SYNTHESIS OF STEMOAMIDE AND SOME NOVEL BICYCLIC NUCLEOSIDES

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PUNE-411008

JULY 2004

SYNTHESIS OF STEMOAMIDE AND SOME NOVEL BICYCLIC NUCLEOSIDES

A THESIS

SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

TO

OSMANIA UNIVERSITY

BY

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JULY 2004

DEDICATED

TO MY BELOVED

PARENTS

DECLARATION

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

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CERTIFICATE

The research work presented in thesis entitled " **Synthesis of stemoamide and some novel bicyclic nucleosides** " has been carried out under my supervision and is a bonafide work of **Mr. Srinivasa Reddy D P**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

Pune-8

July 2004

(Dr. M. K. Gurjar)

Research Guide

Acknowledgements

I take this opportunity with immense pleasure to express my deep sense of gratitude to my teacher and research guide Dr. M. K. Gurjar, Head, Division of Organic Chemistry (Tech.), who has helped me a lot to learn and think more about chemistry. I thank him for his excellent guidance, constant encouragement, sincere advice and unstinted support during all the times of my Ph. D. life. Working with him was a great pleasure and learning experience.

I would like to thank Dr. C. V. Ramana, Dr. Hotha Srinivas, Dr. D. K. Mahapatra and Dr. V. R. Peddireddi for the helpful discussions. The help of Dr. R. A. Joshi, Dr. R. R. Joshi, Mr. I. Shivakumar, Dr. Nagaiah, Dr. M. N. Deshmukh, Dr. Muthukrishnan, Dr. A. Murugan, Dr. Bhanu Chanda, Dr. Kalkote and Dr. Vincent is greatly acknowledged.

I gratefully acknowledge the guidance, training and support extended by my senior colleagues Dr. A. M. S. Murugaiah, Dr. Kishore, Dr. Ranga Reddy, Dr. K. K. Reddy, Dr. S. V. R. Nadh, Dr. Arindam, Dr. Murali Krishna, Dr. Baquer, Mr. B. S. Reddy, Mr. Joseph, Mahesh, Nagaprasad, Sankar and Siddhartha during the tenure of my Ph.D life. I would like to thank all my colleagues Eku, Bhargav, Ramesh, Raghupathi, Tushar, Smriti, Ramdas, Sukhen, Dhananjoy, Manjusha, Seetaram, Bhagwat, Sabita, Gorakh, Kulbhushan, Kiran, Srinivas, Nageshwar, Sahoo, Pradip, Chinmoy, Bhaskar, Sumanth, Rosy, Rehaman, Rita, Abhijit, Anuj, Sharad, Indu, Susheel, Soumitra, Ganesh, Debabrata and Mondal for their cooperation and friendly attitude.

Help from the spectroscopy and mass groups is gratefully acknowledged. I sincerely thank Dr. Rajmohan, Mrs. U. D. Phalgune and Mr. Sathe for the helpful discussions and cooperation.

I sincerely acknowledge the help of Mrs. C. Raphel, Mrs. Kulkarni and all other office staff.

I wholeheartedly thank my colleagues at NCL and GJ hostel for their cheerful company, which made my stay at NCL memorable one. My regards to my friends and all well wishers.

Special thanks are due to my sirs Dr. Ashok, Dr. Ravi Kumar, Mr. Surendher Reddy and Dr. Pulla Rao who taught me the basics of chemistry in my college days.

I would like to thank my friends Maruthi, Venkat Reddy, Chandramouli, C. V. Rao, Mahesh, Hima, Kishore, Ramesh, Brahmanandareddy, Ananth, Venkat, Y. V. N. Reddy and all my M. Sc. and B. Ed. classmates for their helpful suggestions and guidance. I offer special thanks to my childhood friends Praveen, Adaviraju, Pavan, Jangaiah and Venkatesh for their help and guidance.

Whatever I am and whatever I will be in future is because of the goodwill and unstinted support that I have received from my parents. Their kind cooperation helped me in pursuing my PhD and no words are enough to acknowledge them. Their constant encouragement, support and sacrifice made me achieve the goal. My special thanks to my brothers, sister-in-law and all my cousins who stood by me during all difficult times.

My special thanks to my wife Mamatha for the care and cooperation during the preparation of thesis.

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

Srinivasa Reddy D P

ABBREVIATIONS

Ac	-	Acetyl
AcOH	-	Acetic acid
Ac_2O	-	Acetic anhydride
AIBN	-	2,2'-Azobisisobutyronitrile
Bn	-	Benzyl
BnBr	-	Benzyl bromide
BSA	-	*N*,*O*-Bis(trimethylsilyl)acetamide
BH_3·DMS	-	Boron dimethylsulfide complex
BF_3·Et_2O	-	Boron trifluoride diethyl etherate
Boc	-	*tert*-Butoxy carbonyl
$(Boc)_2O$	-	Di-*tert*-butyl dicarbonate
CAN	-	Ceric ammonium nitrate
DMP	-	Dess–Martin periodinane
DCC	-	Dicyclohexylcarbodiimide
DIBAL-H	-	Diisobutylaluminium hydride
DIPEA	-	Diisopropyl ethylamine
DMM	-	Dimethoxymethane (Methylal)
DMA	-	*N*,*N'*-Dimethylacetamide
DMF	-	*N*,*N'*-Dimethylformamide
DMAP	-	*N*,*N'*-Dimethylaminopyridine
DMSO	-	Dimethyl sulfoxide
EtOH	-	Ethanol
Et	-	Ethyl
EtOAc	-	Ethyl acetate
EOE	-	Ethyloxyethyl
HMDS	-	Hexamethyldisilazane
HMPA	-	Hexamethylphosphoramide
Im	-	Imidazole
IBX	-	Iodoxybenzoic acid
LDA	-	Lithium diisopropylamide

MeOH	-	Methanol
MsCl	-	Methanesulfonyl chloride
Me	-	Methyl
MeI	-	Methyl iodide
m-CPBA	-	*meta*-Chloroperbenzoic acid
MTPA	-	2-Methoxy-2-phenyl-2-(trfluoromethyl)acetyl
NaOMe	-	Sodium methoxide
Pd/C	-	Palladium on Carbon
$Pd(OH)_2/C$	-	Palladium hydroxide on Carbon
Ph	-	Phenyl
py	-	Pyridine
PDC	-	Pyridiniumdichromate
p-TSA	-	*para*-Toluenesulfonic acid
TBAI	-	Tetra-*n*-butylammonium iodide
TBAF	-	Tetra-*n*-butylammonium fluoride
TBDMS	-	*tert*-Butyldimethyl silyl
THF	-	Tetrahydrofuran
TMS	-	Trimethylsilyl

GENERAL REMARKS

❋ ^{1}H NMR spectra were recorded on AC-200 MHz, MSL-300 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, and DRX-125 MHz spectrometers.

❋ EI Mass spectra were recorded on Finngan MAT-1020 spectrometer at 70 *eV* using a direct inlet system.

❋ Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.

❋ Optical rotations were measured with a JASCO DIP 370 digital polarimeter.

❋ Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected.

❋ All reactions are monitored by Thin Layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV light, I_2 and anisaldehyde in ethanol as development reagents.

❋ All solvents and reagents were purified and dried by according to procedures given in Vogel's Text Book of Practical Organic Chemistry. All reactions were carried out under Nitrogen or Argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.

❋ All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 40 °C.

❋ Silica gel (60–120) used for column chromatography was purchased from ACME Chemical Company, Bombay, India.

CONTENTS

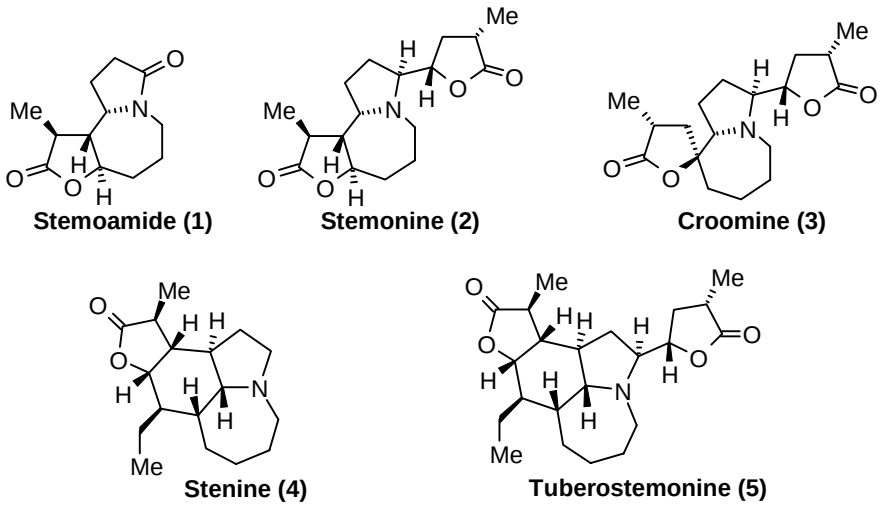
Abstract

Abstract

The thesis entitled "**Synthesis of stemoamide and some novel bicyclic nucleosides**" consists of three chapters and each chapter is further sub-divided into the following sections: Introduction, Present work, Experimental, Spectroscopic data and References. The first chapter describes the carbohydrate-based synthesis of stemoamide. The second chapter deals with the diastereoselective Reformatsky reaction of methyl 4-bromocrotonate with 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose and its application to the synthesis of some novel bicyclic nucleosides, and towards galiellalactone. The third chapter highlights the bis(dealkoxycarbonylation) of nitroarylmaonates leading to nitrotoluenes.

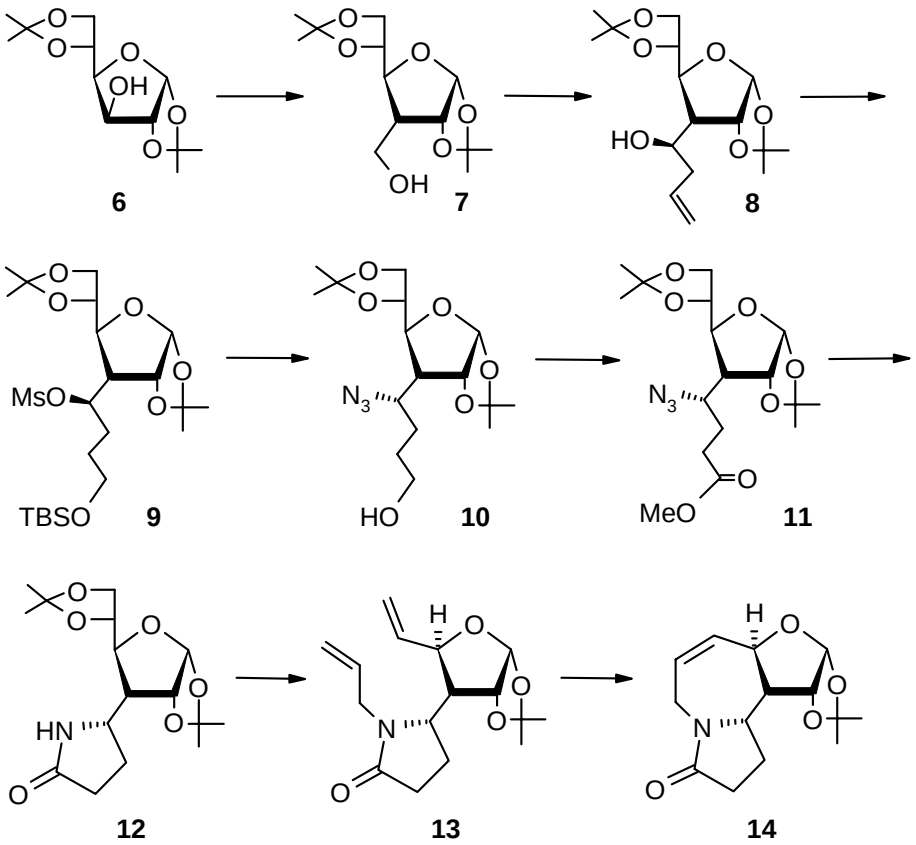
Chapter I: **Carbohydrate-based synthesis of stemoamide**

Stemoamide **1,** a member of the *Stemona* class of alkaloids was isolated in 1992 from *Stemona tuberosa* by Lin *et al*. The structures of stemoamide (**1**) and the related alkaloids such as stemonine (**2**), croomine (**3**), stenine (**4**) and tuberostemonone (**5**) were elucidated by an extensive series of 2D NMR experiments together with IR spectral studies. The extracts of this plant species (both *Stemona* and the closely related *Croominaceae* species) have long been employed as anthelmintics and as anti-tussives in traditional folk medicine of China and Japan. This chapter describes the formal of synthesis of stemoamide starting from D-glucose. The basic strategy of our synthesis involves the stereocontrolled synthesis of the 2-pyrrolidinone derivative at the C-3 position of D-glucose followed by installation of the azepine ring structure using a ring closing metathesis approach.



Our first task was the application of Barbier-type reaction on aldehyde prepared from 3-deoxy-3-*C*-hydroxymethyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose to obtain the required stereochemistry of homoallyl alcohol **8**. Hence, 3-deoxy-3-*C*-hydroxymethyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**7**) obtained from D-glucose diacetonide **6** in three steps, was oxidized under Swern oxidation conditions to give aldehyde which on treatment with allyl bromide, Zn dust and THF-sat. NH_4Cl solution furnished **8.** The optical purity and the absolute stereochemistry at the newly generated center were confirmed by the Mosher ester method.

Scheme 1

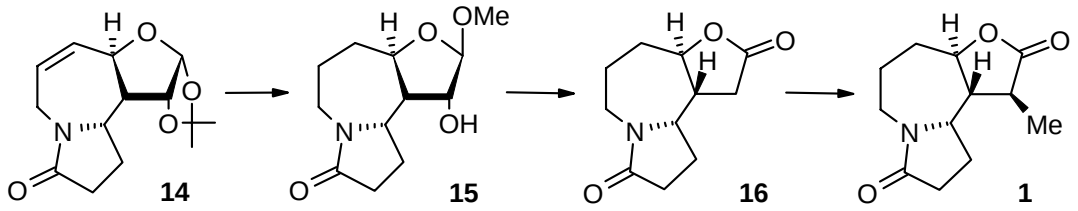


Hydroboration-oxidation of **8** followed by a protection-deprotection sequence furnished the mesylate (**9**), which with NaN_3 in DMF at 85 ^oC gave the azido alcohol (**10**). Compound **10** was oxidized under Swern oxidation conditions, and the resulting aldehyde treated with $NaClO_2$ to give the azido acid isolated after esterification as its methyl ester (**11**). Hydrogenation of **11** over 10% Pd/C in MeOH gave the 2-pyrrolidinone derivative **12**.

Synthesis of the diene derivative **13** was achieved by phase transfer *N*-allylation of **12** in a biphasic system of 50 % solution of KOH-benzene with tetra-*n*-butyl ammonium iodide and then by performing the successive reactions such as acid hydrolysis (0.8% H_2SO_4) of the 5,6-acetonide group, dimesylation of the resulted diol, and olefination with NaI in 2-butanone. The ring closing metathesis reaction of **13** with Grubbs' 1st generation catalyst in refluxing CH_2Cl_2 afforded **14**. The ^{1}H NMR spectrum of **14** showed characteristic olefinic protons at δ 5.75, while H_{7a} and H_{7b} were located at δ 3.39 and δ 4.67 as a broad doublet and a double-doublet, respectively (Scheme 1).

Hydrogenation of **14** over 10% Pd/C in MeOH, and then refluxing with Amberlyst-15 in MeOH gave α,β-mixture of methyl glycoside with β-isomer **15** as a major one. Deoxygenation of the C-2 hydroxyl functionality of **15** was carried out by Barton's radical deoxygenation reaction. Accordingly, compound **15** was converted into the corresponding imidazolyl xanthate derivative using thiocarbonyl diimidazole in refluxing toluene, and by *in situ* addition of *n*-Bu_3SnH and catalytic AIBN gave the 2-deoxy product which, finally transformed into the corresponding γ-lactone derivative **16** by using Grieco's protocol ($BF_3{\cdot}Et_2O$ and *m*-CPBA). The ^{1}H NMR and ^{13}C NMR spectra of **16** were compatible with the reported data. Since **16** has already been transformed into the stemoamide **1** in one step the present synthesis constitutes a formal total synthesis of stemoamide **1** (Scheme 2).

Scheme 2



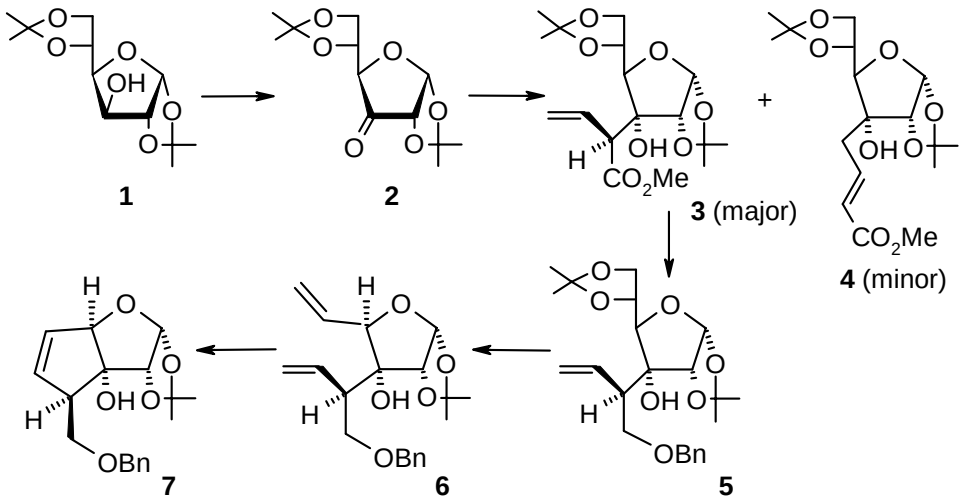
In conclusion, we have achieved a synthesis of stemoamide from D-glucose. The stereo-controlled allylation under Barbier reaction conditions led to the installation of the 2-pyrrolidinone ring at C-3 followed by a ring closing metathesis approach to construct the azepine ring system.

Chapter II: Diastereoselective Reformatsky reaction of methyl 4-bromocrotonate with 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose: application to novel bicyclic nucleosides and towards galiellalactone

Due to the inherent structural complexity associated with carbohydrate precursors, many organometallic C–C bond forming reactions occur with impressive stereoselectivity. For instance, the 3-ulose derivative of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1**) has been particularly targeted with significant successes. The conformationally rigid 1,2-*O*-isopropylidene functionality of **2** dictates the approach of nucleophile from the β-face giving rise to the 3-*C*-substituted-D-allose derivative. In most of the C–C bond forming reactions studied so far, only the one new chiral center at C-3 has been created. We were interested in exploring the organometallic reaction of **2** with a specific organo-metallic reagent, which can be tuned to produce two new chiral centers.

The vinylogous Reformatsky reaction of 3-ulose derivative (**2)** was attempted with methyl 4-bromocrotonate in the presence of Zn-Cu couple in anhydrous ether. This reaction gave two products. The major product obtained in 52% yield was assigned the structure **3** based on the ^{1}H NMR, ^{13}C NMR, mass spectra and elemental analysis. The stereochemical assignment of **3** was confirmed by single crystal X-ray diffraction studies. The minor product obtained in 26% yield was given the structure **4** based on spectroscopic and analytical data. The formation of a single diastereomer **3** could be explained by considering a transition state involving the preferred *E*-dienolate of Zn.

Scheme 1



The carbomethoxy moiety of **3** was reduced with $LiAlH_4$ and then the resulting hydroxyl group was protected as its benzylic ether (**5**) by using benzyl bromide - Ag_2O. In order to derive the diene **6** the successive hydrolysis of 1,2-O-isopropylidene group with 0.8% H_2SO_4 in MeOH, dimesylation of the 5,6-diol derivative with MsCl and DIPEA, and elimination with NaI in ethyl methyl ketone were carried out. Ring closing metathesis reaction of **6** with 4 mol% of Grubbs' 1st genaration catalyst in refluxing benzene furnished bicyclic derivative **7**. The ^{1}H NMR spectrum of **7** indicated signals corresponding to olefinic protons at 5.87 ppm (Scheme 1). The stereochemistry of compound **7** was unambiguously assigned based on the NOE studies, as strong NOE correlations between bridgehead hydroxyl group and the adjacent allylic protons were noticed.

Synthesis of some novel bicylic nucleosides

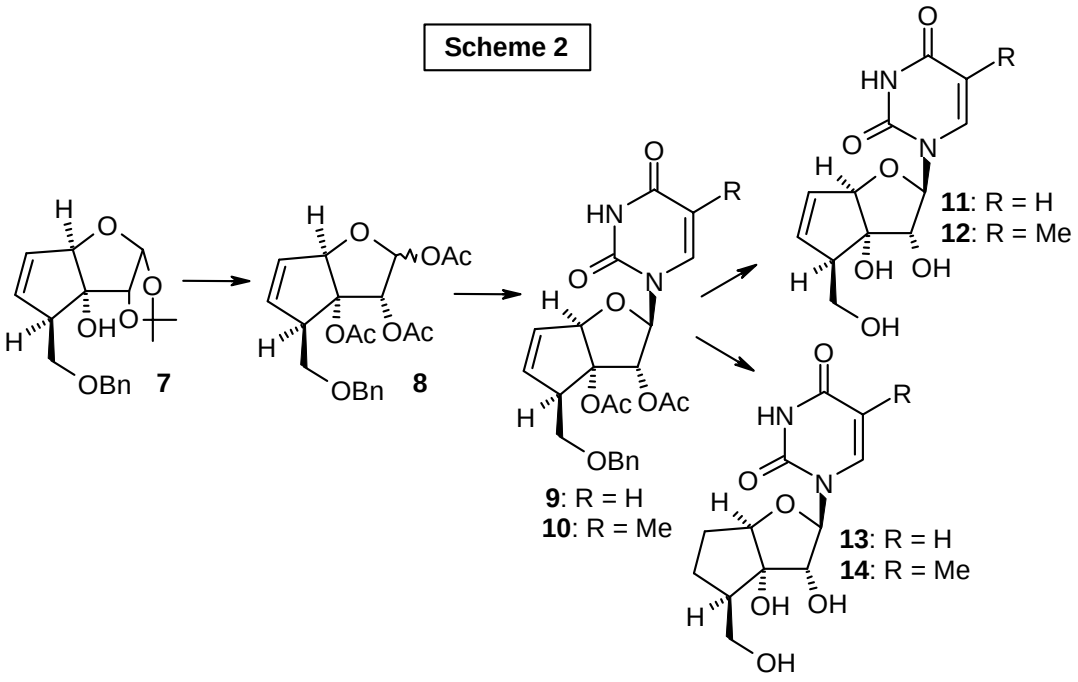
Since the discovery of certain sugar-modified nucleosides and nucleotides having potential antiviral and antitumor effects, many useful strategies for modification of naturally occurring nucleosides have been developed, and the quest for more analogues having significant biological activity is still in progress. In particular, nucleoside analogues with bicyclic carbohydrate moieties have been designed as the potential antiviral agents and as the monomers in conformationally restricted oligonucleotide sequences. Since we have already synthesized the bicyclic intermediate **7**, we focused our attention towards the synthesis of some novel bicyclic nucleosides as **7** represents the combined structure of Carbovir carbocycle and uridine backbone.

Our main objective was to introduce pyrimidine bases at the anomeric center of bicyclic derivative **7**. Thus, the acetonide moiety of **7** was cleaved with 60% aq. AcOH followed by acetylation with Ac_2O and Et_3N to afford the triacetylated derivative **8**. The modified Vorbrüggen-type coupling reaction of **8** with uracil was successfully achieved in the presence of *N,O*-bis(trimethylsilyl)acetamide and TMSOTf to afford exclusively the β-nucleoside **9** in good yield, which was attributed to the anchimeric assistance of acyl group present at 4th position. It was further confirmed by NOE studies.

The de-protections of acyl groups under Zemplén reaction conditions and benzylic ether with BCl_3 of **9** afforded **11**. Simultaneously, the compound **9** was hydrogenated in the presence of 20% $Pd(OH)_2/C$, followed by deacetylation using NaOMe (Zemplén conditions) to give compound **13**. Similarly the triacetate **8** was coupled to thymine using *N,O*-

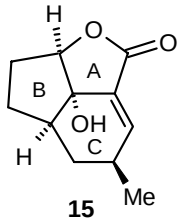
bis(trimethylsilyl)acetamide and TMSOTf to obtain **10**. The compound **10** was transformed into **12** and **14** as described above (Scheme 2).

Scheme 2



Synthetic studies toward galiellalactone

The fungal metabolite galiellalactone (**15**) is a potent and selective inhibitor of interleukin-6 (IL-6) signaling in HepG2 cells. It was isolated from ascomycetes *Galiella rufa* strain A75-86 during a screening for plant growth regulators produced by fungi. It was found to inhibit gibberillic acid-induced synthesis of α-amylase. Recently, Sterner and coworkers have reported the total synthesis of (+)-galiellalactone using (–)-pulegone as chiral starting material, and established the absolute configuration of the natural product as (–)-isomer (**15**). We envisaged that the bicyclic intermediate **7** will serve as a potential synthetic intermediate towards the synthesis of galiellalactone as it is resembling the A and B rings with suitable stereochemistry.



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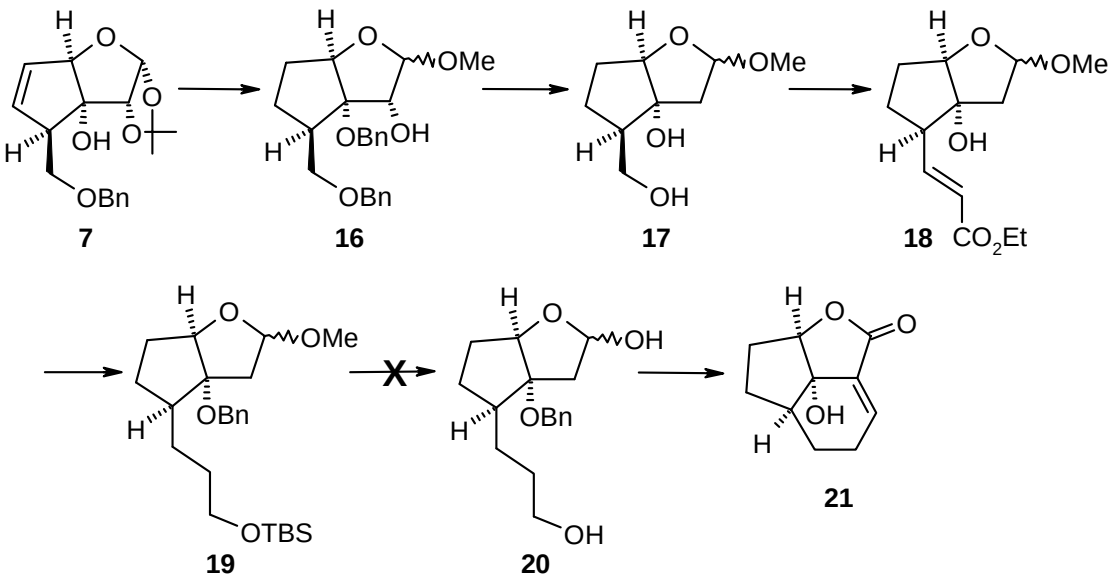
We anticipated that the C-ring of galiellalactone could be constructed through intramolecular aldol reaction. For that endeavor we have chosen the two-carbon homologation at hydroxymethyl moiety of bicyclic system followed by intramolecular aldol reaction to study the feasibility of the 6-membered ring formation. Thus, hydrogenation of **7** in the presence of Raney Ni and H_2 in MeOH, the protection of bridgehead hydroxyl moiety as benzylic ether using NaH and benzyl bromide in DMF, and the deprotection of acetonide group in the presence of Amberlyst-15 in refluxing MeOH were carried out to furnish an anomeric mixture of **16** in 1:1 ratio. Deoxygenation of free OH group in **16** was achieved by Barton-McCombie deoxygenation reaction of the corresponding thiocarbonylimidazolyl xanthate using *n*-Bu_3SnH and AIBN in refluxing toluene and then subjected to hydrogenalysis over 20% $Pd(OH)_2/C$ to obtain **17**.

Scheme 3



Refluxing the mixture of **17**, IBX and (ethoxycarbonylmethylene)triphenylphosphorane in benzene afforded **18** in 80% yield. Reduction of ethyl ester moiety of **18** with $LiAlH_4$, hydrogenation over Raney Ni in MeOH, the selective protection of primary hydroxyl group as TBDMS ether using TBDMSCl and imidazole, and the protection of bridgehead hydroxyl group as benzylic ether using BnBr and NaH in DMF were carried out to afford **19**. In an attempt to cleave both the anomeric OMe and TBDMS ether of **19**, it was treated with boiling 60% aq. AcOH. Unfortunately, this proposition gave mixture of products and

attempted purification of this mixture was failed due to the decomposition on standing (Scheme 3). Having encountered the failures at final stages of our synthetic strategy, we decided to stop this route at this stage and the efforts for the construction of six-membered ring of galiellalactone through other routes are in progress in our laboratory.

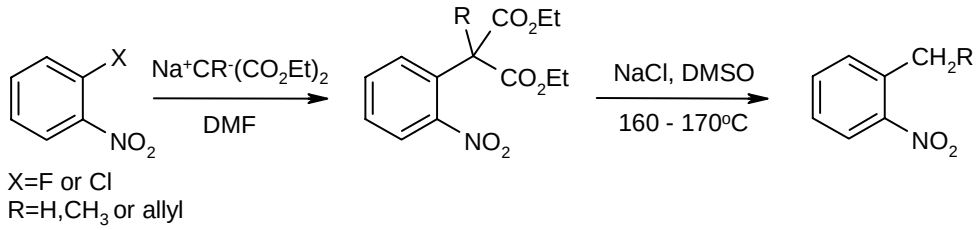
In conclusion, we have developed an efficient methodology to synthesize the novel bicyclic nucleosides having the structural framework of some carbocyclic nucleosides and bridgehead hydroxyl moiety.

Chapter III: Bis(dealkoxycarbonylation) of Nitroarylmalonates

Introduction of alkyl groups in aromatic rings is an important step in organic synthesis. Decarboxylation of aryl substituted malonic esters under Krapcho's conditions are to provide aryl acetic esters in good yield. In continuation of our on going project to synthesize medicinally important oxindole derivatives, we observed by serendipity the complete decarboxylation of nitroaryl malonates under Krapcho's conditions. This observation has been exploited to synthesize alkyl nitroaromatics which otherwise need number of steps.

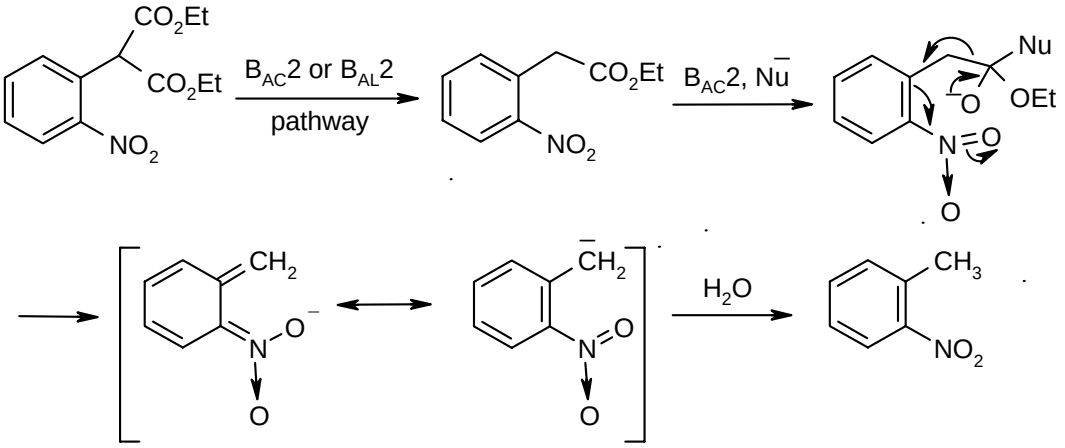
o-Chloro/*o*-fluoronitrobenzenes and *p*-chloro/*p*-fluoronitrobenzenes were treated with sodium salt of diethyl malonate in DMF at ambient temperature to provide corresponding diethyl (nitrophenyl)malonates in good yields. These compounds were subjected to Krapcho's decarboxylation reaction using NaCl in wet DMSO at 160–170 ^{o}C for 24 h to afford the nitrotoluenes and nitroxylenes. Under modified Krapcho's condition i.e. dibasic salt of $MgCl_2 \cdot 6H_2O$ in dimethyl acetamide at 140–150 ^{o}C was employed, shorter reaction times and overall enhancement of yields were observed (Scheme 1).

Scheme 1



The proposed mechanism involves two stages: initial decarboxylation of malonate *via* competitive $B_{AC}2$ or $B_{AL}2$ pathway to give *o*-nitrophenyl acetate. Because of mesomeric stabilization of benzylic anion by nitro group at *o*/*p* position, nitrophenyl acetate undergoes further decarboxylation to give *o*-nitrotoluene (Scheme 2).

Scheme 2



In conclusion, we have developed a mild and efficient procedure for alkylated aromatics which otherwise are difficult to prepare, starting from halonitrobenzenes.

Chapter I

Carbohydrate-based Synthesis of Stemoamide

Introduction

Introduction

Traditional medicine refers to health practices employing plant, animal and mineral based medicines to treat and prevent illnesses or maintain well-being. Countries in Africa, Asia and Latin America use traditional medicines to help to meet some of their primary health care needs. In Africa, up to 80% of the population uses traditional medicine for primary health care. Traditional medicine is widely used in India, particularly in rural areas, where 70% of the population lives. Ayurveda, siddha and unani systems of medicine have coexisted with yoga, naturopathy and homeopathy for centuries. 2860 Indian hospitals provide traditional Indian medicine. Traditional medicine has been fully integrated into the health systems of China, North and South Korea and Viet Nam. In western countries, growing numbers of patients rely on alternative medicine for preventive or palliative care. The global market for traditional therapies stands at US$ 60 billion a year and is steadily growing and about 25% of modern medicines are descended from plants first used traditionally. The Chinese herbal remedy *Artemisia annua* has been found to be effective against resistant malaria and could give hope of preventing many of the 800000 deaths among children from severe malaria each year. In South Africa, studies on the plant *Sutherlandia microphylla* show efficacy in increasing energy, appetite and body mass in people living with HIV.[1]

The pinnacle of achievement for Traditional Western Medicine was during the 17th Century. At this time, many ancient texts and formulas dating back to the Greeks & Arabs were still commonly used; however, the modern chemical tradition was also very strong. So there was a rich blend of Traditional Herbal Formulas along with potent mineral and metal medicines. There was also a strong and constant supply of exotic spices and newly introduced medicines from the East, as well as from Africa and the Americas. All this, combined with the relatively new but flourishing printing trade made this period a time of intense learning. Many foreign language and Latin texts were being translated and printed into English for the first time; there was truly a wealth of information available. In addition, there were many expeditions, both by land and sea, which brought medicines and ideas of how to use them from far away places.

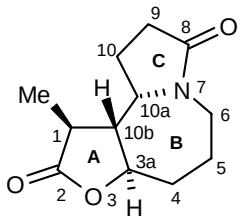
It is important to note at this time that for many centuries there has been a strong cross-communication of ideas and medicines between various cultures. The Arabs appear to have acquired the knowledge of the preparation and use of mineral and metal medicines from the Indians, and this knowledge passed through places like Turkey into Europe. The Silk road, long an important trade link for Silk and other commodities also introduced a wealth of Eastern Spices and Medicines to the West. It is also quite clear that the 4 humors of Galen share many similar attributes to the Humoral system of Ayurveda. Chinese medicine was influenced by Ayurveda, and no doubt, this road was two-way. Tibetan Medicine had direct influence from Ayurveda, yet was also influenced by Chinese medicine, and even by Arabic medicine.[2]

European medicine was influenced by various sources at various times. The Ancient Greek writers such as Galen, Hippocrates and Dioscorides laid the foundation around 2000 years ago. Even parts of these writers information (which was largely collected, and not discovered by them) could very possibly have been influenced by Ancient Vedic texts. During the Middle Ages, the Europeans were also very influenced by certain Arabic and Persian writers such Gerber (Jabir) and Avicenna, amongst others. Later, Europe was much influenced by direct trade contact with the East.

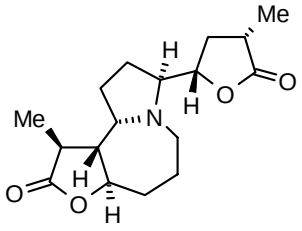
According to WHO estimation, in China, traditional herbal preparations account for 30%-50% of the total medicinal consumption. Traditional Chinese Medicine (TCM) has been practiced as one of the oldest medical disciplines in the world. Since ancient times Chinese drugs largely came from plants and medicinal herbs therefore, they have been called "herbs". The first written record of specially prepared TCM containing "herbs"- the Medicinal Wine, was inscribed on a tortoise shell during the Shang Dynasty in the 11 century BC. The wisdom of Traditional Chinese Medicine is summarized in the Chinese Materia Medica, which provides studies on the properties of Chinese drugs, their origin, preparation, dosage, administration and efficacy. The Materia Medica of the Tang Dynasty written between the year 618-907 is the earliest known pharmacopoeia in the world and is often compared with the Nuremberg Pharmacopoeia issued in 1542.[3]

The roots of *Stemona sessilifolia* (sessile stemona), *Stemona japonica* (Japanese stemona) and *Stemona tuberosa Lour* (tuber stemona) have long been used in the traditional

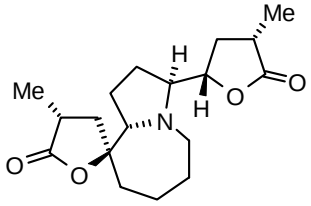
medicines of China and Japan.[4] The water extracts obtained from the roots of above *Stemonaceae* species were widely used in China against human and cattle parasites, agricultural pests and as domestic insecticides.[5] The basic methanolic extracts obtained from fresh leaves of *Stemona japonica* showed strong insecticidal activity against silkworm larvae. The crude extracts of *Stemonaceae* species have also shown antitubercular and antitussive activities. Motivated by the biological activities associated with these plants species many studies were carried out in resulting the isolation of more than 40 alkaloids so far.[6,7]



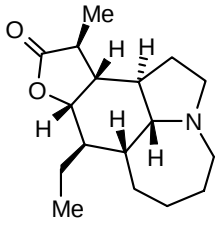
(–)-Stemoamide (1)



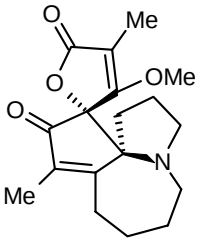
Stemonine (2)



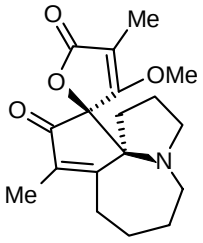
Croomine (3)



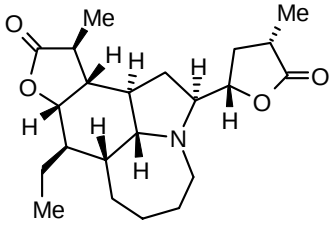
Stenine (4)



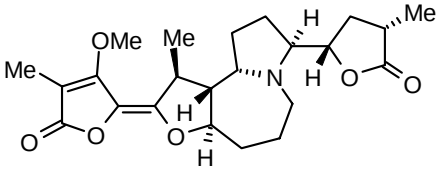
Stemonamine (5)



Isostemonamine (6)



Tuberostemonine (7)



Protostemonine (8)

Stemona tuberosa Lour is mainly produced in the Chinese provinces Anhui, Jiangsu, Hubei, Henan, Fujian, Zhejiang, Shandong, etc. Harvested in spring or autumn, the fibrous roots are removed from the root, with the root washed clean, scalded in boiling water for a while or steamed until it has no white core, taken out, dried in the sun and cut into thick slices for use when raw or after being fried with honey. This herb contains a variety of alkaloids such as stemoamide (**1**), stemonine (**2**), croomine (**3**), stenine (**4**), stemonamine (**5**),

isostemonamine (**6**), tuberostemonine (**7**), protostemonine (**8**), etc. It also contains saccharides, esters, proteins, amber, etc. The stemonine (**2**) has a central antitussive (suppresses coughing) effect and it can relax the isolated animal bronchial smooth muscle affected by histamine. The water decoction and alcohol infusion of this herb have obvious killing effects on head lice and the like, oxyurids, etc. They can also reduce the pathogenicity of Asian influenza-A virus on animals and they also have certain therapeutic effects on the patients affected by this virus. The water decoction and alcohol infusion of this herb can inhibit Mycobacterium tuberculosis hominis and, in addition, inhibit a variety of cocci, bacilli and dermatomyces.

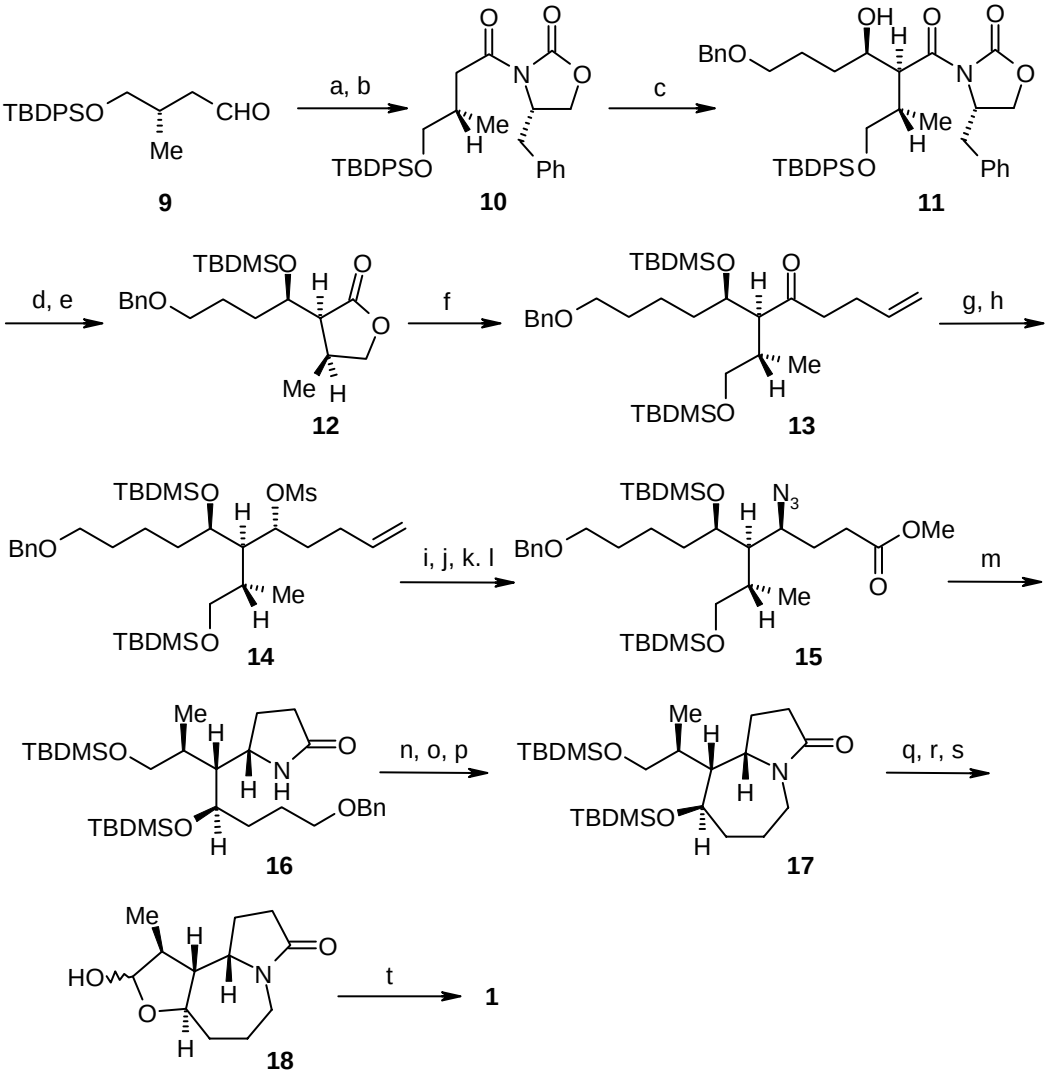
The complex molecular architecture of these *Stemona* alkaloids has stimulated many synthetic chemists resulting in several partial[8] and total syntheses[9] of these alkaloids. The tricyclic alkaloid stemoamide (**1**), a typical representative of these alkaloids was isolated in 1992 from *Stemona tuberosa Lour* by Lin, W.-H. and coworkers,[10] and it has been targeted very often over the last few years, including some very efficient approaches.[11] The first of these was carried out by Williams, D. R. *et al.* (1994),[11a] who prepared (–)-**1** in 25 steps beginning with (*R*)-(–)-methyl 3-hydroxy-2-methylpropionate. Subsequently, Narasaka, K. *et al.* reported a synthesis of (±)-**1** featuring sequential oxidative couplings of appropriately substituted organostannanes with ketone silyl enol ethers (1996).[11b] Also in 1996, Kinoshita and Mori have described a novel synthesis of (–)-**1** utilizing a Ru-catalyzed enyne metathesis reaction.[11c] Jacobi, P. A. and coworkers have reported the total syntheses of (±)-**1** in 1997 and (–)-**1** in 2000 by employing their own methodology, which involved a key transformation, the Diels-Alder reaction of alkyne-oxazole.[11d,e]

(i) Williams' approach (1994)[11a]

An enantiocontrolled total synthesis of the tricyclic alkaloid, (–)-stemoamide (**1**) was achieved starting from aldehyde **9** in 25 steps and 5.6% overall yield. Commercially available methyl (*R*)-3-hydroxy-2-methylpropionate was homologated to **9** and coupled with (*S*)-4-benzyloxazolidin-2-one to afford chiral imide **10** (85% overall yield for 7 steps). An asymmetric boron aldol reaction with 4-benzyloxybutanal installed the stereogenic centers at C-3a and C-10b. The correct stereochemistry at C-10a was established after chain elongation, reduction with $LiEt_3BH$ (exclusively from the carbonyl *si* face), mesylation and methanesulfonate displacement with sodium azide that proceeded with inversion of

configuration. At this point all the carbons and the stereogenic centers of (–)-stemoamide (**1**) were in place and the remaining steps were dedicated to the formation of rings A, B and C and functional group interconversions (Scheme 1).

Scheme 1



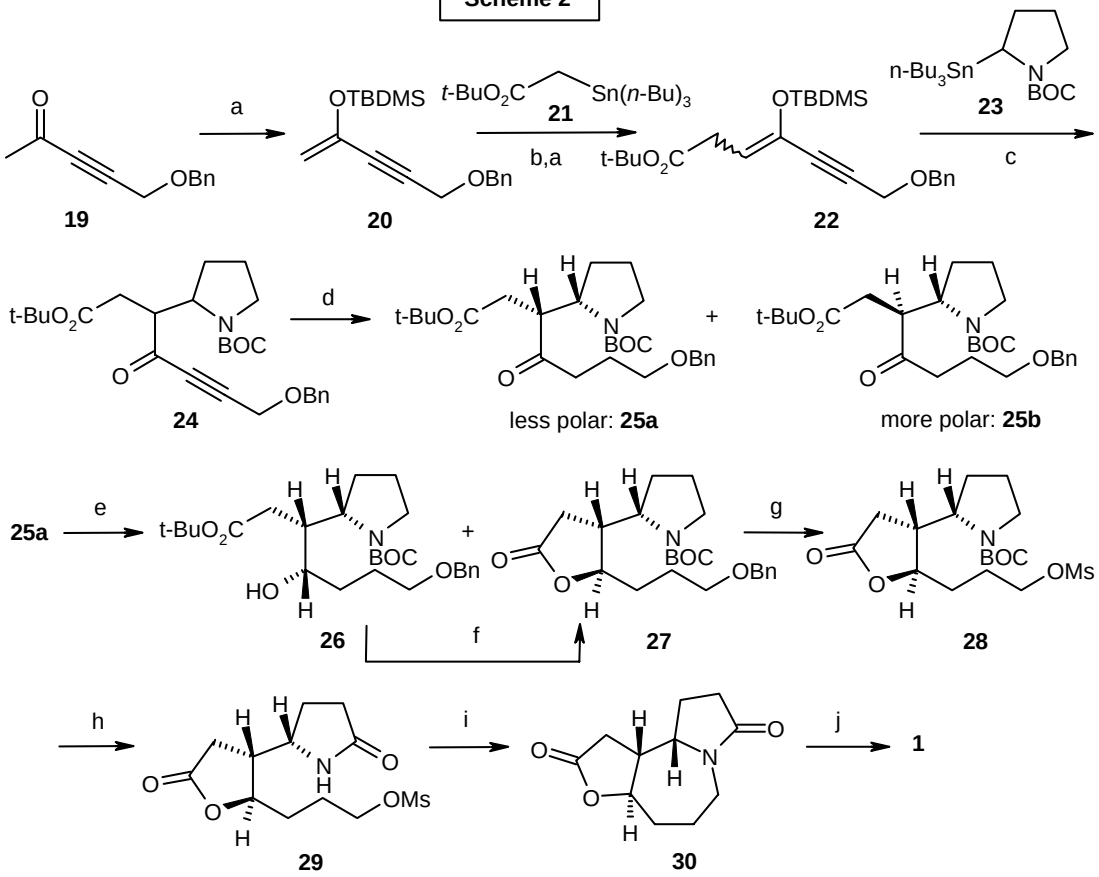
Reagents and conditions: (a) 1M $KMnO_4$, 0.5M NaH_2PO_4, *t*-BuOH; (b) *t*-BuC(O)Cl, Et_3N, THF, 0 ^oC-rt; then (*S*)-4-(benzyl)-2-oxazolidinone, *n*-BuLi , THF, –78 ^oC-rt; (c) *n*-Bu_2BOTf, CH_2Cl_2, –78 ^oC; then Et_3N, –78 ^oC-0 ^oC; then 4-benzyloxybutanal, –78 ^oC-0 ^oC, (d) 48% aq. HF, CH_3CN, rt; then sat aq. $NaHCO_3$, K_2CO_3; (e) *t*-$BuMe_2SiOTf$, collidine, CH_2Cl_2, –78 ^oC-rt; (f) 4-Iodo-l-butene, *t*-BuLi, Et_2O, –100 ^oC; then **12**, –100 ^oC to –78 ^oC; then collidine, *t*-$BuMe_2SiOTf$, –78 ^oC-rt; (g) $LiEt_3BH$, THF, –78 ^oC-rt; (h) MsCl, py, rt; (i) NaN_3, HMPA, rt; (j) O_3, CH_2Cl_2/MeOH (3: 1). –78 ^oC; then Me_2S, –78 ^oC-rt; (k) $NaClO_2$, $NaH_2PO_4{\cdot}H_2O$, CH_3CN, *t*-BuOH, H_2O, 2-methyl-2-butene, 0 ^oC; (1) CH_2N_2 (xs), Et_2O, 0 ^oC; (m) PPh_3, THF/H_2O (100:l), reflux; (n) H_2, 10% Pd/C,

EtOH; (o) MsCl, py, rt; (p) NaH, rt; (q) HF·NEt_3, CH_3CN, rt; (r) Dess-Martin periodinane, py, CH_2C1_2, rt; (s) *n*-Bu_4NF, THF, rt; (t) PDC, CH_2C1_2, reflux.

(ii) Narasaka's approach (1996)[11b]

The total synthesis of (±)-stemoamide (**1**) was accomplished by applying the oxidative coupling reactions of stannyl compounds with silyl enol ethers to construct the carbon skeleton. The key intermediate **24** was produced as a mixture of stereoisomers which led to a separable mixture of diastereoisomers (**25a** : **25b** = 4:1) upon hydrogenation of the acetylenic bond. The formation of **24** was rationalized through the addition of silyl enol ether **22** to an intermediate *N*-acyliminium ion derived from *N*-Boc-2-tributylstannylpyrrolidine. The stereogenic center at C-3a was established after $NaBH_4$ reduction of **25a**, which afforded γ-butyrolactone **27** in 59% yield. In the final stages of the synthesis, ring B was formed by intramolecular nitrogen alkylation and the correct stereochemistry at C-1 was established by stereoselective methylation of the lithium enolate of the γ-lactone. This concise approach required 12 steps from 5-benzyloxypent-3-yn-2-one and provided (±)-stemoamide (**1**) in *ca*. 2% overall yield (Scheme 2).

Scheme 2

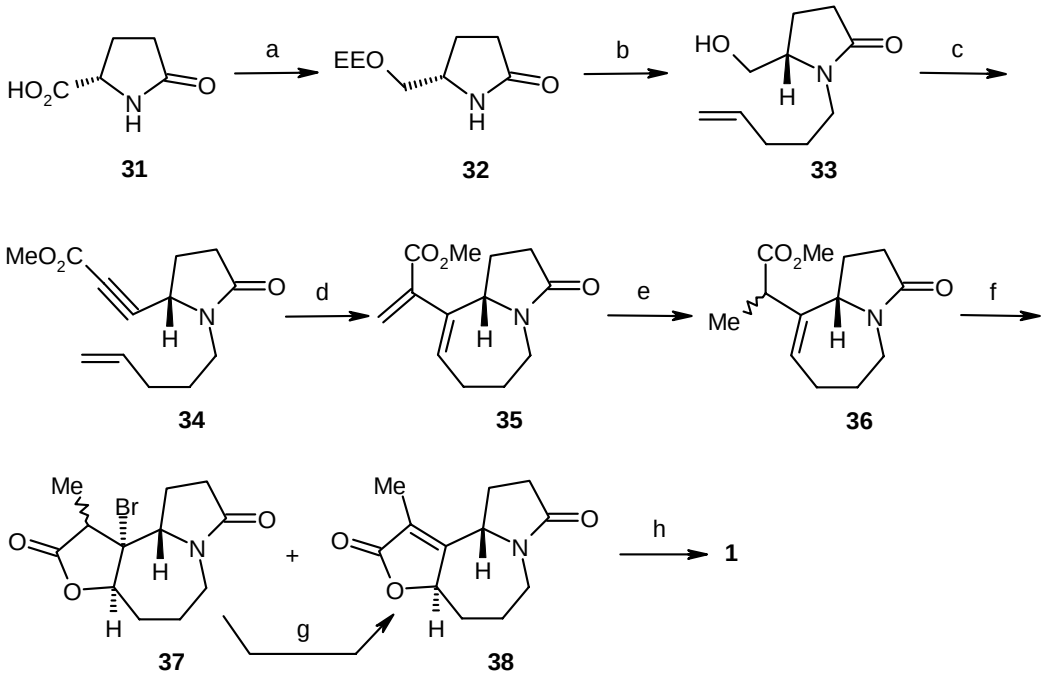


Reagents and conditions: (a) TBDMSCl, Et_3N, NaI, CH_3CN, 50 ^oC; (b) TBACN, K_2CO_3, MS 4Å, EtCN, 0 ^oC; (c) CAN, MS 4Å, EtCN, –45 ^oC; (d) 10% Pd/C, H_2, MeOH, rt; (e) $NaBH_4$, THF-MeOH, rt; (f) (i) CF_3CO_2H; (ii) Boc_2O, Et_3N; (iii) Mitsunobu reaction; (g) (i) 10% Pd/C, 98% HCO_2H, MeOH, rt; (ii) MsCl, Et_3N, CH_2C1_2, rt; (h) (i) cat. RuO_2, $NaIO_4$, EtOAc-H_2O, rt; (ii) 1M HCl-EtOAc, rt; (i) NaH, THF, rt; (j) LDA, THF, –78 ^oC; then MeI, –78 ^oC-rt.

(iii) Mori's approach (1996)[11c]

A concise and efficient approach to (–)-stemoamide (**1**) based on an intramolecular enyne metathesis was developed by Kinoshita and Mori. Starting from lactam **32**, prepared from (–)-pyroglutamic acid (**31**), the acetylene **34** was obtained in 5 steps and 50% overall yield. The construction of ring B was efficiently accomplished by enyne metathesis (87% yield) using catalytic amount of Grubbs' catalyst. Reduction to the saturated ester, followed by bromolactonization of the mixture of epimeric carboxylic acids, afforded unsaturated lactone **38** (31% yield) and the corresponding bromolactone **37** (21% yield) which could be converted to **38** by treatment with Et_3N. The correct stereochemistry at C-1 was established by reduction of **38** with $NaBH_4$ in the presence of $NiCl_2{\cdot}6H_2O$ in MeOH to afford (–)-stemoamide (**1**), in 14 steps from (–)-pyroglutamic acid (**31**) and 9% overall yield (Scheme 3).

Scheme 3



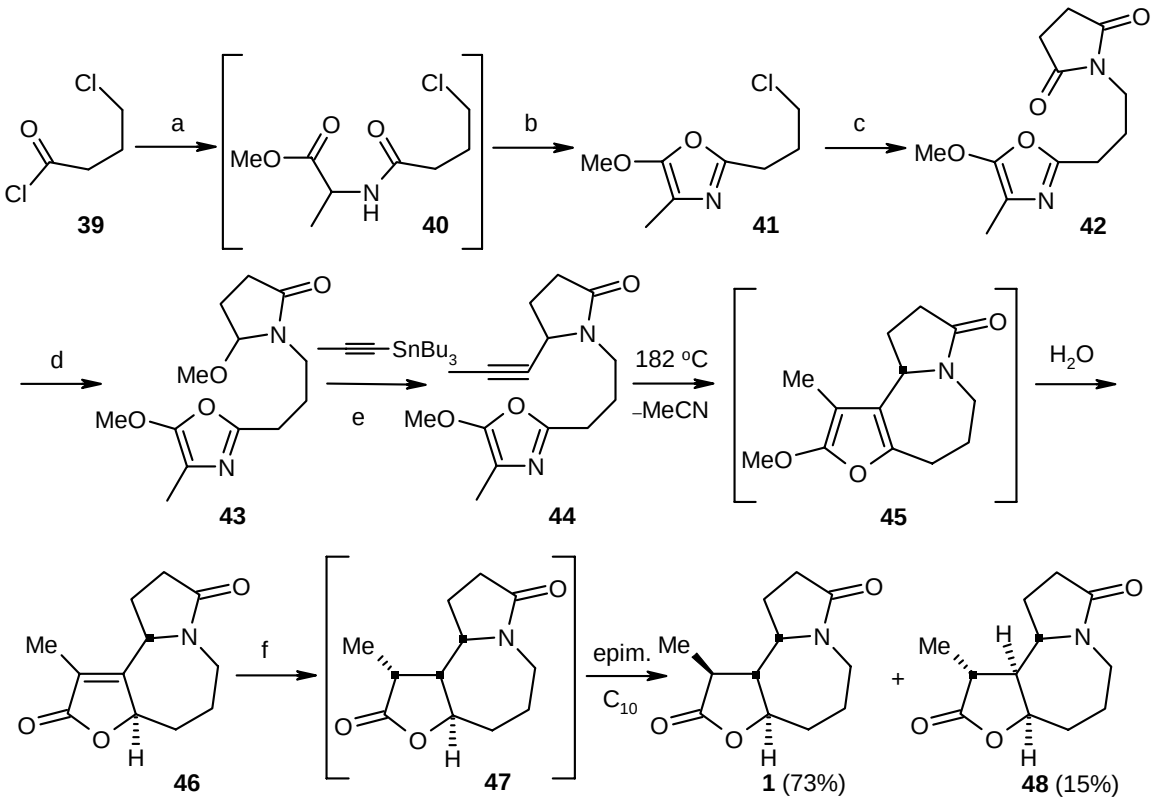
Reagents and conditions: (a) (i) $NaBH_4$, MeOH, rt; (ii) NaH, EOECl; (b) (i) NaH, DMF, 5-bromopent-1-ene; (ii) *p*-TSA, MeOH; (c) (i) $(COCl)_2$, DMSO, Et_3N, –78 ^oC; (ii) CBr_4, Ph_3P; (iii) *n*-BuLi, THF, –98 ^oC; (iv)

LDA, HMPA, $ClCO_2Me$, THF, –98 °C; (d) Grubbs' cat., CH_2C1_2, rt; (e) $NaBH_4$, MeOH; (f) (i) NaOH, MeOH-H_2O; (ii) $CuBr_2$ on Al_2O_3; (g) Et_3N; (h) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, MeOH.

(iv) Jacobi's approach (1997)[11d]

The total synthesis of (±)-stemoamide (**1**) was achieved in seven steps beginning with γ-chlorobutyryl chloride (**39**) and succinimide, which were efficiently converted to the key acetylenic oxazole (**44**) on multigram scale. Intramolecular (Diels-Alder)-(retro-Diels-Alder) reaction of **44**, with *in situ* hydrolysis of methoxyfuran **45**, then gave butenolide **46**, in a novel reaction that may involve the initial formation of the radical cation of **45**. The stereochemistry at C-1 and C-10b was established after nickel boride reduction of the unsaturated butyrolactone ring and epimerization at C-10b to afford (±)-stemoamide (**1**) in 73% yield, together with its epimer at C-1 and C-10b. Overall the total synthesis of (±)-stemoamide (**1**) was achieved in 7 steps from γ-chlorobutyryl chloride (**39**) and 20% overall yield (Scheme 4).

Scheme 4

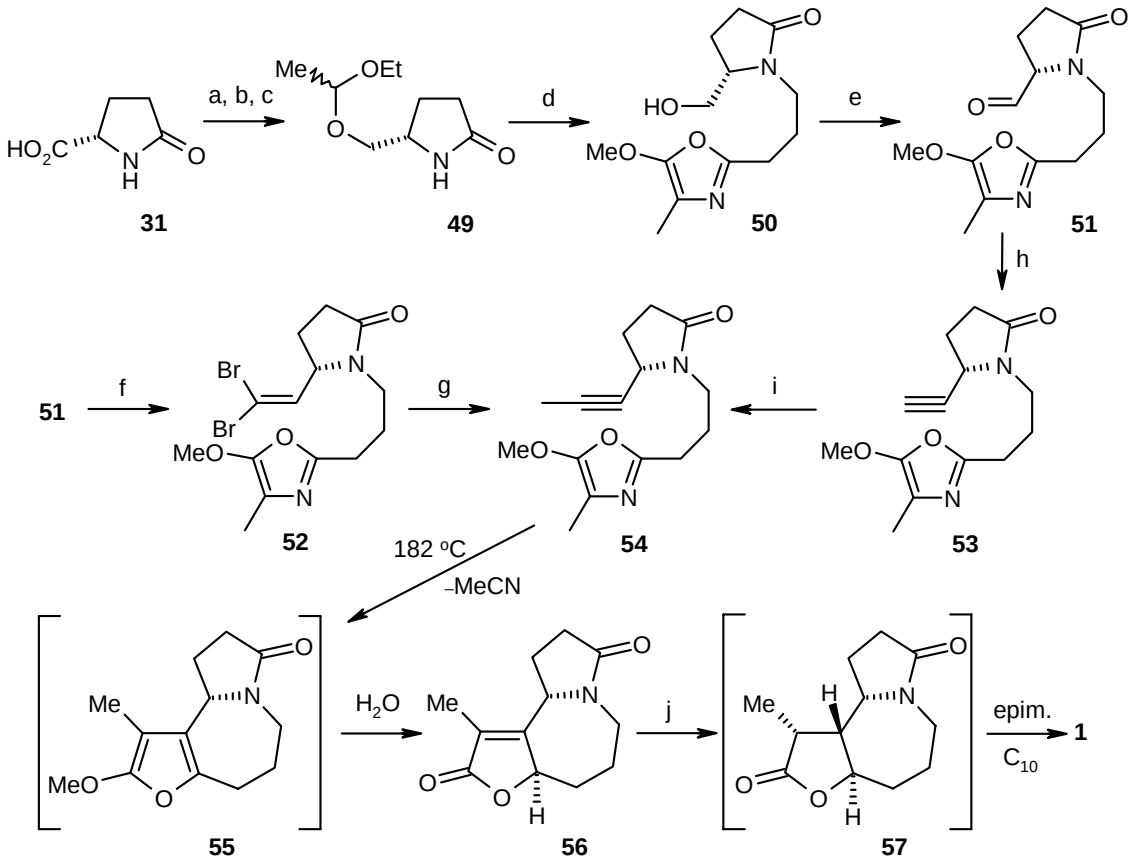


Reagents and conditions: (a) methylalaninate, Py; (b) P_2O_5; (c) NaH, succinimide; (d) (i) $NaBH_4$, MeOH; (ii) H^+, MeOH; (e) $BF_3.Et_2O$; (f) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, MeOH.

(v) Jacobi's approach (2000)[11e]

In analogous fashion (–)-stemoamide (**1**) was prepared in nine steps beginning with γ-chlorobutryl chloride and (–)-pyroglutamic acid (**31**), which were transformed to the key alkyne oxazole (**54**). Intramolecular (Diels-Alder)-(retro-Diels-Alder) reaction of **54** gave butenolide (**56**) directly upon aqueous workup. The remaining two stereocenters in **1** were established in a single step by a highly selective reduction of **56** ($NaBH_4/NiCl_2$), followed by equilibration to the thermodynamically favored natural configuration (Scheme 5).

Scheme 5



Reagents and conditions: (a) $SOCl_2$, MeOH; (b) $NaBH_4$; (c) ethyl vinyl ether, H^+; (d) (i) **41**, NaH; (ii) *p*-TSA, MeOH; (e) $(COCl)_2$, DMSO, Et_3N, –78 °C; (f) CBr_4, Zn, Ph_3P; (g) *n*-BuLi, MeI; (h) $(MeO)_2P(O)CHN_2$, *t*-BuOK, THF; (i) LDA, MeI; (j) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, MeOH.

In the proceeding section the carbohydrate-based synthesis of stemoamide (**1**) has been described.

Present Work

Present Work

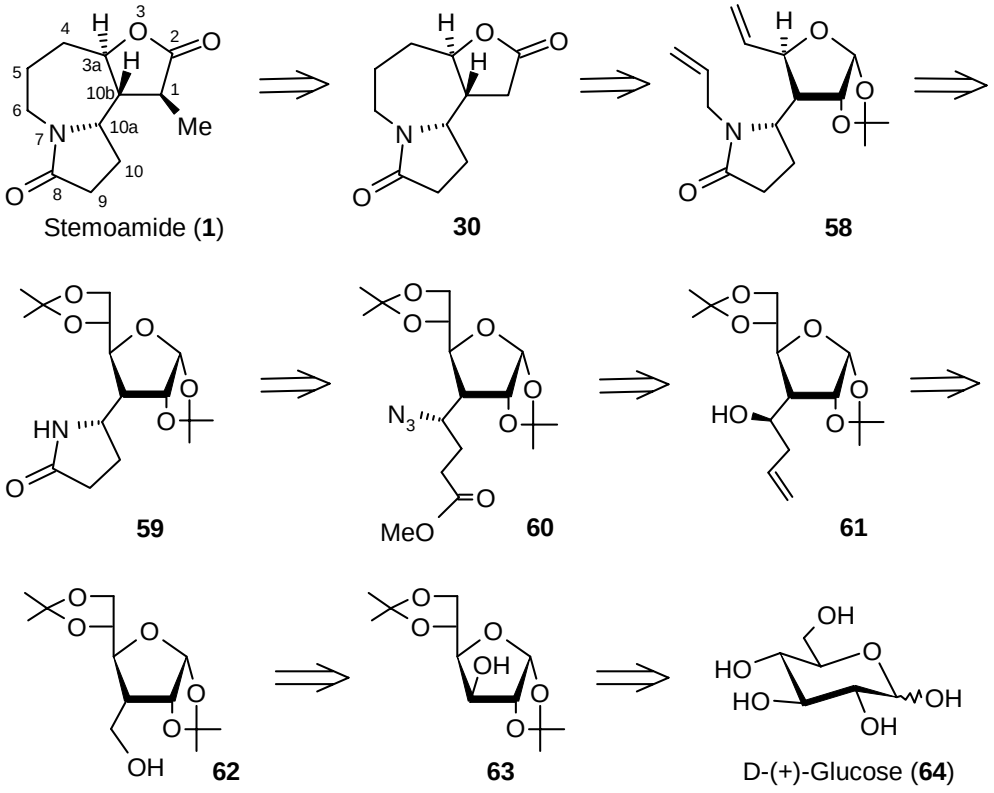
The *Stemona* alkaloids represent a class of polycyclic alkaloids with relatively complex structures, which emerged from the structural elucidation of its first representative, tuberostemonone (**7**) in the sixties. Since then, so far, more than 40 alkaloids were isolated and the investigation for new *stemona* alkaloids is still underway. The chemical investigation of *Stemonaceae* species and the closely related *Croominaceae* species, was initially motivated by their use in the Chinese and Japanese folk medicine in the treatment of respiratory diseases and as anthelmintics. The herb *Radix Stemonae*, known as 'Bai-Bu' in traditional Chinese medicine, is derived from the roots of *Stemona tuberosa Lour*, a perennial plant of the *Stemonaceae* family. Stemoamide (**1**), a member of the *Stemona* class of alkaloids was isolated in 1992 from *Stemona tuberosa Lour* by Lin, W.-H. and coworkers.[10] The structures of stemoamide (**1**), and the closely related alkaloids such as stemonine (**2**), croomine (**3**), stenine (**4**), and tuberostemonine (**7**) were elucidated by an extensive series of 2D NMR experiments together with IR spectral studies. Several of these polycyclic alkaloids, because of their powerful insecticidal activity, have attracted the attention of synthetic chemists resulting in several partial and total syntheses in past few years.[8,9] Particularly in this dimension, stemoamide (**1**) has been targeted more often resulting in 5 total syntheses till date.[11]

A distinguishing feature of this group of alkaloids is the presence of a perhydroazaazulene ring, and the most members also contain an α-methyl-γ-butyrolactone functionality. The intriguing structure and insecticidal activity of stemoamide attracted us to develop a flexible strategy for its synthesis. A modern synthetic design demands better yielding sequences coupled with mild reaction conditions, high stereoselectivity and readily available starting materials. Keeping these features in mind, we have chosen D-glucose as starting material for our synthetic endeavor because of its ready availability in enatiopure form, exceedingly cheap and most importantly, the flexibility of its functional groups for the required organic transformations.

The salient feature of the structure of stemoamide (**1**) is the presence of a perhydroazaazulene ring embedded in α-methyl-γ-butyrolactone moiety with 4 stereogenic centers. The basic strategy for the synthesis of stemoamide (**1**) is delineated in the

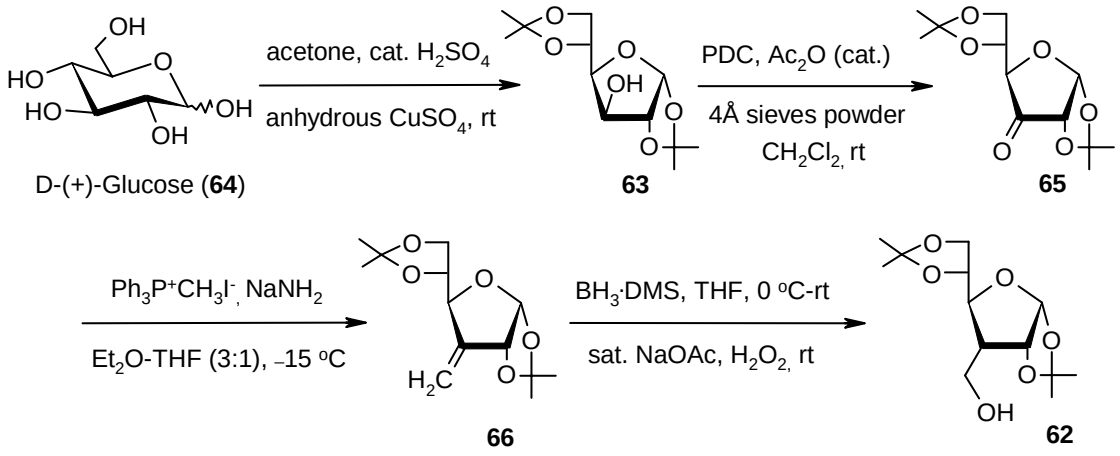
retrosynthetic analysis (Scheme 6). An appealing strategy for the linear synthesis of stemoamide can be envisaged by the stereocontrolled synthesis of the 2-pyrrolidinone derivative **59** at the C-3 position of D-glucose (**64**) and the installation of azepine ring structure using ring closing metathesis approach followed by appropriate functionaliztion of sugar backbone into γ-butyrolactone moiety. In the synthetic direction, it was anticipated that the diene precursor required for RCM approach could be obtained from **59** by *N*-allylation and the functional group transformations of 5,6-*O*-isopropylidene moiety to olefin. The reduction of azide group and the concomitant cyclization of **60** would lead to 2-pyrrolidinone derivative **59**. The compound **60** can easily be synthesized from homoallylic alcohol **61** that in turn can be realized from 3-*C* hydroxymethyl derivative **62** through Swern oxidation followed by Grignard or Barbier-type reaction using allyl bromide. The compound **62** can be prepared from D-glucose (**64**) by employing literature procedures.[12]

Scheme 6: Retrosynthetic analysis



The retrosynthetic analysis outlined in Scheme 6 identified compound **61** as a potential synthetic intermediate, and its synthesis would be the first milestone of the synthetic objective in the total synthesis of stemoamide. For that task, 3-deoxy-3-*C*-hydroxymethyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**62**) was chosen as an appropriate precursor, which could be obtained from D-glucose in 4 steps. Thus, D-glucose was transformed into 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**63**) by combined action of acetone and anhydrous $CuSO_4$ in the presence of conc. H_2SO_4 (cat.). Subsequent oxidation of free OH group at C-3 was carried out using PDC in presence of 4Å molecular sieves powder and Ac_2O (cat.) in anhydrous CH_2Cl_2 to afford 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**65**). One carbon Wittig homologation of **65** with methylenetriphenylphosphorane, generated from $Ph_3P^+CH_3I^-$ by the action of $NaNH_2$ in a solvent mixture of anhydrous ether and THF (3:1) at –15 °C furnished olefin derivative **66**. Hydroboration of olefin **66** using BH_3·DMS in THF followed by the *in vivo* oxidation of the resulted alkyl boronate with H_2O_2 and saturated aq. NaOAc solution provided **62** (Scheme 7).[12]

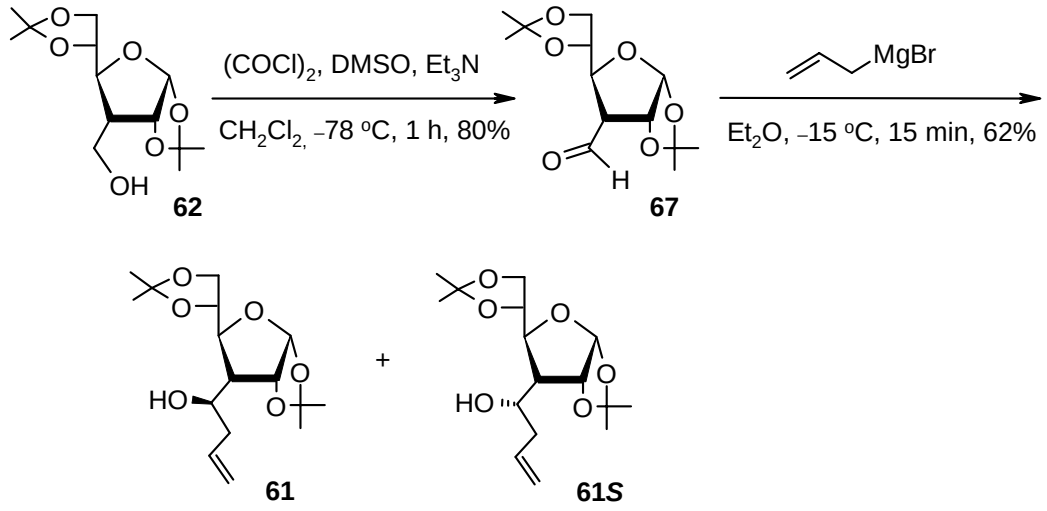
Scheme 7



Having the compound **62**, our next concern was the synthesis of homoallylic alcohol **61** with desired stereochemistry. Thus, **62** was oxidized under Swern oxidation conditions[13] using $(COCl)_2$, DMSO, and Et_3N in anhydrous CH_2Cl_2 at –78 °C to provide aldehyde **67** in 80% yield. In the ^1H NMR spectrum of **67**, formyl proton resonated as a doublet at 9.72 (d, J = 1.4 Hz). Considering the bulkiness of 1,2-acetonide moiety, we anticipated that the

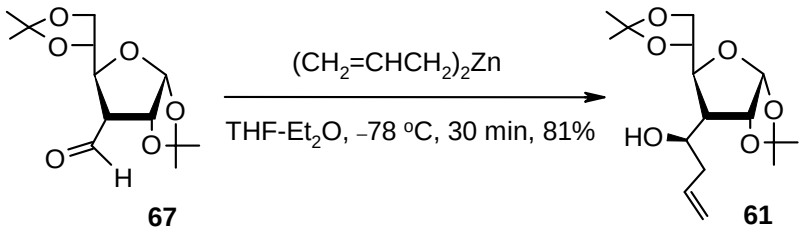
Grignard reaction using allylmagnesiumbromide would deliver the product **61** in good stereoselectivity. Hence, the aldehyde **67** was treated with allylmagnesiumbromide[14] in anhydrous ether at –15 ^{o}C, but this procedure resulted in the formation of a diastereomeric mixture of **61** and **61*S*** (3:1) in 62% yield, which were inseparable by chromatographical means (Scheme 8).

Scheme 8



In view of the above problems, we were in need of a better reagent to deliver **61** in high diastereomeric excess. So we diverted our attention towards Kishi's protocol utilizing diallylzinc.[15] Thus, 1M solution of $ZnBr_2$ in THF was added to allylmagnesiumbromide in ether. And, to the resulting diallylzinc was added a solution of aldehyde **67** in THF at –78 ^{o}C to furnish **61** as a single diastereomer in 80% yield. The ^{1}H NMR spectrum of **61** revealed two multiplets at 5.15 (2 H) and 6.00 ppm (1 H) in accordance with olefinic protons of allylic functionality. The H-1' (of side chain) proton resonated together with H-4, H-5 and H-6 protons as a multiplet at 3.90–4.21 ppm. The anomeric proton resonated as doublet at 5.68 ppm (J = 3.0 Hz) and H-2 as triplet at 4.66 ppm (J = 3.0 Hz), and the rest of the protons had the expected chemical shifts in accordance with the structure of **61**. It was further supported by ^{13}C NMR and mass spectral studies. A peak at 299 (M^{+}–Me) was appeared in the mass spectrum of **61** (Scheme 9).

Scheme 9



67 **61**

Despite the success in accomplishing better yields and stereoselectivity, the laborious reaction sequences such as preparation of $ZnBr_2$, Grignard reagent and diallylzinc, and the final condensation with aldehyde **67** forced us to seek for an easy alternative. In view of the simple reaction conditions and easy work-up we have chosen the Barbier-type reaction using allyl bromide and Zn metal in aqueous media.[16] We envisaged that the reaction of **67** with allylbromide and Zn metal in aqueous media would also proceed in similar fashion.

Barbier-type reactions: a short note

"The combined reaction of an aldehyde or ketone, alkyl halide (preferably allyl or propargyl halide) and appropriate metal in suitable solvent system is known as Barbier reaction".[17] In this procedure all three components; the alkyl halide, the aldehyde/ ketone and the metal are mixed together and allowed to react. The generation of organometalic reagent is *in situ* unlike Grignard reaction where initial generation of organometalic reagent is compulsory. Mg was used as metal in original Barbier reaction, but thereafter many more metals such as Zn, Sn, In, Pb, Fe, etc. were found applicability with promising results.

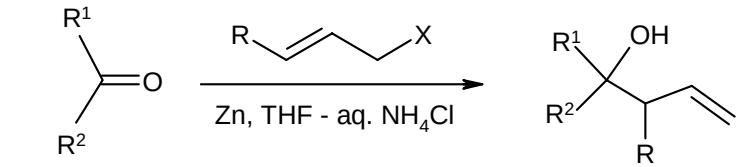
Allylation of carbonyl compounds to give homoallylic alcohols is an important synthetic pathway. It's high potential in the build-up of some natural products has stimulated numerous studies, and methods utilizing organometallics derived from B, Al, In, Ga, Cr, Sn, Ti, Ce, etc. have been developed.[18] A major requisite in these cases is the strict exclusion of moisture. Such a restriction can impose limitations on synthetic design in which various acidic hydrogens in the substrate have to be protected.

On the other hand, some classes of organometallics remain viable in the presence of water. For example, the preparation of arylmercuric chlorides in aqueous media has been

known since 1905.[19] And in the sixties, tribenzylstannyl halide was prepared in large scale in water.[20] In 1977, Wolinsky and coworkers carried out allylation of carbonyl compounds with allyl bromide mediated by Zn in 95% ethanol and t-butanol in moderate yield.[21] Since then, significant progress has been achieved showing that the reaction can be carried out in aqueous medium through the use of a variety of metal mediators such as Zn, Sn, In, Sm, Bi, Pb and Cd because of their less reactivity with water.[22] The use of aqueous media for Barbier-type reaction offers considerable advantages such as practical convenience of not having to handle inflammable and anhydrous organic solvents, the tedious deprotection-protection processes for certain acidic hydrogen containing functional groups and its easy work up.

In 1985 Luche and coworkers found that allylation of aldehydes or ketones can be affected in aqueous media using Zn in a solvent mixture of THF-water under sonication conditions. Generally, all the metals are need to be activated prior to their use in these types of reactions. In that direction Luche and coworkers attempted the activation of metal by chemical and sonochemical methods with appreciable success in rate of reaction and yields. The replacement of water by saturated aq. NH_4Cl solution enhanced the efficiency of reactions.[16] Soon after, this observation has found great applicability on wide variety of substrates with various allyl halides and their analogous compounds (Scheme 10).

Scheme 10



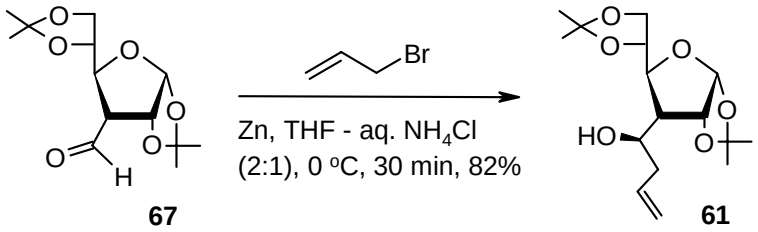
R^1, R^2 = H, alkyl, aryl
R = H or alkyl
X = halogen

The Luche conditions were soon adapted for carbohydrate substrates. Wu and coworkers carried out extensive studies on the propargylation reaction of non-cyclic sugar aldehydes derived from D- and L-glyceraldehyde, D- and L-tetrose, D-xylose and D-arabinose.[23] *Anti* product was obtained as sole or major product in all the cases they studied. Recently, Zamojski and coworkers have successfully applied this reaction for the

propargylation of aldehydes prepared from pentofuranoses and obtained homopropargyl alcohols in high yields with excellent stereocontrol (*anti:syn* > 20:1).[24]

The high stereoselectivity observed in the propargylation reaction of sugar substrates prompted us to adopt this strategy to our substrate **67**. Thus, the Barbier-type reaction of **67** was carried out with allyl bromide in presence of Zn in a mixture of THF and saturated aq. NH_4Cl solution (2:1) at 0 ^oC. Gratifyingly, this reaction afforded **61** in an improved yield of 82% (Scheme 11).[25]

Scheme 11



Although the gross structure of **61** was revealed by its spectral studies, the absolute stereochemistry at the newly born chiral center of C-3 side chain could not be ascertained based on spectral studies. Hence, we have opted for modified Mosher's method to establish the absolute stereochemistry.

Modified Mosher's ester method: Application for stereochemical assignment of 1'-OH of 61

Determination of the absolute stereochemistry of organic compounds has become an important aspect for natural product chemists as well as synthetic chemists. The limitations involved in physical methods such as exciton chirality method and X-ray crystallography forced synthetic chemists for a more reliable alternative. Although there are several chemical methods used to predict the absolute configuration of organic substances, Mosher's method using 2-methoxy-2-phenyl-2-(trfluoromethyl)acetic acid (MTPA) esters has been most frequently used. Mosher proposed that, in solution, the carbinyl proton, ester carbonyl and trifluoromethyl group of the MTPA moiety lie in the same plane (Figure 1).[26]

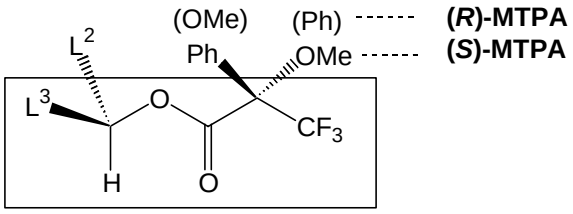


Figure 1: Configurational correlation model for (*R*)-MTPA and (*S*)-MTPA derivatives proposed by Mosher.

When the MTPA group is in the hypothesized conformation, Mosher pointed out that the ^{1}H NMR signal of L_2 of the (*R*)-MTPA ester will appear upfield relative to that of the (*S*)-MTPA ester due to the diamagnetic effect of the benzene ring. The lack of reliability associated with Mosher's ^{19}F method using ^{19}F NMR motivated Kakisawa *et al.* to elaborate this concept for more accuracy.[27] The modified Mosher's ester method (^{1}H) is one of the simple and efficient ways to determine the absolute stereochemistry of the secondary alcohols and amine stereo centers in organic molecules.

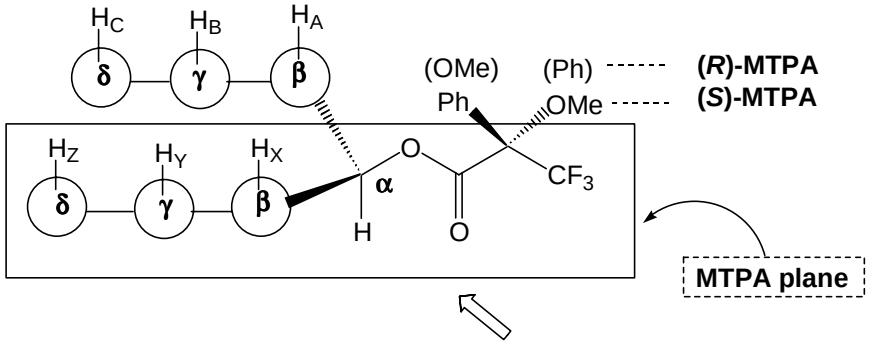


Figure 2: MTPA plane of an MTPA ester is shown. $H_{A,B,C,....}$ and $H_{X,Y,Z,....}$ are on the right and left sides of the plane respectively.

The basic concept of the modified Mosher's ester method is essentially the same as Mosher proposed. The idealized conformation is depicted in Figure 2. The plane and the conformation of MTPA group will be called as the MTPA plane and ideal conformation respectively. Due to the diamagnetic effect of the benzene ring, the $H_{A,B,C....}$ NMR signals of (*R*)-MTPA ester should appear upfield to those of the (*S*)-MTPA ester. The reverse should

hold true for $H_{X,Y,Z....}$. Hence, when $\Delta\delta = (\delta_S - \delta_R)$ x 1000 protons on the right side of the MTPA plane must have positive values ($\Delta\delta > 0$), and the protons on the left side of the MTPA plane must have negative values ($\Delta\delta < 0$). This is illustrated in model A (Figure 3).

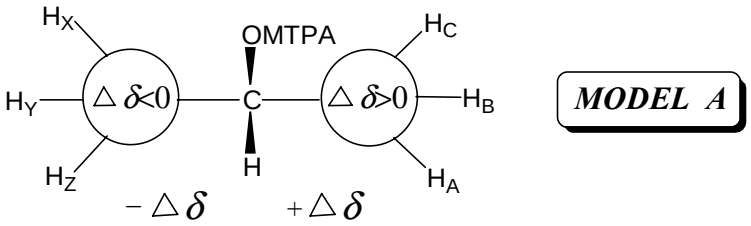


Figure 3: A view of MTPA ester drawn in Figure 2 from the direction indicated by outlined arrow to determine the absolute configuration of secondary alcohol.

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

The absolute values of $\Delta\delta$ must be proportional to the distance from the MTPA moiety. When these conditions are all satisfied, model A will represent the correct absolute configuration of the compound.

In order to assign the absolute stereochemistry of the side chain at C-3 in **61**, the (*S*)-MTPA ester **68** and (*R*)-MTPA ester **69** were independently prepared from **61** by using corresponding (*S*)-MTPA acid and (*R*)-MTPA acid in presence of coupling agent DCC and DMAP (cat.) in anhydrous CH_2Cl_2 at room temperature (Scheme 12). The $\Delta\delta = (\delta_S - \delta_R)$ x 1000 values were calculated for as many protons as possible from the ^{1}H NMR spectrum of (*S*)-MTPA ester **68** and (*R*)-MTPA ester **69** (Table 1). Then, constructed a molecular model of the compound and the $\Delta\delta = (\delta_S - \delta_R)$ x 1000 values were uniformly arranged as shown in Figure 4. On the basis of the model (Figure 4) we have assigned the absolute stereochemistry of side chain at C-3 of **61** as (*R*)-configuration.

Scheme 12

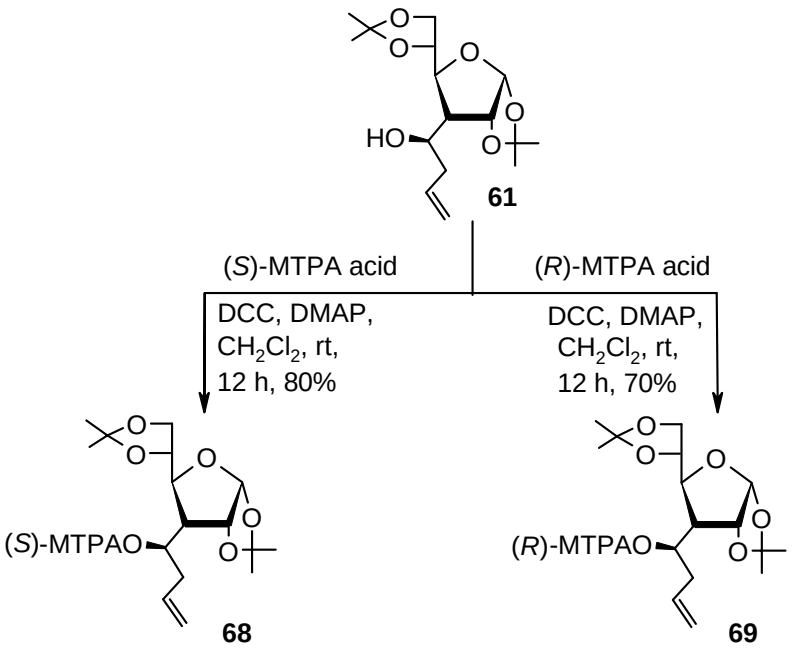


Table 1

Protons	H-3	H-4 & H-5	H-6	H-2	H-1	H-7	H-8a	H-8b	H-9	H-10
δ_S	1.65	3.96	3.79	4.36	5.67	5.56	2.67	2.09	5.80	5.16
δ_R	1.72	4.13	3.83	4.57	5.76	5.52	2.65	2.08	5.65	5.08
$\Delta\delta$	–70	–170	–40	–210	–90	–40	+20	+10	+150	+80

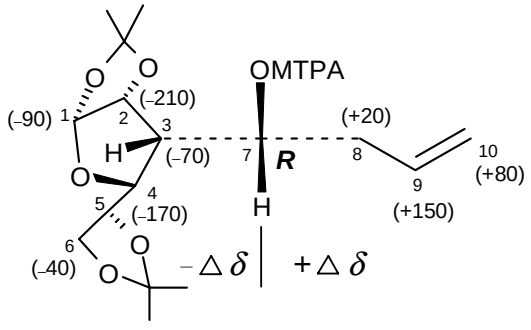


Figure 4: $\Delta\delta = (\delta_S - \delta_R)$ x 1000 for (*S*) and (*R*) MTPA esters of 61

The formation of **61** can be due to the profound affinity of Zn to complex with oxygen atoms. With substrate **67**, this complexation can occur between the carbonyl oxygen and the C-2 oxygen leading to six membered chelated complex. However, due to steric factors induced by the methyl group of 1,2-*O*-isopropylidene moiety, Zn seems to prefer to complex with the C-5 oxygen to produce the seven-membered complex (Figure 5). Therefore, the attack of the nucleophile $(CH_2{=}CH{-}CH_2)^-$ predominantly took place from the preferred β-face to furnish **61**.

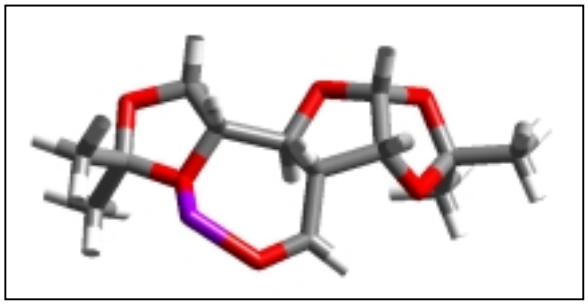
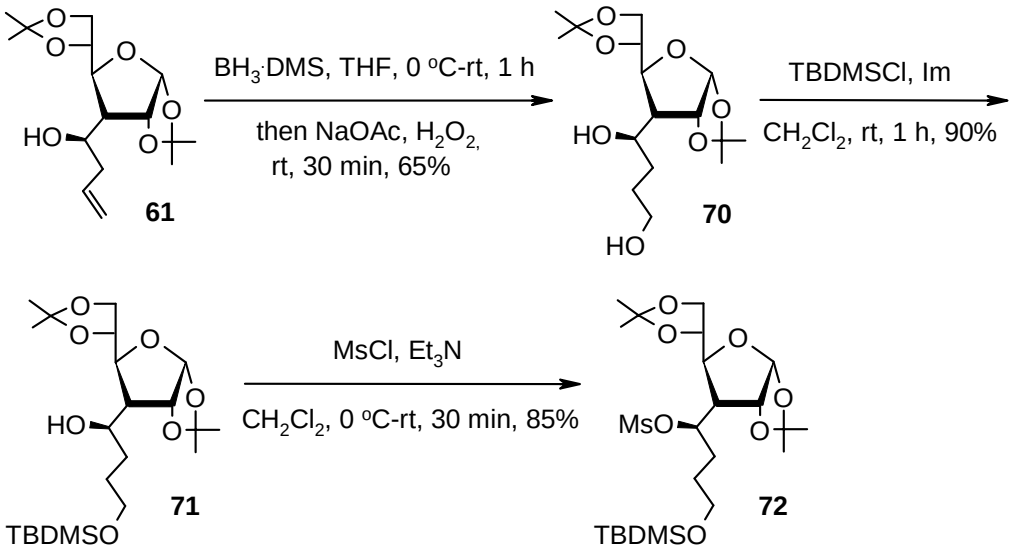


Figure 5: Energy Minimized Conformation for the 7-Membered Transition State

Construction of 2-pyrrolidinone ring

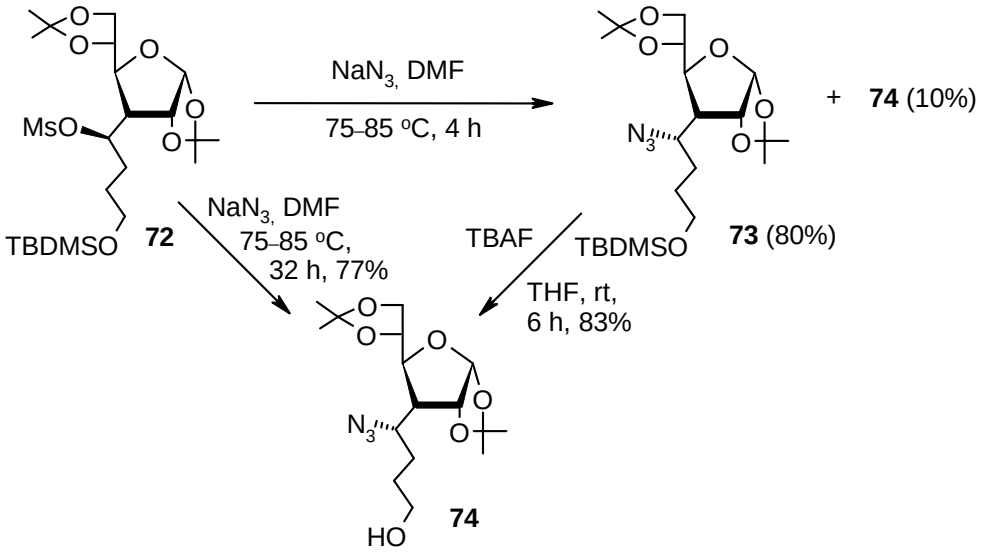
Having secured the absolute configuration of side chain at C-3 of **61** beyond doubt, we focused our attention on the construction of 2-pyrrolidinone derivative **59** from **61**. For that endeavor, **61** was first subjected to hydroboration-oxidation using BH_3·DMS, sat. NaOAc (aq.) and H_2O_2 to provide the diol **70** in 65% yield whose ^{1}H NMR spectrum showed the resonances in accordance with the structure. A triplet integrating for two protons at 3.61 ppm (J = 5.6 Hz) appeared in support of terminal hydroxymethyl moiety. Selective protection of the primary hydroxyl moiety of **70**, as TBDMS ether,[28] was accomplished using TBDMSCl and imidazole in anhydrous CH_2Cl_2 at room temperature to deliver **71** in 90% yield. The ^{1}H NMR spectrum of **71** revealed two clear singlet resonances corresponding to TBDMS group at 0.06 (6 H) and 0.90 ppm (9 H). It was further confirmed by the ^{13}C NMR spectrum of **71**, which showed resonances at –5.4, 18.2, and 25.8 ppm. Treatment of **71** with MsCl and Et_3N in anhydrous CH_2Cl_2 at 0 ^{o}C provided **73** in 85% yield[29, 28b] whose ^{1}H NMR spectrum indicated the singlet at 3.06 ppm integrating for 3 protons in support of mesylate group (Scheme 13).

Scheme 13



Azide mediated nucleophilic displacement reaction of mesylate ester **72** was carried out with NaN_3 in anhydrous DMF at 75–85 °C for 4 h to afford **73** in 80% yield,[30] whose ^1H NMR spectrum evidenced the absence of mesylate moiety and intactness of TBDMS group. Along with **73**, we were delighted to observe **74** as a minor product (10%), which was identical in all respects to the compound obtained from **73** by the deprotection of TBDMS group using TBAF in THF at room temperature. Gratifyingly, continuing the reaction of **72**

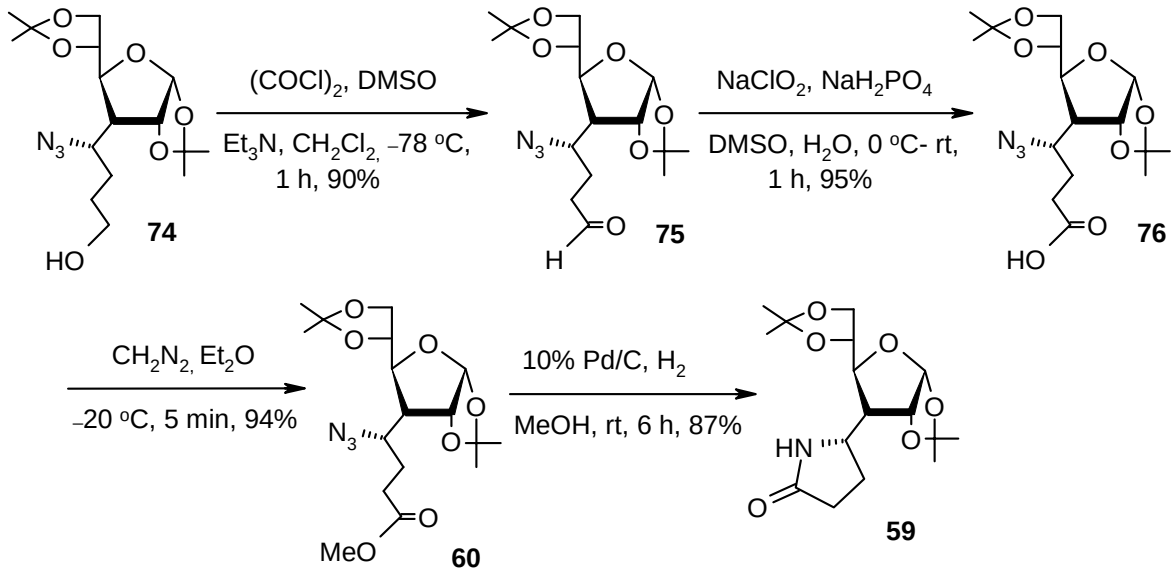
Scheme 14



with NaN_3 at same temperature for 32 h resulted in the formation of **74** exclusively, in 77% yield. The IR spectrum of **74** showed the absorption at 2112 cm^{-1} pertaining to azide functionality. The displacement of mesylate and deprotection of TBDMS moiety was evidenced by both ^1H NMR and ^{13}C NMR spectral studies of **74**. In the ^1H NMR spectrum of **74**, the H-1 resonated at 5.73 (d, 1 H, J = 4.6 Hz), H-2 at 4.72 (t, 1 H, J = 4.6 Hz), and the H-1' and H-4' (of side chain) resonated together as multiplet at 3.70 ppm (3 H) in support of the structure of **74** (Scheme 14).

For the purpose of converting **74** into the corresponding azido acid derivative in single step, the oxidation of **74** was attempted in the presence of $RuCl_3$ and $NaIO_4$ in a solvent mixture of H_2O-CH_3CN-CCl_4 but it turned out to be a poor yielding proposition.[31] Hence, we have adopted a two-step sequence employing Swern oxidation followed by $NaClO_2$ oxidation[32] of the resulting aldehyde to give azido acid. Thus, **74** was first subjected to Swern oxidation by using $(COCl)_2$, DMSO and Et_3N in CH_2Cl_2 at –78 ^oC to furnish an unstable aldehyde **75** which was immediately transformed into the corresponding azido acid derivative **76** treating with aq. $NaClO_2$ solution in DMSO in the presence of a phosphate buffer, NaH_2PO_4. The ^1H NMR spectrum of **76** indicated the absence of methylenic protons due to oxidation and the downfield shift of protons adjacent to the carbinyl moiety. The ^{13}C NMR spectrum of **76** showed the corresponding resonance for carbinyl group at 175.9 ppm. Then, the azido acid **76** was esterfied with diazomethane,[33] generated from nitrosomethylurea (NMU)[34] by treating with 50% aqueous KOH solution in diethyl ether at –15 ^oC to obtain methyl ester derivative **60** in 94% yield. In the ^1H NMR spectrum of **60** a sharp singlet integrating for three protons was appeared at 3.70 ppm confirming the presence of methyl ester moiety. Hydrogenation of **60** over 10% Pd/C in MeOH at normal pressure and temperature took place with concomitant cyclization to give the 2-pyrrolidinone derivative **59** in 87% yield. The structure of **59** was supported by spectral and analytical data. In the ^1H NMR spectrum of **59**, the H-1 and H-2 were resonated as a doublet and a triplet at 5.70 (J = 3.6 Hz) and 4.69 ppm (J = 3.6 Hz) respectively, and the protons corresponding to the lactam moiety were resonated as two multiplets at 2.02 (3 H, $\underline{CH_2}$-CO & $\underline{CH}$-NH) and a broad singlet at 6.15 ppm (1 H, NH) in accordance with the structure. The IR spectrum of **59** revealed the absorption at 1687 cm^{-1} pertinent to lactam moiety (Scheme 15).

Scheme 15

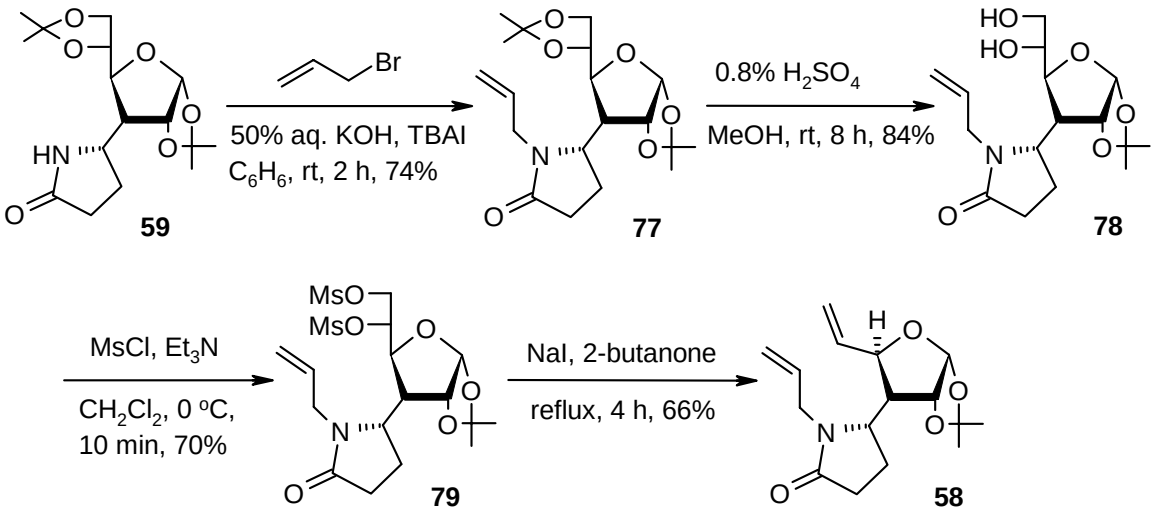


Installation of azepine ring system

Having the 2-pyrrolidinone derivative **59** in hand, our next concern was the installation of seven membered azepine ring system through a ring closing metathesis (RCM) reaction, which necessitated the construction of diene system **58**. Hence, the N-allylation of **59** was carried out under phase transfer conditions using allyl bromide in a biphasic system of 50% aq. KOH solution and benzene in the presence of TBAI to provide **77** in 74% yield.[35] In the ^{1}H NMR spectrum of **77**, protons corresponding to allylic moiety were resonated as two doublet of doublets at 3.52 (1 H, J = 7.2, 15.6 Hz) and 4.40 (1 H, J = 4.8, 15.6 Hz), and two multiplets at 5.11–5.25 (2 H) and 5.65–5.87 ppm (1 H). The formation of 5,6-ene derivative **58** was a straightforward proposition involving selective deprotection of 5,6-*O*-isopropylidene group, dimesylation of the resulting diol and elimination. Thus, **77** was treated with 0.8% H_2SO_4 in MeOH at ambient temperature which underwent selective deprotection of 5,6-*O*-isopropylidene moiety to furnish the diol derivative **78**, whose ^{1}H NMR spectrum indicated the absence of resonances related to 5,6-*O*-isopropylidene moiety. Dimesylation of **78** was achieved by using MsCl in the presence of Et_3N in anhydrous CH_2Cl_2 at 0 ^{o}C to result in the formation of **79**. In the ^{1}H NMR spectrum of **79** protons related to mesyl groups were resonated as two sharp singlets integrating for three protons each at 3.08 and 3.14 ppm. Then, the dimesylate **79** was subjected to iodide-mediated elimination using excess of NaI in

refluxing 2-butanone to afford the diene derivative **58** in good yield.[36] The ^{1}H NMR spectrum of **58** revealed the resonances at 4.98–5.30 (m, 4 H) and 5.51–5.71 ppm (m, 2 H) in accordance with the diene system (Scheme 16).

Scheme 16



The achievement of the diene derivative **58** without any difficulty set a stage for the application of ring closing metathesis reaction to obtain the azepine core, which would be a landmark towards stemoamide.

Ring Closing Metathesis: a brief view

Olefin metathesis is a unique carbon skeleton redistribution in which unsaturated C–C bonds are rearranged in the presence of metal carbene complexes.[37] This can be utilized in three closely related types of reactions such as ring-opening metathesis polymerization (ROMP), ring-closing metathesis (RCM) and acyclic cross metathesis (CM). Ring closing metathesis (RCM), in which two un-substituted (or substituted) olefins undergo ring closure with formal loss of ethylene, is one of the most popular methods of present time. It has received a great deal of attention in recent years for the synthesis of medium or large sized ring systems from acyclic diene precursors.[38] The reasons being:

1) Well designed, stable and highly active catalysts.
2) Very high turnover number was observed in the catalytic process.

3) Its efficacy in medium to macro-ring cyclization.
4) Its superiority over other cyclization methods like macrocyclization, Diels-Alder etc., because of favorable thermodynamic profile.
5) Adaptable for both solution and solid phase reactions.
6) Water solubility enabling the metathesis in water and methanol.
7) Design of recyclable and polymer bound catalysts.
8) Applicability to broad scope of substrates like ene -yne and yne-yne metathesis, in addition to tri- and tetra-substituted systems.
9) Combinatorial RCM libraries.
10) Eco-friendly profile, including viability in solvents like super critical CO_2.
11) Compatible with various functional groups.

Although a number of titanium and tungsten catalysts have been developed for metathesis and related reactions, the Schrock's catalyst (**80**), Grubbs' 1st and 2nd generation catalysts (**81** and **82**), and Hoveyda-Grubbs catalyst (**83**) have greatly attracted the attention of synthetic chemists because of their high reactivity and commercial availability. This reaction has changed the strategy of synthetic chemists and it is very common to find RCM as key transformation in the recent total syntheses of natural products, esp., for ring construction.

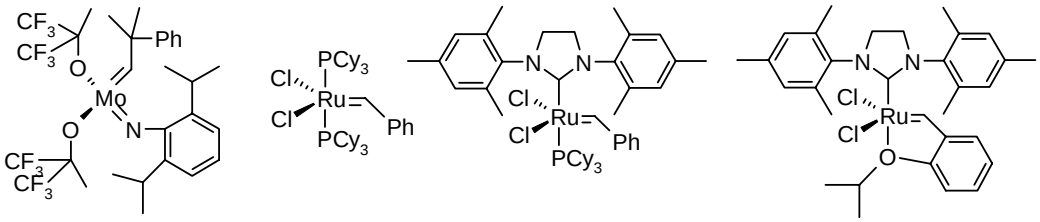
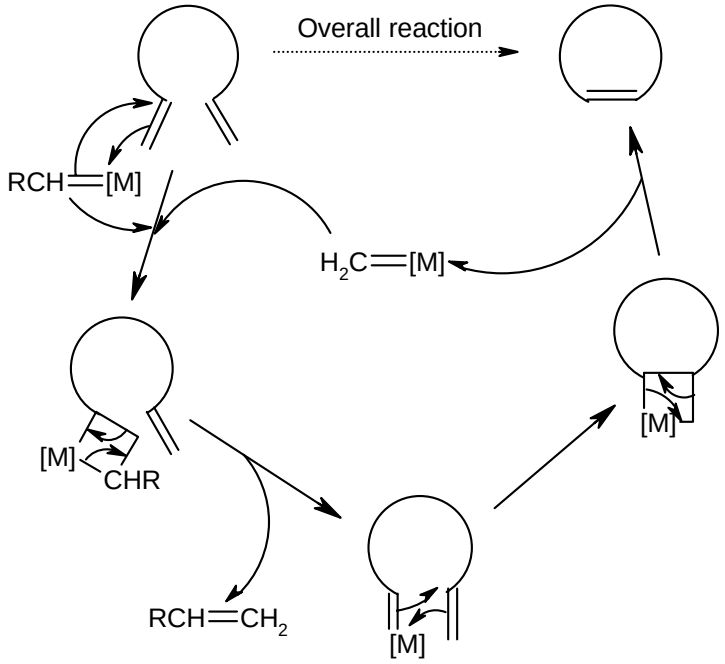


Figure 6: Leading metathesis catalysts

The postulated mechanism involves an iterative process of [2+2] cycloaddition and cycloreversion between the olefins, metal alkylidene and metallocyclobutane species (Scheme 12).[39] The initial retro-type intermolecular [2+2] cycloaddition between the catalyst and one of the olefins of diene leads to the incorporation of the metal alkylidene in the substrate. The second cycloaddition takes place in a facile intramolecular fashion and ring opening of resulting metallocyclobutane leads to the cycloalkene and regeneration of the metal carbene,

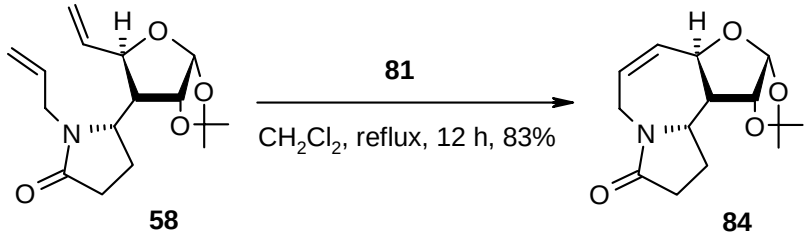
which takes up another diene molecule and acts in same fashion. In the first turn of the cycle, the volatile nature of the alkene by-product (the gaseous ethene in most cases) tends the reaction to proceed forward thermodynamically (Scheme 17).

