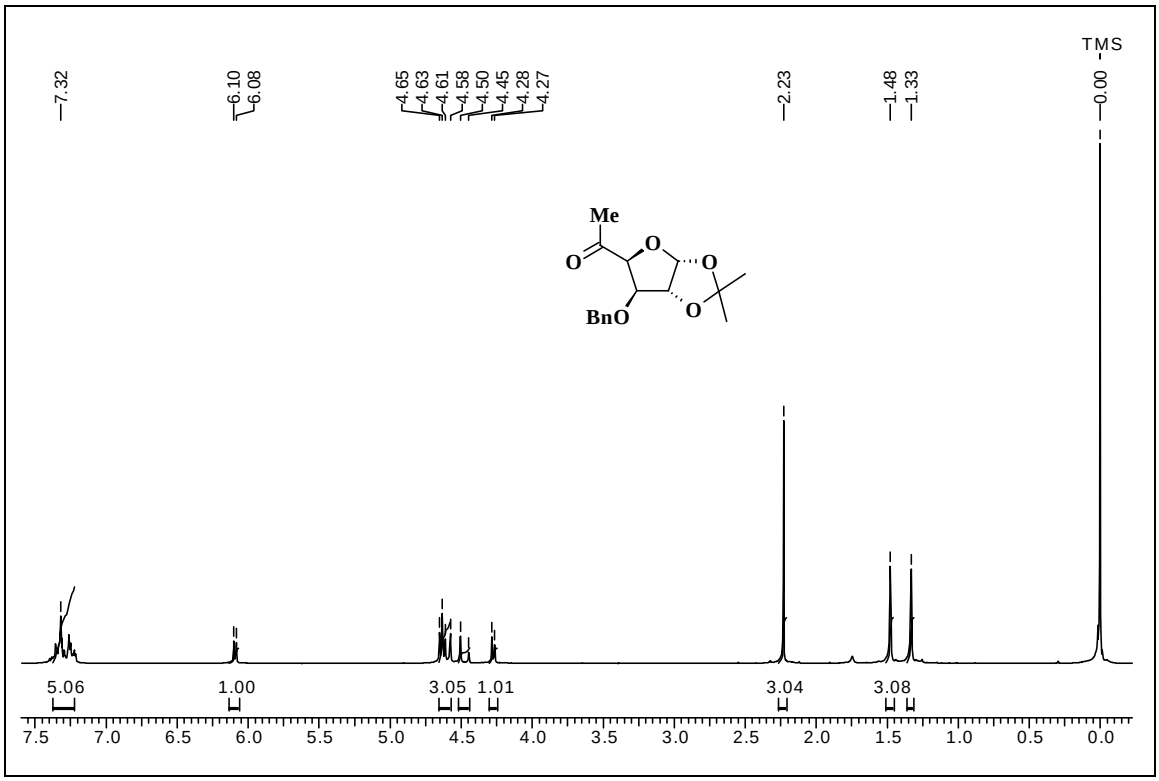


^{1}H NMR spectrum of compound 19 in $CDCl_3$

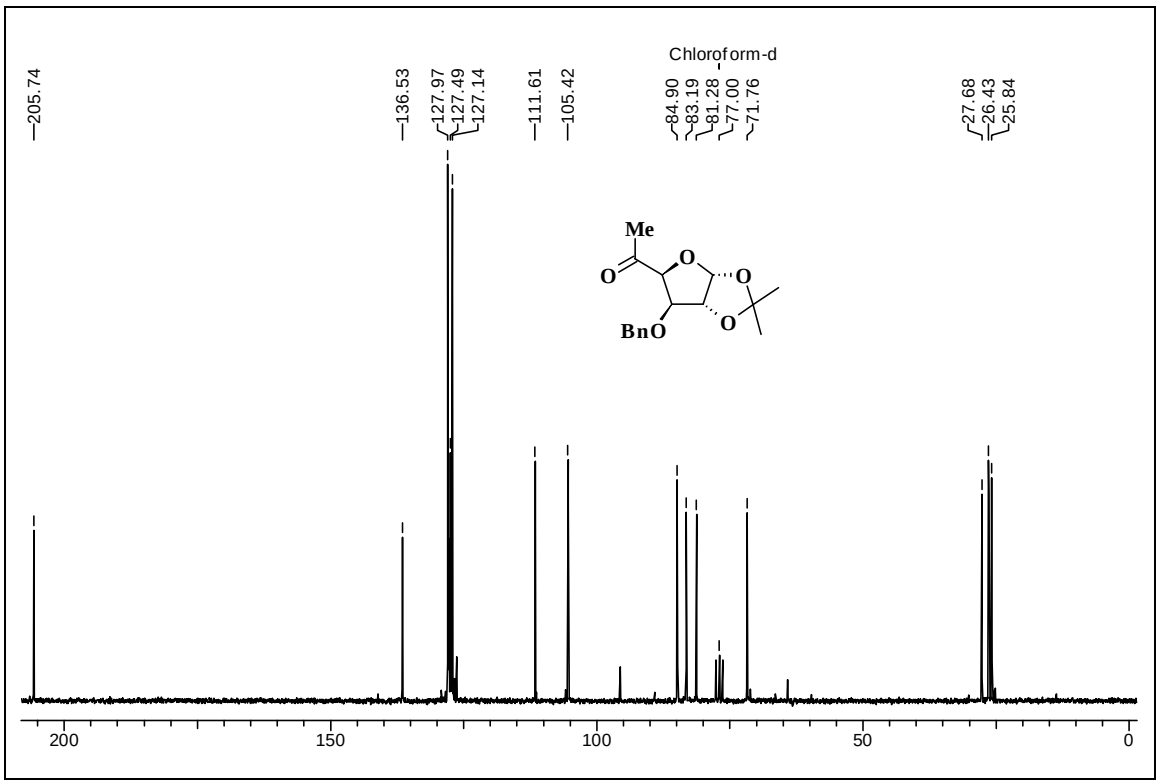




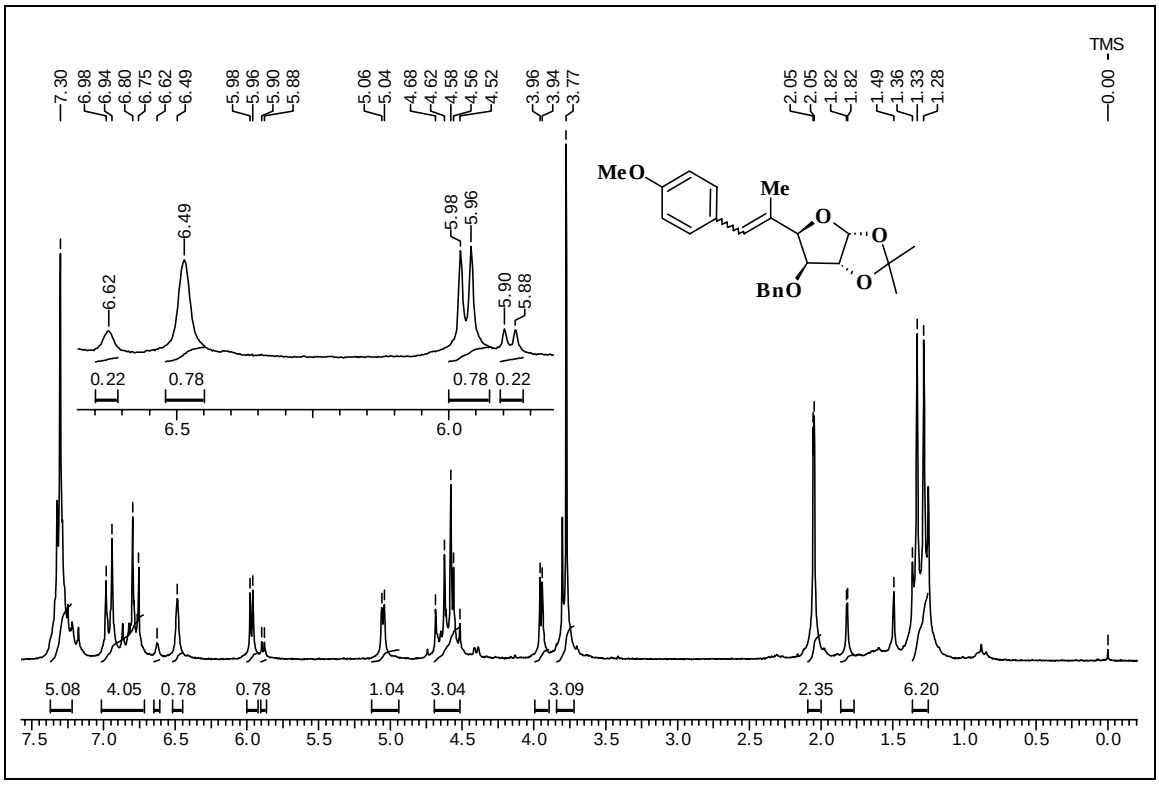
NOESY spectrum of compound 18



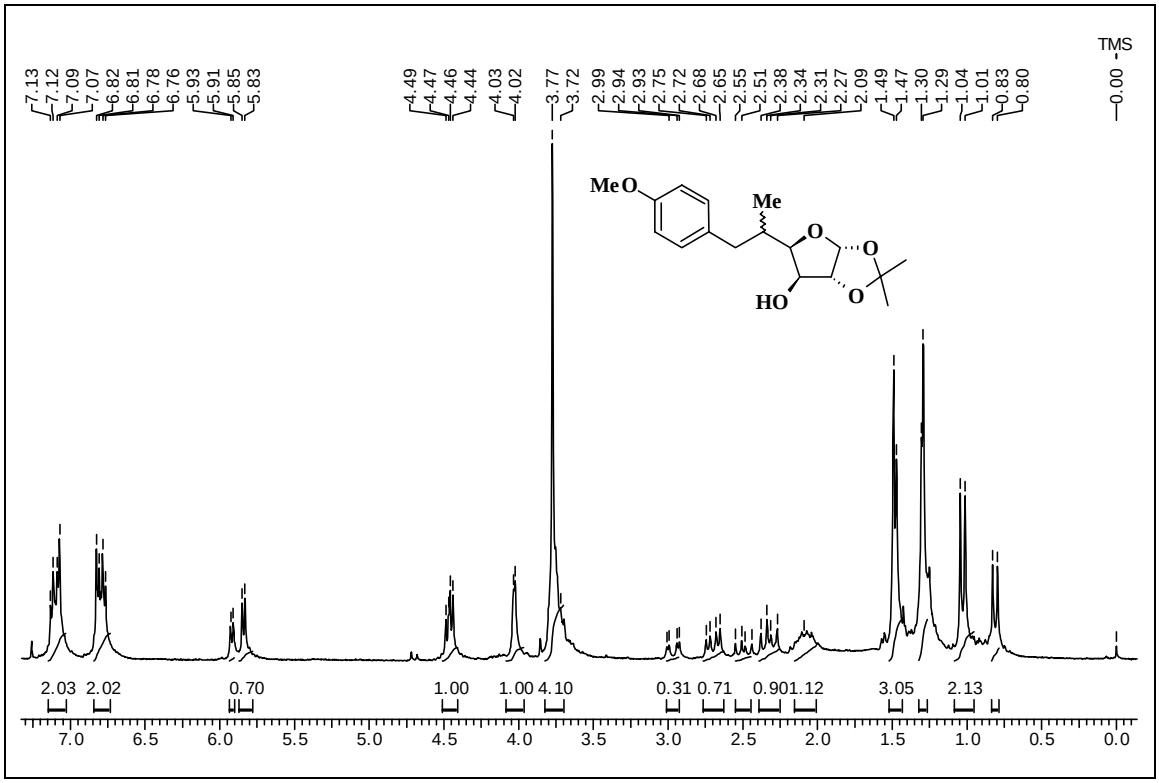
^{1}H NMR spectrum of compound 22 in $CDCl_3$



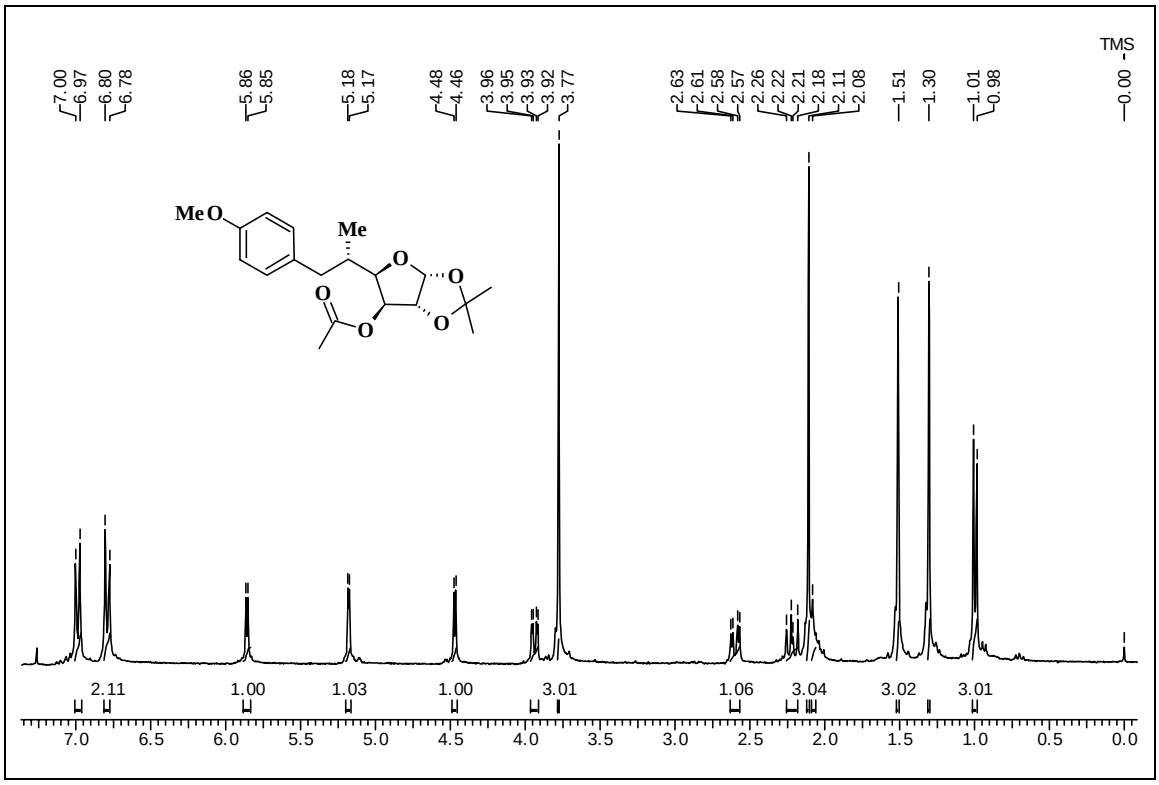
^{13}C NMR spectrum of compound 22 in $CDCl_3$



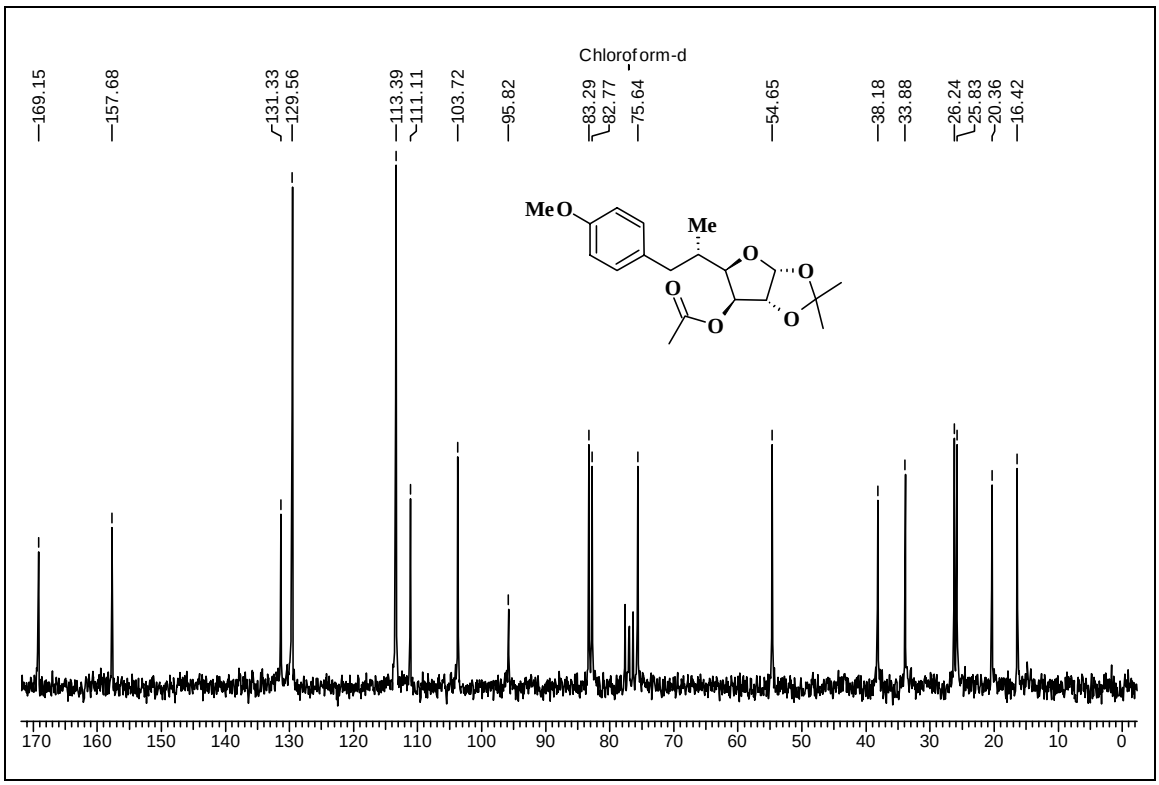
^{1}H NMR spectrum of compound 23 in $CDCl_3$



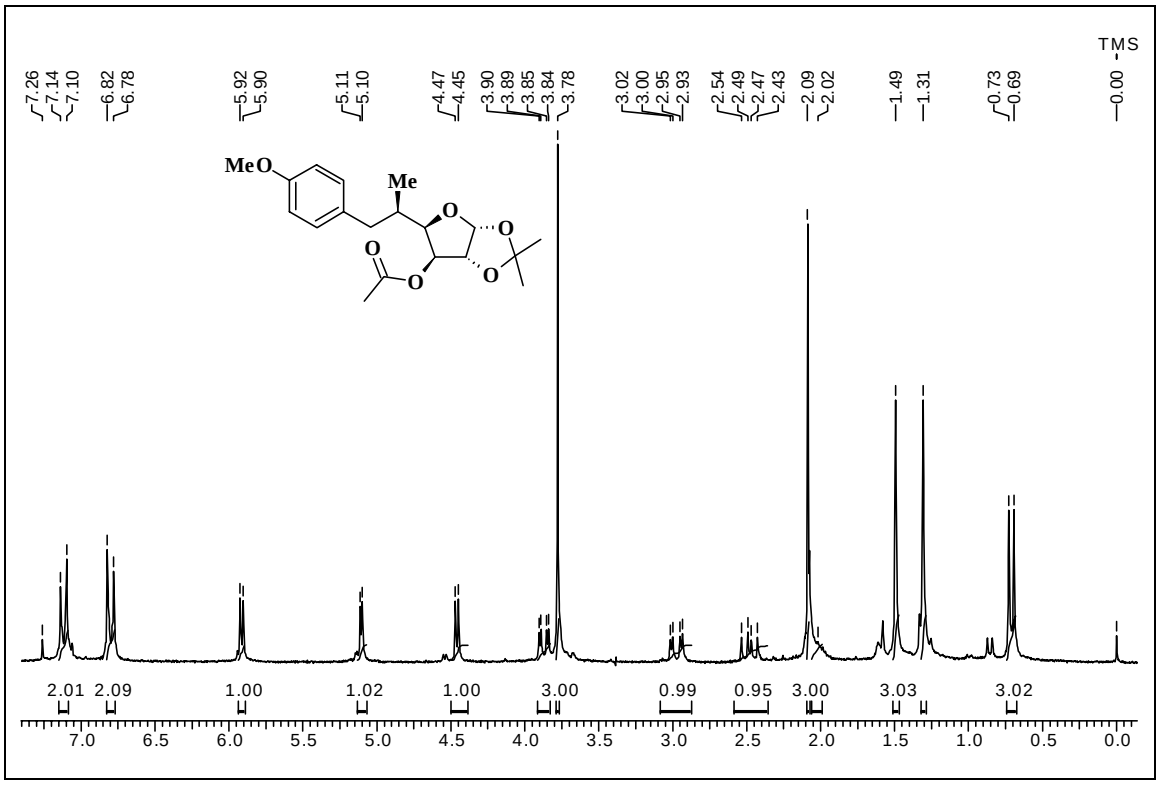
^{1}H NMR spectrum of compound 24 in $CDCl_3$



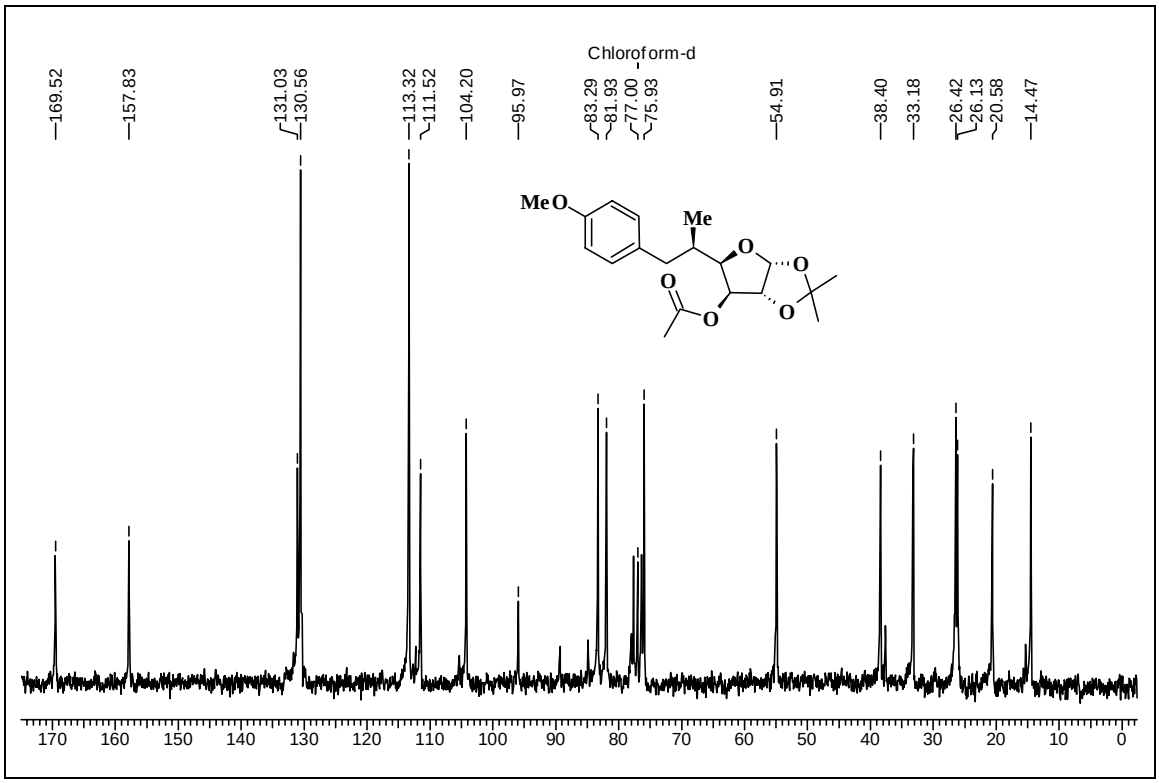
^{1}H NMR spectrum of compound 27a in $CDCl_3$



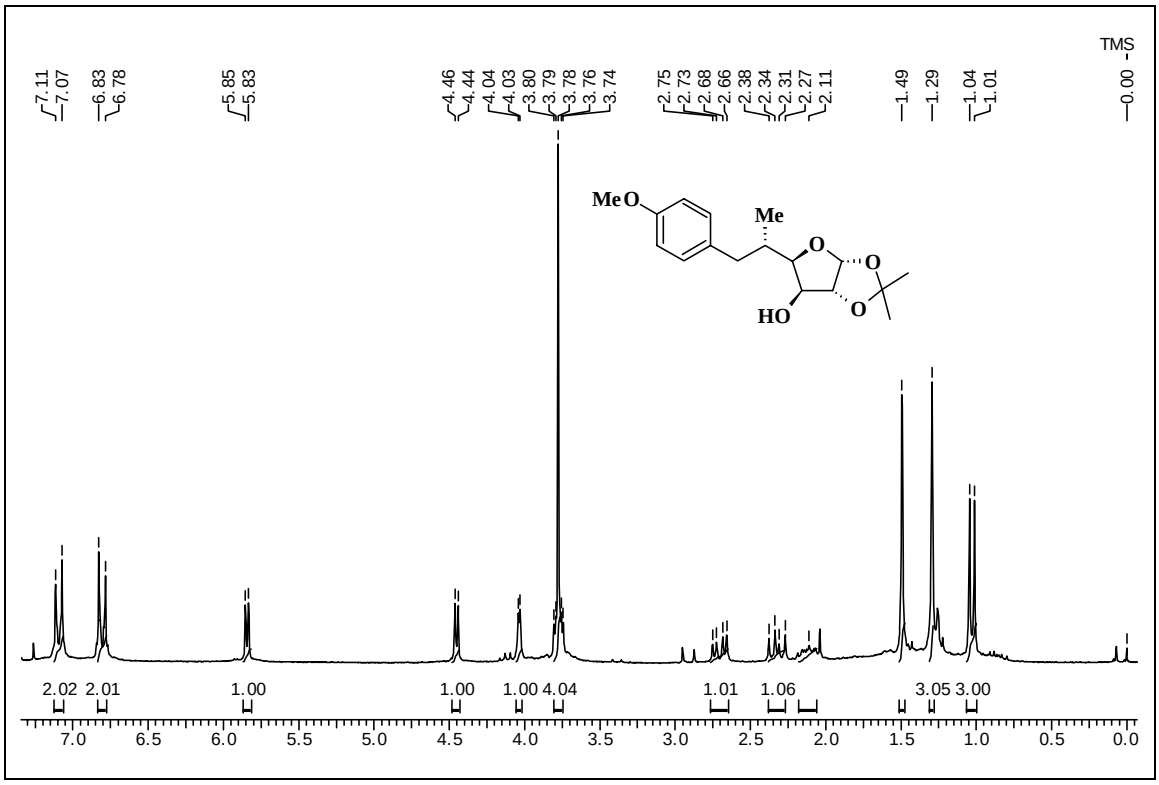
^{13}C NMR spectrum of compound 27a in $CDCl_3$



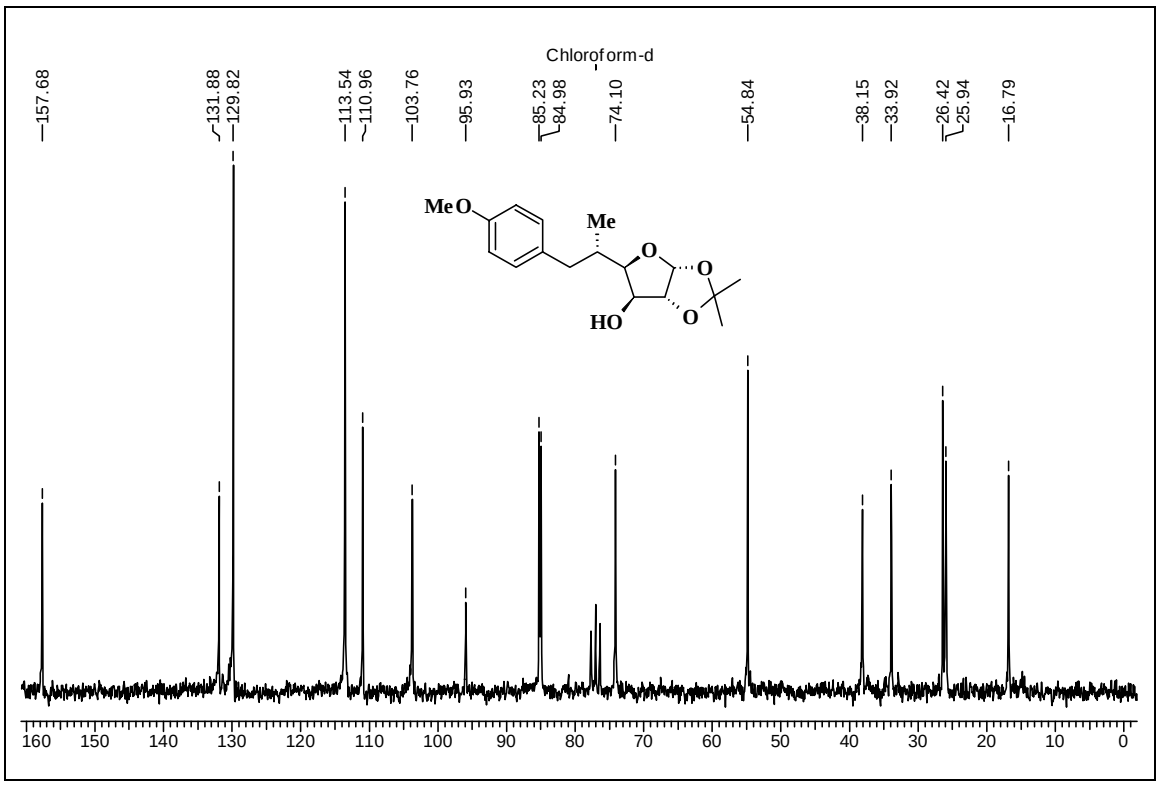
^{1}H NMR spectrum of compound 27b in $CDCl_3$



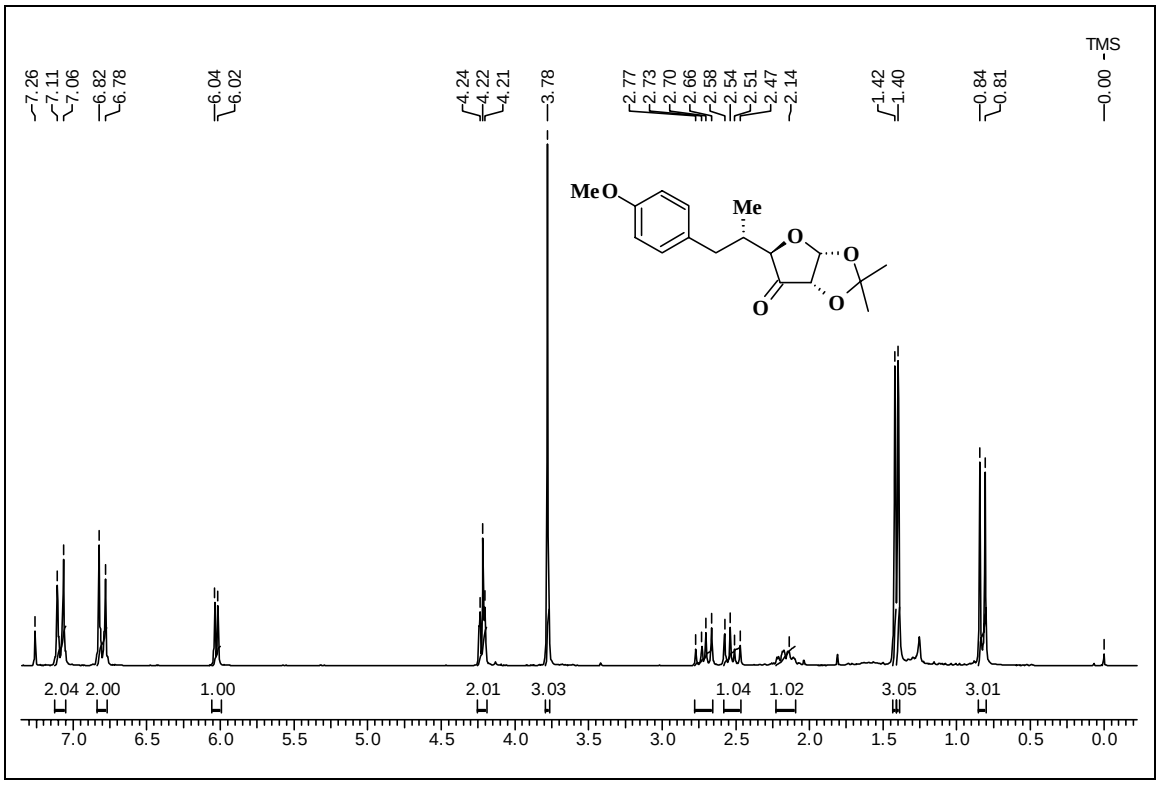
^{13}C NMR spectrum of compound 27b in $CDCl_3$



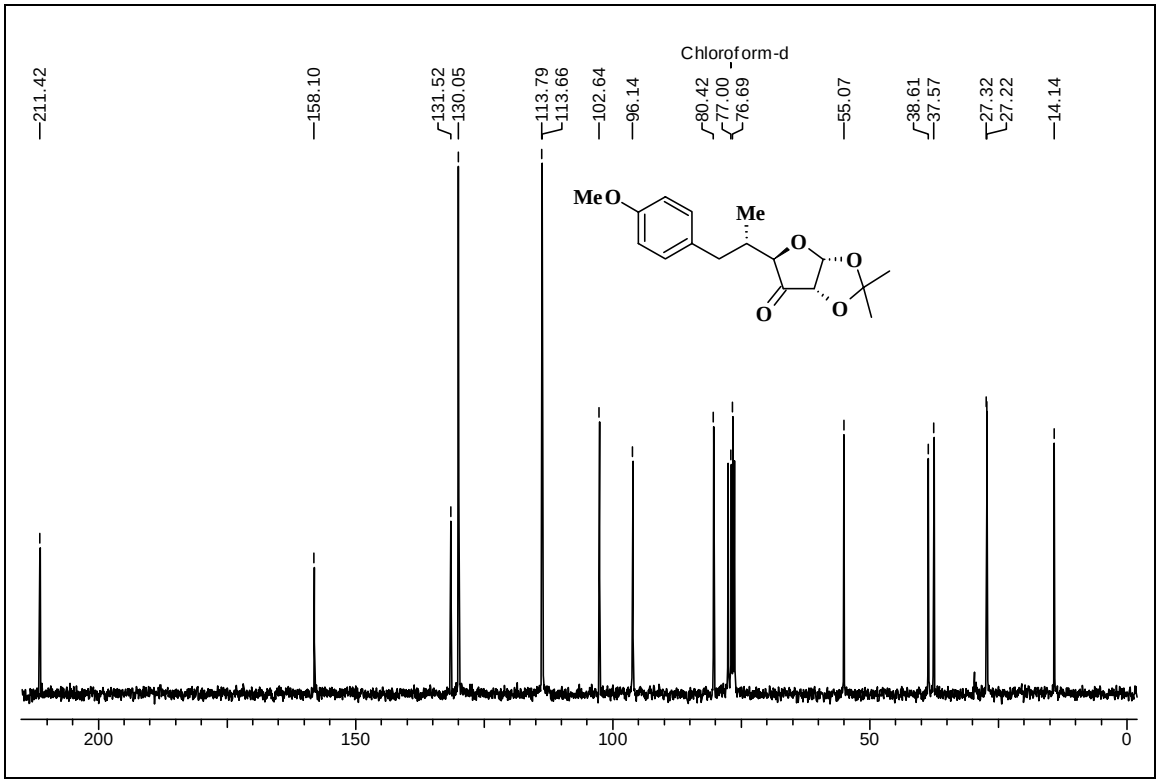
^{1}H NMR spectrum of compound 24a in $CDCl_3$



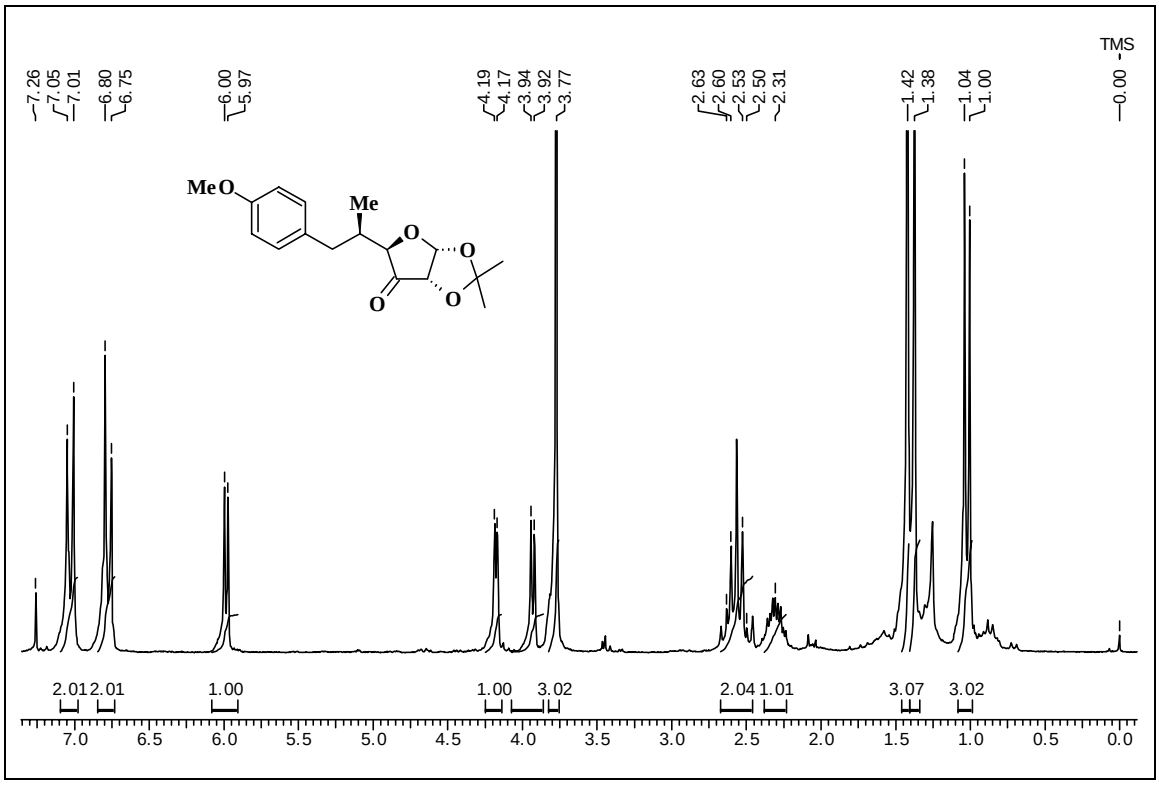
^{13}C NMR spectrum of compound 24a in $CDCl_3$



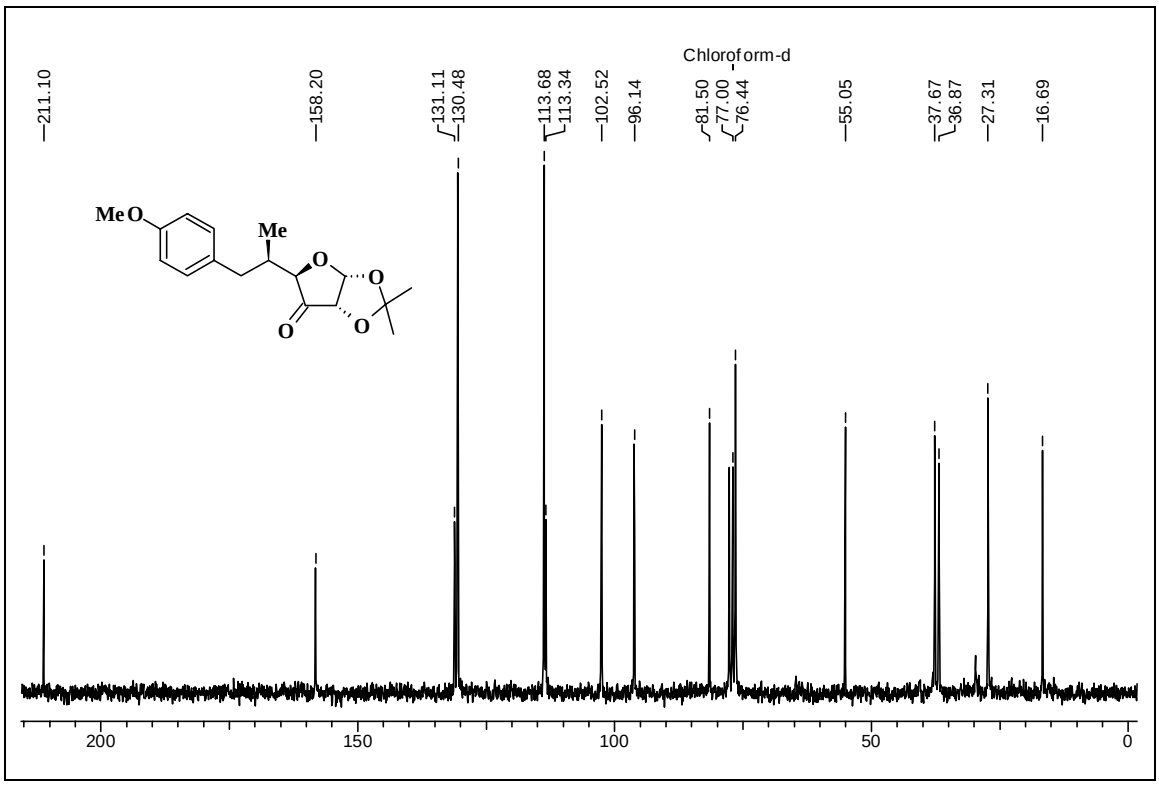
^{1}H NMR spectrum of compound 28a in $CDCl_3$



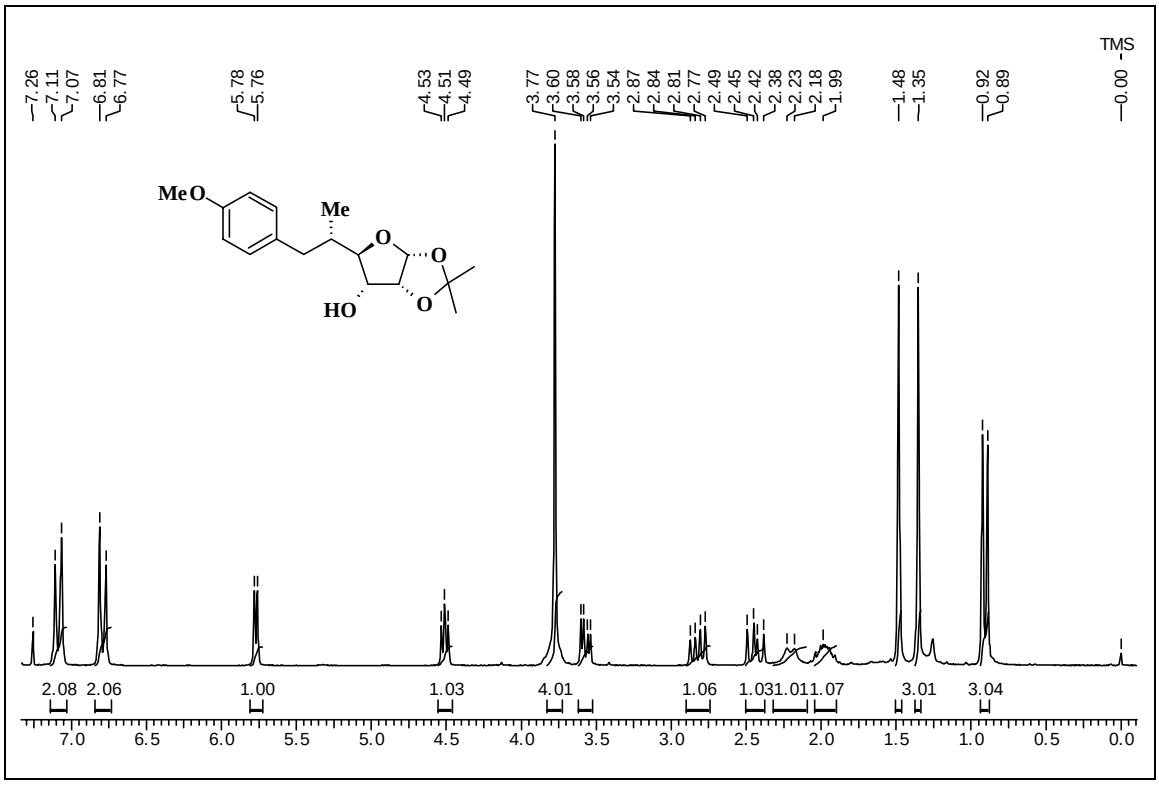
^{13}C NMR spectrum of compound 28a in $CDCl_3$



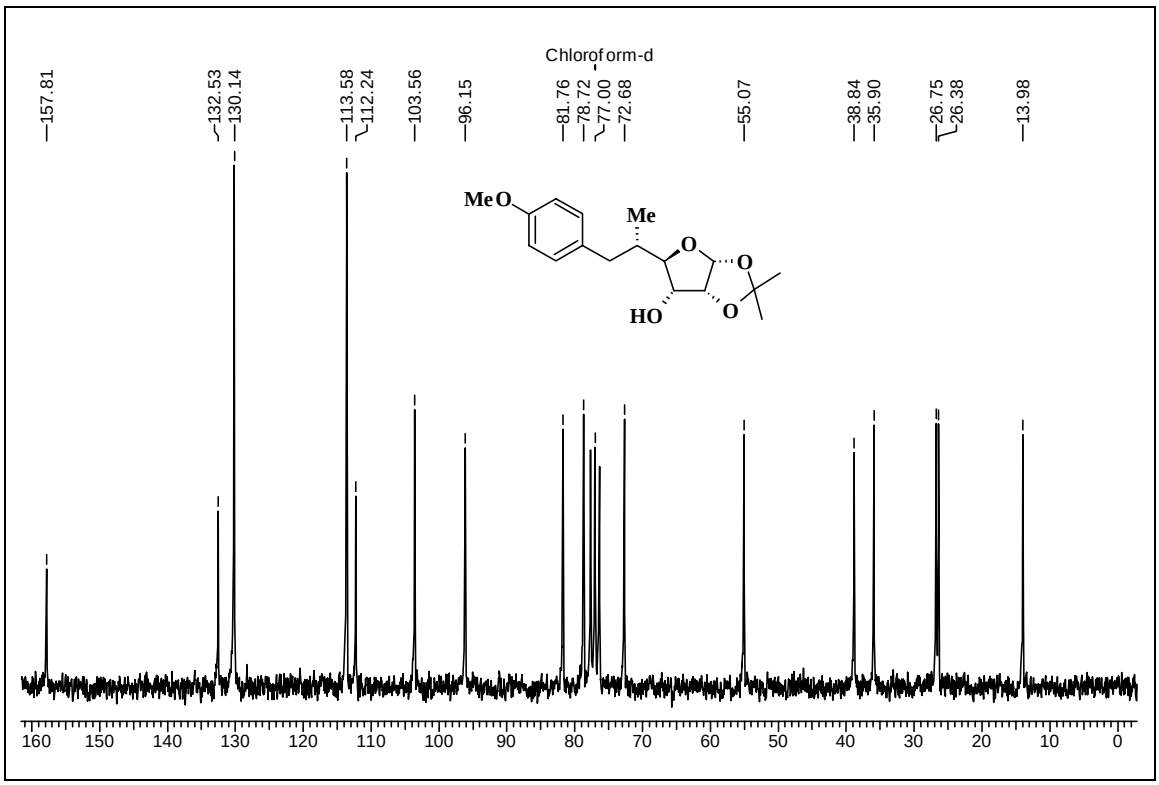
^{1}H NMR spectrum of compound 28b in $CDCl_3$



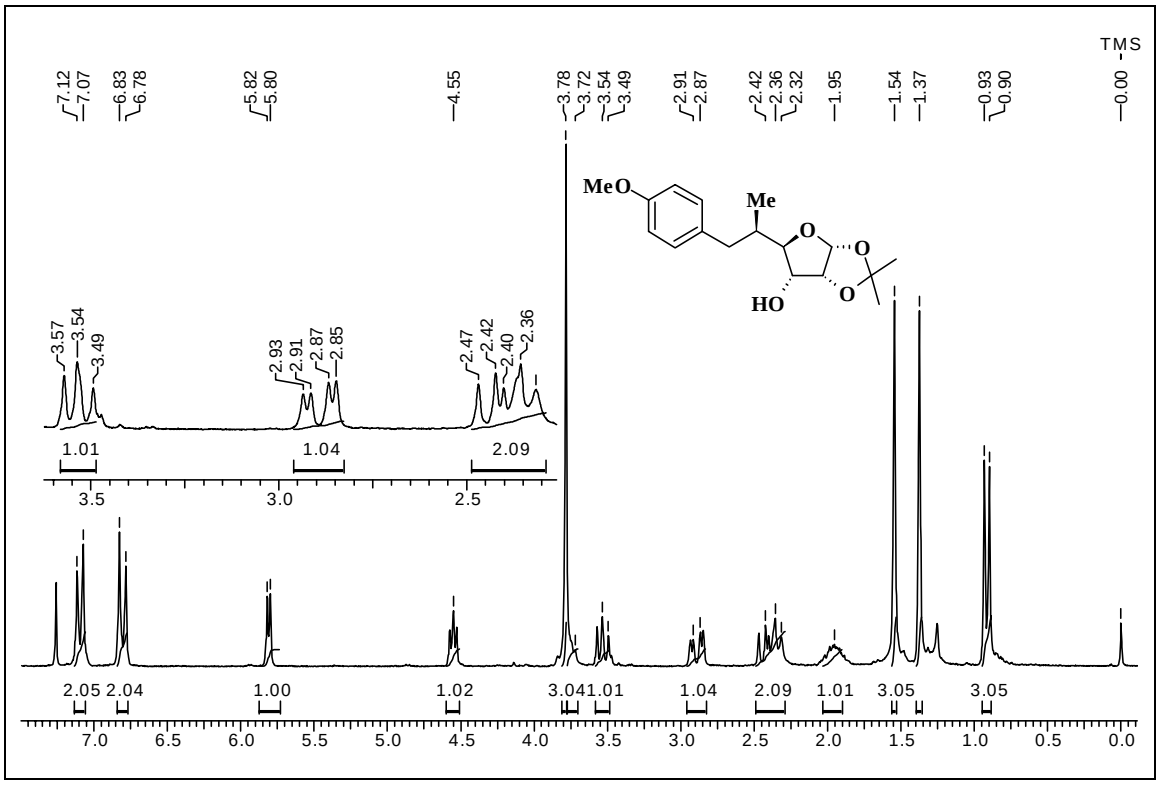
^{13}C NMR spectrum of compound 28b in $CDCl_3$



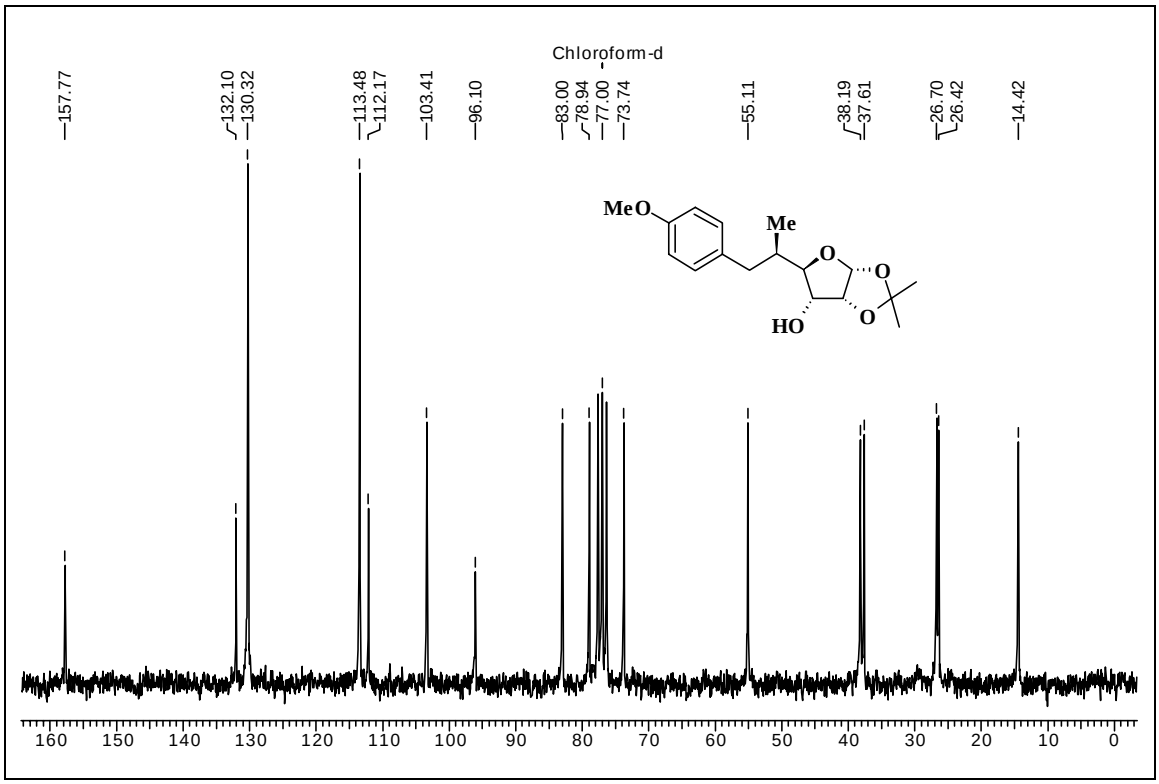
^{1}H NMR spectrum of compound 19a in $CDCl_3$



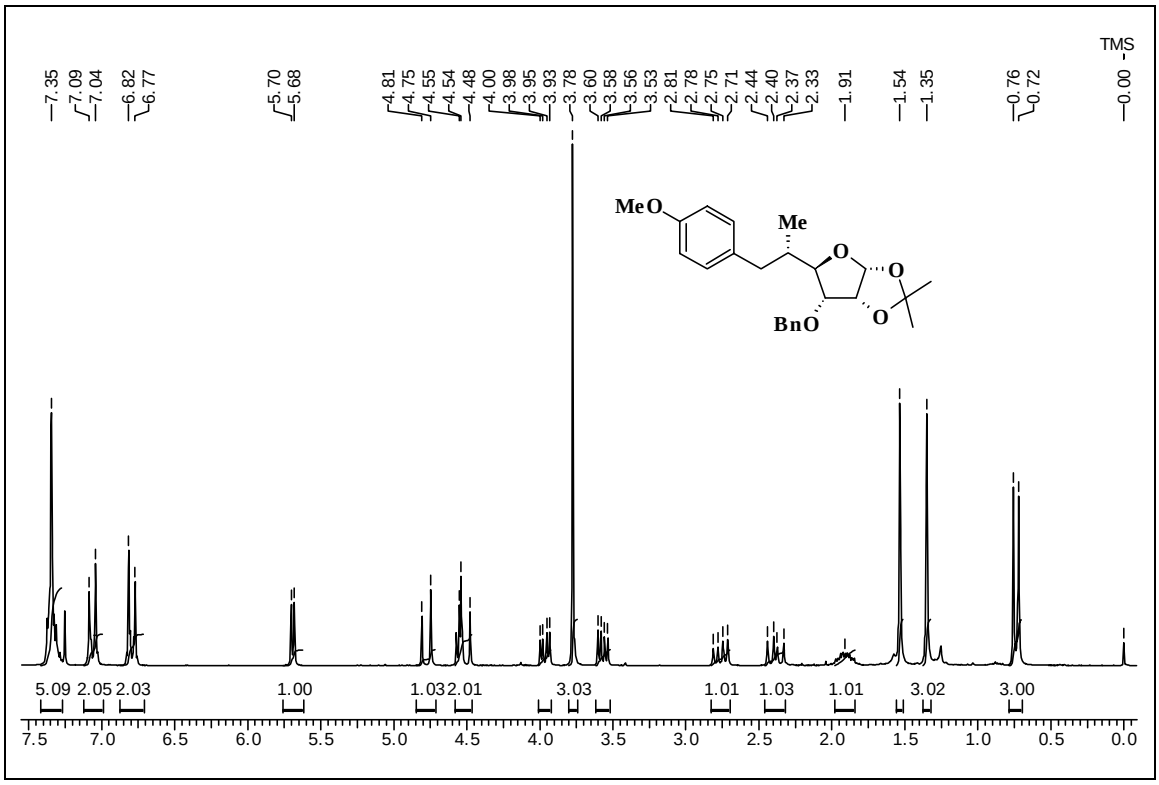
^{13}C NMR spectrum of compound 19a in $CDCl_3$



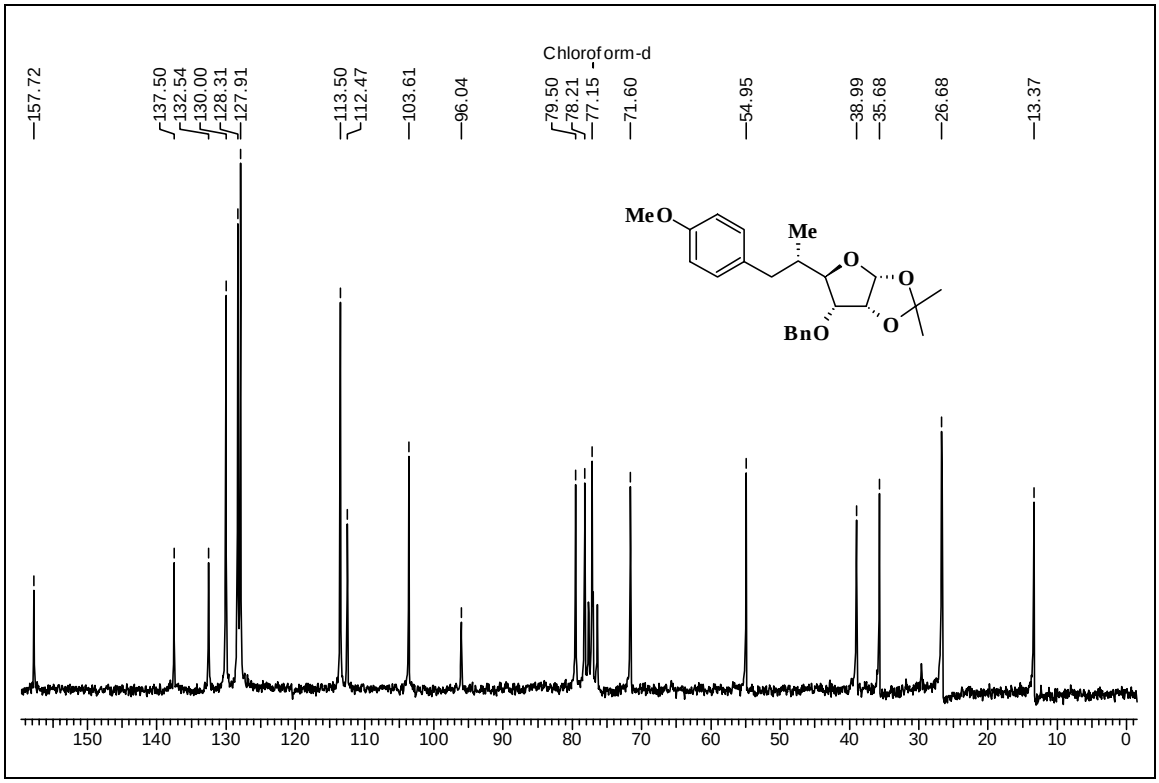
^{1}H NMR spectrum of compound 19b in $CDCl_3$



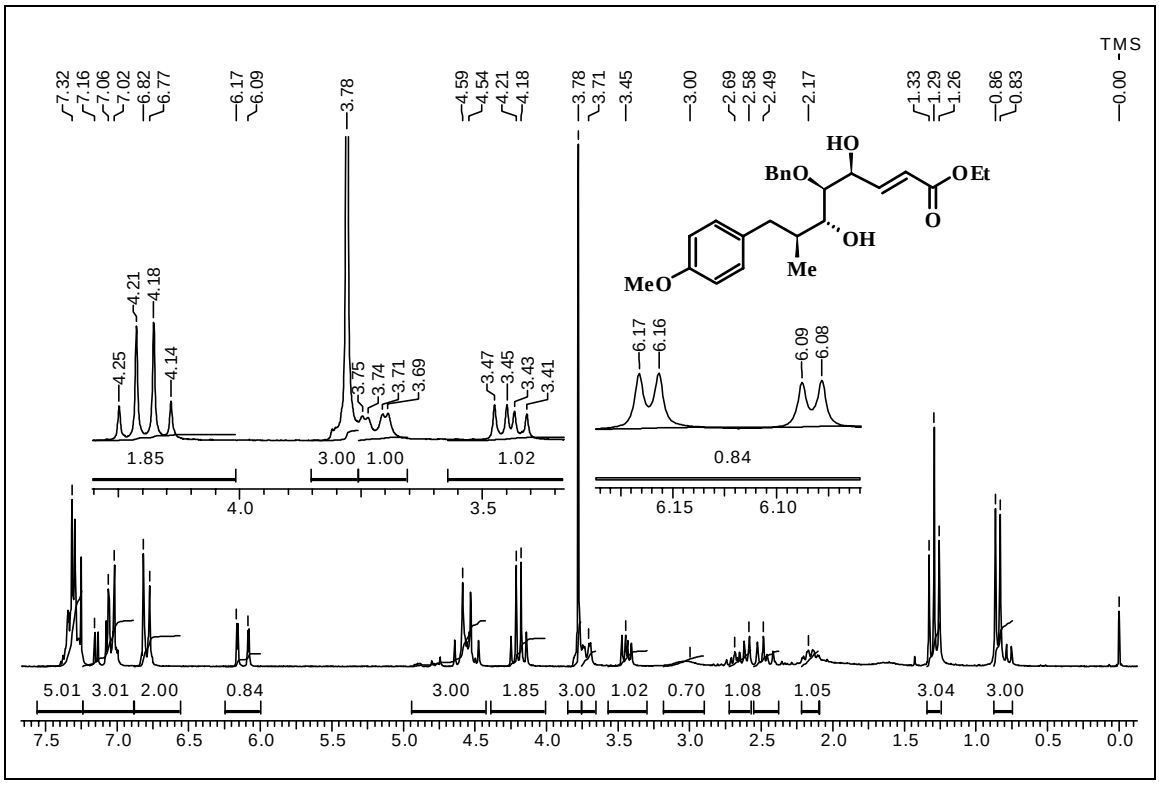
^{13}C NMR spectrum of compound 19b in $CDCl_3$



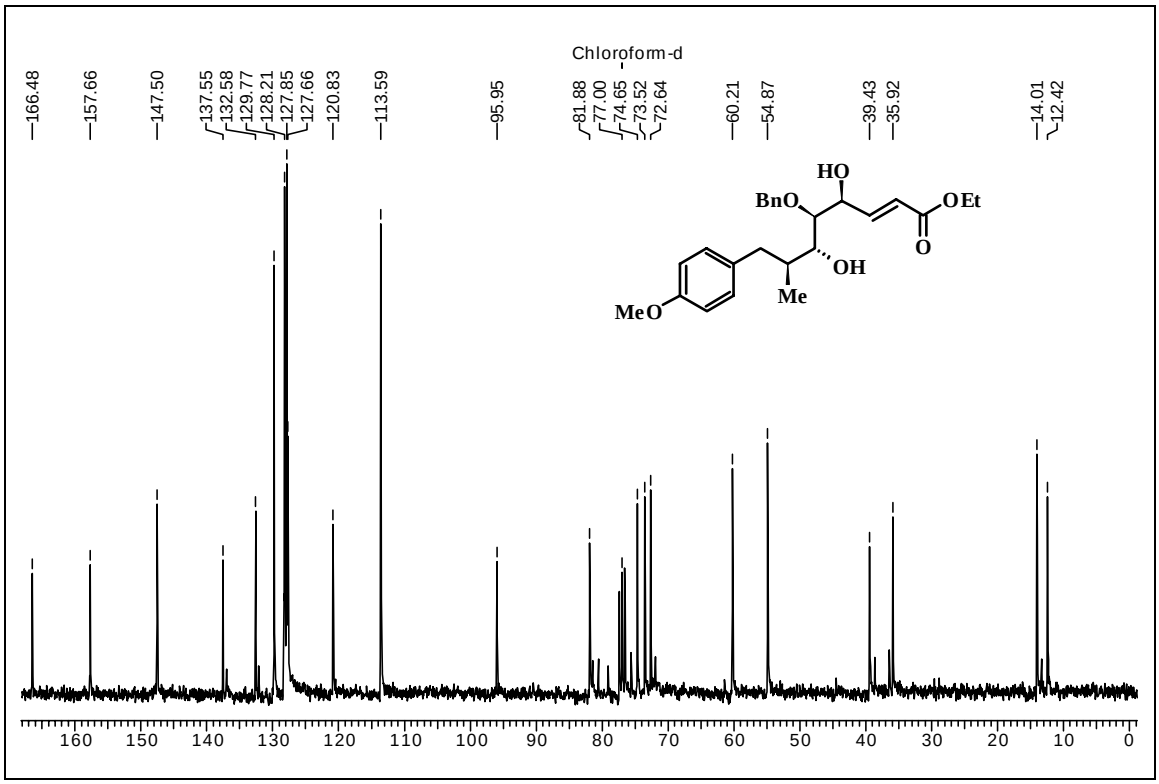
^{1}H NMR spectrum of compound 11 in $CDCl_3$



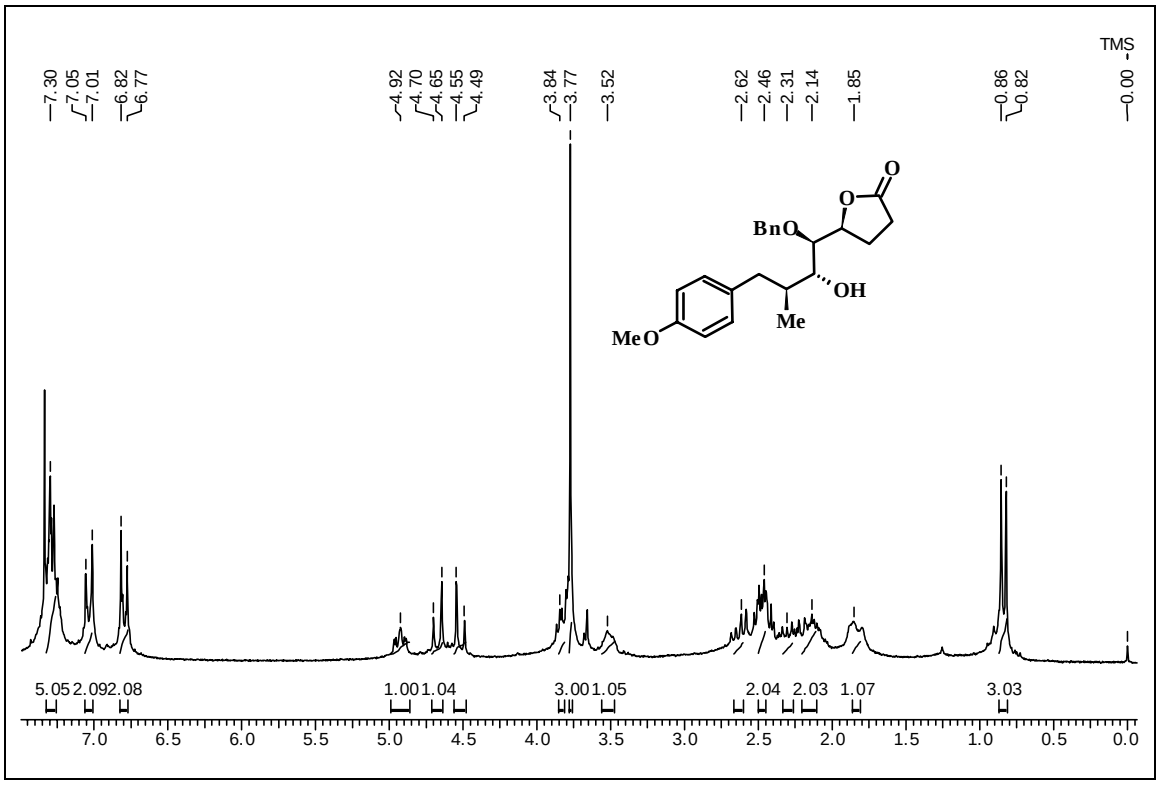
^{13}C NMR spectrum of compound 11 in $CDCl_3$



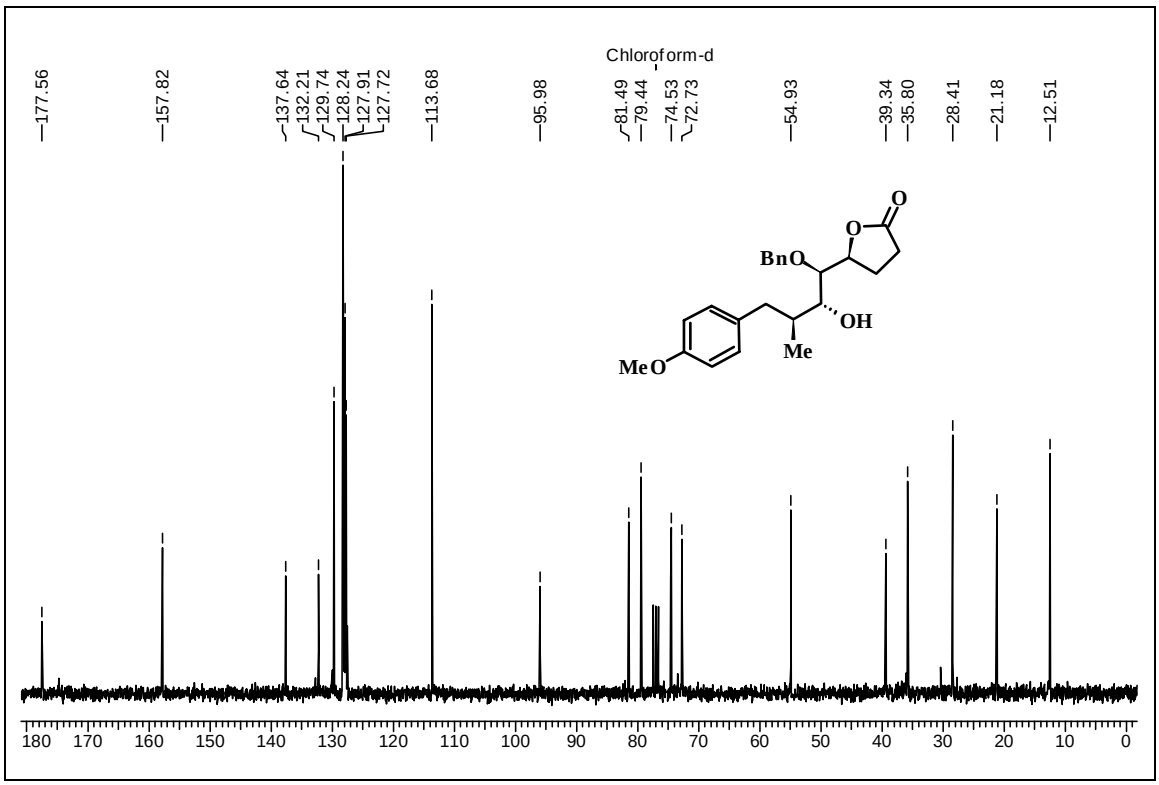
^{1}H NMR spectrum of compound 10 in $CDCl_3$



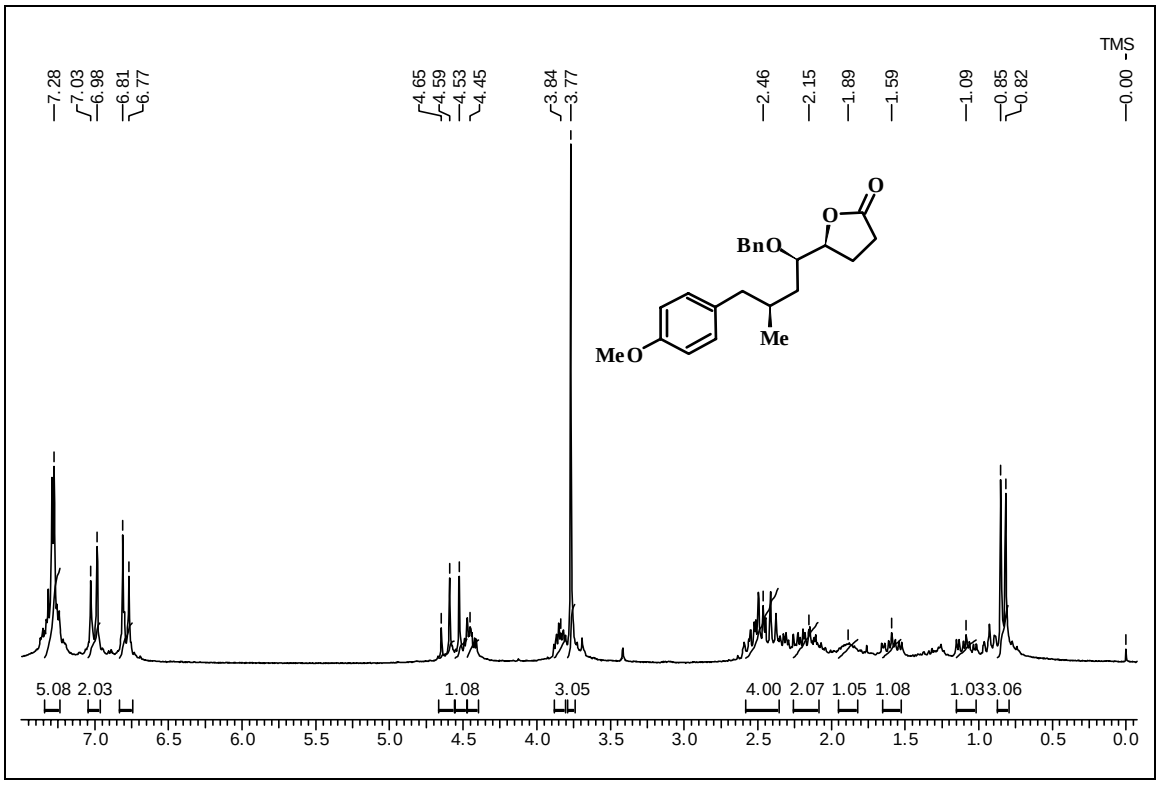
^{13}C NMR spectrum of compound 10 in $CDCl_3$



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



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



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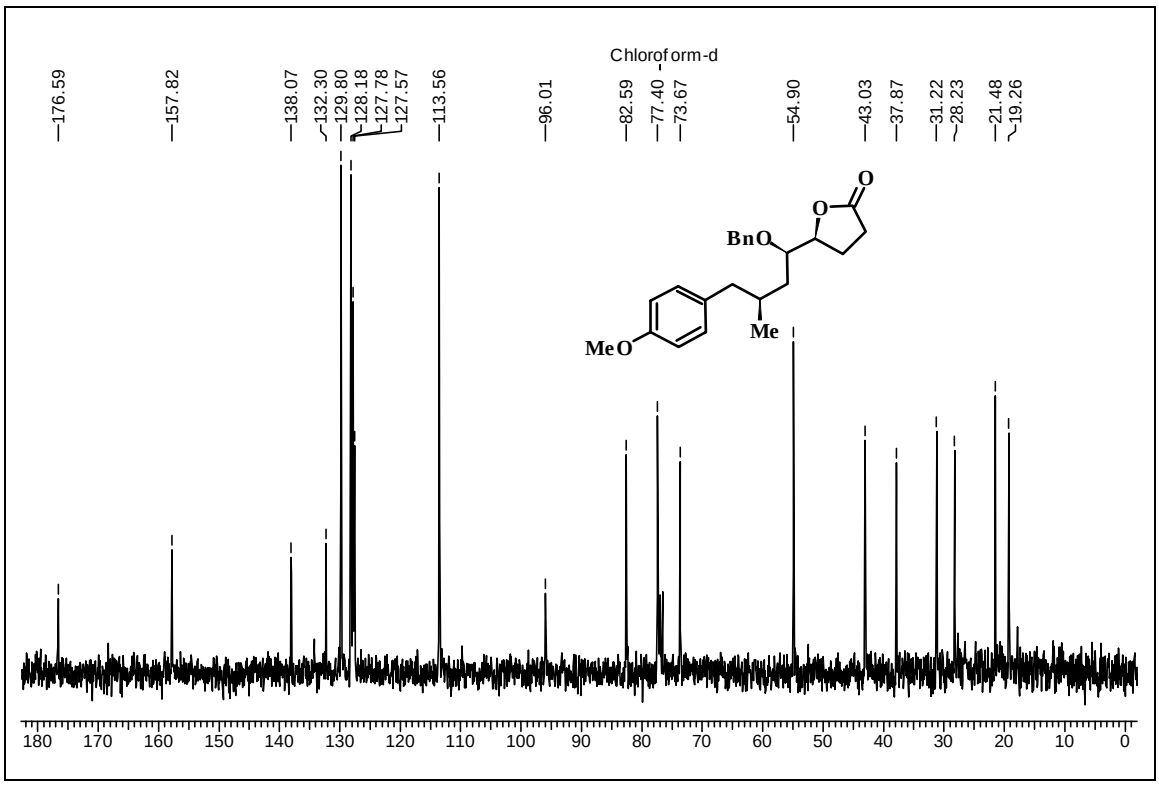
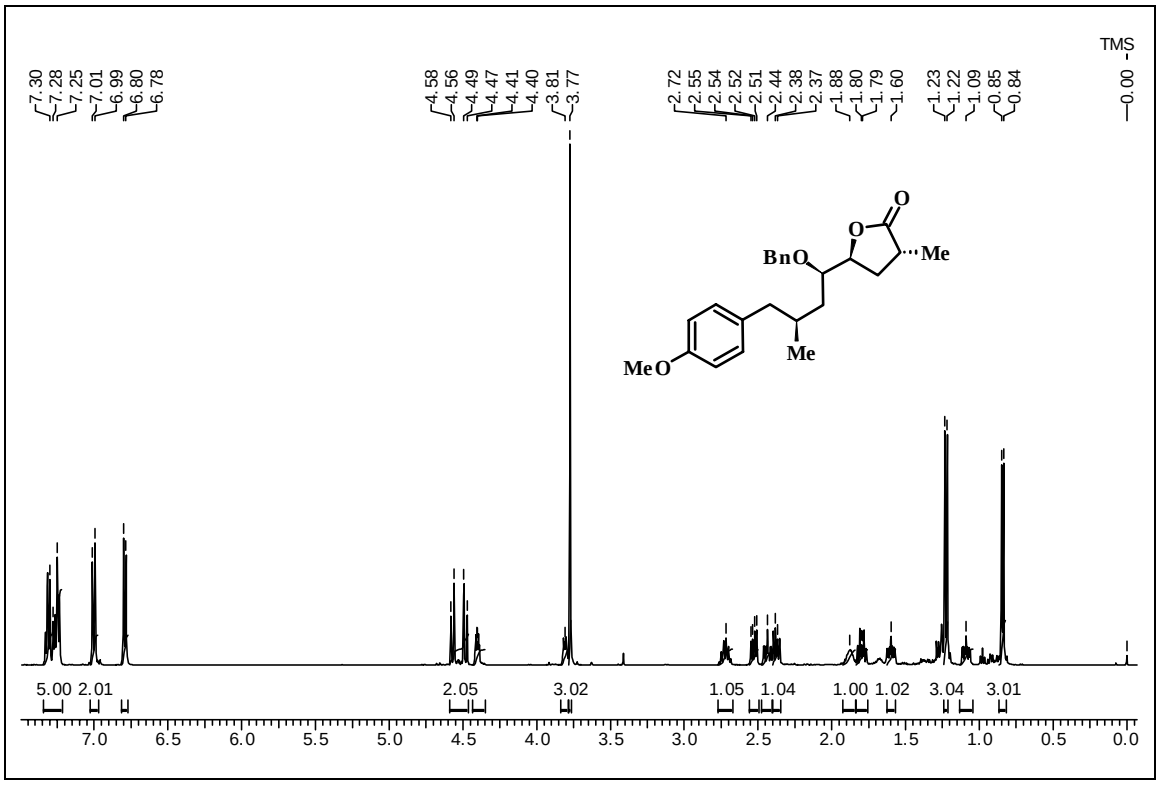
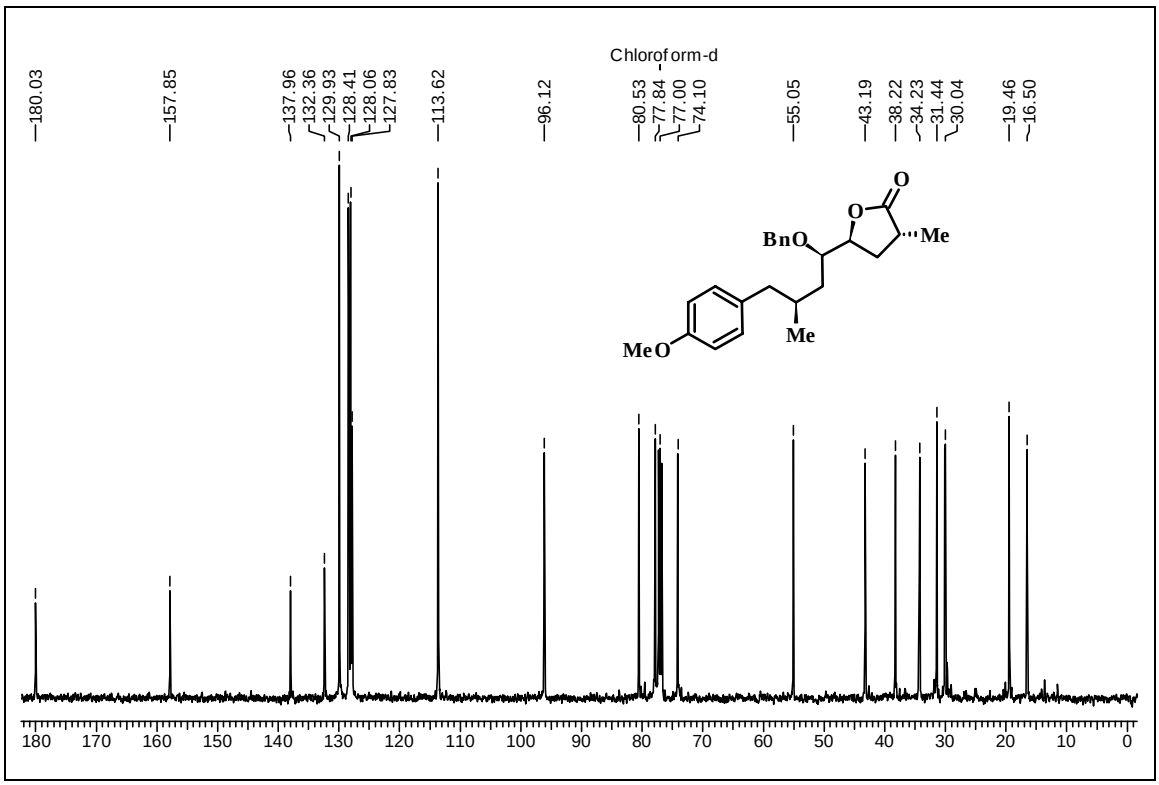


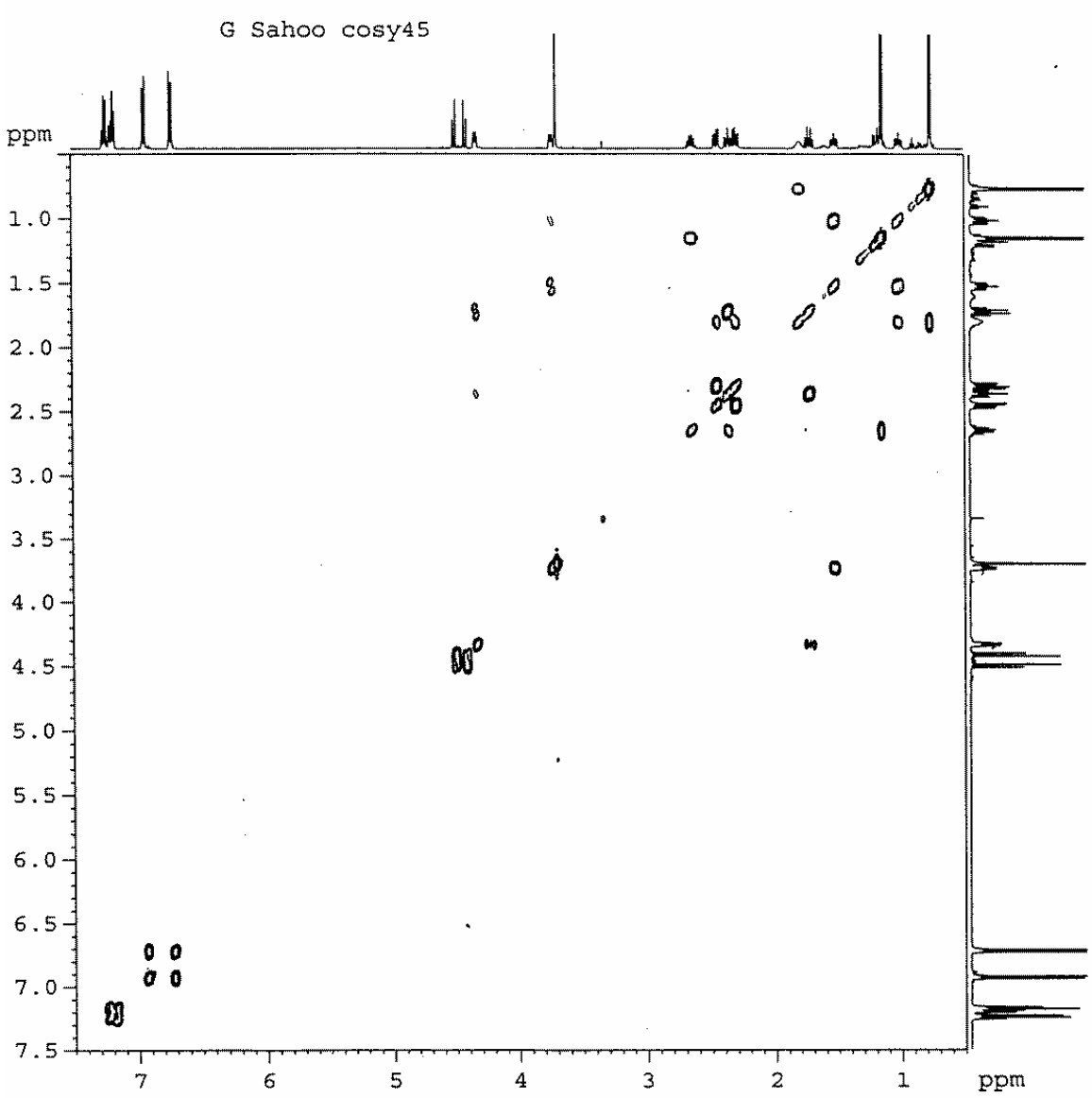
^{13}C NMR spectrum of compound 8 in $CDCl_3$

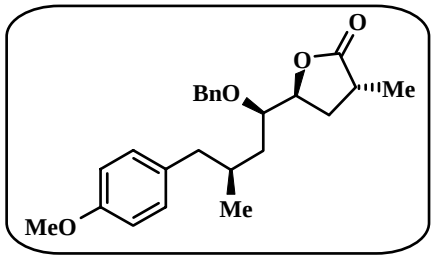


^{1}H NMR spectrum of compound 31 in $CDCl_3$

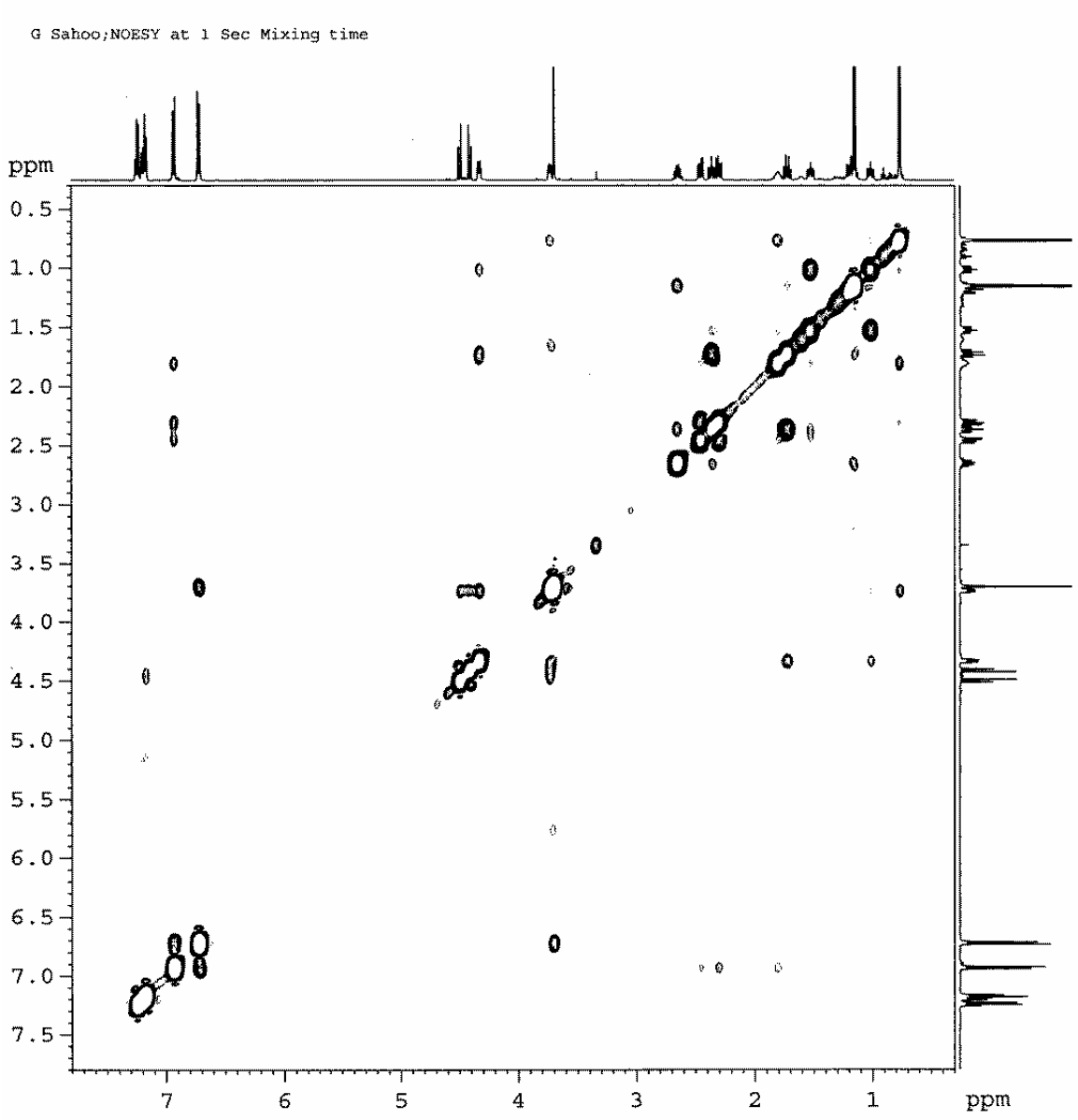


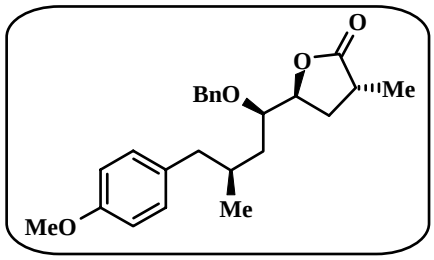
^{13}C NMR spectrum of compound 31 in $CDCl_3$



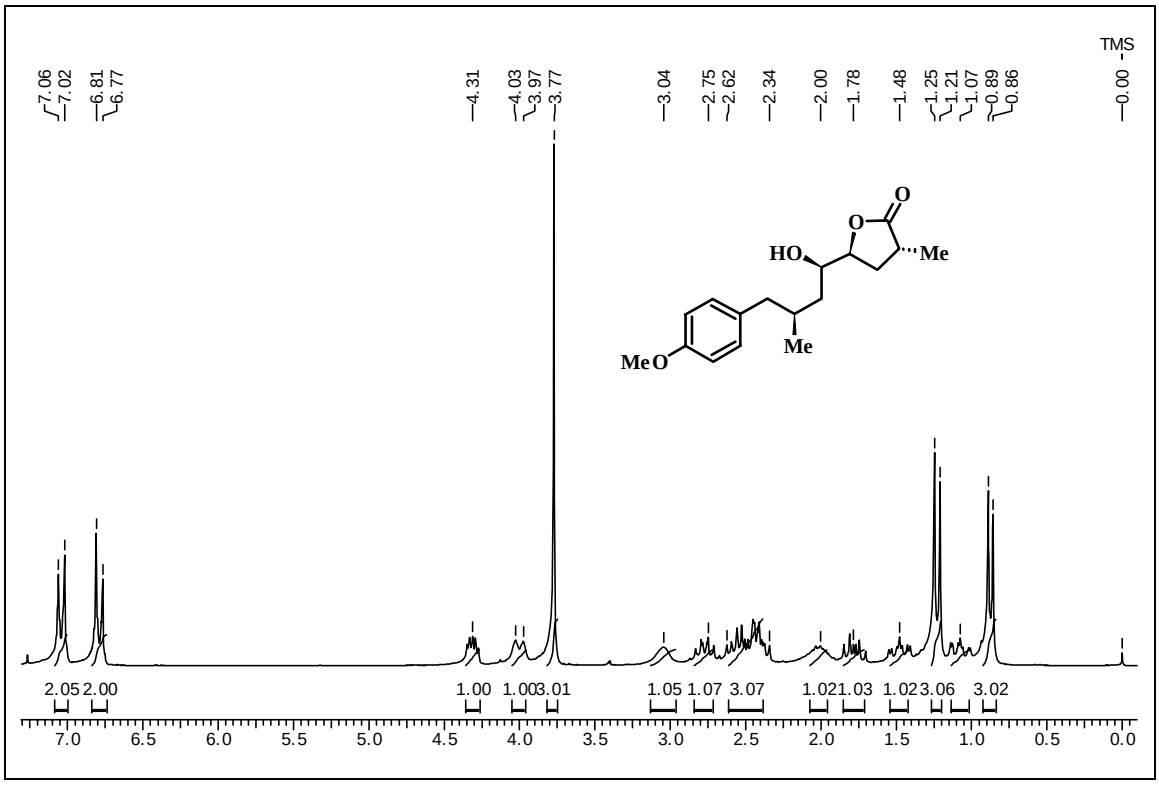


COSY Spectrum of compound 31

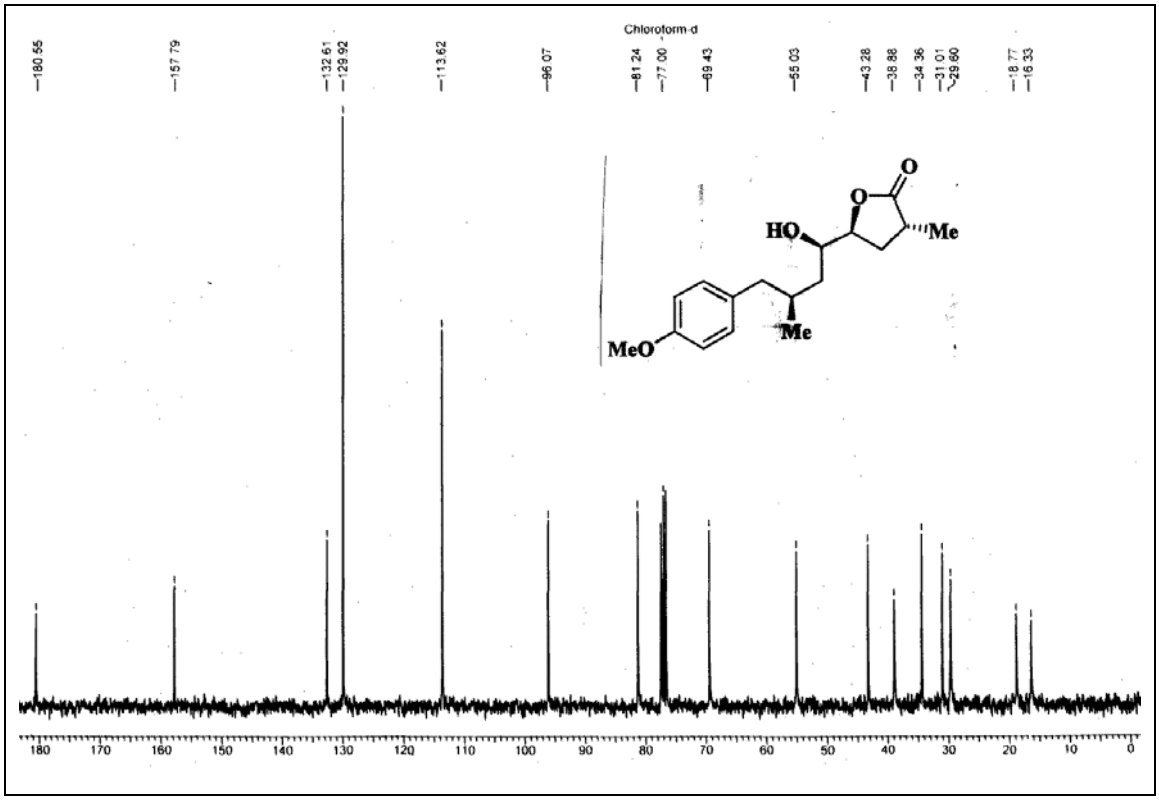




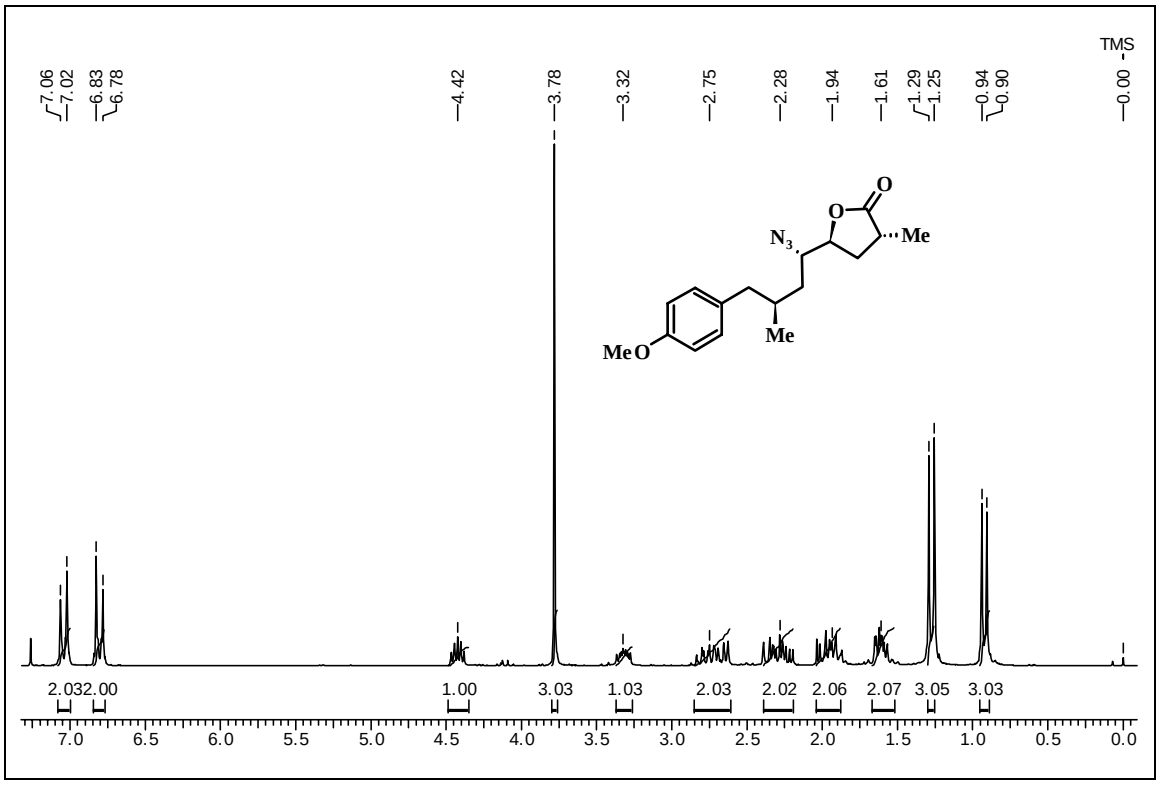
NOESY Spectrum of compound 31



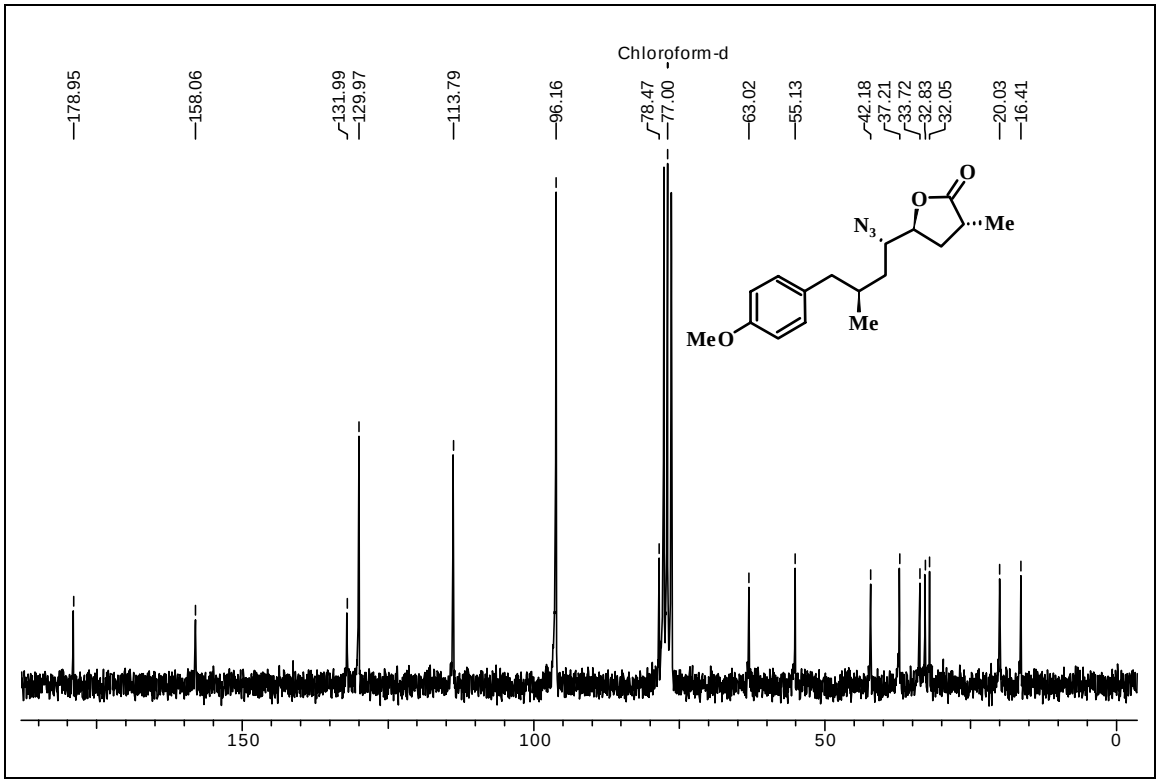
^{1}H NMR spectrum of compound 7 in $CDCl_3$



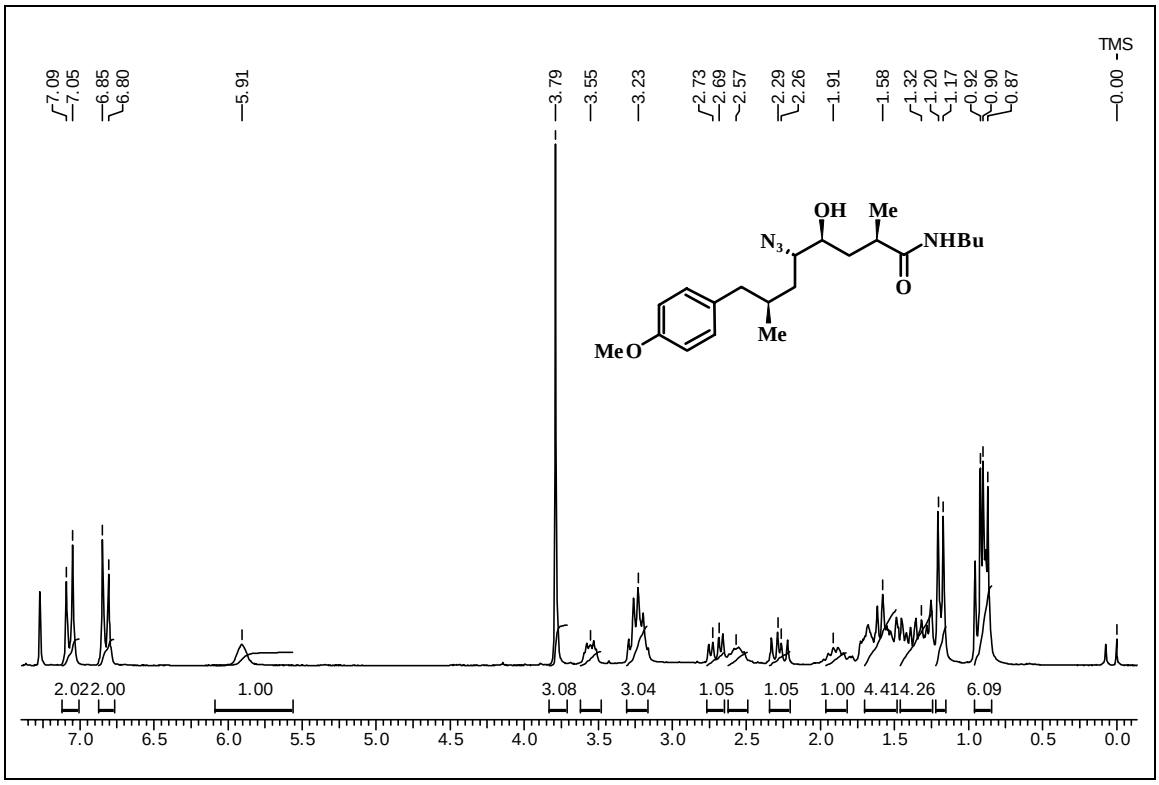
^{13}C NMR spectrum of compound 7 in $CDCl_3$



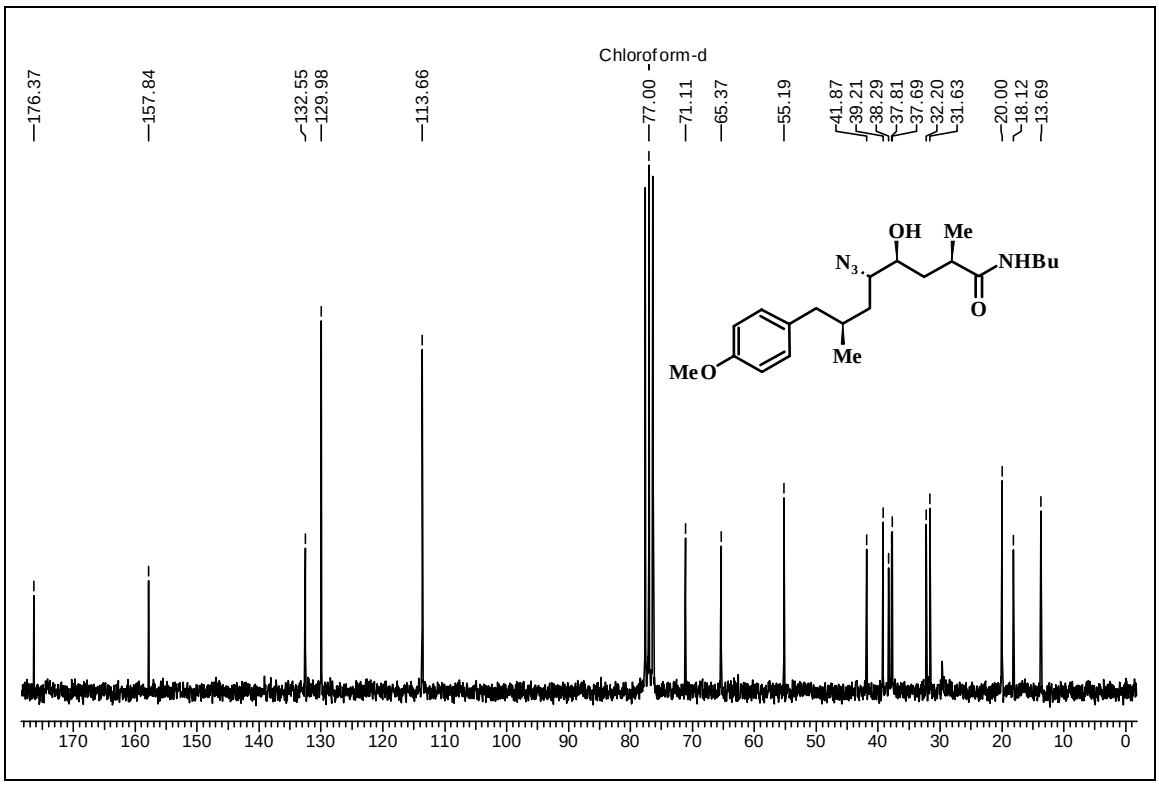
^{1}H NMR spectrum of compound 6 in $CDCl_3$



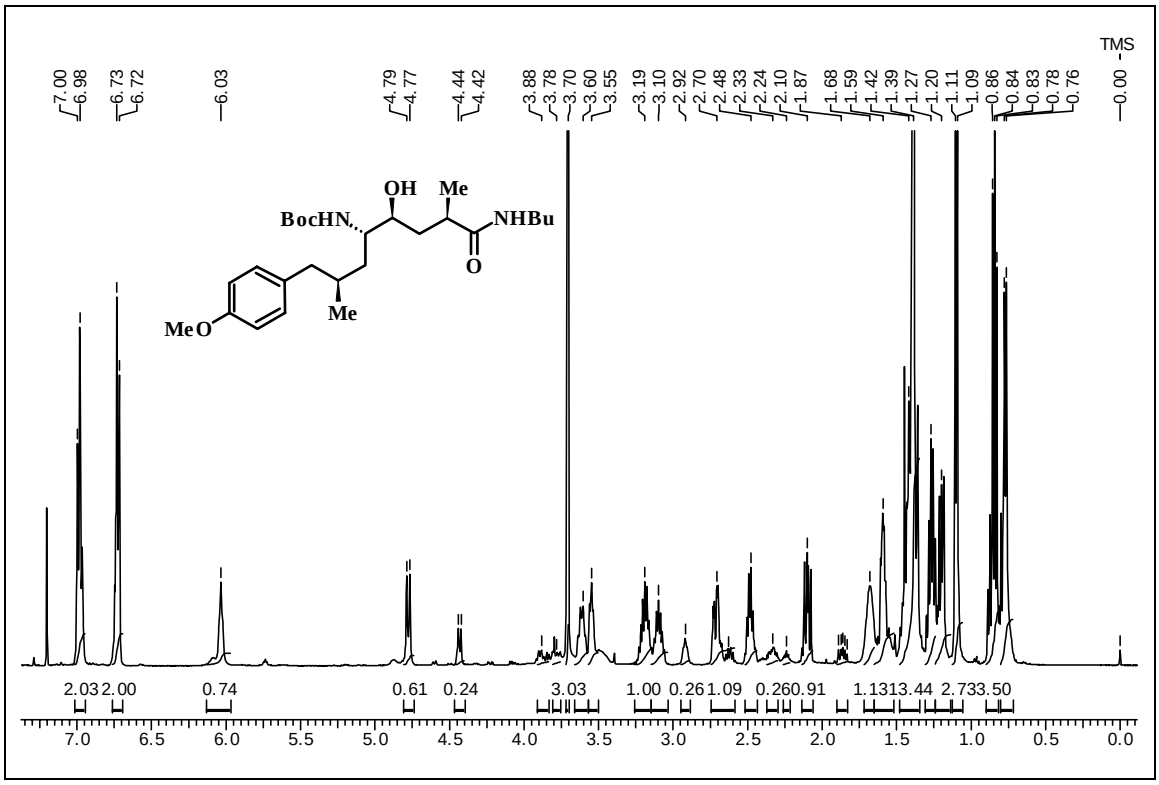
^{13}C NMR spectrum of compound 6 in $CDCl_3$



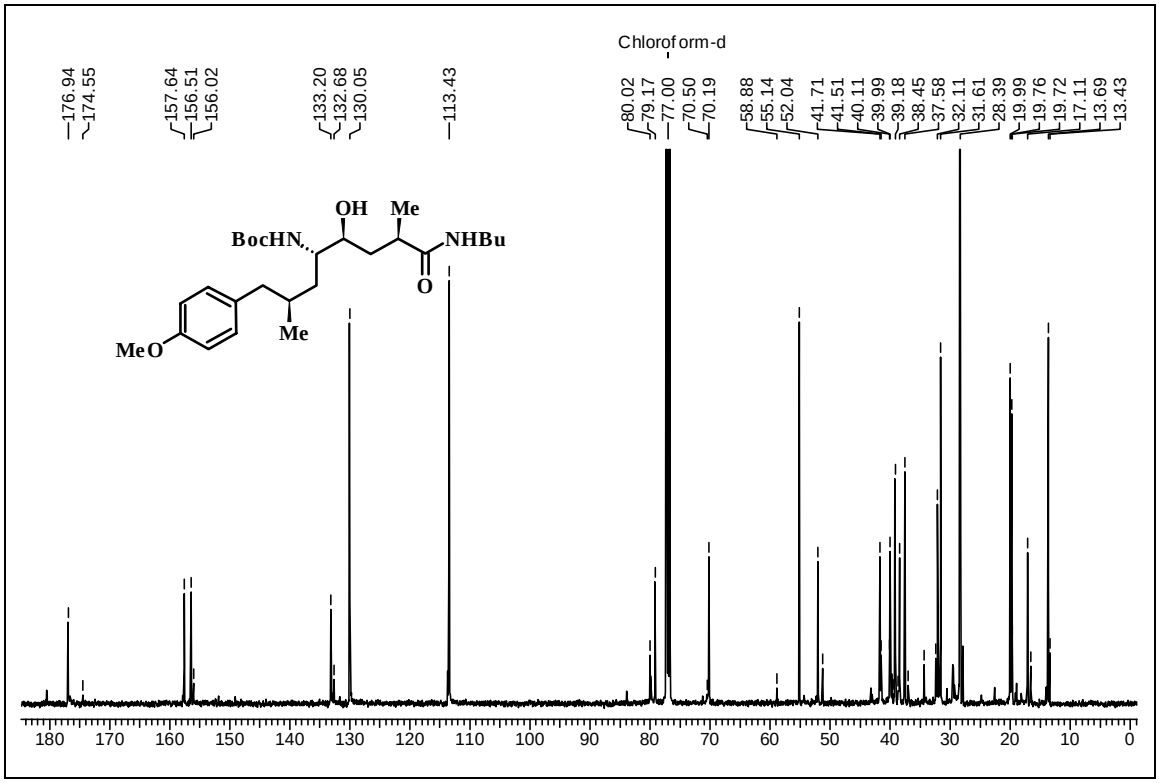
^{1}H NMR spectrum of compound 32 in $CDCl_3$



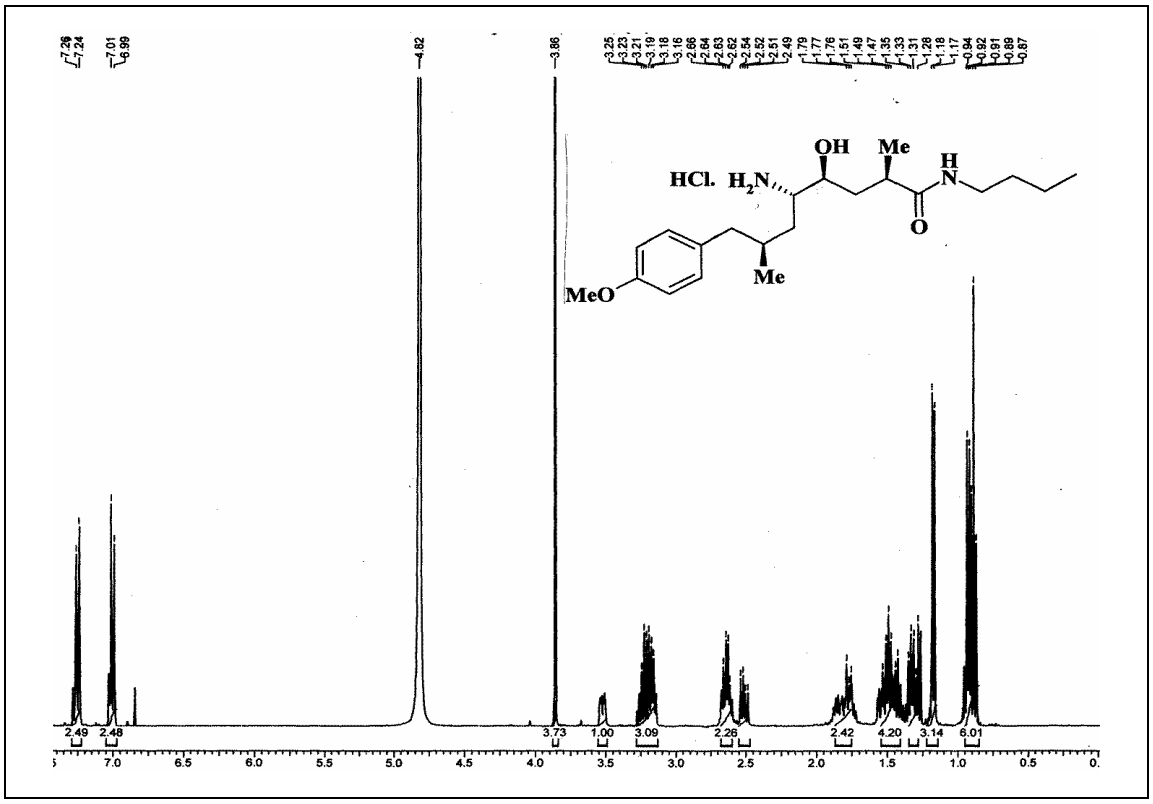
^{13}C NMR spectrum of compound 32 in $CDCl_3$



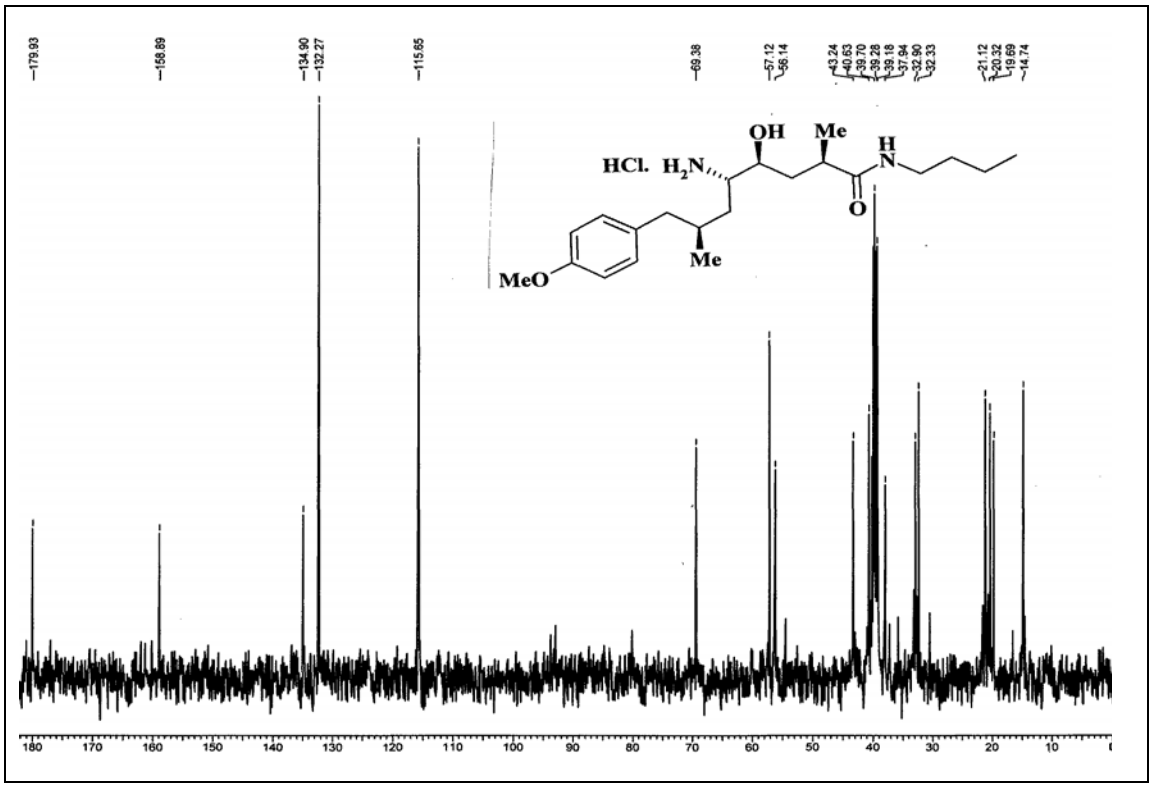
^{1}H NMR spectrum of compound 33 in $CDCl_3$



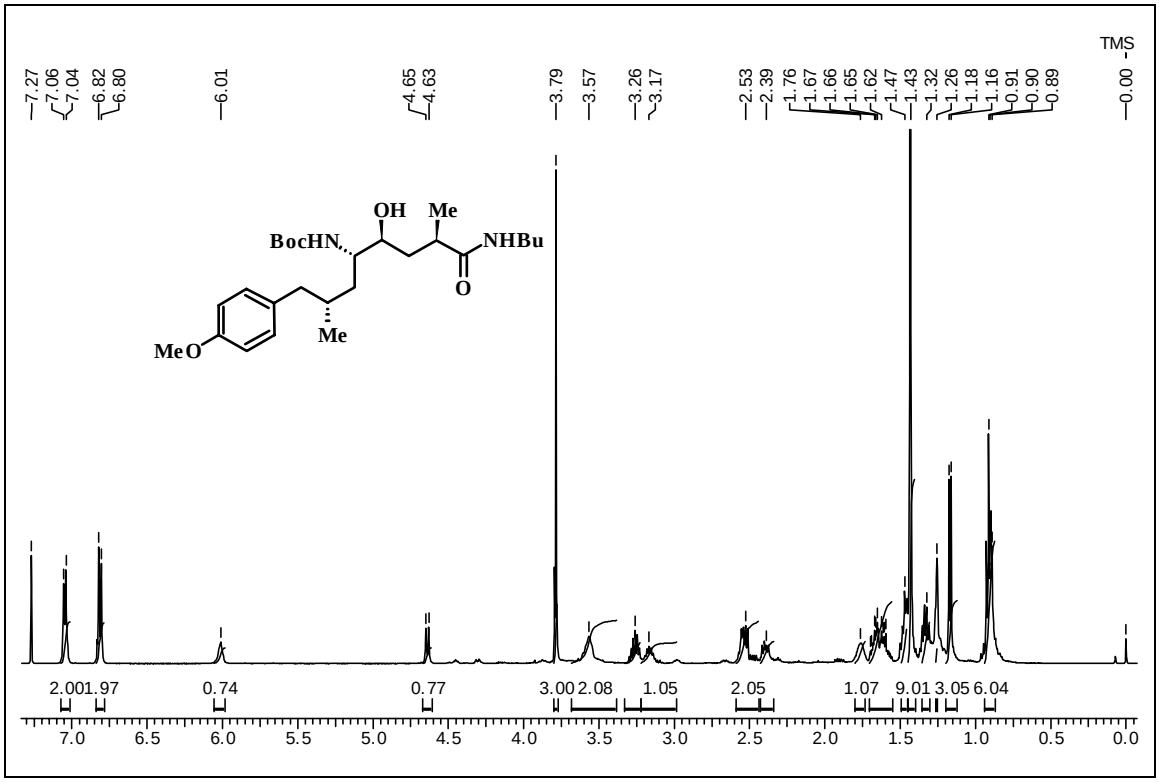
^{13}C NMR spectrum of compound 33 in $CDCl_3$



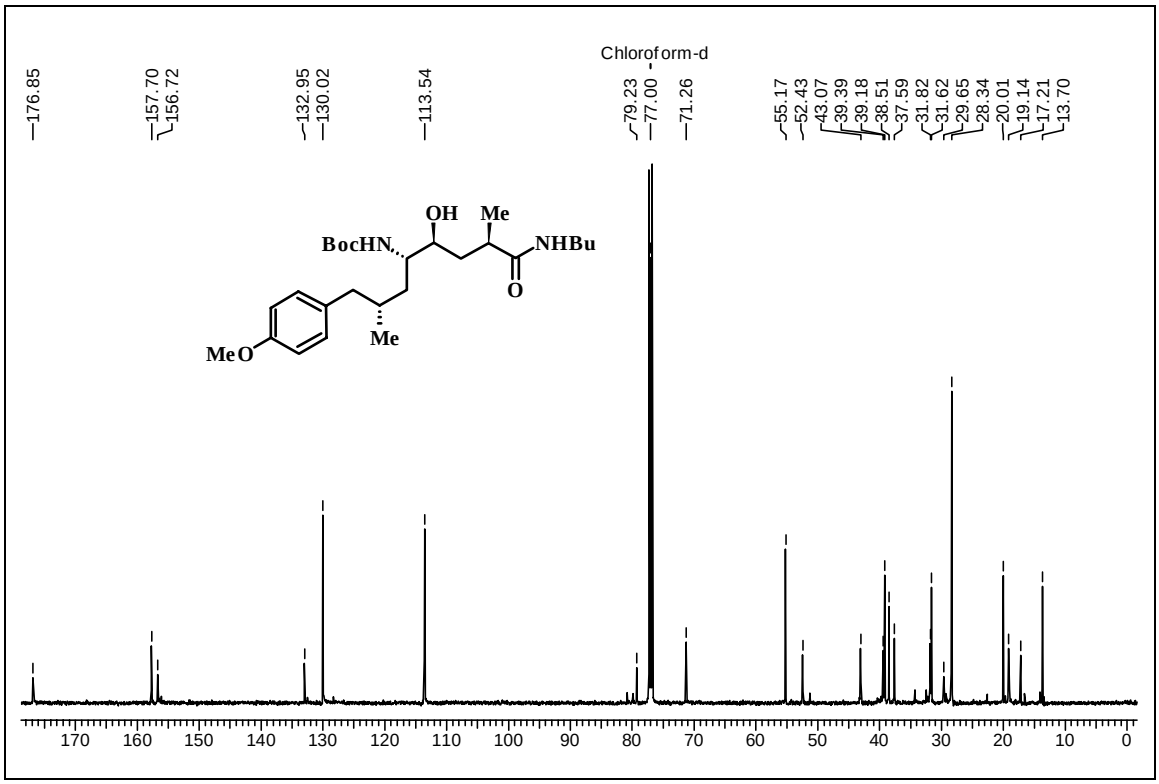
^{1}H NMR spectrum of compound 5 in D_2O



^{13}C NMR spectrum of compound 5 in D_2O



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



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

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32. **Preparation of LiN_3**: Li_2SO_4 (5 g) and NaN_3 (5.909 g) was dissolved in hot water (35 mL). To it 175 mL EtOH was added in three portions with constant stirring. The mixture was stirred for 30 min., when solid Na_2SO_4 precipitated out. The suspension was filtered over celite and the filtrate was concentrated under reduced pressure. The solid LiN_3 was dried in high vaccume at 80 ^oC for 1 h. LiN_3 is a white crystalline solid and kept in a air tight container (LiN_3 is highly hygroscopic).

