# Studies Towards the Synthesis of the C-analog of Glucosyl Asparagine & Glyceroplasmalopsychosine

by

**Ajit K. Parhi**

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements of the degree of Doctor of Philosophy,

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# Abstract

## Studies Towards the Synthesis of the C-analog of Glucosyl Asparagine & Glyceroplasmalopsychosine

By

Ajit. K. Parhi

Advisor: Professor Richard. W. Franck

The C-analog of glucosyl asparagine **1.67** is among the family of artificial and biological stable carbon-linked glycopeptide building blocks, which have applications in the areas of cancer research, immunotherapy, and treatment of inflammatory responses as well as various infectious and pathogenic processes. An unsuccessful attempt to apply the Ramberg-Backlund rearrangement (RB) to connect the asparagine amino acid to the anomeric carbon atom of glucose through a carbon tether has been described in **Chapter 1**. During the course of the synthesis of the required sulfone **1.70** for RB rearrangement, a new 1,3-Dipolar cycloaddition reagent (Weinreb amide functionalized nitrile oxide **1.90)** has been discovered. The methodology to prepare the nitrile oxide **1.90** has been successfully applied for the synthesis of another new cycloaddition reagent *i.e.* Weinreb amide functionalized nitrone **1.105**. The scope of our new cycloaddition reagents has been extended to the synthesis of five membered heterocycles via (3+2) cycloaddition reactions with a range of dipolarophiles.

Glyceroplasmalopsychosine **2.0** is a novel glycolipid extracted from the bovine brain. In this unique glycolipid, a long chain aldehyde (plasmal) is conjugated to the primary hydroxyl group of glycerol and the 6-hydroxyl of the psychosine by an acetal linkage.

Psychosine is cytotoxic, where as glyceroplasmalopsychosine is not. This differnce in cytotoxicity between the two compounds presents an interesting question concerning the pharmacological role of glycerol and long chain aldehyde. **Chapter 2** describes the two different ways of synthesizing the mixed acetal segment of glyceroplasmalopsychosine. The first approach involves a non-stereospecific synthesis of the mixed acetal system by the application of Rychnovsky synthesis of α-acetoxy ethers from esters. The inability to separate the two acetal isomers turned our attention to the stereospecific synthesis of the mixed acetal segment of the target compound. In the second approach, the concept of converting carbohydrate to non-carbohydrate asymmetric molecules has been successfully exploited. The two isomers of mixed acetal of the target compound **2.0** have been stereo-specifically synthesized starting from two simple sugars (lyxose unit **2.66**, **2.98** and galactose unit **2.67**). Some of the key reactions involved in the synthesis are stereospecific O-glycosidation to prepare the required disaccharide **2.76** and **2.99**, protecting group manipulations of the disaccharides to the diol **2.80** and **2.106**, oxidative cleavage of diols to furnish the acetal linkage and lastly the heterogeneous Wittig reaction to construct the long aliphatic chain. The attempt to connect the sphingosine side chain to the acetal segment of the target molecule was not successful.

## Acknowledgements

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# CHAPTER 1

# Studies Towards the Synthesis

# of

# C-Analog of Glucosyl Asparagine

## 1.0 Introduction

In recent years, glycopeptides have become the focus of considerable bioorganic/medicinal research due to their involvement in various cellular biological and pathological processes. Glycosylation of proteins not only affects their physical properties (i.e., folding and conformation) but also influences biological function.[1] Since glycosides anchored to proteins form highly branched structures, it is not surprising that they are involved in cell surface recognition processes such as interactions with bacteria, viruses, and toxins as well as tumor metastates.[2] Glycosylation has also been implicated in the modulation of protein function (i.e., cellular uptake, proteolytic stability) and immune responses.[3] There are two main types of glycosidic linkages in natural glycoproteins that merit particular attention. One involves either oxygen in the side chain of serine and threonine; the other involves the nitrogen of the side chain of asparagines. The most common N-glycopeptide link found involves the amino acid asparagines connected to a polysaccharide via the amide function. A fundamental problem in using O- or N-glycoconjugate-based therapeutic approaches to the treatment of disease is the inherent lack of in vivo stability of such compounds since O- and N-glycopeptides are easily degraded in both acidic and basic media.[1] A solution to this problem lies in obtaining carbon-linked isoteric derivatives of O-and N-glycopeptides.[4]

It has been recognized that the replacement of C-N and C-O bonds with their methylene isosteres can lead to bio-active compounds with improved metabolic stability. Thus increasing attention has been recently turned to unnatural sugar amino acids in which the entire α-amino acid group $CH(NH_2)CO_2H$ is connected either directly or through an all-

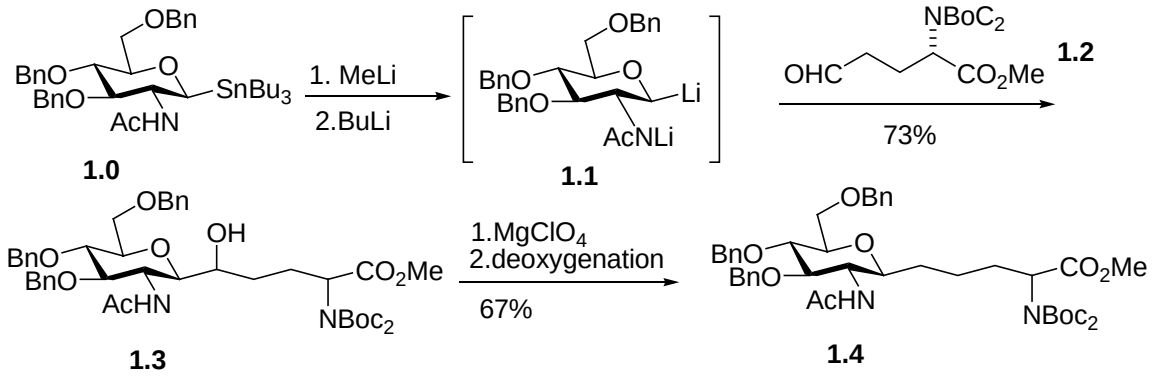
carbon tether to the anomeric carbon atom of the sugar unit. The tether can be saturated or an unsaturated carbon chain or a part of an aromatic ring. Among these compounds there is a special interest in isosteres (C-glycans) of glycosyl L-serine and L-threonine (O-glycans) and glycosyl L-asparagine (N-glycans), the most common components of native glycopeptides.[5] These biologically stable carbon-linked glycopeptides may have applications in the areas of cancer research, immunotherapy, and treatment of inflammatory responses as well as various infection and pathogenic processes.

Replacement of the amide link in N-glycosylasparagines by the carbon isostere is attractive as this minimal modification changes the chemistry of both amide and the glycosidic bonds, and hence should result in materials that are resistant to hydrolysis at both these sites.

## 1.1 Background:

A three-carbon atom bridge holds the carbohydrate and glycinyl moieties of asparagine family of C-glycosyl amino acids. These compounds can be considered as the analogues of N-glycosyl asparagines where the anomeric amidic bond has been substituted by a carbon-carbon bond.

The first synthesis of a C-glycosyl asparagine was reported in 1997 by Kessler and co-workers.[6] The target product was the ethylene isostere of 2-acetamide-2-deoxy-β-D-glucopyranosyl asparagine.

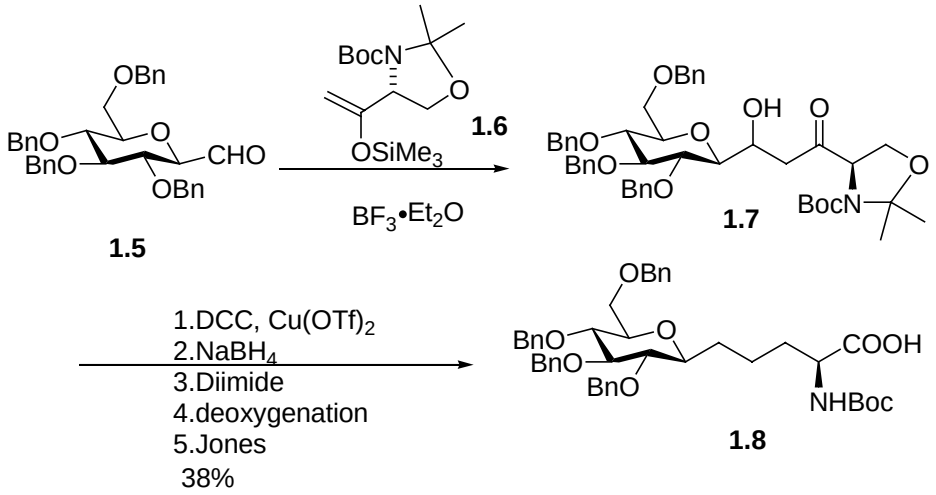



**Scheme 1.1: Kessler's synthesis of glycopeptide.**

The key step in the Kessler synthesis was the stereocontrolled coupling of dilithio N-acetylglucosamine **1.1** with the five-carbon aldehyde **1.2** derived from glutamic acid. The β-D-linked C-glycoside **1.3** was formed exclusively as a mixture of diastereomers, which was then transformed into the target amino acid **1.4** by the removal of BoC-protecting group and the Barton-McCombie dehydroxylation.

The limitations of the above method of Kessler was that in case of compounds carrying a protected hydroxy group at C-2 of the sugar moiety, the metalation at C-1 was accompanied by extensive 1,2-elimination.[7] On the other hand, the presence of an unprotected 2-hydroxy group in the sugar component and generation of a glucosyl dianion in order to prevent the β-elimination would lead to the presence of two free hydroxy groups in the resulting coupling product, making the selective removal of the one in the side chain quite problematic.

In an alternative method Dondoni and co-workers [8,9] synthesized β-linked C-glycosyl L-asparagine by Mukaiyama-type of aldol condensation between formyl C-glycosides and the threonine derived silyl enol ether shown in **Scheme 1.2**.

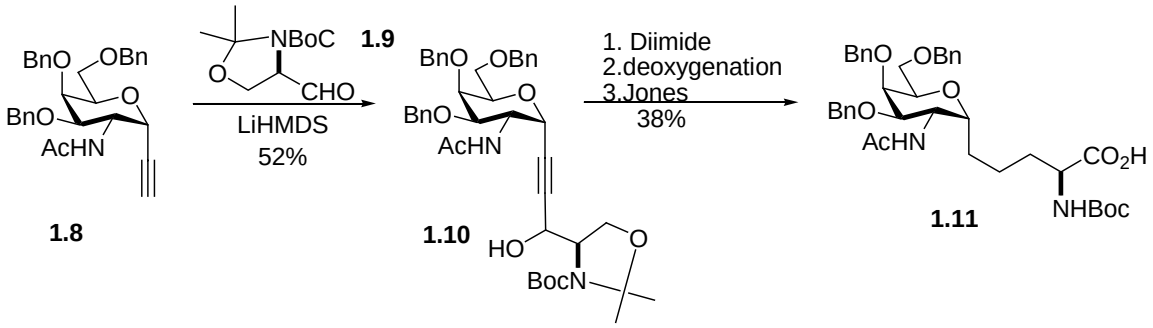



**Scheme 1.2: Dondoni's Synthesis of glycopeptide via aldol condensation.**

This method followed the leading concept of exploiting the existing configuration at the anomeric carbon atom of a sugar building block and at the carbon atom carrying the amino group in an amino acid equivalent. The Lewis acid -promoted condensation of the sugar aldehyde **1.5** with the silyl enol ether **1.6** gave the corresponding aldol **1.7** in fairly good yields. Subsequently aldol **1.7** was transformed into the amino acid **1.8** via complete deoxygenation and Jones hydrolysis and oxidation of the oxazolidine ring.

Although the above method works well for β-linked C-glycosyl amino acids[10], the scope of this method for the α-isomers is rather limited because the tendency of the α aldehyde analog of **1.5** to isomerize under basic conditions.

A quite versatile approach that allowed an entry to the α- and β-anomer pairs of various C-glycosyl asparagines was developed by the Dondoni group.[11] The coupling of configurationally stable anomeric sugar acetylenes **1.8** with the chiral amino aldehyde **1.9** constituted the key carbon-carbon bond forming reaction at the anomeric center of the sugar.




**Scheme 1.3: Dondoni's Synthesis using Sugar acetylene.**

In scheme 3, the sugar acetylene was first metalated (LiHMDS) and then reacted with the protected D-serinal **1.9** The resulting propargylic alcohol **1.10** was reduced and deoxygenated, and the oxazolidine ring was oxidatively cleaved to the glycinyl moiety to give the target amino acid **1.11**.

All amino acids presented above can be considered as ethylene isosteres of natural glycosyl asparagines. Synthesis of a new type of C-glycosyl asparagines isostere [12] is given in the following scheme where the NH of the amide group is substituted by a $CH_2$.

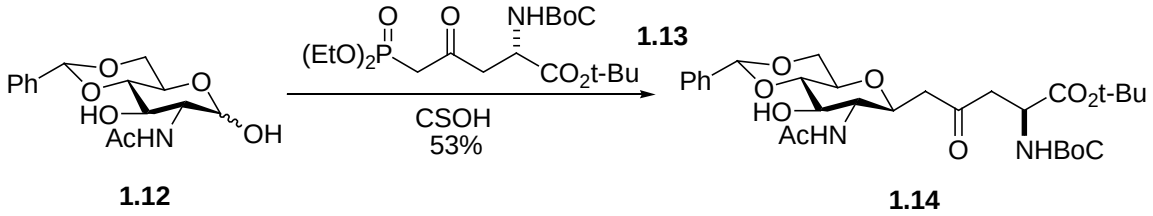
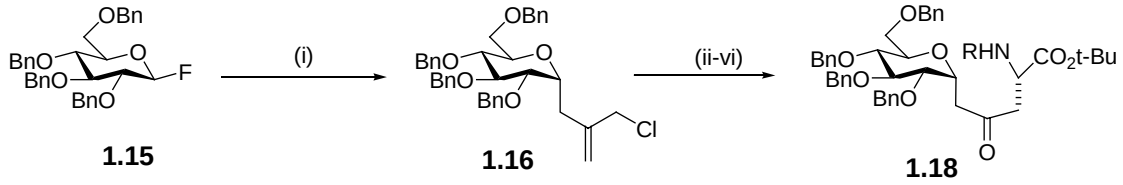



**Figure 1.1: Glycopeptide Synthesis via Horner-Emmons Olefination**.

The key step for the assembly of the carbohydrate and amino acid moirties involved a Horner-Emmons-Wordsworth olefination and Michael addition sequence between the protected N-acetylglucosamine **1.12** and the aspartic acid-derived β-ketophosphonate **1.13.** The coupling product **1.14** was obtained under suitable conditions (CsOH in MeOH, room temperature).

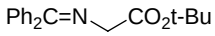
## 1.2 C-glycosylasparagine via Stereoselective formation of the C-glycoside Linkage:

Lygo's synthesis [13]of C-glycosylasparagines **1.18** involved the stereocontrolled addition of a functionalized allylsilane to activated sugar derivatives and the asymmetric phase-transfer alkylation of a glycine imine. Using this approach reaction of **1.15** with commercially-available 2-chloromethyl-3-trimethylsilylpropene provided the C-glycoside **1.16** in good yield and with high selectivity for the desired α-isomer. Chloride **1.16** was then converted into the corresponding iodide, which proved to be an excellent substrate for the asymmetric alkylation using glycine imine **1.17**. For this later process O-benzyl-N-(9-anthracenylmethyl)-dihydrocinchonidinium bromide was employed as the phase-transfer catalyst.




**1.15** **1.16** **1.18**

reagents and conditions: (i) 2-chloro-3-trimethylsilylpropene (1.5 equiv.), $BF_3.OEt_2$ (1.1 equiv.), $CH_3CN$, -30$^oC$ (64%); (ii) NaI, acetone; (iii)glycine imine **1.17**,O-benzyl-N-(9-anthracenylmethyl)dihydrocinchonidinium bromide (10 mol%), 9 M aq. KOH, PhMe, rt; (iv) 15% aq. citric acid, THF, rt; (v) BnOCOCl, $Et_3N$, $CH_2Cl_2$, 0$^oC$-rt (58% overall), or $Boc_2O$, $Et_3N$, $CH_2Cl_2$, 0$^oC$-rt (50% overall), (vi) $O_3$, $CDCl_3$, - 50$^oC$; $Ph_3P$, rt (93% R=Z, 94% R = Boc).




**1.17**

glycine imine derivative

**Scheme 1.4: Stereoselective Approach to C-glycosylaspargine.**

It was our plan to prepare C-glycosyl asparagine derivatives via Ramberg-Backlund rearrangement, which would link the sugar to asparagine masked as an isoxazole. The amino acid would ultimately be generated from the Weinreb amide functionalized isoxazole. Therefore a short review of Ramberg-Backlund rearrangement, isoxazole chemistry and Weinreb amide chemistry is presented in following sections.

## 1.3 a. The Ramberg-Backlund rearrangement:

In 1940, Ramberg and Backlund [14]reported that α-bromoethyl sulfone could be converted to 2-butene in high yield under basic conditions. Since then, the reaction known as the Ramberg-Backlund rearrangement has been used to synthesized a wide variety of

alkenes, such as mono-, 1,1-, or 1,2-di-, tri-, tetra-substituted alkenes, cycloalkenes and conjugated alkenes, including alkenes substituted with a variety of functional groups.

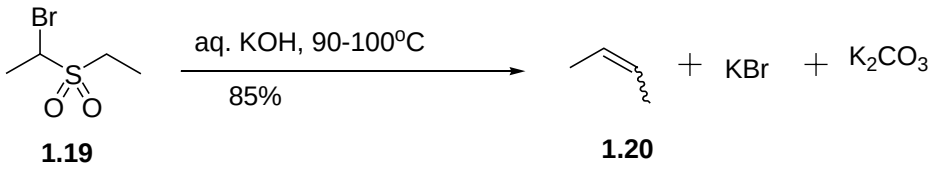



**Figure 1.2 Original Ramberg-Backlund Rearrangement.**

**Mechanism:**

The reaction involves the reversible formation of the α'-anion under basic conditions followed by 1,3-elimination of halide from the sulfone α'-anion to give a thiirane 1,1-dioxide, generally as a mixture of cis and trans isomers. Loss of $SO_2$ from the thirane dioxides then gives the stereomeric alkenes.

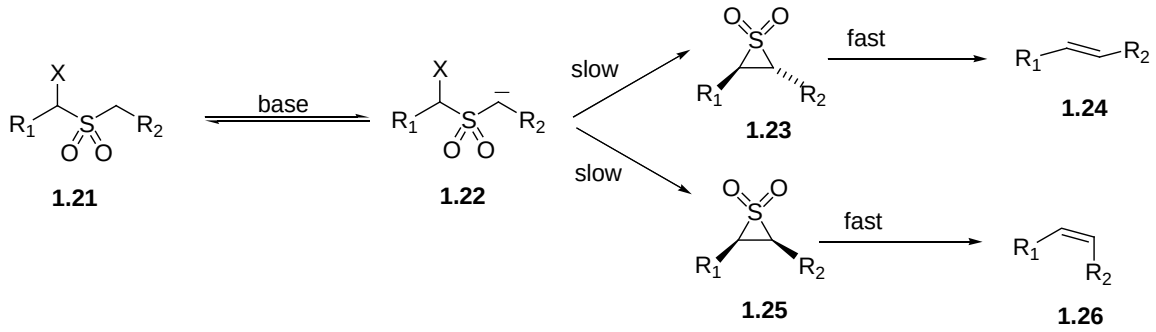
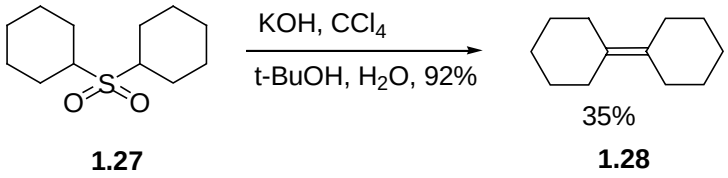



**Figure 1.3. Mechanism of Ramberg-Backlund Rearrangement.**

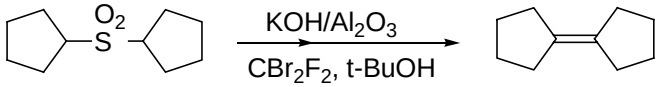
In 1969, Meyers [15] modified the Ramberg-Backlund reaction by using a suspension of powdered KOH in a mixture of $CCl_4$ and t-BuOH with the starting sulfone.




**1.27** **1.28**

**Figure 1.4. Meyer's Modification.**

Mayer's conditions were later modified by Chan [16] where powdered KOH-$CCl_4$-t-BuOH was simply replaced by alumina supported KOH-$CBr_2F_2$-t-BuOH.

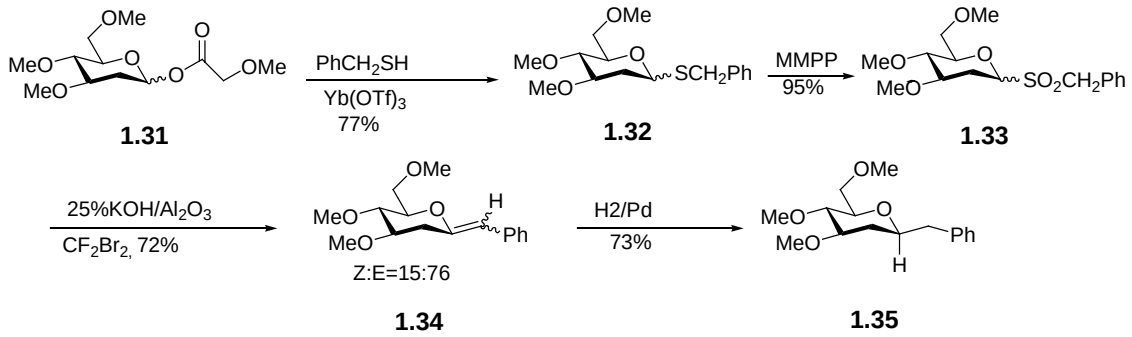



**1.29** **1.30**

**Figure 1.5. Chan's Modified Conditions.**

## 1.3b Application of the Ramberg-Backlund Rearrangement in C-glycoside synthesis:

The Ramberg-Backlund rearrangement has been utilized to convert the sugar sulfone to exoglycal by the Franck[17]and Taylor groups.[18] In 1998, Franck and Belica [17]applied the Chan's modification of the Ramberg-Backlund reaction to synthesize C-glycosides via the exo-glycals. The Ranberg-Backlund sequence to provide C-glycosides is shown in the following scheme.



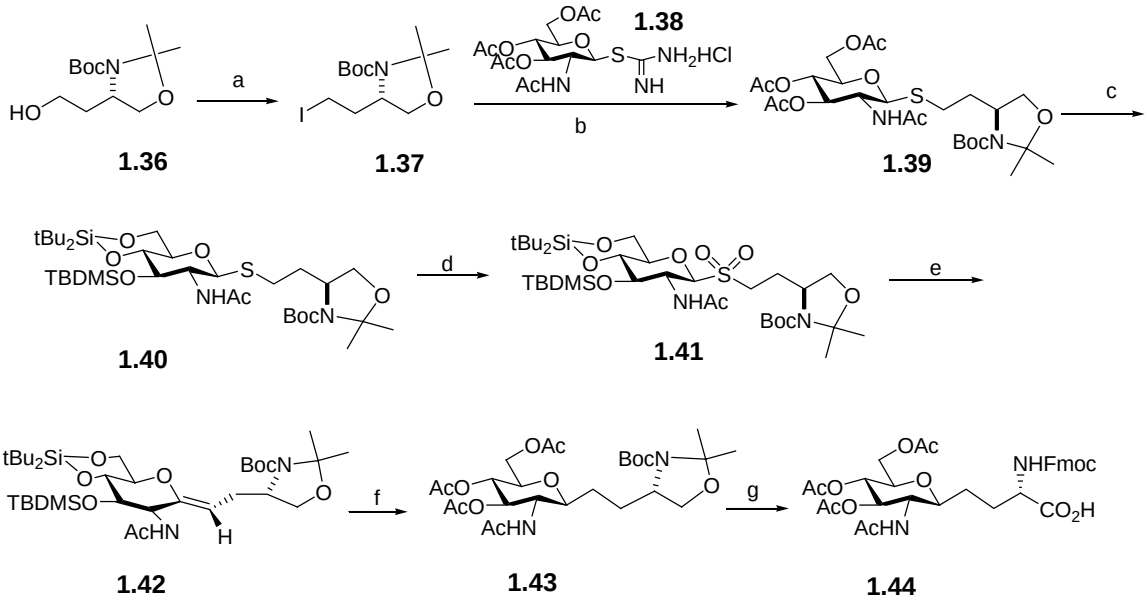

**Scheme 1.5. Application of the Ramberg-Backlund Rearrangement in C-glycoside Synthesis.**

The first two steps are the routine thioglycosidation and the oxidation of sulfide **1.32** to the sulfone. Sulfone **1.33** was exposed to the Chan's conditions using KOH-alumina as base, t-BuOH/methylene chloride as solvent with excess of $CF_2Br_2$ at room temperature. The one flask sequence of bromination, C-C bond formation and $SO_2$ extrusion was quite rapid. The product was hydrogenated with Pd catalysis to afford a mixture of C-glycosides **1.35** with equatorial product as the major isomer. The Taylor group's approach was similar to the Franck's group in the preparation of C-glycosides.

## 1.3 Stereoselective Synthesis of a C-Glycoside Analog of N-Fmoc-Serine β-N-Acetylglucosaminide by Ramberg-Backlund Rearrangement

Ichikawa's synthesis[19] of C-glycopeptide **1.44** started with the coupling of known iodide **1.37**[20] with the isothiourea generated from **1.38** to give the thioglycoside **1.39** in good yield. Replacement of O-acetyl groups by base stable silyl protecting group followed by oxidation of sulfide to sulfone produced the Ramberg-Backlund precursor **1.41**. RB

rearrangement of **1.41** under the Franck conditions afforded the exo-glycal **1.42** in 38% yield. Hydrogenation of **1.42** over Pearlman's catalyst followed by other routine chemistry produced target compound **1.44** in good yield.




Reagents and conditions: (a) imidazole, $PPh_3$, $I_2$/tolunene, 77%; (b) $K_2CO_3$, $Na_2S_2O_5$/acetone-$H_2O$, 98%; (c) (i) $Et_3N$/MeOH - $H_2O$; (ii) $tBu_2Si(OTf)_2$, 2,6-lutidine/DMF, 88% (two steps); (iii) TBDMSCl, imidazole/DMF, 95%; (d) mCPBA, $Na_2HPO_4$ /$CH_2Cl_2$, 77%; (e) KOH/$Al_2O_3$, $CBrF_2CBrF_2$/tBuOH, 50$^oC$, 38%; (f) (i) $H_2$, $Pd(OH)_2$/EtOAc, 78%; (ii) TBAF/THF; (iii) $Ac_2O$/pyridine, 68% (two steps); (g) (i) TFA/$CHCl_3$; (ii) FmocCl/$iPr_2NEt$/$CH_2Cl_2$-MeOH, 69% (two steps); (iii) Jones oxidation/acetone, 77%.

**Scheme 1.6. Glycopeptide Synthesis by RB**

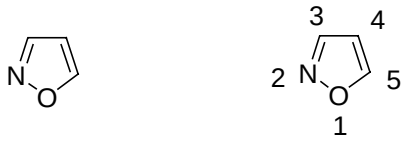
## 1.4 Chemistry of Isoxazole, isoxazolines and Isoxazolidines:

### (a) Introduction:

The chemistry of isoxazole dates from 1888, when Claisen [21] proposed the correct structure and name monoazole for the five-membered ring $C_3NO$, which was modified by Hantsch[22] to isoxazole, a name derived from the already known isomeric ring oxazole. The parent compound of the series, the unsubstituted isoxazole, was synthesized by Claisen in 1903 [23] by oximation of propargyladehyde acetal.

After the fundamental work of Claisen and co-workers on the oximation of β-dicarbonyl compounds, a few other authors, notably Dunstan and Dymond,[24] Moureu,[25] Wieland [26]and Schmidt [27]explored different methods of synthesis of the isoxazole ring. Its peculiar and almost unique properties favored a steadily increasing utilization of this ring as a synthon of various functionalities for the synthesis of heterocycles and complex molecules. On the other hand, the discovery of the interesting pharmacological activities of some isoxazole derivatives, such as sulfa drugs, modified penicillins, antibiotics, and others, has contributed notably to the development of isoxazole chemistry.

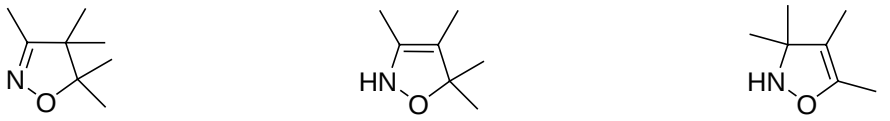
Although the trivial name isoxazole is popular, the more systematic name 1,2-azole is utilized occasionally by some authors. The three ring positions available for the substitution were originally indicated as in structure **A** below, utilizing the Greek letters α, β, and χ starting from the position next to the oxygen atom. A new way of numbering beginning at oxygen atom, as depicted in structure **B** is now used exclusively.




**A** **B**

**Figure 1.6. Numbering of Isoxazole.**

The isoxazole ring can be partially saturated, formally giving rise to three isomeric derivatives containing only one double bond (i.e., **C**, **D**, and **E**).




**C**
2-Isoxazoline

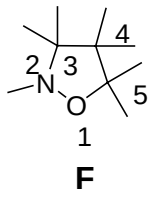
**D**
3-Isoxazoline

**E**
4-Isoxazoline

**Figure 1.7. Isomeric Isoxazolines.**

Of the three classes of dihydroderivatives, the 2-isoxazolines are by far the most easily prepared and widely studied. In contrast, the chemistry of 4-isoxazolines, and, especially, of 3-isoxazolines has been discovered more recently, undoubtedly because of their more difficult preparation and higher lability. The 2-isoxazoline nucleus is formed in some natural products.[28-30]

The parent isoxazolidine **F** can also be named 1,2-oxazolidine or tetrahydroisoxazole. Substitution follows the normal numbering of the isoxazole ring.




**F**

.

**Figure 1.8. Structure of Isoxazolidine.**

## 1.4 a Methods of Preparation:

If we consider the starting materials, it is convenient to organize the several different methods of preparing the isoxazole and isoxazoline rings according to the ring-closure pattern. The following two (3+2), one (3+2+1) and two (4+1) processes can be singled out.

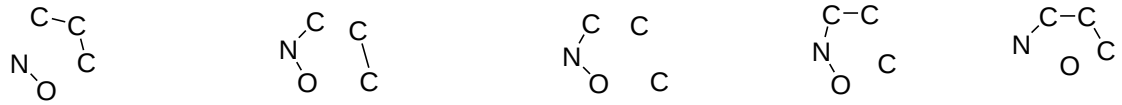


**Figure 1.9. Different Pattern of Ring-closure**

Out of these possible five reaction patterns the first two are practical method for the isoxazole and isoxazoline synthesis.

The next section describes the most important CNO + CC method for the synthesis of five membered heteocycles.

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## 1.4 b [CNO + CC] Processes

## (i) Introduction

The [3 + 2] cyclcoaddition pattern has been the most popular method for constructing the rings of isoxazole and its dihydro and tetrahydro derivatives. In its most general version, summarized in the following scheme, the CNO moiety is represented by the nitrile oxides **1.45** or by the nitrones **1.48**, and the CC moiety is a triple- or a double-bond compound. Isoxazoles, 2- or 4-isoxazolines, and isoxazolidines with the most different substitution pattern can thus be obtained. The cycloaddition of nitrile oxides to alkynes and alkenes has been the object of some reviews.[31-35]

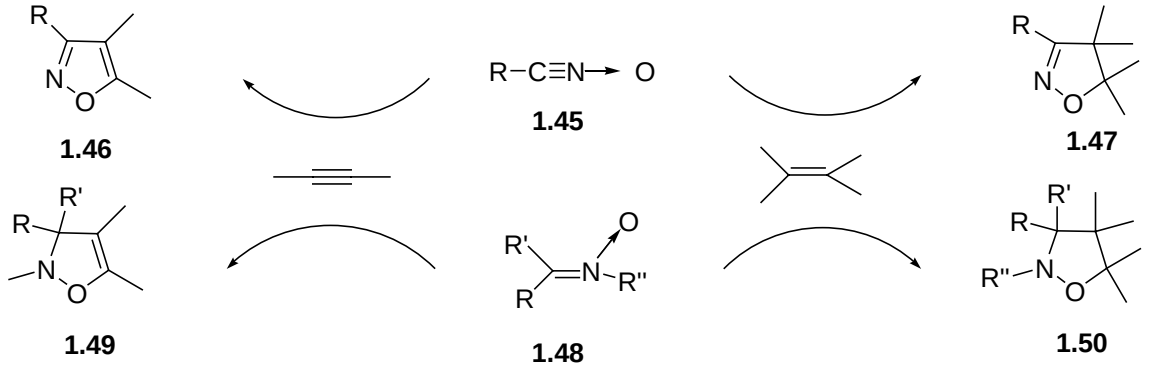



**Figure 1.10. 1,3-dipolar Cycloaddition at a Glance.**

## (ii) Reactivity and Selectivity of Nitrile Cycloaddition reaction:

1,3-Dipolar cycloadditions are considered as [π4s + π2s] "symmetry-allowed" one step concerted reactions; that is, the two new σ-bonds C-C and O-C between the nitrile

oxide/nitrone and the double or triple bond are formed simultaneously, not necessarily in a synchronous manner, at the expense of two π-bonds of the reagents.

The concertedness of the cycloaddition reaction is supported by the following factors:[36,37] (1) the strict cis stereospecificity observed in all cycloadditions with cis-trans isomeric dipolarophiles; (2) the feeble influence of solvent polarity on the reaction rate; (3) the small ρ value in Hammett kinetic studies; (4) the activation enthalpies and strongly negative entropies.

Application of simplest pertubation theory, which only takes into account the interactions between the frontier orbitals (HOMO-LUMO interactions) of the two reagents, has made it possible to interpret most phenomena of reactivity and selectivities encountered in the cycloadditions of nitrile oxides to double bond or triple CC bond compounds. In Sustmann's simplified scheme,[38-40] 1,3-dipoles are classified in three types, according to the prevailing HOMO-LUMO interaction (i.e., the one with smallest HOMO-LUMO distance).

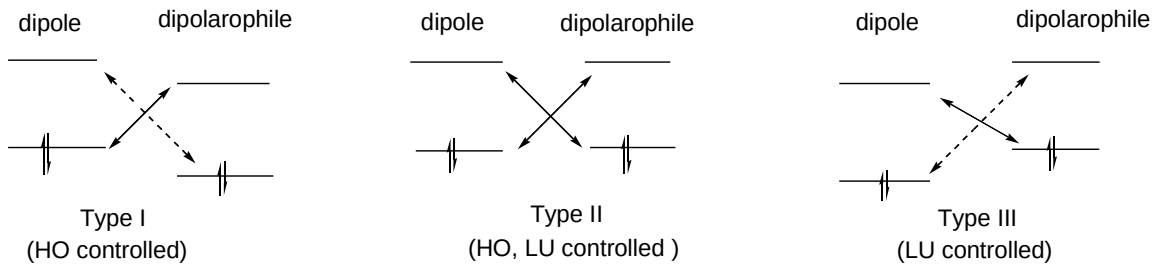



**Figure 1.11. HOMO-LUMO interaction.**

Nitrile oxides being relatively electron-poor dipoles, are usually considered to fall into type II and to undergo dipole HO, LU control. Accordingly, both electron-withdrawing and electron-releasing substituents on the dipolarophiles increase the rate. The following general trend can be summarized to show the relative reactivities of some typical dipolarophiles toward different nitrile oxides.

(1) The n- and π- conjugating substituents on the double bond or triple bonded dipolarophiles increase the rate of the cycloaddition.

(2) A sharp increase in the reactivity is also observed for conjugative electron-withdrawing groups, such as COOR and COR.

(3) A general rate retardation is observed for 1,2-disubstituted that is somewhat more remarkable than for 1,1-disubstitution.

(4) Alkenes react slower than the corresponding alkynes.

**(5)** Trans-alkenes cycloadd to nitrile oxides much faster than do the corresponding cis alkenes.

## (iii) Regioselectivity of nitrile oxide cycloadditions: FMO

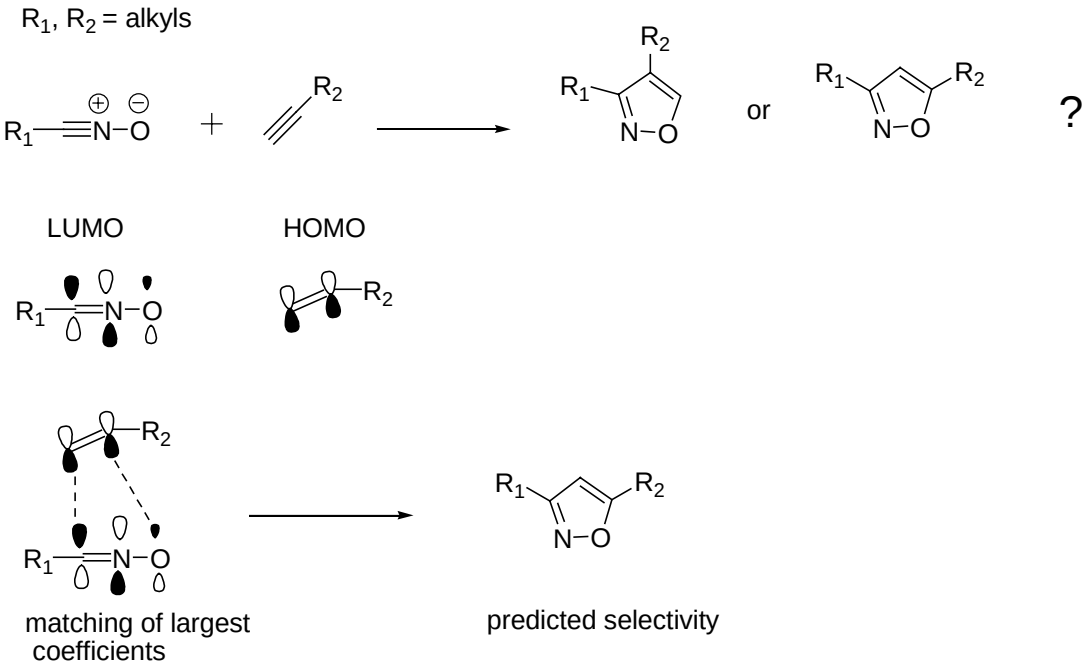



**Figure 1.12. Regioselectivity of 1,3-dipolar cycloadditions: FMO**[41]

The following points can be singled out to give some ideas about the regioselectivity of nitrile oxide cycloadditions with different types of dipolarophiles.

(1) Monoalkyl- and monoarylacetylenes as well as other electron-rich monosubstituted alkynes yield the 5-substituted isoxazoles only, thus showing complete regiospecificity. However, with electron-deficient alkynes, mixtures of the two possible regioisomers are usually obtained.

(2) 1,2-disubstituted electron-deficient acetylenes react with nitrile oxides to yield exclusively regiomeric isoxazole carrying the electron-withdrawing group in the 4-position.

(3) Monosubstituted alkenes show an almost complete regioselectivity, always yielding 5-substituted 2-isoxazolines.

**(4)** 1,2-Disubstituted alkenes usually give rise to a mixture of two possible regioisomers, whose ratio is the result of subtle interplay of steric and electronic factors.

1,3-Dipolar cycloadditions of nitrones [42] have been reported with a variety of alkynes, alkenes, isocyanates, isothiocyanates, thiocarbonyl compounds, phosphoranes, and sulphinyl compounds. All these reactions are usually carried out by heating together in an inert solvent, commonly benzene or toluene, and the products are often easily isolated in high yield.

## (iv) Regioselectivity of Nitrone Addition:[43,44]

In the addition of unsymmetrical dipolarophile to a nitrone, two orientations of addition are possible. It has been found that cycloadditions can be reversible and therefore subject to both thermodynamic and kinetic control. Consequently, regioselectivity applies to addition under conditions of kinetic control. Both steric and electronic factors are important and in general the more hindered end of the dipolarophile adds to the nitrone oxygen atom. Monosubstituted alkenes bearing a variety of groups afford 5-substituted isoxazolidines with some exceptions. Nitrone-alkene cycloadditions can occur with the nitrone and alkene approaching each other in either of two possible regiochemical senses

and in either an endo- or exo- fashion, the four possible transition states giving rise to two pairs of regioisomeric and diastereomeric products.

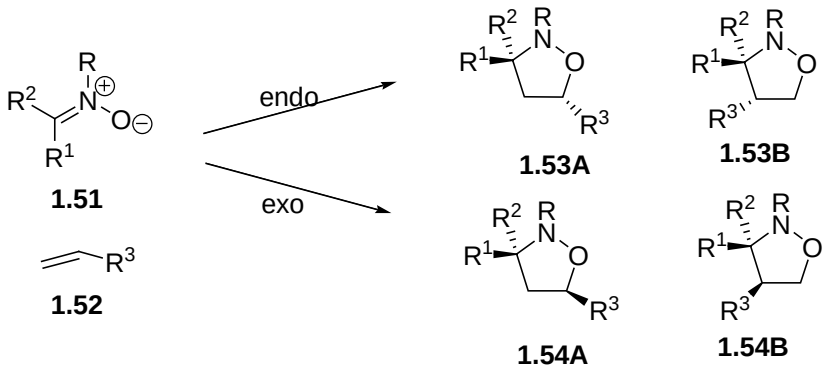



**Figure 1.13. Regiochemistry of Nitrone cycloaddition**

## 1.4 c. CHEMICAL PROPERTIES

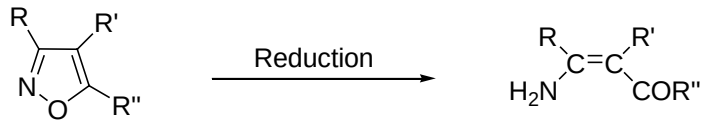
The isoxazole ring system exhibits a characteristics chemical behavior, and occupies a unique position among the heterocyclic rings. Since it is fairly stable toward several common reagents and, on the other hand, is easily opened under well-defined conditions the isoxazole ring is admirably suited to act as a synthon of several functionalities.

The general chemical behavior of the isoxazole ring depends strongly on its substitution pattern. The three positions (3, 4,and 5) available for substitution show fairly different properties. Due to the aromatic character of the isoxazole ring, position 4 is the preferred point of attack for electrophilic substitution. The hydrogen in position 3 is the most easily detachable by basic reagents, and this tendency is enhanced by quaternization of the ring nitrogen. The stability toward bases increases with increasing substitution: 3,5-di- and

trisubstituted alkyl- or arylisoxazole are extremely stable compounds. On the other hand, whatever the substitution pattern may be, the weak N-O bond of the ring (about 52 Kcal/mol) is easily cleaved under well-controlled conditions, usually by hydrogenolytic methods.

## (1.4ci) Hydrogenolytic Ring Cleavage

The isoxazole ring is cleaved at the N-O bond several reducing agents.




**1.55** **1.56**

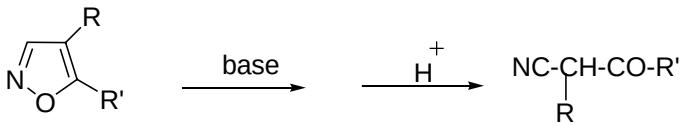
**Figure 1.14. Isoxazole Ring Cleavage at N-O bond.**

The β-enamine ketones generally obtained by this process offers an easy entry to large variety of acylic, homocyclic, and heterocyclic systems.

Some of the chemical reducing agents, leading to β-enamine ketones, are samarium diiodide [45]or transition-metal carbonyls such as molybdenum hexacarbonyl[46] in the presence of water or iron pentacarbonyl in the presence of water and photo-irradiation.[47]

## (ii) Reactions with Nucleophiles

The isoxazole ring is fairly sensitive to the action of nucleophilic reagents, and its reactivity depends strongly on the position and nature of the substituents. As a general rule, the stability of the ring in basic media increases with increasing substitution: monosubstituted isoxazoles are more or less easily ring –cleaved, whereas trisubstituted isoxazoles are usually stable and are more prone to reactions with nucleophiles in the side chains. Isoxazole itself is cleaved to the sodium salt of cyanoacetaldehyde in presence of aqueous sodium hydroxide at room temperature. 3-unsubstituted isoxazoles have been known to be cleaved to α-cyanocarbonyl **1.58** compounds under the influence of bases at room temperature.




**1.57** **1.58**

**Figure 1.15. Isoxazole Ring Cleavage Under the Influences of Bases.**

The reaction is carried out most frequently with sodium methoxide or ethoxde in alcohol, but potassium isopropoxide or *tert*-butoxide, sodium amide or hydride, lithium diisopropylamide in anhydrous solvents, as well as aqueous solutions of sodium or potassium hydroxides have also been used.

Kinetic studies [48]on the isomerization of 3-unsubstituted isoxazoles have established that the mechanism of the reaction belongs to a concerted one stage E2 type, in which the deprotonation precedes the fast ring opening.

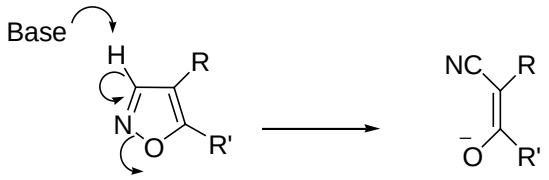
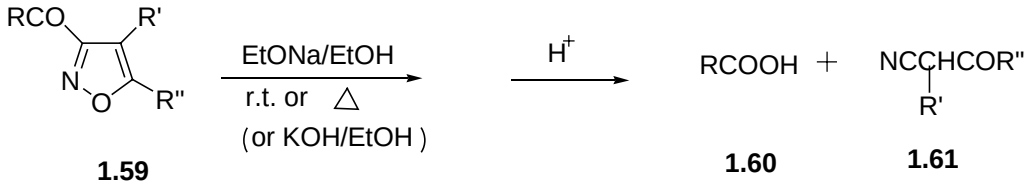



**Figure 1.16. Mechanism of Base promoted Isoxazole Ring Opening.**

The carbonyl group[49]of the 3-acylisoxazoles is preferentially attacked by nucleophiles, independent of whether position 5 is substituted or not. The reaction follows the general pattern.



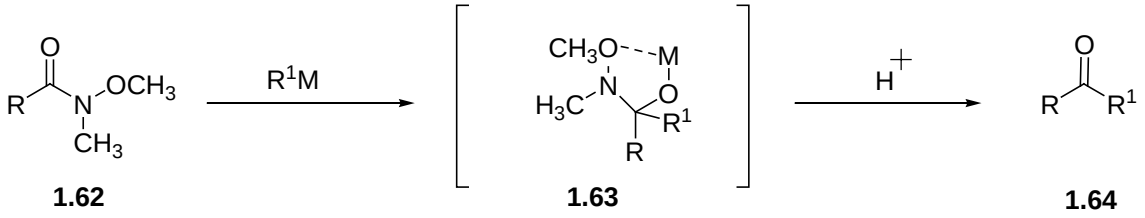

**1.59** **1.60** **1.61**

**Figure 1.17. Attack of Nucleophiles to 3-acylisoxazoles.**

## 1.5 Chemistry of N-Methoxy-N-Methylamides.

Since the initial report of Nahm and Weinreb[50] on the use of N-methoxy-N-methylamides **1.62** as carbonyl equivalents, this functional group has enjoyed tremendous popularity (Scheme 1). The main reasons for the utility of this synthon are: (1) the ease of

preparation, (2) few side reactions during nucleophilic addition, and (3) selective reduction to form aldehydes. These advantages can be ascribed to the stability of the tetrahedral intermediate **1.63** formed by addition of nucleophiles to N-methoxy-N-methylamides due to chelation.



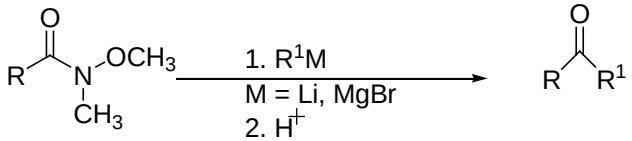

**1.62** **1.63** **1.64**

.

**Fig 1.18. Nucleophilic Additions To N-methoxy-N-methylamides.**

## a Nucleophilic Additions To N-methoxy-N-methylamides.

The reaction between N-methoxy-N-methylamides and nucleophiles provide a general route to the synthesis of ketones. These reactions proceed in good to excellent yields under fairly mild conditions. [51]



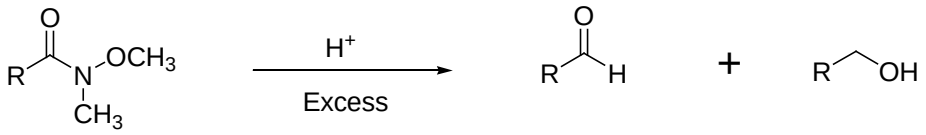

**1.62** **1.64**

**Figure 1.19. Application of N-methoxy-N-methylamide for Ketone Synthesis.**

The reactions work equally well with alkyllithiums as well as Grignard reagents. The reactions are generally carried out at – 78 $^{o}$ C, and solvents such as THF, ether, or DME have been used for these reactions. A large number of nucleophiles with variation in structure have been used to prepare ketones. These reactions are highly selective and the formation of alcohols by over addition of the nucleophile is rarely observed.

## b. Reduction of N-Methoxy-N-Methylamides

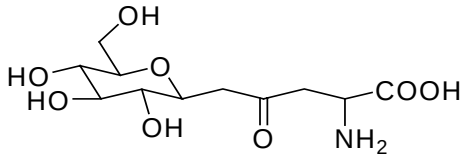
A well-utilized characterstic of the N-methoxy-N-methylamides is the conversion of this functional group to aldehydes under very mild conditions.[50] The underlying basis for the usefulness of N-methoxy-N-methylamides as an aldehyde equivalent is the formation of a stable chelated intermediate after hydride addition which prevents further additions, thus minizing the amount of over reduced products. Several different reducing agents LAH[50], LAD [52], DIBAL-H[50] and Red-Al [53] have been used for these reductions.




**1.62** **1.65** **1.66**

**Figure 1.20. Reduction of N-methoxy-N-methylamides.**

## 1.6 Studies towards the Synthesis of C-analog of Glucosyl Asparagine




**1.67**

**Figure 1.21. Structure of C-analog of Glucosyl Asparagine.**

As described in the introductory section much effort has been invested in developing methods to efficiently construct C-Linked glucosyl asparagines. In my first project we planned to synthesize C-analog of glucosyl asparagine **1.67** where the asparagine side chain is attached to the sugar, glucose unlike the natural counterpart N-acetyl glucosamine by β-linkage. We hoped that this modification in the sugar unit would not affect the biological activity of this C-analog significantly.

Recent work in our laboratory has focused on the use of the Ramberg-Backlund rearrangement of S-Glycosides dioxides as the key step in the formation of substituted exo-glycals, which are useful intermediates for the preparation of more elaborate C-Glycosides. **Section-1.3** illustrates this approach.

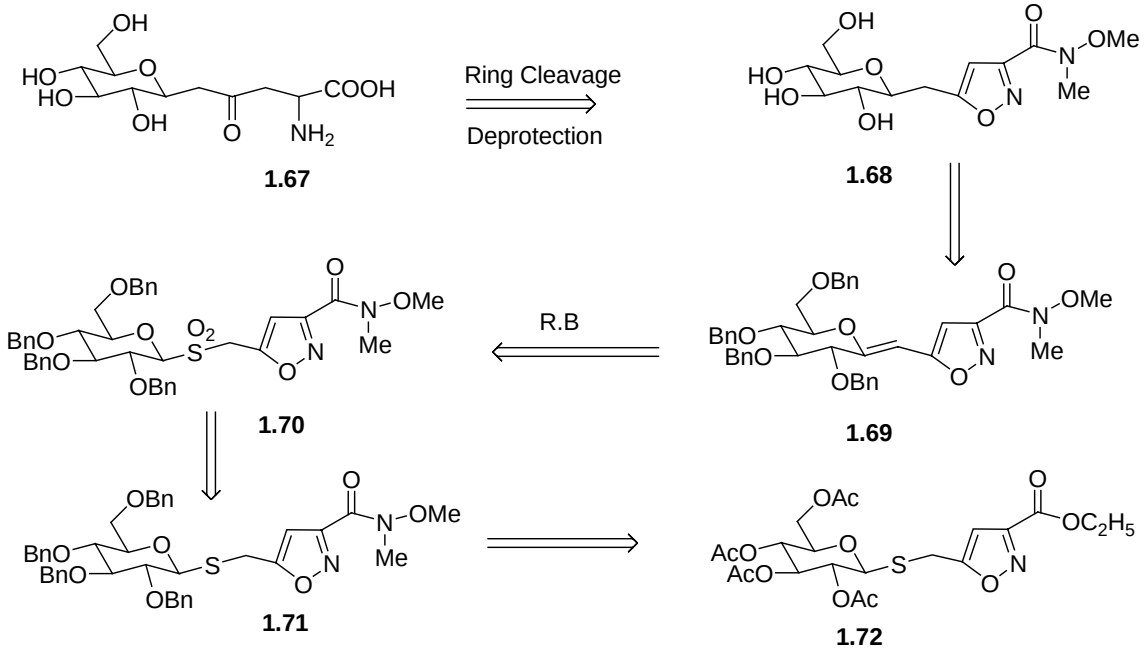
### a. Overview of the synthesis

The central concept of our synthesis lies in the exploitation of isoxazole ring as a synthon for the amino acid functionality and application of Ramberg-Backlund rearrangement to construct a C-C bond.

We planned to construct the C-C bond between the anomeric carbon of glucose and side chain carbon from easily prepared S-Linked precursors. The following scheme describes the approach we undertook for the synthesis.

## b. Retrosynthetic Analysis:

The retrosynthetic plan involves the idea of having sugar sulfide **1.72** as an intermediate compound for the synthesis of target compound **1.67**. There are two distinct advantages of having compound **1.72**. Firstly, by comparing the compound **1.72** to **1.67** one can realize that all the functionalities that are present in **1.67** can be obtained from the sugar sulfide **1.72**. This is possible because as discussed in the **section 1.4ci** the cleavage of the N-O bond of isoxazole ring by reducing agent such as $Mo(CO)_6$ would furnish the amino acid functionalities with a carbonyl group as a part of the side chain. Secondly we hoped that isoxazole ring being aromatic would facilitate the R.B rearrangement as discussed in the **section 1.3**.

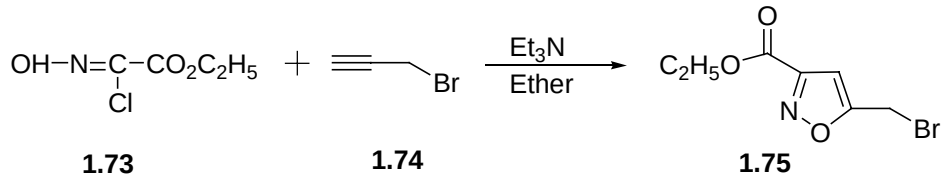



. **Scheme 1.7. Retrosynthetic Plan.**

The sugar sulfide **1.72** can be synthesized by undertaking known reaction sequences. Deprotection of acetyl groups of **1.72** and then protecting the hydroxyl groups as benzyl ethers would provide the molecule **1.71** necessary stability under strongly basic R.B conditions. Although other protecting groups could be tried, the benzyl protection was our first choice as these groups had been shown to work perfectly in some previous C-glycoside syntheses in our laboratory. Also the conversion of the ester moiety to the Weinreb amide would serve the same purpose under R.B reaction protocol. This is because of the fact that Weinreb amide group is quite stable under basic conditions (**section 1.5**). Weinreb amide protected isoxazole sulfone **1.70** can be obtained from isoxazole sulfide **1.71** easily by using reaction conditions routinely used in our laboratory. Exposing the sulfone to the R.B rearrangement would produce the exo-glycal **1.69**. Cleavage of the N-O bond of isoxazole ring followed by the hydrogenolysis would furnish the target compound **1.67**.

## c. Synthesis:

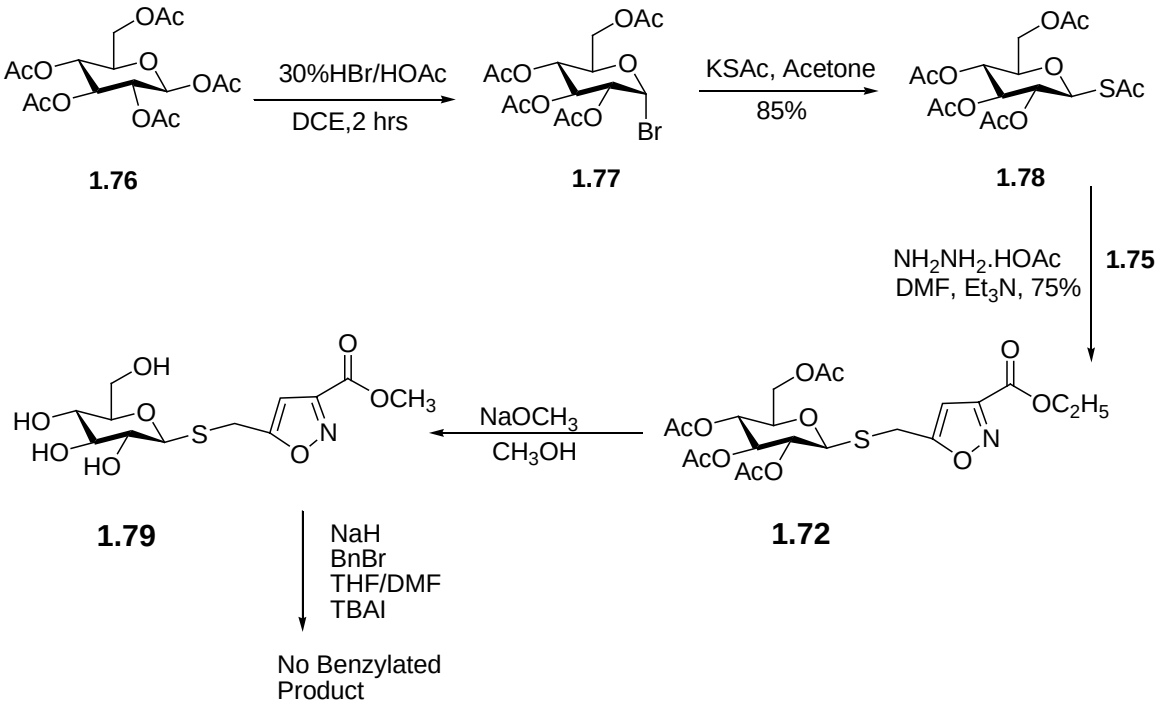
The synthesis began with the preparation of 3-carboethoxy-5-bromo-ethyl isoxazole following a literature method.[54] In this paper substituted isooxazoles were synthesized by {2 + 3} cycloaddition of different nitrile oxides with a range of dipolarophiles. 1,3-dipolar cycloaddition of commercially available ethyl chloroxime acetate **1.73** to propargyl bromide **1.74** produced substituted isoxazole **1.75** in 64% yield. This reaction proceeds with *in situ* generation of nitrile oxide by removal of HCl using triethyl amine, which was then cycloadded to propargyl bromide to furnish the cycloadduct **1.75** as white oil.




**1.73** **1.74** **1.75**

**Figure 1.22. Synthesis of 3-carboethoxy-5-bromo-ethyl isoxazole.**

2,3,4,6-Tetra-O-acetyl-β-glucosylthioacetate **1.78** can be obtained from β-D-glucose pentaacetate **1.76** in two known steps.[17] Peracetylated glucose **1.76** on treatment with HBr in acetic acid gave 2,3,4,6-tetra-O-acetylglucosyl bromide **1.77** in 85% yield. This unstable compound immediately was reacted with Potassium thioacetate under $SN_2$ conditions and the replacement of the bromide by thioacetate yielded the β-thioacetate **1.78** predominately with minor amount of α-thioglycoside.




**Scheme 1.8. Attempted Synthesis of Compound 1.48.**

Treatment of thioacetate **1.78** with hydrazinium acetate in DMF under $N_2$ deprotects thioacetate.[55] The freshly deprotected thio derivative was subsequently treated with electrophile (5-bromo ethyl isoxazole) **1.75** using triethyl amine as base to provide thio-ether **1.72** in 75% overall yield. This reaction was to be performed under strictly inert atmosphere after deoxygenating the DMF for an hour to avoid formation of disulfide compound. Deprotection of acetyl groups by using sodium methoxide in dry methanol gave the unprotected compound **1.79** in 95% yield during which the ethyl ester was converted to the methyl ester. Now the next step of the synthesis would be protection of those four hydroxyl groups by benzyl ether. So the compound **1.79** was treated with NaH in THF/DMF mixed solvent system at 0 $^{o}$C and then was stirred for an hour in room temperature after which the benzyl bromide and phase transfer catalyst TBAI was added. Unfortunately these simple benzylation conditions did not furnish the desired product at all. Unable to obtain the desired product using the popular basic benzylation conditions, we tried some other alternative methods notably acidic (using benzyl trichloro acetimidate and $CF_3SO_3H$) and neutral (using $Ag_2O$ and benzyl bromide). But those conditions did not help either and in our hand we were not able to produce the desired material. At this stage we thought that the ester group in the isoxazole moiety might not be compatible to the basic benzylation conditions. Therefore we planned to introduce the Weinreb amide functionality at the heterocycle synthesis stage and then try for the benzylation afterward.

Although there are several ways one can synthesize the functionalized isoxazole as discussed in the **section 1.4b**, we decided to go through the nitrile oxide route. For that reason we had to first synthesize the Weinreb amide functionalized nitrile oxide to be our new 1,3 dipole. This type of cycloaddition reagent had not been reported earlier and we

planned to synthesize it starting from trans-cinnamic acid. Our main objective was to synthesize Weinreb amide functionalized aldehyde **1.86** which could be then converted to the nitrile oxide by following popular nitrile oxide chemistry**.** Trans- cinnamic acid was a suitable starting material because it is very cheap and secondly the double bond could serve as a masked aldehyde group.

There are several different methods available to convert the acid to Weinreb amide, But we decided to use a most recent procedure developed by an Italian group[56] where 2-chloro-4,6-dimethoxy-{1,3,5} triazine (CDMT) **1.83** was used as the coupling reagent. Treating trans-cinnamic acid with CDMT and N-methylmorpholine (NMM) in THF, the corresponding activated ester **1.84** was quantitatively formed in 1 h (monitored by TLC). This white suspension, containing the activated ester was subsequently treated with N,O-dimethylhydroxylamine.

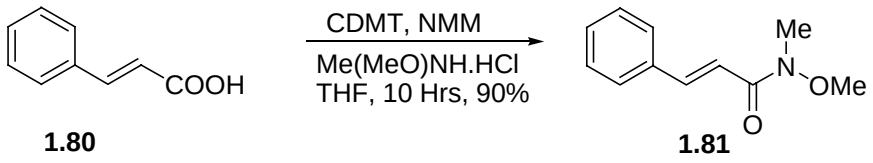



**Figure 1.23. Synthesis of Trans-Cinnamate.**

**Mechanism**

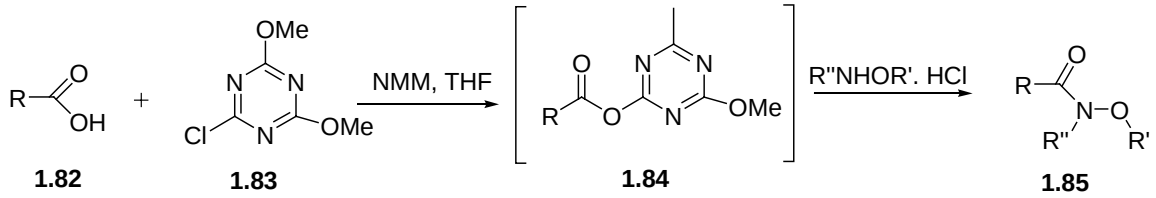



**Figure 1.24. Mechanism of Weinreb amide synthesis Using CDMT.**

This one pot method produced the Weinreb amide **1.81** in more than 90% yield. The next step was the crucial oxidative cleavage of the double bond of trans cinnamate **1.81** to generate the Weinreb amide aldehyde **1.86**. Ozonolysis **1.81** gave the aldehyde **1.86** in 87% yield. Ozonolysis was preferred over the two steps $OsO_4$/ $NaIO_4$ protocol because of the following two factors. Firstly the ozonide product aldehyde **1.86** was obtained as a hemiacetal with methanol used as a cosolvent for ozonolysis. This hemiacetal **1.87** was surprisingly stable and could be kept in the refrigerator for weeks without significant decomposition. Secondly the hemiacetal product **1.87** could be easily separable from the byproduct benzaldehyde by silica gel chromatography.

