SUGAR NITRONE BASED APPROACHES FOR THE TOTAL SYNTHESIS OF BIOLOGICALLY ACTIVE POLYHYDROXYLATED PYRROLIDINE AND PIPERIDINE ALKALOIDS, STUDIES TOWARD THE SYNTHESIS OF LEUSTRODUCSIN-B AND SOME Pd MEDIATED REACTIONS ON SUGAR ALKYNES

A THESIS

SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

TO

UNIVERSITY OF PUNE

BY

BORHADE RAMDAS GANGARAM

UNDER THE GUIDANCE OF

DR. M. K. GURJAR

ORGANIC CHEMISTRY: TECHNOLOGY
NATIONAL CHEMICAL LABORATORY

PUNE-411 008, INDIA

JUNE 2007

DEDICATED

TO MY BELOVED

PARENTS

DECLARATION

I declare that the thesis entitled "**Sugar nitrone based approaches for the Total synthesis of biologically active polyhydroxylated pyrrolidine and piperidine alkaloids, studies toward the synthesis of Leustroducsin- B and Some Pd mediated reactions on sugar alkynes"** submitted by me for the degree of Doctor of Philosophy is the record of work carried out by me during the period from 04-03-2004 to 28-12-2006 under the guidance of **Dr. M. K. Gurjar**, Deputy director and Head, OCT and OCS Division, National Chemical Laboratory, Pune-411 008 and has not formed the basis for the award of any degree, diploma, associateship, fellowship, titles in this or any other University or other institution of Higher learning.

I further declare that the material obtained from other sources has been duly acknowledged in the thesis.

Signature of the Candidate Date:

(BORHADE RAMDAS GANGARAM)

NATIONAL CHEMICAL LABORATORY

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

Dr. M. K. Gurjar
Deputy Director & Head
Division of Organic Chemistry: Technology

Telephone and Fax: + 91-20-25902627
+ 91-20-25902629
E-mail: mk.gurjar@ncl.res.in
Website: http://www.ncl-india.org

CERTIFICATE

CERTIFIED that the work incorporated in the thesis "**Sugar nitrone based approaches for the Total synthesis of biologically active polyhydroxylated pyrrolidine and piperidine alkaloids, studies toward the synthesis of Leustroducsin- B and Some Pd mediated reactions on sugar alkynes**" Submitted by Mr. **Ramdas Gangaram Borhade** was carried out by the candidate under my supervision/ guidance. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

Pune-8 **(Dr. M. K. Gurjar)**

June 2007 (Research Guide)

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Borhade Ramdas Gangaram

Ac	-	Acetyl
AcOH	-	Acetic acid
AIBN	-	2,2'-Azobisisobutyronitrile
Bn	-	Benzyl
BnBr	-	Benzyl bromide
$BH_3 \cdot Me_2S$	-	Boron dimethyl sulfide complex
Boc	-	*tert*-Butoxy carbonyl
$(Boc)_2O$	-	Di-*tert*-butyl dicarbonate
BuLi	-	Butyl Lithium
CSF	-	Colony-stimulating factor
COSY	-	Correlation spectroscopy
DCM	-	Dichloromethane
DDQ	-	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	-	Diisobutylaluminiumhydride
DMP	-	Dess–Martin periodinane
DMP	-	2,2-Dimethoxypropane
DMF	-	*N, N'*-Dimethylformamide
DMAP	-	*N,N'*-Dimethylaminopyridine
DMSO	-	Dimethyl sulfoxide
DOS	-	Diversity oriented synthesis
EtOH	-	Ethanol
Et	-	Ethyl
Et_2O	-	Diethyl ether
EtOAc	-	Ethyl acetate
Et_3N	-	Triethylamine
HETCORE	-	Heteronuclear COrrelated SpectroscopY
HMBC	-	Heteronuclear Multiple Bond Correlation
IBS	-	Iodoxybenzoic Acid

Im	-	Imidazole
LDA	-	Lithium diisopropylamide
MeOH	-	Methanol
MsCl	-	Methanesulfonyl chloride
Ms	-	Methanesulfonyl
Me	-	Methyl
MeI	-	Methyl iodide
MPM	-	*p*-Methoxyphenylmethyl
$NaBH_4$	-	Sodiumborohydride
NaH	-	Sodium hydride
NMR	-	Nuclear magnetic resonance
nOe	-	Neuclear Overhauser Effect
NOESY	-	Nuclear Overhauser effect spectroscopy
Ph	-	Phenyl
Py	-	Pyridine
PDC	-	Pyridiniumdichromate
RCM	-	Ring closing metathesis
TEA	-	Triethylamine
TBAI	-	Tetra-*n*-butylammonium iodide
TBAF	-	Tetra-*n*-butylammonium fluoride
TBDMSCl	-	*tert*-Butyldimethyl chlorosilane
TBDMS	-	*tert*-Butyldimethyl silyl
THF	-	Tetrahydrofuran
TPP	-	Triphenylphosphine
p-TSA	-	*p*-Toluenesulphonic acid
TON	-	Turnover number
TsCl	-	*p*-Toluenesulphonyl chloride
WHO	-	World Health Organization

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

CONTENTS

ABSTRACT

Research Student	: Ramdas G. Borhade
Research Guide	: Dr. Mukund K.Gurjar
Title of Thesis	: "**Sugar nitrone based approaches for the Total synthesis of biologically active polyhydroxylated pyrrolidine and piperidine alkaloids, studies toward the synthesis of Leustroducsin- B and Some Pd mediated reactions on sugar alkynes**"
Registration no.	: EI/05/Ph.D/2004
Date of registration	: 4-03-2004
Place of work	: Division of Organic Chemistry: Technology, National Chemical Laboratory, Pune- 411 008

Abstract

The thesis entitled "**Sugar nitrone based approaches for the Total synthesis of biologically active polyhydroxylated pyrrolidine and piperidine alkaloids, studies toward the synthesis of Leustroducsin- B and Some Pd mediated reactions on sugar alkynes**" has been divided into two chapters along with appendix and each chapter is further sub-divided into the following sections: Introduction, Present work, Experimental, Spectroscopic data and References. The first chapter provides the synthesis of biologically active azasugars based on cyclic sugar nitrone. The second chapter describes the facile Pd catalyzed methodologies for Sonogashira coupling, cycloisomerization of sugar alkynals and one pot Sonigashira-Suzuki-Miyaura cross-coupling reaction on sugar alkynes. The appendix highlights the attempt towards the synthesis of Leustroducsin- B.

CHAPTER I: Total synthesis of biologically active polyhydroxylated pyrrolidine and piperidine alkaloids

After the discovery of nojirimycin, the first azasugar (polyhydroxylated nitrogen heterocycles in which the ring *O*-atom of a carbohydrate is replaced by nitrogen) alkaloid that mimics a sugar, a myriad of naturally occurring azasugars have been isolated. These compounds, which are frequently inhibitors of carbohydrate-processing enzymes, have the potential for use in wide range potential therapeutic strategies including the treatment of

diabetes, cancer, viral infections, tuberculosis, lysosomal storage diseases and as inhibitors of the growth of parasitic protozoa. As a result, the syntheses of polyhydroxylated pyrrolidines and piperidines have attracted a great deal of attention in recent years. Herein, we describe the synthesis of a D-*xylo* and L-*arabino* configured cyclic nitrones and their applications to prepare some naturally occurring polyhydroxylated pyrrolidine and piperidine alkaloids.

Section 1: Total synthesis of (-) Radicamines A & B

Recently the new pyrrolidine alkaloids radicamines **A** (**1**) and **B** (**2**), were isolated as inhibitors of α-glucosidase from the plant *Lobelia chinensis* Lour., a herb that is used as a diuretic, an antidote, a hemostat and as a carcinostatic agent for stomach cancer in Chinese folk medicine. The absolute stereochemistries of these compounds were assigned by comparing the sign of the optical rotation with codonopsine (**3**) and its antipode **4**.

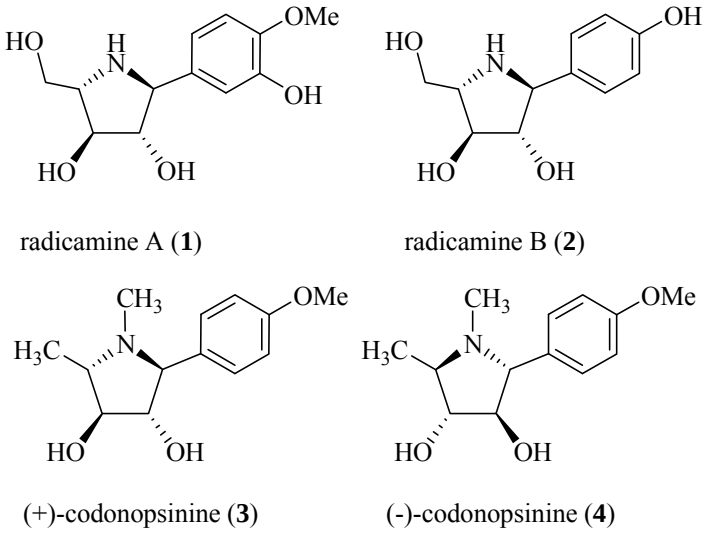


***Figure* 1:** *Naturally occurring polyhydroxy pyrrolidine alkaloids*

Due to their remarkable biological properties we have undertaken the synthesis of radicamine A and radicamine B. Considering their identical stereochemistry of the pyrrolidine ring we have devised a strategy, which involve L-*arabino* configured cyclic nitrone **5**, as an advanced intermediate.

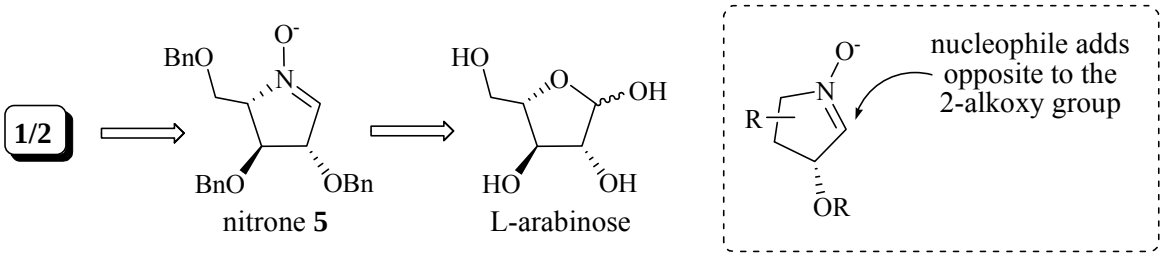
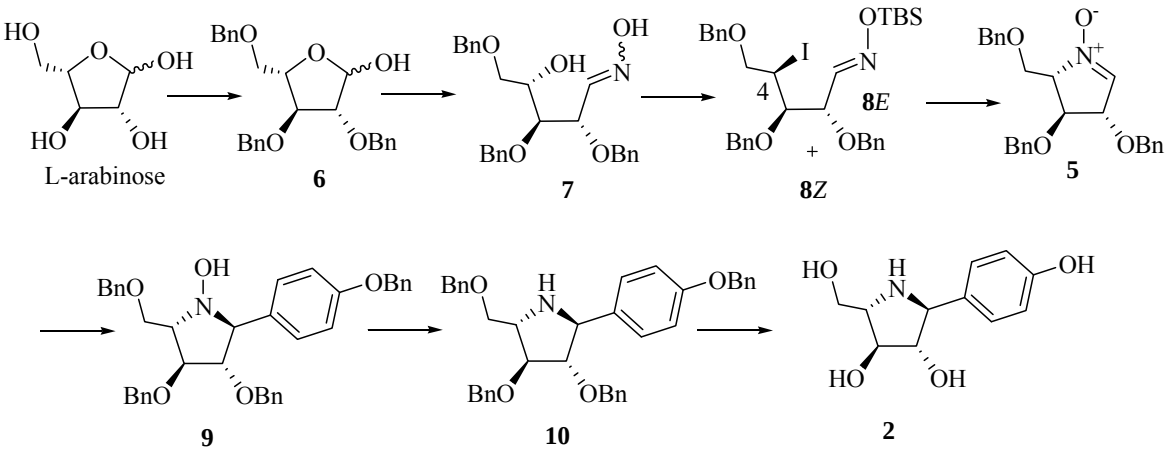


***Figure* 2**. *Retrosynthetic analysis for radicamines*

Following the retrosynthetic analysis (Figure 2), the synthesis of key nitrone **5** was initiated with the preparation of mixture (7:3) of *E*/*Z*-oximes **7** from **6**. The compound **6** was alternatively prepared from L-arabinose using the reported procedure (Scheme 1). After selective protection and iodination with inversion of the configuration at C(4) led to the isolation of a mixture of *E*/*Z*-oxime derivatives **8**. The major isomer **8*E*** was subjected to desilylation and concomitant intramolecular nucleophilic displacement afforded nitrone **5** whose absolute stereochemistry was confirmed by X-ray crystallography. The Grignard reaction of **5** was executed at –78 °C to afford *N*-hydroxypyrrolidine derivative **9** in 78% yield exclusively. The reduction of N-O bond & debenzylation gave **2** in 62% yield. The relative stereochemistry of **2** was confirmed by extensive 2D NMR spectroscopy & the optical rotation of **2** was similar in magnitude but opposite in sign with that of the reported. This confirmed the revision in the absolute configuration of radicamine B.

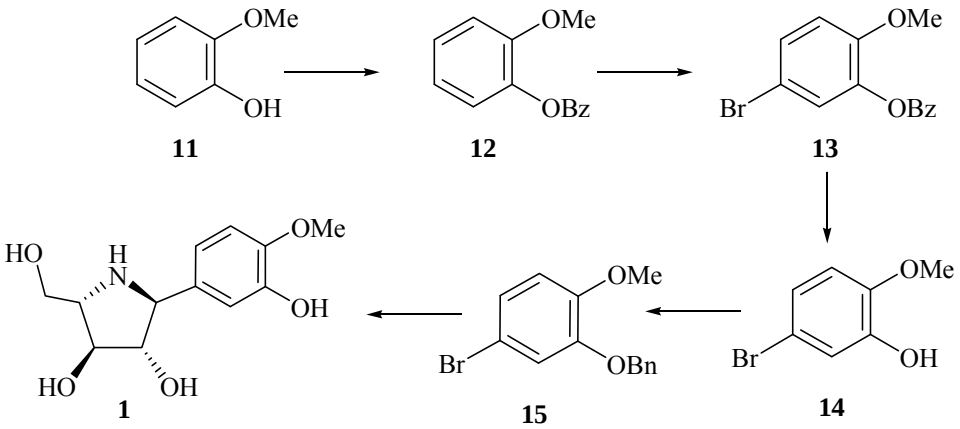
***Scheme* 1**



In the process of completing the total synthesis of radicamine A, we next prepared the requisite aromatic precursor as shown in (Scheme 2**)**. The guiacol **11** was converted to the

compound **13** by using reported procedure. The bromobenzene derivative (**15**) was prepared through a conventional sequence of reactions from **13**.

***Scheme* 2**



Reaction of the Grignard reagent prepared from **15** with nitrone **5** followed by exhaustive hydrogenation completed the total synthesis of radicamine A. However, during the same time Yu *et al.* reported the synthesis of both the radicamines and revised the absolute stereochemistry, which indeed we too observed.

Section 2: Synthesis of LAB 1 (16) and its epimer (17)

After completing the total synthesis of **1** and **2** we next carried out the synthesis of LAB 1 (**16**) and its epimer **17** by simple reduction of the corresponding nitrones **5** and **20** respectively which prompted us to design a shorter and efficient route for the synthesis of the D-*xylo* configured nitrone, based on our earlier approach for the synthesis of L-*arabino* configured nitrone **5.**

A minor modification of synthetic scheme used in preparing the cyclic nitrone **5**, provided the desired epimeric nitrone **20**. Silylation of the compound **7** followed by mesylation of resulting **23** with methanesulphonyl chloride gave **24**.

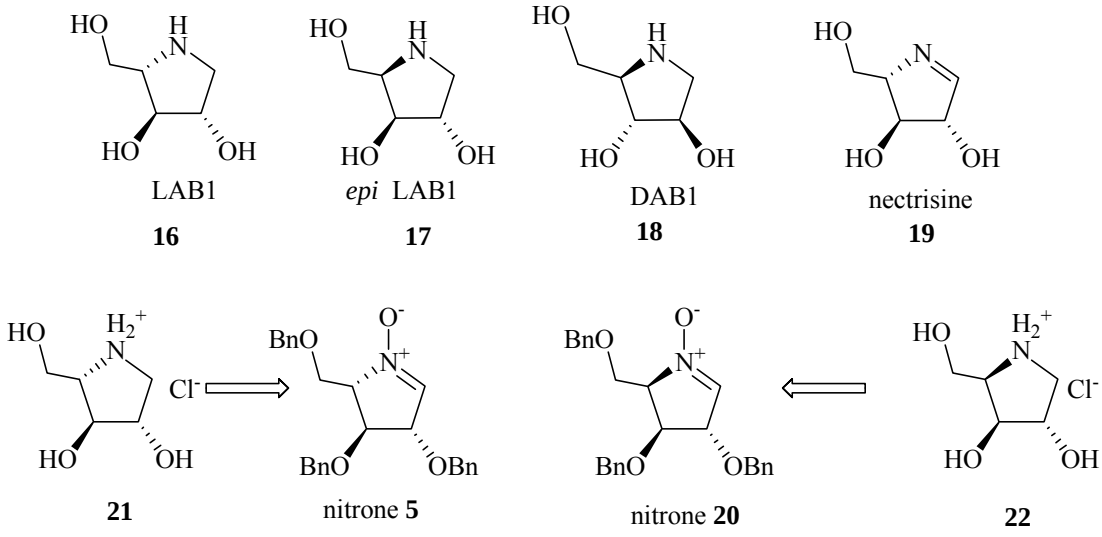
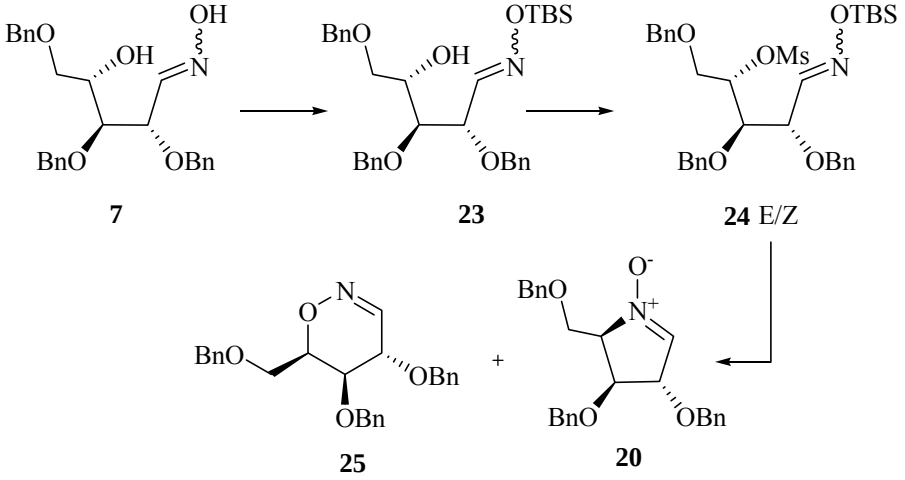


***Figure* 3:** *Bioactive pyrrolidine derivatives and their retrosynthetic schemes*

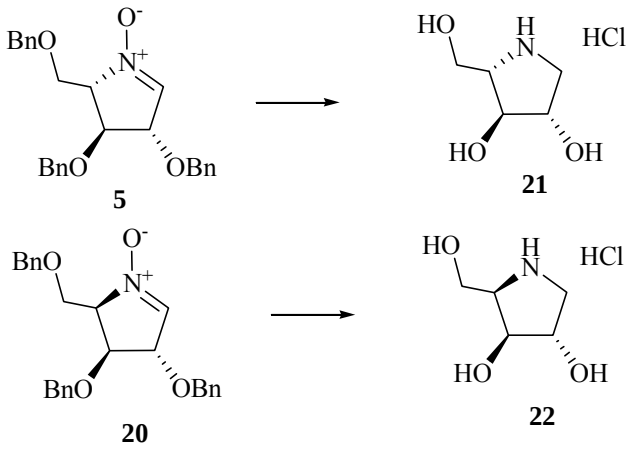
Treatment of **24** with *n*-Bu_4NF in THF at room temperature led to the corresponding oxime, which upon treatment with hydroxylamine.hydrochloride, $NaHCO_3$ in MeOH gave the mixture of desired cyclic nitrone **20** (48%) as well as an oxazine **25** in 26% yield. However, the formation of the side product can be controlled by conducting the silyl deprotection in refluxing toluene with the help of anhydrous *n*-Bu_4NF, which afforded nitrone **20** exclusively in quantitative yield.

***Scheme* 3**



The global reduction of nitrones **5** and **20** by using Pearlman's catalyst afforded hydrochloride salts of LAB 1 (**21**) and 1,4-dideoxy-1, 4-imino-D-xylitol (**22**) in good yields.

***Scheme* 4**



Section 3: Towards the synthesis of Batzellasides A-C

The *C*-alkylated piperidine derivatives Batzellasides A (**26**), B (**27**), and C (**28**) were isolated from a *Batzella* sp. sponge, collected off the west coast of Madagascar. Batzellasides inhibited the growth of *Staphylococcusepidermidis* with MICs of 6.3 μg/mL. The structure of the cyclic core of these natural products shows identity with fagomine the derivatives (Figure 4).

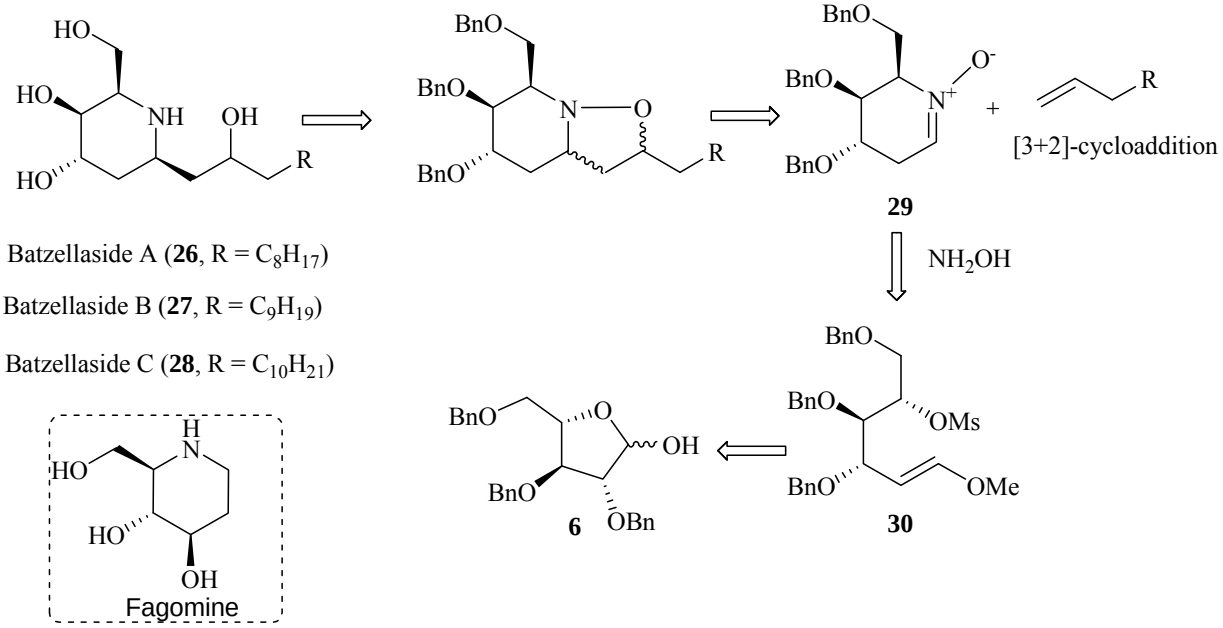
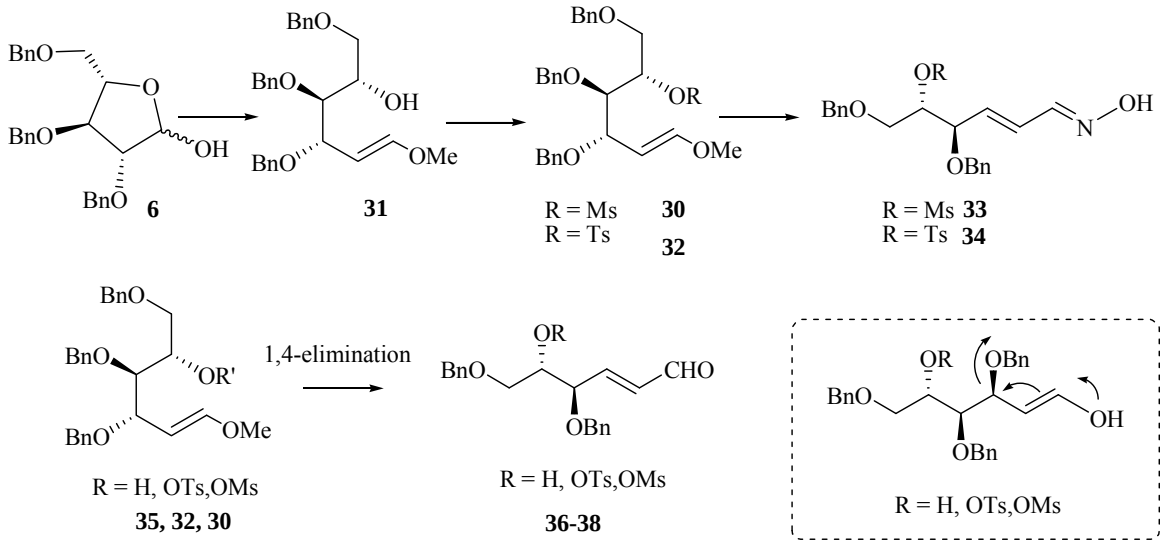


***Figure* 4 :** *Batzellaside natural products and intended retrosynthetic strategy*

We have devised a flexible strategy that should address not only the synthesis of batzellasides A–C, but also the related unnatural analogues by employing commercially available olefins. The retrosynthetic strategy is funded on nitrone cycloaddition as the key step with appropriate side chain olefins. The nitrone **29** could be obtained from the mesylate **30**. This can be made from the lactol **6** which we made in our previous synthesis.

***Scheme* 5**



Thus our synthesis started with Wittig reaction of lactol **6** (Scheme 5). The treatment of **6** with methoxymethyltriphenilphosponium chloride in the presence of *n*-BuLi gave olefin **31** in 55% yield. The mesylation and subsequent treatment of resulting **30** with hydroxylamine hydrochloride afforded a conjugated linear oxime instead of the desired cyclic nitrone. Changing the mesyl to tosyl also provided the same eliminated product. When checked, these substrates **30, 32** and **35** were found to be very sensitive towards the various reaction conditions applied and revealed the fact that this approach for the synthesis of nitrone may not be appropriate. As an alternative strategy we planned the oxidation of piperidine **39** for nitrone **29**. We intended to prepare **39** by an intramolecular hydroboration–cycloalkylation reaction of the azidoalkene **40** (Figure 5).

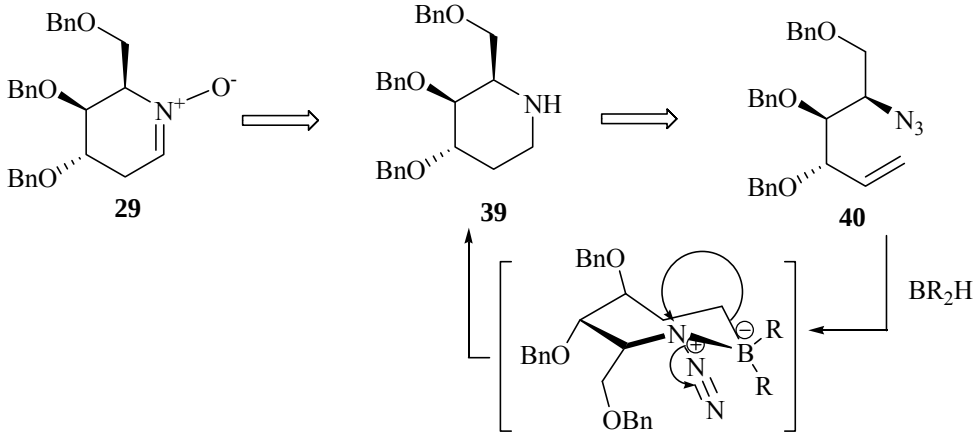
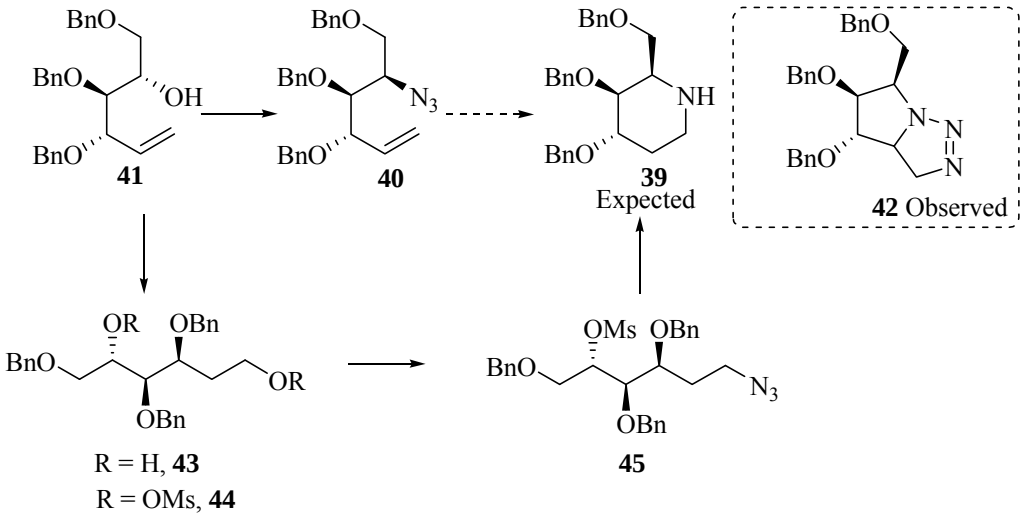


***Figure* 5:** *Alternative Strategy for Nitrone **29** and the key borane mediated piperidine ring construction from an azidoalkene*

However, compound **41** was prepared by one carbon Wittig homologation of lactol **6,** followed by mesylation and subsequent azidation with NaN_3 in DMF afforded the [3+2] cycloaddition product **42** exclusively.

***Scheme* 6**



To circumvent this problem, we followed an alternative approach for the synthesis of **39**. Accordingly hydroboration of olefin **41** gave diol **43**, which was subjected for a sequence of reactions: mesylation of diol and selective primary azidation to procure **45**. Reduction of azide under Staudinger condition provides the cyclised piperidine derivative **39**. As we successfully obtained the piperidine **39**, our next concern was the preparation of cyclic nitrone **29** and completing the total synthesis of Batzellasides. However, all the literature conditions for the oxidation of amine to nitrone fails in our hand may be due to the steric effect of the two bulkier cis substituentes in the six membered ring. This result stopped our way to the natural product.

In conclusion, a concise syntheses of (−)-radicamine A & B are described from L-arabinose based on cyclic sugar nitrone; the short and efficient synthesis of LAB1 and its epimer were also achieved.

CHAPTER II:

Construction of architecturally complex molecules from simple building blocks has emerged as a powerful tool in synthetic organic chemistry because of the increasing demand for molecules with unprecedented diversity. Designing effective routes to construct complex cyclic structures through organotransition-metal catalyzed reactions provides many attractive

possibilities, which by conventional procedures would need a large number of synthetic transformations. A great deal of focus has been directed towards sugar based molecular diversity as these molecules offer inherent rigidity and molecular asymmetry. In this context we have been interested to use Palladium based reactions on sugar alkenes and alkynes to generate the molecular diversity. This part of the thesis deals with the three different couplings on sugar alkynes.

Section 1: Pd mediated cycloisomerisation of sugar alkynals

Endocyclic enol lactones/lactols are versatile synthetic intermediates for organic synthesis and important structural elements of biologically active natural products. In conventional methods, these compounds were prepared by the cyclization of alkynoic acids under acidic conditions or by employing transition-metal complexes as catalysts. However, the utility of the acid-catalyzed process suffers from limited scope, drastic conditions, and poor selectivity. We were particularly interested in the Pd catalyzed C-C bond formation and cycloisomerization to obtain the corresponding endocyclic enol lactones/lactols from sugar templates. As recently, we have shown that the electronic effects in the alkyne, i.e., the presence of strong electron withdrawing or strong electron-donating groups influence mode of the cycloisomerization of sugar alkynol. Herein, we attempted to extend this methodology with sugar alkynals where one can anticipate the formation of fused bicyclic derivatives with predetermined stereochemistries (Figure 6).

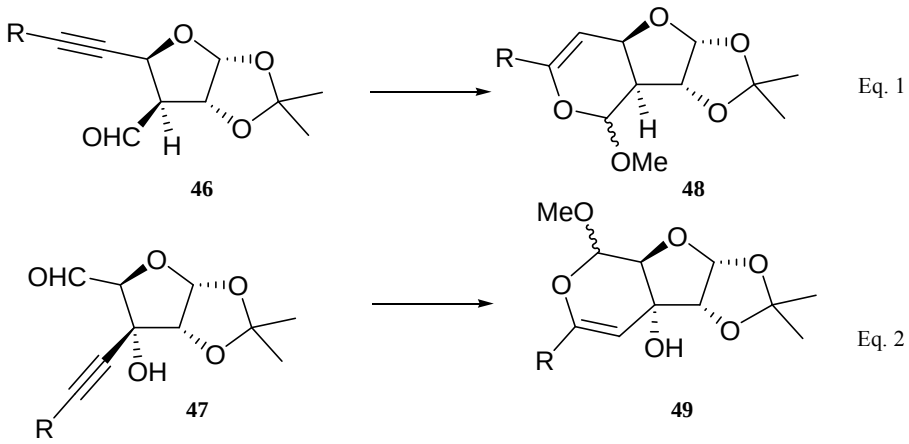
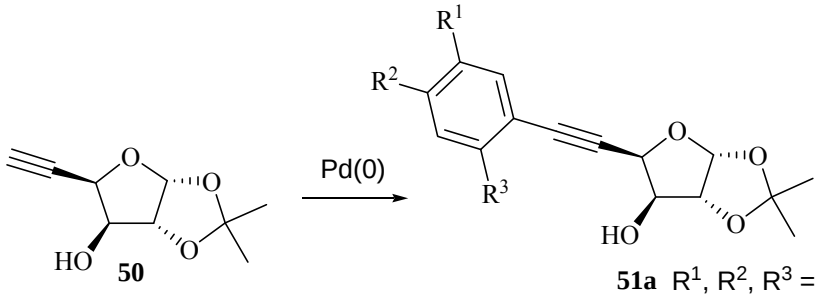


***Figure* 6:** *Proposed Pd mediated transformations on sugar alkynes*

For the preparation of substrate **46** for our intended cycloisomerization, we need to develop C-C bond formation reaction (Sonogashira coupling) on sugar derivatives. Our initial attempts to optimize the reaction conditions were carried out with simple iodobenzene and the alkyne **50**. After a careful examination of various reaction conditions, by changing reaction

temperature, reaction time, base, solvent, and amount of iodobenzene, we concluded that the best result for the intended Sonogashira reaction were obtained by using a piperidine as a solvent (acts as a base also) and conducting the reaction at room temperature in the presences of $Pd(PPh_3)_4$ (7.5 mol%). Later, we have generalized this methodology to prepare various disubstituted alkynes (Figure 7).

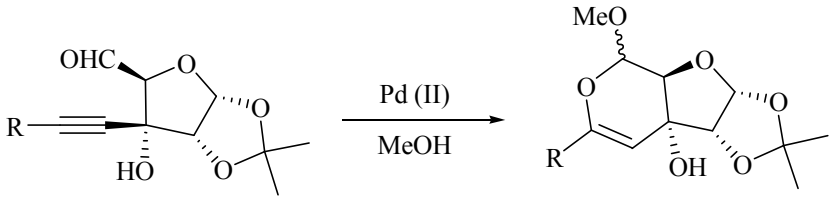


50

51a R^1, R^2, R^3 = H
51b R^1 , R^3 = H; R^2 = OMe
51c R^1 , R^2 = H; R^3 = CO_2Me
51d R^1 = NHAC, R^3 = H; R^2 = OMe
51e R^1 = OH, R^3 = H; R^2 = OMe

***Figure* 7:** *Two component Sonogashira coupling on Sugar alkynes*

After completing the C-C bond formation, we were unable to complete the formation of **46** due to undesired side reaction during the installation of formyl group in compound **46**. So, we turned our attention to substrates **47** which we made by using stereoselective nucleophilic addition of the lithiated salts of the corresponding terminal alkynes on the known 3-ulo derivative of glucose diacetone. The compounds **47a-d** were directly subjected to cycloisomerization by treatment with $Pd(OAc)_2$ (10% mmol), MeOH and maleic anhydride in dry 1,4-dioxan under Argon atmosphere to lead **52b-d**. Amongst four alkynals **47a-d**, only the terminal alkynal **47a**, the reaction led to a complex reactions mixture. In all other case, a diastereomixture of bicyclic derivatives were obtained in moderate to good yields.



47a R = H
47b R = Ph
47c R = C_5H_{11}
47d R = C_6H_{13}

52b R = Ph
52c R = C_5H_{11}
52d R = C_6H_{13}

***Figure* 8:** *Alkynal cycloisomerization*

Section 2: Three component Sonogashira-Suzuki-Miyaura coupling reaction on sugar alkynes

After being established the feasibility of the Sonogashira reaction on sugar alkynes under mild conditions, we next turned our attention to synthesize the trisubstituted olefins by a combination of Sonogashira and Suzuki-Miyaura reactions. Our strategy is funded upon the recent report by Larock *et al.* who used this type of one-pot three-component approach on simple alkynes. Following the reported conditions and using alkyne **50** and iodobenzene in common and 7 different boronic acids, we have successfully made various trisubstituted olefins. In general the intermolecular cross-coupling reaction of an aryl halide, an alkyne & an aryl boronic acid is highly regio- and stereoselective (Figure 9).

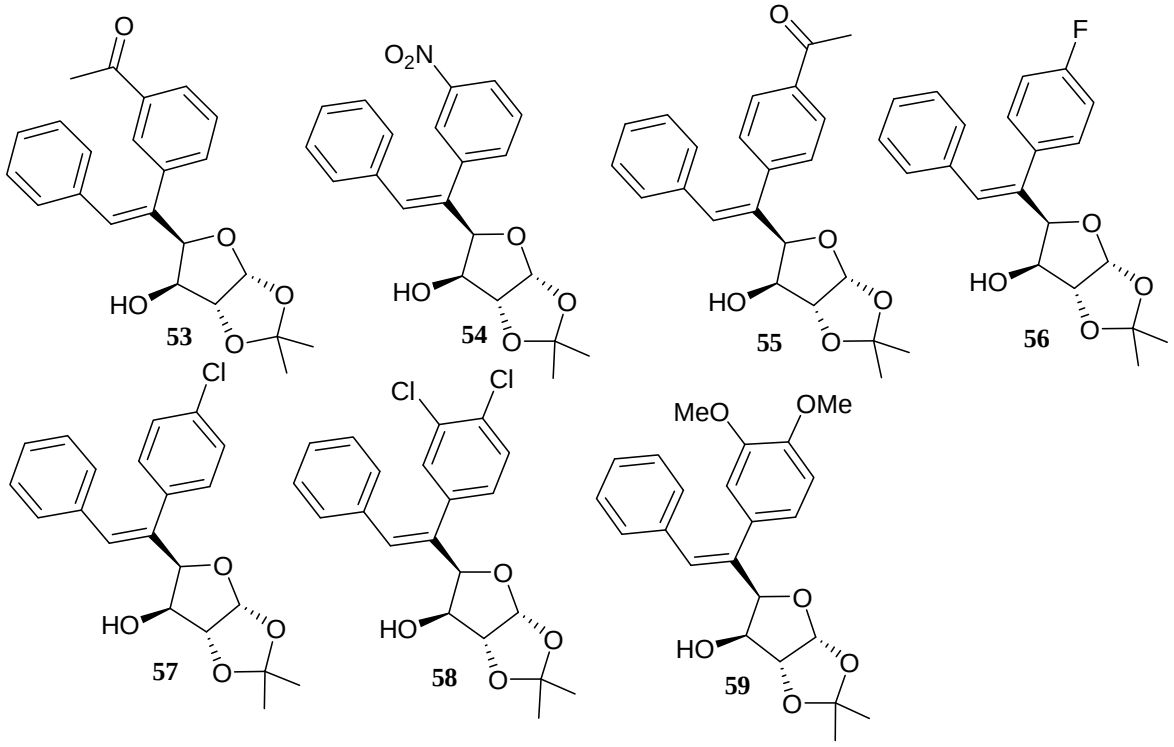


***Figure* 9:** *Three component coupling reactions with sugar alkyne* **50**

In conclusion, different Pd catalyzed methodologies for C-C bond formation in carbohydrates have been developed. These compounds are not only showing the similarity but also have potential as chiral building blocks for the synthesis of some important natural products. The further elaboration of these compounds in natural product synthesis and screening of some these intermediates for biological activity is under progress.

Appendix

Attempts towards the synthesis of Leustroducsin- B

The novel colony-stimulating factor (CSF) inducer Leustroducsin B (LSN-B, **60**), which was isolated from *Streptomyces platensis*, has been shown to have potent cytokine-inducing activities in clonal human bone marrow-derived stromal cell line KM-102 and in primary human bone marrow-derived stromal cells.

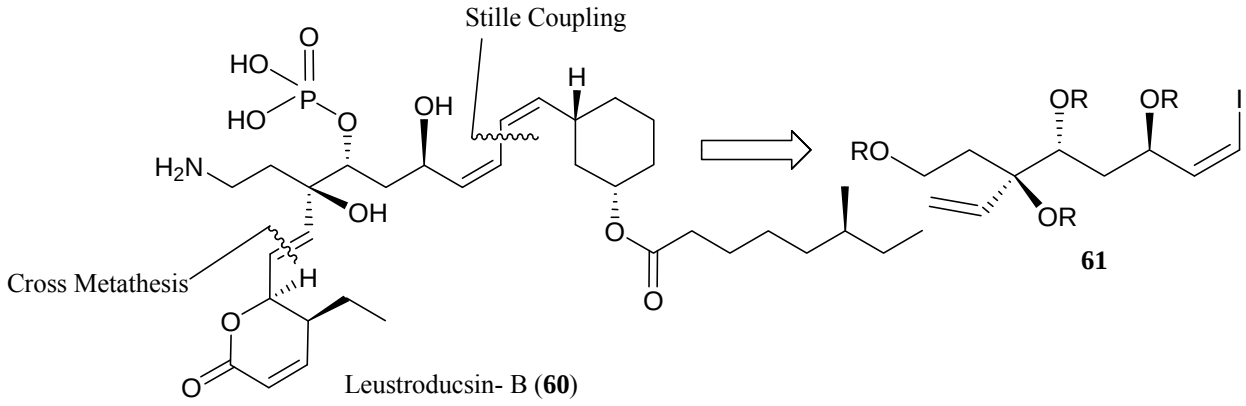
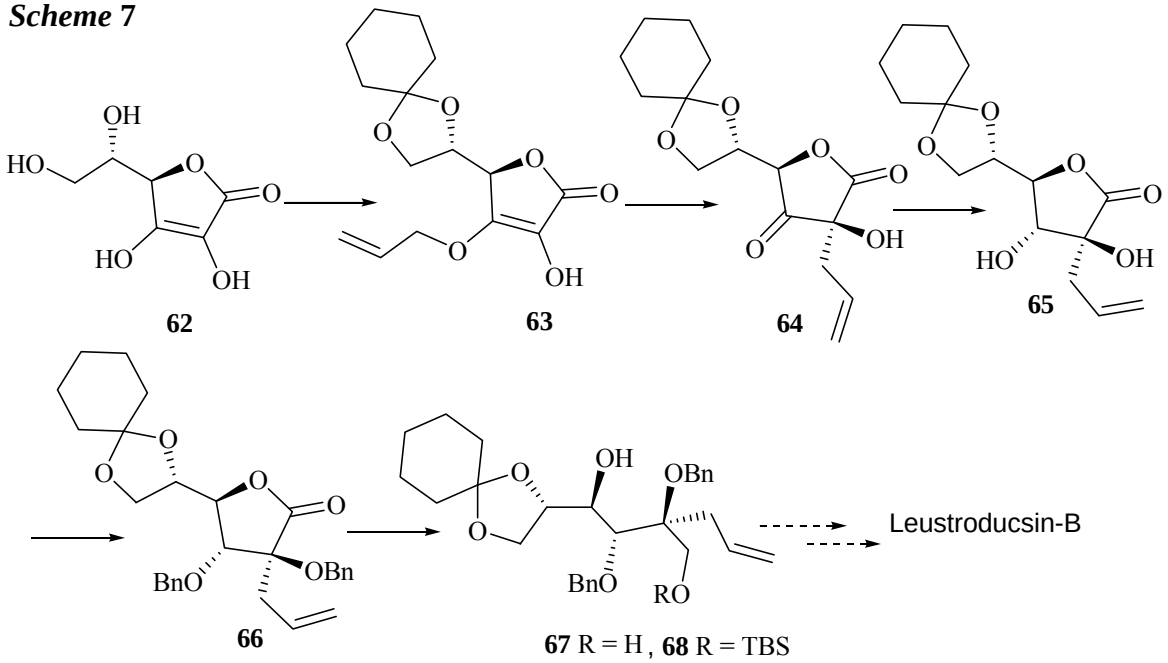


***Figure* 10**: *Retrosynthetic Approach for Leustroducsin B*

Further intensive investigation is necessary to develop LSN-B as a new drug substance for the treatment of various diseases because of its promising biological activity. However, it is restricted due to limited supply of the compound. Therefore chemical synthesis seems to be only way to provide large quantity of the material. Herein, we disclose our synthetic efforts towards C-C fragment (**61**) of LSN-B. According to our reterosynthetic analysis, we began our synthesis with β-keto lactone **64**, readily prepared in three steps from Vitamin-C by modifying literature procedures (Scheme 7). The keto group of **64** was selectively reduced with $NaBH_4$ in MeOH to give diol **65** whose X-ray analysis confirmed the absolute stereochemistry unambiguously. Protection of **65** afforded dibenzyl derivative **66** in good to moderate yield, which was subsequently reduced with $LiAlH_4$ in THF, to give **67**. The primary alcohol was selectively protected with *tert*-butyldimethylsilylchloride followed by Barton deoxygenation furnished the cyclised product with the allyl group, instead of the simple deoxygenation. The other reported procedures for deoxygenation were unsuccessful in our hand. Owing to failure in deoxygenation of secondary alcohol in the presence of allylic olefin, we changed our

strategy. The new strategy which involves the deoxygenation at the later stage of the synthesis after ozonolysis of double bond is in progress in our laboratory.

***Scheme* 7**



In conclusion, our efforts towards the synthesis of Leustroducsin-B is fruitful in obtaining synthetically more demanding L-galactono-γ-lactone derivative, a key intermediate precursor of Vitamin-C biosynthesis in plants. In continuation of this work, efforts are going on in our laboratory to accomplish the total synthesis of Leustroducsin-B and related natural products.

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

CHAPTER -I

TOTAL SYNTHESIS OF BIOLOGICALLY ACTIVE POLYHYDROXYLATED PYRROLIDINE AND PIPERIDINE ALKALOIDS

INTRODUCTION

The work described in this chapter of the thesis is concerned primarily with the synthetic study related to azasugars. The best-known activity of azasugars is that of inhibition of glycosidases. The introduction is divided into two part; the term glycoside, glycosidase, their mechanisms, glycosidase inhibitors and their medicinal importance are discussed in the first part. The second part deals with an overview of nitrone chemistry with emphasis on sugar nitrone; as we utilized this branch of synthetic chemistry for the preparation of azasugars.

PART I

Glycosides and Glycosidases[1]

Glycosides are compounds containing a carbohydrate and a noncarbohydrate residue in the same molecule. The carbohydrate residue is attached by an acetal linkage at carbon atom 1 to a noncarbohydrate residue or AGLYCONE. The nonsugar component is known as the AGLYCONE. The sugar component is called the GLYCONE. If the carbohydrate portion is glucose (**1**), the resulting compound is a GLUCOSIDE. An example is the methyl glucoside (**2**) formation when a solution of glucose in boiling methyl alcohol is treated with 0.5% HCl as a catalyst (Figure 1).

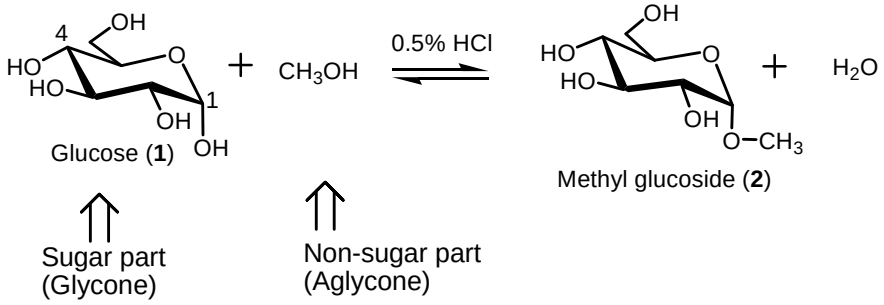
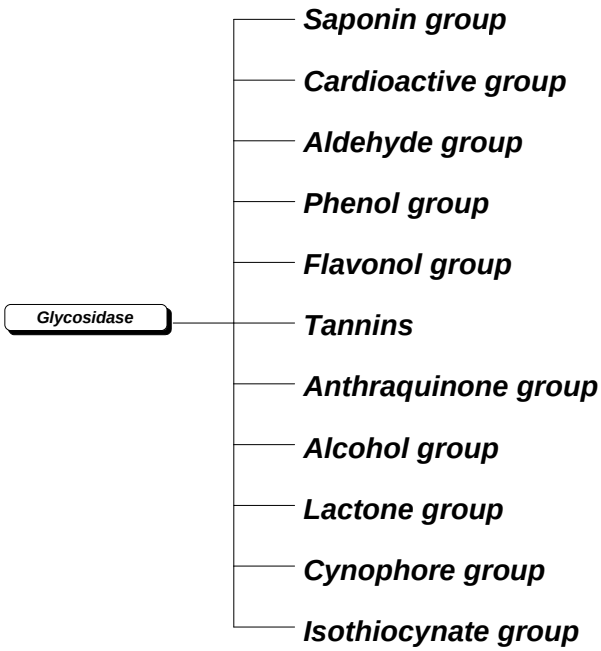


***Figure* 1:** *Glucoside formation*

The aglycone may be alkyl/aryl alcohol, glycerol, a sterol (steroid alcohols), a phenol, etc. An acetal has two ether functions at a single carbon atom. The glycosides can be classified on the basis of the chemical nature of the aglycone part as follows:



Glycosidases (also called glycoside hydrolases) catalyze the hydrolysis of the glycosidic linkage to generate two smaller sugars or (glycone and aglycone). They are extremely common enzymes with roles in nature including degradation of biomass such as cellulose and hemicellulose, in anti-bacterial defense strategies, in pathogenesis mechanisms and in normal cellular function.In particular, glycosidases and glycosyl transferases are ubiquitous macromolecules, which catalyze glycosyl group transfer reactions that assemble, trim and shape bioactive glycoprotein and glycolipid conjugates. Overall, these processes involve cleavage of the glycosidic bond linking to the anomeric carbon of the sugars with an oligo- or polysaccharide or a nucleoside diphosphate group. The liberated glycosyl group is further transferred to water (by glycosidases) or to some other nucleophilic acceptor (by transferases) (Figure 2).

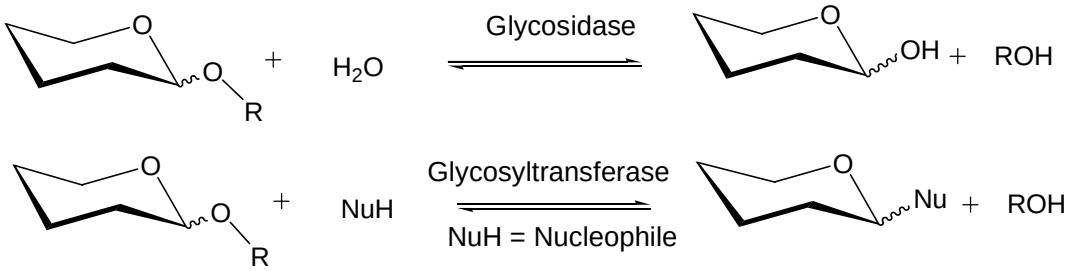


***Figure* 2:** *Glycosidase and glycosyl transferase*

Glycosidases have been classified according to

- The nature of the glycosidic atom as *O*-, *N*-, and *S*-glycosidases
- The ring size of the glycosyl donor as pyranosidases or furanosidases
- The anomeric configuration of the glycosyl donor as α-and β-glycosidases
- The relative configuration of the product with respect to the glycosyl donor as retaining and inverting glycosidases
- The "regioselectivity" in the processing of oligosaccharides as exo-glycosidases acting at a terminus of an oligosaccharide, and endo-glycosidases, acting within an oligosaccharide chain
- The trajectory of protonation by the catalytic acid as *syn*- or *anti*-protonators
- The amino acid sequence (*vide infra*).

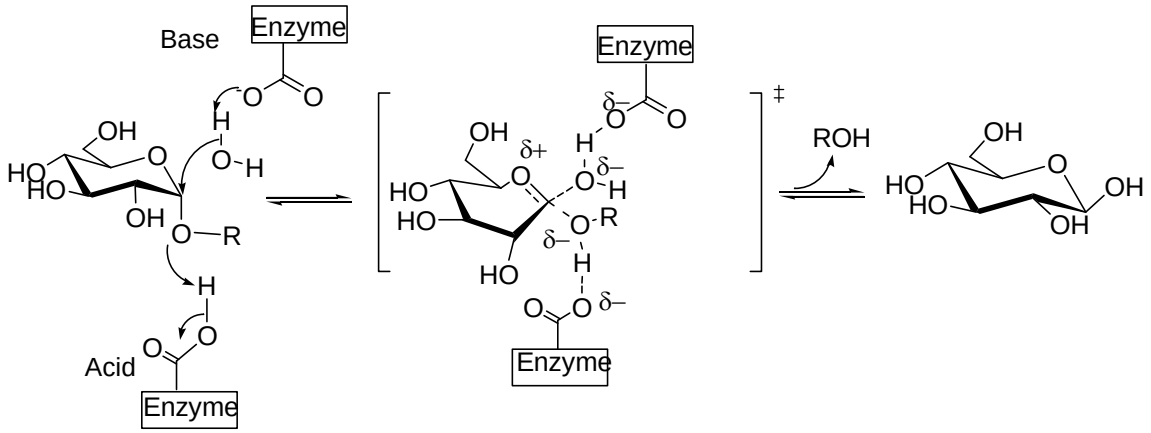
Uses of Glycosidases

Glycosidases are indispensable in the normal functioning of most organisms. They are involved in the breakdown of food carbohydrates[2], in malignant transformation and metastasis[3], viral and bacterial infection[4], the processing of eukaryotic glycoproteins[5] and the catabolism of polysaccharides and glycoconjugates[4b]. The importance of glycosidases in biological processes is reflected by a number of diseases, which result from the lack or dysfunction of a glycosidase. The application of naturally occurring glycosidases in enzyme replacement therapy; in textile, food, and pulp processing; and as catalysts in oligosaccharide synthesis has encouraged the engineering of proteins with improved catalytic properties and stability.

Reaction Mechanism of Glycosidases[6]

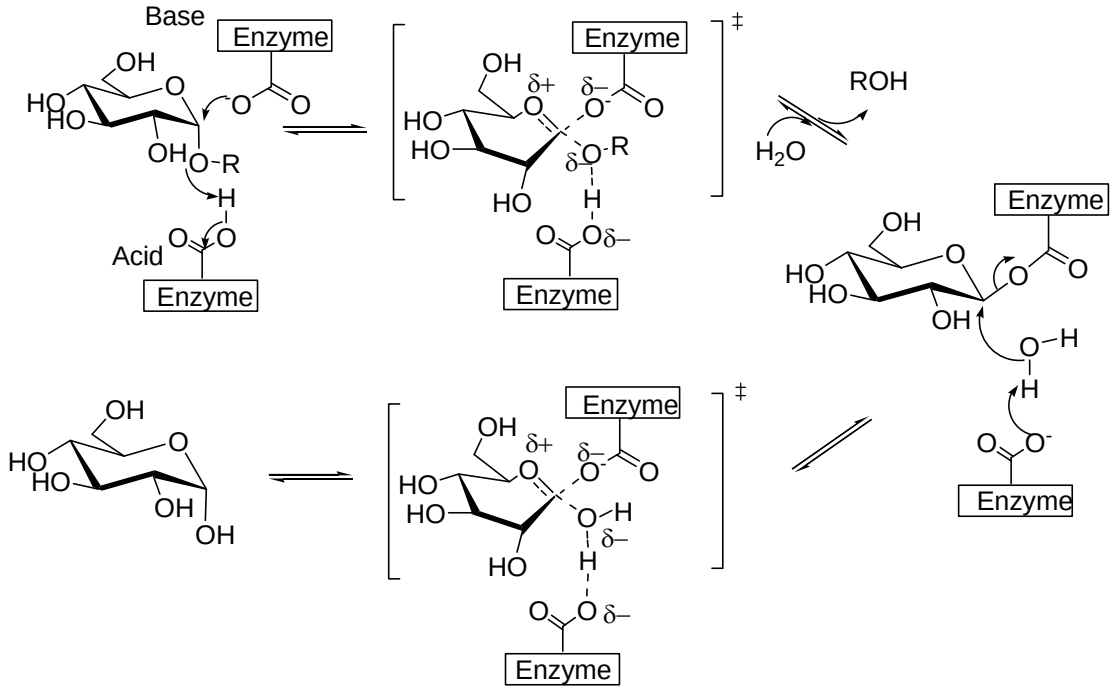
Inverting Glycosidases

Inverting glycosidase utilize two enzymic residues, typically carboxylate residues, that act as acid and base respectively, as shown below for a α-glucosidase.



Retaining Glycosidases

Retaining glycosidases operate through a two-step mechanism, with each step resulting in inversion, for a net retention of stereochemistry.



Glycosidase inhibitors[7-10]

Glycosidase inhibitors are molecules that bind to Glycosidase (enzymes) and decrease their activity. The binding of an inhibitor can stop a substrate from entering the enzyme's active site and/or hinder the enzyme from catalyzing its reaction (Figure 3). Since blocking an enzyme's activity can kill a pathogen or correct a metabolic imbalance, many drugs are enzyme inhibitors. They are also used as herbicides and pesticides.

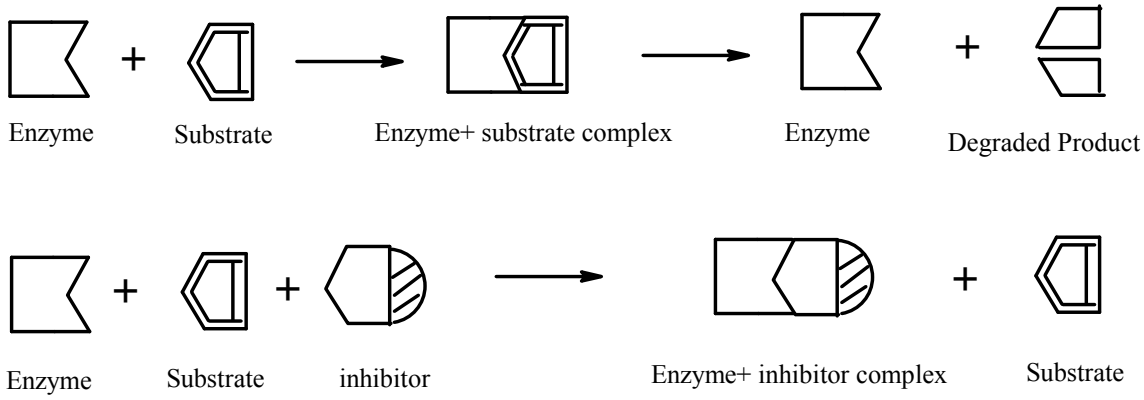
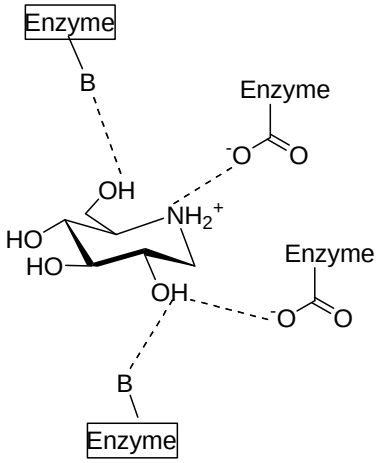


***Figure* 3:** *Inhibitor mimicking the enzyme*

In theory, the best inhibitors should have features similar to those of the glycosyl cation and match the electronic and steric requirements necessary to bind in the enzyme active site.



*F**igure* 4:** *Assumed binding of deoxynojirimycin to enzyme*

Indeed this situation pertains with nojirimycine analogues in some aspects, which can mimic the charge and the positioning of hydroxyl groups on the glycosyl cation. These inhibitors bind to the enzyme by forming ion pair between a protonated inhibitor and an anionic group present in the active site of the enzyme (see Figure 4)

A wide variety of structural motifs characterize glycosidase inhibitors. Prominent amongst them are:

(a) The nitrogen heterocycles incorporating four to seven membered rings [e.g. 2,5-dideoxy-2,5-imino-D-mannitol i.e. 1,3-dideoxy-1, 3-imino-L-xylitol (**8**), DMDP (**3)**, nojirimycin (**4**), (3,4,5,6)-tetrahydroxyazepane (**9**) derivative respectively] as well as

bicyclic like pyrrolizidines [e.g. Alexine (**7**)], indolizidines [e.g. Swainosine (**6**)] and nortropanes [e.g. calystegine (**5**)] (Figure 5).

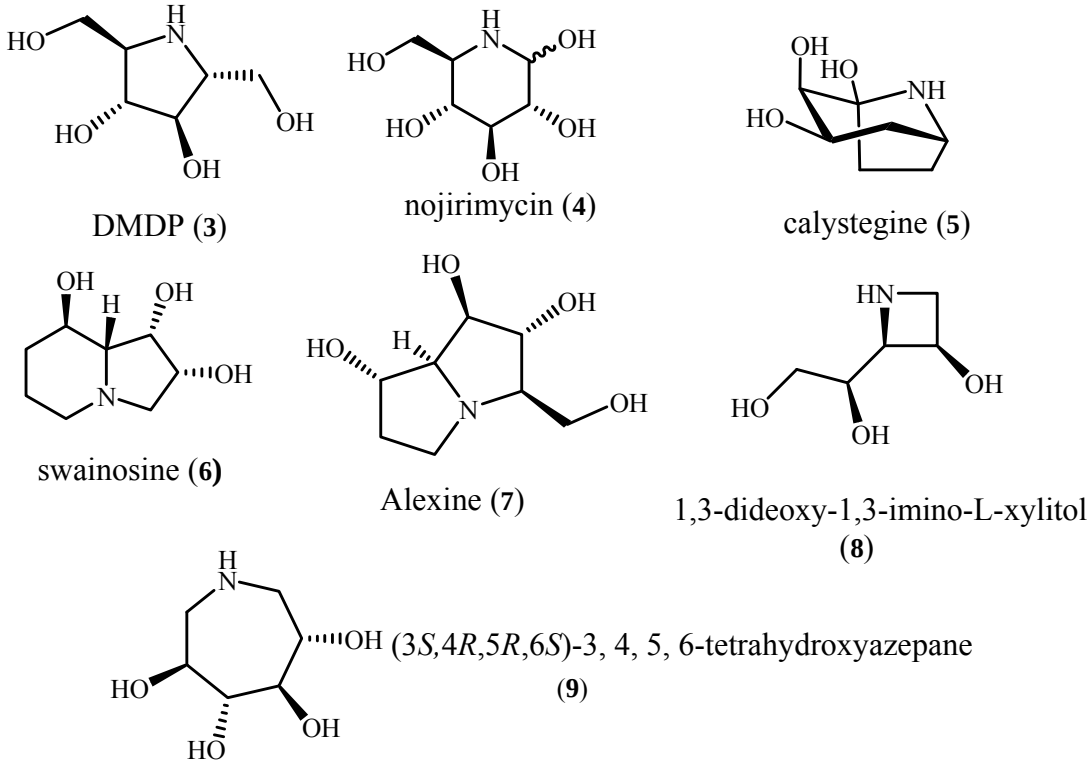


***Figure* 5:** *Representative examples of 4 to7 membered azasugars*

(b) The aminocyclitols like Acarbose (**10**), Trehazolin (**11**), Mannostatins (**12**) and Allosamidins (**13**) (Figure 6).

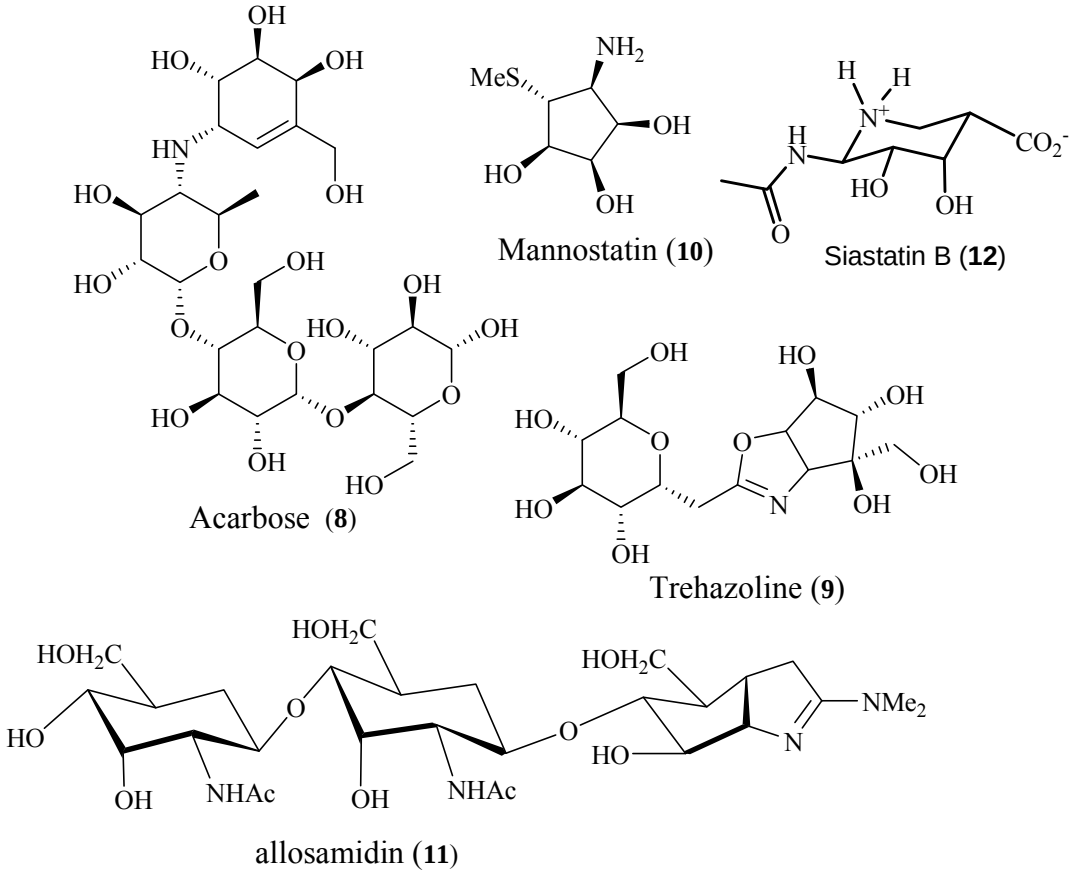


***Figure* 6**: *Aminocyclitols*

(c) Entities incorporating nitrogen in more than one position, including the one in the ring, e.g.; Nagstatins, Siastatins, etc.

After the discovery of nojirimycin, the first azasugars (polyhydroxylated nitrogen heterocycles in which the ring *O*-atom of a carbohydrate is replaced by nitrogen) alkaloid a myriad of naturally occurring azasugars has been isolated. These "sugar-shaped alkaloids" are widespread in plants and microorganisms and are believed to bind to the active site of the glycosidases by closely mimicking the charge and shape of the transition state of the glycosidic cleavage reaction.

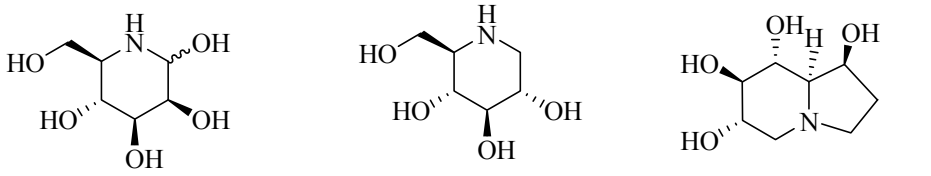
Biological significance of glycosidase inhibitors:

These compounds, which are frequently inhibitors of carbohydrate-processing enzymes, have the potential for use in wide range potential therapeutic strategies including the treatment of diabetes[11], cancer[12], viral infections including HIV[13], lysosomal storage diseases like Gaucher's disease[14] and as inhibitors of the growth of parasitic protozoa[15]. As a

result, the synthesis of polyhydroxylated pyrrolidine and piperidine has attracted a great deal of attention in recent years.

Cancer

Cancer has been one of the serious diseases for many years. This class of disease or disorders characterized by uncontrolled division of cells and the ability to metastasis (spread of cancer from its primary site to other places in the body). Cancer affects people at all ages and it is one of the principal causes of death in developed countries. Though there are many methods are available today to cure the cancer, chemotherapy is the best and can be used at any stage of the disease. It has been observed that the process of the metastasis can be interrupted by the addition of some glycosidase inhibitors.



mannonojirimycin (**15**) deoxynojirimycin (**16**) Castanospermine (**17**)

***Figure* 7:** *Azasugars as anticancer agents*

Although a number of azasugars have been reported to show anticancer activity such as, nojirimycin (**4**), mannonojirimycin (**15**), deoxynojirimycin (**16**) and Swainosine (**6**), research has concentrated on developing Swainosine as a candidate for the management of human malignancies. Clinical trials in humans with very advanced malignancies showed that lysosomal α-mannosidase and Golgi mannosidase II were inhibited and some improvement in clinical status occurred. It inhibits the growth of tumor cells and prevents the dissemination of malignant cells from primary tumor to secondary sites. There is considerable evidence that Swainosine enhances the natural antitumor defense of the body. Castanospermine (**17**) has also been reported to suppress the metastasis in the mice but experiments with this alkaloid have not been as extensive as those with Swainosine.

Diabetes

The main component of human food the carbohydrates, composed of more than 80% of starch and sucrose. The organism utilizes carbohydrates after splitting into

intestinal track by using enzymes that regulate and retard carbohydrate digestion. Glycosidases catalyze the hydrolysis of complex saccharides and convert non-absorbable carbohydrates into absorbable sugars. The rapid action of these enzymes leads to acute undesirable elevations in blood glucose in diabetes.

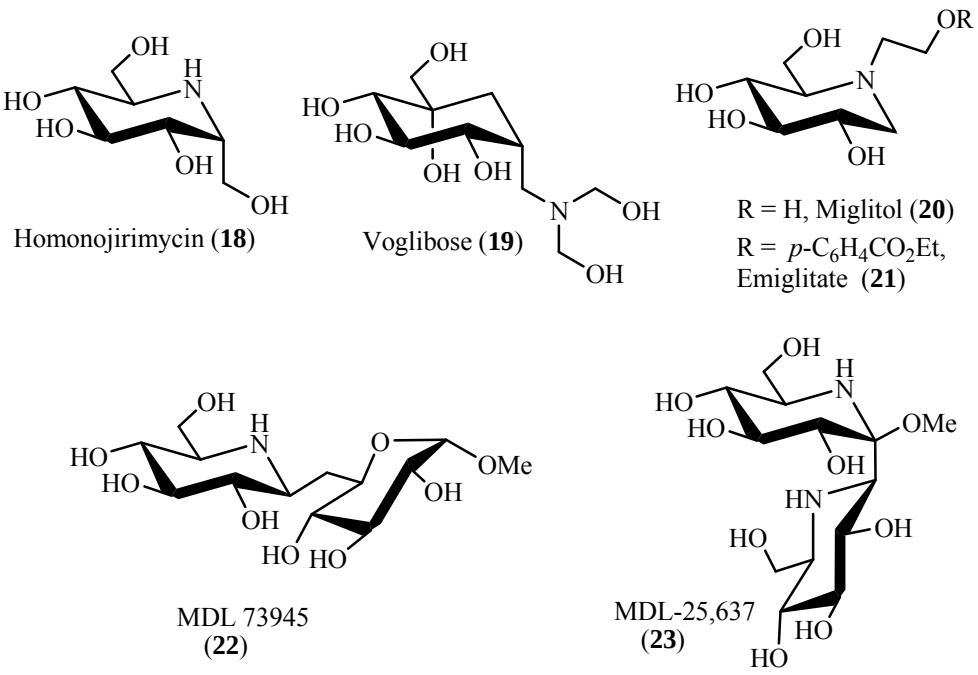


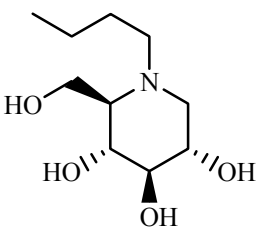
***Figure* 8:** *Azasugars as antdiabetic agents*

Acarbose (**10**), a naturally occurring glycosidase inhibitor, has been used as an anti-diabetic agent. It has been also observed that azasugars are active inhibitors in the treatment of diabetes by suppressing the rise of glucose level in blood. In China, mulberry leaves have been used traditionally as a medicine to cure diabetes. As the mulberry is the natural source of the DNJ able to suppress the rise in blood glucose. The isolation of DNJ prompted to develop new synthetic analogues of DNJ. Though the *in vitro* activity of deoxynojirimycin (DNJ) is good but its efficacy *in vivo* is only moderate. Therefore a myriad of DNJ derivatives have been prepared to increase the *in vivo* activity. Apart from nojirimycin, azasugars like homonojirimycin also prevents the initial formation of glucose in the body. The efforts of preparation of azasugars derivatives lead to many useful antidiabetic agents. The structural modification of deoxynojirimycin, the *N*-hydroxyethyl derivative, Miglitol (**20**) commercialized by Bayer, has been clinically evaluated and released as an antidiabetic drug in insulin and non-insulin dependent

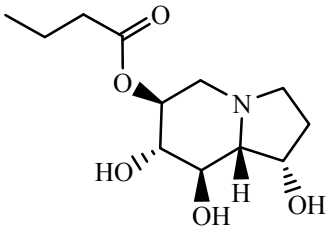
diabetes. Miglitol are used as a substitute for Acarbose. Another glycosidase inhibitor, voglibose (**19**), a synthetic derivative of valiolamine is also being marketed as an anti-diabetic. Moreover MDL-25637 (**23**), emiglitate (**21**) and MDL 73945 (**22**) etc. are also found active against diabetis. The compounds (Figure 8) effectively reduce postprandial elevation of blood glucose and plasma insulin in animals in loading tests with starch and sucrose.

AIDS

Acquired immunodeficiency syndrome (AIDS) is one of the most fatal diseases of the today's human life. The efforts from all over the world to develop the good chemotherapy for AIDS is not completely successful so far. As a consequence, a great effort is being made to develop drugs and vaccines to combat AIDS. The naturally occurring azasugars castanospermine (**17**) is α-glucosidase I inhibitor with marked antiviral activity against a number of viruses.



N-butyl bdeoxy-nojirimycin (**24**)



celgosivir (**25**)

***Figure* 9 :** *Azasugars as anti* HIV *agents*

Unfortunately, the agent also inhibits intestinal sucrases and causes osmotic diarrhea. In contrast, celgosivir the 6-*O*-butanoyl derivative of Castanospermine is a relatively inactive inhibitor of intestinal sucrose and appears to be nontoxic to the gastrointestinal tract. It possesses antiviral activity that is 30-fold greater than the parent compound, its active metabolite. Celgosivir (**25**) has displayed potent antiviral activity *in vitro* and *in vivo* against several viruses, including HIV-1, herpes simplex virus (HSV), bovine viral diarrhea virus (BVDV) and HCV, and the agent was chosen for further development as a treatment for HCV infection. Castanospermine and 1-deoxynojirimycin have been shown to be capable of suppressing the infectivity of a number of retroviruses, including the HIV responsible for AIDS. This effect is a consequence of disruption of

glycoprotein processing enzyme resulting in the changes of the structure of the glycoprotein coat of the virus. Cellular recognition of the host is, thus, prevented and syncytum formation is suppressed. To reduce water-solubility (causative of rapid excretion), 6-O-butyryl Castanospermine and *N*-butyl-deoxynojirimycin have been synthesized and both these compounds have undergone clinical trials against AIDS in humans, either alone or in combination with AZT a α-glucosidase inhibitors, such as DNJ (**16**), *N*-butyl-DNJ (**24**, *n*-Bu-DNJ), Castanospermine (**17**) and celgosivir (**25**) are potent inhibitors of HIV replication and HIV mediated syncytum formation in *vitro*.

Lysosomal Storage diseases

Lysosomes are subcellular organelles responsible for the physiologic turnover of cell constituents containing catabolic enzymes requiring a low optimum pH to function. Lysosomal storage diseases describe a heritable group of heterogeneous human disorders characterized by the accumulation of undigested macromolecules intralysosomally, resulting in an increase in the size and number of these organelles and ultimately in cellular dysfunction and clinical abnormalities. Lysosomal storage diseases are generally classified by the accumulated substrate and they include sphingolipidoses, glycoproteinoses, mucolipidoses, mucopolysaccharidoses (MPSs), and others. No effective treatment of this disorder is available at present. Glycosidase inhibitors are also showing tremendous promise as a new therapeutics for lysosomal storage diseases like Gaucher's disease and Fabry disease.

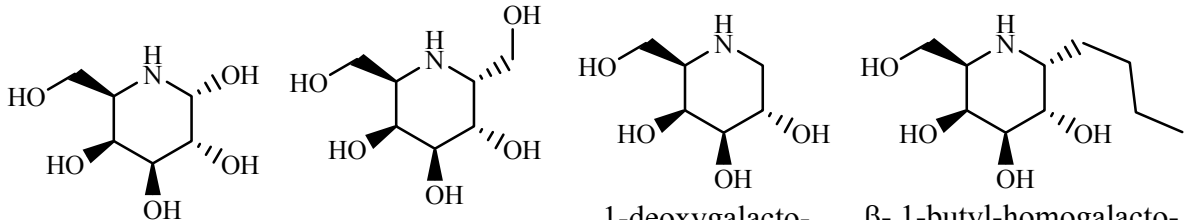


***Figure* 10 :** *Inhibitors effective against lysosomal storage diseases*

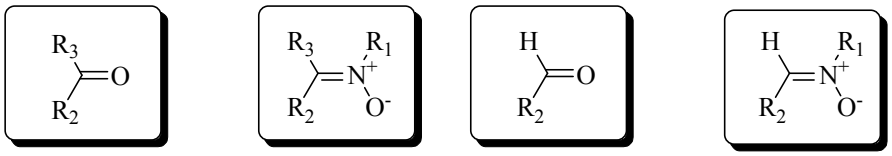
In normal cells, there is balance between the degradation of glycosphingolipids (GLSs) in the lysosomal and their biosynthesis in the ER/Golgi system. In a lysosomal storage disease cell, enzyme activity in the lysosomal cell is so low that GLSs accumulate. Thus, drugs that could

regulate the biosynthesis of GLSs to concentration that fits well in the residual enzymatic activity could prevent storage. Fabry disease is caused by deficiency of human lysosomal α-galactosidase A (α-Gal A), resulting in a renal failure along with premature myocardial infarction and strokes. Fan *et al.* demonstrated that DGJ (**28**) inhibits α-galalctosidase A in a competitive manner, effectively enhanced the mutant enzyme activity in lymphoblasts established from Fabry patients [α-HGJ (**27**) and β-1-*C*-butyl-DGJ (**29**) also showed potent inhibition of α-Gal A] . In order to establish the concept of using competitive inhibitors as specific chemical chaperones, a number of naturally occurring and chemically synthesized DGJ derivatives were tested for intracellular enhancement of mutant α-galactosidase. This strategy can be extensively applicable to the lysosomal storage diseases.

PART II

NITRONES

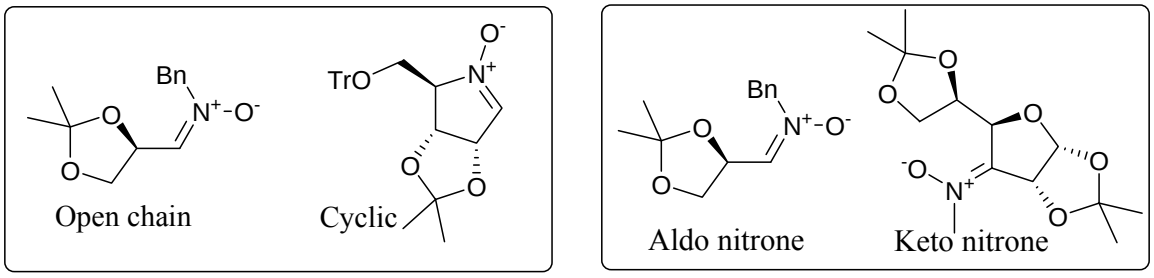
The first nitrone compound was reported by Beckmann in 1890[16]. The word nitrone (azomethine oxide) is a shortening of the word "Nitrogen-Ketones"was suggested by Pfeiffer[17]. The name and the structure of the nitrones clearly indicate their similarity with the carbonyl compounds. Therefore, they undergo all reactions that carbonyl compounds undergo except spin trapping[18] and 1, 3–dipolar cycloaddition reactions.[19] The nitrones are reviewed many times[20-22].

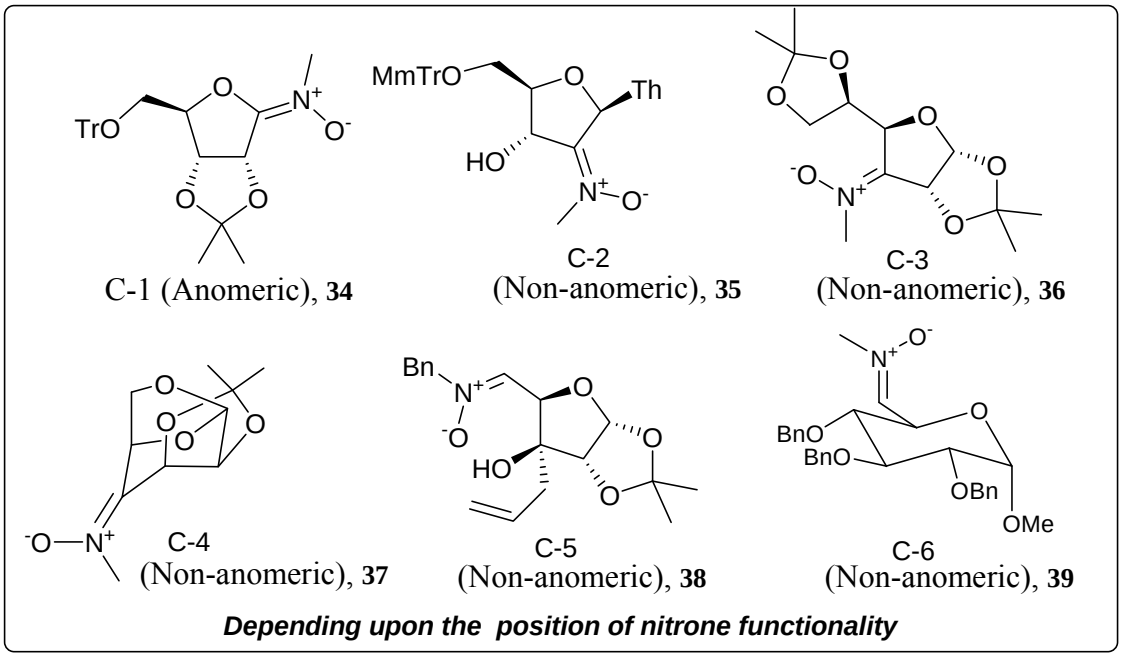


This introduction will be confined to the synthetic methods for sugar nitrones and some of their reactions.

SUGAR NITRONES

The first sugar nitrone was reported in 1972 by Mihaly *et al.*,[23] then Vasella group[24] explored the sugar nitrone chemistry followed by many synthetic efforts appeared in the literature in the last decade[25-29].Carbohydrate derived nitrones can be classified by using different criteria as follows:





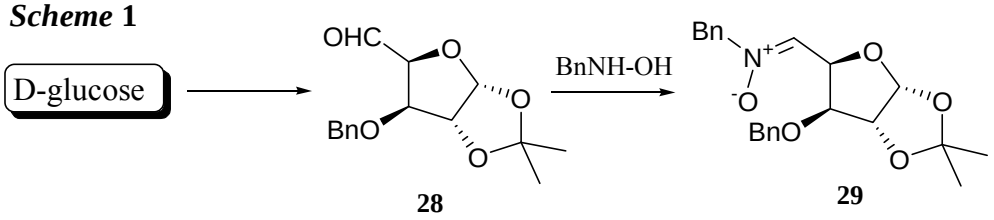
For the sake of simplicity in this review, we divided the sugar nitrone into two broad categories like open chain nitrone and cyclic nitrone.

Synthesis of open chain sugar nitrones

Several methods exist for the preparation of sugar nitrones, these include the condensation of sugar aldehydes or ketones with *N*-substituted hydroxyl amine, *N*-alkylation of oximes, oxidations of *N, N*-disubstituted hydroxyl amines, imines and amines and the zinc mediated reduction of nitroalkanes and nitroarenes, in the presence of aldehydes, etc. But the first few methods have been found most useful for the formation of sugar nitrone and are therefore discussed here in more detail.

(a) **Synthesis of open chain sugar nitrone by condensation of sugar carbonyls with *N*-substituted hydroxylamine:** The treatment of sugar aldehyde or ketones with *N*-substituted hydroxylamine affords the required nitrones. This is the most versatile method to carbohydrate-derived nitrones in which the aldehydes react at ambient temperature whilst ketone sometimes requires heating or longer reaction time. An illustrative example is the formation of glucose derived sugar nitrone **41** reported by Dhavale *et al.*[30] and used for the synthesis of azasugars (Scheme 1).

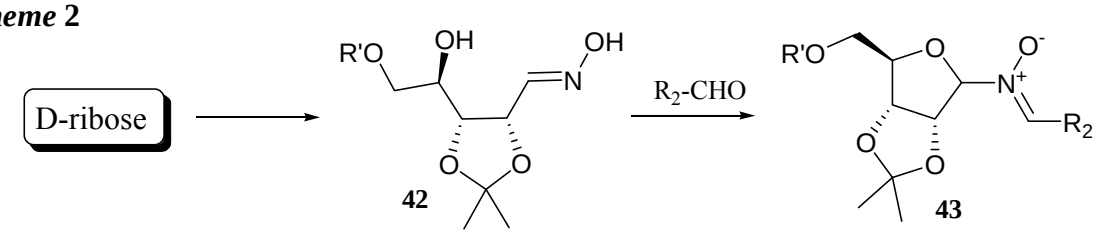
***Scheme* 1**



28 **29**

(b) **Synthesis of open chain sugar nitrone by condensation of carbonyl compounds with sugar based oximes :** Alternatively nitrones can be formed by using two-step sequences like the formation sugar oxime in the first step followed by treatment with carbonyl compounds. One of the advantages of this approach is that, one can incorporate variety of carbonyl moieties in sugar oxime. e.g. D- ribose derived oxime **42** condensed with aldehyde R_2-CHO to afford the open chain sugar nitrone **43**[24b] (Scheme 2).

***Scheme* 2**

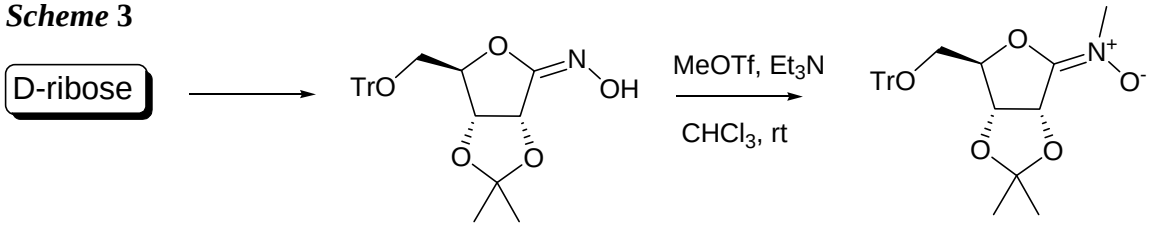


42 **43**

(c) **Synthesis of open chain sugar nitrone by alkylation of sugar based oximes:**

The large number of alkylating agents likes alkyl halides, epoxides, suitably placed alkenes, alkyl triflates, alkyl sulphonates, etc. have been used for the preparation of sugar nitrones. The more nucleophilic character of nitrogen in the oxime than oxygen favors the formation of nitrone for aldehyde derived sugar oxime whereas the ketone derived sugar oxime resulted into *O*-alkylation. e.g. The *N*-methylation of D-ribose derived oxime **44** by using MeOTf afforded the open chain nitrone **45**[31] (Scheme 3).

***Scheme* 3**



44 **45**

(d) **Synthesis of open chain sugar nitrone by 1, 3-azaprotiocyclotransfer (1, 3-APT)**

Process of sugar oximes: Ochiai *et al.*[32] in 1967 reported the isoxazolidine formation from oxime and by using two equivalents of alkenes. The first equivalent acts as a Michael acceptor, alkylating the nitrogen of oxime to afford the nitrone and the second equivalent of alkene then undergoes 1,3-dipolar cycloaddition (1,2-DC) to lead oxazolidine. Grigg has proposed common mechanism for the first step[33], described it as a 1,3-azaprotiocyclotransfer (1,3-APT) for reaction of oxime with alkenes (Figure 11). For example, D-ribose derived oxime (**44**) after 1,3-APT process with

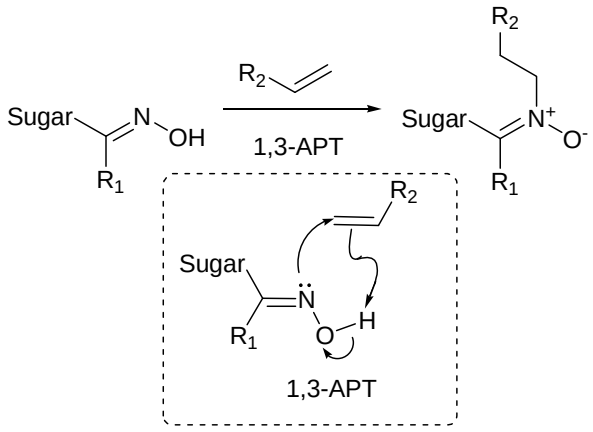
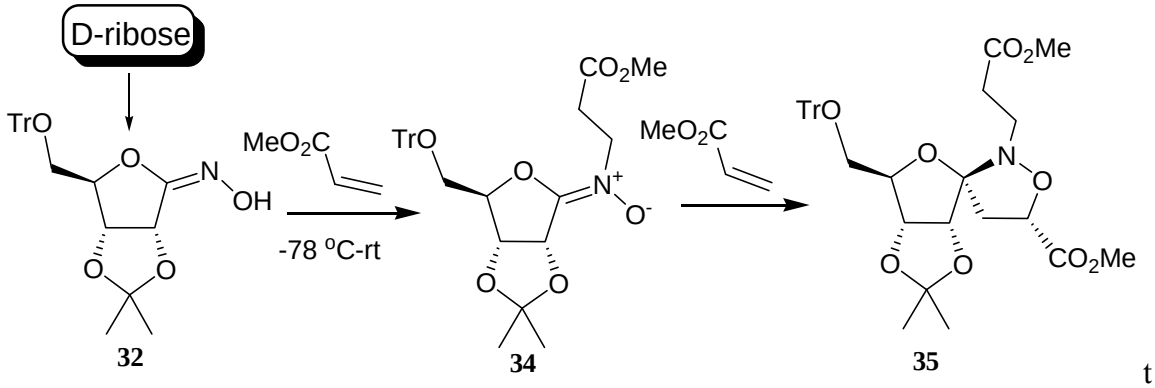


***Figure* 11:** *1, 3-APT process and mechanism proposed by Grigg*

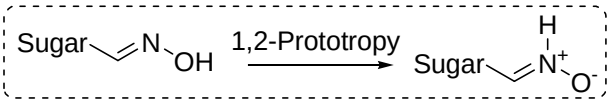
***Scheme* 4**



t

he first equivalent of methyl acrylate generates nitrone **46**. The second mole of methyl acrylate then adds with the nitrone to afford the cycloadduct **47** (Scheme 4)**.**

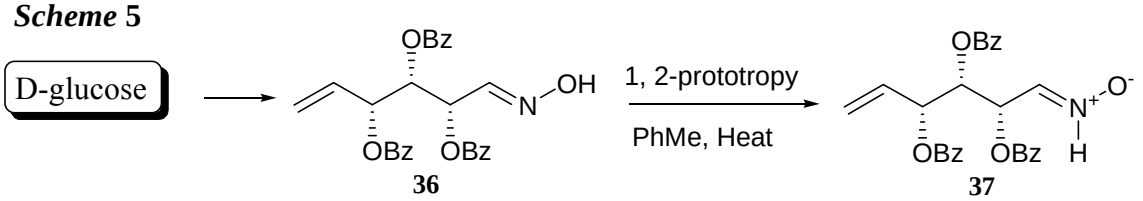
e) **Synthesis of open chain sugar nitrone by 1,2-prototropic shift of sugar oximes:**



The sugar oximes can undergoes proton transfer from *O* to *N* (1, 2-prprototropy) to afford nitrone. Moutel and Shipman[34]

derived the nitrone **49** from D-glucose by 1, 2-Protropic shift of oxime **48** as the key reaction for the synthesis of aminocyclopentitols (Scheme 5).

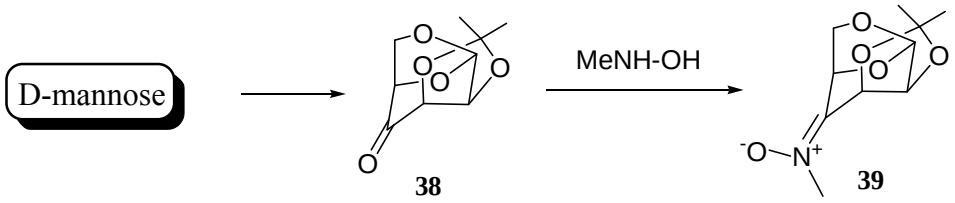
***Scheme* 5**



Synthesis of cyclic sugar nitrones

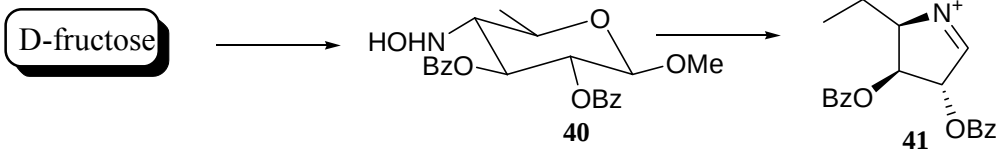
(a) **Synthesis of cyclic sugar nitrone by condensation with *N*-substituted hydroxyl amine:** There are only few reports so far for the synthesis of carbohydrate-derived ketonitrones e.g. Alonso *et al.*[35] have described the formation of the carbohydrate derived ketonitrones (**51**) *via* reaction of *N*-methylhydroxyl amine with 4-oxomannopyranose **50** (scheme 6).

***Scheme* 6**



(b) **Synthesis of cyclic sugar nitrone by intramolecular condensation of sugar hydroxyl amine with carbonyl compounds:** The synthesis of cyclic sugar nitrone has been reported by the intramolecular condensation of the hydroxylamine with aldehyde or ketone functionality. e.g The hydroxyl amine **52,** prepared in sex steps from fructose, has been used for the generation of cyclic sugar nitrone **53** (Scheme 7)[36]**.**

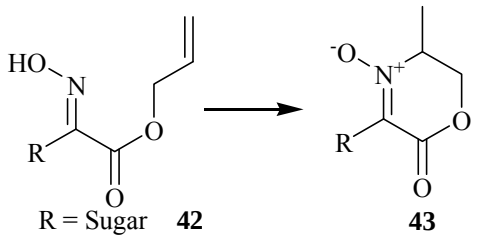
***Scheme* 7**



(c) **Synthesis of cyclic sugar nitrone by 1,3-azaprotiocyclotransfer (1,3-APT) processes of sugar oximes:** The reaction of sugar oxime with alkenes, allenes, and alkynes generates cyclic sugar nitrone [by (1,3-APT) intramolecular process] e.g.

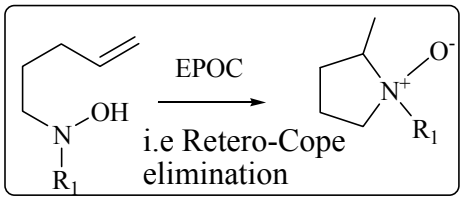
Intramolecular cycloaddition reaction of oxime **54** gives nitrone **55** (Scheme 8)**.**

***Scheme* 8**



(d) **Synthesis of cyclic sugar nitrone by EPOC process of sugar hydroxylamine:**

House *et al.* [37] in 1976 reported the addition of hydroxylamine to alkenes and alkynes to generate nitrones as shown in the following figure. The reaction proceeds by retero-Cope[38-40] elimination or "EPOC" the name derived from the inverse of "COPE".



<u>Reactions of sugar nitrones and their applications in the total synthesis</u>

With the wealth of sugar-derived nitrone in the literature, we have sought to arrange this survey according to the reaction types (e.g. 1, 3-dipolar cycloaddition reactions, nucleophilic reactions, etc.) Some of the reactions cover a broad range and we have collected some of the most significant reports in which the major aim of the work is to characterize novel sugar nitrone reactions

❖ **1, 3-dipolar cycloaddition:**

The most sugar-derived nitrones undergoes 1, 3-dipolar cycloaddition (DC)[19] reaction with alkene dipolarophiles to lead isoxazolidenes (Figure 12). The other multiply bonded dipolarophiles systems have been used (Alkynes, allenes, isocynates, nitriles, thiocarbonyls, etc.).The cycloadduct isoxazolidine contains up to three new chiral centres and the highly ordered transition states often allows the regio- and stereochemical preference based on steric and electronic factor as well as frontier molecular orbital (FMO) theory of a given sugar nitrone to be predicted. Isoxazolidines regarded as the synthetic equivalents of 1,3-aminoalcohol, which is the

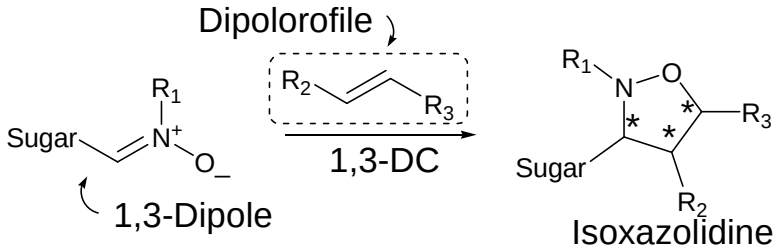


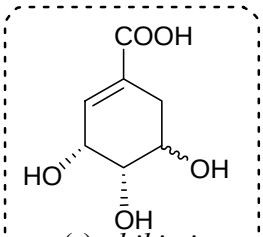
***Figure* 12:** *1,3-DC giving Isoxazolidine*

essential part of many natural products, particularly alkaloids, amino acids and amino sugars. The 1,3-dipolar cycloaddition is the concerted and [4π+2π] suprafacial process. In this reaction nitrone and alkene approaches each other in either of two possible regiochemical senses and in an *endo*-or *exo*-fashion, the four possible transition states giving rise to two pairs of regioisomeric and diastereoisomeric products. There have been many reports regarding regioselectivity and stereoselectivbity[41], in both intermolecular and intramolecular versions. In 1972 Tronchet reported the first example of intramolecular 1,3-dipolar cycloaddition[23] by using the sugar nitrone. Since then many researchers investigated the intramolecular 1,3- dipolar reactions of sugar nitrones.[42-44]

❖ **Intramolecular 1,3-dipolar cycloaddition:**

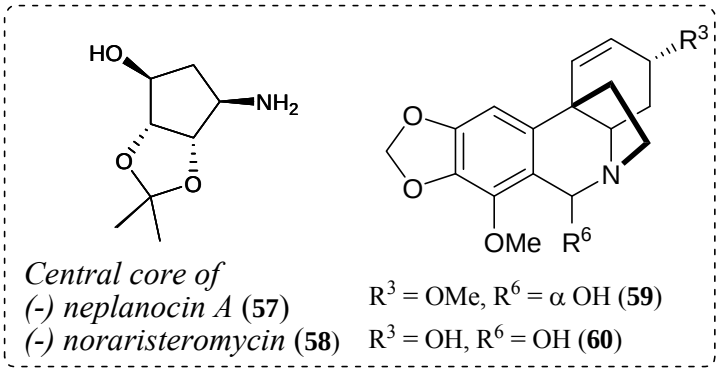
The *intramolecular nitrone- alkene cycloaddition* (INAC) method introduced by Heaney [45] or Padwa and Norman[46] used for sugar nitrones and large number of natural products has been synthesized by using this tool. The intramolecular 1,3-dipolar cycloaddition reactions by using sugar derived nitrones have several advantages including its high distereoselectivity than those of intermolecular variant, because the flexibility of the reactant is much more restricted and due to entropy factor, the activation barrier for this reaction is lower, allowing reactions at lower temperature and the use of dipoles & dipolarophiles of lower reactivity.

The intramolecular 1,3-dipolar cycloaddition reactions of sugar derived nitrone allowed the synthesis of a variety of natural products and related compounds including alkaloides,[47] oxepanes,[48] nucleosides,[49] carbapenems,[50] enzyme inhibitors,[51] vitamins,[52] and other related compounds.[53] Vasella *et al.* prepared variety of bicyclic isoxazolidenes from simple hexoses,[54] workers in New Zealand have subsequently used this strategy to prepare optically pure prostaglandins from D-glucose.[55] Mondal and co-workers prepared five and six membered carbocyclic nucleosides from D-glucose and its enantiomers[56] by applying INAC process. The important precursor to aromatic metabolites in plants, fungi and micro-organisms, namely (–)-shikimic acid (**56**), have been synthesized from nitrone derived from D-ribose by using intramolecular 1,3-DC reaction[57]**.** The aminocyclopentitol is an intermediate in the synthesis of the carbocylic nucleosides (–)-neplanocin A (**57**)



(-)-*shikimic acid* (**56**)

and (–)-noraristeromycin (**58**), which was prepared from sugar nitrone by the intramolecular cycloaddition reaction[58]. Similarly the *intramolecular oxime-alkene cycloaddition* (IOAC) reaction which proceeds *via* N-H nitrones have been used by Wildman and co-workers[59] into the synthesis of 6-hydroxybuphanidine (**59**) and 6-hydroxypowelline (**60**) and since then many researchers have been utilized this reaction. Moutel and Shipman[34] used the IOAC reaction for the preparation of aminocyclopentitols, from D-glucose by 1, 2-Protropic shift as the key step. Dhavale *et al.*[60] also reported some novel aminocyclopentanol derivatives by using intramolecular cycloaddition as the key reaction from glucose derived nitrones.



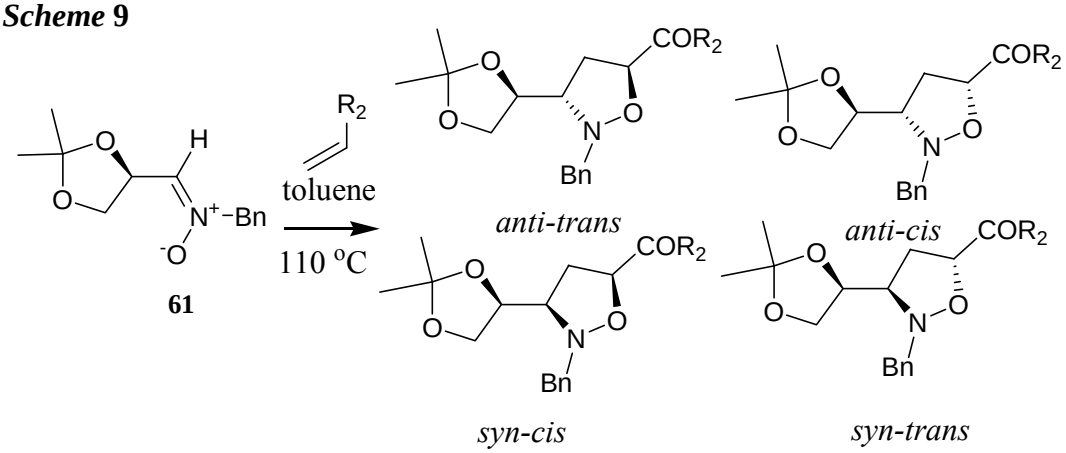
Central core of
(-) neplanocin A (**57**)
(-) noraristeromycin (**58**)

R^3 = OMe, R^6 = α OH (**59**)
R^3 = OH, R^6 = OH (**60**)

❖ **Intermolecular 1,3-Dipolar cycloaddition:**

The pioneering work in this field by Belzecki[61] and Vasella[62] independently demonstrated in the late 1970's that optically active nitrones undergoes intermolecular 1,3-dipolar cycloaddition reaction to led variety of optically active compounds like nucleoside analogues[62a] amino acids and amino sugars,[62c-e] alkaloides and related compounds.[63-65]

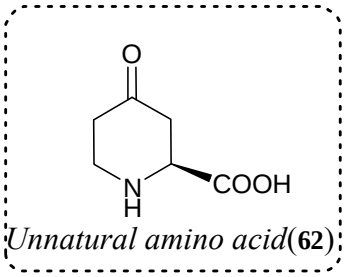
***Scheme* 9**



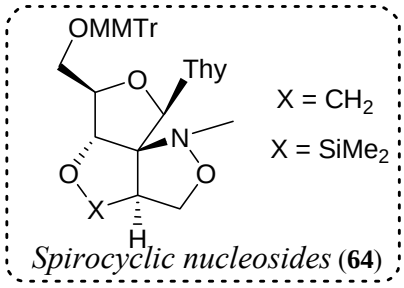
R_2 = OMe, 95% (anti-trans:anti-cis:syn-cis: syn-trans) = 63:23:11:3

R_2 = OMe, 66% (anti-trans:anti-cis:syn-cis: syn-trans) = 53:20:11:3

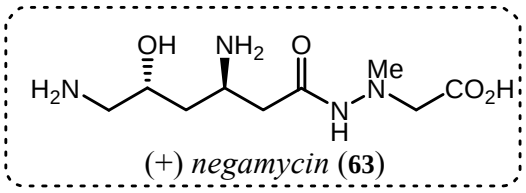
The simplest sugar derived nitrone that undergoes intermolecular 1,3-dipolar cycloaddition reaction is the D-glyceraldehyde derived nitrone. Thus reactions of the nitrone **61** derived from D-glyceraldehyde with acrylate was studied by Merino *et al.* and applied for the synthesis of 4-hydroxy pyroglutamic acid derivatives (Scheme 9)[66].