Scheme 17: Ring Closing Metathesis mechanism



The ring closing metathesis reaction of **58** was successfully accomplished using 10% mol of Grubbs' 1st generation catalyst (**81**) in refluxing CH_2Cl_2 to obtain **84** in 83% yield.[40] The ^1H NMR spectrum of **84** showed characteristic olefinic protons at 5.75 (m, 2 H) while H_{7a} and H_{7b} were resonated as a broad doublet at 3.39 (J = 17.5 Hz) and a double doublet at 4.67 ppm (J = 17.5 Hz) respectively. The rest of the protons had the expected chemical shifts (Scheme 18).

Scheme 18



58 **84**

Although we determined the absolute stereochemistry of C-11 at early stage by modified Mosher's ester method, we were interested to study the NOE interactions in compound **84** to check the reliability of the method. Gratifyingly, the NOE studies of **84** revealed cross correlations between H_{11a}–H_{11c}, H_{11b}–H_{5a}, H_{11b}–H_{11c} and H_{5a}–H_{11c} confirming the structure of **84** (Figure 7).

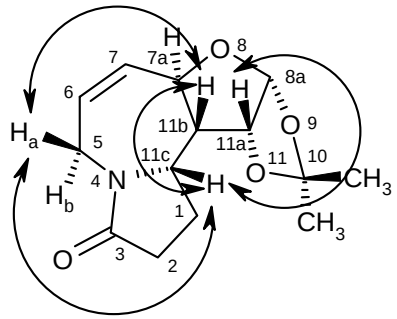


Figure 7: NOE studies on 84

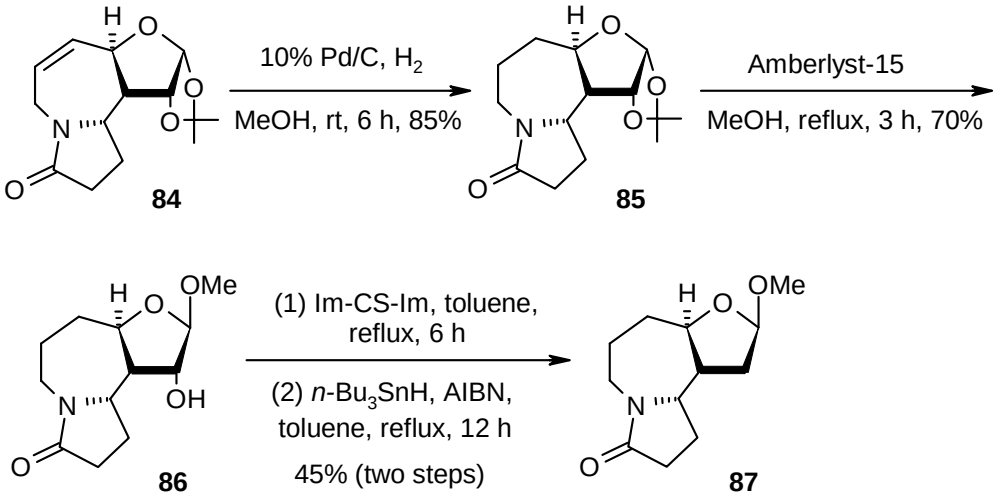
Modification of sugar skeleton into γ-butyrolactone moiety

After successful installation of the azepine ring system, our next objective was to carry out the necessary functional group manipulations to modify the sugar backbone into α-methyl-γ-butyrolactone moiety that would complete the total synthesis of stemoamide **1**. In that direction, we have chosen Barton-McCombie radical deoxygenation reaction to deoxygenate the C-2 hydroxyl moiety and Grieco's procedure for converting the methyl glycoside into the corresponding lactone derivative.

Hydrogenation of the double bond of **84** was carried out in presence of 10% Pd/C to give **85** whose ^{1}H NMR spectrum indicated the absence of olefinic protons. Treatment of **85** with MeOH and the acidic resin, Amberlyst-15 under reflux afforded α,β-mixture of methyl glycosides with β-isomer **86** being isolated in 90% yield after silica gel column chromatography. In the ^{1}H NMR spectrum of **86**, anomeric OMe moiety resonated as a sharp singlet integrating for three protons at 3.38 ppm. Anomeric proton resonated as singlet at 4.74 ppm in evidence of the β-linkage of OMe moiety. The proton at C-2 resonated as doublet at 4.31 ppm (J = 5.7 Hz) and the rest of the protons had the expected chemical shifts. For the execution of Barton-McCombie reaction,[41] the compound **86** was first converted into

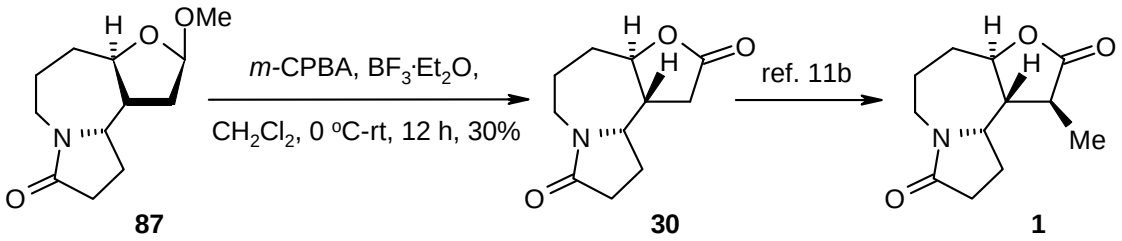
the corresponding imidazolyl xanthate derivative using 1,1'-thiocarbonyldiimidazole in refluxing toluene, and then *in situ* addition of *n*-Bu_3SnH and catalytic AIBN was affected to furnish the 2-deoxy product **87** in 45% yield, for two steps. The C-2 deoxygenation in **87** was well supported by ^1H NMR, ^{13}C NMR and mass spectral studies together with elemental analysis. The ^{13}C NMR and DEPT spectra of **87** showed the corresponding resonances for 6 methylenic moieties, and the mass spectra recorded M^+ peak at 224 in support of the assigned structure (Scheme 19).

Scheme 19



Having had the compound **87** in hand, our immediate concern was the transformation of **87** into the corresponding γ-butyrolactone derivative **30**. Thus, **87** was subjected to acidic hydrolysis using 40% aq. AcOH followed by the oxidation of resulted lactol derivative with Dess-Martin periodinane.[42] But this reaction sequence failed to afford the expected γ-butyrolactone derivative **30**. Hence, we have diverted our attention towards Grieco's protocol,[43] according to which **87** was treated with *m*-CPBA and $BF_3{\cdot}Et_2O$ in anhydrous CH_2Cl_2 at room temperature to obtain the requisite compound **30**. The ^1H NMR and ^{13}C NMR spectra of **30** were compatible with the reported data (Table 2). Since the compound **30** has already been transformed into the stemoamide (**1**) in one step the present synthesis constitutes a formal total synthesis of stemoamide **1** (Scheme 20).[11b]

Scheme 20



87 **30** **1**

Table 2: Comparison of ^{1}H NMR data of 30 with the reported one

^{1}H NMR δ values for compound **30** (500 MHz, $CDCl_3$) synthesized by Gurjar, M. K. and Reddy, D. S.[25]	^{1}H NMR δ values for compound **30** (400 MHz, $CDCl_3$) synthesized by Narasaka, K. *et al.*[11b]
1.50–1.75 (m, 3 H)	1.52–1.60 (m, 2 H), 1.73 (qui, 1 H, J = 10.7 Hz)
1.87 (m, 1 H)	1.84–1.90 (m, 1 H)
2.05–2.12 (m, 1 H)	2.05–2.12 (m, 1 H)
2.30–2.45 (m, 4 H)	2.36–2.45 (m, 4 H)
2.52 (dd, 1 H, J = 12.5, 17.1 Hz)	2.51 (dd, 1 H, J = 8.8, 17.1 Hz)
2.65 (dd, 1 H, J = 8.9, 17.1 Hz)	2.64 (dd, 1 H, J = 12.7, 17.1 Hz)
2.80–2.90 (m, 1 H)	2.65–2.76 (m, 1 H)
4.00 (dt, 1 H, J = 6.3, 10.7 Hz)	4.00 (dt, 1 H, J = 6.4, 10.7 Hz)
4.16 (m, 1 H)	4.11–4.16 (m, 1 H)
4.29 (dt, 1 H, J = 2.4, 10.3 Hz)	4.30 (dt, 1 H, J = 2.9, 10.3 Hz)

Conclusion

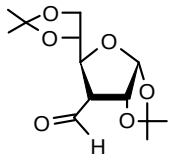
In conclusion, we have achieved the carbohydrate based synthesis of stemoamide **1** from easily accessible D-glucose. The stereocontrolled allylation under Barbier reaction conditions in aqueous media led to the construction of 2-pyrrolidionone ring at C-3 position. The ring closing metathesis reaction of diene derivative **58** furnished the azepine ring system followed by Barton-McCombie reaction to deoxygenate C-2 hydroxyl moiety. Finally,

application of Grieco's protocol completed the formal total synthesis of stemoamide **1**. During these studies, we have developed an efficient, simple and novel strategy for the stereoseletive allylaton of aldehyde **67** taking the advantage of the bulkiness of 1,2-*O*-isopropylidene moiety, which would attract the attention of synthetic chemists in the near future.

Experimental Section

Experimental

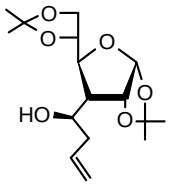
3-Deoxy-3-*C*-formyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (67)



A solution of DMSO (7.8 mL, 110.02 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise to a solution of $(COCl)_2$ (4.0 mL, 45.85 mmol) in anhydrous CH_2Cl_2 (60 mL) under argon atmosphere at –78 ^oC. The mixture was stirred for 5 min and then a solution of **62** (8.0 g, 36.47 mmol) in anhydrous CH_2Cl_2 (30 mL) was added dropwise. After 30 min Et_3N (20.0 mL, 143.49 mmol) was added dropwise and then it was allowed to attain room temperature. The reaction mixture was diluted with water, extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated on rotavapor to give crude aldehyde **67** (6.35 g, 80%).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (s, 6 H), 1.38, 1.51 (2 s, 6 H), 2.82–2.94 (m, 1 H), 3.86–3.98 (m, 1 H), 4.00–4.18 (m, 2 H), 4.56 (dd, 1 H, J = 5.6, 2.8 Hz), 5.03 (t, 1 H, J = 3.5 Hz), 5.85 (d, 1 H, J = 3.5 Hz), 9.72 (d, 1 H, J = 1.4 Hz).

3-Deoxy-3-*C*-[(1*R*)-1-hydroxy-but-3-enyl]-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (61)



Grignard reaction: To a suspension of Mg turnings (0.29 g, 11.93 mmol) in anhydrous ether (15 mL) were added allyl bromide (0.1 mL of total 1.0 mL, 11.82 mmol) and a pinch of iodine. The mixture was stirred vigorously at room temperature, whereupon a rise in temperature and clouding of the reaction mixture occurred indicating the beginning of reaction. The remainder of the allyl bromide (1.4 mL) solution was added dropwise with continued stirring at such a rate as to maintain a gentle reflux. The mixture was refluxed for

an additional 20 min and allowed to attain room temperature. The resulted allyl magnesium bromide was added to a solution of aldehyde **67** (1.0 g, 3.68 mmol) in anhydrous ether (15 mL) through a cannula at –15 ^{o}C and stirred for 15 min at same temperature. Reaction mixture was quenched with saturated aq. NH_4Cl solution, extracted with ether, washed with brine, dried (Na_2SO_4), and concentrated on rotavapor. The residue on purification by silica gel column chromatography using EtOAc–light petroleum (1:9) afforded an inseparable diastereomeric mixture of **61** and **61*S*** in 3:1 ratio (0.72 g, 62%) as syrup.

(**or**)

Kishi's protocol: To a solution of 1M $ZnBr_2$ in THF (29.4 mL, 29.41 mmol) was added allyl magnesium bromide in ether, prepared as described earlier using Mg turnings (0.45 g, 18.51 mmol) and allyl bromide (1.6 mL, 18.91 mmol) in anhydrous ether (25 mL), slowly through syringe at 0 ^{o}C and stirred for 10 min at room temperature. The mixture was cooled to –78 ^{o}C and then added a solution of aldehyde **67** (1.0 g, 3.68 mmol) in THF (10 mL) slowly over a period of 10 min. After being stirred for 10 min, the mixture was poured into ether and saturated aq. NH_4Cl, and the aqueous layer extracted twice with ether (2 x 20 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using EtOAc–light petroleum (1:9) to yield **61** (0.94 g, 81%) as syrup.

(**or**)

Barbier-type reaction: To a mixture of **67** (7.0 g, 25.73 mmol) and allyl bromide (4.4 mL, 52.01 mmol) in THF-saturated aq. NH_4Cl solution (40 mL : 20 mL) was added Zinc dust (5.0 g, 76.49 mmol) slowly in portions at 0 ^{o}C, and stirred for 30 min at same temperature. The reaction mixture was filtered through a Celite pad, extracted with EtOAc, washed with brine, dried (Na_2SO_4), and concentrated on rotavapor. The residue was purified by silica gel column chromatography using EtOAc–light petroleum (1:9) to afford **61** (6.64 g, 82%) as syrup.

$[\alpha]_D$ +31.6 (*c* 1, $CHCl_3$).

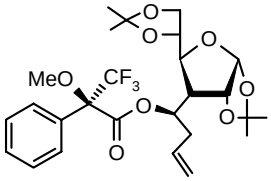
^{1}H NMR (200 MHz, $CDCl_3$): ***δ*** 1.31, 1.38, 1.47, 1.52 (4 s, 12 H), 1.91 (m, 1 H), 2.33 (dd, 1 H, *J* = 6.0, 15.1 Hz), 2.60 (m, 1 H), 3.90–4.21 (m, 5 H), 4.66 (t, 1 H, *J* = 3.0 Hz), 5.15 (m, 2 H), 5.68 (d, 1 H, *J* = 3.0 Hz), 6.00 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.2, 26.1, 26.2, 26.7, 39.1, 55.3, 67.9, 68.1, 77.0, 81.7, 82.4, 104.3, 110.0, 112.0, 116.6, 135.0.

EI-MS (*m/z*): 299 (M^+–Me).

Anal. Calcd for $C_{16}H_{26}O_6$: C, 61.13; H, 8.34. Found: C, 60.82; H, 8.64.

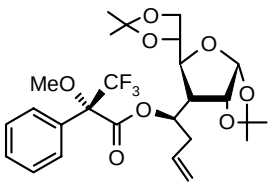
3-Deoxy-3-*C*-[(1*R*)-1-(*S'*)-(–)-α-methoxy-α-trifluoromethylphenylacetoxy-but-3-enyl]-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (68)



To a solution of **61** (0.02 g, 0.06 mmol) in anhydrous CH_2Cl_2 (4 mL) were added (*S*)-(–)-α-methoxy-α-trifluoromethylphenylacetic acid (*S*-MTPA) (0.03 g, 0.13 mmol), DCC (0.026 g, 0.13 mmol) and DMAP (0.002 g, 0.02 mmol), and stirred for12 h at room temperature. The reaction mixture was diluted with water, extracted with CH_2Cl_2, washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography with EtOAc–light petroleum (1:9) as an eluent to afford **68** (0.027 g, 80%) as syrup.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26, 1.27, 1.40, 1.51 (4 s, 12 H), 1.59–1.71 (m, 1 H), 2.08–2.19 (m, 1 H), 2.69 (dd, 1 H, J = 6.8, 1.0 Hz), 3.58 (d, 3 H, J = 1.3 Hz), 3.77–4.15 (m, 4 H), 4.37 (dd, 1 H, J = 3.6, 0.8 Hz), 5.10–5.22 (m, 2 H), 5.52–5.61 (m, 1 H), 5.68 (d, 1 H, J = 3.6 Hz), 5.72–5.89 (m, 1 H), 7.37–7.45 (m, 3 H), 7.53–7.61 (m, 2 H).

3-Deoxy-3-*C*-[(1*R*)-1-(*R'*)-(+)-α-methoxy-α-trifluoromethylphenylacetoxy-but-3-enyl]-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (69)

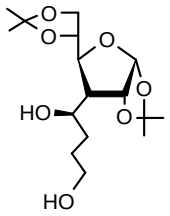


The reaction was carried out as described earlier using compound **61** (0.02 g, 0.06 mmol), (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (*R*-MTPA) (0.03 g, 0.13

mmol), DCC (0.026 g, 0.13 mmol) and DMAP (0.002 g, 0.02 mmol), in anhydrous CH_2Cl_2 (4 mL). The residue was purified by silica gel column chromatography with EtOAc–light petroleum (1:9) as eluent to afford **69** (0.024 g, 70%) as syrup.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.28, 1.32, 1.42, 1.54 (4 s, 12 H), 1.66–1.78 (m, 1 H), 2.04–2.15 (m, 1 H), 2.63–2.71 (m, 1 H), 3.51 (s, 3 H), 3.77–3.91 (m, 2 H), 4.05–4.22 (m, 2 H), 4.59 (t, 1 H, *J* = 3.5 Hz), 5.01–5.13 (m, 2 H), 5.46–5.73 (m, 2 H), 5.76 (d, 1 H, *J* = 3.5 Hz), 7.40–7.46 (m, 3 H), 7.51–7.58 (m, 2 H).

3-Deoxy-3-*C*-[(1*R*)-1,4-dihydroxybutyl]-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (70)



To a solution of **61** (6.5 g, 20.68 mmol) in anhydrous THF (30 mL) was added BH_3·DMS (2.3 mL, 24.25 mmol) slowly at 0 ^oC and stirred for 2 h at room temperature. MeOH (5 mL) and saturated aq. NaOAc (5 mL) were added to the reaction mixture at –15 ^oC until the effervescence ceased and stirring continued for 30 min. Then 30% H_2O_2 was added and stirred at room temperature for 30 min. THF and MeOH were removed on rotavapor, and extracted twice with EtOAc (2 x 50 mL). The combined organic fractions were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel by using EtOAc-light petroleum (1:1) to give **70** (4.47 g**,** 65%).

$[\alpha]_D$ –35.8 (*c* 1, $CHCl_3$).

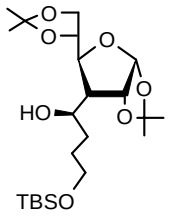
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.23, 1.31, 1.39, 1.44 (4 s, 12 H), 1.55–1.77 (q, 3 H, *J* = 6.2 Hz), 1.80–1.98 (m, 2 H), 3.15–3.45 (br s, 1 H), 3.61 (t, 2 H, *J* = 5.6 Hz), 3.76–4.01 (m, 4 H), 4.04–4.16 (m, 1 H), 4.60 (t, 1 H, *J* = 3.6 Hz), 5.64 (d, 1 H, *J* = 3.6 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 24.9, 25.9, 26.3, 28.2, 31.3, 55.1, 61.9, 67.2, 67.9, 76.5, 81.6, 81.7, 95.6, 103.9, 109.5, 111.5.

EI-MS (*m/z*): 317 (M^+–Me).

Anal. Calcd for $C_{16}H_{28}O_7$: C, 57.82; H, 8.49. Found: C, 57.68; H, 8.52.

3-Deoxy-3-*C*-[(1*R*)-1-hydroxy-4-(1,1,2,2-tetramethyl-1-silapropoxy)butyl]-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (71)



TBDMSCl (2.2 g, 14.60 mmol) was added to a mixture of **70** (4.4 g, 13.24 mmol) and imidazole (1.3 g, 19.12 mmol) in anhydrous CH_2Cl_2 (30 mL) and stirred at room temperature for 1 h. The reaction mixture was quenched with saturated aq. $NaHCO_3$ solution (2 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), concentrated and the residue was purified by silica gel column chromatography using EtOAc–light petroleum (1:8) as an eluent to afford **71** (5.32 g, 90%) as colorless syrup.

$[\alpha]_D$ +36.0 (*c* 1.02, $CHCl_3$).

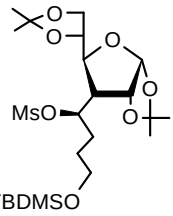
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.06 (s, 6 H), 0.90 (s, 9 H), 1.28, 1.38, 1.47, 1.50 (4 s, 12 H), 1.56–1.97 (m, 5 H), 3.68 (t, 2 H, *J* = 5.9 Hz), 3.81–4.05 (m, 4 H), 4.11–4.22 (m, 1 H), 4.64 (t, 1 H, *J* = 3.4 Hz), 5.66 (d, 1 H, *J* = 3.4 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ –5.4, 18.2, 25.3, 25.8, 26.1, 26.3, 26.7, 28.5, 31.2, 56.2, 63.1, 68.1, 68.2, 76.9, 82.0, 82.4, 104.3, 110.0, 112.0.

EI-MS (*m/z*): 432 (M^+–Me).

Anal. Calcd for $C_{22}H_{42}O_7Si$: C, 59.16; H, 9.48. Found: C, 59.08; H, 9.75.

3-Deoxy-3-*C*-[(1*R*)-1-methylsulfonyloxy-4-(1,1,2,2-tetramethyl-1-silapropoxy)butyl]-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (72)



To a solution of **71** (5.2 g, 11.64 mmol) in anhydrous CH_2Cl_2 (40 mL) were added Et_3N (2.3 mL, 16.50 mmol) and MsCl (1.0 mL, 12.89 mmol) at 0 ^oC, and stirred for 30 min at

room temperature. The reaction mixture was quenched with water, washed with brine, dried (Na_2SO_4), and concentrated. The crude oily compound was chromatographed on silica gel with EtOAc-light petroleum (1:5) to afford mesylate derivative **72** (5.2 g, 85%) as clear oil.

$[\alpha]_D$ +47.1 (*c* 0.4, $CHCl_3$).

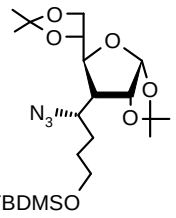
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.04 (s, 6 H), 0.88 (s, 9 H), 1.32, 1.33, 1.41, 1.52 (4 s, 12 H), 1.58–1.71 (m, 2 H), 1.92–2.18 (m, 2 H), 2.29–2.42 (m, 1 H), 3.06 (s, 3 H), 3.63 (t, 2 H, *J* = 6.0 Hz), 3.86–3.94 (m, 1 H), 3.98–4.16 (m, 3 H), 4.75 (t, 1 H, *J* = 3.5 Hz), 5.13 (dt, 1 H, *J* = 7.8, 2.9 Hz), 5.73 (d, 1 H, *J* = 3.5 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ –5.5, 18.1, 25.0, 25.8, 26.2, 26.3, 26.8, 28.8, 29.0,38.5, 51.2, 62.5, 66.4, 77.4, 79.7, 81.1, 104.9,109.5,112.6.

EI-MS (*m/z*): 509 (M^+–Me).

Anal. Calcd for $C_{23}H_{44}O_9SSi$: C, 52.64; H, 8.45; S, 6.11. Found: C, 52.48; H, 8.74; S, 6.16.

3-*C*-[(1*S*)-1-Azido-4-(1,1,2,2-tetramethyl-1-silapropoxy)-butyl]-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (73)



A mixture of **72** (1.0 g, 1.91 mmol) and NaN_3 (1.24 g, 19.07 mmol) in anhydrous DMF (20 mL) were heated at 75–85 ^oC for 4 h. Then the reaction mixture was diluted with water, extracted twice with ether (2 x 20 mL), the combined organic fractions were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using EtOAc–light petroleum (1:9) as an eluent to afford **73** (0.75 g, 80%) as colorless syrup.

$[\alpha]_D$ +63.9 (*c* 0.86, $CHCl_3$).

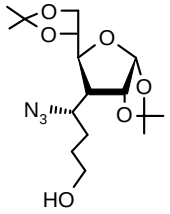
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.09 (s, 6 H), 0.92 (s. 9 H), 1.35 (s, 6 H), 1.44, 1.59 (2 s, 6 H), 1.65–2.08 (m, 5 H), 3.63–3.80 (m, 3 H), 3.93–4.28 (m, 4 H), 4.75 (t, 1 H, *J* = 3.7 Hz), 5.80 (d, 1 H, *J* = 3.7 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ –5.9, 17.7. 24.7, 25.4, 25.8, 26.3, 26.0, 28.4, 29.1, 51.4, 57.9, 61.7, 66.8, 77.2, 78.8, 80.7, 104.3, 109.0, 111.8.

EI-MS (*m/z*): 456 (M^+–Me).

Anal. Calcd for $C_{22}H_{41}N_3O_6Si$: C, 56.02; H, 8.76; N, 8.91. Found: C, 56.08; H, 8.85; N, 8.86.

3-*C*-[(1*S*)-1-Azido-4-hydroxybutyl]-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (74)



To a solution of **73** (0.7 g, 1.42 mmol) in anhydrous THF (10 mL) was added 1M solution of TBAF in THF (1.7 mL, 1.71 mmol) and stirred at room temperature for 6 h. After completion of the reaction, solvent was removed on rotavapor and the resulted residue was purified on silica gel using EtOAc–light petroleum (1:2) as an eluent to obtain **74** (0.42 g, 83%) as colorless syrup.

(**or**)

The reaction was carried out as described earlier using compound **72** (4.0 g, 7.62 mmol) and NaN_3 (5.0 g, 76.91 mmol) in anhydrous DMF (40 mL), and heated at 75–85 ^oC for 32 h. Reaction mixture was diluted with water, extracted with ether, washed with brine, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel with EtOAc–light petroleum (1:9) as an eluent to afford **74** (2.1 g, 77%) as colorless syrup.

IR ($CHCl_3$): ν = 2112 cm^{-1} (azide).

$[\alpha]_D$ +64.3 (*c* 0.66, $CHCl_3$).

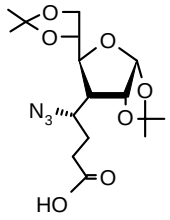
^{1}H NMR (200 MHz, $CDCl_3$): ***δ*** 1.35 (s, 6 H), 1.44, 1.57 (2 s, 6 H), 1.85 (m, 5 H), 3.70 (m, 3 H), 3.80–4.20 (m, 4 H), 4.72 (t, 1 H, *J* = 4.6 Hz), 5.73 (d, 1 H, *J* = 4.6 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): ***δ*** 24.9, 25.9, 26.1, 26.4, 28.6, 29.3, 51.5, 58.4, 61.4, 66.9, 77.1, 78.9, 80.8, 104.4, 109.5, 112.3.

EI-MS (*m/z*): 342 (M^+–Me).

Anal. Calcd for $C_{16}H_{27}N_3O_6$: C, 53.77; H, 7.61; N, 11.76. Found: C, 53.63; H, 7.52; N, 11.83.

3-*C*-[(1*S*)-1-Azido-4-hydroxy-4-oxobutyl]-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (76)



The reaction was carried out as described earlier using compound **74** (2.0 g, 5.60 mmol), DMSO (1.2 mL, 16.93 mmol), $(COCl)_2$ (0.8 mL, 9.17 mmol) and Et_3N (3.9 mL, 27.98 mmol) in anhydrous CH_2Cl_2 (30 mL) at –78 °C to give the crude aldehyde **75** (1.79 g, 90%).

A solution of $NaClO_2$ (0.68 g, 7.52 mmol) in water (10 mL) was added dropwise in 5 min at 0 °C to the stirred mixture of **75** (1.78 g, 5.01 mmol) in DMSO (8 mL) and NaH_2PO_4 (0.4 g. 2.56 mmol) in water (3 mL). The mixture was stirred at room temperature for 1 h. Then the reaction mixture was diluted with water, extracted twice with CH_2Cl_2 (2 x 20 mL), and concentrated. The residue treated with 5% aqueous solution of $NaHCO_3$ and the aqueous layer was washed with CH_2Cl_2 to remove the impurities, i.e. DMSO and dimethyl sulphone. 2N HCl was added to the aqueous layer, and then extracted with CH_2Cl_2 (2 x 20 mL). All CH_2Cl_2 fractions were combined, washed with brine, dried (Na_2SO_4) and concentrated to give pure **76** (1.77 g, 95%) as syrup.

$[\alpha]_D$ +60.3 (*c* 1, $CHCl_3$).

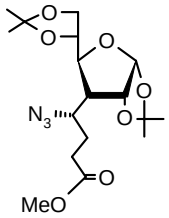
^{1}H NMR (200 MHz, $CDCl_3$): ***δ*** 1.33, 1.34, 1.42, 1.57 (4 s, 12 H), 1.93–2.26 (m, 3 H), 2.42–2.68 (m, 2 H), 3.69–3.81 (m, 1 H), 3.86–4.17 (m, 4 H), 4.73 (t, 1 H, *J* = 3.6 Hz), 5.74 (d, 1 H, *J* = 3.6 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): ***δ*** 24.6, 25.6, 25.9, 26.2, 27.3, 30.5, 51.2, 58.1, 66.7, 76.8, 78.8, 80.7, 104.2, 109.2, 112.0, 175.9.

EI-MS (*m/z*): 356 (M^+–Me).

Anal. Calcd for $C_{16}H_{25}N_3O_7$: C, 51.74; H, 6.78; N, 11.31. Found: C, 51.66; H, 6.92; N, 11.23.

3-*C*-[(1*S*)-1-Azido-4-methoxy-4-oxobutyl]-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (60)



50% aq. solution of KOH was added slowly to a solution of nitrosomethylurea (NMU) (1.8 g, 17.48 mmol) in anhydrous ether (20 mL) while shaking at –20 ^{o}C. The ether layer containing diazomethane was decanted into another conical flask and dried over KOH pellets. It was then added to the solution of **76** (1.6 g, 4.31 mmol) in anhydrous ether (15 mL) at –20 ^{o}C and stirred for 5 min at same temperature. The solvent was removed on rotavapor and the residue purified by silica gel column chromatography using EtOAc–light petroleum (1:5) as an eluent to afford **60** (1.56 g, 94%) as colorless syrup.

$[\alpha]_D$ +65.0 (*c* 0.7, $CHCl_3$).

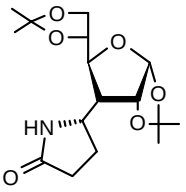
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32, 1.34, 1.41, 1.56 (4 s, 12 H), 1.96–2.26 (m, 3 H), 2.37–2.62 (m, 2 H), 3.70 (s, 3 H), 3.67–3.79 (m, 1 H), 3.86–4.03 (m, 2 H), 4.06–4.17 (m, 2 H), 4.72 (t, 1 H, *J* = 3.6 Hz), 5.73 (d, 1 H, *J* = 3.6 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.1, 26.1, 26.3, 26.7, 28.1, 30.9, 51.4, 52.1, 58.8, 67.4, 77.5, 79.5, 81.3, 104.6, 109.7, 112.6, 172.9.

EI-MS (*m/z*): 370 (M^+–Me).

Anal. Calcd for $C_{17}H_{27}N_3O_7$: C, 52.98; H, 7.06; N, 10.90. Found: C, 52.90; H, 6.95; N, 10.97.

3-Deoxy-3-*C*-[(2*S*)-5-oxo-2-pyrrolidinyl]-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (59)



To a solution of **60** (1.5 g, 3.89 mmol) in MeOH (10 mL) was added 10% Pd/C (0.1 g) and the mixture was degassed with argon and flushed with H_2 for 5 min. After stirring under an atmosphere of H_2 for 6 h at room temperature, the mixture was filtered through a pad of

Celite and the solvent concentrated. The residue was purified on silica gel with MeOH–CH_2Cl_2 (1:9) to give **59** (1.11 g, 87%) as colorless syrup.

IR ($CHCl_3$): ν = 1687 cm^{-1} (amide).

$[\alpha]_D$ +59.4 (*c* 1, $CHCl_3$).

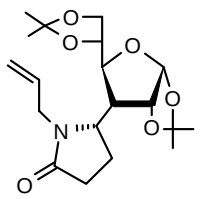
^{1}H NMR (200 MHz, $CDCl_3$): ***δ*** 1.31, 1.32, 1.40, 1.52 (4 s, 12 H), 2.02 (m, 2 H), 2.36 (m, 3 H), 3.85 (m, 4 H), 4.06 (m, 1 H), 4.69 (dd, 1 H, *J* = 3.6 Hz), 5.70 (d, 1 H, *J* = 3.6 Hz), 6.15 (br s, 1 H, NH).

^{13}C NMR (50 MHz, $CDCl_3$): ***δ*** 24.8, 25.8, 25.9, 26.2, 26.7, 29.5, 52.2, 53.5, 66.9, 76.6, 80.5, 81.7, 104.0, 109.0, 111.8, 177.6.

EI-MS (*m/z*): 327 (M^+).

Anal. Calcd for $C_{16}H_{25}NO_6$: C, 58.70; H, 7.70; N, 4.28. Found: C, 59.02; H, 7.73; N, 4.22.

3-Deoxy-3-*C*-[(2*S*)-5-oxo-1-(prop-2-enyl)-2-pyrrolidinyl]-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (77)



To a solution of **59** (1.0 g, 3.05 mmol) in benzene (15 mL) were added 50% aq. solution of KOH (15 mL), TBAI (1.13 g, 3.06 mmol) and allyl bromide (0.3 mL, 3.55 mmol), and then stirred at room temperature for 2 h. Reaction mixture was extracted with EtOAc (2 x 20 mL) and the combined organic fractions were washed with brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel using EtOAc–light petroleum (1:2) to afford **77** (0.83 g, 74%) as colorless syrup.

$[\alpha]_D$ +60.6 (*c* 0.77, $CHCl_3$).

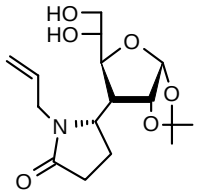
^{1}H NMR (200 MHz, $CDCl_3$): ***δ*** 1.31 (s, 6 H), 1.39, 1.53 (2 s, 6 H), 2.12–2.50 (m, 5 H), 3.52 (dd, 1 H, *J* = 7.2, 15.6 Hz), 3.76–3.89 (m, 2 H), 3.99–4.17 (m, 3 H), 4.40 (dd, 1 H, *J* = 4.8, 10.8 Hz), 4.66 (t, 1 H, *J* = 3.6 Hz), 5.11–5.25 (m, 2 H), 5.65–5.87 (m, 1 H), 5.72 (d, 1 H, *J* = 3.6 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): ***δ*** 21.7, 24.4, 25.4, 26.0, 29.3, 42.7, 48.6, 54.2, 67.1, 76.7, 78.6, 81.7, 103.7, 108.9, 111.7, 116.5, 132.5, 174.1.

EI-MS (*m/z*): 367 (M^+).

Anal. Calcd for $C_{19}H_{29}NO_6$: C, 62.11; H, 7.96; N, 3.81. Found: C, 62.22; H, 7.99; N, 3.92.

3-Deoxy-3-*C*-[(2*S*)-5-oxo-1-(prop-2-enyl)-2-pyrrolidinyl]-1,2-*O*-isopropylidene-α- D-allo-furanose (78)



The compound **77** (0.7 g, 1.90 mmol) and 0.8% H_2SO_4 (4 mL) in MeOH (12 mL) were stirred at room temperature for 8 h. After neutralization with solid $NaHCO_3$, the reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by silica gel column chromatography with EtOAc–light petroleum (3:1) to give the diol derivative **78** (0.525 g, 84%) as syrup.

$[\alpha]_D$ +30.7 (*c* 0.7, MeOH).

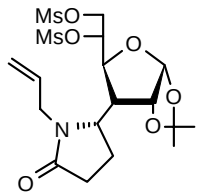
^{1}H NMR (200 MHz, $CDCl_3$): ***δ*** 1.31, 1.52 (2 s, 6 H), 2.15–2.63 (m, 5 H), 3.47–3.77 (m, 4 H), 4.10–4.24 (m, 2 H), 4.41 (dd, 1 H, *J* = 4.4, 15.7 Hz), 4.65 (t, 1 H, *J* = 3.7 Hz), 5.15–5.26 (m, 2 H), 5.64–5.84 (m, 1 H), 5.75 (d, 1H, *J* = 3.7 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): ***δ*** 22.1, 26.0, 26.5, 30.1, 43.2, 46.7, 55.2, 63.7, 73.4, 78.9, 82.3, 104.0, 112.2, 117.8, 132.4, 175.9.

EI-MS (*m/z*): 327 (M^+).

Anal. Calcd for $C_{16}H_{25}NO_6$: C, 58.70; H, 7.70; N, 4.28. Found: C, 58.62; H, 7.85; N, 4.22.

3-Deoxy-5,6-dimethylsulfonyloxy-3-*C*-[(2*S*)-5-oxo-1-(prop-2-enyl)-2-pyrrolidinyl]-1,2-*O*-isopropylidene-α- D-allofuranose (79)



To a solution of the diol **78** (0.45 g, 1.37 mmol) in anhydrous CH_2Cl_2 (8 mL) were added Et_3N (1.0 mL, 7.17 mmol) and MsCl (0.3 mL, 3.87 mmol) at 0 ^oC, and stirred for 10

min at same temperature. The reaction mixture was quenched with water, washed with brine, dried (Na_2SO_4) and concentrated. The crude oily compound was purified on silica gel with EtOAc–light petroleum (1:1) to afford 5,6-dimesylate derivative **79** (0.465 g, 70%) as clear oil.

$[\alpha]_D$ +37.2 (*c* 1.2, $CHCl_3$).

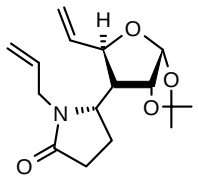
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33, 1.53 (2 s, 6 H), 2.10–2.63 (m, 5 H), 3.08, 3.14 (2 s, 6 H), 3.56 (dd, 1 H, *J* = 7.2, 15.9 Hz), 4.06–4.17 (m, 1 H), 4.34–4.58 (m, 4 H), 4.69 (t, 1 H, *J* = 3.5 Hz), 4.78 (q, 1 H, *J* = 3.2 Hz), 5.15–5.31 (m, 2 H), 5.65–5.84 (m, 1 H), 5.77 (d, 1 H, *J* = 3.5 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 22.4, 25.9, 26.5, 29.5, 37.2, 38.3, 43.3, 46.2, 54.4, 66.6, 77.6, 78.6, 81.4, 104.3, 112.7, 117.5, 132.2, 175.2.

EI-MS (*m/z*): 483 (M^+).

Anal. Calcd for $C_{18}H_{29}NO_{10}S_2$: C, 44.71; H, 6.04; N, 2.90; S, 13.26. Found: C, 44.64; H, 6.18; N, 2.75; S, 13.08.

3,5,6-Trideoxy-3-*C*-[(2*S*)-5-oxo-1-(prop-2-enyl)-2-pyrrolidinyl]-1,2-*O*-isopropylidene-α-D-*ribo*-hex-5-enofuranose (58)



5,6-Dimesylate derivative **79** (0.44 g, 0.91 mmol) and NaI (1.4 g, 9.34 mol) in 2-butanone (20 mL) were heated under reflux for 4 h and concentrated. The residue was partitioned between EtOAc and saturated aq. $Na_2S_2O_3$. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using EtOAc–light petroleum (1:3) to afford **58** (0.176 g, 66%) as syrup.

$[\alpha]_D$ +41.0 (*c* 1.1, $CHCl_3$).

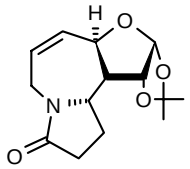
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.19, 1.40 (2 s, 6 H), 1.84–2.07 (m, 3 H), 2.11–2.29 (m, 2 H), 3.49 (dd, 1 H, *J* = 6.7, 15.7 Hz), 3.84–3.95 (m, 1 H), 4.15–4.36 (m, 2 H), 4.56 (t, 1 H, *J* = 3.7 H z), 4.98–5.30 (m, 4 H), 5.51–5.71 (m, 2 H), 5.66 (d, 1 H, *J* = 3.7 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 22.8, 25.8, 26.3, 29.7, 43.4, 51.2, 54.5, 79.3, 81.1, 104.1, 111.5, 117.0, 119.4, 132.7, 135.6, 174.7.

EI-MS (*m/z*): 293 (M^+).

Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.46; H, 7.97; N, 4.65.

(7a*R*,8a*R*,11a*R*,11b*R*,11c*S*)-Octahydro-10,10-dimethyl-3*H*-[1,3]dioxolo[4,5]furo[3,2-*c*]pyrrolo[1,2-*a*]azepin-3-one (84)



To a solution of **58** (0.16 g, 0.54 mmol) in anhydrous CH_2Cl_2 (20 mL) was added Grubbs' 1st generation catalyst **81** (0.045 g, 0.05 mmol), degassed with argon for 5 min and heated at reflux for 12 h. The solvent was concentrated and the residue purified by flash column chromatography on silica gel (200–400 mesh) with EtOAc–light petroleum (1:2) to obtain **84** (0.12 g, 83%) as colorless solid.

mp: 162 ^{o}C.

$[\alpha]_D$ –48.0 (*c* 1.1, $CHCl_3$).

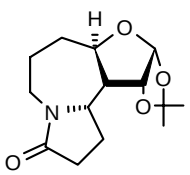
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.31, 1.52 (2 s, 6 H), 2.20 (m, 2 H), 2.37 (m, 2 H), 2.54 (m, 1 H), 3.39 (br d, 1 H, *J* = 17.5 Hz), 4.16 (m, 1 H), 4.67 (dd, 1 H, *J* = 7.2, 17.5 Hz), 4.79 (t, 1 H, *J* = 3.6 Hz), 4.90 (dd, 1 H, *J* = 1.2, 9.3 Hz), 5.75 (m, 2 H), 5.87 (d, 1 H, *J* = 3.6 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 24.4, 26.1, 26.6, 31.4, 39.0, 49.2, 56.9, 76.3, 81.1, 105.2, 112.3, 127.4, 130.7, 174.0.

EI-MS (*m/z*): 265 (M^+).

Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.19; H, 7.41; N, 5.21.

(7a*R*,8a*R*,11a*R*,11b*R*,11c*S*)-Decahydro-10,10-dimethyl-3*H*-[1,3]dioxolo[4,5]furo[3,2-*c*]pyrrolo[1,2-*a*]azepin-3-one (85)



The reaction was carried out as described earlier using compound **84** (0.11 g, 0.41 mmol) and 10% Pd/C (0.01 g) in MeOH (4 mL) under H_2 atmosphere at normal temperature and pressure. The mixture was filtered through a pad of Celite and the solvent concentrated. The residue was purified on silica gel with EtOAc–light petroleum (3:1) to give **85** (0.094 g, 85%) as colorless solid.

mp: 121 ^{o}C.

[α]$_D$ –63.2 (*c* 1.1, $CHCl_3$).

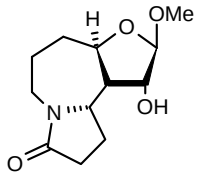
^{1}H NMR (200 MHz, $CDCl_3$): *δ* 1.24 (s, 3 H), 1.16–1.33 (m, 2 H), 1.44 (s, 3 H), 1.64-1.78 (m, 1 H), 2.05–2.34 (m, 6 H), 2.53 (dd, 1 H, *J* = 10.8, 14.1 Hz), 3.98–4.23 (m, 3 H), 4.69 (t, 1 H, *J* = 3.6 Hz), 5.77 (d, 1 H, *J* = 3.6 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): *δ* 25.8, 25.9, 26.3, 26.8, 31.1, 35.6, 40.3, 51.0, 56.6, 78.5, 81.9, 105.4, 112.5, 174.5.

EI-MS (*m/z*): 265 (M^+).

Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 62.79; H, 7.76; N, 5.34.

(1*R*,2*R*,3a*R*,10a*S*,10b*R*)-Decahydro-1-hydroxy-2-methoxy-8*H*-furo[3,2-*c*]pyrrolo[1,2-*a*]azepin-8-one (86)



To a solution of **85** (0.09 g, 0.34 mmol) in anhydrous MeOH (5 mL) was added Amberlyst-15 (0.1 g) and refluxed for 3 h. The resin was filtered off through a plug of cotton and the filtrate concentrated. The residue was purified on silica gel with MeOH–CH_2Cl_2 (1:9) to give β-isomer of **86** (0.057 g, 70%) as colorless solid.

mp: 168–171 ^{o}C.

[α]$_D$ –130.9 (*c* 0.9, MeOH).

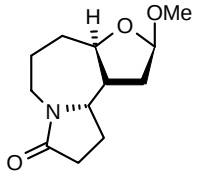
^{1}H NMR (200 MHz, $CDCl_3$): *δ* 1.41 (m, 2 H), 2.25 (m, 5 H), 2.64 (m, 3 H), 3.38 (s, 3 H), 4.1 (m, 3H), 4.31 (d, 1 H, *J* = 5.7 Hz), 4.74 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): *δ* 25.1, 26.2, 31.3, 37.3, 40.1, 49.2, 54.1, 56.9, 76.8, 78.6, 110.0, 174.9.

EI-MS (*m/z*): 241 (M^+).

Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.33; H, 7.63; N, 5.69.

(2*R*,3a*R*,10a*S*,10b*R*)-Decahydro-2-methoxy-8*H*-furo[3,2-*c*]pyrrolo[1,2-*a*]azepin-8-one (87)



A mixture of **86** (0.055 g, 0.23 mmol) and 1,1'-thiocarbonyldiimidazole (0.12 g, 0.67 mmol) in anhydrous toluene (5 mL) was stirred under reflux for 6 h. The reaction mixture was allowed to attain room temperature and then were added AIBN (0.01 g, 0.06 mmol) and *n*-Bu_3SnH (0.1 mL, 0.38 mmol). The mixture was flushed with argon for 5 min and heated at reflux for 12 h. After being allowed the mixture to attain room temperature, the solvent was removed under vacuo and the residue chromatographed on silica gel using MeOH–CH_2Cl_2 (1:9) as an eluent to give **87** (0.023 g, 45%) as colorless solid.

mp: 91 ^oC.

$[\alpha]_D$ −143.1 (*c* 0.83, MeOH).

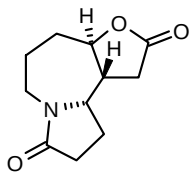
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.49 (m, 2 H), 1.67 (t, 1 H, *J* = 11.0 Hz), 1.74–1.78 (m, 1 H), 1.83 (dt, 1 H, *J* = 12.5, 4.6 Hz), 1.94 (ddd, 1 H, *J* = 2.7, 6.9, 12.2 Hz), 1.99 (dd, 1 H, *J* = 6.4, 12.2 Hz), 2.23–2.26 (m, 1 H), 2.36–2.40 (m, 2 H), 2.69 (t, 1 H, *J* = 12.7 Hz), 2.76–2.82 (m, 1 H), 3.34 (s, 3 H), 3.84 (dt, 1 H, *J* = 9.8, 2.0 Hz), 3.96 (dt, 1 H, *J* = 10.6, 6.3 Hz), 4.08 (dd, 1 H, *J* = 2.3, 13.9 Hz), 4.96 (d, 1 H, *J* = 4.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ 22.3, 26.0, 30.9, 34.9, 36.8, 40.3, 45.2, 54.3, 56.6, 79.9, 104.7, 17.1.

EI-MS (*m/z*): 224 (M^+).

Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 63.82; H, 8.68; N, 6.29.

(3a*R*,10a*S*,10b*R*)-Octahydro-2*H*-furo[3,2-*c*]pyrrolo[1,2-*a*]azepin-2,8(1*H*)-dione (30)

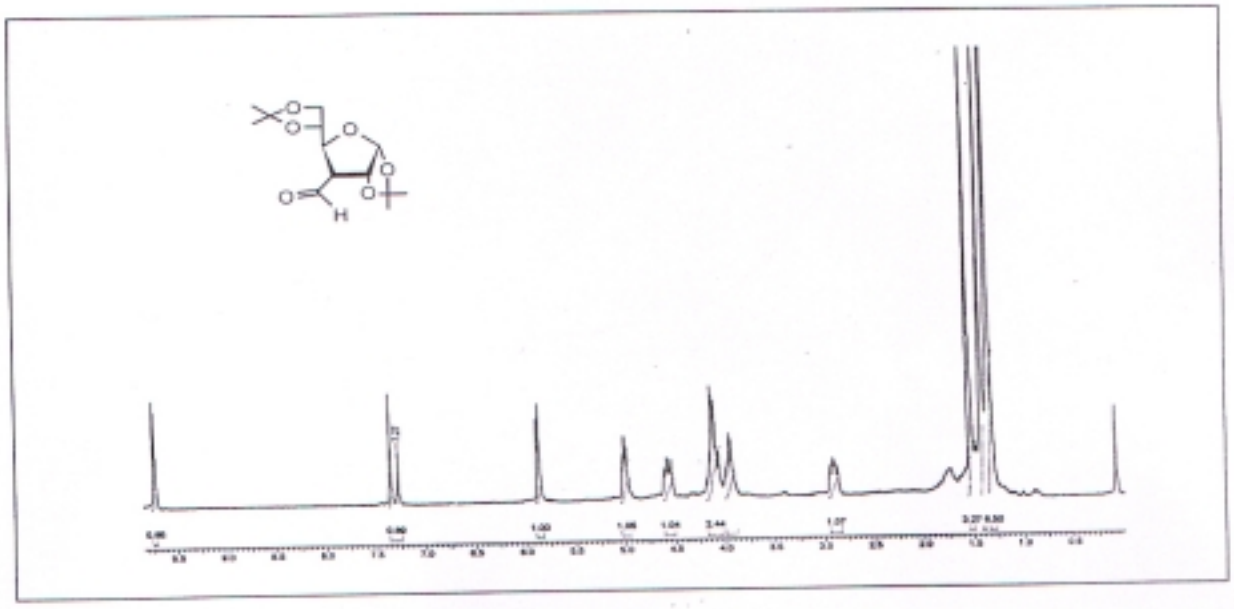


To a solution of the compound **87** (0.01 g, 0.04 mmol) in anhydrous CH_2Cl_2 (2 mL) were added 70% of *m*-CPBA (0.02 g, 0.08 mmol) and $BF_3{\cdot}Et_2O$ (0.01 mL, 0.01 mmol) at 0 ^oC, and stirred at room temperature for 12 h. Ether was added to the reaction mixture and washed with aq. $Na_2S_2O_3$, aq. Na_2CO_3, water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using MeOH–CH_2Cl_2 (1:9) as an eluent to give **30** (0.003 g, 30%) as colorless syrup.

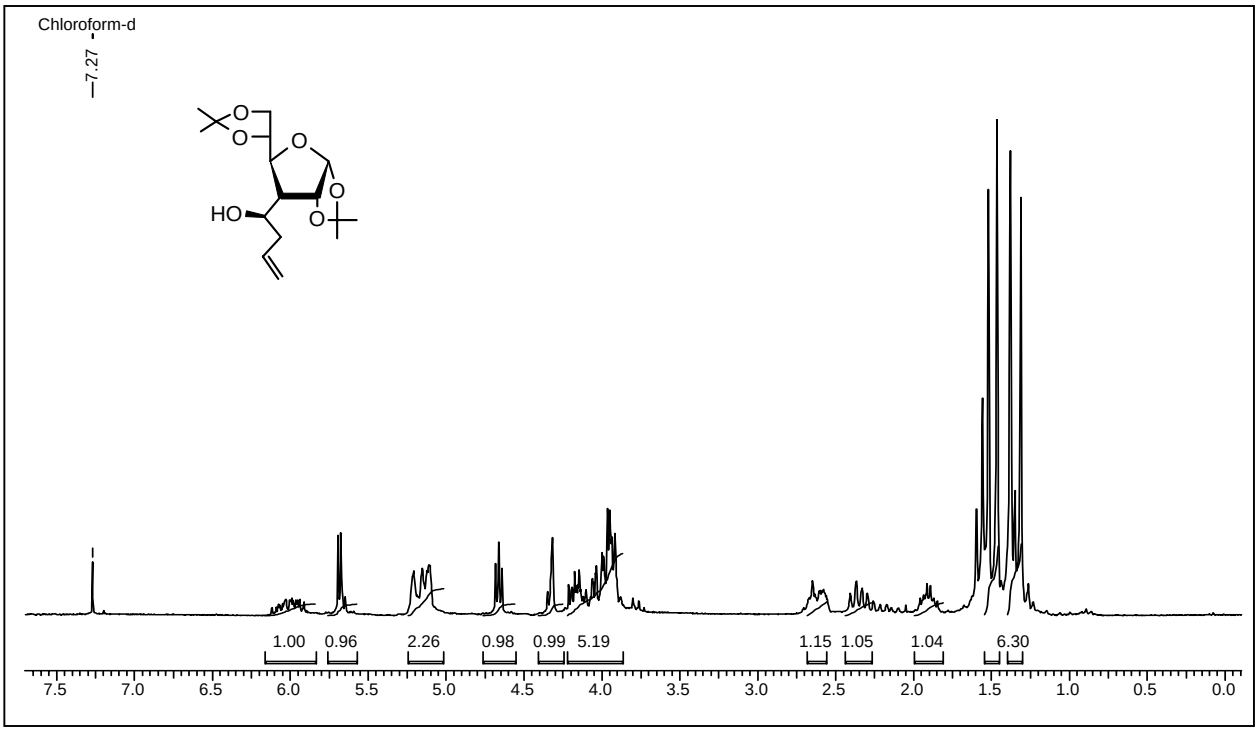
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.50–1.75 (m, 3 H), 1.87 (m, 1 H), 2.05–2.12 (m, 1 H), 2.30–2.45 (m, 4 H), 2.52 (dd, 1 H, *J* = 12.5, 17.1 Hz), 2.65 (dd, 1 H, *J* = 8.9, 17.1 Hz), 2.80–2.90 (m, 1 H), 4.00 (dt, 1 H, *J* = 6.3, 10.7 Hz), 4.16 (m, 1 H), 4.29 (dt, 1 H, *J* = 2.4, 10.3 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ 22.7, 25.5, 30.5, 31.0, 34.7, 40.2, 45.0, 56.1, 79.8, 174.0.

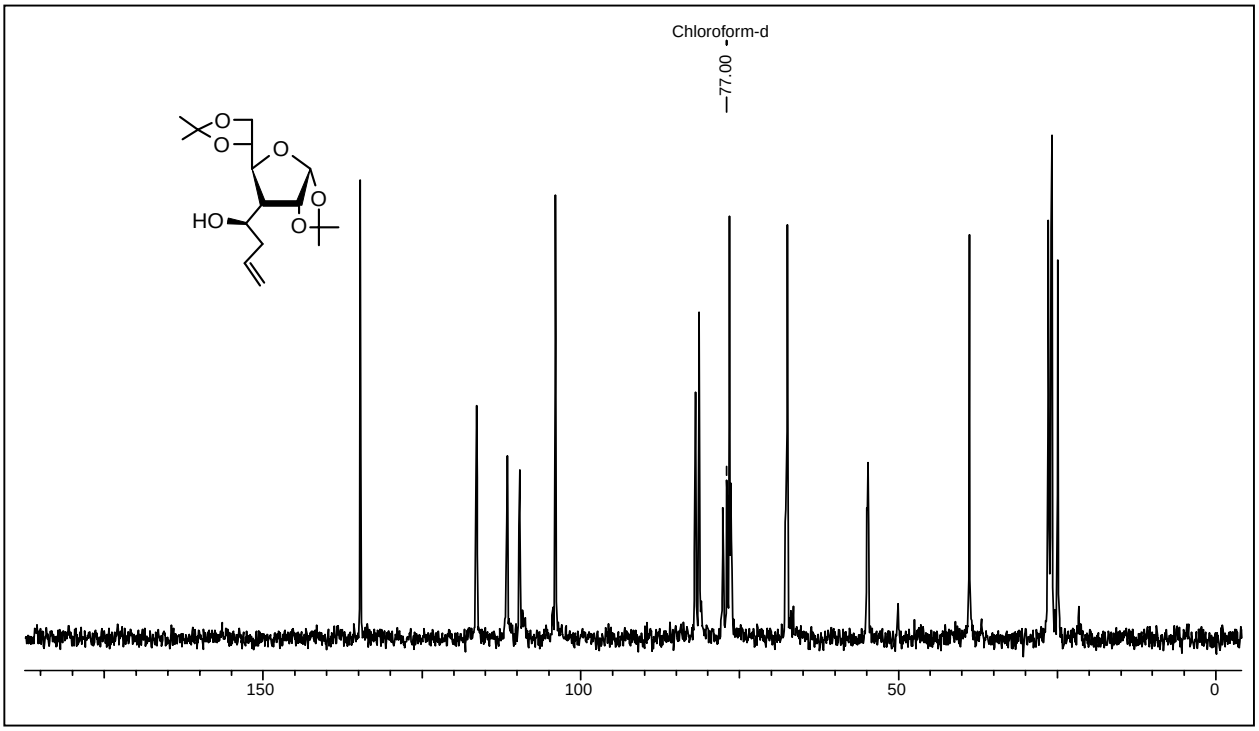
Spectra



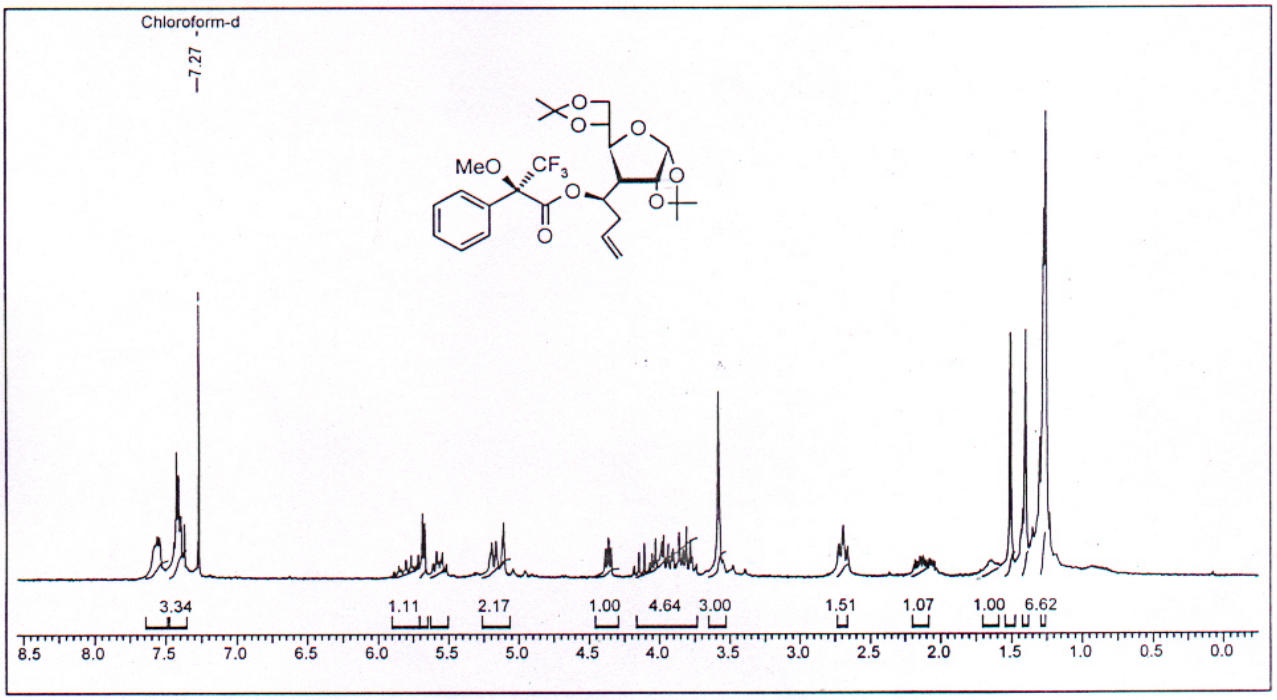
^{1}H NMR Spectrum of compound 67 in $CDCl_3$



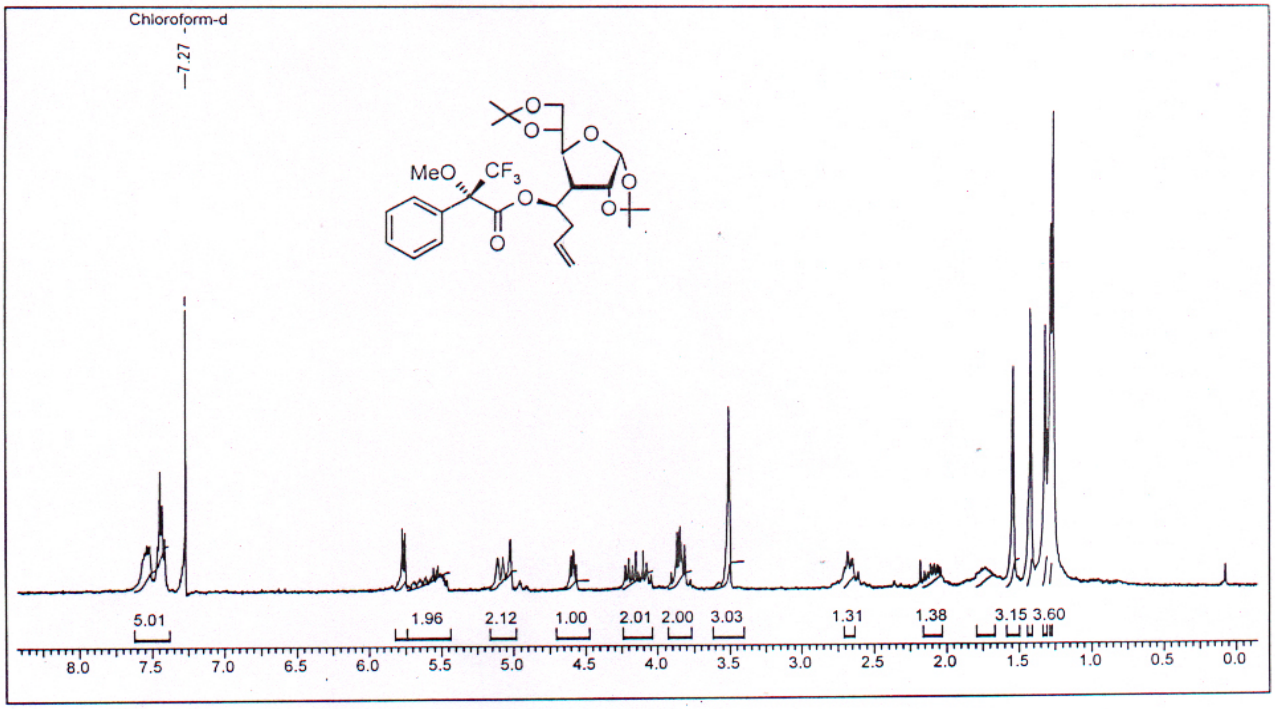
^{1}H NMR Spectrum of compound 61 in $CDCl_3$



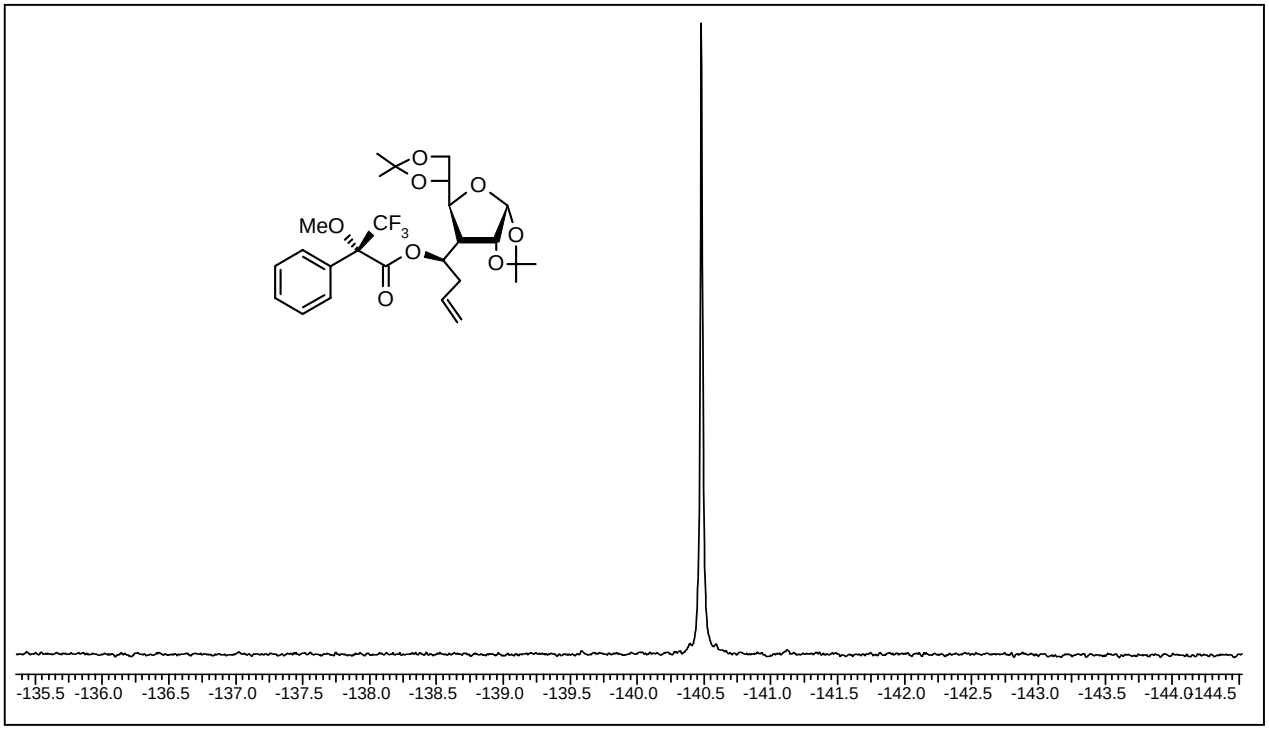
^{13}C NMR Spectrum of compound 61 in $CDCl_3$



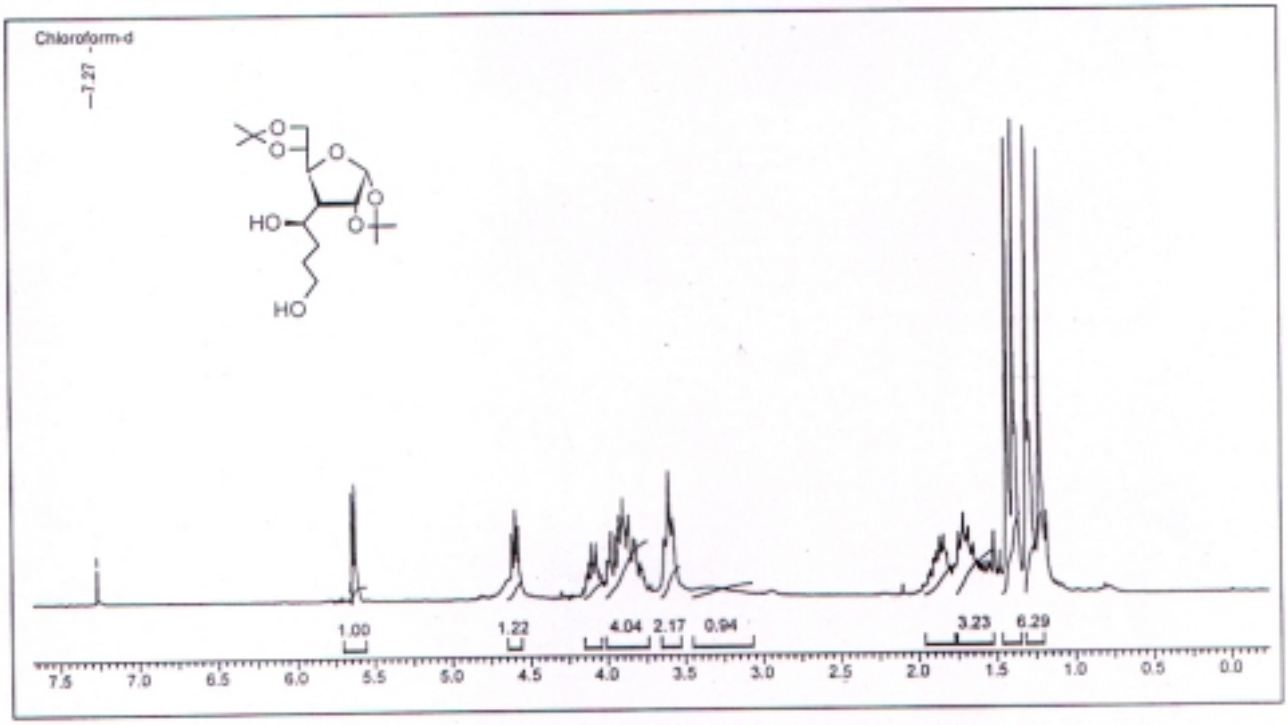
^{1}H NMR Spectrum of compound 68 in $CDCl_3$ (*S*-MTPA ester)



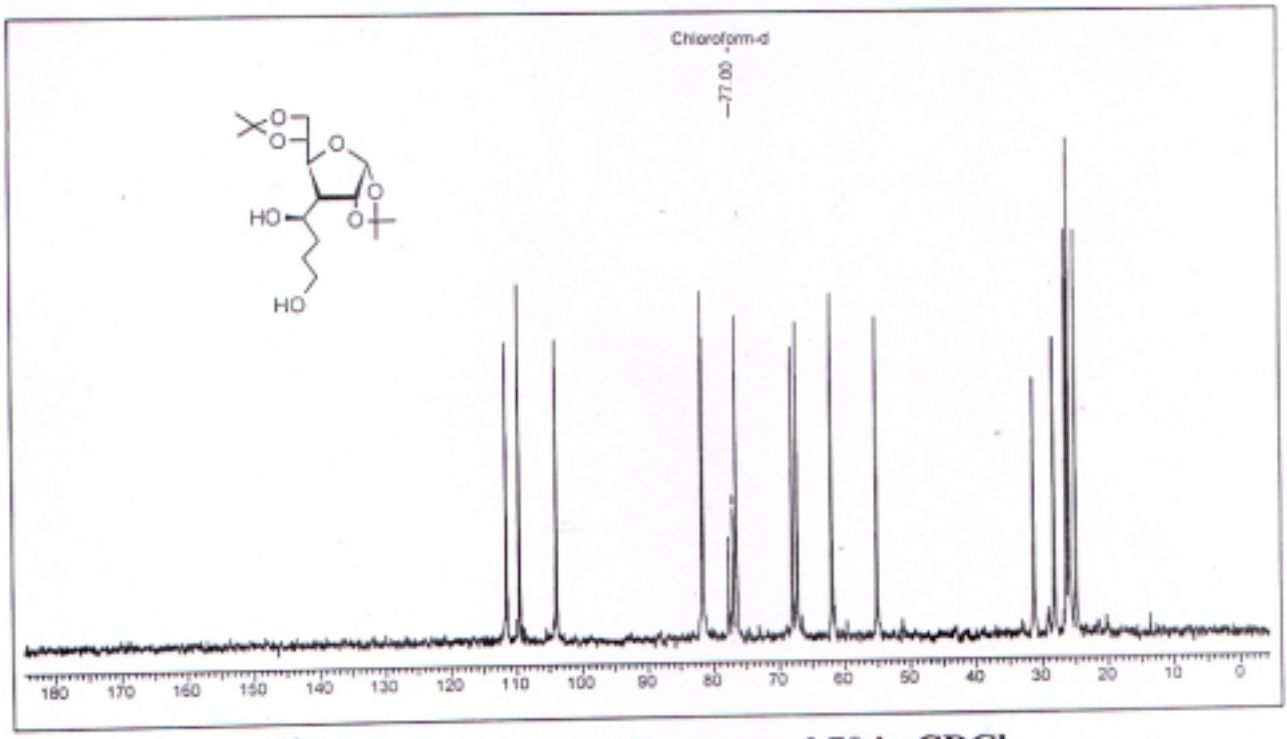
^{1}H NMR Spectrum of compound 69 in $CDCl_3$ (*R*-MTPA ester)



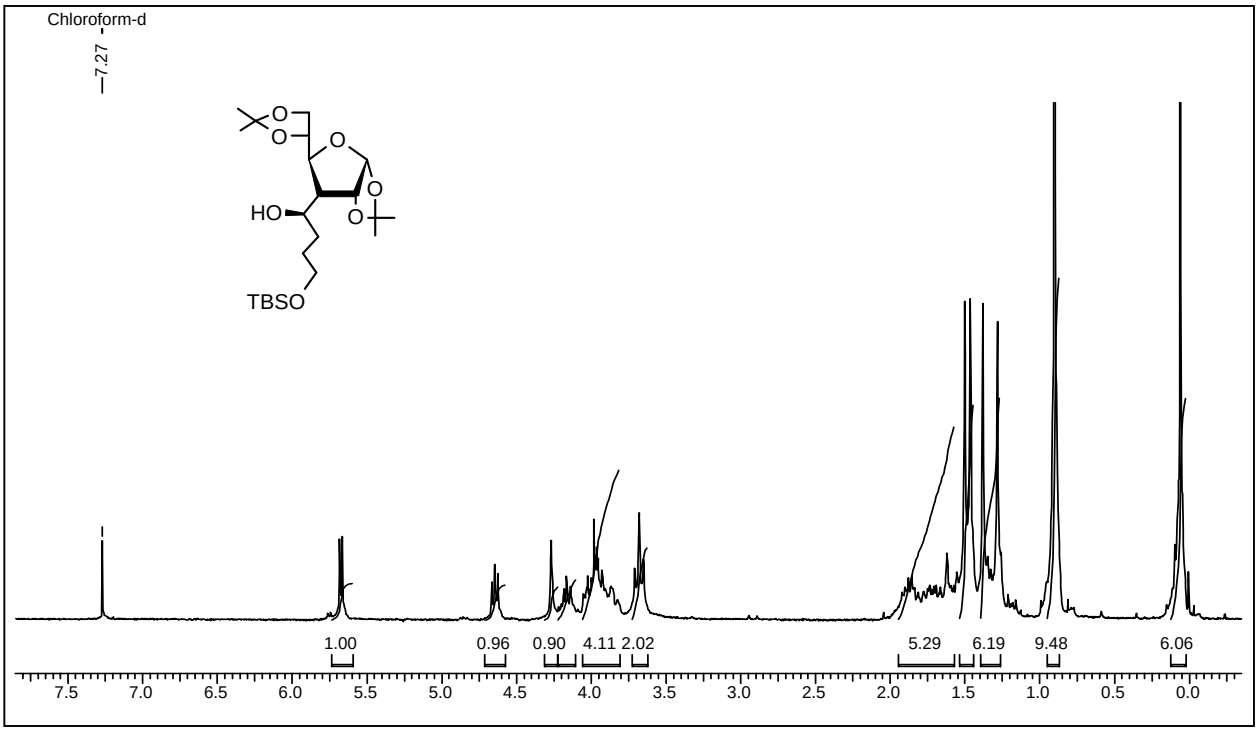
^{19}F NMR Spectrum of compound 69 in $CDCl_3$



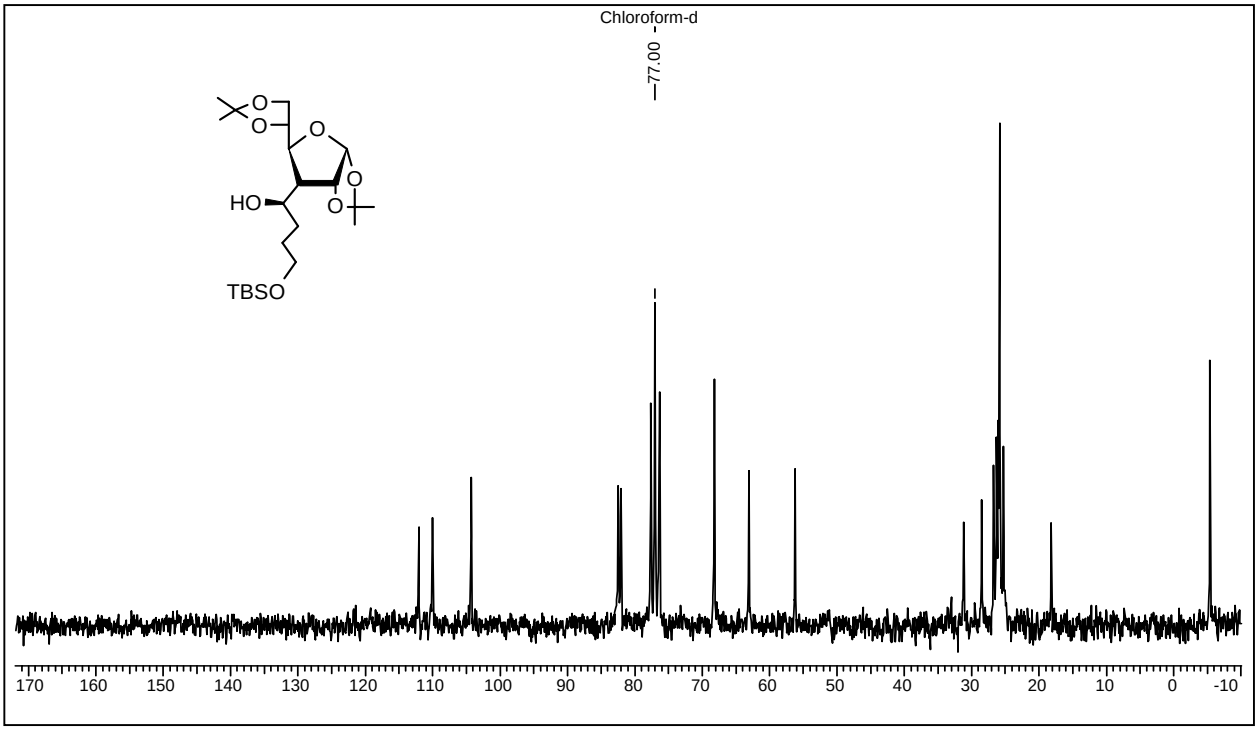
^{1}H NMR Spectrum of compound 70 in $CDCl_3$



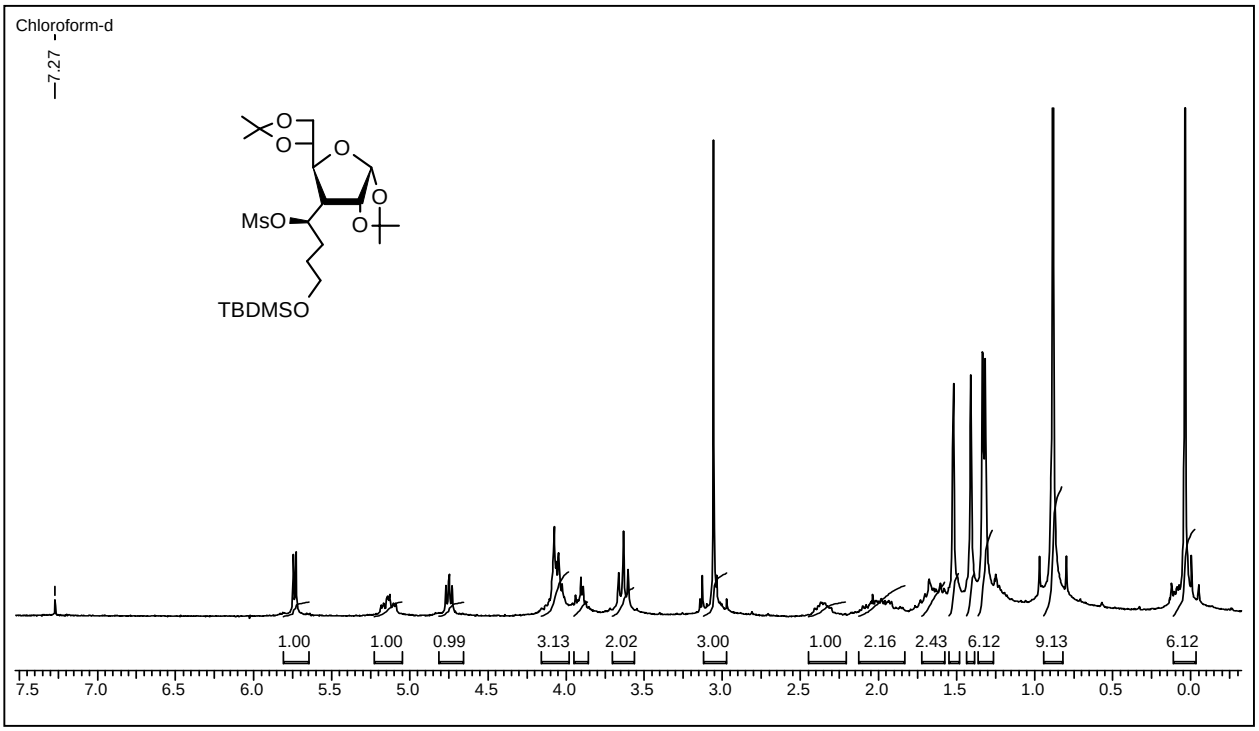
^{13}C NMR Spectrum of compound 70 in $CDCl_3$



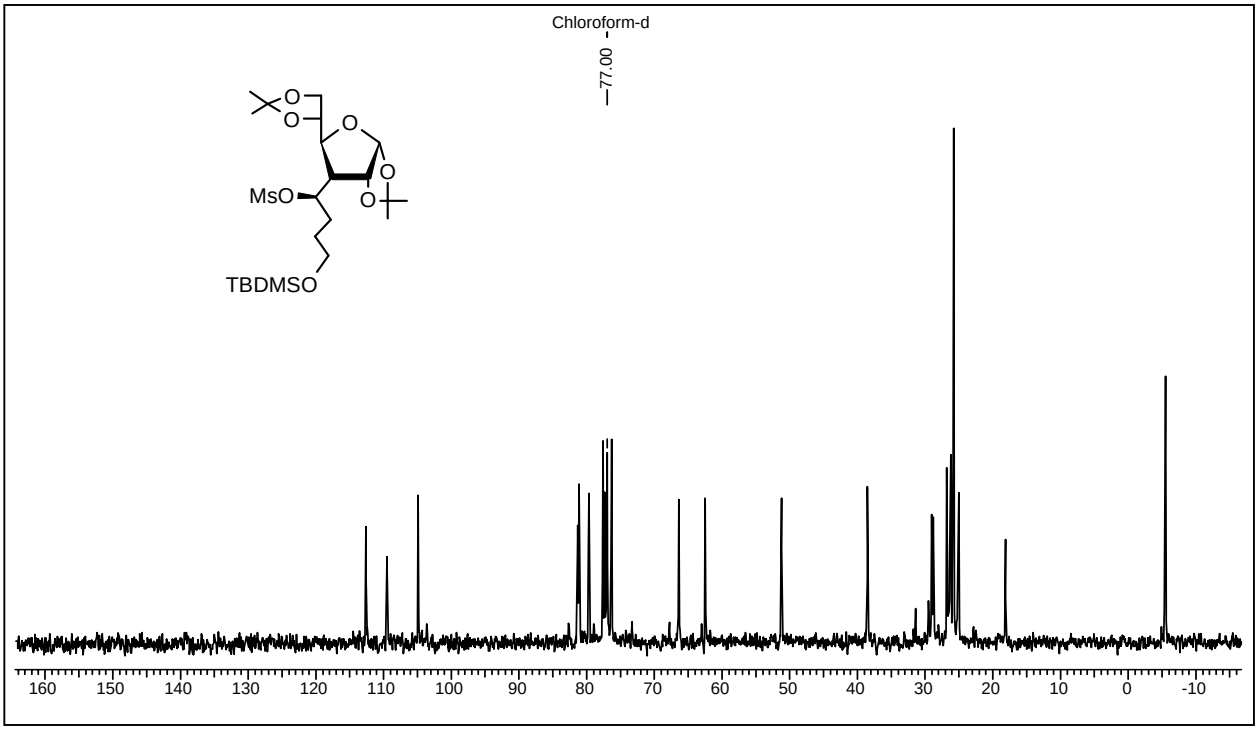
^{1}H NMR Spectrum of compound 71 in $CDCl_3$



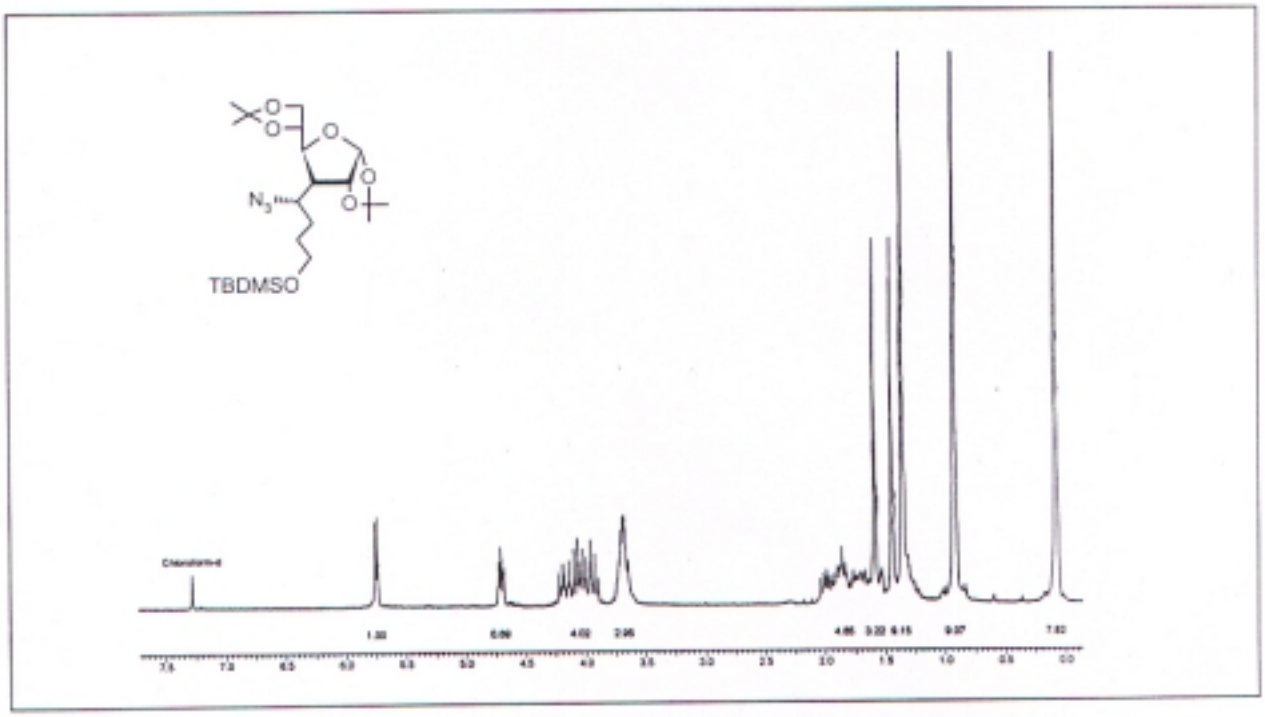
^{13}C NMR Spectrum of compound 71 in $CDCl_3$



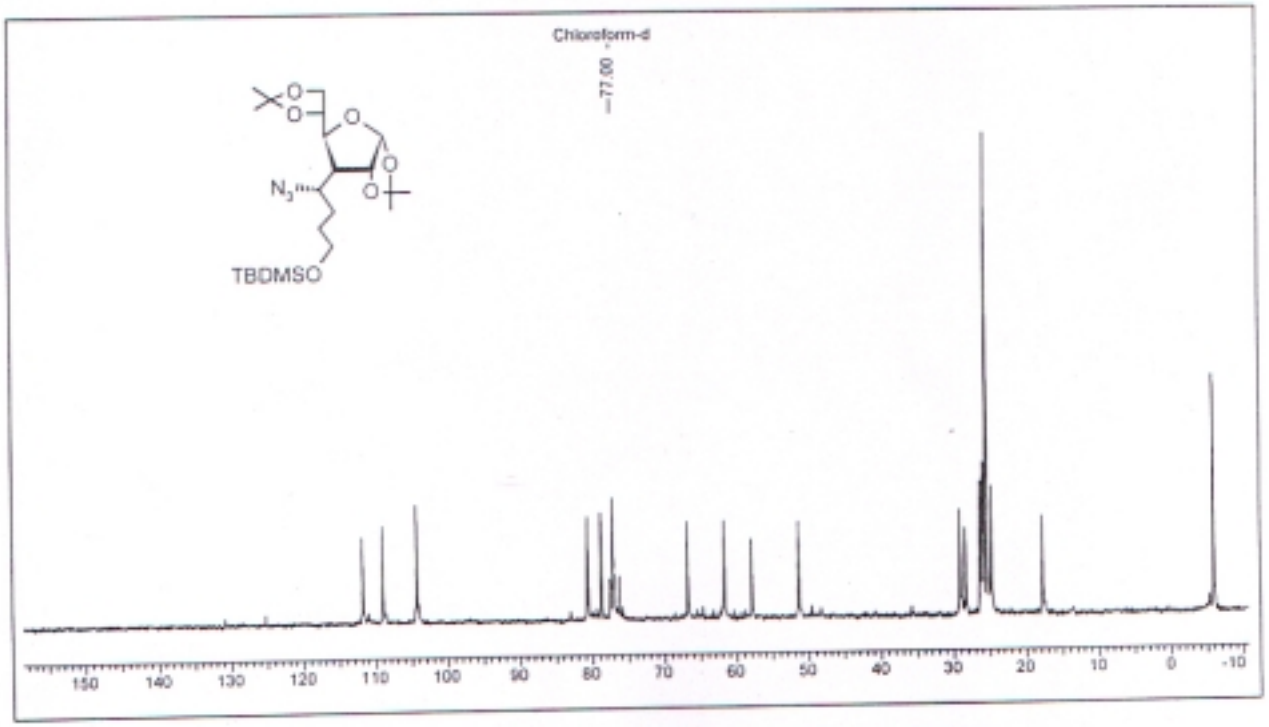
^{1}H NMR Spectrum of compound 72 in $CDCl_3$



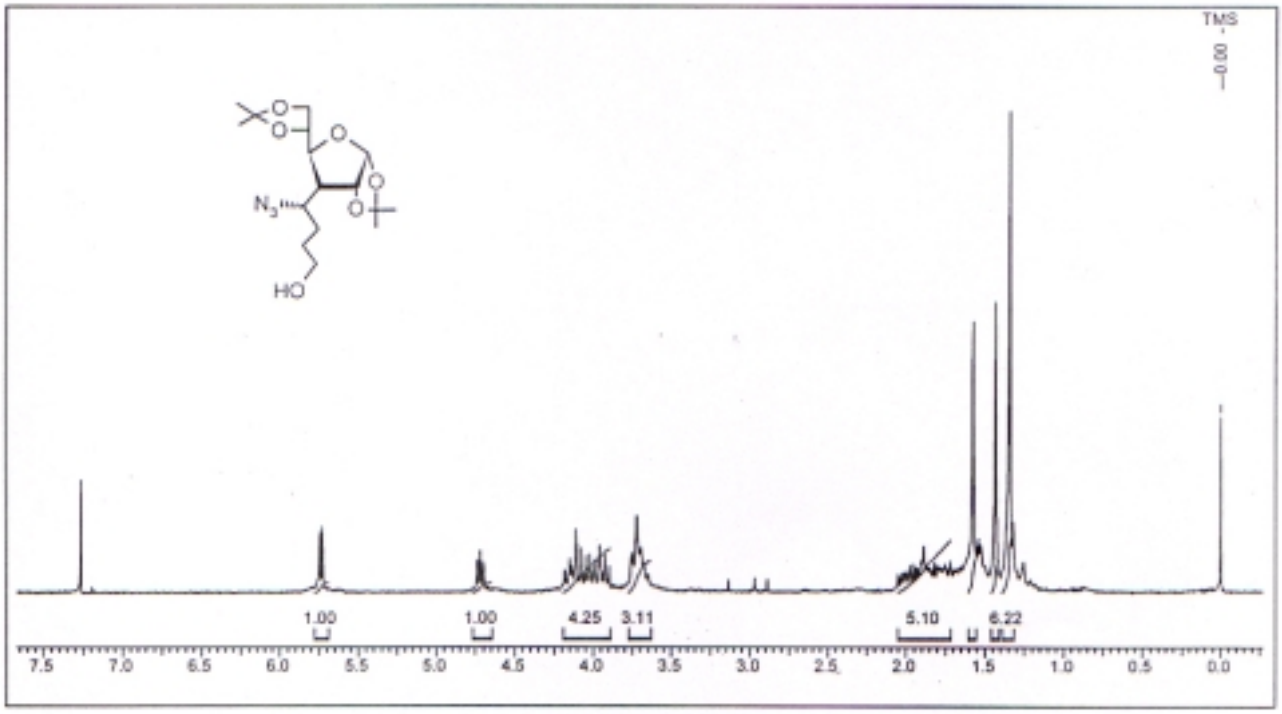
^{13}C NMR Spectrum of compound 72 in $CDCl_3$



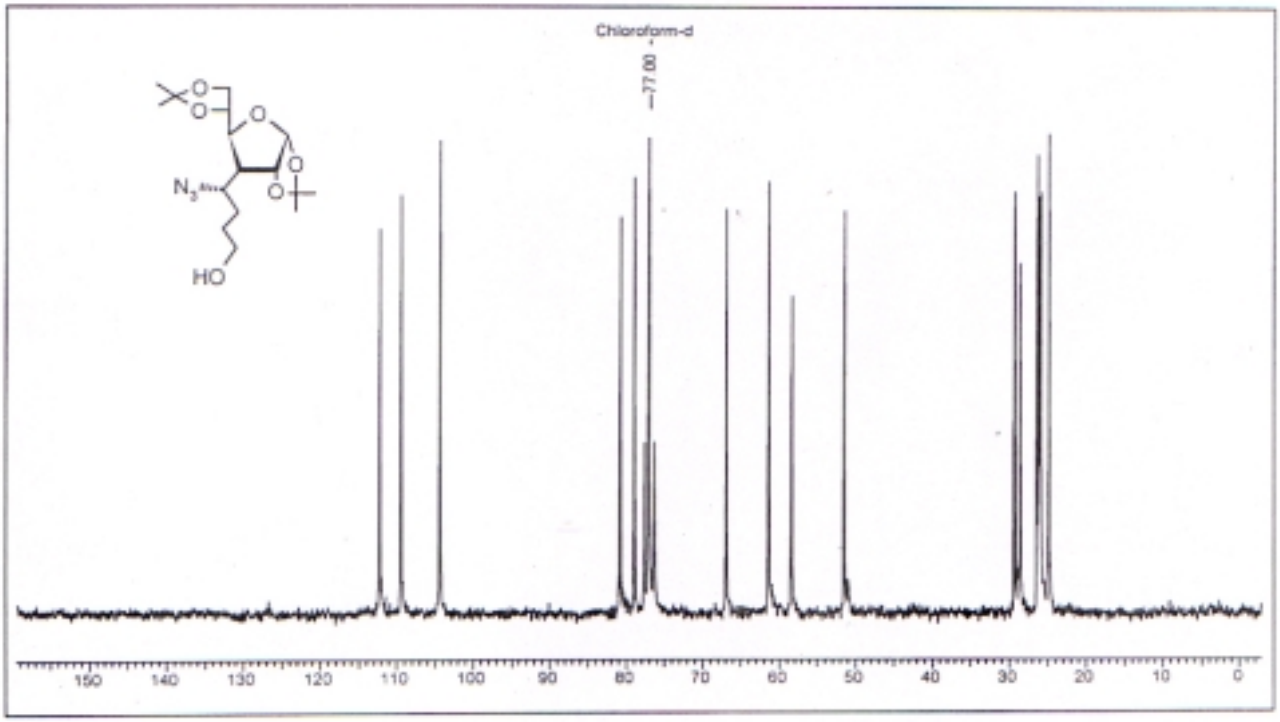
^{1}H NMR Spectrum of compound 73 in $CDCl_3$



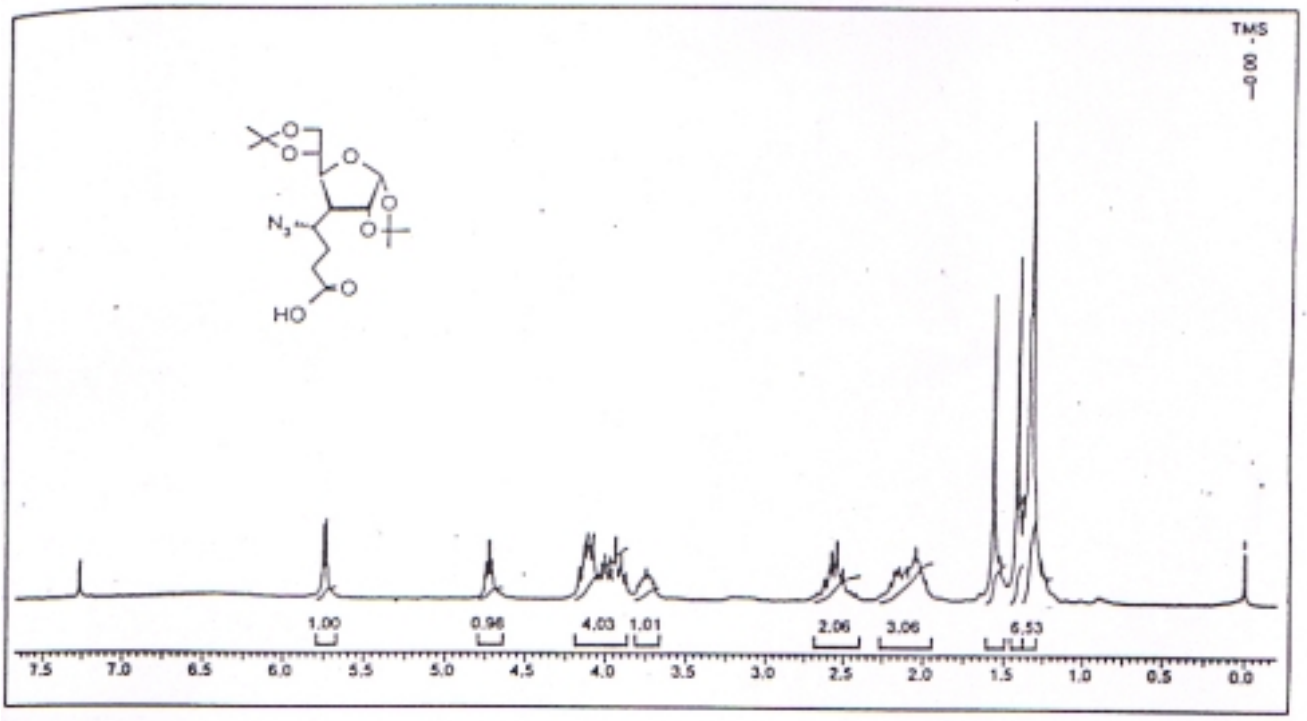
^{13}C NMR Spectrum of compound 73 in $CDCl_3$



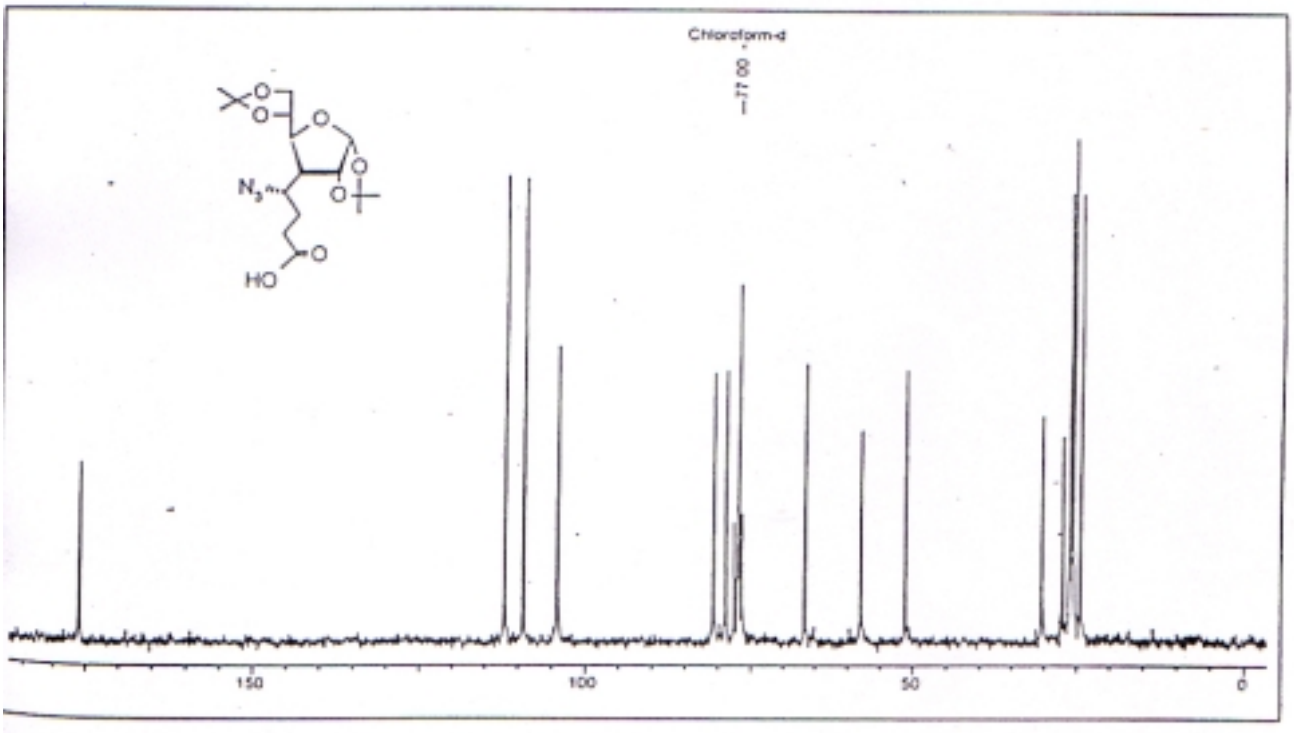
^{1}H NMR Spectrum of compound 74 in $CDCl_3$



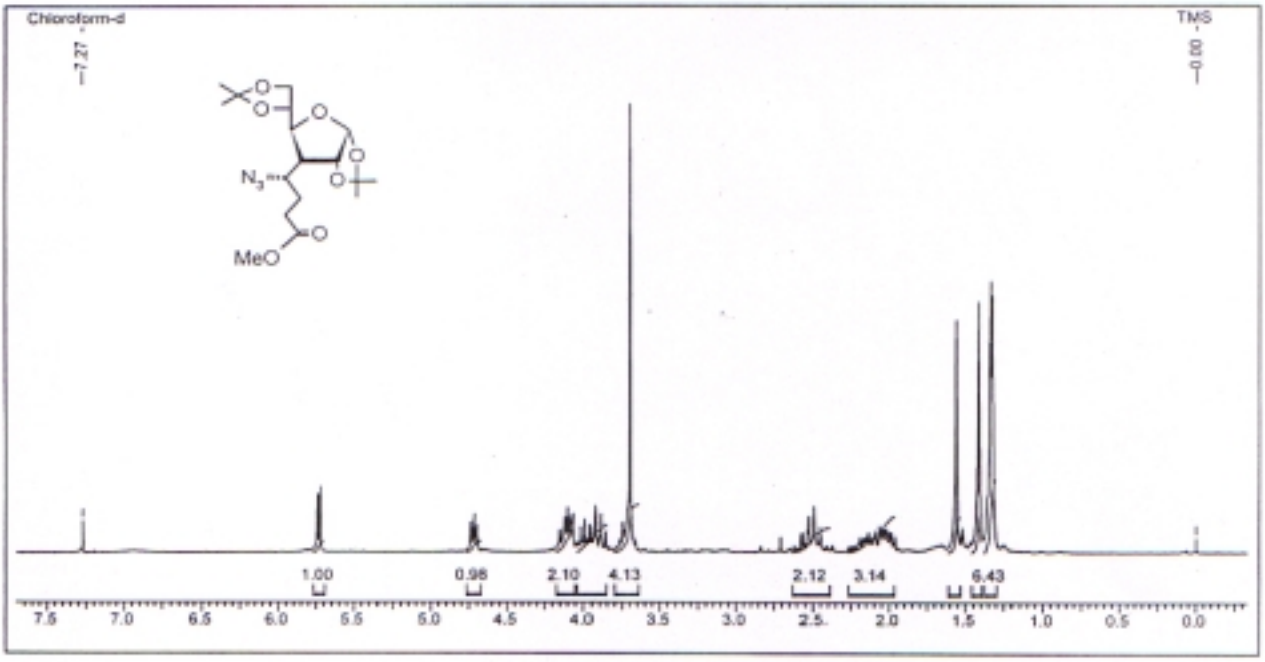
^{13}C NMR Spectrum of compound 74 in $CDCl_3$



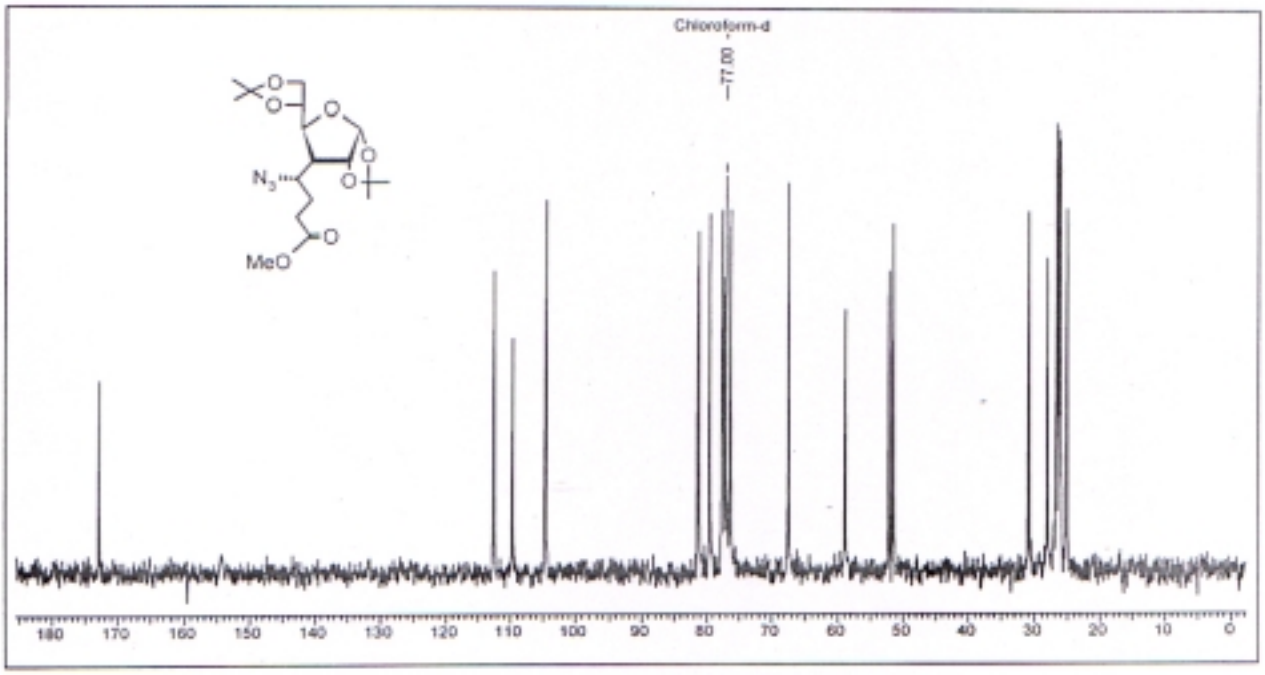
^{1}H NMR Spectrum of compound 76 in $CDCl_3$



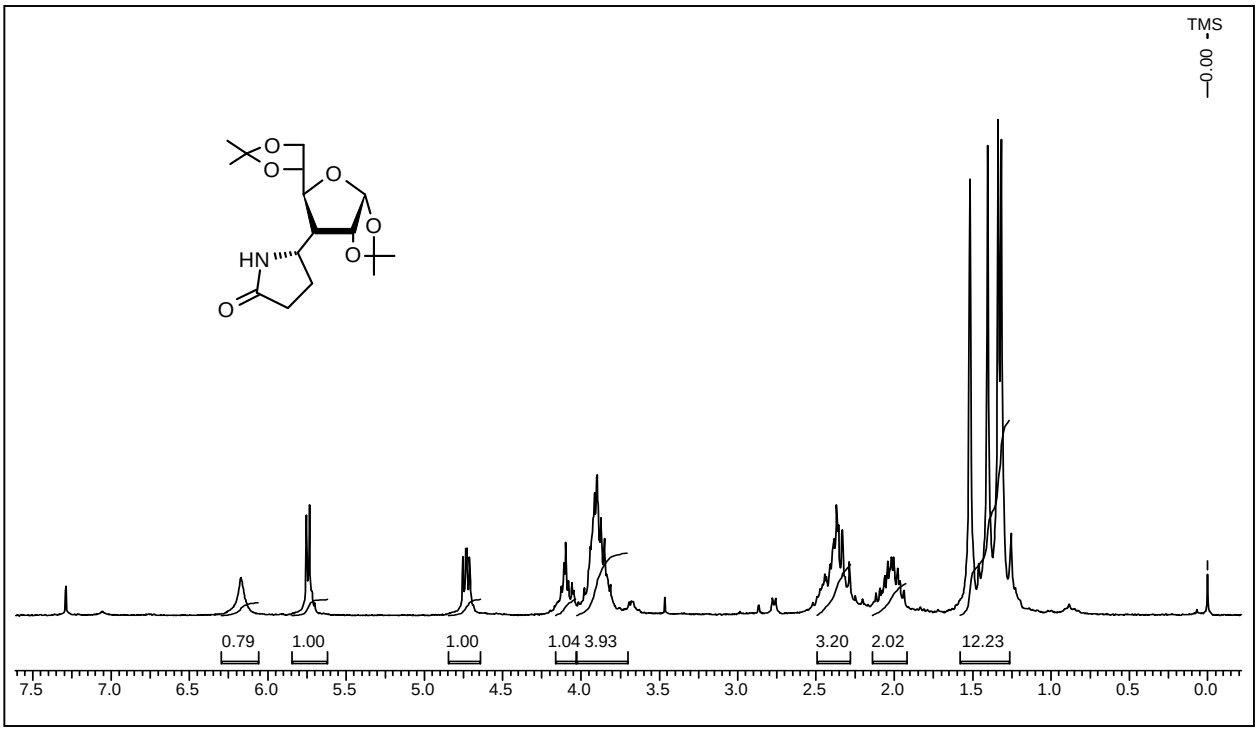
^{13}C NMR Spectrum of compound 76 in $CDCl_3$