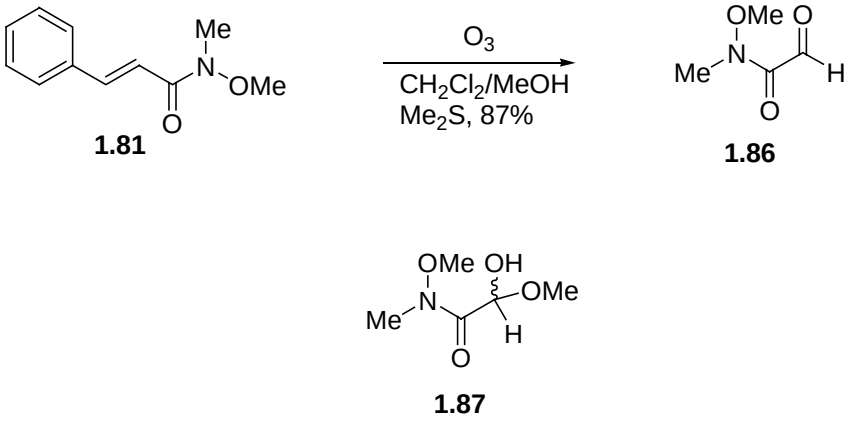
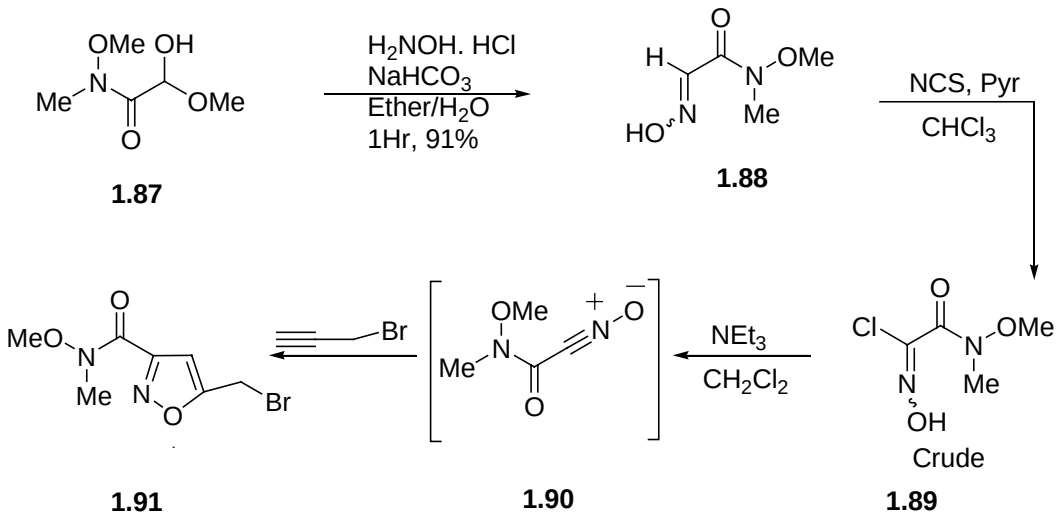



**Figure 1.25. Ozonolysis of Trans-Cinnamate and Structure of Hemiacetal.**

Although during this reaction we lost nearly half of the mass of the reactant as the by product, this way of synthesizing Weinreb amide functionalized aldehyde was still very elegant taking into consideration the cost of trans-cinnamic acid as the starting material.

Treatment of **1.87** with hydroxylamine hydrochloride in $H_2O$ and ether solvent system (1:1) and $Na_2CO_3$ produced crude W.A-Oxime **1.88** in quantitative yield [57]as a white solid. This product was used for the next step without further purification.

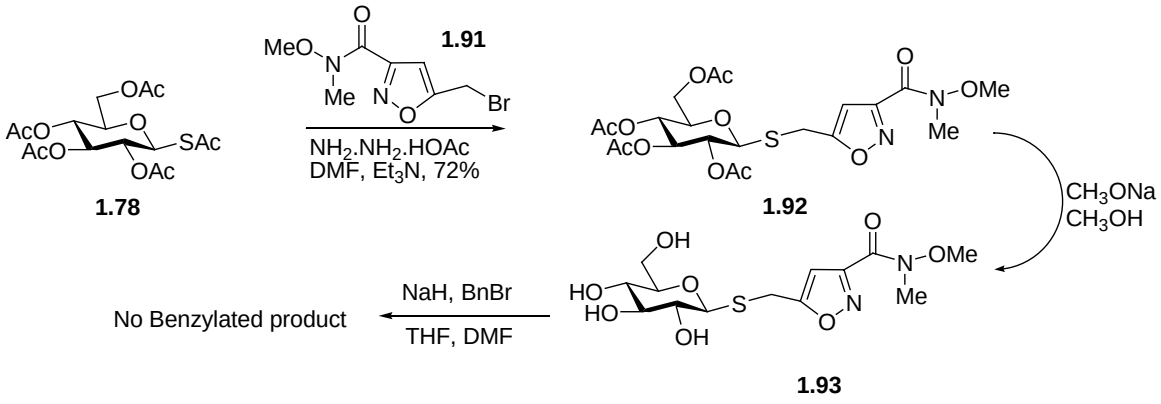



**Scheme 1.9. Synthesis of Weinreb amide Functionalized Isoxazole.**

The hydroximic acid chloride **1.89**,[57] the ultimate precursor of the required nitrile oxide was obtained via chlorination of aldoxime **1.88**. The chlorination of the hydroxylamine was performed by treating it with freshly recrystalized NCS and pyridine in chloroform. The completion of chlorination was observed by the disappearance of suspended NCS. Elimination of HCl from the chloroxime by using triethylamine produced the labile Weinreb amide functionalized nitrile oxide **1.90**. The nitrile oxide generated *in situ* was then subjected to {3+2} cycloaddition with the dipolarophile, propargyl bromide. The reaction proceeded with the addition of dipolarophile to an ice-cold stirred solution of chloroxime in $CH_2Cl_2$. This one pot 2 steps process produced Weinreb amide functionalized 5-bromo-ethyl isoxazole **1.91** in 55-60% overall yield calculated from the

crude hydroxylamine **1.88**. The reaction proceeded regioselectively to give one product in accordance with the FMO theory.

With the new electrophile in our hand, preparation of Weinreb amide functionalized thioglycoside **1.92** and conversion to **1.93** was effected by employing the same reaction sequence used before in **Scheme 1.8**.

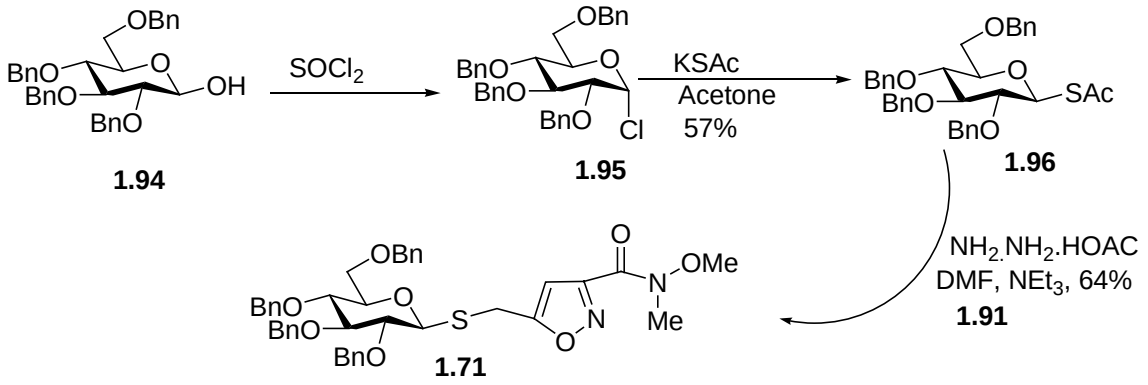



**Scheme 1.10. Attempted Synthesis of 1.48 using 1.68 as Electrophile**.

Coupling of our new electrophile **1.91** with thioacetate **1.78** using hydrazinium acetate produced the thiosulfide **1.92** in 72% yield. Deprotection of acetyl groups using sodium methoxide yielded the unprotected sulfide **1.93** ready for the benzylation step. Employing the basic benzylation conditions we were surprised to find that even now we were not successful in benzylating the sugar. The spot corresponding to the polar starting material did not change after the addition of benzyl bromide indicating the failure of the reaction.

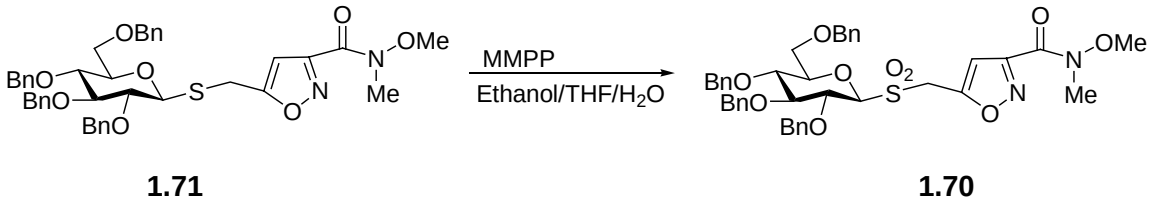
Finally the 2,3,4,6-O-tetrabenzyl thioglycoside **1.71**[58] was prepared by indirect methods given in **scheme 1.11**. 2,3,4,6-O-tetrabenzyl-α-glucosyl chloride **1.95** was prepared from

its commercially available 1-hydroxy precursor **1.94** by treating with thionyl chloride. This crude chloride was further reacted with KSAc in $SN_2$ conditions to give the thioacetate **1.96** in 57% yield. Coupling of **1.73** with W.A functionalized isooxazole bromide **1.91** yielded the required primary target **1.71** ready for R.B rearrangement sequences.




**Scheme 1.11. Succsessful Synthesis of 1.48.**

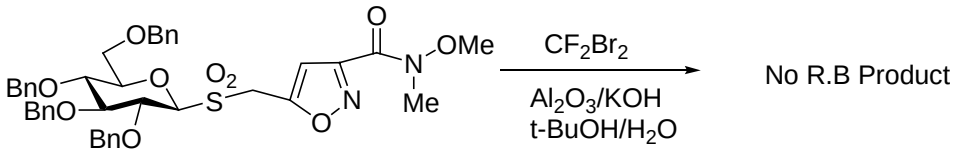
The next step of the synthesis was the oxidation of sulfide to sulfone, the starting material for Ramberg-Backlund rearrangement. Out of several oxidizing reagents available for the purpose, MMPP was preferred over other reagents as this was found to work perfectly in some of our previous syntheses. The sulfide **1.71** was converted to sulfone **1.70** by treatment with MMPP in ethanol /THF/$H_2O$ as solvent.[17] The sulfone **1.70** was obtained in about 78 % yield as white solid. With the sulfone in hand, we were ready for the most important step, i.e. Ramberg-backlund rearrangement to produce the exo-glycal.




**1.71** **1.70**

**Figure 1.26. Oxidation of Sulfide to Sulfone.**

All the previous C-glycoside syntheses in our laboratory have employed Chan's condition (**section 1.3**) where freshly prepared alumina-KOH slurry was used as base, $CBr_2F_2$ as halogenating reagent and t-BuOH as the solvent. Exposure of glucosyl sulfone **1.70** to the Ramberg-Backlund (Chan's) conditions unfortunately yielded no RB product.




**1.70**

**Figure 1.27. Unsuccessful Ramberg-backlund Rearrangement.**

What we observed in this reaction was that as soon as we added the base, the spot corresponding to the sulfone (on TLC) vanished immediately and moved to the base line, which did not go up at all even with polar solvents. We were not able to separate or identify the material corresponding to this spot.

In spite of employing different RB conditions we were not able to produce the exo-glycal. In all cases we always got the same highly polar spot, which did not change, in the reaction conditions.

The failure of RB rearrangement was a very unfortunate experience for us and we tried to find out the reason of such failure.

The first point came to our mind was that the isoxazole ring in combination with carbonyl functionality might be unstable to the basic RB conditions and somehow the isoxazole ring was getting cleaved to give very polar material. As described in the section xx it has been known that the carbonyl group of the 3-acylisoxazoles is preferentially attacked by nucleophiles, independent of whether position 5 is substituted or not. The reaction follows the general pattern

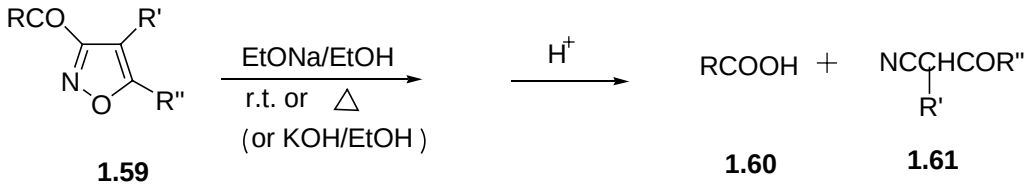



**Figure 1.28. Attack of Nucleophiles to 3-acylisoxazoles.**

The above reaction may be the best example to explain the failure of the RB reaction. We thought that KOH being a nucleophile attacks the carbonyl group of the Weinreb amide functionality, which results in the cleavage of the isoxazole ring to produce the cyano compound in the following manner.

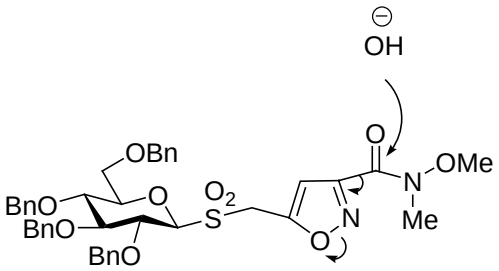



**Figure 1.29. Possible Explanation of Failure of Ramberg-backlund rearrangement.**

At this time we understood why the benzylation step did not work. This may be due to the fact that the alkoxide anion generated by treatment of NaH attacks the amide carbonyl in a similar way.

It has been also known that $Li^+$ stabilizes the Weinreb amide functionality by co-ordinating to the oxygen atoms to form a stable chelation shown in the following figure.

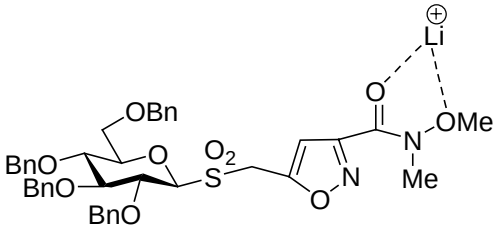
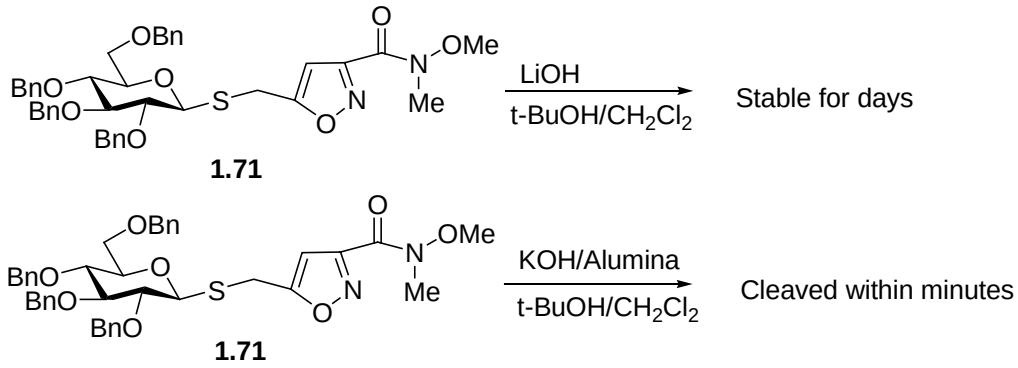



**Figure 1.30. Lithium Stabilization.**

In order to prove our argument that bases like alkoxide, KOH indeed cleave the isoxazole ring substituted by a Weinreb amide group at 3-position, and such a system is stable to LiOH, we undertook some simple experiments. Firstly we ran two parallel reactions i.e. treating Weinreb amide thioglycoside **1.71** with KOH and LiOH. The findings are given in the following scheme.

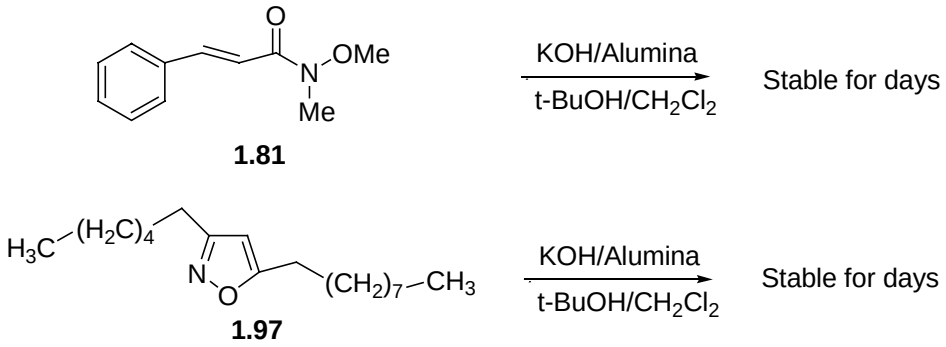



**Scheme 1.12. Parallel Experiments Showing the stability of Sulfide 1.71.**

Exposing the same sulfide **1.71** to both KOH and LiOH in two parallel reactions we observed two distinctly different outcomes.

Similar to our anticipation the thioglycoside **1.71** was stable to LiOH where as with KOH it was cleaved within minutes to give some unidentified polar material.

To prove that Weinreb amide or isoxazole ring alone is not responsible for this cleavage we again did two simple experiments. The results are given below.

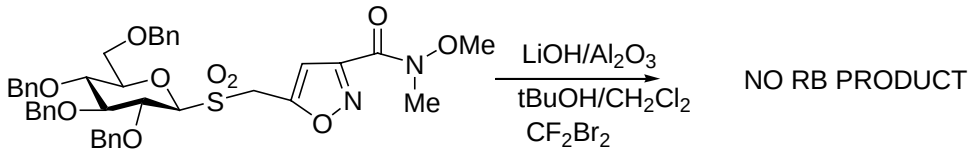



**Scheme 1.13. Experiments Showing the Stability of Wienreb amide and Isoxazole Separately.**

Again we were proved to be right. The N-methyl-N-O-methoxy cinnamate **1.81** was stable to KOH for days, so as the simple isoxazole **1.97**. These simple experiments definitely proved one point that isoxazole substituted by a Weinreb amide functionality at 3 position was indeed unstable to basic and nucleophilic reagents.

Our main objective of this project was to extend the scope of Ramberg-Backlund rearrangement as a methodology to synthesize different C-glycosides. Unfortunately the reaction conditions employed in the RB reaction was found to be too basic for the isoxazole system forcing us to give up the synthesis using normal RB reaction conditions.

Lastly, we tried to undertake RB with some modifications. Instead of using KOH as base we used LiOH to make LiOH/$Al_2O_3$ slurry and then employed RB on the sulfone **170.**




**1.70**

**Figure 1.31. Attempted RB using LiOH.**

Unfortunately we did not get any desired product as there was no change to the sulfone even after two days and we decided to give up at this point completely.

## 1.7 1, 3-Dipolar Cycloadditions of Weinreb amide-nitrile oxides/nitrones with dipolarophiles

### (a) Introduction:

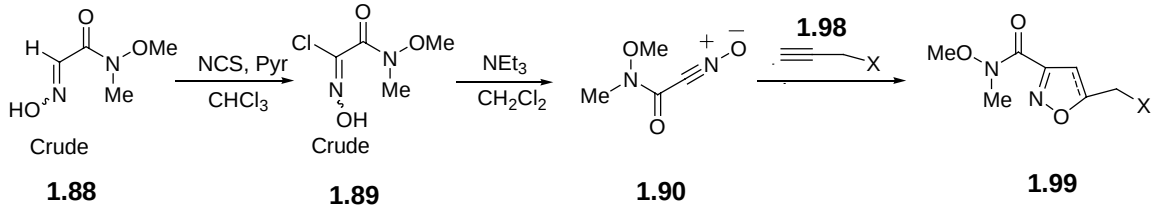
1.3-Dipolar cycloaddition reactions are among the most important synthetic manipulations allowing the construction of five-membered ring carbocycles and heterocycles. **Section 1.4b** represents the chemistry of nitrile oxides and nitrones as effective 1,3 dipoles for the construction of substituted isoxazoles, isoxazolines and isoxazolidines.

As discussed earlier in **Scheme 1.9**, we [59]have successfully synthesized W.A functionalized isoxazole **1.91** by [2+3] cycloaddition reaction between Weinreb amide-nitrile oxide and propargyl bromide. We thought that this new type of nitrile oxide could be used to construct Weinreb amide functionalized isoxazoles and isoxazolines. Also Weinreb amide being an excellent gateway for various functional groups, would lead a novel way to synthesize substituted isoxazoles / isoxazolines. Similarly the Weinreb amide-nitrone would be utilized to have an entry into substituted isoxazolidines.

So in order to extend the scope of our 1,3-Dipolar cycloaddition reagents, we investigated the cycloaddition of Weinreb amide functionalized nitrile oxides/nitrones with a range of dipolarophiles.[59]

## (b) Cycloaddition of Weinreb-amide nitrile oxide with dipolarophiles

**Fig 1.25** and **Scheme 1.9** deal with the generation of Weinreb amide-aldehyde and its subsequent conversion to the Weinreb amide-nitrile oxide **1.90**. This approach can be generalized by the following scheme.



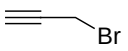
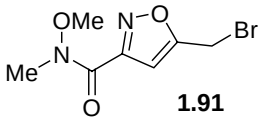
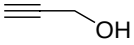
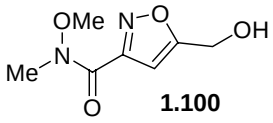
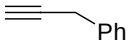
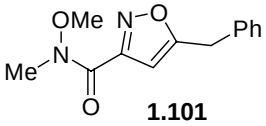
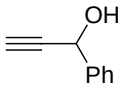
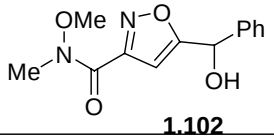

**Scheme 1.14. Cycloaddition of Weinreb-amide nitrile oxide with dipolarophiles.**

## (i) Cycloaddition with alkynes, Preparation of Isoxazoles

The labile W.A- nitrile oxide **1.90** generated *in situ* was allowed to react with different alkynes to produce Weinreb amide functionalized isoxazoles. The general procedure follows the addition of dipolarophiles to an ice-cold stirred solution of chloroxime in $CH_2Cl_2$. A solution of triethylamine in $CH_2Cl_2$ was added drop wise maintaining the temperature between 1 $^oC$ to 4 $^oC$. Work-up as described in experimental section produced the cycloadducts in moderate yields calculated from the crude hydroxylamine.

The results are shown in **Table 1.1**.

**Table 1.1. Preparation of substituted isoxazoles**

| Entry | Nitrile Oxide | Dipolarophile | Cycloadduct | Yield |
|---|---|---|---|---|
| 1 | **1.90** |  |  **1.91** | 55-60% |
| 2 | **1.90** |  |  **1.100** | 58% |
| 3 | **1.90** |  |  **1.101** | 62% |
| 4 | **1.90** |  |  **1.102** | 51% |

Entry 1 in the above **Table 1.1** was the cycloaddition between propargyl bromide and WA-nitrile oxide to form the cycloadduct **1.91** in 55-60 % yield. The cycloadduct 5-bromoethyl-3-N-methoxy-N-methyl amide isoxazole **1.91** was formed exclusively as single regioisomer. The formation of 5-substituted isoxazole is in accordance with FMO theory as discussed earlier. $^{1}$H NMR of compound **1.91** also proves the regeoselectivity of the cycloaddition. The only isoxazole proton shows a signal at δ 6.66 as a singlet in $CDCl_3$. The PMR data of isoxazole, neat or dissolved in various solvents, have been reported in many papers. These data are shown in **Table 1.2**.

**Table 1.2. PMR Data of Isoxazole (δ)**

| $H_3$ | $H_4$ | $H_5$ | Solvent | References |
|---|---|---|---|---|
| 8.34 | 6.41 | 8.51 | CDCl3 | 60 |
| 8.44 | 6.53 | 8.64 | neat | 61 |
| 8.40 | 6.40 | 8.61 | neat | 62 |

In all the reported examples the signals of $H_4$ proton absorb at a higher field (6.40-6.53) then do $H_3$ (8.34-8.44) $H_5$ (8.51-8.64). Presence of a methyl substitution at 5 position shifts the $H_4$ proton to δ 6.06 where as the methyl group at 4 position makes the $H_5$ proton to appear at δ 8.35. Comparing these data with the signal obtained in cycloadduct **1.91** we were quite sure about the proposed structure. If the other regioisomer were formed then the only isoxazole proton would have been the $H_5$ and the signal would be obsereved in much downfield i.e around δ 8.5-9.0. So the large difference in the chemical shifts of unsubstituted or substituted isoxazole protons enabled us to propose the correct isoxazole structures unambiguously. $^{13}C$ NMR spectra also supports the above argument. In the unsubstituted isoxazole,[63,64] the three carbon atoms absorb at 104.5 ppm ($C_4$), 150.0 ppm ($C_3$), and 158.9 ppm ($C_5$). Introduction of a methyl group in the ring shifts down field (8-10 ppm) the signal of the carbon atom to which the methyl group is linked.[65] The cycloadduct **1.91** shows isoxazole carbons at δ 158.2, 104.8. The signal at 104.8 ppm clearly shows that this carbon is free and thus must be $C_4$. The other carbon signal clearly has shifted down field indicating the fact that this carbon is substituted.

The 2nd entry in the **Table 1.1** is the cycloaddition of nitrile oxide with propargyl alcohol. This reaction led to a single regioisomer in moderate yield. The regiochemistry is determined from $^{1}H$ and $^{13}C$ NMR spectra. These data clearly supports the formation of 5-substituted isoxazole **1.100**. The 3rd and 4th entries are the cycloadditions of phenyl propyne and 1-Phenyl-2-propyn-1-ol with Weinreb amide-nitrile oxides respectively. These cycloadducts were formed as single isomers in 50-60% yield in accordance with FMO theory and were characterized as 3,5-disubstituted isoxazoles. The $^{1}H$ and $^{13}C$ data of these four cycloadducts are presented in **Table 1.3**.

**Table 1.3. $^{1}H$ and $^{13}C$ data of Cycloadducts.**

| Cycloadduct | $^{1}H$ signal of Isoxazole proton | $^{13}C$ signals of isoxazole carbons |
|---|---|---|
| 1.91 | 6.66 | 158.2, 104.8, - |
| 1.100 | 6.53 | 160.8 (br), 157.6, 102.8 |
| 1.101 | 6.27 | 158.0, 103.1, - |
| 1.102 | 6.47 | 160.6(br), 157.5, 102.8 |

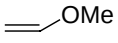
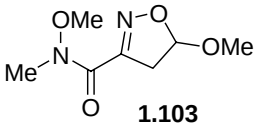
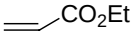
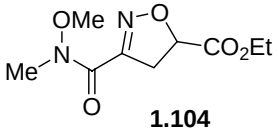
One point to be noted in both proton and carbon NMR spectra of these compounds is that some signals appear broad. For example in all cases the $^{1}H$ signal of N-methyl of Weinreb amide always appear broad in the region $\delta$ 3.34-3.38. Similarly one of the isoxazole $^{13}C$ signal some times does not appear and in other cases appear as a broad peak with very low intensity. We think this is the $C_3$ of the isoxazole unit to which Weinreb amide group is attached. The broadening and low intensity of this carbon peak may be due to the restricted rotation about this C-C bond resulting in such observation.

## (ii) Cycloaddition with Alkenes, Preparation of Isoxazolines:

Cycloaddition of nitrile oxide with alkenes produces isoxazolines. With Weinreb amide-nitrile oxide it would produce Weinreb amide functionalized isoxazolines. These kinds of isoxazolines can be converted to very useful materials exploiting the N-methoxy-N-methylamide chemistry.

In order to show the versatility of our nitrile oxide, we reacted it with two different dipolarophiles, and the results are given below.

**Table 1.4. Preparation of substituted isoxazolines**

| Entry | Nitrile Oxide | Dipolarophile | Cycloadduct | Yield |
|---|---|---|---|---|
| 1 | **1.90** |  |  **1.103** | 67% |
| 2 | **1.90** |  |  **1.104** | 70% |

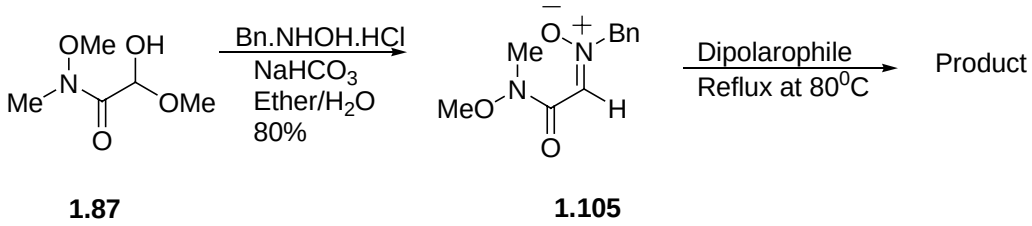
In the first entry of **Table 1.4,** dipolarophile methyl vinyl ether added to nitrile oxide **1.90** to give the cycloadduct **1.103** in about 67% yield as a single regioisomer. Similarly in entry 2, ethyl acrylate formed the compound **1.104** in slightly better yield again as single compound. The regioselectivity was not surprising for us as we obtained the similar results during the alkyne cycloaddition. The structures of those compounds were again

confirmed by consulting the published [66] $^{1}H$ and $^{13}C$ data of isoxazolines and substituted isoxazolines.

In the PMR spectrum the unsubstituted 2-isoxazoline shows three well-separated signals at δ 2.9 (m, 2H) for $H_4$, δ 4.1 (m, 2H) for $H_5$, and δ 7.1 (m, 1H) for $H_3$. When the isoxazoline is substituted by a methyl group at 3 position and methyl ester at 5 position the signals for the two C-4 hydrogens appear at δ 3.25 and $H_5$ appears at δ 5.00. The $^{1}H$ spectra of compound **1.103** showed a signal at δ 3.6-3.4 as a multiplet, which must be the protons at 4 position. That proved that position 4 was not substituted and indeed 3,5-disubstituted isoxazoline was formed. Similarly the cycloadduct **1.104** was assigned the given structure based on the proton NMR spectra of the compound.

## c. Weinreb amide-nitrone and subsequent cycloaddition:

After the successful application of Weinreb amide-nitrile oxide as a versatile 1,3-dipole, we then turned our attention to the chemistry of nitrone. We thought that the preparation of Weinreb amide-nitrone would be easy as the starting material for it was the same Weinreb amide-hemiacetal **1.87**. So Weinreb amide- nitrone **1.105** was synthesized by treating Weinreb amide-hemiacetal **1.87** with N-benzyl hydroxylamine hydrochloride. The reaction was completed within one hour and the crude nitrone was isolated and was used for the cycloaddition[67] without further purification. (**Scheme-1.15**)



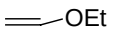
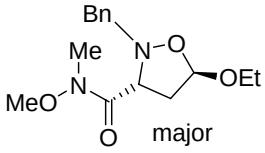
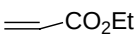
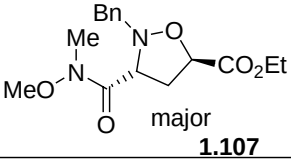

**1.87** **1.105**

**Scheme 1.15. Preparation of Nitrone and Subsequent Cycloaddition.**

The reaction was carried out by heating the Weinreb nitrone **1.105** with excess of dipolarophiles. After removal of the excess reagents, the resulting mixture was chromatographed to produce the pure products.

**Table 1.5** illustrates the cycloaddition of Weinreb amide-nitrone with vinyl ethyl ether and ethyl acrylate.

**Table 1.5. Preparation of substituted isoxazolidines**

| Entry | Nitrone | Dipolarophile | Cycloadduct | Yield |
|---|---|---|---|---|
| 1 | **1.105** |  |  major **1.106** | 84% |
| 2 | **1.105** |  |  major **1.107** | 80% |

As described in **section 1.4.b.iv** such a cycloaddition can produce four compounds, two regioisomers and each regioisomer can form two diastereoisomers. But in our case we only obtained two compounds, which were diastereoisomers to each other. In both the entries the single regioisomer gave rise to two diastereoisomers in a 1:20 ratio favoring the trans isomers in very good yield.

The proof of regiochemistry was easy by comparining the PMR of such compounds with the parent isoxazolidine.

The stereochemistry of the cycloaddducts can be explained in terms of the approach of the reagents leading to the diastereomers. Both high *endo/exo* diastereoselectivity and *re/si* facial diastereoselectivity was thought to be observed for the reaction.

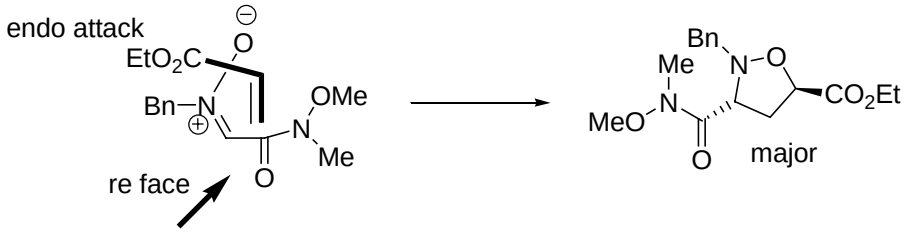



**Figure 1.32. Approach of Reagents**.

The stereochemistry was also assigned from the coupling constant (4Hz) of the hydrogen atom at the carbon 5 of the compound **1.108**. This assignment is based on the work of Deshong [67] and Gomez-Guillen,[68] who had similar isoxazolidines and coupling constants at the C-5 hydrogen.

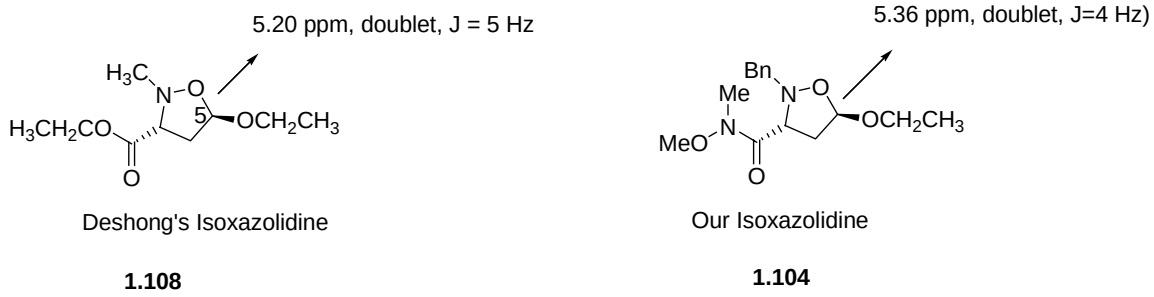



**Figure 1.33. Comparision of Deshong's isoxazolidine with 1.104**

## d. Synthetic Utility

Lastly it remained to show the synthetic significance of our cycloaddition reagents.

To demonstrate the utility of 1,3-dipolar cycloadditions, the cycloadducts were transformed into multifunctionalized materials.

Firstly isoxazole **1.101** was converted to its ketone derivative **1.109** by treating it with methyl magnesium bromide in THF.[69] In a very clean reaction the 3-methyl ketone 5-benzyl isoxazole was obtained in over 95% yield.

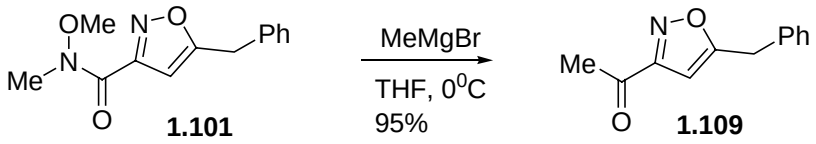



**Figure 1.34**. **Synythetic Utility-1.**

Similarly the reduction of Weinreb amide with LAH[50] furnished the corresponding aldehyde **1.110** again in a very nice and clean reaction. The reaction was done in THF at $0^{o}$C to produce the 4-substituted aldehyde **1.110** in about 92% yield.

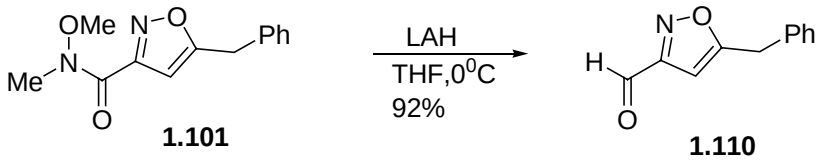



**Figure 1.35. Synthetic Utility-2.**

## e. Conclusion:

Although this project did not start on a positive note, the end result was however satisfactory. Unfortunately our main objective, i.e. the synthesis of C-analog of glucosyl asparagine via Ramberg-Backlund rearrangement was not achieved. The reason behind the failure of Ramberg-Backlund reaction was attributed to the instability of substituted Weinreb amide isoxazole towards the strong basic conditions required for such reactions. The findings that the isoxazole or Weinreb amide, were stable to R.B conditions but their combination was not, was in accordance with the previous findings. Since our main aim was to extend the scope of R.B as a methodology to synthesize C- glycosides, other possible routes to the target compound were not tried.

At the same time, one of the positive outcomes from this project was the successful synthesis of Weinreb amide functionalized isoxazole, isoxazolines and isoxazolidines. These materials were prepared by the {3+2} cycloaddition of Weinreb amide functionalized nitrile oxides and nitrones with dipolarophiles. These kinds of dipoles were not known before. Since Weinreb amide can be converted to different functionalities, this methodology provides an easy entry to substituted isoxazoles, isoxazolines and isoxazolidines. These products can be used as important starting material for various useful purposes.

# Instruments and Materials

NMR spectra were recorded at 300 MHz or 500 MHz ($^{1}H$) and 75 MHz or 125 MHz ($^{13}C$) in deuterated solvent. The assignment of proton and carbon NMR peaks was supported by routine COSY and for some cases by NOESY spectra.

Electrospray ionization (ESI) mass spectra experiments were performed by Dr. Clifford E. Soll at the Hunter College Mass Spectrometry Facility. Typical ESI method: solvent: 1/1 acetonitrile/water + 0.1% HOAc + 50 μL $NH_4Ac$, flow: 0.50 mL/min, positive ion mode, fragmentor voltage: 30-200 V, drying gas at 175 $^{0}C$.

All air-moisture sensitive reactions were performed under a positive pressure of dry nitrogen. All solvents and reagents were purified prior to use according to standard laboratory procedures. Low temperatures were recorded as bath temperatures.

Thin layer chromatography analyses were carried out on precoated aluminium sheets of silica gel 60 F 254. UV light and vanillin, potassium permanganate or phosphomolybdic acid spray was used to visualize the components on the TLC plates.

Flash column chromatography was carried out with silica gel 60 (230-400 mesh), using ACS reagent grade petroleum ether, ethyl acetate, methylene chloride, hexane, chloroform, ethyl ether.

# Experimental procedures and compound characterization data

### 3-carboethoxy-5-bromo-ethyl isoxazole 1.75

Propargyl bromide **1.74** (3.72 g, 2.78 mL, 31.2 mmol) was added over a 15 min period to an ice-cold stirred solution of ethyl chloroximeacetate **1.73** (2.32 g, 15.3 mmol) in ether (10 mL). After stirring for 10 min at 0 $^{o}$C, a solution of triethylamine (2.55 mL) in ether (6.6 mL) was added dropwise over a 5.5 h period maintaining the temp between 1 $^{o}$C to 4 $^{o}$C. The reaction mixture was stirred for an additional 20 min at 0 $^{o}$C, filtered to remove the triethylamine hydrochloride, washed the solid with ether. The combined filtrate was washed with brine, then 2N HCl, dried, filtered and concentrated to give the crude product which was subjected to flash column chromatography to give **1.75** (2.3 g, 64%). $^{1}$H NMR: (300 MHz, $CDCl_3$) δ 1.45 (t, 3H, J = 7.0 Hz), 4.46 (q, 2H, J = 7.0 Hz), 4.58 (s, 2H), 6.77 (s, 1H).

### Thioether 1.72

To a solution of thoroughly degassed ($N_2$) thioacetate **1.78**[17] (1.01 g, 2.5 mmol) in anhydrous DMF (5 mL) was added hydrazinium acetate (0.270 g, 2.5 mmol). After 1 h at room temperature, the bromoisoxazole **1.75** (0.58 g, 2.5 mmol) and triethyl amine (0.43 mL) were added. The reaction mixtute was stirred at room temp until TLC showed complete transformation after which E.A and $H_2O$ were added. The resulting organic phase was washed with $H_2O$ followed by saturated NaCl, then dried, filtered and

evaporated to dryness under vauum. The residue was purified by column chromatography. $^{1}$H NMR: (300 MHz, $CDCl_3$) δ 6.63 (s, 1H), 5.22 (m, 1H), 5.09 (m, 2H), 4.53 (d, 1H, J = 9.9 Hz), 4.44 (q, J = 7.3 Hz, 7.0 Hz, 2H), 4.22 (dd, J = 7.7 Hz, 4.8 Hz, 1H), 4.13 (m, 2H), 3.88 (d, J = 15.7 Hz, 1H), 3.7(m, 1H), 2.09, 2.04, 2.03, 2.0 (all s, 3H ea), 1.45 (t, 3H). MS ($ES^+$): m/z: 535.1 (M+ Na).

**Tetra-O-benzyl-β-D-glucose thioacetate 1.96**

2,3,4,6-tetra-O-benzyl-α-D-glucose **1.94** (2.91 g, 4.7 mmol) was added to thionyl chloride (10 mL) and the solution was kept at 70 $^{o}$C for 3 h. After concentrating *in vacuo*, excess thionyl chloride was removed by adding toluene and then evaporating to dryness. This procedure was carried out 3 times giving the glucosyl chloride **1.95** as dark yellow syrup. Crude glucosyl chloride **1.95** (294 mg) was dissolved in benzene (4.5 mL). KSAc (100 mg) dissolved in absolute ethanol (4.5 mL) was added. The reaction mixture was stirred overnight at room temperature, partitioned between chloroform and water, and the organic layer was dried ($Na_2SO_4$) and concentrated under reduced pressure. Chromatographic separation of the crude material produced **1.96** (180 mg, 57%). $^{1}$H NMR: (300 MHz, $CDCl_3$) δ 5.15 (d, 1H), 4.9-4.72 (m, 4H), 4.60-4.42 (m, 4H), 3.8-3.72 (m, 3H), 3.6-3.55 (m, 3H), 2.35 (s, 3H); $^{13}$C: NMR (75 MHz, $CDCl_3$) δ 192.6, 138.8, 138.5, 138.4, 138.2, 128.5, 128.0, 127.9, 127.8, 127.7, 87.1, 82.2, 80.8, 79.9, 78.1, 75.9, 75.5, 75.1, 73.8, 69.1, 29.8.

**Thioether 1.71**

Applying the same procedure used for the synthesis of compound **1.72**, compound **1.71** was synthesized in 64% yield. $^{1}$H NMR: (500 MHz, $CDCl_3$) δ 7.40-7.10 (m, 20 H), 6.58 (s, 1H), 4.86-4.70 (m, 4H), 4.62-4.46 (m, 4H), 4.41 (d, J = 15.2 Hz, 1H), 3.89 (d, 1H, J = 15.1 Hz), 3.744 (s, 3H), 3.7-3.69 (m, 4H), 3.49-3.37 (m, 3H), 3.33 (s, 3H); $^{13}$C: NMR (125 MHz, $CDCl_3$) δ 170.5, 161.4, 144.0, 138.9, 138.6, 138.5, 138.2, 129.6, 129.4, 129.0, 128.9, 128.8, 128.6, 128.5, 128.4, 128.3, 128.2, 116.3, 104.4, 87.1, 84.0, 82.6, 79.7, 78.3, 77.4, 76.3, 76.1, 75.6, 73.9, 69.3, 62.9, 34.6.

**Sulfone 1.70**

A solution of MMPP (0.166 g, 0.336 mmol) in $H_2O$ (1 mL) was added to a solution of the above sulfide (0.121 g, 0.168 mmol) in EtOH (1mL) and THF (1mL). The mixture was kept at 55$^{o}$C for 2 h, then concentrated *in vacuo* to dryness. The residue was treated with saturated aqueous $NaHCO_3$ solution (20 mL) and extracted with EtOAc, dried ($Na_2SO_4$) and evaporated to dryness. The residue was purified by silica gel chromatography to afford **1.70** (0.1 g, 78%) as white solid. $^{1}$H NMR: (300 MHz, $CDCl_3$) δ 7.31-7.15 (m, 20 H), 6.79 (s, 1H), 5.00-4.85 (m, 3H), 4.80-4.75 (m, 3H), 4.70 (m, 4H), 4.40 (m, 2H), 3.81 (s, 3H), 3.74 (m, 1H), 3.60 (d, 2H), 3.41 (s, 3H). ESI calculated 756.86, found 774.1 ($M+NH_4^+$).

**Cinnamate 1.81**

To a solution of trans- cinnamic acid (740 mg, 5 mmol), in THF (13 mL), at room temperature, were added CDMT (1.03 g, 5.9 mmol) and NMM (1.6 mL, 15 mmol). A white precipitate was formed during stirring for 1h, and then N,O-dimethylhydroxylamine hydrochloride (480 mg, 5 mmol) was added. The mixture was stirred for additional 10 h and then quenched with 18 mL of $H_2O$ and extracted two times with diethyl ether (10 mL). The combined organic phases were washed two times with saturated aqueous solution of $Na_2CO_3$ (15 mL), followed by 1 N HCl (15 mL) and brine. The organic layer was dried ($Na_2SO_4$) to give, after evaporation of solvent, and chromatography the compound **1.81** (860 mg, 90%). $^1$H NMR: (300 MHz, $CDCl_3$) δ 7.59 (d, 2H, J = 15.8 Hz), 7.38 (d, 2H), 7.26-7.11 (m, 3H), 6.90 (d, 2H, J = 15.8 Hz), 3.54 (s, 3H), 3.12 (s, 3H); $^{13}$C: NMR (75 MHz, $CDCl_3$) δ 167.1, 143.6, 135.1, 130.1, 128.9, 128.4, 117.4.

**Weinreb amide-aldehyde 1.86**

Ozone was bubbled through a solution of cinnamate **1.81** (2.2 g, 11.5 mmol) in 1:1 $CH_2Cl_2$-MeOH (80 mL) at – 78 $^o$C for 5 h. After persistence of the blue color of the solution, the excess of $O_3$ was removed with a stream of $O_2$. Nitrogen was then bubbled into the mixture until the blue color disappeared. $Me_2S$ (1.7 mL, 23.04 mmol) was added, and the solution was allowed to stir at room temperature overnight. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel

(EtOAc / PE, 2:3) to give the product (1.2 g, 78%). $^1$H NMR: (300 MHz, $CDCl_3$) δ 5.22 (1H, d, J = 10.9 Hz), 4.38 (1H, d, J = 10.9 Hz), 3.77 (3H, s), 3.48 (3H, s), 3.26 (3H, s); ESI MS (calcd for $C_5H_{11}NO_4$, 149) *m/z*: 150 ($M + H^+$).

## General method for cycloaddition

To a solution of Weinreb amide functionalized hemiacetal **1.87** (2.06 mmol) in 7 mL of 1:1 mixture of $H_2O$ and ether was added hydroxylamine hydrochloride (357 mg, 5.1 mmol, 2.5 equiv.) and $NaHCO_3$ (519 mg). The mixture was stirred for 30 min and then extracted with $CH_2Cl_2$ three times. The combined extract was dried with $Na_2SO_4$, filtered and concentrated to give crude **1.88**. A solution of crude **1.88** (360 mg, 2.7 mmol in 2 mL of $CHCl_3$) was added to a suspension of NCS (545 mg, 4 mmol) in 2 mL of anhydrous $CHCl_3$ and pyridine (50μL) at room temperature. The completion of chlorination was observed by the disappearance of suspended NCS (about 30 min). The reaction mixture was concentrated in vacuum and co-evaporated with toluene. Dipolarophiles (2 equiv) was added to an ice-cold stirred solution of **1.89** in 2 mL of $CH_2Cl_2$. After stirring for 10 min at 0 $^0$C, a solution of triethylamine (150 μL) in 1 mL of $CH_2Cl_2$ is added drop wise over a 3 h period, maintaining the temperature between 1 $^o$C to 4 $^o$C. The reaction mixture was stirred for an additional 20 min at 0 $^o$C, filtered to remove the triethylamine hydrochloride, which was washed with ether. The combined filtrate was washed with brine, then aqueous HCl, dried, filtered and concentrated to give the crude product which was subjected to flash column chromatography to give pure product in 50-60% yield. (Potassium permanganate spray was used to visualize the components on the TLC plates).

**Cycloaddition with Propargyl bromide. 1.91 (entry-1, Table-1.1**)

$^{1}$H NMR: (300 MHz, $CDCl_3$) δ 6.66 (1H, s), 4.66 (1H, s), 4.5 (1H, s), 3.79 (3H, s), 3.38 (3H, brs); $^{13}$C: NMR (75 MHz, $CDCl_3$) δ 167.8, 158.2, 104.8, 62.3, 34.2, 33.4 (br); ESI MS (calcd for $C_7H_9BrN_2O_3$, 248) *m/z*: 266.0, 267.9 ($M + NH_4^+$).

**Cycloaddition with Propargyl alcohol. 1.100 (entry-2, Table-1.1)**

$^{1}$H NMR: (300 MHz, $CDCl_3$) δ 6.53 (1H, s), 4.78 (2H, s), 3.76 (3H, s), 3.38 (3H, brs). $^{13}$C NMR: (75 MHz, $CDCl_3$) δ 172.3, 160.8(br), 157.6, 102.8, 62.3, 56.5, 33.2(br); ESI MS (calcd for $C_7H_{10}N_2O_4$, 186) *m/z*: 204.1 ($M + NH_4^+$)

**Cycloaddition with 3-Phenyl-1-propyne. 1.101 (entry-3, Table-1.1)**

$^{1}$H NMR: (300 MHz, $CDCl_3$) δ 7.35-7.24 (5H, m), 6.27 (1H, s), 4.11 (2H, s), 3.77 (3H, s), 3.37 (3H, brs). $^{13}$C NMR: (75 MHz, $CDCl_3$) δ 172.5, 158.0, 135.6, 130.0, 128.9, 127.4, 103.1, 62.2, 33.4 (br), 33.3; ESI MS (calcd for $C_{13}H_{14}N_2O_3$, 246) *m/z*: 264.1 ($M + NH_4^+$).

**Cycloaddition with 1-Phenyl-2-propyn-1-ol. 1.102 (entry-4, Table-1.1)**

$^{1}$H NMR: (500 MHz, $CDCl_3$) δ 7.44-7.35 (5H, m), 6.47 (1H, s), 5.94 (1H, s), 3.75 (3H, s), 3.34 (3H, brs); $^{13}$C: NMR (75 MHz, $CDCl_3$) δ 174.4, 160.6(br), 157.5, 139.6, 128.8, 128.7, 126.7, 102.8, 69.4, 62.2, 33.8(br); ESI MS (calcd for $C_{13}H_{14}N_2O_4$, 262) *m/z*: 280 ($M + NH_4^+$).

**Cycloaddition with ethyl acrylate. 1.104 (entry-2, Table-1.4)**

$^{1}$H NMR: (500 MHz, $CDCl_3$) δ 5.03 (1H, dd, J = 7 Hz, 11.5Hz), 4.17 (2H, qt, J = 7 Hz) 3.69 (3H,s), 3.6-3.4 (2H, m), 3.23 (3H, brs), 1.23 (3H, t, J = 7Hz); $^{13}$C NMR: (75 MHz, $CDCl_3$) δ 168.9, 160.1(br), 151.7, 77.8, 61.9, 61.8, 39.8, 33.4(br), 13.9; ESI MS (calcd for $C_9H_{14}N_2O_5$, 230) *m/z*: 248.1 ($M + NH_4^+$).

## W-A nitrone and subsequent cycloaddition.

To a solution of Weinreb amide functionalized hemiacetal **1.87** (185 mg, 1.2 mmol) in 4 mL of 1:1 mixture of $H_2O$ and ether was added benzyl hydroxylamine hydrochloride (250 mg, 1.6 mmol, 1.3 equiv) and $NaHCO_3$ (320 mg). The mixture was stirred for 30 min and then extracted with $CH_2Cl_2$ three times. The combined extract was dried with $Na_2SO_4$, filtered and concentrated to give crude **1.105**. N-benzyl nitrone **1.105** (1.7 mmol) was dissolved in an excess of ethyl vinyl ether or ethyl acrylate (37 mmol). The reaction mixture was heated at 80 $^{o}$C for two days. After cooling, the excess solvent was removed by evaporation under high vacuum. The resulting reaction mixture was chromatographed to give product

**Cycloaddition with ethyl vinyl ether. 1.106 (entry-1, Table-1.5)**

$^{1}$H NMR: (500 MHz, $CDCl_3$) δ 7.45-7.20 (5H, m), 5.36 (1H, d, J = 4 Hz), 4.41 (2H, d, J = 13 Hz), 4.15 (1H, d, J = 12.5 Hz), 3.73 (1H, m), 3.48-3.43 (4H, m), 3.11 (3H, s), 2.93 (1H, m), 2.55-2.51 (1H, m), 1.2 (3H, t); $^{13}$C NMR: (75 MHz, $CDCl_3$) δ 171.2, 137.6, 129.4, 128.3, 127.4, 105.7, 64.5, 64.0, 63.2, 61.1, 38.3, 32.8,15.3; ESI MS (calcd for $C_{15}H_{22}N_2O_4$, 294) *m/z*: 295.1 ($M + H^+$).

**Cycloaddition with ethyl acrylate. 1.107 (entry-2, Table-1.5)**

$^{1}$H NMR: (500 MHz, $CDCl_3$) δ 7.42-7.25 (5H, m), 4.77 (1H, t, J = 8.5 Hz), 4.37 (1H, m), 4.27-4.20 (3H, m), 3.92 (1H, d, J = 13.0 Hz), 3.41 (3H, s), 3.12 (3H, s), 2.95 (1H, m), 2.71-2.65 (1H, m), 1.29 (3H, t, J = 7 Hz); $^{13}$C NMR: (75 MHz, $CDCl_3$) δ 172.2, 170.2, 136.7, 129.7, 128.3, 127.5, 77.8, 63.8, 62.7, 61.4, 61.2, 34.6, 32.6, 14.3; ESI MS (calcd for $C_{15}H_{22}N_2O_4$, 322) *m/z*: 323.1 ($M + H^+$).

**Isoxazole ketone 1.109**

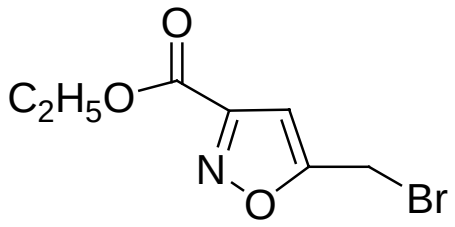
To a solution of **1.101** (**entry-3, Table-1.1**) (156 mg, 0.634 mmol) in 5 mL of anhydrous THF was added 4 equiv of methyl magnesium bromide (2.6 mmol) at 0 $^{o}$C. The reaction mixture was stirred at 0 $^{o}$C until TLC showed no starting amide. The reaction mixture was poured into 5% HCl in ethanol at 0 $^{o}$C and the mixture was partitioned between brine and a 1:1 mixture of ether and $CH_2Cl_2$. The organic extract was dried with $Na_2SO_4$ and evaporated in vacuum. The concentrate was purified by column chromatography (silica

gel, 25% EtOAc / petroleum ether) to provide 125 mg of the product. $^{1}$H NMR: (300 MHz, $CDCl_3$) δ 7.36-7.23 (5H, m), 6.30 (1H, s), 4.11 (2H, s), 2.61 (3H, s); $^{13}$C NMR: (75 MHz, $CDCl_3$) δ 192.1, 174.0, 162.4, 135.5, 129.1, 128.9, 127.5, 100.6, 33.5, 27.4; ESI MS (calcd for $C_{12}H_{11}NO_2$, 201) *m/z*: 219 ($M^+ + NH_4^+$).

**Isoxazole aldehyde 1.110**

Lithium aluminium hydride (0.53 mmol) was added to a stirred solution of isoxazole **1.101** (**entry-3, Table-1.1**) (0.43 mmol) in 5 mL of THF at 0 $^{o}$C. Reduction was completed within 15 min. The mixture was hydrolyzed with a solution of potassium hydrogen sulfate (0.74 mmol) in 3 mL of water. Then ether 10 mL was added, the aqueous phase was separated and extracted with ether. The organic phases were combined, washed with 3 N HCl, sat. $NaHCO_3$, and sat. NaCl and dried with $Na_2SO_4$. Evaporation of the solvent gave crude aldehyde. $^{1}$H NMR: (300 MHz, $CDCl_3$) δ 10.10 (1H, s), 7.37-7.24 (5H, m), 6.32 (1H, s), 4.14 (2H, s); $^{13}$C NMR: (75 MHz, $CDCl_3$) δ 184.7, 174.5, 162.4, 135.2, 129.2, 128.9, 127.6, 99.3, 33.5.