Unnatural amino acid(**62**)

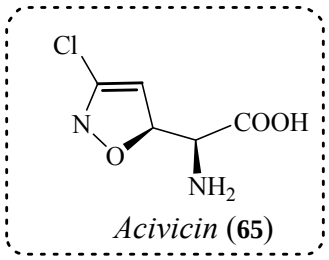


Spirocyclic nucleosides (**64**)



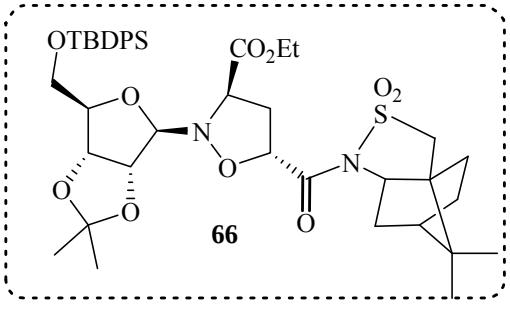
(+) *negamycin* (**63**)

Encouraging by the pioneer work by Vasella many sugar nitrones have been synthesized and used for the synthesis of biologically active natural products. Brandi and co-workers reported the synthesis of unusual amino acid **62** from the related hydroxyl amine by using the similar reactions [67].



Acivicin (**65**)

By using 1,3-dipolar cycloaddition of D-gulose derived nitrone with allylic amine derivative as the key step the synthesis of antibiotic (+)-negamycin (**63**) has been reported by Kibayashi and co-workeres[68]. On the other hand Chattopadhya and co-workers synthesized spirocyclic nucleosides (**64**) anti-HIV-1 activity[69]**.** There are some reports of the intermolecular sugar nitrone-alkene cycloaddition reactions using both the partners were optically active. One of the example of such reaction involves the vasell's sugar derived nitrone and amino acid derived allyl amines[70] and some reports include the partial kinetic resolution of vinylic phosphine oxides with D-glyceraldehyde nitrones.[71] Whitney and co-workers have described the synthesis of the antimetabolite antibiotic acivicin[72](**65**) An interesting example of double asymmetric induction was reported by Merino *et al.*, involving the asymmetric dipolar



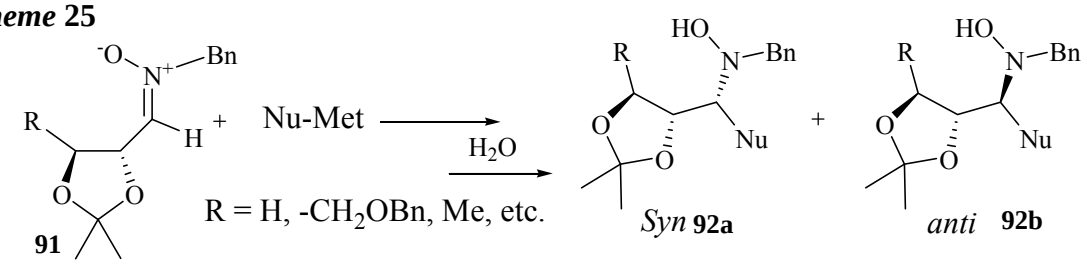
cycloaddition between Oppolzer's sultam acrylamide and sugar nitrone to give **66**[73]. The first report which involves ynolates in intermolecular 1,3 dipolar reactions reported by Shindo *et al*. appeared in 2003[74]. The *N*-benzyl-1,3-di-*O*-isopropylidene-D-glyceraldehyde reacts with ynolate to furnish the isoxazolidineones that could be converted into β-amino acids.The new metal catalyzed version of intramolecular 1,3-dipolar cycloaddition has been reported by Fisera *et al.* in 2005, which gives only two diastereomers of the corresponding chiral products[75].

Nucleophilic reactions

Nucleophilic addition reactions of nitrone offer one of the most versatile synthetic routes to the synthesis of optically active as well as optically inactive compounds. The first report of the addition of Grignard reagent to nitrones is credited to an Italian group dating from 1911[76] and 1922[77]. The interest has been devoted in recent years to widen the scope of reaction of nitrones with the Grignard reagent to different nucleophiles, including allylic organomettalic compounds, sulfur stabilized anions, acetylides, lithiated heteroatomic compounds, silylated nucleophiles etc. The stereochemical outcome of the addition of nucleophiles on nitrones seems to depend on the nitrogen-protecting group and on the substituent on the β-position. Moreover, attention has been also paid to develop the stereocontrolled process using chiral nitrones (sugar & other chiral pool derived nitrones), chiral nucleophiles and chiral catalysts. But the nucleophilic addition reactions on sugar nitrones have not been much explored. The classical substrate to study the stereochemical outcome of such reaction on sugar nitrone is D-glyceraldehyde. Two general trends rise here: i) *syn*-adducts are favored in the absence of a nitrone complexing agent and ii) *anti*-adducts are favored in the presence of Et_2AlCl. The result of stereochemical outcome reflects the conformation of different sugar nitrone in different experimental conditions.

The reactions of variety of nucleophiles in the presence of Lewis acid and in the absence of Lewis acid have been tested for diastereoselectivity for Scheme 10.[78-82]

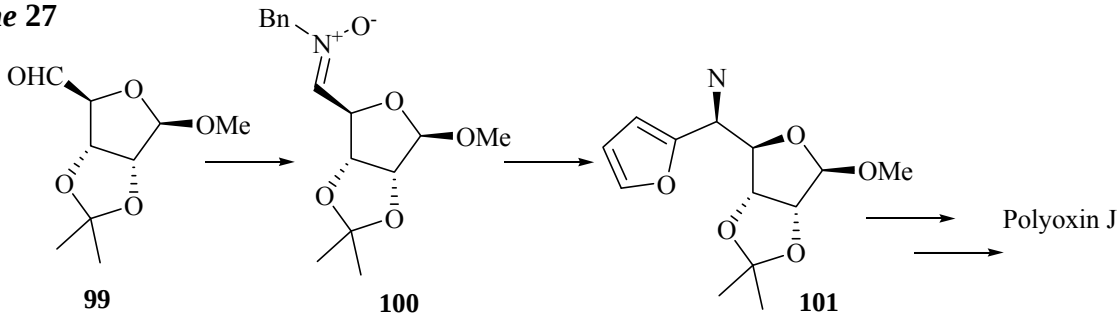
***Scheme* 25**



In the recent years many groups studied the outcome of the nucleophilic reactions on sugar nitrones including Vasella who studied the addition of phosphorous nucleophile to *N*-glycosyl nitrones as a route for the synthesis of α-aminophosphonic acid [83].

Moreover, Merino and co-workers reported the total synthesis of (+)-polyoxin J & I the antibiotics that are potent inhibitors of the biosynthesis of the chitin, a major structure component of the cell wall of most fungi by using nucleophilic addition to chiral nitrone as a key step (Scheme 11) [84].

***Scheme* 27**



There are some reports for the addition of nucleophilic reagents on cyclic sugar nitrone by Holfazel[85] and Tamura *et al.*[86], both independently studied the nucleophilic reactions on sugar nitrone and applied for the synthesis of biologically active compound.

PRESENT WORK

Section 1: Total synthesis of (–) Radicamines A & B

Enzymatic processes controlling the synthesis and break down of oligosaccharides involving glucose residue play an important role in cellular events at different levels. Key enzymes involved in this regard are glucosidases, which can be classified further depending upon the anomeric selectivity, site of cleavage and the direction of protonation. α-Glucosidases carry out hydrolytic cleavage of glucose from the nonreducing end of substrates bearing α-glucosidic linkage, such as disaccharides, oligosaccharides. This class of enzyme is involved in several important biological processes including digestion and maturation of glycoproteins. In *vitro* studies have shown that α-glucosidase inhibitors prevent replication of viruses (e.g., HIV and hepatitis B) by disrupting the proper folding of mature viral glycoproteins that require the aid of the chaperone calnexin. α-Glucosidase is also expressed in the microvilli of the small intestine. Since only monosaccharides can be absorbed and taken up through the small intestine, α-glucosidase is required to catalyze the breakdown of sugars in the final step of carbohydrate digestion. Several naturally occurring aza sugar mimics comprising both polyhydroxy piperidine and pyrrolidine structural units were isolated and shown to be potential inhibitors of this enzyme. Some of these aza sugar analogues were found to be therapeutically relevant for the treatment of type II non-insulin-dependent diabetes mellitus by interfering with the enzymatic action in the bowel, slowing the breakdown of dietary polysaccharides and disaccharides to glucose.

Naturally occurring DAB-1 (**76**) and LAB-1 (**72**) isolated[87] from *Angilocalix boutiqueanus* and *Arachniodes standishii* are powerful inhibitors of a range of α-glucosidases. The 1,4-dideoxy-1,4-imino-D-xylitol (**73**), also showed promising α-glucosidases activity. Very recently, radicamine A & B new pyrrolidine alkaloids acting as an inhibitors of a α-glucosidase are isolated[88] from the plant *Lobelia chinensis* Lour., a herb that is used as a diuretic, an antidote, a hemostat and as a carcinostatic agent for stomach cancer in Chinese folk medicine.

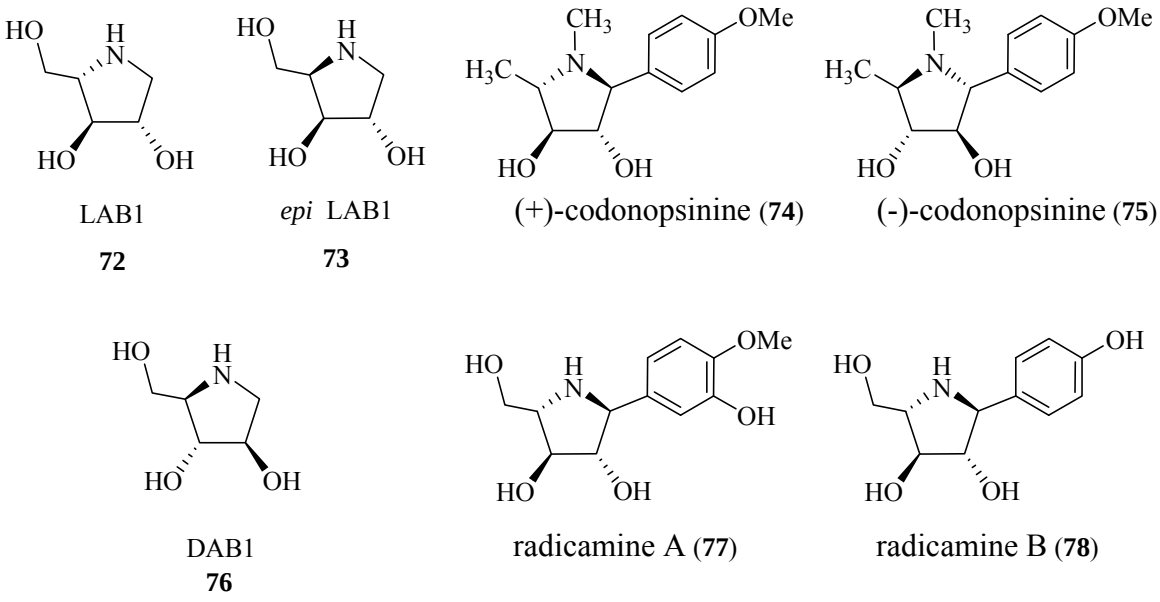


***Figure* 13:** *Naturally occurring polyhydroxy pyrrolidine alkaloids*

The structures and relative stereochemistry of both these compounds (Figure 13) were determined on the basis of extensive NMR studies. However, the absolute configuration of these compounds was assigned by comparing the specific rotation with the natural Codonopsinine **74** and with its antipode **75**. The absolute stereochemistry of radicamine A was determined to be (2*S*,3S,4S,5S) by the comparison of the positive $[\alpha]_D$ value of N-methylradicamine A {$[\alpha]_D$ = +6.3 (*c* = 0.80, MeOH)}with that of (+)-Codonopsinine (**74**) {$[\alpha]_D$ = +12.5 (*c* = 2.55, MeOH)}, and by a similar method, the radicamine B was concluded to be (2*S*,3*S*,4*S*,5*S*)-2-hydroxymethyl-3,4-dihydroxy-5-(4-hydroxyphenyl)-pyrrolidine. A further support for the assigned absolute stereostructres of radicamines A and B were deduced from the CD spectral study of their benzoate derivatives. Due to their remarkable biological properties and the structural relation with the known α-glucosidase inhibitor LAB-1, we have undertaken the synthesis of radicamines A and B. Considering their identical stereochemistry of the pyrrolidine ring with LAB-1, we have devised a strategy which involves an L-*arabino* configured cyclic nitrone **79**, as an advanced intermediate from which one can indeed make both radicamines including the know LAB-1.

The retrosynthetic analysis revealed that the facial selective addition of a suitable aryl Grignard reagent to the L-*arabino* configured cyclic nitrone **79** provides the key ap-

proach of our intended synthesis of **77** and **78**. Synthesis of the key nitrone **79** was envisaged from L-arabinose as the suitable chiral pool (Figure 14).

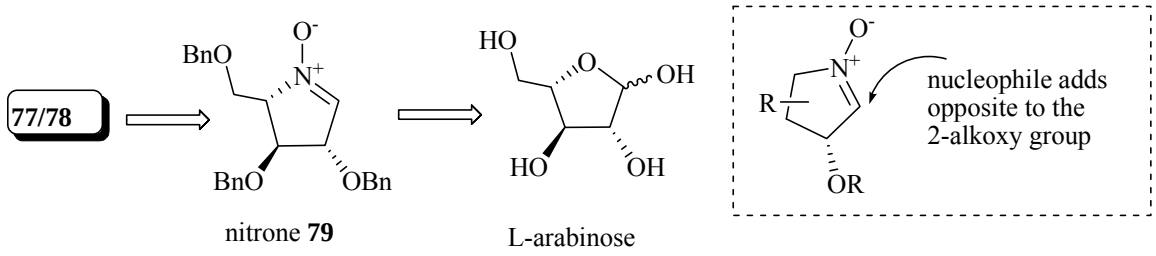
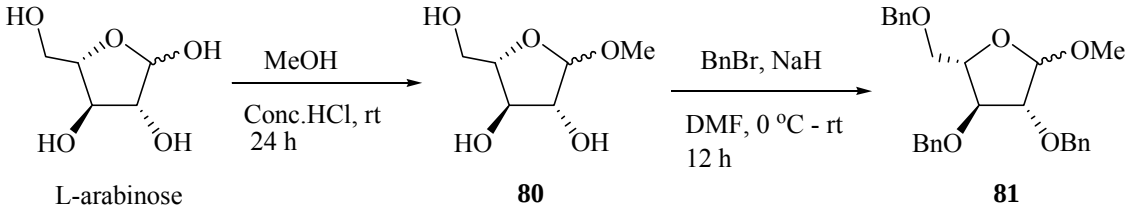


***Figure* 14:** *Retrosynthetic Analysis*

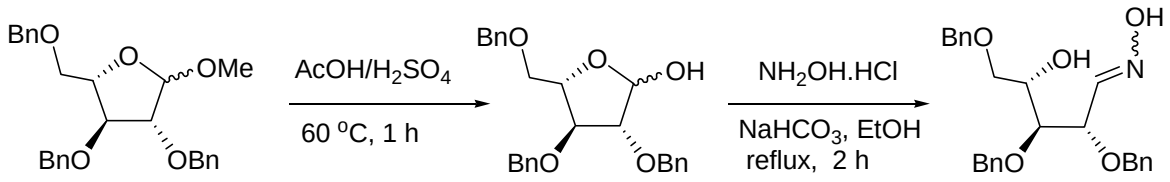
Our synthesis began with the preparation of methyl 2,3,5-tri-*O*-benzyl-L-arabinofuranoside **81** from commercially available L-arabinose adopting a protocol reported by Fletcher *et al* [89a] (Scheme 12). The anomeric group of sugar was first temporarily protected as its methyl glycoside by using MeOH and conc. HCl to afford methyl furanosides **80,** which were directly subjected to the next step without any separation.

***Scheme* 12**



Protection of the rest of the three hydroxyl groups as benzyl ethers was carried out by treating **80** with NaH/BnBr in DMF to afford **81**. The structure of compound **81** was confirmed by the ^{1}H and ^{13}C NMR spectral analysis. The hydrolysis of methyl furanosides **81** in AcOH /H_2SO_4 at 60 ^{o}C gave the lactol **82**. The overall yield of three steps is 48%. The ^{1}H NMR and ^{13}C NMR spectrum of **82** indicates that it is the mixture of α/β anomers. We observed that optical rotation of **82** changes from $[\alpha]_D = +3.5$ to $[\alpha]_D = -4.3$ on standing. This implies that the β-furanoside was slowly converted into α-furanoside. The final constant optical rotation was in complete agreement with that of the reported[89b] value for the α-glycoside.

***Scheme* 13**

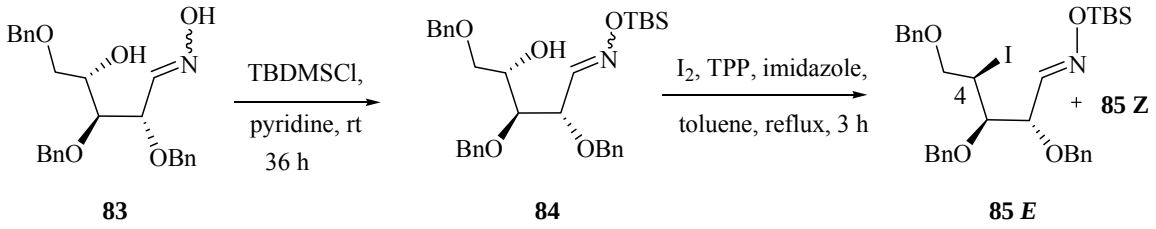


81 **82** **83**

After having a preparative method for procuring large quantities of **82**, we next turned out attention for the synthesis of the key nitrone intermediate **79**. Thus, the reaction of **82** with hydroxylamine.hydrochloride, and $NaHCO_3$ as a base, in EtOH at reflux temperature afforded an inseparable mixture of *E*/*Z*-oximes **83** (7:3) in 95% yield (Scheme 13**)**. The aldoximes configuration can be easily deduced from the ^{1}H NMR and ^{13}C NMR spectra. In the ^{1}H NMR spectrum of **83,** the olefinic proton resonated as a doublet at 7.48 ppm (J = 7.7 Hz) for *E*-isomer and singlet at 6.90 ppm for the *Z*-isomer. In the ^{13}C NMR spectrum, the carbon of the imine functionality (**C**H=N) resonated at 152.3 ppm (*Z*-isomer) while for the *E*-isomer it was found at 150.0 ppm. This was in accordance with the earlier reports[105]. A comprehensive compilation and analyses of the ^{1}H NMR chemical shift data of large number of *anti*- and *syn*-aldoximes by Karabatsos & Taller[90a] concluded that C**H**=N protons of *anti*-isomer resonate at downfield than its counterpart *syn*-isomer and the observed deshielding in *E*-*anti*-isomers was attributed to the anisotropy of the *cis*-oxygen, which was absent in case of the *syn*-isomer. The further proof came from Roberts *et al.*[90b]on the basis of the ^{13}C NMR spectral data, according to which study the imine carbon (**C**H=N) of *syn*-isomer resonated downfield than that of *anti*-isomer. The elemental analysis and mass spectra of **83** were compatible with the assigned structure. In the IR spectrum of **83**, the peak corresponding to the C=N appeared at 2248 cm^{-1} and a hydroxy peak at 3368 cm^{-1}. The selective protection of oxime hydroxyl with TBDMSCl in dry pyridine gave the corresponding TBS ether **84**, whose ^{1}H NMR spectrum showed singlets due to Me_2Si group at (0.16, 018) ppm integrating for 6H and *t*-BuSi group at (0.91, 0.95) ppm integrating for 9H. Due to protection the notable shift in the IR spectrum was observed (oxime peak shifted to 2252 cm^{-1} and hydroxyl is shifted to 3401 cm^{-1}). The compound **84** was then treated with I_2 and imidazole in toluene at reflux condition to give the mixture of

E/*Z*-oxime derivatives **85** with inversion of the configuration at C-(4) (Scheme 14). The plausible mechanism for the iodination is shown in Figure 15.

***Scheme* 14**



83 **84** **85 *E***

The olefin proton of the *Z*-isomer showed singlet at 6.94 ppm while that of *E*-isomer was appeared as a doublet at 7.38 ppm (J = 7.8 Hz).

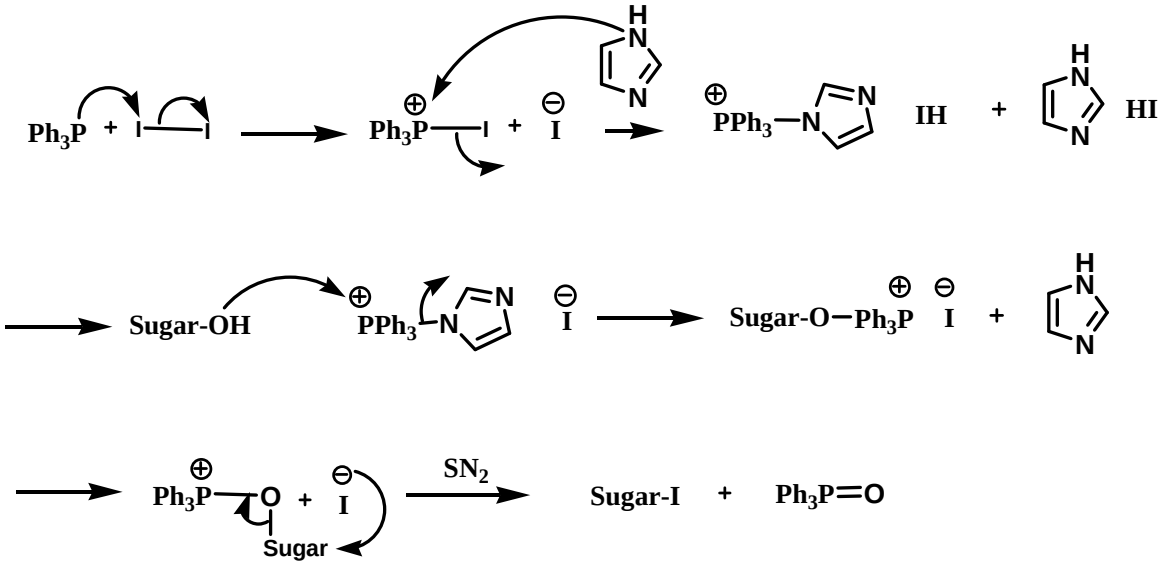
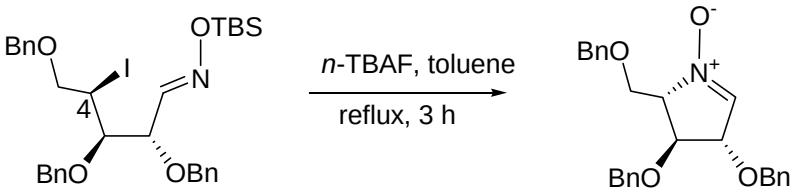


***Figure* 15:** *Plausible mechanism for iodination*

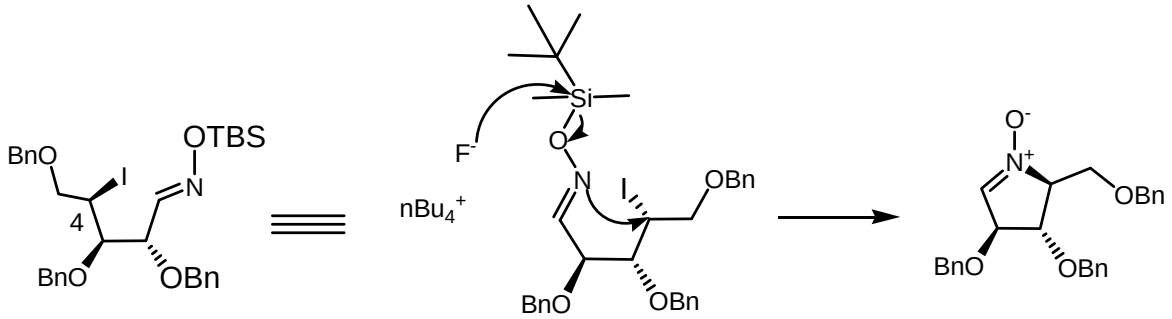
The major isomer ***E*-85** was purified by flash chromatography on silica gel and subjected to the key desilylation and concomitant intramolecular nucleophilic displacement with anhydrous TBAF in refluxing toluene to afford the nitrone **79** as a crystalline solid (Scheme 15). The mechanism for *in situ* deprotection of TBS group and the formation of nitrone is shown in Figure 16.

***Scheme* 15**



85 *E* **79**

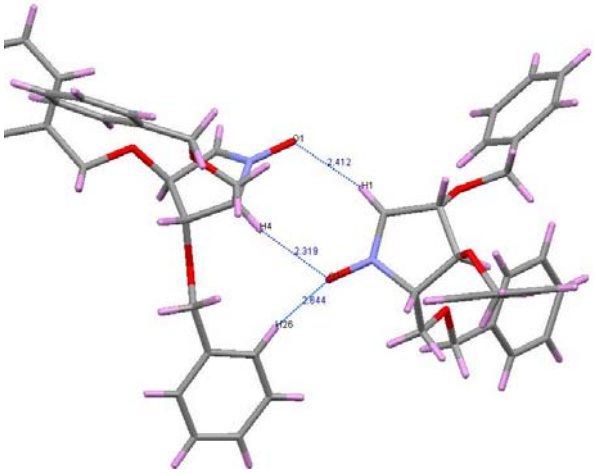
The spectral and analytical data of **79** were in agreement with the reported data of *ent*-**79**[91]. A single crystal X-ray structural analysis of **79** confirmed the structure.



85*E* **79**

***Figure* 16 :** *Inversion of configuration*

X-ray analysis revealed the conformation of **79**. The molecules form dimmers via C-H…O hydrogen bonding (Figure 17).



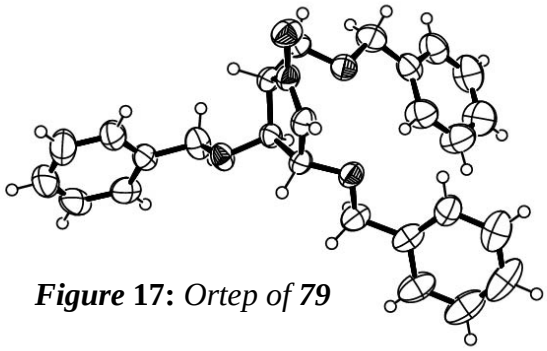


Figure* 17:** *Ortep of* ***79

No.	Atom1	Atom 2	Symm.op.1	Symm.op.2	Length in Å
1	O1	H4	x,y,z	1-x,1/2+y,1-z	2.319
2	O1	H26	x,y,z	1-x,1/2+y,1-z	2.644
3	H1	O1	x,y,z	1-x,1/2+y,1-z	2.412

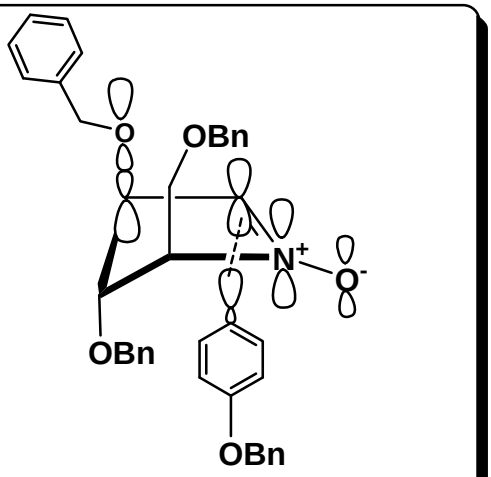
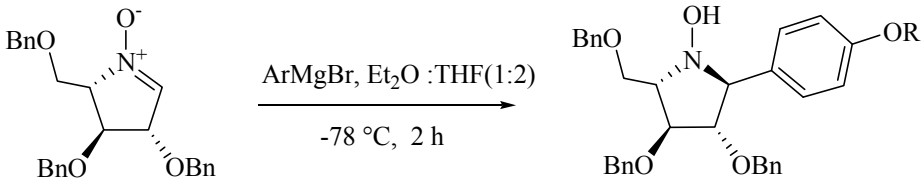


***Figure* 18 :** *Proposed transition state for addition of Grignard reagent*

By the literature survey, it was evident that the addition of nucleophiles on chiral cyclic nitrone **79** could be achieved stereoselectively encashing the stereoelectronic control by the neighbouring electronegative substituents.[92] Thus relying on the prediction that the incoming nucleophile approaches from the opposite face as that of the C_2-alkoxy group, we studied initially, the Grignard reaction of easily available *p*-methoxyphenylmagnesium bromide (a) at reflux condition and at –78 ^{o}C, the best stereoselectivity was observed at lower temperature. The Felkin-Anh TS model[93] (Figure 18) in which the more electronegative group at C-2 is antiperiplanar to the incoming Grignard nucleophile to minimize the electronic repulsions is operative. These results encouraged us to extend this study on *p*-benzyloxyphenylmagnesium bromide (b), the Grignard reaction of the cyclic nitrone **79** at various reaction conditions was executed and the results have been summarized in **Table 1**. The lowering of reaction temperature enhances the stereoselectivity of the Grignard reaction. The reaction in Et_2O-THF at –78 °C thus afforded the *N*-hydroxypyrrolidine derivative **87** exclusively in 78% yield (Scheme 16). The stereochemical outcomes of the Grignard reaction were determined by using the analytical HPLC. {Column: YMC PACK ODS-A 250 x 4 .6 mm; Mobile phase: MeOH: H_2O 95:05; Wavelength: 254 nm; Flow rate: 0.5 mL/min}. The ^{1}H NMR spectrum of **87** showed the presence of 1,4-disubstituted

aromatic ring and disappearance of olefin proton. Further, ESI MS analysis of **87** showed the mass at *m/z*: 602 accounting for $[M+H]^+$.

***Scheme* 16**



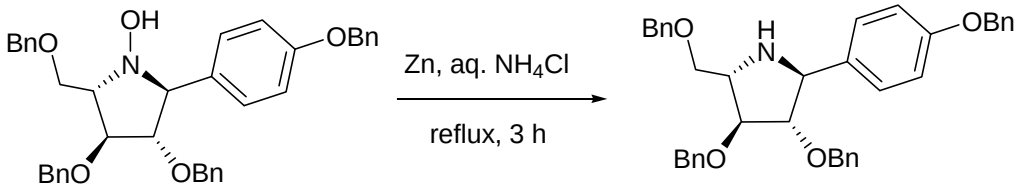
79

R = OMe **86**
R = OBn **87**

Table 1: *Stereoselectivity observed for Grignard reagents*

Sr. No	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Reagent	a	a	b	b	b	b	b
Condition	reflux	–78 °C	reflux	rt	0 °C	– 40 °C	–78 °C
Diastereoselectivity	70:30	100: 0	65:35	70:30	75:25	80:20	100: 0

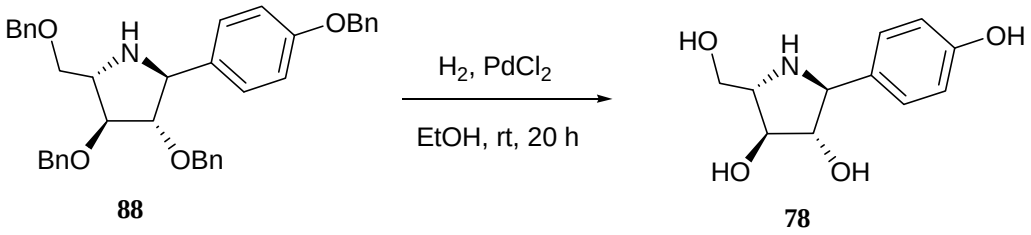
***Scheme* 17**



87 **88**

The reduction of N-O bond in **87**, using Zn in aq. NH_4Cl gave the pyrrolidine derivative **88** in 98% yield (Scheme 17). The structure of **88** was confirmed by its ^1H and ^{13}C NMR spectra and further supported by the mass spectral analysis where the peak corresponding to $[M+H]^+$ was observed at *m/z*: 586. The protected pyrrolidine **88** upon exhaustive hydrogenolysis with H_2 over $PdCl_2$ in ethanol gave **78** in 62% yield (Scheme 18).

***Scheme* 18**



88 **78**

The relative stereochemistry of **78** was confirmed from ^{1}H-^{1}H coupling constants, COSY and NOESY spectra. The ^{1}H NMR and ^{13}C NMR spectra of **78** were in agreement with the assigned structure, while the NOESY spectra showed the strong correlation between H-C(2), H-C(4) & H-C(3), H-C(5) (Figure 19)**.** Although, the spectral data of synthetic**78** had minor deviations (chemical shifts) from the reported data of the natural product, which was expected due to the exceptional chelating ability of these polyhydroxy pyrrolidine compounds with a metal or a proton.[94] Wormald and co-workers[95] reported this type of deviations during the synthesis of 1-epiaustraline. They had noted chemical shift differences between different samples of the same compound. However, the coupling constants were similar and are independent of the variations in the chemical shift. The optical rotation however, of **78** was found similar in magnitude but opposite in sign; this confirmed the revision in the absolute configuration of radicamine B.

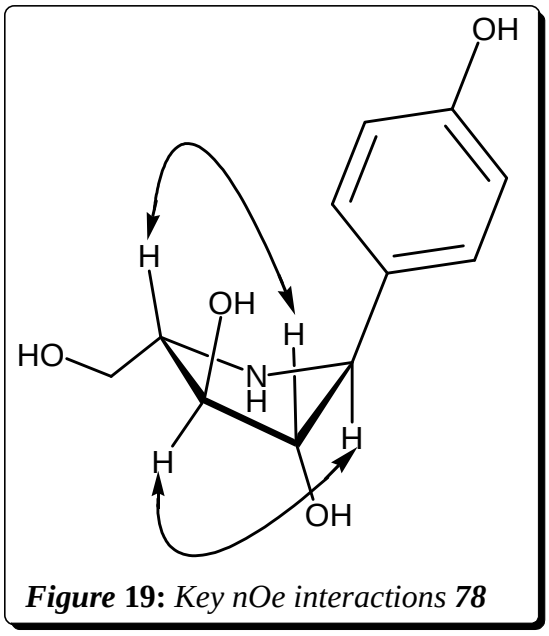
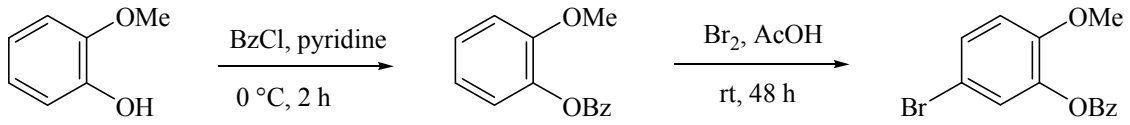


Figure* 19:** *Key nOe interactions **78

In the process of completing the total synthesis of radicamine A, we next prepared the requisite aromatic precursor as shown in (Scheme 19).

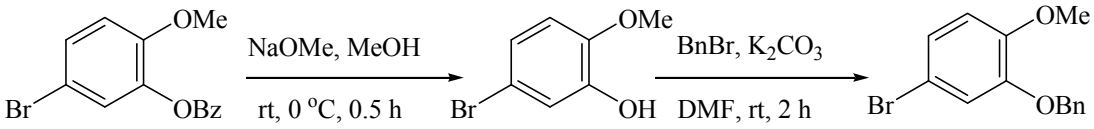
***Scheme* 19**



89 **90** **91**

Commercially available guiacol **89** was treated with benzoyl chloride in pyridine at 0 ^{o}C to obtain **90**, which was brominated selectively at para to methoxy group to procure **91** in 85% yield. The spectral and analytical data of compound **91** is in agreement with the reported values.[96]

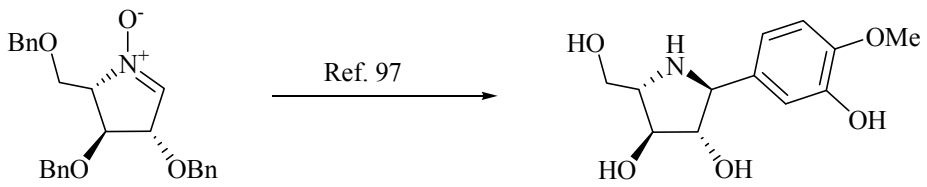
***Scheme* 20**



91 **92** **93**

The benzoyl group of **91** was selectively deprotected by using sodium methoxide in methanol to furnish **92** in 89% yield. The ^{1}H NMR of the compound **92** showed broad singlet at 5.61 ppm. The compound **92** then treated with benzyl bromide and K_2CO_3 in DMF to afford benzyl ether derivative **93** whose ^{1}H and ^{13}C NMR shows the characteristics peaks of benzyl group and further supported by ESI-MS analysis of which showed the mass at *m/z*: 315 accounting for $[M+Na]^{+}$ (Scheme 20). As the bromo compound **93** in our hand our next concern was its stereoselective addition of Grignard reagent to the nitrone **79** (Scheme 21).

***Scheme* 21**



79 **77**

However, during the same time Yu *et al.*[97] reported the synthesis of both the radicamines and revised the absolute stereochemistry, which indeed was observed by us. Considering the overlapping synthetic strategy we have abandoned the synthesis of radicamine A at this stage and proceeded further for the synthesis of LAB-1 and its C-4 epimer.

In conclusion, we have achieved the total synthesis of radicamine B (**78**)**,** thus leading to a revision of the structure **78** originally proposed for natural radicamine B. Of particular note, the absolute stereochemistry of radicamine A (**77**) and radicamine B (**78**) has now been revised through our synthesis. This method is viable for the synthesis of related polyhydroxylated pyrrolidine natural products starting from different sugars and following the same reaction sequence discussed and established in this section.

Table 1

Crystal data and structure refinement for compound **79**

Empirical formula	$C_{26}H_{27}NO_4$
Formula weight	417.49
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P_{21}
Unit cell dimensions	a = 8.3581(7) Å b = 7.5875 (6) Å β= 99.3° c = 17.7297(15) Å
Volume	1109.56(16) $Å^3$
Z, Calculated density	2, 1.250 mg/m^3
Absorption coefficient	0.084 mm^{-1}
F (000)	444
Crystal size	0.15 x 0.05 x 0.04 mm
Theta range for data collection	2.33 to 25.50 deg.
Limiting indices	-9<=h<=10, -9<=k<=5, -20<=l<=21
Reflections collected / unique	4567 / 2682 [R (int) = 0.0324]
Completeness to theta = 25.50	91.4 %
Max. and min. transmission	0.9965 and 0.9873
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2682 / 1 / 280
Goodness-of-fit on F^2	1.138
Final R indices [I^2sigma (I)]	R1 = 0.0696, wR2 = 0.1664
R indices (all data)	R1 = 0.1047, wR2 = 0.1837

Absolute structure parameter	1(2)
Largest diff. peak and hole	0.314 and -0.243 e. Å $^{-3}$

Table 2
Bond lengths [Å] and angles [^{o}] for **79**

O(1)-N	1.284(4)	C(6)-O(2)-C(5)	113.0(4)	C(11)-C(12)-C(7)	121.8(6)
O(2)-C(6)	1.389(6)	C(3)-O(3)-C(20)	112.1(3)	C(7)-C(6)-H(6A)	109.5
O(2)-C(5)	1.431(6)	C(2)-O(4)-C(13)	114.6(3)	O(2)-C(6)-H(6B)	109.5
O(3)-C(3)	1.410(5)	O(1)-N-C(1)	127.7(3)	C(7)-C(6)-H(6B)	109.5
O(3)-C(20)	1.434(5)	O(1)-N-C(4)	18.2(3)	H(6A)-C(6)-H(6B)	108.1
O(4)-C(2)	1.413(6)	C(1)-N-C(4)	114.0(3)	C(12)-C(7)-C(8)	117.4(5)
O(4)-C(13)	1.424(4)	N-C(1)-C(2)	111.7(4)	C(12)-C(7)-C(6)	120.5(5)
N-C(1)	1.292(5)	N-C(1)-H(1)	124.2	C(8)-C(7)-C(6)	122.2(5)
N-C(4)	1.489(5)	C(2)-C(1)-H(1)	124.2	C(7)-C(8)-C(9)	120.5(6)
C(1)-C(2)	1.494(5)	O(4)-C(2)-C(1)	106.7(3)	C(7)-C(8)-H(8)	119.8
C(1)-H(1)	0.9300	O(4)-C(2)-C(3)	115.2(4)	C(9)-C(8)-H(8)	119.8
C(2)-C(3)	1.541(6)	C(1)-C(2)-C(3)	103.7(3)	C(10)-C(9)-C(8)	120.5(6)
C(2)-H(2)	0.9800	O(4)-C(2)-H(2)	110.3	C(10)-C(9)-H(9)	119.8
C(3)-C(4)	1.533(5)	C(1)-C(2)-H(2)	110.3	C(8)-C(9)-H(9)	119.8
C(3)-H(3)	0.9800	C(3)-C(2)-H(2)	110.3	C(9)-C(10)-C(11)	120.5(7)
C(4)-C(5)	1.472(6)	O(3)-C(3)-C(4)	111.6(3)	C(9)-C(10)-H(10)	119.7
C(4)-H(4)	0.9800	O(3)-C(3)-C(2)	108.0(3)	C(10)-C(11)-C(12)	119.3(7)
C(5)-H(5A)	0.9700	C(4)-C(3)-C(2)	105.8(3)	C(10)-C(11)-H(11)	120.3
C(5)-H(5B)	0.9700	O(3)-C(3)-H(3)	110.4	C(12)-C(11)-H(11)	120.3
C(6)-C(7)	1.484(7)	C(4)-C(3)-H(3)	110.4	C(11)-C(12)-H(12)	119.1
C(6)-H(6A)	0.9700	C(2)-C(3)-H(3)	110.4	C(7)-C(12)-H(12)	119.1
C(6)-H(6B)	0.9700	C(5)-C(4)-N	111.2(3)	O(4)-C(13)-C(14)	108.7(4)
C(7)-C(12)	1.382(8)	C(5)-C(4)-C(3)	117.4(4)	O(4)-C(13)-H(13A)	110.0
C(7)-C(8)	1.382(7)	N-C(4)-C(3)	103.2(3)	C(14)-C(13)-H(13A)	110.0

C(8)-C(9)	1.393(9)	C(5)-C(4)-H(4)	108.3	O(4)-C(13)-H(13B)	110.0
C(8)-H(8)	0.9300	N-C(4)-H(4)	108.3	C(14)-C(13)-H(13B)	110.0
C(9)-C(10)	1.341(10)	C(3)-C(4)-H(4)	108.3	H(13A)-C(13)-H(13B)	108.3
C(9)-H(9)	0.9300	O(2)-C(5)-C(4)	109.5(3)	C(19)-C(14)-C(15)	118.7(5)
C(10)-C(11)	1.368(10)	O(2)-C(5)-H(5A)	109.8	C(19)-C(14)-C(13)	122.7(4)
C(10)-H(10)	0.9300	C(4)-C(5)-H(5A)	109.8	C(15)-C(14)-C(13)	118.5(5)
C(11)-C(12)	1.377(9)	O(2)-C(5)-H(5B)	109.8	C(16)-C(15)-C(14)	119.2(6)
C(11)-H(11)	0.9300	C(4)-C(5)-H(5B)	109.8	C(16)-C(15)-H(15)	120.4
C(12)-H(12)	0.9300	H(5A)-C(5)-H(5B)	108.2	C(14)-C(15)-H(15)	120.4
C(13)-C(14)	1.506(7)	O(2)-C(6)-C(7)	110.6(4)	C(17)-C(16)-C(15)	121.1(5)
C(13)-H(13A)	0.9700	O(2)-C(6)-H(6A)	109.5	C(17)-C(16)-H(16)	119.5
C(13)-H(13B)	0.9700	C(7)-C(6)-H(6A)	109.5	C(15)-C(16)-H(16)	119.5
C(14)-C(19)	1.358(7)	O(2)-C(6)-H(6B)	109.5	C(16)-C(17)-C(18)	119.9(6)
C(14)-C(15)	1.399(6)	C(7)-C(6)-H(6B)	109.5	C(16)-C(17)-H(17)	120.1
C(15)-C(16)	1.396(10)	H(6A)-C(6)-H(6B)	108.1	C(18)-C(17)-H(17)	120.1
C(15)-H(15)	0.9300	C(12)-C(7)-C(8)	117.4(5)	C(17)-C(18)-C(19)	120.2(7)
C(16)-H(16)	0.9300	C(12)-C(7)-C(6)	120.5(5)	C(17)-C(18)-H(18)	119.9
C(16)-C(17)	1.347(11)	C(8)-C(7)-C(6)	122.2(5)	C(19)-C(18)-H(18)	119.9
C(17)-C(18)	1.363(9)	C(7)-C(8)-C(9)	120.5(6)	C(14)-C(19)-C(18)	121.0(5)
C(18)-C(19)	1.389(9)	C(7)-C(8)-H(8)	119.8	C(14)-C(19)-H(19)	119.5
C(18)-H(18)	0.9300	C(9)-C(8)-H(8)	119.8	C(18)-C(19)-H(19)	119.5
C(19)-H(19)	0.9300	C(10)-C(9)-C(8)	120.5(6)	O(3)-C(20)-C(21)	109.2(4)
C(20)-C(21)	1.487(7)	C(10)-C(9)-H(9)	119.8	O(3)-C(20)-H(20A)	109.8
C(20)-H(20A)	0.9700	C(8)-C(9)-H(9)	119.8	C(21)-C(20)-H(20A)	109.8
C(20)-H(20B)	0.9700	C(9)-C(10)-C(11)	120.5(7)	O(3)-C(20)-H(20B)	109.8
C(21)-C(22)	1.389(6)	N-C(4)-C(3)	103.2(3)	C(21)-C(20)-H(20B)	109.8
C(21)-C(26)	1.390(7)	C(5)-C(4)-H(4)	108.3	H(20A)-C(20)-H(20B)	108.3
C(22)-C(23)	1.416(9)	N-C(4)-H(4)	108.3	C(22)-C(21)-C(26)	118.6(5)
C(22)-H(22)	0.9300	C(3)-C(4)-H(4)	108.3	C(22)-C(21)-C(20)	121.1(5)
C(23)-C(24)	1.333(9)	O(2)-C(5)-C(4)	109.5(3)	C(26)-C(21)-C(20)	120.3(4)
C(23)-H(23)	0.9300	O(2)-C(5)-H(5A)	109.8	C(21)-C(22)-C(23)	118.7(5)

C(24)-C(25)	1.363(9)	C(4)-C(5)-H(5A)	109.8	C(21)-C(22)-H(22)	120.7
C(24)-H(24)	0.9300	O(2)-C(5)-H(5B)	109.8	C(23)-C(22)-H(22)	120.7
C(25)-C(26)	1.363(8)	C(4)-C(5)-H(5B)	109.8	C(24)-C(23)-C(22)	120.2(5)
C(25)-H(25)	0.9300	H(5A)-C(5)-H(5B)	108.2	C(24)-C(23)-H(23)	119.9
C(26)-H(26)	0.9300	O(2)-C(6)-C(7)	110.6(4)	C(22)-C(23)-H(23)	119.9
C(23)-C(24)-C(25)	121.7(6)	C(24)-C(25)-H(25)	120.3		
C(23)-C(24)-H(24)	119.1	C(26)-C(25)-H(25)	120.3		
C(25)-C(24)-H(24)	119.1	C(25)-C(26)-C(21)	121.3(5)		
C(24)-C(25)-C(26)	119.4(6)	C(21)-C(26)-H(26)	119.3		
C(25)-C(26)-H(26)	119.3				

Table 3
Torsion angles [^{o}] for **79**

O(1)-N-C(1)-C(2)	-177.5(4)	C(7)-C(8)-C(9)-C(10)	-2.2(10)
C(4)-N-C(1)-C(2)	4.0(5)	C(8)-C(9)-C(10)-C(11)	2.3(12)
C(13)-O(4)-C(2)-C(1)	168.7(4)	C(9)-C(10)-C(11)-C(12)	-1.2(12)
C(13)-O(4)-C(2)-C(3)	-76.9(5)	C(10)-C(11)-C(12)-C(7)	0.1(11)
N-C(1)-C(2)-O(4)	111.4(4)	C(8)-C(7)-C(12)-C(11)	-0.1(9)
N-C(1)-C(2)-C(3)	-10.7(5)	C(6)-C(7)-C(12)-C(11)	179.2(6)
C(20)-O(3)-C(3)-C(4)	77.3(4)	C(2)-O(4)-C(13)-C(14)	-159.6(4)
C(20)-O(3)-C(3)-C(2)	-166.8(3)	O(4)-C(13)-C(14)-C(19)	-18.3(7)
O(4)-C(2)-C(3)-O(3)	137.0(3)	O(4)-C(13)-C(14)-C(15)	158.4(5)
C(1)-C(2)-C(3)-O(3)	-106.8(4)	C(19)-C(14)-C(15)-C(16)	-1.4(8)
O(4)-C(2)-C(3)-C(4)	-103.4(4)	C(13)-C(14)-C(15)-C(16)	-178.1(5)
C(1)-C(2)-C(3)-C(4)	12.8(5)	C(14)-C(15)-C(16)-C(17)	1.2(10)
O(1)-N-C(4)-C(5)	59.2(5)	C(15)-C(16)-C(17)-C(18)	-0.9(11)
C(1)-N-C(4)-C(5)	-122.1(4)	C(16)-C(17)-C(18)-C(19)	0.7(11)
O(1)-N-C(4)-C(3)	-174.1(4)	C(15)-C(14)-C(19)-C(18)	1.3(8)
C(1)-N-C(4)-C(3)	4.6(5)	C(13)-C(14)-C(19)-C(18)	177.9(6)
O(3)-C(3)-C(4)-C(5)	-130.8(4)	C(17)-C(18)-C(19)-C(14)	-1.0(10)

C(2)-C(3)-C(4)-C(5)	111.9(4)	C(3)-O(3)-C(20)-C(21)	-168.0(3)
O(3)-C(3)-C(4)-N	106.6(4)	O(3)-C(20)-C(21)-C(22)	-118.9(5)
C(2)-C(3)-C(4)-N	-10.7(4)	O(3)-C(20)-C(21)-C(26)	63.1(6)
C(6)-O(2)-C(5)-C(4)	179.7(4)	C(26)-C(21)-C(22)-C(23)	-1.1(7)
N-C(4)-C(5)-O(2)	77.4(4)	C(20)-C(21)-C(22)-C(23)	-179.2(4)
C(3)-C(4)-C(5)-O(2)	-41.0(5)	C(21)-C(22)-C(23)-C(24)	-0.1(8)
C(5)-O(2)-C(6)-C(7)	-162.9(4)	C(22)-C(23)-C(24)-C(25)	1.4(9)
O(2)-C(6)-C(7)-C(12)	169.1(5)	C(23)-C(24)-C(25)-C(26)	-1.4(10)
O(2)-C(6)-C(7)-C(8)	-11.6(7)	C(24)-C(25)-C(26)-C(21)	0.2(10)
C(12)-C(7)-C(8)-C(9)	1.1(8)	C(22)-C(21)-C(26)-C(25)	1.1(8)
C(6)-C(7)-C(8)-C(9)	-178.2(6)	C(20)-C(21)-C(26)-C(25)	179.2(5)

Section 2: Synthesis of LAB 1 (**72**) and 1, 4-dideoxy-1, 4-imino-D-xylitol (**73**)

As the plethora of biological roles played by carbohydrates has become understood, scientists have realized the great potential of carbohydrate mimics to not only elucidate these processes, but also for their potential therapeutic benefits. One class of such carbohydrate analogs that are of particular interest are the polyhydroxylated pyrrolidine derivatives. Many polyhydroxylated pyrrolidine either isolated from the natural sources or synthesized in the laboratory showed their potential as a glycosidase inhibitors. Particularly 1, 4-dideoxy-1, 4-imino-D-arabinitol (DAB-1) (**76**), isolated from *Angilocalix boutiqueanus* and *Arachniodes standishii* found to inhibit α-glucosidase, while the compounds **72** and **73** are powerful inhibitors of a range of α-glycosidases. Nectrisine **94**[98], a fungal metabolite isolated from *Nectria htckla,* is also a potent α-glucosidase and α-mannosidase inhibitor. Moreover the nitrogen congeners of salacinol[99] **96** and **97** showed the powerful inhibitor activity against glucoamylase (Figure 20).

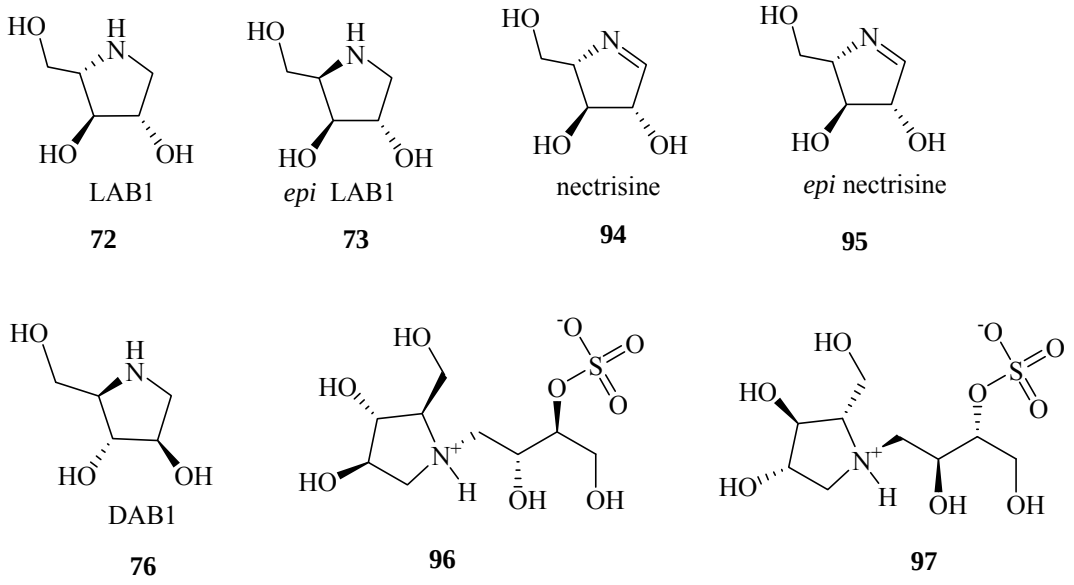


***Figure* 20:** *Bioactive pyrrolidine derivatives*

The structural simplicity and important biological profile for these compounds led to the culmination of a variety of synthesis from several groups[100-105]. However, considering

the ease of synthesis of nitrone **79**, we intended to extend its utility for the synthesis of LAB-1. It can be envisioned that LAB-1 (**72**) and its epimer **73** could be derived from the cyclic nitrones **79** and **98** respectively by exhaustive hydrogenolysis (Figure 21). The synthesis of the C-4 epimeric nitrone could be envisioned from the aldoximes **83** by a simple mesylation and subsequent one pot desilylation-cyclization.

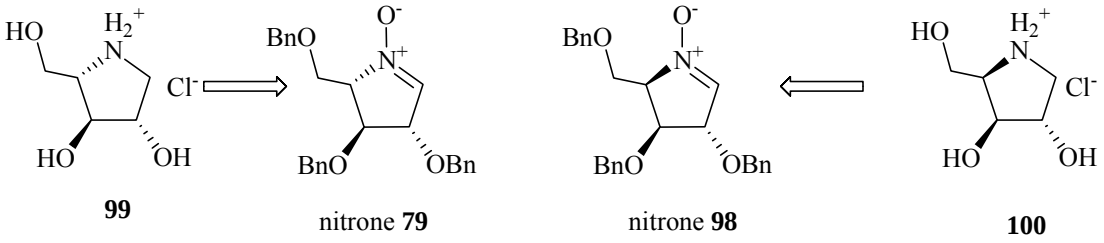
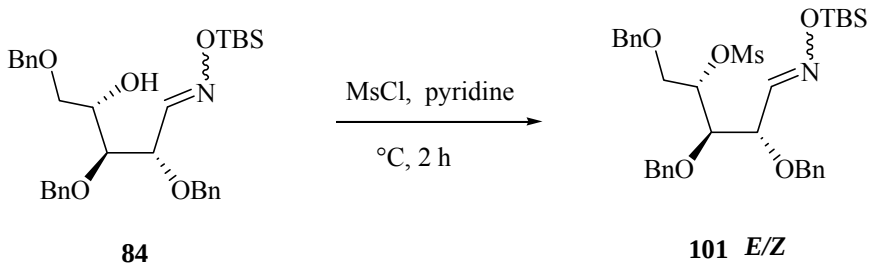


***Figure* 21:** *Retrosynthetic scheme for LAB1 and its epimer*

As intended a minor modification of synthetic scheme used in preparing the cyclic nitrone **79**, provided the desired epimeric nitrone **98**. Thus the mesylation of the compound **83**with methanesulphonyl chloride gave **101** as ***E/Z*** mixture (Scheme 22).

***Scheme* 22**

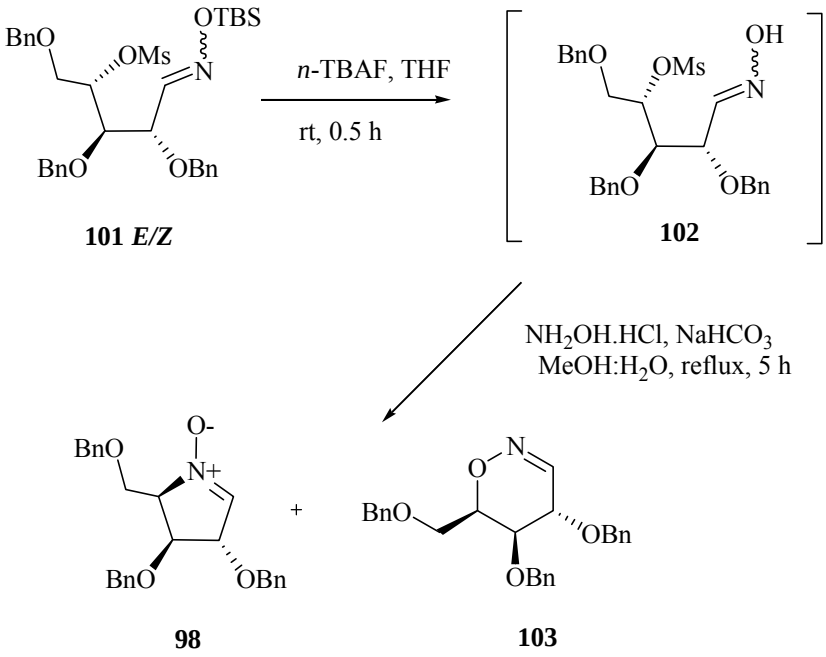


The two singlets at 2.92 ppm (for minor isomer) and 2.93 ppm (for major isomer) due to mesyl groups were identified in the ^{1}H NMR spectrum of **101** while the rest of the spectrum was in complete agreement with the assigned structure. Our next concern was the deprotection of TBS ether and concomitant cyclisation to get nitrone **101**.

The reaction of **101** with *n*-Bu_4NF in THF at an ambient temperature led to the corresponding oxime, the separation of which was not possible by silica gel chromatography, therefore the mixture of (*E/Z*)-isomers was directly used for the cyclisation. Thus, compound **102** upon treatment with hydroxylamine hydrochloride, $NaHCO_3$ in MeOH gave the mixture of desired cyclic nitrone **98** (48%) as well as an oxazine **103** in 26% (Scheme 23).

Depending on the configuration of **102**, the oxime group could act either as an oxygen nucleophile or a nitrogen nucleophile and furnished the corresponding cyclic products. The *Z* isomer produced oxine **103** while *E* isomer ends up with **98**. In the ^{1}H NMR spectrum of the **98,** singlets at 2.92 and 2.93 ppm (mix. of both isomers) due to mesyl groups were missing. The peak at 6.80 ppm of olefin appeared while the rest of the spectrum was in complete agreement with the assigned structure. Further confirmation of the structure of **98** came from its ^{13}C NMR and DEPT spectral data. For example, in the ^{13}C NMR spectrum, olefin carbon was identified at 133.9 ppm. In addition, ESI-MS analysis of **98** indicated peaks at m/z: 418 $[M+H]^+$ and 440 accounting for $[M+Na]^+$. The elemental analysis of **98** was satisfactory (Calcd. for $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.35% Found: C, 74.35; H, 6.81; N, 3.43%).

***Scheme* 23**



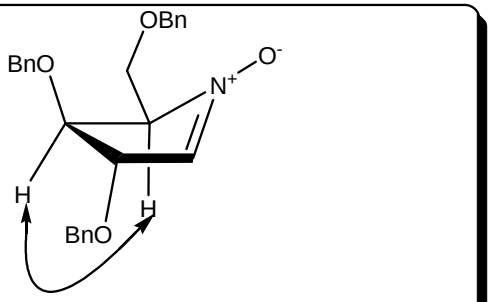
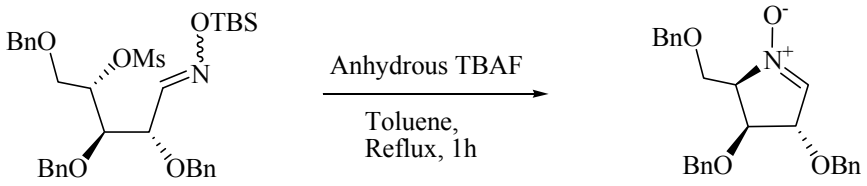


Figure* 22 :** *Key nOe interaction for nitrone **98

The study of relative stereochemistry of cyclic nitrone was carried out by extensive 1D and 2D NMR spectroscopy. Thus by using COSY and NOESY spectra of the nitrone **98** the *cis* pattern for (C-3) and (C-4) substituentes was revealed. In the NOESY spectrum the correlation between the H-C(4) and H-C(3) observed while interactions between H-C(2) with either H-C(3) or with H-C(4) were not found, which clearly confirmed the assigned stereochemistry beyond the doubt (Figure 22). The side product **103** was observed due to competitive intramolecular nucleophilic attack of oxygen. The NMR spectral data of **103** was in full agreement with the assigned structure. Moreover the mass analysis suggested the structure of cyclic hydroxylamine derivative by showing the highest mass peak at *m/z*: 418 $[M+H]^+$

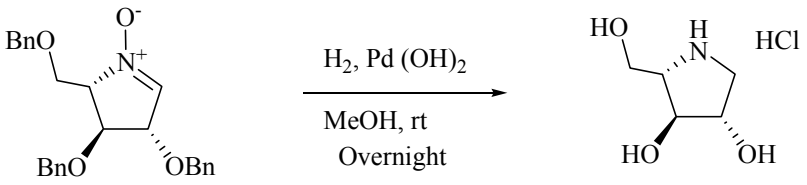
***Scheme* 24**



101 *E/Z* **98**

However, the formation of **103** could be controlled by conducting the silyl deprotection in refluxing toluene with the help of anhydrous *n*-Bu_4NF, which afforded nitrone **98** exclusively in quantitative yield (Scheme 24). The exclusive nitrone formation was expected due to the known thermal stability of *E*-isomer in the equilibrium, which enables nitrogen to act as a nucleophile. As both the chiral cyclic nitrones were in our hand, we next attempted the exhaustive hydrogenolysis to make the bioactive pyrrolidine derivatives.

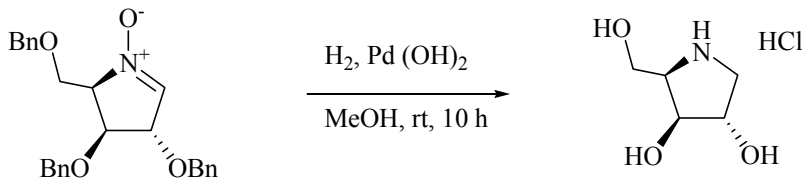
***Scheme* 25**



79 **99**

The direct reduction of nitrone **79** to final products was successfully conducted by using Pd/C in MeOH-HCl under hydrogen at NTP to give the hydrochloride salt of LAB1 (**99**) (Scheme 25). The optical rotation of LAB1 $[\alpha]_D$ –32.5 is in agreement with reported value[106] { $[\alpha]_D$ –34.6}. ^{1}H NMR and ^{13}C NMR in D_2O were showed the positions of all the peaks at their respective positions those reported earlier. Similarly the global reduction of nitrone **98** by using Pearlman's catalyst afforded hydrochloride salts of 1,4-dideoxy-1,4-imino-D-xylitol (**100**) in good yields (95%)(Scheme 26). Here also the optical rotation of **100** was found to be $[\alpha]_D$ +7.3 {Reported optical rotation[107] is {$[\alpha]_D$ + 8.8}. ^{1}H NMR and ^{13}C NMR spectra's of **100** were in full agreement with the reported data [107].

***Scheme* 26**

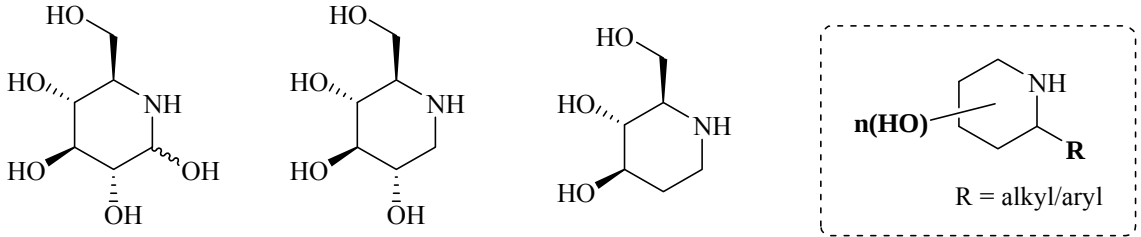


98 **100**

In summary, the synthesis of LAB-1 **(72)** and 1,4-dideoxy-1,4-imino-D-xylitol (**73**) by ready utilization of the sugar cyclic nitrones, which can be derived from a common advanced intermediate is documented. Considering the potential of cyclic nitrones for addition of a variety of nucleophiles, we believe that the reported epimeric nitrones **79** & **98** could serve as a potential precursors for glycosidase inhibitors library syntheses, combined with their biochemical evaluations is progressing in our group.

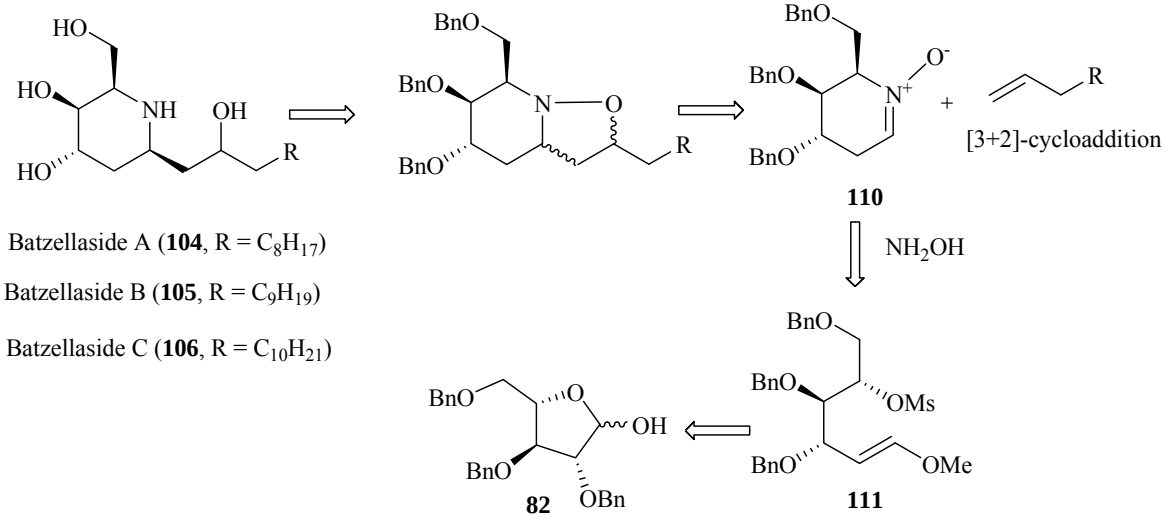
Section 3: Towards the synthesis of Batzellaside A-C

Naturally occurring polyhydroxylated piperidine alkaloids such as deoxymanno-jirimycin and fagomine derivatives have received much attention in recent years (Figure 23). The C-alkylated derivatives of fagomine, Batzellasides A (**104**), B (**105**), and C (**106**) [108] isolated from a *Batzella* sp. sponge, collected off the west coast of Madagascar were attracted the attention because of their intresting activites. Batzellasides inhibited the growth of *Staphylococcus epidermidis* with MICs of 6.3 μg/mL.



Nojirimycin (**107**) 1-deoxynojirimycin (**108**) Fagomine (**109**)

***Figure* 23 :** *Polyhydroxylated piperidine derivatives*



Batzellaside A (**104**, R = C_8H_{17})

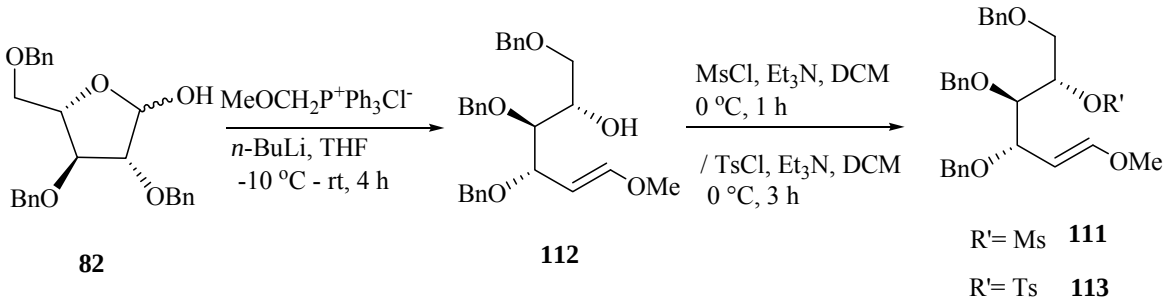
Batzellaside B (**105**, R = C_9H_{19})

Batzellaside C (**106**, R = $C_{10}H_{21}$)

***Figure* 24 :** *Batzellaside natural products and intended retrosynthetic strategy*

We have devised a flexible strategy funded upon our nitrone-based approach that should address not only the synthesis of batzellasides A-C but also the related unnatural analogues by employing commercially available olefins. The retrosynthetic strategy was based on nitrone cycloaddition as a key step with appropriate side chain olefins (Figure 24). The nitrone **110** could be obtained from the mesylate **111**, which in turn could be made from the lactol **82**, an intermediate used in our previous synthesis of radicamines and related pyrrolidine alkaloids.

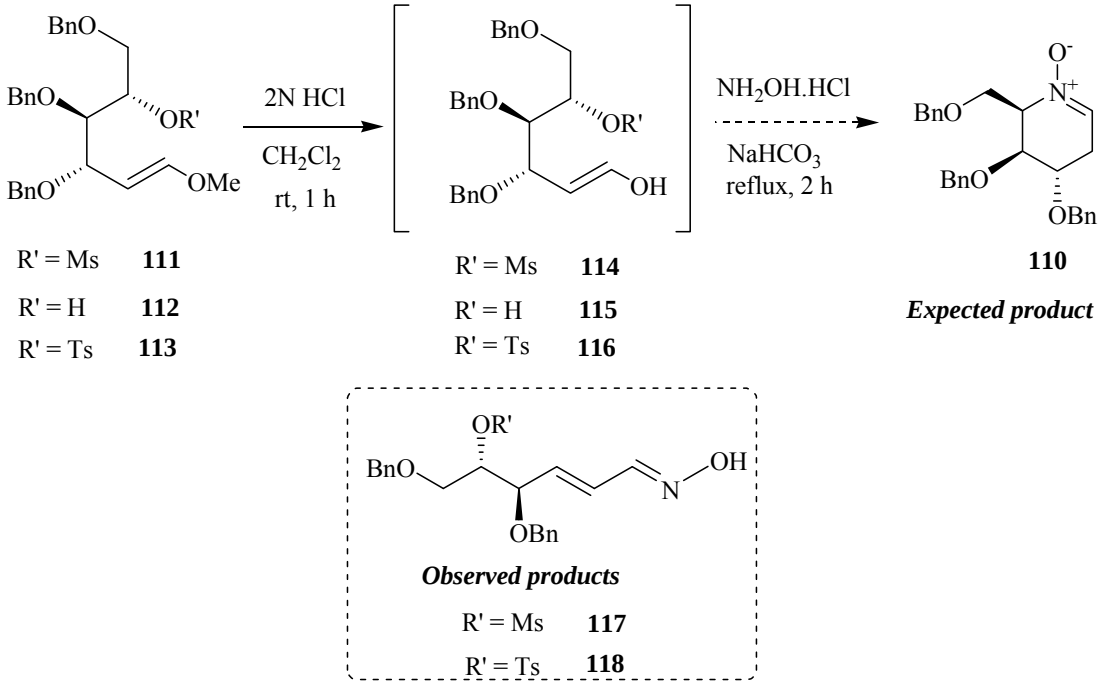
***Scheme* 27**



82 **112**

Thus our synthesis started with Wittig reaction of the lactol **82** (Scheme 27). Treatment of **82** with methoxymethyltriphenylphosponiumchloride[109] in the presence of *n*-BuLi gave the olefin **112** in 55% yield. In the ^{1}H NMR spectrum of **112**, a singlet due to methoxy group at 3.52 ppm, the doublet of a doublet at 4.83 ppm ($J_{1,2}$ = 9.5 Hz, $J_{1,3}$ = 13 Hz) and a doublet at 6.45 ppm ($J_{1,2}$ = 13 Hz) were observed. The ESI-MS showed peak at *m/z*: 449 accounting for $[M+H]^+$. The mesylation of **112** by using MsCl and Et_3N in DCM afforded **111**. This compound was subsequently subjected to hydrolysis and then reacted with hydroxylamine.hydrochloride in presence of $NaHCO_3$ (Scheme 28).

***Scheme* 28**



The spectral data of the resulting product were not in agreement with the structure of expected nitrone **110**. In the ^{1}H NMR of the product resulted, we noticed the presence of two benzyl groups instead of three and also the mesyl group was intact. In addition to 10 aromatic protons there are four more H, appeared above 6.0 ppm [5.96 (dd, 1H, *J* = 16.1, 7.3 Hz), 6.40 (dd, 1H, *J* = 16.1, 10.3 Hz), 7.80 (d, 1H, *J* = 10.3 Hz), 9.0 (br. s, 1H)] which indicated the presence of a conjugated oxime. The downfield broad peak at 8.92 ppm was assigned to hydroxyl proton and the doublet at 7.80 ppm was assigned as H-C=N-OH. The large coupling constant 16.1 clearly indicated the *E*-configuration of the internal olefin. Coupled with ^{13}C NMR spectra, we concluded that the product obtained was a conjugated oxime **117** resulting from the 1,4-elimination of a benzyloxy group. The plausible way for the elimination of benzyl alcohol is the 1,4-elimination as shown in Figure 25. Changing the leaving group from mesyl to tosyl also provided the same type of elimination product **118**.

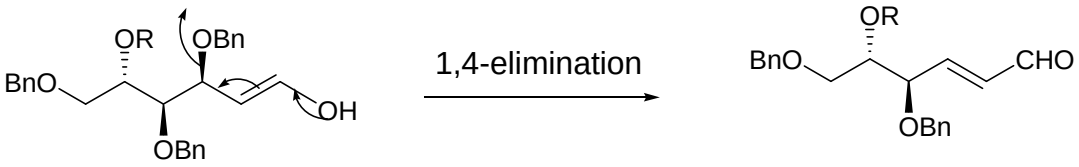


***Figure* 25:** *Facile 1,4-elimination*

Later it was found that the **112** was unstable in solution. When left at room temperature for some hours in $CDCl_3$, **112** transformed completely to the corresponding conjugated aldehyde **119** (Scheme 29)**.** The assigned structure of **119** was confirmed by ^1H NMR and ^{13}C NMR spectra. In the ^1H NMR spectrum, the characteristic doublet at 9.43 ppm (J = 7.8 Hz) due to aldehydic proton was observed. The olefin protons resonated at 6.19 ppm (ddd, J = 16, 7.8, 0.89 Hz) and at 6.72 ppm (dd, J = 16, 5.8 Hz). In addition, the ^{13}C NMR spectrum showed peak at 193 ppm due to α,β-unsaturated aldehyde while the olefin carbons resonated at 133.7 ppm and 153.7 ppm.

After hydrolysis of **119,** the crude mixture obtained (**115**) was subjected to LAH reduction which afforded the allylic alcohol **120** instead of the corresponding saturated 1,5-diol derivative. This compound was characterized by spectral as well as by analytical data. The compound **115** was also subjected to linear nitrone formation by using the standard reaction conditions to afford conjugated nitrone **121** whose structure was confirmed by single crystal X-ray structural analysis (Figure 26).

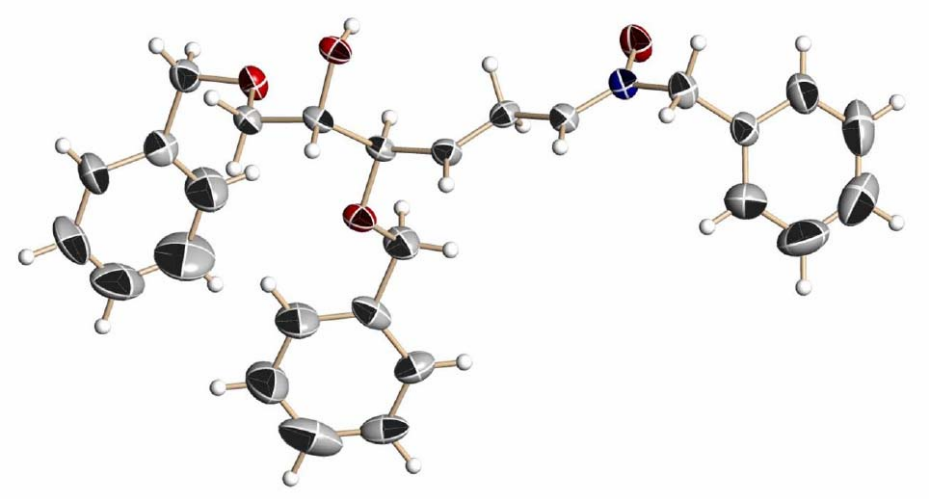
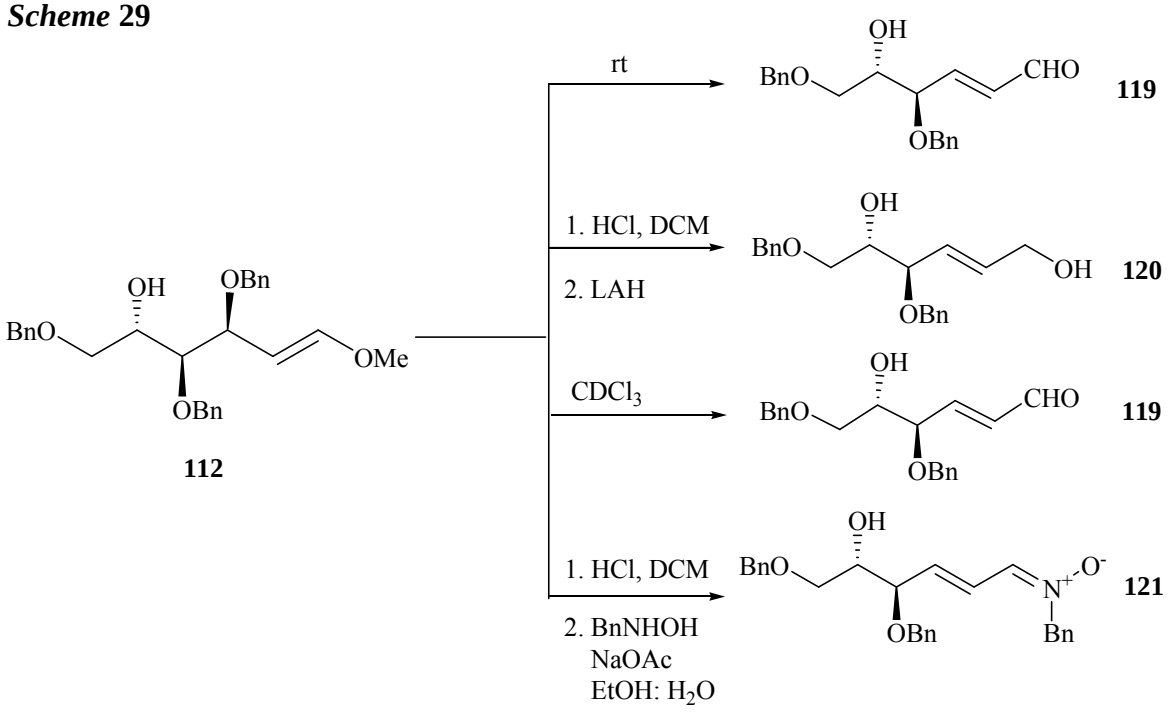


***Figure* 26:** *ORTEP digram for conjugated nitrone* **121**

***Scheme* 29**



Considering the inadvertent sensitivity of the intermediates we prepared, we opted for an alternative strategy, which involves the prior construction of piperidine ring followed by the oxidation of piperidine **122** to derive the key nitrone **110**. The synthesis of piperidine **122** was anticipated by an intramolecular hydroboration–cycloalkylation[110] reaction of the azidoalkene **123** (Figure 27).

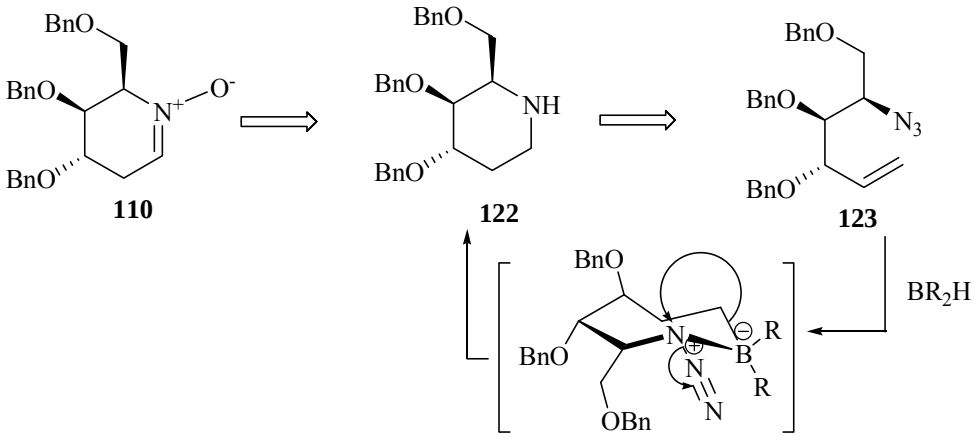
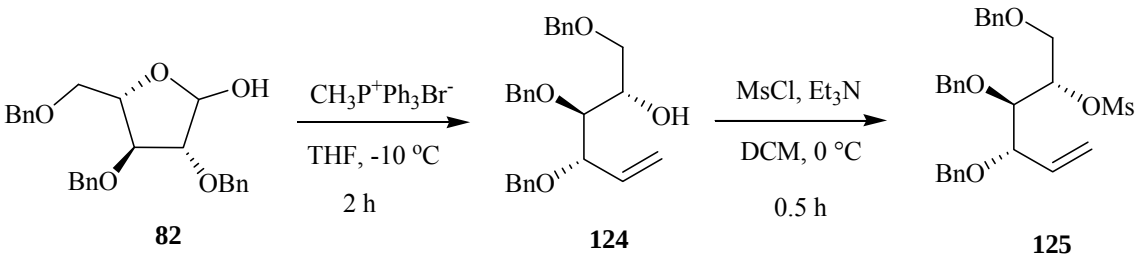


***Figure* 27:** *Alternative Strategy for Nitrone **110** and the key borane mediated piperidine ring construction from an azidoalkene*

The synthesis of key azidoalkene **123** was started with the one carbon Wittig homologation of lactol **82** to afford compound **124**. The spectral and analytical data of the compound **124** was in accordance with the assigned structure.

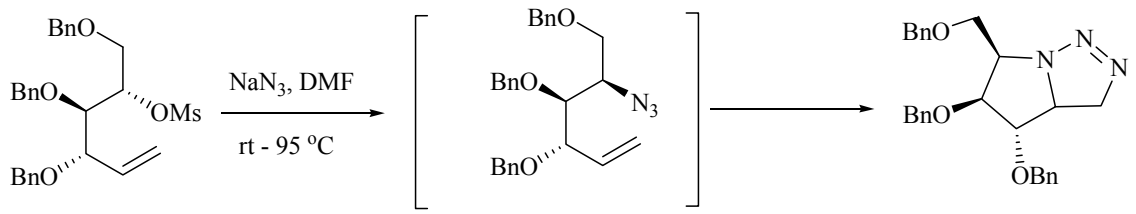
***Scheme* 30**



In order to incorporate azide functionality at C5 carbon, the hydroxyl group was first converted into its mesyl derivative (**125**) by using MsCl and Et_3N in good to moderate yield. The characteristic methyl signal of mesyl group was identified at 2.94 ppm as a singlet in the ^{1}H NMR spectrum of **125** and at 38.6 ppm in ^{13}C NMR spectrum. The structure of **125** was further confirmed by observing its mass spectrum (the peak located at *m/z*: 497 due to $[M+H]^+$) and satisfactory elemental analysis.

The attempted nucleophilic displacement reaction of mesylate **125** was carried out with NaN_3 in DMF was found to sluggish and even at 95 ^{o}C in presence of the phase transfer catalyst and took nearly 4-5 days for the complete disappearance of the starting compound and discouragingly provided the [3+2] cycloaddition product **126** in moderate yield (Scheme 31). The missing of terminal double bond {5.28 (dd, 1H, J = 9.1, 1.5 Hz), 5.35 (d, 1H, J = 1.5 Hz), 5.75-5.96 (m, 1H)}**,** and mesyl group {2.95 (s, 3H)} in ^{1}H NMR indicates that intramolecular [3+2] cycloaddition reaction takes place between azide and terminal olefin. This was also supported by ^{13}C NMR showing all peaks of assigned cycloadduct **126**. In DEPT, five negative peaks were observed which compliments our observation. Changing the leaving group from mesyl to a tosyl or a triflate derivatives were found to be no use and their reaction with NaN_3 resulted in the complex mixtures.

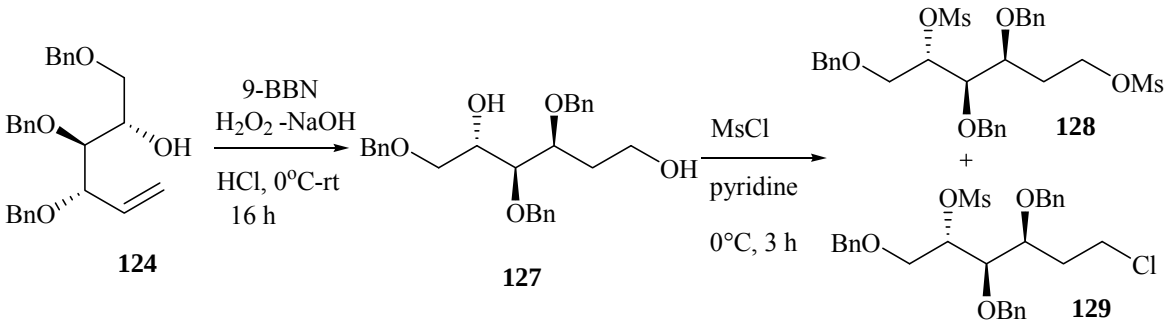
***Scheme* 31**



125 **123** **126**

To circumvent this problem, we followed an alternative approach for the synthesis of **122**. Hydroboration followed by oxidation of olefin **124** by using 9-BBN and $NaOH/H_2O_2$ gave **127**. The ^1H NMR and ^{13}C NMR spectra of **127** showed resonances characteristic for diol compound. The compound **127** was then treated with 2.5 equivalents of mesyl chloride in pyridine to afford **128** along with chloromesyl derivative (**129**) (Scheme 32).

***Scheme* 32**

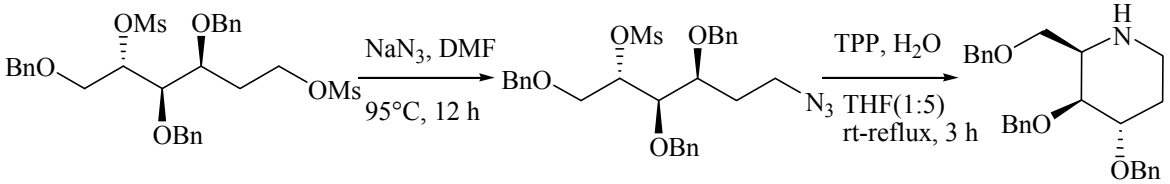


124 **127**

In the ^1H NMR of **128**, two clear singlets at 2.87 ppm and at 2.97 ppm due to two diferent mesyloxy group were observed while in the ^1H NMR of **129** only one singlet at 2.96 ppm was observed and rest of the signals were found inconsistent to the assigned structure.

Subsequently, the dimesylate **128** was treated with NaN_3 in DMF at 95 ^oC to afford the mono azide derivative **130** selectively. In the ^1H NMR of **130**, the characteristic singlet of primary mesyloxy group at 2.87 ppm was absent and C1-protons shifted up field. The presence of a moderately strong peak at 2101 cm^{-1} in the IR spectrum of compound **130** confirmed the presence of an azide group.

***Scheme* 33**

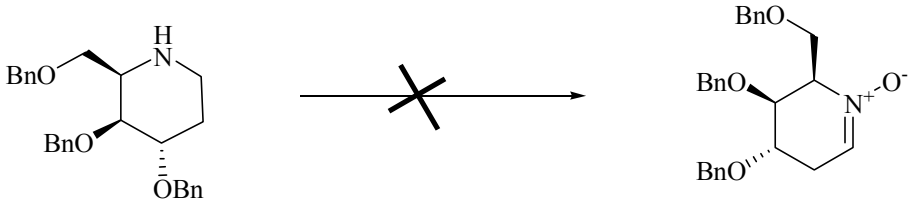


128 **130** **122**

Reduction of azido compound **130** under Staudinger conditions[111] provided the fagomine derivative **122**. The ^{1}H, ^{13}C NMR and Maldi-TOF MS spectral data clearly confirmed the structure of **122.** The optical rotation of the protected piperidine **122** was similar in magnitude but opposite in sign with that of reported *ent*-**122**[112] (Scheme 33).

As we successfully obtained the piperidine derivative (**122)**, our next concern was the preparation of cyclic nitrone **110** and completing the total synthesis of Batzellasides. However, under a variety of conditions[113] generally used for the oxidation of secondary cyclic amines to nitrones, oxidation of **122** was failed in our hand, which is unexpected and the synthesis of Batzellasides A-C using the nitrone approach was terminated at this stage (Scheme 34).

***Scheme* 34**



122 **110**

Sr.No	Reagents	Results
1	*m*-CPBA	No reaction
2	H_2O_2/ HgO	Decomposed
3	H_2O_2/ SeO_2	No reaction
4	Dimethyldioxirane (DMD)	No reaction

Table 1
Crystal data and structure refinement for **121**

Identification code	Compound
Empirical formula	$C_{27}H_{30}NO_4$
Formula weight	432.52
Temperature	297(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, $P2_1$
Unit cell dimensions	a = 13.941(6) Å, α = 90°. b = 4.982(2) Å, β = 106.9(7)°. c = 17.996(8) Å, γ = 90°.
Volume	1196.0(9) $Å^3$
Z, Calculated density	2, 1.201 mg/m^3
Absorption coefficient	0.080 mm^{-1}
F(000)	462
Crystal size	0.45 x 0.34 x 0.11 mm
Theta range for data collection	2.37 to 25.00°
Limiting indices	-16<=h<=16, -5<=k<=5, -21<=l<=21
Reflections collected / unique	8568 / 3997 [R(int) = 0.0180]
Completeness to theta = 25.00	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9914 and 0.9652
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3997 / 7 / 338

Goodness-of-fit on F^2	1.091
Final R indices [I^2 sigma(I)]	R1 = 0.0602, wR2 = 0.1523
R indices (all data)	R1 = 0.0729, wR2 = 0.1616
Absolute structure parameter	0.9(17)
Largest diff. peak and hole	0.260 and -0.247 e. $Å^{-3}$

Table 2
Bond lengths [Å] and angles [°] for **121**

O(1)-C(6)	1.404(4)	C(2)-C(3)-C(4)	126.3(3)
O(1)-C(7)	1.428(4)	O(3)-C(4)-C(3)	111.4(2)
O(2)-C(5)	1.428(3)	O(3)-C(4)-C(5)	105.9(2)
O(3)-C(21)	1.414(4)	C(3)-C(4)-C(5)	111.3(2)
O(3)-C(4)	1.431(3)	O(2)-C(5)-C(6)	111.7(2)
O(4)-N(1)	1.281(3)	O(2)-C(5)-C(4)	109.5(2)
N(1)-C(1)	1.300(4)	C(6)-C(5)-C(4)	114.7(2)
N(1)-C(14)	1.487(4)	O(1)-C(6)-C(5)	111.0(3)
C(1)-C(2)	1.436(4)	C(8')-C(7)-O(1)	121.5(3)
C(2)-C(3)	1.319(4)	C(8')-C(7)-C(8)	17.37(6)
C(3)-C(4)	1.489(4)	O(1)-C(7)-C(8)	110.0(3)
C(4)-C(5)	1.522(4)	C(9')-C(8')-C(13')	120.0
C(5)-C(6)	1.504(4)	C(9')-C(8')-C(7)	127.9(4)
C(7)-C(8')	1.418(5)	C(13')-C(8')-C(7)	112.1(4)
C(7)-C(8)	1.530(5)	C(8')-C(9')-C(10')	120.0
C(8')-C(9')	1.3900	C(11')-C(10')-C(9')	120.0
C(8')-C(13')	1.3900	C(12')-C(11')-C(10')	120.0
C(9')-C(10')	1.3900	C(11')-C(12')-C(13')	120.0
C(10')-C(11')	1.3900	C(12')-C(13')-C(8')	120.0
C(11')-C(12')	1.3900	C(9)-C(8)-C(13)	120.0
C(12')-C(13')	1.3900	C(9)-C(8)-C(7)	119.2(3)

C(8)-C(9)	1.3900	C(13)-C(8)-C(7)	120.7(3)
C(8)-C(13)	1.3901	C(10)-C(9)-C(8)	120.0
C(9)-C(10)	1.3900	C(9)-C(10)-C(11)	120.0
C(10)-C(11)	1.3901	C(12)-C(11)-C(10)	120.0
C(11)-C(12)	1.3899	C(11)-C(12)-C(13)	120.0
C(12)-C(13)	1.3900	C(12)-C(13)-C(8)	120.0
C(14)-C(15)	1.499(5)	N(1)-C(14)-C(15)	110.6(3)
C(15)-C(20)	1.348(6)	C(20)-C(15)-C(16)	117.1(4)
C(15)-C(16)	1.375(6)	C(20)-C(15)-C(14)	121.5(4)
C(16)-C(17)	1.354(7)	C(16)-C(15)-C(14)	121.4(4)
C(17)-C(18)	1.339(9)	C(17)-C(16)-C(15)	122.1(5)
C(18)-C(19)	1.357(11)	C(18)-C(17)-C(16)	119.9(6)
C(19)-C(20)	1.398(9)	C(17)-C(18)-C(19)	120.9(6)
C(21)-C(22')	1.470(4)	C(18)-C(19)-C(20)	118.4(6)
C(21)-C(22)	1.516(4)	C(15)-C(20)-C(19)	121.6(6)
C(22)-C(23)	1.3900	O(3)-C(21)-C(22')	109.9(3)
C(22)-C(27)	1.3900	O(3)-C(21)-C(22)	109.2(3)
C(23)-C(24)	1.3900	C(22')-C(21)-C(22)	1.1
C(24)-C(25)	1.3900	C(23)-C(22)-C(27)	120.0
C(25)-C(26)	1.3900	C(23)-C(22)-C(21)	118.1(3)
C(26)-C(27)	1.3900	C(27)-C(22)-C(21)	121.8(3)
C(22')-C(23')	1.3900	C(22)-C(23)-C(24)	120.0
C(22')-C(27')	1.3900	C(25)-C(24)-C(23)	120.0
C(23')-C(24')	1.3900	C(24)-C(25)-C(26)	120.0
C(24')-C(25')	1.3900	C(27)-C(26)-C(25)	120.0
C(25')-C(26')	1.3900	C(26)-C(27)-C(22)	120.0
C(26')-C(27')	1.3900	C(23')-C(22')-C(27')	120.0
C(6)-O(1)-C(7)	111.1(3)	C(23')-C(22')-C(21)	121.7(3)
C(21)-O(3)-C(4)	112.6(2)	C(27')-C(22')-C(21)	118.1(3)
O(4)-N(1)-C(1)	124.4(3)	C(24')-C(23')-C(22')	120.0
O(4)-N(1)-C(14)	115.0(3)	C(23')-C(24')-C(25')	120.0

C(1)-N(1)-C(14)	120.5(3)	C(26')-C(25')-C(24')	120.0
N(1)-C(1)-C(2)	123.0(3)	C(25')-C(26')-C(27')	120.0
C(3)-C(2)-C(1)	122.4(3)	C(26')-C(27')-C(22')	120.0

Table 3
Torsion angles [°] for **121**

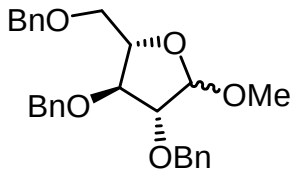
O(4)-N(1)-C(1)-C(2)	-1.1(5)	C(8)-C(9)-C(10)-C(11)	0.0
C(14)-N(1)-C(1)-C(2)	179.7(3)	C(9)-C(10)-C(11)-C(12)	0.0
N(1)-C(1)-C(2)-C(3)	176.3(3)	C(10)-C(11)-C(12)-C(13)	0.0
C(1)-C(2)-C(3)-C(4)	176.4(3)	C(11)-C(12)-C(13)-C(8)	0.0
C(21)-O(3)-C(4)-C(3)	-77.1(3)	C(9)-C(8)-C(13)-C(12)	0.0
C(21)-O(3)-C(4)-C(5)	161.8(3)	O(4)-N(1)-C(14)-C(15)	67.8(4)
C(2)-C(3)-C(4)-O(3)	128.8(3)	C(1)-N(1)-C(14)-C(15)	111.5(3)
C(2)-C(3)-C(4)-C(5)	-113.3(3)	N(1)-C(14)-C(15)-C(20)	80.6(5)
O(3)-C(4)-C(5)-O(2)	179.7(2)	N(1)-C(14)-C(15)-C(16)	98.8(4)
C(3)-C(4)-C(5)-O(2)	58.5(3)	C(20)-C(15)-C(16)-C(17)	-0.4(7)
O(3)-C(4)-C(5)-C(6)	-53.9(3)	C(14)-C(15)-C(16)-C(17)	179.8(4)
C(3)-C(4)-C(5)-C(6)	-175.0(3)	C(15)-C(16)-C(17)-C(18)	0.9(9)
C(7)-O(1)-C(6)-C(5)	-173.3(2)	C(16)-C(17)-C(18)-C(19)	-1.5(10)
O(2)-C(5)-C(6)-O(1)	69.8(3)	C(17)-C(18)-C(19)-C(20)	1.6(11)
C(4)-C(5)-C(6)-O(1)	-55.5(3)	C(16)-C(15)-C(20)-C(19)	0.6(8)
C(6)-O(1)-C(7)-C(8')	-57.3(5)	C(14)-C(15)-C(20)-C(19)	179.9(5)
C(6)-O(1)-C(7)-C(8)	-71.8(4)	C(18)-C(19)-C(20)-C(15)	-1.2(10)
O(1)-C(7)-C(8')-C(9')	94.1(5)	C(4)-O(3)-C(21)-C(22')	-173.6(3)
C(8)-C(7)-C(8')-C(9')	146.2(3)	C(4)-O(3)-C(21)-C(22)	-174.5(3)
O(1)-C(7)-C(8')-C(13')	-83.9(5)	O(3)-C(21)-C(22)-C(23)	37.6(4)
C(8)-C(7)-C(8')-C(13')	-31.79(11)	C(22')-C(21)-C(22)-C(23)	-91.5(4)
C(13')-C(8')-C(9')-C(10')	0.0	O(3)-C(21)-C(22)-C(27)	-145.4(3)
C(7)-C(8')-C(9')-C(10')	-177.9(4)	C(22')-C(21)-C(22)-C(27)	85.5(5)
C(8')-C(9')-C(10')-C(11')	0.0	C(27)-C(22)-C(23)-C(24)	0.0
C(9')-C(10')-C(11')-C(12')	0.0	C(21)-C(22)-C(23)-C(24)	177.0(3)

C(10')-C(11')-C(12')-C(13')	0.0	C(22)-C(23)-C(24)-C(25)	0.0
C(11')-C(12')-C(13')-C(8')	0.0	C(23)-C(24)-C(25)-C(26)	0.0
C(9')-C(8')-C(13')-C(12')	0.0	C(24)-C(25)-C(26)-C(27)	0.0
C(7)-C(8')-C(13')-C(12')	178.2(4)	C(26)-C(27)-C(22)	0.0
C(8')-C(7)-C(8)-C(9)	-5.4(3)	C(25)-C(23)-C(22)-C(27)-C(26)	0.0
O(1)-C(7)-C(8)-C(9)	128.9(4)	C(21)-C(22)-C(27)-C(26)	-176.9(3)
C(8')-C(7)-C(8)-C(13)	177.00(6)	O(3)-C(21)-C(22')-C(23')	-27.4(5)
O(1)-C(7)-C(8)-C(13)	-48.8(5)	C(22)-C(21)-C(22')-C(23')	23.8(3)
C(13)-C(8)-C(9)-C(10)	0.0	O(3)-C(21)-C(22')-C(27')	158.6(3)
C(7)-C(8)-C(9)-C(10)	-177.7(4)	C(22)-C(21)-C(22')-C(27')	-150.2(6)
C(27')-C(22')-C(23')-C(24')	0.0	C(21)-C(22')-C(23')-C(24')	-173.9(3)
C(22')-C(23')-C(24')-C(25')	0.0	C(23')-C(24')-C(25')-C(26')	0.0
C(24')-C(25')-C(26')-C(27')	0.0	C(25')-C(26')-C(27')-C(22')	0.0
C(23')-C(22')-C(27')-C(26')	0.0	C(21)-C(22')-C(27')-C(26')	174.1(3)

Symmetry transformations used to generate equivalent atoms:

EXPERIMENTAL

Methyl 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**81**).

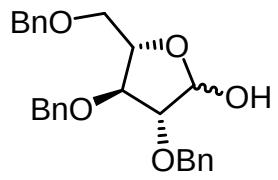


A solution of L-arabinose (3.2 g, 21.3 mmol) and con. H_2SO_4 (0.25 mL) in dry methanol (50 mL) was stirred for 24 h at room temperature. The reaction mixture was neutralized with $NaHCO_3$, filtered through Celite, washed with methanol and concentrated. The resulting syrup was used in the next step without further purification. To the above residue (3.5 g, 21.3 mmol) in DMF (50 mL), NaH (60% dispersion in mineral oil, 4.3 g, 106.7 mmol) and BnBr (9.1 mL, 76.8 mmol) were added slowly at 0 ^oC. After being stirred at room temperature for 12 h, 50 mL of saturated aqueous NH_4Cl was added. The resulting crude syrupy mixture was extracted with EtOAc, washed with water, brine, dried (Na_2SO_4) and concentrated to give methyl furanoside **81** as a syrup.

^{1}H NMR (200 MHz) **:** δ 3.39-3.41 (2s, 3H), 3.60-3.64 (m, 2 H), 3.88-3.93 (m, 1H), 3.98-4.03 (m, 1H), 4.17-428 (m, 1H), 4.42-4.62 (m, 6H), 4.97 (d, 1H, *J* = 3.0 Hz), 7.28-7.41 (m, 15H)

^{13}C NMR (50 MHz) **:** 54.9, 69.8, 71.8, 72.1, 73.3, 80.9, 83.4, 88.0, 107.2, 127.5, 127.8, 128.3, 137.5, 137.8, 138.0 ppm

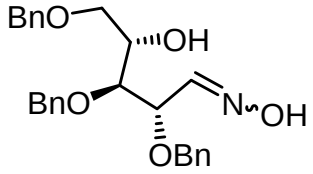
2,3,5-Tri-*O*-benzyl-L-arabinofuranose (82).



Methyl 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**81**) thus obtained was dissolved in 40 mL of glacial acetic acid, treated with 6N HCl (6 mL) and heated at 65 ^{o}C for 1 h. The reaction mixture was cooled, diluted with water and extracted by using EtOAc. The combined organic extract was washed with aqueous $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated to give crude lactol, which was purified on silica gel using ethyl acetate-light petroleum ether (1:6) to afford **82** as a white solid.

Yield	**:**	5.1 g, 57% after 3 steps.
Mol. Formula	**:**	$C_{26}H_{28}O_5$
M.P.	**:**	79 °C Lit.[36a] 79-81 ^{o}C
$[\alpha]_D^{25}$	**:**	–4.3 (*c* = 4.3, CH_2Cl_2) {Lit.[36b] – 4.4 (*c* = 5, CH_2Cl_2)}
Elemental Analysis		Calcd: C, 74.29; H, 6.67%
		found: C, 73.99; H, 6.70%

1*E*/*1Z*-2,3,5-Tri-*O*-benzyl-L-arabinose oxime (**83**).