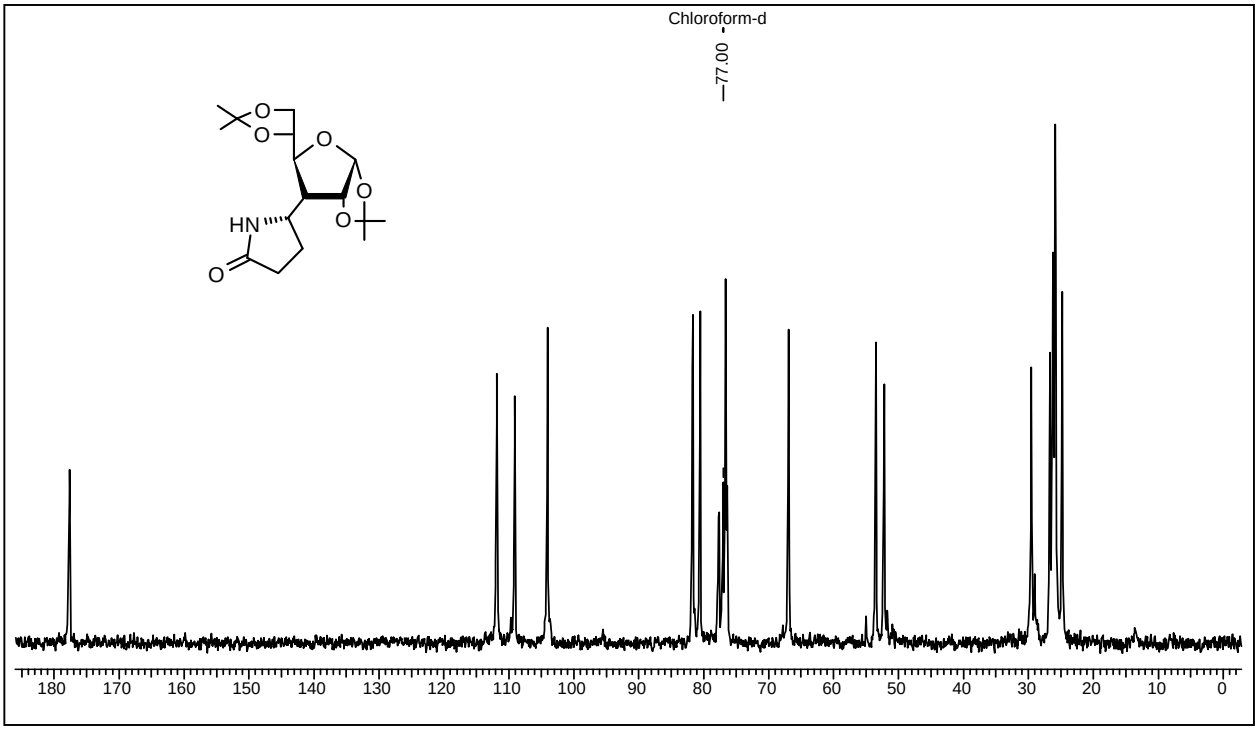
^{1}H NMR Spectrum of compound 60 in $CDCl_3$



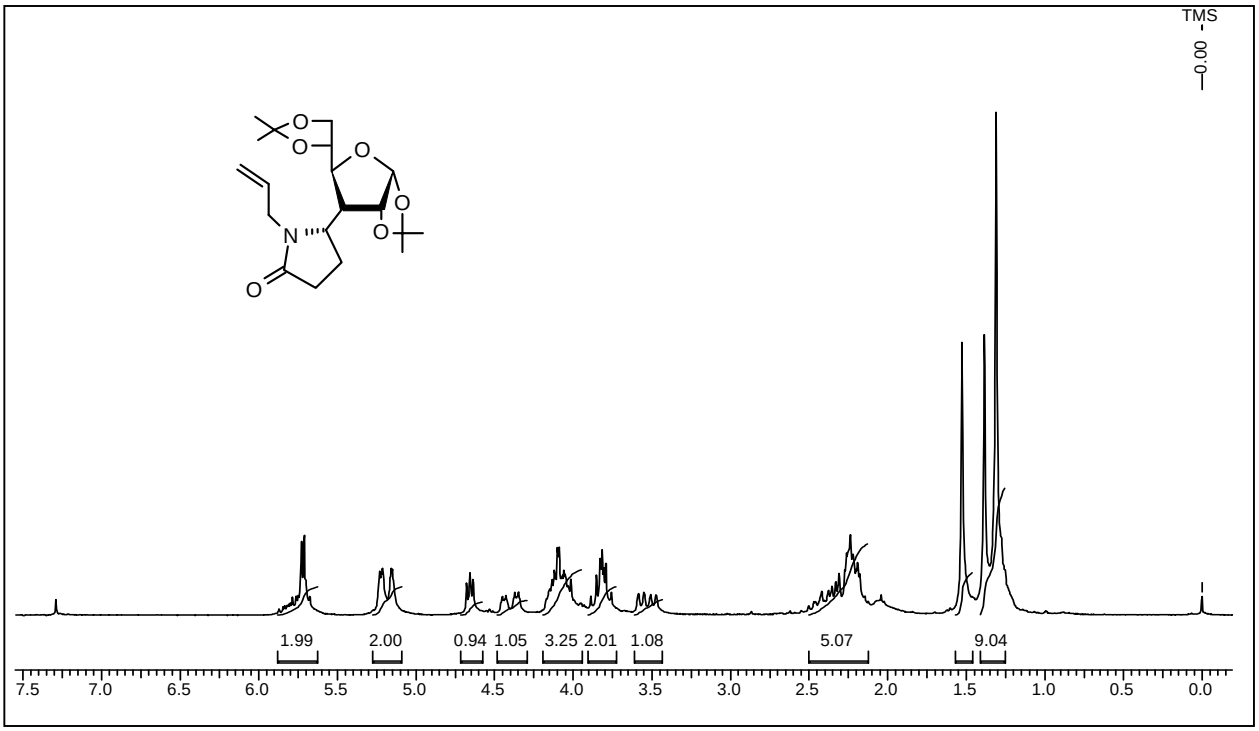
^{13}C NMR Spectrum of compound 60 in $CDCl_3$



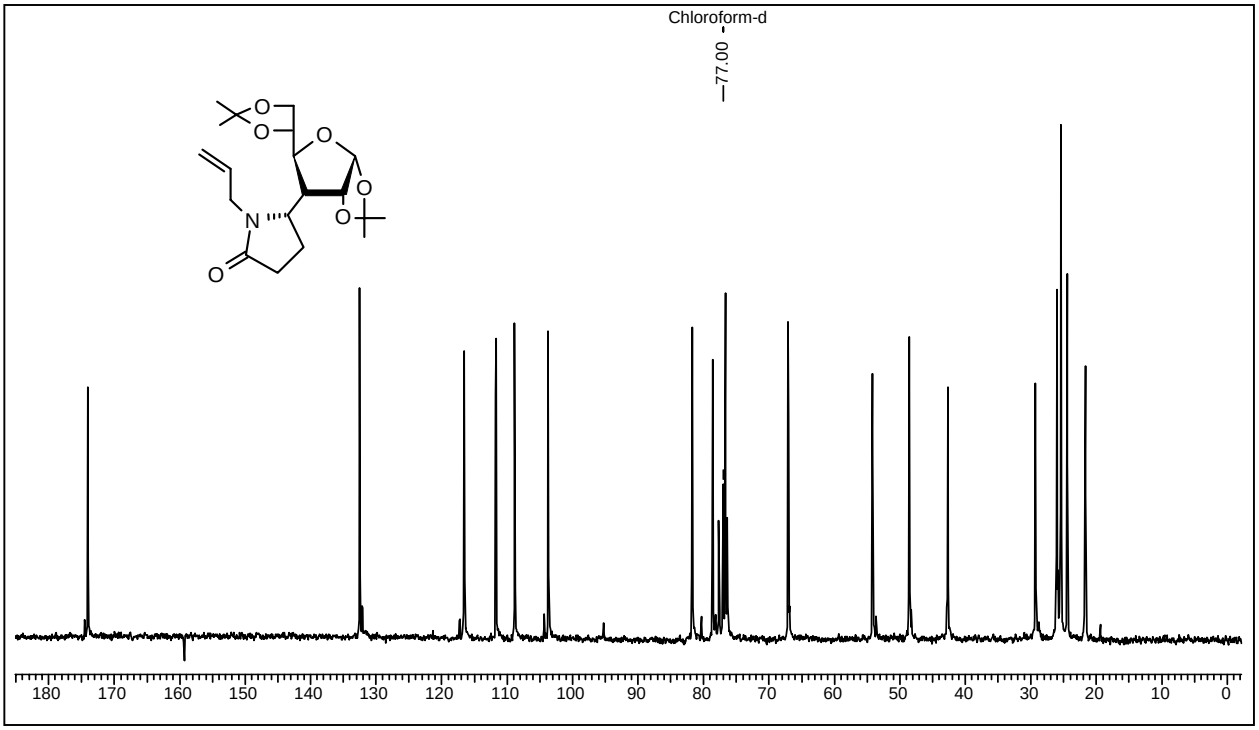
^{1}H NMR Spectrum of compound 59 in $CDCl_3$



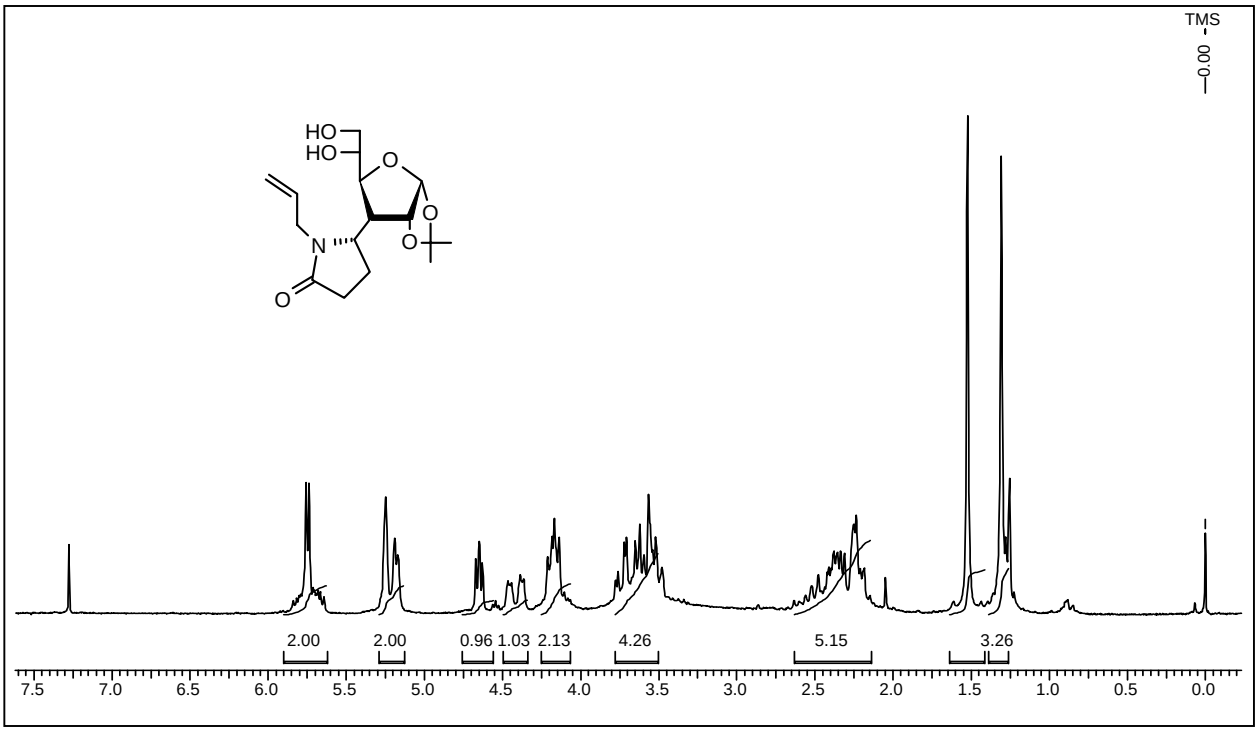
^{13}C NMR Spectrum of compound 59 in $CDCl_3$



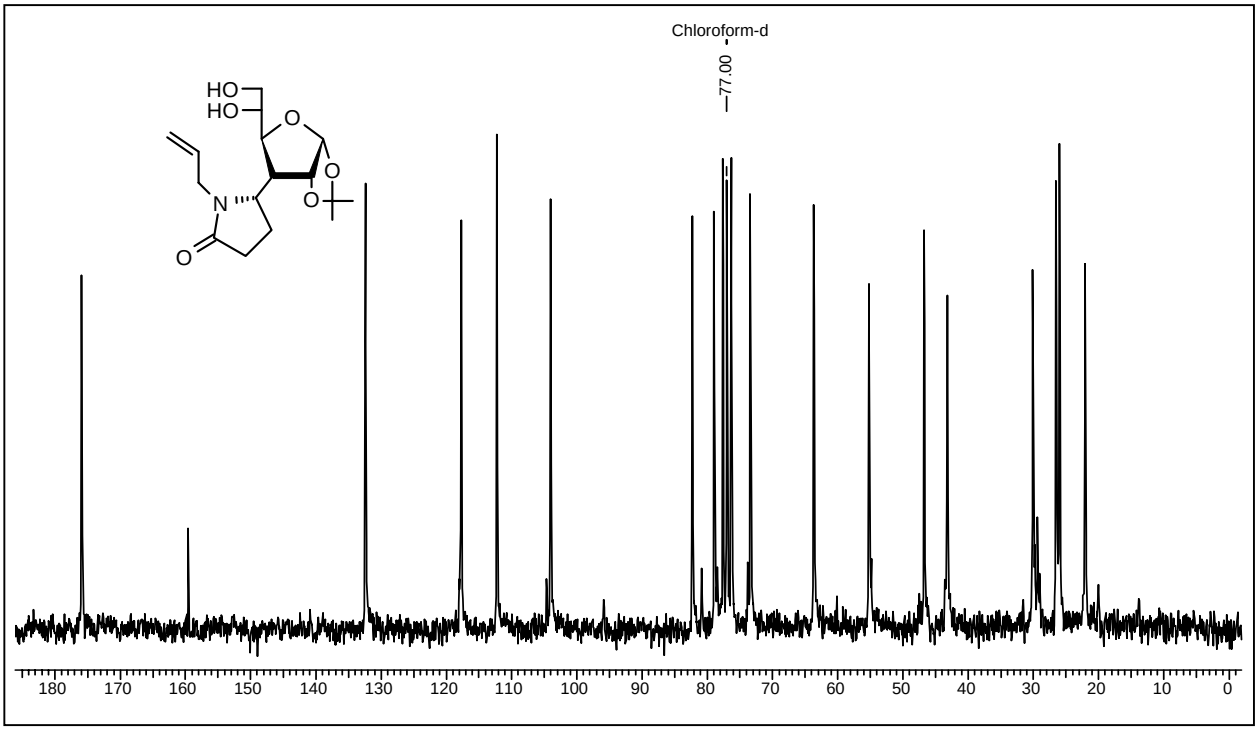
^{1}H NMR Spectrum of compound 77 in $CDCl_3$



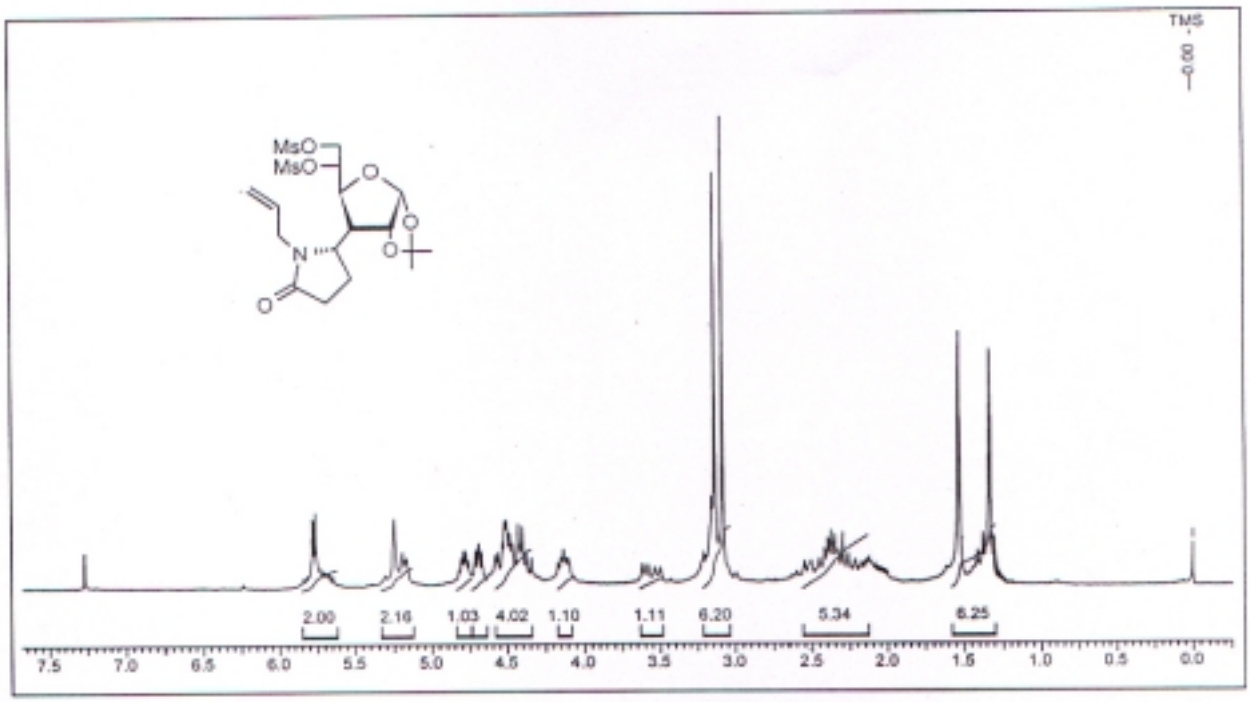
^{13}C NMR Spectrum of compound 77 in $CDCl_3$



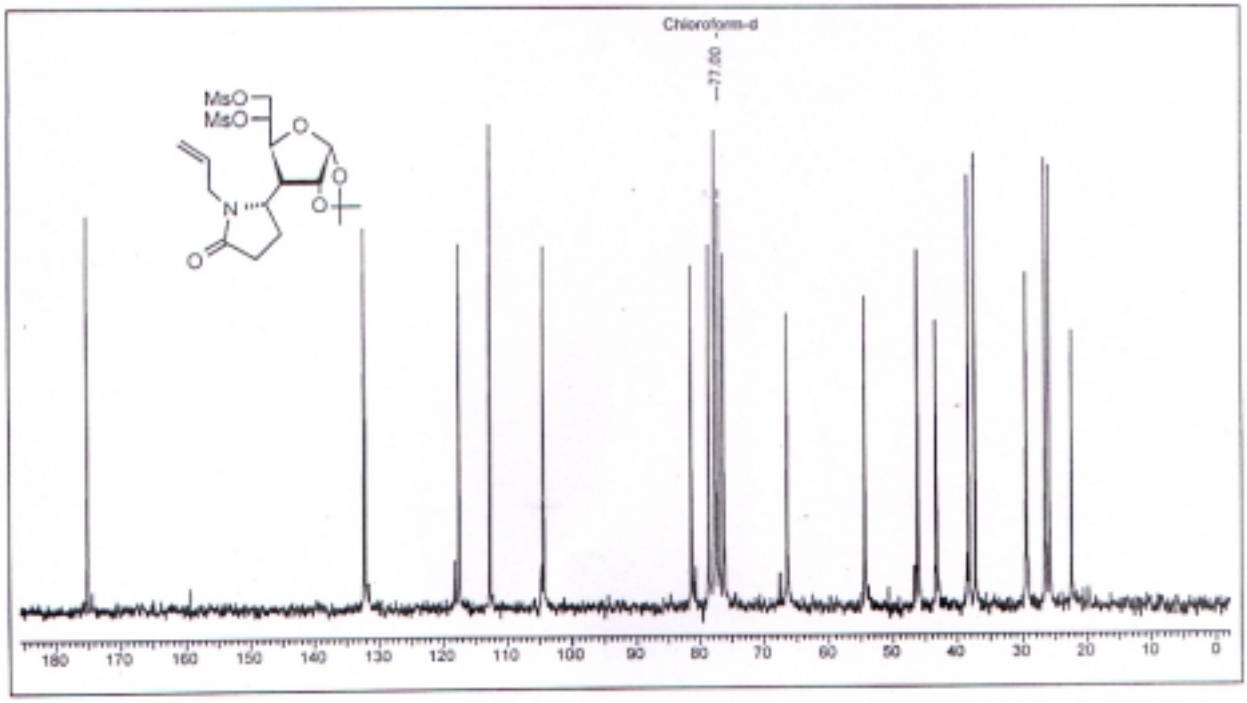
^{1}H NMR Spectrum of compound 78 in $CDCl_3$



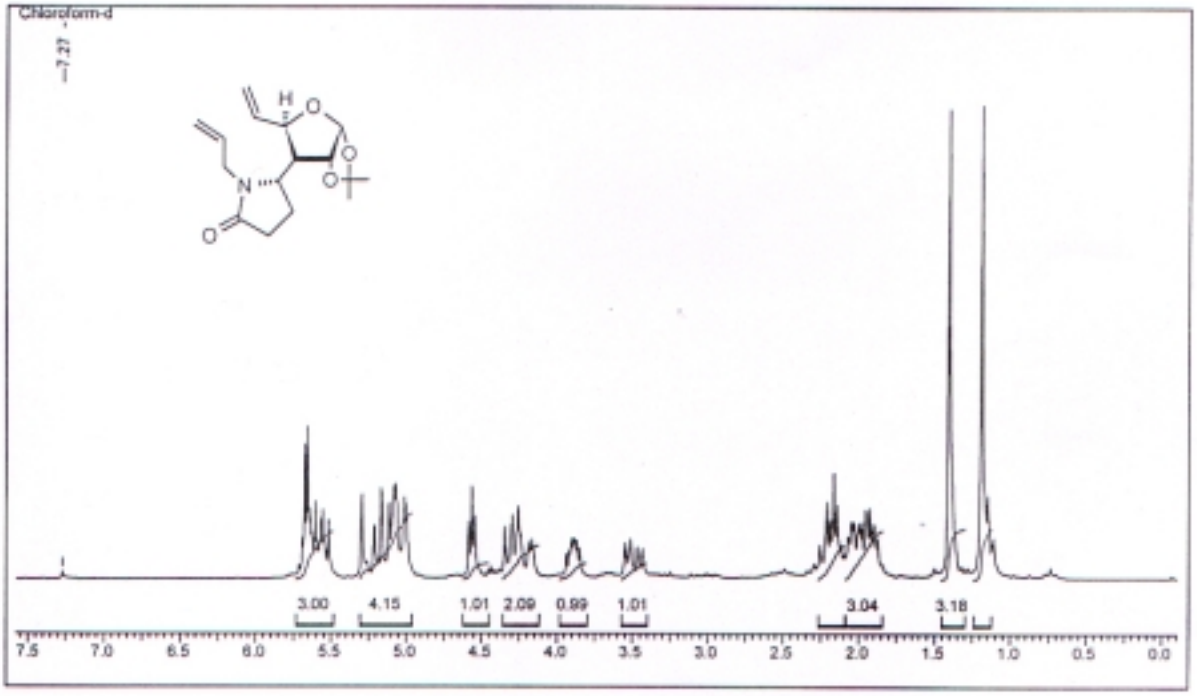
^{13}C NMR Spectrum of compound 78 in $CDCl_3$



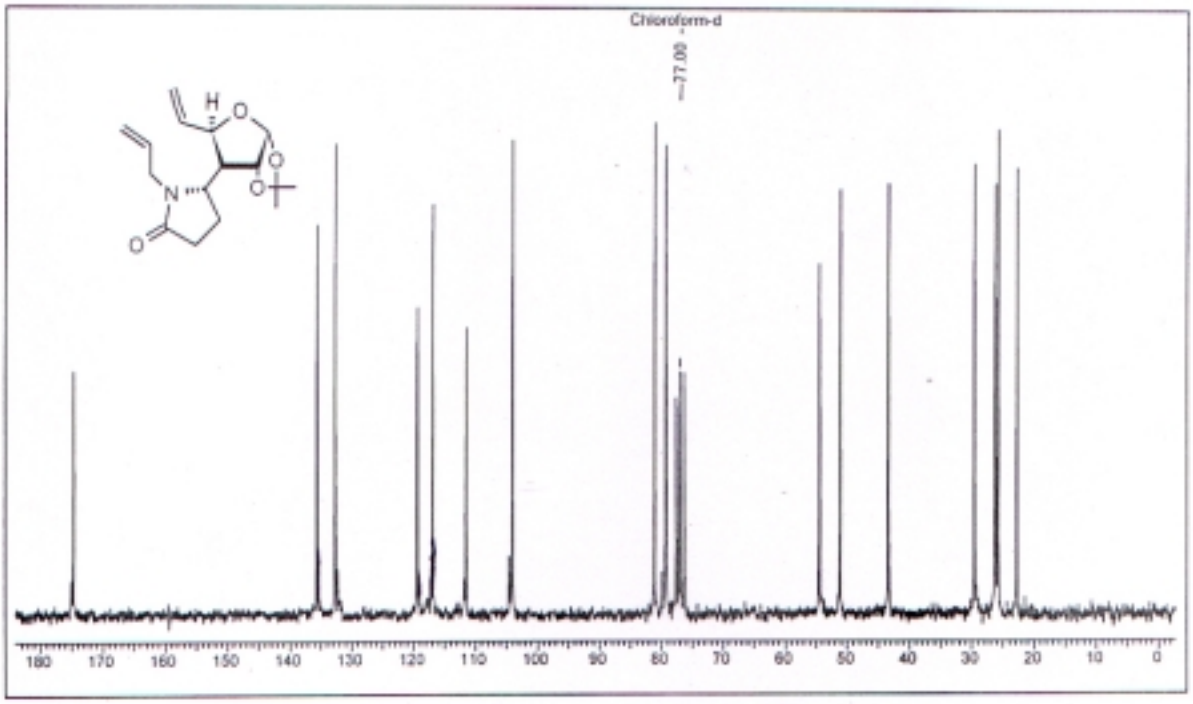
^{1}H NMR Spectrum of compound 79 in $CDCl_3$



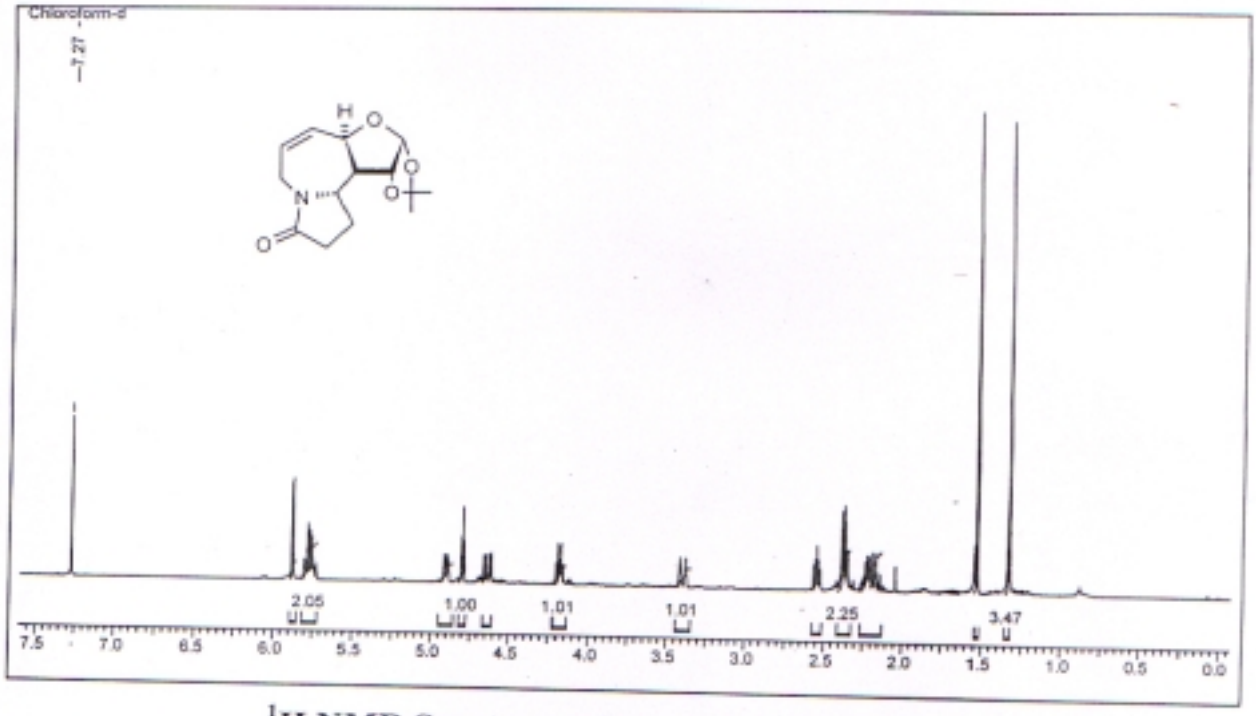
^{13}C NMR Spectrum of compound 79 in $CDCl_3$



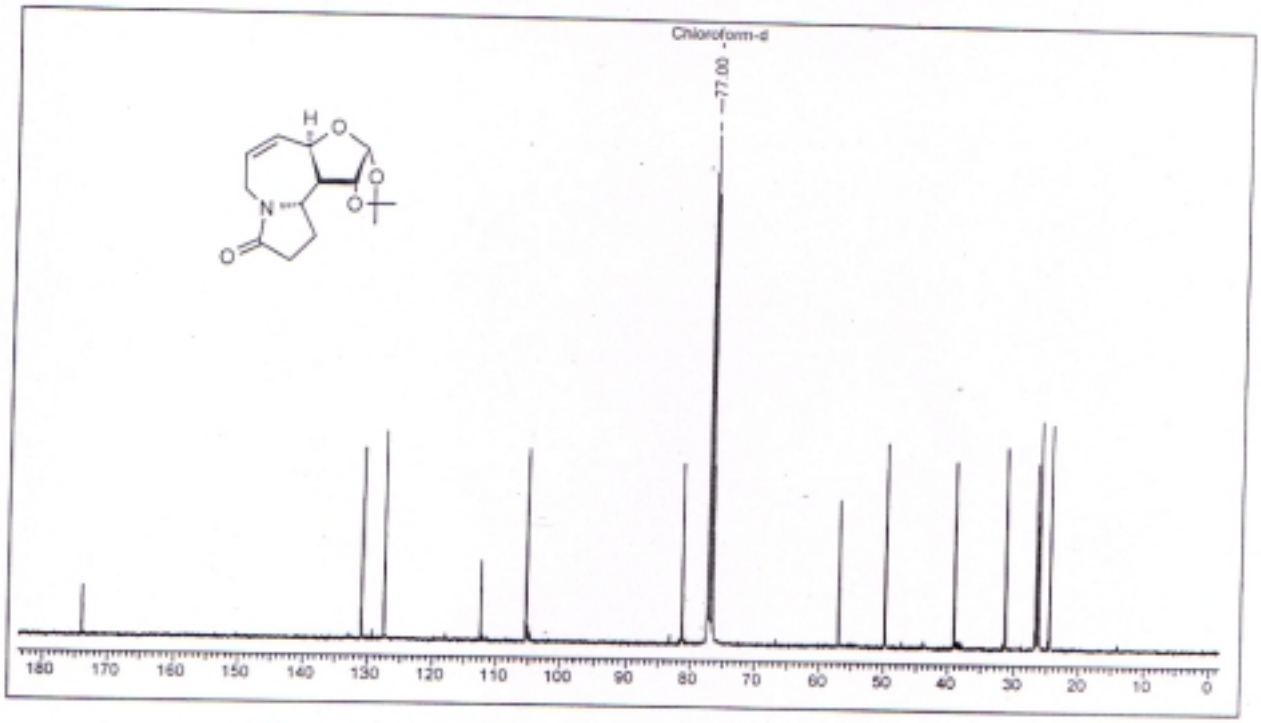
^{1}H NMR Spectrum of compound 58 in $CDCl_3$



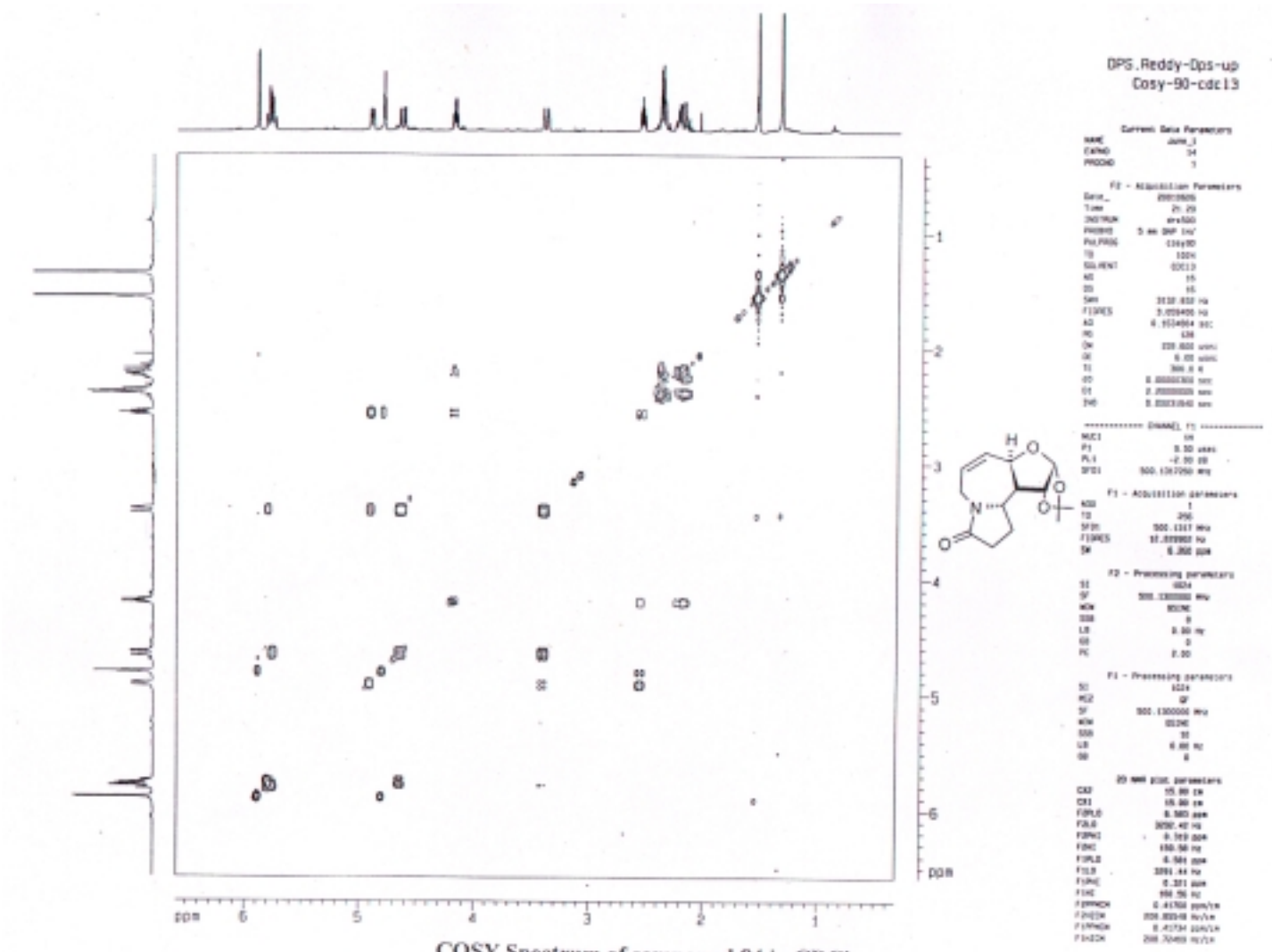
^{13}C NMR Spectrum of compound 58 in $CDCl_3$



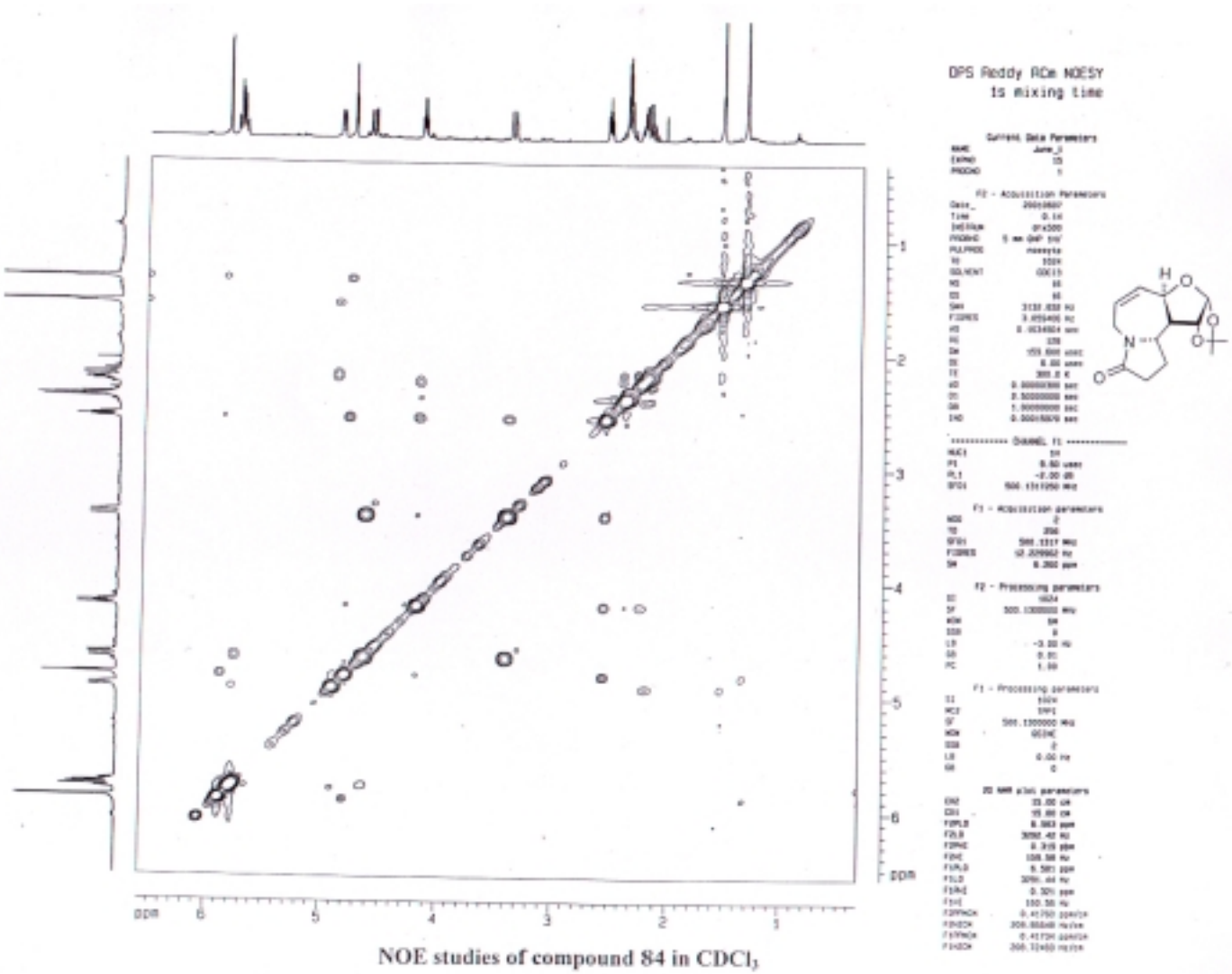
^{1}H NMR Spectrum of compound 84 in $CDCl_3$



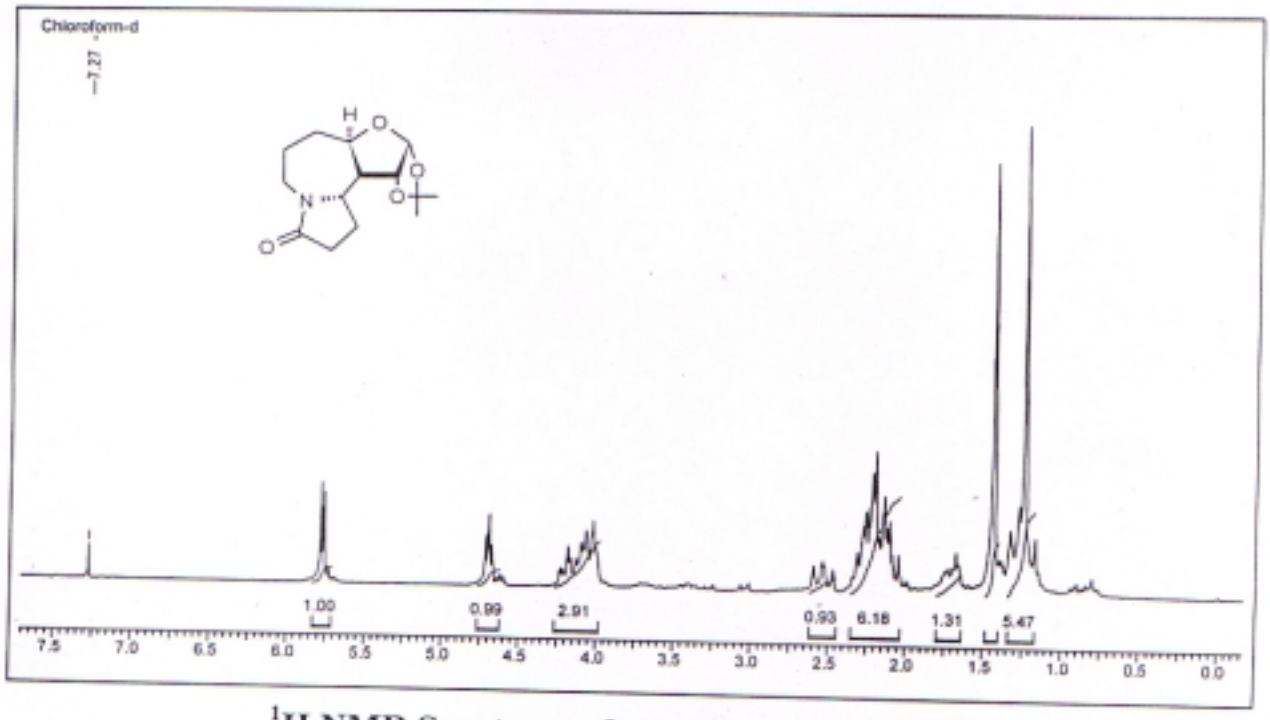
^{13}C NMR Spectrum of compound 84 in $CDCl_3$



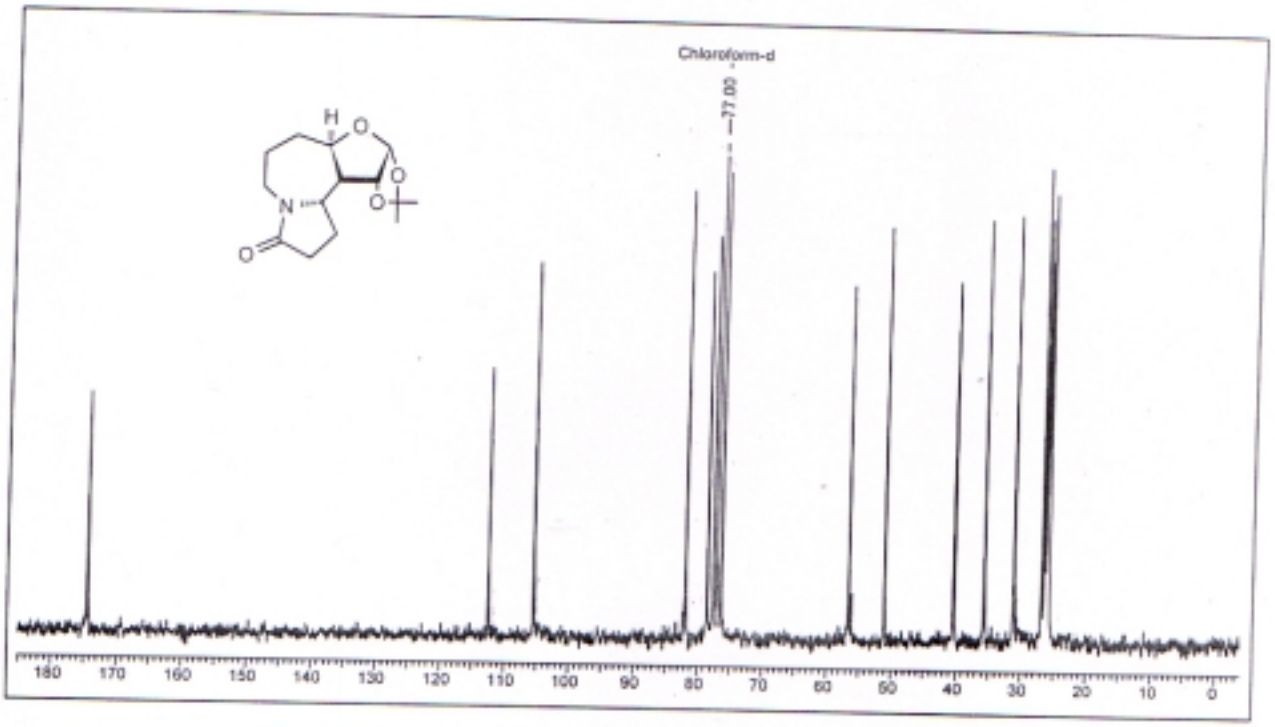
COSY Spectrum of compound 84 in $CDCl_3$



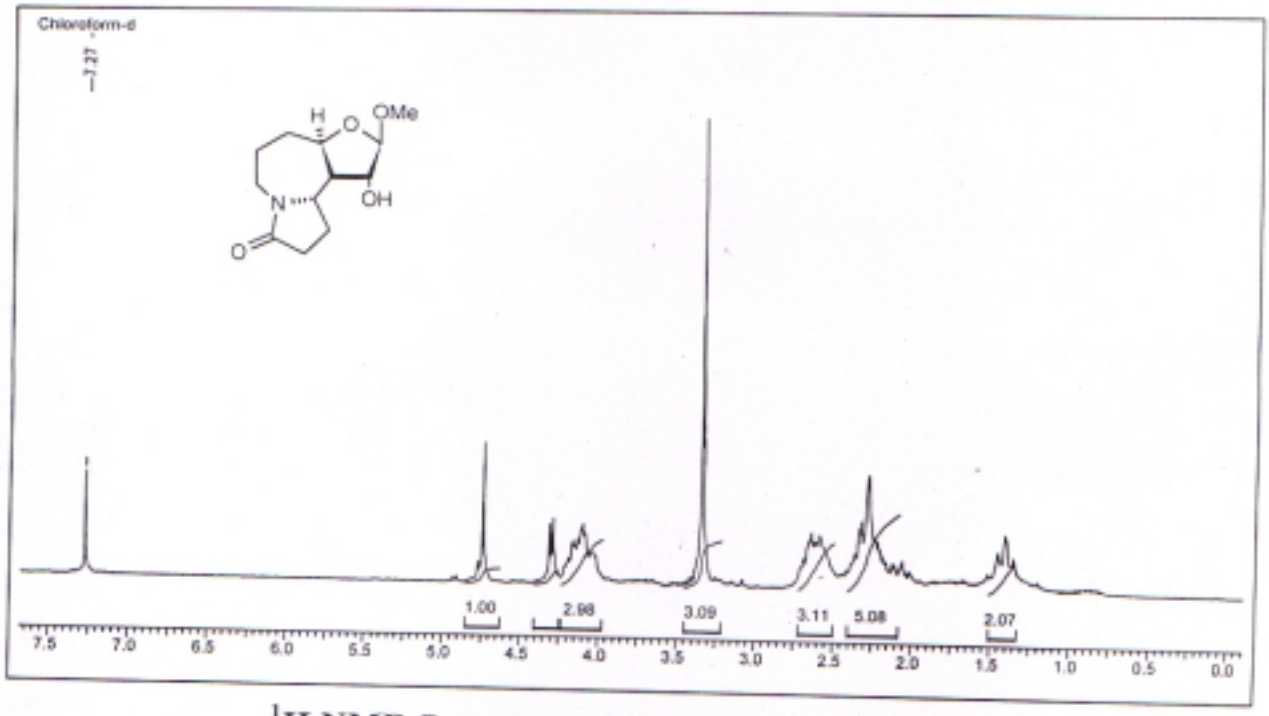
NOE studies of compound 84 in $CDCl_3$



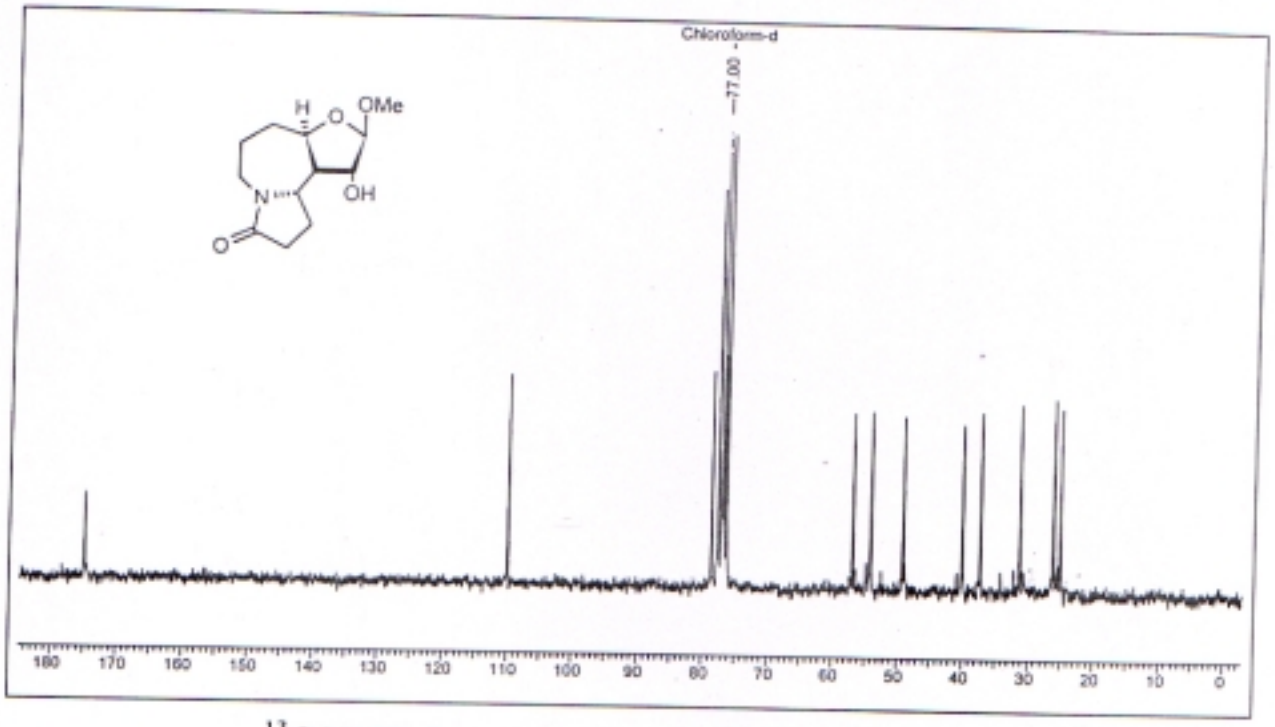
^{1}H NMR Spectrum of compound 85 in $CDCl_3$



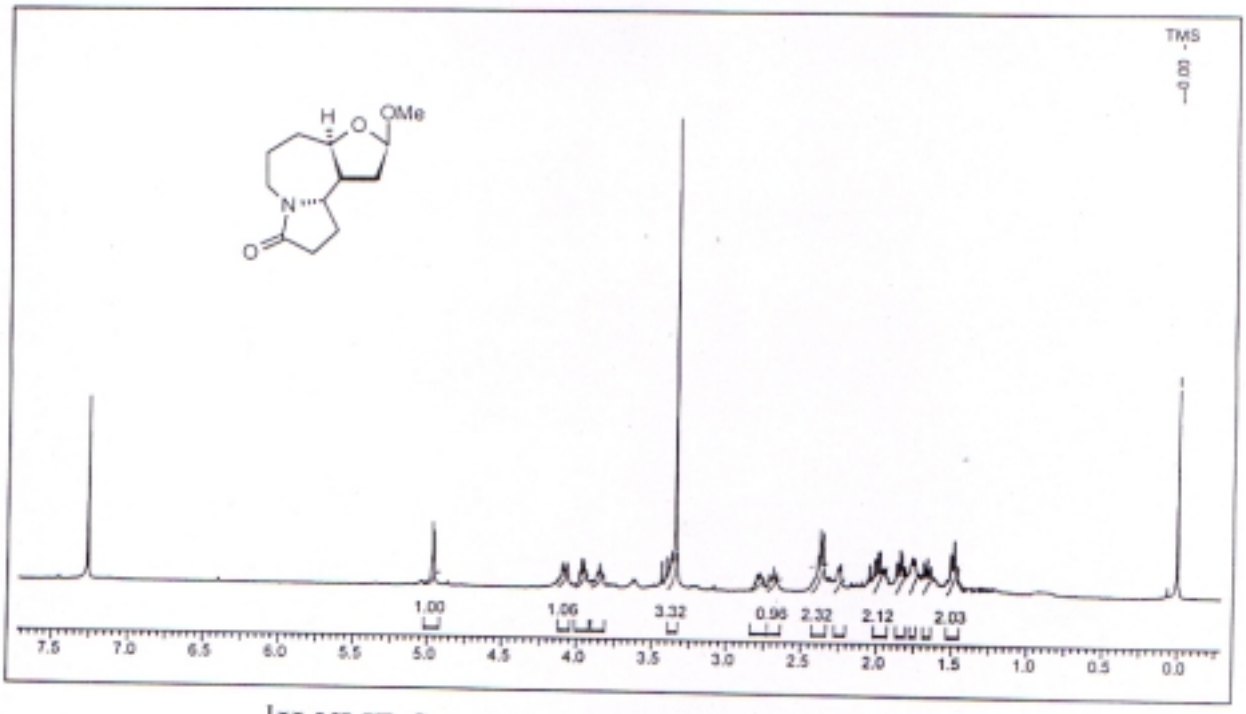
^{13}C NMR Spectrum of compound 85 in $CDCl_3$



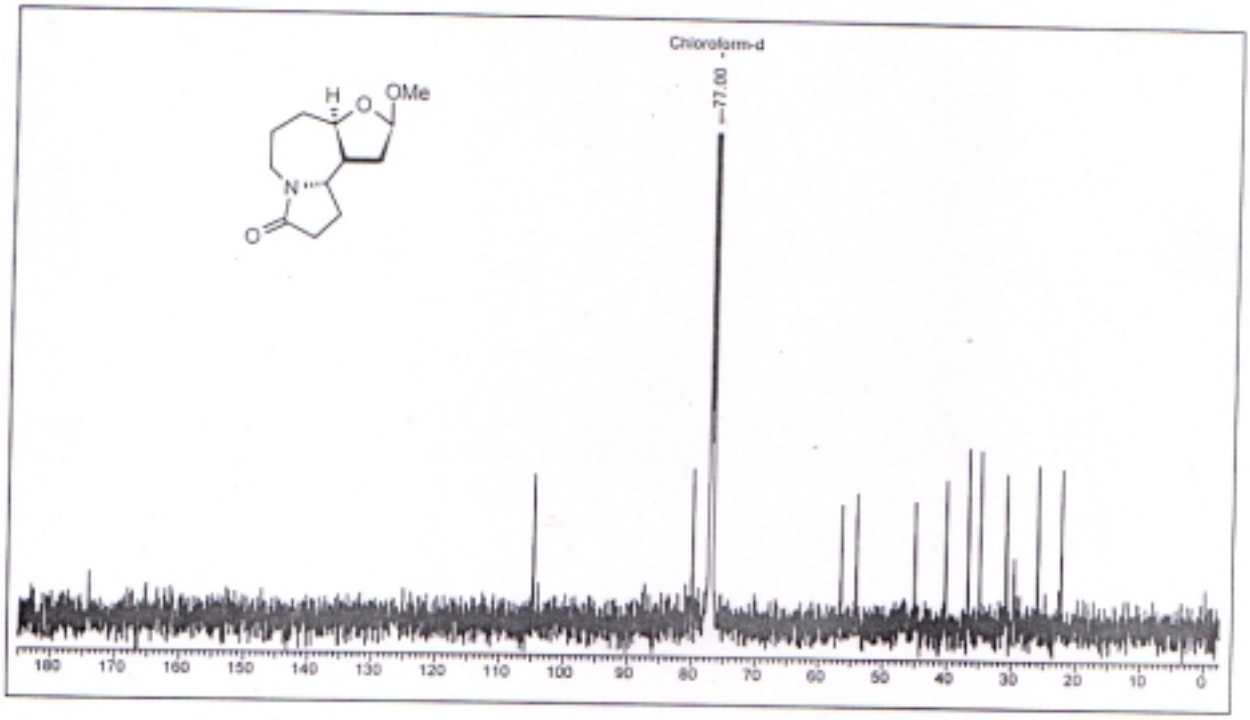
^{1}H NMR Spectrum of compound 86 in $CDCl_3$



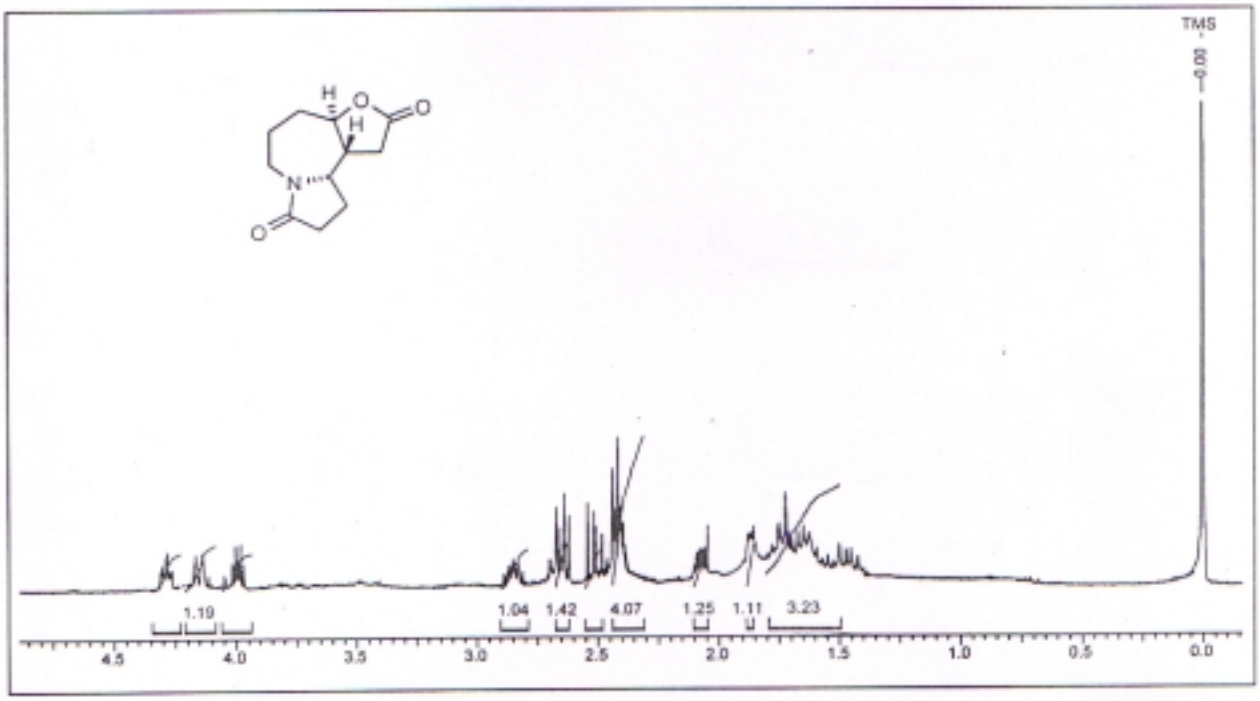
^{13}C NMR Spectrum of compound 86 in $CDCl_3$



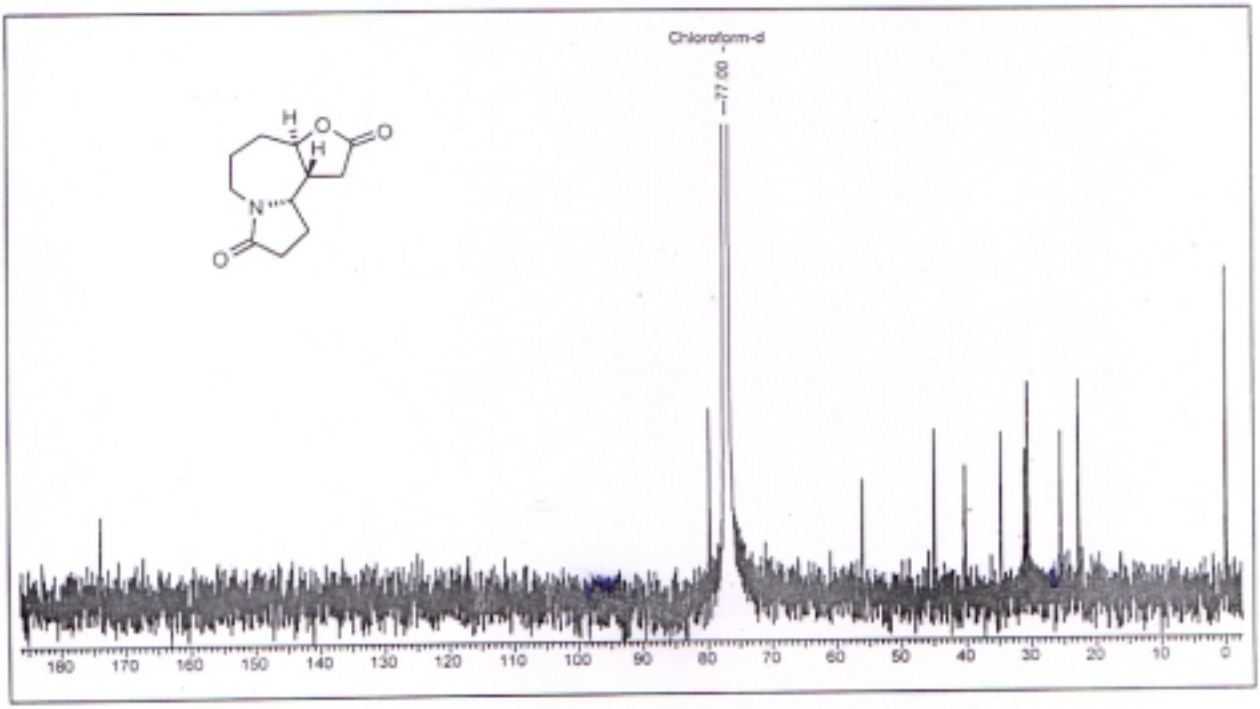
^{1}H NMR Spectrum of compound 87 in $CDCl_3$



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



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



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

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(2) Information from home page of traditional medicinal company, www.tradmedco.com.au.

(3) Information from www.herborium.com.

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Chapter II

Diastereoselective Reformatsky reaction of Methyl 4-bromocrotonate with 1,2:5,6-Di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose: Application to Novel Bicyclic Nucleosides and Towards Galiellalactone

Introduction

Introduction

Carbohydrates are the single most abundant class of enantiopure organic compounds associated with living matter. This auspicious fact together with the bulk-scale availability at low cost renders them ideal starting materials for organic preparative purposes. The acquisition of an enantiomerically homogeneous target molecule through sugar-based approach is a most attractive alternative to the construction of enantiopure target molecules by asymmetric synthesis.

The generation of enantiopure non-carbohydrate natural products from readily available sugars is of practical value only, if the individual reactions employed allow simple reagents, proceed uniformly, and avoid complex separations in work-up procedures to ultimately enable favorable overall yields. Such practical criteria entail the transformation of a sugar, overfunctionalized with chirality and hydroxyl groups, into an enantiopure building block with suitable functionalities.

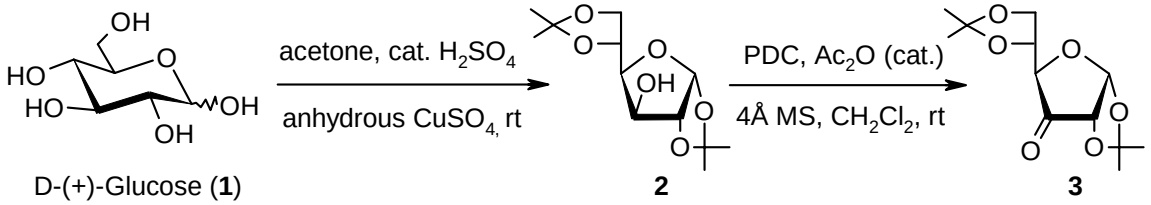
Glucose, a simple monosaccharide sugar, is one of the most important carbohydrates and is used as a source of energy in animals and plants. The natural form, D-(+)-glucose (**1**) is also referred as dextrose**,** especially in the food industry. D-(+)-Glucose (**1**) has been the most popular starting material, due to its easy availability in large quantities, to the large number of its known derivatives and to the ease with which the *trans*–relationship of its OH-groups can be preparatively exploited. In solutions D-(+)-glucose exists preferably in pyranose form. The composition of D-(+)-glucose in aqueous solution is, α-pyranose: 38%, β-pyranose: 62%, β-furanose: 0.14% and acyclic carbonyl form: 0.02%.

1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (**2**) is one of the most important and easily available D-glucose derivatives.[1] Because of the easy preparation and commercially cheaply available starting material (D-glucose), 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**2**) has been employed as synthon for many synthetic sequences. The utilization of this compound is conditioned by the sequence in which synthetic transformations may most easily be accomplished. The free OH group at C-3 can immediately be transformed. Mild acid treatment cleaves the less substituted dioxolane ring selectively exposing the 5,6-glycol group, which can in turn be elaborated in various ways. Further acid treatment cleaves the second dioxolane ring, exposing either both the C-1 and C-

2 OH groups (aqueous acid) or leading to a 2-hydroxy-glucoside (alcohol and acid). Finally the hidden C-4 OH group may be exposed whilst further functionalization of C-4 is possible at an early stage; elimination leading to the 3,4-unsaturated product.

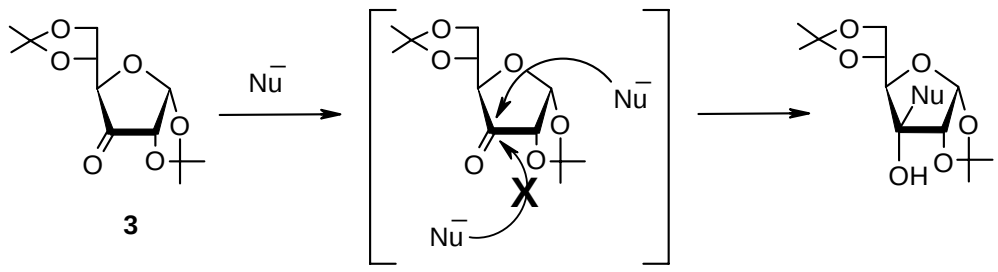
The oxidation of secondary alcohol group to a carbonyl group in a suitably protected carbohydrate derivative is one of the recently exploited reactions in this field by which convenient routes to rare unbranched- and branched-chain monosaccharides, aminosugars, and many biologically active compounds may be devised.[2] 1,2:5,6-Di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**3**) is one of the important intermediates in this category and it can be prepared from D-glucose in two steps. The conversion of D-(+)-glucose (**1**) into 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**2**) can be carried out by the combined action of acetone, anhydrous $CuSO_4$, and H_2SO_4 (cat.).[3] Subsequent oxidation of free OH at C-3 with PDC, 4Å molecular sieves powder and Ac_2O (cat.) furnishes 3-ulose derivative **3** (Scheme 1).[4]

Scheme 1



Most of the reactions at C-3 OH or C-3 ulose derivative of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**2**) are influenced by conformationally rigid 1,2-*O*-isopropylidene functionality.[5] Since it blocks the α-face of the sugar plane, the attack of the

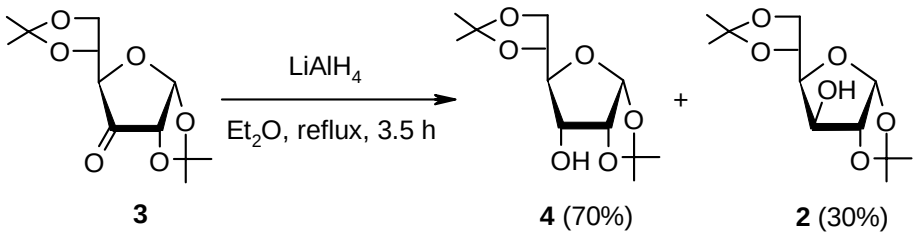
Scheme 2



nucleophiles always takes place from the sterically less crowded face, i.e. β-face, leading to the formation of allose derivatives in excellent yields (Scheme 2). This phenomenon has extensively been studied with wide variety of nucleophiles toward numerous 3-*C*-substituted-D-allose derivatives useful for the construction of various natural products and synthetic drugs.[2,5,6]

The transformation of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**2**) into 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**4**) is a classical representative of this type of reactions. Configurational inversion at C-3 was achieved by an oxidation-stereoselective reduction sequence. This is the general way to prepare D-allose derivative **4** and in particular it's otherwise practically inaccessible, since the attempted acetonation of D-allose under conditions of thermodynamic control leads to 2,3:5,6-di-*O*-isopropylidene-α-D-allofuranose.[7] Collins, P. M. (1965) observed that the $LiAlH_4$ reduction of 3-ulose derivative **3** affords a mixture of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (diisopropylideneallose) (**4**) and its gluco-isomer **2** (diacetonide-D-glucose) in a ratio of 7:3, shown by analyzing the crude reaction product polarimetrically and NMR spectrometrically (Scheme 3).[8]

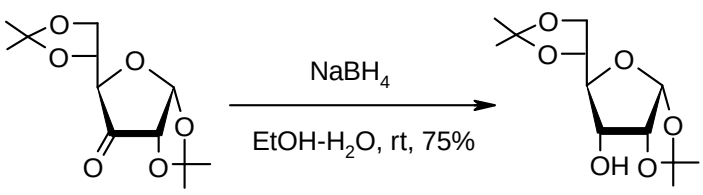
Scheme 3



3 **4** (70%) **2** (30%)

The synthetic utility of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**4**) prompted Horton, D. *et al.* (1972) to develop a simple and flexible alternative to the preparation of **4** from 3-ulose derivative **3**. To circumvent the formation of the mixture of products, they have

Scheme 4

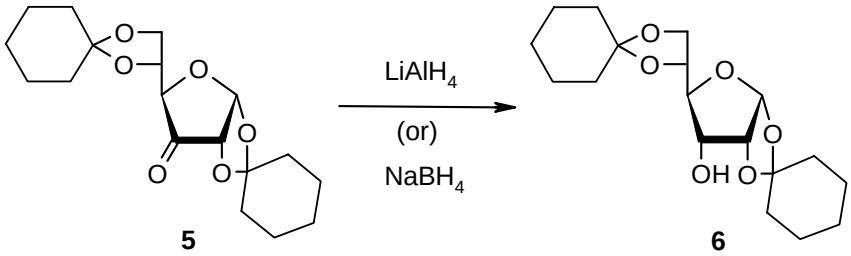


3 **4**

carried out the reduction of **3** with $NaBH_4$, which was more promising in terms of yields and reproducibility. This transformation gave 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**4**) exclusively in 75% yield (Scheme 4).[9]

The formation of above mixture of products can also be circumvented by replacing the 1,2- and 5,6-*O*-isopropylidene moieties with corresponding cyclohexylidene groups. James, K. and coworkers (1967) were carried out the stereoselective reduction of 1,2:5,6-di-*O*-cyclohexylidene-α-D-*ribo*-hexofuranos-3-ulose (**5**) using $LiAlH_4$ or $NaBH_4$ and obtained 1,2:5,6-di-*O*-cyclohexylidene-α-D-allofuranose (**6**) in high yield.[10] Careful inspection of NMR spectra of the reduction products (before purification) in the region of the proton resonance for the anomeric hydrogen showed neither case was any of the gluco-configuration present (Scheme 5). This observation clearly states that 1,2-*O*-cyclohexylidene moiety induces more sterical crowding than 1,2-*O*-isopropylidene moiety and it's a best alternative to solve the problems of stereoselectivity, if any.

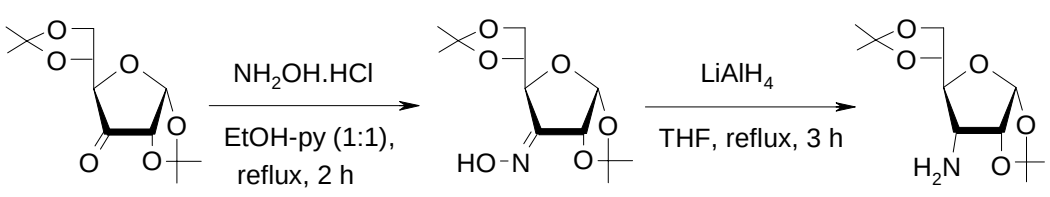
Scheme 5



5 **6**

In 1967, Onodera, K. *et al.* prepared 3-amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**8**) by treating the 3-ulose derivative **3** with hydroxylamine hydrochloride followed by the reduction of the resulted oxime with $LiAlH_4$.[11] The gluco isomer was not detected on paper chromatograms of the crude amine. This was in accordance with the earlier observed behavior of 1,2-*O*-isoppropylidene-α-D-ribo- or erythro-aldofuranos-3-ulose on reduction with metal hydrides (Scheme 6).

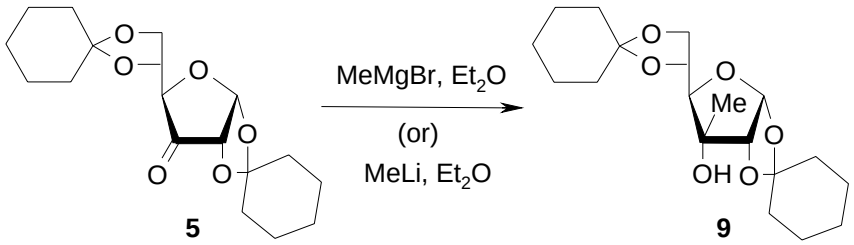
Scheme 6



3 **7** **8**

The addition of carbon nucleophiles to ketones derived from carbohydrates is the most frequently used method to prepare branched chain sugars. One of the most popular synthetic methods to the formation of simple alkyl branched-chain sugars is the addition of Grignard reagents. It can be adopted to give functionalized branch substituents since alkene and alkyne groups, similarly introduced, may be subsequently elaborated by chemical means. Addition of Grignard reagents and alkyllithium to 1,2:5,6-di-*O*-cyclohexylidene-α-D-*ribo*-hexofuranos-3-ulose (**5**) was well studied by Rees, R. D. *et al.* (1968).[12] Because of the steric effects induced by 1,2-*O*-cyclohexylidene moiety, the addition of Grignard reagents such as MeMgBr, EtMgBr, CH_2=CHMgBr and PhMgBr took place from the sterically less crowded face giving preferentially C-3 branched chain derivatives with the allo-configuration. In similar fashion, the attack of alkyllithiums such as MeLi and PhLi took place to give the corresponding C-3 branched chain derivatives with the allo-configuration (Scheme 7).

Scheme 7



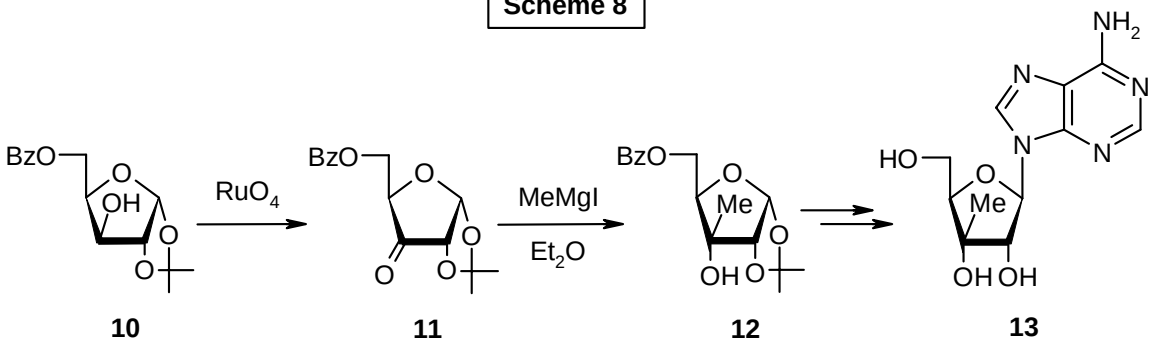
5 **9**

CH_2=CHMgBr, EtMgBr, PhMgBr and PhLi were also proceeded in same fashion

As part of their interest in the syntheses of nucleosides of branched-chain sugars, Nutt, R. F. *et al.* (1968) were in need of a key intermediate, 3-*C*-methyl-D-ribose. For that task, they have carried out the addition of methylmagnesium iodide on 5-*O*-benzoyl-l,2-*O*-isopropylidene-α-D-erythro-pentofuranos-3-ulose (**11**). Reaction of **11** with methylmagnesium iodide was essentially stereospecific and afforded 5-*O*-benzoyl-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-ribofuranose (**12**). The bulky isopropylidene group of C-1 and C-2 hydroxyls in **11** interferes with the addition of the Grignard reagent from the underside of the ring and none of the corresponding 3-*C*-methylxylose derivatives was detected among the reaction products. 5-*O*-Benzoyl-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-

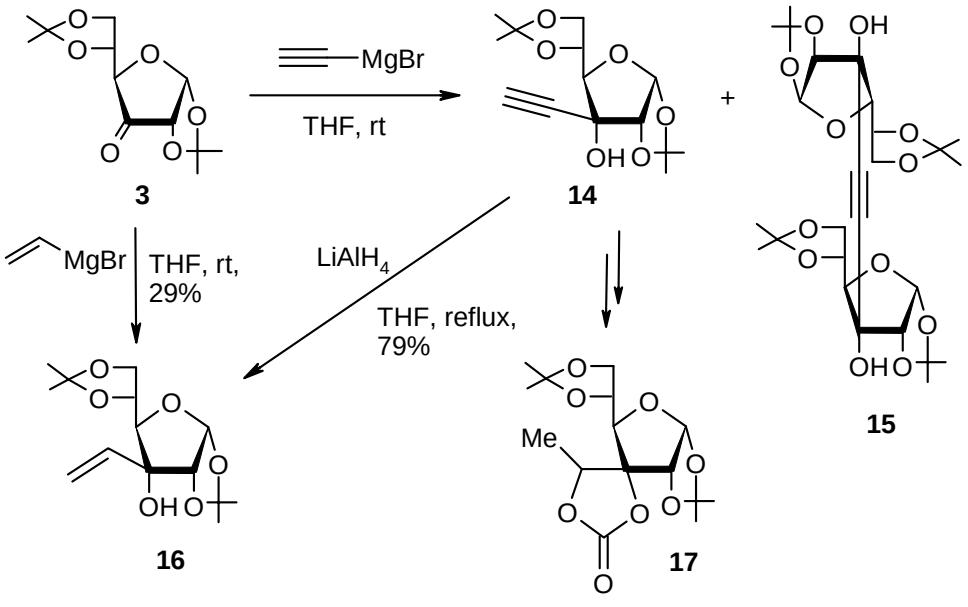
ribofuranose (**12**) was further functionalized and coupled with chloromercuri-6-benzamidopurine to give the acylated nucleoside which was deacylated to yield the first synthetic nucleoside containing a branched-chain sugar, 3'-*C*-methyladenosine (**13**) (Scheme 8).[13]

Scheme 8



In 1974, Baker, D. C. *et al.* have synthesized a branched-chain sugar derivative (**17**) related to aldogarose, a constituent of the antibiotic aldgamycin E, by employing the stereoselective ethynylation reaction as a key transformation. The nucleophilic addition of ethynylmagnesium bromide (prepared by passing the acetylene into ethylmagenesium bromide up to saturation) on 3-ulose derivative **3** gave 3-*C*-ethynyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**14**) in 86% yield. When the initial reaction-mixture for the Grignard reaction with **3** was not fully saturated with acetylene, a by-product, 1,2-bis(1,2:5,6-

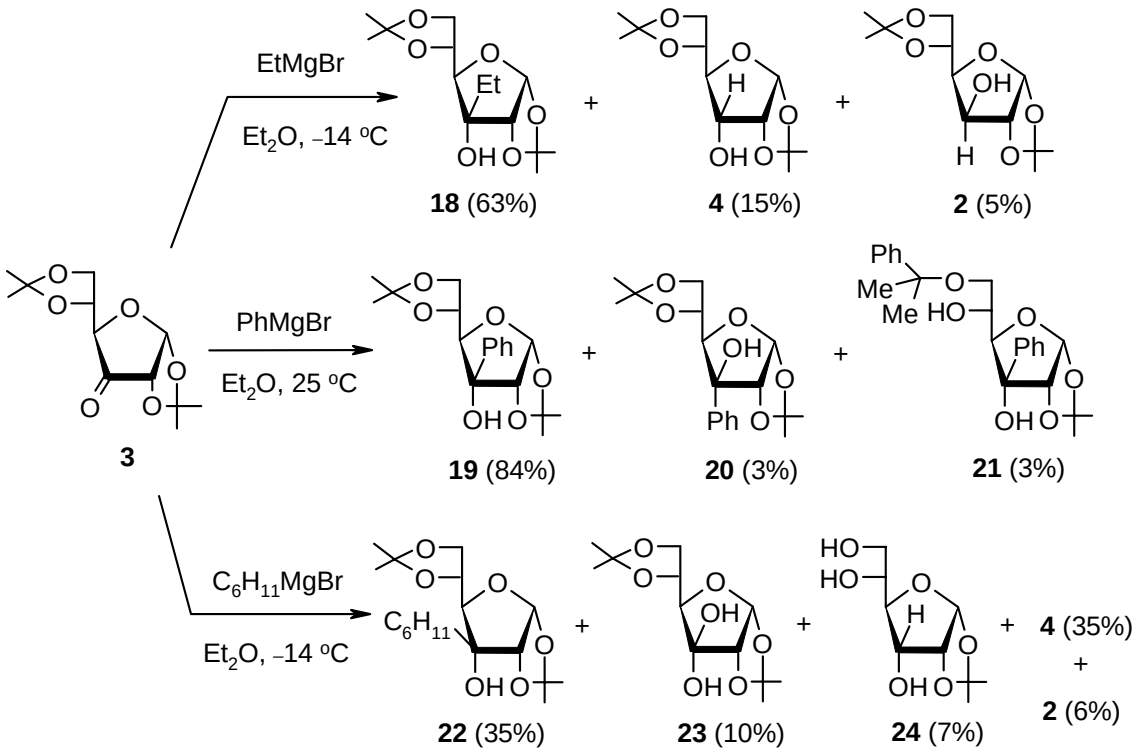
Scheme 9



di-*O*-isopropylidene-α-D-allofuranos-3-yl)acetylene (**15**) amounting to 25–30% of the total product, was formed. The attempted synthesis of 3-*C*-vinyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**16**) using vinylmagnesium chloride in THF was low yielding step, but they prepared **16** from **14** by $LiAlH_4$ mediated reduction in 79% yield (Scheme 9).[14]

In 1977, Horton, D. *et al.* have carried the extensive study on the addition of several Grignard reagents to 3-ulose derivative **3**.[15] The course of Grignard addition-reactions to 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**3**) has been examined as a function of the nature of the reagent, the solvent, the halide, and the temperature. Ethylmagnesium bromide in ether at –14 °C converted **3** into 60% of the 3-*C*-ethyl-D-allo adduct **18**. The use of THF or THF-ether at higher temperatures, or of ethylmagnesium iodide, lowered the yield of **18** and gave substantial proportions of side products such as 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**4**), 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**2**), and the hydrate (**23**) of the starting ketone **3**. Phenylmagnesium bromide in ether or THF converted **3** into the 3-*C*-phenyl-D-allo derivative **19** in 84% yield, accompanied by only minor proportions of side products; the latter were the 3-*C*-phenyl-D-gluco adduct **20** and the product (**21**) of 5,6-dioxolane ring-opening. Cyclohexylmagnesium

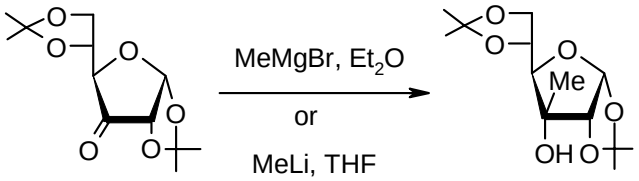
Scheme 10



bromide reacted with **3** in ether or THF at various temperatures to give 3-*C*-cyclohexyl-l,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**22**) in low yields. The main product generally encountered was **22**, with variable proportions of the hydrate **23**, 1,2-*O*-isopropylidene-α-D-allofuranose (**24**), the diacetonide-D-allose (**4**), and diacetonide-D-glucose (**2**) (Scheme 10).

In 1979, Ganem, B. *et al.* have prepared 1,2:5,6-di-*O*-isopropylidene-3-*C*-methyl-α-D-allofuranose (**25**) as part of their synthetic studies directed towards an enantioselective synthesis of maytansine. 3-ulose derivative **3** was reacted with methylmagnesium bromide in diethyl ether or methyllithium in THF to furnish 1,2:5,6-di-*O*-isopropylidene-3-*C*-methyl-α-D-allofuranose (**25**) in 65% yield (Scheme 11).[16]

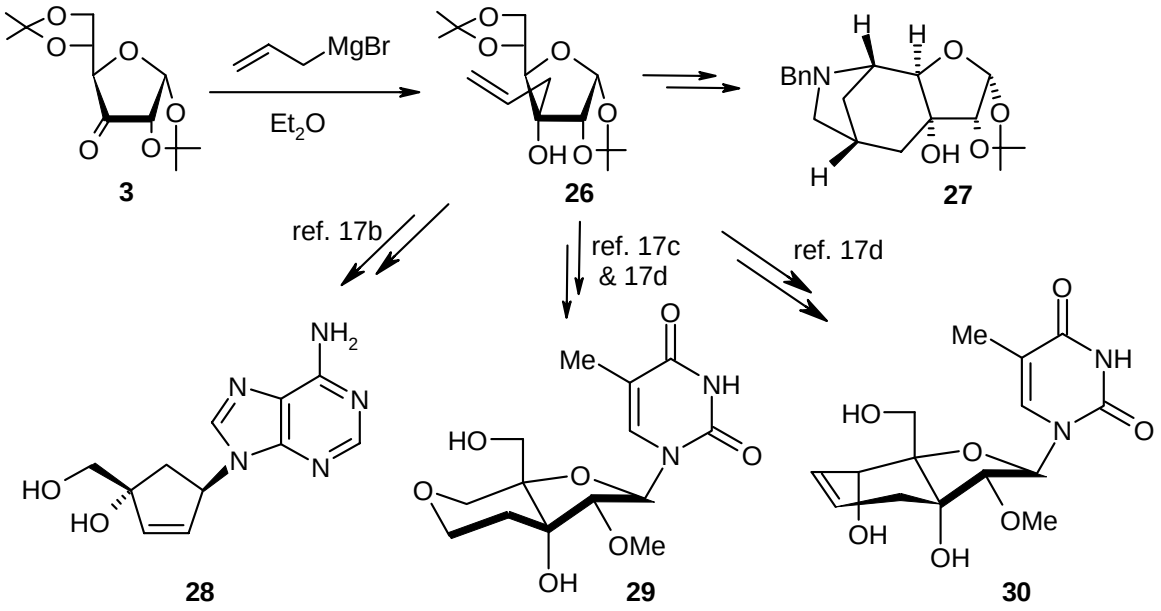
Scheme 11



3 **25**

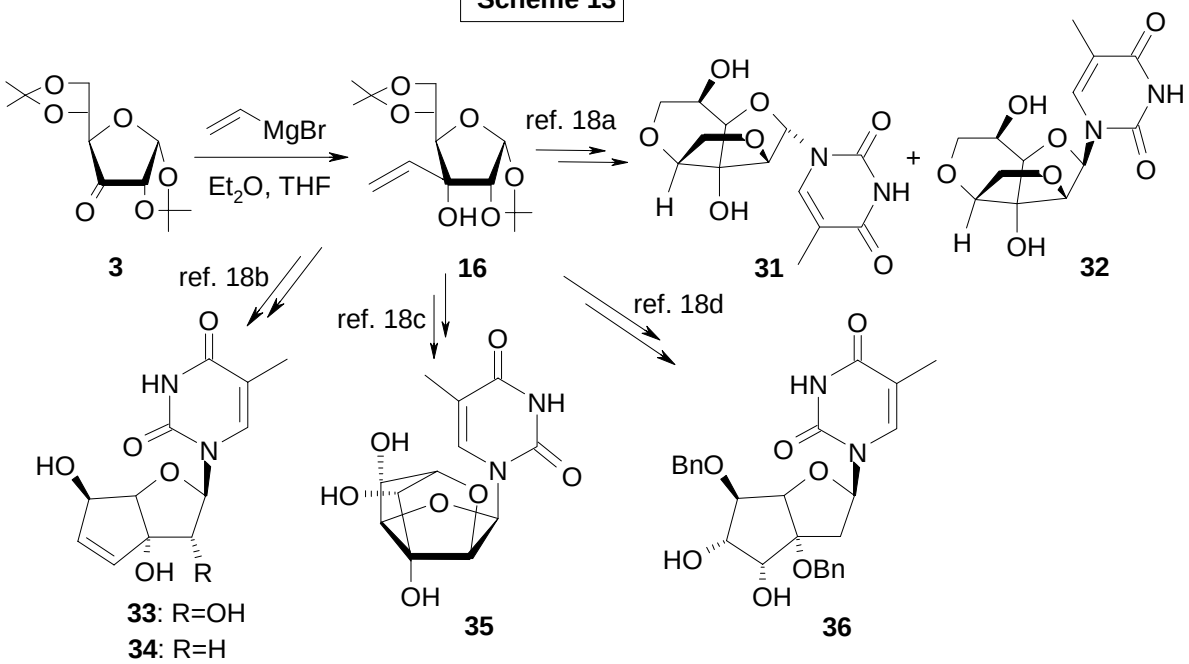
Mandal, S. B. and coworkers (1996) have synthesized useful precursors for unnatural bioactive chiral carbocyclic nucleosides and for glycosidase inhibitors from D-glucose through intramolecular 1,3-dipolar cycloaddition as a key step. They prepared 1,2:5,6-di-*O*-isopropylidene-3-*C*-prop-2-enyl-α-D-allofuranose (**26**) by the addition of allylmagnesium bromide on 3-ulose derivative **3**.[17a] In 2001, Gurjar, M. K. *et al.* have successfully utilized this intermediate for the synthesis of novel carbocyclic nucleoside (**28**) through RCM approach.[17b] In 2002, Imanishi, T. *et al.* achieved a synthesis of novel bridged nucleoside **29**, with S-type sugar puckering, *trans*-3'-4'-BNA monomer bearing a 4,7-dioxabicyclo[4.3.0]nonane skeleton starting from the compound **26**.[17c] Also in 2002, Nielsen, P. *et al.* synthesized a novel class of 3',4'-*trans*-linked bicyclic nucleosides **29** and **30** with locked S-type furanose conformations.[17d] The bicyclic nucleoside **29** was obtained by cyclic ether formation and **30** by ring-closing metathesis methodology (Scheme 12).

Scheme 12



In 2000, Neilsen, P. and coworkers have synthesized two novel anomeric nucleosides **31** and **32** with tricyclic carbohydrate moieties in 11 steps starting from diacetone-D-glucose (**2**), taking advantage of a stereoselective Grignard reaction, a stereoselective dihydroxylation and a regioselective tandem ring-closing metathesis reaction.[18a] 3-*C*-Vinyl-D-allose

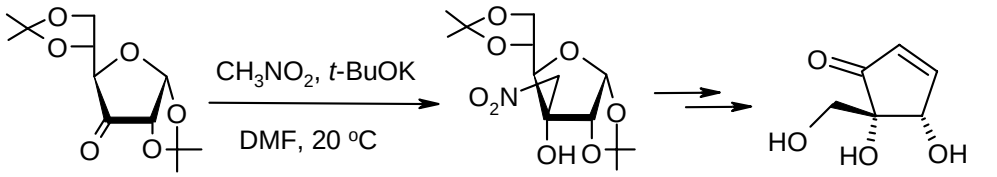
Scheme 13



derivative (**16**) was prepared in two steps from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**2**) using PDC oxidation followed by a stereoselective vinylmagnesium bromide mediated Grignard reaction. In 2001, they have synthesized bicyclic nucleosides **33** and **34** by employing ring closing metathesis reaction.[18b] In the same year they also achieved the synthesis of tricyclic nucleoside **35** by applying a stereoselective dihydroxylation, a regioselective tosylation and an intermolecular ether formation.[18c] In 2003 they have carried out the stereoselective dihydroxylation and 2'-deoxygenation to prepare a series of polyhydroxylated bicyclic nucleoside derivatives (**36** and related compounds) (Scheme 13).[18d]

For the preparation of branched-chain sugars containing functionalized branch substituents, base-catalyzed addition of nitromethane or acetonitrile (nitro-aldol reaction) and Reformatsky reaction are also important transformations. In 1978, Moffatt, J. G. and coworkers achieved the synthesis of an antibiotic, pentenomycin (**38**) from 3-ulose derivative **3**. Nitro-aldol reaction of 3-ulose derivative **3** with nitromethane in presence of t-BuOK furnished **37** in high yield. The compound **37** was further subjected to functional group manipulations and finally intramolecular aldol reaction to obtain pentenomycin (**38**) (Scheme 14).[19]

Scheme 14

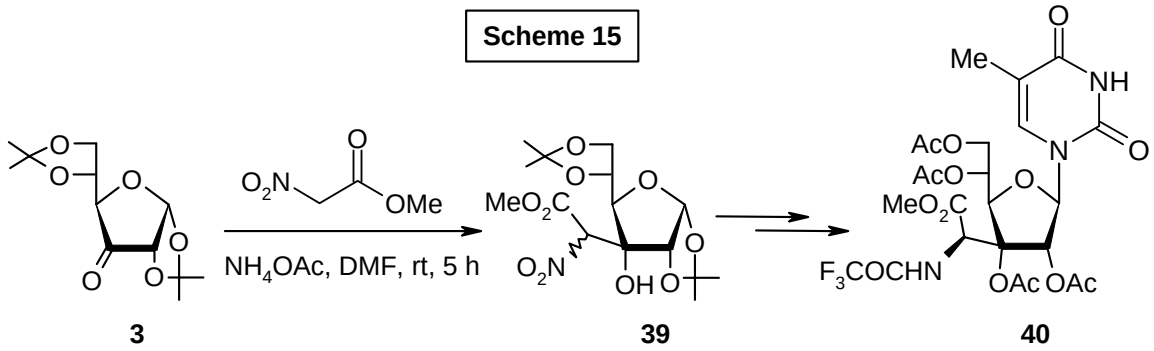


3 **37** Pentenomycin (**38**)

Later, Rosenthal, A. and coworkers (1980) have successfully employed the nitro-aldol reaction (Henry's reaction) of methyl nitroacetate with 3-ulose derivative **3** in the presence of ammonium acetate in anhydrous DMF to afford 1,2:5,6-di-*O*-isopropylidene-3-*C*-(*R*,*S*)nitro(methoxy-carbonyl)methyl-α-D-allofuranose (**39**) in 82% yield.[20] Since the compound **39** was subjected to hydrogenation in the presence of Raney Ni which proceeds through the corresponding oxime intermediate, the absolute stereochemistry of **39** has not been confirmed. This intermediate was then converted into an analogue of the nucleoside

moiety of the Polyoxins, l-[2,3,5,6-tetra-*O*-acetyl-[3-*C*-(methyl *N*-trifluoroacetyl-L-2-glycinate)]-β-D-allofuranosyl]thymine (**40**) (Scheme 15).

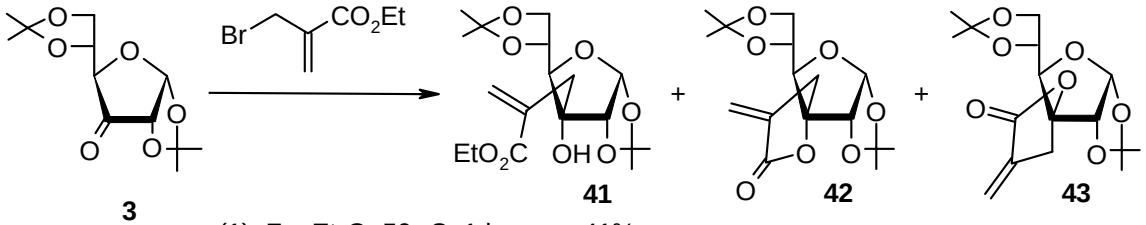
Scheme 15



3 **39** **40**

In 1987, Rauter, A. P. *et al.* have carried out the Reformatsky reaction of ethyl 2-bromomethyl-2-propenoate with 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**3**) in the presence of Zn as well as Zn/Ag couple. The Zn dust mediated Reformatsky reaction at 50 ^{o}C afforded 3-*C*-(2'-ethoxycarbonyl-prop-2'-enyl)-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**41**) in 41% yield and its cyclized product, **42** in 35% yield, and the cyclised gluco-isomer **43** in 24% yield while Zn/Ag couple mediated reaction at –78 ^{o}C gave **42** as a sole product. In this reaction, the degree of the reactivity of Zn has also had an important influence on the stereoselectivty. Although asymmetric induction of 1,2-*O*-isopropylidene moiety is a major factor in this reaction, it is the very mild conditions that enables the reaction to proceed by high or even complete kinetic control (Scheme 16).[21]

Scheme 16



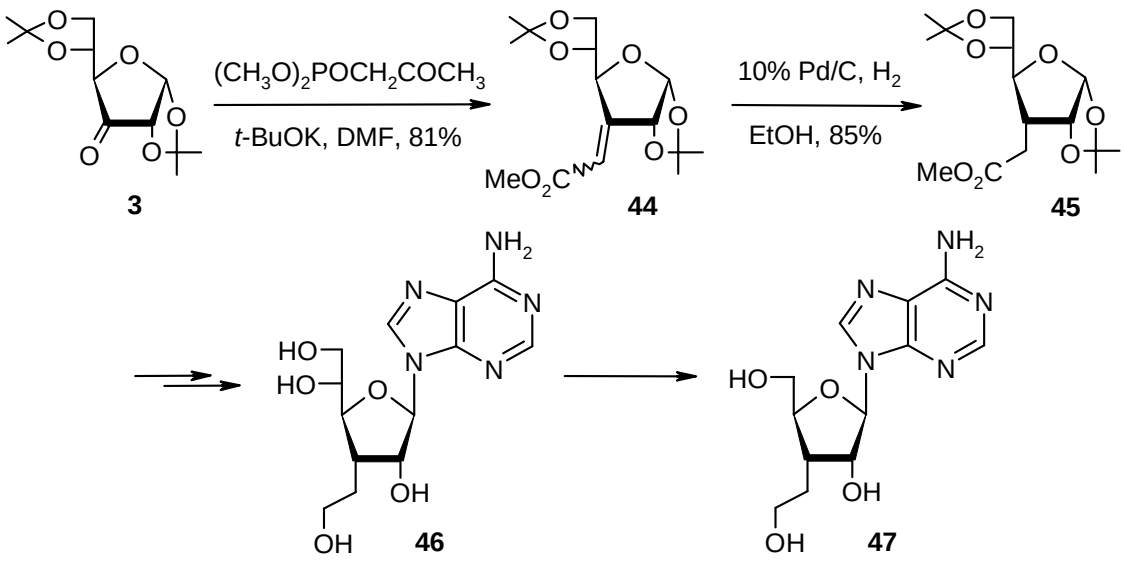
3

	41	**42**	**43**
(1). Zn, Et_2O, 50 ^{o}C, 1 h	41%	35%	24%
(2). Zn/Ag couple, Et_2O, –78 ^{o}C, 10 min	0%	96%	0%

Similar to the stereoselective reduction of 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**3**) the olefination - reduction sequence is a classical way to synthesize

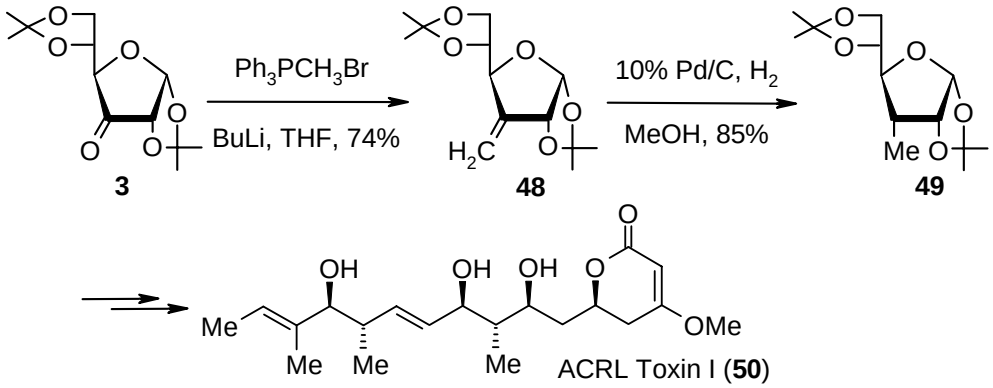
deoxy class of branched-chain sugars stereoselectively. In 1969, Rosenthal, A. *et al.* have first utilized this strategy for the synthesis of two novel branched-chain sugar nucleosides, **46** and **47**. The key intermediate in this synthesis, 3-*C*-(carbomethoxymethyl)-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**45**), was prepared by application of a Wittig reaction to 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**3**) followed by stereoselective hydrogenation of the olefin derivative **44** (Scheme 17).[22]

Scheme 17



3-Deoxy-3-*C*-methyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**49**) is a highly versatile building block derived from 3-ulose derivative **3**, which has been utilized as the key compound in a convergent total synthesis of ACRL Toxin I (**50**).[23] Its elaboration from **3**

Scheme 18



started with one-carbon Wittig olefination using methyl (triphenyl)phosphonium bromide followed by hydrogenation. Due to the asymmetric induction of 1,2-*O*-isopropylidene moiety in **48**, the approach of hydride takes place from the β-face to give exclusively 3-Deoxy-3-*C*-methyl-allose derivative **49** (Scheme 18). Hydroboration-oxidation of the olefin derivative **48** also undergoes stereoselectively to afford exclusively the corresponding 3-deoxy-3-*C*-hydroxymethyl-allose derivative.[24]

The asymmetric induction of 1,2-*O*-isopropylidene moiety of 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**3**) is an interesting phenomenon and still it can be applied for various nucleophiles, whichever have not been used in the past. Several more useful synthetic transformations were appeared in the literature based on the steric hindrance induced by 1,2-*O*-isopropylidene or 1,2-*O*-cyclohexylidene moieties.[2,5,6]

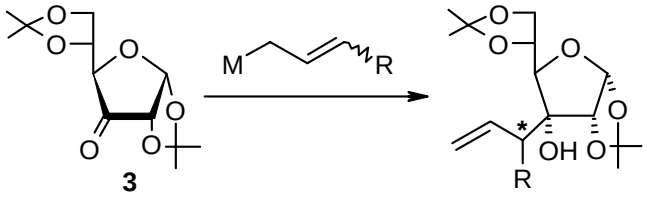
Present Work

Present Work

Over the decades, carbohydrates have been recognized as naturally occurring organic compounds endowed with a wealth of stereochemical attributes. The thrust of this area has been inspired by biochemical events and the advent of antibiotics has fostered an accelerated effort in synthesis and chemical modification of component sugar units. Since carbohydrates are relatively cheap and rich source of chiral carbon compounds endowed with a plethora of functional, stereochemical and conformational features, they have often been subjected to chemical exploitation towards the synthesis of various compounds including natural products and nucleoside based drugs. These features also ensure a measure of regio-, and stereocontrol in several bond forming reactions.

Due to the inherent structural complexity associated with carbohydrate precursors, many organometallic C–C bond forming reactions occur with impressive stereoselectivity.[5b] For instance, the 3-ulose derivative of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**2**) has been particularly targeted with significant successes. The conformationally rigid 1,2-*O*-isopropylidene functionality of **3** dictates the approach of the nucleophile from the β-face giving rise to the 3-*C*-substituted-D-allose derivative.[2,5,6] In most of the C–C bond forming reactions studied so far, only one new chiral center at C-3 has been created.[25] We were interested in exploring the organometallic reaction of **3** with a specific organo-metallic reagent which is tuned to produce two new chiral centers as delineated in Scheme 19. We believe that this study would be of significant interest for synthesizing novel molecules including the bicyclic derivatives.

Scheme 19



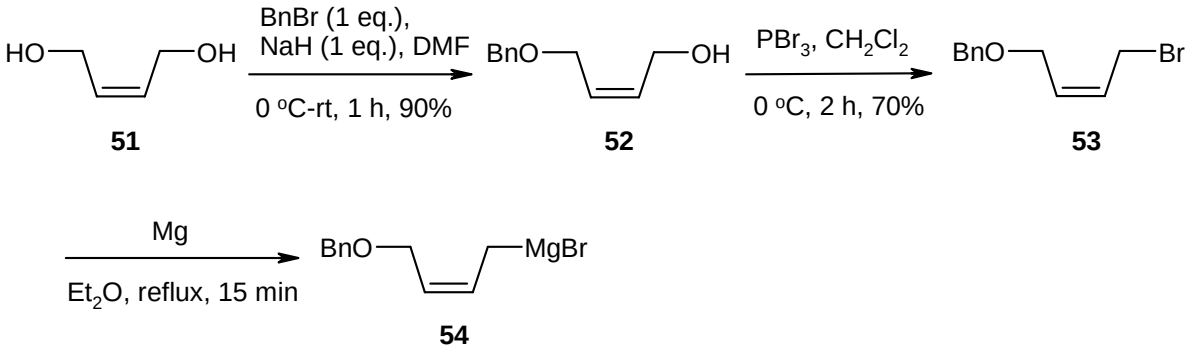
3

This chapter highlights about the diastereoselective Reformatsky reaction of methyl 4-bromocrotonate with 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**3**) and its application to synthesis of some novel bicyclic nucleosides and towards galiellalactone.

1,2:5,6-Di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**3**) can be prepared from D-glucose in two steps by employing literature procedures.[3,4] Thus, D-glucose (**1**) was converted into 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**2**) by the combined action of acetone and anhydrous $CuSO_4$ in presence of catalytic H_2SO_4. Subsequent oxidation of free OH at C-3 with PDC, 4Å molecular sieves powder and Ac_2O (cat.) in anhydrous CH_2Cl_2 at room temperature furnished 3-ulose derivative **3** (Scheme 1).

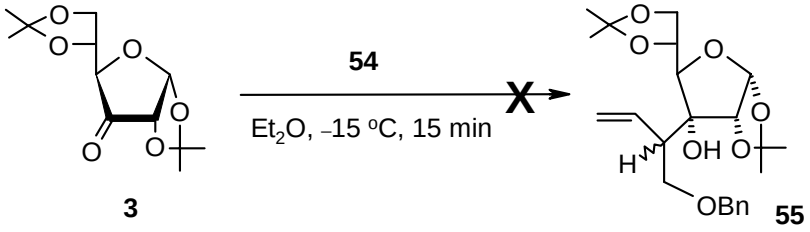
We have envisaged that the addition of Grignard reagent **54** to 3-ulose derivative **3** would lead to the formation of compound **55**. In that direction, the Grignard reagent **54** was prepared starting from *cis*-butene diol (**51**). Thus, *cis*-butene diol (**51**) was protected as monobenzylic ether[26a] using NaH and benzyl bromide followed by the nucleophilic displacement of hydroxyl group with bromine in presence PBr_3 to give bromo compound **53**,[26b] which was then treated with Mg metal under Grignard reaction conditions to afford **54** (Scheme 20).

Scheme 20



The addition of Grignard reagent **54** to 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**3**) resulted in the reduction of carbonyl functionality without yielding any desired product (Scheme 21). To circumvent this problem, we diverted our attention to the vinylogous Reformatsky reaction using methyl 4-bromocrotonate and Zn-Cu couple.[27]

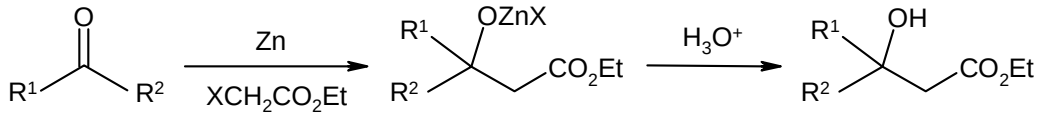
Scheme 21



Reformatsky reaction: a brief account

The reaction of an ethyl α-halo ester with an aldehyde or ketone in the presence of zinc metal is known as Reformasky reaction.[28] The usual product of the reaction is a β-hydroxy ester, which may be dehydrated, in subsequent step to give an unsaturated ester, an easy alternative to the Wittig reaction. These restricted conditions were soon found to be also applicable to various other alkyl 2-haloalkanoates and the scope of the Reformatsky reaction was extended beyond aldehydes and ketones, and the results of the most recent developments now call for a more comprehensive definition (Scheme 22).[29]

Scheme 22



A zinc ester enolate, the so-called Reformatsky reagent, is an intermediate in the reaction and the sequence is thus classified as an aldol condensation. The distinguishing features of the Reformatsky reaction, compared to the usual base promoted aldol procedures, are the use of metal-halogen redox reaction rather than an acid-base reaction to form the enolate, and the fact that the counter ion of the enolate is zinc. Since it's discovery in 1887, it has been extensively studied and widely utilized in organic synthesis. Heathcock has recently reviewed the stereochemical aspects of the reaction of a variety of zinc enolates with aldehydes and ketones.[30]

In extending the scope of the Reformatsky reaction, numerous parameters such as metal activation, solvent, reaction temperature, appropriately designed reagents and educts, factors influencing chemo-, regio- and stereoselectivity, as well as the design of sophisticated synthesis, have been studied. As a result, considerable progress has been achieved by continuously increasing the reactivity of the zinc or by application of various other metals such as magneisium,[31] cadmium,[32] nickel,[33] indium,[34] cerium,[35] lithium[36] and rhodium.[37] A great many solvents have been tested, and although ether solvents such as diethyl ether, THF, 1,4-dioxane or dimethoxymethane are generally preferred, mixtures of these with aromatic hydrocarbons or the more polar solvents like CH_3CN, DMF, DMSO or HMPT were found to be appropriate in some specific transformations. Both the use of highly activated zinc metals such as Rieke-Zn,[38] Zn-Cu couple[39] and Zn/Ag-graphite,[40] and the proper selection of the solvent not only allow the separate preparation of zinc enolates, but also help to suppress the various long-known side reactions and to improve selectivities. Recently, samarium(II)iodide promoted Reformatsky reactions have been extensively studied.[41] Although little attention has been focused on the catalytic version of this type of reaction, there is an interesting variant, which utilized zinc and a catalytic amount of titanocene dichloride.[42]

The Reformatsky reaction is most commonly conducted in a single step by addition of a mixture of α-halo ester and carbonyl substrate to a suspension of zinc in a suitable solvent. This one step procedure clearly minimizes any problems due to instability of the Reformatsky reagent while two-step procedure allows the unambiguous characterization of the stable Reformatsky reagents.