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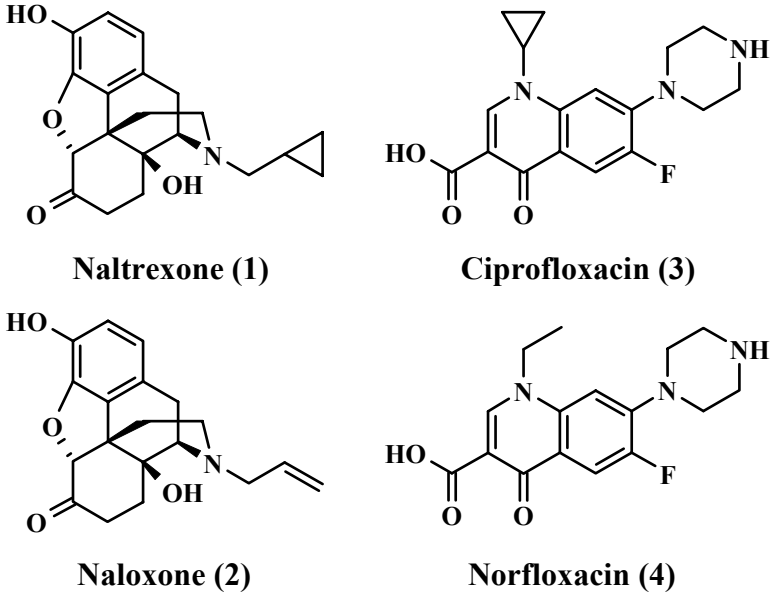
Chapter II, Section I:

Studies toward Stereoselective Simmons-Smith cyclopropanation on Carbohydrate Templates

A bird's eye view on "cyclopropane":

Cyclopropane, the smallest carbocycle, plays a crucial role in medicinal and synthetic chemistry. Cyclopropanes can serve natural demands in many ways. In some stable compounds they can constitute a space element of a certain dimension and lipophilicity with an orientation or position differing from that of closely related open-chain moieties. A cyclopropyl is a little smaller than an isopropyl unit, spirocyclopropyl is a little smaller than a geminal dimethyl group, and an annulated cyclopropane is smaller and its *exo*-carbon is twisted sideways compared to a methyl group. **Naltrexone** (**1**) is an opioid receptor antagonist used primarily in the management of alcohol dependence and opioid dependence, whereas **Naloxone** (**2**) is used in emergency cases of overdose rather than for longer-term dependence control. **Ciprofloxacin** (**3**) is a broad-spectrum antibiotic active against both Gram-positive and Gram-negative bacteria and **Norfloxacin** (**4**) is an oral broad-spectrum fluoroquinolone antibacterial agent used in the treatment of urinary tract infections and stomach infections (Figure 1).



Naltrexone (1) **Ciprofloxacin (3)**

Naloxone (2) **Norfloxacin (4)**

Figure 1

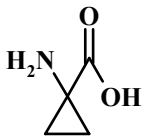
Cyclopropanes can also serve as rigid structural motifs, conferring reduced conformational flexibility in their annulated, spiro, or di- to oligosubstituted forms. This

can lead to interesting properties in cyclopropane amino acids and peptides.[1] The bond angles are locked, reduced within the ring, and substituent angles are enlarged in spiro or 1,1-disubstituted cyclopropanes (to about 118° versus 109.5° in saturated systems). 1,2-Disubstituted cyclopropanes can serve as rigid two-carbon *cis* or *trans* connections comparable to a double bond, but with different bond lengths (about 1.51 Å versus 1.34 Å for a double bond), bond angles (119° in alkenes versus 123° in cyclopropanes), and dihedral angles (about 141° for *trans*-1,2-dimethylcyclopropane compared to 180° for *trans*-1,2-dimethylethylene, Scheme 1). In addition to steric effects, the stereoelectronic and electronic properties of cyclopropane bonds, with their stronger s-orbital influence (sp^2-likeness) and banana shape, differ from simple sp^3 bonds and also affect the neighborhood.[2] The strained cyclopropane moiety could represent a labile element, with its stored strain energy as a driving force (some 115 kJ mol^{-1}, depending on the substitution pattern). Cyclopropanes can serve as high-energy intermediates in metabolism, as storage elements to release energy-rich compounds, or as trigger components to provide a driving force and ensure irreversibility in mechanism-based inhibition.[3]

Cyclopropane containing natural products:

Cyclopropanes are integral substructures of a number of natural products; the importance of cyclopropanes is further enhanced by their ability to serve as mechanistic[4] and biological[5] probes as well as synthetic intermediates[6]. Diastereoselectively generated cyclopropanes have proven to be useful synthons for further transformation to stereodefined cyclic and acyclic compounds.[7]

Cyclopropane subunits occur in many natural products of secondary metabolism.[8] The majority of cyclopropane-containing natural compounds have been isolated from plants, fungi, or microorganisms. Many show biological activity and may serve as potential drug leads or provide new ideas for the study of enzyme mechanisms. Examples include coronatin as a strong elicitor of stress response in plants, pyrethroids as insecticides,[9] carcinomas,[10] curacin A and D[11], CC-1065,[12] and 1-aminocyclopropane-1-carboxylic acid (ACC)[13] as the general precursor of the plant hormone ethylene, as drug leads.



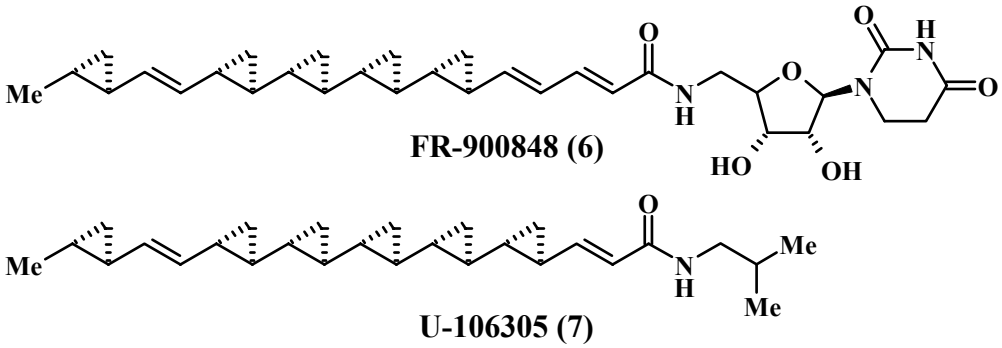
5

1-aminocyclopropane-
1-carboxyllic acid (ACC)

Figure 2

ACC (**5**) is the general precursor of the plant hormone ethylene (Figure 2). It plays an important role in the biosynthesis of the plant hormone ethylene. It is synthesized by the enzyme ACC synthase from methionine and converted to ethylene by ACC oxidase. ACC is also a non-physiological partial agonist of the mammalian NMDA receptor.

Inspired endeavors to mimic efficiency and elegance of nature have lead to new advances in chemistry, biology, and medicine, e.g. the structurally fascinating oligocyclopropanes **FR-900848** (**6**)[14] and **U-106305** (**7**).[15] **FR-900848** (**6**) was isolated from the fermentation broth of *Streptoverticillium fervens* and functions as antifungal agent. **U-106305** (**7**) was isolated from the fermentation broth of *Streptomyces* sp (Figure 3).



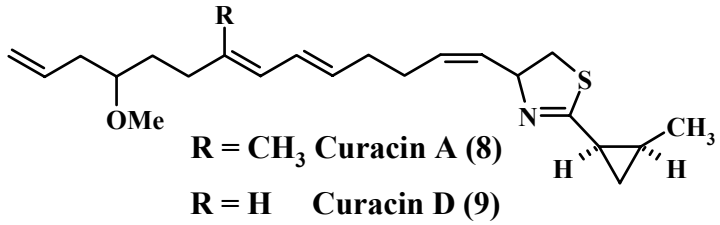
FR-900848 (6)

U-106305 (7)

Figure 3

Curacins A and D with potential against human diseases such as cancer have been reported by Marquez *et al.*[11] These originate from marine cyanobacteria (blue-green algae).[16] **Curacin A** (**8**) was found to be an inhibitor of tubulin polymerization and binds to the colchicine drug binding site. **Curacin D** (**9**) was isolated from *Lyngbya majuscula* and is very likely synthesized by methylene transfer from SAM.[11] Potentially the involvement of cyclopropane ring opening in any of the biological activities could be

nucleophilic or radical, with the thiazoline as the acceptor or electron donor, respectively (Figure 4).

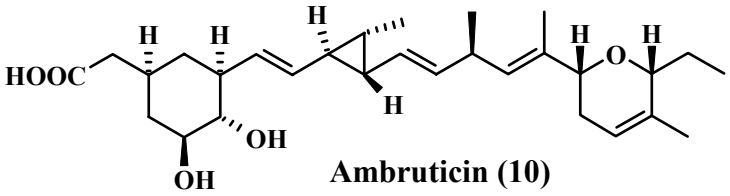


R = CH_3 Curacin A (8)

R = H Curacin D (9)

Figure 4

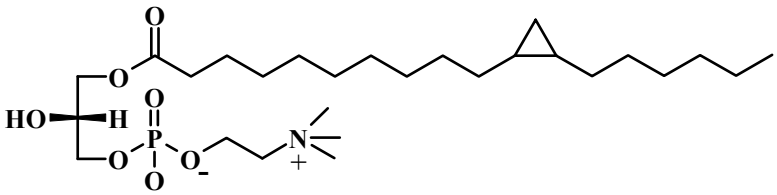
Ambruticin[17] **(10)** (also named as **W-7783** or trivially **5,6-dihydroxypolyangioic acid**) is a unique, orally active antifungal agent and exhibits *in vitro* and *in vivo* activity against a variety of pathogenic fungi (Figure 5). Significantly, **10** is effective against *Histoplasma capsuiatum* and *Coccidioides immitis,* which have been best treated previously with the highly toxic agent amphotericin B. It is produced by growth under appropriate conditions from a soil inhabiting myxobacteriale *Polyangium cellulosum* var. *fuluum.*



Ambruticin (10)

Figure 5

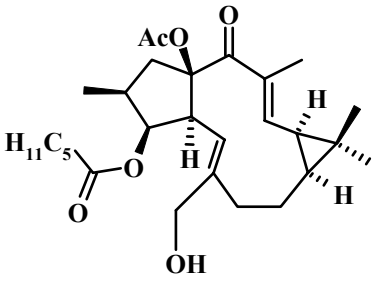
In 1999, Shin *et al.* disclosed the isolation and structure elucidation of several marine sponge (*Spirastrella abata*) phospholipids with inhibitory activity against cholesterol biosynthesis in the Chang liver cell. These compounds specifically block the conversion of lanosterol into cholesterol, which is quite *downstream* in the cholesterol biosynthetic pathway. Among the phospholipids, **Lysophosphatidylcholine** (**11**) showed an IC_{50} value of 60 μg/mL. It bears the important cyclopropane moiety, which is used to probe biological processes (Figure 6).[18]



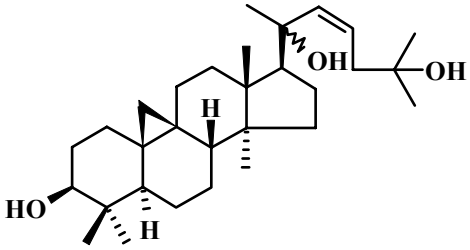
Lysophosphatidylcholine (11)

Figure 6

The macrocyclic lathyrane polyester *Euphorbia* factor L_{10} (**12**) (Figure 7) has been isolated from the seeds of the caper spurge (*E. lathyris*). The interaction of L_{10} (**9**) with P-glycoprotein, a multidrug transporter overexpressed in cancer cells and responsible for resistance to chemotherapy, established lathyrane diterpenoid as a novel chemotype for P-glycoprotein inhibitors.[19]



P-Glycoprotein Inhibitor from the Caper Spurge (12)



Cycloclarkeanol (13)

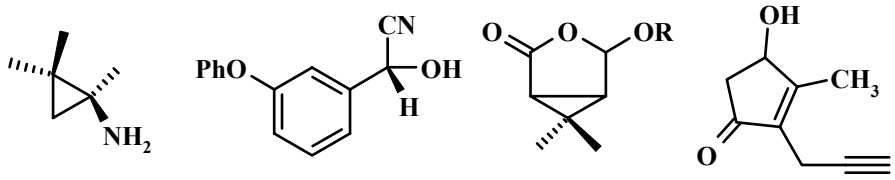
Figure 7

The genus ***Euphorbia*** (Euphorbiaceae) consists of about 2000 species occurring in the form of lacticiferous herbs, shrubs, and small trees, inhabiting the tropical and temperate zones of Asia and other parts of the world. A large number of these are used in indigenous medicine for the treatment of a variety of ailments including cancer, rheumatism, neuralgia, asthma, and bacterial infections. Systematic study of the hexane extract of ***E. clarkeuna*** has resulted in the isolation of many natural products, the important being a new cycloartane triterpene named **cycloclarkeanol** (**13**) (Figure 7).[20]

Cyclopropanes as resolving agents:

2,2-Dimethylcyclopropylamine **14**, a useful intermediate for pharmaceuticals and agrochemicals, also works as efficient resolving reagent for optical isomers.[21a] Racemic cyanohydrin **15** was resolved by etherification with cis-(1*R*,3*S*) acid lactone **16a** and subsequent hydrolysis.[21b] Likewise, resolution of cyclopentenolone **17** was carried out by

etherification with optically active lactone **16a** and subsequent methanolysis of **16b** (Figure 8).[21c]



14 **15** **16a, R = H** **16b, R = 17** **17**

Figure 8

Thermodynamic Considerations/Strain Energy: Formation of a cyclopropane ring requires that three -CH_2- groups be accommodated into a cyclic arrangement with all C-C-C bond angles equal to 60°. These bond angles are considerably less than the ideal 109.5' for sp^3-hybridized orbitals, resulting in significant angular (Bayer) strain. Further, cyclopropane suffers additional torsional (Pitzer) strain because the coplanar arrangement of the carbon atoms mandates that the C-H bonds be eclipsed. The relief of strain associated with ring opening is often invoked to rationalize the high reactivity of the cyclopropyl group. However, the strain energies of cyclopropane and cyclobutane are similar: 27.5 and 26.5 kcal/mol, respectively.[22]This similarity is also revealed by considering the energy required for homolytic C-C cleavage, $(CH_2)_{n+2}$ to $^{\cdot}CH_2(CH_2)_nCH_2^{\cdot}$: 61 kcal/mol for n = 1 and 62.5 kcal/mol for n = 2.5. In contrast, whereas the chemistry of a cyclopropane ring resembles that of a carbon-carbon double bond (i.e., susceptible to electrophilic attack, easily oxidizable etc.), the chemistry of cyclobutane is unremarkable. Consequently, thermochemical considerations alone are insufficient to explain the unusual reactivity of cyclopropane, which is advantageous, yet mysterious.

Bonding in Cyclopropane

A. The Coulson-Moffitt Model: A popular description of bonding in cyclopropane, advanced by Coulson and Moffitt, imagines the construction of the cyclopropane ring from three sp^3-hybridised –CH_2- groups (Figure 9).[23]As such, the sp^3 hybrids are pointed ca, 22^o outward from the imagenary line connecting the nuclei, resulting in about 20% less effective overlap than the C-C bond of ethane. For this reason, the bonds are often referred to as "bent". This diminished overlap is reckoned to be the source of the angular

strain. Other formulations of the Coulson-Moffitt model involve utilizing $sp^{2.3}$ and sp^5-hybridized orbitals to describe the carbon-hydrogen and carbon-carbon bonds, respectively. The greater p-character in the C-C σ-bonds is frequently invoked to explain the similarity of cyclopropane chemistry to that of olefins. Various physical properties (e.g., $J(^1H-^{13}C)$ and $J(^{13}C-^{13}C)$ NMR coupling constants) are adequately explained by this deviation from sp^3 hybridization.

B. The Walsh Model: The Walsh model[24] envisions cyclopropane as being constructed from three sp^2- hybridized -CH_2-'s (Figure 9), arranged such that the sp^2 hybrids are oriented radially toward the center of the cyclopropane ring. The molecular orbital diagram depicted in Figure 9 results from the use of this basis set. By this model, angular strain is also attributed to poor overlap. For example, the overlap of the orbitals comprising ψ_1 (**a**) is diminished because the lobes of the sp^2 hybrids are oriented inward from the imaginary lines connecting the carbon atoms. Similarly, ψ_2 (**b**) can be viewed as a distorted π bond. (This distorted π bond description of ψ_2 offers an intuitively appealing explanation of the reactivity of cyclopropane toward electrophilic reagents.)

C. The Notion of σ-Aromaticity: The classical organic chemistry has treated σ-bonds as localized entities. However, as articulated by Dewar[25] in 1984**,** this assumption is often incorrect. The concept of "σ conjugation" provides an especially intriguing explanation of the physical and chemical properties of cyclopropane: the three C-C σ bonds provide a cyclic array of 6 electrons; by the *4n* + 2 rule, cyclopropane is aromatic. In contrast, cyclobutane, with *4n* electrons *(n = l) ,* is antiaromatic. A slight modification of this approach, advocated by Cremer,[26] utilizes the Walsh basis set and the molecular orbital diagram depicted in Figure **3.** σ Aromaticity is postulated to arise from occupation of the "surface orbital", ψ_1 (**a**), resulting in a three-center, two-electron bond.[26] Several chemical and physical properties of cyclopropane, previously considered anomalous, are easily explained when σ-aromaticity is invoked. Some of these are highlighted below.

1. Strain Energy. The strain energy of cyclopropane (27.5 kcal/mol) is substantially lower than that calculated from the C-C-C bending force constant obtained from vibrational spectroscopy (104 kcal/mo1);[25] the discrepancy is attributable to σ aromaticity.

2. NMR Characteristics. Coupling constants (e.g., $J(^{1}H\text{-}^{13}C)$ and $J(^{13}C\text{-}^{13}C)$) are explicable by approximate sp^2 hybridization of carbon reflecting either the Coulson-Moffitt or Walsh models (vide supra). Ring-current effects provide a satisfactory explanation for the observed upfield shift of the protons of cyclopropane because its protons are shielded from the applied magnetic field (Figure 9).[25]

3. Reactivity of Cyclopropane toward Electrophiles. The high reactivity of cyclopropane toward electrophiles, frequently explained on the basis of a relief of strain, can be better understood on the basis of σ aromaticity. For the reaction of C_3H_6 with an electrophile, aromaticity is maintained in the transition state Thus, the fact the cyclopropyl group remains essentially *intact* in the transition state accounts for its high reactivity. In contrast, the ring strain (thermodynamic) argument would suggest the cyclopropane ring is substantially broken in the transition state.

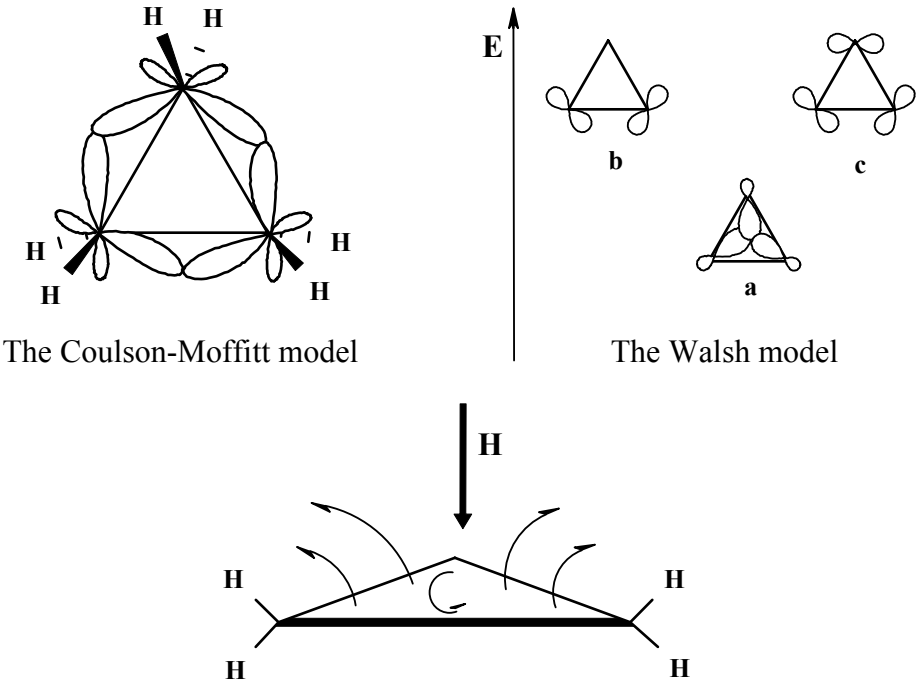


Figure 9

Biosynthesis of cyclopropanes: An excellent overview of biosynthetic pathways and metabolisms of cyclopropane-containing natural products was written by Liu and Walsh in 1987 (Figure 10).[8]

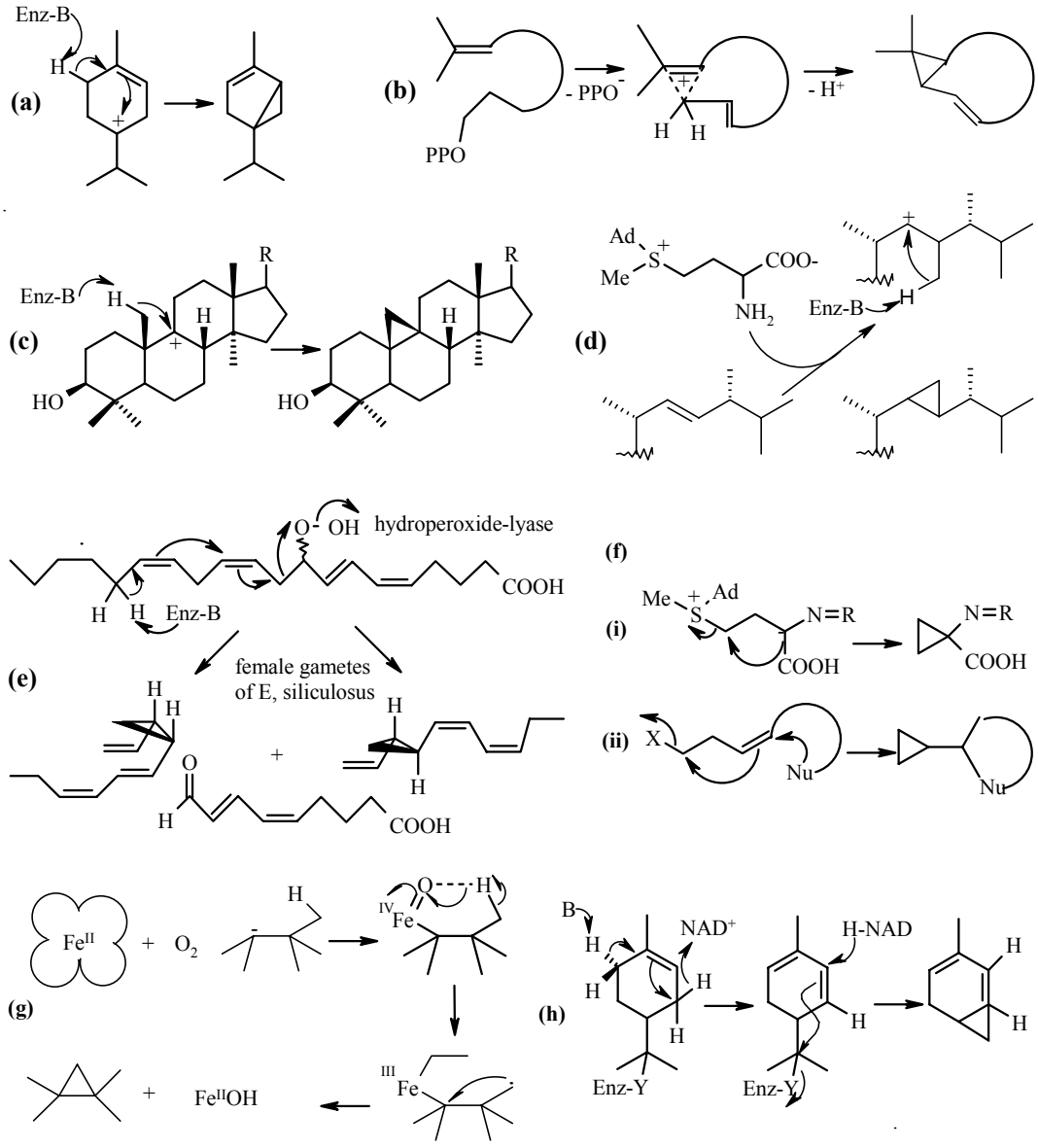


Figure 10: (a) Reaction of an intermediate cation with a homoconjugated double bond (homoallyl cation ring closure). (b) Reaction of an intramolecular (allyl) cation with a double bond to form a protonated cyclopropane species and its subsequent deprotonation. (c) Reaction of an intermediate cation with an enzyme-activated α-methyl group. (d) Reaction of an intermediate cation with a neighboring methyl group generated by a methyl transfer from S-adenosylmethionine (SAM) to a precursor double bond acting as a nucleophile. (e) Reaction of a radical intermediate with a homoconjugated double bond (derived from a peroxide fragmentation). (f) Internal nucleophilic substitution (S_Ni). (g) Transition metal-assisted radical cyclization. (h) Redox mechanism supported by NAD(P) [$H^{\bullet}$ or H^- transfer mechanism].

Laboratory synthesis of cyclopropane:

There are few methodologies for the synthesis of cyclopropanes, developed in last couple of decades. These include free carbenes, transition metal catalyzed diazo decomposition, Michael initiated ring closure, Simmons-Smith reaction etc.

Simmons-Smith reaction: In late 1950's, Howard Ensign Simmons, Jr. and Ronald D. Smith made a path breaking discovery in organic synthesis. Addition of unsubstituted methylene to alkene moieties was achieved by the reaction with CH_2I_2 and Zn-Cu couple complex. Since then it has been the most used methodology for the synthesis of the strained yet versatile cyclopropane moiety. Improvements in this area have included the asymmetric version, reagent modification etc. In this reaction a carbenoid reacts with an alkene (or alkyne) to form a cyclopropane (Figure 11).[27,28,29]

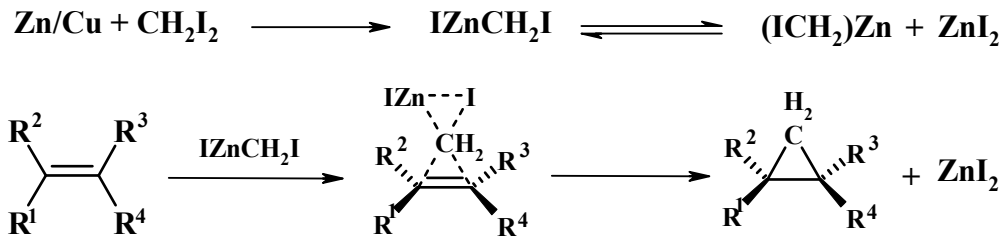
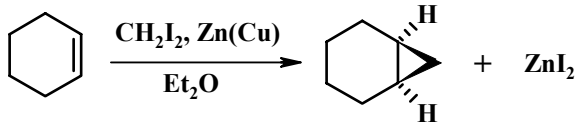


Figure 11

e.g. Cyclohexene (**18**), diiodomethane, and a zinc-copper couple (as *(iodomethyl)zinc iodide*, ICH_2ZnI) yield bicyclo[4.1.0]heptane (**19**) (Scheme 1).[30,31]



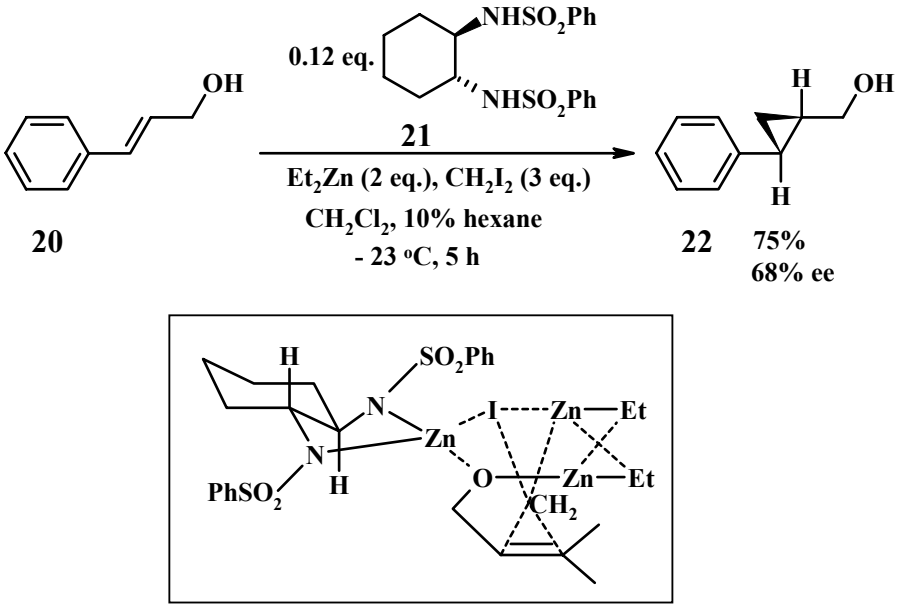
18 Bicyclo[4.1.0]heptane (**19**)

Scheme 1

The Simmons-Smith reaction is generally subject to steric effects, and thus cyclopropanation usually takes place on the less hindered face.[32,33] However, when hydroxy substituents are present on chiral carbons, the zinc coordinates with the hydroxy substituents, directing cyclopropanation to the same face, which may or may not be sterically favorable.[34]

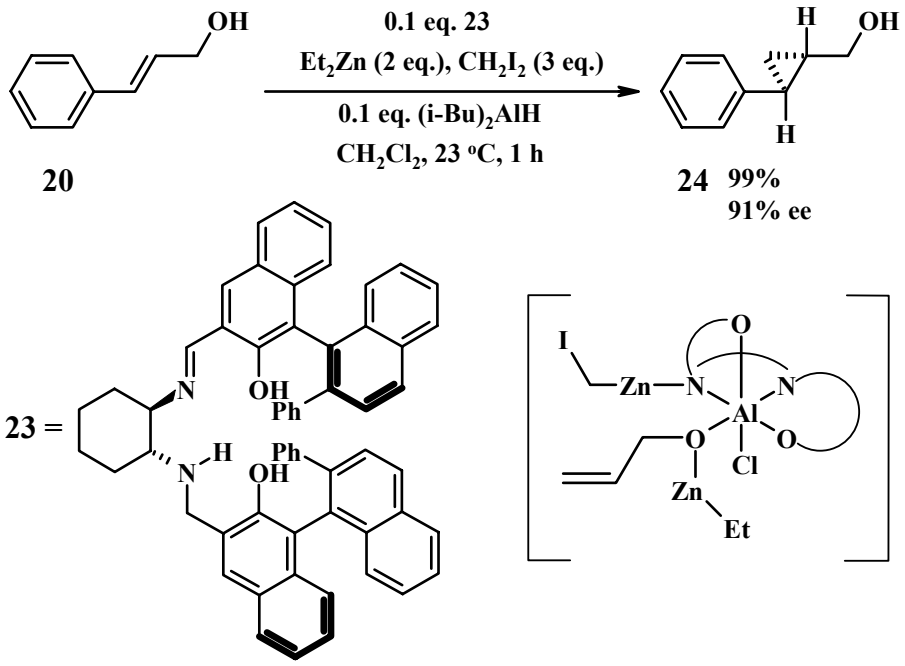
Modification of Simmons-Smith reaction by Furukawa *et al*:[35] Junji Furukawa *et al* found new Zinc reagents (R_2Zn) capable of substituting the Zn/Cu couple in Simmons-Smith cyclopropanation reaction during the course of a study of the catalytic activity of metal alkyl-polyhalomethane systems for vinyl polymerization.[35a] The essential feature of this reaction is quite similar to that of Simmons-Smith reaction. But added to its advantage, this method is much more rapid and particularly suitable for the conversion of cationically polymerizable olefins such as vinyl ethers into the corresponding cyclopropanes in good yields, which otherwise gives low yield of cyclopropanes in Simmons-Smith reaction due to polymerization.[35a,b] Furukawa *et al.* later reported[35c] that **Et_2Zn** could also be replaced by **Et_2Cd** for Simmons-smith cyclopropanation reactions.

Asymmetric Simmons-Smith reaction: Although asymmetric cyclopropanation methods based on diazo compounds have existed since 1966, the asymmetric Simmons-Smith reaction was introduced in 1992 with a reaction of cinnamyl alcohol with diethylzinc, diiodomethane and a chiral disulfonamide in dichloromethane (Scheme 2).[36]



Scheme 2

The hydroxyl group was found to be a prerequisite anchor for zinc. In another variant of this reaction a ligand based on salen and Lewis acid DIBAL-H was added (Scheme 3).[37]

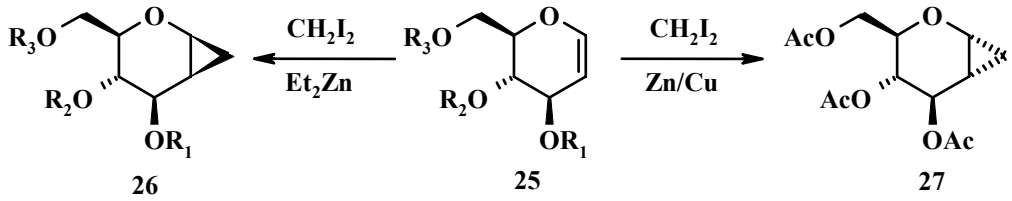


Scheme 3

Cyclopropanation on carbohydrate templates: The incorporation of cyclopropanes into a carbohydrate provides for an interesting mixture of strained and reactive cyclopropanes combined with the optical activity inherent in carbohydrates. Thus, one may envision use of the chemistry normally associated with cyclopropanes in conjunction with enantiopure building blocks. This combination has started to generate much interest as an increasing number of reports on 'strained' carbohydrates have appeared in the synthesis of bioactive compounds and the development of new synthetic methods. Examples include the formation of seven-membered rings, application to the synthesis of natural products and transition metal-catalyzed reactions. Traditionally carbohydrates have been considered difficult to work with, as a number of protection and deprotection reactions can be necessary. This is perhaps due to the fact that each hydroxy group represents a unique chemical environment. Cyclopropanated carbohydrates however usually start with the removal of two of these hydroxy groups, thereby making the use of the carbohydrate very facile.

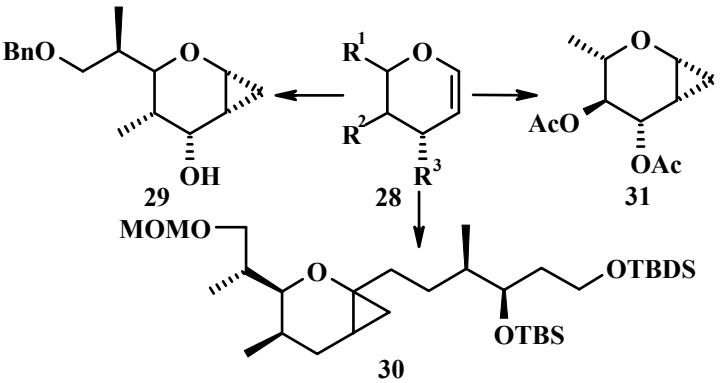
Cyclopropanation using the Simmons-Smith reaction: Hoberg *et al.* reported the cyclopropanation of a wide variety of protected glycols.[38] The efficacy of Furukawa modification has been demonstrated with yields upto 96% and diastereoselectivities of

>250:1. The *syn* diastereomer **26** (w. r. to OR_3) was the major product, as was expected because of the coordination to the oxygen atom. Nagarajan *et al.* used acetyl chloride as an activator for several benzylated glycal systems and reported the formation of a single cyclopropanated product **27** in greater than 80% yield.[39]A different outcome for the triacetylated glycal was reported by Lorica *et al.*, attributing the result to steric hindrance from the upper face by acetate groups[40] (Scheme 4)



Scheme 4

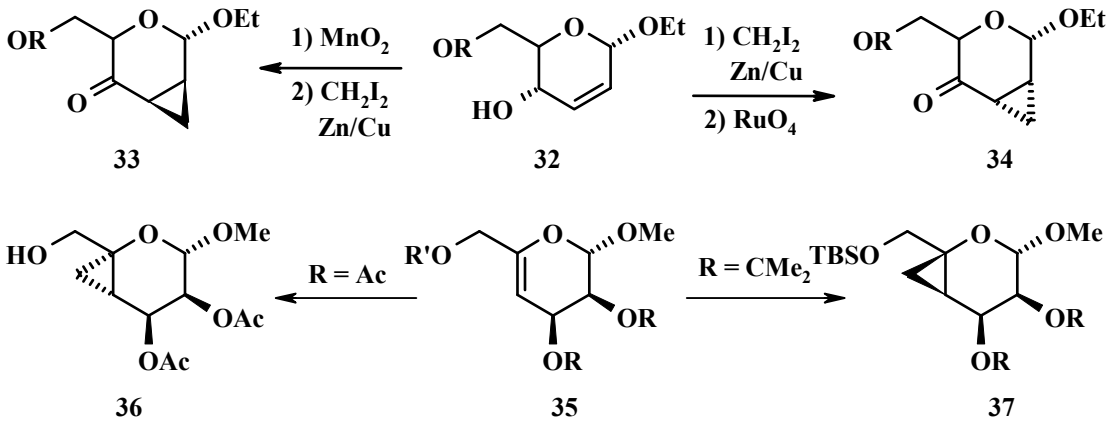
The effectiveness of the directed cyclopropanation with carbohydrates can further be seen with the glycals in Scheme 5. Synthesis of cyclopropane **29** was achieved stereospecifically in 93% yield,[41] while the formation of **30**, in which R^3 is a proton, produced an equal mixture of diastereomeric cyclopropanes.[42] Additionally, a method has been reported which alleviates the problem associated with acetate protecting groups to get the chelated cyclopropanated product.[38] Cyclopropanation of the diol (R^1 = Me, R^2, R^3 = OH) with Et_2Zn–CH_2I_2 followed by *in situ* quenching with Ac_2O provides **31** in 85% yield and 8:1 selectivity (Scheme 5).



Scheme 5

Cyclopropanation of 2,3- and 4,5-unsaturated carbohydrates has also been reported, (Scheme 6). Fraser-Reid and co-workers devised a strategy for the formation of either isomer from a 2,3-unsaturated carbohydrate using the classic Simmons-Smith Zn/Cu

couple.[43] In the formation of **33** with the cyclopropane *anti* to the ethoxy group, the hydroxy group at C-4 was oxidized with manganese dioxide then cyclopropanated; yields ranged from 22% to 93%. Synthesis of **34** involved initial formation of the cyclopropane, presumably directed by the C-4 hydroxy group, and then oxidation with ruthenium oxide. Overall yields for these two steps ranged from 45% to 80%. One example of the cyclopropanation of a 4,5-glycal has been reported.[44] Synthesis of **36** was performed by the Furukawa modification providing a mixture of diastereoisomers in a combined 74% yield. In an attempt to improve the diastereoselectivity of the reaction, the system was modified by switching from the diacetate protecting groups to the acetonide. Cyclopropane **37** was then formed as the exclusive isomer, presumably by complexation of the zinc to the acetonide oxygen.



Scheme 6

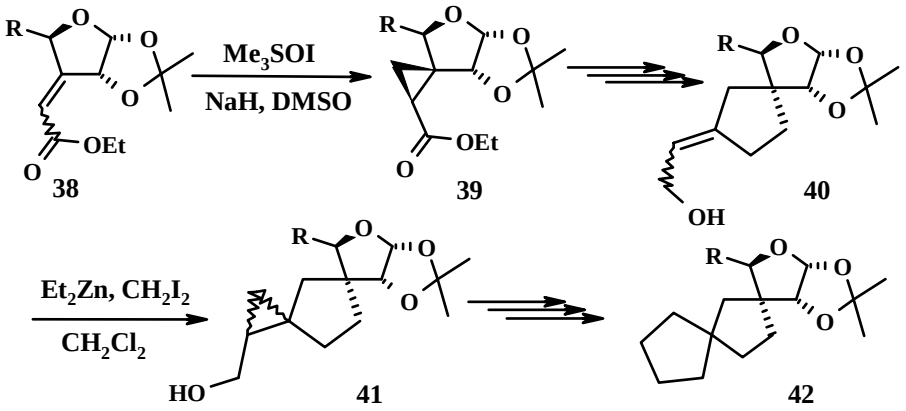
In conclusion, considering the influential properties of cyclopropanes in active biological entities, we focused on the substrate controlled stereospecific synthesis of this moiety on carbohydrate templates.

The cyclopropane subunit has long been imprinting its important impression on natural and unnatural substances of biological interest. Its strained structure, interesting bonding characteristics and its utility as an internal mechanistic probe continue to draw the attention of physical organic chemists.[45] The prevalence of cyclopropane containing compounds with biological activities, whether isolated naturally or incorporated into rationally designed pharmaceutical agents, has inspired chemists to delve into designing novel and diverse approaches to synthesis. The pioneering work by Simmons and Smith dramatically expanded the utility, facility and sereoselectivity of the transformation.

Versatility of Carbohydrate Chemistry: Since their discovery and elaboration of properties by Emil Fisher in late 1800s, carbohydrates have been comprehensively studied and used for many chemical endeavors. These represent a unique family of polyfunctional compounds, which can be chemically manipulated in a multitude of ways. Presence of specific stereocenters makes carbohydrate molecules a very useful chiral pool. The availability of many oxygen atoms renders high stereoselectivity in organic transformations due to hydrogen bonding and co-ordination. Consequently carbohydrates may be considered to be highly versatile and manageable materials for biologically important molecules and as model compounds on which the whole gamut of standard reactions in the organic chemists repertoire may be performed. By the early 1970s, carbohydrates were recognized as suitable chiral starting materials for the synthesis of plethora of non-carbohydrate compounds and as chiral auxiliaries in synthesis.

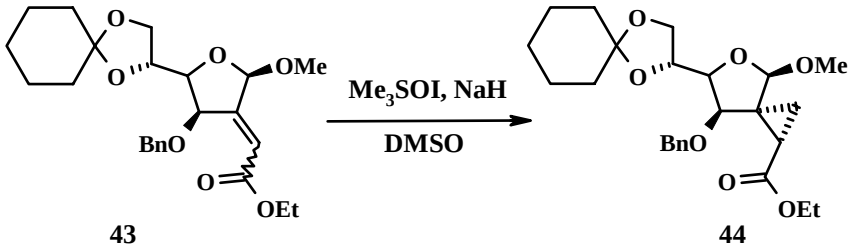
Previous reports from our group in this direction:[46]

In our laboratory there has been extensive study of off-template stereoselection on carbohydrate models. Recently a series of publications described the cyclopropanation on glucofuranose and xylofuranose moieties. The exocyclic double bond at C3 has been cyclopropanated under Corey-Chaykovsky reaction condition and Simmons-Smith cyclopropanation protocol yielding crucial intermediates, which finally led to the formation of spirocompounds **40** and **42** (Scheme 7).



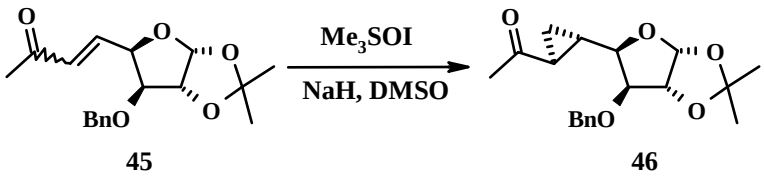
Scheme 7: Cyclopropanation at C3 exocyclic olefin

In the same report, the C2 exocyclic double bond has also been subjected to cyclopropanation using Corey's method (Scheme 8). The stereoselectivity in all these methods was explained by steric constraint of the ring appendages.



Scheme 8: Cyclopropanation at C2 exocyclic olefin

In the synthesis of the polyketide fragment of Nagahamide A, we have adopted[47] the Corey-Chaykovsky's cyclopropanation procedure for stereospecific cyclopropanation at C5=C6 olefin of glucofuranose moiety. The stereospecificity has been attributed to the stereocontrol by the 3(*S*)-OBn group (Scheme 9).



Scheme 9: Cyclopropanation at C5=C6 olefin

In continuation of these efforts on such off-template phenomena, herein we report the stereoselective Simmons-Smith cyclopropanation on carbohydrate substrates. The

carbofuranose system has been used as the scaffold, upon which the reaction has been conducted. As shown in figure 12, the *E* olefin at C5=C6 has been the reaction site for cyclopropanation and the substituent effect at C3 has been extensively studied. Then to examine the versatility of the reaction, the C4 stereocenter, found to be the coordinating site, has been altered for studying its influence on the cyclopropanation. The glucofuranose, allofuranose, and the galactofuranose templates have been studied for this Simmons-Smith cyclopropanation reaction.

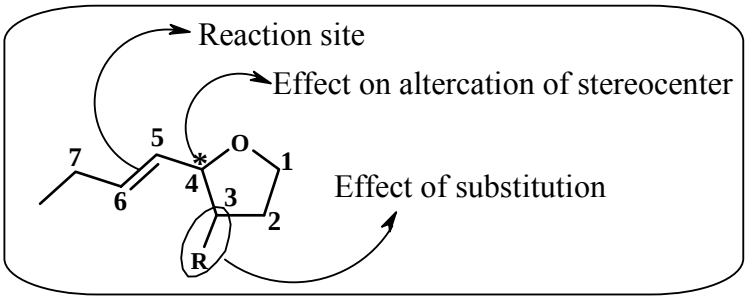
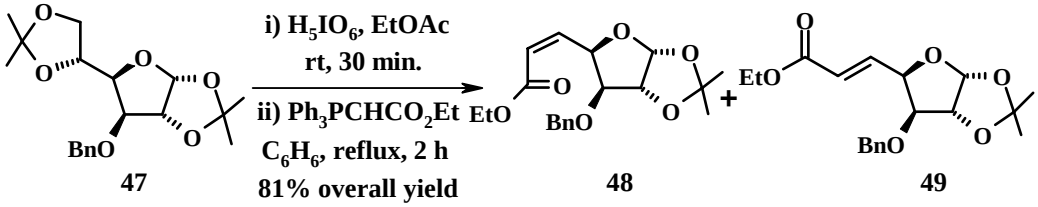


Figure 12: *Schematic presentation of the methodology*

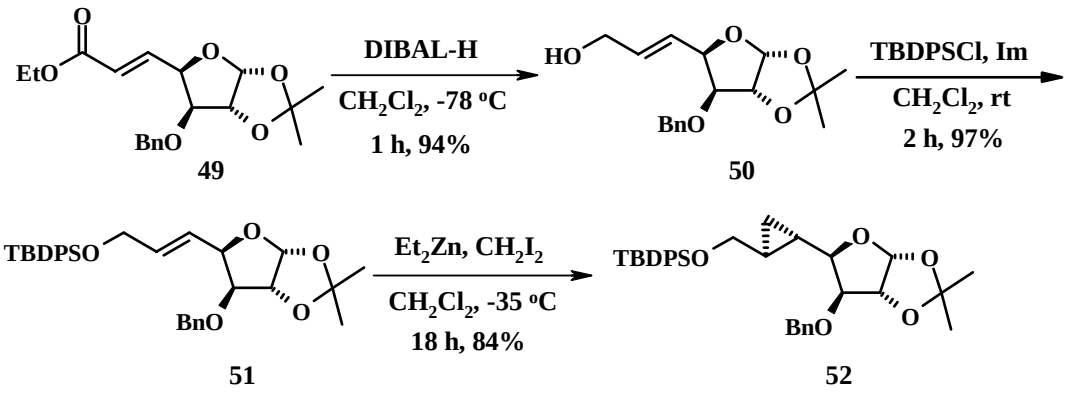
Entry 1: **Study on glucofuranose moiety**:

The known compound **47** was prepared from D(+)-glucose as described in chapter 1. The 5,6-*O*-isopropylidine was oxidatively cleaved by H_5IO_6 in EtOAc at room temperature to yield the 5-ulose derivative, which was quickly exposed to stable two carbon Wittig ylide, (ethoxycarbonylmethylene)triphenylphosphorane in refluxing benzene for 2 h. The result was the formation of geometrical isomers *Z* olefin **48** and *E* olefin **49** in 15:85 ratio. The products were indeed proven satisfactorily from the spectral data (Scheme 10). The PMR spectrum of compound **48** showed resonances at 6.30 ppm (dd, 1H, J = 6.6, 11.8 Hz) and 5.84 ppm (dd, 1H, J = 1.8, 11.8 Hz) for the cis olefin protons. For the *E* olefin **49**, the PMR spectrum showed the resonances at 6.88 ppm (dd, 1H, J = 5.1, 15.8 Hz) and 6.08 ppm (dd, 1H, J = 1.5, 15.8 Hz) for the trans olefin protons.



Scheme 10

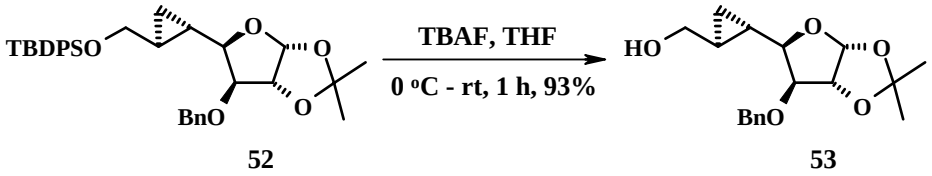
The *E* olefin **49** was reduced with DIBAL-H in CH_2Cl_2 at -78 °C to furnish the *E* allyl alcohol **50**. The characteristic *E* olefinic protons resonated at 5.79 ppm and 5.94 ppm with their mutual coupling constant being 15.7 Hz. The ^{13}C NMR, IR, mass spectral and elemental analysis supported the regioselective conversion. To inhibit the α achiral primary hydroxyl group from co-ordinating to the complex, it was confined by a bulky substituent. Accordingly the alcohol **50** was treated with TBDPSCl in presence of imidazole in CH_2Cl_2 at room temperature to yield the silyl ether **51** in quantitative yield. The manifestation of peaks at 562.75 for $[M+H_2O]^+$, 567.66 (base peak) for $[M+Na]^+$ and 583.67 for $[M+K]^+$ in the mass spectrum confirmed the protection. In ^1H NMR, the *t*-butyl protons appeared as a singlet at 0.98 ppm and the additional 10 aromatic protons appeared in the low magnetic field range of 7.08-7.63 ppm. In ^{13}C NMR the quaternary carbon linked directly to silicon (more electropositive to carbon) appeared to the right of the spectrum at 19.3 ppm and the methyl carbons of the t-butyl group appeared at 26.9 ppm. Now the substrate was well set for the Simmons-Smith cyclopropanation reaction.



Scheme 11

In our endeavor to check the substrate oriented selectivity, we took all precautions to avoid any other influences, particularly the reaction condition. The olefin was treated with Et_2Zn and CH_2I_2 in CH_2Cl_2 at -78 ^oC. Even after 5 h, thin layer chromatography study didn't show the progress of reaction. Gradually the reaction temperature was increased. Finally progress was observed at -40 ^oC to -35 ^oC, so the reaction was continued at -35 ^oC. TLC studies at regular intervals confirmed the reaction to be complete after 18 h. The spectral information from ^1H NMR, ^{13}C NMR studies of the

column purified product showed exclusive formation of single diastereomer **52**. The cyclopropane protons appeared cleanly in the range of 0.57 ppm to 0.84 ppm. The anomeric proton and the other α hydroxyl protons appeared as singular peaks. In ^{13}C NMR the cyclopropane methylene carbon appeared at 8.9 ppm and the methylidine carbons appeared at 13.7 ppm, 18.3 ppm, which additionally confirmed the stereospecific product **52** (Scheme 11).



52 **53**

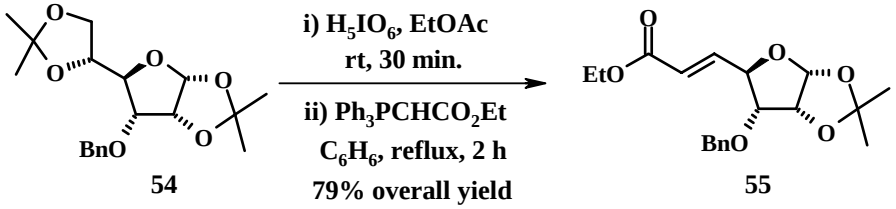
Scheme 12

The TBDPS group was next detached from the primary hydroxyl group by reacting with TBAF in THF at 0 ^{o}C. The cyclopropane methyl carbinol **53** thus formed was solid in nature. The alcohol compound on recrystallization from EtOAc/Pet ether formed thin needle like crystals, which couldn't be studied for single crystal X-ray crystallographic studies. Our attempts at recrystallization by changing the solvent system failed to produce X-ray study-appropriate crystals. In ^{1}H NMR spectrum, the characteristic TBDPS group protons disappeared; the cyclopropane protons were evident in the range of 0.58 ppm to 1.06 ppm. Other protons were at their appropriate magnetic field value, like the isopropylidine methyl protons at 1.23 and 1.37 ppm as two singlets, the exchangeable hydroxy proton at 1.92 ppm as a broad singlet, the anomeric proton at 5.84 as a doublet, and five aromatic protons at 7.27 as a multiplet (Scheme 12).

Entry 2: **Study on allofuranose moiety**:

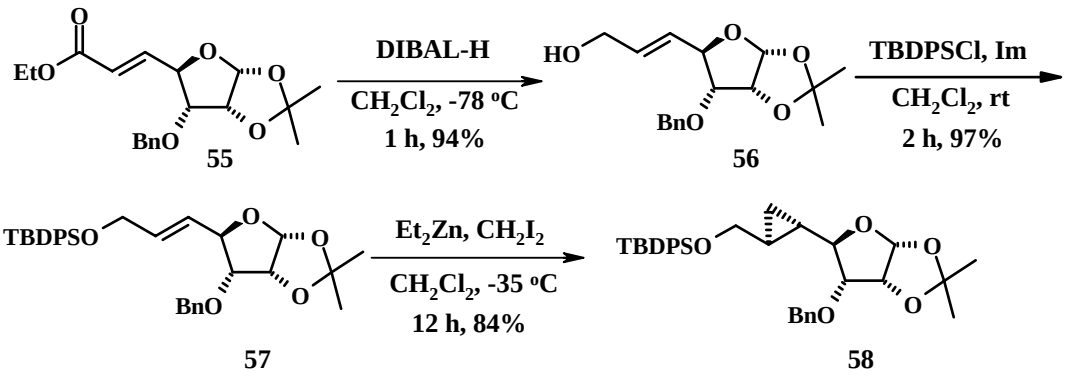
After confirming the stereoselective cyclopropanation, the effect of substitution at C3 position of the furanose ring on cyclopropanation was experimented on next. In the first attempt, the C3 stereocenter was inverted to form the allofuranose moiety and the effect on facial selectivity of the cyclopropanation was studied. Thus compound **54** (prepared earlier in chapter 1) was exposed to the same sequence of reactions. The 5,6-isopropylidine group was removed directly by H_5IO_6 in EtOAc at room temperature to yield the 5-ulose derivative, which without characterization was exposed to

(ethoxycarbonylmethylene)triphenylphosphorane in benzene under reflux condition to furnish the complete stereoselective *E* olefin **55**. Presence of peaks at 6.94 ppm and 6.15 ppm as dd with mutual coupling constant 15.73 Hz accounted for the trans olefin. A triplet at 1.30 ppm (J = 7.1 Hz) and a quartet at 4.23 ppm (J = 7.1 Hz) in ^{1}H NMR signified the ethyl ester functionality, which was additionally supported by the appearance of corresponding carbons at 14.2 ppm, 72.4 ppm respectively alongwith the carbonyl carbon at 165.9 ppm in ^{13}C NMR spectrum. All other protons and carbons were located as expected. In mass spectra $[M+Na]^+$ appeared at 371.31 and $[M+K]^+$ appeared at 387.34 (Scheme 13).



Scheme 13

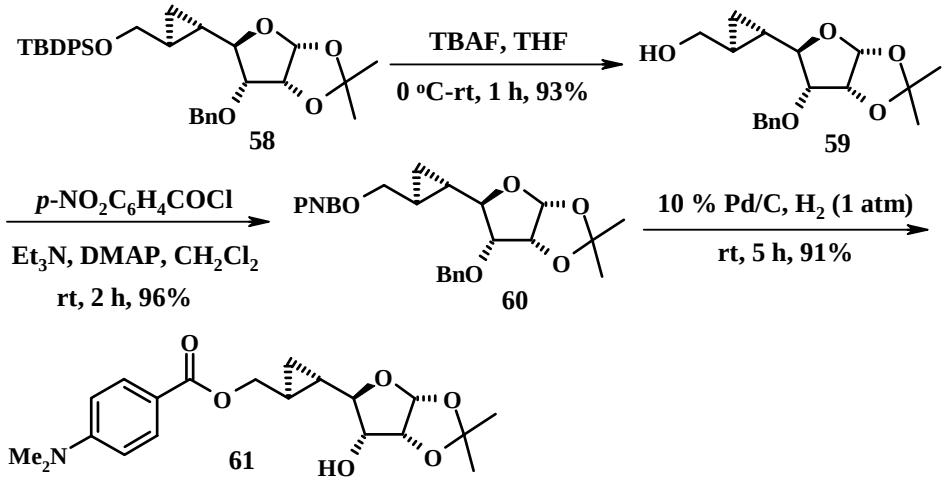
The ester group was then selectively reduced with DIBAL-H in CH_2Cl_2 at -78 ^{o}C to furnish the *E* allyl alcohol **56**. Dislocation of the ethoxy carbonyl peaks and appearance of a broad singlet at 1.66 ppm for the exchangeable hydroxyl proton confirmed the conversion. Now the alcohol was inactivated by reacting with TBDPSCl, imidazole in CH_2Cl_2 at room temperature to produce the silyl ether compound **57**. The conversion was confirmed by the presence of characteristic *t*-butyldiphenylsilyl peaks in spectral study, in which the *t*-butyl methyl protons appeared as a singlet at 0.99 ppm, the additional ten aromatic protons surfaced in the range 7.17 ppm to 7.61 ppm. The PMR spectral data was substantially confirmed by CMR spectra, mass spectra and elemental analysis study. The key transformation Simmons-Smith cyclopropanation was then reacted by exposure of the olefin **57** to Et_2Zn, CH_2I_2 in CH_2Cl_2 at -35 ^{o}C (the optimized condition for the previous example) for 12h. The resulting cyclopropane **58** was found to be a single diastereomer. The cyclopropane protons were located in the range 0.55 ppm to 1.28 ppm with other protons appeared as singular peaks with well explained coupling patterns at their appropriate values (Scheme 14).



Scheme 14

Attempts for determination of stereochemistry by derivatisation method:

Once again derivatisation was resorted to the substrate **58** for transforming it to a crystalline solid compound. The TBDPS ether compound was decomposed to the free hydroxyl compound **59** by treating with TBAF in THF at 0 °C in quantitative yield. The product **59** was fully characterized by ^{1}H, ^{13}C, DEPT, IR, HRMS spectral studies. Attempts for getting single crystal of the alcohol **59** failed despite of its solid nature.



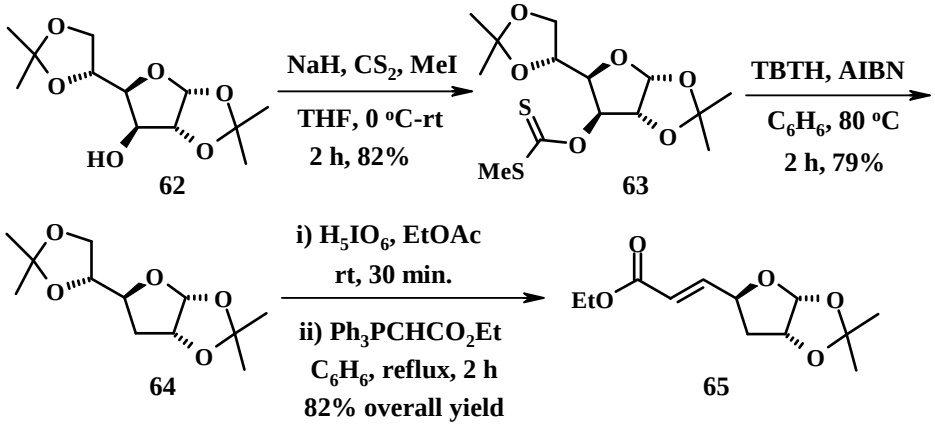
Scheme 15

The hydroxyl group was then derivatised to corresponding *p*-nitrobenzoate ester **60** by reacting with *p*-$NO_2C_6H_4COCl$, Et_3N, and DMAP in CH_2Cl_2 at room temperature in 96% yield. The downfield shift of the associated methylene protons signaled the ester formation. The liquid nature of the product couldn't serve our purpose. Then to deprotect the benzyl ether, the compound **60** was hydrogenated at 1 atm. H_2 pressure with 10%

Pd/C in MeOH at room temperature. This gave an over reacted product **61**, in which the nitro group was reduced and the aniline was methylated by the solvent MeOH with the assistance of the mild acidic nature of the catalyst. The structure was confirmed by the combined spectral studies. But to our disappointment, the compound was liquid (Scheme 15).

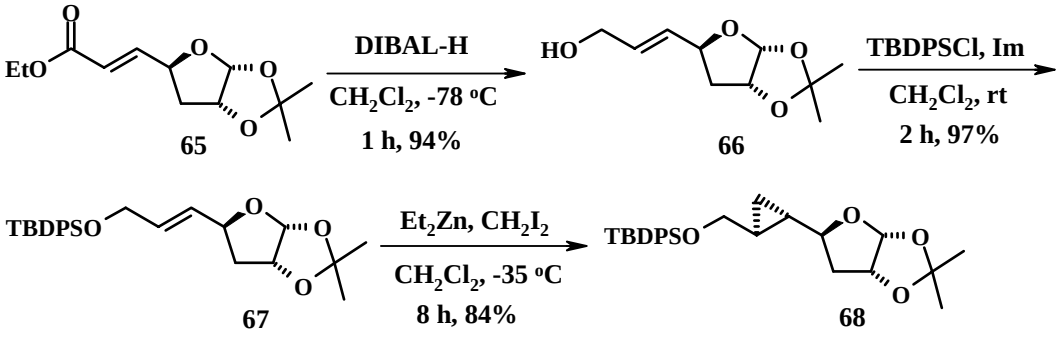
Entry 3: No substitution effect:

The result for achiral C3 position was next investigated. Avoiding any steric control due to substituents at C3, the stereoselectivity in cyclopropanation reaction was examined. For achieving a chiral C3 carbon, a very common established practice is to deoxygenate the hydroxyl group of 1,2:5,6-*O*-diisopropylidine-glucofuranose (**62**) with the Barton-McCombie method. Oxidative cleavage of the 5,6-*O*-isopropylidine group with H_5IO_6 in EtOAc at room temperature provided the aldehyde, which on subsequent treatment with (ethoxycarbonylmethylene) triphenylphosphorane in benzene under reflux condition provided *E* olefin **65** as the major product with trace amount of the *Z* olefin (seen as a cap to the major spot in TLC). The slower moving *E* olefin was purified by flash column chromatography. The *E* olefin was portrayed fully by spectral, analytical studies. In ^{1}H NMR, the olefin protons were visible at 6.08 and 6.92 ppm as dd with mutual coupling constant of 15.7 Hz, while the corresponding carbons surfaced at 121.5 and 144.9 ppm. The downfield appearance of β-olefin proton (6.9 ppm) and the corresponding carbon (144.9 ppm) signifies the conjugation of the olefin (Scheme 16).



Scheme 16

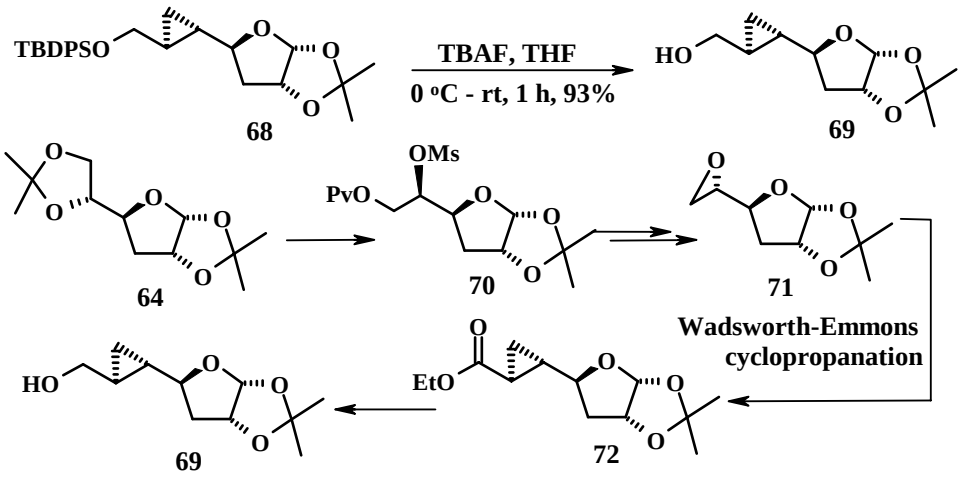
The ester group was then reduced with DIBAL-H in CH_2Cl_2 at -78 ^oC to yield the *E* allylic alcohol **66**. The product was confirmed by the disappearance of the significant ethoxy carbonyl peaks in spectral studies. There was a remarkable upfield shift of the β olefin proton due to loss of conjugation. The primary hydroxyl group was now confined by reaction with TBDPSCl, imidazole in CH_2Cl_2 at room temperature. The key step of the methodology was now to operate on the olefin **67** by exposing it to Et_2Zn, CH_2I_2 in CH_2Cl_2 at -35 ^oC. The column chromatography purified product **68** was found to be stereospecific from spectral studies. The magnetically hindered cyclopropane protons appeared in the high magnetic field region between 0.44 ppm to 1.06 ppm. The furanose ring C3 methylene protons appeared at 1.63 ppm (ddd, 1H, *J* = 4.7, 10.8, 13.5 Hz) and 2.18 ppm (dd, 1H, *J* = 4.2, 13.5 Hz) and all other protons and carbons emerged at their apposite field value as singular peaks (Scheme 17).



Scheme 17

Determination of stereochemistry by correlation method:

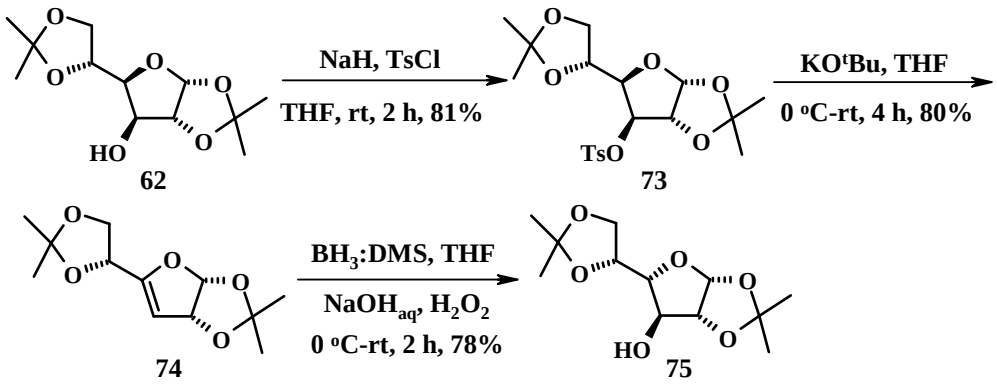
The silyl ether **68** was decomposed to the corresponding alcohol **69** with the help of TBAF in THF at 0 ^oC in 84% yield. Absence of peaks belonging to the TBDPS group and appearance of an exchangeable broad singlet at 2.18 ppm for the free hydroxyl proton unambiguously supported the deprotection reaction with additional evidences from HRMS study. At this juncture our synthetic product could be correlated to the reported compound.[48] Wadsworth-Emmons cyclopropanation method has been utilized for the synthesis of the reported compound (Scheme 18). The ^1H NMR, ^{13}C NMR of both compounds were in good agreement with each other alongwith their close specific rotation values {$[\alpha]_D$ +10.30 (*c* 1.0, $CHCl_3$), lit. $[\alpha]_D$ +8.20 (*c* 1.3, $CHCl_3$)}.



Scheme 18

Entry 4: Study on galactofuranose moiety:

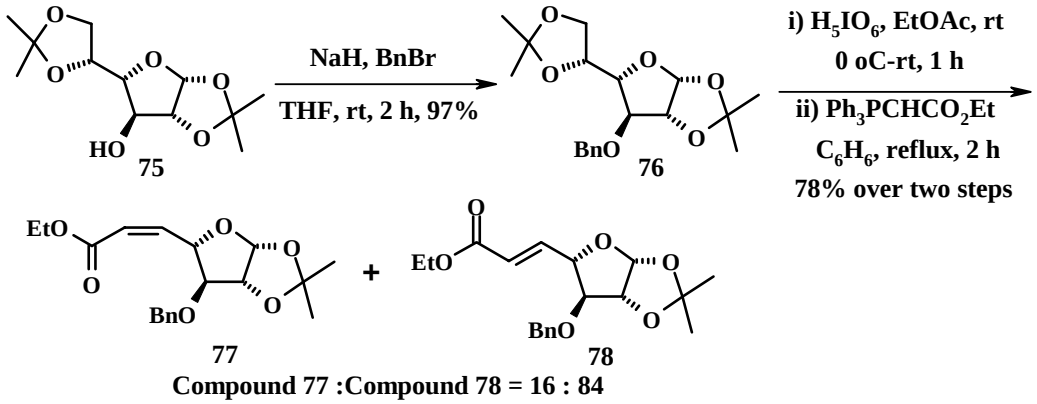
Completing the study on for glucofuranose, allofuranose and C3 achiral substrates and concluding the exclusive Stereoselective Simmons-Smith cyclopropanation despite the substitutional changes at C3 position, we focused on galactofuranose substrates. The basic difference between the substrates would be the stereochemical configuration at C4. This would certainly extend the scope of our methodology.



Scheme 19

D(+)-galactose does not form furanose ring on exposure to acetone in acidic medium and D(+)-glucose and D(+)-galactose are C4 epimers. So we inverted the stereocenter at C4 of glucose-diacetonide (**62**) by a sequence of *anti*-dehydration and *syn*-hydration. Accordingly the secondary hydroxyl group of GDA (**62)** was tosylated by reaction with NaH, TsCl in THF at room temperature. Then *anti* elimination of *p*-

toluenesulphonic acid from compound **73** was achieved by the reaction of sulphonate with KO^{t}Bu in THF at room temperature. The double bond obtained was hydrated by hydroboration-oxidation sequence with BH_3:DMS in THF at 0 ^oC to yield 1,2;5,6-*O*-isopropylidine-galactofuranose (**75**) in good yield (Scheme 19).



Scheme 20

The secondary hydroxyl group was then protected as its benzyl ether by reacting with NaH, BnBr in THF at room temperature. Oxidative cleavage of the isopropylidine group by H_5IO_6 in EtOAc followed by Wittig homologation with (ethoxycarbonylmethylene)triphenylphosphorane in benzene under reflux condition resulted *E* olefin **78** and *Z* olefin **77** in 84:16 ratio. The minor *Z* isomer **77** was characterized by the olefinic protons appearing at 6.54 ppm (dd, 1H, J = 7.1, 11.8 Hz) and 5.79 ppm (dd, 1H, J = 2.0, 11.8 Hz) in PMR spectrum. The major *E* isomer **78** was characterized by the olefinic protons at 6.07 ppm and 7.00 ppm with mutual coupling constant 15.6 Hz (Scheme 20).

2D NMR study of both ester compounds:

2D NMR studies of both olefins assigned their structural features adequately. At first the COSY analysis allocated the connectivity for both the compounds and subsequent n*O*e analysis clearly picturised the spatial proximity of the protons. For the *Z* olefin **77**, strong n*O*e interactions were observed between the olefinic protons at 5.79 ppm and 6.54 ppm; H1 (6.02 ppm) and H2 (4.62 ppm). No relevant n*O*e interaction between H2 (4.62 ppm) and H3 (4.06 ppm) claimed the *Z* configuration of the olefin alongwith *anti* nature of H2 and H3. Where as, in the major *E* olefin **78**, there was a very weak n*O*e interaction

between the olefinic protons at 6.07 ppm and 7.00 ppm. Strong n*O*e interactions were observed between H1 (5.95 ppm) and H2 (4.67 ppm); H2 (4.62 ppm) and H4 (4.62 ppm). This concluded the *syn* nature of H1, H2 and H4 in the furanose ring and the *E* configuration of the olefin **78** (Figure 13).

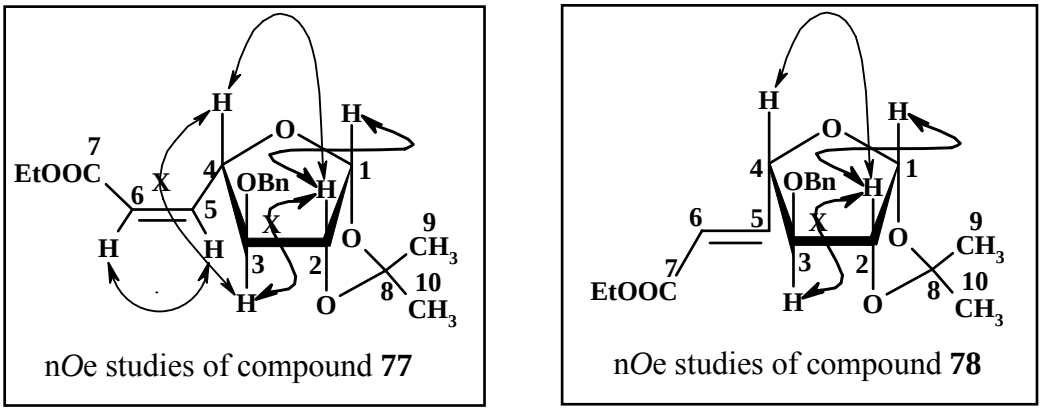
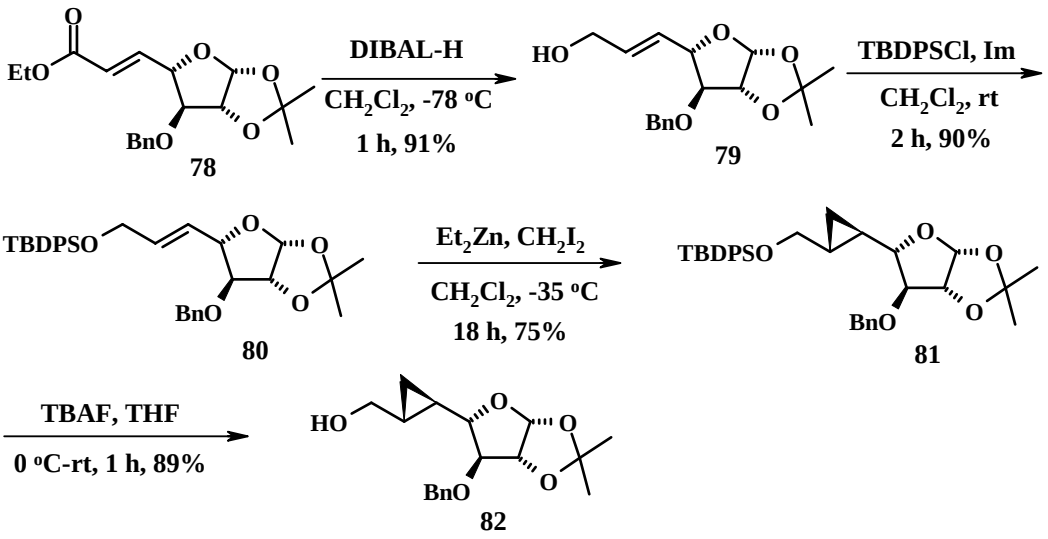


Figure 13

The ester group was next selectively reduced to the corresponding allyl alcohol **79** on treatment with DIBAL-H in CH_2Cl_2 at -78 ^oC. The *E* allyl alcohol was confirmed by the presence of a broad singlet peak at 1.61 ppm and the disappearance of ethoxy carbonyl protons. The hydroxyl group was confined to its silyl ether derivative **80** by reacting with TBDPSCl, imidazole in CH_2Cl_2 at room temperature. The olefin was proved by the resonances at 5.84 ppm and 6.00 ppm with mutual coupling constant of 15.52 Hz. The surge in the integration values in the aromatic region (3xPh = 15H) and the characteristic singlet at 1.09 ppm ($3xCH_3$ = 9H) duly supported it. The olefin **80** was then subjected to Simmons-Smith cyclopropanation condition, which yielded a complete stereospecific product **81**. The product **81** was characterized from spectral studies. The cyclopropane methylene protons appeared at 0.66 ppm (dd, 2H, *J* = 6.44, 7.03 Hz), the other two methine protons appeared as multiplets at 1.03 and 1.26 ppm. Mass spectral analysis and elemental analysis substantially proved the Stereoselective cyclopropanation product. The silyl ether compound was next treated with TBAF in THF at 0 °C to give the corresponding hydroxy compound **82**. The structural proof of **82** was codified from the ^1H NMR, ^{13}C NMR and HRMS studies (Scheme 21).



Scheme 21

Plausible mechanistic path:

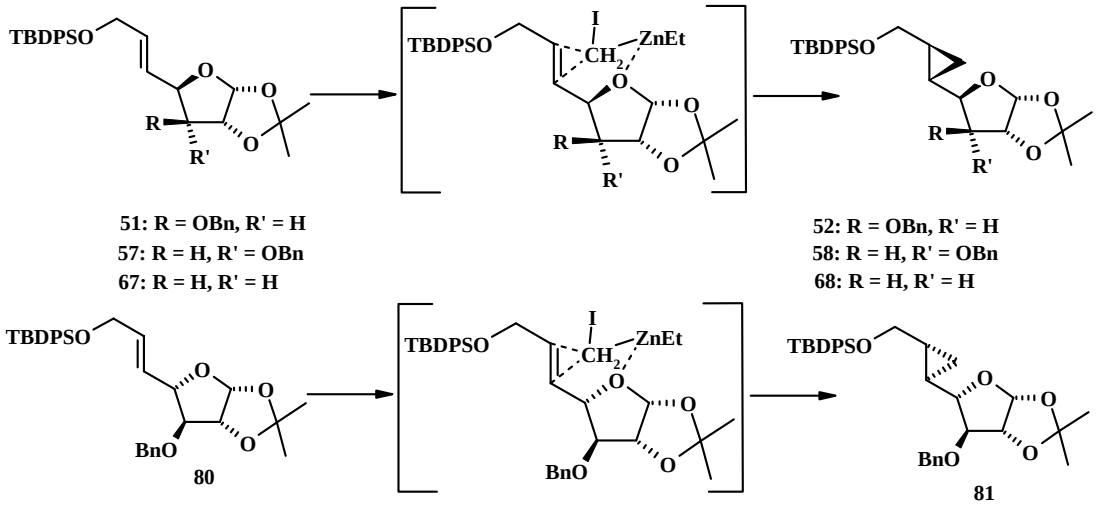


Figure 14

As observed in the above carbohydrate templates, differing in the substituent patterns, the outcome of the Simmons-Smith cyclopropanation reaction has been stereospecific. The first three entries led us to assume that the cyclopropanation reaction is not influenced by the steric constraints due to the substituent at C3. Then entry 4 extends the idea to Galactofuranose template, wherein the C4 stereocenter is inverted to those of entries 1-3. Following the reports from literature,[49] that the Simmons-Smith cyclopropanation of chiral secondary alcohols progress through a transition state

comprising of coordination of the alcohol oxygen to the Zinc atom, we propose the mechanistic path in our format (Figure 14). The confinement of the primary allyl hydroxy group leaves only the furanose ring oxygen as the sole controlling element in the cyclopropanation reaction.

EPILOGUE:

In conclusion, we have just discussed a generalized methodology explaining Stereospecific Simmons-Smith cyclopropanation reaction on carbohydrate templates. This methodology would serve as a platform for synthesis of chiral cyclopropanated natural products from carbohydrates. We have also utilized this methodology for synthesis of basiliskamides A and B, which has been explained in the following section.

General Procedures:

(A) Two carbon Wittig homologation: The diacetonide compound (1 equiv.) was taken in EtOAc and cooled to 0 ^{o}C. To it 1.2 equivalents of periodic acid was added and the reaction mixture was warmed to room temperature. After 30-45 mins, the suspension mixture was filtered through a pad of Celite and concentrated to get the crude aldehyde, which was taken for the Wittig reaction without further purification. The aldehyde in minimum amount of anhydrous toluene was added to a solution of (carboethoxymethylene) triphenylphoshorane in toluene at 80 °C. The reaction mixture was stirred at the same temperature for 1-3 h. After completion of the reaction, the organic solvent was evaporated in vacuo and the residue was purified by column chromatography to get the pure α, β-unsaturated olefin.

(B) Reduction of α,β-unsaturated ester to allyl alcohol: The α, β-unsaturated olefin was dissolved in anhydrous CH_2Cl_2 and cooled to -78 °C. To it 2.5 equivalents of DIBAL-H in toluene was added slowly. The reaction mixture was stirred at the same temperature for 1-2 h and then quenched with saturated aqueous sodium potassium tartarate. After stirring the reaction mixture for 30 min. at room temperature, the clear biphasic mixture was separated and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated and purified by column chromatography to get the pure allylic alcohol.

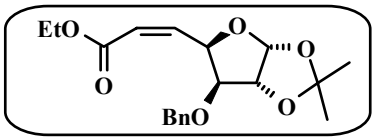
(C) TBDPS protection of allyl alcohol: The allylic alcohol was dissolved in anhydrous CH_2Cl_2. To it 1.5 equivalents of imidazole was added followed by 1.2 equivalents of TBDPSCl and the reaction mixture was stirred at room temperature for 1-2 h. After completion of the reaction, the organic solvent was concentrated in vacuo and the crude product was purified by column chromatography to furnish the *tert*-butyldiphenylsillyl ether compound.

(D) Cyclopropanation reaction: The CH_2Cl_2 solution of the allyl OTBDPS compound was cooled to -35 °C and to it 5 equivalents of Et_2Zn was added slowly followed by 10 equivalents of CH_2I_2. The white suspension thus formed was stirred at -35 °C for 8-24 h.

After completion of the reaction, it was quenched with aqueous NH_4Cl. The suspension mixture was filtered through a sintered funnel and the biphasic mixture was separated. The aqueous layer was extracted with EtOAc and the combined organic layer was washed with brine, dried over Na_2SO_4, concentrated. The crude product was purified by flash column chromatography to get the pure cyclopropane compound.

(E) Deprotection of the TBDPS ether: The OTBDPS compound was dissolved in THF and cooled to 0 °C. To it, 1M. THF solution of TBAF was added slowly. The reaction mixture was warmed to room temperature and stirred for 30 min-1 h. After completion of the reaction, it was quenched with aqueous NH_4Cl. The aqueous organic solvent mixture was separated and the aqueous layer was extracted with EtOAc. The organic extracts were added, dried over Na_2SO_4, concentrated and purified by column chromatography to achieve the cyclopropane alcohol.

(*Z*)-ethyl 3-((3a*R*,5*R*,6*S*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)acrylate (**48**):

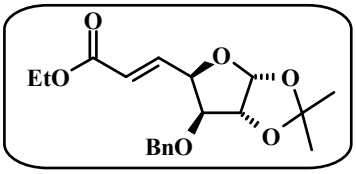


Following general procedure A, compound **48** (12%, colorless liquid) was obtained as a minor product from compound **47**.

Mol. Formula	:	$C_{19}H_{24}O_6$
Mol. Weight	:	348.40
ESI-MS *m/z*	:	371.51 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	2984, 2933, 1718, 1654, 1454, 1416, 1384, 1195, 1165, 1077, 1027, 830, 738, 699
Elemental Analysis	:	Calcd: C, 65.50; H, 6.94 Found: C, 65.61; H, 7.03
$[\alpha]_D^{25}$	:	-214.2 (*c* 0.8, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 1.19 (t, 3H, *J* = 7.1 Hz), 1.25 (s, 3H), 1.44 (s, 3H), 4.04 (q, 2H, *J* = 7.1 Hz), 4.20 (d, 1H, *J* = 3.4 Hz), 4.38 (d, 1H,

		J = 12.0 Hz), 4.55 (d, 1H, *J* = 3.8 Hz), 4.54 (d, 1H, *J* = 12.0 Hz), 5.54 (ddd, 1H, *J* = 1.8, 3.4, 6.7 Hz), 5.84 (dd, 1H, 1.8, 11.8 Hz), 5.92 (d, 1H, *J* = 3.8 Hz), 6.30 (dd, 1H, *J* = 6.6, 11.8 Hz), 7.15-7.27 (m, 5H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 14.2 (q), 26.5 (q), 27.0 (q), 60.3 (t), 72.2 (t), 78.2 (d), 83.2 (d), 83.9 (d), 105.2 (d), 111.8 (s), 121.1 (d), 127.7 (d), 127.8 (d), 128.4 (d), 137.5 (s), 145.4 (d), 165.4 (s)

(*E*)-ethyl 3-((3a*R*,5*R*,6*S*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)acrylate (**49**):

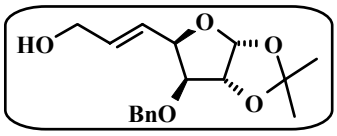


Following general procedure A, compound **47** was converted to compound **49** (69%, major isomer) as a colorless liquid.

Mol. Formula	:	$C_{19}H_{24}O_6$
Mol. Weight	:	348.40
ESI-MS *m/z*	:	371.56 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	2985, 2935, 1719, 1666, 1455, 1374, 1304, 1264, 1180, 1165, 1077, 1028, 886, 859, 753, 699
Elemental Analysis	:	Calcd: C, 65.50; H, 6.94 Found: C, 65.51; H, 7.07
$[\alpha]_D^{25}$	:	-33.4 (*c* 1, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 1.24 (t, 3H, *J* = 7.1 Hz), 1.25 (s, 3H), 1.41 (s, 3H), 3.88 (d, 1H, *J* = 3.2 Hz), 4.15 (q, 2H, *J* = 7.1 Hz), 4.42 (d, 1H, *J* = 12.1 Hz), 4.55 (d, 1H, *J* = 3.8 Hz), 4.56 (d, 1H, *J* = 12.1 Hz), 4.71 (m, 1H), 5.90 (d, 1H, J = 3.8 Hz), 6.08 (dd, 1H, *J* = 1.5, 15.8 Hz), 6.88 (dd, 1H, *J* = 5.1, 15.8 Hz), 7.19-7.26 (m, 5H)

^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 14.3 (q), 26.3 (q), 26.9 (q), 60.3 (t), 72.2 (t), 79.5 (d), 82.9 (d), 83.0 (d), 105.0 (d), 111.9 (s), 123.3 (d), 127.8 (d), 128.0 (d), 128.5 (d), 137.1 (s), 141.4 (d), 165.9 (s)

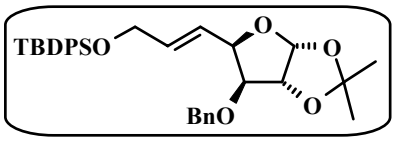
(*E*)-3-((3a*R*,5*R*,6*S*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)prop-2-en-1-ol (**50**):



Following general procedure B, compound **49** was converted to compound **50** (94%) as a thick colorless liquid.

Mol. Formula	:	$C_{17}H_{22}O_5$
Mol. Weight	:	306.36
ESI-MS *m/z*	:	329.49 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 66.65; H, 7.24 Found: C, 66.84; H, 7.39
$[\alpha]_D^{25}$	:	-50.6 (*c* 2, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 1.25 (s, 3H), 1.42 (s, 3H), 1.79 (bs, 1H), 3.78 (d, 1H, *J* = 3.1 Hz), 4.09 (m, 2H), 4.45 (d, 1H, *J* = 12.1 Hz), 4.57 (m, 2H), 4.59 (d, 1H, *J* = 12.1 Hz), 5.79 (ddt, 1H, *J* = 1.3, 6.7, 15.7 Hz), 5.87 (d, 1H, *J* = 3.8 Hz), 5.94 (dt, 1H, *J* = 3.8, 15.7 Hz), 7.24 (m, 5H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 26.2 (q), 26.8 (q), 62.9 (t), 72.1 (t), 80.6 (d), 82.9 (d), 83.3 (d), 104.7 (d), 111.5 (s), 124.9 (d), 127.7 (d), 127.9 (d), 128.4 (d), 134.2 (d), 137.4 (s)

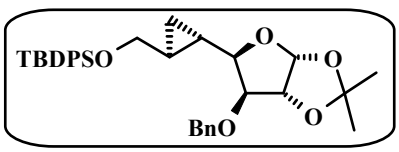
((*E*)-3-((3a*R*,5*R*,6*S*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)allyloxy)(*tert*-butyl)diphenylsilane (**51**):



Following general procedure C, compound **50** was converted to compound **51** (97%) as a light yellow liquid.

Mol. Formula	:	$C_{33}H_{40}O_5Si$
Mol. Weight	:	544.77
ESI-MS *m/z*	:	567.66 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 72.76; H, 7.40; Si, 5.16 Found: C, 72.95; H, 7.53; Si, 5.29
$[\alpha]_D^{25}$	:	-29.7 (*c* 1, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.99 (s, 9H), 1.25 (s, 3H), 1.43 (s, 3H), 3.78 (d, 1H, *J* = 3.0 Hz), 4.17 (d, 2H, *J* = 3.4 Hz), 4.48 (d, 1H, *J* = 12.1 Hz), 4.58 (d, 1H, *J* = 12.1 Hz), 4.59 (dt, 2H, *J* = 3.5, 9.4 Hz), 5.88 (dt, 1H, *J* = 3.2, 15.5 Hz), 5.90 (d, 1H, *J* = 3.9 Hz), 6.01 (ddt, 1H, *J* = 1.4, 6.5, 15.5 Hz), 7.25 (m, 11H), 7.60 (m, 4H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 19.3 (s), 26.3 (q), 26.9 (2q), 63.6 (t), 72.1 (t), 80.9 (d), 82.9 (d), 83.3 (d), 104.7 (d), 111.4 (s), 123.1 (d), 127.5 (d), 127.7 (d), 127.8 (d), 128.4 (d), 129.7 (d), 133.5 (s), 133.9 (d), 135.5 (d), 137.6 (s)

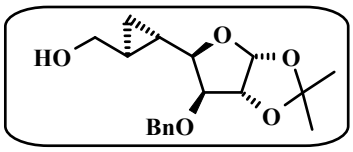
(((1*S*,2*S*)-2-((3a*R*,5*R*,6*S*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)cyclopropyl)methoxy)(*tert*-butyl)diphenylsilane (**52**):



Following general procedure D, compound **51** was converted to compound **52** (84%) as colorless syrup.

Mol. Formula	:	$C_{34}H_{42}O_5Si$
Mol. Weight	:	558.80
ESI-MS *m/z*	:	581.90 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 73.08; H, 7.58; Si, 5.03 Found: C, 72.89; H, 7.73; Si, 5.21
$[\alpha]_D^{25}$	:	-2.6 (*c* 1, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.61 (m, 2H), 0.81 (m, 1H), 0.96 (s, 9H), 1.22 (s, 3H), 1.37 (s, 3H), 1.51 (m, 1H), 3.36 (dd, 1H, *J* = 2.9, 9.2 Hz), 3.44 (dd, 1H, *J* = 6.0, 10.7 Hz), 3.57 (dd, 1H, *J* = 5.5, 10.7 Hz), 3.72 (d, 1H, *J* = 2.9 Hz), 4.49 (d, 1H, *J* = 3.9 Hz), 4.53 (d, 2H, *J* = 1.6 Hz), 5.82 (d, 1H, *J* = 3.9 Hz), 7.25 (m, 11H), 7.56 (m, 4H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 8.9 (t), 13.7 (d), 18.3 (d), 19.2 (s), 26.1 (q), 26.7 (q), 26.9 (q), 66.0 (t), 72.1 (t), 82.3 (d), 82.7 (d), 85.0 (d), 104.6 (d), 111.1 (s), 127.4 (d), 127.6 (d), 128.4 (d), 129.6 (d), 133.8 (s), 135.6 (d), 137.7 (s)

((1*S*,2*S*)-2-((3a*R*,5*R*,6*S*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)cyclopropyl)methanol (**53**):

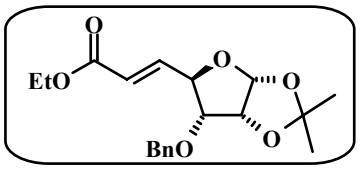


Following general procedure E, compound **52** was converted to compound **53** (93%) as white solid.

Mol. Formula	:	$C_{18}H_{24}O_5$
Mol. Weight	:	320.39
ESI-MS *m/z*	:	343.40 $[M+Na]^+$

Elemental Analysis	:	Calcd: C, 67.48; H, 7.55 Found: C, 67.54; H, 7.69
$[\alpha]_D^{25}$	:	-55.2 (*c* 1, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.63 (m, 2H), 1.02 (m, 2H), 1.23 (s, 3H), 1.37 (s, 3H), 1.92 (bs, 1H), 3.18 (dd, 1H, *J* = 7.5, 11.2 Hz), 3.39 (dd, 1H, *J* = 3.2, 9.1 Hz), 3.48 (dd, 1H, *J* = 6.2, 11.2 Hz), 3.79 (d, 1H, *J* = 3.3 Hz), 4.49 (d, 1H, *J* = 11.9 Hz), 4.56 (d, 1H, *J* = 3.9 Hz), 4.68 (d, 1H, *J* = 11.9 Hz), 5.84 (d, 1H, *J* = 3.9), 7.27 (m, 5H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 9.7 (t), 14.5 (d), 18.3 (d), 26.1 (q), 26.7 (q), 66.1 (t), 71.8 (t), 82.2 (d), 82.5 (d), 84.5 (d), 104.6 (d), 111.2 (s), 127.7 (d), 128.0 (d), 128.5 (d), 137.3 (s)

(*E*)-ethyl 3-((3a*R*,5*R*,6*R*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)acrylate (**55**):

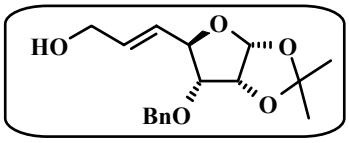


Following general procedure A, compound **54** was converted to compound **55** (79%) exclusively as a colorless liquid.

Mol. Formula	:	$C_{19}H_{24}O_6$
Mol. Weight	:	348.40
ESI-MS *m/z*	:	371.31 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 65.50; H, 6.94 Found: C, 66.64; H, 7.19
$[\alpha]_D^{25}$	:	+51.2 (*c* 2, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 1.30 (t, 3H, *J* = 7.1 Hz), 1.36 (s, 3H), 1.61 (s, 3H), 3.52 (dd, 1H, *J* = 4.3, 9.1 Hz), 4.21 (q, 2H, *J* = 7.1 Hz), 4.58 (d, 1H, *J* = 12.0 Hz), 4.60 (m, 2H), 4.73 (d, 1H, *J* = 12.0

		Hz), 5.76 (d, 1H, *J* = 3.7 Hz), 6.11 (dd, 1H, *J* = 1.6, 15.7 Hz), 6.91 (dd, 1H, *J* = 5.1, 15.7 Hz), 7.34 (m, 5H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 14.2 (q), 26.5 (q), 26.8 (q), 60.4 (t), 72.4 (t), 76.9 (d), 77.4 (d), 81.9 (d), 104.0 (d), 113.1 (s), 122.4 (d), 128.0 (d), 128.1 (d), 128.5 (d), 137.1 (s), 143.4 (d), 165.9 (s)

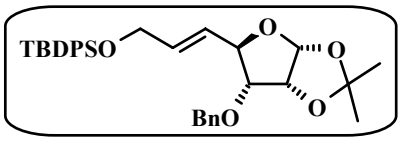
(*E*)-3-((3a*R*,5*R*,6*R*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)prop-2-en-1-ol (**56**):



Following general procedure B, compound **55** was converted to compound **56** (94%) as colorless syrup.

Mol. Formula	:	$C_{17}H_{22}O_5$
Mol. Weight	:	306.36
ESI-MS *m/z*	:	329.28 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 66.65; H, 7.24 Found: C, 66.74; H, 7.36
$[\alpha]_D^{25}$	:	+60.7 (*c* 2, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 1.36 (s, 3H), 1.62 (s, 3H), 1.66 (bs, 1H), 3.49 (dd, 1H, *J* = 4.3, 9.0 Hz), 4.14 (dd, 2H, *J* = 1.1, 5.1 Hz), 4.47 (dd, 1H, *J* = 7.2, 8.6 Hz), 4.56 (d, 1H, *J* = 12.1 Hz), 4.57 (t, 1H, *J* = 4.0 Hz), 4.75 (d, 1H, *J* = 12.1 Hz), 5.66 (ddt, 1H, *J* = 1.5, 6.9, 15.5 Hz), 5.72 (d, 1H, *J* = 3.8 Hz), 6.02 (ddt, 1H, *J* = 0.6, 5.1, 15.5 Hz), 7.34 (m, 5H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 26.5 (q), 26.7 (q), 62.7 (t), 72.3 (t), 77.5 (d), 78.1 (d), 81.9 (d), 103.7 (d), 112.9 (s), 127.3 (d), 128.0 (d), 128.1 (d), 128.4 (d), 133.9 (d), 137.5 (s)

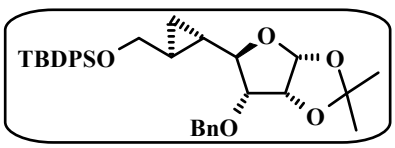
((*E*)-3-((3a*R*,5*R*,6*R*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)allyloxy)(*tert*-butyl)diphenylsilane (**57**):



Following general procedure C, compound **56** was converted to compound **57** (97%) as a colorless liquid.

Mol. Formula	:	$C_{33}H_{40}O_5Si$
Mol. Weight	:	544.77
ESI-MS *m/z*	:	567.18 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 72.76; H, 7.40; Si, 5.16 Found: C, 72.87; H, 7.60; Si, 5.24
$[\alpha]_D^{25}$	:	+24.4 (*c* 2.4, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.99 (s, 9H), 1.28 (s, 3H), 1.54 (s, 3H), 3.42 (dd, 1H, *J* = 4.3, 8.9 Hz), 4.15 (d, 2H, *J* = 3.2 Hz), 4.45 (m, 2H), 4.54 (d, 1H, *J* = 12.2 Hz), 4.67 (d, 1H, *J* = 12.2 Hz), 5.65 (d, 1H, *J* = 3.7 Hz), 5.74 (ddt, 1H, *J* = 1.3, 6.6, 15.4 Hz), 5.91 (ddt, 1H, *J* = 0.6, 3.9, 15.4 Hz), 7.26 (m, 11H), 7.61 (m, 4H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 19.3 (s), 26.5 (q), 26.8 (q), 26.9 (q), 63.5 (t), 72.2 (t), 77.6 (d), 78.4 (d), 81.8 (d), 103.6 (d), 112.8 (s), 126.0 (d), 127.7 (d), 127.9 (d), 128.4 (d), 129.7 (d), 133.5 (d), 133.7 (d), 134.8 (s), 135.5(d), 137.5 (s)

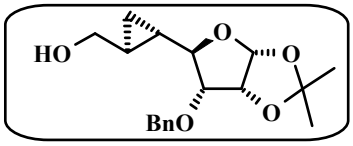
(((1*S*,2*S*)-2-((3a*R*,5*R*,6*R*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)cyclopropyl)methoxy)(*tert*-butyl)diphenylsilane (**58**):



Following general procedure D, compound **57** was converted to compound **58** (84%) as a colorless liquid.

Mol. Formula	:	$C_{34}H_{42}O_5Si$
Mol. Weight	:	558.80
ESI-MS *m/z*	:	581.44 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 73.08; H, 7.58; Si, 5.03 Found: C, 72.94; H, 7.69; Si, 5.13
$[\alpha]_D^{25}$	:	+54.0 (*c* 1.5, $CHCl_3$)
^{1}H NMR (400 MHz, $CDCl_3$)	:	δ 0.55 (m, 2H), 0.87 (m, 1H), 1.06 (s, 9H), 1.28 (m, 1H), 1.34 (s, 3H), 1.57 (s, 3H), 3.50 (dd, 1H, *J* = 4.3, 8.8 Hz), 3.55 (dd, 1H, *J* = 5.9, 10.6 Hz), 3.59 (dd, 1H, *J* = 7.3, 8.8 Hz), 3.74 (dd, 1H, *J* = 5.0, 10.6 Hz), 4.51 (t, 1H, *J* = 4.1 Hz), 4.59 (d, 1H, *J* = 12.2 Hz), 4.73 (d, 1H, *J* = 12.2 Hz), 5.66 (d, 1H, *J* = 3.8 Hz), 7.27 (m, 5H), 7.38 (m, 6H), 7.66 (m, 4H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 7.1 (t), 17.3 (d), 19.3 (s), 26.5 (q), 26.8 (q), 27.0 (q), 65.7 (t), 72.1 (t), 77.7 (d), 80.7 (d), 82.0 (d), 103.5 (d), 112.6 (s), 127.7 (d), 127.8 (d), 128.4 (d), 129.6 (d), 133.8 (s), 133.9 (s), 135.6 (d), 137.8 (s)

((1*S*,2*S*)-2-((3a*R*,5*R*,6*R*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)cyclopropyl)methanol (**59**):

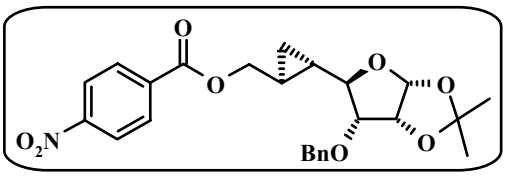


Following general procedure E, compound **58** was converted to compound **59** (93%) as white solid.

Mol. Formula	:	$C_{18}H_{24}O_5$
Mol. Weight	:	320.39

ESI-MS *m/z*	:	343.28 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	3436, 2989, 2926, 1455, 1374, 1168, 1134, 1097, 1022, 872, 772, 700
Elemental Analysis	:	Calcd: C, 67.48; H, 7.55 Found: C, 67.63; H, 7.71
$[\alpha]_D^{25}$	:	+103.2 (*c* 1.2, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.48 (dt, 1H, *J* = 5.1, 8.5 Hz), 0.63 (dt, 1H, *J* = 4.9, 8.5 Hz), 0.81 (m, 1H), 1.25 (m, 1H), 1.34 (s, 3H), 1.56 (s, 3H), 2.18 (bs, 1H), 3.41 (dd, 1H, *J* = 7.0, 11.2 Hz), 3.49 (dd, 1H, *J* = 6.8, 11.2 Hz), 3.57 (m, 2H), 4.56 (t, 1H, *J* = 3.8), 4.61 (d, 1H, *J* = 12.0 Hz), 4.81 (d, 1H, *J* = 12.0 Hz), 5.68 (d, 1H, *J* = 3.8 Hz), 7.37 (m, 5H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 7.2 (t), 17.8 (d), 18.1 (d), 26.3 (q), 26.5 (q), 65.9 (t), 72.0 (t), 77.3 (d), 80.3 (d), 81.8 (d), 103.4 (d), 112.6 (s), 127.9 (d), 128.4 (d), 137.4 (s)

((1*S*,2*S*)-2-((3a*R*,5*R*,6*R*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)cyclopropyl)methyl 4-nitrobenzoate (**60**):

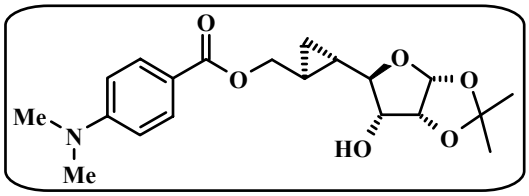


A CH_2Cl_2 (2 mL) solution of the alcohol **59** (0.07 g, 0.22 mmol) was treated with *p*-nitrobenzoyl chloride (0.05 g, 0.26 mmol), Et_3N (0.06 mL, 0.44 mmol) and catalytic amount of DMAP. After stirring the reaction mixture at room temperature for 2 h, it was quenched with water. The biphasic mixture was separated and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, concentrated and purified by column chromatography using EtOAc:Petroleum ether (1:8) as eluent to get the pure benzoate ester compound **60** (0.098 g, 96%) as a liquid.

Mol. Formula : $C_{25}H_{27}NO_8$

Mol. Weight	:	469.50
ESI-MS *m/z*	:	492.36 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	2932, 1724, 16.8, 1529, 1455, 1348, 1275, 1168, 1102, 1024, 873, 720
Elemental Analysis	:	Calcd: C, 63.96; H, 5.80; N, 2.98 Found: C, 63.81; H, 5.93; N, 2.88
$[\alpha]_D^{25}$	:	+59.4 (*c* 1, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.64 (dt, 1H, *J* = 5.2, 8.5 Hz), 0.80 (dt, 1H, *J* = 5.2, 8.5 Hz), 1.08 (m, 1H), 1.37 (s, 3H), 1.51 (m, 1H), 1.59 (s, 3H), 3.60 (dd, 1H, *J* = 4.2, 8.8 Hz), 3.73 (dd, 1H, *J* = 6.8, 8.8 Hz), 4.28 (d, 2H, *J* = 7.1 Hz), 4.56 (d, 1H, *J* = 12.0 Hz), 4.61 (t, 1H, *J* = 4.0 Hz), 4.80 (d, 1H, *J* = 12.0 Hz), 5.73 (d, 1H, *J* = 3.8 Hz), 7.35 (m, 5H), 8.20 (m, 4H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 7.4 (t), 14.1 (d), 18.8 (d), 26.3 (q), 26.6 (q), 67.0 (t), 71.9 (t), 77.3 (d), 79.6 (d), 82.1 (d), 103.6 (d), 112.7 (s), 123.4 (d), 127.5 (d), 127.9 (d), 128.4 (d), 130.6 (d), 135.5 (s), 137.4 (s), 150.4 (s), 164.6 (s)

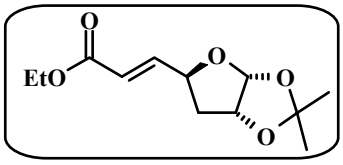
((1*S*,2*S*)-2-((3a*R*,5*R*,6*R*,6a*R*)-6-hydroxy-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)cyclopropyl)methyl 4-(dimethylamino)benzoate (**61**):



The *p*-nitrobenzoate compound **60** (0.065 g, 0.14 mmol) in MeOH (2 mL) was subjected to H_2 at balloon pressure in presence of 10% Pd/C (catalytic). The reaction mixture was stirred at room temperature for 5 h and filter through a small pad of celite. The filtrate was concentrated and purified by column chromatography using EtOAc:petroleum ether (1:1) as eluent to obtain the pure alcohol compound **61** (0.048 g, 91%) as a viscous liquid.

Mol. Formula	:	$C_{20}H_{27}NO_6$
Mol. Weight	:	377.44
ESI-MS *m/z*	:	400.35 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 63.65; H, 7.21; N, 3.71 Found: C, 63.72; H, 7.17; N, 3.84
$[\alpha]_D^{25}$	:	+27.4 (*c* 0.7, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.66 (dt, 1H, *J* = 5.2, 8.5 Hz), 0.74 (dt, 1H, *J* = 5.2, 8.5 Hz), 1.04 (m, 1H), 1.35 (s, 3H), 1.41 (m, 1H), 1.54 (s, 3H), 2.52 (bs, 1H), 3.03 (s, 6H), 3.34 (dd, 1H, *J* = 7.6, 8.3 Hz), 3.75 (m, 1H), 4.10 (dd, 1H, *J* = 7.3, 11.4 Hz), 4.26 (dd, 1H, *J* = 6.5, 11.4 Hz), 4.55 (dd, 1H, *J* = 4.1, 5.0 Hz), 5.76 (d, 1H, *J* = 3.9 Hz), 6.64 (d, 2H, *J* = 9.1 Hz), 7.92 (d, 2H, *J* = 9.1 Hz)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 7.6 (t), 14.2 (d), 18.3 (d), 26.4 (q), 40.0 (q), 67.1 (t), 76.0 (d), 78.6 (d), 82.2 (d), 103.5 (d), 110.7 (d), 112.3 (s), 117.0 (s), 131.2 (d), 153.3 (s), 167.1 (s)

(*E*)-ethyl 3-((3a*R*,5*S*,6a*R*)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)acrylate (**65**):

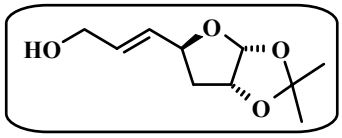


Following general procedure A, compound **64** was converted to compound **65** exclusively (82%) as a colorless liquid.

Mol. Formula	:	$C_{12}H_{18}O_5$
Mol. Weight	:	242.27
ESI-MS *m/z*	:	265.15 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 59.49; H, 7.49 Found: C, 59.63; H, 7.51

$[\alpha]_D^{25}$	:	- 59.1 (*c* 2.2, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 1.29 (t, 3H, *J* = 7.2 Hz), 1.33 (s, 3H), 1.53 (s, 3H), 1.64 (ddd, 1H, *J* = 4.6, 11.1, 13.3 Hz), 2.27 (dd, 1H, *J* = 4.4, 13.3 Hz), 4.20 (q, 2H, *J* = 7.2 Hz), 4.80 (m, 2H), 5.88 (d, 1H, *J* = 3.5 Hz), 6.10 (dd, 1H, *J* = 1.5, 15.7 Hz), 6.93 (dd, 1H, *J* = 5.2, 15.7 Hz)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 14.2 (q), 26.0 (q), 26.6 (q), 39.1 (t), 60.4 (t), 76.2 (d), 80.3 (d), 105.5 (d), 111.4 (s), 121.5 (d), 144.9 (d), 166.1(s)

(*E*)-3-((3a*R*,5*S*,6a*R*)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)prop-2-en-1-ol (**66**):

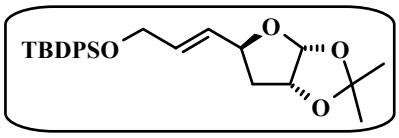


Following general procedure B, compound **65** was converted to compound **66** (94%) as colorless syrup.

Mol. Formula	:	$C_{10}H_{16}O_4$
Mol. Weight	:	200.24
ESI-MS *m/z*	:	223.26 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	3402, 2986, 2934, 1383, 1209, 1191, 1163, 1059, 1017, 849, 785, 562, 536, 526
Elemental Analysis	:	Calcd: C, 59.98; H, 8.05 Found: C, 60.15; H, 8.16
$[\alpha]_D^{25}$	:	-31.8 (*c* 1, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 1.32 (s, 3H), 1.53 (s, 3H), 1.62 (ddd, 1H, *J* = 4.7, 10.9, 13.4 Hz), 1.75 (bs, 1H), 2.18 (dd, 1H, *J* = 4.3, 13.4 Hz), 4.16 (dd, 2H, *J* = 0.7, 5.0 Hz), 4.66 (ddd, 1H, *J* = 4.4, 6.5, 11.0 Hz), 4.75 (t, 1H, *J* = 4.2 Hz), 5.72 (ddt, 1H, *J* = 1.2,

		6.7, 15.5 Hz), 5.84 (d, 1H, *J* = 3.7 Hz), 5.97 (ddt, 1H, *J* = 0.6, 5.0, 15.5 Hz)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 26.0 (q), 26.6 (q), 39.4 (t), 62.7 (t), 77.7 (d), 80.5 (d), 105.3 (d), 111.0 (s), 129.0 (d), 132.5 (d)

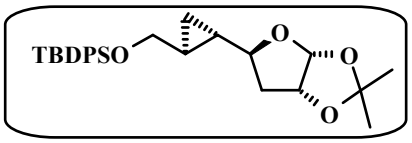
***tert*-butyl((*E*)-3-((3a*R*,5*S*,6a*R*)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)allyloxy)diphenylsilane** (**67**):



Following general procedure C, compound **66** was converted to compound **67** (97%) as a colorless liquid.

Mol. Formula	:	$C_{26}H_{34}O_4Si$
Mol. Weight	:	438.64
ESI-MS *m/z*	:	456.53 $[M+H_2O]^+$, 461 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	2932, 2857, 1428, 1382, 1191, 1163, 1113, 1058, 1020, 702, 505
Elemental Analysis	:	Calcd: C, 71.19; H, 7.81; Si, 6.40 Found: C, 71.26; H, 7.69; Si, 6.24
$[\alpha]_D^{25}$	:	-16.8 (*c* 1.2, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 1.07 (s, 9H), 1.35 (s, 3H), 1.55 (s, 3H), 1.63 (ddd, 1H, *J* = 4.7, 10.8, 13.4 Hz), 2.17 (dd, 1H, *J* = 4.3, 13.4 Hz), 4.22 (d, 2H, *J* = 3.2 Hz), 4.68 (dd, 1H, *J* = 5.1, 10.9 Hz), 4.76 (t, 1H, *J* = 4.2 Hz), 5.86 (m, 3H), 7.42 (m, 6H), 7.70 (m, 4H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 19.2 (s), 26.1 (q), 26.6 (q), 26.8 (q), 39.6 (t), 63.5 (t), 77.9 (d), 80.5 (d), 105.3 (d), 110.9 (s), 127.6 (d), 129.6 (d), 132.2 (d), 133.5 (s), 134.8 (d), 135.5 (d)

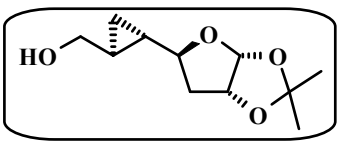
***tert*-butyl(((1*S*,2*S*)-2-((3a*R*,5*S*,6a*R*)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)cyclopropyl)methoxy)diphenylsilane** (**68**):



Following general procedure D, compound **67** was converted to compound **68** (84%) as a colorless liquid.

Mol. Formula	:	$C_{27}H_{36}O_4Si$
Mol. Weight	:	452.67
ESI-MS *m/z*	:	475.59 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 71.64; H, 8.02; Si, 6.20 Found: C, 71.79; H, 7.99; Si, 6.33
$[\alpha]_D^{25}$	:	+18.2 (*c* 1.1, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.51 (dt, 1H, J = 5.0, 8.3 Hz), 0.62 (dt, 4.9, 8.3 Hz), 0.80 (m, 1H), 0.98 (m, 1H), 1.06 (s, 9H), 1.32 (s, 3H), 1.50 (s, 3H), 1.63 (ddd, 1H, *J* = 4.7, 10.8, 13.5 Hz), 2.18 (dd, 1H, *J* = 4.2, 13.5 Hz), 3.41 (dd, 1H, *J* = 6.8, 10.6), 3.62 (ddd, 1H, *J* = 4.1, 8.1, 10.7 Hz), 3.73 (dd, 1H, *J* = 5.4, 10.6 Hz), 4.72 (t, 1H, *J* = 4.2 Hz), 5.81 (d, 1H, *J* = 3.7 Hz), 7.41 (m, 6H), 7.67 (m, 4H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 8.3 (t), 18.1 (d), 19.2 (s), 19.4 (d), 26.1 (q), 26.6 (q), 26.9 (q), 39.0 (t), 66.3 (t), 80.4 (d), 81.6 (d), 105.3 (d), 110.6 (s), 127.6 (d), 129.6 (d), 133.6 (s), 135.6 (d)

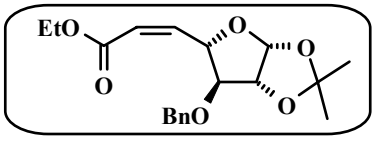
((1*S*,2*S*)-2-((3a*R*,5*S*,6a*R*)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)cyclopropyl)methanol (**69**):



Following general procedure E, compound **68** was converted to compound **69** (93%) as a sticky liquid.

Mol. Formula	:	$C_{11}H_{18}O_4$
Mol. Weight	:	214.26
ESI-MS *m/z*	:	437.12 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	3435, 2988, 2936, 1620, 1383, 1215, 1161, 1054, 1019, 848
Elemental Analysis	:	Calcd: C, 61.66; H, 8.47 Found: C, 61.73; H, 8.59
$[\alpha]_D^{25}$	:	+17.3 (*c* 1.1, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.52 (dt, 1H, *J* = 5.0, 8.4 Hz), 0.64 (dt, 1H, *J* = 5.0, 8.4 Hz), 0.84 (m, 1H), 1.05 (m, 1H), 1.28 (s, 3H), 1.46 (s, 3H), 1.57 (ddd, 1H, *J* = 4.8, 10.8, 13.4 Hz), 2.11 (dd, 1H, *J* = 4.2, 13.4 Hz), 2.18 (bs, 1H), 3.40 (dd, 1H, *J* = 7.00, 11.4 Hz), 3.50 (dd, 1H, *J* = 6.8, 11.4 Hz), 3.75 (ddd, 1H, *J* = 4.2, 7.5, 10.7 Hz), 4.70 (t, 1H, *J* = 4.3 Hz), 5.78 (d, 1H, *J* = 3.8 Hz)
^{13}C NMR ($CDCl_3$)	:	δ 8.2 (t), 18.0 (d), 19.4 (d), 25.9 (q), 26.5 (q), 38.3 (t), 65.9 (t), 80.3 (d), 80.5 (d), 105.1 (d), 110.7 (s)

(*Z*)-ethyl 3-((3a*R*,5*S*,6*S*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)acrylate (**77**):

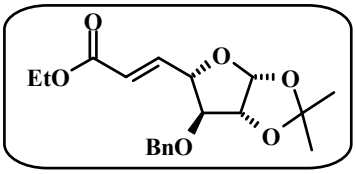


Following general procedure A, compound **77** (12%) was obtained as a minor product from compound **76** as a colorless liquid.

Mol. Formula	:	$C_{19}H_{24}O_6$
Mol. Weight	:	348.40

ESI-MS *m/z*	:	371.25 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	3803, 3647, 1719, 1655, 1404, 1305, 1269, 1165, 1077, 1021, 861, 756, 700
Elemental Analysis	:	Calcd: C, 65.50; H, 6.94 Found: C, 65.43; H, 7.21
$[\alpha]_D^{25}$	:	+95.8 (*c* 1, $CHCl_3$)
^{1}H NMR (400 MHz, $CDCl_3$)	:	δ 1.31 (t, 3H, *J* = 7.1 Hz), 1.31 (s, 3H), 1.53 (s, 3H), 4.06 (s, 1H), 4.19 (dd, 1H, *J* = 2.5, 7.1 Hz), 4.22 (dd, 1H, *J* = 2.7, 7.1 Hz), 4.62 (d, 1H, *J* = 3.8 Hz), 4.74 (d, 1H, *J* = 12.0 Hz), 4.88 (d, 1H, *J* = 12.0 Hz), 5.74 (dd, 1H, *J* = 1.7, 7.1 Hz), 5.79 (dd, 1H, *J* = 2.0, 11.8 Hz), 6.02 (d, 1H, *J* = 3.8 Hz), 6.54 (dd, 1H, *J* = 7.1, 11.8 Hz), 7.34 (m, 5H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 14.3 (q), 25.5 (q), 26.1 (q), 60.2 (t), 71.5 (t), 83.2 (d), 84.1 (d), 87.0 (d), 106.8 (d), 111.6 (s), 119.1 (d), 127.7 (d), 127.9 (d), 128.3 (d), 137.9 (s), 149.8 (d), 165.6 (s)

(*E*)-ethyl 3-((3a*R*,5*S*,6*S*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)acrylate (**78**):

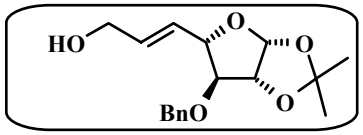


Following general procedure A, compound **76** was converted to compound **78** (66%, major product) as a colorless liquid.

Mol. Formula	:	$C_{19}H_{24}O_6$
Mol. Weight	:	348.40
ESI-MS *m/z*	:	371.19 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	3647, 1713, 1645, 1407, 1193, 1078, 1021, 756, 699
Elemental Analysis	:	Calcd: C, 65.50; H, 6.94 Found: C, 65.59; H, 7.09

$[\alpha]_D^{25}$	:	-40.7 (*c* 0.9, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$)	:	δ 1.29 (t, 3H, *J* = 7.2 Hz), 1.33 (s, 3H), 1.49 (s, 3H), 3.97 (d, 1H, *J* = 2.8 Hz), 4.20 (q, 2H, *J* = 7.2 Hz), 4.59 (d, 1H, *J* = 11.6 Hz), 4.66 (d, 1H, *J* = 11.6 Hz), 4.67 (m, 2H), 5.95 (d, 1H, *J* = 4.0 Hz), 6.07 (dd, 1H, *J* = 1.8, 15.6 Hz), 7.00 (dd, 1H, *J* = 5.3, 15.6 Hz), 7.34 (m, 5H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 14.2 (q), 26.3 (q), 26.6 (q), 60.4 (t), 72.0 (t), 83.5 (d), 84.6 (d), 85.9 (d), 106.0 (d), 113.0 (s), 121.9 (d), 127.8 (d), 128.1 (d), 128.6 (d), 136.8 (s), 144.9 (d), 166.0 (s)

(*E*)-3-((3a*R*,5*S*,6*S*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)prop-2-en-1-ol (**79**):

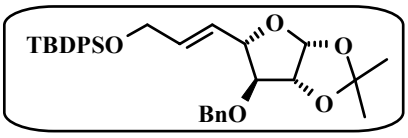


Following general procedure B, compound **78** was converted to compound **79** (91%) as a colorless sticky liquid.

Mol. Formula	:	$C_{17}H_{22}O_5$
Mol. Weight	:	306.36
ESI-MS *m/z*	:	329.21 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	3437, 3031, 2925, 1723, 1455, 1361, 1272, 1209, 1102, 1024, 751, 699
Elemental Analysis	:	Calcd: C, 66.65; H, 7.24 Found: C, 66.91; H, 7.45
$[\alpha]_D^{25}$	:	-41.5 (*c* 1.2, $CHCl_3$)
^{1}H NMR (400 MHz, $CDCl_3$)	:	δ 1.35 (s, 3H), 1.53 (s, 3H), 1.61 (bs, 1H), 3.91 (d, 1H, *J* = 3.0 Hz), 4.15 (m, 2H), 4.54 (m, 1H), 4.58 (d, 1H, *J* = 11.8 Hz), 4.64 (d, 1H, *J* = 4.2 Hz), 4.65 (m,1H), 5.90 (m, 3H), 7.34 (m, 5H)

^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 26.4 (q), 27.0 (q), 62.7 (t), 71.9 (t), 84.8 (d), 85.1 (d), 86.4 (d), 105.6 (d), 112.9 (s), 127.8 (d), 128.0 (d), 128.5 (d), 129.1 (d), 132.2 (d), 137.2 (s)

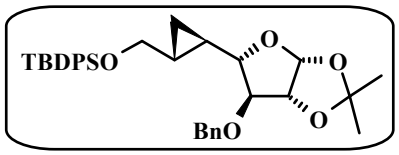
((*E*)-3-((3a*R*,5*S*,6*S*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)allyloxy)(*tert*-butyl)diphenylsilane (**80**):



Following general procedure C, compound **79** was converted to compound **80** (90%) as a colorless liquid.

Mol. Formula	:	$C_{33}H_{40}O_5Si$
Mol. Weight	:	544.77
ESI-MS *m/z*	:	567.63 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	2932, 2858, 1590, 1456, 1428, 1383, 1113, 1074, 1021, 757, 702, 505
Elemental Analysis	:	Calcd: C, 72.76; H, 7.40; Si, 5.16 Found: C, 72.81; H, 7.65; Si, 5.20
$[\alpha]_D^{25}$	:	-30.8 (*c* 1.3, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 1.09 (s, 9H), 1.37 (s, 3H), 1.52 (s, 3H), 3.93 (d, 1H, *J* = 3.0 Hz), 4.22 (m, 2H), 4.58 (dd, 1H, *J* = 3.0, 6.4 Hz), 4.59 (d, 1H, *J* = 11.8 Hz), 4.67 (d, 1H, *J* = 11.8 Hz), 4.68 (dd, 1H, *J* = 0.8, 4.0 Hz), 5.84 (ddt, 1H, *J* = 0.5, 3.8, 15.5 Hz), 5.93 (d, 1H, *J* = 3.8 Hz), 6.00 (ddt, 1H, *J* = 1.5, 6.6, 15.5 Hz), 7.38 (m, 11H), 7.70 (m, 4H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 19.3 (s), 26.6 (q), 26.8 (q), 27.2 (q), 63.6 (t), 71.9 (t), 84.9 (d), 85.2 (d), 86.6 (d), 105.6 (d), 112.9 (s), 127.6 (d), 127.7 (d), 127.8 (d), 127.9 (d), 128.5 (d), 129.7 (d), 131.8 (d), 133.5 (s), 135.5 (d), 137.3 (s)

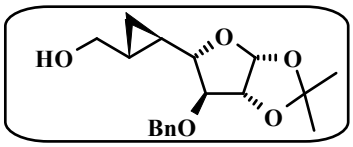
(((1*R*,2*R*)-2-((3a*R*,5*S*,6*S*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)cyclopropyl)methoxy)(*tert*-butyl)diphenylsilane (**81**):



Following general procedure D, compound **80** was converted to compound **81** (75%) as a colorless liquid.