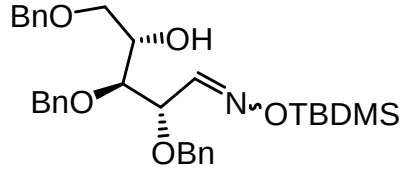


To a solution of **82** (5.0 g, 11.9 mmol) in ethanol (30 mL) was added hydroxylamine.hydrochloride (6.6 g, 95.2 mmol), $NaHCO_3$ (8.0 g, 95.2 mmol) and the mixture was heated to reflux for 2 h. The reaction mixture was filtered through Celite and the Celite pad was washed several times with ethanol. After concentration, the residue was extracted with EtOAc, washed with brine, dried (Na_2SO_4) and concentrated. The crude

product was purified on silica gel using ethyl acetate-light petroleum ether (1:4) to afford an inseparable mixture of *E*-**83** and *Z*-**83** as thick oil**.**

Yield	**:**	4.9 g, 95%
Mol. Formula	**:**	$C_{26}H_{29}NO_5$
$[\alpha]_D^{25}$	**:**	9.4 (*c* = 1.5, CH_2Cl_2)
IR ($CHCl_3$) $\tilde{\nu}$	**:**	3368, 3064, 3031, 2867, 2248,1496, 1365,1092, 910, 698 cm^{-1}
^{1}H NMR (200 MHz)	**:**	δ 3.57-3.66 (m, 2.7H), 3.69 (d, 0.3H, *J* = 3.5 Hz), 3.85 (dd, 0.3H, *J* = 7.6, 2.8 Hz), 4.02 (m, 1H), 4.26 (dd, 0.7H, *J* = 7.9, 3.7 Hz), 4.35-4.66 (m, 6H), 6.90 (s, 0.3H), 7.25-7.31 (m, 15H), 7.48 (d, 0.7H, *J* = 7.7 Hz), 8.13 (br. s, 1H)
^{13}C NMR (50 MHz)	**:**	69.8, 69.9, 70.95, 70.99, 71.4, 71.9, 72.6, 73.4, 73.6, 74.2, 74.3, 76.7, 79.2, 80.2, 127.8-128.5, 137.4, 137.6, 137.7-137.8, 150.0, 152.3 ppm
ESI MS *m/z*	**:**	436 $[M+H]^+$, 458 $[M+Na]^+$
Elemental Analysis		Calcd: C, 71.72; H, 6.67; N, 3.22%
		Found: C, 71.65; H, 6.83; N, 3.41%

1*E* /1*Z*-2,3,5-Tri-*O*-benzyl-L-arabinose-*O*-[*tert*-butyldimethylsilyl]oximes (84).



The oximes **83** (4.5 g, 10.3 mmol) were dissolved in dry pyridine (30 mL) and treated with TBDMSCl (1.9 g, 12.4 mmol) at 0 ^oC and the reaction mixture was allowed to stir at room temperature for 36 h. To this, water (30 mL) was added and extracted with EtOAc. The combined organic layer was successively washed with aqueous $CuSO_4$, brine,

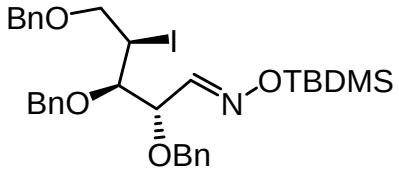
dried (Na_2SO_4) and concentrated. Purification of the residue on silica gel using ethyl acetate-light petroleum ether (1:4) gave a mixture of *E*-**84**/*Z*-**84** as colorless oil.

Yield	**:**	5.2 g, 91%
Mol. Formula	**:**	$C_{32}H_{43}NO_5Si$
$[\alpha]_D^{25}$	**:**	–13.4 (*c* = 0.6, EtOH)
IR ($CHCl_3$) $\tilde{\nu}$	**:**	3401, 2926, 2869, 2252, 1496, 1454, 1364, 1098, 909, 698 cm^{-1}
^{1}**H NMR** (200 MHz)	**:**	δ 0.16, 0.18 (2s, 6H), 0.91 (s, 3H), 0.95 (s, 6H), 3.55-3.59 (m, 2H), 3.67 (dd, 0.7H, *J* = 6.6, 3.7 Hz), 3.84 (dd, 0.3H, *J* = 6.6, 3.5 Hz), 4.0 (br. s, 1H), 4.27 (dd, 0.7H, *J* = 7.7, 3.6 Hz), 5.06 (m, 0.3H), 4.34-4.67 (m, 7H), 7.12 (d, 0.3H, *J* = 6.0 Hz), 7.25-7.30 (m, 15H), 7.56 (m, 0.7H)
^{13}**C NMR** (50 MHz)	**:**	–5.34, –5.26, 18.0, 18.2, 25.9, 26.1, 69.8, 70.0, 70.7, 70.8, 71.1, 72.1, 72.5, 73.3, 73.4, 74.0, 74.1, 76.3, 79.0, 80.0, 127.7, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 137.3, 137.8, 137.9. 153.1, 156.1 ppm
ESI MS *m/z*	**:**	550 $[M+H]^+$, 572 $[M+Na]^+$
Elemental Analysis		Calcd: C, 69.94; H, 7.83; N, 2.55%
		Found: C, 69.58; H, 7.30; N, 2.44%

1*E*/1*Z*-2,3,5-Tri-*O*-benzyl-4-deoxy-4-iodo-D-xylose-*O*-[*tert*-butyldimethylsilyl]oximes (*E*-85/*Z*-85).

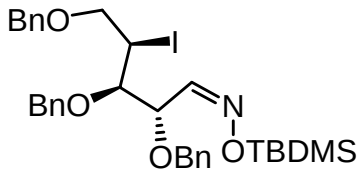
A mixture of **84** (3.5 g, 6.4 mmol), imidazole (1.3 g, 19.2 mmol), Ph_3P (5.1 g, 19.2 mmol) and I_2 (3.2 g, 12.8 mmol) in toluene (50 mL) was stirred under reflux for 3 h. The reaction mixture was cooled, an equal volume of sat. $NaHCO_3$ solution was added and stirred for 10 min. I_2 was added in portion until the organic phase remained violet and stirring continued for an additional 15 min. To this $Na_2S_2O_3$ solution was added to quench

excess iodine and diluted with toluene. The phases were separated and the organic phase was washed with H_2O, brine, dried (Na_2SO_4) and concentrated. Purification of the residue on flash silica gel using ethyl acetate-light petroleum ether (1:4) afforded ***E*-85/*Z*-85** as colorless oils.



***E*-85**

Yield	**:**	2.5 g, 59%
Mol. Formula	**:**	$C_{32}H_{42}INO_4Si$
$[\alpha]_D^{25}$	**:**	–4.38 (*c* = 1.1, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	**:**	3683, 3619, 2930, 2859, 1731, 1047, 930, 840 cm^{-1}
^{1}H NMR (400 MHz)	**:**	δ 0.2 (s, 6H, *J* = 3.0 Hz), 0.97 (s, 9H), 3.52 (dd, 1H, *J* = 7.3, 3.0 Hz), 3.66 (dd, 1H, *J* = 9.8, 5.3 Hz), 3.76 (t, 1H, *J* = 9.8 Hz), 4.15 (m, 1H), 4.32 (t, 1H, *J* = 7.8 Hz), 4.38 (s, 2H), 4.43, 4.57, 4.69, 4.92 (4d, 4H, *J* = 11.5 Hz), 7.25-7.32 (m, 15H), 7.38 (d, 1H, *J* = 7.8 Hz)
^{13}C NMR (50 MHz)	**:**	–5.2, 18.2, 26.1, 31.4, 71.5, 72.6, 72.8, 74.8, 77.5, 81.4, 127.5, 127.7, 127.8, 128.0, 128.2, 128.3, 128.4, 137.6, 138.4, 151.7 ppm
ESI MS *m/z*	**:**	660 $[M+H]^+$
Elemental Analysis		Calcd: C, 58.27; H, 6.37; N, 2.12%
		Found: C, 58.79; H, 6.36; N, 2.10%



***Z*-85**

Yield : 0.4 g, 9%

Mol. Formula : $C_{32}H_{42}INO_4Si$

$[\alpha]_D^{25}$: 11.6 (c = 3, CH_2Cl_2)

IR ($CHCl_3$) $\tilde{\nu}$: 3442, 2955, 2930, 2859, 2253, 1454, 1253, 1092, 785, 690 cm^{-1}

^{1}H NMR (400 MHz) : δ 0.18 (s, 6H), 0.94 (s, 9H), 3.59 (dd, 1H, J = 10.5, 5.8 Hz), 3.70 (m, 2H), 4.30 (m, 1H), 4.35, 4.40 (2d, 2H, J = 11.8 Hz), 4.39, 4.54 (2d, 2H, J = 11.5 Hz), 4.67, 4.75 (2d, 2H, J = 11.3 Hz), 5.14 (t, 1H, J = 5.8 Hz), 6.94 (d, 1H, J = 6.5 Hz), 7.25-7.32 (m, 15H)

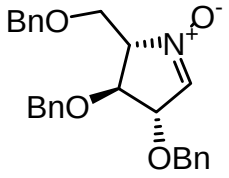
^{13}C NMR (125 MHz) : –5.2, –5.1, 18.0, 26.0, 31.3, 72.2, 72.7, 72.8, 73.9, 74.6, 78.6, 127.7, 127.8, 127.9, 128.0, 128.3, 128.4, 137.4, 137.8, 138.0, 154.0 ppm

ESI MS *m/z* : 660 $[M+H]^+$

Elemental Analysis Calcd: C, 58.27; H, 6.37; N, 2.12%

Found: C, 58.14; H, 6.13; N, 2.67%

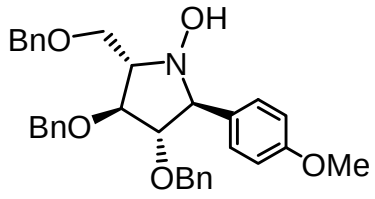
1,4-Anhydro-2,3,5-tri-*O*-benzyl-1-deoxy-1-imino-L-arabinitol-*N*-oxide (79).



To a solution of ***E*-85** (2.3 g, 3.5 mmol) in toluene (30 mL) was added anhyd *n*-Bu_4NF (1.3 g, 4.2 mmol) and the mixture was heated to reflux for 3 h. The reaction mixture was concentrated under reduced pressure and the resulting crude product was purified on silica gel using methanol-diethyl ether (1:9) to afford **79** as a white crystalline solid.

Yield	**:**	1.3 g, 89%
Mol. Formula	**:**	$C_{26}H_{27}NO_4$
M.P.	**:**	82-84 ^oC
$[\alpha]_D^{25}$	**:**	42.0 (c = 2, CH_2Cl_2)
IR ($CHCl_3$) $\tilde{\nu}$	**:**	2927, 2855, 1584, 1454, 1111, 699 cm^{-1}
^{1}**H NMR** (200 MHz)	**:**	δ 3.74-3.78 (m, 1H), 4.02-4.09 (m, 2H), 4.37 (dd, 1H, J = 3.4, 2.2 Hz), 4.47-4.49 (m, 6H), 4.66 (t, 1H, J = 2.4 Hz), 6.90 (d, 1H, J = 1.9 Hz), 7.24-7.36 (m, 15H)
^{13}**C NMR** (125 MHz)	**:**	66.1, 71.7, 72.0, 73.3, 77.5, 80.3, 82.8, 127.7, 128.1, 128.2, 128.4, 128.5, 128.6, 130.0, 133.0, 137.1, 137.2, 137.7 ppm
ESI MS *m/z*	**:**	418 $[M+H]^+$, 440 $[M+Na]^+$
Elemental Analysis		Calcd: C, 74.82; H, 6.47; N, 3.36%
		Found: C, 75.00; H, 6.88; N, 3.71%.

(2*S*,3*S*,4*S*,5*S*)-2-Benzyloxymethyl-3,4-dibenzyloxy-5-(4-methoxyphenyl)-*N*-hydroxypyrrolidine (86).



To a stirred solution of 4-methoxyphenyl magnesium bromide, prepared from Mg (26 mg, 1.1 mmol) and 1-bromo-4-methoxybenzene (200 mg, 1.1 mmol) in THF (5 mL), was added **79** (150 mg, 0.36 mmol) in THF at –78 ^{o}C. After being stirred for 2 h at the same temperature, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl solution (10 mL). The organic layer was separated, the aqueous layer was extracted with $CHCl_3$, and the combined organic extract was washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified on flash silica gel using ethyl acetate-light petroleum ether (1:5) to yield **86** as thick syrup.

Yield : 154 mg, 81%

Mol. Formula : $C_{33}H_{35}NO_5$

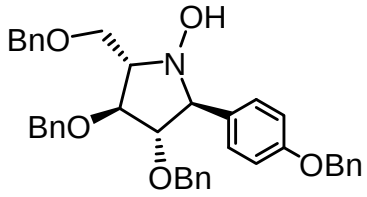
^{1}H NMR (200 MHz) : δ 3.57-3.74 (m, 3H), 3.76-3.85 (m, 4H), 4.04-4.18 (m, 3H), 4.29, 4.36 (2d, 2H, *J* = 11.9 Hz), 4.46, 4.49, 4.56, 4.58 (4d, 4H, *J* = 12.0 Hz), 6.84 (dd, 2H, *J* = 6.7, 2.0 Hz), 7.08 (dd, 2H, *J* = 7.3, 3.7 Hz), 7.21-7.33 (m, 15H)

ESI MS *m/z* : 525 $[M]^+$

Elemental Analysis Calcd: C, 77.40; H, 6.71; N, 2.66%

Found: C, 77.49; H, 6.68; N, 2.47%

(2*S*,3*S*,4*S*,5*S*)-2-Benzyloxymethyl-3,4-dibenzyloxy-5-(4-benzyloxyphenyl)-*N*-hydroxypyrrolidine (87).

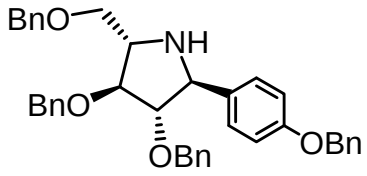


Grignard reaction of 4-benzyloxyphenyl magnesium bromide with the nitrone **79** was performed as described earlier for the preparation of compound **86** and by using 4-benzyloxyphenyl magnesium bromide, prepared from Mg (17 mg, 0.72 mmol) and 1-[(4-bromophenoxy)methyl] benzene (200 mg, 0.72 mmol) in THF (5 mL), was added **79** (100

mg, 0.24 mmol) in THF at –78 ^{o}C to provide compound **87** as a white solid after purification on flash silica gel using ethyl acetate-light petroleum ether (1:5).

Yield	**:**	112 mg, 78%
Mol. Formula	**:**	$C_{39}H_{39}NO_5$
M.P.	**:**	127-128 ^{o}C
$[\alpha]_D^{25}$	**:**	15 (c = 4.9, CH_2Cl_2)
IR ($CHCl_3$) $\tilde{\nu}$	**:**	3685, 3444, 2929, 1732, 1611, 1514, 1424, 1251, 1102, 1045, 925 cm^{-1}
^{1}H NMR (500 MHz)	**:**	δ 3.73 (m, 1H), 3.78 (dd, 1H, J = 9.3, 7.1 Hz), 3.88 (dd, 1H, J = 9.3, 3.8 Hz), 4.05 (dd, 1H, J = 7.1, 3.3 Hz), 4.11 (t, 1H, J = 3.3 Hz), 4.21 (d, 1H, J = 7.1 Hz), 4.33, 4.37 (2d, 2H, J = 11.5 Hz), 4.50, 4.59, 4.55, 4.58 (4d, 4H, J = 12.1 Hz), 5.06 (s, 2H), 6.95 (d, 2H, J = 8.8 Hz), 7.10 (dd, 2H, J = 6.6, 3.8 Hz), 7.23-7.43 (m, 20H)
^{13}C NMR (125 MHz)	**:**	67.0, 68.9, 70.0, 71.6, 72.0, 73.3, 73.4, 83.6, 87.2, 114.6, 127.5-127.7, 127.9-128.5, 129.9, 137.0, 137.9, 138.1, 138.2, 158.6 ppm
ESI MS *m/z*	**:**	602 $[M+H]^+$
Elemental Analysis		Calcd: C, 77.87; H, 6.49; N, 2.33%
		Found: C, 77.23; H, 6.38; N, 2.74%

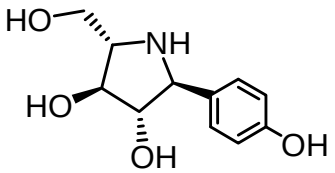
(2*S*,3*S*,4*S*,5*S*)-2-Benzyloxymethyl-3,4-dibenzyloxy-5-(4-benzyloxyphenyl)pyrrolidine (88).



To a solution of **87** (75 mg, 0.12 mmol) in ethanol (5 mL) were added sat. NH_4Cl (5 mL) and Zn dust (80 mg, 1.2 mmol). The resulting mixture was refluxed until all the starting was reacted (3 h, TLC showing brownish spot by ninhydrin reaction). After removal of solvent under reduced pressure, the residue was treated with a saturated Na_2CO_3 solution (10 mL), extracted with EtOAc, washed with brine, dried (Na_2SO_4) and concentrated. The purification of the crude residue on silica gel using ethyl acetate-light petroleum ether (1:5) afforded the pyrrolidine **88** as colorless oil.

Yield	**:**	72 mg, 98%
Mol. Formula	**:**	$C_{39}H_{39}NO_4$
$[\alpha]_D^{25}$	**:**	–18 (*c* = 0.9, CH_2Cl_2)
^{1}H NMR (200 MHz)	**:**	δ 3.53-3.61 (m, 3H), 3.95 (t, 1H, *J* = 4 Hz), 4.03 (dd, 1H, *J* = 6.6, 4.3 Hz), 4.15 (d, 1H, *J* = 6.6 Hz), 4.39 (s, 2H), 4.54 (s, 2H), 4.57 (s, 2H), 5.07 (s, 2H), 6.93 (d, 2H, *J* = 8.7 Hz), 7.15 (d, 2H, *J* = 7.5, 3.5 Hz), 7.26-7.42 (m, 20H)
^{13}C NMR (100 MHz)	**:**	61.4, 64.9, 70.1, 70.8, 71.9, 72.3, 73.3, 85.7, 91.1, 114.9, 127.5-128.0, 128.3-128.6, 134.6, 137.1, 138.1, 138.2, 158.2 ppm
ESI MS *m/z*	**:**	586 $[M+H]^+$
Elemental Analysis		Calcd: C, 79.97; H, 6.71; N, 2.39%
		Found: C, 80.10; H, 6.43; N, 2.40%

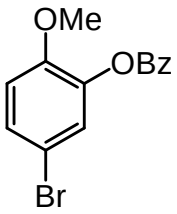
(2*S*,3*S*,4*S*,5*S*)-2-hydroxymethyl-3,4-dihydroxy-5-(4-hydroxyphenyl)pyrrolidine (78).



To a solution of **88** (50 mg, 0.1 mmol) in ethanol (3 mL) was added $PdCl_2$ (10 mol %) and the resulting mixture was stirred under H_2 atmosphere (balloon pressure) at room temperature for 20 h. The reaction mixture was filtered through Celite and the Celite pad was washed several times with ethanol. The combined filtrate was evaporated under reduced pressure to afford compound **78** as colorless oil.

Yield	**:**	12 mg, 62%
Mol. Formula	**:**	$C_{11}H_{15}NO_4$
$[\alpha]_D^{25}$	**:**	–69 (*c* = 0.2, H_2O), {Lit.[35] –72.7 (*c* = 0.1, H_2O)}
^{1}H NMR (D_2O, 500 MHz)	**:**	δ 3.68-3.70 (m, 1H), 3.96 (dd, 1H, *J* = 12.5, 5.8 Hz) , 4.01 (dd, 1H, *J* = 12.5, 3.9 Hz), 4.23 (t, 1H, *J* = 7.8 Hz), 4.43 (d, 1H, *J* = 10.1 Hz), 4.51 (dd, 1H, *J* = 10.1, 7.8 Hz), 7.05 (d, 2H, *J* = 8.2 Hz), 7.49 (d, 2H , *J* = 8.2 Hz)
^{13}C NMR (D_2O, 125 MHz)	**:**	58.5, 61.4, 62.7, 73.9, 77.6, 115.9, 123.8, 129.8, 156.7 ppm
ESI MS *m/z*	**:**	226 $[M+H]^+$
Elemental Analysis		Calcd: C, 58.66; H, 6.71; N, 6.22%
		Found: C, 58.78; H, 6.53; N, 6.12%

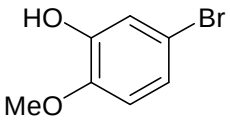
5-Bromo-2-methoxyphenyl benzoate (91).



To a stirred solution of **89** (1.3 g, 10.5 mmol) in dry pyridine (30 mL) at 0 ^{o}C was added benzoyl chloride (3 mL, 26.4 mmol) and the reaction mixture was stirred at room temperature for 2 h. Water (30 mL) was added and the mixture was extracted with EtOAc. The combined organic layer was successively washed with 2N HCl, brine, dried (Na_2SO_4) and concentrated. Purification of the residue on silica gel using ethyl acetate-light petroleum ether (1:5) gave **90** (4.8 g, 96%). A solution of bromine (4.4 g, 27.7 mmol) in AcOH (5 mL) was slowly added to a solution of **90** (4.8 g, 21.0 mmol) in AcOH (25 mL) at 0 ^{o}C. The reaction mixture was stirred at room temperature for 24 h and then additional bromine (2.4 g, 13.8 mmol) in AcOH (5 mL) was added and the stirring was continued for another 24 h. The acetic acid was removed on rotavapour at room temperature and the residue obtained was dissolved in CH_2Cl_2 and washed with sat. $NaHCO_3$. The combined organic extract was washed with brine, dried (Na_2SO_4) and concentrated. The residue was solidified by the addition of petroleum ether yielded 5-bromo-2-methoxyphenol **91** as a colorless liquid**.**

Yield	**:**	5.3 g, 82%
Mol. Formula	**:**	$C_{14}H_{11}BrO_3$
^{1}**H NMR** (200 MHz)	**:**	δ 3.77 (s, 3H), 6.86 (d, 1H, *J* = 8.5 Hz), 7.30-7.37 (m, 2H), 7.45-7.54 (m, 2H), 7.58-7.67 (m, 1H), 8.16-8.22 (m, 2H)
^{13}**C NMR** (50 MHz)	**:**	56.0, 111.9, 113.7, 126.1, 128.5, 128.8, 129.5, 130.2, 133.6, 140.5, 150.7, 164.2 ppm
+TOF MS *m/z*	**:**	330 $[M+Na]^+$
Elemental analysis		Calcd: C, 54.75; H, 3.61 %
		Found: C, 54.49; H, 3.85%

5-Bromo-2-methoxyphenol (92).



The benzoylated compound **91** (1.0 g, 3.3 mmol) was dissolved in dry MeOH (5 mL) and a few drops of a 1M methanolic NaOMe solution were added. The mixture was kept at room temperature and monitored by TLC (1:9 Ethyl acetate–Hexanes). When the starting material and the partially debenzoylated products disappeared (1/2 h), the reaction mixture was neutralized with *Amberlyst-15* resin (H^+ form). After removal of the solvent the residue obtained which was pure enough to use in the next reaction.

Yield : 0.6 g, 89%

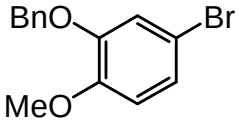
Mol. Formula : $C_7H_7BrO_2$

^{1}H NMR (200 MHz) : δ 3.89 (s, 3H), 5.63 (br. s, 1H), 6.71 (d, 1H, *J* = 8.5 Hz), 6.96 (dd, 1H, *J* = 8.5, 2.4 Hz), 7.06 (d, 1H, *J* = 2.4 Hz)

Elemental Analysis Calcd: C, 41.41; H, 3.48%

Found: C, 40.81; H, 3.65%

2-Benzyloxy-4-bromo-1-methoxybenzene (93).



To a solution of 5-bromo-2-methoxyphenol **92** (0.5 g, 2.5 mmol) in DMF (10 mL) was added K_2CO_3 (0.9 g, 6.3 mmol) followed by addition of benzyl bromide (0.3 mL, 2.8 mmol) the reaction mixture was stirred at room temperature for 2 h. When TLC indicated the disappearance of the starting material, the reaction mixture was poured into the ice water (25 mL). The white solid precipitated from the solution was filtered and recrystallized from EtOAc/light petroleum ether (1:1) to give **93** as colorless needles.

Yield : 0.6 g, 92%

Mol. Formula : $C_{14}H_{13}BrO_2$

M.P. : 108-109 ºC Lit.[44] 106-107 °C

^{1}H NMR (200 MHz) : δ 3.85 (s, 3H), 5.10 (s, 2H), 6.75 (d, 1H, *J* = 9.2 Hz), 7.01-7.05 (m, 2H), 7.30-7.45 (m, 5H)

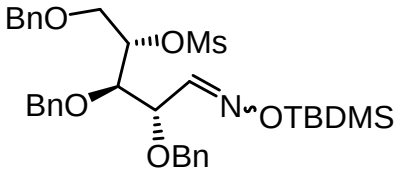
^{13}C NMR (50 MHz) : 56.0, 71.1, 112.5, 113.1, 117.1, 123.9, 127.3, 128.0, 128.5, 136.4, 149.0 ppm

ESI MS *m/z* : 315 $[M+Na]^+$

Elemental Analysis Calcd: C, 57.36; H, 4.47%

Found: C, 57.54; H, 4.76%

1*E*/1*Z*-2,3,5-tri-*O*-benzyl-4-*O*-methanesulfonyl-L-arabinose-*O*-[*tert*-butyldimethylsilyl] oximes (101).



Methanesulphonyl chloride (0.24 mL, 3.1 mmol) was added to a solution of oximes **84** (1.4 g, 2.6 mmol) in pyridine (10 mL) at 0 °C. After 2 h stirring at the same temperature, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed successively with water (30 mL), aqueous $CuSO_4$ and saturated aqueous sodium bicarbonate solution (30 mL). The CH_2Cl_2 solution was dried (Na_2SO_4), evaporated under reduced pressure and the residue purified on silica gel using ethyl acetate-light petroleum ether (1:19) to afford 1*E*/1*Z*-2,3,5-tri-*O*-benzyl-4-*O*-methanesulfonyl-L-arabinose-*O*-[(*tert*-butyldimethylsilyl] oximes **101** as an oil, The ^{1}H NMR indicates the presence of *E/Z* mixture (*E/Z* ~ 7:3).

Yield : l.5 g, 93%

Mol. Formula : $C_{33}H_{45}NO_7SSi$

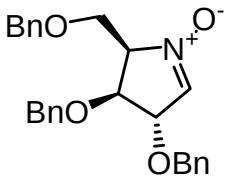
IR ($CHCl_3$) $\tilde{\nu}$: 1713, 1497, 1455, 1358, 1176, 1075, 1028, 927, 699 cm^{-1}

^{1}H NMR (200 MHz) : δ 0.16, 0.18 (s, 6H), 0.93, 0.96 (2s, 9H), 2.92, 2.93 (2s, 3H), 3.71-3.81 (m, 1H), 3.84-4.01 (m, 2H), 4.10-4.22 (m, 1H), 4.38-4.74 (m, 6H), 4.92-5.01 (m, 1H), 7.05 (d, *J* = 5.8 Hz, 0.3 H), 7.23-7.36 (m, 15 H), 7.50 (d, 0.7 H, *J* = 7.8 Hz)

^{13}C NMR (100 MHz) : –5.4, –5.3, 18.0, 18.1, 25.9, 26.0, 38.4, 38.5, 68.6, 69.1, 71.3, 72.0, 72.5, 73.3, 73.4, 74.9, 75.0, 76.6, 79.0, 80.2, 81.3, 81.5, 127.7-128.4, 137.2-137.6, 152.5, 155.0 ppm

Elemental Analysis Calcd: C, 63.13; H, 7.22; N, 2.23; S, 5.11%
Found: C, 63.74; H, 7.10; N, 2.15; S, 4.80%

2,3,5-Tri-*O*-benzyl-1,4-dideoxy-1,4-imino-D-xylitol-*N*-oxide (98).



Method A:

Compounds **101** (1.0 g, 1.6 mmol) in dry THF (30 mL) was treated with 1M solution of anhydrous TBAF (0.6 g, 1.9 mmol) and the contents were stirred at room temperature for 30 min. Water (30 mL) was added and the mixture was extracted with EtOAc. The combined organic layer was dried (Na_2SO_4) and concentrated to give free oxime derivative. The resulting oximes (0.8 g, 1.5 mmol) were taken in a 3:1 mixture of methanol-water (20 mL) and treated with $NaHCO_3$ (1.0 g, 12.2 mmol), hydroxylamine. hydrochloride (0.9 g, 12.2 mmol). The reaction mixture was heated to reflux for 5 h. After concentration under vacuum, the residue was dissolved in CH_2Cl_2 and water was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extract was washed with brine, dried (Na_2SO_4) and concentrated. The crude

reaction mixture was purified on silica gel using ethyl acetate-light petroleum ether (1:5) afforded the nitrone **98** and (4*S*,5*R*,6*R*)-4,5-bis(benzyloxy)-6-benzyloxymethyl-5,6-dihydro-4*H*-1,2-oxazine (**103**).

Data for 98:

Yield : 0.3 g, 48%

Mol. Formula : $C_{26}H_{27}NO_4$

$[\alpha]_D^{25}$: 70 (c = 1.9, CH_2Cl_2)

IR ($CHCl_3$) $\tilde{\nu}$: 2927, 2976, 1585, 1522, 1454, 1100, 699, 629 cm^{-1}

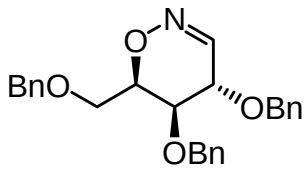
^{1}H NMR (400 MHz) : δ 3.80 (dd, 1H, J = 10.0, 1.8 Hz), 3.96 (dd, 1H, J = 10.0, 4.3 Hz), 4.14 (m, 1H), 4.35 (dd, 1H, J = 7.8, 4.5 Hz), 4.48-4.66 (m, 6H), 4.74 (m, 1H), 6.81 (s, 1H), 7.26-7.35 (m, 15H)

^{13}C NMR (100 MHz) : 64.3, 72.2, 73.0, 73.4, 74.0, 80.4, 83.0, 127.4-128.4, 133.9, 137.1, 137.2, 137.8 ppm

ESI MS *m/z* : 418 $[M+H]^+$, 440 $[M+Na]^+$

Elemental Analysis Calcd: C, 74.80; H, 6.52; N, 3.35%

Found: C, 74.35; H, 6.81; N, 3.43%



103

Data for 103:

Yield : 0.18 g, 26%

Mol. Formula : $C_{26}H_{27}NO_4$

$[\alpha]_D^{25}$: 132.8 (c = 3.1, $CHCl_3$)

IR ($CHCl_3$) $\tilde{\nu}$: 2923, 2868, 2252, 1735, 1496, 1454, 1373, 1244, 1096, 945, 698 cm^{-1}

^{1}H NMR (200 MHz) : δ 3.51 (t, 1H, *J* = 2.8 Hz), 3.64-3.82 (m, 3H), 4.07 (ddd, 1H, *J* = 6.0, 1.8, 1.4 Hz), 4.43-4.65 (m, 6H), 7.21-7.41 (m, 16H)

^{13}C NMR (100 MHz) : 65.0, 67.3, 70.5, 71.6, 72.4, 73.5, 74.3, 127.2-128.6, 137.2, 137.4, 137.8, 145.8 ppm

ESI MS *m/z* : 418 $[M+H]^+$, 440 $[M+Na]^+$

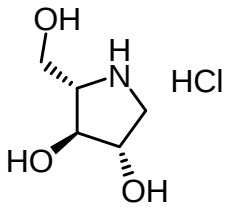
Elemental Analysis Calcd.: C, 74.80; H, 6.52; N, 3.35%

Found: C, 74.60; H, 6.66; N, 3.55%

Method B:

To a solution of **101** (1.2 g, 1.9 mmol) in toluene (30 mL) was added anhydrous *n*-Bu_4NF (0.8 g, 2.4 mmol) and mixture was refluxed for 1 h. After evaporation, the residue was purified on silica gel using methanol-diethyl ether (1:9) to afford compound **98** (0.8 g, 97%) as a colorless oil.

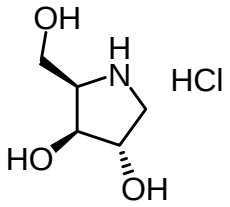
1,4-Dideoxy-1,4-imino-L-arabinitol.hydrochloride (99).



A suspension nitrone **79** (100 mg, 0.24 mmol), 20% $Pd(OH)_2/C$ (10 mg) in MeOH (5 mL) and conc. HCl (10 μL) was stirred under hydrogen atmosphere (balloon pressure) at room temperature for overnight. The catalyst was removed by filtration and the reaction mixture was concentrated to give hydrochloride salt of LAB-1 (**99**).

Yield	**:**	40 mg, 97%
Mol. Formula	**:**	$C_5H_{12}ClNO_3$
$[\alpha]_D^{25}$	**:**	–32.5 (*c* = 1, H_2O); Lit.[48] {–34.6 (*c* = 0.1, H_2O)}
^{1}H NMR (D_2O, 200 MHz)	**:**	δ 3.39 (dd, 1H, *J* = 12.5, 2.2 Hz), 3.52-3.78 (m, 2H), 3.83 (dd, 1H, *J* = 12.2, 8.2 Hz), 3.99 (dd, 1H, *J* = 12.2, 4.6 Hz), 4.13 (t, 1H, *J* = 3.5 Hz), 4.36 (ddd, 1H, *J* = 5.2, 2.7, 2.4 Hz)
^{13}C NMR (D_2O, 125 MHz)	**:**	50.0, 58.9, 66.6, 74.3, 75.7 ppm
ESI MS *m/z*	**:**	134 $[M+H]^+$
Elemental Analysis		Calcd: C, 35.41; H, 7.13, N, 8.26%
		Found: C, 35.38; H, 7.29, N, 8.43%

1,4-Dideoxy-1,4-imino-D-xylitol.hydrochloride(100).



The nitrone **98** (100 mg, 0.24 mmol) dissolved in MeOH (5 mL) and stirred under hydrogen atmosphere (balloon pressure) in the presence of 20% Pd $(OH)_2$/C (10 mg) and conc. HCl (10 μL) for 10 h at room temperature. The catalyst was removed by filtration and the reaction mixture was concentrated to give hydrochloride salt of **100**.

Yield : 39 mg, 95%

Mol. Formula : $C_5H_{12}ClNO_3$

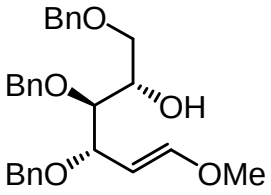
$[\alpha]_D^{25}$: 7.3 (*c* =1, H_2O); Lit.[49]{ 8.8 (*c* = 0.7, H_2O)}

^{1}H NMR (200 MHz) : δ 3.31 (d, 1H, *J* = 13.0 Hz), 3.67 (dd, 1H, *J* = 13.0, 4.0 Hz), 3.89-4.05 (m, 3H), 4.33 (d, 1H, *J* = 2.5 Hz), 4.40 (dt, 1H, *J* = 4.2, 1.3 Hz)

^{13}C NMR (125 MHz) : 50.8, 57.5, 63.3, 74.6, 74.6 ppm

ESI MS *m/z* : 169 $[M+H]^+$

5*E*-(2*S*,3*S*,4*S*)-1,3,4-Tri-*O*-benzyloxy-6-methoxyhex-5-en-2-ol (112).



To a stirred suspension of (methoxymethyl)triphenylphosphonium chloride (20.4 g, 59.5 mmol) in dry THF (100 mL) was added *n*-BuLi (29.8 mL, 1.6 M in hexane, 47.6 mmol) over 30 minutes at 0 °C. After stirring at 0 °C for 10 minutes, to the reaction mixture was added a solution of **82** (5.0 g, 11.9 mmol) in dry THF (25 mL) over 1 hour at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 4 hours. The reaction was quenched with saturated aqueous NH_4Cl (50 mL) and the solvent was evaporated under reduced pressure. The residue was diluted with Et_2O, and the organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The crude product was purified on silica gel using ethyl acetate-light petroleum ether (1:8) to give methyl ether **112** as thick oil.

Yield : 4.3 g, 81%

Mol. Formula : $C_{27}H_{29}NO_4$

$[\alpha]_D^{25}$: 5.0 (*c* = 1.1, $CHCl_3$)

^{1}H NMR (200 MHz) **:** δ 2.98 (br. s, 1H), 3.52 (s, 3H), 3.58-3.60 (m, 2H), 3.72 (m, 1H), 3.92-4.11 (m, 2H), 4.28-4.67 (m, 6H), 4.83 (dd, 1H, *J* = 13.0, 9.5 Hz), 6.45 (d, 1H, *J* = 13.0 Hz), 7.28-7.31 (m, 15H)

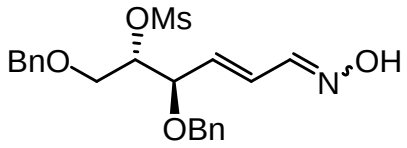
^{13}C NMR (75 MHz) **:** 55.9, 69.4, 70.5, 71.1, 74.0, 77.4, 81.4, 99.0, 127.6-128.3, 129.8, 138.1, 138.3, 151.4 ppm

ESI MS *m/z* **:** 449 $[M+H]^+$

Elemental Analysis Calcd: C, 74.97; H, 7.19%

Found: C, 74.94; H, 6.94%

(1*E*/*Z*, 2*E*)-4,6-Bis(benzyloxy)-5-mesyloxy-hex-2-enal oxime (117).



To a solution of **112** (2.0 g, 4.5 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C, methanesulphonyl chloride (3.5 mL, 44.6 mmol) and triethylamine (6.2 mL, 44.6 mmol) were added and the reaction mixture was stirred at the same temperature for 1 h. After completion, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and extracted with water. The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The resulting residue was directly subjected to the next reaction.

To the solution of above mesylate **111** (100 mg, 0.2 mmol) in CH_2Cl_2 (10 mL) was added 2N HCl (5 mL) and the reaction mixture was allowed to stir at room temperature for 1 h. After completion, the reaction mixture was extracted with CH_2Cl_2. The combined organic layer was washed with aqueous $NaHCO_3$ solution till neutralization of organic layer and then washed with brine, dried (Na_2SO_4) and concentrated. To the above residue of **114** (60 mg, 0.1 mmol) in ethanol (5 mL) was added hydroxylamine.hydrochloride (56 mg, 0.8 mmol), $NaHCO_3$ (0.7 g, 0.8 mmol) and the mixture was heated to reflux for 2 h. The reaction mixture was filtered through Celite and the Celite pad was washed several times with ethanol. After removal of solvent under reduced pressure, the residue obtained

was extracted with EtOAc, dried (Na_2SO_4) and concentrated. The crude product was purified on silica gel using ethyl acetate-light petroleum ether (1:2) to afford **117** as yellow color oil.

Yield : 40 mg, 80%

Mol. Formula : $C_{21}H_{25}NO_6S$

^{1}H NMR (300 MHz) : δ 2.98 (s, 3H), 3.61-3.74 (m, 2H), 4.23 (dd, 1H, *J* = 7.7, 3.7 Hz), 4.43, 4.59 (2d, 2H, *J* = 11.7 Hz), 4.51 (s, 2H), 4.87-4.92 (m, 1H), 5.96 (dd, 1H, *J* = 16.1, 7.3 Hz), 6.40 (dd, 1H, *J* = 16.1, 10.3 Hz), 7.24-7.35 (m, 10H), 7.80 (d, 1H, *J* = 10.3 Hz), 9.0 (br. s, 1H)

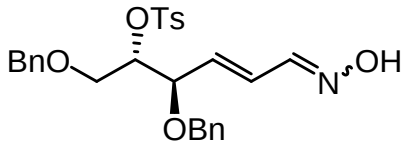
^{13}C NMR (50 MHz) : 38.4, 68.2, 71.2, 73.3, 77.9, 81.8, 127.7-128.4, 128.8, 134.3, 137.1, 150.0 ppm

ESI MS *m/z* : 418 $[M]^+$

Elemental Analysis Calcd: C, 60.13; H, 6.01; N, 3.34; S, 7.64%

Found: C, 60.54; H, 6.28; N, 3.12; S, 8.02%

(1*E*/*Z*, 2*E*)-4,6-Bis(benzyloxy)-5-tosyloxy-hex-2-enal oxime (118).



To a solution of **112** (2.0 g, 4.5 mmol) in dry CH_2Cl_2 (10 mL) at 0 ^oC *p*-toluenesulphonyl chloride (2.6 g, 13.5 mmol) and triethylamine (2.5 mL, 18.0 mmol) were added. The reaction mixture was stirred at the same temperature for 3 h, diluted with CH_2Cl_2 (30 mL) and extracted with water, the combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated to give a residue which was used in the next reaction immediately. The tosylate compound (**113**) (100 mg, 0.2 mmol) was dissolved in CH_2Cl_2 and treated with 2N HCl (5 mL) at room temperature. After the completion of

reaction, the reaction mixture was extracted with CH_2Cl_2, the combined organic layer was successively washed with aqueous $NaHCO_3$ solution (till neutralization of organic layer), with brine, dried (Na_2SO_4), concentrated and the residue obtained was used in the next step without purification. To the above residue **116** (73 mg, 0.13 mmol) in ethanol (5 mL) was added hydroxylamine.hydrochloride (76 mg, 1.1 mmol), $NaHCO_3$ (92 mg, 1.1 mmol) and the mixture was heated to reflux for 2 h. The reaction mixture was filtered through Celite and the Celite pad was washed several times with ethanol. After concentration the residue obtained was extracted by using EtOAc, dried (Na_2SO_4) and concentrated. The crude product was purified on silica gel using ethyl acetate-light petroleum ether (1:2) to afford **118** as yellow color oil.

Yield : 30 mg, 49%

Mol. Formula : $C_{27}H_{29}NO_6S$

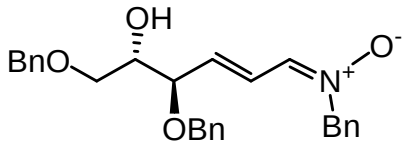
IR ($CHCl_3$) $\tilde{\nu}$ 3342, 2249, 1765, 1681, 1598, 1496, 1454, 1366, 910 cm^{-1}

^{1}H NMR (200 MHz) : δ 2.34 (s, 3H), 3.61 (dd, 1H, *J* = 11.0, 4.2 Hz), 3.75 (dd, 1H, *J* = 11.0, 4.8 Hz), 3.96-4.14 (m, 1H), 4.32, 4.48 (2d, 2H, *J* = 11.5 Hz), 4.40 (s, 2H), 4.60 (dd, 1H, *J* = 10.5, 4.7 Hz), 5.69 (dd, 1H, *J* = 15.8, 7.3 Hz), 6.24 (dd, 1H, *J* = 15.8, 9.9 Hz), 7.13-7.28 (m, 12H), 7.56 (d, 1H, *J* = 9.9 Hz), 7.68 (d, 2H, *J* = 8.1 Hz), 8.29 (br. s, 1H)

Elemental Analysis Calcd: C, 65.44; H, 5.90; N, 2.83; S, 6.47%

Found: C, 65.23; H, 6.34; N, 2.56; S, 6.11%

(1*E*)-*N*-[(4*R*,5*S*)-4,6-Bis(benzyloxy)-5-hydroxyhex-2-enylidiene)] (phenyl)methanamine oxide (121).

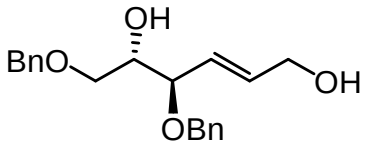


The compound **112** (1.0 g, 2.2 mmol) was dissolved in CH_2Cl_2 and treated with 2N HCl (5 mL) at room temperature. After completion, the reaction mixture was extracted

with CH_2Cl_2, the combined organic layer was washed successively with aqueous $NaHCO_3$ solution (till neutralization of organic layer), brine, dried (Na_2SO_4), concentrated and the residue obtained is used in the next step without purification. To the above residue (0.6 g, 1.4 mmol) in ethanol:H_2O (3:2) (10 mL) was added *N*-benzylhydroxylamine.hydrochloride (0.3 g, 1.7 mmol), sodium acetate (0.15 g, 1.7 mmol) and the mixture was stirred at room temperature for 1 h. The reaction mixture was filtered through Celite and the Celite pad was washed several times with ethanol. After removal of solvent under reduced pressure the residue obtained was extracted with EtOAc, dried (Na_2SO_4) and concentrated. The crude product was purified on silica gel using methanol-diethyl ether (1:9) to afford **121** as yellow color oil.

Yield	**:**	0.5 g, 83%
Mol. Formula	**:**	$C_{27}H_{29}NO_4$
$[\alpha]_D^{25}$	**:**	15 (*c* = 4.5, CH_2Cl_2)
^{1}**H NMR** (200 MHz)	**:**	δ 3.51-3.57 (m, 2H), 3.86-4.04 (m, 2H), 4.33, 4.59 (2d, 2H, *J* = 11.7 Hz), 4.49 (s, 2H), 4.92 (s, 2H), 6.20 (dd, 1H, *J* = 14.5, 7.7 Hz), 6.93-7.12 (m, 2H), 7.25-7.42 (m, 15H)
^{13}**C NMR** (50 MHz)	**:**	69.3, 70.4, 70.9, 72.3, 73.3, 79.9, 124.0, 127.6, 128.3, 128.9, 129.4, 132.5, 135.1, 137.7 ppm
ESI MS *m/z*	**:**	454 $[M+Na]^+$
Elemental Analysis		Calcd: C, 75.15; H, 6.77, N, 3.25%
		Found: C, 74.99; H, 6.85, N, 3.30%

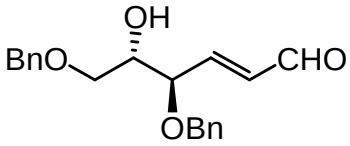
(1*E*,4*R*,5*S*)-4,6-Bis(benzyloxy)hex-2-ene-1,5-diol (120).



The compound **112** (1.0 g, 2.2 mmol) was dissolved in CH_2Cl_2 (15 mL) and treated with 2N HCl (5 mL) at room temperature. After completion, the reaction mixture was extracted with CH_2Cl_2, the combined organic layer was washed successively with aqueous $NaHCO_3$ solution (till neutralization of organic layer), brine, dried (Na_2SO_4), the solvent removed and the resulting residue was subjected to the next reaction without purification. To the above residue (0.6 g, 1.4 mmol) in THF (10 mL) was added LAH (11 mg, 2.8 mmol) at 0 ^oC. The mixture was warmed to room temperature and stirred for 0.5 h. The reaction was quenched by the addition of H_2O (20 mL) and 15% aqueous NaOH (20 mL) and the solution was filtered through a short column of silica gel. Concentration afforded **120** as a pure diol.

Yield	**:**	0.4 g, 80%
Mol. Formula	**:**	$C_{20}H_{24}O_4$
$[\alpha]_D^{25}$	**:**	–20.6 (*c* = 0.9, CH_2Cl_2)
IR ($CHCl_3$) $\tilde{\nu}$	**:**	3416, 3015, 2923, 2868, 1606, 1454, 1216, 1089, 909, 757 cm^{-1}
^{1}H NMR (200 MHz)	**:**	δ 2.47 (br. s, 2H), 3.49-3.63 (m, 2H), 3.87 (d, 2H, *J* = 4.7 Hz), 4.16 (d, 2H, *J* = 4.7 Hz), 4.35, 4.59 (2d, 2H, *J* = 11.7 Hz), 4.51 (s, 2H), 5.70 (dd, 1H, *J* = 15.6, 6.0 Hz), 5.92 (dt, 1H, *J* = 15.6, 4.8 Hz), 7.25-7.36 (m, 10H)
^{13}C NMR (50 MHz)	**:**	62.3, 70.1, 70.8, 72.2, 73.1, 79.5, 127.4, 127.5, 127.7, 127.9, 128.1, 128.2, 135.5, 137.7, 138.0 ppm
ESI MS *m/z*	**:**	351 $[M+Na]^+$
Elemental Analysis		Calcd: C, 73.15; H, 7.37%
		Found: C, 73.19; H, 7.29%

(4*R*,5*S*,*E*)-4,6-Bis(benzyloxy)-5-hydroxyhex-2-enal (119).



The compound **112** decomposes when left at room temperature for longer period and the same thing was observed by the treatment of $CDCl_3$, even at low temperature also (kept in fridge).

Mol. Formula : $C_{20}H_{22}O_4$

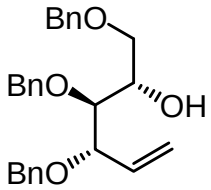
^{1}H NMR (200 MHz) : δ 2.85 (br. s, 1H), 3.38-3.52 (m, 2H), 3.77 (dd, 1H, *J* = 11.0, 4.8 Hz), 4.05 (ddd, 1H, *J* = 6.8, 5.8, 0.9 Hz), 4.27, 4.46 (2d, 2H, *J* = 11.5 Hz), 4.37 (s, 2H), 6.19 (ddd, 1H, *J* = 16.0, 7.9, 0.9 Hz), 6.72 (dd, 1H, *J* = 16.0, 5.8 Hz), 7.12-7.23 (m, 10H), 9.43 (d, 1H, *J* = 7.8 Hz)

^{13}C NMR (50 MHz) : 70.2, 71.8, 72.1, 73.3, 78.5, 127.5-128.4, 133.7, 137.2, 137.5, 153.7 , 193.0 ppm

Elemental Analysis Calcd: C, 73.61; H, 6.75%

Found: C, 74.13; H, 6.86%

(2*S*,3*S*,4*S*)-1,3,4-Tris(benzyloxy)hex-5-en-2-ol (124).

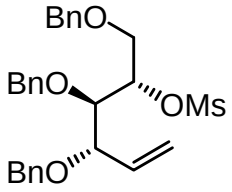


To a suspension of methyltriphenylphosphonium bromide (8.1 g, 20 mmol) in THF (50 mL) at 0 °C under Argon was added *n*-BuLi (11.1 mL, 1.6 M in hexane, 17.9 mmol) and stirred at room temperature for 6 h. To this a solution of **82** (3.0 g, 7.1 mmol) in THF (10 mL) was added dropwise at 0 °C and the reaction mixture was allowed to warm to room temperature for 2 h. The reaction was quenched by adding a saturated solution of NH_4Cl (20 mL) and diluted with Et_2O (15 mL). The aqueous layer was extracted with Et_2O

(25 mL) and combined organic extract was washed with brine (15 mL), dried over (Na_2SO_4) and concentrated. The residue was purified on silica gel using ethyl acetate-light petroleum ether (1:8) to afford compound **124** as colorless oil.

Yield	**:**	2.8 g, 93%
Mol. Formula	**:**	$C_{27}H_{30}O_4$
^{1}H NMR (200 MHz)	**:**	δ 3.58-3.65 (m, 3H), 3.97-4.11 (m, 2H), 4.35, 4.64 (2d, 2H, *J* = 11.9 Hz), 4.50 (s, 2H), 4.51-4.73 (m, 2H, Overlapped), 5.26-5.36 (m, 2H), 5.87-6.05 (m, 1H), 7.25-7.35 (m, 15H)
^{13}C NMR (75 MHz)	**:**	70.3, 70.6, 70.9, 73.2, 74.0, 80.2, 80.7, 118.6, 127.5-128.2, 135.1, 137.8, 138.0 ppm
ESI MS *m/z*	**:**	441 $[M+Na]^+$
Elemental Analysis		Calcd: C, 77.48; H, 7.22%
		Found: C, 77.41; H, 7.26%

(2*S*,3*S*,4*S*)-1,3,4-Tris(benzyloxy)hex-5-en-2-yl-methanesulfonate (125).



To a solution of alcohol **124** (0.5 g, 1.2 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C, were added methanesulphonyl chloride (1 mL, 12.0 mmol) and triethylamine (1.7 mL, 12.0 mmol) and the reaction mixture was stirred at the same temperature for 2 h. After the completion of reaction, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried (Na_2SO_4), concentrated and the residue was purified on silica gel using ethyl acetate-light petroleum ether (1:16) to afford **125** as a colorless oil.

Yield : 0.6 g, 97%

Mol. Formula : $C_{28}H_{32}O_6S$

^{1}H NMR (200 MHz) : δ 2.95 (s, 3H), 3.79-3.85 (m, 2H), 3.89-3.95 (m, 2H), 4.36, 4.58 (2d, 2H, *J* = 11.6 Hz), 4.50 (s, 2H), 4.72 (s, 2H), 4.93-5.00 (m, 1H), 5.28 (dd, 1H, *J* = 9.1, 1.5 Hz), 5.35 (d, 1H, *J* = 1.5 Hz), 5.75-5.96 (m, 1H), 7.27-7.39 (m, 15H)

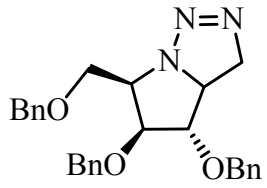
^{13}C NMR (50 MHz) : 38.0, 68.1, 70.2, 72.7, 74.6, 80.2, 81.2, 81.7, 119.4, 127.2-128.0, 134.2, 137.2, 137.4, 137.6 ppm

ESI MS *m/z* : 497 $[M+H]^+$

Elemental Analysis Calcd: C, 67.74; H, 6.45; S, 6.45%

Found: C, 67.89; H, 6.15; S, 5.74%

(4*S*,5*S*,6*R*)-4,5-Bisbenzyloxy-6-benzyloxymethyl-3a,4,5,6-tetrahydro-3*H*-pyrrolo[1,2-e][1,2,3]-triazole (126).



A suspension of compound **125** (0.5 g, 1.0 mmol) and sodium azide (0.1 g, 1.5 mmol) in dry DMF (10 mL) was heated at 95 °C for 24 h. The solvent was removed *in vacuo* and the residue partitioned between water and $CHCl_3$. The $CHCl_3$ layer was dried (Na_2SO_4) and concentrated. Purification of the crude residue on silica gel using ethyl acetate-light petroleum ether (1:4) afforded the compound **126** as colorless oil.

Yield : 0.3 g, 66 %

Mol. Formula : $C_{27}H_{29}N_3O_3$

IR ($CHCl_3$) $\tilde{\nu}$: 3343, 2099, 1496, 1453, 1364, 1268, 1096, 910 cm^{-1}

^{1}H NMR (200 MHz) : δ 3.34-3.46 (m, 2H), 3.52-3.65 (m, 4H), 3.93-4.04 (m, 2H), 4.46-4.58 (m, 6H), 7.27-7.39 (m, 15H)

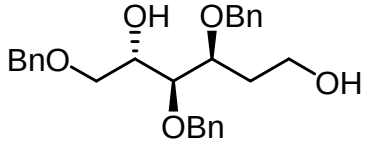
^{13}C NMR (75 MHz) : 51.6, 58.3, 58.6, 69.1, 72.1, 72.2, 73.3, 82.1, 82.2, 127.5-127.6, 128.0, 128.3, 137.8, 138.0, 138.2 ppm

+TOF MS *m/z* : 482 $[M+K]^+$

Elemental Analysis Calcd: C, 73.11, H, 6.59, N, 9.47%

Found: C, 73.23, H, 6.58, N, 9.58%

(3*S*,4*S*,5*S*)-3,4,6-Tris(benzyloxy)hexane-1,5-diol (127).



To the neat compound **124** (1.4 g, 3.3 mmol) at 0°C under nitrogen was added 9-BBN (6.6 mL, 0.5 M in THF, 3.3 mmol). The reaction mixture was warmed to room temperature and stirred for 8 h. To the reaction mixture, were added 3N NaOH (5 mL) 30% H_2O_2 (5 mL) and the mixture was stirred vigorously at room temperature for 8 h. The reaction mixture was partitioned between with EtOAc and water. The combined organic extract was washed with brine, dried (Na_2SO_4) and concentrated. The crude product was purified on silica gel using ethyl acetate-light petroleum ether (1:2) to obtain the diol **127** as colorless oil.

Yield : 3.0 g, 87 %

Mol. Formula : $C_{27}H_{32}O$

^{1}H NMR (200 MHz) : δ 1.75-1.84 (m, 2H), 2.57 (br. s, 2H), 3.508-3.64 (m, 5H), 3.74-3.82 (m, 1H), 3.89-3.97 (m, 1H), 4.40-4.58 (m, 6H),

7.16-7.27 (m, 15H)

^{13}C NMR (50 MHz) **:** 32.8, 59.8, 70.7, 71.8, 72.7, 73.4, 73.6, 77.2, 77.7, 127.7-128.4, 137.6, 137.8, 138.0 ppm

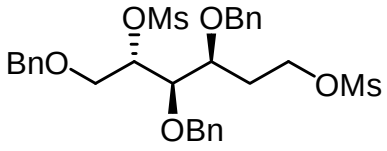
+TOF MS *m/z* **:** 482 $[M+K]^+$

Elemental Analysis Calcd: C, 74.29, H, 7.39%

Found: C, 74.37, H, 7.32%

(3*S*,4*S*,5*S*)-3,4,6-Tris(benzyloxy)hexane-1,5-dimethanesulphonate (128).

Methanesulphonyl chloride (0.6 mL, 7.5 mmol) was added to a solution of diol **127** (1.4 g, 3.32 mmol) in pyridine (10 mL) at 0 ^oC. After 3 h, the reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed successively 2N HCl (25 mL), water (25 mL) and saturated aqueous sodium bicarbonate solution (25 mL). The combined organic layer was dried (Na_2SO_4), concentrated and the residue purified on silica gel using ethyl acetate-light petroleum ether (1:5) to afford dimesylate **128** and chloromesylate **129** both as a colorless oils.



128

Data for 128:

Yield **:** 0.9 g, 50%

Mol. Formula **:** $C_{29}H_{36}O_9S_2$

IR ($CHCl_3$) $\tilde{\nu}$ **:** 1496, 1454, 1358, 1174, 1086, 918 cm^{-1}

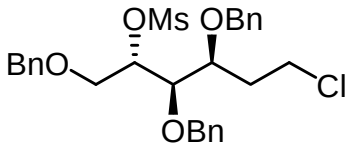
^{1}H NMR (200 MHz) **:** δ 1.26 (t, 2H, *J* = 7.1 Hz), 2.87 (m, 3H), 2.97 (m, 3H), 3.82-3.85 (m, 2H), 3.91 (dd, 1H, *J* = 5.0, 3.0 Hz), 4.06-4.20 (m, 3H), 4.43-4.79 (m, 6H), 4.96 (m, 1H), 7.26-7.32

(m, 15H)

+TOF MS *m/z* **:** 615 $[M+Na]^+$

Elemental Analysis Calcd: C, 58.76, H, 6.12; S, 10.82%

Found: C, 58.53, H, 6.35; S, 9.81%



129

Data for 129:

Yield 0.6 g, 36%

Mol. Formula **:** $C_{28}H_{33}ClO_6S$

IR ($CHCl_3$) $\tilde{\nu}$ **:** 2927, 1500, 1454, 1361, 1176, 1084, 699, 668 cm^{-1}

^{1}H NMR (200 MHz) **:** δ 1.95 (q, 2H, *J* = 6.3 Hz), 2.96 (s, 3H), 3.48 (t, 2H, *J* = 6.3 Hz), 3.53-3.77 (m, 1H), 3.80-3.85 (m, 2H), 3.92 (dd, 1H, *J* = 5.0, 2.5 Hz), 4.44-4.78 (m, 6H), 4.93-4.99 (m, 1H), 7.23-7.31 (m, 15H)

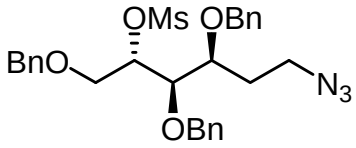
^{13}C NMR (50 MHz) **:** 33.7, 38.4, 41.2, 69.0, 73.3, 73.4, 74.2, 75.7, 79.8, 82.6, 127.5-128.4, 137.3, 137.7 ppm

+TOF MS *m/z* **:** 555 $[M+Na]^+$

Elemental Analysis Calcd: C, 63.09 H, 6.24; S, 6.02%

Found: C, 63.43 H, 6.28; S, 6.10 %

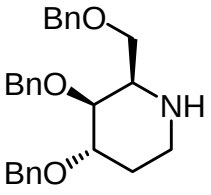
1-Azido-2,3,5-tri-*O*-benzyl-1-deoxy-4-*O*-methanesulfonyl-L-arabinitol (130).



Compound **128** (0.5 g, 0.84 mmol) was dissolved in dry DMF (10 mL) and stirred at 95 °C with sodium azide (82 mg, 1.26 mmol) for 12 h. The solvent was removed *in vacuo* and the residue partitioned between water and chloroform. The $CHCl_3$ layer was dried (Na_2SO_4) and concentrated. The residue was purified on flash silica gel using ethyl acetate-light petroleum ether (1:7) to yield the azide **130** as colorless liquid.

Yield	**:**	0.3 g, 65 %
Mol. Formula	**:**	$C_{28}H_{33}N_3O_6S$
IR ($CHCl_3$) $\tilde{\nu}$	**:**	2101, 1732, 1620, 1454, 1358, 1085, 699 cm^{-1}
^{1}H NMR (200 MHz)	**:**	δ 1.69-1.82 (m, 2H), 2.96 (s, 3H), 3.09-3.36 (m, 2H), 3.45-3.68 (m, 2H), 3.81-3.85 (m, 1H), 3.91 (dd, 1H, *J* = 5.0, *2.8* Hz), 4.39-4.78 (m, 6H), 4.92-4.99 (m, 1H), 7.23-7.39 (m, 15H)
+TOF MS *m/z*	**:**	562 $[M+Na]^+$
Elemental Analysis		Calcd: C, 62.32; H, 6.16; N, 7.79, S, 5.94%
		Found: C, 62.38; H, 6.00; N, 7.92, S, 5.74%

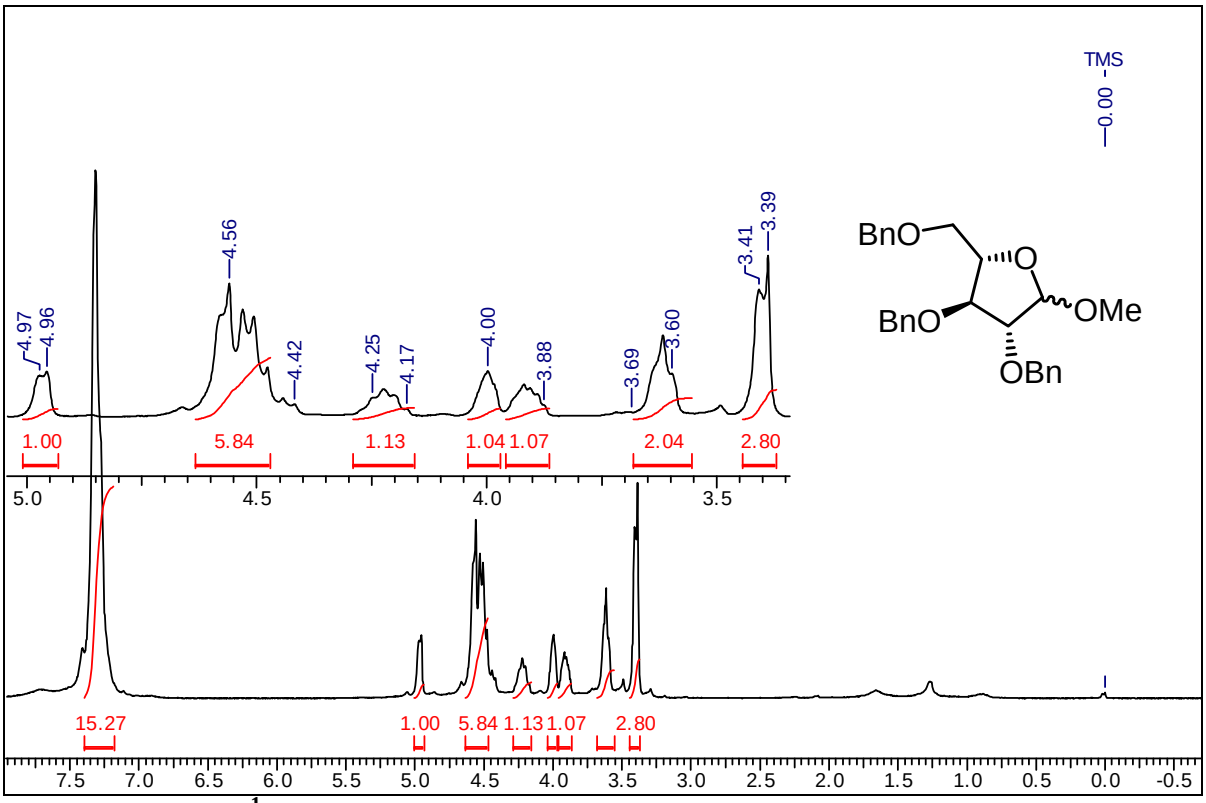
(2*R*,3*S*,4*S*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)piperidine (122).



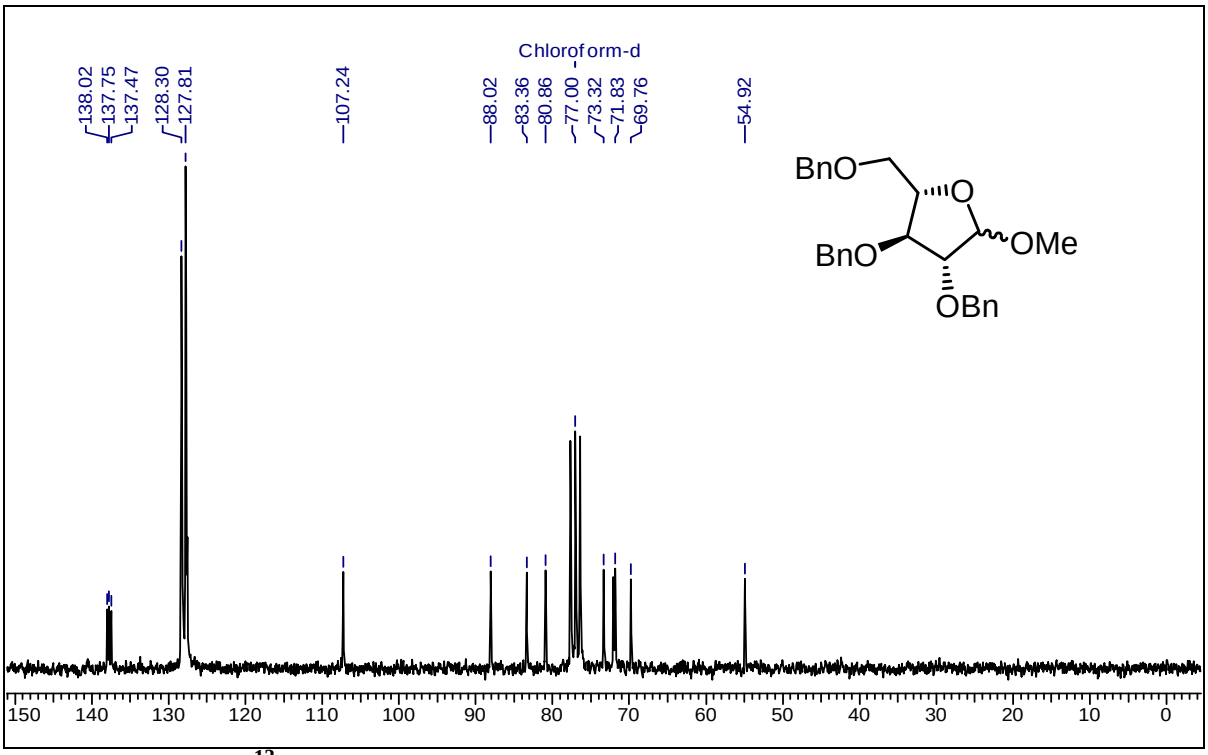
To a solution of **131** (0.3 g, 0.72 mmol) in dry THF (5 mL) was added PPh_3 (0.6 g, 2.2 mmol) and refluxed for 1 h. To this water (1 mL) was added and continued to reflux for another 1 h. The reaction mixture was cooled to room temperature and diluted with ethyl acetate. The solution was washed with 5% $NaHCO_3$, H_2O, brine, dried (Na_2SO_4) and concentrated to afford **122** as a thick liquid.

Yield	**:**	0.15 g, 65 %
Mol. Formula	**:**	$C_{27}H_{31}NO_3$
$[\alpha]_D^{25}$	**:**	4.9 (*c* = 1.1, $CHCl_3$); *ent*-**59** lit.[55] {– 4.9 (*c* = 1.1, $CHCl_3$)}
^{1}H NMR (200 MHz)	**:**	δ 1.66-1.83 (m, 2H), 2.76-3.04 (m, 2H), 3.27-3.57 (m, 4H), 3.68-3.73 (m, 1H), 4.39-4.62 (m, 6H), 7.26-7.38 (m, 15H)
^{13}C NMR (50 MHz)	**:**	24.7, 49.4, 59.3, 66.4, 70.5, 71.1, 71.7, 73.2, 73.4, 127.5, 127.7-128.0, 128.3, 128.4, 137.5, 137.8, 137.9 ppm
+TOF MS *m/z*	**:**	418 $[M+H]^+$
Elemental Analysis		Calcd: C, 77.67; H, 7.48; N, 3.35%
		Found: C, 77.71; H, 7.45; N, 3.21%

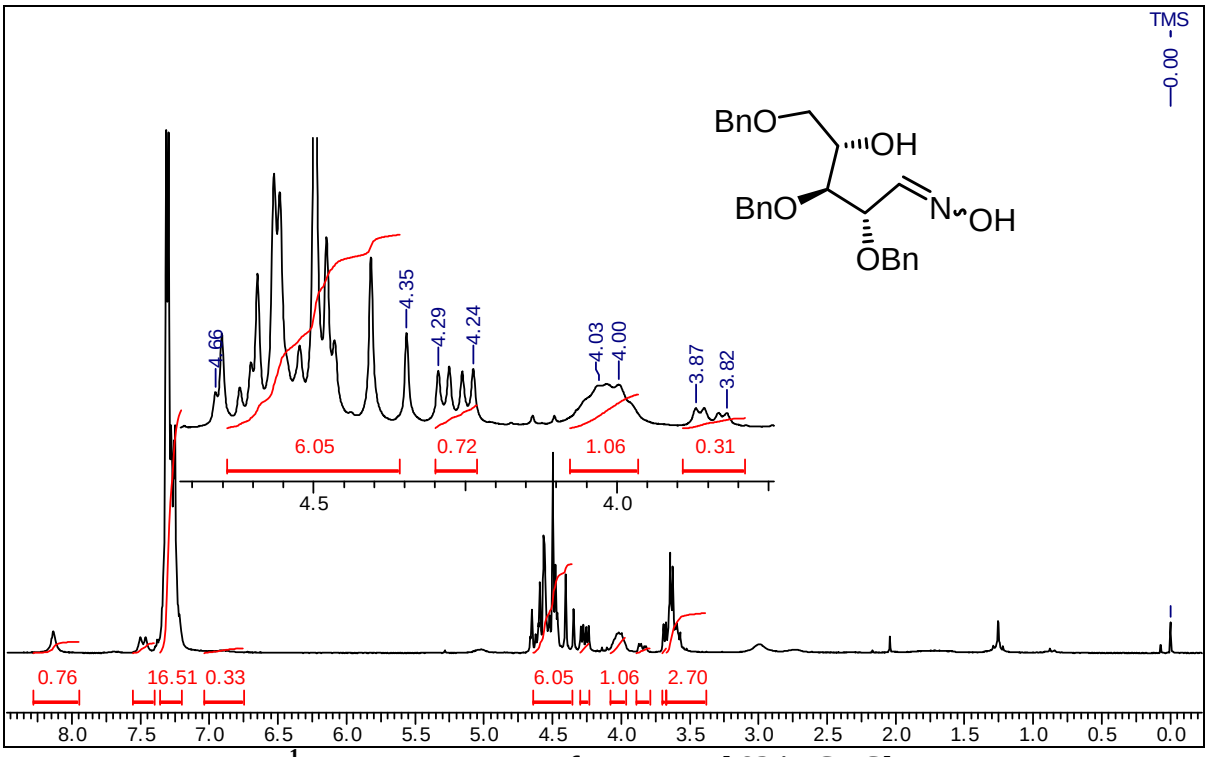
SPECTRA



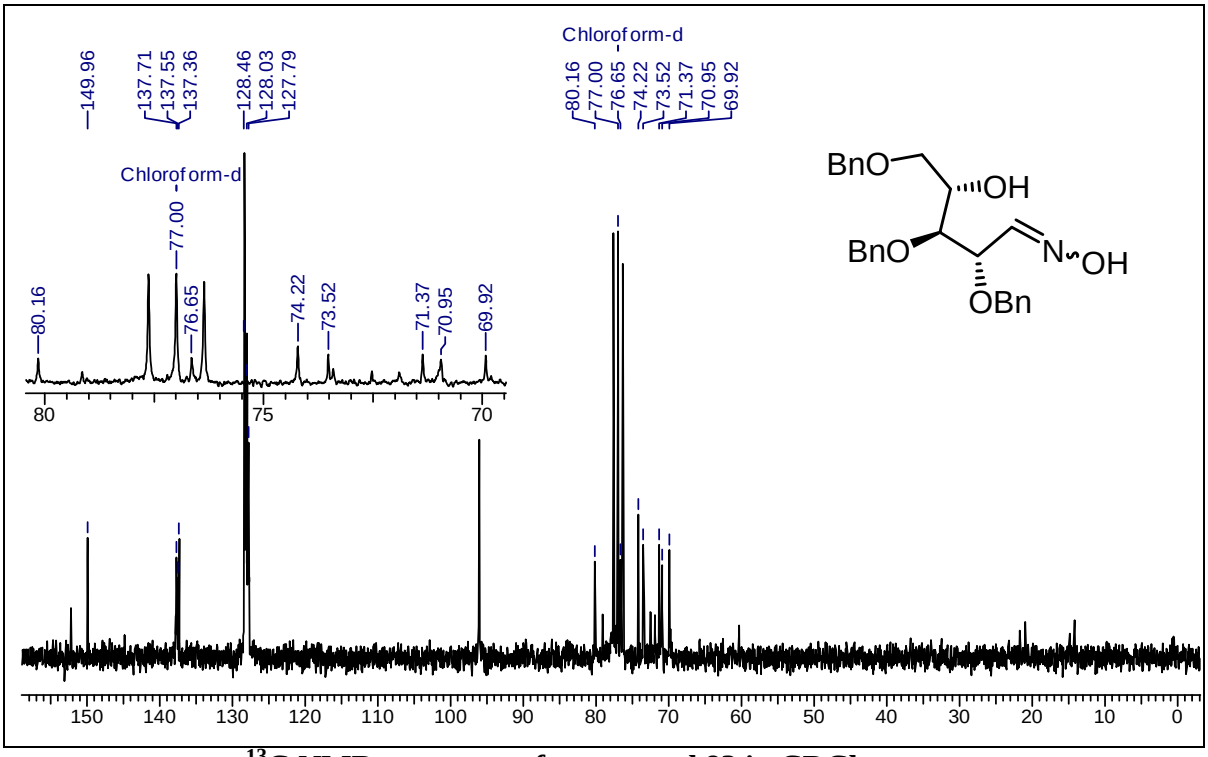
^{1}H NMR spectrum of compound 81 in $CDCl_3$



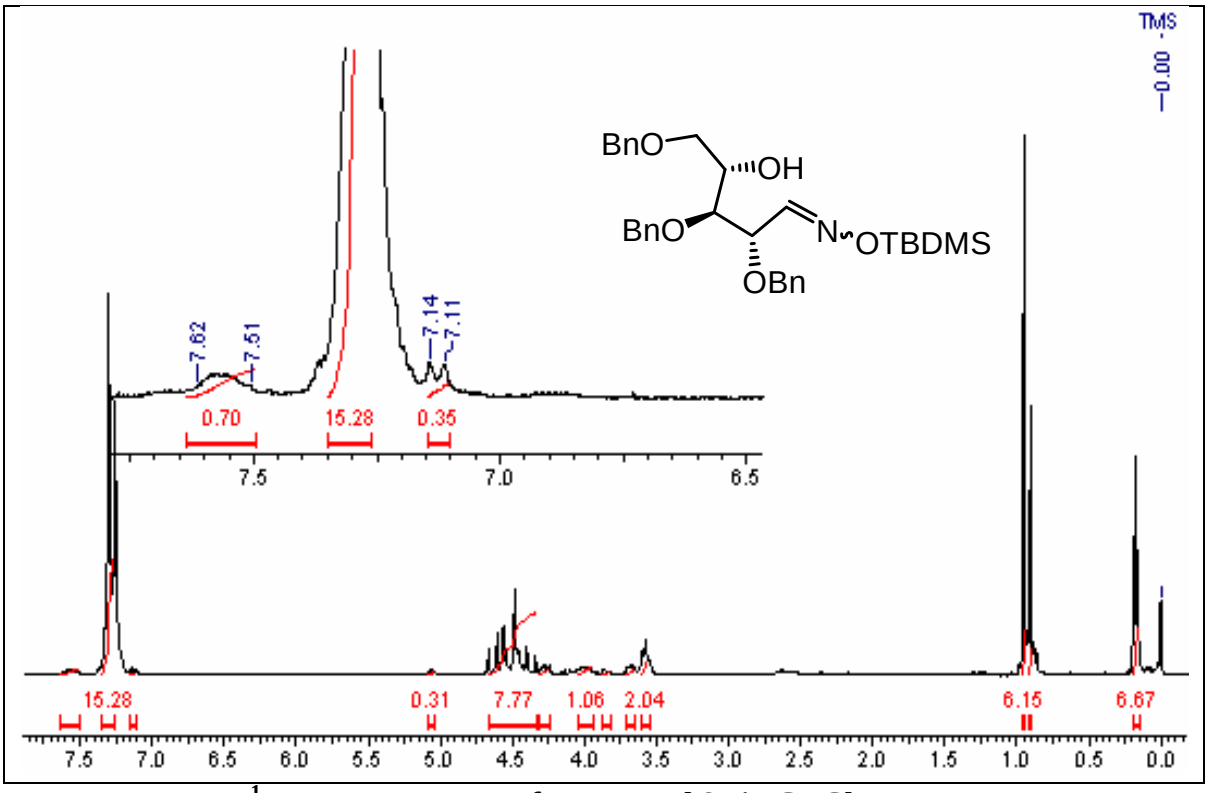
^{13}C NMR spectrum of compound 81 in $CDCl_3$



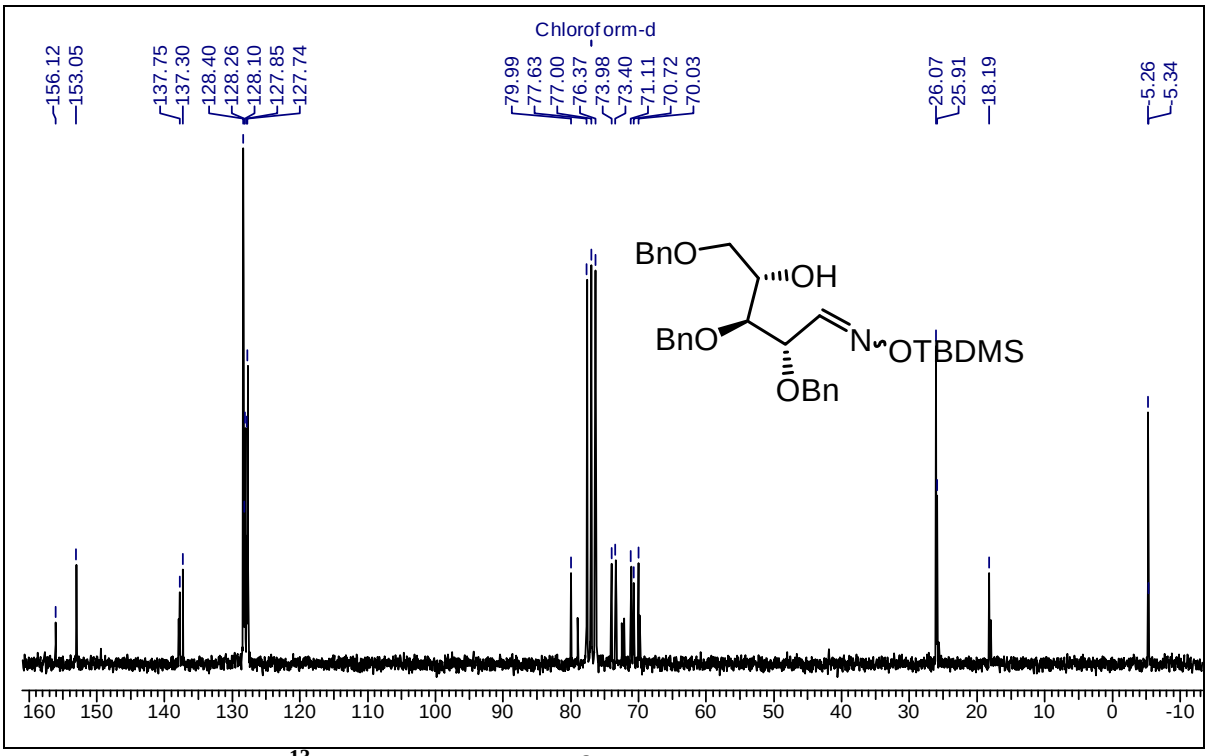
^{1}H NMR spectrum of compound 83 in $CDCl_3$



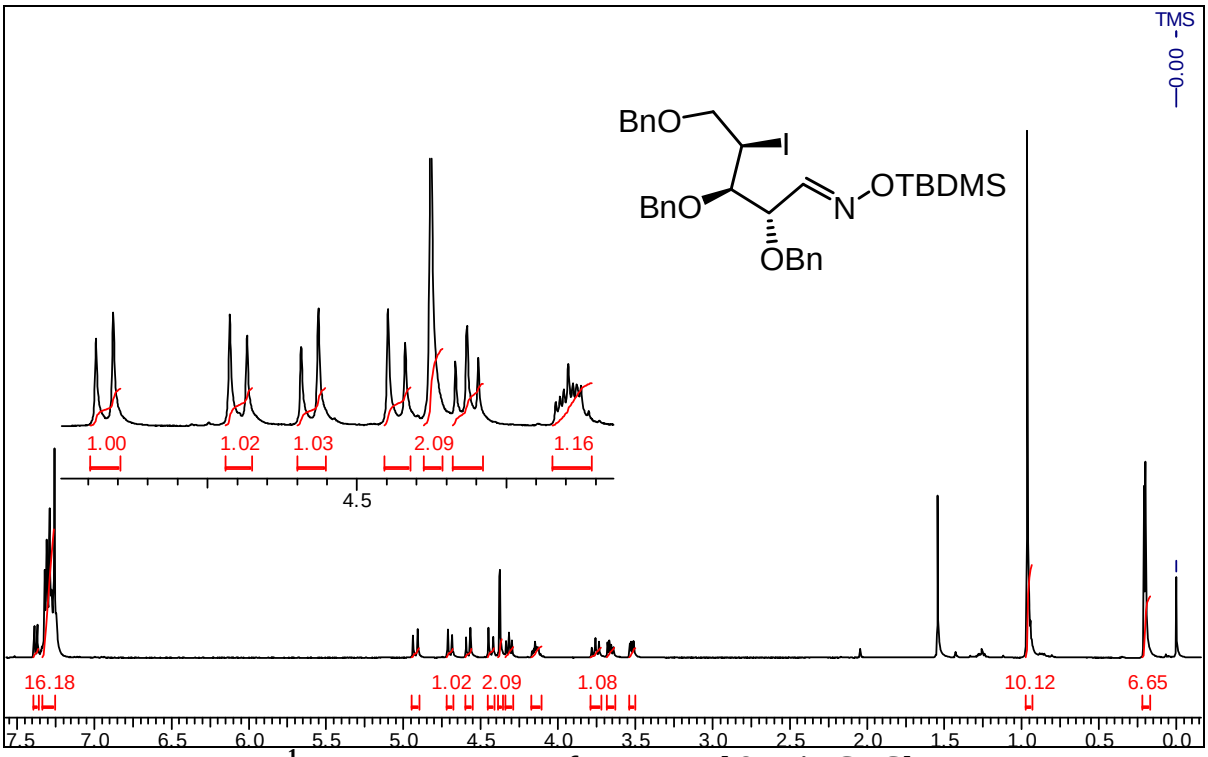
^{13}C NMR spectrum of compound 83 in $CDCl_3$



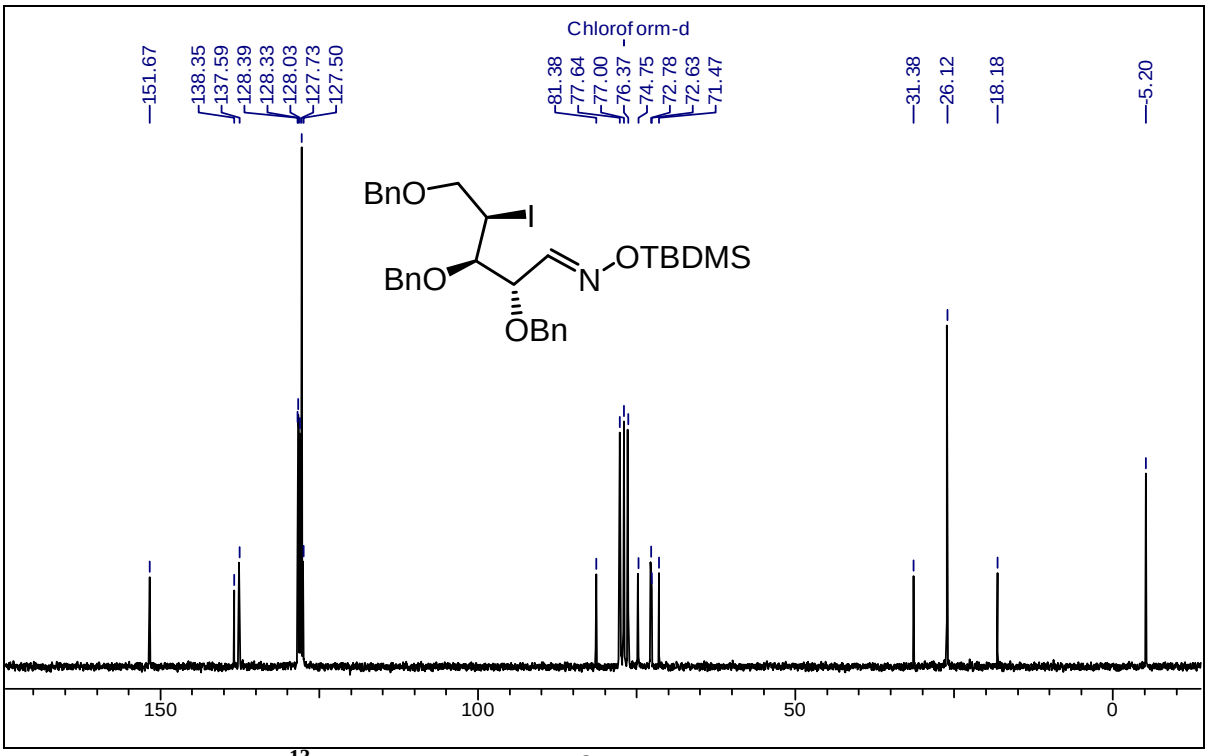
^{1}H NMR spectrum of compound 84 in $CDCl_3$



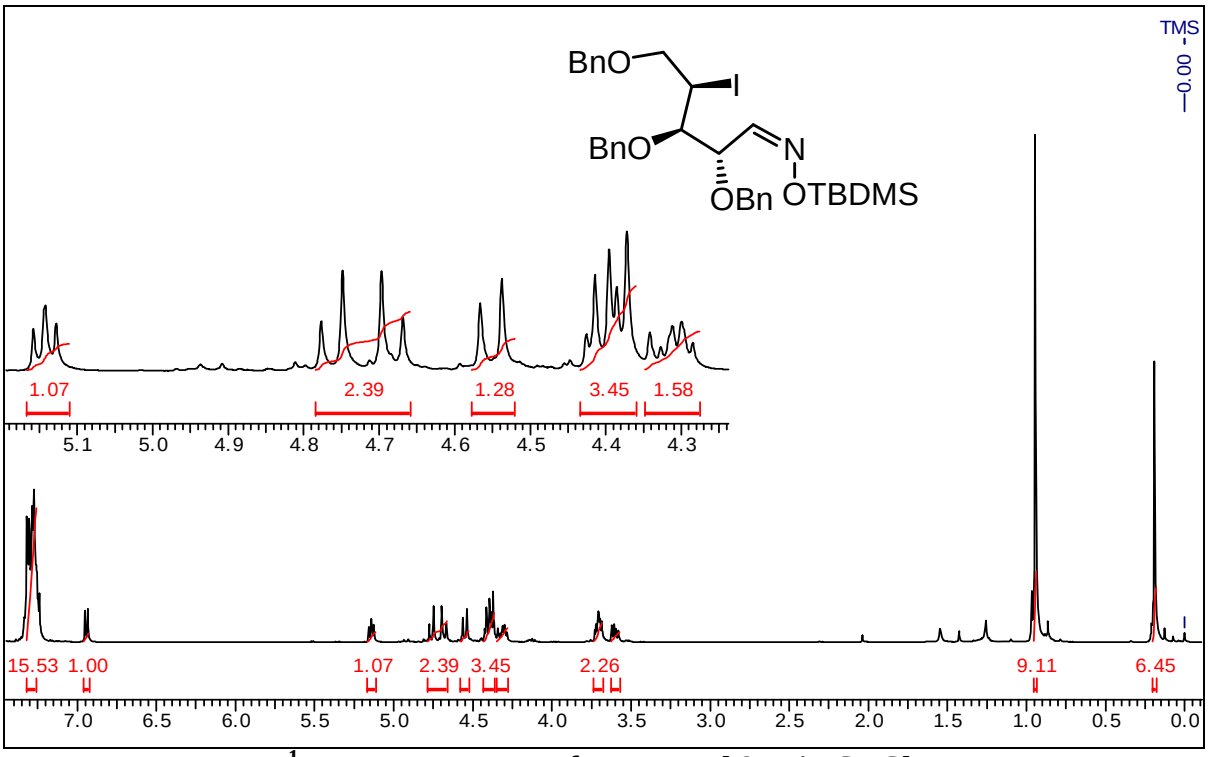
^{13}C NMR spectrum of compound 84 in $CDCl_3$



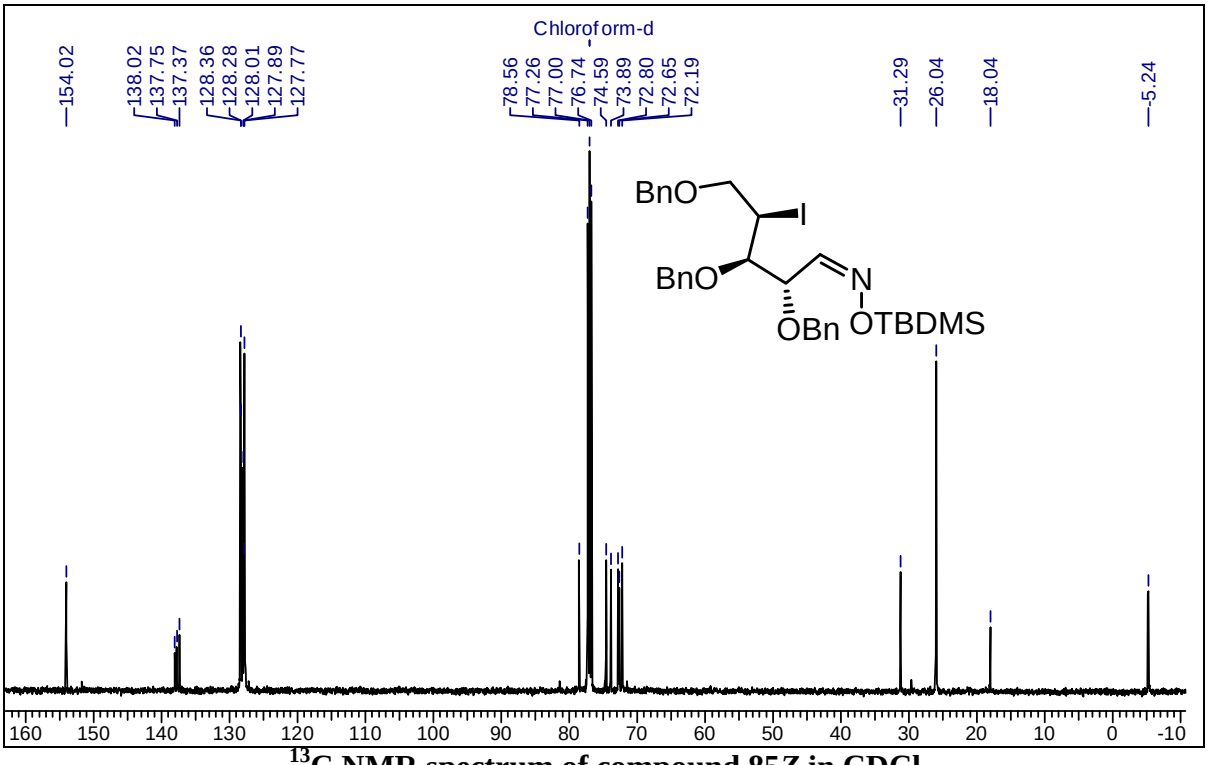
^{1}H NMR spectrum of compound 85*E* in $CDCl_3$



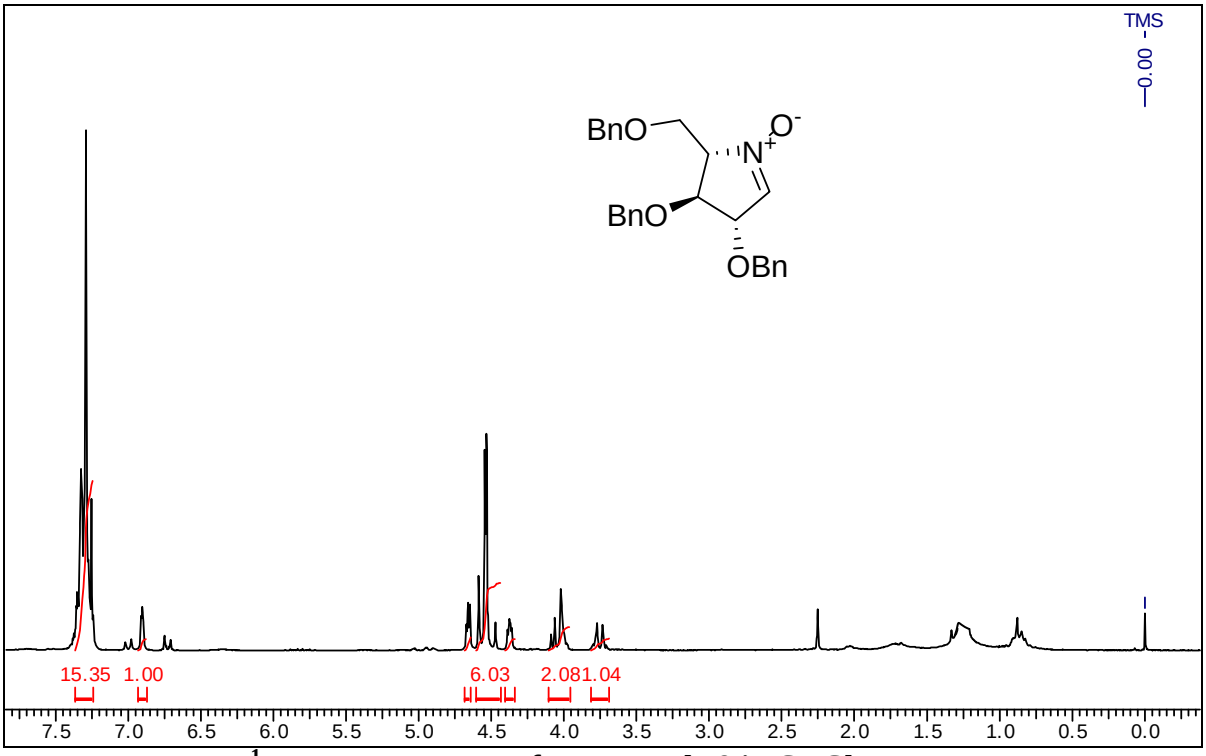
^{13}C NMR spectrum of compound 85*E* in $CDCl_3$



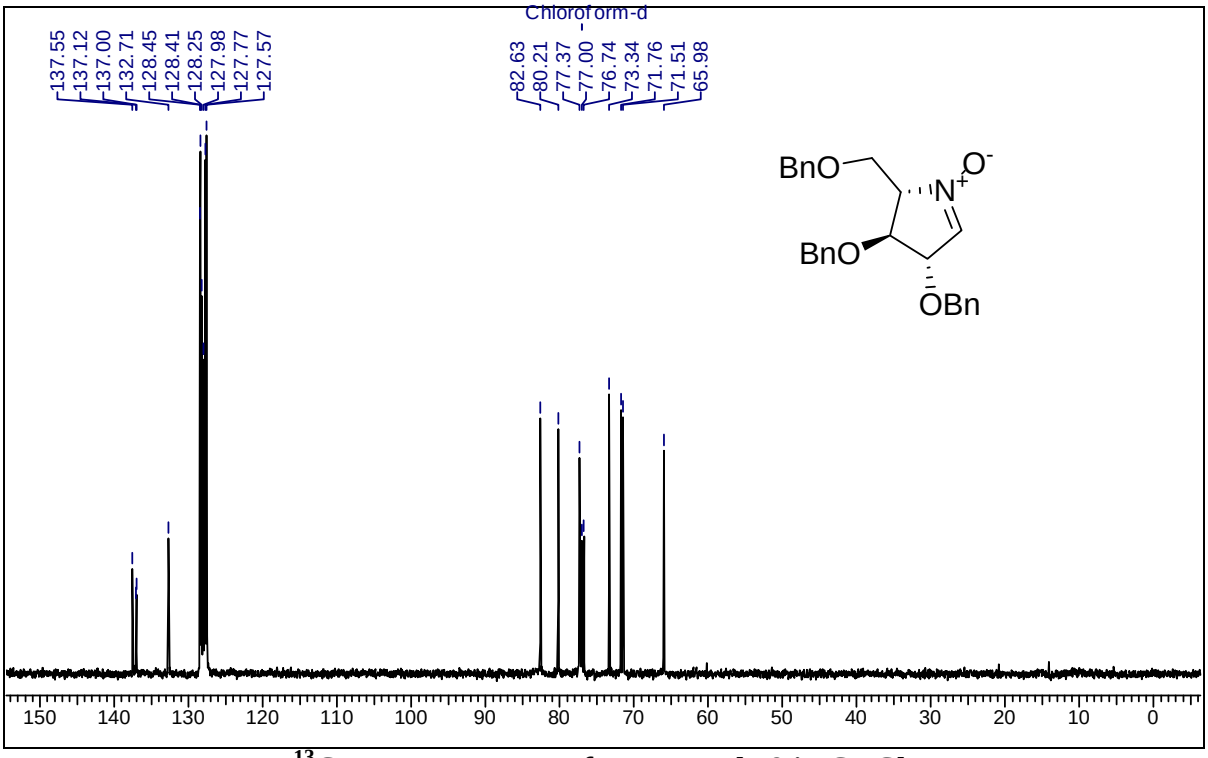
^{1}H NMR spectrum of compound 85*Z* in $CDCl_3$



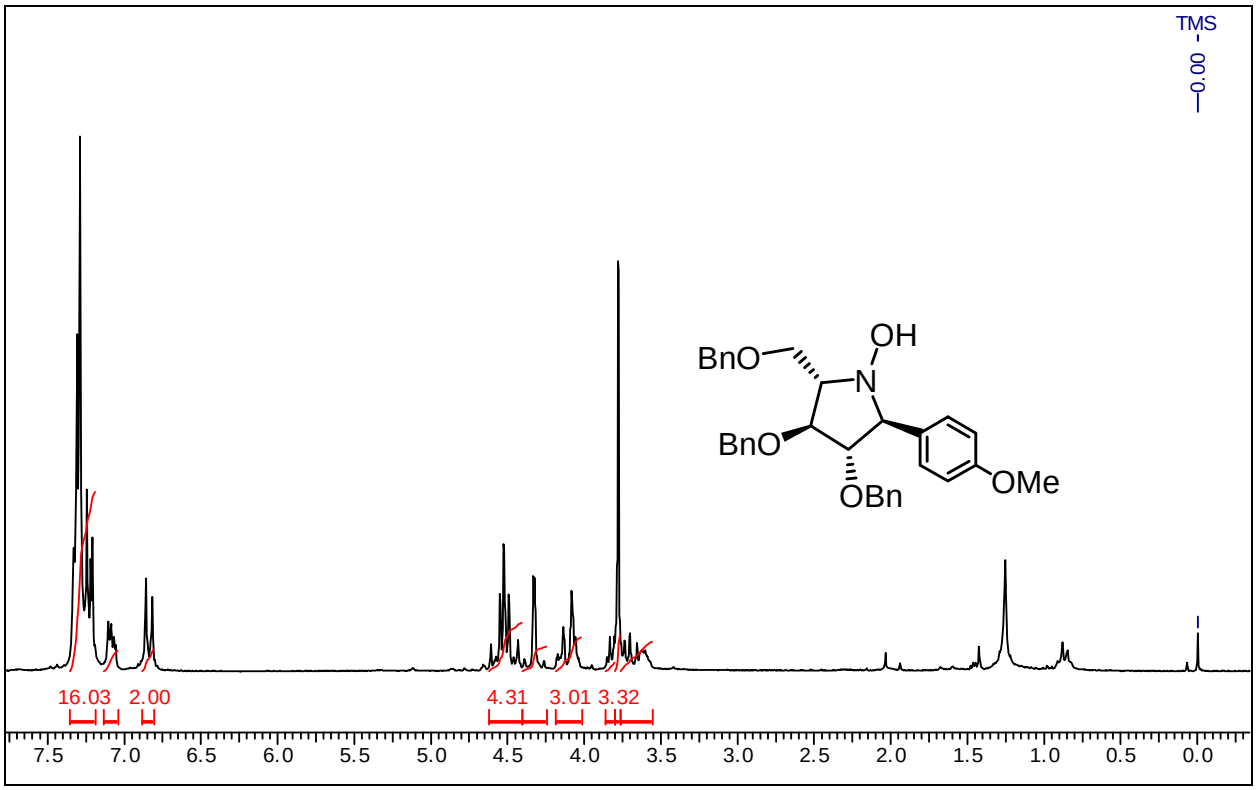
^{13}C NMR spectrum of compound 85*Z* in $CDCl_3$



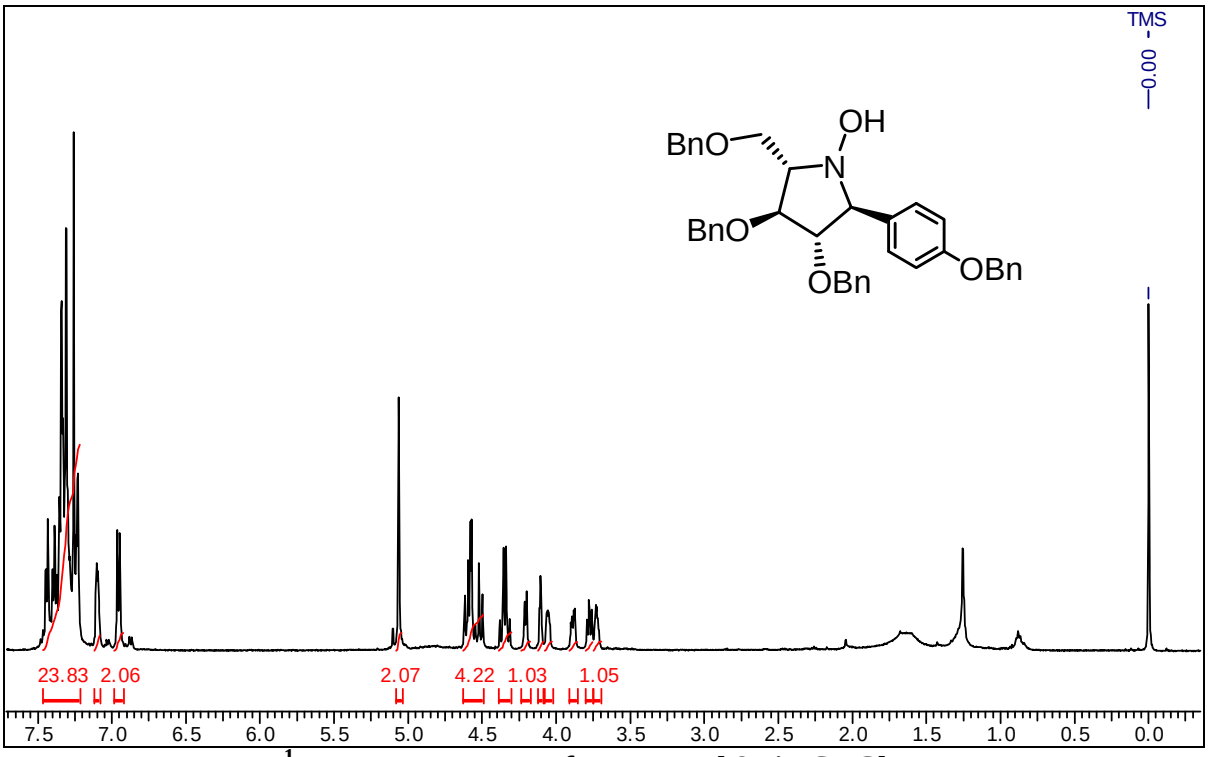
^{1}H NMR spectrum of compound 79 in $CDCl_3$