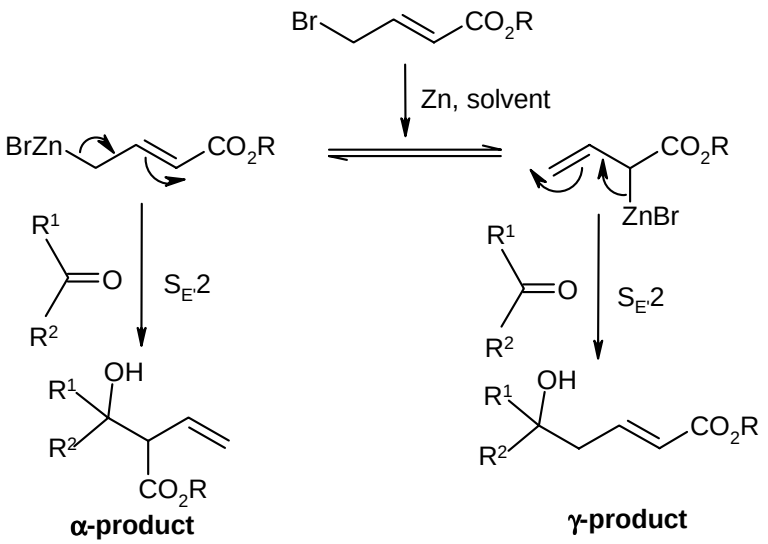
Metal enolates may have structures with either a metal-oxygen or metal-carbon bond. Zinc ester enolates prefer carbon-bonded structure like mercury enolates[43] while zinc ketone enolates prefer oxygen-bonded structure as in the case of lithium enolates.[44] The preference of zinc ester enolates for carbon bonding was well supported by the spectral data and X-ray diffraction studies of the crystalline zinc enolate of *tert*-butyl acetate.[45]

The vinylogous Reformatsky reaction of alkyl 4-bromocrotonates can give either α- or γ-products. Gaudemar and coworkers have proposed that one-step Reformatsky reactions of zinc ester dienolates will produce mainly α-products in kinetically controlled processes, and mainly γ-products in thermodynamically controlled processes.[46] Similar conclusions were reached for the corresponding reactions of lithium ester dienolates.[47] Hudlicky and coworkers

extensively studied the regioselectivity of the Reformatsky reactions with zinc ester dienolate of alkyl 4-bromocrotonates,[27] but the stereoselectivity of α-products was not addressed as they carried out the reaction on achiral substrates. Though the Reformatsky reaction has widely been applied to carbohydrate substrates,[29a,48,49] the vinylogous Reformatsky reaction with alkyl 4-bromocrotonates has not been studied in the past.

To address this phenomenon, Gaudemar and coworkers have proposed that the zinc ester dienolate of 4-bromocrotonate esters exists in two different forms (Scheme 23).[50] The thermodynamically controlled product (γ-product) can be obtained at higher temperatures, prolonged reaction times and preferably in aromatic hydrocarbon solvents while the kinetically controlled product (α-product) can be achieved by using highly active form of zinc such as Zn-Cu or Zn-Ag couple, low boiling solvents and decreased reaction timings.

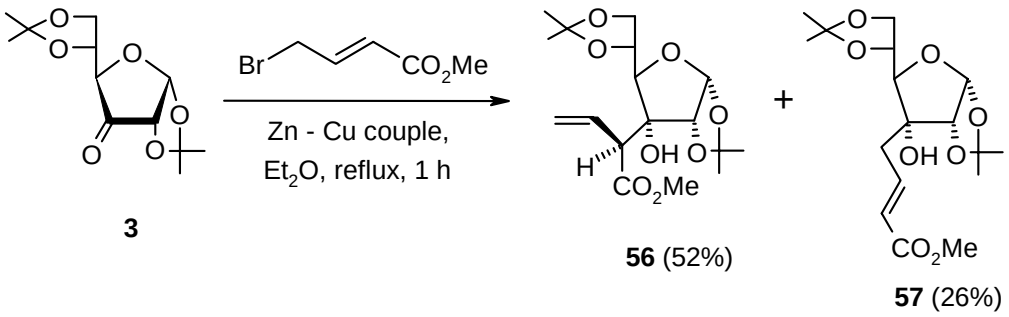
Scheme 23



Since the reaction using Grignard reagent (**54**) on 3-ulose derivative **3** failed to afford the desired product, we anticipated that the application of vinylogous Reformatsky reaction on **3** with methyl 4-bromocrotonate and highly active form of Zn metal in low boiling solvent would give the desired product. Even if it results in the mixture of products (α- and γ-product), the products can easily be separated and the α-product would be an interesting compound for knowing the stereoselectivity in side chain.

Thus, the one-stage vinylogous Reformatsky reaction of 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**3**) with methyl 4-bromocrotonate in the presence of acid (AcOH) washed Zn-Cu couple in anhydrous diethyl ether was carried out to furnish α-product **56** and γ-product **57,** which were easily separable by simple silica gel column chromatography. The α-product **56** was obtained in 52% yield and γ-product **57** in 26% respectively (Scheme 24). The yields of α- and γ-products in the Reformatsky reaction of 3-ulose derivative **3** with methyl 4-bromocrotonate in the presence of simple and unactivated zinc in anhydrous THF were 31% and 25% respectively. As expected, kinetically controlled α- product was obtained as major product,[27] and attempts to enhance it's ratio were carried out using Zn-Ag couple in the reaction, but no improvement in ratio and yields of the products was achieved.

Scheme 24



3

56 (52%)

57 (26%)

The structure of α-product **56** was assigned based on ^{1}H NMR, ^{13}C NMR and mass spectral data together with elemental analysis. In the ^{1}H NMR spectrum of **56**, two singlets at 3.74 (3 H, for carbomethoxy moiety) and at 3.32 ppm (1 H), a doublet of doublet of doublet at 5.83 (1 H, J = 8.6, 10.1, 17.5 Hz) and a multiplet at 5.28-5.35 ppm (2 H) were observed in accordance with the side chain at C-3 as shown in **56**. The anomeric proton and H-2 were resonated as two doublets at 5.61 (1 H, J = 4.1 Hz) and 5.04 ppm (1 H, J = 3.9 Hz) respectively. ^{13}C NMR spectrum of **56** showed the resonances at 171.0 (–CO–), and at 119.6 and 130.0 ppm for olefinic carbons.

The assignment of stereochemistry of newly generated chiral centers in **56** was made based on single crystal X-ray crystallographic studies.[51] The ORTEP diagram of **56** (Figure

1) revealed the *anti* configuration of tertiary OH and the ethene moiety of the side chain. The details of crystal data and structure refinement (Table 1), bond lengths and bond angles (Table 2) are given at the end of this section (Page No. 100 to 102).

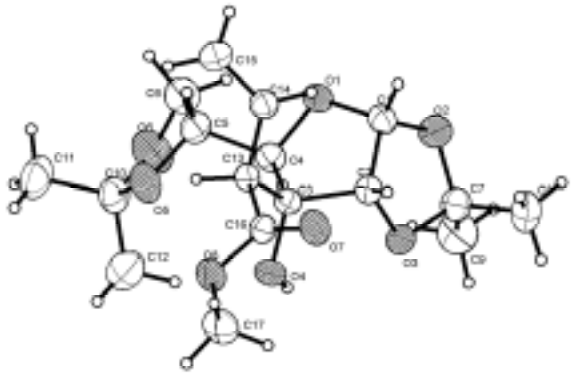


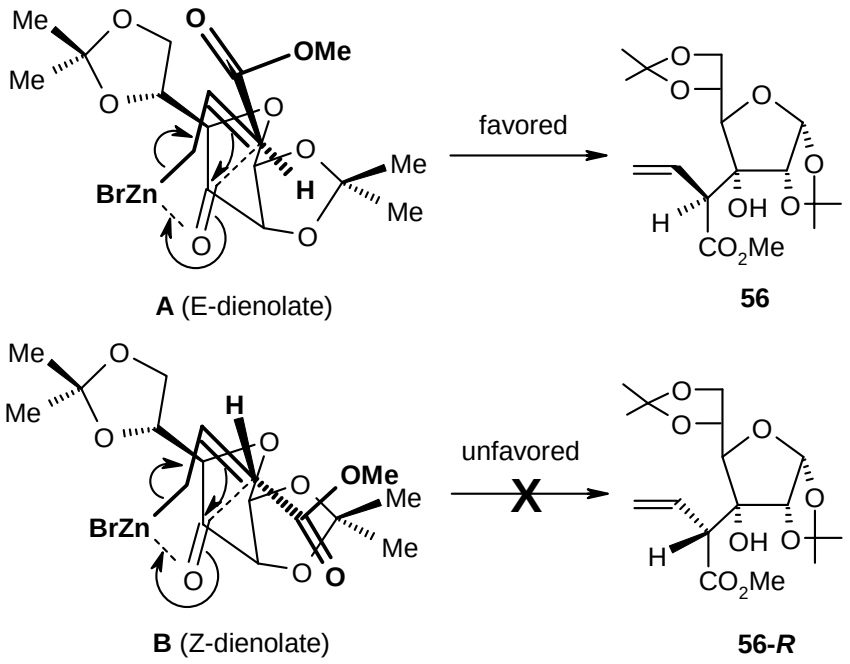
Figure 1: ORTEP diagram of 56

The exclusive formation of *anti* product can be explained as depicted in Scheme 25. It is apparent that the geometry of metal enolate participating in reaction decides the stereochemistry of resulting product. In general, the reactions involving *Z*-enolates will give *syn* products and *E*-enolates in the generation of *anti* products.[52] The exclusive formation of *anti* product **56** is due to the *E*-dienolate of Zn (transition state **A**) mediated Reformatsky reaction. The non-formation of *syn* adduct **56-*R*** might be because of the possible crowding between carbomethoxy moiety of *Z*-dienolate and 1,2-*O*-isopropylidene group (transition state **B**).

The structure of γ-product **57** was assigned based on ^{1}H NMR, ^{13}C NMR and mass spectra data. In the ^{1}H NMR spectrum of γ-product **57**, carbomethoxy moiety resonated as singlet at 3.75 ppm, and the olefinic protons were resonated as a doublet and a doublet of doublet of doublet at 5.94 (J = 15.8 Hz) and 7.10 ppm (J = 5.4, 8.8, 15.8 Hz) respectively. *Trans* configuration of olefin was confirmed through the large coupling constant values of the

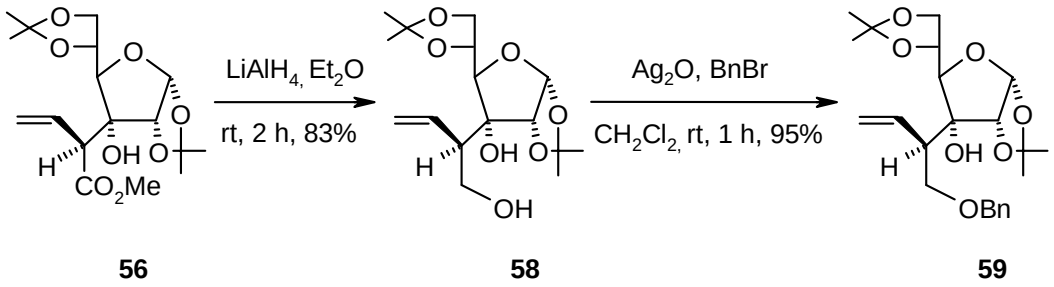
protons. Presence of suitable resonances at 124.7, 143.1 and 166.3 ppm in ^{13}C NMR spectrum of **57** further supported the assigned structure.

Scheme 25



The excellent stereoselectivity obtained in the vinylogous Reformatsky reaction of **3** prompted us to construct the bicyclic ring system through ring closing metathesis reaction of suitable diene derivative. Thus, the compound **56** was treated with $LiAlH_4$ in anhydrous diethyl ether at room temperature to afford the diol derivative **58** in good yield. The absence of relevant resonances of carbomethoxy moiety was evidenced by both ^1H NMR and ^{13}C NMR spectra of **58**. In the ^1H NMR spectrum of **58**, protons due to reduction of carbomethoxy moiety were resonated as multiplet at 3.68–3.90 ppm. Selective protection of primary hydroxyl functionality of **58** as benzylic ether was accomplished by treating **58** with benzyl bromide in the presence of a mild base, Ag_2O to yield **59** in 95% yield.[53] The ^1H NMR spectrum of **59** indicated the corresponding resonances at 4.46–4.55 ppm (m, CH_2 of Ph-CH_2) and at 7.26–7.42 (m, Ph of Ph-CH_2) supporting the presence of benzylic ether moiety (Scheme 26).

Scheme 26

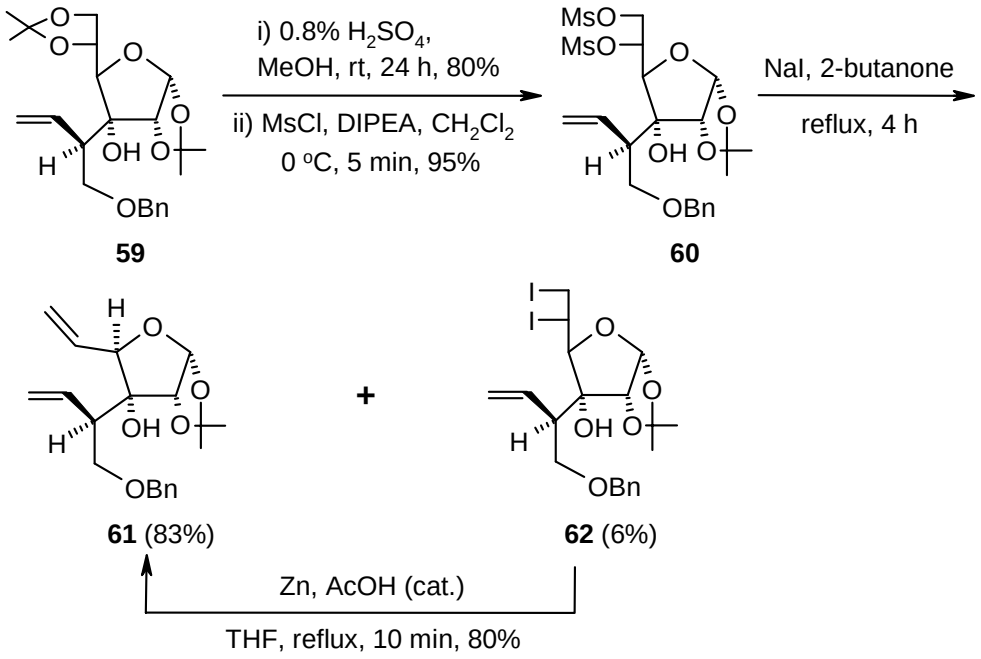


56 **58** **59**

Selective hydrolysis of the 5,6-*O*-isopropylidene group of **59** was carried out by treating the compound **59** with 0.8% H_2SO_4 in MeOH at ambient temperature for 24 h to afford triol derivative, and the subsequent selective activation of C-5 and C-6 hydroxyl moieties as their corresponding mesylate esters to afford **60** was successfully achieved by treating with MsCl and DIPEA at 0 ^oC for 5 min, as the triol derivative was susceptible to trimesylation on longer duration which would pose problems in next step. In the ^1H NMR spectrum of **60**, the two singlet resonances integrating for three protons each at 3.06 and 3.13 ppm, due to mesyl groups were observed.

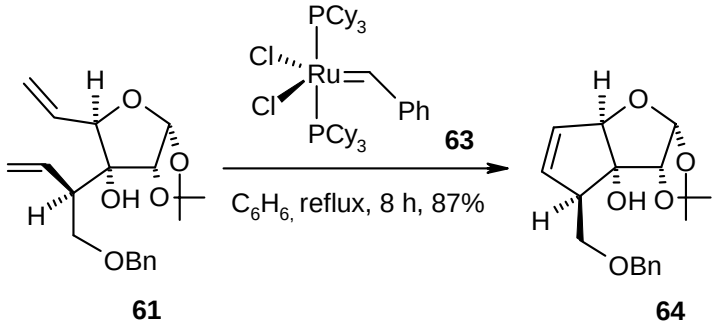
The dimesylate derivative **60** on subjecting to iodide mediated elimination using NaI in refluxing 2-butanone gave diene derivative **61** in 83% yield,[54] and 5,6-diiodo substituted compound **62** in 6%. In the ^1H NMR spectrum of **61**, the 5,6-ene protons resonated together with the olefinic protons of C-3 side chain at 5.09–5.46 (m, 4 H) and at 5.70–6.00 ppm (m, 2 H). The formation of the 5,6-diiodo substituted compound **62** was evidenced by both ^1H NMR and ^{13}C NMR spectral studies. The ^1H NMR spectrum of **62** revealed the downfield shift of both the protons of C-6 at 3.33 (dd, J = 5.4, 10.4 Hz) and at 3.56 ppm (dd, J = 2.5, 10.4 Hz), and the proton of C-5 at 3.74–3.86 ppm (m) compared to their counterparts in **60**. In the ^{13}C NMR spectrum of **62**, the resonances corresponding to C-6 and C-5 were observed at 14.9 (C-6) and 67.1 ppm (C-5) further supporting the assigned structure of **62**. In general, the 5,6-diido substituted compound **62** could be obtained in low temperatures, but surprisingly, it was formed at reflux conditions also as a minor product. To our delight, de-iodination of **62** in the presence of Zn and AcOH (cat.) in boiling THF readily underwent to furnish the diene derivative **61** in 80% yield (Scheme 27).[55]

Scheme 27



After having synthesized the diene derivative **61**, our next endeavor was to apply the ring closing metathesis reaction[56] to achieve the synthesis of bicyclic intermediate **64**. Thus, the diene **61** was treated with 4 mol% of Grubbs' 1st generation catalyst (**60**) in refluxing benzene to afford the bicyclic intermediate **64** in 87% yield. The ^{1}H NMR spectrum of **64** indicated the resonances pertaining to olefinic protons at 5.85 (dt, 1 H, J = 5.9, 2.1 Hz) and 5.89 ppm (dd, 1H, J = 2.1, 5.9 Hz) in support of the structure of **64** (Scheme 28).

Scheme 28



The assigned stereochemistry of **64** was further proved unambiguously based on NOE studies. Strong NOE interactions were observed between bridgehead OH – H_8, H_8 – H_{11} and bridgehead OH – H_{11} (Figure 2).

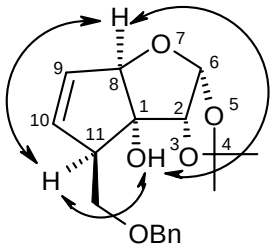


Figure 2: NOE studies on 64

Synthesis of some novel biyclic nucleosides

The design of conformationally restricted nucleosides is a very important approach towards potentially antiviral agents and monomers in conformationally restricted oligonucleotides for potential antisense therapeutic and diagnostic purposes.[57] Anticipating the better biological activity, many useful strategies for modification of naturally occurring nucleosides have been developed in the recent past, and the quest for more analogues is still in progress. In particular nucleoside analogues with bicyclic carbohydrate moieties have been designed as potential antiviral agents. Due to the decrease in conformational freedom introduced by the bicyclic nucleosides, these oligonucleotides have displayed very promising results as compounds with improved recognition of complementary RNA and DNA sequences.[58] Leumann and coworkers introduced the concept of bicyclic oligonucleotides by synthesizing the several bicyclic nucleosides and incorporating them into oligonucleotides.[59] Since then numerous approaches for variety of bicyclic sugar nucleosides have been appeared in the literature.[60] Recently, Nielson and coworkers have synthesized various bicyclic nucleoside analogues from diacetone-D-glucose and carried out extensive studies on their ability to incorporate into oligonucleotides.[18b,18d]

AZT (3'-azido-2',3'-dideoxythymidine), Dideoxyinosine (ddI), Dideoxycytidine (ddC), β-fluorodideoxyadenosine (β-FddA), Stavudine, Carbovir, and Abacavir are the important nucleoside based drugs, which are being used against AIDS. Carbovir and its analogue, Abacavir are the most promising carbonucloeside analogues in that dimension. As part of our

interest toward the synthesis of novel nucleosides[17b] we have designed a new synthetic strategy, so that we could incorporate the carbovir carbocyclic into the uridine skeleton, and thereby leading to new series of nucleoside analogues. Since we have had the bicyclic compound **64** in hand, we focused our attention towards the synthesis of some novel bicyclic nucleosides by introducing pyrimidine bases at the anomeric center, as it represents the combined structure of Carbovir carbocycle and sugar backbone of uridine. For that endeavor we have taken up three strategies taking different bicyclic compounds derived from **64**.

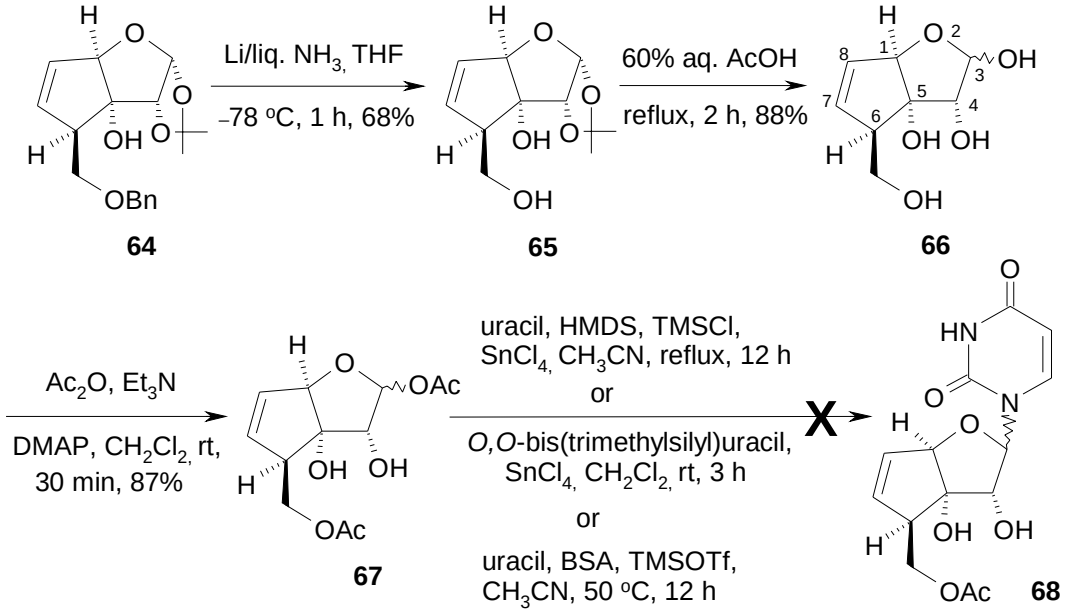
Strategy I

In an attempt to retain the double bond of bicyclic intermediate **64** for further functionalization, the benzylic ether of **64** was cleaved in the presence of Li/liq. NH_3 at –78 ^oC to afford debenzylated compound **65**.[61] In the ^1H NMR spectrum of **65**, the anomeric proton resonated together with olefinic protons as a multiplet at 5.86–6.02 ppm, and the proton resonances due to hydroxy methyl moiety were appeared as a multplet at 3.37–3.52 (m, 1 H) and a doublet at 3.68 ppm (1 H, J = 5.2, 11.7 Hz). The treatment of **65** with boiling 60% aq. AcOH resulted in the deprotection of acetonide moiety to give tetrol **66**. The ^1H NMR spectrum of **66** showed the resonances at 5.92–6.04 (m, 2 H, H-7 & H-8), 4.98 (s, 1 H, H-3), 4.44 (d, 1 H, J = 2.5 Hz, H-1), 4.10 ppm (br s, 1 H, H-4) in support of the structure (***Note:*** Numbering was adopted based on the bicyclic system, irrespective of sugar skeleton and henceforth same has been followed through out this chapter). Conventional acetylation of tetrol **66** with Ac_2O and DMAP (cat.) using DIPEA as a base obtained di-acyl derivative **67**. Surprisingly, no tetra-acyl derivative formation was detected even after longer reaction times and with using strong base such as Et_3N. This anomaly might be due to the possible hydrogen bonding between the carbonyls of acyl groups and the hydroxyl groups present in their vicinity. The presence of two singlets integrating each for three protons at 2.09 and 2.12 ppm in the ^1H NMR spectrum of **67** indicated the presence of two acyl groups in support of the assigned structure. In an attempt to bring the above two-step sequence into one step, we have carried out the deprotection of 1,2-*O*-isopropylidene moiety and concomitant acetylation by Reist-Goodmann method[62] using Ac_2O, AcOH and H_2SO_4 but it turned out to be a poor yielding transformation.

Though we could not get tetra-acyl derivative, which would be the ideal precursor for next reaction, we were interested to study the feasibility of coupling of the pyrimidine base

with di-acyl derivative **67**. Thus, the modified Hilbert-Johnson coupling reaction[63] of **67** with uracil in the presence of HMDS, TMSCl and $SnCl_4$ in refluxing anhydrous CH_3CN was tried. Unfortunately, this reaction was resulted in the formation of a mixture of products making the isolation and characterization of the products impossible. Considering the above difficulties, we changed our approach toward the other similar transformation, the Vorbrüggen-type coupling reaction.[64] As a first step towards this proposition, *O,O*-bis(trimethylsilyl)uracil was prepared employing the literature procedure.[65] Accordingly, the mixture of uracil and HMDS in anhydrous DMF was refluxed for 24 h and distilled under vacuum to give pure *O,O*-bis(trimethylsilyl)uracil. Then, the Vorbrüggen-type coupling reaction of diacetate **67** was carried out with *O,O*-bis(trimethylsilyl)uracil and $SnCl_4$, but it too gave the similar results like earlier reaction. The modified Vorbrüggen-type coupling reaction[66] of diacetate **67** using uracil, *N,O*-bis(trimethylsilyl)acetamide (BSA) and TMSOTf was also failed to progress smoothly and gave mixture of products (Scheme 29).

Scheme 29



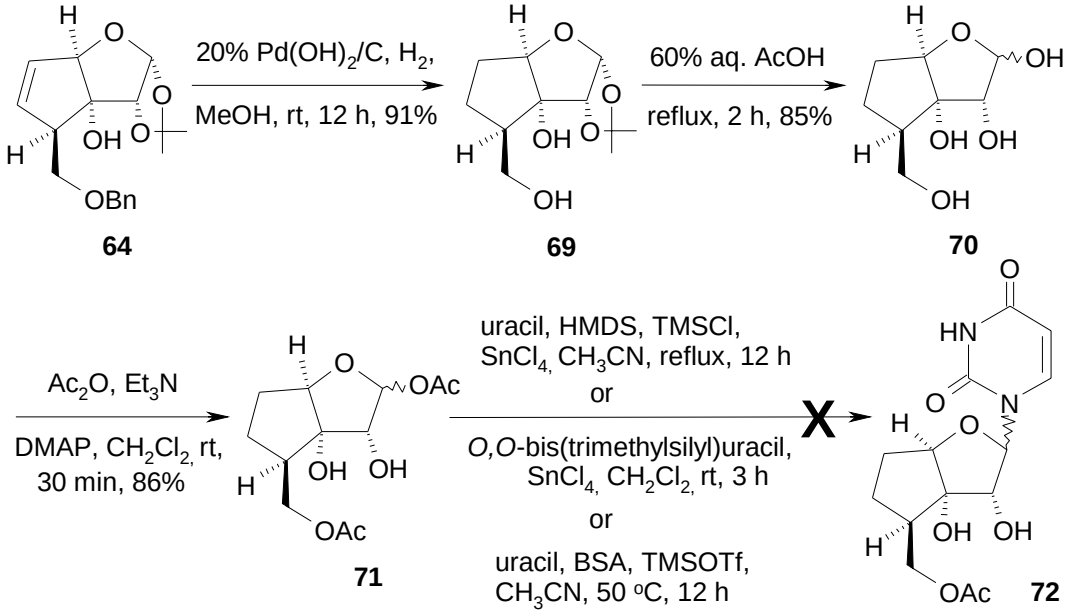
Strategy II

After all of these foregoing failed efforts, we wanted to examine our second strategy, which involved the use of saturated bicyclic compound **64** for coupling with uracil to construct the bicyclic nucleosides. Catalytic hydrogenation of the compound **64** in the

presence of 20% $Pd(OH)_2/C$ in MeOH at normal temperature and pressure resulted both in the reduction of olefinic double bond and breakage benzylic ether linkage to provide **69**. The ^1H NMR spectrum of **69** revealed the characteristic resonances at 1.72–1.93 (m, 4 H), 4.22 (d, 1 H, J = 2.3 Hz), 4.72 (d, 1 H, J = 3.8 Hz), 5.79 ppm (d, 1 H, J = 3.8 Hz). Subjecting the compound **69** to acidic hydrolysis using 60% aq. AcOH deprotected the acetonide moiety to give tetrol derivative **70**, whose ^1H NMR spectrum showed the resonances at 5.13 (s, 1 H, H-3), 4.10–4.25 ppm (m, 2 H) supporting the deprotection of acetonide group. Similarly, the tetrol **70**, on treatment with Ac_2O, Et_3N and DMAP (cat.) in anhydrous CH_2Cl_2 afforded the di-acyl derivative **71**. In the ^1H NMR spectrum of **71**, two singlet resonances integrating each for three protons at 2.07 and 2.11 ppm were observed in accordance of two acyl moieties. The downfield shift in the resonances relating to H-3 and hydroxymethyl group located at C-6 supported the assigned structure of **71**.

Treatment of **71**, under modified Hilbert-Johnson conditions,[63] with uracil, HMDS, TMSCl and $SnCl_4$ in refluxing anhydrous CH_3CN resulted in the mixture of products, similar to our earlier strategy. Subjecting the di-acyl derivative **71** to Vorbrüggen-type coupling[64] reaction and it's modified version again failed to achieve the desired nucleoside derivative **71** (Scheme 30).

Scheme 30

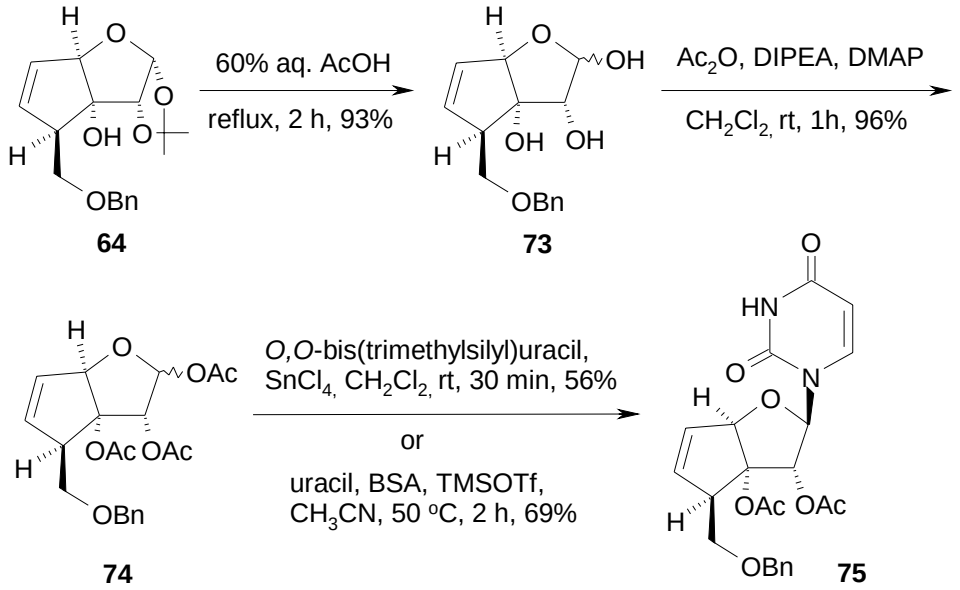


Strategy III and Results

The setbacks encountered in our earlier strategies forced us to rethink our strategy. In that direction, we sought a modification to synthesize the suitable nucleobase acceptor. Considering the above difficulties in making tetra-acyl derivative, we have decided not to disconnect the benzylic ether linkage as well as olefinic double bond of bicyclic intermediate **64** prior to coupling with nucleobase. Hence, **64** was first converted into triol **73** and then tri-acyl derivative **74**. Thus, the deprotection of acetonide moiety was carried out in refluxing 60% aq. AcOH followed by the conventional acetylation with Ac_2O, DIPEA and DMAP (cat.) accomplished **74** as an inseparable anomeric mixture of α- and β-isomers in good yield. The ^1H NMR spectrum of **74** showed three virtual singlets at 2.01, 2.09 and 2.13 ppm in evidence of three acyl groups. The downfield shift in resonances of H-3 and H-4 was attributed to the presence of acyl groups. It was further supported by ^{13}C NMR spectrum of **74**, which had the relevant resonances at 168.6, 169.0 and 169.6 ppm for the carbonyls of acyl moieties.

We envisaged that the Vorbrüggen-type coupling reaction[64] of tri-acyl derivative **74** with *O,O*-bis(trimethylsilyl)uracil would transform into the desired nucleoside derivative **75** without any complications. Thus, the compound **74** was condensed with *O,O*-bis(trimethylsilyl)uracil using $SnCl_4$ as a Lewis acid in anhydrous CH_3CN or CH_2Cl_2 at room temperature to afford the β-product **75** in 56% yield (Scheme 31).

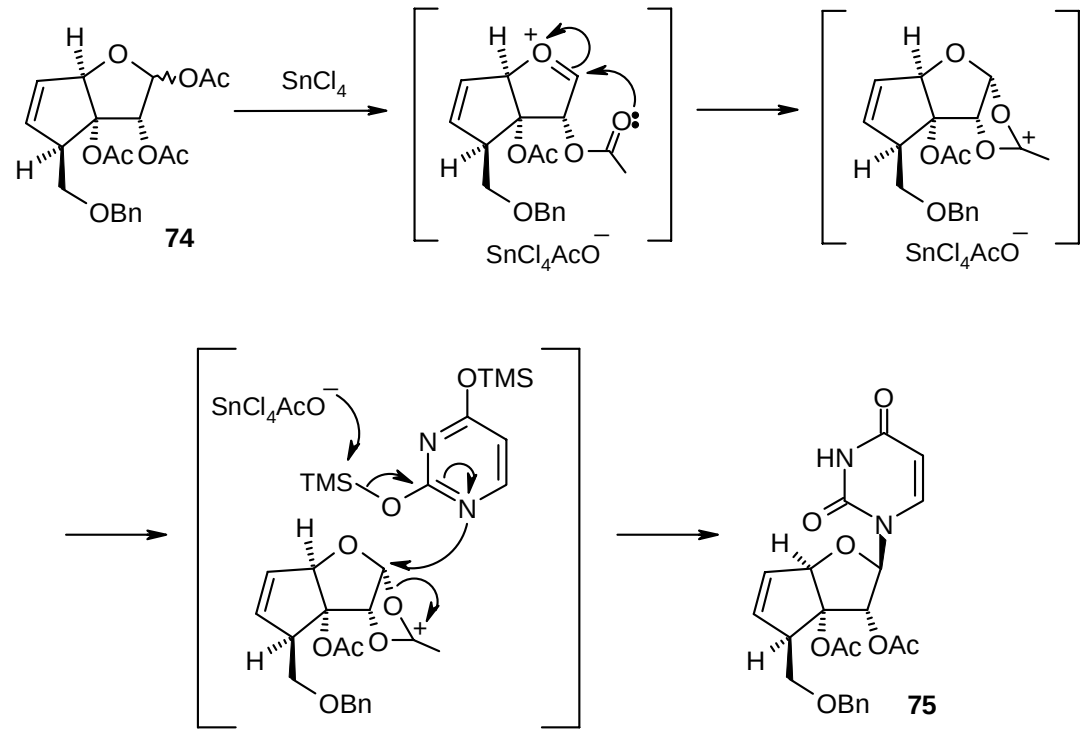
Scheme 31



The ^{1}H NMR spectrum of **75** was in full accordance with the assigned structure. The singlets integrating each for three protons at 2.02 and 2.15 ppm were appeared due to two acyl moieties. The two doublets at 6.17 (J = 7.7 Hz) and 7.08 ppm (J = 7.7 Hz) integrating each for one proton were attributed to uracil moiety. The amine proton (NH) present preferably in its tautomeric enol form resonated at 9.62 ppm as a broad singlet and the anomeric proton resonated as multiplet together with olefinic protons of sugar moiety. Gratifyingly, the application of modified Vorbrüggen-type coupling method[66] to condense the triacetate **74** with uracil in the presence of *N,O*-bis(trimethylsilyl)acetamide (BSA) and TMSOTf in anhydrous CH_3CN at 50 ^oC cleanly underwent to afford the β-product **75**, in an improved yield of 69%.

The exclusive formation of the β-product **75** can be explained by the participation of the neighboring acyl group at 4th position (anchimeric assistance). The mechanism of the coupling reaction can be visualized as in Scheme 32.[66b]

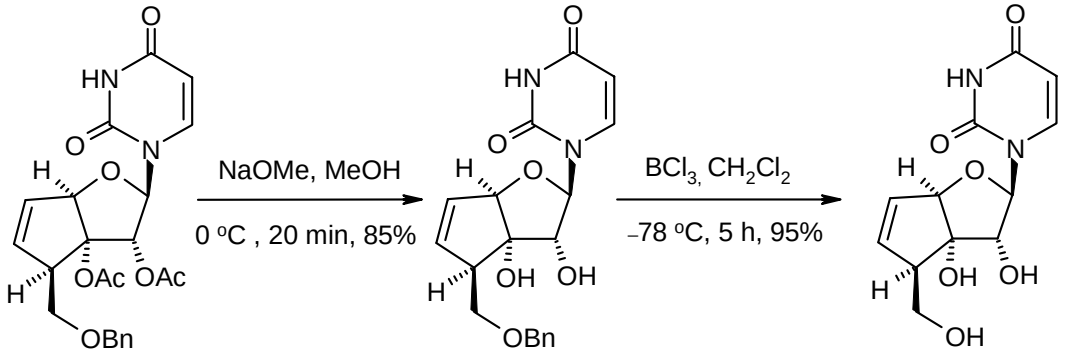
Scheme 32



After successful condensation of tri-acyl derivative **74** with uracil, our next task was the removal of the protecting groups of **75** to deliver the naked nucleosides. In that direction, we have opted for two different synthetic sequences and ended up with two nucleoside analogues.

De-acetylation of **75** under Zemplén conditions[67] using NaOMe in MeOH at 0 ^{o}C provided the compound **76** in quantitative yield. The absence of corresponding resonances to acyl groups was evidenced both in ^{1}H NMR and ^{13}C NMR spectrum of **76**. For the cleavage of ether linkages with retention of the olefinic double bond, various reagents such as LiDBB, Li/liq. NH_3, BCl_3, BBr_3, TMSI, etc. have been reported in the literature.[68] BCl_3 is widely used in nucleoside chemistry because of its ready availability, easy handling and simple workup. Hence, the compound **76** was treated with 1M solution of BCl_3 at –78 ^{o}C to afford **77** in excellent yield. In the ^{1}H NMR spectrum of **77**, the olefinic protons corresponding to uracil moiety were resonated as two doublets at 5.92 and 7.42 ppm (J = 8.1 Hz), and the enol proton (NH) resonated as a sharp singlet at 11.35 ppm. The rest of the protons had the expected chemical shifts confirming the assigned structure of **77** (Scheme 33).

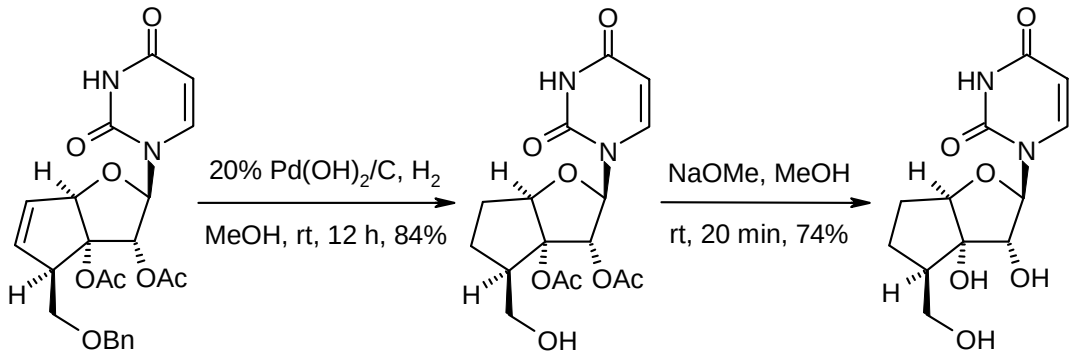
Scheme 33



Alternatively, hydrogenation of the compound **75** in the presence of 20% $Pd(OH)_2/C$ in MeOH under normal temperature and pressure provided **78** in quantitative yield. In the ^{1}H NMR spectrum of **78**, a multiplet integrating for four protons resonated at 1.89–1.98 ppm supporting the reduction of olefinic double bond. Treating the compound **78** with NaOMe in MeOH (Zemplén condition) at room temperature delivered the nucleoside **79** in 74% yield whose structure was supported by ^{1}H NMR and ^{13}C NMR spectral data together with

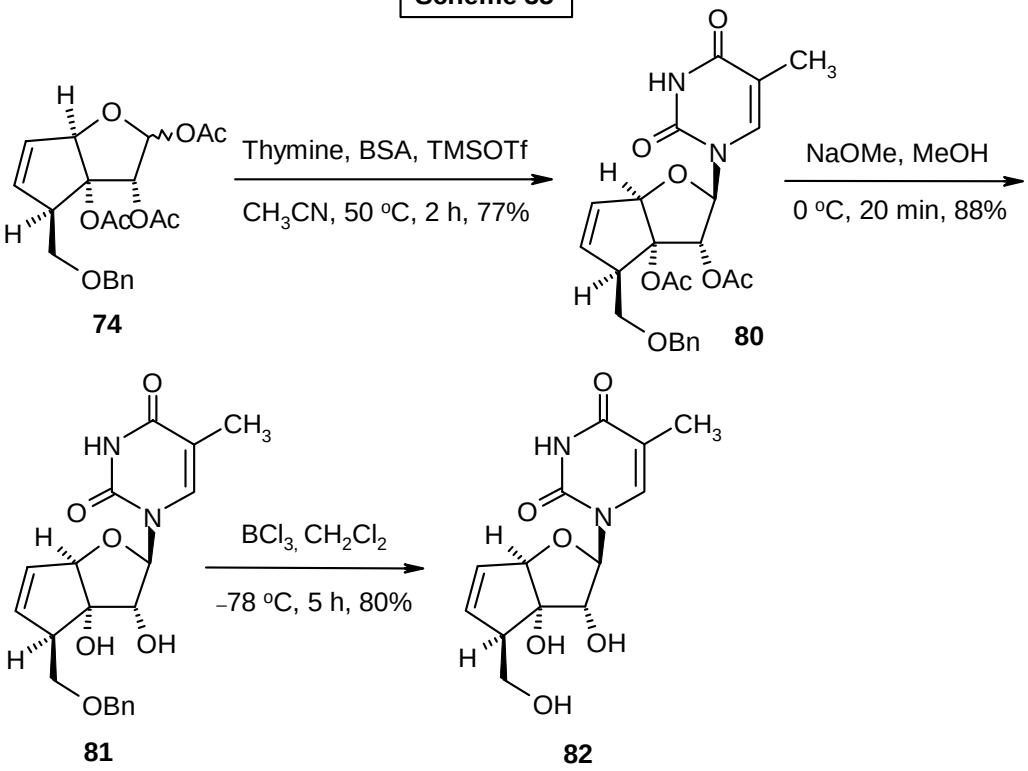
combustion data. In the ^{1}H NMR spectrum of **79**, the upfield shift of H-4 resonance as doublet at 4.10 ppm (J = 6.7 Hz) compared to its precursor **78** was observed. The two doublets integrating each for one proton resonated at 5.66 (J = 8.1 Hz) and 7.7 ppm (J = 8.1 Hz) were assigned to olefinic protons of uracil moiety. The rest of the protons had the expected chemical shifts (Scheme 34).

Scheme 34



The successful synthesis of uracil incorporated novel nucleoside analogues **77** and **79** through an elegant sequence of reactions prompted us to study the condensation with thymine by following the same reaction sequences. This transformation and subsequent functionalization would lead to two more novel nucleoside analogues. For this endeavor, we have chosen a straightforward synthetic sequence using modified Vorbrüggen-type coupling reaction,[66] as it was more promising in terms of yields in our earlier approach. Accordingly, the tri-acyl derivative **74** was condensed with thymine in presence of BSA and TMSOTf in anhydrous CH_3CN at 50 ^oC to furnish the β-nucleoside derivative **80** in 77% yield. The ^{1}H NMR spectrum of **80** showed a sharp singlet resonance integrating for three protons at 1.61 ppm (Me), a doublet and a broad singlet integrating each for one proton at 7.08 (J = 1.3 Hz), and 9.22 ppm (NH) confirming the condensation of thymine moiety. The anomeric proton (H-3) resonated as doublet at 6.24 ppm (J = 7.7 Hz) and rest of the protons had expected chemical shifts. The small coupling constant (J = 7.7 Hz) supported the β-linkage of thymine moiety (Scheme 35).

Scheme 35

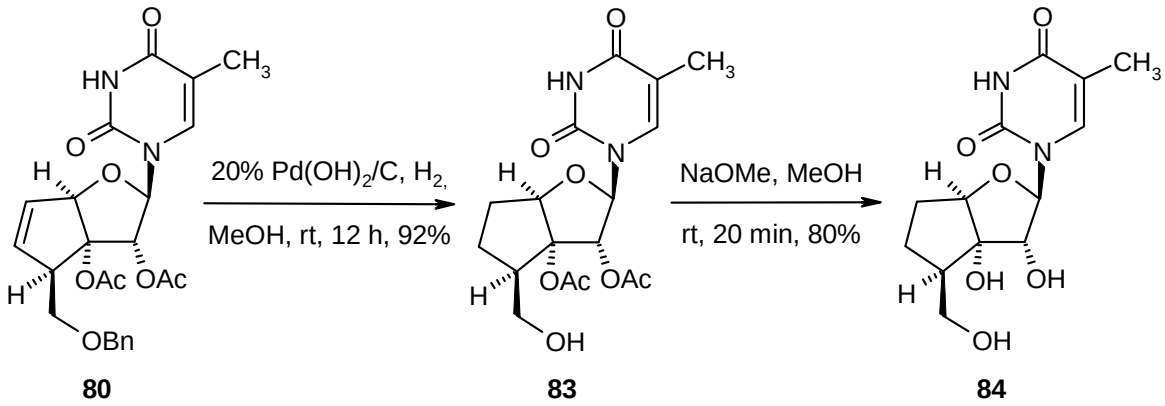


Having had the β-nucleoside derivative **80** in hand, our immediate concern was to utilize the same sequence of reactions, as in the case of uracil based nucleosides, to achieve the respective thymine based nucleosides. Under standard Zemplén reaction conditions,[67] the β-nucleoside derivative **80** was treated with NaOMe in MeOH at 0 ^{o}C to furnish de-acetylated product **81**. In the ^{1}H NMR spectrum of **81**, the significant upfield shift in the resonance of H-4 (at 4.23 ppm as doublet) compared to its precursor (at 5.88–5.99 ppm as multiplet) was observed. Lewis acid mediated cleavage of benzylic ether linkage was affected in the presence of 1M solution of BCl_3 in CH_2Cl_2 to furnish the nucleoside **82** in 80% yield. The ^{1}H NMR spectrum of **82** indicated characteristic singlets for thymine moiety at 1.80 (Me), 7.29 (H-2') and 11.34 ppm (NH). The resonances at 4.73 (s), 5.21 (d, J = 6.9 Hz) and 5.45 ppm (s) were attributed to three hydroxyl groups of **82** as all these resonances disappeared on deuterium exchange by adding two drops of the D_2O to DMSO-d6 solution of **82**.

Simultaneously, the compound **80** was hydrogenated over 20% $Pd(OH)_2$/C in MeOH under normal temperature and pressure to deliver the compound **83**, whose ^{1}H NMR spectrum confirmed the reduction of olefinic double bond and the reductive cleavage of benzylic ether

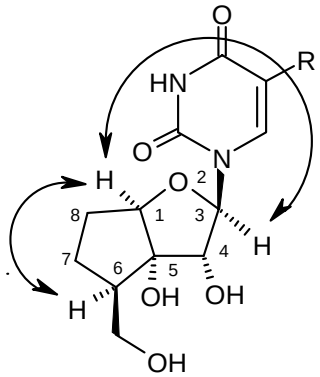
linkage. The proton resonances due to reduction of olefinic double bond appeared together as multiplet at 1.93–1.96 ppm. Finally, the de-acetylation of compound **83** was carried out under Zemplén conditions[67] using NaOMe in MeOH to provide the nucleoside **84** in good yield. In the ^{1}H NMR spectrum of **84**, the protons corresponding to thymine moiety were resonated as singlets at 1.82 (Me), 7.49 (H-2') and 11.32 ppm (NH). The anomeric proton was resonated as doublet at 5.65 ppm (J = 8.5 Hz). The resonances at 4.32 (t, J = 4.9 Hz), 4.97 (s) and 5.13 ppm (d, J = 6.9 Hz) were assigned to three hydroxyl groups based on the deuterium exchange experiment (Scheme 36).

Scheme 36



80 **83** **84**

The β-linkage of base moiety in the above-synthesized nucleosides was further supported by the NOE studies carried out on **79** and **84**. Strong NOE interactions between H-1 and H-3, and H-1 and H-6 were observed in support of the assigned structures of **79** and **84** (Figure 3).

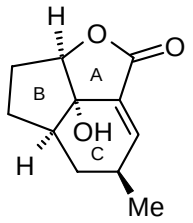


79: R = H
84: R = CH_3

Figure 3: NOE Studies

Synthetic studies toward galiellalactone

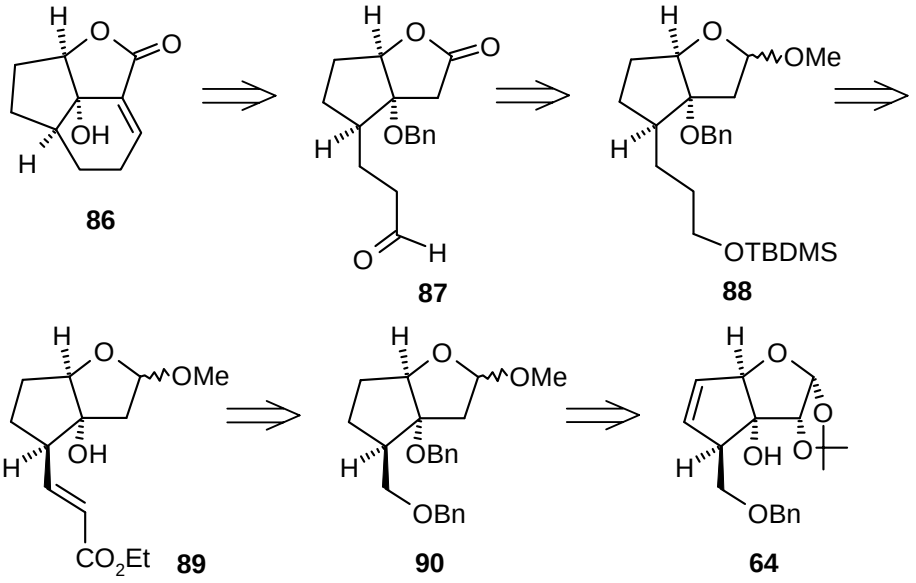
The fungal metabolite galiellalactone (**85**) is a potent and selective inhibitor of interleukin-6 (IL-6) signaling in HepG2 cells.[69] It was isolated from ascomycetes *Galiella rufa* strain A75-86 during a screening for plant growth regulators produced by fungi.[70] It was found to inhibit gibberillic acid-induced synthesis of α-amylase. Recently, Sterner and coworkers have reported the total synthesis of (+)-galiellalactone using (–)-pulegone as chiral starting material, and established the absolute configuration of the natural product as (–)-isomer.[71] We envisaged that the bicyclic intermediate **64** would serve as a potential synthetic intermediate towards the synthesis of (–)-galiellalactone as it is resembling the A and B rings of it with suitable stereochemistry.



Galiellalactone (**85**)

Our synthetic strategy towards galiellalactone is delineated in the retrosynthetic analysis (Scheme 37). We anticipated that the C-ring of galiellalactone could be constructed through intramolecular aldol reaction. For that endeavor, we have chosen two-carbon

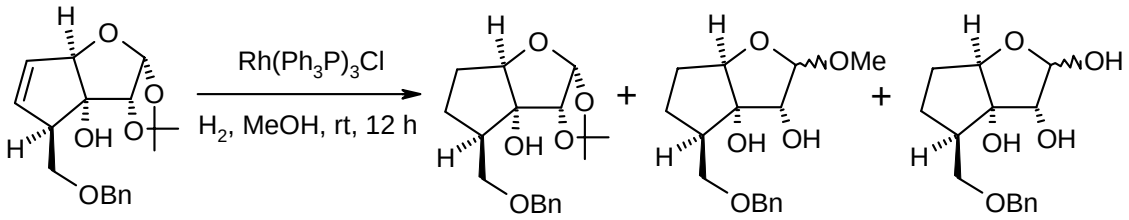
Scheme 37: Retrosynthetic analysis



homologation at hydroxymethyl moiety of bicyclic system followed by intramolecular aldol reaction to study the feasibility of the 6-membered ring formation. We envisaged that the precursor **87**, needed for intramolecular aldol reaction can be obtained from **88** by suitable functional group transformations. The compound **88** can be synthesized from the bicyclic intermediate **64** by conducting Barton-McCombie radical deoxygenation reaction followed by Wittig reaction.

Selective reduction of the double bond of **64** was attempted under hydrogenation conditions using Wilkinson's catalyst [$Rh(Ph_3P)_3Cl$] in MeOH at ambient temperature,[72] but it furnished a mixture of three products, **91**, **92** and **93** in 37%, 16% and 47% yields respectively. The ^{1}H NMR spectrum of **91** revealed the resonances corresponding to benzylic moiety as two multiplets at 4.48–4.61 (2 H) and 7.29–7.41 ppm (5 H). The protons resulted due to reduction of olefinic double bond appeared as multplet at 1.66–1.91 (4 H) and the rest of the protons had expected chemical shifts. The structure of **92** was assigned based on ^{1}H NMR and ^{13}C NMR spectral studies together with combustion data. In the ^{1}H NMR spectrum of **92**, a sharp singlet at 3.48 (3 H) and a multiplet at 1.26–1.97 ppm (4 H) were observed in accordance to the assigned structure of **92**. The ^{1}H NMR spectrum of **93** showed the relevant proton resonances at 5.29 (d, 1 H, J = 4.1 Hz, H-3), 3.90 (d, 1 H, J = 4.1 Hz, H-4) and 2.74–3.10 ppm (br s, 3 H, 3 OH) in support of the assigned structure, and rest of the protons had expected chemical shifts (Scheme 38).

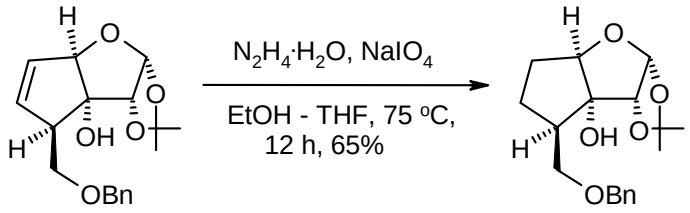
Scheme 38



64 **91** (37%) **92** (16%) **93** (47%)

Since hydrogenation of **64** in the presence of Wilkinson's catalyst resulted in the formation of mixture of products, we focused our attention towards diimide reduction.[73] Thus, **64** was treated with *in situ* generated diimide from $N_2H_4{\cdot}H_2O$ and $NaIO_4$ in a solvent mixture of EtOH-THF to afford **91** in 65% yield (Scheme 39).

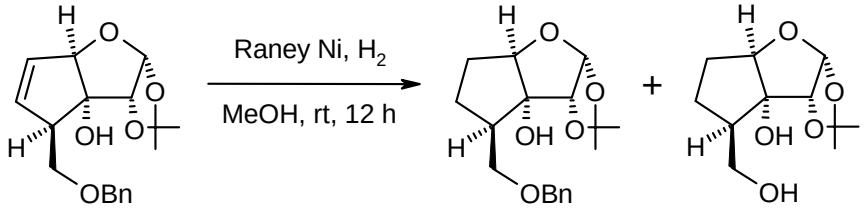
Scheme 39



64 **91**

Also, olefinic reduction can be conveniently conducted in the presence of Raney Ni and H_2 in MeOH at normal temperature and pressure. This reaction gave the compound **91** in 92% yield along with debenzylated product **69** in 6% yield. Although it was giving both **91** and **69**, the ease of separation and the improved yield of **91** prompted us to prefer this transformation for the reduction of olefinic double bond of **64** (Scheme 40).

Scheme 40

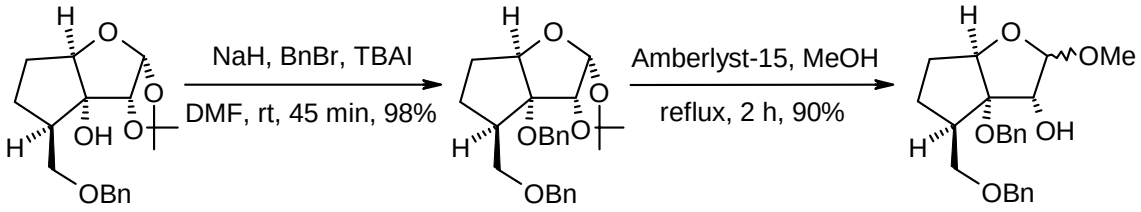


64 **91** (92%) **69** (6%)

The proposed intramolecular aldol reaction necessitated the deoxygenation of free hydroxyl group resulted after the cleavage of acetonide moiety and two-carbon homologation at hydroxymethyl moiety of bicyclic system. For that endeavor, the bridgehead hydroxyl group needs to be protected prior to the deoxygenation step. Thus, the protection of bridgehead hydroxyl moiety of **91** as benzylic ether was carried out using NaH and benzyl bromide in the presence of TBAI (cat.) in anhydrous DMF at room temperature to furnish dibenzylated compound **94** in 98% yield.[74] The ^{1}H NMR spectrum of **94** indicated the resonances relating to two benzylic moieties at 4.44–4.64 (m) and at 7.21–7.43 ppm (m, 10 H) in support of the structure of **94**. Refluxing **94** in MeOH in the presence of acidic resin, Amberlyst-15 resulted in the cleavage of acetonide moiety to furnish an α- and β-isomers of **95** in 1:1 ratio, which were separated by silica gel column chromatography. In the ^{1}H NMR

spectrum of **95** (α-isomer was taken for the sake of clarity in the spectra), a sharp singlet integrating for three protons was appeared at 3.43 ppm confirming the presence of methyl glycosidic linkage. The anomeric proton resonated as a doublet at 4.81 ppm (1 H, J = 4.3 Hz) (Scheme 41).

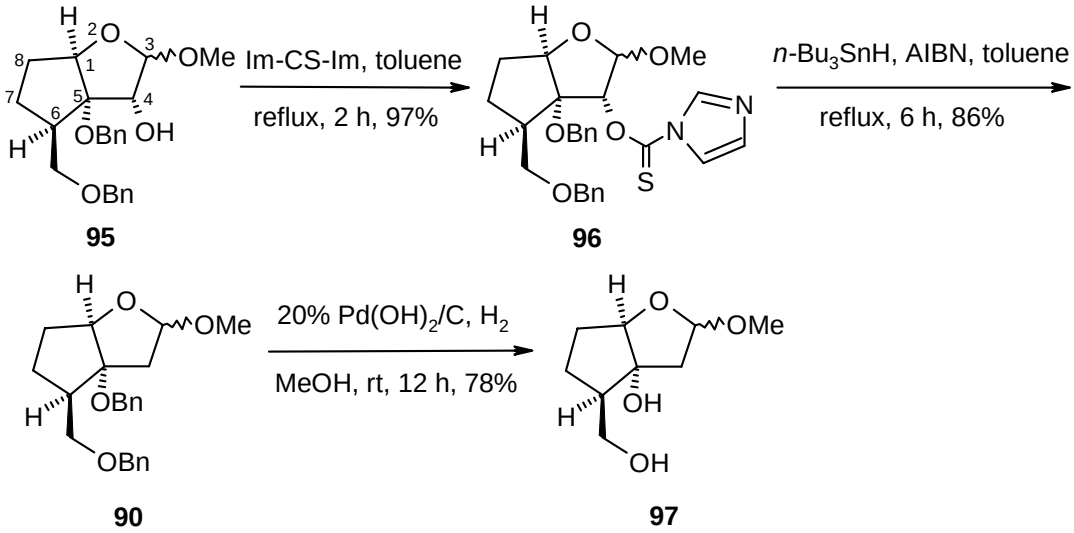
Scheme 41



91 **94** **95**

For achieving the deoxygenation of free hydroxyl group of **95**, first it need be converted into the corresponding xanthate derivative and then be subjected to Barton-McCombie radical deoxygenation reaction.[75] Accordingly, **95** was treated with thiocarbonyldiimidazole in refluxing toluene to give **96**, whose ^{1}H NMR spectrum showed three sharp singlet resonances each integrating for one proton at 6.91, 7.47 and 8.21 ppm in support of 4-(*N*-imidazolylthiocarbonyloxy) moiety. The appearance of resonance at 183.5 ppm in the ^{13}C NMR spectrum of **96** further supported the presence of 4-(*N*-imidazolylthiocarbonyloxy) moiety. Then **96** was subjected to Barton-McCombie radical

Scheme 42

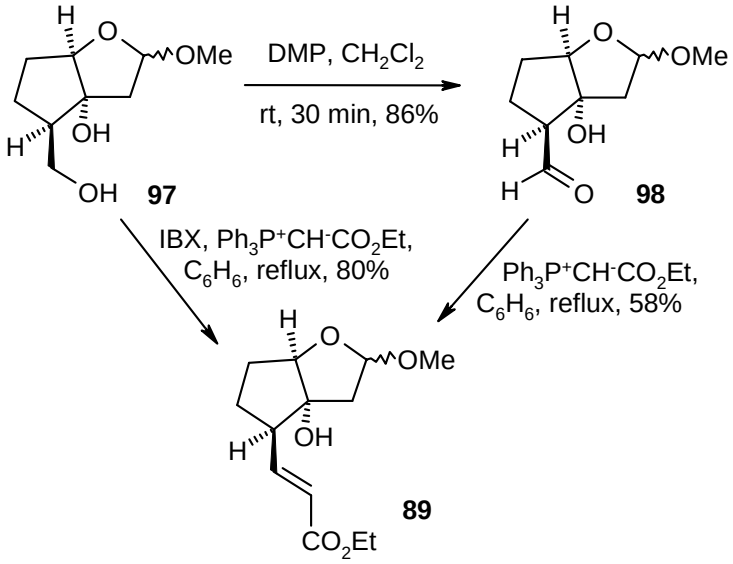


95 **96** **90** **97**

deoxygenation reaction with *n*-Bu_3SnH and AIBN (cat.) in refluxing toluene to obtain **90** in 86% yield. In the ^1H NMR spectrum of **90**, two double doublets integrating each for one proton were appeared at 2.12 (J = 0.9, 14.5 Hz) and 2.21 (J = 5.5, 14.5 Hz) due to deoxygenation. Hydrogenolysis of **90** in the presence of 20% $Pd(OH)_2/C$ in MeOH at normal temperature and pressure afforded **97**, whose structure was evidenced by the disappearance of resonances corresponding to benzylic groups in the ^1H NMR spectrum (Scheme 42).

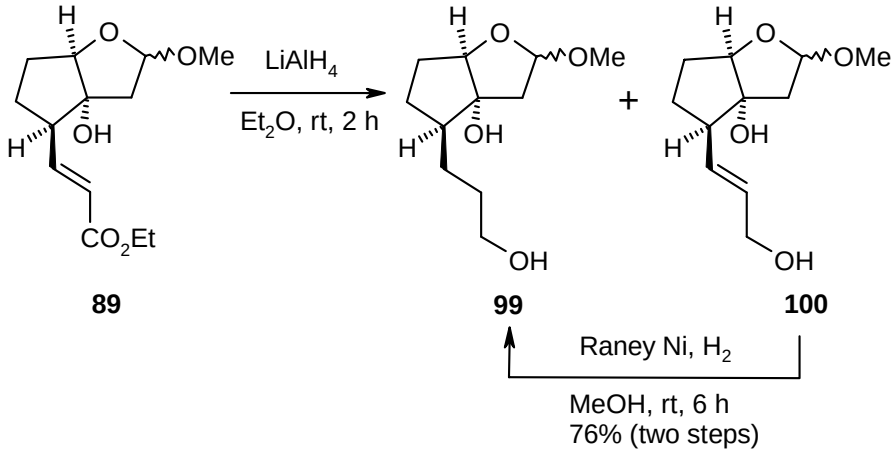
After having accomplished the deoxygenation of free hydroxyl group of **95** through **96**, our next concern was the two-carbon homologation at hydroxymethyl moiety of bicyclic intermediate **97**. Thus, **97** was oxidized using Dess-Martin periodinane (DMP)[76] in anhydrous CH_2Cl_2 at room temperature to afford an unstable aldehyde **98**, which was immediately treated with (ethoxycarbonylmethylene)triphenylphosphorane in refluxing benzene to obtain **89** in 58% yield. However, oxidation of primary hydroxyl group to aldehyde and Wittig olefination was successfully accomplished in one pot by using IBX and (ethoxycarbonylmethylene)triphenylphosphorane[77] in refluxing benzene to furnish **89** in 80% yield. The ^1H NMR spectrum of **89** revealed two double doublets at 5.88 (1 H, J = 1.6, 15.8 Hz) and 6.98 (1 H, J = 6.2, 15.8 Hz), a triplet at 1.30 (3 H, J = 7.1 Hz), and a quartet at 4.19 ppm (2 H, J = 7.1 Hz) in accordance to the structure of **89**. Further evidence came from its ^{13}C NMR and DEPT spectral data. In the ^{13}C NMR spectrum of **89** resonances at 122.7 and 146.5 ppm relating to olefinic double bond, and at 166.5 ppm corresponding to carbinyl group were observed (Scheme 43).

Scheme 43



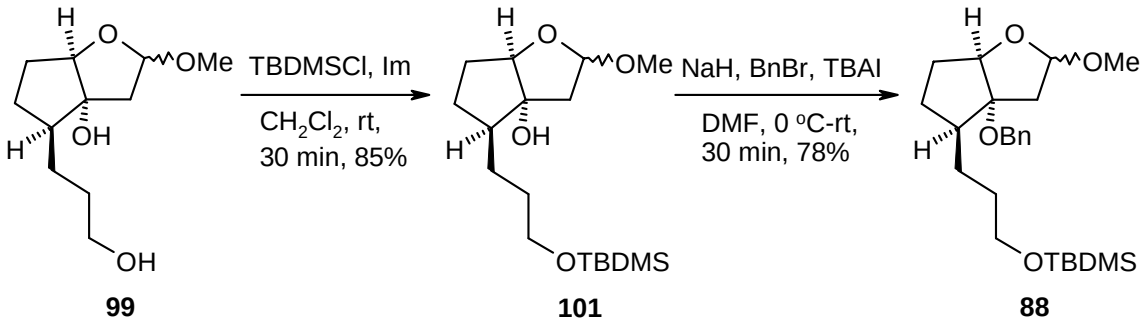
The reduction of **89** with $LiAlH_4$ in anhydrous ether gave inseparable mixture of compounds **99** and **100** in 1:2 ratio, which was evidenced by ^1H NMR and ^{13}C NMR spectral studies. Subjecting this mixture to hydrogenation in the presence of Raney Ni in MeOH at normal temperature and pressure provided **99** as a sole product. In the ^1H NMR spectrum of **99**, a multiplet integrating for 11 protons was appeared at 1.54–2.08 ppm supporting the reduction of olefinic double bond and the rest of the resonances were in full agreement with the structure of **99** (Scheme 44).

Scheme 44



The final intramolecular aldol reaction for the construction of six-membered ring necessitated the protection of bridgehead hydroxyl group to arrest its elimination in reaction conditions. Hence, the primary hydroxyl moiety of **99** was protected as its TBDMS ether[68,78] using TBDMSCl and imidazole in anhydrous CH_2Cl_2 to furnish **101**. In the ^1H NMR spectrum of **101**, protons corresponding to TBDMS group were resonated as two clear

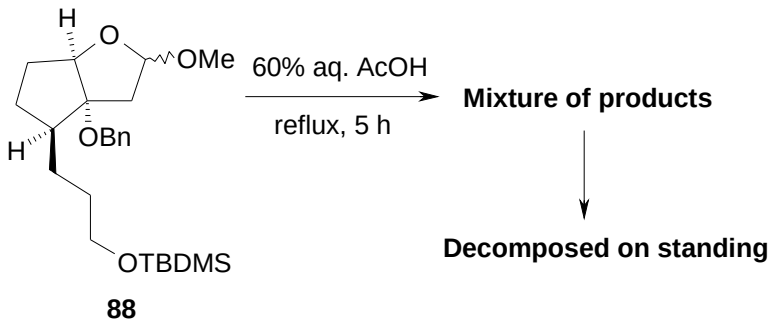
Scheme 45



singlets at 0.05 (6 H) and 0.89 ppm (9 H). And then the bridgehead hydroxyl group of **101** was protected as its benzylic ether[64] by using NaH, BnBr and TBAI (cat.) in anhydrous DMF to afford **88** in 78% yield. The ^{1}H NMR spectrum **88** revealed the two multiplets at 4.47–4.67 (3 H, resonated along with H-1) and at 7.23–7.38 (5 H) in accordance with benzylic moiety (Scheme 45).

In an attempt to cleave both the anomeric OMe and TBDMS ether of **88**, it was treated with boiling 60% aq. AcOH. Unfortunately, this proposition gave mixture of products and attempted purification of this mixture was failed due to the decomposition on standing (Scheme 46). Having encountered the failures at final stages of our synthetic strategy we decided to stop this route at this stage and the efforts for the construction of six-membered ring of galiellalactone through other routes are in progress in our laboratory.

Scheme 46



88

Conclusions

(a) The diastereoselective Reformatsky reaction of zinc dienolate, derived from methyl 4-bromocrotonate, with 3-ulose derivative **3** resulted in the generation of two new stereocenters. This diastereoselective transformation would definitely become an interesting topic to the synthetic chemists being involved in this field. (b) Ring closing metathesis reaction was applied on diene derivative **61** to form the bicyclic intermediate **64**. (c) We have developed an elegant synthetic route to novel bicyclic nucleosides having the structural framework of some carbocyclic nucleosides.[79] (d) We have also carried out the studies toward the synthesis of galiellalactone. (e) Because of the structural similarities, the bicyclic intermediate **64** would further be functionalized toward the synthesis of prostaglandins and jasmonoids. The biological activity of the novel bicyclic nucleosides is under study.

Crystal data and structure refinement for compound 56

Table 1

Identification code	shrini1
Empirical formula	$C_{17} H_{26} O_8$
Formula weight	358.38
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions	a = 19.534(7) Å alpha = 90º
	b = 9.901(4) Å beta = 90º
	c = 9.955(4) Å gamma = 90º
Volume	1925.3(12) $Å^3$
Z, Calculated density	4, 1.236 Mg/m^3
Absorption coefficient	0.098 mm^{-1}
F(000)	768
Crystal size	0.41 x 0.23 x 0.16 mm
Theta range for data collection	2.30 to 27.98 deg.
Limiting indices	–25<=h<=18, –9<=k<=12, –13<=l<=12
Reflections collected / unique	11092 / 4288 [R(int) = 0.0226]
Completeness to theta = 27.98	95.3 %
Absorption correction	Multi-scan
Max. and min. transmission	0.9850 and 0.9609
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4288 / 0 / 231
Goodness-of-fit on F^2	1.028
Final R indices [I>2sigma(I)]	R1 = 0.0491, wR2 = 0.1311
R indices (all data)	R1 = 0.0557, wR2 = 0.1370
Absolute structure parameter	–0.2(10)
Largest diff. peak and hole	0.542 and –0.249 e. $Å^{-3}$

Table 2: Bond lengths [Å] and angles [°] for Compound 56

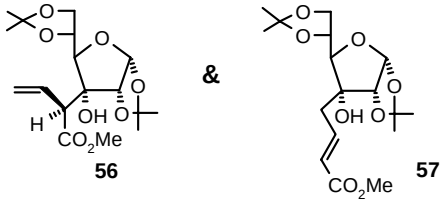
C1 O2 1.393 (3)
C1 O1 1.412 (2)
C1 C2 1.521 (3)
C2 O3 1.422 (2)
C2 C3 1.544 (3)
C3 O4 1.408 (2)
C3 C13 1.545 (3)
C3 C4 1.551 (3)
C4 O1 1.437 (2)
C4 C5 1.528 (3)
C5 O5 1.416 (3)
C5 C6 1.528 (3)
C6 O6 1.396 (3)
C7 O3 1.424 (3)
C7 O2 1.432 (3)
C7 C9 1.512 (4)
C7–C8 1.524 (4)
C10 O6 1.408 (3)
C10 O5 1.432 (3)
C10–C11 1.498 (4)
C10 C12 1.505 (4)
C13 C14 1.507 (3)
C13 C16 1.520 (3)
C14 C15 1.305 (3)
C16 O7 1.194 (2)
C16 O8 1.327 (2)
C17 O8 1.440 (3)
O2 C1 O1 112.19 (18)
O2 C1 C2 106.20 (16)
O1 C1 C2 107.33 (15)
O3 C2 C1 103.24 (15)
O3 C2 C3 107.20 (15)
C1 C2 C3 105.43 (15)
O4 C3 C2 111.67 (15)
O4 C3 C13 104.96 (15)
C2 C3 C13 114.04 (15)
O4 C3 C4 112.25 (15)
C2 C3 C4 99.85 (15)
C13 C3 C4 114.34 (15)
O1 C4 C5 106.80 (16)
O1 C4 C3 104.70 (15)
C5 C4 C3 117.93 (17)
O5 C5 C6 103.71 (18)
O5 C5 C4 110.05 (18)
C6 C5 C4 113.0 (2)
O6 C6 C5 102.9 (2)
O3 C7 O2 105.21(16)
O3 C7 C9 108.1(2)
O2 C7 C9 109.4 (2)
O3 C7 C8 110.4 (2)
O2 C7 C8 109.5 (2)
C9 C7 C8 113.8 (2)
O6 C10 O5 105.24 (19)
O6 C10 C11 114.2 (2)
O5 C10 C11 108.1 (2)
O6 C10 C12 107.2 (3)
O5 C10 C12 110.1 (2)
C11 C10 C12 111.7 (3)
C14 C13 C16 107.76 (16)
C14 C13 C3 115.88 (16)
C16 C13 C3 108.85 (15)
C15 C14 C13 123.9 (2)
O7 C16 O8 122.98 (18)
O7 C16 C13 124.79 (17)
O8 C16 C13 112.22 (16)
C1 O1 C4 109.05 (14)
C1 O2 C7 109.77 (16)
C2 O3 C7 108.10 (16)
C5 O5 C10 109.81 (17)
C6 O6 C10 109.2 (2)
C16 O8 C17 116.29 (17)
O2 C1 C2 O3 –16.4 (2)
O1 C1 C2 O3 103.82 (17)
O2 C1 C2 C3 –128.69 (17)
O1 C1 C2 C3 –8.5 (2)
O3 C2 C3 O4 36.1 (2)
C1 C2 C3 O4 145.59 (15)
O3 C2 C3 C13 154.85 (15)
C1 C2 C3 C13 –95.63 (18)
O3 C2 C3 C4 –82.77 (17)
C1 C2 C3 C4 26.74 (18)
O4 C3 C4 O1 –154.77 (15)
C2 C3 C4 O1 –36.35 (18)
C13 C3 C4 O1 85.81 (18)
O4 C3 C4 C5 86.7 (2)
C2 C3 C4 C5 –154.86 (18)
C13 C3 C4 C5 –32.7(2)
O1 C4 C5 O5 –173.06 (17)
C3 C4 C5 O5 –55.7 (2)
O1 C4 C5 C6 71.5 (2)

C3 C4 C5 C6 –171.1 (2)
O5 C5 C6 O6 –25.5 (3)
C4 C5 C6 O6 93.6 (3)
O4 C3 C13 C14 172.44 (15)
C2 C3 C13 C14 49.9 (2)
C4 C3 C13 C14 –64.1 (2)
O4 C3 C13 C16 50.84 (18)
C2 C3 C13 C16 –71.69 (19)
C4 C3 C13 C16 174.28 (15)
C16 C13 C14 C15 –109.5 (3)
C3 C13 C14 C15 128.3 (2)
C14 C13 C16 O7 –44.9 (3)
C3 C13 C16 O7 81.5 (2)
C14 C13 C16 O8 133.51 (17)
C3 C13 C16 O8 –100.08 (17)
O2 C1 O1 C4 100.57 (19)
C2 C1 O1 C4 –15.7 (2)
C5 C4 O1 C1 159.43 (16)
C3 C4 O1 C1 33.6 (2)
O1 C1 O2 C7 –116.70 (19)
C2 C1 O2 C7 0.3 (2)
O3 C7 O2 C1 16.0 (2)
C9 C7 O2 C1 132.0 (2)
C8 C7 O2 C1 –102.6 (2)
C1 C2 O3 C7 26.7 (2)
C3 C2 O3 C7 137.70 (16)
O2 C7 O3 C2 –27.1 (2)
C9 C7 O3 C2 –143.9 (2)
C8 C7 O3 C2 91.0 (2)
C6 C5 O5 C10 11.6 (3)
C4 C5 O5 C10 –109.6 (2)
O6 C10 O5 C5 6.7(3)
C11 C10 O5 C5 –115.7 (3)
C12 C10 O5 C5 121.9 (2)
C5 C6 O6 C10 31.1 (3)
O5 C10 O6 C6 –24.6 (3)
C11 C10 O6 C6 93.9 (3)
C12 C10 O6 C6 –141.8 (2)
O7 C16 O8 C17 –0.9 (3)
C13 C16 O8 C17 –179.36 (19)

Experimental Section

Experimental

3-*C*-[(*S*)-1-Carbomethoxy-prop-2-enyl]-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (56) and 3-*C*-(3-carbomethoxy-prop-2-enyl]-1,2:5,6-di-*O*-*i*sopropylidene-α-D-allofuranose (57)



To a suspension of activated Zn-Cu couple (40.0 g, 611.7 mmol) in anhydrous ether (140 mL) were added iodine (50 mg), methyl 4-bromocrotonate (1 mL of total 29 mL, 247 mmol) and an ether solution of **3** (1 mL of 50 ml of ether containing 40.0 g, 155.0 mmol). After 10 min at room temperature the reaction set in as evident by the disappearance of iodine coloring and onset of gentle reflux. The reaction mixture was then heated to reflux, and rest of the ether solution of **3** (49 mL) and methyl 4-bromocrotanate (28 mL) were added successively over a period of 30 min, and the reflux continued for additional 30 min. After completion of the reaction monitored by tlc, reaction mixture was cooled to room temperature, poured over saturated NH_4Cl (40 mL), the organic layer was separated, washed with brine, dried (Na_2SO_4), and concentrated. The residue was chromatoghraphed on silica gel by using EtOAc–light petroleum (1:7) as an eluent to give **56** (28.9 g**,** 52%) as colorless crystals.

mp: 88–90 ^{o}C.

$[\alpha]_D$ –42.5 (*c* 1, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37, 1.45, 1.58 (3 s, 12 H), 3.32 (s, 1 H), 3.74 (s, 3 H), 3.78–3.81 (m, 2 H), 3.87 (dd, 1 H, *J* = 5.1, 8.8 Hz), 4.08–4.12 (m, 1 H), 4.21 (dt, 1 H, *J* = 9.1, 5.6 Hz), 5.04 (d, 1 H, *J* = 3.9 Hz), 5.28–5.35 (m, 2 H), 5.61 (d, 1 H, *J* = 4.1 Hz), 5.83 (ddd, 1 H, *J* = 8.6, 10.1, 17.5 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 24.9, 26.0, 26.2, 51.3, 51.4, 67.9, 72.2, 79.5, 79.6, 82.9, 103.5, 109.3, 111.6, 119.6, 130.0, 171.0.

EI-MS (*m/z*): 343 (M^+–Me).

Anal. Calcd for $C_{17}H_{26}O_8$: C, 56.97; H, 7.31. Found: C, 56.68; H, 7.52.

Further elution of the above residue with EtOAc–light petroleum (1:5) gave the compound **57** (14.43 g, 26%) as colorless crystals.

mp: 106–108 ^oC.

$[\alpha]_D$ –25.6 (*c* 1, $CHCl_3$).

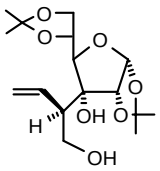
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34, 1.36, 1.45, 1.59 (4 s, 12 H), 2.30 (dd, 1 H, *J* = 9.1, 14.7 Hz), 2.78 (s, 1 H, OH), 2.80 (ddd, 1 H, *J* = 1.6, 5.8, 14.7 Hz), 3.75 (s, 3 H), 3.78 (m, 1 H), 3.87–3.95 (m, 1 H), 4.06–4.14 (m, 2 H), 4.24 (d, 1 H, *J* = 3.8 Hz), 5.66 (d, 1 H, *J* = 3.8 Hz), 5.94 (d, 1 H, *J* = 15.8 Hz), 7.12 (ddd, 1 H, *J* = 5.4, 8.8, 15.8 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ 25.2, 26.4, 26.6, 26.7, 34.9, 51.6, 68.1, 73.2, 78.9, 81.3, 81.9, 103.5, 109.9, 112.8, 124.7, 143.1, 166.3.

EI-MS (*m/z*): 343 (M^+–Me).

Anal. Calcd for $C_{17}H_{26}O_8$: C, 56.97; H, 7.31. Found: C, 56.86; H, 7.27.

3-*C*-[(*R*)-1-Hydroxymethyl-prop-2-enyl]-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (58)



To a solution of **56** (28.0 g, 78 mmol) in anhydrous ether (150 mL) was added $LiAlH_4$ (4.15 g, 109 mmol) in portions slowly over a period of 15 min at 0 ^oC and stirring continued for 2 h at room temperature. Reaction mixture was cooled to 0 ^oC, quenched with 50 mL of EtOAc 5 mL of ice water. The resulted solid material was filtered off through a plug of Celite, and the filtrate concentrated and purified by silica gel column chromatography with EtOAc–light petroleum (1:3) to afford diol **58** (16.84 g, 83%) as colorless solid.

mp: 78–80 ^oC.

$[\alpha]_D$ –3.4 (*c* 1.1, $CHCl_3$).

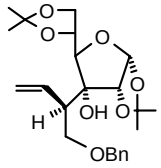
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.38 (s, 6 H), 1.45, 1.59 (2 s, 6 H), 2.72–2.89 (br s, 1 H, OH), 2.91–3.07 (m, 1 H), 3.12 (s, 1 H, OH), 3.68–3.90 (m, 3 H), 3.99–4.17 (m, 2 H), 4.24–4.36 (m, 1 H), 4.50 (d, 1 H, *J* = 3.9 Hz), 5.17–5.32 (m, 2 H), 5.60 (d, 1 H, *J* = 3.9 Hz), 5.71 (ddd, 1 H, *J* = 8.7, 10.7, 17.1 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.3, 26.3, 26.5, 26.6, 47.1, 63.2, 68.4, 72.5, 80.5, 81.0, 84.1, 103.9, 109.7, 112.2, 118.5, 134.3.

EI-MS (*m/z*): 315 (M^+–Me).

Anal. Calcd for $C_{16}H_{26}O_7$: C, 58.17; H, 7.93. Found: C, 57.87; H, 8.18.

3-*C*-[(*R*)-1-Benzyloxymethyl-prop-2-enyl]-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (59)



Freshly prepared Ag_2O (33.7 g, 145.4 mmol) and benzyl bromide (6.9 mL, 58 mmol) were added to a solution of the diol derivative **58** (16.0 g, 48.4 mmol) in CH_2Cl_2 (100 mL) and stirred for 1 h at room temperature. The reaction mixture was filtered through Celite, the residue washed with excess of CH_2Cl_2 and the combined CH_2Cl_2 fractions were concentrated to give residue, which was purified on silica gel EtOAc–light petroleum (1:9) to get pure **59** (19.4 g, 95%) as syrup.

$[\alpha]_D$ +13.7 (*c* 1.1, $CHCl_3$).

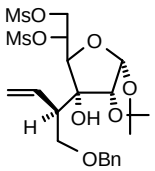
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33, 1.35, 1.44, 1.59 (4 s, 12 H), 2.85–2.94 (m, 1 H), 3.17 (s, 1 H, OH), 3.75–3.96 (m, 4 H), 4.08–4.16 (m, 1 H), 4.25–4.36 (m, 1 H), 4.46–4.55 (m, 2 H), 4.75 (d, 1 H, J = 7.7 Hz), 5.18–5.29 (m, 2 H), 5.62 (d, 1 H, J = 3.8 Hz), 5.75–5.94 (m, 1 H), 7.26–7.42 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.2, 26.2, 26.4, 45.6, 68.2, 70.7, 72.4, 72.9, 79.7, 81.0, 83.9, 103.6, 109.2, 111.5, 117.5, 127.1, 127.8, 135.2, 138.2.

EI-MS (*m/z*): 405 (M^+–Me).

Anal. Calcd for $C_{23}H_{32}O_7$: C, 65.69; H, 7.67. Found: C, 65.47; H, 7.58.

3-*C*-[(*R*)-1-Benzyloxymethyl-prop-2-enyl]-5,6-dimethylsulfonyloxy-1,2-*O*-isopropylidene-α-D-allofuranose (60)



Compound **59** (16.0 g, 38 mmol) in a mixture of 0.8% H_2SO_4 (20 mL) and MeOH (50 mL) was stirred at room temperature for 24 h, and neutralized with solid $NaHCO_3$. The solid was filtered off, the filtrate concentrated, and the residue was purified by silica gel column chromatography with EtOAc–light petroleum (1:2) to give 3-*C*-[(*R*)-1-benzyloxymethyl-prop-2-enyl]-1,2-*O*-isopropylidene-α-D-allofuranose (11.6 g, 80%) as syrup.

$[\alpha]_D$ −11.4 (*c* 1, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34, 1.58 (2 s, 6 H), 2.37–2.53 (br s, 1 H, OH), 2.90–3.07 (m, 2 H), 3.56–3.88 (m, 6 H), 3.91–4.03 (m, 1 H), 4.46–4.57 (m, 2 H), 4.66 (d, 1 H, *J* = 3.9 Hz), 5.17–5.27 (m, 2 H), 5.57 (d, 1 H, *J* = 3.9 Hz), 5.66–5.84 (m, 1 H), 7.21–7.37 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.0, 26.1, 44.9, 64.3, 68.9, 70.3, 72.8, 80.0, 80.2, 80.7, 103.7, 111.5, 117.7, 127.1, 127.8, 134.3, 137.8.

EI-MS (*m/z*): 322 (M^+–58).

Anal. Calcd for $C_{20}H_{28}O_7$: C, 63.14; H, 7.42. Found: C, 62.88; H, 7.74.

To a solution of the above triol derivative (10.0 g, 26.3 mmol) in CH_2Cl_2 (100 mL), were added DIPEA (16 mL, 92.0 mmol), and MsCl (5 mL, 65.7 mmol) at 0 °C, and stirred for 5 min at the same temperature. The reaction mixture was washed with saturated Na_2CO_3, water, and brine successively, dried (Na_2SO_4), and concentrated. The crude oily compound was purified on silica gel with EtOAc–light petroleum (1:5) to afford 5,6-dimesylate derivative **60** (13.4 g, 95%) as clear oil.

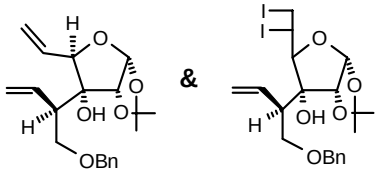
$[\alpha]_D$ −10.1 (*c* 1.45, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.35, 1.58 (2 s, 6 H), 3.00–3.04 (m, 1 H), 3.06 (s, 3 H), 3.13 (s, 3 H), 3.56–3.67 (m, 1 H), 3.74 (dd, 1 H, *J* = 5.4, 9.4 Hz), 3.94 (dd, 1 H, *J* = 3.9, 9.4 Hz), 4.00 (d, 1 H, *J* = 9.1 Hz), 4.32 (dd, 1 H, *J* = 5.7, 11.5 Hz), 4.45–4.63 (m, 3 H), 4.83 (d, 1 H, *J* = 3.8 Hz), 5.21–5.41 (m, 2 H), 5.55–5.74 (m, 1 H), 5.62 (d, 1 H, *J* = 3.8 Hz), 7.21–7.39 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.0, 26.1, 37.0, 39.0, 44.8, 68.3, 70.6, 72.7, 73.6, 78.8, 79.7, 103.4, 111.8, 118.9, 127.1, 127.9, 133.3, 137.6.

Anal. Calcd for $C_{22}H_{32}O_{11}S_2$: C, 49.24; H, 6.01; S, 11.95. Found: C, 48.97; H, 5.77; S, 12.14.

3-*C*-[(*R*)-1-Benzyloxymethyl-prop-2-enyl]-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*ribo*-hex-5-enofuranose (61) and 3-*C*-[(*R*)-1-benzyloxymethyl-prop-2-enyl]-5,6-diiodo-1,2-*O*-isopropylidene-α-L-talofuranose (62)



61 **62**

A mixture of 5,6-dimesylate derivative **60** (12.0 g, 22.36 mmol) and NaI (33.5 g, 223.5 mol) in 2-butanone (100 mL) were heated under reflux for 4 h and concentrated. The residue was partitioned between EtOAc and saturated aq. $Na_2S_2O_3$. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel with EtOAc–light petroleum (1:9) to afford **61** (6.4 g, 83%) as colorless syrup.

$[\alpha]_D$ −15.2 (*c* 0.95, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.35, 1.58 (2 s, 6 H), 2.68 (dt, 1 H, *J* = 9.2, 5.1 Hz), 3.46 (s, 1 H, OH), 3.75–3.82 (m, 2 H), 4.33 (dt, 1 H, *J* = 1.4, 2.8 Hz), 4.46–4.53 (m, 2 H), 4.59 (d, 1 H, *J* = 3.9 Hz), 5.09–5.46 (m, 4 H), 5.64 (d, 1 H, *J* = 3.9 Hz), 5.70–6.00 (m, 2 H), 7.23–7.39 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.9, 26.0, 44.6, 69.8, 72.6, 79.9, 80.2, 83.8, 103.4, 111.1, 117.1, 117.3, 126.9, 127.7, 131.4, 134.1, 137.7.

EI-MS (*m/z*): 331 (M^+–Me).

Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.56. Found: C, 69.18; H, 7.71.

Further elution of the above residue with EtOAc–light petroleum (1:7) gave **62** (0.8 g, 6%) as colorless syrup.

$[\alpha]_D$ −15.0 (*c* 1.4, $CHCl_3$).

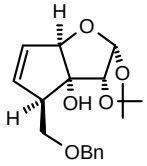
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.35, 1.62 (2 s, 6 H), 3.02 (dt, 1 H, *J* = 8.8, 5.2 Hz), 3.33 (dd, 1 H, *J* = 5.4, 10.4 Hz), 3.56 (dd, 1 H, *J* = 2.5, 10.4 Hz), 3.67 (dd, 1 H, *J* = 2.5, 5.3 Hz), 3.74–3.86 (m, 3 H), 4.49–4.57 (m, 2 H), 4.67 (d, 1 H, *J* = 3.9 Hz), 5.19–5.27 (m, 2 H), 5.58 (d, 1 H, *J* = 3.9 Hz), 5.74 (ddd, 1 H, *J* = 8.6, 10.2, 17.4 Hz), 7.28–7.36 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.9, 26.4, 26.5, 45.0, 67.1, 70.4, 73.0, 79.9, 80.4, 83.2, 103.4, 111.9, 118.2, 127.2, 128.0, 134.0, 137.6.

EI-MS (*m/z*): 475 (M^+–125).

Anal. Calcd for $C_{20}H_{26}O_5I_2$: C, 40.02; H, 4.37. Found: C, 40.14; H, 4.18.

(1*R*,2*R*,6*R*,8*R*,11*R*)-11-Benzyloxymethyl-1-hydroxy-4,4-dimethyl-3,5,7-trioxatricyclo-[6.3.0.0^{2,6}]undec-9-ene (64)



To a solution of **61** (6.0 g, 17.3 mmol) in anhydrous benzene (250 mL) was added Grubbs' 1st generation catalyst **63** (0.57 g, 0.69 mmol), degassed with argon for 10 min and then the reaction mixture was heated at reflux for 8 h. The solvent was evaporated and the residue purified on silica gel with EtOAc–light petroleum (1:4) to obtain **64** (4.8 g, 87%) as oil.

$[\alpha]_D$ +112.0 (*c* 1.1, $CHCl_3$).

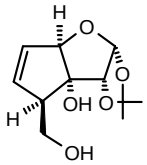
^{1}H NMR (500 MHz, $CDCl_3$): ***δ*** 1.37, 1.59 (2 s, 6 H), 3.06–3.10 (m, 1 H), 3.29 (s, 1 H, OH), 3.40 (dd, 1 H, *J* = 7.2, 10.1 Hz), 3.53 (dd, 1 H, *J* = 4.2, 10.1 Hz), 4.50 (ABq, 2 H, *J* = 12.1 Hz), 4.61 (d, 1 H, *J* = 3.8 Hz), 4.75 (d, 1 H, *J* = 1.9 Hz), 5.62 (d, 1 H, *J* = 3.8 Hz), 5.85 (dt, 1 H, *J* = 5.9, 2.7 Hz), 5.89 (dd, 1 H, *J* = 2.7, 5.9 Hz), 7.29–7.37 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): ***δ*** 27.1, 27.4, 54.2, 68.6, 73.2, 80.3, 86.2, 93.1, 106.9, 112.6, 127.9, 128.0, 128.5, 129.8, 136.9, 137.7.

EI-MS (*m/z*): 318 (M^+).

Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 67.96; H, 7.18.

(1*R*,2*R*,6*R*,8*R*,11*R*)-1-Hydroxy-11-hydroxymethyl-4,4-dimethyl-3,5,7-trioxatricyclo-[6.3.0.0^{2,6}]undec-9-ene (65)



Freshly cut Li metal (0.09 g, 12.97 mmol) was added in small pieces to distilled liquid NH_3 (15 mL) at –78 °C and allowed to dissolve (15 min), and THF solution containing

compound **64** (1.0 g, 3.14 mmol) was added by syringe. After being stirred at same temperature for 45 min, solid NH_4Cl was added to discharge the blue color, most of the liquid ammonia was allowed to evaporate, and EtOAc was added. The EtOAc layer was filtered through a pad of Celite and the inorganic salts were rinsed thoroughly with EtOAc. The EtOAc solution was washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using EtOAc–light petroleum (1:2) to give diol **65** (0.49 g, 68%) as colorless syrup.

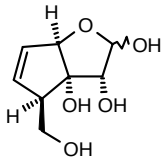
$[\alpha]_D$ +142.3 (*c* 1.2, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): ***δ*** 1.43, 1.62 (2 s, 6 H), 2.98–3.05 (m, 1 H), 3.37–3.52 (m, 1 H), 3.68 (dd, 1 H, *J* = 5.2, 11.7 Hz), 3.78–3.91 (m, 1 H), 4.74–4.78 (m, 2 H), 5.86–6.02 (m, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): ***δ*** 26.5, 26.8, 56.1, 60.2, 79.5, 85.6, 92.2, 106.5, 112.0, 129.5, 136.8.

Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 57.76; H, 7.21.

(3*R/S*,1*R*,4*R*,5*R*,6*R*)-3,4,5-Trihydroxy-6-hydroxymethyl-2-oxa-bicyclo[3.3.0]oct-7-ene (66)

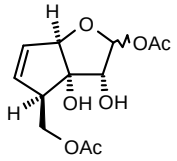


Compound **65** (0.4 g, 1.75 mmol) in 60% aq. AcOH (10 mL) was heated under reflux for 2 h. The reaction mixture was neutralized with solid Na_2CO_3 and evaporated. The residue was extracted with EtOAc, dried (Na_2SO_4), concentrated, and purified by silica gel column chromatography using EtOAc–light petroleum (4:1) to give tetrol **66** (0.29 g, 88%) as colorless syrup.

^{1}H NMR (200 MHz, CD_3COCD_3): ***δ*** 2.83 (dd, 1 H, *J* = 2.9, 4.6 Hz), 3.38 (d, 1 H, *J* = 11.5 Hz), 3.93 (dd, 1 H, *J* = 4.7, 11.5 Hz), 4.10 (br s, 1 H), 4.44 (d, 1 H, *J* = 2.5 Hz), 4.98 (s, 1 H), 5.92–6.04 (m, 2 H).

Anal. Calcd for $C_8H_{12}O_5$: C, 51.06; H, 6.43. Found: C, 51.14; H, 6.58.

(3*R/S*,1*R*,4*R*,5*R*,6*R*)-3-Acetoxy-6-acetoxymethyl-4,5-dihydroxy-2-oxa-bicyclo[3.3.0]oct-7-ene (67)



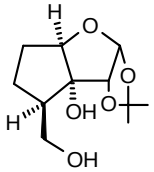
To a solution of **66** (0.2 g, 1.06 mmol) in anhydrous CH_2Cl_2 (10 mL) were added Ac_2O (1.0 mL, 10.57 mmol), Et_3N (1.8 mL, 12.91 mmol) and DMAP (0.05 g, 0.41 mmol), and stirred at room temperature for 30 min. The reaction mixture was diluted with water, extracted with CH_2Cl_2, washed with saturated aq. $NaHCO_3$, dried (Na_2SO_4), and the residue purified by silica gel column chromatography with EtOAc–light petroleum (1:3) as an eluent to afford **67** (0.25 g, 87%) as colorless syrup.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.09, 2.12 (2 s, 6 H), 3.40 (t, 1H, *J* = 3.5 Hz), 3.62 (d, 1 H, *J* = 11.8 Hz), 4.24 (dd, 1 H, *J* = 4.4, 11.8 Hz), 4.87 (d, 1 H, *J* = 2.4 Hz), 5.36 (s, 1 H), 5.88 (s, 1 H), 5.88 (dd, 1 H, *J* = 2.8, 5.6 Hz), 6.24 (dd, 1 H, *J* = 2.1, 5.6 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 20.3, 20.6, 50.7, 63.8, 70.9, 85.3, 87.6, 101.8, 131.7, 134.9, 169.2, 169.8.

Anal. Calcd for $C_{12}H_{16}O_7$: C, 52.94; H, 5.92. Found: C, 52.79; H, 6.08.

(1*R*,2*R*,6*R*,8*R*,11*R*)-1-Hydroxy-11-hydroxymethyl-4,4-dimethyl-1-3,5,7-trioxatricyclo-[6.3.0.0^{2,6}]undecane (69)



To a solution of **64** (1.0 g, 3.14 mmol) in MeOH (10 mL) was added 20% $Pd(OH)_2/C$ (0.05 g), and the mixture was degassed with argon and flushed with H_2 for 5 min. After stirring under an atmosphere of H_2 for 12 h, the mixture was filtered through a pad of Celite and the solvent concentrated. The residue was purified on silica gel using EtOAc–light petroleum (1:2) to give **69** (0.66 g, 91%) as colorless solid.

mp: 97–99 ^oC.

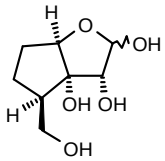
$[\alpha]_D$ +36.5 (*c* 1.5, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.39, 1.57 (2 s, 6 H), 1.72–1.93 (m, 4 H), 2.17–2.35 (m, 1 H), 3.04 (s, 1 H), 3.56–3.89 (m, 2 H), 4.22 (d, 1 H, J = 2.3 Hz), 4.72 (d, 1 H, J = 3.8 Hz), 5.79 (d, 1 H, J = 3.8 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.3, 26.6, 26.8, 28.7, 49.5, 61.4, 80.9, 87.3, 88.4, 105.3, 111.8.

Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.00; H, 7.92.

(3*R/S*,1*R*,4*R*,5*R*,6*R*)-3,4,5-Trihydroxy-6-hydroxymethyl-2-oxa-bicyclo[3.3.0]octane (70)



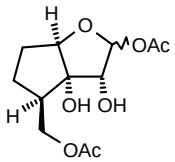
The reaction was carried out as described earlier using the compound **69** (0.4 g, 1.74 mmol) in 60% aq. AcOH (10 mL) to furnish **70** (0.28 g, 85%) as colorless syrup.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.56–1.79 (m, 1 H), 1.83–2.08 (m, 2 H), 2.24–2.46 (m, 2 H), 3.38–3.50 (m, 1 H), 3.78–3.88 (m, 1 H), 4.10–4.25 (m, 2 H), 4.70 (br s, 1 H, OH), 5.13 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 29.8, 29.9, 46.4, 64.6, 72.0,83.6, 86.7, 102.1.

Anal. Calcd for $C_8H_{14}O_5$: C, 50.52; H, 7.42. Found: C, 50.41; H, 7.58.

(3*R/S*,1*R*,4*R*,5*R*,6*R*)-3-Acetoxy-6-acetoxymethyl-4,5-dihydroxy-2-oxa-bicyclo[3.3.0]octane (71)



The reaction was carried out as described earlier using the compound **70** (0.2 g, 1.05 mmol) Ac_2O (1.0 mL, 10.57 mmol), Et_3N (1.8 mL, 12.91 mmol) and DMAP (0.05 g, 0.41 mmol) in anhydrous CH_2Cl_2 (10 mL) to afford **71** (0.245 g, 86%) as colorless syrup.

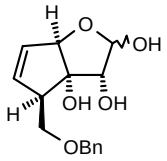
mp: 74–76 ^oC.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.69–1.89 (m, 2 H), 2.07, 2.11 (2 s, 6 H), 2.15 (m, 2 H), 2.73–2.85 (m, 1 H), 3.49 (d, 1 H, J = 11.2 Hz), 4.12 (dd, 1 H, J = 3.3, 11.2 Hz), 4.42 (d, 1 H, J = 2.0 Hz), 5.23 (s, 1 H), 5.82 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 20.0, 20.4, 28.4, 29.4, 44.4, 63.8, 71.5, 83.1, 83.5, 100.2, 168.9, 169.3.

Anal. Calcd for $C_{12}H_{18}O_7$: C, 52.55; H, 6.62. Found: C, 52.45; H, 6.83.

(3*R/S*,1*R*,4*R*,5*R*,6*R*)-6-Benzyloxymethyl-3,4,5-trihydroxy-2-oxa-bicyclo[3.3.0]oct-7-ene (73)



The reaction was carried out as described earlier using the compound **64** (2.0 g, 6.28 mmol) in 60% aq. AcOH (15 mL) at reflux conditions to furnish triol **73** (1.63 g, 93%) as colorless solid.

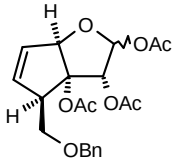
mp: 92–94 ^{o}C.

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.06–3.19 (m, 1 H), 3.35 (d, 1 H, *J* = 4.7 Hz, OH), 3.44 (s, 1 H, OH), 3.60–3.79 (m, 2 H), 3.86 (d, 1 H, *J* = 5.8 Hz, OH) 4.07 (t, 1 H, *J* = 4.0 Hz), 4.54–4.60 (m, 2 H), 5.14 (s, 1 H), 5.29–5.32 (m, 1 H), 5.57 (d, 1 H, *J* = 6.0 Hz), 5.79 (dt, 1 H, *J* = 6.0, 2.1 Hz), 7.28–7.39 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 52.7, 68.8, 72.0, 73.0, 85.6, 92.8, 97.4, 127.5, 128.2, 130.7, 132.8, 137.5.

Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.39; H, 6.42.

(3*R/S*,1*R*,4*R*,5*R*,6*R*)-3,4,5-Triacetoxy-6-benzyloxymethyl-2-oxa-bicyclo[3.3.0]oct-7-ene (74)



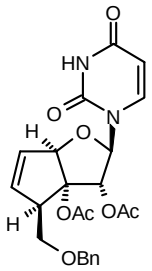
The reaction was carried out as described earlier using triol **73** (1.5 g, 5.39 mmol), Ac_2O (3.1 mL, 32.76 mmol), Et_3N (7.5 mL, 53.80 mmol), and DMAP (0.13 g, 1.0 mmol) in anhydrous CH_2Cl_2 (20 mL) to obtain **74** (2.1 g, 96%) as clear oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.01, 2.09, 2.13 (3 s, 9 H), 3.39 (t, 1 H, J = 5.2 Hz), 3.69–3.74 (m, 2 H), 4.49 (ABq, 2 H, J = 11.9 Hz), 5.50 (s, 1 H), 5.58 (d, 1 H, J = 4.3 Hz), 5.80–5.89 (m, 2 H), 6.29 (d, 1 H, J = 4.3 Hz), 7.20–7.34 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 20.1, 20.6, 21.2, 51.4, 68.4, 70.9, 72.9, 90.0, 92.6, 95.2, 95.9, 127.4, 128.1, 135.4, 137.8, 168.6, 169.0, 169.6.

Anal. Calcd for $C_{21}H_{24}O_8$: C, 62.37; H, 5.98. Found: C, 62.09; H, 6.12.

(1*R*,3*R*,4*R*,5*R*,6*R*)-4,5-Diacetoxy-6-benzyloxymethyl-3-(uracil-1-yl)-2-oxa-bicyclo[3.3.0]-oct-7-ene (75)



To a mixture of **74** (0.5 g, 1.23 mmol) and *O,O*-bis(trimethylsilyl)uracil (0.47 g, 1.83 mmol) [*O,O*-bis(trimethylsilyl)uracil was prepared according to the lit. procedure][64] in anhydrous CH_3CN (10 mL) was added $SnCl_4$ (0.2 mL, 1.70 mmol) dropwise at 0 ^oC and stirred for 30 min at room temperature. The reaction mixture was quenched with ice-cold saturated aq. $NaHCO_3$ (5 mL) and extracted with EtOAc (2 x 20 mL). The combined extracts were dried (Na_2SO_4), concentrated, and purified on silica gel with EtOAc–light petroleum (1:1) to furnish **75** (0.315 g, 56%) as syrup.

(**or**)

To a mixture of **74** (0.36 g, 0.89 mmol) and uracil (0.2 g, 1.78 mmol) in anhydrous CH_3CN (8 mL) was added *N,O*-bis(trimethylsilyl)acetamide (1.1 mL, 4.45 mmol) and stirred under reflux for 15 min. After cooling the mixture to 0 ^oC, TMSOTf (0.32 mL, 1.78 mmol) was added dropwise and the solution stirred at 50 ^oC for 2 h. The reaction mixture was quenched with ice-cold saturated aq. $NaHCO_3$ (5 mL) and extracted with EtOAc (2 x 20 mL). The combined extracts were dried (Na_2SO_4), concentrated, and purified on silica gel with EtOAc–light petroleum (1:1) to give **75** (0.28 g, 69%) as syrup.

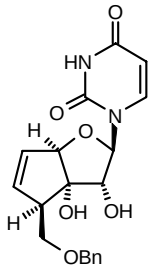
$[\alpha]_D$ +16.8 (*c* 0.8, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): ***δ*** 2.02, 2.15 (2 s, 6 H), 3.26–3.36 (m, 1 H), 3.80 (dd, 1 H, *J* = 4.3, 10.0 Hz), 4.02–4.13 (m, 1 H), 4.50 (ABq, 2 H, *J* = 11.2 Hz), 5.03 (dd, 1 H, *J* = 2.0, 8.1 Hz), 5.16 (d, 1 H, *J* = 1.6 Hz), 5.86–6.01 (m, 3 H), 6.17 (d, 1 H, *J* =7.5 Hz), 7.08 (d, 1 H, *J* = 8.1 Hz), 7.25–7.37 (m, 5 H), 9.62 (br s, 1 H, NH).

^{13}C NMR (50 MHz, $CDCl_3$): ***δ*** 20.3, 21.2, 53.2, 68.6, 71.8, 73.1, 86.3, 90.8, 92.2, 103.2, 127.1, 127.7, 128.4, 137.4, 137.7, 139.3, 150.8, 162.9, 169.1, 169.9.

Anal. Calcd for $C_{23}H_{24}O_8N_2$: C, 60.52; H, 5.30; N, 6.14. Found: C, 60.29; H, 5.00; N, 6.32.

(1*R*,3*R*,4*R*,5*R*,6*R*)-6-Benzyloxymethyl-4,5-dihydroxy-3-(uracil-1-yl)-2-oxa-bicyclo[3.3.0]-oct-7-ene (76)



To a solution of **75** (0.21 g, 0.46 mmol) in anhydrous MeOH (4 mL) was added NaOMe (0.062 g, 1.15 mmol) and stirred at 0 ^oC for 20 min. The reaction mixture was neutralized with conc. HCl, the inorganic salts were filtered off and the filtrate concentrated. The residue was purified by silica gel column chromatography with MeOH–CH_2Cl_2 (1:9) to afford **76** (0.145 g, 85%) as colorless solid.

mp: 150–152 ^oC.

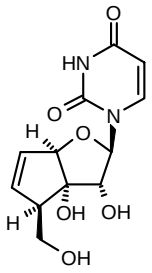
$[\alpha]_D$ –24.1 (*c* 0.95, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): ***δ*** 3.10 (t, 1 H, *J* = 6.5 Hz), 3.72 (d, 2 H, *J* = 6.5 Hz), 4.07 (br s, 1 H, OH), 4.25 (d, 1 H, *J* = 7.2 Hz), 4.53 (s, 2 H), 4.60 (br s, 1 H, OH), 5.05 (s, 1 H), 5.66 (d, 1 H, *J* = 8.2 Hz), 5.82 (dd, 2 H, *J* = 6.4, 12.3 Hz), 6.13 (d, 1 H, *J* = 7.6 Hz), 7.25–7.35 (m, 6 H), 10.0 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$ + MeOD): ***δ*** 52.8, 68.1, 73.1, 74.8, 85.4, 88.3, 92.8, 102.6, 127.5, 128.1, 130.0, 134.5, 137.5, 139.5, 151.1, 163.8.

Anal. Calcd for $C_{19}H_{20}O_6N_2$: C, 61.28; H, 5.41; N, 7.52. Found: C, 61.09; H, 5.42; N, 7.69.

(1*R*,3*R*,4*R*,5*R*,6*R*)-4,5-Dihydroxy-6-hydroxymethyl-3-(uracil-1-yl)-2-oxa-bicyclo[3.3.0]-oct-7-ene (77)



A solution of **76** (0.125 g, 0.34 mmol) in anhydrous CH_2Cl_2 (4 mL) was stirred at –78 ^oC and a 1M solution of BCl_3 in CH_2Cl_2 (0.53 mL, 0.67 mmol) was added dropwise. After stirring for 5 h at –78 ^oC the mixture was treated with MeOH (3 mL) and water (0.2 mL), and stirred at room temperature for 1 h. The solvents were removed on rotavapor and the residue was purified on silica gel using MeOH–CH_2Cl_2 (1:9) to afford **77** (0.09 g, 95%) as colorless solid.

mp: 62–64 ^oC.

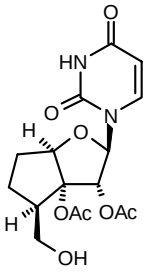
$[\alpha]_D$ –47.4 (*c* 0.75, MeOH);

^{1}H NMR (500 MHz, DMSO-d$_6$): δ 2.67–2.72 (m, 1 H), 3.47 (dd, 1 H, *J* = 9.0, 10.6 Hz), 3.77 (dd, 1 H, *J* = 5.2, 10.6 Hz), 4.00 (d, 1 H, *J* = 8.4 Hz), 4.74 (s, 1 H), 5.68 (dd, 1 H, *J* = 2.0, 8.1 Hz), 5.80 (dt, 1 H, *J* = 1.8, 6.2 Hz), 5.90 (d, 1 H, *J* = 6.2 Hz), 5.92 (d, 1 H, *J* = 8.1 Hz), 7.42 (d, 1 H, *J* = 8.1 Hz), 11.35 (s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d$_6$): δ 55.5, 59.3, 72.6, 84.5, 86.8, 92.2, 102.4, 130.1, 135.0, 140.2, 150.9, 162.9.