Mol. Formula	:	$C_{34}H_{42}O_5Si$
Mol. Weight	:	558.80
ESI-MS *m/z*	:	581.72 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	2931, 2858, 1618, 1456, 1428, 1383, 1164, 1112, 1074, 759, 702, 505
Elemental Analysis	:	Calcd: C, 73.08; H, 7.58; Si, 5.03 Found: C, 72.99; H, 7.43; Si, 5.19
$[\alpha]_D^{25}$	:	-18.0 (*c* 2, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.66 (dd, 2H, *J* = 6.4, 7.0 Hz), 1.03 (m, 1H), 1.10 (s, 9H), 1.25 (m, 1H), 1.41 (s, 3H), 1.60 (s, 3H), 3.43 (dd, 1H, *J* = 2.8, 9.6 Hz), 3.50 (dd, 1H, *J* = 6.3, 10.6 Hz), 3.69 (dd, 1H, *J* = 5.5, 10.6 Hz), 4.09 (d, 1H, *J* = 2.8 Hz), 4.55-4.63 (ABq, 2H, *J* = 11.6 Hz), 4.67 (d, 1H, *J* = 3.9 Hz), 5.90 (d, 1H, *J* = 3.9 Hz), 7.41 (m, 11H), 7.71 (m, 4H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 9.2 (t), 18.4 (d), 19.3 (s), 19.9 (d), 26.5 (q), 26.9 (q), 27.4 (q), 66.0 (t), 71.9 (t), 85.2 (d), 86.5 (d), 89.0 (d), 105.5 (d), 112.7 (s), 127.6 (d), 127.8 (d), 128.4 (d), 129.6 (d), 133.7 (d), 133.7 (s), 135.6 (d), 137.4 (s)

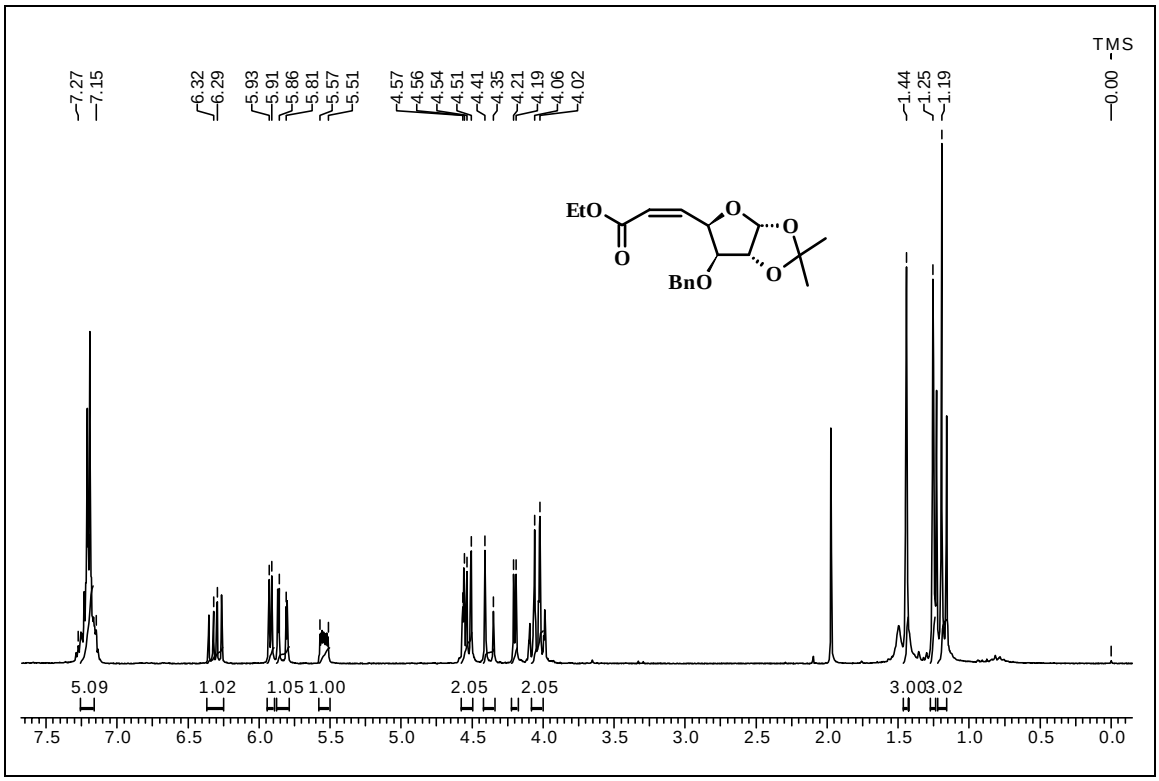
((1*R*,2*R*)-2-((3a*R*,5*S*,6*S*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)cyclopropyl)methanol (**82**):



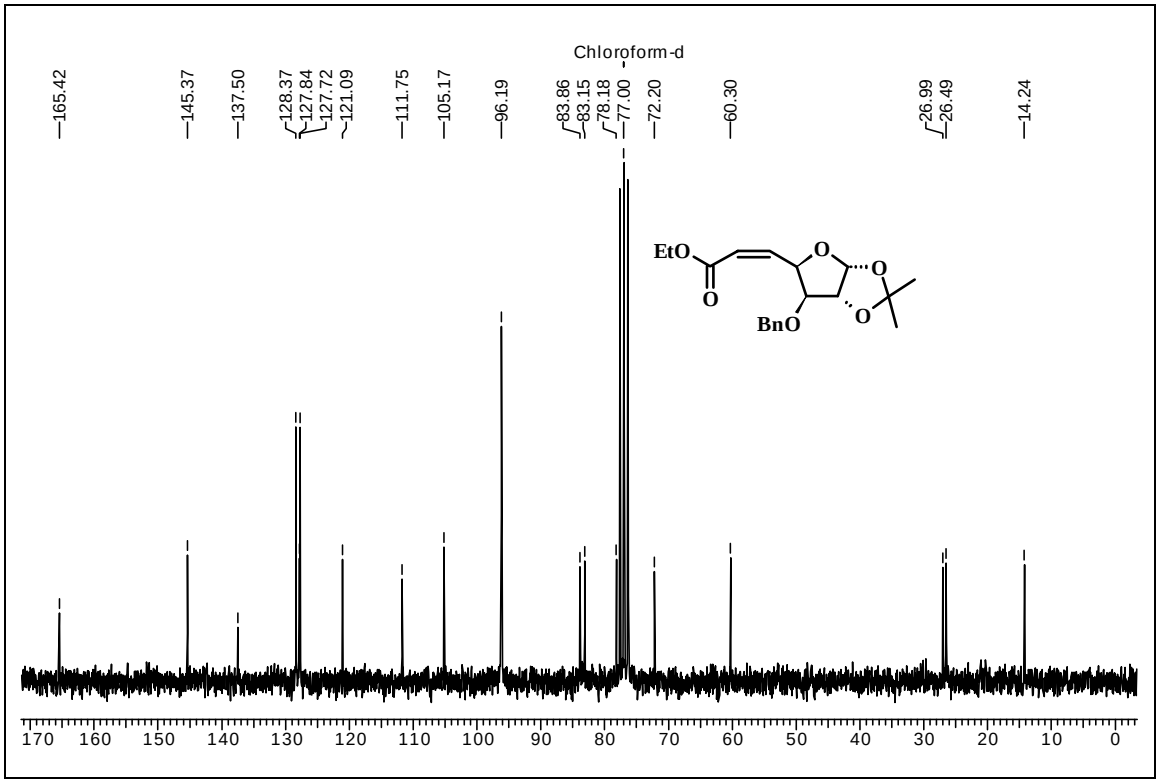
Following general procedure E, compound **81** was converted to compound **82** (89%) as a colorless syrup.

Mol. Formula	:	$C_{18}H_{24}O_5$
Mol. Weight	:	320.39
ESI-MS *m/z*	:	343.28 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	3436, 2999, 2928, 1653, 1455, 1384, 1164, 1059, 1028, 754, 699, 667
Elemental Analysis	:	Calcd: C, 67.48; H, 7.55 Found: C, 67.39; H, 7.63
$[\alpha]_D^{25}$	:	-44.6 (*c* 1, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.59 (dt, 1H, *J* = 5.2, 8.3 Hz), 0.67 (dt, 1H, *J* = 5.0, 8.3 Hz), 1.07 (m, 2H), 1.36 (s, 3H), 1.55 (s, 3H), 2.08 (bs, 1H), 3.36 (dd, 1H, *J* = 6.8, 11.3 Hz), 3.41 (dd, 1H, *J* = 3.4, 9.1 Hz), 3.49 (dd, 1H, *J* = 6.6, 11.3 Hz), 3.98 (dd, 1H, *J* = 1.0, 3.0 Hz), 4.55 (d, 1H, *J* = 11.9 Hz), 4.63 (dd, 1H, *J* = 1.0, 4.4 Hz), 4.66 (d, 1H, *J* = 11.9 Hz), 5.85 (d, 1H, *J* = 3.9 Hz), 7.35 (m, 5H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 9.3 (t), 18.7 (d), 20.1 (d), 26.4 (q), 27.2 (q), 65.9 (t), 71.2 (t), 85.0 (d), 85.8 (d), 88.1 (d), 105.3 (d), 112.9 (s), 127.9 (d), 128.0 (d), 128.5 (d), 137.2 (s)

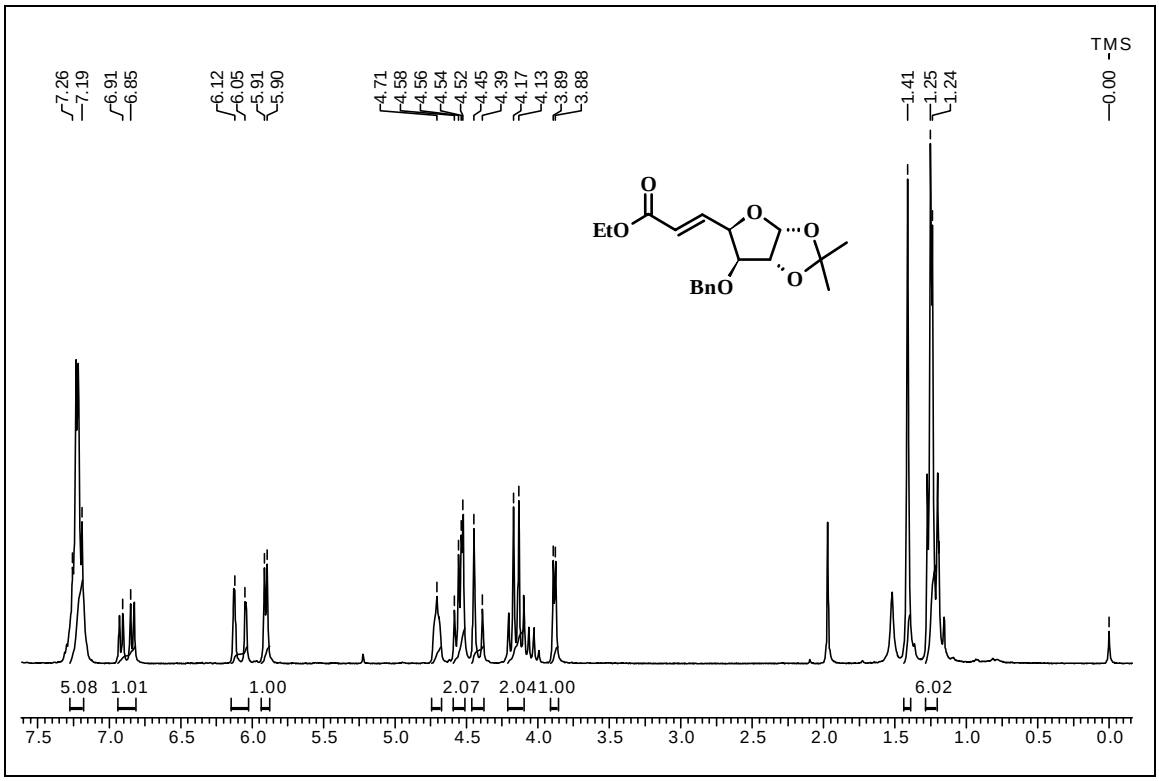
Spectra



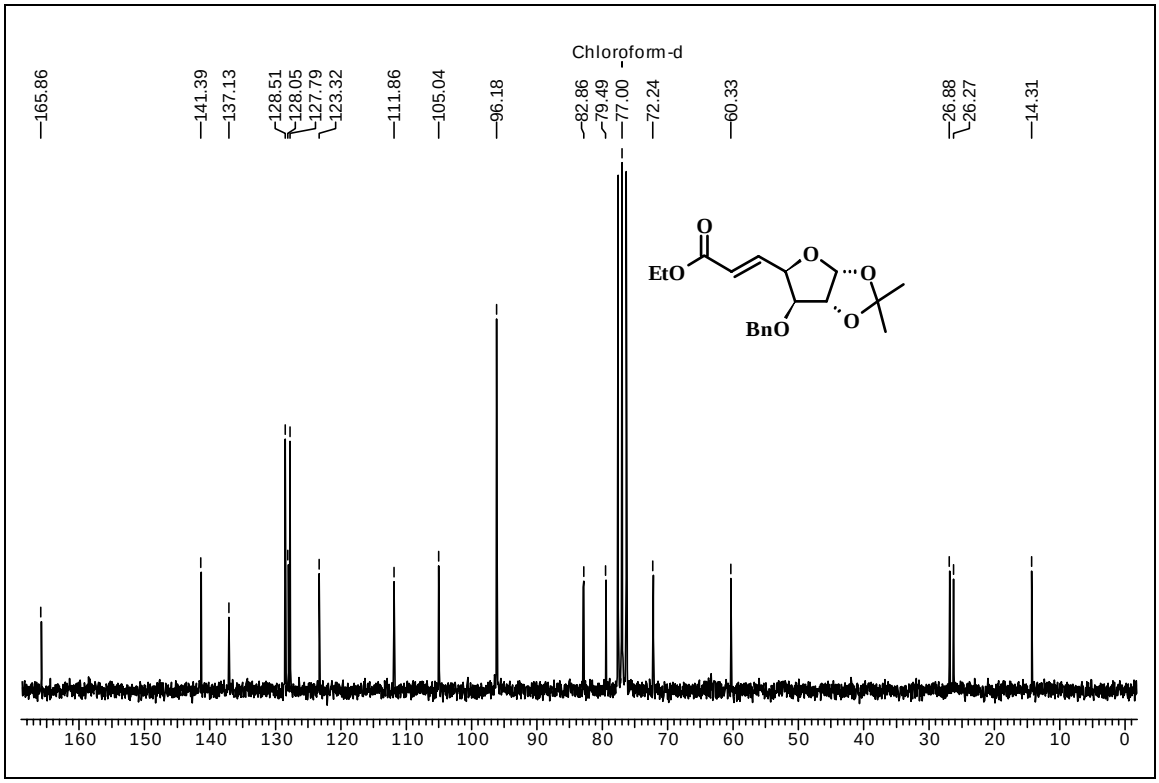
^{1}H NMR spectrum of compound 48 in $CDCl_3$



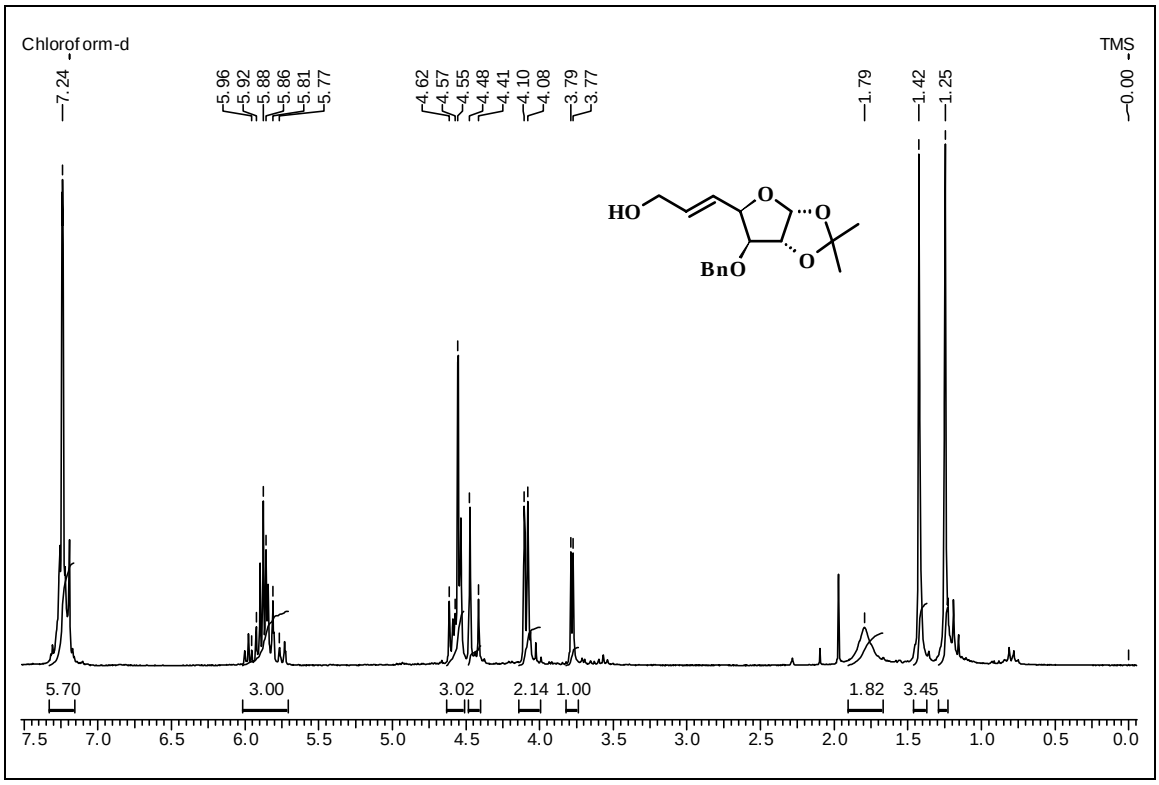
^{13}C NMR spectrum of compound 48 in $CDCl_3$



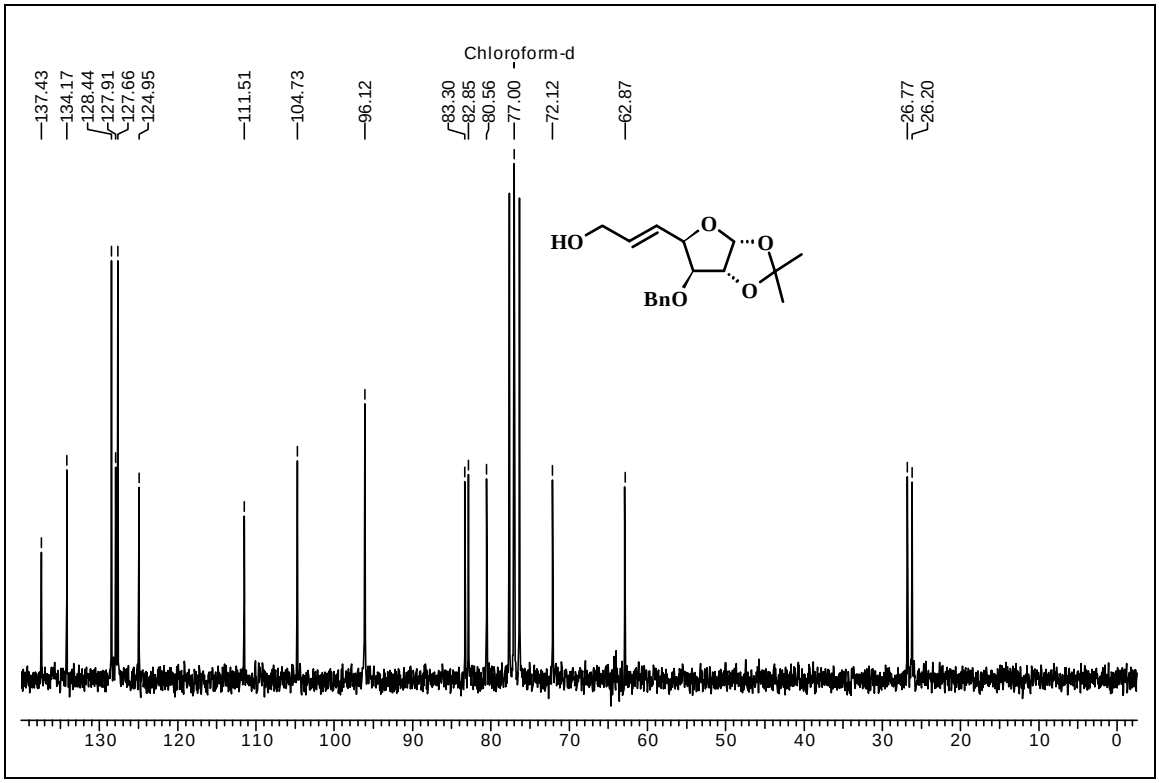
^{1}H NMR spectrum of compound 49 in $CDCl_3$



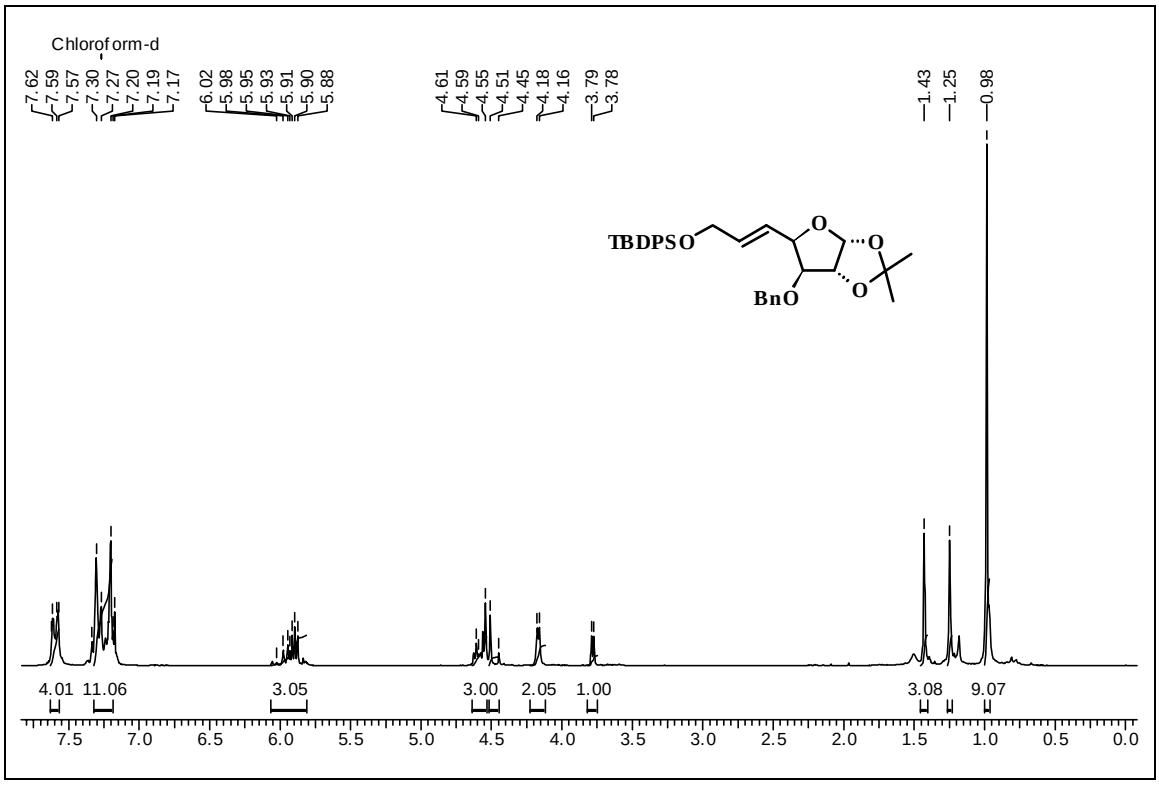
^{13}C NMR spectrum of compound 49 in $CDCl_3$



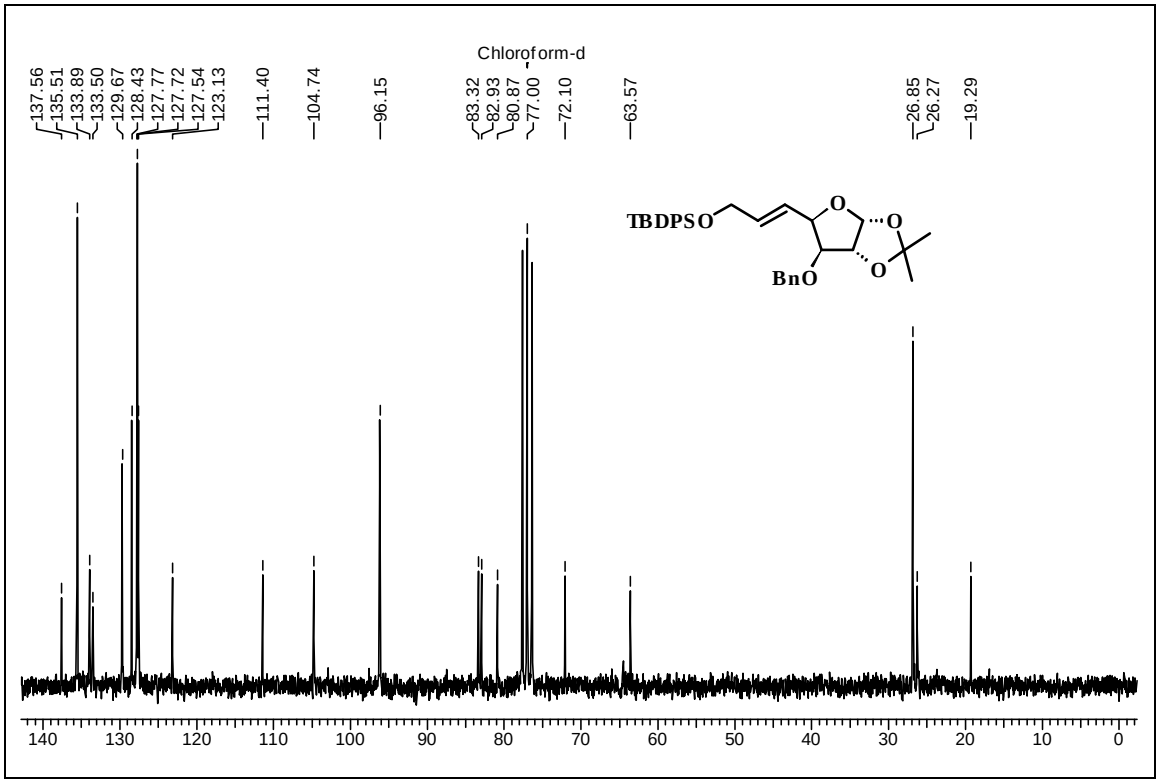
^{1}H NMR spectrum of compound 50 in $CDCl_3$



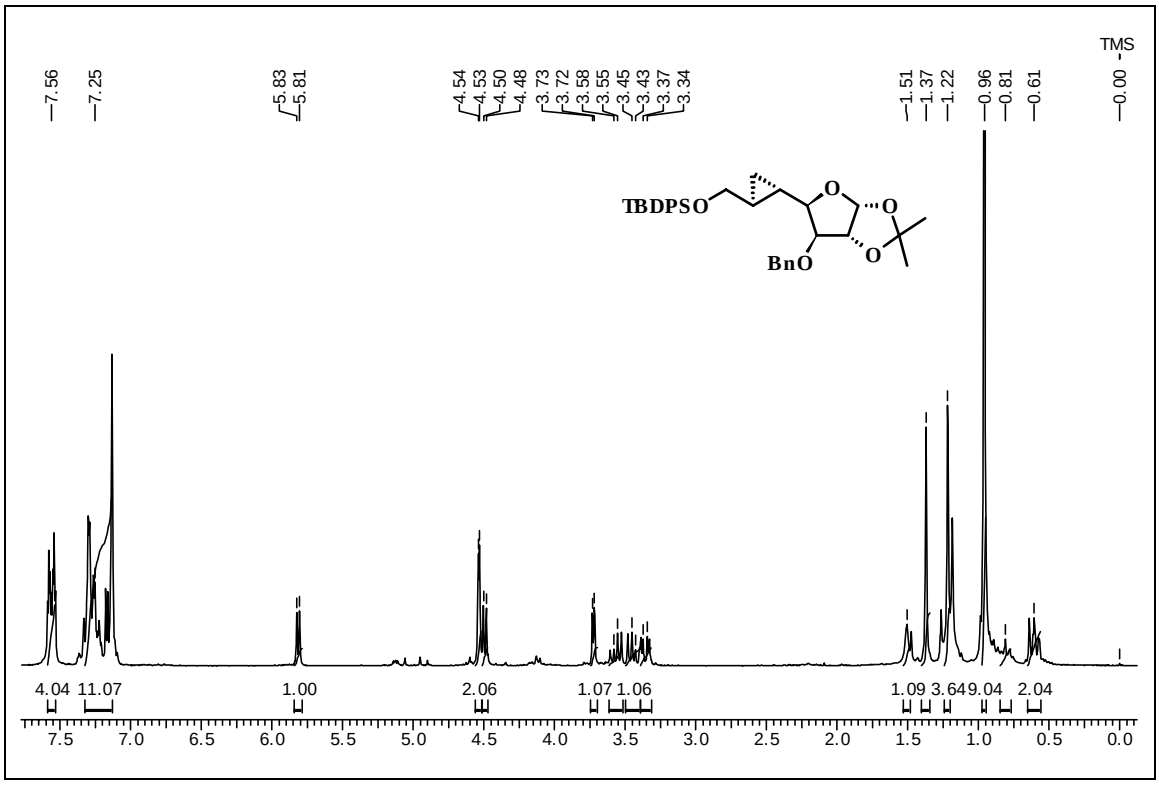
^{13}C NMR spectrum of compound 50 in $CDCl_3$



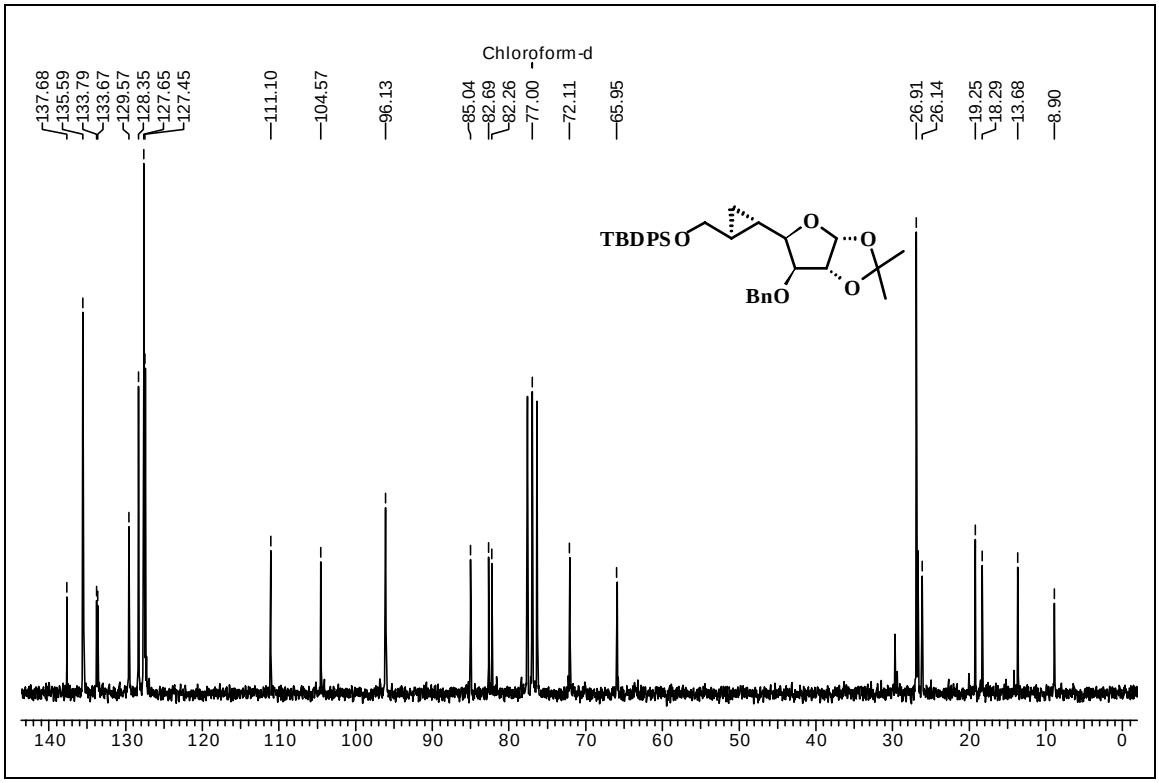
^{1}H NMR spectrum of compound 51 in $CDCl_3$



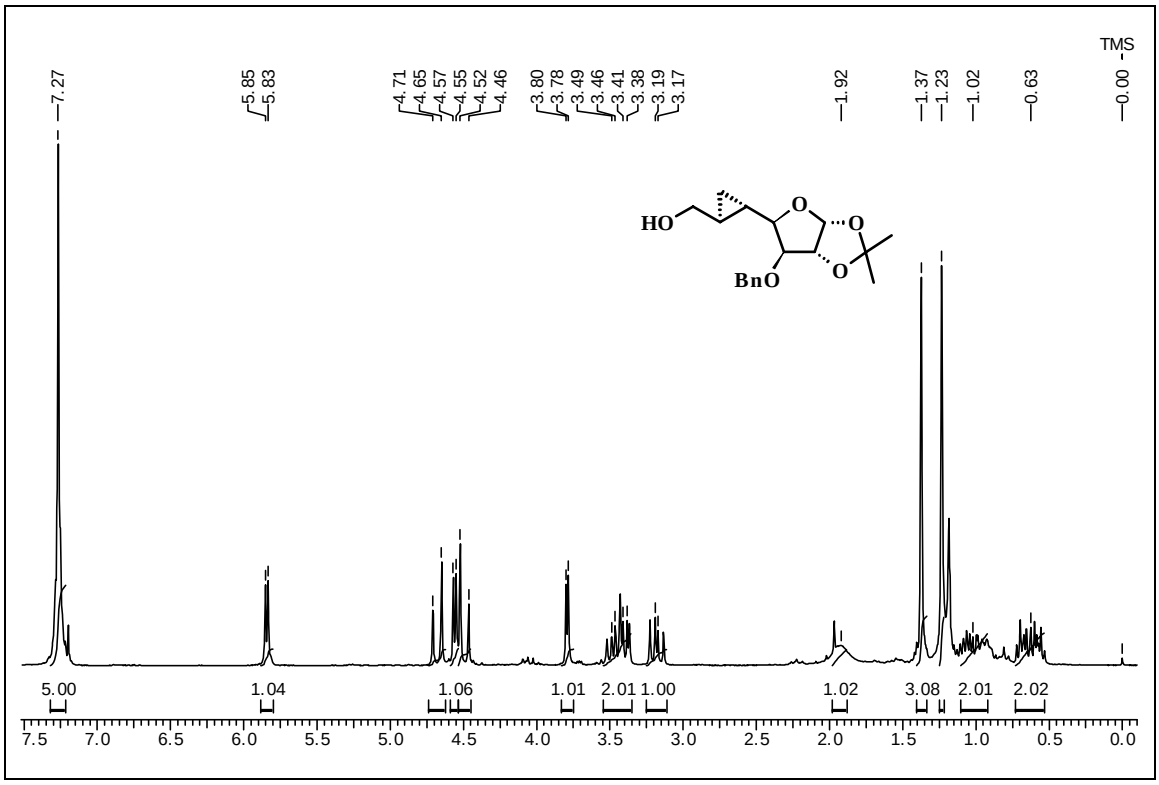
^{13}C NMR spectrum of compound 51 in $CDCl_3$



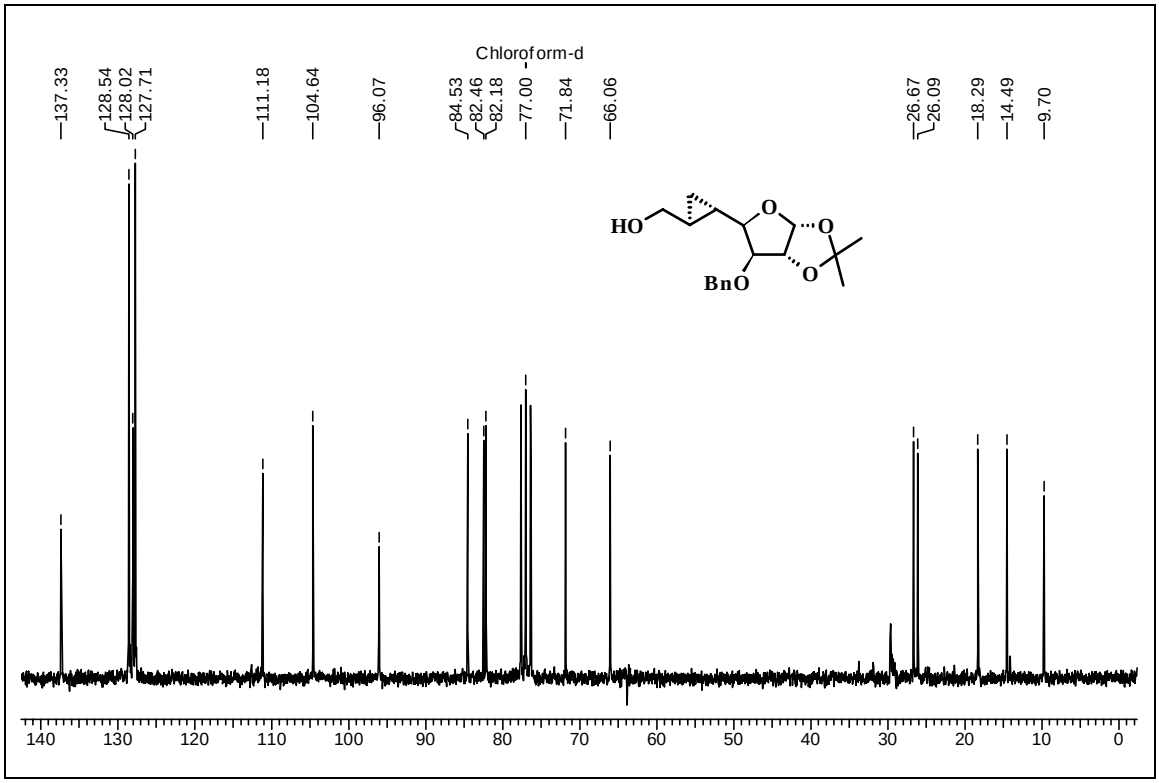
^{1}H NMR spectrum of compound 52 in $CDCl_3$



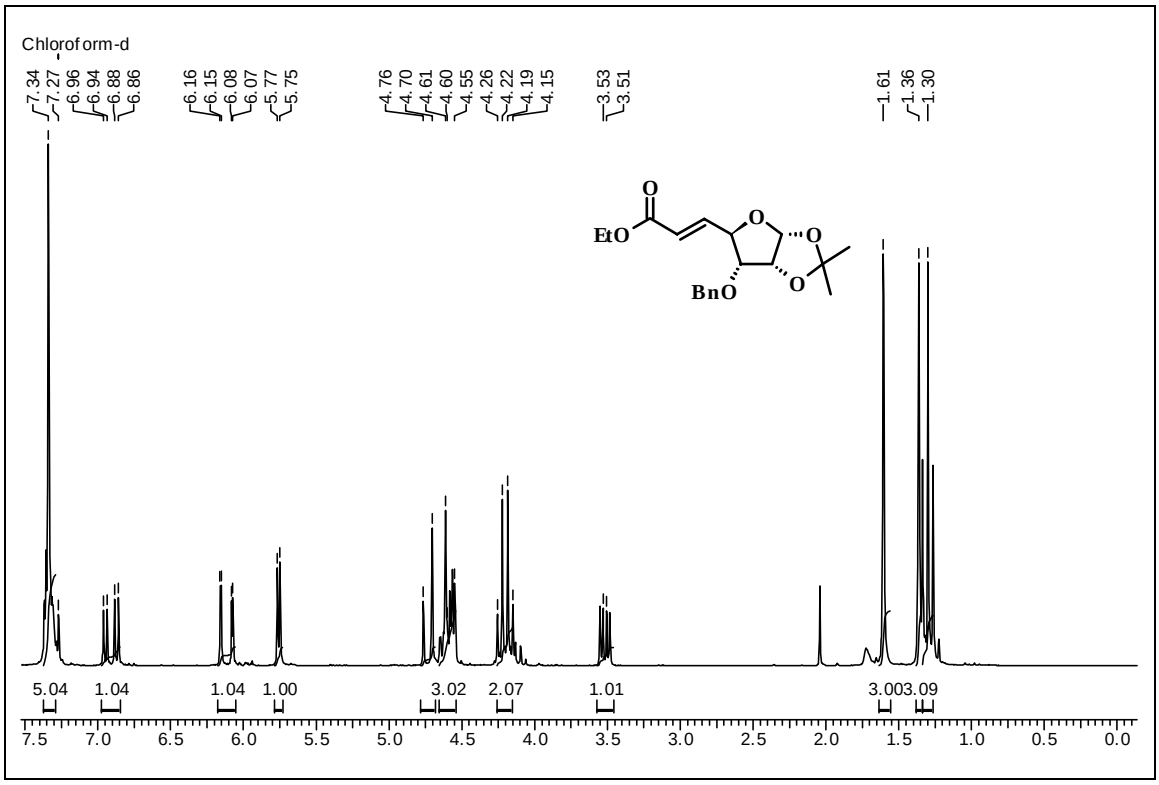
^{13}C NMR spectrum of compound 52 in $CDCl_3$



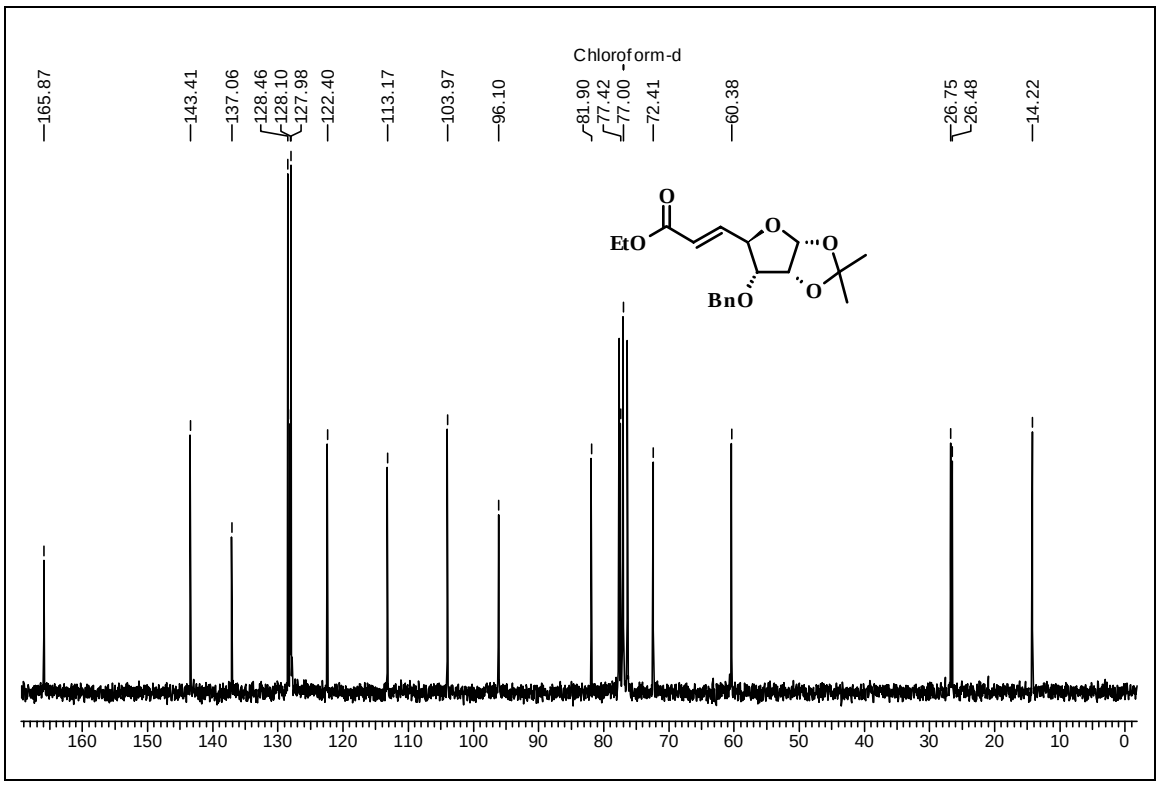
^{1}H NMR spectrum of compound 53 in $CDCl_3$



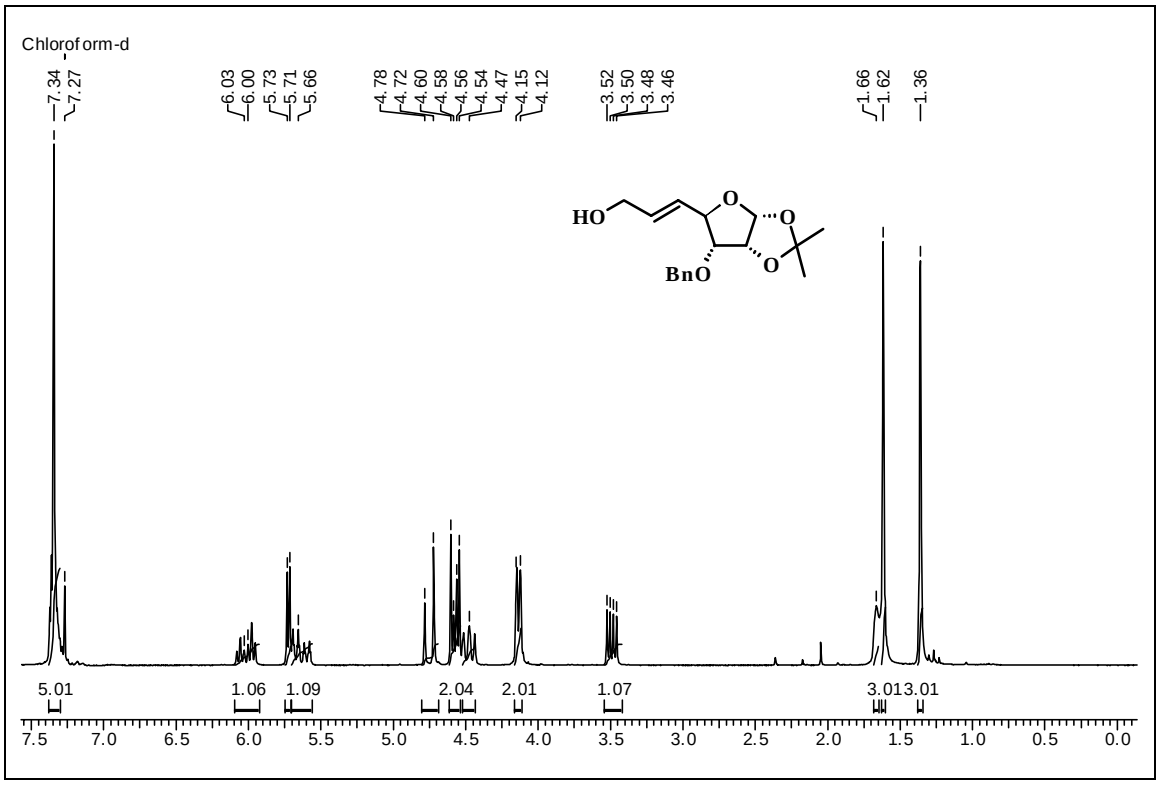
^{13}C NMR spectrum of compound 53 in $CDCl_3$



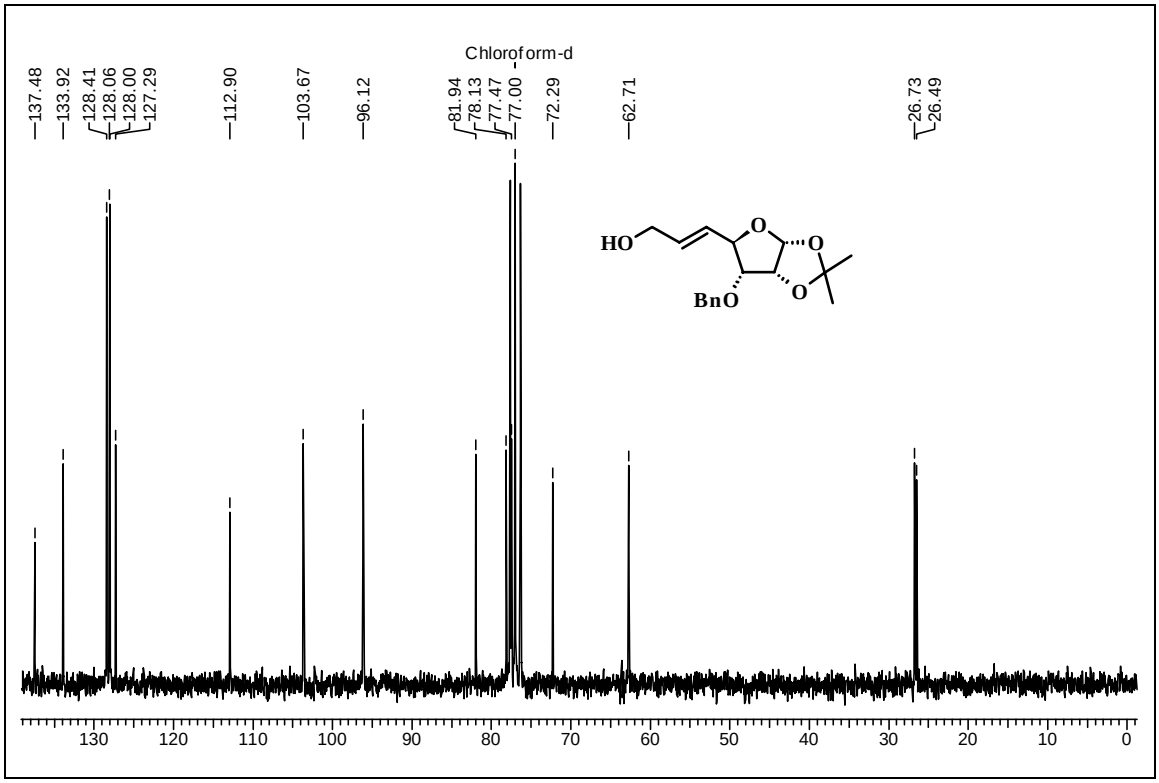
^{1}H NMR spectrum of compound 55 in $CDCl_3$



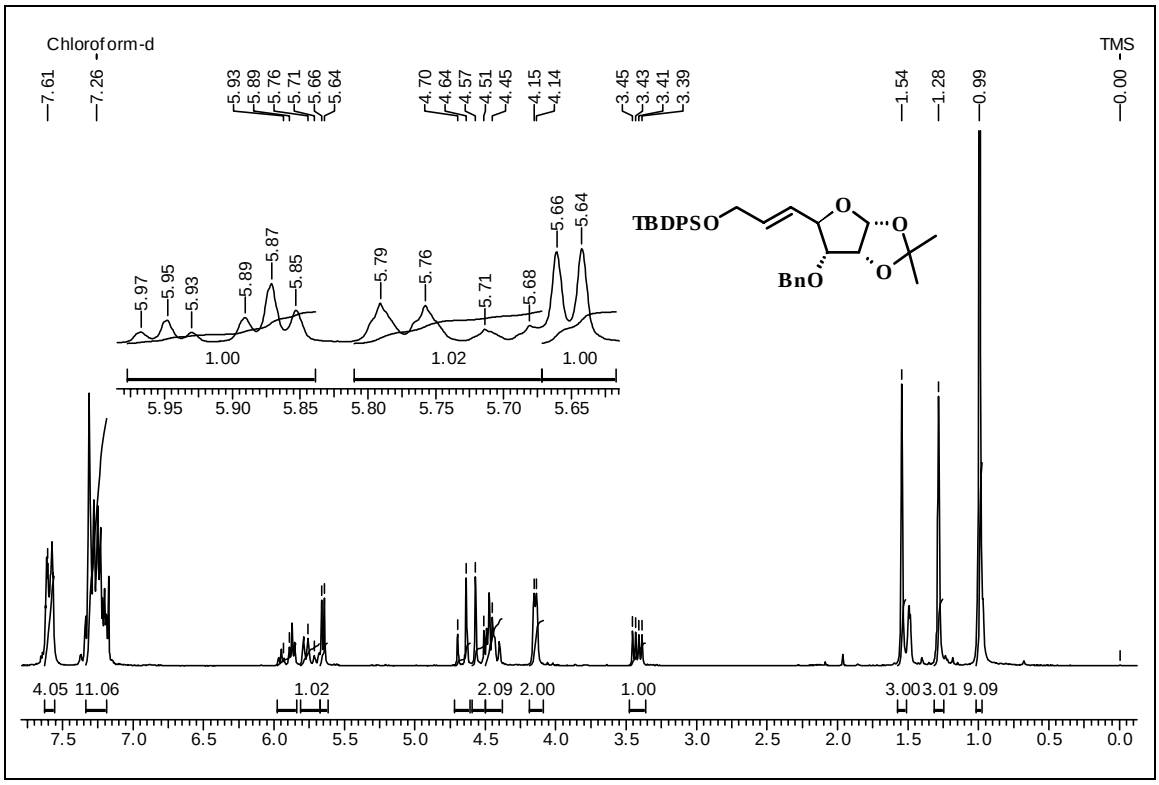
^{13}C NMR spectrum of compound 55 in $CDCl_3$



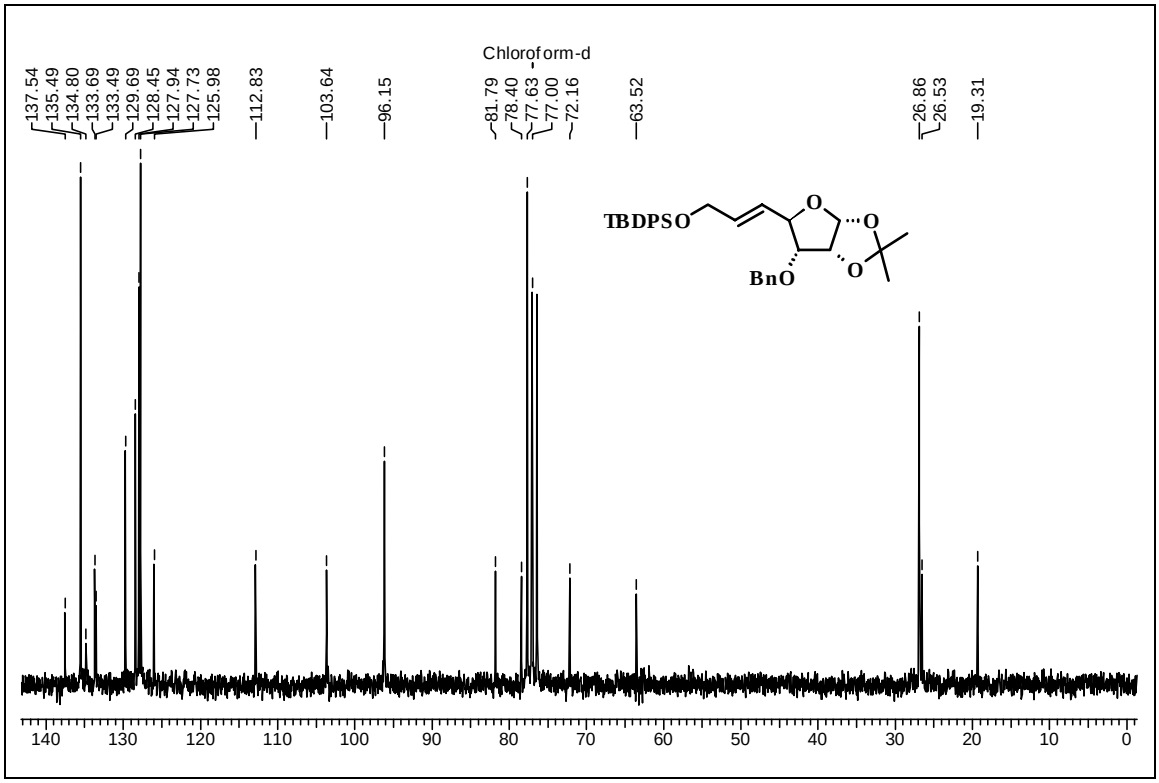
^{1}H NMR spectrum of compound 56 in $CDCl_3$



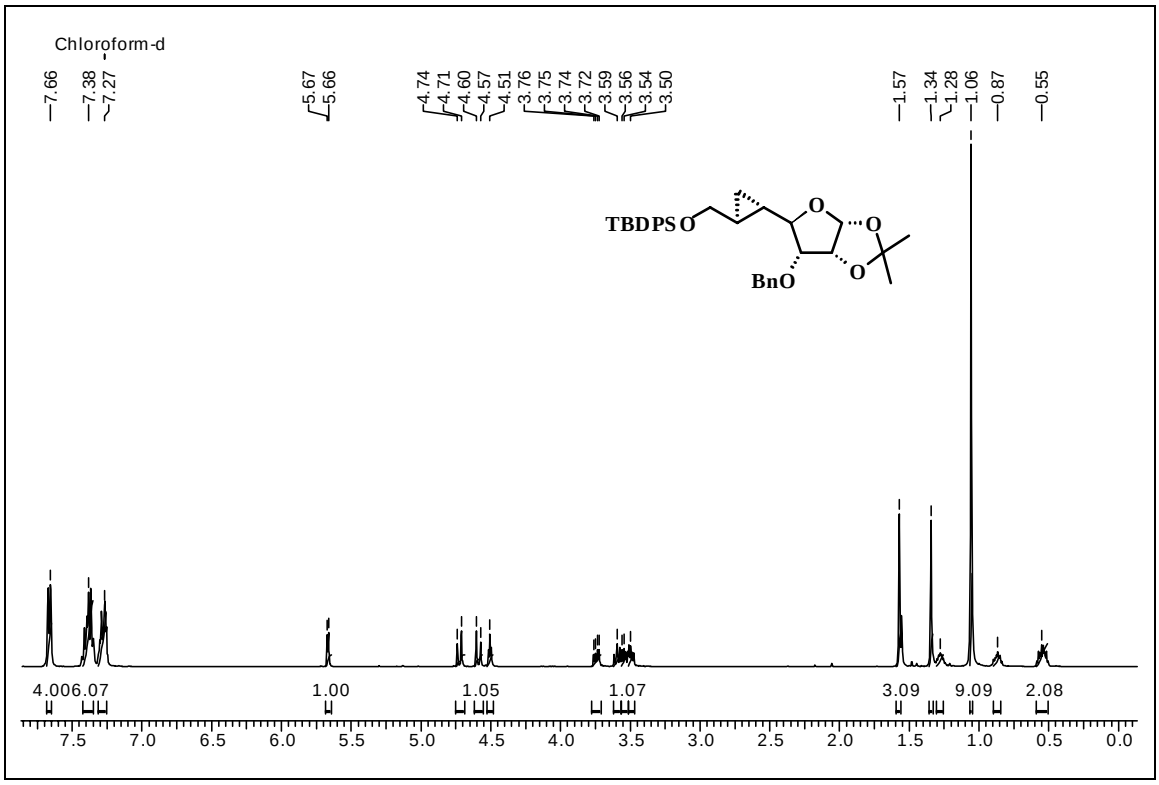
^{13}C NMR spectrum of compound 56 in $CDCl_3$



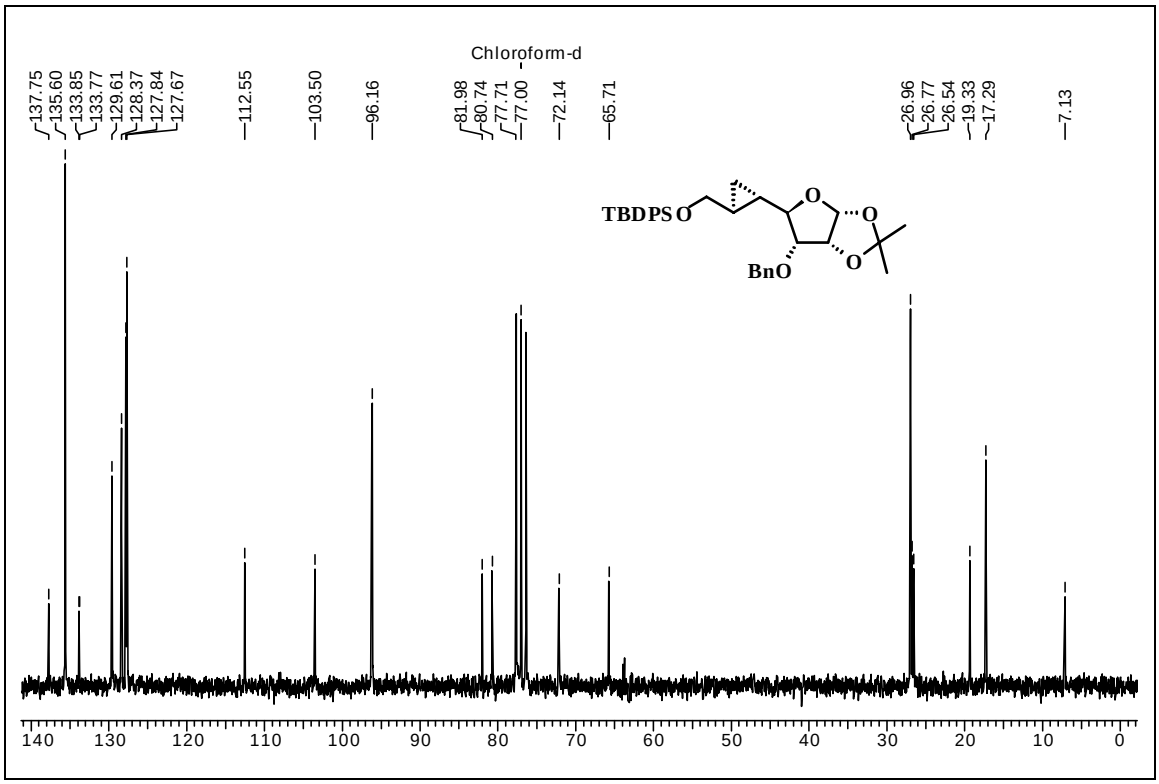
^{1}H NMR spectrum of compound 57 in $CDCl_3$



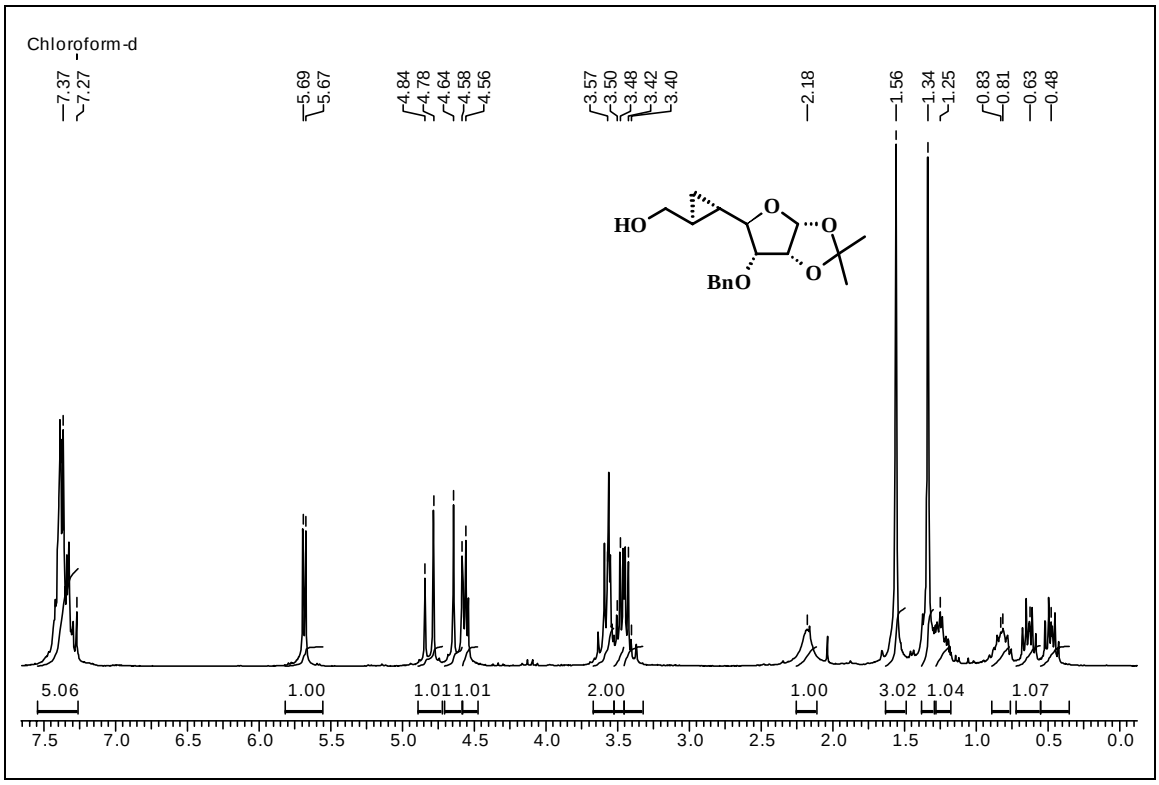
^{13}C NMR spectrum of compound 57 in $CDCl_3$



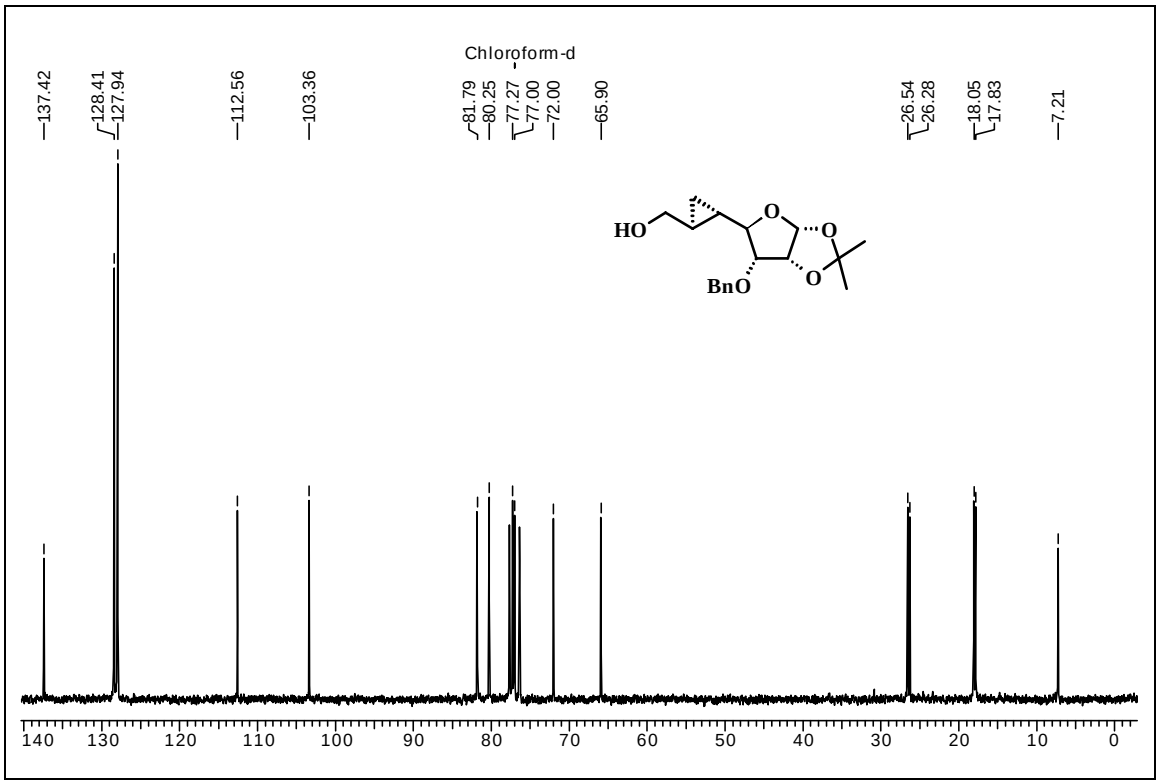
^{1}H NMR spectrum of compound 58 in $CDCl_3$



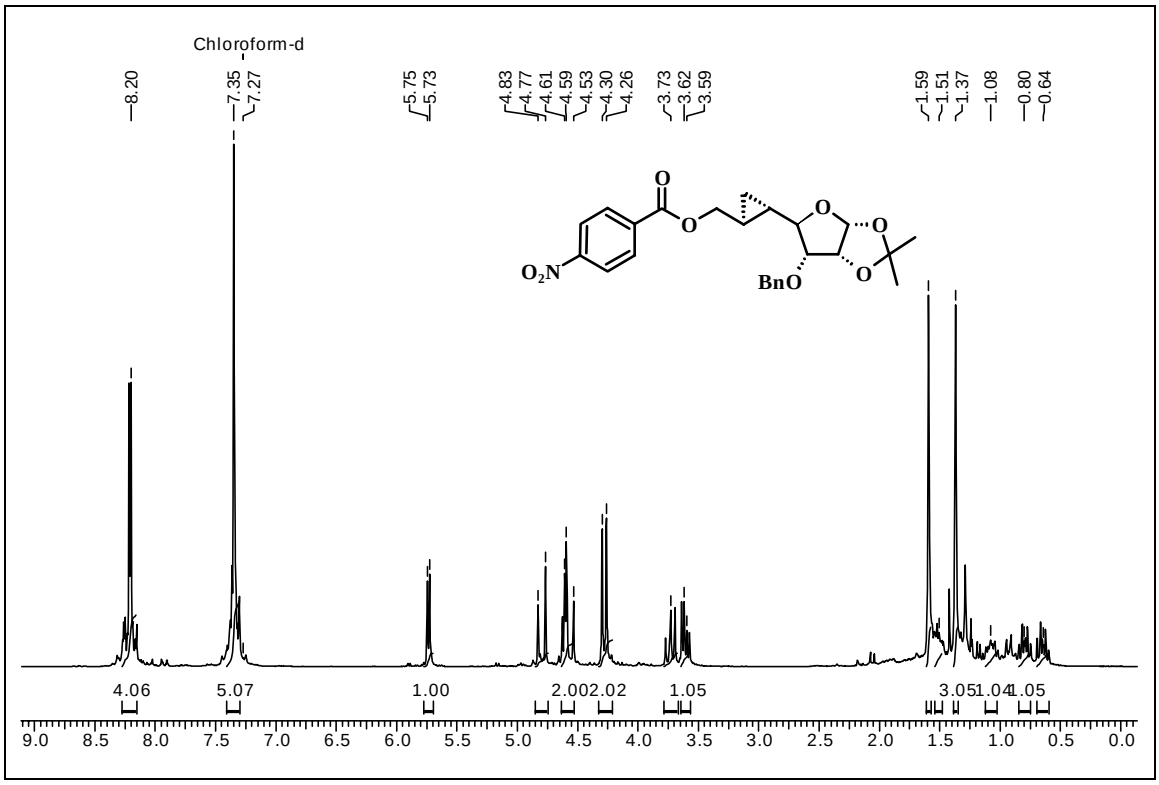
^{13}C NMR spectrum of compound 58 in $CDCl_3$



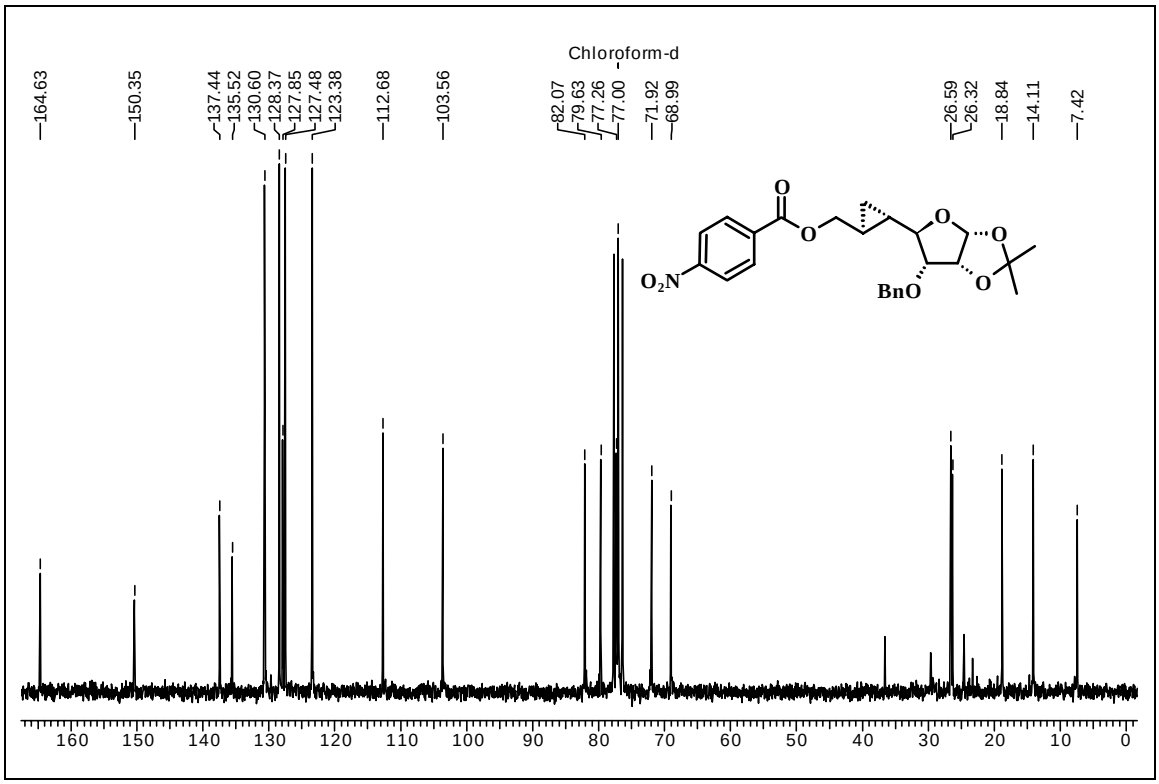
^{1}H NMR spectrum of compound 59 in $CDCl_3$



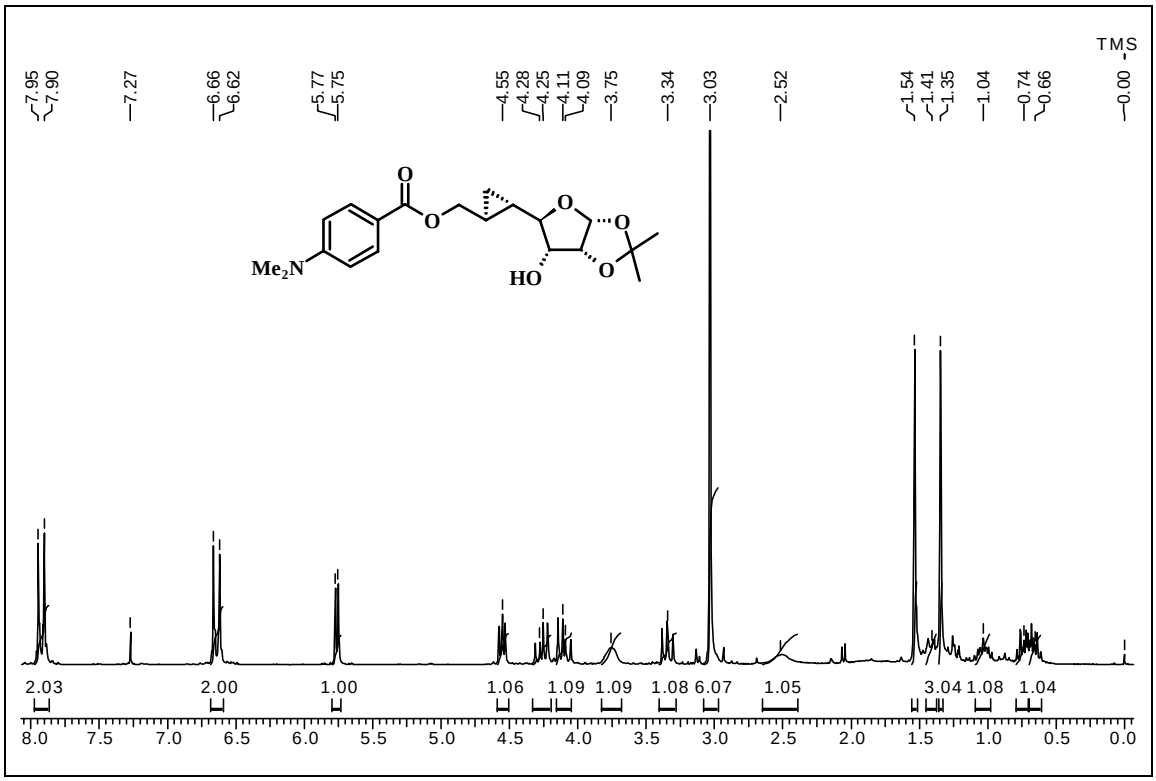
^{13}C NMR spectrum of compound 59 in $CDCl_3$



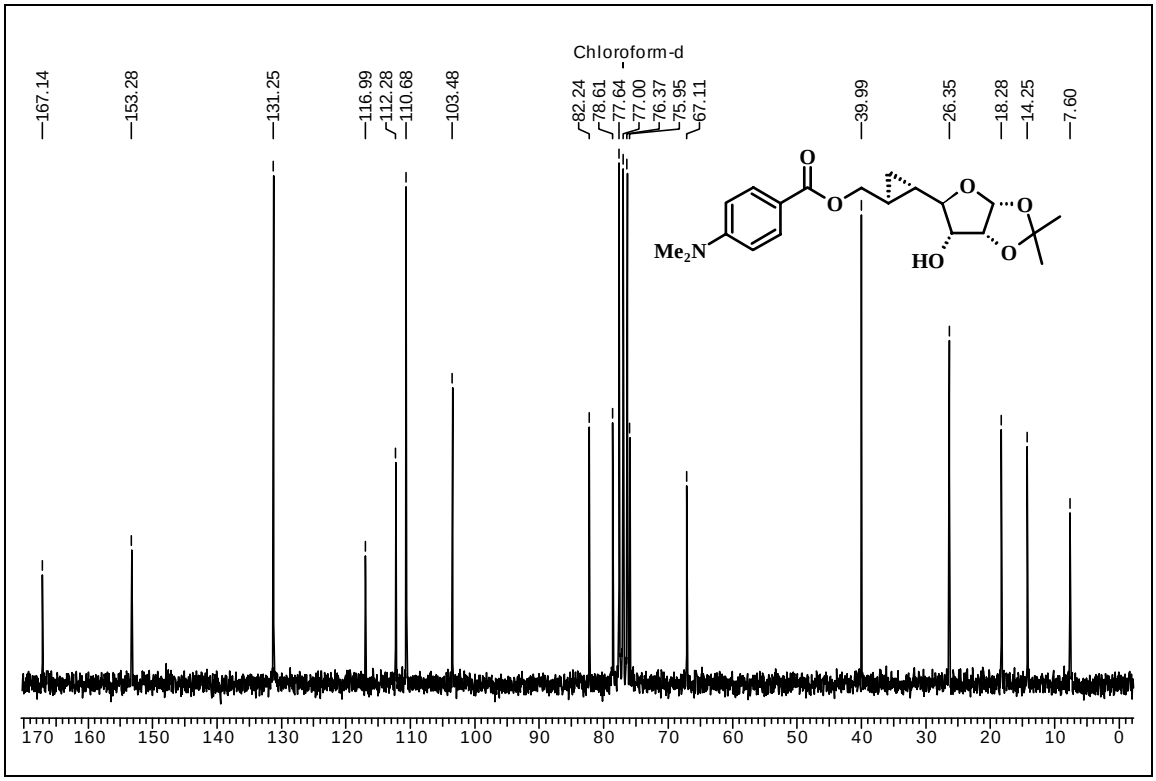
^{1}H NMR spectrum of compound 60 in $CDCl_3$



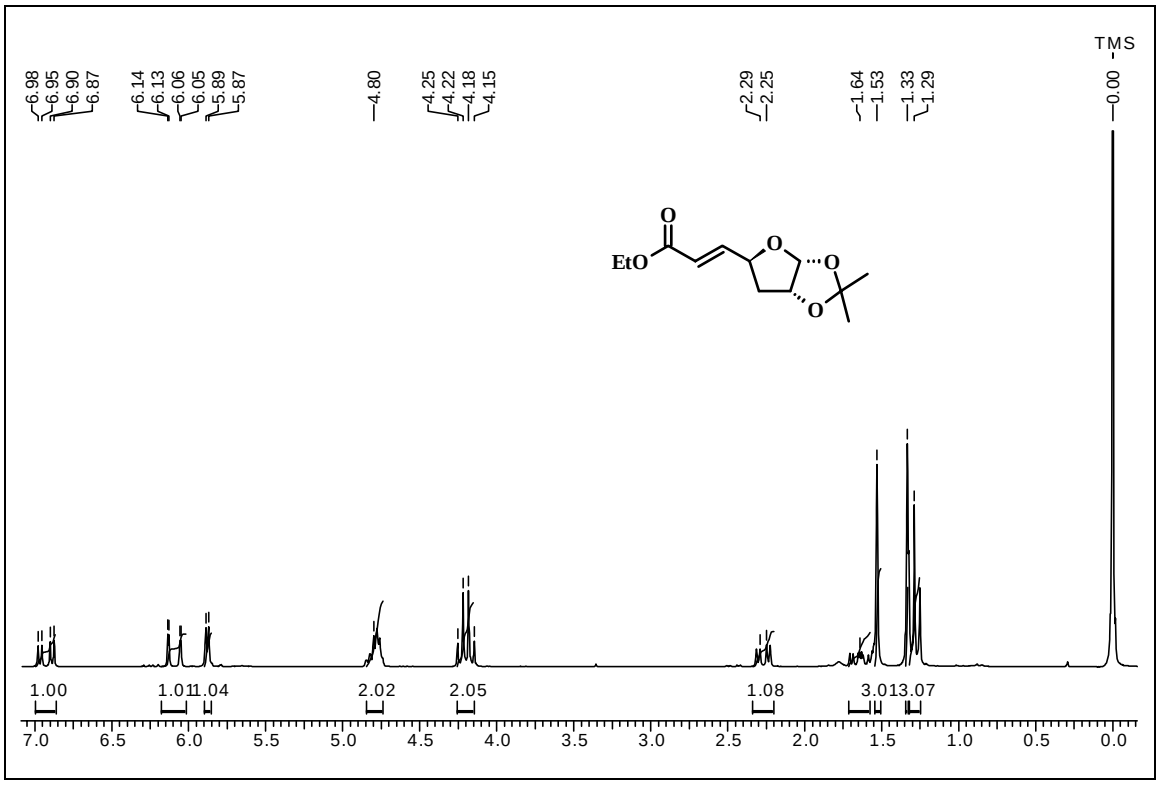
^{13}C NMR spectrum of compound 60 in $CDCl_3$



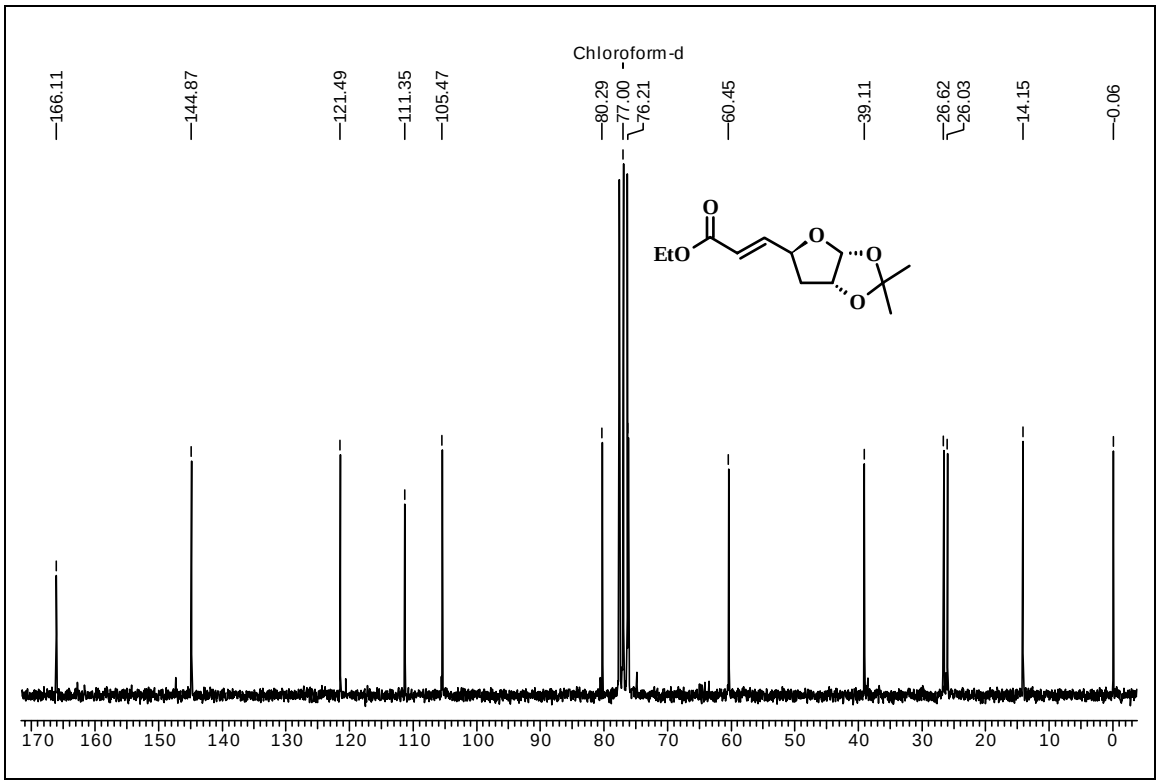
^{1}H NMR spectrum of compound 61 in $CDCl_3$



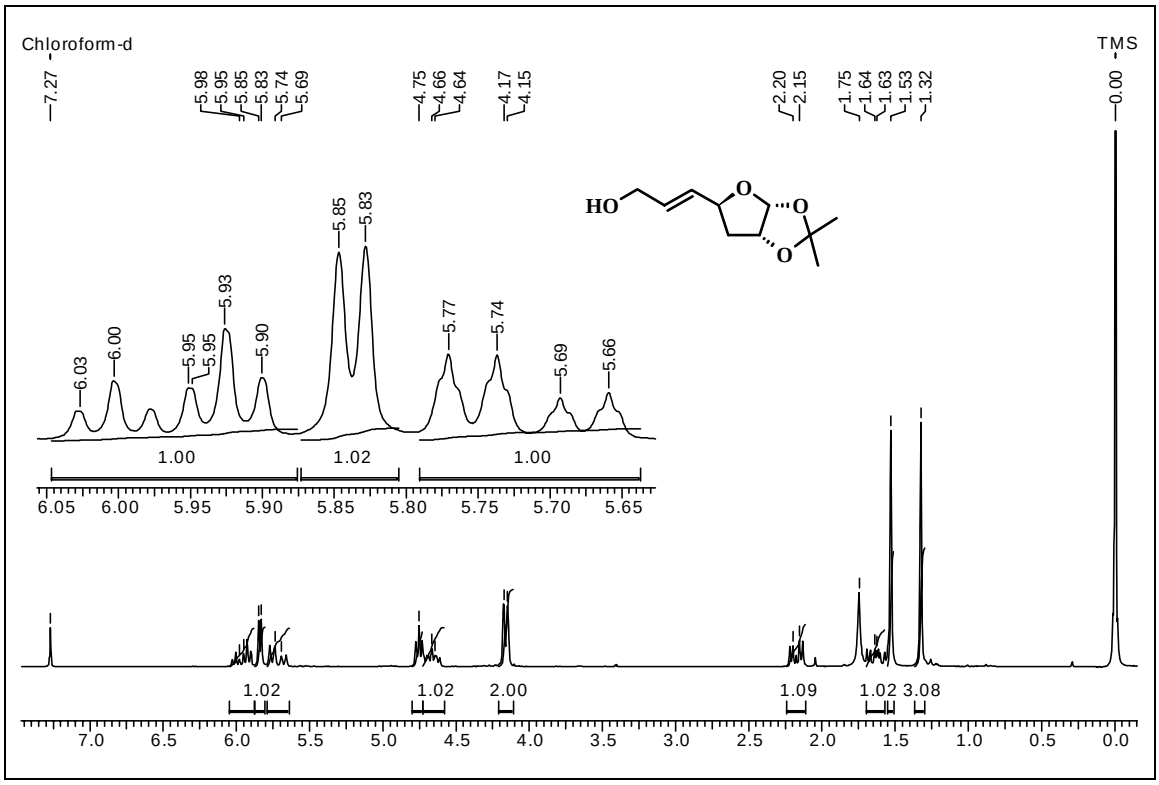
^{13}C NMR spectrum of compound 61 in $CDCl_3$



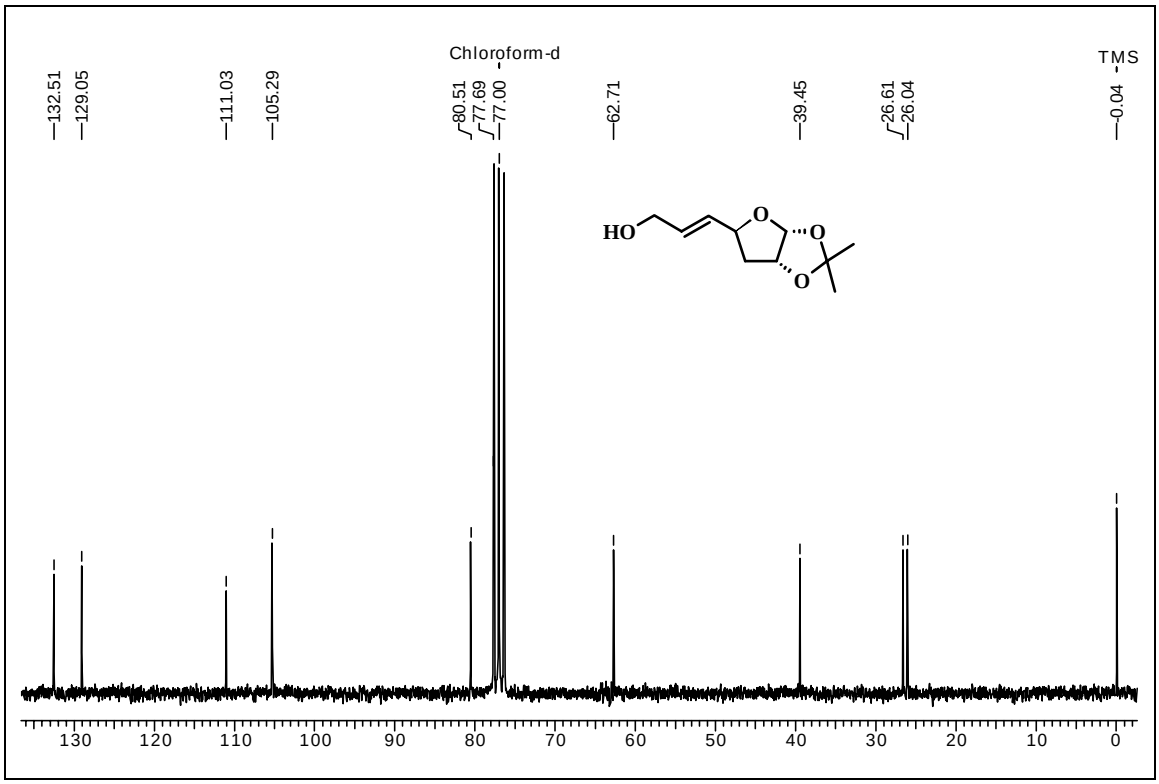
^{1}H NMR spectrum of compound 65 in $CDCl_3$



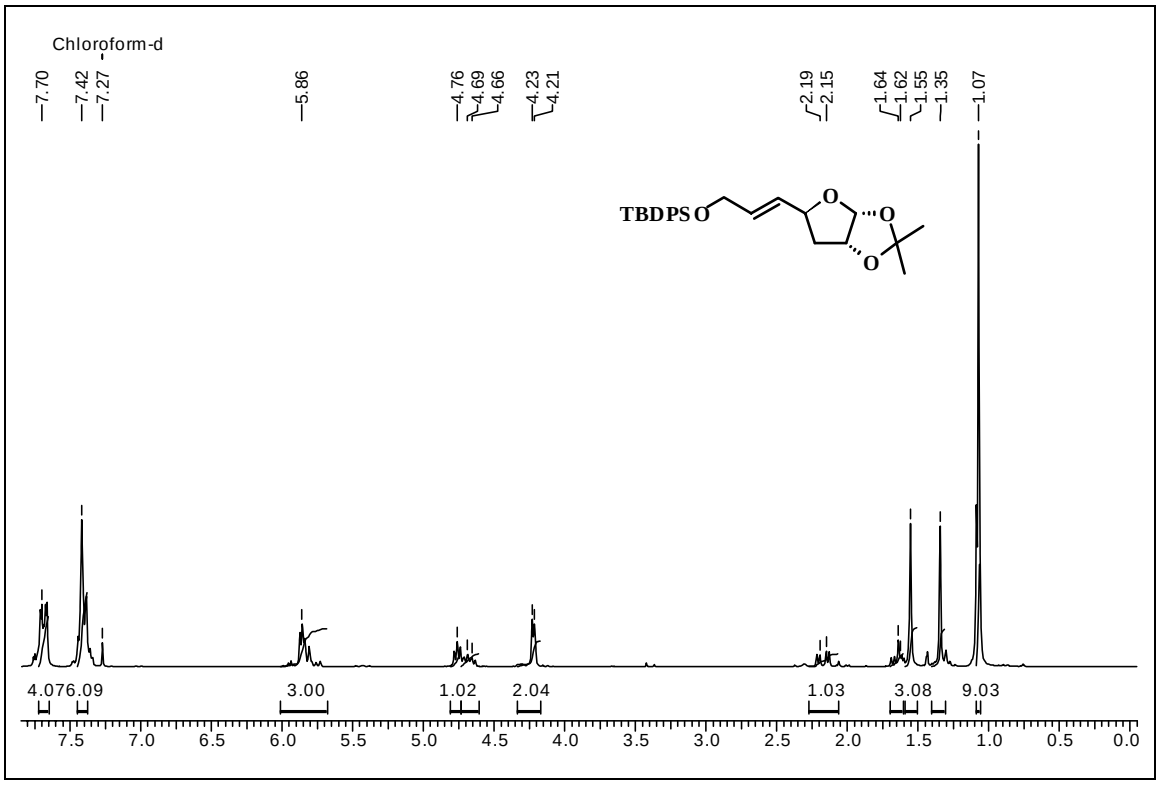
^{13}C NMR spectrum of compound 65 in $CDCl_3$



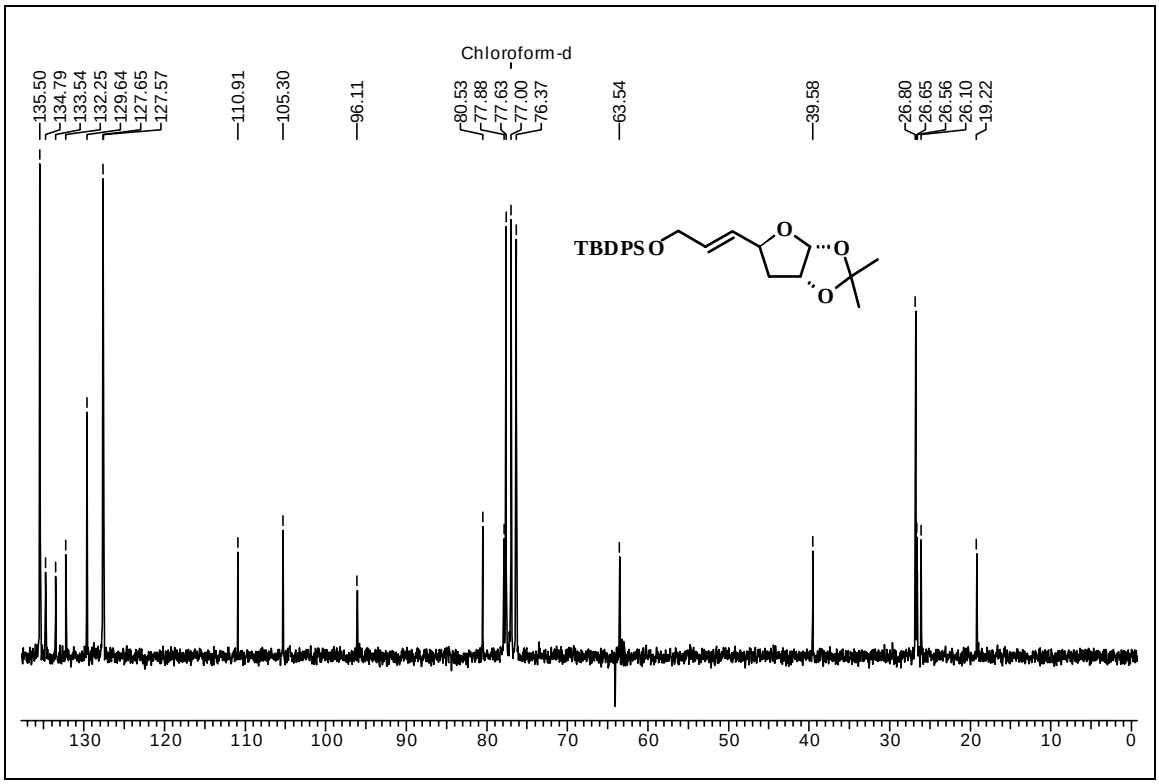
^{1}H NMR spectrum of compound 66 in $CDCl_3$



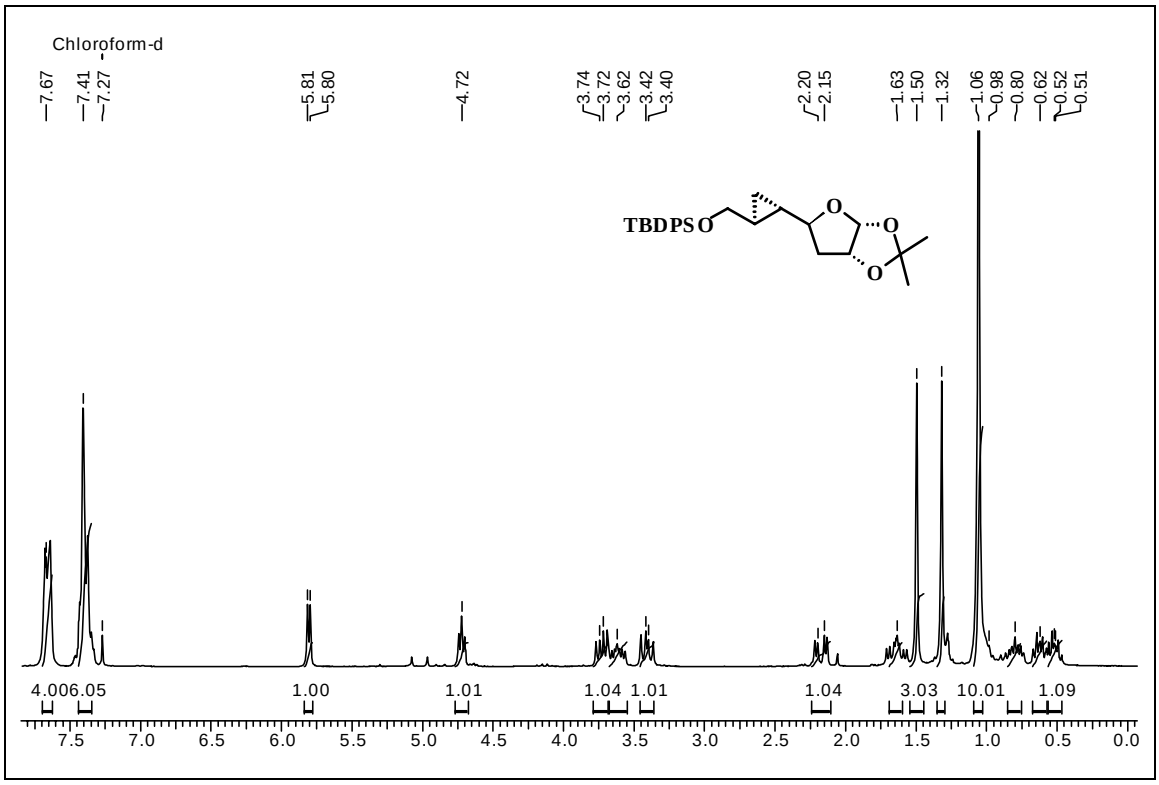
^{13}C NMR spectrum of compound 66 in $CDCl_3$



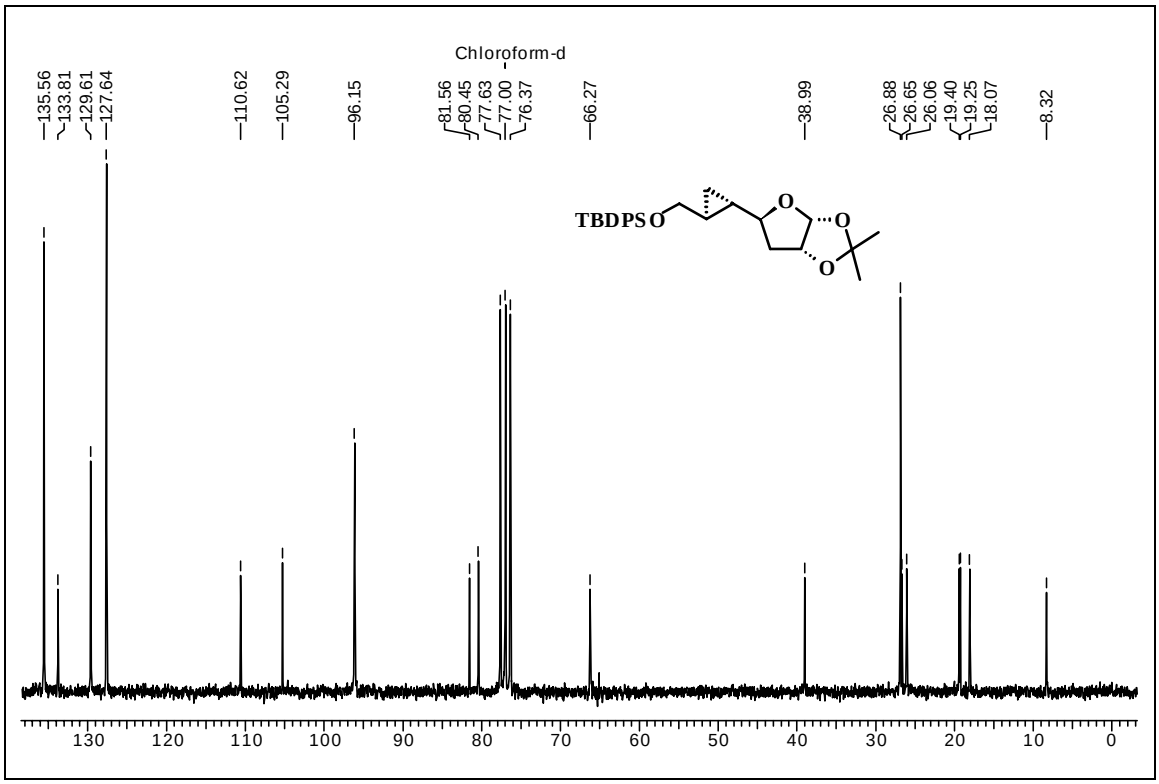
^{1}H NMR spectrum of compound 67 in $CDCl_3$



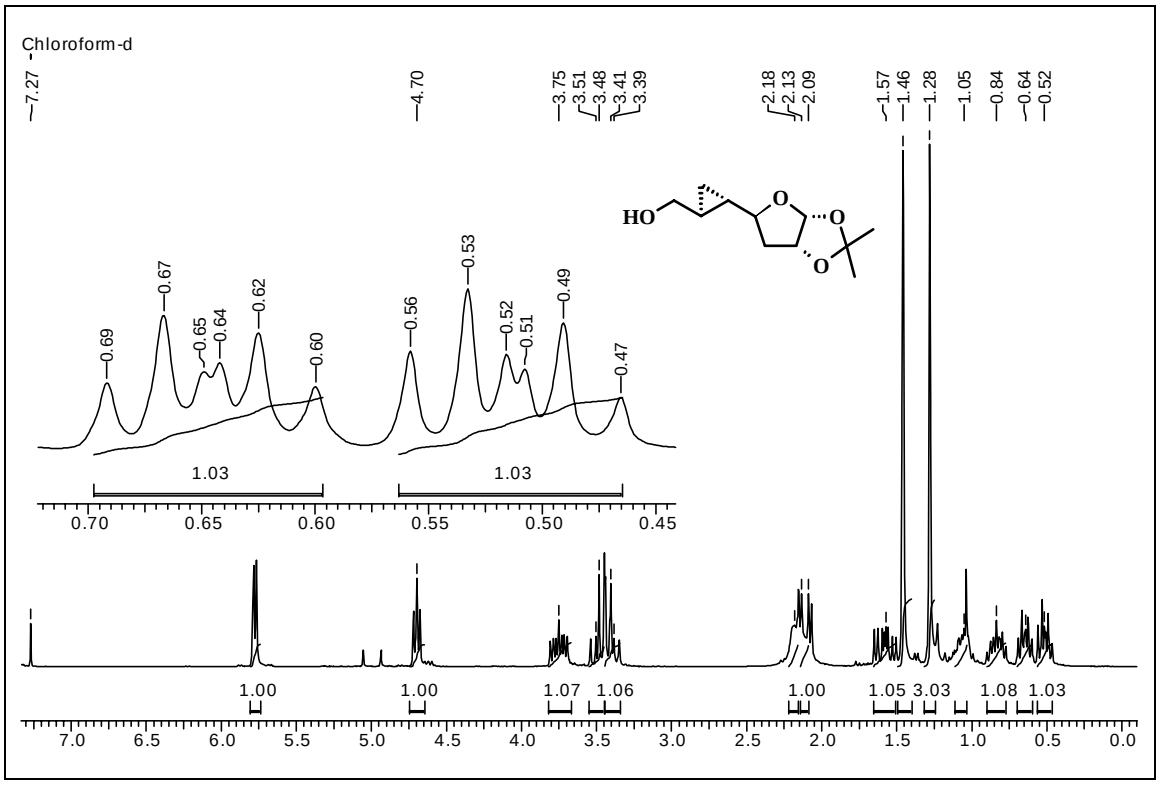
^{13}C NMR spectrum of compound 67 in $CDCl_3$



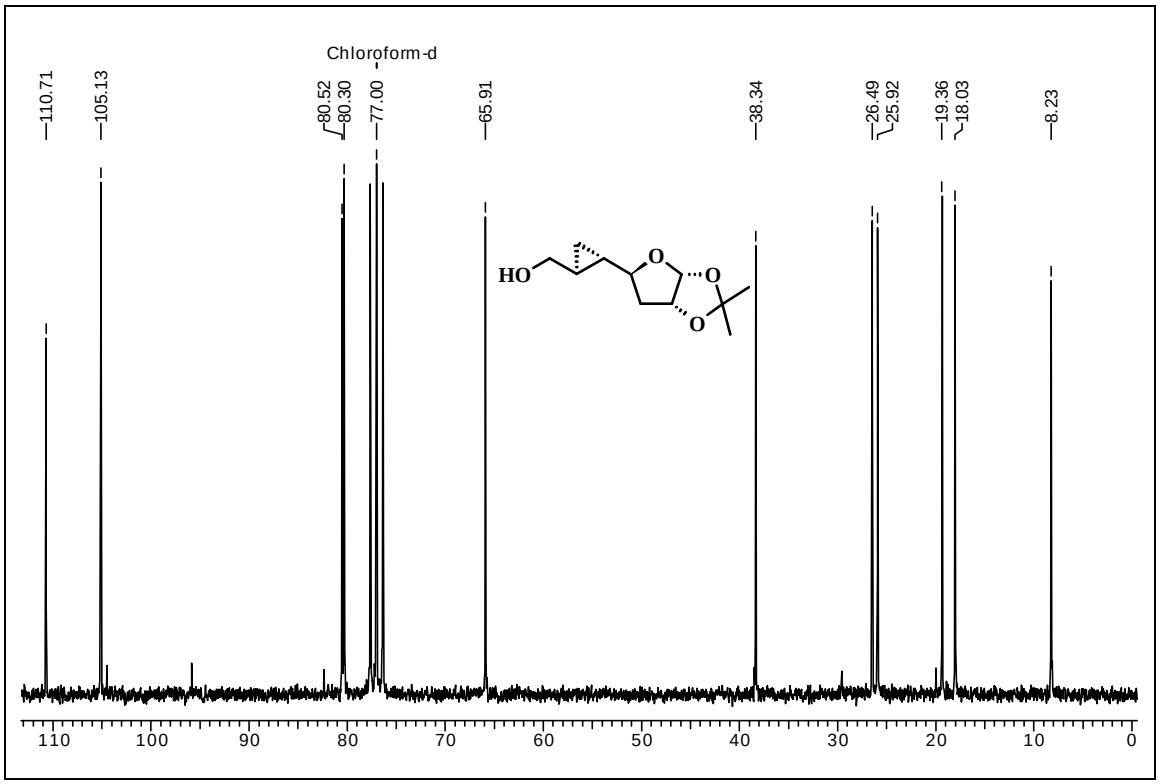
^{1}H NMR spectrum of compound 68 in $CDCl_3$



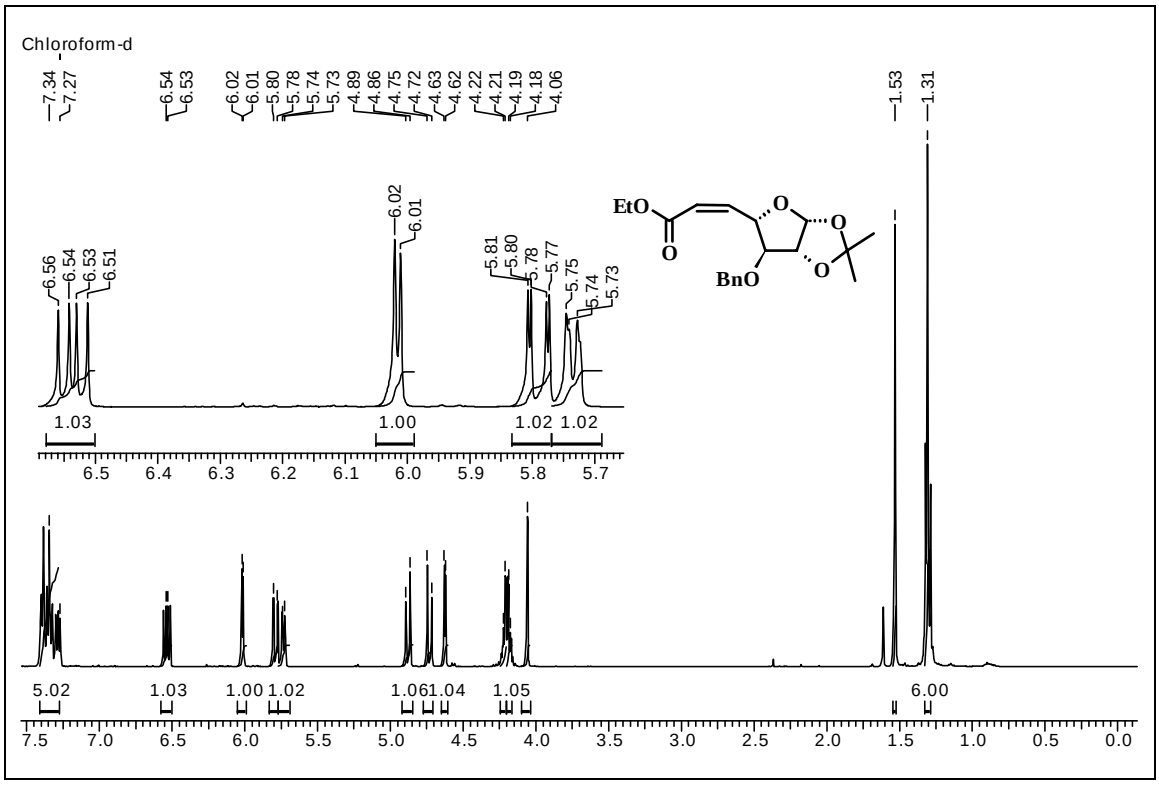
^{13}C NMR spectrum of compound 68 in $CDCl_3$



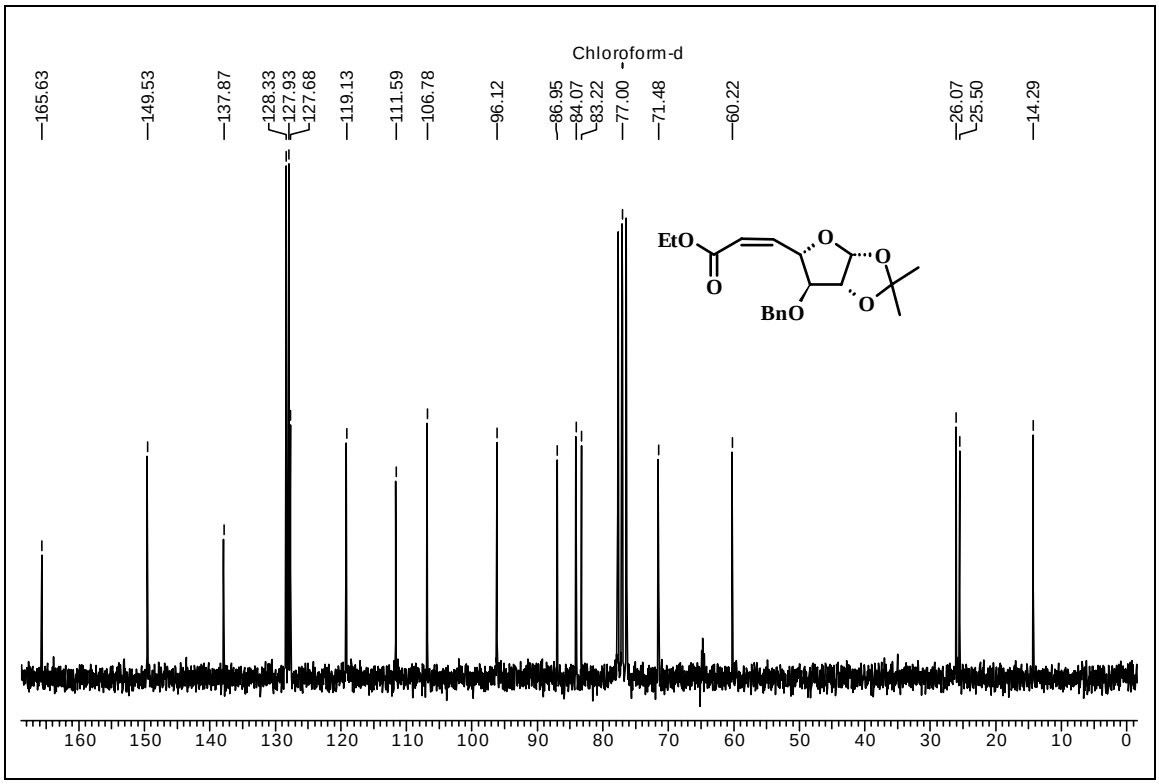
^{1}H NMR spectrum of compound 69 in $CDCl_3$



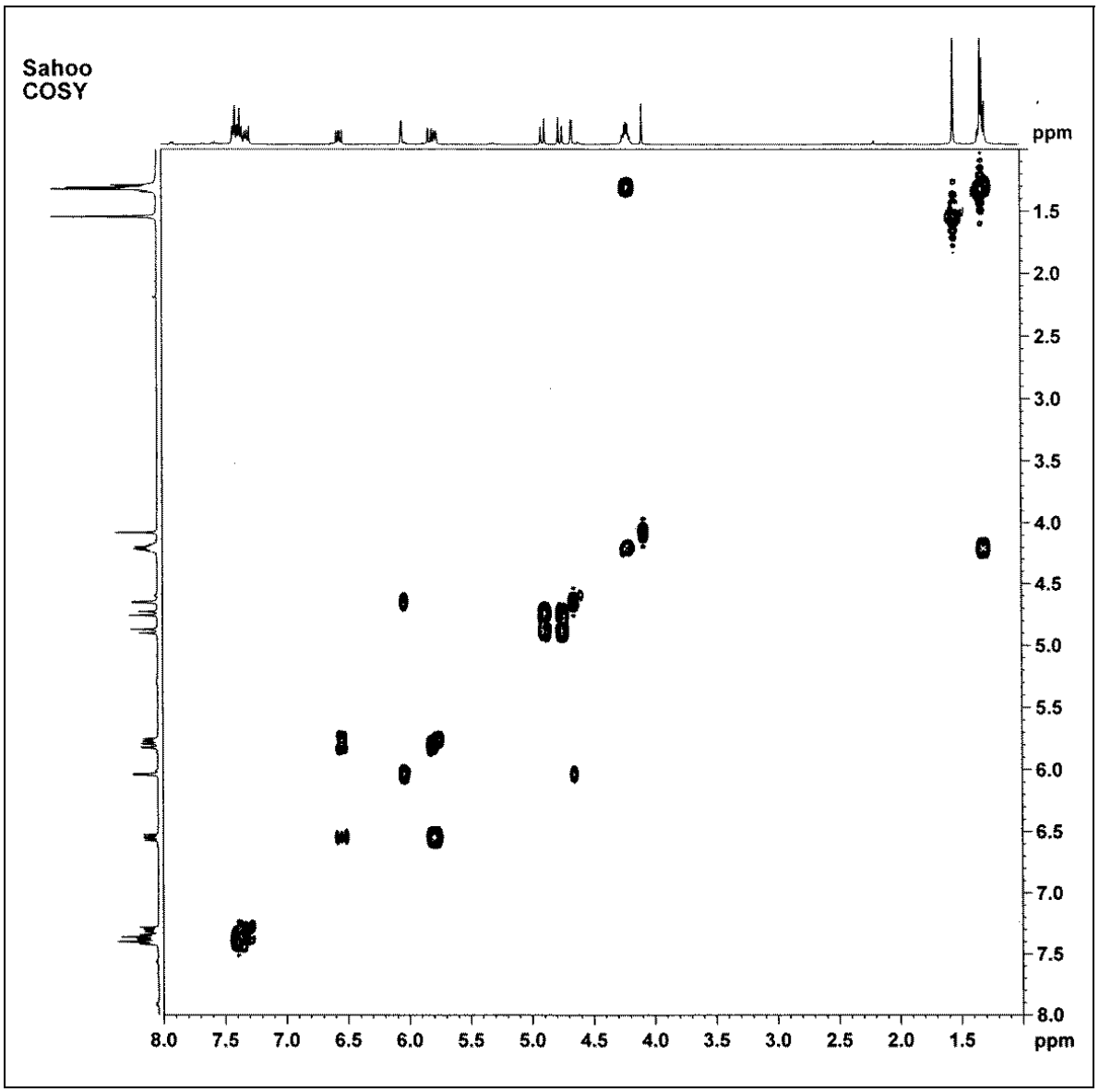
^{13}C NMR spectrum of compound 69 in $CDCl_3$

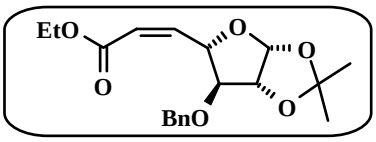


^{1}H NMR spectrum of compound 77 in $CDCl_3$

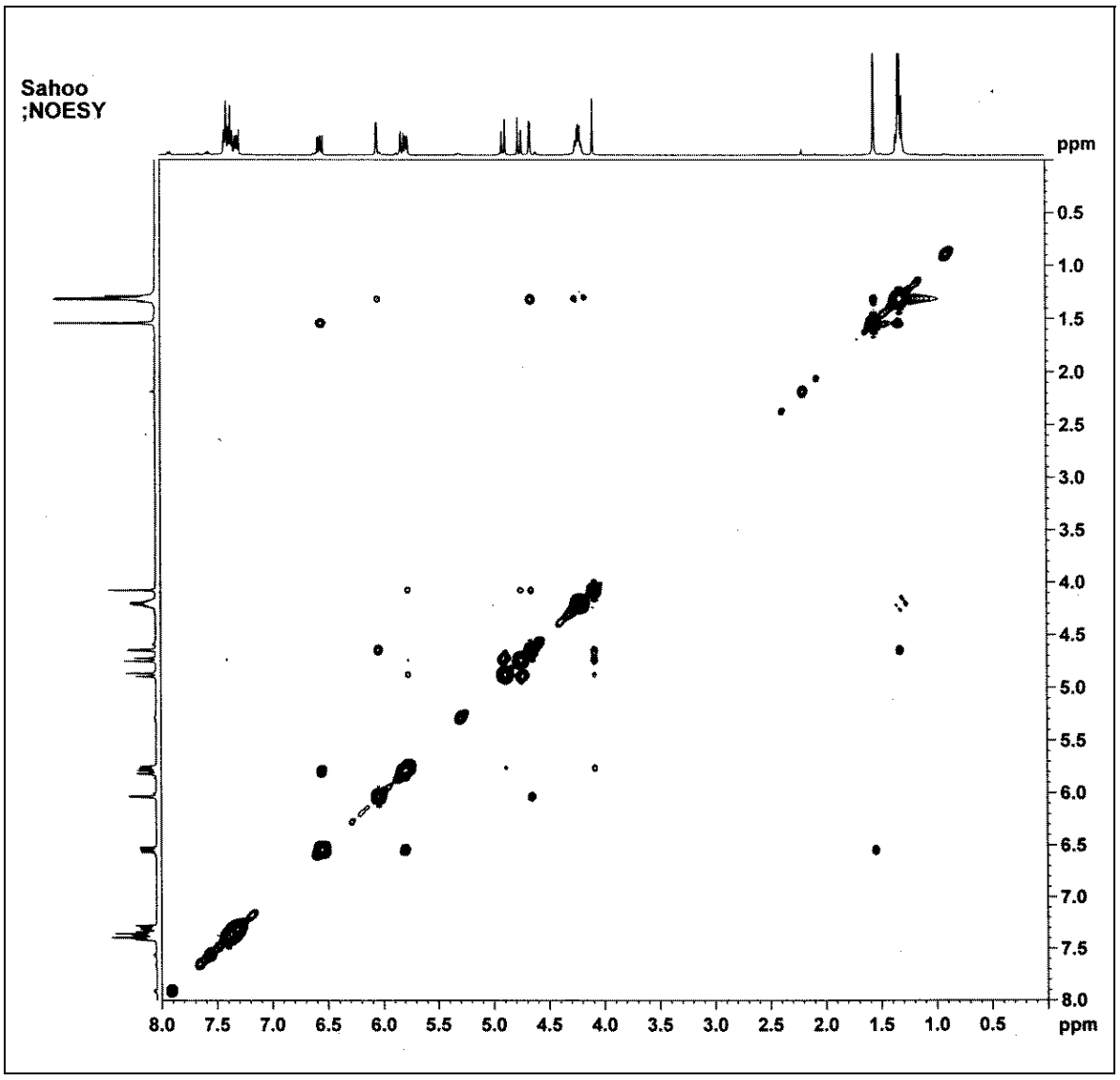


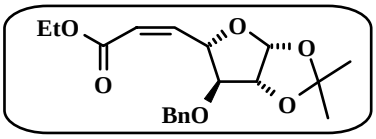
^{13}C NMR spectrum of compound 77 in $CDCl_3$



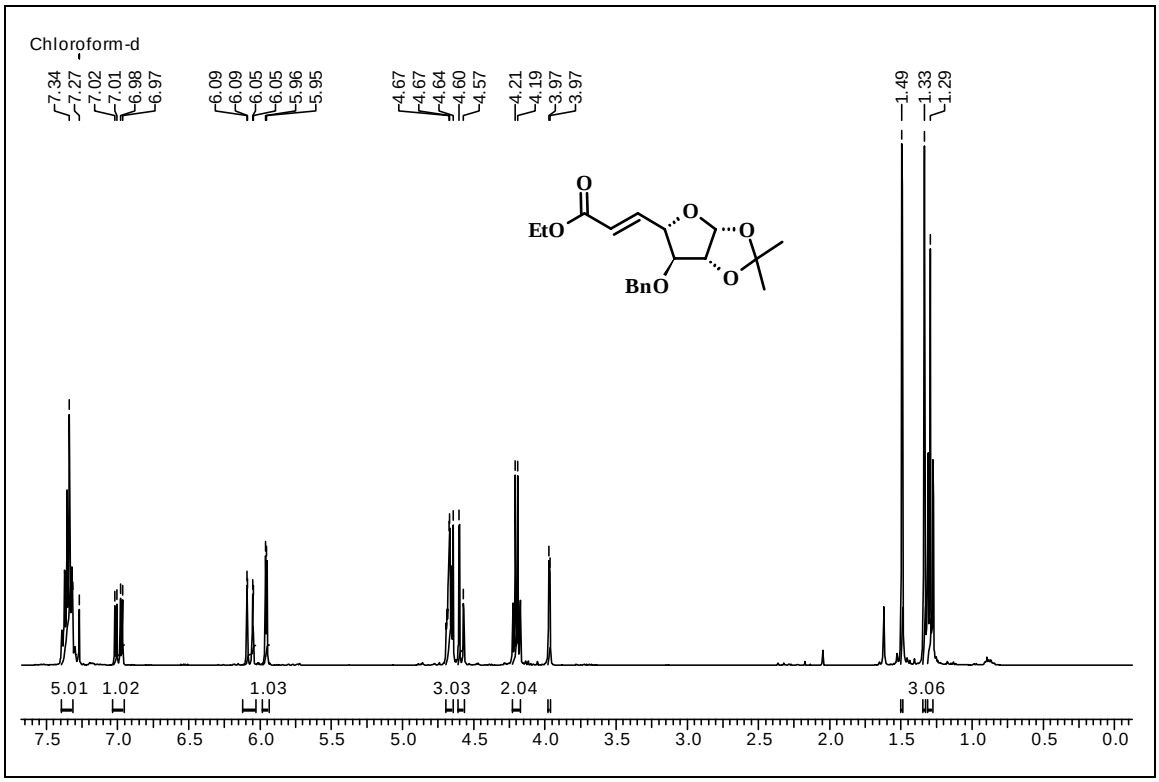


COSY spectrum of compound 77

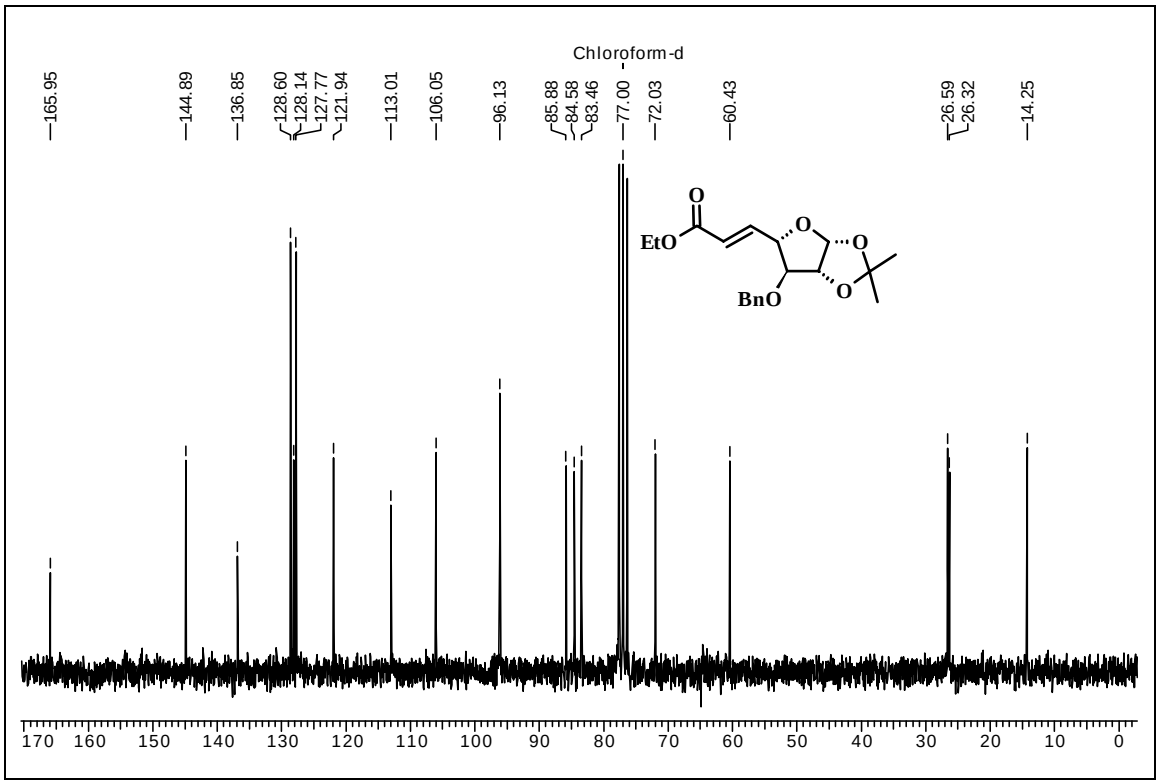




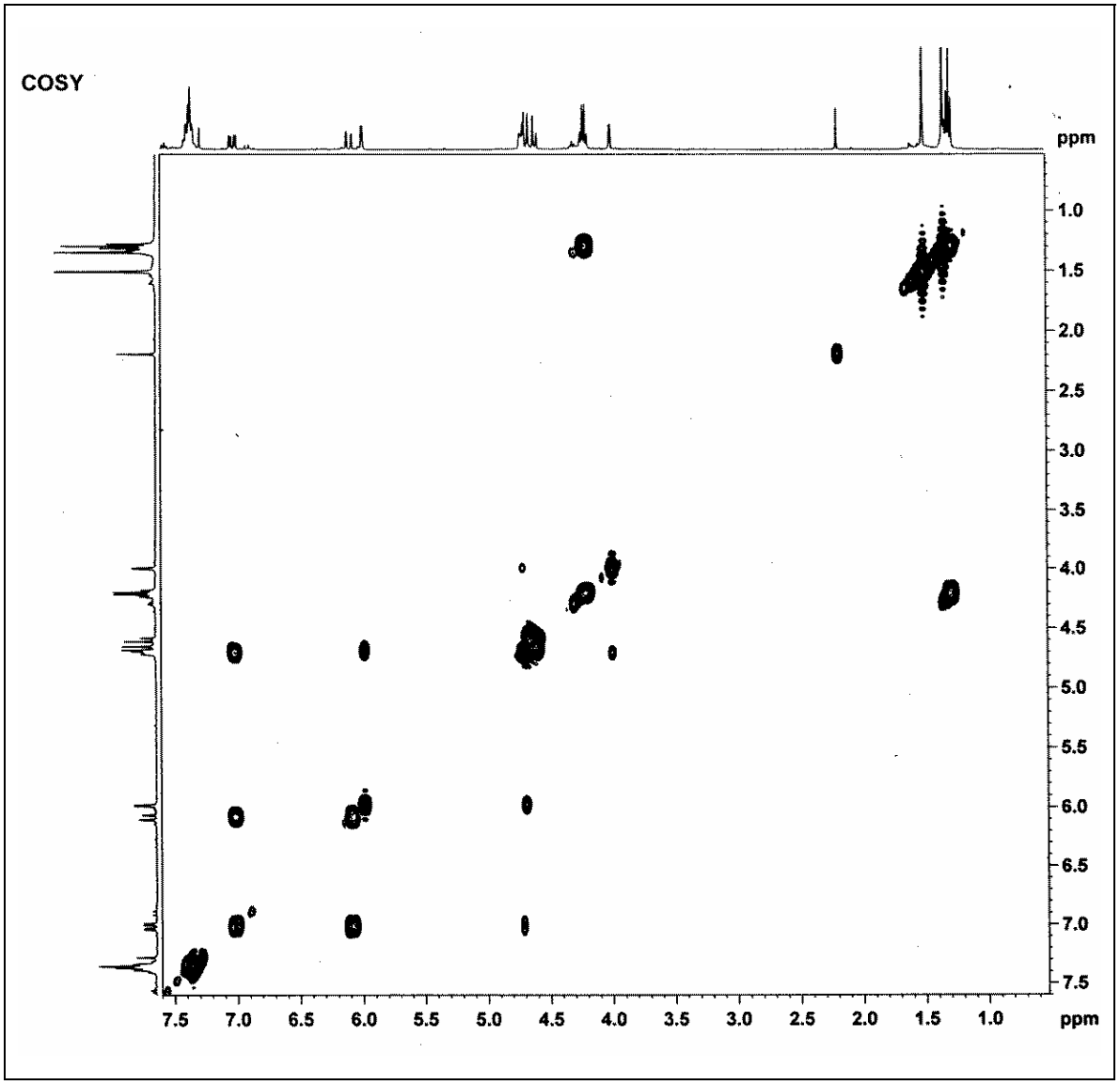
NOESY spectrum of compound 77

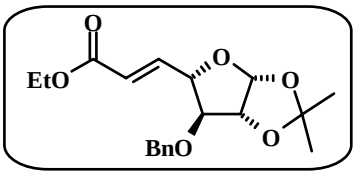


^{1}H NMR spectrum of compound 78 in $CDCl_3$

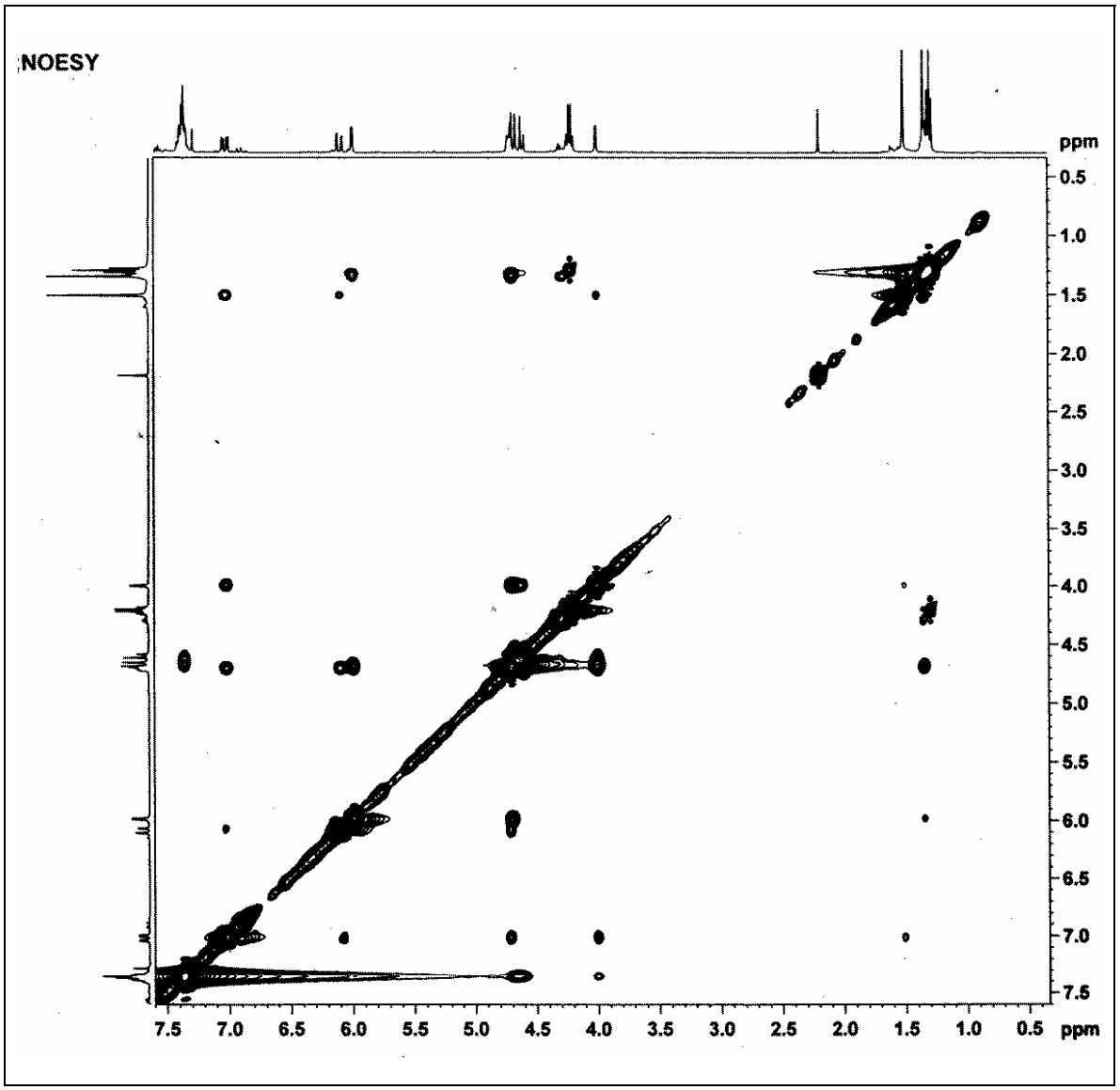


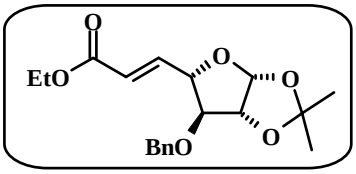
^{13}C NMR spectrum of compound 78 in $CDCl_3$