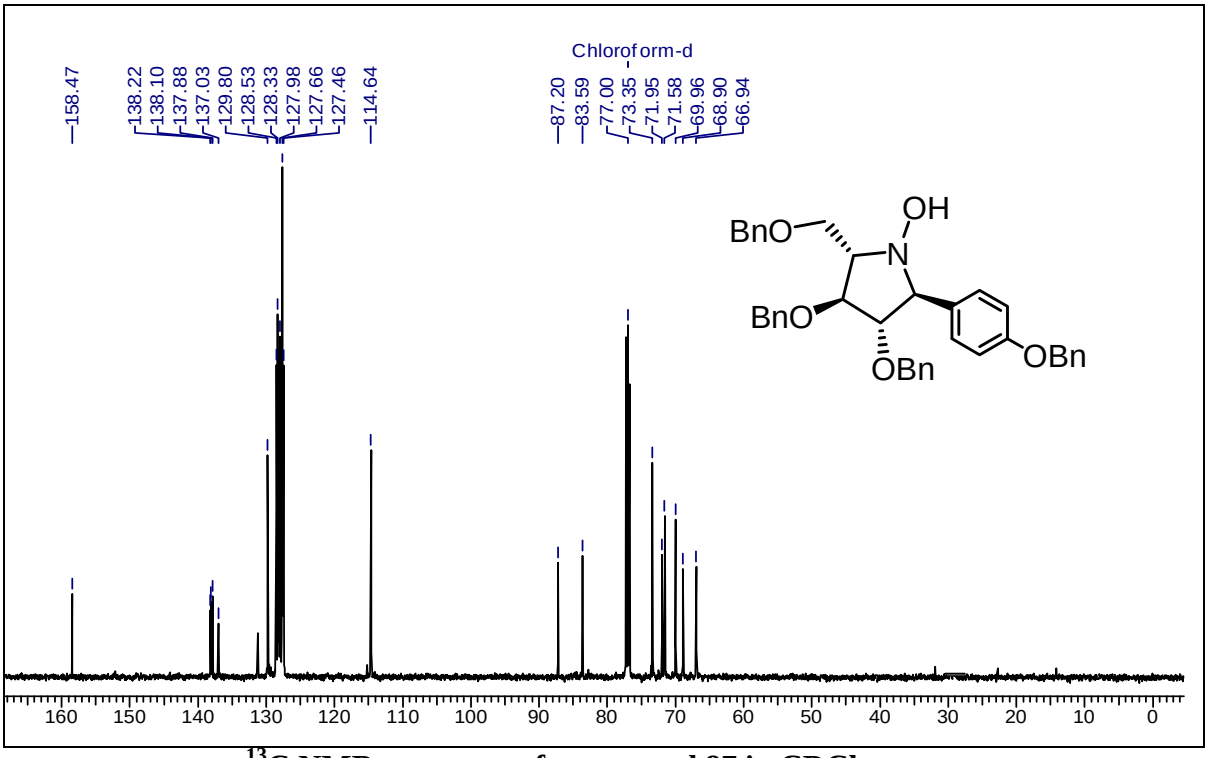
^{13}C NMR spectrum of compound 79 in $CDCl_3$



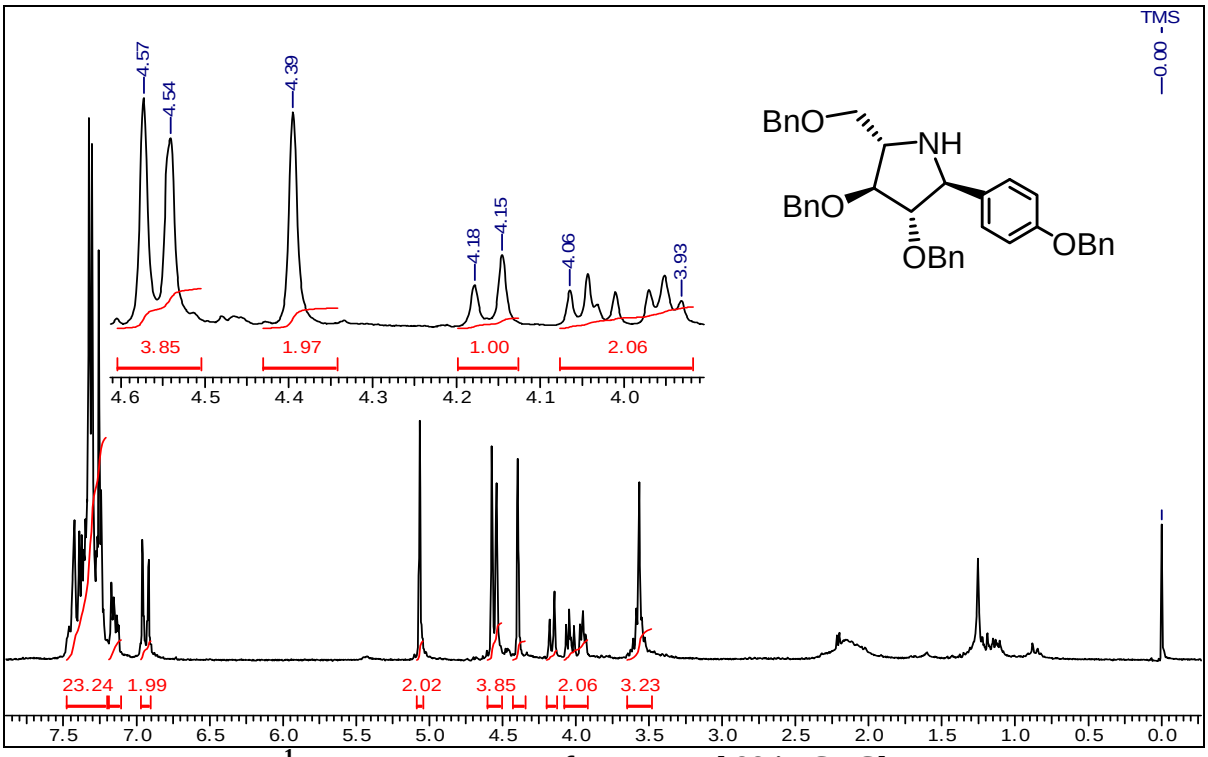
^{1}H NMR spectrum of compound 86 in $CDCl_3$



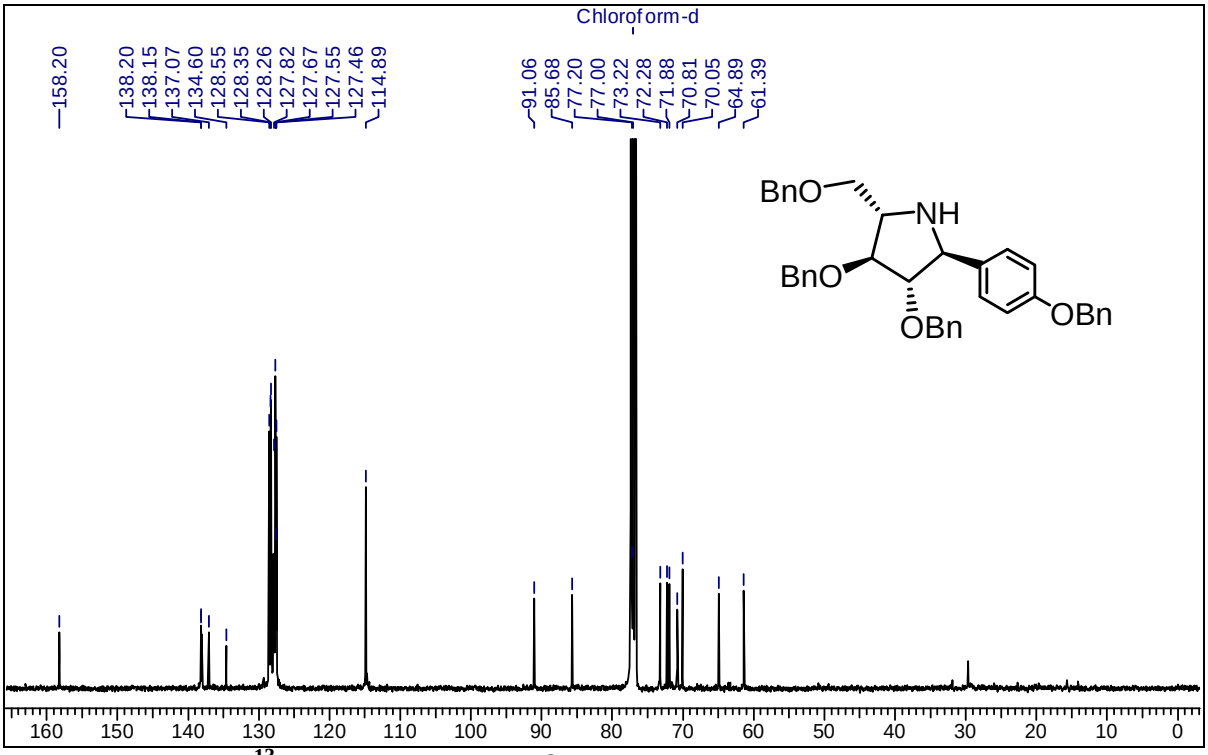
^{1}H NMR spectrum of compound 87 in $CDCl_3$



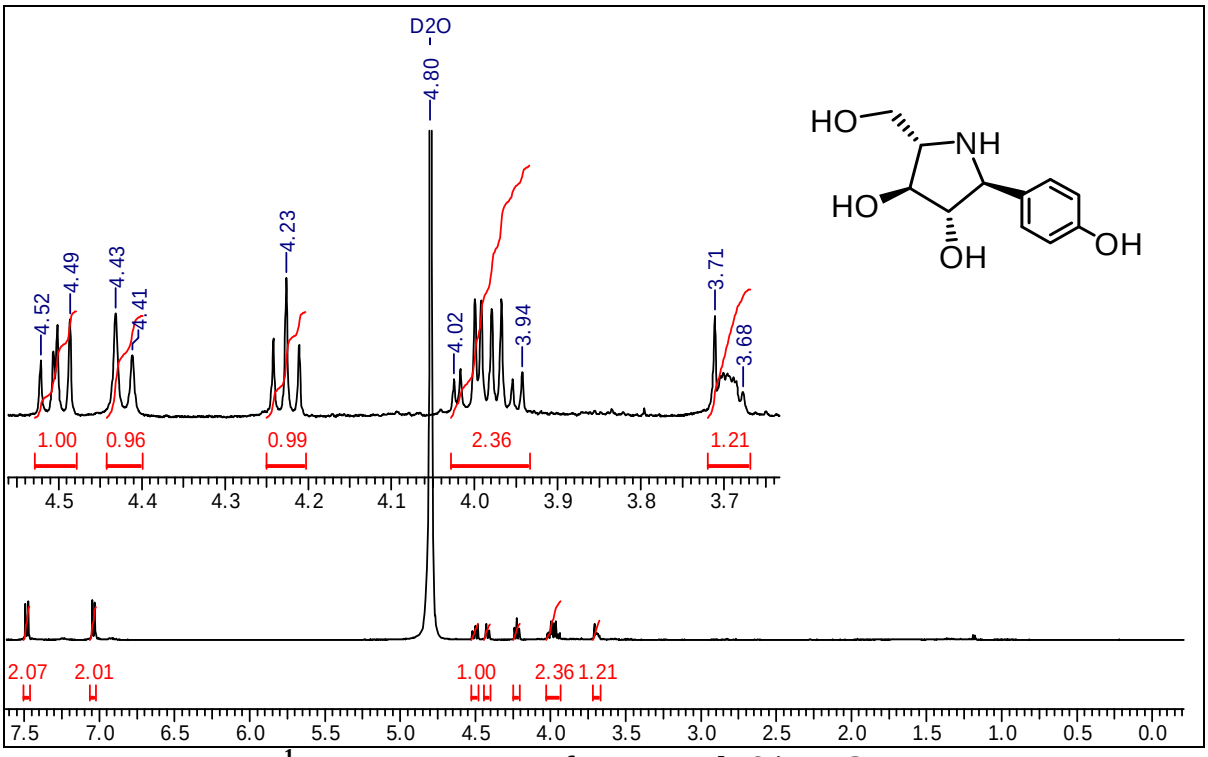
^{13}C NMR spectrum of compound 87 in $CDCl_3$



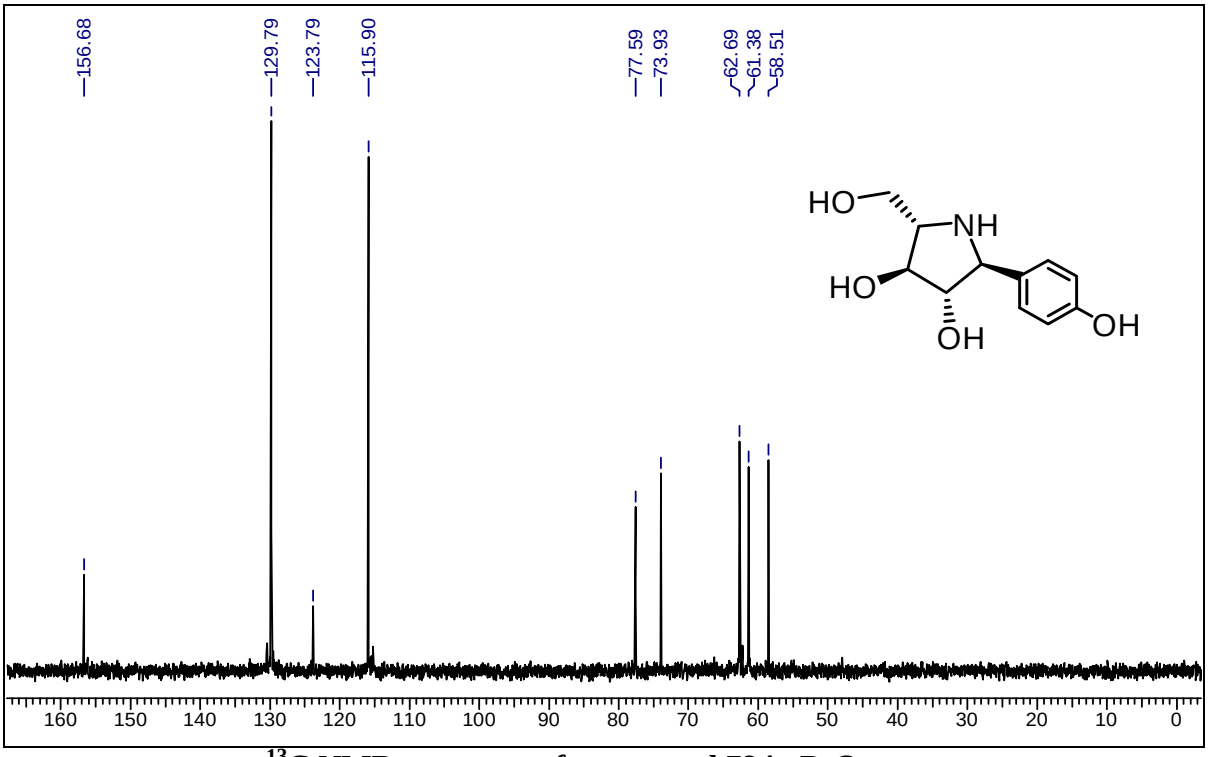
^{1}H NMR spectrum of compound 88 in $CDCl_3$



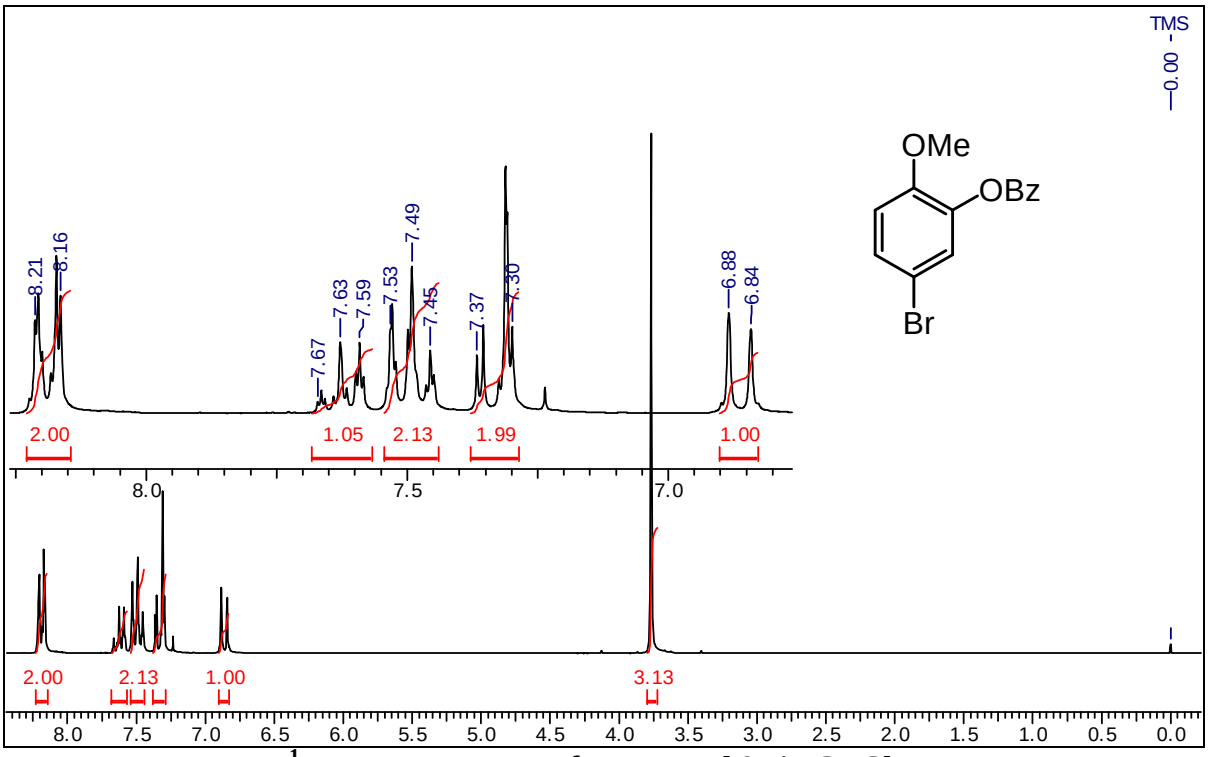
^{13}C NMR spectrum of compound 88 in $CDCl_3$



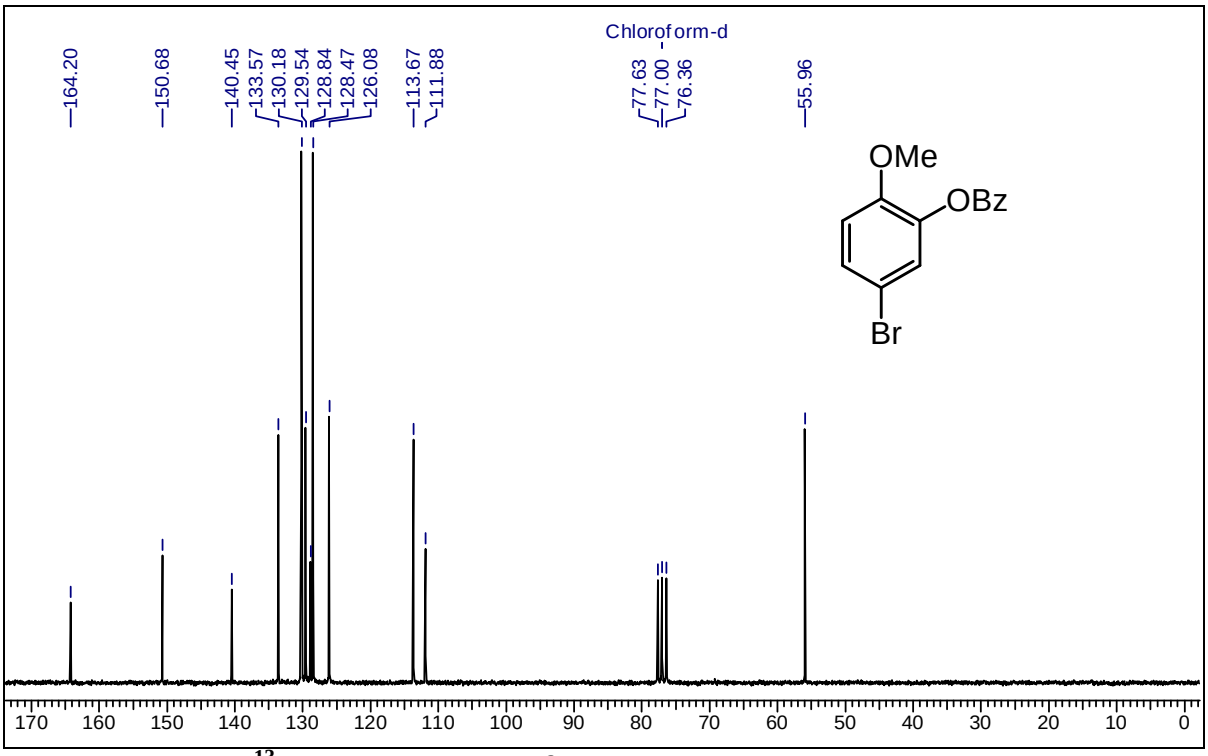
^{1}H NMR spectrum of compound 78 in D_2O



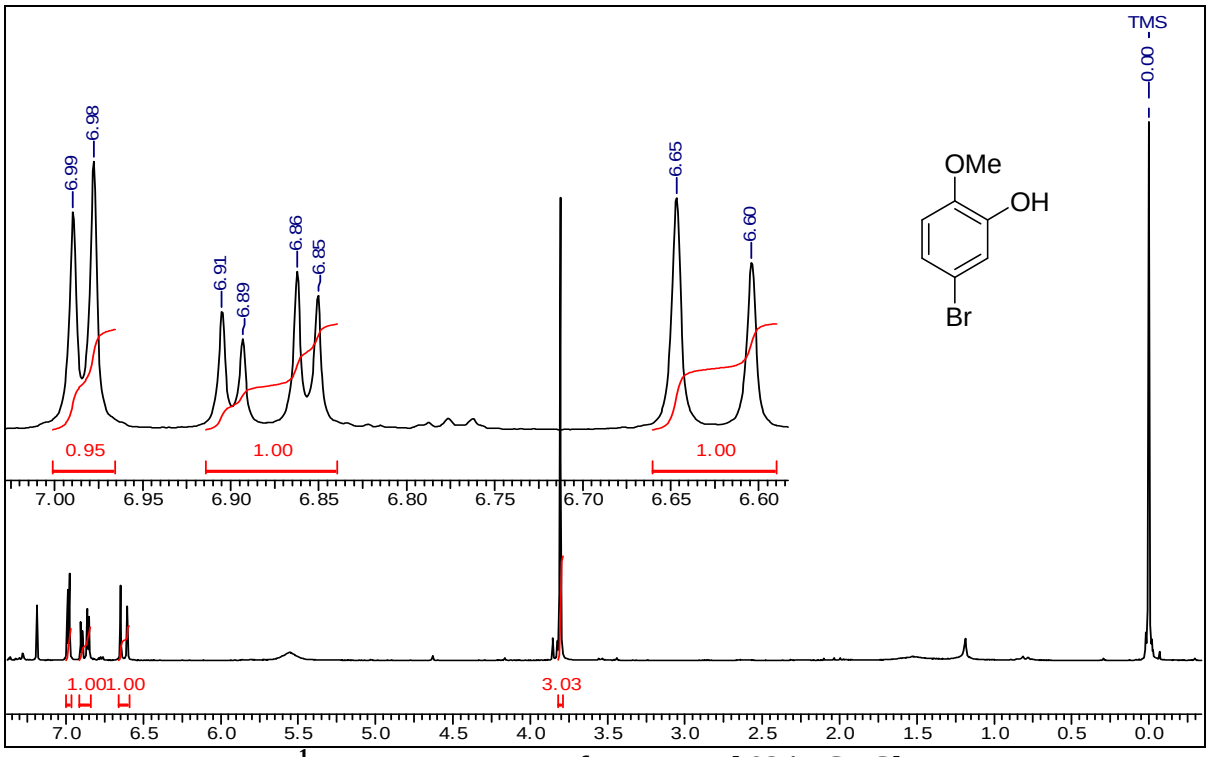
^{13}C NMR spectrum of compound 78 in D_2O



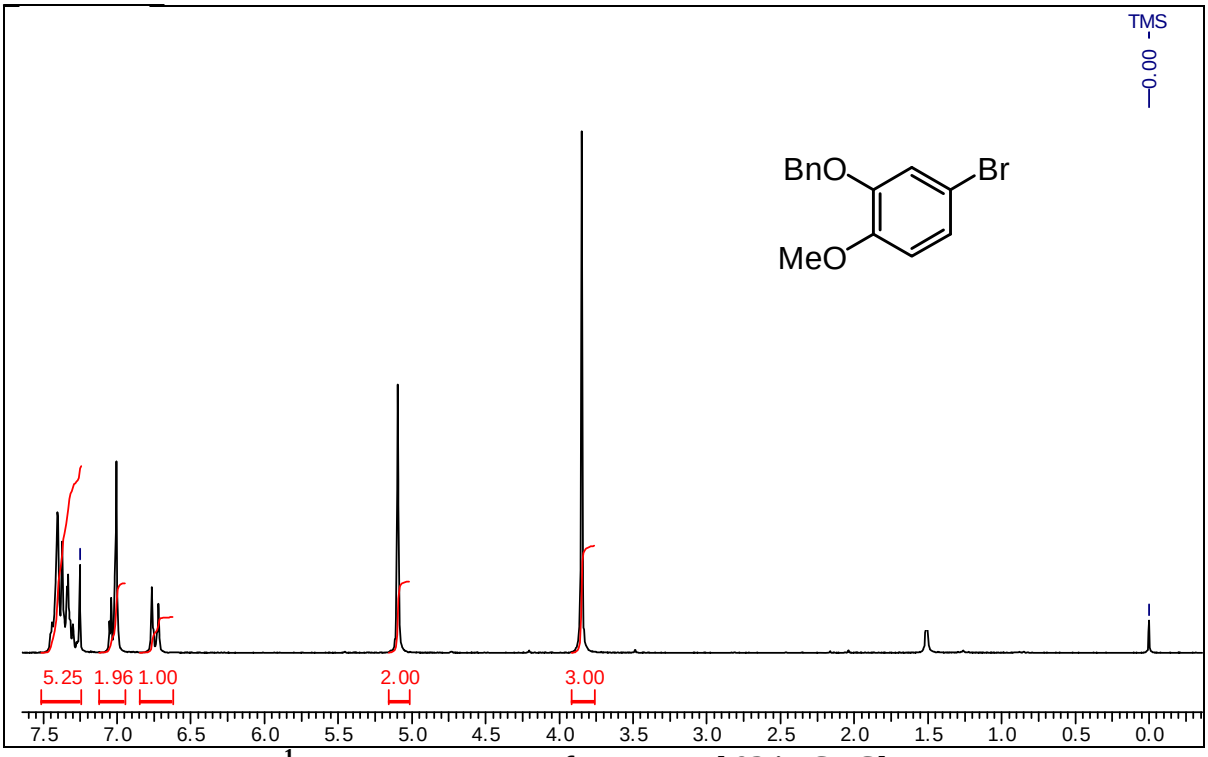
^{1}H NMR spectrum of compound 91 in $CDCl_3$



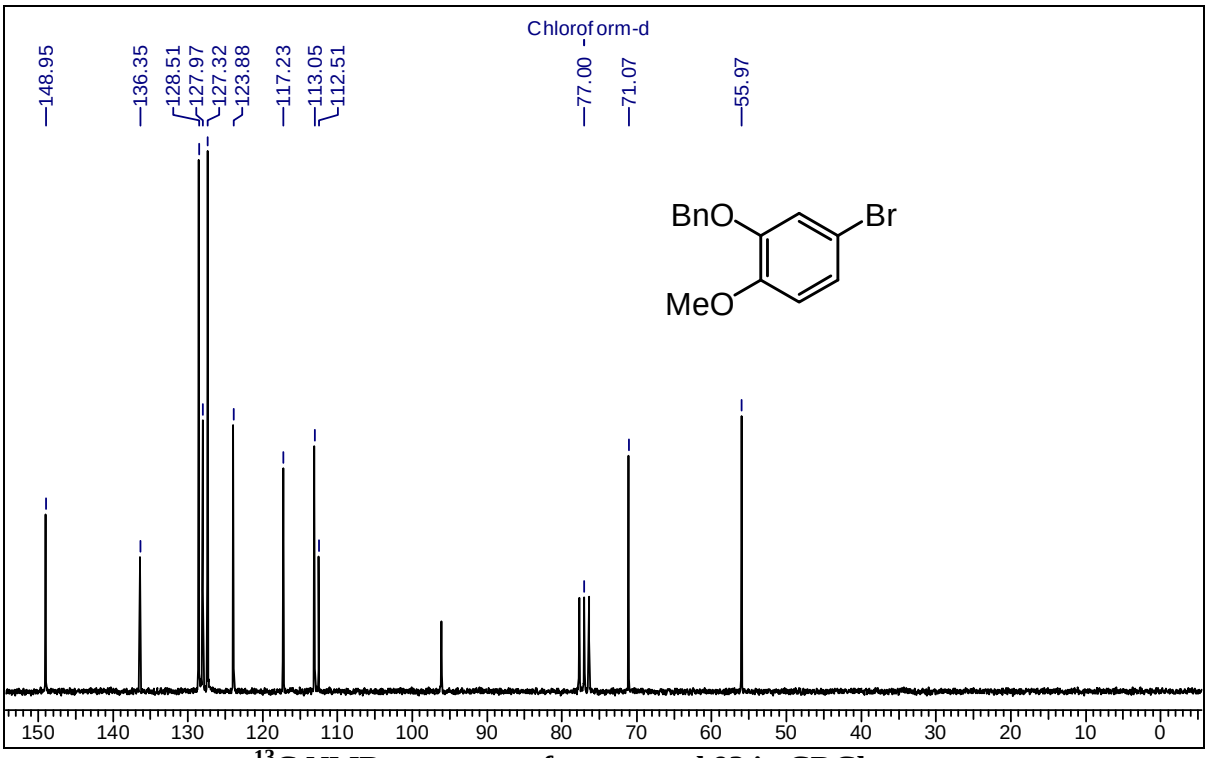
^{13}C NMR spectrum of compound 91 in $CDCl_3$



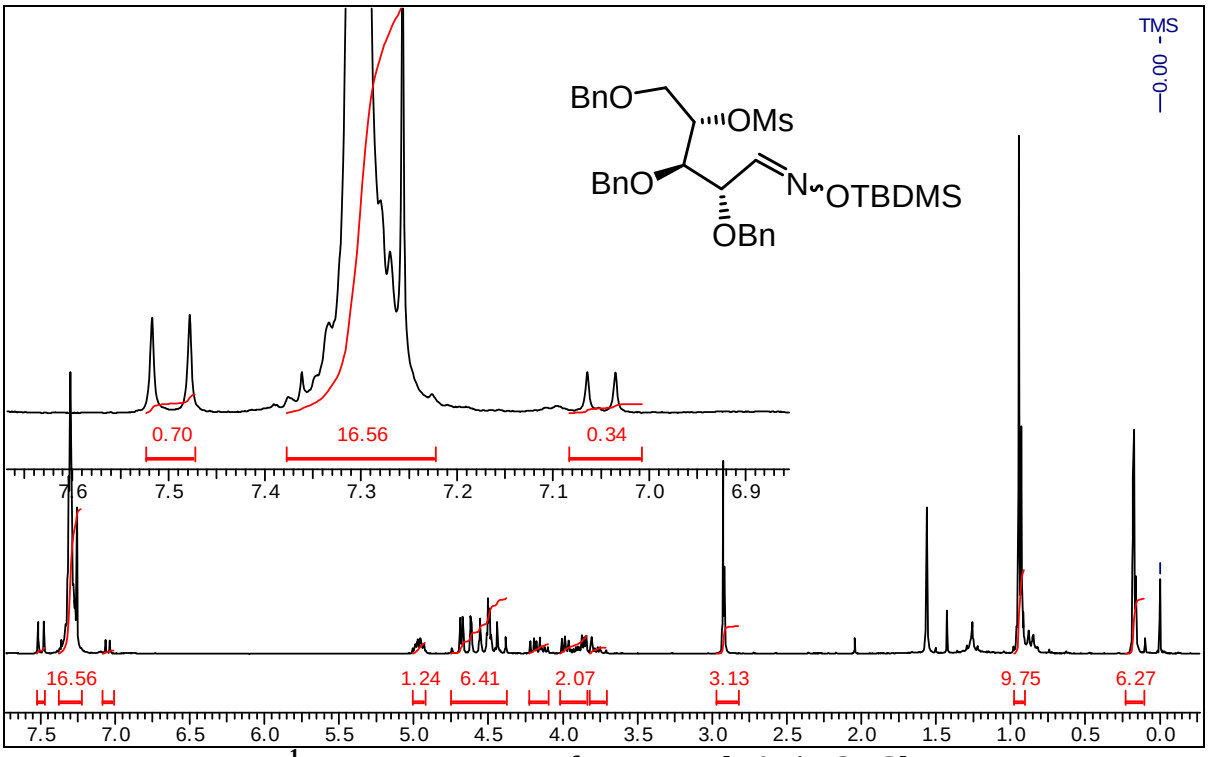
^{1}H NMR spectrum of compound 92 in $CDCl_3$



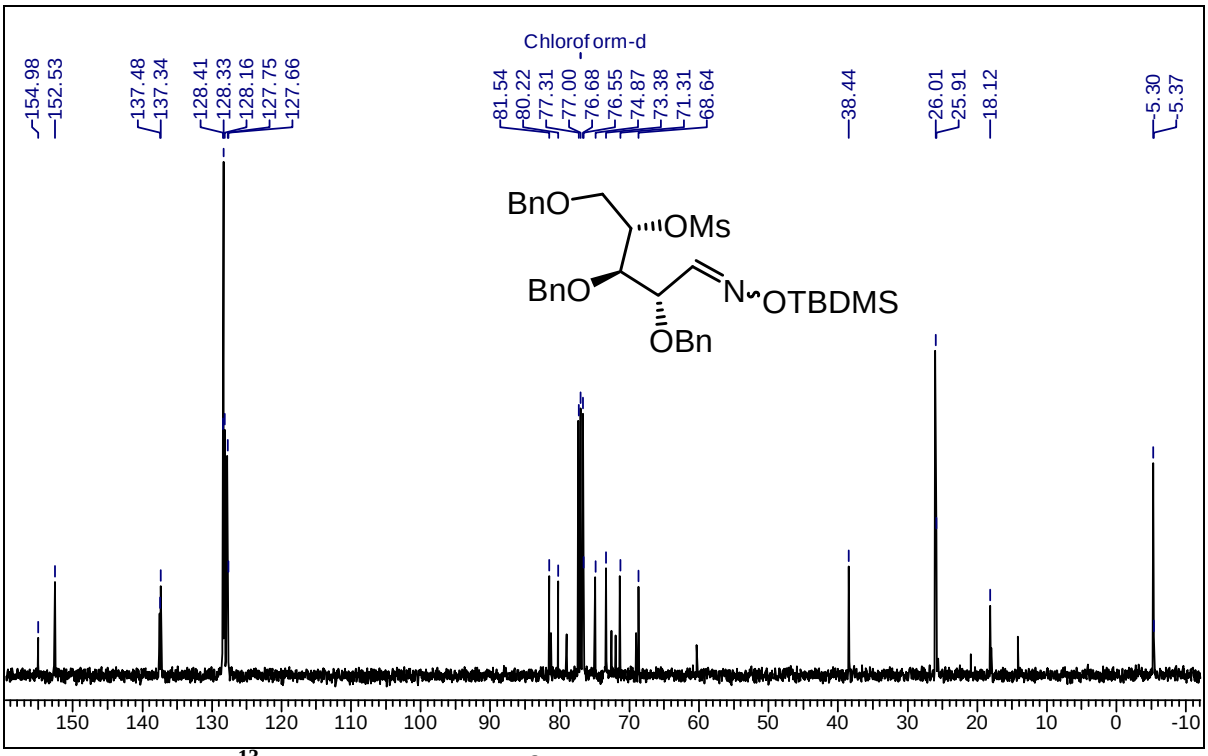
^{1}H NMR spectrum of compound 93 in $CDCl_3$



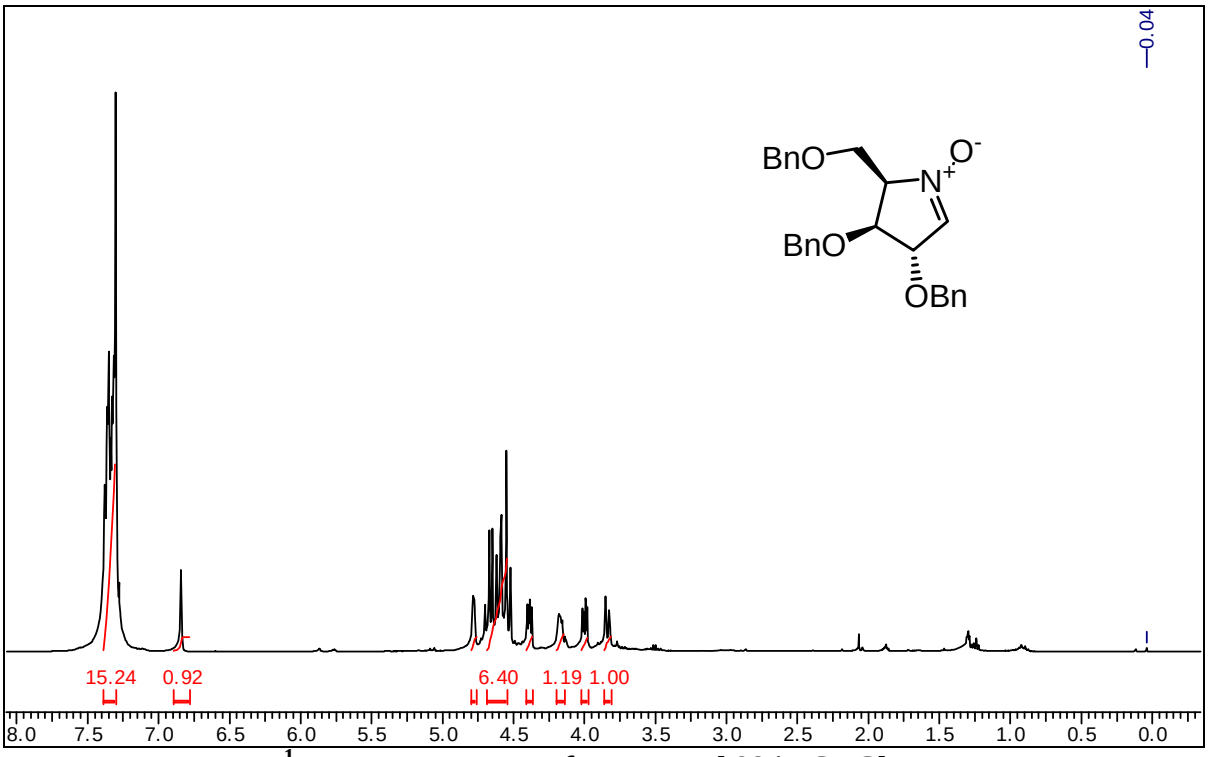
^{13}C NMR spectrum of compound 93 in $CDCl_3$



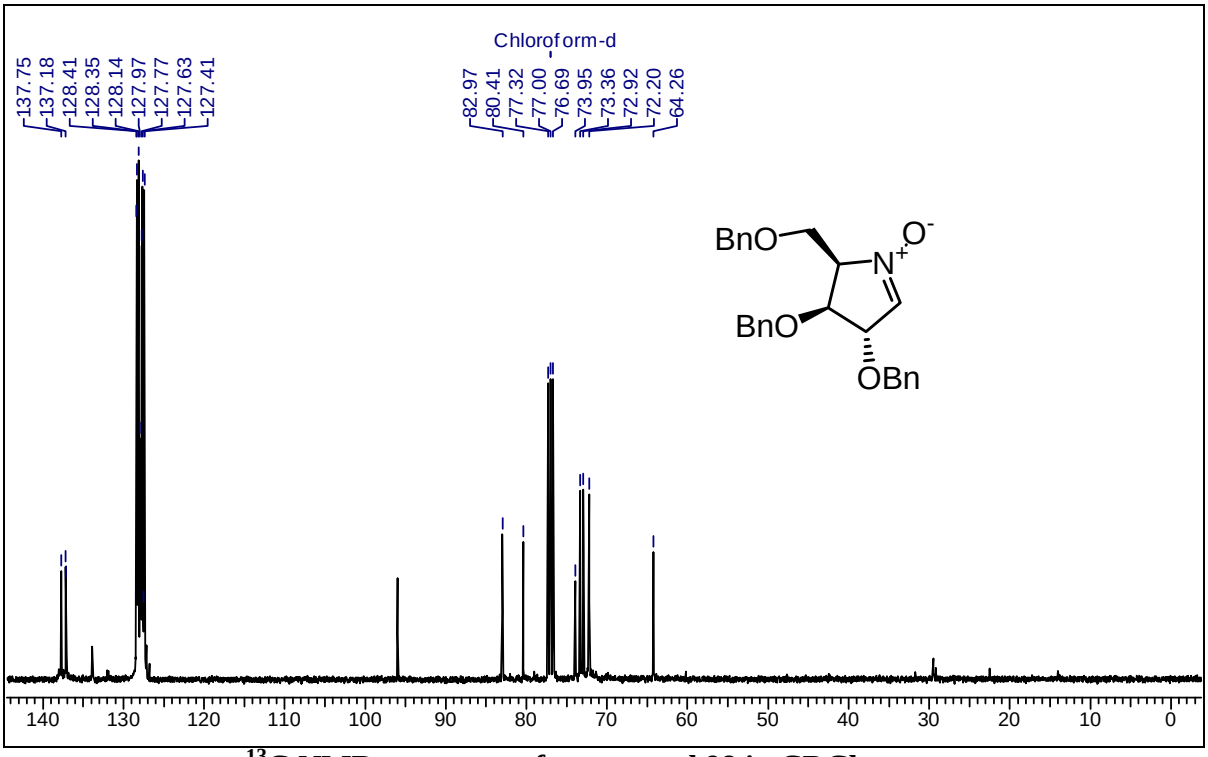
^{1}H NMR spectrum of compound 101 in $CDCl_3$



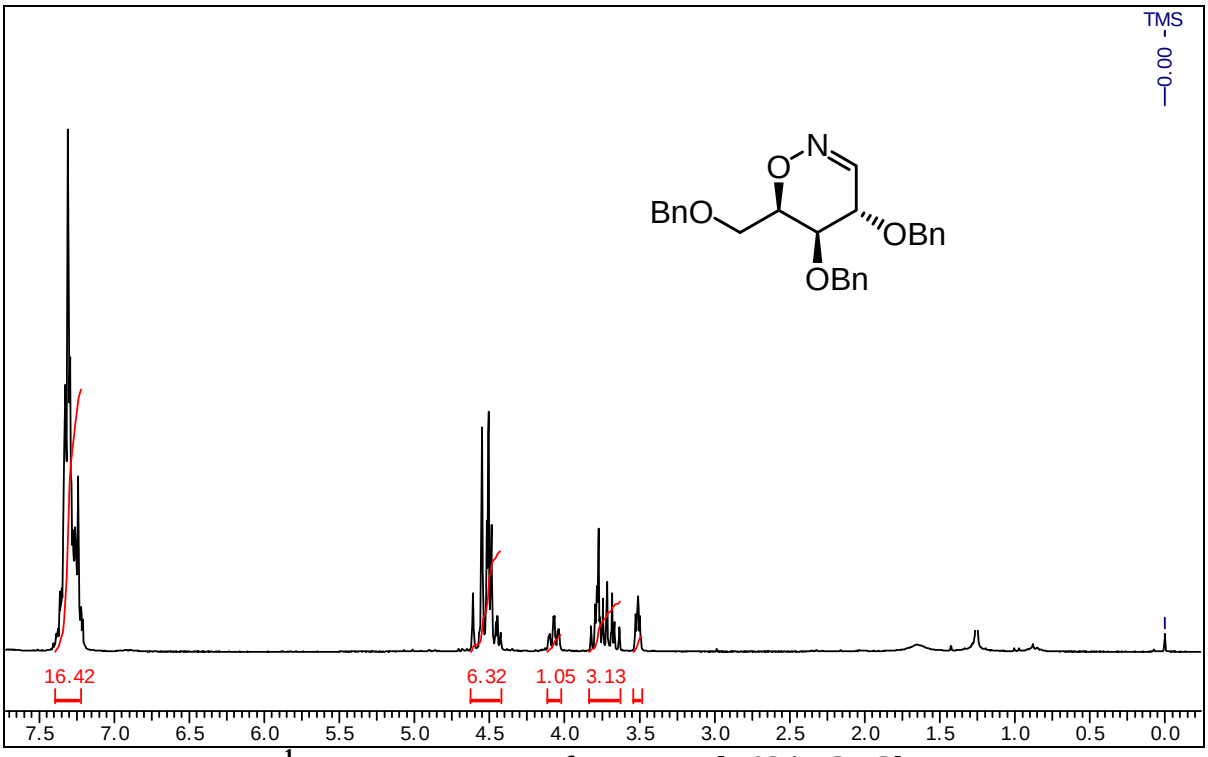
^{13}C NMR spectrum of compound 101 in $CDCl_3$



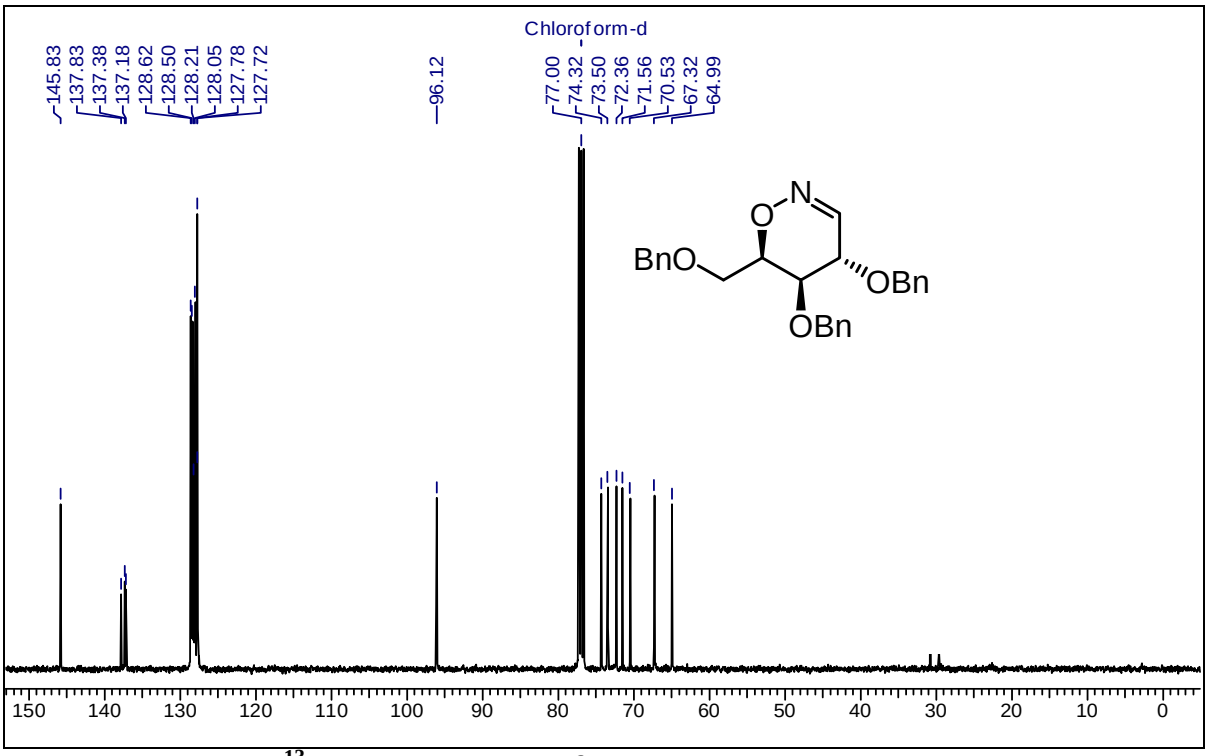
^{1}H NMR spectrum of compound 98 in $CDCl_3$



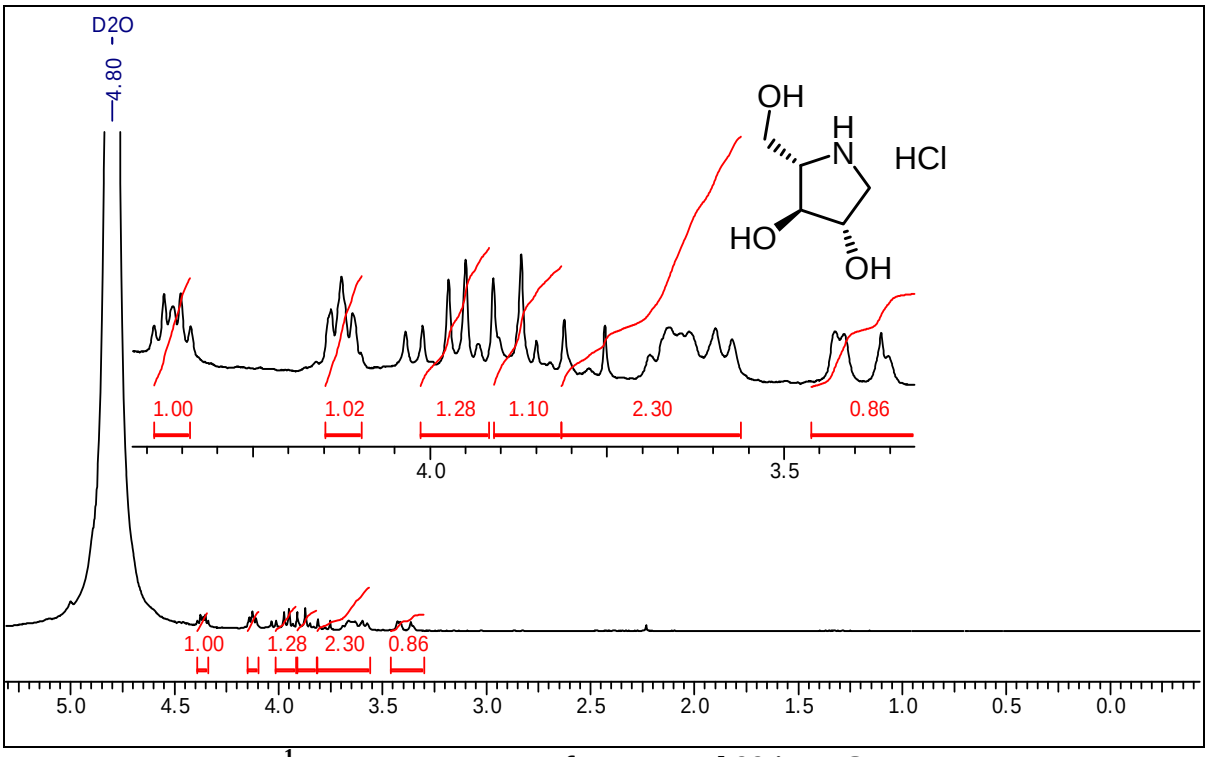
^{13}C NMR spectrum of compound 98 in $CDCl_3$



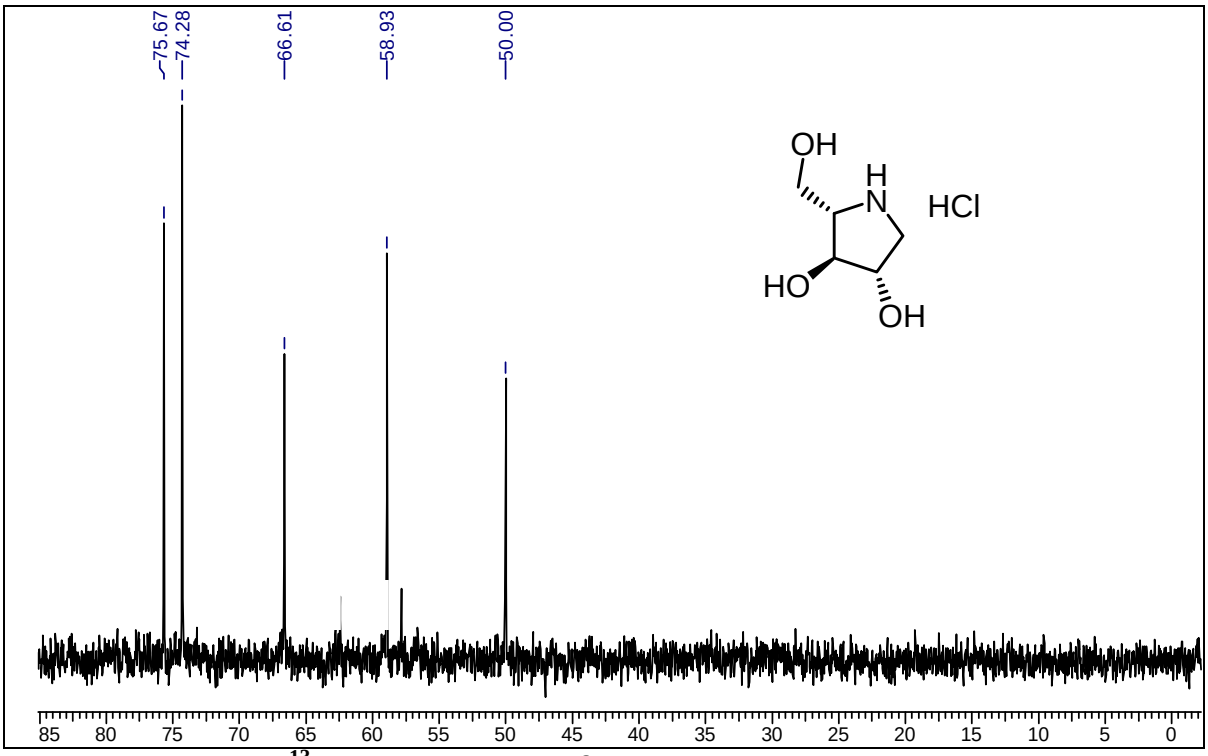
^{1}H NMR spectrum of compound 103 in $CDCl_3$



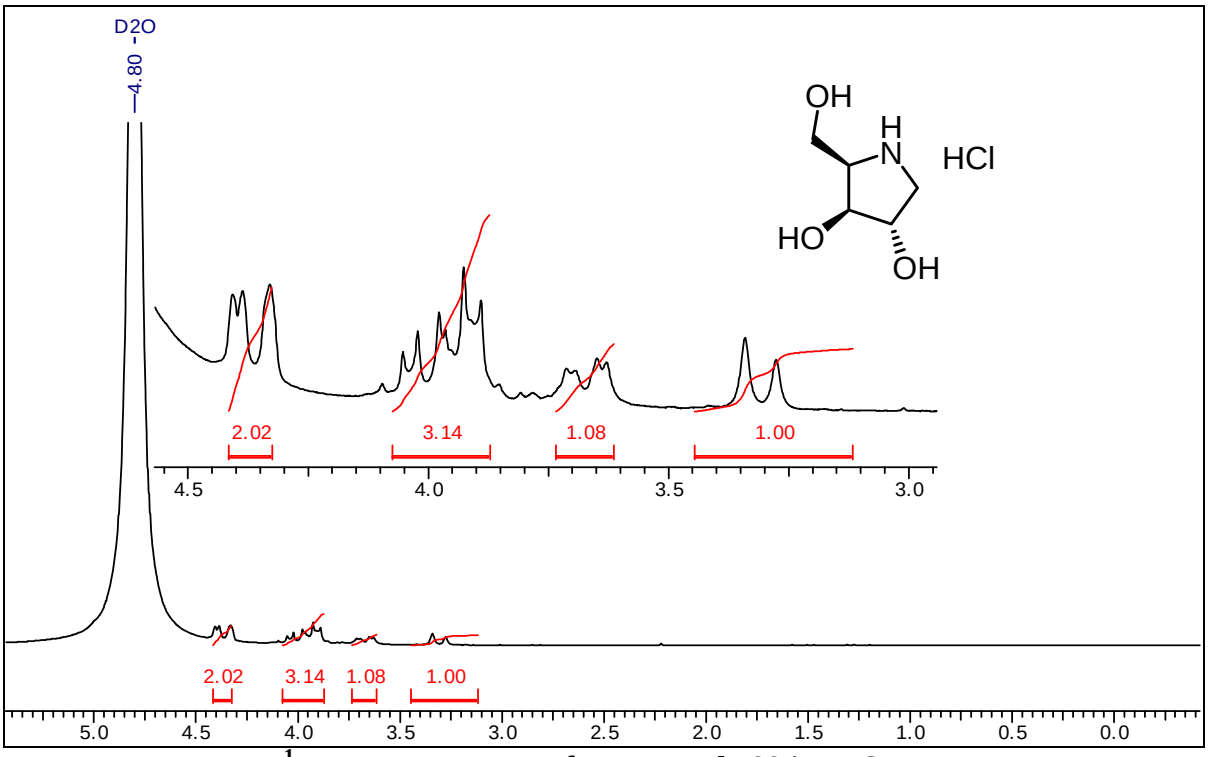
^{13}C NMR spectrum of compound 103 in $CDCl_3$



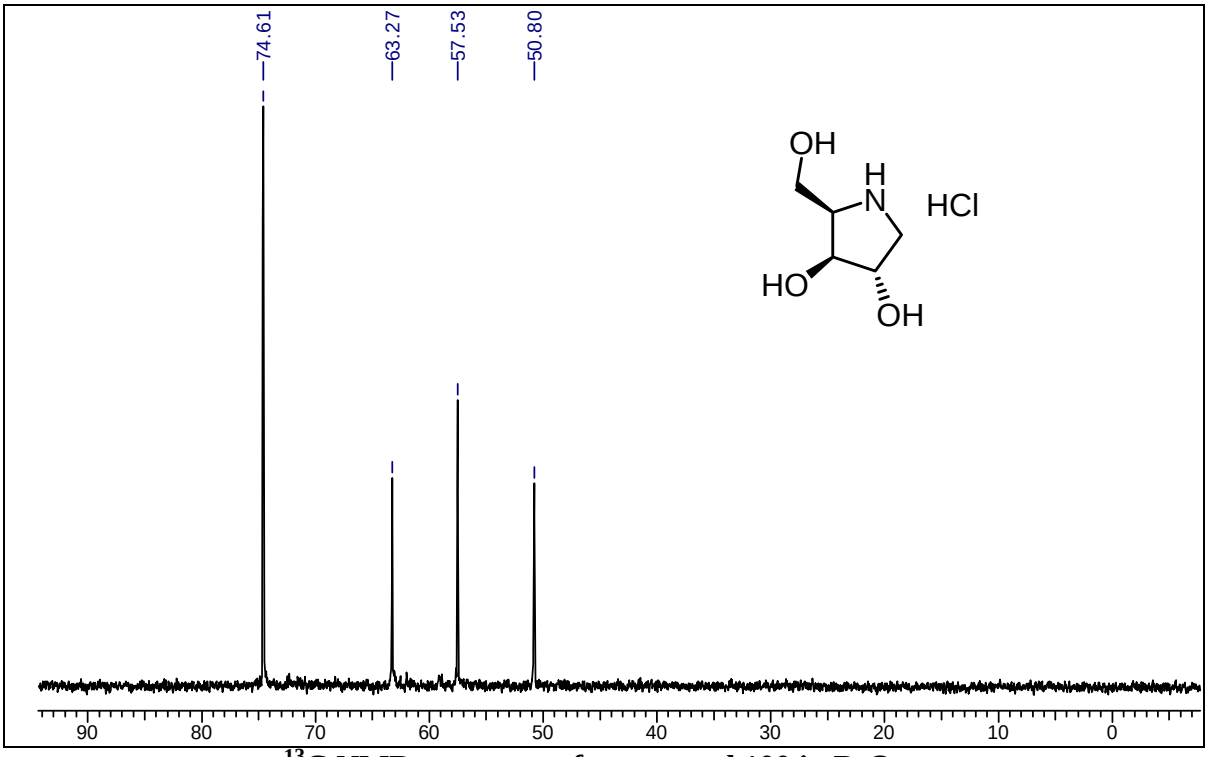
^{1}H NMR spectrum of compound 99 in D_2O



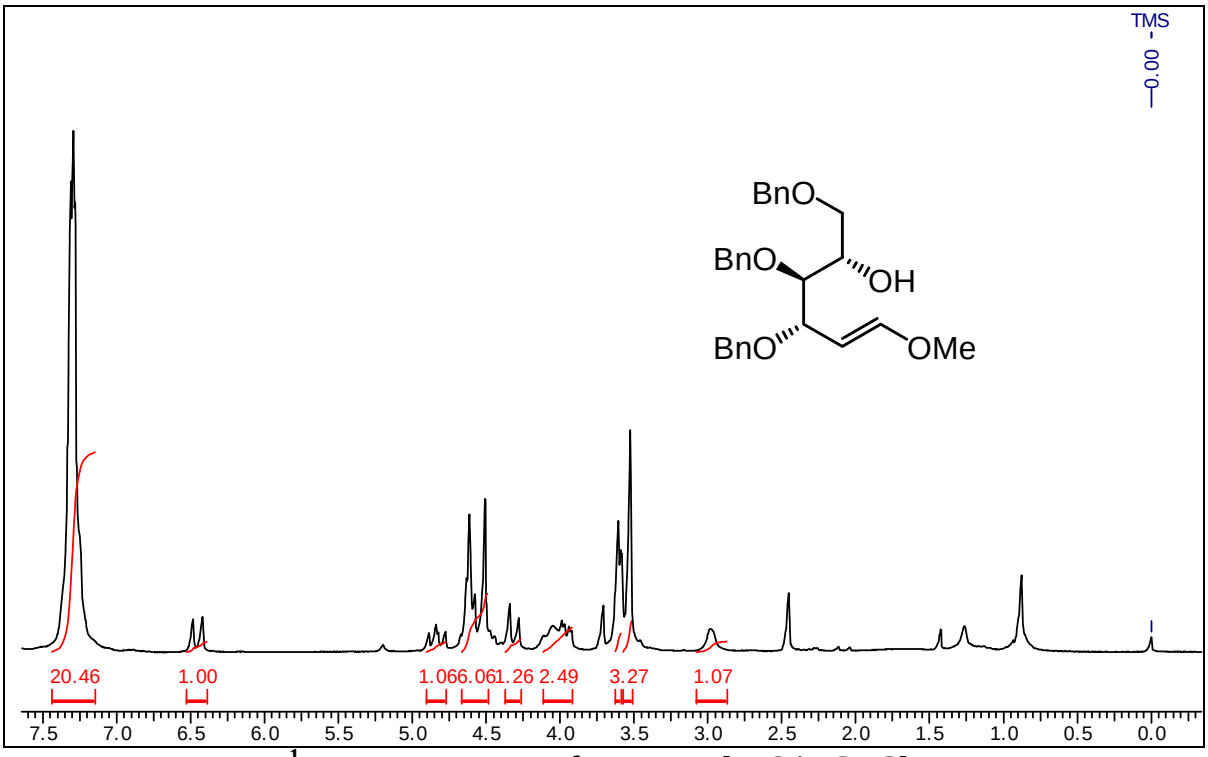
^{13}C NMR spectrum of compound 99 in D_2O



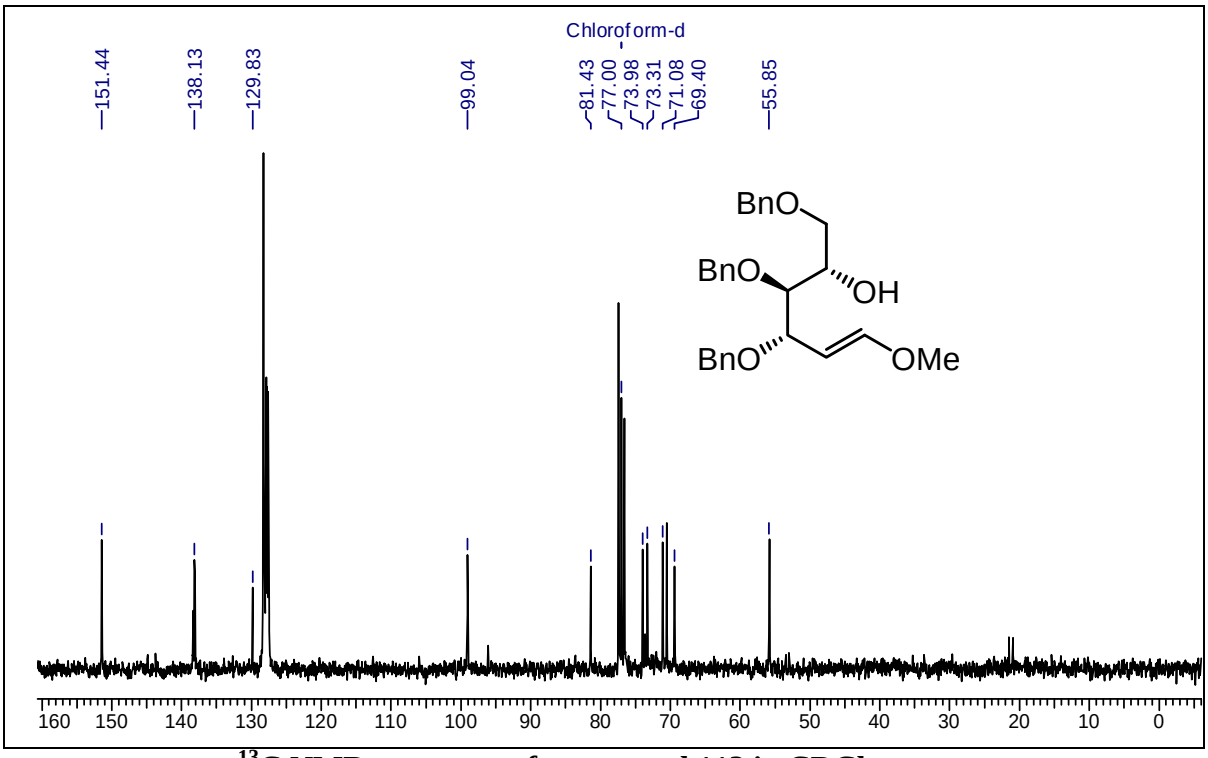
^{1}H NMR spectrum of compound 100 in D_2O



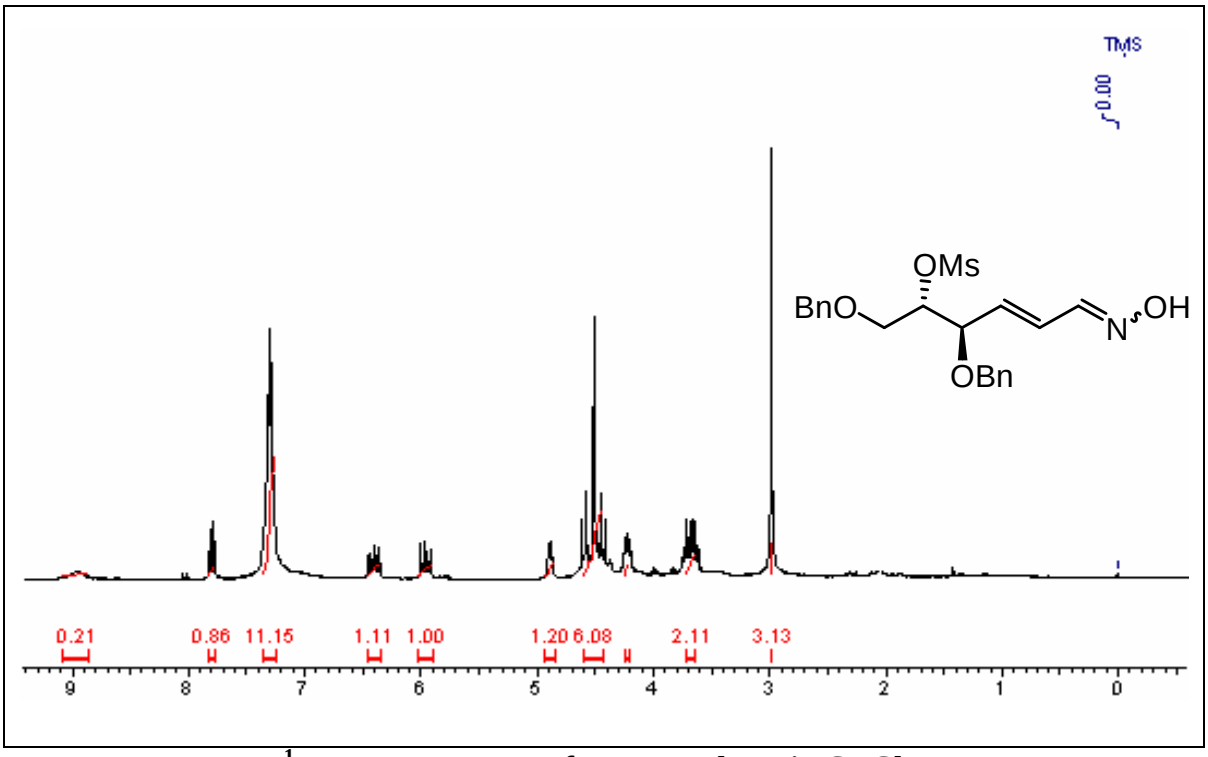
^{13}C NMR spectrum of compound 100 in D_2O



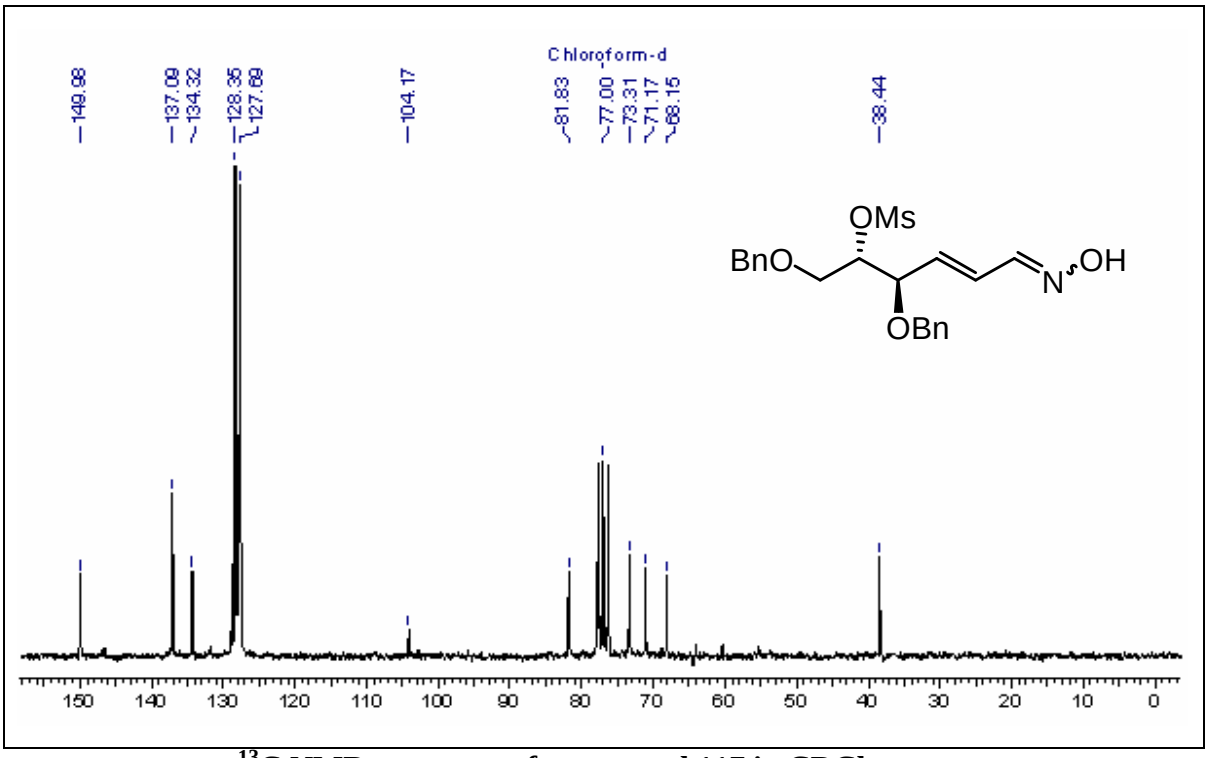
^{1}H NMR spectrum of compound 112 in $CDCl_3$



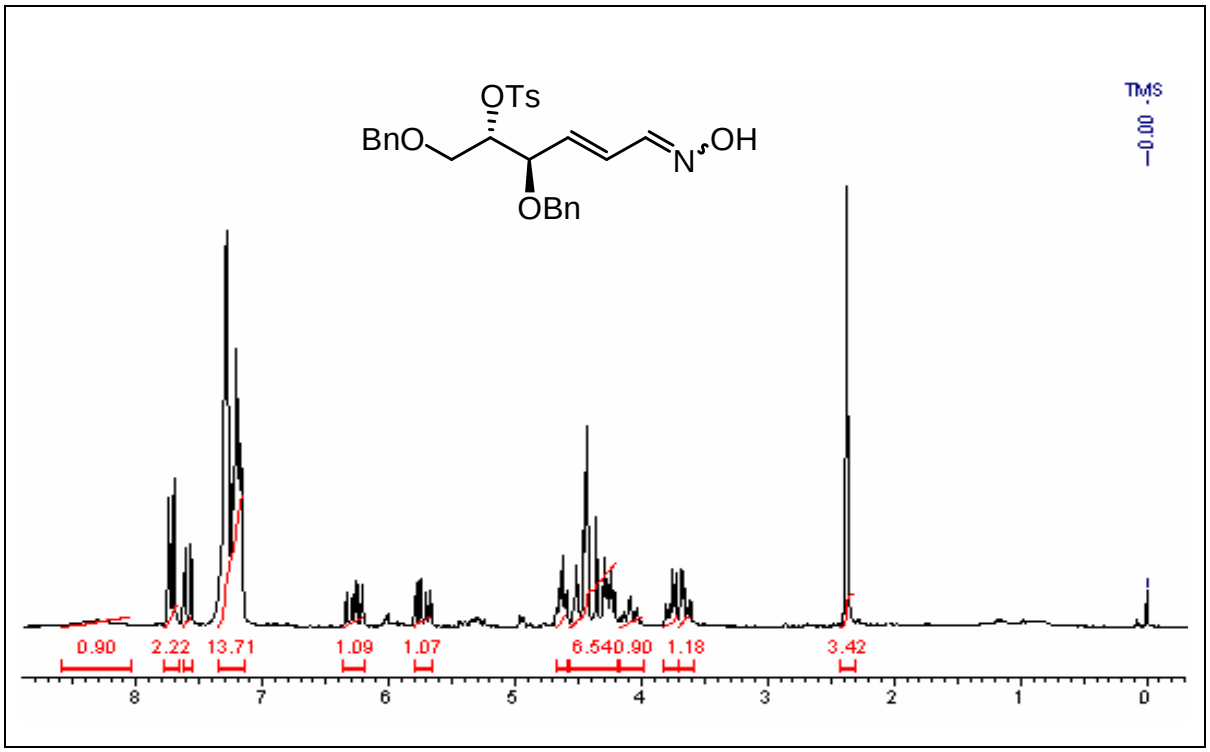
^{13}C NMR spectrum of compound 112 in $CDCl_3$



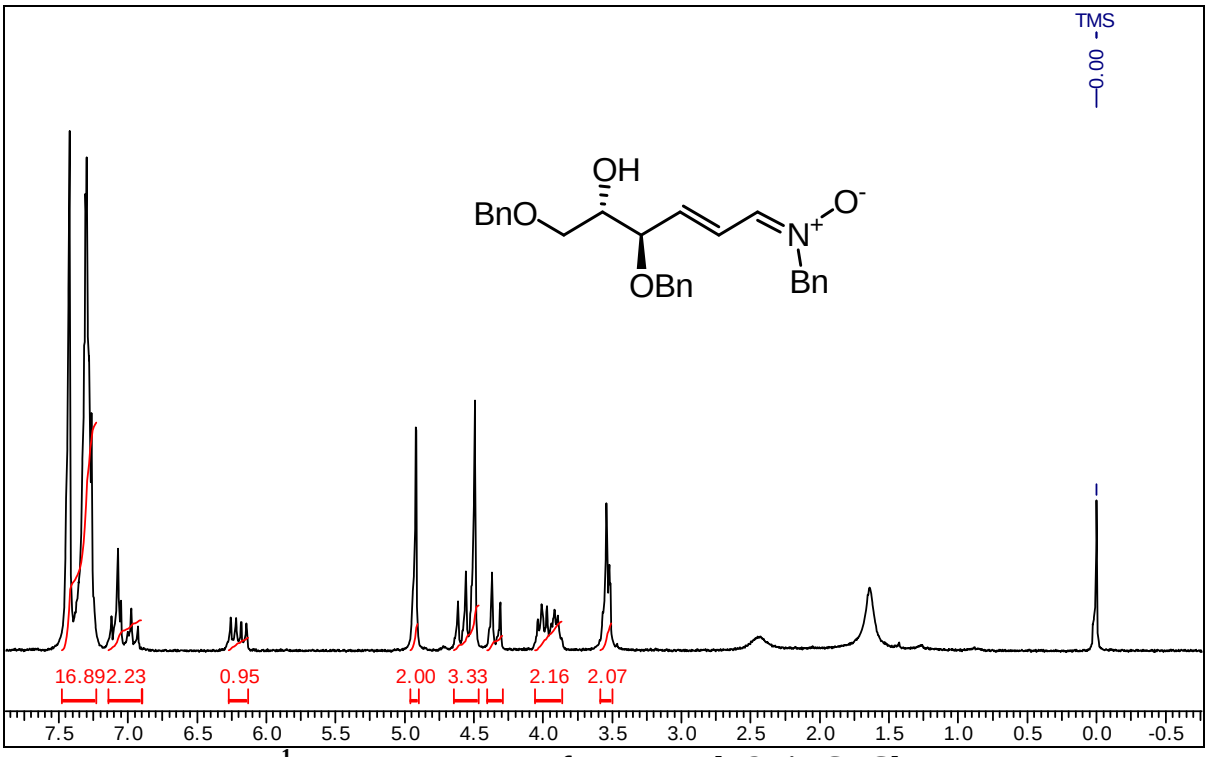
^{1}H NMR spectrum of compound 117 in $CDCl_3$



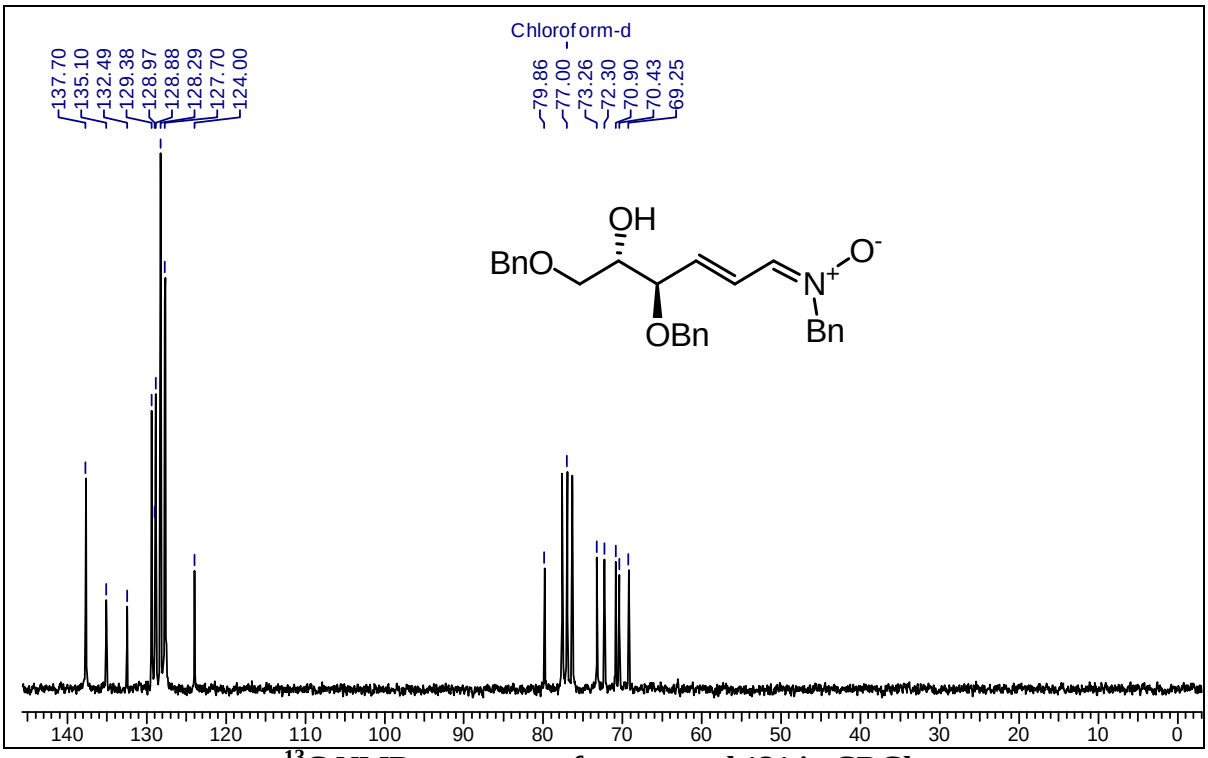
^{13}C NMR spectrum of compound 117 in $CDCl_3$



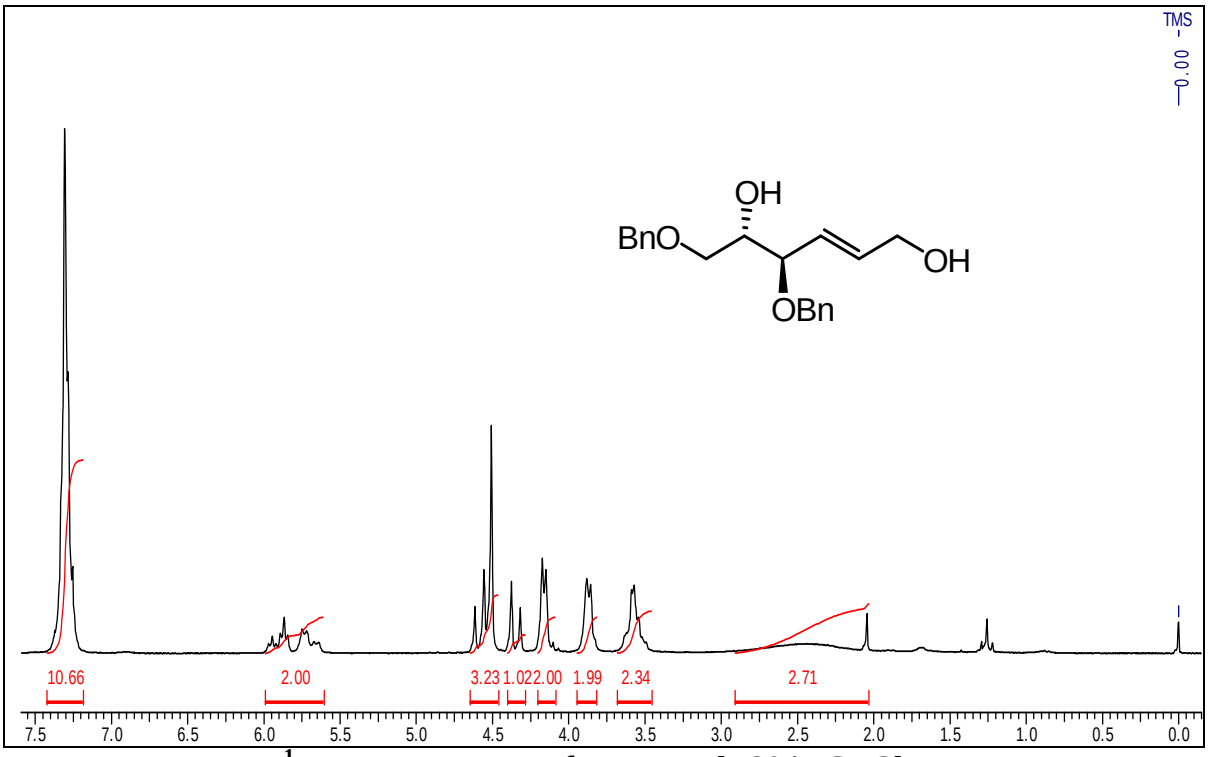
^{1}H NMR spectrum of compound 118 in $CDCl_3$



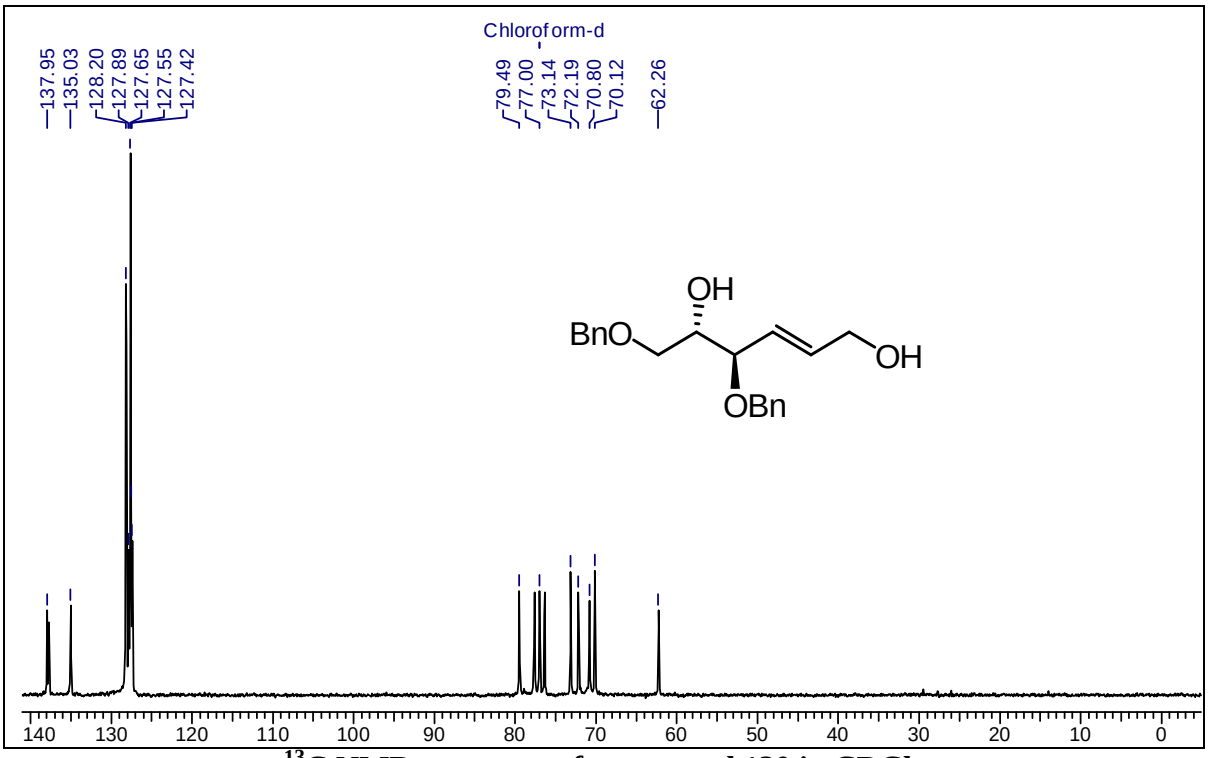
^{1}H NMR spectrum of compound 121 in $CDCl_3$



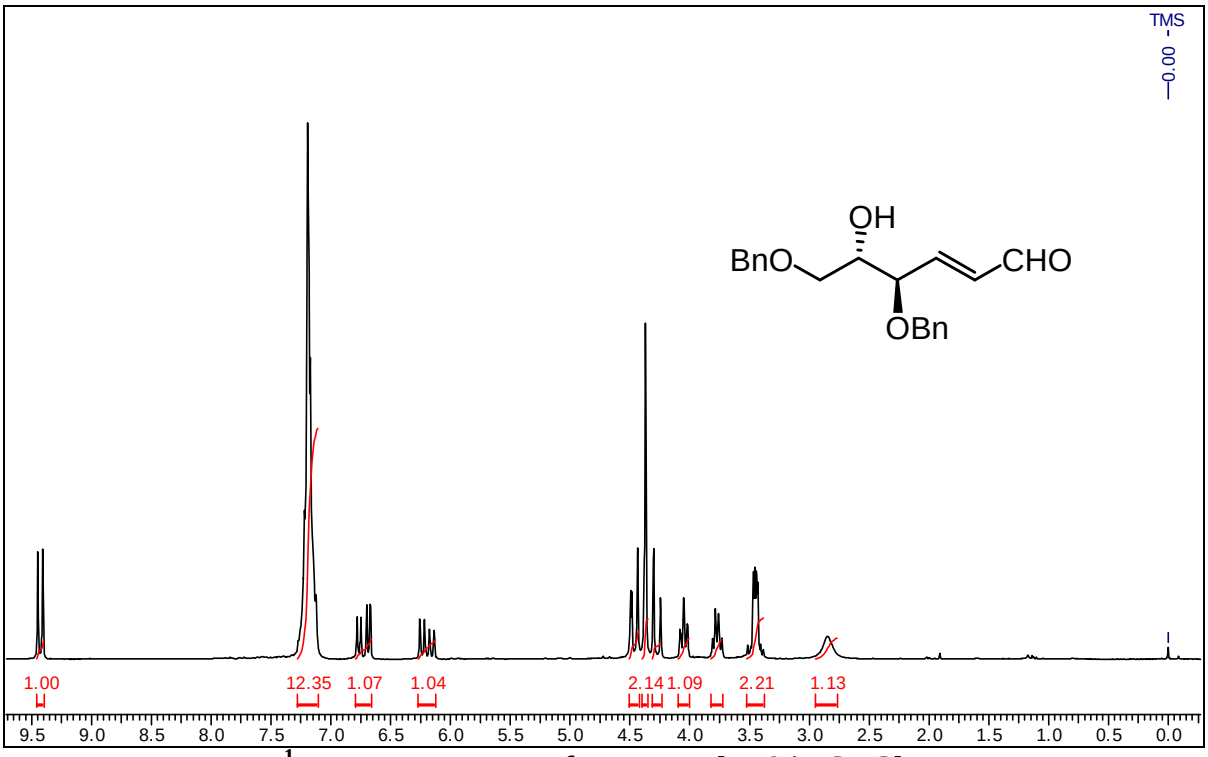
^{13}C NMR spectrum of compound 121 in $CDCl_3$



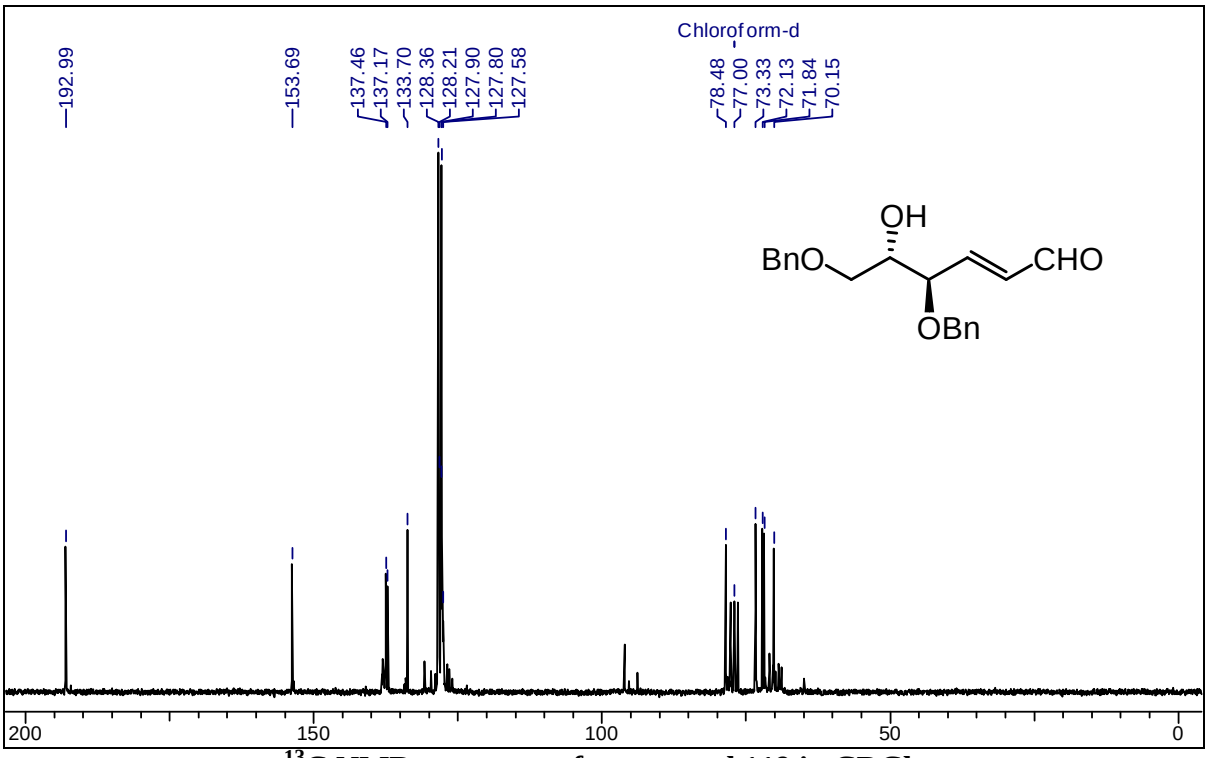
^{1}H NMR spectrum of compound 120 in $CDCl_3$



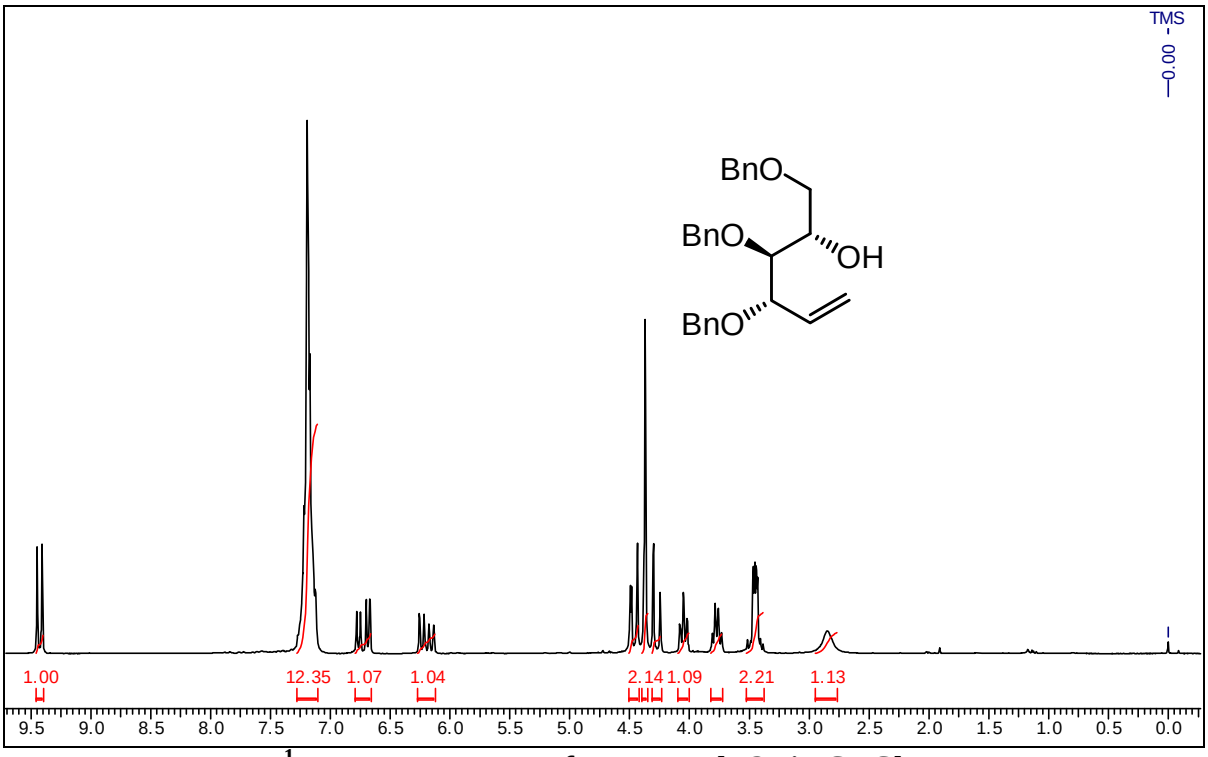
^{13}C NMR spectrum of compound 120 in $CDCl_3$



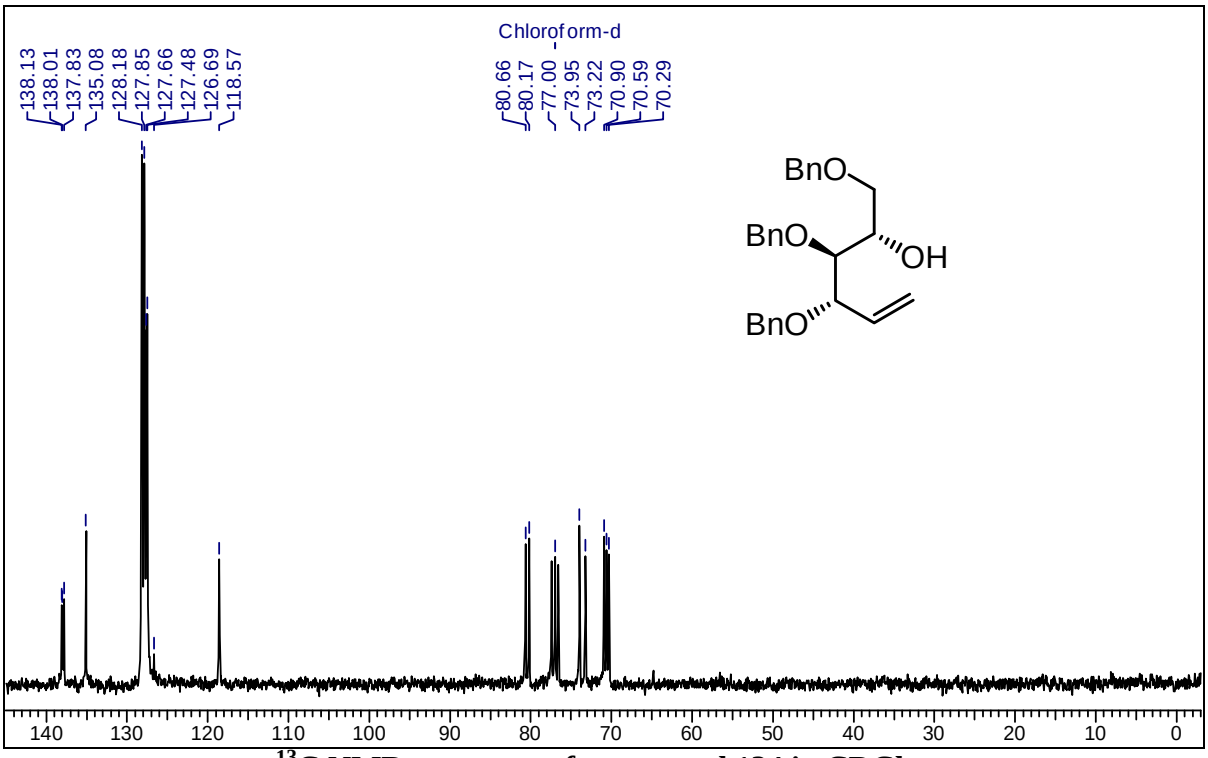
^{1}H NMR spectrum of compound 119 in $CDCl_3$



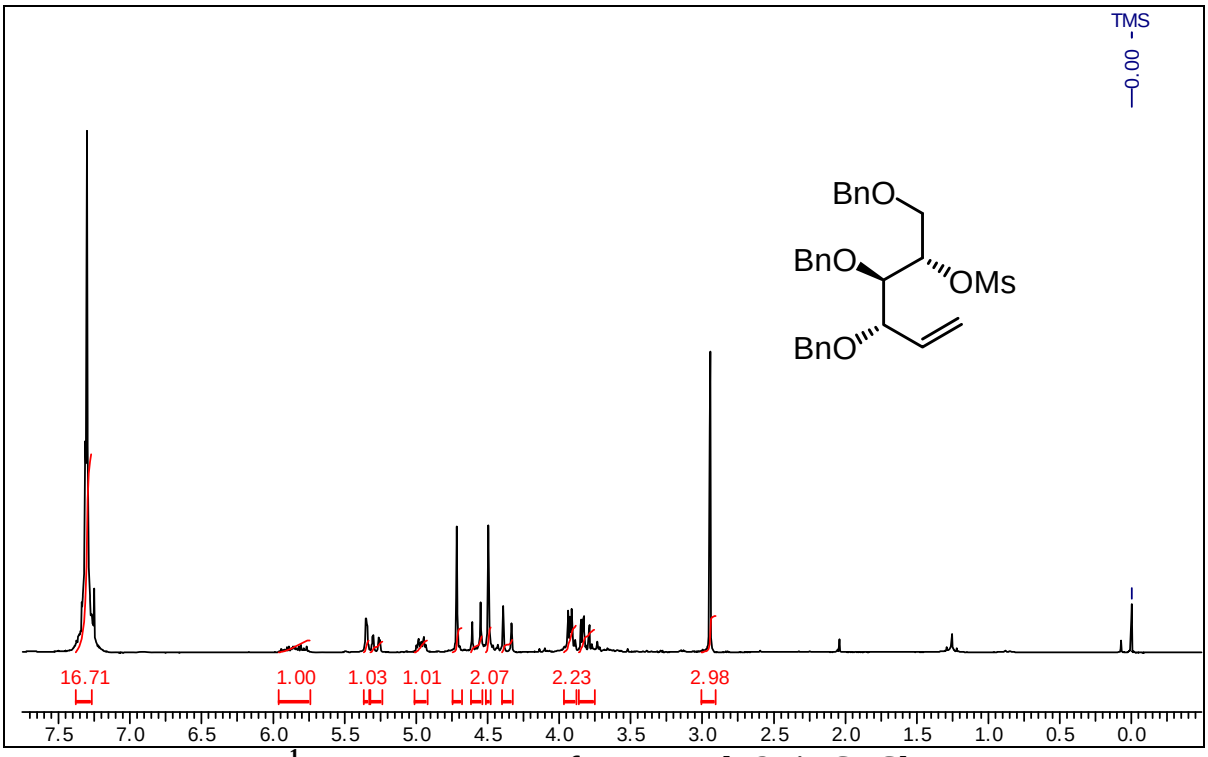
^{13}C NMR spectrum of compound 119 in $CDCl_3$



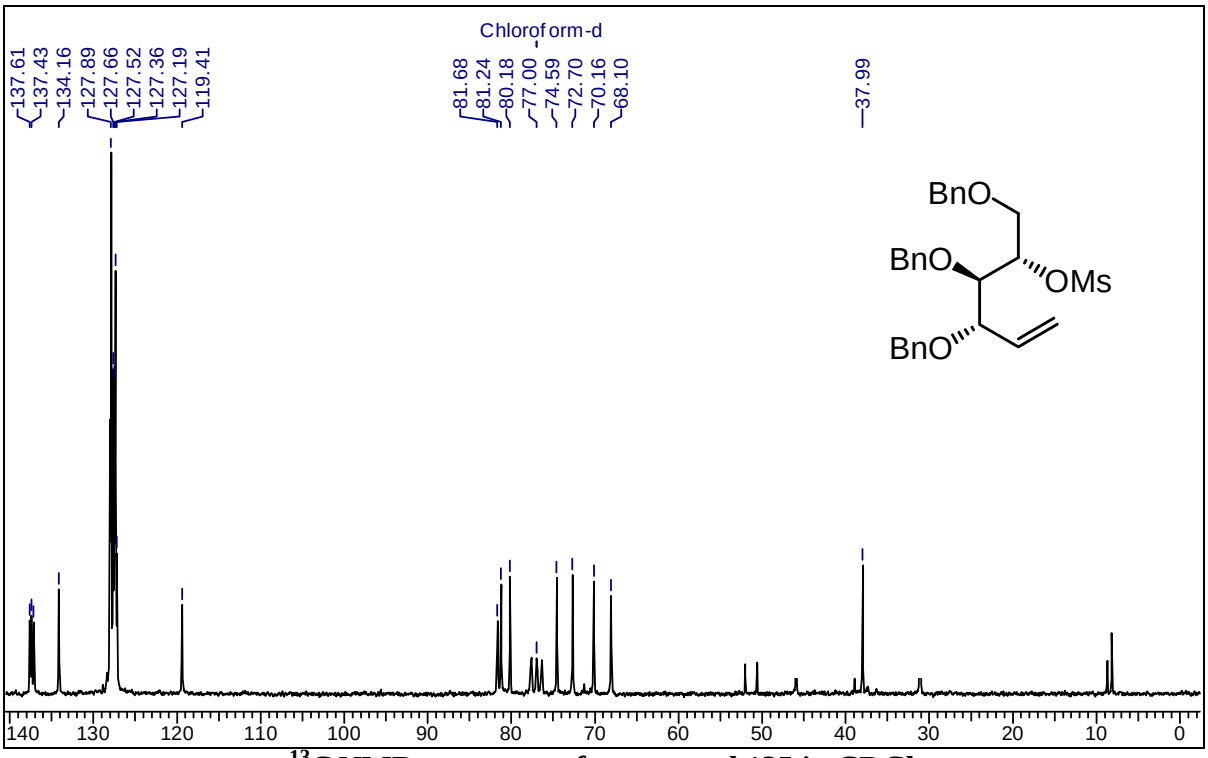
^{1}H NMR spectrum of compound 124 in $CDCl_3$



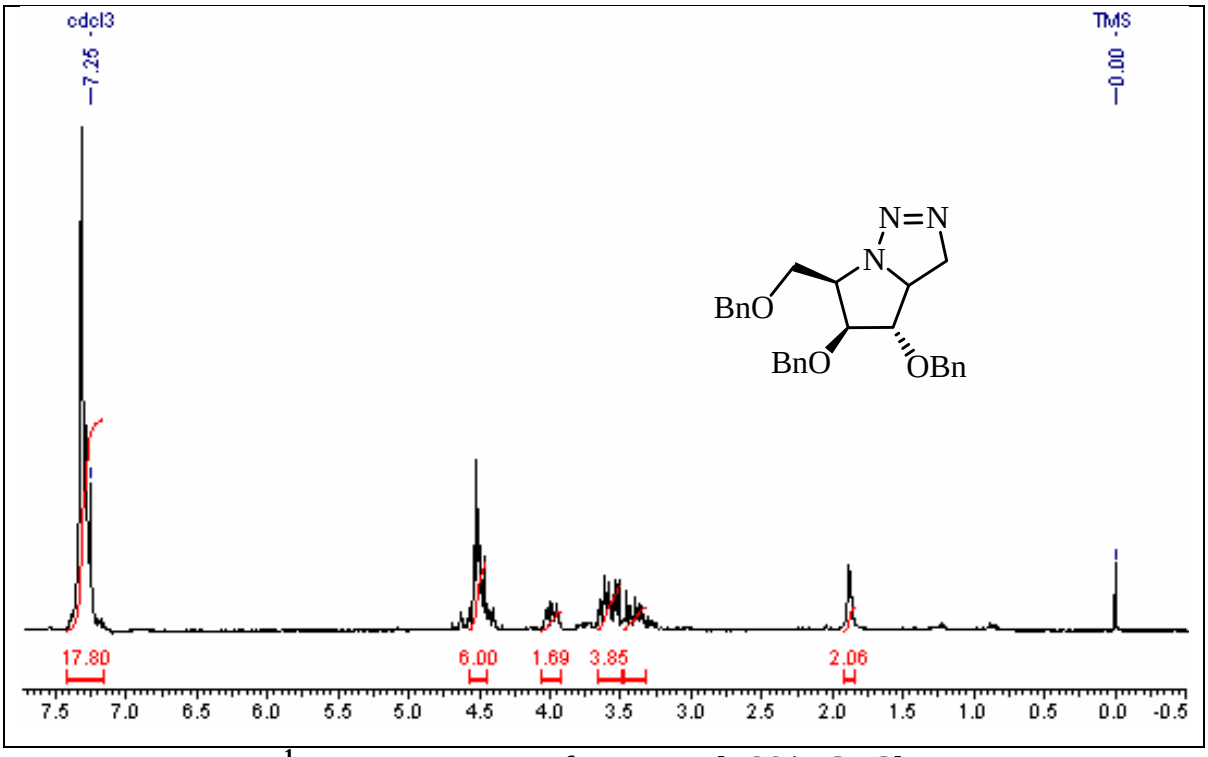
^{13}C NMR spectrum of compound 124 in $CDCl_3$