Anal. Calcd for $C_{12}H_{14}O_6N_2$: C, 51.06; H, 4.99; N, 9.92. Found: C, 51.19; H, 4.81; N, 9.69.

(1*R*,3*R*,4*R*,5*R*,6*R*)-4,5-Diacetoxy-6-hydroxymethyl-3-(uracil-1-yl)-2-oxa-bicyclo[3.3.0]oc-tane (78)



The reaction was carried out as described earlier using the compound **75** (0.11 g, 0.24 mmol) and 20% $Pd(OH)_2/C$ (0.025 g) in MeOH (4 mL) under hydrogen atmosphere at normal temperature and pressure to give **78** (0.075 g, 84%) as colorless syrup.

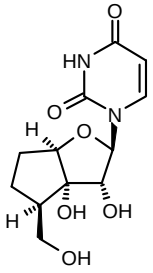
$[\alpha]_D$ –30.4 (*c* 1, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): ***δ*** 1.89–1.98 (m, 4 H), 2.05, 2.13 (2 s, 6 H), 2.43–2.53 (m, 1 H), 3.79 (dd, 1 H, *J* = 5.7, 11.2 Hz), 4.06 (dd, 1 H, *J* = 4.0, 11.2 Hz), 4.77 (d, 1 H, *J* = 2.7 Hz), 5.74 (d, 1 H, *J* = 7.4 Hz), 5.77 (dd, 1 H, *J* = 2.2, 7.4 Hz), 6.07 (d, 1 H, *J* = 7.5 Hz), 7.52 (d, 1 H, *J* = 7.5 Hz), 9.45 (br s, 1 H, NH).

^{13}C NMR (50 MHz, $CDCl_3$): ***δ*** 20.4, 21.2, 26.3, 29.4, 49.9, 60.8, 71.5, 87.2, 87.3, 90.6, 102.9, 140.0, 150.6, 163.3, 169.6, 170.1.

Anal. Calcd for $C_{16}H_{20}O_8N_2$: C, 52.17; H, 5.47; N, 7.60. Found: C, 52.29; H, 5.76; N, 7.71.

(1*R*,3*R*,4*R*,5*R*,6*R*)-4,5-Dihydroxy-6-hydroxymethyl-3-(uracil-1-yl)-2-oxa-bicyclo[3.3.0]-octane (79)



The reaction was carried out as described earlier using the compound **78** (0.07 g, 0.19 mmol) in anhydrous MeOH (4 mL) and NaOMe (0.02 g, 0.38 mmol) at room temperature to yield **79** (0.04 g, 74%) as colorless solid.

mp: 185–187 ^oC.

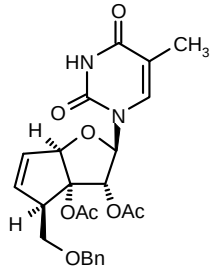
$[\alpha]_D$ –20.2 (*c* 1, MeOH);

^{1}H NMR (500 MHz, DMSO-d_6): ***δ*** 1.54–1.65 (m, 2 H), 1.70–1.83 (m, 2 H), 1.88–1.94 (m, 1 H), 3.41 (dd, 1 H, *J* = 8.7, 10.5 Hz), 3.72 (dd, 1 H, *J* = 4.7, 10.5 Hz), 3.88 (d, 1 H, *J* = 8.2 Hz), 4.12 (d, 1 H, *J* = 6.7 Hz), 4.90–5.07 (br s, 1 H, OH), 5.11–5.27 (br s, 1 H, OH), 5.66 (d, 2 H, *J* = 8.8 Hz), 7.67 (d, 1 H, *J* = 8.8 Hz), 11.34 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): ***δ*** 27.0, 29.3, 51.6, 60.1, 70.9, 83.2, 85.3, 88.5, 102.0, 140.6, 150.8, 162.7.

Anal. Calcd for $C_{12}H_{16}O_6N_2$: C, 50.70; H, 5.67; N, 9.85. Found: C, 50.49; H, 6.02; N, 9.69.

(1*R*,3*R*,4*R*,5*R*,6*R*)-4,5-Diacetoxy-6-benzyloxymethyl-3-(thymin-1-yl)-2-oxa-bicyclo-[3.3.0]oct-7-ene (80)



The reaction was carried out as described earlier using the compound **74** (0.5 g, 1.23 mmol), thymine (0.31 g, 2.46 mmol), *N,O*-bis(trimethylsilyl)acetamide (1.5 mL, 6.18 mmol) and TMSOTf (0.45 mL, 2.47 mmol)) in CH_3CN (10 mL) to obtain **80** (0.45 g, 77%) as colorless syrup.

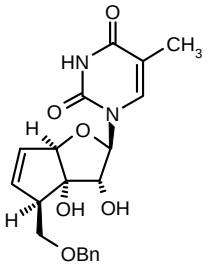
$[\alpha]_D$ –20.9 (*c* 1.7, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.61 (s, 3 H), 2.01, 2.15 (2 s, 6 H), 3.35–3.40 (m, 1 H), 3.75 (dd, 1 H, *J* = 5.1, 10.2 Hz), 3.96 (dd, 1 H, *J* = 3.2, 10.2 Hz), 4.53 (ABq, 2 H, *J* = 11.9 Hz), 5.2 (s, 1 H), 5.88–5.99 (m, 3 H), 6.24 (d, 1 H, *J* = 7.7 Hz), 7.08 (d, 1 H, *J* = 1.3 Hz), 7.28–7.34 (m, 5 H), 9.22 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 12.0, 20.2, 21.2, 52.4, 68.2, 71.9, 72.8, 86.1, 90.9, 91.7, 111.7, 127.3, 127.5, 128.2, 134.5, 136.9, 137.7, 150.9, 163.5, 169.2, 169.9.

Anal. Calcd for $C_{24}H_{26}O_8N_2$: C, 61.27; H, 5.57; N, 5.95. Found: C, 60.94; H, 5.81; N, 5.83.

(1*R*,3*R*,4*R*,5*R*,6*R*)-6-Benzyloxymethyl-4,5-dihydroxy-3-(thymin-1-yl)-2-oxa-bicyclo-[3.3.0]oct-7-ene (81)



The reaction was carried out as described earlier using the compound **80** (0.16 g, 0.34 mmol) and NaOMe (0.046 g, 0.85 mmol) in MeOH (5 mL) at 0 ^oC to give **81** (0.115 g, 88%) as colorless syrup.

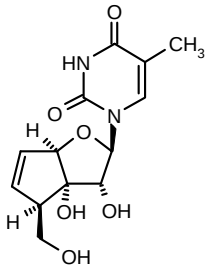
$[\alpha]_D$ –51.6 (*c* 0.6, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.86 (s, 3 H), 3.12 (br s, 1 H), 3.73 (d, 2 H, *J* = 6.4 Hz), 4.23 (d, 1 H, *J* = 7.2 Hz), 4.54 (s, 2 H), 5.06 (s, 1 H), 5.83 (ABq, 2 H, *J* = 5.9 Hz), 6.10 (d, 1 H, *J* = 7.4 Hz), 7.12 (s, 1 H), 7.27–7.36 (m, 5 H), 9.56 (br s, 1 H, NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ 12.5, 52.7, 68.5, 73.5, 75.6, 86.6, 89.1, 93.1, 111.4, 127.8, 127.9, 128.5, 130.6, 134.2, 134.9, 137.6, 151.5, 163.7.

Anal. Calcd for $C_{20}H_{22}O_6N_2$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.12; H, 5.86; N, 7.52.

(1*R*,3*R*,4*R*,5*R*,6*R*)-4,5-Dihydroxy-6-hydroxymethyl-3-(thymin-1-yl)-2-oxa-bicyclo[3.3.0]-oct-7-ene (82)



The reaction was carried out as described earlier using the compound **81** (0.065 g, 0.17 mmol) in CH_2Cl_2 (5 mL) and a 1M solution of BCl_3 in CH_2Cl_2 (0.42 mL, 0.42 mmol) at 78 ^oC to afford **82** (0.04 g, 80%) as colorless solid.

mp: 90–92 ^oC.

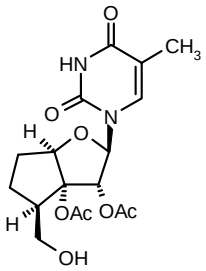
$[\alpha]_D$ –57.1 (*c* 0.75, MeOH).

^{1}H NMR (500 MHz, DMSO-d_6): δ 1.80 (s, 3 H), 2.69–2.73 (m, 1 H), 3.50 (dt, 1 H, *J* = 9.9, 5.6 Hz), 3.79 (dt, 1 H, *J* = 9.9, 4.8 Hz), 4.05 (t, 1 H, *J* = 7.7 Hz), 4.58 (t, 1 H, *J* = 5.0 Hz), 4.73 (s, 1 H, OH), 5.21 (d, 1 H, *J* = 6.9 Hz, OH), 5.45 (s, 1 H, OH), 5.79–5.81 (m, 1 H), 5.90–5.93 (m, 2 H), 7.29 (s, 1 H), 11.33 (s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ 11.9, 55.6, 59.3, 72.0, 84.3, 86.5, 92.0, 109.8, 129.8, 134.9, 135.4, 150.9, 163.4.

Anal. Calcd for $C_{13}H_{16}O_6N_2$: C, 52.70; H, 5.44; N, 9.45. Found: C, 52.52; H, 5.76; N, 9.52.

(1*R*,3*R*,4*R*,5*R*,6*R*)-4,5-Diacetoxy-6-hydroxymethyl-3-(thymin-1-yl)-2-oxa-bicyclo[3.3.0]-octane (83)



The reaction was carried out as described earlier using the compound **80** (0.2 g, 0.42 mmol) and 20% $Pd(OH)_2/C$ (0.035 g) in MeOH (6 mL) under hydrogen atmosphere at normal temperature and pressure to furnish **83** (0.15 g, 92%) as colorless syrup.

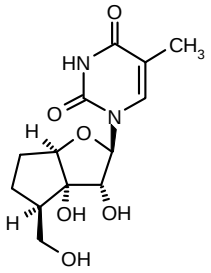
$[\alpha]_D$ –28.7 (*c* 1.2, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.92 (s, 3 H), 1.93–1.96 (m, 4 H), 2.07, 2.12 (2 s, 6 H), 2.45–2.54 (m, 1 H), 2.60–2.74 (m, 1 H, OH), 3.81 (dd, 1 H, *J* = 5.8, 11.3 Hz), 4.01–4.09 (m, 1 H), 4.76 (d, 1 H, *J* = 2.6 Hz), 5.76 (d, 1 H, *J* = 6.8 Hz), 6.05 (d, 1 H, *J* = 6.8 Hz), 7.31 (s, 1 H), 9.48–9.62 (m, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 12.2, 20.2, 21.1, 26.3, 29.3, 49.8, 60.7, 71.1, 86.9, 90.5, 111.1, 135.6, 150.7, 163.7, 169.4, 170.0.

Anal. Calcd for $C_{17}H_{22}O_8N_2$: C, 53.40; H, 5.80; N, 7.33. Found: C, 53.54; H, 5.52; N, 7.56.

(1*R*,3*R*,4*R*,5*R*,6*R*)-4,5-Dihydroxy-6-hydroxymethyl-3-(thymin-1-yl)-2-oxa-bicyclo[3.3.0]-octane (84)



The reaction was carried out as described earlier using the compound **83** (0.12 g, 0.31 mmol) and NaOMe (0.05 g, 0.94 mmol) in MeOH (5 mL) at room temperature to obtain **84** (0.075 g, 80%) as colorless solid.

mp: 182–184 ^oC.

$[\alpha]_D$ –32.9 (*c* 0.8, MeOH).

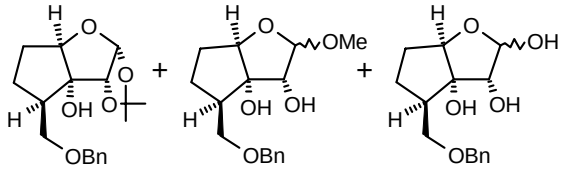
^{1}H NMR (500 MHz, DMSO-d_6): δ 1.56–1.60 (m, 1 H), 1.65–1.80 (m, 2 H), 1.82 (s, 3 H), 1.81–1.85 (m, 1 H), 1.89–1.96 (m, 1 H), 3.45 (dt, 1 H, *J* = 9.6, 5.5 Hz), 3.73 (dt, 1 H, *J* = 9.6,

4.4 Hz), 3.92 (t, 1 H, *J* = 7.7 Hz), 4.1 (d, 1 H, *J* = 6.1 Hz), 4.32 (t, 1 H, *J* = 4.9 Hz, OH), 4.97 (s, 1 H, OH), 5.13 (d, 1 H, *J* = 6.9 Hz, OH), 5.65 (d, 1 H, *J* = 8.5 Hz), 7.49 (s, 1 H), 11.32 (s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d$_6$): δ 11.7, 27.0, 29.3, 51.7, 60.1, 70.5, 83.2, 85.0, 88.4, 109.7, 135.8, 150.9, 163.4.

Anal. Calcd for $C_{13}H_{18}O_6N_2$: C, 52.34; H, 6.08; N, 9.39. Found: C, 52.12; H, 6.36; N, 9.37.

(1*R*,2*R*,6*R*,8*R*,11*R*)-11-Benzyloxymethyl-1-hydroxy-4,4-dimethyl-3,5,7-trioxatricyclo-[6.3.0.0^{2,6}]undecane (91), (3*R/S*,1*R*,4*R*,5*R*,6*R*)-6-benzyloxymethyl-4,5-dihydroxy-3-methoxy-2-oxa-bicyclo[3.3.0]octane (92) and (3*R/S*,1*R*,4*R*,5*R*,6*R*)-6-benzyloxymethyl-3,4,5-trihydroxy-2-oxa-bicyclo[3.3.0]octane (93)



91 **92** **93**

To a solution of **64** (0.5 g, 1.57 mmol) in MeOH (10 mL) was added $Rh(Ph_3P)_3Cl$ (0.1 g) and the mixture was degassed with argon, and flushed with H_2 for 5 min. After being stirred under an atmosphere of H_2 for 12 h, the mixture was filtered through a pad of Celite and the solvent concentrated. The residue was purified on silica gel with EtOAc–light petroleum (1:4) to give **91** (0.186 g, 37%) as colorless syrup.

$[\alpha]_D$ +37.8 (*c* 1.1, $CHCl_3$).

^{1}H NMR (200 MHz, CDCl$_3$): δ 1.33, 1.54 (2 s, 6 H), 1.66–1.91 (m, 4 H), 2.27–2.45 (m, 1 H), 2.85–3.15 (br s, 1 H), 3.38–3.47 (m, 1 H), 3,56 (dd, 1 H, *J* = 4.3, 9.8 Hz), 4.22 (d, 1 H, *J* = 1.9 Hz), 4.48–4.61 (m, 3 H), 5.64 (d, 1 H, *J* = 3.9 Hz), 7.29–7.41 (m, 5 H).

^{13}C NMR (50 MHz, CDCl$_3$): δ 26.7, 26.9, 28.9, 47.5, 68.8, 72.9, 81.2, 87.4, 88.5, 105.4, 111.8, 127.6, 128.2, 137.9.

Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.39; H, 7.48.

Further elution with EtOAc–light petroleum (1:3) gave anomeric mixture of **92** (0.075 g, 16%) as colorless syrup.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26–1.97 (m, 4 H), 2.22–2.41 (m, 1 H), 2.90–3.22 (br s, 1 H, OH), 3.48 (s, 3 H), 3.56–3.81 (m, 2 H), 4.31 (d, 1 H, *J* = 5.6 Hz), 4.45–4.61 (m, 2 H), 4.74 (d, 1 H, *J* = 5.6 Hz), 7.28–7.76 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.5, 29.9, 48.8, 54.7, 69.5, 71.6, 73.1, 84.5, 89.1, 103.1, 127.5, 128.2, 137.8.

Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.12; H, 7.72.

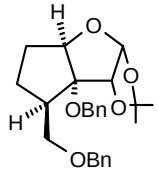
Further elution with EtOAc–light petroleum (1:2) afforded **93** (0.21 g, 47%) as syrup.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26–1.48 (m, 1 H), 1.65–1.97 (m, 3 H), 2.24–2.40 (m, 1 H), 2.74–3.10 (br s, 3 H, 3 OH), 3.58–3.74 (m, 2 H), 3.90 (d, 1 H, *J* = 4.1 Hz), 4.46–4.61 (m, 2 H), 5.29 (d, 1 H, *J* = 4.1 Hz), 7.28–7.40 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.7, 29.8, 48.8, 69.6, 71.3, 73.0, 84.7, 88.8, 96.8, 127.4, 128.1, 137.9.

Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.18; H, 7.31.

(1*R*,2*R*,6*R*,8*R*,11*R*)-5-Benzyloxy-11-benzyloxymethyl-4,4-dimethyl-3,5,7-trioxatricyclo-[6.3.0.0^{2,6}]undecane (94)



A 60% oily dispersion of NaH (0.78 g, 19.52 mmol) was suspended in anhydrous DMF (15 mL) and the mixture was cooled to 0 ^oC. A solution of **91** (2.5 g, 7.80 mmol) in anhydrous DMF (4 mL) was added dropwise over a period of 15 min and after being stirred at room temperature for 30 min, benzyl bromide (1.8 mL, 15.13 mmol) and TBAI (0.3 g, 0.8 mmol) were added, and stirring continued for another 30 min at room temperature. Reaction mixture was quenched with ice water (2 mL), extracted with ether (2 x 20 mL), washed with brine, dried (Na_2SO_4), and concentrated on rotavapor. The residue was purified by silica gel column chromatography with EtOAc–light petroleum (1:5) to give **94** (3.14 g, 98%) as syrup.

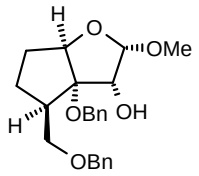
$[\alpha]_D$ +82.0 (*c* 0.6, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33, 1.58 (2 s, 6 H), 1.65–1.99 (m, 4 H), 2.48–2.64 (m, 1 H), 3.27 (t, 1 H, *J* = 9.9 Hz), 3.47 (dd, 1 H, *J* = 4.6, 9.9 Hz), 4.44–4.64 (m, 5 H), 4.78 (d, 1 H, *J* = 3.7 Hz), 5.57 (d, 1 H, *J* = 3.7 Hz), 7.21–7.43 (m, 10 H).

^{13}C NMR (50 MHz, $CDCl_3$): ***δ*** 26.8, 27.0, 27.3, 28.5, 45.8, 66.4, 70.0, 72.8, 79.8, 87.5, 92.6, 105.9, 111.8, 126.8, 127.2, 127.4, 127.8, 128.1, 137.6, 138.8.

Anal. Calcd for $C_{25}H_{30}O_5$: C, 73.15; H, 7.37. Found: C, 73.08; H, 7.48.

(1*R*,3*S*,4*R*,5*R*,6*R*)-5-Benzyloxy-6-benzyloxymethyl-4-hydroxy-3-methoxy-2-oxa-bicyclo-[3.3.0]octane (95)



To a solution of **94** (3.0 g, 7.31 mmol) in anhydrous MeOH (20 mL) was added Amberlyst-15 (2.0 g) and refluxed for 2 h. After completion of the reaction, the resin was filtered off through a plug of cotton and the filtrate was concentrated on rotavapor. The residue was purified by flash-column chromatography on silica gel using EtOAc–light petroleum (1:4) to furnish pure α-isomer of **95** (1.26 g, 45%) and β-isomer of **95** (1.26 g, 45%) as syrups.

Note: Though we have often carried out the reactions with a mixture of α- and β-isomers, spectral data of α-isomeric compounds has been taken for the sake of clarity and henceforth the same has been reported.

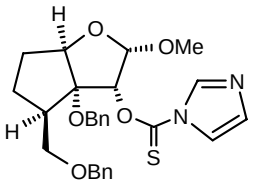
$[\alpha]_D$ +88.7 (*c* 1.2, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): ***δ*** 1.38–1.85 (m, 3 H), 1.94–2.11 (m, 1 H), 2.46–2.71 (m, 1 H), 3.08–3.17 (m, 1 H), 3.43 (s, 3 H), 3.56 (dd, 1 H, *J* = 8.4, 9.5 Hz), 3.82 (dd, 1 H, *J* = 4.6, 9.5 Hz), 3.91 (dd, 1 H, *J* = 4.4, 10.9 Hz), 4.47–4.68 (m, 5 H), 4.81 (d, 1 H, *J* = 4.3 Hz), 7.24–7.35 (m, 10 H).

^{13}C NMR (50 MHz, $CDCl_3$): ***δ*** 27.0, 30.7, 44.6, 54.6, 65.9, 69.6, 73.2, 84.1, 88.5, 103.1, 126.8, 127.4, 128.2, 138.5.

Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 71.58; H, 7.48.

(1*R*,3*S*,4*R*,5*R*,6*R*)-5-Benzyloxy-6-benzyloxymethyl-4-(*N*-imidazolylthiocarbonyloxy)-3-methoxy-2-oxa-bicyclo[3.3.0]octane (96)



To a solution of **95** (2.0 g, 5.20 mmol) in anhydrous toluene (20 mL) was added 1,1'-thiocarbonyldiimidazole (1.4 g, 7.85 mmol) and stirred under reflux for 2 h. The mixture was allowed to cool to room temperature and the solvent was removed under vacuum. The residue was purified by silica gel column chromatography with EtOAc–light petroleum (1:4) as an eluent to furnish **96** (2.49 g, 97%) as syrup.

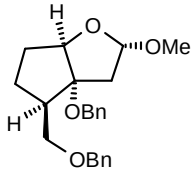
$[\alpha]_D$ +63.4 (*c* 0.5, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60–1.92 (m, 4 H), 2.50–2.63 (m, 1 H), 3.40 (s, 3 H), 3.51–3.64 (m, 2 H), 4.38 (d, 2 H, *J* = 1.4 Hz), 4.68–4.85 (m, 3 H), 5.29 (d, 1 H, *J* = 4.6 Hz), 5.62 (d, 1 H, *J* = 4.6 Hz), 6.91 (s, 1 H), 7.16–7.32 (m, 10 H), 7.47 (s, 1 H), 8.21 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 26.6, 30.1, 47.9, 55.0, 67.2, 69.2, 73.4, 79.5, 84.1, 90.0, 100.8, 117.9, 126.3, 127.1, 127.4, 128.0, 128.2, 130.5, 136.9, 137.6, 139.1, 183.5.

Anal. Calcd for $C_{27}H_{30}O_5N_2S$: C, 65.57; H, 6.11; N, 5.66; S, 6.48. Found: C, 65.46; H, 6.27; N, 5.49; S, 6.30.

(1*R*,3*S*,5*R*,6*R*)-5-Benzyloxy-6-benzyloxymethyl-3-methoxy-2-oxa-bicyclo[3.3.0]octane (90)



To a mixture of **96** (2.4 g, 4.85 mmol) and AIBN (0.16 g, 0.97 mmol) in anhydrous toluene (30 mL) was added *n*-Bu_3SnH (2 mL, 7.54 mmol), degassed with argon for 20 min and then stirred under reflux for 6 h. The mixture was allowed to attain room temperature and the solvent was removed under vacuo. The residue was chromatographed on silica gel with EtOAc–light petroleum (1:5) to obtain **90** (1.54 g, 86%) as syrup.

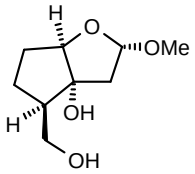
$[\alpha]_D$ +44.0 (*c* 1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.40–1.49 (m, 1 H), 1.71–1.82 (m, 2 H), 1.87–1.96 (m, 1 H), 2.12 (dd, 1 H, *J* = 0.9, 14.5 Hz), 2.21 (dd, 1 H, *J* = 5.5, 14.5 Hz), 2.44 (dt, 1 H, *J* = 18.8, 6.6 Hz), 3.35 (s, 3 H), 3.47 (dd, 1 H, *J* = 6.5, 9.5 Hz), 3.53 (dd, 1 H, *J* = 6.5, 9.5 Hz), 4.47–4.53 (m, 3 H), 4.57 (ABq, 2 H, *J* = 12.3 Hz), 4.97 (dd, 1 H, *J* = 1.0, 5.5 Hz), 7.20–7.33 (m, 10 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 27.8, 30.1, 38.7, 48.3, 54.5, 66.7, 70.9, 73.1, 86.4, 94.3, 105.5, 127.1, 127.5, 128.2, 128.3, 138.3, 139.5.

Anal. Calcd for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 75.18; H, 7.78.

(1*R*,3*S*,5*R*,6*R*)-5-Hydroxy-6-hydroxymethyl-3-methoxy-2-oxa-bicyclo[3.3.0]octane (97)



The reaction was carried out as described earlier using compound **90** (1.5 g, 4.07 mmol) and 20% $Pd(OH)_2/C$ (0.1 g) in MeOH (15 mL) under H_2 atmosphere at normal temperature and pressure. After usual work-up and purification on silica gel using EtOAc–light petroleum (4:1) furnished **97** (0.6 g, 78%) as syrup.

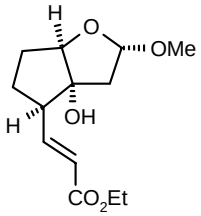
$[\alpha]_D$ +78.0 (*c* 0.5, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.21–1.30 (m, 1 H), 1.64–1.75 (m, 3 H), 1.87–1.94 (m, 1 H), 1.97–1.99 (m, 1 H), 2.20–2.28 (m, 1 H), 3.16 (s, 1 H), 3.36 (s, 3 H), 3.64 (t, 1 H, J = 9.9 Hz), 3.70–3.76 (m, 1 H), 4.29 (d, 1 H, J = 7.3 Hz), 5.07 (d, 1 H, J = 3.6 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.2, 29.9, 41.5, 49.7, 54.4, 63.0, 89.7, 90.4, 105.6.

Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.38; H, 8.78.

(1*R*,3*S*,5*R*,6*R*)-6-[Ethyl-3-(prop-2-ene)-ate]-5-hydroxy-3-methoxy-2-oxa-bicyclo[3.3.0]octane (89)



To a suspension of IBX (1.5 g, 5.36 mmol) and **97** (0.5 g, 2.65 mmol) in anhydrous benzene (30 mL) was added (ethoxycarbonylmethylene)triphenylphosphorane (1.85 g, 5.31 mmol) and stirred under reflux for 2 h. The residue was filtered off through a plug of Celite and the filtrate concentrated on rotavapor to give crude syrup. The crude syrup was chromatographed on silica gel with EtOAc–light petroleum (1:3) to give **89** (0.55 g, 81%) as colorless syrup.

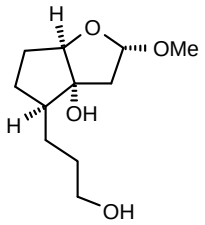
$[\alpha]_D$ +46.0 (*c* 0.5, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, 3 H, *J* = 7.1 Hz), 1.50–1.71 (m, 2 H), 1.74–1.96 (m, 4 H), 2.65–2.80 (m, 1 H), 3.35 (s, 3 H), 4.19 (q, 2 H, *J* = 7.1 Hz), 4.29 (d, 1 H, *J* = 6.6 Hz), 5.04 (t, 1 H, *J* = 2.2 Hz), 5.88 (dd, 1 H, *J* = 1.6, 15.8 Hz), 6.98 (dd, 1 H, *J* = 6.2, 15.8 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2, 27.9, 29.7, 42.9, 50.6, 54.4, 60.3, 89.8, 90.1, 105.4, 122.7, 146.5, 166.5.

Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.74; H, 7.98.

(1*R*,3*S*,5*R*,6*R*)-5-Hydroxy-3-methoxy-6-[3-(propan-1-ol)]-2-oxa-bicyclo[3.3.0]octane (99)



The reaction was carried out as described earlier using compound **89** (0.5 g, 1.95 mmol) and $LiAlH_4$ (0.15 g, 3.95 mmol) in anhydrous ether (15 mL), and then subjected to hydrogenation conditions using Raney Ni (0.05 g) in MeOH (6 mL) under H_2 atmosphere for 6 h to afford **99** (0.32 g, 76%) as syrup.

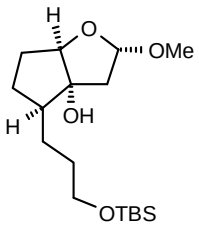
$[\alpha]_D$ +48.6 (*c* 0.5, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.54–2.08 (m, 11 H), 3.36 (s, 3 H), 3.61–3.72 (m, 2 H), 4.27 (d, 1 H, *J* = 6.7 Hz), 5.07 (d, 1 H, *J* = 3.8 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.8, 29.5, 29.7, 31.2, 41.7, 47.5, 54.3, 62.7, 90.0, 90.8, 105.5.

Anal. Calcd for $C_{11}H_{20}O_5$: C, 61.09; H, 9.32. Found: C, 61.24; H, 9.52.

(1*R*,3*S*,5*R*,6*R*)-5-Hydroxy-3-methoxy-6-[3-(1,1,2,2-tetramethyl-1-silapropoxy)prop-yl]-2-oxa-bicyclo[3.3.0]octane (101)



TBDMSCl (0.125 g, 0.83 mmol) was added to a mixture of **99** (0.15 g, 0.69 mmol) and imidazole (0.07 g, 1.03 mmol) in anhydrous CH_2Cl_2 (6 mL) and stirred at room temperature for 30 min. The reaction mixture was quenched with saturated aq. $NaHCO_3$ solution (2 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), concentrated and the residue was purified by silica gel column chromatography using EtOAc–light petroleum (1:7) as an eluent to afford **101** (0.195 g, 85%) as syrup.

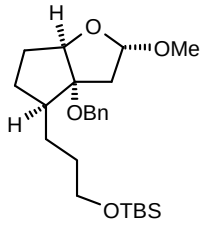
$[\alpha]_D$ +51.7 (*c* 1, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): ***δ*** 0.05 (s, 6 H), 0.89 (s, 9 H), 1.48–2.05 (m, 11 H), 3.36 (s, 3 H), 3.61 (dt, 2 H, *J* = 6.1, 1.7 Hz), 4.27 (d, 1 H, *J* = 6.8 Hz), 5.06 (d, 1 H, *J* = 3.7 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): ***δ*** –5.3, 18.3, 25.9, 29.6, 29.7, 31.7, 41.8, 47.9, 54.4, 63.5, 90.0, 90.9, 105.6.

Anal. Calcd for $C_{17}H_{34}O_4Si$: C, 61.77; H, 10.37. Found: C, 61.57; H, 10.56.

(1*R*,3*S*,5*R*,6*R*)-5-Benzyloxy-3-methoxy-6-[3-(1,1,2,2-tetramethyl-1-silapropoxy)prop-yl]-2-oxa-bicyclo[3.3.0]octane (88)



The reaction was carried out as described earlier using **101** (0.15 g, 0.45 mmol), benzyl bromide (0.07 mL, 0.59 mmol), TBAI (0.02 g, 0.05 mmol) and 60% oily dispersion of NaH (0.027 g, 0.68 mmol) in anhydrous DMF (5 mL) to give **88** (0.15 g, 78%) as syrup.

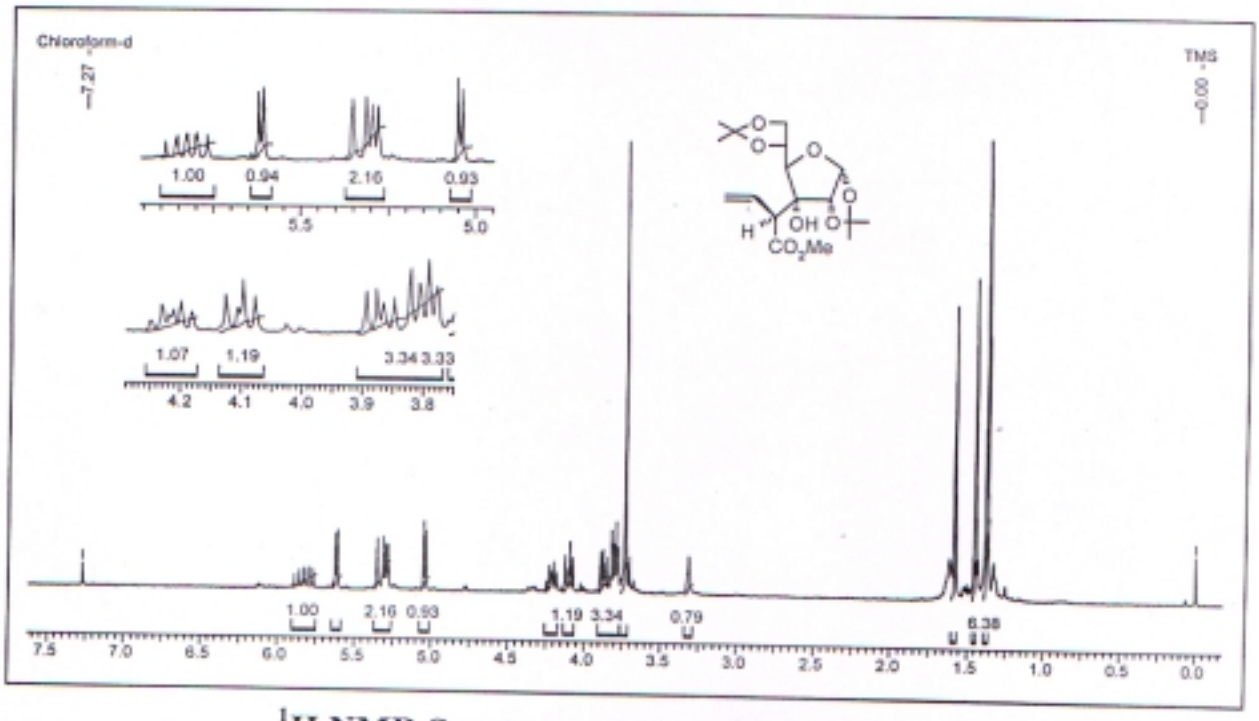
$[\alpha]_D$ +53.7 (*c* 1.5, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): ***δ*** 0.04 (s, 6 H), 0.89 (s, 9 H), 1.22–1.33 (m, 1 H), 1.43–1.88 (m, 8 H), 1.98–2.14 (m, 2 H), 3.38 (s, 3 H), 3.54–3.67 (m, 2 H), 4.47–4.67 (m, 3 H), 5.03 (dd, 1 H, *J* = 2.2, 3.9 Hz), 7.23–7.38 (m, 5 H).

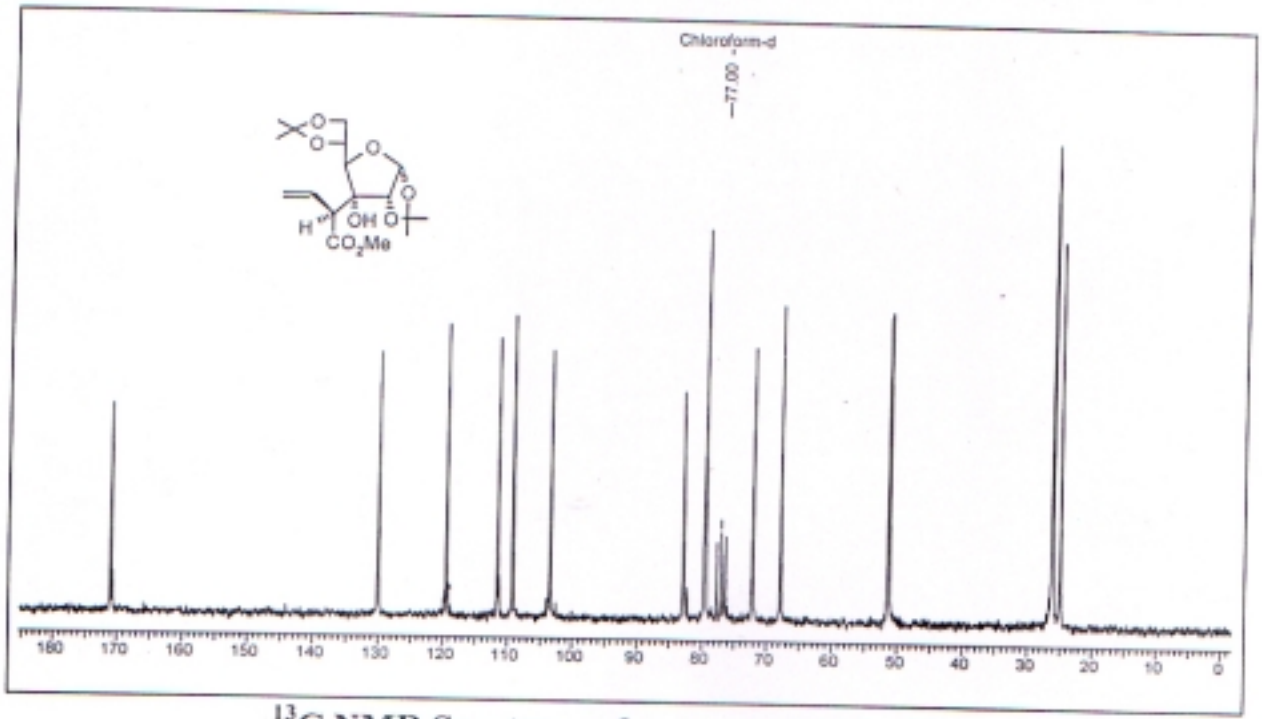
^{13}C NMR (50 MHz, $CDCl_3$): ***δ*** –5.3, 18.3, 25.9, 26.7, 29.5, 30.7, 31.8, 38.8, 48.1, 54.5, 63.3, 66.4, 85.6, 95.4, 105.4, 127.0, 128.2, 139.7.

Anal. Calcd for $C_{24}H_{40}O_4Si$: C, 68.53; H, 9.58. Found: C, 68.61; H, 9.67.

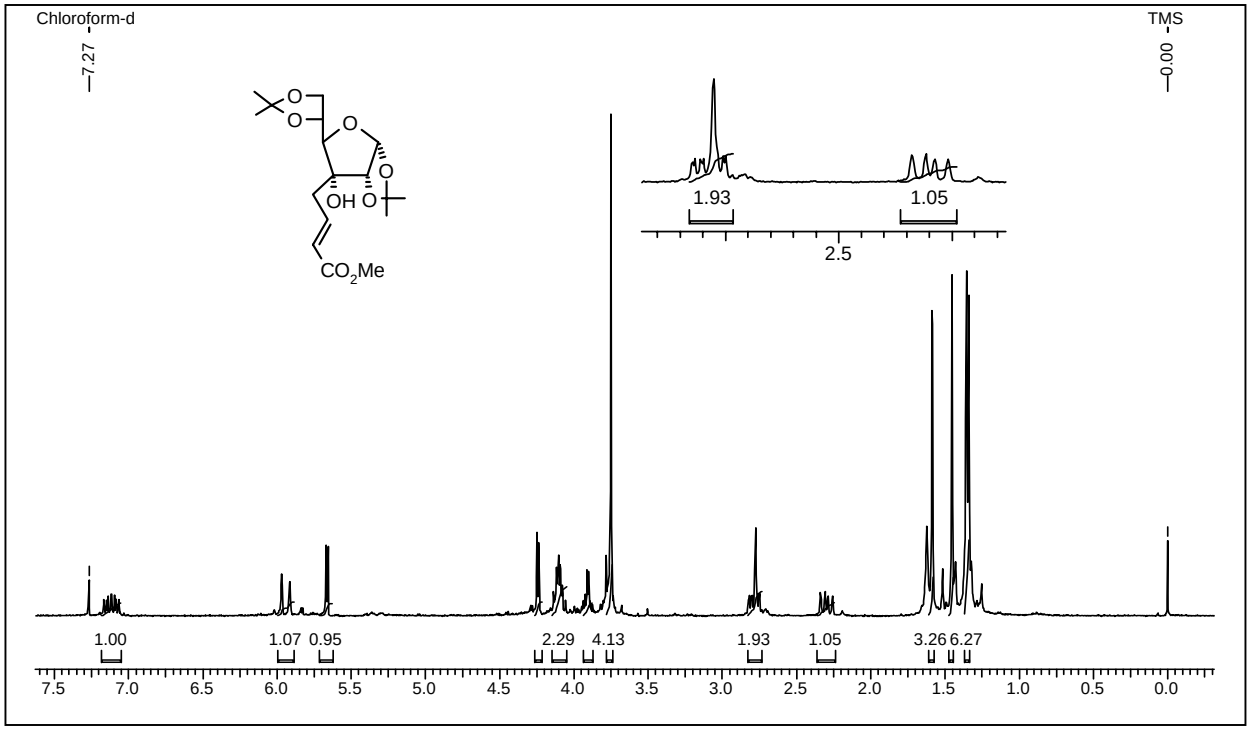
Spectra



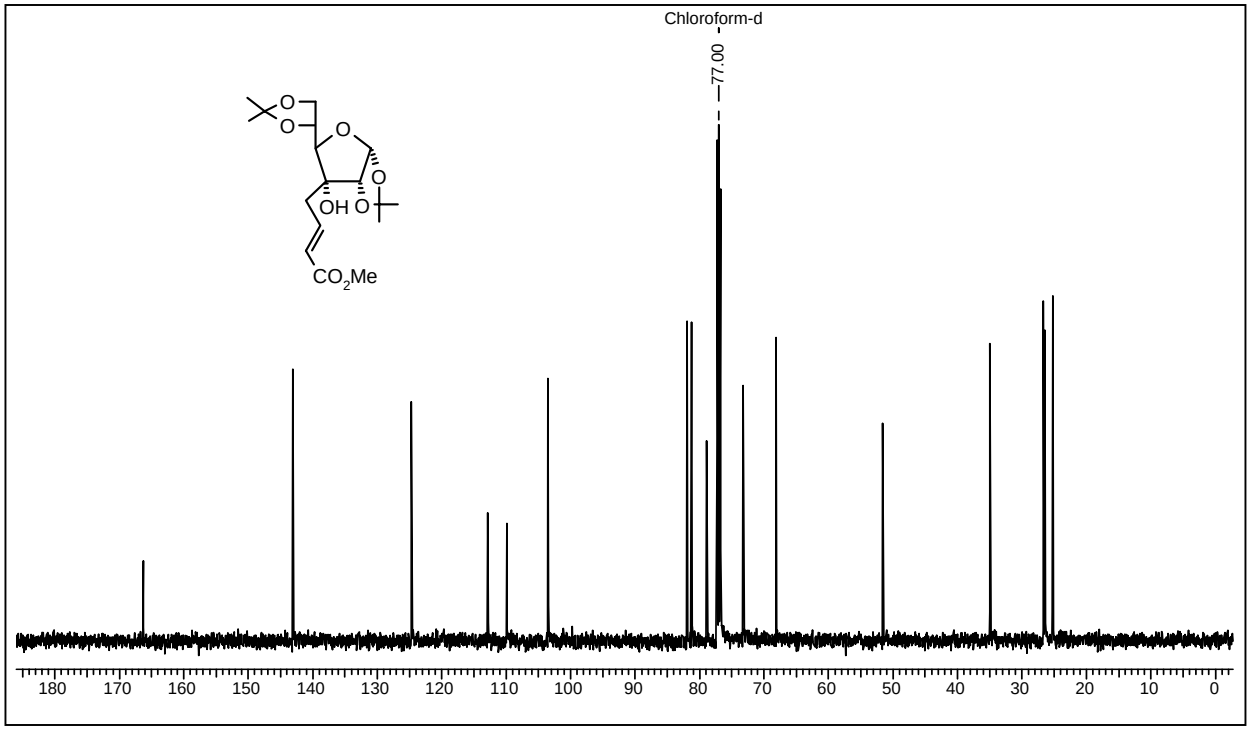
^{1}H NMR Spectrum of compound 56 in $CDCl_3$



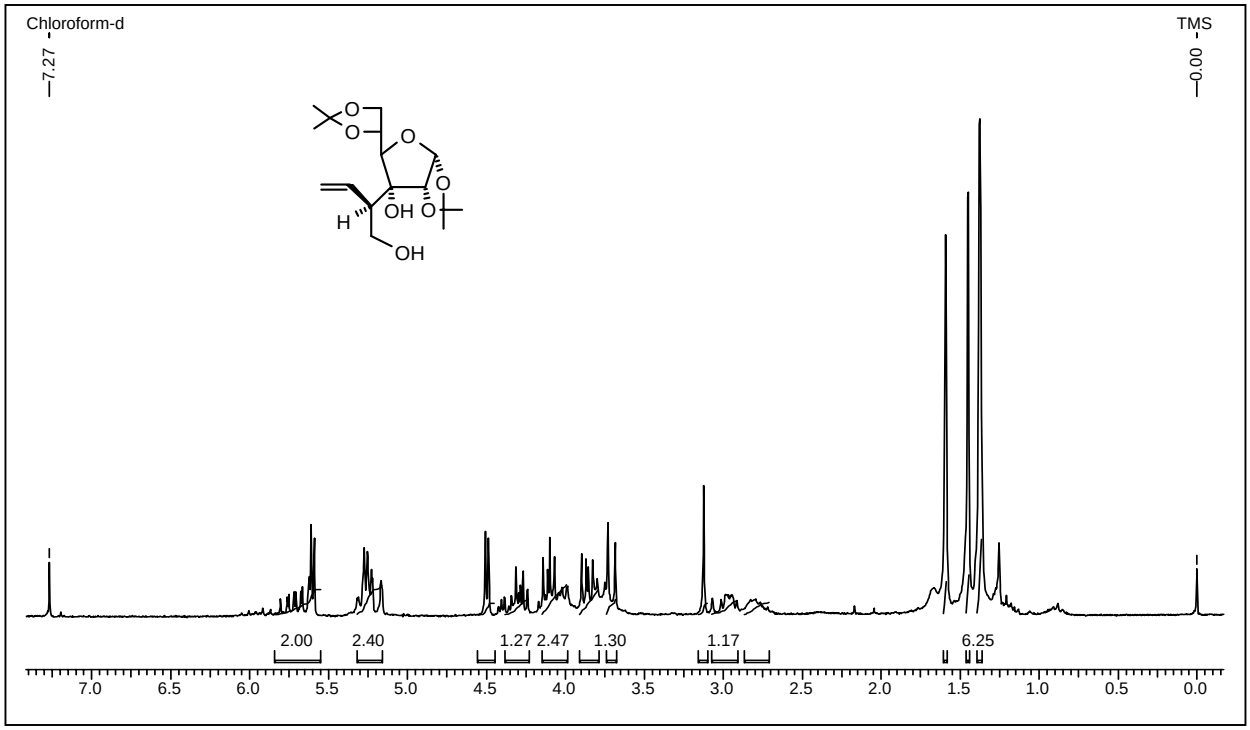
^{13}C NMR Spectrum of compound 56 in $CDCl_3$



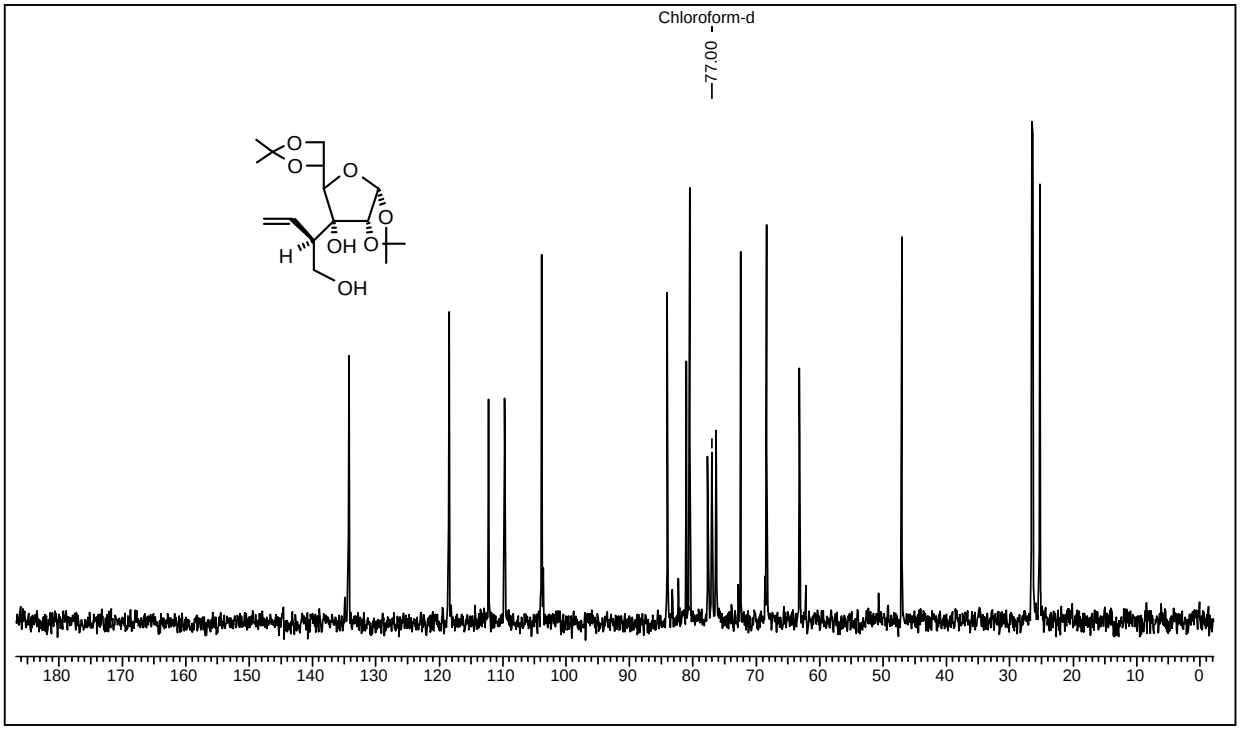
^{1}H NMR Spectrum of compound 57 in $CDCl_3$



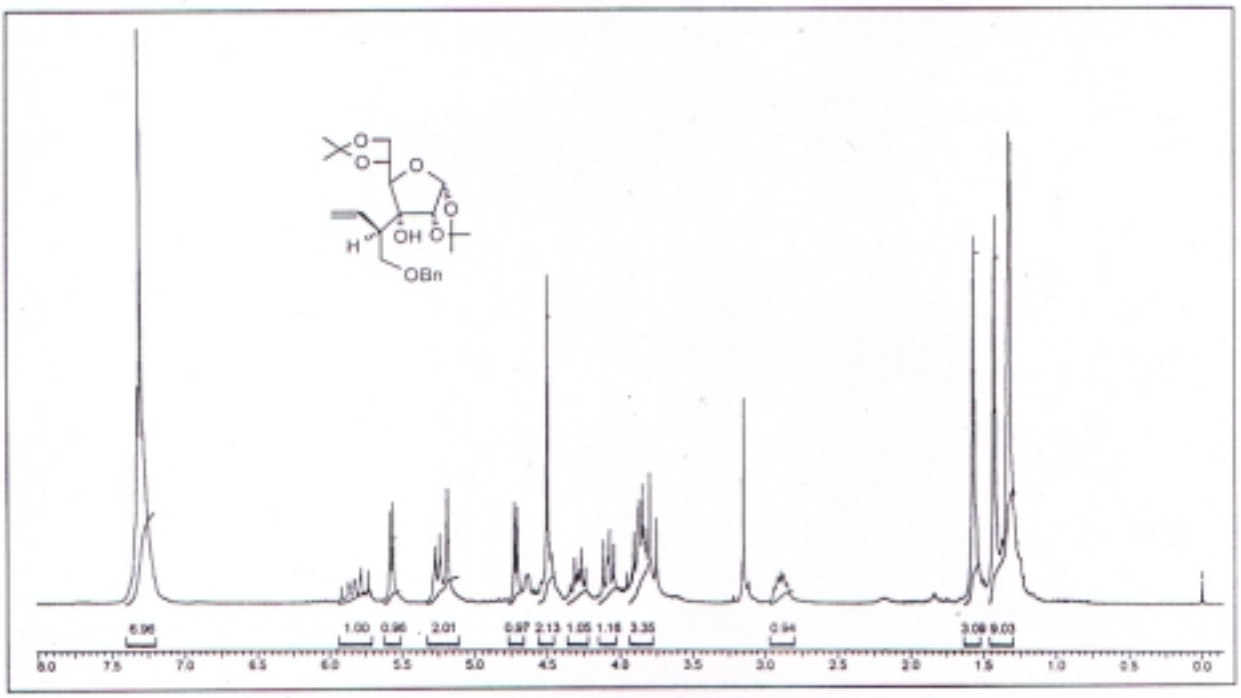
^{13}C NMR Spectrum of compound 57 in $CDCl_3$



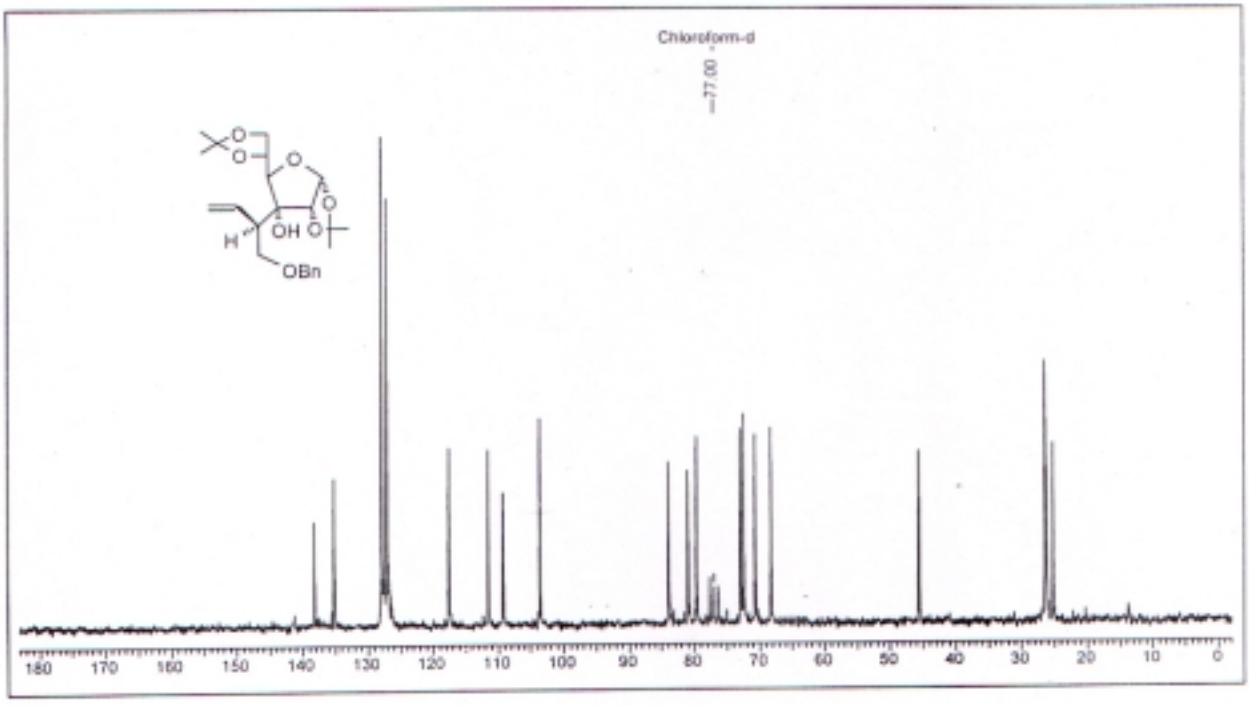
^{1}H NMR Spectrum of compound 58 in $CDCl_3$



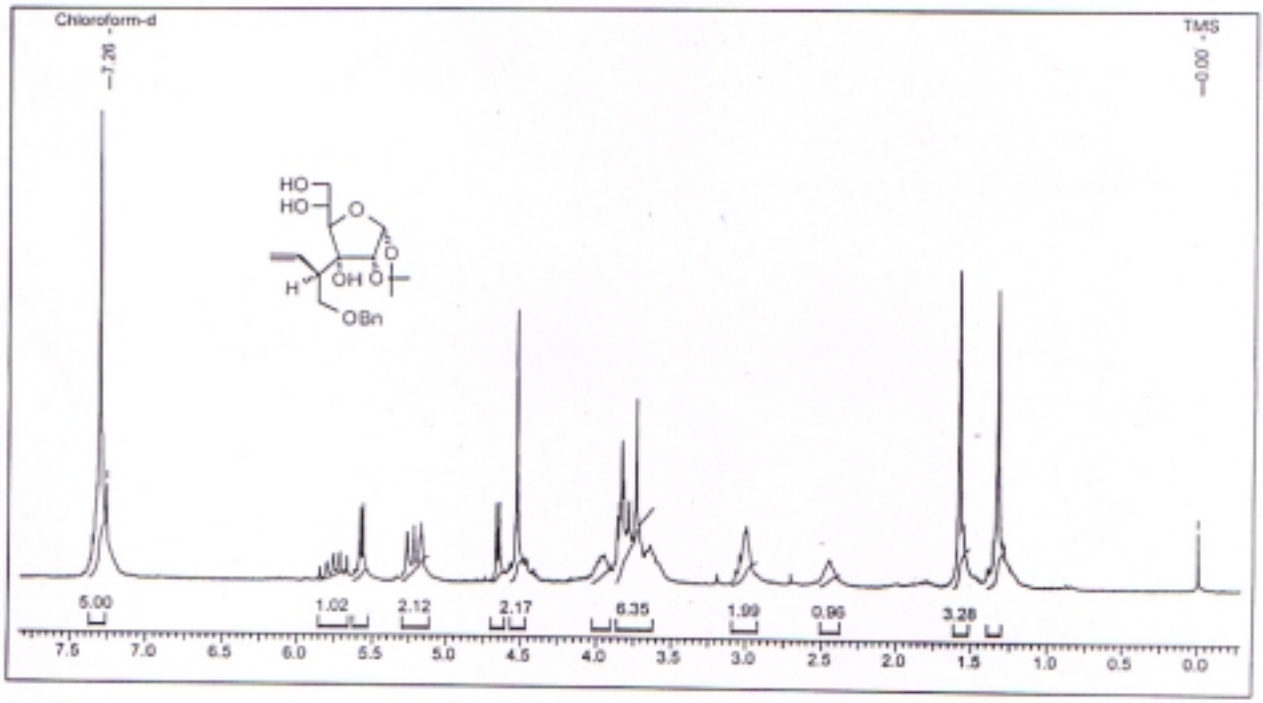
^{13}C NMR Spectrum of compound 58 in $CDCl_3$



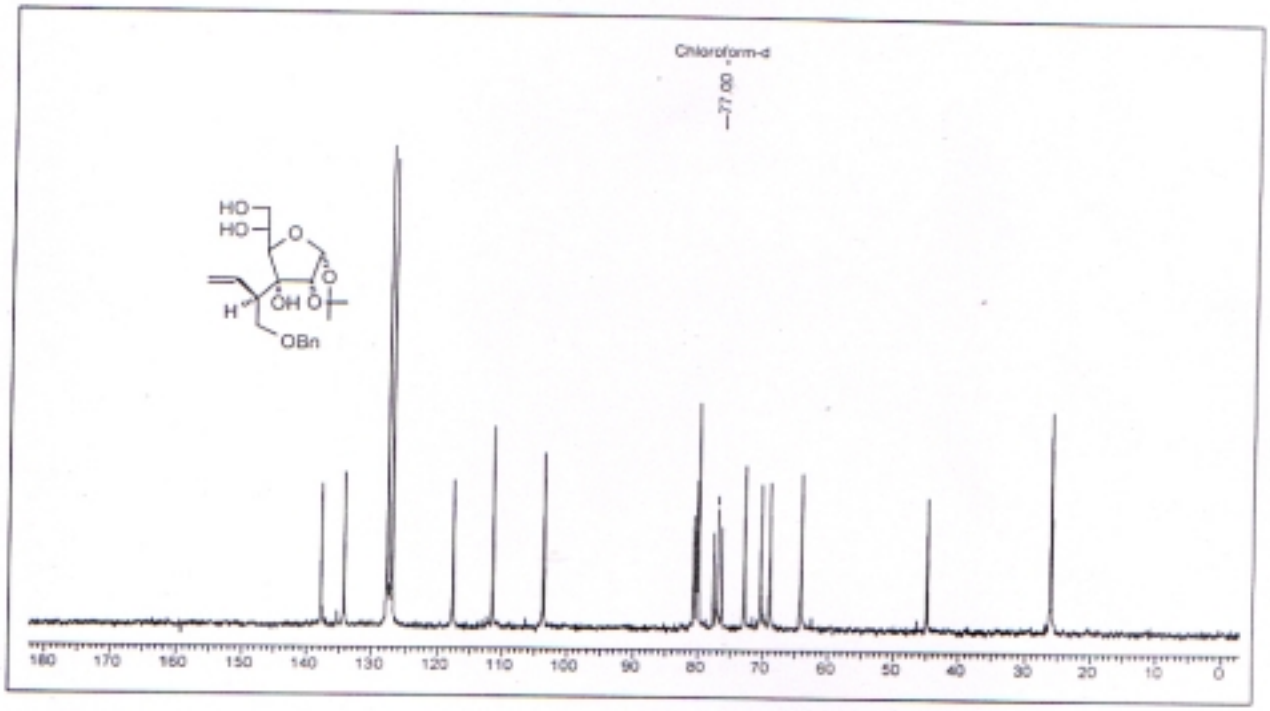
^{1}H NMR Spectrum of compound 59 in $CDCl_3$



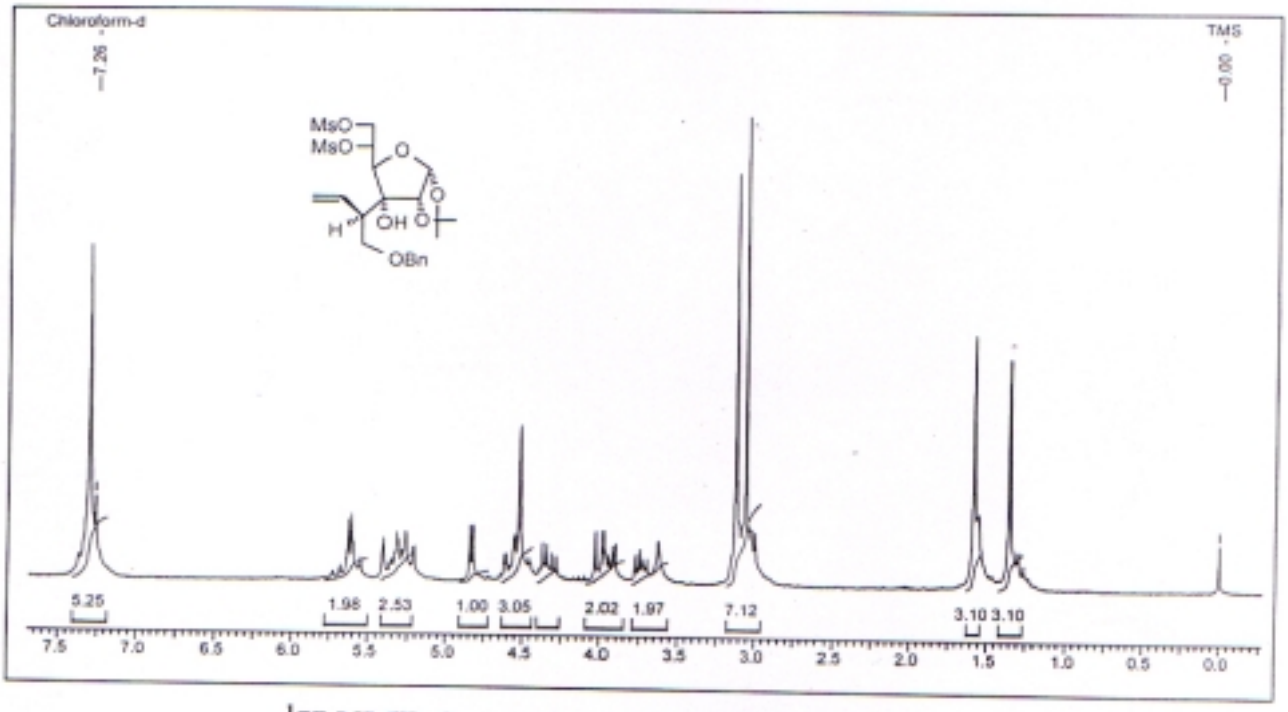
^{13}C NMR Spectrum of compound 59 in $CDCl_3$



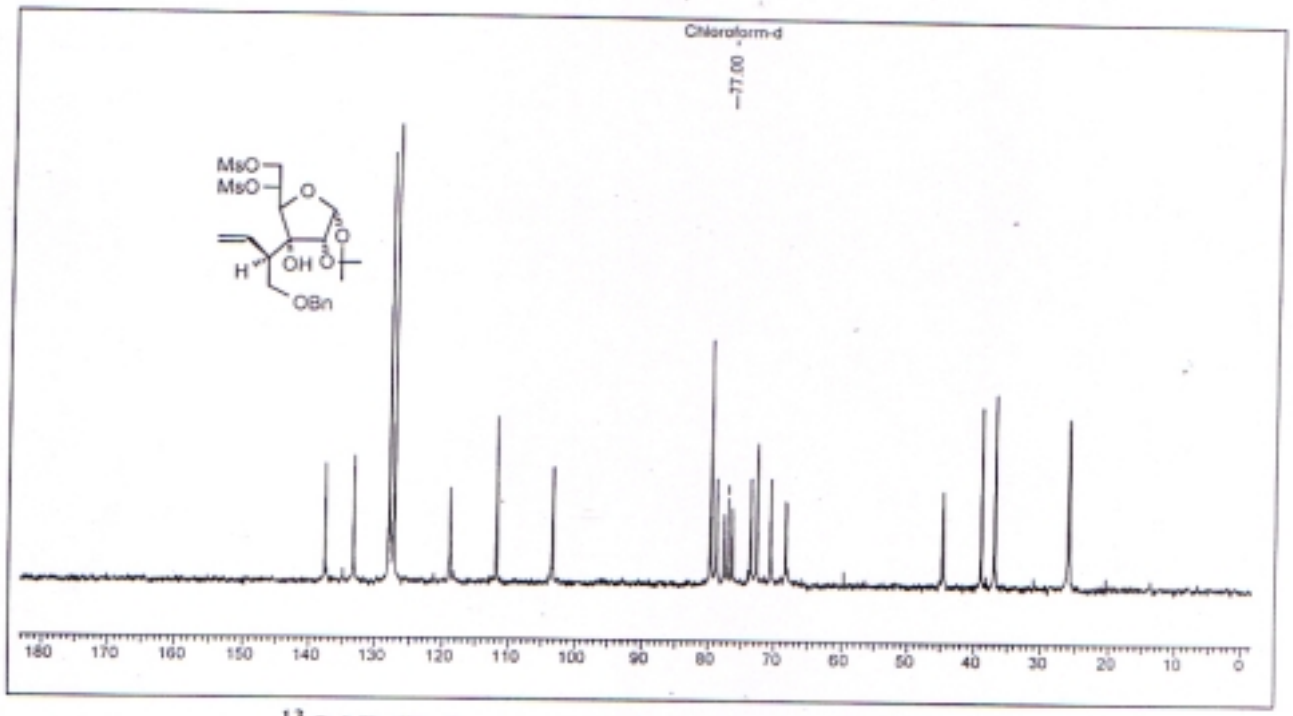
^{1}H NMR Spectrum of 3-*C*-[(*R*)-1-benzyloxymethyl-prop-2-enyl]-1,2-*O*-isopropylidene-α- D-allofuranose in $CDCl_3$



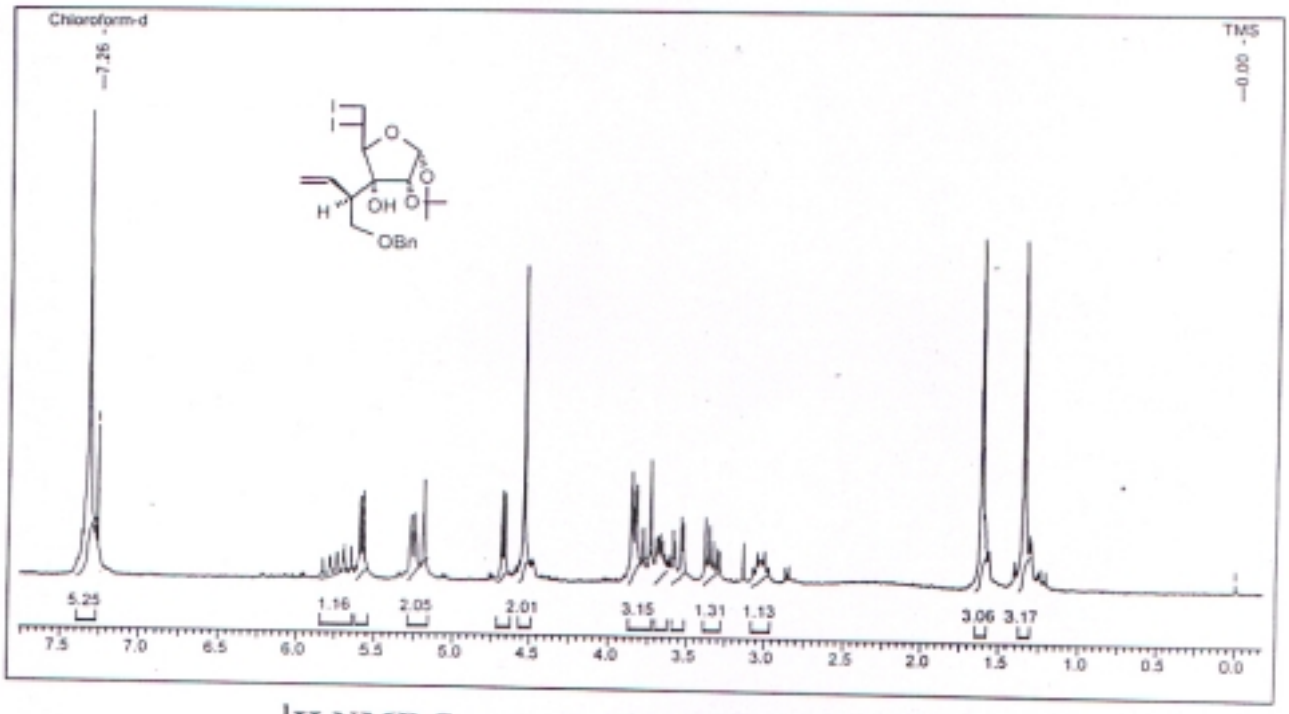
^{13}C NMR Spectrum of 3-*C*-[(*R*)-1-benzyloxymethyl-prop-2-enyl]-1,2-*O*-isopropylidene-α- D-allofuranose in $CDCl_3$



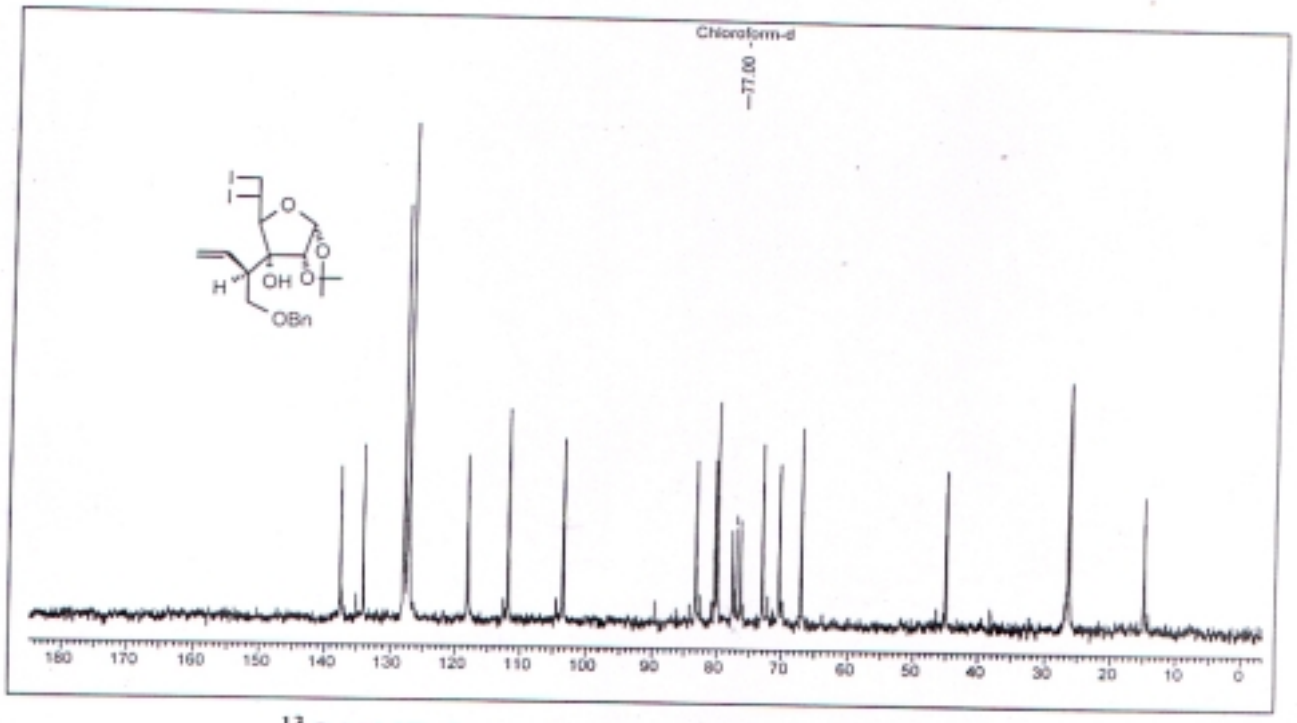
^{1}H NMR Spectrum of compound 60 in $CDCl_3$



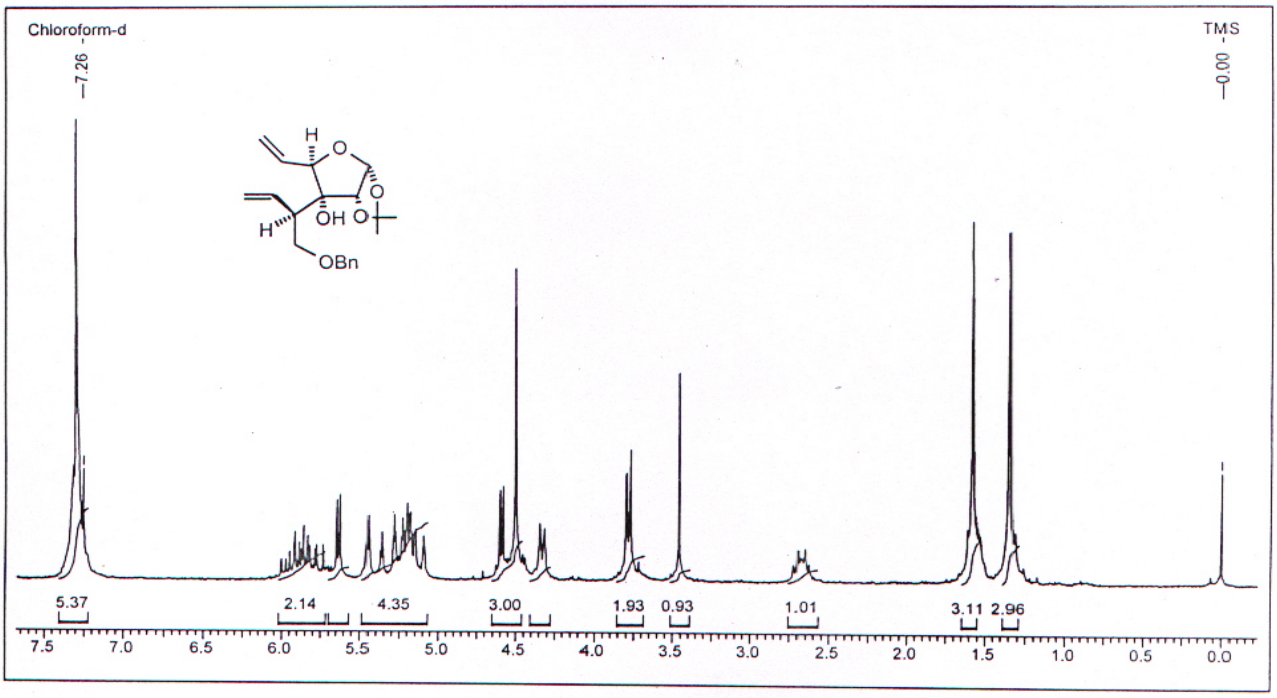
^{13}C NMR Spectrum of compound 60 in $CDCl_3$



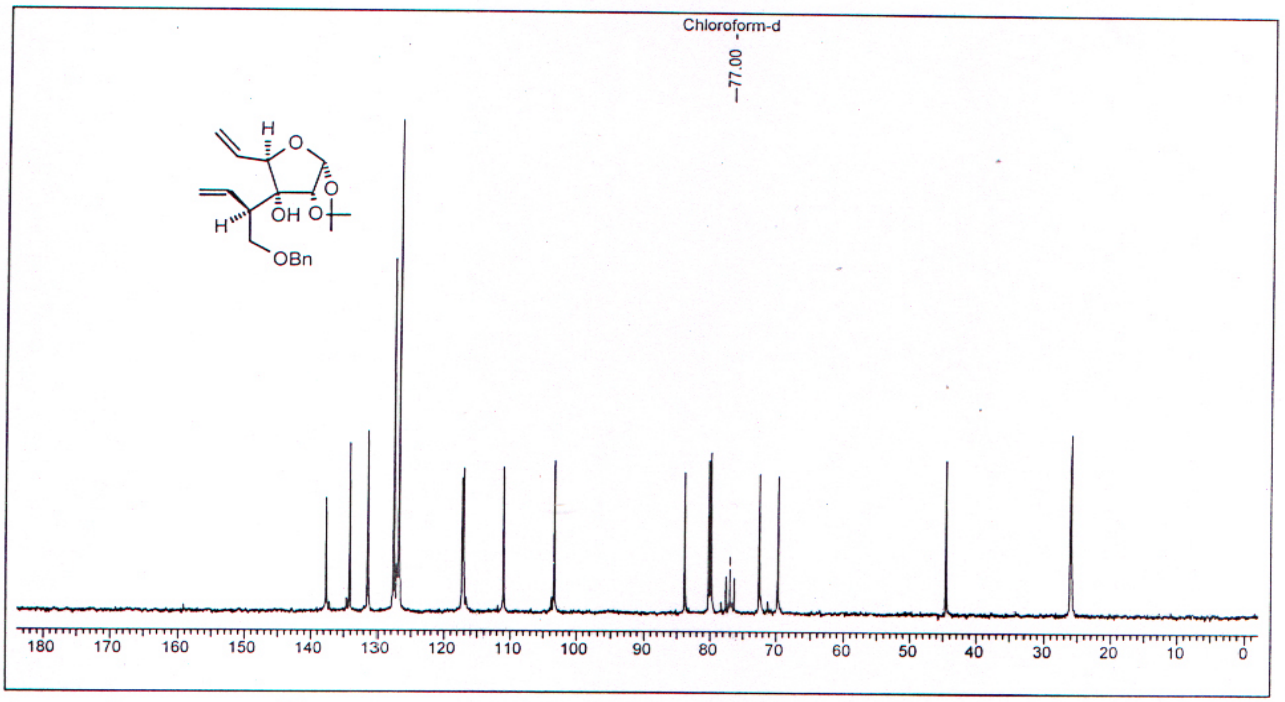
^{1}H NMR Spectrum of compound 62 in $CDCl_3$



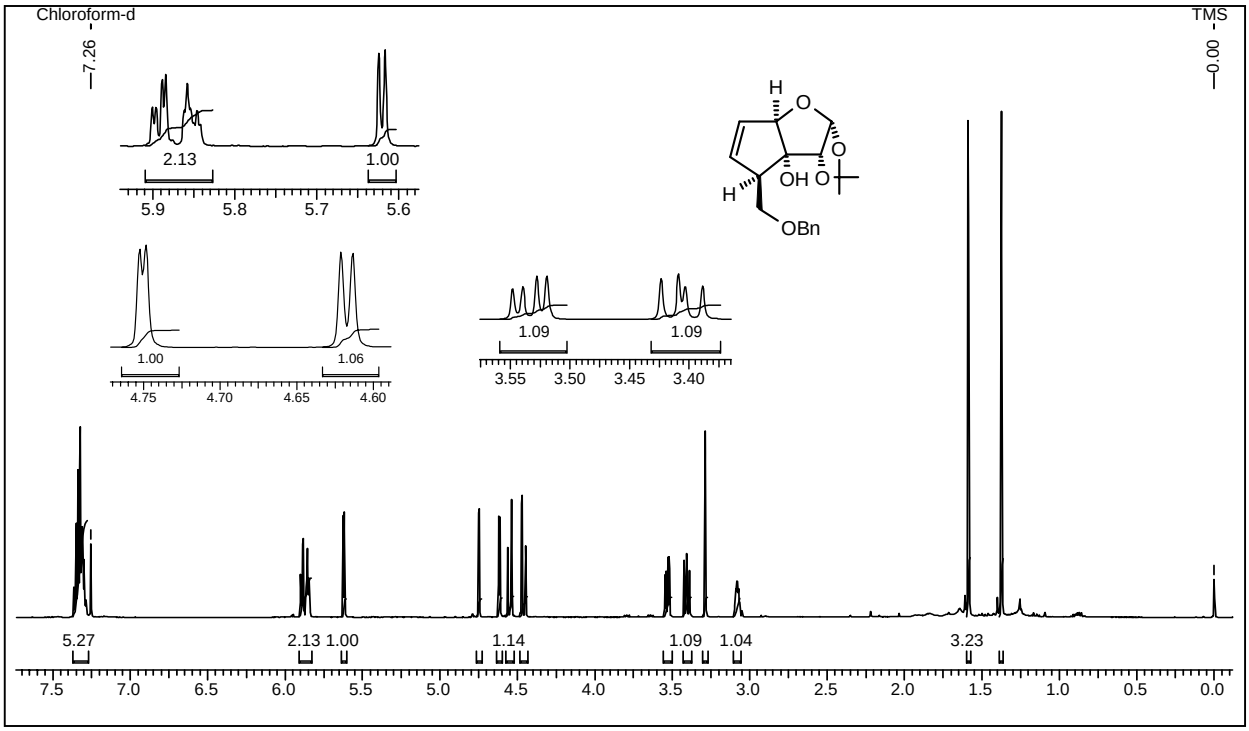
^{13}C NMR Spectrum of compound 62 in $CDCl_3$



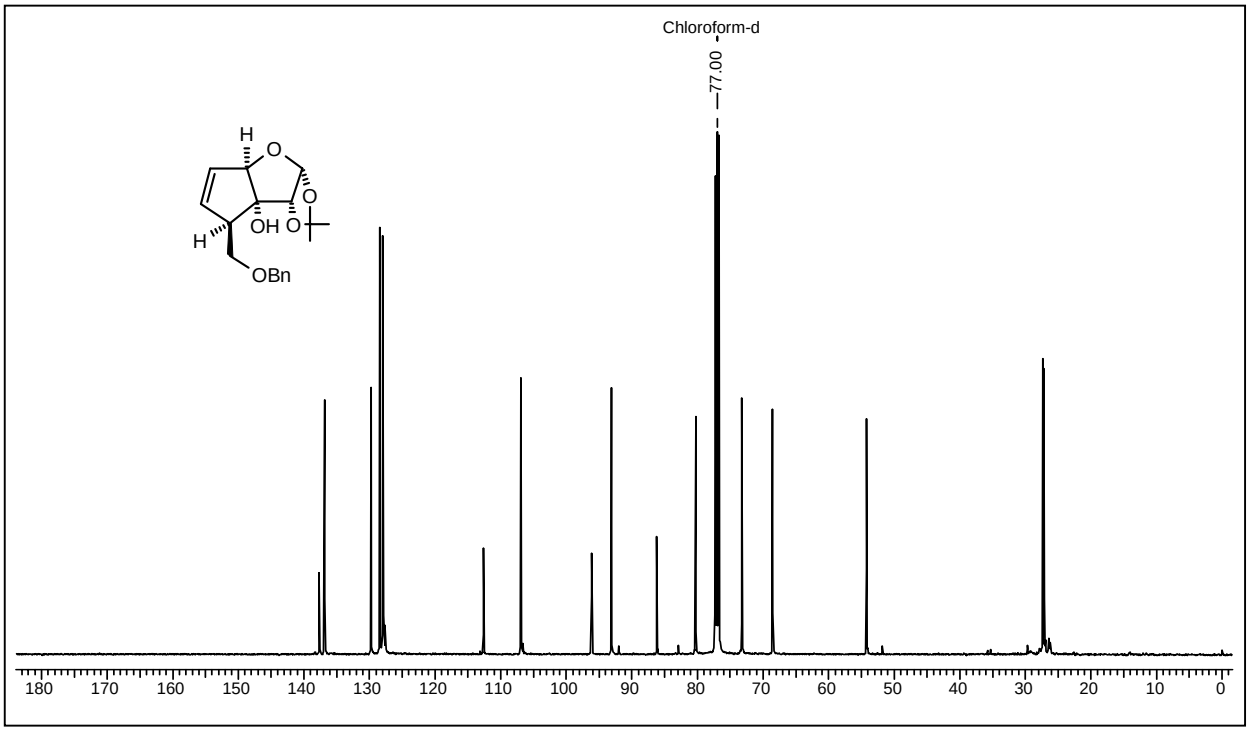
^{1}H NMR Spectrum of compound 61 in $CDCl_3$



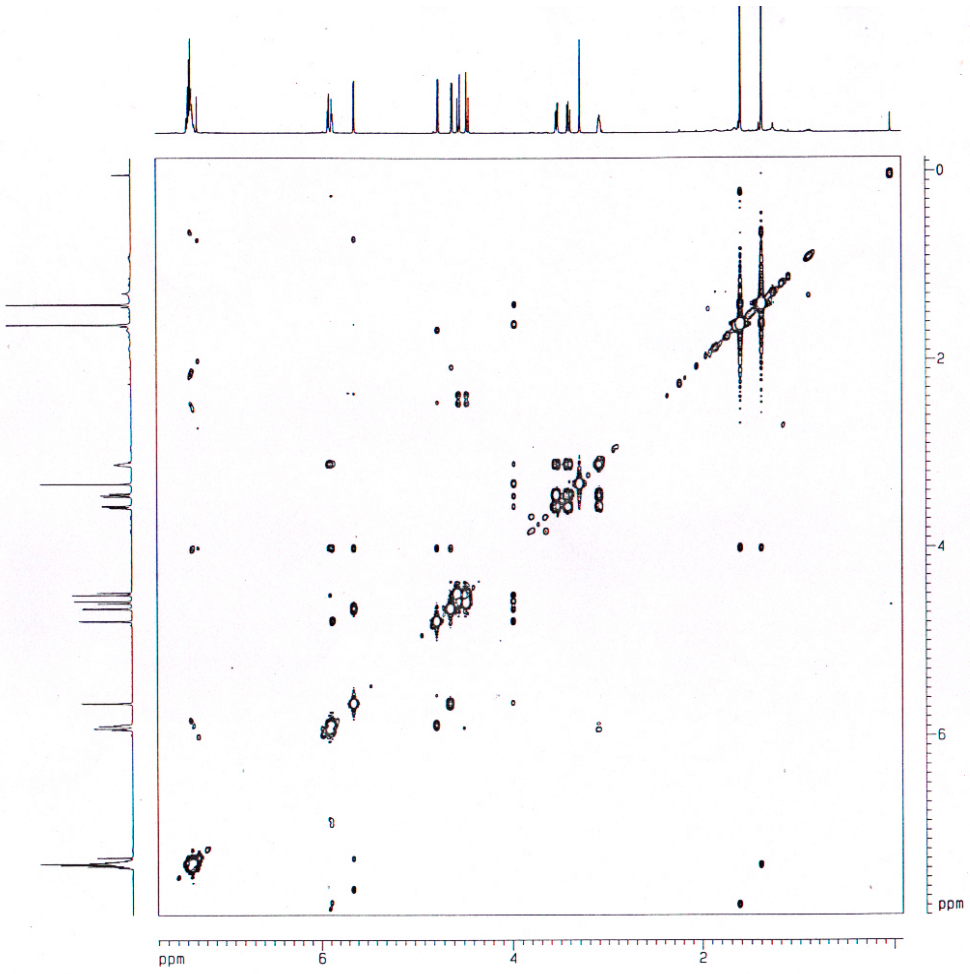
^{13}C NMR Spectrum of compound 61 in $CDCl_3$



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



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



COSY Spectrum of compound 64 in $CDCl_3$

D.P.S.Reddy;
Cosy; cdcl3

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EXPNO                          6
PROCNO                         1

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AQ                     0.1196532 sec
RG                          90.5
DW                       116.800 usec
DE                         6.00 usec
TE                       300.0 K
d0                     0.00000300 sec
D1                     2.50000000 sec
INO                    0.00023360 sec

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P1                          9.50 usec
PL1                        -2.00 dB
SFO1                 500.1320037 MHz

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TD                           256
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FIDRES                 16.721960 Hz
SW                         8.559 ppm

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WDW                        QSINE
SSB                            0
LB                          0.00 Hz
GB                             0
PC                          1.00

            F1 - Processing parameters
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MC2                           QF
SF                   500.1300000 MHz
WDW                        QSINE
SSB                            1
LB                          0.00 Hz
GB                             0

          2D NMR plot parameters
CX2                        15.00 cm
CX1                        15.00 cm
F2PLO                      7.709 ppm
F2LO                    3855.63 Hz
F2PHI                      -0.090 ppm

F1PLO                      7.902 ppm
F1LO                    3951.78 Hz
F1PHI                      -0.148 ppm
F1HI                      -74.03 Hz
F2PPMCM                 0.51992 ppm/cm
F2HZCM                260.02649 Hz/cm
F1PPMCM                 0.53654 ppm/cm
F1HZCM                268.38745 Hz/cm
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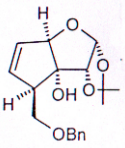
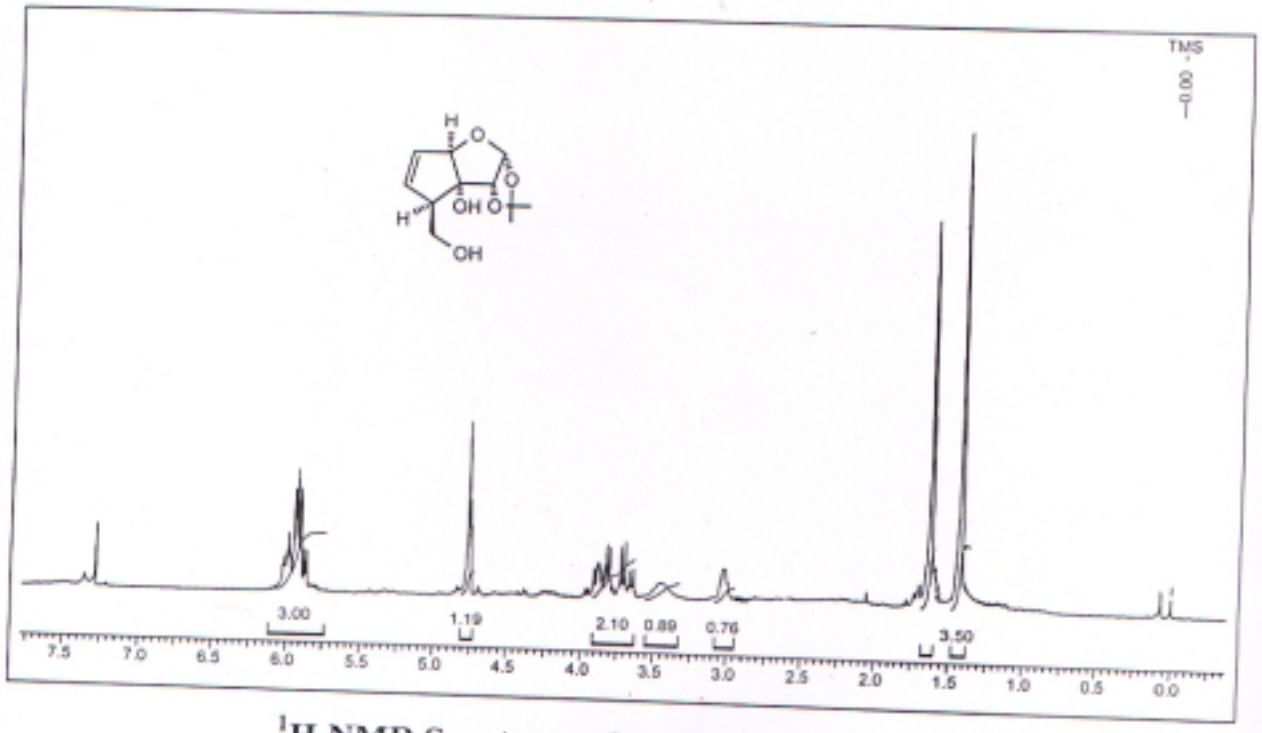
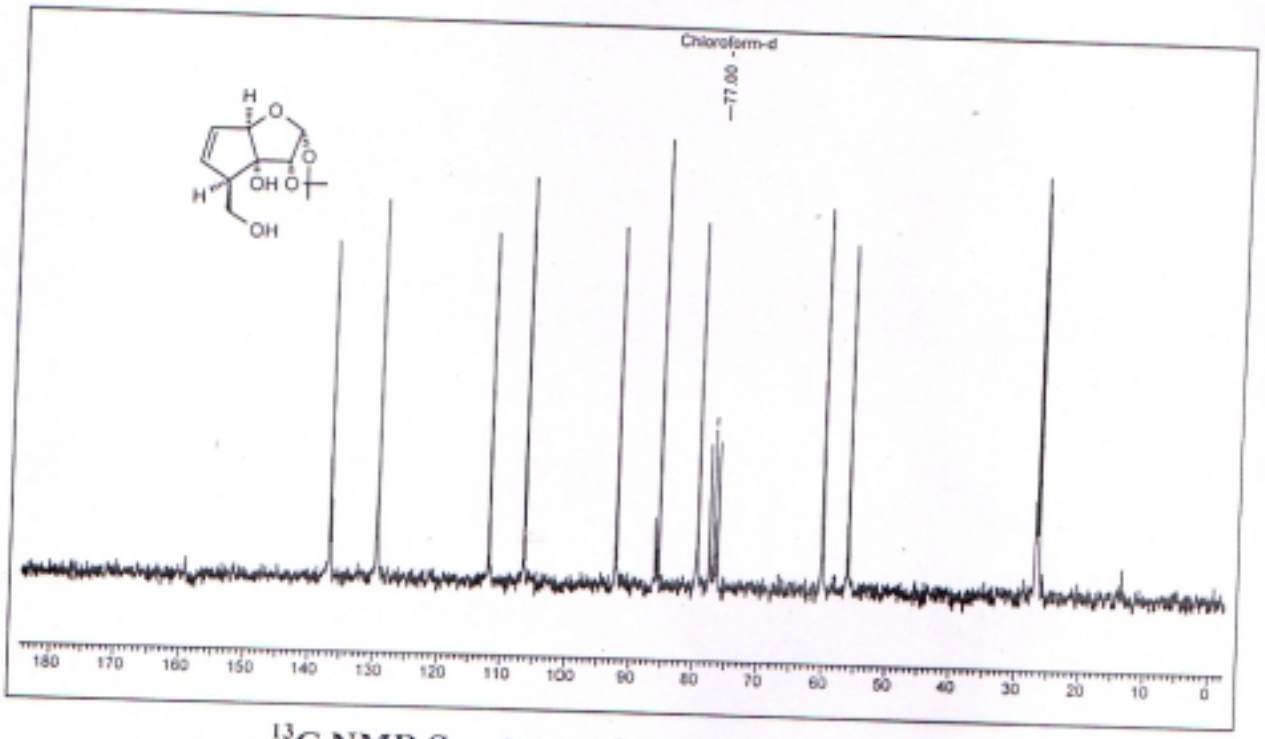
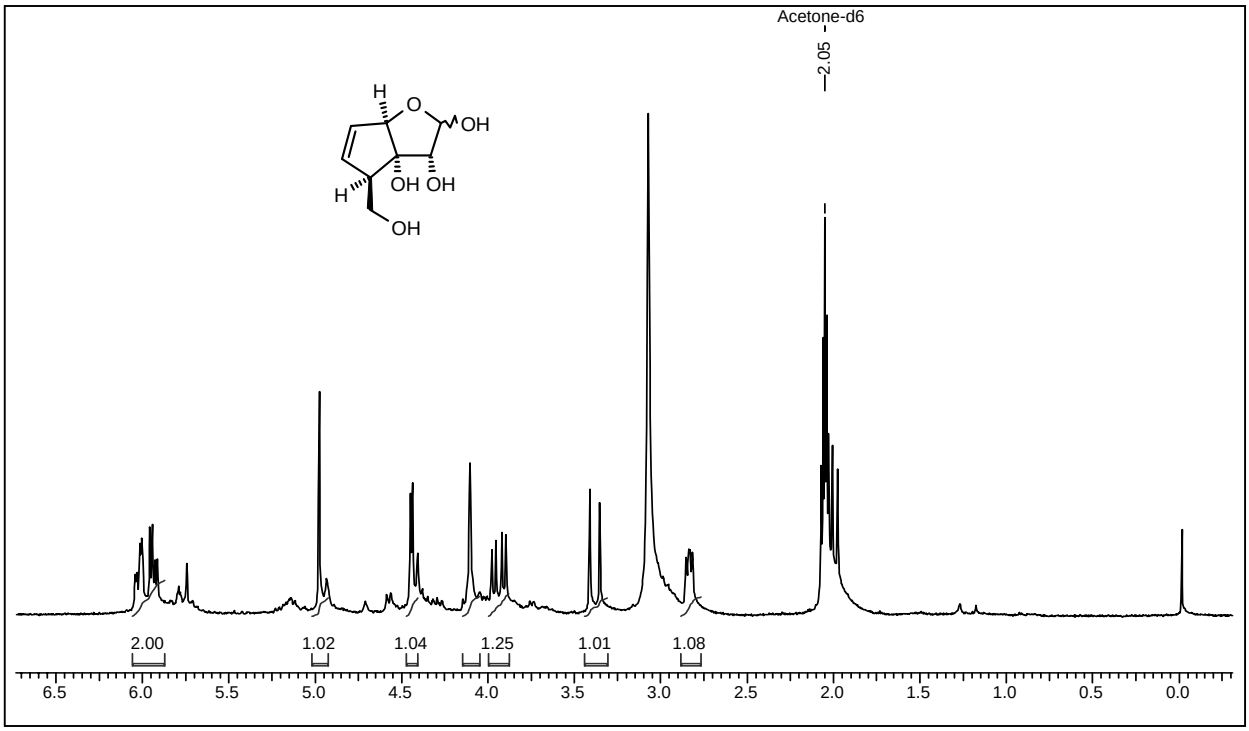




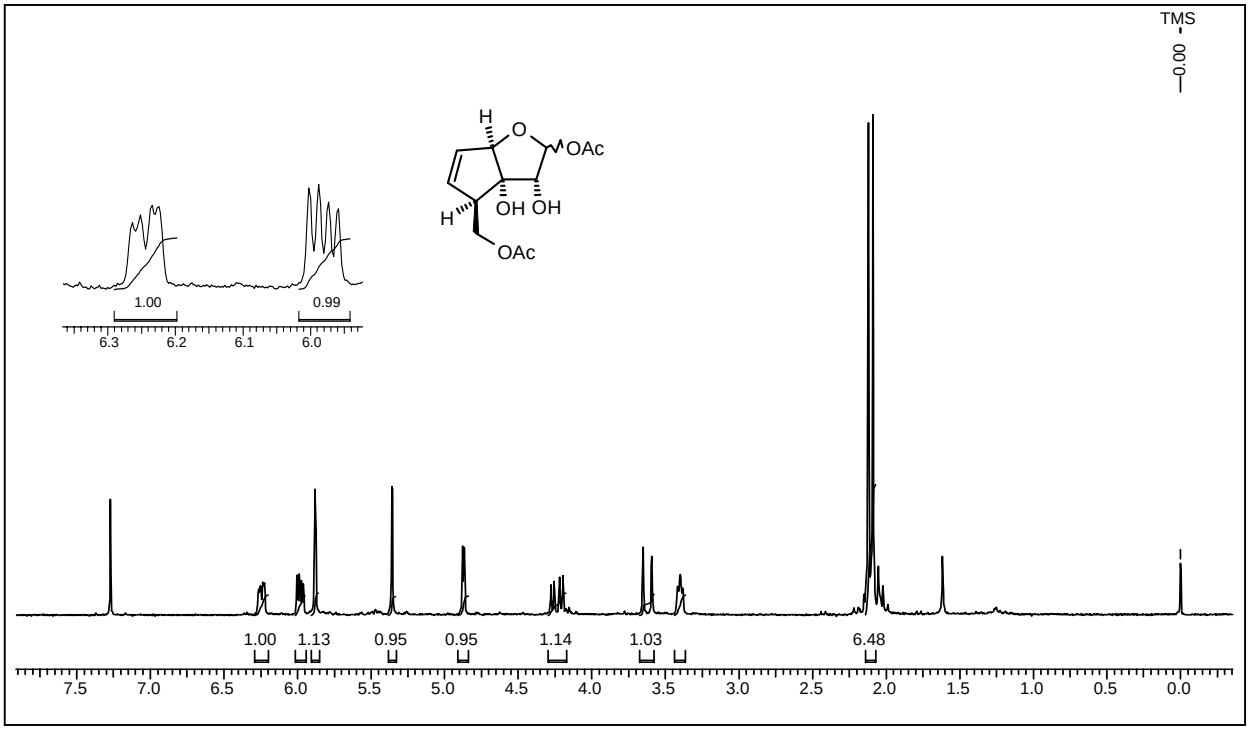
^{1}H NMR Spectrum of compound 65 in $CDCl_3$



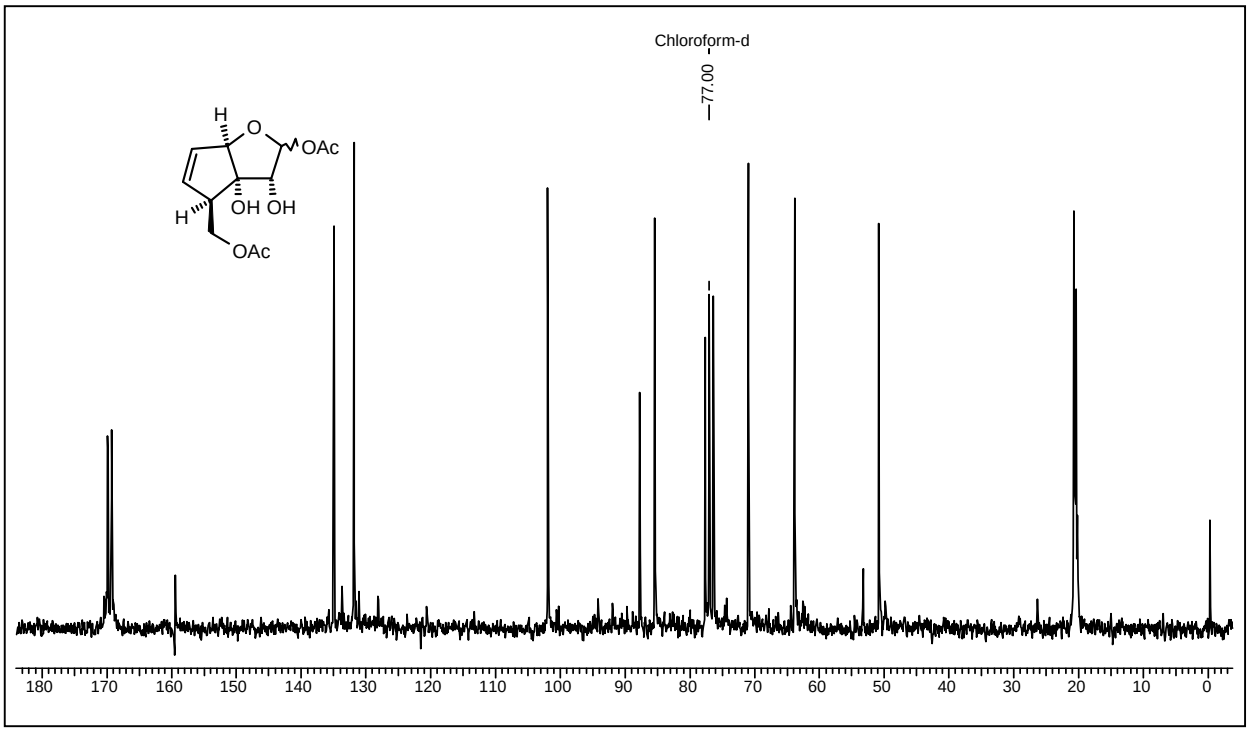
^{13}C NMR Spectrum of compound 65 in $CDCl_3$



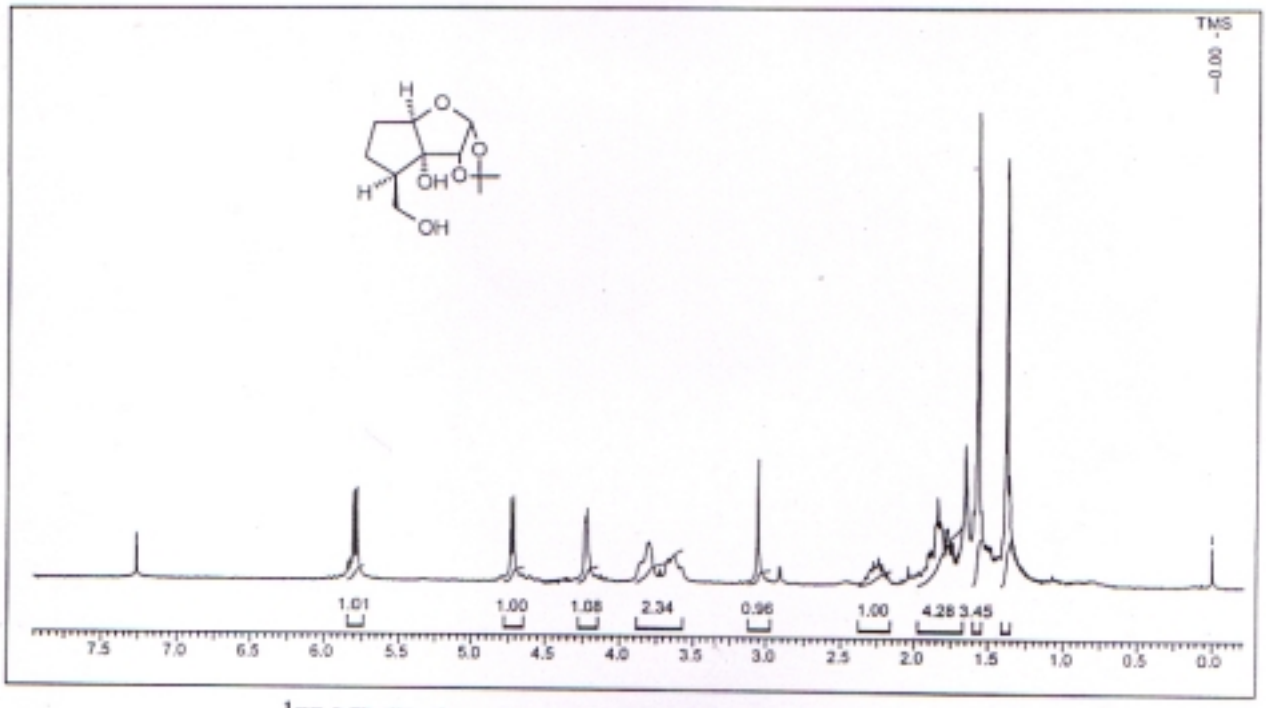
^{1}H NMR Spectrum of compound 66 in $CDCl_3$



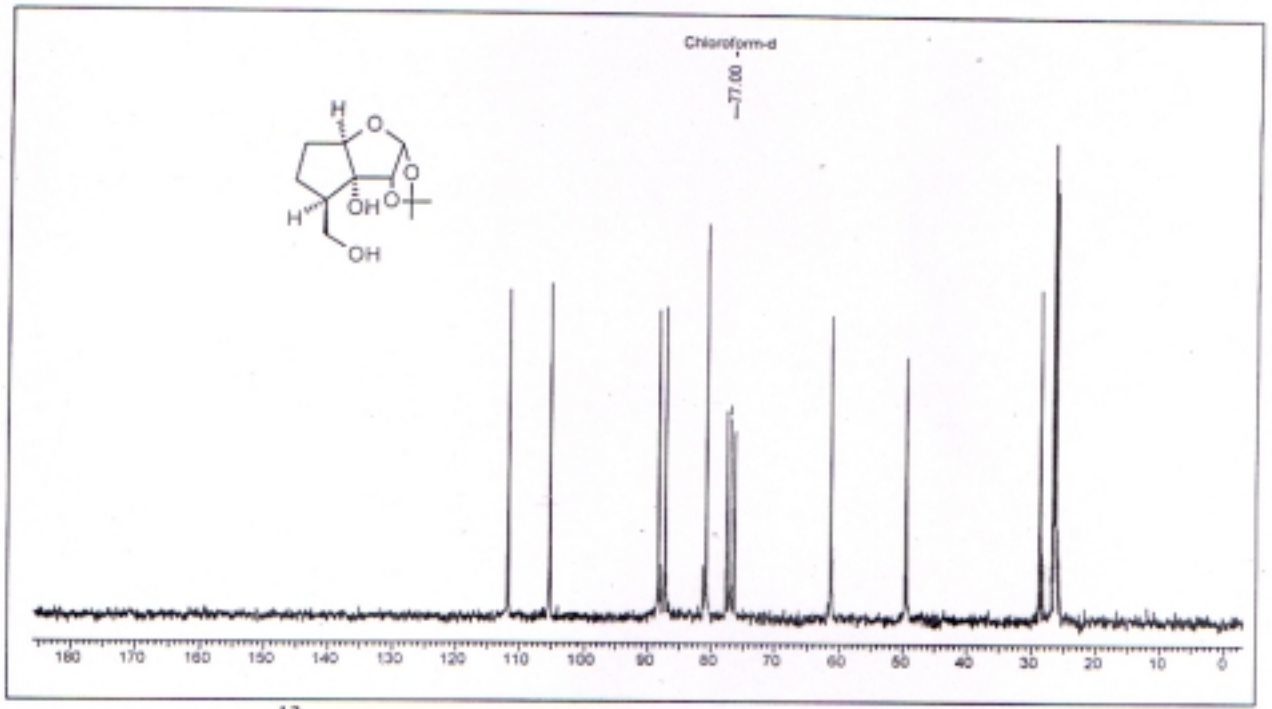
^{1}H NMR Spectrum of compound 67 in $CDCl_3$