# Appendix 1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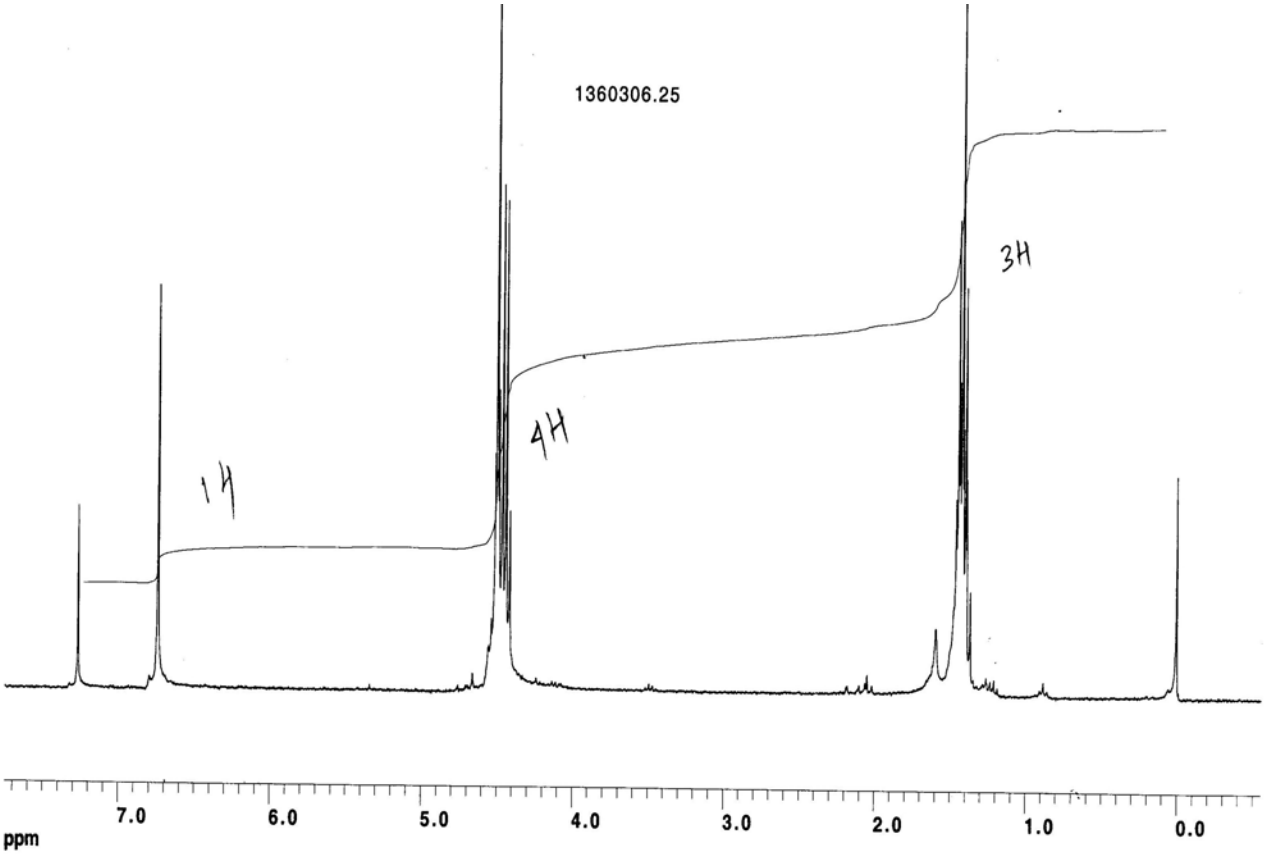
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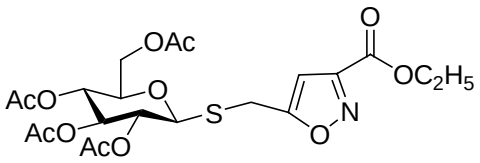
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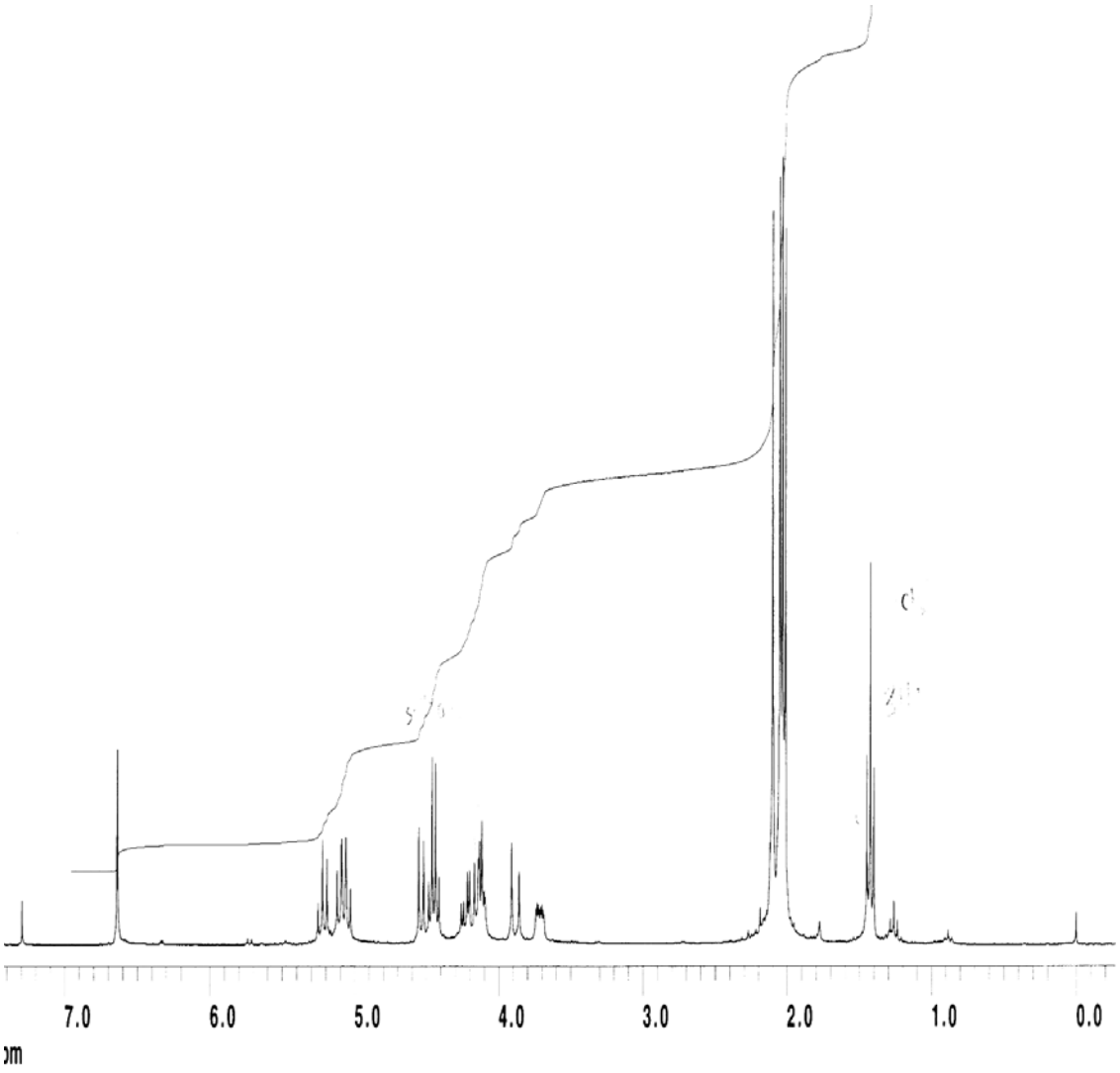
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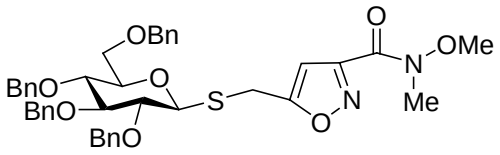
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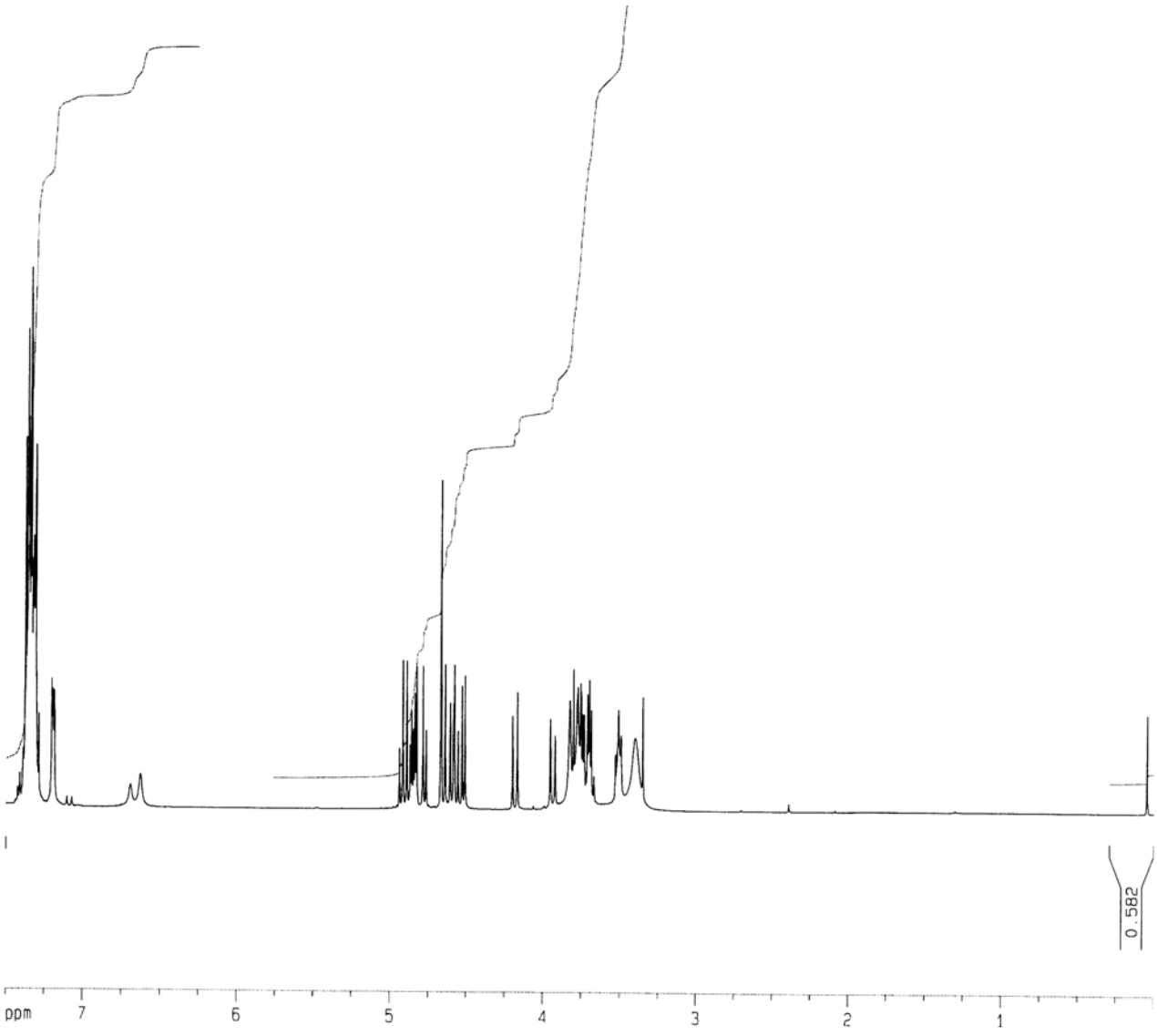
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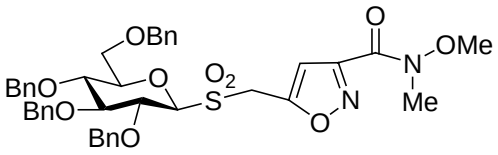
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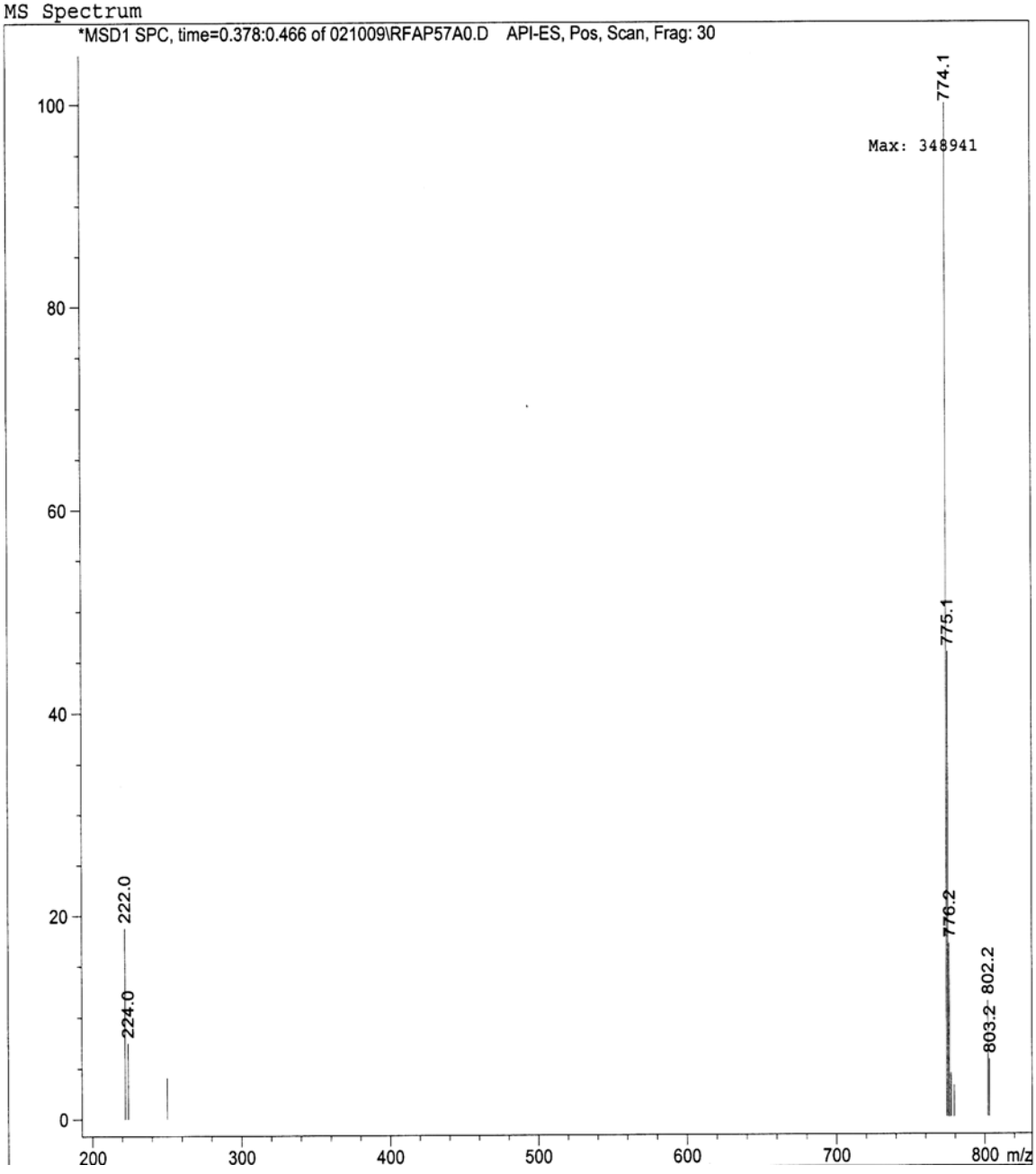
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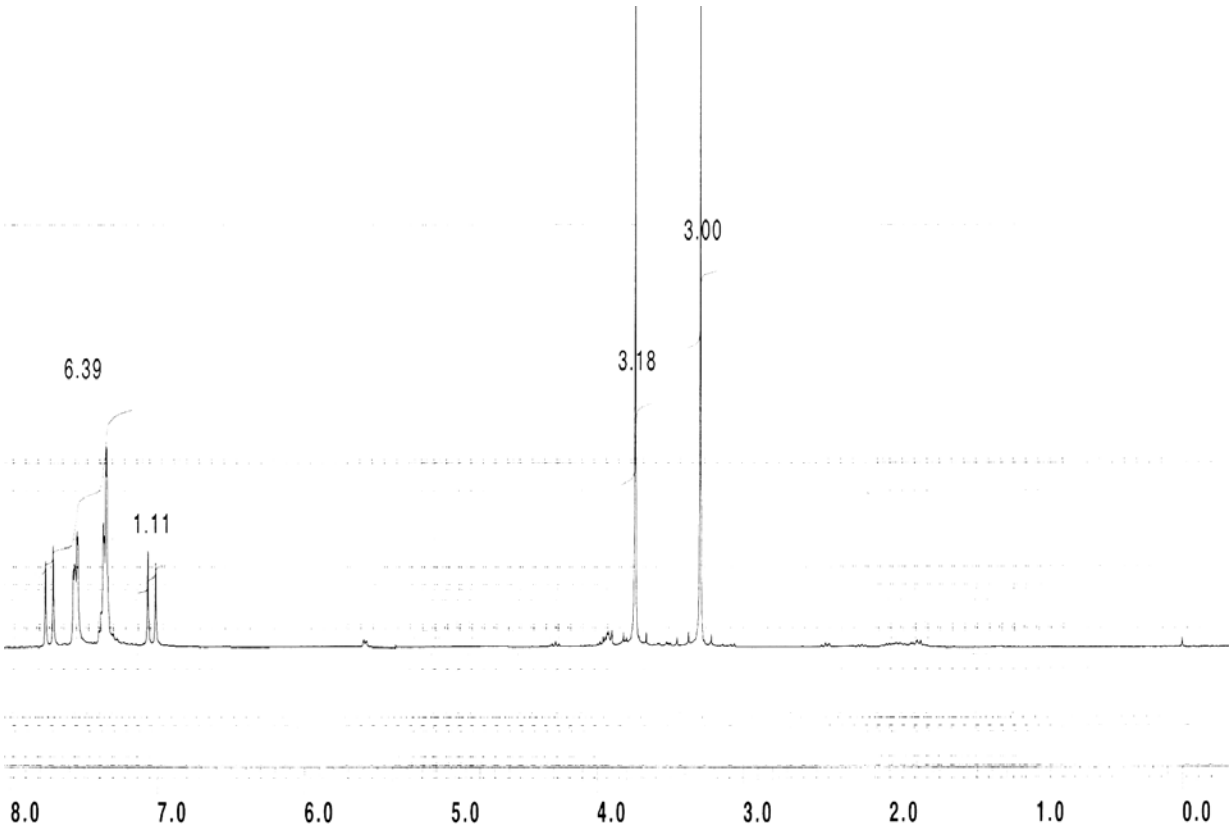
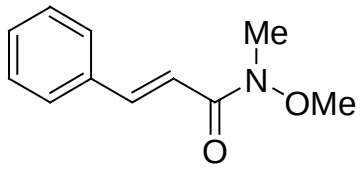
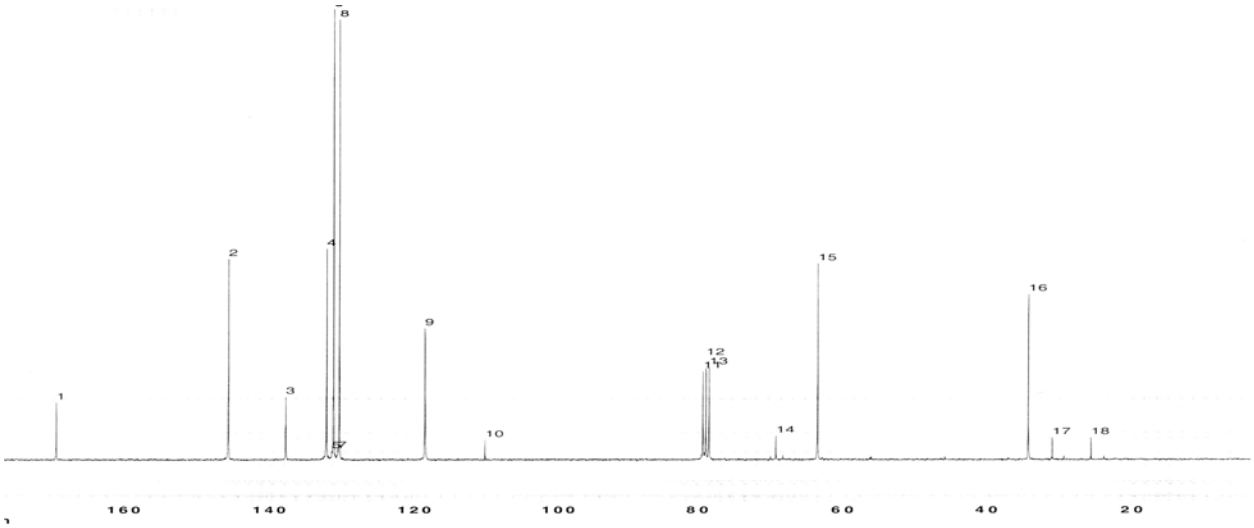
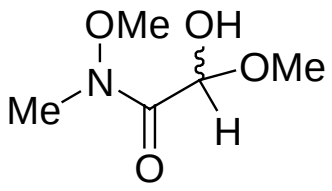
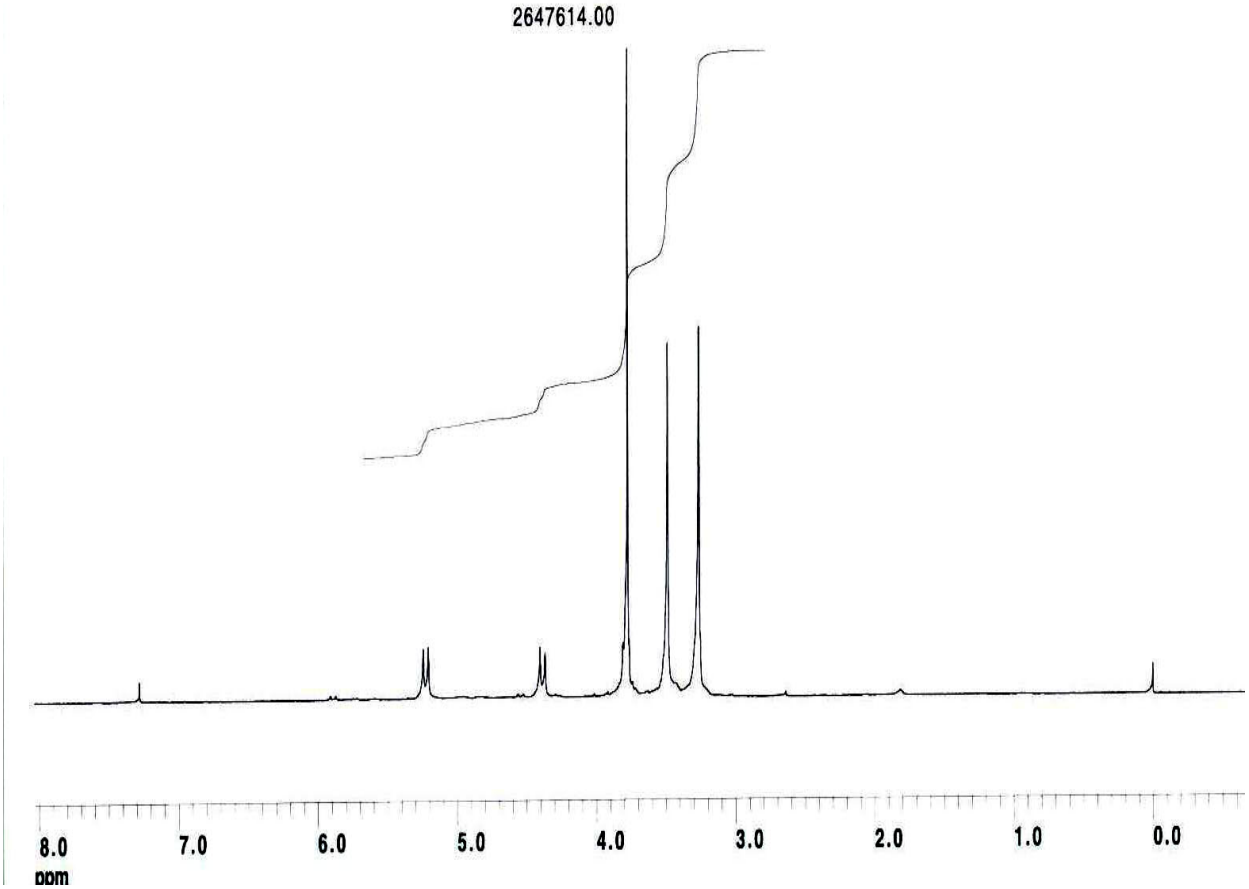
500
600
700
800 m/z

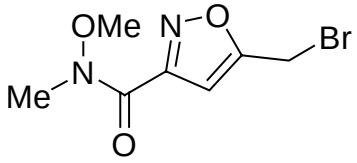

3.00
3.18
6.39
1.11
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

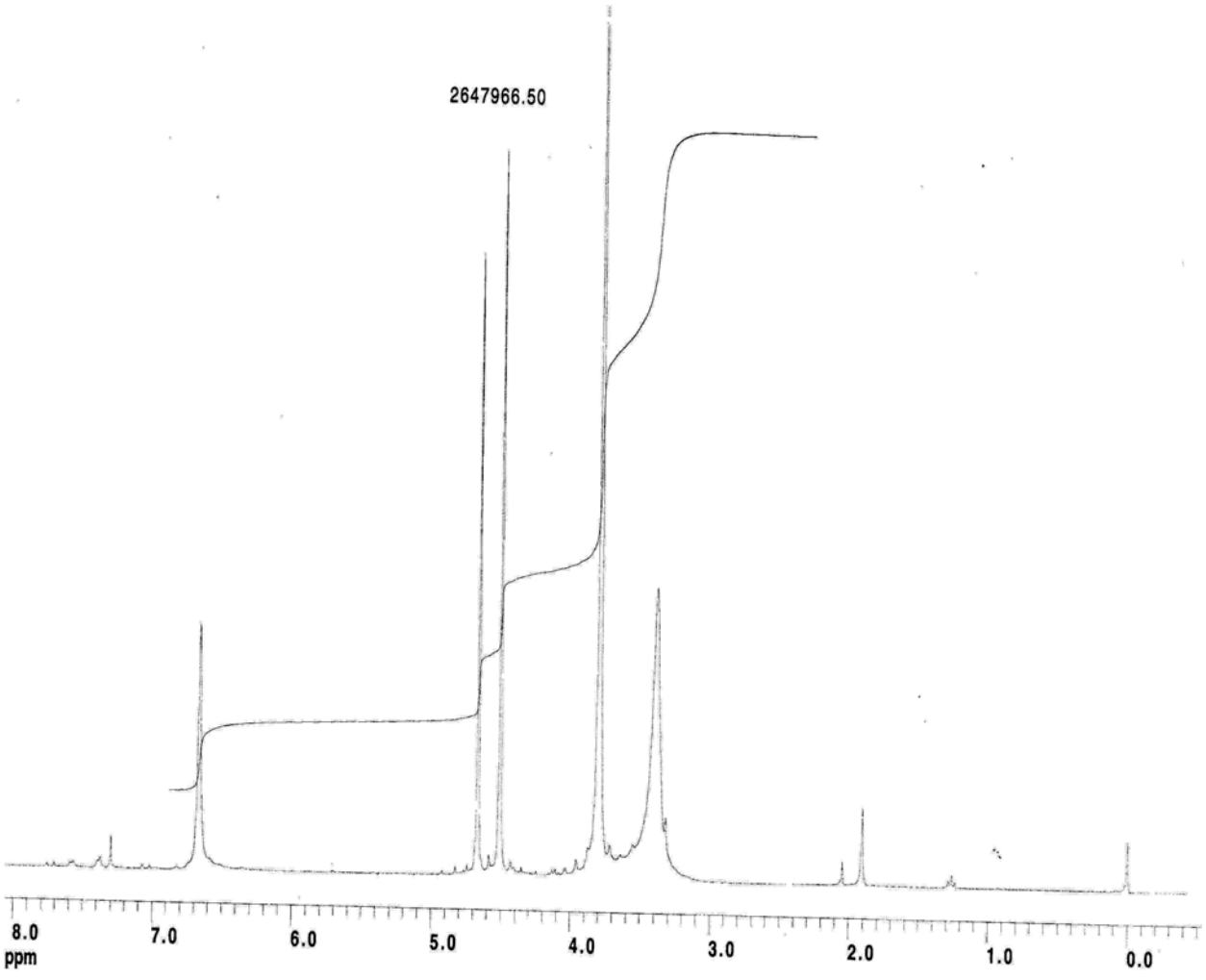

Me
N
OMe
O

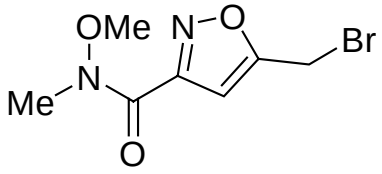

160
140
120
100
80
60
40
20

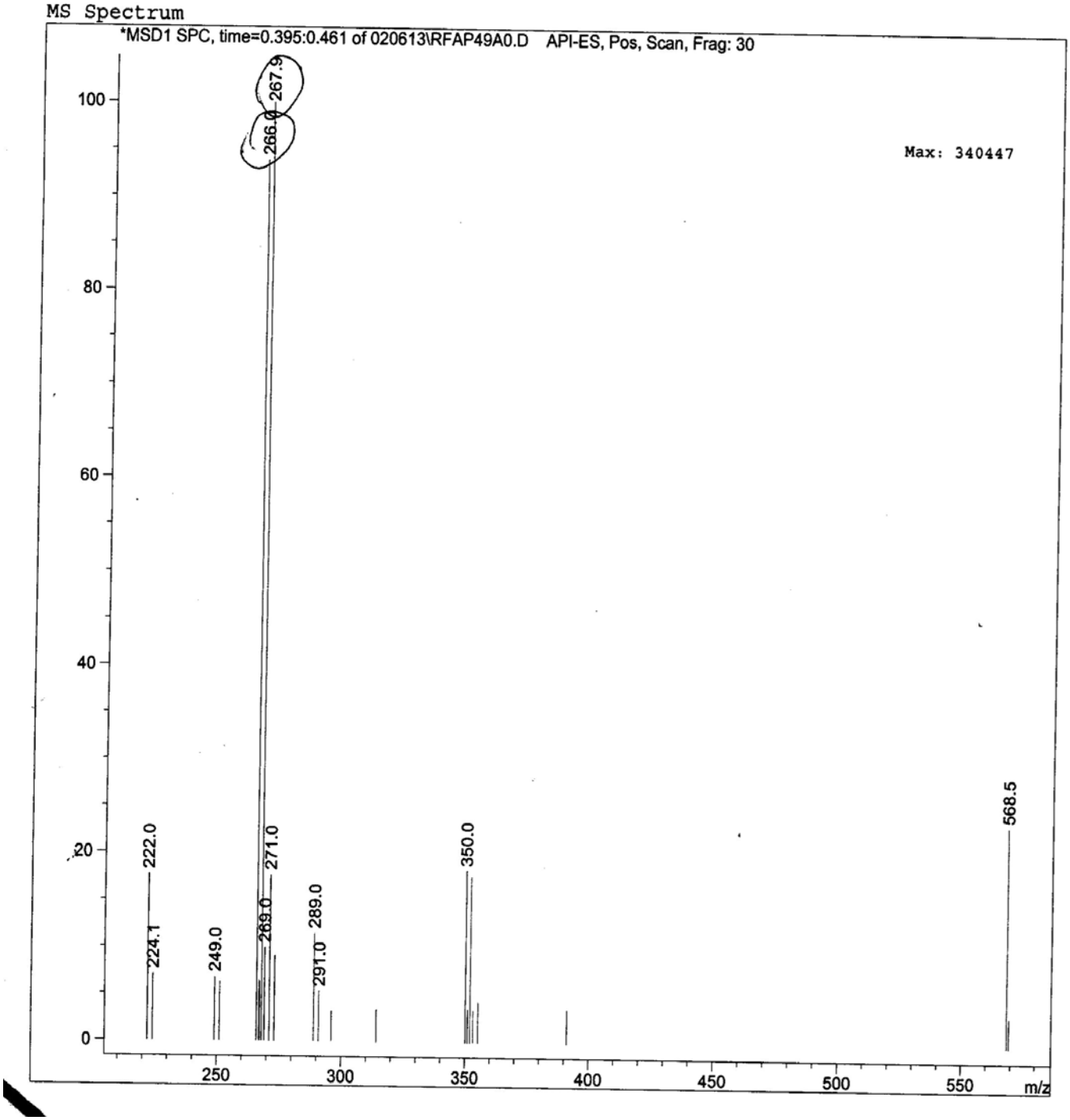

OMe
OH
N
OMe
Me
H
O

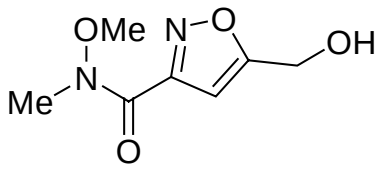

2647614.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm

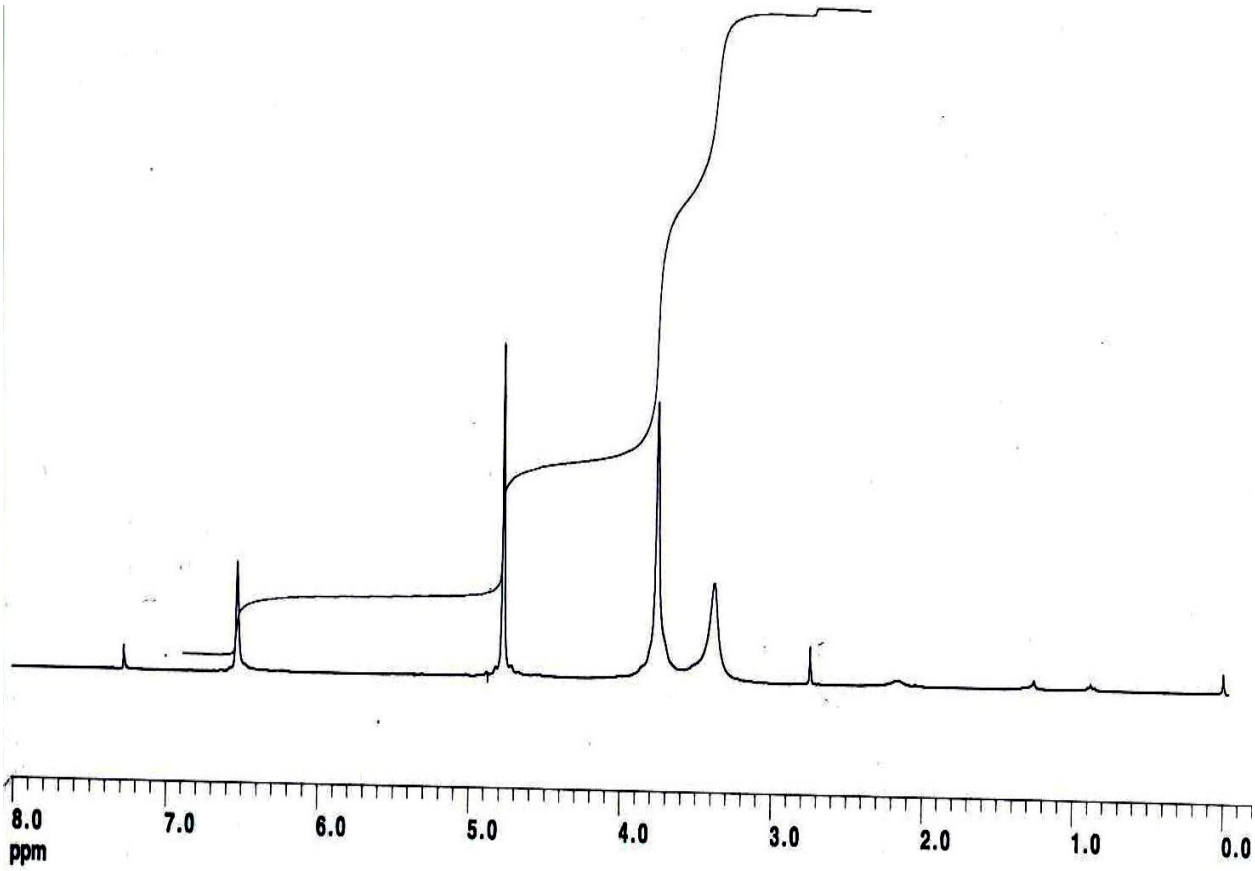

OMe
N
O
Br
N
Me
O

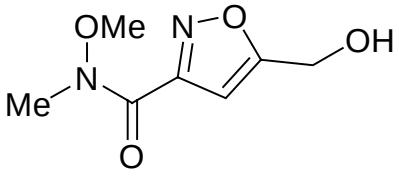

2647966.50
8.0
ppm
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

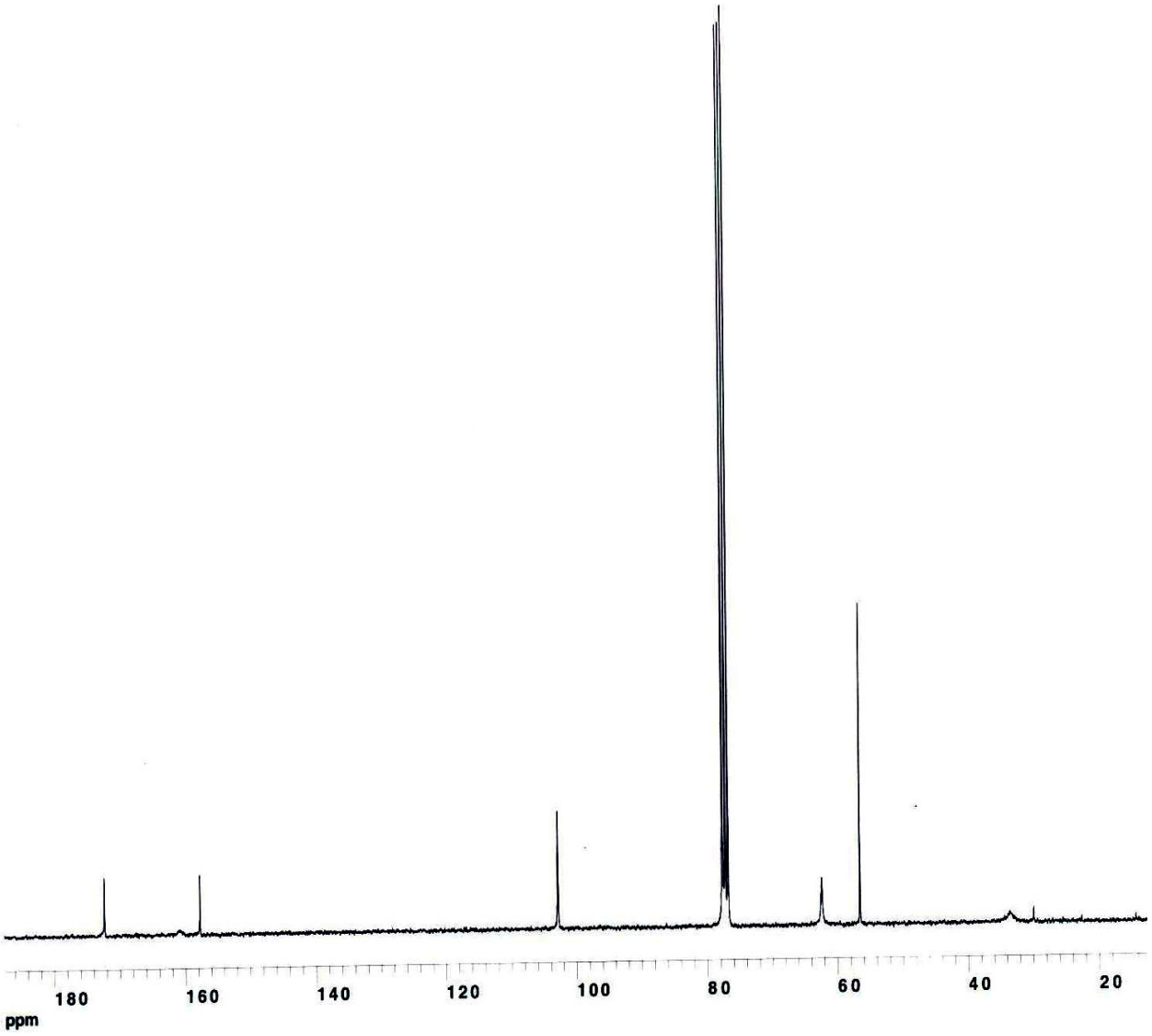

OMe
N
O
Br
N
Me
O

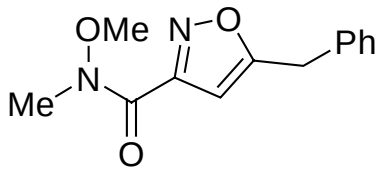

MS Spectrum
*MSD1 SPC, time=0.395:0.461 of 020613\RFAP49A0.D API-ES, Pos, Scan, Frag: 30
Max: 340447
100
80
60
40
20
0
250
300
350
400
450
500
550
m/z
267.9
266.0
222.0
224.1
249.0
269.0
271.0
289.0
291.0
350.0
568.5

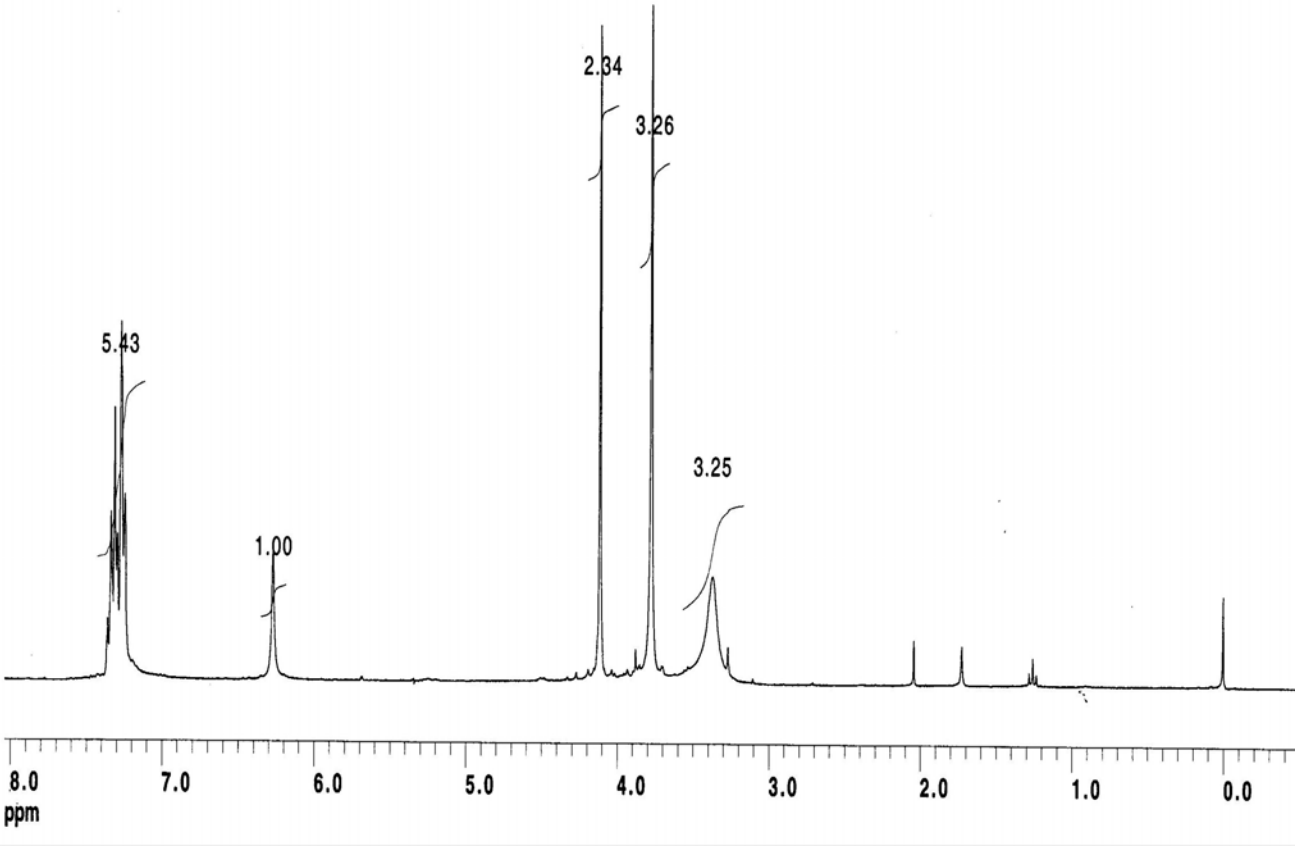

OMe
N
O
OH
N
Me
O

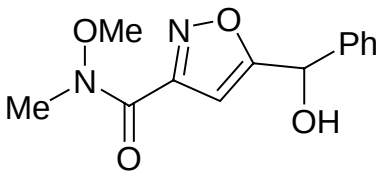

8.0
ppm
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

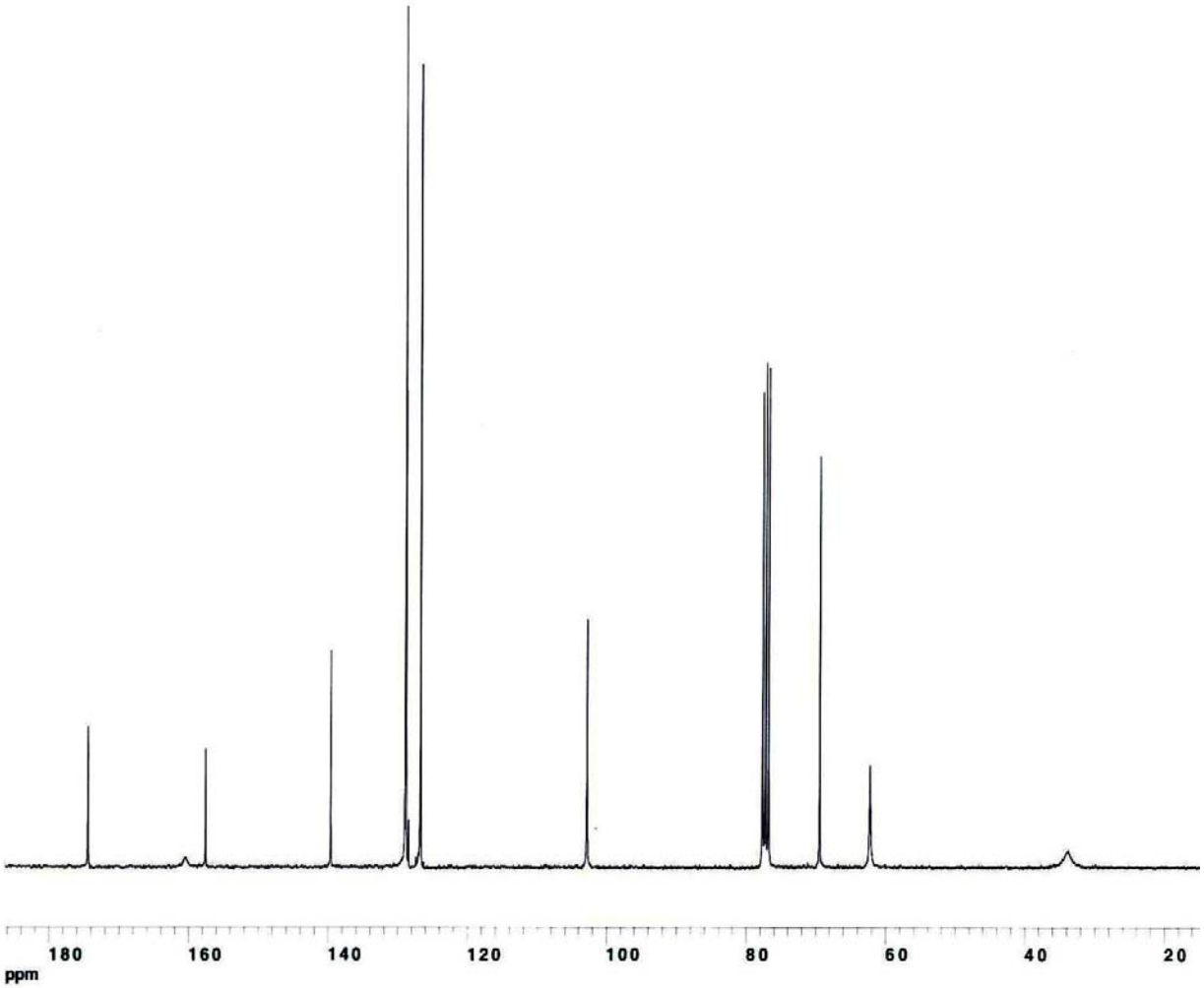

OMe
N
O
OH
N
Me
O

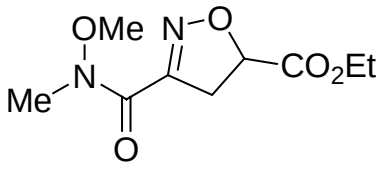

180
160
140
120
100
80
60
40
20
ppm

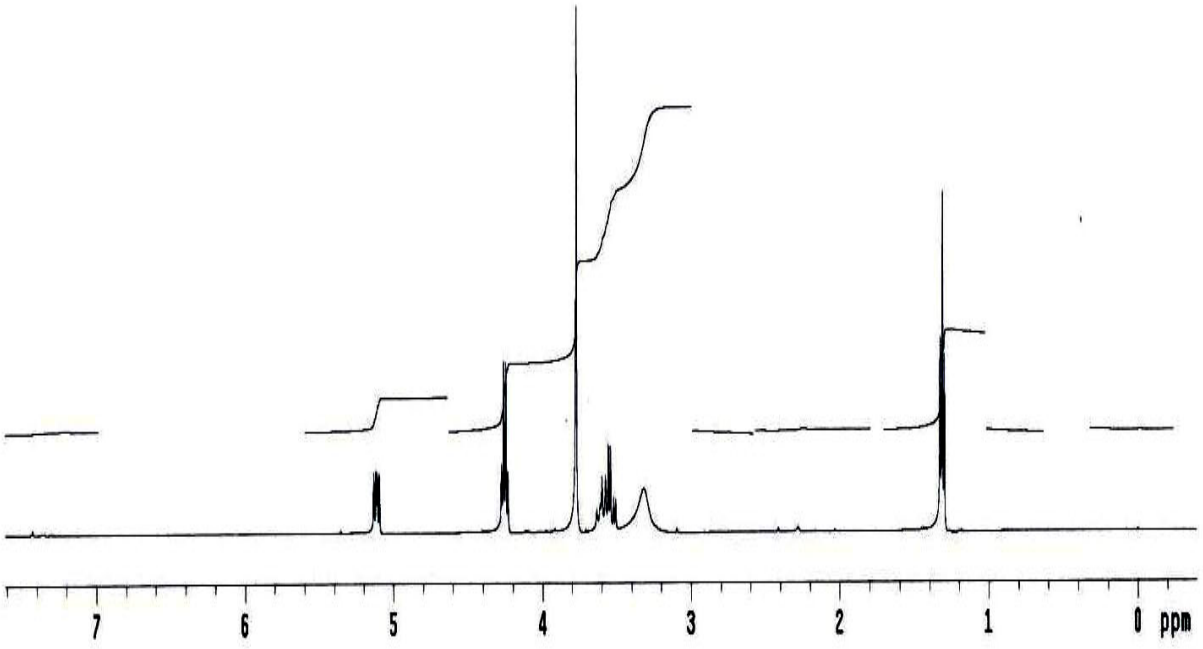

OMe
N
O
Ph
Me
N
O

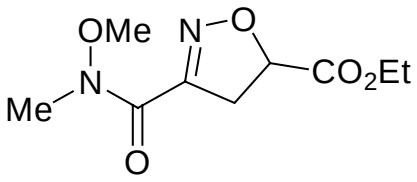

2.34
3.26
5.43
3.25
1.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm

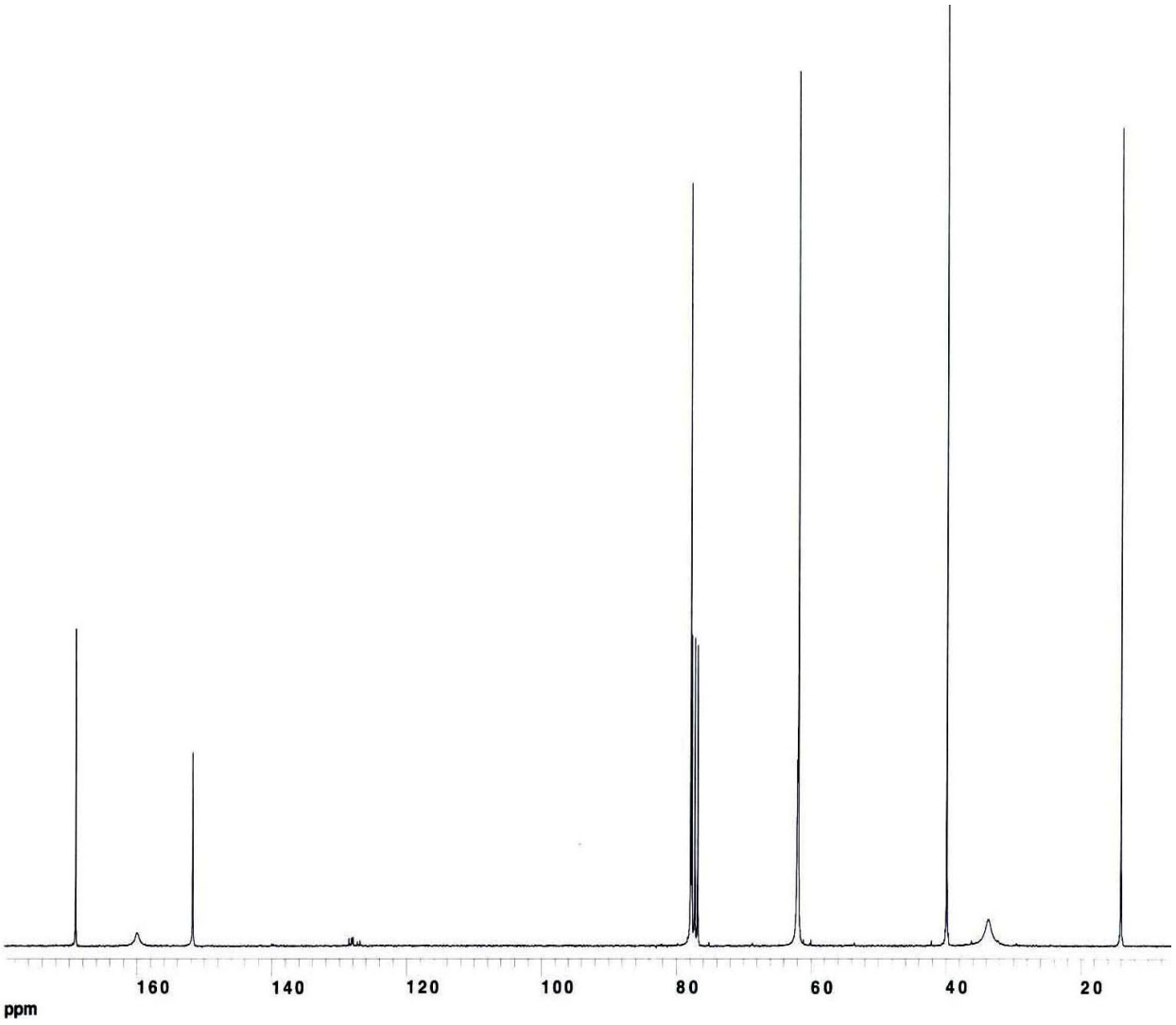

OMe
N
O
Ph
N
Me
OH
O

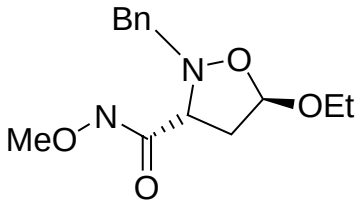

180
160
140
120
100
80
60
40
20
ppm

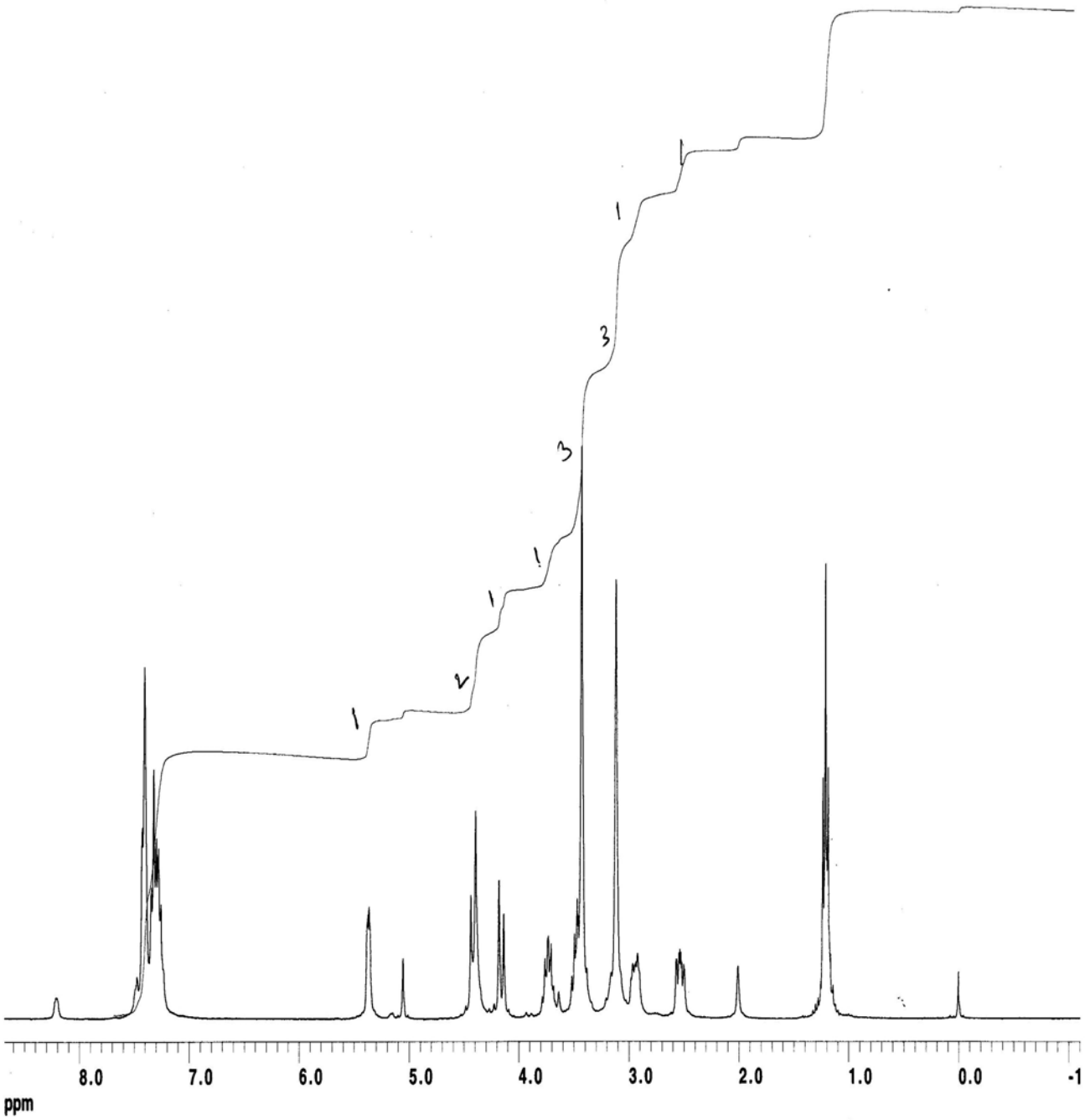

OMe
N
O
N
Me
CO2Et
O

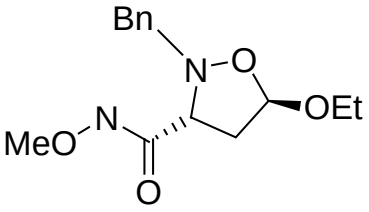

7
6
5
4
3
2
1
0 ppm

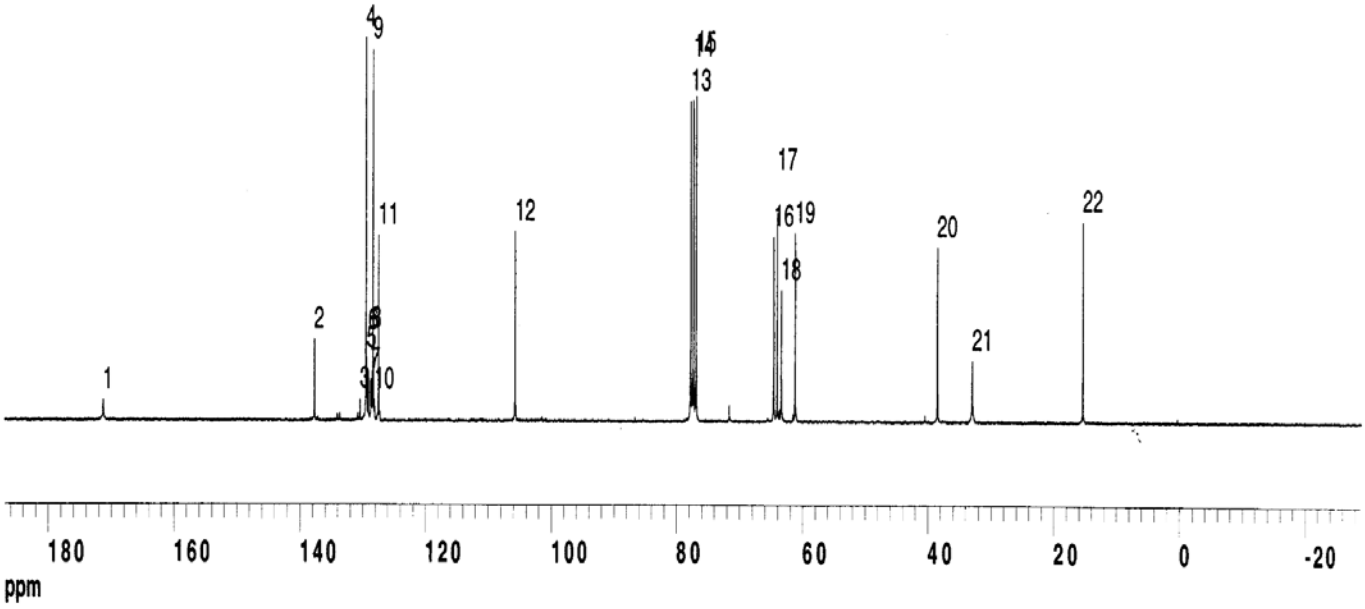

OMe
N
O
N
Me
CO2Et
O

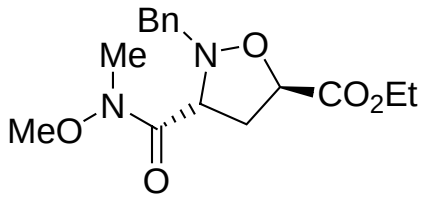

160
140
120
100
80
60
40
20
ppm

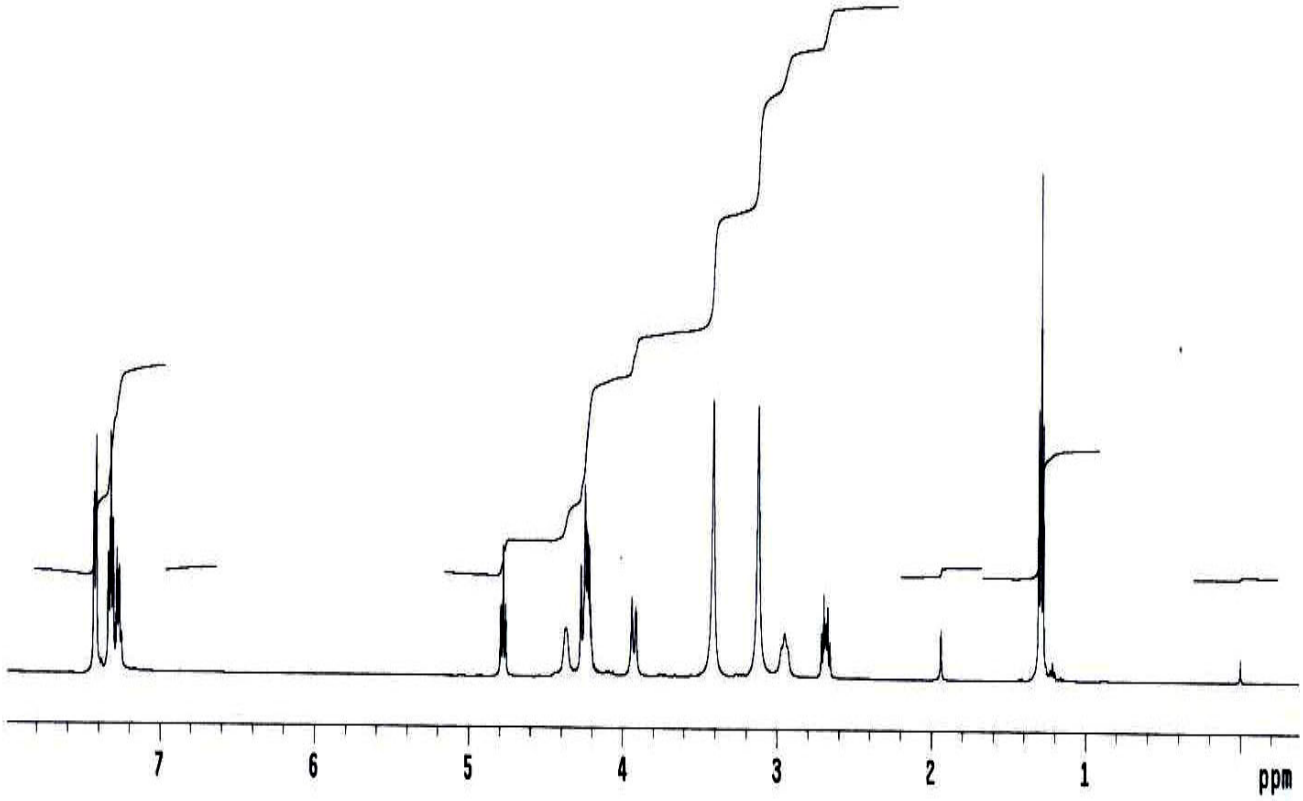

Bn
N
O
OEt
MeO
N
O

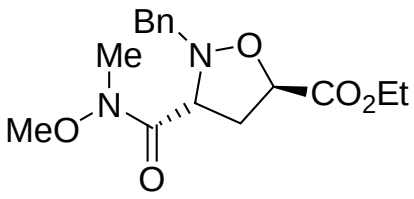

1
2
1
1
3
3
1
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1
ppm

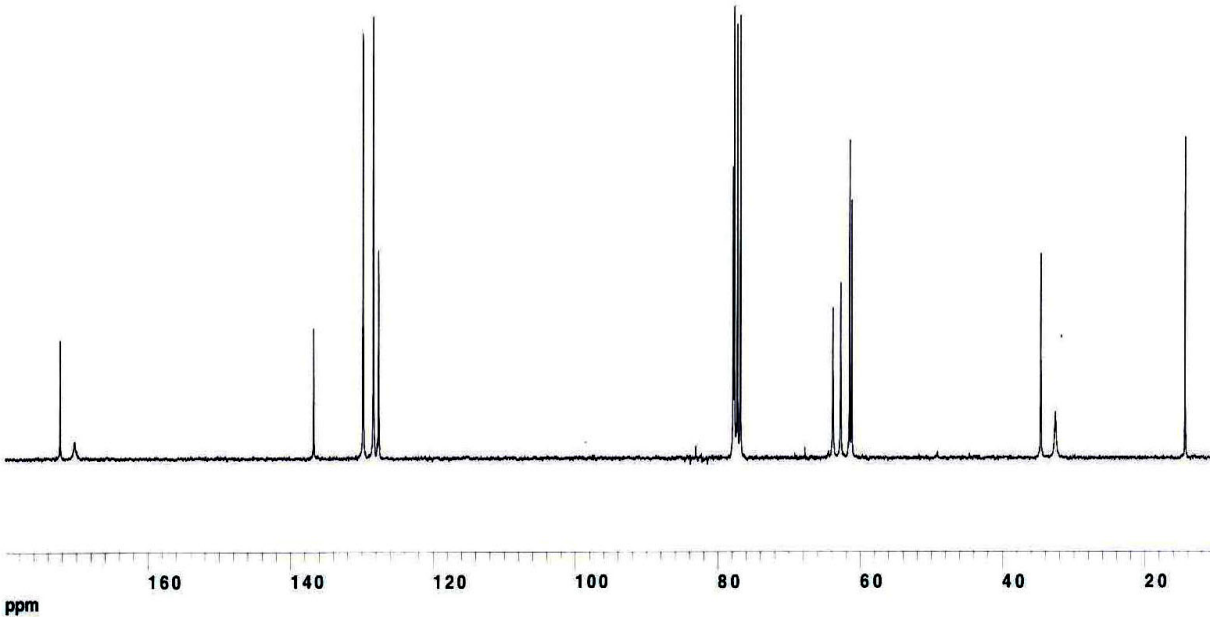

Bn
N
O
OEt
MeO
N
O

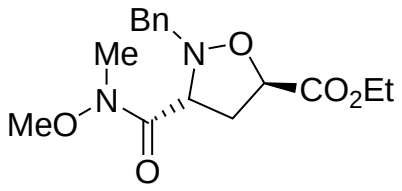

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
180
160
140
120
100
80
60
40
20
0
-20
ppm