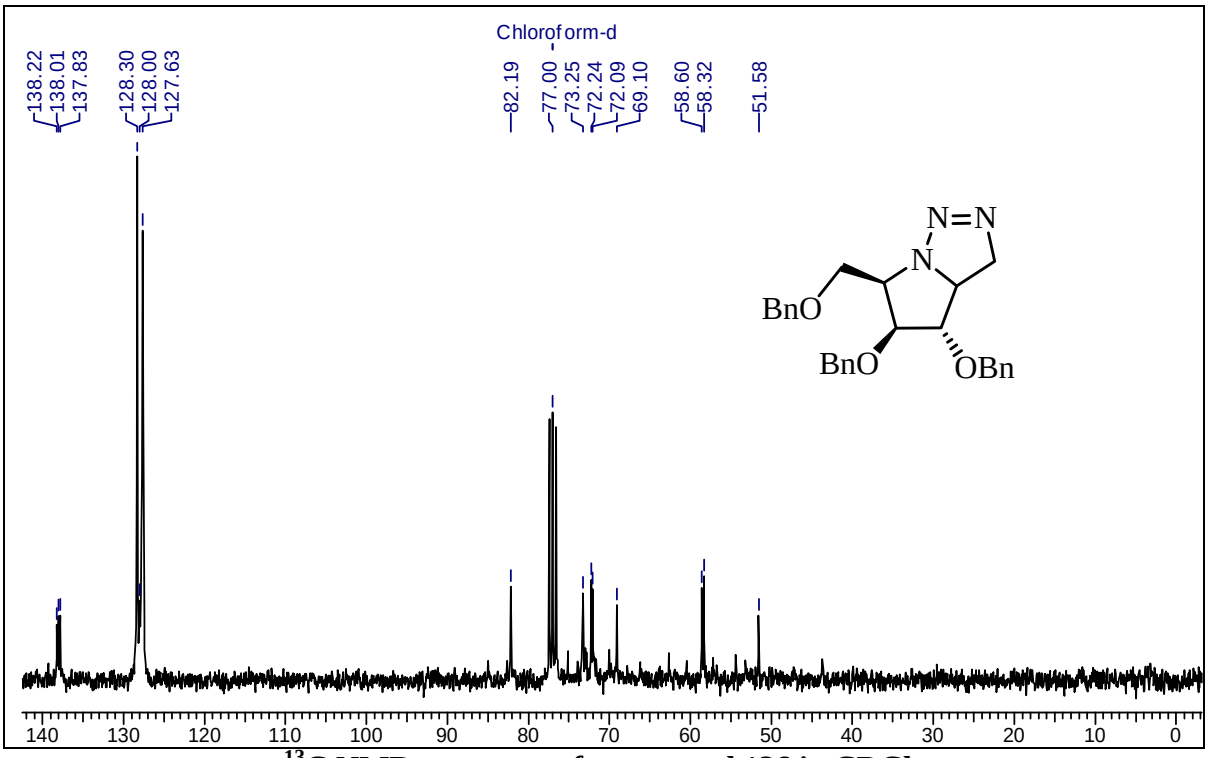
^{1}H NMR spectrum of compound 125 in $CDCl_3$



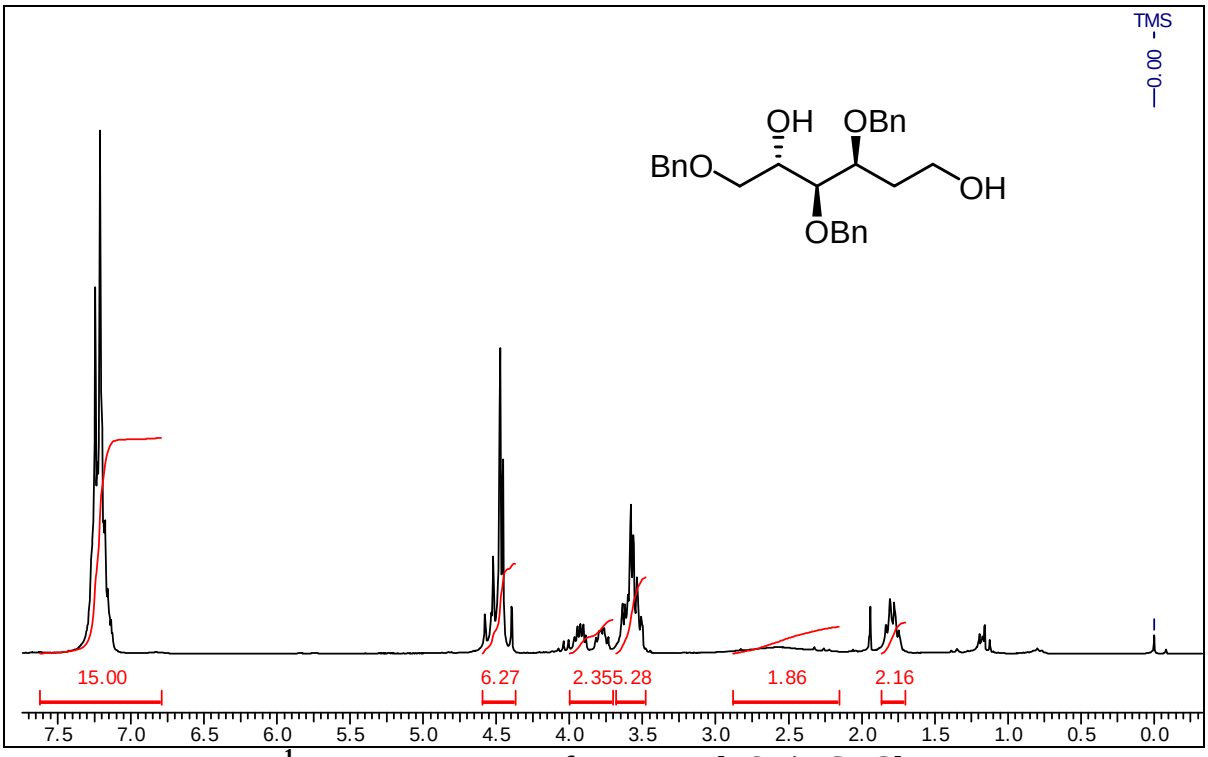
^{13}C NMR spectrum of compound 125 in $CDCl_3$



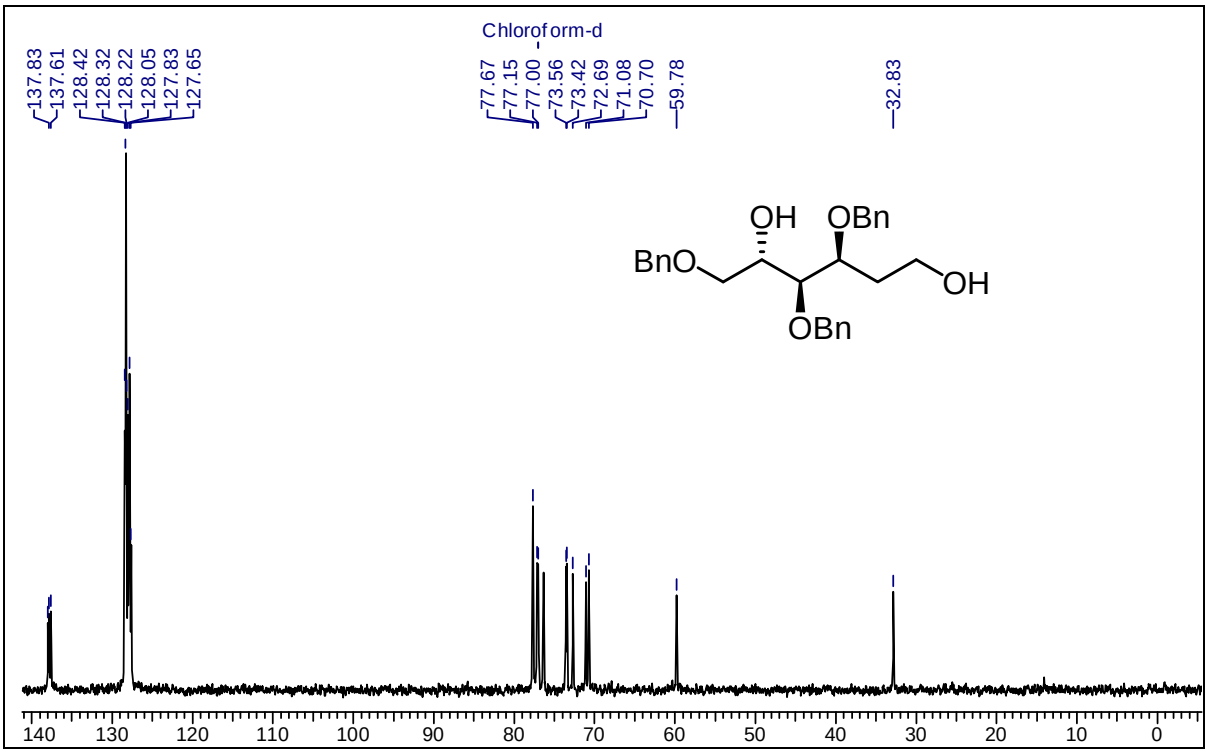
^{1}H NMR spectrum of compound 126 in $CDCl_3$



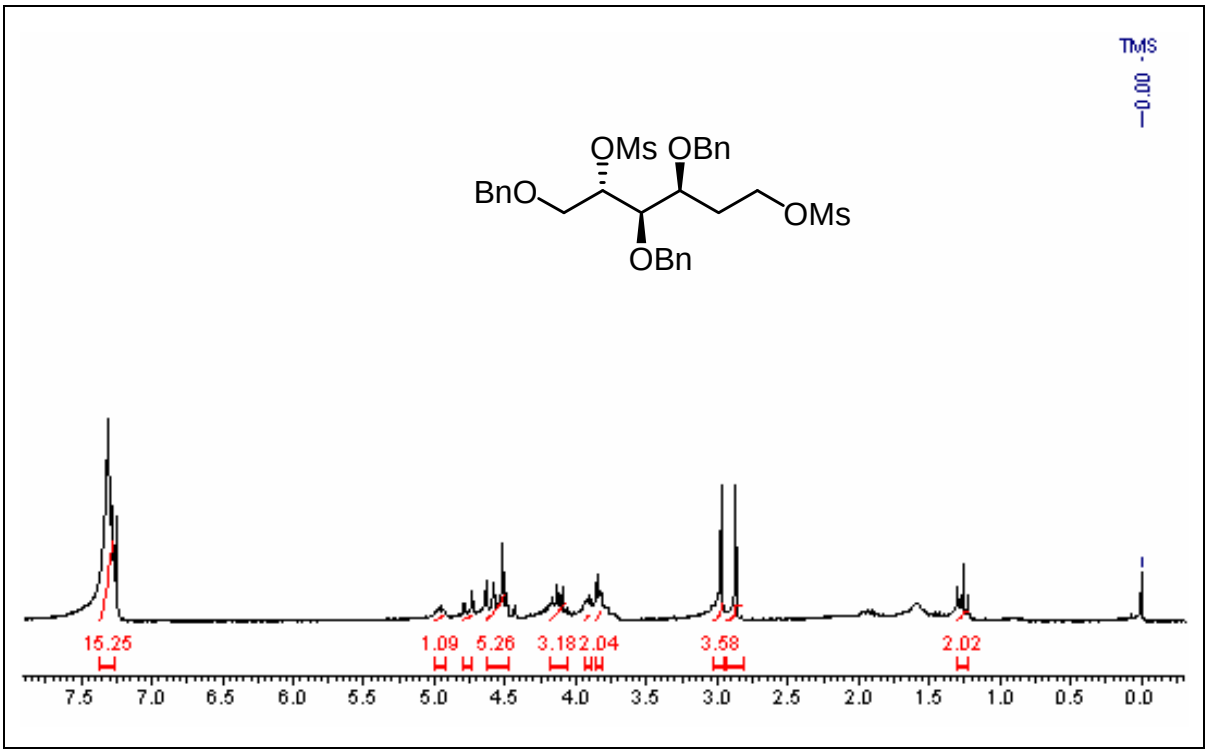
^{13}C NMR spectrum of compound 126 in $CDCl_3$



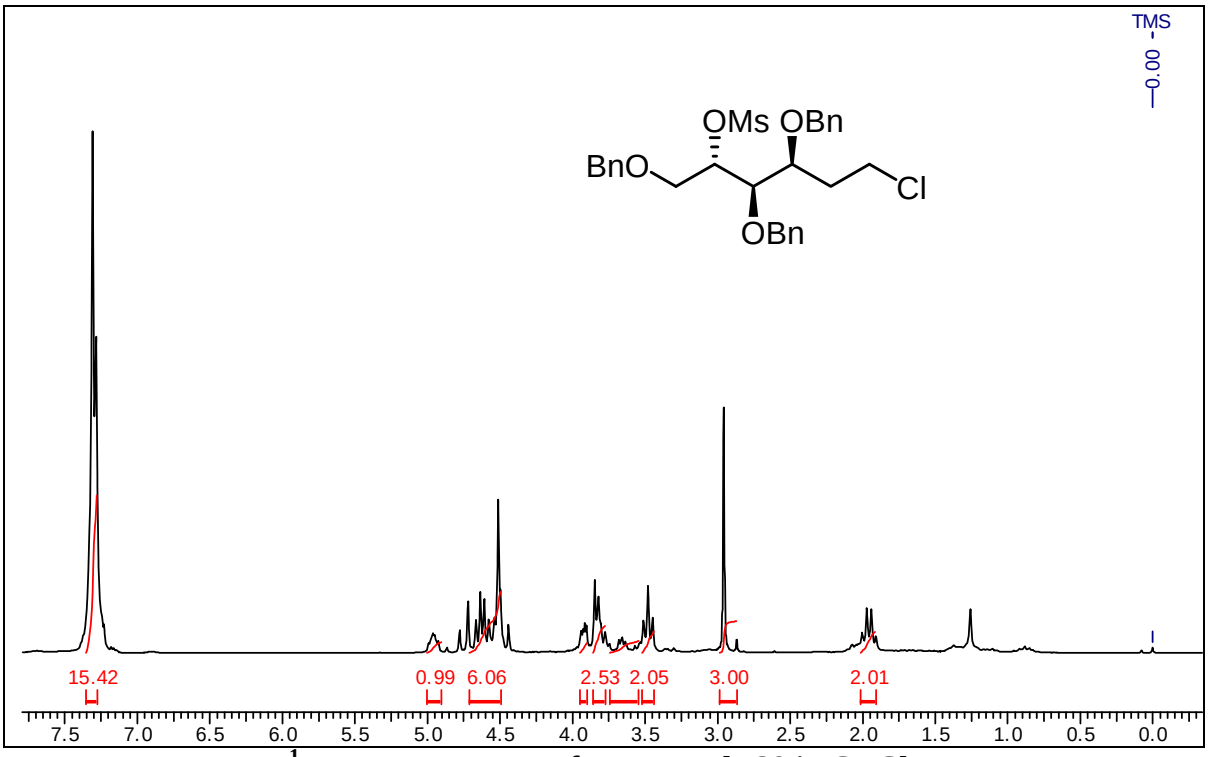
^{1}H NMR spectrum of compound 127 in $CDCl_3$



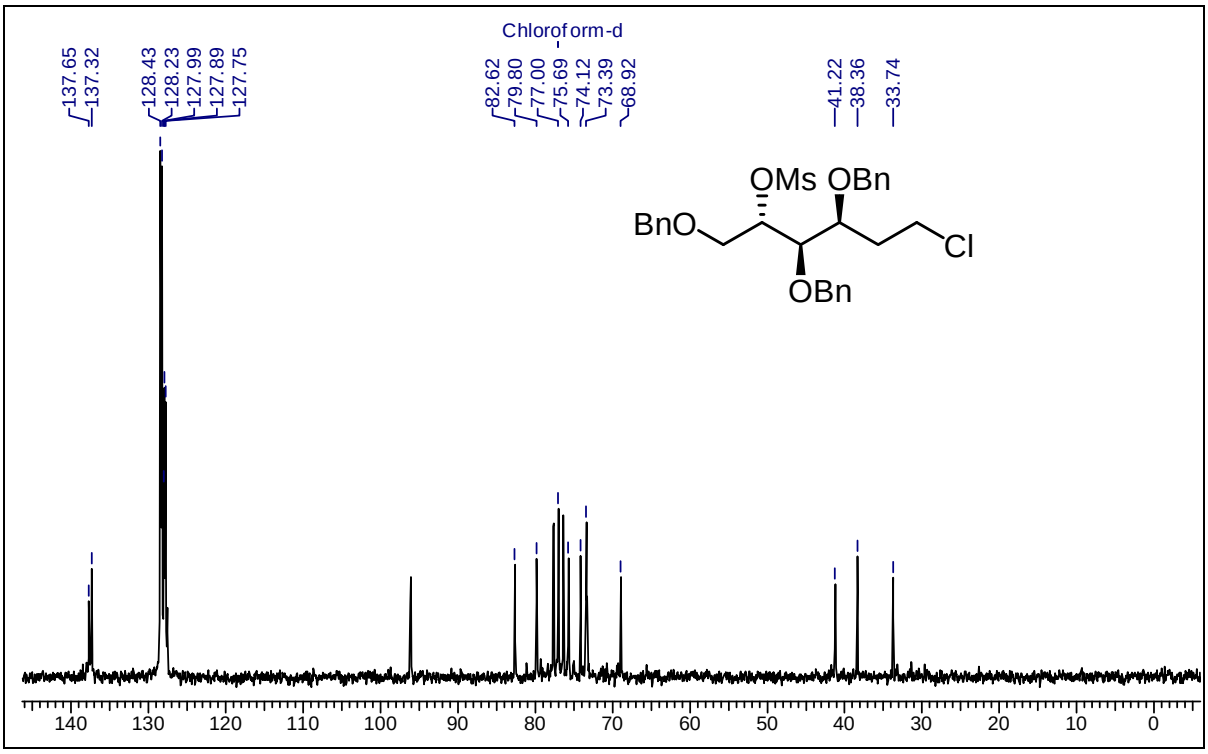
^{13}C NMR spectrum of compound 127 in $CDCl_3$



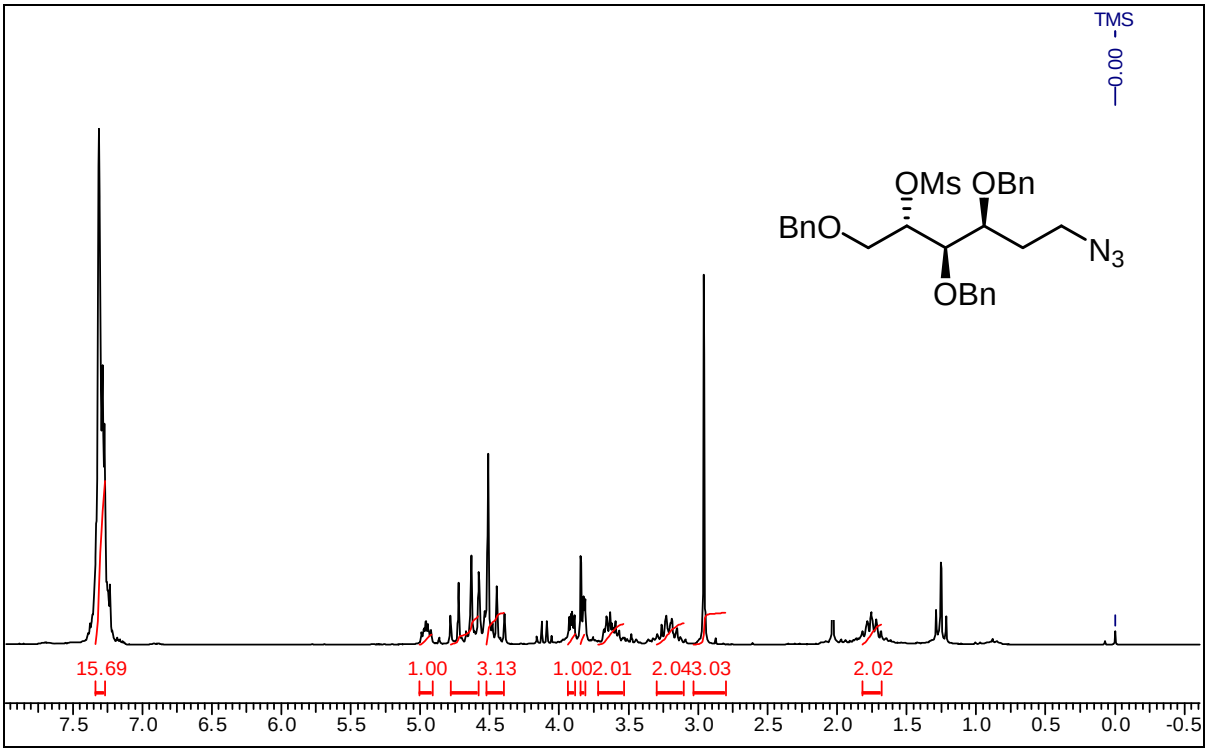
^{1}H NMR spectrum of compound 128 in $CDCl_3$



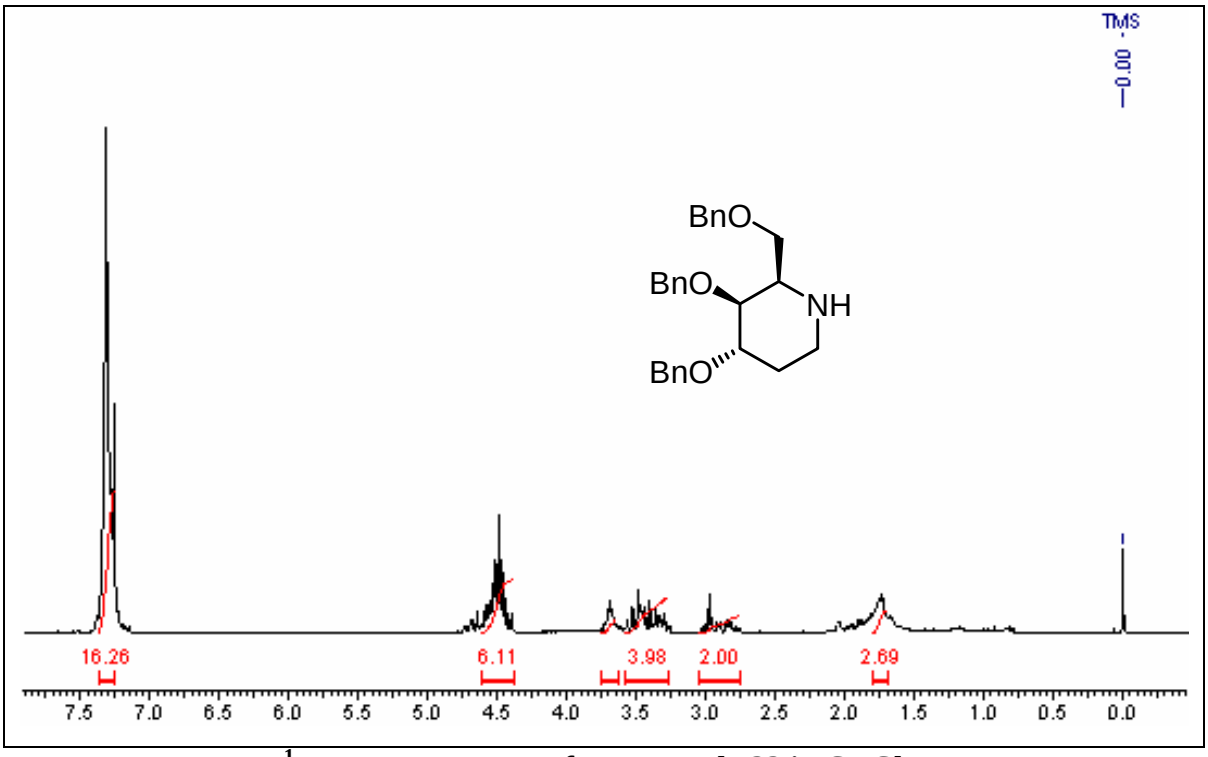
^{1}H NMR spectrum of compound 129 in $CDCl_3$



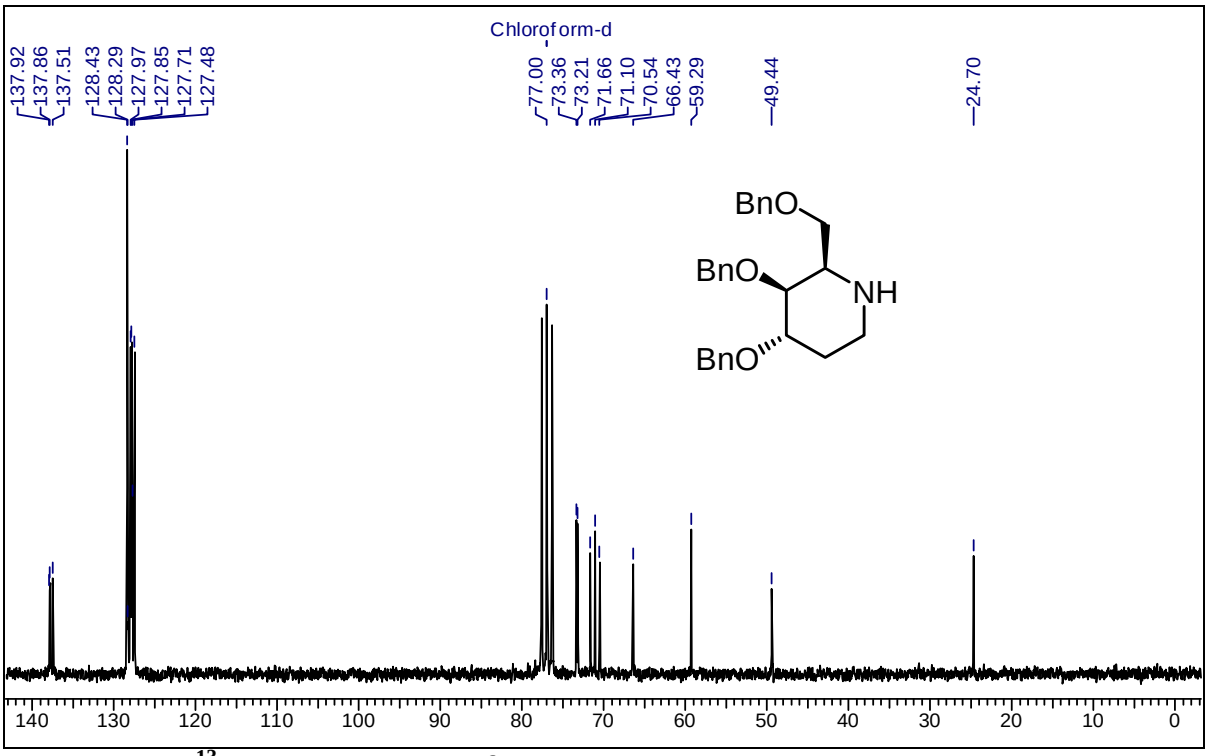
^{13}C NMR spectrum of compound 129 in $CDCl_3$



^{1}H NMR spectrum of compound 130 in $CDCl_3$



^{1}H NMR spectrum of compound 122 in $CDCl_3$



^{13}C NMR spectrum of compound 122 in $CDCl_3$

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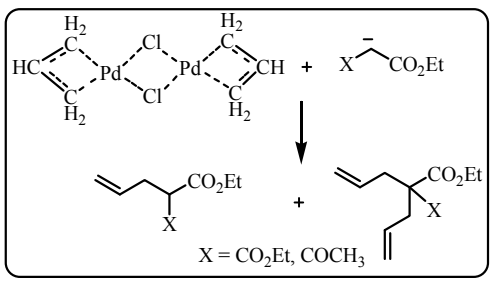
CHAPTER II

Pd MEDIATED CROSS-COUPLING REACTIONS ON SUGAR ALKYNES

INTRODUCTION

Construction of architecturally complex molecules from simple building blocks has emerged as a powerful tool in synthetic organic chemistry because of the increasing demand for molecules with unprecedented diversity. Designing effective routes to construct complex cyclic structures through organotransition-metal catalyzed reactions provides many attractive possibilities, which by conventional procedures would need a large number of synthetic transformations. The formation of carbon-carbon and carbon-heteroatom bonds are extremely important for the synthesis of biologically active natural products.[1] The use of transition metals, especially Pd, for the formation of C-C and C-heteroatom bonds have been extensively documented as demonstrated by numerous reviews and books.[2-6] The great interest in palladium catalysis stems from the fact that they often provide greater chemo, regio, and enantioselectivity and relatively inexpensive in comparison to the traditional organic synthetic routes. Moreover the ability of palladium to tolerate a wide range of functional groups including carbonyl, hydroxyl, amide, and ester makes the Palladium as one of the most versatile reagent available to organic chemists. The synthesis of "Acetic Acid" is the first known compound synthesized by C-C bond formation reaction by Kolbe in 1845 and the Wurtz reaction (1855) is the oldest reaction for C-C bond formation. The C-C bond formation reaction is now became the greatest tool for synthetic chemist. The metal catalyzed C-C bond formation reaction particularly attracted much attention including the palladium catalyzed cross coupling reactions. Pd catalyzed reactions were studied and explored in the last 40 years. One of the earliest cross coupling reactions using Pd was reported in 1965 by Tsuji and co-workers[7] for the synthesis of C-C bond formation on allylic system and using ethyl malonate/acetoacetate as shown below:



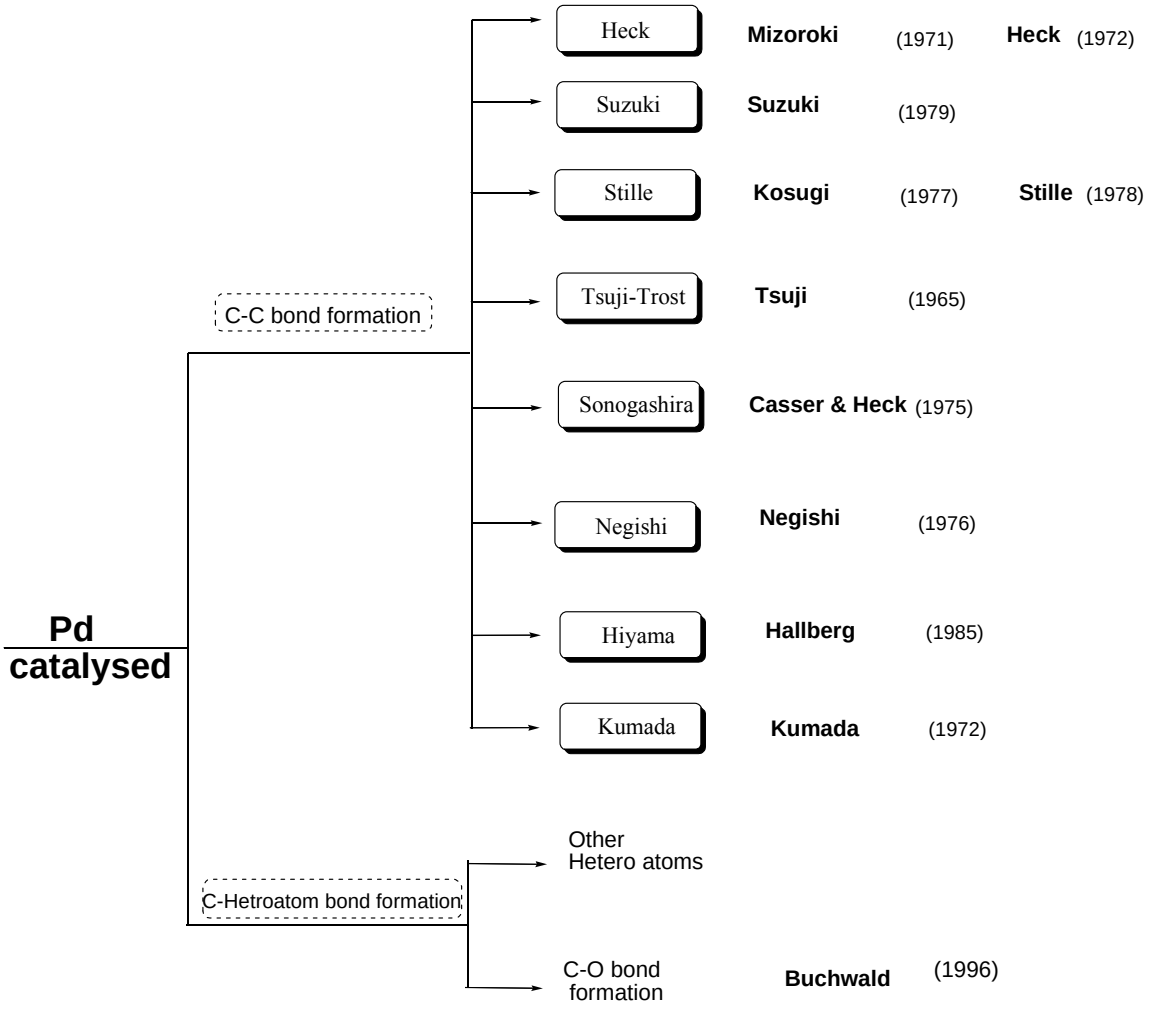
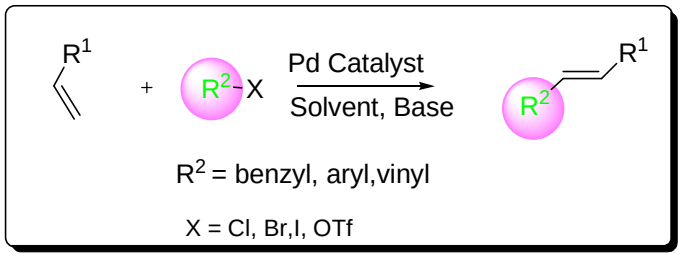


***Figure* 1:** *Pd catalyzed C-C & C-heteroatom bond formation reaction*

Palladium is the soft metal and hence according to HSAB (Hard Soft Acid Base) theory it reacts preferably with soft bases like aryls, alkenes and alkynes. Herein, we are going to discuss only the most useful C-C and C-O bond formation reactions, for the mechanistic point of view with emphasis on more explored C-C bond formation reactions like Heck[1, 8], Suzuki[9], Stille,[10,11] Tsuji-Trost[12], Sonogashira[13, 14] Negeshi,[15] Hiyama,[16] Kumada[17] and C-O bond formation reaction.[18]

Heck coupling:

The Heck reaction is the carbon-carbon bond forming reaction, which couples the two sp^2-hybridised species by using Palladium catalyst.



Mizoroki and co-workers[19] showed that Pd metal can assist the coupling of olefin with aryl halides in 1971 and latter the scope of this reaction was increased when Heck improved the generality of this reaction. The inter- and intramolecular versions of the Heck reaction have been widely applied for the total synthesis of myriad of bioactive organic compounds. By applying Heck reaction it is possible to form polyene, to couple fragments and to form cyclic frameworks. The numerous reviews[20] covering the utility of the Heck reaction attest to it being one of the most widely utilized methodologies for the formation of C-C bonds. In view of large number of excellent reviews we want to discuss the mechanistic pathway, which impart the regio- and enantio control necessary for Heck reaction. The regioselectivity of the Heck reaction depends upon the following major factors;

- The regioselectivity in case of unsymmetrical alkenes depends on the electronic and steric environment.
- In case of availability of both the β and β′ hydrogen, there is possibility of competition for the hydrogen elimination.

Substrates

A traditional Heck reaction requires one electrophilic partner and one nucleophilic partner. Aryl/benzyl/vinyl halides as well as aryl/benzyl/vinyl triflates can acts as the electrophilic partner and alkenes as the nucleophilic partner. However, the rate of reaction is high for olefins containing electron-withdrawing groups.

The most widely used halide partners (electrophilic) for the coupling reactions are aryl halides. Reactivity of aryl halides toward the coupling reaction depends on the bond dissociation energy of the C-X bond. In the Halogen family of the periodic table, the bond dissociation energy decreases from top to bottom and hence the reactivity order of these aryl halides increases in the same order accordingly (Figure 2).

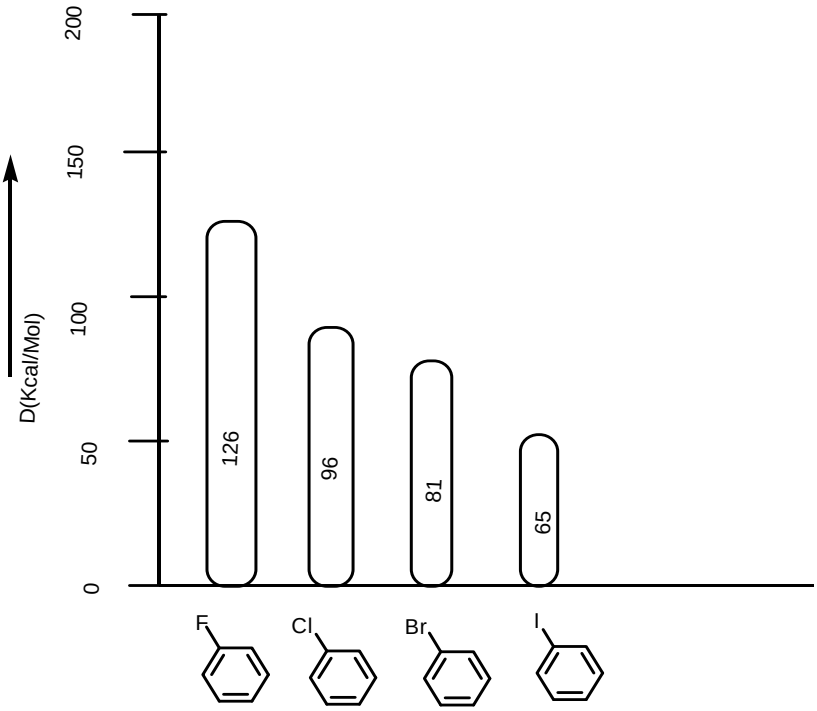


***Figure* 2: The bond dissociation energy for C-X bond**

Reaction temperature

Reaction temperature ranges from 50-160 ^{0}C can be used which generally depends on the organic halide to be activated and the stability limit of the catalyst.

Catalytic system

Various catalytic systems have been developed for Pd catalyzed Heck reactions including homogenous as well as heterogeneous catalysts, ligands as well as ligand free system, stable colloids, nanoparticles and polymer supported catalyst. For the Heck reactions catalyzed by Pd the turnover number (TON) is good. The TON is a value calculated by the ratio of the amount of product formed and the amount of catalyst present in the reaction and is used to evaluate the efficiency of the catalyst in a given reaction. The number of ligands are being developed in order to enhance the reactivity of the catalytic system and to increase the TON. Nitrogen and phosphorous compounds are commonly used ligands in transition metal chemistry. Palladium complexes with various phosphines as ligands have been most commonly used as catalysts for the Mizoroki-Heck

reaction. The ligand free catalytic system have been also reported including an automated reactor performing ligand-free Heck reactions in continuous flow mode utilizing a monolithic reactor cartridge with Pd(0) nanoparticles. A ligand free Heck reaction proceeds in the presence of an ionic liquid.

Solvents

Polar solvents (DMF, DMSO, DMA and acetonitrile) are often used. Aqueous methanol also has been successfully used.

Bases and additives

Generally bases like Et_3N, K_2CO_3, $NaHCO_3$, KOAc and NaOAc are most common.

Mechanism

The first step for the catalytic cycle in Heck reaction involves the oxidative addition of Pd(0).The adduct formed due to the insertion of Pd is then coordinates with an unsaturated substrate in the second step. In the next step, reductive elimination releases the product along with palladium-hydride complex that can be converted to the starting Pd(0) with the help of suitable base (Figure 3).

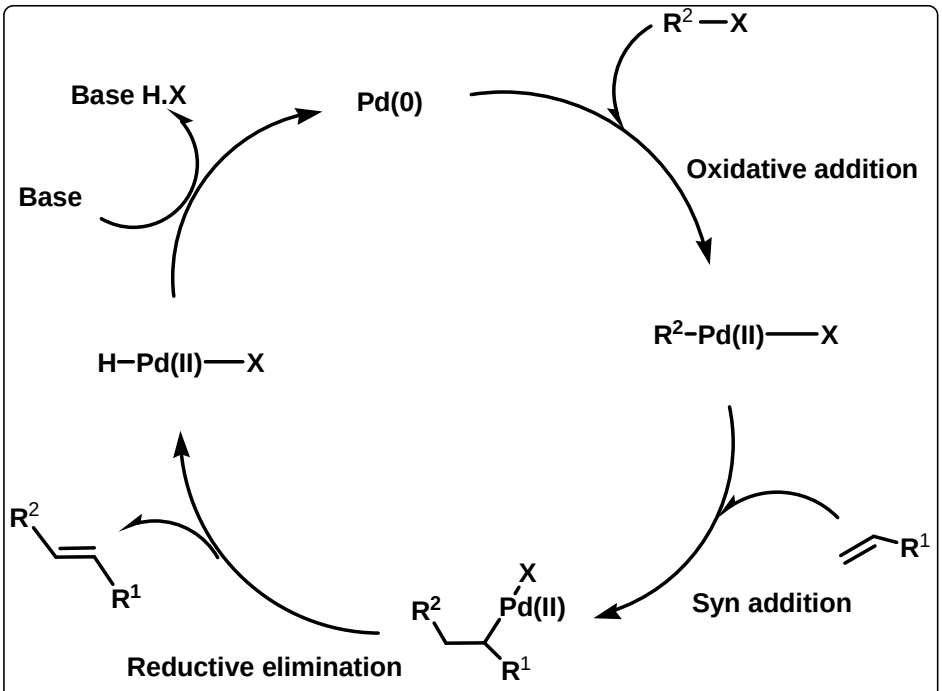


***Figure* 3:** *The mechanism for the Heck cross-coupling reaction (Ligands are not shown)*

In case of unsymmetrical substrate, the addition of the alkyl group can either take place at α or the β position. The syn addition of the aryl complex to such an unsymmetrical olefin prefers the aryl group addition to the less hindered β position due to the steric reseason. However, this pathway requires the dissociation of one of the ligands coordinated to the Pd as shown in Figure 4.

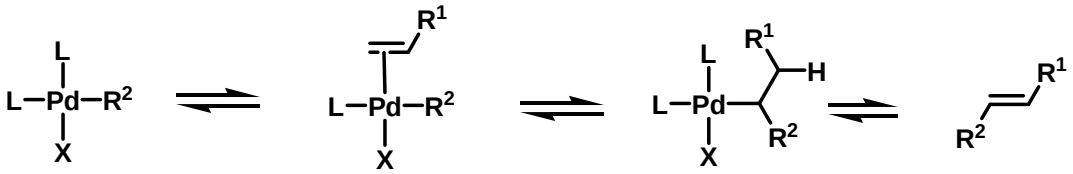


***Figure* 4:** *Neutral pathway*

The neutral pathway is favored when X = I, Br or Cl. By contrast when X = OTf, the weakly coordinating anion will dissociate readily instead of ligand, L. As a result a positive charge generate on the Pd atom placing a negative charge on the R^1 group simultaneously. Accordingly insertion occurs with R^2 group adding to the more substituted carbon.

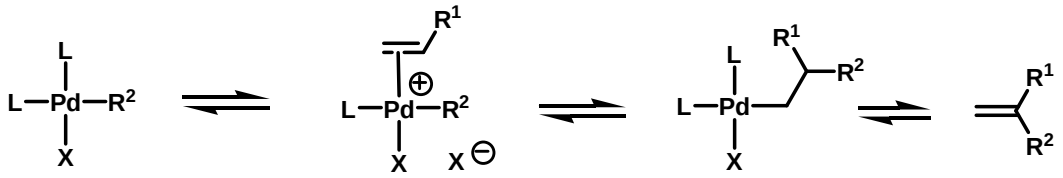


***Figure* 5:** *Cationic pathway*

The cationic pathway is shown in Figure 5. The electronic nature of the olefin determines the regioselectivity. The electron rich alkenes favor the neutral pathway while the electron poor alkenes prefer the cationic pathway. Furthermore, the cationic pathway is dominant when halide-sequestering agents such as Ag (I) salts are added. In contrast, the addition of exogenous halide ions will favors the neutral pathway. In case of the asymmetric version of the Heck reaction, the enantioselectivity depends on the pathway of the reaction. The cationic pathway gives the higher % ee than the neutral pathway.

Advantages and disadvantages

The advantages of Heck reaction are

a) Outstanding trans –selectivity;
b) High functional group tolerance;
c) Inexpensive and readily available olefins as precursors and
d) Inexpensive and readily available aryl bromides and aryl chlorides as substrates.

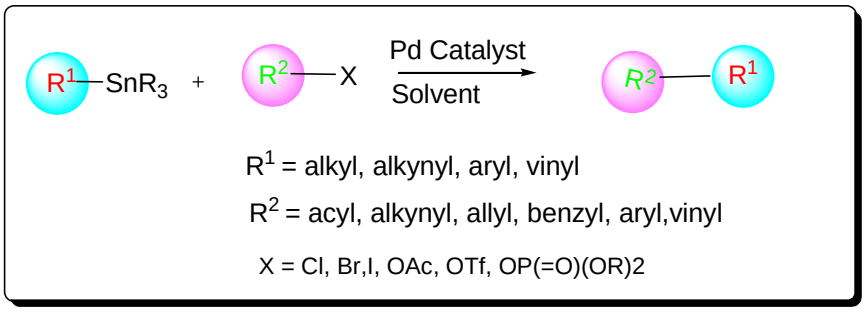
The disadvantages (drawbacks) includes

a) With common ligands low reactivity;
b) Difficulty in handling of the ligands;
c) Harmfulness of ligands;
d) Difficulty in removing the unwanted organic and inorganic impurities contaminated with the desired product;
e) High sensitivity of ligands to air and moisture and
f) Need for use of additives such as tetra butyl ammonium chloride (Bu_4NCl) and tetra butyl ammonium bromide (Bu_4NBr).

Stille coupling:

The Stille reaction emerged as one of the very important tool especially for the synthesis of five and six-membered rings. The utility of this process for the creation of variety of ring sizes and macrocycles was demonstrated[21] in the recent years. Eaborn and co-

workers reported the first use of a Pd based catalyst for the coupling of an aryl halide with an organotin reagent for the synthesis of diaryls in 1976[22].



Later in 1978, Stille widen the scope of reaction to include the synthesis of ketones from acid chlorides and organotin compounds.

Substrates

The electrophilic partners typically used for the Stille coupling reactions are aryl, benzyl, acetyl halides, allylic halides, aromatic halides and vinyl halides or pseudo-halides such as a triflate, while the nucleophilic partners are organostannens.

Catalytic system

The organometals like Pd, Ni along with variety of ligands, mostly the phosphorous ligands such as P(*t*-Bu)$_2$Me, PCy(pyrrodinyl)$_2$ etc. gives the best result .

Mechanism

The mechanism for the Stille coupling involves three steps as shown in Figure 6. As usual like other catalytic cycles, the first step is the oxidative addition of sp^2 hybridized halide compound to the Palladium catalyst to form the Pd(II) halide intermediate. The second step involves the transmetallation of the organotin reagent with the above Pd(II) complex to lead bis(alkyl)Pd(II) complex. Finally, the reductive elimination of the R^2-Pd-R^1 releases the coupled product and regenerates the Pd (0). The halide-leaving group attached to the vinylic or aromatic substrate impacts the rate of reaction. The oxidative addition to the Pd(0) catalyst depends upon the reactivity of the leaving group with I > OTf > Br.

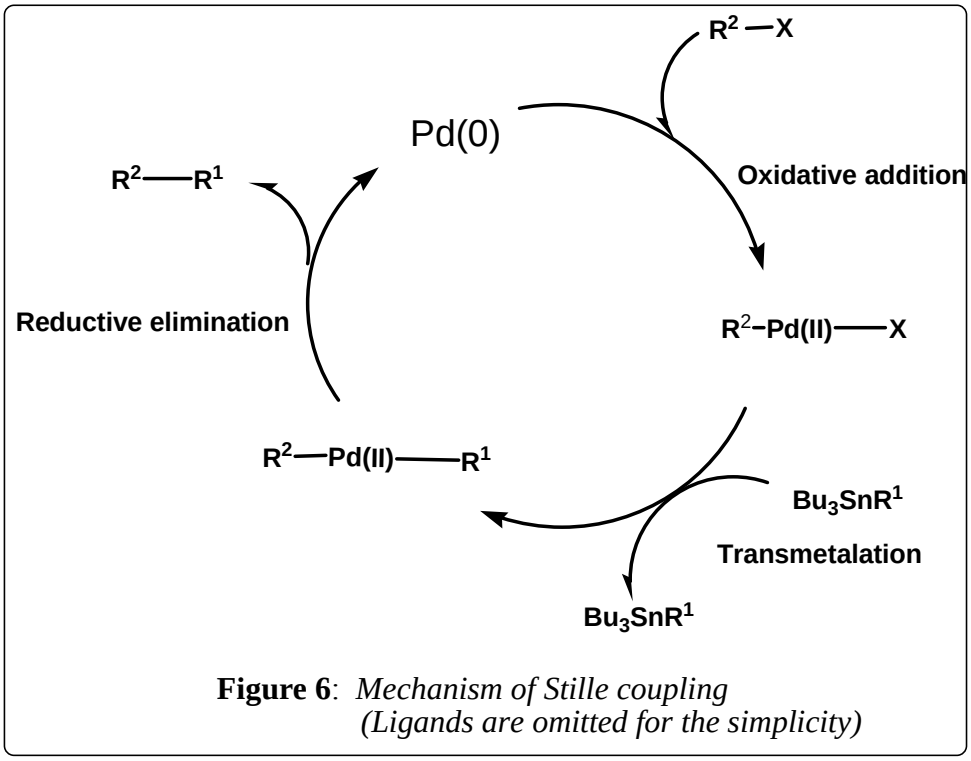


Figure 6: *Mechanism of Stille coupling*
(Ligands are omitted for the simplicity)

Reaction temperature

The reaction temperature varies from room temperature to 140 ^{o}C depending upon the reactivity and stability of the substrates.

Solvents

Strongly polar solvents such as HMTP, DMF or dioxane are the best for the low reactive alkyl stannanes also. The other solvents like *t*-BuOH:*i*-BuOH, THF, toluene have been also proved to be fertile for the coupling reaction.

Bases and additives

The bases used for Stille reactions are *t*-BuOMe, KO*t*-Bu, Et_3N, $CsCO_3$, NaOH depending upon the reactivity of the substrate. To improve the yield of the reaction, the additives like lithium chloride, 3Å molecular sieves, Me_4NF, 2,2'-bipyridine, KF, CsF etc are often added to the reaction mixture. Reactivity and specificity of the Stille reaction can also be improved by the addition of stoichiometric amounts of Cu(I) or Mn(II) salts.

Catalytic system:

The cross-coupling reaction can be inhibited by ligands of a high donor number. Rate of ligand transfer (transmetallation) from tin is in the order; alkynyl > alkenyl > aryl > allyl = benzyl > α-alkoxyalkyl > alkyl. Commercially available catalysts like

$Pd(PPh_3)_4$, $Pd(OAc)_2$, $Pd_2(dba)_3$+PR_3 or AsR_3 are generally useful for this reaction. Large rate enhancements occur with ligands which are poor σ-donors in the order $AsPh_3$ > P(2-furyl)$_3$ > PPh_3. The Stille cross-coupling reactions can be inhibited by ligands of a high donor number.

Advantages and disadvantages

The advantages of the Stille reactions are

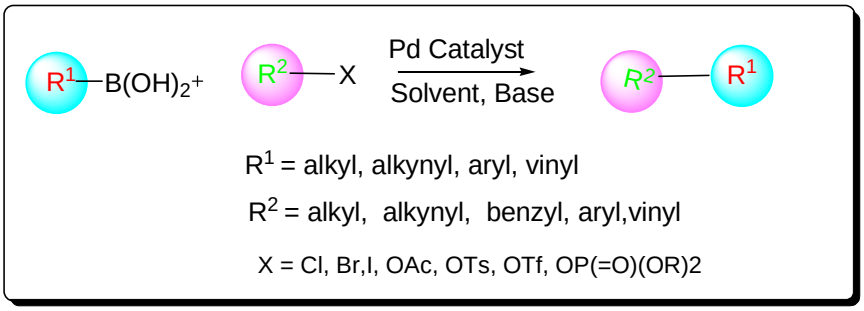
a) Stannanes are readily synthesized and are air and moisture stable (often distillable) and
b) High functional group tolerance;

The disadvantages of Stille reactions are

a) The reactivity of alkyl stannanes are low;
b) Toxicity of the tin compounds used ;
c) Side reaction gives homo coupled product;
d) Their low polarity, which makes them poorly soluble in water and
e) The yields are low for the conventional Stille coupling of aryl chlorides.

Suzuki coupling:

The Palladium catalyzed coupling reaction between an aryl halide (electrophile) and aryl boronic acid (nucleophile) is known as Suzuki coupling. This reaction is useful especially for the synthesis of the biaryl systems, which are the important part of many bioactive compounds.



The two research groups namely Buchwald[23] and Fu[24] independently explored this reaction for the coupling of aryl chlorides under non-harsh conditions. Like the Heck reaction it also tolerates the many functional groups.

Substrates

The suitable substrates for the Suzuki coupling reaction are the aryl/alkyl/alkyl/benzyl/vinyl halides (chlorides, bromides, and iodides) and aryl/alkyl/alkyl/vinyl triflates substituted with electron-withdrawing groups. The triflates and sulphonates of these compounds are regarded as the synthetic equivalents of their corresponding halides. But it has been observed that triflates decomposes normally due to their thermal labiality. Moreover triflates are expensive and undergoes hydrolysis easily, which makes them difficult to use in the Suzuki reaction. The sulphonates are an attractive option because they are easily prepared, more stable and cheap staring material.

The other coupling partner can be used are boronic acids [$RB(OH)_2$], boronic esters [$RB(OR')_2$] and borinates [R_2BOR'].

Solvents

The nature and the polarity of the solvent play the crucial role in the cross-coupling reactions. It has been observed that the same reaction with different solvents affords different results. The Suzuki cross-coupling reactions generally employ organic solvents such as THF, DME, toluene, benzene, dioxane, diethyl ether, and 1-butanol. They also employed organic solvent with water. Appropriate solvent system is also a solution to favor cross-coupling reaction.

Reaction temperature

The temperature normally around the room temperature is most suitable but may vary depending upon the solvent system and the category of the substrates used.

Catalytic system

Pd catalyst along with different ligands has proven to be very effective. Ni on charcoal, Rh catalyst and Ag_2O mediated palladium catalyst also has been used. The phosphine ligands like PPh_3, PCy_3, P(*i*-Pr)$_3$, P(*t*-Bu)$_3$, P(*n*-Bu)$_3$, dcpe, BINAP etc. The variety of nucleophilic *N*-heterocyclic carbenes (imidazol-2-ylidenes) i.e. NHC; also called "phosphine mimics" have been developed[25].

Bases and additives

In contrast to the Heck and Stille reaction, the Suzuki reaction does not work under neutral conditions. The choice of the suitable base has played an important role in Suzuki

coupling reaction. Various bases accelerate the rate of reaction in Suzuki coupling reactions are K_3PO_4, Na_2CO_3, $CsCO_3$, KOMe etc.

Mechanisms

In the initial step, the halides or triflates oxidatively adds to the Pd catalyst to give R^2-Pd-X complex. This complex then reacts with the base to form more reactive complex R^2-Pd-OR". The next step is the transmetallation of R^2-Pd-OR" with boron derivatives led to R^2-Pd-R^2. In the final step the reductive elimination produced R^1-R^2 and recycling the Pd(0) catalyst (Figure 7).

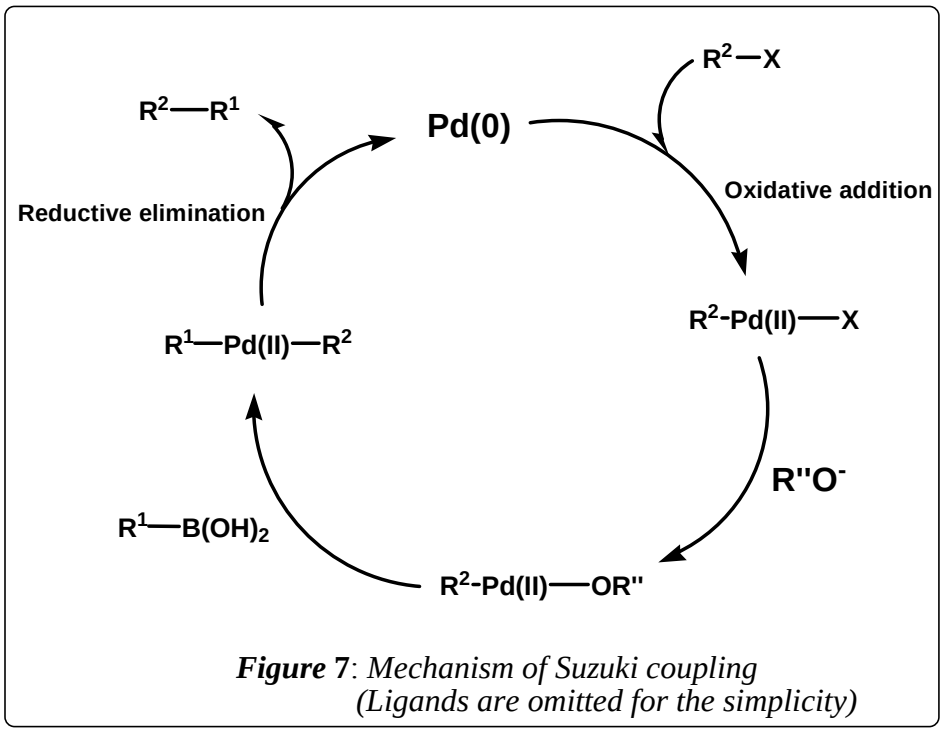


***Figure* 7**: *Mechanism of Suzuki coupling*
(Ligands are omitted for the simplicity)

The low reactivity of the organoborane compounds makes the use of a base necessary because of its low reactivity with R^2-Pd-X complex. However, the quarternization of the boron atom to form the 'ate'-complex renders the use of a base unnecessary. The enhanced nucleophilicity of the organic substituent attached to the boron enables direct alkylation of the R^2-Pd-X complex. Several reactive 'ate'-complexes are known like Bu_4BLi, $[ArB(Bu)_3]Li$, Ph_4BNa, $[R_3BOMe]Na$, $[ArB(R)(OR)_2]Li$, $[ArBF_3]K$.

Advantages and disadvantages

The advantages of the Stille reactions are

a) Stability;

b) Ease of preparation and

c) Low toxicity of the boronic acid compounds

The disadvantages of Stille reactions are

a) Homocoupling of the starting material;

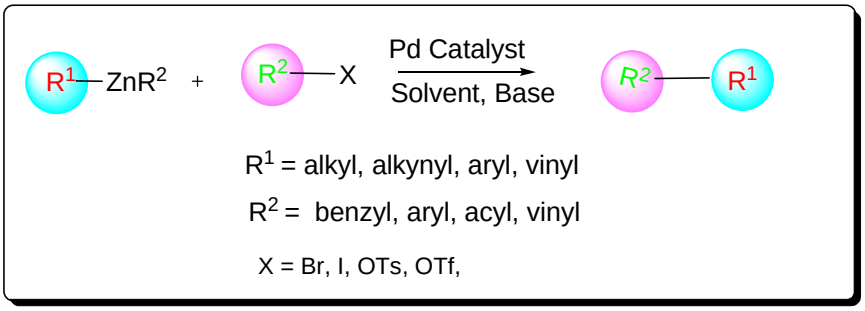
b) Dehalogenation of the organic halide;

c) Protodeboronation with water and

d) Some highly sensitive compounds do not tolerate the basic conditions required for Suzuki coupling.

Negishi coupling:

The Negishi coupling reaction reported in 1977[26] for the C-C bond formation and was the first reaction for the synthesis of unsymmetrical biaryls in good yields. It is the versatile Palladium or Nickel-catalyzed coupling reactions of organozinc compounds with various halides. This reaction has broad scope and is not restricted to the biaryls.



Substrates

Alkyl, alkenyl and alkynyl zinc halides as nucleophilic partner while variety of substrates like aryl-, alkyl- and alkenyl halides and –tosylates as an electrophilic partner can be used for Negishi coupling. Also heterocycles like halogen furans and halogenated thiazoles have been utilized successfully.

Reaction temperature

The reaction temperature ranging from –35 ^{o}C to 40 ^{o}C is most suitable for many combinations of substrate and solvents.

Solvents

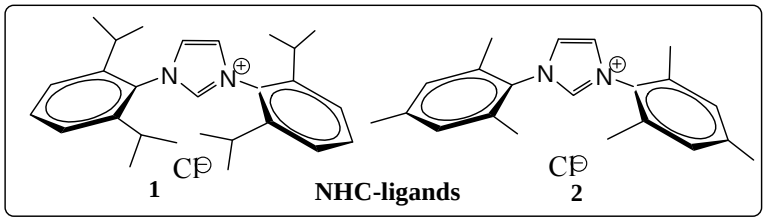
THF, NMP, DMA (*N*,*N*-dimethylacetamide), DMI (1,3-dimethyl-2-imidazolidinone), diethyl ether, DMF etc. have been used as a reaction media for this transformation.

Bases and additives

LiI, I-$(CH_2)_nCO_2R$ (R= Me, Et, THP etc.), $PhCOCH_3$, styrene(*m*-CF_3)

Catalytic system

The variety of metals like Ni, Rh, and Zn can be effectively used for Negishi coupling. Different ligands enhances the power of catalyst such as triphenylphosphine, dppe, dppf, BINAP or CHIRAPHOS etc. Negishi reaction capable of coupling sp^3-sp^3 centers in high yield of unactivated, primary bromides and alkyl organozinc reagents have been developed by using Pd-N-heterocyclic carbene (NHC) catalyst(**1** & **2**).[27]



Advantages and disadvantages

The advantages of Negishi coupling reactions are

a) Due to the mildness, (stereo- and chemo) selectivity is good and
b) High yields

The disadvantages are

a) The incapability of organozinc reagents with many common functional groups and
b) Relative sensitivity towards oxygen and water.

Mechanisms

The first step is the oxidative addition of halides to the Pd catalyst to give R^2-Pd-X complex. The transmetallation of R^2-Pd-X with R^1-Zn-X led to R^2-Pd-R^1 in the next step. The *cis-trans* isomerisation of R^2-Pd-R^1 followed by reductive elimination produced R^1-R^2 and recycling the Pd(0) catalyst (Figure 8).

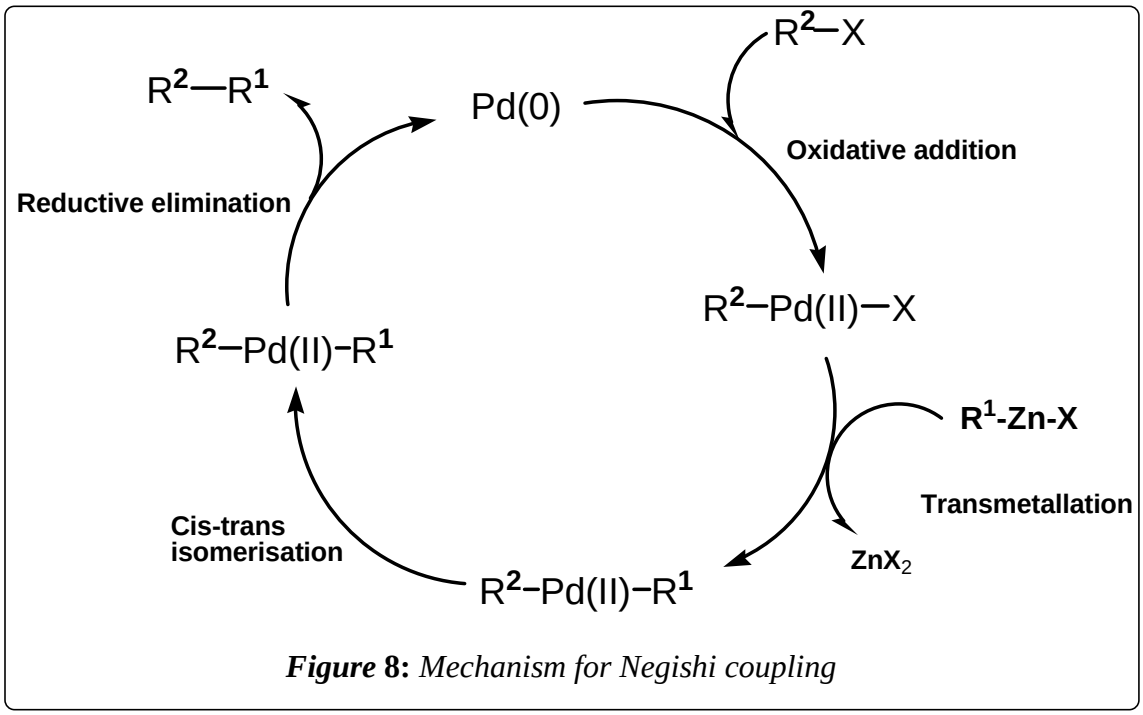
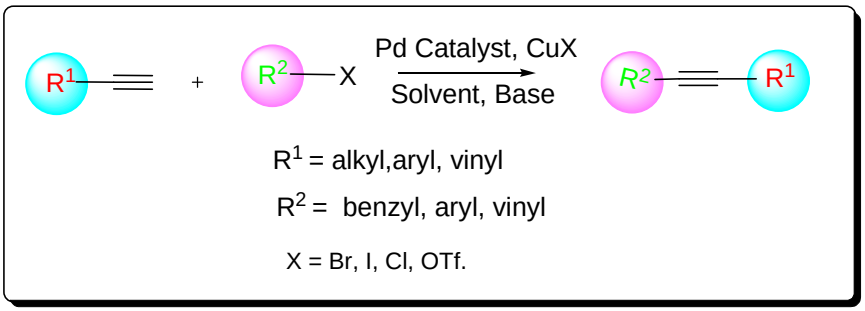


***Figure* 8:** *Mechanism for Negishi coupling*

Sonogashira coupling:

The Sonogashira reaction (can be viewed as an alkyne version of the Heck reaction) provides a valuable method for the synthesis of substituted alkynes; which are the important part of many natural products and pharmaceuticals. Both the biotechnology and nanotechnology utilized this tool of reaction for the construction of complex and designed molecules. The C-C bond forming reaction of terminal alkynes with organohalogen compounds in the presence of palladium (II)/ Copper (II) catalyst, is known as Sonogashira coupling reaction



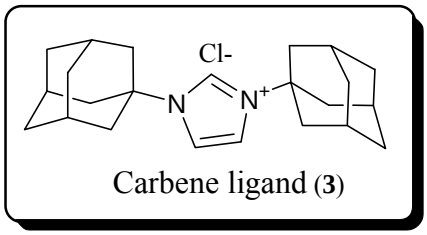
The reaction medium must be basic to neutralize the hydrogen halide produced as the byproduct and also to assist the transmetallation by abstracting the proton from the substrate. In addition the aerobic conditions are formally needed because of the sensitivity of Pd(0) to air, but the relevant development of air-stable palladium-catalysts enable this reaction to be conducted in the open atmosphere. The plausible mechanism for the Cu involved Sonogashira reaction is given here for example, in (Figure 6).

Substrates

The terminal alkynes are the suitable nucleophilic partners while aryl, vinyl or benzyl halides/triflate are the electrophilic partner for the Sonogashira reaction.

Catalytic system

Homogeneous Pd complexes often catalyze the traditional Sonogashira reaction, but recently Cai *et al.* reported heterogeneous Pd catalyzed Sonogashira also[28].



Carbene ligand (**3**)

Typically, co-catalysts such as Zn, Sn, B, Al, Ag_2O and Ag_2OTf have also proven to be efficient. The first application of carbene ligand (**3**) for cross- coupling reaction of alkyl electrophiles has been recently reported by Fu *et al.*[29]

Reaction temperature

Reaction temperature varies from room temperature to 150^{o}C. (Depending upon the electrophilic partner)

Solvents

The polar solvents like THF, DMF, Et_2O, DMSO, dioxane, NMP etc. have been used for Sonogashira reaction. The aqueous and mixed aqueous organic solvents are also effective.

Bases and additives

Reaction medium must be basic to neutralize, so alkyl amine compounds such as Et3N, iPr_2NH**,** diethyl amine, pyrrolidine, piperidine etc. and other bases such as TBAF, CS_2CO_3 are used.

The additives such as CuI can be often added.

Mechanism

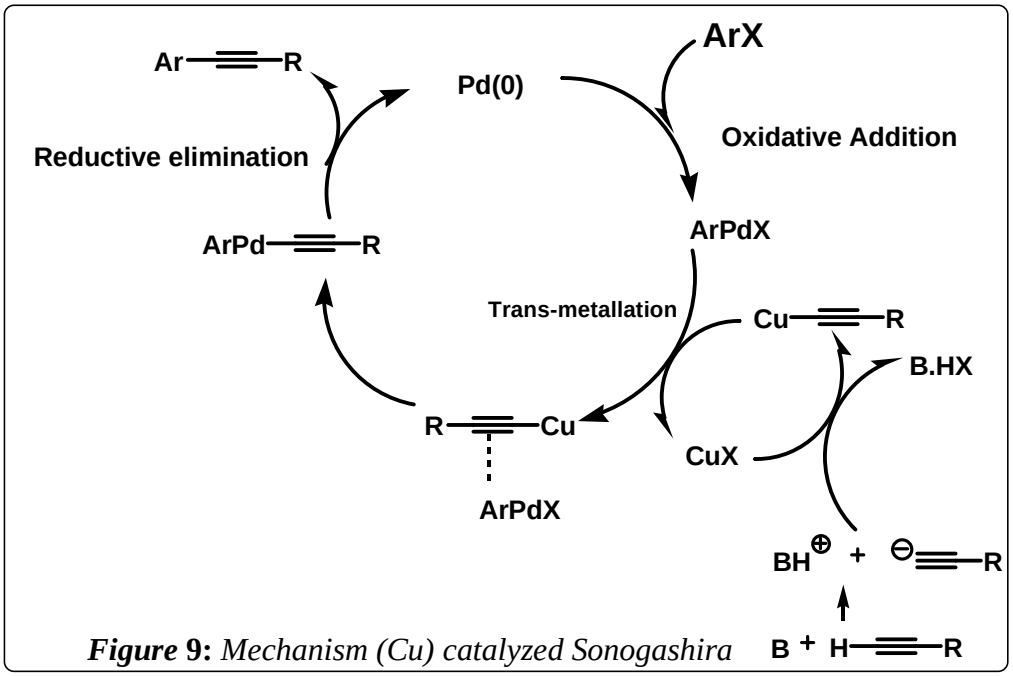


***Figure* 9:** *Mechanism (Cu) catalyzed Sonogashira*

The catalytic cycle involves number of steps, but the stationary regime more easily reached if the intrinsic reaction rates of all steps are close as possible to each other. In other words to increase the efficiency of the catalytic cycle one must either accelerate the rate determining step (i.e., destabilize the stable intermediate complexes) or decelerate the fast reactions (by stabilizing the high energy species). Though the number of metal acetylides (Mg, B, Al, Zn, & Sn) and the reagents like Ag_2O, Ag_2Otf, tetra butyl ammonium fluoride (TBAF), tetra butyl ammonium hydroxide provides as a useful nucleophiles in the oxidative addition step of catalytic cycle, the Cu acetylides has emerged as the most widely used for the synthesis of C-C bond formation Sonogashira coupling. The Sonogashira reactions have been modified, and the newer procedures including Cu free, amine free, solvent free reactions and reactions in aqueous media have been developed.

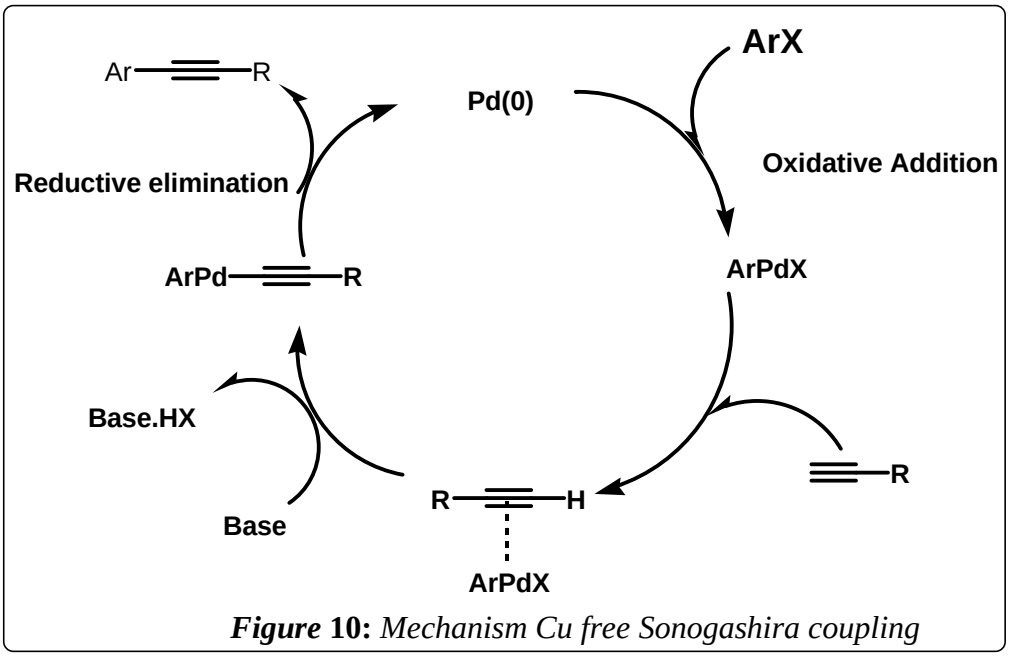


***Figure* 10:** *Mechanism Cu free Sonogashira coupling*

Advantages and disadvantages

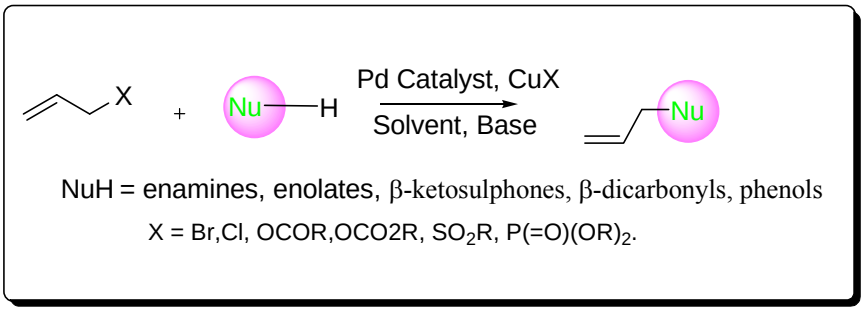
The advantage of Sonogashira reaction is that one can form different alkyne derivatives easily under very mild reaction conditions.

The main drawbacks of Sonogashira coupling are

a) Under the standard conditions, electron deficient alkyne gives low yields and
b) Homocoupled side product.

Tsuji-Trost coupling:

The nucleophilic substitution of allylic compounds by using Pd catalyst is known as the Tsuji-Trost reaction.



The asymmetric allylic alkylation is now provides a powerful method for the ring formation, 1,3-chirality transfer, desymmetrization of *meso* substrates, the resolution of racemic compounds, and a variety of other applications.

Substrates

Activated allyl alcohol derivatives, in particular, allylic halides, acetates, and carbonates acts as electrophilic partner while the nucleophiles such as soft anions like active methylenes, enolates, amines and phenols are generally used.

Reaction temperature

The range of temperatures generally used for this type of transformations is from room temperature to around 100 ^{o}C and depends on the substrates, solvent system and stability of the catalyst used.

Solvents

Water, EtOAc, THF, MeCN etc. have been used as reaction media for these transformation.

Bases and additives

The bases like Na_2CO_3, benzyl amine, LDA often used for effective coupling. Activators such as acids, Lewis acids, Et_3B, and CO_2, due to inherent low leaving aptitude of the hydroxy group are needed.

Catalytic system

A wide variety of catalytic systems have been developed for Tsuji-Trost reaction. The Pd catalyst along with plethora of ligands has been utilized successfully in the recent years for the nucleophilic displacements.

Mechanism

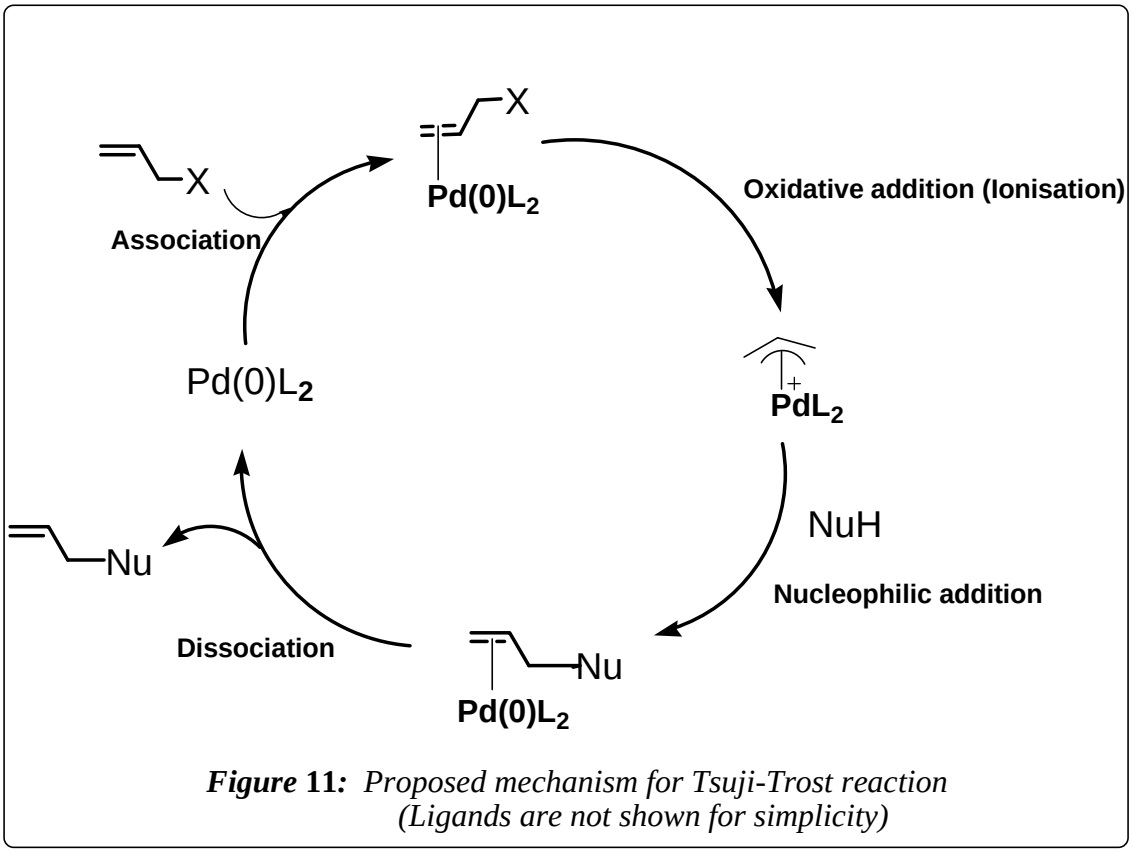
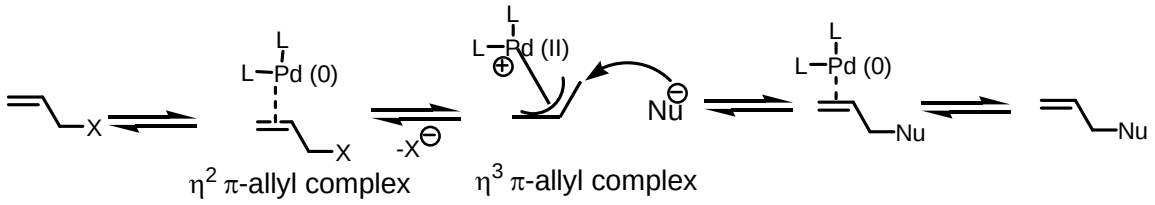


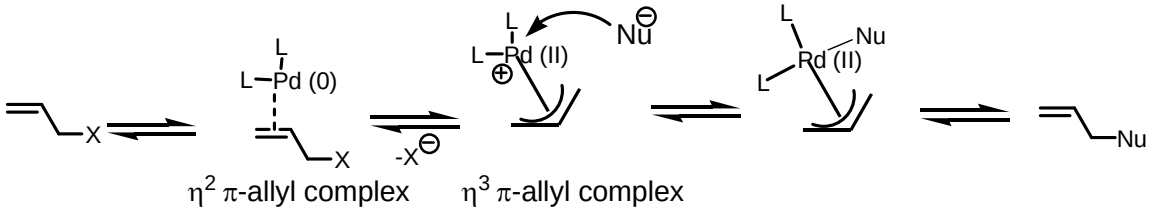
***Figure* 11:** *Proposed mechanism for Tsuji-Trost reaction (Ligands are not shown for simplicity)*

The Pd(0) forms η^2 π-allyl complex with substrate in the initial step which helps the oxidative addition and expelling the leaving group to form η^3 π-allyl complex. This step is also called as ionization. The second step is the addition of nucleophile to η^3 π-allyl complex (electrophilic) to form the allyl-Pd(II)-Nu complex. Depending on the strength of the nucleophile, the reaction can take two different pathways. Soft nucleophiles, such as those derived from conjugate acids with a pKa <25, normally add directly to the allyl moiety, whereas hard nucleophiles first attack the Pd (II) centre. The final step is the reductive elimination (or may be referred as dissociation), which gives the allylic substituted product, and association recycled the catalyst.

Soft nucleophile



Hard nucleophile



These two mechanistic paths provide the different results of asymmetric induction at allylic position.

Advantages and disadvantages

The advantages are

a) The main advantage of this reaction is that the net reaction at sp^3–hybridized carbon centers which enables to develop asymmetric allylic alkylation.

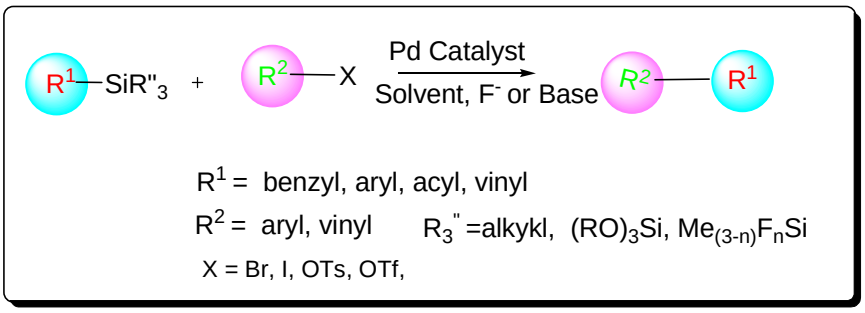
b) Under mild conditions, heigh chemo-, regio- & stereoselectivity and

c) Range of hetreoatom nucleophiles (e.g. N, O & S) also make excellent coupling partner.

There are no major disadvantages for this transformation.

Hiyama Coupling:

The Hiyama coupling is the palladium catalyzed C-C bond formation reaction between organohalides and organosilanes.



Substrates

Activated silicates (aryl, benzyl, acyl and vinyl) are the nucleophilic partner and aryl/vinyl halides, tosylates and triflates may be the electrophilic partner.

Reaction temperature

Like other Pd catalyzed C-C bond forming reactions the reaction temperature for Hiyama coupling varies for substrate to substrates and the most acceptable range is again 20 ^{o}C-120 ^{o}C.

Solvents

The polar solvents like DMF, MeCN and MeOH gives the best results

Bases and additives

The activating agent like base or fluoride ion (KF, TBAF, TASF etc.) is essential for this reaction. Generally CuI gives the best result as an activator and different inorganic bases like Ag_2CO_3, K_2CO_3 enhances the rate of reaction efficiently.

Catalytic system

The Pd catalyst along with phosphine ligands such as PPh_3, Pcy_3, P*t*Bu_3 etc. has proven to be good giving the cross-coupled product in high yield.

Mechanism

The polarization of C-Si bond is the crucial step in this reaction. The activation of the organosilanes by using fluoride ion/base leading to a pentavalent silicon compound, which was used in the transmetallation step with R^2-Pd-X to give R^1-Pd-R^2. This palladium complex was then undergoes the cis-trans isomerisation followed by reductive elimination affords the coupling product R^1 -R^2.

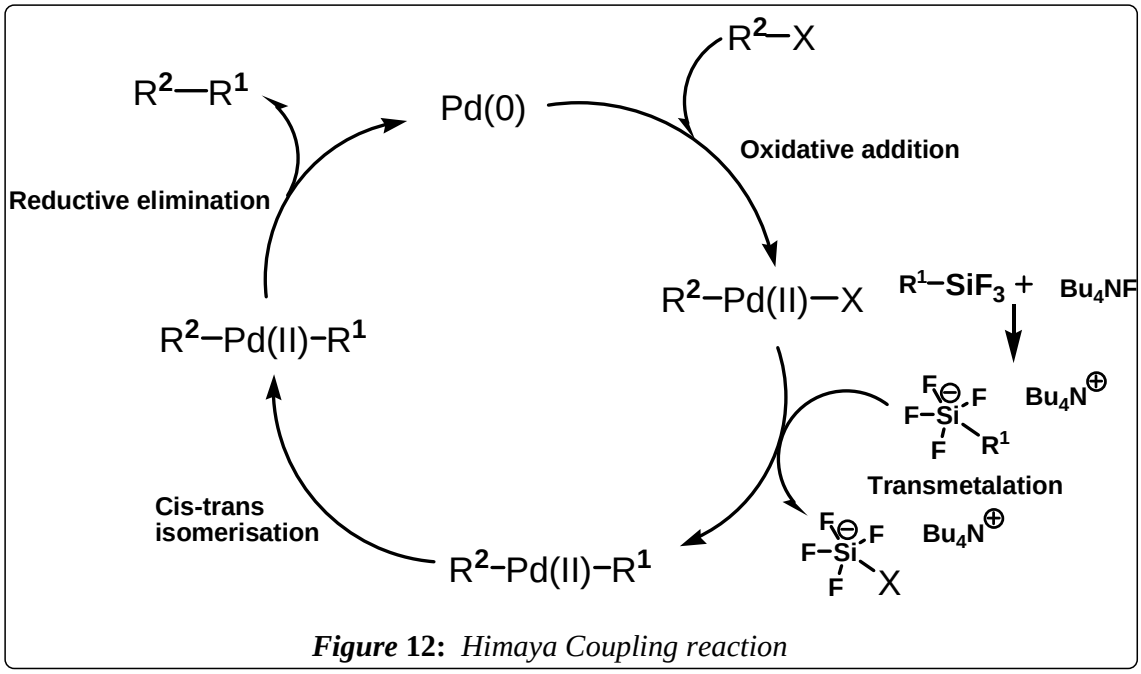


***Figure* 12:** *Himaya Coupling reaction*

Advantages and disadvantages

The advantages of Hiyama coupling reaction are

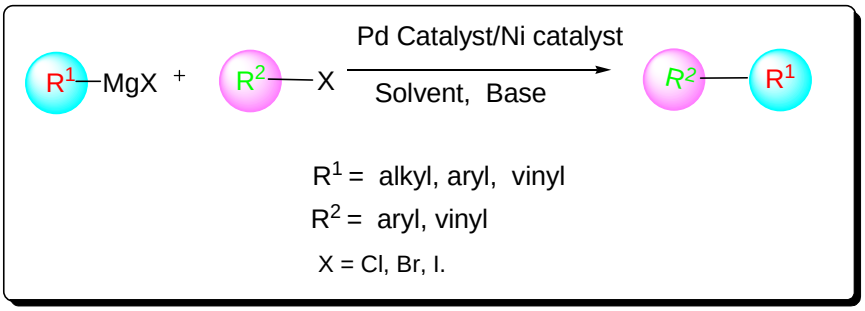
a) Low environmental impact (low toxicity),
b) The organosilicone compounds are stable and easily prepared compounds
c) High atom efficiency, and
d) Easy handling compared with the coupling reactions of organoboron, organozinc, or organotin compounds.

The disadvantages are

a) Silanes are considerably less reactive toward transmetallation;
b) Stoichiometric amounts of a fluoride salt is needed as the activating agent

Kumada coupling:

This reaction involves the coupling of Grignard reagents with different halides under metal catalyst. This reaction was developed by two groups independently in 1972, Kumada group prepared the styrene derivative by using Ni catalyst and in the same year Corriu group also reported Kumada cross-coupling for the preparation of stilbene derivatives with Ni catalyst. Later in 1975, Murahashi reported Pd catalyzed cross–coupling reaction.[30] Fürstner *et al.*[17d,e] developed an iron catalyzed Kumada coupling of aryl chlorides and activated aryl and heteroaryl tosylates with alkylmagnesium chlorides.



Substrates

The aryl/vinyl or alkyl Grignard reagents have been generally used as nucleophilic partner, while aryl/ vinyl halides are found to be effective electrophilic partners for this type of transformation.

Reaction temperature

The most applicable range for Kumada coupling is –78 ^{o}C to room temperature.

Solvents

THF, dioxane, toluene, DMF, DMAc (*N*,*N*-Dimethylacetamide), NMP(*N*-methylpyrrolidinone)

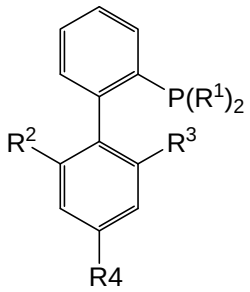
Bases and additives

Et_3N, NMP, DABCO, TMEDA (*N*,*N'*,*N'*-tetramethylethylenediamine)

Additives such as 1,3-butadiene, $BnN(C_5H_7)_2$ usually increase activity of the substrates.

Catalytic system

Apart from different Pd catalyst the Ni, Fe, Co and Cu catalyzed Kumada coupling reactions are also well known. Various ligands like PCy_3, TPP, P(*o*-tol)$_3$, P(*t*-Bu)$_3$, dppp {1,3-bis(diphenyphosphino)propane, dmpe, dppe can assist the coupling reaction. Pd-catalyzed Kumada coupling at low temperatures for Knochel-type Grignard Reagents have been developed recently using ligands **L1-L5** provided the best results[31].

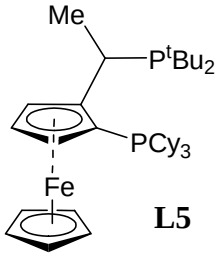


R^1=Cy; R^2=R^3=R^4=^{i}Pr, **L1**

R^1=Cy; R^2=R^3=OMe;R^4=H, **L2**

R^1=Cy; R^2=NMe_2;R^3=R^4=H, **L3**

R^1=^{t}Bu; R^2=NMe_2;R^3=R^4=H, **L4**



L5

Mechanism

Like all other Pd catalyzed coupling reaction the first step of Kumada coupling reaction involves the oxidative addition of R^2 -X over the Pd catalyst to give R^2-Pd-X complex. This complex then undergoes the transmetallation with R^1-Mg-X led to R^2-Pd-R^1 in the second step of the catalytic cycle. The third step is the *cis-trans* isomerisation of the complex R^2-Pd-R^1. In the final step the reductive elimination produced R^1-R^2 and recycling the Pd(0) catalyst (Figure 11).

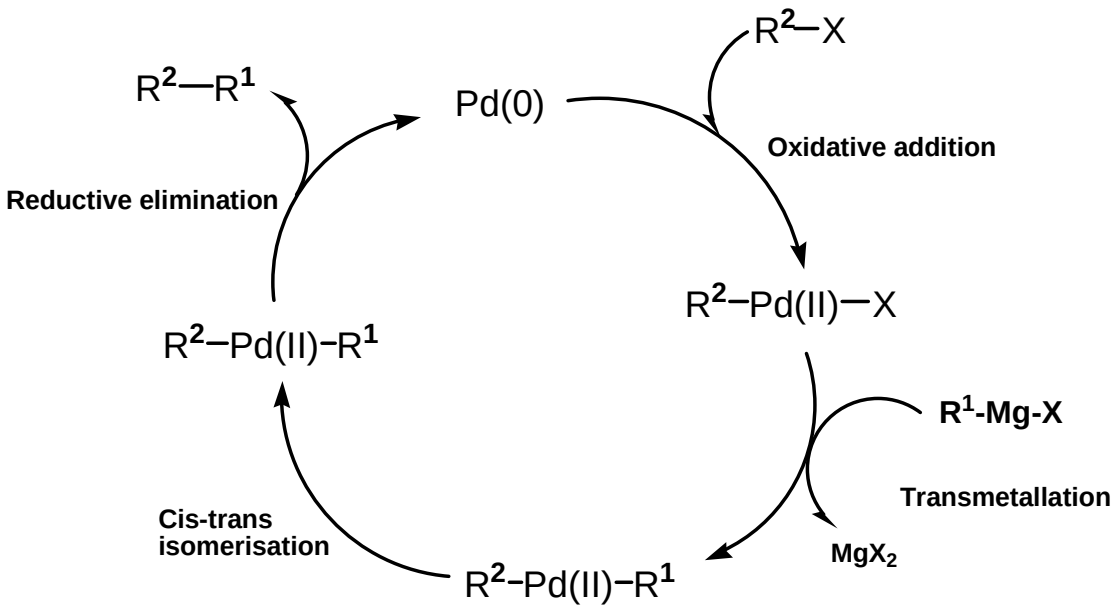


***Figure* 13:** *Mechanism for Kumada Coupling reaction*

Advantages and disadvantages

The advantages of Kumada coupling are

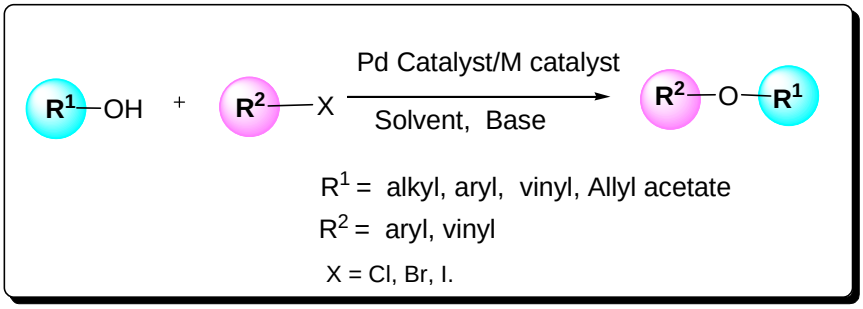
a) The one of the advantage of this reaction over Negishi-coupling reaction is that, it is direct coupling of Grignard reagent, which avoids additional reaction step such as the conversion of Grignards regent to the organozinc compounds;

b) Low-cost synthesis of unsymmetrical sterically hindered biaryls

The main disadvantage of Kumada coupling is incompatibility of Grignard-reagents with certain functional groups

Pd catalyzed C-O bond formation reaction:

The first C-O bond formation reaction reported by using transition metal is the Ullmann reaction.[32] However the Ullmann reaction is neither catalytic nor reliable at the crucial C-O bond formation step. In an effort to improve the existing method the Palladium chemistry attracted the attention of the organic community.



In addition to the C-C bond formation, palladium-catalyzed chemistry has been explored further for the formation of C-O bonds. Buchwald and co-workers lead the way and then Hartwig and other groups from all over the world have been engaged in developing the plethora of palladium catalysts successfully for the formation of intra- and intermolecular C-O bond. This method is efficient and reliable alternative for the traditional way of the lengthy organic schemes for the diaryl ethers (Pharmaceutical intermediates).

Substrates

Organic halides (aryl/vinyl) and allylic acetates are the most reactive class of electrophiles used for this reaction. On the other hand, alkyl/aryl/vinyl alcohol derivatives are good nucleophiles.

Reaction temperature

The reaction temperature varies for substrate to substrate but most of the reactions the temperature in the vicinity of ambient proved to be fruitful.

Solvents

Like other coupling reactions the solvents such as toluene, dioxane, THF etc. can be used for C-O bond formation.

Bases and additives

Weak bases such as $K_3PO_4.H_2O$, K_3PO_4, CS_2CO_3, K_2CO_3 and stroner base like NaO^tBu have been also applied. Some reports by using Et_2Zn as activator.

Catalytic system

Amongst the metal used for C-O bond formation reactions are Cu, Ir, Pt and Ni.

Mechanism

The alcohol arylation reaction by using the Palladium catalyzed reaction follows the same mechanistic path as that for the amination of aryl halide suggested by Buchwald-Hartwig.[34] Thus the proposed mechanism cycle for the ether formation is shown in Figure 12.

In the initial step, the aryl halides react with the Pd catalyst to give Ar-Pd-X complex. This complex is then reacts with the base to form more reactive complex Ar-Pd-OR". The next step is the addition of the alcohol ROH to the Ar-Pd-OR" to form Ar-Pd-R. In the final step the reductive elimination produced Ar-O-R and recycling the Pd(0) catalyst.

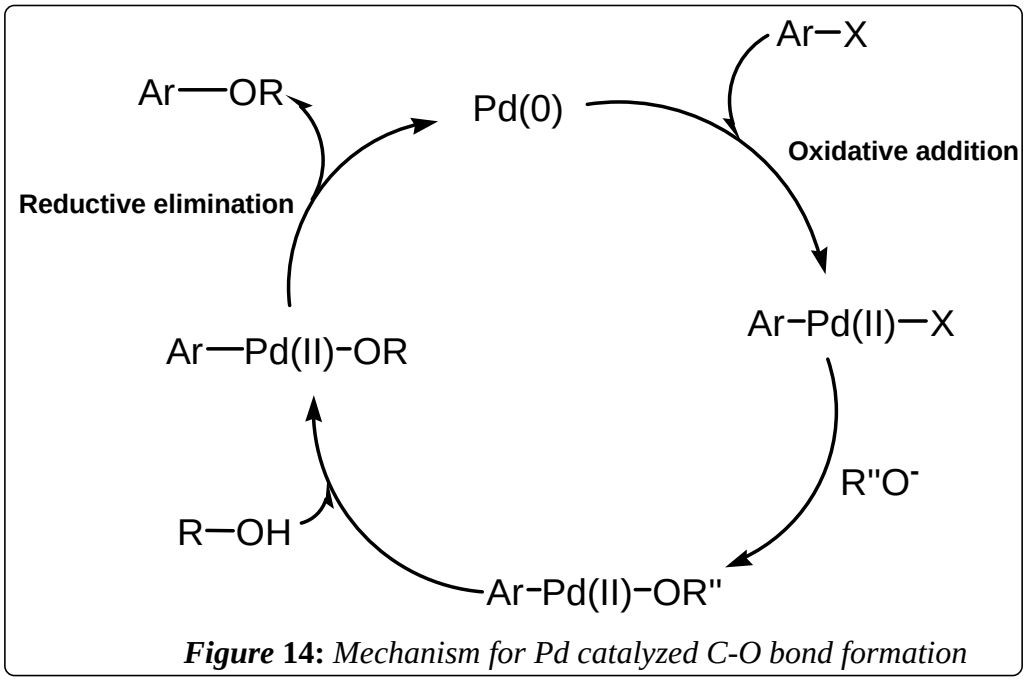


***Figure* 14:** *Mechanism for Pd catalyzed C-O bond formation*

Advantages and disadvantages

The advantages are

a) It linkage aryl-oxygen under mild condition;
b) Many bioactive compounds can be synthesized by using intramolecular C-O bond formation effectively.

The disadvantages are

In case of secondary alcohol, dehalogenation of the aryl halides and sometimes the oxidation of the alcohol to the ketone are the competitive reactions.

PRESENT WORK

The field of discovery and synthesis of biologically active natural products represents a dynamic and largely growing research area. By the use of new strategies to discover natural products of interest, many molecules with novel structural features have been isolated and their structures have been elucidated. The development of flexible strategies for total synthesis combined with the synthesis of related analogues provided an ideal platform for new drug discovery. However, considering the length and synthetic manipulations involved in synthesizing natural product or analogues, a conceptually new approach has been disclosed recently which does take the inspiration from the skeletal diversity of natural products, however does mainly aim in producing natural product like molecules with a minimum effort. Diversity oriented synthesis (DOS)[34], conceptualized by Schriber has been regarded as promising tool to make many new connections to biology and medicine in the future. Development of new chemical platforms for constructing useful molecular diversity taken together with the design and development of effective routes for the construction of cyclic compounds have been considered as controlling elements in the DOS. The inherent rich chiral diversity and skeletal rigidity of carbohydrates has been recognized and explored in the context of synthesis of combinatorial libraries involving selective functionalization and synthetic manipulations.

Carbohydrates constitute an abundant and relatively inexpensive source of chiral carbon compounds. Through simple chemical manipulation, these readily available sugars can be transformed into a variety of intermediates bearing functional groups such as alkene and alkyne with predetermined chiral centers and with defined structural framework. In this regard, studies in this laboratory have been engaged in exploring the synthesis and utility of functionalized *Chirons* in the total synthesis of a wider variety of natural products. Funded upon the DOS, combined with the palladium mediated inter- and intramolecular functionalization of alkynes that has been well explored in organic synthesis for the construction of carba/heterocyclic derivatives, we have devised an approach to construct the architecturally complex skeletons through sugar alkynes either by using intra- or intermolecular nucleophilic addition reactions. A general description of our intended strategies is described in Figure 15.

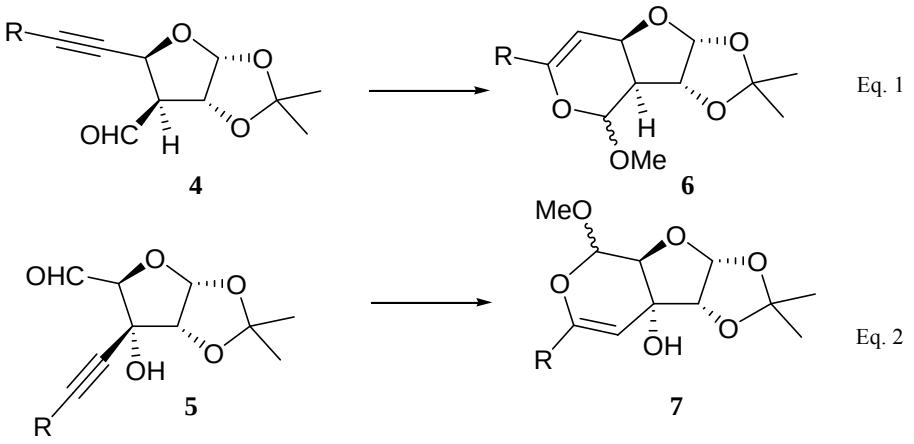
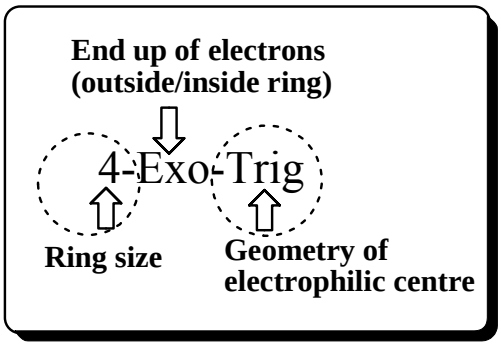


***Figure* 15:** *Proposed Pd mediated transformations on sugar alkynes*

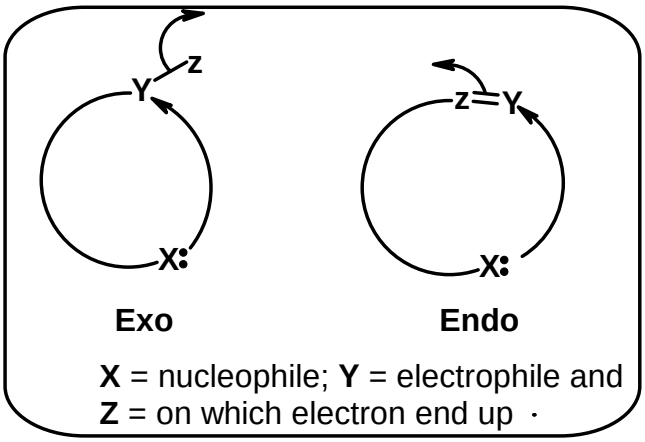
Section 1: Cycloisomerization of sugar alkynals

Palladium mediated addition of *C*-and heteroatom nucleophiles across the carbon-carbon triple bond, is one of the most interesting and intriguing reaction in organic chemistry. Cycloisomerization of alkynals and alkynols is projected as a tool to synthesize the oxygen containing heterocycles encompassing functionalized furan, pyran, and benzopyran skeletons. However, majority of the metal mediated cycloisomerization reactions of carbohydrate precursors have been less explored and mainly confined to glycals, *exo*-glycals and related derivatives. Almost all the cycloisomerization reactions followed the Baldwin rules[35].

Short account of Baldwin rules for ring closure



Baldwin suggested a set of empirical rules for the predication of ring closure outcome of the intramolecular addition of nucleophiles or radicals to electrophilic centre. The nomenclature of these rules is written as e.g. ***4-Exo-Trig****.*



4- *indicate the ring size being formed*

Exo-*indicate where displaced electron end up (if it ends up out side the ring being formed; then Exo and if it ends up within the ring being formed; then Endo)*

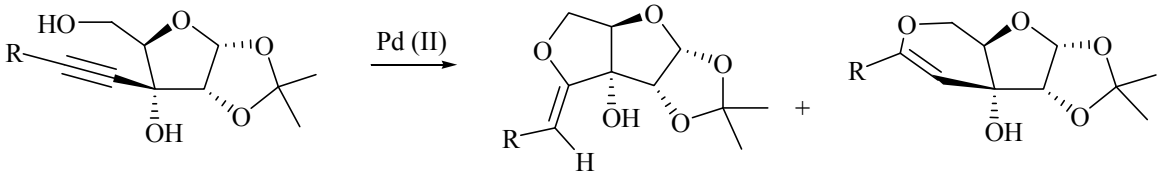
Trig- *indicates the geometry of electrophilic atom on which attack takes place {if it is sp^3; then Tet (tetrahedral), if it is sp^2; then Trig (trigonal) and if it is sp; then Dig (diagonal)}.*

The Baldwin rules are listed in the tabulated form below. These rules suggest whether the ring closure is favored (√) or disfavored (×).