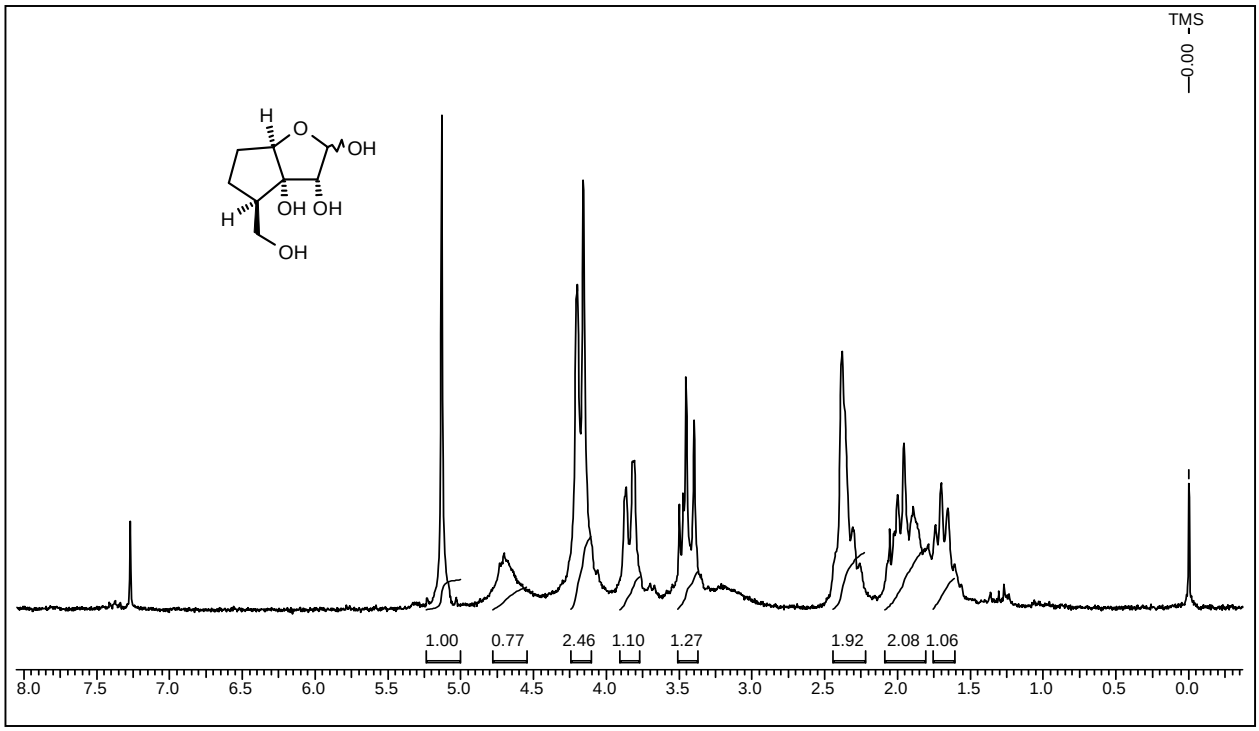
^{13}C NMR Spectrum of compound 67 in $CDCl_3$



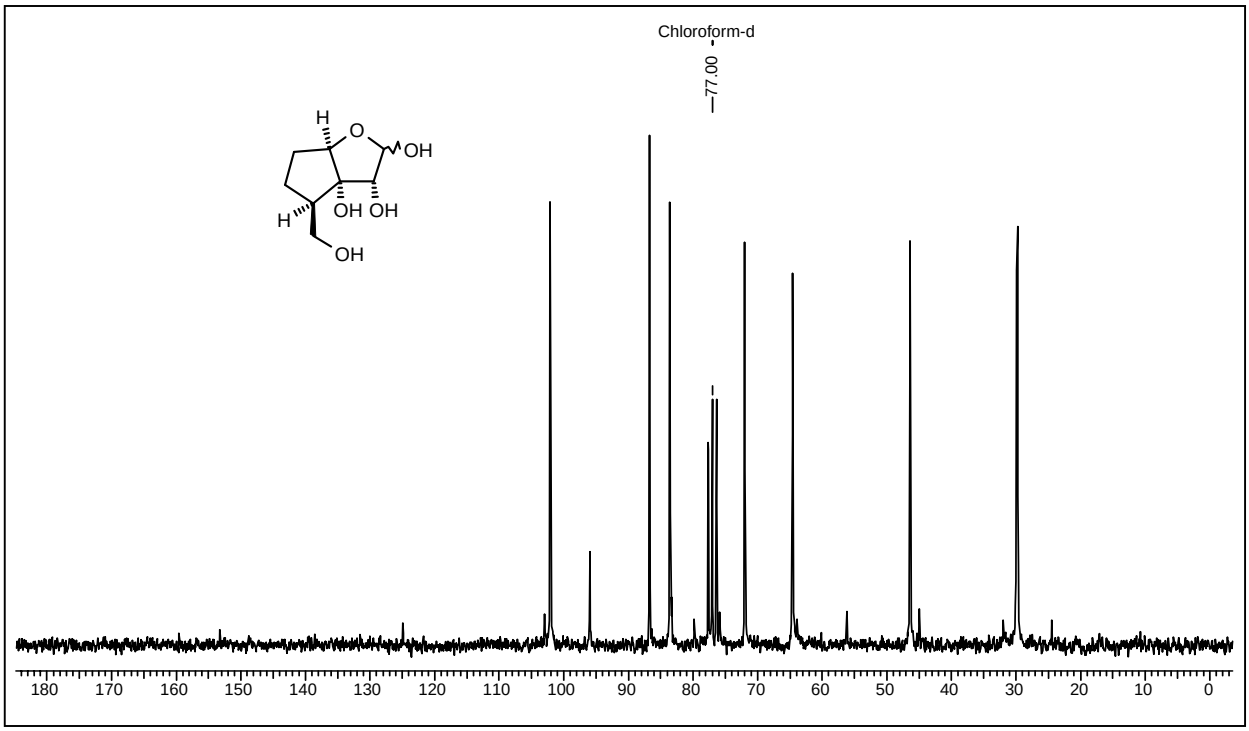
^{1}H NMR Spectrum of compound 69 in $CDCl_3$



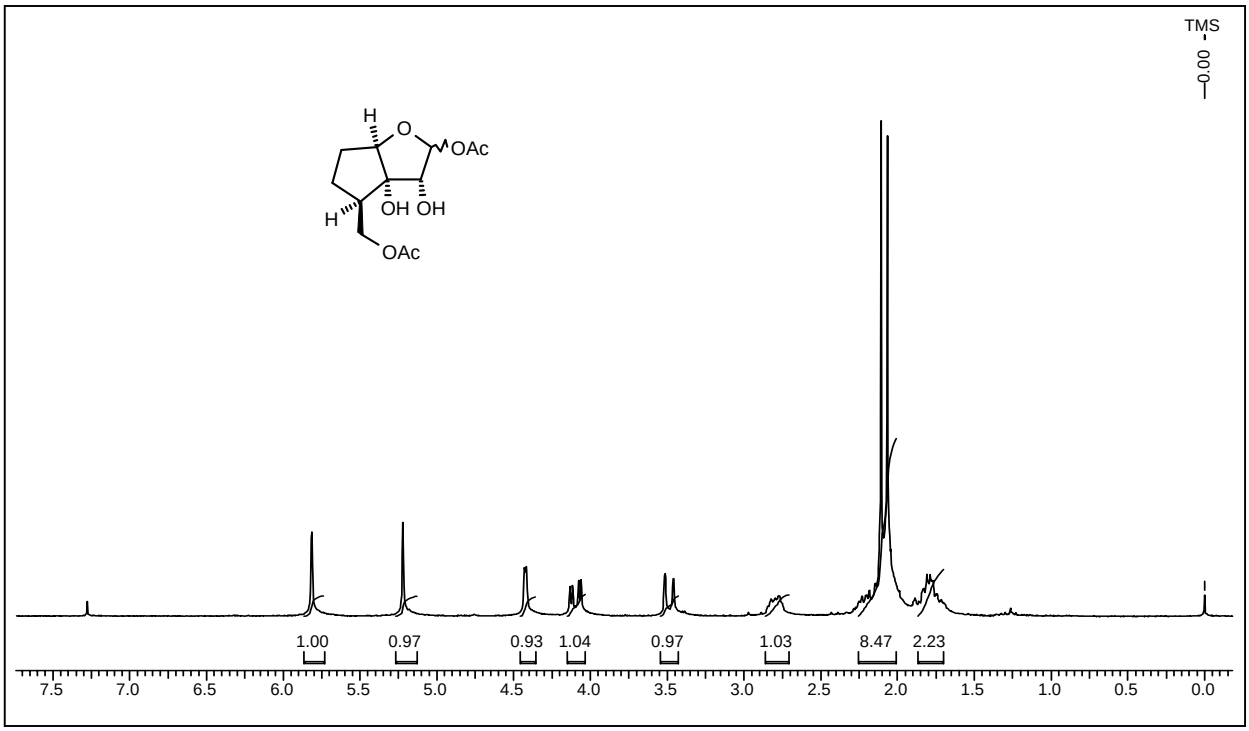
^{13}C NMR Spectrum of compound 69 in $CDCl_3$



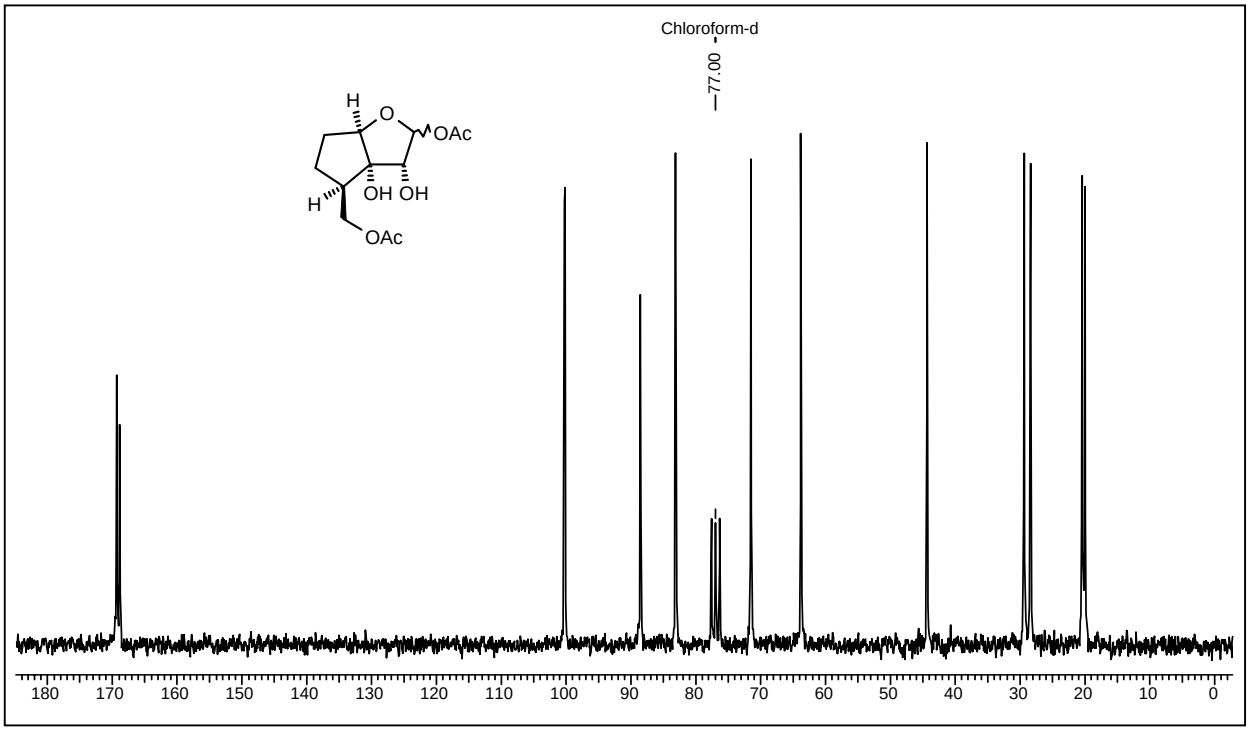
^{1}H NMR Spectrum of compound 70 in $CDCl_3$



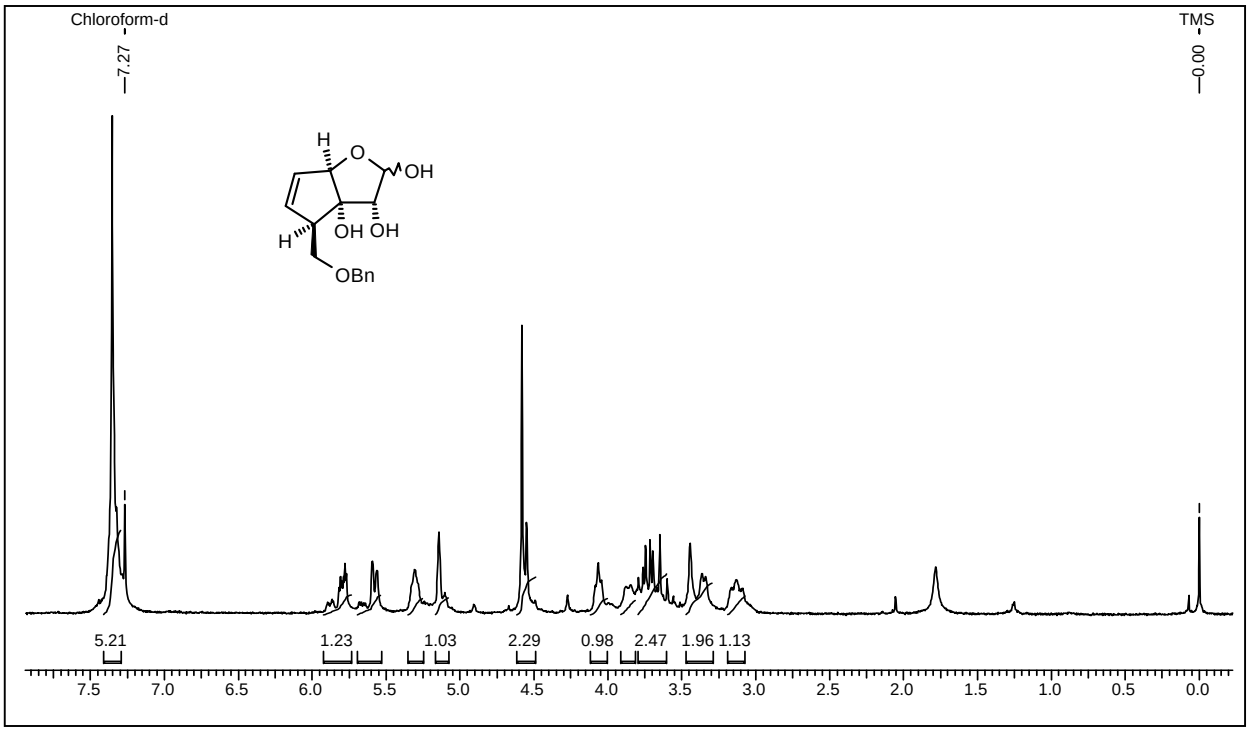
^{13}C NMR Spectrum of compound 70 in $CDCl_3$



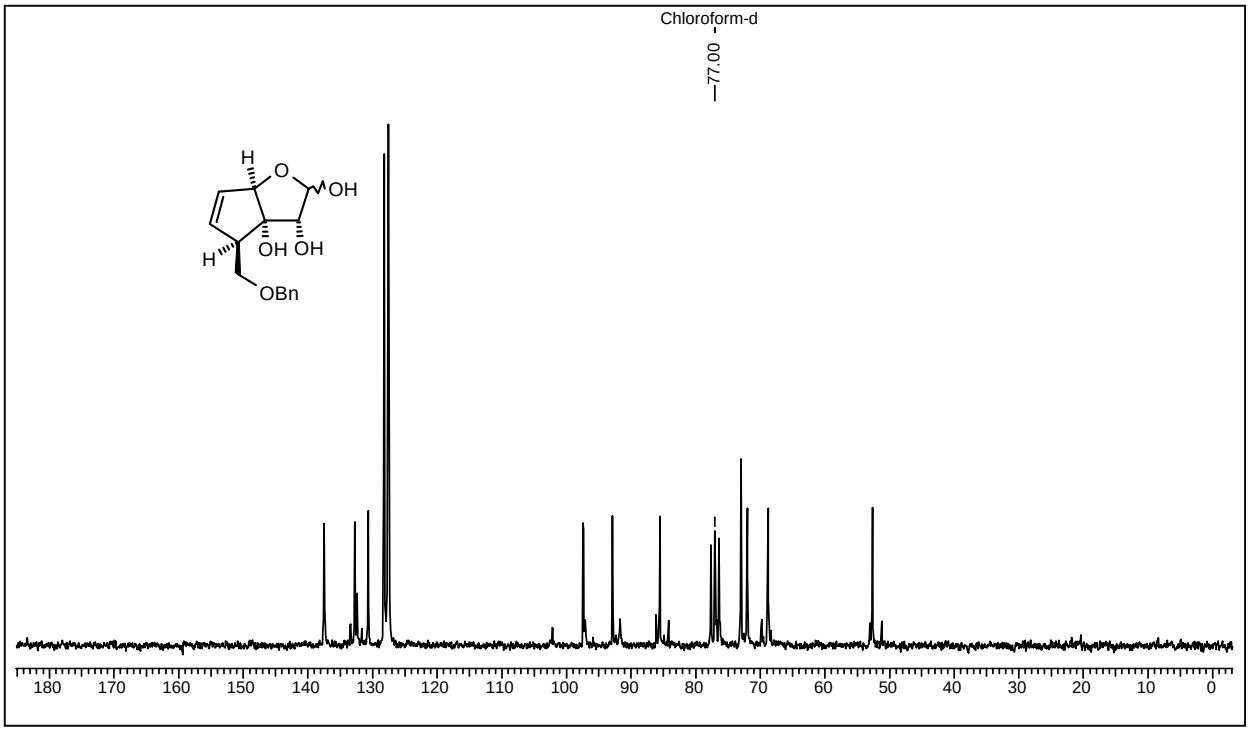
^{1}H NMR Spectrum of compound 71 in $CDCl_3$



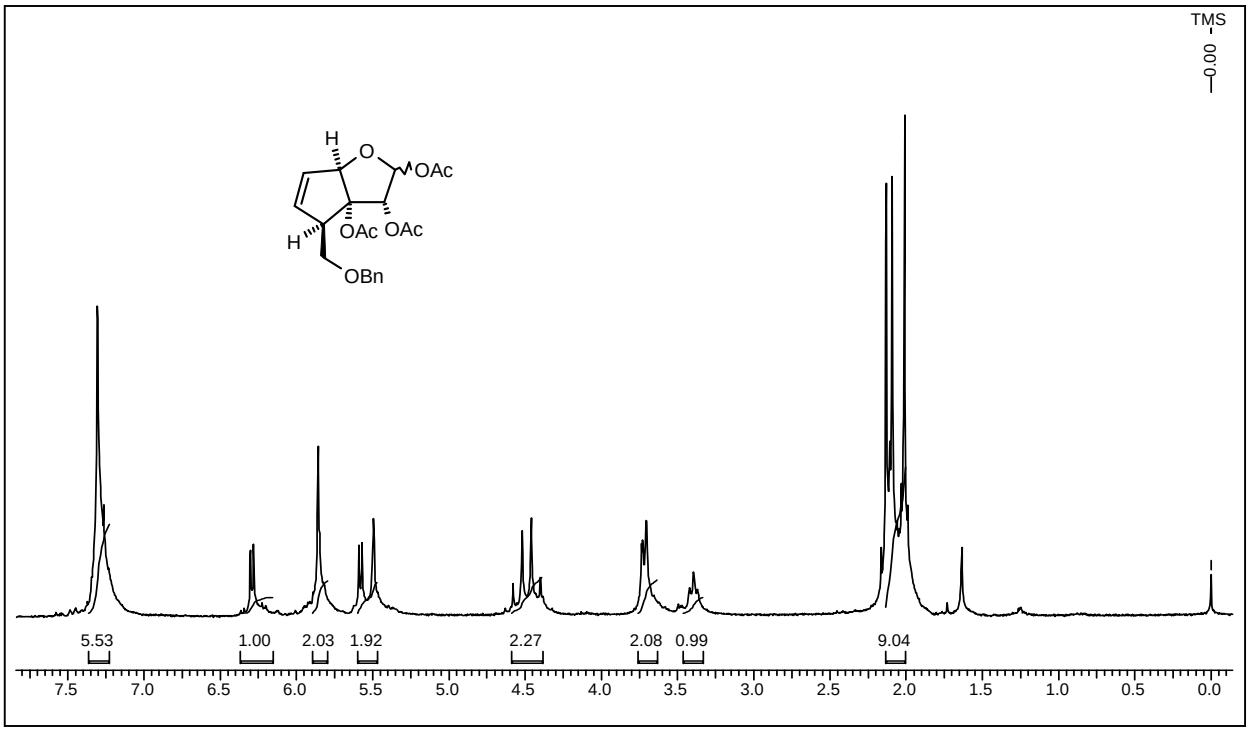
^{13}C NMR Spectrum of compound 71 in $CDCl_3$



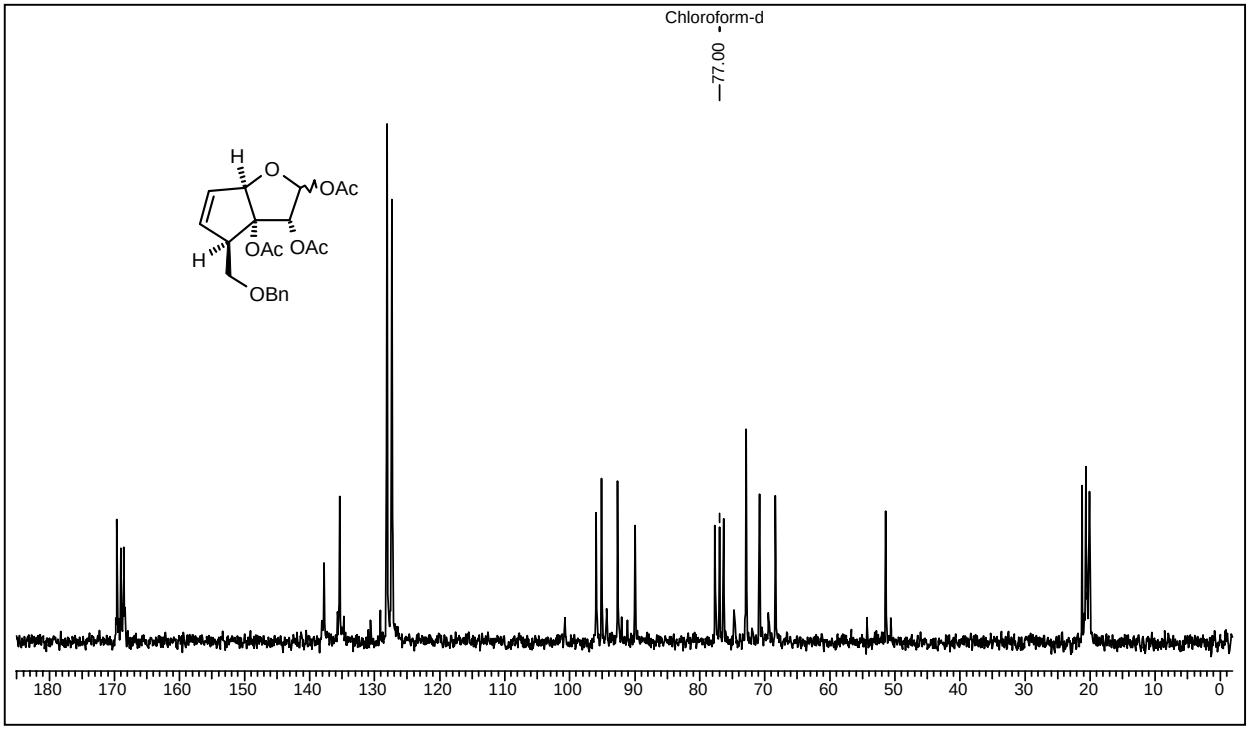
^{1}H NMR Spectrum of compound 73 in $CDCl_3$



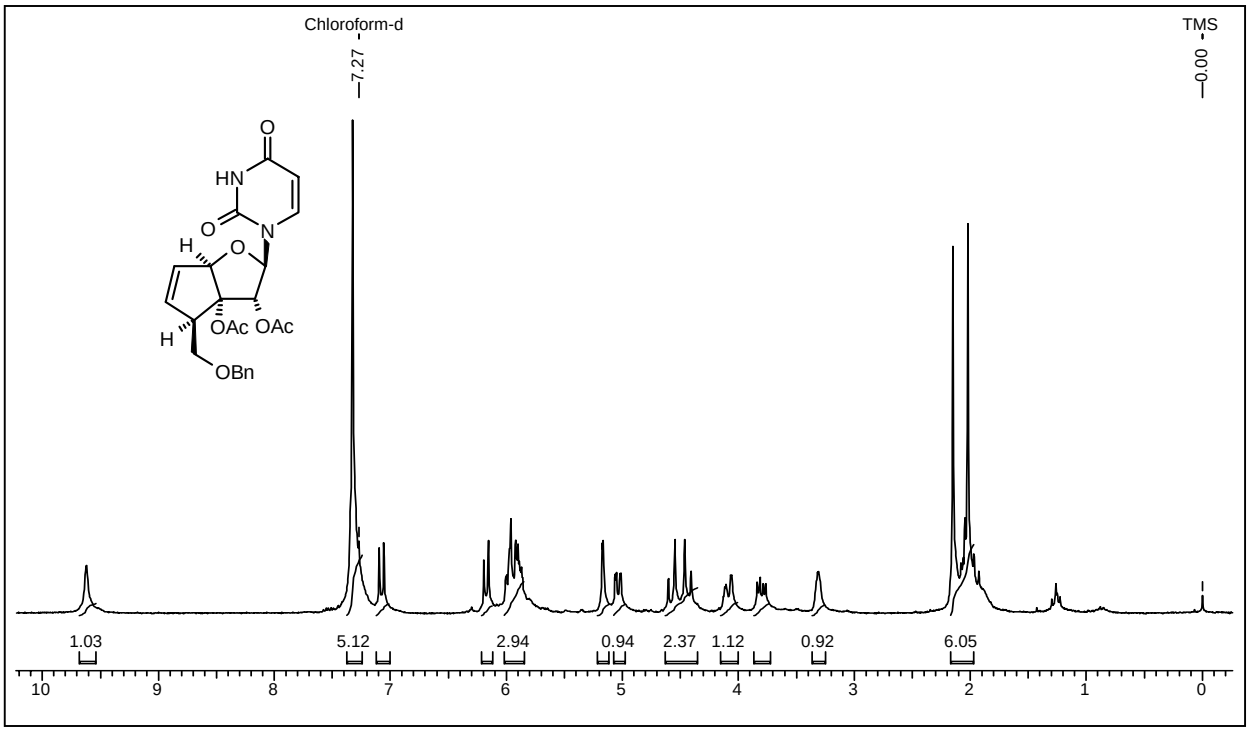
^{13}C NMR Spectrum of compound 73 in $CDCl_3$



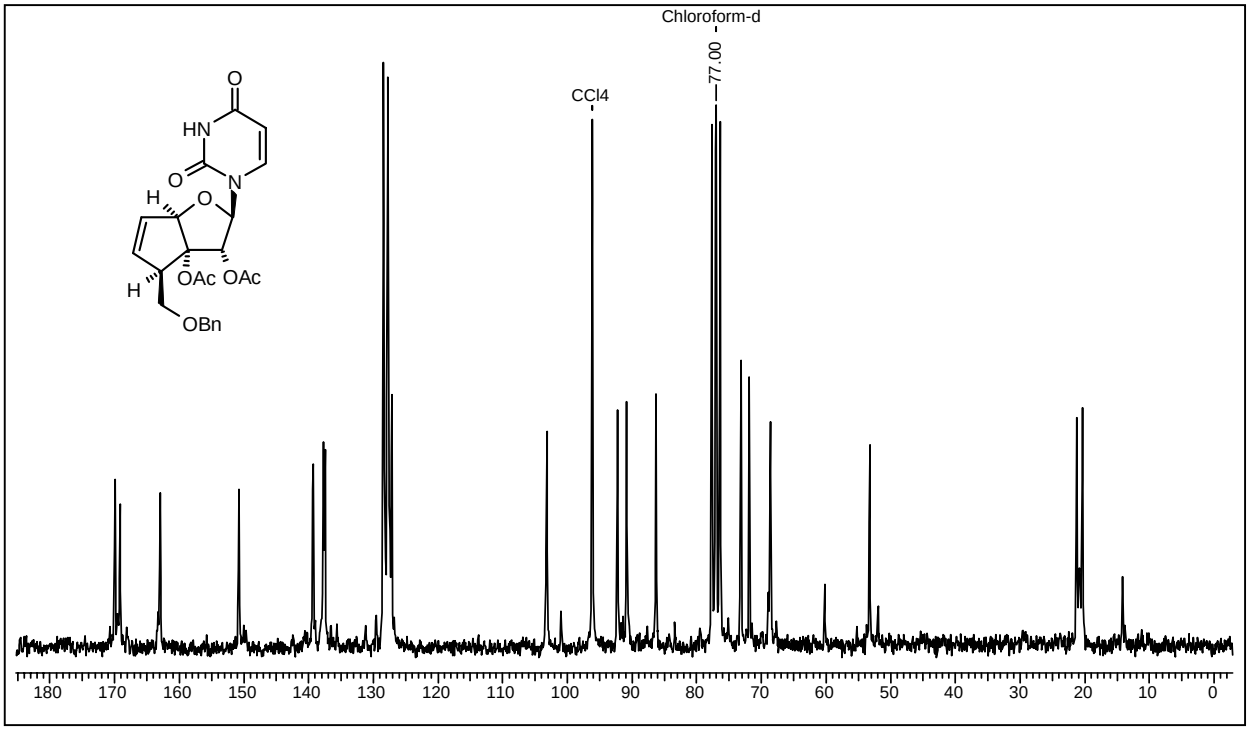
^{1}H NMR Spectrum of compound 74 in $CDCl_3$



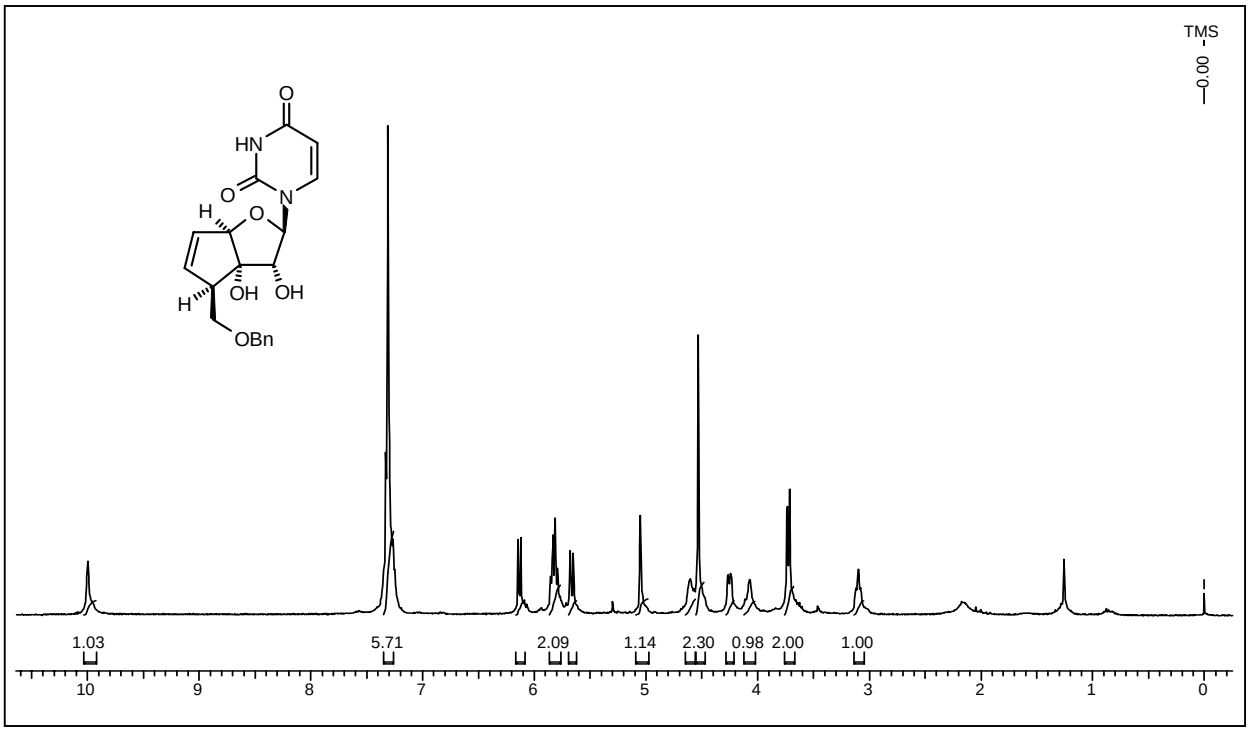
^{13}C NMR Spectrum of compound 74 in $CDCl_3$



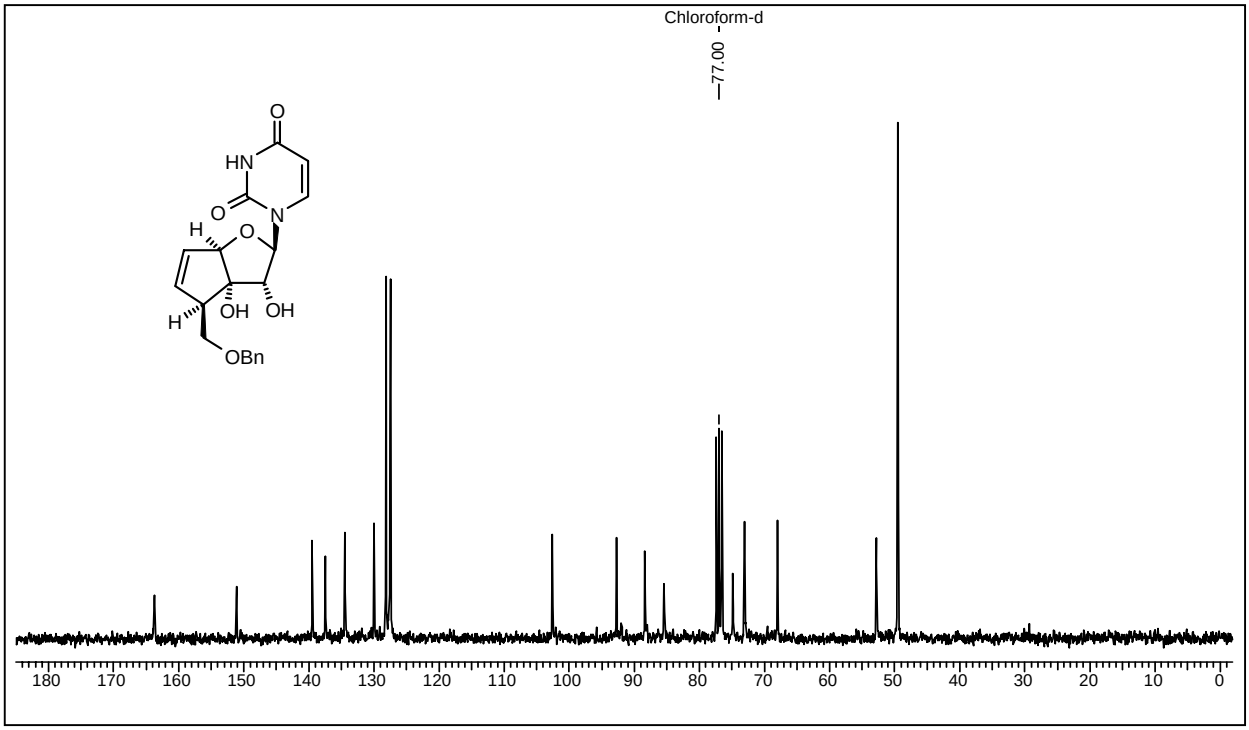
^{1}H NMR Spectrum of compound 75 in $CDCl_3$



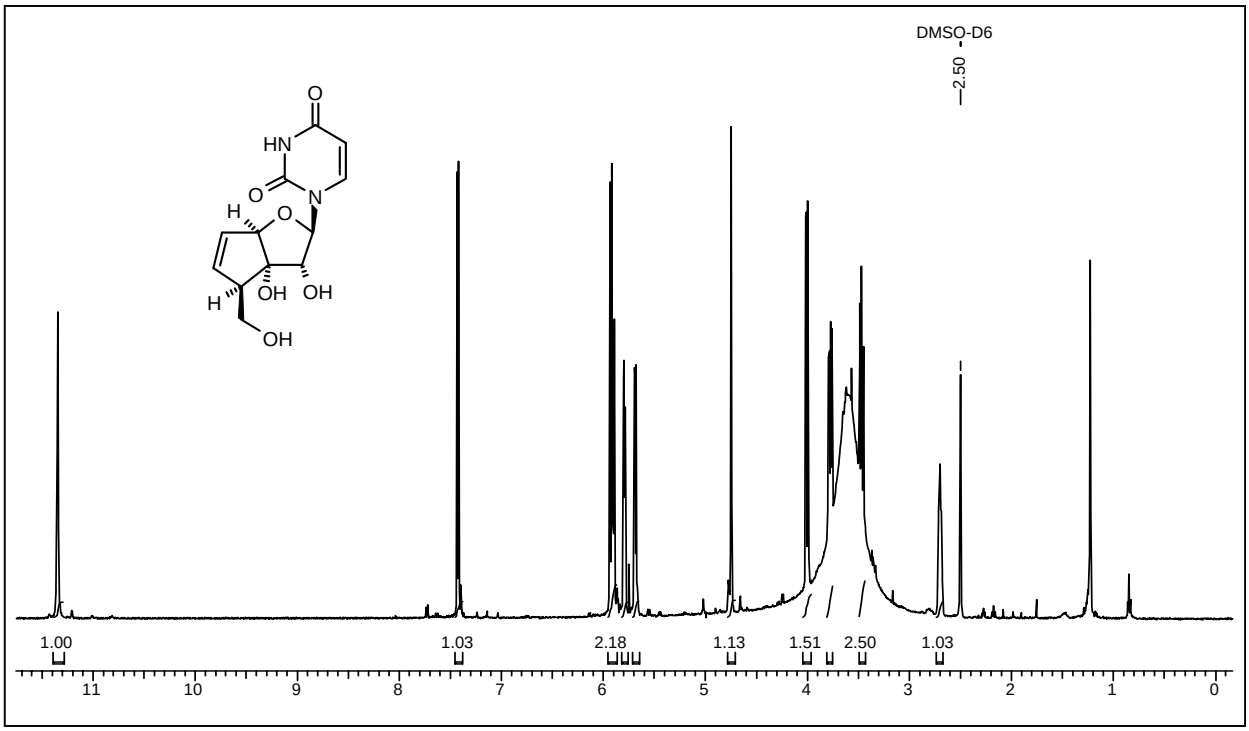
^{13}C NMR Spectrum of compound 75 in $CDCl_3$



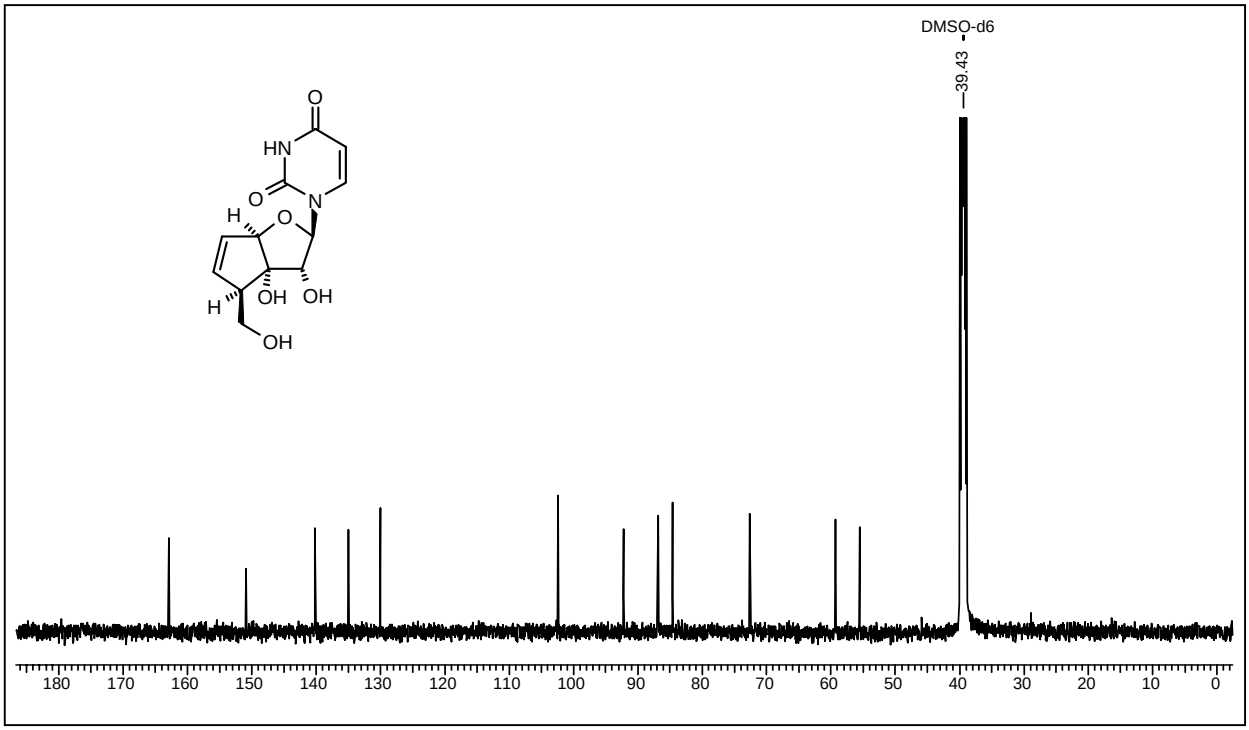
^{1}H NMR Spectrum of compound 76 in $CDCl_3$



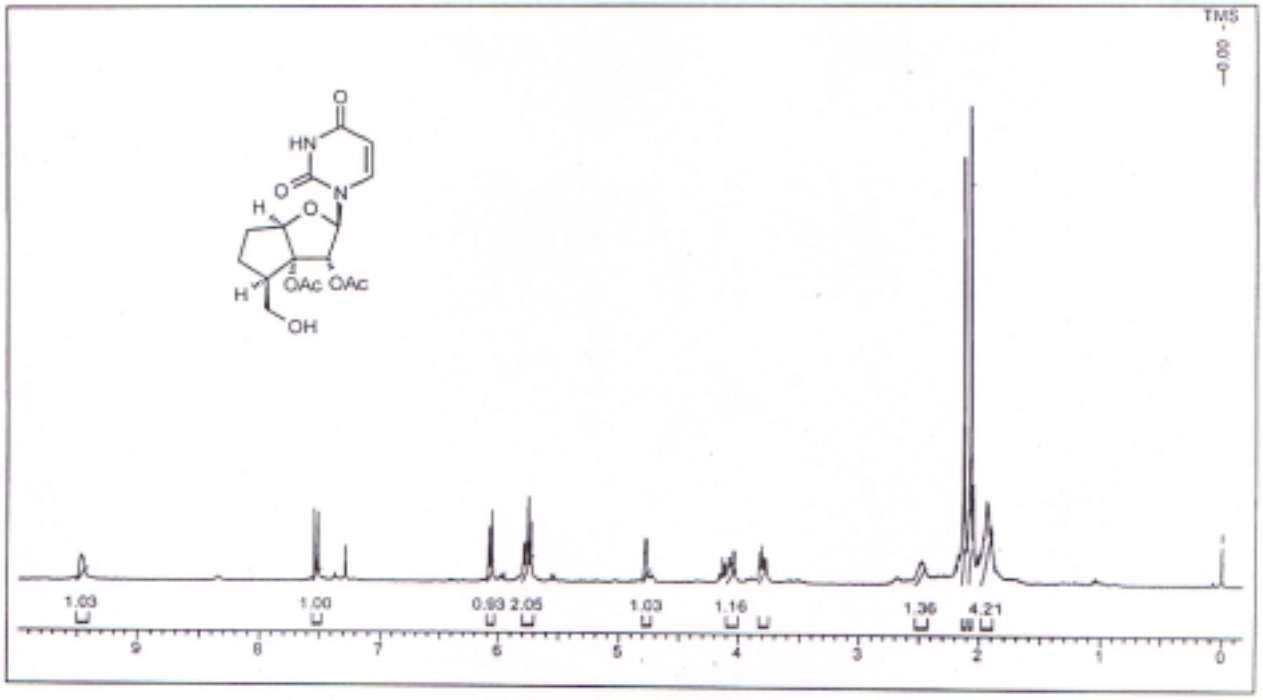
^{13}C NMR Spectrum of compound 76 in $CDCl_3$ +MeOD



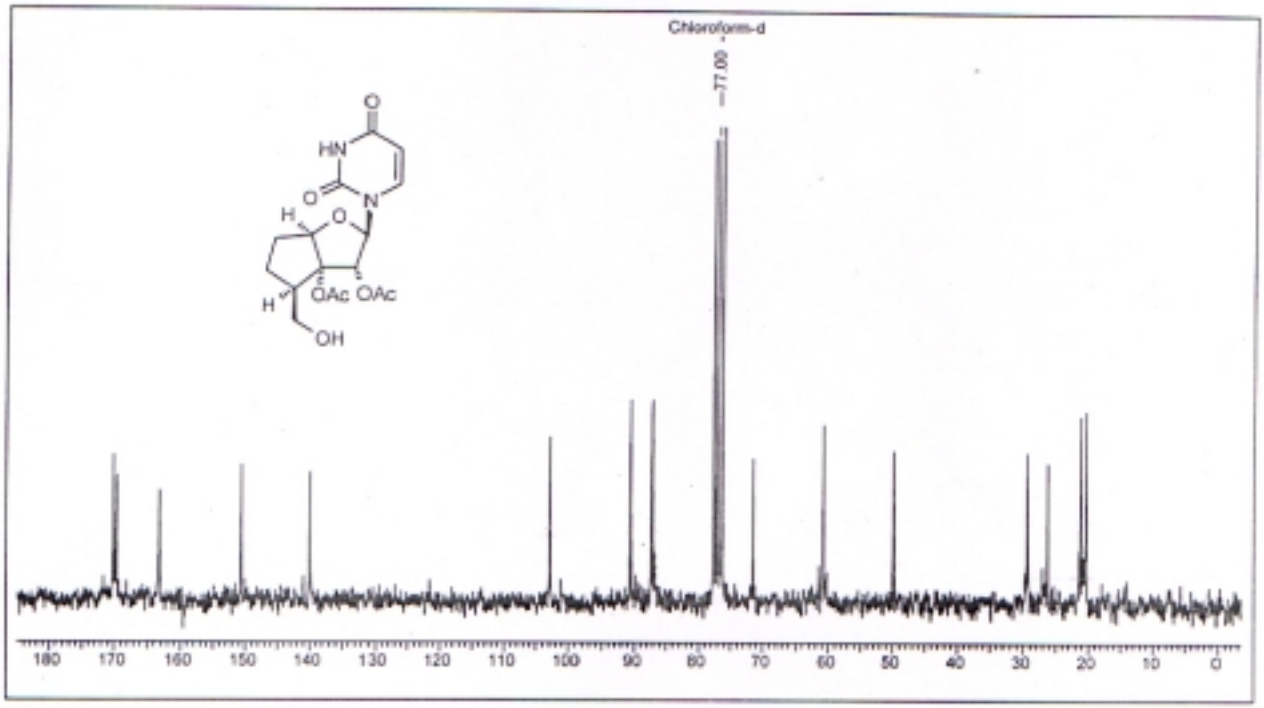
^{1}H NMR Spectrum of compound 77 in DMSO-d_6



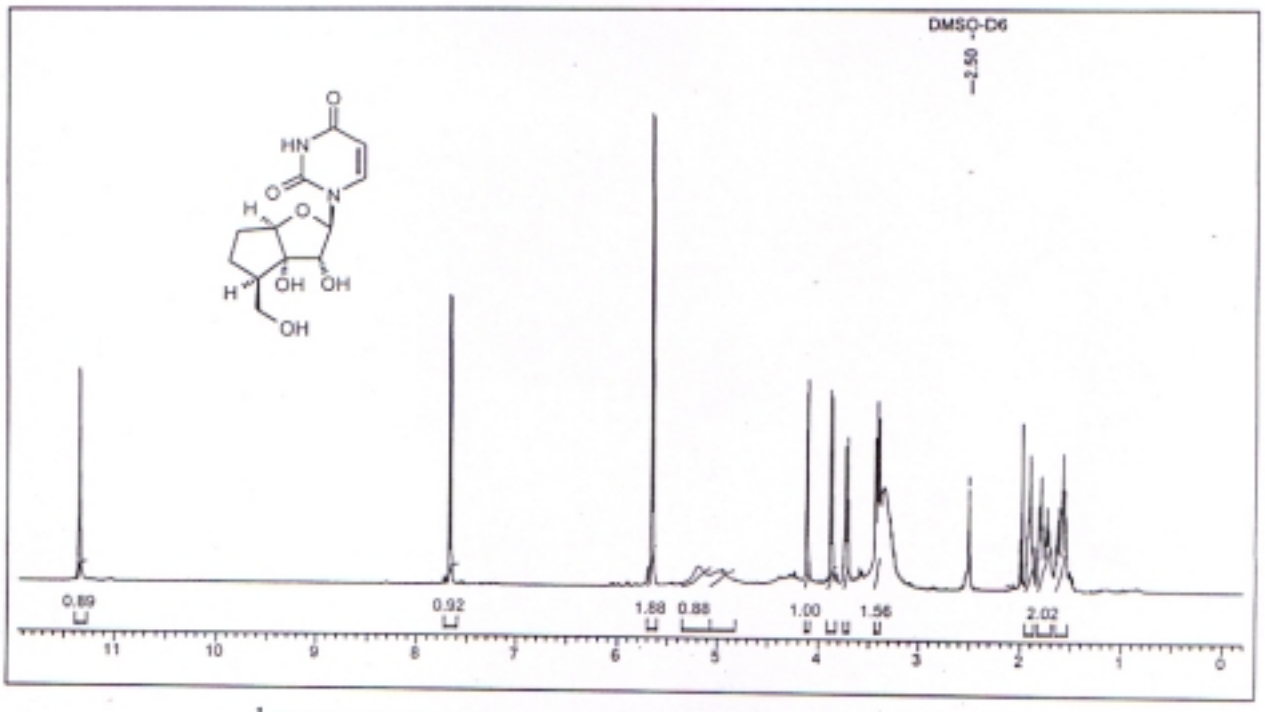
^{13}C NMR Spectrum of compound 77 in DMSO-d_6



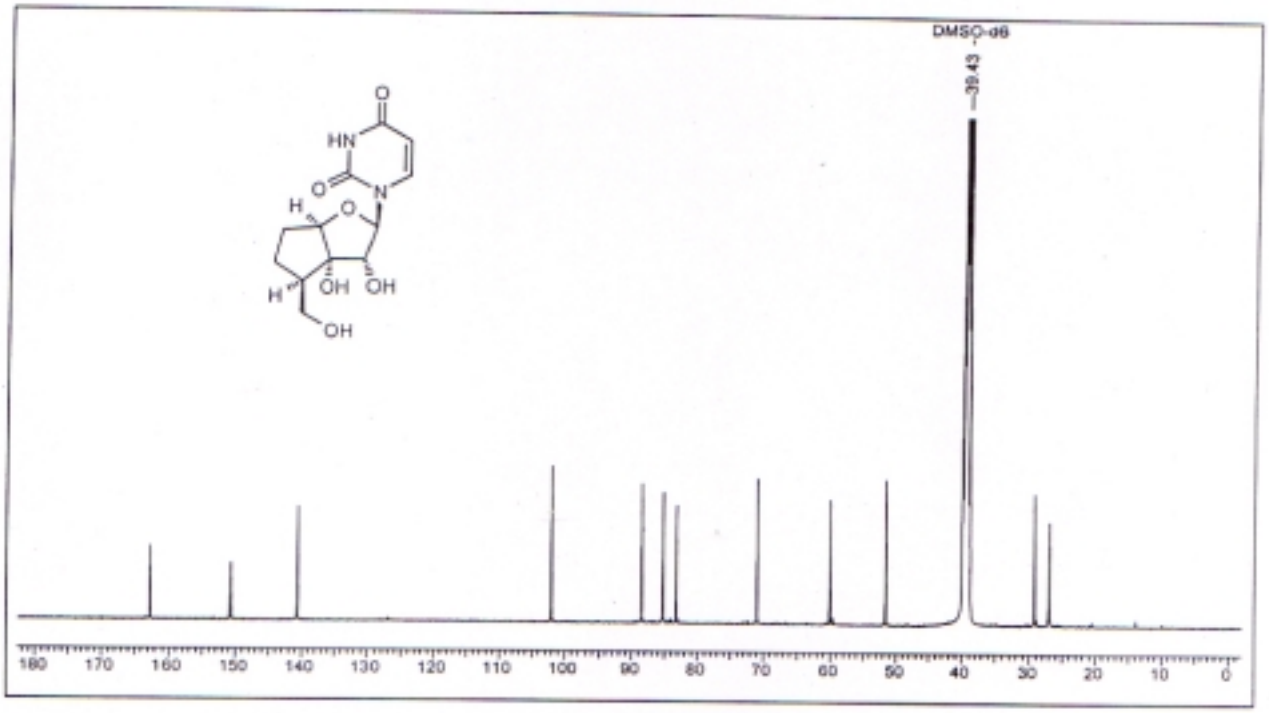
^{1}H NMR Spectrum of compound 78 in $CDCl_3$



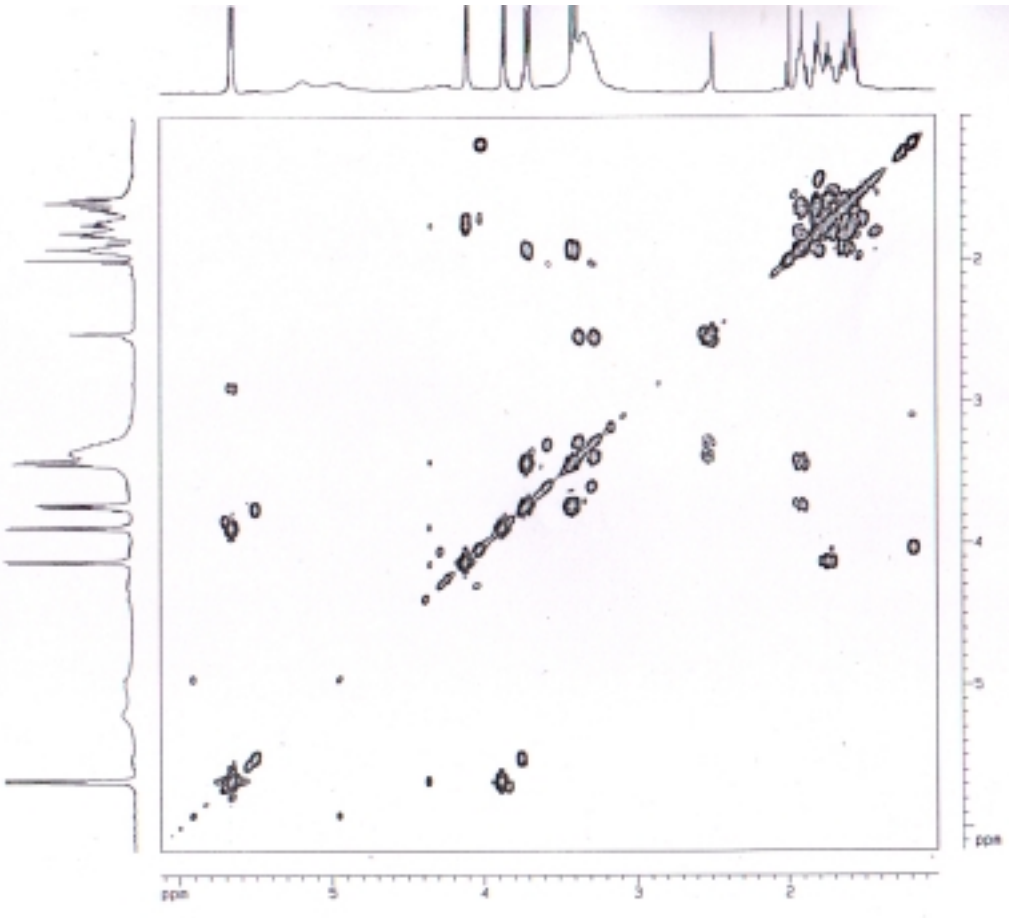
^{13}C NMR Spectrum of compound 78 in $CDCl_3$

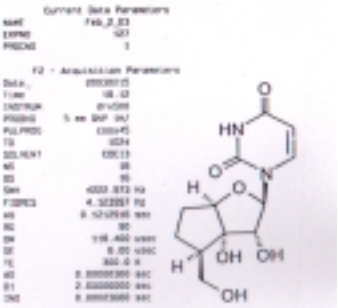


^{1}H NMR Spectrum of compound 79 in DMSO-d_6

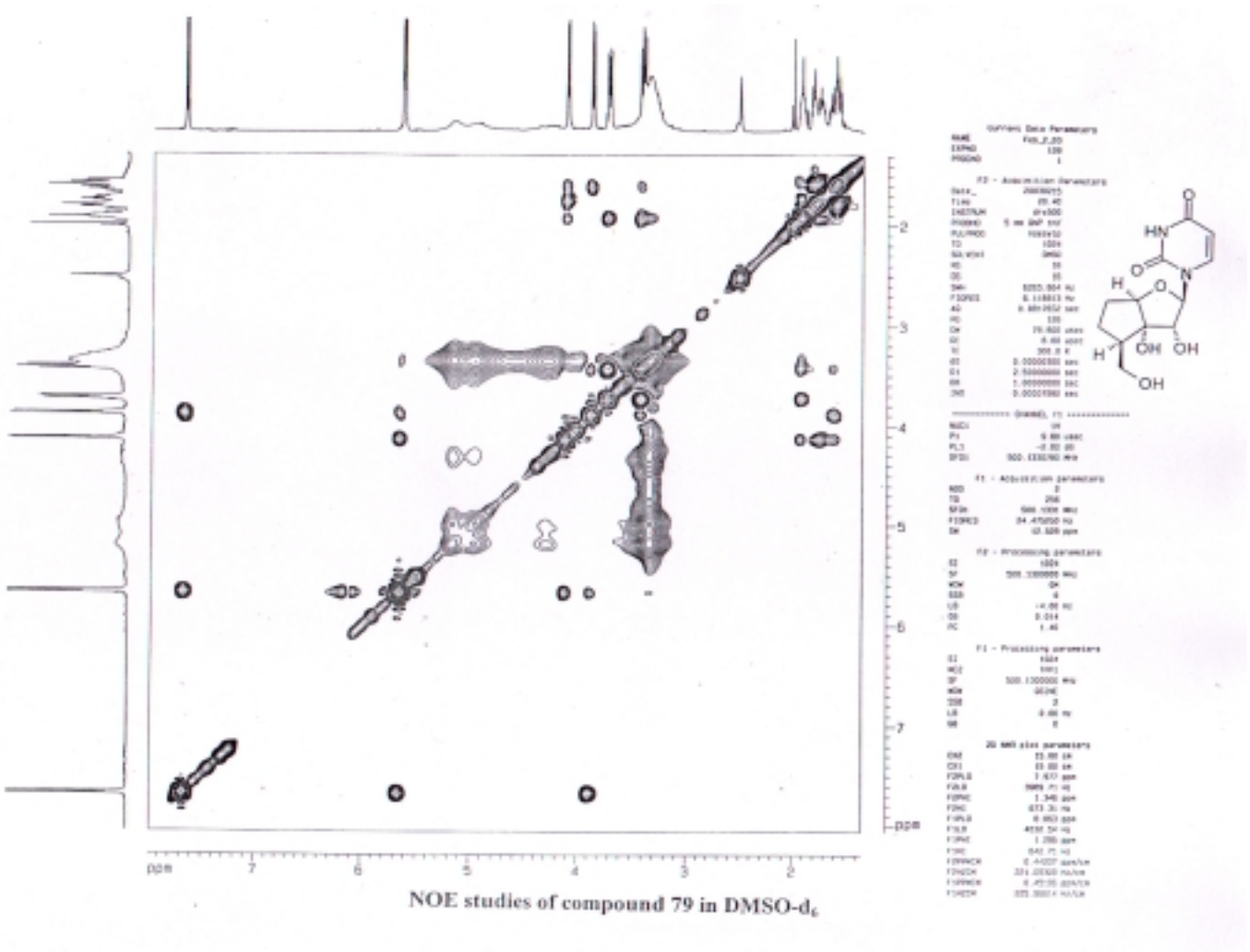


^{13}C NMR Spectrum of compound 79 in DMSO-d_6

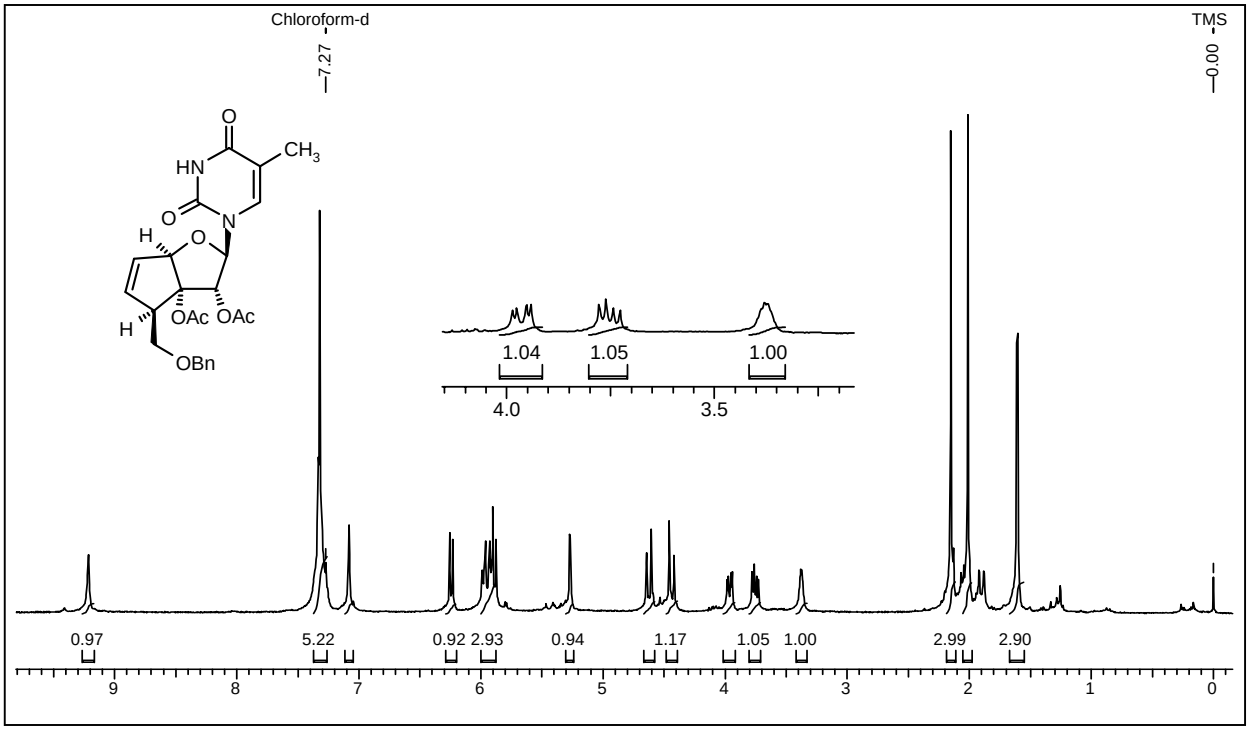




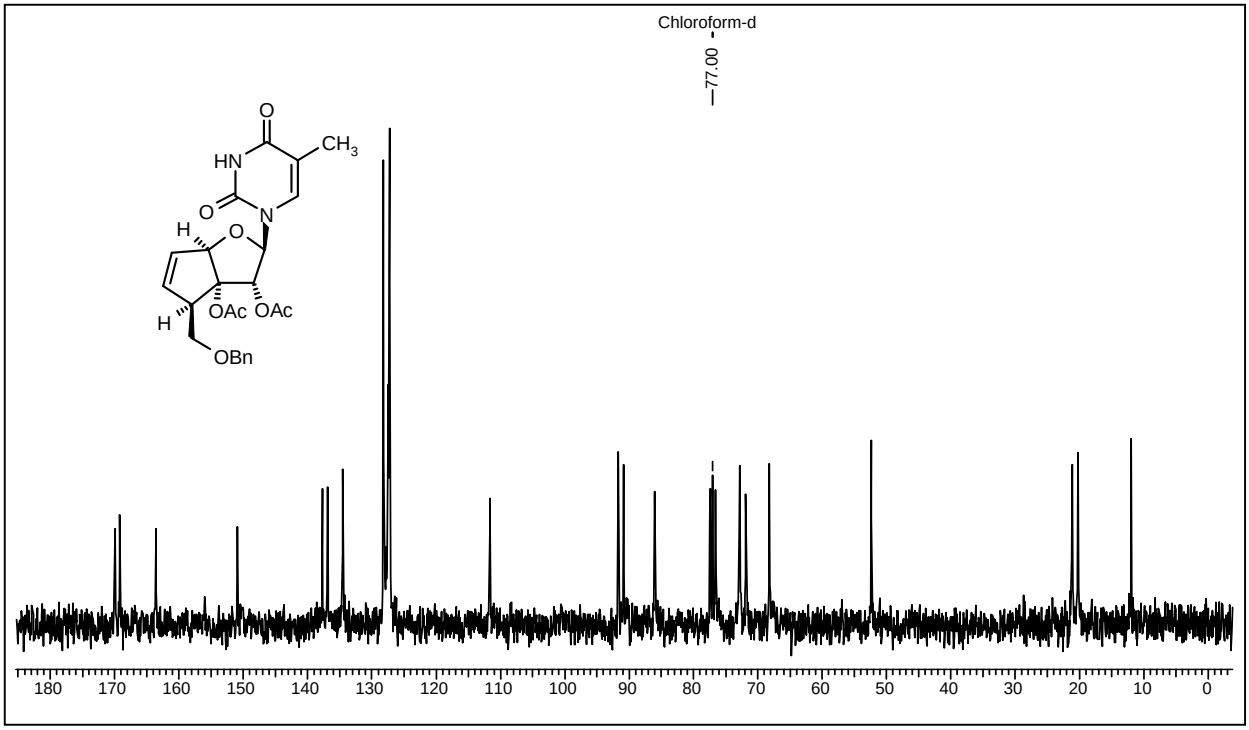
COSY Spectrum of compound 79 in DMSO-d_6



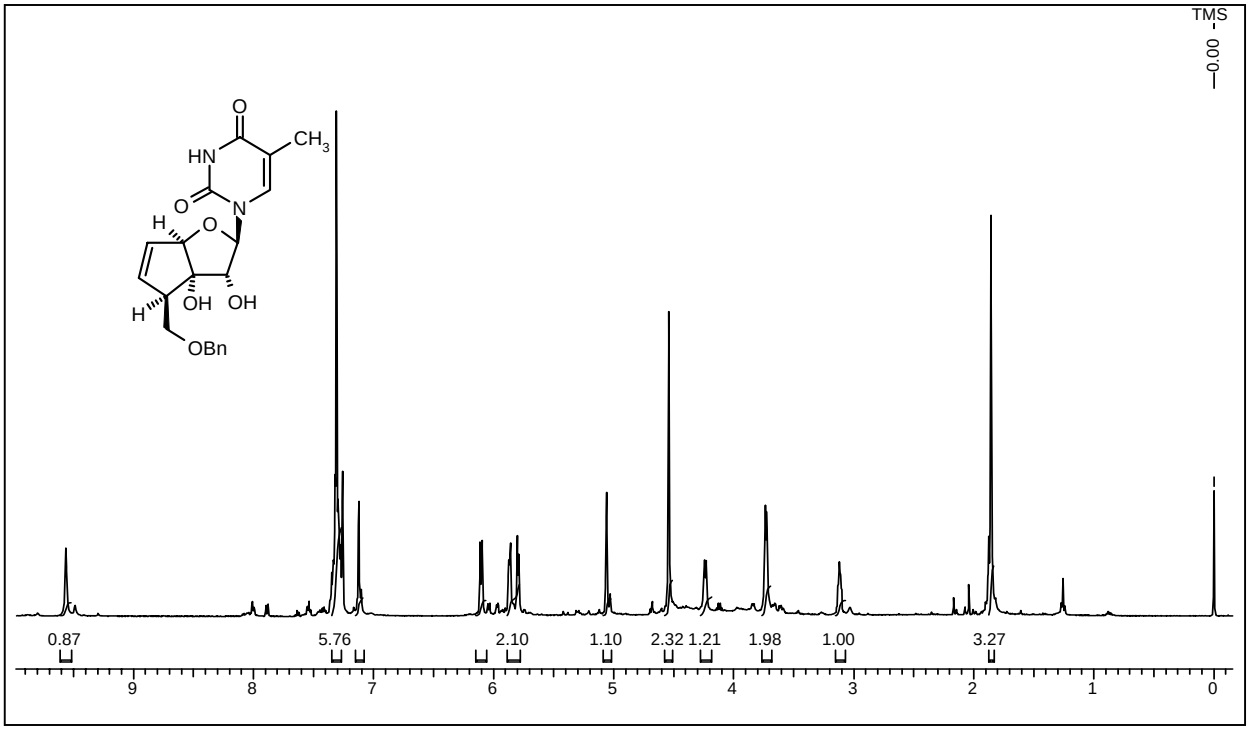
NOE studies of compound 79 in DMSO-d_6



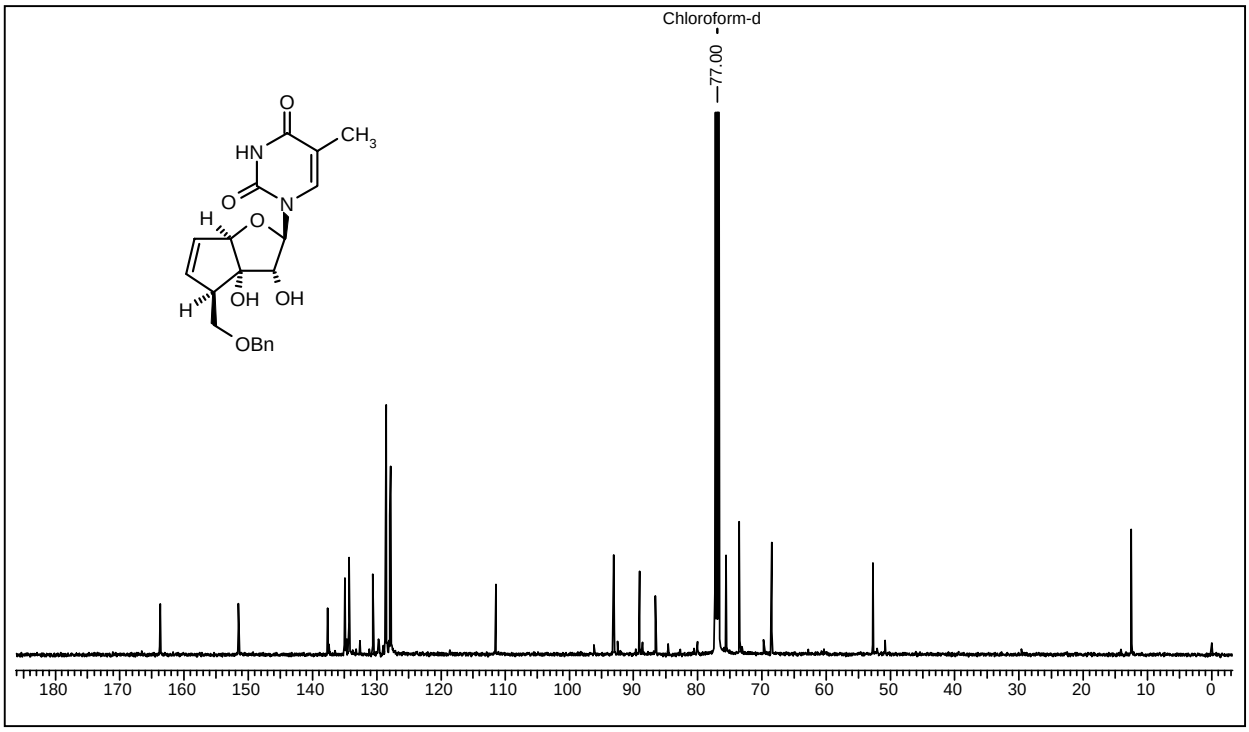
^{1}H NMR Spectrum of compound 80 in $CDCl_3$



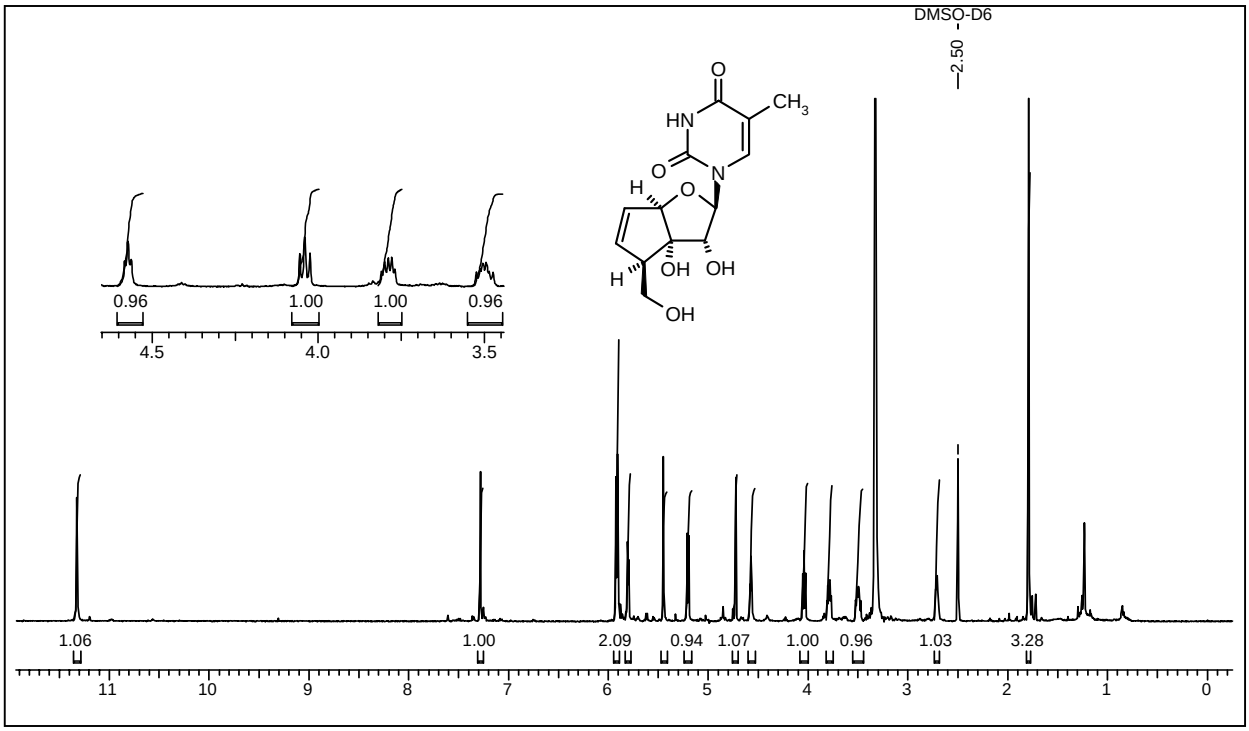
^{13}C NMR Spectrum of compound 80 in $CDCl_3$



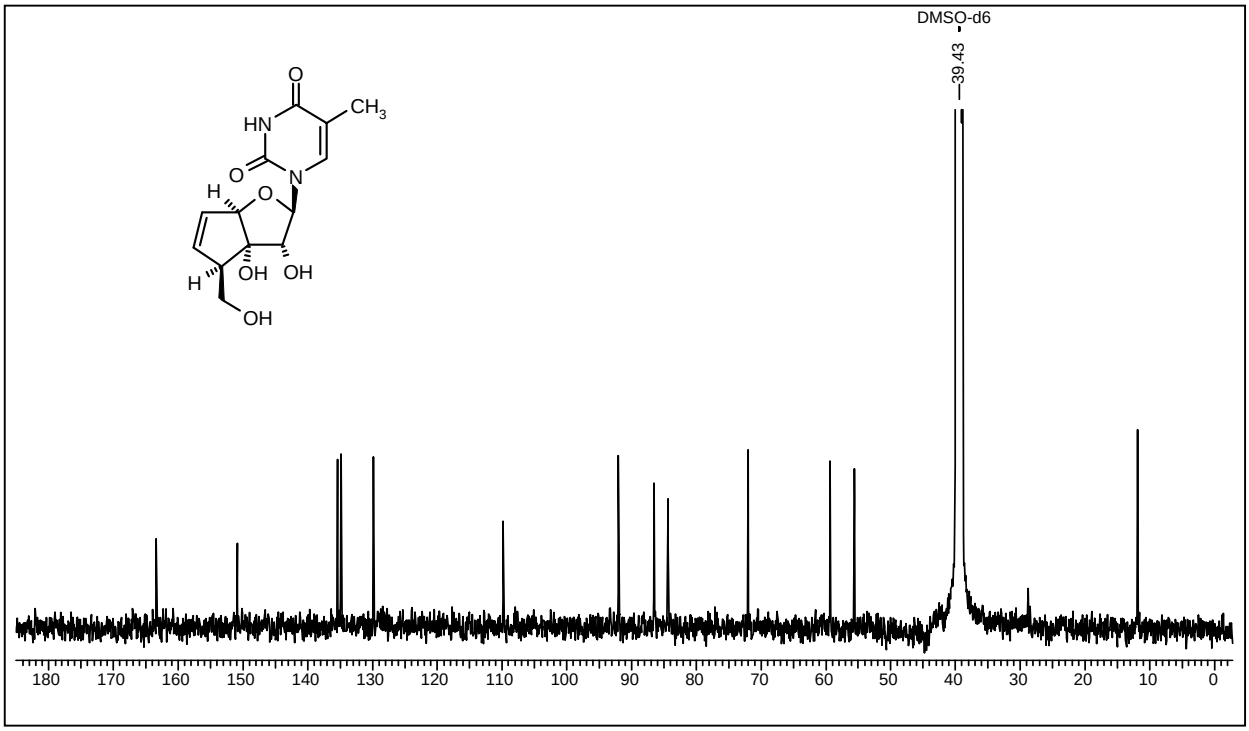
^{1}H NMR Spectrum of compound 81 in $CDCl_3$



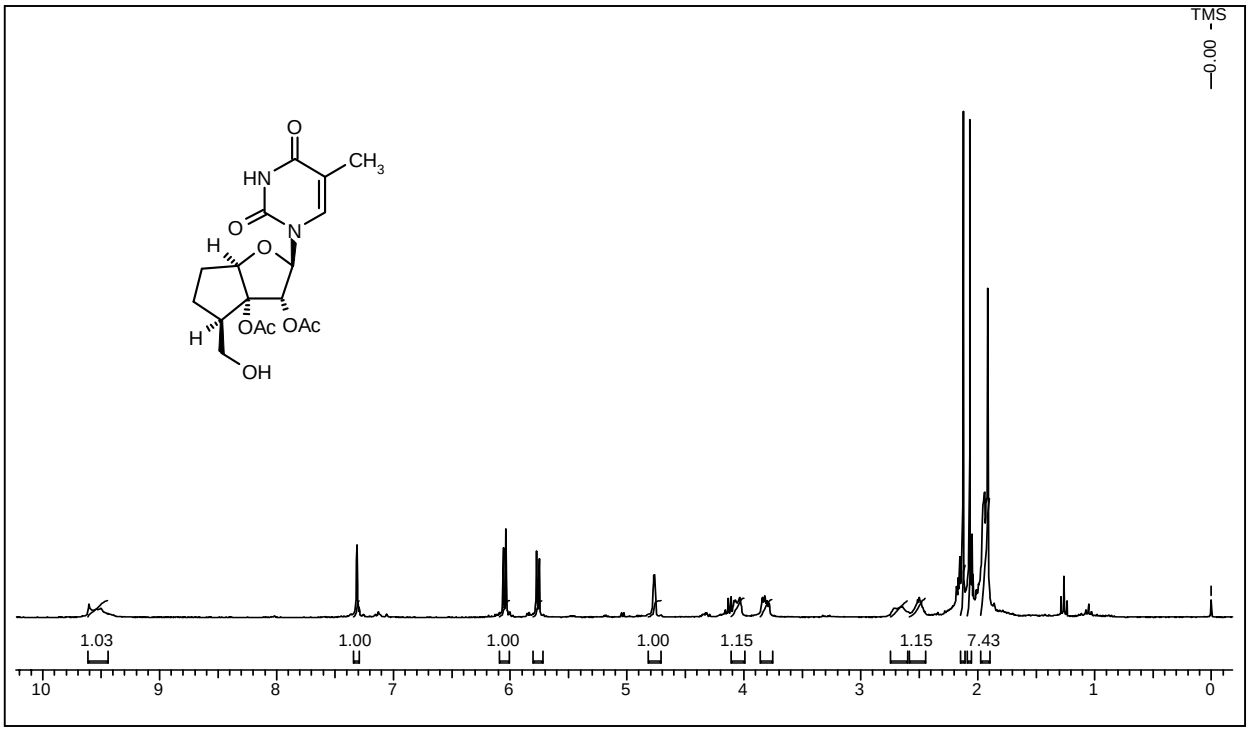
^{13}C NMR Spectrum of compound 81 in $CDCl_3$



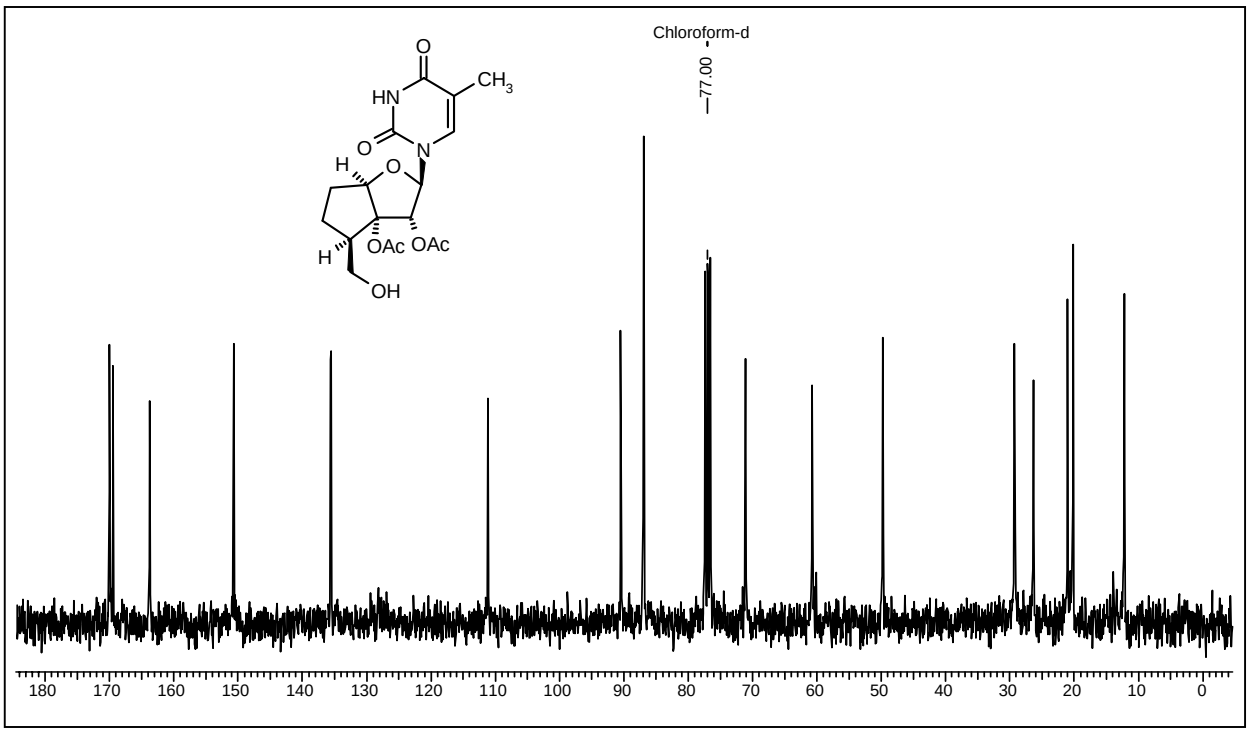
^{1}H NMR Spectrum of compound 82 in DMSO-d_6



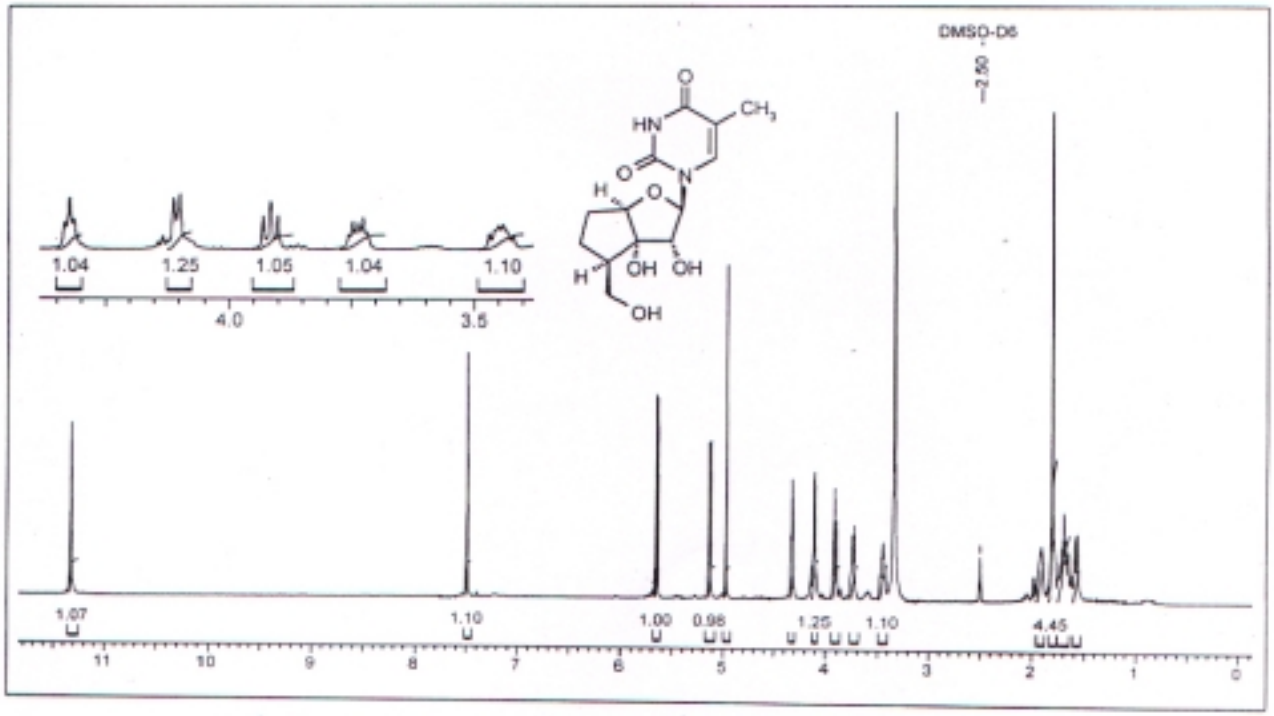
^{13}C NMR Spectrum of compound 82 in DMSO-d_6



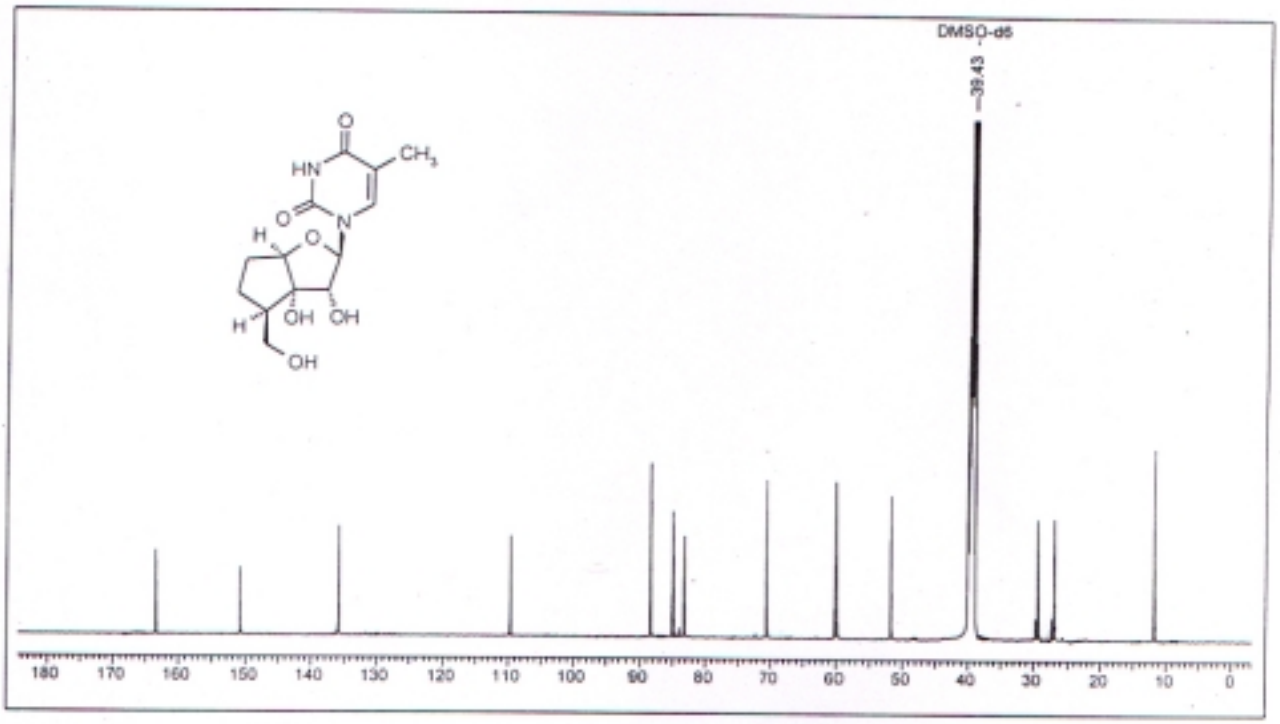
^{1}H NMR Spectrum of compound 83 in $CDCl_3$



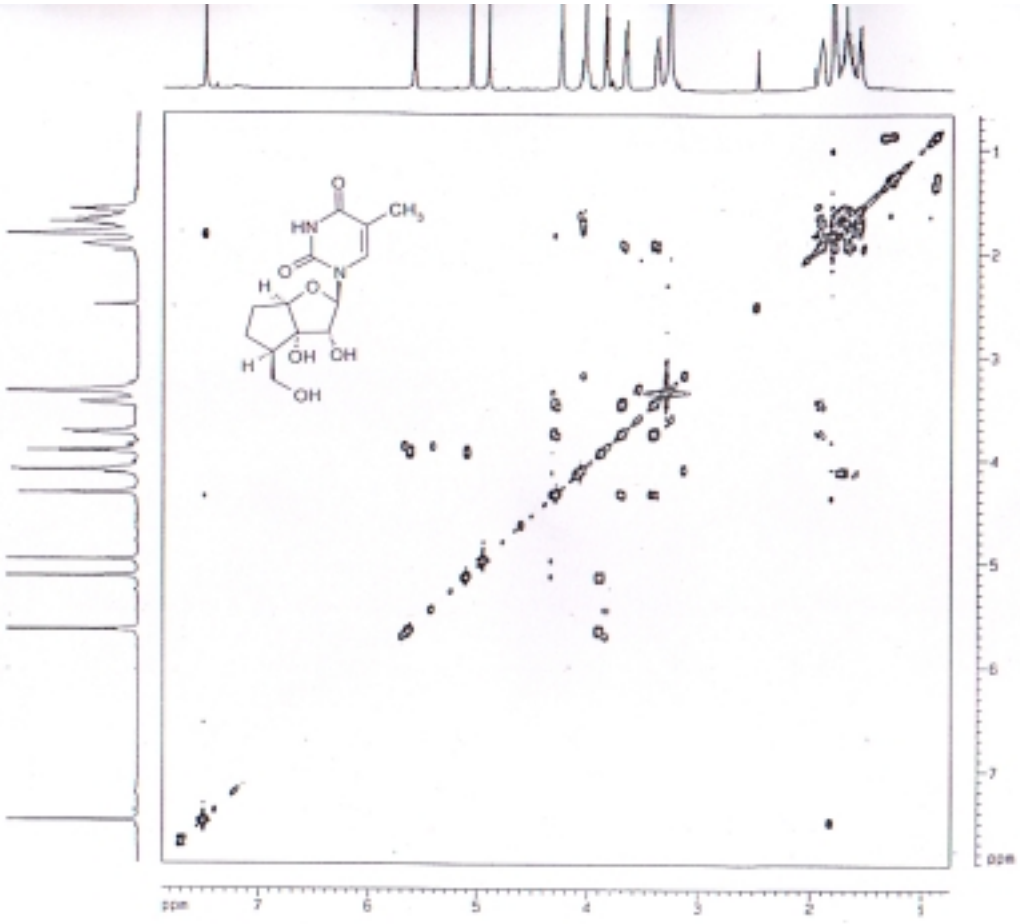
^{13}C NMR Spectrum of compound 83 in $CDCl_3$



^{1}H NMR Spectrum of compound 84 in DMSO-d_6



^{13}C NMR Spectrum of compound 84 in DMSO-d_6



COSY Spectrum of compound 84 in DMSO-d_6

DPS Reddy;
THYM-FIN; 2D 1H Cosy45

Current Data Parameters

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PROCNO	1

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DS	16
SWH	4333.873 Hz
FIDRES	4.233857 Hz
AQ	0.1179136 sec
RG	90
DW	115.400 usec
DE	6.00 usec
TE	300.0 K
d0	0.00000300 sec
D1	2.00000000 sec
d4	0.00003000 sec

======== CHANNEL f1 ========

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PL1	-2.00 dB
SFO1	500.1325800 MHz

F1 - Acquisition parameters

MDD	1
TD	256
SFO1	500.1325 MHz
FIDRES	16.895980 Hz
SW	8.444 ppm

F2 - Processing parameters

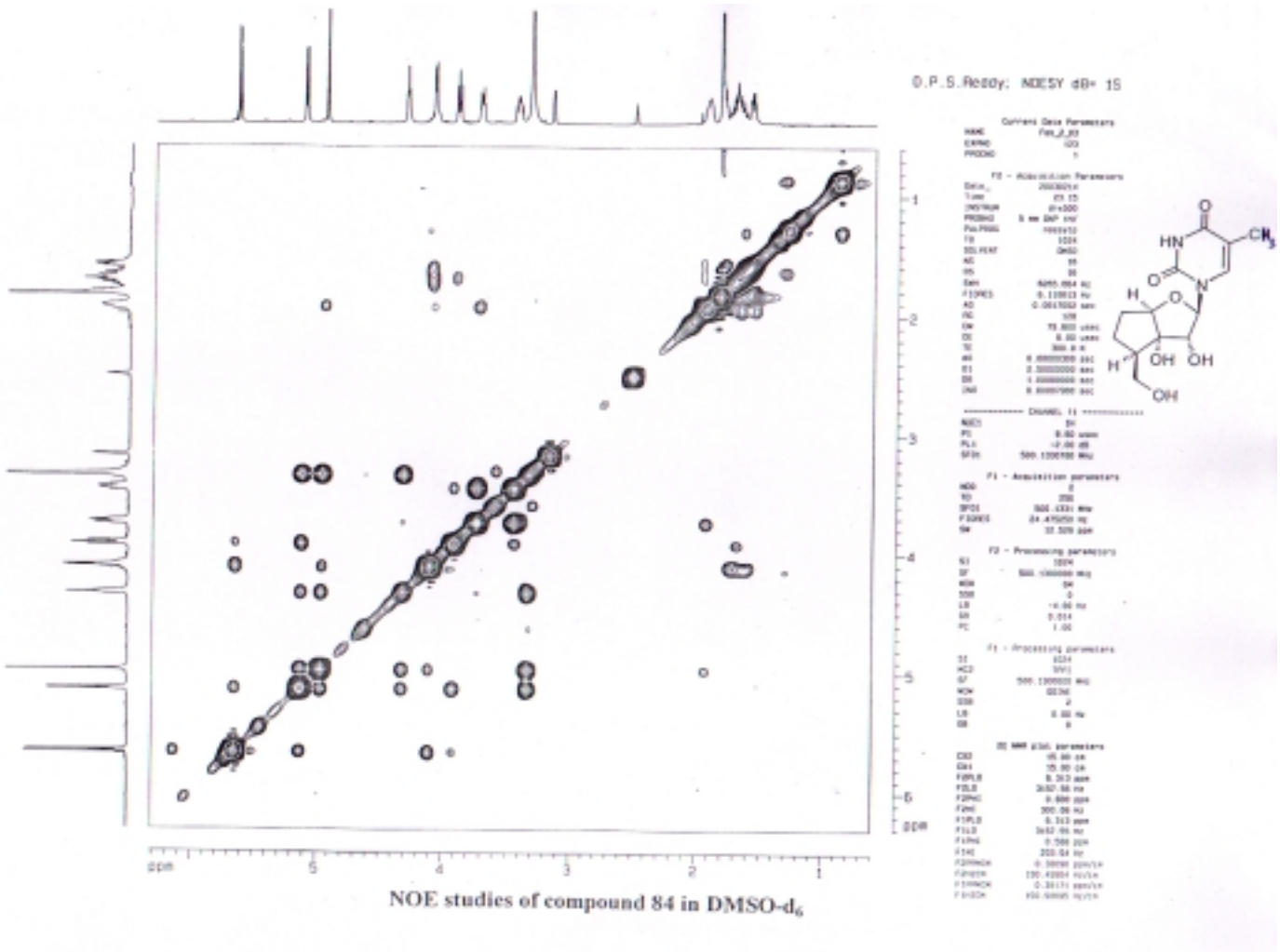
SI	1024
SF	500.1300000 MHz
WDW	SINE
SSB	02
LB	0.00 Hz
GB	0
PC	1.00

F1 - Processing parameters

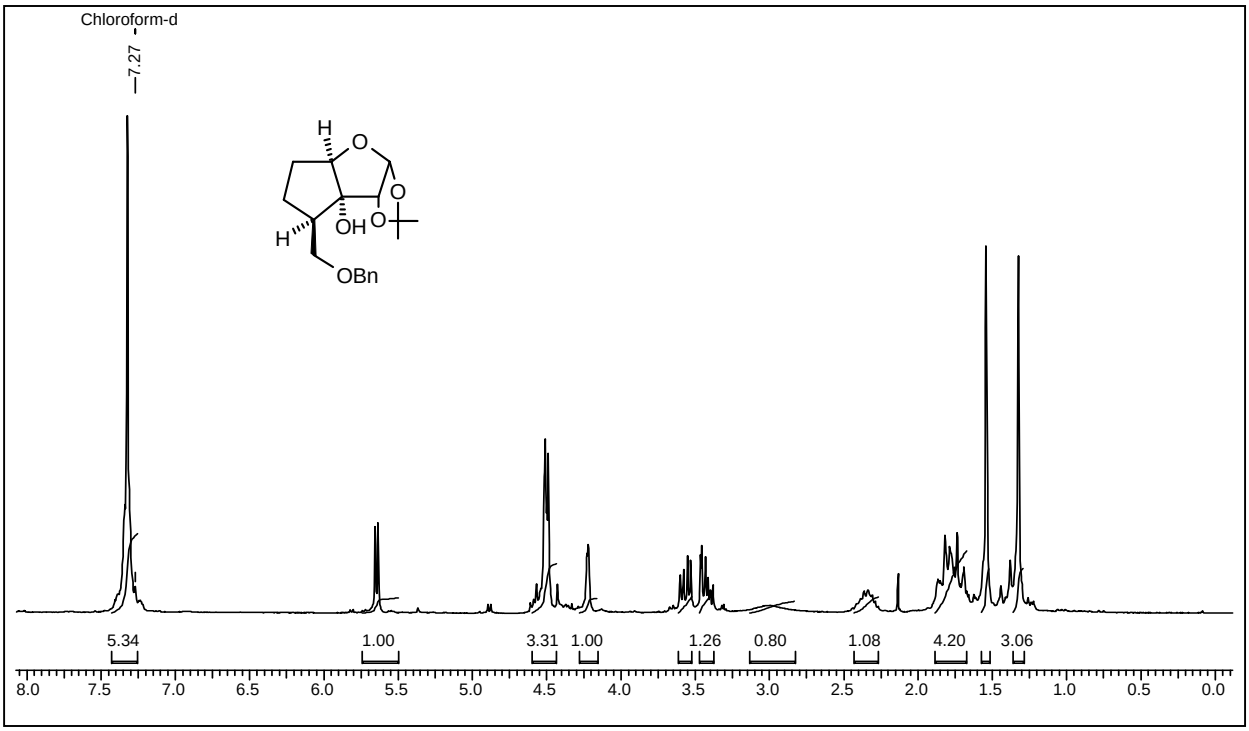
SI	1024
MC2	QF
SF	500.1300000 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0

2D acq. parameters

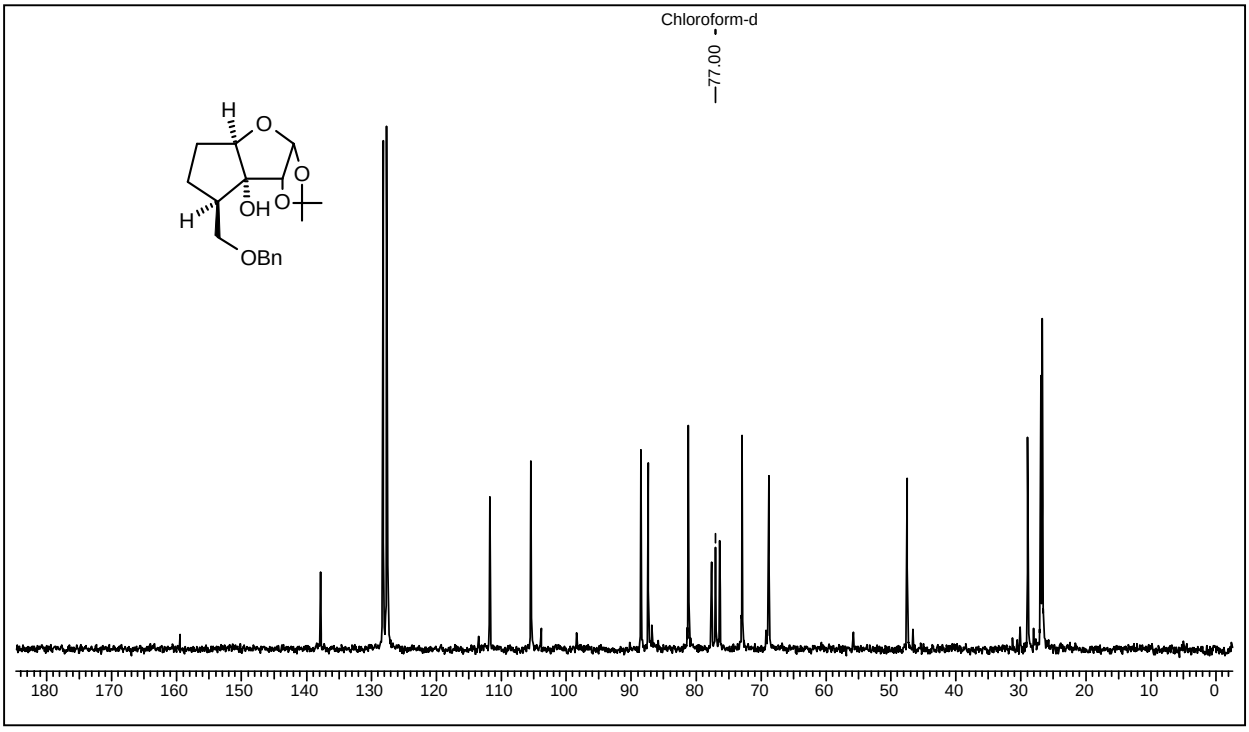
D12	0.00 sec
D11	0.000 sec
F2PLO	7.873 ppm
F1PLO	3337.70 Hz
F2PH1	8.704 ppm
F1PH1	382.18 Hz
F2PL0	7.925 ppm
F1L0	3959.20 Hz
F2PH1	8.556 ppm
F1H1	329.21 Hz
F2PPMPC	0.47831 ppm/pt
F1HZPT	236.38722 Hz/pt
F2PPMPT	0.48275 ppm/pt
F1HZPT	241.54443 Hz/pt



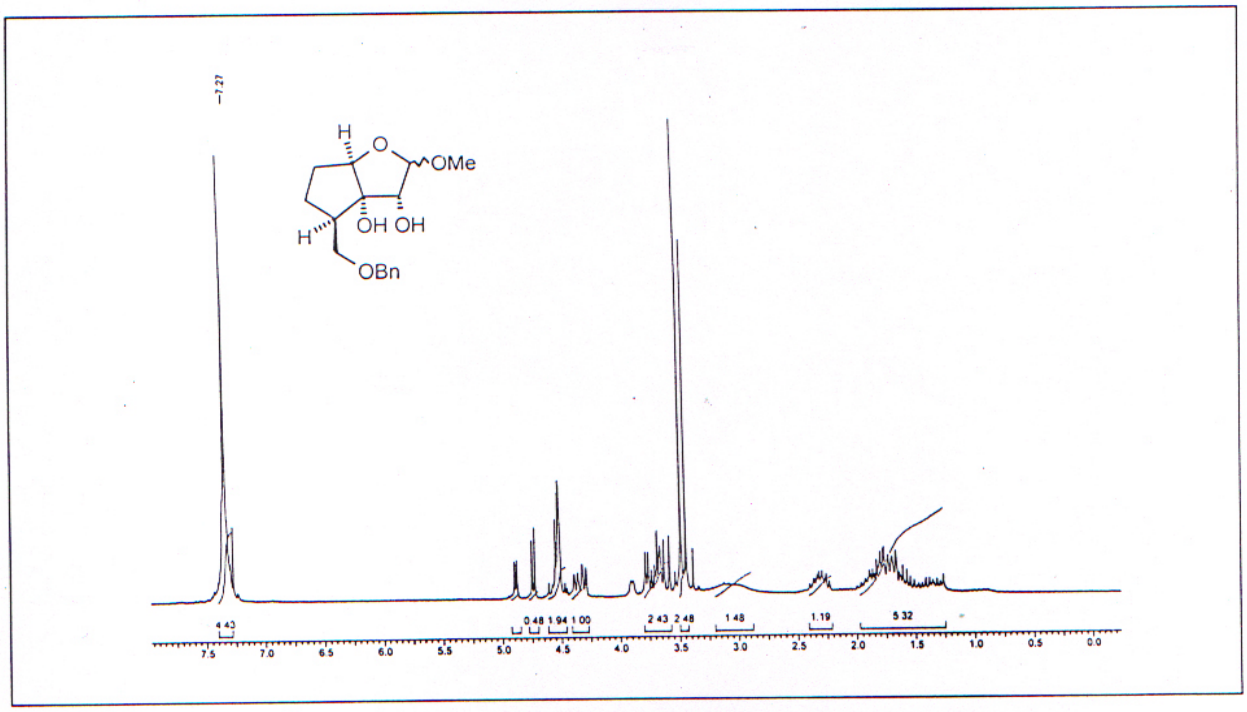
NOE studies of compound 84 in DMSO-d_6



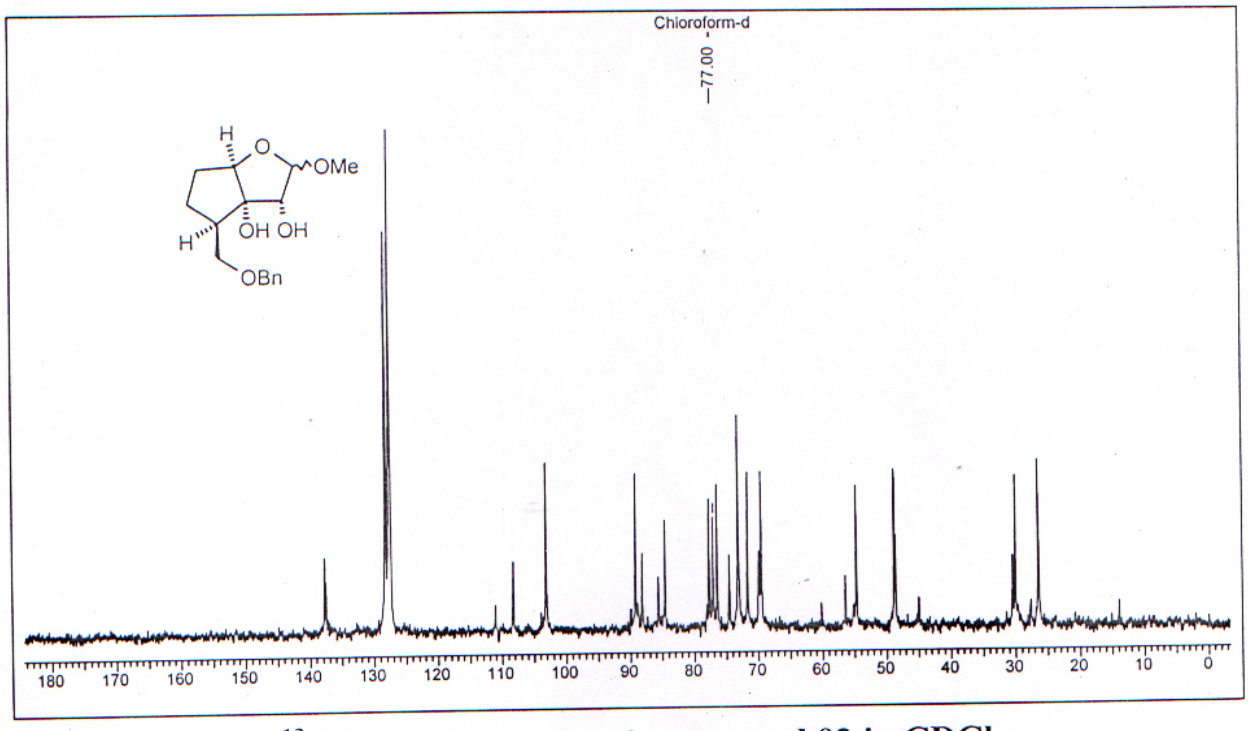
^{1}H NMR Spectrum of compound 91 in $CDCl_3$



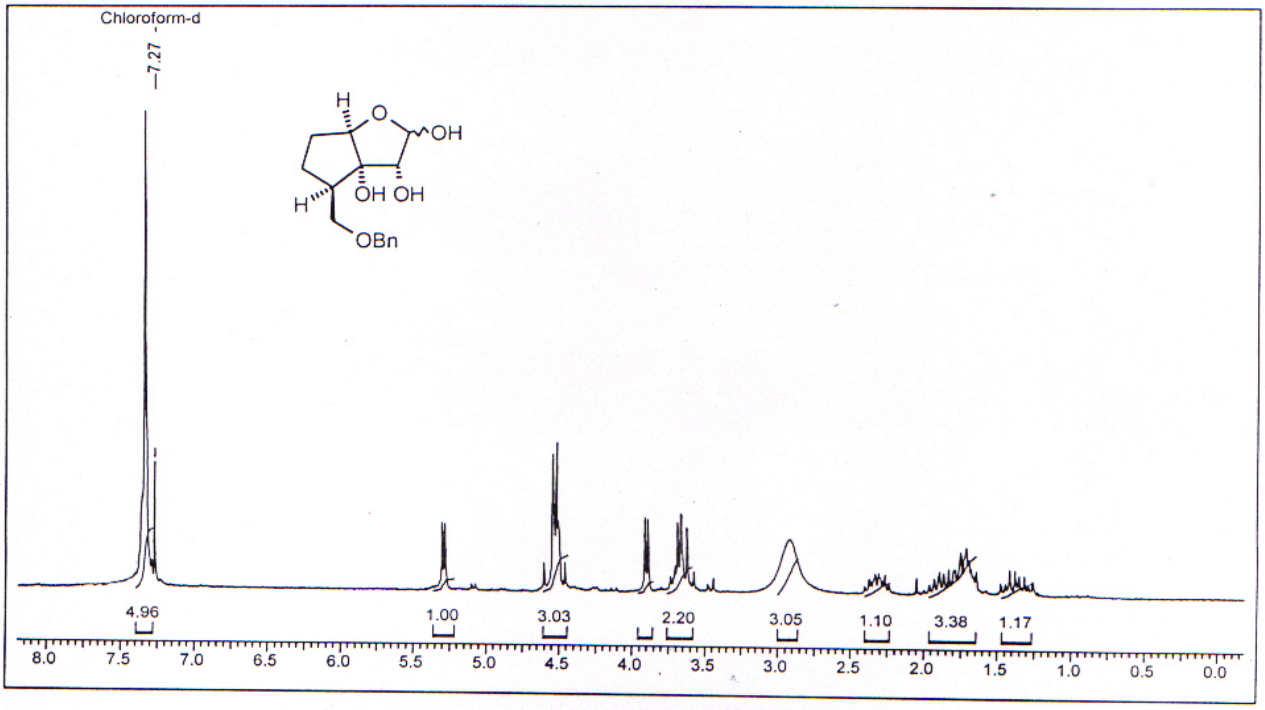
^{13}C NMR Spectrum of compound 91 in $CDCl_3$