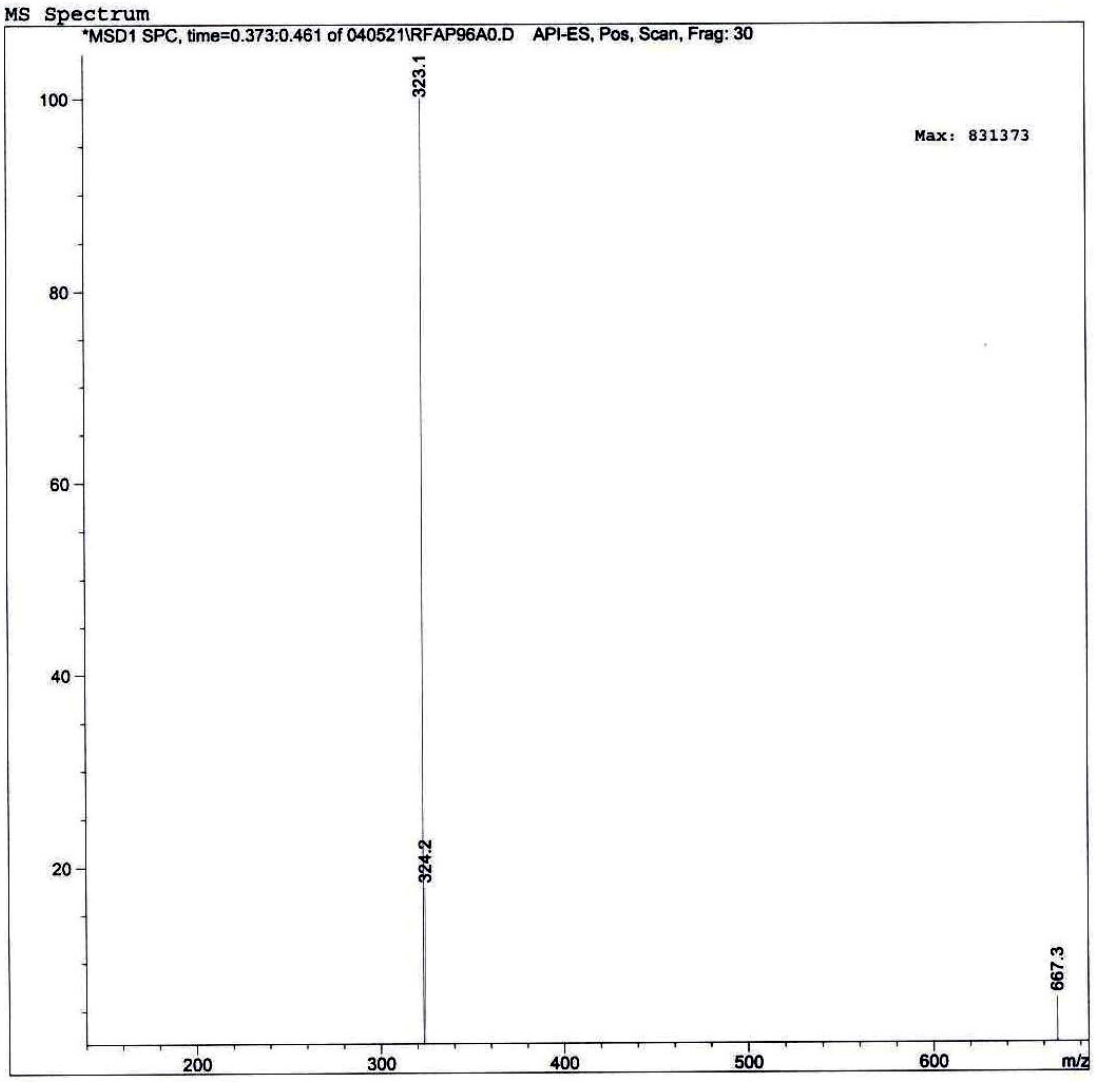

Bn
Me
N
O
N
MeO
CO2Et
O

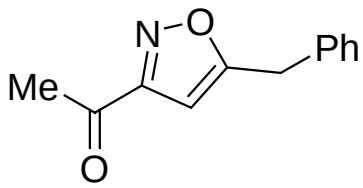

7
6
5
4
3
2
1
ppm

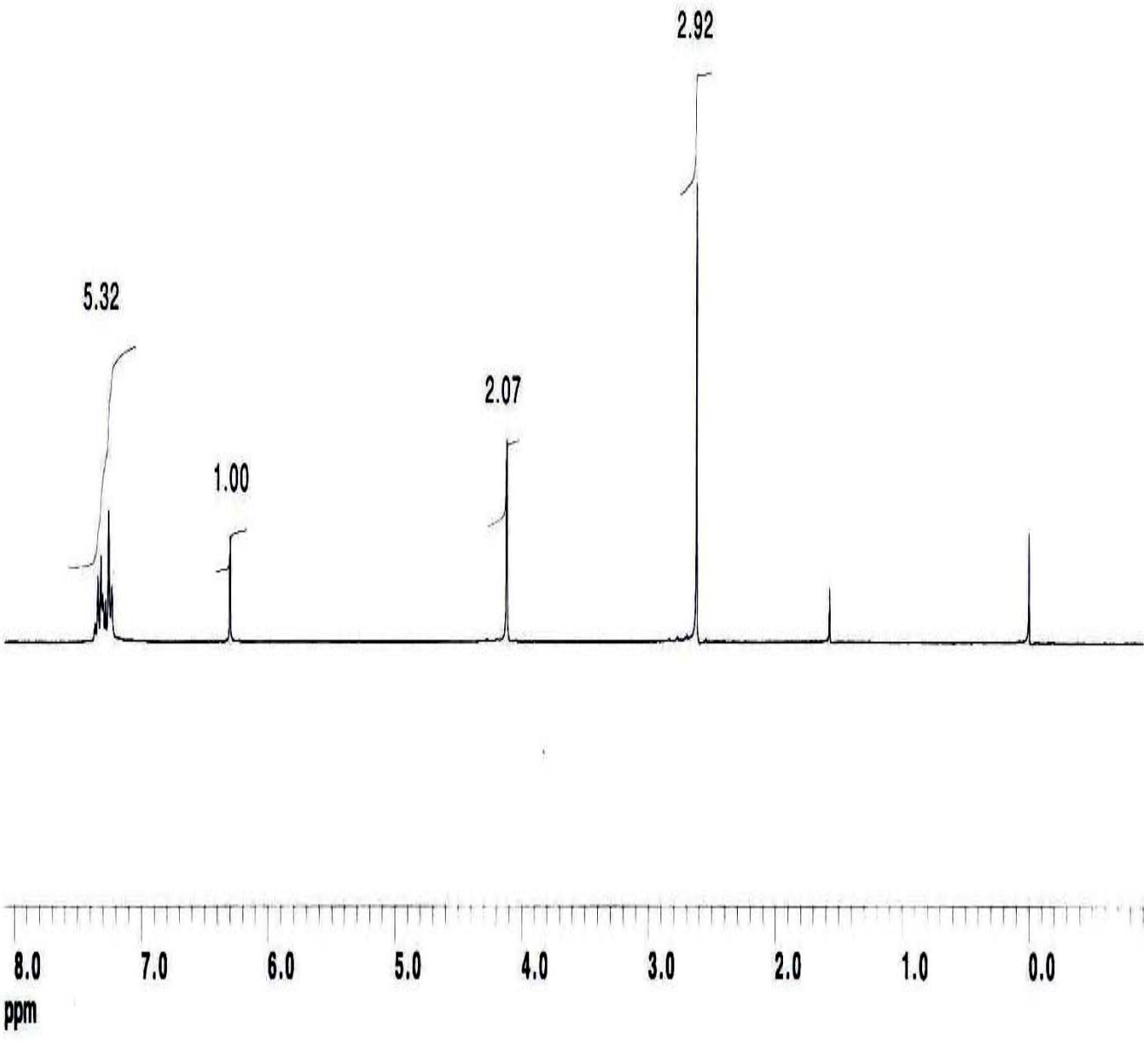

Bn
Me
N
O
CO2Et
MeO
N
O

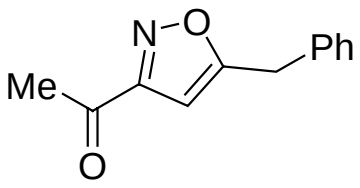

160
140
120
100
80
60
40
20
ppm

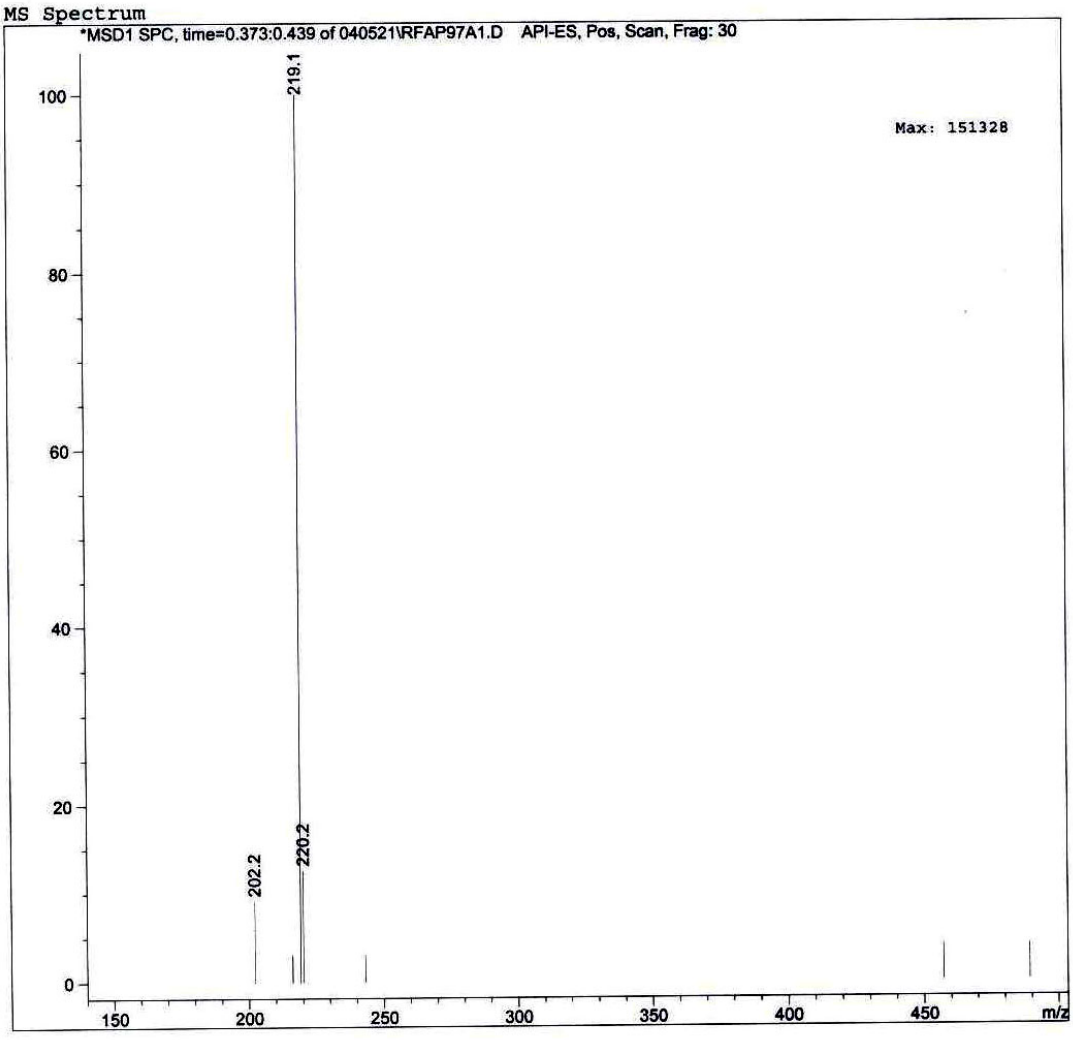

Bn
Me
N
O
N
MeO
O
CO2Et

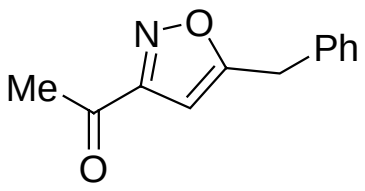

MS Spectrum
*MSD1 SPC, time=0.373:0.461 of 040521\RFAP96A0.D API-ES, Pos, Scan, Frag: 30
Max: 831373
323.1
324.2
667.3
100
80
60
40
20
200
300
400
500
600
m/z

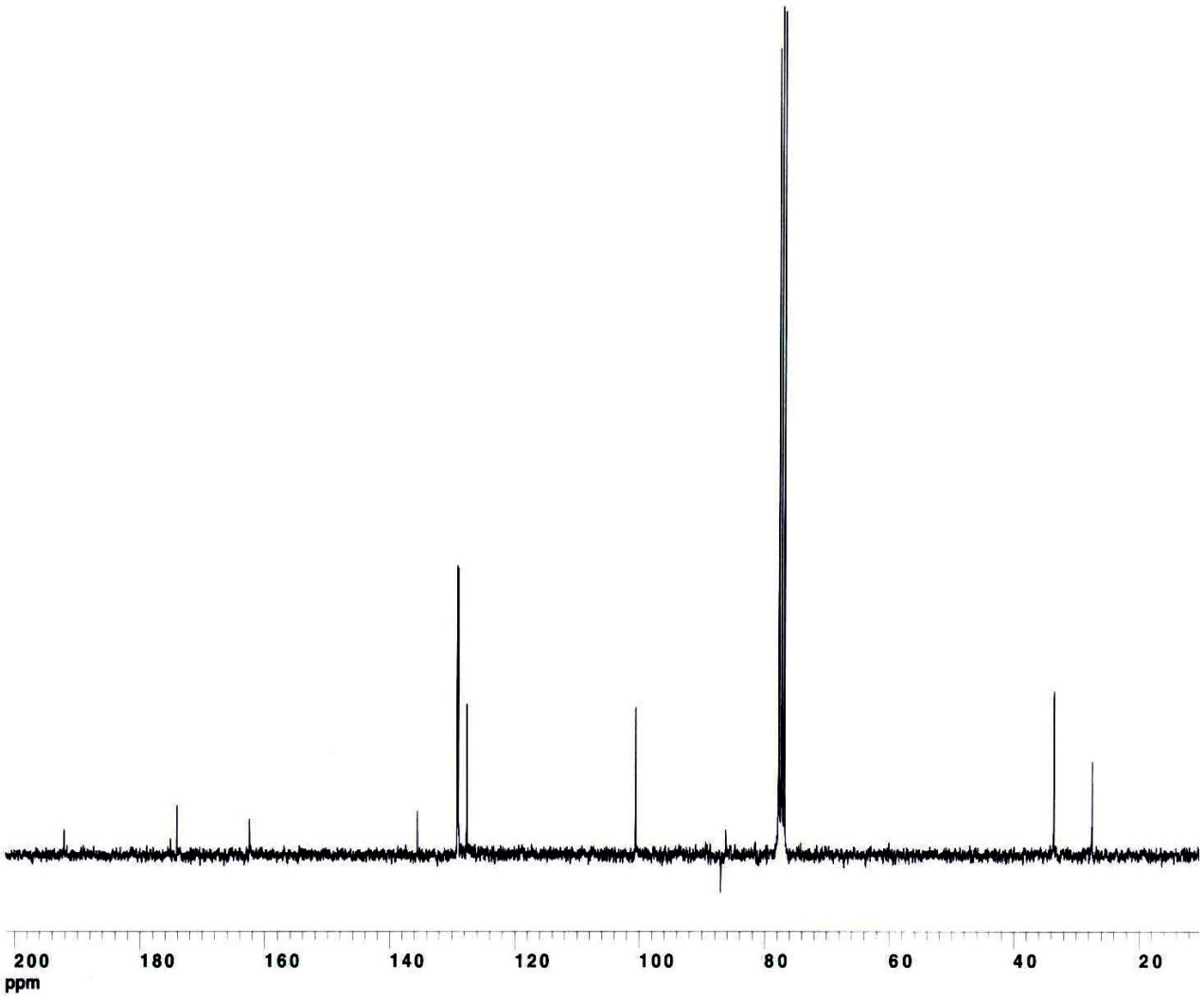

N
O
Ph
Me
O

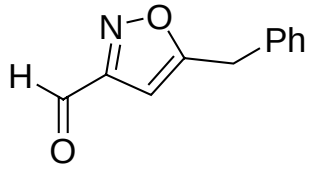

2.92
5.32
2.07
1.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm

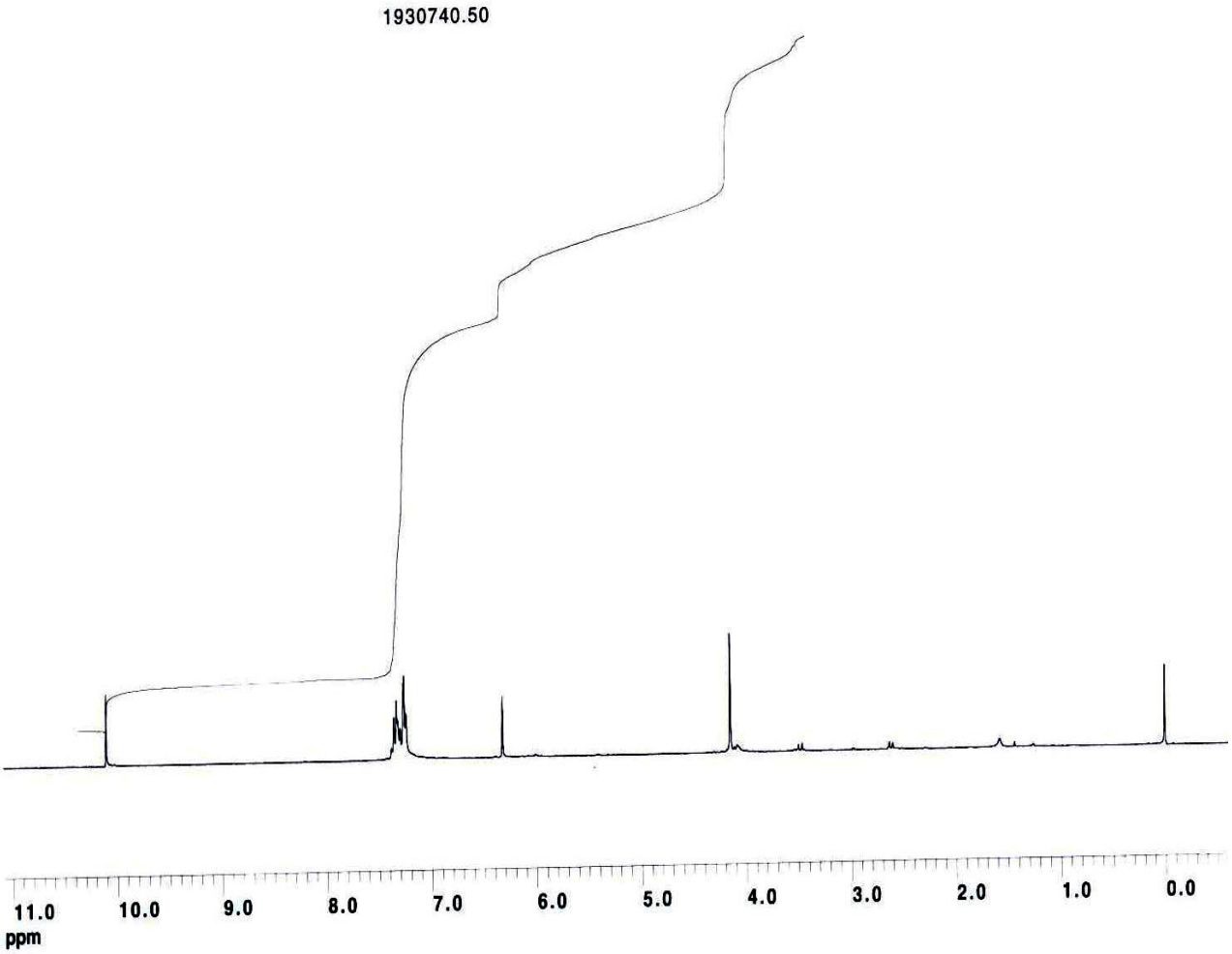

N
O
Ph
Me
O


MS Spectrum
*MSD1 SPC, time=0.373:0.439 of 040521\RFAP97A1.D API-ES, Pos, Scan, Frag: 30
Max: 151328
219.1
220.2
202.2
100
80
60
40
20
0
150
200
250
300
350
400
450
m/z


N
O
Ph
Me
O


200
180
160
140
120
100
80
60
40
20
ppm


N
O
Ph
H
O


1930740.50
11.0
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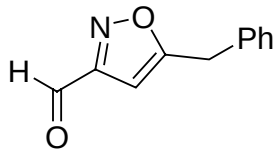
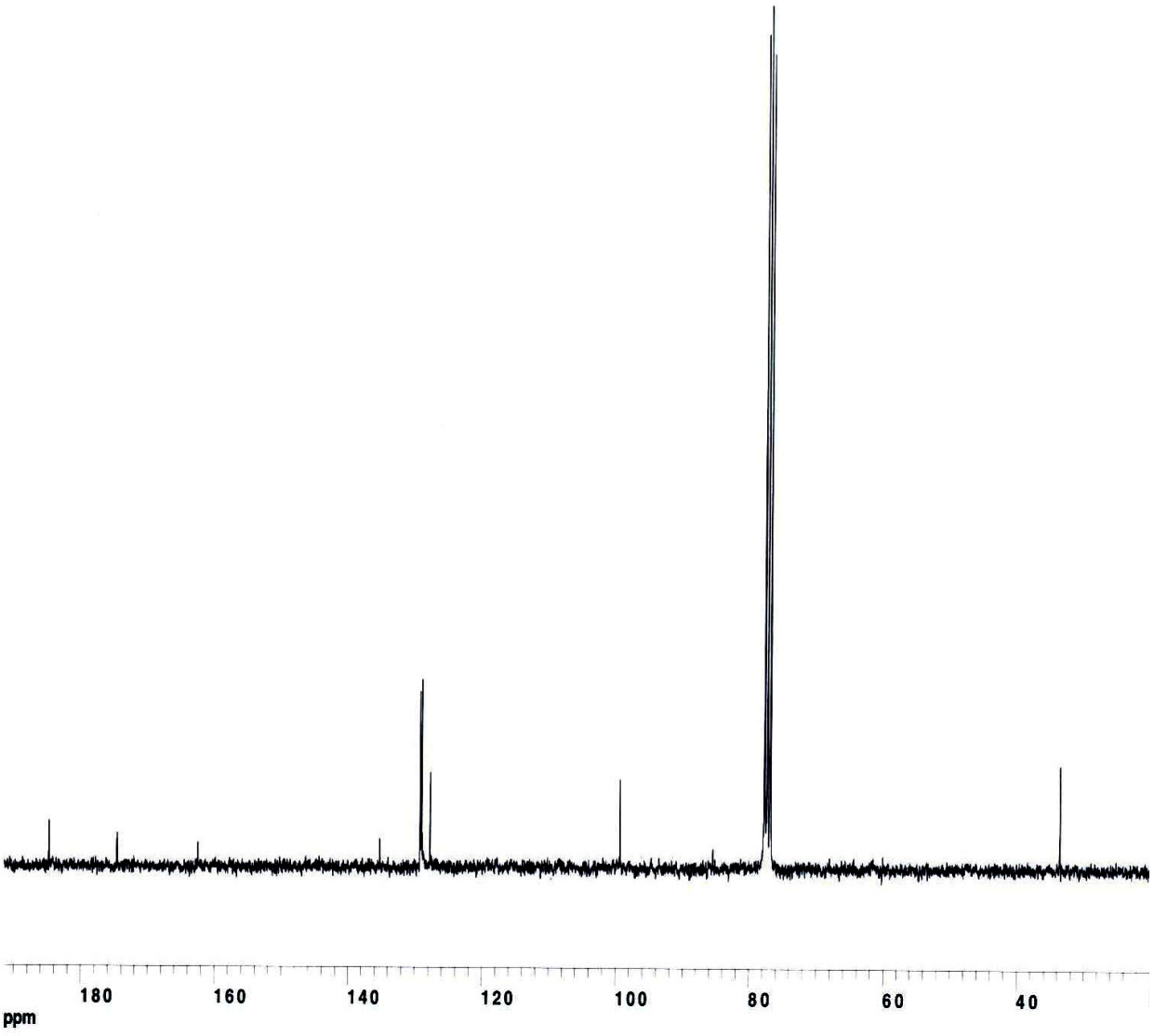
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm


N
O
Ph
H
O


180
160
140
120
100
80
60
40
ppm

# Bibliography 1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# Chapter 2

## Synthetic studies on “Glyceroplasmalopsychosine”

## 2.0 Introduction

This chapter describes studies towards the synthesis of two isomers of a novel glycolipid "glyceroplasmalopsychosine"[1] **2.0** and **2.1**. This glycolipid was isolated by Hakomari[1] *et.al.* from the white matter of bovine brain and named as glyceroplasmalopsychosine based on its structural constituents. As the name suggests it contains a glycerol moiety, a plasmal (long chain aldehyde) and a psychosine (β-galactosyl 1-1 sphingosine). In this unique glycolipid, the plasmal is conjugated to the primary hydroxyl group of the glycerol and the 6-hydroxyl of the psychosine by an acetal linkage.[2,3] The two stereoisomers differs with respect to the asymmetric C-1 carbon of the aldehyde. The structures of both the isomers are shown below.

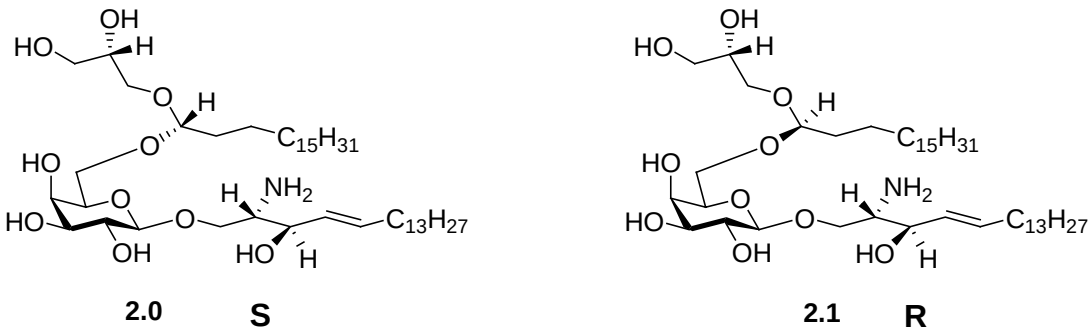



**Fig-2.0: Structures of both isomers of glyceroplasmalopsychosine**

As discussed in the following section, observation that glyceroplasmalopsychosine showed no cytotoxic effect but only weak protein kinase C (PKC) inhibition in contrast

with strong cytotoxicity as well as PKC inhibitory activity of psychosine, presented interesting questions concerning the function of the fatty aldehyde chain of glycolipids on the membrane surface. The purpose of this work was to provide synthetic samples of both the isomers of glyceroplasmalopsychosine to assign the configuration of the glycerol and acetal stereocenters and to facilitate PKC-related studies.

## 2.1 Background:

In general, lipids can be classified as acidic, neutral, zwitterionic, or cationic based on their ionic properities. The majority of membrane lipids are glycerophospholipids, sphingophospholipid (sphingomyelin), and cholesterol. They are mainly amphoteric (zwitterionic), acidic (anionic), or neutral. Glycolipids are a relatively minor constituent of membrane and also consist of acidic (gangoliosides, sulfolipids) or neutral components. Cationic lipids[4] comprise an extremely minor subgroup, which includes psychosine (galactosyl sphingosine) and other lyso-glycosphingolipids, sphingosine, and dimethyl-sphingosine. The positive ionic properties of cationic lipids are due to the protonated amino group of sphingosine. Cationic lipids having free sphingosine amino group, though a minor component, modulate activity of growth factor receptor kinase, protein kinase C, or signal transducer molecules located at upstream regions of signal transduction pathways. These findings of PKC inhibition[5-7]by the sphingosine bases promoted a number of subsequent studies leading to the current understanding of glycoshingolipd biology.[8-10]

Long chain aldehydes, hexadecanal and octadecanal, with or without a double bond, are collectively called plasmal.[11,12] They are a common component of a recently found novel type of glycosphingolipid (GSL) in which a plasmal is conjugated to two hydroxyl

groups of psychosine or galactosylceremide through a cyclic acetal linkage. These were originally isolated from human brain white matter and are termed, respectively, plasmalopsychosine (PLPS) and plasmalocerebroside. Depending on the position of hydroxyl group involved in acetal linkages, 3,4-and 4,6-cyclic plasmal conjugates of PLPS and plasmalocerebroside are termed, respectively PLPS A or B,[13]and plasmalocerebroside A or B.[14] More recently, a GSL having the same structure as plasmalocerebroside B (4,6-cyclic acetal) was isolated from equine brain.[14] The orientation of the acetal chain linked to galactosyl residue through asymmetric carbon 1 of plasmal was identified as "endo" type.[15]A similar 4,6-cyclic acetal conjugate of plasmal to galactosyl alkylglyceride was isolated and characterized.[16]The structures of these PLPS are shown below.

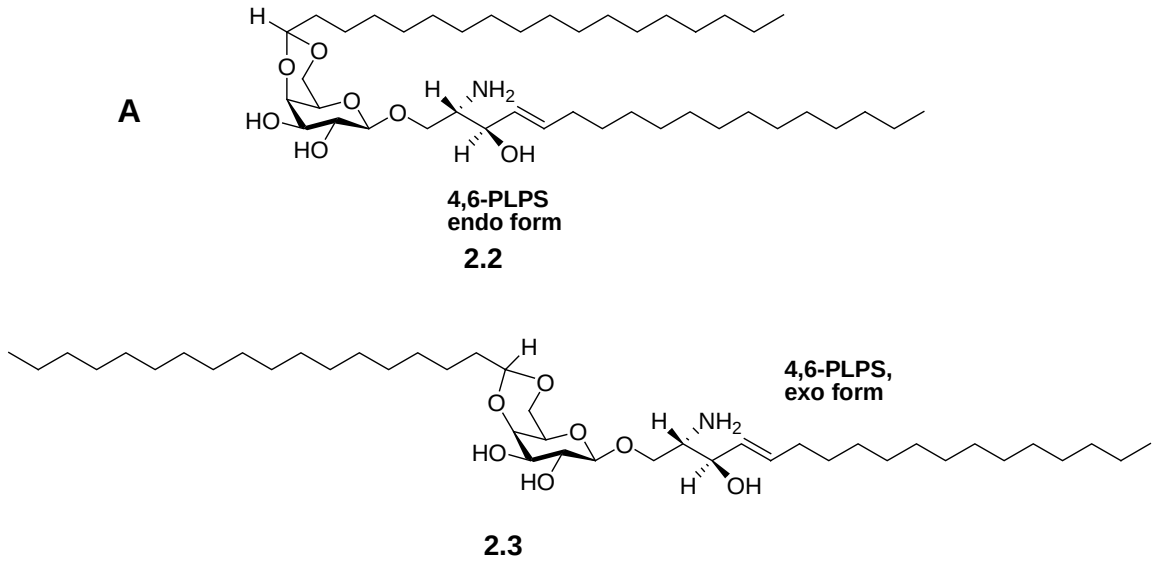



**Fig 2.1: Structures of endo and exo form of 4,6-Plasmalopsychosine (PLPS B)**

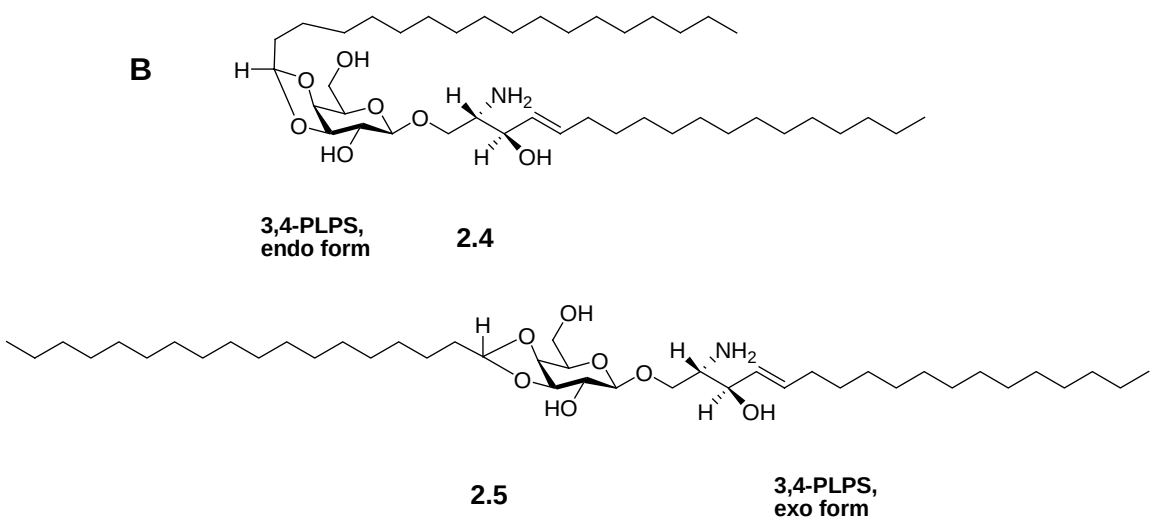



**Fig 2.2: Structures of endo and exo form of 3.4-Plasmalopsychosine (PLPS A)**

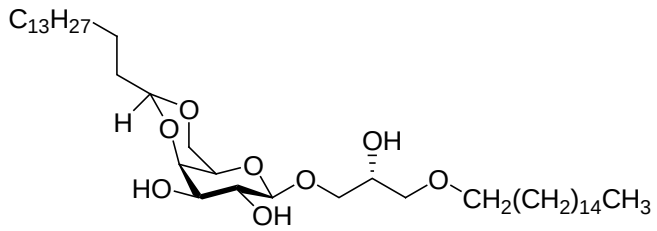



**Fig 2.3: Structure of Plasmalopsychosine Isolated from Equine Brain**

Glyceroplasmalppsychosine is the most recent cationic sphingolipid extracted from the white matter of bovine brain. Although glyceroplasmalopsychosine is characterized by properties similar to those of PLPS A and B, it has certain properties distinct from them due to the presence of an additional polar group i.e. glycerol.

The novelity of the glyceroplasmalopsychosine structure lies in the mode of plasmal conjugation, i.e. the way that O-plasmal conjugate is linked at C1 at two primary hydroxyl groups at glycerol and galactose. The glycerol residue may interact with galactosyl residue to achieve steric stability, such that axes of two aliphatic chains, sphingosine and plasmal, are oriented in parallel regardless of the C1 stereoisomer of plasmal. NMR data indicate that two stereoisomers with regard to the asymmetric C1 carbon of plasmal in glyceroplasmalopsychosine are detected in a ratio of ~1:1 whereas those of PLPS are found exclusively in only one form ("endo type"). This may reflect a difference in stability of plasmal linkage in these two compounds, i.e. the linkage in glyceroplasmalopsychosine is much more unstable than that in PLPS.

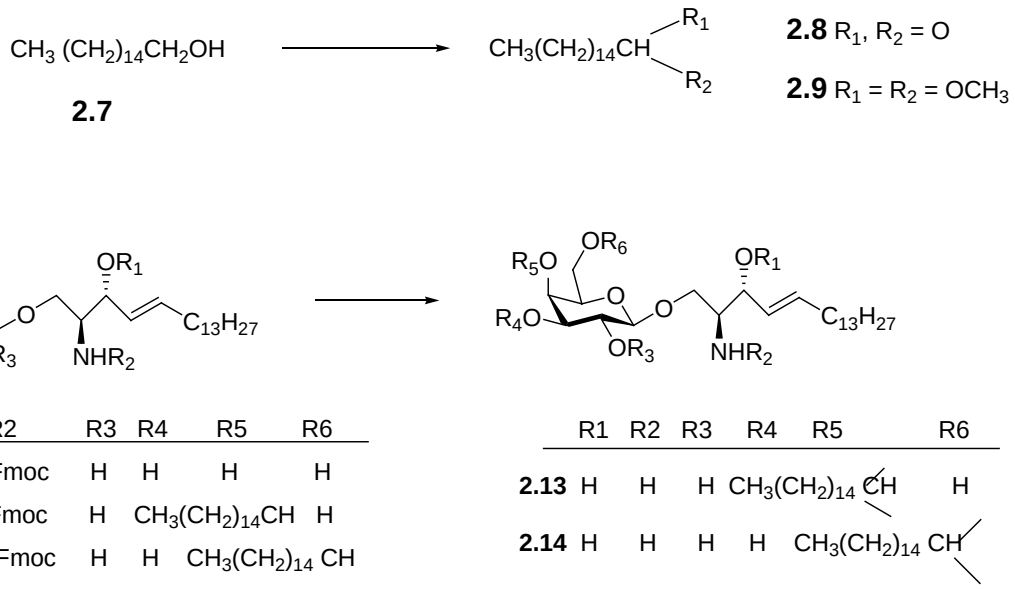
Systematic chemical analysis of cationic lipids from bovine brain revealed the following interesting points. (i) Although it was reported to be absent from human brain[13], psychosine was clearly detectable in bovine brain matter; (ii) PLPS A and B, originally found in human brain white matter, were also detected in bovine brain, where their levels were, respectively, 12 and 18 times lower than in human; (iii) glyceroplasmalopsychosine was isolated as a major plasmal conjugate in bovine brain. Whether it occurs in human brain remains to be determined.

The large differnce in PLPS level between human and bovine brain, and its association with neuritogenesis, raises the question of whether this compound is involved in neuronal communication, which may be qualitatively much higher in human brain. Although the structure of glyceroplasmalpsychosine is distinct from that of PLPS in that it contains glycerol, they have in common the structure of psychosine with plasmal conjugate. Therefore an important topic for future study is how glyceroplasmalopsychosine affects signal transduction in neuronal cells

Psychosine is neurotoxic and strongly inhibits brain PKC activity. Its PKC-inhibitory effect is much stronger than that of PLPS.[13] Although it was reported to be absent in normal human brain, psychosine is detectable in brains of patients with Krabbe's disease.[17,18] An interesting question is whether conversion of psychosine to PLPS or glyceroplasmalopsychosine may result in entirely different neuronical signaling, because PLPS is neurotrophic whereas psychosine is neurotoxic.

## 2.2 Synthesis of Plasmalopsychosines A and B, two novel lysosphingolipids found in human brain.[19]

The long chain aldehyde, hexadecanal **2.8** was converted to 1,1-dimethoxyhexadecane **2.9** with treatment of trimethyl orthoformate and Amberlite IR-120. Treatment of psychosine in 3:1 chloroform-water, with 9-fluorenylmethyl chloroformate (FmocCl) in the presence of $K_2CO_3$ gave N-protected Fmoc-psychosine **2.10**. When compound **2.10** was treated with 1,1-dimethoxyhexadecane in DMF containing a trace of p-tolunesulfonic acid gave a mixture of 3,4- and 4,6-cyclic acetals **2.11**, **2.12,** which could not be separated by chromatography. Removal of the Fmoc protecting group by treatment with piperidine followed by HPLC purification gave target compounds **2.13** and **2.14**. The $^1$H NMR of **2.14** showed a signal for the methine proton of the acetal function at 4.99 ppm, whereas the signal for the same proton in **2.13** appeared at 4.58 ppm. These chemical shifts are indicative of a five-membered cyclic structure in **2.13** and a six-membered cyclic structure in **2.14**.




| | R1 | R2 | R3 | R4 | R5 | R6 |
|---|---|---|---|---|---|---|
| **2.10** | H | Fmoc | H | H | H | H |
| **2.11** | H | Fmoc | H | $CH_3(CH_2)_{14}CH$ | H | |
| **2.12** | H | Fmoc | H | H | $CH_3(CH_2)_{14}$ CH | |

| | R1 | R2 | R3 | R4 | R5 | R6 |
|---|---|---|---|---|---|---|
| **2.13** | H | H | H | $CH_3(CH_2)_{14}$ CH | | H |
| **2.14** | H | H | H | H | $CH_3(CH_2)_{14}$ CH | |

**Scheme 2.0: Synthesis of PLPS A and B**

There has been no synthetic work reported on glyceroplasmalopsychosine till date.

## 2.3 General Synthesis of α-Acetoxy Ethers from Esters by DIBALH-reduction and Acetylation:

This section describes our application of the Rychnovsky synthesis[20] of α-acetoxy ethers from esters, which we have used in the synthesis of mixed acetal segment of glyceroplasmalopsychosine.

The preparation of 4-(phenylthio)-1,3-dioxanes **2.19** from 1,3-dioxan-4-ones is shown in figure **2.4**. The route A is untenable because of the instability of hemiacetal **2.16**, which spontaneously loses acetone to give β-hydroxy aldehyde. A possible solution is illustrated in route B.

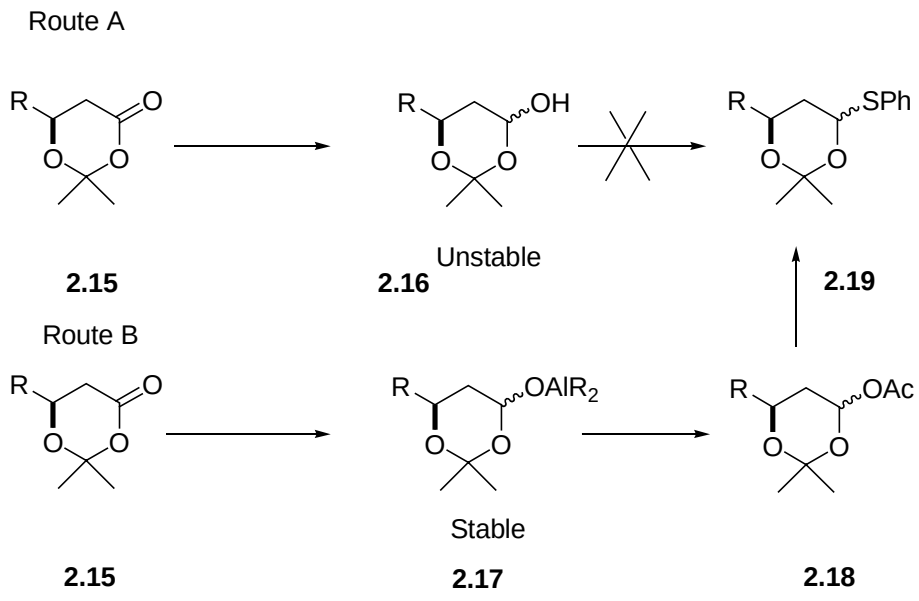



**Fig 2.4: Possible Synthesis of 4-(phenylthio)-1,3-dioxane from 1,3-dioxan-4-one**

Kiyooka[21] and Polt[22] independently showed that diisobutylaluminium alkoxides of hemeacetals, prepared by DIBALH reduction of esters, are much more stable than free hemiacetals and can be trapped *in situ* with TMSOTf-pyridine or (trimethylsilyl)imidazole. The mixed alkyl trimethylsilyl acetals that result react with nucleophiles in the presence of a Lewis acid to give alcohols or ethers depending upon whether the alkoxy or silyolxy substituent acts as the leaving group. In most cases the alkoxy group departs, and nucleophilic addition of the resulting aldehyde produces a secondary alcohol. On the other hand, activation of the (trimethylsilyl)oxy group in the presence of a nucleophile would lead to a branched ether. Several examples of this branched ether synthesis have been reported, but the regiochemistry of the alkyl trimethylsilyl acetal cleavage is substrate dependant. The mixed alkyl trimethylsilyl acetals do not appear to be reliable intermediate for the synthesis of branched ethers. Rychnovsky *et.al* showed that replacement of the TMS group with an acetate group would change the regioselectivity of the acetal cleavage and should provide an entry into the 4-(phenylthio)-1,3-dioxanes, and a possible synthesis of α-substituted ethers. The strategy of using acetoxy leaving group is outlined in the above fig **2.4**. Diisobutylaluminium alkoxides of hemiacetals, prepared by DIBALH reduction of esters, can be trapped *in situ* with acetic anhydride in the presence of pyridine and DMAP. The acetate group in the resulting α-acetoxy ether is a much better leaving group than the alkoxy group, and these mixed acetals react with nucleophiles regioselectively in the presence of a Lewis acid to give α-substituted ethers.[23] The DIBALH reduction and acetylation of a variety of simple esters and cyclic esters is illustrated in Table **2.0**.

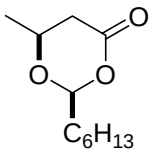
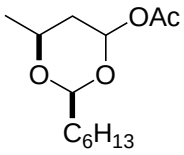
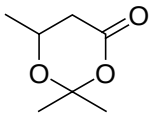
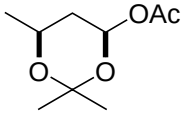
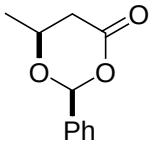
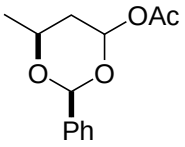
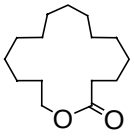
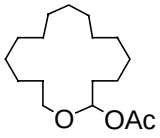
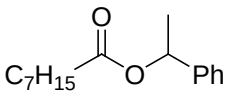
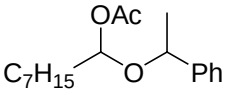
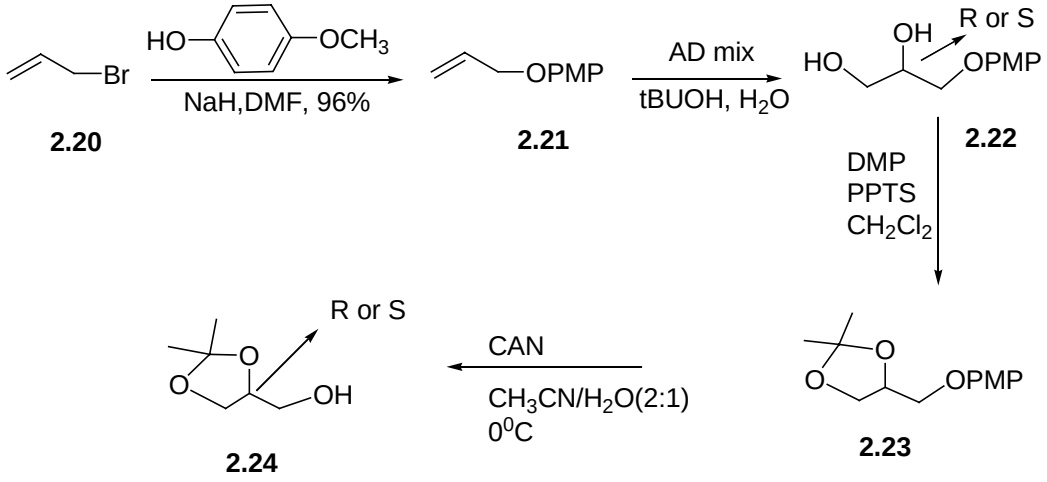
| Entry | Starting Ester | Product | % Yield | Ratio |
|---|---|---|---|---|
| 1 |  |  | 91 | >10: 1 |
| 2 |  |  | 61 | >10: 1 |
| 3 |  |  | 79 | >10: 1 |
| 4 |  |  | 71 | - |
| 5 |  |  | 82 | 2:1 |

**Table 2.0: DIBALH reduction and acetylation of simple esters and cyclic esters**

# Synthetic Study on Glyceroplasmalopsychosine

## 2.4 Preparation of Optical active Solketal and Sphingosine side Chain

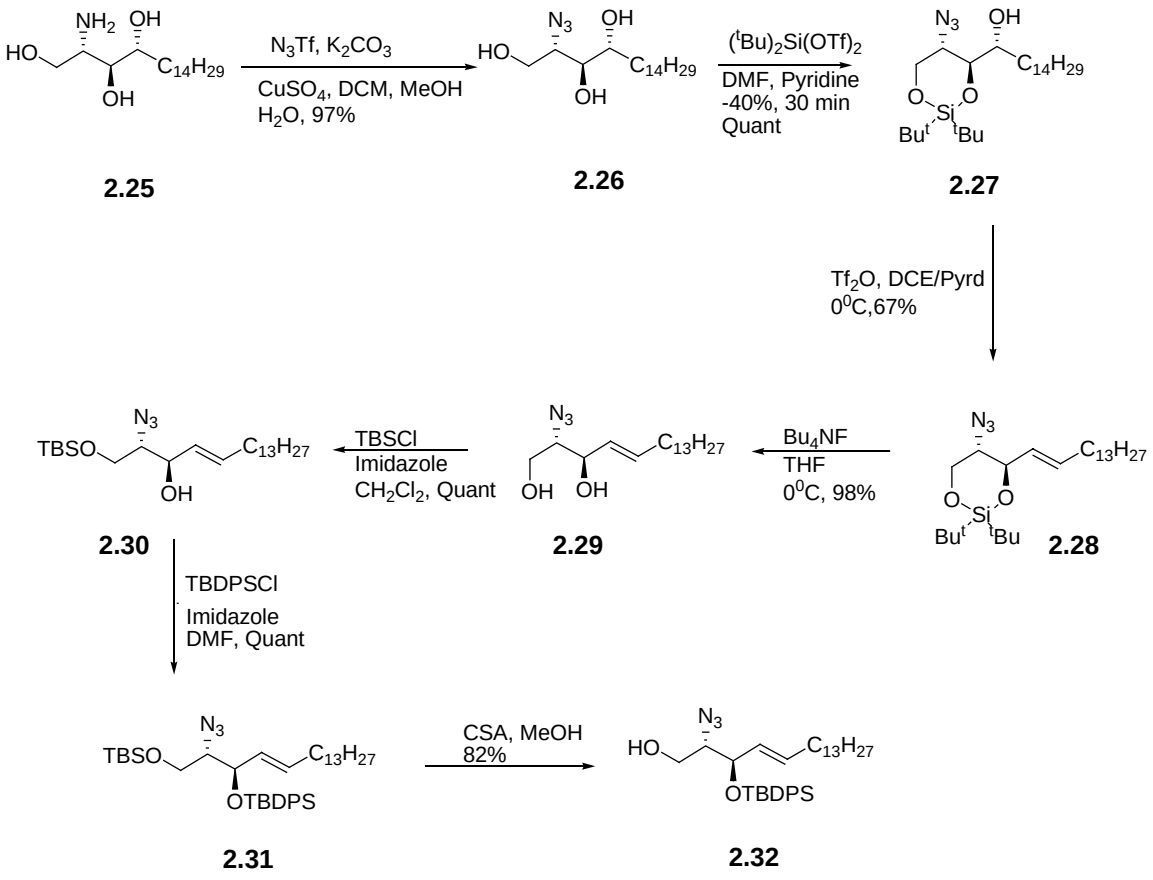
The synthetic study on Glyceroplasmalopsychosine began with the preparation of homochiral solketal and the sphingosine side chain since these are two important constituents of the target compound. The optical glycerol **2.24** was prepared from allylic bromide **2.20** using conventional chemistry.[24] PMP protection followed by hydroxylation gave an optically active D or L glycerol derivative depending on whether AD mix α or AD mix β was used. Acetonide protection of diol **2.22** and cleavage of PMP group using CAN gave optical active solketal **2.24** in very good yield.




**Scheme 2.1: Synthesis of R and S Solketal**

There are several methods available for the synthesis of sphingosines, which has been reviewed by many authors. [25]From the many available routes, we chose a recent synthesis of sphingosine by Van Boom.[26]**Scheme 2.2** outlines the synthesis of 2-azidosphingosine from phytosphingosine **2.25.** In the first step phytosphingosine was subjected to Wong's

diazo transfer[27] to furnish the azido derivative **2.26**. Regioselective protection of 1,3-diol with the di-tert-butyl silylene protective group[28] afforded alcohol **2.27** in a yield of 93% over two steps. Trifilation of **2.27** with triflic anhydride in the presence of pyridine gave after work up and purification, the E-olefin **2.28**. Ensuing deblocking of the di-tert-butyl-silylene protecting group in **2.28** afforded 2-azidosphingosine **2.29**. TBS protection of the primary and TBDPS protection of secondary alcohol produced **2.31** in more then 90% yield in two steps. Desillyation of primary alcohol now furnished the required side chain **2.32** in quantitative yield ready for the glycosidation.

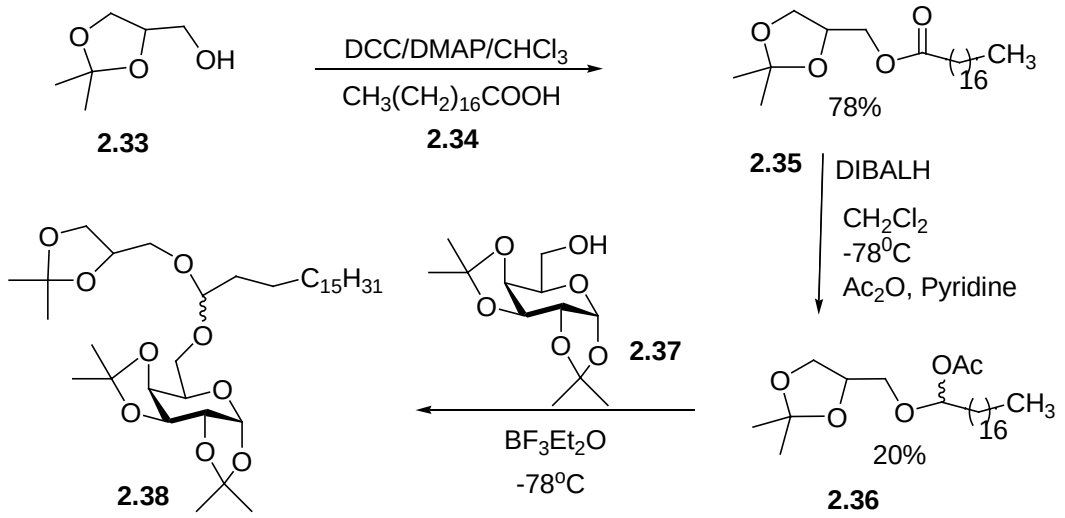



**Scheme 2.2: Synthesis of Sphingosine side chain.**

## 2.5 Non-Stereospecific Synthesis of Mixed Acetal of Glyceroplasmalopsychosine

The most challenging part of the synthesis of glyceroplasmalopsychosine[1-3] is the construction of acetal linkage where the long chain aldehyde is conjugated to galactose and glycerol. Before we began our synthesis of target **2.0** or **2.1**, we planned to construct these types of acetal linkages following the work of Rychnovsky[20] where he reduced ester with DIBAL and then trapped the intermediate with $Ac_2O$ to produce α-acetoxy ethers. These kind of α-acetoxy ethers are otherwise difficult to prepare. Lewis acid activation of α-acetoxyethers generates an oxonium ion that can couple with carbon or heteroatom nucleophiles.

In a model study, presented in **scheme 2.1**, racemic solketal **2.33** was esterfied[29] with stearic acid **2.34** to produce ester **2.35** in 75% yield. DIBAL reduction[20]of the ester was carried out with 1.1 equiv of DIBAL at –78 $^{o}$C for 2h in DCM. The intermediate aluminium hemiacetal was treated with pyridine (3 equiv), DMAP (1.1equiv) and acetic anhydride at –78 $^{o}$C, and the mixture was allowed to warm slowly to –20 $^{o}$C. After aqueous work up the α-acetoxyether **2.36** was isolated only in 20-25% yield.

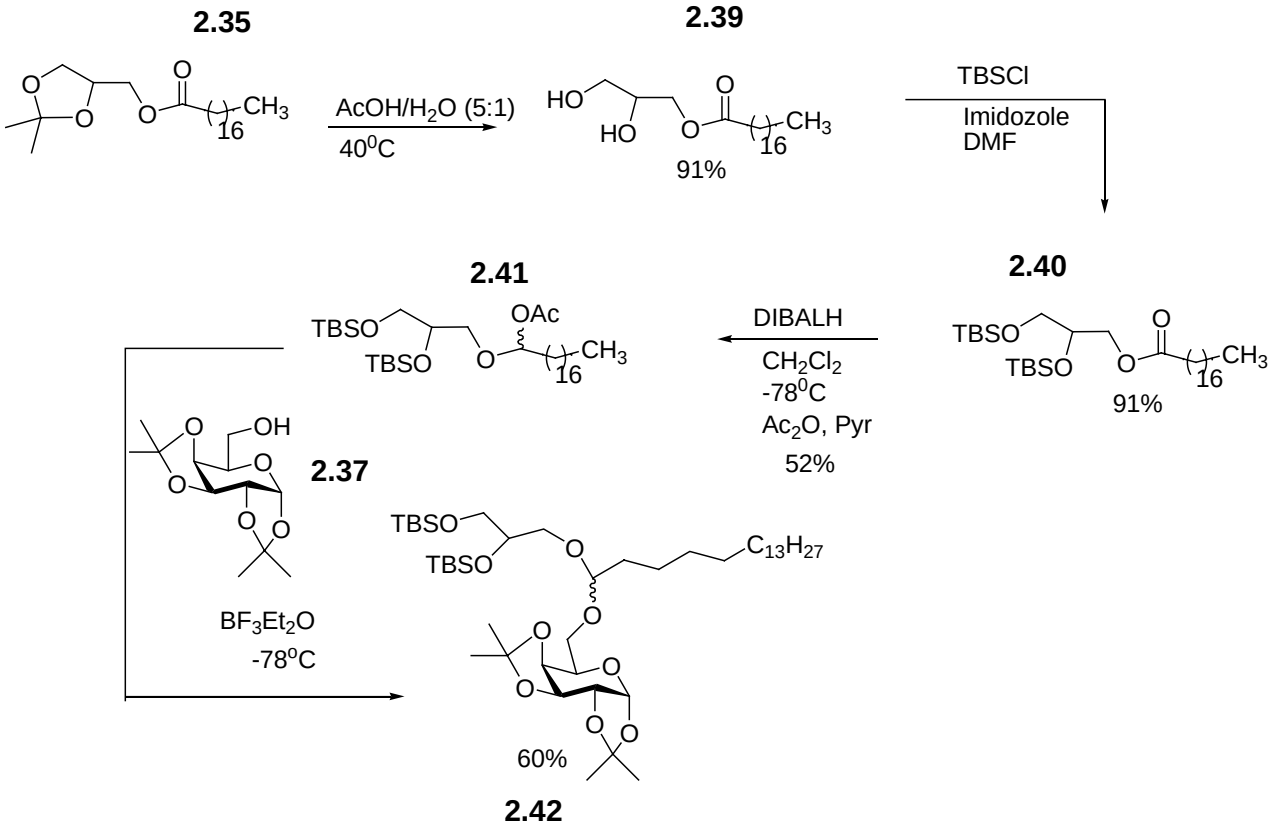



**Scheme 2.3 Synthesis of mixed acetal 2.38**

This step is hampered by both over reduction and recovery of starting material. In spite of trying different solvents and conditions, the yield could not be improved. The acetate **2.36** was isolated as a mixture of two stereoisomers, which was inseparable in a range of solvent systems. However, when acetate **2.36** was coupled with 1,2,3,4-di-O-isoproplydinegalactose **2.37** in the presence of $BF_3.Et_2O$, compound **2.38** was obtained in 50-60% yield again as an inseparable mixture of two diastereoisomers.

In order to improve the yield of reduction step we then investigated the effect of the protecting groups in glycerol moiety. We thought that some other protecting groups might influence the reaction and would increase the yield and possibly help in separating the two diastereoisomers. Silyl protection, more precisely TBDMS ether was our first choice because of easy of preparation[30] of these ethers. Deprotection[31]of the

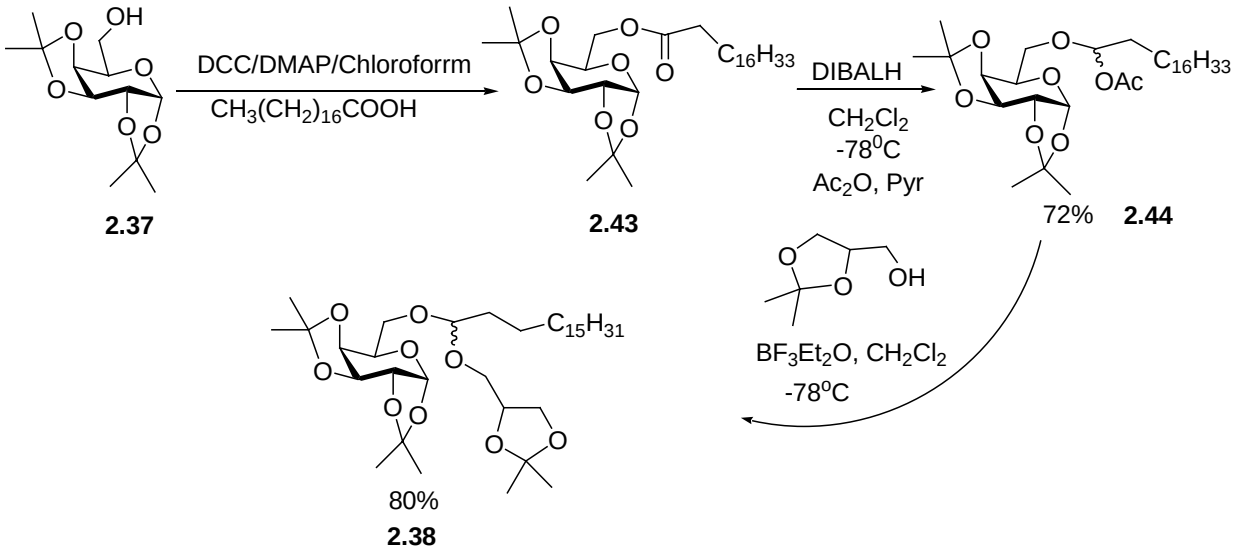
isopropyldine group was performed by heating the ester **2.35** with aqueous acetic acid, which yielded the diol **2.39** in 91 % yield. Treating **2.39** with TBSCl and imidazole in DMF produced the TBS protected ester **2.40** in very good yield.




**Scheme 2.4: Influence of Protecting group on DIBAL reduction step**

Exposing the TBS protected ester **2.40** to the Rychonovsky's DIBAL reduction conditions, the acetoxy ether **2.41** and then the mixed acetal **2.42** were obtained as a mixture of two isomers in slightly better yield. But the separation problem was not overcome as the diastereoisomers were not separable in spite of trying different solvent systems.

In an alternate route, the compound **2.38** was prepared starting from the sugar component in high yield. The proton NMR of these compounds shows a multiplet at δ 4.58 ppm, which corresponds to the acetal proton. From the Proton NMR and $^{13}C$ NMR it was apparent that the two diastereoisomers were formed approximately in 1: 1 ratio.




**Scheme 2.5: Alternate route to mixed acetal 2.38**

It was good that we successfully constructed the acetal linkage in acceptable yield, but at the same time the two inseparable isomers would not permit assignment of the absolute configuration at the acetal center.

This problem may be due to the lack of stereo control in both DIBAL reduction and the coupling step. The acyclic esters undergo non-stereospecific reduction and the two

diastereoisomers formed in all cases are so similar that they have exactly same $R_f$ values in all solvent systems we tried.

The important question of stereochemistry at the acetal center has to be answered in order to conclude the authenticity of the proposed structures of glyceroplasmalopsychosine. We now understood that proving stereochemistry at the acetal linkage was really a challenging task due to the flexibility of the molecule at this center.

We thought that if the acetal center was constrained, then it might be possible to separate the two diastereoisomers. Our plan was to introduce rigidity to the acetal center by making it a part of a ring.

Our plan involved the construction of a cyclic model compound **2.45** similar to the natural product without the sphingosine side chain. We hoped that the cyclic compound **2.45** would be obtained as single isomer, which would be ideal for spectroscopic analysis. It may, now be possible to distinguish the two different acetal protons by means of NOE experiments. The two different acetal protons would have different NOEs with the hydrogen at the α-carbon due to the differential spatial relationships between these hydrogens. From those NOEs values we would ultimately lead to the acetal stereochemistry. The cyclic compound **2.45** may be derived from either of the two non-cyclic partners **2.46** or **2.47**.

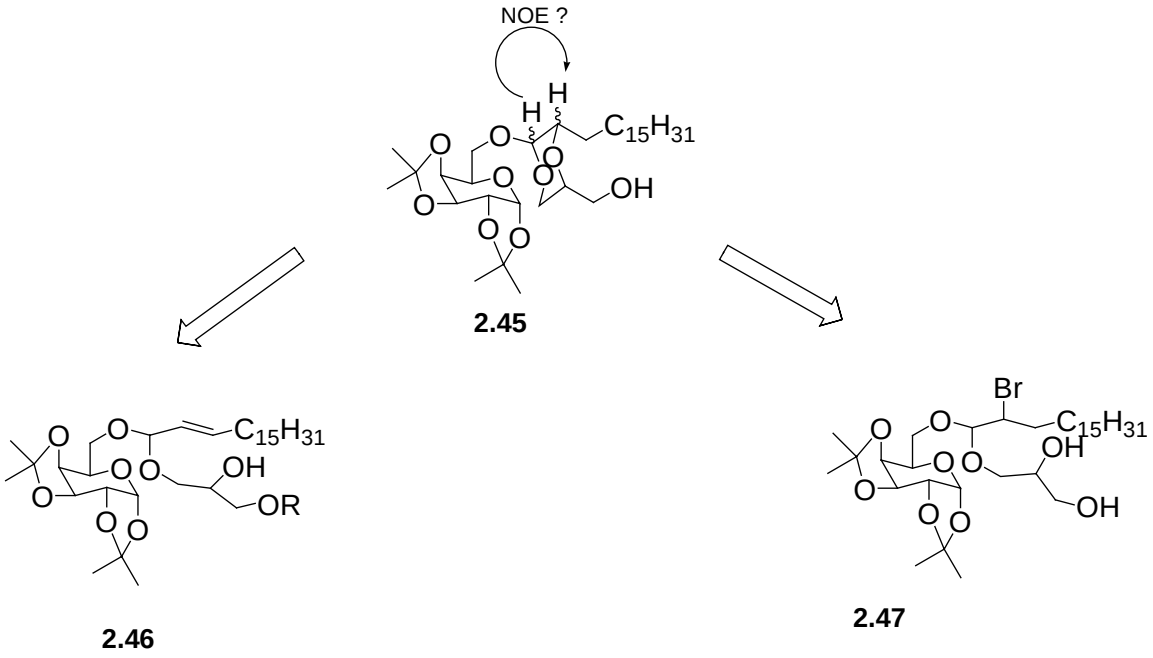
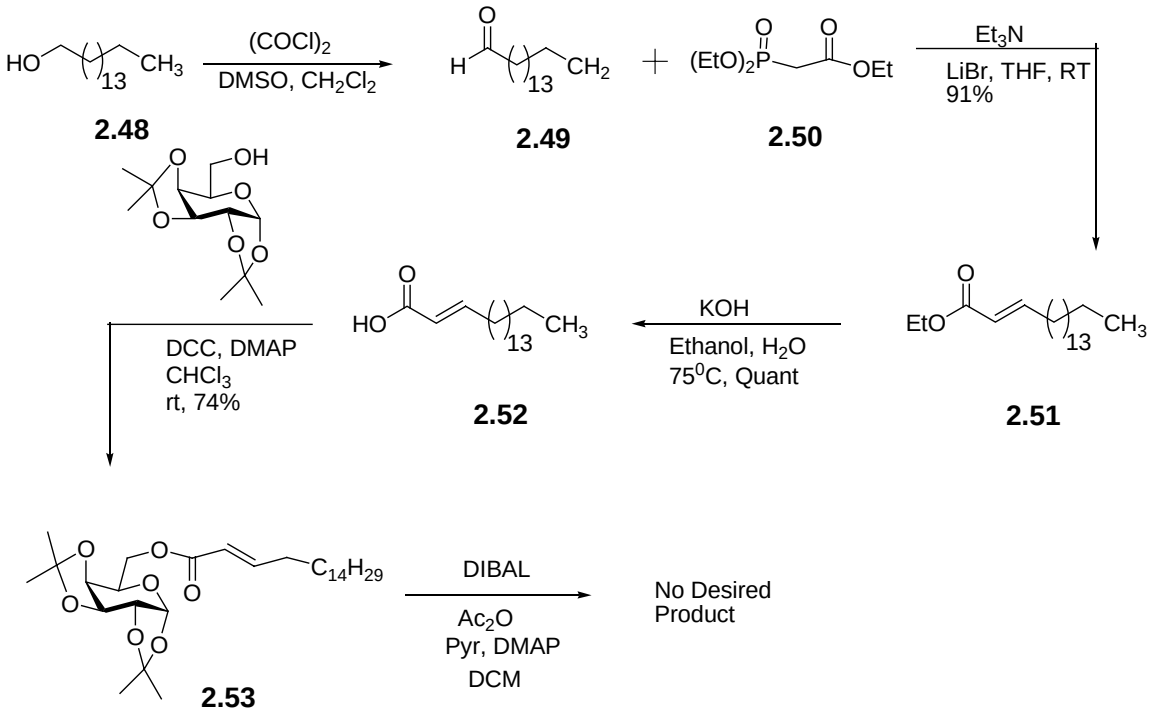



**Figure 2.5:Possible Precursors for Cyclization to prove the acetal stereochemistry**

## Synthesis of 2.46:

Firstly we tried to synthesize the acyclic compound **2.46** (Scheme 2.6). The required unsaturated acid **2.52** was obtained from haxadecanol **2.48** in 3 simple steps. Swern oxidation[32] of **2.48** gave the aldehyde **2.49** which underwent Horner Emmons condensation[33] with the phosponate ester **2.50** to furnish the unsaturated ester **2.51** exclusively as trans isomer in very good yield. Basic hydrolysis of the ester **2.51** by refluxing with KOH in ethanol-water produced the unsaturated acid **2.52** in more than 88% yield over 3 steps. Esterification of this acid with 1,2,3,4-di-O-isopropylidine galacto pyranose gave the ester **2.53** in 74% yield. DIBAL reduction of **2.53** as previously described did not produce the desired product and harsh conditions only gave over reduction product together with decomposition of the ester.