Ring size being formed	**Exo**			**Endo**		
	Dig	**Trig**	**Tet**	**Dig**	**Trig**	**Tet**
3	×	√	√	√	×	√
4	×	√	√	√	×	√
5	√	√	√	√	×	×
6	√	√	√	√	√	×
7	√	√	√	√	√	√

Recently, we have shown that the electronic effects in the alkyne[36], i.e., the presence of strong electron withdrawing or strong electron-donating groups influence mode of the

cyclizations (Figure 16)[42].



	5-exo product	6-endo product
R = H	only	——
R = alkyl	——	only
R = *p*MeO-Ph	——	only
R = *p*NO_2-Ph	only	——

***Figure* 16:** *Competitive 5-exo vs 6-endo-dig cyclizations and role of electronic factors*

In order to extend this methodology and to understand such an electronic control over the cycloisomerization of sugar alkynals, we have designed two types of alkynals (Figure 3) where one can anticipate the formation of fused bicyclic derivatives with predetermined stereochemistries, which can be further elaborated as starting chiral intermediates for the synthesis of related natural products. Two modes of cyclisation i.e. 5-*exo-dig* and 6-*endo-dig* are possible as shown in Figure 17**.**

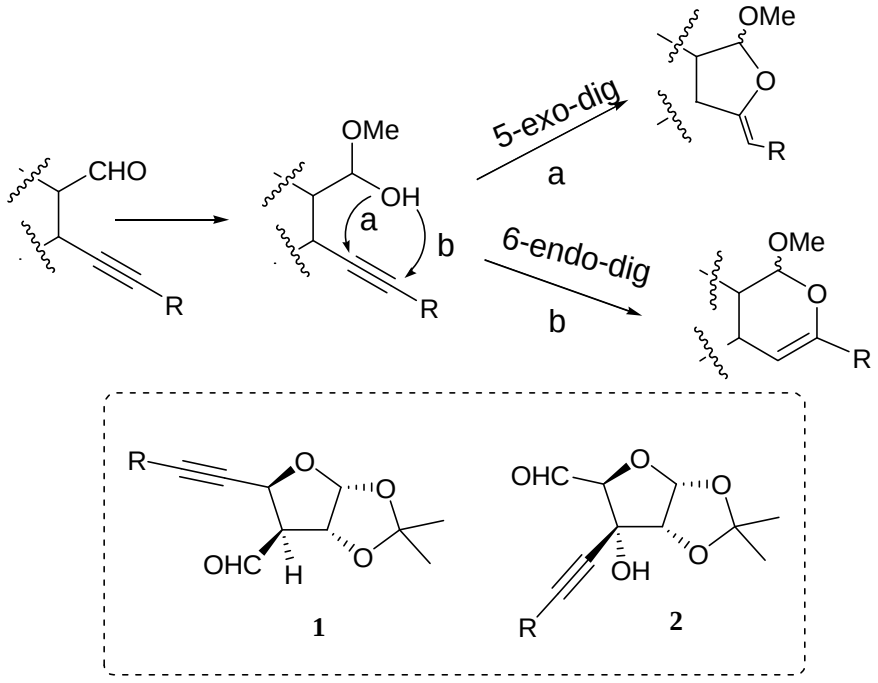
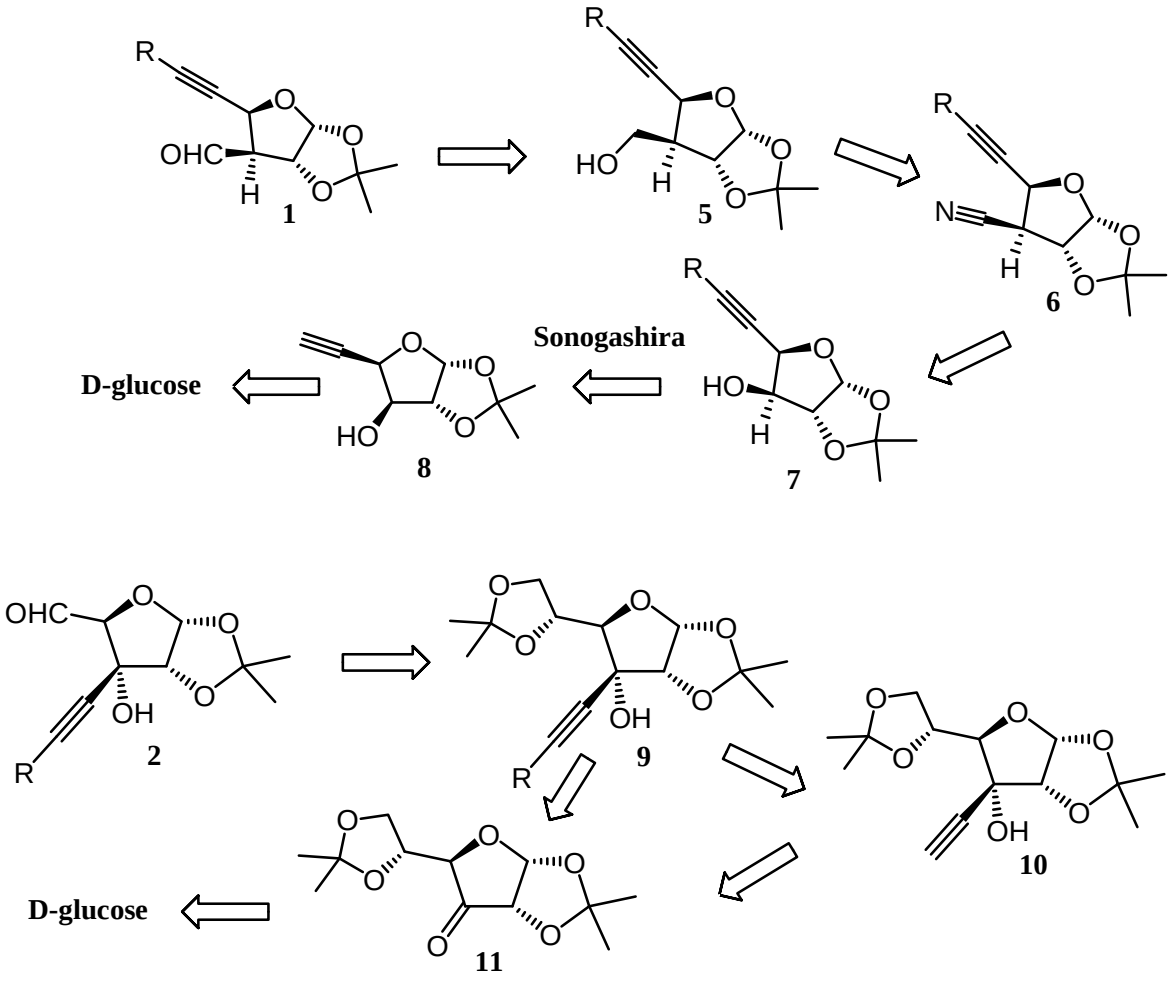


***Figure* 17**: *Modes of cycloisomerization*

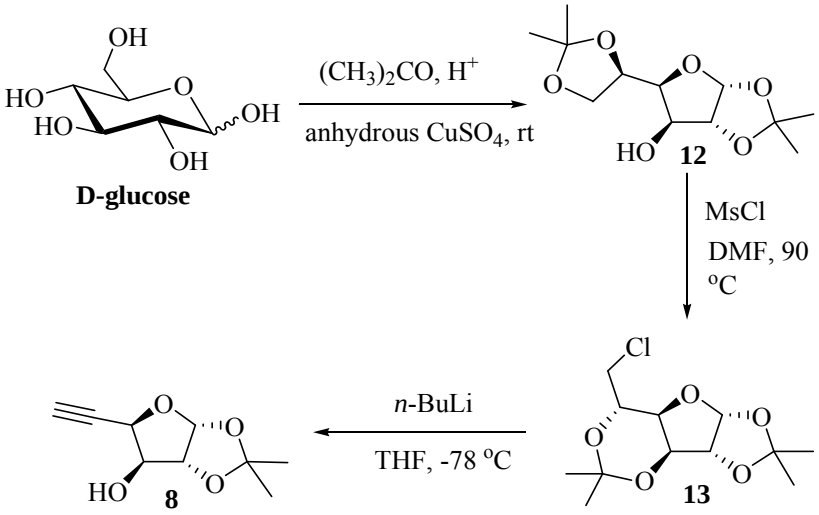
A retrosynthetic strategy for alkynals **4** and **5** is given in Scheme 1. As shown in scheme 1, the key cyano intermediate can be obtained from the alkynol **10** by a double inversion consisting conversion of C(3)-OH to corresponding iodo derivative followed by nucleophilic displacement with cyano group. The synthesis of differently substituted alkynols **10** is a direct proposition from known alkynol **11** by means of Sonogashira reaction. On the other hand synthesis of the alkynal **5** is straight forward from known alkynol **13**[37] which can be subjected for Sonogashira coupling (or direct C-3 alkylation on **14**) followed by selective *insitu* 5,6-acetonide deprotection and periodate mediated cleavage of the resulting diol.



***Scheme* 1:** *Retrosynthetic strategy for substrates* **4** *and* **5.**

Our initial target was the synthesis of C-4 alkyne **11**. Synthesis of the alkyne **11** started with conversion of the D-glucose into 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**15**) by following the known procedure by treating glucose in acetone with anhydrous $CuSO_4$ in the presence of catalytic H_2SO_4. Subsequent treatment of **15** with methanesulphonyl chloride in DMF at 90 ^oC for 6 h afforded 6-chloro-6-deoxy-1,2:3,5-di-*O*-isopropylidene-α-D-glucofuranose (**16**). Finally by using the base induced double elimination of the β-alkoxy chloride protocol, the compound **16** was converted into alkyne **11**[38] (Scheme 2).

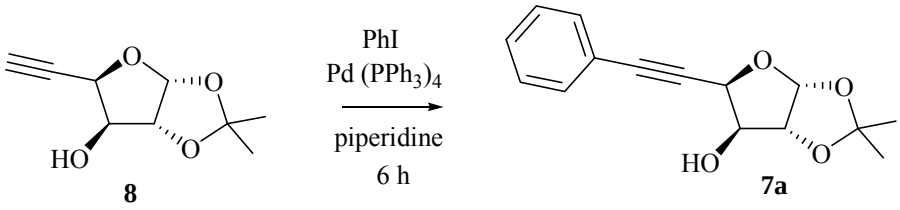
***Scheme* 2**



In the ^1H NMR spectra of **11**, the characteristic alkyne proton was observed as a doublet at 2.65 ppm (J = 2.5 Hz) and the peaks due to isopropylidene moiety were absent. The quaternary carbon located at 77.5 ppm in ^{13}C NMR spectrum and mass spectral analysis further supported the structure of **11**. Our next concern was to introduce the alkyl group on the terminal alkyne by using Sonogashira reaction. The initial optimization of Sonogashira coupling was carried out by using phenyl iodide as the coupling partner, $Pd(PPh_3)_4$ as the catalyst and after a careful examination of various reaction conditions, by changing reaction temperature, reaction time, base, solvent, and amount of iodobenzene, we concluded that the best result for the intended Sonogashira reaction were obtained by

using a piperidine as a solvent (also acts as a base) and conducting the reaction at room temperature in the presences of $Pd(PPh_3)_4$ (5 mol%).

***Scheme* 3**



Thus the Sonogashira reaction of compound **11** afforded the coupled product **10a** in 85% yield. In the ^{1}H NMR spectrum of compound **10a**, the absence of signal due to the terminal alkyne proton resonated as a doublet (J = 2.5 Hz) at 2.65 ppm and the presence of characteristic signals for phenyl group in aromatic region (two multiplates, one at 7.29-7.57 resonating for 3H and another at 7.46-7.51 resonating for 2H) were noted. In addition the structure of compound **10a** was further supported by its mass spectral analysis (Scheme 3).

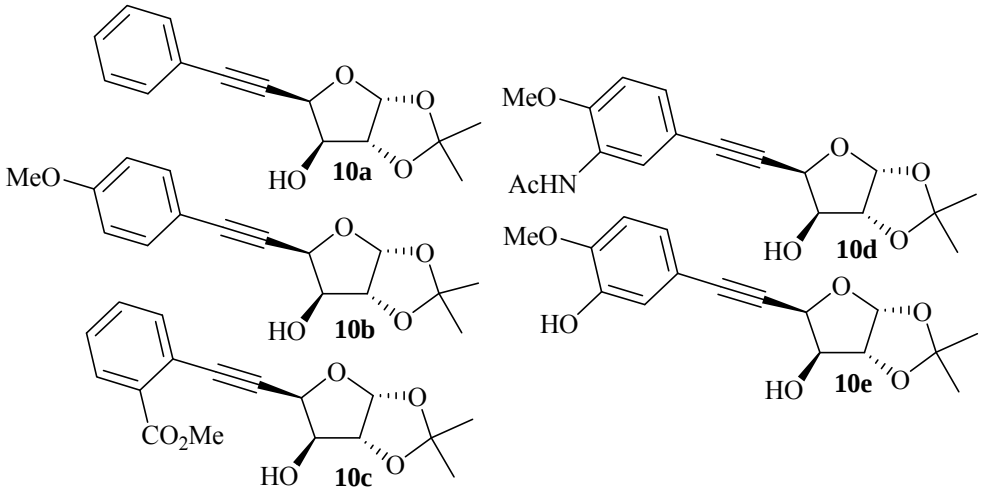
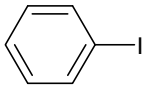
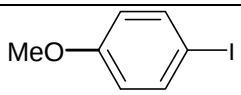
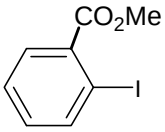
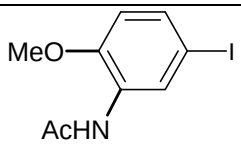
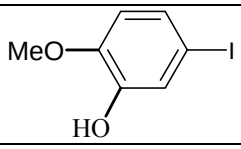


***Figure* 18:** *Two component Sonogashira coupling on Sugar alkynes*

Later, in order to show the generality of the Sonogashira reaction on sugar templates, various aryl iodides were employed and the results are summarized in Table 1. As shown in Table 1, the optimized catalyst system is quite general and tolerant of a range of functionalities and the substrates. We have generalized this methodology[39] to prepare

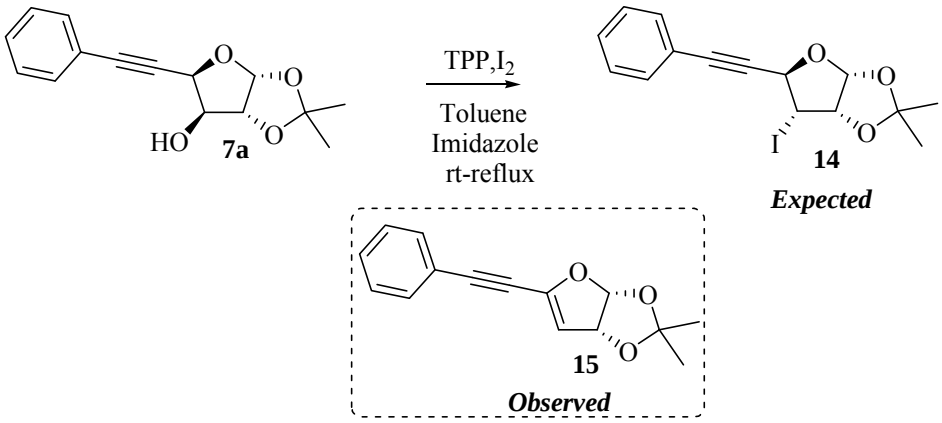
various disubstituted alkynes with different aromatic halides, in excellent yields (Figure 18).

Table 1

Entry	*Substrate*	*Halide*	*Product*	*Time (h)*	*Yeild (%)*
1	**11**		**10a**	6	85
2	**11**		**10b**	6	81
3	**11**		**10c**	18	65
4	**11**		**10d**	16	80
5	**11**		**10e**	18	60

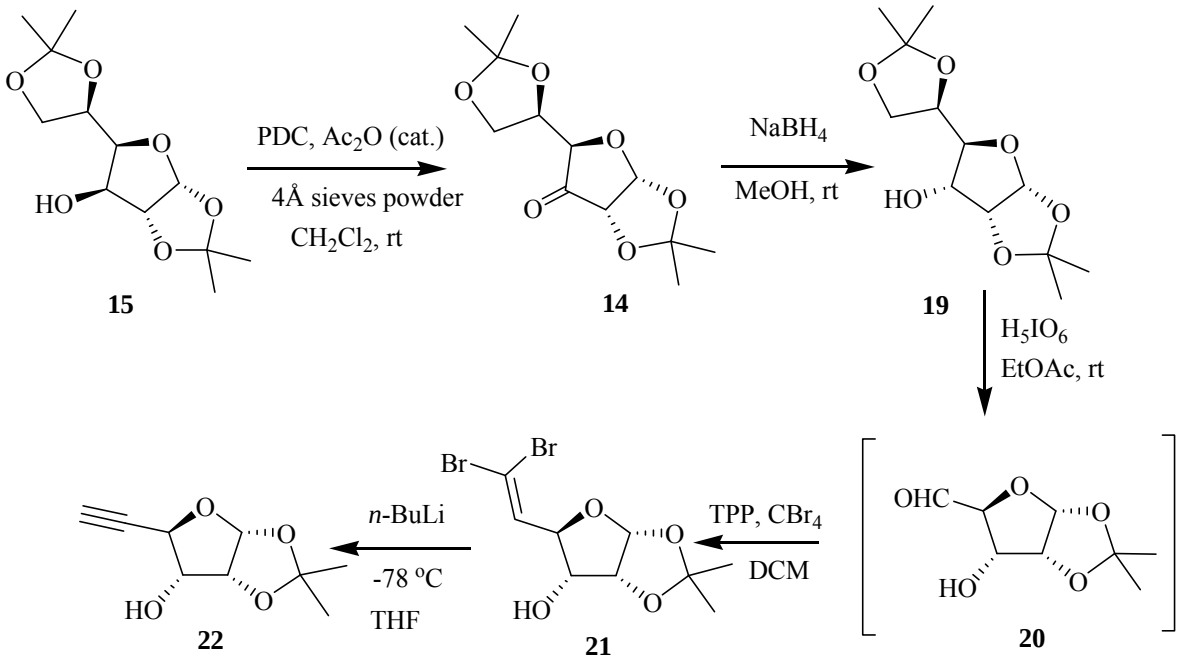
After being executed the synthesis of various alkyne partners for the cycloisomerization, our next aim was to introduce the formyl group at C-3 on these alkyne derivatives. According to our plan double inversion (first iodination and then cyanation i.e. net retention) at C-3 could give 3-*C*-formyl derivative of glucose. For this purpose, the compound **10a** was treated with TPP, iodine and imidazole in refluxing toluene, which afforded the eliminated product **18** instead of iodo derivative **17.** The motive behind this *insitu* facile elimination is highly acidic nature of H-C(4). In the ^{1}H NMR of the compound **18,** the olefin signal (downfield) was appeared as a doublet (J = 5.4 Hz) at 6.03 ppm.

***Scheme* 4**



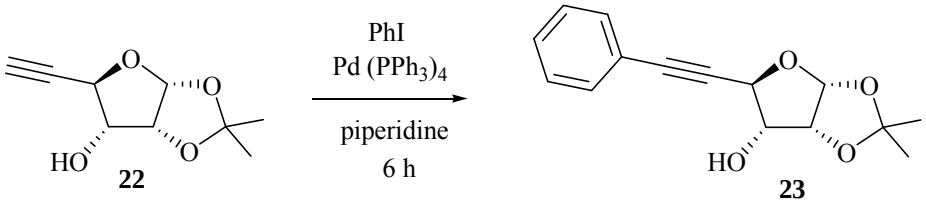
Due to the elimination problem encountered during iodination (double Walden inversion at C-3 on **10a,** as envisioned), we changed our strategy. The new strategy, which involves the single Walden inversion (tosylation and then cyanation) at C-3 of compound **19**, was adopted as shown in (Scheme 5). The compound **15** was subjected to the series of well-reported reactions[40] to afford **223**. Accordingly the oxidation of free OH group at C-3 of 15 using PDC in the presence of 4Å molecular sieves powder and Ac_2O (cat.) in anhydrous CH_2Cl_2 afforded 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**14**) which was after reduction with $NaBH_4$ in MeOH at room temperature gave compound **19**. The compound **19** was then converted into its 4-C formyl derivative **20** by the treatment of H_5IO_6 in dry ethyl acetate at 0 ^oC which was directly treated with CBr_4 and TPP to give dibromo derivative (**21)**. Finally the elimination of **21** by using *n*-BuLi as a base in THF at 0 ^oC afforded alkyne **22.** On TLC, the spot of the alkyne **22** matched with the authentic sample of the alkyne **11**. In the proton NMR spectrum of the compound **22**, the alkyne proton was resonated as a doublet (J = 2.5 Hz) at 2.54 ppm, and the rest of the peaks were in complete agreement with the structure of alkyne **22** (Scheme 5)**.**

***Scheme* 5**



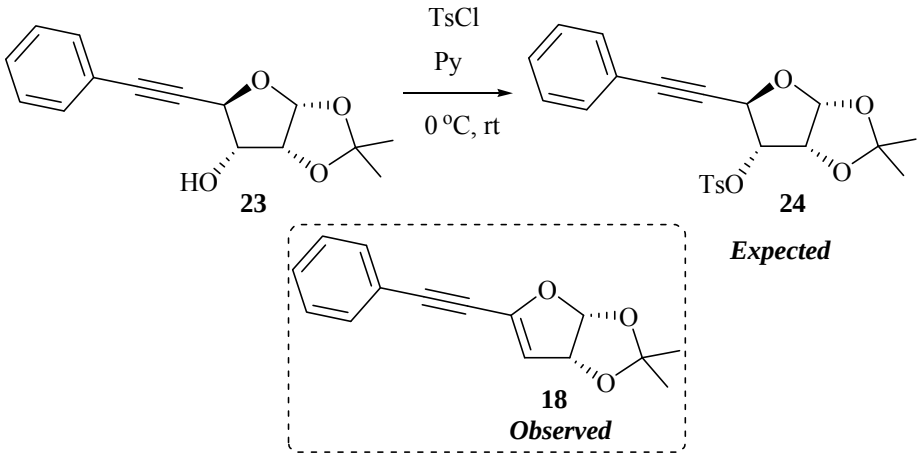
The alkyne **22** was then subjected to the Sonogashira coupling reaction by following the same procedure as described for alkyne **11**. The resulting coupled product **23** was characterized by using ^{1}H NMR spectroscopy, mass spectroscopy and elemental analysis. All these data were in accord with the assigned structure for the compound **23** (Scheme 6)**.**

***Scheme* 6**



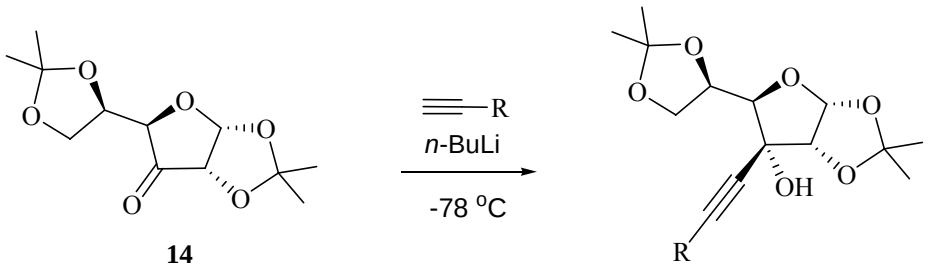
The compound **23** was then treated with tosyl chloride in pyridine at 0 °C to afford an undesired elimination product **18** again. By replacing the tosyl with mesyl or triflate also afforded an undesired elimination product **18** (Scheme 7)**.**

***Scheme* 7**



After being met with elimination problem in both the strategies adopted we next focused on the second system, which contains the alkyne at C-3 and aldehyde at C-4. The 3-ulo derivative of glucose diacetone (**14**) was subjected to the stereoselective nucleophilic addition with the lithiated salts of the corresponding terminal alkynes to afford the requisite C-3 alkynyl derivatives **12a-12d (**Scheme 8). The compounds **12a-12d** were fully characterized by using ^{1}H NMR, ^{13}C NMR, mass spectroscopy and elemental analysis.

***Scheme* 8**



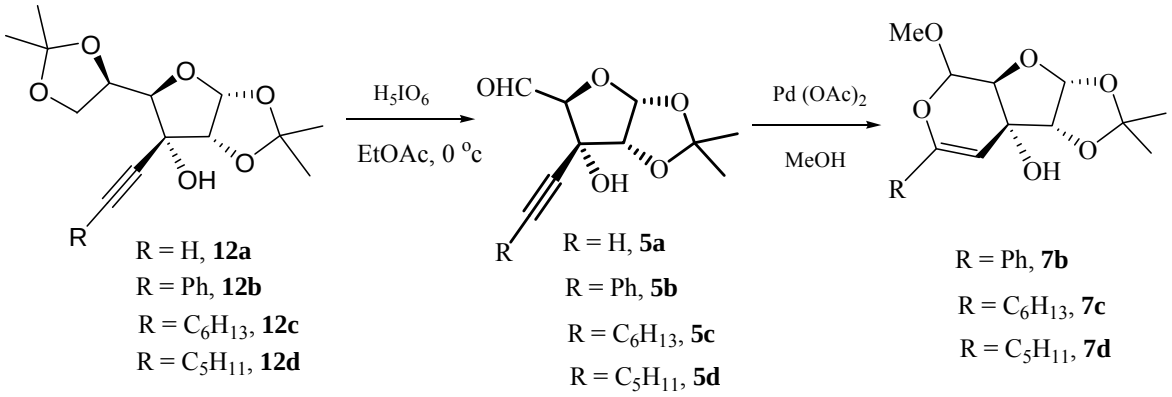
14

R = H, **12a** R = C_6H_{13},**12c**
R = Ph, **12b** R = C_5H_{11}, **12d**

The reaction of **12a–12d** with periodic acid in dry EtOAc at room temperature gave the corresponding aldehyde derivatives **5a–5d**. The compound **5b** was directly subjected to cycloisomerization by treatment with $Pd(OAc)_2$ (10% mmol), MeOH and maleic anhydride in dry 1,4-dioxan under Argon atmosphere at 10 ^{0}C for 6 h to lead **7b**. The compound **7b** was characterized by using ^{1}H NMR and ^{13}C NMR spectra. The same

procedure was followed for the cycloisomerization of **5a, 5c** and **5d** to give the different derivatives of cyclic sugar alkenyl ethers **7c** and **7d** (Scheme 9).

***Scheme* 9**



R = H, **12a**
R = Ph, **12b**
R = C_6H_{13}, **12c**
R = C_5H_{11}, **12d**

R = H, **5a**
R = Ph, **5b**
R = C_6H_{13}, **5c**
R = C_5H_{11}, **5d**

R = Ph, **7b**
R = C_6H_{13}, **7c**
R = C_5H_{11}, **7d**

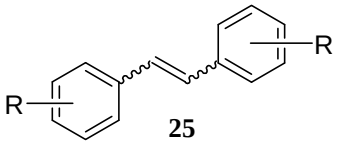
Amongst four alkynals as shown in (Scheme 9), only with the terminal alkynal (compound **5a**), the reaction led to a complex reactions mixture. In all other cases, a diastereomixture of bicyclic derivatives were obtained in moderate to good yields. The exclusive formation of six membered cyclic alkenyl ethers (6-*endo-dig* mode) in each case was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopic data. For example, in the ^{1}H NMR of compound **7b** the characteristic signals of the enolic protons were observed as doublets at 5.73 and 5.79 ppm for major and minor isomers respectively. No traces of the five membered compounds (5-*exo-dig* mode) were observed because of the expected *–I* effect of the furanose ring over the alkyl side chain.

Section 2: Pd catalyzed tandem approach for the formation of trisubstituted sugar olefins

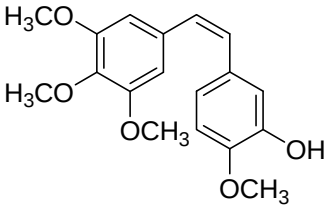
(Three-component Sonogashira type coupling)

Di, tri-and tetrasubstituted olefins especially aryl substituted are an important class of natural products with promising biological activities. A huge number of documented methods available indicate their synthetic and biological importance. Amongst them the series of *cis*- and *trans*-stilbene derivatives (**25**) found importance as an anticancer drugs such as combretastatin A-4 (**26**)[41], resveratrol (**27**)[42] and septicine (**28**)[43]. The molecular simplicity of this class of compounds have attracted the attention of synthetic chemist to design the new routes and such efforts in recent years have been devoted to detailed studies of the structure-activity relationships (SAR) of variously substituted stilbenes.

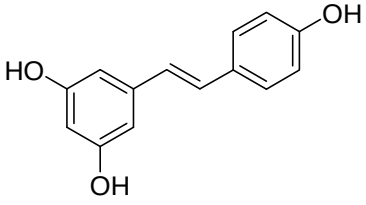
Considering the success we had with Sonogashira reaction on sugar alkynes under mild conditions; we next turned our attention to synthesize the trisubstituted combretastatin analogues (**29**) by a combination of Sonogashira and Suzuki-Miyaura reactions wherein one of the substituent will be sugar furanose.



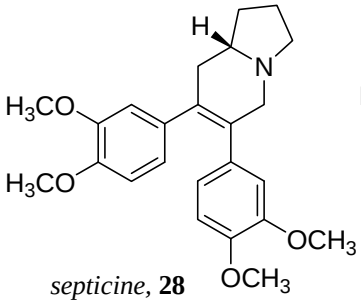
25



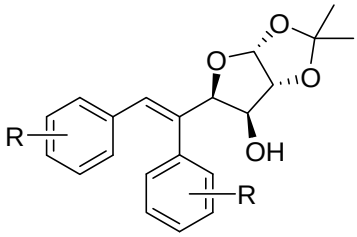
combretastatin A-4, **26**



resveratrol, **27**



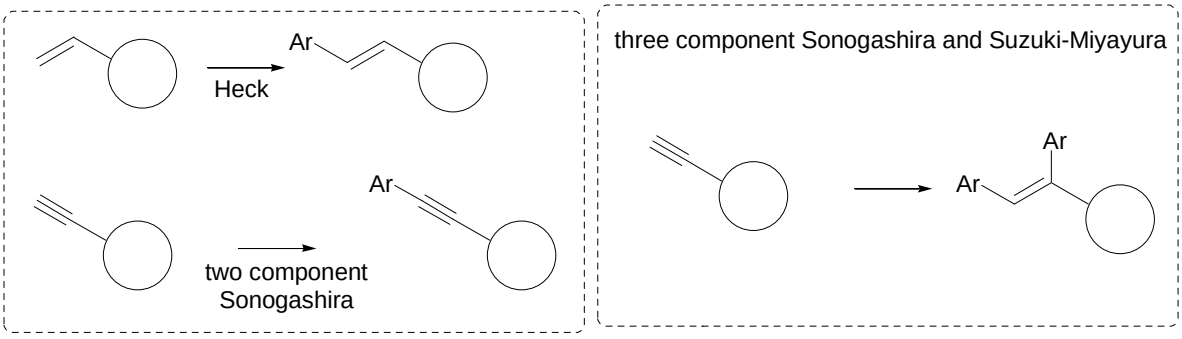
septicine, **28**

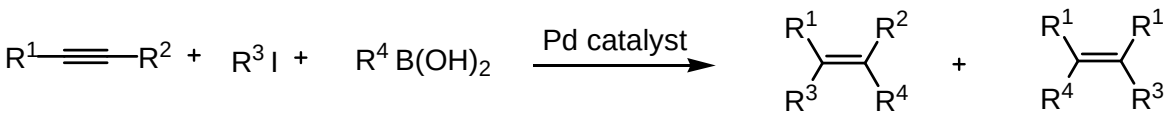


C-Glycosylated Combretastatin analogues, **29**

Though a variety of methods are available for the synthesis of stilbenes however, the regio-and stereoselectivity is the main obstacle in getting the *cis*-olefinated products. Normal Wittig reaction results in the formation of mixture of olefins. Only modified Wittig reagents have been successes in obtaining *Z* olefins with excellent selectivities. The uses of phosphines (Horner reagents) and phosphonates (Wadsworth-Emmons reagents) have proved less successful. Availability of reliable methods to reduce the alkynes selectively resulted in identifying alkyne functionality as a surrogate for olefin.

Coming to the Wittig based approaches for tri- and tetra-substituted olefins the out come of regioselectivity is very poor and often suffer with the difficulties in isolating the *E*/*Z* mixtures. In this regard, once again alkynes were served as valuable surrogates. Recently, Larock *et al.* reported a one-pot three-component approach on simple alkynes to afford tri- and tetrasubstituted alkenes in highly regioselective process[44]. He reported efficient, palladium-catalyzed synthesis of tetrasubstituted olefins involving the intermolecular cross coupling of an aryl iodide, an internal alkyne, and an aryl boronic acid (Equation 3).





…Eq 3**.**

The general mechanism for palladium catalyzed cross-coupling reactions involves three principle steps: 1) oxidative addition, 2) transmetallation, and 3) reductive elimination (Figure 19).

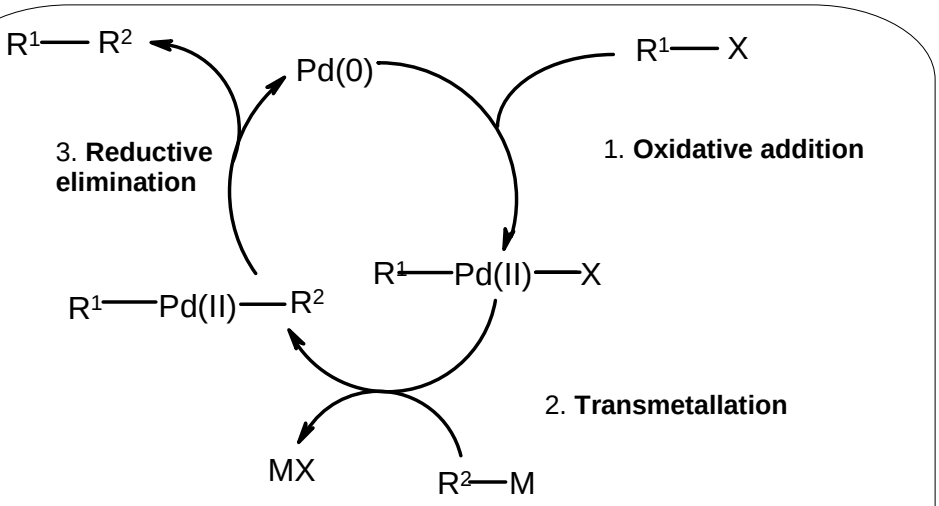


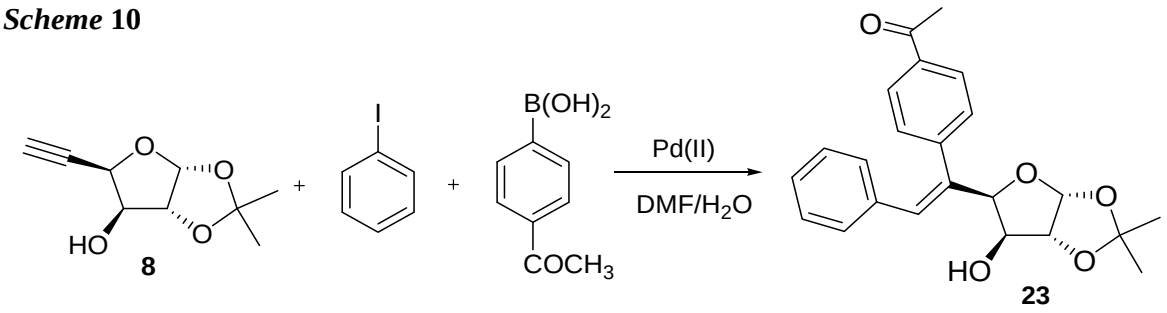
***Figure* 19:** *Catalytic cycle for Pd catalysed cross coupling reactions*

This approach is highly stereoselective but the regioselectivity is not very good. The two-regio isomers have usually been obtained as shown in above equation. The steric as well as electronic effects are responsible for the regioselectivity in case of the simple alkynes. Thus, the aryl group from the aryl iodide generally favors the less hindered end of the alkyne, while the aryl group from the aryl-boronic acid favors the more hindered end of the alkyne. Due to electronic effects aryl group from the aryl boronic acid is more likely to add to the more electron poor end of the alkyne.

Based upon our earlier study of the palladium catalyzed cycloisomerization of sugar alkynols, we anticipated that the regioselectivity on the sugar alkynes due to electron pulling nature of the sugar ring would be better. Initially the alkyne **11** treated with iodobenzene and 4-acetylphenyl boronic acid by using $Pd(CN)_2Cl_2$ in DMF/H_2O (4:1) at

100 °C, to gave the trisubstituted olefin derivative (**30**) in 45% Yield.

***Scheme* 10**



The biphenyl side product was also formed during the reaction. The ^{1}H NMR and ^{13}C NMR spectra, mass spectral data coupled with elemental analysis of the compound **30** were in conformity with the assigned structure. For example, in the ^{1}H NMR spectra of **30,** the aromatic peaks due to monosubstituted phenyl ring containing one extra peak due to the olefin proton, which was observed as a doublet at 6.99 ppm (J = 1.8 Hz). However the regioselectivity of the two different phenyl rings were not known from the above data, but the extensive study of the 2-D spectroscopy solved this problem. The combined study of COSY, NOESY, HSQC and HMBC confirmed the connectivity pattern unambiously. The HMBC spectra showed the three bond coupling between olefinic proton H-C(6) resonating at δ 6.99 with C-4 (δ 83.4), C-8 (δ 129.1) and C-13 (δ 143.2). The position of olefinic carbon established by the observed correlations of the C-6 at δ 129.8 with the H-C(8) (δ 6.95) and H-C(4) (δ 5.0). Other key correlations shown in Figure 20 were in perfect agreement with the assigned structure. The

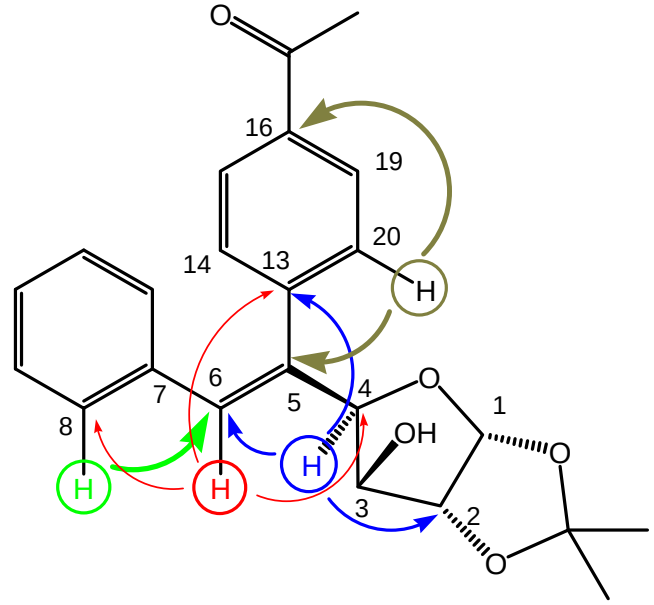


***Figure* 20:** *The key HMBC correlations*

cis pattern of both phenyl rings was also confirmed by using NOESY and COSY spectra. The NOESY spectra showed the strong correlation of H-C(4) with H-C(6), H-C(20) or H-C(14) and at the same time the absence of correlation between H-C(4) with H-C(8) or H-C(12) reinforced our observation.

Following the procedure for compound **30**, using alkyne **11**, iodobenzene in common and 6 different boronic acids, we have successfully made various trisubstituted olefins. In general the intermolecular cross-coupling reaction of an aryl halide, an alkyne & an aryl boronic acid is highly regio- and stereoselective aryl group from the aryl halide adds to the terminal alkyne carbon and the aryl group from the boronic acid to the internal alkyne carbon in cis fashion.

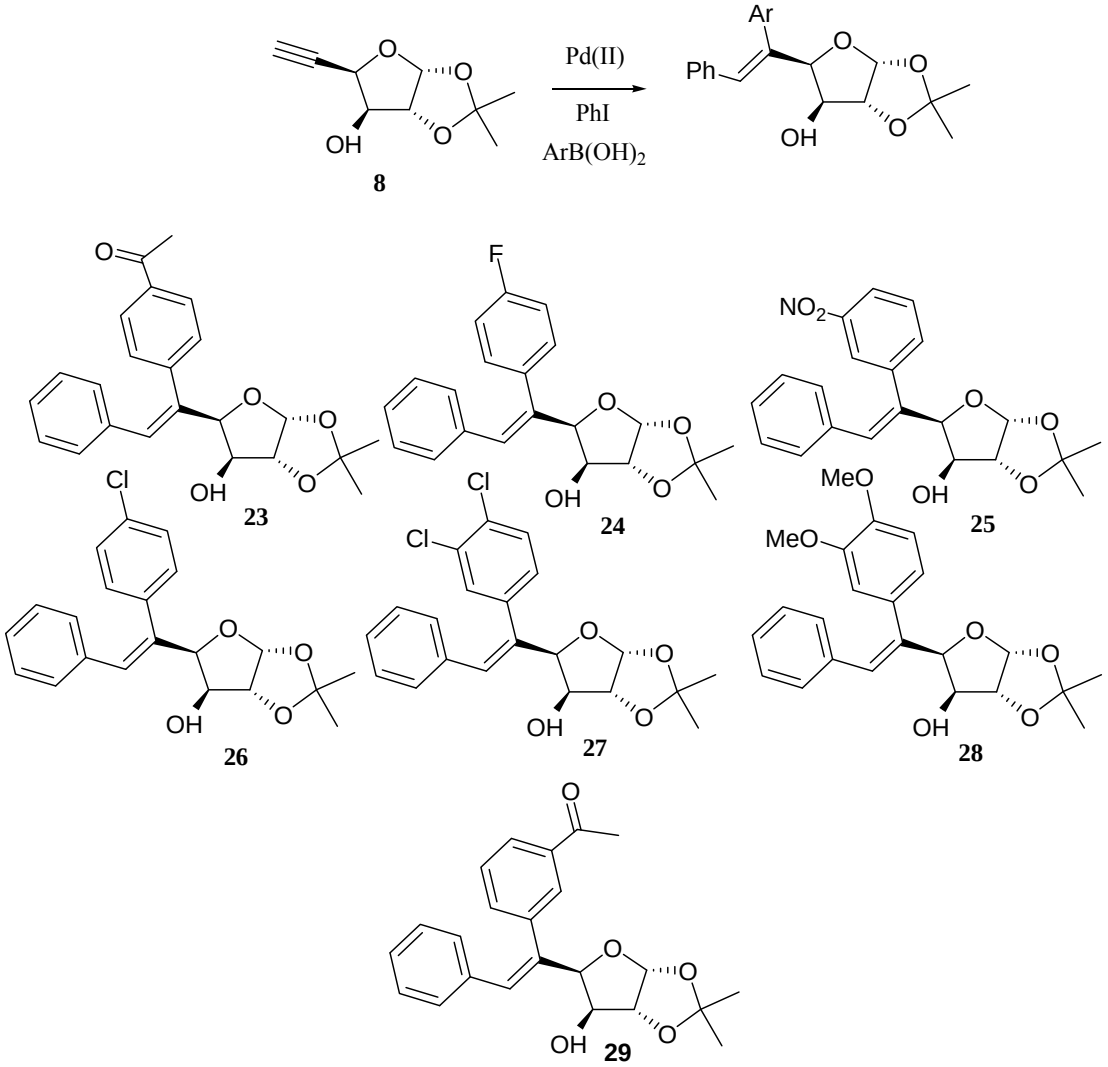
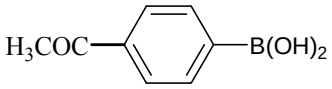
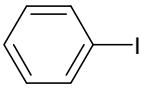
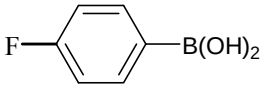
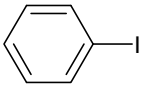
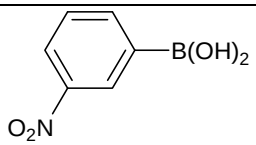
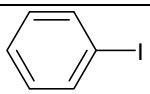
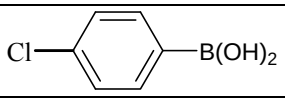
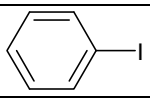
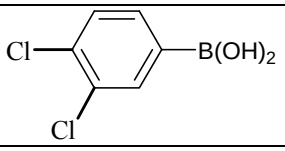
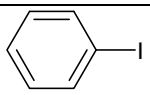
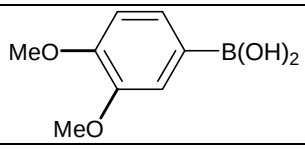
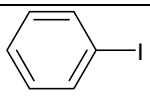
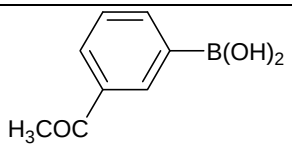
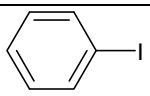
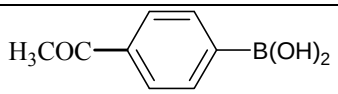
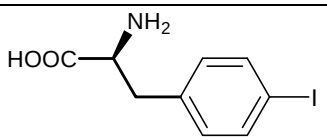
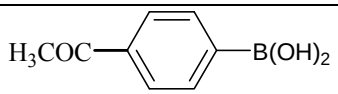
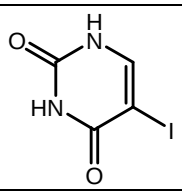


***Figure* 21 :** *Three component coupling reactions with sugar alkyne* **8**

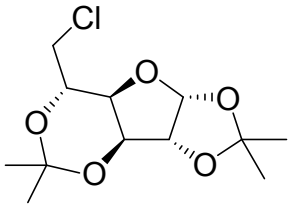
Table 2:

Entry	*Boronic acid*	*Iodides*	*Product*	*Time (h)*	*Yeild (%)*
1			**30**	5	45
2			**31**	4	42
3			**32**	4	40
4			**33**	2	35
5			**34**	3	30
6			**35**	2	43
7			**36**	3	38
8			complex reaction mix.	3	-
9			complex reaction mix.	5	-

In conclusion, we have executed novel Pd-catalyzed reaction on sugar substrates namely: cycloisomerization of sugar alkynals, Sonogashira and a three component Sonigashira-Suzuki-Miyaura reaction to address the synthesis of novel chiral building blocks which resemble structural units of some important natural products. The further elaboration of these compounds in natural product synthesis and screening of some these intermediates for biological activity is under progress.

EXPERIMENTAL

6-Chloro-6-deoxy-1,2:3,5-di-*O*-isopropylidene-α-D-glucofuranose (**16**).



Methanesulphonyl chloride (3.9 mL, 50.0 mmol) was added, with stirring to a solution of **15** (10.0 g, 38.5 mmol) in DMF (50 mL) at room temperature. The reaction mixture was then heated at 90 ^{o}C for 6 h. After completion of the reaction, the dark reddish solution was obtained which was poured in ice-cold water, extracted with CH_2Cl_2 and washed with brine, dried (Na_2SO_4), concentrated and the resulting residue was purified on silica gel using ethyl acetate-light petroleum ether (1:9) to afford chloro derivative **16** as oil.

Yield : 9.1 g, 85%

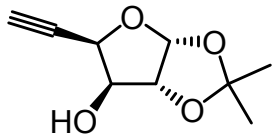
Mol. Formula : $C_{12}H_{19}ClO_5$

^{1}H NMR (200 MHz) : δ 1.25 (s, 3H), 1.30 (s, 3H), 1.31 (s, 3H), 1.41 (s, 3H), 3.51 (dd, 1H, *J* = 12.2, 7.8 Hz), 3.61-3.70 (m, 2H), 4.14 (d, 1H, *J* = 3.9 Hz), 4.25 (dd, 1H, *J* = 6.8, 3.9 Hz), 4.49 (d, 1H, *J* = 3.9 Hz), 5.90 (d, 1H, *J* = 3.9 Hz)

^{13}C NMR (50 MHz) : 23.7, 23.8, 26.5, 27.1, 44.7, 72.1, 74.9, 80.3, 83.8, 101.0, 106.2, 112.1 ppm

ESI MS *m/z* : 263 $[M-15]^{+}$

5,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-ynofuranose (11)[38].



To a solution of chloro-derivative **16** (1.0 g, 3.1 mmol) in dry THF at –78 ^{o}C, *n*-BuLi (5.6 mL, 1.6 M solution in hexane, 9.3 mmol) was added dropwise and stirred at the same temperature for 3 h. After completion, saturated solution of NH_4Cl was added, extracted with EtOAc, washed with brine, dried (Na_2SO_4) and concentrated. The column chromatography of the crude product on silica gel using ethyl acetate-light petroleum ether (1:5) afforded **11** as a white solid.

Yield : 0.15 g, 27%

Mol. Formula : $C_9H_{12}O_4$

^{1}H NMR (200 MHz) : δ 1.24 (s, 3H), 1.42 (s, 3H), 2.65 (d, 1H, *J* = 2.5 Hz), 2.89 (br. s, 1H), 4.14 (d, 1H, *J* = 2.5 Hz), 4.53 (d, 1H, *J* = 3.4 Hz), 4.77 (t, 1H, *J* = 2.5 Hz), 5.90 (d, 1H, *J* = 3.9 Hz)

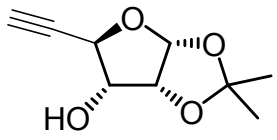
^{13}C NMR (75 MHz) : 25.9, 26.6, 71.9, 75.8, 77.0, 77.5, 84.0, 104.7, 111.9 ppm

ESI MS *m/z* : 169 $[M-15]^+$

Elemental Analysis : Calcd: C, 58.70; H, 6.52%

Found: C, 58.50; H, 6.54%

5,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*ribo*-hex-5-ynofuranose (22)[40].



To a stirred solution of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**19**) (5.0 g, 19.2 mmol) in dry EtOAc (100 mL), H_5IO_6 (5.24 g, 23 mmol), was added at 0 ^oC and stirring was continued for 1 h. The reaction mixture was filtered through Celite, the Celite pad was washed (EtOAc) and the combined filtrate was concentrated. The residue obtained was dissolved in dry CH_2Cl_2 (100 mL) and the solution was cooled to 0 ^oC. The CBr_4 (12.8 g, 38.4 mmol) and TPP (20.0 g, 76.8 mmol) were added and the brown solution was allowed to stir overnight. After completion of the reaction, water was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was successively washed with $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel using ethyl acetate-light petroleum ether (1:9) to give 6,6-Dibromo-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*ribo*-hex-5-enofuranose (**21**) (3.2 g, 49%) as thick oil. To the above residue (3.0 g, 8.72 mmol) in dry THF (50 mL) at –78 °C, was added *n*-BuLi (43.6 mL, 1.6 M solution in hexane, and 69.8 mmol) dropwise and stirred at the same temperature for 2 h. The reaction mixture was neutralized by using AcOH, concentrated, and extracted by using CH_2Cl_2. The combined organic extract was washed with brine, dried (Na_2SO_4), and concentrated. The residue obtained was purified on silica gel using ethyl acetate-light petroleum ether (1:8) to give **22** (1.2 g, 75%) as a viscous liquid.

Yield : 1.2 g, 75%

Mol. Formula : $C_9H_{12}O_4$

^{1}H NMR (200 MHz) : δ 1.37 (s, 3H), 1.57 (s, 3H), 2.54 (d, 1H, *J* = 2.0 Hz), 3.98-4.10 (m, 1H), 4.34 (dd, 1H, *J* = 8.8, 2.0 Hz), 4.59 (t, 1H, *J* = 4.4 Hz), 5.85 (d, 1H, *J* = 4.0 Hz)

ESI MS *m/z* : 169 $[M–15]^+$

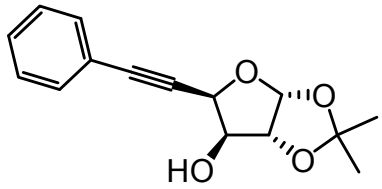
Elemental Analysis Calcd: C, 58.70; H, 6.52%

Found: C, 58.89; H, 6.45%

General procedure for the palladium-catalyzed Sonogashira reaction:

A mixture of **11** (0.3 g, 1.6 mmol), iodobenzene (0.2 mL, 1.6 mmol), $Pd(PPh_3)_4$ (100 mg, 0.08 mmol) in piperidine (5 mL) was stirred at room temperature for 6 h (all reagents were added under aerobic condition). The mixture was cooled, and evaporation of piperidine under reduced pressure on rota vapor gave the crude mixture, which was purified on silica gel using ethyl acetate-light petroleum ether (1:2) to afford **10a** (0.36 g, 85%) as a colorless oil.

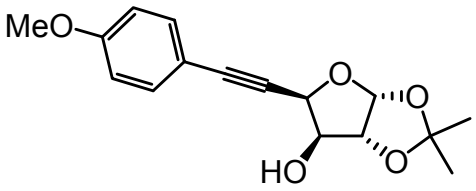
5,6-Dideoxy-1,2-*O*-isopropylidene-6-*C*-phenyl-α-D-*xylo*-hex-5-ynofuranose (10a).



Yield	**:**	85%
Mol. Formula	**:**	$C_{15}H_{16}O_4$
$[\alpha]_D^{25}$	**:**	–31.6 (*c* = 0.5, $CHCl_3$)
^{1}H NMR (200 MHz)	**:**	δ 1.33 (s, 3H), 1.53 (s, 3H), 2.28 (br. s, 1H), 4.25 (d, 1H, *J* = 4.0 Hz), 4.64 (d, 1H, *J* = 4.0 Hz), 5.11 (d, 1H, *J* = 4.0 Hz), 6.01 (d, 1H, *J* = 4.0 Hz), 7.29–7.37 (m, 3H), 7.46–7.51 (m, 2H)
^{13}C NMR (50 MHz)	**:**	26.1, 26.8, 72.9, 76.1, 81.6, 84.0, 89.2, 104.8, 111.8, 121.6, 128.3, 128.9, 131.9, 159.7 ppm
ESI MS *m/z*		260 $[M]^+$
Elemental Analysis		Calcd: C, 69.23; H, 6.15%

Found: C, 68.80; H, 6.80%

5,6-Dideoxy-1,2-*O*-isopropylidene-6-*C*-(4-methoxyphenyl)-α-D-*xylo*-hex-5-ynofuranose (10b).



Yield : 81%

Mol. Formula : $C_{16}H_{18}O_5$

$[\alpha]_D^{25}$: –18.2 (*c* = 1.1, $CHCl_3$)

^{1}H NMR (200 MHz) : δ 1.29 (s, 3H), 1.49 (s, 3H), 2.78 (br. s, 1H), 3.78 (s, 3H), 4.20 (d, 1H, *J* = 2.5 Hz), 4.59 (d, 1H, *J* = 3.9 Hz), 5.04 (d, 1H, *J* = 3.0 Hz), 5.96 (d, 1H, *J* = 3.9 Hz), 6.80 (d, 2H, *J* = 8.7 Hz), 7.38 (d, 2H, *J* = 8.7 Hz)

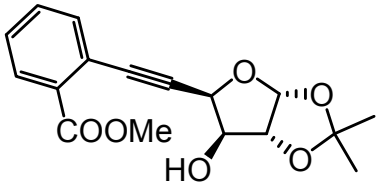
^{13}C NMR (50 MHz) : 25.9, 26.6, 55.1, 72.8, 75.9, 80.2, 84.0, 89.1, 104.6, 111.7, 113.4, 113.8, 113.8, 133.3, 133.3, 159.9 ppm.

ESI MS *m/z* : 290 $[M]^+$

Elemental Analysis Calcd: C, 66.21; H, 6.21%

Found: C, 66.57; H, 6.74%

6-*C*-(2-Carboxymethylphenyl)-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-ynofuranose (10c) .



Yield : 65%

Mol. Formula : $C_{17}H_{18}O_6$

^{1}H NMR (200 MHz) : δ 1.34 (s, 3H), 1.53 (s, 3H), 3.92 (s, 3H), 4.28 (s, 1H), 4.36 (d, 1H, *J* = 2.5 Hz), 4.64 (d, 1H, *J* = 3.4 Hz), 5.06 (d, 1H, *J* = 2.5 Hz), 6.04 (d, 1H, *J* = 3.9 Hz), 7.38–7.64 (m, 3H), 8.00–8.05 (m, 1H)

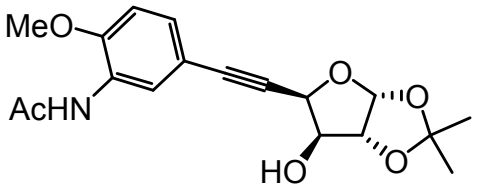
^{13}C NMR (50 MHz) : 27.1, 52.5, 73.6, 77.1, 84.4, 87.3, 88.2, 105.6, 111.9, 123.2, 128.7, 130.7, 132.2, 134.5, 166.2 ppm

ESI MS *m/z* : 318 $[M]^+$

Elemental Analysis Calcd: C, 64.15; H, 5.66%

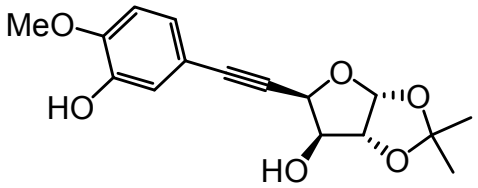
Found: C, 63.98; H, 5.52%

6-*C*-(3-Acetamido-4-methoxyphenyl)-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-ynofuranose (10d).



Yield	**:**	80%
Mol. Formula	**:**	$C_{18}H_{21}NO_6$
$[\alpha]_D^{25}$	**:**	–15.0 (*c* = 2.2, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	**:**	3425, 2233, 1731, 1688, 1585,1530, 1481, 1076, 910, 758 cm^{-1}
^{1}H NMR (200 MHz)	**:**	δ 1.31 (s, 3H), 1.50 (s, 3H), 2.18 (s, 3H), 3.27 (br. s, 1H), 3.86 (s, 3H), 4.23 (d, 1H, *J* = 3.4 Hz), 4.61 (d, 1H, *J* = 3.4 Hz), 5.04 (t, 1H, *J* = 3.0 Hz), 5.97 (d, 1H, *J* = 3.4 Hz), 6.74 (d, 1H, *J* = 8.3 Hz), 7.13 (dd, 1H, *J* = 8.3, 1.5 Hz), 7.77 (s, 1H), 8.38 (d, 1H, *J* = 1.5)
^{13}C NMR (50 MHz)	**:**	24.5, 26.0, 26.7, 55.5, 72.9, 75.9, 80.6, 84.2, 88.6, 104.6, 111.5, 128.3, 128.5, 131.8, 131.8, 132.0, 148.2, 168.1 ppm
ESI MS *m/z*	**:**	370 $[M+Na]^+$
Elemental Analysis		Calcd: C, 62.25; H, 6.05; N, 4.03%
		Found: C, 62.59; H, 5.85; N, 3.63%

5,6-Dideoxy-6-*C*-(3-hydroxy-4-methoxyphenyl)-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-ynofuranose(10e).



Yield : 60%

Mol. Formula : $C_{16}H_{18}O_6$

$[\alpha]_D^{25}$: –9.6 (*c* = 2.0, $CHCl_3$)

^{1}H NMR (200 MHz) : δ 1.33 (s, 3H), 1.52 (s, 3H), 3.88 (s, 3H), 4.23 (d, 1H, *J* = 2.5 Hz), 4.64 (d, 1H, *J* = 3.4 Hz), 5.08 (d, 1H, *J* = 3.0 Hz), 6.01 (d, 1H, *J* = 3.9 Hz), 6.76 (d, 1H, *J* = 8.3 Hz), 6.98 (d, 1H, *J* = 2.0 Hz), 7.03 (s, 1H), 8.0 (s, 1H)

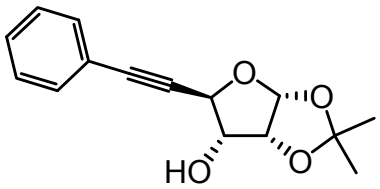
^{13}C NMR (50 MHz) : 26.1, 26.8, 55.9, 73.1, 76.1, 79.9, 84.1, 89.4, 104.9, 111.9, 114.2, 118.0, 124.7, 128.6, 132.0, 148.5 ppm

ESI MS *m/z* : 306 $[M]^+$

Elemental Analysis Calcd: C, 62.75; H, 5.88%

Found: , 62.52; H, 5.97%

5,6-Dideoxy-1,2-*O*-isopropylidene-6-*C*-phenyl-α-D-*ribo*-hex-5-ynofuranose (23).



Yield : 71%

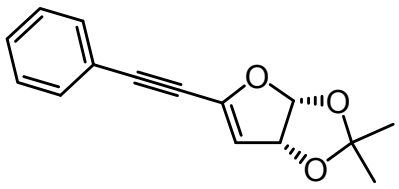
Mol. Formula : $C_{15}H_{16}O_4$

^{1}H NMR (200 MHz) : δ 1.39 (s, 3H), 1.60 (s, 3H), 2.68 (br. s, 1H), 4.16 (m, 1H), 4.60-4.67 (m, 2H), 5.91 (d, 1H, *J* = 3.9 Hz), 7.30–7.36 (m, 3H), 7.46-7.50 (m, 2H)

Elemental Analysis Calcd: C, 69.23; H, 6.15%

Found: C, 68.73; H, 6.34%

2,2-Dimethyl-5-phenylethynyl-6a*H*-furo[2,3-d][1,3]dioxole (18).



A mixture of compound **10a** (0.1 g, 0.4 mmol), imidazole (0.08 g, 1.2 mmol), Ph_3P (0.3 g, 1.2 mmol) and I_2 (0.2 g, 0.8 mmol) in toluene (10 mL) was stirred initially at room temperature and then refluxed for 3 h. The reaction mixture was cooled, an equal volume of saturated $NaHCO_3$ solution was added, and stirred for 10 min. I_2 was added in portion until the organic phase remained violet. It was then again stirred for an additional 15 min., and the excess I_2 was destroyed by the addition of $Na_2S_2O_3$. The mixture was diluted with toluene and the organic phase was washed with H_2O, brine, dried (Na_2SO_4) and concentrated. The purification of the crude residue on silica gel using ethyl acetate-light petroleum ether (1:9) affords **18** as colorless oil.

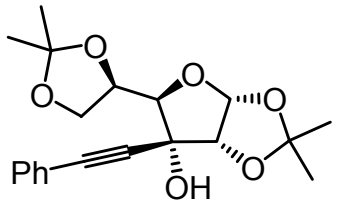
Yield : 0.08 g, 86%

Mol. Formula : $C_{15}H_{14}O_3$

^{1}H NMR (200 MHz) : δ 1.47 (s, 3H), 1.53 (s, 3H), 5.37 (dd, 1H, *J* = 5.4, 2.5 Hz), 5.56 (d, 1H, *J* = 2.5 Hz), 6.10 (d, 1H, *J* = 5.4 Hz), 7.31–7.39 (m, 3H), 7.48–7.53 (m, 2H)

Elemental Analysis : Calcd: C, 74.38; H, 5.79%
Found: C, 75.10; H, 6.19%

1,2:5,6-Di-*O*-isopropylidene-3-*C*-(phenyl acetylene)-α-D-*allo*furanose (12b).



To a solution of phenylacetylene (1.27 mL, 11.63 mmol) in dry THF at –78 ^{o}C, *n*-BuLi (14.55 mL, 1.6 M solution in hexane, 23.26 mmol) was added dropwise and stirred at the same temperature for 1 h. Then the solution **19** (3.0 g, 11.63 mmol) in THF was added and stirring was continued for 10 min. Saturated solution of NH_4Cl was then added, diluted with EtOAc, washed with brine, dried (Na_2SO_4) and concentrated. The crude product was purified on silica gel using ethyl acetate-light petroleum ether (1:8) afforded **12b** as a white solid.

Yield : 3.2 g, 76%

Mol. Formula : $C_{20}H_{24}O_6$

M. P. : 131 ^{o}C

$[\alpha]_D^{25}$: –8.43 (*c* = 0.4, $CHCl_3$)

^{1}H NMR (400 MHz) : δ 1.40 (s, 6H), 1.48 (s, 3H), 1.63 (s, 3H), 3.16 (m, 1H), 3.95 (d, 1H, *J* = 7.3 Hz), 4.05-4.21 (m, 2H), 4.45-4.54 (m, 1H), 4.70 (d, 1H, *J* = 3.4 Hz), 5.87 (d, 1H, *J* = 3.4 Hz), 7.29-7.41 (m, 3H), 7.43-7.48 (m, 2H)

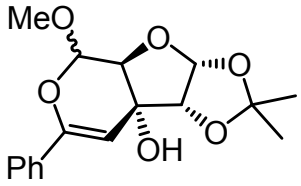
^{13}C NMR (50 MHz) : 25.2, 26.7, 66.8, 74.9, 76.2, 81.4, 84.1, 85.6, 88.5, 104.1, 109.5, 113.6, 121.6, 128.3, 128.3, 129.0, 131.8, 131.8 ppm

+TOF MS *m/z* : 361 $[M+H]^+$, 383 $[M+ Na]^+$

Elemental Analysis Calcd: C, 66.67; H, 6.67%

Found: C, 67.19; H, 6.26%

(3a*S*)-2,3-*O*-Isopropylidene-7-methoxy-5-phenyl-3,3a,7,7a-tetrahydro-2*H*-furo[2,3-c]pyran-3a-ol (7b).



H_5IO_6 (2.27 g, 9.99 mmol) was added to a solution of **12b** (3.0 g, 8.33 mmol) in dry EtOAc (100 mL) at ambient temperature and stirring was continued for 2 h. The reaction mixture was filtered, the filter cake was washed (EtOAc) and the combined filtrate was evaporated. The aldehyde thus obtained was directly used in the next step without further purification. To the compound **5b** (2.1 g, 7.29 mmol) in dry 1,4-dioxan was added $Pd(OAc)_2$ (0.16 g, 10% mmol), MeOH (0.6 mL, 14.6 mmol) and maleic anhydride (0.74 g, 7.29 mmol) under Argon atmosphere. The resulting reaction mixture was allowed to stir at 10 ^{0}C for 2 h and then at room temperature for further 4 h. The solvent was evaporated the

residue thus obtained was purified on silica gel using ethyl acetate-light petroleum ether (1:7) to give **7b** as a diastereomeric mixture (3:2).

Yield : 0.63 g, 27 %

Mol. Formula : $C_{17}H_{20}O_6$

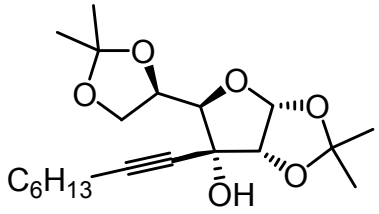
^{1}H NMR (200 MHz) : δ 1.39 (s, 3H), 1.62 (s, 1.2H), 1.64 (s, 1.8H), 2.05 (s, 0.4H), 2.18 (s, 0.6H), 3.56 (s, 1.6H), 3.78 (s, 1.4H), 4.11 (t, 0.6H, *J* = 1.5 Hz), 4.28 (t, 0.4H, *J* = 2.0 Hz), 4.36 (dd, 1H, *J* = 5.4, 3.4 Hz), 4.94 (s, 0.4H), 5.24 (d, 0.6H, *J* = 1.5 Hz), 5.36 (d, 0.4H, *J* = 2.0 Hz), 5.40 (d, 0.6H, *J* = 2.0 Hz), 5.73 (d, 0.6H, *J* = 3.4 Hz), 5.79 (d, 0.4H, *J* = 4.0 Hz), 7.34-7.39 (m, 3H), 7.62-7.68 (m, 2H)

^{13}C NMR (50 MHz) : 26.8, 26.9, 27.1, 27.2, 57.1, 57.7, 72.1, 75.7, 77.6, 78.8, 83.0, 84.2, 95.5, 96.1, 97.6, 99.0, 104.3, 104.9, 113.3, 113.5, 125.1, 125.1, 125.2, 125.2, 128.2, 128.2, 129.2, 129.3, 133.7, 134.1, 150.1, 153.0 ppm

Elemental Analysis Calcd: C, 63.75; H, 6.25%

Found: C, 63.46; H, 6.33%

1,2:5,6-Di-*O*-isopropylidene-3-*C*-(oct-1-ynyl)-α-D-*allo*furanose (12c).



To a solution of diisopropylamine (0.6 mL, 4.26 mmol) in dry THF (5 mL) at –78 ^{o}C, *n*-BuLi (2.42 mL, 1.6 M solution in hexane, 3.88 mmol) was added dropwise and stirred for 30 min. Then the solution of 1-octyne (0.6 mL, 3.88 mmol) in THF was added to the reaction mixture and stirred for 1 h followed by the addition of **19** (1.0 g, 3.88 mmol) in THF and stirring was continued at –78 ^{o}C for 15 min. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl solution. It was allowed to reach room temperature and diluted with EtOAc, washed with brine, dried (Na_2SO_4) and concentrated. The crude product was purified on silica gel using ethyl acetate-light petroleum ether (1:8) afforded **12c** as light yellow syrup.

Yield : 1.2 g, 83%

Mol. Formula : $C_{20}H_{32}O_6$

^{1}H NMR (200 MHz) : δ 0.89 (t, 3H, *J* = 6.8 Hz), 1.26-1.63 (m, 8H, overlapped), 1.36 (s, 6H), 1.45 (s, 3H), 1.59 (s, 3H), 2.25 (t, 2H, *J* = 6.8 Hz), 2.92 (br. s, 1H), 3.83 (d, 1H, *J* = 7.3 Hz), 3.98-4.15 (m, 2H), 4.33-4.42 (m, 1H), 4.53 (d, 1H, *J* = 3.4 Hz), 5.76 (d, 1H, *J* = 3.4 Hz)

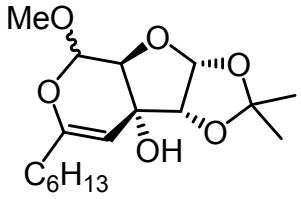
^{13}C NMR (50 MHz) : 13.3, 18.0, 21.8, 24.6, 26.0, 27.8, 30.6, 65.9, 74.2, 74.9, 76.8, 80.9, 83.8, 88.7, 103.4, 108.5, 112.6 ppm

ESI MS *m/z* : 353 $[M–15]^{+}$

Elemental Analysis Calcd: C, 65.22; H, 8.82%

Found: C, 65.31; H, 8.66%

(3a*S*)-5-Hexyl-2,3-*O*-isopropylidene-7-methoxy-3,3a,7,7a-tetrahydro-2*H*-furo[2,3-c]pyran-3a-ol (7c).



H_5IO_6 (0.9 g, 3.91 mmol) was added to a solution of **12c** (1.2 g, 3.26 mmol) in dry EtOAc (20 mL) at ambient temperature, and stirring was continued for 2 h. The mixture was filtered, the filter cake was washed (EtOAc), and the combined filtrate was evaporated. The aldehyde thus obtained was used as such for the next step without further purification. To a stirred solution of **5c** (0.82 g, 2.77 mmol), MeOH (0.24 mL, 5.54 mmol) and maleic anhydride (0.27 g, 2.77 mmol) in dry 1,4-dioxan, under Argon atmosphere, was added $Pd(OAc)_2$ (0.06 g, 10 mol%) and stirring was continued at 10 ^oC for 2 h and then for another 6 h at room temperature. The reaction mixture was concentrated and the residue thus obtained was purified on silica gel using ethyl acetate-light petroleum ether (1:6) to give **7c** as a diastereomeric mixture (4:1).

Yield : 0.17 g, 19%

Mol. Formula : $C_{17}H_{28}O_6$

^{1}H NMR (200 MHz) : δ 0.9 (t, 3H, *J* = 7.3 Hz), 1.25-1.35 (m, 8H), 1.37 (s, 3H), 1.61 (s, 3H), 2.01-2.18 (m, 2H), 2.77 (s, 0.8H), 2.91 (s, 0.2 H), 3.50 (s, 2.4H), 3.65 (s, 0.6H), 3.97 (m, 0.2H), 4.14 (t, 0.8H, *J* = 2.4 Hz), 4.21 (m, 0.2H), 4.22 (d, 0.8H, *J* = 3.7 Hz), 4.44 (m, 0.2H), 4.59 (d, 0.8H, *J* = 1.5 Hz), 4.71 (m, 0.2H), 5.11 (d, 0. 8H, *J* = 2.2 Hz), 5.67 (d, 0.8H, *J* = 3.0 Hz), 5.74 (d, 0.2H, *J* = 3.7 Hz)

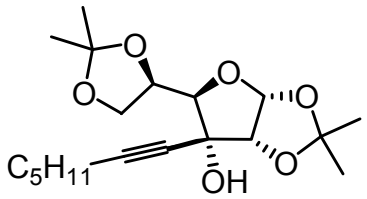
^{13}C NMR (50 MHz) : 14.1, 22.6, 26.6, 26.7, 26.9, 27.0, 27.2, 27.3, 28.7, 28.8, 29.8, 31.7, 33.8, 34.2, 55.8, 57.4, 71.8, 75.4, 76.9, 78.7,

83.3, 84.6, 95.2, 97.1, 97.5, 98.6, 104.4, 105.0, 113.3, 113.4, 154.5, 157.5 ppm

Elemental Analysis Calcd: C, 62.20; H, 8.54%

Found: C, 62.43; H, 8.26%

1,2:5,6-Di-*O*-isopropylidene-3-*C*-(hept-1-ynyl)-α-D-*allo*furanose (12d).



To a solution 1-heptyne (0.60 mL, 4.65 mmol) in dry THF was added *n*-BuLi (1.6 M in hexane, 2.42 mL, 3.88 mmol) at –78 ^{0}C and the reaction mixture was stirred for 1 h at the same temperature. Then a solution of **19** (1.0 g, 3.88 mmol) in THF was added and stirring was continued for another 10 min. A saturated solution of NH_4Cl was then added, diluted with EtOAc, washed with brine, dried (Na_2SO_4) and concentrated. The crude product was purified on silica gel using ethyl acetate-light petroleum ether (1:7) to give **12d** as a colorless liquid.

Yield **:** 1.2 g, 83%

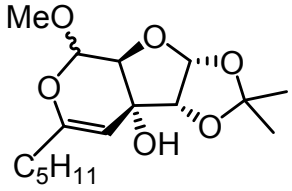
Mol. Formula **:** $C_{19}H_{30}O_6$

$[\alpha]_D^{25}$ **:** 5.72 (*c* = 2.2, $CHCl_3$)

^{1}H NMR (200 MHz) δ 0.90 (t, 3H, *J* = 6.8 Hz), 1.24-1.36 (m, 12H), 1.45 (s, 3H), 1.59 (s, 3H), 2.25 (t, 2H, *J* = 6.8 Hz), 2.96 (s, 1H), 3.83 (d, 1H, *J* = 7.8 Hz), 3.97-4.15 (m, 2H), 4.33-4.42 (m, 1H), 4.52 (d, 1H, *J* = 3.4 Hz), 5.77 (d, 1H, *J* = 3.9 Hz)

^{13}C NMR (125 MHz)	13.6, 18.4, 21.8, 25.0, 26.4, 26.4, 26.4, 26.5, 27.8, 30.7, 66.5, 74.6, 75.5, 81.2, 84.2, 89.3, 103.8, 108.9, 113.1 ppm
+TOF MS *m/z*	355 $[M+H]^+$, 377 $[M+Na]^+$
Elemental Analysis	Calcd: C, 64.41; H, 8.47%
	Found: C, 64.72; H, 8.80%

(3a*S*)-2,3-*O*-isopropylidene-7-methoxy-5-pentyl-3,3a,7,7a-tetrahydro-2*H*-furo[2,3-c]pyran-3a-ol (7d).



H_5IO_6 (0.85 g, 3.70 mmol) was added to a solution of **12d** (1.0 g, 3.09 mmol) in dry EtOAc (20 mL) at ambient temperature, and stirring was continued for 2 h. The mixture was filtered, the filter cake was washed (EtOAc), and the combined filtrate was evaporated. The aldehyde thus obtained was directly used in the next step without further purification. To a stirred solution of **5d** (0.64 g, 2.27 mmol), MeOH (0.2 mL, 4.54 mmol) and maleic anhydride (0.22 g, 2.27 mmol) in dry 1,4-dioxan, under Argon atmosphere, was added $Pd(OAc)_2$ (0.05 g, 10 mol%) and stirring was continued at 10 ^oC for 2 h and then for another 6 h at room temperature. The reaction mixture was concentrated the residue thus obtained was purified on silica gel using ethyl acetate-light petroleum ether (1:6) to give **7d** as a diastereomeric mixture (3:1).

Yield	**:**	0.27 g, 31%
Mol. Formula	**:**	$C_{16}H_{26}O_6$
^{1}H NMR (200 MHz)	**:**	δ 0.86-0.92 (m, 3H), 1.27-1.63 (m, 6H, Overlapped), 1.36

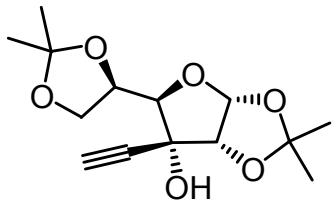
(s, 3H), 1.58 (s, 2H), 1.60 (s, 1H), 2.04-2.15 (m, 2H), 2.79 (s, 0.35H), 2.93 (s, 0.65H), 3.49 (s, 1H), 3.65 (m, 2H), 3.97 (t, 0.65H, *J* = 1.4 Hz), 4.14 (t, 0.35H, *J* = 2.0 Hz), 4.20-4.24 (m, 1H), 4.43 (d, 0.65H, *J* = 1.5 Hz), 4.59 (d, 0.35H, *J* = 1.5 Hz), 4.71 (m, 0.65H), 5.10 (d, 0.35H, *J* = 1.5 Hz), 5.67 (d, 0.35H, *J* = 4.0 Hz), 5.74 (d, 0.65H, *J* = 3.5 Hz)

^{13}C NMR (125 MHz**)** **:** 13.8, 21.2, 26.0, 26.1, 26.6, 26.7, 26.9, 27.0, 30.9, 31.0, 33.4, 33.9, 56.5, 57.1, 71.5, 75.1, 76.6, 78.4, 83.0, 84.3, 95.0, 96.8, 97.2, 98.3, 104.1, 104.6, 113.0, 113.1, 154.1, 157.0 ppm.

Elemental Analysis Calcd: C, 61.15; H, 8.28%

Found: C, 61.75; H, 7.87%

3-*C*-Acytelene-1,2:5,6-di-*O*-isopropylidene-α-D-*allo*furanose (12a) .



A 50 mL three necked R.B flask was charged with magnesium turnings (0.40 g, 16.30 mmol) and dry THF (10 mL). The mixture was heated to reflux temperature under N_2 atmosphere, and a crystal of iodine was added. The 1-chlorobutane (1.3 g, 13.58 mmol) was added to the boiling THF mixture and heated the mixture until all the magnesium has been consumed (0.5-1 h). The purified acetylene gas was slowly introduced to the reaction

mixture for 1 h. A solution **19** (1.0 g, 3.88 mmol) in THF was added dropwise and stirring was continued for another 1h. A saturated aqueous NH_4Cl solution was added, extracted with EtOAc, washed with 1N HCl, brine, dried (Na_2SO_4) and concentrated. The residue obtained was purified on silica gel using ethyl acetate-light petroleum ether (1:5) to afford **12a** as a colorless solid.

Yield : 0.89 g, 73%

Mol. Formula : $C_{14}H_{20}O_6$

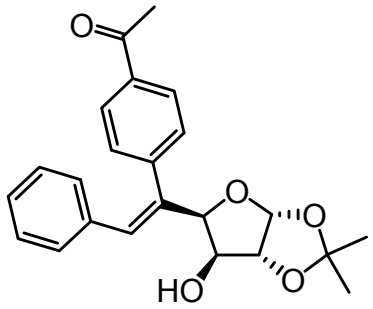
M. P. : 72-75 ^oC

^{1}H NMR (300 MHz) : δ 1.37 (s, 6H), 1.42 (s, 3H), 1.60 (s, 3H), 2.65 (s, 1H), 3.06 (s, 1H), 3.83 (d, 1H, *J* = 8.1 Hz), 4.02 (dd, 1H, *J* = 8.8, 4.4 Hz), 4.13 (dd, 1H, *J* = 8.8, 6.6 Hz), 4.38-4.44 (m, 1H), 4.60 (d, 1H, *J* = 3.7 Hz), 5.79 (d, 1H, *J* = 3.7 Hz)

General procedure for the palladium-catalyzed formation of trisubstituted olefins:

DMF (8 mL), H_2O (2 mL), $KHCO_3$ (0.75 mmol), the ArI (0.50 mmol), the boronic acid (0.75 mmol), and the alkyne (0.25 mmol) were stirred and heated at 100 °C for 10 min. The $PdCl_2(PhCN)_2$ catalyst (2.5 μmol, in 0.1 mL of DMF) was added. The reaction mixture was then heated at 100 °C until palladium black appeared (usually in 3-24 h). After completion, the reaction mixture was cooled, quenched with brine (30 mL) and the aqueous layer was extracted with diethyl ether. The combined organic layer was dried (Na_2SO_4) and concentrated. The product was isolated by silica gel column chromatography.

5-*C*-(4-Acetylphenyl)-5,6-dideoxy-6-*C*-phenyl-1,2-O-isopropylidene-α-D-*xylo*-5-en-hexofuranoside (30).



Yield	**:**	45%
Mol. Formula	**:**	$C_{23}H_{24}O_5$
M. P.	**:**	109 °C
$[\alpha]_D^{25}$	**:**	–27.99 (*c* = 2.1, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	**:**	3382, 1678, 1601, 1264, 1163, 1073,1011, 958, 925, 668 cm^{-1}
^{1}H NMR (400 MHz)	**:**	δ 1.33 (s, 3H), 1.51 (s, 3H), 1.85 (d, 1H, *J* = 4.8 Hz), 2.60 (s, 3H), 3.95 (dd, 1H, *J* = 4.3, 2.8 Hz), 4.62 (d, 1H, *J* = 3.5 Hz), 5.03 (t, 1H, *J* = 2.3 Hz), 6.06 (d, 1H, *J* = 3.8 Hz), 6.95

(dd, 2H, *J* = 7.5, 2.3 Hz), 6.99 (d, 1H, *J* = 1.8 Hz), 7.09–7.33 (m, 3H), 7.33 (d, 2H, *J* = 8.3 Hz), 7.93 (d, 2H, *J* = 8.3 Hz)

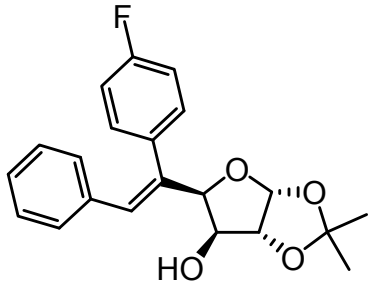
^{13}C NMR (100 MHz) : 26.2, 26.6, 26.8, 74.0, 77.2, 83.4, 84.7, 104.6, 112.0, 127.4, 128.1, 129.1, 129.2, 129.3, 129.8, 134.2, 135.4, 136.6, 143.2, 197.6 ppm.

+TOF MS *m/z* : 403 $[M+Na]^+$

Elemental Analysis Calcd: C, 72.61; H, 6.36%

Found: C, 72.80; H, 7.03%

5-*C*-(4-Flurophenyl)-5,6-dideoxy-6-*C*-phenyl-1,2-O-isopropylidene-α-D-*xylo*-5-en-hexofuranoside (31).



Yield : 42%

Mol. Formula : $C_{21}H_{21}FO_4$

$[\alpha]_D^{25}$: –35.9 (*c* = 0.6, $CHCl_3$)

^{1}H NMR (200 MHz) : δ 1.27 (s, 3H), 1.36 (s, 3H), 1.98-2.34 (m, 1H), 4.18 (dd, 1H, *J* = 3.9, 2.7 Hz), 4.45 (d, 1H, *J* = 3.9 Hz), 5.42 (d, 1H, *J* = 2.5 Hz), 5.94 (d, 1H, *J* = 3.8 Hz), 6.87 (s, 1H), 7.30–

7.38 (m, 7H), 7.56-7.61 (m, 2H)

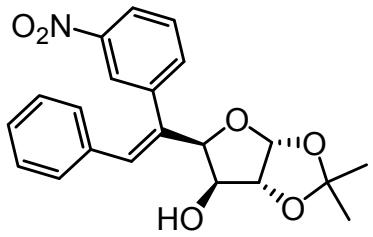
^{13}C NMR (100 MHz) : 26.3, 26.6, 78.2, 78.6, 84.9, 104.3, 111.6, 127.5, 127.8, 128.3, 128.3, 128.9, 135.7, 136.4, 136.6 ppm

+TOF MS *m/z* : 379 $[M+Na]^+$

Elemental Analysis Calcd: C, 70.79; H, 5.90%

Found: C, 70.83; H, 6.17%

5-*C*-(3-Nitrophenyl)-5,6-dideoxy-6-*C*-phenyl-1,2-*O*-isopropylidene-α-D-*xylo*-5-en-hexofuranoside (32).



Yield : 40%

Mol. Formula : $C_{21}H_{21}NO_6$

$[\alpha]_D^{25}$: –61.4 (*c* = 1.3, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3414, 1720, 1531, 1472, 1351, 1075, 1018, 668 cm^{-1}

^{1}H NMR (200 MHz) : δ 1.33 (s, 3H), 1.52 (s, 3H), 1.85 (d, 1H, *J* = 4.8 Hz), 3.97 (s, 1H), 4.62 (d, 1H, *J* =3.7 Hz), 5.01 (t, 1H, *J* = 2.3 Hz), 6.06 (d, 1H, *J* = 3.7 Hz), 6.88-6.93 (m, 2H), 7.04 (d, 1H, *J* = 1.6 Hz), 7.09-7.13 (m, 3H), 7.46-7.57 (m, 2H), 8.12-8.21 (m, 2H)

^{13}C NMR (50 MHz) : 26.1, 26.8, 29.7, 74.1, 83.1, 84.7, 104.5, 112.1, 122.9,

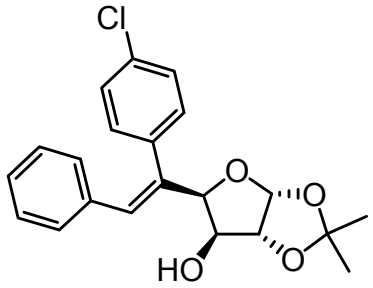
124.0, 127.6, 128.3, 128.7, 129.3, 130.0, 130.6, 133.1, 135.0, 139.8, 218.4 ppm.

+TOF MS *m/z* **:** 406 $[M+Na]^+$

Elemental Analysis Calcd: C, 65.80; H, 5.48%

Found: C, 65.95; H, 4.87%

5-*C*-(4-Chlorophenyl)-5,6-dideoxy-6-*C*-phenyl-1,2-*O*-isopropylidene-α-D-*xylo*-5-en-hexofuranoside (33).



Yield **:** 35%

Mol. Formula **:** $C_{21}H_{21}ClO_4$

$[\alpha]_D^{25}$ **:** –42.9 (*c* = 1, $CHCl_3$)

^{1}H NMR (500 MHz) **:** δ 1.33 (s, 3H), 1.51 (s, 3H), 1.84 (br. s, 1H), 3.96 (d, 1H, *J* = 1.8 Hz), 4.61 (d, 1H, *J* = 3.7 Hz), 4.99 (s, 1H), 6.05 (d, 1H, *J* = 3.0 Hz), 6.95 (s, 1H), 6.97 (m, 2H), 7.11-7.13 (m, 3H), 7.16 (d, 2H, *J* = 8.3 Hz), 7.32 (d, 2H, *J* = 8.3 Hz)

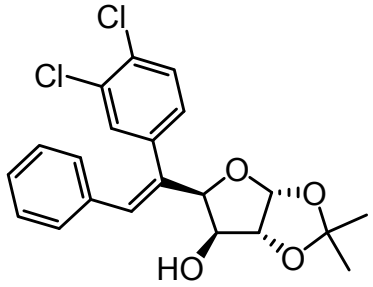
^{13}C NMR (125 MHz) **:** 26.2, 26.8, 74.0, 83.6, 84.7, 104.6, 112.0, 127.3, 128.1, 129.2, 129.3, 129.4, 129.5, 130.2, 130.5, 134.0, 135.6, 136.4 ppm.

+TOF MS *m/z* **:** 395 $[M+Na]^+$

Elemental Analysis Calcd: C, 67.74; H, 5.65%

Found: C, 68.13; H, 6.34%

5-*C*-(3,4-Dichlorophenyl)-5,6-dideoxy-6-*C*-phenyl-1,2-*O*-isopropylidene-α-D-*xylo*-5-en-hexofuranoside (34).



Yield **:** 30%

Mol. Formula **:** $C_{21}H_{20}Cl_2O_4$

M. P. **:** 162 °C

$[\alpha]_D^{25}$ **:** –26.8 (*c* = 0.8, $CHCl_3$)

IR ($CHCl_3$) $\tilde{\nu}$ **:** 3443, 1650, 1548, 1472, 1385, 1376, 1215, 1092, 910, 698 cm^{-1}

^{1}H NMR (200 MHz) **:** δ 1.34 (s, 3H), 1.53 (s, 3H), 1.83 (br. s, 1H), 3.99 (s, 1H), 4.63 (d, 1H, *J* = 3.7 Hz), 4.97 (t, 1H, *J* = 2.3 Hz), 6.07 (d, 1H, *J* = 3.8 Hz), 6.95-7.00 (m, 2H), 7.07 (dd, 1H, *J* = 8.2, 2.0 Hz), 7.12–7.22 (m, 3H), 7.35-7.44 (m, 3H)

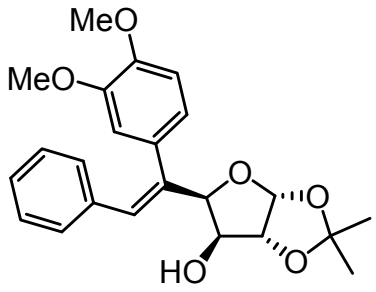
^{13}C NMR (100 MHz) **:** 26.1, 26.7, 74.0, 83.2, 84.6, 104.5, 112.0, 127.6, 128.2, 128.5, 129.3, 130.0, 131.1, 132.2, 132.7, 133.2, 135.1, 138.0 ppm.

ESI MS *m/z* **:** 408 $[M+H]^+$

Elemental Analysis Calcd: C, 62.07; H, 4.93%

Found: C, 62.32; H, 5.13%

5,6-Dideoxy-5-*C*-(3,4-dimethoxyphenyl)-1,2-*O*-isopropylidene-6-*C*-phenyl-α-D-*xylo*-hex-5-enofuranoside (35).



Yield : 43%

Mol. Formula : $C_{23}H_{26}O_6$

^{1}H NMR (200 MHz) : δ 1.34 (s, 3H), 1.52 (s, 3H), 1.63 (br. s, 1H), 3.72 (s, 3H), 380-3.88 (m, 1H), 3.89 (s, 3H), 4.00 (d, 1H, *J* = 2.4 Hz), 4.63 (d, 1H, *J* = 3.7 Hz), 5.04 (t, 1H, *J* = 2.0 Hz), 6.07 (d, 1H, *J* = 3.8 Hz), 6.69-6.90 (m, 3H), 6.98-7.05 (m, 2H), 7.08-7.16 (m, 3H)

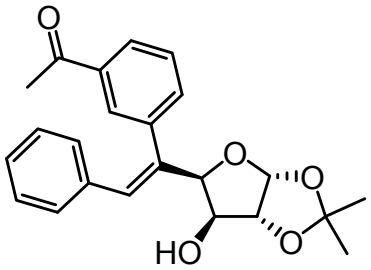
^{13}C NMR (125 MHz) : 26.2, 26.8, 55.85, 55.88, 73.9, 83.9, 84.6, 104.6, 111.7, 111.9, 112.0, 120.8, 127.1, 128.0, 128.8, 129.3, 130.2, 134.7, 136.0, 148.8, 149.3 ppm

ESI MS *m/z* : 399 $[M+H]^+$

Elemental Analysis Calcd: C, 69.35; H, 6.53%

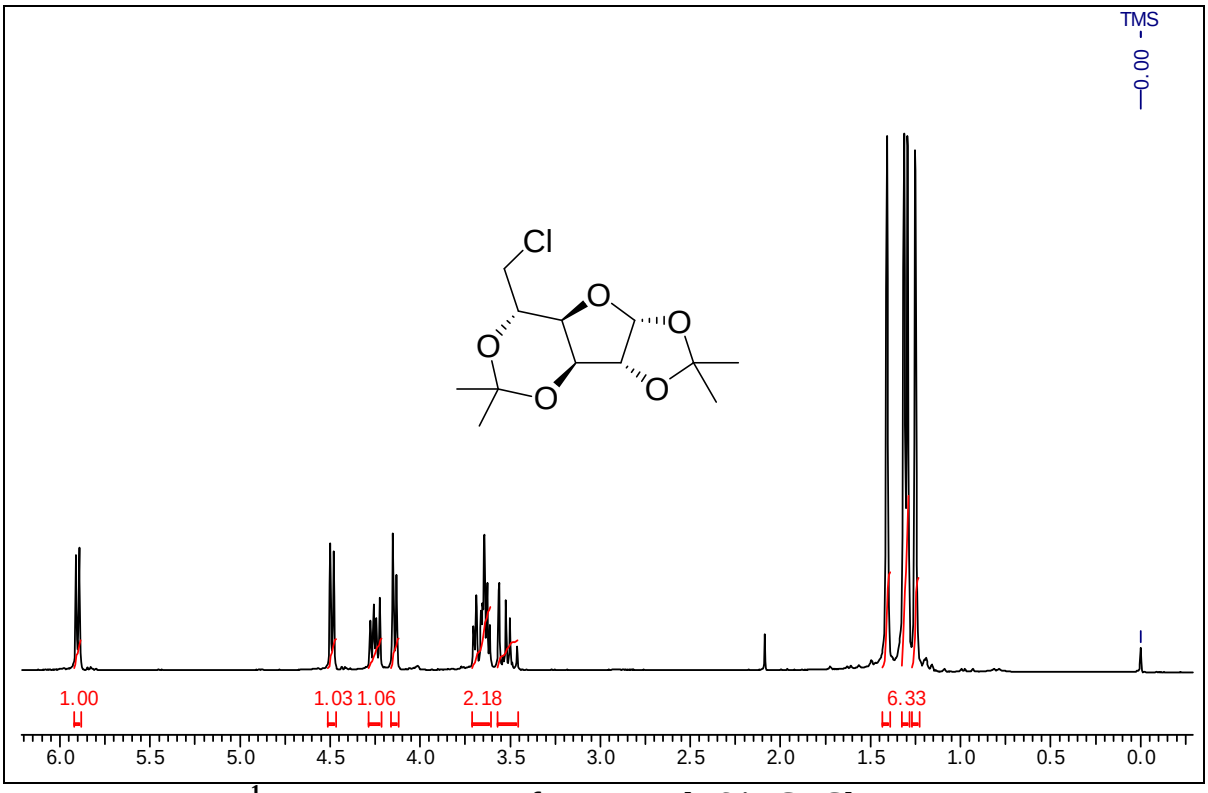
Found: C, 69.65; H, 6.96%

5-*C*-(3-Acetylphenyl)-5,6-dideoxy-6-*C*-phenyl-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranoside (36).