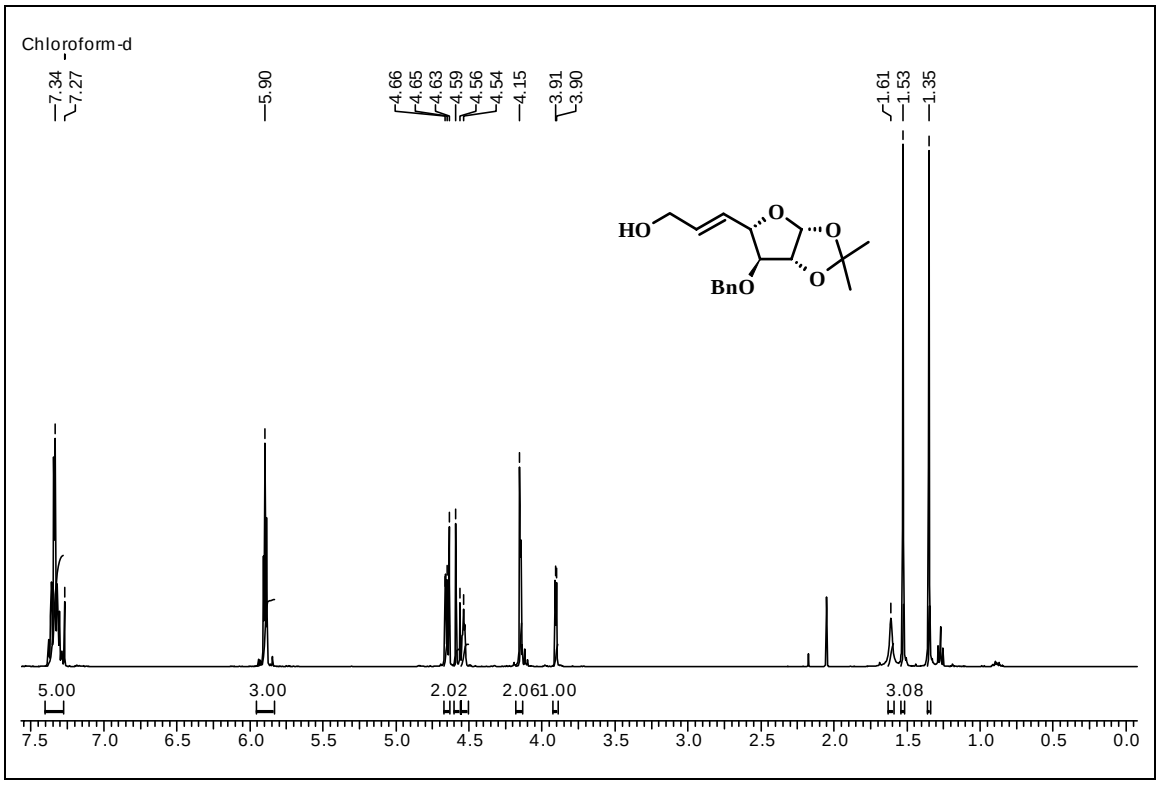


COSY spectrum of compound 78

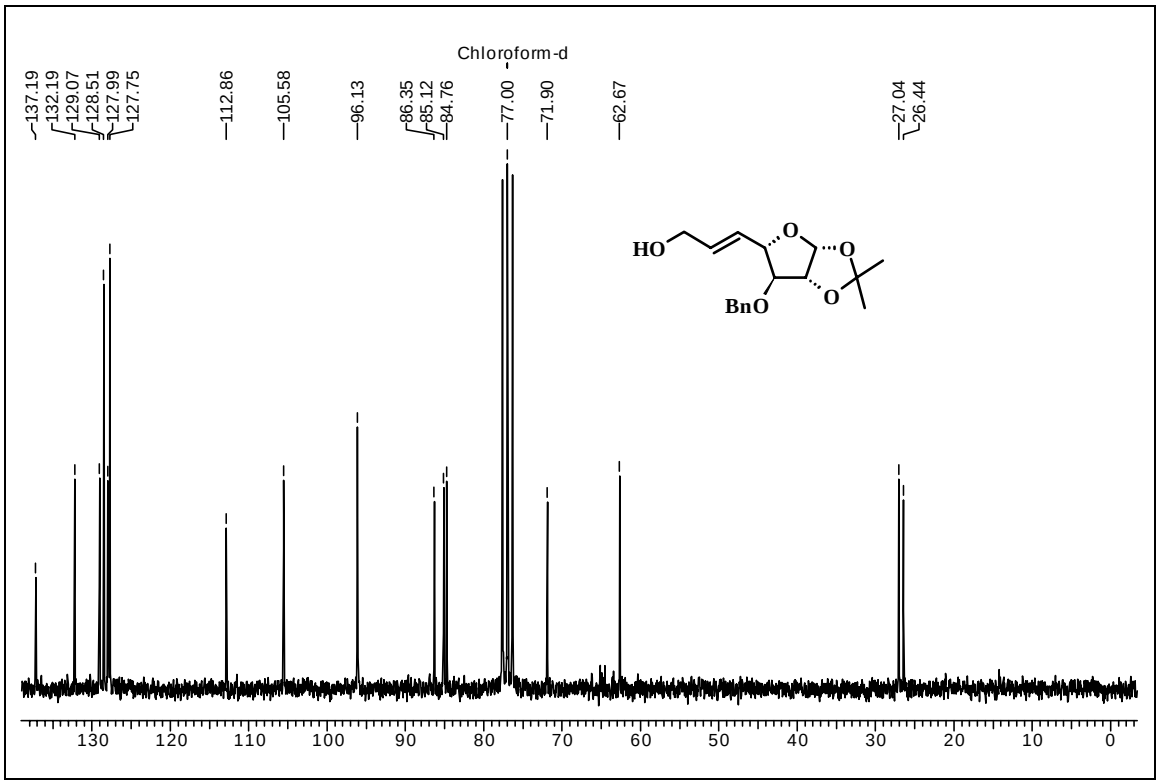




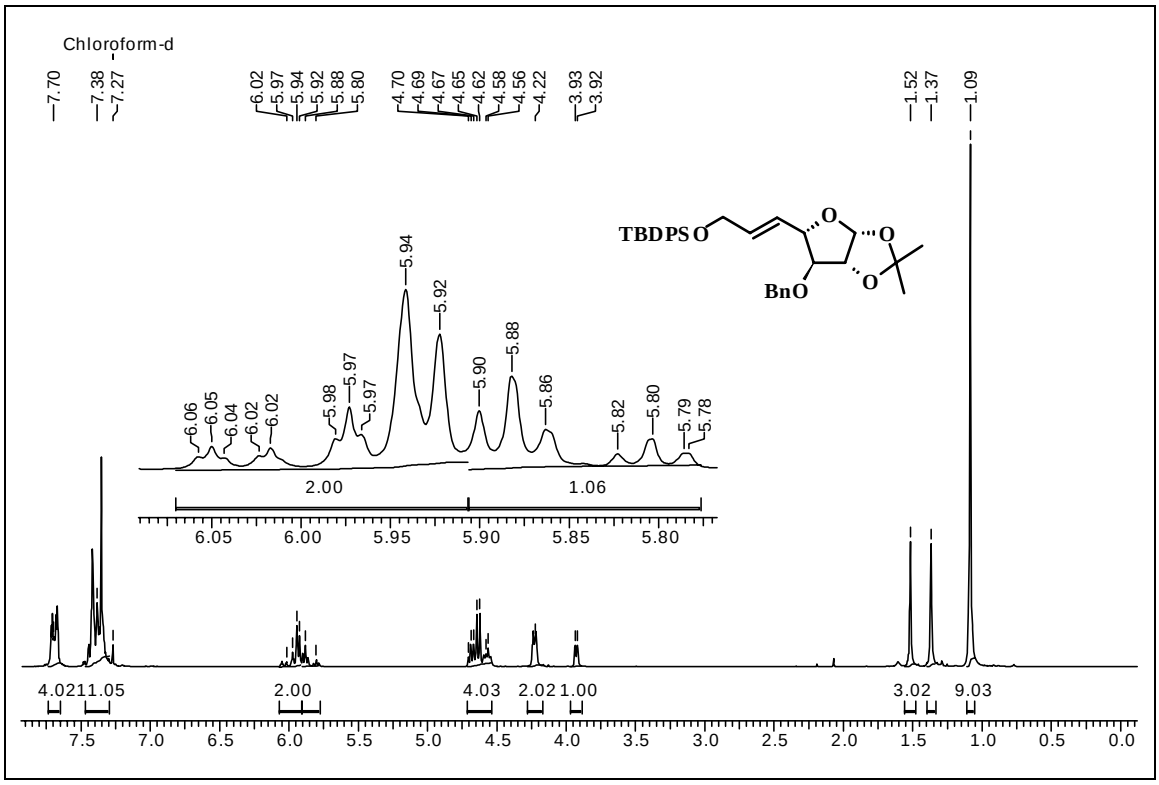
NOESY spectrum of compound 78



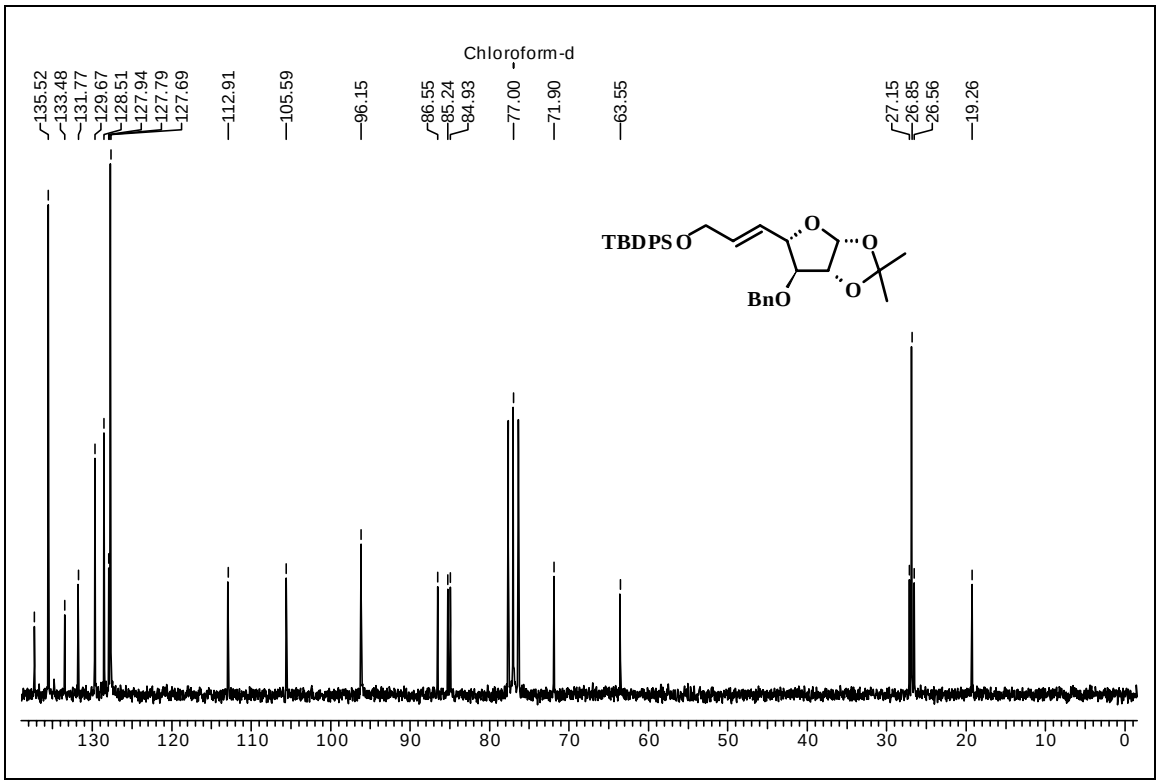
^{1}H NMR spectrum of compound 79 in $CDCl_3$



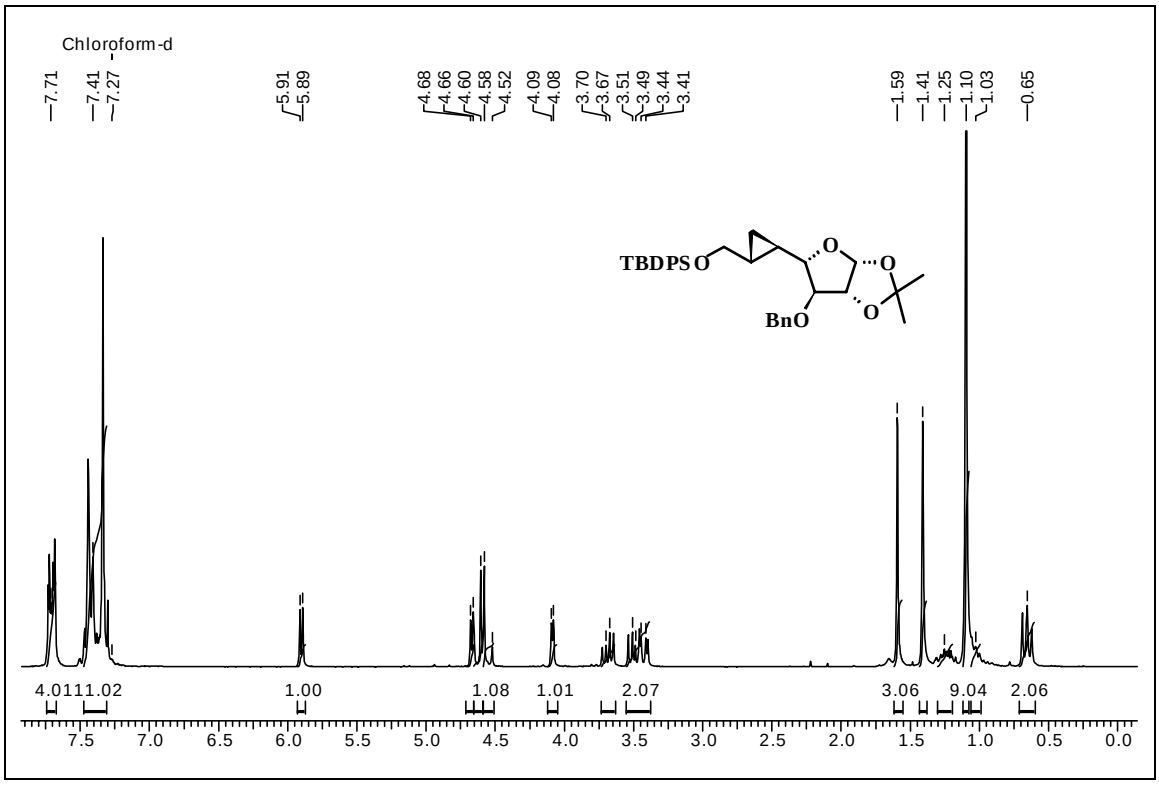
^{13}C NMR spectrum of compound 79 in $CDCl_3$



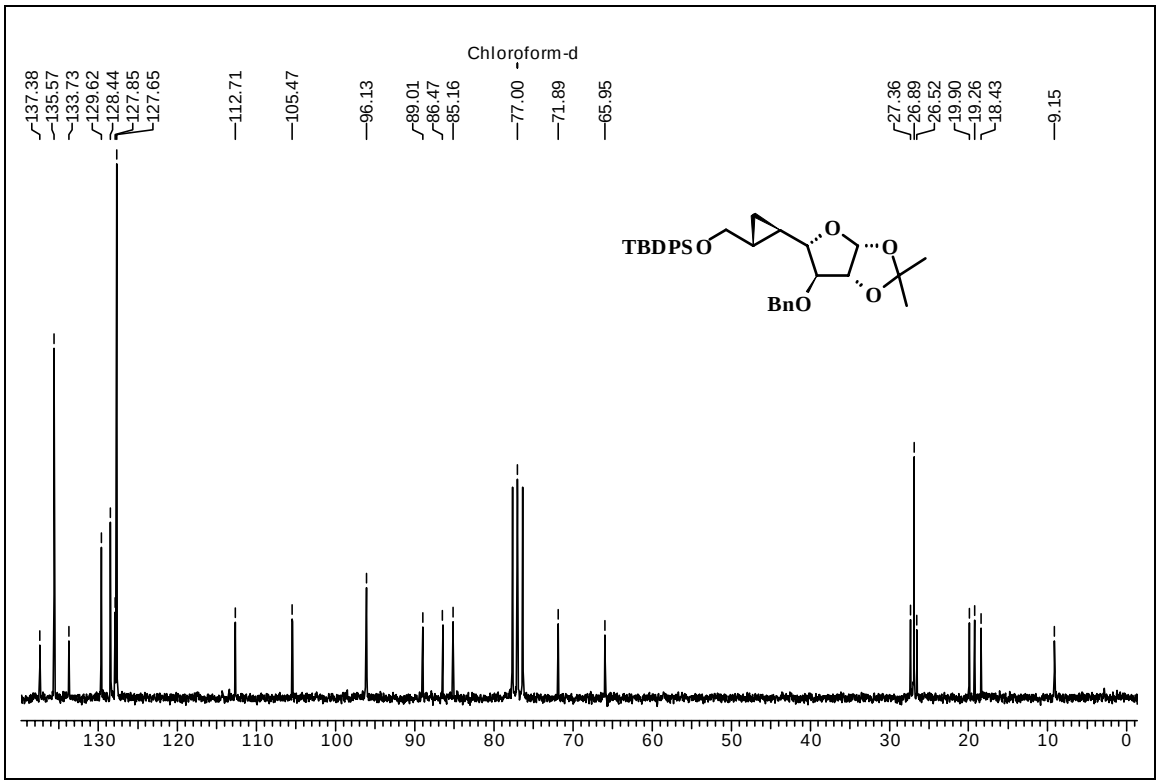
^{1}H NMR spectrum of compound 80 in $CDCl_3$



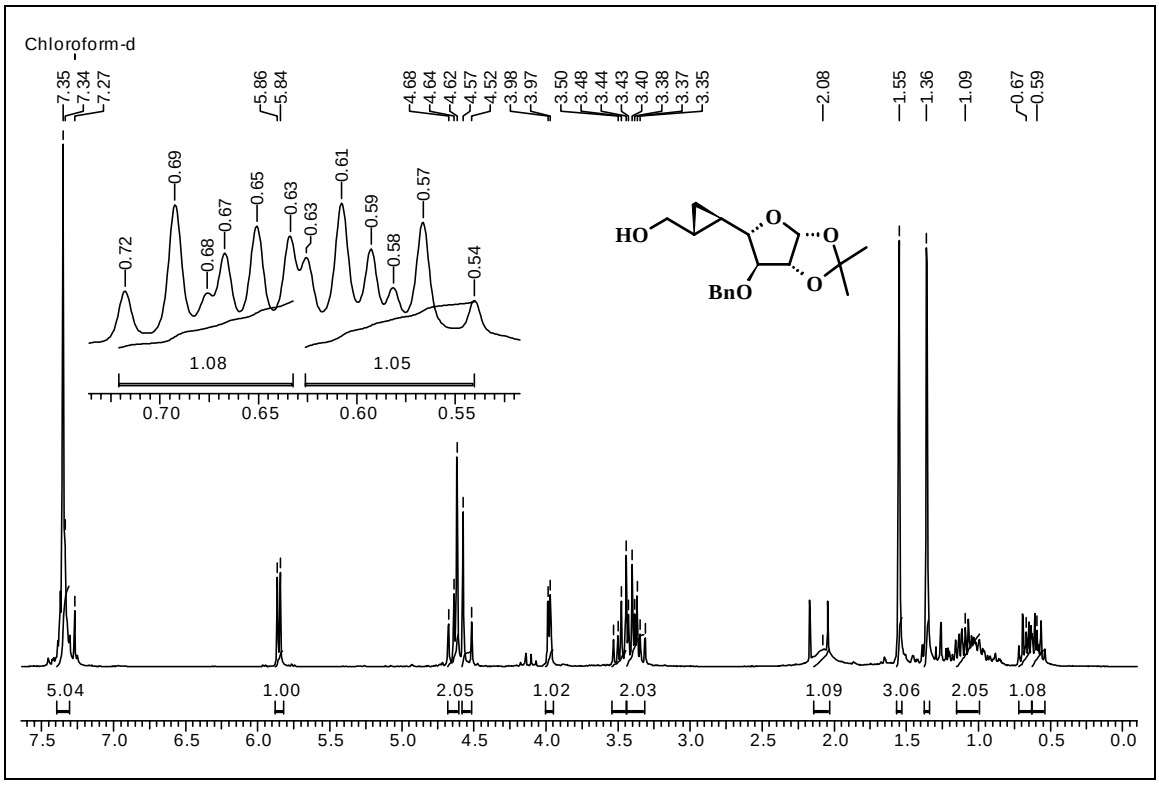
^{13}C NMR spectrum of compound 80 in $CDCl_3$



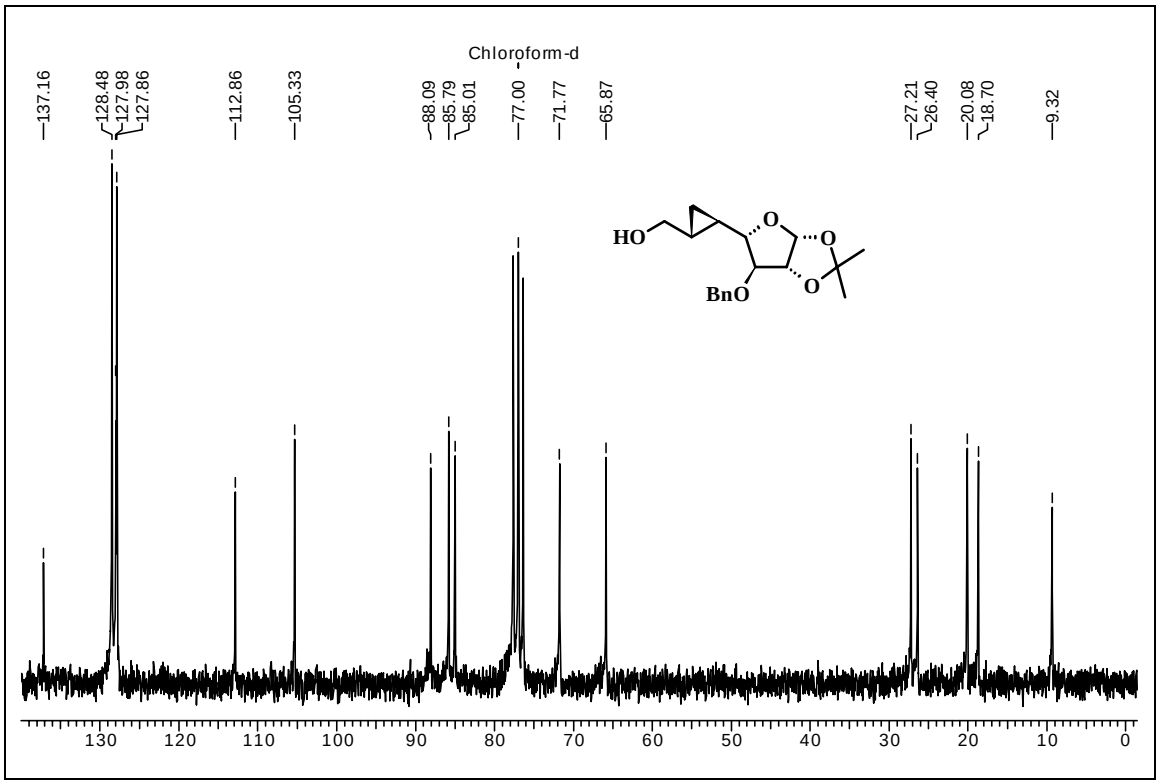
^{1}H NMR spectrum of compound 81 in $CDCl_3$



^{13}C NMR spectrum of compound 81 in $CDCl_3$



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



^{13}C NMR spectrum of compound 82 in $CDCl_3$

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Chapter II, Section II:

Studies toward the total synthesis of basiliskamides A and B

Introduction

There is no doubt that the existing arsenal of antimicrobial agents we have in hand for the treatment of infectious diseases is insufficient to protect us over the long term. The primary reason for this state of affairs is the inexorable drive of evolution that leads to antimicrobial resistance.[1] At the same time, we must also acknowledge our inability to predict with any accuracy the nature of new emerging infections. Witness the stunning impact of HIV over the past 20 years, the unexpected causative link between peptic ulcer disease and *Helicobacter pylori*, the recent emergence of SARS and avian influenza, and the ensuing dramatic impact these epidemics have had on human and animal health as well as the international economy. Our continued vulnerability to the effects of microbes should be humbling.

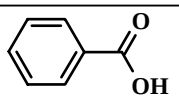
Resistance to antibiotics is an unavoidable side effect of their use. The time scales of the life cycle of microbes and the 'adapt or die' paradigm that is imposed with the current arsenal of agents that either stop growth or cause cell death conspire against the indefinite longevity of antibiotics. We cannot avoid resistance nor can we predict with any accuracy the emergence of new infectious agents, but we can work to mitigate these issues with research that will yield new agents of novel mechanism and chemical class. Main classes of this broad aspect i.e. antimicrobial agent include (i) **antibiotics**, (ii) **antivirals**, (iii) **antifungals**, (iv) **antiparasitics** etc. We will be concentrating on the various aspects and types of antifungal activities with some important drug molecules.

Antifungal (Latin word "*anti*" means against) is a chemotherapeutic agent that inhibits or abolishes the growth of fungi microorganisms. An antifungal drug is a medication used to treat fungal infections such as ringworm, candidiasis (thrush), serious systemic infections such as cryptococcal meningitis, and others.

How antifungals work! Antifungals work by exploiting differences between mammalian and fungal cells to kill off the fungal organism without dangerous effects on the host. Unlike bacteria, both fungi and humans are eukaryotes. Thus fungal and human cells are similar at the molecular level. This means it is more difficult to find a target for an antifungal drug to attack that does not also exist in the infected organism. Consequently,

there are often side-effects to some of these drugs. Some of these side-effects can be life-threatening if not used properly. Such drugs are usually obtained by a doctor's prescription or purchased over-the-counter.

Benzoic acid (**1**) is the simplest antifungal organic molecule (Figure 1) and it is used in combination with a keratolytic agent. In 1875 Salkowski discovered the antifungal abilities of benzoic acid, which was used for a long time in the preservation of benzoate containing foods.



(1) Benzoic acid: simplest antifungal organic molecule

Figure 1

Depending upon the chemical structure; there are several classes of antifungal drugs like polyene antifungals, imidazole and triazole antifungals, allyl amine antifungals etc.

Polyene antifungals: A polyene is a circular molecule consisting of a hydrophobic and hydrophilic region. This makes polyene, an amphoteric molecule. The polyene antimycotics bind with sterols in the fungal cell membrane, principally ergosterol. This changes the transition temperature of the cell membrane, thereby placing the membrane in a less fluid, more crystalline state. As a result, the cell's contents leak out (usually the hydrophilic contents) and the cell dies. Animal cells contain cholesterol instead of ergosterol and so they are much less susceptible. (Note: as polyene's hydrophobic chain is reduced, its sterol binding activity is increased. Therefore, increased reduction of the hydrophobic chain may result in it binding to cholesterol, making it toxic to animals.). Although the polyene macrolide antibiotics exhibit potent antifungal activity, most are too toxic for therapeutic applications, with the exceptions of amphotericin B and nystatin.

Nystatin (**2**)[2] {named after the New York State Public Health Department (now known as the Wadsworth Center) in 1954 by Hazen and Brown} is a polyene antifungal drug to which many molds and yeast infections are sensitive, including *Candida* sp (Figure 2). Nystatin has some toxicity associated with it when given intravenously, but it is not absorbed across intact skin or mucous membranes. It is considered a relatively safe drug for treating oral or gastrointestinal fungal infections. Like many other antifungals and antibiotics, nystatin is of bacterial origin. It was isolated from *Streptomyces noursei*

in 1950 by Elizabeth Lee Hazen and Rachel Fuller Brown. The soil sample where they discovered nystatin was from the garden of Hazen's friends called Nourses, therefore the strain was called *noursei*.

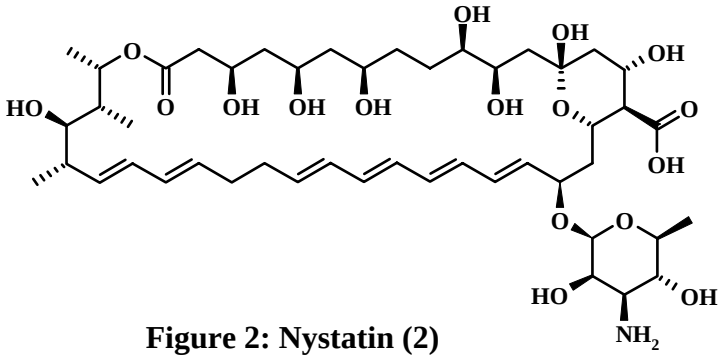


Figure 2: Nystatin (2)

Nystatin (**2**) binds to ergosterol, a major component of the fungal cell membrane. When present in sufficient concentrations, it forms pores in the membrane that lead to K^+ leakage and death of the fungus. Ergosterol is fairly unique to fungi, so the drug does not have such catastrophic effects on animals. Nystatin is often used as prophylaxis in patients who are at risk for fungal infections, such as AIDS patients with a low $CD4^+$ count[3] and patients receiving chemotherapy.

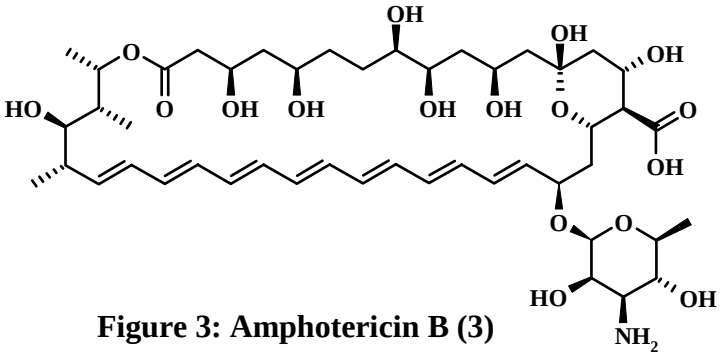


Figure 3: Amphotericin B (3)

Amphotericin B (**3**)[4] is a well-known polyene antifungal drug (Figure 3), with famous brand names such as Fungilin, Fungizone, Abelcet, AmBisome, Fungisome, Amphocil, Amphotec, often used intravenously for systemic fungal infections. It was originally extracted from *Streptomyces nodosus*, a filamentous bacterium, in 1955 at the Squibb Institute for Medical Research from cultures of an undescribed streptomycete isolated from the soil collected in the Orinoco River region of Venezuela. Its name originates from the chemical's amphoteric properties. Oral preparations of amphotericin

B are used to treat oral thrush; these are virtually nontoxic. The main use is in systemic fungal infections (e.g. in immunocompromised patients), and in visceral leishmaniasis. Aspergillosis, Naegleria fowleri primary amoebic meningoencephalitis, cryptococcus infections (e.g. meningitis) and candidiasis are treated with amphotericin B. It is also used empirically in febrile immunocompromised patients who do not respond to broad-spectrum antibiotics. Amphotericin B is believed to interact with membrane sterols (ergosterol) to produce an aggregate that forms a transmembrane channel. Intermolecular hydrogen bonding interactions among hydroxyl, carboxyl and amino groups stabilize the channel in its open form, destroying activity and allowing the cytoplasmic contents to leak out.

Imidazole and triazole antifungals:

The imidazole and triazole antifungal drugs inhibit the enzyme cytochrome P450 14α-demethylase. This enzyme converts lanosterol to ergosterol, and is required in fungal cell membrane synthesis. These drugs also block steroid synthesis in humans.

Miconazole (**4**)[5] is an imidazole antifungal agent (Figure 4), developed by Janssen Pharmaceutica, and commonly applied topically (to the skin or mucus membranes) to cure fungal infections. It works by inhibiting the synthesis of ergosterol, a critical component of fungal cell membranes. It is also active against certain species of Leishmania protozoa (which are a type of unicellular parasite), as these also contain ergosterol in their cell membranes. In addition to its antifungal and antiparasitic actions, it also has some limited antibacterial properties.

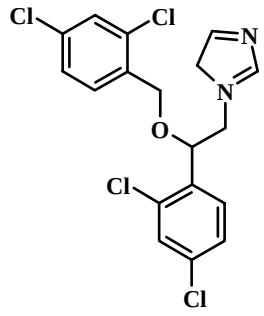


Figure 4: Miconazole (4)

Itraconazole (**5**)[6] (marketed as **Sporanox** by Janssen Pharmaceutica), invented in 1984, is a triazole antifungal agent that is prescribed to patients with fungal infections (Figure 5). The drug may be given orally or intravenously. The mechanism of action of itraconazole is the same as the other azole antifungals. It inhibits the fungal cytochrome P450 oxidase-mediated synthesis of ergosterol. Because of its ability to inhibit

cytochrome P450 3A4, caution should be taken when considering interactions with other medications. it is active against aspergillus.

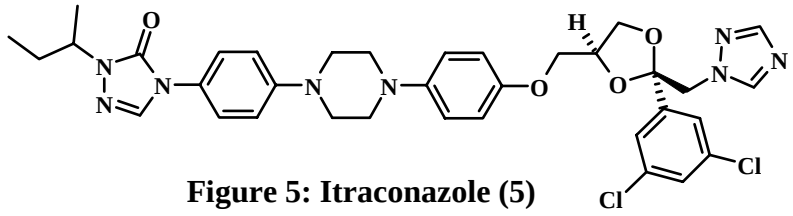
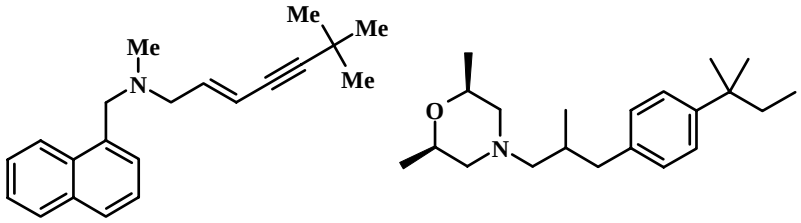


Figure 5: Itraconazole (5)

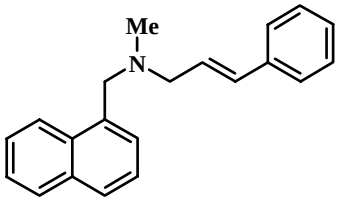
Allylamines:

Allylamines inhibit the enzyme squalene epoxidase, another enzyme required for ergosterol synthesis. Some examples include: Terbinafine (**6**)[7] - marketed as "Lamisil" in North America, Australia, the UK and Germany, Amorolfine (**7**),[8] Naftifine (**8**)[7] - marketed as "Naftin" in North America, Butenafine (**9**)[7] - marketed as Lotrimin Ultra (Figure 6).

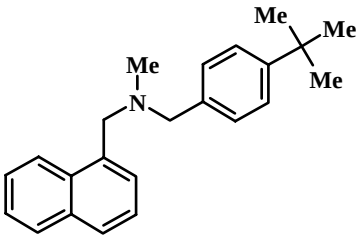


Terbinafine (6)

Amorolfine (7)



Naftifine (8)



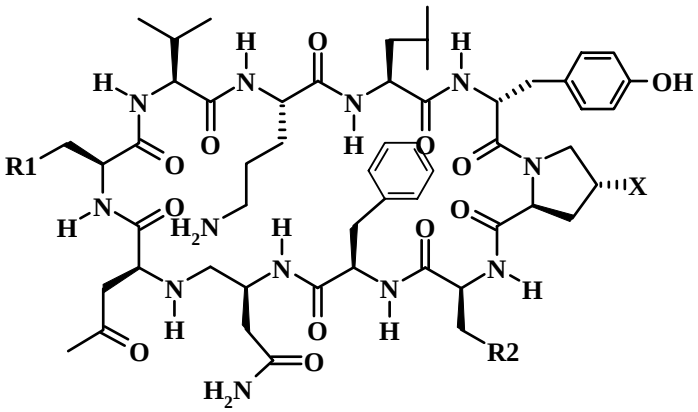
Butenafine (9)

Figure 6

Novel antimicrobial agents from a marine species *Bacillus laterosporus*:

Anderson, R. J. *et al.* first reported[9b] the isolation of Loloatin B (**11**) from a marine species *Bacillus laterosporus* from the tropical waters off the coast of Papua New Guinea, showing *in vitro* antibacterial activity against a number of gram positive antibiotic resistant human pathogens. The marine bacterial isolate MK-PNG-276A,

tentatively identified as a *Bacillus laterosporus* by MIDI analysis of cellular fatty acids, was obtained from the tissues of an unidentified tube worm collected at -15 m off of Loloata Island, Papua New Guinea. Later the same group reported[9c] the series of this cyclic decapeptide antibiotics Loloatins A-D (**10-13**), isolated by bioassay-guided fractionation of MK-PNG-276A culture extracts (Figure 7). Furthermore, Loloatins A-D exhibit in vitro antimicrobial activity against methicillin-resistant *Staphyloccoccus aureus*, vancomycin-resistant enterococci, and drug-resistant *Streptococcus pneumoniae*.



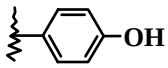
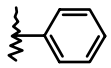
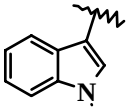
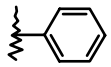
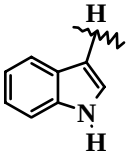
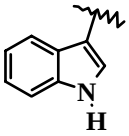
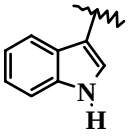
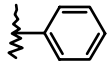
	R_1	R_2	X
Loloatin A (10)			H
Loloatin B (11)			H
Loloatin C (12)			H
Loloatin D (13)			OH

Figure 7: The Loloatin series

Later in the same year, Anderson et al. isolated[9e] novel "cationic antibiotic peptide" Bogorol A (**14**) from the same species by analysis of cellular fatty acids and 16S RNA (Figure 8).

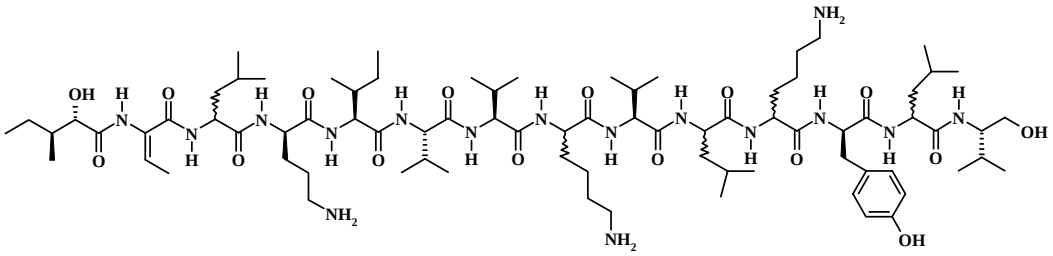
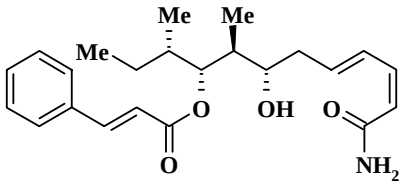
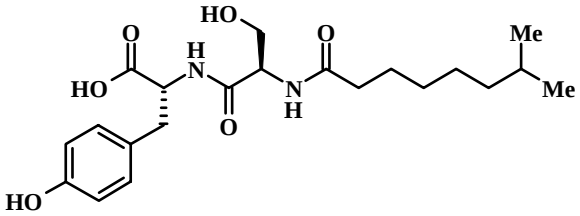


Figure 8: **Bogorol A (14)**

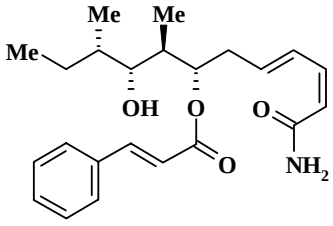
As part of their program designed to identify new antibiotics produced by marine microorganisms,[9a-e] further chemical investigations of PNG276 cultures grown both on solid agar and in liquid broth, in an attempt to identify the compounds responsible for the remaining biological activity exhibited by the culture extracts, resulted in the isolation[10] of the novel antifungal metabolites basiliskamides A (**15**) and B (**16**) and two new acyldipeptides, tupuseleiamides A (**17**) and B (**18**) (Figure 9).



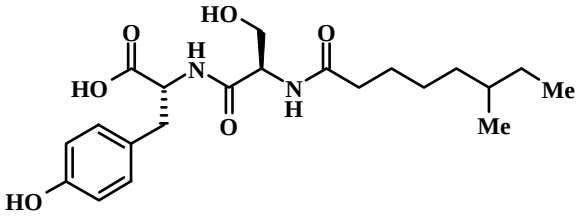
Basiliskamide A (15)



Tupuseleiamides A (17)



Basiliskamoide B (16)



Tupuseleiamides B (18)

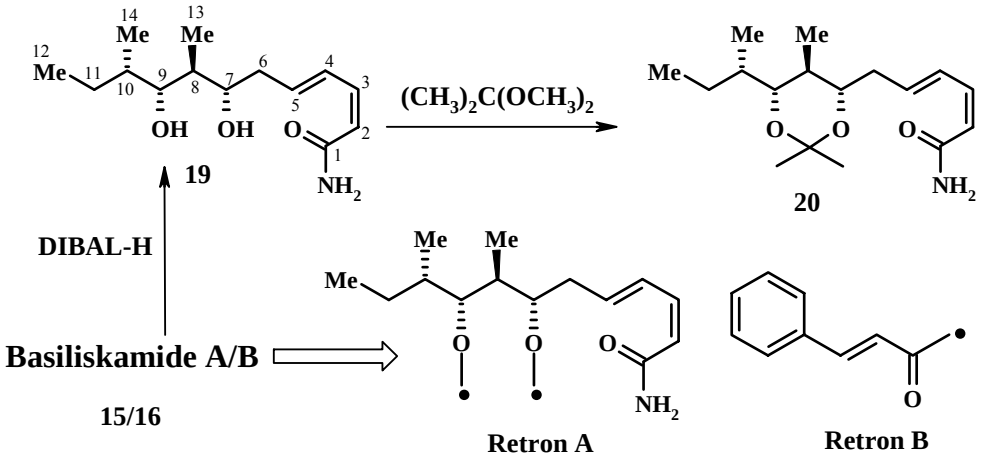
Figure 9

To detail the isolation process, the PNG-276 bacterium was cultured as lawns on trays of solid tryptic soy agar supplemented with NaCl to a final concentration of 1%. After 5 days, the cells were scrapped off the agar surface and extracted exhaustively with MeOH. Bioassay guided fractionation of the concentrated combined MeOH extract by sequential application of solvent partitioning, Sephadex LH 20, reversed-phase flash

chromatography, and reversed-phase HPLC gave a pure samples of basiliskamides A (**15**) and B (**16**). Basiliskamides A and B showed potent *in vitro* activity against *Candida albicans* while basiliskamide A exhibited activity comparable to amphotericin B (**3**), but was at least four-fold less cytotoxic to human fibroblast cells.[10]

Structure elucidation of basiliskamides A and B:

Both basiliskamides A and B were isolated as clear solids, giving [M+H] ion peaks at *m/z* 386.2336 in the high-resolution FABMS, appropriate for the molecular formula of $C_{23}H_{31}NO_4$. The PMR and CMR spectrum of both compounds were all well dispersed, enabling the easy interpretation of the COSY, HMQC and HMBC spectra. Considering the 21 well-resolved resonances (for 23 carbons indicating elements of symmetry in the structure) and other spectral datas, two major fragments A and B were assigned. Both basiliskamides A and B on DIBAL-H reduction yielded the same diol **19**, indicating identical configuration for both molecules.



Scheme 1

NMR informations for basiliskamide A:

1) Broad peaks at 7.41-7.40 ppm (3H, showing HMQC correlations to carbon resonances at 130.4 ppm and 128.9 ppm), and at 7.71 ppm (2H, showing HMQC correlation to a carbon resonance at 128.4 ppm) accounted for a monosubstituted phenyl group, thus explaining for the element of symmetry.

2) Peaks at 7.65 ppm (d, 1H) and 6.61 ppm (d, 1H), showing COSY relations to each other, were assigned to a vinyl group. The scalar coupling of 16 Hz between the vinyl protons demonstrated their *E* configuration. The link of the vinyl group to the phenyl ring was proved by the HMBC correlations between the peak at 7.65 ppm (vinyl resonance) and the peak at 128.4 ppm (phenyl resonance).

3) A carbon resonance at 166.0 ppm (for carbonyl carbon) and its HMBC correlations with both vinyl protons showed that the phenyl and vinyl fragments were part of a cinnamoyl residue.

4) A routine analysis of COSY, HMQC and HMBC data collected for the natural product identified the substructure A, with the position of the conjugated olefins at C2-C3 and C4-C5, the methyl appendages at C8 and C10, and the presence of C-O linkages at C7 and C9.

5) HMBC correlations, observed between both 5.55 ppm (H2) and 6.31 ppm (H3) and a carbon resonance at 167.4 ppm, explained that C2 was attached to a carbonyl carbon. A pair of broad one proton resonances at 7.31 ppm and 6.83 ppm, which showed COSY relations to each other but didn't show HMQC correlations to any carbon resonances, accounted for primary amide protons. The HMBC correlation of NH proton at 6.83 ppm with C2 carbon at 119.3 ppm, confirms the presence of the primary amide at the terminus of the linear fragment A.

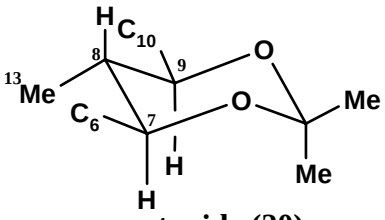
6) A COSY relation between the OH proton at 4.57 ppm and a resonance at 3.49 ppm (H7) showed the presence of hydroxy appendage at C7 and therefore the cinnamoyl fragment B had to be linked to C8 *via* ester linkage. A HMBC correlation between the methine resonance at 4.92 ppm and cinnamoyl carbonyl resonance at 166.0 ppm confirmed the ester linkage and completed the constitution of basiliskamide A.

Stereochemical determination:

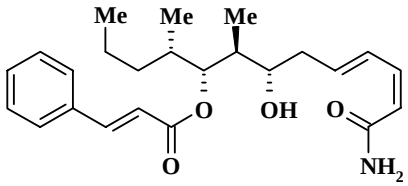
1) The scalar coupling of 11 Hz between H2 and H3 identified their *Z* configuration, and the vicinal coupling of 15 Hz between H4 and H5 showed their *E* configuration. Also the relevant NOE interactions between H2 and H3; H3 and H5 were consistent with the olefinic configurations.

2) Rychnovsky's protocol was used for the acetonide derivative of the diol, obtained by DIBAL reduction of the natural product. The resonance of the geminal methyl carbons at 19.8 and 30.4 ppm explained the syn nature of the hydroxy stereocenters (Figure 17).

3) PMR analysis revealed the acetonide **20** existed in chair confirmation, with C6 and C10 appendages equatorial. Irradiation of the H10 resonance simplified the H9 resonance to a doublet, with a vicinal coupling constant of 9.5 Hz with H8, signifying both H8 and H9 to be axial and C13 to be in equatorial position (Figure 10).



acetonide (20)



YM47522 (15')

Figure 10

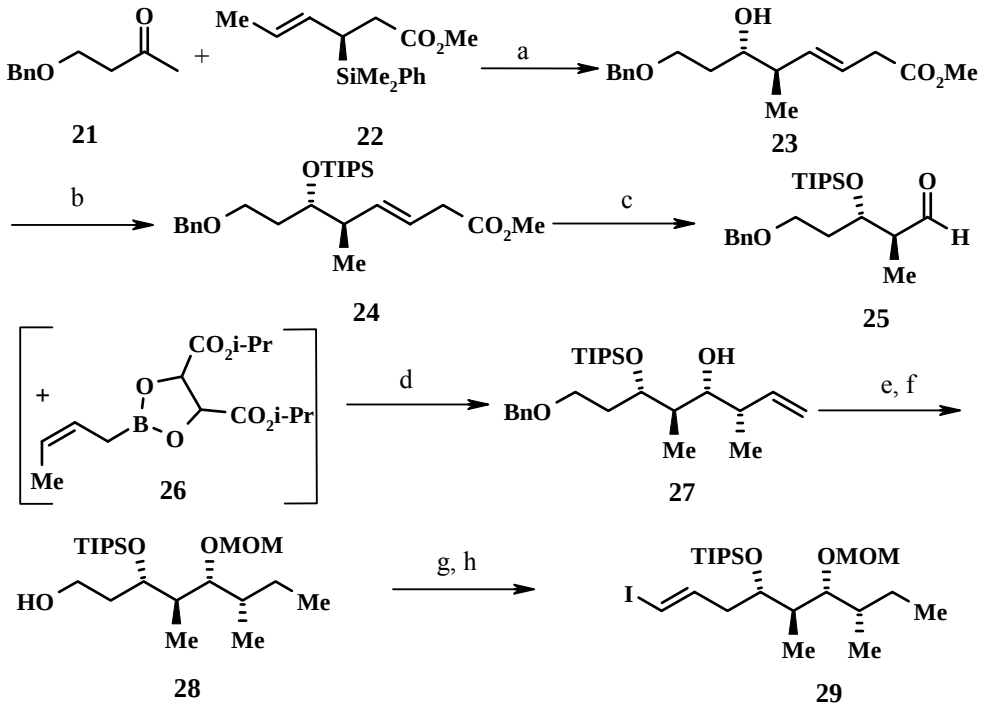
4) The *S* configuration of the C7 hydoxyl stereocenter was established using Ohtani's method of Mosher ester analysis.

5) The correlation between basiliskamide A and YM-47522 (**15'**) revealed the C10 hydroxyl stereocenter to be *S*. So the chiral centers in basilsikamide A (**15**) have the configuration (7*S*, 8*S*, 9*R*, 10*S*). As basiliskamide B (**16**) is a regioisomer of basiliskamide A, differing in the position of the ester linkage, the structures of both natural products was deduced (Figure 9).

Synthesis of basiliskamide A and B (by Panek, J. S. *et al.*):[11]

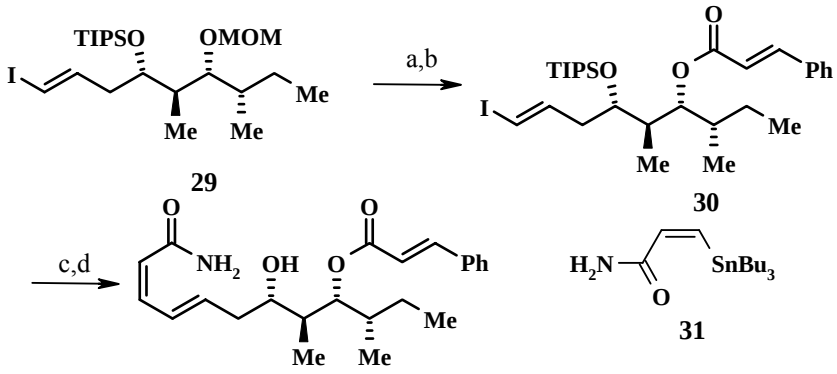
Recently Panek, J. S. *et al.* reported the total synthesis of basiliskamides A and B starting from non-chiral aldehyde **21** and using their own methodology[12] of crotylation with organosilane compound (for *anti*-addition) followed by organoborane (for *syn*-addition) for creating the four contiguous stereocenters sequentially. The diene moiety has been obtained by Stille coupling of two vinyl iodide and vinyl stannane fragments. In the final stages both natural products have been synthesized from a common intermediate by protection-deprotection manipulation.

Synthesis of common intermediate 29:



Scheme 2: *Reagents and conditions*: a) $TiCl_4$, CH_2Cl_2, 74%, crude dr > 20:1; b) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 99%; c) O_3, Py, MeOH:Me_2S; d) molecular sieves, toluene, crude dr > 20:1 (64% over two steps); e) MOMCl, *i*-Pr_2EtN, DMAP, CH_2Cl_2, 84%; f) H_2, Pd-C, MeOH, 86%; g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 98%; h) $CrCl_2$, CHI_3, dioxane/THF, 83%, *E:Z* = 9.5:1.

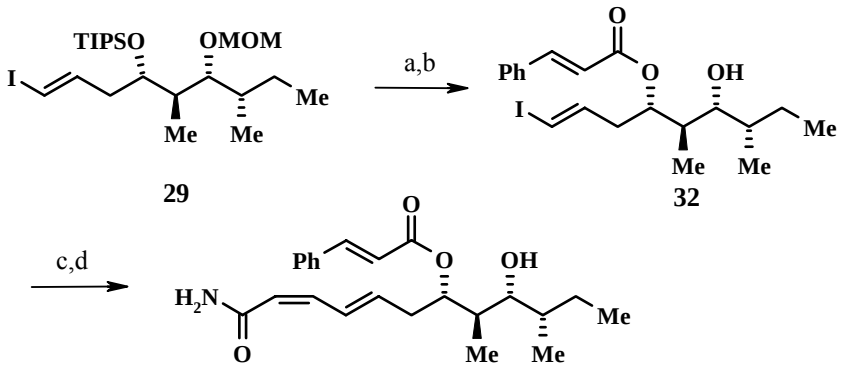
Synthesis of basiliskamide A:



Basiliskamide A (15)

Scheme 3: *Reagent and condition*: a) BCl_3, CH_2Cl_2, 75%; b) (*E*)-cinnamoyl chloride, Et_3N, DMAP, CH_2Cl_2, 92%; c) **31**, $Pd(CH_3CN)_2Cl_2$, DMF, 76%; d) HF/Py, THF, 84%.

Synthesis of basiliskamide B:

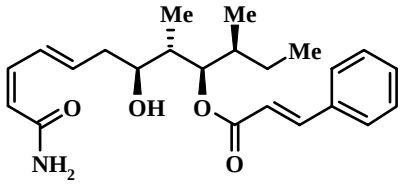


Basiliskamide B (16)

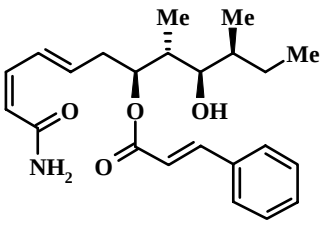
Scheme 4: *Reagent and condition*: a) HF/Py, THF, 96%; b) (*E*)-cinnamoyl chloride, Et_3N, DMAP, CH_2Cl_2, 85%; c) BCl_3, CH_2Cl_2, 99%; d) **31**, $Pd(CH_3CN)_2Cl_2$, DMF, 76%.

In conclusion the cause of fungal disease is a complicated matter and their remedy is more challenging as both fungi and humans are eukaryotes. Due to the similarity in the fungal and human cells at molecular level, killing of the fungal cell selectively without affecting the host human cell poses as the most demanding task for medicinal chemists, searching and designing for appropriate drug candidates. The tedious effort of Anderson *et al.* has resulted in the isolation and the structure elucidation of novel antifungal metabolites Loloatins A-D (**10-13**), Bogorol A (**14**), basiliskamides A and B (**15-16**), Tupusleiamides A and B (**17-18**) from the same species. But the paucity of these metabolites in nature demands for their laboratory synthesis.

The importance of antifungal agents and natural products of medicinal significance, as deliberated in the preceding section, should constitute the strong drive to undertake rapid and efficient synthesis of new metabolites to ameliorate fungal infections and concerned diseases. Moreover the widespread occurrence of antibiotic-resistant human pathogens and the paucity of effective antifungal drugs have created an urgent need for new antimicrobial agents. Microorganisms isolated from marine habitats represent a potentially rich and relatively unexplored resource for the discovery of new antibiotics. It has been previously discussed in the prologue to this section that the bacterium PNG-276, obtained from the tropical waters off the coast of Papua New Guinea and tentatively identified as *Bacillus laterosporus,* produces the cyclic decapeptide antibiotics loloatins A-D[9c] and the linear cationic peptide antibiotic bogorol A[9e] in laboratory culture. Crude organic extracts obtained from PNG-276 cultures also show potent inhibition of *Candida albicans* and *Escherichia coli*. Further chemical investigations of PNG-276 cultures grown both on solid agar and in liquid broth in an attempt to identify the compounds for the remaining biological activity exhibited by the culture extracts have resulted in the isolation of novel antifungal metabolites basiliskamides A (**15**) and B (**16**).[10]



Basiliskamide A (15)

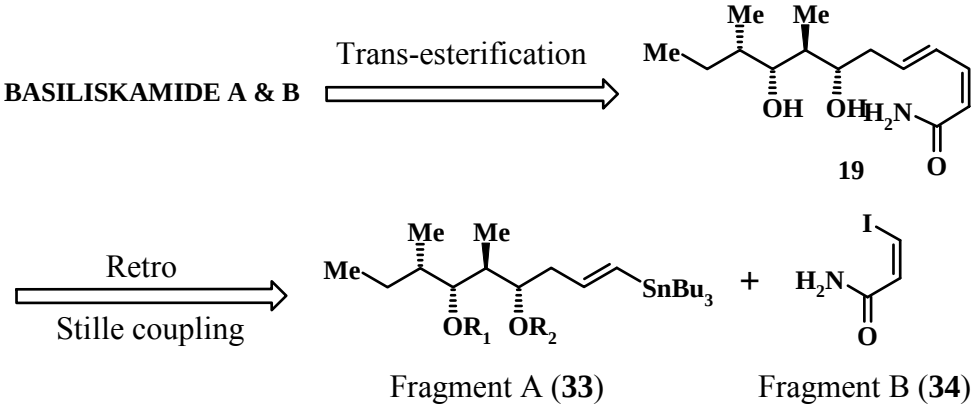


Basiliskamide B (16)

Figure 11: Our synthetic targets

Retrosynthetic strategy: "Conversion of carbohydrates to novel natural products" has prevailed as one of the thematic strategies in our laboratory.[13] With the inherent chiral pool, high enantiomeric purity, easy availability with low cost, this area of "carbohydrate based synthesis of natural products" surely is a unique and advantageous branch of

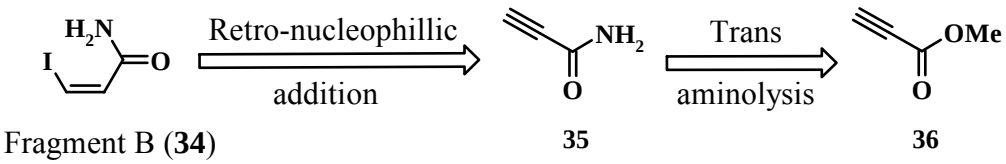
synthetic organic chemistry. The added advantages of different templates of these starting stuffs (furanose and pyranose) and the off-template stereoselection rendered by the hydroxyl groups capable of coordinating and forming hydrogen bonds provoked us to conceptualize the many advantages of these carbohydrate moieties.



Scheme 5

The retrosynthetic strategy for our synthetic endeavor was planned with the initial disconnection of the ester linkages of both basiliskamide A and B. This revealed that both basiliskamides bear the same backbone, i.e. a diol, which with the cinnamate ester adjunct at either OH groups completes the structural features of both natural products. Structurally complex and rare, the diol back bone which contains a conjugated *E* and *Z* olefinic double bond in further conjugation to an amide functionality, compel us to design a suitable synthetic way, devoid of harsh acidic or basic conditions (for avoiding any chance of isomerization). For this a heterogeneous catalytic path was preferred. The extrication of the two olefins in retro-Stille coupling manner established a vinyl tributylstannane {fragment A (**33**)} and vinyl iodide {fragment B (**34**)} as the next synthons (Scheme 5).

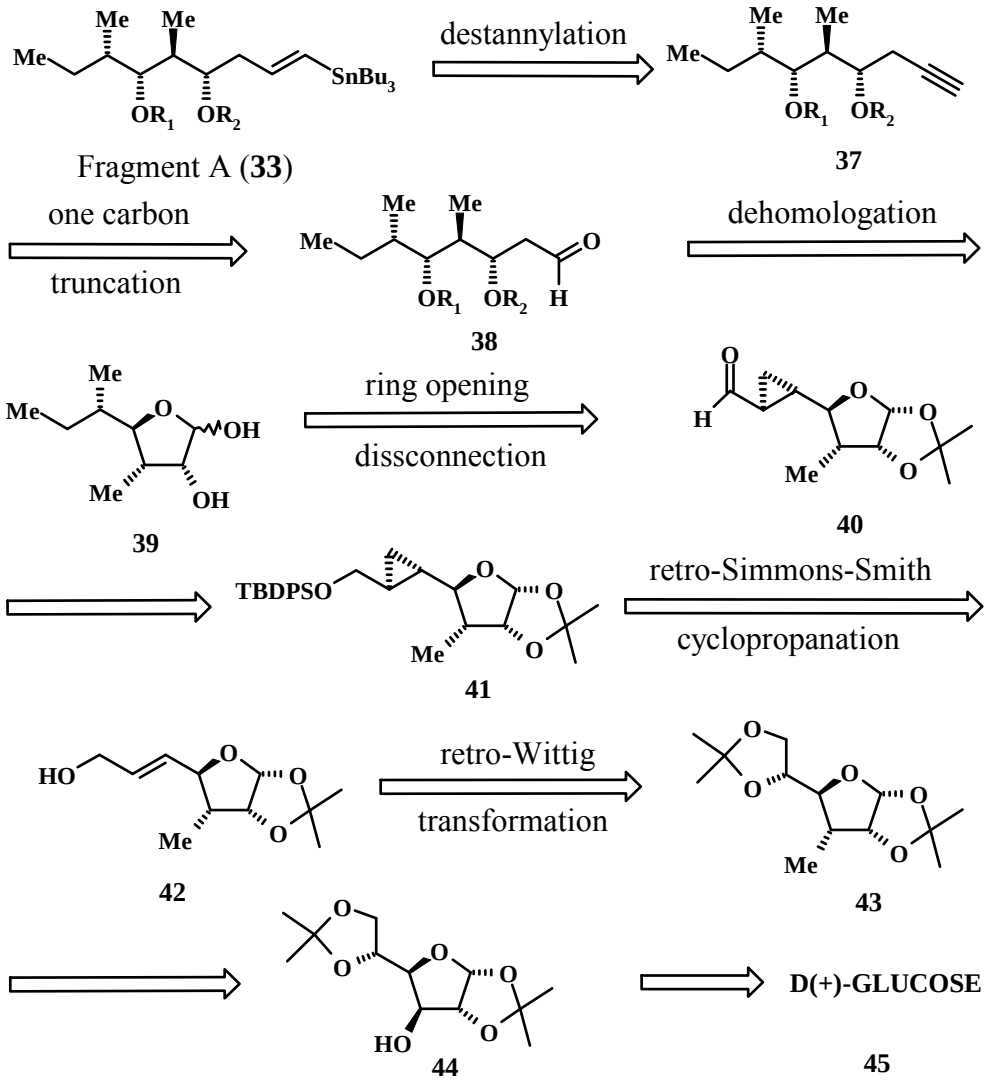
Retrosynthetic strategy for fragment B:



Scheme 6

The *Z* α,β-unsaturated amide (**34**) dubbed as the vinyl iodo coupling partner for Stille reaction, could be accomplished by more favorable *anti* nucleophillic addition to the terminal alkyne, propionamide (**35**). Trans-aminolysis of the propionamide duly intended methyl propiolate (**36**) as the fitting starting point for the synthesis of fragment B (Scheme 6).

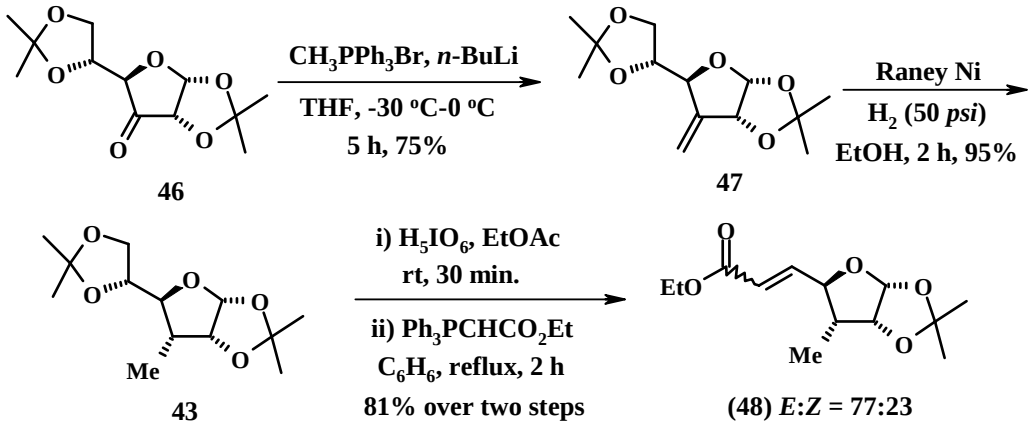
Retrosynthetic strategy for fragment A:



Scheme 7

Fragment A constitutes the major scrap of both basiliskamides, which has four contiguous stereogenic carbon atoms with alternative methyl and hydroxyl appendages. The retrosynthesis of this major fragment was lineated through well executed chemical

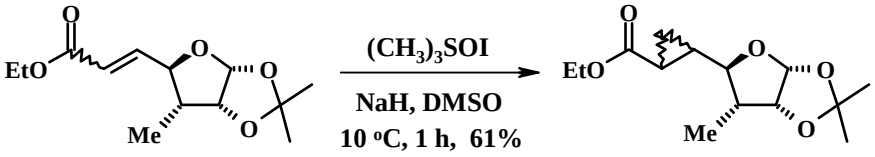
transformations, solely rested on the prospects of "chiron approach". The vinyl stannane **33**, on the right side, was envisaged to arise from the terminal alkyne **37** through *anti* nucleophillic addition of tributyltin hydride. Then the aldehyde **38** was thought to be the unequivocal retron for the alkyne **37** under the application of well known transformation using Ohira-Bestmann reagent. Dehomologation of the aldehyde **38** would imply its lower homologous aldehyde, which in its masked version can be substantially correlated with the lactol **39**. At this juncture, further scrutinizations of the molecular architecture to locate the elements of symmetry, chirality and functionality, decoding such information and transposing it onto the carbon framework of suitable synthetic precursors should imply GDA **44** by systematic functionalization. The advantage of natural inherent chirality and subsequent finding of the C7, C9 hydroxyl stereocenters already in the pool, necessitate D(+)-glucose as the chiron progenitor to start with. The pivotal step in this strategy is our generalized methodology; the stereoselctive Simmons-Smith cyclopropanation, which has been elaborated in the previous section of this chapter. The terminal gem methyl, ethyl attachments could be established by regioselective opening of the cyclopropane moiety. The internal methyl substituent can, in principle, be generated by a prudent practice of converting the preoccupied hydroxyl substituent to methylene functionality through oxidation followed by Wittig homologation and substrate constrained stereoselective reduction of the methylene (Scheme 7).



Scheme 8

The synthesis began with the compound **46**, which was synthesized earlier in previous chapter. For incorporating the methyl appendage, the 3-ulose compound **46** was

subjected to one carbon Wittig homologation to achieve the exocyclic 3-methylene derivative **47** in good yield, followed by heterogeneous catalytic reduction of the exocyclic double bond with Raney Nickel in H_2 atmosphere of 50 *psi* internal pressure. The facial selectivity of the reaction is duly explained to the "half opened book" shape of the fused [3,3,0] bicyclic furanose-oxazole moiety, directing the outerside of the assumed book for complexation, thus hydrogenation. The 5,6-*O*-isopropylidine was then oxidatively cleaved[14] by treatment of periodic acid in EtOAc at ambient temperature to provide the corresponding aldehyde, which was then elongated on reaction with stable Wittig ylide, (ethoxycarbonylmethylene)triphenylphosphorane in benzene under reflux condition to yield the α,β-unsaturated ester **48** as a mixture of geometrical isomers. The chromatographic separation of the isomers was failed. Though the peaks of corresponding geometrical isomers were very much merged on each other, a little separation of the C3-methyl doublets at 1.08 ppm approximately speaks of the dr to be 77:23. The diastereomeric nature diminished the clarity of the peaks in ^{1}H NMR spectrum, although the peaks accounted for the overall number and environment of protons (Scheme 8).



48
[*E* & *Z* mix.]

49
[47 : 53 diastereomeric mixture]
[from NMR]

Scheme 9

The important transformation of the synthetic sequence, i.e. formation of cyclopropane with appropriate stereochemistry (*S*,*S*), was investigated next. Accordingly the olefin **48** was subjected to Corey-Chaykovsky's protocol[15] with sulpher ylide (generated in situ from NaH and trimethylsulphoxonium iodide in DMSO) at the lowest possible temperature i.e. 10 ^{o}C for 1 h (Scheme 9). The resulted cyclopropane compound **49** was a mixture of diastereomers in 53:47 ratio, as concluded from PMR spectroscopy. Peaks at higher magnetic field due to magnetically hindered cyclopropane protons in turn

of peaks at lower magnetic field due to anisotropic magnetic field assisted double bond protons approved the conversion.

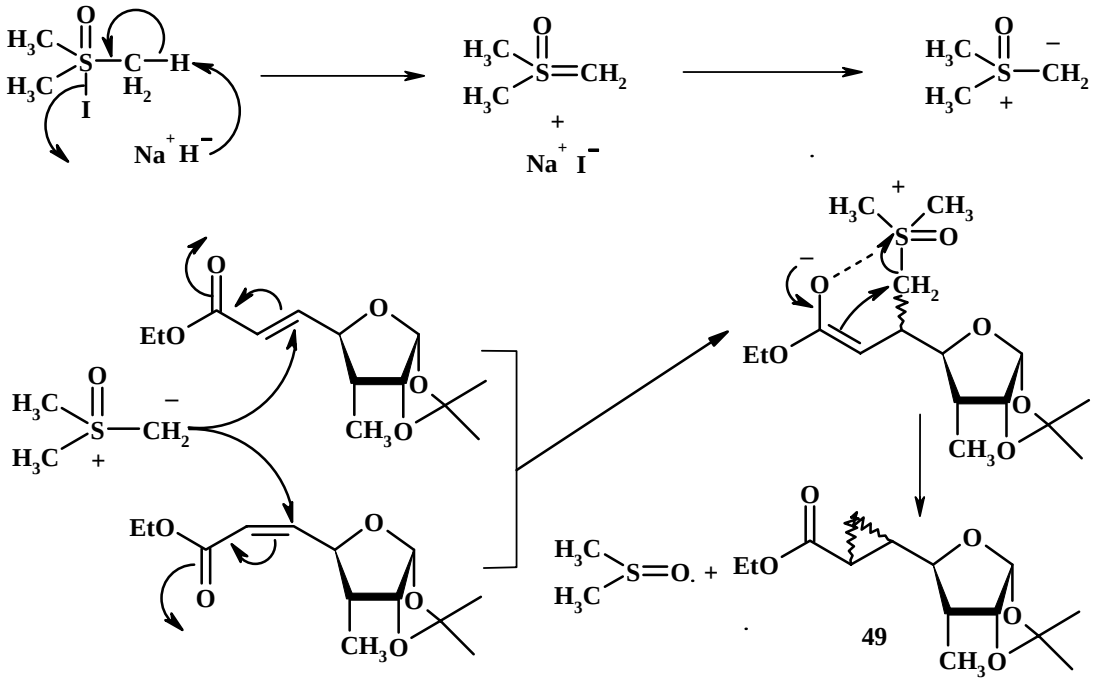
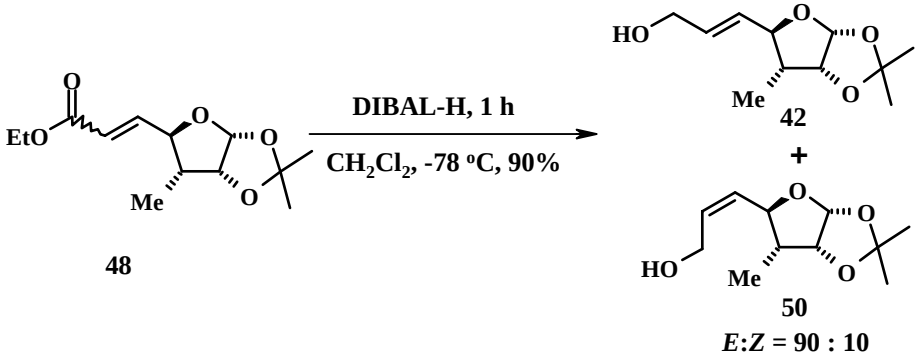


Figure 12: Mechanism of Corey's cyclopropanation

The schematic diagram in figure 12 explains the virtue and shortcoming of Corey-Chaykovsky's cyclopropanation reaction in our format. The inseparable geometrical olefins don't influence the outcome of the reaction,[16] as in the course, both leads to the same transition state. Formation of the enolate species converts the double bond (restricting free rotation to differentiate the geometrical isomers) into a single bond and the electrostatic desirability between the ions (O^- and S^+) brings the rotamers to a stable, low energy transition state. But *anti* nature of the C3 and C4 position of the furanose ring expels any steric constraint to block one face of the double bond for nucleophillic attack, which clarified the poor stereoselectivity. The near racemic nature of the product and difficulty encountered in separation of the diastereomers at this stage precluded us to advance further.

Being failed at this juncture, we needed to resurrect the strategy so as to generate the C5 methyl stereocenter stereospecifically. The ecstasy generated in our generalized methodology in previous section seemed suffice to carry forward *en route* to the

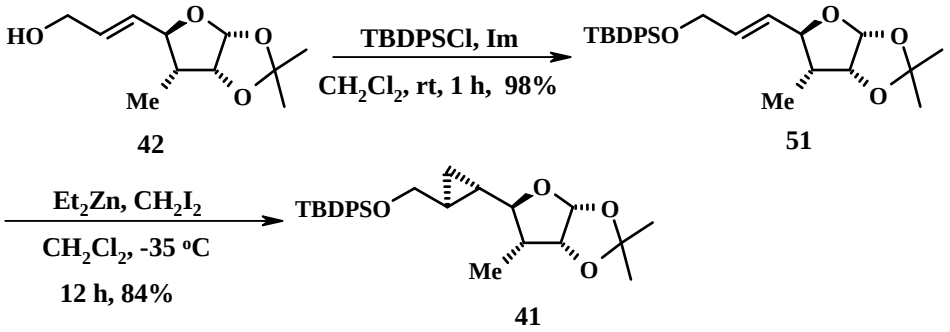
promised target. The entire sequence, in parallel to the various ester schemes, as described in previous section was deployed. The diastereomeric α,β-unsaturated ester **48** was reduced selectively to subsequent *E* allylic alcohol **42** and the *Z* isomer **50** in quantitative yield. To the advantage of this step, the diastereomeric allylic alcohols could be easily separated by flash column chromatography (Scheme 10). The PMR spectra highlighted the major structural features evidently. Disappearance of the ethoxy protons at 1.30 ppm (for $OCH_2C\underline{H}_3$), 4.20 ppm (for $OC\underline{H}_2CH_3$) and corresponding carbons at 13.8 ppm and 60.1 ppm alongwith the ester carbonyl carbon at 165.6 ppm clearly indicated the nature of the reaction. Both the products were unambiguously supported by spectral studies. In ^{1}H NMR spectrum for faster moving *Z* isomer **50**, the olefinic protons resonated at 5.43 and 5.87 ppm with *J* value 11.2 Hz and that for the slower moving *E* isomer **42**, those appeared at 5.64 and 5.96 ppm with *J* value 15.5 Hz. The characteristic mutual coupling constants, duly supported by other peaks in the PMR spectrum suggested the formation of both allylic alcohols.



Scheme 10

Now the major *E* isomer was executed to Furukawa's modified Simmons-smith cyclopropanation.[17] As for the requirement, the primary hydroxyl group was secluded as its silyl ether by uniting with TBDPSCl in CH_2Cl_2 and imidazole at room temperature for 1h in 98 % yield. First and foremost the UV active spot in TLC at R_f 0.3 in 1:9 EtOAc and light petroleum ether validated the transformation. The product **51** was adequately substantiated by spectral studies. Additional peaks at 1.05 ppm {-$Si(C_6H_5)_2C(C\underline{H}_3)_3$} and at 7.36-7.70 ppm {-$Si(C_6\underline{H}_5)_2C(CH_3)_3$} in ^{1}H NMR apparently proved it. In ^{13}C NMR the quaternary carbon linked to Silicon appeared at 19.1 ppm, the t-butyl methyl carbons

appeared at 26.7 ppm and the unsaturated phenyl alongwith the olefin carbons appeared in the range 127.0-135.4 ppm.



Scheme 11

Simmons-Smith's protocol was then deployed to achieve the stereoselective methylene insertion, apparently through treatment with Et_2Zn, CH_2I_2 at -35 °C for 12 h (Scheme 11). Quite expectedly, the cyclopropanation was stereospecific as was confirmed by NMR studies. The diastereomeric purity was fully secured on the basis of information from PMR and CMR studies. Appearance of peaks at higher magnetic field (in range of 0.39 to 0.79 ppm) with disappearance of the olefinic protons at 5.72 ppm and 5.83 ppm in ^1H NMR assured the methylene insertion in the C=C π bond. Adequately in ^{13}C NMR the triplet peak at 6.8 ppm for the cyclopropane methylene commend the transformation.

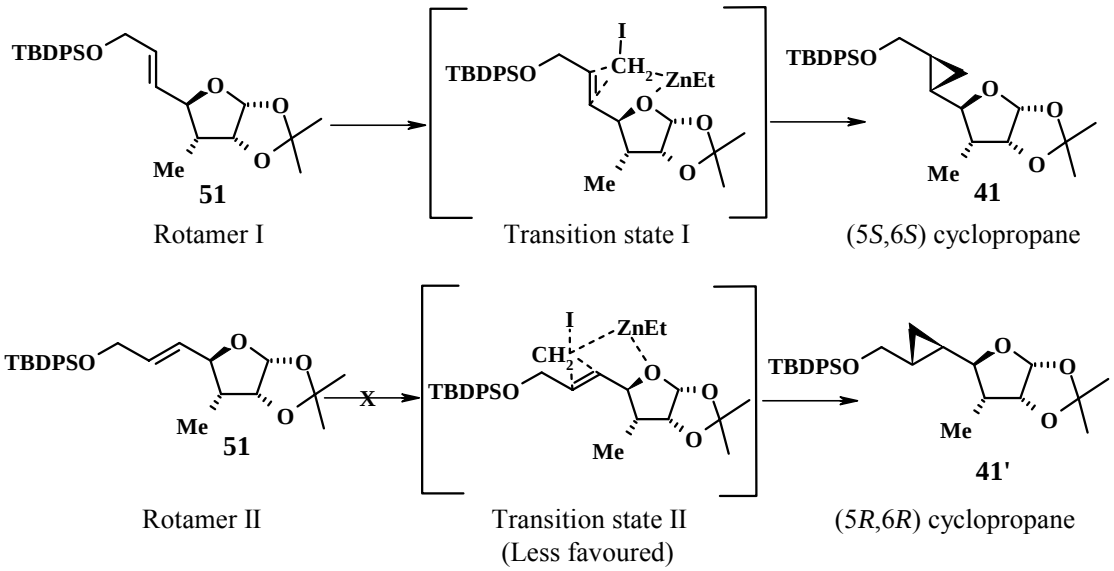
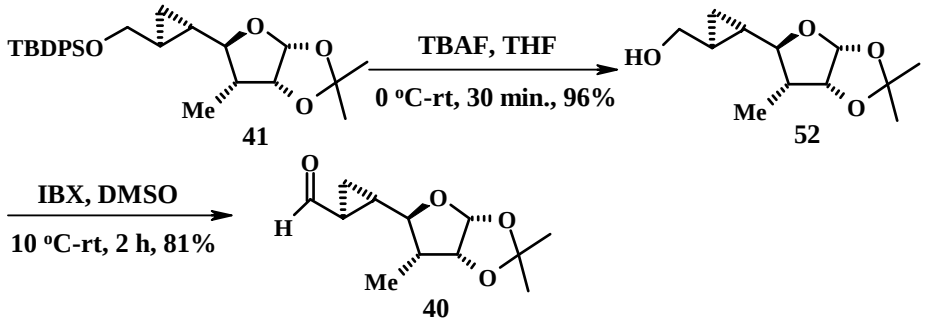


Figure 13

The schematic diagram in figure 13 explains the (*S*,*S*) configuration of the cyclopropane on the basis of the stable transition state and with ample evidences from previous section. The kinetic controlled complexation for low energy transition state divulges the theoretical explanation. For the complex as shown, comprising the co-ordination of the Zn atom to the furanose oxygen and the methylene to the C=C bond, rotamer I would be more favorable than rotamer II, because of away placement of the olefin from the furanose oxygen in rotamer II. The "above the plane" placement of the Furanose oxygen would deliver the methylene from the β-face of the olefin, stereospecifying the reaction (Figure 13).

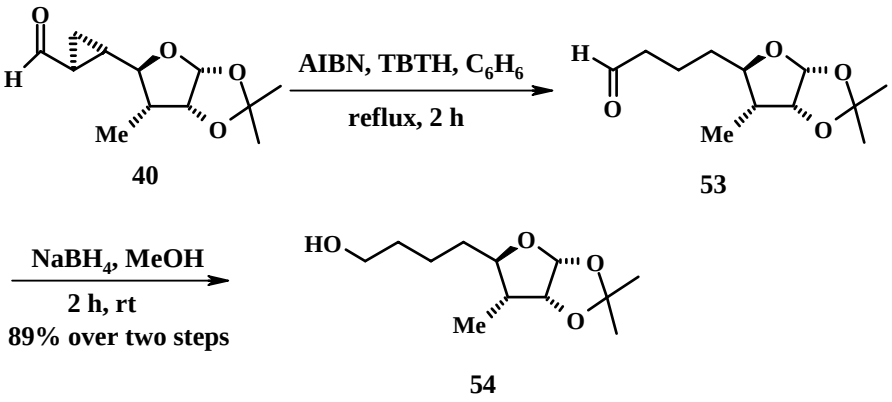


Scheme 12

The next phase of our endeavor was to translate the cyclopropane moiety to a methyl substituent. Breaking of a C-C σ bond is a high energy barrier chemical transformation and again breaking regioselectively needs right tune of the substrate.[18] So it needs activation. For that the shrouded primary hydroxyl group was unmasked by treatment with TBAF in dry THF at 0 ^{o}C in quantitative yield. The product **52** was confirmed by dint of ^{1}H NMR, ^{13}C NMR studies, that showed the absence of characteristic *t*-butyldiphenylsilyl peaks with other features of signals remaining intact. Activation of the cyclopropane ring towards reduction was realized by converting the electron pushing methyl carbinol to electron pulling aldehyde. Thus the primary hydroxyl group was exposed to IBX oxidation[19] in DMSO at room temperature with quantitative conversion to provide the cyclopropane formaldehyde **40**. The cyclopropane formaldehyde was quite a stable compound and appears as a clean spot on TLC (Scheme 12). So it could be easily purified by 60-120 mesh silica gel and the spectral data were recorded. In ^{1}H NMR a doublet appeared at 9.19 ppm for the highly deshielded aldehyde

proton. The peak at 3.51 ppm for 2 protons (for C$\underline{H_2}$OH) was disappeared. The notable shifting of the cyclopropane protons to low magnetic field region advocated the shrink in electron density around the cyclopropane proton, which correlates to the fact of activation of the cyclopropane functionality towards reduction.

The reductive opening[18] of the cyclopropane was then planned through radical initiation. So the cyclopropane formaldehyde **40** was treated with TBTH and radical initiator AIBN in benzene under reflux condition to yield the opened chain aldehyde **53**. The product however was of no significance as the opening has yielded a straight chain aldehyde with no required methyl appendage (Scheme 13). The ^{1}H NMR, with no additional doublet for the desired methyl in the higher magnetic field region, staked claim for the undesired transformation.



Scheme 13

For further clarification, reductive chemistry of **53** was undertaken with $NaBH_4$ in MeOH at room temperature to provide the corresponding alcohol **54** in overall 89% yield. The alcohol thus formed was fully characterized by ^{1}H NMR spectrum with clinching evidences from ^{13}C NMR spectrum. In ^{1}H NMR, multiplets at higher magnetic field value with only one doublet of intensity for 3Hs for the preoccupied C3 methyl group and emergence of three triplet carbons in DEPT NMR, summarizes that the opening of the cyclopropane has not been in our desired way. However quite arguably, this was attributed to the formation of more stable secondary carbon radical. The mechanistic detail is sketched in figure 14. Existence of carbonyl group stimulates the Cα-Cβ bonds, thus implying two C-C σ bonds, which can be reduced preferably to the Cβ-Cγ σ bond so

as to open the cyclopropane. In this radical transformation the reaction may proceed through path a or path b. But staring at the stability of the transition states for both paths, transition state II (secondary radical) seems more stable than transition state I (primary radical). So the reaction proceeds through path b, yielding the straight chain product. This radical opening reaction was of negative consequence as the newly created stereocenters in Simmons-Smith cyclopropanation were gone astray, needing renaissance (Figure 14).

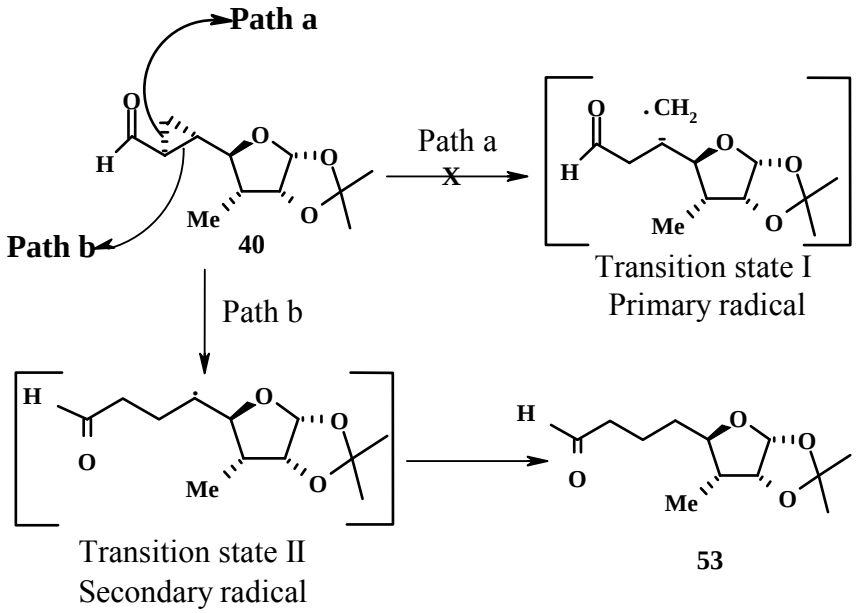
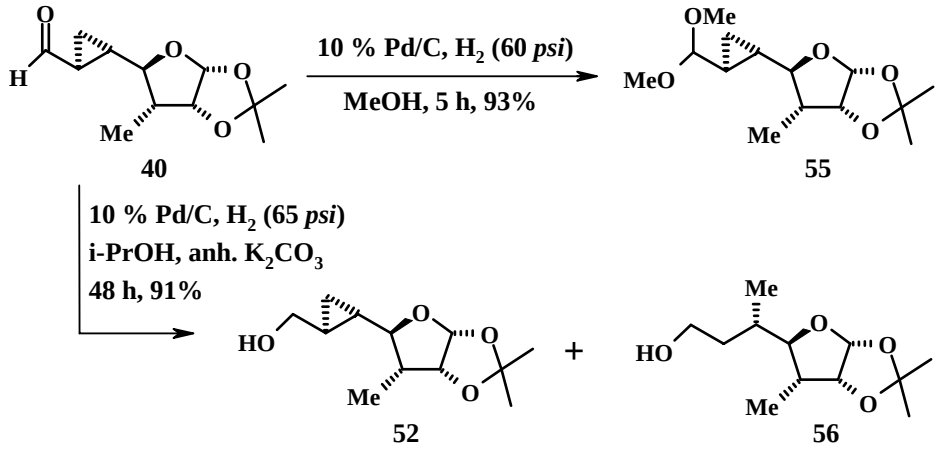


Figure 14

In a modification to the reductive cyclopropane opening,[18] heterogeneous catalytic hydrogenation[18] was employed next. At first the cyclopropane formaldehyde was exposed to H_2 atmosphere at 80 *psi* with 10% Pd/C in MeOH. To our disappointment, the aldehyde got transformed to its methyl acetal **55** by reacting with the solvent MeOH, being catalyzed by mild acidic palladium catalyst (Scheme 14). The methyl acetal **55** was readily characterized by ^{1}H NMR spectrum. While the proton specifying the –CHO group at 9.19 ppm was no more, peaks at 3.34 ppm as a singlet of intensity for 6Hs {for $CH(OC\underline{H}_3)_2$} and at 4.06 ppm as a doublet {for $C\underline{H}(OCH_3)_2$} were observed in ^{1}H NMR spectrum. So the reaction needed a precautionary measure and a change of reaction condition. The solvent MeOH was changed to a more bulky high molecular solvent $(CH_3)_2CHOH$ and the mild acidic nature of the catalyst was neutralized by addition of anhydrous K_2CO_3. Now the hydrogenation of the cyclopropane

formaldehyde in dry isopropnaol with anhydrous K_2CO_3 resulted in the formation of two compounds, one is over reduced product **56** and the other is only aldehyde reduced product **52**. The required over reduced product **56** was assigned the corresponding structure by the ample resonances in the ^1H NMR spectrum. Two characteristic doublets for two C-methyl functionalities were located at 0.89 ppm and 1.03 ppm. The broad singlet at 2.08 ppm for the exchangeable hydroxyl proton reiterated the over reduction. The antagonism of carbonyl reduction and cyclopropane reduction had to be optimized to get more of cyclopropane reduction product and our requirement needed the cyclopropane to be reduced faster than the carbonyl group. We got the best result at 65 *psi* H_2 pressure, in which the ratio of **56** and **52** was 8:2. The side reduced product, cyclopropane methyl carbinol **52** was recycled each time to get the desired product **56**.

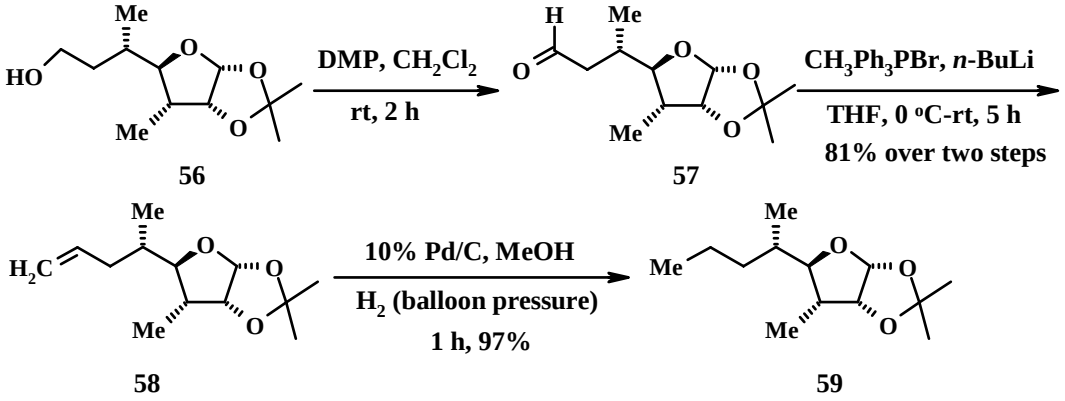


Scheme 14

Correlation study for stereochemical determination:

Although the stereochemistry of the cyclopropane ring in compound **41** was exemplified theoretically, yet we confirmed the stereocenter by a correlation process. The methyl stereocenter of compound **56** would ultimately imply the stereocenter of the cyclopropane as cyclopropanation reaction is a facial transformation. Then, to determine the configuration of the methyl group at C5 in compound **56**, it was correlated to a compound **59** of same stature, reported[16] by us earlier for the synthesis of the polyketide chain of **Nagahamide A** (Scheme 15). For the same, the hydroxyl group (-OH) of compound **56** was transformed to its carbon counterpart ($-CH_3$) by a sequence of

oxidation, one carbon Wittig homologation and reduction reactions. Dess-Martin periodinane mediated oxidation[20] of compound **56** furnished the aldehyde **57**, which on quick exposure to highly active methylidine triphenylphosphorane (generated *in situ*) in THF at 0 ^{o}C to room temperature yielded the terminal olefin compound **58**. The structural features of olefin **58** were clearly evident from the spectral studies. The heterogeneous hydrogenation of the olefin was next achieved by exposing to H_2 atmosphere (balloon pressure) in MeOH and being catalysed by 10% Pd/C. The compound **59** thus formed, exactly agrees with the previous reported compound spectroscopically. Moreover close proximity of their specific rotation attested their identity.

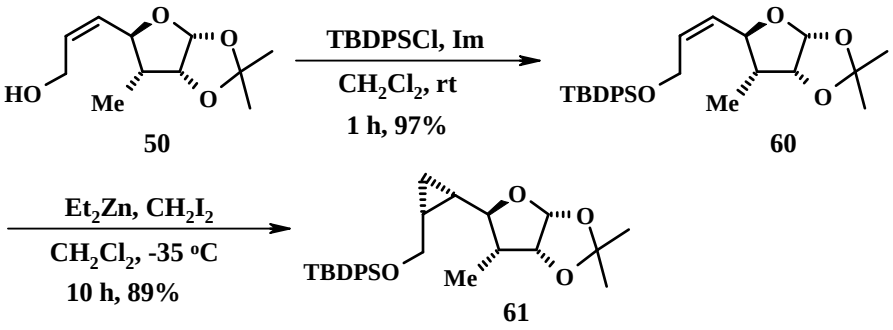


56 **57** **58** **59**

Scheme 15

Stereoselective Simmons-Smith cyclopropanation of *Z* olefin:

Being satisfied at the outcome of the reaction scheme starting from the major *E* olefin **42**, the minor *Z* olefin **50** was executed to the entire sequence, in parallel to the *E* olefin. This would certainly broaden the scope and versatility of the Simmons-Smith protocol in our frame of reference, i.e. off-template stereoselective cyclopropanation.



50 **60** **61**

Scheme 16

We believed to land up with the required product **56**, if the same facial selectivity happens for both the isomers, as the chirality differentiating the *E* and *Z* isomer will be destroyed in the ring opening reaction. The *Z* allylic alcohol **50** was treated with TBDPSCl, imidazole in CH_2Cl_2 at room temperature for 1 h to confine the free hydroxy group (as its TBDPS ether) from participating in the next key transformation. The product **60** was confirmed by the presence of additional peaks in PMR and CMR spectra for the *t*-butyldiphenyl silyl group. The critical, but standardized Simmons-Smith cyclopropanation of the *Z* olefin uneventfully gave stereoselective product **61**, which was structurally consistent with the PMR and CMR spectra (Scheme 16). The cyclopropane protons emerged in the range 0.36-0.90 ppm and the other protons were at their characteristic values. In ^{13}C NMR, the cyclopropane methylene carbon appears at the highest magnetic field value 6.85 ppm and the methylidine carbons appeared at 18.4 and 18.7 ppm. The hindsight gained from earlier studies in the proposed aspect of the mechanistic path propelled us to assume the configuration of the cyclopropane as (5*S*,6*R*). The minimization energy study duly supported it (Figure 15).

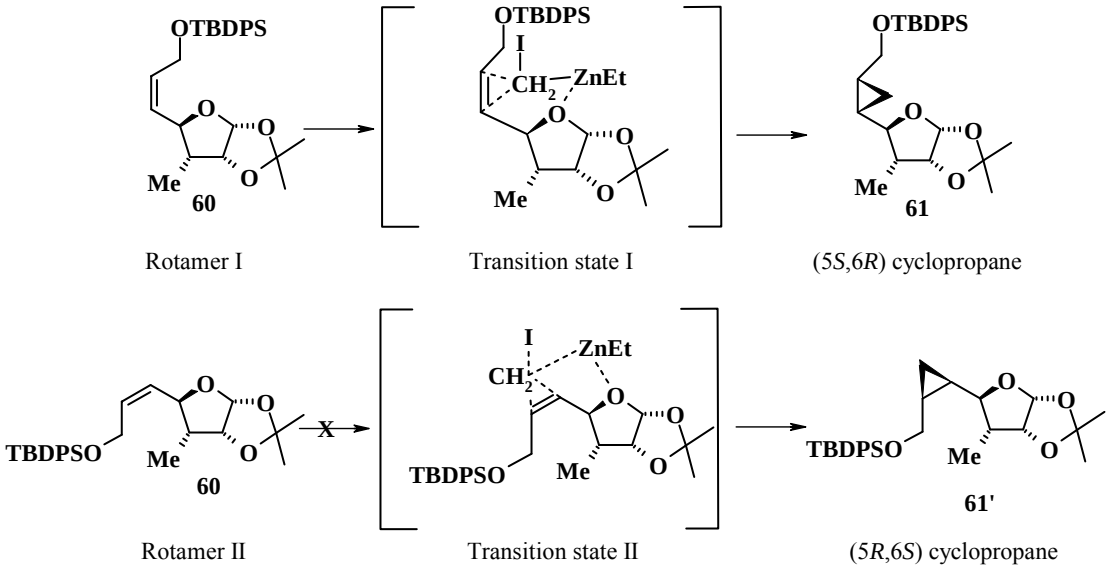
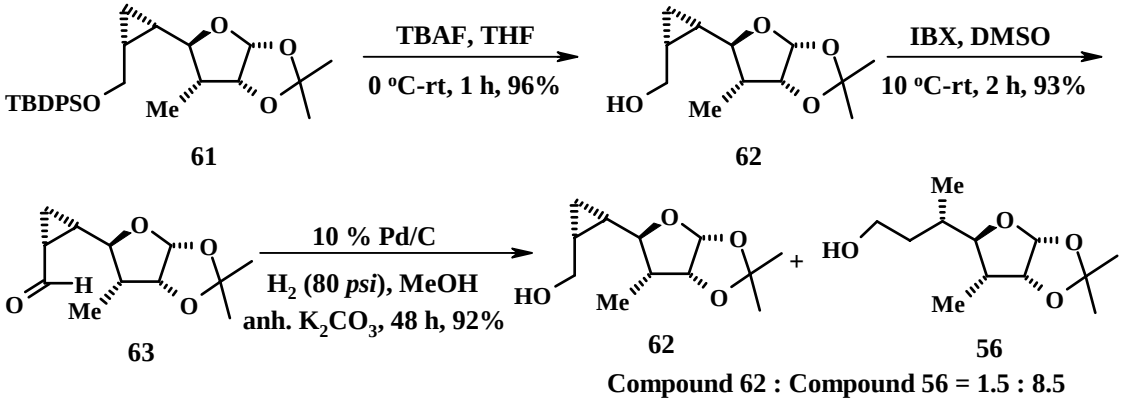


Figure 15

Following the same sequence as for the trans olefin, the TBDPS ether was then cleaved by reacting with TBAF in THF at 0 ^{o}C in 96% yield. In the spectral data of **62** the ebb away of distinctive peaks of the TBPDPS group authenticated the transformation. Now the free primary hydroxyl group was oxidized with IBX in DMSO at room

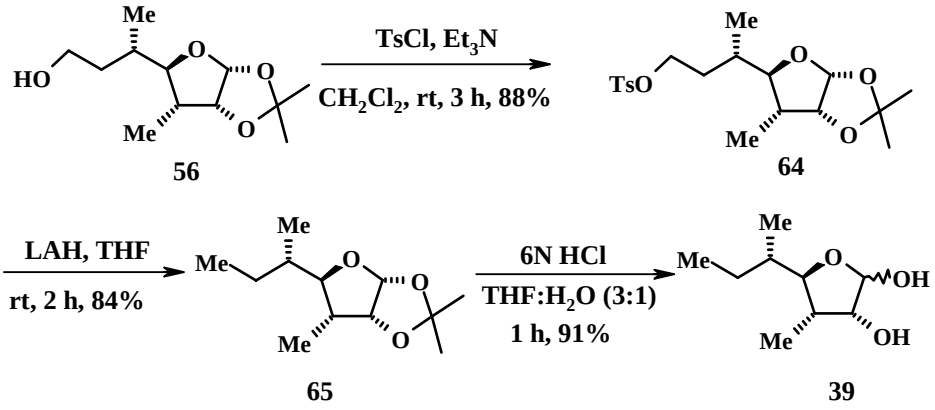
temperature for 1 h to furnish the corresponding aldehyde in excellent yield. The aldehyde **63**, hence formed was subjected to hydrogenation in the optimized condition as of **40**. Again not surprisingly, the outcome was a mixture of two alcohols, one with cyclopropane intact **62** and the other with opened cyclopropane **56** in 1.5:8.5 ratio respectively (Scheme 17). The spectral data were in complete harmony with that of compound **56**. The chiral homogeneity of the compound was checked by matching specific rotation with the compound **56** {$[\alpha]_D$ = + 29.03 (*c* 1, $CHCl_3$) against $[\alpha]_D$ for **56** = + 28.96 (*c* 1, $CHCl_3$)} These informations substantially attested the similarity of the outcome for both *E* and *Z* olefins.



Scheme 17

After fixing all the substituents with requisite stereocenters in place, we advanced further to complete the carbon backbone. The unwanted primary hydroxyl group was removed by converting it into a super leaving sulphonate group. The alcohol **56** was combined with TsCl in presence of Et_3N in CH_2Cl_2 to yield the *p*-toluenesulphonate derivative **64** in 88% yield. The PMR spectrum highlighted the major structural features evidently. For instance, the distinguishing singlet resonated at 2.46 ppm for the $C\underline{H}_3C_6H_4SO_2$- and two distinct doublets surfaced at 7.34 and 7.79 ppm with *J* value of 8.35 Hz for aromatic ortho coupling protons, characterized the para substituted phenyl functionality. The ^{13}C NMR spectrum, IR and analytical study furthermore approved it. Nucleophilic substitution of the *p*-toluenesulphonate with hydride ion was easily accomplished on treatment with $LiAlH_4$ in THF at room temperature in moderate yield. The conspicuous absence of *p*-toluenesulphonate peaks and the appearance of a triplet at

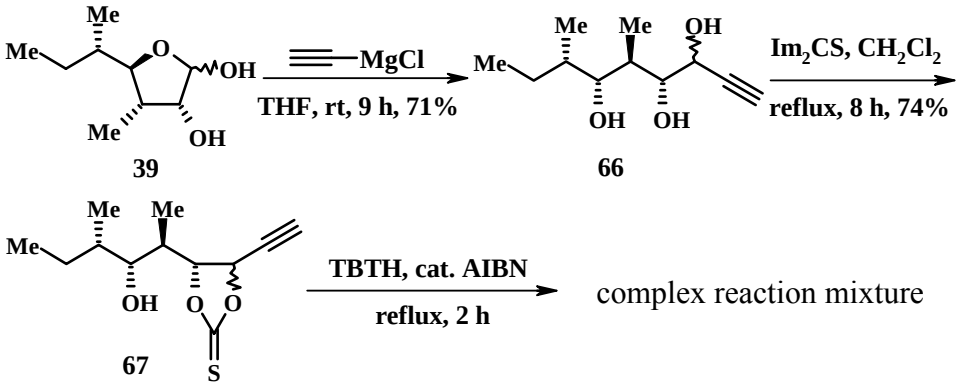
0.93 ppm, characteristic of the newly formed methyl group in ^{1}H NMR indicated the product **65**. Now, with the left part of the Basiliskamides being constructed and to incorporate the right part of the Basiliskamides, the unfolding of the furanose ring was essential. So the compound **65** was next treated with 6N HCl in a biphasic mixture of THF and H_2O under reflux condition to yield the lactol **39**, i.e. a masked aldehyde, (scheme 18) which would serve as the flood gate for further extrapolations.



Scheme 18

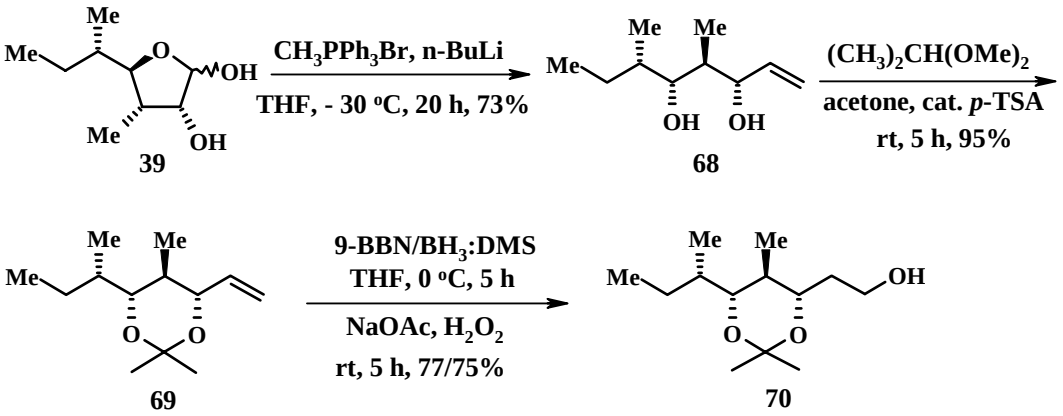
We now focused on our strategy, which involves the installation of the terminal alkyne extension beforehand and thereafter to construct the vinyl stannane in the required direction, bearing in mind, Stille reaction[21] as a key transformation. In this regard, the lactol was inducted to nucleophilic attack by metal acetylide. The ethynyl magnesium chloride was prepared by metal exchange reaction[22] between moisture free acetylene gas and *n*-BuMgCl (made *in situ* by refluxing *n*-BuCl, Mg in THF being activated by catalytic iodine) and reacted with the lactol **39** to furnish a diastereomeric mixture of triols **66**. The stereocenter newly generated was of no significance, as in later stages it has to be obliterated.

The introduction of acetylene to the carbon back bone was proved by the presence of a doublet at 2.48 ppm in ^{1}H NMR spectrum. Other protons were at their desired magnetic field values. The triol **66** was then exposed to 1,1'-thiocarbonyldiimidazole[23] in CH_2Cl_2 under reflux condition to find the 5 membered thiocarbonate **67** being more favourable heterocyclic ring than 6 or 7 membered ones (Scheme 19).



Scheme 19

This reaction served many purposes. One is that it helped us to evade further protection deprotection steps to discriminate the hydroxyl groups and the other; it could be used for the deoxygenation[24] of propargylic hydroxyl group selectively in the next step. The thiocarbonate formation was established from mass spectral analysis. For the triol **66**, the $[M+1]^+$ isotopic peak appeared at 200.83 and the $[M+Na]^+$ peak appeared at 222.77 as the base peak, where as for the thiocarbonate **67**, the $[M+1]^+$ isotopic peak appeared at 243.26 and the $[M+Na]^+$ peak appeared at 265.13 as the base peak. ^{1}H NMR spectrum meticulously supported the thiocarbonate protection as there was a remarkable down field shift of the homopropargylic methine proton from 3.67 ppm to 4.10 ppm. With the desire for twin reactions of tributyltin hydride addition to acetylene and Barton McCombie radical deoxygenation in one step, the thiocarbonate **67** was treated with TBTH and radical initiator AIBN in benzene under reflux condition. But to our disappointment, we landed up with a complex mixture.

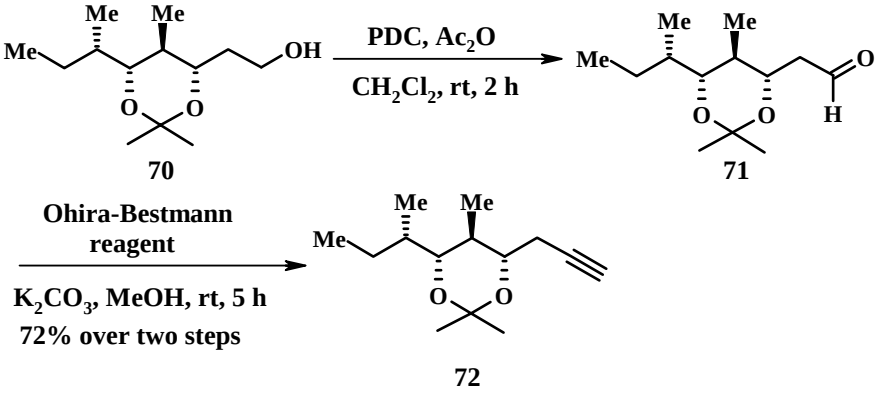


Scheme 20

After the above failed effort, we chose a path of less complexity and sequential transformations. Now the chain extension was attained through a sequence of simplified chemical transformations. The lactol **39** was subjected to one carbon Wittig elongation reaction through highly reactive CH_2PPh_3 (prepared in situ by action of *n*-BuLi with CH_3PPh_3Br in THF) at ambient temperature in moderate yield. The terminal olefin **68** obtained was well characterized by spectral studies. In ^1H NMR the internal olefin proton appeared at 5.86 ppm as ddd splitted peak and the two terminal olefinic protons appeared at 5.20 ppm as two merged ddd coupled peaks. The two exchangeable hydroxyl protons appeared as a broad singlet at 3.21 ppm. The diol **68** was then protected as its isopropylidine derivative **69** with dimethoxy propane in acetone catalyzed by *p*-TSA at room temperature in quantitative yield. The introduction of isopropylidine group at this stage could serve a dual role, i) as a protecting group for next couple of steps, and ii) as a derivatisation method for proving the relative, thus absolute stereochemistry of the oxazole ring. The resonance of isopropylidine methyl carbons at 19.6 ppm and 30.1 ppm and the quaternary carbon at 97.9 ppm adequately established the *syn* nature[25] of the hydroxyl substituents, thus eradicating any probable epimerization in the preceding Wittig reaction. The terminal olefin **69** was then exposed to hydroboration-oxidation sequence for further extrapolation. The primary alcohol **70** was derived out of the olefin in 77% yield on exposure to 9-BBN[26] in THF at room temperature for 5 h, followed by oxidation with H_2O_2 in presence of aqueous NaOH. It is noteworthy to mention that the same result was attained by displacing 9-BBN with BH_3:DMS in 75% yield. Disappearance of resonances due to olefinic protons between 5.0 to 6.0 ppm and appearance of 4 protons in the range of 3.45 ppm-3.80 ppm for the methine protons carrying the hydroxyl groups implied the oxidation reaction. Presence of three triplet carbons in DEPT NMR spectrum added to the evidence (Scheme 20).

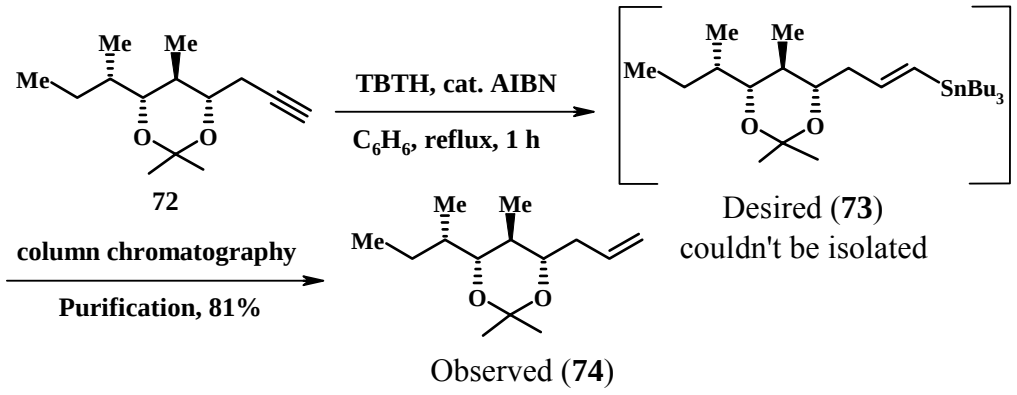
For further extension of one carbon, the hydroxyl group was oxidized with PDC[27] and Ac_2O in CH_2Cl_2 at room temperature for 1 h in 87% yield, which on quick exposure to Ohira-Bestmann reagent[28] in MeOH with anhydrous K_2CO_3 at room temperature quantitatively yielded the terminal alkyne **72**. The transformation was substantially confirmed by the presence of a triplet at 1.98 ppm for the terminal acetylene proton.

Furthermore peaks at 69.9 and 81.1 ppm in ^{13}C NMR for the alkyne carbons additionally proved the transformation (Scheme 21).



Scheme 21

The alkyne **72** was next subjected to radical addition reaction with tributyl tin hydride to yield the Stille precursor. Experimentally the alkyne was reacted with TBTH, radical initiator AIBN in benzene under reflux condition for 1 h for complete consumption of the starting material. After purification of the crude product through silica gel, the spectral studies revealed a terminal olefin compound **74** rather than the desired vinyl stannane compound **73** (Scheme 22).

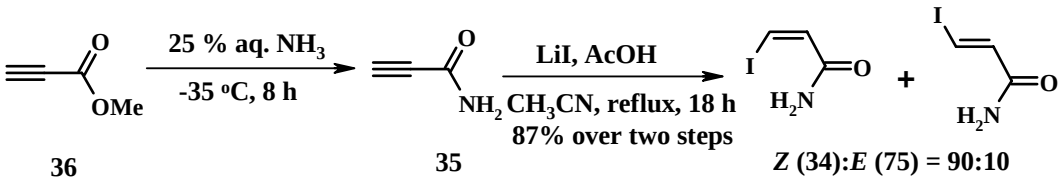


Scheme 22

The known unpredictability in the stability of the vinyl stannane compounds and earlier reports of protiodestannylation during chromatographic separation[29] made us to conclude that the destannylation has occurred by SiO_2 during column chromatography. However the terminal olefin was reliably characterized by the analysis of ^{1}H NMR, ^{13}C

NMR, IR and EI mass spectra. The olefinic protons (3 protons) appeared in between 4.50-6.00 ppm and the allylic protons appeared at 2.14-2.31 ppm, while in ^{13}C NMR the terminal triplet olefin carbon surfaced at 116.1 ppm and the doublet internal olefin carbon surfaced at 135.3 ppm. In an alternative, yet risky procedure, we planned to examine the stille reaction with the crude vinyl stannane compound as that may contain a trace amount of TBTH, which should not affect the Stille reaction.

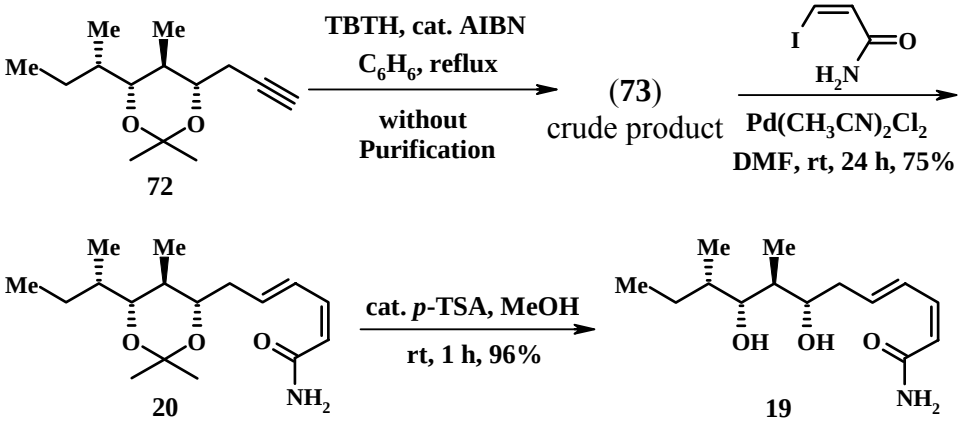
Synthesis of vinyl iodide coupling partner: [30] As sketched in the retrosynthetic strategy (Scheme 6), synthesis of the minor Stille precursor was planned next. Aminolysis of methyl propiolate was achieved by treatment of the ester with 25% aqueous ammonia at -35 ^oC for 8 h. The notable difference in the R_f (0.2 for **35** against 0.7 for methyl propiolate (**36**) in 70% EtOAc/Petroleum ether system) in thin layer chromatographic study, claimed the transformation primarily. Without further characterization, the propionamide (**35**) was then reacted with LiI, AcOH in CH_3CN under reflux condition for 18 h. The reaction resulted both geometrical isomers *E* and *Z*, in 1:9 ratio respectively, which could be easily separated by flash column chromatography and characterized separately by PMR and CMR studies with ancillary information from combustion analysis (Scheme 23). The faster moving *E* isomer **75** showed two doublets at 7.08 ppm and 7.65 ppm with *J* value 14.6 Hz, which confirmed their dihedral angle as 180°. The slower moving *Z* isomer **34** showed the same pattern at 6.94 ppm and 7.11 ppm with *J* value 8.6 Hz, which confirmed their *cis* nature.



Scheme 23

Coupling of fragments 73 and 34: The stage is well set for the all important stille coupling.[21] The acetylene compound was thus reacted with TBTH as described earlier. After completion of the reaction, the solvent was removed and the crude vinyl stannane was reacted with the *Z* vinyl iodo compound **34** in presence of $Pd(CH_3CN)_2Cl_2$ catalyst[31] in DMF, being protected from light for 24 h at ambient temperature to obtain the Stille

coupled product **20**. After achieving the common intermediate **20** for both natural products, the cinnamate ester linkages at either hydroxy group would culminate the total synthesis of basiliskamide A and B. So the hydroxy groups were unmasked by treatment with catalytic *p*-TSA in protic solvent MeOH at ambient temperature in quantitative yield (Scheme 24). The diol **19** thus formed was characterized satisfactorily from spectral studies and could correlate to the reported spectral data.[10] In ^{1}H NMR spectrum, the olefinic protons resonated at their apposite values, e.g. H2 at 5.58 ppm (d, 1H, J = 11.4 Hz), H3 at 6.40 ppm (t, 1H, J = 11.4 Hz), H4 at 7.34 ppm (dd, 1H, J = 11.4, 15.4 Hz), and H5 at 6.04 ppm (dt, 1H, J = 7.2, 15.4 Hz). In ^{13}C NMR spectrum, the corresponding carbons appeared at 119.3, 141.8, 143.3, 130.2 ppm respectively. The mutual coupling constant value between H2 and H3 (J = 11.4 Hz) signified *Z* configuration and between H4 and H5 (J = 15.4 Hz) signified the *E* configuration respectively.

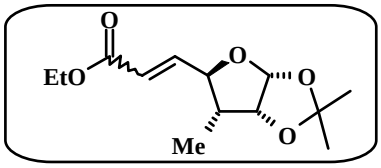


Scheme 24

EPILOGUE:

We have described the synthesis of the common intermediate to both natural products basiliskamide A and B, where in the incorporation of suitable appendages of appropriate stereochemistry has been stereospecific. We anticipate that the enantiospecific synthetic strategy, detailed above, could be extended to prepare both natural products by selective esterification.

Ethyl 3-((3a*R*,5*R*,6*R*,6a*R*)-2,2,6-trimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)acrylate (**48**):

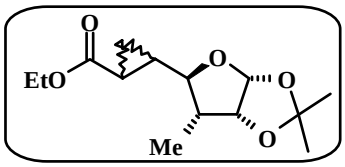


The diacetonide compound **43** (12.6 g, 48.84 mmol) was taken in EtOAc (50 mL) and cooled to 0 °C. To it H_5IO_6 (13.36 g, 58.61 mmol) was added slowly and the reaction mixture was stirred at room temperature for 30 min. TLC showed the complete consumption of starting material. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated to get the crude aldehyde, which was used for next reaction without further purification. (Ethoxycarbonylmethylene) triphenylphosphorane (20.39 g, 58.61 mmol) in benzene (100 mL) was heated to reflux. To it benzene solution (30 mL) of the aldehyde was added slowly and the reaction mixture was refluxed for 2 h. Then the solvent was evaporated in vacuo and the crude ester was purified by column chromatography using EtOAc:Petroleum ether (1:9) to yield the diastereomeric mixture of geometrical isomers **48** (*E* and *Z*) (10.12 g, 81% over two steps) as a liquid.

Mol. Formula	:	$C_{13}H_{20}O_5$
Mol. Weight	:	256.30
ESI-MS *m/z*	:	279.21 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 60.92; H, 7.87 Found: C, 60.81; H, 7.73
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 1.08 (d, 3H, *J* = 6.6 Hz), 1.30 (t, 3H, *J* = 7.2 Hz), 1.33 (s, 3H), 1.52 (s, 3H), 1.81 (m, 1H), 4.20 (q, 2H, *J* = 7.2 Hz), 4.23 (m, 1H), 4.57 (t, 1H, *J* = 3.8 Hz), 5.84 (d, 1H, *J* = 3.8 Hz), 6.08 (dd, 1H, *J* = 0.9, 15.5 Hz), 6.86 (dd, 1H, *J* = 5.8, 15.5 Hz)
^{13}C NMR	:	δ 8.5 (q), 13.8 (q), 25.9 (q), 26.2 (q) and 26.3 (q), 44.1 (d)

(50 MHz, $CDCl_3$) and 44.7 (d), 60.0 (t) and 60.1 (t), 77.0 (d) and 81.0 (d), 82.2 (d) and 82.3 (d), 104.8 (d) and 105.0 (d), 111.3 (s), 121.7 (d) and 122.2 (d), 144.1 (d) and 145.1 (d), 165.0 (s) and 165.6 (s)

ethyl 2-((3a*R*,5*R*,6*R*,6a*R*)-2,2,6-trimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)cyclopropanecarboxylate (**49**):



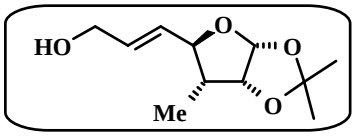
NaH (0.014 g, 0.58 mmol) was added to a DMSO (2 mL) solution of trimethylsulphoxonium iodide (0.103 g, 0.47 mmol) at 10 °C. The reaction mixture was stirred for 10 min. To it, the ester **48** (0.1 g, 0.39 mmol) in DMSO (1 mL) was added slowly and stirred for 1 h at the same temperature. Then it was quenched with ice water and extracted with EtOAc. The combined organic layer was washed with water, brine solution, dried over Na_2SO_4, concentrated and purified by column chromatography using EtOAc:Petroleum ether (1:9) to afford a diastereomeric mixture of the cyclopropane esters **49** (0.064 g, 61%) as a yellow liquid.