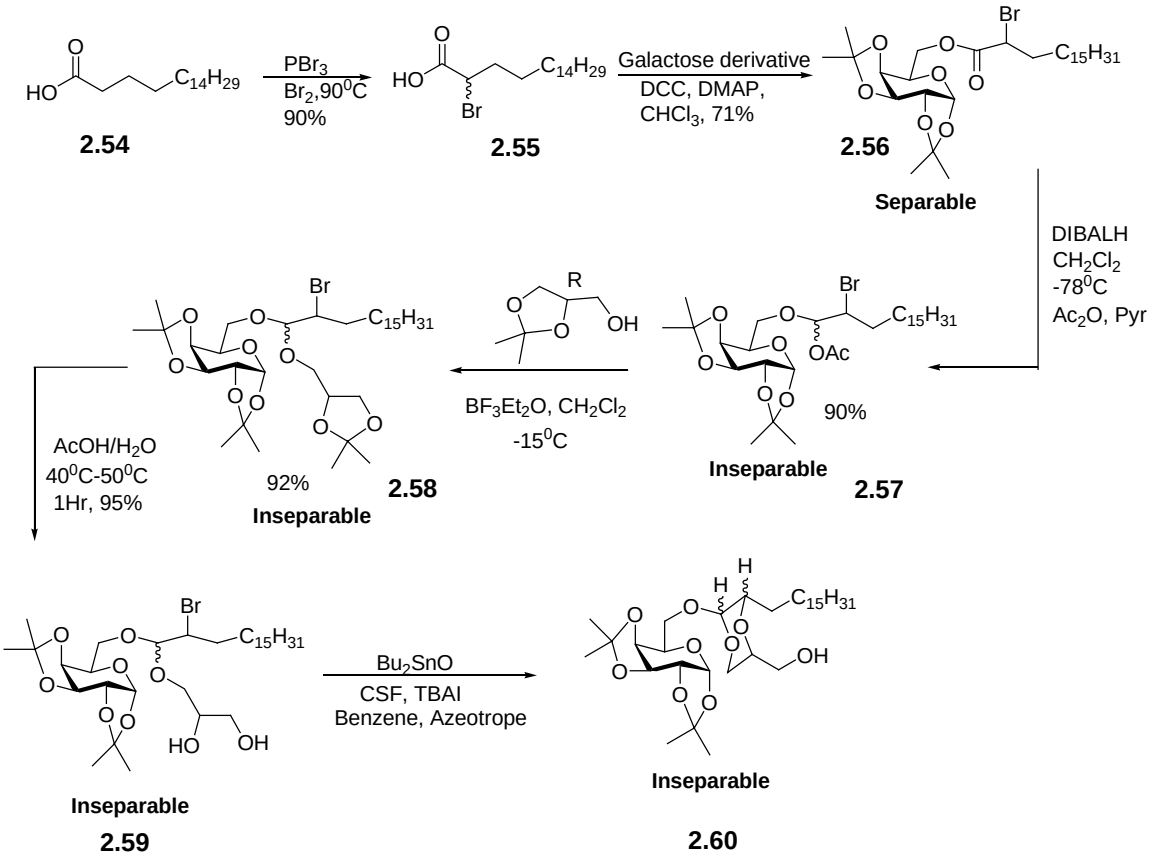



**Scheme 2.6: Attempted Synthesis of Acyclic Precursor 2.46 for Cyclization**

After failing to produce the compound **2.46**, the synthesis of the second acyclic partner **2.47** was next attempted (Scheme 2.7).

By treatment of stearic acid **2.54** under Hell-Volhard-Zelinskii reaction conditions, the α-Bromo acid **2.55** was produced in 90% yield. Esterification of the bromo acid with 1,2,3,4-di-O-isopropylidine galacto pyranose produced the ester **2.56** as a mixture of two stereoisomers in the ratio 2:1, which were separable by silica gel chromatography. The major isomer **2.56** was subjected to Rychnovsky's DIBAL reduction conditions as described earlier to produce the α-Bromo acetoxy ether **2.57**. Unlike the reduction of

unsaturated ester **2.53**, the reaction worked surprisingly clean and the α-bromo acetate **2.57** was obtained in high yield (90%), as an inseparable mixture of two diastereoisomers. The reaction proceeded without any over reduction or recovery of starting material.



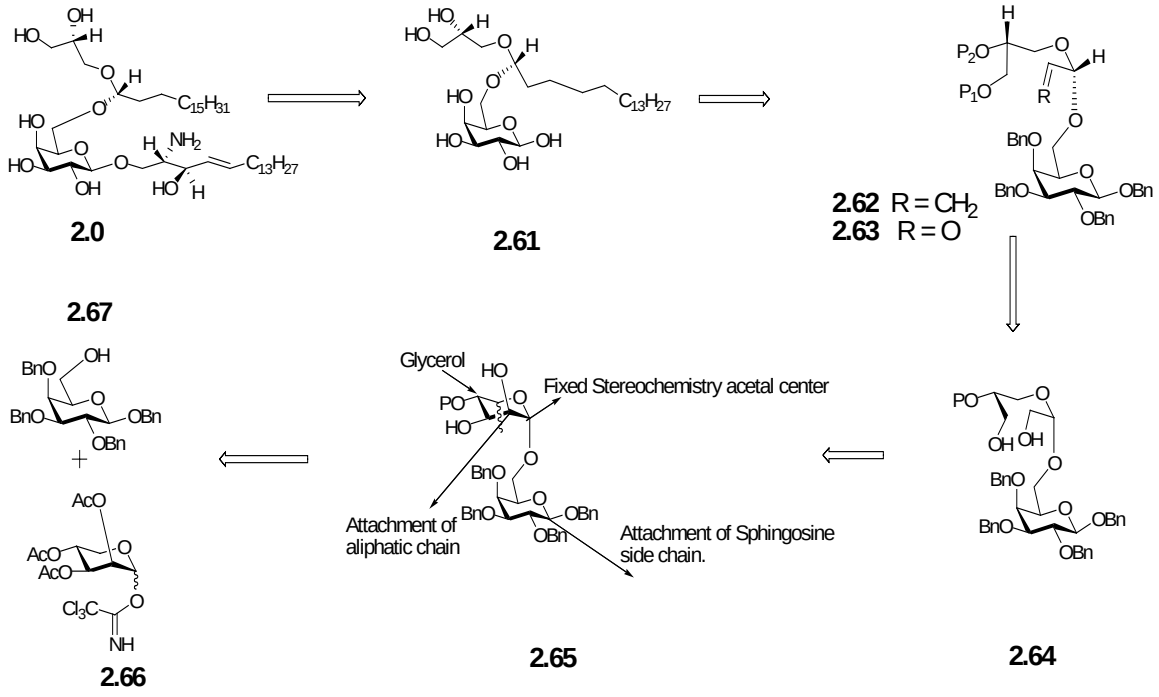

**Scheme 2.7: Successful synthesis of Cyclization product 2.60**

Next step of the synthesis would be the coupling of R-solketal with acetoxy ether **2.57** to prepare the mixed acetal **2.58**. No reaction was observed when compound **2.57** was treated with R-solketal and $BF_3$-$Et_2O$ at –78 $^oC$ in DCM. Coupling of **2.57** with R-solketal proceeded smoothly when the temperature was raised to –15 $^oC$ and the mixed

acetal **2.58** was obtained as a mixture of two diastereoisomers in 92 % yield. This outcome can be explained in terms of the stability of the bromo-acetoxy ether **2.57**. The electron withdrawing nature of α- bromide makes the cleavage of the C-OAc bond to form the oxonium ion more difficult than in the absence of the bromide. Regioselective cleavage of glycerol acetonide produced the diol **2.59** in quantitative yield. The use of acidic conditions to remove the isopropylidine group without the cleavage of the mixed acetal also agrees with this concept. The diol **2.59** obtained as a mixture of two diastereoisomers, could not be separated. The inability of getting a pure diastereoisomer of compound **2.59** was an unfortunate result that seriously jeopardized our hope for the spectroscopic analysis of the cyclic partner **2.45**. However we decided to proceed with the cyclisation of acyclic partner **2.59**. At first a mixture of **2.59** and $Bu_2SnO$[30,35] in benzene was heated for 1 day with azeotropic removal of water. However none of the desired product was obtained. The reaction was successful when catalytic amounts of CSF and TBAI were added. The cyclic compound **2.60** was obtained in fairly good yield again as a non-seperable mixture of two compounds. Due to the failure in obtaining pure diastereomers of diols **2.47** or **2.45**, we could not assign the absolute configuration at the acetal center. This strategy for synthesizing the mixed acetal was therefore abandoned and a proposed the new stereoselective synthesis of the target compound was proposed.

## 2.6 Stereoselective Synthesis of Glyceroplasmalopsychosine

### Retrosyntheis:




**Scheme 2.8: Retrosynthetic plan for the synthesis of S-glycero-S-acetalplasmalopsychosine**

## (i) Retrosynthetic Analysis

The approach outlined in Scheme 2.9 is a classic example of conversion of carbohydrate to a non-carbohydrate asymmetric molecule[36,37]where chiral centers of the carbohydrate are incorporated into the product. The disaccharide **2.65** is a suitable intermediate for the target compound **2.0** in that it may be elaborated to several of the important functionalities of the target compound **2.0.** In particular the glycerol and acetal moieties could be derived from this molecule. We reasoned that oxidative cleavage of the C2-C3 bond of the lyxose unit in **2.65**, and reduction of the product would lead to diol **2.64** in which the C3, C4, C5 of the lyxose unit corresponds to the C1, C2 and C3 respectively of the glycerol. Also as in the natural product, the glycerol moiety would be attached to the rest of the molecule by the C1 and we would established the **S** stereochemistry at the C2 of the glycerol (previously the C4 of the lyxose). During this process, the C1 of the lyxose would now be converted to the acetal center with a two carbon aliphatic chain. So by one disconnection we would have the glycerol unit with correct stereochemistry at the C2 and the acetal center with a two carbon aliphatic chain. The second important point would be the control of the stereochemistry at the acetal center. In that context, our anticipation was that by proper choice of the C2 protecting group in the lyxose donor, we would control the acetal stereochemistry as an S or R isomer. For example, an acetate-protecting group at C2 of D-Lyxose donor would give rise to the S acetal isomer. This is possible because of the fact that, the axial acetate-protecting group at the C2 would influence the glycosidation by neighbouring group participation and hopefully would furnish predominately the α-disaccharide. By doing that we would fix the stereochemistry at the anomeric carbon. Later on by cleaving the C2-C3 bond of the

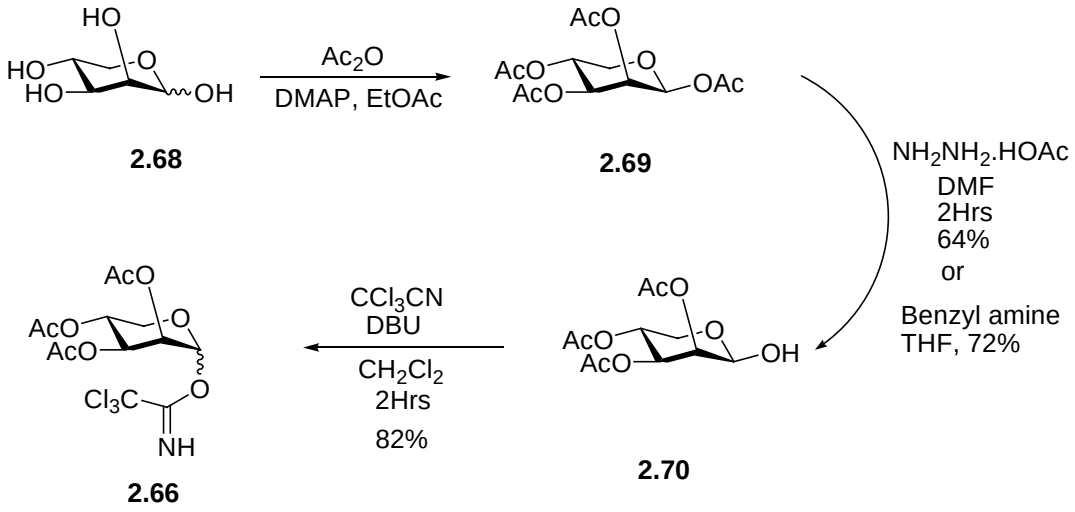
lyxose unit, the anomeric carbon would now be our acetal center, which would retain the stereochemistry of the anomeric carbon. So out of three existing stereocenters of the lyxose donor we would exploit two, one for retaining the glycerol stereochemistry and the other to influence the glycosidation. The disaccharide **2.65** would be obtained from the two monosaccharides, a lyxose donor **2.66** and a galactose acceptor **2.67**. As discussed earlier, after the C2-C3 bond cleavage, the molecule would look like **2.64**. Our next objective would be to grow the already existing two-carbon chain to eighteen carbon aliphatic chain as in the natural product. After protecting the hydroxyl group of the glycerol, the required sixteen carbon aliphatic chain would be stitched to the existing aliphatic chain possibly by doing aldehyde chemistry or by alkene chemistry. At this stage the molecule would look like **2.61** after the reduction of the double bond and the global deprotection. With the carbohydrate acetal segment similar to the natural product, the remaining sphingosine side chain could be attached to the rest of the molecule at this stage of the synthesis. Attachment of the sphingosine side chain and removing the existing protecting groups would complete the first total synthesis of S-Glyceroplasmalopsychosine.

## (ii) **Synthesis:**

Our first important target was the disaccharide **2.65**, the required intermediate compound precursor to the target **2.0**. Although there are several glycosidation methods available to effectively synthesize the disaccharides, we opted for the trichloroacetimidate-mediated glycosidation procedure first reported by Schmidt in 1980.[38]Glycosidation with anomeric trichloroacetimidate donor is currently one of the most frequently applied strategies for

the preparation of O-glycosides. The trichloroacetimidate donors are easily prepared from the lactols and trichloroacetonitrile in the presence of a base such as NaH and DBU.

Our synthesis began with the preparation of D-lyxose trichloroacetimidate donor **2.66** from commercially available D-lyxose. Acetylation of **2.68** in ethyl acetate afforded the peracetylated D-lyxose pyranoside **2.69** in 3:1 ratio of two anomers, the β-anomer being the major one. The proton NMR of compound **2.69** matched with the literature value[39], thus ensuring the pyranose form of D-lyxose. The regioselective deacetylation of the anomeric acetate can be achieved in different ways. One of the popular methods is the use of hydrazinium acetate in DMF, which effectively deprotect the anomeric acetate. Using this method the triacetly **2.70** was produced in 64% yield similar to the literature value. The yield improved slightly by using benzyl amine in THF[40], which afforded the product in 72 % yield in a longer reaction time.



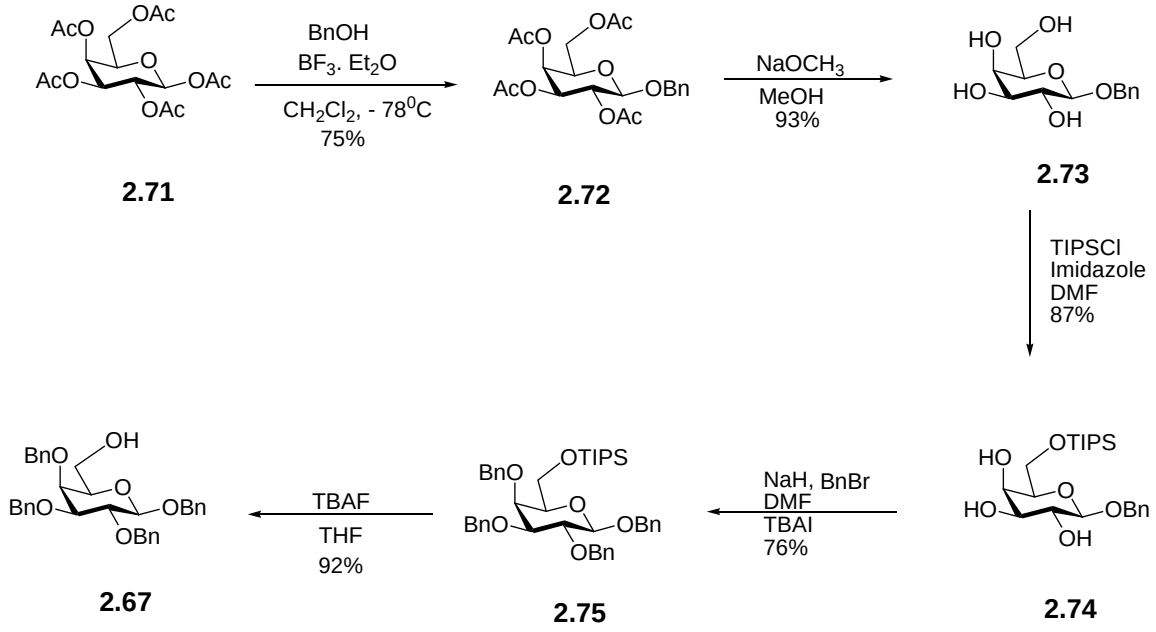

**Scheme 2.9: Synthesis of lyxose donor 2.66**

The next step involved the formation of donor **2.66** by reaction of lactol **2.70** with trichloroacetonitrile in presence of DBU as base[41]. The reaction smoothly furnished the trichloroacetimidate **2.66** in two hours as a mixture of two anomers in about 82% yield.

After the synthesis of the lyxose donor **2.66**, our next target was it's coupling partner **2.67**, a galactose acceptor. The choice of protecting groups in the galactose moiety had to be considered carefully. We were aware of the fact that most of the chemistry would be done in the lyxose unit of the disaccharide while the galactose moiety would be a participant until late stage of the synthesis. A protecting group that would survive the earlier reaction conditions and which be easily deprotected afterward was needed. A benzyl ether was selected because this protecting group is known to be stable to acidic, basic and the proposed carbon-carbon bond formation reaction conditions and can be easily deprotected by hydrogenolysis towards the end of the synthesis.

Although the galactose acceptor **2.67** contains all four protecting groups as benzyl ether, the four hydroxyl groups can't be protected in one step due to the differential reactivity of the galactose hydroxyl groups. Firstly the most reactive anomeric hydroxyl has to be protected stereospecifically in order to avoid unnecessary complexity due to the possibility of the formation of mixture of two anomers. After the anomeric hydroxyl group the next reactive group is the 6-OH which has to be taken care of. All other hydroxyl groups have more or less similar reactivity and can be protected simultaneously.

The synthesis began from peracetylated galactose **2.71**, which was glycosylated with benzyl alcohol under $BF_3$-etherate catalysis to give β-glycoside **2.72** in 75% yield.[42]

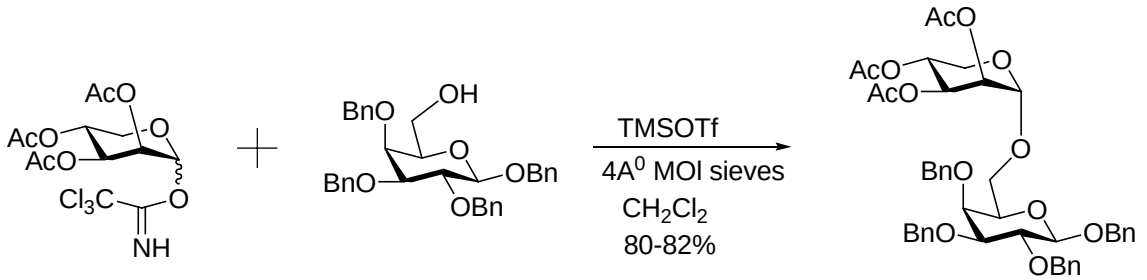



**Scheme 2.10: Synthesis of galactose acceptor 2.67**

Subsequent cleavage of acetates by sodium methoxide in methanol produced the deprotected compound **2.73** in 93% yield. At this point our next job was to differentiate the 6-OH group from other hydroxyl groups so that it would be free for the glycosidation. The common practice in this case would be to form a 4,6-benzylidine acetal and cleaving it regioselectively to furnish the 6-free OH group afterward. But we decided to follow a protocol used by Chi-Huey Wong [43]in the synthesis of α-galactosyl ceramide. In this protocol the unprotected benzyl galactose **2.73** was selectively silylated at 6-OH using TIPSCl [44]to provide the silyl ether **2.74** in 87% yield. The choice of silyl protection group was important since it has been known that use of TBDMS and TBDPS leads to cleavage or migration of the silyl group during the benzylation. The benylation of the remaining three-hydroxyl groups went uneventfully to provide the fully protected galactose derivative **2.75** in 76% yield. The final step of the synthesis of the galactose acceptor **2.67**

involved the removal of TIPS using TBAF [45]in THF, which converted the compound **2.75** into the product **2.67** in quantitative yield.

With both the coupling partners in hand, we were ready for the key glycosidation step. Normally in the glycosidation method involving trichloroacetimidate donors, the activation is performed in the presence of catalytic amounts of $BF_3.Et_2O$[38], TMSOTf,[46] AgOTf or $ZnBr_2$.



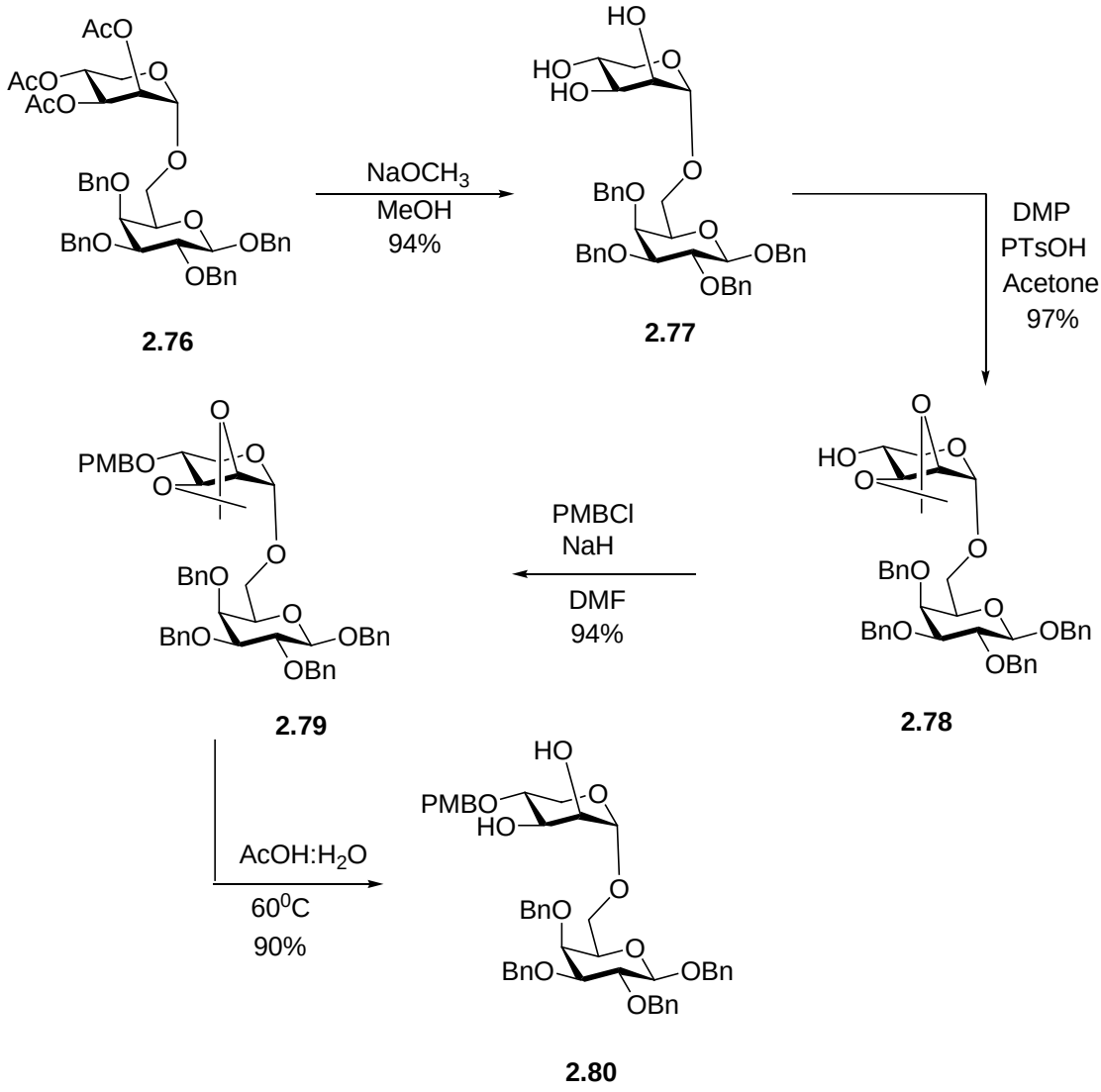

**2.66** **2.67** **2.76**

**Scheme 2.11: Preparation of Disaccharide 2.76**

Condensation [47]of lyxose donor **2.66** and galactose acceptor **2.67** in presence of catalytic amount of TMSOTf gave the disaccharide **2.76** exclusively as the α-glycoside in 80-82% yield. No trace of β-product was detected in this glycosidation. The NMR spectrum of the disaccharide **2.76** has two doublets in the anomeric region: a 1.8 Hz doublet at δ 4.53 assigned to H-1 of lyxose unit and a 9.7 Hz doublet at δ 4.55 assigned to H-1 of galactose unit. The presence of three acetyl proton signals at δ 2.18, 2.07, 1.99 and of benzyl proton signals in the appropriate region are in the agreement with the proposed structure. The α configutation was assigned to the newly formed glycoside bond on the basis of mechanistic considerations (neighbouring group participation by the axial C2-OAc of the

lyxose), by the J value of 1.8 Hz for H-1 of lyxose and $^{13}C$ shift of 97.4 ppm for the C-1 of lyxose. Other Lewis acids such as $BF_3$-$Et_2O$ or the mixture of TMSOTf and $BF_3$-$Et_2O$ were also tried but TMSOTf gave the best yield. Here it should be noted that keeping the temperature below – 20 $^oC$ during the addition of catalyst was necessary in order to avoid the formation of the uncharacterized by-product.

Once we obtained our disaccharide **2.76** we were ready for the protecting group manipulations in lyxose unit. Firstly the acetyl groups were removed by using sodium methoxide in methanol[48] to give the triol **2.77** in 94 % yield. Our next aim was to differentiate C2-C3 hydroxyl groups of lyxose from C4 hydroxyl group. This differentiation could be achieved by exploiting the cis relationships between the C2-C3 hydroxyl groups. Treating **2.77** with dimethoxypropane




**2.76** **2.77** **2.78** **2.79** **2.80**

**Scheme 2.12: Protecting group manipulations**

and p-TsOH in acetone gave the cis acetonide **2.78** in 97% yield.[49] No trace of trans-acetonide was detected and during the process the 4-OH group was exposed for further protection.

Careful thinking was needed for the proper choice of the protecting group for the 4-OH group. The use of an acid sensitive group would be risky because the acetonide protecting group had to be removed later for the oxidative cleavage of the C2-C3 bond of the lyxose

unit of the disaccharide. PMB protection was thought to be the best option considering the fact that it was stable to the acidic conditions used to cleave the isopropylidine protecting group. Also the same PMB group would be utilized to protect the resulting primary hydroxyl group of the glycerol moiety after the cleavage of the C2-C3 bond.

Treating **2.78** with NaH and PMBCl in DMF furnished the PMB ether **2.79** in quantitative yield.[50]

Various acidic conditions were tried to deprotect the isopropylidine protecting group without cleaving the PMB or benzyl protecting groups. The best result was obtained with 5:1 AcOH-$H_2O$ at 60 $^oC$, which gave the diol **2.80** in 90% yield.[51,25] Although this reaction did not go to completion, the starting material could be recycled and one could obtain combined product in more than 90% yield.

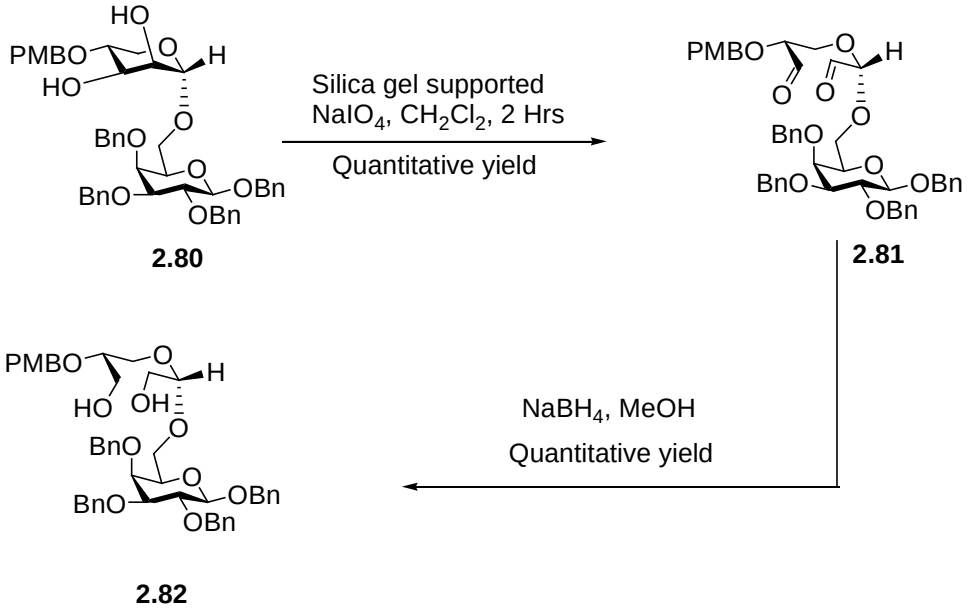
Now the desire diol in hand, we were ready for the key oxidative cleavage of the C2-C3 bond of the lyxose unit. Sodium metaperiodate has been an attractive and popular reagent for the oxidative cleavage of vicinal diols into dicarbonyls.[52] The popularity stems from its specificity, its reactivity under neutral and mild conditions, which is compatible with a wide range of functionalities, its stability and its low cost.[53]

Glycol scission oxidations using sodium metaperiodate are generally performed in aqueous alcohols or THF, which sometimes prove to be difficult to monitor. Also these solvents are not good for vicinal diols that are not readily soluble in aqueous alcohols or THF and for aldehydes that are water-soluble.[54]

Considering the above facts we decided to use an efficient and facile glycol cleavage oxidation using silica gel supported sodium metaperiodate.[55] The oxidative cleavage reagent, a free-flowing powder, is easily and conveniently prepared by adding silica gel to aqueous sodium metaperiodate and can be stored in a bottle for months with negligible

loss of activity. Glycol oxidative fission reactions are easily carried out by stirring a suspension of the reagent and the vicinal diol in dichlromethane at room temperature. The work up is also very simple-just filter the solid and the pure aldehyde can be obtained in very good yield.

Following the above method, when the diol **2.80** was subjected to the oxidative cleavage, in a very nice and clean reaction the di-aldehyde **2.80** was obtained in quantitative yield. The neutral condition in the diol cleavage was important for the absence of epimerization at the acetal center. Due to the possibility of epimerization, the dialdehyde was not purified further and was immediately reduced with sodium borohydride in methanol to afford the diol **2.82** in very good yield.[56] These two-step reaction sequences worked nicely to furnish the desired diol in more than 90% yield starting from the vicinal diol **2.80**.

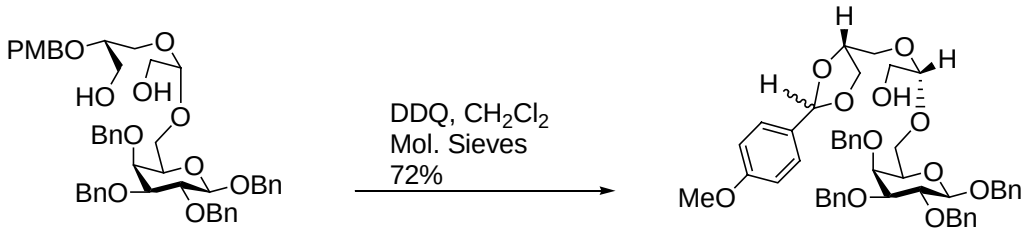



**Scheme 2.13: Oxidative cleavage and Reduction**

As discussed in the retrosynthetic plan the cleavage of the C2-C3 bond of lyxose unit produced the acetal center stereospecifically along with the glycerol moiety and two-carbon aliphatic chain. Our next job was to protect the newly formed glycerol primary hydroxyl group so that the other hydroxyl group would be exposed for further elaboration.

Here we had two options to differentiate the two-hydroxyl groups and to protect one in presence of other. The first option was to deprotect the PMB group to get the triol and protect the 1,2 diol with some protecting group which could be removed under basic conditions.

Instead of opting for the two step sequences we decided to undertake our second option i.e, one step protection exploiting the presence of the PMB protecting group at the secondary carbon of the glycerol moiety.




**2.82** **2.83**

**Scheme 2.14: DDQ Assisted Protection of Glycerol Hydroxyl Group**

When the compound **2.82** was treated with DDQ[57] in presence of molecular sieves, the PMB ether was converted to the p-methoxy benzylidine derivative **2.83** in 72 % yield.

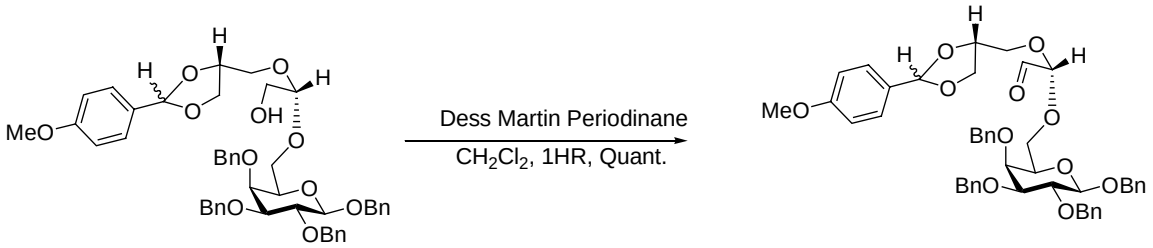
The conversion of PMB ether **2.82** to p-methoxybenzylidine derivative **2.83** produced the desired product in 1:4 ratios of two diasteroisomers. The proton NMR of the compound **2.83** showed two singlets at δ 5.8 ppm and δ 5.9 ppm corresponding to the benzylidine acetal proton in 4:1 ratio. This result is obvious from mechanistic point of view. During the course of reaction there is a hydride shift from the benzylic carbon of the p-methoxy group to DDQ and the resulting carbocation can be attacked by the nearby hydroxyl group either from the top or from the bottom face to give rise to two diastereoisomers. This was not an issue for us as it was merely a protecting group, which could be removed later to produce the single isomer.

The next task would be to grow the already existing two-carbon aliphatic side chain to give the eighteen-carbon chain. The choice of strategy was important because of the sensitive nature of compound **2.83**. This compound would be very acid sensitive as there is a possibility of acetal cleavage in acidic conditions.

Considering the above facts, we first tried the free radical allylation of the corresponding iodide of **2.83**, which did not yield the satisfactory result. Also Sonogashira coupling of the long chain alkyne with iodide of compound **2.83** did not work to form the required alkyne long chain.

After the failure of these two reactions we thought of undertaking aldehyde chemistry to construct the eighteen-carbon side chain. Looking at the required aldehyde we realized that the compound **2.84** was both acid and base sensitive. The base sensitivity raised the distinct possibility of epimerization at the acetal center in basic conditions. At this point we needed a mild oxidizing reagent, which would convert the alcohol **2.83** to the corresponding aldehyde **2.84** under neutral or near neutral conditions

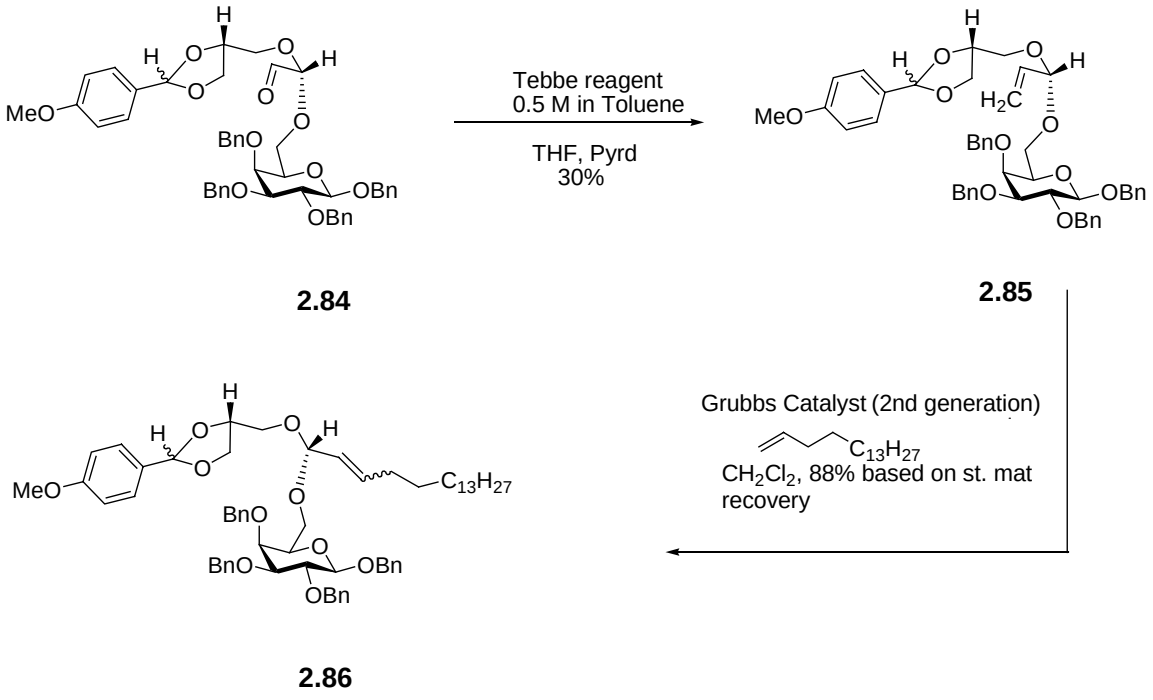
So the best choice was the use of Dess-Martin periodinane,[58] which converted **2.83** to **2.84** without any epimerzation at the acetal center in very good yield.




**2.83** **2.84**

**Scheme 2.15: Dess-Martin Oxidation of Primary Alcohol to Aldehyde**

Immediate olefination of the aldehyde **2.84** with Tebbe reagent[59] produced the corresponding terminal alkene **2.85** in only 30% yield when pyridine was used in the reaction mixture. Without the use of pyridine, the yield was even less giving complex reaction mixture. When there was no pyridine in the reaction mixture, we observed significant acetal cleavage. This result although surprising to us, could be explained in terms of the Lewis acidity of the titanium complexes in Tebbe reagent, which might cause the acetal cleavage. This result was a hint of the acid sensitive nature of these kinds of compounds.




**2.84** **2.85** **2.86**

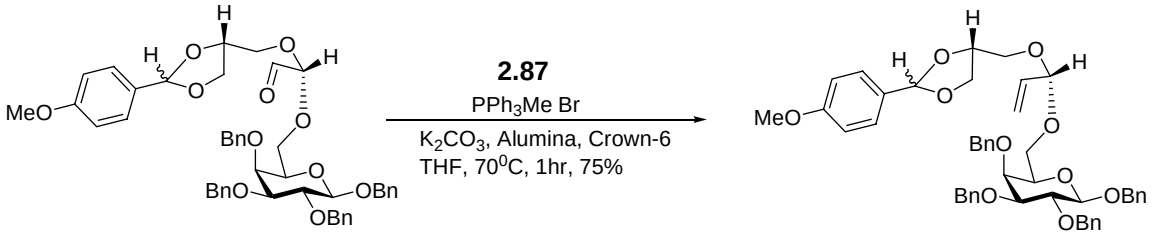
**Scheme 2.16: Methylation and Cross-Metathesis.**

However when compound **2.85** was subjected to cross metathesis[60] with the seventeen carbon terminal alkene using second-generation Grubbs catalyst, the compound **2.86** was formed as mixture of cis and trans alkene. The yield was about 88 %, which was based on the recovery of the starting material as the reaction did not go to the completion.

Although we could successfully attach the required carbons to the already existing aliphatic chain, the 30% yield in Tebbe reaction was not acceptable since several more synthetic steps were required to complete our synthesis. This led us to think some other alternative routes to construct the eighteen carbon aliphatic chain.

Although, Wittig protocol was obviously a risky proposition owing to the base sensitive nature of the aldehyde **2.84**, we decided to undertake a less used Wittig modification, namely the hetrogeneous Wittig reaction.[61] This reaction requires potassium carbonate as

base, THF as solvent and a phase transfer catalyst. Our reasoning was that potassium carbonate being a weak base would not epimerize the acetal center adjacent to the aldehyde. When the aldehyde **2.84** was treated with methyl phosphonium salt **2.87**, grounded with $K_2CO_3$ and some basic alumina in THF followed by some crown-6 ether at 60 $^oC$, compond **2.85** was obtained in more than 75% yield over two steps, as a pure product.



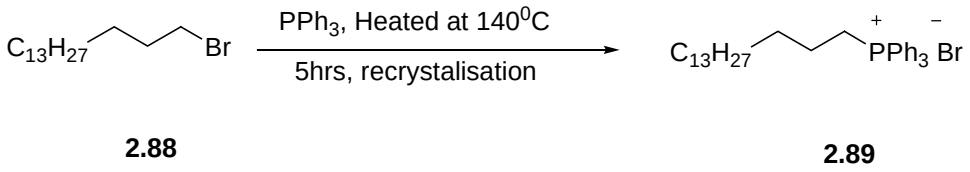

**2.84** **2.85**

**Scheme 2.17: Heterogeneous Wittig Reaction to Prepare 2.85.**

Identical proton NMR of Wittig product and that of the Tebbe product ensured the fact that there was indeed no epimerization at the acetal center.

After the successful one carbon-Wittig reaction, we decided to try the same protocol with sixteen carbon-phosphonium salt to construct the eighteen carbon-aliphatic chain.

The required sixteen carbon-phosphonium salt **2.89** was prepared following the literature method[62] from hexadecyl bromide.

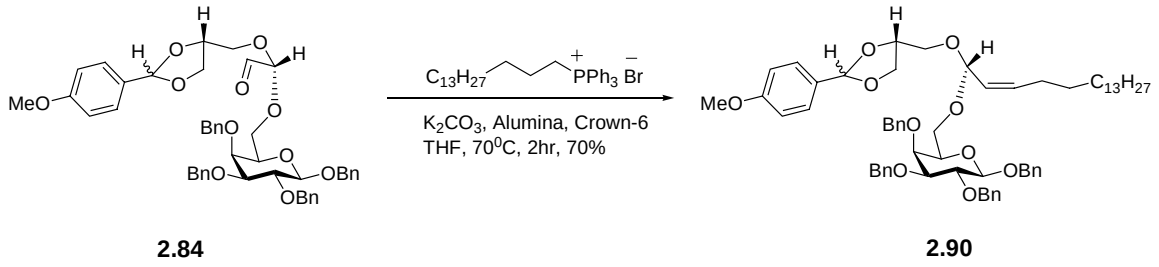



**2.88** **2.89**

**Scheme 2.18: Preparation of Sixteen-Carbon Phosphonium Salt.**

Heterogeneous Wittig reaction conditions applied to the long chain phosphonium salt **2.89** and the aldehyde **2.84** produced the cis alkene **2.90** in a very clean reaction in 70% yield over two steps. The alkene configuration was assigned by decoupling experiment from coupling constant 11.2 Hz for the C2 proton of the aliphatic chain. The acetal proton appeared at δ 5.25 ppm as a multiplet. The two double bond protons appeared at δ 5.76 ppm (multiplet) and 5.68 ppm (multiplet). The two dimensional correlation spectra showed a cross peak between δ 5.25 and δ 5.76 ppm. So the signal at δ 5.35 ppm was assigned to the acetal proton, which was coupled to the C2 proton (δ 5.76 ppm) of the long chain alkene.

The other proton signals and carbon NMR spectra of the compound **2.90** were completely in agreement with the proposed structure.

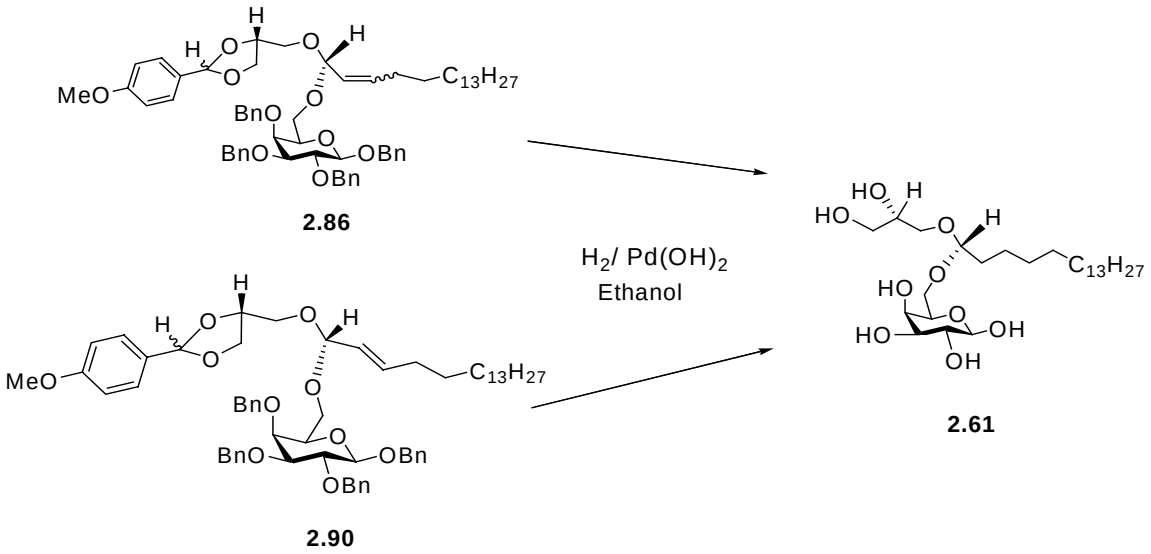



**2.84** **2.90**

**Scheme 2.19: Preparation of Alkene 2.90 by Heterogeneous Wittig Reaction**

Now both the isomers of the internal alkene in hand, we were ready for the global deprotection and reduction of the double bond to furnish the most advanced intermediate **2.61**.

Thinking of achieving our goal in one step, we subjected both the compounds **2.86** and **2.90** to hydrogenolysis and hydrogenation by using $Pd(OH)_2$ as catalyst.[63]

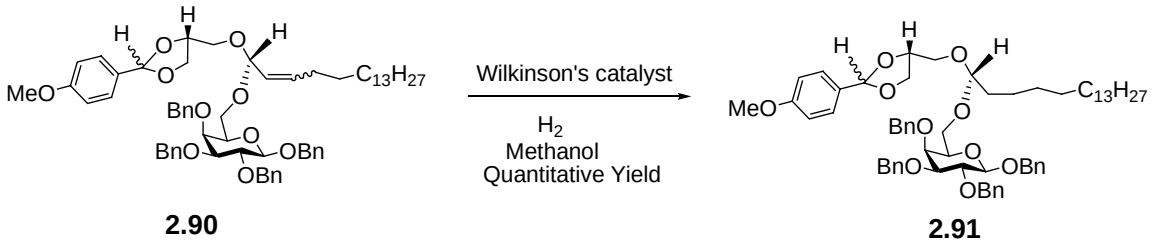



**Scheme 2.20: Hydrogenolysis and Hydrogenation**

The reaction was performed using stochiometric amount of the catalyst for 24 hours after which, TLC showed no starting material, but there were multiple polar spots, which did not change with reaction time. Although chromatographic purification of the product was unsuccessful, the mass spectra [M + $NH_4^+$] confirmed the presence of product **2.61**.

Since we were unable to purify the product **2.61**, we opted to do the deprotection and reduction of double bond in stepwise fashion. We decided to reduce the double bond first, than try for debenzylation by Birch reduction.[64]

The reduction of the double bond was achieved using Wilkinson's catalyst,[65] which furnished the product **2.91** without deprotecting the benzyl or benzylidine protecting groups. Using stoichiometric amount of catalyst, the product was isolated in more than 95% yield. The proton NMR of the compound showed a signal at δ 4.47 as a multiplet corresponding to the acetal proton (the multipltet for this proton is due to the mixture obtained for benzylidine proton). The acetal proton was assigned from the two dimensional correlation spectra, which showed a cross peak between acetal proton and C2 methylene proton of the long aliphatic chain which appeared as multiplet at δ 1.56 ppm.




**2.90** **2.91**

**Scheme 2.21: Synthesis of Mixed Acetal 2.91**

When **2.91** was subjected to Birch reaction conditions,[64] surprisingly there was no reaction as no change was detected to the starting material even after 6 hours.

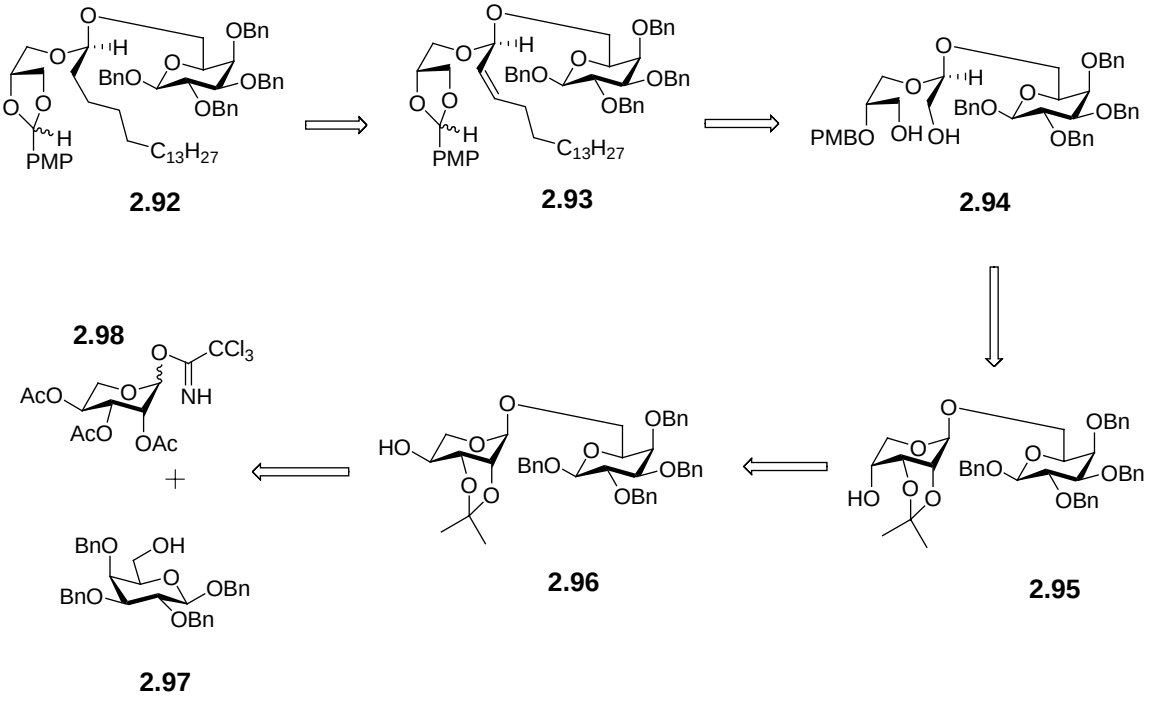
The failure of getting pure product **2.61** either from one step hydrogenation reaction or two-step protocol unfortunately ended our hope to synthesize the target compound **2.0**.

However we believe that the **2.91** is a very important compound in synthetic point of view as the acetal center and the glycerol center were successfully synthesized in a stereospecific manner. This of course was not a trivial task owing to the flexibility of the molecule at that center.

After successful synthesis of S isomer of the mixed acetal, we decide to apply our strategy to synthesize the R isomer of the mixed acetal. The following section describes the synthesis of R isomer of the mixed acetal of Glyceroplasmalopsychosine.

## 2.7 Stereoselective Synthesis of Mixed Acetal of R Isomer of Glyceroplasmalopsychosine

## Retrosynthesis:




**Scheme 2.22: Retrosynthetic Plan for Synthesis of Mixed Acetal of R – glyceroplasmalopsychosine**

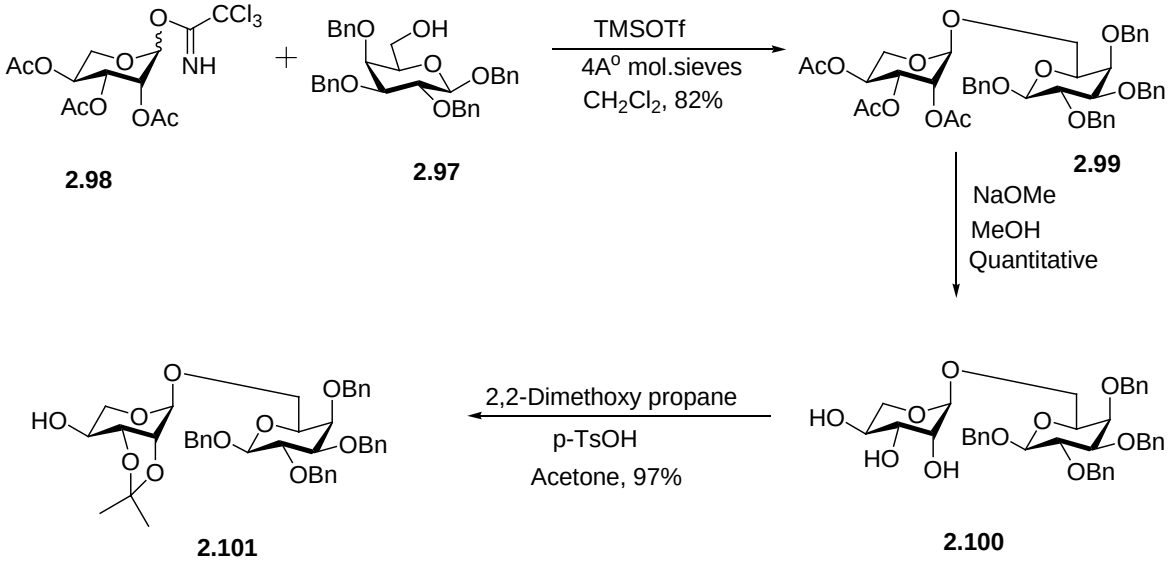
### (i) Retrosynthetic Analysis:

The retrosynthetic plan for the synthesis of R isomer of Glyceroplasmalopsychosine mixed acetal is similar to the S isomer. Here also we decided to exploit the C-2 stereochemistry of donor sugar to influence the acetal stereochemistry. For that reason L-lyxose trichloroacetimidate **2.98** was thought to be the appropriate sugar donor. We

hoped that the O-acetyl group at C-2 of L-lyxose would predominately furnish the β-disaccharide. Protecting group manipulations and inversion of C-4 stereochemistry would produce the compound **2.95**. All other chemistry being exactly similar to the previous synthesis, we hoped to synthesize the mixed acetal **2.92** with R acetal configuration without any major problem.

## (ii) Synthesis

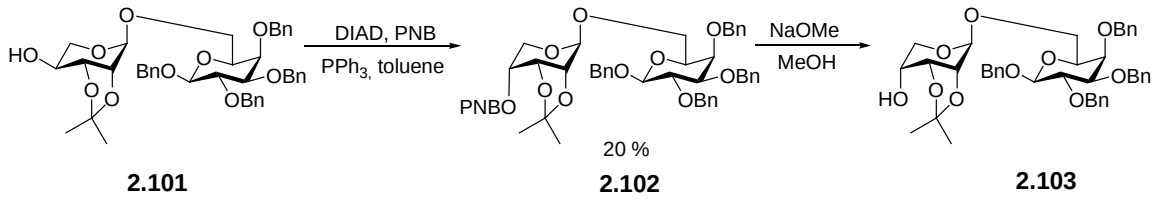
The synthesis began with the condensation of the L-Lyxose donor **2.98** (prepared by same method as in D-Lyxose series) and the galactose acceptor **2.97** under TMSOTf catalysis to furnish the β-disaccharide **2.99** exclusively without any trace of the α-isomer.




**Scheme 2.23: Glycosidation and Further.**

The β-connection was confirmed from the $^1$H NMR and also from mechanistic considerations. Deprotection of the acetyl groups using sodium methoxide in methanol and protection of the cis-diol with isopropylidine went smoothly to furnish the compound **2.101** in very good overall yield.

Our next job would be the inversion of C-4 Lyxose stereochemistry, which would ultimately be our glycerol stereo center. For that we first tried the Mitsunobu conditions,[66] which provided the required product **2.102** only in 20% yield. In all attempted Mitsonobu conditions, the reaction stopped after some time to furnish very low yield of product **2.102** and rest was the recovered starting material.

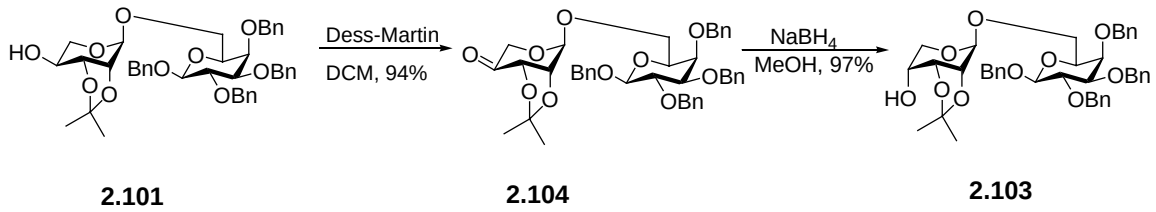



**2.101** **2.102** **2.103**

**Scheme 2.24: Inversion of C4 Stereocenter of Lyxose Unit by Mitsunobu Protocol.**

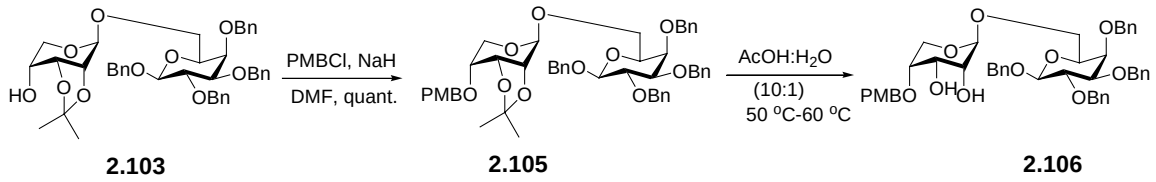
This led us to undertake two step sequences: oxidation followed by reduction. Oxidation of the alcohol **2.101** to the corresponding ketone **2.104** was achieved using Dess-Martin periodinane, which produced the desired product in quantitative yield. Reduction of the ketone with excess $NaBH_4$ furnished the alcohol in quantitative yield. The inversion of the C-4 stereo center was confirmed by comparing the $^1$H NMR of both reactant and product. Also the fact that the Mitsunobu product (**Scheme-2.25**) and reduced product

(**Scheme-2.26**) had identical $^1$H NMR further confirmed the inversion. Mechanistically it is also reasonable to predict that the hydride ion should approach the ketone from top face, which is sterically less hindered.



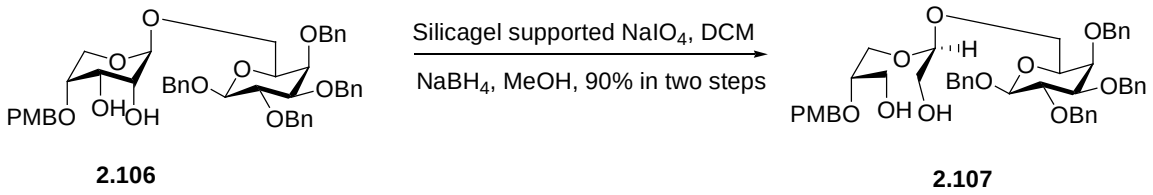

**Scheme 2.25: Inversion of C4 Stereochemistry by Two-step Protocol.**

After having the alcohol **2.103** in hand, the next two steps were the protecting group manipulations similar to the first isomer to furnish the required diol **2.106**, to be used for the oxidative cleavage.




**Scheme 2.26: Protecting Group Manipulations to Yield 2.106**

When the diol **2.106** was subjected to silca-gel supported $NaIO_4$, it smoothly formed the dialdehyde in quantitative yield. Immediate reduction of the dialdehyde with $NaBH_4$ in methanol afforded the diol **2.107** in 90% yield over two steps.