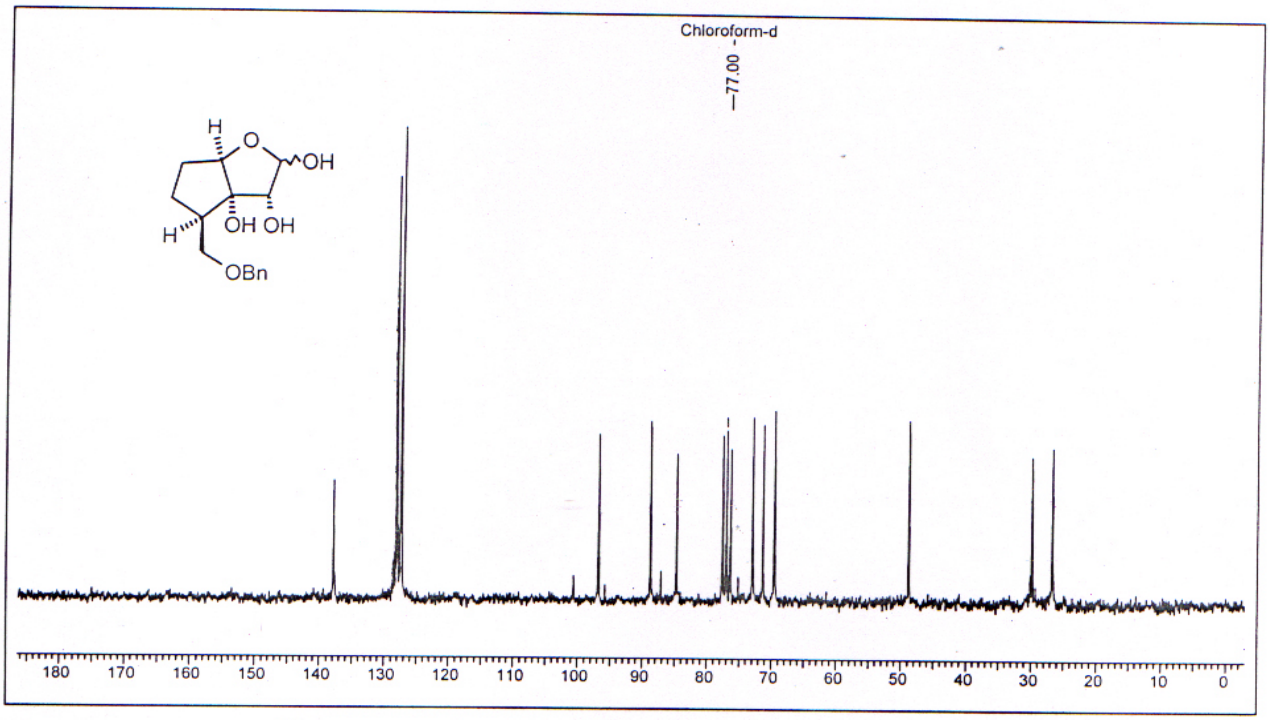
^{1}H NMR Spectrum of compound 92 in $CDCl_3$



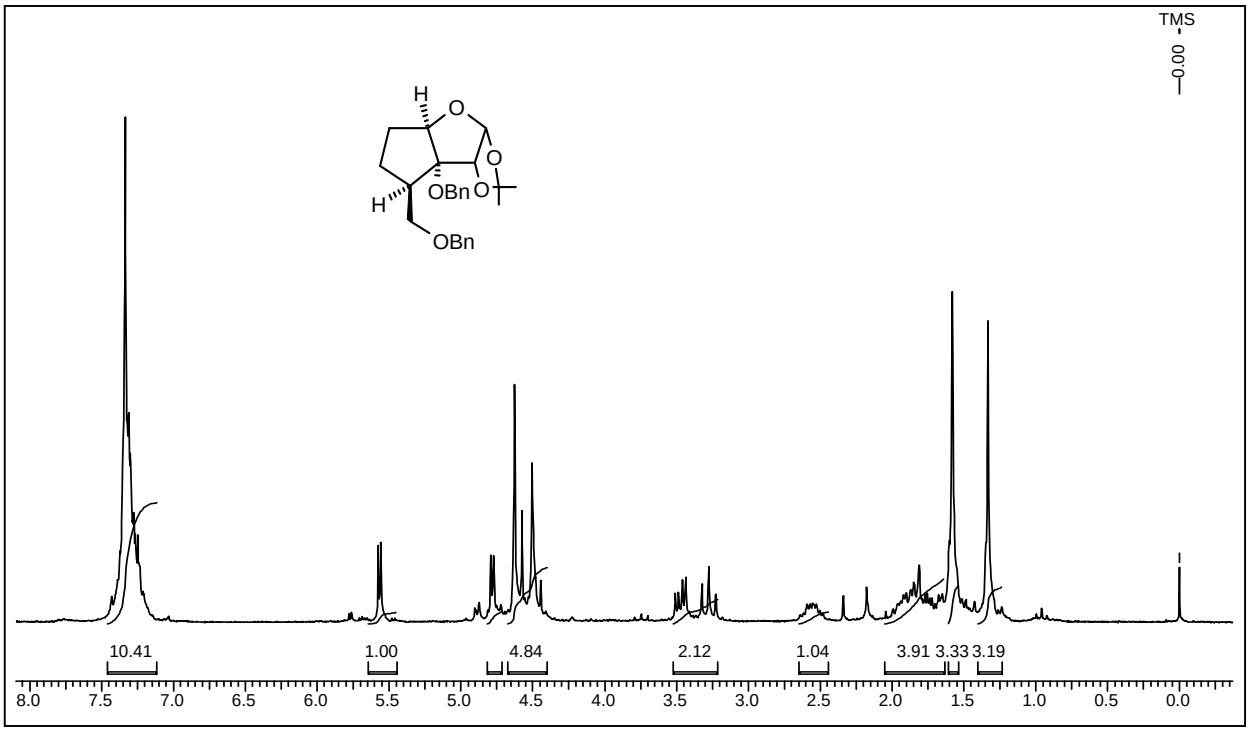
^{13}C NMR Spectrum of compound 92 in $CDCl_3$



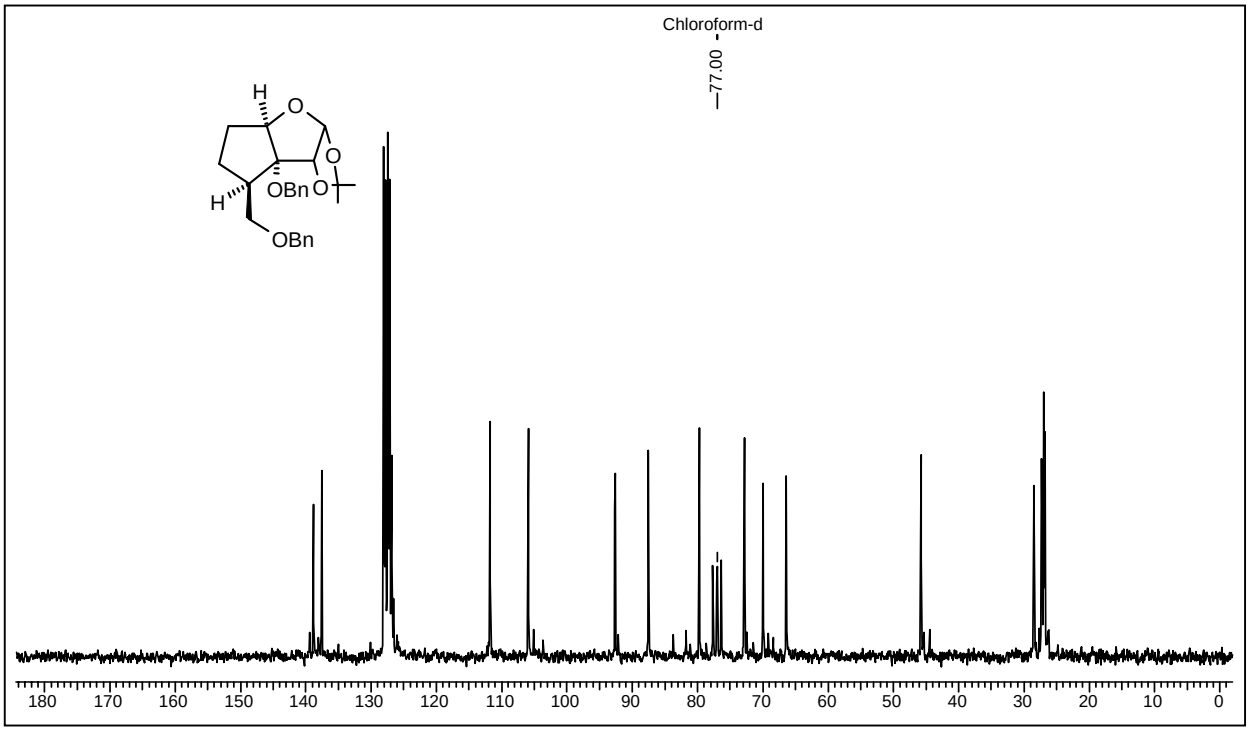
^{1}H NMR Spectrum of compound 93 in $CDCl_3$



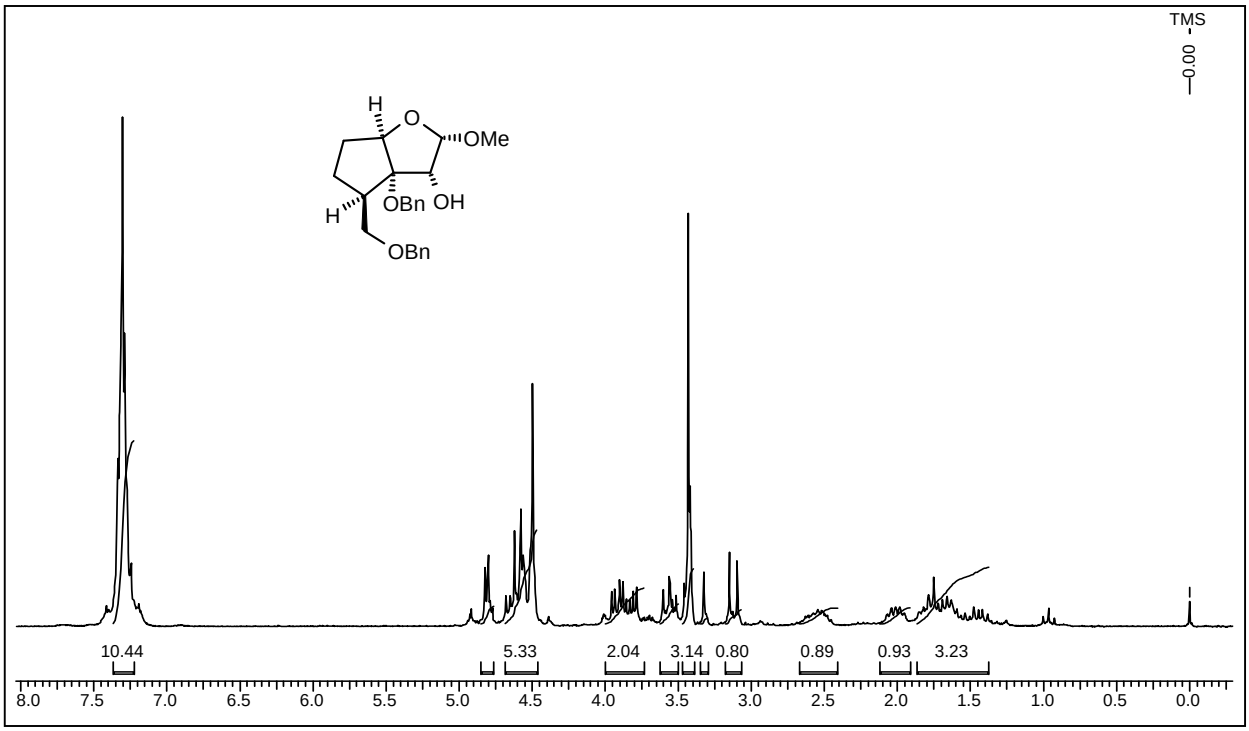
^{13}C NMR Spectrum of compound 93 in $CDCl_3$



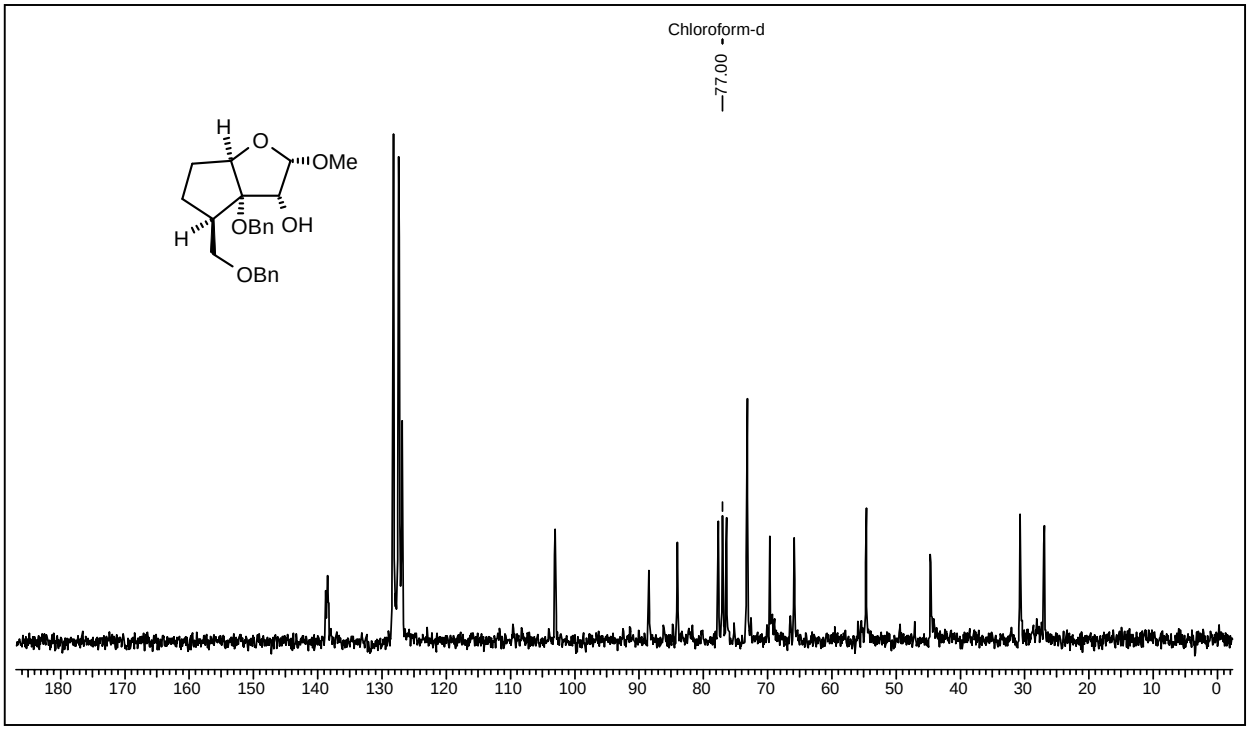
^{1}H NMR Spectrum of compound 94 in $CDCl_3$



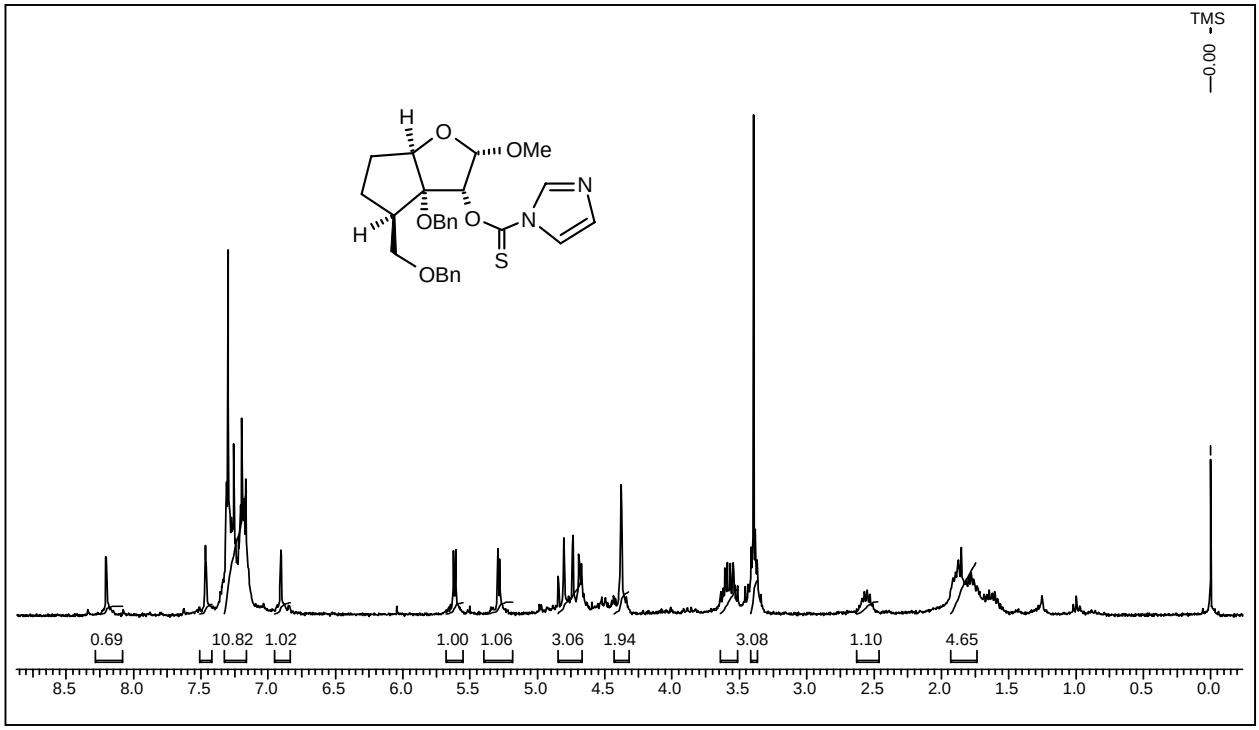
^{13}C NMR Spectrum of compound 94 in $CDCl_3$



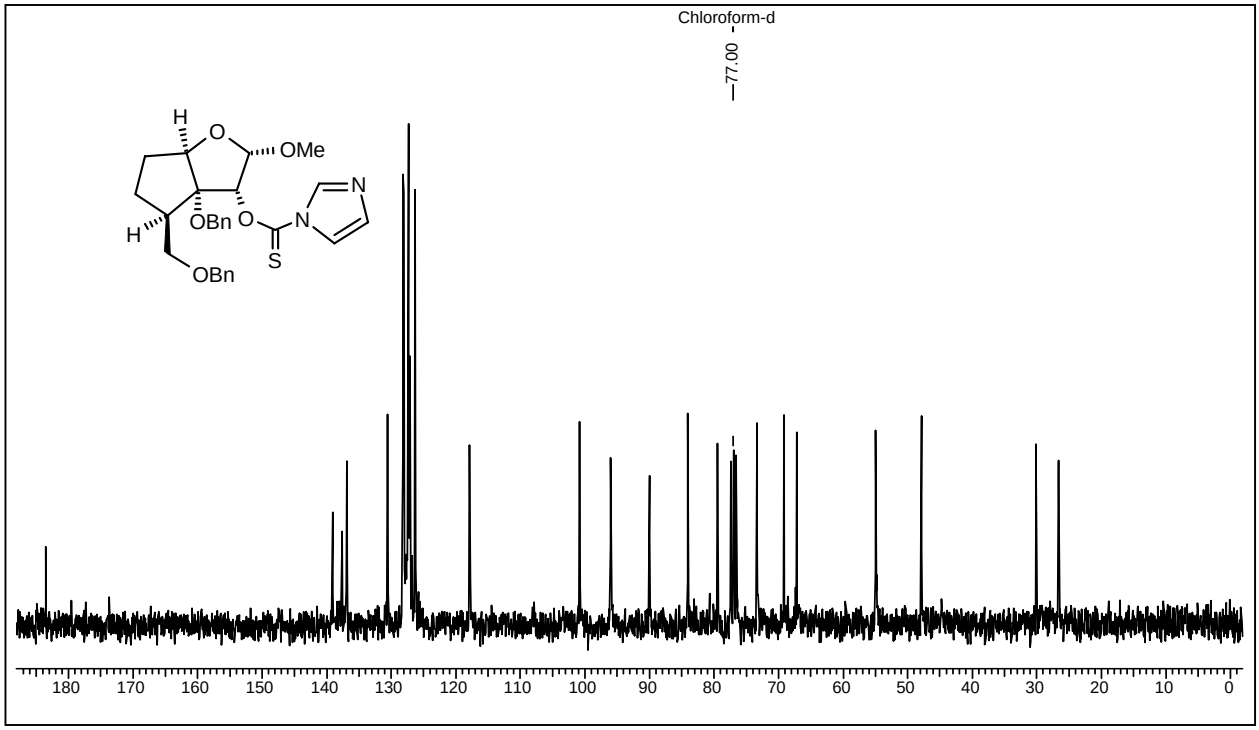
^{1}H NMR Spectrum of compound 95 in $CDCl_3$



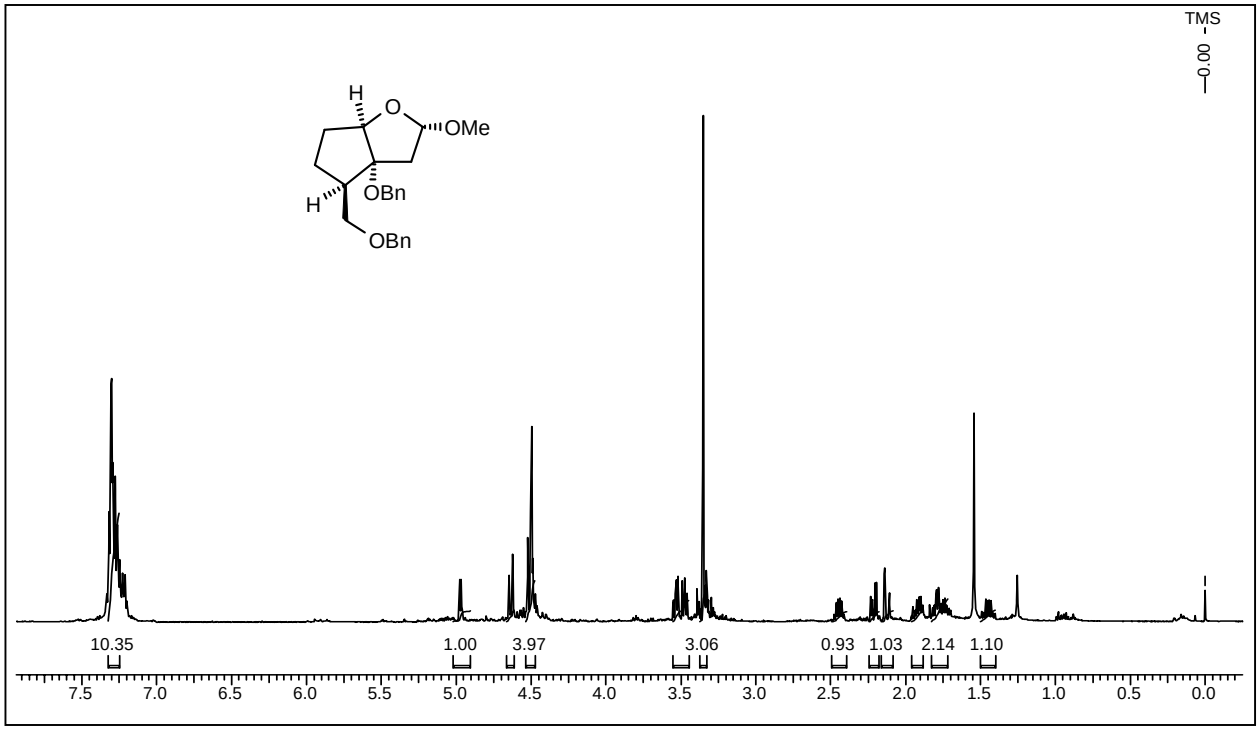
^{13}C NMR Spectrum of compound 95 in $CDCl_3$



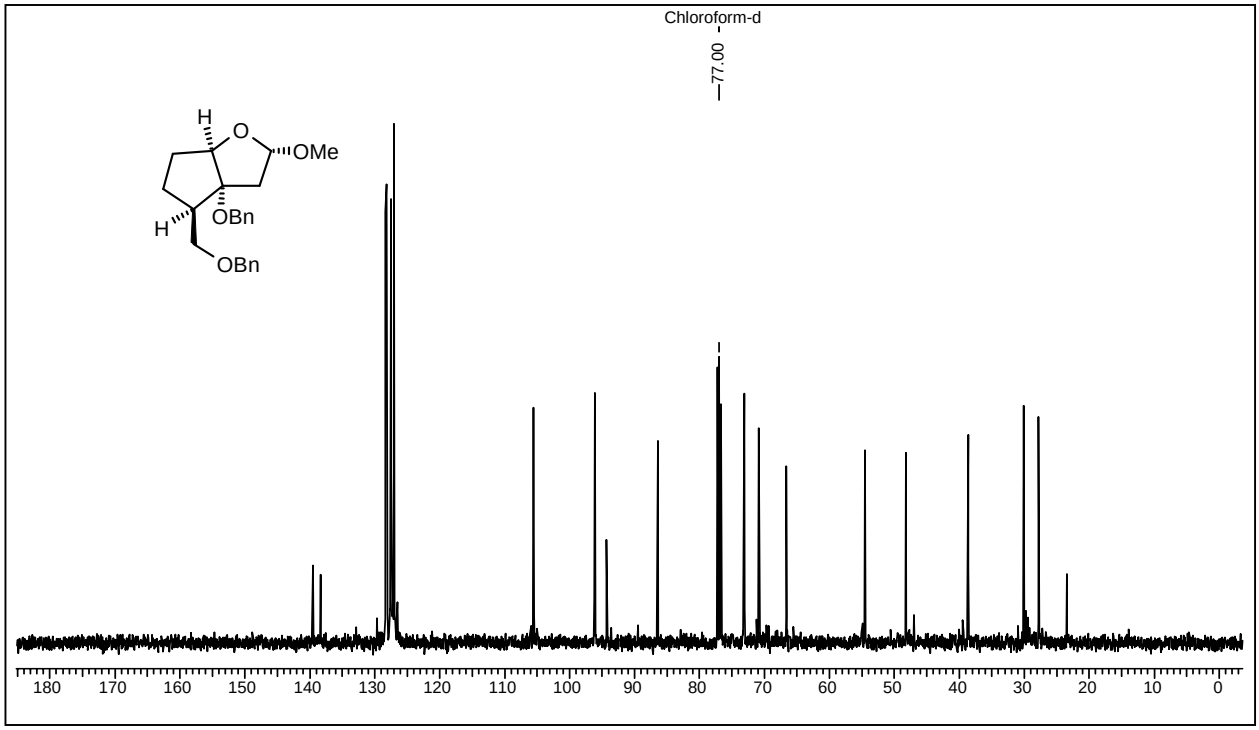
^{1}H NMR Spectrum of compound 96 in $CDCl_3$



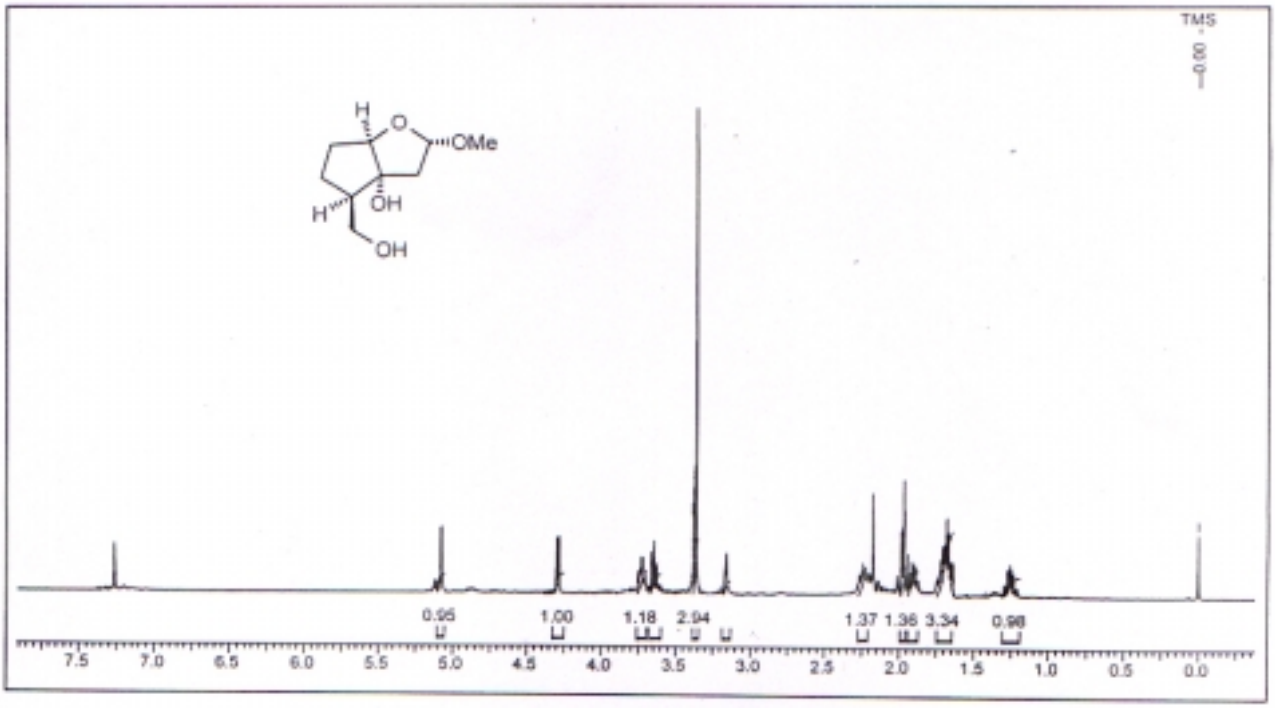
^{13}C NMR Spectrum of compound 96 in $CDCl_3$



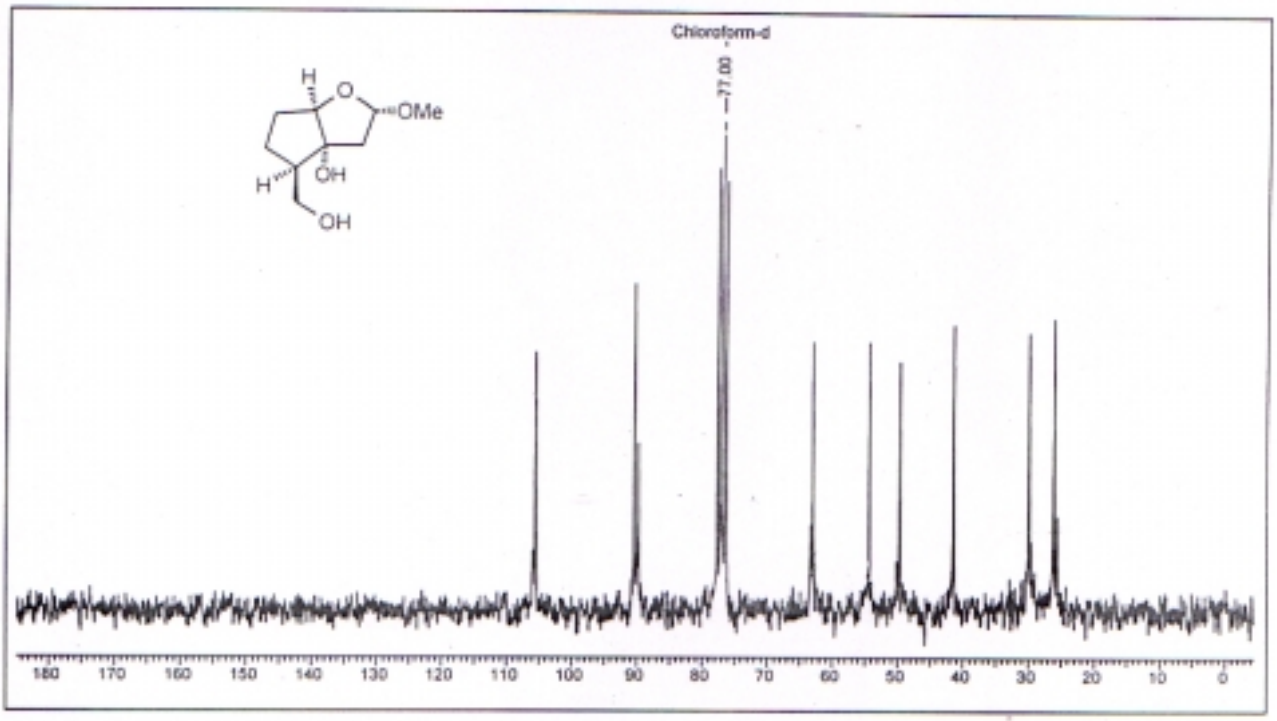
^{1}H NMR Spectrum of compound 90 in $CDCl_3$



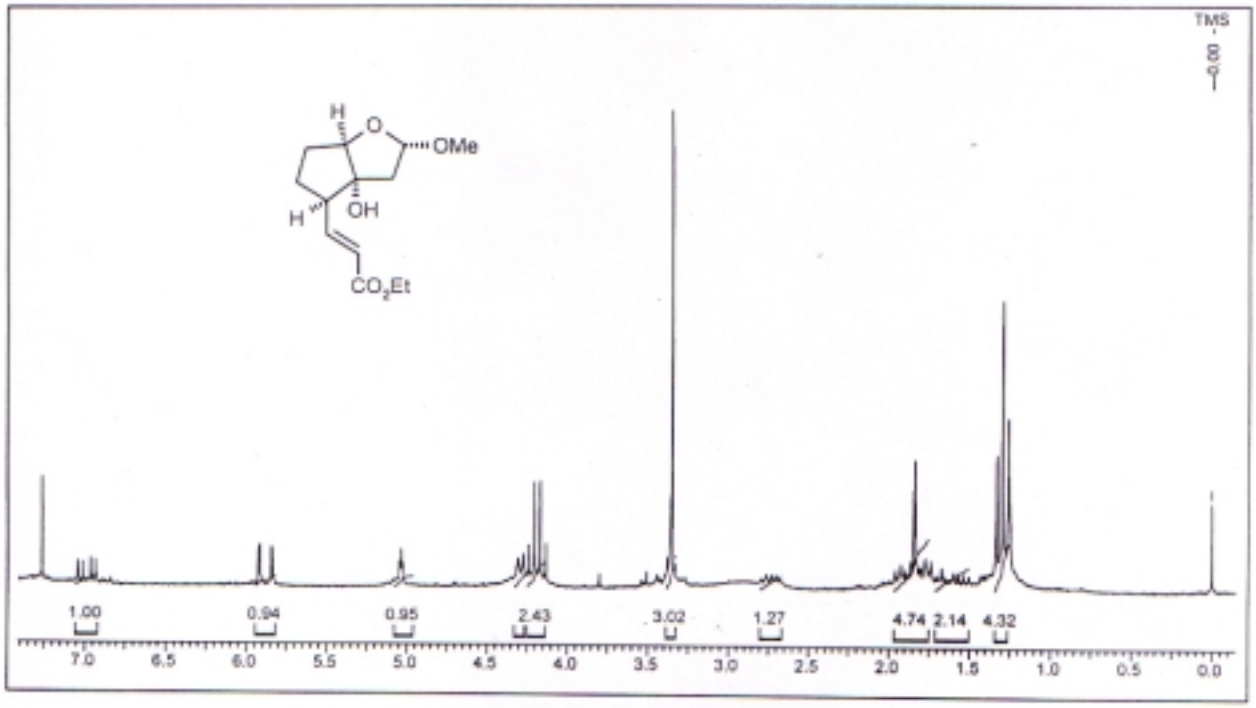
^{13}C NMR Spectrum of compound 90 in $CDCl_3$



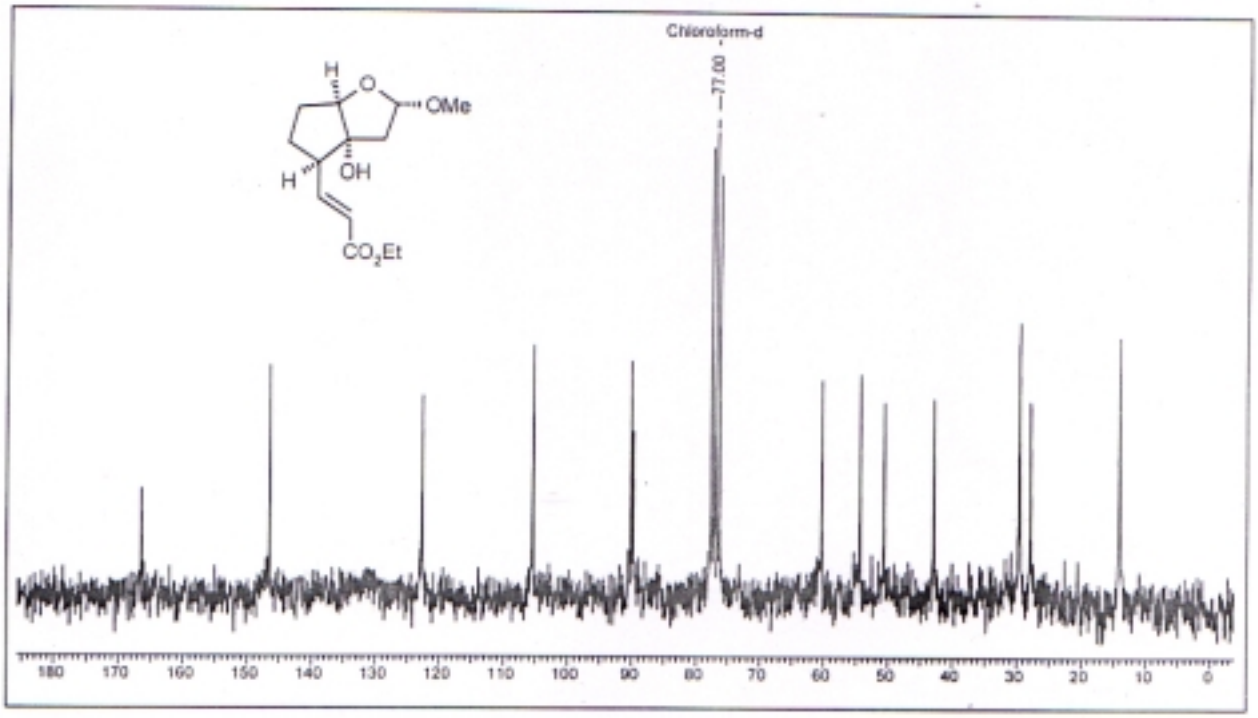
^{1}H NMR Spectrum of compound 97 in $CDCl_3$



^{13}C NMR Spectrum of compound 97 in $CDCl_3$



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



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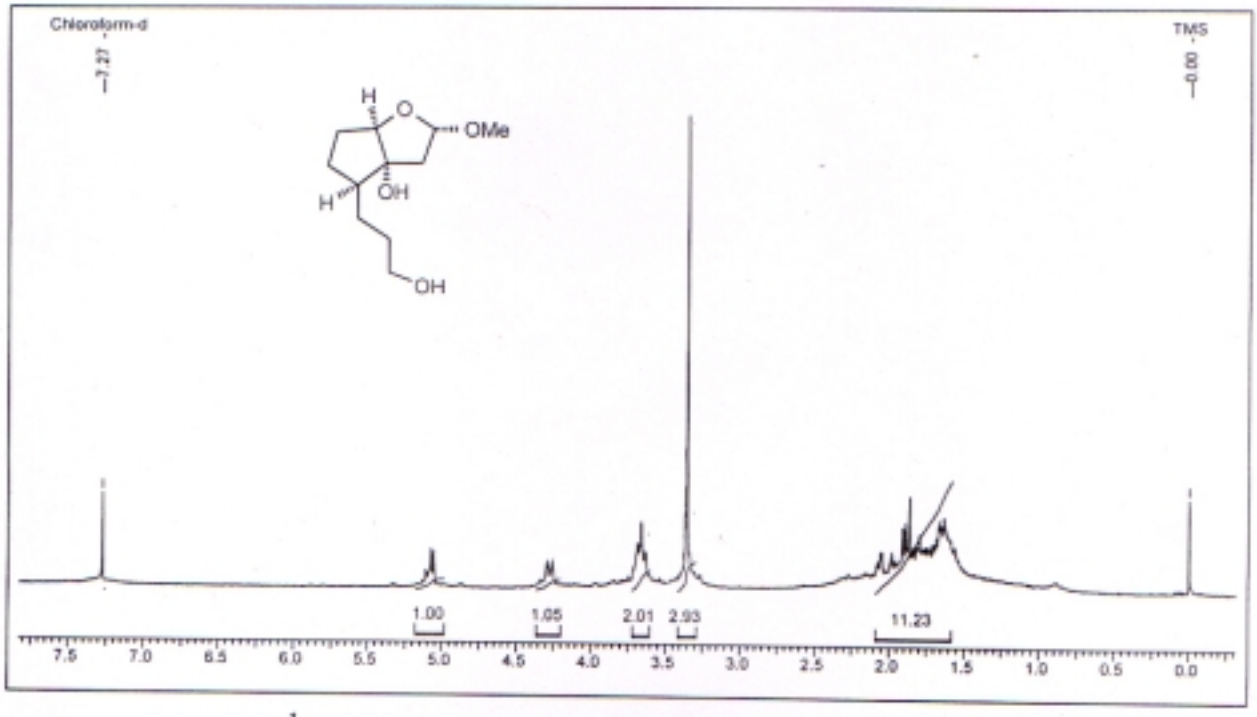

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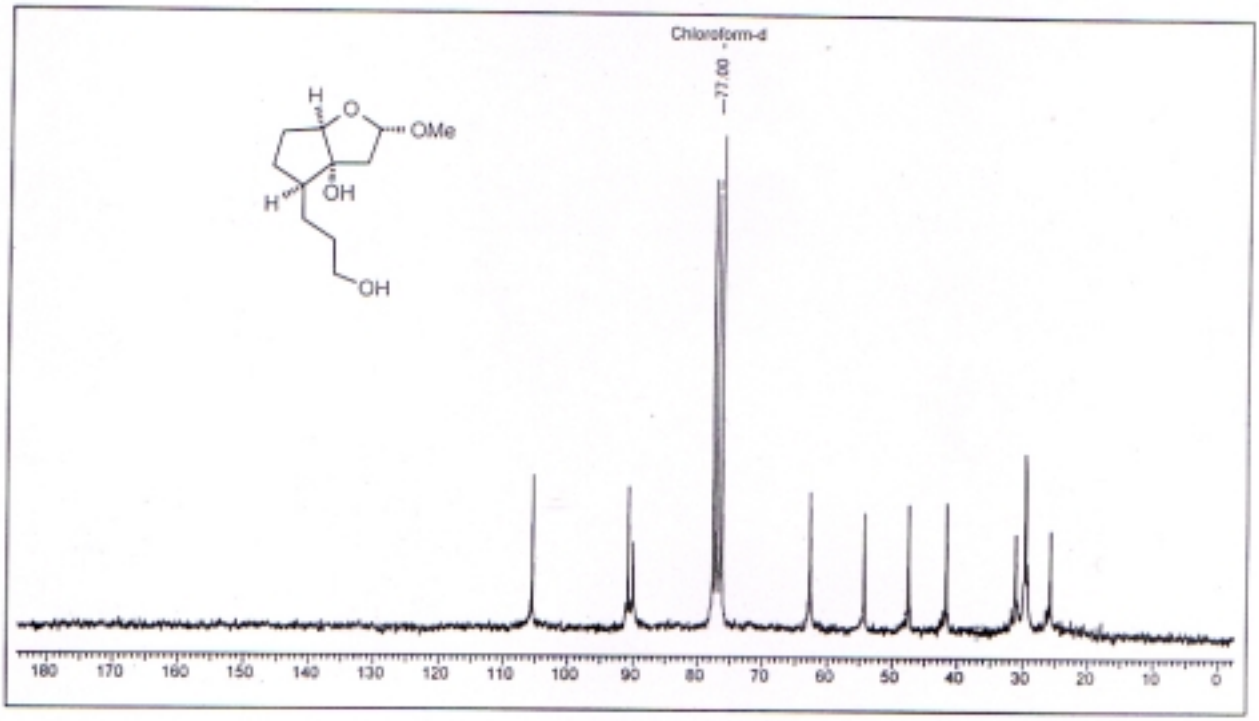
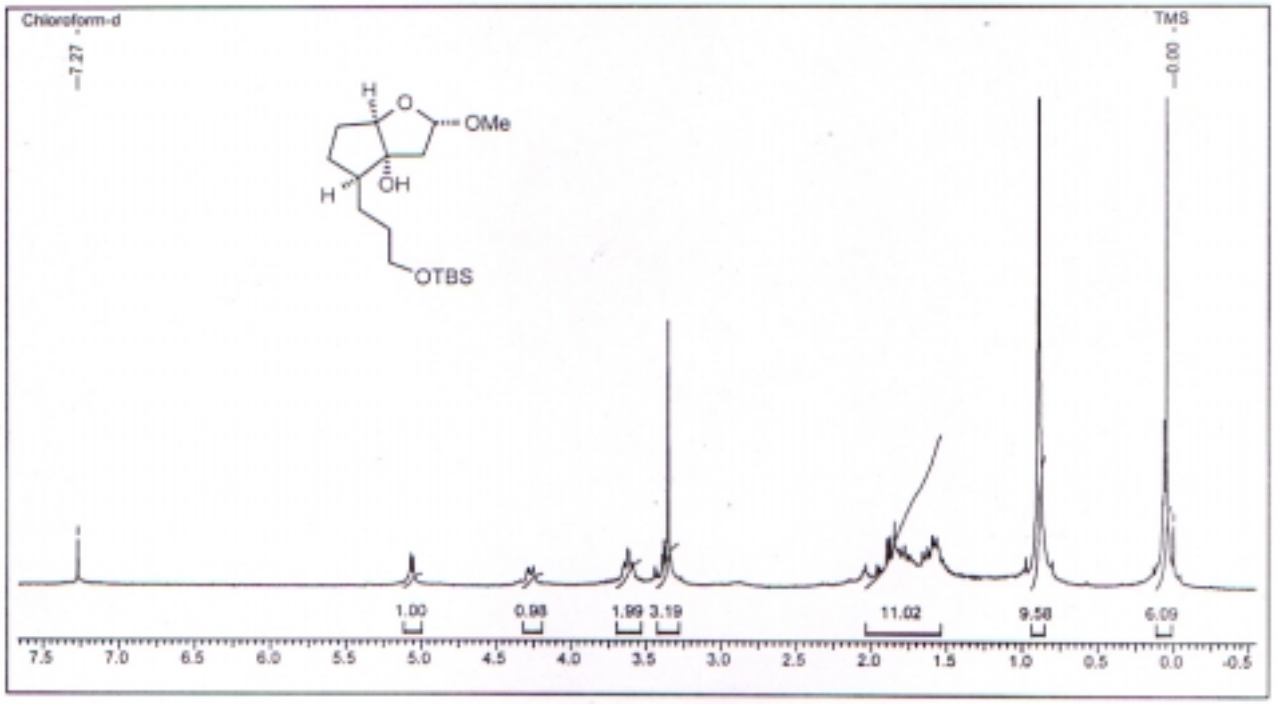
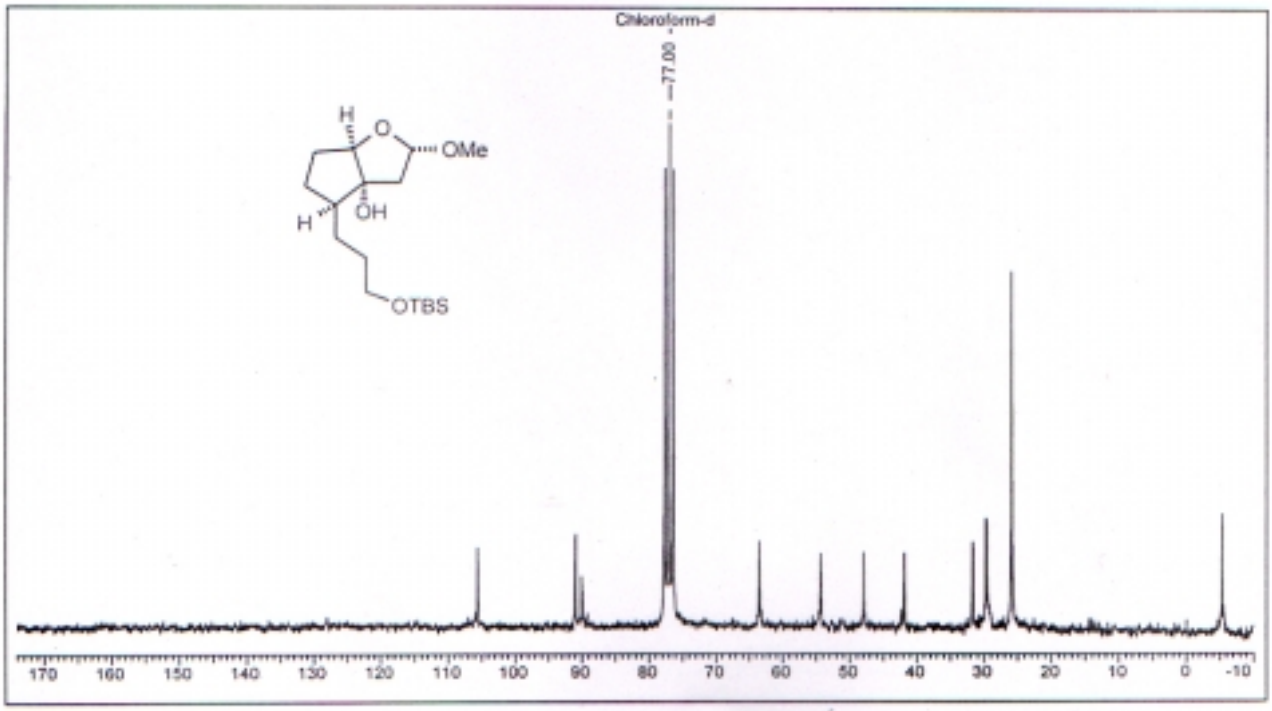


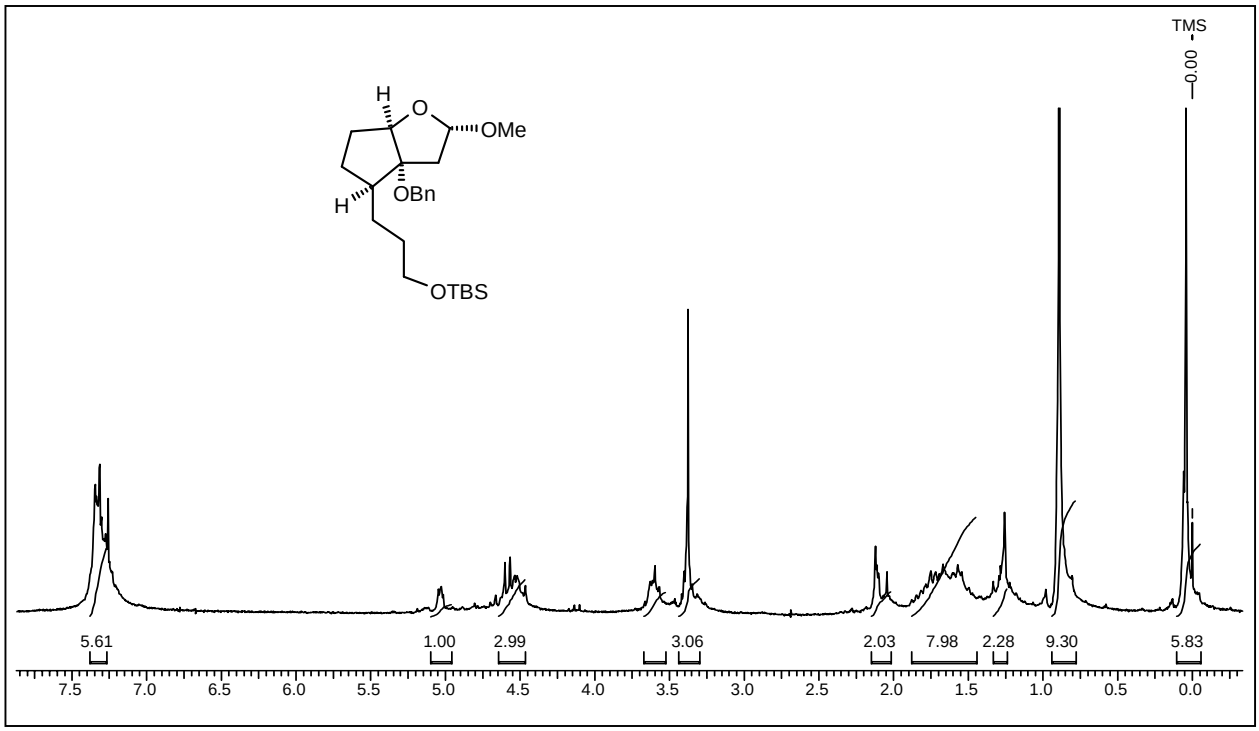
^{13}C NMR Spectrum of compound 99 in $CDCl_3$



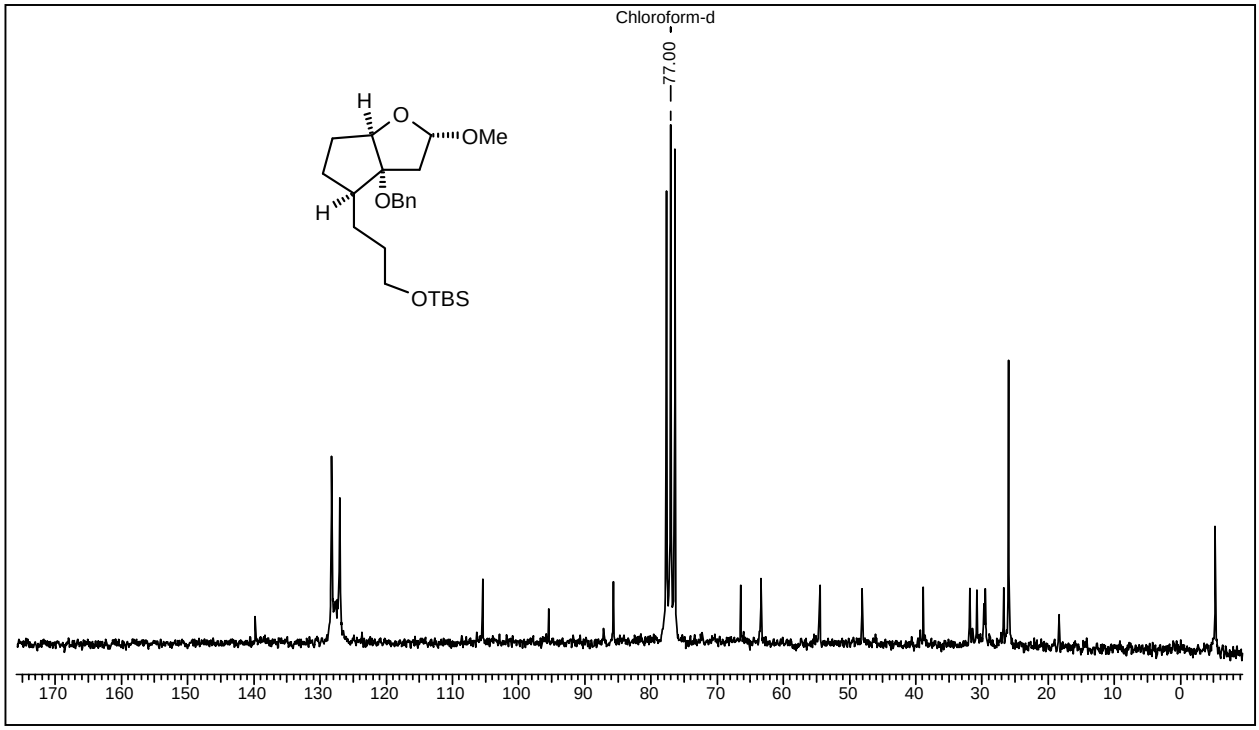
^{1}H NMR Spectrum of compound 101 in $CDCl_3$



^{13}C NMR Spectrum of compound 101 in $CDCl_3$



^{1}H NMR Spectrum of compound 88 in $CDCl_3$



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

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Chapter III

Bis(dealkoxycarbonylation) of Nitroarylmalonates

Introduction

Introduction

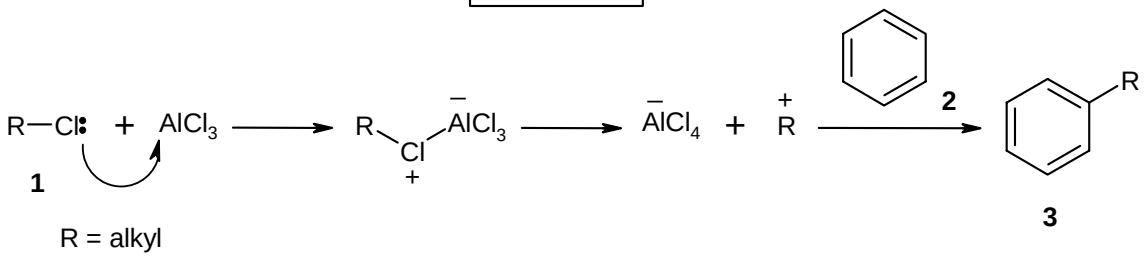
The alkylation of aromatic hydrocarbons with olefins is applied on a large scale in the chemical industry.[1] About 70% of the 29.3 million tonnes accounting the world benzene demand in 1999, were expected to be consumed by acid catalyzed alkylation with ethylene and propylene, 53 and 17%, respectively for the production of ethylbenzene (EB) and cumene. Analogously, *p*-diisopropylbenzene, C10–C14 linear alkylbenzenes (LABs), cymene, *p*-ethyltoluene and 4-*t*-butyltoluene are also important chemical intermediates obtained by acid alkylation of benzene or toluene aromatic ring. The other chemical intermediates, such as 5-(*o*-tolyl)-pentene-2, isobutylbenzene and *t*-amylbenzene, are produced by side-chain alkylation of aromatics, catalyzed by base.[2] Huge improvements towards the development of environmentally friendly processes have been achieved in the alkylations of aromatics with olefins, since the last four or five decades. Particularly, many efforts have been devoted to the research of solid catalysts adequate to substitute mineral or Lewis acids and free bases traditionally employed as catalysts in the acid or base catalyzed alkylations.

In many industrial processes these alkylations are often performed with acid catalysts such as strong mineral acids or Lewis acids (e.g. HF, H_2SO_4, and $AlCl_3$), which are highly toxic and corrosive. They are dangerous to handle and to transport as they corrode storage and disposal containers. Often, the products need to be separated from the acid with a difficult and energy consuming process. To circumvent these problems many alternatives have been developed for the preparation of alkyl aromatics. The other possibility for the alkylation of electron deficient aromatics is to introduce carbon nucleophiles onto such aromatics possessing leaving groups such as halides. Even though introducing 'N' and 'O' nucleophiles to such aromatics is a standard aromatic nucleophilic substitution reaction in organic synthesis, there are not many successful examples of arylation of carbanions by nucleophilic aromatic substitution. The major limitation for this addition-elimination process is that the nitro aromatics often react with carbanions by electron-transfer processes.

Alkylation of aromatic rings is one of the important transformations in organic synthesis. Electrophilic substitution is the usual route for the preparation of substituted aromatic compounds, and in which both Friedel–Crafts acylation and Friedel–Crafts

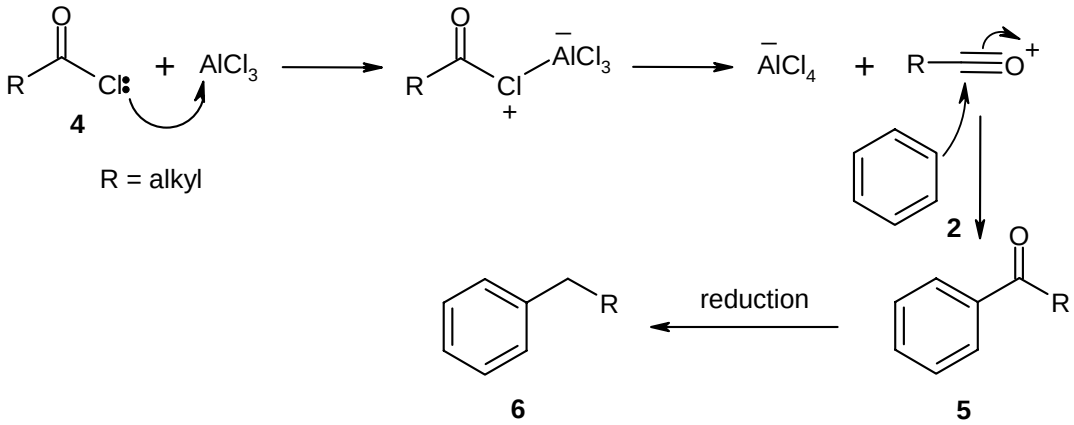
alkylation reactions are the most important reactions for synthesizing the acyl- and alkyl-substituted aromatic compounds.[3] Friedel–Crafts alkylation reaction works well with relatively stable cations especially with tertiary cations. The cation can be generated in a number of ways such as the protonation of an alkene, the acid catalyzed decomposition of tertiary alcohol, or the Lewis–acid catalyzed decomposition of tertiary-alkyl chloride. While the Friedel–Crafts alkylation procedure continues to occupy center stage for the alkylation of numerous aromatic rings, it does not proceed successfully with aromatic substrates having electron-withdrawing groups. In addition, the Friedel–Crafts method has the disadvantage of rearrangement of the alkyl group being used and it often leads to alkylation at more than one site (Scheme 1).

Scheme 1



The Friedel–Crafts acylation reaction is much more reliable method than Friedel–Crafts alkylation. In the case of Friedel–Crafts acylation, the acyl group in the product withdraws electrons from π-system making multiple substitutions harder, and the rearrangement of cations is no longer a problem because the electrophile, acylium cation is already relatively stable. Hence, the Friedel–Crafts acylation reaction is generally used an

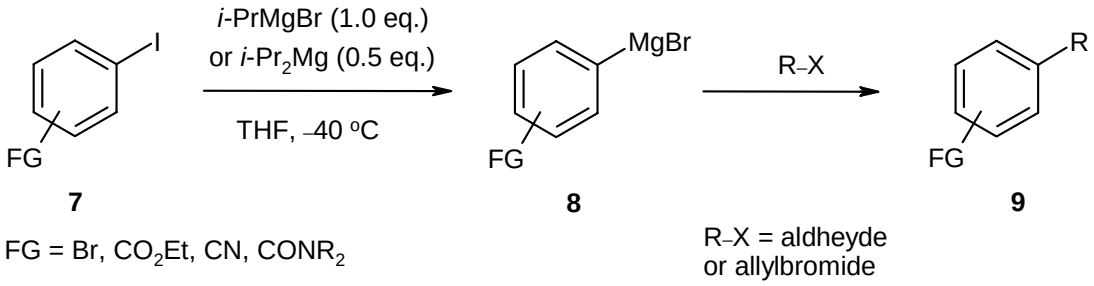
Scheme 2



alternative to the alkylation reaction where acylation is carried out first and then the reduction of carbonyl group to a methylene moiety. If the ring is too deactivated to start off with, Friedel–Crafts acylation reaction not be possible at all. Nitrobenzene is inert to Friedel–Crafts acylation reaction and it is often used as a solvent for these reactions (Scheme 2).

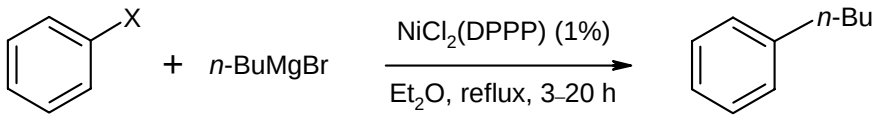
Organomagnesium reagents are extremely important in synthetic organic chemistry. Since their discovery, there has great interest in these versatile reagents, and numerous industrial applications have been reported.[4] Grignard reagents can be conveniently synthesized from organic halides and exhibit high reactivity and satisfactory chemoselectivity, which can be further improved by transmetallation. Recently, Knochel, P. *et al.* (1998) reported a general route for the preparation of alkyl aromatics.[5] The highly functionalized arylmagnesium halides containing functional groups such as ester, amide, or cyano groups, or a halogenide substituent were synthesized from functionalized aryl iodides by an iodine-magnesium exchange reaction (Scheme 3).

Scheme 3



Primary alkyl Grignard reagents, regardless of the presence of or absence of β-hydrogens couple with aromatic halides most efficiently in the presence of $NiCl_2L_2$ as catalyst, $NiCl_2$(DPPP) being most active and general use. While Pd catalysts are usually used for coupling of β-H lacking alkyl (Me or $PhCH_2$) Grignard reagents with aromatic bromides and iodides. $PdCl_2$(DPPF) is also effective for coupling of β-H bearing alkyl Grignard reagents with aryl bromides. The reactivity order of aromatic halides is generally ArI > ArBr > ArCl >> ArF for Ni catalysed reactions and ArI > ArBr >> ArCl > ArF for Pd catalysed reactions (Scheme 4).[6]

Scheme 4

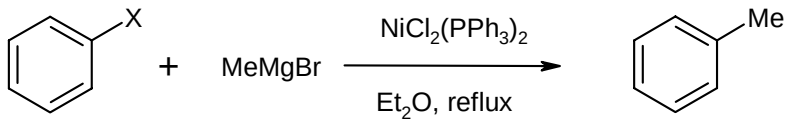


10 **11**

X =	F	Cl	Br	I
%	31	95	54	80

Takei, H. *et el.* found that aryl selenides, aryl sulfides, aryl sulfites and aryl sulfones smoothly couple with Grignard reagents in the presence of Ni(II)-phosphine complexes as catalysts to afford the corresponding unsaturated compounds in good yields. The reactivity order of coupling reaction with BuMgBr catalyzed by $NiC1_2[Ph_2PCH_2CH_2CH_2PPh_2]$ was found to be PhSeMe >> PhCl > PhSMe by the competitive reactions (Scheme 5).[7]

Scheme 5



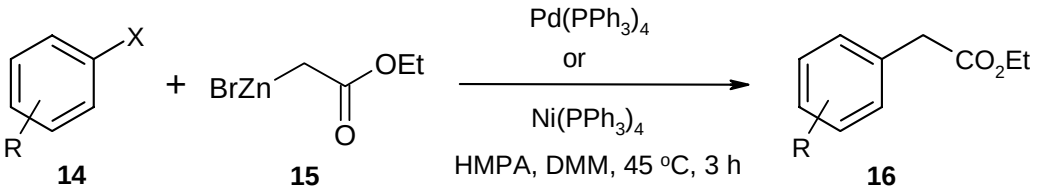
12 **13**

X =	SH	SMe	SOPh	SO_2Ph
% =	64	97	77	97

Fauvarque, J. F. and coworkers (1979) performed aromatic nucleophilic substitution of a halogen by the enolate-like reagent $BrZnCH_2CO_2Et$ in the presence of transition metal complexes.[8] Arylatlon of $BrZnCH_2CO_2Et$ by aromatic halides proceeded smoothly and in a fair yield in a mixture of dimethoxymethane and a dipolar aprotic solvent (HMPA, *N*-methylpyrrolidone, DMF, DMSO) when catalyzed by soluble nickel or palladium complexes. This reaction was also applied to functional aromatic halides and proceeded smoothly even with aromatic chlorides. The catalytic arylation of the Reformatsky reagent was compatible

with many functional groups. When this reaction can't be conducted catalytically it can be conducted stoichiometrically with pre-formed ArMX complexes (Scheme 6).

Scheme 6



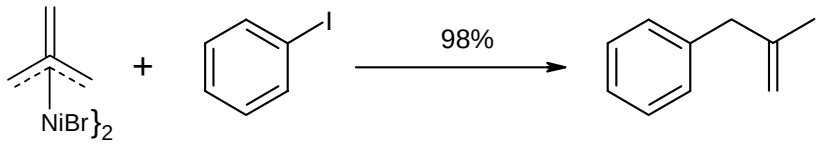
14 **15** **16**

X = Cl, Br, I

R = CO_2H, CN, OMe, COMe, NO_2

In recent years transition metal π-allyl complexes have emerged as efficient reagents for the introduction of allyl units into organic substrates.[9] Two classes of organic reagents have proved particularly valuable, the π-allyl complexes of palladium and π-allyl nickel halides. These complexes are complimentary, since π-allyl palladium complexes react with electron-rich centers (e.g. stabilized anions) and π-allyl nickel halides react with electron-poor centers (e.g. alkyl halides and carbonyl groups). The high reactivity of π-allyl nickel halides towards alkyl halide coupled with their chemoselectivity and the use of hetero-atom, substituted reagents make these reagents valuable alternatives to the normal Wurtz-type reagents. This method was well exploited to prepare alkyl aromatics as shown in Scheme 7.

Scheme 7

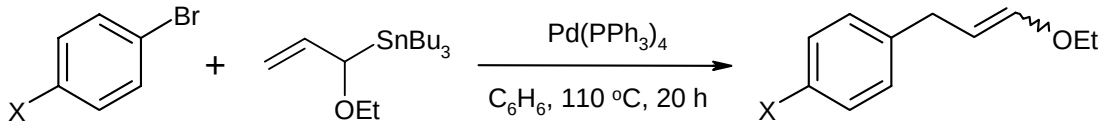


17 **18** **19**

In 1977, Kosugi, M. *et al.* have prepared various allyl-substituted aromatics in good yields by treating the bromo-substituted aromatics with allyltributyltin in the presence of $Pd(PPh_3)_4$.[10] In 1983, Quintard, J.-P. *et al.* studied the reactions involving the coupling of (α-ethoxybuteny1)tributyltin and (α-ethoxy-allyl)tributyltins, obtained from the appropriate

Grignard reagents and (chloroethoxymethyl)tributyltin, and used for the synthesis of carbonyl compounds *via* enol ethers or monoprotected 1,2-diols. This methodology was expanded for the preparation of alkyl-substituted aromatics using $Pd(PPh_3)_4$ as a catalyst, in which substitution accompanied by complete allylic shift (Scheme 8).[11]

Scheme 8

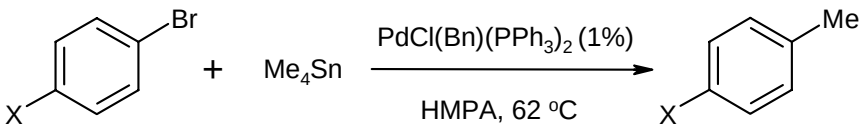


20 **21** **22**

X = H, Cl, F

In 1979, Stille, J. K. *et al.* carried out extensive studies on palladium complexes catalyzed alkylation of aromatic halides.[12] Palladium complexes catalyze the coupling of tetraorganotin compounds with benzyl and aryl halides, benzylchloro-bis(triphenylphosphine)palladium(II) being the catalyst of choice. Various functional groups were tolerated by this reaction and generally high yields of the cross-coupled products were obtained. Oxygen had a considerable accelerating effect on the reaction whereas triphenylphosphine had little effect. The reaction of substituted bromobenzenes with tetramethyltin catalyzed by benzylchloro-bis(triphenylphosphine)palladium(II) was accelerated by electron-withdrawing groups; however, a simple Hammett correlation was not observed. Optically active α-deuteriobenzyl bromide on treatment with tetramethyltin afforded optically active α-deuterioethylbenzene with inversion of configuration. Homocoupling was the main reaction observed when lithium or Grignard reagents reacted with benzyl chloride under the influence of various palladium catalysts (Scheme 9).

Scheme 9

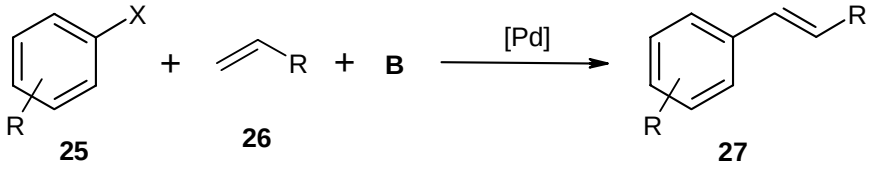


23 **24**

X = F, Me, OMe, COMe

The Heck reaction has developed into a standard method of organic synthesis since its discovery in 1971.[13,14] By employing this reaction, styrene derivatives, amongst others, can be prepared as vinylic C–C coupling products in one step from iodo- and bromoarenes. Because the reaction is both regio- and stereoselective, it has often been used in heterocycle and natural product cheimistry.[15] However, attempts to submit the cheap chloroarenes to the Heck olefination were not an unqualified success. Herrmann, W. A. *et al.* have found structurally defined and easy-to-handle palladium complexes, that surpass all previously known catalysts of the Heck reaction as regards stability and lifetime. They also enable the activation of chloroarenes. The styrene derivatives obtained can be converted to saturated alkyl aromatics by reduction of the double bond (Scheme 10).[16]

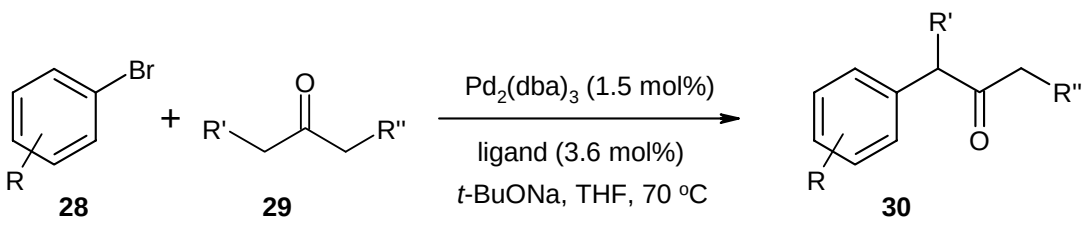
Scheme 10



X = Br, I
[Pd] = $Pd(OAc)_2/PPh_3$
B = base, e.g. Et_3N, K_2CO_3, NaOAc

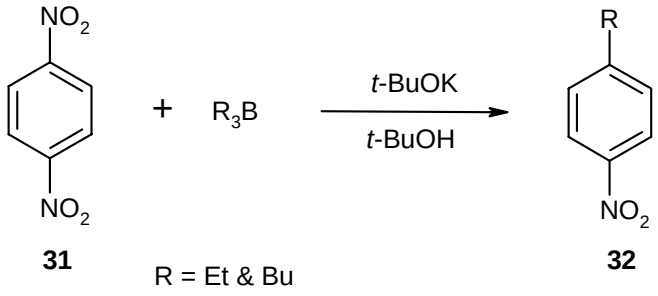
Recently, Buchwald, S. L. and coworkers (1997) have developed a general method for the direct synthesis of α-aryl ketones from ketones and aryl bromides. This process displayed good functional group tolerance and high regioselectivity. Ketones containing α,ά-hydrogens are preferentially arylated at the least-hindered side (methyl > methylene >> methine) (Scheme 11).[17]

Scheme 11



In 2000, Hoz, S. et al. reported the application of trialkylboranes in base-promoted alkylation of nitroaromatics.[18] When *p*-dinitrobenzene (**31**) was treated with trialkylborane in the presence of potassium tert-butoxide in tert-butyl alcohol at room temperature for five minutes, it furnished *p*-alkylnitrobenzene (**32**) in high yield. Equivalent amounts of the three components **31**, trialkylborane, and base were found to be essential for the completion of the reaction. When the amount of trialkylborane or base was reduced below this ratio, the substrate was consumed in an amount equivalent to the reagent present in the minimum concentration. Since an excessive amount of base resulted in the formation of *p-tert*-butoxynitrobenzene, a small excess (approximately 10%) of the borane reagent was usually employed (Scheme 12). Aluminum, the homologue of borane, was found to be much less reactive. Treatment with triethylaluminum, under identical reaction conditions gave only 19% of *p*-ethylnitrobenzene after 12 h at room temperature although over 40% of **31** was consumed.

Scheme 12



Present Work

Present Work

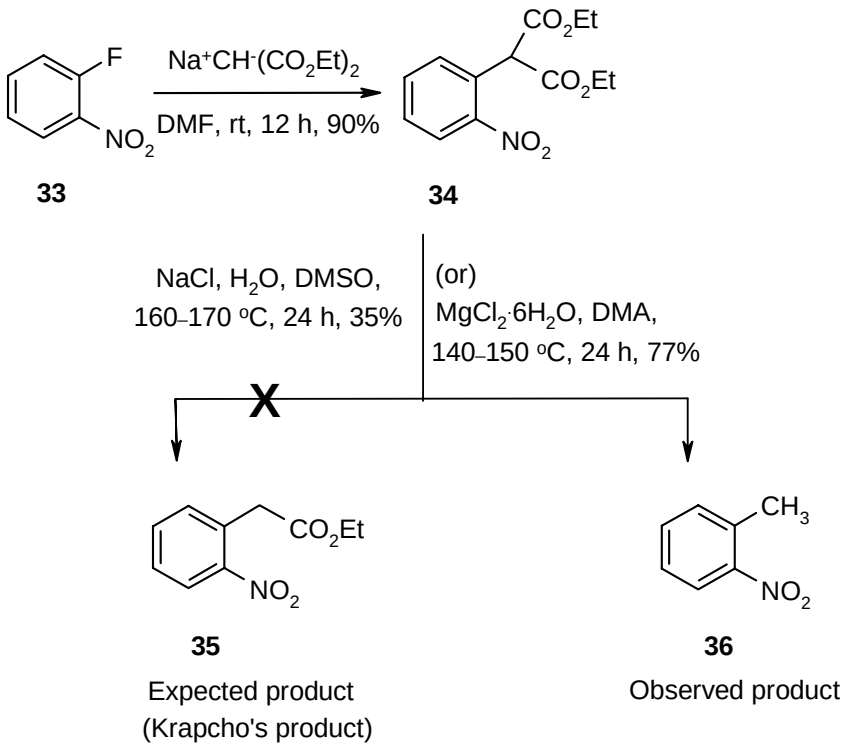
Incorporation of alkyl groups in aromatic rings is an important step in organic synthesis. The conventional Friedel–Crafts alkylation,[3] alkylation of metallated arenes, particularly in the presence of directed metallating groups (*ortho* effect),[4] transition metal catalysed nucleophilic substitution of aryl halides,[16,17] nucleophilic addition to arene-transition metal carbonyl complexes,[19] aromatic substitution via nucelophilic addition to electron deficient arenes (including *vicarious* and *ipso*)[20] and olefin insertion *via* C-H activation[21] are some of the elegant methods to realise the phenomenon. Hoz and coworkers have recently demonstrated the application of trialkylboranes in base-promoted alkylation of nitroaromatics.[18]

As part of our ongoing project to synthesize medicinally important oxindole derivatives,[22] we have taken up a synthetic strategy utilizing nitroaromatics as starting materials. The basic premise of our synthetic approach is based on S_NAr reaction of aromatic halides with a carbon nucleophile. For that endeavor, we have adopted Quallich's protocol[23] by taking appropriate starting materials. Decarboxylation of aryl substituted malonic esters under Krapcho's conditions is known to provide aryl acetic esters in good yield.[24] However, attempted Krapcho's decarboxylation of nitroaryl-substituted malonic esters resulted in the complete decarboxylation leading to the formation of nitrotoluenes in excellent yields. We have expanded this serendipitous observation to several *o/p*-substituted nitroaromatics and synthesized various alkylated nitroaromatic derivatives. This chapter describes about bis(dealkoxycarbonylation) of nitroaryl malonate esters leading to the corresponding alkylnitrobenzenes.[25]

Towards our first attempt, *o*-fluoronitrobenzene (**33**) was treated with sodium salt of diethyl malonate in anhydrous DMF at room temperature to furnish diethyl (2-nitrophenyl)malonate (**34**) in 90% yield. The ^{1}H NMR spectrum of **34** revealed the resonances at 1.30 (t, 6 H, J = 7.1 Hz), 4.26 (q, 4 H, J = 7.1 Hz) and 5.27 ppm (s, 1 H) in accordance with malonate functionality. The aromatic protons resonated as three multiplets at 7.48–7.56 (2 H), 7.61–7.71 (1 H) and 8.04–8.09 ppm (1 H). Diethyl (2-nitrophenyl)malonate (**34**) was then subjected to Krapcho's decarboxylation conditions in the presence of NaCl and water in DMSO at 160–170 ^{o}C. This transformation underwent complete decarboxylation of

malonate moiety to provide 1-methyl-2-nitrobenzene (**36**) in 35% yield, whose ^{1}H NMR spectrum indicated a singlet integrating for three protons at 2.62 ppm in support of the bis(dealkoxycarbonylation) of malonate moiety of **34**. The aromatic protons resonated as three multiplets at 7.31–7.38 (2 H), 7.45–7.54 (1 H) and 7.94–8.01 ppm (1 H). In an attempt to achieve better yields, we have employed NaCN in DMF, LiCl in DMSO[26] and $MgCl_2{\cdot}6H_2O$ in DMA, in which the dibasic salt $MgCl_2{\cdot}6H_2O$ in DMA[27] was more promising with improved yields and reduced reaction times. Accordingly, diethyl (2-nitrophenyl)malonate (**34**) was subjected to Krapcho's conditions in the presence of $MgCl_2{\cdot}6H_2O$ in DMA at 140–150 ^oC, which resulted in the formation of 1-methyl-2-nitrobenzene (**36**) in 77% yield (Scheme 13).

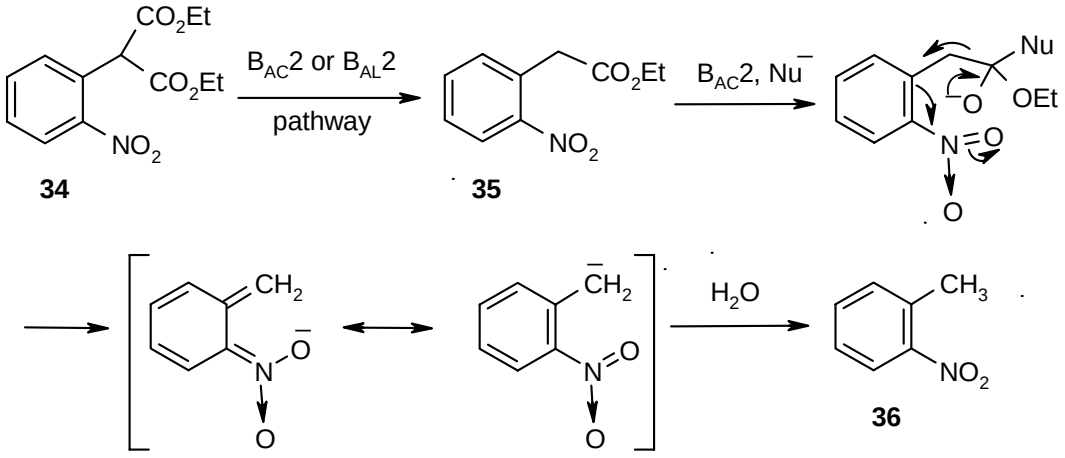
Scheme 13



This kind of bis(dealkoxycarbonylation) of aryl malonates to toluene derivatives has been observed for the first time under Krapcho's conditions in nitroaryl malonates. Simple aryl malonates (without electron-withdrawing NO_2 group) are known at first decarboxylation itself providing the respective phenylacetates. Hence, one can emphasize that the NO_2 group present because of its electron-withdrawing nature, may accelerate the second

decarboxylation by stabilizing the transition states/intermediate across the pathway. The proposed mechanism involves two stages: initial decarboxylation of malonate derivative **34** via competitive $B_{AC}2$ or $B_{AL}2$ pathway[24] to give *o*-nitrophenyl acetate (**35**) which then undergoes further decarboxylation to give *o*-nitrotoluene (**36**). Since simple aryl malonic esters (without electron-withdrawing NO_2 group) stops at first decarboxylation itself, a rationale can be suggested that the second decarboxylation in the case of nitroarylmalonic esters becomes viable because of mesomeric stabilization of benzylic anion by nitro group at *o/p* position (Scheme 14).

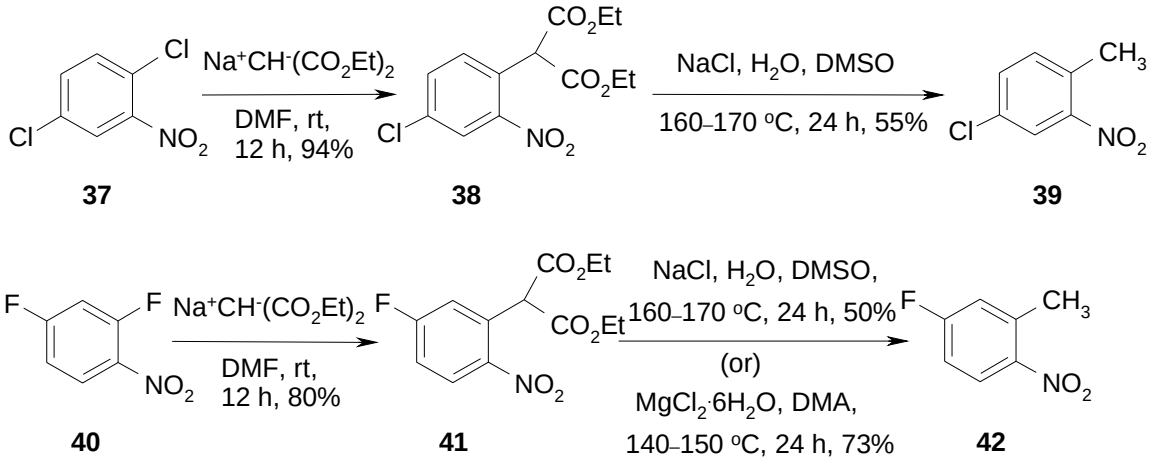
Scheme 14: Proposed mechanism



Encouraged with this, we were delighted to elaborate the scope of this transformation to synthesize various alkylated aromatics. Thus, 1,4-dichloro-2-nitrobenzene (**37**) was treated with sodium salt of diethyl malonate in anhydrous DMF at ambient temperature to afford **38** in 94% yield whose ^{1}H NMR spectrum showed a triplet at 1.30 (6 H, J = 7.1), a doublet at 4.26 (4 H, J = 7.1) and a singlet at 5.23 ppm (1 H) supporting the presence of malonate moiety. The malonate derivative **38**, under Krapcho's conditions with NaCl and H_2O in DMSO at 160–170 ^oC provided 4-chloro-1-methyl-2-nitrobenzene (**39**) in 55% yield. In the ^{1}H NMR spectrum of **39**, protons related to methyl moiety were appeared as a singlet at 2.58 ppm, and the aromatic protons had the suitable resonances. Simultaneously, 2,4-difluoro-1-nitrobenzene (**40**) was treated with sodium salt of diethyl malonate in anhydrous DMF at room temperature to furnish **41** in 80% yield whose ^{1}H NMR spectrum revealed the

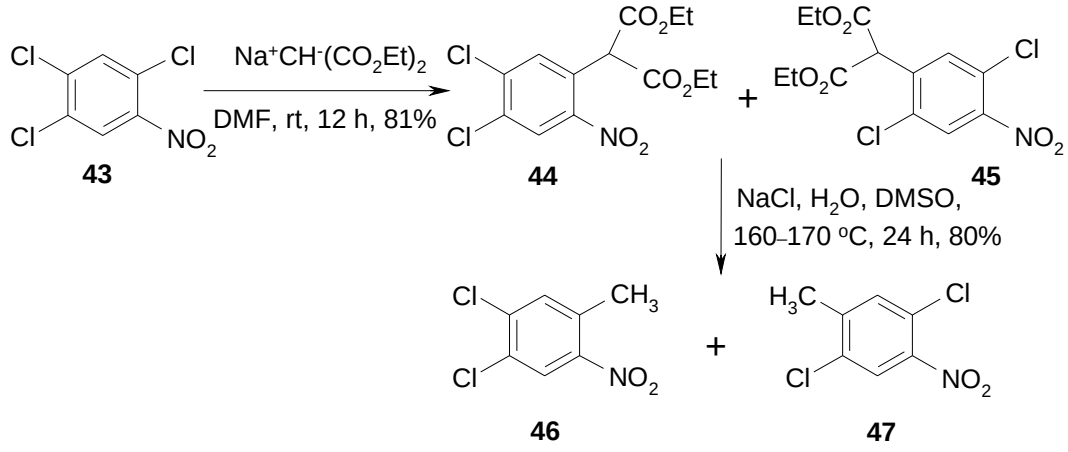
characteristic resonances of malonate moiety at 1.30 (t, 6 H, J = 7.0 Hz), 4.27 (q, 4 H, J = 7.0 Hz) and 5.27 ppm (s, 1 H). Then **41** was subjected to Krapcho's decarboxylation using NaCl and H_2O in boiling DMSO to afford 5-fluoro-1-methyl-2-nitrobenzene (**42**) in 50% yield. The ^{1}H NMR spectrum of **42** showed a characteristic singlet at 2.62 (3 H), two multiplets at 7.33–7.40 (1 H) and 7.49–7.57 (1 H), and a doublet at 7.99 (1 H, J = 6.6 Hz) in support of the assigned structure. However, **42** under modified Krapcho's conditions employing $MgCl_2 \cdot 6H_2O$ in DMA at 140–150 ^{o}C gave **42** in an improved yield of 73% (Scheme 15).

Scheme 15



Treatment of 1,2,4-trichloro-5-nitrobenzene (**43**) with sodium salt of diethyl malonate resulted in the formation of an inseparable mixture of **44** and **45** (3:1) whose ^{1}H NMR

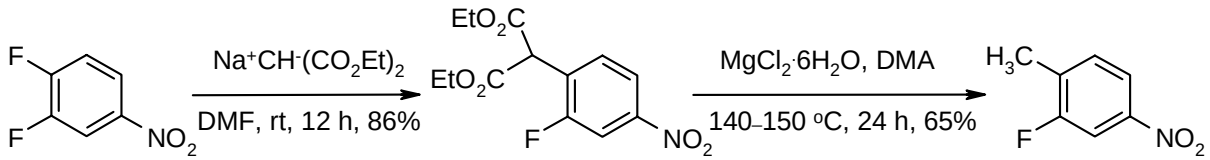
Scheme 16



spectrum indicated the resonances at 1.31 (t, 6 H, J = 7.1 Hz), 4.28 (q, 4 H, J = 7.1 Hz), 5.24 (s, 1 H), 7.65 (s, 1 H) and 8.20 ppm (s, 1 H) in support of the structure of **45**. This inseparable mixture was treated with NaCl and H_2O in boiling DMSO to afford a mixture of **46** and **47** in 80% yield. In the ^{1}H NMR spectrum of this mixture, protons corresponding to the major product appeared as three sharp singlets at 2.59 (3 H), 7.46 (1 H) and 8.13 ppm (1 H) (Scheme 16).

Having prepared the *o*-substituted nitrotoluenes in good yields, we next focused our attention towards the synthesis of *p*-substituted nitrotoluenes. Accordingly, 1,2-difluoro-4-nitrobenzene (**48**) was converted into malonate derivative **49** using sodium salt of diethyl malonate in anhydrous DMF. The ^{1}H NMR and ^{13}C NMR spectra of **49** were in full agreement with the structure. Since the bis(dealkoxycrbonylation) of malonate derivatives in the presence of $MgCl_2$·$6H_2O$ in DMA was more promising in terms of yields, we have carried out further reactions with $MgCl_2$·$6H_2O$ in DMA. Thus the compound **49** was then subjected to modified Krapcho's conditions using $MgCl_2$·$6H_2O$ in DMA to obtain 2-fluoro-1-methyl-4-nitrobenzene (**50**) whose ^{1}H NMR spectrum revealed the resonance at 2.40 ppm (s, 3 H) confirming the complete decarboxylation of malonate moiety. The aromatic protons resonated as a triplet at 7.36 (1 H, J = 7.9 Hz), and two double doublets at 7.88 (1 H, J = 2.2, 9.2 Hz) and 7.94 ppm (1 H, J = 2.2, 8.4 Hz) (Scheme 17).

Scheme 17

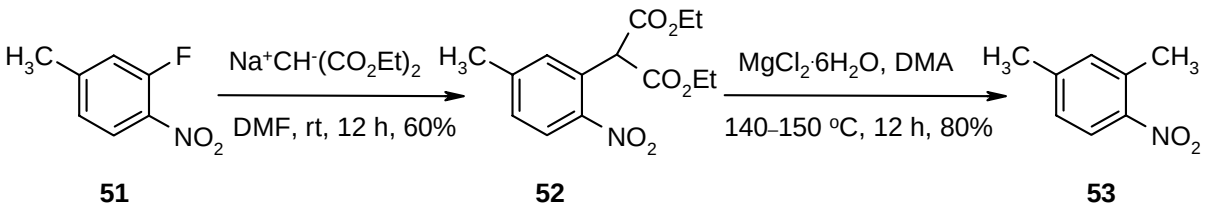


48 **49** **50**

In an attempt to elaborate this methodology for the preparation of nitroxylenes, 2-fluoro-4-methyl-1-nitrobenzene (**51**) was treated with sodium salt of diethyl malonate in anhydrous DMF at ambient temperature to furnish **52**. Subjecting **52** to modified Krapcho's conditions in the presence of $MgCl_2$·$6H_2O$ in DMA afforded 2,4-dimethyl-1-nitrobenzene (**53**) in 80% yield. The ^{1}H NMR spectrum of **53** showed two singlet resonances integrating

each for three protons at 2.32 and 2.50 ppm in support of the two methyl groups of **53** (Scheme 18).

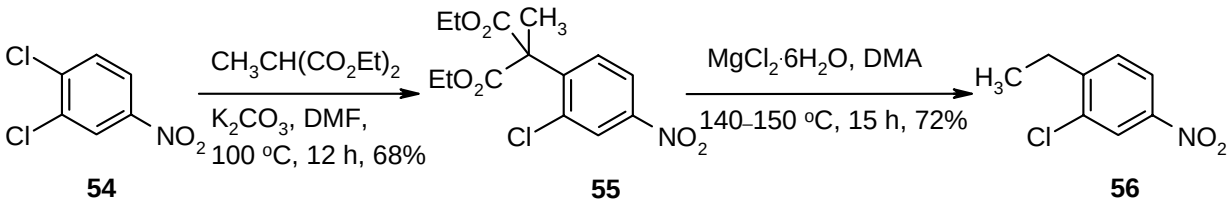
Scheme 18



51 **52** **53**

The successful transformation of nitroarylmalonates into the corresponding nitrotoluenes under Krapcho's conditions prompted us to expand this methodology for the preparation of ethyl-substituted nitrobenzenes. For that endeavor, we have chosen diethyl methylmalonate as an alkylating agent. Thus, 1,2-dichloro-4-nitrobenzene (**54**) was stirred with diethyl methylmalonate and K_2CO_3 in anhydrous DMF at 100 ^oC to furnish **55** in 68% yield. The ^1H NMR spectrum of **55** showed a triplet at 1.28 (6 H, J = 7.1 Hz), a singlet at 1.93 (3 H) and a multiplet at 4.20–4.36 ppm (4 H) in accordance of diethyl methylmalonate moiety, and the rest of the protons had suitable chemical shifts. The bis(dealkoxycarbonylation) of **55** was carried out under modified Krapcho's conditions with $MgCl_2{\cdot}6H_2O$ in DMA to give 2-chloro-1-ethyl-4-nitrobenzene (**56**) in 72% yield. In the ^1H NMR spectrum of **56** a triplet at 1.28 (3 H, J = 10.4 Hz) and a quartet at 2.86 ppm (2 H, J = 10.4 Hz) were appeared in support of the ethyl group. The ^{13}C NMR and DEPT spectra of **56** further confirmed the presence of ethyl substitution (Scheme 19).

Scheme 19

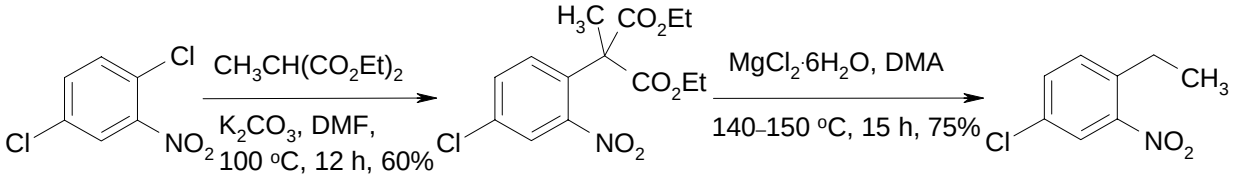


54 **55** **56**

Similarly, 1,4-dichloro-2-nitrobenzene (**37**) was treated with diethyl methylmalonate and K_2CO_3 in anhydrous DMF at 100 ^oC to afford **57** whose ^1H NMR spectrum indicated the

resonances corresponding to substituted diethyl methylmalonate moiety at 1.24 (t, 6 H, J = 7.2 Hz), at 1.98 (s, 3 H) and at 4.12–4.30 ppm (m, 4 H). Subjecting **57** to bis(dealkoxycarbonylation) in the presence of $MgCl_2 \cdot 6H_2O$ in DMA (modified Krapcho's condition) afforded 4-chloro-1-ethyl-2-nitro-benzene (**58**) in 75% yield. The ^{1}H NMR spectrum of **58** revealed a triplet at 2.88 (3 H, J = 8.5 Hz) and a quartet at 2.88 ppm (2 H, J = 8.5 Hz) in support of the ethyl moiety. It was further supported by the ^{13}C NMR, DEPT, IR and mass spectral studies (Scheme 20).

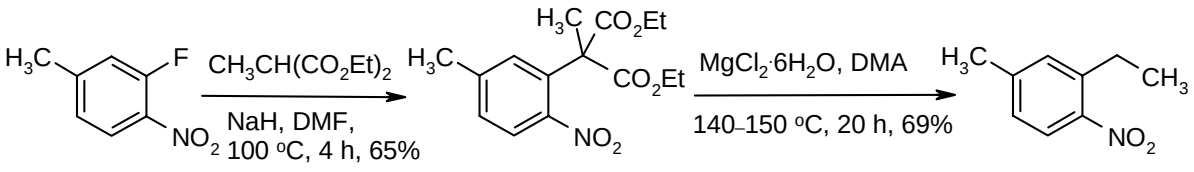
Scheme 20



37 **57** **58**

Treatment of 2-fluoro-4-methyl-1-nitrobenzene (**51**) with diethyl methylmalonate and an oily dispersion of NaH in anhydrous DMF at 100 °C furnished **59** in good yield, whose ^{1}H NMR spectrum showed a triplet at 1.24 (6 H, J = 7.1 Hz), and two singlets at 1.98 and 2.43 (3 H each), and a multiplet at 4.09–4.34 ppm (4 H) in accordance to diethyl methylmalonate group. The bis(dealkoxycarbonylation) of **59** in the presence of $MgCl_2 \cdot 6H_2O$ in DMA (modified Krapcho's condition) resulted in the formation of 1-ethyl-5-methyl-2-nitrobenzene (**60**) in 69% yield. The ^{1}H NMR spectrum of **60** indicated the resonances at 1.28 (t, 3 H, J = 8.3 Hz), 2.41 (s, 3 H), and at 2.91 (q, 2 H, J = 8.3 Hz) in support of its structure (Scheme 21).

Scheme 21

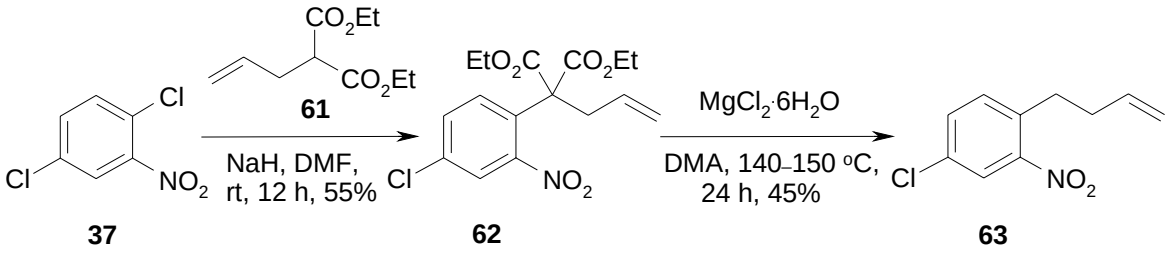


51 **59** **60**

After successful preparation of the ethylnitrobenzenes in good yield, we focused our attention towards allyl-substituted nitrobenzenes. For that endeavor we preferred diethyl

allylmalonate for alkylation reaction. Thus, sodium salt of diethyl malonate was treated with allyl bromide in anhydrous DMF to obtain diethyl allylmalonate (**61**).[28] The reaction of 1,4-dichloro-2-nitrobenzene (**37**) with diethyl allylmalonate and NaH in anhydrous DMF at room temperature provided **62** in 55% yield. The ^{1}H NMR spectrum of **62** showed the corresponding resonances of allylic moiety at 3.25 (d, 2 H, J = 6.5 Hz), 4.97–5.25 (m, 2 H) and 5.64–5.86 ppm (m, 1 H). Subjecting **62** to bis(dealkoxycarbonylation) in the presence of $MgCl_2 \cdot 6H_2O$ in DMA (modified Krapcho's condition) furnished 2-(but-3-enyl)-5-chloronitrobenzene (**63**) in 45% yield.[25] In the ^{1}H NMR spectrum of **63** a quartet at 2.38 (2 H, J = 8.2 Hz), a triplet at 2.96 (2 H, J = 8.2 Hz), and two multiplets at 5.05 (2 H) and at 5.79 ppm (1 H) were appeared in accordance to allylic moiety. It was further supported by ^{13}C NMR, DEPT and IR spectral studies together with elemental analysis (Scheme 22).

Scheme 22



37 **62** **63**

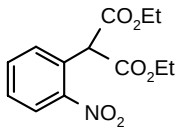
Conclusion

In conclusion, we have developed a mild and efficient procedure for alkylated aromatics which otherwise are difficult to prepare, starting from halonitrobenzenes. Needless to mention that the nitro group present in these products can be a surrogate for introducing a variety of functionalities in the aromatic ring. Further efforts in utilizing this methodology in total synthesis of nitrogen containing heterocycles are underway.

Experimental Section

Experimental

Diethyl (2-nitrophenyl)malonate (34)

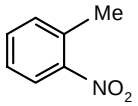


To a solution of 1-fluoro-2-nitrobenzene (**33**) (2.0 g, 14.17 mmol) in anhydrous DMF (25 mL) was added sodium salt of diethyl malonate (5.0 g, 27.45 mmol) and stirred for 12 h at room temperature. The reaction mixture was acidified with 10 % dilute HCl, diluted with water and extracted with ether (2 x 25 mL). The combined ether fractions were washed with brine, dried (Na_2SO_4) and concentrated. The crude product was chromatographed on silica gel with EtOAc–light petroleum (1:8) as an eluent to give **34** (3.6 g, 90%) as syrup.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, 6 H, J = 7.1 Hz), 4.26 (q, 4 H, J = 7.1 Hz), 5.27 (s, 1 H), 7.48–7.56 (m, 2 H), 7.61–7.71 (m, 1 H), 8.04–8.09 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.3, 54.2, 61.6, 124.6, 127.7, 128.8, 130.8, 133.1, 148.2, 166.6.

1-Methyl-2-nitrobenzene (36)



A mixture of compound **34** (1.0 g, 3.55 mmol), NaCl (0.83 g, 14.20 mmol) and H_2O (0.2 mL, 11.11 mmol) in DMSO (10 mL) was heated at 160–170 °C for 24 h. After being allowed to attain room temperature, the mixture was partitioned between ether (30 mL) and H_2O (30 mL), the ether layer was dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using EtOAc–light petroleum (1:9) to afford the pure **36** (0.17 g, 35%) as syrup.

(**or**)

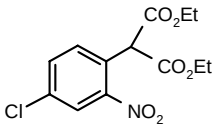
A mixture of compound **34** (1.0 g, 3.55 mmol) and $MgCl_2 \cdot 6H_2O$ (1.5 g, 7.39 mmol) in DMA (15 mL) was heated at 140–150 °C for 24 h. After being allowed to attain room

temperature, the reaction mixture was diluted with water, extracted with ether, washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel using EtOAc–light petroleum (1:9) to furnish **36** (0.37 g, 77%) as syrup.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.62 (s, 3 H), 7.31–7.38 (m, 2 H), 7.45–7.54 (m, 1 H), 7.94–8.01 (m, 1 H).

Anal. Calcd for $C_7H_7NO_2$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.35; H, 5.26; N, 10.32.

Diethyl (4-chloro-2-nitrophenyl)malonate (38)

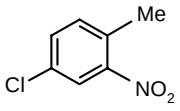


The reaction was carried out as described earlier using 1,4-dichloro-2-nitrobenzene (**37**) (2.0 g, 10.42 mmol) and sodium salt of diethyl malonate (3.8 g, 20.86 mmol) in anhydrous DMF (25 mL) at room temperature for 12 h. After usual work-up and purification by silica gel column chromatography with EtOAc–light petroleum (1:8) as eluent afforded **38** (3.1 g, 94%) as syrup.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, 6 H, J = 7.1 Hz), 4.26 (q, 4 H, J = 7.1 Hz), 5.23 (s, 1 H), 7.49 (d, 1 H, J = 8.4 Hz), 7.62 (dd, 1 H, J = 2.1, 8.4 Hz), 8.05 (d, 1 H, J = 2.1 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.5, 53.7, 61.9, 124.8, 126.4, 132.4, 133.1, 134.5, 148.7, 166.4.

4-Chloro-1-methyl-2-nitrobenzene (39)

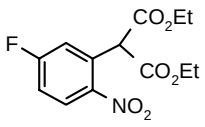


The reaction was carried out as described earlier using the compound **38** (1.5 g, 4.74 mmol), NaCl (1.1 g, 18.82 mmol) and H_2O (0.2 mL, 11.11 mmol) in DMSO (20 mL) at 160–170 °C for 24 h. After usual work-up, the residue was chromatographed on silica gel using EtOAc–light petroleum (1:9) as eluent to afford the pure **39** (0.45 g, 55%) as syrup.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.58 (s, 3 H), 7.29 (d, 1 H, J = 8.2 Hz), 7.47 (dd, 1 H, J = 2.1, 8.2 Hz), 7.97 (d, 1 H, J = 2.1 Hz).

Anal. Calcd for $C_7H_6ClNO_2$: C, 49.00; H, 3.52; N, 8.16. Found: C, 48.95; H, 3.67; N, 8.20.

Diethyl (5-flouro-2-nitrophenyl)malonate (41)

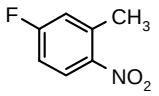


The reaction was carried out as described earlier using 2,4-difluoro-1-nitrobenzene (**40**) (2.0 g, 12.57 mmol) and sodium salt of diethyl malonate (4.6 g, 25.25 mmol) in anhydrous DMF (25 mL) at room temperature for 12 h. After usual work-up and purification by silica gel column chromatography with EtOAc–light petroleum (1:8) as eluent afforded **41** (3.0 g, 80%) as syrup.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (t, 6 H, J = 7.0 Hz), 4.27 (q, 4 H, J = 7.0 Hz), 5.27 (s, 1 H), 7.49–7.55 (m, 1 H), 7.62–7.68 (m, 1 H), 8.05–8.08 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.6, 54.3, 61.9, 124.9, 127.9, 129.0, 131.0, 133.3, 148.4, 166.9.

5-Flouro-1-methyl-2-nitrobenzene (42)



The reaction was carried out as described earlier using the compound **41** (1.0 g, 3.34 mmol), NaCl (0.78 g, 13.35 mmol), and H_2O (0.2 mL, 11.11 mmol) in DMSO (10 mL) at 160–170 °C for 48 h to afford **42** (0.26 g, 50%) as syrup.

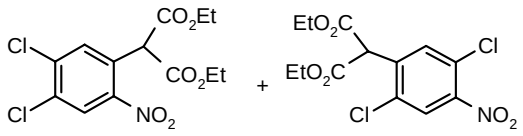
(**or**)

The reaction was carried out as described earlier using the compound **41** (1.0 g, 3.34 mmol) and $MgCl_2{\cdot}6H_2O$ (1.36 g, 6.70 mmol) in DMA (15 mL) at 140–150 °C for 20 h. After usual work-up and purification by silica gel column chromatography with EtOAc–light petroleum (1:9) afforded **42** (0.38 g, 73%) as syrup.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.62 (s, 3 H), 7.33–7.40 (m, 1 H), 7.49–7.57 (m, 1 H), 7.99 (d, 1 H, J = 6.6 Hz).

Anal. Calcd for $C_7H_6FNO_2$: C, 54.20; H, 3.90; N, 9.03. Found: C, 54.16; H, 3.98; N, 9.12.

Diethyl (4,5-dichloro-2-nitrophenyl)malonate (44) and Diethyl (2,5-dichloro-4-nitrophenyl)malonate (45)



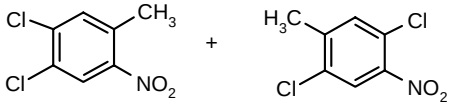
44 **45**

The reaction was carried out as described earlier using 1,2,4-trichloro-5-nitrobenzene (**43**) (2.0 g, 8.83 mmol) and sodium salt of diethyl malonate (2.0 g, 10.98 mmol) in anhydrous DMF (25 mL) at room temperature for 12 h. After usual work-up and purification by silica gel column chromatography with EtOAc–light petroleum (1:8) as eluent afforded inseparable mixture of **44** and **45** (2.5 g, 81%) as syrup in 3:1 ratio.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (t, 6 H, J = 7.1 Hz), 4.28 (q, 4 H, J = 7.1 Hz), 5.24 (s, 1 H), 7.65 (s, 1 H), 8.20 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.3, 53.3, 62.0, 126.4, 127.7, 132.7, 137.5, 146.7, 165.8.

1,2-Dichloro-4-methyl-5-nitrobenzene (46) and 1,4-Dichloro-2-methyl-5-nitrobenzene (47)



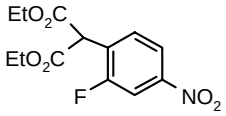
46 **47**

The reaction was carried out as described earlier using the mixture of **44** and **45** (1.5 g, 4.28 mmol), NaCl (1.0 g, 17.11 mmol) and H_2O (0.2 mL, 11.11 mmol) in DMSO (10 mL) at 160–170 °C for 12 h to afford inseparable mixture of **46** and **47** (0.7 g, 80%) as syrup, in 3:1 ratio.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.59 (s, 3 H), 7.46 (s, 1 H), 8.13 (s, 1 H).

Anal. Calcd for $C_7H_5Cl_2NO_2$: C, 40.81; H, 2.45; N, 6.80. Found: C, 41.09; H, 2.48; N, 6.72.