Mol. Formula	:	$C_{14}H_{22}O_5$
Mol. Weight	:	270.33
ESI-MS *m/z*	:	293.15 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 62.20; H, 8.20
		Found: C, 62.38; H, 8.31
^{1}H NMR	:	δ 1.10 (m, 3H), 1.14 (two doublets, 3H, *J* = 6.4 Hz), 1.23
(200 MHz, $CDCl_3$)		(two merged triplets, 3H, *J* = 7.4 Hz), 1.30 (s, 3H), 1.47 (s, 3H), 1.63 (m, 1H), 1.85 (m, 1H), 3.29 (dd, 0.57 H, *J* = 7.2, 8.9 Hz), 3.43 (0.43 H, *J* = 7.2, 8.9 Hz), 4.13 (two merged quartets, 2H, *J* = 7.4 Hz), 4.52 (t, 1H, *J* = 3.8 Hz), 5.72 (two doublets, 1H, *J* = 3.8 Hz)

Preparation of compounds 42 and 50:

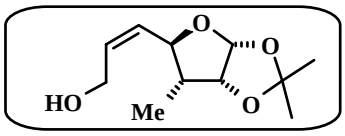
DIBAL-H (48.33 mL 2M solution in toluene, 96.66 mmol) was added slowly to a CH_2Cl_2 solution (50 mL) of the ester compound **48** (9.8 g, 38.66 mmol) at -78 °C. The reaction mixture was stirred at same temperature for 1 h. It was quenched with saturated aqueous sodium potassium tartarate solution. The biphasic mixture was stirred at room temperature for 30 min till complete separation of the phases occur. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, concentrated and purified by flash column chromatography using EtOAc:Petroleum ether (1:4) to yield the *E* allylic alcohol **42** (6.64 g, 81%) and *Z* allyl alcohol **50** (0.73 g, 9%) as a colorless viscous liquid.

(*E*)-3-((3a*R*,5*R*,6*R*,6a*R*)-2,2,6-trimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)prop-2-en-1-ol (**42**):



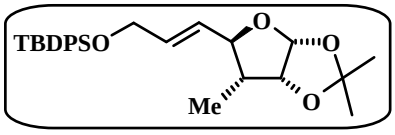
Mol. Formula	:	$C_{11}H_{18}O_4$
Mol. Weight	:	214.26
ESI-MS *m/z*	:	237.12 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	3433, 2987, 2936, 2880, 1457, 1383, 1375, 1172, 1153, 1110, 1086, 1020, 873, 757, 667
Elemental Analysis	:	Calcd: C, 61.66; H, 8.47 Found: C, 61.75; H, 8.59
$[\alpha]_D^{25}$	:	+13.5 (*c* 1.4, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ1.04 (d, 3H, *J* = 6.8 Hz), 1.34 (s, 3H), 1.53 (s, 3H), 1.78 (m, 1H), 2.75 (bs, 1H), 4.11-4.19 (m, 3H), 4.58 (t, 1H, *J* = 4.2 Hz), 5.64 (ddt, 1H, *J* = 1.5, 7.4, 15.5 Hz), 5.83 (d, 1H, *J* = 3.7 Hz), 5.96 (ddt, 1H, *J* = 0.6, 5.0, 15.5 Hz)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 8.4 (q), 25.9 (q), 26.3 (q), 43.8 (d), 61.8 (t), 82.1 (d), 82.7 (d), 104.4 (d), 110.9 (s), 127.4 (d), 133.5 (d)

(*Z*)-3-((3a*R*,5*R*,6*R*,6a*R*)-2,2,6-trimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)prop-2-en-1-ol (**50**):



Mol. Formula	:	$C_{11}H_{18}O_4$
Mol. Weight	:	214.26
ESI-MS *m/z*	:	237.15 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	3437, 3017, 2990, 2936, 2882, 1457, 1383, 1377, 1172, 1153, 1108, 1021, 872, 668
Elemental Analysis	:	Calcd: C, 61.66; H, 8.47 Found: C, 61.73; H, 8.41
$[\alpha]_D^{25}$	:	+2.5 (*c* 1.05, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 1.01 (d, 3H, *J* = 6.8 Hz), 1.33 (s, 3H), 1.53 (s, 3H), 1.76 (m, 1H), 2.17 (bs, 1H), 4.13 (m, 1H), 4.32 (ddd, 1H, *J* = 1.2, 7.4, 13.3 Hz), 4.48 (t, 1H, *J* = 9.2 Hz), 4.56 (t, 1H, *J* = 4.1 Hz), 5.43 (ddt, 1H, *J* = 1.4, 8.5, 11.2 Hz), 5.81 (d, 1H, *J* = 3.7 Hz), 5.87 (dddd, 1H, *J* = 1.1, 5.9, 7.4, 11.2 Hz)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 8.4 (q), 26.0 (q), 26.4 (q), 44.3 (d), 58.1 (t), 77.6 (d), 82.1 (d), 104.7 (d), 111.2 (s), 128.2 (d), 134.0 (d)

***tert*-butyldiphenyl((*E*)-3-((3a*R*,5*R*,6*R*,6a*R*)-2,2,6-trimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)allyloxy)silane** (**51**):

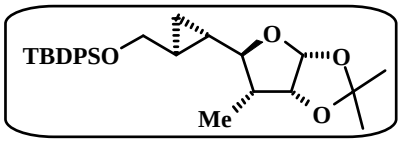


The *E* allyl OH **42** (10.8 g, 50.46 mmol) was dissolved in CH_2Cl_2 (50 mL). To it imidazole (5.15 g, 75.70 mmol) was added followed by TBDPSCl (15.52 mL, 60.56 mmol) and stirred for 1 h at room temperature. The reaction mixture was concentrated in

vacuo and purified by column chromatography using EtOAc:Petroleum ether (1:9) to get the pure *E* allyl OTBDPS compound **51** (22.35 g, 98%) as a colorless liquid.

Mol. Formula	:	$C_{27}H_{36}O_4Si$
Mol. Weight	:	452.67
ESI-MS *m/z*	:	475.63 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	3073, 3018, 2962, 2860, 1428, 1383, 1113, 1020, 759, 703, 668
Elemental Analysis	:	Calcd: C, 71.64; H, 8.02; Si, 6.20 Found: C, 71.73; H, 8.11; Si, 6.35
$[\alpha]_D^{25}$	:	+4.9 (*c* 1.8, $CHCl_3$).
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 1.04 (d, 3H, *J* = 6.8 Hz), 1.05 (s, 9H), 1.34 (s, 3H), 1.53 (s, 3H), 1.74 (m, 1H), 4.14 (dd, 1H, *J* = 7.2, 10.2 Hz), 4.22 (m, 2H), 4.56 (t, 1H, *J* = 4.2 Hz), 5.69 (ddt, 1H, *J* = 1.5, 7.1, 15.4 Hz), 5.83 (d, 1H, *J* = 3.5 Hz), 5.86 (dt, 1H, *J* = 4.1, 15.4 Hz), 7.40 (m, 6H), 7.69 (m, 4H)
^{13}C NMR (100 MHz, $CDCl_3$)	:	δ 8.7 (q), 19.1 (s), 26.2 (q), 26.6 (q), 26.7 (q), 44.2 (d), 63.5 (t), 82.4 (d), 83.0 (d), 104.8 (d), 111.2 (s), 127.0 (d), 127.6 (d), 129.6 (d), 133.5 (s), 134.7 (d), 135.4 (d)

***tert*-butyldiphenyl(((1*S*,2*S*)-2-((3a*R*,5*R*,6*R*,6a*R*)-2,2,6-trimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)cyclopropyl)methoxy)silane** (**41**):

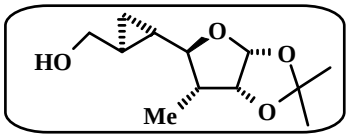


The olefin **51** (5.9 g, 13.05 mmol) was dissolved in CH_2Cl_2 and cooled to -35 °C. To it Et_2Zn (32.63 mL of 2M solution in hexane, 65.27 mmol) was added slowly followed by CH_2I_2 (10.52 mL, 130.5 mmol). The reaction mixture was stirred at -35 °C for 12 h. As TLC confirmed the complete consumption of the starting material, the reaction was quenched with saturated aqueous NH_4Cl and the colloidal mixture was filtered through a sintered funnel. The biphasic solution was separated and the aqueous

layer was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, concentrated and purified by column chromatography using EtOAc:Petroleum ether (1:19) to yield the cyclopropane compound **41** (5.11 g, 84%) as a colorless liquid.

Mol. Formula	:	$C_{28}H_{38}O_4Si$
Mol. Weight	:	466.699
ESI-MS *m/z*	:	489.65 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	3019, 2933, 2860, 1428, 1384, 1112, 1075, 1023, 759, 704, 669, 506
Elemental Analysis	:	Calcd: C, 72.06; H, 8.21; Si, 6.02 Found: C, 72.13; H, 8.39; Si, 6.21
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.44 (dt, 1H, *J* = 5.1, 8.4 Hz), 0.56 (dt, 1H, *J* = 4.9, 8.5 Hz), 0.71 (m, 1H), 1.04 (s, 9H), 1.07 (m, 1H), 1.13 (d, 3H, *J* = 7.0 Hz), 1.31 (s, 3H), 1.47 (s, 3H), 1.83 (m, 1H), 3.07 (dd, 1H, *J* = 8.7, 9.7 Hz), 3.37 (dd, 1H, *J* = 7.0, 10.6 Hz), 3.74 (dd, 1H, *J* = 5.3, 10.6 Hz), 4.52 (t, 1H, *J* = 3.8 Hz), 5.75 (d, 1H, *J* = 3.8 Hz), 7.39 (m, 6H), 7.64 (m, 4H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 6.8 (t), 9.5 (q), 17.9 (d), 18.5 (d), 19.1 (s), 26.1 (q), 26.5 (q), 26.8 (q), 44.6 (d), 66.4 (t), 82.7 (d), 85.7 (d), 104.2 (d), 110.7 (s), 127.5 (d), 129.5 (d), 133.5 (s), 135.4 (d)

((1*S*,2*S*)-2-((3a*R*,5*R*,6*R*,6a*R*)-2,2,6-trimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)cyclopropyl)methanol (**52**):

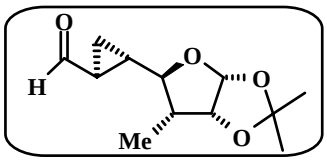


TBAF (11.97 mL of 2 M solution in THF, 23.95 mmol) was added to a THF solution (35 mL) of **41** (9.3 g, 19.96 mmol) at 0 °C and the mixture was warmed to room temperature. After 30 min., it was quenched with saturated aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, concentrated, purified by column chromatography using

EtOAc:Petroleum ether (1:3) to yield the hydroxy compound **52** (4.37 g, 96%) as a viscous liquid.

Mol. Formula	:	$C_{12}H_{20}O_4$
Mol. Weight	:	228.29
ESI-MS *m/z*	:	241.18 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	3436, 2985, 2937, 1458, 1381, 1175, 1156, 1113, 1060, 872, 519
Elemental Analysis	:	Calcd: C, 63.14; H, 8.83 Found: C, 63.19; H, 8.99
$[\alpha]_D^{25}$	:	+48.7 (*c* 2.5, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.49 (dt, 1H, *J* = 5.0, 8.4 Hz), 0.65 (dt, 1H, *J* = 4.9, 8.4 Hz), 0.76 (m, 1H), 1.09 (m, 1H), 1.13 (d, 3H, *J* = 7.0 Hz), 1.31 (s, 3H), 1.47 (s, 3H), 1.62 (bs, 1H), 1.84 (m, 1H), 3.20 (dd, 1H, *J* = 7.8, 9.9 Hz), 3.45 (dd, 1H, J = 7.0, 11.2 Hz), 3.56 (dd, 1H, *J* = 6.7, 11.2 Hz), 4.53 (t, 1H, *J* = 4.2 Hz), 5.75 (d, 1H, *J* = 3.8 Hz)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 6.9 (t), 9.4 (q), 18.1 (d), 18.3 (d), 26.0 (q), 26.4 (q), 44.3 (d), 65.5 (t), 82.7 (d), 85.0 (d), 104.1 (d), 110.6 (s)

(1*S*,2*S*)-2-((3a*R*,5*R*,6*R*,6a*R*)-2,2,6-trimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)cyclopropanecarbaldehyde (**40**):

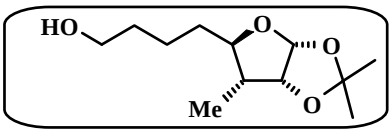


IBX (6.04 g, 21.58 mmol) was added to a DMSO (45 mL) solution of the alcohol **52** (4.1 g, 17.98 mmol) at 10 ^oC. The reaction mixture was stirred for 2 h. It was quenched with saturated aqueous $NaHCO_3$ solution. The colloidal solution was filtered with a sintered funnel. EtOAc was added to the biphasic filtrate and the layers were separated. The aqueous layer was extracted with EtOAc. The combined organic layer was

washed with water, brine solution, dried over Na_2SO_4, concentrated and purified by column chromatography using EtOAc:Petroleum ether (1:4) to yield the pure cyclopropane formaldehyde **40** (3.29 g, 81%) as a yellow liquid.

Mol. Formula	:	$C_{12}H_{18}O_4$
Mol. Weight	:	226.27
ESI-MS *m/z*	:	249.18 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	3341, 2923, 2853, 1709, 1586, 1458, 1383, 1107, 1022, 873, 616, 521
Elemental Analysis	:	Calcd: C, 63.70; H, 8.02 Found: C, 63.93; H, 8.22
$[\alpha]_D^{25}$	:	+124.0 (*c* 1.2, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 1.12 (d, 3H, *J* = 6.8 Hz), 1.23 (m, 2H), 1.31 (s, 3H), 1.47 (s, 3H), 1.61 (m, 1H), 1.83 (m, 1H), 1.98 (m, 1H), 3.47 (dd, 1H, *J* = 6.1, 9.9 Hz), 4.53 (t, 1H, *J* = 4.1 Hz), 5.72 (d, 1H, *J* = 3.7 Hz), 9.20 (d, 1H, *J* = 4.8 Hz)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 9.3 (d), 10.9 (t), 23.1 (d), 26.1 (q), 26.5 (q), 26.9 (q), 44.3 (d), 82.1 (d), 82.7 (d), 104.5 (d), 111.4 (s), 200.2 (d)

4-((3a*R*,5*R*,6*R*,6a*R*)-2,2,6-trimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)butan-1-ol (**54**):

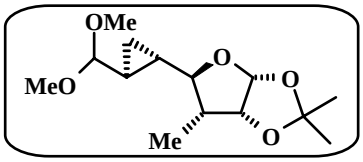


The aldehyde **40** (0.25 g, 11.06 mmol), AIBN (0.36 mL, 13.27 mmol), TBTH was taken with benzene (2 mL) and the mixture was degassed with argon and heated to reflux. After 2 h, the reaction mixture was concentrated and purified by short pad of silica gel to get the cyclopropane aldehyde **53**, which was dissolved in dry MeOH (3 mL). To it $NaBH_4$ (0.063 g, 16.59 mmol) was added at 0 ^oC. The reaction mixture was warmed to room temperature and stirred for 2 h. Then it was quenched with ice water and the solvent was evaporated in vacuo. The residue was dissolved in EtOAc and partitioned

between EtOAc and water. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, concentrated and purified by column chromatography using EtOAc:Petroleum ether (1:3) to get the straight chain alcohol **54** (0.226 g, 89% over two steps) as a sticky liquid.

Mol. Formula	:	$C_{12}H_{22}O_4$
Mol. Weight	:	230.31
ESI-MS *m/z*	:	253.19 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 62.58; H, 9.63
		Found: C, 62.71; H, 9.85
^{1}H NMR	:	δ 1.03 (d, 3H, *J* = 7.0 Hz), 1.31 (s, 3H), 1.40 (m, 2H),
(200 MHz, $CDCl_3$)		1.49 (s, 3H), 1.61 (m, 5H), 1.77 (bs, 1H), 3.64 (m, 3H),
		4.50 (t, 1H, *J* = 4.2 Hz), 5.74 (d, 1H, *J* = 3.8 Hz)
^{13}C NMR	:	δ 9.4 (q), 22.5 (t), 26.4 (q), 26.7 (q), 32.3 (t), 32.8 (t), 43.6
(50 MHz, $CDCl_3$)		(d), 62.6 (t), 82.2 (d), 82.8 (d), 104.6 (d), 111.2 (s)

(3a*R*,5*R*,6*R*,6a*R*)-5-((1*S*,2*S*)-2-(dimethoxymethyl)cyclopropyl)-2,2,6-trimethyltetrahydrofuro[2,3-*d*][1,3]dioxole (**55**):

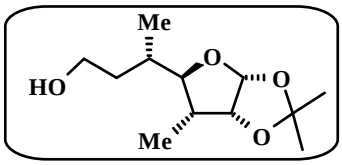


The undesired acetal **55** was obtained when the compound **40** with 10% Pd/C (catalytic) in MeOH was exposed to H_2 atmosphere.

Mol. Formula	:	$C_{14}H_{24}O_5$
Mol. Weight	:	272.34
ESI-MS *m/z*	:	295.18 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 61.74; H, 8.88
		Found: C, 61.93; H, 8.99
^{1}H NMR	:	δ 0.64 (dd, 2H, *J* = 6.7, 7.1 Hz), 0.90 (ddd, 1H, *J* = 4.7,
(200 MHz, $CDCl_3$)		7.1, 14.1 Hz), 1.14 (d, 3H, *J* = 6.8 Hz), 1.16 (m, 1H), 1.30

(s, 3H), 1.47 (s, 3H), 1.84 (m, 1H), 3.24 (dd, 1H, *J* = 7.5, 9.8 Hz), 3.34 (s, 6H), 4.06 (d, 1H, *J* = 5.4 Hz), 4.53 (t, 1H, *J* = 4.2 Hz), 5.74 (d, 1H, *J* = 3.7 Hz)

(*S*)-3-((3a*R*,5*R*,6*R*,6a*R*)-2,2,6-trimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)butan-1-ol (**56**):

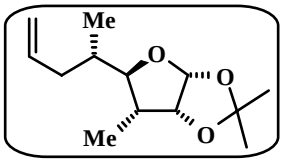


The cyclopropane formalaldehyde **40** (1.1 g, 4.87 mmol) was dissolved in dry isopropnaol (100 mL). To it anhydrous K_2CO_3 (1.1 g) and 10% Pd/C was added and subjected to H_2 atmosphere at 65 *psi*. After 48 h, TLC showed complete consumption of the starting material. The reaction mixture was filtered through a small pad of celite and the filtrate was concentrated and purified through column chromatography using EtOAc:Petroleum ether (1:2) to yield the over reduced alcohol **56** (0.82 g, 73%) and cyclopropane methyl alcohol **52** (0.2 g, 18%) as viscous liquid substances.

Mol. Formula	:	$C_{12}H_{22}O_4$
Mol. Weight	:	230.31
ESI-MS *m/z*	:	253.19 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	3447, 2966, 2936, 2880, 1458, 1382, 1373, 1161, 1102, 1026, 874
Elemental Analysis	:	Calcd: C, 62.58; H, 9.63 Found: C, 62.65; H, 9.77
$[\alpha]_D^{25}$	:	+29.0 (*c* 1, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.89 (d, 3H, *J* = 6.8 Hz), 1.03 (d, 3H, *J* = 6.8 Hz), 1.31 (s, 3H), 1.49 (s, 3H), 1.70 (m, 2H), 1.86 (m, 2H), 2.08 (bs, 1H), 3.58-3.80 (m, 3H), 4.51 (t, 1H, *J* = 4.2 Hz), 5.72 (d, 1H, *J* = 3.7 Hz)
^{13}C NMR	:	δ 9.4 (q), 12.7 (q), 26.3 (q), 26.6 (q), 29.6 (d), 37.5 (t),

(50 MHz, $CDCl_3$) 39.5 (d), 60.1 (t), 83.0 (d), 84.8 (d), 104.3 (d), 111.2 (s)

(3a*R*,5*R*,6*R*,6a*R*)-2,2,6-trimethyl-5-((*S*)-pent-4-en-2-yl)tetrahydrofuro[2,3-*d*][1,3]dioxole (**58**):

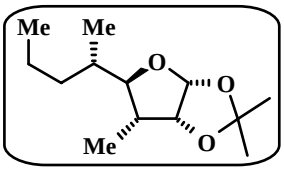


The primary alcohol **56** (0.25 g, 1.1 mmol) was taken in CH_2Cl_2 (5 mL) and Dess-Martin periodinane (0.69 g, 1.6 mmol) was added to it. The reaction mixture was stirred at room temperature for 2 h. After completion of the reaction, the reaction mixture was filtered and the filtrate was concentrated to give the crude aldehyde **5**7, which was used directly for the next Wittig reaction. The aldehyde **57** was dissolved in dry THF (5 mL) and cooled to 0 °C. To it methylene triphenyl phosphorane {prepared by reaction of methyl triphenylphosphonium bromide (1.16 g, 3.3 mmol) with *n*-BuLi (1.72 mL, 2.75 mmol) in THF} was added and the reaction mixture was stirred at room temperature for 5 h. Then the reaction mixture was quenched with aqueous NH_4Cl solution and the organic solvent was removed in rotavapor. The crude product was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc and the organic layer was dried over Na_2SO_4, concentarted and purified by column chromatography with EtOAc:petroleum (2:98) to get the terminal olefin **58** (0.2 g, 81% over two steps) as a colorless liquid.

Mol. Formula	:	$C_{13}H_{22}O_3$
Mol. Weight	:	226.32
ESI-MS *m/z*	:	249.15 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 68.99; H, 9.80
		Found: C, 69.08; H, 9.95
^{1}H NMR	:	δ 0.86 (d, 3H, *J* = 6.9 Hz), 1.02 (d, 3H, *J* = 6.9 Hz), 1.32
(200 MHz, $CDCl_3$)		(s, 3H), 1.49 (s, 3H), 1.65 (m, 1H), 1.84 (m, 1H), 2.06 (m, 1H), 2.25 (m, 1H), 3.74 (dd, 1H, *J* = 2.4, 10.3 Hz), 4.50

(t, 1H, *J* = 4.2 Hz), 5.03 (m, 2H), 5.72 (d, 1H, *J* = 3.8 Hz), 5.77 (ddt, 1H, *J* = 7.1, 10.0, 17.0 Hz)

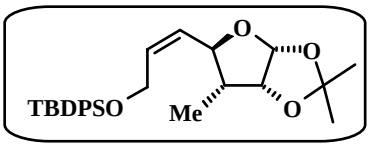
(3a*R*,5*R*,6*R*,6a*R*)-2,2,6-trimethyl-5-((*S*)-pentan-2-yl)tetrahydrofuro[2,3-*d*][1,3]dioxole (59):



The olefin **58** (0.15 g, 0.66 mmol) in MeOH (2 mL) was subjected to H_2 atmosphere at balloon pressure with 10% Pd/C (catalytic). After stirring the suspension for 1 h, it was filtered through a small pad of celite and the filtrate was concentrated. The crude product was purified by column chromatography using EtOAc:petroleum ether (2:98) to yield the pure product **59** (0.147 g, 97%) as a colorless liquid.

Mol. Formula	:	$C_{13}H_{24}O_3$
Mol. Weight	:	228.33
ESI-MS *m/z*	:	251.21 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 68.38; H, 10.59 Found: C, 68.51; H, 10.48
$[\alpha]_D^{25}$	:	+45.3 (*c* 1, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.84 (d, 3H, *J* = 6.6 Hz), 0.90 (t, 3H, *J* = 7.1 Hz), 1.02 (d, 3H, *J* = 6.6 Hz), 1.26-1.29 (m, 2H), 1.32 (s, 3H), 1.35-1.42 (m, 2H), 1.50 (s, 3H), 1.63 (m, 1H), 1.83 (m, 1H), 3.70 (dd, 1H, *J* = 2.2, 10.2 Hz), 4.50 (t, 1H, *J* = 4.4 Hz), 5.72 (d, 1H, *J* = 4.4 Hz)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 9.6 (q), 13.3 (q), 14.3 (q), 20.6 (t), 26.5 (q), 26.7 (q), 33.0 (d), 36.82 (t), 39.7 (d), 83.1 (d), 85.0 (d), 104.5 (d), 111.0 (s)

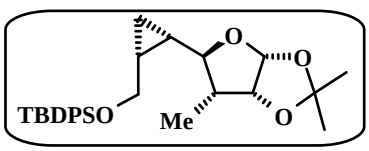
***tert*-butyldiphenyl((*Z*)-3-((3a*R*,5*R*,6*R*,6a*R*)-2,2,6-trimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)allyloxy)silane** (**60**):



Following the same procedure for compound **51**, the *Z* allylic alcohol **50** was converted to its silyl ether compound **60** in 97% yield.

Mol. Formula	:	$C_{27}H_{36}O_4Si$
Mol. Weight	:	452.67
ESI-MS *m/z*	:	475.55 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	3073, 3019, 2963, 2859, 1462, 1473, 1428, 1384, 1112, 1025, 758, 704, 669, 506
Elemental Analysis	:	Calcd: C, 71.64; H, 8.02; Si, 6.20 Found: C, 71.78; H, 7.95; Si, 6.11
$[\alpha]_D^{25}$	:	-2.6 (*c* 1.2, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.89 (d, 3H, *J* = 6.8 Hz), 1.04 (s, 9H), 1.29 (s, 3H), 1.39 (s, 3H), 1.66 (m, 1H), 4.21-4.37 (m, 3H), 4.48 (t, 1H, *J* = 4.2 Hz), 5.32 (ddt, 1H, *J* = 1.5, 8.7, 11.1 Hz), 5.74 (d, 1H, *J* = 3.7 Hz), 5.85 (ddt, 1H, *J* = 0.9, 6.4, 11.1 Hz), 7.38 (m, 6H), 7.66 (m, 4H)
^{13}C NMR ($CDCl_3$)	:	δ 8.6 (q), 19.2 (s), 26.3 (q), 26.6 (q), 26.8 (q), 44.7 (d), 60.2 (t), 78.0 (d), 82.3 (d), 105.0 (d), 111.2 (s), 127.7 (d), 128.1 (d), 129.6 (d), 133.6 (s), 134.0 (d), 135.5 (d)

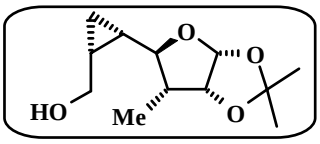
***tert*-butyldiphenyl(((1*R*,2*S*)-2-((3a*R*,5*R*,6*R*,6a*R*)-2,2,6-trimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)cyclopropyl)methoxy)silane** (**61**):



Following the same procedure for compound **41**, the compound **60** was cyclopropanated in Simmons-Smith condition to yield compound **61** in 89% yield.

Mol. Formula	:	$C_{28}H_{38}O_4Si$
Mol. Weight	:	466.699
ESI-MS *m/z*	:	489.10 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 72.06; H, 8.21; Si, 6.02 Found: C, 72.21; H, 8.32; Si, 6.22
$[\alpha]_D^{25}$	:	-0.5 (*c* 1.3, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.38 (dd, 1H, *J* = 5.6, 10.7 Hz), 0.78 (ddd, 1H, *J* = 4.8, 8.5, 16.9 Hz), 0.88 (m, 2H), 1.05 (s, 9H), 1.12 (d, 3H, *J* = 6.9 Hz), 1.31 (s, 3H), 1.43 (s, 3H), 1.81 (m, 1H), 3.47 (dd, 1H, *J* = 8.6, 9.6 Hz), 3.68 (d, 2H, *J* = 6.9 Hz), 4.53 (t, 1H, *J* = 3.8 Hz), 5.76 (d, 1H, *J* = 3.8 Hz), 7.38 (m, 6H), 7.67 (m, 4H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 6.8 (t), 9.4 (q), 18.4 (d), 18.7 (d), 19.2 (s), 26.3 (q), 26.6 (q), 26.9 (q), 45.3 (d), 63.9 (t), 81.8 (d), 83.0 (d), 104.4 (d), 110.9 (s), 127.6 (d), 129.5 (d), 133.8 (s), 135.6 (d)

((1*R*,2*S*)-2-((3a*R*,5*R*,6*R*,6a*R*)-2,2,6-trimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)cyclopropyl)methanol (**62**):

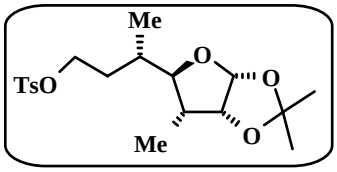


Following the same procedure for compound **52**, the compound **61** was deprotected to the corresponding alcohol **62** in 96% yield.

Mol. Formula	:	$C_{12}H_{20}O_4$
Mol. Weight	:	228.29
ESI-MS *m/z*	:	241.18 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 63.14; H, 8.83

		Found: C, 63.23; H, 8.92
$[\alpha]_D^{25}$	:	+30.9 (*c* 1, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.49 (dt, 1H, *J* = 4.8, 5.7 Hz), 0.84 (m, 1H), 0.97 (m, 1H), 1.11 (d, 3H, *J* = 6.8 Hz), 1.28 (m, 1H), 1.31 (s, 3H), 1.47 (s, 3H), 1.81 (m, 1H), 2.01 (bs, 1H), 3.60 (dd, 1H, *J* = 7.7, 10.0 Hz), 3.61 (dd, 1H, *J* = 4.7, 11.4 Hz), 3.70 (dd, 1H, *J* = 7.3, 11.4 Hz), 4.54 (t, 1H, *J* = 4.2 Hz), 5.77 (d, 1H, *J* = 3.8 Hz)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 6.9 (t), 9.2 (q), 17.8 (d), 18.8 (d), 26.1 (q), 26.5 (q), 44.8 (d), 62.6 (t), 81.4 (d), 82.8 (d), 104.2 (d), 111.0 (s)

(*S*)-3-((3a*R*,5*R*,6*R*,6a*R*)-2,2,6-trimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)butyl 4-methylbenzenesulfonate (**64**):

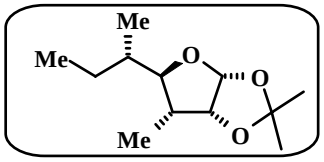


The alcohol **56** (3.2 g, 13.91 mmol) was taken with Et_3N (2.9 mL, 20.87 mmol) in CH_2Cl_2 (18 mL). To it TsCl (3.18 g, 16.70 mmol) was added at room temperature and the reaction mixture was stirred for 3 h. After completion of the reaction, the reaction mixture was partitioned between water and CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, concentrated and purified by column chromatography using EtOAc:Petroleum ether (1:5) to get the tosyl compound **64** (4.70 g, 88%) as a yellow liquid.

Mol. Formula	:	$C_{19}H_{28}O_6S$
Mol. Weight	:	384.50
ESI-MS *m/z*	:	407.41 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	2978, 2936, 1618, 1598, 1363, 1176, 1099, 1021, 769, 664, 555
Elemental Analysis	:	Calcd: C, 59.35; H, 7.34; S, 8.34

		Found: C, 59.49; H, 7.48; S, 8.39
$[\alpha]_D^{25}$	:	+21.8 (*c* 1, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.80 (d, 3H, *J* = 3.6 Hz), 0.98 (d, 3H, *J* = 3.8 Hz), 1.30 (s, 3H), 1.45 (s, 3H), 1.66 (m, 1H), 1.76-1.90 (m, 3H), 2.46 (s, 3H), 3.60 (dd, 1H, *J* = 1.8, 10.4 Hz), 4.10 (m, 2H), 4.49 (t, 1H, *J* = 4.2 Hz), 5.67 (d, 1H, *J* = 3.7 Hz), 7.34 (d, 2H, *J* = 8.4 Hz), 7.79 (d, 2H, *J* = 8.4 Hz)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 9.3 (q), 12.4 (q), 21.6 (q), 26.3 (q), 26.6 (q), 28.8 (d), 33.6 (t), 39.5 (d), 68.8 (t), 82.9 (d), 83.8 (d), 104.4 (d), 111.1 (s), 127.9 (d), 129.8 (d), 133.2 (s), 144.6 (s)

(3a*R*,5*R*,6*R*,6a*R*)-5-*sec*-butyl-2,2,6-trimethyltetrahydrofuro[2,3-*d*][1,3]dioxole (**65**):

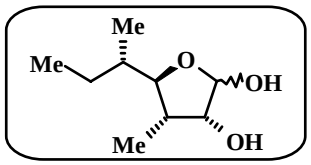


$LiAlH_4$ (0.889 g, 23.44 mmol) was added to a THF solution (25 mL) of the tosyl compound **64** (4.5 g, 11.72 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. Then it was quenched with saturated aqueous Na_2SO_4 till the grey suspension turned white. It was filtered and the residue was washed with EtOAc. The organic filtrate was concentrated in vacuo at low temperature (20 °C) and purified by column chromatography using EtOAc:Petroleum ether (1:19) to get the compound **65** (2.11 g, 84%) as a liquid.

Mol. Formula	:	$C_{12}H_{22}O_3$
Mol. Weight	:	214.31
ESI-MS *m/z*	:	237.15 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	2965, 2937, 2879, 1459, 1372, 1381, 1306, 1253, 1236, 1157, 1023, 875, 758, 667
Elemental Analysis	:	Calcd: C, 67.26; H, 10.35
		Found: C, 67.39; H, 10.48

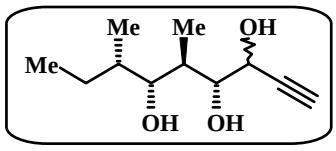
$[\alpha]_D^{25}$	:	+44.0 (*c* 1, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.86 (d, 3H, *J* = 6.7 Hz), 0.93 (t, 3H, *J* = 7.2 Hz), 1.03 (d, 3H, *J* = 6.8 Hz), 1.33 (s, 3H), 1.36-1.48 (m, 2H), 1.50 (s, 3H), 1.57 (m, 1H), 1.84 (m, 1H), 3.74 (dd, 1H, *J* = 2.2, 10.3 Hz), 4.51 (t, 1H, *J* = 4.3 Hz), 5.74 (d, 1H, *J* = 3.8 Hz)
^{13}C NMR (100 MHz, $CDCl_3$)	:	δ 9.4 (q), 12.0 (q), 12.9 (q), 26.4 (q), 26.6 (q), 27.2 (t), 35.0 (d), 39.7 (d), 83.1 (d), 84.7 (d), 104.5 (d), 110.9 (s)

(3*R*,4*S*,5*R*)-5-*sec*-butyl-4-methyltetrahydrofuran-2,3-diol (**39**):



The deoxy compound **65** (1.9 g, 88.79 mmol) was treated with 3:1 mixture of THF and water (30 mL). To it 6N aqueous HCl (5 mL) was added and the reaction mixture was heated to reflux for 1 h. After completion of the reaction, it was quenched with solid $NaHCO_3$. The solvent was evaporated in vacuo and partitioned between EtOAc and water. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, concentrated and purified by column chromatography using EtOAc:Petroleum ether (1:3) to yield the lactol **39** (1.41 g, 91%) as sticky liquid.

(4*R*,5*R*,6*R*,7*S*)-5,7-dimethylnon-1-yne-3,4,6-triol (**66**):

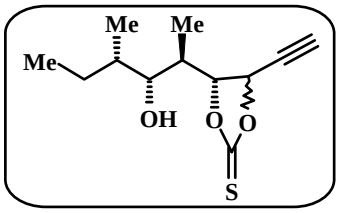


Magnesium (0.413 g, 17.2 mmol) and iodine (catalytic) in THF (5 mL) were taken in a three neck round bottomed flask fitted with a water condenser. To it *n*-BuCl (1.8 mL, 17.2 mmol) was added slowly and refluxed for 1 h. Then excess dry acetylene

gas was bobbled through a syringe needle, and the reaction mixture was stirred for 30 min. A THF solution of the lactol **39** (0.3 g, 1.72 mmol) was next added to it and stirred for 8 h. After completion of the reaction, the mixture was quenched with aqueous NH_4Cl. The biphasic mixture was separated and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, concentrated and purified by column chromatography using EtOAc:Petroleum ether (1:2) to give a mixture of triol **66** (0.244 g, 71%).

Mol. Formula	:	$C_{11}H_{20}O_3$
Mol. Weight	:	200.28
ESI-MS *m/z*	:	222.77 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 65.97; H, 10.07 Found: C, 66.02; H, 10.18
^{1}H NMR (500 MHz, $CDCl_3$)	:	δ 0.87 (d, 3H, *J* = 6.9 Hz), 0.91 (d, 3H, *J* = 6.9 Hz), 0.95 (t, 3H, *J* = 7.4 Hz), 1.26 (bs, 2H), 1.33 (m, 1H), 1.42 (m, 1H), 1.50 (bs, 1H), 1.57 (m, 1H), 1.94 (m, 1H), 2.47 (d, 1H, *J* = 2.3 Hz), 3.67-3.74 (m, 2H), 4.46-4.50 (t, 1H, *J* = 2.5 Hz)

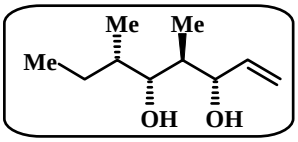
(*R*)-4-ethynyl-5-((2*R*,3*R*,4*S*)-3-hydroxy-4-methylhexan-2-yl)-1,3-dioxolane-2-thione (**67**):



The triol compound **66** (0.189 g, 0.945 mmol) was dissolved in CH_2Cl_2 (5 mL) and 1,1'-thiocarbonyldiimidazole (0.185 g, 10.40 mmol) was added to it and heated to reflux for 8 h. Then the reaction mixture was concentrated and purified by column chromatography using EtOAc:Petroleum ether (1:4) to get the diastereomeric thiocarbonate acetylene mixture **67** (0.169 g, 74%) as a colorless liquid.

Mol. Formula	:	$C_{12}H_{18}O_3S$
Mol. Weight	:	242.34
ESI-MS *m/z*	:	265.13 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 59.84; H, 7.49; S, 13.23 Found: C, 59.97; H, 7.65; S, 13.25
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.86 (d, 3H, *J* = 6.6 Hz), 0.88 (t, 3H, *J* = 7.2 Hz), 0.98 (d, 3H, *J* = 6.8 Hz), 1.36-1.53 (m, 3H), 1.71 (m, 1H), 2.19 (m, 1H), 2.40-2.55 (d, 1H, *J* = 2.2 Hz), 3.60-3.74 (dd, 1H, *J* = 3.0, 9.7 Hz), 4.05-4.14 (dd, 1H, *J* = 1.6, 4.9 Hz), 4.37-4.54 (t, 1H, *J* = 1.9 Hz)

(3*S*,4*S*,5*R*,6*S*)-4,6-dimethyloct-1-ene-3,5-diol (**68**):

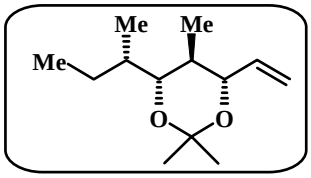


A THF solution of methyltriphenylphosphonium bromide (19.5 g, 54.6 mmol) was cooled to 0 °C. To it *n*-BuLi (30.7 mL, 49.14 mmol) was added slowly and stirred for 2 h at 0 °C. Then the reaction was allowed to stand still. The supernatant was cannulated to a THF solution of the lactol **39** (0.95 g, 5.46 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 18 h. Then it was quenched with ice water, the solvent was evaporated and the residue was partitioned between EtOAc and water. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, concentrated and purified by column chromatography using EtOAc:Petroleum ether (1:4) to yield the terminal olefin **68** (0.686 g, 73%) as viscous liquid.

Mol. Formula	:	$C_{10}H_{20}O_2$
Mol. Weight	:	172.27
ESI-MS *m/z*	:	195.16 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	3340, 2965, 2935, 2876, 1463, 1380, 1144, 1016, 991,

		956, 925, 758
Elemental Analysis	:	Calcd: C, 69.72; H, 11.70 Found: C, 69.88; H, 11.65
$[\alpha]_D^{25}$	:	+13.0 (*c* 1.6, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.75 (d, 3H, *J* = 7.0 Hz), 0.86 (d, 3H, *J* = 6.6 Hz), 0.93 (t, 3H, *J* = 7.3 Hz), 1.36 (m, 2H), 1.53 (m, 1H), 1.69 (m, 1H), 3.21 (bs, 2H), 3.57 (dd, 1H, *J* = 2.0, 9.3 Hz), 4.09 (t, 1H, *J* = 7.8 Hz), 5.20 (m, 2H), 5.86 (ddd, 1H, *J* = 7.5, 10.2, 17.2 Hz)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 11.4(q), 12.0 (q), 12.9 (q), 26.9 (t), 36.7 (d), 40.6 (d), 78.8 (d), 79.2 (d), 116.7 (t), 139.5 (d)

(4*R*,5*S*,6*S*)-4-((*S*)-*sec*-butyl)-2,2,5-trimethyl-6-vinyl-1,3-dioxane (**69**):

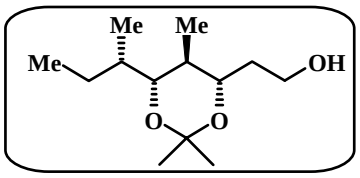


The diol **68** (0.65 g, 3.78 mmol) was dissolve in dry acetone (3 mL) and to it was added 2,2-dimethoxypropane (1.89 mL, 15.12 mmol) followed by catalytic amount of *p*-TSA. The reaction mixture was stirred for 5 h. The reaction mixture was quenched with Et_3N and the organic solvent was removed in vacuo. The crude residue was purified by column chromatography using EtOAc:Petroleum ether (1:19) to yield the acetonide olefin **69** (0.761 g, 95%) as a colorless liquid.

Mol. Formula	:	$C_{13}H_{24}O_2$
Mol. Weight	:	212.34
ESI-MS *m/z*	:	235.19 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	2964, 2936, 2876, 1464, 1380, 1254, 1202, 1181, 1055, 1013, 924, 899
Elemental Analysis	:	Calcd: C, 73.54; H, 11.39 Found: C, 73.59; H, 11.51

$[\alpha]_D^{25}$	:	+57.4 (*c* 1, $CHCl_3$
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.65 (d, 3H, *J* = 6.7 Hz), 0.78 (d, 3H, *J* = 6.7 Hz), 0.81 (t, 3H, *J* = 7.4 Hz), 1.26 (m, 2H), 1.31 (s, 3H), 1.38 (s, 3H), 1.40-1.57 (m, 2H), 3.44 (dd, 1H, *J* = 2.1, 10.3 Hz), 3.81 (dd, 1H, *J* = 7.5, 10.1 Hz), 5.15 (ddd, 1H, *J* = 0.5, 1.9, 10.1 Hz), 5.20 (ddd, 1H, *J* = 0.8, 1.9, 17.2 Hz) , 5.69 (ddd, 1H, *J* = 7.5, 10.1, 17.2 Hz)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 11.7 (q), 12.0 (q), 12.3 (q), 19.6 (q), 26.6 (t), 30.1 (q), 35.0 (d), 75.2 (d), 77.4 (d), 97.9 (s), 118.1 (t), 137.5 (d)

2-((4*S*,5*S*,6*R*)-6-((*S*)-*sec*-butyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)ethanol (**70**):

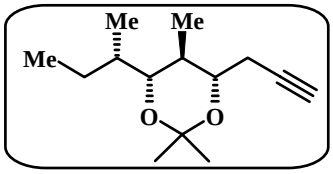


The olefin **69** (0.59 g, 2.78 mmol) was dissolved in dry THF (3 mL), to it was added 9-BBN (1.02 g, 4.17 mmol), and the reaction was stirred for 5 h. After the mixture was treated with aqueous NaOH solution (1 mL) followed by H_2O_2 (1 mL) and the mixture was stirred for 5 h. Then, the biphasic layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, concentrated and purified by column chromatography using EtOAc:Petroleum ether (1:5) to yield the primary alcohol **70** (0.493 g, 77%) exclusively as colorless liquid.

Mol. Formula	:	$C_{13}H_{26}O_3$
Mol. Weight	:	230.35
ESI-MS *m/z*	:	253.17 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	3371, 2963, 2934, 2875, 1460, 1380, 1255, 1203, 1173, 1054, 1026
Elemental Analysis	:	Calcd: C, 67.79; H, 11.38 Found: C, 67.91; H, 11.51
$[\alpha]_D^{25}$	:	+6.8 (*c* 1, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$)	:	δ 0.73 (d, 3H, *J* = 6.5 Hz), 0.84 (d, 3H, *J* = 6.8 Hz), 0.88 (t, 3H, *J* = 7.5 Hz), 1.26-1.32 (m, 2H), 1.35 (s, 3H), 1.43 (s, 3H), 1.50-1.59 (m, 2H), 1.67 (m, 1H), 1.92 (m, 1H), 2.61 (bs, 1H), 3.46 (dd, 1H, *J* = 1.8, 10.1 Hz), 3.69-3.82 (m, 3H)
^{13}C NMR (100 MHz, $CDCl_3$)	:	δ 11.7 (q), 12.0 (q), 12.4 (q), 19.5 (q), 26.6 (t), 30.2 (q), 34.8 (t), 35.0 (d), 35.3 (d), 61.4 (t), 75.3 (d), 75.9 (d), 97.9 (s)

(4*R*,5*S*,6*S*)-4-((*S*)-*sec*-butyl)-2,2,5-trimethyl-6-(prop-2-ynyl)-1,3-dioxane (**72**):



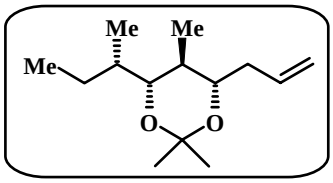
The primary alcohol **70** (0.415 g, 1.80 mmol) was dissolved in CH_2Cl_2 (4 mL) and to it was added PDC (1.02g, 2.71 mmol) and catalytic amount of Ac_2O at 0 °C. The mixture was warmed to room temperature and stirred for 2 h. Then it was concentrated and the residue was dissolved in EtOAc and filtered through a pad of celite and silica gel. The filtrate was concentrated to yield the crude aldehyde, which was dissolved in MeOH (2 mL). The methanolic solution was treated with Bestmann reagent (0.52 g, 2.71 mmol) and anhydrous K_2CO_3 (0.499 g, 3.61 mmol). After stirring for 5 h at room temperature, it was concentrated and partitioned between EtOAc and water. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, concentrated and purified by column chromatography using EtOAc:Petroleum ether (4:96) to yield the terminal alkyne **72** (0.291 g, 72% over two steps) as yellow liquid.

Mol. Formula	:	$C_{14}H_{24}O_2$
Mol. Weight	:	224.35
ESI-MS *m/z*	:	247.50 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	3314, 2965, 2936, 2875, 1464, 1381, 1261, 1202, 1173,

		1063, 1017, 970, 761, 637, 517
Elemental Analysis	:	Calcd: C, 74.95; H, 10.78 Found: C, 75.03; H, 11.59
$[\alpha]_D^{25}$	:	+23.4 (*c* 1, $CHCl_3$)
^{1}H NMR (500 MHz, $CDCl_3$)	:	δ 0.79 (d. 3H, *J* = 6.6 Hz), 0.85 (d, 3H, *J* = 6.9 Hz), 0.88 (t, 3H, *J* = 7.4 Hz), 1.25-1.35 (m, 2H), 1.36 (s, 3H), 1.41 (s, 3H), 1.54 (m, 1H), 1.63 (m, 1H), 1.98 (t, 1H, *J* = 2.6 Hz), 2.39 (ddd, 1H, *J* = 2.5, 5.8, 17.0 Hz), 2.47 (dd, 1H, *J* = Hz), 3.46 (dd, 1H, *J* = 1.9, 10.2 Hz), 3.59 (ddd, 1H, *J* = 4.1, 5.8, 9.9 Hz
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 11.7 (q), 12.0 (q), 12.4 (q), 19.5 (q), 23.9 (t), 26.7 (t), 30.0 (q), 35.0 (d), 69.9 (d), 73.3 (d), 75.1 (d), 81.1 (s), 98.0 (s)

(4*S*,5*S*,6*R*)-4-allyl-6-*sec*-butyl-2,2,5-trimethyl-1,3-dioxane (**74**):

The terminal alkyne **72** (0.03 g, 0.13 mmol) was taken with TBTH (0.05 mL, 0.2 mmol), AIBN (catalytic) in benzene (3 mL). The homogeneous solution was degassed with argon atmosphere followed by refluxing for 1 h. After TLC showed the complete consumption of starting material, the organic solvent was evaporated in vacuo and the crude product was purified by column chromatography using 2% EtOAc in light petroleum ether as eluent to produce the terminal olefin **74** (0.025 g, 81%) as yellow liquid in stead of the vinyl tributyl tin compound **73**.



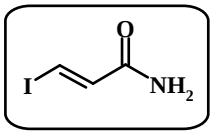
Mol. Formula	:	$C_{14}H_{24}O_2$
Mol. Weight	:	226.36
ESI-MS *m/z*	:	249.26 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	2961, 2927, 2856, 1743, 1641, 1460, 1379, 1201, 1177,

		1014, 954, 910
Elemental Analysis	:	Calcd: C, 74.29; H, 11.58 Found: C, 74.37; H, 11.63
$[\alpha]_D^{25}$	:	+6.4 (*c* 1.5, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.67 (d, 3H, *J* = 6.6 Hz), 0.76 (d, 3H, *J* = 6.7 Hz), 0.80 (t, 3H, *J* = 7.2 Hz), 1.27 (s, 3H), 1.32 (s, 3H), 1.38-1.48 (m, 2H), 2.14 (m, 1H), 2.31 (dddd, 1H, *J* = 1.6, 3.3, 6.6, 14.9 Hz), 3.37 (m, 1H), 3.47 (m, 1H), 4.99 (m, 2H), 5.85 (m, 1H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 11.6 (q), 12.0 (q), 12.3 (q), 19.4 (q), 26.7 (t), 30.0 (q), 34.8 (d), 34.9 (d), 37.6 (t), 74.3 (d), 75.2 (d), 97.6 (s), 116.1 (t), 135.3 (d)

Preparation of vinyl-iodo fragment:

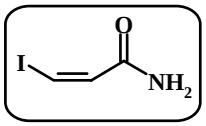
Methyl propiolate (0.5 g, 5.95 mmol) was treated with aqueous ammonia at -30 ^oC for 8 h. Then the ammonia solution was evaporated in vacuo and the mixture was partitioned between EtOAc and water. The organic layer was concentrated to get the crude propionamide and directly used for the next step. The propionamide thus formed was dissolved in CH_3CN (2 mL), to it LiI (0.876 g, 6.54 mmol) followed by glacial CH_3COOH was added and the mixture was heated to reflux for 18 h. Then the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The biphasic mixture was separated and the aqueous layer was extracted with EtOAc. The organic layers were mixed, dried over Na_2SO_4, concentrated and purified by flash column chromatography using EtOAc:Petroleum ether (1:5) to get the *trans* amide **75** (0.12 g, 9%) and the *cis* amide **34** (1.12 g, 78%), both as solids.

(*E*)-3-iodoacrylamide (**75**):



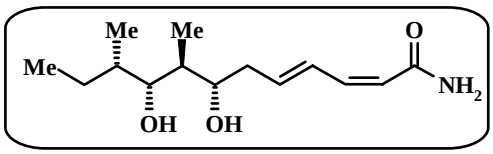
Mol. Formula	:	C_3H_4ONI
Mol. Weight	:	196.98
ESI-MS *m/z*	:	220.01 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 18.29; H, 2.05; N, 7.11; I, 64.43
		Found: C, 18.35; H, 2.09; N, 7.23; I, 64.23
^{1}H NMR (200 MHz, Acetone-d6)	:	δ 6.57 (bs, 1H), 7.01 (bs, 1H), 7.07 (d, 1H, *J* = 14.6 Hz), 7.65 (d, 1H, *J* = 14.6 Hz)

(*Z*)-3-iodoacrylamide (**34**):



Mol. Formula	:	C_3H_4ONI
Mol. Weight	:	196.98
ESI-MS *m/z*	:	220.05 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 18.29; H, 2.05; N, 7.11; I, 64.43
		Found: C, 18.41; H, 1.96; N, 7.27; I, 64.31
^{1}H NMR (200MHz, DMSO-d6)	:	δ 6.94 (d, 1H, *J* = 8.6 Hz), 7.11 (d, 1H, *J* = 8.6 Hz), 7.19 (bs, 1H), 7.50 (bs, 1H)
^{13}C NMR (50 MHz, DMSO-d6)	:	δ 87.2 (d), 130.7 (d), 163.7 (s)

(2*Z*,4*E*,7*S*,8*S*,9*R*,10*S*)-7,9-dihydroxy-8,10-dimethyldodeca-2,4-dienamide (**19**):

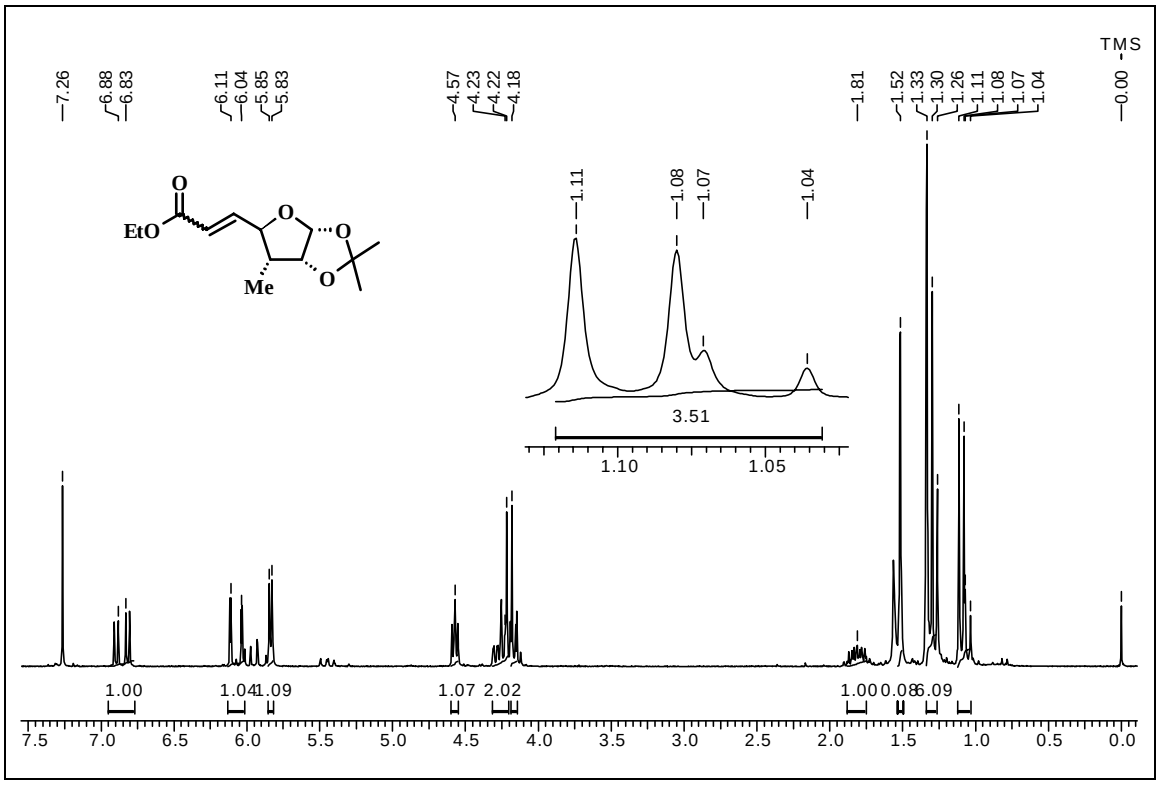


Following the earlier for the compound **74**, the crude product **73** without column chromatography purification was obtained from the alkyne **72** (0.03 g, 0.13 mmol). The crude product was dissolved in dry DMF. To it the *Z*-iodo propionamide (**34**) (0.026 g,

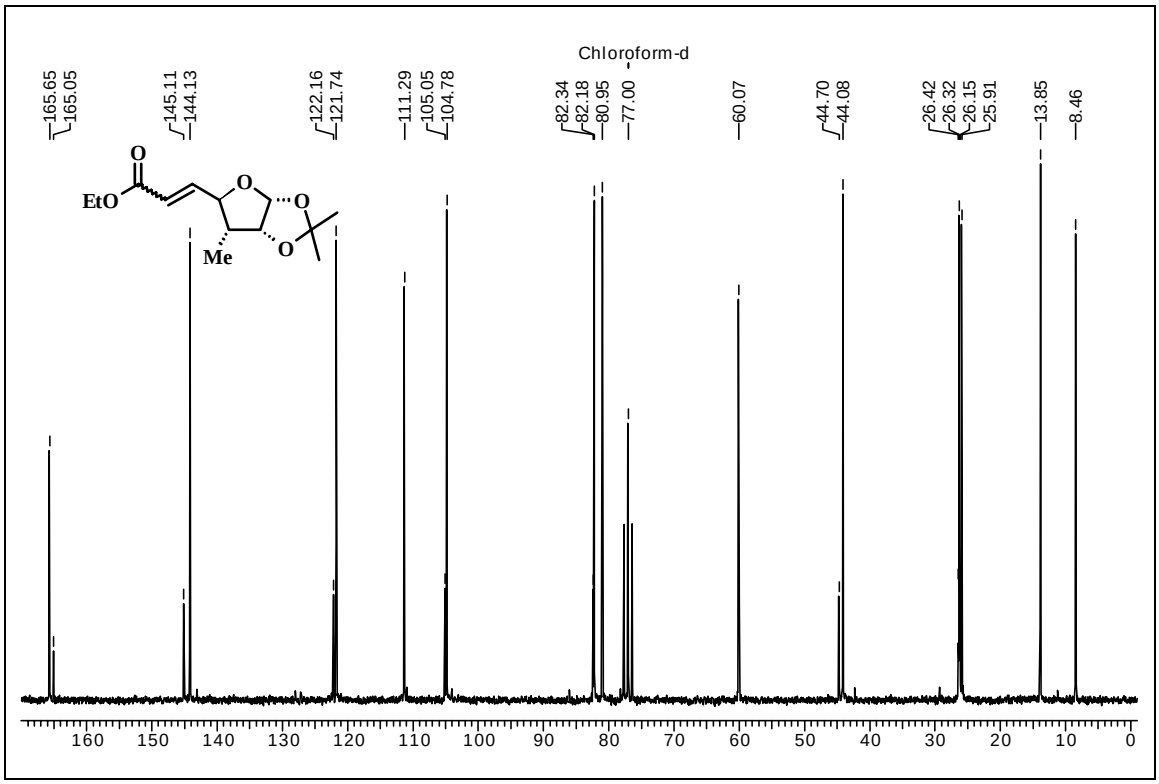
0.13 mmol) was added followed by catalytic amount of $Pd(CH_3CN)_2Cl_2$. The reaction mixture was kept away from light and stirred for 24 h at room temperature. TLC showed complete consumption of starting material. The reaction mixture was partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc and the combined organic layer was washed with water and brine solution. Then the extracts were dried over Na_2SO_4, concentrated and purified by column chromatography using EtOAc:petroleum ether (3:7) to yield the Stille product **20** (0.03 g, 75%). The coupled product **20** was then dissolved in MeOH and the mixture was treated with catalytic amount of *p*-TSA. After stirring the reaction mixture for 1 h, the organic solvent was concentrated and the crude product was purified by silica gel column chromatography using EtOAc:Petroleum ether (1:1) as eluent to get the diol **19** as a sticky solid (0.025 g, 96%).

Mol. Formula	:	$C_{14}H_{25}NO_3$
Mol. Weight	:	255.36
ESI-MS *m/z*	:	378.29 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	3379, 3182, 2923, 2846, 1634, 1405, 1092, 1048, 1021, 771
Elemental Analysis	:	Calcd: C, 65.85; H, 9.87; N, 5.49 Found: C, 66.07; H, 9.94; N, 5.40
$[\alpha]_D^{25}$	:	-3.0 (*c* 0.2, MeOH)
^{1}H NMR (500 MHz, CD_3OD)	:	δ 0.72 (d, 3H, *J* = 6.9 Hz), 0.76 (d, 3H, *J* = 6.7 Hz), 0.85 (t, 3H, *J* = 6.9 Hz), 1.24 (m, 1H), 1.34 (m, 1H), 1.42 (m, 1H), 1.70 (m, 1H), 2.18 (m, 1H), 2.36 (m, 1H), 3.34 (m, 1H), 3.84 (ddd, 1H, *J* = 3.0, 5.8, 8.8 Hz), 4.54 (bs, 1H), 5.58 (d, 1H, *J* = 11.4 Hz), 6.04 (dt, 1H, *J* = 7.2, 15.4 Hz), 6.40 (t, 1H, *J* = 11.4 Hz), 7.34 (dd, 1H, *J* = 11.4, 15.4 Hz)
^{13}C NMR (100 MHz, CD_3OD)	:	δ 11.9 (q), 12.3 (q), 12.5 (q), 28.4 (t), 37.5 (t), 38.2 (d), 42.7 (d), 74.9 (d), 77.7 (d), 119.3 (d), 130.2 (d), 141.8 (d), 143.3 (d), 171.7 (s)

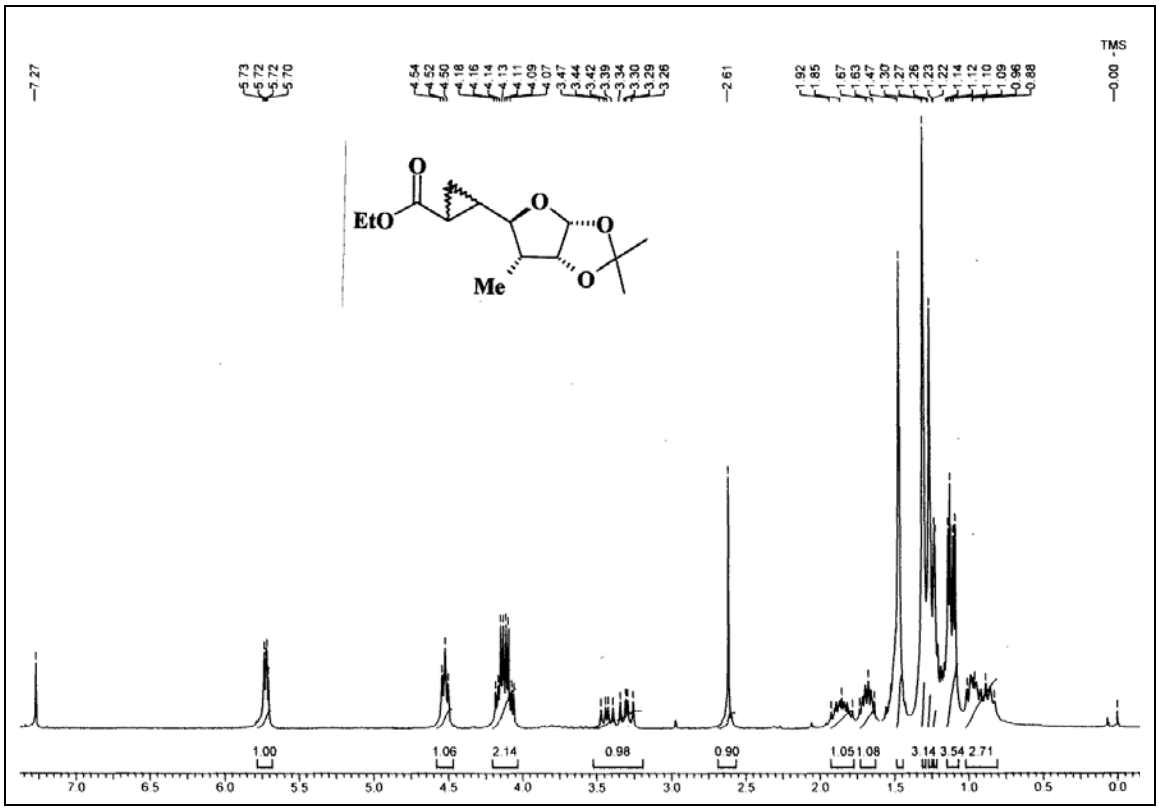
Spectra



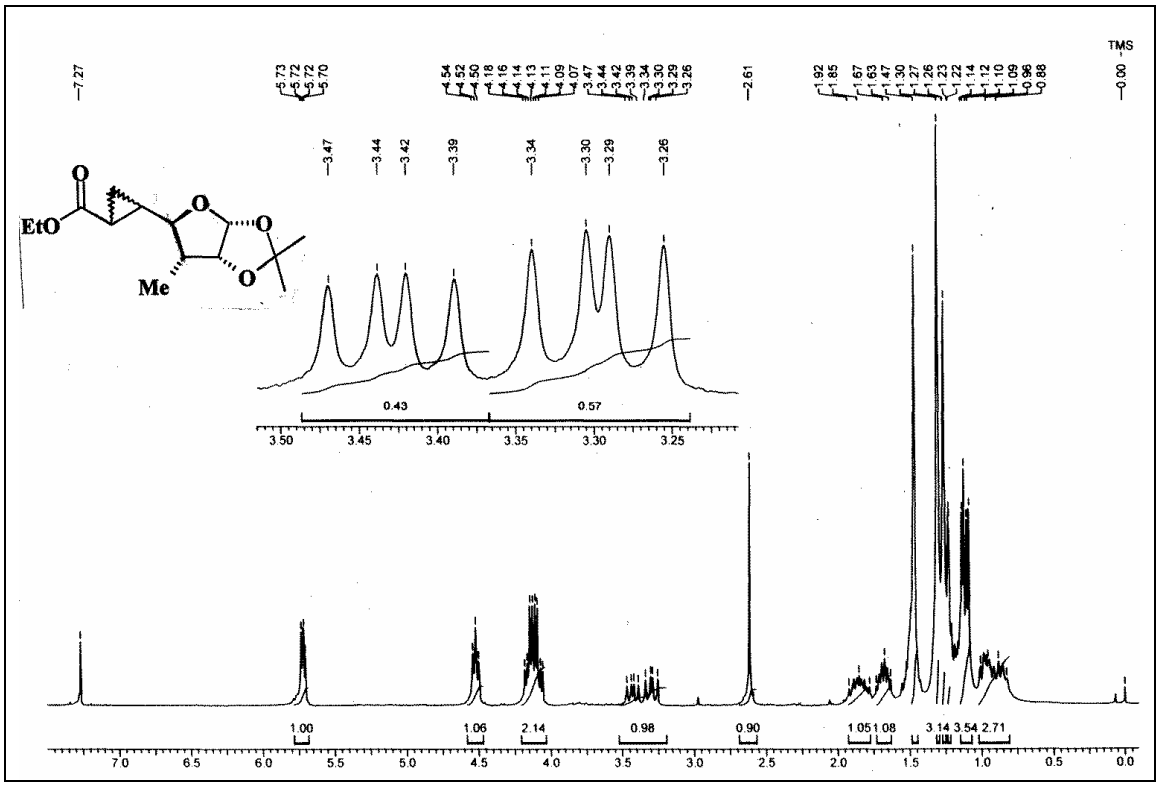
^{1}H NMR spectrum of compound 48 in $CDCl_3$



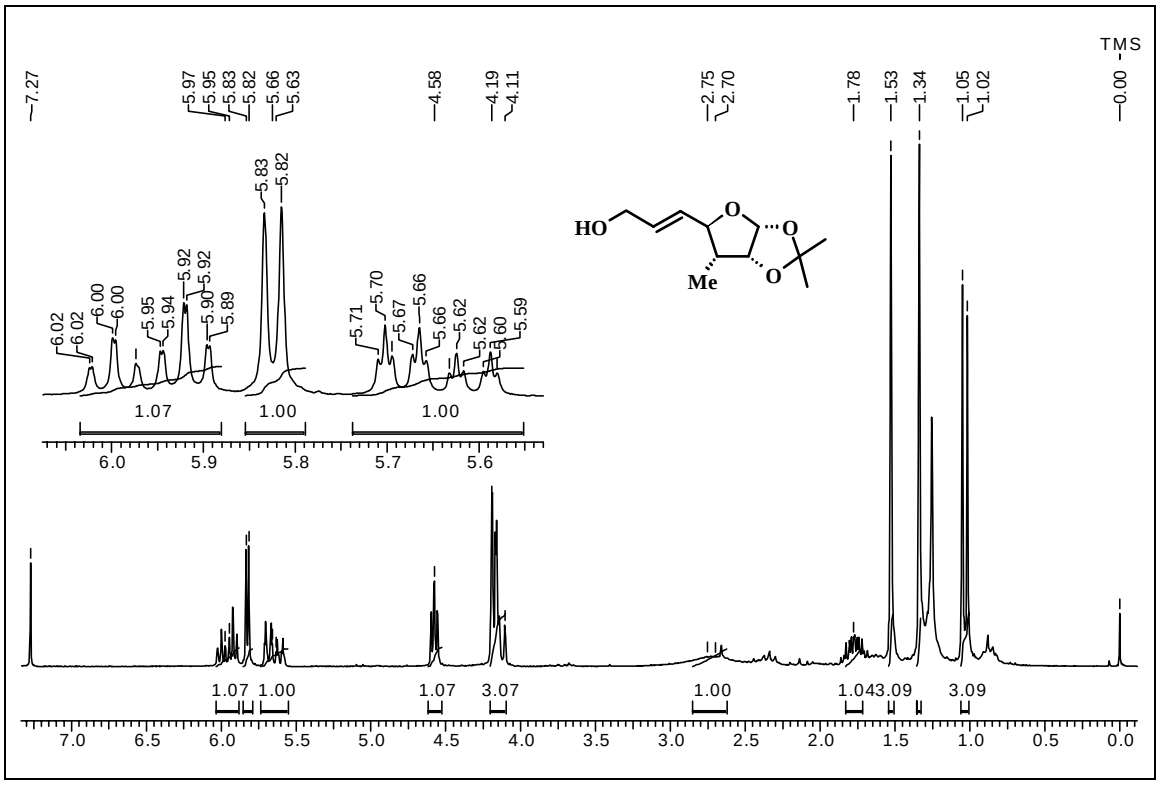
^{13}C NMR spectrum of compound 48 in $CDCl_3$



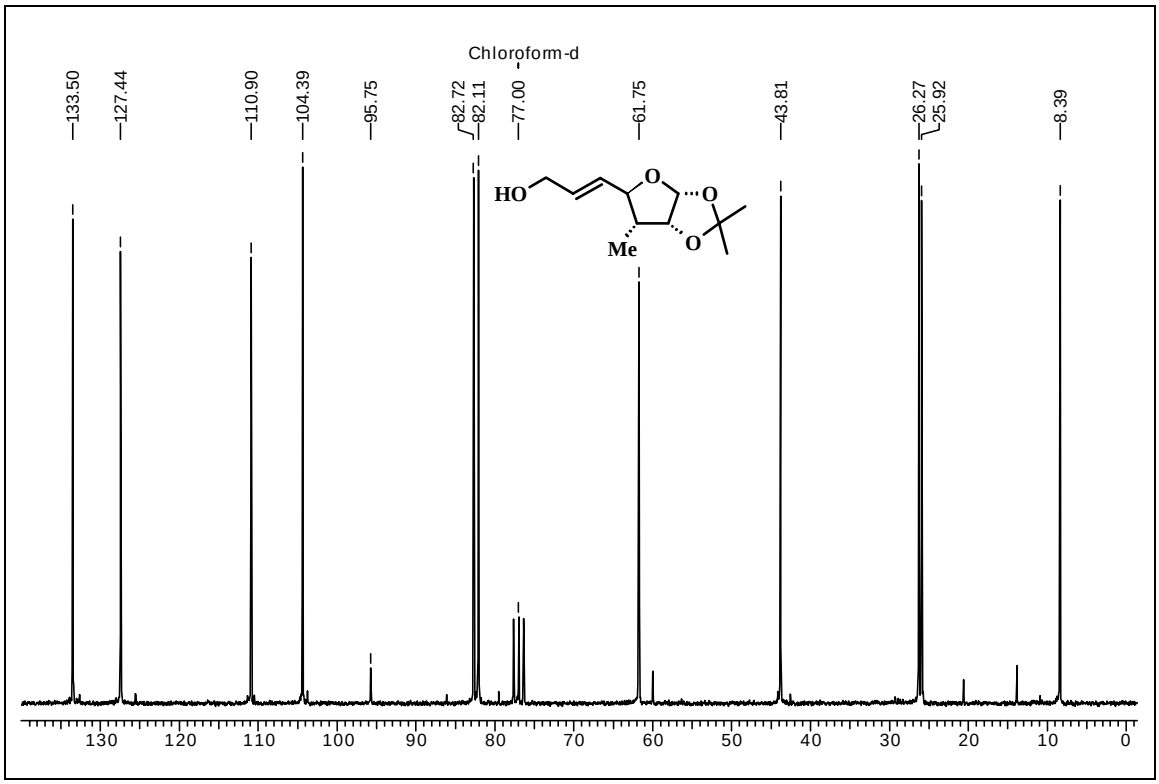
^{1}H NMR spectrum of compound 49 in $CDCl_3$



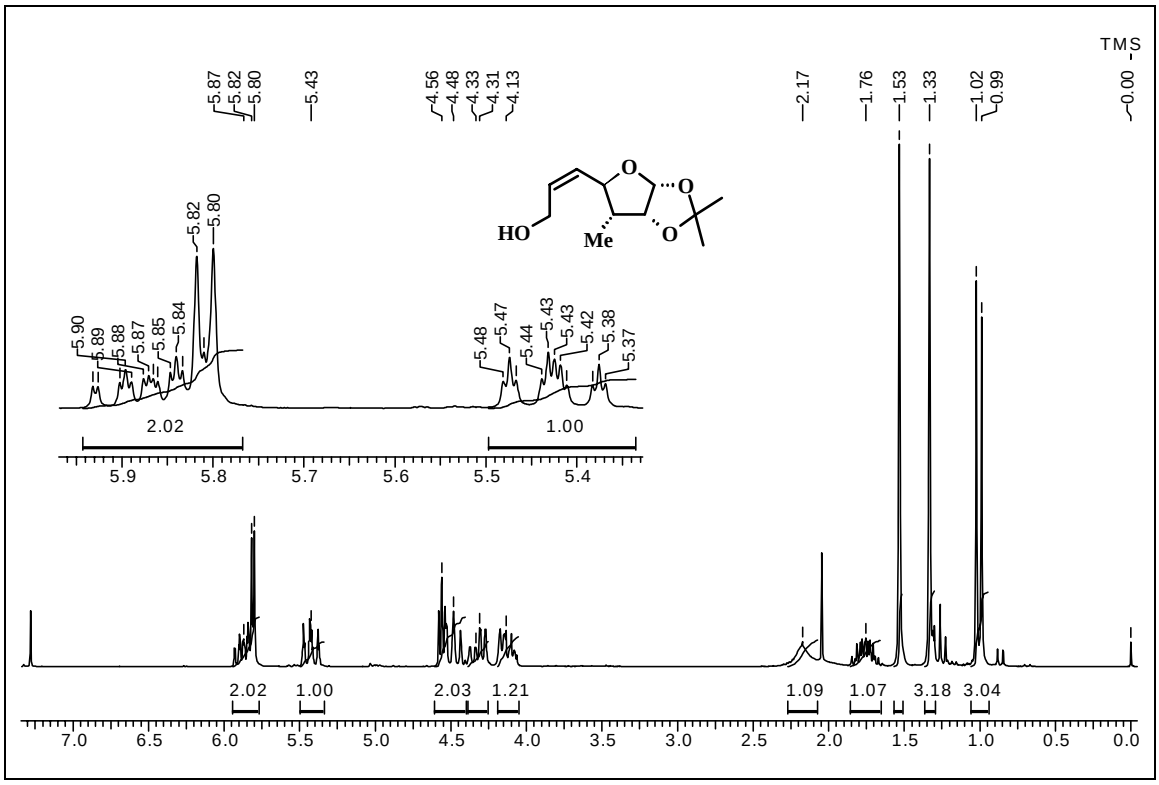
^{1}HNMR spectrum of compound 49 in $CDCl_3$



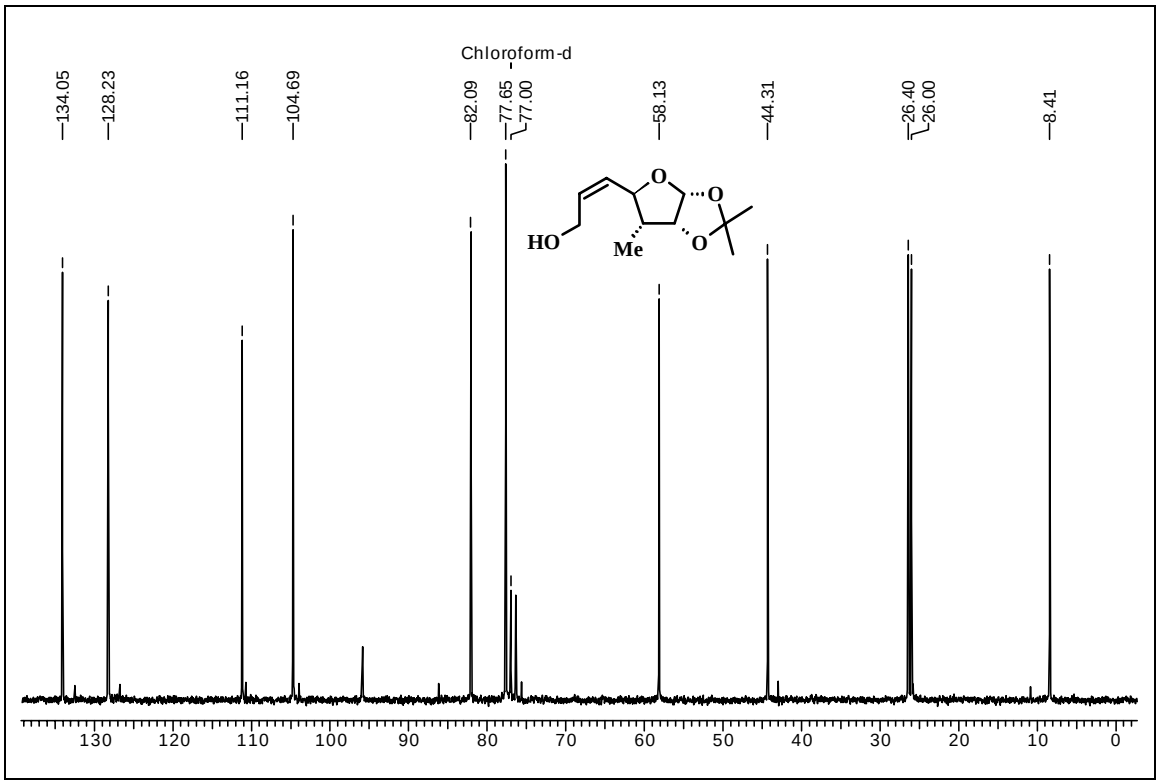
^{1}H NMR spectrum of compound 42 in $CDCl_3$



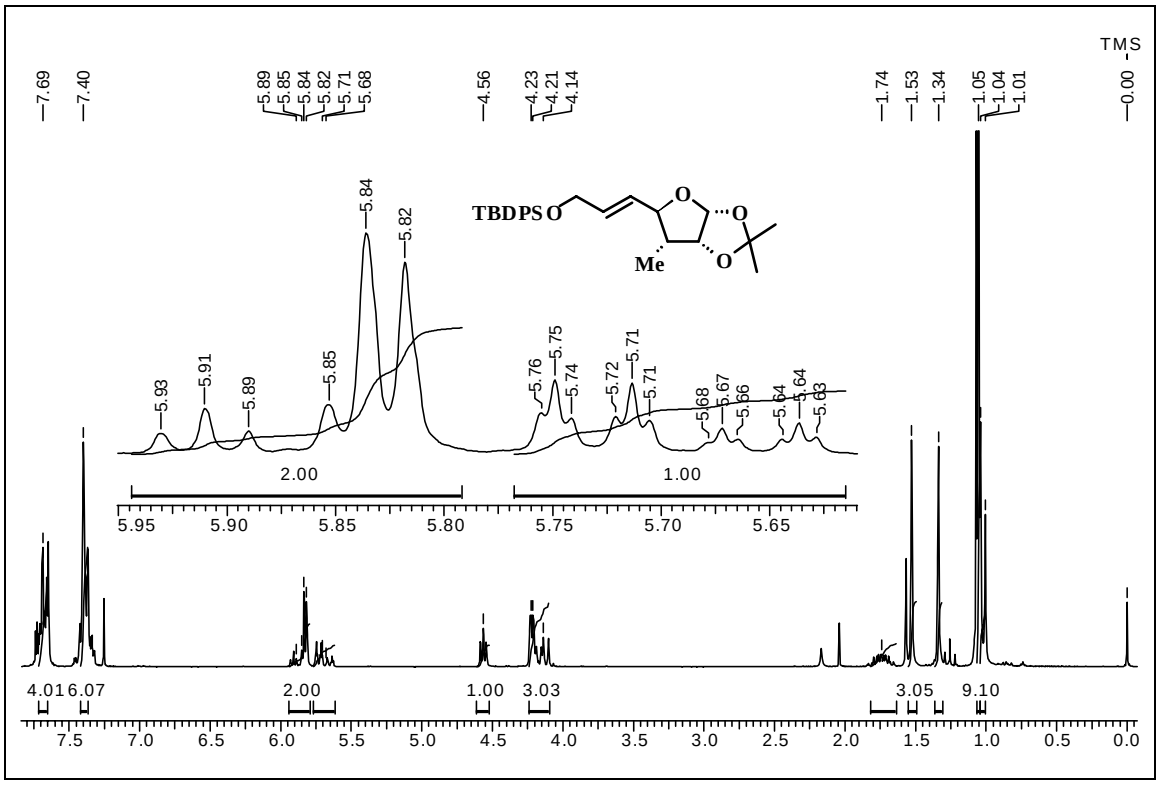
^{13}C NMR spectrum of compound 42 in $CDCl_3$



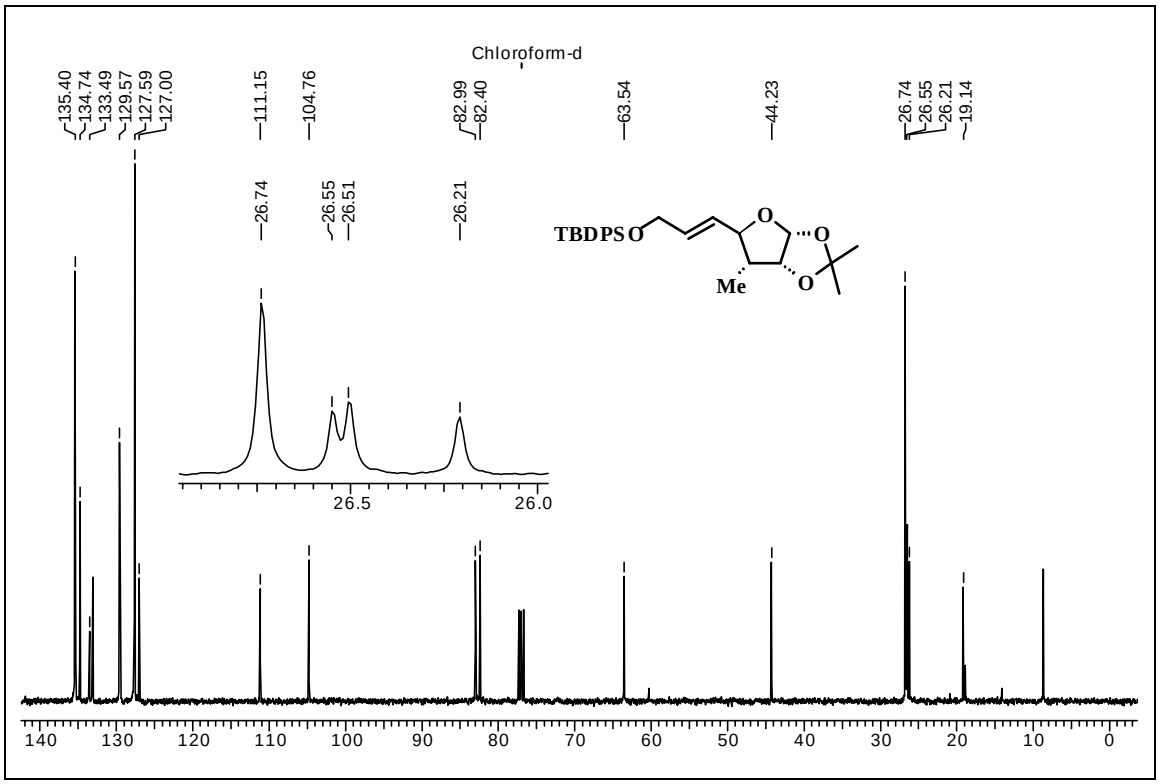
^{1}H NMR spectrum of compound 50 in $CDCl_3$



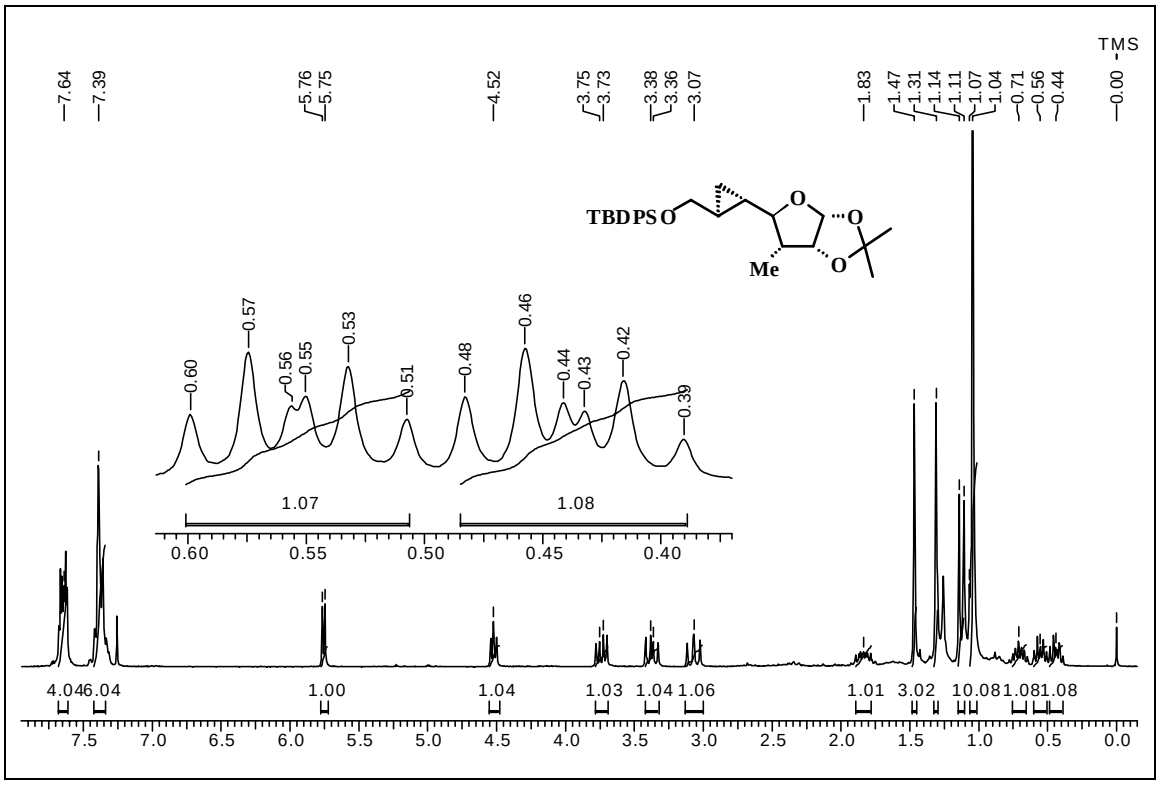
^{13}C NMR spectrum of compound 50 in $CDCl_3$



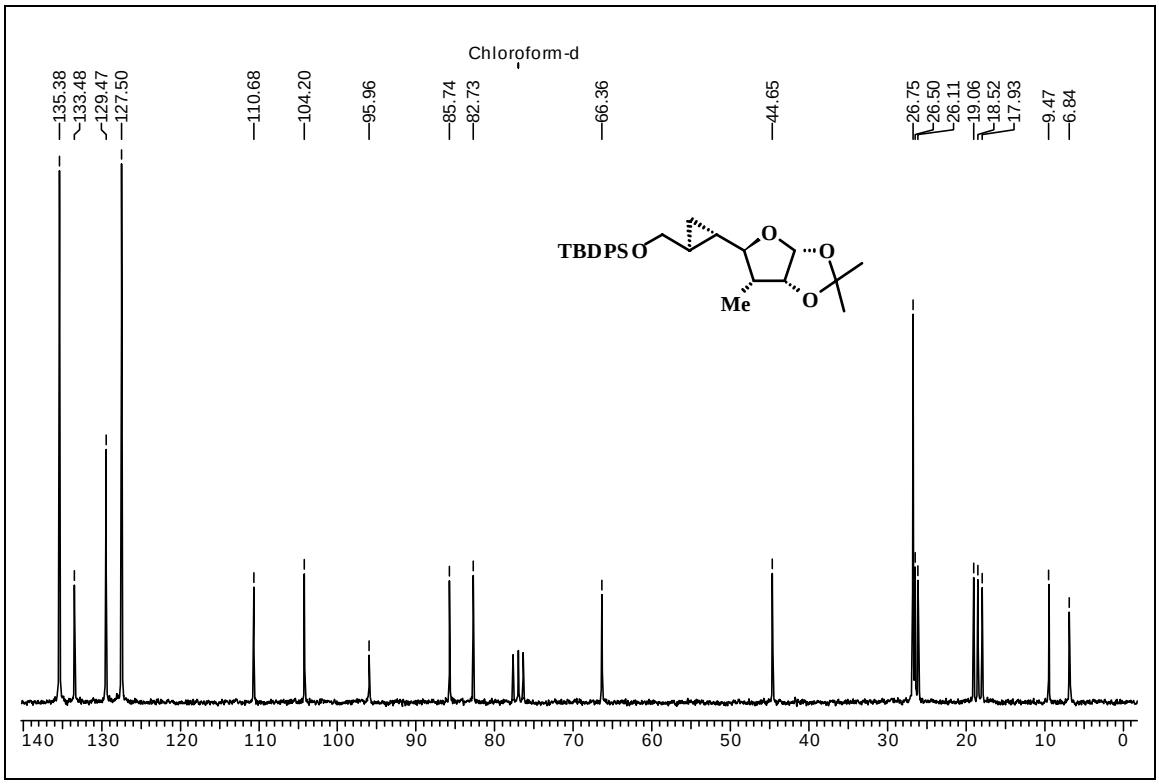
^{1}H NMR spectrum of compound 51 in $CDCl_3$



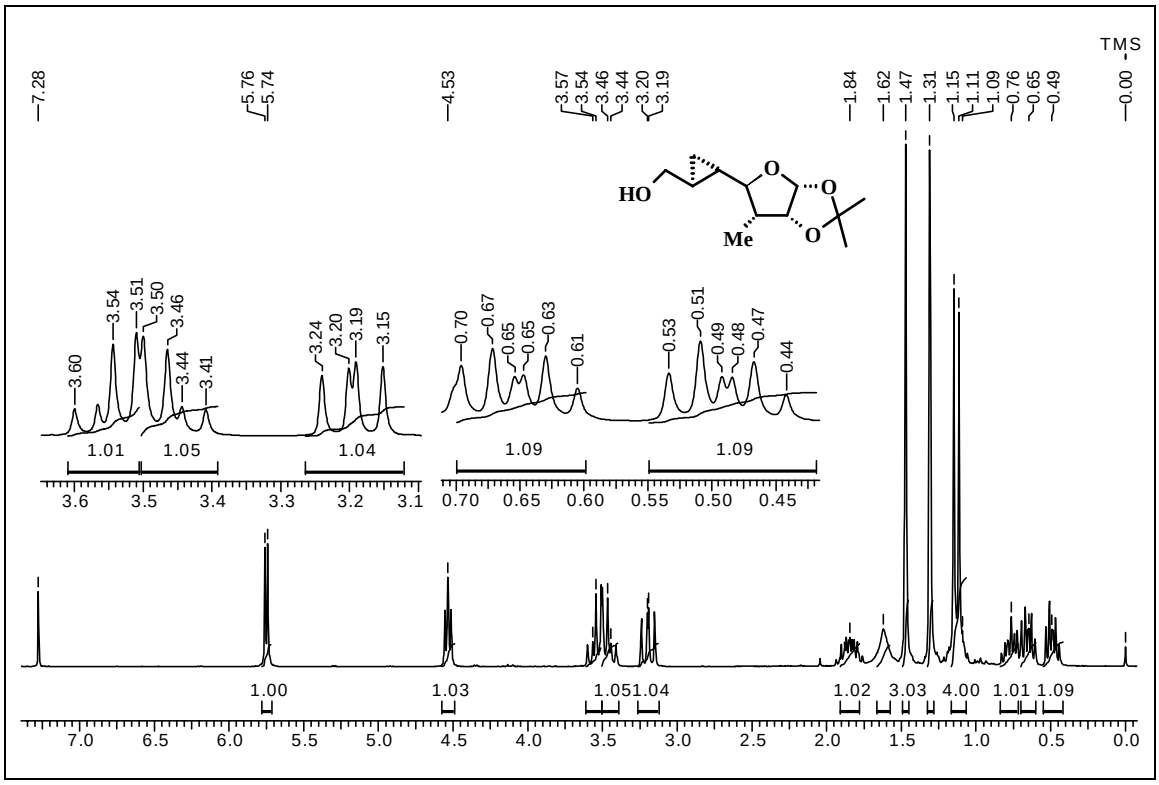
^{13}C NMR spectrum of compound 51 in $CDCl_3$



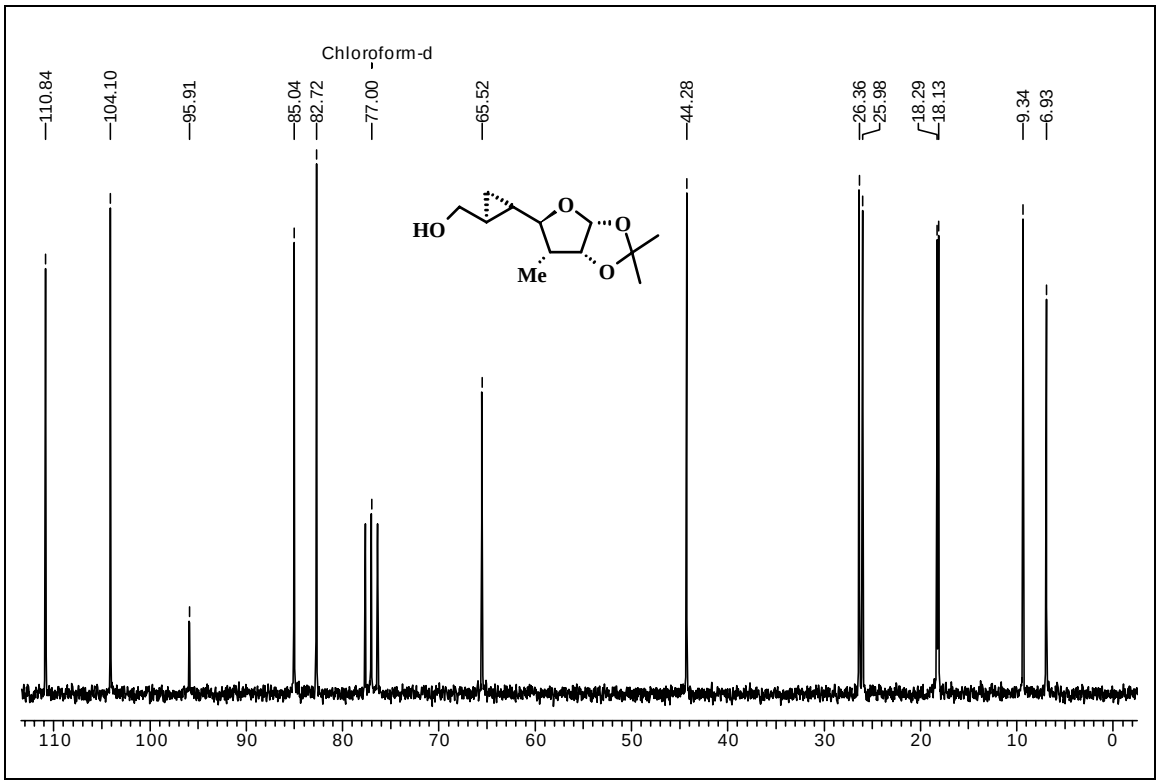
^{1}H NMR spectrum of compound 41 in $CDCl_3$



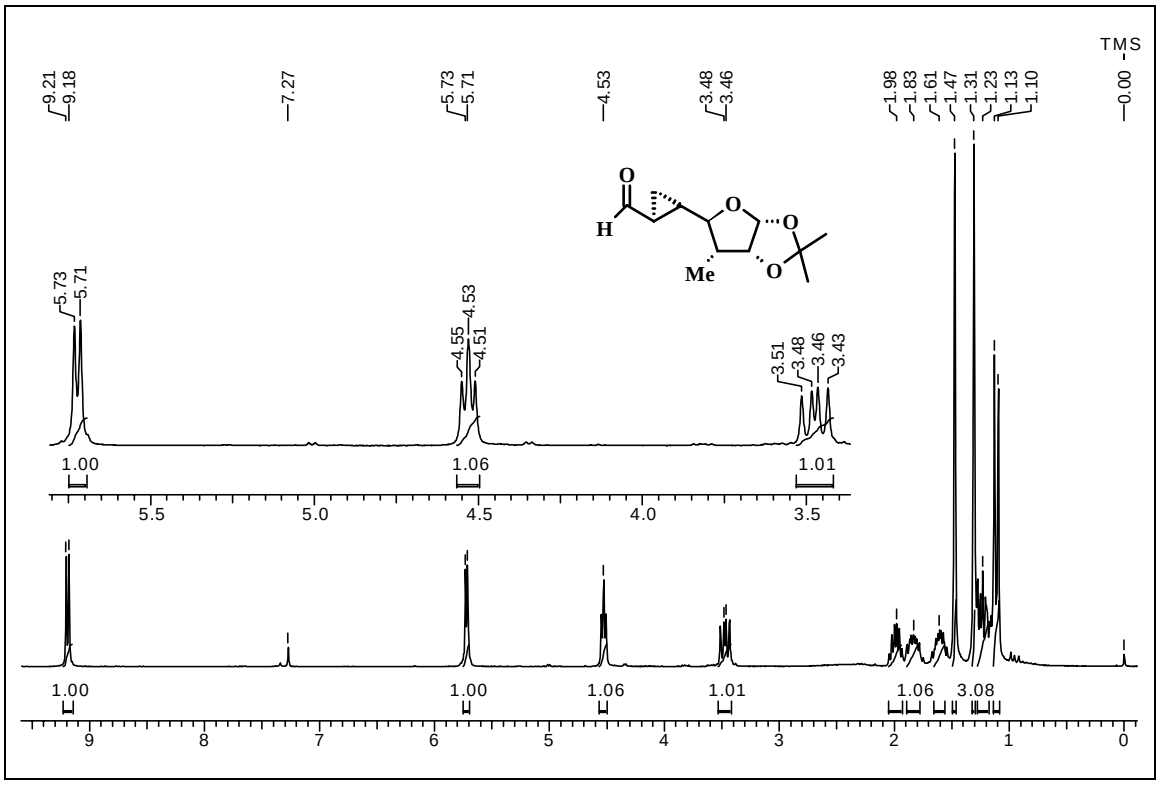
^{13}C NMR spectrum of compound 41 in $CDCl_3$



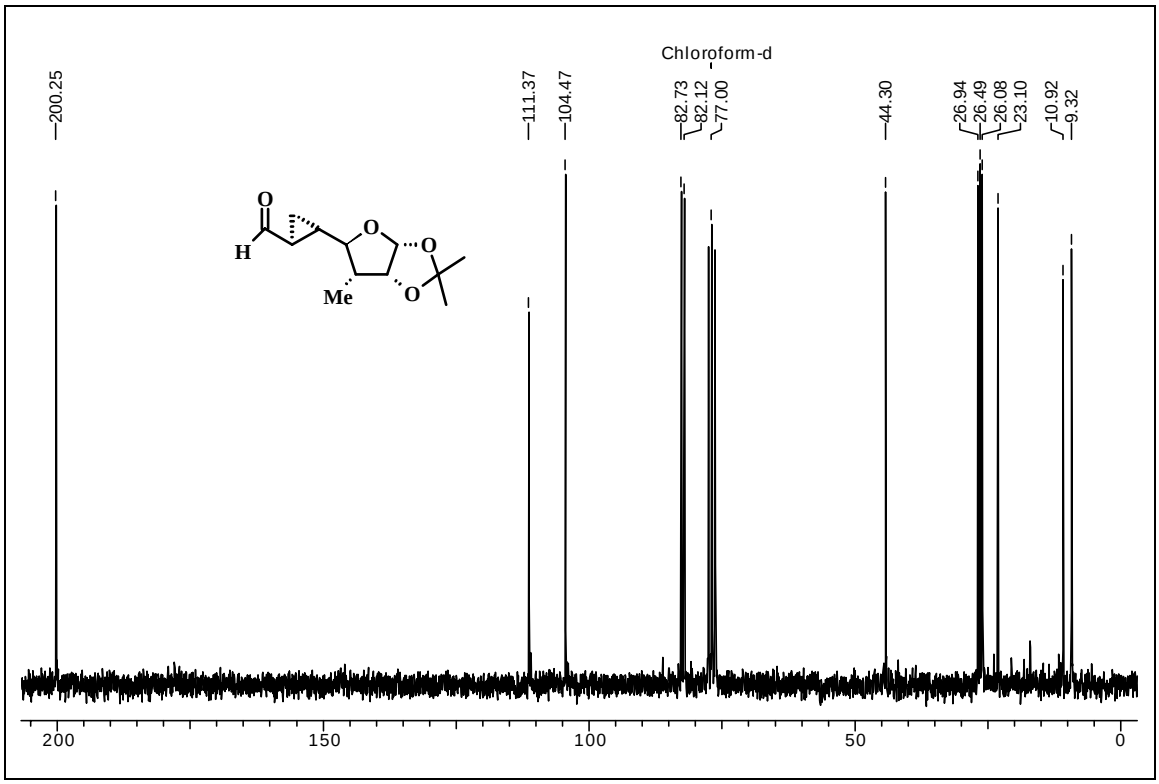
^{1}H NMR spectrum of compound 52 in $CDCl_3$



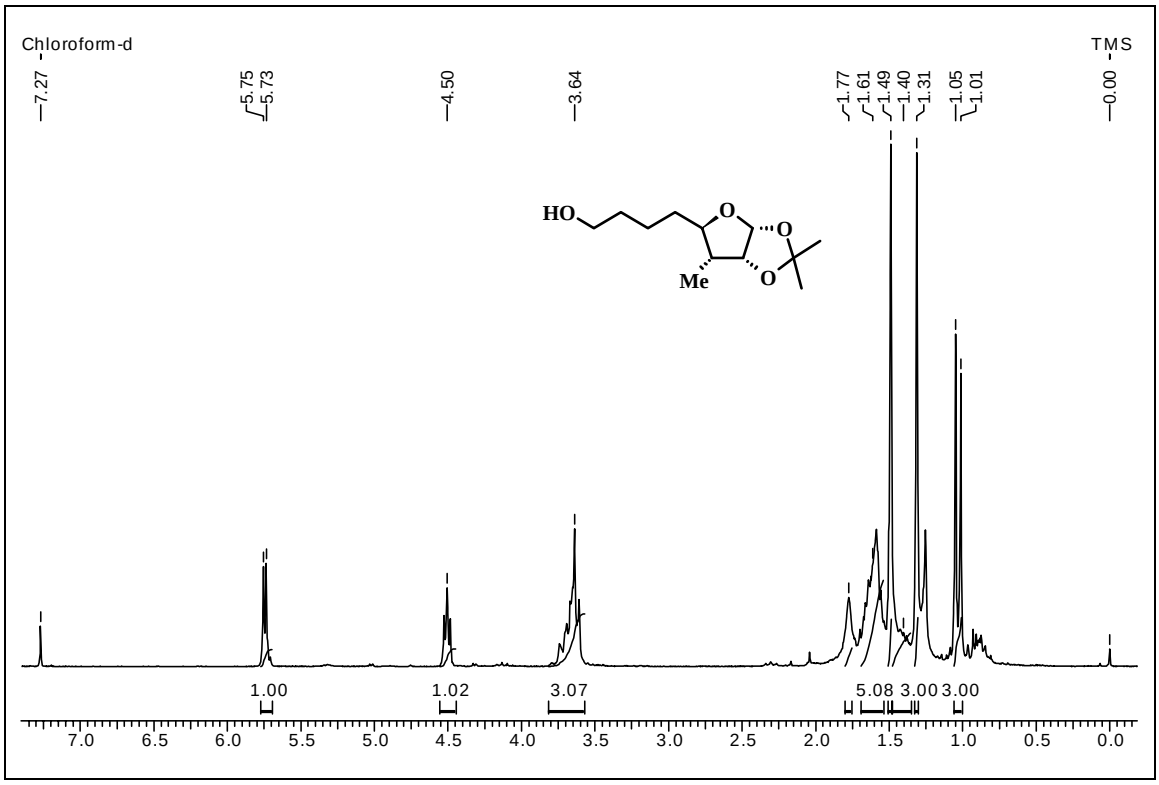
^{13}C NMR spectrum of compound 52 in $CDCl_3$



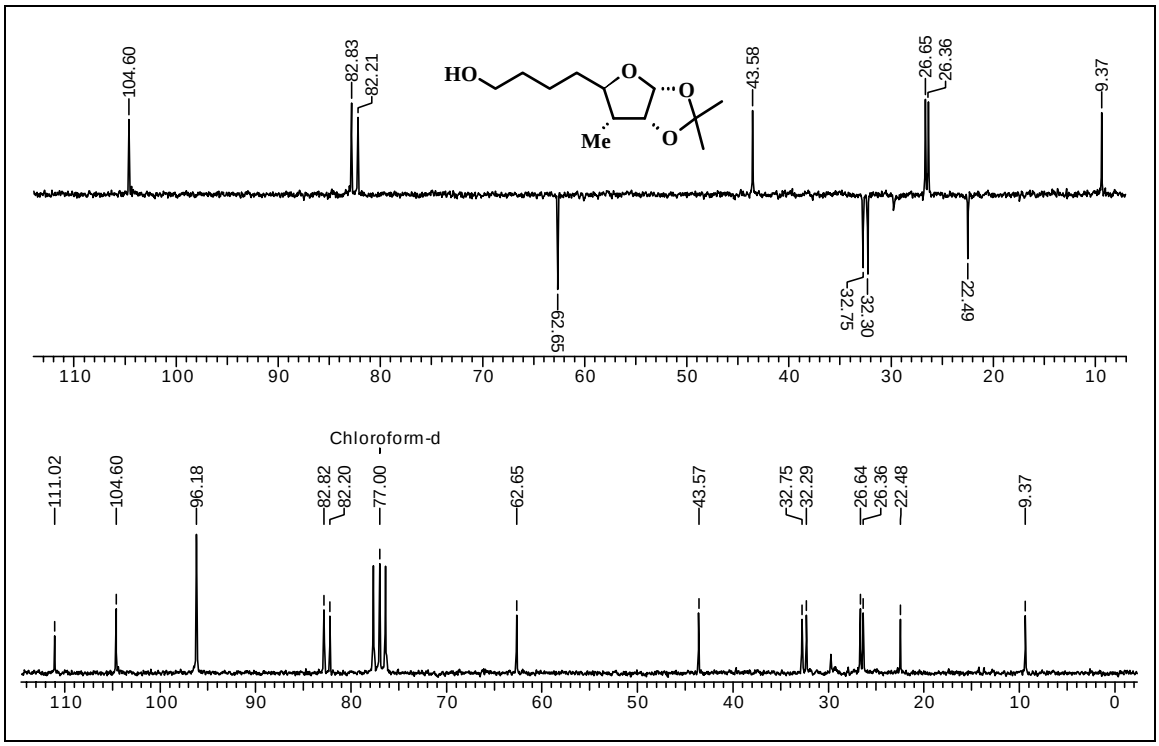
^{1}H NMR spectrum of compound 40 in $CDCl_3$



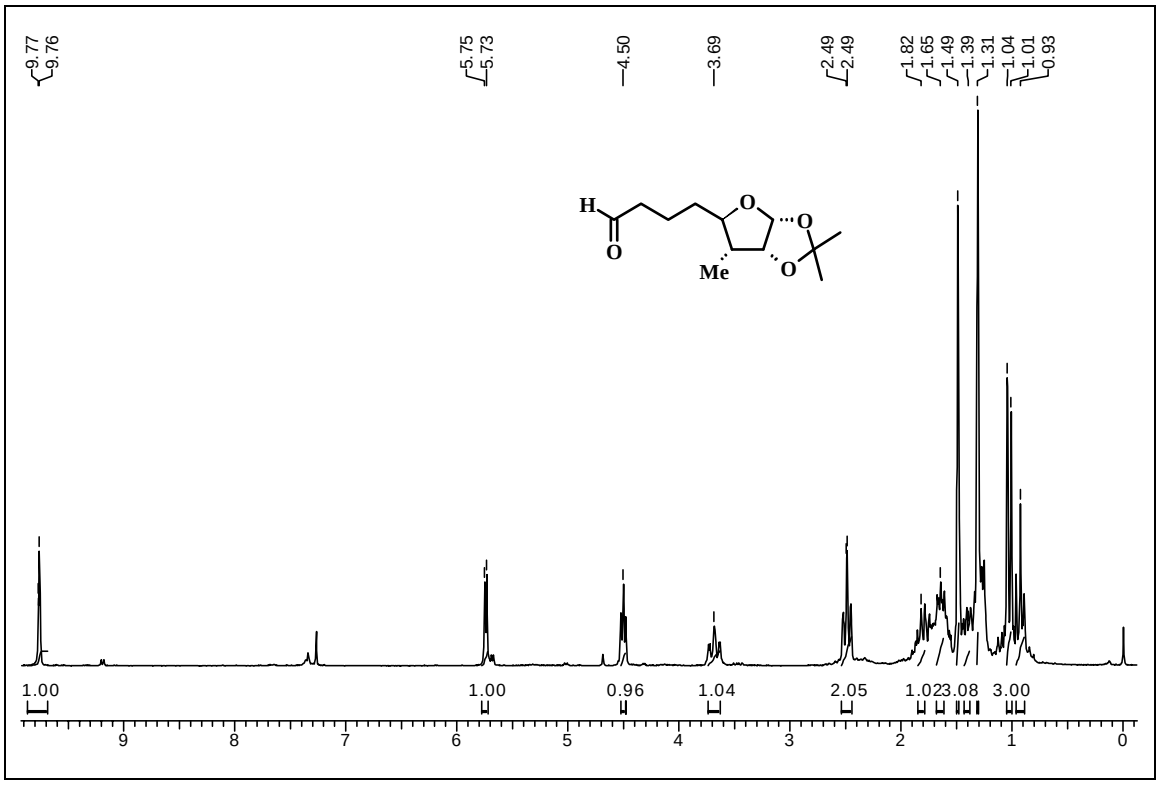
^{13}C NMR spectrum of compound 40 in $CDCl_3$



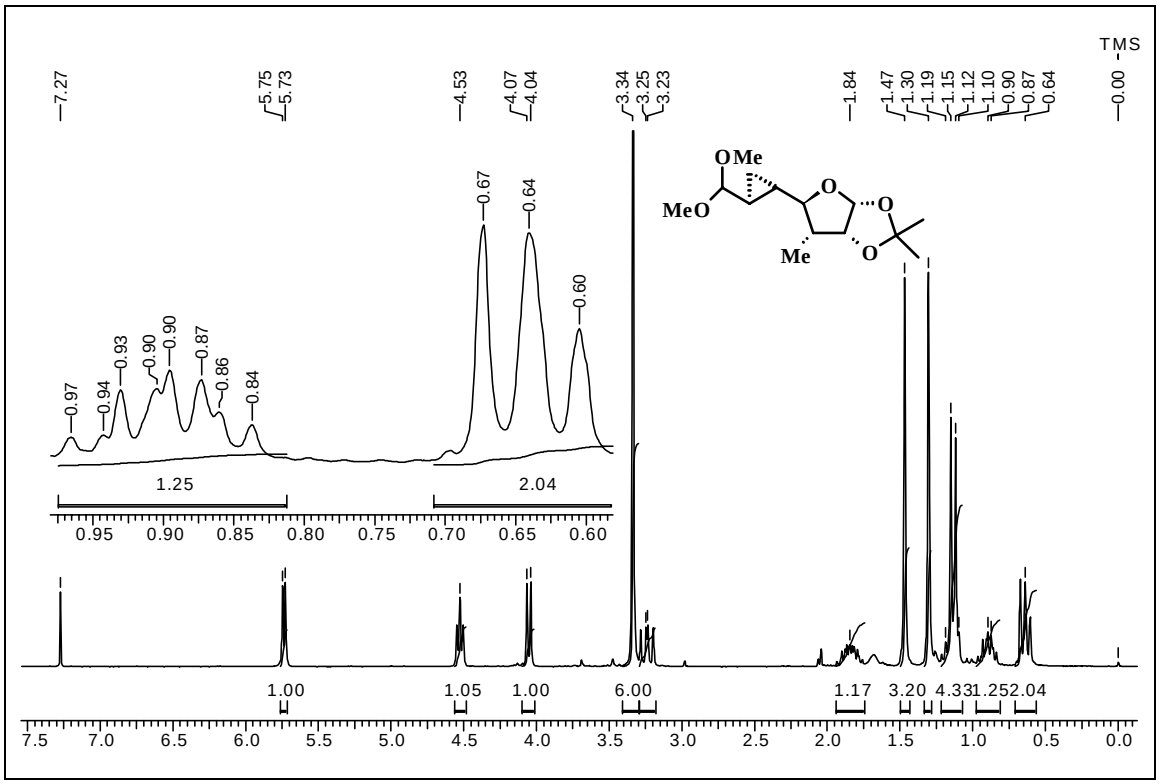
^{1}H NMR spectrum of compound 54 in $CDCl_3$



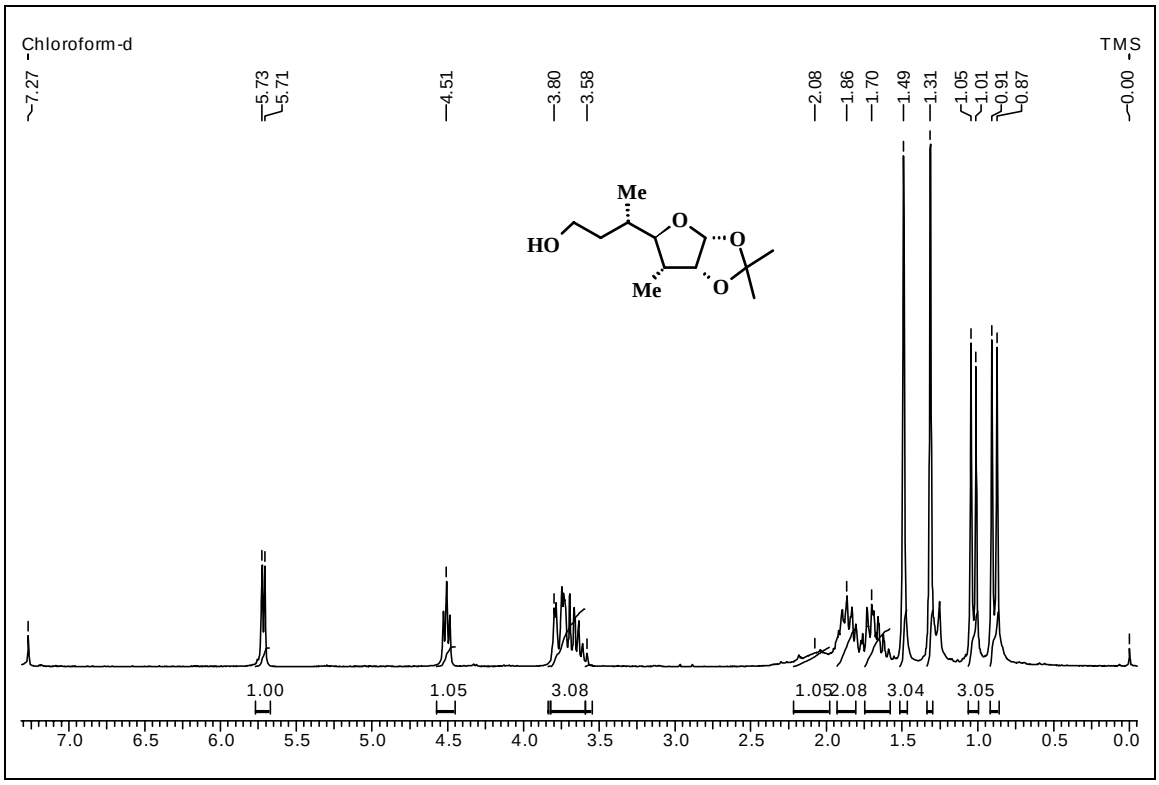
^{13}C NMR and DEPT spectrum of compound 54 in $CDCl_3$



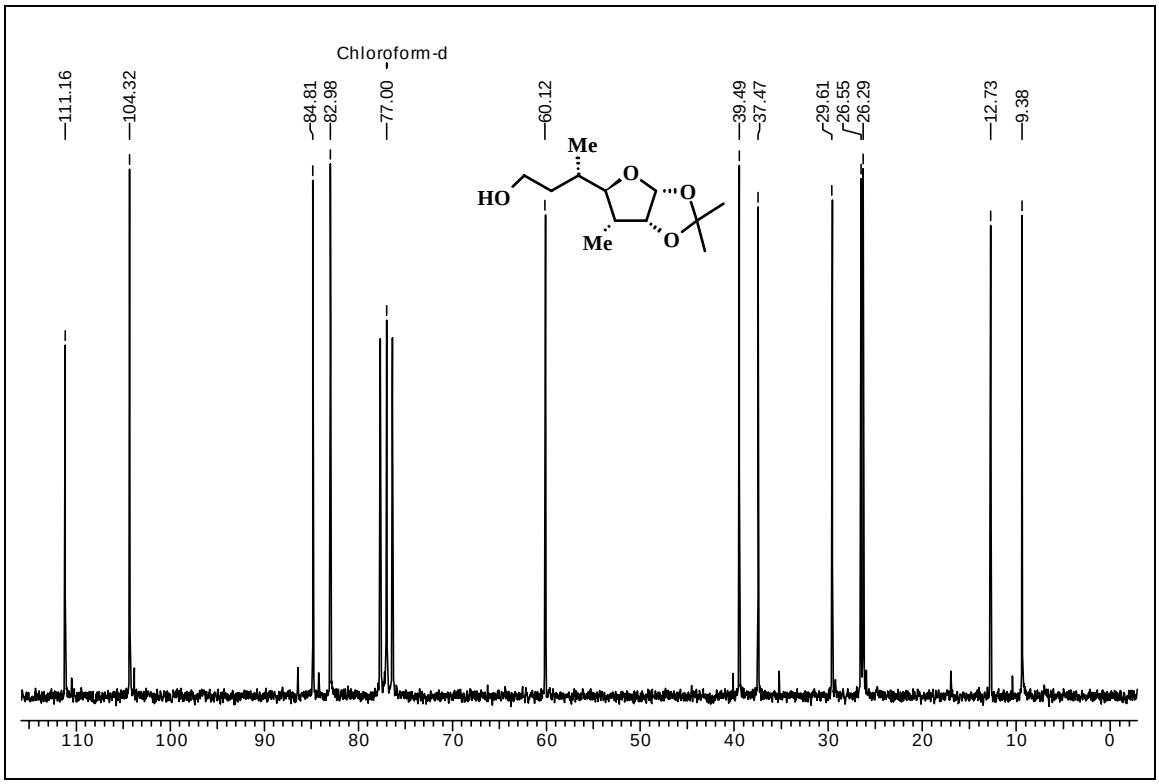
^{1}H NMR spectrum of compound 53 in $CDCl_3$



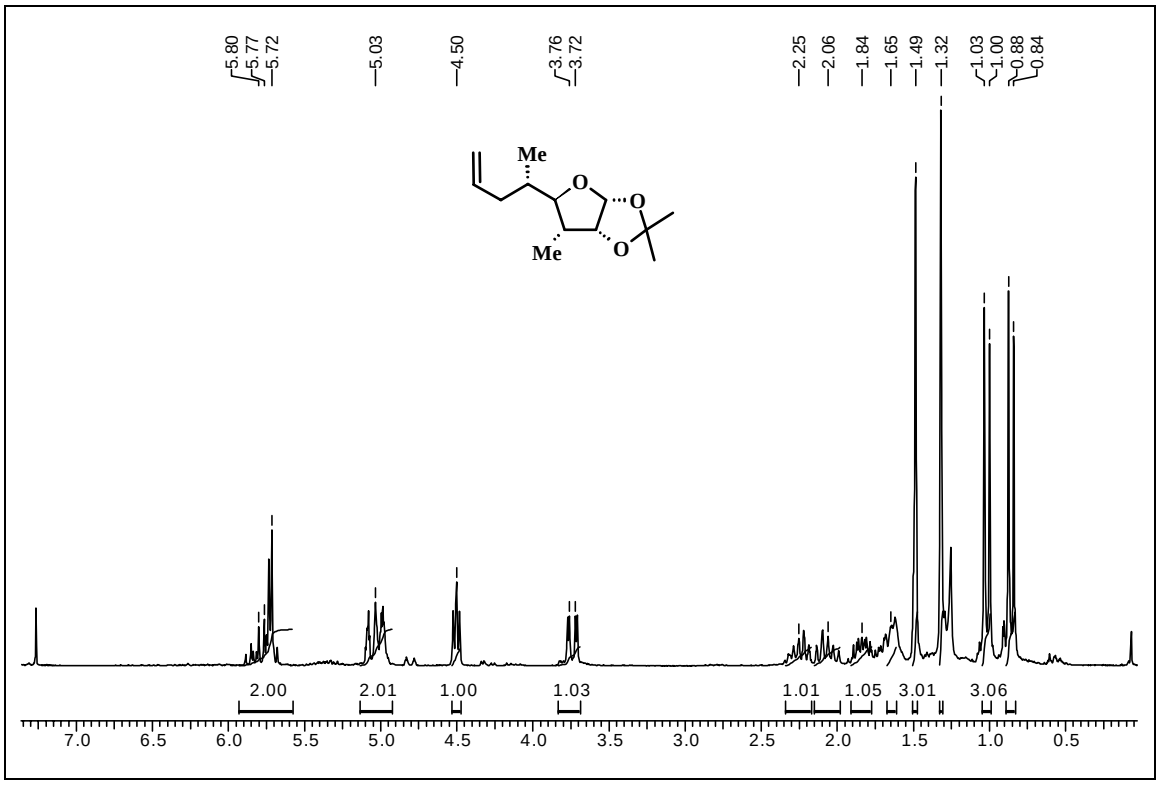
^{13}C NMR spectrum of compound 55 in $CDCl_3$



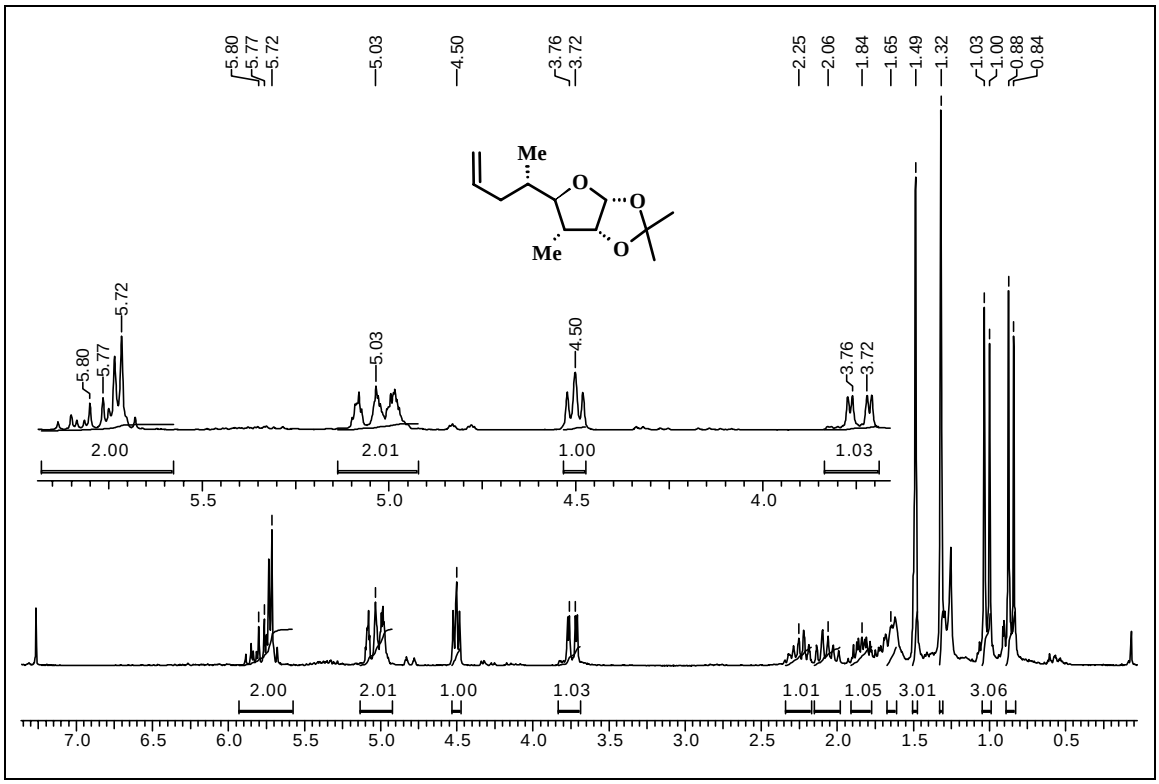
^{1}H NMR spectrum of compound 56 in $CDCl_3$



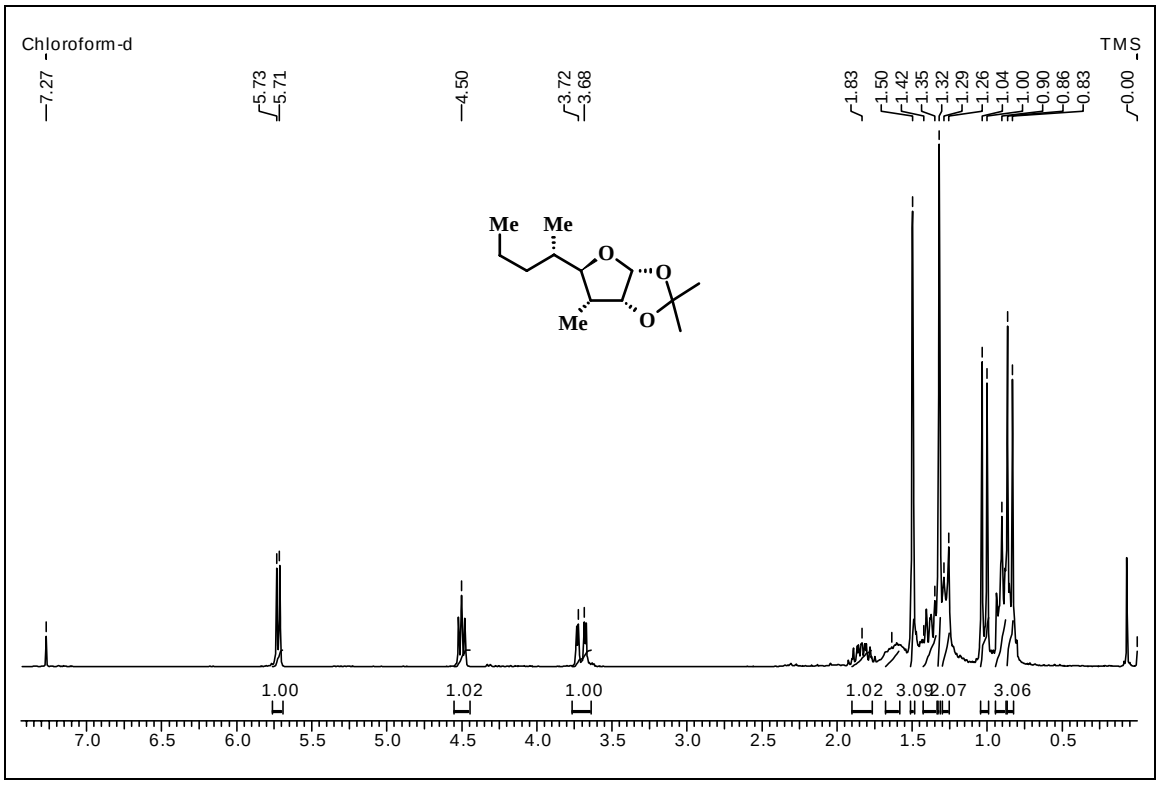
^{13}C NMR spectrum of compound 56 in $CDCl_3$