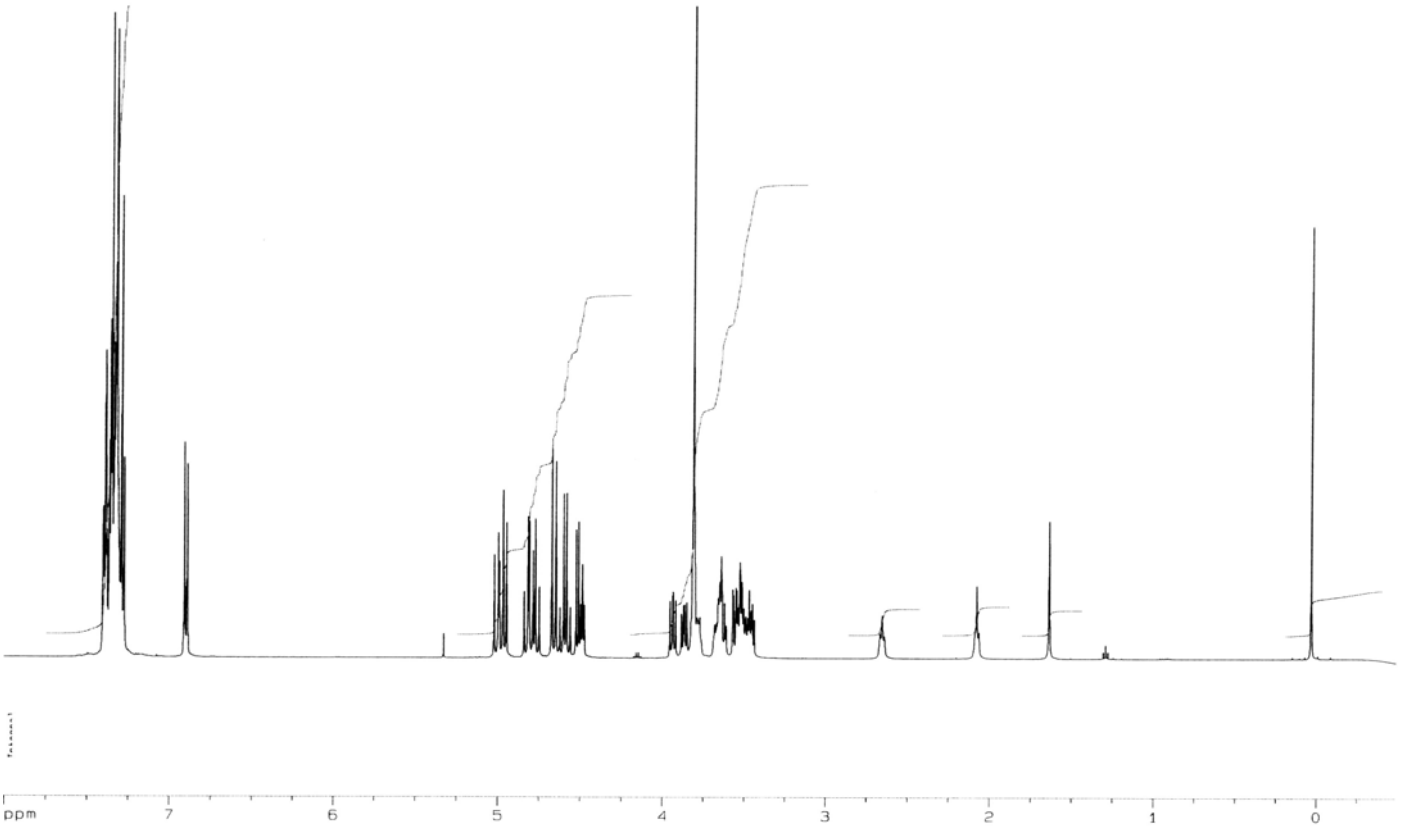


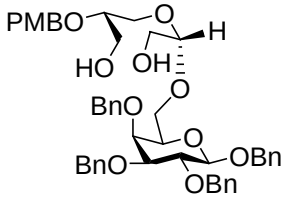

**2.106** **2.107**

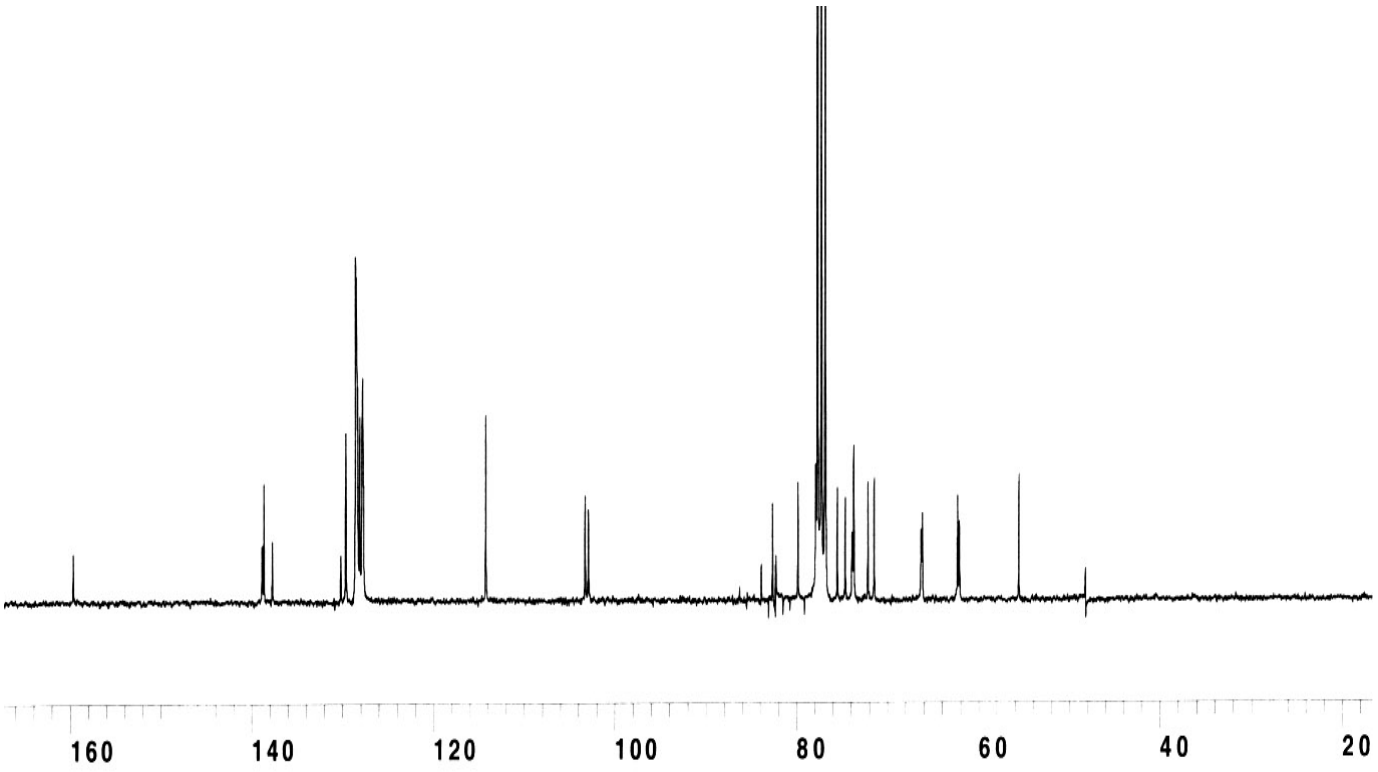
**Scheme 2.27: Oxidative Cleavage and Reduction to Produce Compound 2.107.**

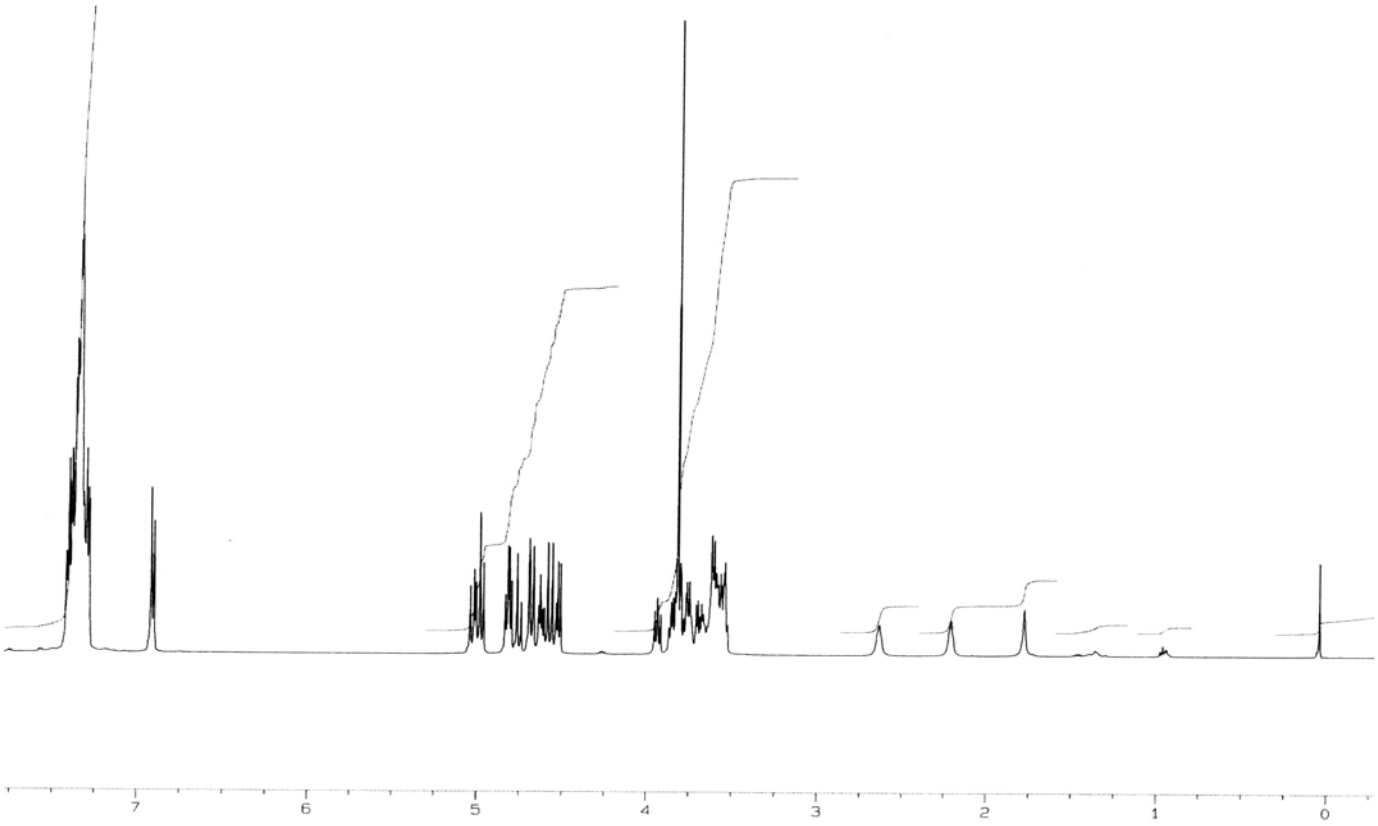
The compounds **2.82** (scheme 2.14) and **2.107** are now two stereoisomers, which vary at the acetal centers. Surprisingly $^{1}H$ NMR of both compounds are very different. This may be explained in terms of differential hydrogen bondings in these isomers.

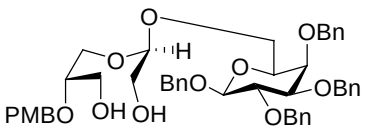
The proton and carbon spectra of both isomers were given below for comparision.


ppm
7
6
5
4
3
2
1
0


PMBO
O
H
HO
OH
O
BnO
O
BnO
OBn
OBn

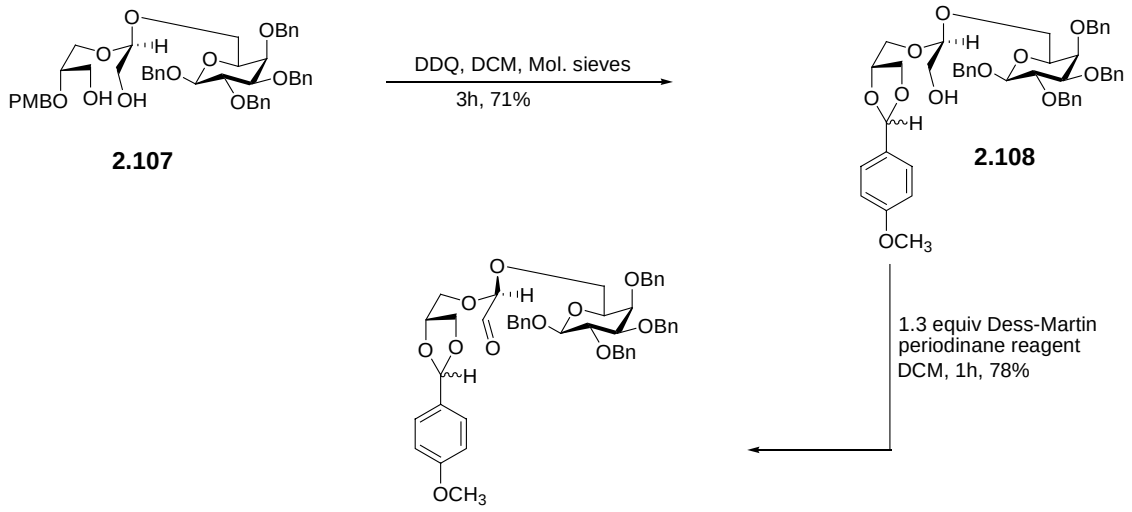

160
140
120
100
80
60
40
20


7
6
5
4
3
2
1
0


O
OBn
O
H
BnO
O
OBn
PMBO
OH
OH
OBn


ppm
140
120
100
80
60

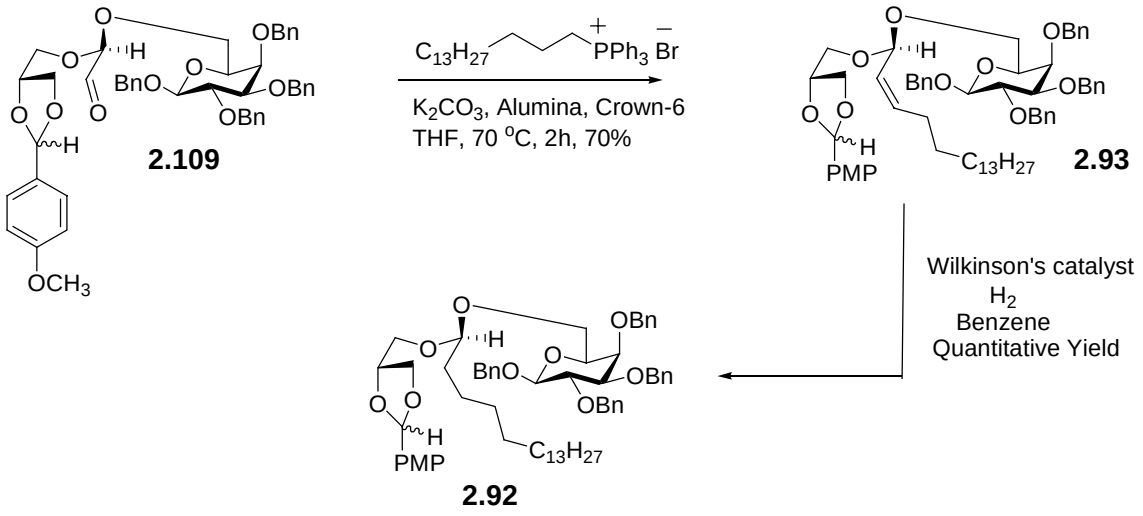
DDQ assisted protection of the glycerol primary hydoxyl group of alcohol **2.107** once again formed the *p*-methoxy benzylidine derivative **2.108** as 5:1 mixture of two diastereomers. Dess-Martin oxidation of the alcohol **2.108** produced the aldehde **2.109** without any major event.




**2.107** **2.108**

**Scheme 2.28: DDQ Assisted Protection of Alcohol Followed by Oxidation.**

Heterogeneous Wittig reaction of **2.109** with sixteen-carbon alkyl phosphonium salt completed the alkyl chain to provide the cis alkene **2.93** in 65% yield. Here again the double bond configuration was assigned from the coupling constant (11.2 Hz) for the C2 proton of the aliphatic chain. Acetal proton showed a signal at δ 5.31 ppm as a multiplet. The acetal proton signal was assigned based on the two dimensional correlation spectra.




**Scheme 2.29: Heterogeneous Wittig Reaction Followed by Hydrogenation**

Hydrogenation of the double bond using Wilkinson's catalyst produced the desired mixed acetal **2.94** in quantitative yield.

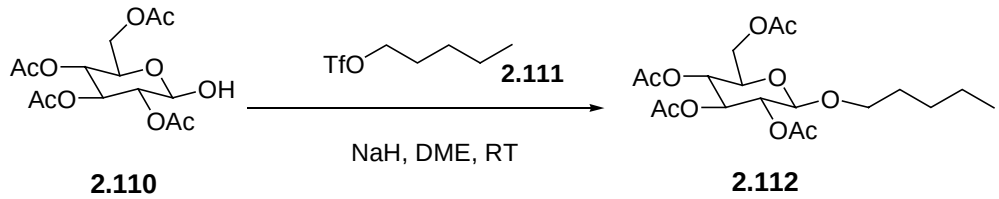
The compound **2.91**(scheme 2.22) and **2.92** are stereoisomers with respect to the acetal centers. The $^1$H NMR showed some differences for the acetal signal between these two isomers. For S isomer the acetal proton appeared at δ 4.47 ppm where as for the R isomer it showed a signal at δ 4.58 ppm.

# 2.8 COMPLETION OF THE SYNTHESIS

## (i) Strategy-1

The synthesis may be completed in two possible ways. The first path involves the use of the compound **2.61** as an intermediate compound to the target **2.0** as described in the retrosynthetic plan.

The difference between the compound **2.61** and the target compound is the sphingosine side chain. We know that the attachment of the sphingosine side chain to **2.61** is not a trivial task considering the sensitive nature of this compound. As we found from the Tebbe reaction **(scheme 2.17)**, the acetal linkage is indeed very unstable to the acidic reagent. So glycosidation with sphingosine side chain would be tricky since most of the glycosidation method requires lewis acid activation. Here we need a method where we can attach the sphingosine side chain to rest of the molecule using basic or neutral conditions. The best option for this purpose would be using a glycosidation, also developed by Schmidt, that relies on basic conditions.[67] In a series of papers, Schmidt showed that anomeric hydroxyl group could be alkylated using NaH as base and alkylating reagents having good leaving groups like triflates or iodides. Using such conditions he successfully alkylated the anomeric hydroxyl group of tetraacetylglucose **2.110** with pentnyl-triflate **2.111** to produce the glycoside **2.112** in acceptable yield.

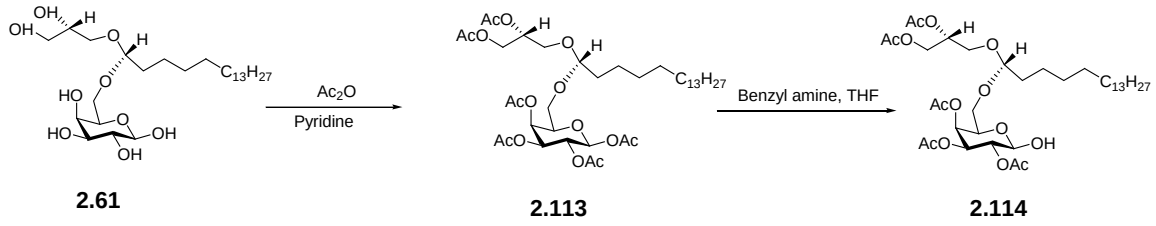



**2.110** **2.112**

**Scheme 2.30: Schmidt Glycosidation Method Under Basic Conditions.**

Though in such reactions, there is no preference for either α or β anomers, it is definitely a method worth of trying for our system.

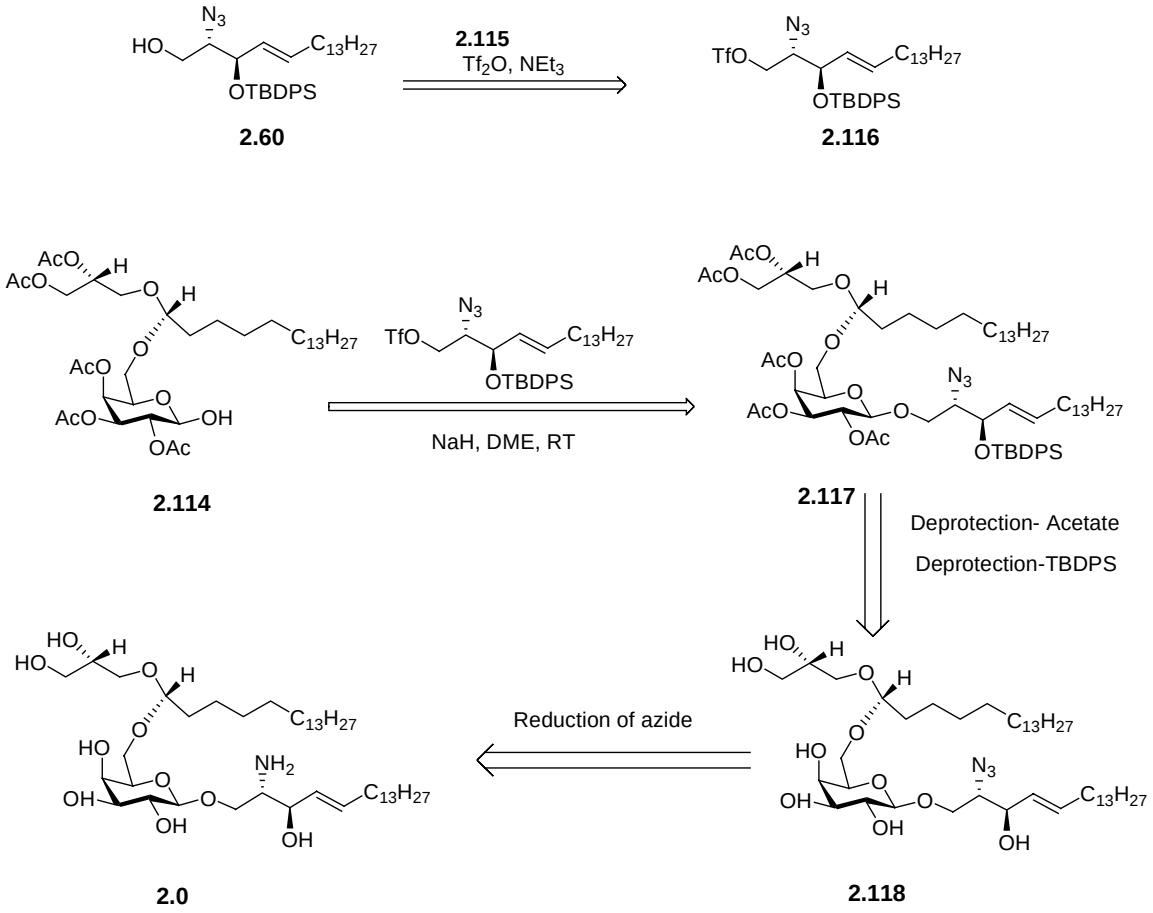
On that context, possible next step after debenzylation and reduction of double bond (**scheme 2.21**) would be the acetylation of crude product **2.61** to give the peracetylated compound **2.113**. Regioselective deprotection of the anomiric acetate should produce the hemiacetal **2.114** to be used for glycosidation.




**Scheme 2.31: Synthesis of Sugar Coupling Partner 2.114 for Schmidt Glycosidation**

The alkylating partner would be the sphingosine triflate **2.116** prepared from the sphingosine derivative **2.60** in one step.

Reaction between the two coupling partners **2.114** and **2.116** under basic conditions will hopefully produce the desired glycoside **2.117**. Even if it produces some amount of α-glycoside, we believe, that can be separated from the β-glycoside by silica gel chromatography. The rest of the synthesis would be the deprotection of existing protecting groups and reduction of azide to furnish the target **2.20**.




**Scheme 2.32: Completion of Synthesis-1**

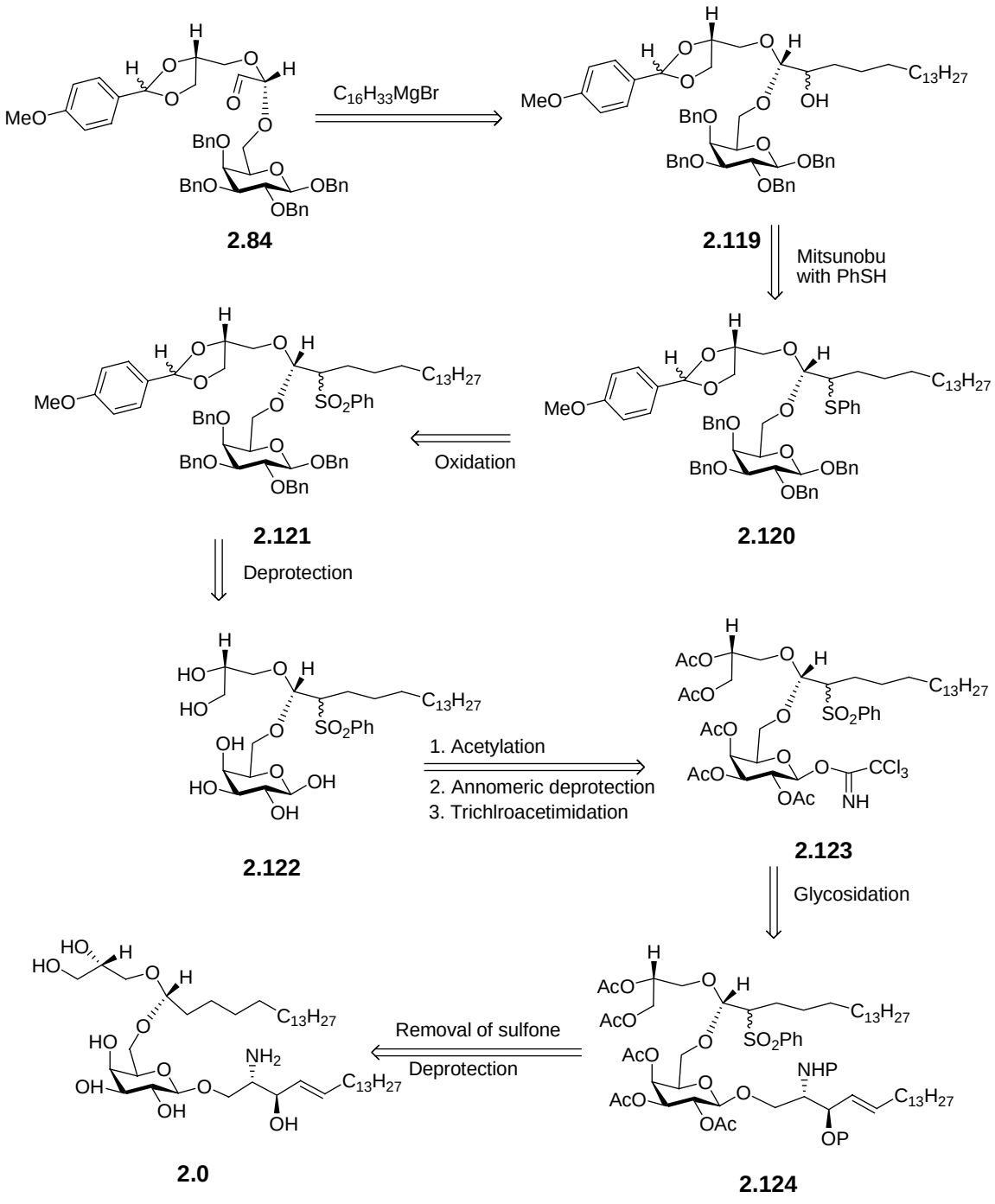
## (ii) Alternate strategy for the completion of synthesis:

The second possible way to complete the synthesis is based on stabilizing the acetal linkage toward conventional glycosidation conditions. We have previously seen in **Scheme 2.7** that a bromide α to the acetal linkage increases its stability many times. This is evident from the acidic cleavage of isopropylidine group of **2.50** without cleaving the acetal linkage.

As described earlier, this can be explained in terms of electron withdrawing nature of the α-bromide, which makes the acetal linkage stable to the acidic reaction conditions.

Our second idea basically involves the introduction of an electron withdrawing group (sulfone) α to the acetal linkage and then to attach the sphingosine side chain using normal lewis acid catalyzed glycosidation methodology, followed by removal of sulfone.

The second synthetic plan would start from the aldehyde **2.84**. Grignard reaction between the aldehyde **2.84** and long chain Grignard reagent would produce the alcohol **2.119**, which will complete the aliphatic chain. The alcohol **2.119** can be easily converted to the sulfide **2.120** by condensation with PhSH using Mitsunobu conditions. Conversion of sulfide **2.120** to the sulfone **2.121** should make the molecule very stable with respect to the acetal center. The rest of the chemistry would rely on the protecting influence of the sulfone group on the acetal linkage. Global deprotection of the protecting groups and acetylation would produce the peracetylated product **2.122**. Normal trichloroacetimidate chemistry would hopefully lead to the donor **2.123** to be used for the glycosidation with




**Scheme 2.33: Completion of Synthesis-2**

the sphingosine side chain. Lewis acid catalyzed glycosidation between **2.123** and sphingisine side chain should preferentially produce the β-glycoside **2.124**. Deprotection of the existing protecting groups and removal of the sulfone using Raney-nickel should complete the synthesis.

## 2.9 Conclusion

Total synthesis of Glyceroplasmalopsychosine indeed is a challenge due to it's unstable mixed acetal center. In our synthetic study we presented two ways of synthesizing the mixed acetal system of the natural product-one involved the non-stereospcecific synthesis and the other exploited the classical way of converting carbohydrate to non-carbohydrate asymmetric molecules. The non-stereospecific synthesis is attractive considering the number of steps required to construct the mixed acetetal center. Although we could not separate the two stereoisomers by conventional silica-gel column chromatography, it may be possible to separate them by using HPLC methods. If these isomers are separable, then the configuration of the acetal stereo center can be verified by comparing with the natural product. The synthesis of the target compound would not then be very difficult if we undertake the second approach (**Scheme 2.34**) to complete the synthesis. The α-Br would stabilize the acetal center (**Scheme 2.7**) and after glycosidation, debromination would complete the synthesis.

The stereospecific approach really shows the beauty of carbohydrate chemistry in utilizing the existing stereochemistry to synthesize complex asymmetric molecules. This approach enabled us to prepare the two isomers of mixed acetal of

glyceroplasmalopsychosine starting from two simple monosaccharides. We successfully used the existing stereocenters of lyxose unit to construct the required stereocenters of our target mixed acetal. The attractiveness of the second approach is somewhat reduced if one considers the number of steps involved in the synthesis and requirement of excessive protecting group manipulations. The identity of the acetal stereocenters of the natural product was not proved due to the inability of getting a pure sample of the globally deprotected mixed acetal **2.61** of established configuration for comparing with the natural product. More effort is needed to purify this compound, possibly by HPLC technique. At the same time we strongly believe that we have synthesized the two isomers of the mixed acetal of Glyceroplasmalopsychosine (minus the sphingosine aglycone) in pure form. We think that this synthetic work lays the foundation for a definitive study of Glyceroplasmalopsychosine.

# Experimental Procedure and Data

**Azido phytosphingosine 2.26**

A solution of $NaN_3$ (2.97 g, 45.75 mmol) in 7.5 mL of $H_2O$ was cooled in an ice-bath and treated with 12.5 mL of $CH_2Cl_2$. The resulting biphasic mixture was stirred vigorously and treated with $Tf_2O$ (2.61 g, 9.25 mmol) over a period of 5 min. The reaction was stirred at the ice bath temp: for 2hr, the organic phase separated and the aq phase was extracted twice with $CH_2Cl_2$. The total volume of the reagent solution is 25 mL. The organic phases were extracted once with sat. $NaHCO_3$ solution and was used without further purification. Phytosphingosine (1.5 g, 4.65 mmol) was dissolved in 15 ml of $H_2O$ and treated with $K_2CO_3$ (960 mg, 6.95 mmol) and $CuSO_4$ hydrate (7 mg). To this solution was added MeOH (30mL) and $TfN_3$ solution. Then, more MeOH was added to homogeneity. The solution was stirred for 18 h at room temp. The solvent was removed and the residue was subjected to silicagel chromatography using ethyl acetate as solvent to give the pure product as oil. $^1H$ NMR: (300 MHz, $CDCl_3$) δ 0.88 (t, 3H), 1.25 (s, H, $CH_2$), 1.56 (br, s, 4H), 3.68 (m, 1H), 3.80 (m, 1H), 3.87 (dd, 1H, J = 11.7 Hz, J = 4.4 Hz), 4.01 (dd, 1H, J = 11.7 Hz, 5.9 Hz). MS ($ES^+$): m/z: 366.5 (M+ Na).

**Di-tert-butyl silylene protected alcohol 2.27**

To a solution of azidosphingosine **2.26** (1.029 g, 3 mmol) in 12 mL of DMF at –20 $^{o}$C was added $^{t}$BuSi(OTf)$_2$ (3.3 mmol, 1.1 equiv,1.2 mL) drop wise over 15 minutes. The solution was stirred an additional 30 min; and pyridine (3.6 mmol, 1.2 equiv, 0.3 mL) was added and stirred 5 minutes. The solution was diluted to 60 mL of ether and was washed once with 15 ml of sat. $NaHCO_3$, twice with 15 mL of $H_2O$ and dried, filtered and concentrated. The residue was subjected to silica gel chromatography to give pure product as colorless oil. $^1$H NMR: (300 MHz, $CDCl_3$) δ 0.88 (t, 3H), 1.05 (s, 9H), 1.10 (s, 9H), 1.25 (s, H, $CH_2$), 1.50 (br, s, 4H), 3.5 (m, 1H), 3.75 (m, 1H), 3.95 (m, 2H), 4.25 (dd, 1H).

**Alkene 2.28**

To a solution of compound **2.27** (0.428g, 0.88 mmol) in DCE (5 mL) containing pyridine (0.2 mL) was added trifluromethane sulfonic anhydride (0.18 mL) and stirred overnight at ambient temperature. The solvent was concentrated in vacuo and the residue was taken up in diethyl ether (50 mL) and washed with aq 10% $NaHCO_3$ (50 mL). The organic phase was dried, filtered and concentrated. Column chromatography of the residue over silicagel with 10% P.E/EA gave the product as colorless oil. $^1$H NMR: (500 MHz, $CDCl_3$) δ 0.88 (t, 3H), 1.01 (s, 9H), 1.04 (s, 9H), 1.26 (s, 22H), 2.09 (m, 2H,), 3.30 (m, 1H), 3.80 (t, 1H, J = 11.0 Hz, 11.1 Hz), 4.10-4.28 (m, 2H), 5.51 (dd, 1H, J = 6.6 Hz, 15.4 Hz), 5.87 (ddd, 1H, J = 6.6 Hz, 6.5 Hz, 15.4 Hz). $^{13}$C: NMR (75 MHz, $CDCl_3$) δ 14.1,

20.0, 22.7, 27.0, 27.4, 28.9, 29.4, 29.7, 31.9, 32.3, 62.5, 66.4, 78.1, 129.1, 134.7. MS ($ES^+$): m/z: 488.5 (M+ Na).

**TBS protected 2-azidosphingosine 2.30**

Treating **2.28** with TBAF removed the silyl protection to produce the 2-azidosphingosine **2.29**. To a solution of **2.29** (334 mg, 1.03 mmol) and imidazole (210 mg, 3.08 mmol) in THF (5ml) was added TBSCl (230mg, 1.53 mmol) at 0°C. After standing at 0-4°C for 18h, the mixture was diluted with ether (50 mL) and washed with $H_2O$ (30mL). The aqueous layer was extracted with ether and the combined organic layer were washed with brine, dried and evaporated. Chromatography of the residue on silica gel in 10:1 P.E: ethyl ether gave **2.30**. $^1$H NMR: (300 MHz, $CDCl_3$) δ 5.08 (dt, 1H), 5.47 (dd, 1H), 4.21 (m, 1H), 3.80 (m, 2H), 3.42 (m, 1H), 2.32 (d, 1H), 2.07 (m, 2H), 1.3 (aliphatic chain), 0.9 (s, 9H), 0.1 (s, 6H).

**TBDPS protected Sphingosine side chain 2.32**

Compound **2.30** was silylated with TBDPSCl to produce **2.31.** To a solution of **2.31** (100 mg, 0.15 mmol) in 2 mL of MeOH was added CSA (~ 10 mg) at 0°C. After 6 h at 0°C, the reaction mixture was concentrated and the residue was subjected to chromatography on silica gel in 20: 1 P.E: Ethyl acetate to produce the desired compound 65 mg (77 %) as colorless oil. $^1$H NMR: (500 MHz, $CDCl_3$) δ 7.72-7.67 (m, 4H), 7.43-7.39 (m, 6H), 5.46 (m, 1H), 5.22-5.17 (m, 1H), 4.20 (dd, J = 8.3 Hz, 4.4 Hz, 1H), 3.62 (m, 1H), 3.57 (m,

1H), 3.51 (m, 1H), 1.83 (m, 2H), 1.29 (aliphatic chain), 1.1 (m, 9H), 0.91 (t, 3H). $^{13}C$: NMR (125 MHz, $CDCl_3$) δ 137.1, 136.6, 136.5, 136.3, 134.1, 133.8, 130.5, 130.2, 128. 3, 128.1, 128.0, 76.3, 69.2, 62.7, 32.7, 32.5, 30.3, 30.2, 30.0, 29.9, 29.7, 29.2, 27.5, 25.3, 19.8, 14.7.

## General Method for Esterification

Alcohol (1.5mmol), acid (1 mmol) and DMAP (1mmol) were dissolved in 5 mL of chloroform and then DCC (1mmol) in 3 mL of chloroform was added. After the solution was stirred at rt overnight, the urea was filtered and the filtrate was concentrated. The crude product was purified by column chromatography to afford the pure product.

## Hell-Volhard-Zelinskii reaction

A dry 3 necked flask fitted with a sealed mechanical stirrer, an addition funnel, and a reflux condenser capped with $CaCl_2$ drying tube, was charged with 7.1 g of stearic acid and 0.2 mL of $PBr_3$. the mixture was heated at 90-95 $^oC$ (bath temperature) and 1.5 mL of $Br_2$ (27.5 mL) was added in one portion with stirring. After stirring for 3 hours at 90-95 $^oC$, an additional 1.5 mL of dry $Br_2$ was added, and the heating and stirring was continued for an additional 7 hours. The dark reaction mixture was then cooled, dissolved in about 20 mL of $CCl_4$, and shaken vigorously with two portion of water. The organic solution was filtered through $Na_2SO_4$, and the solvent and bromine are removed by distillation at

steam-bath temperature and reduced pressure to afford the crude product. The bromo acid was used as such without further purification.

### General Procedure for the One-Pot DIBALH Reduction and Acetylation of an Ester:

To 25 mL flamed-dried, two-neck flask equipped with a low temperature thermometer and an $N_2$ inlet was added a solution of the starting ester (1.0 mmol) in dry $CH_2Cl_2$ (5 mL). After the mixture was cooled to – 78 $^oC$, DIBALH (1.0 M in toluene, 1.1 mL, 1.1 equiv) was added drop wise. After being stirred for 2 h the reaction mixture was treated with pyridine (237 mg, 0.24 mL, 3.0 mmol, 1.1 equiv), and then a solution of DMAP (134 mg, 1.1 mmol, 1.1 equiv) in dry $CH_2Cl_2$ (2 mL) was added slowly. Finally, $AC_2O$ (408 mg, 0.38 ml, 4.0 mmol, 4.0 equiv) was added drop wise. After 12 h, the mixture was warmed to – 20 $^oC$ and the reaction was quenched by adding saturated $NH_4Cl$ (5 mL) solution. The reaction mixture was stirred for 30 min, allowed to warm to room temperature, and then extracted with $CH_2Cl_2$. The combined $CH_2Cl_2$ extracts were washed with iced cold 1N $NaHSO_4$, saturated $NaHCO_3$ and brine. After drying and evaporation of $CH_2Cl_2$ extracts, the residue obtained was purified by flash chromatography on silica gel.

### General Method For coupling

Acetate (0.50 mmol) was dissolved in dry $CH_2Cl_2$ (5 mL) and Solketal or galactose derivative **2.24** (2 equiv) was added. After being cooled to – 78 $^oC$ (for α-bromo acetate

**2.49**, the temperature was maintained at –15 $^{o}$C), the reaction mixture was treated with $BF_3.Et_2O$ (85 mg, 71μL, 0.6 mmol, 1.2 equiv). After being stirred for 1 h, the reaction was quenched by adding 1N NaOH (5 mL) at –78 $^{o}$C. The mixture was warmed to room temperature and extracted with $CH_2Cl_2$. The combined organic extracts were washed with 1N NaOH, brine and dried over anhydrous $Na_2SO_4$. Evaporation of solvent followed by chromatography gave the desired product.

**Mixed Acetal 2.38**

$^{1}$H NMR: (500 MHz, $CDCl_3$) δ 5.54 (d, J = 5.0 Hz, 1H), 4.61 (m, 1H), 4.32 (m, 1H), 4.28 (m, 2H), 4.08 (m, 1H), 3.95 (m, 1H), 3.76 (m, 1H), 3.71-3.58 (m, 4H), 3.49 (m, 1H), 1.62 (m, 1H), 1.55 (s, 3H), 1.44 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H), 1.30 (s, 6H), 1.25 (aliphatic chain), 0.9 (t, 3H). $^{13}$C: NMR (75 MHz, $CDCl_3$) δ 110.0, 109. 8, 109.7, 109.0, 104.2, 104.1, 104.0, 97.0, 75.3, 71.7, 71.6, 71.5, 71.2, 71.1, 67.7, 67.6, 67.5, 67.2, 67.1, 66.2, 33.7, 33.6, 32.5, 30.3, 30.2, 30.1, 30.0, 29.9, 27.3, 26.6, 26.5, 26.0, 25.5, 25.2, 25.0, 23.3, 14.7.

**Mixed Acetal 2.42**

$^{1}$H NMR: (500 MHz, $CDCl_3$) δ 5.54 (m, 1H), 4.62-4.58 (m, 2H), 4.33-4.31 (m, 2H), 3.95 (m, 1H), 3.82 (m, 1H), 3.75 (m, 1H), 3.65 -3.56 (m, 4H). $^{13}$C: NMR (75 MHz, $CDCl_3$) δ 109.7, 109.6, 109.0, 104.7, 104.5, 96.9, 73.4, 71.7, 71.5, 71.2, 68.3, 68.0, 67.8, 67.2, 65.8,

65.6, 64.6, 34.0, 32.5, 30.3, 30.2, 29.9, 26.7, 26.5, 26.4, 25.5, 25.4, 25.2, 25.0, 23.2, 19.0, 18.7, 1.7, -4.1, -4.8.

**Sugar Ester Bromide 2.56**

$^{1}$H NMR: (500 MHz, $CDCl_3$) δ 5.54 (m, 1H), 4.64 (dd, J = 7.9 Hz, 2.4 Hz, 1H), 4.42 (m, 1H), 4.34 (m, 1H), 4.30-4.25 (m, 3H), 4.06 (m, 1H), 2.07 (m, 1H), 1.99 (m, 1H), 1.53 (s, 3H), 1.51 (s, 3H), 1.47 (s, 6H), 1.35 -1.26 (aliphatic chain), 0.9 (t, 3H). $^{13}$C: NMR (125 MHz, $CDCl_3$) δ 170.4, 110.2, 109.4, 96.8, 71.6, 71.5, 71.2, 71.0, 70.9, 66.5, 66.2, 65.3, 65.0, 46.5, 46.3, 32.5, 30.3, 30.2, 30.1, 30.0, 29.9, 29.4, 27.8, 26.6, 26.5, 25.5, 25.0, 23.3, 14.7.

**Sugar Bromo acetate 2.57**

$^{1}$H NMR: (500 MHz, $CDCl_3$) δ 5.9 (m, 1H), 5.52 (d, J = 2.5 Hz, 1H), 4.61 (m, 1H), 4.32 (m, 1H), 4.26-4.20 (m, 1H), 4.1-3.76 (m, 4H), 2.15 and 2.14 (2 s for 2 acetates), 1.96 (m, 1H), 1.8 (m, 1H), 1.56 (s, 3H), 1.45 (s, 3H), 1.33 (s, 6H), 1.27 (m, aliphatic chain), 0.89 (t, 3H); $^{13}$C: NMR (75 MHz, $CDCl_3$) δ 171.0, 109.7, 109.5, 108.8, 108.8, 98.6, 97.7, 96.5, 71.4, 71.0, 70.9, 70.8, 69.8, 68.8, 68.0, 66.1, 55.1, 54.8.

**Mixed Acetal 2.58**

$^{1}$H NMR: (500 MHz, $CDCl_3$) δ 5.5 (m, 1H), 4.72-4.60 (m, 2H), 4.32-4.26 (m, 3H), 4.07 (m, 3H), 3.98 (m, 3H), 3.76-3.55 (m, 2H), 1.96 (m, 1H), 1.75 (m, 1H), 1.57-1.26 (m, 46 H), 0.88 (t, 3H); $^{13}$C: NMR (125 MHz, $CDCl_3$) δ 109.63, 109.18, 109.12, 105.78, 105.55, 105.37, 105.28, 105.100, 96.82, 74.97, 74.91, 71.61, 71.58, 71.15, 71.09, 68.32, 67.92, 67.88, 67.83, 67.76, 67.60, 67.49, 67.42, 56.35, 56.20, 33.88, 32.48, 30.26, 30.22, 30.05, 29.92, 29.61, 27.00, 27.93, 27.82, 27.35, 26.61, 26.53, 25.96, 25.91, 25.50, 24.93, 23.25, 14.69.

**Sugar Diol 2.59**

$^{1}$H NMR: (500 MHz, $CDCl_3$) δ 5.52 (m, 1H), 4.62 (m, 2H), 4.32 (m, 1H), 4.25 (m, 1H), 4.1-3.97 (m, 2H), 3.89 (m, 1H), 3.85-3.80 (m, 1H), 3.76-3.67 (m, 4H), 2.94-2.82 (m, 1H), 2.32-2.16 (m, 1H), 1.95 (m, 1H), 1.75 (m, 1H, 1.60 (s, 3H), 1.34 (s, 6H), 1.26 (m, 28 H), 0.88 (t, 3 H). ESI calculated 680/682, found 698.3.

**Cyclized Product 2.60**

A solution of diol (100 mg, 0.147 mmol) and $Bu_2SnO$ (43 mg, 0.176 mmol) in Toluene (3 mL) was heated under reflux for 2 h in presence of molecular sieve. To this solution was added CsF (66 mg) and few crystals of TBAI. The reaction mixture was heated under reflux with azeotropic removal of water for overnight after which the solvent was

removal under reduced pressure. The crude residue was subjected to silica gel chromatography to afford the pure product (40 mg). $^{1}$H NMR: (500 MHz, $CDCl_3$) δ 5.54 (m, 1H), 4.61 (m, 1H), 4.44 (m, 1H), 4.3 (m, 2H), 4.04 (m, 1H), 3.88 (m, 3H), 3.76-3.68 (m, 1H), 3.63 (m, 3H), 3.56.3.48 (m, 1H), 1.95 (m, 1H), 1.8 (m, 1H), 1.53 (s, 3H), 1.45 (s, 3H), 1.33 (s, 6H), 1.26 (m, 28H), 0.89 (t, 3H).

**1,2,3,4-Tetra-O-acetyl-β-D-lyxopyranose 2.66**

To a solution of D-lyxopyranose **2.68** (0.3 g, 2 mmol) and DMAP (244mg, 2 mmol) in 10 mL of EtOAc was added $Ac_2O$ (3.2 mL) and the suspension was stirred at room temperature for 1 hour. After 1 h the solution became clear. The solvent was then evaporated and the unreacted acetic anhydride was removed under high vacuum. The residue was subjected to column chromatography (petroleum ether: ethyl acetate 3:2) to give 445 mg (70%) product as colorless oil. $^{1}$H NMR: (500 MHz, $CDCl_3$) δ 6.02 (d, J = 2.8 Hz, 1H), 5.39 (t, J = 3.3 Hz, 1H), 5.23 (dd, J = 6.5 Hz, 3.0 Hz, 1H), 5.04 (ddd, J = 5.3 Hz, 3.3 Hz, 1H), 4.20 (dd, J = 12.4 Hz, 1 H), 3.61 (dd, 1H), 2.13, 2.11, 2.10, 2.09 (four acetates). $^{13}$C: NMR (125 MHz, $CDCl_3$) δ 89. 6, 67.6, 67.5, 66.2, 61.2, 20.8, 20.7, 20.6, 20.5. ESI MS (calcd for $C_{13}H_{18}O_9$ 318) *m/z*: 336 ($M + NH_4^+$).

**2,3,4-Tri-O-acetyl-D-lyxose 2.70**

Peracetylated β-D-lyxose **2.69** (0.73 g, 2.31 mmol) in THF (6 mL) was treated with benzylamine (0.38 mL, 3.47 mmol) for 20 h. The reaction was diluted with chloroform

(80 mL) and washed with cold 0.2 M hydrochloric acid (150 mL), saturated solution of sodium hydrogencarbonate (150 mL) and water (150 mL). The organic layer was dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (eluent: 50 to 60% gradient of ethyl acetate in petroleum ether) of the residue affored the hemiacetal **2.70** as a syrup. $^1$H NMR: (500 MHz, $CDCl_3$) δ 5.38 (dd, J = 8 Hz, 3 Hz, 1H), 5.17 (dd, J = 3 Hz, 3 Hz, 1H), 5.08 (m, 2H), 3.88 (m, 2H), 2.11, 2.06, 2.0 (3 acetates). $^{13}$C: NMR (125 MHz, $CDCl_3$) δ 170.4 (2 acetates carbonyl), 169.9, 92.4, 70.0, 68.3, 67.3, 60.6, 20.8 (2), 20.7.

**2,3,4-Tri-O-acetyl-α-D-lyxopyranoside trichloroacetimidate 2.66**

To a solution of **2.70** (1.93 g, 6.99 mmol), and trichloacetonitrile (2.8 ml, 28 mmol, 4 eq) with 4 molecular sieves (0.5 g) in methylene chloride (20 ml)**,** 1, 8-diazabicyclo 0.1[5,4,0] undec-7-ene (0.105 ml; 0.70 mmol, 0.1 eq) was added. The reaction was complete after 2 h. Concentration in vacuo and purification by column chromatography yielded 2.66 (2.42 g, 82%) as a viscous oil. $^1$H NMR: (500 MHz, $CDCl_3$) δ 8.76 (s, 1H), 6.18 (d, J = 2.6 Hz, 1H), 5.46 (dd, J = 3.4 Hz, 2.6 Hz), 5.42 (dd, J = 9.6 Hz, 3.4 Hz), 5.29 (ddd, J=9.9, 9.6, 5.4 Hz, 1H), 4.07 (dd, J = 11.3 Hz, 5.4 Hz), 3.81 (dd, J = 11.3 Hz, 9.9 Hz, 1H), 2.17, 2.08, 2.04 (3 acetates).

**1-O-benzyl-β-D-galactopyranoside 2.72**

To a stirred solution of β-D galactose pentaacetate **2.71** (7.8 g, 20 mmol), flame-dried 4A$^{o}$ molecular sieves (3.5 g) and benzyl alcohol (4.3 g, 40 mmol) in DCM was added $BF_3.Et_2O$ (2.52 mL) at –78 $^{o}$C. The reaction mixture was slowly allowed to warm up to the room temperature. The reaction mixture was stirred for 12 h at ambient temperature, diluted with DCM, and washed with $NaHCO_3$. The aqueous layer was extracted with DCM, and the combined organic phases were washed with brine and dried over $Na_2SO_4$. After filtration and concentration in vacuo, the crude product was purified by flash silica gel chromatography (2:3 EtOAc-petroleum ether) to afford 6.6 g (75%) of product as white oil. $^1$H NMR: (500 MHz, $CDCl_3$) δ 7.45-7.20 (m, 5H), 5.39 (dd, J = 3.6 Hz, 1.3 Hz, 1H), 5.28 (dd, J = 10.6 Hz, 7.9 Hz, 1H), 4.99 (dd, J = 10.6 Hz, 3.6 Hz, 1H), 4.92 (d, J = 12.7 Hz, 1H), 4.64 (d, J = 12.7 Hz, 1H), 4.52 (d, J = 7.9 Hz, 1H), 4.22 (dd, J = 11.2 Hz, J = 6.6 Hz, 1H), 4.15 (dd, J = 11.2 Hz, 6.6 Hz, 1H), 3.89 (dt, J = 6.6 Hz, 1.3 Hz, 1H), 2.16 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H), 1.98 (s, 3H).

**1-O-benzyl-β-D-galactopyranoside 2.73**

A solution of the above galactopyranoside **2.72** (3.52 g, 8.05 mmol) in dry MeOH (90 mL) was treated with NaOMe (0.15 mL, concentrated solution in methanol). The reaction mixture was stirred for 2 h, then neutralized with 1 N HCl. Removal of the solvent afforded the crude product which was used for the next step without further purification.

**1,2,3,4-O-tetrabenzyl-6-*O*-triisopropylsilyl--β-D-galactopyranoside: 2.75**

To a stirred solution of **2.73** (2.27 g, 8.4 mmol) in dry DMF (60 mL) at 0 $^{o}$C, was added imidazole (0.63 g, 9.24 mmol) and triisopropylchlorosilane (1.94 g, 10.08 mmol). After 14 h, the reaction was quenched by the addition of water (80 mL). The aqueous layer was extracted with brine, dried over $Na_2SO_4$, filtered, and concentrated in vacuo. Purification by silica gel chromatography (EtOAc) afforded 1-O-benzyl-6-O-triisopropylsilyl-β-galactopyranoside **2.74** as a white oil. Compound **2.74** (1.8 g, 4.22 mmol) was dissolved in DMF (22 mL). The reaction mixture was cooled to 0 $^{o}$C. NaH (0.33 g, 13.92 mmol) was added after which the reaction mixture was allowed to attain the room temperature. Stirring was continued for 1 h at room temperature. The reaction mixture was again cooled to 0$^{o}$C to which 2 mL of BnBr and catalytic amount of TBAI were added. After 12 h, the reaction was quenched by addition of solid $NH_4Cl$, diluted with water, and the reaction mixture was extracted with water and brine, dried over sodium sulfate, and evaporated. The residue was subjected to column chromatography (petroleum ether: ethyl acetate 15:1) to give the product **2.75** (2.23 g, 76 % yield). $^{1}$H NMR: (500 MHz, $CDCl_3$) δ 7.41-7.28 (m, 20H), 5.03-4.97 (m, 3H), 4.82 (d, J = 10.4 Hz, 2H), 4.76-4.78 (m, 3H), 4.50 (d, J = 7.7 Hz, 1H), 3.94 (m, 2H), 3.88 (m, 1H), 3.83-3.79 (m, 1H), 3.56 (dd, J = 9.8 Hz, J = 2.7 Hz, 1H), 3.42 (m, 1H), 0.55 (m, 21 H). $^{13}$C: NMR (125 MHz, $CDCl_3$) δ 139.0, 138.7, 137.8, 128.4, 128.4, 128.2, 128.0, 127.9, 127.6, 127.5, 102.9, 82.5, 79.9, 75.7, 75.3, 74.8, 74.0, 73.3, 70.9, 62.6, 18.3, 12.2.

**1,2,3,4-tetra-O-benzyl-β-D-galactopyranoside 2.67**

To a stirred solution of **2.75** (1.1 g, 1.57 mmol) in 20 mL of dry THF was added TBAF (2.2 mL, 2.2 mmol, 1 M in THF). After 1.5 h, the reaction was quenched by the addition of saturated $NaHCO_3$ (50 mL), and the aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic phases were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated in vacuo. Purification by flash silica gel chromatography (1:1 ethyl acetate: petroleum ether) afforded 780 mg (92%) of product as white solid. $^1H$ NMR: (500 MHz, $CDCl_3$) δ 7.37-7.24 (m, 20H), 4.97-4.92 (m, 3H), 4.81-4.71 (m, 3H), 4.66 (d, J = 12 Hz, 2H), 4.47 (d, J = 7.5, 1H), 3.90 (dd. J = 9.5 Hz, J = 8.0 Hz, 1H), 3.75 (m, 2H), 3.52 (m, 2H), 3.36 (m, 1H), 1.45 (m, 1H); $^{13}C$: NMR (125 MHz, $CDCl_3$) δ 138.7, 139.4, 138.3, 137.6, 128.4, 128.3, 128.2, 128.0, 127.8 (2), 127.6, 127.5, 127.4, 103.1, 82.4, 79.7, 75.2, 74.8, 74.3, 73.4, 73.3, 71.2, 62.0. ESI MS (calcd for $C_{34}H_{36}O_6$ 540) *m/z*: 558.6 ($M + NH_4^+$).

**1,2,3,4-tetra-O-benzyl-6-O-(2,3,4-tri-O-acetyl-α-D-lyxopyranosyl)-β-D-galactopyranoside:2.76**

2,3,4-Tri-O-acetyl-D-lyxopyranosyl trichloroacetimidate **2.66** (0.56 g, 1.35 mmol) and 1,2,3,4-tetra-O-benzyl-β-D-galactopyranoside **2.67** (0.69 g, 1.3 mmol) were dried together under high vacuum for 2 h. To the flask containing the donor, acceptor and some $4A^o$ molecular sieves, 15 mL anhydrous DCM was added and the resulting mixture was

stirred for 1 h. TMSOTf (5 μL, 0.02 mmol) was added dropwise at – 25 $^{o}$C with $N_2$ protection. The reaction mixture was stirred for 3 h, during which time the temperature was gradually warmed to ambient temperature. Then the mixture was neutralized with $Et_3N$ and filtered, concentrated to dryness to afford the crude disaccharide, which was subjected to silica gel chromatography (1:5 ethyl acetate: petroleum ether) to yield 716 mg product **2.76** as white solid. $^{1}$H NMR: (500 MHz, $CDCl_3$) δ 7.43-7.34 (m, 20 H), 5.38 (dd, J = 9.8 Hz, 3.4 Hz, 1H), 5.25 (m, 1H), 5.20 (m, 1H), 5.0 (m, 3H), 4.89-4.80 (m, 3H), 4.7 (dd, J = 18.1 Hz, 12.0 Hz, 2H), 4.55 (d, J = 9.7 Hz, 1H), 4.53 (d, J = 1.8 Hz, 1H), 3.99-3.89 (m, 3H), 3.87 (d, J = 2.5 Hz, 1H), 3.76 (m, 1H), 3.62 (dd, J = 9.7 Hz, 2.8 Hz), 3.58 (m, 1H), 3.40 (dd, J = 9.5 Hz, 5.6 Hz, 1H), 2.18 (s, 3H), 2.07 (s, 3H), 1.99 (s, 3H); $^{13}$C: NMR (125 MHz, $CDCl_3$) δ 169.9 (2), 169.8, 138.8, 138.6, 138.5, 137.6, 129.1, 128.6, 128.5 (2), 128.4, 128.3, 128.2, 128.0, 127.7, 127.6, 102.8, 97.4, 82.6, 79.7, 75.4, 74.6, 73.8, 73.7, 73.3, 71.1, 69.7, 68.8, 67.1, 66.9, 60.0, 21, 20.9 (2). ESI calculated 798, found 816.3 ($M+NH_4^+$).

**1,2,3,4-tetra-O-benzyl-6-O- (α-D-lyxopyranosyl)-β-D-galactopyranoside: 2.77**

To a stirred solution of **2.76** (1.15 g, 1.44 mmol) in 90 mL of anhyd methanol was added 1.2 mL of 0.5 M $NaOCH_3$ solution. The reaction mixture was stirred for 12 h, then neutralized with 1 N HCl. Removal of the solvent afforded the crude product which was purified by flash column chromatography (EtOAc) to give the pure product **2.77** (908 mg 94% yield) as white solid. $^{1}$H NMR: (500 MHz, $CDCl_3$) δ 7.37-7.25 (m, 20H), 4.95 (m, 3H), 4.82-4.72 (m, 3H), 4.65 (t, J = 11.5, 2H), 4.46 (m, 2H), 3.91 (t, J = 9 Hz, 1H), 3.82-

3.80 (m, 3H), 3.73 (m, 2H), 3.64 (bs, 1H), 3.54 (m, 3H), 3.49-3.46 (m, 1H), 2.45 (d, J = 5 Hz, 1H), 2.13 (d, J = 3.5 Hz, 1H), 2.07 (d, J = 3.5 Hz, 1H); $^{13}$C: NMR (125 MHz, $CDCl_3$) δ 138.8, 138.6, 137.6, 128.6, 128.5, 128.4, 128.2, 128.0, 127.8, 127.7, 103.0, 100.2, 82.6, 79.8, 75.4, 74.5, 73.7, 73.2, 72.0, 71.2, 70.5, 68.0, 66.7, 63.1; ESI calculated 672, found 690.3 ($M+NH_4^+$).

**1,2,3,4-tetra-O-benzyl-6-O-(2,3-O-isopropylidine-α-D-lyxopyranosyl)-β-D-galactopyranoside: 2.78**

To a stirred suspension of **2.77** (1 g, 1.48 mmol) in 15 mL of acetone was added 4.5 mL of di-methoxypropane and 50 mg of p-toluenesulfonic acid. After 12 h, at room temperature 60 mL of 1:1 hexane-diethyl ether was added, and the solution was washed once with aqueous sodium bicarbonate solution and twice with water and concentrated in vacuo. The resulting material was chromatographed (1:1 ethyl acetate: petroleum ether) over silica gel to yield colourless oil (1.02 g, 97%). $^1$H NMR: (500 MHz, $CDCl_3$) δ 7.43-7.33 (m, 20H), 5.04-4.9 (m, 3H), .4.86-4.69 (m, 5H), 4.63 (d, J = 2.4 Hz, 1H), 4.5 (d, 7.7, 1H), 4.25 (m, 1H), 4.03 (m, 2H), 3.97 (dd, J = 9.7 Hz, 7.7 Hz, 1H), 3.90 (dd, J = 11.5 Hz, 3.7 Hz, 1H), 3.86-3.82 (m, 2H), 3.78 (dd, J = 11.3 Hz, 4.6 Hz, 1H), 3.57 (dd, J = 9.8 Hz, 2.8 Hz, 1H), 3.54 (m, 1H), 3.44 (dd, J = 9.5 Hz, 6.0 Hz, 1H), 3.18 (d, J = 8.4 Hz, 1H), 1.54 (s, 3H), 1.41 (s, 3H); $^{13}$C: NMR (125 MHz, $CDCl_3$) δ 138.8, 138.6, 138.5, 137.8, 129.1, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.8, 127.7, 127.6, 109.6, 102.9, 98.7, 82.5, 79.8, 76.1, 75.4, 74.5, 74.3, 73.6, 73.3, 71.1, 67.5, 67.2, 63.5, 27.6, 25.7; ESI calculated 712, found 730.3 ($M+NH_4^+$).

**1,2,3,4-tetra-O-benzyl-6-O-(2,3-O-isopropylidine-4-O-PMB-α-D-lyxopyranosyl)-β-D-galactopyranoside: 2.79**

Compound **2.78** (1.0 g, 1.4 mmol) was azeotroped with toluene (3 x 10 mL), dried under vacuum for 1 h, and dissolved in DMF (8 mL). The solution was cooled to 0 $^{o}$C, sodium hydride (112 mg, 2.8 mmol, 60% dispersion in mineral oil) was added, and the reaction mixture was stirred for 1 h. After addition of PMBCl (0.43 g, 2.8 mmol), the solution was warmed to room temperature and stirred for 12 h. the reaction was quenched by the dropwise addition of water. The aqueous layer was extracted with Ethyl acetate, and the combined organic phases were washed with brine and dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. Purification by flash silica gel chromatography (1:4 EtOAc-petroleum ether) afforded the pure product **2.79** (1.09 g, 94%). $^{1}$H NMR: (500 MHz, $CDCl_3$) δ 7.43-5.32 (m, 22H), 6.9 (m, 2H), 5.04-4.99 (m, 3H), 4.87-4.60 (m, 8H), 4.53 (d, J = 7.7 Hz, 1H), 4.23 (t, J = 5.7 Hz, 1H), 3.98 (dd. J = 9.7 Hz, 7.7 Hz, 1H), 3.94-3.91 (m, 2H), 3.89 (dd, J = 8.0 Hz, 4.3 Hz, 1H), 3.8 (s, 3H), 3.66-3.58 (m, 4H), 3.56-3.50 (m, 2H), 1.56 (s, 3H), 1.48 (s, 3H); $^{13}$C: NMR (125 MHz, $CDCl_3$) δ 159.5, 138.9, 138.7, 137.8, 130.5, 129.5, 128.6, 128.5, 128.4, 128.3, 128.0, 127.8, 127.7, 127.6, 114.0, 109.3, 103.0, 98.5, 82.7, 79.9, 75.5, 75.4, 74.5, 74.4, 73.6, 73.4, 73.2, 71.9, 71.1, 66.4, 59.7, 55.5, 28.3, 26.6. ESI calculated 832.97, found 850.4 ($M+NH_4^+$).

**1,2,3,4-tetra-O-benzyl-6-O-(4-O-PMB-α-D-lyxopyranosyl)-β-D-galactopyranoside: 2.80**

A solution of 2.79 (1.1 g, 1.32 mmol) in AcOH-$H_2O$ (10:1, 20 mL) was heated to 60$^oC$ for 1.5 hours. The reaction was cooled to room temperature and then concentrated to give a white solid, which was purified by silica gel chromatography (3:2 EtOAc: Petroleum ether) to furnish the pure product 2.80 (940 mg, 90%) as white solid. $^1H$ NMR: (500 MHz, $CDCl_3$) δ 7.40-7.25, (m, 22 H), 6.88 (m, 2H), 5.01-4.97 (m, 3 H), 4.85-4.76 (m, 3H), 4.70 (d, J = 11.90 Hz, 1H), 4.66 (d, J = 12.1 Hz, 1H), 4.60-4.53 (m, 2H), 4.50 (m, 1H), 3.95 (dd, J = 9.7 Hz, 7.9 Hz, 1H), 3.87-3.82 (m, 2H), 3.69 (m, 1H), 3.57 (m, 2H), 3.47 (m, 2H), 2.58 (d, 1H), 2.39 (d, 1H); $^{13}C$: NMR (75 MHz, $CDCl_3$) δ 159.6, 138.9, 138.6, 137.7 130.3, 129.5, 128.6, 128.5, 128.4 (2), 128.3 (2), 128.1, 127.8, 127.7, 127.6, 114.2, 103.0, 99.7, 82.7, 79.9, 75.4, 75.2, 74.5, 73.7, 73.5, 73.3, 72.4, 71.1, 70.7, 70.4, 66.6, 61.1, 55.5. . ESI calculated 792.35, found 810.4 ($M+NH_4^+$).

## Preparation of Silica Gel-Supported $NaIO_4$ Reagent:

$NaIO_4$ (2.57 g, 12.0 mmol) was dissolved in 5 mL of hot water (~70 $^oC$) in 25 mL round-bottomed flask. To the hot solution was added silica gel (230-400 mesh, 10g) with vigorous swirling and shaking. The resultant silica gel coated with $NaIO_4$ was kept in a bottle for 1 month with negligible loss of activity.

## Procedure for Glycol Cleavage Oxidations.

To a vigorously stirred suspension of silica gel-supported reagent (2.0 g) in DCM (5 mL) in a 25 mL round-bottomed flask was added a solution of the vicinal diol (1 mmol) in DCM (5 mL). The reaction was monitored by TLC until disappearance of the starting material (generally 2-3 h). The mixture was filtered through a sintered glass funnel, and the silica gel was thoroughly washed with chloroform (3 x 10 mL). Removal of the solvent from the filtrate afforded the aldehyde that was pure enough for next step.

## $NaBH_4$ Reduction

The resulting aldehyde from the oxidative cleavage was dissolved in dry MeOH (5 mL/ mmol of aldehyde). To the cooled solution (0 $^oC$) of the aldehyde in MeOH, $NaBH_4$ (excess) was added and the reaction mixture was allowed to attain the room temperature slowly. The mixture was stirred for overnight, and was diluted with $H_2O$. The reaction mixture was extracted with chloroform and the organic layer was washed with water. The combined organic phases dried over $Na_2SO_4$, filtered and concentrated in vacuo. Purification by flash silica gel chromatography afforded the pure product.

**Diol 2.82 (Prepared from Oxidative Cleavage Followed by Reduction)**

The oxidative cleavage of **2.80** afforded the crude aldehyde **2.81**, which was immediately reduced with $NaBH_4$ to afford the diol **2.82**. (From 500 mg of 2.80: Yield -451 mg, 90%).

$^{1}$H NMR: (500 MHz, $CDCl_3$) δ 7.39-7.27 (m, 22H), 6.90 (m, 2H), 5.0-4.93 (m, 3H), 4.84-4.75 (m, 3H), 4.66 (d, J = 11.9 Hz, 2H), 4.59 (m, 2H), 4.52 (d, J = 7.7 Hz, 1H), 4.49 (m, 1H), 3.94 (dd, J = 9.7 Hz, 7.7 Hz, 1H), 3.87 (dd, J = 9.8 Hz, 6.4 Hz, 1H), 3.81 (m, 6H), 3.66-3.62 (m, 3H), 3.55-3.45 (m, 5H); $^{13}$C: NMR (125 MHz, $CDCl_3$) δ 159.6, 138.8, 138.6, 137.7, 130.1, 129.6, 128.5, 128.4 (2), 128.3, 128.1, 127.8, 127.7, 127.6, 114.2, 103.2, 102.9, 83.9, 82.6, 82.2, 79.8, 77.8, 75.5, 74.6, 73.8, 73.6, 72.1, 71.4, 66.2, 66.1, 62.3, 62.1, 55.5. ESI calculated 794, found 812.4 ($M+NH_4^+$).