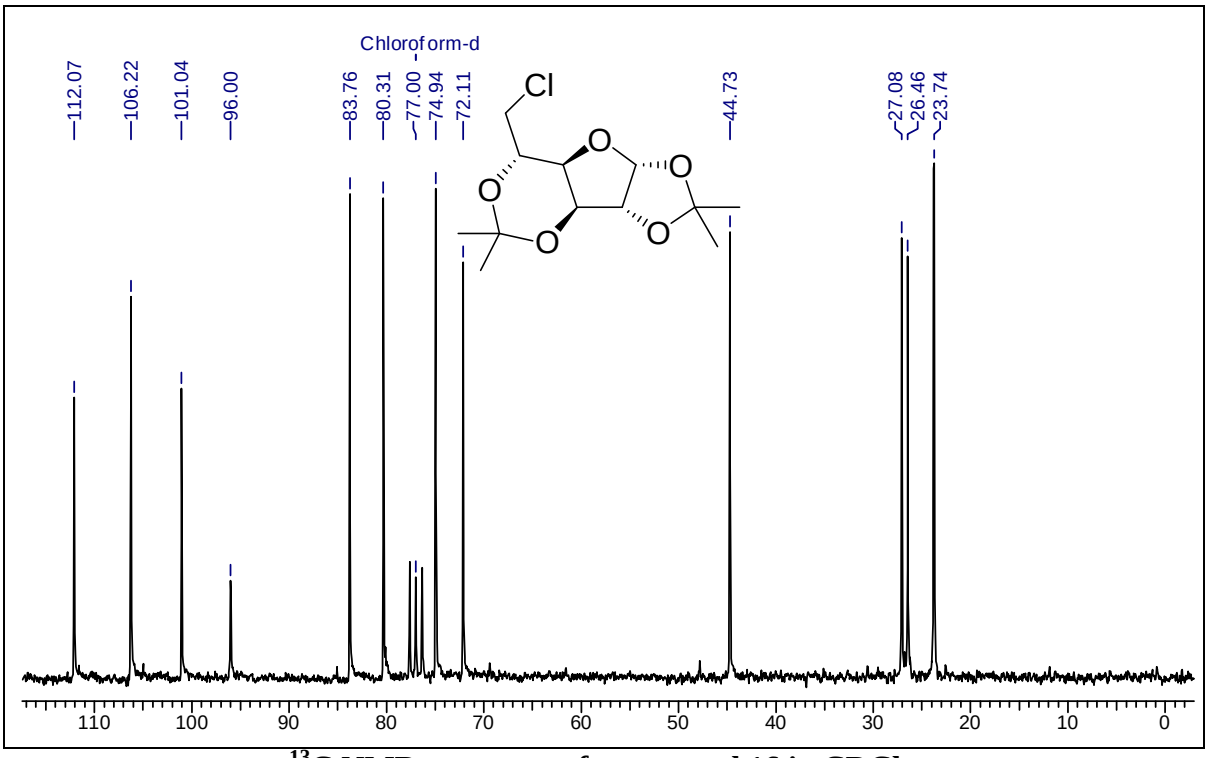


Yield	**:**	38%
Mol. Formula	**:**	$C_{23}H_{24}O_5$
$[\alpha]_D^{25}$	**:**	–32.4 (*c* = 2.6, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	**:**	3410, 1683, 1424, 1385, 1376, 1075, 1019, 929, 668 cm^{-1}
^{1}H NMR (200 MHz)	**:**	δ 1.33 (s, 3H), 1.52 (s, 3H), 1.97 (br. s, 1H), 2.52 (s, 3H), 3.98 (s, 1H), 4.63 (d, 1H, *J* = 3.7 Hz), 5.04 (t, 1H, *J* = 2.3 Hz), 6.08 (d, 1H, *J* = 3.7 Hz), 6.91-6.96 (m, 2H), 7.00 (d, 1H, *J* = 1.4 Hz), 7.08–7.11 (m, 3H), 7.42-7.45 (m, 2H), 7.82 (m, 1H), 7.88-7.94 (m, 1H)
^{13}C NMR (50 MHz)	**:**	26.1, 26.6, 26.7, 73.9, 83.5, 84.6, 104.5, 112.0, 127.3, 127.8, 128.1, 128.1, 128.8, 129.3, 129.3, 129.4, 129.6, 133.6, 134.2, 135.5, 137.8, 138.5, 197.8 ppm
+TOF MS *m/z*	**:**	403 $[M+Na]^+$
Elemental Analysis.		Calcd: C, 72.61; H, 6.36%
		Found: C, 72.80; H, 6.17%

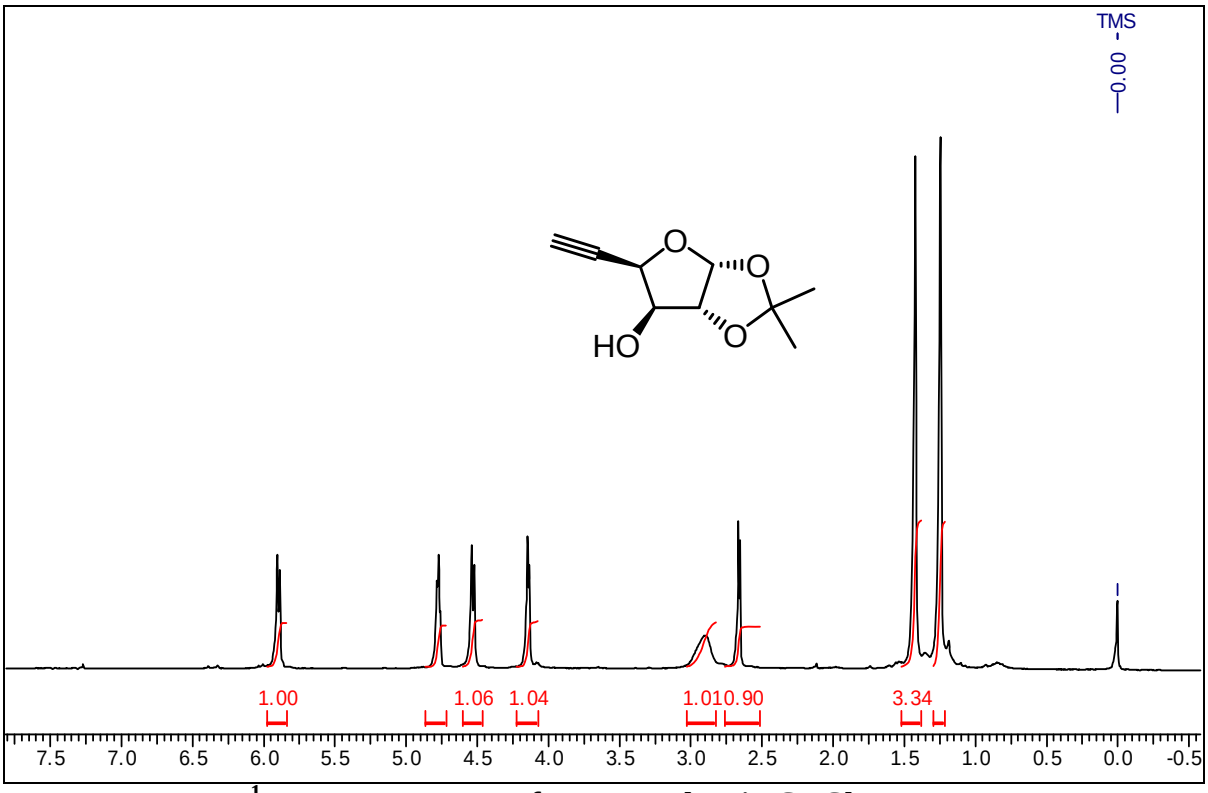
SPECTRA



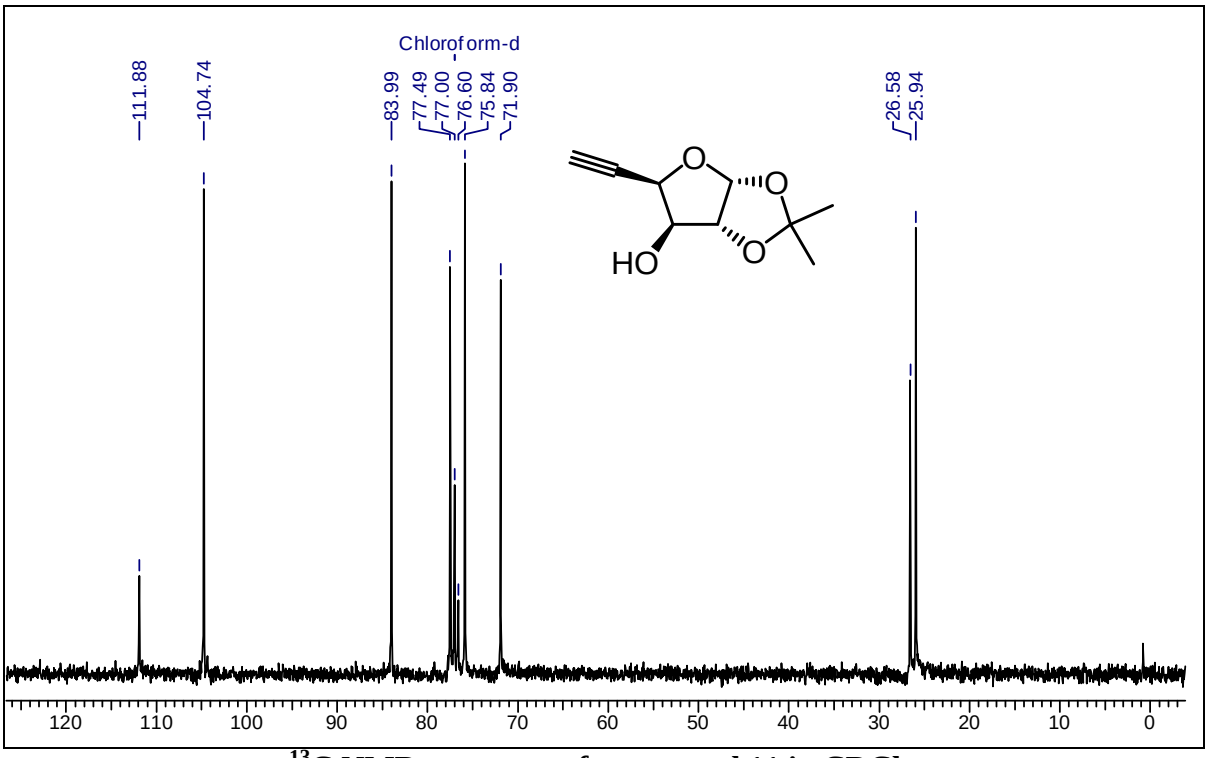
^{1}H NMR spectrum of compound 16 in $CDCl_3$



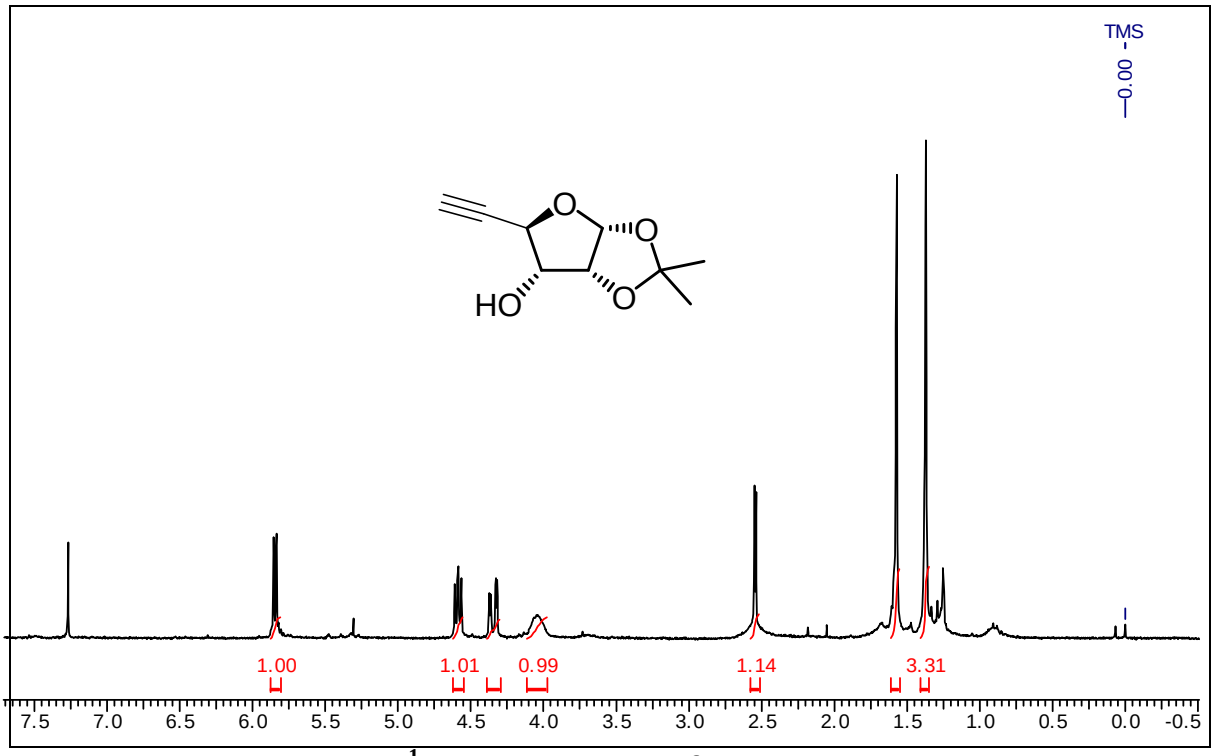
^{13}C NMR spectrum of compound 16 in $CDCl_3$



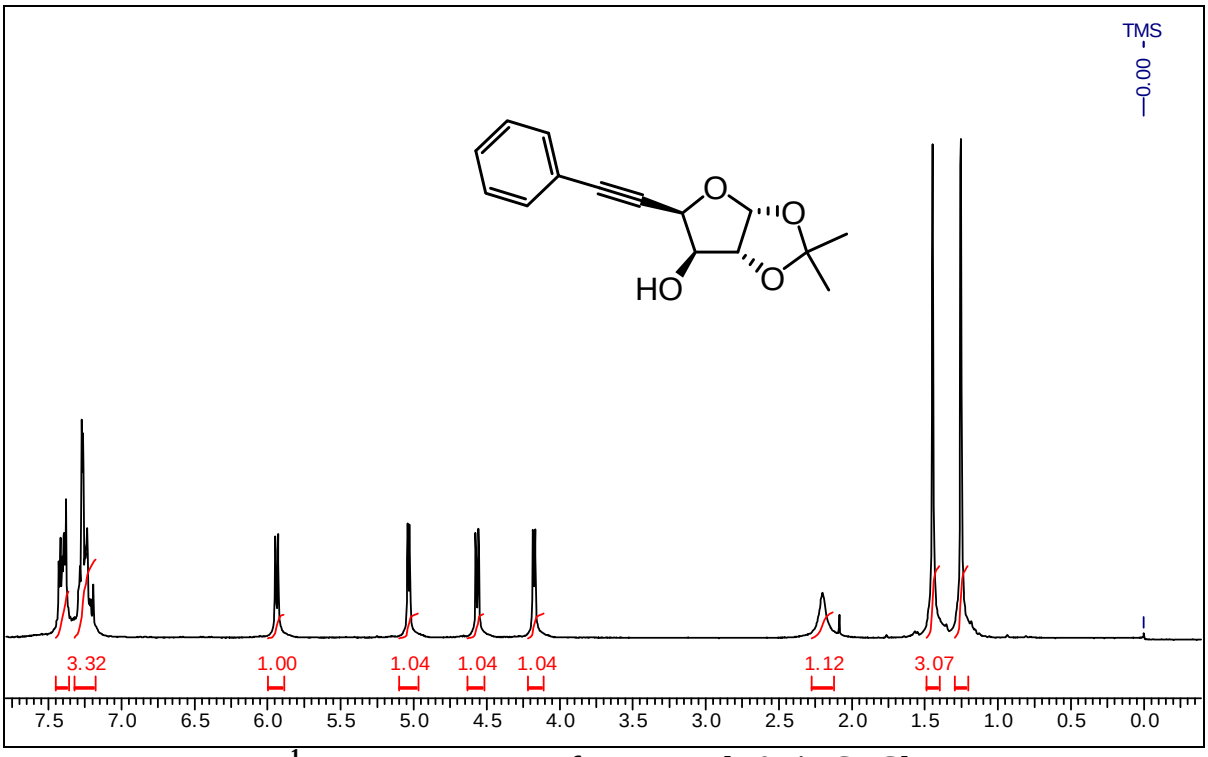
^{1}H NMR spectrum of compound 11 in $CDCl_3$



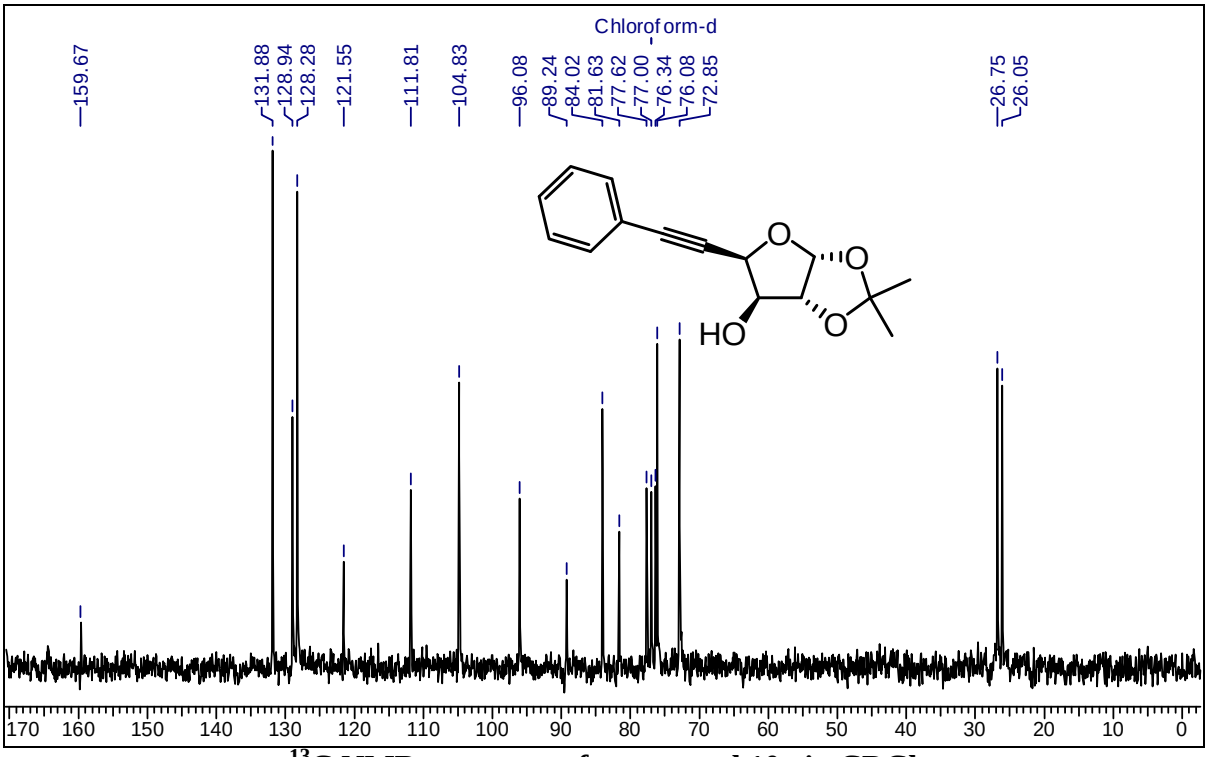
^{13}C NMR spectrum of compound 11 in $CDCl_3$



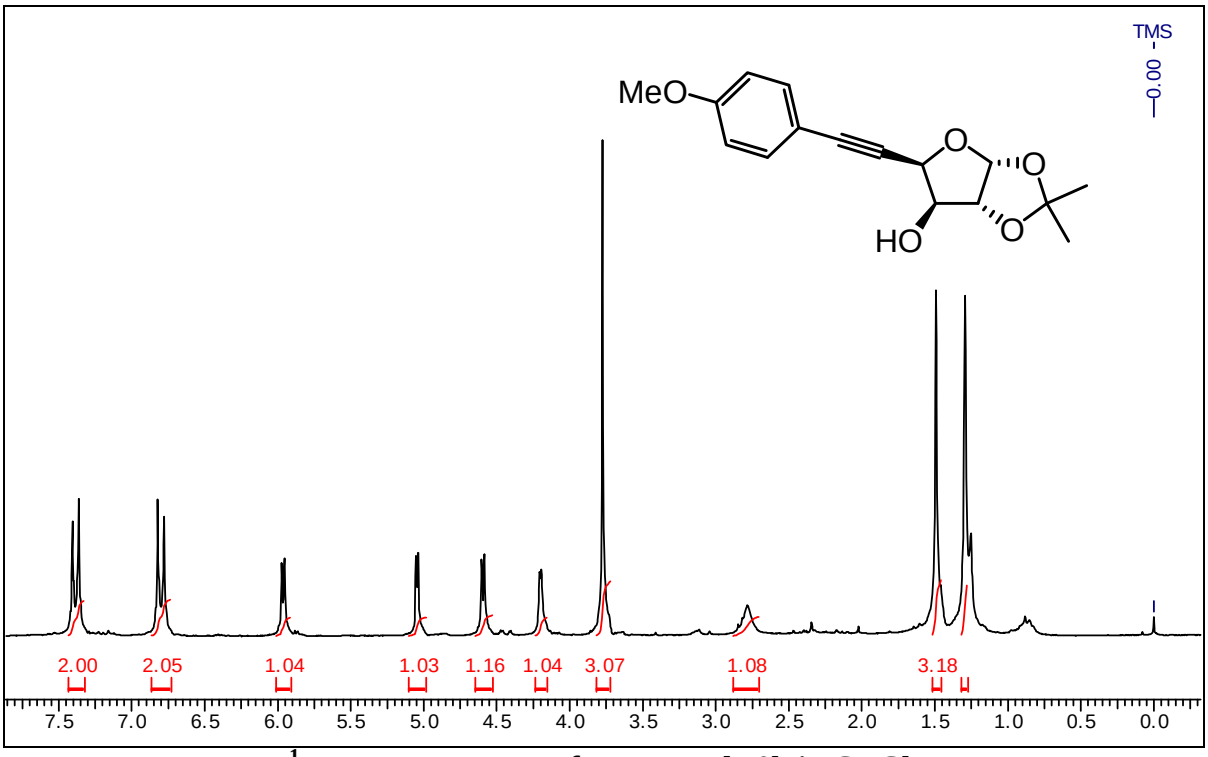
^{1}H NMR spectrum of compound 22 in $CDCl_3$



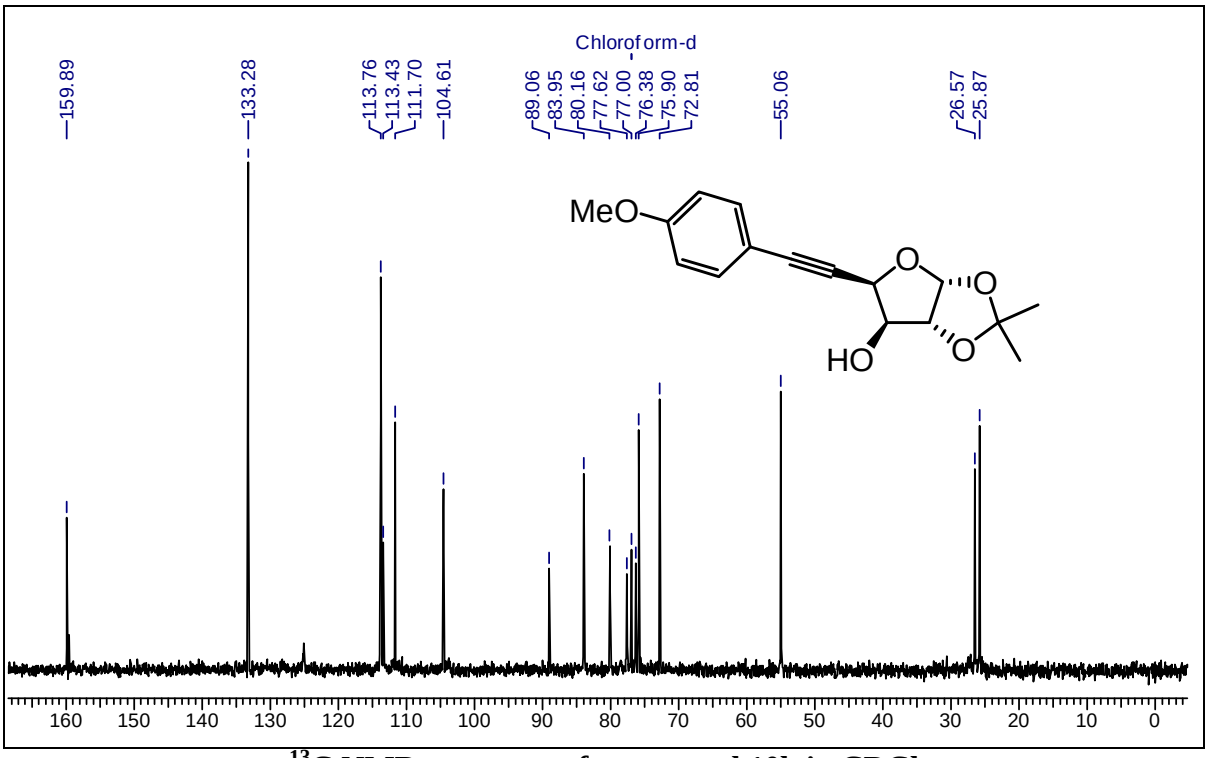
^{1}H NMR spectrum of compound 10a in $CDCl_3$



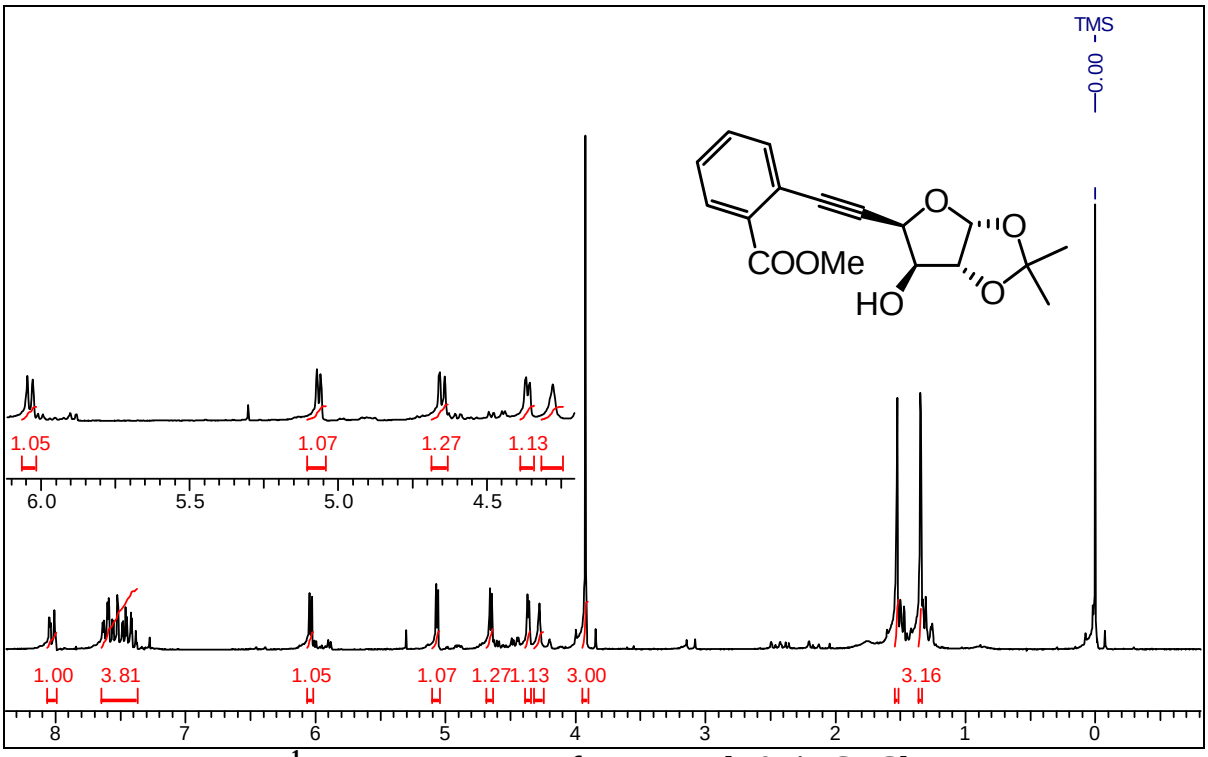
^{13}C NMR spectrum of compound 10a in $CDCl_3$



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



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



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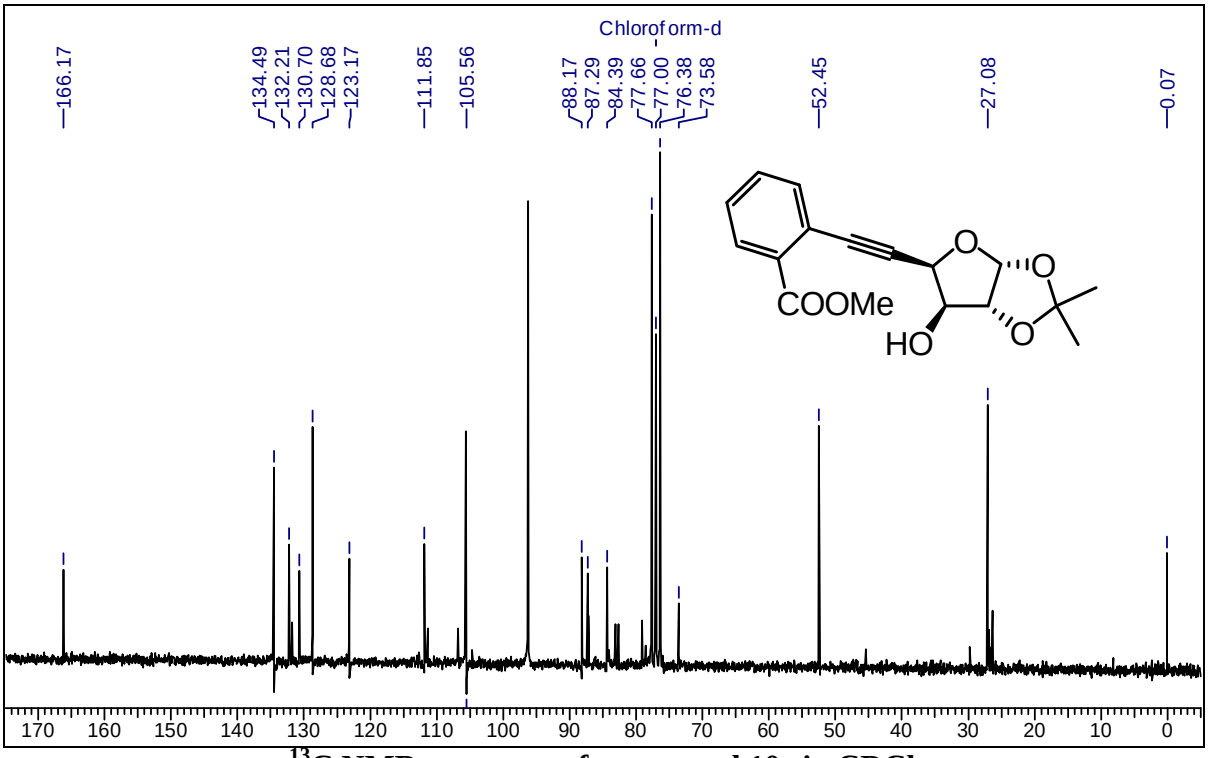
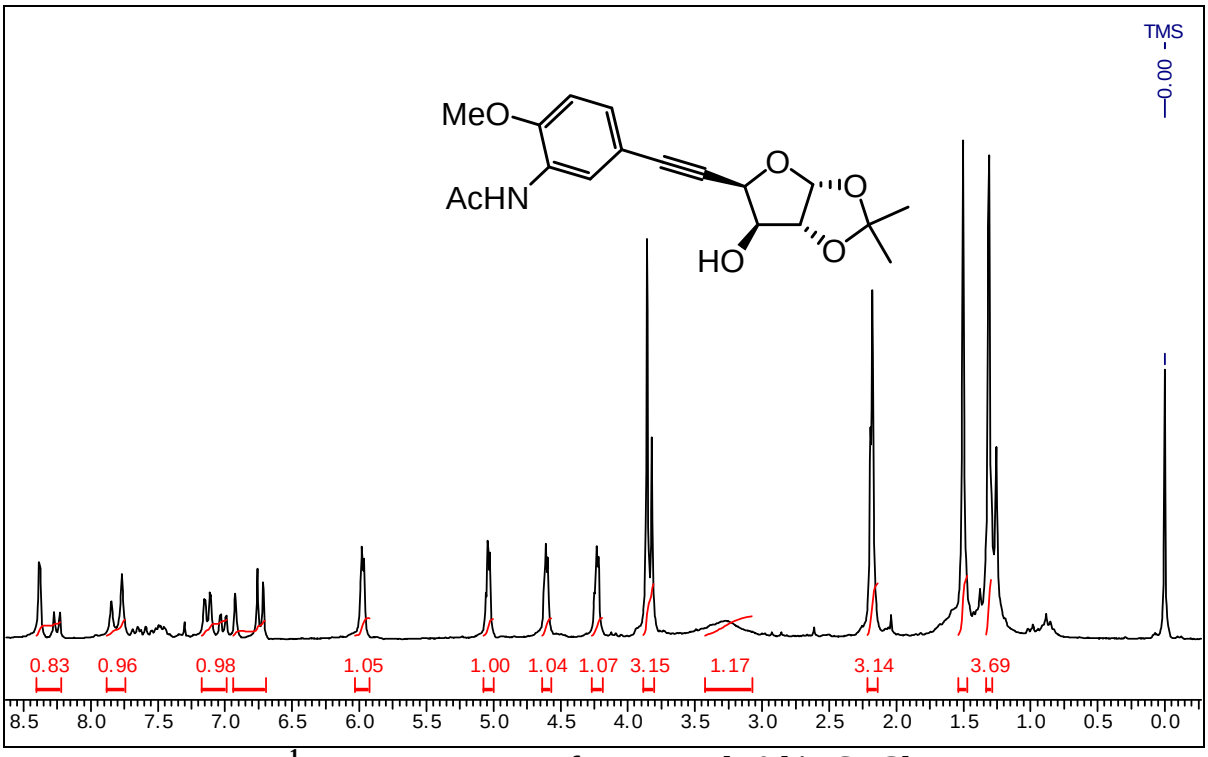
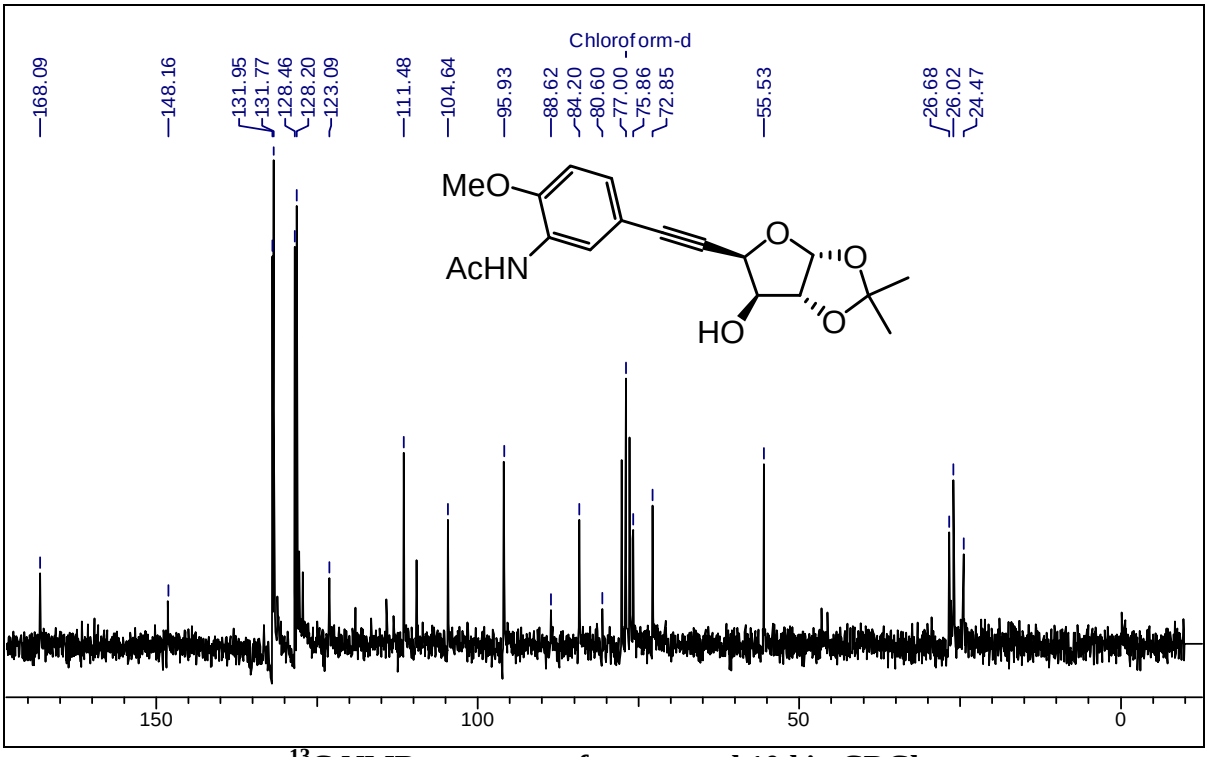


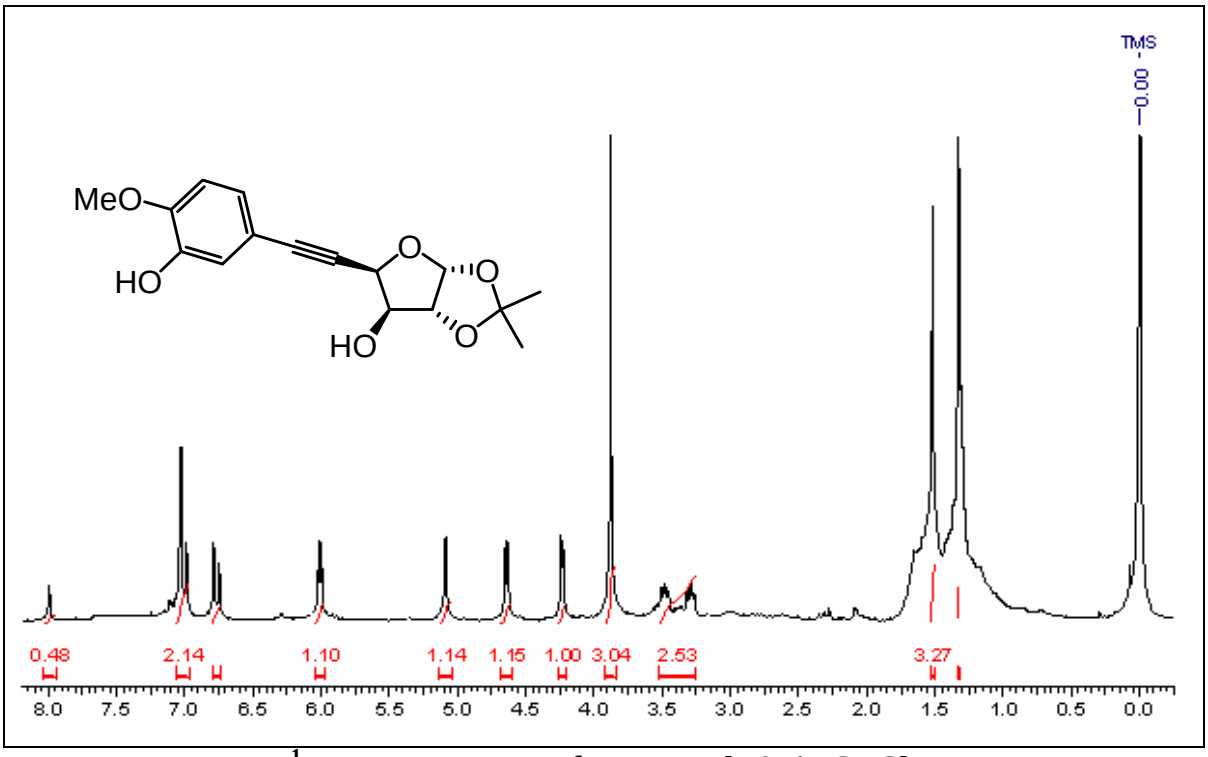
^{13}C NMR spectrum of compound 10c in $CDCl_3$



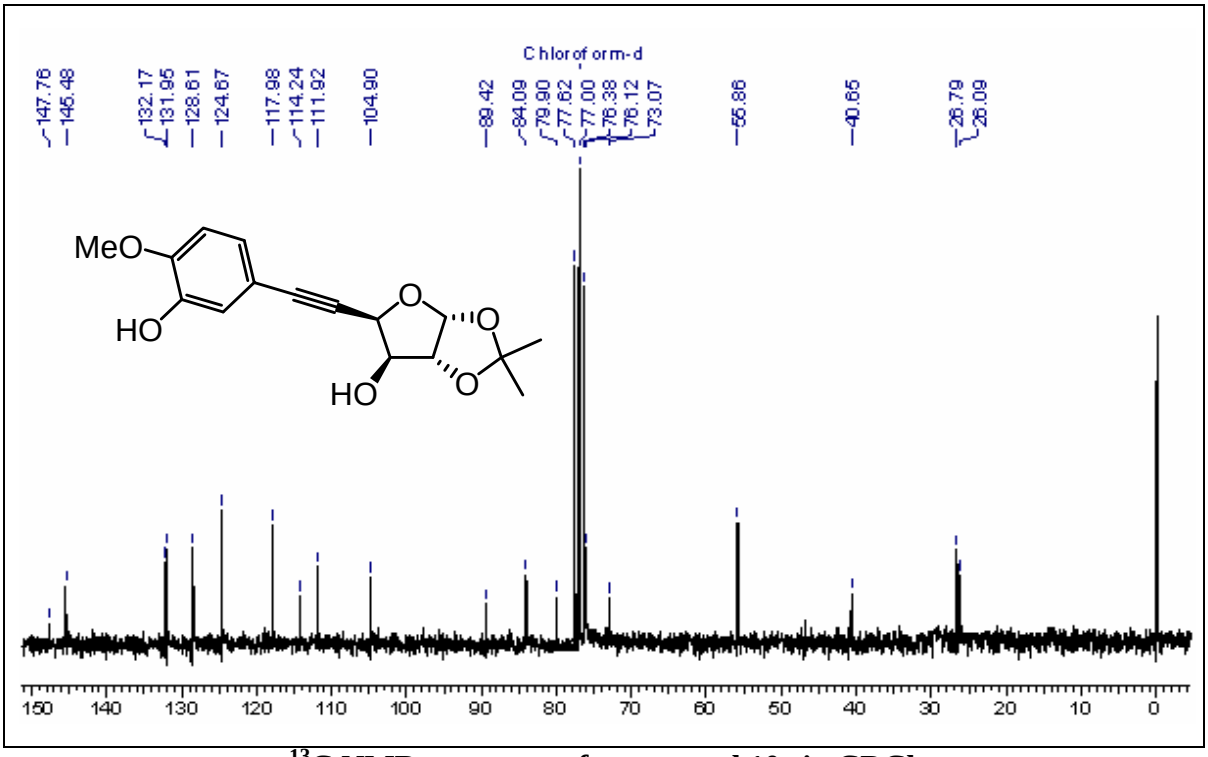
^{1}H NMR spectrum of compound 10d in $CDCl_3$



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



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



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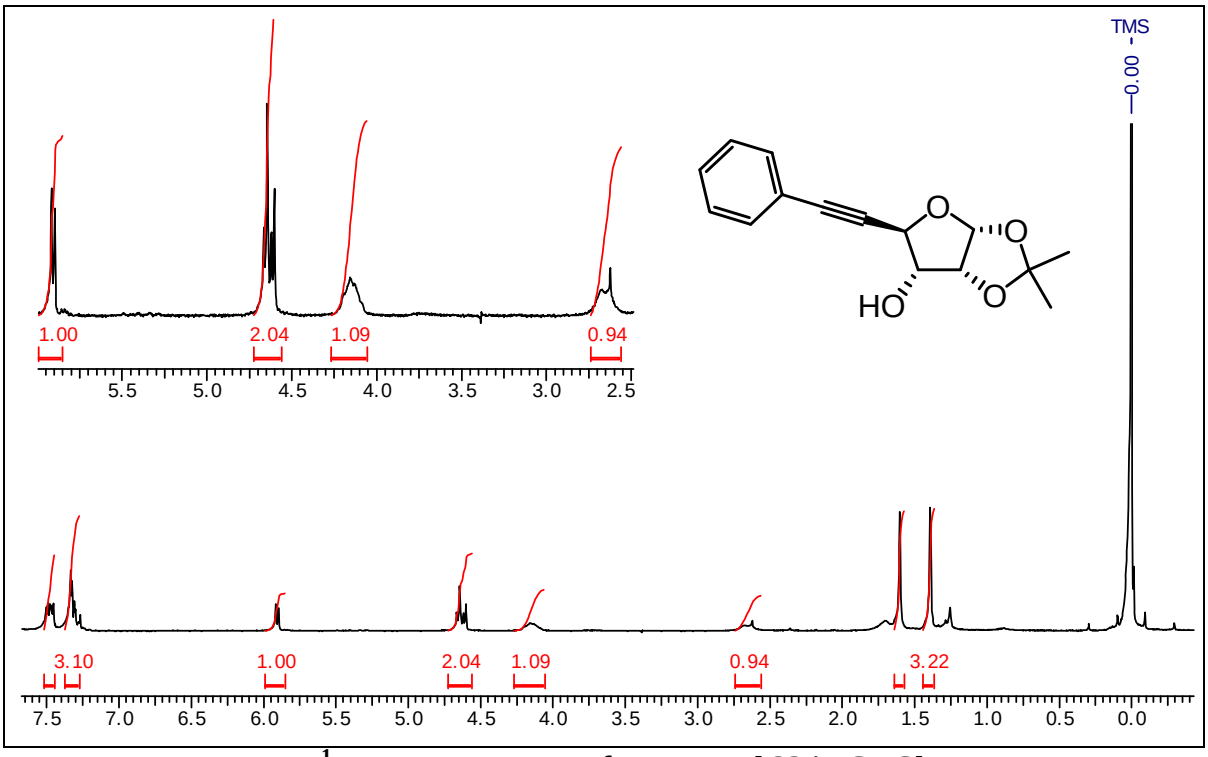
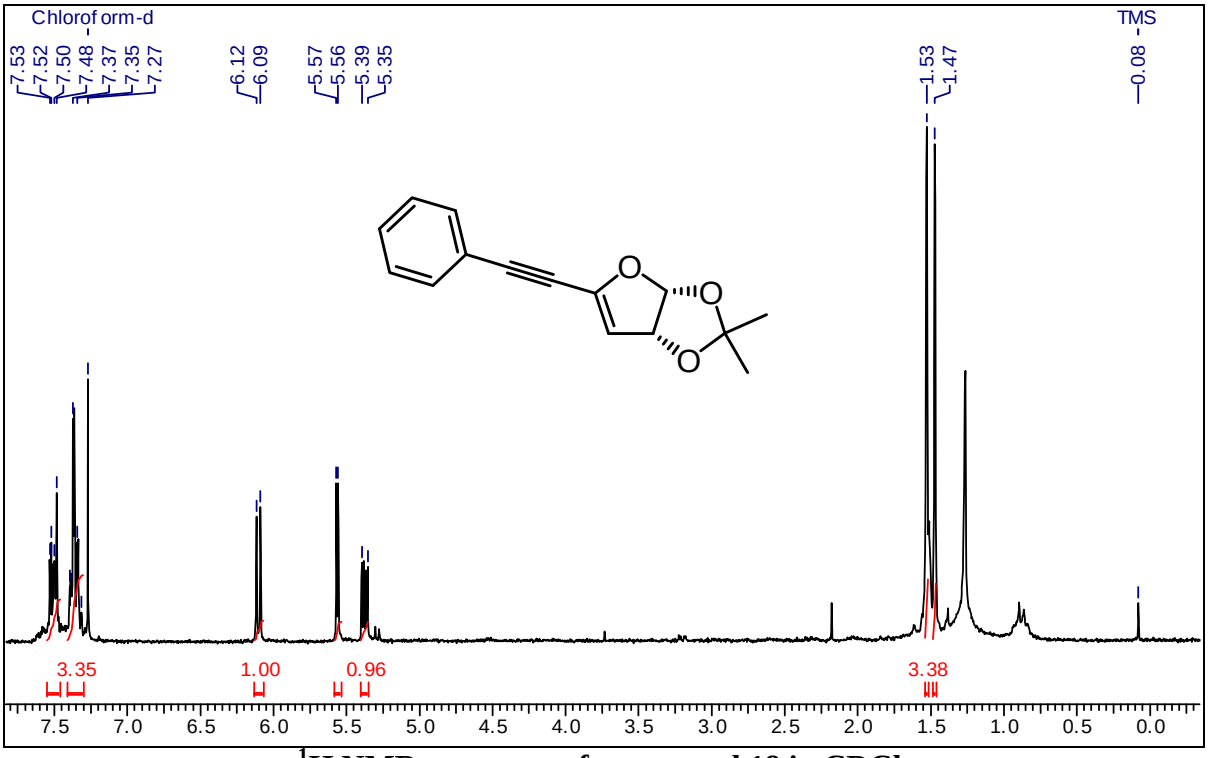
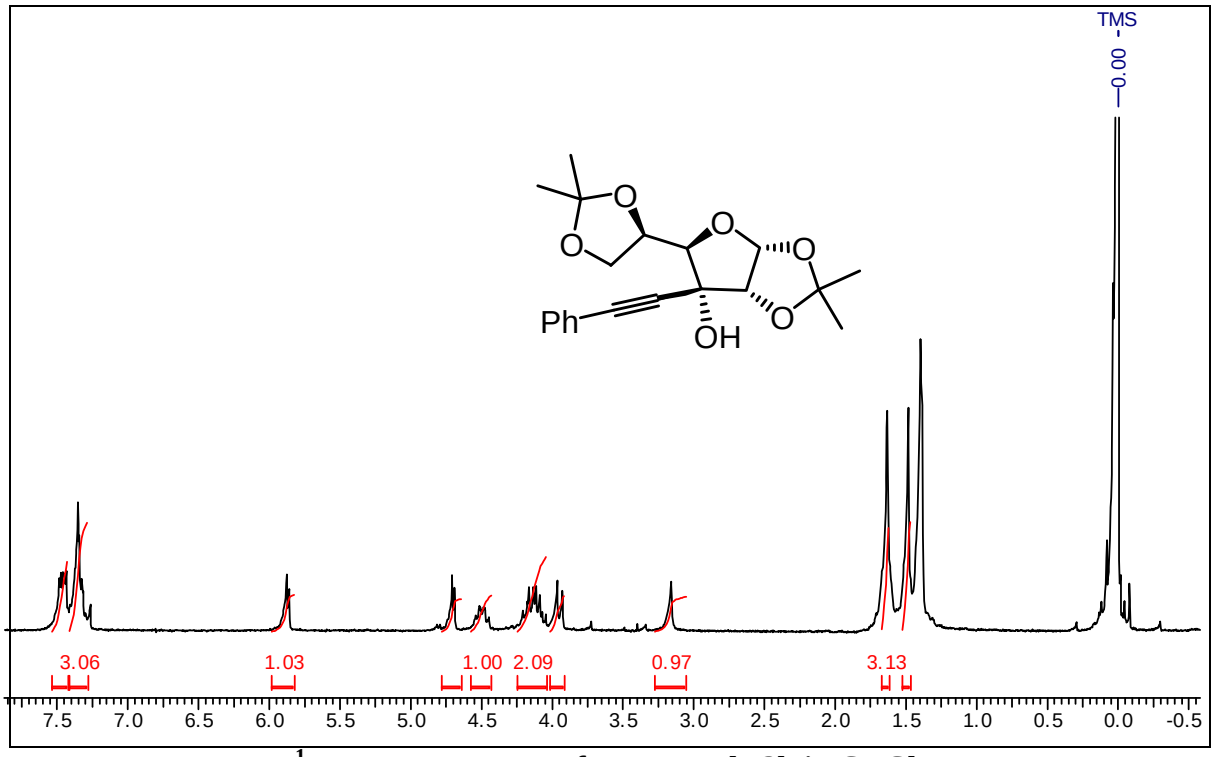


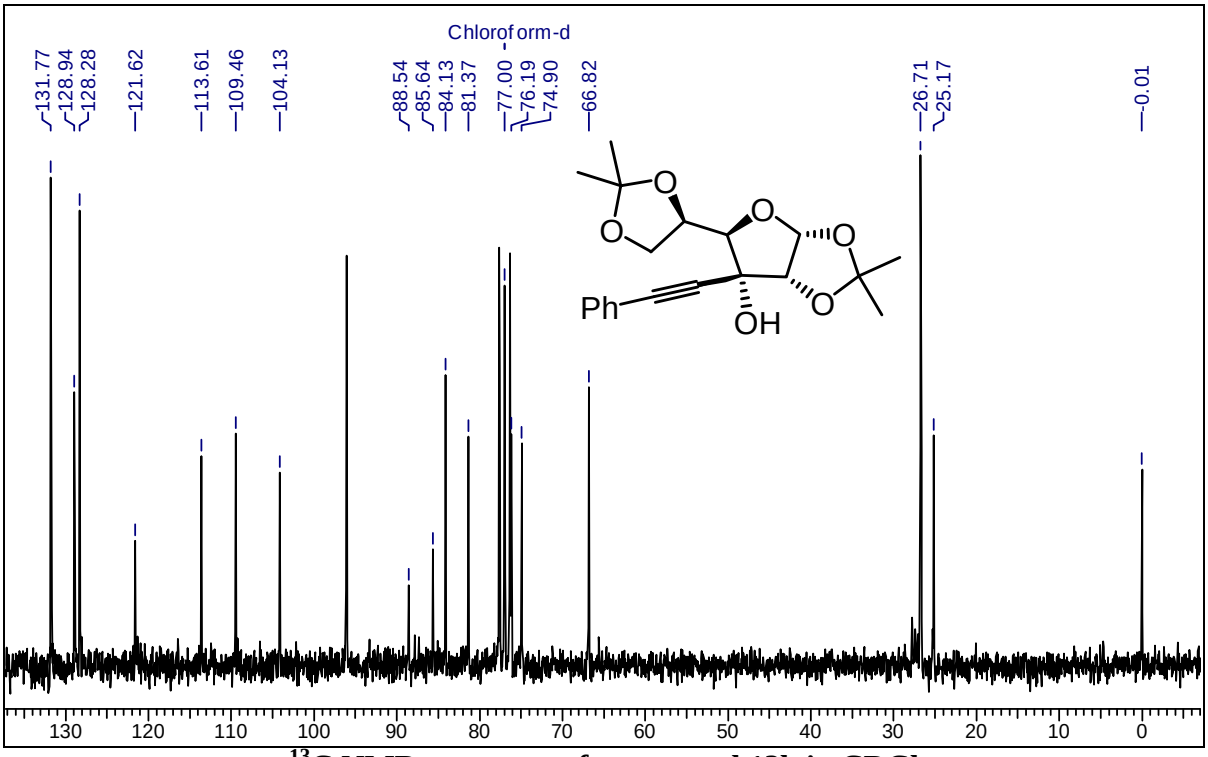
^{1}H NMR spectrum of compound 23 in $CDCl_3$



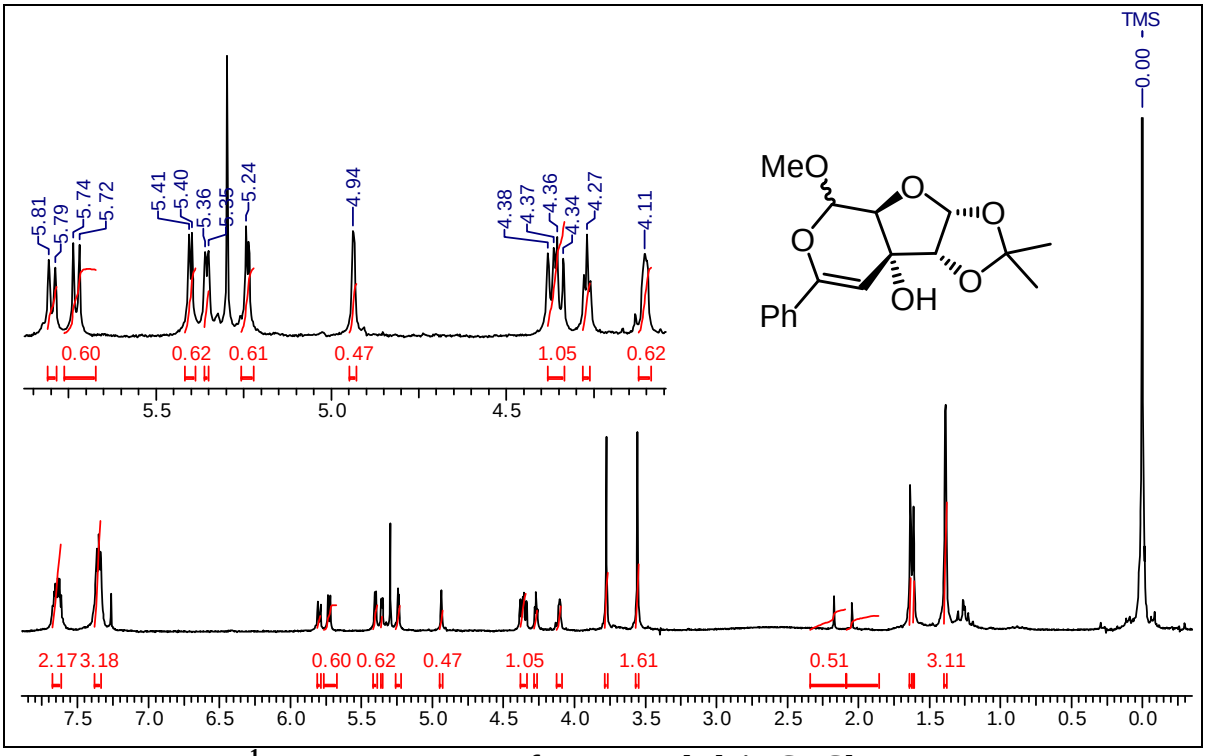
^{1}H NMR spectrum of compound 18 in $CDCl_3$



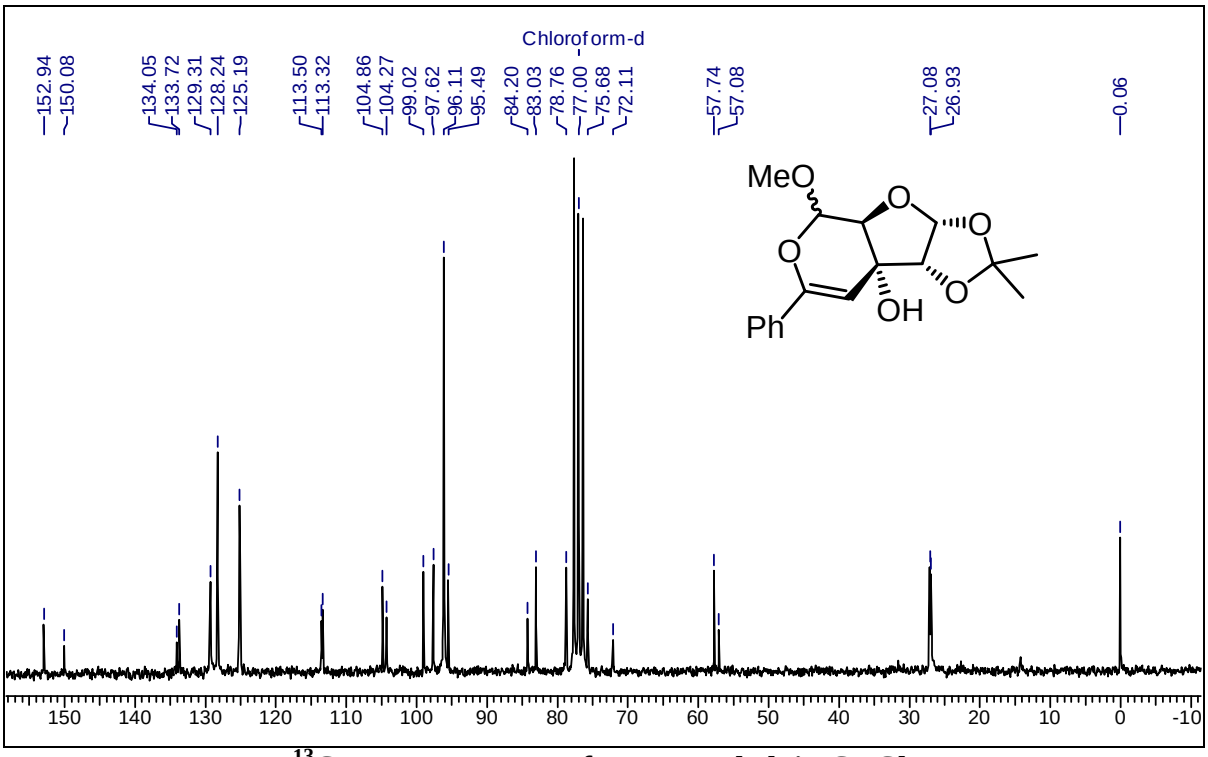
^{1}H NMR spectrum of compound 12b in $CDCl_3$



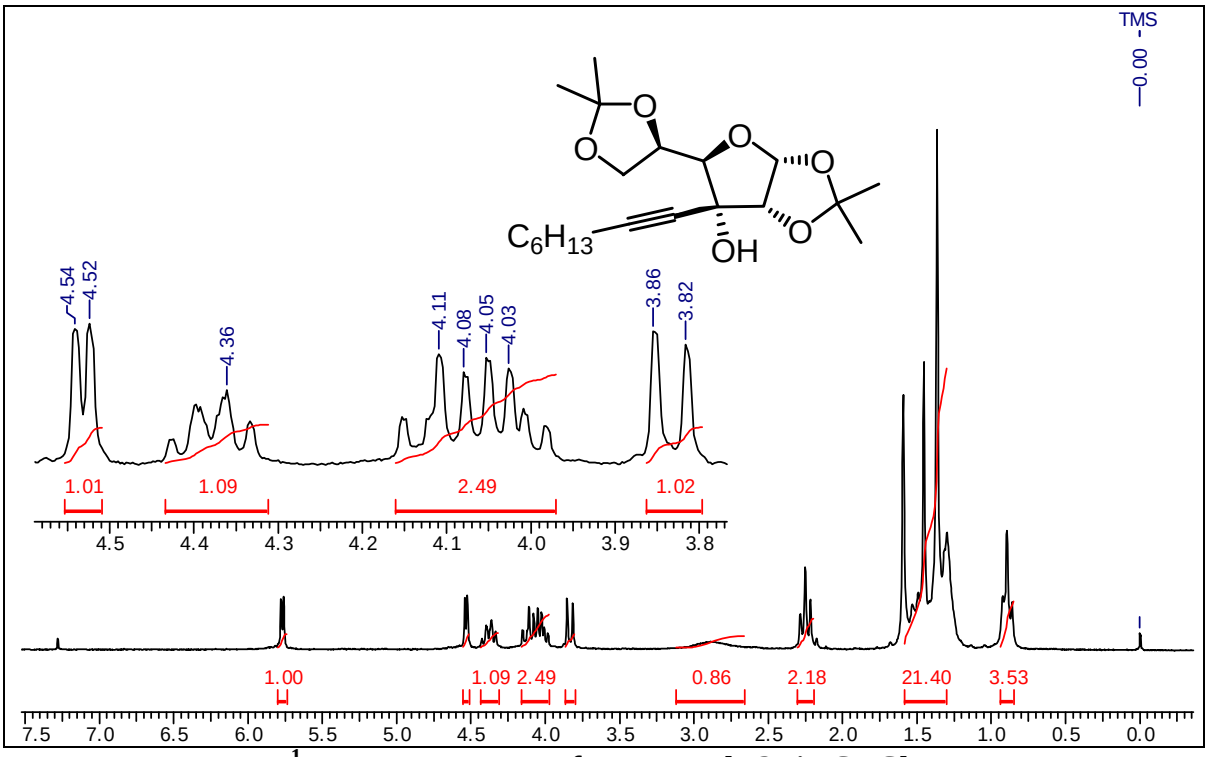
^{13}C NMR spectrum of compound 12b in $CDCl_3$



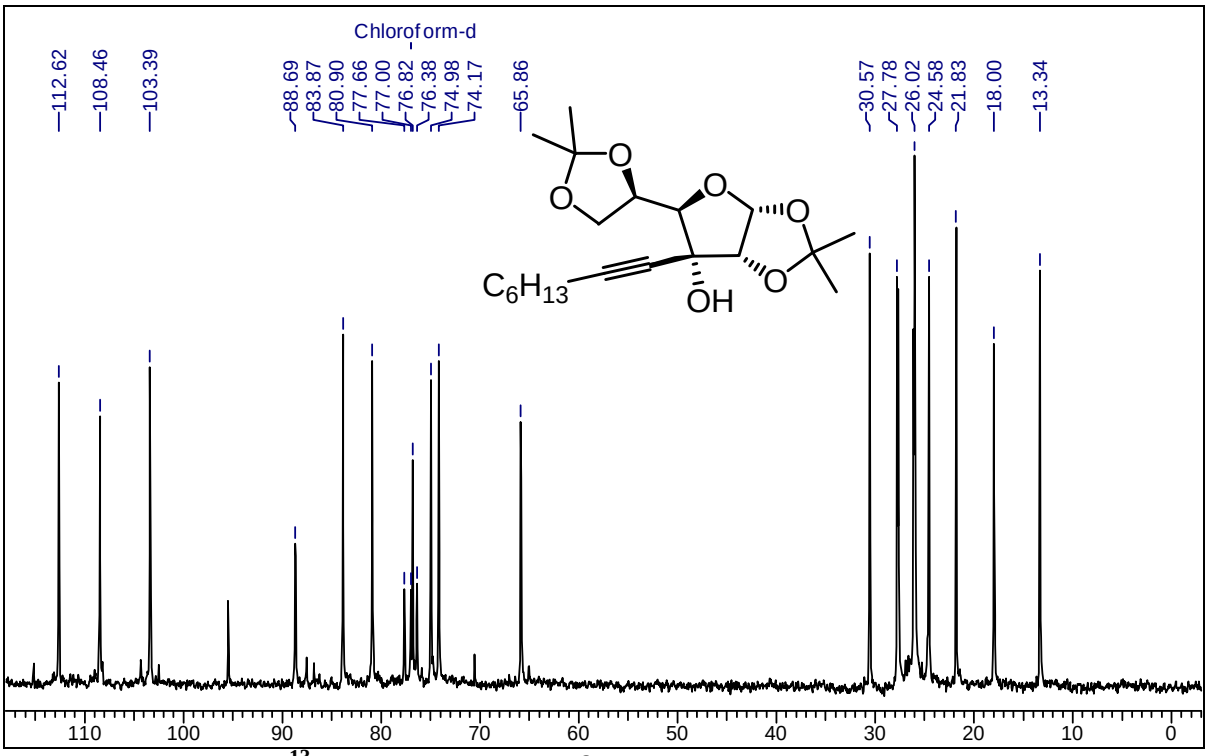
^{1}H NMR spectrum of compound 7b in $CDCl_3$



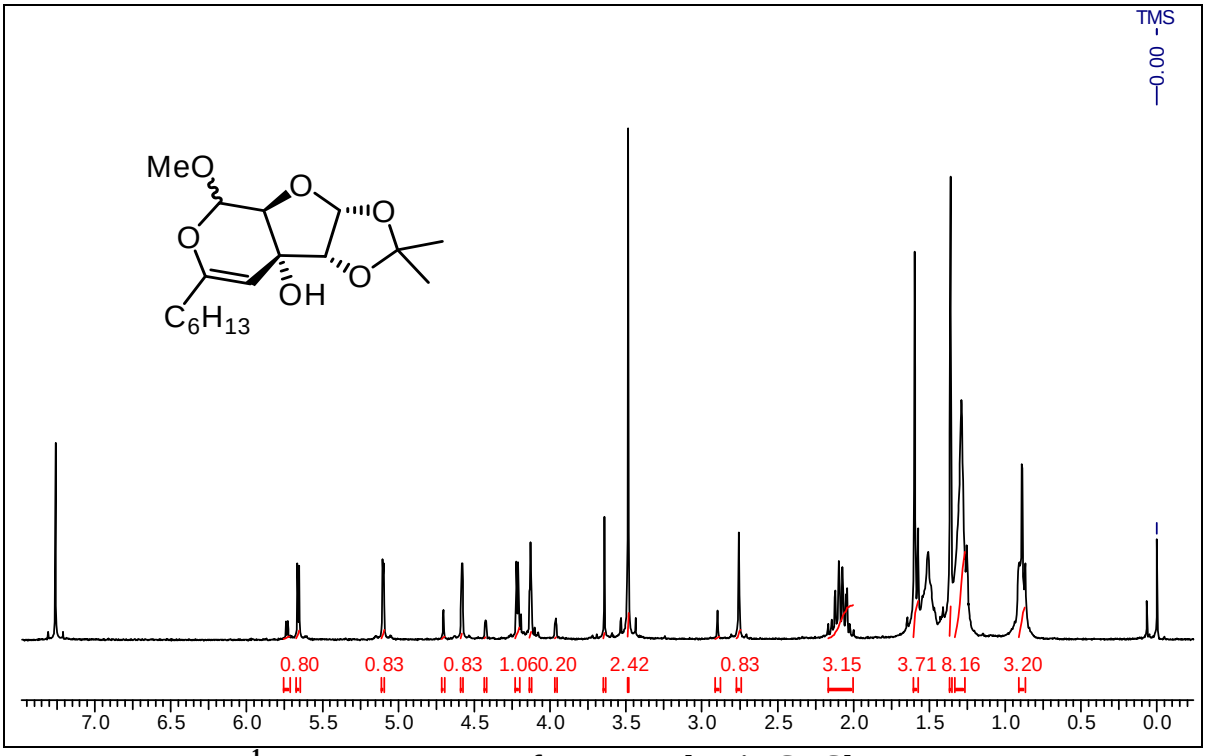
^{13}C NMR spectrum of compound 7b in $CDCl_3$



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



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



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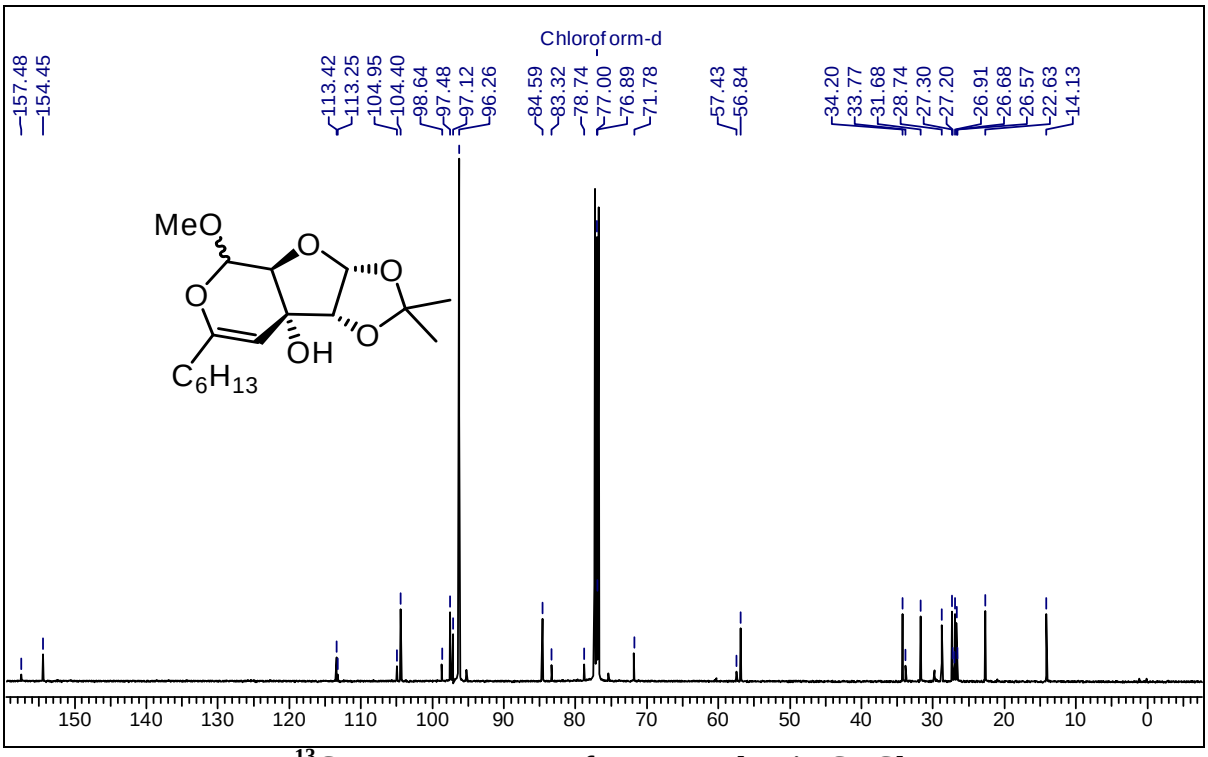

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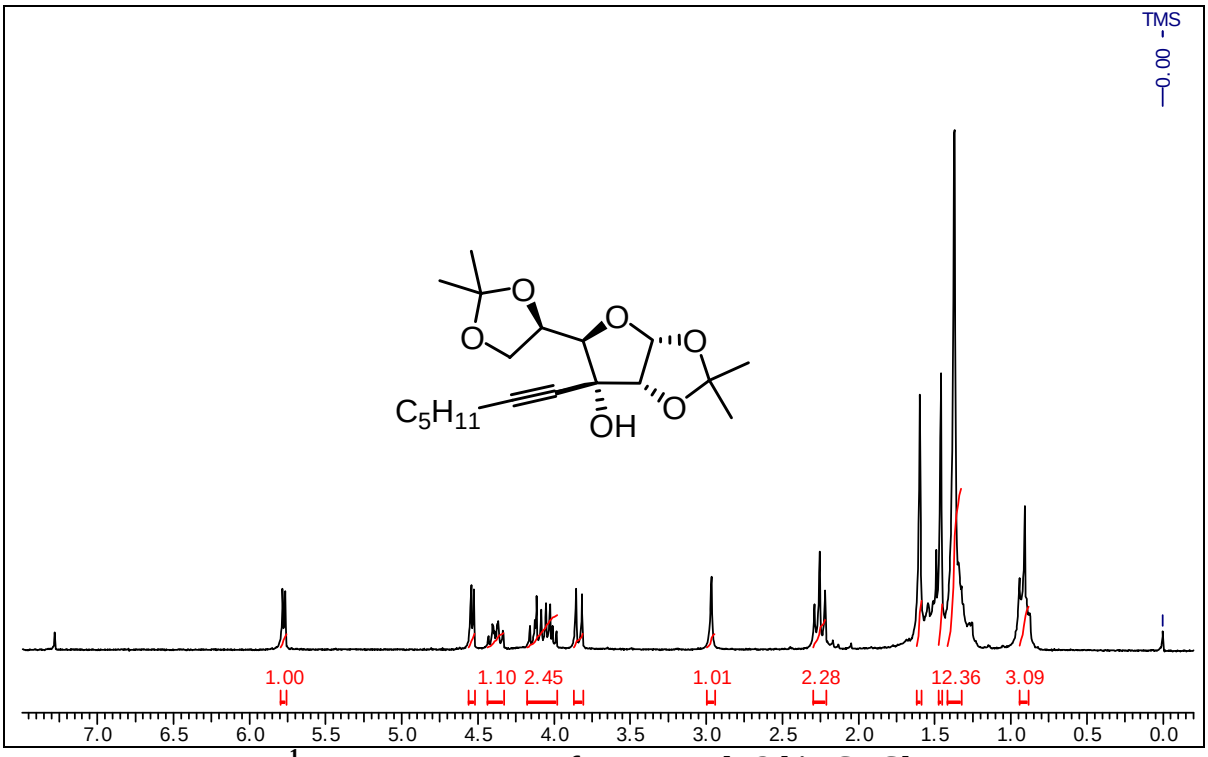
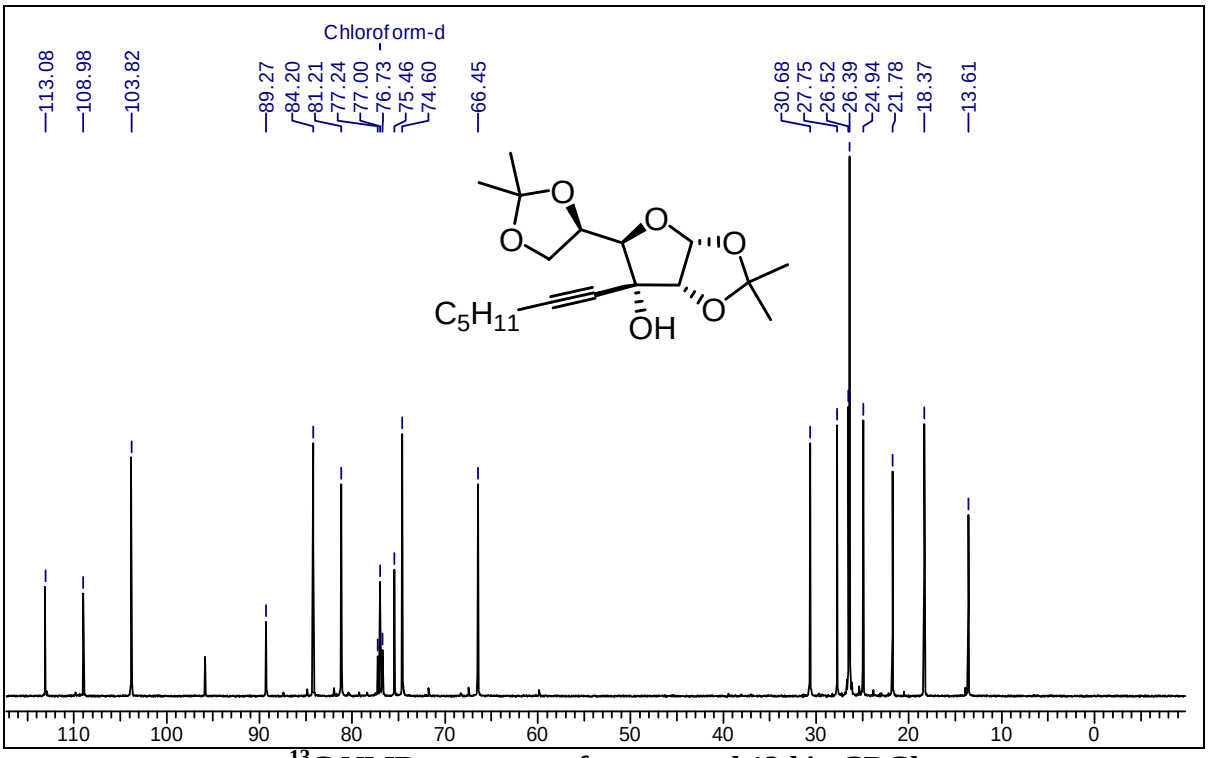
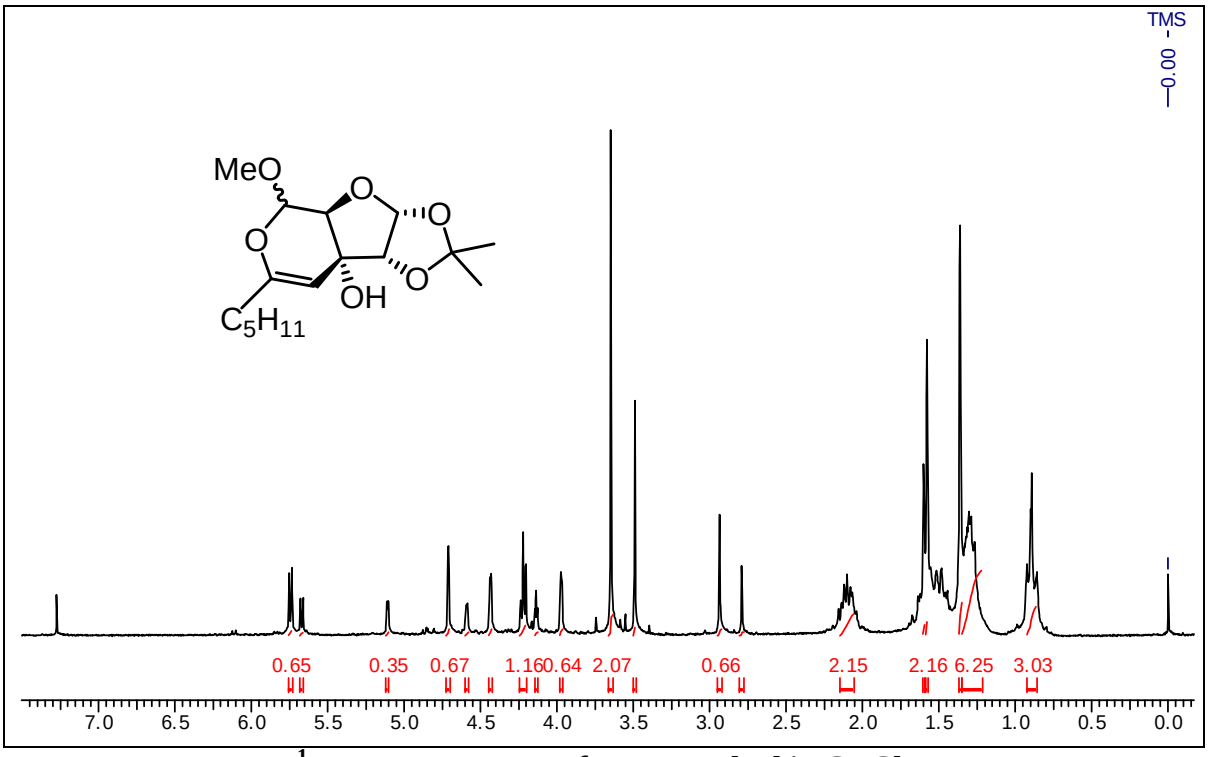


^{1}H NMR spectrum of compound 12d in $CDCl_3$



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



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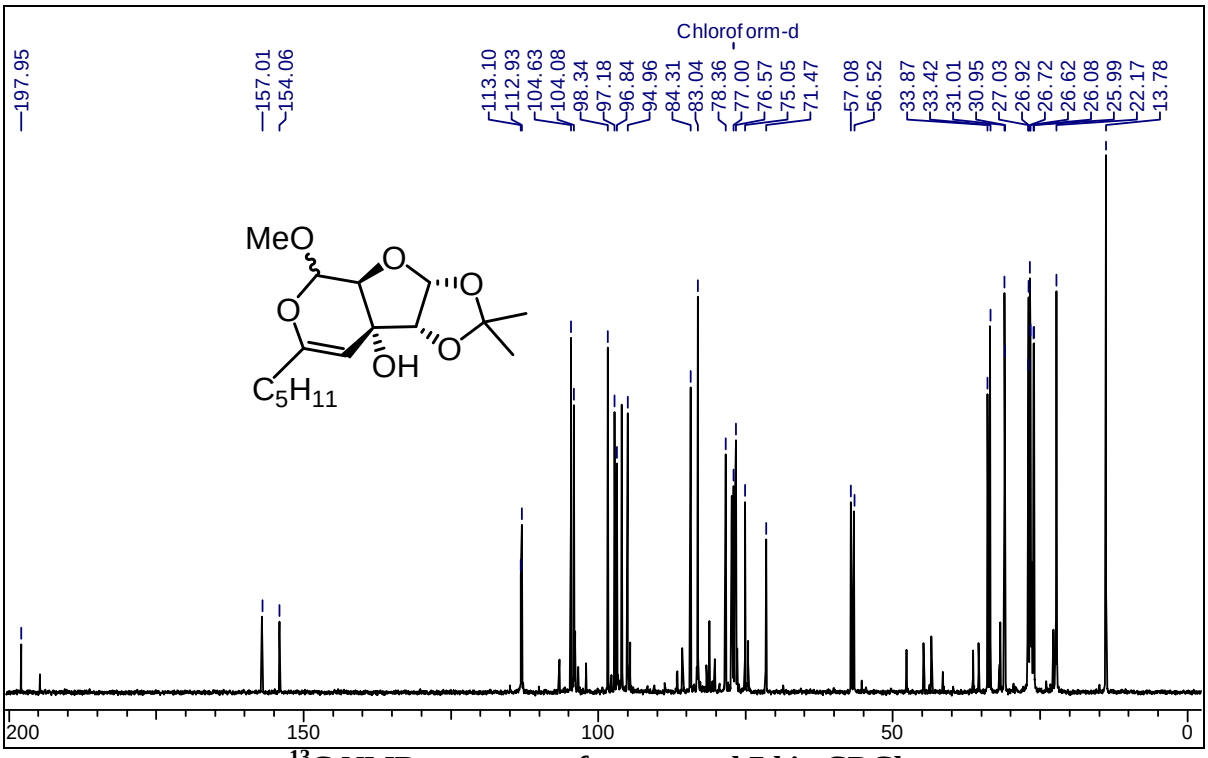
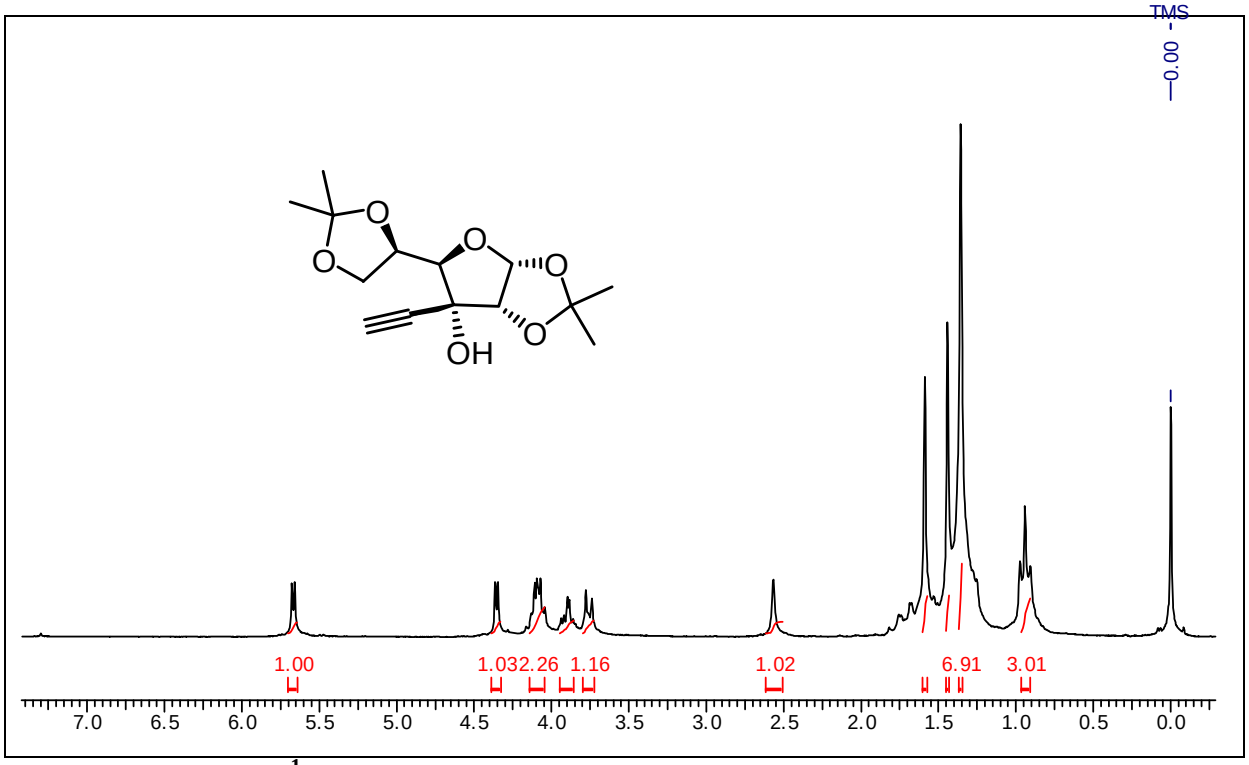
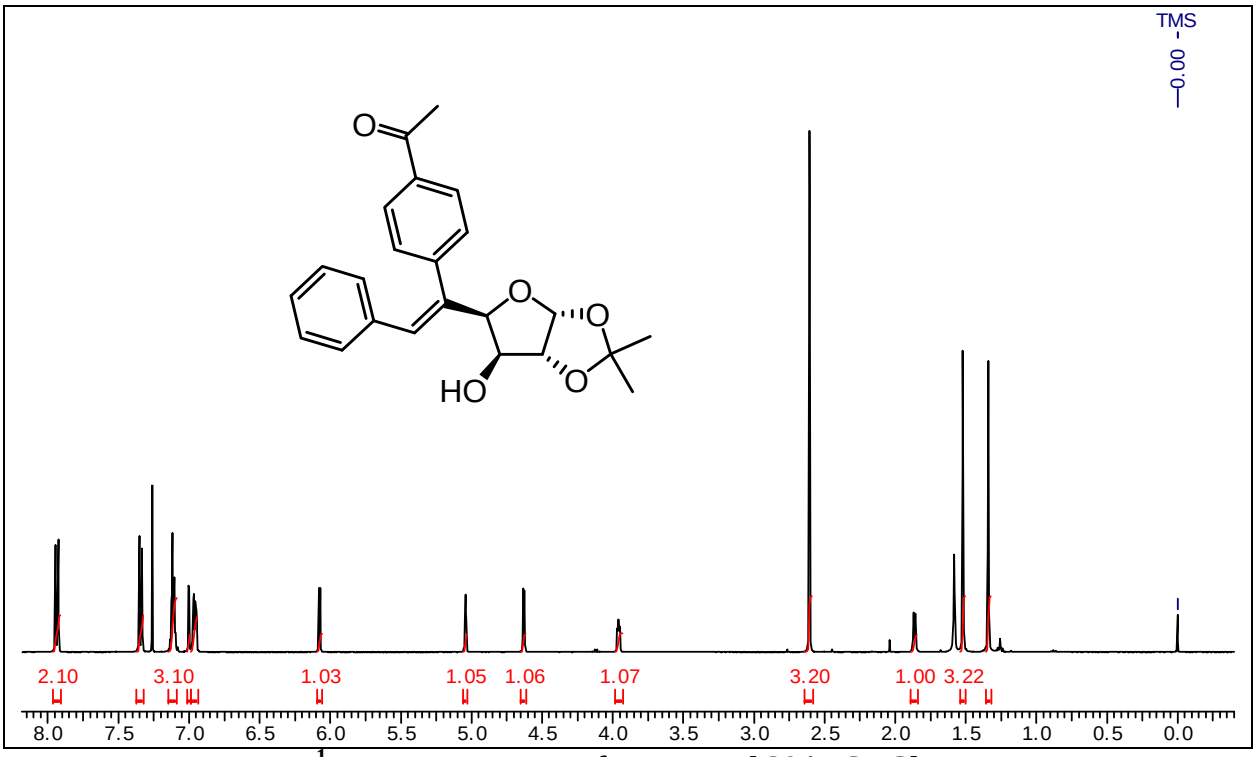


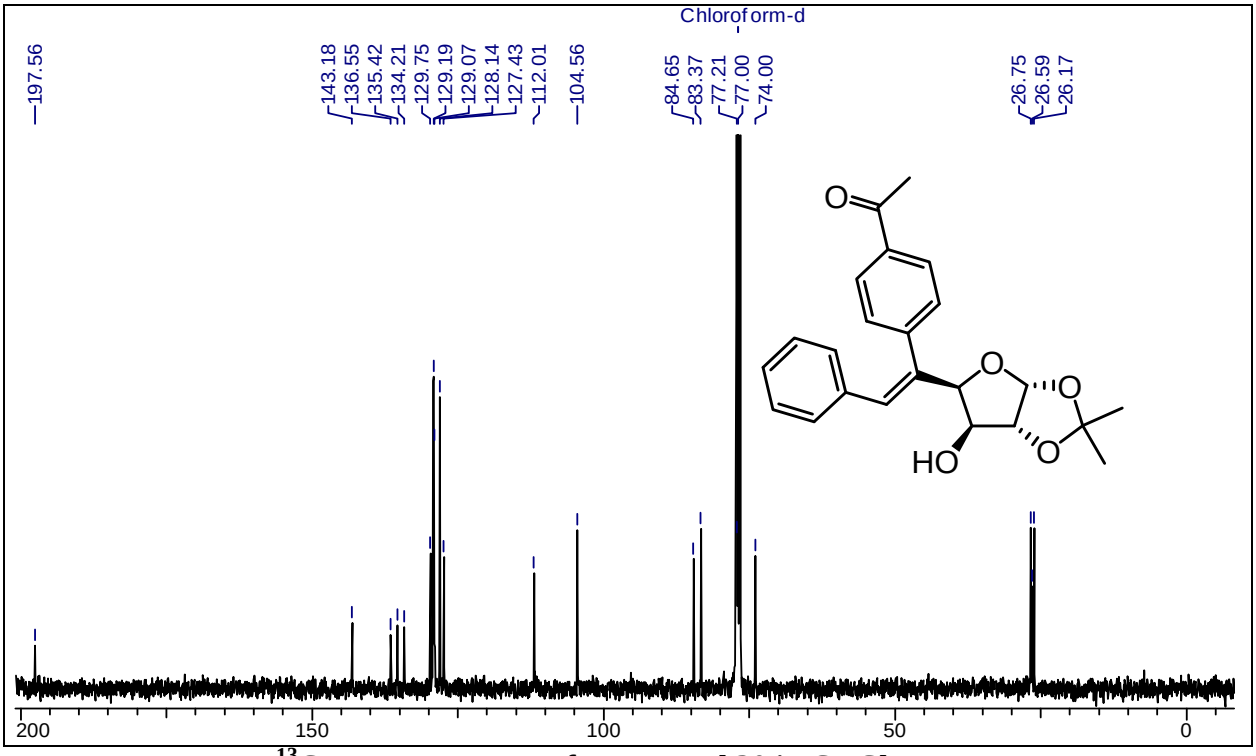
^{13}C NMR spectrum of compound 7d in $CDCl_3$



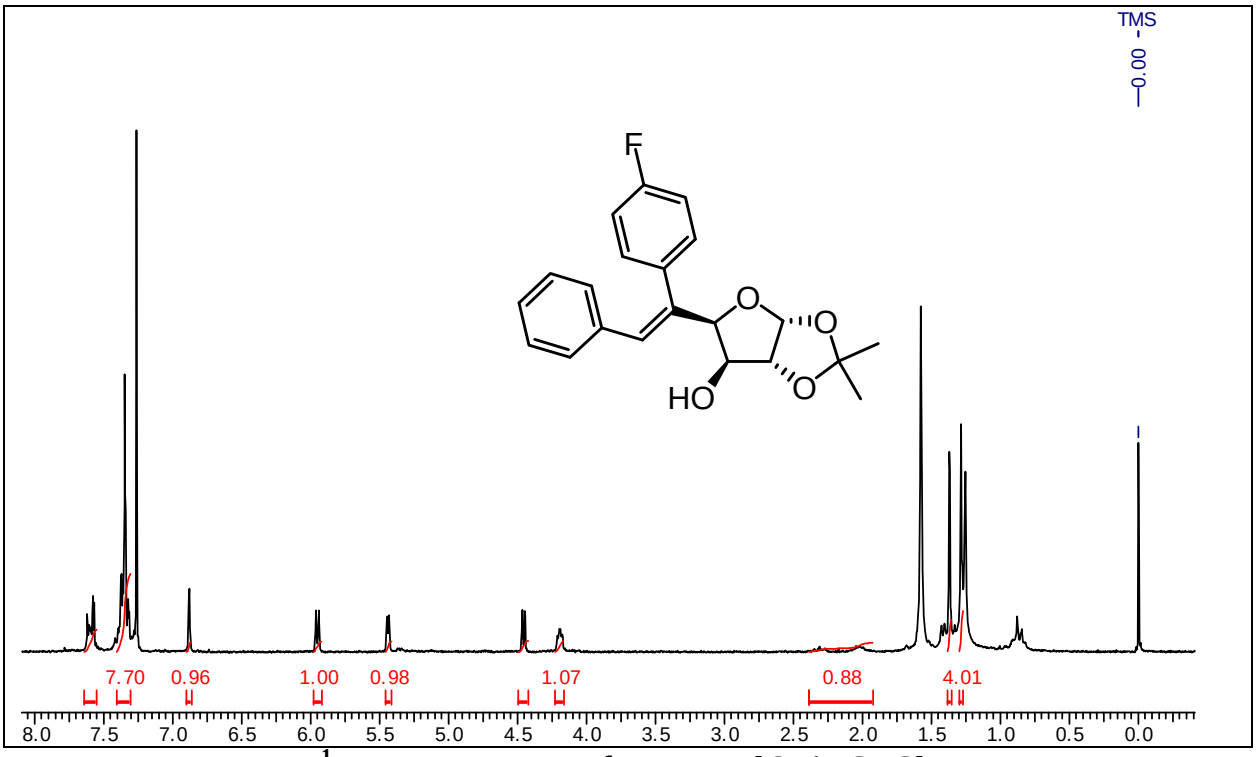
^{1}H NMR spectrum of compound 12a in $CDCl_3$



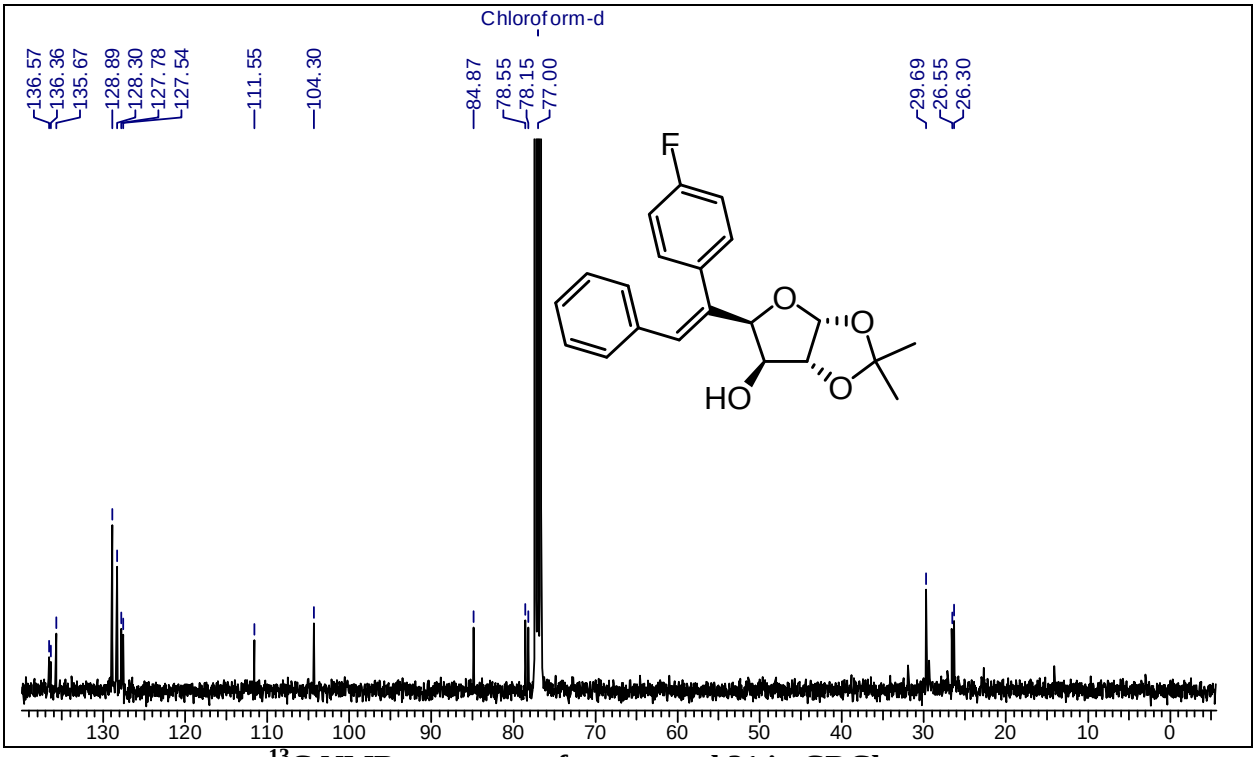
^{1}H NMR spectrum of compound 30 in $CDCl_3$



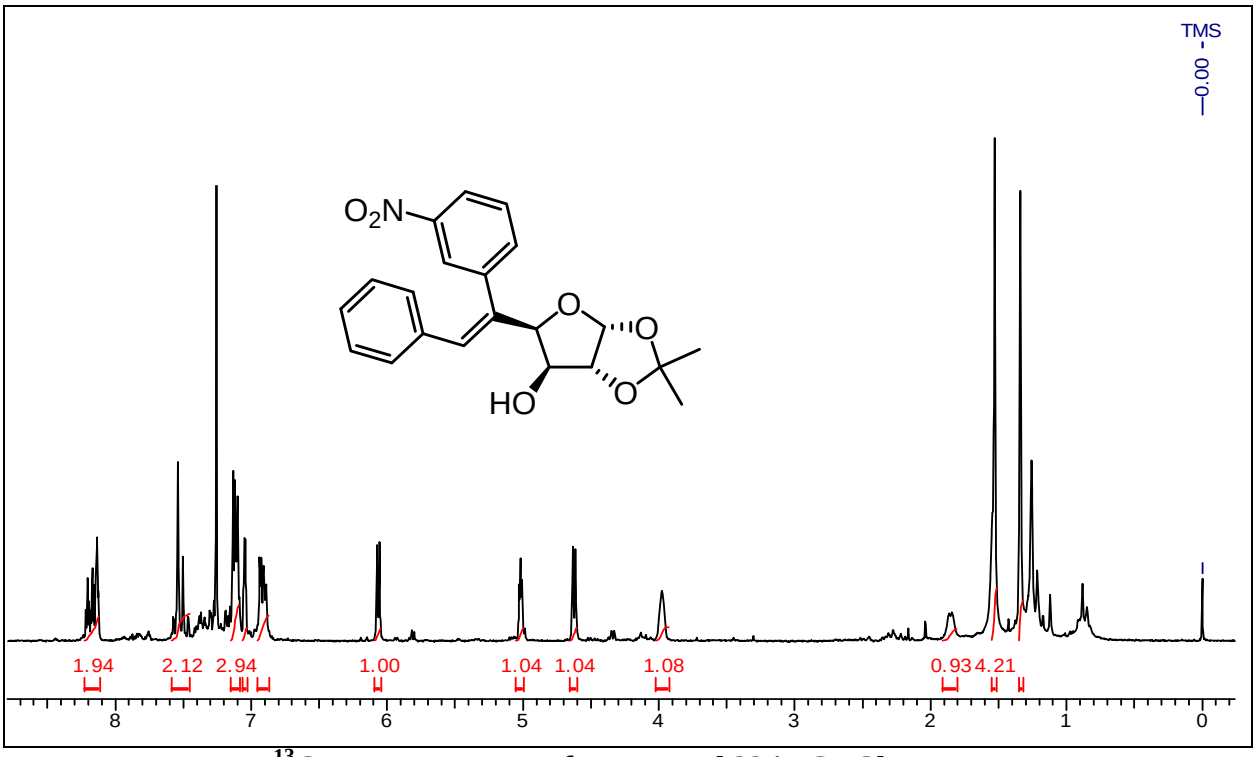
^{13}C NMR spectrum of compound 30 in $CDCl_3$



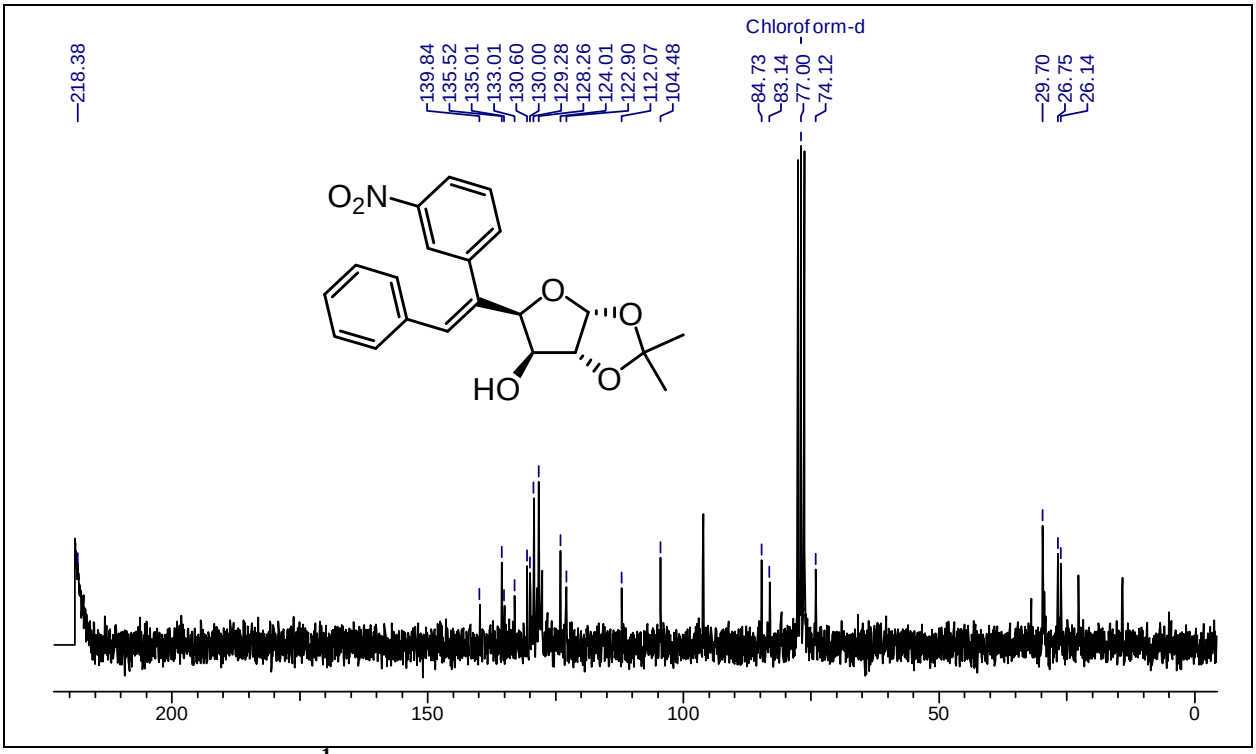
^{1}H NMR spectrum of compound 31 in $CDCl_3$



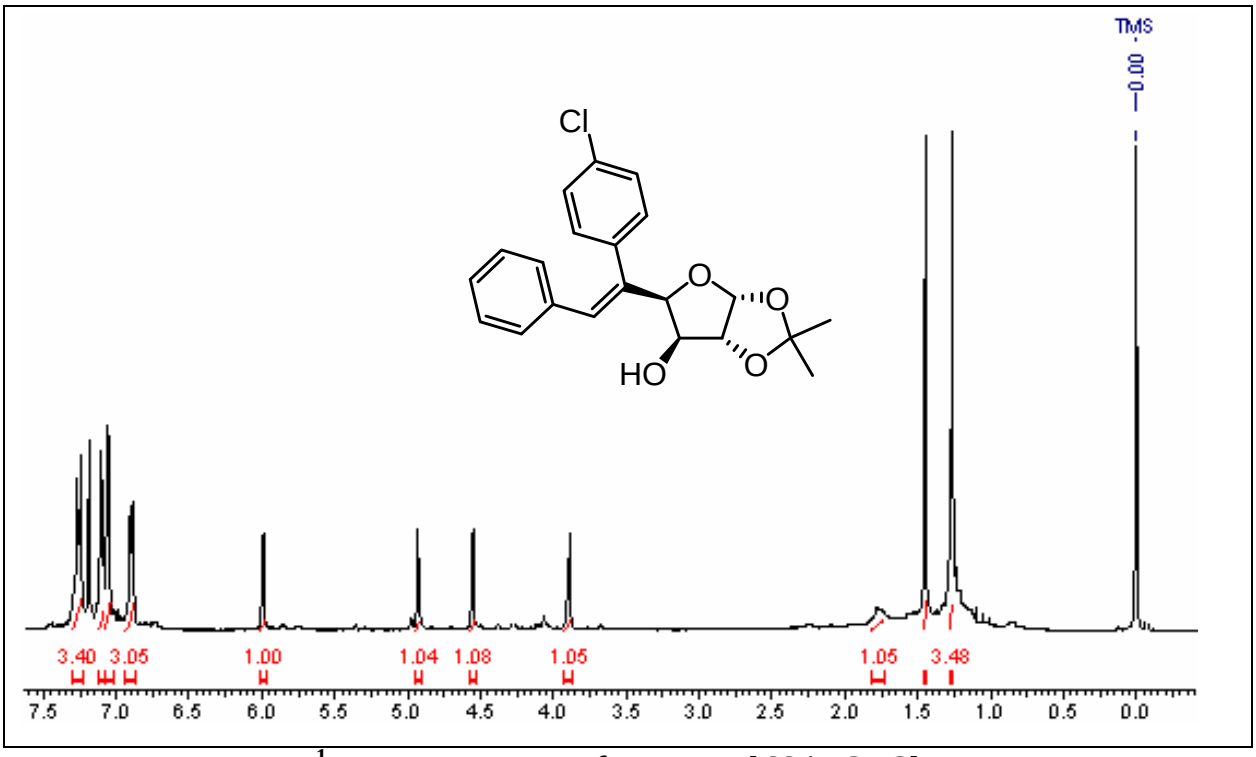
^{13}C NMR spectrum of compound 31 in $CDCl_3$



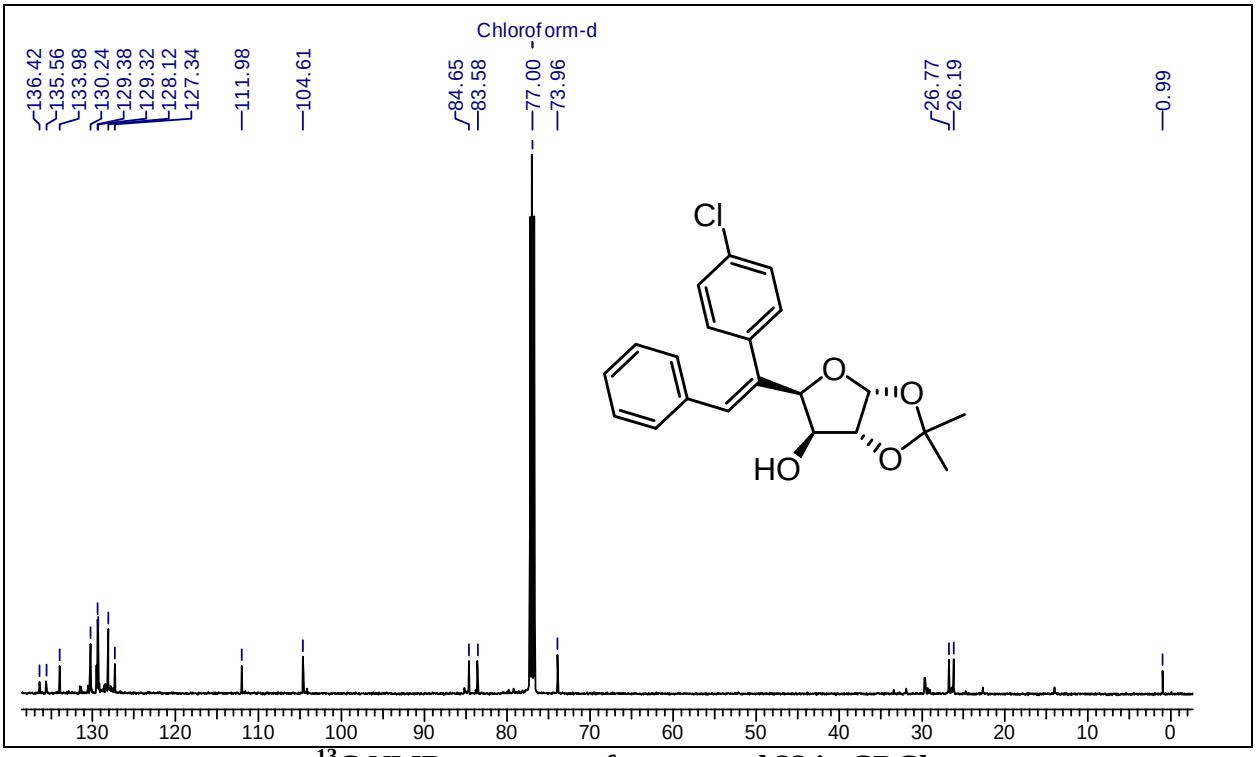
^{13}C NMR spectrum of compound 32 in $CDCl_3$



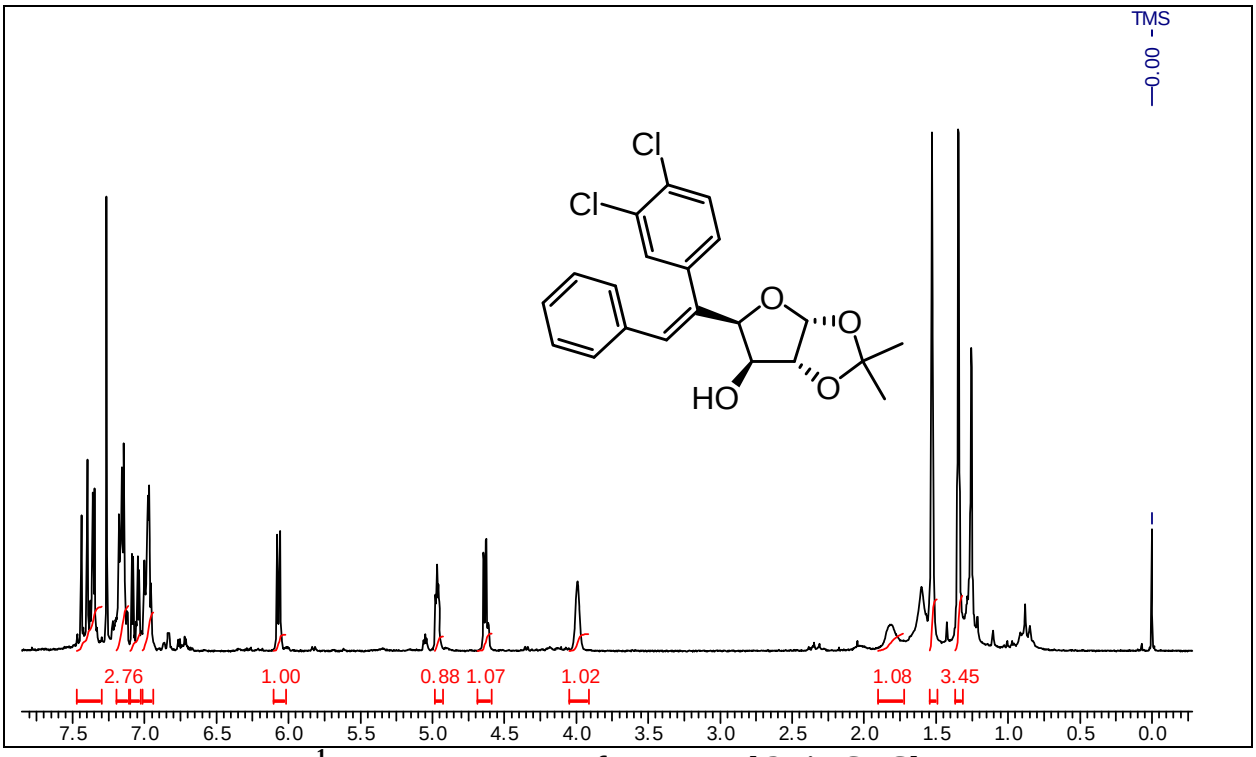
^{1}H NMR spectrum of compound 32 in $CDCl_3$



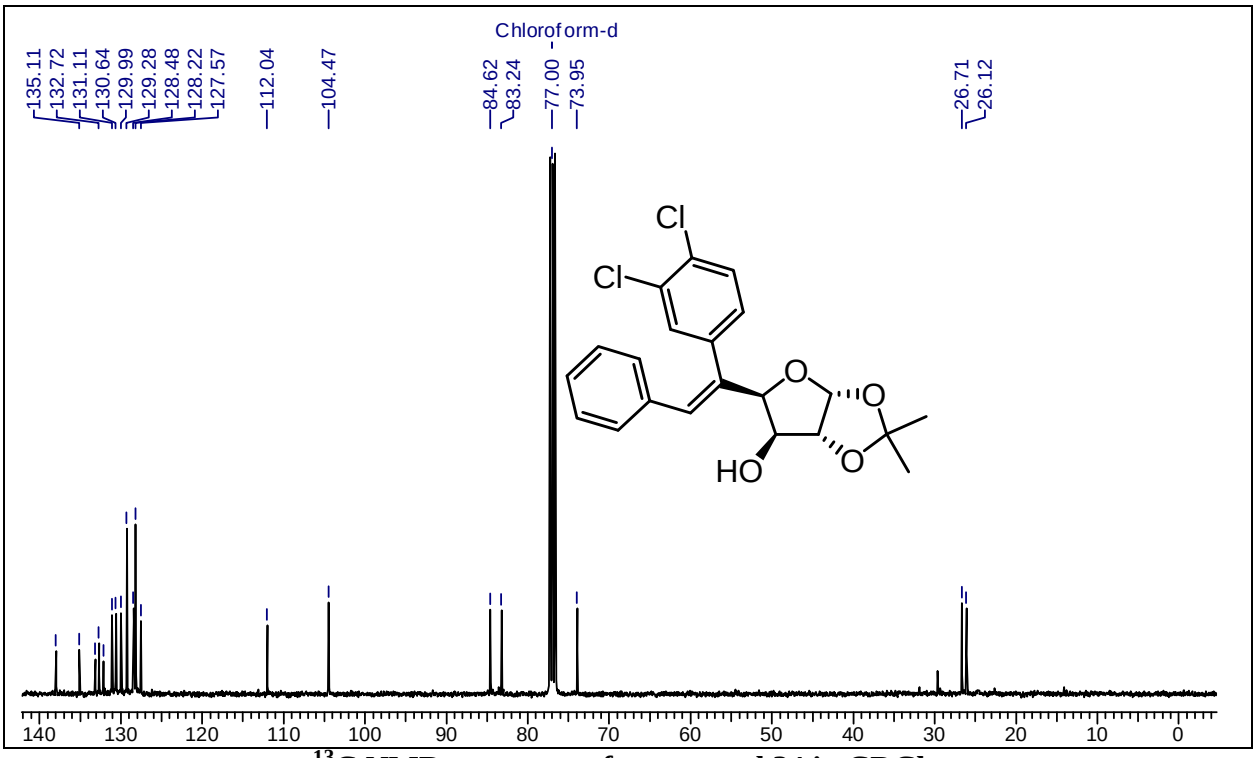
^{1}H NMR spectrum of compound 33 in $CDCl_3$



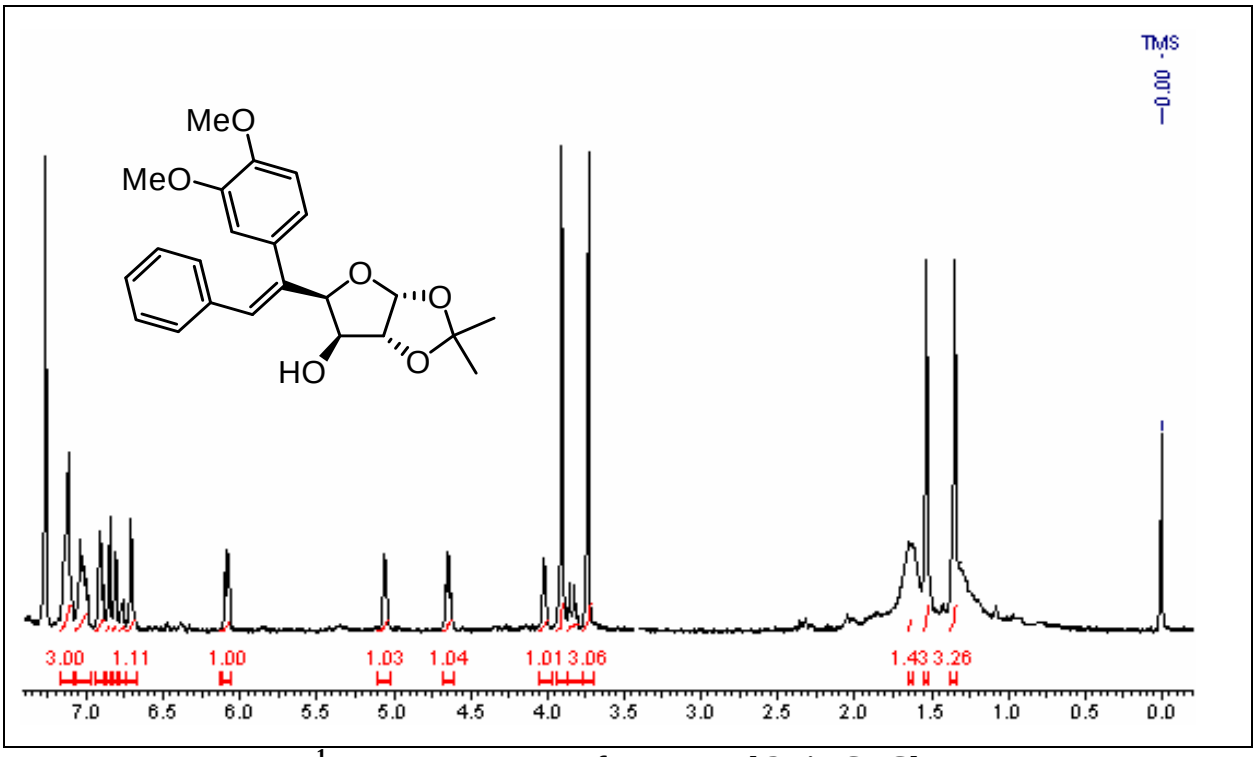
^{13}C NMR spectrum of compound 33 in $CDCl_3$



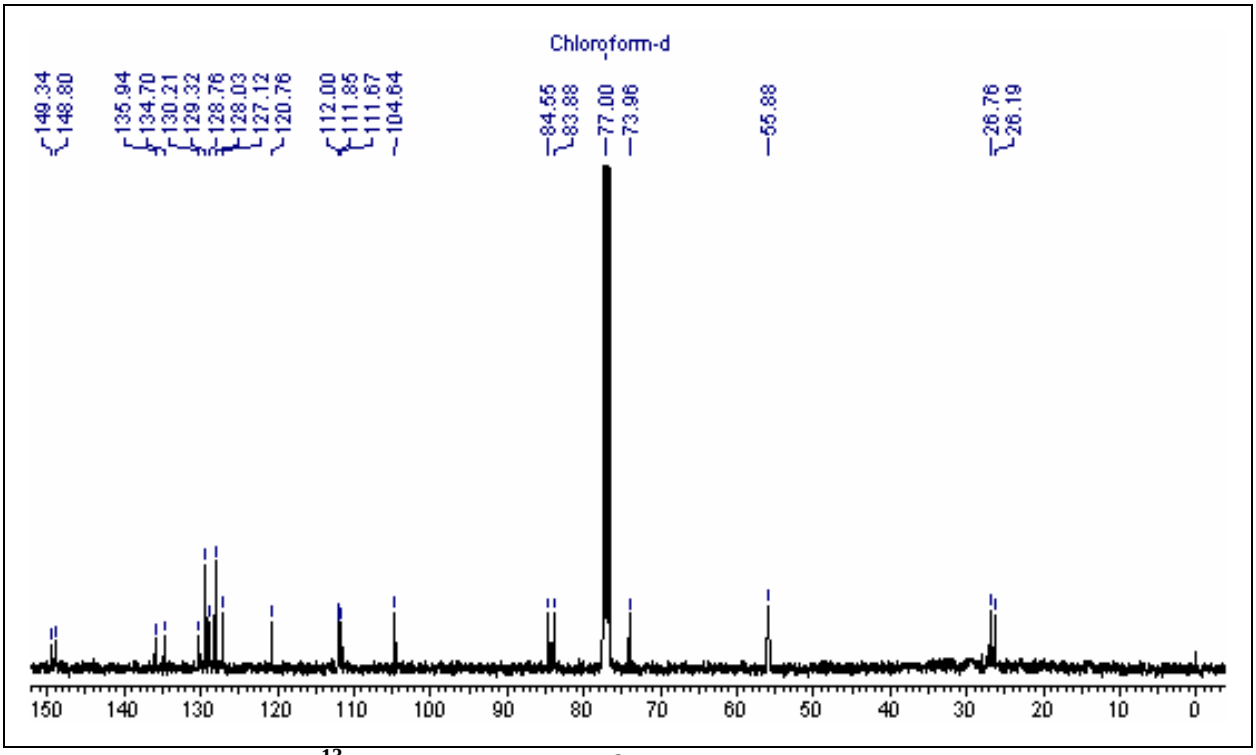
^{1}H NMR spectrum of compound 34 in $CDCl_3$



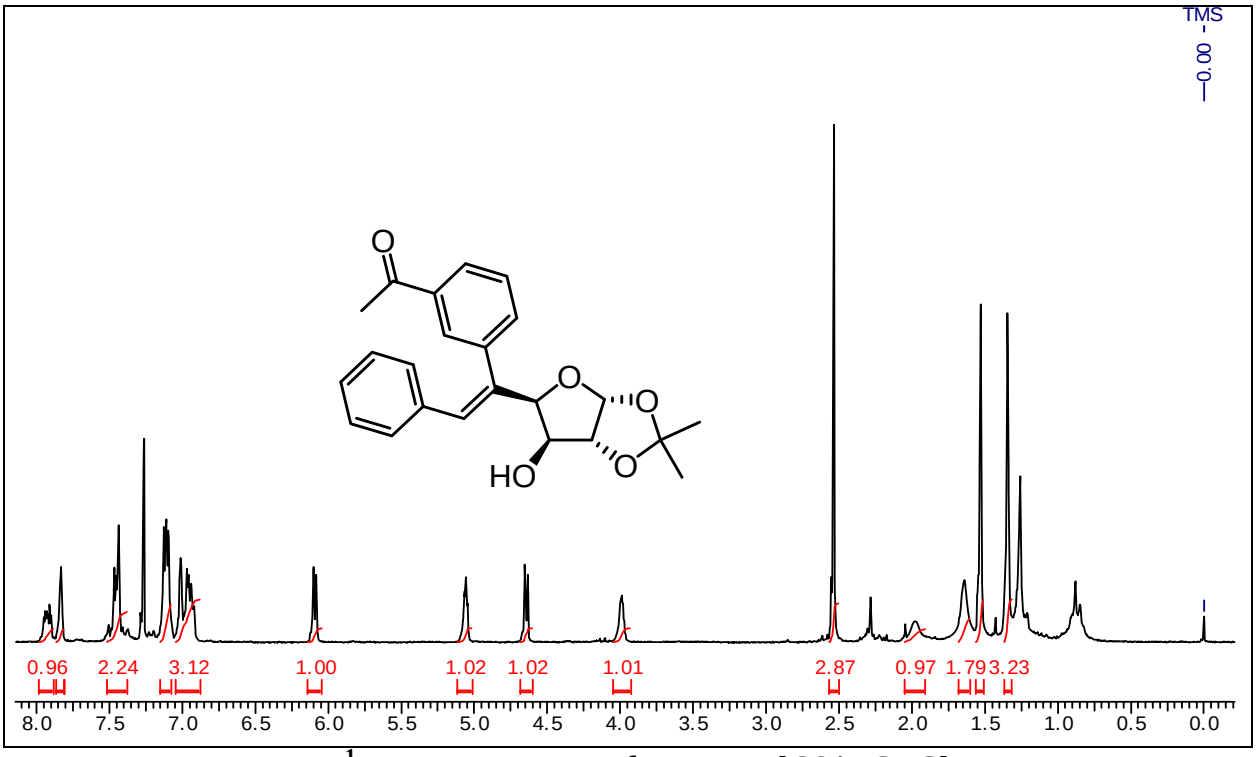
^{13}C NMR spectrum of compound 34 in $CDCl_3$



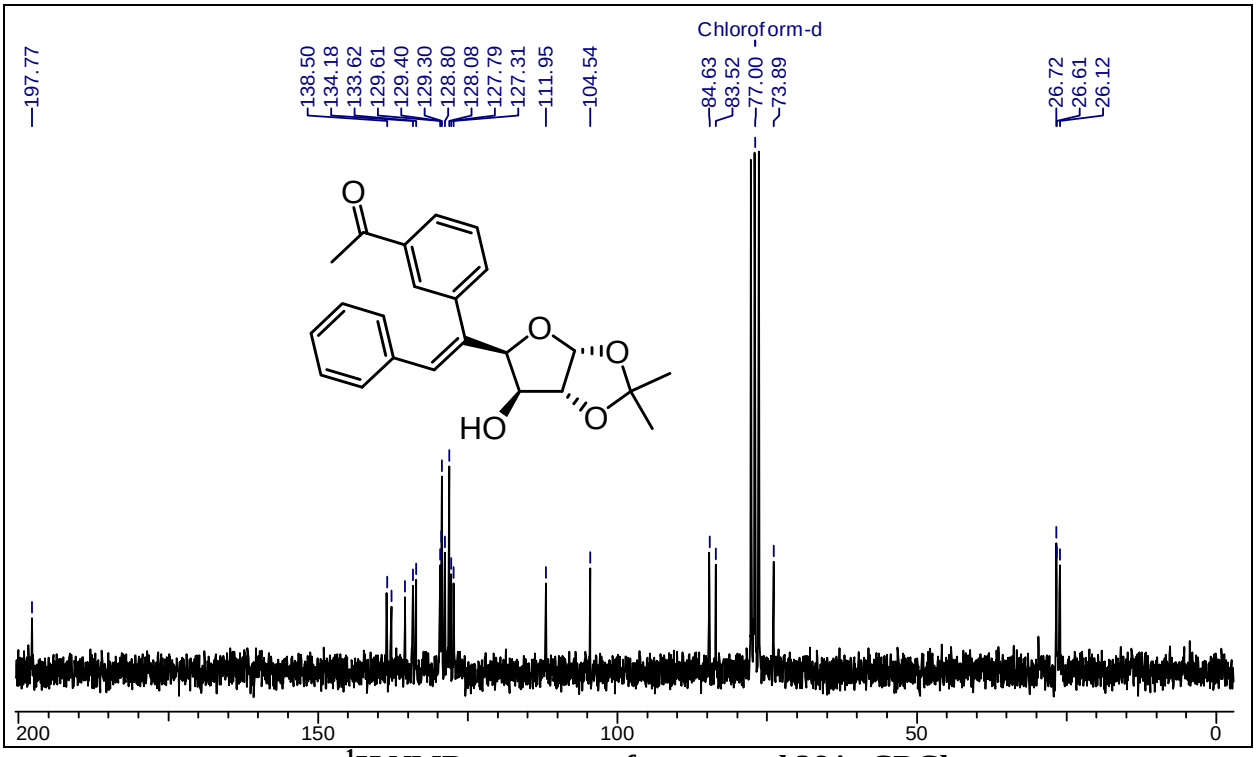
^{1}H NMR spectrum of compound 35 in $CDCl_3$



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



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



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

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APPENDIX

ATTEMPTS TOWARDS THE SYNTHESIS OF LEUSTRODUCSIN- B

Leustroducsin B (LSN-B, **1**) was isolated from *Streptomyces platensis* 60192, shown to have potent cytokine-inducing activities in clonal human bone marrow-derived stromal cell line KM-102 and in primary human bone marrow-derived stromal cells.[1] Leustroducsin B has been identified as a potential candidate for post-cancer chemotherapy treatment bi virtue of its colony-stimulating factor (CSF) inducing activity.