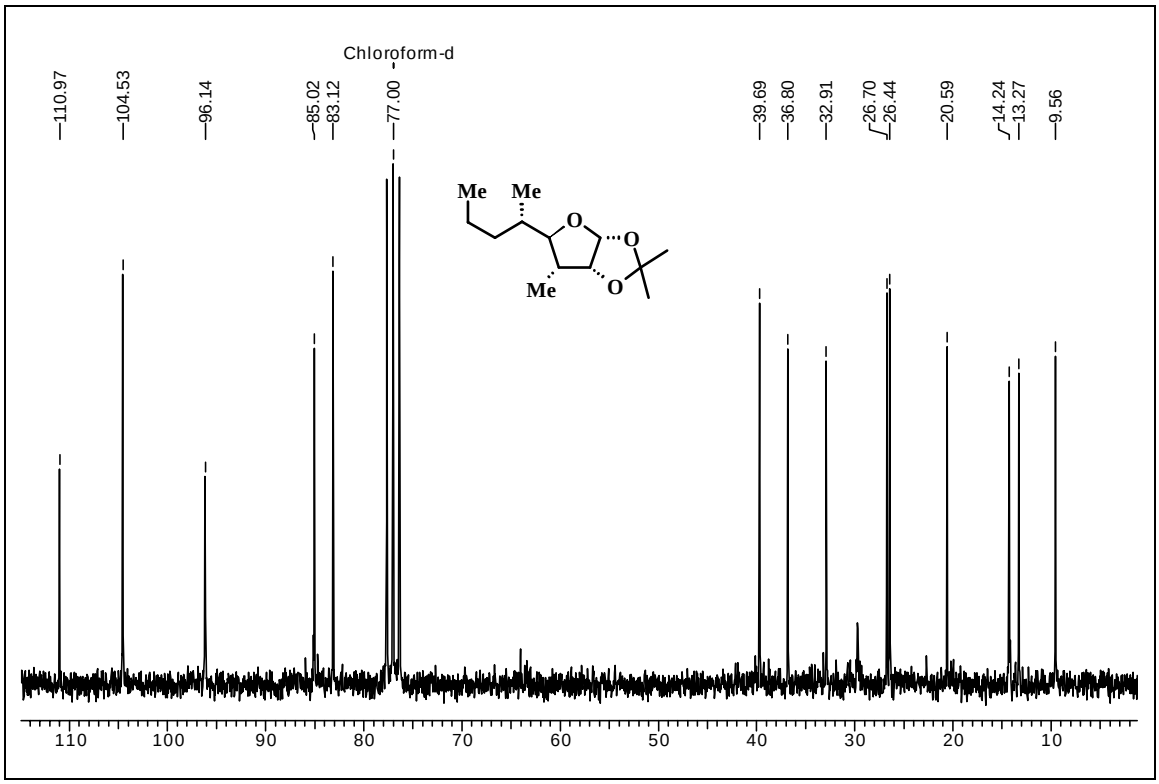
^{1}H NMR spectrum of compound 58 in $CDCl_3$



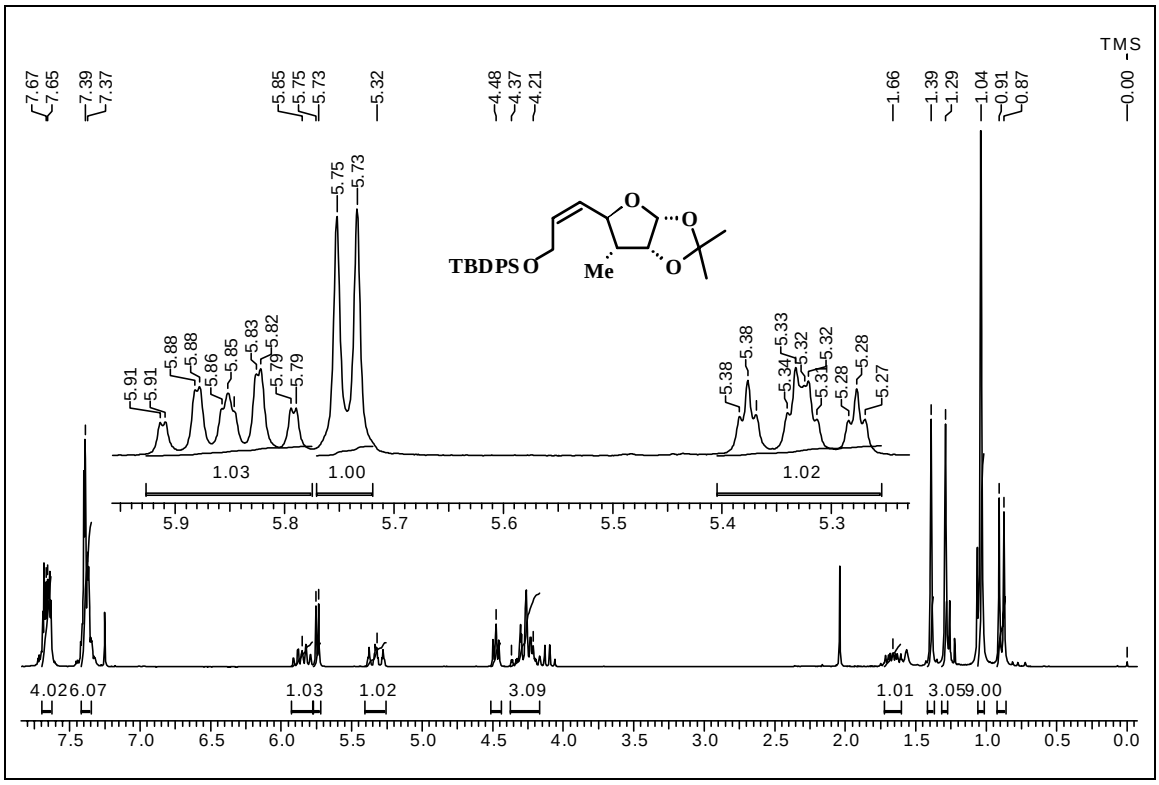
^{1}H NMR spectrum of compound 58 in $CDCl_3$



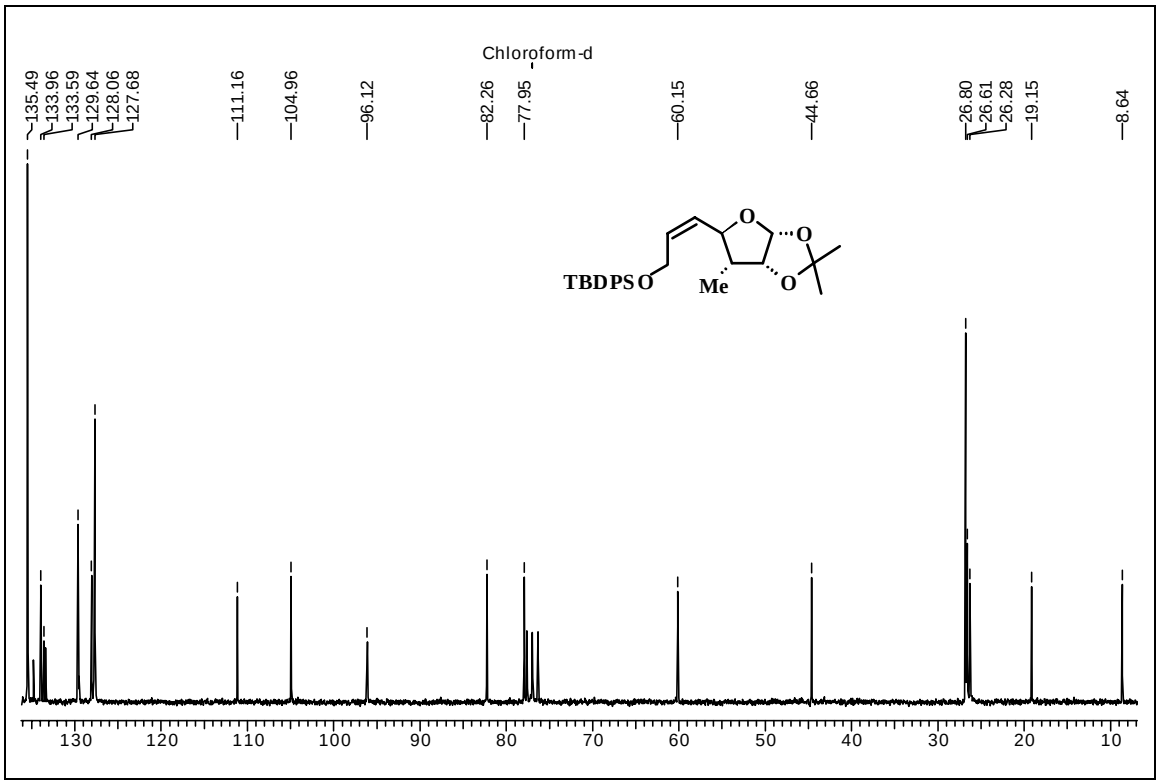
^{1}H NMR spectrum of compound 59 in $CDCl_3$



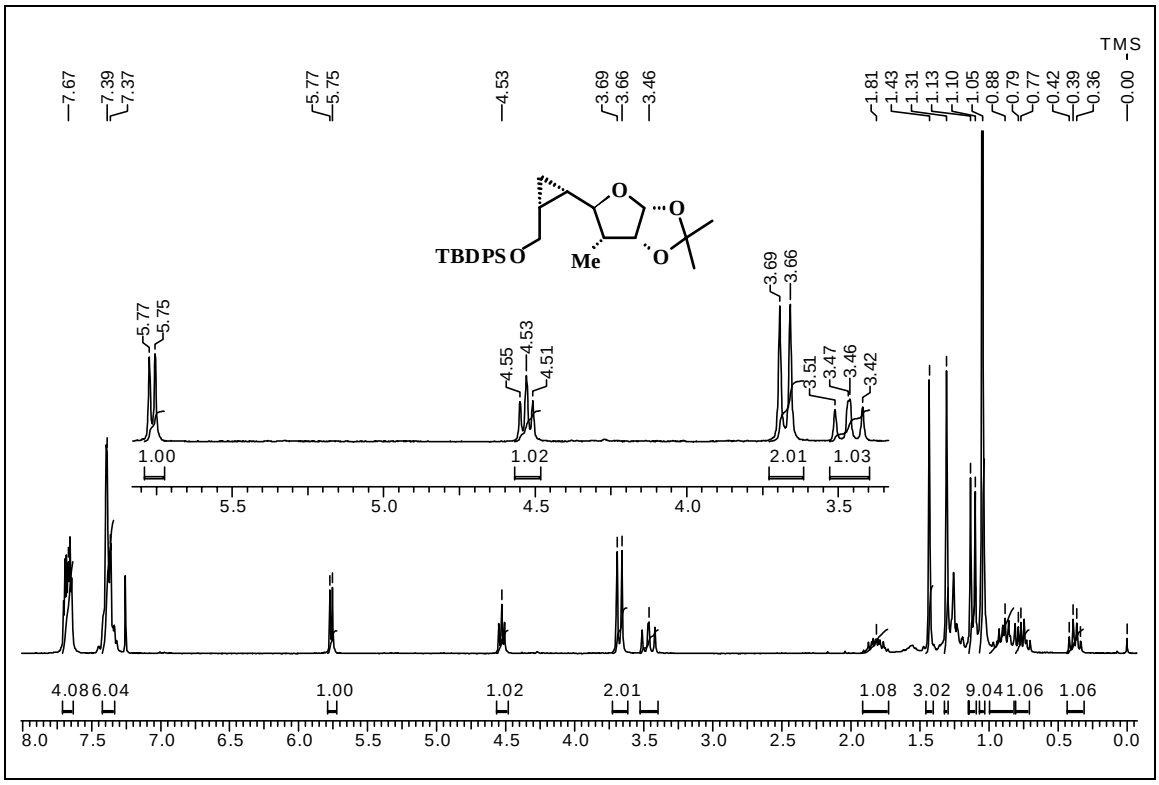
^{13}C NMR spectrum of compound 59 in $CDCl_3$



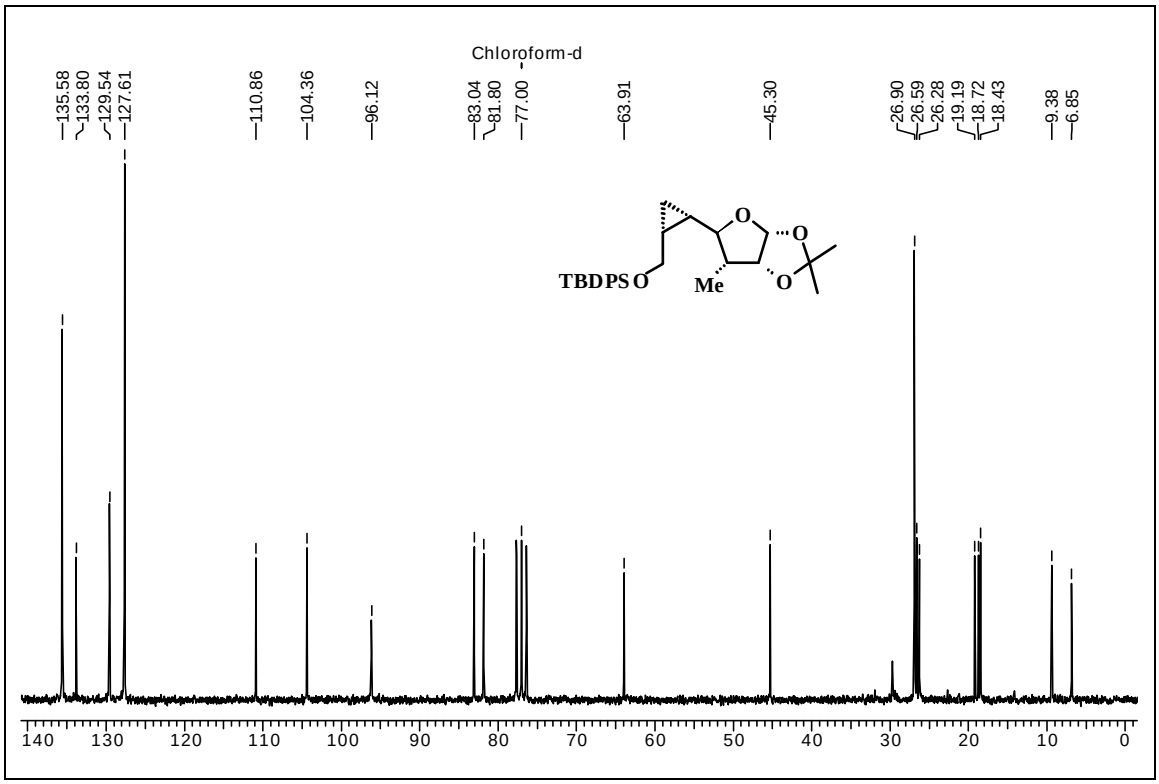
^{1}H NMR spectrum of compound 60 in $CDCl_3$



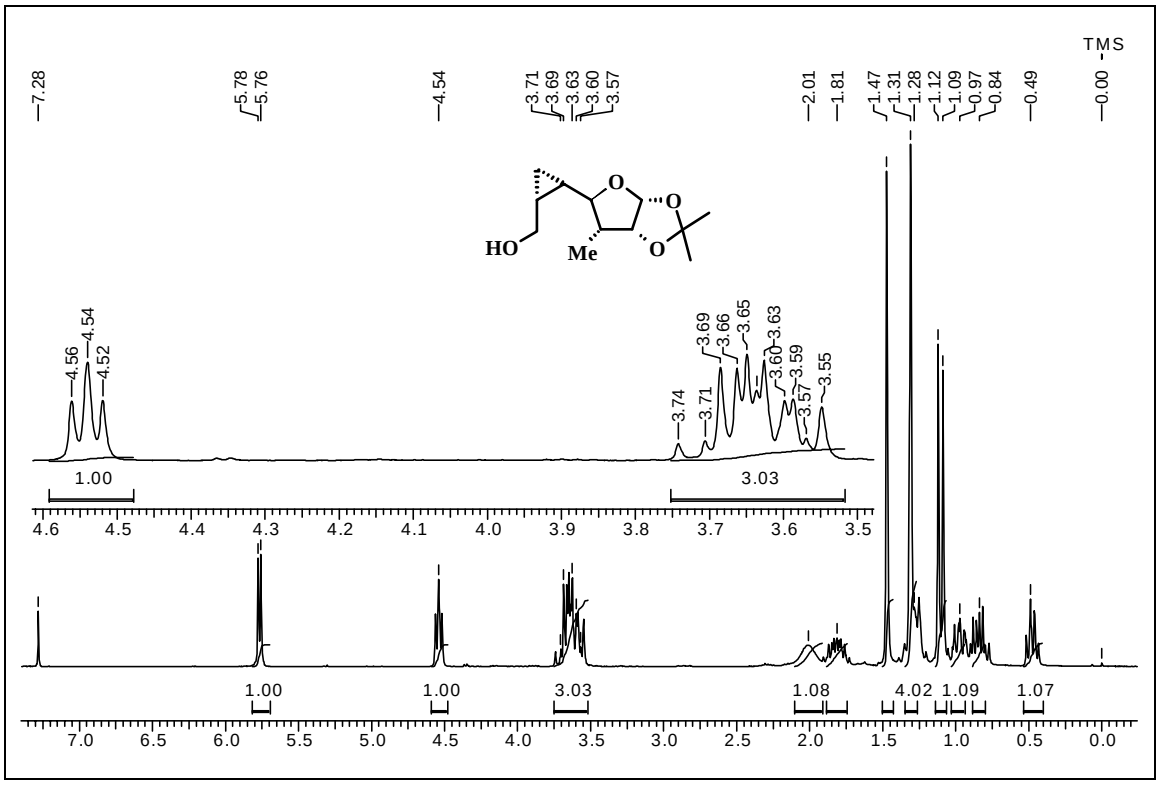
^{13}C NMR spectrum of compound 60 in $CDCl_3$



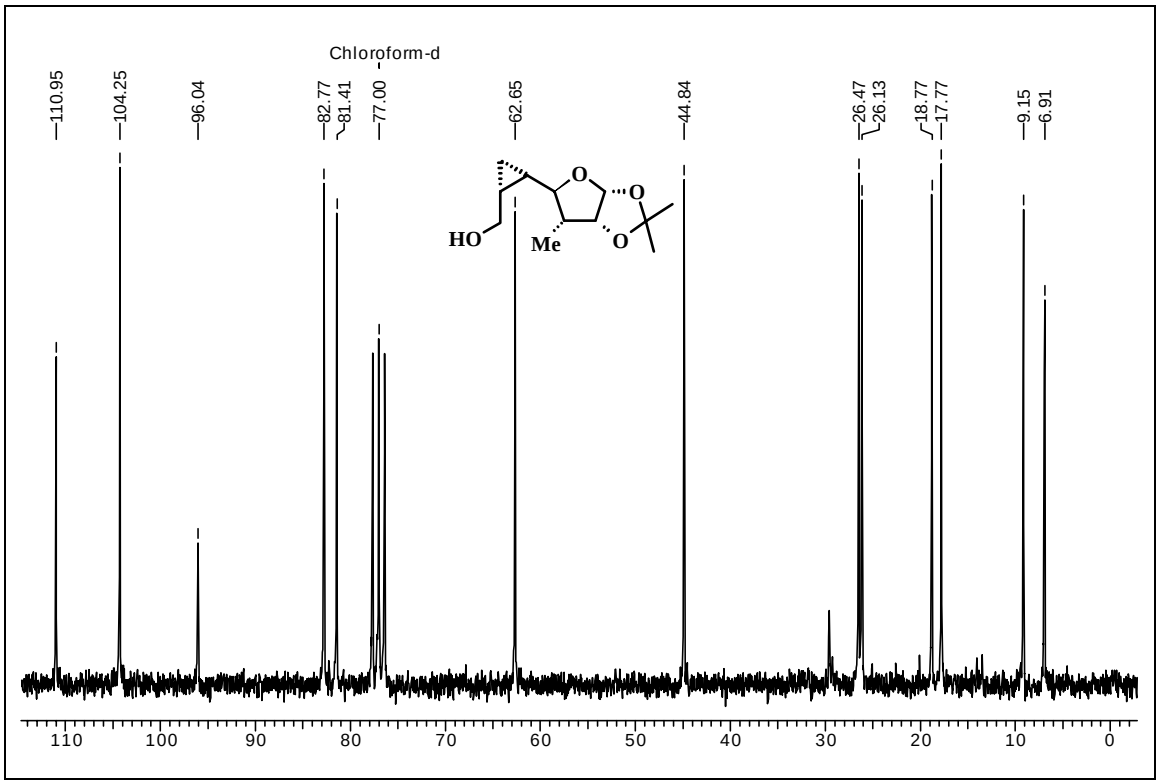
^{1}H NMR spectrum of compound 61 in $CDCl_3$



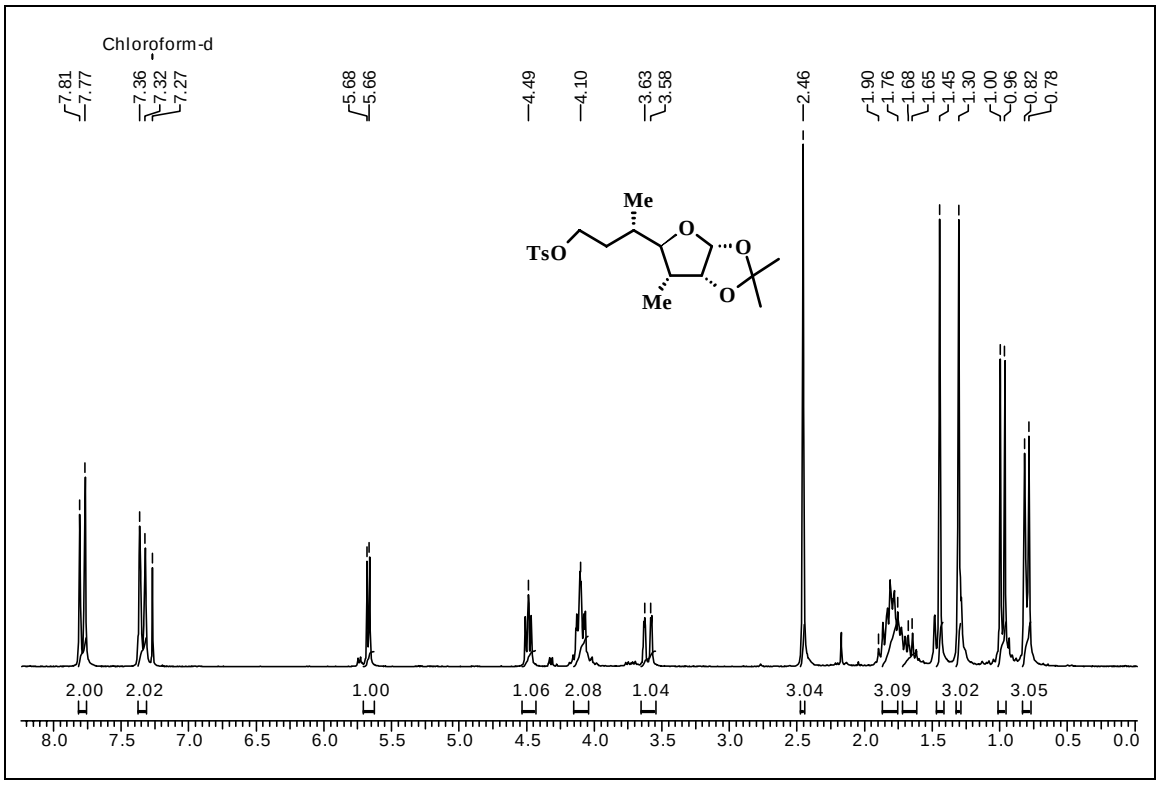
^{13}C NMR spectrum of compound 61 in $CDCl_3$



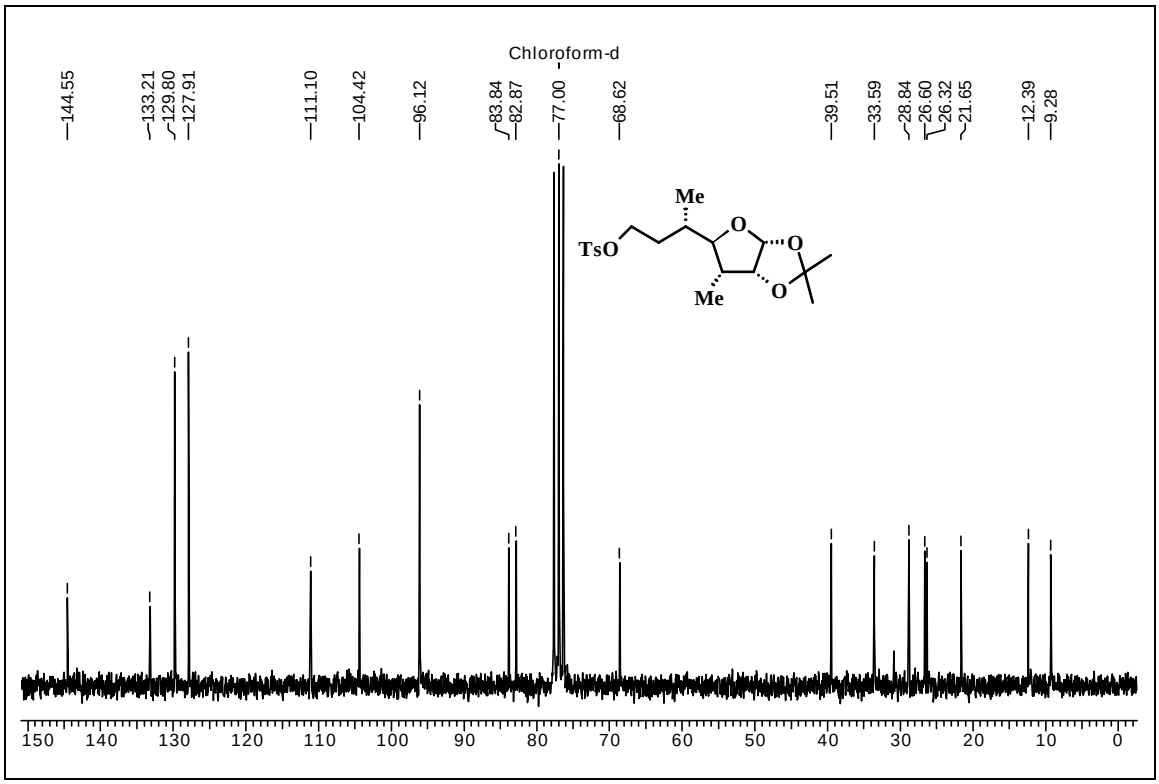
^{1}H NMR spectrum of compound 62 in $CDCl_3$



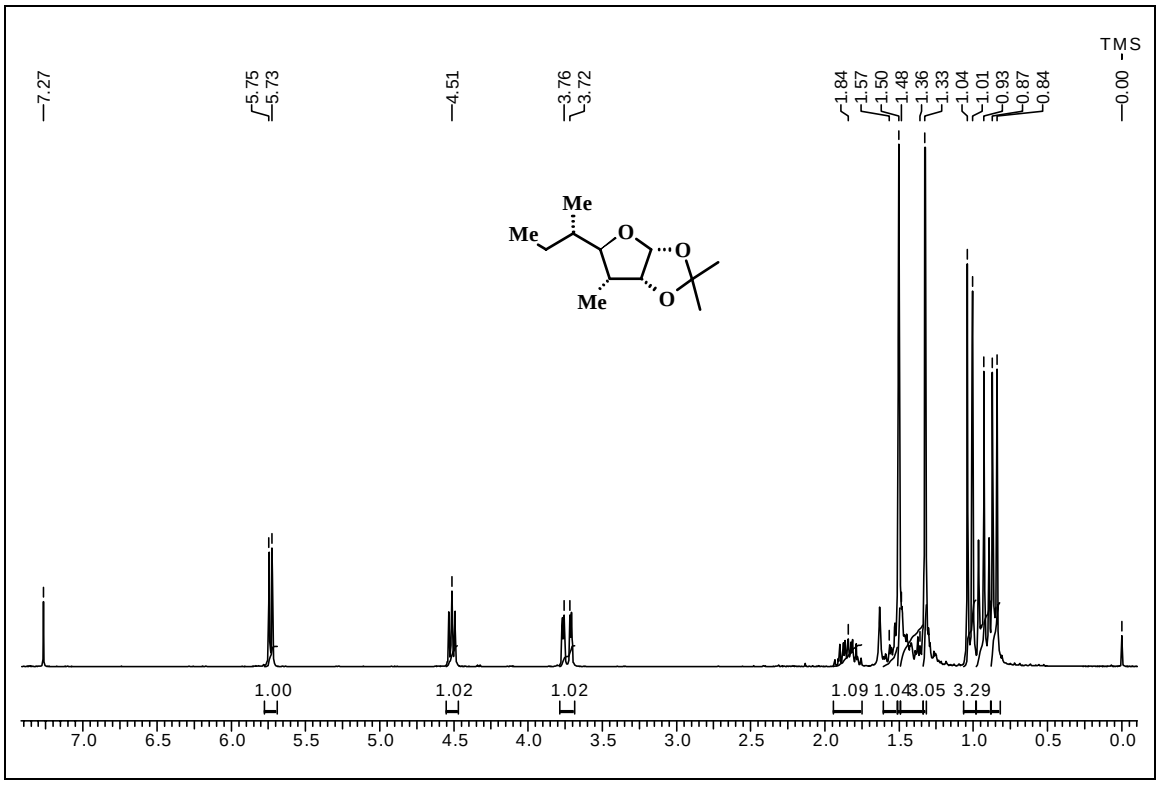
^{13}C NMR spectrum of compound 62 in $CDCl_3$



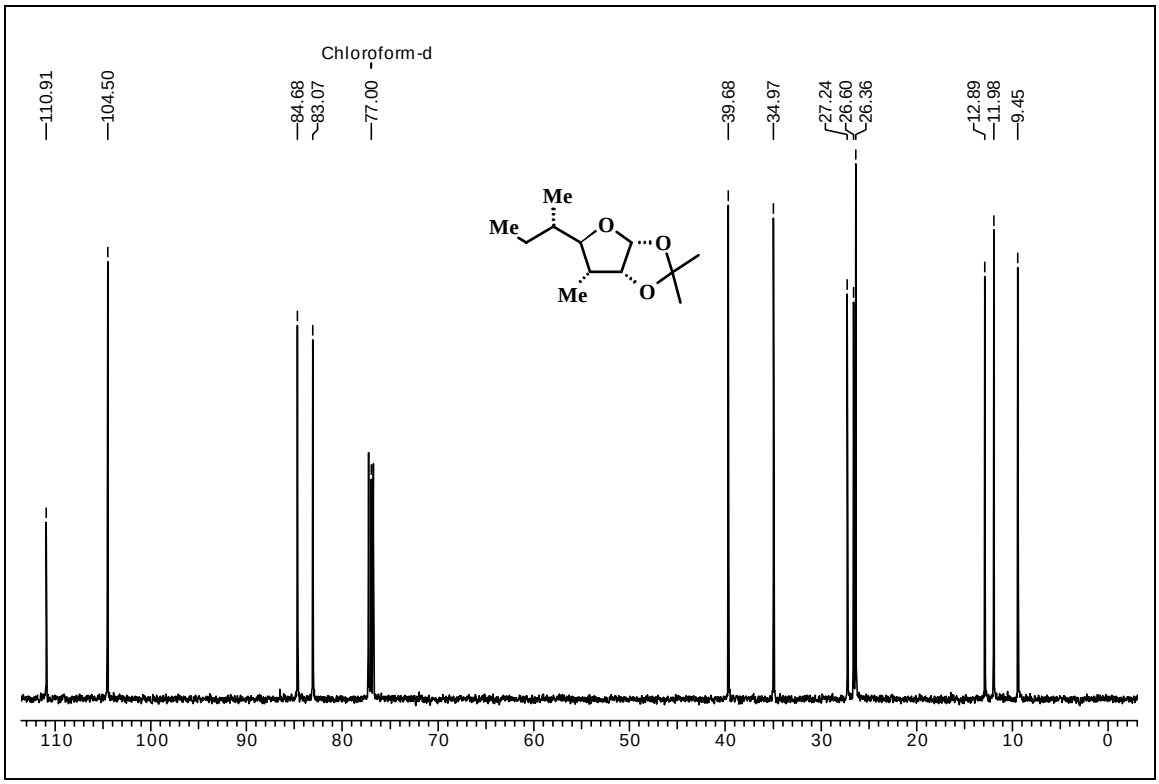
^{1}H NMR spectrum of compound 64 in $CDCl_3$



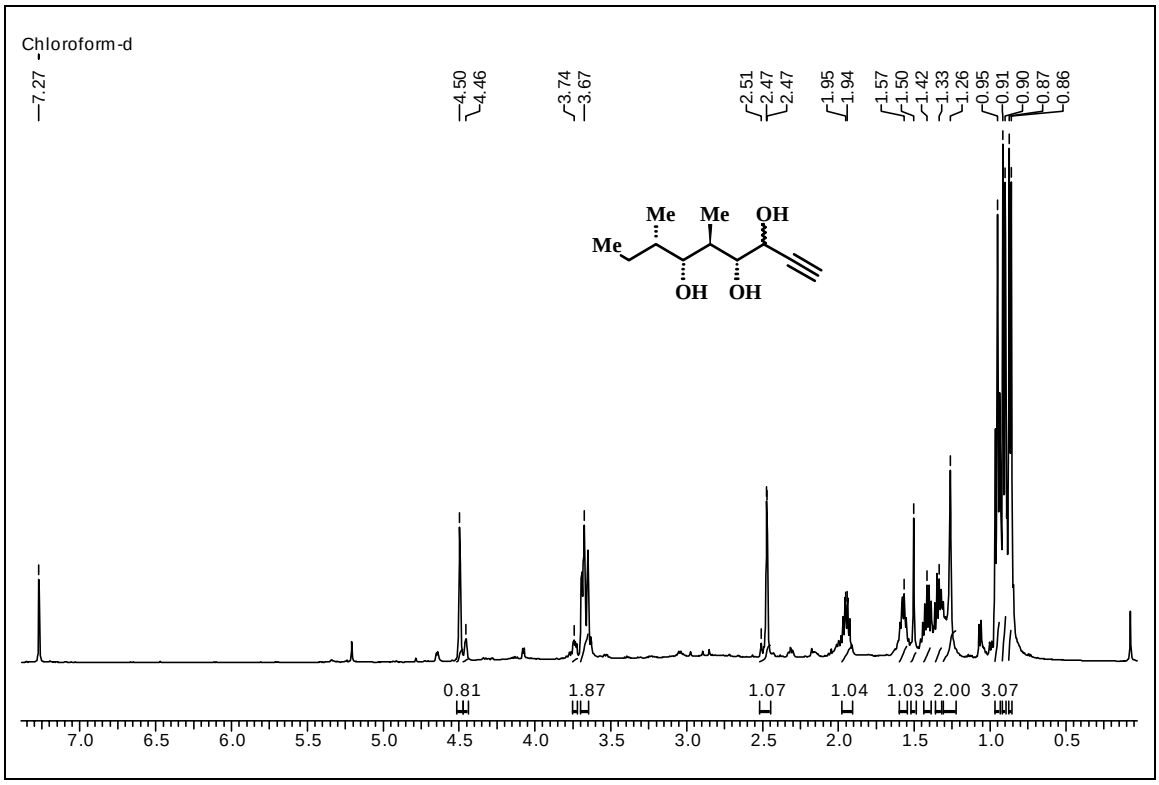
^{13}C NMR spectrum of compound 64 in $CDCl_3$



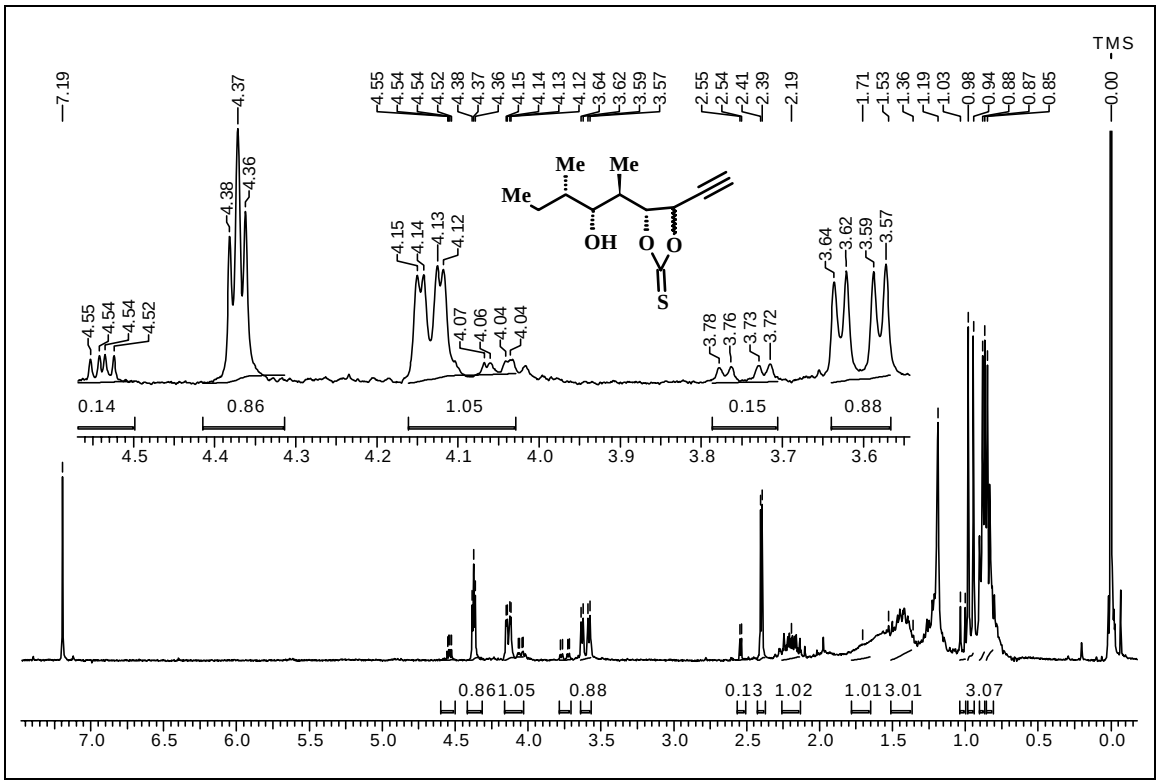
^{1}H NMR spectrum of compound 65 in $CDCl_3$



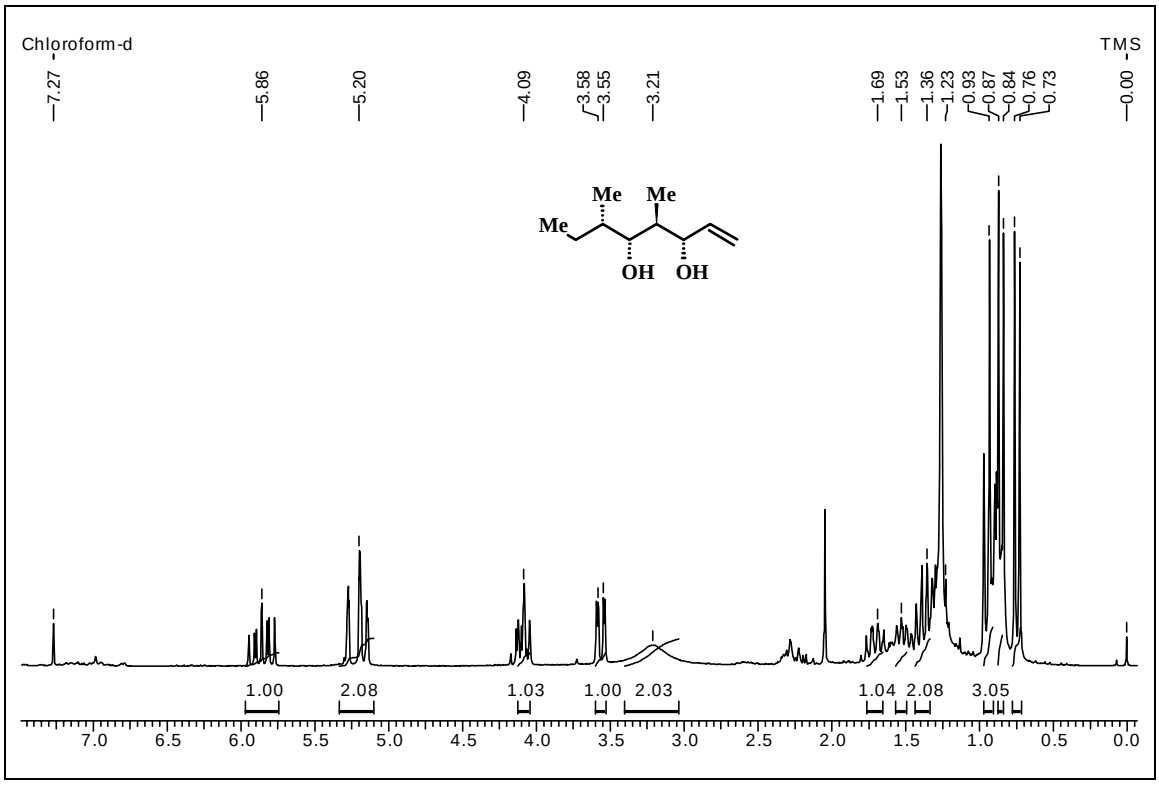
^{13}C NMR spectrum of compound 65 in $CDCl_3$



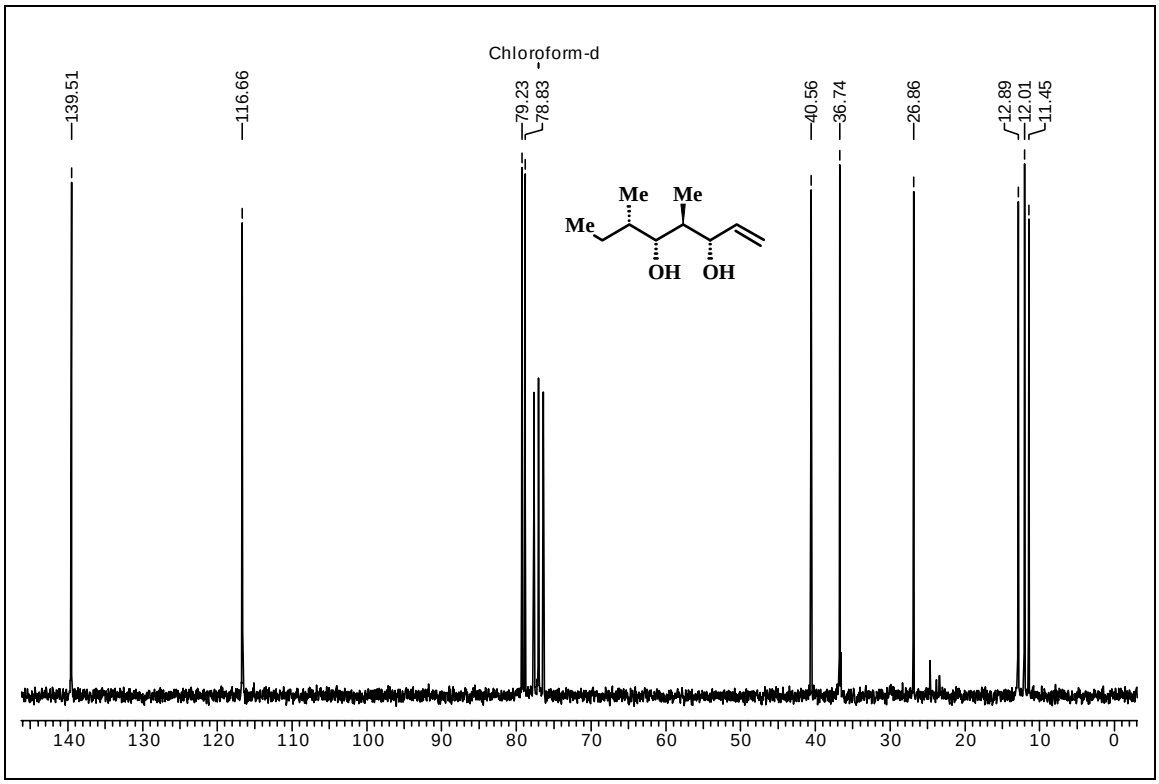
^{1}H NMR spectrum of compound 66 in $CDCl_3$



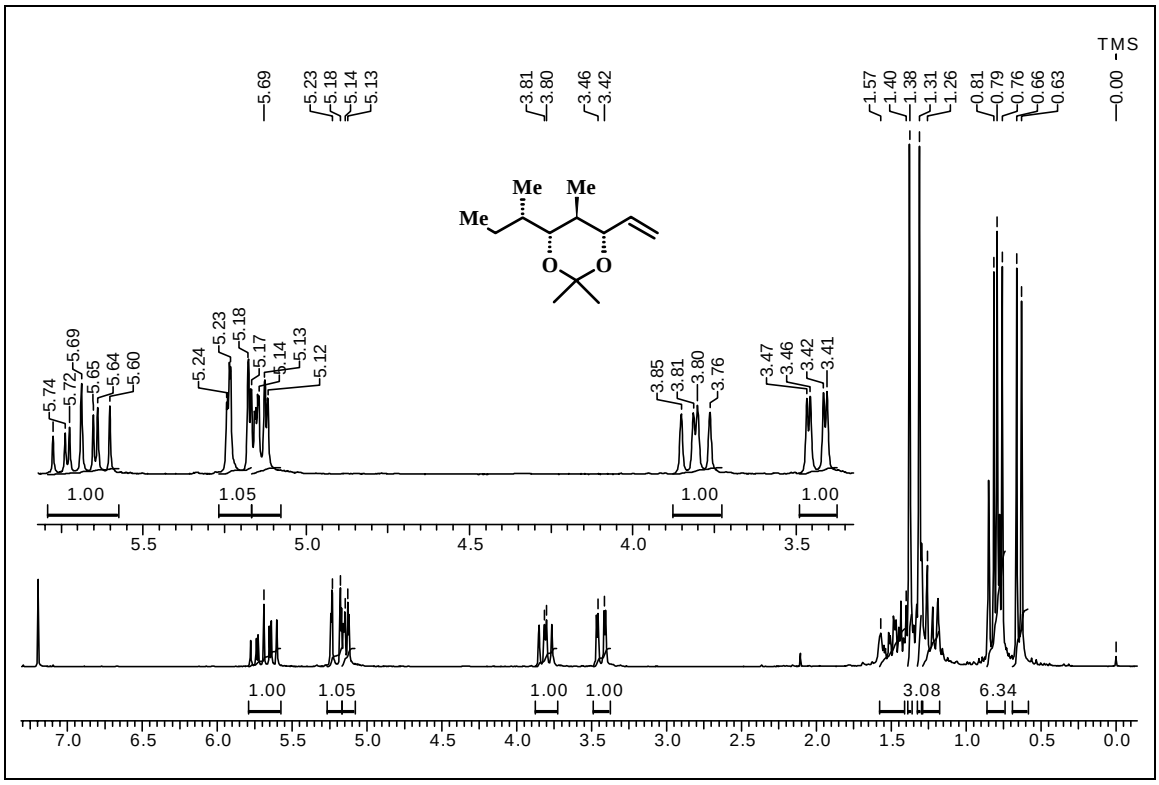
^{1}H NMR spectrum of compound 67 in $CDCl_3$



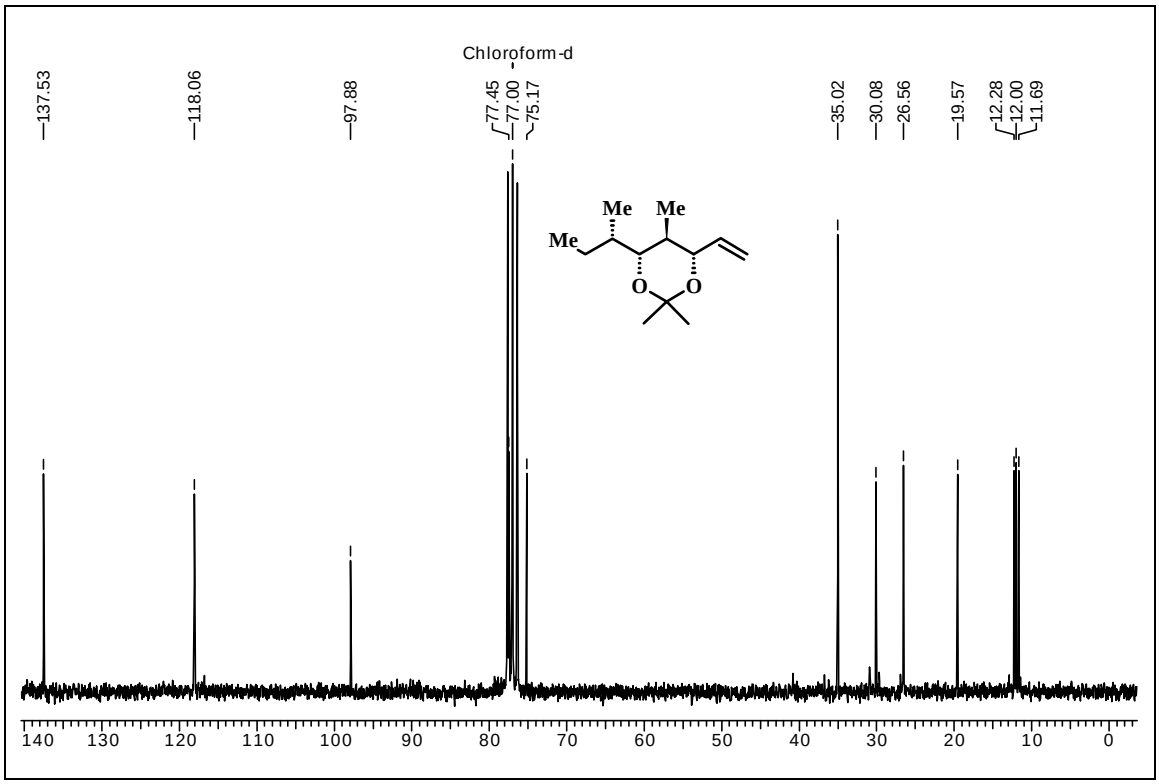
^{1}H NMR spectrum of compound 68 in $CDCl_3$



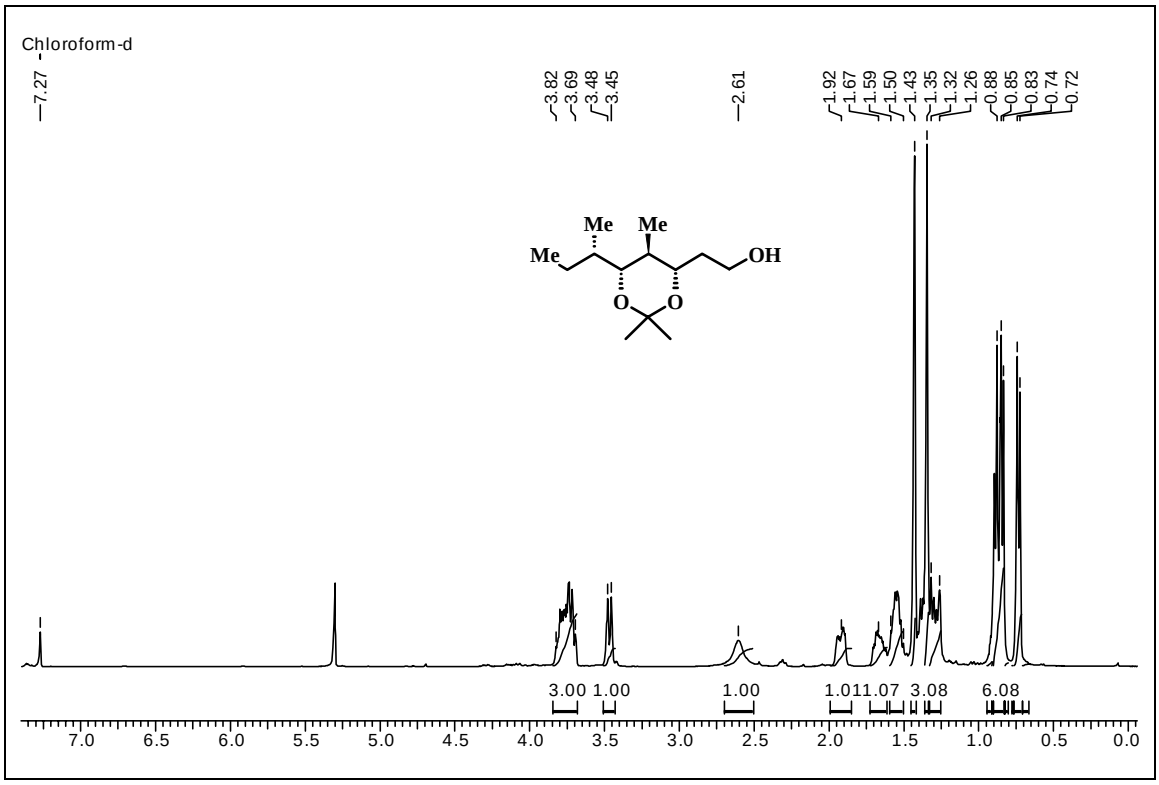
^{13}C NMR spectrum of compound 68 in $CDCl_3$



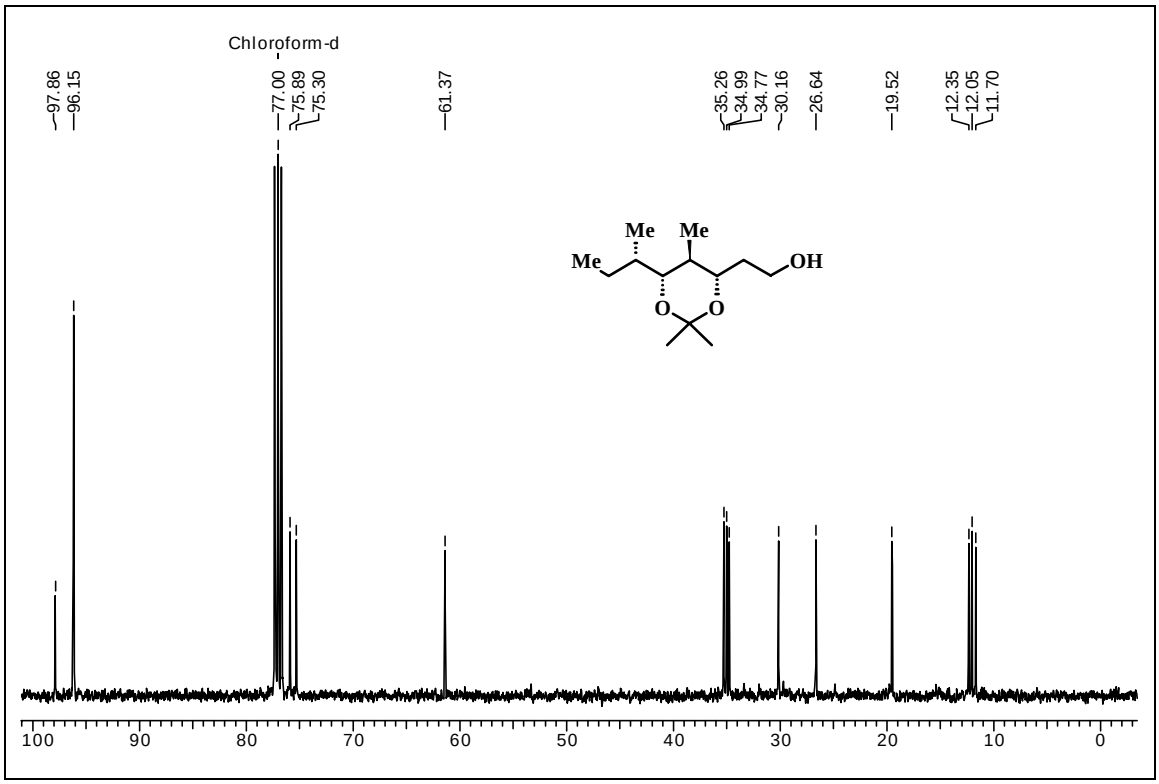
^{1}H NMR spectrum of compound 69 in $CDCl_3$



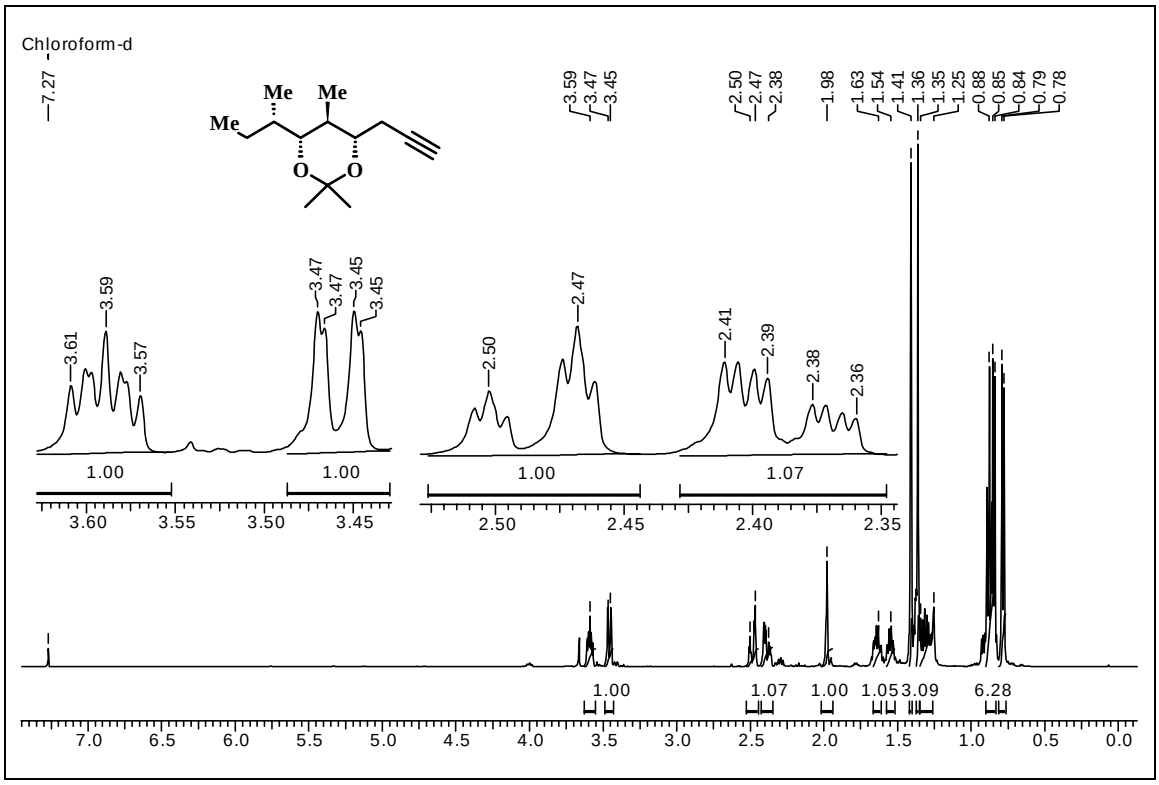
^{13}C NMR spectrum of compound 69 in $CDCl_3$



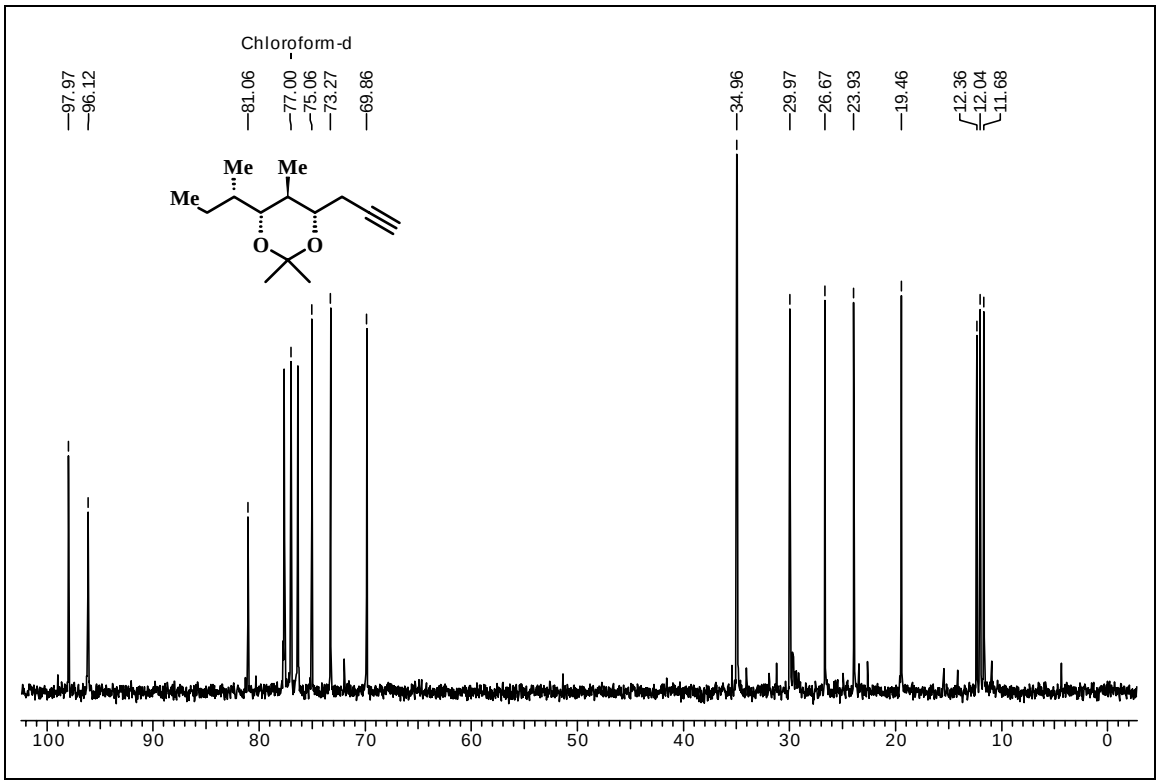
^{1}H NMR spectrum of compound 70 in $CDCl_3$



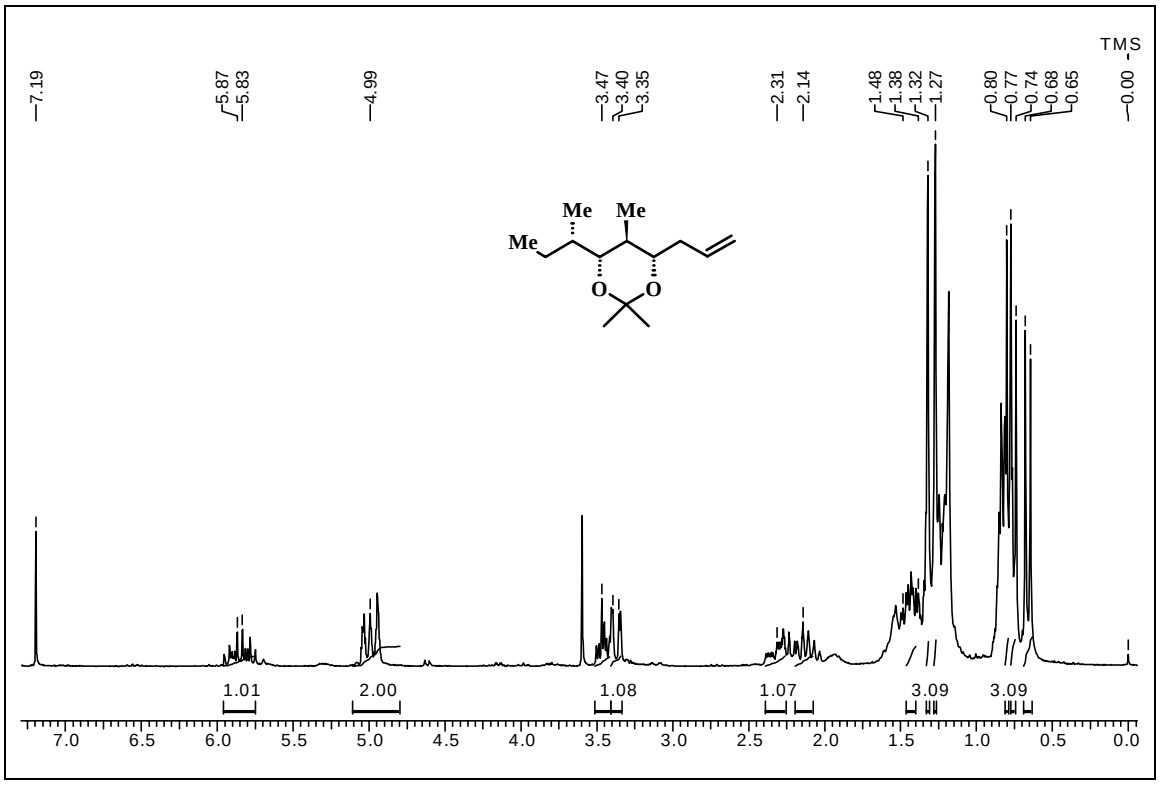
^{13}C NMR spectrum of compound 70 in $CDCl_3$



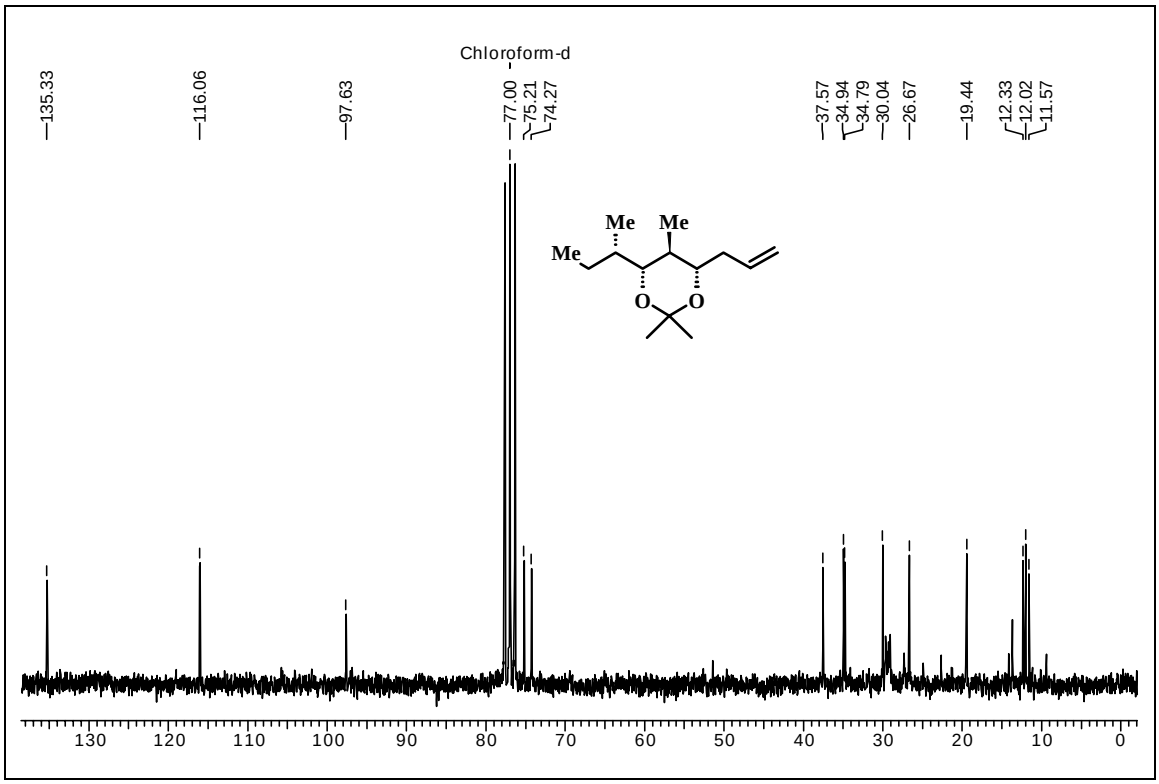
^{1}H NMR spectrum of compound 72 in $CDCl_3$



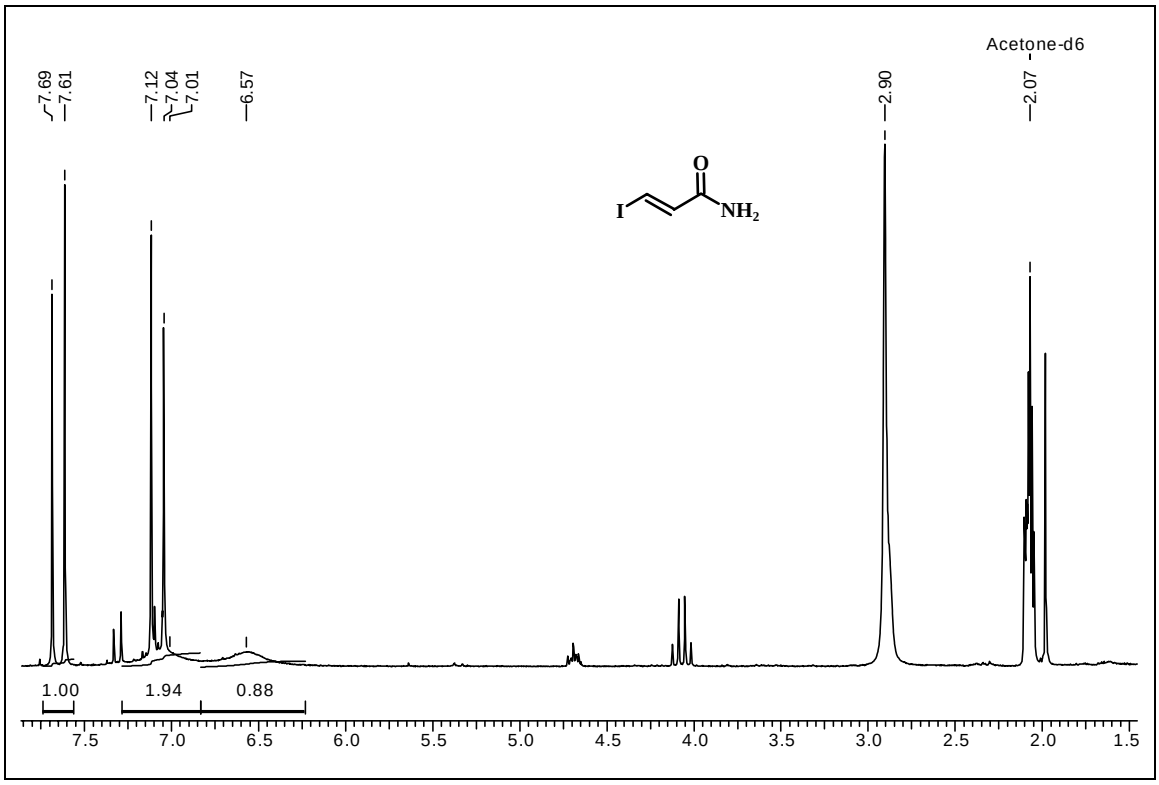
^{13}C NMR spectrum of compound 72 in $CDCl_3$



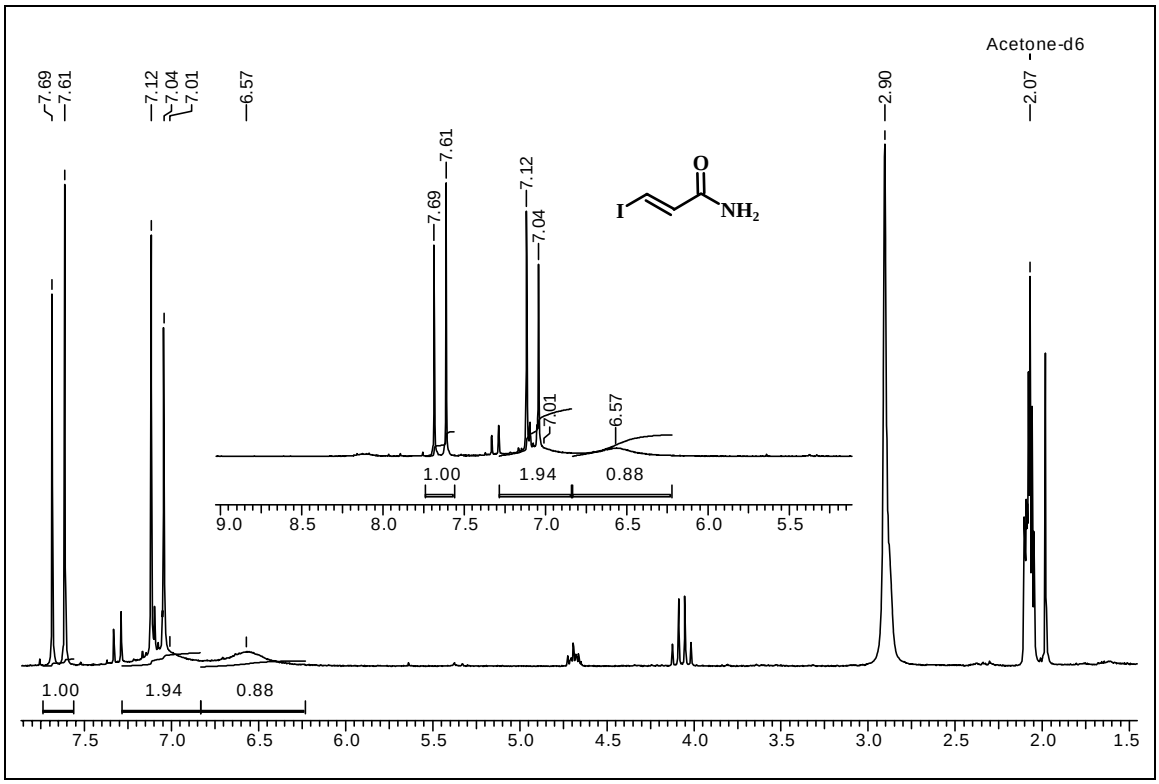
^{1}H NMR spectrum of compound 74 in $CDCl_3$



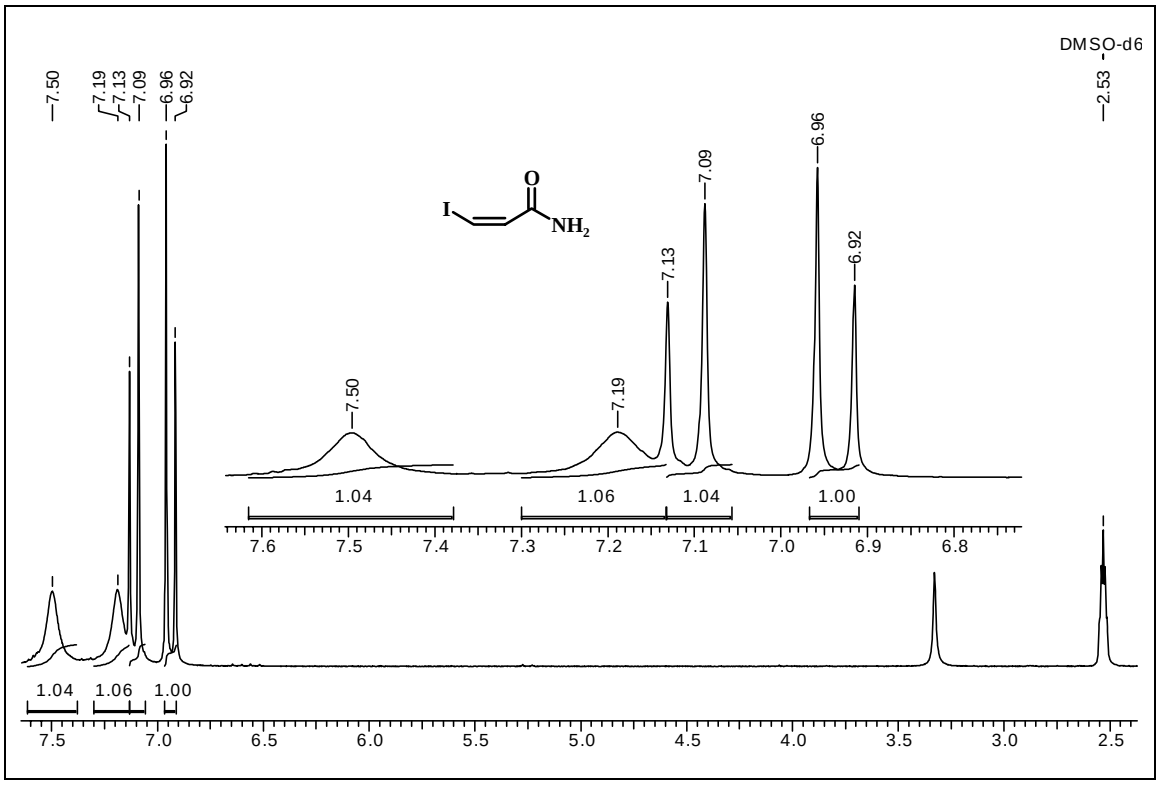
^{13}C NMR spectrum of compound 74 in $CDCl_3$



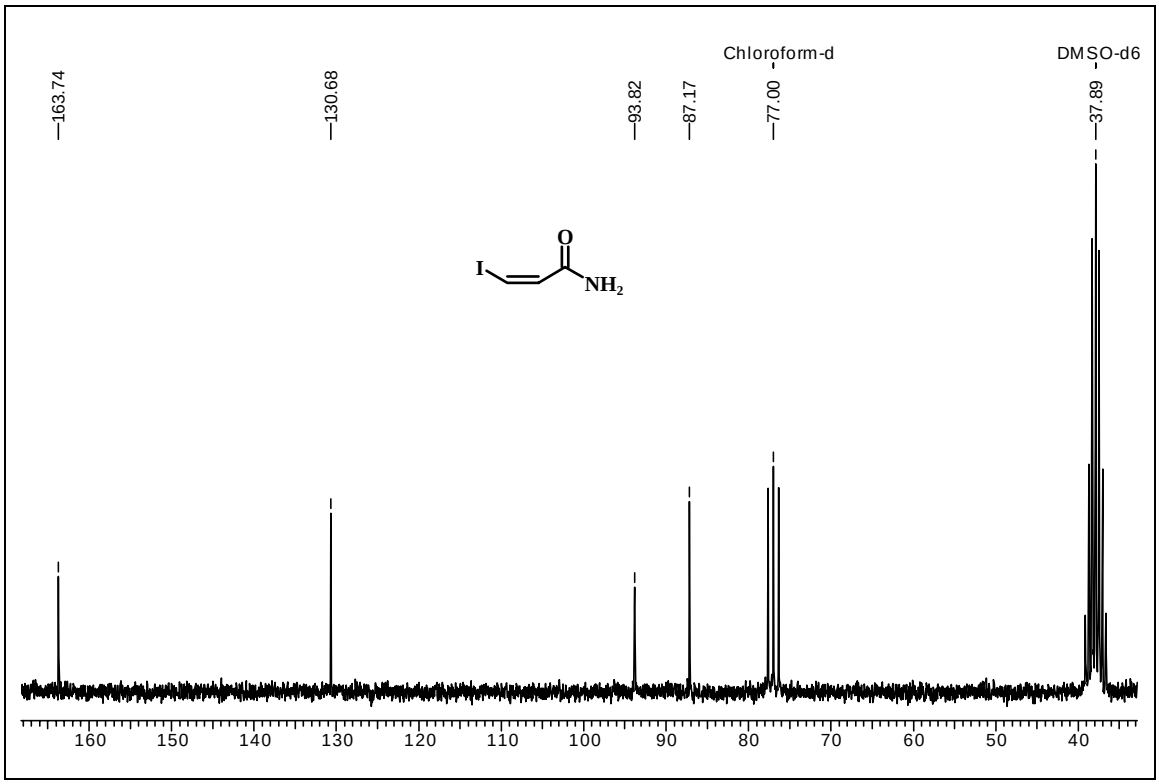
[1]H NMR spectrum of compound 75 in Acetone-d6



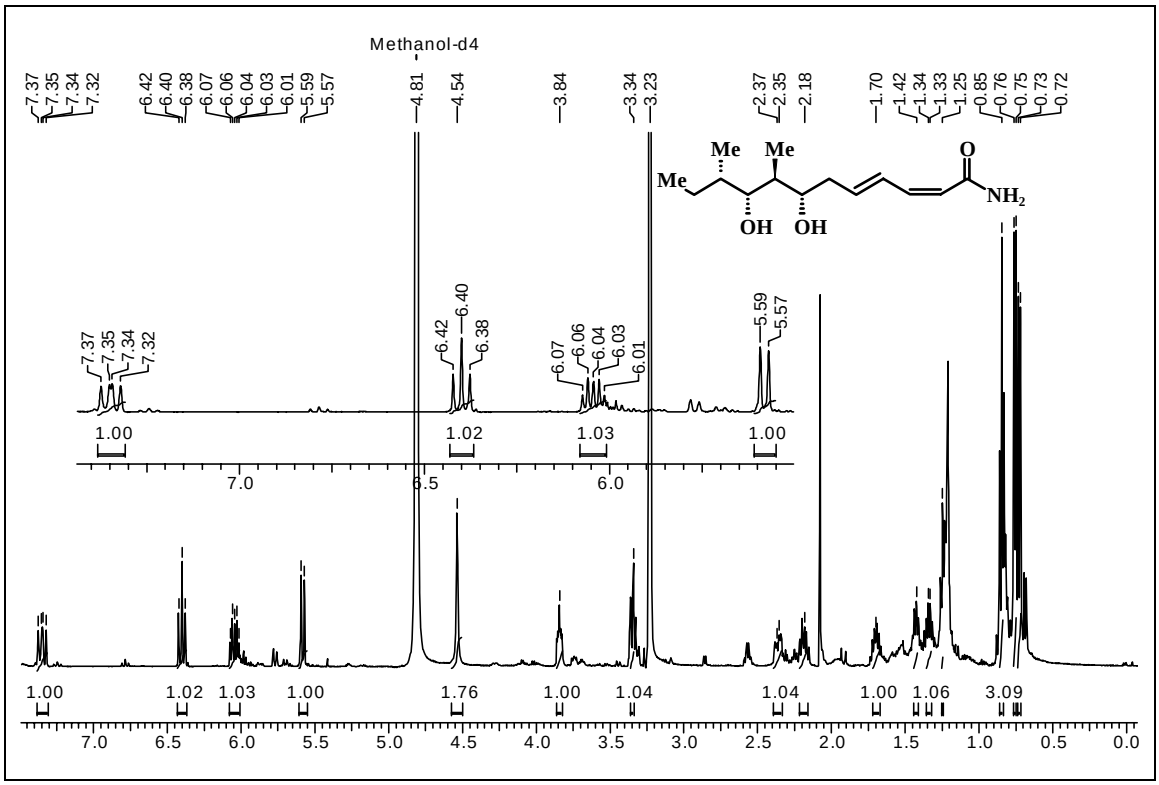
[1]H NMR spectrum of compound 75 in Acetone-d6



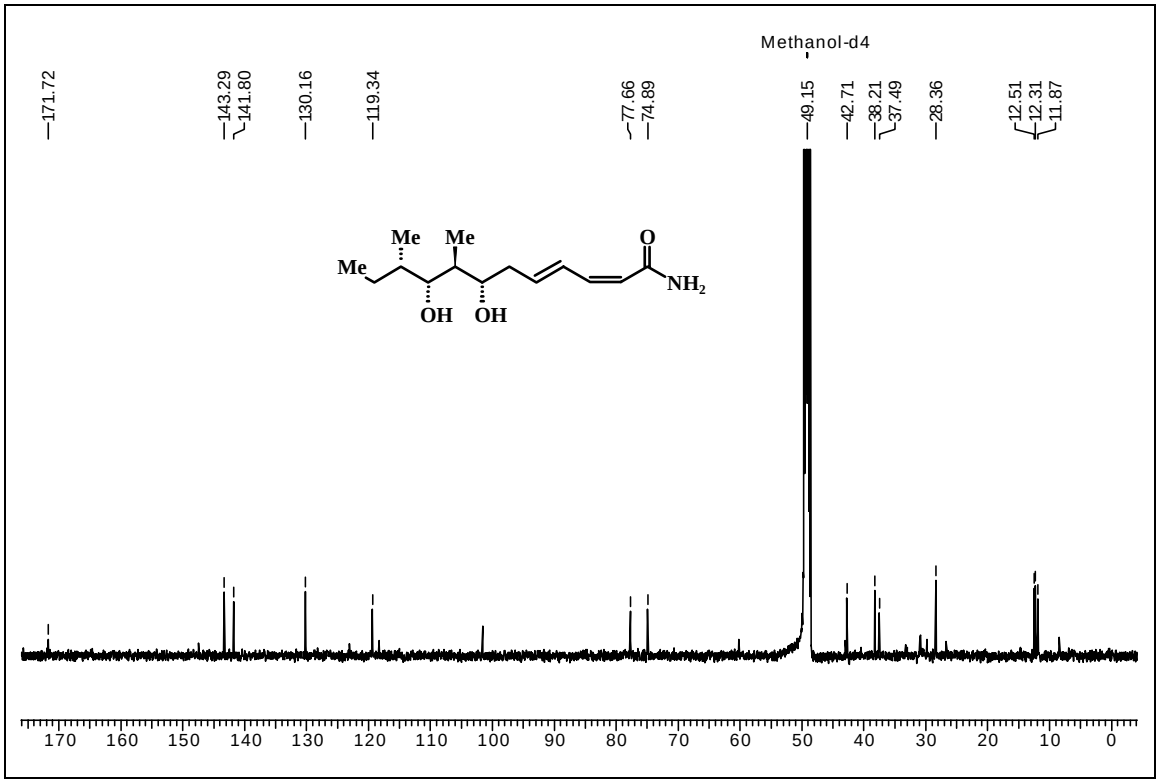
^{1}H NMR spectrum of compound 34 in DMSO-d6 + $CDCl_3$



^{13}C NMR spectrum of compound 34 in DMSO-d6 + $CDCl_3$



^{1}H NMR spectrum of compound 19 in CD_3OD



^{13}C NMR spectrum of compound 19 in CD_3OD

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31. **Preparation of $Pd(CH_3CN)_2Cl_2$**: $PdCl_2$ was taken with dry CH_3CN and refluxed for 2 h, till it completely dissolved. The unreacted $PdCl_2$ was filtered at hot condition and the filtrate was allowed to cool slowly. Nice Crystals of $Pd(CH_3CN)_2Cl_2$ was obtained and was taken out of the mother liquor. The catalyst was then dried in vacuo and kept in a dark and airtight container.

Chapter III:

Total Synthesis of Decarestrictine C_1

Introduction

Cholesterol is a fatty steroid made primarily in the liver of most animals and humans. It is an integral component in the synthesis of hormones, can also be found in cell walls of animals and humans. Isolated cholesterol is a white, flanky solid that is insoluble in aqueous environments. In order to transport the steroid through blood, cholesterol is attached to a set of proteins. There are two types of lipoproteins.

1) **High-density lipoproteins**: These collect cholesterol particles as they travel through blood vessels and deposit them in the liver where they are transferred to bile acids and disposed off.

2) **Low-density lipoproteins**: These deposit on the walls of blood vessels, and overtime, builds up into cholesterol plaque and blocks blood vessels, especially arteries that feed blood to the heart.

The liver manufactures, secrets and removes LDL cholesterol from the body. There are special LDL receptors on the surface of liver cells, which remove LDL cholesterol particles from the blood and transport them inside the liver. A high number of active LDL receptors on the liver surface are necessary for the rapid removal of LDL cholesterol from the blood and low blood LDL cholesterol levels. A deficiency of LDL receptors is associated with high LDL cholesterol blood levels. Diets that are high in cholesterol diminish the activity of LDL receptors.

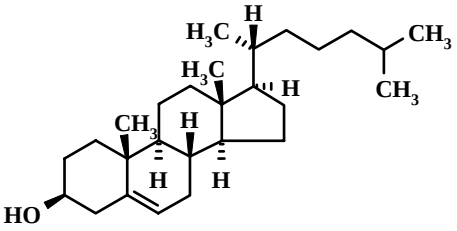
Hypercholestraemia: High blood cholesterol level, usually a result of high LDL/low HDL cholesterol levels, leads to narrowing of artery walls (atherosclerosis), decreased blood and oxygen supply to heart, heart attack, and ultimately death.

Coronary heart disease: This is one of the leading causes of death in western countries. Initial treatment of hypercholesteraemia was directed toward limiting LDL-cholesterol levels through low-cholesterol diet and regular exercise. Exercise burns fat so that it can not be converted to cholesterol which the body will have to dispose off. This approach was not very successful because high blood cholesterol is also hereditary (Familial Hypercholestraemia (FH)) and a chronic condition. People with FH have defective or

nonexistent LDL receptors and need rigorous, long-term treatment. To have the medication program for curing such diseases, we should know and understand how the body makes cholesterol and next we have to find a way to effectively control cholesterol levels with minimum adverse effects.

Introduction to cholesterol metabolism:

Cholesterol (**1**) is an extremely important biological molecule that has roles in membrane structure as well as being a precursor for the synthesis of the steroid hormones and bile acids. Both dietary cholesterol and that synthesized *de novo* are transported through the circulation in lipoprotein particles. The same is true for cholesteryl esters, the form in which cholesterol is stored in cells. The synthesis and utilization of cholesterol must be tightly regulated in order to prevent over-accumulation and abnormal deposition within the body. Deposition of cholesterol and cholesterol-rich lipoproteins in the coronary arteries, eventually leading to atherosclerosis, is the leading contributory factor in diseases of the coronary arteries (Figure 1).



Cholesterol (1)
{Cholest-5-en-3(*S*)-ol}

Figure 1

Biological roles of cholesterol: i) It is an important component of cell linings. ii) It helps in the digestion of lipids. iii) It is a key component in the building of hormones.

Biosynthesis of Cholesterol:[1]

Slightly less than half of the cholesterol in the body derives from biosynthesis *de novo*. Biosynthesis in the liver accounts for approximately 10% and in the intestines approximately 15%, of the amount produced each day. Cholesterol synthesis occurs in the cytoplasm and microsomes from the two-carbon acetate group of acetyl-CoA. The acetyl-CoA utilized for cholesterol biosynthesis is derived from an oxidation reaction

(e.g. fatty acids or pyruvate) in the mitochondria and is transported to the cytoplasm. Acetyl-CoA can also be derived from cytoplasmic oxidation of ethanol by ***acetyl-CoA synthetase***. All the reduction reactions of cholesterol biosynthesis use NADPH as a cofactor (Scheme 1).

Scheme 1

The process has nine major steps (Figure 2):

1. Acetyl-CoAs are converted to 3-hydroxy- 3-methyl glutaryl-CoA (HMG-CoA). Unlike the HMG-CoA formed during ketone body synthesis in the mitochondria, this form is synthesized in the cytoplasm. However, the pathway and the necessary enzymes are the same as those in the mitochondria. Two moles of acetyl-CoA are condensed in a reversal of the *thiolase* reaction, forming acetoacetyl-CoA. Acetoacetyl-CoA and a third mole of acetyl-CoA are converted to HMG-CoA by the action of *HMG-CoA synthase*.

2. HMG-CoA is converted to mevalonate by *HMG-CoA reductase* (this enzyme is bound to the endoplasmic reticulum). *HMG-CoA reductase* absolutely requires NADPH as a cofactor and two moles of NADPH are consumed during the conversion of HMG-CoA to mevalonate. The reaction catalyzed by *HMG-CoA reductase* is the rate limiting step of cholesterol biosynthesis, and this enzyme is subject to complex regulatory controls.

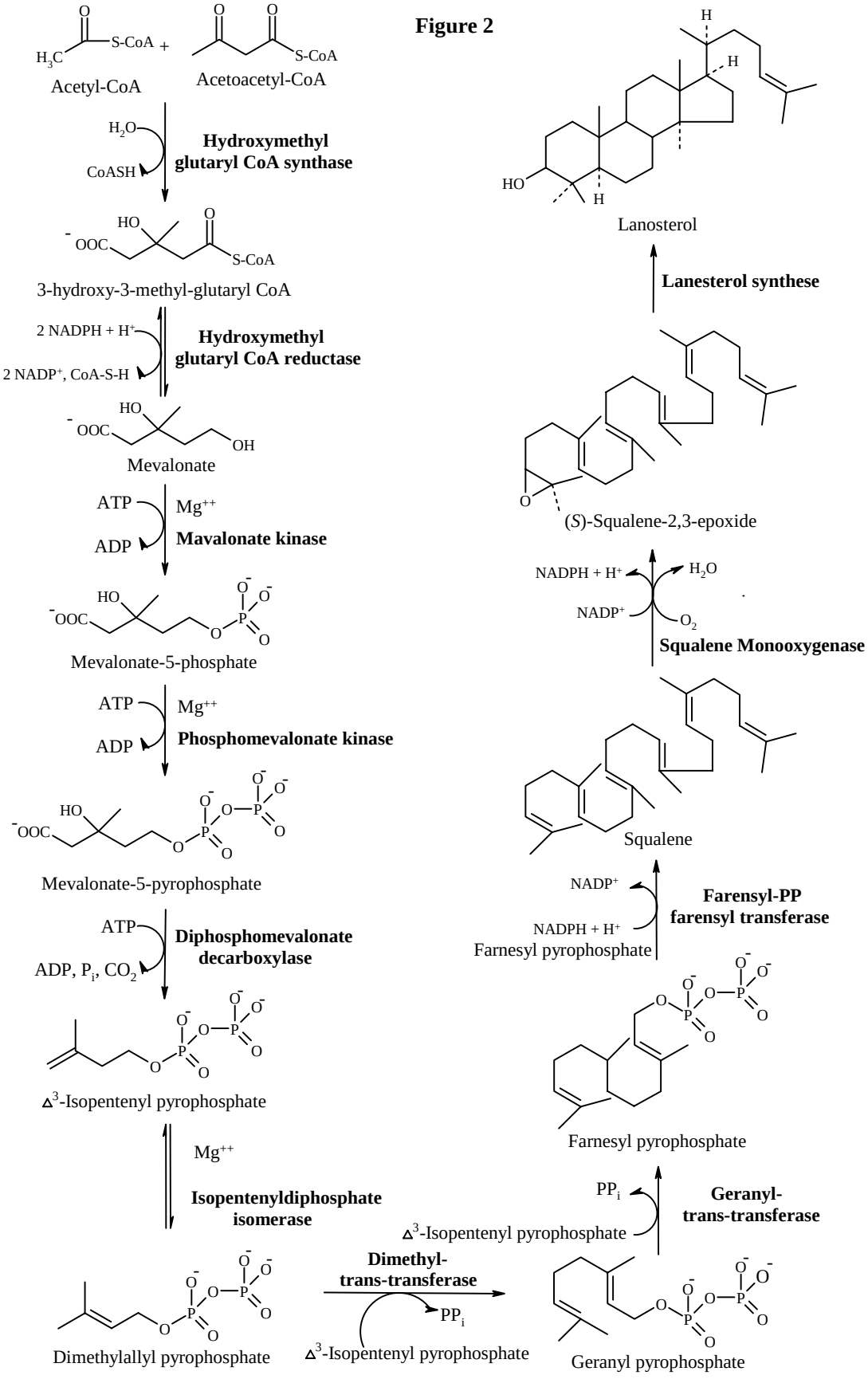
3. Mevalonate is then activated by two successive phosphorylations, yielding 5-pyrophosphomevalonate. In addition to activating mevalonate, the phosphorylations maintain its solubility, since otherwise it is insoluble in water.

4. Mevalonate is converted to the isoprene based molecule, isopentenyl pyrophosphate (IPP), with the concomitant loss of CO_2 .Isopentenyl pyrophosphate is in equilibrium with its isomer, dimethylallyl pyrophosphate, (DMPP).

5. One molecule of IPP condenses with one molecule of DMPP to generate geranyl pyrophosphate, (GPP).

6. GPP further condenses with another IPP molecule to yield farnesyl pyrophosphate.

Figure 2


Acetyl-CoA
Acetoacetyl-CoA
Hydroxymethyl glutaryl CoA synthase
3-hydroxy-3-methyl-glutaryl CoA
Hydroxymethyl glutaryl CoA reductase
Mevalonate
Mavalonate kinase
Mevalonate-5-phosphate
Phosphomevalonate kinase
Mevalonate-5-pyrophosphate
Diphosphomevalonate decarboxylase
Δ3-Isopentenyl pyrophosphate
Isopentenyldiphosphate isomerase
Dimethylallyl pyrophosphate
Dimethyl-trans-transferase
Δ3-Isopentenyl pyrophosphate
Geranyl pyrophosphate
Geranyl-trans-transferase
Farnesyl pyrophosphate
Farensyl-PP farensyl transferase
Squalene
Squalene Monooxygenase
(S)-Squalene-2,3-epoxide
Lanesterol synthese
Lanosterol

7. Finally, the NADPH-requiring enzyme, ***squalene synthase*** catalyzes the head-to-tail condensation of two molecules of FPP, yielding squalene (squalene synthase also is tightly associated with the endoplasmic reticulum).

8. Squalene undergoes a two step cyclization to yield lanosterol. The first reaction is catalyzed by ***squalene monooxygenase***. This enzyme uses NADPH as a cofactor to introduce molecular oxygen as an epoxide at the 2,3 position of squalene.

9. Through a series of 19 additional reactions, lanosterol is converted to cholesterol with zymosterol, demosterol as important intermediates.

Regulating cholesterol synthesis:

Normal healthy adults synthesize cholesterol at a rate of approximately 1 g/day and consume approximately 0.3 g/day. A relatively constant level of cholesterol in the body (150 - 200 mg/dL) is maintained primarily by controlling the level of *de novo* synthesis. The level of cholesterol synthesis is regulated in part by the dietary intake of cholesterol. Cholesterol from both diet and synthesis is utilized in the formation of membranes and in the synthesis of the steroid hormones and bile acids. The greatest proportion of cholesterol is used in bile acid synthesis. The cellular supply of cholesterol is maintained at a steady level by three distinct mechanisms:

1. Regulation of *HMG-CoA reductase* activity and levels.

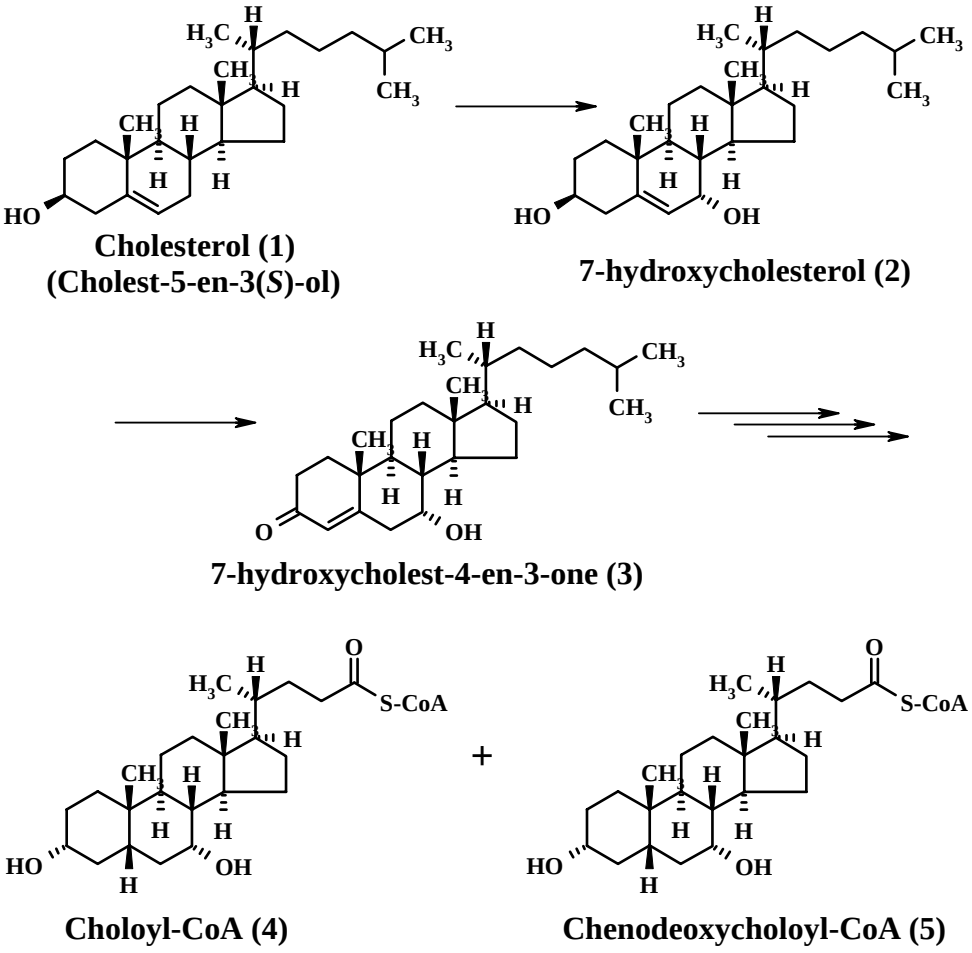
2. Regulation of excess intracellular free cholesterol through the activity of acyl-CoA:cholesterol acyltransferase, ACAT.

3. Regulation of plasma cholesterol levels via LDL receptor-mediated uptake and HDL mediated reverse transport.

The utilization of cholesterol:[2]

The end products of cholesterol utilization are the bile acids, synthesized in the liver (Scheme 2). Synthesis of bile acids is the predominant mechanism for the excretion of excess cholesterol. However, the excretion of cholesterol in the form of bile acids is insufficient to compensate for an excess dietary intake of cholesterol. The most abundant bile acids in human bile are chenodeoxycholic acid (45%) and cholic acid (31%). These are referred to as the primary bile acids. Within the intestines the primary bile acids are

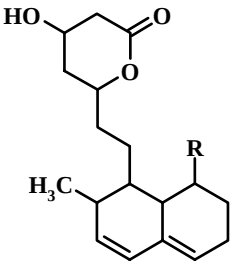
acted upon by bacteria and converted to the secondary bile acids, identified as deoxycholate (from cholate) and lithocholate (from chenodeoxycholate). Both primary and secondary bile acids are reabsorbed by the intestines and delivered back to the liver via the portal circulation.



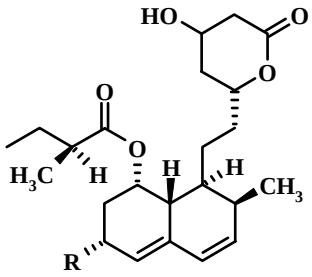
Scheme 2: Decomposition of cholesterol to bile acids

Some natural products inhibiting biosynthesis of cholesterol:

ML-236A (6), ML-236B (7), ML-236C (8) metabolites isolated from a fungus (*Penicillium citrinum*), were found to reduce serum cholesterol levels in rats. This work was done by Akira Endo, Masao Kuroda and Yoshio Tsujita at the Fermentation Research Laboratories, Tokyo, Japan.[3]



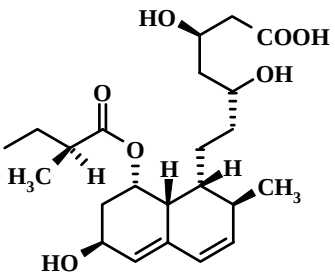
ML-236A (6): R = OH
ML-236B (7): R = $OCOCH(CH_3)CH_2CH_3$
ML-236C (8): R = H



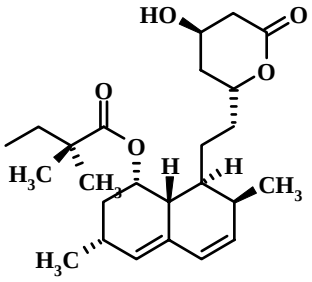
Lovastatin (9): R = CH_3
Compactin (10): R = H

Figure 3

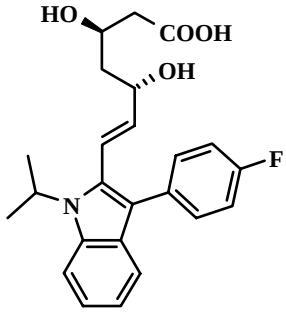
ML-236B (7) was later called **compactin (10)**[4] (6-demethylmevinolin or mevastatin). A related fungal metabolite called lovastatin (mevinolin) was also found to be another good inhibitor of HMG-CoA reductase (Figure 3).



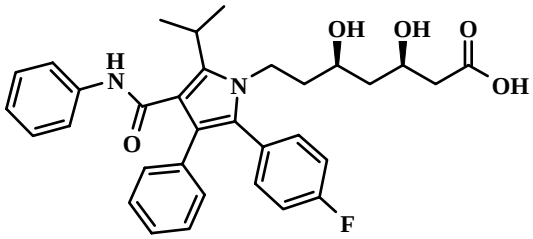
Pravastatin (11)



Simvastatin (12)



Fluvastatin (13)



Atorvastatin (14)

Figure 4

Lovastatin (**9**)[5] was isolated from *Aspergillus terreus*. Statins are competitive inhibitors of HMG-CoA reductase.[6] They are bulky and literally get "stuck" in the active site. This prevents the enzyme from binding with its substrate, HMG-CoA. Today, there are two classes of statins (Figure 4): [7]

1) Natural Statins: Lovastatin (mevacor) (**9**), Compactin (**10**), Pravastatin (pravachol) (**11**), Simvastatin (Zocor) (**12**).[8]

2) Synthetic Statins: Fluvastatin (Lescol) (**13**), Atorvastatin (Lipitor) (**14**).[9]

A short review on medium-sized ring lactones

Medium-sized[10] heterocyclic rings are becoming increasingly important in organic chemistry, as they are contained in an ever-growing number of biologically active natural products and medicinally important compounds. Quite a few methodologies have been developed for their synthesis. They are much more difficult to synthesize by cyclization methods than other cyclic compounds (ring sizes>12) because the formation of medium ring compounds is disfavored by entropy as well as enthalpy.[11]

Naturally occurring 10-membered lactones

Natural products containing ten-member framework are abundant in plants, insects (pheromones) and bacteria (antibiotics). They originate from terrestrial, fungal or marine sources. Jasmine (**15**) is one of the oldest natural products possessing an oxecan-2-one framework isolated[12] in 1942 from essential oil of *Jasminum grandiflorium*.

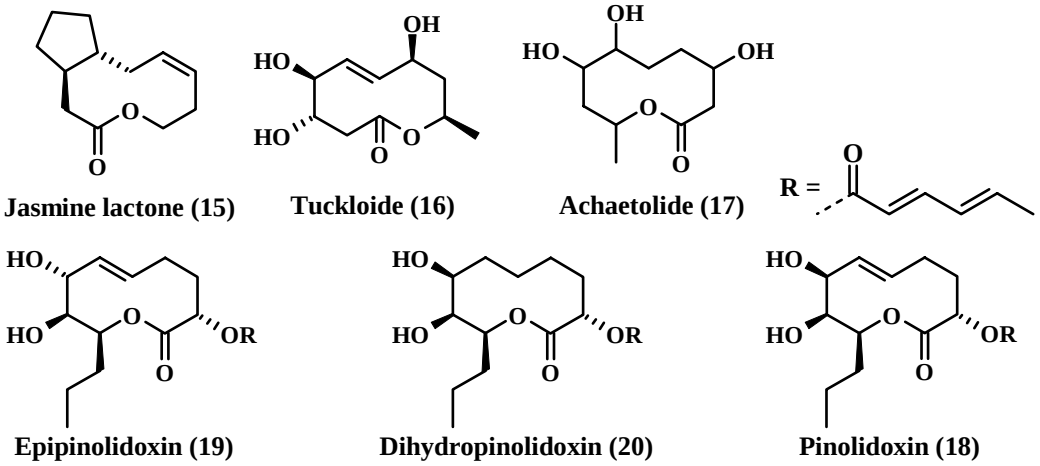


Figure 5

More recently, tuckolide (**16**) was isolated as metabolite of the Canadian tuckahoe, the sclerotium of *Polyporus tuberaster* a subterranean fungus.[13] Some more examples are: Achaetolide (**17**) was isolated from the fungus of *Achaetomium cristalliferum*.[14a] Pinolidoxin (**18**), a phytotoxin was produced from the fungus of

Aschochyta pinodes,[14b] subsequently new metabolites of this fungus were found as epipinolidoxins (**19**) and dihydropinolidoxins (**20**) (Figure 5).[14c]

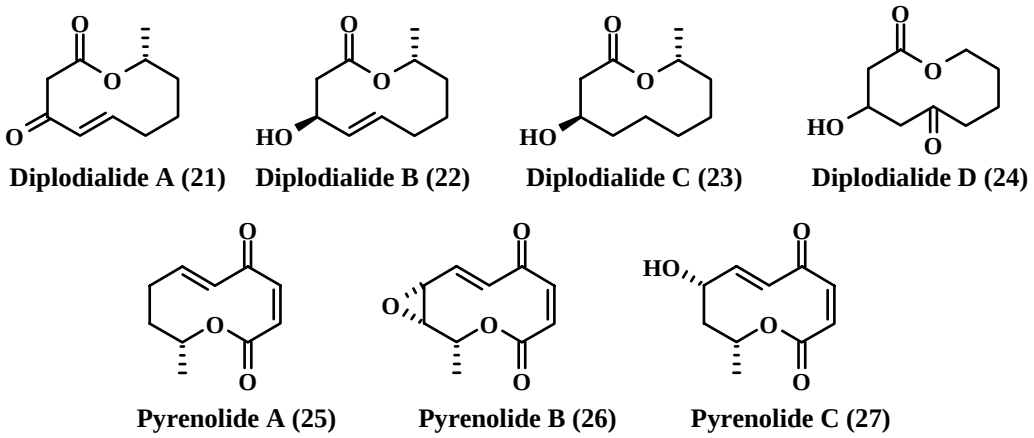


Figure 6

Diplodialides[15] A (**21**), B (**22**), C (**23**), and D (**24**), four new metabolites from the culture filtrate of the plant pathogenic fungus *Diplodia pinea*, are the first members of ten-membered lactones belonging to pentaketides. Diplodialide A, has been reported to be a steroid hydroxylase inhibitor. Similarly Pyrenolides A (**25**), B (**26**), and C (**27**), having similar structures to diplodialides, were isolated from pathogenic fungus, *Pyrenophora teres*.[16]These compounds show inhibitory activity against fungi (Figure 6).

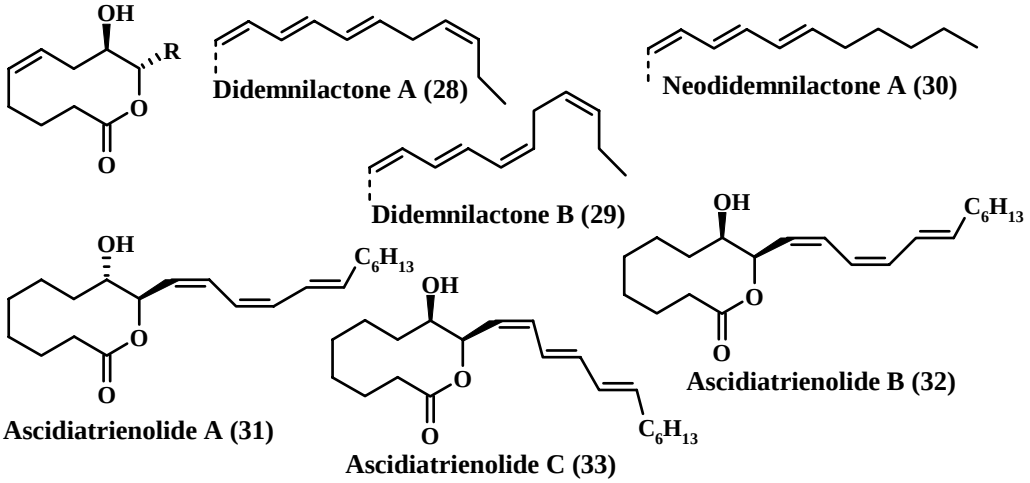


Figure 7

Metabolites of *Didenmum moseleyi* (herdman), didemnilactones A (**28**), B (**29**), and neodidemnilactone A (**30**) were found to be 10-membered lactones.[17]These

compounds exhibit weak binding activity to leukotriene B_4 receptors in human polymorphonuclear leukocyte membrane. Ascidiatrienolides A (**31**), B (**32**) and C (**33**),[18a]whose structures are recently reinvestigated,[18b]were found in marine ascidian (*Didemnum candidum*) and correspond to oxidation products of C_{20} fatty acid (Figure 7).

Trichlogoniolides (**34**-**37**) are complex lactones, in which a 10-membered lactone is fused to another 5-membered lactone and were isolated from the aerial part of *Trichogonia* species (vide *supra*) (Figure 8).[19]

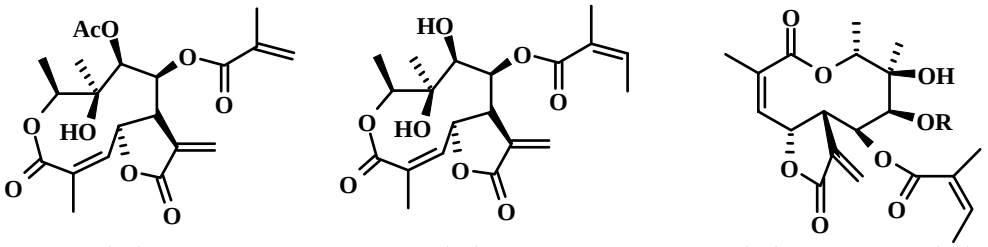


Figure 8: Trichlogoniolides series

A new structurally complex alkaloid aspidochibine (**38**) was isolated from the tree bark of the *Aspidosperma quebracho blanco*, which is used for the treatment of bronchial asthma and dyspnoe in South America.[20]Nargenicin A_1 (**40**)[21] and nodusmicin (**39**)[22] are antibiotics produced by *Nocardia argentinensis* and *Saccharopolyspora hirsuta* respectively (Figure 9).

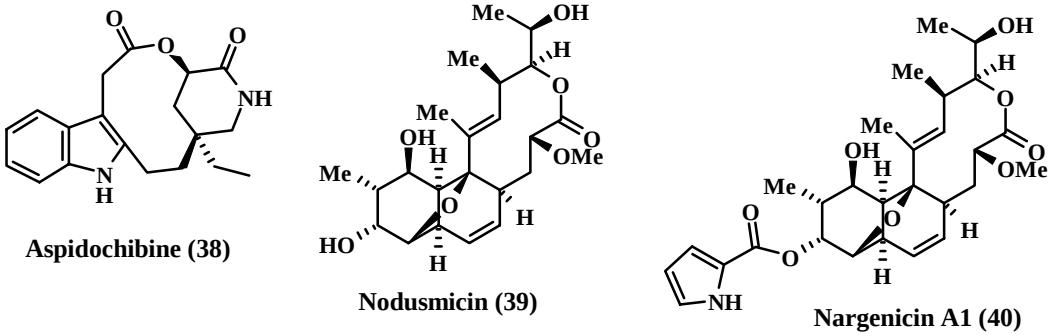


Figure 9

Some examples of Flavanones, containing 10-membered lactone fragments, are kurzichalcolatones (**41**-**43**), isolated from the leaves of a Malaysian plant, *Cryptocarya kurzeii* and have a weak cytotoxicity against **KB** cells.[23] Four new decarestrictine

analogues named botryolides A-D (**44-47**) have been isolated from cultures of fungicolous isolate of *Botryotrichum* sp (Figure 10).[24]

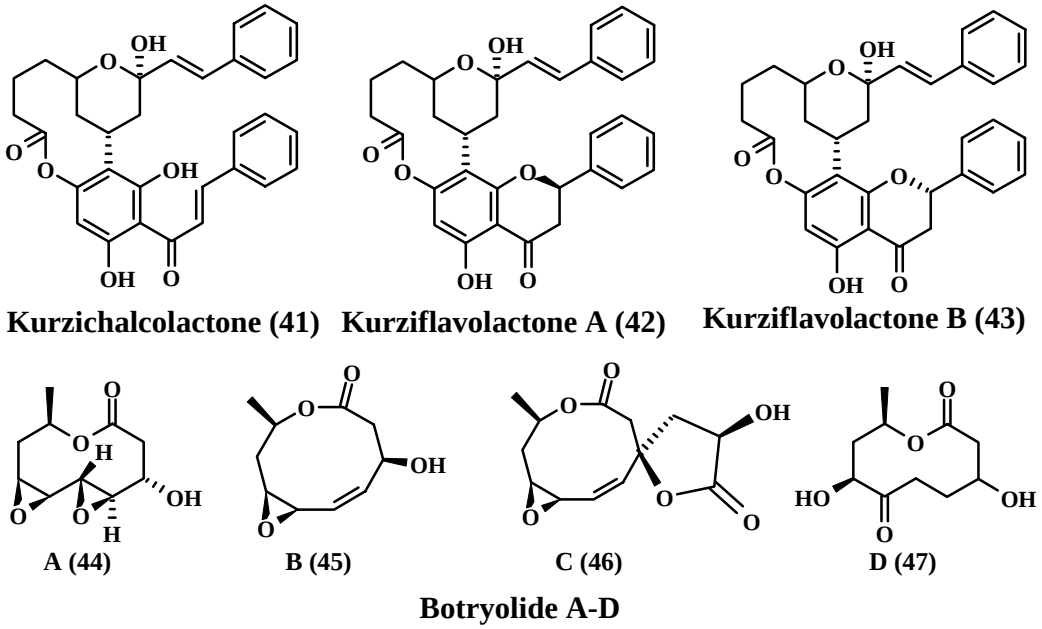


Figure 10

Novel decarestrictine family: isolation, structure and biological properties:

Isolation: A collaborative work[25] by Wink, J. *et al.* from Hoechst AG, Germany {currently named as *Industriepark Höchst* (*Industrial Park Höchst*)}and Zeeck, A. *et al.* from institute of Gottingen, Germany was reported in 1992 describing the isolation of Decarestrictine A-D (**55-60**) from soil samples collected in Bryce Canyon (Utah, U.S.A.), Oak Greek Canyon (Arizona, U.S.A.), and Portugal (Aljezun). Their regular effort and vivid research[26] in isolation and characterization of microorganisms from various natural sources, *e.g.* soil samples, plant materials, and food stuff etc. by extracting the strains, cultivated on the culture broths, resulted many natural products of biological interest. In this continued effort, they found that different *pencillium* species (strains FH-A 6090, FH-A 6099, FH-A 6530, and FH-A 6360) exhibit a similar but unusual secondary metabolite pattern. By taxonomic investigations the strains have been classified to be the members of the species *penicillium simplicissimum* and *penicillium corylophilum*, which can be combined in the subgenus *Furcatum*. Later, in the same year the same group reported[27] the addition to this decarestrictine family i.e. Decarestrictine E-M (**61**-**69**). A

more detailed examination of the culture broth of *penicillium simplicissimum* (strain FH-A 6090) resulted in the detection of these minor components of decarestrictine family.

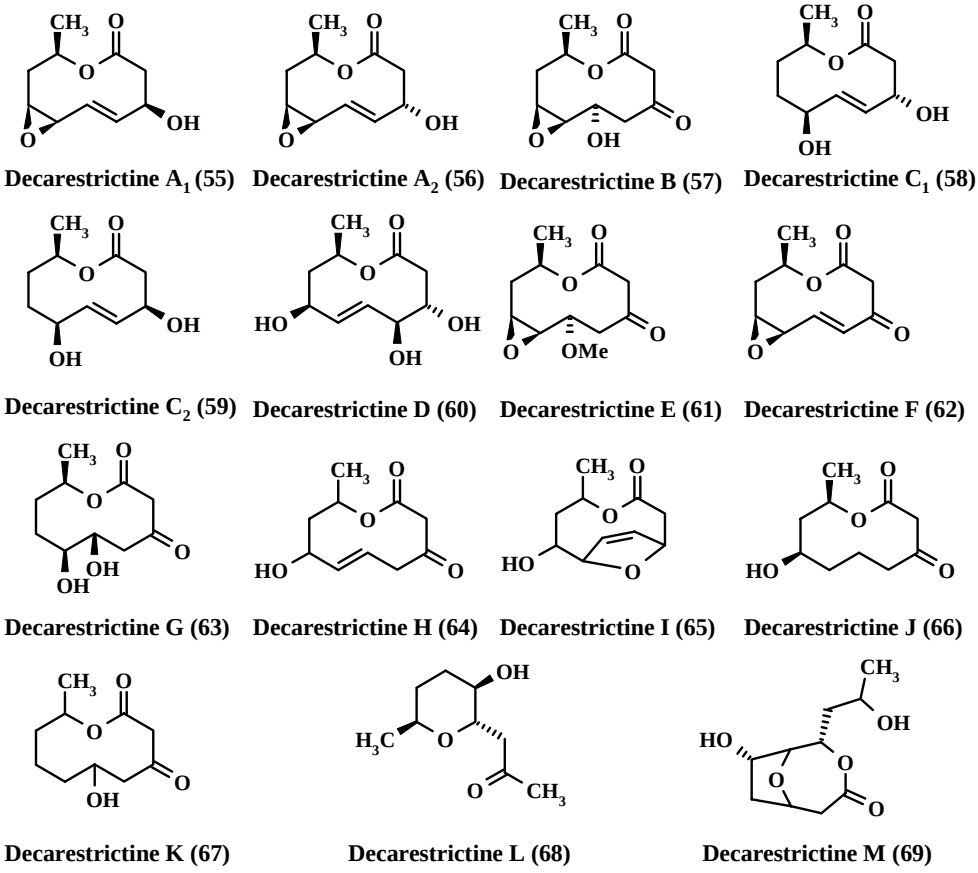


Figure 11: Novel decarestrictine family

Structural features: These metabolites were characterized spectroscopically, their molecular formulae were determined by high resolution mass spectra, and their structures were elucidated by ^{1}H, ^{13}C, IR, ^{1}H-^{1}H-correlation and ^{1}H-^{13}C-shift-correlation data etc. Additional information concerning the stereochemistry was obtained from X-ray analysis. The structural features of these fungal metabolites are the presence of: i) 10-membered lactone ring, ii) an exocyclic methyl appendage, and iii) oxygen appendages at positions varying from C3 to C7. With the exception, lack of 10-membered lactone ring was observed for decarestrictine L (**68**) and M (**69**). Decarestrictine I (**65**) possesses a bicyclic ring system, in which the 10-membered lactone is bridged forming an ether linkage between C3 and C6 (Figure 11).

Biological activities: It is considered that these metabolites are structurally related to each other based on their physico-chemical properties. Pharmacological interest is based on the biological activities of the decarestrictines, especially on component D. This metabolite appears to resemble a potent inhibition of the cholesterol biosynthesis, which yields favorable effects on lipid metabolism *in vivo*. The decarestrictines show interesting activity in cell line tests with HEP-G2 liver cells due to an inhibitory effect on cholesterol biosynthesis. This was tested via sodium acetate incorporation into cholesterol. The 10^{-7} mol/liter concentration of each decarestrictine resulted in inhibition effects of about 40% (decarestrictine A), 20% (decarestrictine B), 30% (decarestrictine C), and 50% (decarestrictine D), respectively[1]. In this test the IC_{50} for the standard compound lovastatin (**9**) is 2.4 x 10^{-8}. Due to the lack of pathologic changes of defined safety parameters, decarestrictine D revealed a good tolerability. These decarestrictines are selective in drug parameters as they exhibit no significant antibacterial, antifungal, antiprotozoal, and antiviral activity.

Earlier synthetic reports of 10-membered lactone natural products from our group:

Our research group has reported[28] the synthesis of a few 10-memebered lactone natural products recently (Figure 12). These include Microcarpalide (**48**), Herbarumin III (**49**), Nonenolide (**50**), Multiplolide A (**52**) etc. The striking common strategy has been the esterification of two alcohol and acid fragments with terminal olefin functionality, followed by ring closing metathesis (Figure 12).

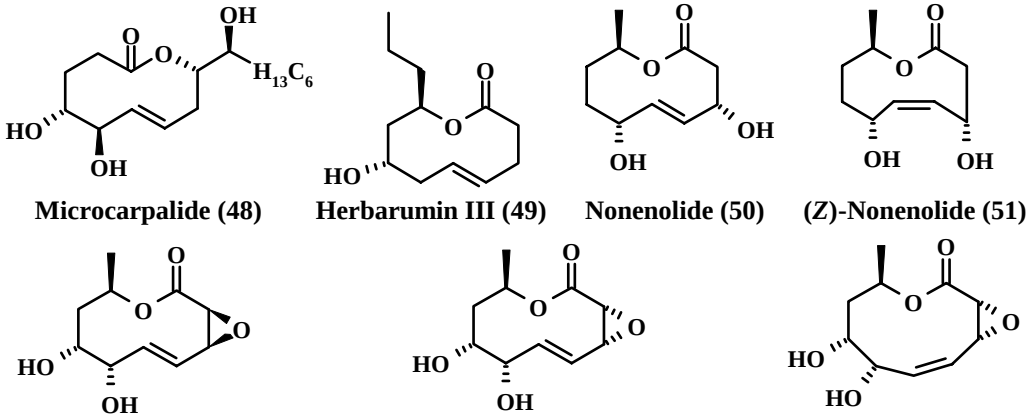
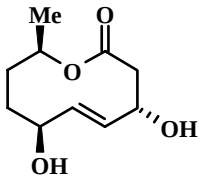


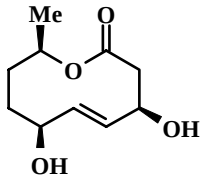
Figure 12

As alluded to in the preceding prologue isolation of decarestrictines A-D was reported in 1992 by a joint group of Hoechst AG and the University of Gottingen. These metabolites revealed potent inhibitory effects on cholesterol biosynthesis in cell line tests via sodium acetate incorporation into cholesterol, with HEP-G2 liver cells. These appeared to be selective, in that antibacterial, antifungal or antiviral activities were not discernible. The interesting biological activity of decarestrictine has been responsible for stimulating synthetic efforts targeted at this scaffold.

The isolated decarestrictines A and C were reported as comprising a diastereomeric mixture of A_1/A_2 (3:1 ratio) and C_1/C_2 (1:1 ratio) respectively. The report[25a] further claimed that decarestrictine C consists of two components as determined from NMR spectra. Based on ^1H, ^{13}C, 2D-COSY experiments, two sets of peaks were identified and assigned to decarestrictine C_1 and C_2. Correlation with the other members of this family resulted in the postulation of the structures of decarestrictine C_1 and C_2 as **58** and **59** respectively (Figure 14). Later, Kibayashi *et al.* reported[29] the total synthesis of decarestrictine C_2, from D-mannitol. The striking dissimilarity in the spectral data of their synthesized decarestrictine C_2 with that of the isolated natural product prompted them to suggest that the isolated natural product in solution may be a 1:1 molecular complex of both C_1 and C_2. These intriguing discrepancies led us to undertake the synthesis of Decarestrictine C_1.