Diethyl (2-flouro-4-nitrophenyl)malonate (49)

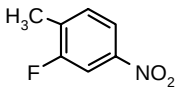


The reaction was carried out as described earlier using 1,2-difluoro-4-nitrobenzene (**48**) (2.4 g, 15.08 mmol) and sodium salt of diethyl malonate (3.3 g, 18.12 mmol) in anhydrous DMF (30 mL) at room temperature for 12 h to obtain **49** (4.17 g, 86%) as syrup.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, 6 H, *J* = 7.1 Hz), 4.26 (dq, 4 H, *J* = 2.3, 7.1 Hz), 5.02 (s, 1 H), 7.74 (dd, 1 H, *J* = 7.1, 8.5 Hz), 7.98 (dd, 1 H, *J* = 2.2, 9.3 Hz), 8.07 (dd, 1 H, *J* = 2.2, 8.5 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.3, 50.1, 62.0, 110.3, 110.8, 118.8, 127.5, 131.4, 148.1, 165.9.

2-Flouro-1-methyl-4-nitrobenzene (50)

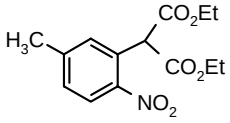


The reaction was carried out as described earlier using the compound **49** (1.5 g, 4.67 mmol) and $MgCl_2 \cdot 6H_2O$ (1.9 g, 9.36 mmol) in DMA (20 mL) at 140–150 °C for 24 h. After usual work-up and purification by silica gel column chromatography with EtOAc–light petroleum (1:9) furnished **50** (0.72 g, 65%) as syrup.

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.40 (s, 3 H), 7.36 (t, 1 H, *J* = 7.9 Hz), 7.88 (dd, 1 H, *J* = 2.2, 9.2 Hz), 7.94 (dd, 1 H, *J* = 2.2, 8.4 Hz).

Anal. Calcd for $C_7H_6FNO_2$: C, 54.20; H, 3.90; N, 9.03. Found: C, 54.26; H, 3.94; N, 9.22.

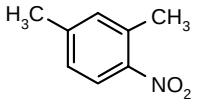
Diethyl (5-methyl-2-nitrophenyl)malonate (52)



The reaction was carried out as described earlier using 2-fluoro-4-methyl-1-nitrobenzene (**51**) (2.0 g, 12.89 mmol) and sodium salt of diethyl malonate (2.8 g, 15.37 mmol) in anhydrous DMF (25 mL) at room temperature for 12 h to yield **52** (2.28 g, 60%) as syrup.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.20–1.39 (m, 6 H), 2.47 (s, 3 H), 4.19–4.33 (m, 4 H), 5.31 (s, 1 H), 7.24–7.34 (m, 2 H), 8.00 (dd, 1 H, J = 1.3, 4.7 Hz).

2,4-Dimethyl-1-nitrobenzene (53)



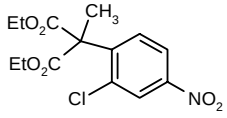
The reaction was carried out as described earlier using the compound **52** (1.0 g, 3.39 mmol) and $MgCl_2 \cdot 6H_2O$ (1.38 g, 6.80 mmol) in DMA (15 mL) at 140–150 °C for 12 h. After usual work-up and purification by silica gel column chromatography with EtOAc–light petroleum (1:9) furnished **53** (0.41 g, 80%) as syrup.

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 3 H), 2.50 (s, 3 H), 7.01–7.05 (m, 2 H), 7.81 (d, 1 H, J = 8.8 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 20.7, 21.3, 124.9, 127.4, 133.3, 133.7, 143.9.

Anal. Calcd for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.49; H, 6.14; N, 9.18.

Diethyl (2-chloro-4-nitrophenyl)methylmalonate (55)

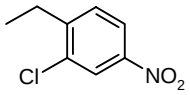


A mixture of 1,2-dichloro-4-nitrobenzene (**54**) (2.0 g, 10.42 mmol), diethyl methylmalonate (3.5 mL, 20.53 mmol) and K_2CO_3 (4.3 g, 31.11 mmol) in anhydrous DMF (20 mL) was heated at 100 ^oC for 12 h. The reaction mixture was acidified with 10% dilute HCl, diluted with water, extracted twice with ether (2 x 25 mL), the combined ether fractions were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel using EtOAc–light petroleum (1:8) to give **55** (2.34 g, 68%) as syrup.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.28 (t, 6 H, *J* = 7.1 Hz), 1.93 (s, 3 H), 4.20–4.36 (m, 4 H), 7.41 (d, 1 H, *J* = 8.8 Hz), 8.10 (dd, 1 H, *J* = 2.2, 8.8 Hz), 8.26 (d, 1 H, *J* = 2.4 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.4, 21.2, 59.5, 62.1, 121.5, 125.5, 129.0, 134.7, 144.3, 147.0, 169.1.

2-Chloro-1-ethyl-4-nitrobenzene (56)



The reaction was carried out as described earlier using the compound **55** (1.0 g, 3.03 mmol) and $MgCl_2 \cdot 6H_2O$ (1.2 g, 5.91 mmol) in DMA (15 mL) at 140–150 °C for 15 h to afford **56** (0.4 g, 72%) as syrup.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.28 (t, 3 H, *J* = 10.4 Hz), 2.86 (q, 2 H, *J* = 10.4 Hz), 7.41 (d, 1 H, *J* = 10.3 Hz), 8.05 (dd, 1 H, *J* = 3.4, 10.3 Hz), 8.20 (s, 1 H).

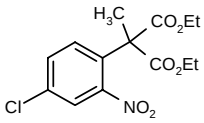
^{13}C NMR (75 MHz, $CDCl_3$): δ 13.3, 26.9, 121.7, 124.3, 129.7, 134.5, 146.4, 149.0.

IR ($CHCl_3$): ν = 890, 1124, 1348, 1520, 2974 cm^{-1}.

EI-MS (*m/z*): 185 (M^+).

Anal. Calcd for $C_8H_8ClNO_2$: C, 51.77; H, 4.34; N, 7.55. Found: C, 52.10; H, 4.37; N, 7.80.

Diethyl (4-chloro-2-nitrophenyl)methylmalonate (57)

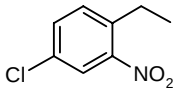


The reaction was carried out as described earlier using 1,4-dichloro-2-nitrobenzene (**37**) (2.0 g, 10.42 mmol), diethyl methylmalonate (3.5 mL, 20.53 mmol) and K_2CO_3 (4.3 g, 31.11 mmol) in anhydrous DMF (20 mL) at 100 ^oC for 10 h. After usual work-up and purification by silica gel column chromatography with EtOAc–light petroleum (1:8) as eluent furnished **57** (2.06 g, 60%) as syrup.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.24 (t, 6 H, *J* = 7.1 Hz), 1.98 (s, 3 H), 4.12–4.30 (m, 4 H), 7.28 (d, 1 H, *J* = 8.5 Hz), 7.56 (dd, 1 H, *J* = 8.5, 2.3 Hz), 8.01 (d, 1 H, *J* = 2.3 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): ***δ*** 13.6, 23.3, 58.8, 62.2, 125.7, 130.4, 132.8, 132.9, 134.1, 149.0, 169.1.

4-Chloro-1-ethyl-2-nitrobenzene (58)



The reaction was carried out as described earlier using the compound **57** (1.0 g, 3.03 mmol) and $MgCl_2 \cdot 6H_2O$ (1.2 g, 5.91 mmol) in DMA (15 mL) at 140–150 °C for 15 h to afford **58** (0.42 g, 75%) as syrup.

^{1}H NMR (200 MHz, $CDCl_3$): ***δ*** 1.28 (t, 3 H, *J* = 8.5 Hz), 2.88 (q, 2 H, *J* = 8.5 Hz), 7.32 (d, 1 H, *J* = 10.1 Hz), 7.48 (dd, 1 H, *J* =2.3, 10.5 Hz), 7.85 (s, 1 H).

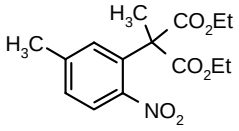
^{13}C NMR (75 MHz, $CDCl_3$): ***δ*** 14.8, 25.8, 124.6, 132.3, 132.9, 138.0.

IR ($CHCl_3$): ν = 760, 764, 1120, 1354, 1530 cm^{-1}.

EI-MS (*m/z*): 185 (M^+).

Anal. Calcd for $C_8H_8ClNO_2$: C, 51.77; H, 4.34; N, 7.55. Found: C, 51.85; H, 4.43; N, 7.76.

Diethyl (5-methyl-2-nitrophenyl)methylmalonate (59)

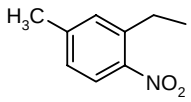


A 60% oily dispersion of NaH (1.3 g, 32.50 mmol) was suspended in anhydrous DMF (15 mL) and added diethyl methylmalonate (4.4 mL, 25.81 mmol) at 0 °C. After being stirred for 1 h at 100 °C, the reaction mixture was allowed to attain room temperature, and a solution of 2-fluoro-4-methyl-1-nitrobenzene (**51**) (2.0 g, 12.89 mmol) in anhydrous DMF (4 mL) was added and then stirred at 100 °C for 4 h. The reaction mixture was quenched with 10% dilute HCl, diluted with water, and extracted twice with ether (2 x 25 mL). The combined ether layers were washed with brine, dried (Na_2SO_4), concentrated and the resulted residue was chromatographed on silica gel using EtOAc–light petroleum (1:8) as eluent to furnish **59** (2.59 g, 65%) as syrup.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.24 (t, 6 H, J = 7.1 Hz), 1.98 (s, 3 H), 2.43 (s, 3 H), 4.09–4.34 (m, 4 H), 7.07 (d, 1 H, J = 1.1 Hz), 7.25 (dd, 1 H, J = 1.1, 8.2 Hz), 7.95 (d, 1 H, J = 8.2 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.6, 21.3, 23.2, 59.3, 61.9, 125.9, 128.8, 129.6, 134.3, 144.3, 146.2, 169.5.

1-Ethyl-5-methyl-2-nitrobenzene (60)



The reaction was carried out as described earlier using the compound **59** (1.0 g, 3.23 mmol) and $MgCl_2{\cdot}6H_2O$ (1.3 g, 6.40 mmol) in DMA (15 mL) at 140–150 °C for 20 h to obtain **60** (0.37 g, 69%) as syrup.

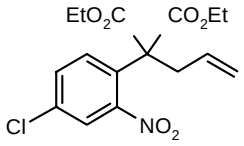
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.28 (t, 3 H, J = 8.3 Hz), 2.41 (s, 3 H), 2.91 (q, 2 H, J = 8.3 Hz), 7.15 (m, 2 H), 7.82 (d, 1 H, J =8.3 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 14.9, 21.3, 26.3, 124.9, 127.3, 131.1, 139.1, 143.3.

IR ($CHCl_3$): ν = 836, 1344, 1520, 1588, 2928 cm^{-1}.

Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.20; H, 6.92; N, 8.40.

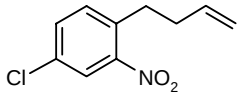
Diethyl (4-chloro-2-nitrophenyl)allylmalonate (62)



The reaction was carried out as described earlier using 1,4-dichloro-2-nitrobenzene (**37**) (2.6 g, 13.54 mmol), diethyl allylmalonate (**61**) (5.4 g, 26.97 mmol) and 60% oily dispersion of NaH (1.35 g, 33.75 mmol) in anhydrous DMF (25 mL) at room temperature for 12 h. After usual work-up and purification by silica gel column chromatography with EtOAc–light petroleum (1:8) gave **62** (2.65 g, 55%) as syrup.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.18–1.43 (m, 6 H), 3.25 (d, 2 H, *J* = 6.5 Hz), 4.14–4.38 (m, 4 H), 4.97–5.25 (m, 2 H), 5.64–5.86 (m, 1 H), 7.26–7.34 (m, 1 H), 7.52–7.59 (m, 1 H), 8.01 (d, 1 H, *J* = 1.3 Hz).

1-(But-3-enyl)-4-chloro-2-nitrobenzene (63)



The reaction was carried out as described earlier using the compound **62** (1.7 g, 4.78 mmol) and $MgCl_2 \cdot 6H_2O$ (2.0 g, 9.85 mmol) in DMA (20 mL) at 140–150 °C for 24 h to afford **63** (0.45 g, 45%) as syrup.

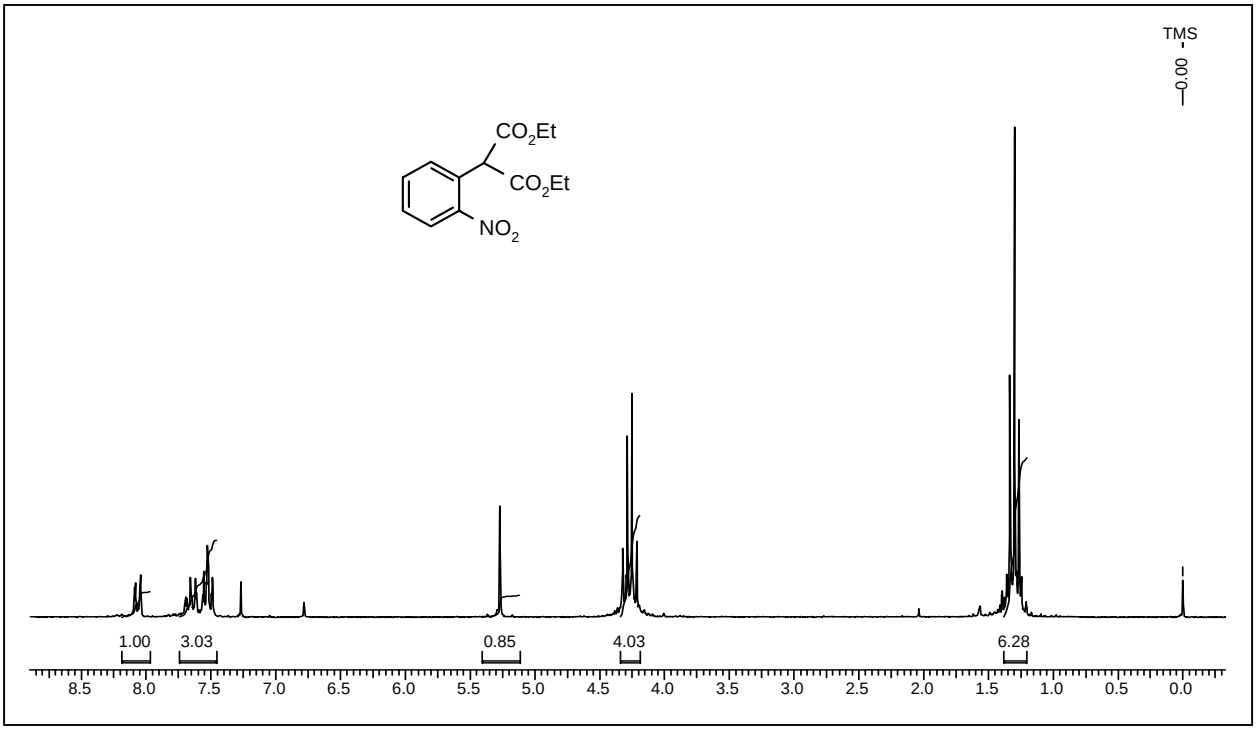
^{1}H NMR (200 MHz, $CDCl_3$): δ 2.38 (q, 2 H, *J* = 8.2 Hz), 2.96 (t, 2 H, *J* = 8.2 Hz), 5.05 (m, 2 H), 5.79 (m, 1 H), 7.29 (d, 1 H, *J* = 9.6 Hz), 7.45 (d, 1 H, *J* = 9.6 Hz), 7.90 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 31.9, 34.3 116.1, 124.6, 132.7, 133.0, 135.1, 136.5, 149.6.

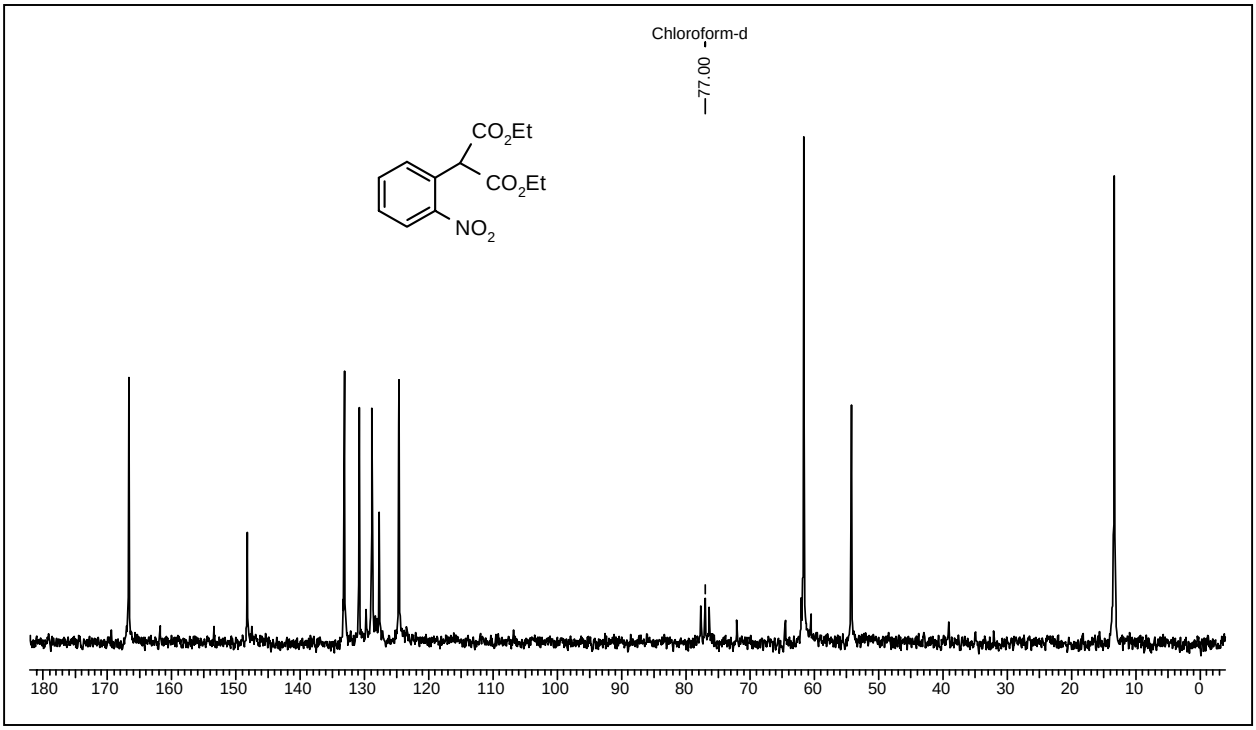
IR ($CHCl_3$): ν = 1278, 1350, 1530, 3080 cm^{-1}.

Anal. Calcd for $C_{10}H_{10}ClNO_2$: C, 56.75; H, 4.76; N, 6.62. Found: C, 56.62; H, 4.47; N, 6.82.

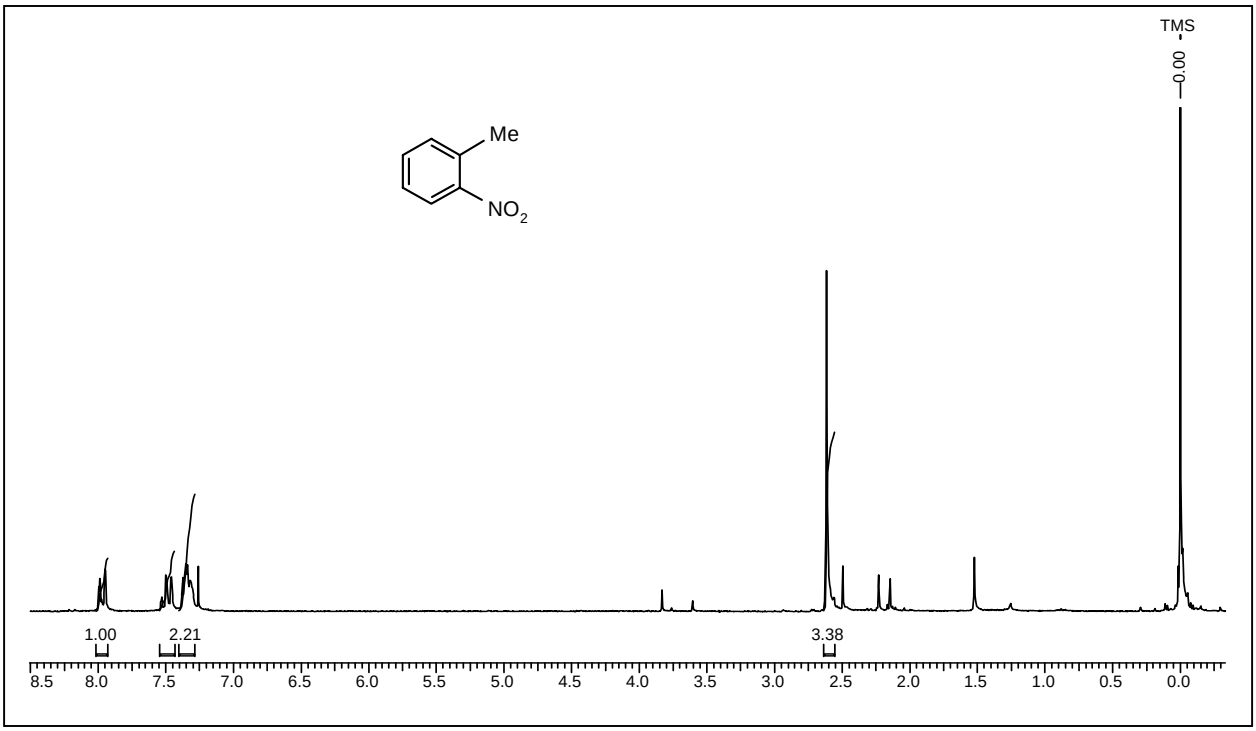
Spectra



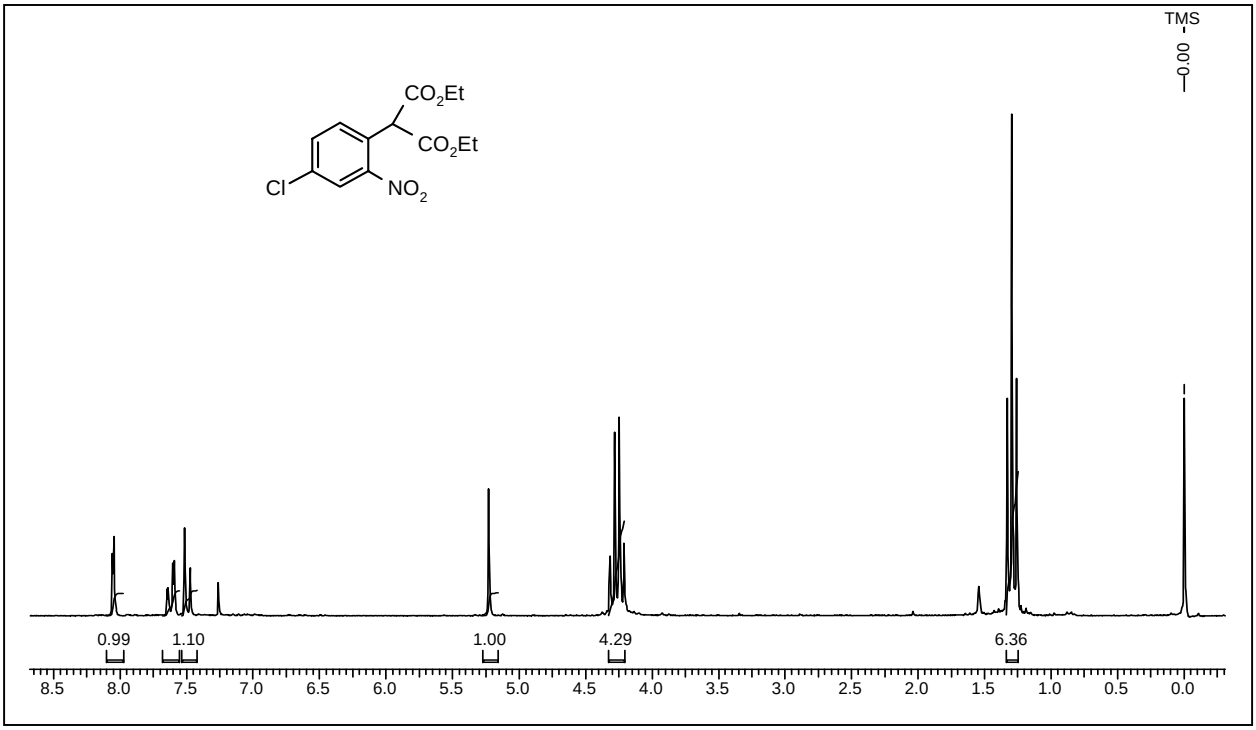
^{1}H NMR Spectrum of compound 34 in $CDCl_3$



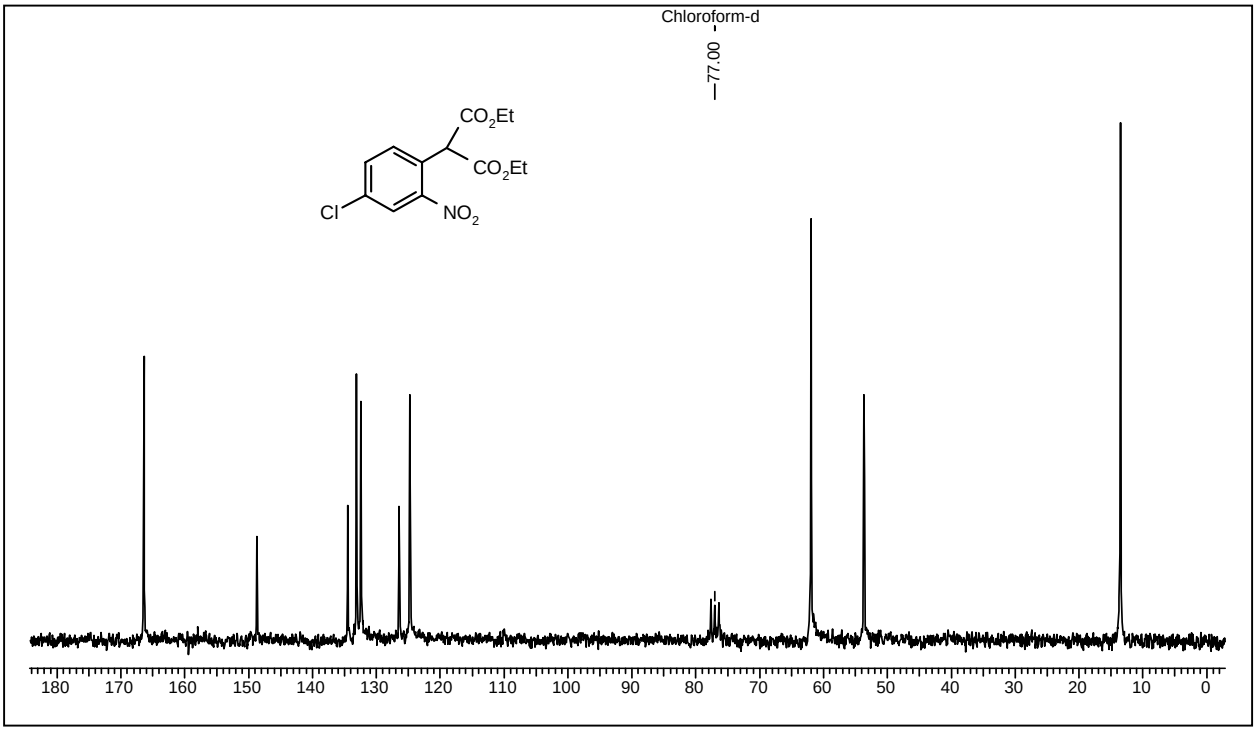
^{13}C NMR Spectrum of compound 34 in $CDCl_3$



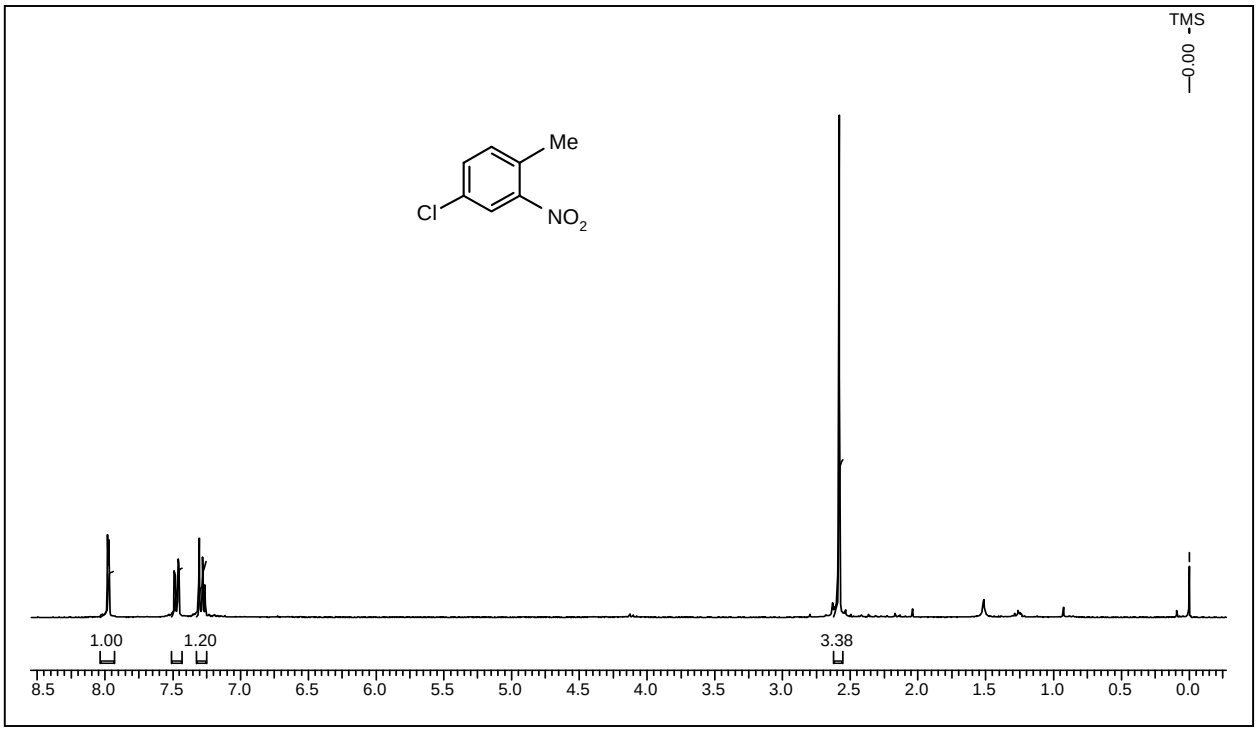
^{1}H NMR Spectrum of compound 36 in $CDCl_3$



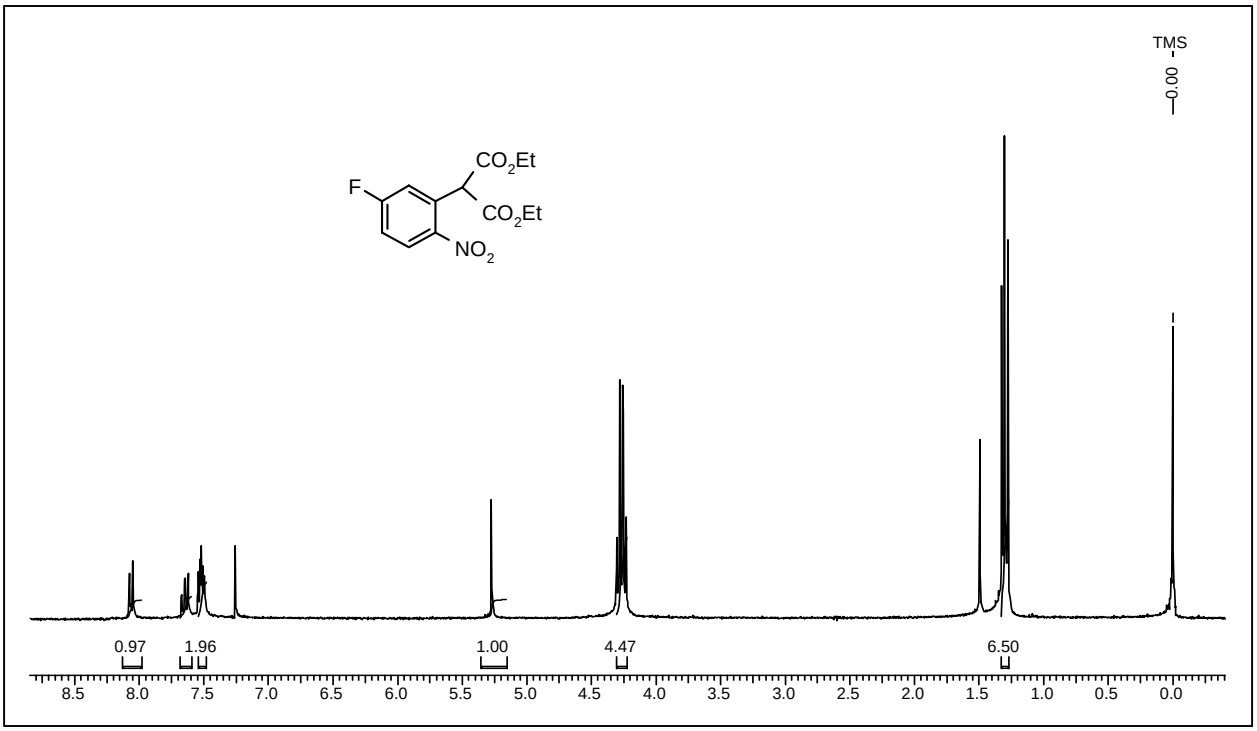
^{1}H NMR Spectrum of compound 38 in $CDCl_3$



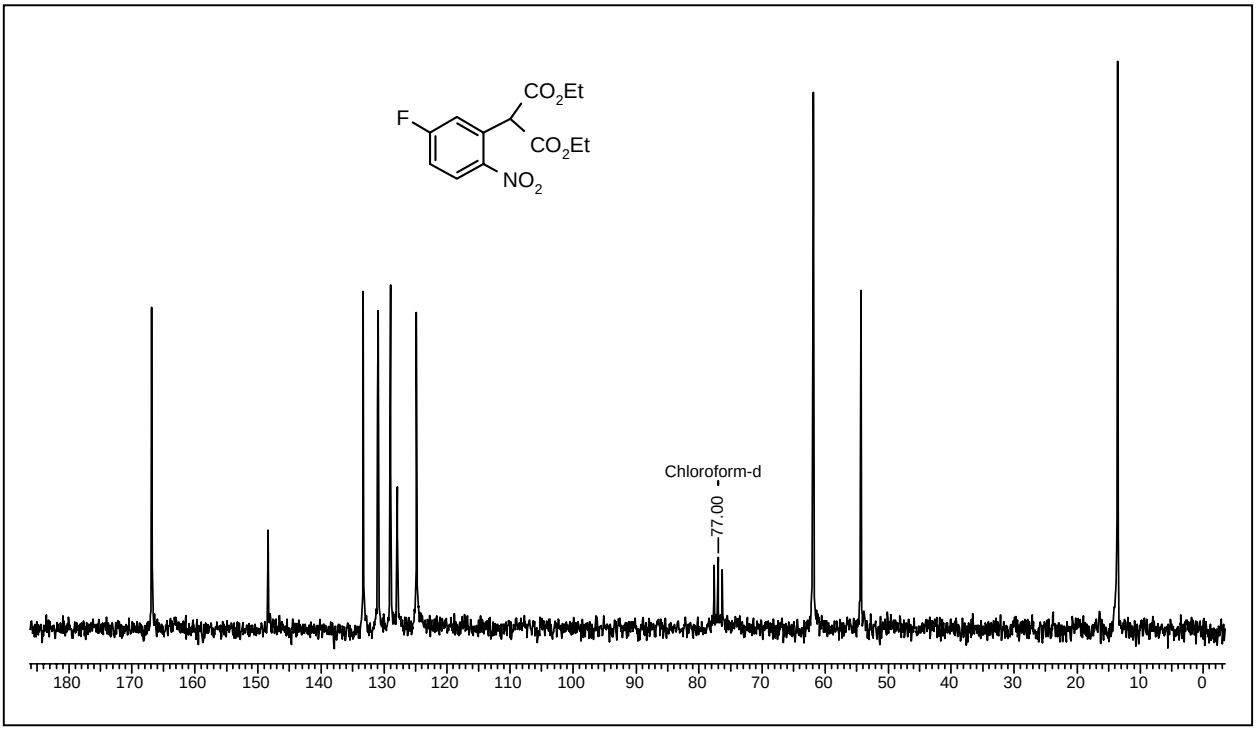
^{13}C NMR Spectrum of compound 38 in $CDCl_3$



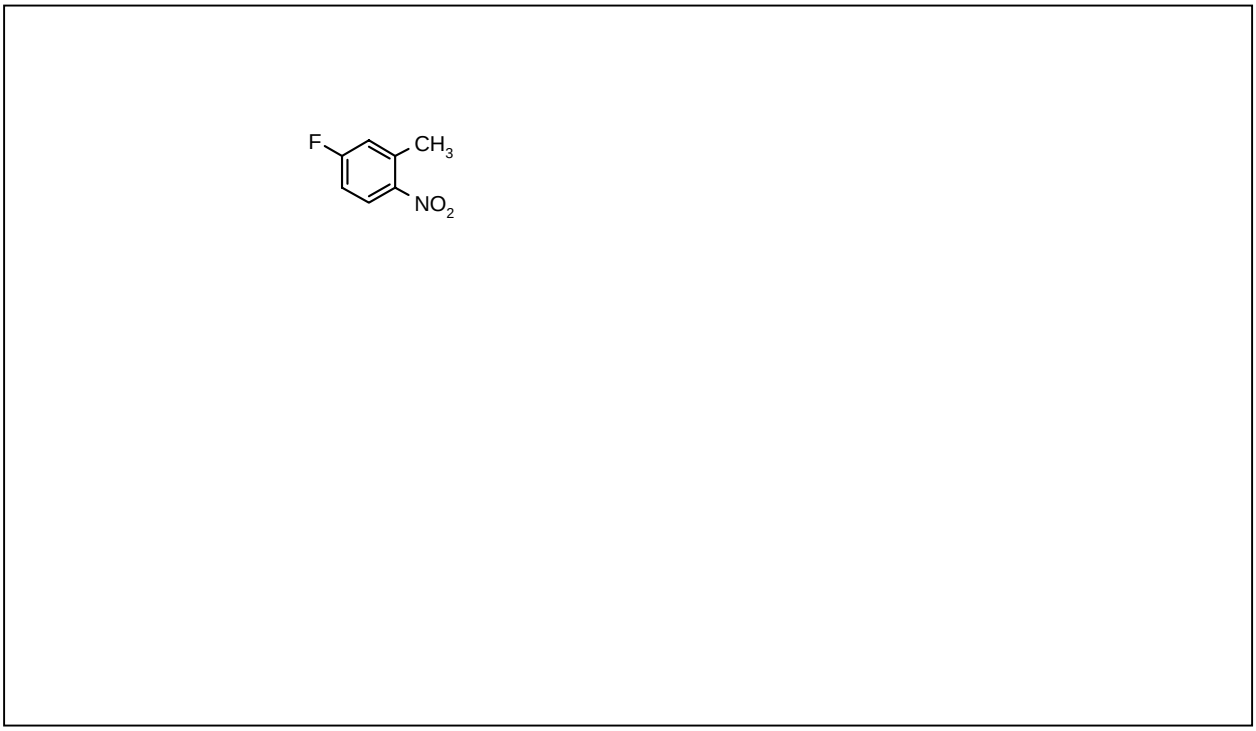
^{1}H NMR Spectrum of compound 39 in $CDCl_3$



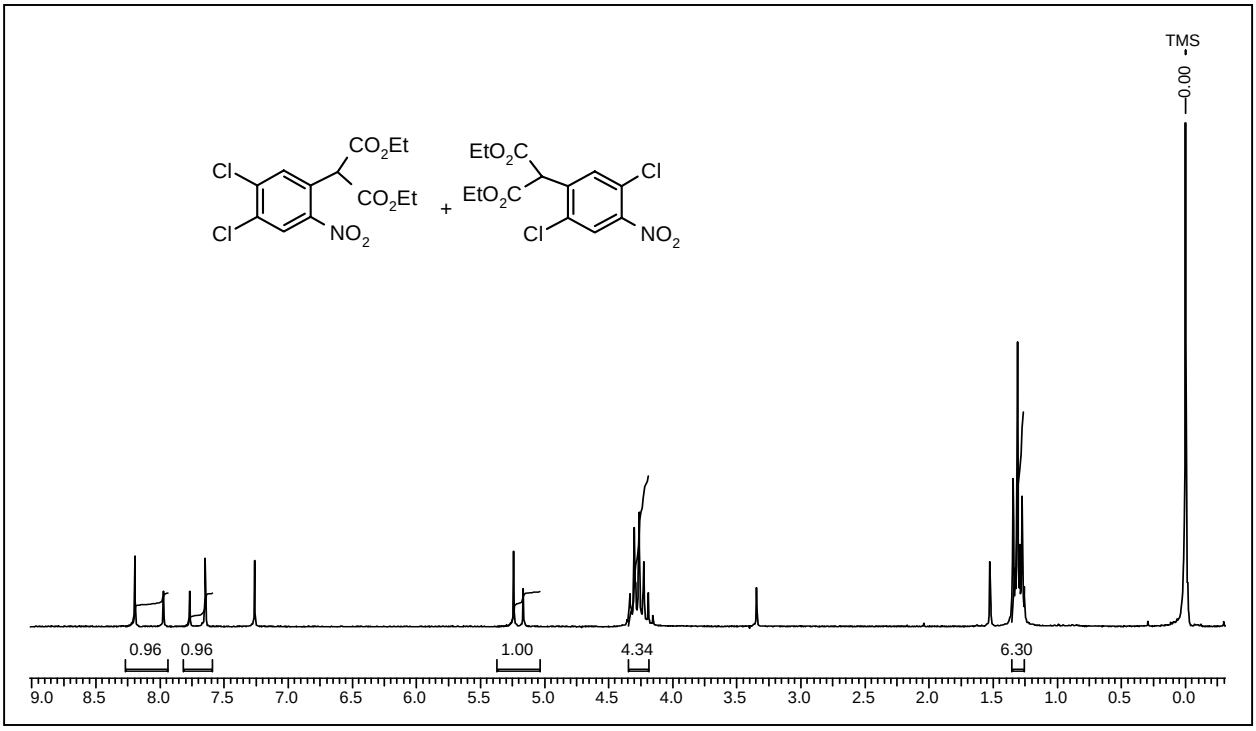
^{1}H NMR Spectrum of compound 41 in $CDCl_3$



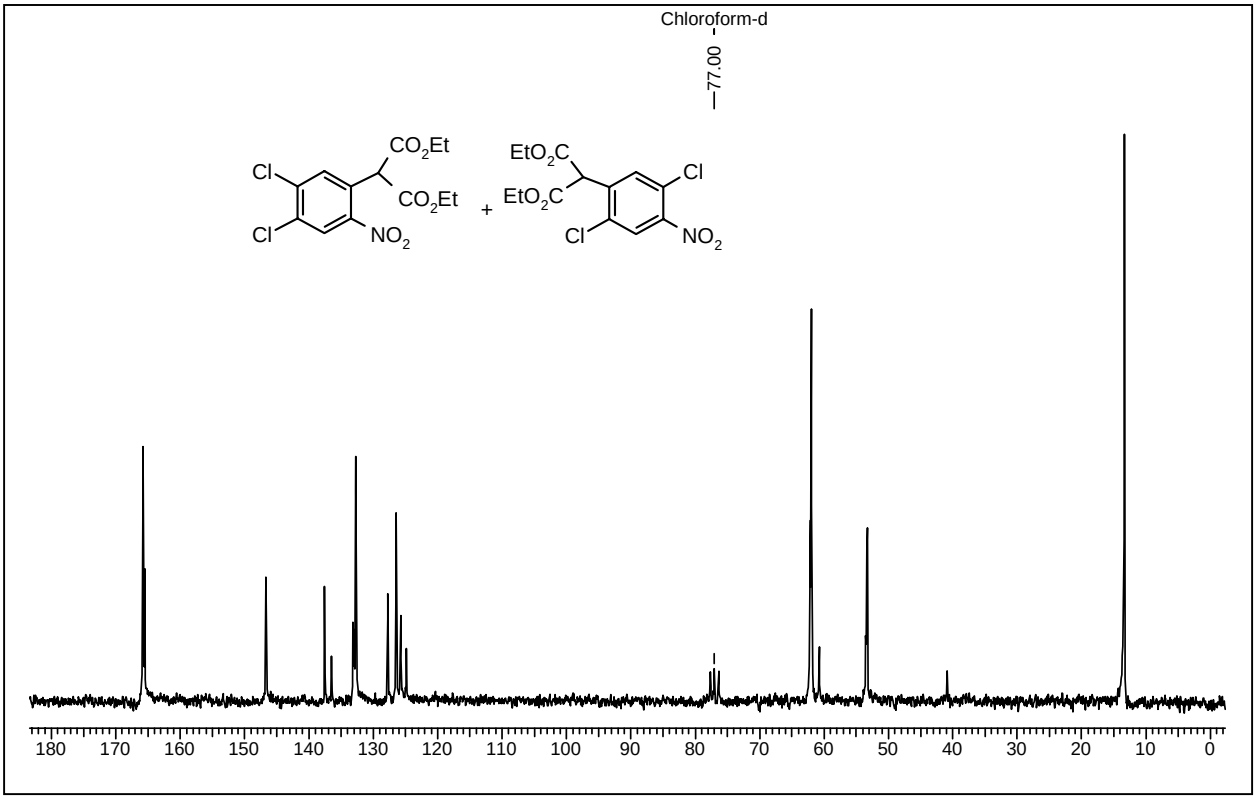
^{13}C NMR Spectrum of compound 41 in $CDCl_3$



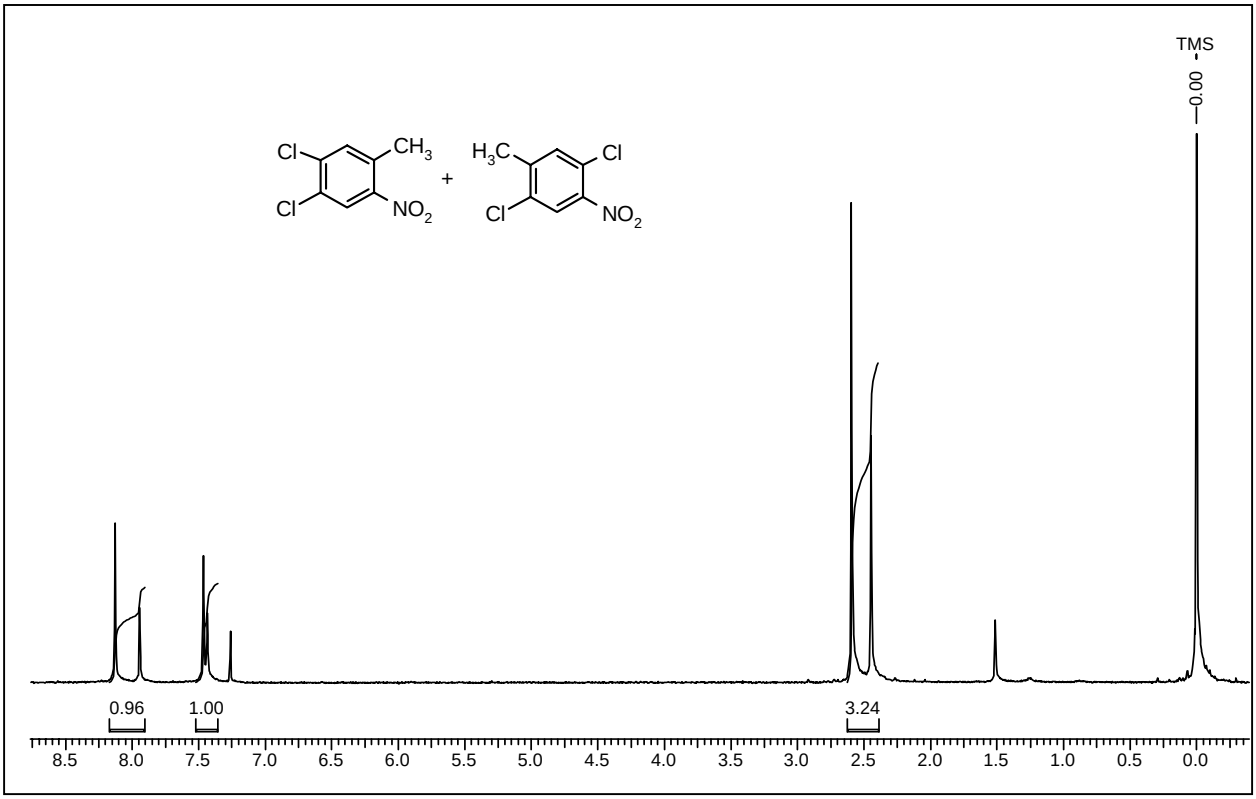
^{1}H NMR Spectrum of compound 42 in $CDCl_3$



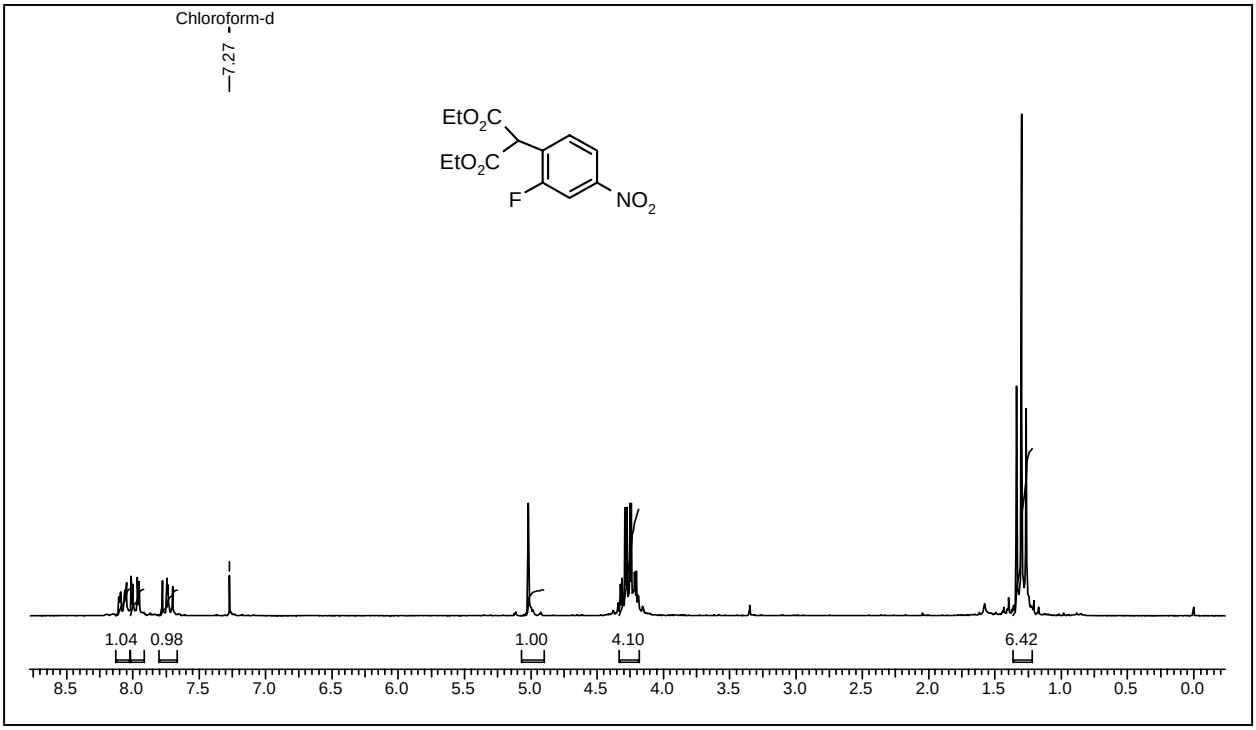
^{1}H NMR Spectrum of compounds 44 & 45 in $CDCl_3$



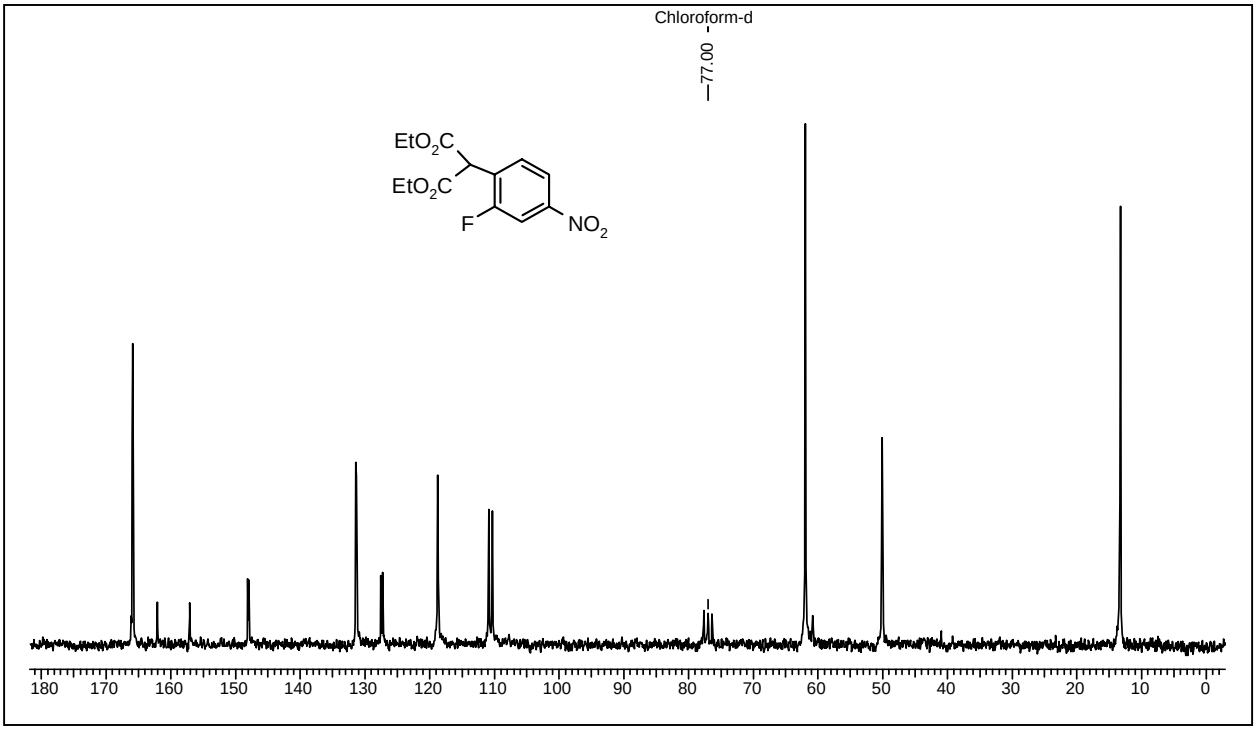
^{13}C NMR Spectrum of compounds 44 & 45 in $CDCl_3$



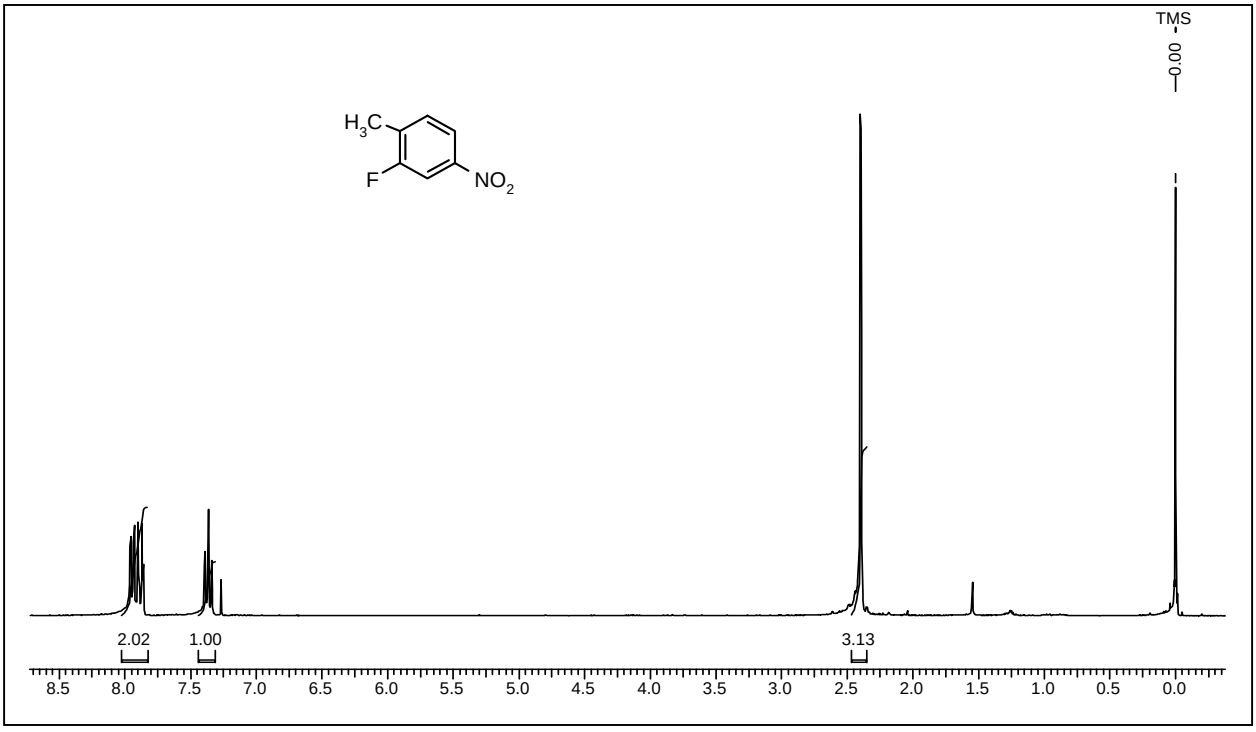
^{1}H NMR Spectrum of compounds 46 & 47 in $CDCl_3$



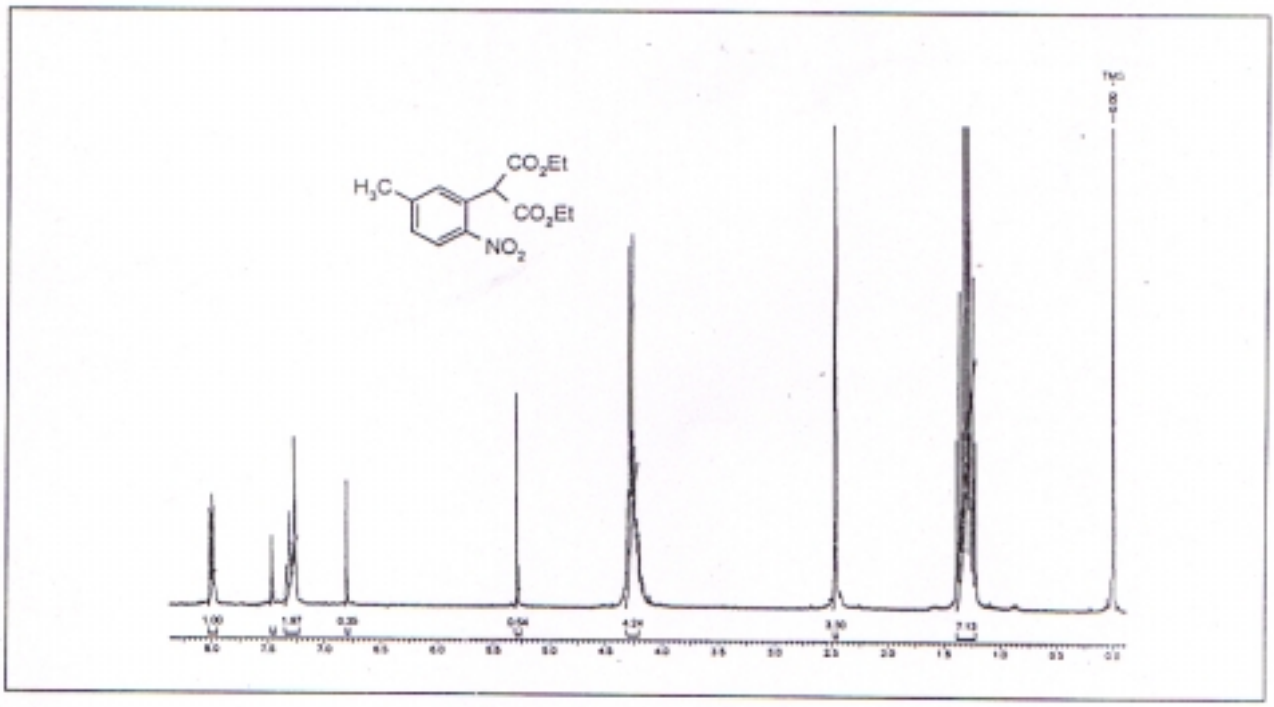
^{1}H NMR Spectrum of compound 49 in $CDCl_3$



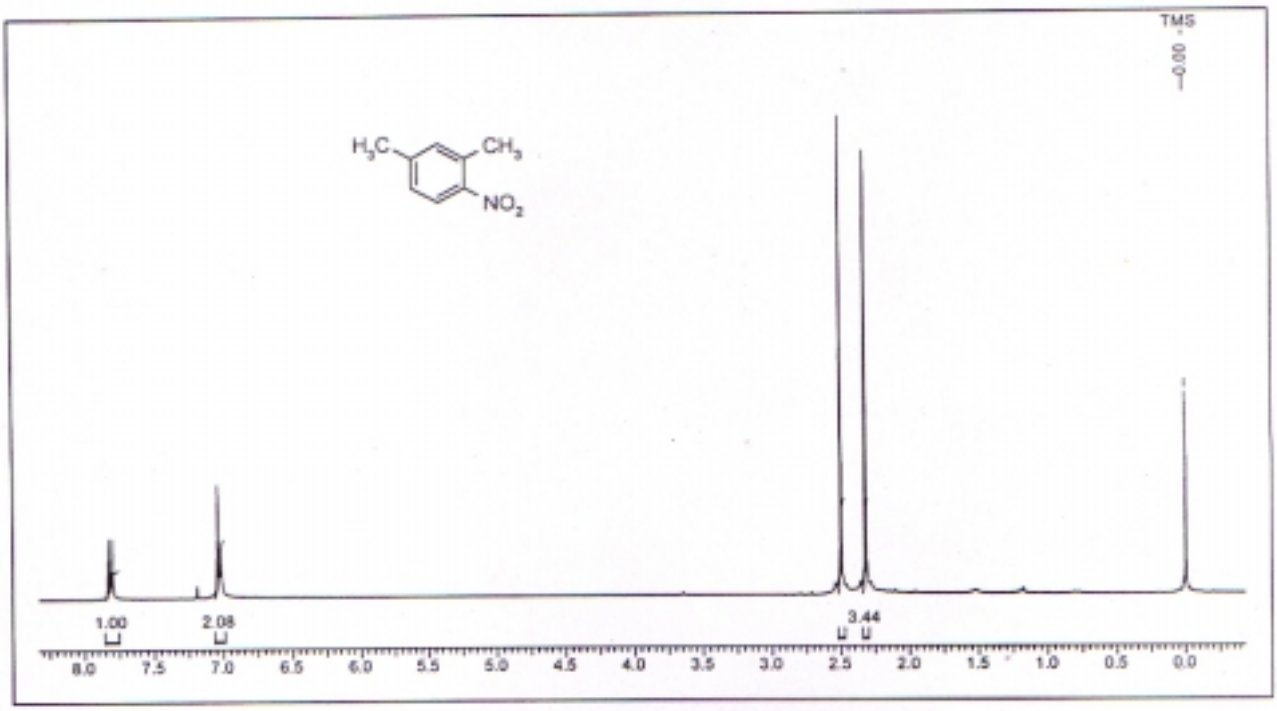
^{13}C NMR Spectrum of compound 49 in $CDCl_3$



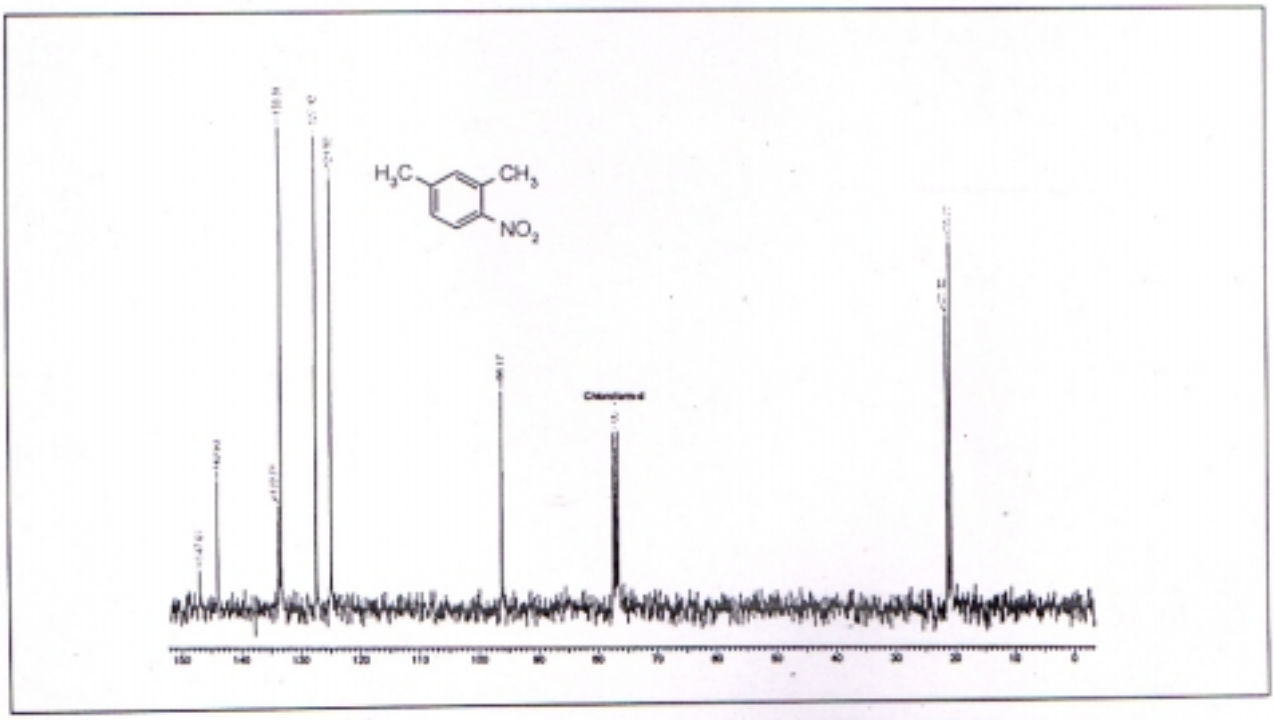
^{1}H NMR Spectrum of compound 50 in $CDCl_3$



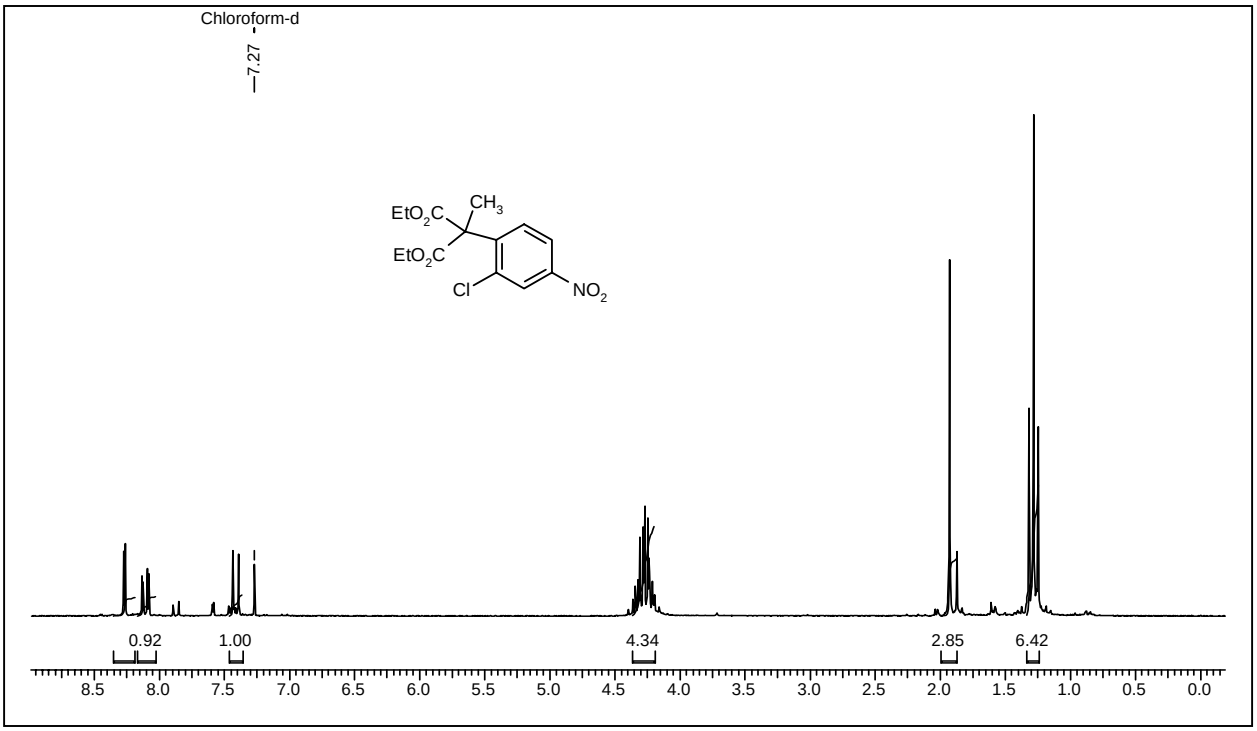
^{1}H NMR Spectrum of compound 52 in $CDCl_3$



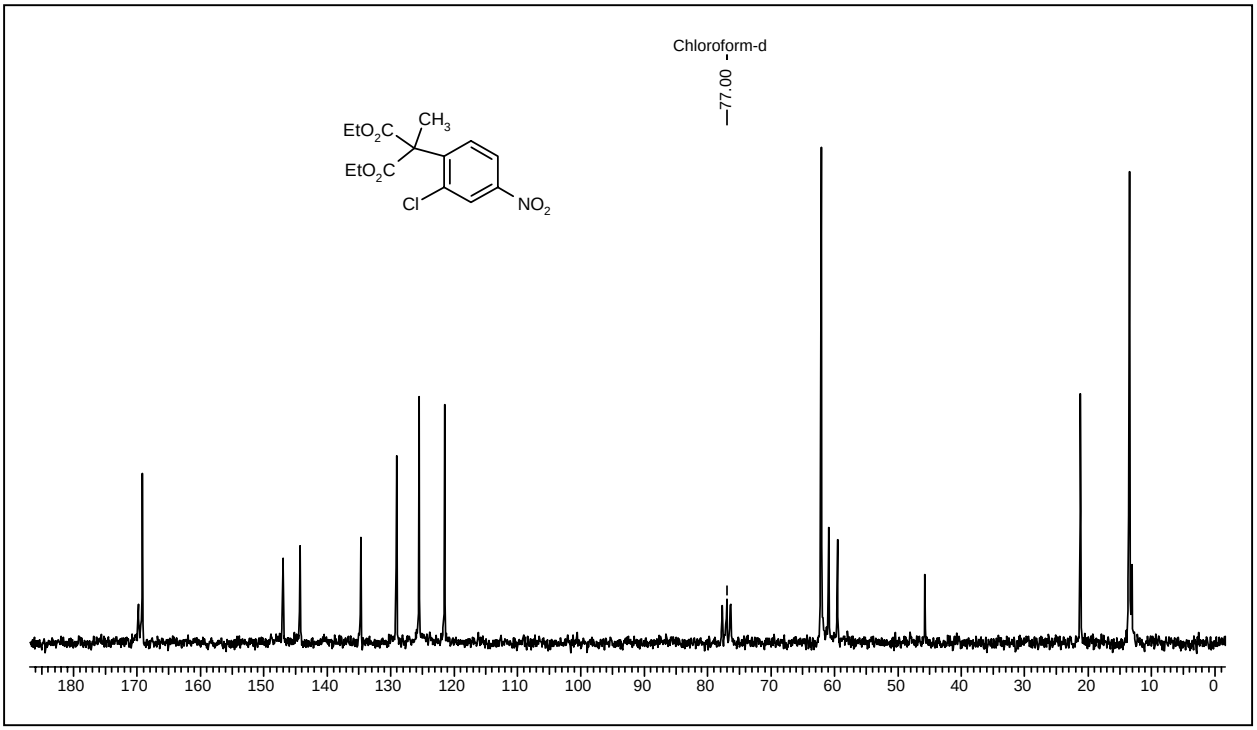
^{1}H NMR Spectrum of compound 53 in $CDCl_3$



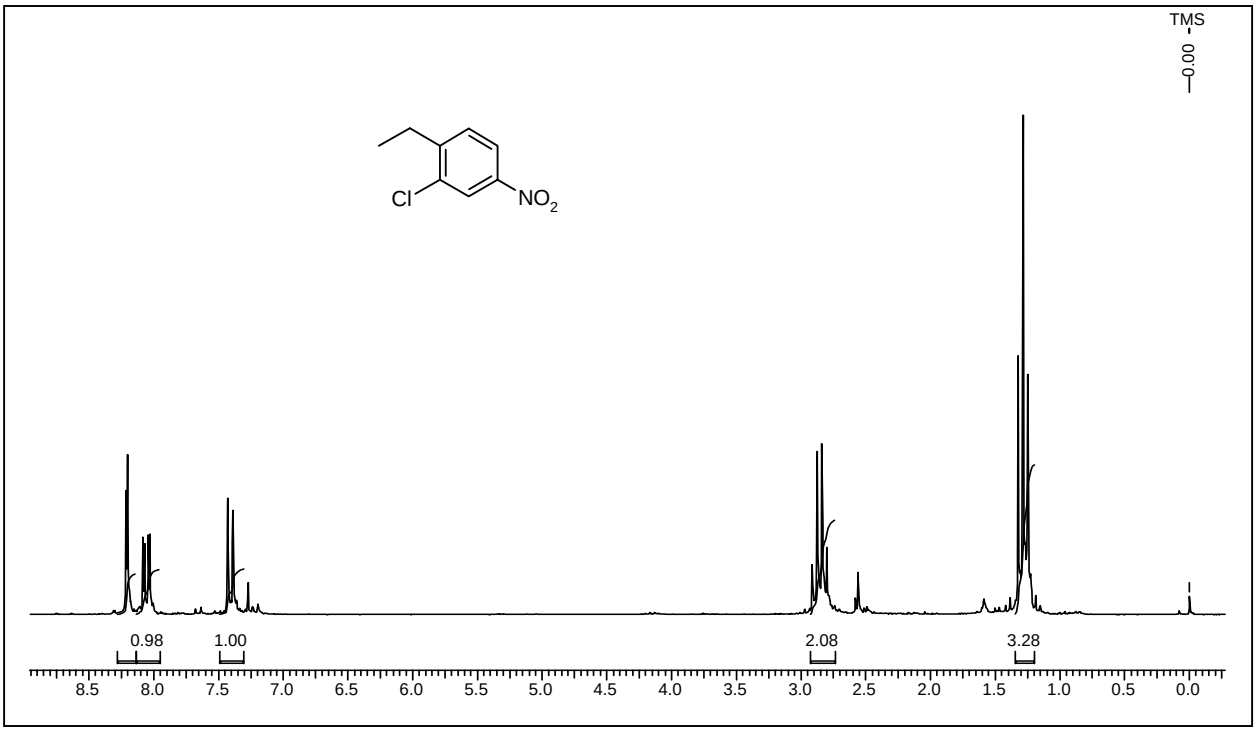
^{13}C NMR Spectrum of compound 53 in $CDCl_3$



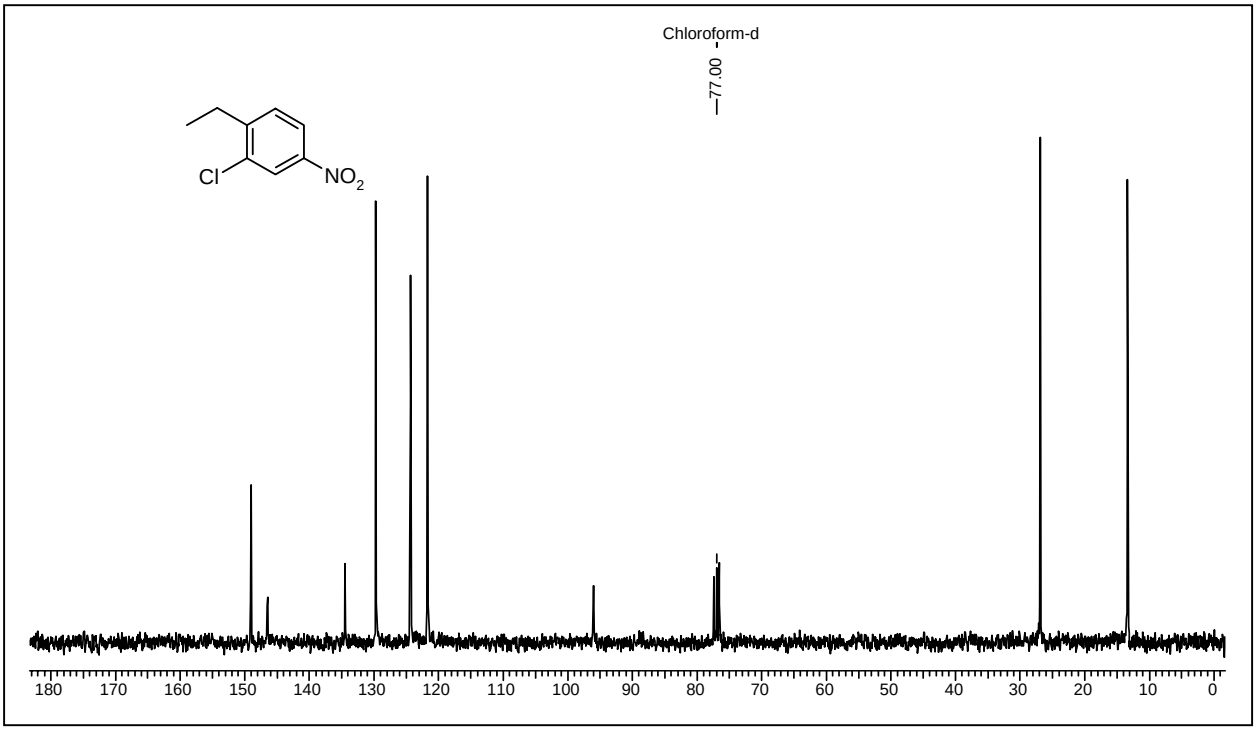
^{1}H NMR Spectrum of compound 55 in $CDCl_3$



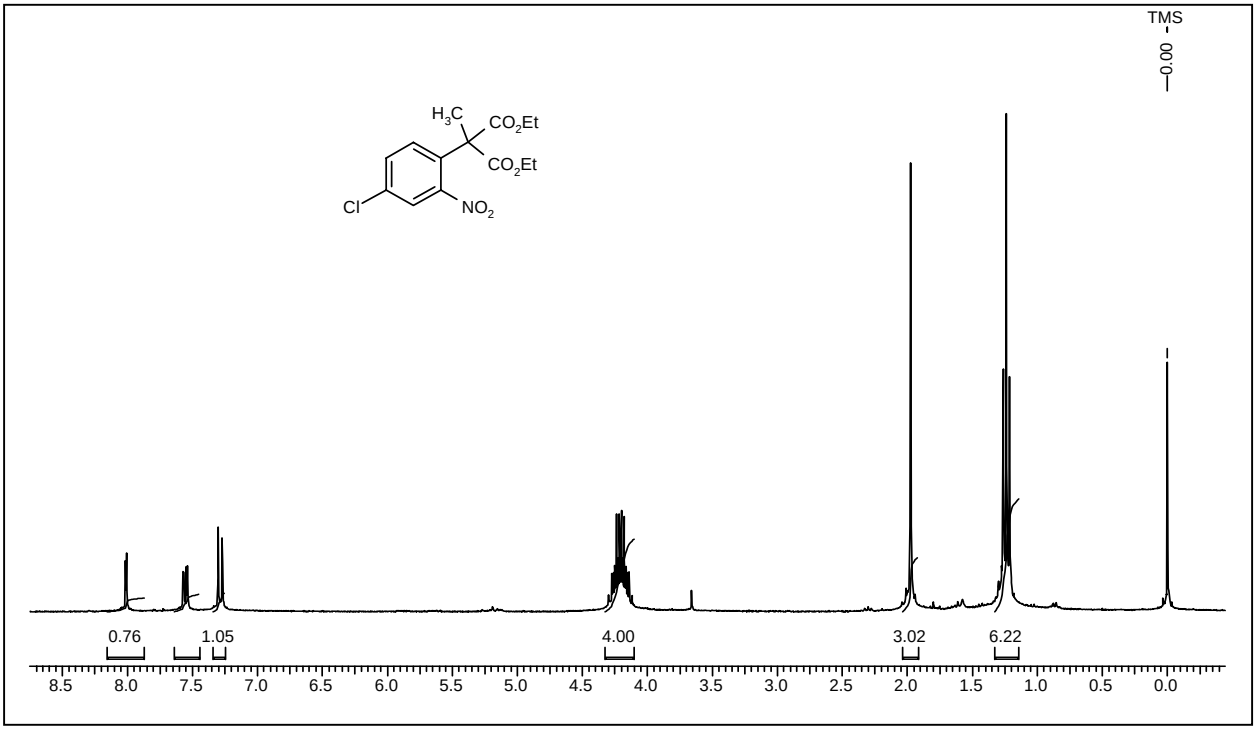
^{13}C NMR Spectrum of compound 55 in $CDCl_3$



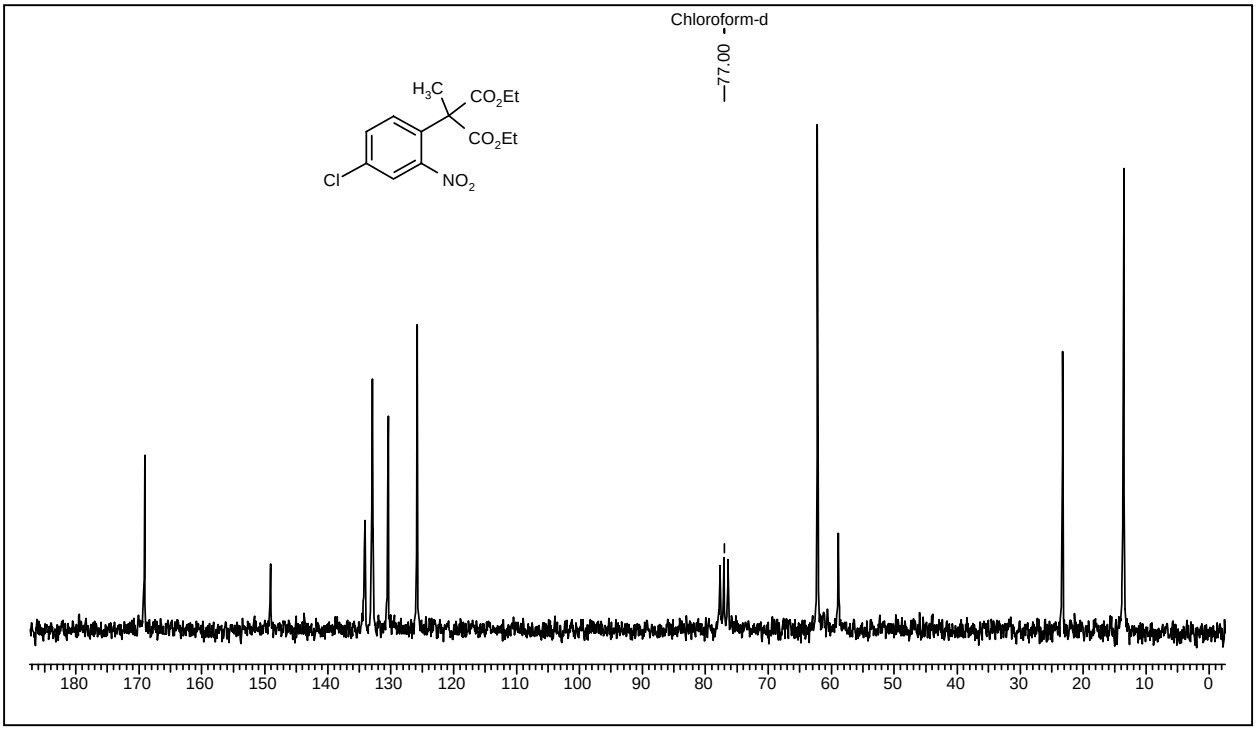
^{1}H NMR Spectrum of compound 56 in $CDCl_3$



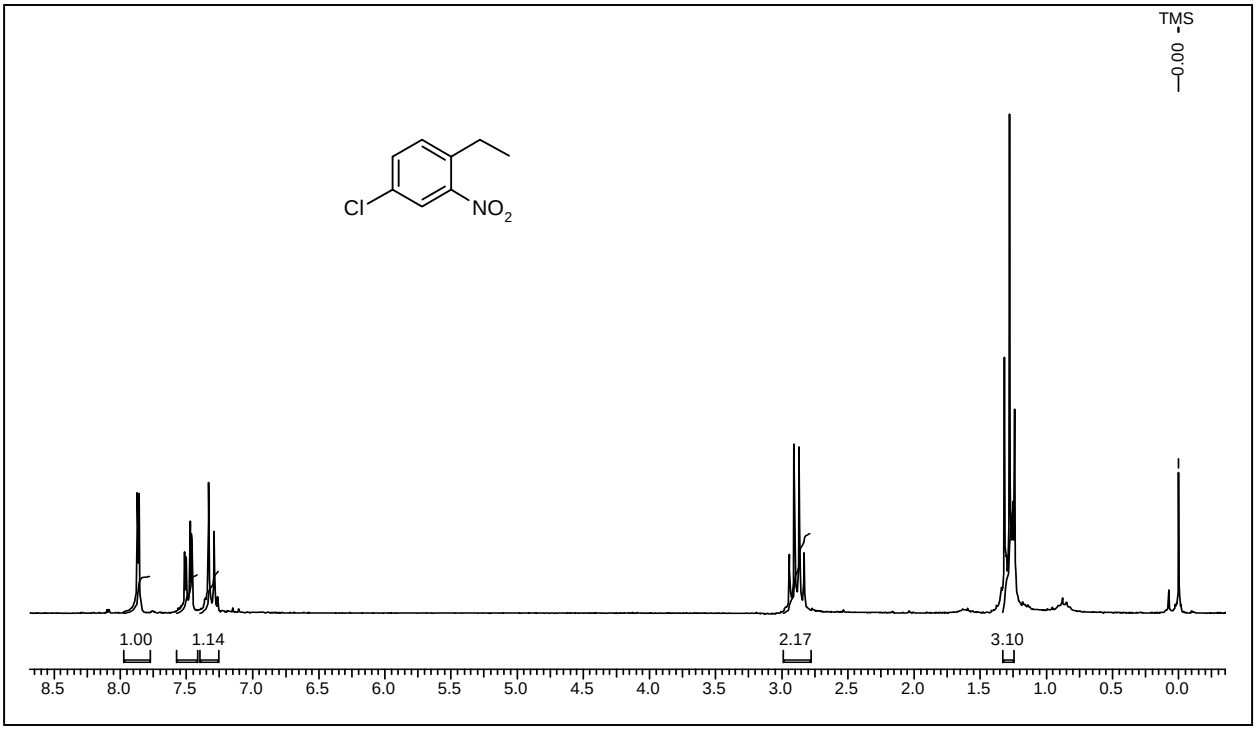
^{13}C NMR Spectrum of compound 56 in $CDCl_3$



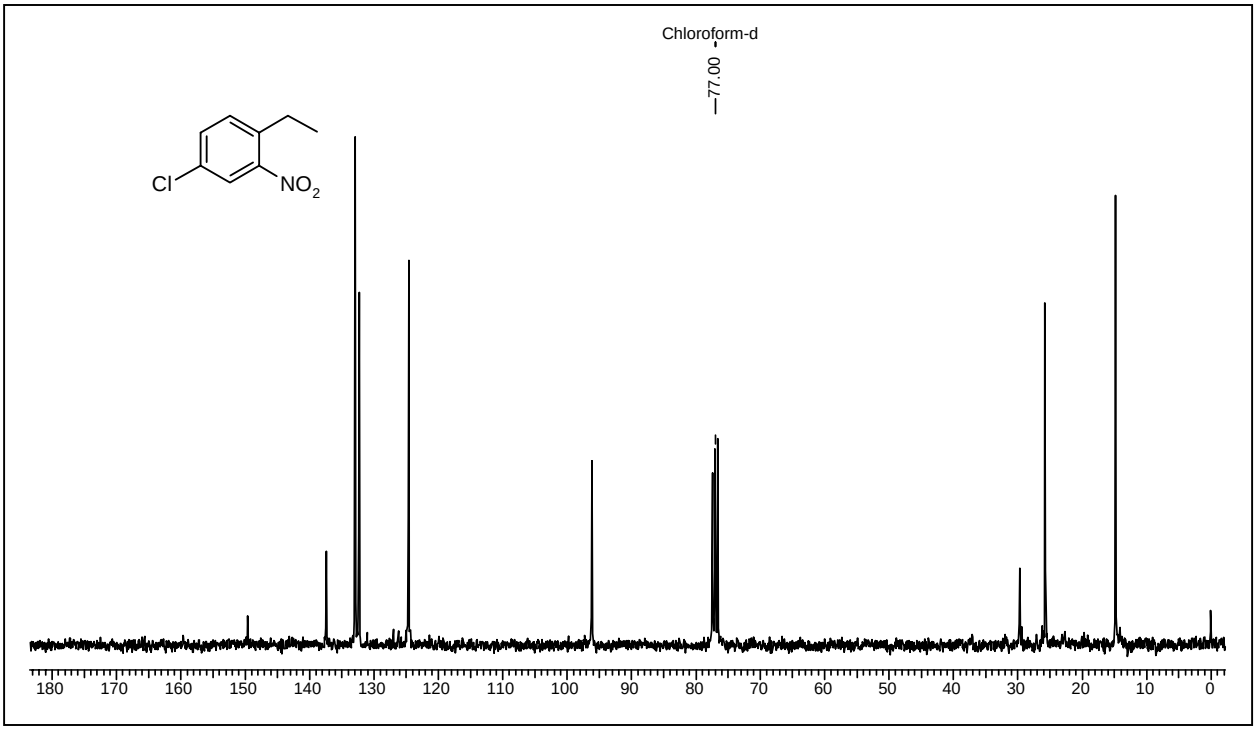
^{1}H NMR Spectrum of compound 57 in $CDCl_3$



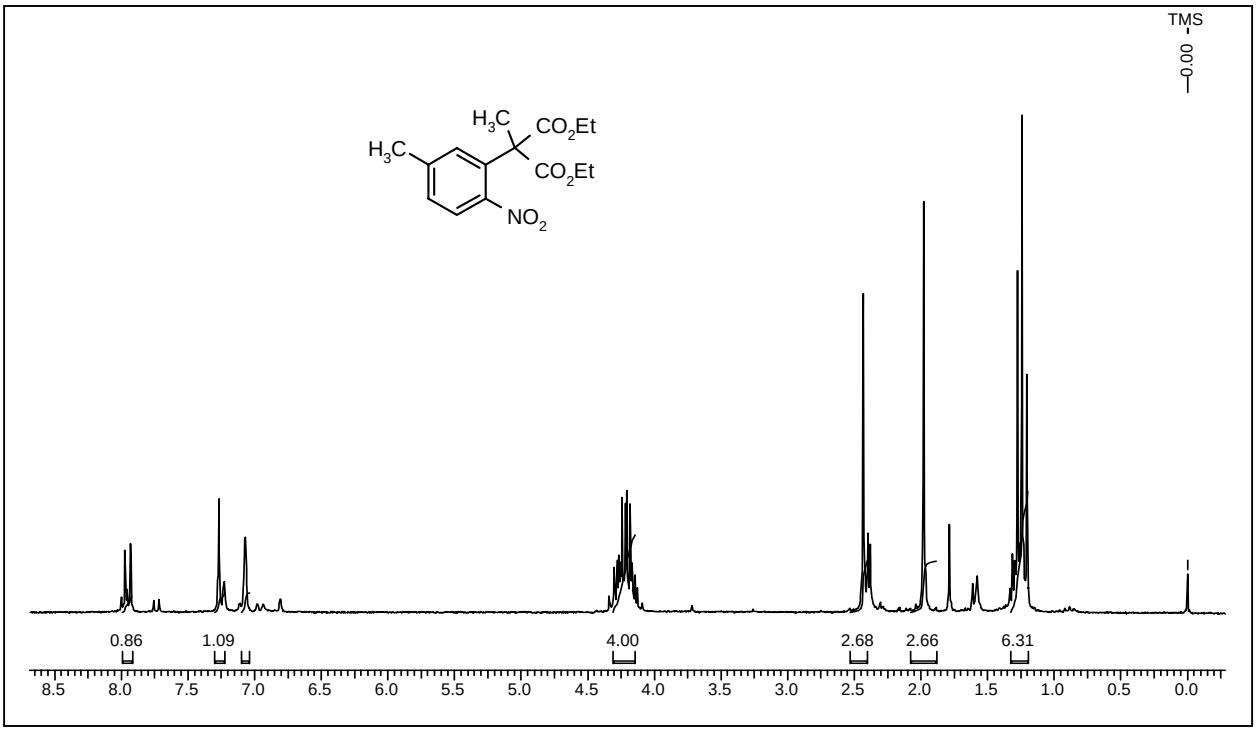
^{13}C NMR Spectrum of compound 57 in $CDCl_3$



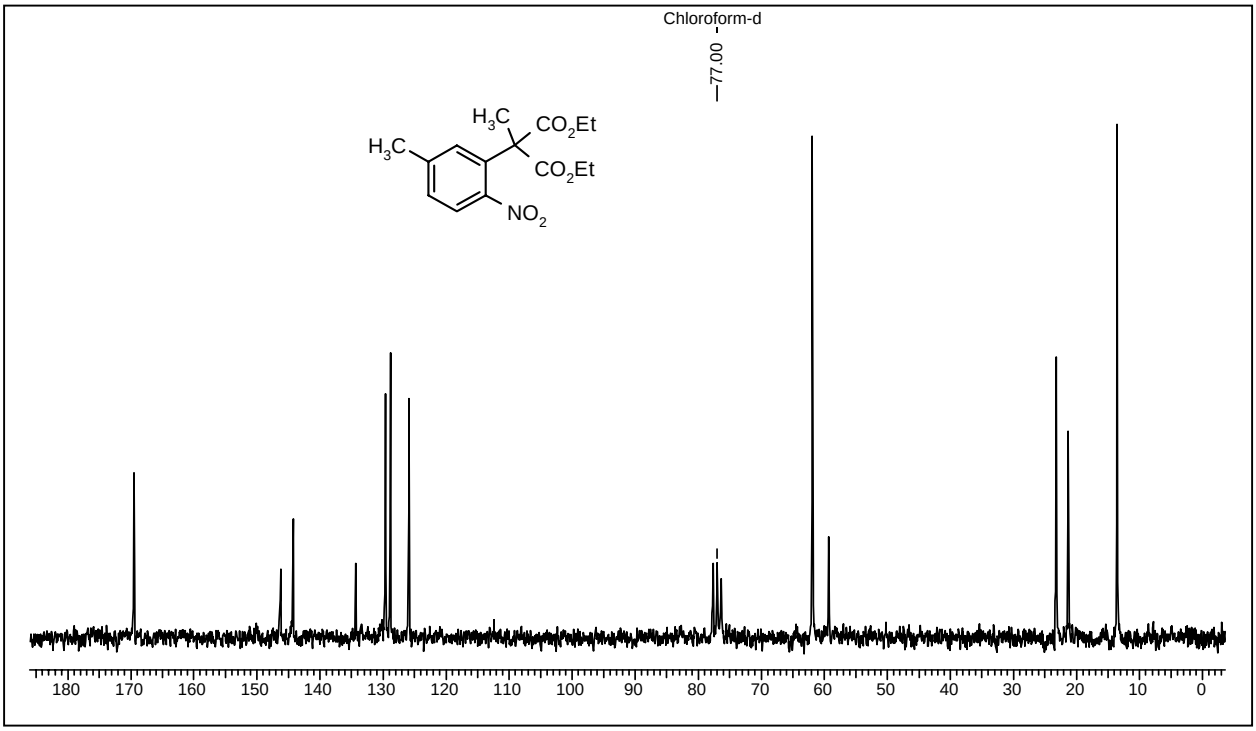
^{1}H NMR Spectrum of compound 58 in $CDCl_3$



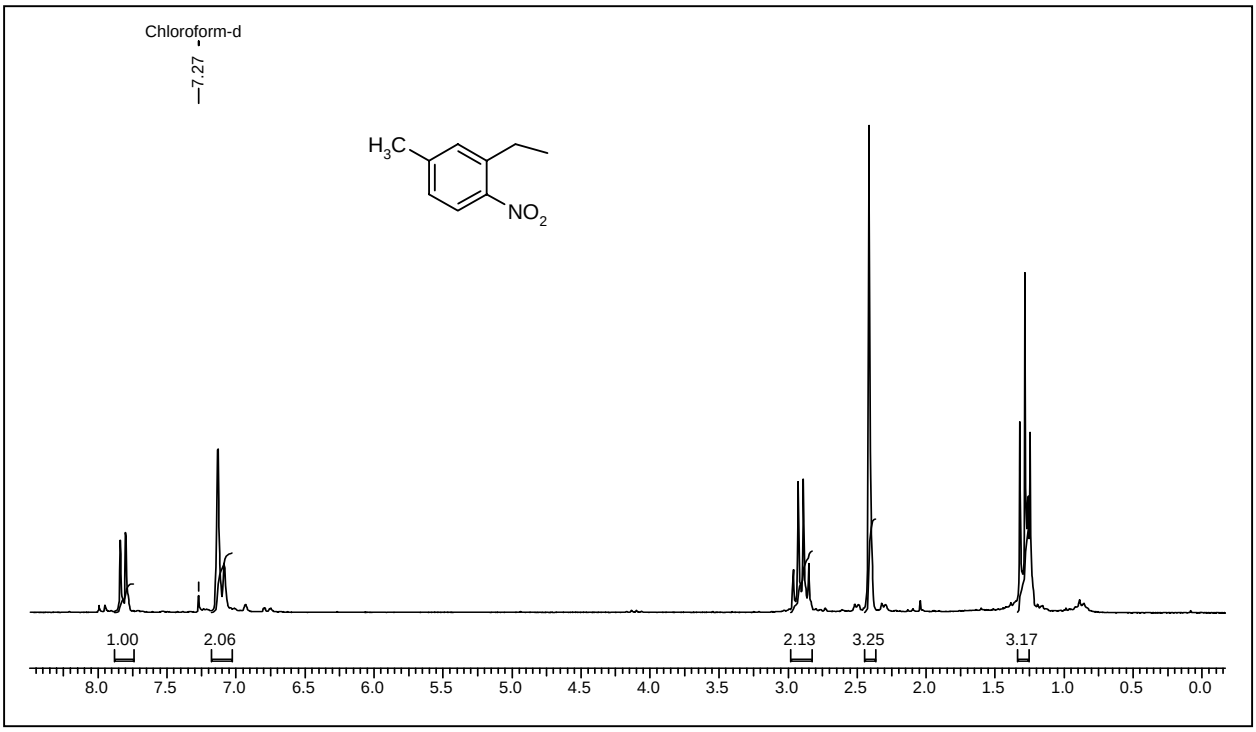
^{13}C NMR Spectrum of compound 58 in $CDCl_3$



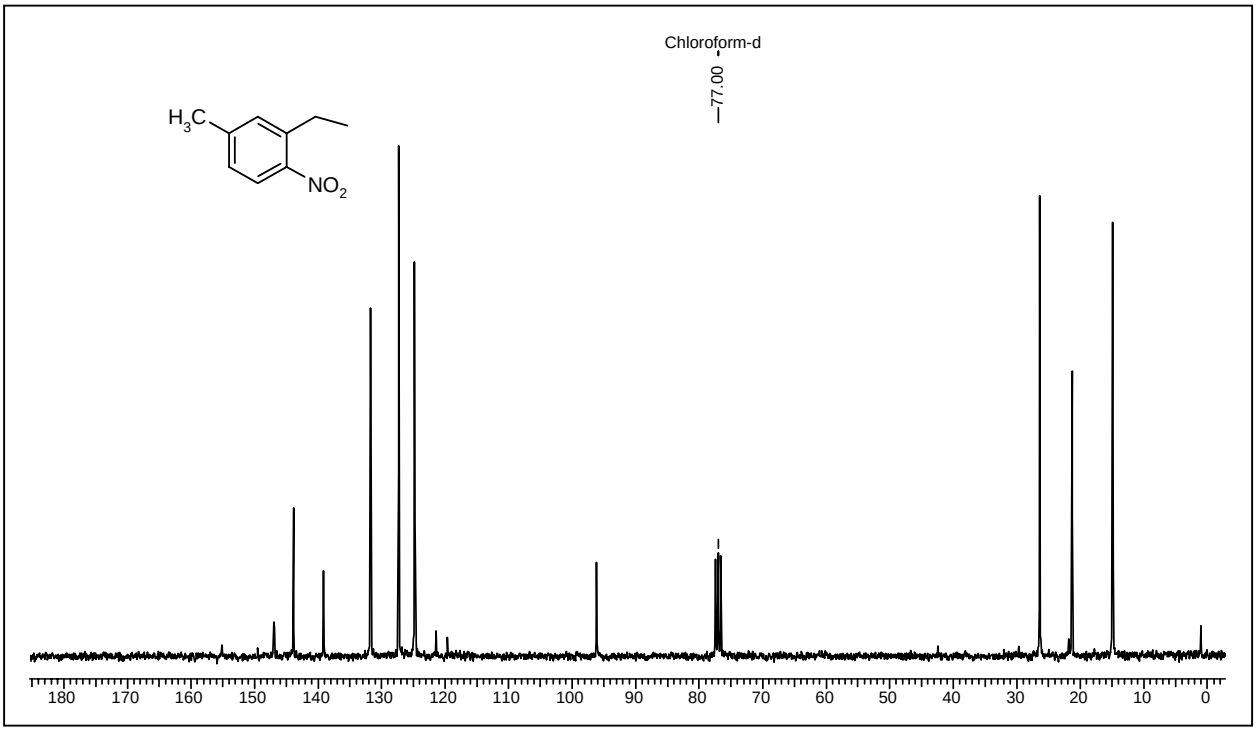
^{1}H NMR Spectrum of compound 59 in $CDCl_3$



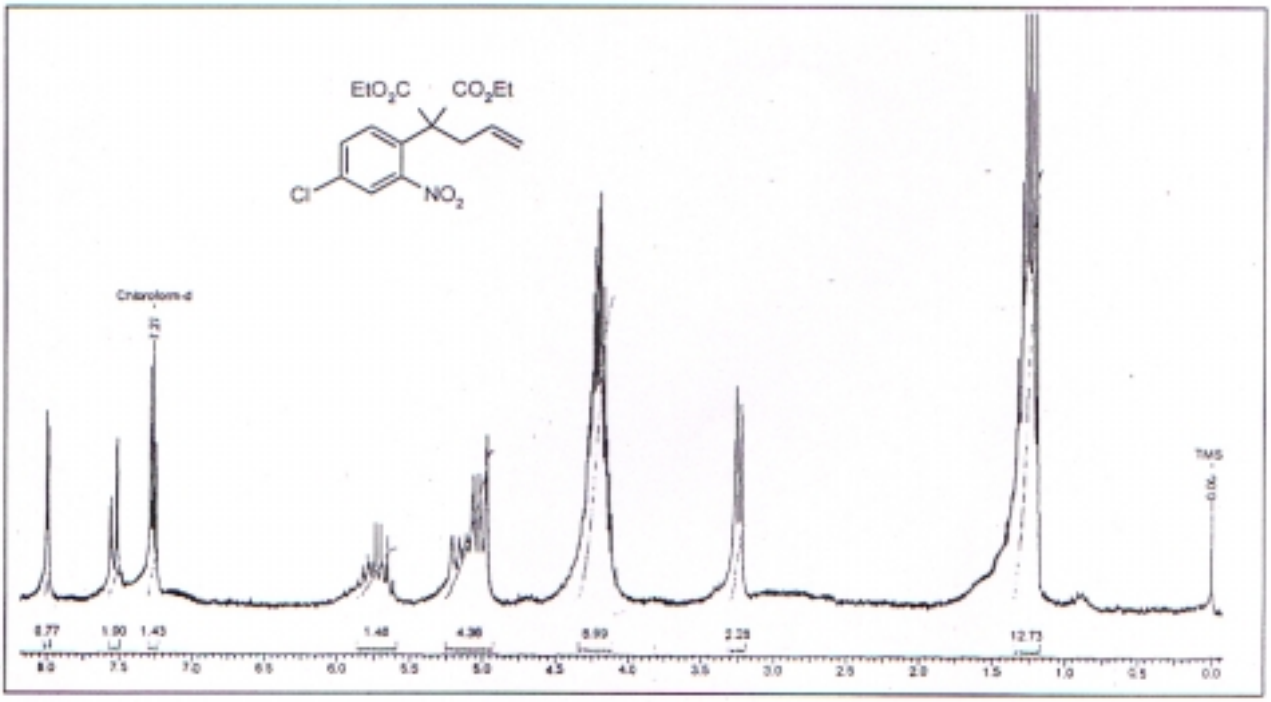
^{13}C NMR Spectrum of compound 59 in $CDCl_3$



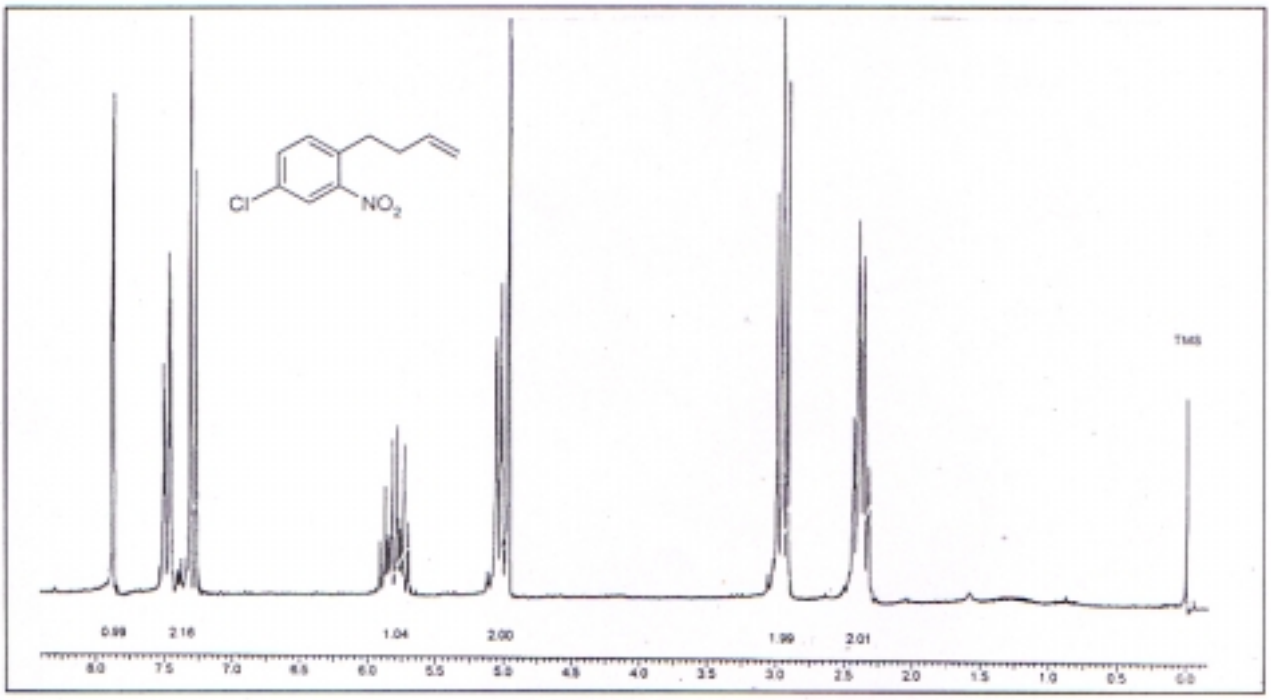
^{1}H NMR Spectrum of compound 60 in $CDCl_3$



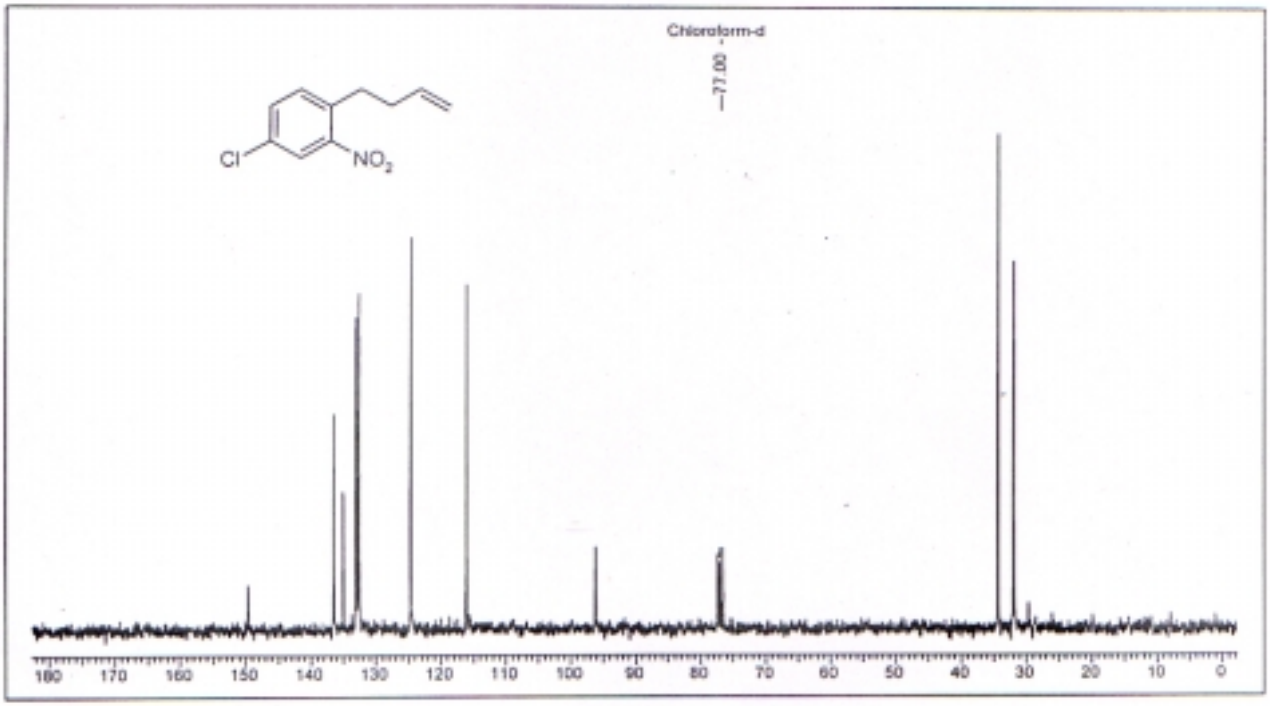
^{13}C NMR Spectrum of compound 60 in $CDCl_3$



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



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



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

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