**p-methoxy benzylidine derivative 2.83**

Molecular sieves (3 g) were finely ground and suspended in dichloromethane (15 mL). Compound 2.82 (1.11 g, 1.4 mmol) in dichloromethane (15 mL) was added and the mixture was cooled to 0 $^{o}$C. DDQ (0.35g, 1.55 mmol) in THF (3mL) was added slowly. The mixture was stirred for 3 h and filtered over celite and concentrated under reduced pressure. The residue was chromatographed (3:2 ethyl acetate: petroleum ether) to give the product 2.83 (798 mg, 72%) as colorless oil. $^{1}$H NMR: (500 MHz, $CDCl_3$) δ 7.45-7.29 (m, 22H), 6.92 (m, 2H), 5.8 (s, 1H), 5.03-4.95 (m, 3H), 4.85-4.75 (m, 3H), 4.69 (d, J = 2.9 Hz, 1H), 4.65 (d, J = 3.6, 1H), 4.54-4.51 (m, 2H), 4.39 (m, 1H), 4.09 (m, 1H), 3.94 (m, 2H), 3.89 (m, 1H), 3.81 (m, 3H), 3.67 (dd, J = 10.4 Hz, 5.8 Hz, 1H), 3.57-3.52 (m, 4H), 3.46 (dd, J = 99.9 Hz, 5.6 Hz, 1H), 2.35 (t, 1H); $^{13}$C: NMR (125 MHz, $CDCl_3$) δ 161.1, 139.1, 139.0, 138.9, 138.0, 129.5, 129.3, 129.2, 129.0 (2), 128.9 (2), 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 114.4, 105.0, 104.3, 103.5, 82.8, 80.1, 75.9, 75.7, 74.8,

73.9, 73.8, 73.7, 71.7, 68.6, 68.0, 66.2, 66.1, 62.5, 55.8. ESI calculated 792.35, found 810.3 ($M+NH_4^+$).

## General Method for Dess-Martin Oxidation

Dess-martin periodinane (1.3 equiv) was added to a solution of alcohol in DCM (4 mL/0.2 mmol of alcohol) under nitrogen. Reaction stirred at room temperature for 1 h, to generate a milky suspension. When all starting material was gone, a 10% solution of sodium hydrosulfite in a solution of saturated aqueous $NaHCO_3$ was added slowly to suspensions and stirred until two separate layer formed. The aqueous layer was extracted with DCM (3 x 10 mL). The combined organic phases were dried over $NaSO_4$, filtered and concentrated to give the crude aldehyde as colourless oil, which was used for the next step without further purification.

## General Procedure for Heterogeneous Wittig Reaction

Alkylphosphonium salt (1.2 equiv) was grinded with anhydrous oven dried $K_2CO_3$ (1.2 equiv) and basic alumina. THF (10 mL/ mmol of aldehyde) was added to the flask followed by the solution of aldehyde in THF (10 mL/ mmol) and some crystals of crown-6 ether. The color of the mixture turned yellow immediately after the addition of the aldehyde, which was refluxed at 70$^o$C for 1-2 hours. After all the starting materials were gone, the reaction mixture was allowed to come to the room temperature. The solids were

filtered and washed with THF. The combined solvents were concentrated and the residue was subjected to chromatography to produce the pure product in good yield.

**Alkene 2.90**

The alkene **2.90** was prepared by heterogeneous Wittig reaction given above in 70 % yield calculated from the crude aldehyde **2.84**. (From 60 mg of aldehyde **2.84**: Yield-53 mg, 70%) as colorless oil. $^{1}$H NMR: (500 MHz, $CDCl_3$) δ 7.39-7.24 (m, 22H), 6.85 (m, 2H), 5.76 (s, 1H), 5.68 (m, 1H), 5.43 (m, 1H), 5.25 (m, 1H), 5.0-4.94 (m, 3H), 4.79-4.73 (m, 3H), 4.65 (m, 2H), 4.48 (m, 1H), 4.34 (m, 1H), 4.06 (m, 1H), 3.94-3.88 (m, 2H), 3.8 (m, 1H), 3.77 (s, 3H), 3.68 (m, 1H), 3.54 (m, 3H), 2.10 (m, 2H), 1.25 (aliphatic chain), 0.87 (t, 3H); $^{13}$C: NMR (125 MHz, $CDCl_3$) δ 161.1, 139.1, 138.7, 138.6, 137.8, 136.6, 128.9, 128.8, 128.7, 128.6, 128.4, 128.1, 128.0, 126.6, 114.3, 104.8, 103.4, 99.1, 82.8, 80.1, 75.8, 75.3, 75.1, 74.7, 73.6, 73.3, 71.1, 68.3, 68.1, 65.8, 65.2, 65.0, 55.5, 32.5, 30.3, 29.9, 29.6, 28.5, 23.0, 14.7. ESI calculated 998, found 1016.6 ($M+NH_4^+$).

**Wilkinson's Hydrogenation Product, mixed acetal 2.91**

To the solution of alkene 2.90 (20 mg, 0.015 mmol) in 1 mL of anhydrous benzene was added Wilkinson's catalyst (15 mg). The resulting mixture was stirred for overnight under an atmosphere of $H_2$ (balloon) after which the solution was evaporated to dryness in vacuo. The residue was purified by column chromatography (10: 1, PE: EtOAc) to afford the pure product (15 mg). $^{1}$H NMR: (500 MHz, $CDCl_3$) δ 7.37-7.28 (m, 22H), 6.89 (m, 2H), 5.77 (s, 1H), 5.02-4.94 (m, 3H), 4.81-4.73 (m, 3H), 4.67-4.62 (m, 2H), 4.51-

4.43 (m, 2H), 4.36 (t, 1H), 4.07 (m, 1H), 3.95-3.90 (m, 2H), 3.87 (m, 1H), 3.82-3.78 (m, 4H), 3.68-3.61 (m, 1H), 3.56-3.49 (m, 3H), 1.56 (m, 2H), 1.27 (aliphatic chain), 0.91 (t, 3H); $^{13}$C: NMR (125 MHz, $CDCl_3$) δ 161.1, 139.3, 139.1, 138.2, 128.9, 128.8, 128.7, 128.6, 128.4, 128.2, 128.1, 114.3, 104.9, 104.2, 103.5, 82.9, 80.2, 75.8, 75.3, 75.4, 74.9, 74.2, 74.1, 74.0, 73.9, 73.7, 71.5, 68.6, 68.4, 66.5, 65.8, 65.7, 55.8, 33.7, 32.5, 30.3, 30.2, 30.0, 29.9, 25.2, 23.3, 14.7. ESI calculated 1000, found 1018.5 ($M+NH_4^+$).

**1,2,3,4-tetra-O-benzyl-6-O-(2,3,4-tri-O-acetyl-β-L-lyxopyranosyl)-β-D-galactopyranoside:2.99.**

Following the procedure used for the synthesis of **2.76**, compound **2.99** was synthesized in 82 % yield. $^1$H NMR: (500 MHz, $CDCl_3$) δ 7.32-7.28 (m, 20H), 5.34 (m, 1H), 5.28 (m, 1H), 5.19 (m, 1H), 5.06 (d, J = 11.6 Hz, 1H), 4.98 (m, 2H), 4.86-4.77 (m, 4H), 4.67 (m, 2H), 4.51 (dd, J = 7.7 Hz, 1.8 Hz, 1H), 3.93 (m, 1H), 3.85-3.81 (m, 2H), 3.77 (m, 1H), 3.65 (dd, J = 10.9 Hz, 4.8Hz, 1H), 3.59-3.52 (m, 3H), 2.14, 2.09, 2.05 (3 acetates). $^{13}$C: NMR (125 MHz, $CDCl_3$) δ 170.6, 170.5 (2), 139.1, 139.0, 138.9, 138.0, 129.5, 129.0, 128.9, 128.8 (2), 128.5, 128.3, 128.2, 103.2, 98.8, 82.7, 80.0, 75.8, 74.9, 74.3, 74.2, 74.0, 71.5, 69.8, 69.0, 68.1, 67.4, 60.5, 21.4 (2).

**1,2,3,4-tetra-O-benzyl-6-O-(2,3-O-isopropylidine-β-L-lyxopyranosyl)-β-D-galactopyranoside: 2.101.**

The acetonide protection of 2.100 using DMP and p-TsOH produced 2.101 in 97% yield. (1 g of 2.100 yielded 1.02 g of 2.101, 97%) as colorless oil. $^{1}$H NMR: (500 MHz, $CDCl_3$) δ 7.37-7.29 (m, 20H), 5.06-4.97 (m, 3H), 4.84-4.76 (m, 4H), 4.72 (d, J = 4.8 Hz, 1H), 4.69 (d, J = 4.3 Hz, 1H), 4.52 (d, J = 7.7 Hz, 1H), 4.28 (m, 1H), 4.16 (dd, J = 6.1 Hz, 2.9 Hz, 1H), 3.95 (dd, J = 9.6 Hz, 7.8 Hz, 1H), 3.87-3.81 (m, 4H), 3.75 (dd, J = 10.9 Hz, 5 Hz, 1H), 3.69 (dd, J = 11.7 Hz, 4.9 Hz, 1H), 3.61-3.56 (m, 2H), 3.01 (d, 1H), 1.54 (s, 3H), 1.40 (s, 3H); $^{13}$C: NMR (125 MHz, $CDCl_3$) δ 139.2, 139.0, 138.9, 138.1, 129.6, 129.0, 128.9 (2), 128.8 (2), 128.6, 128.3, 128.2, 100.1, 103.3, 100.2, 82.7, 80.0, 76.7, 75.9, 75.0, 74.8, 74.1, 74.0, 73.8, 71.35, 68.9, 67.7, 64.0, 28.2, 26.1.

**Ketone 2.104**

The compound **2.104** was prepared by following the general method for Dess-Martin oxidation. The crude product was purified by silica gel chromatography to afford the product in 94 % yield. $^{1}$H NMR: (500 MHz, $CDCl_3$) δ 7.37-7.29 (m, 20H), 5.06 (d, J = 11.6 Hz, 1H), 4.99 (d, J = 11.0 Hz, 2H), 4.95 (d, J = 1.8 Hz, 1H), 4.86-4.76 (m, 3H), 4.69 (d, J = 12.0 Hz, 1H), 4.66 (d, J = 11.7 Hz, 1H), 4.51 (d, J = 7.7 Hz, 1H), 4.46-4.42 (m, 2H), 4.18 (d, J = 16.9 Hz, 1H), 4.01 (d, J = 16.8 Hz, 1H), 3.95 (dd, J = 9.7 Hz, 7.7 Hz, 1H), 3.82 (dd, J = 10.9 Hz, 7.1 Hz, 1H), 3.77 (d, J =2.5 Hz, 1H), 3.64 (dd, J = 10.9 Hz, 4.8 Hz, 1H), 3.58-3.53 (m, 2H), 1.54 (s, 3H), 1.41 (s, 3H); $^{13}$C: NMR (125 MHz, $CDCl_3$)

δ 204.0, 139.1, 138.9, 138.8, 138.0, 129.0, 128.9, 128.8, 128.5, 128.3, 128.2, 112.7, 103.2, 99.3, 82.8, 80.6, 80.0, 78.3, 76.0, 75.9, 74.7, 74.1, 74.0, 71.5, 68.8, 66.8, 27.3, 25.9.

**1,2,3,4-tetra-O-benzyl-6-O-(2,3-O-isopropylidine-β-D-ribopyranosyl)-β-D-galactopyranoside: 2.103.**

Compound **2.103** was prepared either by Mitsunobu protocol or two step-oxidation and reduction protocol. Reduction of **2.104** by excess $NaBH_4$ in methanol as described for the preparation of **2.82** produced the alcohol in quantitative yield. $^1$H NMR: (500 MHz, $CDCl_3$) δ 7.37-7.29 (m, 20 H), 5.01-4.95 (m, 3H), 4.81-4.78 (m, 3H), 4.72 (d, J = 4.1 Hz, 1H), 4.69 (d, J = 6 Hz, 1 H), 4.67 (d, J = 6.6 Hz, 1H), 4.49 (d, J = 7.7 Hz, 1H), 4.42 (dd, J = 6.2 Hz, 4.3 Hz, 1H), 4.02 (m, 1H), 3.92 (dd, J = 9.7 Hz, 7.7 Hz, 1H), 3.86 (d, J = 2.7 Hz, 1H), 3.82 (m, 1H), 3.78-3.75 (m, 2H), 3.60-3.53 (m, 3H), 1.56 (s, 3H), 1.41 (s, 3H); $^{13}$C: NMR (125 MHz, $CDCl_3$) δ 139.2, 139.0, 138.9, 138.1, 129.5, 129.0, 128.9, 128.8, 128.7, 128.5, 128.2, 128.1, 110.1, 103.3, 100.2, 82.8, 80.1, 76.5, 75.8, 75.0, 74.8, 74.1, 74.0, 73.9, 71.5, 68.9, 67.6, 64.0, 28.0, 26.1.

**1,2,3,4-tetra-O-benzyl-6-O-(2,3-O-isopropylidine-4-O-PMB--β-D-ribopyranosyl)-β-D-galactopyranoside:**

The PMB protection of the alcohol **2.103** was achieved by following the procedure used for the preparation of compound **2.79.** The yield was quantitative for this step**.** $^1$H NMR:

(500 MHz, $CDCl_3$) δ 7.37-7.29 (m, 22 H), 6.90 (m, 2H), 4.98-4.94 (m, 3H), 4.80-4.72 (m, 3H), 4.69-4.64 (m, 3H), 4.62 (d, J = 3.9 Hz, 1H), 4.50 (d, J = 5.4 Hz, 1H), 4.47 (m, 2H), 3.93-3.85 (m, 4H), 3.84 (m, 1H), 3.82 (s, 3H), 3.76-3.72 (m, 2H), 3.66-3.61 (m, 1H), 3.55-3.51 (m, 2H), 1.57 (s, 3H), 1.41 (s, 3H); $^{13}C$: NMR (125 MHz, $CDCl_3$) δ 161.0, 161.1, 139.2, 139.1, 139.0, 138.2, 130.3, 130.2, 129.2, 129.0, 128.9, 128.8, 128.7, 128.5, 128.2, 128.1, 128.0, 114.5, 111.1, 103.3, 102.2, 82.7, 80.1, 76.9, 75.8, 75.1, 75.1, 73.8 (2), 73.6, 72.0, 71.4, 71.0, 68.2, 62.0, 55.8, 28.2, 26.4.

**1,2,3,4-tetra-O-benzyl-6-O- (4-O-PMB-β-D-ribopyranosyl)-β-D-galactopyranoside**

The cleavage of isopropylidine group was performed following the method used for the synthesis of compound **2.80.** Quantitative yield**.** White solid**.** $^1H$ NMR: (500 MHz, $CDCl_3$) δ 7.40-7.28 (m, 22H), 6.90 (m, 2H), 5.03 (d, J = 11.6 Hz, 1H), 4.99 (d, J = 5.6 Hz, 1H), 4.97 (d, J = 4.4 Hz, 1H), 4.84-4.74 (m, 4H), 4.68 (d, J = 4.8 Hz, 1H), 4.66 (d, J = 4.3 Hz, 1H), 4.59 (m, 1H), 4.54-4.49 (m, 2H), 3.95-3.89 (m, 3H), 3.82 (s, 3H), 3.79-3.71 (m, 4H), 3.70-3.66 (m, 1H), 3.57-3.52 (m, 3H), 2.60 (d, J = 2.8 Hz, 1H), 2.55 (d, J = 2.6 Hz, 1H); $^{13}C$: NMR (125 MHz, $CDCl_3$) δ 161.1, 139.0, 138.9, 138.1, 130.6, 130.0, 129.0, 128.9, 128.8 (2), 128.5, 128.3, 128.2, 128.1, 114.5, 103.3, 100.9, 82.8, 80.1, 75.8, 75.4, 75.0, 74.3, 74.2, 73.9, 72.6, 71.5, 70.8, 70.7, 68.3, 61.6.

**Diol 2.107 (prepared from oxidative cleavage followed by reduction)**

The diol **2.107** was prepared by the same protocol used to synthesize compound **2.82**. 1.2 g of **2.106** produced 842 mg of product over two steps (90%). White solid. $^{1}$H NMR: (500 MHz, $CDCl_3$) δ 7.37-7.28 (m, 22H), 6.90 (m, 2H), 5.02-.94 (m, 2H), 4.8-4.73 (m, 3H), 4.67-4.63 (m, 3H), 4.57 (m, 2H), 4.50 (m, 1H), 3.92 (m, 1H), 3.81-3.74 (m, 5H), 3.68-3.52 (m, 9H), 2.63 (m, 1H), 2.20 (m, 1H); $^{13}$C: NMR (125 MHz, $CDCl_3$) δ 161.1, 139.1, 139.0, 138.9, 138.0, 130.4, 130.1, 129.0, 128.9, 128.8, 128.7, 128.5, 128.2, 128.1, 114.5, 104.6, 103.4, 82.7, 80.1, 78.1, 75.9, 74.9, 74.3, 74.2, 73.9, 72.3, 71.6, 67.9, 67.5, 63.6, 62.4, 55.8. ESI calculated 794, found 812.4 ($M+NH_4^+$).

**p-methoxybenzylidine derivative 2.108**

This compound was prepared following the protocol used for the synthesis of **2.83**. From 500 mg of **2.107**. Yield: 354 mg, 71%. Colorless oil. $^{1}$H NMR: (500 MHz, $CDCl_3$) δ 7.69-7.42 (m, 22H), 6.91 (m, 2H), 5.73 (s, 1H), 5.03-4.95 (m, 3H), 4.80 (m, 2H), 4.74 (d, J = 11.8 Hz, 1H), 4.68-4.64 (m, 3H), 4.49 (d, J = 7.7 Hz, 1H), 4.37 (m, 1H), 4.05 (m, 1H), 3.95-3.90 (m, 2H), 3.84-3.75 (m, 6H), 3.59 (dd, J=10.5, J=5.2, 1H), 3.56-3.43 (m, 5H), 2.16 (t, J =6.4 Hz, 1H); $^{13}$C: NMR (125 MHz, $CDCl_3$) δ 161.1, 139.1, 139.0, 138.0, 129.6, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 128.2, 128.1, 114.3, 104.9, 104.3, 103.4, 82.7, 80.1, 75.9, 75.6, 74.8, 74.3, 74.1, 73.9, 71.6, 68.4, 68.1, 68.0, 63.4, 55.8. ESI calculated 792.35, found 810.3 ($M+NH_4^+$).

**Alkene 2.93**

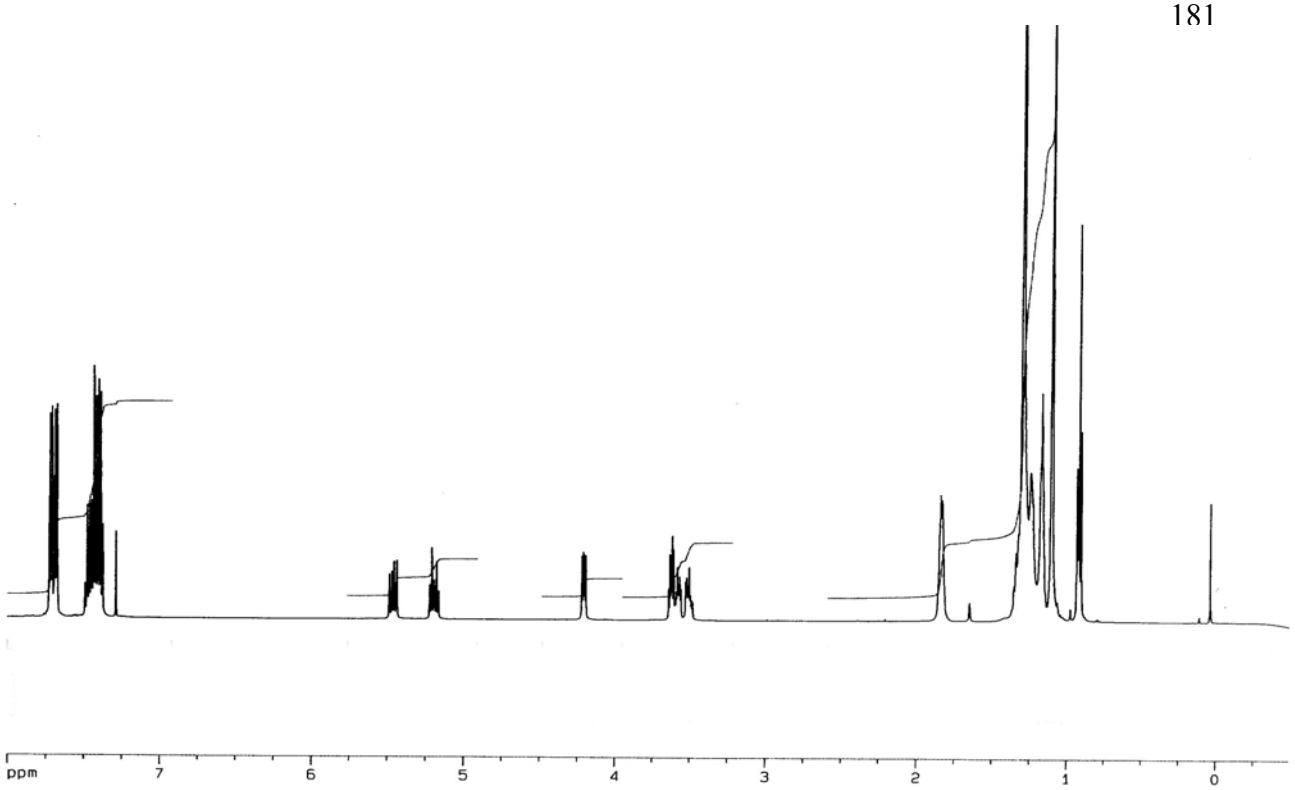
Heterogeneous Wittig protocol produced the alkene **2.93** in 65 % yield from the crude aldehyde **2.109**. (From 55 mg of the crude aldehyde **2.109**. Yield: 45 mg, 65%). Colorless oil. $^{1}$H NMR: (500 MHz, $CDCl_3$) δ 7.42-7.29 (m, 22H), 6.91-6.87 (m, 2H), 5.75 (s, 1H), 5.68 (m, 1H), 5.45 (m, 1H), 5.31 (d, J = 6.7 Hz, 1H), 5.01-4.94 (m, 3H), 4.80-4.64 (m, 5H), 4.48 (d, J = 7.5 Hz, 1H), .4.37 (m, 1H), 4.08 (m, 1H), 3.91 (m, 1H), 3.85-3.74 (m, 6H), 3.70 (m, 1H), 3.54-3.51 (m, 3H), 2.12 (m, 2H), 1.31 (aliphatic chain), 0.91 (t, 3H); $^{13}$C: NMR (125 MHz, $CDCl_3$) δ 161.1, 139.1, 138.2, 136.5, 128.9 (2), 126.6, 126.7, 128.4, 128.1, 126.6, 114.3, 104.8, 103.3, 99.2, 82.8, 80.1, 75.8, 75.5, 75.0, 74.3, 73.7, 71.4, 68.7, 66.7, 55.8, 32.5, 30.3, 29.9, 23.3, 14.7. ESI calculated 998, found 1016.6 ($M+NH_4^+$).

**Mixed acetal 2.92 (Wilkinson's hydrogenation Product)**

The hydrogenation of alkene by using Wilkinson's catalyst produced the desired mixed acetal 2.92.15 mg of the alkene 2.93 yielded 12 mg of the product. $^{1}$H NMR: (500 MHz, $CDCl_3$) δ 7.43-7.28 (m, 22H), 6.90 (m, 2H), 5.77 (s, 1H), 5.01-4.95 (m, 3H), 4.79 (d, J = 10.4 Hz, 2H), 4.74 (d, J = 11.9 Hz, 1H), 4.69-4.64 (m, 2H), 4.58 (m, 1H), 4.48 (m, 1H), 4.35 (t, 1H), 4.24 (m, 1H), 4.05 (m, 1H), 3.97-3.90 (m, 2H), 3.82-3.78 (m, 4H), 3.72 (m, 1H), 3.56-3.48 (m, 4H), 1.59 (m, 2H), 1.28 (aliphatic chain), 0.92 (t, 3H); $^{13}$C: NMR (125 MHz, $CDCl_3$) δ 161.1, 139.2, 139.0, 138.2, 131.4, 129.4, 128.9, 128.8, 128.7, 128.6, 128.5, 128.2, 128.1, 114.3, 104.8, 104.6, 103.3, 82.8, 80.1, 75.8, 75.6, 74.9, 74.4, 74.3,

73.8, 71.4, 68.7, 68.5, 67.1, 55.8, 32.5, 30.3, 30.2, 30.1, 30.0, 29.5, 25.3, 23.3, 14.7. ESI calculated 1000, found 1018.5 ($M+NH_4^+$).