Decarestrictine C_1 (58)



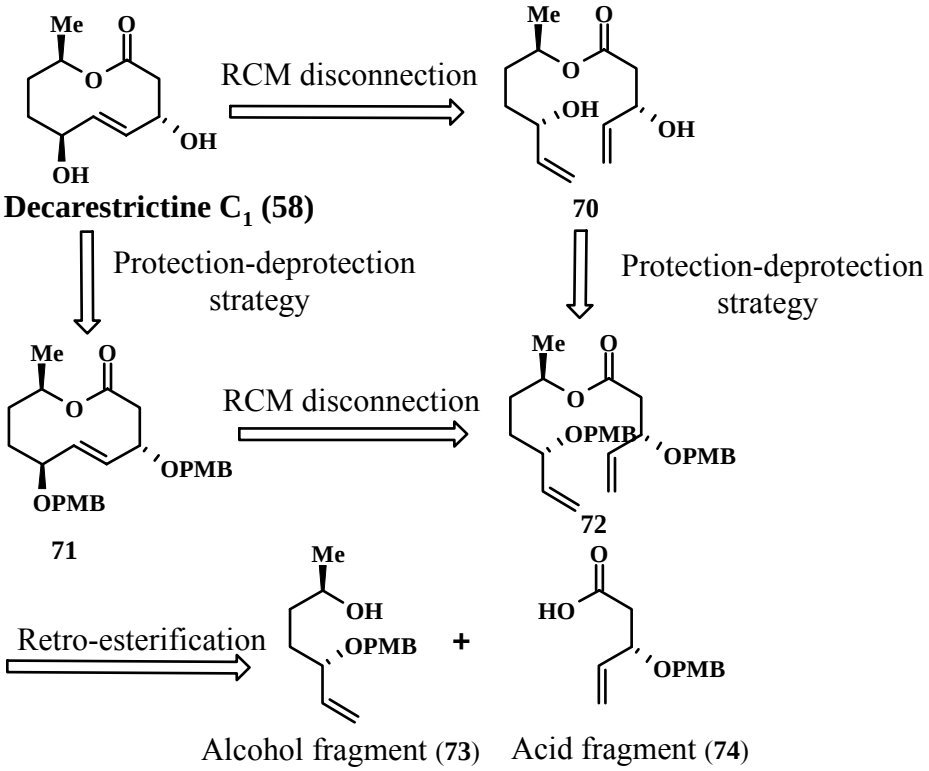
Decarestrictine C_2 (59)

Figure 13

Retrosynthetic strategy:

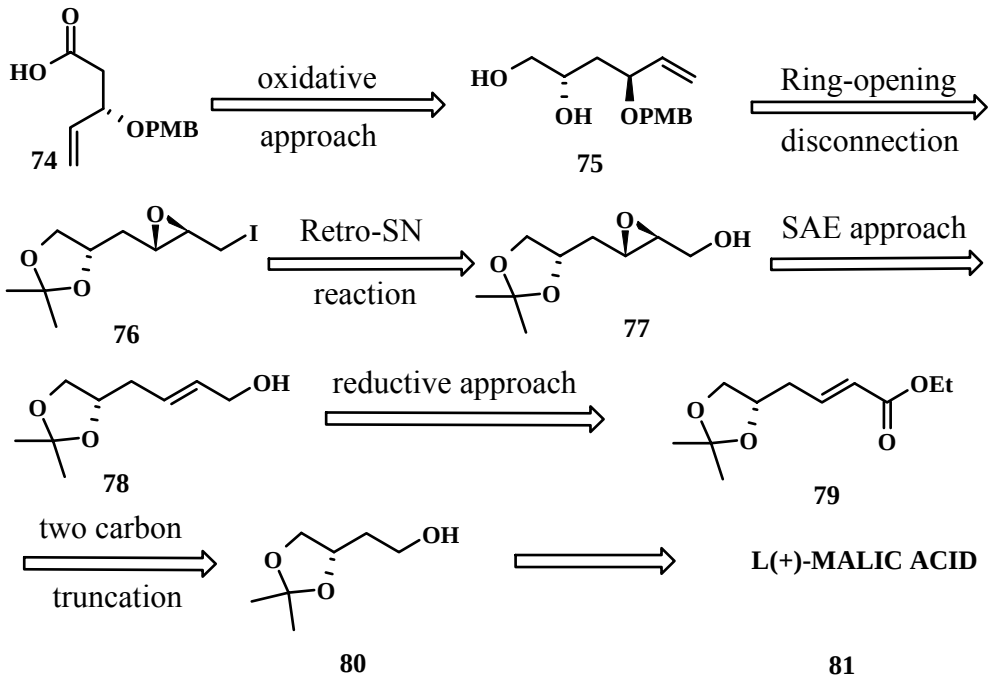
Our retrosynthetic approach and strategy is delineated in scheme 3: it involves a key disconnection of the double bond producing the diene ester synthon. Our ongoing collaboration[28c] on "protecting group directed RCM reactions", with Prof. Robert H.

Grubbs made the precursors **70** and **72** for the RCM reaction[30] fairly obvious. Strategic bond disconnection in ester **72** leads to alcohol fragment **73** and acid fragment **74**.



Scheme 3: retrosynthetic pathway for decarestrictine C_1

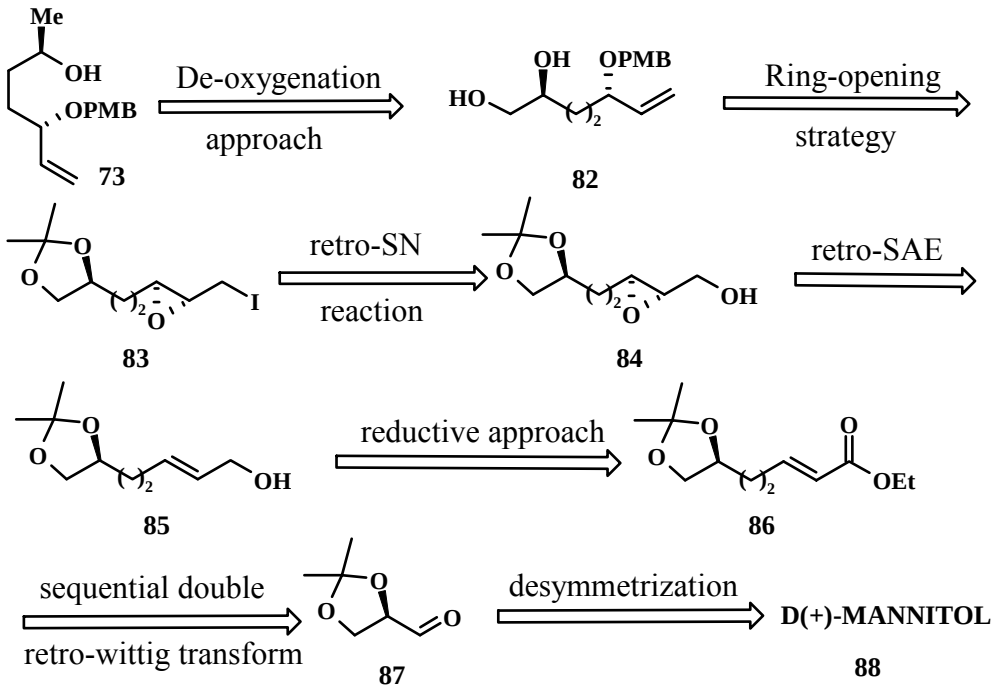
Retrosynthetic strategy for the acid fragment 74: The acid fragment **74** could be synthesized from the diol by a sequence of oxidation reactions on the diol **75**. The allyl ether **75**, on the right side, was envisaged to arise from epoxy methanol through base mediated ring opening of epoxymethyl iodide after simple FGT. The allyl alcohol **78** was assumed to be an unambiguous retron for the epoxy methanol **77** to be produced by stereoflexible and stereocontrolled transformations. Appropriate oxidation/reduction reactions and C=C Wittig disconnections would imply the alcohol **80**, which could be conceivably synthesized from L(+)-Malic acid through regioselective transformations. Our choice of chiral Malic acid (**81**) over the racemic one (as the inherent chirality of the starting material has no relevant role in the synthetic sequence and is destroyed in the final step) was to ensure complete characterization of the intermediates and to avoid any misleading diastereomeric product in the Sharpless asymmetric epoxidation (Scheme 4).



Scheme 4: retrosynthetic pathway for the acid fragment (**74**)

Retrosynthetic strategy for the alcohol fragment 73: A similar retrosynthetic strategy was planned for the alcohol fragment **73** with the deployment of a final reductive transformation of the diol instead of oxidation and the starting material to start with.

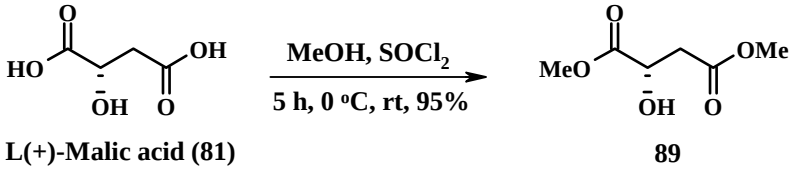
The alcohol fragment **73** could be prepared from the diol **82** through deoxygenation reaction. As depicted in scheme 5, the diol **82** can be generated from the allylic alcohol **85** by adapting a similar synthetic sequence as for the acid fragment. Twice retro Wittig reactions with prudent application of oxidation/reduction imply the three carbon synthon, *O*-isopropylidine-D-glyceraldehyde (**87**) as next synthon. Cheap and ready availability, high enantiomeric purity and equivalence to double unit of chiral building block due to C2 symmetry provided strong incentives for us to start with D(+)-mannitol (**88**).



Scheme 5: retrosynthetic pathway for the alcohol fragment (**73**)

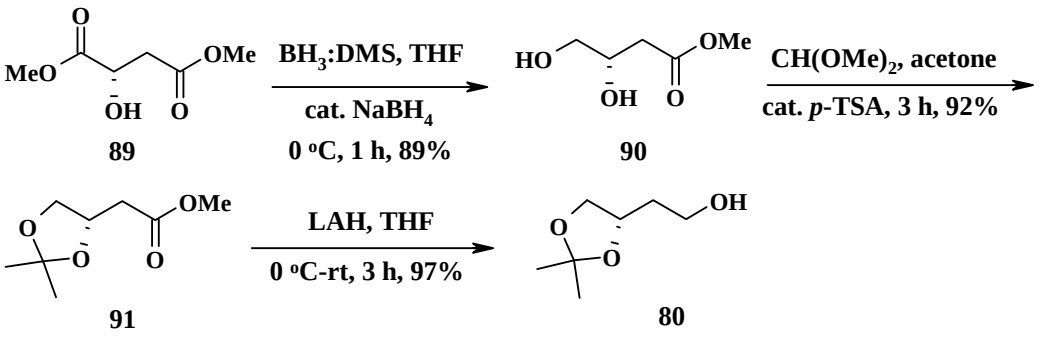
Syntheses of Acid fragment (74)

The synthesis of the acid fragment **74** began with methylation of L(+)-Malic acid (**81**) by reaction with MeOH, $SOCl_2$ at 0 °C to room temperature (Scheme 6). Methylation was confirmed by the analysis of spectral datas. The dimethyl maliate (**89**) was next converted to the primary alcohol **80** in two parallel sequences.



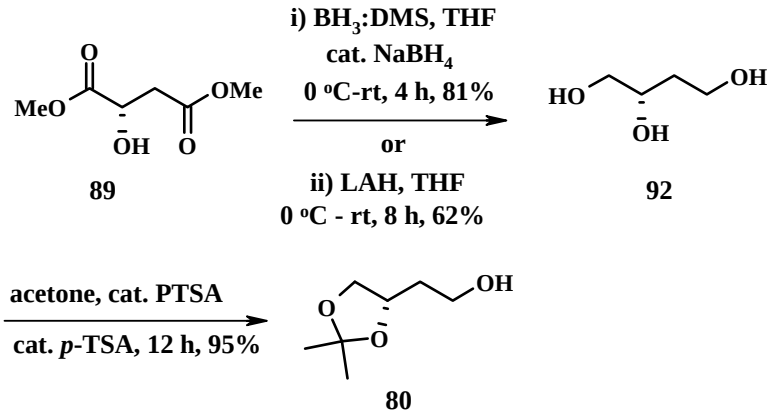
Scheme 6

First strategy involved a three-step reaction sequence, the initial reaction being the regioselective reduction of the ester group (β to the hydroxyl group) with borane-dimethyl sulfide complex (BH_3:DMS) and catalytic sodium borohydride ($NaBH_4$) in anhydrous THF to the corresponding diol[31] **90** in 89% yield. The product **90** was unambiguously supported by its ^{1}H NMR, ^{13}C NMR spectral data and elemental analysis.



Scheme 7

Next, the ketalization of diol **90** in acidic medium was achieved in 92% yield by the reaction with 2,2'-dimethoxypropane, acetone and *p*-toulenesulfonic acid. The second ester group of **91** was then reduced with lithium aluminium hydride in dry THF at 0 °C to room temperature to yield alcohol **80** in good yield. The conspicuous absence of peaks due to the ester group and the appearance of a broad peak at 2.37 ppm for the exchangeable hydroxyl proton indicated the product **80** (Scheme 7).



Scheme 8

An alternative route involves a shorter path, wherein a complete reduction of Dimethylmaliate (**89**) to the corresponding triol **92** followed by regioselective ketalization of the vicinal hydroxyl groups yielded the primary alcohol **80**. Ketalization of the vicinal hydroxyl groups leading to the product **80**, was achieved regioselectively with anhydrous acetone in acidic medium (catalytic *p*-TSA) at room temperature. This regioselectivity could well be explained on the basis of the free energy of the products (Figure 14).

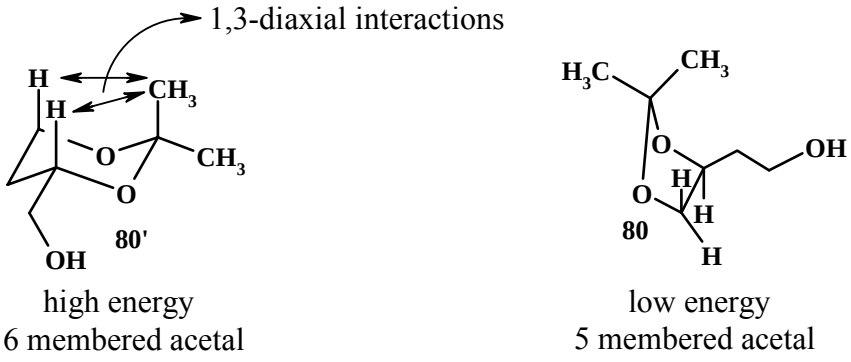
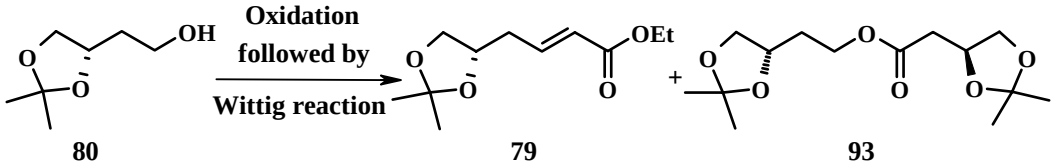


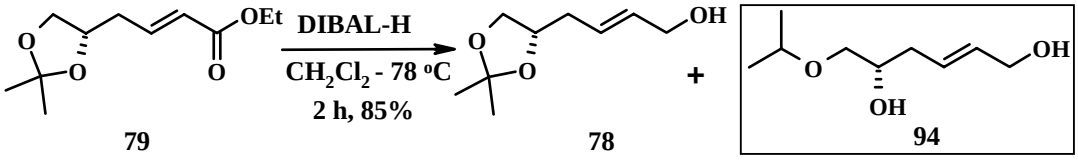
Figure 14

Having the primary alcohol **80** in hand, two carbon extension to the carbon back bone was planned next. The hydroxyl group was oxidized by (i) PDC, 4 A° molecular sieves powder, Ac_2O in CH_2Cl_2 at 0 °C- room temperature; (ii) PCC, celite in CH_2Cl_2 at room temperature. The aldehyde thus obtained was quickly exposed to stable Wittig ylide (ethoxycarbonylmethylene)triphenylphosphorane in refluxing benzene for 2-3h to furnish two chromatographically separable products. While the faster moving product was the desired *E* olefin **79**, the slower moving polar product was the dimeric ester product **93**. Both products were characterized fully by spectral and analytical study. For compound **79**, the PMR spectrum showed new resonances at 5.89 ppm (dt, 1H, J = 1.5, 15.7 Hz) and 6.91 ppm (dt, 1H, J = 7.2, 15.7 Hz) for the olefinic protons; the CMR spectrum displayed the respective carbons at 123.9 ppm, 143.6 ppm. Additional ethyl ester peaks were also evident in PMR and CMR spectrum. The structure of **79** was further confirmed by IR spectrum and elemental analysis. The dimeric ester product was confirmed from the HRMS with ancillary information from PMR and CMR spectral analysis. The most significant peaks at 2.50 ppm (dd, 1H, J = 6.4, 16.0 Hz) and 2.60 ppm (dd, 1H, J = 7.1, 16.0 Hz) for the methylene protons, α to the ester carbonyl group were indicative of the transformation. Also, appearance of five triplet carbons in DEPT NMR spectrum confirmed the product **93**. Finally, two carbon elongation of the primary alcohol **80** was accomplished exclusively by sequential one-pot oxidation and Wittig reaction. The compound was treated with IBX in DMSO at room temperature, followed by a THF solution of (ethoxycarbonylmethylene) triphenylphosphorane in the same reaction vessel. The result was the exclusive formation of *E* α,β-unsaturated ester **79** with a negligible amount of *Z* olefin (as observed by TLC) (Scheme 9).



Scheme 9

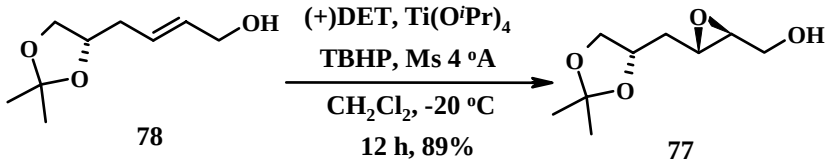
Reductive transformation of the *E* olefin **79** was next achieved selectively with DIBAL-H in CH_2Cl_2 at -78 °C. This reaction was remarkably sensitive and the ratio of the allyl alcohol **78** and acetonide opened allyl alcohol **94** was dependent on the bath temperature. Small scale reactions (not more than 4 g of ester **79**), slow addition rate of DIBAL-H and a constant bath temperature at -78 °C were precautionary measures instrumental in achieving the allyl alcohol in 82-85% yield. In PMR spectrum, resonances of olefinic protons moved upfield and were observed in the region 5.58-5.78 ppm as multiplets. The compound **94** showed the characteristic resonance of isopropoxy methine proton at 3.72 ppm (heptate, 1H, J = 6.1 Hz) and methyl protons at 1.16 ppm (d, 6H, J = 6.1 Hz). In ^{13}C NMR, the absence of the quaternary carbon of the isopropylidine ring confirmed the ring opening product **94** (Scheme 10).



Scheme 10

Now the platform was set for a Sharpless asymmetric epoxidation[32] that would install the chiral center relevant to the target. SAE figures prominently in modern asymmetric synthesis for external chiral induction for two contiguous chiral centers under passive substrate control because of factors like (i) oxidation of wide spectrum of substrates with different substituent patterns including meso compounds (ii) inexpensive reagents (iii) compatibility of various functional groups (iv) excellent ee's (v) feasibility of either enantiomeric product (vi) predictability of product configuration by mnemonic device. Thus, catalytic asymmetric epoxidation of appropriate precursor **78** was conducted at -20 °C with *t*-butyl hydrogen peroxide as oxo donor and $Ti(O^iPr)_4$- [(+)-

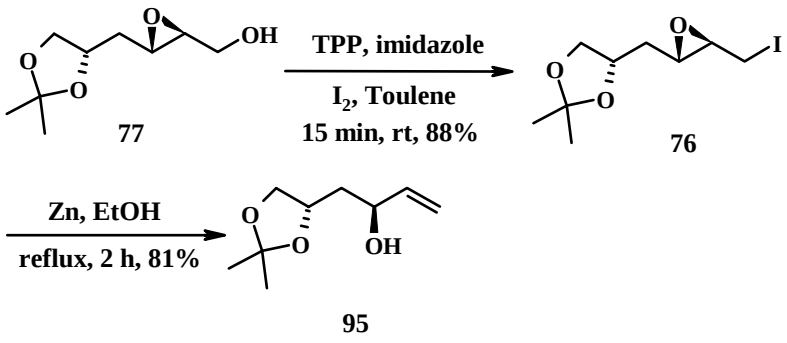
DET] complex as chiral adjuvant in anhydrous CH_2Cl_2 in presence of activated 4A° molecular sieves powder to afford (2*S*, 3*S*)-epoxide **77** in 89% yield.



Scheme 11

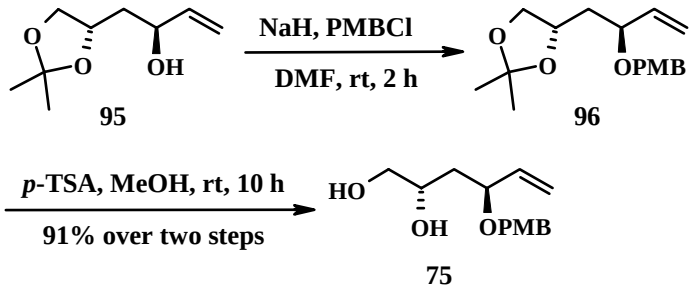
The epoxy alcohol **77** gave satisfactory spectral data with singular peaks indicating single diastereomer formation. The ^{1}H NMR spectrum illustrated new resonances attributed to methine protons of epoxide at 3.60 ppm (dd, 1H, J = 6.82, 8.0 Hz), and 3.67 ppm (dd, 1H, J = 12.1, 16.2 Hz), while the involved carbons resonated at 53.0 and 58.7 ppm in ^{13}C NMR spectrum. In addition, the elemental analysis data supported it (Scheme 11).

Conversion of epoxy methanol **77** to corresponding epoxy methyl iodide **76** was smooth as the exposure to triphenylphosphine, imidazole and iodine in toluene at room temperature resulted the iodo compound **76** in good yield. The iodo compound was stable to silica gel column chromatography, but susceptibility to high temperature was observed while removing toluene (solvent used in the reaction) in vacuo. The epoxy methyl iodide compound **76** was decomposing favorably to our next intermediate, the secondary allyl alcohol **95**. Both the products were reliably confirmed by the analysis of the ^{1}H NMR, ^{13}C NMR, IR and EI mass spectra. In the ^{1}H NMR spectrum of **76**, upfield shift of peaks belonging to methylene protons (C$\underline{H}_2$I) compared to that of **77** was noticed. This was further confirmed by a peak at (*m/z*) 321 $[M+Na]^+$ in the EI mass spectrum. Quantitative conversion of the epoxy methyl iodide **76** to the secondary allylic alcohol **95** was achieved with activated Zn dust in refluxing EtOH.[33] The ^{1}H NMR spectrum of the secondary alcohol **95** showed characteristic terminal olefin peaks at 5.12 ppm (dt, 1H, J = 1.5, 10.4 Hz), 5.28 ppm (dt, 1H, J = 1.5, 17.2 Hz), 5.90 ppm (ddd, 1H, J = 5.4, 10.4, 17.2 Hz) and a broad singlet at 2.49 ppm for the hydroxyl proton (Scheme 12).



Scheme 12

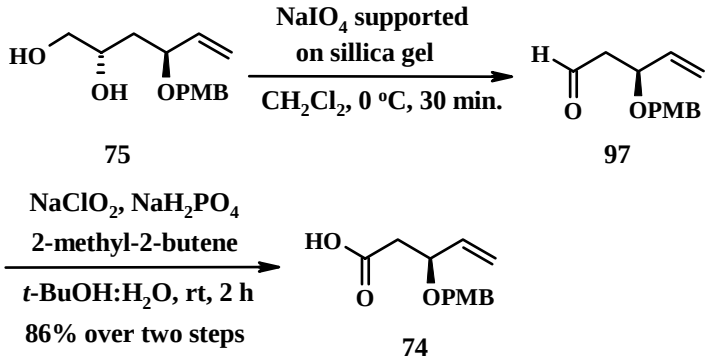
The secondary hydroxyl group was then protected as its PMB ether by reaction with PMBCl, being activated by NaH in DMF at room temperature in good yield. Close proximity of R_f values of the product **96** and PMBCl made the purification and characterization of the new intermediate difficult. However, the next acid catalysed deketalization of the acetal moiety in protic solvent (MeOH) resulted in a highly polar diol intermediate **75**, which could be purified and characterized completely. The new A_2B_2 doublets at 6.87 ppm and 7.25 ppm with *J* value 8.8 Hz (for aromatic ortho coupling) alongwith the singlet at 3.79 ppm for Ar-OC$\underline{H}_3$ signals the introduction of the *p*-methoxybenzyl moiety (Scheme 13).



Scheme 13

In order to secure the acid fragment **74**, the diol **75** was oxidatively cleaved using $NaIO_4$ support on silica gel to afford aldehyde **97**, which was subsequently transformed to carboxylic acid *via* Pinnick oxidation[34] ($NaClO_2$ in presence of NaH_2PO_4 buffer and 2-methyl-2-butene as a scavenger) in 86% yield. In proton NMR spectrum, resonances of α-methylene protons to acid appeared at 2.54 ppm (dd, 1H, *J* = 5.3, 15.4 Hz), and 2.70 ppm (dd, 1H, *J* = 8.1, 15.4 Hz) alongwith the corresponding carbon at 40.8 ppm. The

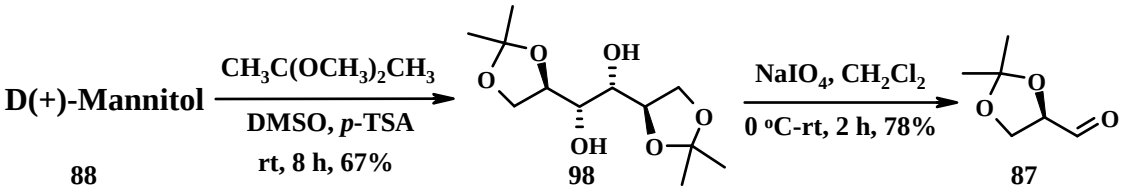
exchangeable acidic proton resonated at a very low magnetic field (8.57 ppm) and the acid carbonyl carbon appeared at 175.9 ppm (Scheme 14).



Scheme 14

Synthesis of alcohol Fragment (73):

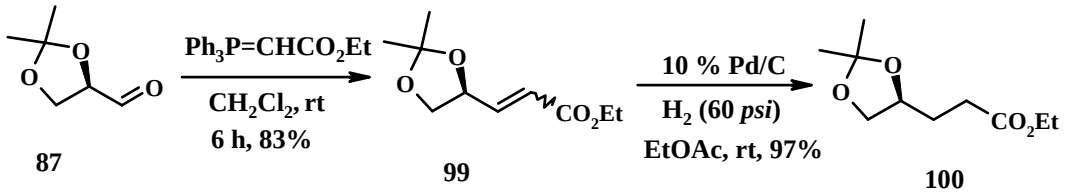
Retrosynthetic analysis outlined in scheme 5 suggested that the allyl alcohol **85** could be a key synthetic intermediate and objective for the construction of alcohol fragment **73**. The synthesis of **85**, commenced from commercially available D-mannitol (**88**), which was converted to 1,2:5,6-*O*-diisopropylidine-D-mannitol (**98**) in 67% yield by treatment with 2,2'-dimethoxypropane and catalytic *p*-toulenesulfonic acid in DMSO at room temperature. Subsequently, the 3,4-glycol linkage of **98** was oxidatively cleaved with sodium metaperiodate supported on silica gel to provide 2,3-*O*-isopropylidene-D-glyceraldehyde (**87**) in 78% yield. ^{1}H NMR, ^{13}C NMR, IR spectra and elemental analysis data were in good agreement with reported values[35] (Scheme 15).



Scheme 15

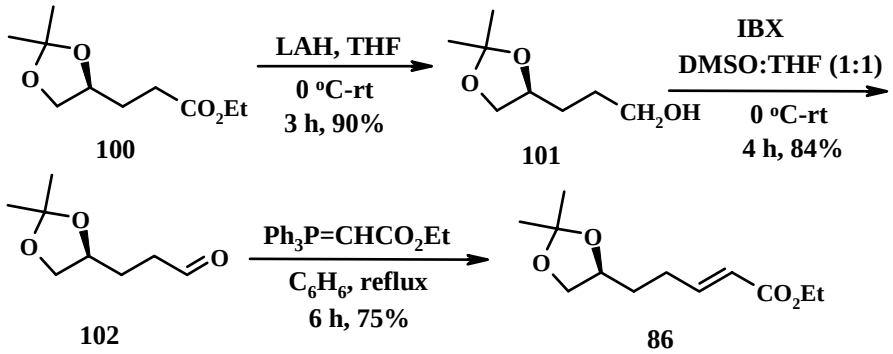
The D-glyceraldehyde derivative **87**, when subjected to two-carbon Wittig olefination using (ethoxycarbonylmethylene)triphenylphosphorane in CH_2Cl_2 at room temperature for 6 h, yielded the conjugated ester **99** as a mixture of geometrical isomers (*E* and *Z*) in 83% yield. Since the geometry of the double bond in **99** was of no

immediate consequence (it would be hydrogenated in the subsequent step), the mixture was carried forward for the next reaction. Compound **99** was next subjected to heterogeneous catalytic hydrogenation with 10% Palladium on activated carbon powder at a H_2 pressure of 60 *psi* at room temperature to afford **100** in quantitative yield (97%) (Scheme 16).



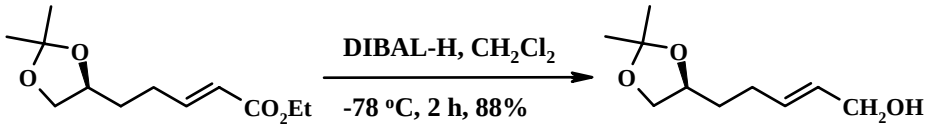
Scheme 16

For further elongation of the carbon chain by two carbons, the ester **100** was subjected to reductive transformation with lithium aluminium hydride in anhydrous THF at 0 °C-room temperature for 3 h to furnish the alcohol **101** in 90% yield (Scheme 17). The primary hydroxy group was next oxidized with IBX in DMSO and THF solvent mixture at room temperature to afford the corresponding aldehyde, which was quickly exposed to stable Wittig ylide, (ethoxycarbonylmethylene)triphenylphosphorane in benzene at reflux, to furnish **86** as a mixture of *E* and *Z* isomers in ratio 9:1 (From TLC). The major *E* isomer could be characterized on the basis of spectral studies. The ^{1}H NMR spectrum showed characteristic coupling constant (J = 15.7 Hz) for olefinic protons {resonated at 5.84 ppm (d, 1H) and 6.96 ppm (dt, 1H)}. The relevant resonances due to the ester group $CO_2C\underline{H}_2C\underline{H}_3$ (triplet at 1.29 and quartet at 4.18 ppm) further confirmed the product **86**. The ^{13}C NMR spectrum displayed olefin carbons at 121.7 ppm, 147.7 ppm and 166.1 ppm corresponding to C=O group.



Scheme 17

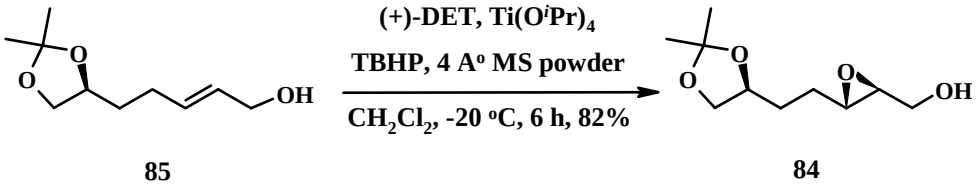
Selective reductive transformation of the ester was next undertaken with DIBAL-H in anhydrous CH_2Cl_2 at -78 °C for 2 h to afford the key precursor **85** in 88% yield (Scheme 18). The structural integrity of the product **85** was adequately confirmed by NMR and IR spectral studies. In the ^1H NMR spectrum, resonances due to olefinic protons moved upfield and were observed between 5.66-5.71 ppm; methylene group of ally alcohol was localized between 3.99-4.08 ppm. The ^{13}C NMR spectral signals the absence of specified ethoxycarbonyl peaks. The IR spectrum showed a broadband absorption at 3422 cm^{-1}.



86 **85**

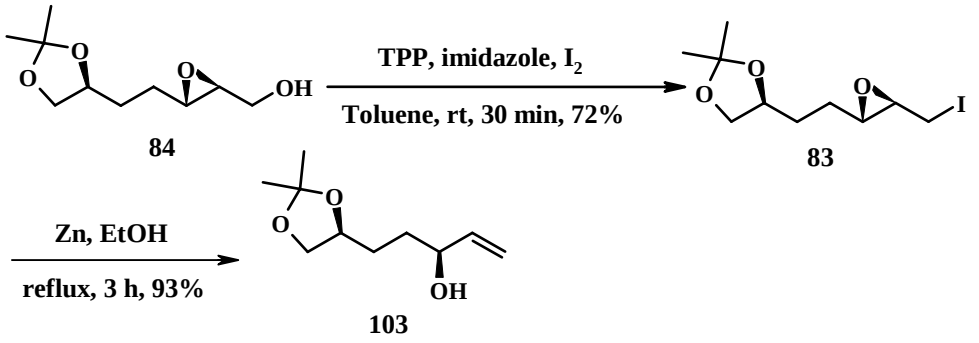
Scheme 18

After achieving the suitable precursor, Sharpless asymmetric epoxidation in a catalytic fashion was planned next, that would install the second chiral center relevant to the target. Thus, **85** was treated with (+) DET-Ti(O^iPr)$_4$ complex as the chiral ligand, and TBHP (the oxo donor) at -20 °C, in anhydrous CH_2Cl_2 in presence of activated 4A° molecular sieves powder to furnish (2*S*,3*S*)-epoxide **84** in 82% yield. The NMR spectrum, elemental analysis was in good agreement with the structural features (Scheme 19). In the ^1H NMR spectrum, the epoxide showed absence of the resonances corresponding to the olefin protons of allylic alcohol in the region of 5.66-5.71 ppm (m, 2H). New resonances attributed to methine protons of epoxide were apparent at 2.87-3.02 ppm along with other proton resonances attributable to assigned structure of **84**. ^{13}C NMR spectrum showed absence of resonances corresponding to olefinic carbons with the appearance of bright resonances at 55.2, and 58.4 ppm corresponding to epoxy carbons. In addition, elemental analysis data supported the formation of **84**.



Scheme 19

The next challenge, deoxygenation of epoxide to secondary allylic alcohol in high regioselectivity, was achieved through base mediated ring opening of the corresponding epoxymethyl iodide **83**. The epoxymethyl iodide **83** was synthesized by nucloephilic displacement of the hydroxy group by iodide ion. A mixture of triphenyl phosphine, imidazole and iodine in toluene resulted the nucleophillic displacement transformation.

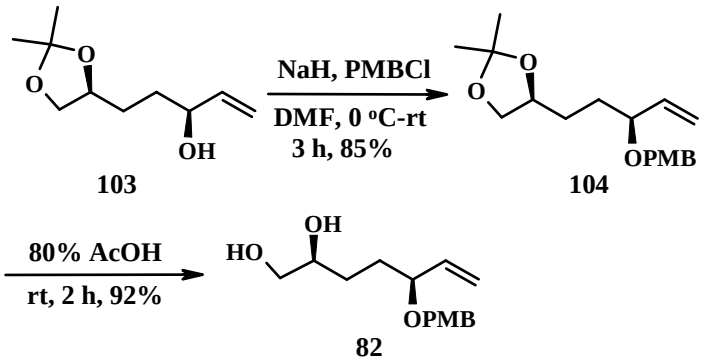


Scheme 20

Direct reduction of compound **83** with commercial zinc dust gave the diastereomerically pure terminal alkenic alcohol **103** in 93% yield (Scheme 20).[33] The spectral information from ^{1}H NMR, ^{13}C NMR, IR and HRMS studies proved the structure of **103** beyond doubt. In PMR spectrum, characteristic terminal olefin signals between 5.11-5.87 ppm were observed; in CMR spectrum corresponding carbons surfaced at 114.5, 140.9 ppm respectively.

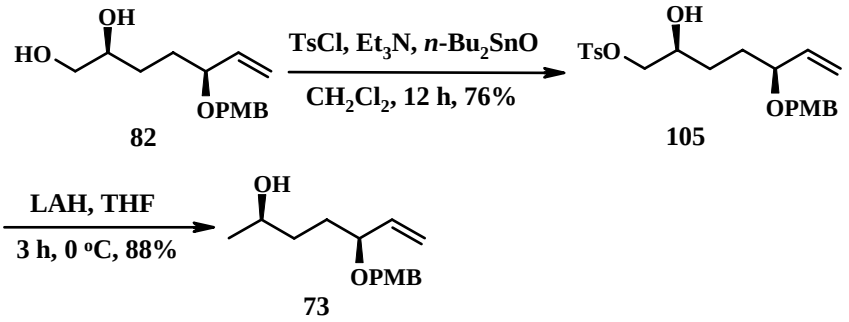
The secondary alcohol **103** was converted to its *p*-methoxybenzyl ether **104** using NaH, PMBCl in DMF at room temperature in quantitative yield. The *p*-methoxybenzyl group at this stage served a dual purpose: protection of functionality for next couple of steps and as a template for the study of geometrical outcome of the RCM reaction in the final stage. The later was pivotal to our efforts in the synthesis of 10 membered lactones, where the double bond precursor is flanked by hydroxyl groups. The protection was

confirmed by the presence of new resonances at 4.27 ppm, 4.53 ppm for benzyl methylene protons, at 3.81 ppm corresponding to aromatic methoxy group and in 6.75-7.80 ppm as A_2B_2 pattern for the aromatic protons. The isopropylidene group of **104** was hydrolyzed under acidic conditions with 80% AcOH at room temperature, to furnish **82** in 92% yield. The structure was unambiguously corroborated from the combined spectral data of ^{1}H NMR, ^{13}C NMR and elemental analysis. In the IR spectrum broad absorption band at 3409 cm^{-1} corresponding to hydroxyl group was present (Scheme 21).



Scheme 21

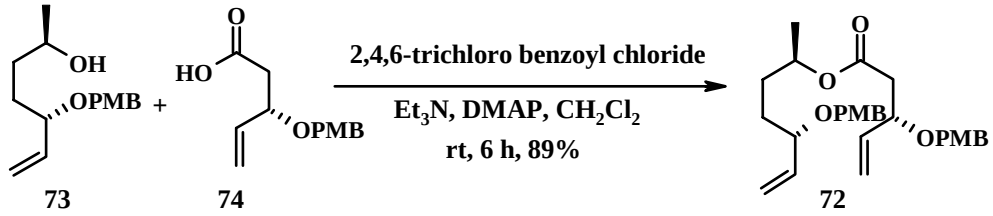
In order to secure the alcohol fragment **73**, primary hydroxyl group of diol was selectively deoxygenated by hydro-detosylation of the corresponding primary sulfonate compound **105**. The diol **82** was selectively converted to its *p*-toluenesulphonate derivative **105** by reaction with TsCl, Et_3N, *n*-Bu_2SnO in CH_2Cl_2 at 0 °C to room temperature for 12 h in 76% yield.[36] The structure was confirmed by the presence of additional peaks in the ^{1}H NMR spectrum due to tosylate group, i.e., a singlet at 2.45 ppm for aryl methyl and a A_2B_2 peak between 7.18-7.80 ppm for the *ortho* aromatic protons. The hydro-detosylation protocol was executed by treating compound **105** with excess of lithium aluminium hydride at 0 °C for 3 h in dry THF to provide requisite coupling partner **73** in 88% yield. New resonances due to methyl group at δ 1.16 (d, 3H, *J* = 6.2 Hz) in PMR, corresponding carbon at 23.3 ppm in CMR reasonably attributed to the structure **73**, with additional support from elemental analysis and ESI mass spectral studies (Scheme 22).



Scheme 22

Coupling between the acid fragment and the alcohol fragment:

The two bifunctional coupling partners having functional groups at both end, may unite in two ways to form the cyclic lactone compounds. Either cross metathesis followed by lactonization or esterification followed by ring closing metathesis are the reaction sequences for the synthesis of these 10 membered lactones. In our protcol, we adopted the later sequence so as to observe and generalize the outcome of RCM reaction of the protected ester **72** and the naked ester **70**. So Yamaguchi's protocol[37] was then employed to unite both the fragments to furnish the diolefinic ester **72** in 89% yield. The product **72** was confirmed for its structure by the ^{1}H NMR spectrum with clinching evidence from ^{13}C NMR, IR, ESI-mass spectral data (Scheme 23).

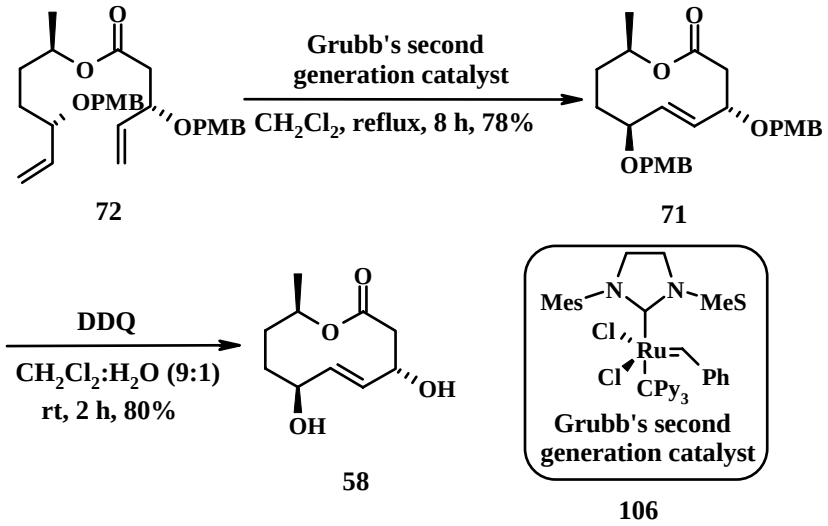


Scheme 23

RCM reaction of the protected diolefinic ester 72:

The key precursor **72** was treated with Grubbs second generation catalyst[30] in dry, degassed CH_2Cl_2 under reflux for 8 h to provide the desired 10-membered lactone **71** with *E*-geometry of the olefin as the exclusively product in 78% yield. The exclusive *E* isomer, showed distinct coupling constant (J = 16.1 Hz) for olefinic protons in the PMR spectrum. The other protons resonated at routine positions. The synthesis of

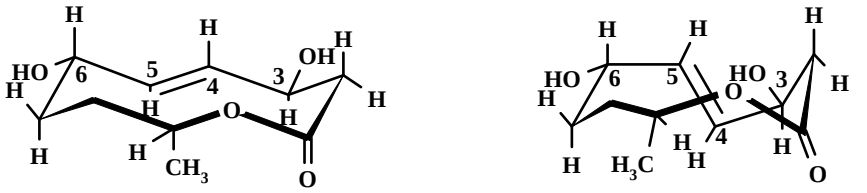
decarestrictine C_1 was culminated by deprotection of the PMB groups with DDQ in biphasic solvent mixture of CH_2Cl_2 and water at room temperature in 80% yield (Scheme 24).



Scheme 24

Existence of conformational isomers in solution:

The product, obtained by the deprotection of *p*-methoxybenzyl ether group, showed a mixture of two compounds in ^{1}H NMR spectrum, while the *p*-methoxybenzyl ether derivative of the natural product **71** was observed as a single compound in the ^{1}H NMR spectrum. Expecting no epimerization in DDQ mediated deprotection, we assumed the existence of different conformers in solution state, which are not interconvertible at room temperature. The major factor inhibiting the interconvertibility might be attributed to the intramolecular hydrogen bonding, which was absent in case of compound **71**. We examined the NMR spectrum of compound **58** at various temperatures, ranging from -40 °C to 110 °C. We observed that the conformers coalesce at 110 ^{o}C as observed from ^{1}H NMR of decarestrictine C_1 (**58**) in DMSO-d_6. 2D NMR experiments (COSY, NOESY, HMBC, HSQC) were also used for the confirmation of two conformational isomers at room temperature.



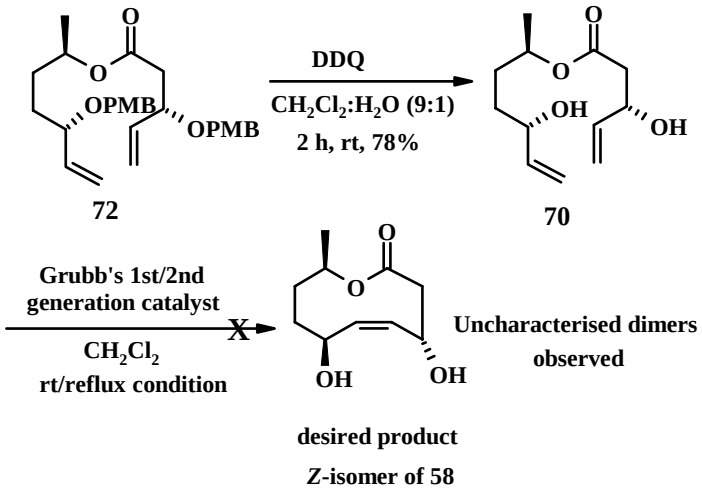
Conformational isomer I **Conformational isomer II**

Figure 15

Literature survey[38] allow us to propose two conformers (Figure 15). The energy difference between these two conformational isomers (which is not attained at room temperature) is attributed to the hydrogen bonding between suitably placed hydroxyl groups and the lactone oxygen.

RCM reaction of the naked-hydroxy diolefinic ester 70:

Despite its effectiveness in the synthesis of rings of all sizes, two factors still limit the scope of the RCM reaction; (i) in ring sizes ≥8, no control over *E*/*Z* stereochemistry of the double bond generated is possible. Stereochemical control is probably of thermodynamic origin,[39](ii) the reports that describe application of the RCM to medium sized-particularly 10-membered rings, are still rare, especially when dense functionality close to the reaction centre is involved.[40]Recently our group reported[28c] the substrate oriented stereoselective formation of both isomers in RCM reaction.



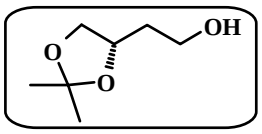
Scheme 25

Further enquiry into the result of the RCM reaction in our substrate was executed with the naked-hydroxy diolefinic ester **70**. For the same, the two ether linkages were deprotected to the free hydroxy derivative by DDQ in CH_2Cl_2:H_2O at room temperature in 78% yield. The RCM reaction was next carried out with the diol **70** with Grubbs' second-generation catalyst in CH_2Cl_2 under reflux. TLC showed the starting material to be completely reacted after 2h, yielding two polar separable spots. Those two spots were dimmers, assigned mainly from the ESI-mass spectrum and PMR and CMR spectral studies. Assuming the substrate to be very active towards RCM reaction, we changed the reaction conditions, substituting Grubbs' second-generation catalyst with 1st generation catalyst; refluxing condition to room temperature reaction. The result was the same two spots each time (Scheme 25).

EPILOGUE:

We have successfully synthesized decarestrictine C_1 by employing a convergent synthetic route with ring closing metathesis as the key step. This route exemplifies coupling of two different fragments, coupled via esterification and ring closing metathesis sequentially. Both the fragments have been synthesized in a similar fashion: Sharpless asymmetric epoxidation introduced chirality. We believe that this synthetic sequence can be a stepping stone for synthesis of 10- membered lactones in general and other decarestrictines in particular.

(*S*)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (**80**):



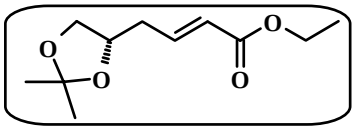
$LiAlH_4$ (4.8 g, 126 mmol) in dry THF (30 mL) was cooled to 0 °C. Then the ester compound **91** (11 g. 63 mmol) in THF (50 mL) was added slowly through an addition funnel. The reaction mixture was stirred at room temperature for 3 h. Then the reaction mixture was quenched with saturated aqueous Na_2SO_4 till the suspension turned from grey to white. After that it was filtered through a small pad of celite. The filtrate was concentrated and purified by column chromatography using EtOAc:petroleum ether (1:4) as eluent to get the acetonide alcohol **80** (8.95 g, 97%) as a colorless liquid.

The triol **92** (13.5 g, 127.36 mmol) was dissolved in dry acetone (100 mL) and to it catalytic amount of *p*-TSA (242 mg, 12.7 mmol) was added. The reaction mixture was stirred at room temperature for 12 h. TLC showed the completion of reaction. The reaction mixture was quenched with dry Et_3N and the solvent was evaporated in vacuo at room temperature and the crude product was purified by column chromatography using EtOAc:petroleum ether (1:4) as eluent to get the 5-membered acetonide **80** with trace amount of 6-membered acetonide (observed from ^{13}C NMR) (17.66 gm, 95%) as a colorless liquid.

Mol. Formula	:	$C_7H_{14}O_3$
Mol. Weight	:	146.19
ESI-MS *m/z*	:	169.16 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 57.51; H, 9.65
		Found: C, 57.69; H, 9.78
^{1}H NMR	:	δ 1.36 (s, 3H), 1.42 (s, 3H), 1.81 (m, 2H), 2.37 (bs, 1H),
(200 MHz, $CDCl_3$)		3.59 (dd, 1H, *J* = 7.8, 7.3 Hz), 3.79 (t, 2H, *J* = 5.7 Hz),
		4.08 (dd, 1H, *J* = 5.9, 8.0 Hz), 4.26 (p, 1H, *J* = 6.0 Hz)
^{13}C NMR	:	δ 25.6 (q), 26.8 (q), 35.7 (t), 60.0 (t), 69.3 (t), 74.6 (d),

(125 MHz, $CDCl_3$) 108.8 (s)

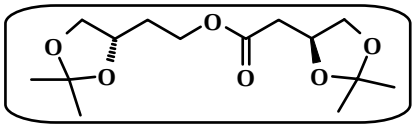
(*S*,*E*)-ethyl 4-(2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enoate (**79**):



The alcohol **80** (11.2g, 84.85 mmol) was dissolve in DMSO (100 mL) and to it IBX (26.9 g, 101.82 mmol) was added slowly while cooling the reaction mixture in cold water. The reaction mixture as stirred at rt for 2 h. After completion of the oxidation reaction, stable two carbon Wittig ylide (ethoxycarbonylmethylene)triphenylphosphorane (35.43 g, 101.82 mmol) in 75 mL DMSO was added and the reaction mixture was stirred at room temperature for 5 h. Then the reaction mixture was quenched with aqueous $NaHCO_3$ solution and the colloidal solution was filtered with a sintered funnel. The filtrate was extracted with ethyl acetate. The combined organic layer was washed with water and brine solution. Then the organic portion was dried over Na_2SO_4, concentrated and purified by column chromatography using EtOAc:petroleum ether (1:9) as eluent to give *E* olefin **79** (13.95 g, 85%) as a colorless liquid.

Mol. Formula	:	$C_{11}H_{18}O_4$
Mol. Weight	:	214.26
ESI-MS *m/z*	:	237.15 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 61.66; H, 8.47 Found: C, 61.85; H, 8.63
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 1.29 (t, 3H, *J* = 7.15 Hz), 1.35 (s, 3H), 1.42 (s, 3H), 2.34-2.60 (m, 2H), 3.57 (dd, 1H, *J* = 6.6, 8.1 Hz), 4.05 (dd, 1H, *J* = 6.1, 8.1 Hz), 4.18 (q, 2H, *J* = 7.2 Hz), 4.21 (m, 1H), 5.89 (dt, 1H, *J* = 1.5, 15.7 Hz), 6.91 (dt, 1H, *J* = 7.2, 15.7 Hz)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 14.3 (q), 25.6 (q), 26.9 (q), 36.5 (t), 60.2 (t), 68.8 (t), 74.2 (d), 109.3 (s), 123.9 (d), 143.6 (d), 166.0 (s)

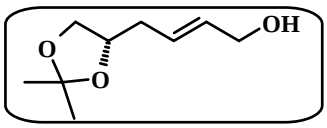
2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl 2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl) acetate (**93**):



The sequential oxidation of compound **80** by PDC oxidation procedure or PCC oxidation procedure followed by two carbon Wittig homologation as above resulted a 1:1 mixture of the *E* olefin **79** and ester **93** (viscous liquid).

Mol. Formula	:	$C_{14}H_{24}O_6$
Mol. Weight	:	288.34
ESI-MS *m/z*	:	301.05 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 58.32; H, 8.39 Found: C, 58.47; H, 8.59
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 1.34 (s, 3H), 1.35 (s, 3H), 1.40 (s, 3H), 1.41 (s, 3H), 1.83-1.95 (m, 2H), 2.50 (dd, 1H , *J* = 6.4, 16.0 Hz), 2.60 (dd, 1H, *J* = 7.1, 16.0 Hz), 3.56 (dd, 1H, *J* = 6.8, 7.7 Hz), 3.64 (dd, 1H, *J* = 6.4, 8.3 Hz), 4.02-4.22 (m, 4H), 4.27 (m, 1H), 4.45 (m, 1H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 25.5 (q), 25.6 (q), 26.9 (2 ovlp q), 32.8 (t), 38.9 (t), 61.6 (t), 69.1 (t), 69.2 (t), 72.0 (d), 73.0 (d), 108.9 (s), 109.2 (s), 170.4 (s)

(*S*,*E*)-4-(2,2-dimethyl-1,3-dioxolan-4-yl)but-2-en-1-ol (**78**):

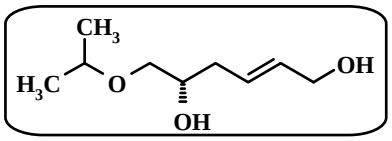


The *E* olefin **79** (12.5 g, 58.41 mmol) was dissolved in CH_2Cl_2 (50 mL) and cooled to -78 °C. To it DIBAL-H (73 mL of 2M solution in toluene, 146 mmol) was added dropwise and the reaction mixture was stirred at -78 °C for 2 h. After the completion of the reaction, it was quenched with aqueous sodium potassium tartarate solution and

stirred at room temperature for 30 min. Then the two layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over Na_2SO_4, concentrated and purified by column chromatography using EtOAc:petroleum ether (4:6) as eluent to yield the trans allylic alcohol **78** (8.54 g, 85%) as a viscous liquid.

Mol. Formula	:	$C_9H_{16}O_3$
Mol. Weight	:	172.23
ESI-MS *m/z*	:	195.12 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 62.77; H, 9.36
		Found: C, 62.98; H, 9.16
$[\alpha]_D^{25}$	:	+8.2 (*c* 1, MeOH)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 1.35 (s, 3H), 1.41 (s, 3H), 2.21-2.45 (m, 3H), 3.56 (dd, 1H, *J* = 6.7, 7.8 Hz), 4.02 (dd, 1H, *J* = 6.1, 7.8 Hz), 4.08 (m, 2H), 4.16 (dd, 1H, *J* = 6.3, 12.8 Hz), 5.58-5.8 (m, 2H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 25.5 (q), 26.8 (q), 36.4 (t), 63.1 (t), 68.7 (t), 75.2 (d), 108.9 (s), 127.0 (d), 132.2 (d)

(*S*,*E*)-6-isopropoxyhex-2-ene-1,5-diol (**94**):

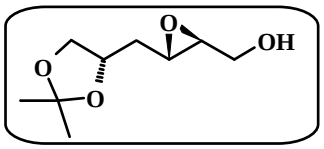


The reduction of the unsaturated ester by DIBAL-H at a higher temperature beyond -50 °C or fast addition of DIBAL-H was resulting mixture of products, i.e. allylic alcohol **78** and diol **94**. The proportion of the diol was increasing with the increase in reaction temperature, but not with time.

Mol. Formula	:	$C_9H_{18}O_3$
Mol. Weight	:	174.24
ESI-MS *m/z*	:	197.19 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 62.04; H, 10.41

		Found: C, 62.16; H, 10.55
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 1.16 (d, 6H, *J* = 6.1 Hz), 2.26 (t, 2H, *J* = 5.5 Hz), 2.55 bs, 2H), 3.41-3.60 (m, 3H), 3.72 (heptate, 1H, *J* = 6.1 Hz), 4.07 (d, 2H, *J* = 3.5 Hz), 5.67 (m, 2H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 22.4 (q), 22.9 (q), 34.4 (t), 62.9 (t), 63.9 (t), 70.3 (d), 76.9 (d), 127.5 (d), 131.9 (d)

((2*S*,3*S*)-3-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)oxiran-2-yl)methanol (**77**):

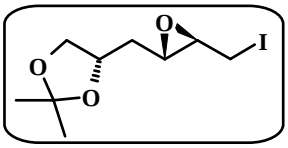


Flame dried powdered 4 A° molecular sieves (5 g) were taken with dry CH_2Cl_2 (50 mL) in a dry clean two neck round bottom flask. To it (+) DET (1.9 mL, 8.7 mmol) was added and cooled to -20 °C followed by $Ti(O^iPr)_4$ (1.7 mL, 5.8 mmol). After 10 min, *t*-BuOOH (10 mL 5-6M solution in decane, 58 mmol) was added to the reaction mixture and stirred at -20 °C for 30 min. Then a CH_2Cl_2 (15 mL) solution of the allylic alcohol **78** (5g, 29 mmol) was added slowly and the stirring was continued for 12 h. After completion of the reaction, it was quenched with 2 mL of saturated aqueous solution of NaOH and NaCl (1:9). The mixture was filtered through a small pad of celite and concentrated. The crude product was purified by column chromatography using EtOAc:petroleum ether (1:1) as eluent to get the (*S*,*S*) epoxide **77** (4.86 g, 89%) as a viscous liquid.

Mol. Formula	:	$C_9H_{16}O_4$
Mol. Weight	:	188.23
ESI-MS *m/z*	:	211.15 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 57.43; H, 8.57
		Found: C, 57.31; H, 8.76
$[\alpha]_D^{25}$	:	-33.3 (*c* 1, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 1.37 (s, 3H), 1.42 (s, 3H), 1.62 (ddd, 1H, *J* = 5.1, 7.6, 13.9 Hz), 1.98 (ddd, 1H, *J* = 4.1, 7.6, 13.9 Hz), 2.14 (bs,

		1H), 2.96 (m, 1H), 3.11 (m, 1H), 3.60 (dd, 1H, *J* = 6.82, 8.0 Hz), 3.67 (dd, 1H, *J* = 12.1, 16.2 Hz), 3.90 (dd, 1H, *J* = 3.5, 12.6 Hz), 4.11 (dd, 1H, *J* = 8.1, 6.1 Hz), 4.30 (m, 1H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 25.5 (q), 26.8 (q), 36.2 (t), 53.0 (d), 58.7 (d), 61.5 (t), 69.2 (t), 73.4 (d), 109.0 (s)

(*S*)-4-(((2*S*,3*R*)-3-(iodomethyl)oxiran-2-yl)methyl)-2,2-dimethyl-1,3-dioxolane (**76**):

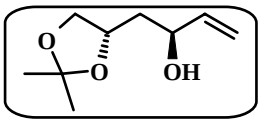


The alcohol **77** (2.4 g, 12.77 mmol) was dissolved in toluene (30 mL). To it imidazole (1.074 g, 25.53 mmol), triphenyl phosphine (4.02 g, 15.32 mmol) and iodine (3.89 g, 15.32 mmol) was added sequentially keeping the reaction temperature at 25 °C and the reaction mixture was stirred at room temperature for 15 min. As TLC showed the completion of the reaction, it was concentrated in vacuo and purified by column chromatography using EtOAc:petroleum ether (1:9) as eluent to get the iodo compound **76** (3.35 g, 88%) as a yellow liquid.

Mol. Formula	:	$C_9H_{15}IO_3$
Mol. Weight	:	298.12
ESI-MS *m/z*	:	321.09 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 36.26; H, 5.07; I, 42.57 Found: C, 36.45; H, 5.31; I, 42.68
$[\alpha]_D^{25}$	:	-8.9 (*c* 1.4, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 1.36 (s, 3H), 1.42 (s, 3H), 1.62 (m, 1H), 1.98 (m, 1H), 2.95 (ddd, 1H, *J* = 1.5, 3.3, 7.4 Hz), 3.04 (m, 1H), 3.09 (dd, 1H, *J* = 1.5, 6.3 Hz), 3.20 (dd, 1H, *J* = 2.2, 8.8 Hz), 3.57 (dd, 1H, *J* = 2.2, 7.4, 8.1 Hz), 4.08 (ddd, 1H, *J* = 2.7, 6.0, 8.0 Hz), 4.25 (m, 1H)
^{13}C NMR	:	δ 4.3 (t), 25.6 (q), 27.0 (q), 36.2 (t), 58.4 (d), 59.4 (d),

(50 MHz, $CDCl_3$) 69.2 (t), 73.1 (d), 109.9 (s)

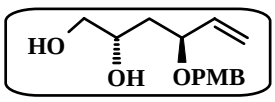
(*S*)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-2-ol (**95**):



The iodo compound **76** (2.6 g, 8.7 mmol) in ethanol was mixed with activated Zn dust (2.85 g, 43.62 mmol). The resulted suspension was refluxed for 2 h. The suspension was filtered through a small pad of celite and the filtrate was concentrated and purified by column chromatography using EtOAc:petroleum ether (3:7) as eluent to obtain terminal olefin **95** (1.21 g, 81%) as colorless liquid.

Mol. Formula	:	$C_9H_{16}O_3$
Mol. Weight	:	172.23
ESI-MS *m/z*	:	195.18 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 62.77; H, 9.36
		Found: C, 62.55; H, 9.48
$[\alpha]_D^{25}$	:	+7.3 (*c* 1, $CHCl_3$)
^{1}H NMR	:	δ 1.36 (s, 3H), 1.42 (s, 3H), 1.79 (ddABq, 2H, *J* = 3.5,
(200 MHz, $CDCl_3$)		3.7, 4.7, 4.6, 7.7, 7.8, 8.2, 8.1, 14.2 Hz), 2.49 (br s, 1H),
		3.57 (t, 1H, *J* = 7.7 Hz), 4.07 (dd, 1H, *J* = 6.0, 8.1 Hz),
		4.33 (m, 2H), 5.12 (dt, 1H, *J* = 1.5, 10.4 Hz), 5.28 (dt, 1H,
		J = 1.5, 17.2 Hz), 5.90 (ddd, 1H, *J* = 5.4, 10.4, 17.2 Hz)
^{13}C NMR	:	δ 25.7 (q), 27.0 (q), 39.8 (t), 69.5 (t), 70.0 (d), 73.8 (d),
(50 MHz, $CDCl_3$)		108.9 (s), 114.5 (t), 140.6 (d)

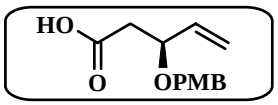
(2*S*,4*S*)-4-(4-methoxybenzyloxy)hex-5-ene-1,2-diol (**75**):



NaH (0.419 g of 60% suspension in paraffin oil, 10.47 mmol) was added to a DMF solution (10mL) of the alcohol **95** (0.9 g, 5.23 mmol) at 0 °C. After stirring the reaction mixture for 15 min, PMBCl (1.42 mL, 10.47 mmol) was added slowly and the reaction mixture was stirred at room temperature for 2 h. Then it was quenched by water and the layers were separated. The aqueous layer was washed with ethyl acetate and the combined organic layer was dried over Na_2SO_4, concentrated and purified by column chromatography. The resulted compound **96** was dissolved in MeOH (8 mL) and to it catalytic amount of *p*-TSA was added. The mixture was stirred at room temperature for 10 h. Then it was quenched with Et_3N. The reaction mixture was concentrated and purified by column chromatography using EtOAc:petroleum ether (7:3) as eluent to get the pure diol **75** (1.2g, 91%) as a highly viscous liquid.

Mol. Formula	:	$C_{14}H_{20}O_4$
Mol. Weight	:	252.31
ESI-MS *m/z*	:	275.19 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 66.65; H, 7.99 Found: C, 66.78; H, 8.23
$[\alpha]_D^{25}$	:	-34.1 (*c* 1, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 1.58-1.78 (m, 2H), 2.82 (bs, 2H), 2.91 (d, 1H, *J* = 14.7 Hz), 3.42 (dd, 1H, *J* = 7.1, 10.1 Hz), 3.48 (dd, 1H, *J* = 3.1, 10.1 Hz), 3.79 (s, 3H), 4.08 (m, 1H), 4.28 (d, 1H, *J* = 11.3 Hz), 4.55 (d, 1H, *J* = 11.3 Hz), 5.29 (m, 2H), 5.81 (ddd, 1H, *J* = 7.3, 10.2, 17.2 Hz), 6.87 (d, 2H, *J* = 8.8 Hz), 7.25 (d, 2H, *J* = 8.8 Hz)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 38.3 (t), 55.2 (q), 66.6 (t), 69.0 (d), 70.0 (t), 77.2 (d), 113.8 (d), 117.2 (t), 129.4 (d), 130.1 (s), 138.0 (d), 159.1 (s)

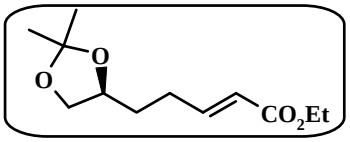
(*S*)-3-(4-methoxybenzyloxy)pent-4-enoic acid (**74**):



The diol **75** (1.05 g, 4.17 mmol) was dissolved in CH_2Cl_2 (15 mL) and silica supported $NaIO_4$ (1.34 g, 6.25 mmol) was added to it. The reaction mixture was stirred at room temperature for 30 min. The suspension was then filtered and the filtrate was concentrated to give the crude aldehyde **97**. The crude aldehyde **97** and 2-methyl-2-butene (0.8 mL, 8.33 mmol) was dissolved in *t*-BuOH: H_2O (9:3 mL) solvent mixture. To it NaH_2PO_4 (1.0 g, 8.33 mmol) was added followed by $NaClO_2$ (0.753 g, 8.33 mmol). The reaction mixture was stirred at room temperature for 2 h. Then the reaction mixture was concentrated in vacuo and partitioned between ethyl acetate and water. The aqueous layer was washed with ethyl acetate. The combine organic layer was dried over Na_2SO_4, concentrated and purified by flash column chromatography using EtOAc:petroleum ether (2:8) as eluent to give the pure acid **74** (0.846 g, 86%) as a colorless liquid.

Mol. Formula	:	$C_{13}H_{16}O_4$
Mol. Weight	:	236.27
ESI-MS *m/z*	:	259.19 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 66.09; H, 6.83 Found: C, 66.27; H, 6.69
$[\alpha]_D^{25}$	:	-32.6 (*c* 1, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 2.54 (dd, 1H, *J* = 5.3, 15.4 Hz), 2.70 (dd, 1H, *J* = 8.1, 15.4 Hz), 3.80 (s, 3H), 4.25 (dt, 1H, *J* = 5.5, 8.1 Hz), 4.34 (d, 1H, *J* = 11.2 Hz), 4.55 (d, 1H, *J* = 11.2 Hz), 5.29 (ddd, 1H, *J* = 0.6, 1.5, 10.1 Hz), 5.33 (ddd, 1H, *J* = 0.9, 1.5, 17.2 Hz), 5.79 (ddd, 1H, *J* = 7.5 10.1, 17.2 Hz), 6.85 (d, 2H, *J* = 8.7 Hz), 7.23 (d, 2H, *J* = 8.7 Hz), 8.57 (br s, 1H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 40.8(t), 55.2 (q), 70.2 (t), 76.2 (d), 113.8 (d), 11.5 (t), 129.5 (d), 136.7 (d), 159.2 (s), 175.9 (s)

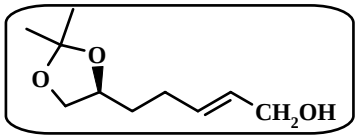
(*S*,*E*)-ethyl 5-(2,2-dimethyl-1,3-dioxolan-4-yl)pent-2-enoate (**86**):



A stirred solution of **101** (12.08 g, 75.4 mmol) in DMSO-THF (1:1, 50 mL) at 0 °C was treated with IBX (25.4 g, 90.7 mmol) in portion wise and allowed to stir at room temperature for 4 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution, filtered through celite and washed with EtOAc. The organic layer was separated and washed with water, brine and dried over Na_2SO_4. Evaporation of the solvent gave **102** (10.02 g, 84%) as a yellow liquid, which was used in subsequent experiments without any further purification. The solution of **102** (9.5 g, 60.0 mmol) in dry benzene (50 mL) was treated with (ethoxycarbonylmethylene)triphenylphosphorane (25.0 g, 71.8 mmol) and heated at reflux for 6 h. The solvent was evaporated and the residue was purified by column chromatography using EtOAc:petroleum ether (1:19) as eluent to afford **86** as pale yellow liquid (10.3 g, 75%).

Mol. Formula	:	$C_{12}H_{20}O_4$
Mol. Weight	:	228.29
ESI-MS *m/z*	:	251.18 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	2987, 2938, 2876, 1722, 1663, 1456, 1372, 1178, 1035, 758.
Elemental Analysis	:	Calcd: C, 63.14; H, 8.83 Found: C, 63.09; H, 8.78
$[\alpha]_D^{25}$	:	+6.0 (*c* 1.0, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 1.29 (t, 3H, *J* = 7.2 Hz), 1.35 (s, 3H), 1.41 (s, 3H), 1.64-1.79 (m, 2H), 2.20-2.40 (m, 2H), 3.52 (t, 1H, *J* = 6.2 Hz), 4.00-4.10 (m, 2H), 4.18 (q, 2H, *J* = 7.2 Hz), 5.84 (dt, 1H, *J* = 1.6, 15.7 Hz), 6.96 (dt, 1H, *J* = 6.8, 15.7 Hz)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 14.1 (q), 25.5 (q), 26.8 (q), 28.3 (t), 31.9 (t), 60.0 (t), 69.0 (t), 74.9 (d), 108.7 (s), 121.7 (d), 147.7 (d), 166.1 (s)

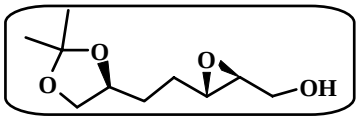
(*S*,*E*)-5-(2,2-dimethyl-1,3-dioxolan-4-yl)pent-2-en-1-ol (**85**):



DIBAL-H (48.3 mL, 96.5 mmol, 2M in toluene) was added to a stirred solution of **86** (10.0 g, 43.8 mmol) in dry CH_2Cl_2 (100 mL) at -20 °C drop wise in 30 min. After 2 h, the reaction mixture was warm to 0 °C and quenched with MeOH (5 mL) to obtain a gelatinous cake. The mixture was diluted with CH_2Cl_2 (100 mL) and stirred for 15 min. A saturated solution of Na-K tartarate (10 mL) was added dropwise and stirred for an additional 45 min. the reaction mixture was filtered through celite and washed with CH_2Cl_2. The organic layer was washed with water, brine, dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography using EtOAc:petroleum ether (3:7) as eluent to afford **85** as a colorless liquid (7.2 g, 88%).

Mol. Formula	:	$C_{10}H_{18}O_3$
Mol. Weight	:	186.25
ESI-MS *m/z*	:	209.18 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	3422, 2986, 2935, 2868, 1670, 1455, 1379, 1216, 1157, 1062, 752
Elemental Analysis	:	Calcd: C, 64.49; H, 9.74 Found: C, 64.26; H, 9.65
$[\alpha]_D^{25}$	:	+15.6 (*c* 1.0, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 1.35 (s, 3H), 1.40 (s, 3H), 1.58-1.72 (m, 3H), 2.07-2.21 (m, 2H), 3.51 (t, 1H, *J* = 6.6 Hz), 3.99-4.08 (m, 4H), 5.66-5.71 (m, 2H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 25.6 (q), 26.8 (q), 28.3 (t), 32.9 (t), 63.1 (t), 69.1 (t), 75.3 (d), 108.6 (s), 129.7 (d), 131.3 (d)

((2*S*,3*S*)-3-(2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)oxiran-2-yl)methanol (**84**):

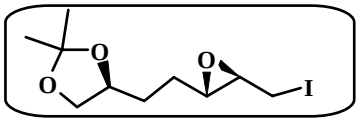


To a stirred and cooled (-20 °C) suspension of molecular sieves (4 A°, 2.0 g) in CH_2Cl_2 (50 mL) under N_2 atmosphere, (+)DET (2.0 g, 9.7 mmol) in CH_2Cl_2 (25 mL), $Ti(O^iPr)_4$ (2.30 g, 8.1 mmol) and TBHP (9.75 mL, 5.0-6.0 M solution in decane, 53.8 mmol) were added sequentially. After 20 min, the resulting mixture was treated with a

solution of **85** (5.0 g, 26.85 mmol) in CH_2Cl_2 (25 mL). After 6 h, the reaction mixture was quenched with 10% NaOH solution in saturated with NaCl (10 mL) and filtered through celite. Evaporation of the solvent and purification of the residue by column chromatography using EtOAc:petroleum ether (1:1) as eluent afforded **84** as a colorless liquid (4.5 g, 82%).

Mol. Formula	:	$C_{10}H_{18}O_4$
Mol. Weight	:	202.25
ESI-MS *m/z*	:	225.17 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 59.39, H, 8.97
		Found: C, 59.35; H, 8.79
$[\alpha]_D^{25}$	:	-22.6 (*c* 1.0, $CHCl_3$)
^{1}H NMR	:	δ 1.34 (s, 3H), 1.40 (s, 3H), 1.67-1.74 (m, 3H), 1.83 (m,
(200 MHz, $CDCl_3$)		1H), 2.06 (br s, 1H), 2.94 (dt, 1H, *J* = 2.5, 4.2 Hz), 3.00 (m, 1H), 3.52 (dd, 1H, *J* = 6.9, 7.5 Hz), 3.65 (m, 1H), 3.89 (m, 1H), 4.03 (dd, 1H, *J* = 6.0, 7.6), 4.15 (m, 1H)
^{13}C NMR	:	δ 25.4 (q), 26.7 (q), 27.4 (t), 29.4 (t), 55.2 (d), 58.4 (d),
(50 MHz, $CDCl_3$)		61.5 (t), 68.9 (t), 74.9 (d), 108.6 (s)

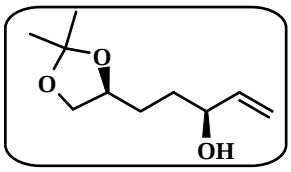
(*S*)-4-(2-((2*S*,3*R*)-3-(iodomethyl)oxiran-2-yl)ethyl)-2,2-dimethyl-1,3-dioxolane (83):



To a solution of **84** (2.02 g, 10.0 mmol) in dry toluene (30 mL) were added imidazole (2.04 g, 30.0 mmol), triphenylphosphine (3.93 g, 15.0 mmol) and iodine (3.02 g, 12.0 mmol) at room temperature. The reaction mixture was stirred for 30 min. at same temperature (monitored by TLC) and quenched the reaction mixture by saturated $NaHCO_3$ solution. The aqueous layer was washed with EtOAc, and the combined organic layer was dried over Na_2SO_4, and evaporated in vacuo. Purification of the residue by column chromatography using EtOAc:petroleum ether (1:9) as eluent afforded iodo compound **83** (2.23 g, 72%) as a light yellowish liquid.

Mol. Formula	:	$C_{10}H_{17}IO_3$
Mol. Weight	:	312.15
ESI-MS *m/z*	:	335.05 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 38.48; H, 5.49
		Found: C, 38.55; H, 5.59
^{1}H NMR	:	δ 1.35 (s, 3H), 1.40 (s, 3H), 1.63-1.72 (m, 4H), 2.84 (m,
(200 MHz, $CDCl_3$)		1H), 2.96-3.06 (m, 2H), 3.27 (dd, 1H, *J* = 8.7, 13.0 Hz),
		3.52 (dd, 1H, *J* = 7.0, 7.6 Hz), 4.04 (dd, 1H, *J* = 6.0, 7.6
		Hz), 4.15 (m, 1H)
^{13}C NMR	:	δ 4.6 (t), 25.6 (q), 26.9 (q), 27.8 (t), 29.6 (t), 58.2 (d), 61.8
(50 MHz, $CDCl_3$)		(d), 69.1 (t), 75.0 (d), 108.9 (s)

(*S*)-5-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-1-en-3-ol (**103**):

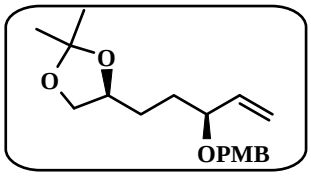


A solution of the iodo compound **83** (2.23 g, 7.13 mmol) and Zn dust (4.64 g, 71.3 mmol) in absolute EtOH (30 mL) was heated to reflux for 3 h. The reaction mixture was filtered through a small celite pad and the filtrate was evaporated, and purification of the residue by column chromatography using EtOAc:petroleum ether (1:3) as eluent afforded **103** as a colorless liquid (1.24 g, 93%).

Mol. Formula	:	$C_{10}H_{18}O_3$
Mol. Weight	:	186.25
ESI-MS *m/z*	:	209.17 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	3436, 3079, 2986, 2871, 1644, 1455, 1379, 1216, 1058,
		922, 757.
Elemental Analysis	:	Calcd: C, 64.49, H, 9.74
		Found: C, 64041; H, 9.62
$[\alpha]_D^{25}$	:	+22.0 (*c* 1.0, $CHCl_3$)
^{1}H NMR	:	δ 1.35 (s, 3H), 1.41 (s, 3H), 1.61-1.69 (m, 4H), 2.68 (br s,

(200 MHz, $CDCl_3$)		1H), 3.52 (t, 1H, *J* = 7.2 Hz), 4.01-4.18 (m, 3H), 5.11 (dt, 1H, *J* = 1.3, 10.4 Hz), 5.24 (dt, 1H, *J* = 1.5, 17.2 Hz), 5.87 (ddd, 1H, *J* = 5.9, 10.4, 17.2 Hz)
^{13}C NMR	:	δ 25.6 (q), 26.8 (q), 29.4 (t), 33.1 (t), 69.2 (t), 72.5 (d),
(50 MHz, $CDCl_3$)		75.8 (d), 108.8 (s), 114.5 (t), 140.9 (d)

(*S*)-4-((*S*)-3(4-methoxybenzyloxy)pent-4-enyl)-2,2-dimethyl-1,3-dioxolane (**104**):

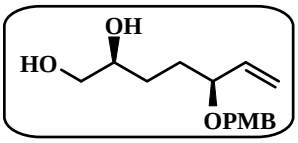


To a solution of **103** (2.5 g, 13.4 mmol) in dry DMF (40 mL) was added NaH (0.80 g, 33.5 mmol, 60% dispersion in mineral oil) at 0 °C, stirred for 30 min. Then *p*-methoxy benzyl chloride (2.5 g, 16.0 mmol) was added and the reaction mixture was stirred for additional 3 h at room temperature. The reaction mixture was quenched by cold water and aqueous layer washed with EtOAc, dried over Na_2SO_4, The solvent was evaporated in vacuo and the residue was purified by column chromatography using EtOAc:petroleum ether (1:9) as eluent to afford **104** (3.5 g, 85%) as a yellow liquid.

Mol. Formula	:	$C_{18}H_{26}O_4$
Mol. Weight	:	306.41
ESI-MS *m/z*	:	329.35 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 70.56, H, 8.55
		Found: C, 70.48; H, 8.56
$[\alpha]_D^{25}$	:	-23.3 (*c* 0.8, $CHCl_3$)
^{1}H NMR	:	δ 1.33 (s, 3H), 1.39 (s, 3H), 1.50-1.59 (m, 2H), 1.65-1.75
(200 MHz, $CDCl_3$)		(m, 2H), 3.48 (m, 1H), 3.62-3.78 (m, 2H), 3.81 (s, 3H), 3.98 (m, 1H) 4.27 (d, 1H, *J* = 11.5 Hz), 4.53 (d, 1H, *J* = 11.5 Hz), 5.18-5.28 (m, 2H), 5.73 (m, 1H), 6.86 (d, 2H, *J* = 8.6 Hz), 7.24 (d, 2H, *J* = 8.6 Hz)
^{13}C NMR	:	δ 25.7 (q), 26.9 (q), 29.1 (t), 31.3 (t), 55.1 (q), 69.2 (t),

(50 MHz, $CDCl_3$)	69.6 (t), 75.7 (d), 79.5 (d), 108.6 (s), 113.6 (d), 117.3 (t), 129.2 (d), 130.6 (s), 138.7 (d), 159.0 (s)

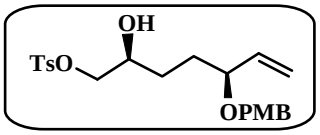
(2*S*,5*S*)-5-(4-methoxybenzyloxy)hept-6-ene-1,2-diol (**82**):



A solution of **104** (1.53 g, 5.0 mmol) in 80% AcOH (20 mL) was stirred for 2 h at room temperature and quenched the reaction mixture with saturated $NaHCO_3$ solution. The aqueous layer was washed with EtOAc and the organic layer was dried over Na_2SO_4, concentrated and purified by column chromatography using EtOAc:petroleum ether (1:1) as eluent to afford **82** as a colorless liquid (1.22 g, 92%)..

Mol. Formula	:	$C_{15}H_{22}O_4$
Mol. Weight	:	266.34
ESI-MS *m/z*	:	289.29 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	3409, 3076, 3000, 2936, 2868, 1612, 1514, 1442, 1302, 1248, 1174, 1072, 995, 821.
Elemental Analysis	:	Calcd: C, 67.64; H, 8.33 Found: C, 67.62; H, 8.22
$[\alpha]_D^{25}$	:	-37.5 (*c* 1.2, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 1.44-1.56 (m, 2H), 1.61-1.76 (m, 2H), 2.41 (br s, 1H), 3.04 (br s, 1H), 3.37 (dd, 1H, *J* = 7.2, 11.0 Hz), 3.53-3.65 (m, 2H), 3.73 (m, 1H), 3.80 (s, 3H), 4.26 (d, 1H, *J* = 11.4 Hz), 4.54 (d, 1H, *J* = 11.4 Hz), 5.23 (m, 2H), 5.75 (m, 1H), 6.86 (d, 2H, *J* = 8.7 Hz), 7.23 (d, 2H, *J* = 8.7 Hz)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 28.9 (t), 31.6 (t), 55.1 (q), 66.5 (t), 69.7 (t), 71.9 (d), 80.0 (d), 113.7 (d), 117.3 (t), 129.4 (d), 130.2 (s), 138.6 (d), 159.1 (s)

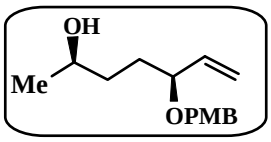
(2*S*,5*S*)-2-hydroxy-5-(4-methoxybenzyloxy)hept-6-enyl 4-methylbenzenesulfonate (**105**):



To a solution of **82** (1.0 g, 3.75 mmol) in dry CH_2Cl_2 (30 mL), were added Et_3N (0.44 g, 4.27 mmol), *n*-Bu_2SnO (0.47 g, 1.89 mmol), DMAP (catalytic) and TsCl (0.74 g, 3.84 mmol) at 0 °C. The reaction mixture was stirred for 12 h at room temperature, quenched with saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography using EtOAc:petroleum ether (1:5) as eluent to afford **105** as a colorless liquid (1.2 g, 76%).

Mol. Formula	:	$C_{22}H_{28}O_6S$
Mol. Weight	:	420.53
ESI-MS *m/z*	:	443.48 $[M+Na]^+$
Elemental Analysis	:	Calcd: C, 62.84; H, 6.71; S, 7.63 Found. C, 62.74; H, 6.58; S, 7.79
$[\alpha]_D^{25}$	:	-29.20 (*c* 1.0, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 1.43-1.71 (m, 4H), 2.34 (br s, 1H), 2.45 (s, 3H), 3.66-3.78 (m, 2H), 3.80 (s, 3H), 3.86 (dd, 1H, *J* = 6.1, 9.8 Hz), 3.95 (dd, 1H, *J* = 4.2, 9.8 Hz), 4.24 (d, 1H, *J* =11.5 Hz), 4.52 (d, 1H, *J* =11.4 Hz), 5.16-5.26 (m, 2H), 5.71 (ddd, 1H, *J* = 7.6, 10.7, 18.4 Hz), 6.84 (d, 2H, *J* = 8.7 Hz), 7.20 (d, 2H, *J* = 7.7 Hz), 7.33 (d, 2H, *J* = 8.3 Hz), 7.78 (d, 2H, *J* = 8.3 Hz)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 21.4 (d), 28.6 (t), 31.0 (t), 55.0 (q), 68.8 (d), 69.6 (t), 73.5 (t), 79.4 (d), 113.6 (d), 117.4 (t), 127.8 (d), 129.3 (d), 129.7 (d), 129.9 (s), 132.6 (s), 138.2 (d), 144.6 (s), 159.0 (s)

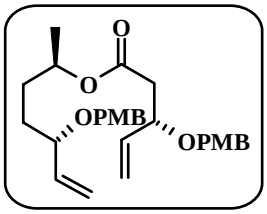
(2*R*,5*S*)-5-(4-methoxybenzyloxy)hept-6-en-2-ol (**73**):



To a solution of compound **105** (0.210 g, 0.5 mmol) in dry THF (10 mL) at 0 ^{o}C was added LAH (0.076 g, 2.0 mmol) and stirred for 3 h. Excess of LAH was quenched by addition of a saturated Na_2SO_4 solution (1 mL). The solid formed was filtered, washed with ethyl acetate and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography using EtOAc:petroleum ether (1:4) as eluent to afford **73** as a colorless liquid (0.011 g, 88%).

Mol. Formula	:	$C_{15}H_{22}O_3$
Mol. Weight	:	250.34
ESI-MS *m/z*	:	273.29 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	3409, 3076, 3006, 2966, 2934, 1613, 1513, 1248, 1173, 1036, 994, 756.
Elemental Analysis	:	Calcd: C, 71.97; H, 8.86 Found: C, 71.94; H, 8.72
$[\alpha]_D^{25}$	:	-43.8 (*c* 1.2, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 1.16 (d, 3H, *J* = 6.2 Hz), 1.47-1.74 (m, 4H), 2.17 (br s, 1H) 3.69-3.77 (m, 2H), 3.80 (s, 3H), 4.28 (d, 1H, *J* = 11.4 Hz), 4.54 (d, 1H, *J* = 11.4 Hz), 5.17-5.26 (m, 2H), 5.75 (ddd, 1H, *J* = 7.7, 11.1, 19.0 Hz), 6.87 (d, 2H, *J* = 8.7 Hz), 7.25 (d, 2H, *J* = 8.7 Hz)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 23.3 (q), 31.8 (t), 35.0 (t), 55.0 (q), 67.5 (d), 69.6 (t), 80.0 (d), 113.6 (d), 117.1 (t), 129.3 (d), 130.3 (s), 138.7 (d), 158.9 (s)

(3*S*)-(2*R*,5*S*)-5-(4-methoxybenzyloxy)hept-6-en-2-yl-3-(4-methoxybenzyloxy)-pent-4-enoate (**72**):

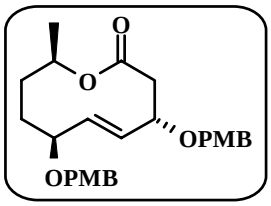


To a stirred solution of the acid fragment **74** (0.050 g, 0.211 mmol) in dry CH_2Cl_2 (5 mL), were added Et_3N (0.06 mL, 0.422 mmol) and a solution of 2,4,6-trichlorobenzyolchloride (0.077 g, 0.315 mmol) in dry CH_2Cl_2 (5 mL) and the mixture was stirred at 0 °C for 20 min. Then a solution of the alcohol fragment **73** (0.055 g, 0.219 mmol) in dry CH_2Cl_2 (5 mL) and DMAP (catalytic) were added, stirred for 6 h at room temperature (Checked by TLC). The solvent was evaporated, the crude was purified by column chromatography using EtOAc:petroleum ether (1:9) as eluent to afford **72** (0.088 g, 89%) as a colorless liquid.

Mol. Formula	:	$C_{28}H_{36}O_6$
Mol. Weight	:	468.60
ESI-MS *m/z*	:	491.54 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	3076, 3005, 2978, 2935, 2864, 1729, 1642, 1613, 1513, 1464, 1248, 1036, 994, 822, 756.
Elemental Analysis	:	Calcd: C, 71.77; H, 7.74 Found: C, 71.68; H, 7.64
$[\alpha]_D^{25}$	:	-36.5 (*c* 1.0, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 1.17 (d, 3H, *J* = 6.3 Hz), 1.46-1.70 (m, 4H), 2.44 (dd, 1H, *J* = 5.7, 14.9 Hz), 2.63 (dd, 1H, *J* = 8.0, 14.9 Hz), 3.69 (m, 1H), 3.79-3.81 (2s, 3H), 3.81 (s, 3H), 4.21 (m, 1H), 4.32 (d, 2H, *J* = 11.4 Hz), 4.48 (2d, 2H, *J* = 11.4 Hz), 4.90 (m, 1H), 5.14-5.35 (m, 4H), 5.60-5.86 (m, 2H), 6.82-6.88 (2d, 4H, *J* = 8.7 Hz), 7.20-7.26 (2d, 4H, *J* = 8.7 Hz)
^{13}C NMR	:	δ 19.9 (q), 31.0 (t), 31.4 (t), 41.3 (t), 55.0 (q), 69.6 (t),

(50 MHz, $CDCl_3$)	70.0 (t), 70.7 (d), 76.7 (d), 79.4 (d), 113.6 (d), 117.1 (t), 117.8 (t), 129.1 (d), 130.2 (s), 130.6 (s), 137.3 (d), 138.7 (d), 159.0 (s), 170.2 (s)

(4*S*,5*E*,7*S*,10*R*)-4,7-bis(4-methoxybenzyloxy)-3,4,7,8,9,10-hexahydro-10-methyl oxecin-2-one (**71**):



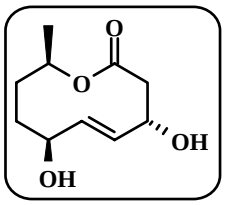
To a solution of **72** (0.094 g, 0.20 mmol, 0.001M) in freshly distilled degassed anhydrous CH_2Cl_2 (200 mL) was added Grubb's second generation catalyst (0.017 g, 0.02 mmol) and heated at reflux for 8 h under an argon atmosphere until the complete consumption of starting material (monitored by TLC). The solvent was evaporated to a brown residue, which was purified by column chromatography using EtOAc:petroleum ether (1:9) as eluent to afford **71** (0.069 g, 78%) as a colorless liquid.

Mol. Formula	:	$C_{26}H_{32}O_6$
Mol. Weight	:	440.54
ESI-MS *m/z*	:	463.50 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	2978, 2932, 2864, 1612, 1513, 1459, 1247, 1172, 1086, 1035, 821, 756
Elemental Analysis	:	Calcd: C, 70.89; H, 7.32 Found: C, 70.72; H, 7.28
$[\alpha]_D^{25}$	:	-53.1 (*c* 1.0, $CHCl_3$)
^{1}H NMR (500 MHz, $CDCl_3$)	:	δ 1.15 (d, 3H, *J* = 6.6 Hz), 1.63-1.70 (m, 3H), 1.84 (m, 1H), 2.44 (dd, 1H, *J* = 7.3, 14.2 Hz), 2.91 (dd, 1H, *J* = 8.3, 14.2 Hz), 3.71 (m, 1H), 3.75 (2s, 6H), 4.24-4.29 (m, 2H), 4.36 (d, 1H, *J* = 11.5 Hz), 4.46 (d, 1H, *J* = 11.7 Hz), 4.51 (d, 1H, *J* = 11.5 Hz), 5.00 (m, 1H), 5.47 (dd, 1H, *J* = 8.5, 16.1 Hz), 5.63 (dd, 1H, *J* = 9.3, 16.1 Hz), 6.83-6.85

(2d, 4H, J = 8.7 Hz), 7.20-7.23 (2d, 4H, J = 8.7 Hz)

^{13}C NMR (125 MHz, $CDCl_3$) : δ 18.6 (q), 27.9 (t), 29.9 (t), 42.3 (t), 55.2 (q), 70.2 (t), 70.3 (t), 71.1 (d), 76.2 (d), 79.2 (d), 113.7 (d), 113.8 (d), 128.9 (d), 129.2 (d), 129.3 (d), 129.4 (d), 130.0 (d), 130.4 (s), 138.9 (s), 159.1 (s), 159.2 (s), 170.3 (s)

(4*S*,7*S*,10*R*,*E*)-4,7-dihydroxy-10-methyl-3,4,7,8,9,10-hexahydrooxecin-2-one (58) (Decarestrictine C_1):



To a solution of compound **71** (0.05 g, 0.113 mmol) in CH_2Cl_2:H_2O mixture (20:1 mL), was added DDQ (0.057 g, 0.25 mmol) and stirred at room temperature for 2 h. The reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$, the organic layer was separated, washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography using MeOH:$CHCl_3$ (1:19) as eluent afforded **58** (0.018 g, 80%) as white solid.

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

Mol. Weight : 200.24

ESI-MS *m/z* : 223.15 $[M+Na]^+$

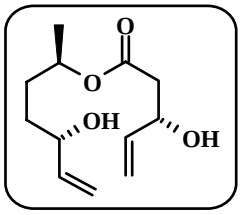
Elemental Analysis : Calcd: C, 59.98; H, 8.05
Found C, 60.15; H, 8.23

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

^{1}H NMR (500 MHz, CD_3OD) (**Rotamers**) : δ 1.16 (d, 3H, J = 6.6 Hz), 1.21 (d, 3H, J = 6.9 Hz), 1.43 (dd, 1H, J = 6.8, 15.7 Hz), 1.62-1.74 (m, 4H), 1.76 (m, 1H), 1.87-2.01 (m, 2H), 2.31 (dd, 1H, J = 5.6, 13.4 Hz), 2.49 (dd, 1H, J = 3.5, 11.9 Hz), 2.53 (dd, 1H, J = 3.6, 11.9 Hz), 2.92 (dd, 1H, J = 7.5, 13.4 Hz), 3.94 (dt, 1H, J = 3.2, 8.6 Hz), 4.39 (m, 1H), 4.56 (m, 1H), 4.69-4.75 (m, 2H),

		5.00 (m, 1H), 5.41 (dd, 1H, *J* = 7.5, 16.2 Hz), 5.55 (dd, 1H, *J* = 8.2, 16.2 Hz), 5.80 (dd, 1H, *J* = 15.9 Hz), 5.90 (dd, 1H, *J* = 15.9 Hz)
^{13}C NMR (125 MHz, $CDCl_3$) (**Rotamers**)	:	δ 18.9 (q), 22.1 (q), 28.6 (t). 29.2 (t), 32.6 (t), 45.4 (t), 45.8 (t), 68.7 (d), 69.1 (d), 70.4 (d), 72.4 (d), 74.2 (d), 130.7 (d), 131.9 (d), 138.2 (d), 172.0 (s), 172.5 (s)

(*S*)-((2*R*,5*S*)-5-hydroxyhept-6-en-2-yl)-3-hydroxypent-4-enoate (**70**).

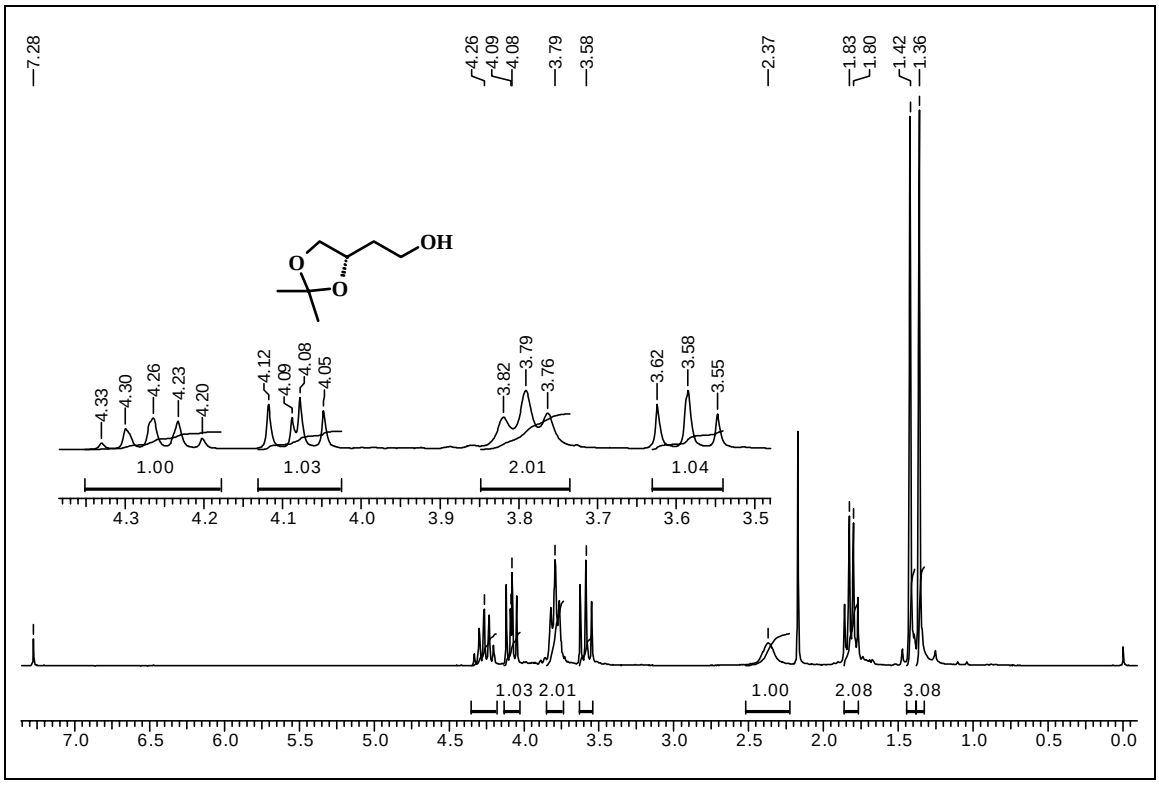


To a solution of compound **72** (0.200 g, 0.427 mmol) in CH_2Cl_2:H_2O mixture (20:1) was added DDQ (0.203 g, 0.896 mmol) and stirred at room temperature for 2 h. The reaction mixture was quenched with saturated solution of $NaHCO_3$, the organic layer was separated, washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography using EtOAc:petroleum ether (1:2) as eluent to afford **70** (0.076 g, 78%) as a colorless liquid.

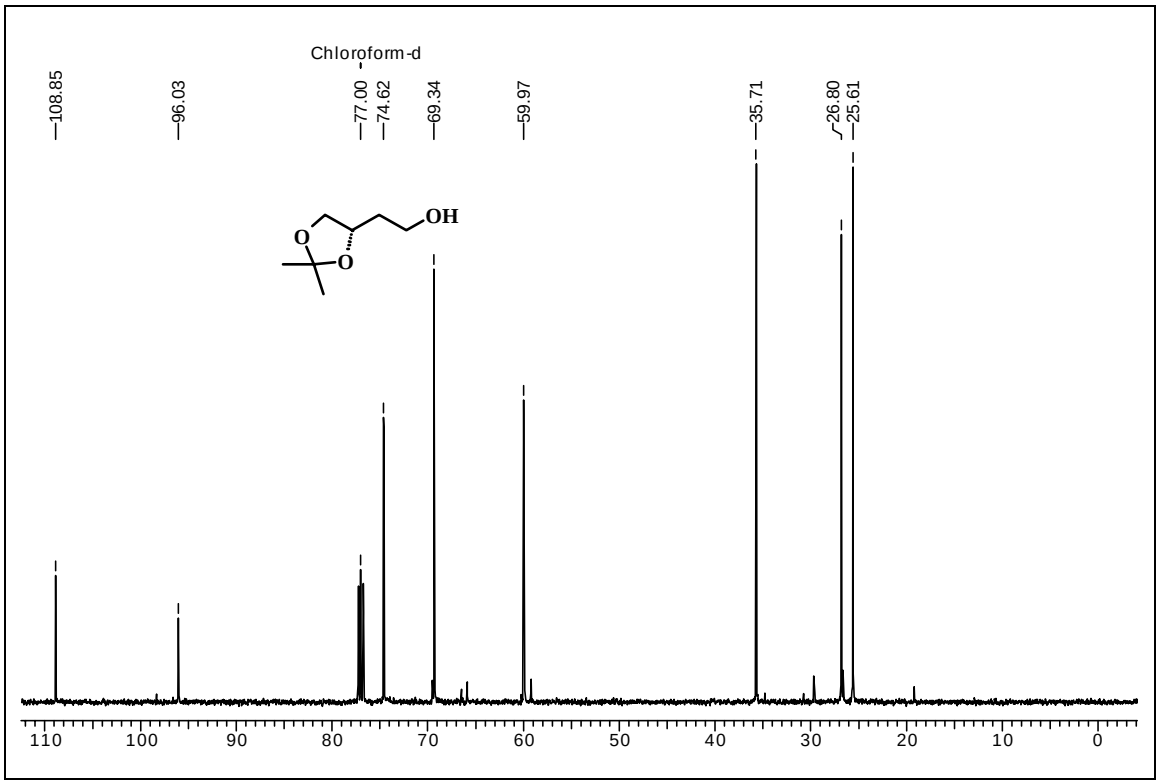
Mol. Formula	:	$C_{12}H_{20}O_4$
Mol. Weight	:	228.29
ESI-MS *m/z*	:	251.17 $[M+Na]^+$
IR ($CHCl_3$, cm^{-1})	:	3417, 3083, 2980, 2927, 1714, 1645, 1426, 1378, 1277, 1178, 1032
Elemental Analysis	:	Calcd: C, 63.14; H, 8.83 Found C, 62.94; H, 8.72
$[\alpha]_D^{25}$	:	-5.7 (*c* 1.0, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 1.25 (d, 3H, *J* = 6.3 Hz), 1.51-1.74 (m, 5H), 2.49 (dd, 1H, *J* = 7.7, 16.0 Hz), 2.59 (dd, 1H, *J* = 4.5, 16.0 Hz), 2.99 (br s, 1H), 4.10 (m, 1H), 4.53 (m, 1H), 5.01 (m, 1H),

		5.10-5.37 (m, 4H), 5.78-5.98 (m, 2H).
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 20.0 (q), 31.5 (t), 32.4 (t), 41.5 (t), 68.9 (d), 71.3 (d), 72.5 (d), 114.9 (t), 115.3 (t), 138.9 (d), 140.8 (d), 171.9 (s)

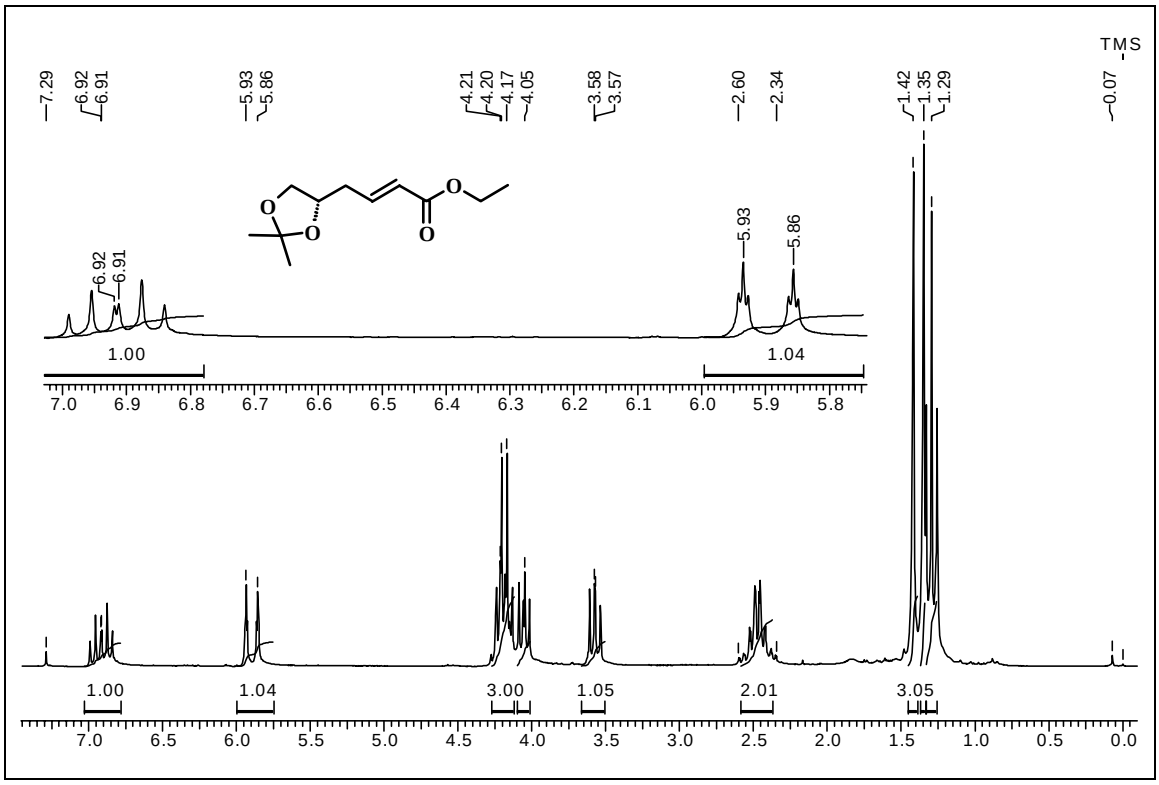
Spectra



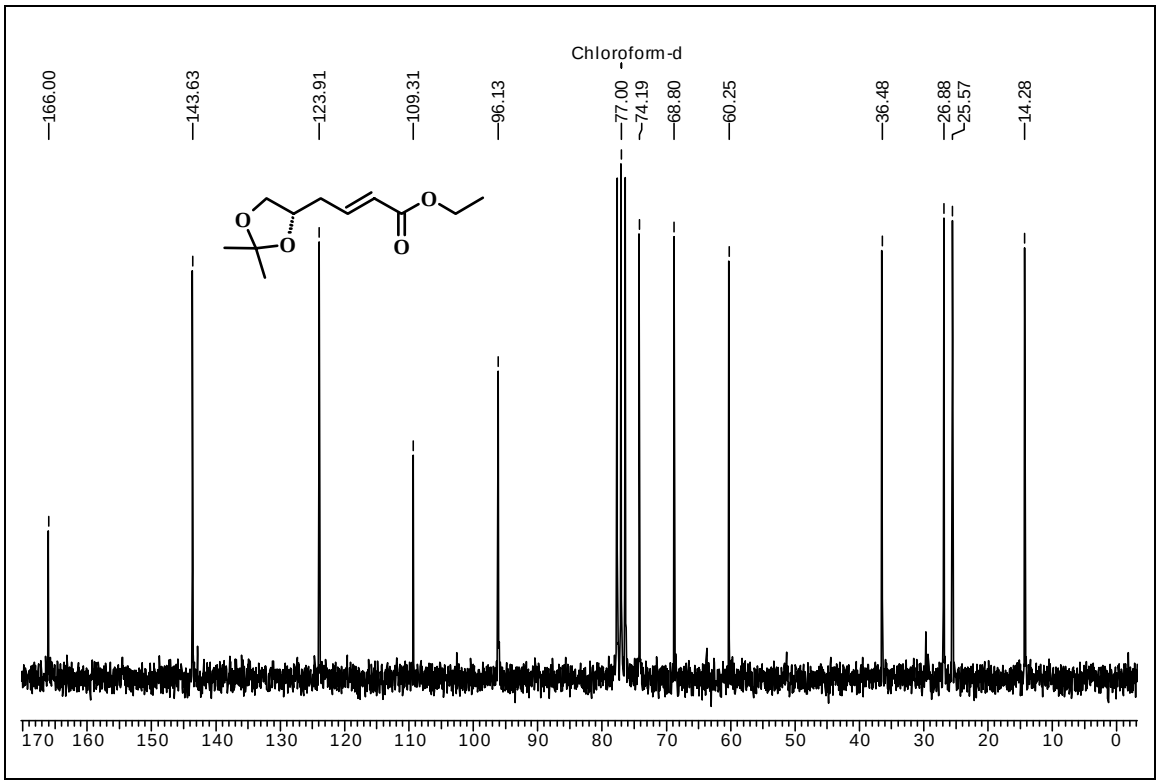
^{1}H NMR spectrum of compound 80 in $CDCl_3$



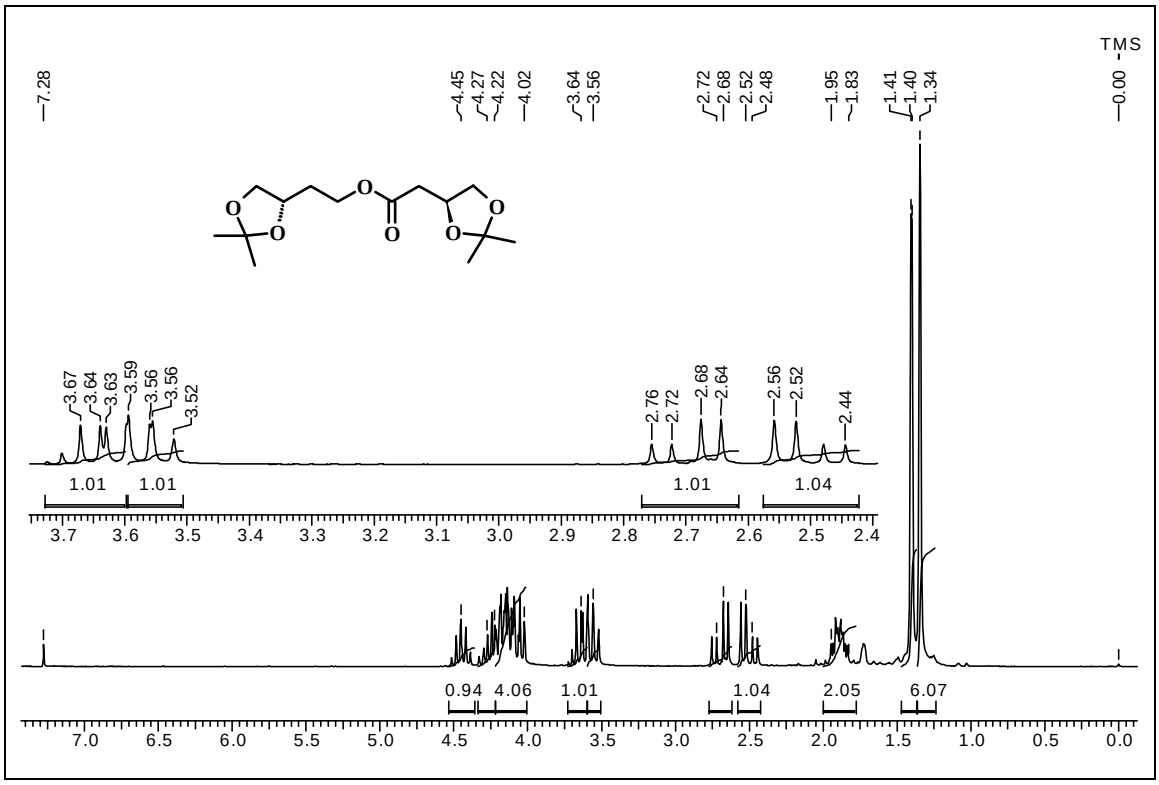
^{13}C NMR spectrum of compound 80 in $CDCl_3$



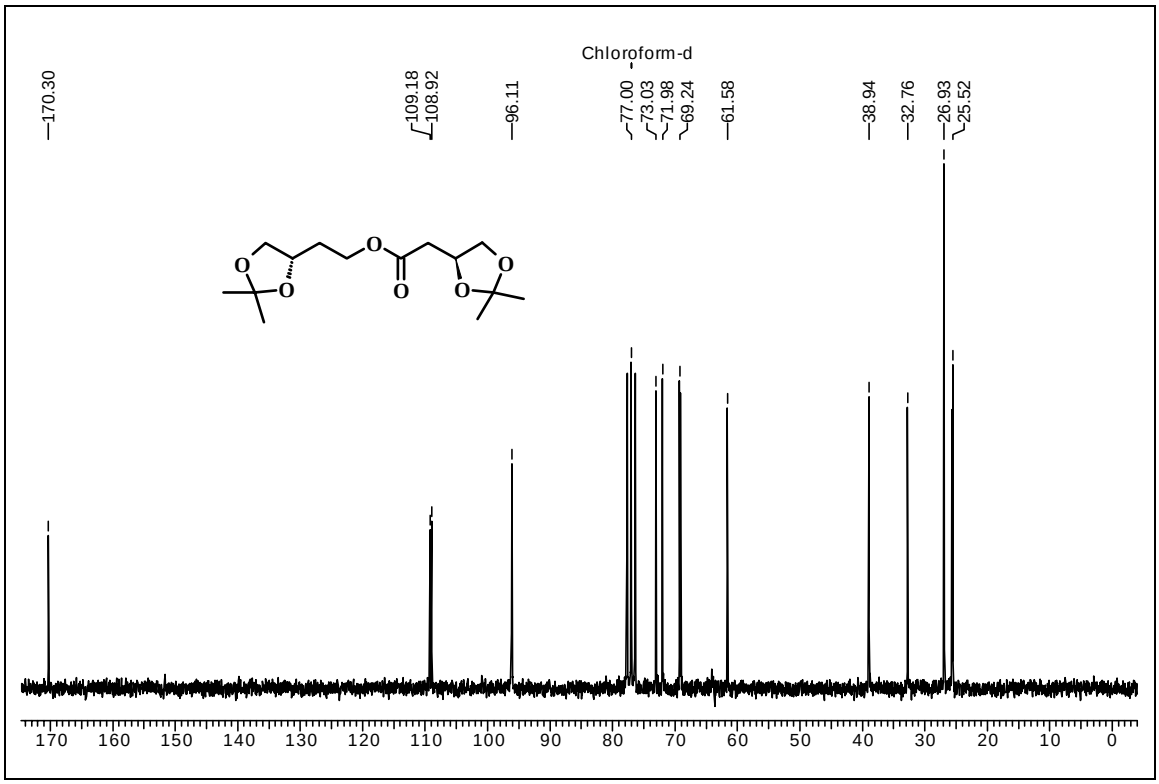
^{1}H NMR spectrum of compound 79 in $CDCl_3$



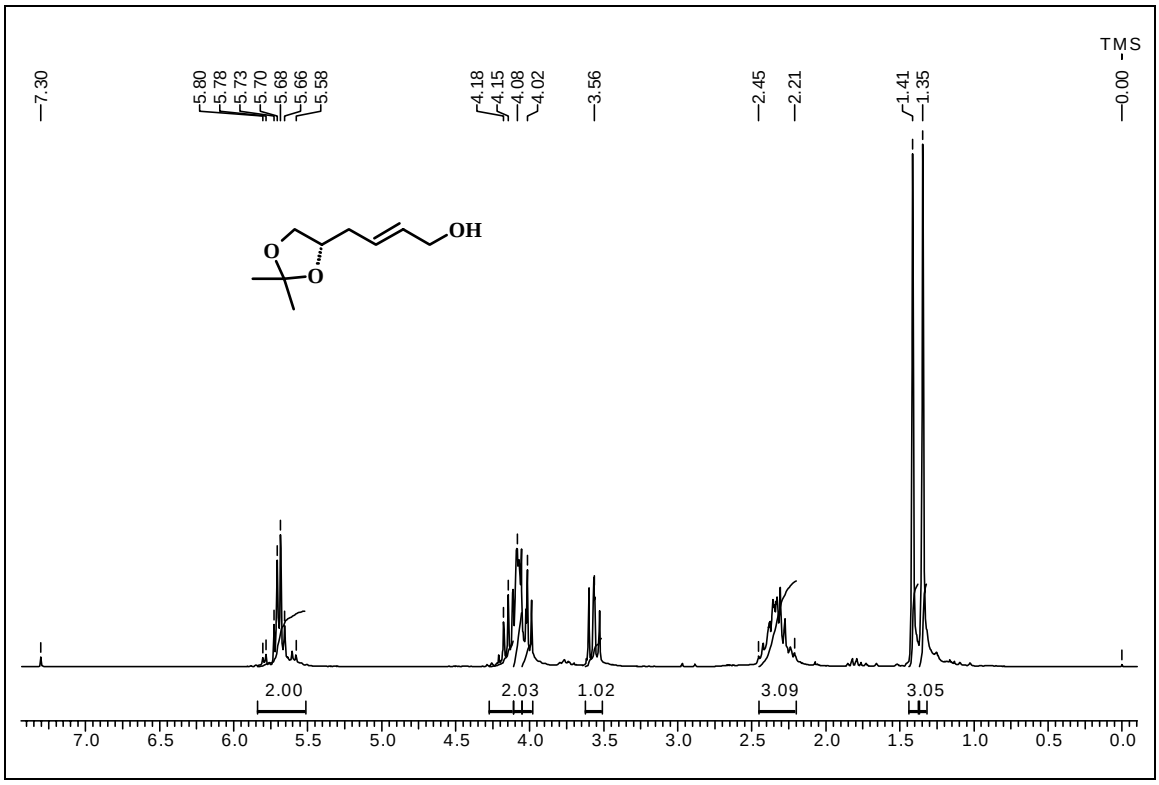
^{13}C NMR spectrum of compound 79 in $CDCl_3$



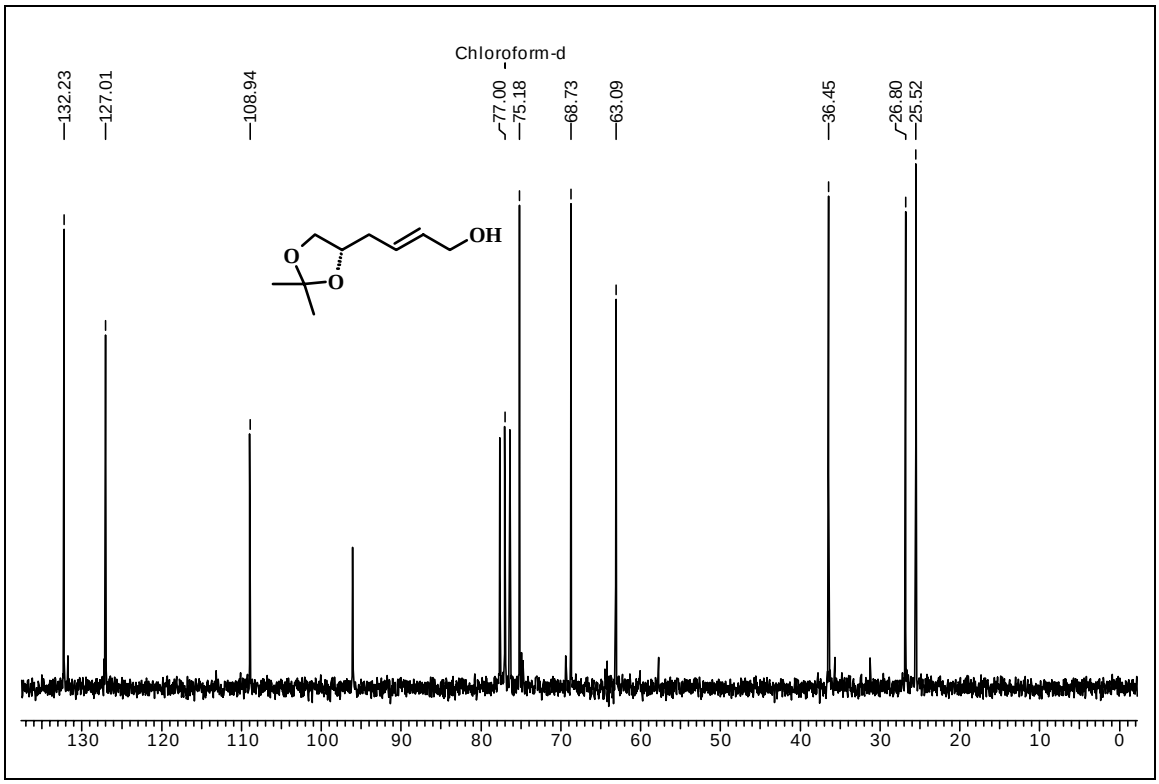
^{1}H NMR spectrum of compound 93 in $CDCl_3$



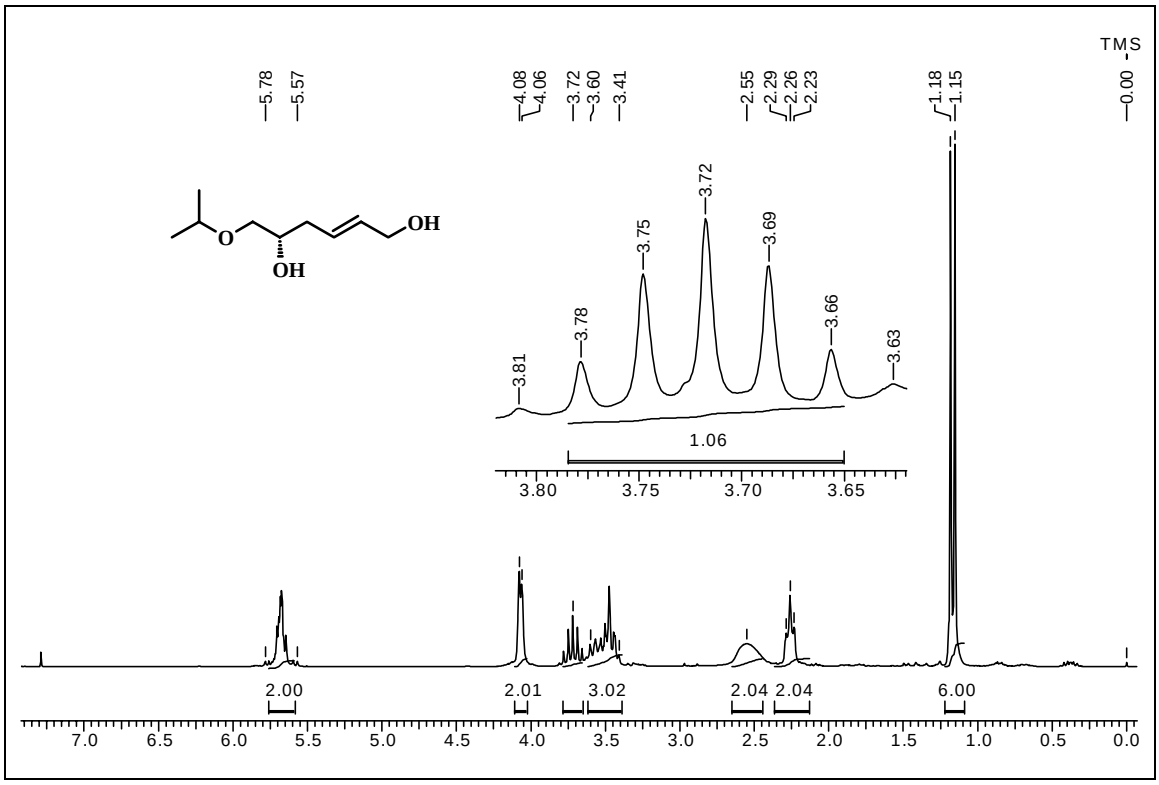
^{13}C NMR spectrum of compound 93 in $CDCl_3$



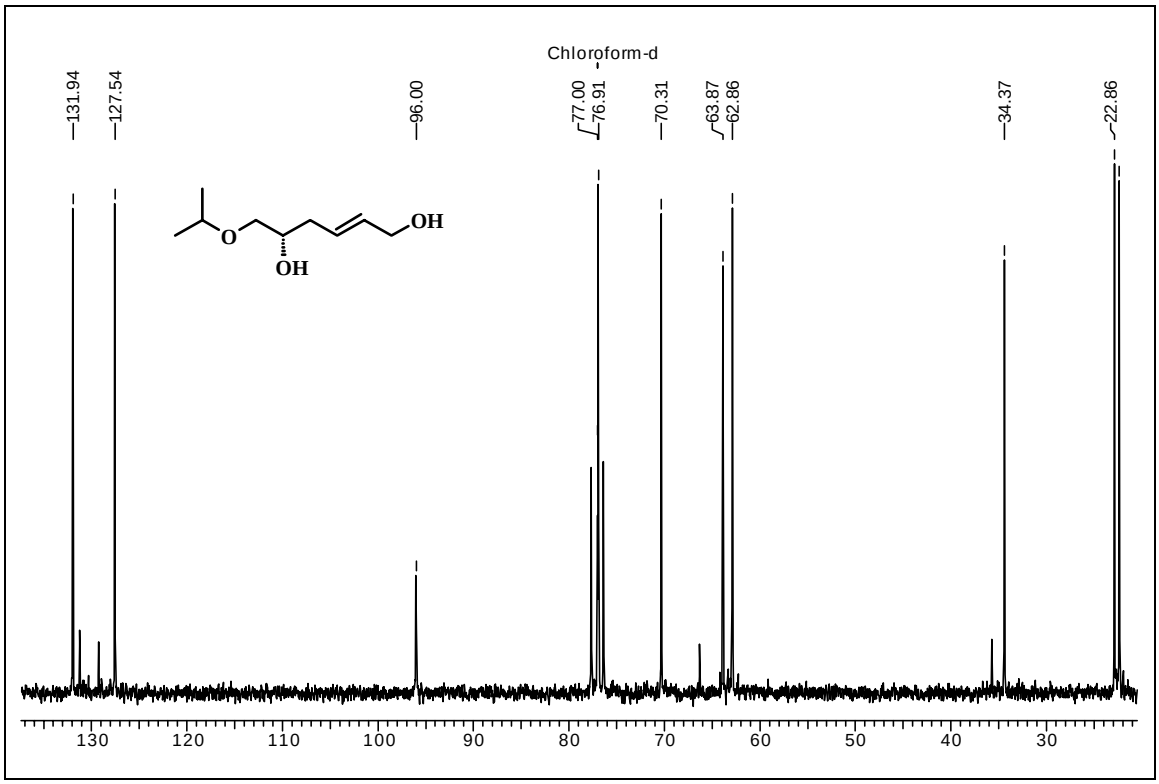
^{1}H NMR spectrum of compound 78 in $CDCl_3$



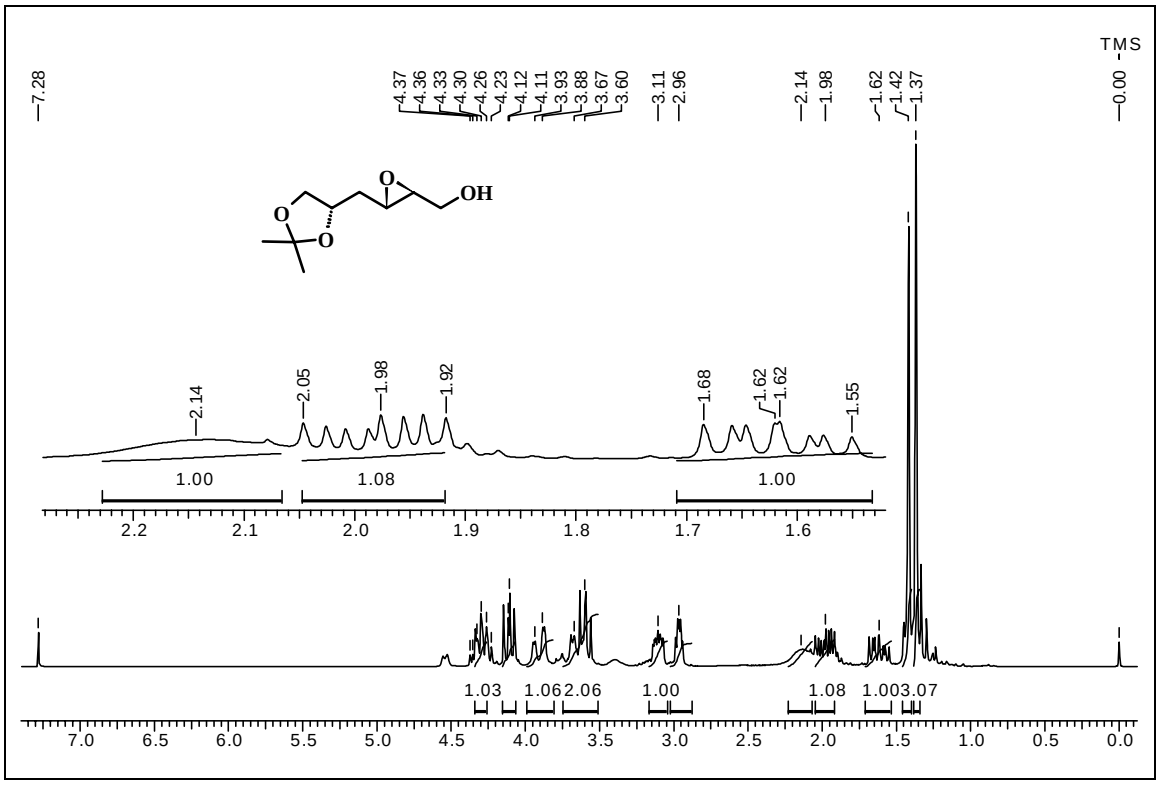
^{13}C NMR spectrum of compound 78 in $CDCl_3$