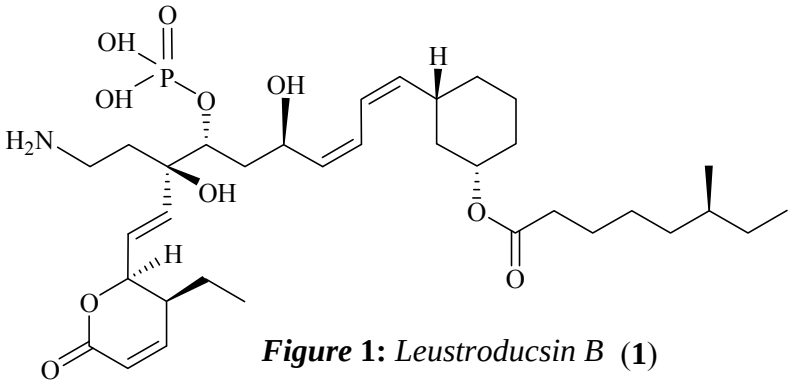


***Figure* 1:** *Leustroducsin B* (**1**)

Despite its promising biological activities, the further investigations to develop LSN-B as a new drug substance were hampered by limited supply of the compound. Currently, it is only available as a minor component of a mixture of LSNs. Therefore chemical synthesis seems to be only way to provide large quantity of the material. Fukuyama ***et al.*** led to the way with first total synthesis of LSN-B in 2003[2]. Till date, no other synthesis of Leustroducsin-B has been reported. Considering its important therapeutic potential we have under taken the total synthesis of leustroducsin-B featuring the easily available starting material. A retrosynthetic strategy in this regard is depicted in Figure 2.

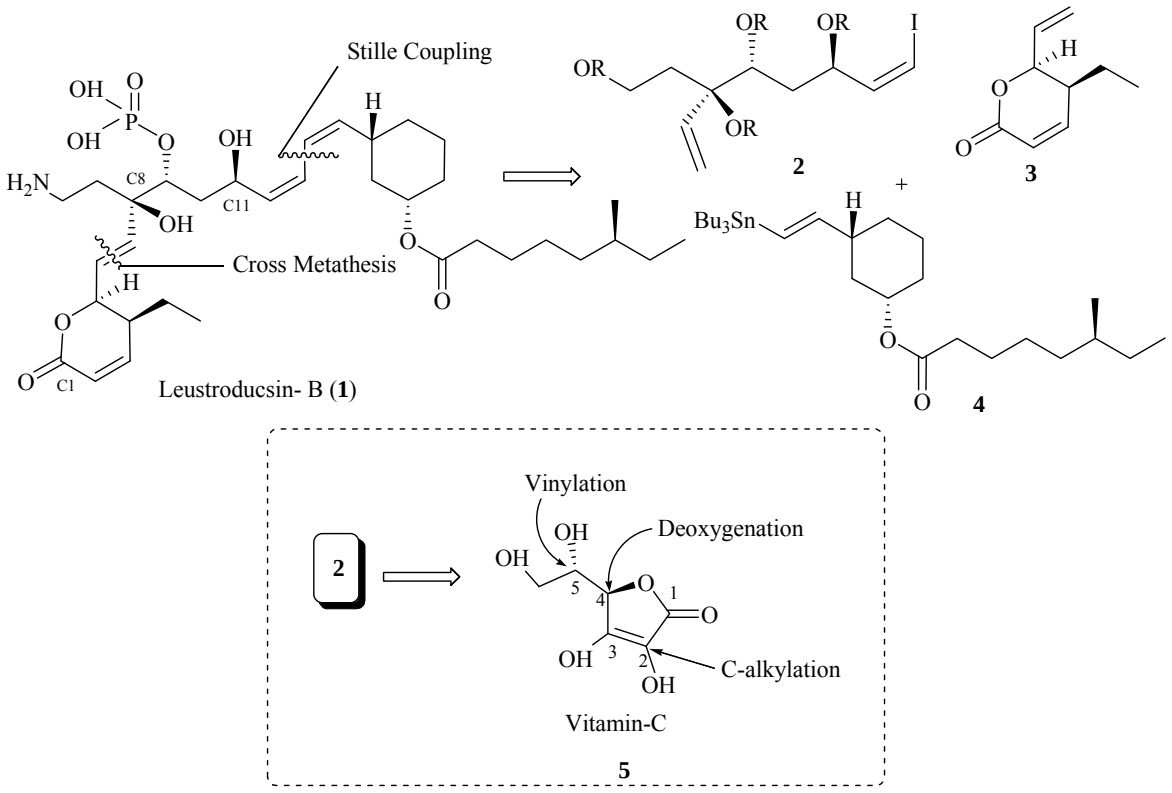


***Figure* 2:** *Reterosynthetic plan for Leustroducsin- B*

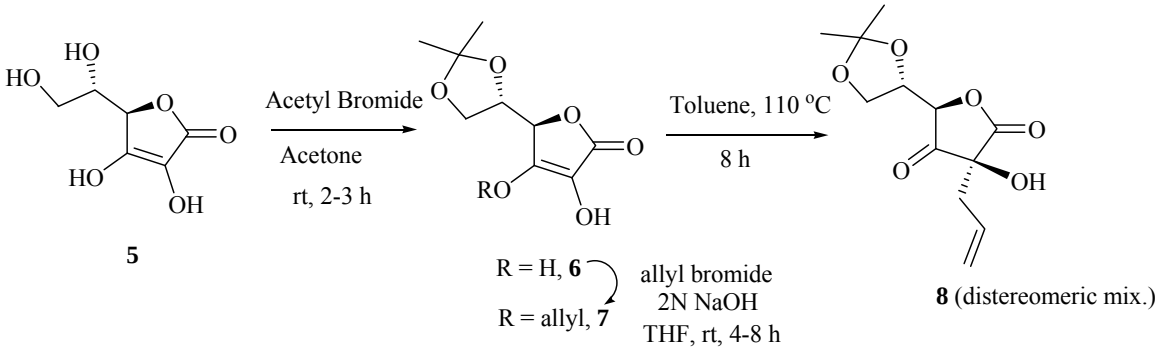
As shown in Figure 2, the central carbon skeleton of Leustroducsin-B was dissected into three fragments, a tetrol unit with an appended vinyliodide (**2**), C-6 vinyl δ-valerolactone (**3**) and the cyclohexanol unit **4**. The Stille coupling and Cross-Metathesis reactions could be envisaged as the key reactions for the coupling of three fragments **2**, **3** and **4**. The convergent synthesis of Leustroducsin B relies on a late stage Pd-catalyzed cross-coupling event to bring together the C1-13 and C14-21 fragments were envisaged from the sub units **2** and **3**. Each of these fragments should form the basic objective of the total plan of our synthesis. In our laboratory, the total synthesis of Leustroducsin-B has been identified as an overall objective and the investigations related the synthesis of fragment **2** of Leustroducsin-B form this part of the thesis.

The synthesis of key C6-C13 core (fragment **2**) was envisaged from easily available starting material vitamin-C after considering the stereochemical comparisons. A retrosynthetic strategy for fragment **2**, from L-ascorbic acid was depicted in (Figure 2)

which involves stereoselective alkylation at C-2, installation of *anti* diol functionality in lactone ring, deoxygenation at C-4 and vinylation at C-5 position on Vitamin-C.

According to the intended strategy, the synthesis of key intermediate **2** began with the formation of β-keto lactone **8** readily prepared in three steps from Vitamin-C by using the method by reported Wimalasena *et al*[3]. In the first step, the 5,6-diol of L-ascorbic acid was protected as its isopropylidene derivative (**6**) by using acetyl bromide and acetone at room temperature. The regioselective allylation at C-3 position of compound **6** was carried out by using allyl bromide and 2N NaOH as a base to afford **7**. The [3, 3] sigmatropic thermal rearrangement of 3-*O*-allyl derivative **7** in refluxing toluene furnished the required β-keto derivative **8** as an inseparable diastereomeric mixture (Scheme 1).

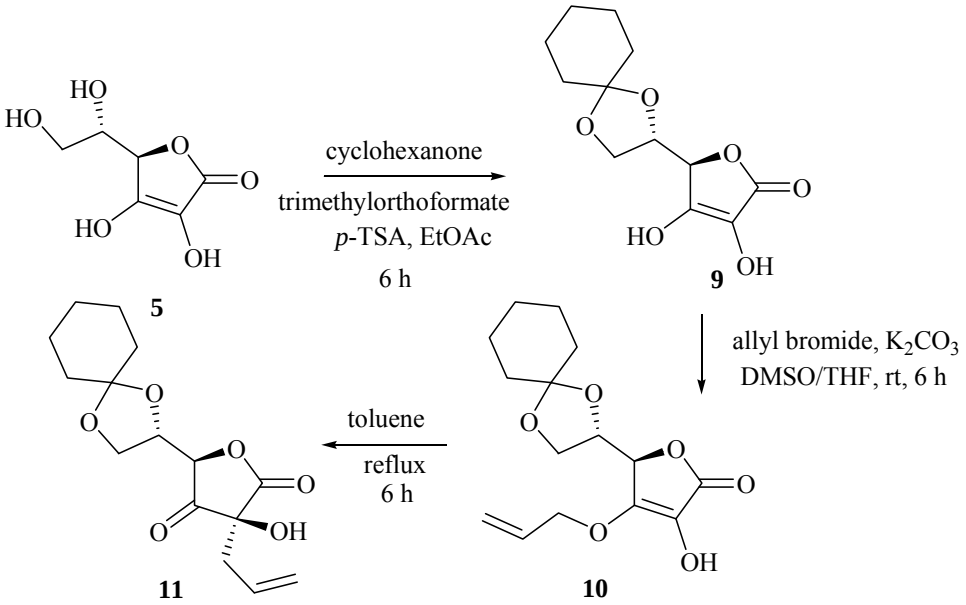
***Scheme* 1**



Due to the formation of diastereomeric mixture and the labiality of isopropylidene group (even the traces of acetic acid remained is sufficient to deprotection of isopropylidene group), we switched from isopropylidene to more stable cyclohexylidene as a protecting group for 5,6-diol. Accordingly, cyclohexylidene derivative **9** was prepared by using the procedure[4] available for isoascorbic acid. Thus treating L-ascorbic acid with trimethyl orthoformate, cyclohexanone and *p*-TSA (cat) afforded **9** in excellent yields. The ^{1}H NMR spectrum of compound **9** was in full agreement with the reported data. The regioselective allylation at C-3 hydroxyl by using allyl bromide and K_2CO_3 in DMSO/THF afforded a compound **10,** which was directly subjected for the next transformation without further purification. The Claisen rearrangement under thermal condition of **10** gave 3-keto derivative **11** exclusively (Scheme 2). The preferential migration of the allylic moiety from the bottom face of the cyclic system due to the steric constraints imposed by the bulky C-4 substituent (1,2-*O*-cyclohexylidene-1,2-ethanediol) on the top face of the lactone. The

steric factor of the C-4 bulky substituent must be even more pronounced for cyclohexylidene moiety than the corresponding isopropylidene group. The ^{1}H NMR and ^{13}C NMR is in accordance with the assigned structure of the compound **11.**

***Scheme* 2**



Our next objective was the stereoselective reduction of compound **11** to give diol **12a**. In this regard, the reported reduction of related compound **8** with different H- sources and subsequent analyses of the products formed with the help of theoretical models by Wimalasena *et al.* is helpful. There are two different models are available for the prediction of stereochemical outcome of the reduction reaction of **11** by using $NaBH_4$**;** one of them proceeds *via* a five-membered ring chelated by sodium ion and furnishes *erythro* diols[5] (Figure 3). While the other model affords the *threo* product through six-membered cyclic transition state chelated by boron atom[6] (Figure 3).

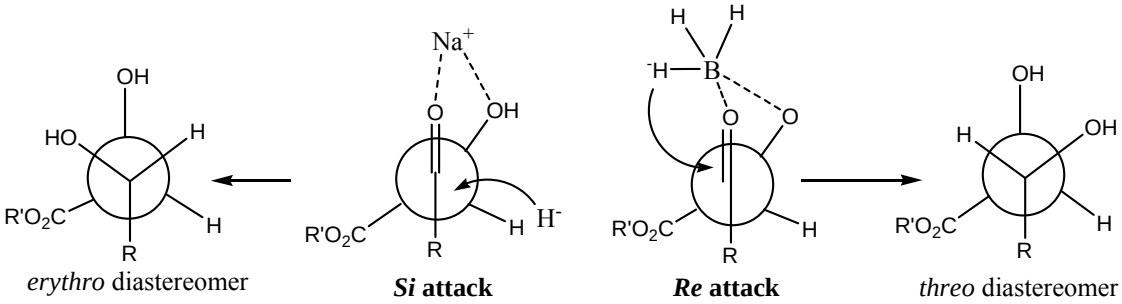
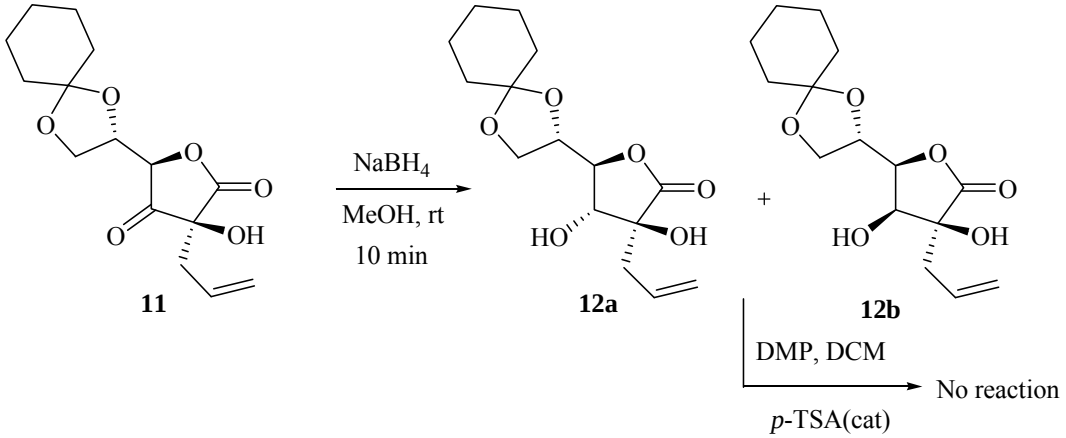


***Figure* 3.** Metal Co-ordination and inter- (with Na) and intramolecular (with B) delivary of hydride ion

So by considering above facts, we carried out the reaction at 0 ^{o}C and not exceeding the reaction time for more than 30 min. afforded diol **12a** as a single diastereoisomer. The crude product obtained was treated with 2,2-dimethoxypropane in acetone and *p*-TSA (cat) for longer time but failed to give the corresponding isopropylidene derivative, which confirms the presence of single diastereomer in the crude reaction mixture (Scheme 3).

***Scheme* 3**



The structure of the compound **12a** was identified from the ^{1}H & ^{13}C NMR characteristics. For example, in the ^{1}H NMR the doublet due to H-C(4) at 4.64 ppm is shifted at 4.17 ppm (doublet of doublet) after reduction. The new signal also appeared in the ^{1}H NMR at 4.35 ppm due to newly created H-C(3) of compound **12a**. In addition, ^{13}C NMR shows disappearance of the characteristic peak due to β-carbonyl of the starting material at 201.3 ppm upon reduction. After purification of **12** by silica gel column chromatography and keeping leaving the eluant to evaporate at rt lead to the deposition of fine crystals suitable for single crystal X-ray analysis. The single crystal X-ray structural analyses indeed confirmed the relative stereochemistry proposed for the diol **12a** beyond the doubt (Figure 4). The analysis of the crystal structure of **12a** needs a mention here.

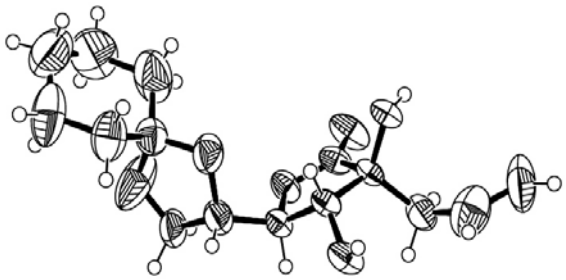


***Figure* 4:** *Molecular Structure of* **12a**

The diol **12a** displays catemeric aggregation along the *a*-axis, involving hydrogen bonds progressing from the C2-OH of one molecule to the C3-OH of the other molecule initially forming a linear chain and the two progressing adjacent linear chains aggregate in a haid-to-tail fashion thus C2-OH of one chain participating in hydrogen bonding with C3-OH of the adjacent chain thus forming a ring. The donor-acceptor distances of these hydrogen bonds are given in table 2.

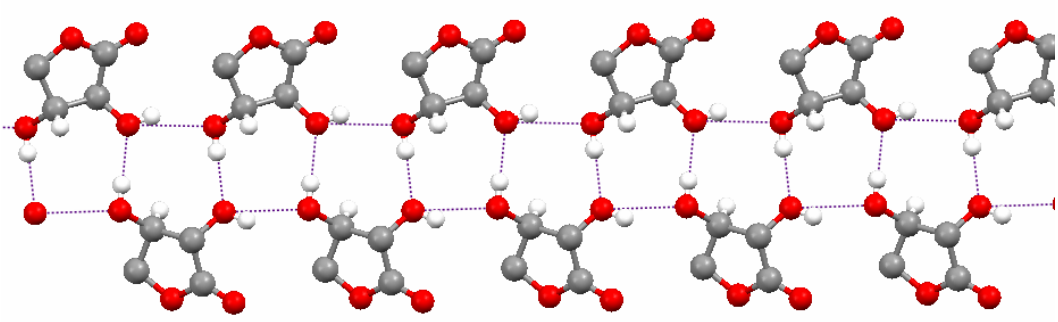


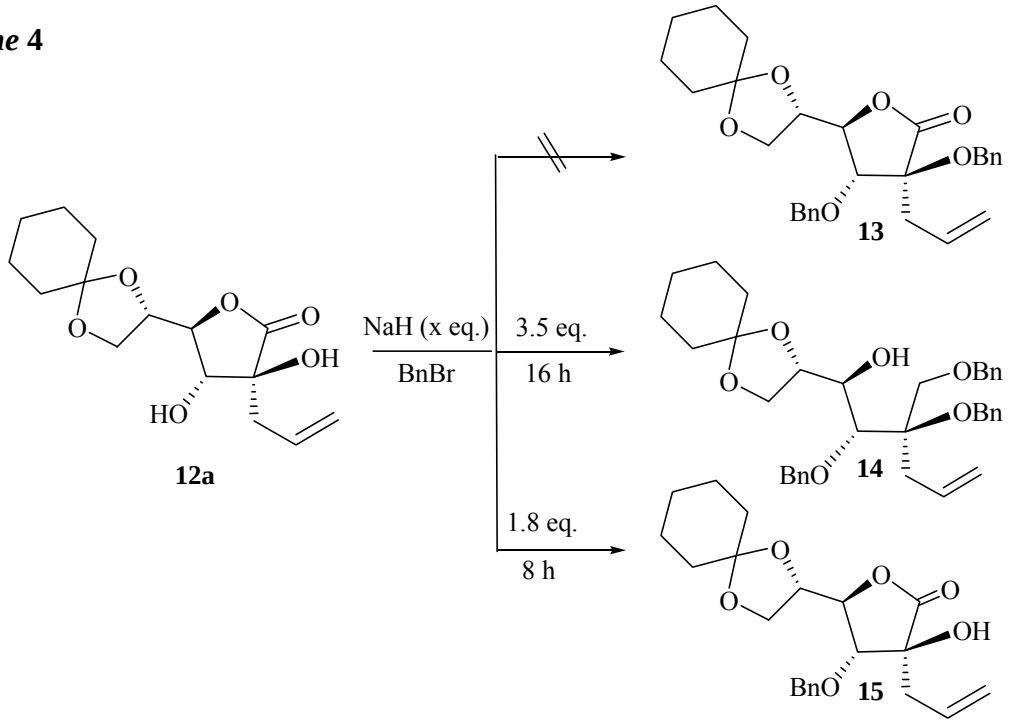
***Figure* 5:** *An infinite tape T6(2) hydrogen bonding pattern diaplayed by compound* **12a**

(Only the carbons and oxygens of the butyrolactone ring were shown for clarity)

After having the key diol **12a** in hand, our next concern was the deoxygenation at C-4. For that we needed to protect the remaining diol at this stage only. Treatment of the diol **12a** with BnBr (3.5 eq) & NaH in THF at 0 ^{o}C afforded the open chain tribenzyl derivative (**14**) instead of the expected compound **13**. The structure of **14** was confirmed by spectroscopic data. In the ^{1}H NMR spectra, the characteristic peaks due to three benzyl groups and two extra peaks due to methylene were observed. In addition the ^{13}C NMR

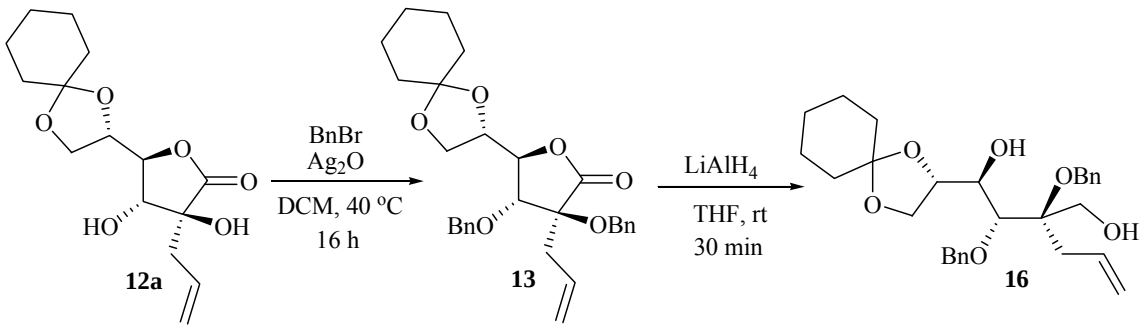
spectrum reveals the structure of **14**, not showing the lactone peak at 175.7 ppm; while in DEPT, twelve methylene peaks were observed. On the other hand, reducing the amount of BnBr (1.8 eq) lead to isolation of the monobenzylated product **15** whose structure was confirmed by using ^{1}H NMR and satisfactory elemental analysis (Scheme 4).

***Scheme* 4**



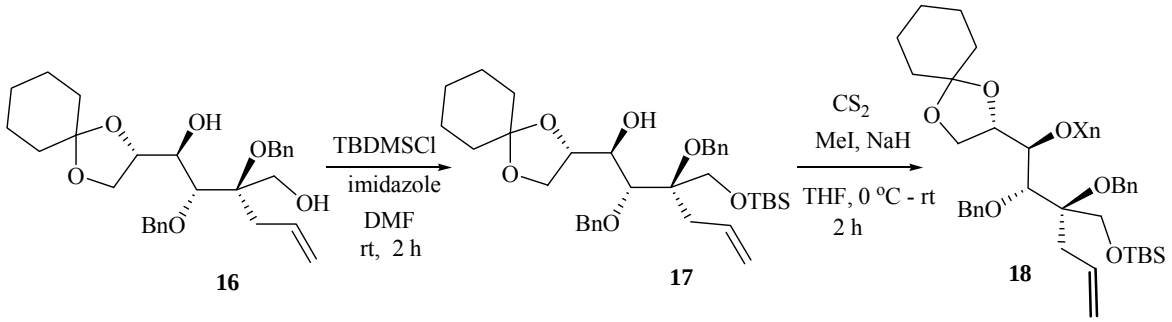
The trouble in getting the dibenzylated product in basic media forced us to use the mild acidic media for the benzylation procedure. Thus the compound **12a** was treated with BnBr, Ag_2O in DCM to afford dibenzyl derivative **13** in good to moderate yield (Scheme 5). The ^{1}H NMR and ^{13}C NMR of the compound **13** was in accordance with the assigned structure. Due to the known labiality of the substrate, taking the help 2D spectroscopy techniques like COSY, NOSEY and HET-CORE further supported the absolute stereochemistry of the compound **13**.

***Scheme* 5**



In the next step, the lactone ring of **13** was reduced to 1,4-diol derivative (**16)** by the treatment with LAH in diethyl ether at room temperature. The spectroscopic data coupled with the satisfactory mass and elemental analysis confirmed the structure of **16**. The primary alcohol of **16** was selectively protected with *tert*-butyldimethylsilylchloride in the presence of imidazole to give **17**, which was treated with methyl iodide, carbon disulfide and using sodium hydride as a base in dry THF to give dithiocarbonate derivative (**18)** (Scheme 6).

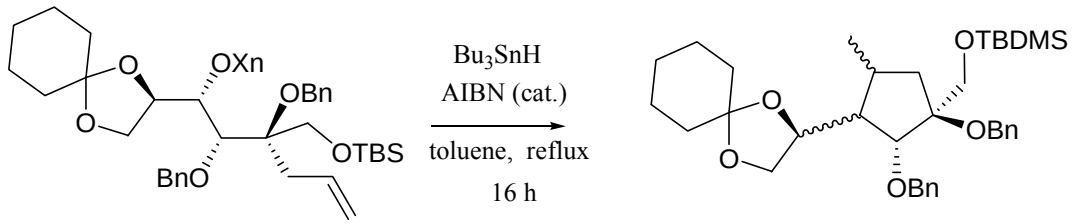
***Scheme* 6**



The compound **18** was directly used in the next step without any delay. The reductive degradation of dithiocarbonate derivative (**18)** by TBTH in refluxing toluene for 16 h gave unexpected cyclic compound **19** as a diastereomeric mixture, which was inseparable by routine as well as high pressure column chromatography (Scheme 7). However in the ^{1}H NMR spectrum of the compound **19**, the protons in olefin region were completely vanished from the starting material that confirmed the intramolecular free

radical cyclisation to afford the cyclic derivative.

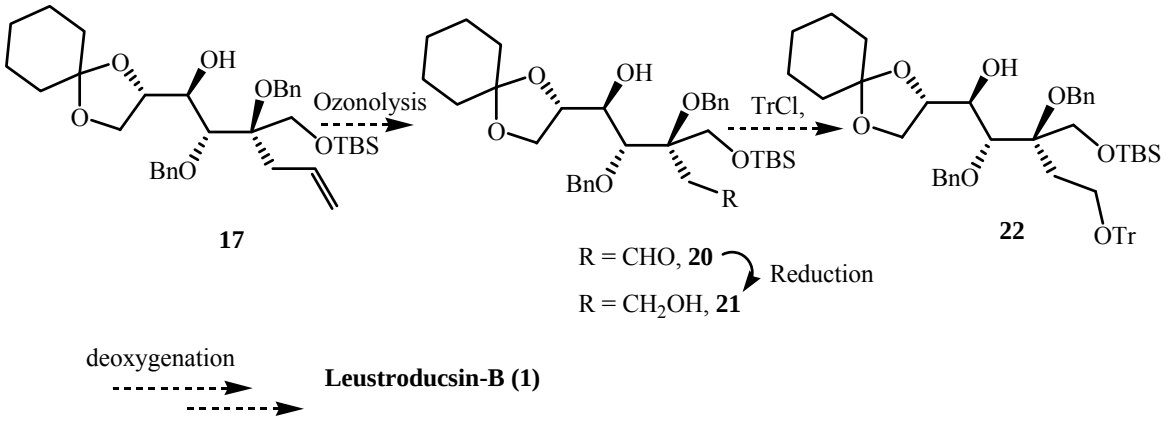
***Scheme* 7**



18 **19**

All other alternatives for deoxygenation[7] were also not successful on this secondary alcohol. Owing to failure in deoxygenation of secondary alcohol in the presence of allylic olefin, we changed our strategy. The new strategy that involves the deoxygenation at the later stage of the synthesis after ozonolysis of double bond and following the path as shown in (scheme 8), is in progress in our laboratory in order to complete the total synthesis of Leustroducsin-B.

***Scheme* 8**



17 **22**

In conclusion, we have developed a concise route to the C6-C13 fragment of Leustroducsin-B from the Vitamin-C featuring the introduction of the stereocentres at C8 and C9, affording the desired C8 quaternary centre with complete stereocontrol.

Experimental:

3-*O*-Allyl-5,6-*O*-isopropylidene-L-ascorbic acid (7)[3].

To a solution of L-ascorbic acid **5** (10.0 g, 57.0 mmol) in acetone (40 mL) was added acetyl bromide (1 mL, 13.5 mmol), a calcium chloride drying tube was placed on the flask and the slurry stirred at room temperature for 2-3 h. Then the reaction mixture was allowed to cool in the refrigerator for 4-8 h. The solid obtained was filtered off and washed with a small amount of cold acetone to afford compound **6** (9.7 g, 80 %) {M. P. 221-225 ^{o}C; lit.[3] 218-219 ^{o}C}. The aqueous 2N NaOH was added at room temperature to a stirred solution of **6** (2.0 g, 9.26 mmol) in 10 mL of THF maintaining the pH at around neutral. Allyl bromide (1 mL, 11.11 mmol) was then added dropwise and stirring was continued at the same temperature while TLC monitored the progress of the reaction. After completion (4-8 h), the reaction mixture was diluted with H_2O and extracted by using EtOAc. The combined organic extract was washed with brine, dried (Na_2SO_4) and concentrated. The crude residue was purified on neutral silica gel using ethyl acetate-light petroleum ether (1:5) to afford **7** as light greenish oil.

Yield : 11.6 g, 80 % (after two step)

Mol. Formula : $C_{12}H_{16}O_6$

^{1}H NMR (300 MHz) : δ 1.36 (s, 3H), 1.39 (s, 3H), 2.62 (br. s, 1H), 4.04 (dd, 1H, *J* = 8.8, 6.6 Hz), 4.14 (dd, 1H, *J* = 8.8, 6.6 Hz), 4.30 (dd, 1H, *J* = 6.6, 3.2 Hz), 4.54-4.68 (m, 2H), 4.96 (d, 1H, *J* = 5.9 Hz), 5.34 (m, 2H), 5.98 (m, 1H)

5,6-*O*-Isopropylidene-3-keto-2-*C*-(1-prop-2-enyl)-L-galactono-γ-lactone (8).

The compound **7** (10.0 g, 39.1 mmol) was dissolved in toluene (50 mL) and heated to reflux for 8 h after which time the solvent was removed *in vacuo* to obtain the crude *C*-2 allyl compound **8** as a diastereomeric mixture.

Yield : 9.1 g, 91 %

Mol. Formula : $C_{12}H_{16}O_6$

IR ($CHCl_3$) $\tilde{\nu}$: 3347, 1740, 1365, 1305, 1172, 1111, 938, 910, 698 cm^{-1}

+TOF MS *m/z* : 279 $[M+Na]^+$

5,6-*O*-Cyclohexylidene-L-ascorbic acid (9)[4].

A mixture of trimethyl orthoformate (13.0 mL, 119.3 mmol), cyclohexanone (11.8 mL, 113.6 mmol) and *p*-TSA (100 mg) in EtOAc (300 mL) was stirred under reflux for 1 h. Then Vitamin-C (10.0 g, 56.8 mmol) was added and reflux was continued for 6 h. Distillation of EtOAc (200 mL) at atmospheric pressure gave the residue solution which was filtered through the bed of neutral alumina in order to remove the acid catalyst. The crude white crystalline product was deposited by the addition of light petroleum ether, which was filtered, dried at room temperature to afford **9** as a pure white crystalline solid.

Yield : 11.9 g, 82 %

Mol. Formula : $C_{12}H_{16}O_6$

M.P. : 179-182 ^oC; Lit[4]. 184-185 ^oC

$[\alpha]_D^{25}$: 45.2 (*c* = 1.0, MeOH);{ Lit[3] 46.3 (*c* = 1.08, MeOH)}

IR ($CHCl_3$) $\tilde{\nu}$: 3347, 1740, 1365, 1305, 1172, 1111, 938, 910, 698 cm^{-1}

^{1}H NMR (DMSO-d^6, 500 MHz) : δ 1.78-1.85 (m, 2H), 1.94-2.04 (m, 8H), 4.45 (dd, 1H, *J* = 8.4, 6.8 Hz), 4.62 (dd, 1H, *J* = 8.4, 7.2 Hz), 4.80 (ddd, 1H, *J* = 9.9, 6.8, 3.2 Hz), 5.15 (d, 1H, *J* = 3.6 Hz)

5,6-*O*-Cyclohexylidene-3-keto-2-*C*-(1-prop-2-enyl)-L-galactono-γ-lactone (11).

A mixture of **9** (2.0 g, 7.8 mmol) and K_2CO_3 (1.4 g, 9.4 mmol) in 10 mL DMSO/THF (5:4) was stirred for 1 h at room temperature. The allyl bromide (0.8 mL, 9.4 mmol) in the same solvent was added dropwise, and the mixture was vigorously stirred for 6 h at room temperature. The reaction mixture was diluted with H_2O and extracted with EtOAc. The organic layer was washed with brine**,** dried (Na_2SO_4) and concentrated. The crude orange color oil obtained was subjected to the next step without purification. The compound **10** (1.7 g, 5.4 mmol) was dissolved in toluene (25 mL) and heated to reflux for 6 h after which time the solvent was removed *in vacuo* to obtain the crude *C*-2 allyl compound which was purified on silica gel using ethyl acetate-light petroleum ether (1:3) to furnish **11** as a dark orange oil.

Yield **:** 1.2 g , 71 %

Mol. Formula **:** $C_{15}H_{20}O_6$

IR ($CHCl_3$) $\tilde{\nu}$ **:** 3341, 1743,1770, 1315, 1172, 1115, 947, 911, 699 cm^{-1}

^{1}H NMR (500 MHz) **:** δ 1.34-1.43 (m, 2H), 1.53-1.68 (m, 8H), 2.67 (m, 2H), 4.06 (dd, 1H, *J* = 8.6, 7.2 Hz), 4.18 (dd, 1H, *J* = 8.6, 6.8 Hz), 4.52 (dt, 1H, *J* = 8.7, 1.6 Hz), 4.64 (d, 1H, *J* = 2.0 Hz), 5.26 (m, 2H), 5.69 (m, 1H)

^{13}C NMR (125 MHz) **:** 23.8, 24.0, 25.1, 34.9, 36.6, 37.2, 64.9, 75.0, 75.1, 85.0, 110.7, 123.4, 126.6, 172.0, 201.3 ppm

+TOF MS *m/z* **:** 319 $[M+Na]^+$

5,6-*O*-Cyclohexylidene-2-*C*-(1-prop-2-enyl)-L-gulono-γ–lactone (12a).

To a solution of **11** (1.1 g, 3.7 mmol) in dry MeOH was slowly added $NaBH_4$ (0.2 g, 4.1 mmol) at 0 ^oC with stirring. The reaction mixture was allowed to stir at 0 ^oC for a period of no more than 30 min., then diluted with water and extracted by using EtOAc. The combined organic extract was washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel using ethyl acetate-light petroleum ether (1:3) to give pure **12a** as a white crystalline solid.

Yield	:	0.8 g, 73%
Mol. Formula	:	$C_{15}H_{22}O_6$
M.P.	:	105 ^oC
$[\alpha]_D^{25}$	:	42.8 (*c* = 1, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	:	3435, 3019, 1782, 1439, 1305, 1367, 1098, 1043, 926 cm^{-1}
^{1}**H NMR** (500 MHz)	:	δ 1.35-1.43 (m, 2H), 1.58-1.66 (m, 8H), 2.53 (dd, 1H, *J* = 14.6, 9.2 Hz), 2.58 (d, 1H, *J* = 3.7 Hz), 2.63 (dd, 1H, *J* = 14.6, 5.5 Hz), 3.66 (br. s, 1H), 4.00 (dd, 1H, *J* = 8.3, 7.3 Hz), 4.13 (dd, 1H, *J* = 8.7, 6.9 Hz), 4.17 (dd, 1H, *J* = 5.5, 2.8 Hz), 4.35 (dt, 1H, *J* = 9.6, 6.9 Hz), 4.43 (dd, 1H, *J* = 5.5, 4.1 Hz), 5.29 (d, 1H, *J* = 10.2 Hz), 5.31 (d, 1H, *J* = 17.4 Hz), 5.97 (m, 1H)
^{13}**C NMR** (125 MHz)	:	23.9, 23.9, 25.0, 35.2, 35.4, 36.5, 64.8, 74.1, 75.9, 77.8, 80.0, 111.2, 121.2, 130.9, 175.7 ppm
EI MS *m/z*	:	299 $[M+H]^+$, 316 $[M+H_2O]^+$
Elemental Analysis		Calcd: C, 60.40; H, 7.38%
		Found: C, 60.40; H, 7.54%

5,6-*O*-Cyclohexylidene-1,2,3-*tri*-*O*-benzyl-2-*C*-(1-prop-2-enyl)-D-iditol *(*14).

A mixture of **12a** (0.7 g, 2.35 mmol), benzyl bromide (0.84 mL, 7.05 mmol), and NaH (60% dispersion in oil, 2.9 g, 9.4 mmol) in DMF (70 mL) was stirred for 16 h at 0 ^oC. The reaction mixture was quenched by ice-cold water and extracted with EtOAc. The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The

residue was purified on silica gel using ethyl acetate-light petroleum ether (1:6) to obtain **14** as a syrupy liquid.

Yield : 1.2 g, 89%

Mol. Formula : $C_{36}H_{44}O_6$

^{1}H NMR (500 MHz) : δ 1.33-1.40 (m, 2H), 1.51-1.63 (m, 8H), 2.83 (dd, 1H, *J* = 15.6, 6.4 Hz), 2.92 (dd, 1H, *J* = 15.6, 7.3 Hz), 3.56 (t, 1H, *J* = 7.8), 3.72 (t, 1H, *J* = 7.3 Hz), 3.83 (t, 1H, *J* = 6.4 Hz), 3.93 (d, 1H, *J* = 5.5 Hz), 4.35 (q, 1H, *J* = 6.9 Hz), 4.49, 4.54 (2d, 2H, *J* = 10.5 Hz), 4.66 (m, 3H), 4.74 (d, 1H, *J* = 10.5 Hz), 4.86, 4.92 (2d, 2H, *J* = 12.4 Hz), 5.07-5.11 (m, 2H), 5.94 (m, 1H), 7.19-7.27 (m, 15H)

^{13}C NMR (125 MHz) : 24.0, 24.1, 25.3, 35.1, 36.3, 36.9, 66.4, 66.8, 67.4, 74.0, 74.7, 77.5, 80.0, 83.9, 84.6, 109.0, 118.3, 127.3, 127.5, 128.2, 128.5, 133.1, 135.6, 138.2, 138.6 ppm

Elemental Analysis Calcd: C, 75.39; H, 7.68%

Found: C, 75.61; H, 7.23%

5,6-*O*-Cyclohexylidene-3-*O*-benzyl-2-*C*-(1-prop-2-enyl)-L-gulono-γ-lactone (15).

A mixture of **12a** (100 mg, 0.34 mmol), benzyl bromide (50 μL, 0.39 mmol), and freshly prepared NaH (60% dispersion in oil, 24 mg, 0.61 mmol) in DMF (10 mL) was stirred for 8 h at 0 ^{o}C. The solids were removed by filtration (Celite bed) and thoroughly washed with DMF and the filtrate and washings were combined and evaporated to dryness. The residue was purified on silica gel using ethyl acetate-light petroleum ether (1:3) to give **15** as a syrupy liquid.

Yield : 110 mg, 85%

Mol. Formula : $C_{22}H_{28}O_6$

^{1}H NMR (500 MHz) : δ 1.34-1.59 (m, 10H), 2.74 (m, 2H), 3.85-4.22(m, 4H), 4.50-4.80 (m, 4H), 4.22 (m, 2H), 5.96 (m, 1H), 7.25-7.35 (m, 5H)

Elemental Analysis Calcd: C, 68.04; H, 7.22%

Found: C, 68.21; H, 7.08%

5,6-*O*-Cyclohexylidene-2,3-di-*O*-benzyl-2-*C*-(1-prop-2-enyl)-L-gulono-γ-lactone (13).

A mixture of **12a** (0.7 g, 2.35 mmol), benzyl bromide (0.84 mL, 7.05 mmol), and freshly prepared Ag_2O (2.9 g, 9.4 mmol) in DMF (70 mL) was stirred for 16 h at 40 ^oC. The solids were removed by filtration (Celite bed) and thoroughly washed with DMF and the filtrate and washings were combined and concentrated. The residue was purified on silica gel using ethyl acetate-light petroleum ether (1:9) to give **13** as a syrupy liquid.

Yield : 1.1 g, 94%

Mol. Formula : $C_{29}H_{34}O_6$

$[\alpha]_D^{25}$: 54.3 (*c* = 1, $CHCl_3$)

IR ($CHCl_3$) $\tilde{\nu}$: 1788, 1740, 1497, 1454, 1103, 927 cm^{-1}

^{1}H NMR (500 MHz) : δ 1.36-1.40 (m, 2H), 1.51-1.64 (m, 8H), 2.74 (dd, 1H, *J* = 14.2, 7.8 Hz), 2.78 (dd, 1H, *J* = 14.2, 7.3 Hz), 3.92 (dd, 1H, *J* = 8.3, 7.3 Hz), 4.01 (dd, 1H, *J* = 8.3, 6.9 Hz), 4.11 (dd, 1H, *J* = 7.3, 2.8 Hz), 4.19 (dt, 1H, *J* = 9.6, 6.9 Hz), 4.55-4.64 (m, 4H), 4.79 (d, 1H, *J* = 11.5 Hz), 5.20-5.26 (m, 2H), 5.94-6.02 (m, 1H), 7.30-7.39 (m, 10H)

^{13}C NMR (125 MHz) : 23.9, 23.9, 25.1, 35.3, 35.6, 36.5, 64.8, 67.4, 73.1, 74.0, 77.8, 78.3, 84.5, 110.6, 120.1, 127.8, 127.9, 128.0, 128.3,

128.4, 128.6, 130.9, 137.0, 137.8, 172.6 ppm

+TOF MS *m/z* **:** 502 $[M+Na]^+$

Elemental Analysis Calcd: C, 72.80; H, 7.11%

Found: C, 72.94; H, 7.28%

5,6-*O*-Cyclohexylidene-2,3-di-*O*-benzyl-2-*C*-(1-prop-2-enyl)-D-iditol (16).

A solution of **13** (1.0 g, 2.1 mmol) in dry THF (5 mL) was added to a suspension of LAH (34 mg, 0.9 mmol) in dry THF. The resulting mixture was stirred at room temperature for 30 min., then quenched with EtOAc, diluted with water, treated with 5% aqueous KOH (2 mL), and stirred until two layers separated. The water layer was extracted with EtOAc and the combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified on silica gel using ethyl acetate-light petroleum ether (1:3) to afford pure **16** as colorless oil.

Yield **:** 0.9 g, 90 %

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

^{1}H NMR (200 MHz) **:** δ 1.29-1.36 (m, 2H), 1.38-1.58 (m, 8H), 2.28-2.37 (m, 2H), 3.25-3.27 (br. s, 1H, overlapped), 3.26 (t, 1H, *J* = 6.9 Hz), 3.40 (dd, 1H, *J* = 8.3, 6.4 Hz), 3.49 (t, 1H, *J* = 11.9 Hz), 3.76 (dd, 1H, *J* = 8.3, 3.2 Hz), 3.86 (dd, 1H, *J* = 12.9, 3.2 Hz), 4.27 (d, 1H, *J* = 11.0 Hz), 4.45 (q, 1H, *J* = 6.9 Hz), 4.59-4.62 (m, 2H), 4.68, 4.87 (2d, 2H, *J* = 11.5 Hz), 4.97 (d, 1H, *J* = 16.0 Hz), 5.05 (d, 1H, *J* = 10.1 Hz), 5.69-5.78 (m, 1H), 7.32-7.47 (m, 10H)

^{13}C NMR (125 MHz) **:** 23.8, 24.2, 25.3, 34.4, 35.8, 36.8, 61.5, 64.0, 66.2, 75.2, 78.0, 80.2, 80.8, 81.3, 109.1, 118.7, 127.3, 127.7, 127.8, 128.3, 128.4, 128.8, 133.1, 137.8, 137.9, 138.1 ppm

+TOF MS *m/z* **:** 506 $[M+Na]^+$

Elemental Analysis Calcd: C, 72.19; H, 7.88%

Found: C,72.46; H, 8.10%

1-*O*-*tert*-Butyldimethylsilane-5,6-*O*-Cyclohexylidene-2,3-di-*O*-benzyl-2-*C*-(1-prop-2-enyl)-D-iditol (17).

To a stirred solution of **16** (0.8 g, 1.7 mmol) in dry DMF (30 mL) at 0 ^oC was added *tert*-butyldimethylchlorosilane (0.26 g, 1.7 mmol), imidazole (0.13 g, 1.9 mmol) and the reaction mixture was stirred at room temperature for 2 h. Water was added (30 mL) and extracted with EtOAc, washed with brine. The combined organic layer was dried (Na_2SO_4), filtered and concentrated. Purification of the residue on silica gel using ethyl acetate-light petroleum ether (1:4) gave **17** as colorless oil.

Yield **:** 0.8 g, 84%

Mol. Formula **:** $C_{35}H_{52}O_6Si$

^{1}H NMR (200 MHz) **:** δ 0.07 (m, 6H), 0.91 (m, 9H), 1.22-1.65 (m, 10H), 2.39-2.83 (m, 1H), 3.20-3.54 (m, 1H), 3.70-3.82 (m, 2H), 3.84-3.95 (m, 3H), 4.01-4.16 (m, 2H), 4.29-4.38 (m, 1H), 4.59-4.85 (m, 3H), 4.98-5.21 (m, 2H), 5.85-6.11 (m, 1H), 7.25-7.36 (m, 10H)

EI MS *m/z* **:** 598 $[M+H]^+$

Elemental Analysis Calcd: C, 70.47; H, 8.72%

Found: C, 70.71; H, 8.43%

(–/+)-1-[(*2R,3S*)-2,3-Bis(benzyloxy)-3-(*tert*-butyloxydimethylsilanehydroxymethyl)-5-methylcyclopentyl]ethane-1,2-cyclohexylidene (19).

To a solution of **17** (0.75 g, 1.26 mmol) in dry THF (15 mL) at 0 °C was added sodium hydride (60% dispersion in mineral oil, 0.1 g, 1.89 mmol) followed by carbon disulfide (0.25 mL, 2.56 mmol) after 30 min. The stirring continued for 30 min and then methyl iodide (0.12 mL, 1.89 mmol) was introduced. After 2 h, reaction mixture was quenched by the addition of ice-water and repeatedly extracted with EtOAc. The combined organic extract was washed with water, dried (Na_2SO_4) and concentrated. The crude xanthate (0.9 g, 1.31 mmol) was dissolved in toluene (5 mL) & this solution was added dropwise under an Argon to a boiling solution of tri-*n*-butyltinhydride (0.7 mL, 2.41 mmol) in toluene (25 mL) containing AIBN (10 mg) as a free radical initiator. The contents were heated under reflux for 16 h and concentrated. The residue was purified on silica gel using ethyl acetate-light petroleum ether (1:20) to afford **19** as oil.

Yield : 0.6 g, 82%

Mol. Formula : $C_{35}H_{52}O_5Si$

^{1}H NMR (200 MHz) : δ 0.02 (m, 6H), 0.91 (m, 12H), 1.33-1.55 (m, 10H), 2.02-2.06 (m, 3H), 3.54-4.80 (m, 10H), 7.26-7.34 (m, 10H)

EI MS *m/z* : 582 $[M+H]^+$

Elemental Analysis Calcd: C, 72.41; H, 8.97%

Found: C, 72.92; H, 9.12%

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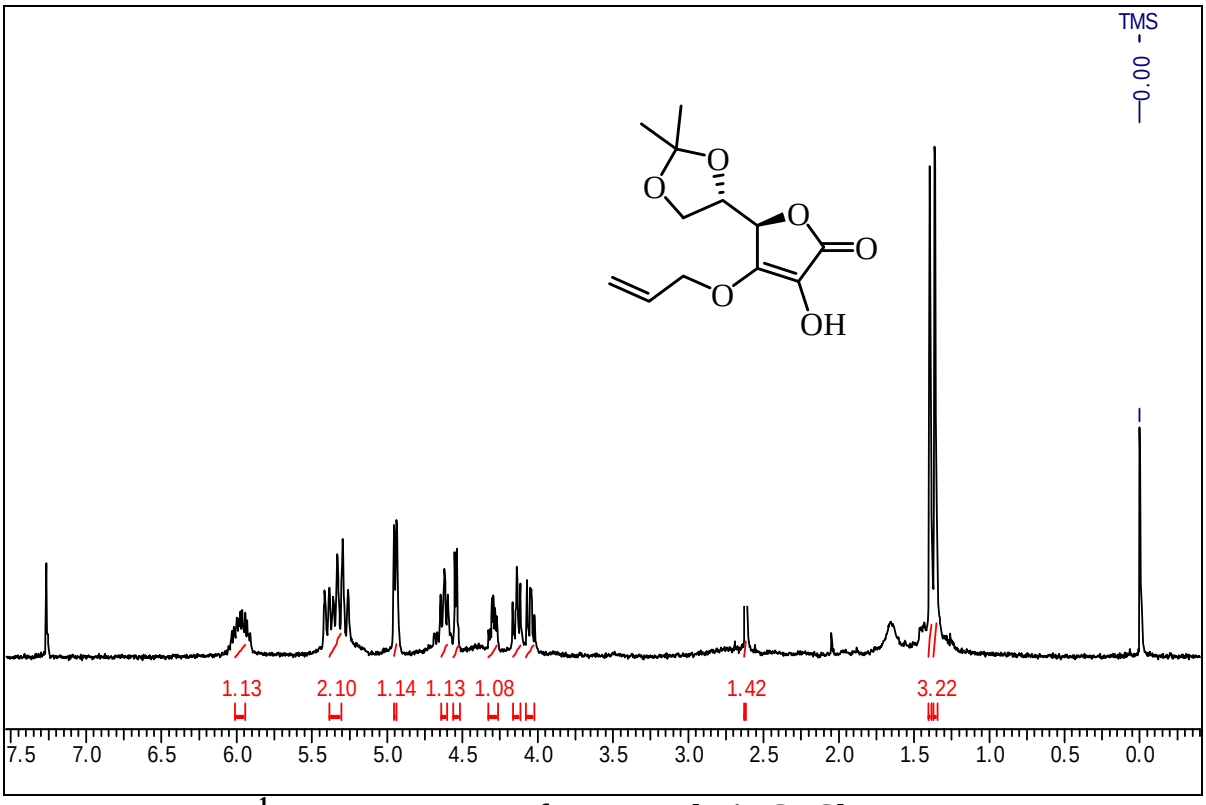
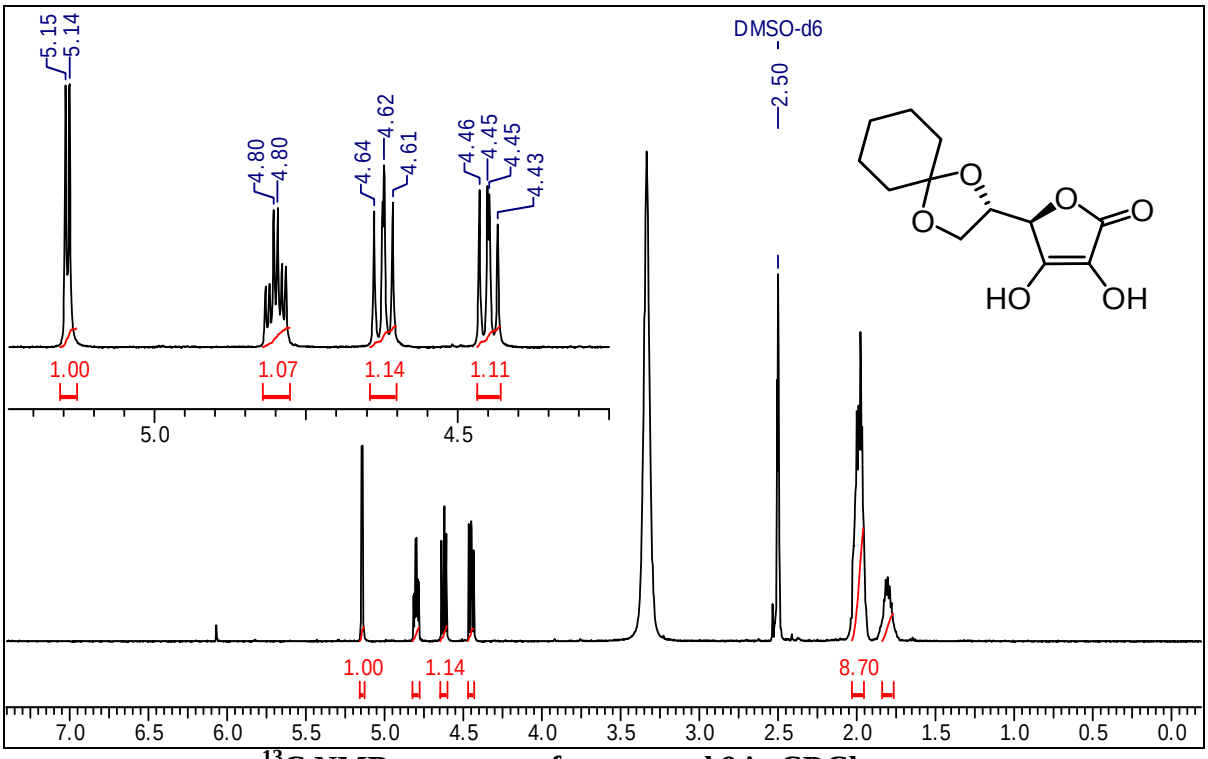
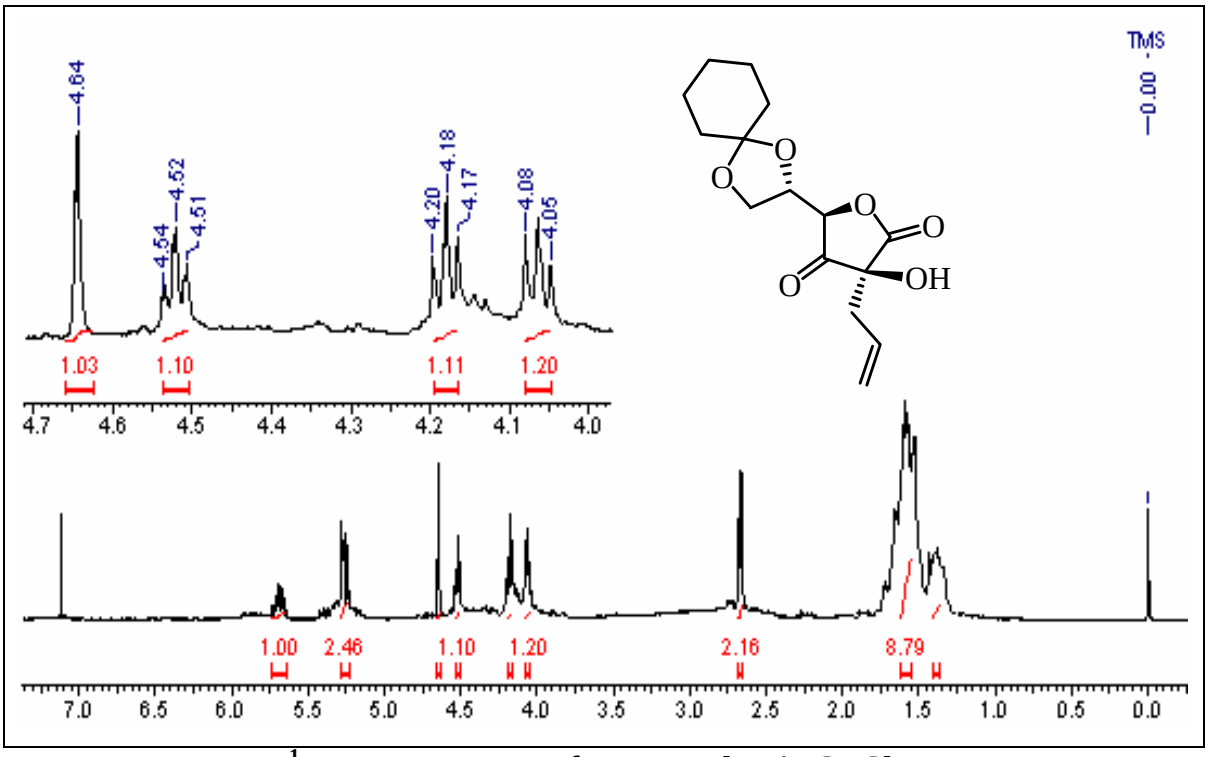
SPECTRA



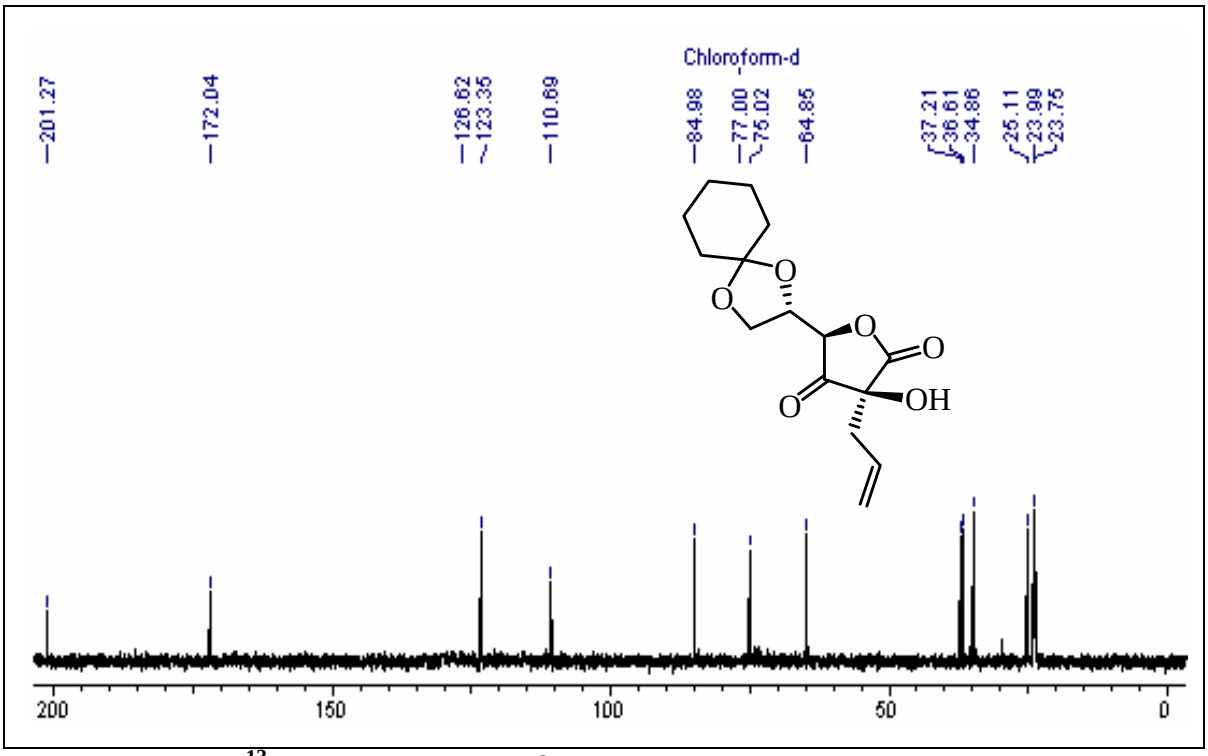
^{1}H NMR spectrum of compound 7 in $CDCl_3$



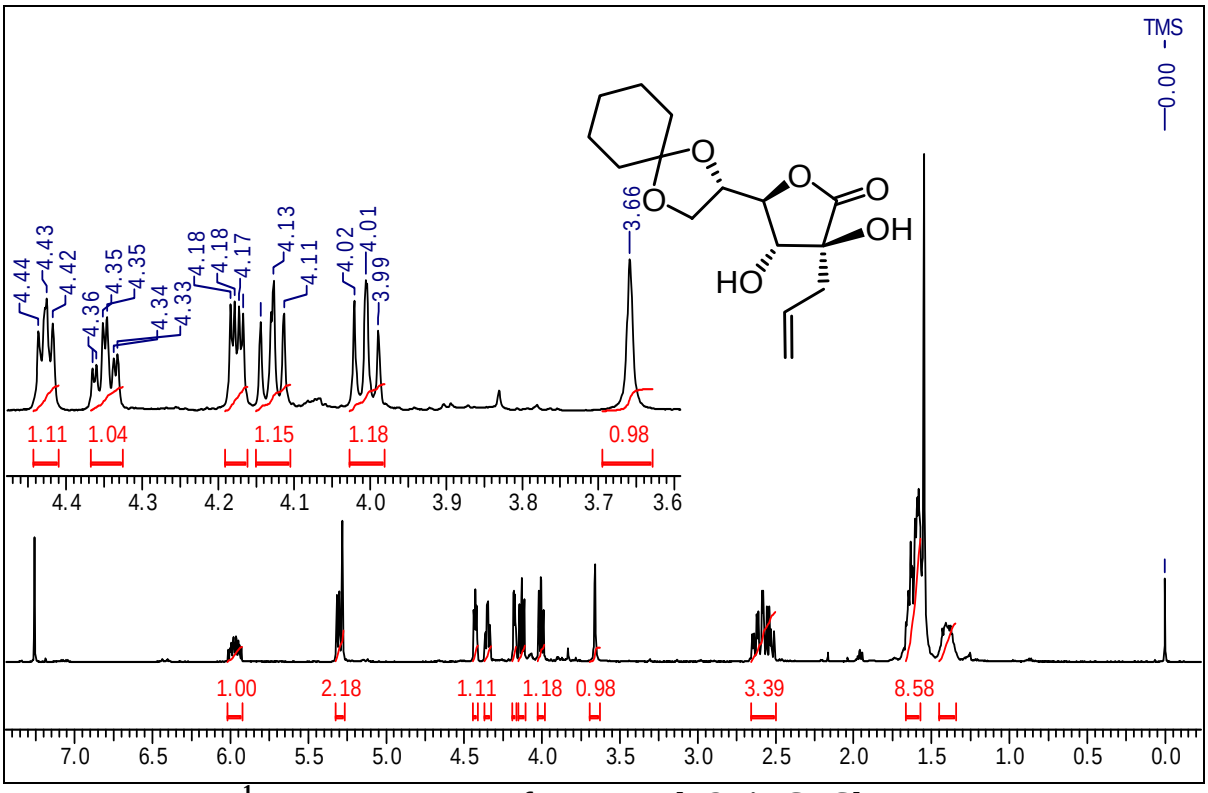
^{13}C NMR spectrum of compound 9 in $CDCl_3$



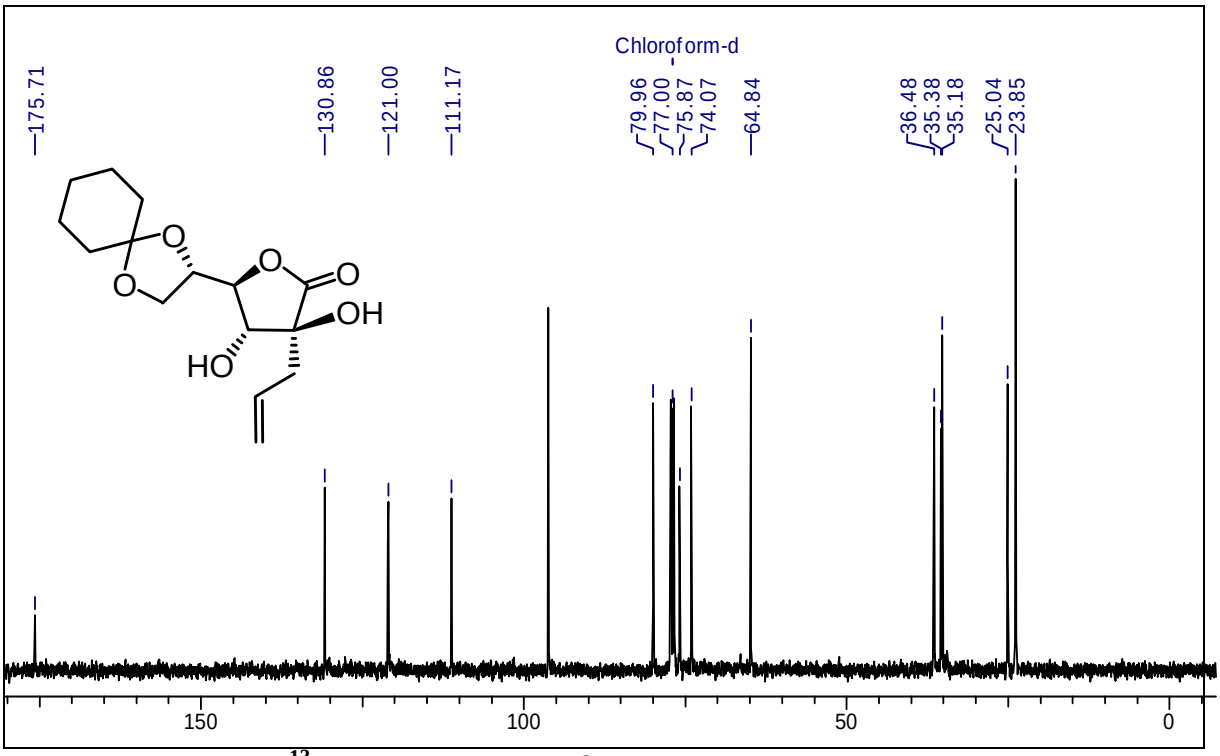
^{1}H NMR spectrum of compound 11 in $CDCl_3$



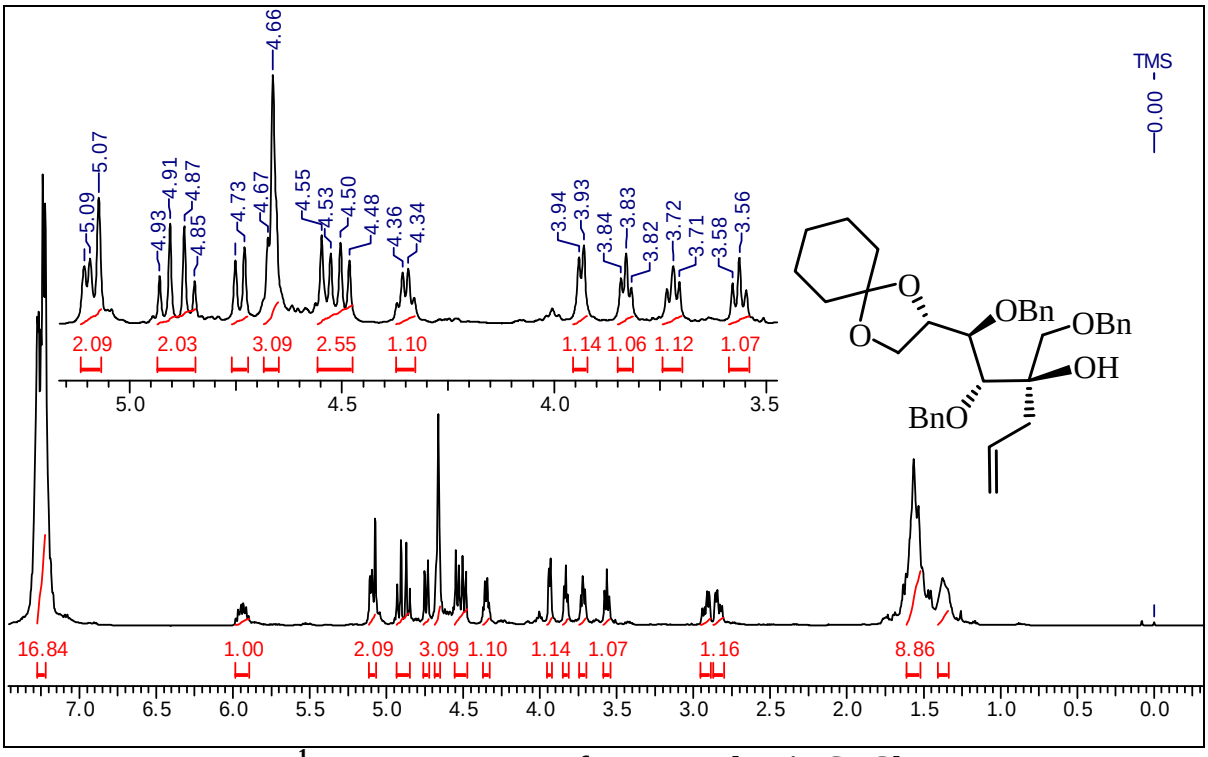
^{13}C NMR spectrum of compound 11 in $CDCl_3$



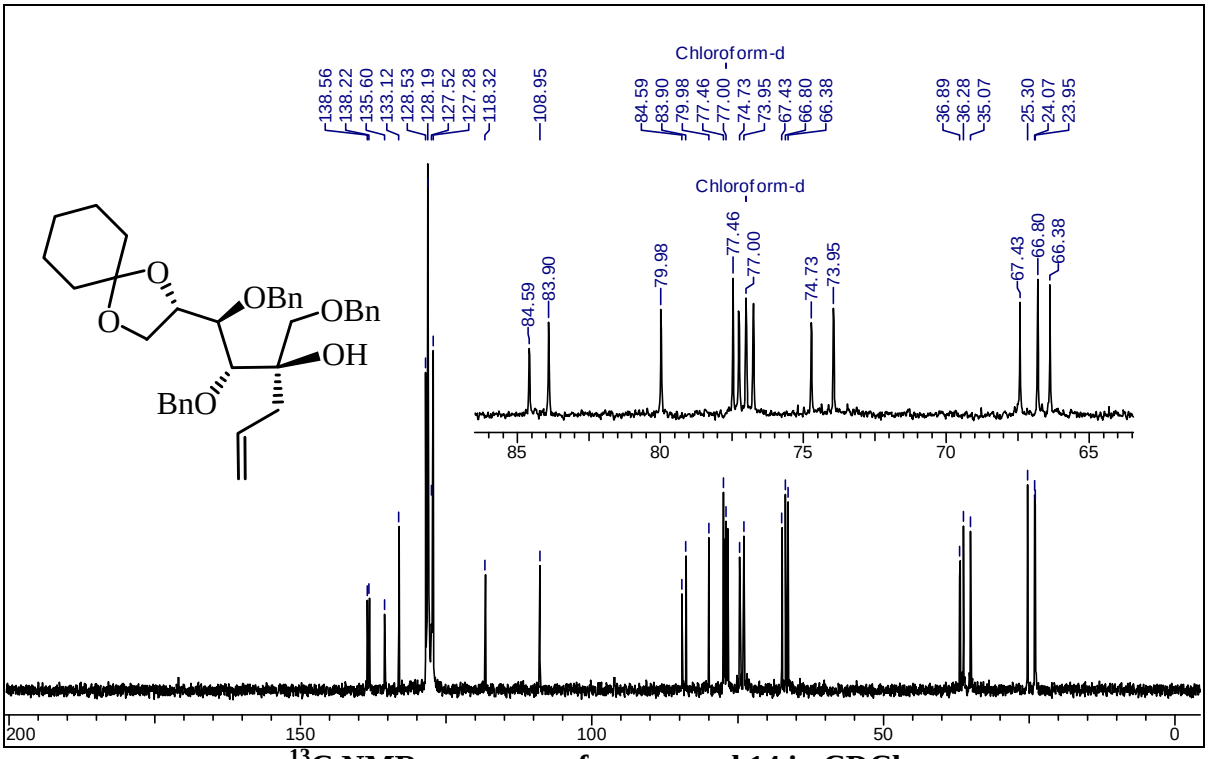
^{1}H NMR spectrum of compound 12a in $CDCl_3$



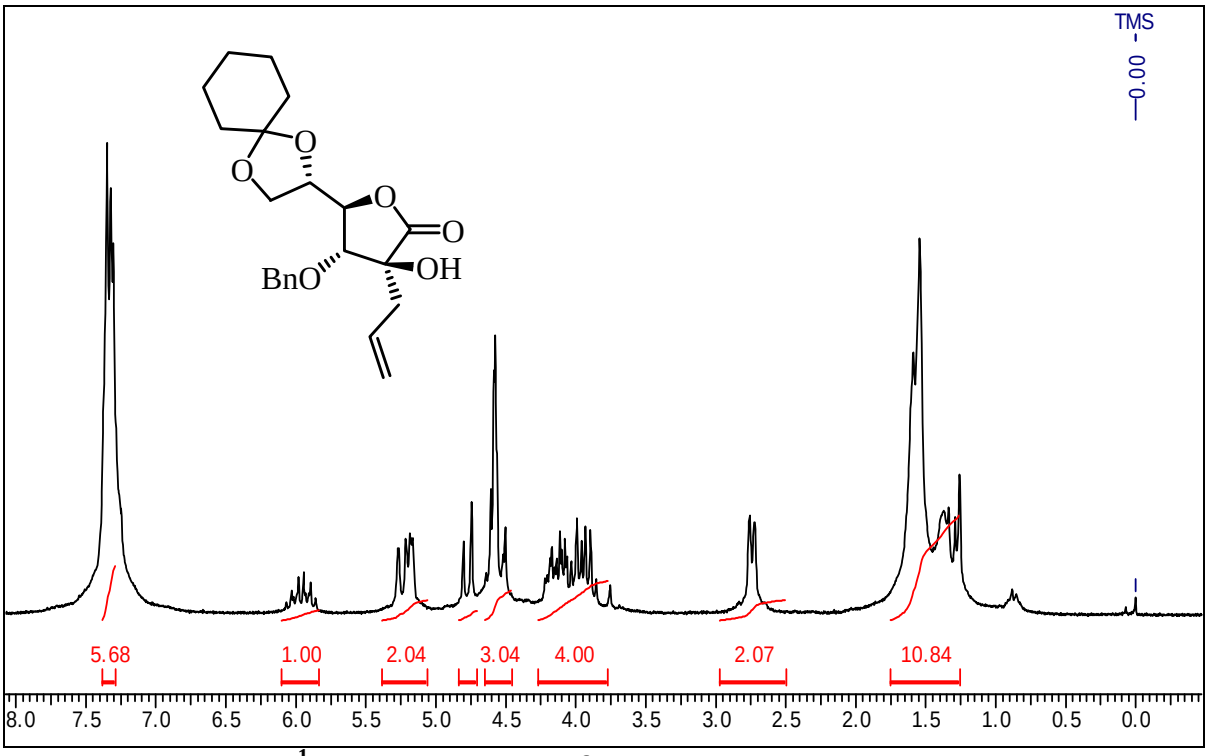
^{13}C NMR spectrum of compound 12a in $CDCl_3$



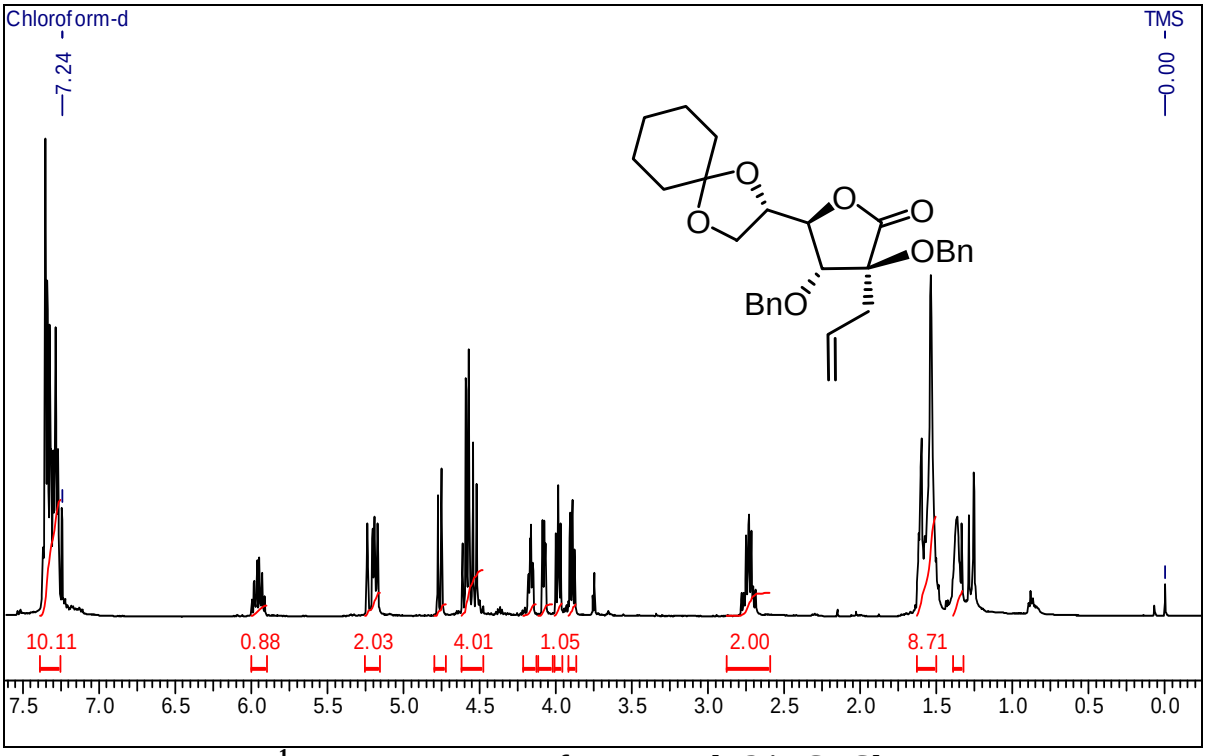
^{1}H NMR spectrum of compound 14 in $CDCl_3$



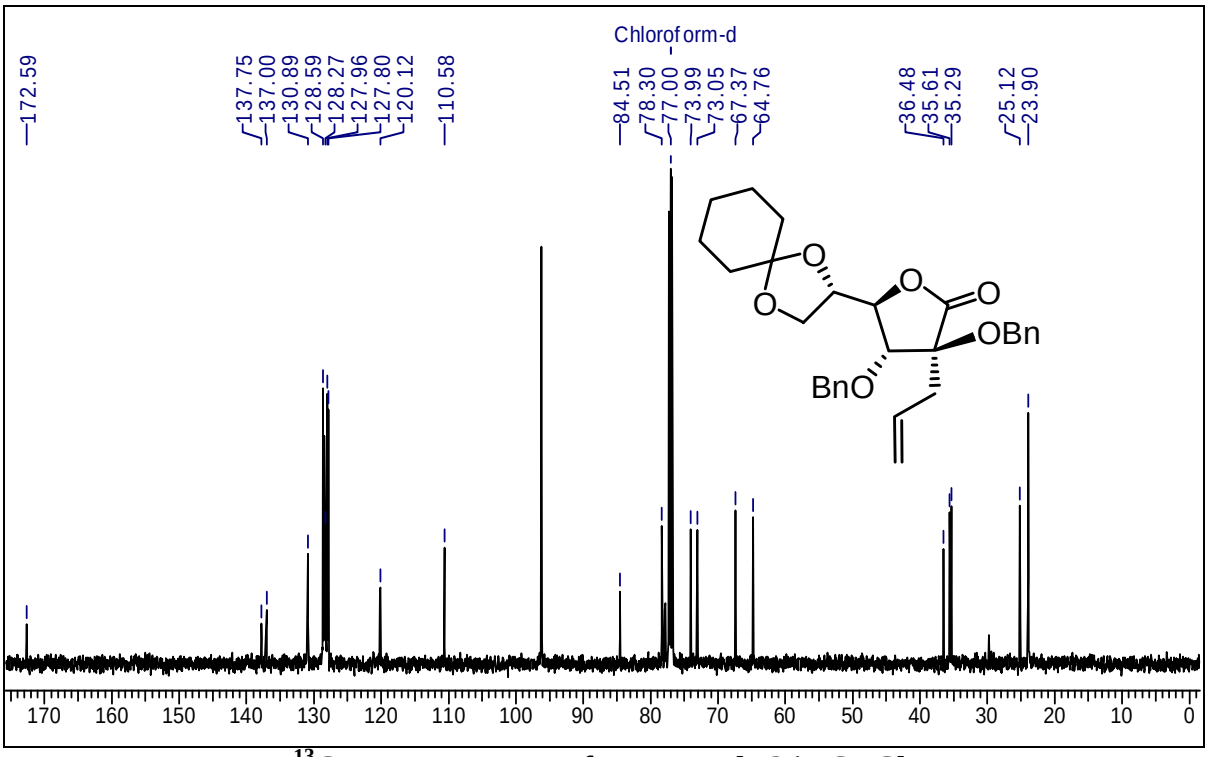
^{13}C NMR spectrum of compound 14 in $CDCl_3$



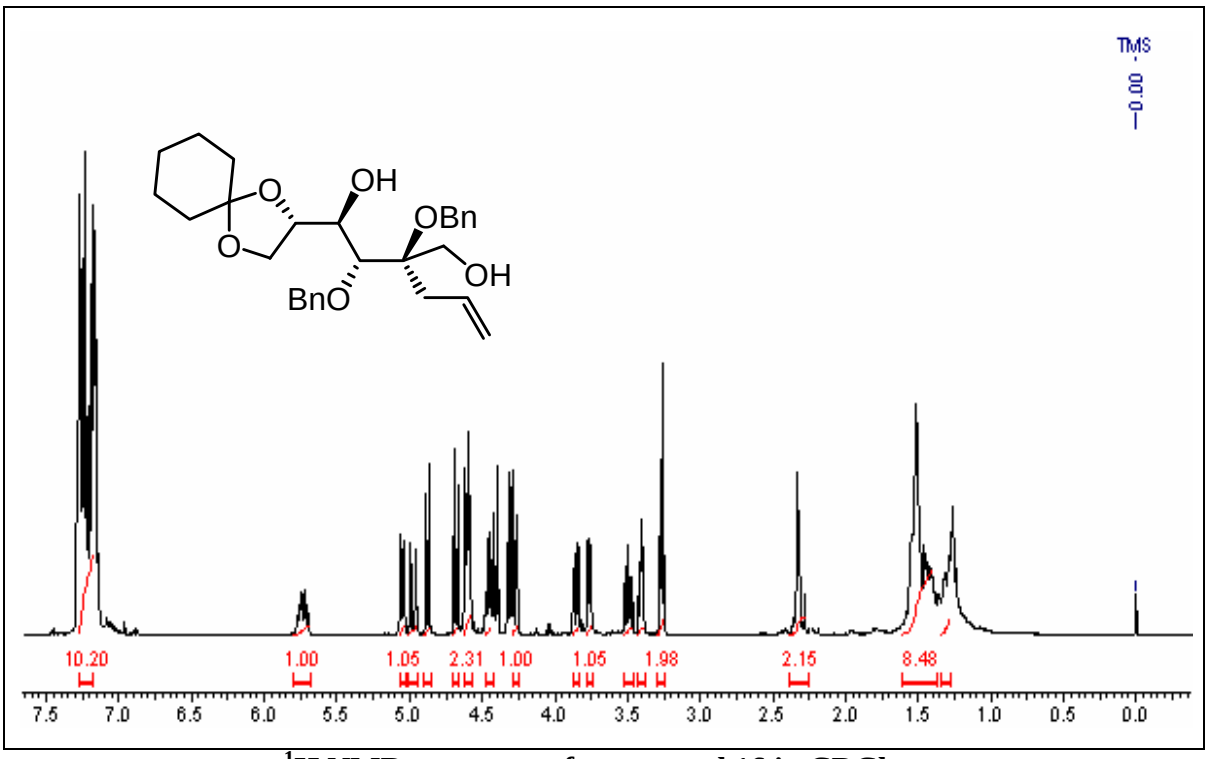
^{1}H NMR spectrum of compound 15 in $CDCl_3$



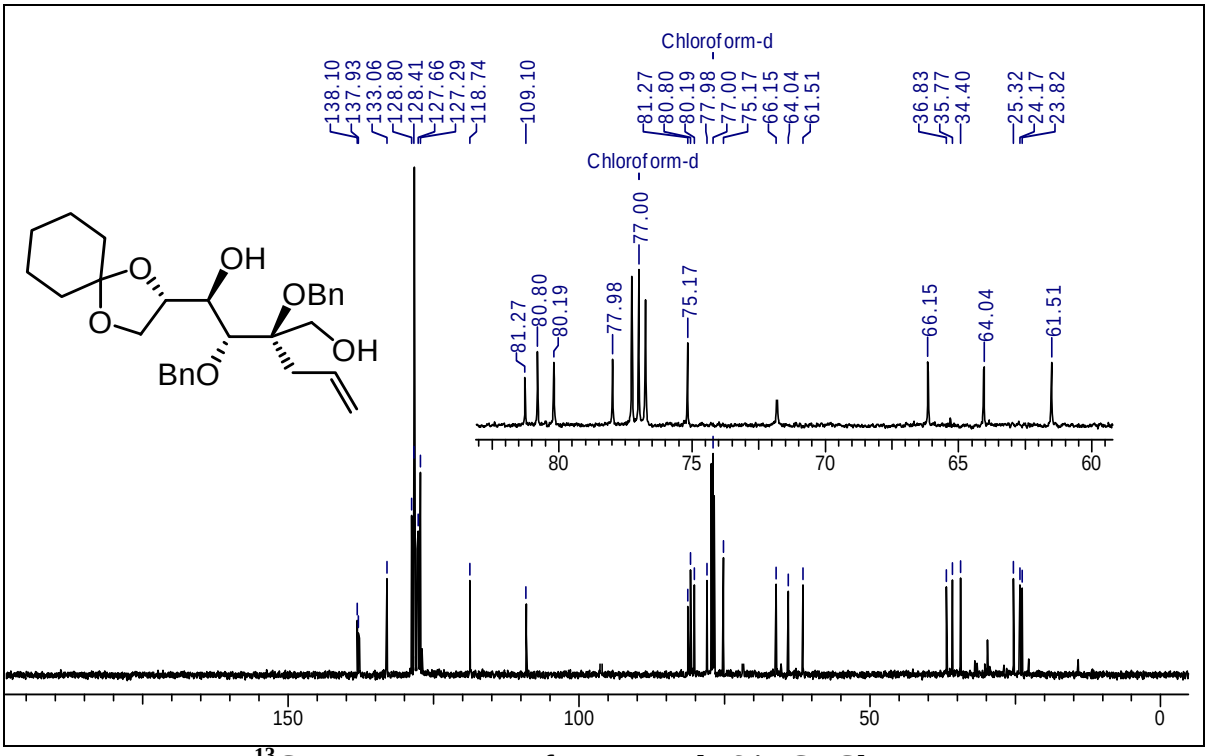
^{1}H NMR spectrum of compound 13 in $CDCl_3$



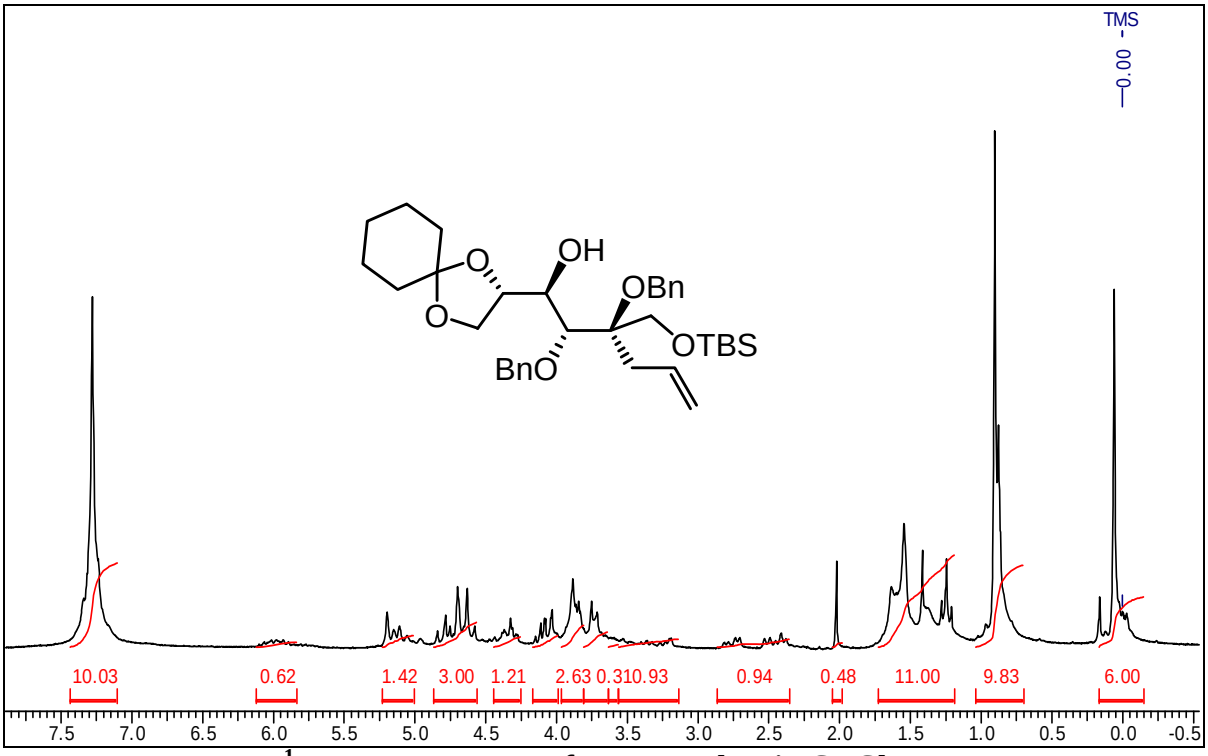
^{13}C NMR spectrum of compound 13 in $CDCl_3$



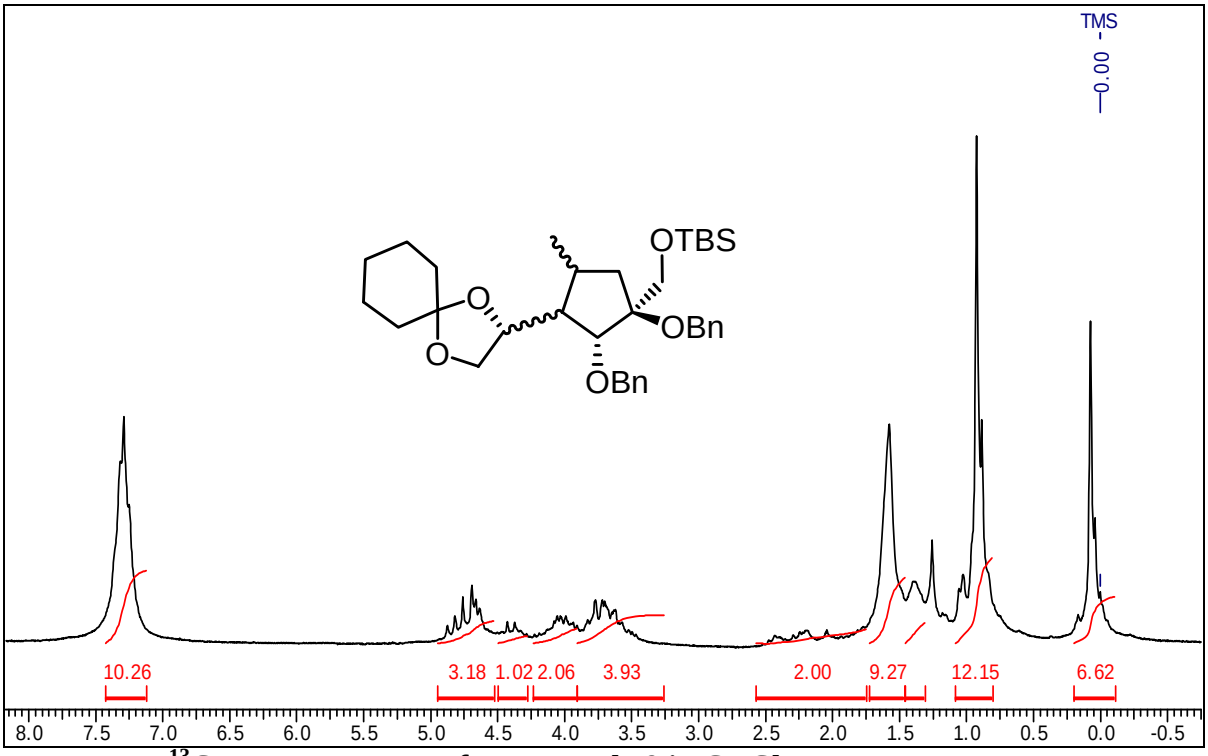
^{1}H NMR spectrum of compound 16 in $CDCl_3$



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



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



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

PUBLICATIONS

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3. Mukund K. Gurjar, **Ramdas G. Borhade**, Vedavati G. Puranik and C.V. Ramana **(communicated to** *Tetrahedron)* "Total synthesis Polyhydroxylated pyrrolidine alkaloids", **2007**.
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