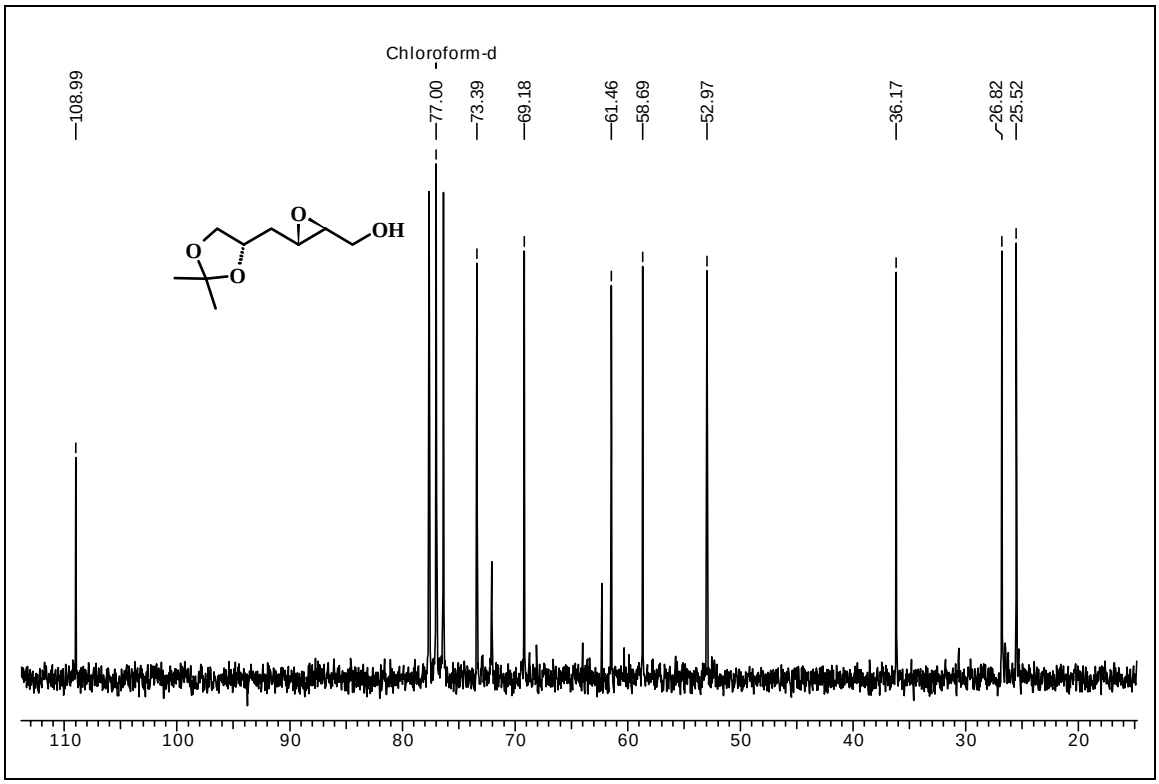
^{1}H NMR spectrum of compound 94 in $CDCl_3$



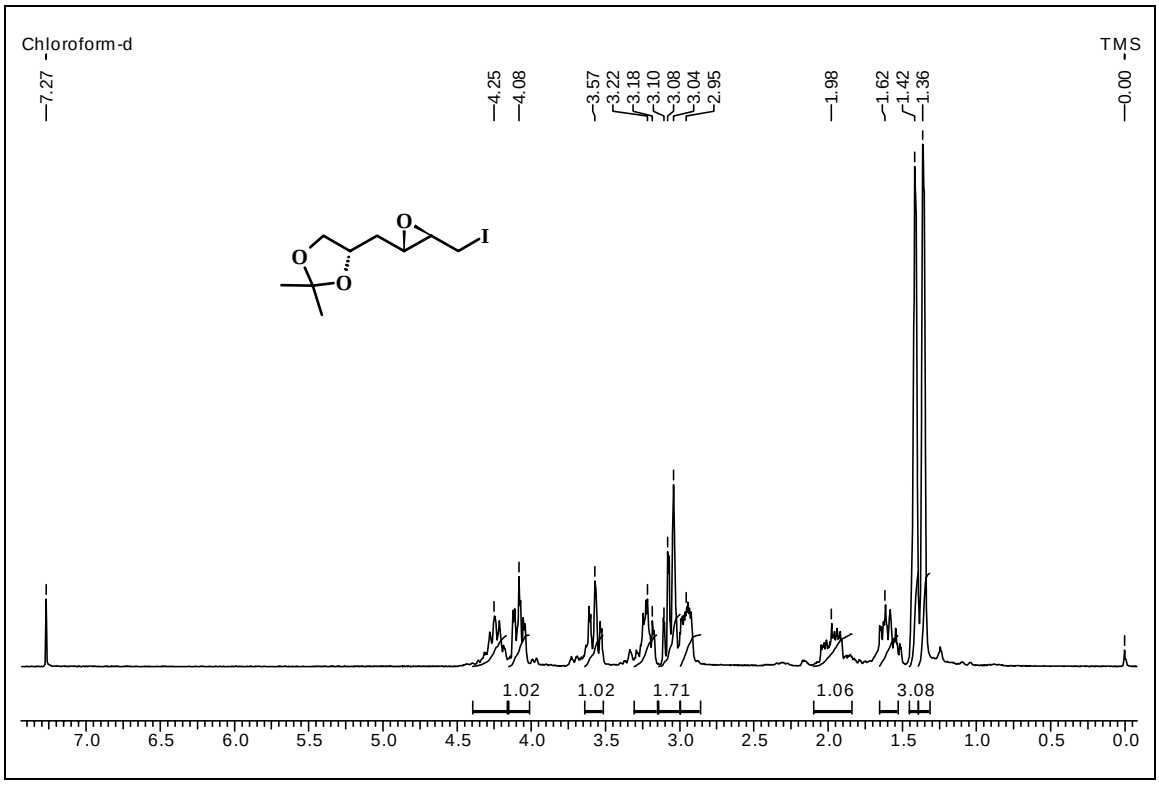
^{13}C NMR spectrum of compound 94 in $CDCl_3$



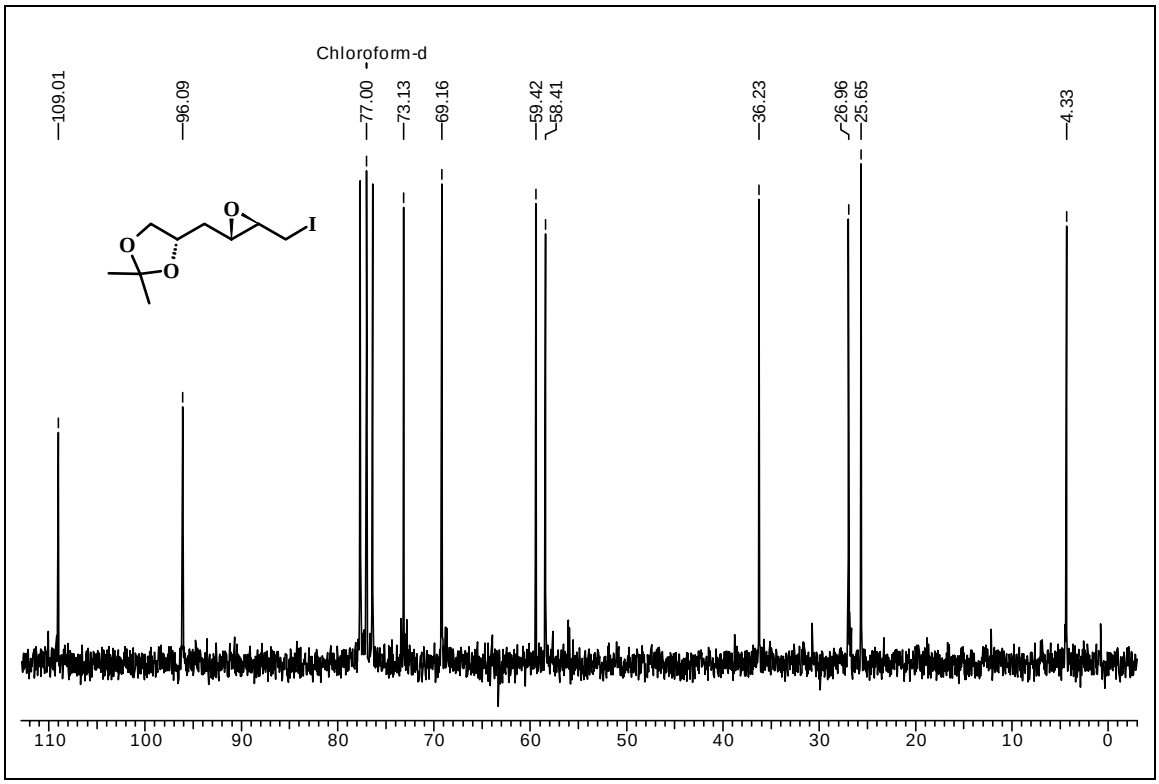
^{1}H NMR spectrum of compound 77 in $CDCl_3$



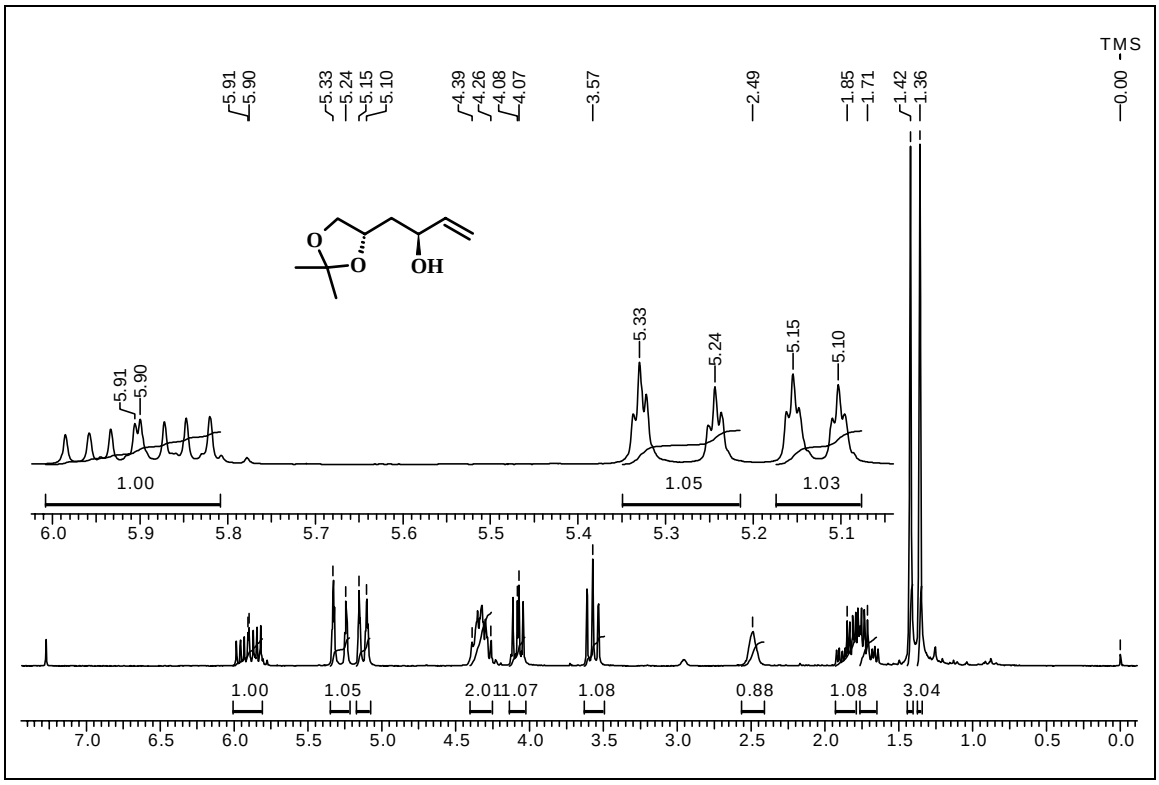
^{13}C NMR spectrum of compound 77 in $CDCl_3$



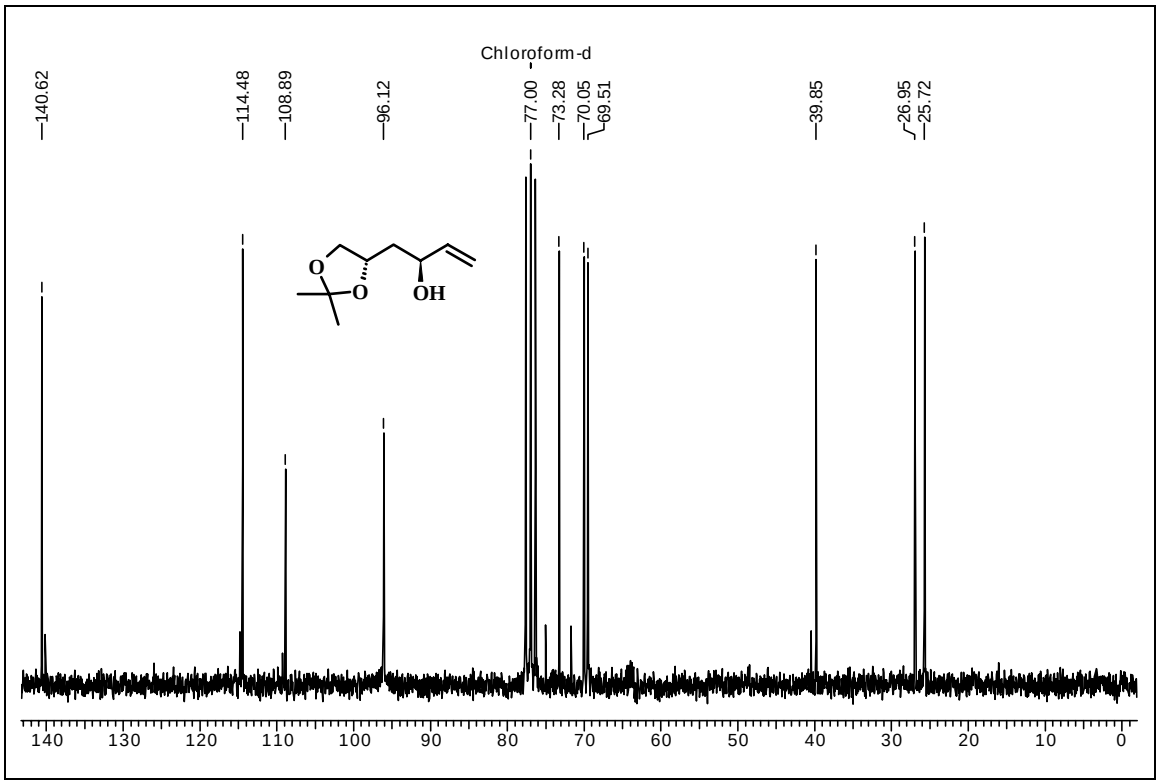
^{1}H NMR spectrum of compound 76 in $CDCl_3$



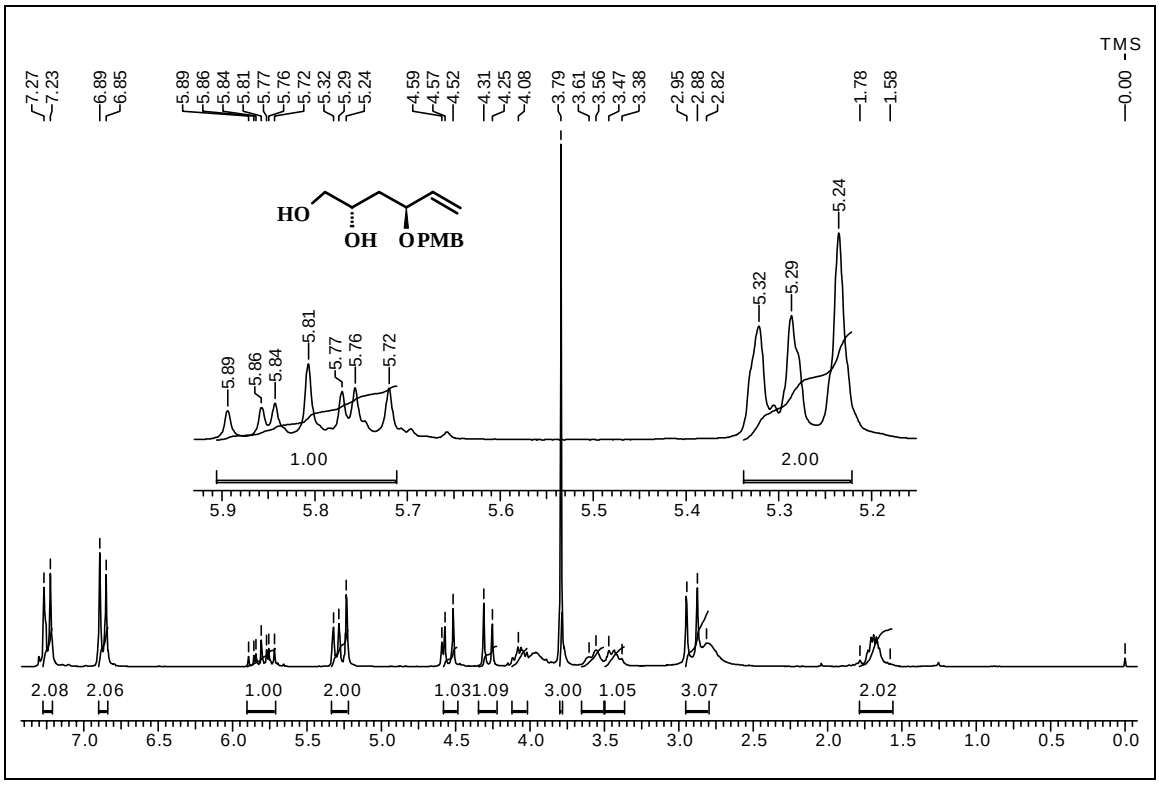
^{13}C NMR spectrum of compound 76 in $CDCl_3$



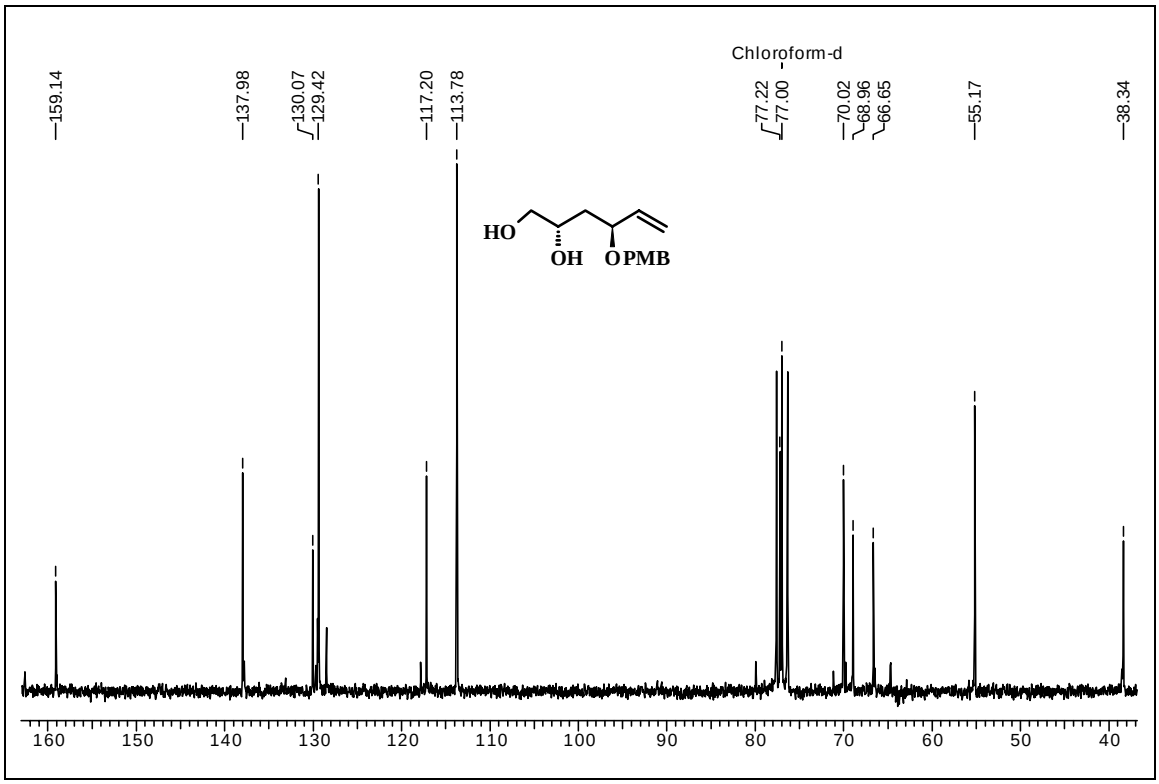
^{1}H NMR spectrum of compound 95 in $CDCl_3$



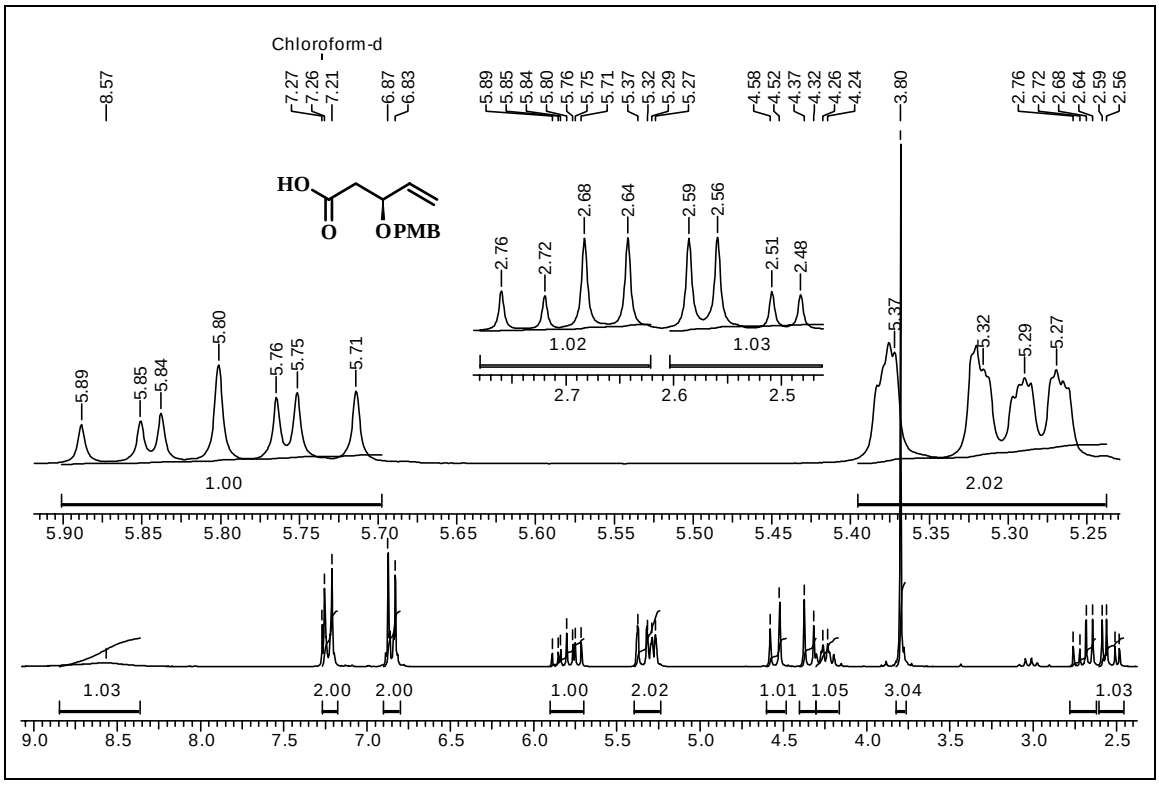
^{13}C NMR spectrum of compound 95 in $CDCl_3$



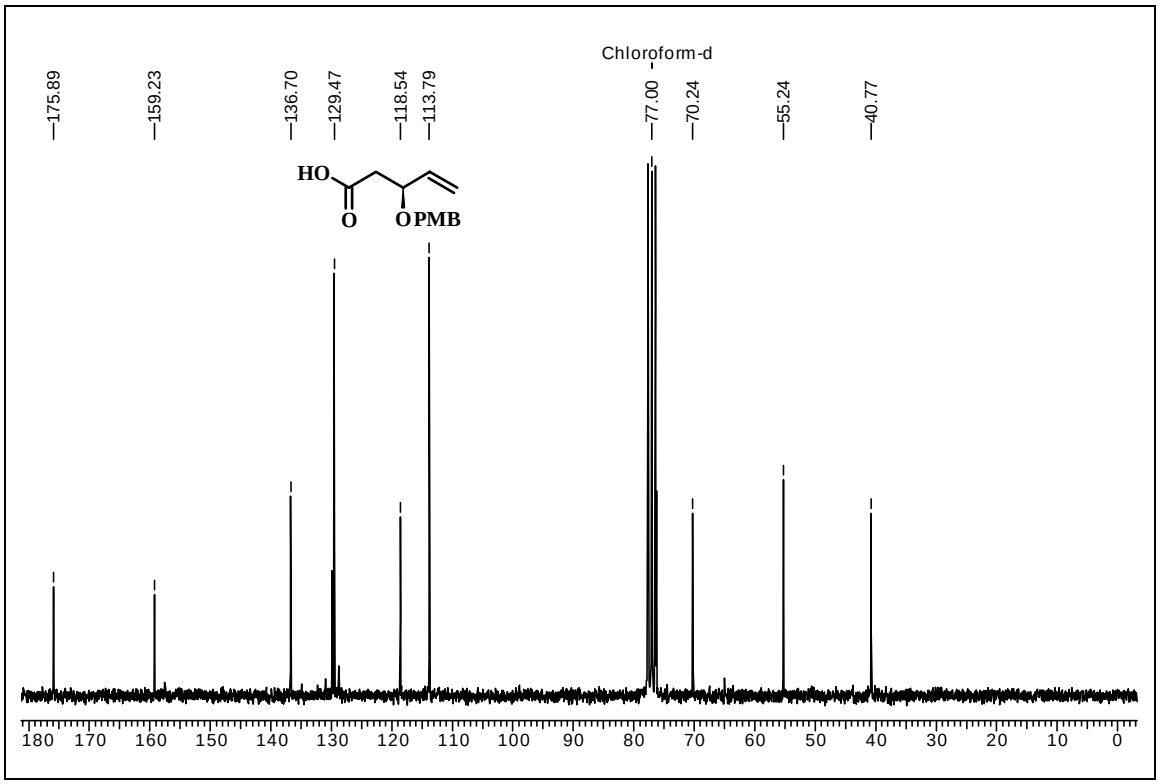
^{1}H NMR spectrum of compound 75 in $CDCl_3$



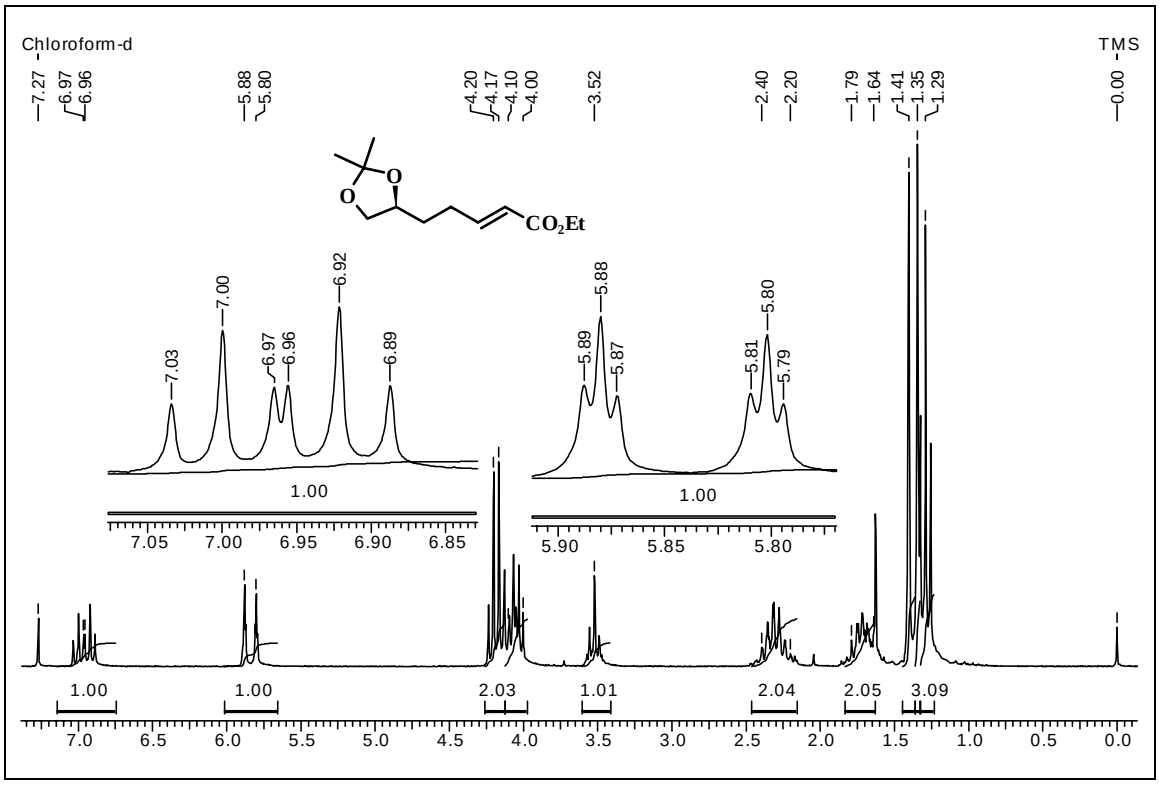
^{13}C NMR spectrum of compound 75 in $CDCl_3$



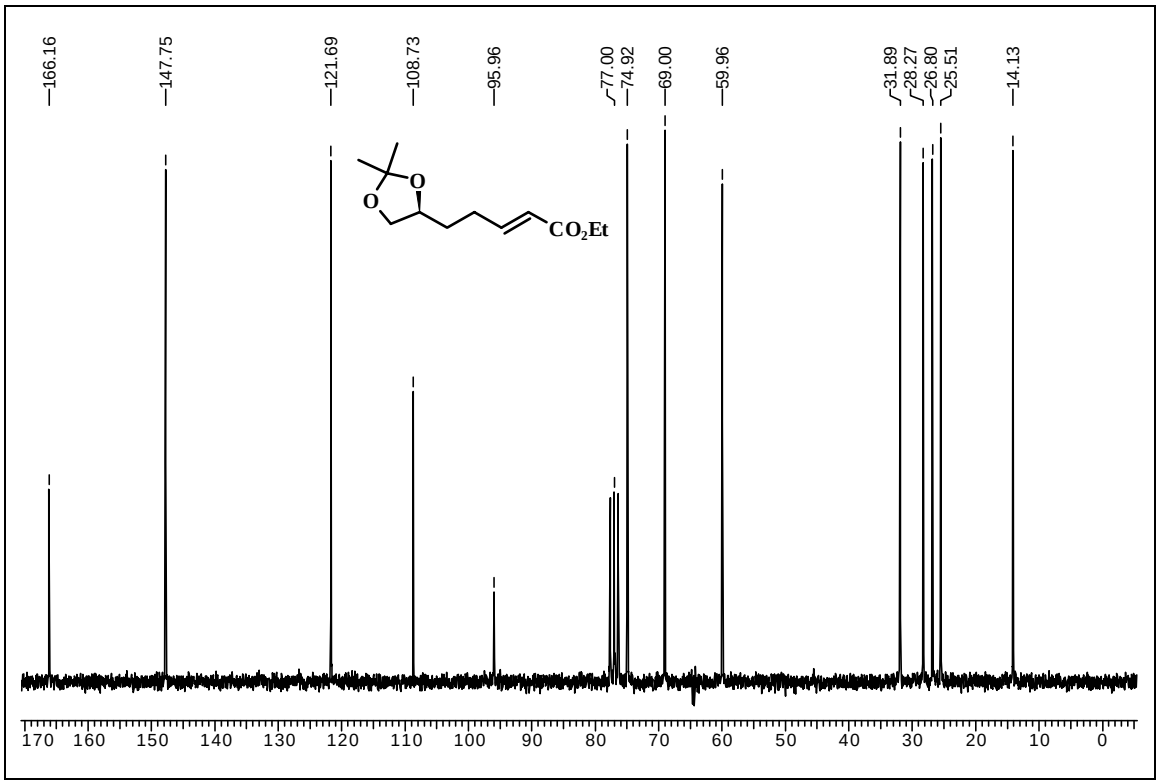
^{1}H NMR spectrum of compound 74 in $CDCl_3$



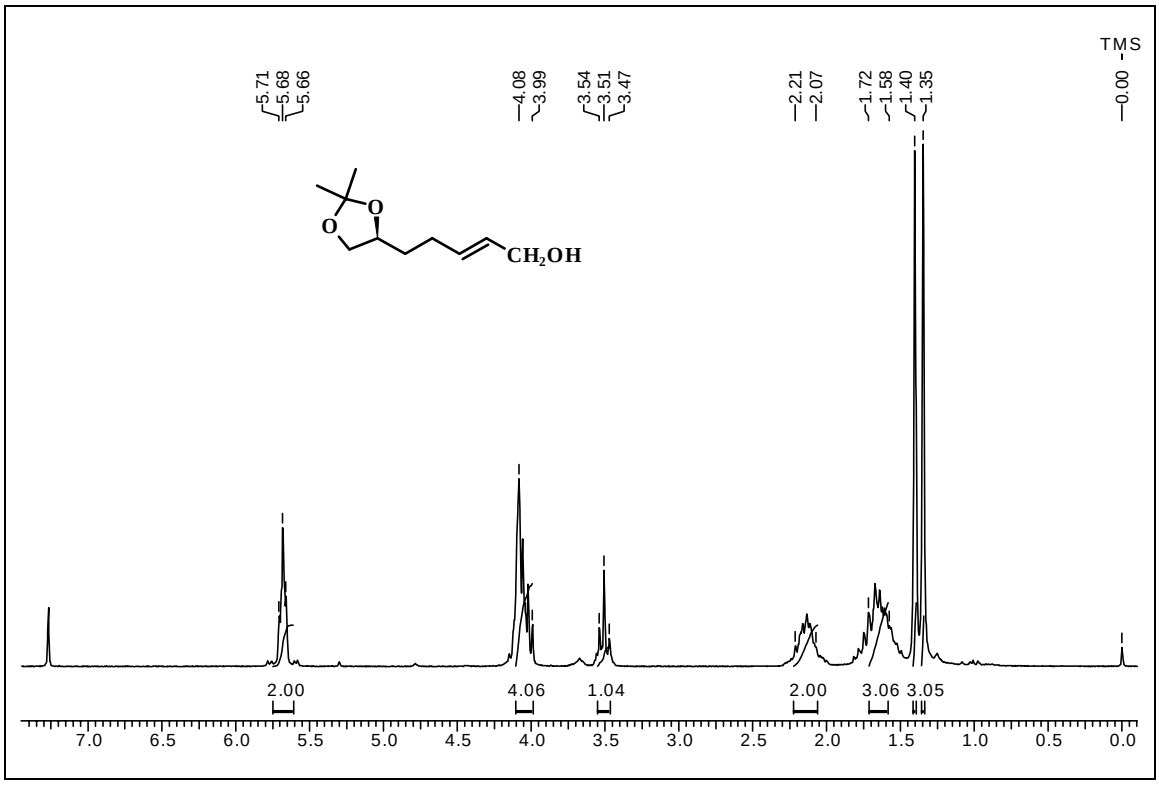
^{13}C NMR spectrum of compound 74 in $CDCl_3$



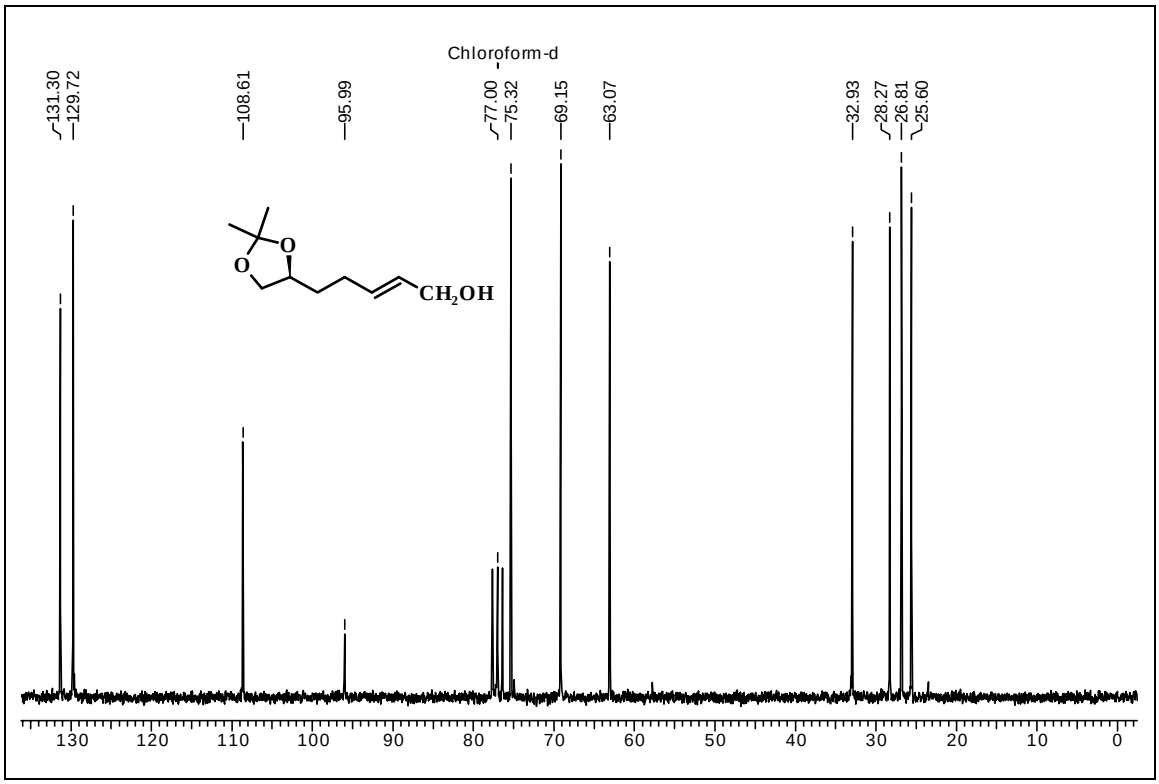
^{1}H NMR spectrum of compound 86 in $CDCl_3$



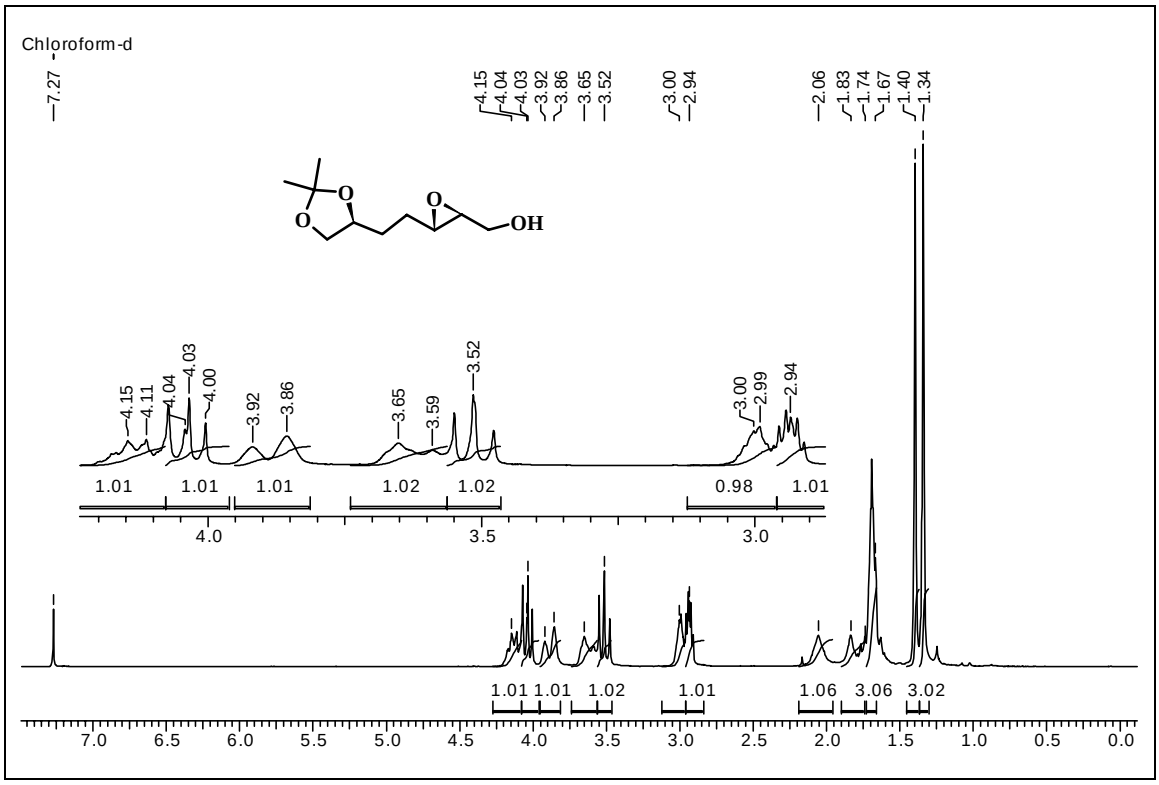
^{13}C NMR spectrum of compound 86 in $CDCl_3$



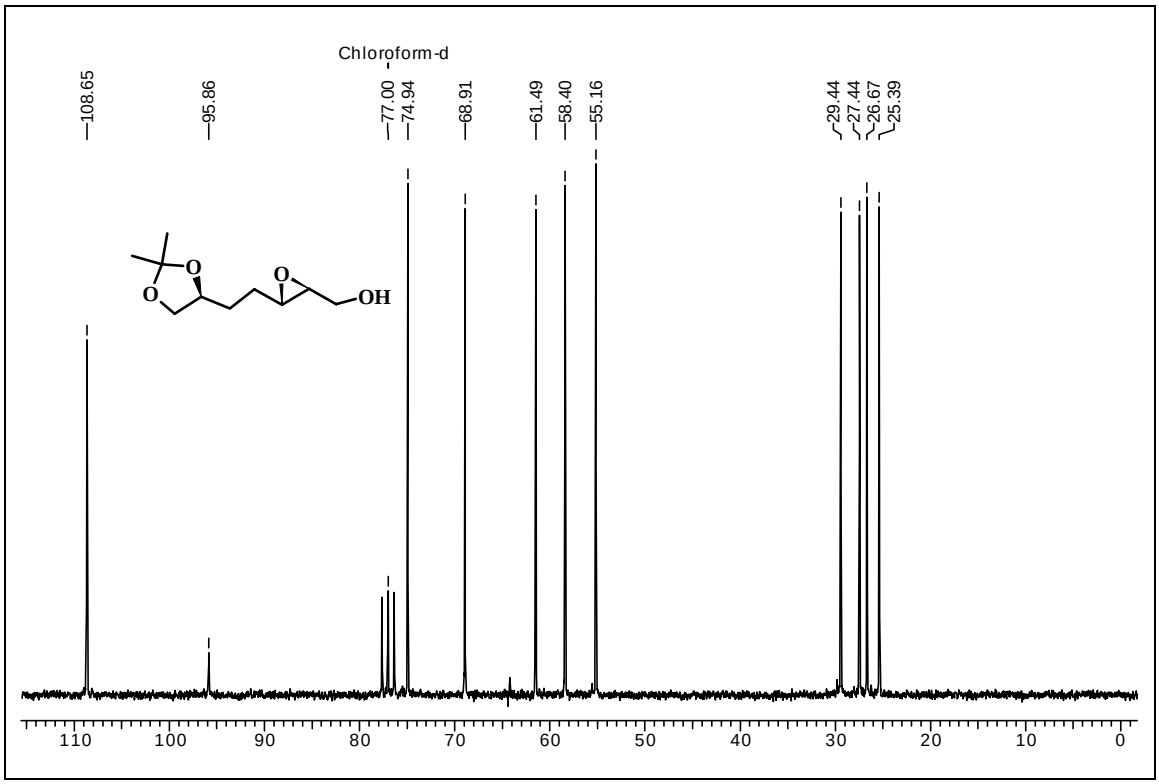
^{1}H NMR spectrum of compound 85 in $CDCl_3$



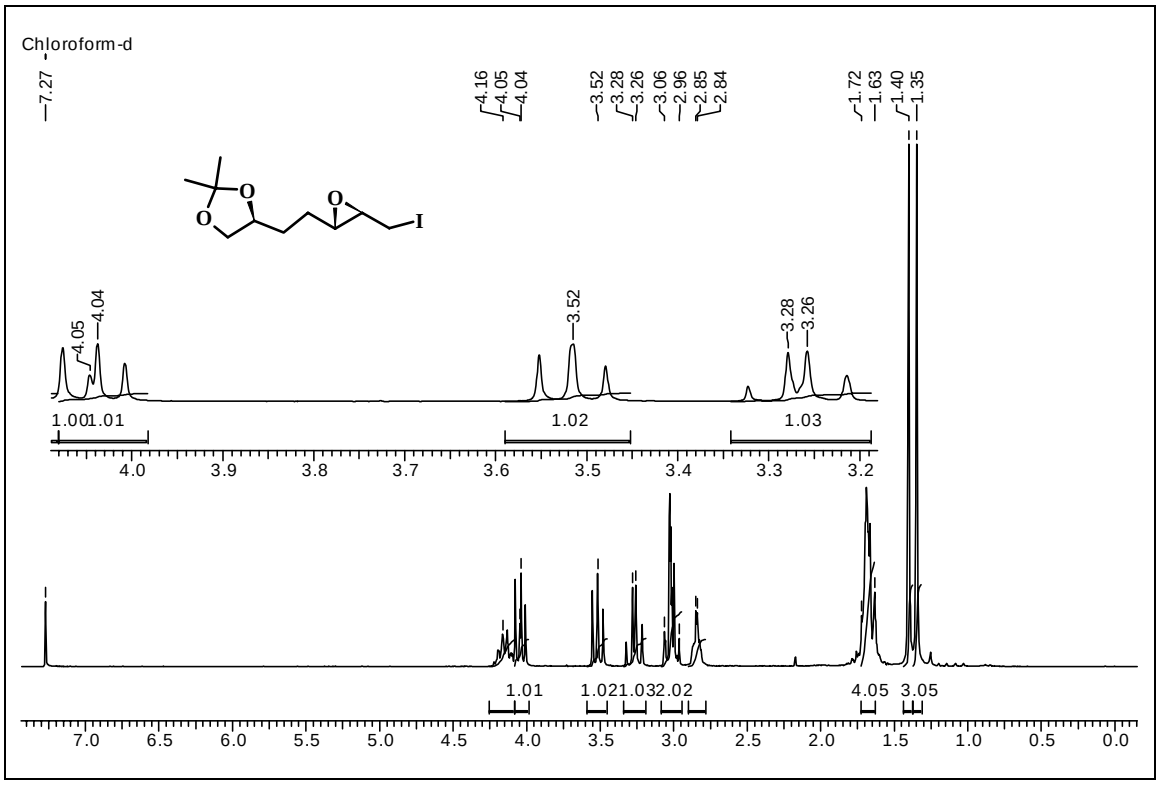
^{13}C NMR spectrum of compound 85 in $CDCl_3$



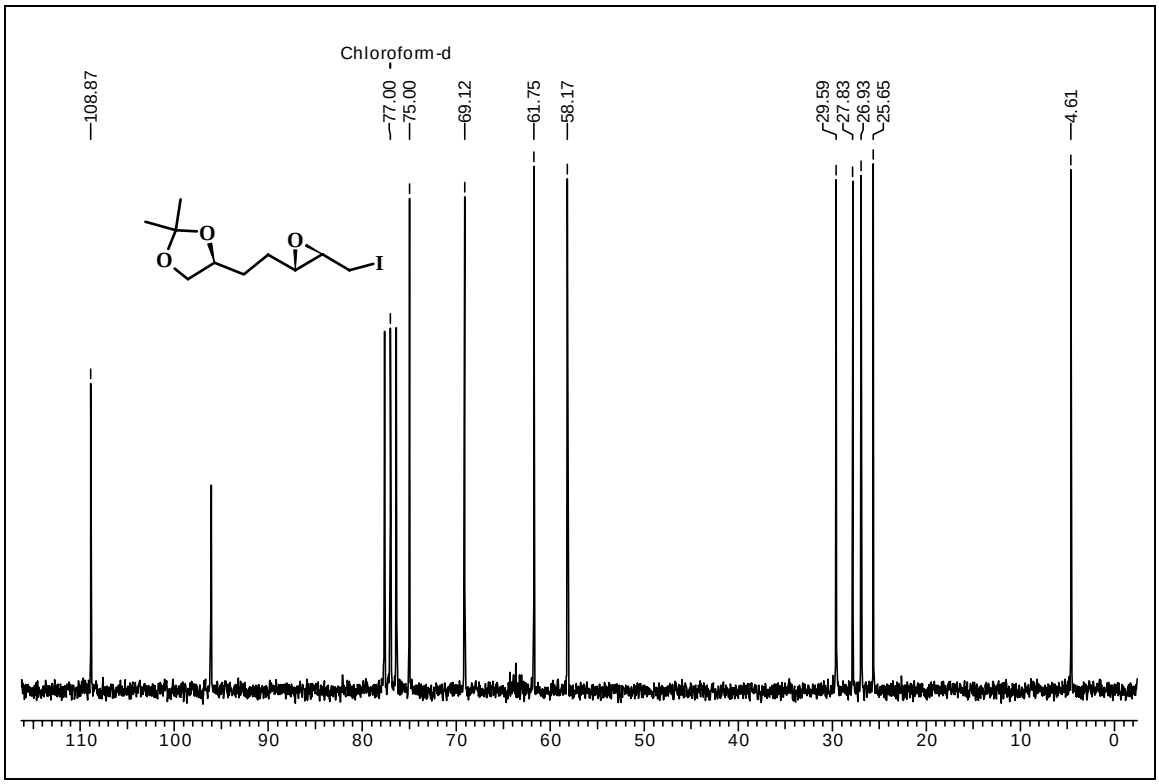
^{1}H NMR spectrum of compound 84 in $CDCl_3$



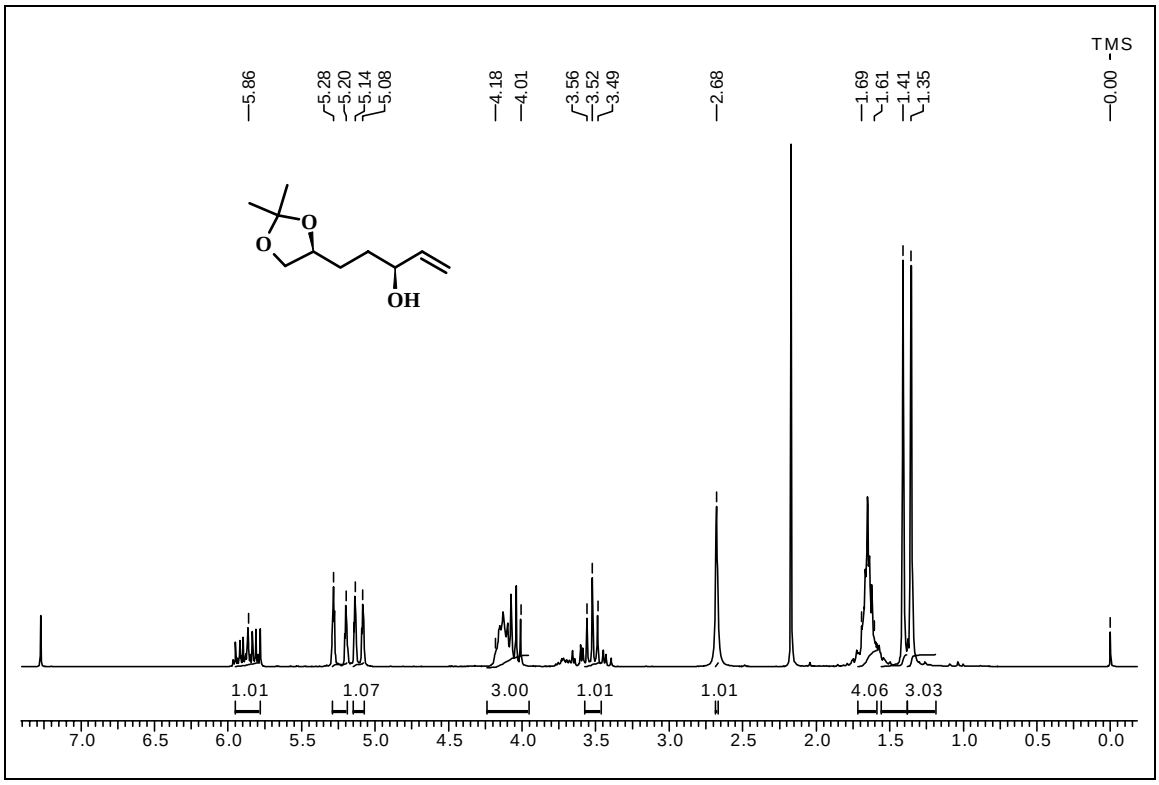
^{13}C NMR spectrum of compound 84 in $CDCl_3$



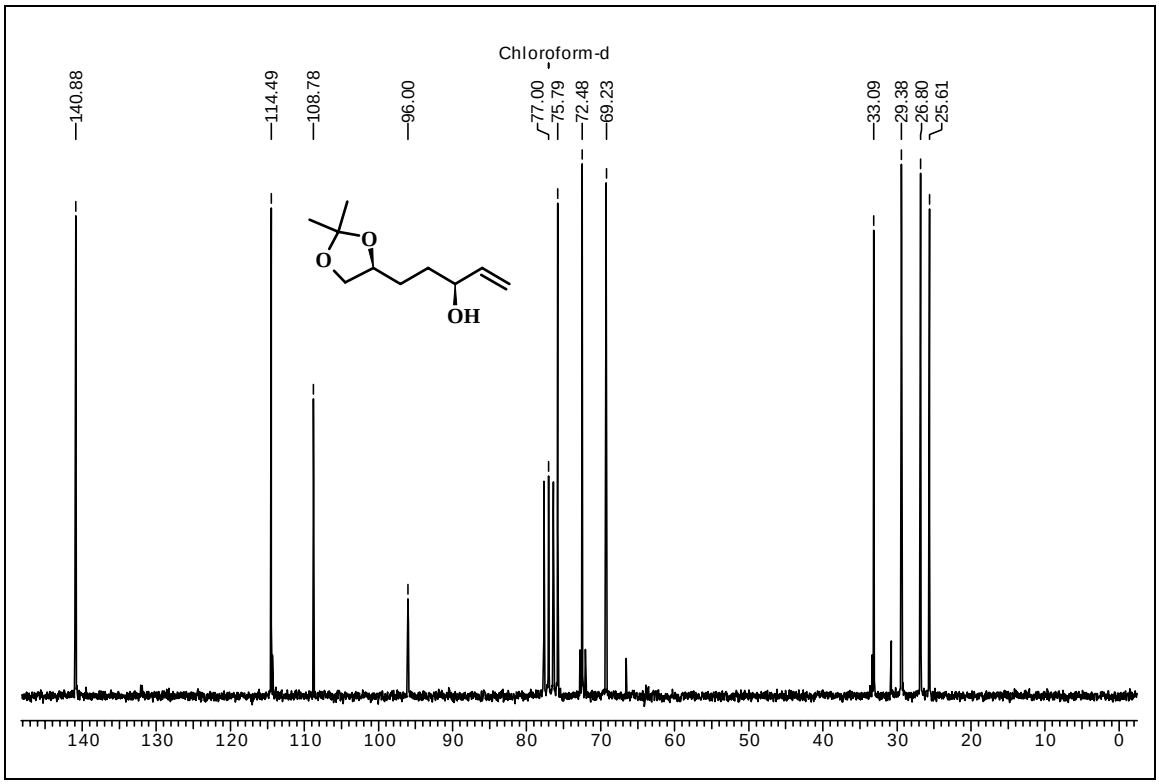
^{1}H NMR spectrum of compound 83 in $CDCl_3$



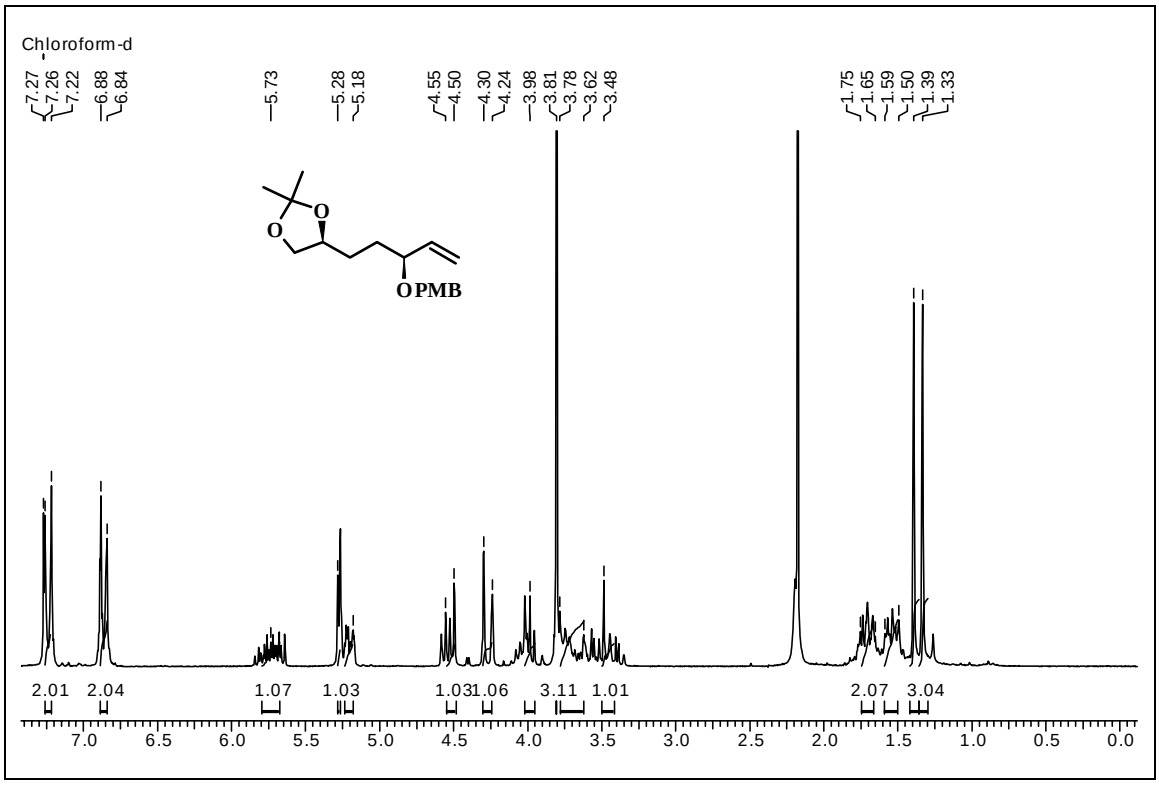
^{13}C NMR spectrum of compound 83 in $CDCl_3$



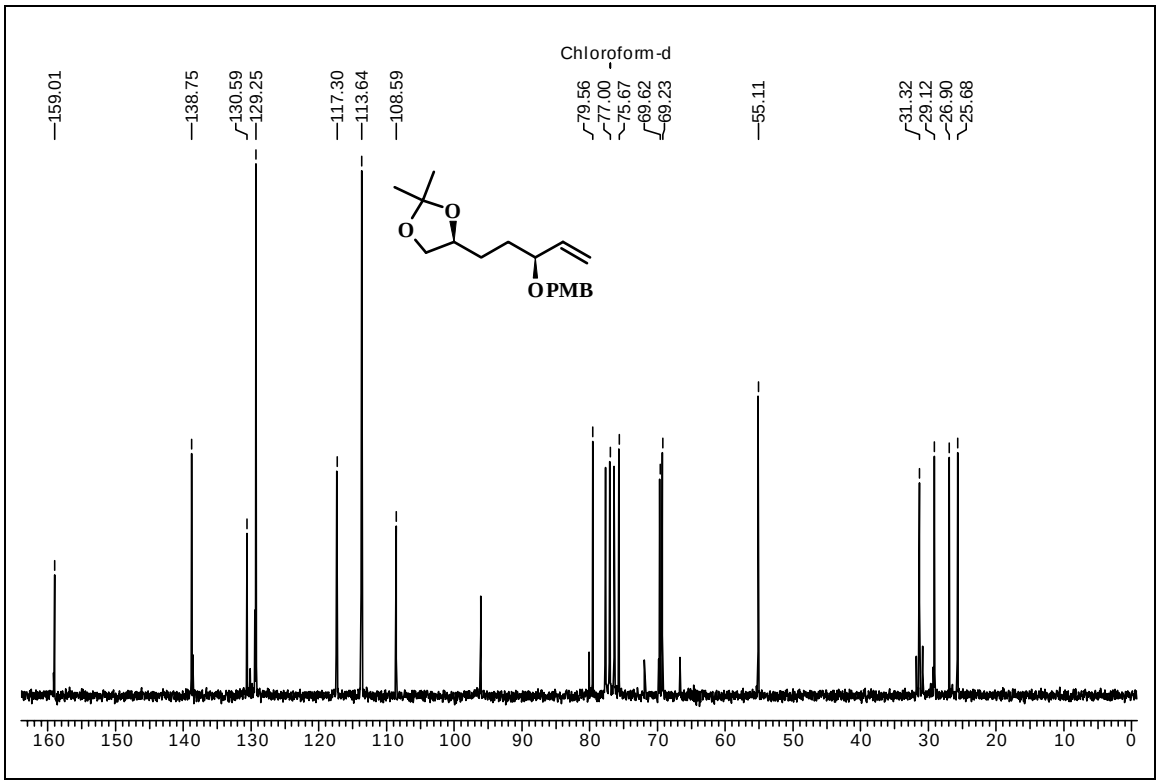
^{1}H NMR spectrum of compound 103 in $CDCl_3$



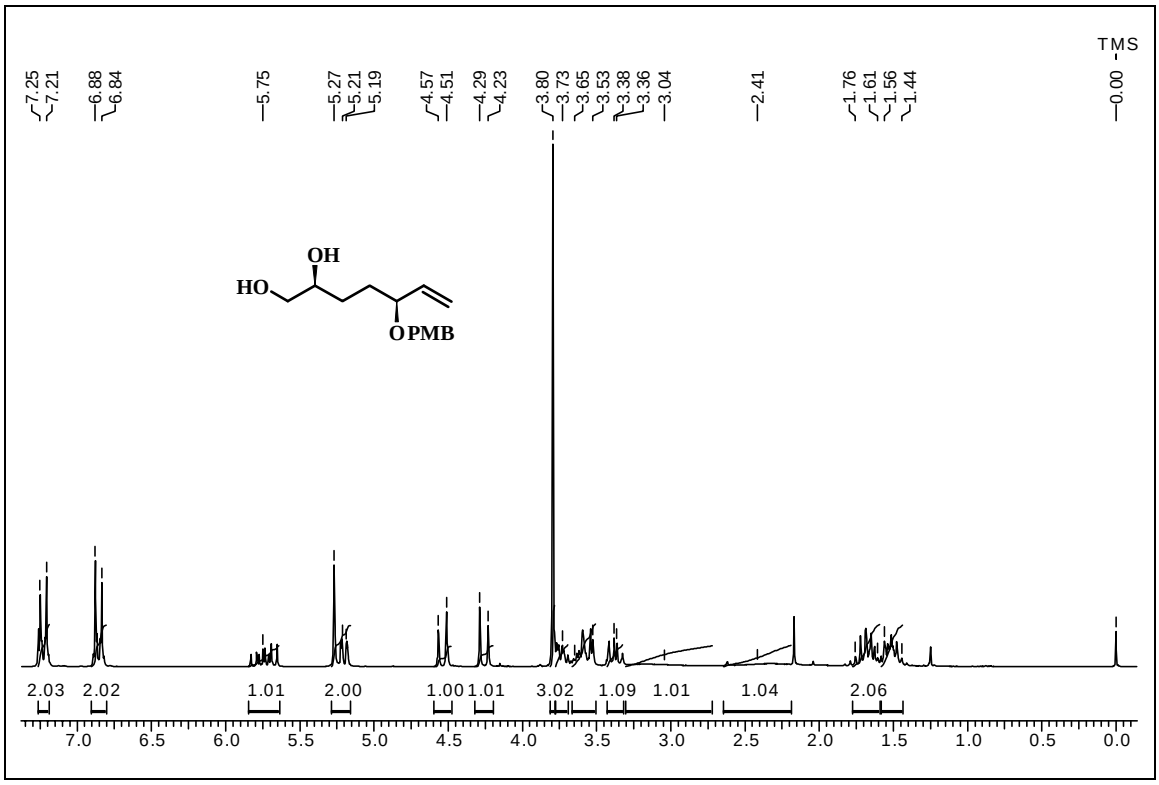
^{13}C NMR spectrum of compound 103 in $CDCl_3$



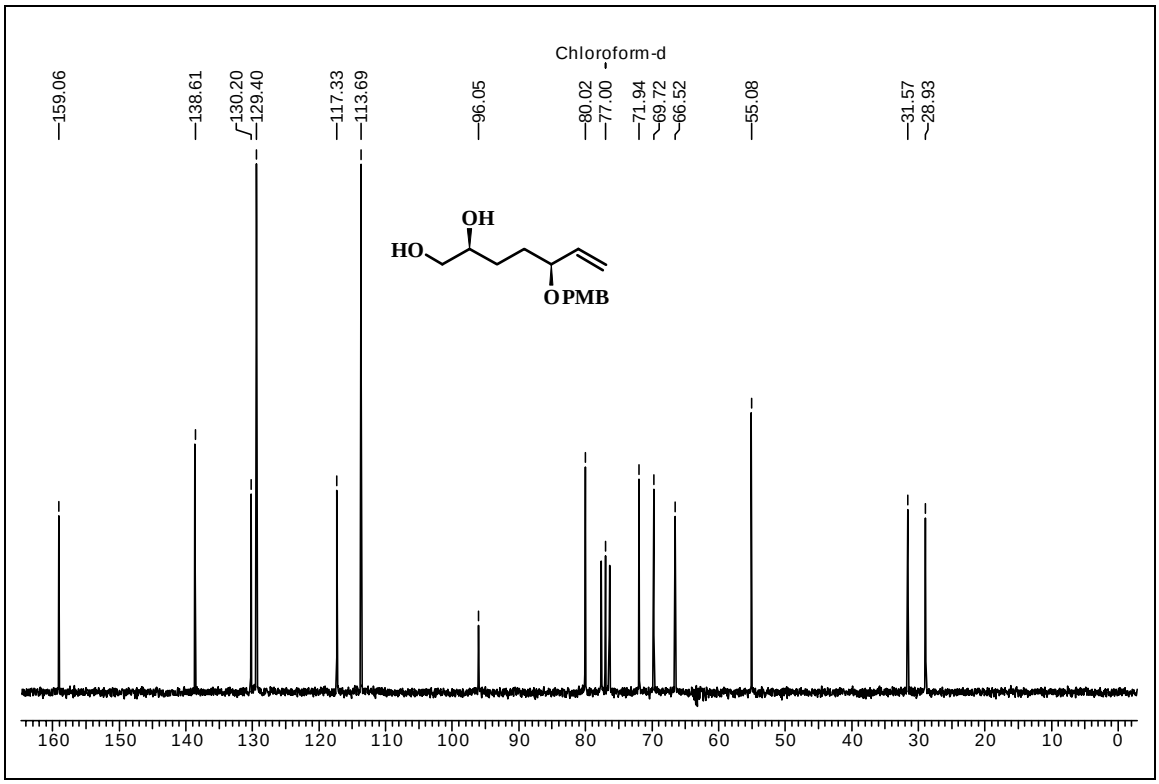
^{1}H NMR spectrum of compound 104 in $CDCl_3$



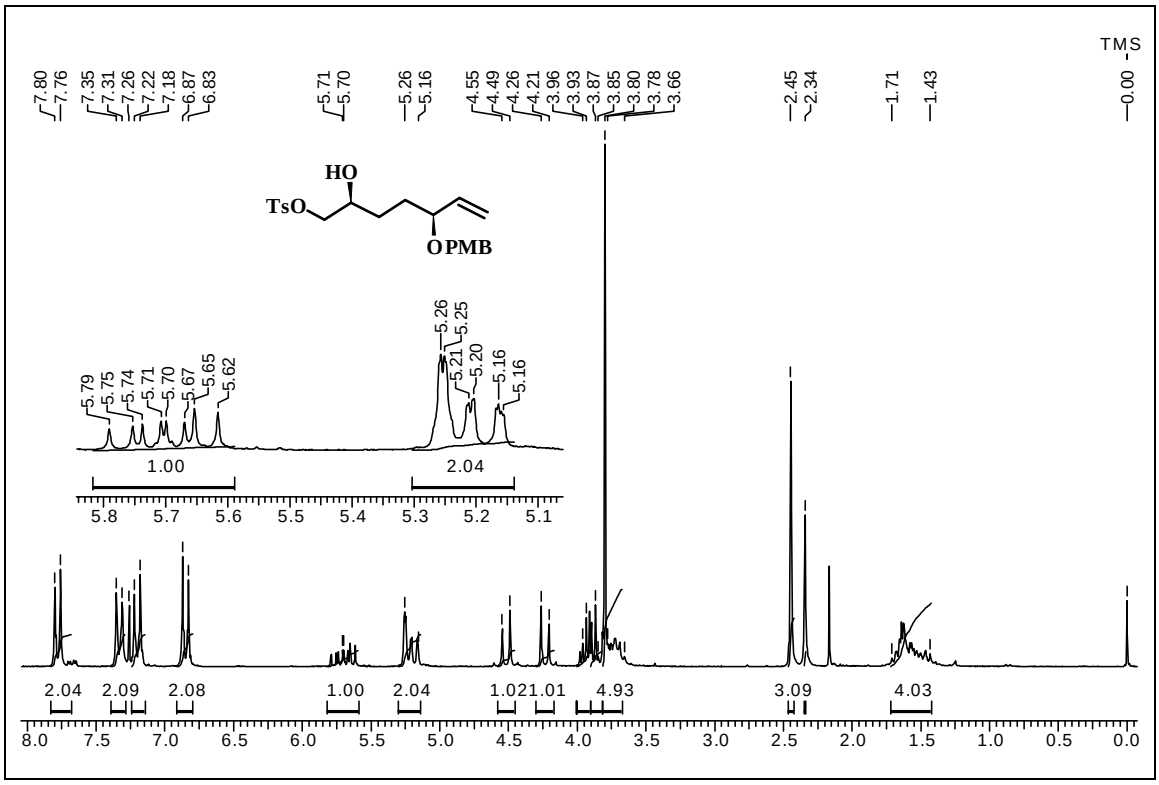
^{13}C NMR spectrum of compound 104 in $CDCl_3$



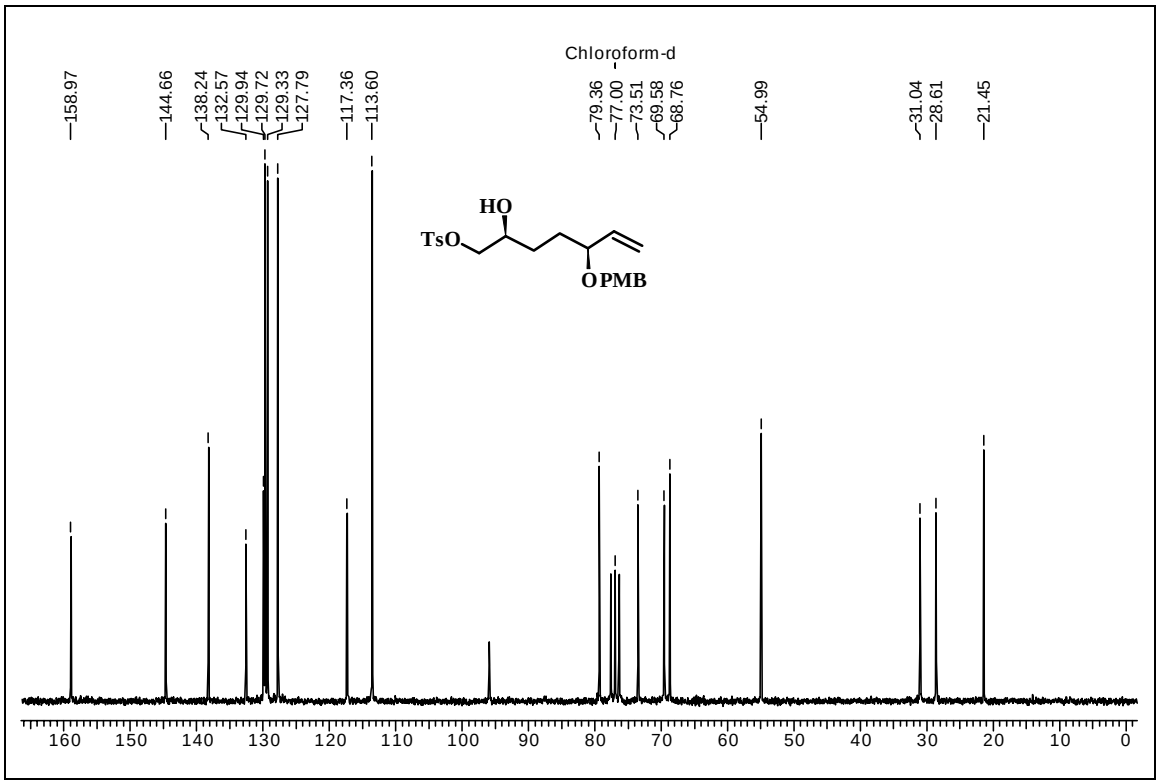
^{1}H NMR spectrum of compound 82 in $CDCl_3$



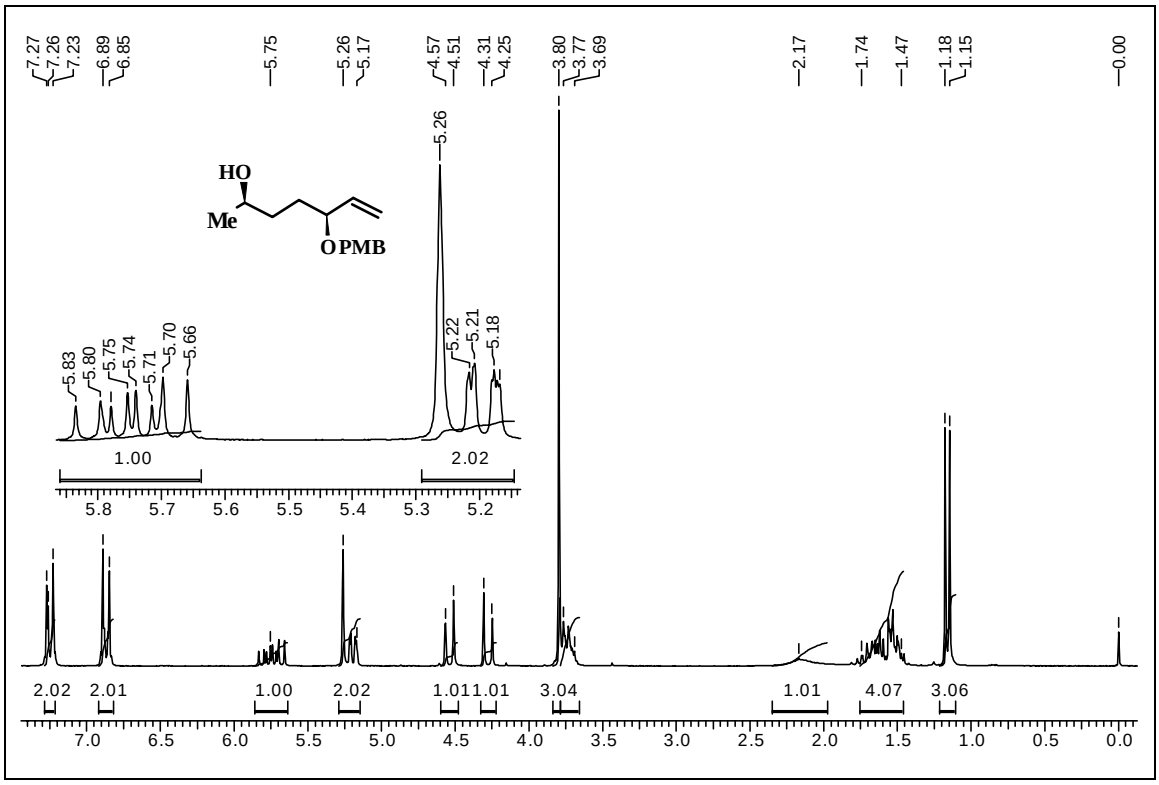
^{13}C NMR spectrum of compound 82 in $CDCl_3$



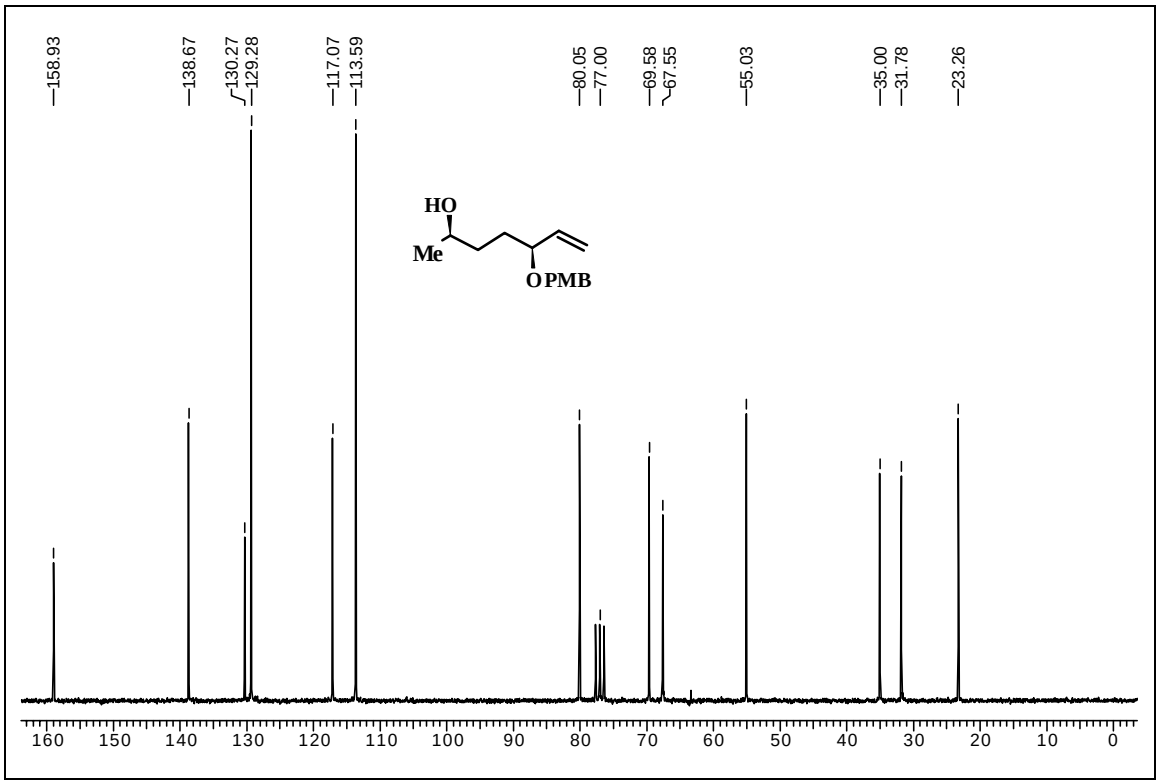
^{1}H NMR spectrum of compound 105 in $CDCl_3$



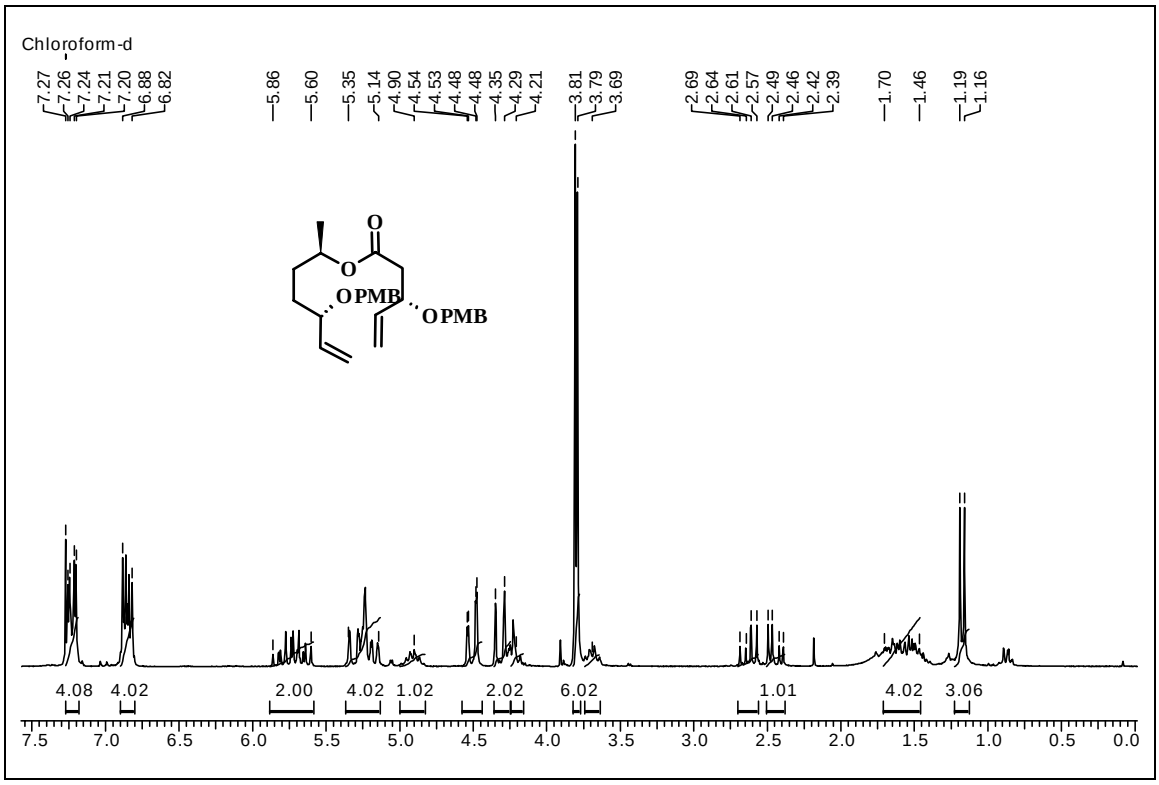
^{13}C NMR spectrum of compound 105 in $CDCl_3$



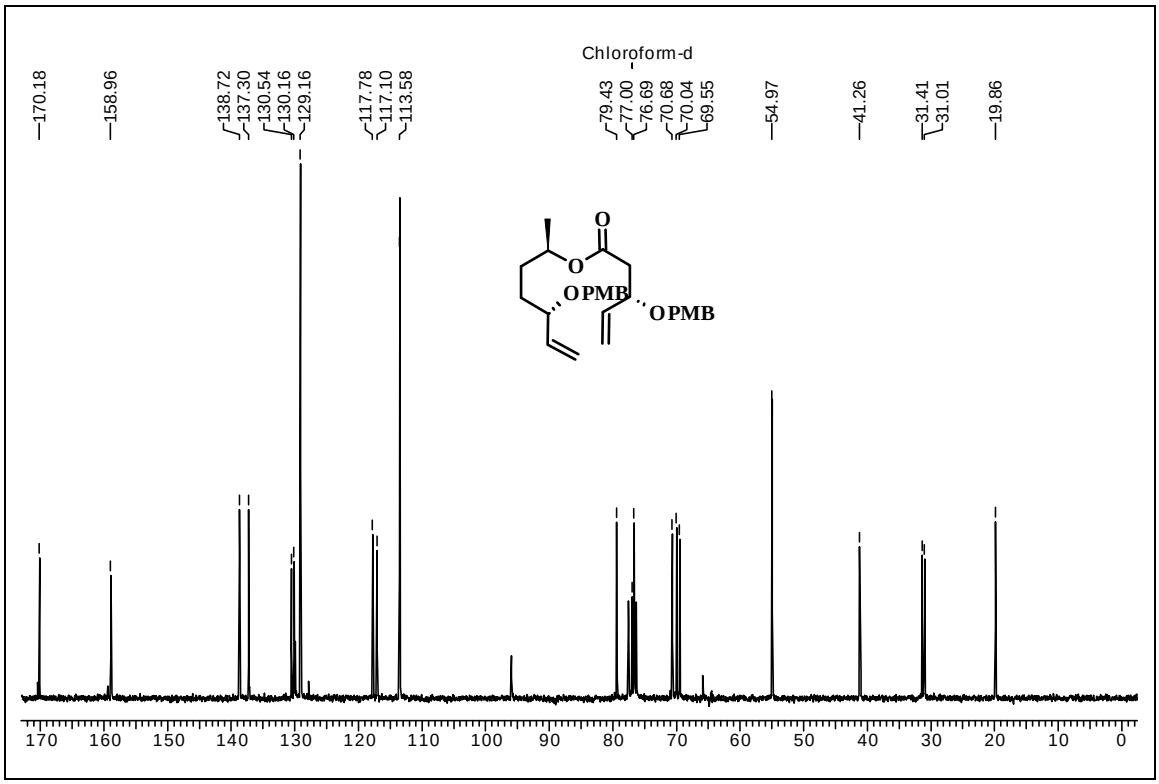
^{1}H NMR spectrum of compound 73 in $CDCl_3$



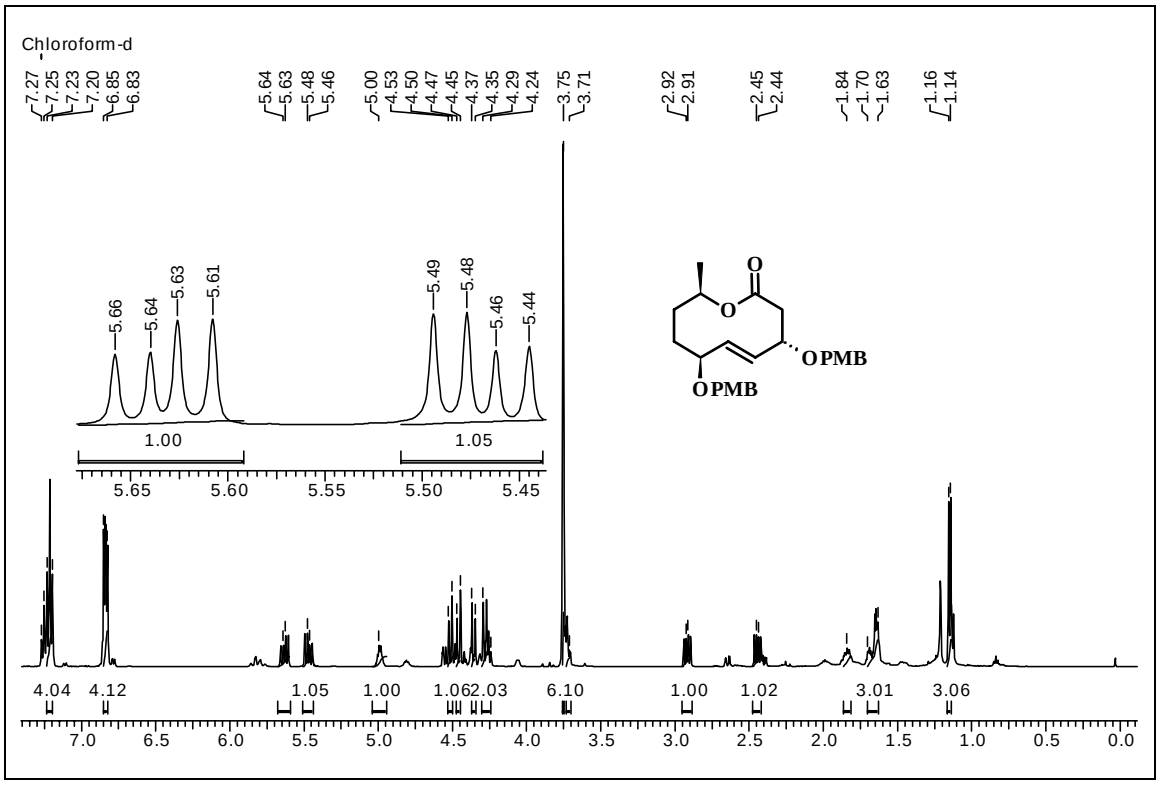
^{13}C NMR spectrum of compound 73 in $CDCl_3$



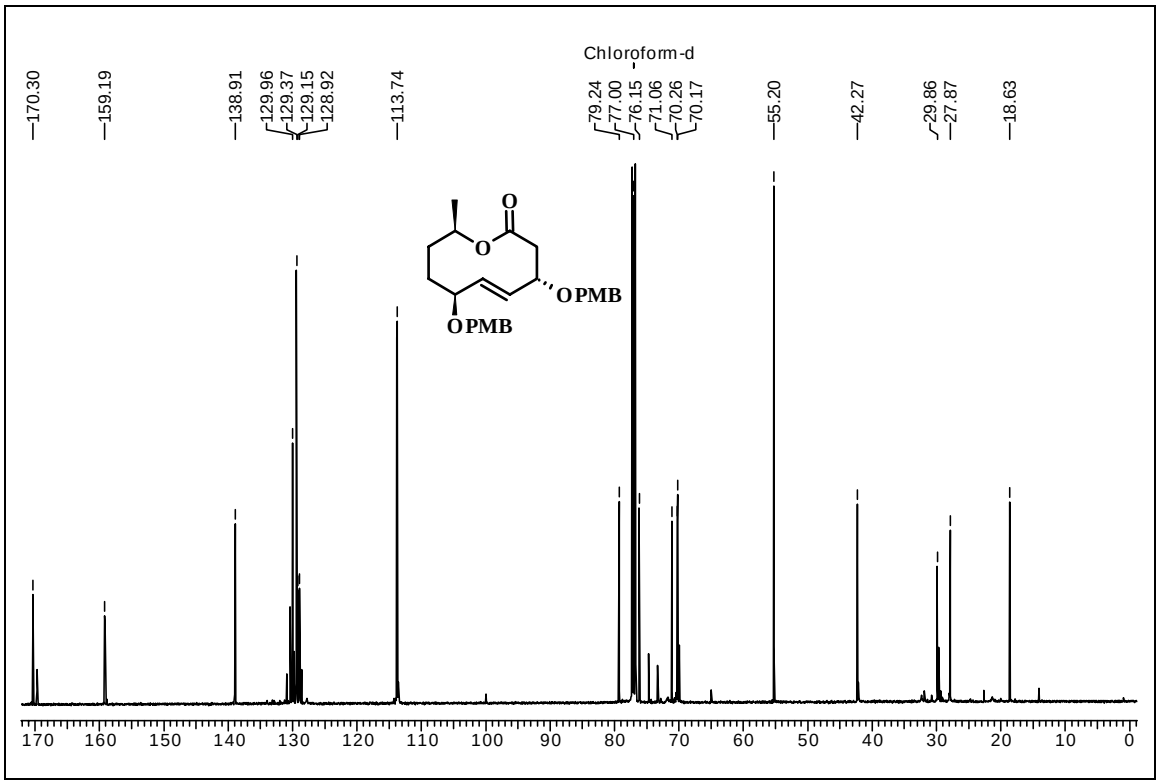
^{1}H NMR spectrum of compound 72 in $CDCl_3$



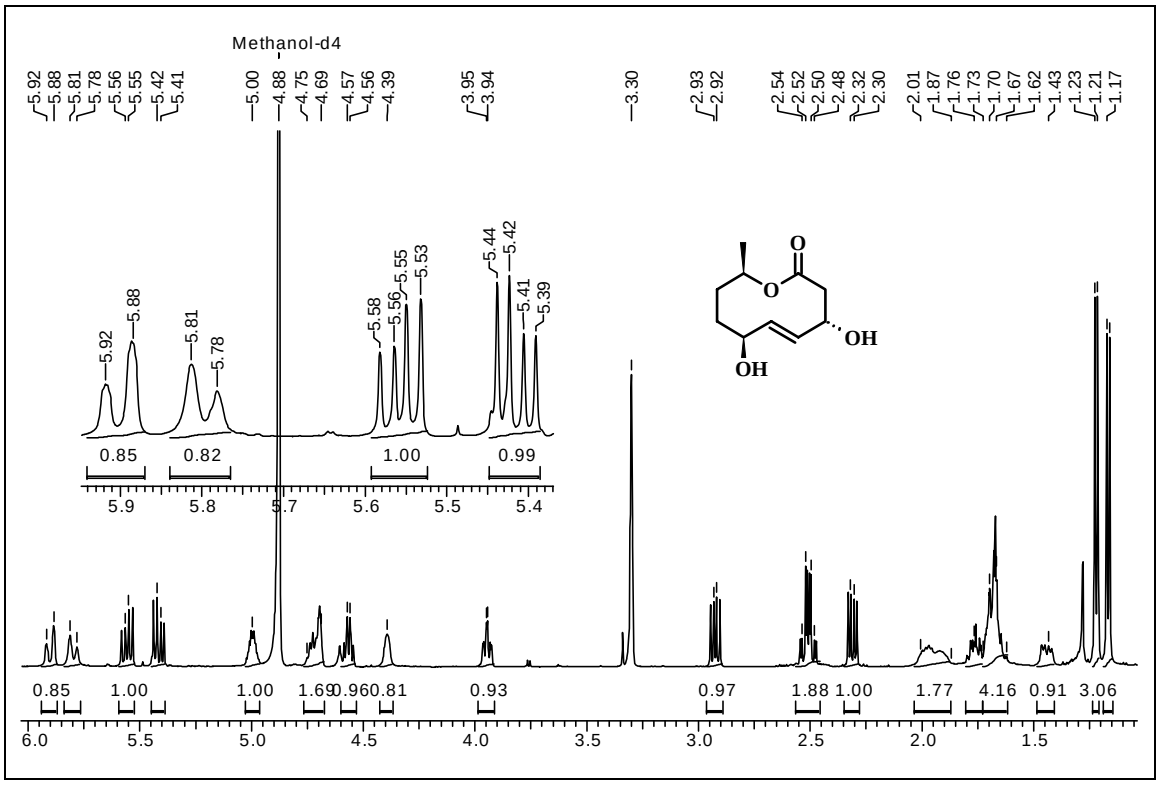
^{13}C NMR spectrum of compound 72 in $CDCl_3$



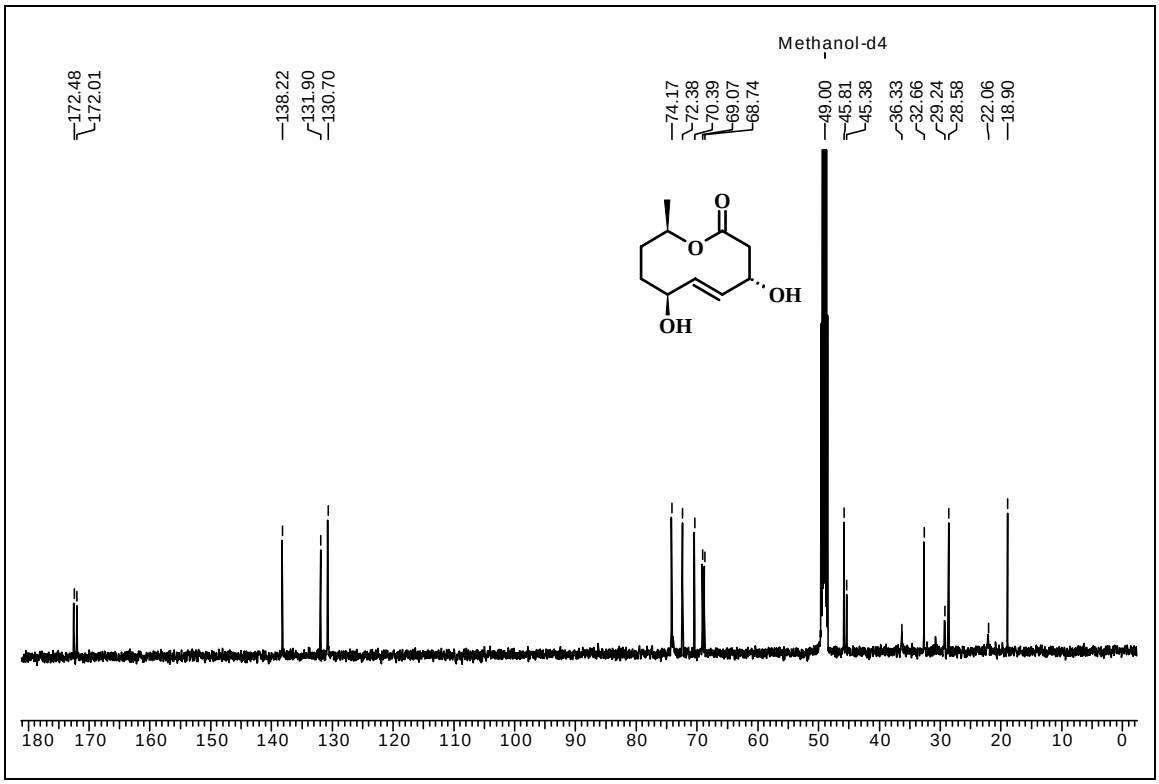
^{1}H NMR spectrum of compound 71 in $CDCl_3$



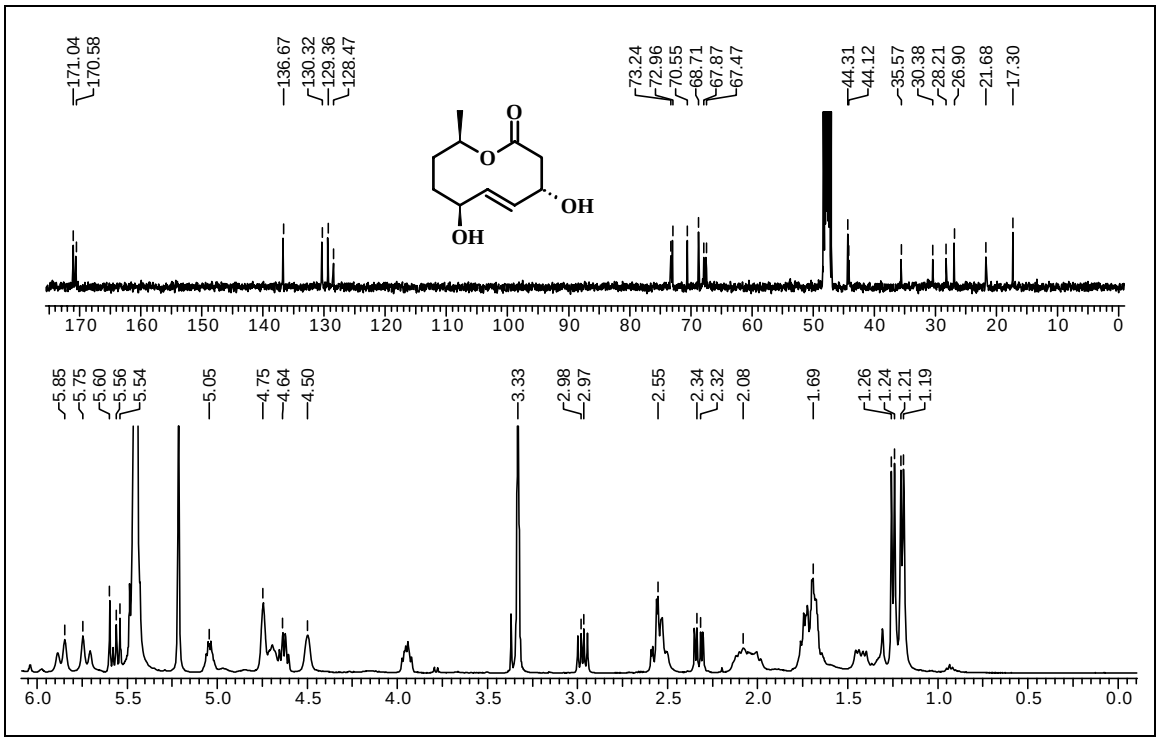
^{13}C NMR spectrum of compound 71 in $CDCl_3$



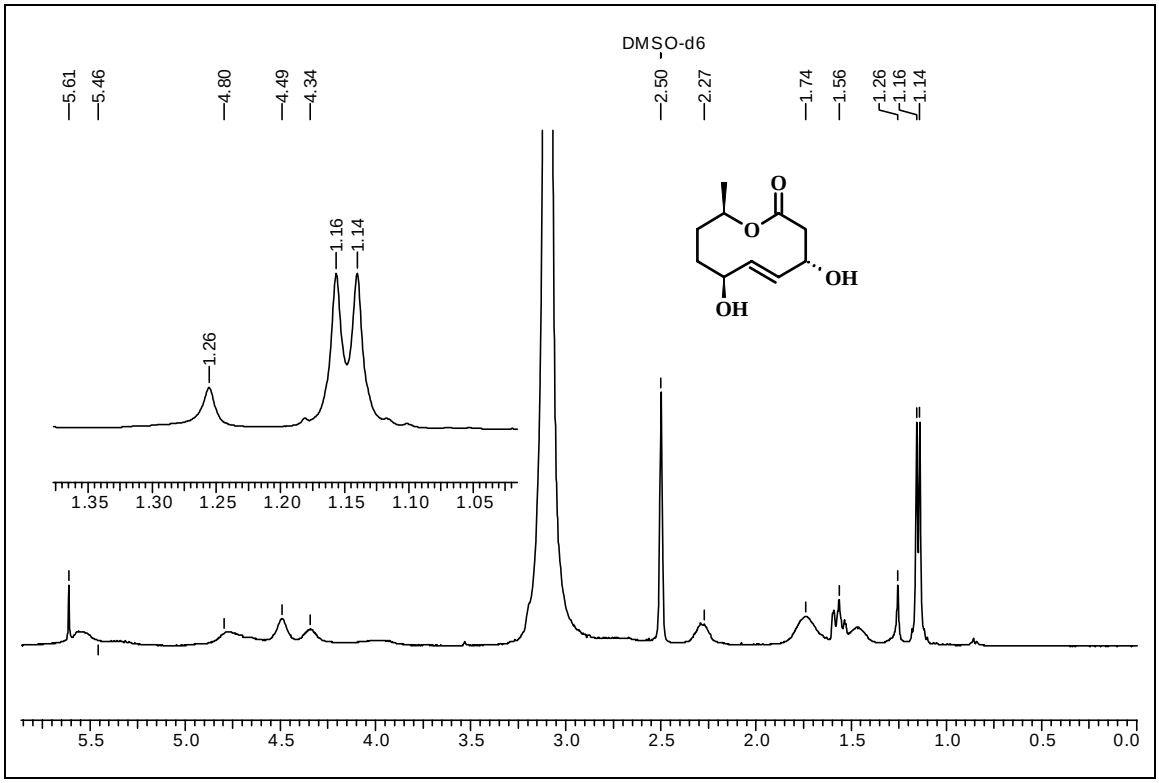
^{1}H NMR spectrum of compound 58 in CD_3OD



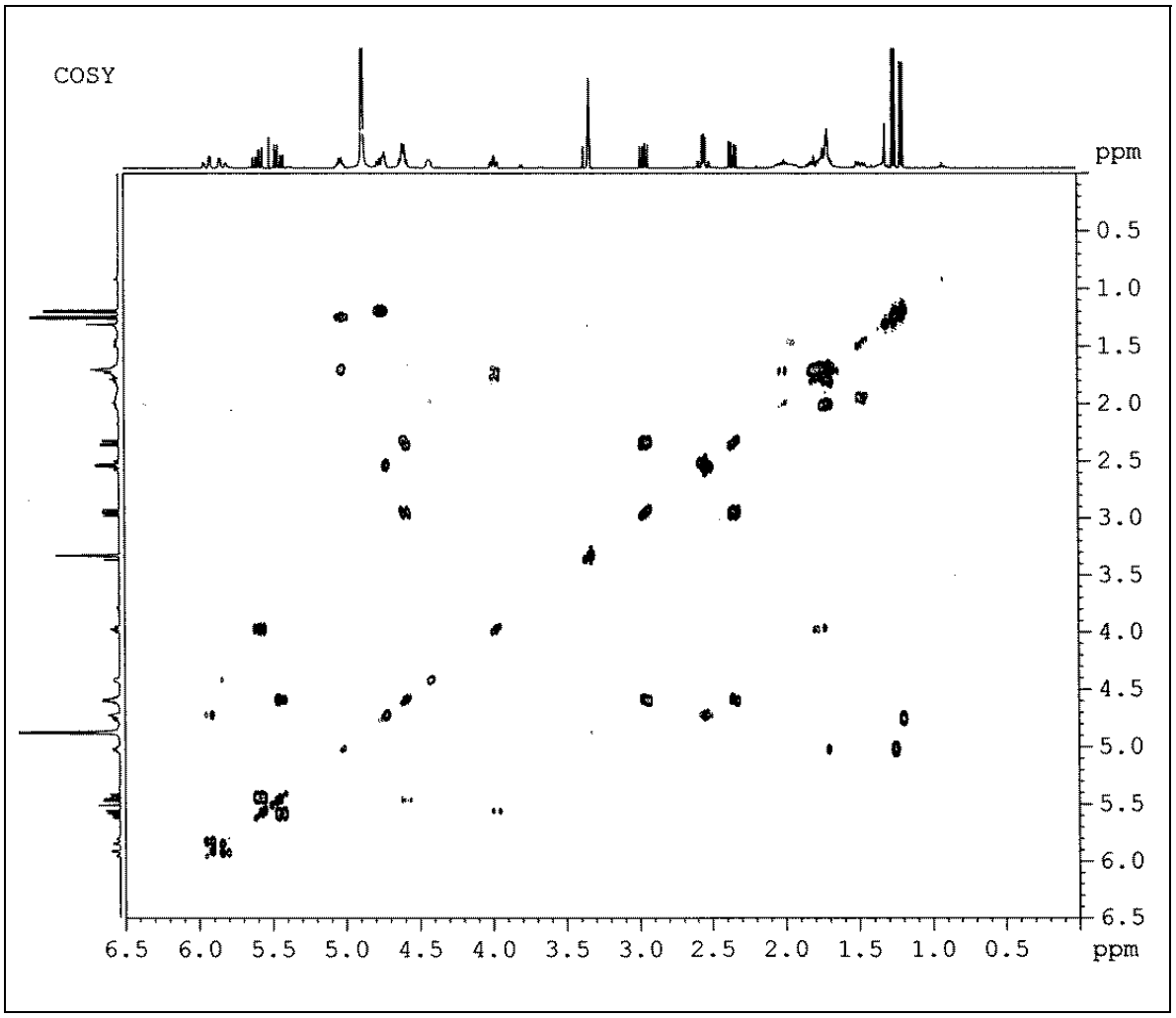
^{13}C NMR spectrum of compound 58 in CD_3OD

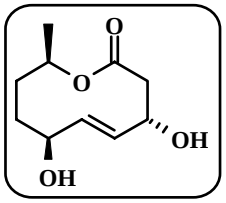


^{1}H NMR & ^{13}C NMR of spectrum of compound 58 in CD_3OD at -40°C

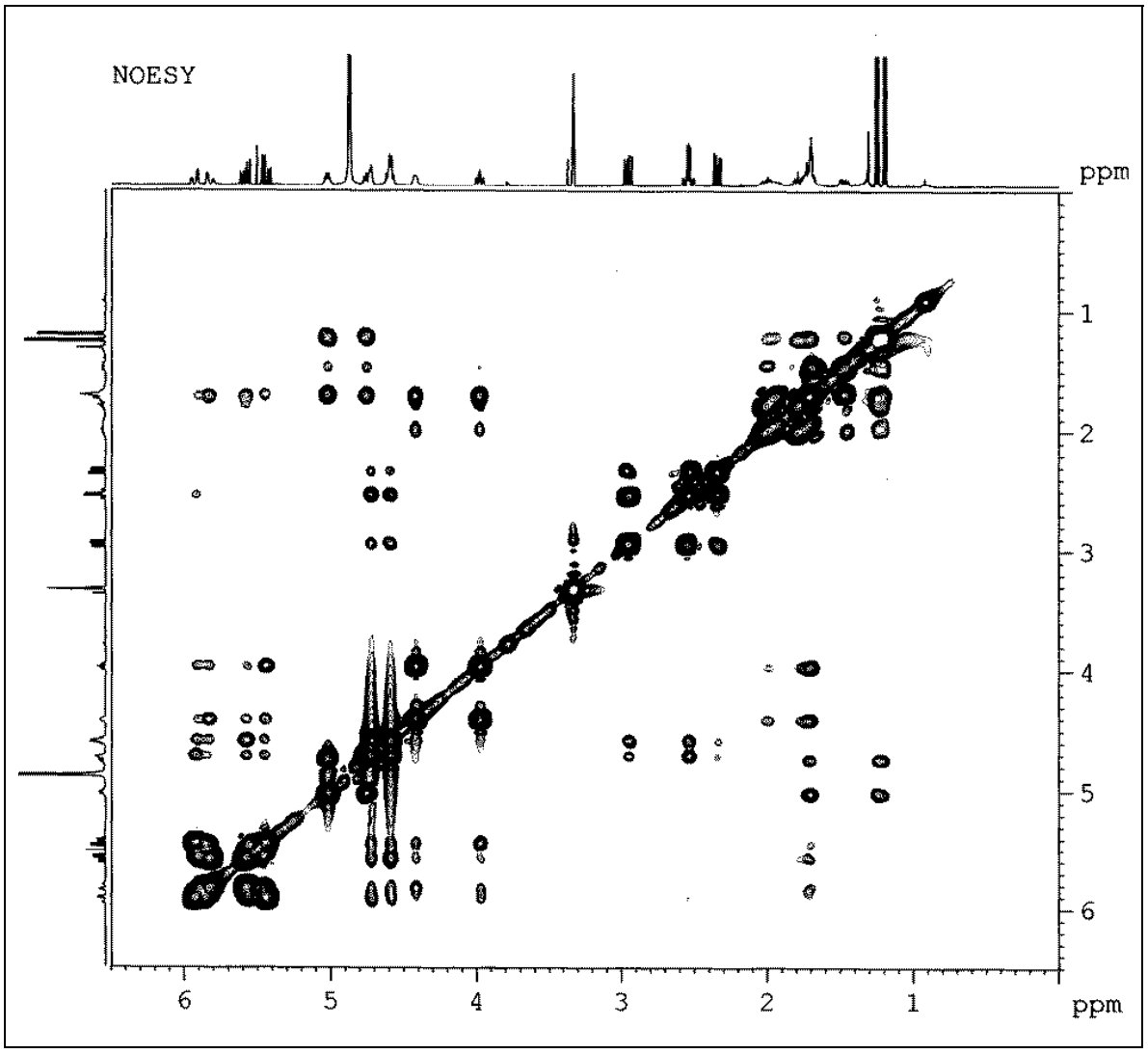


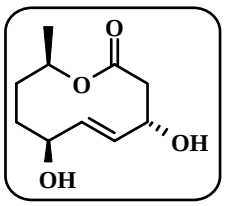
^{1}H NMR of spectrum of compound 58 in DMSO-d_6 at 110 °C



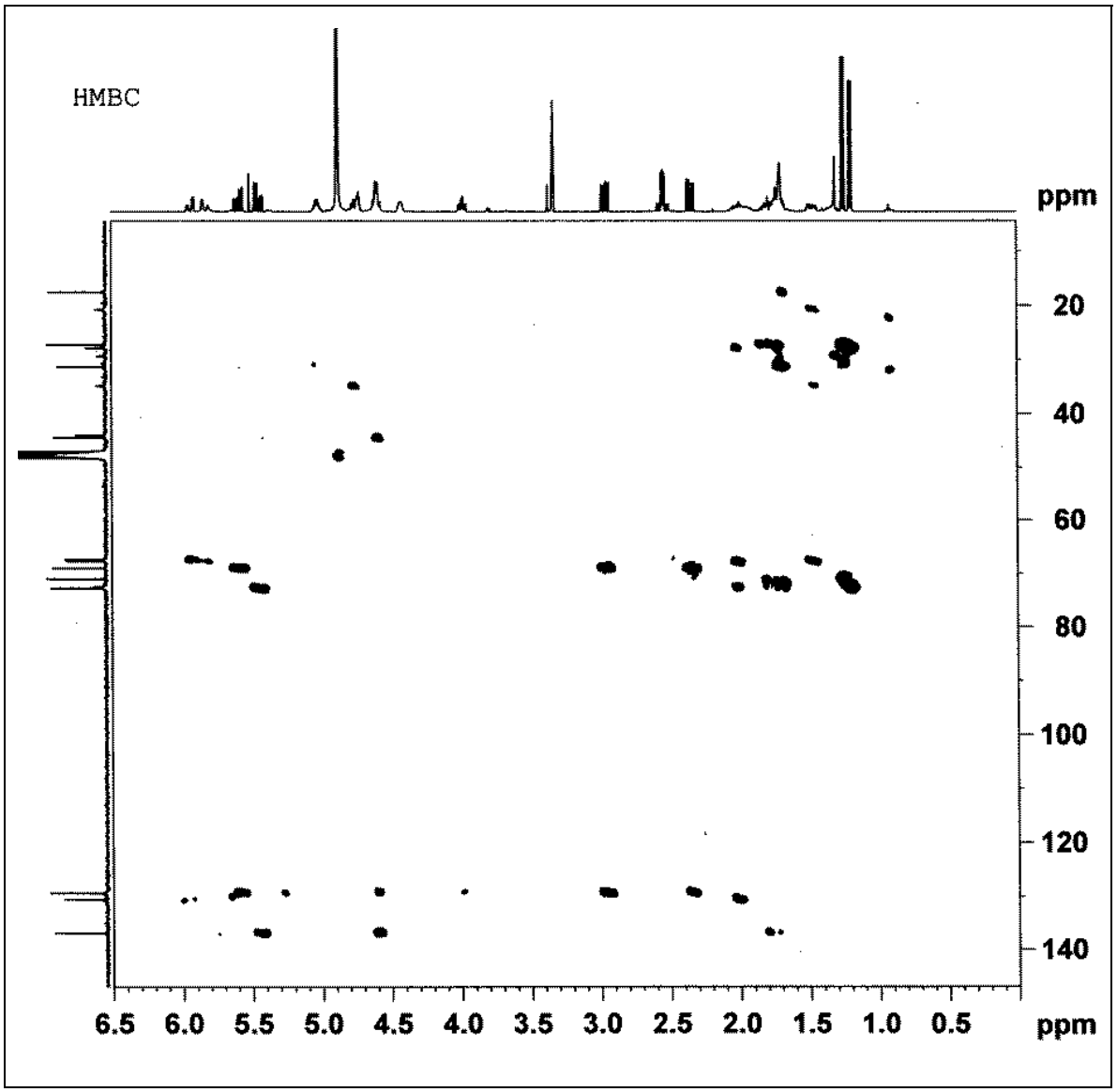


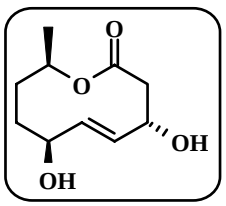
COSY spectrum of decarestrictine C_1



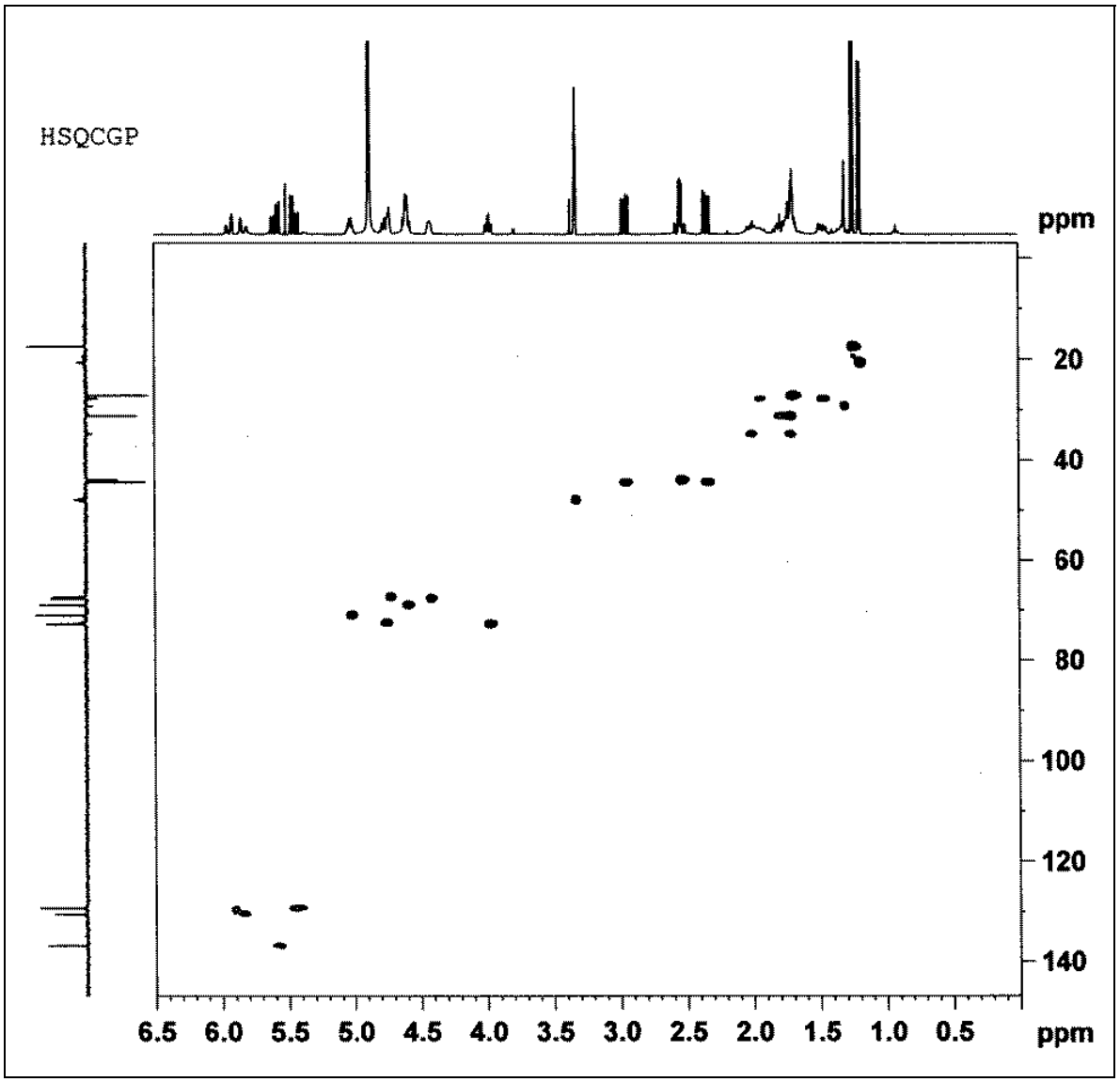


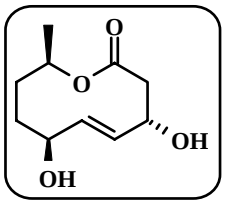
NOESY spectrum of decarestrictine C_1



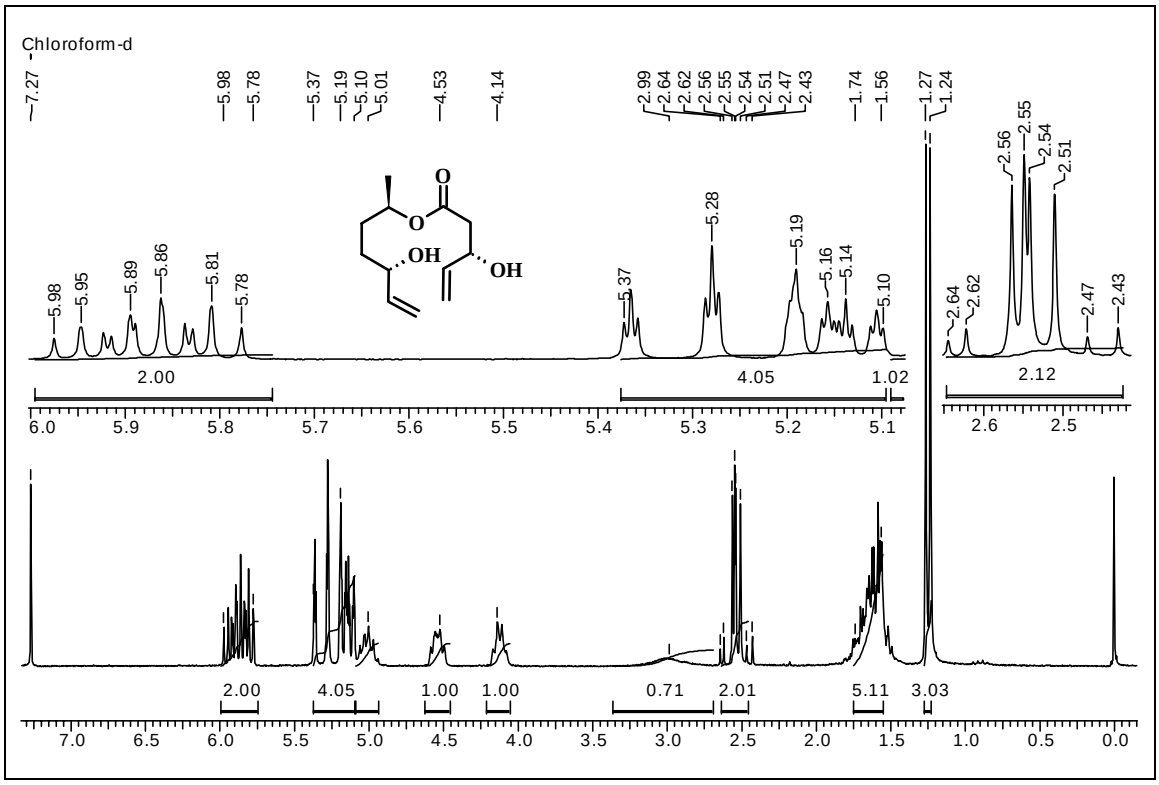


HMBC spectrum of decarestrictine C_1

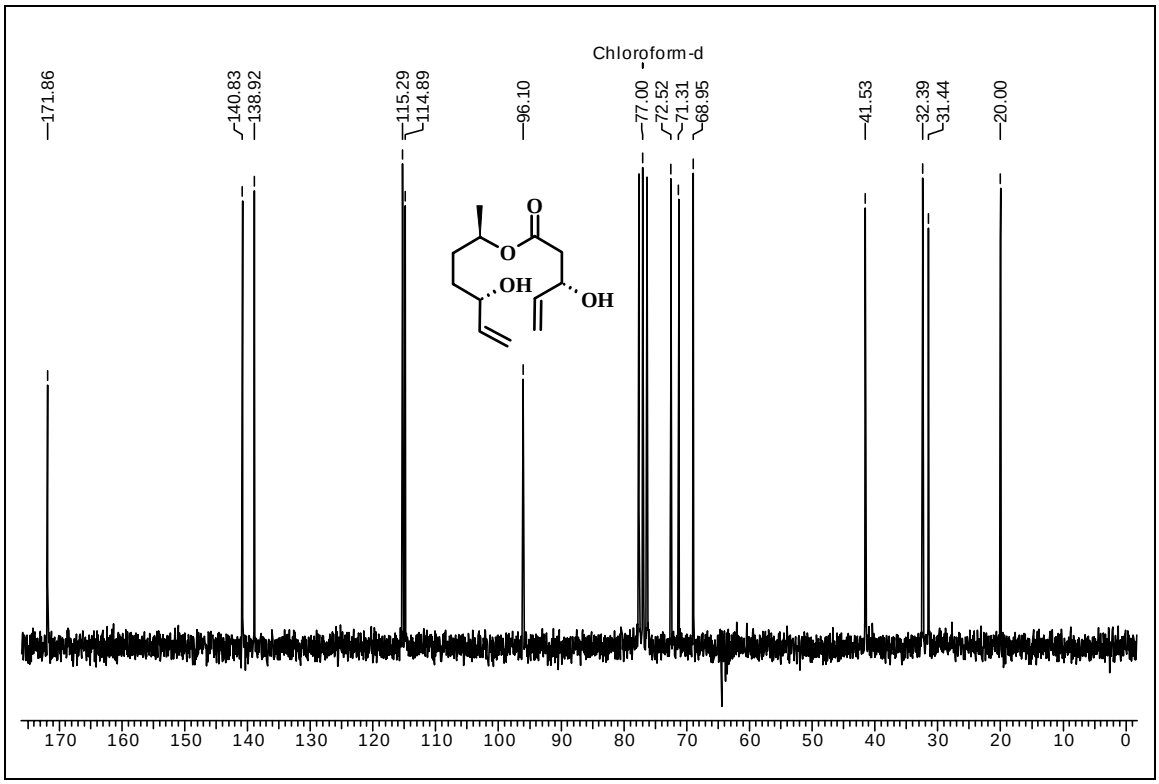




HSQC spectrum of decarestrictine C_1



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



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

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LIST OF PUBLICATIONS

1. Stereoselective synthesis of the polyketide chain of nagahamide A. Debendra K. Mohapatra, Siddhartha Ray Chaudhuri, **Gokarneswar Sahoo**, Mukund K. Gurjar, *Tetrahedron: Asymmetry* **2006**, *17*, 2609.
2. Practical syntheses of 4-fluoroprolines. Mukund S. Chorghade, Debendra K. Mohapatra, **Gokarneswar Sahoo**, Mukund K. Gurjar, Manish V. Mandlecha, Nitin Bhoite, Santosh Moghe, Ronald T. Raines, *J. Flourine Chem.* **2008**, *in press* (doi: 10.1016/j.jfluchem.2008.06.024).
3. Carbohydrate templates for synthesis of prototype renin inhibitors. Debendra K. Mohapatra, **Gokarneswar Sahoo**, Kuppusamy Sankar, Mukund K. Gurjar, communicated.
4. Total syntheses of decarestrictine C_1 and C_2: synthesis based structure modification. Debendra K. Mohapatra, **Gokarneswar Sahoo**, Dhondi K. Ramesh, Mukund S. Chorghade, Mukund K. Gurjar, Michael A. Giardello, and Robert H. Grubbs, communicated.
5. 1,1'-Thiocarbonyldiimidazole: a reagent for many transformations. **Gokarneswar Sahoo**, *Spotlight, Synlett*, communicated.
6. Stereoselective Simmons-Smith cyclopropanation on carbohydrate templates. Mukund K. Gurjar, **Gokarneswar Sahoo**, Debendra K. Mohapatra, manuscript under preparation.
7. Formal total synthesis of basiliskamides A and B. Mukund K. Gurjar, **Gokarneswar Sahoo**, Debendra K. Mohapatra, manuscript under preparation.
8. Protecting group directed ring-closing metathesis; Mathematical calculations. Debendra K. Mohapatra, **Gokarneswar Sahoo**, Dhondi K. Ramesh, Mukund S. Chorghade, Mukund K. Gurjar, Michael A. Giardello, and Robert H. Grubbs, manuscript under preparation.

ERRATUM