# Appendix-2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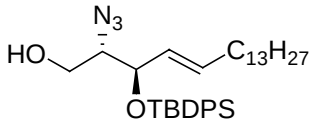
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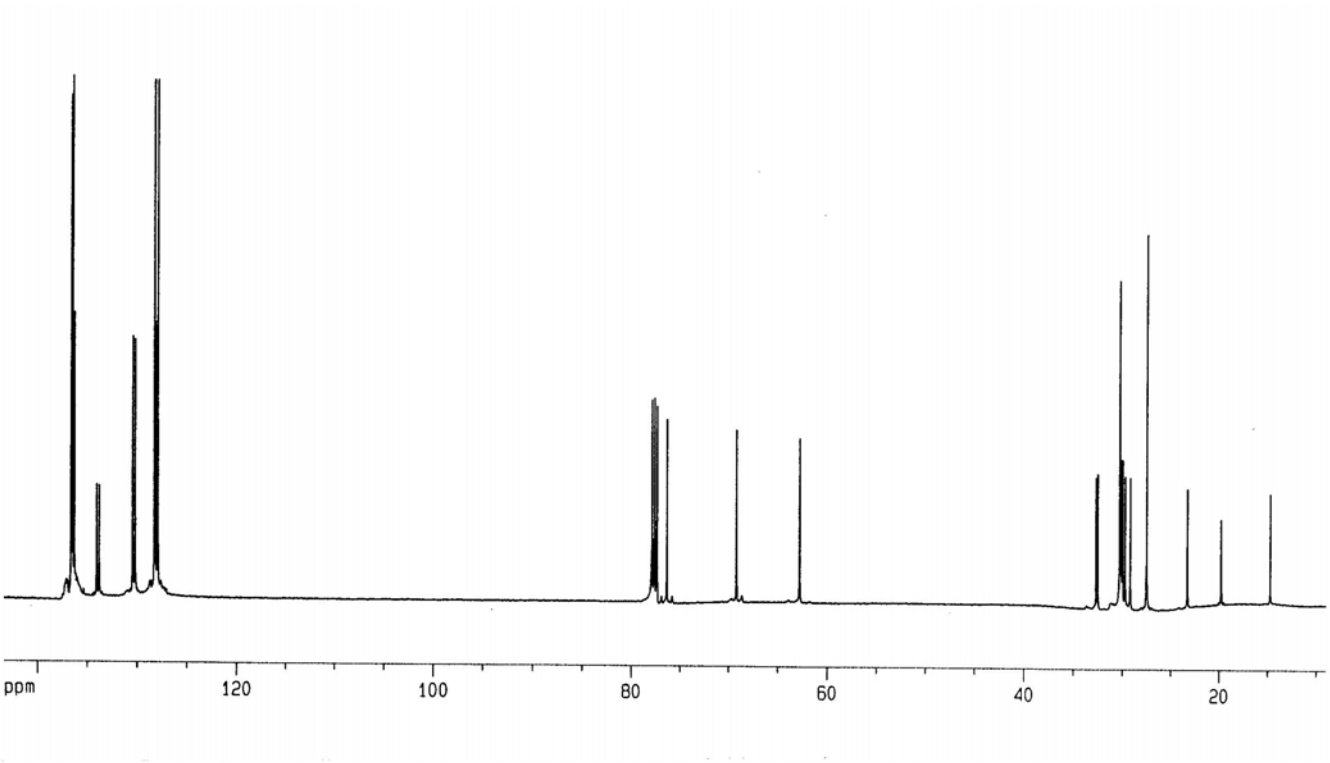
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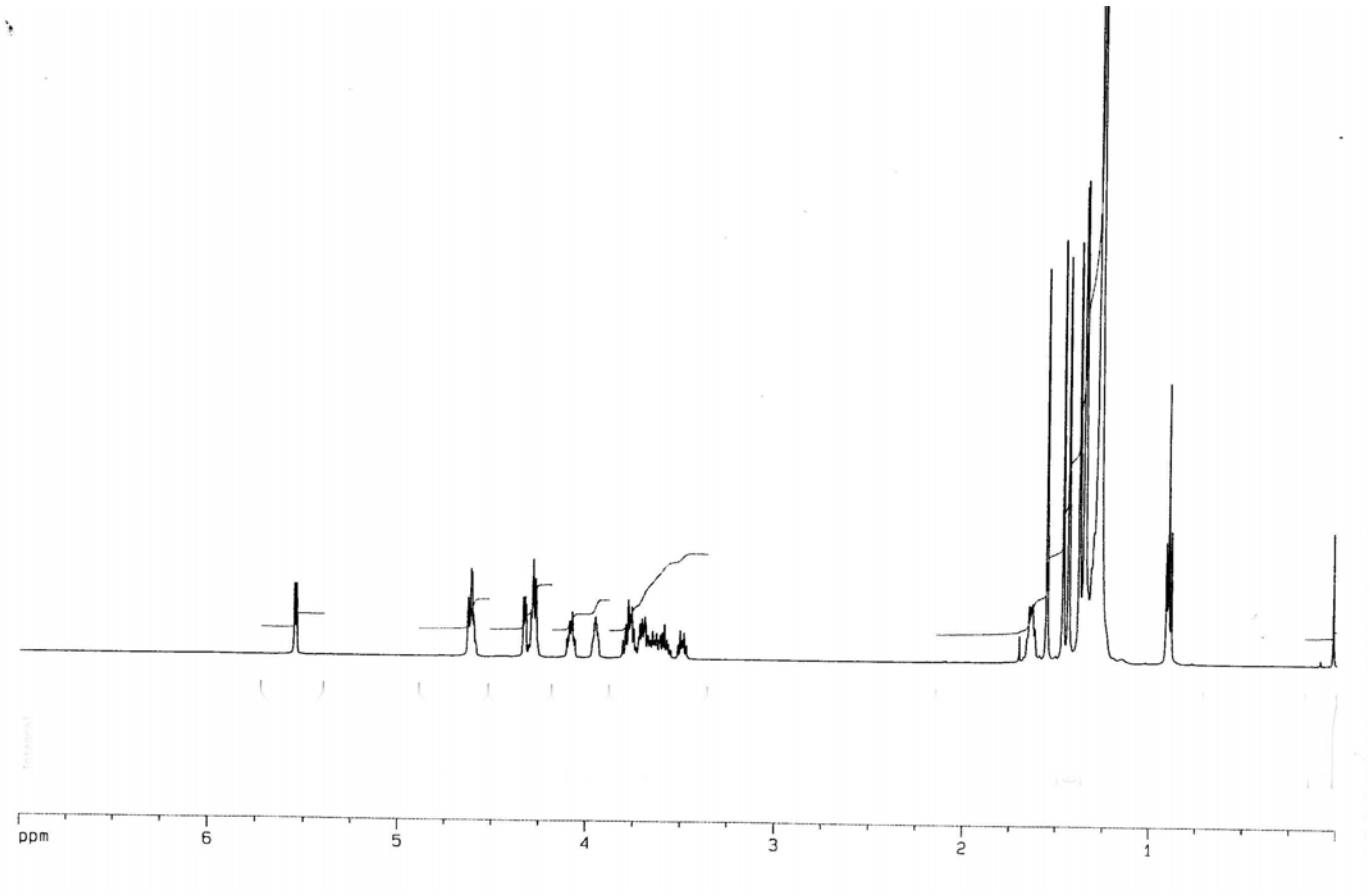
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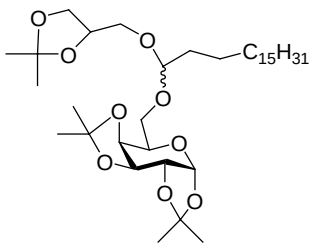
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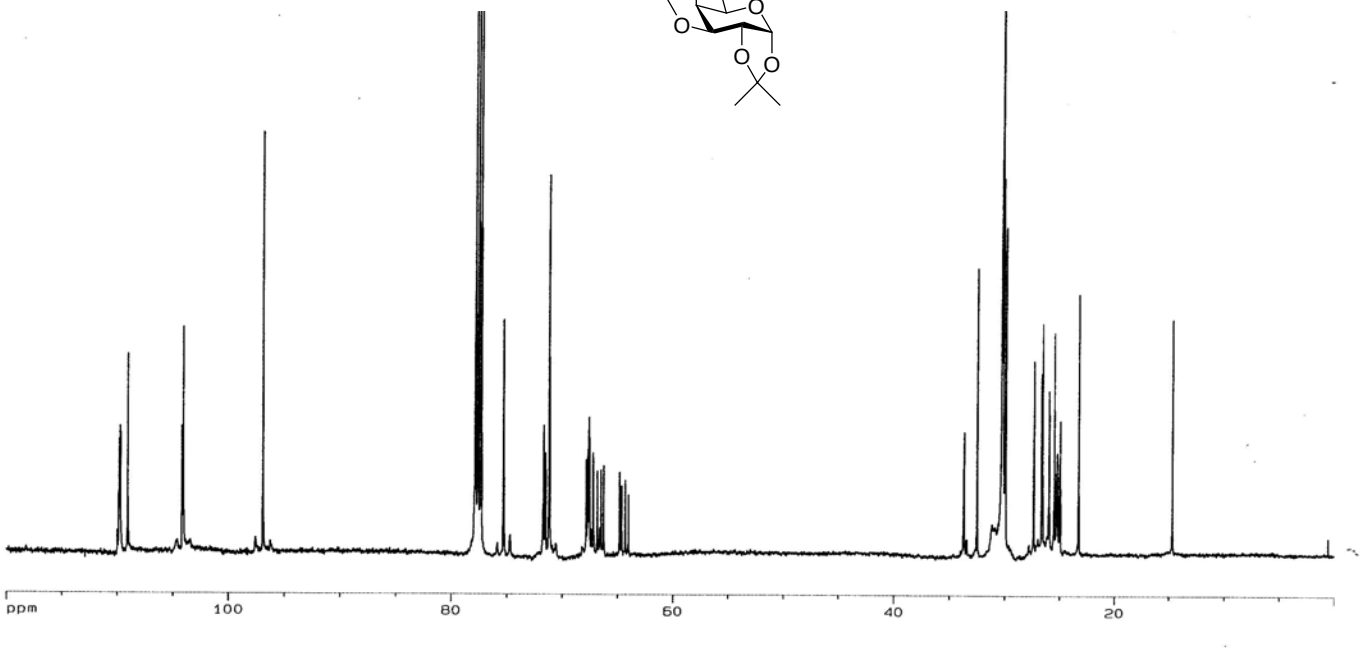
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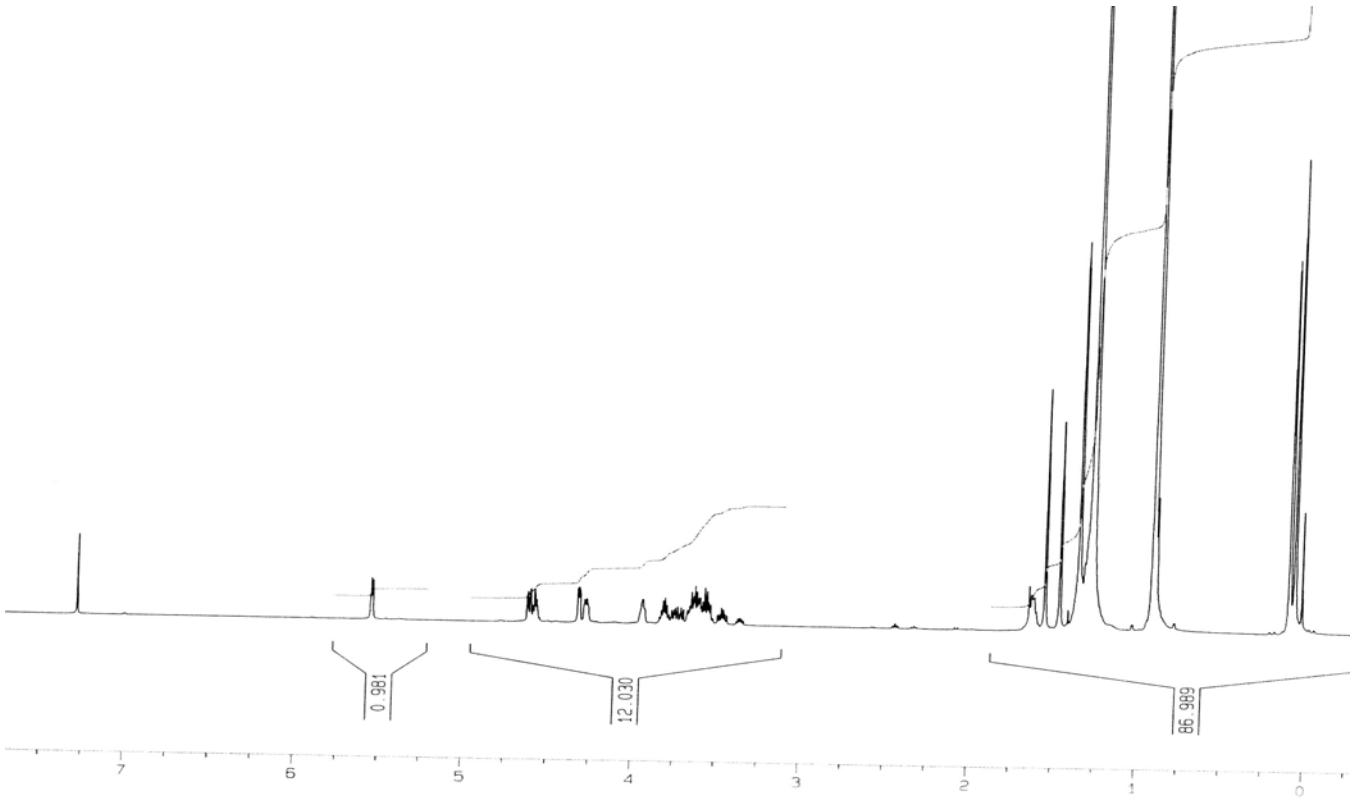
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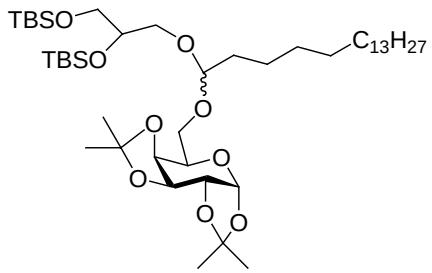
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O
O
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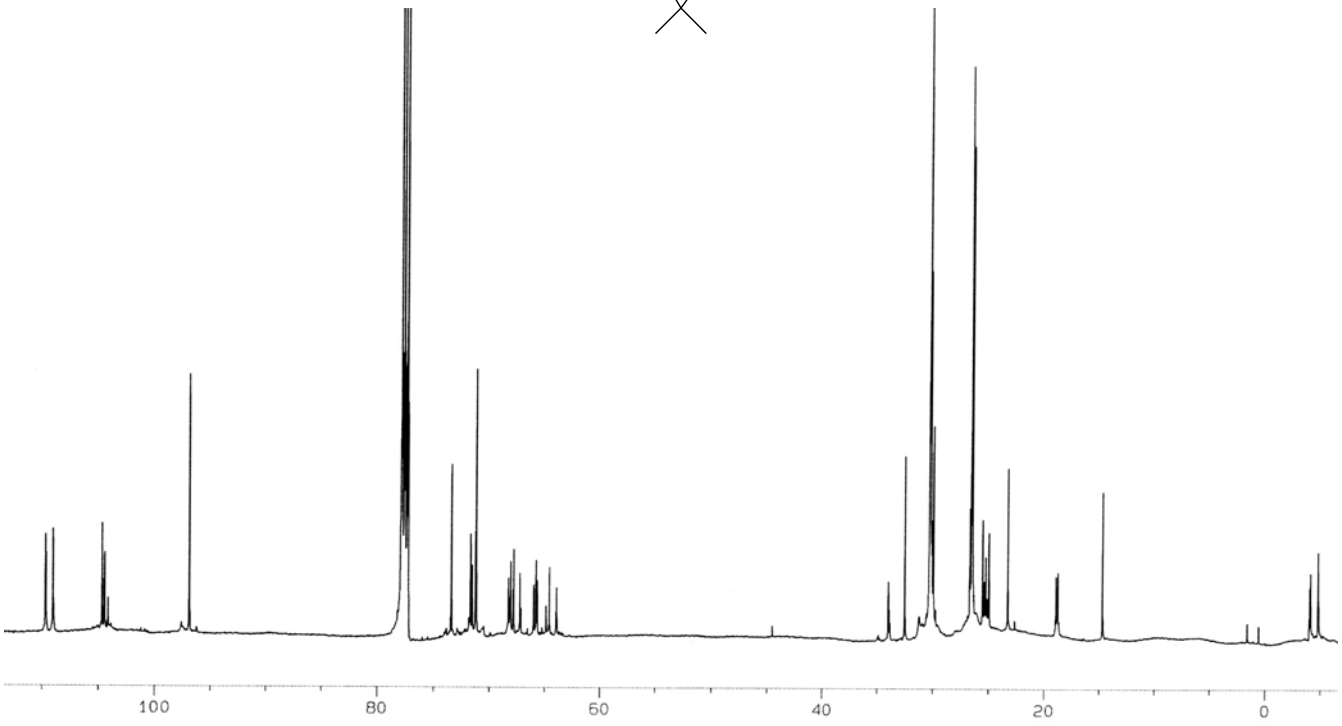
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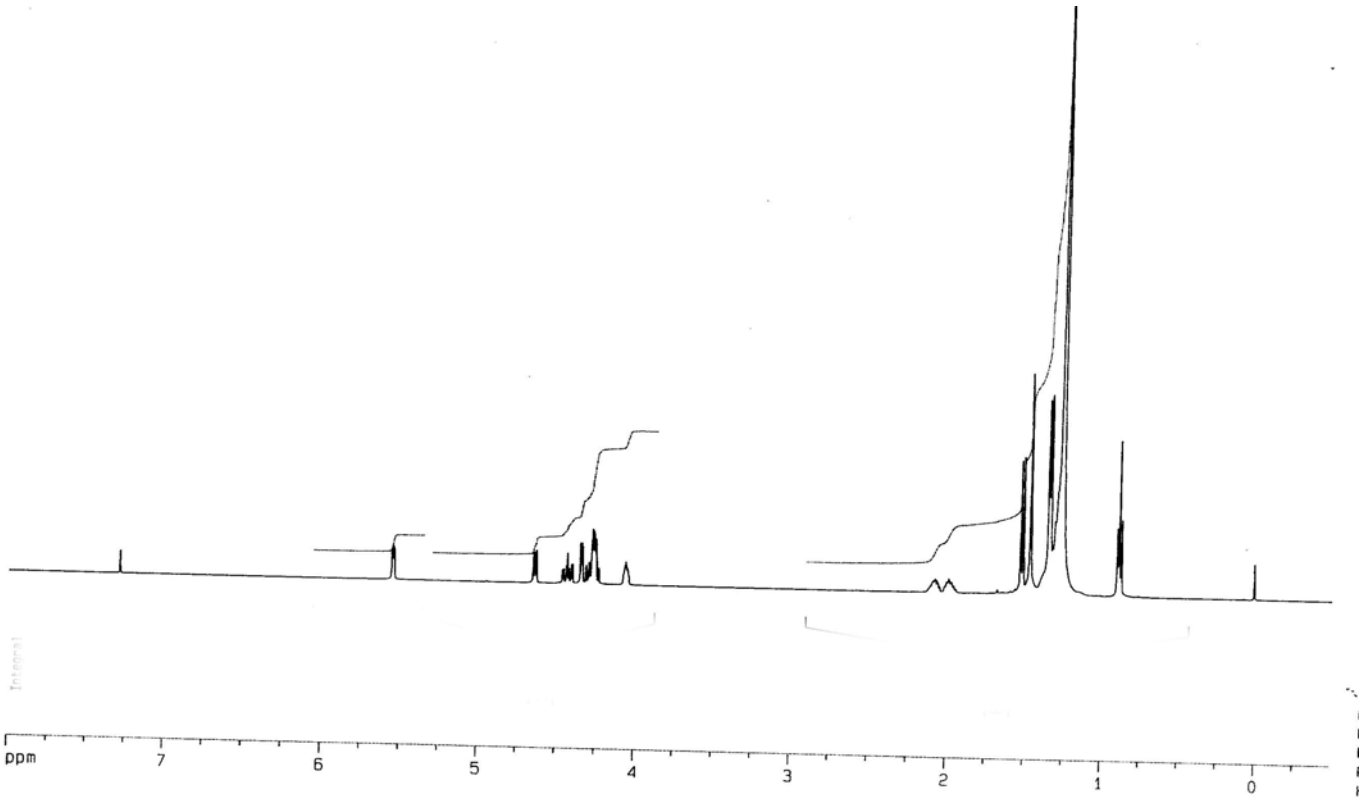
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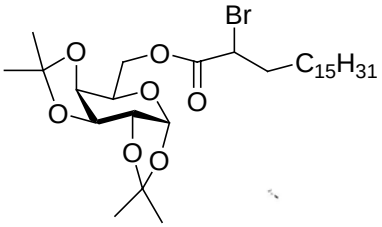
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O
O
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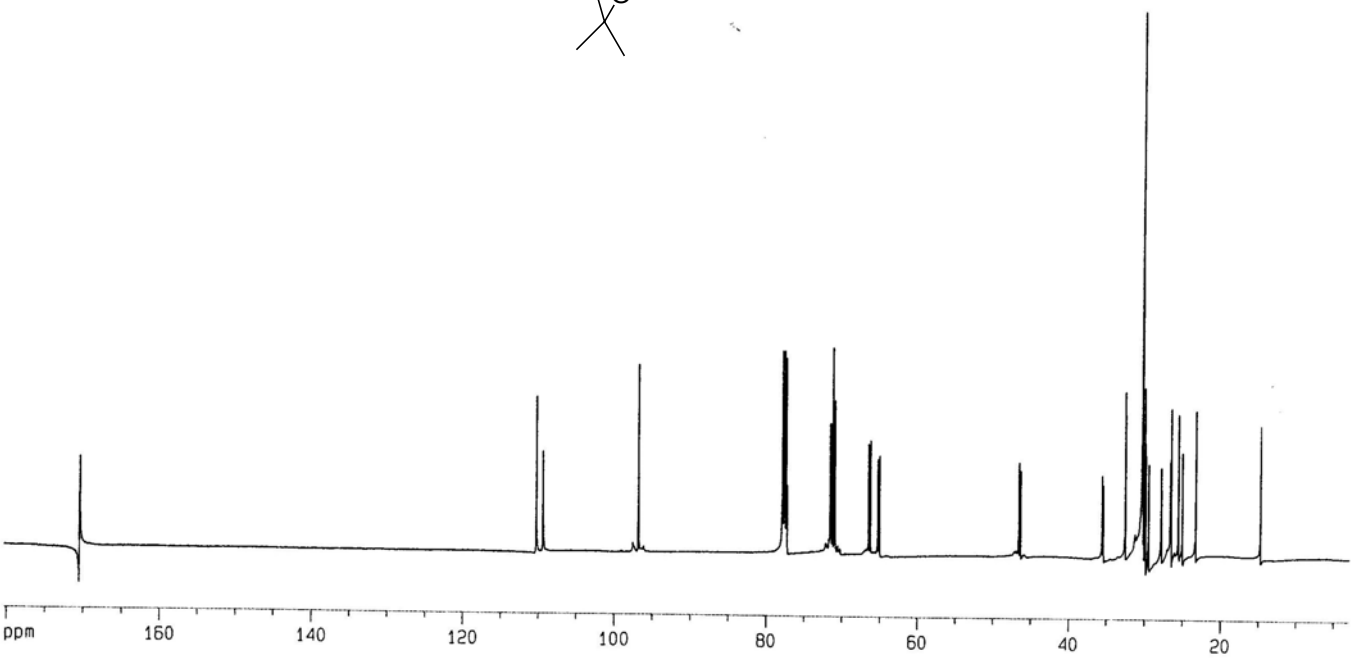
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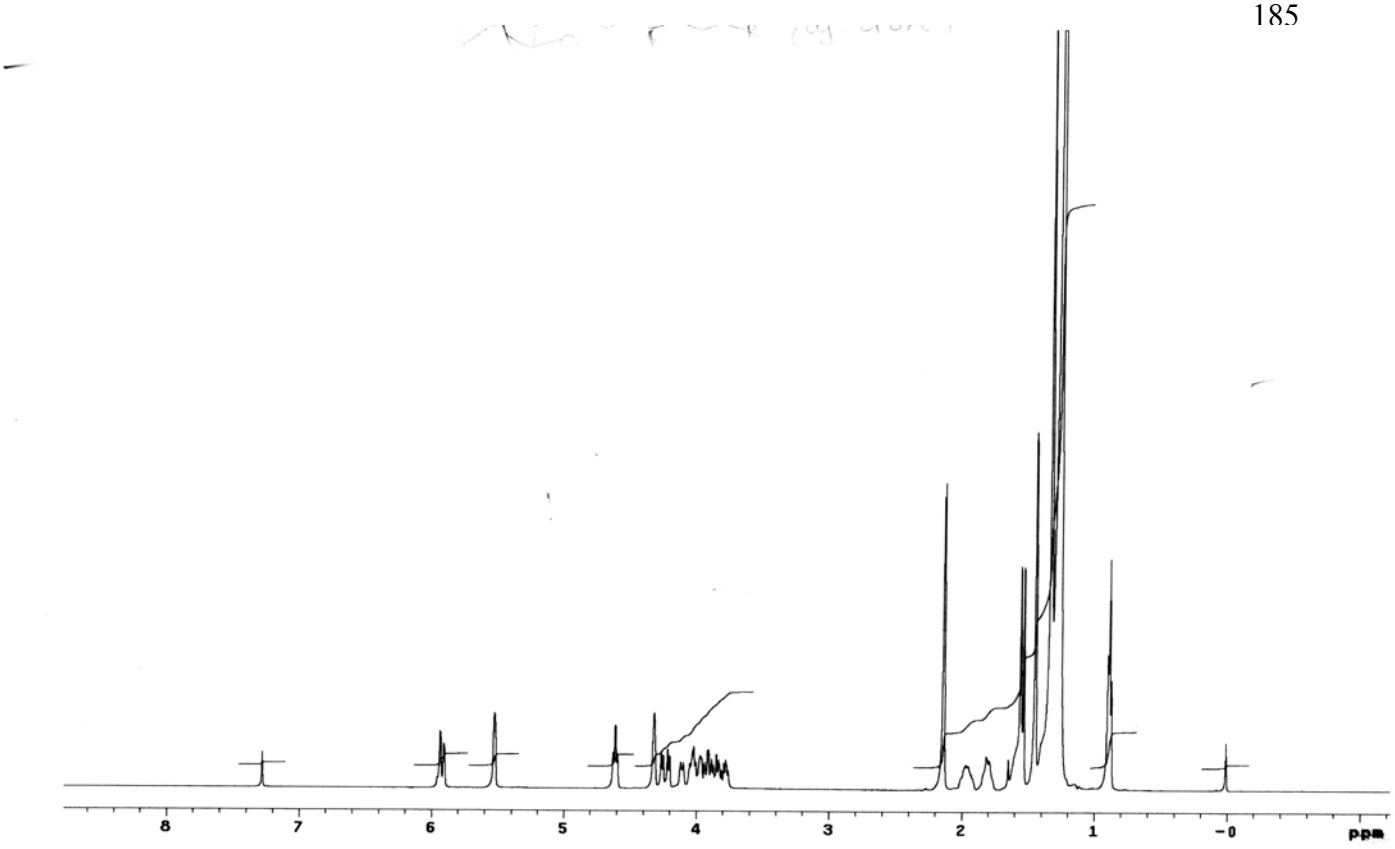
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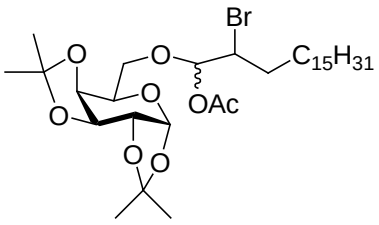
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O
OAc
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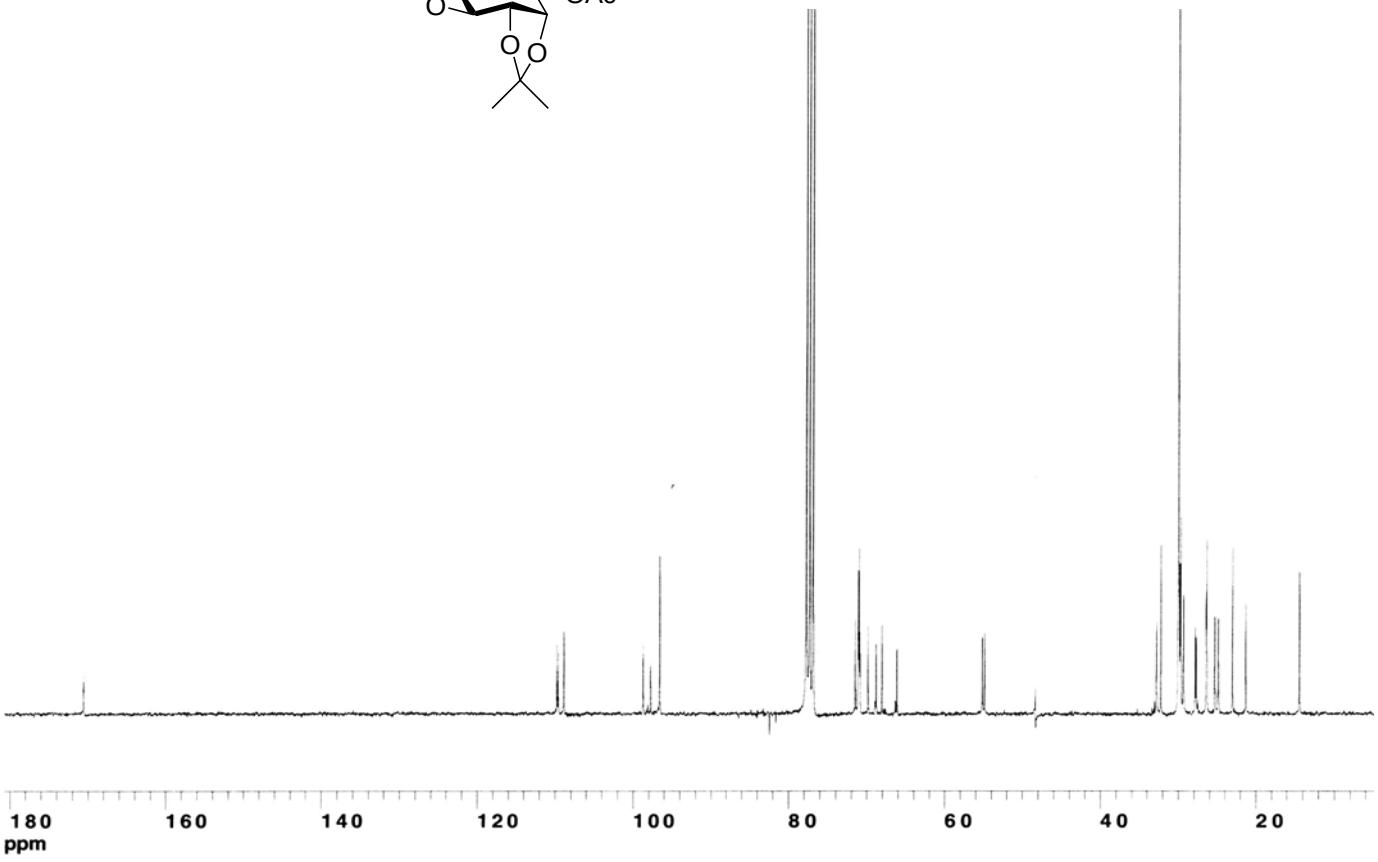
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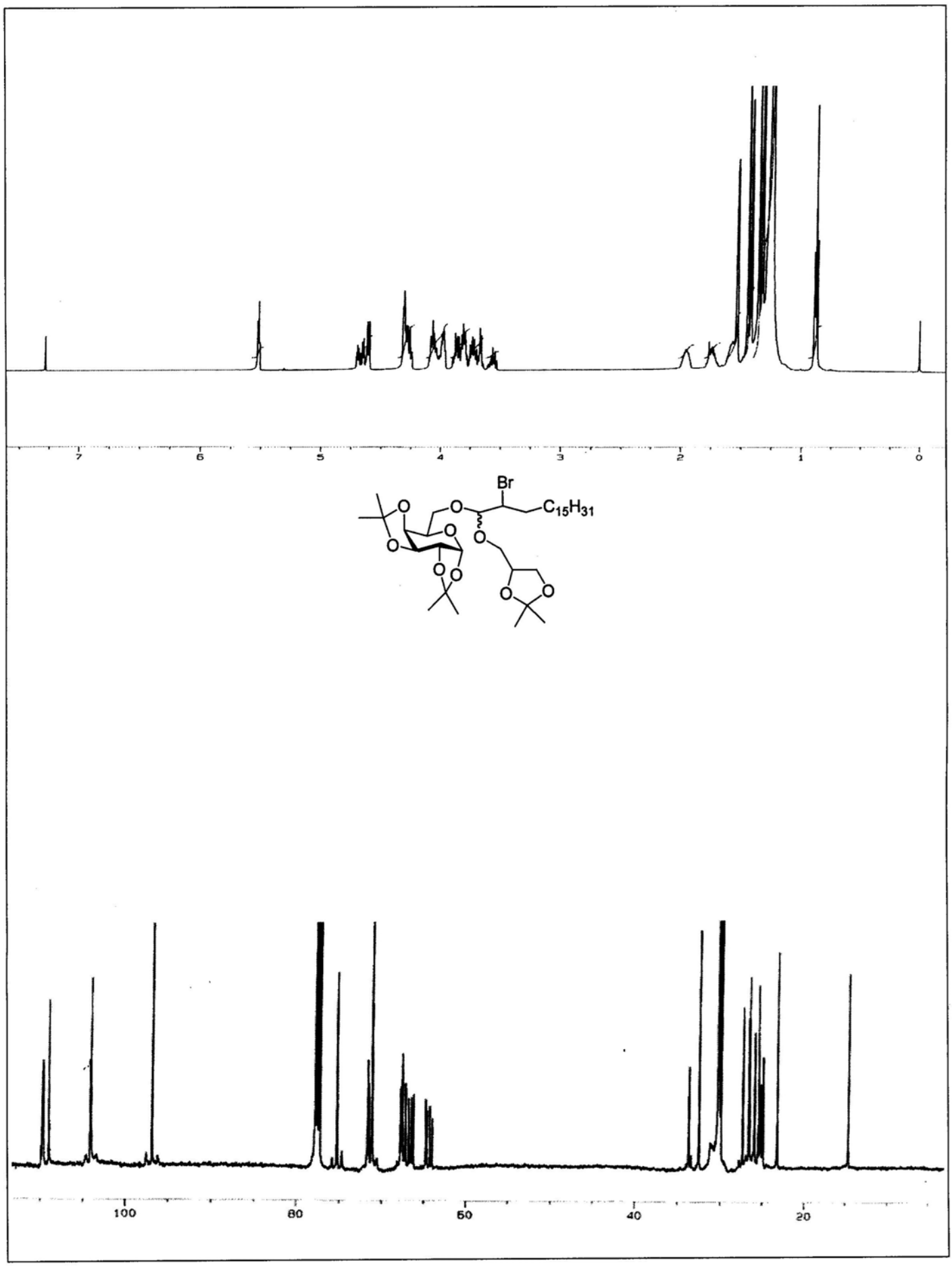
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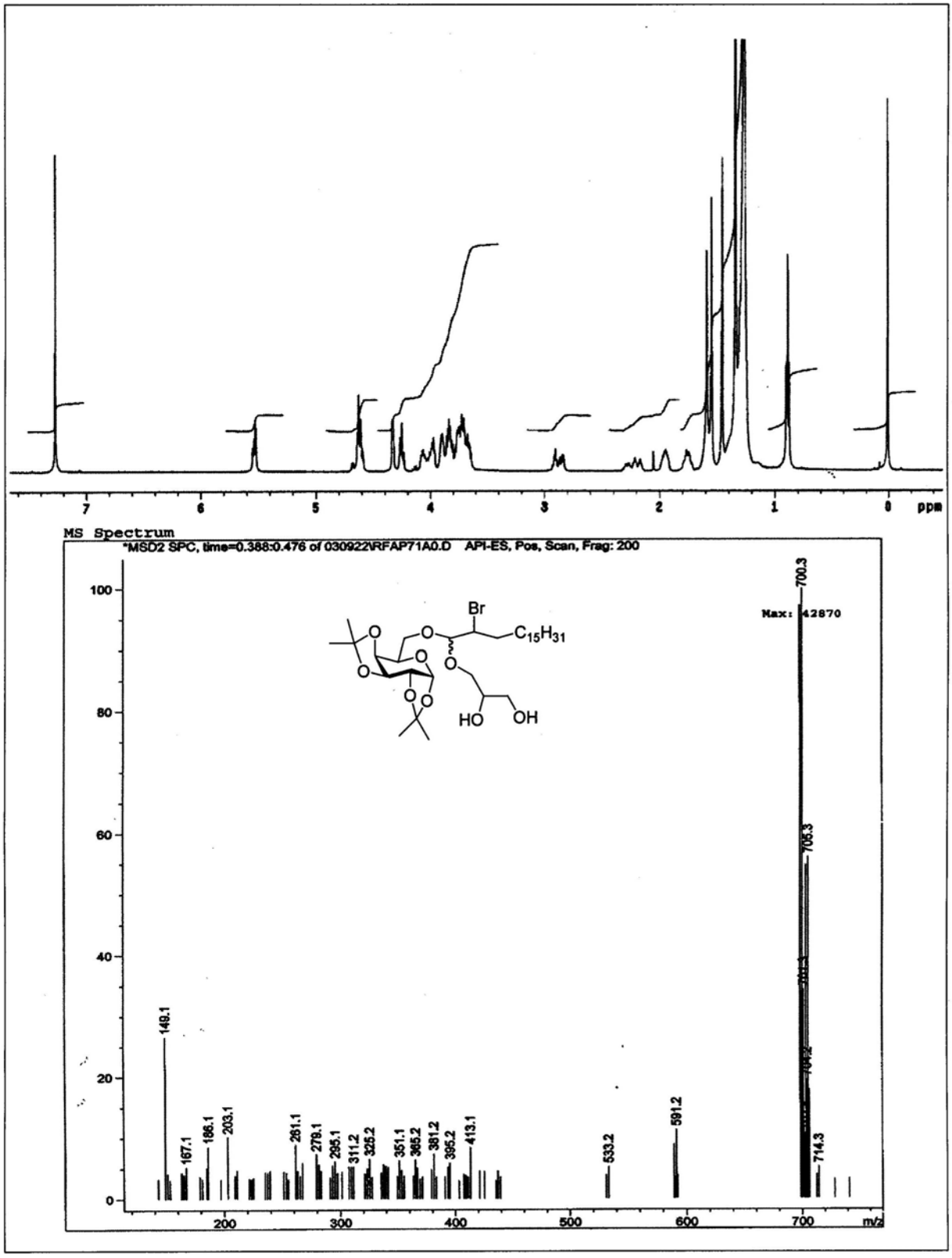
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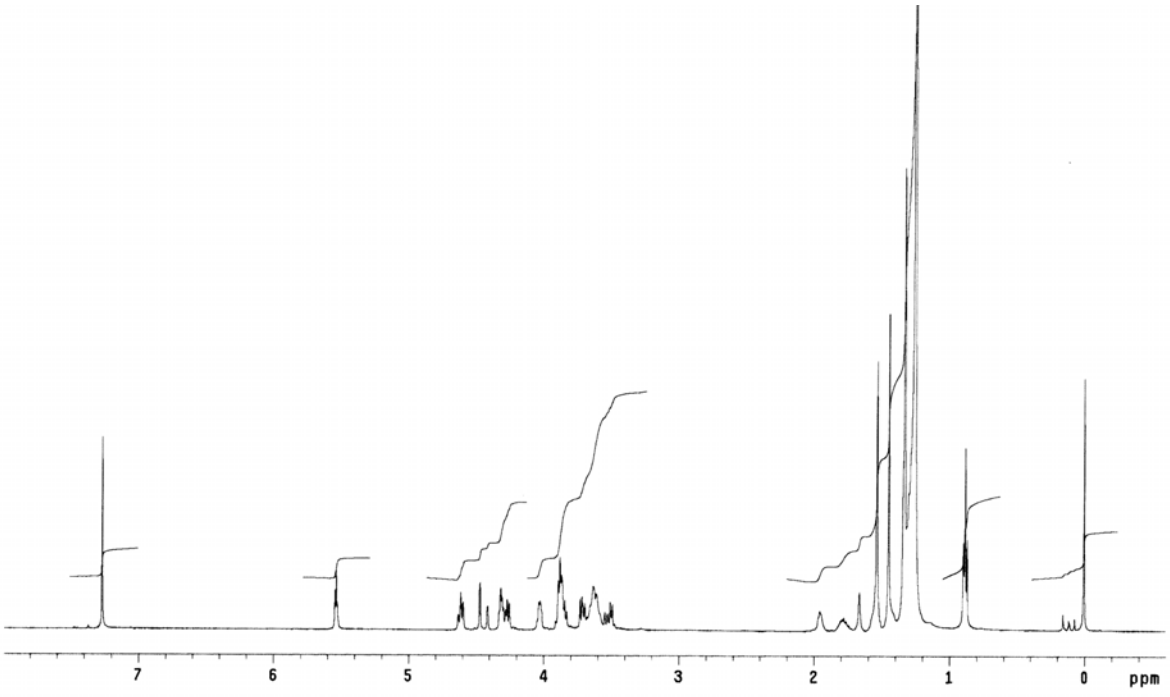
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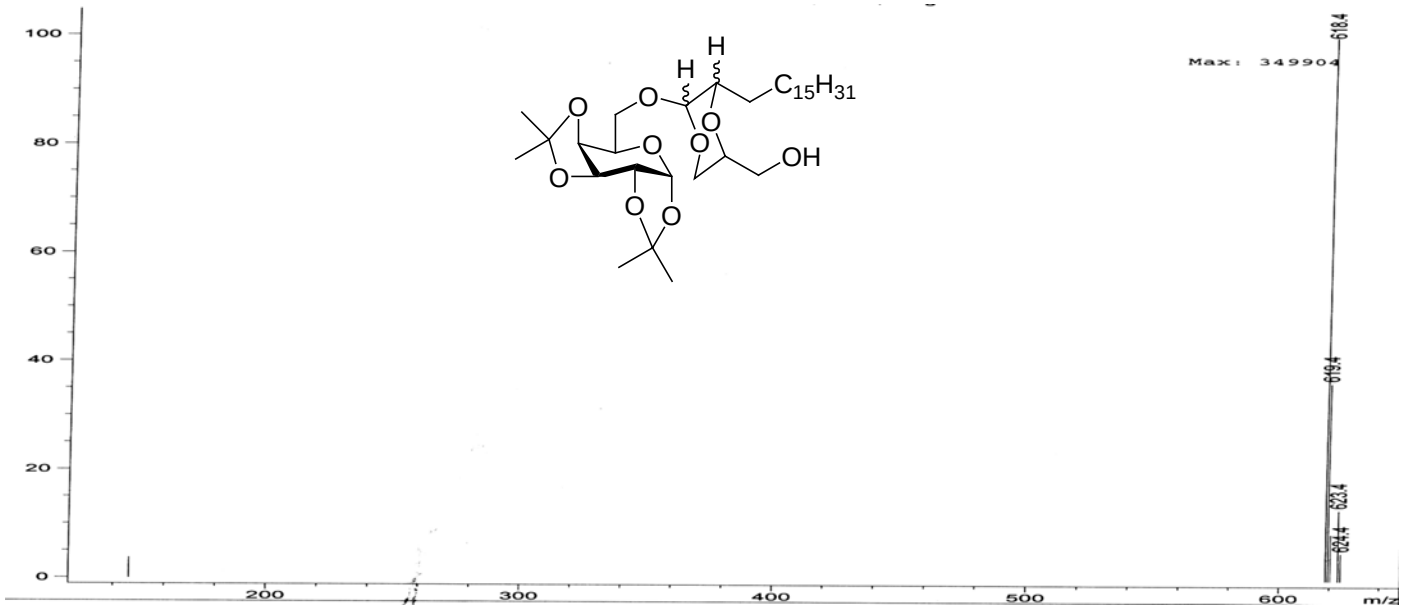
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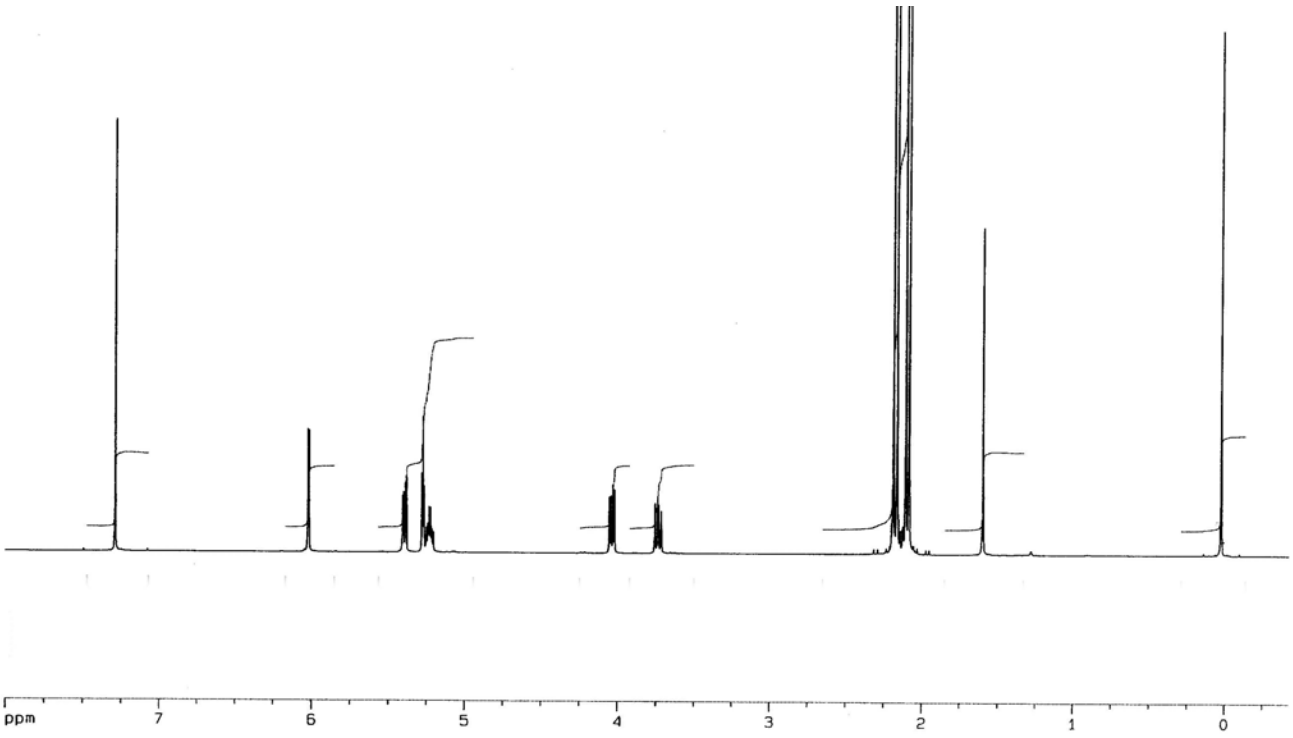
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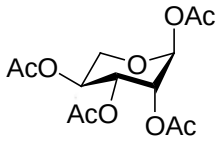
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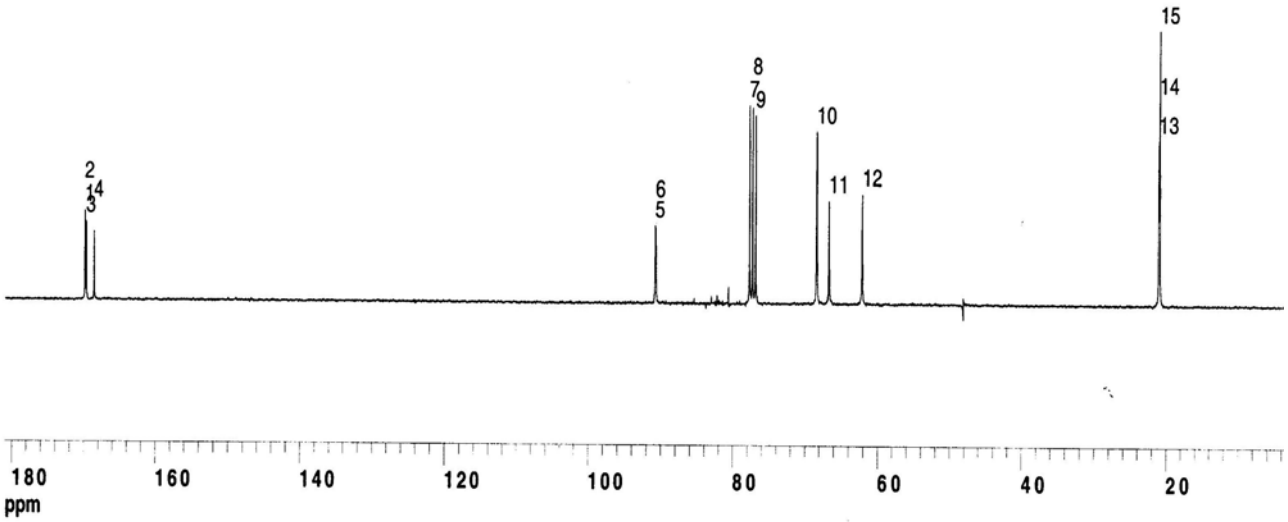
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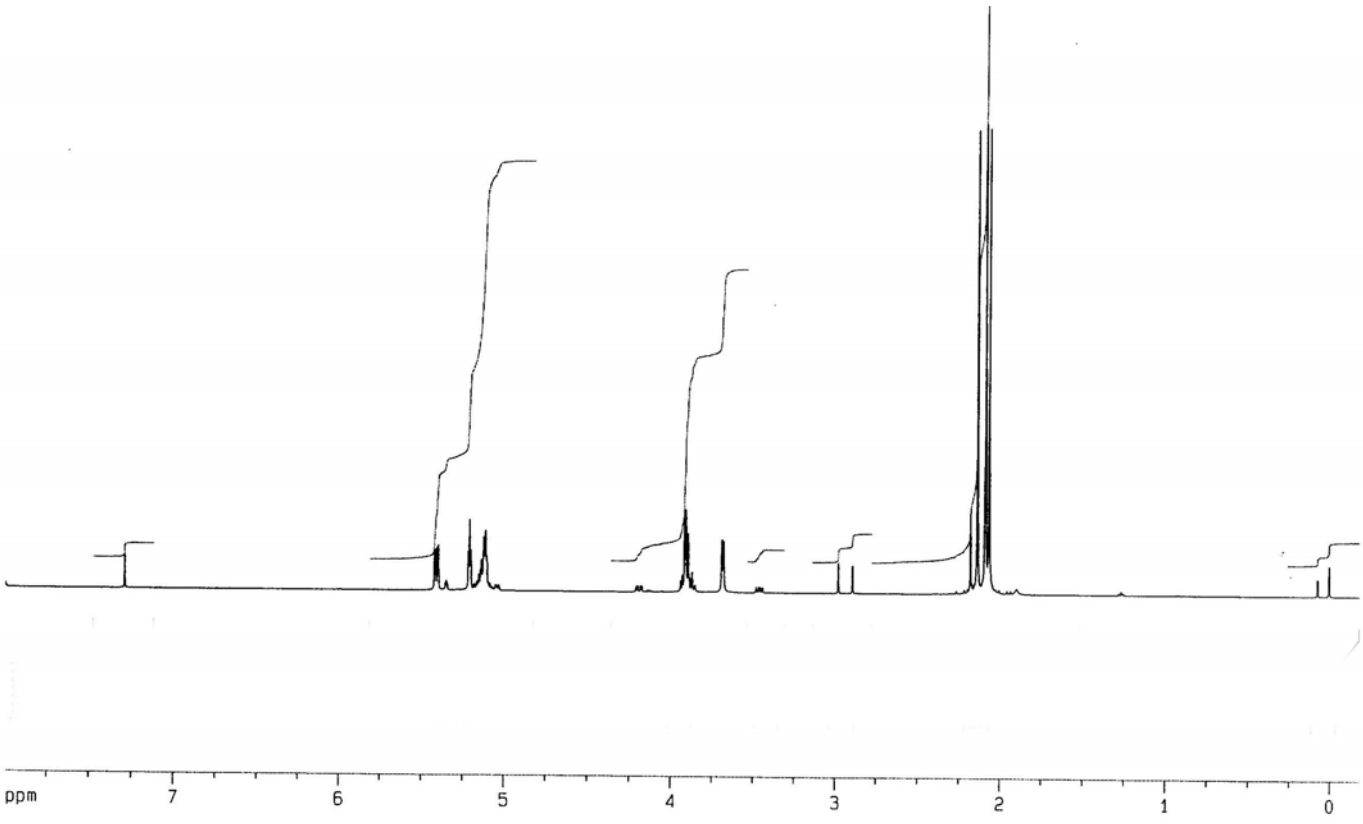
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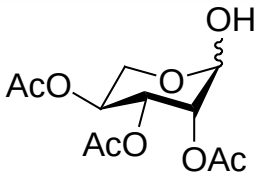
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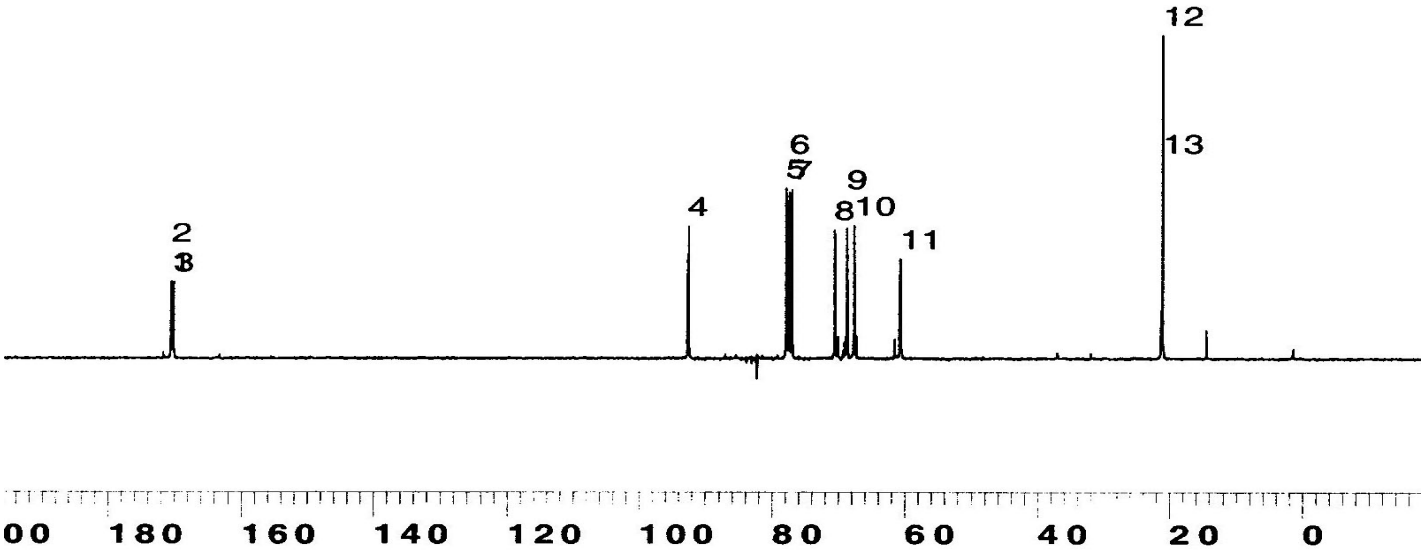
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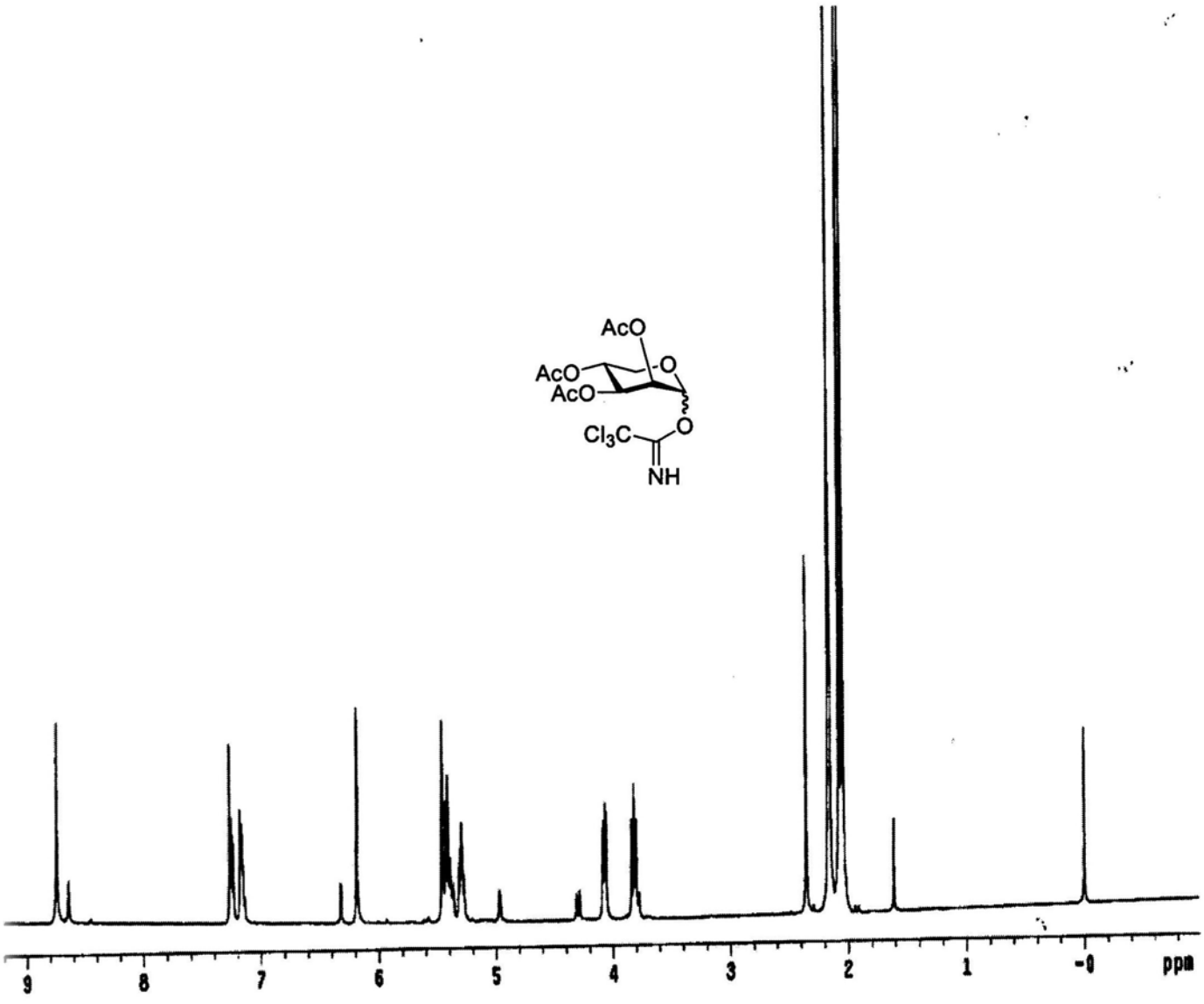
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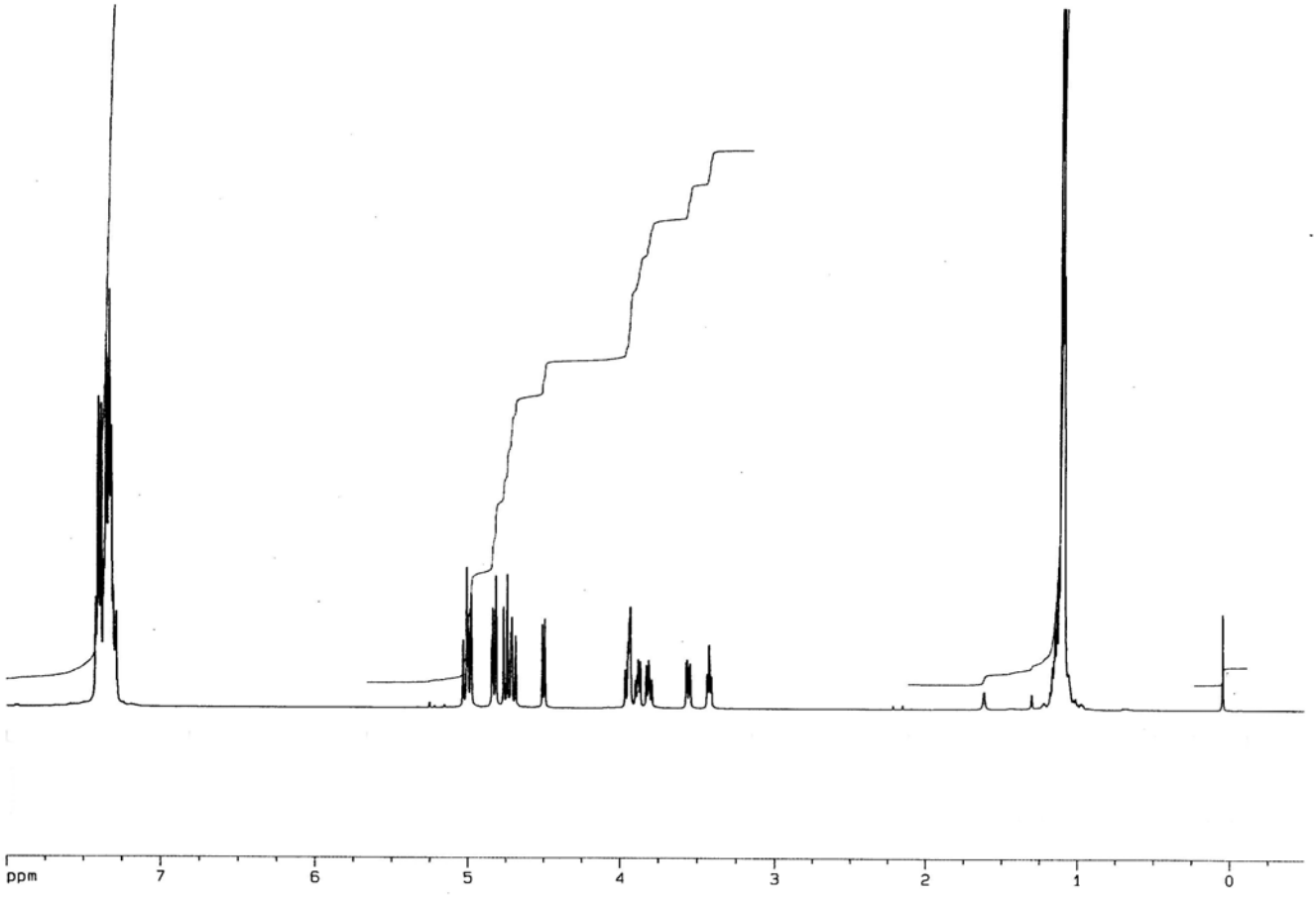
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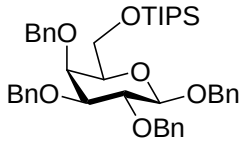
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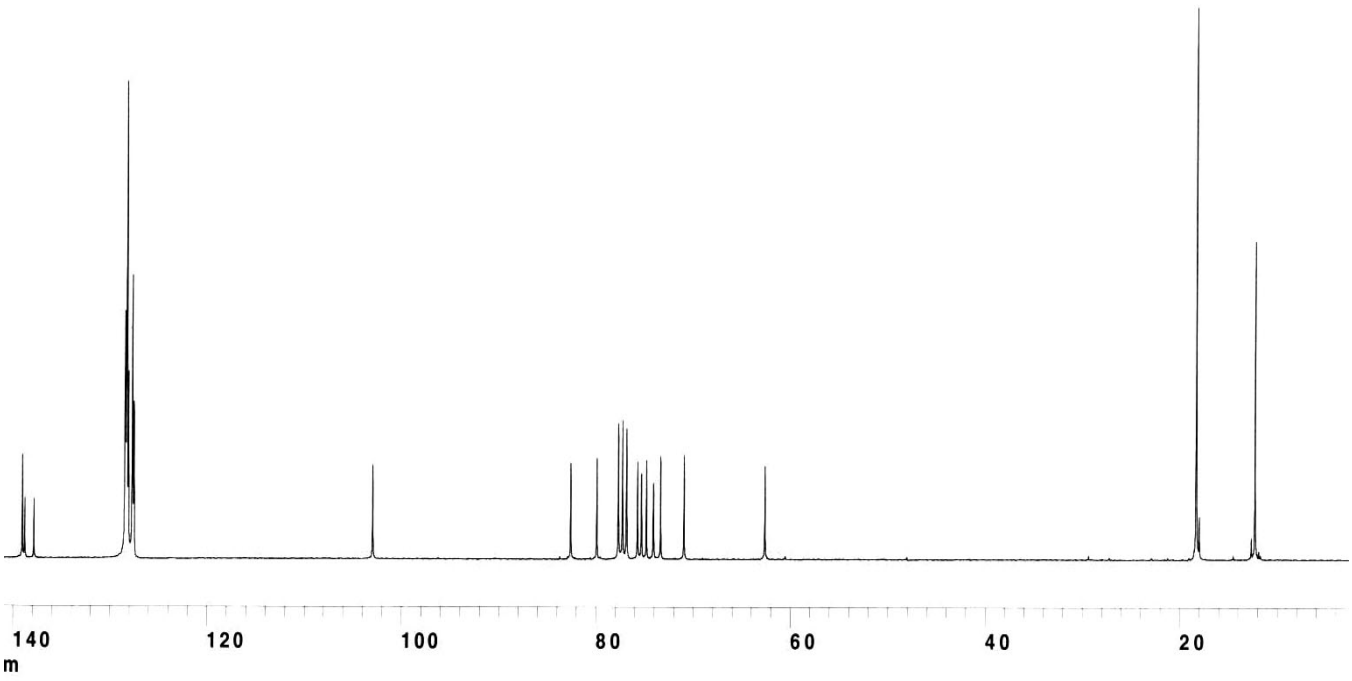
BnO
OBn
OBn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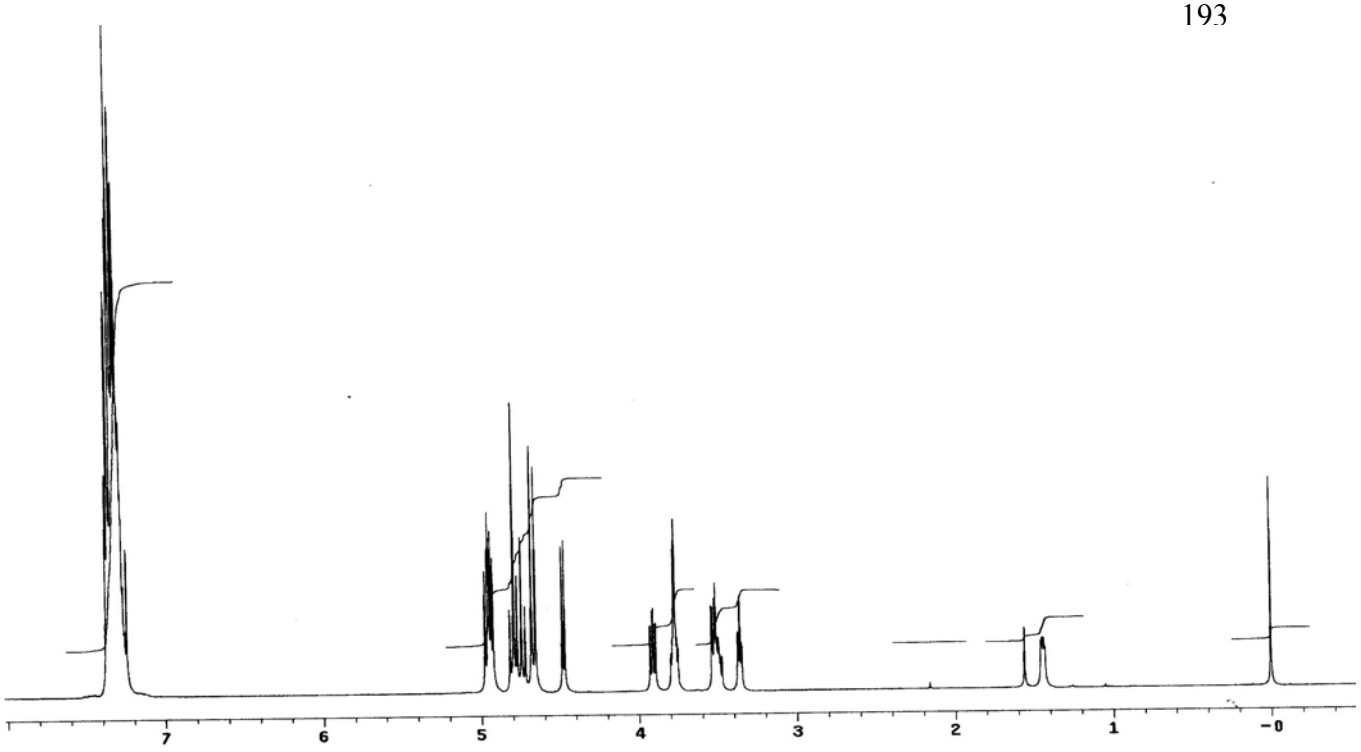
m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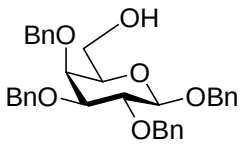
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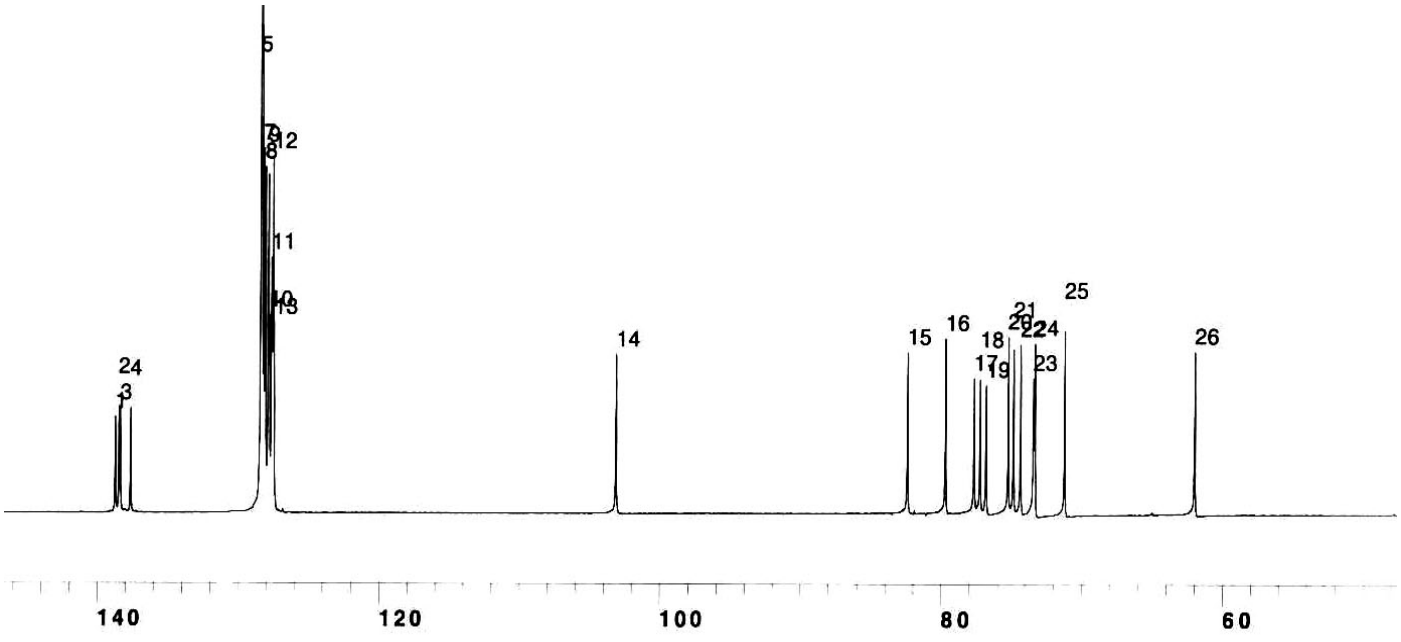
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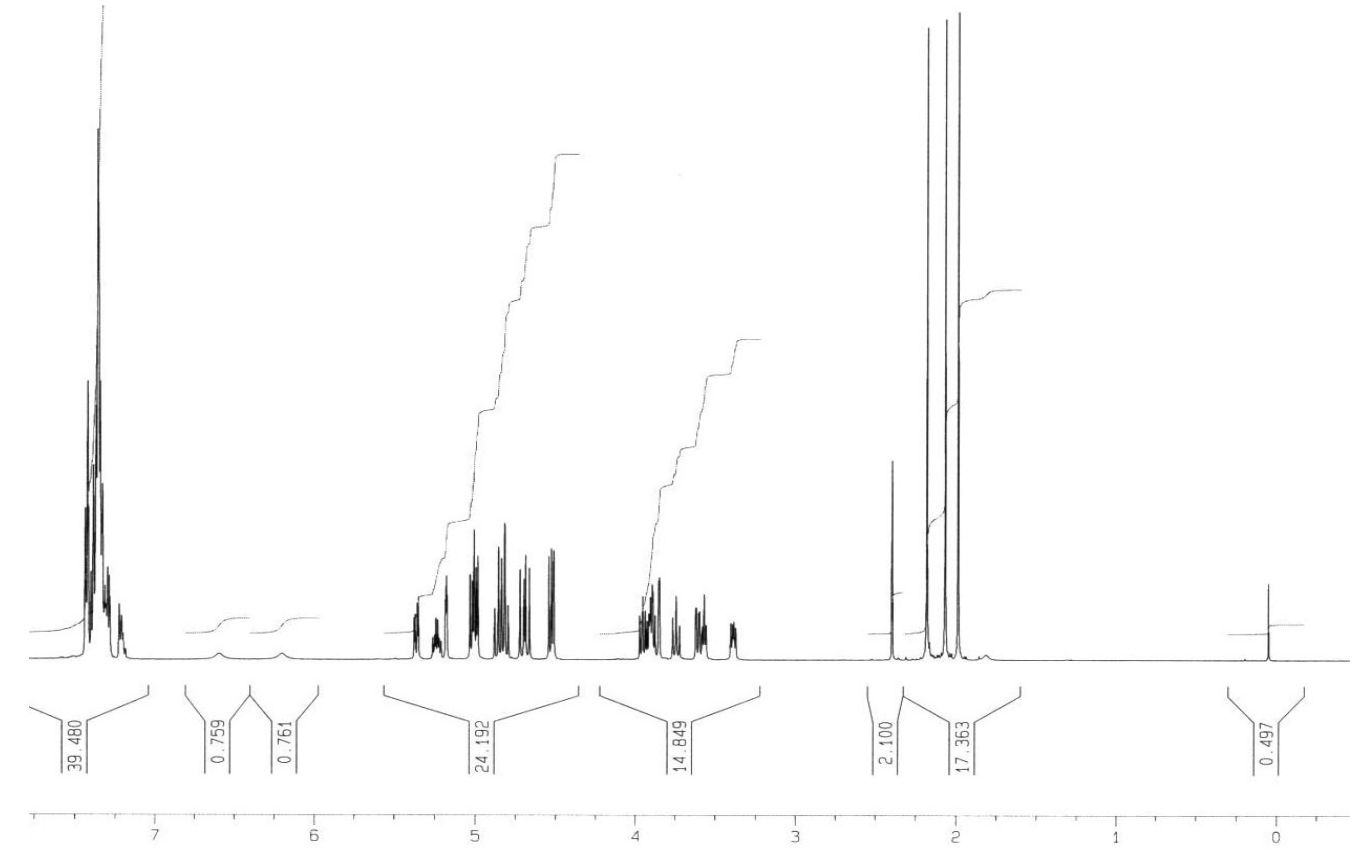
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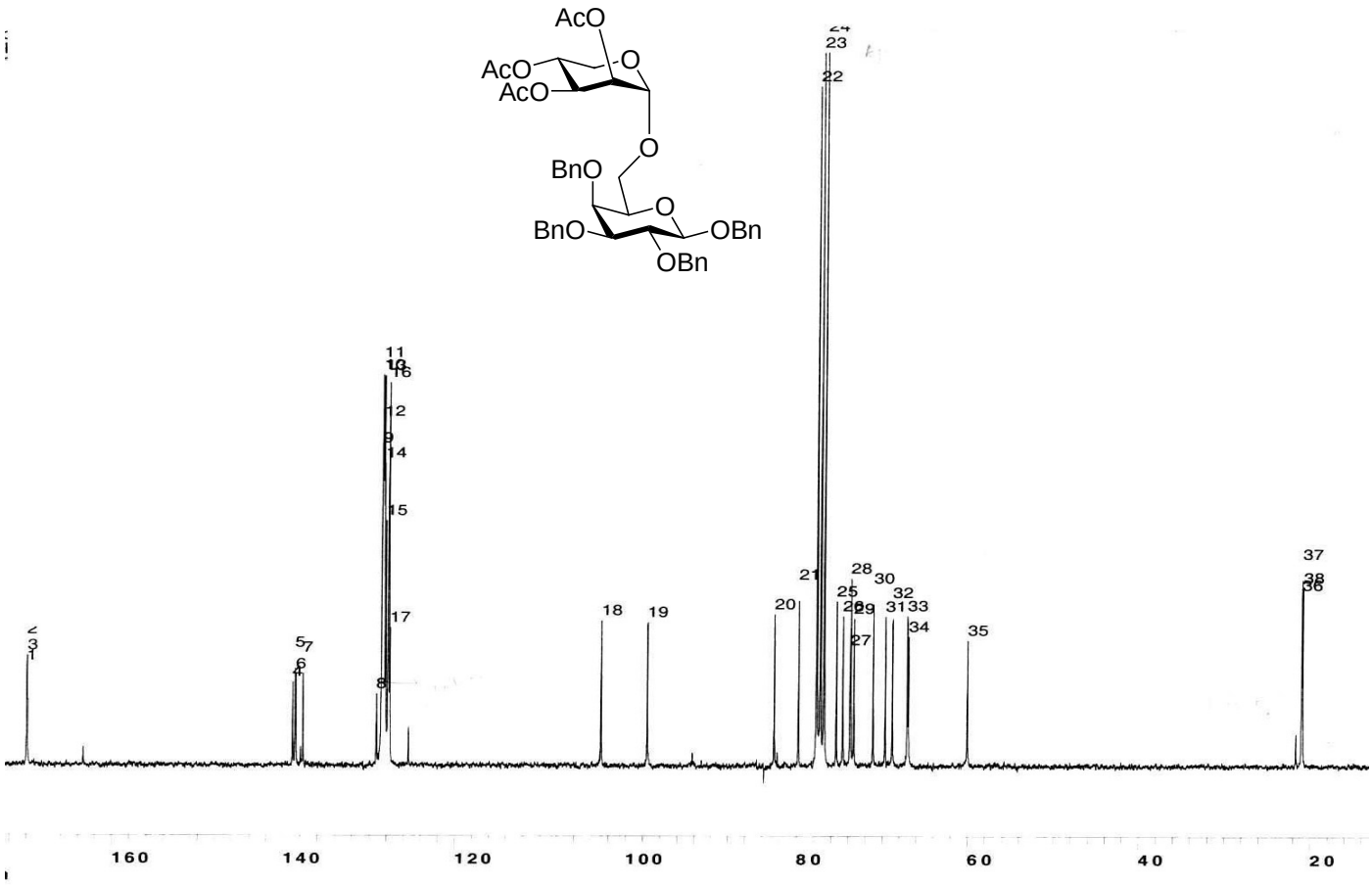
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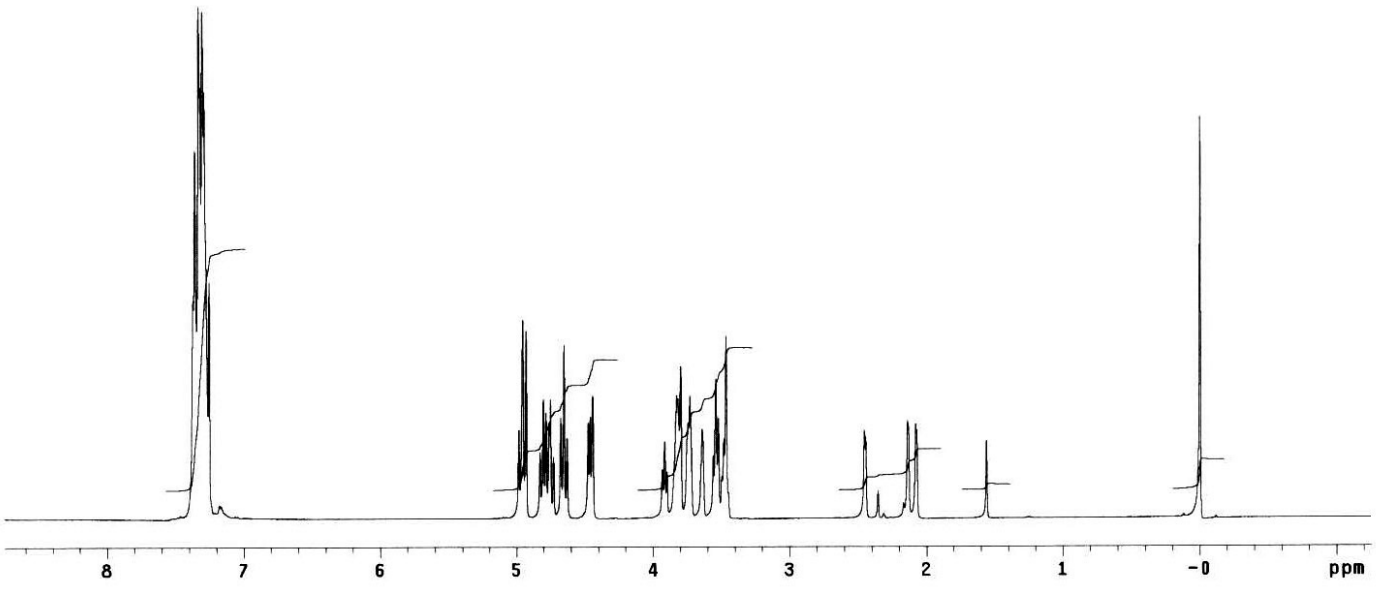
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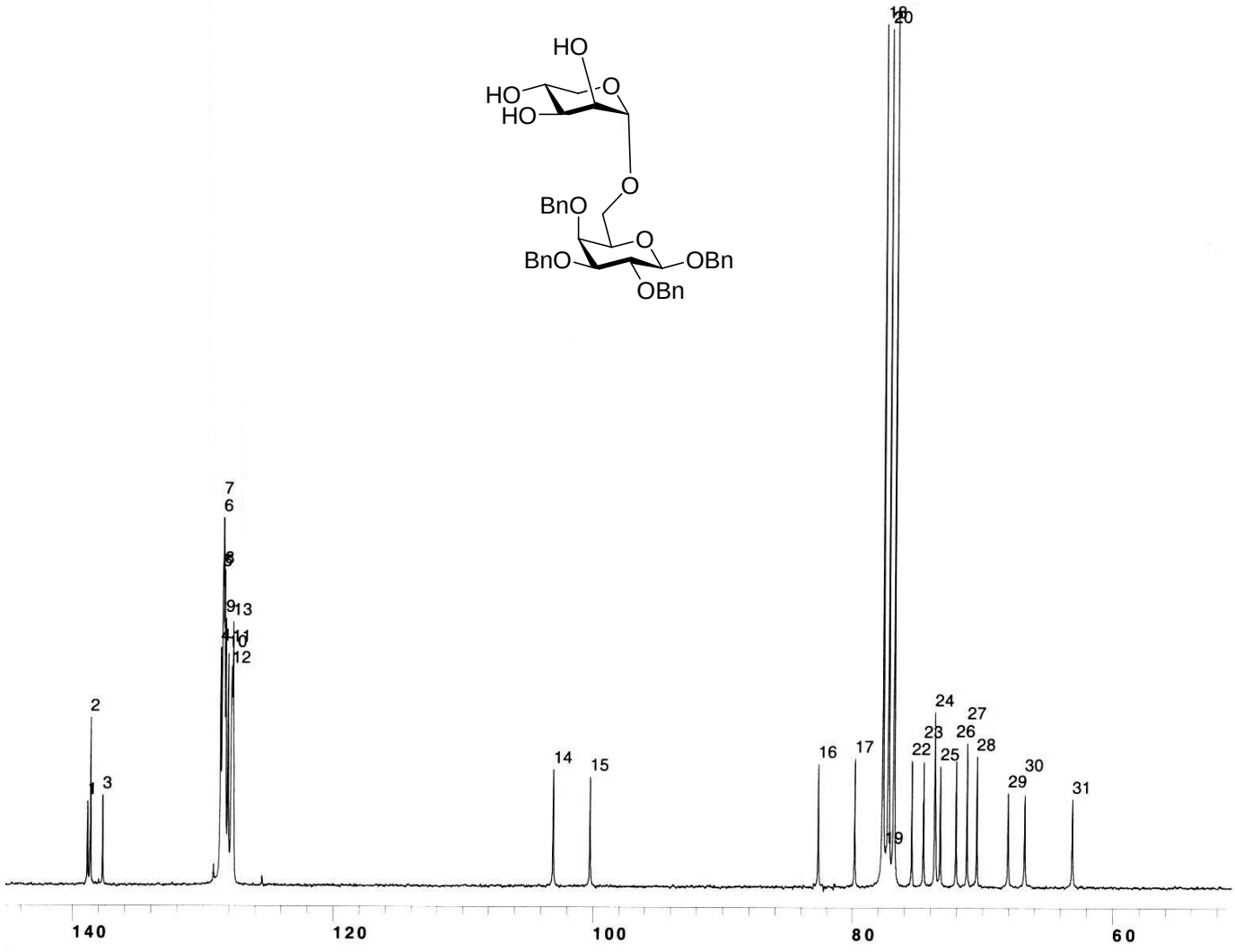
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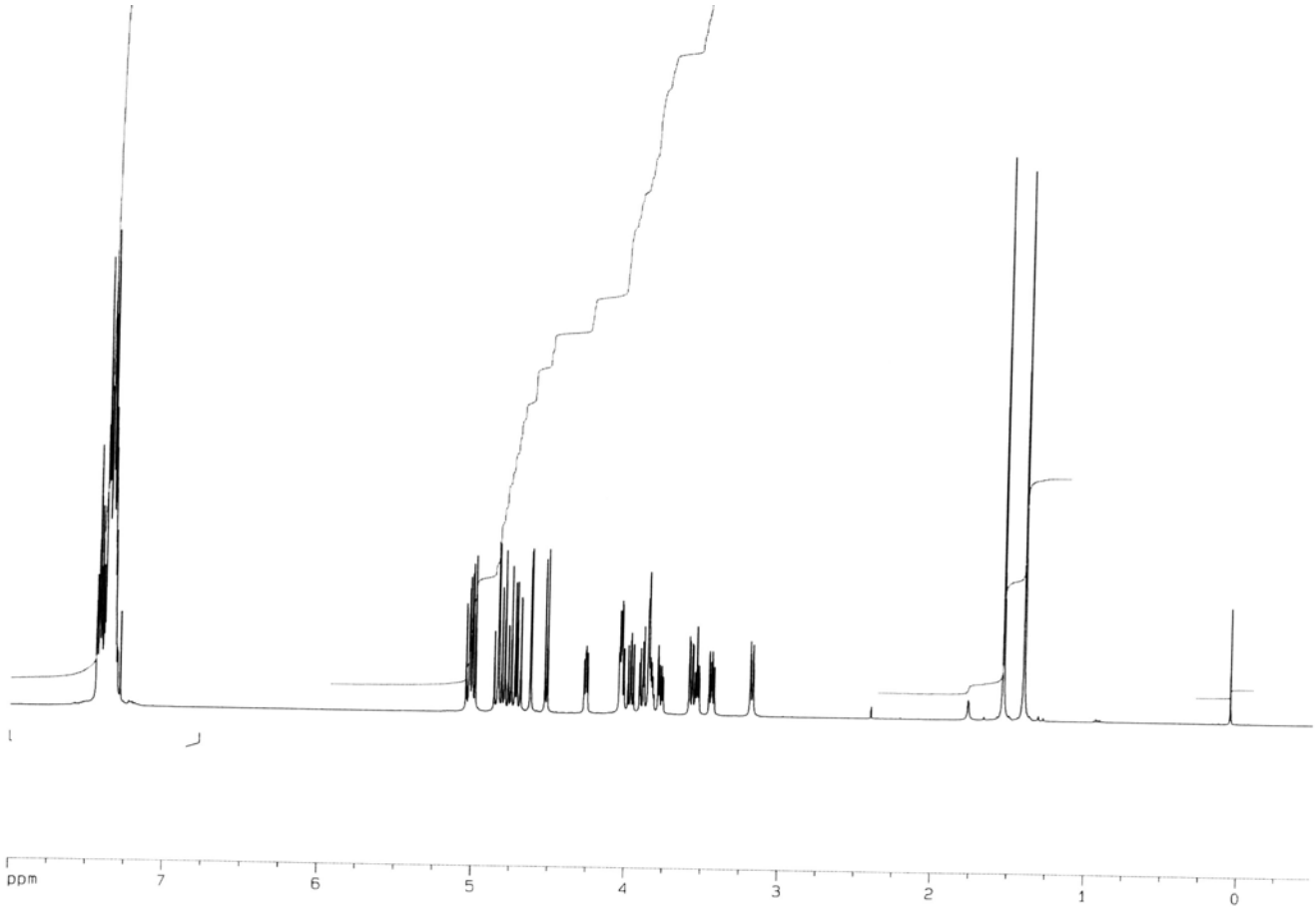
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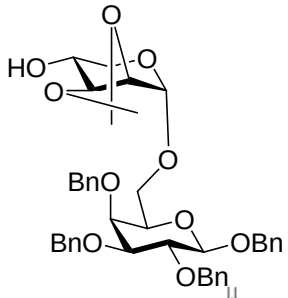
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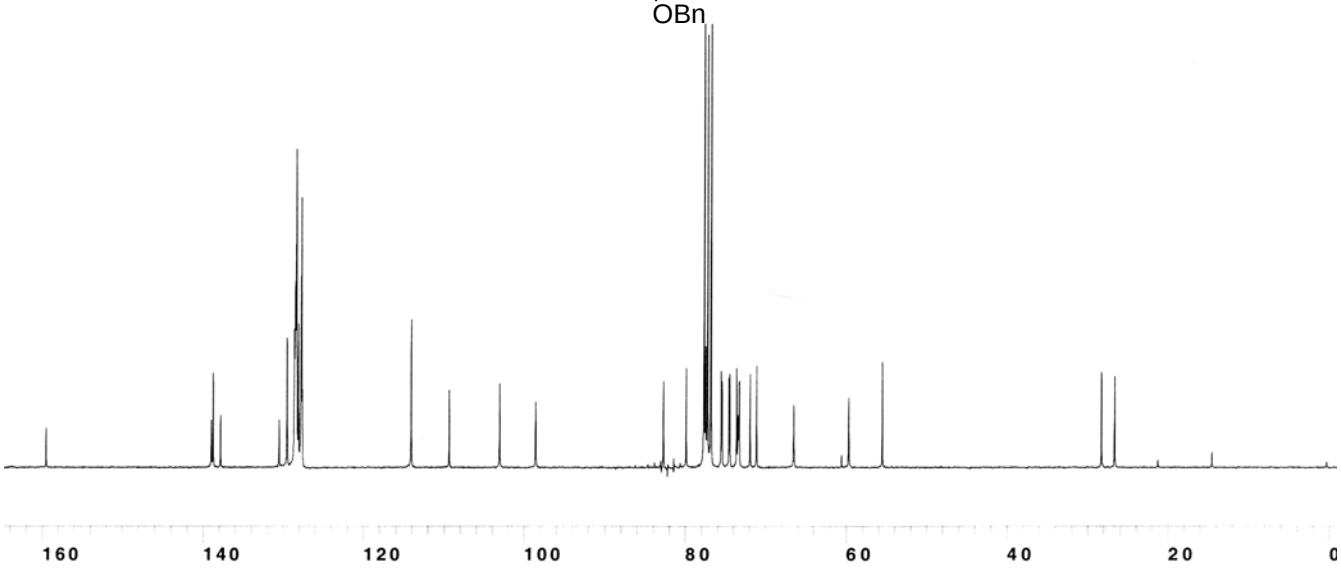
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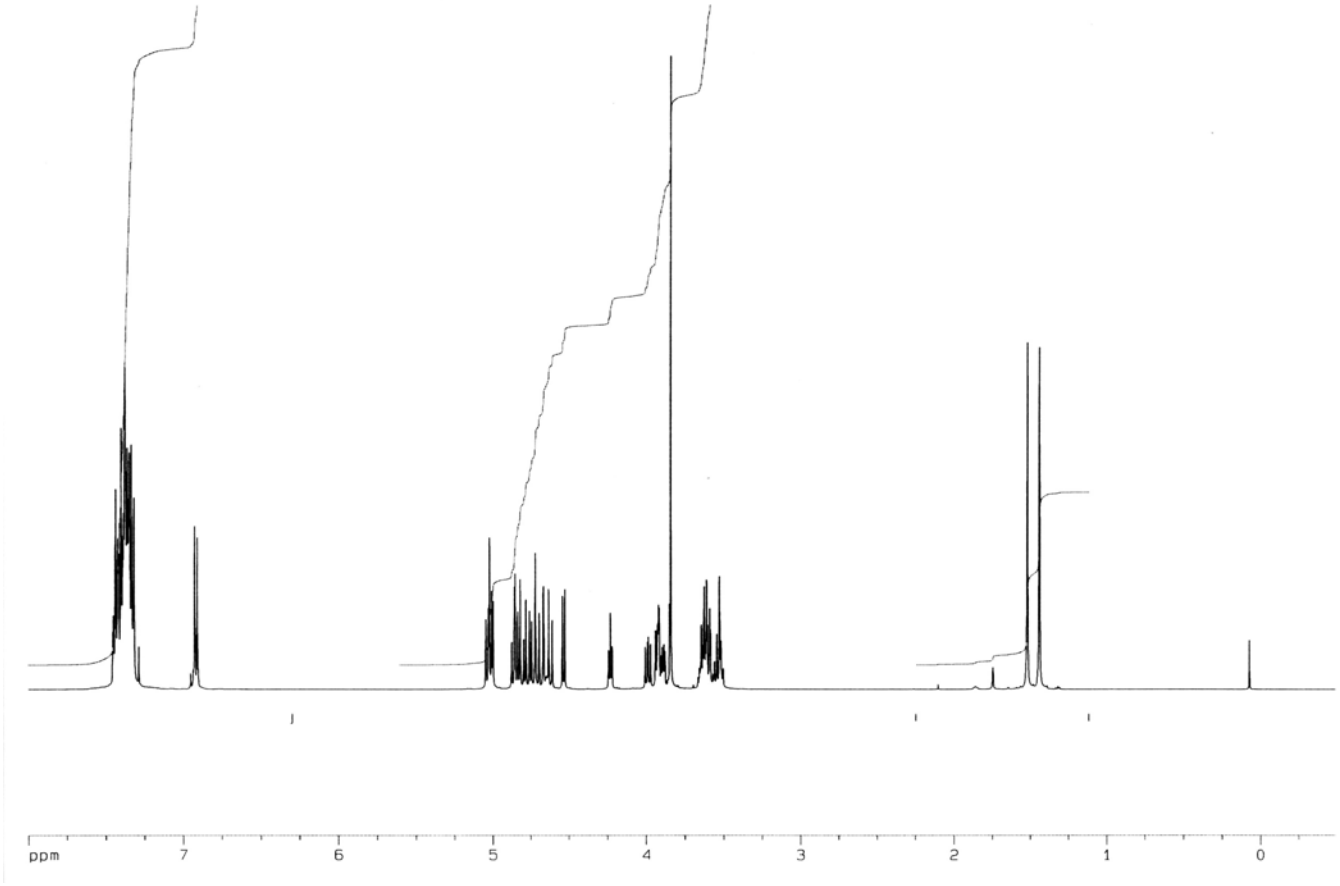
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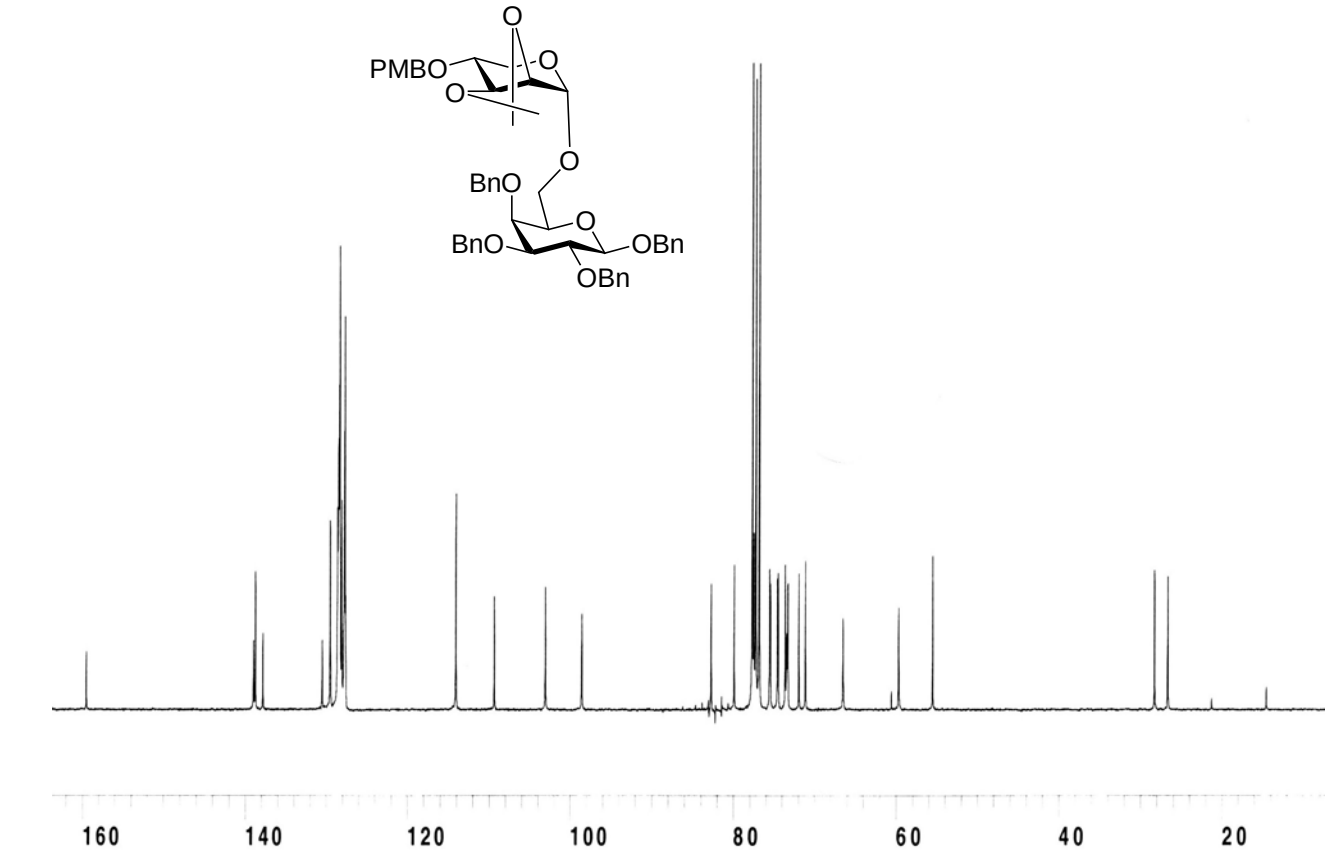
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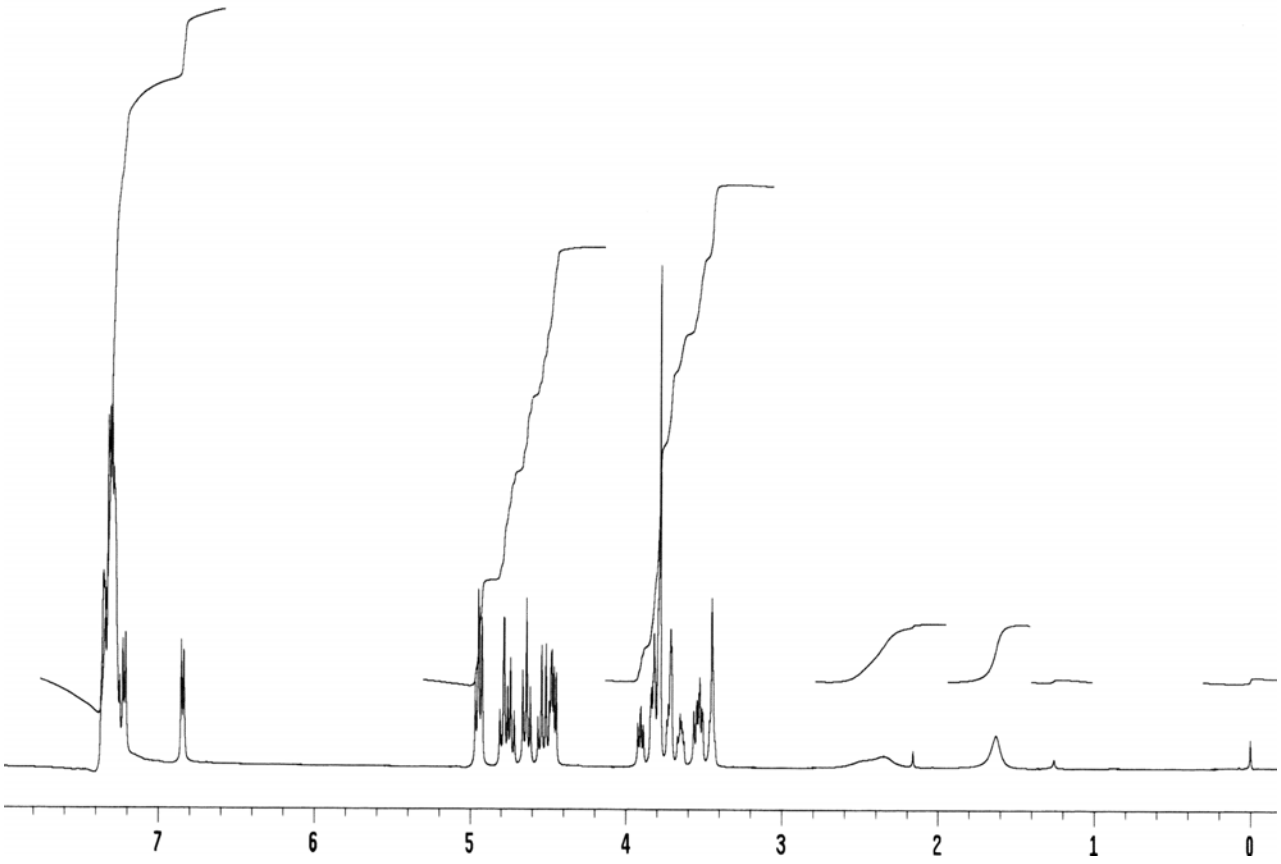
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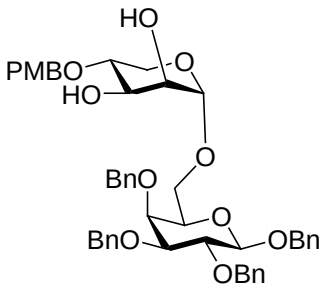
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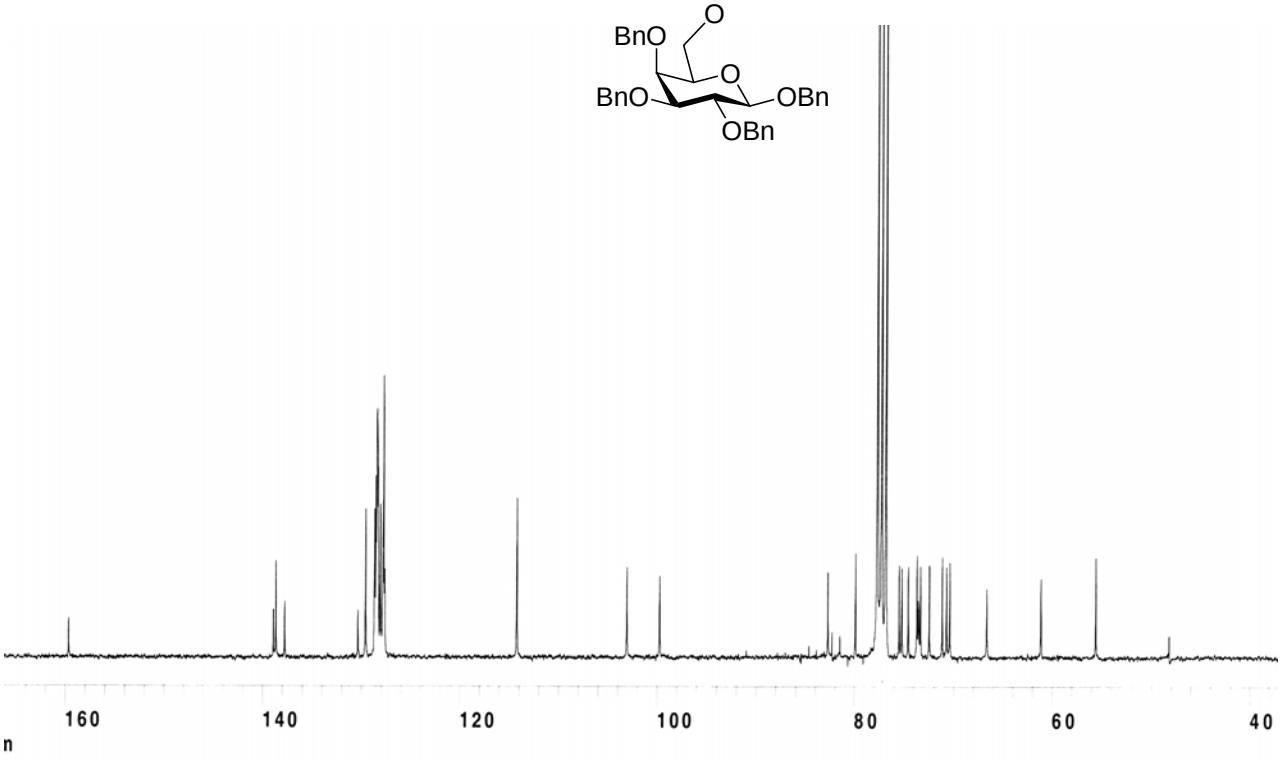
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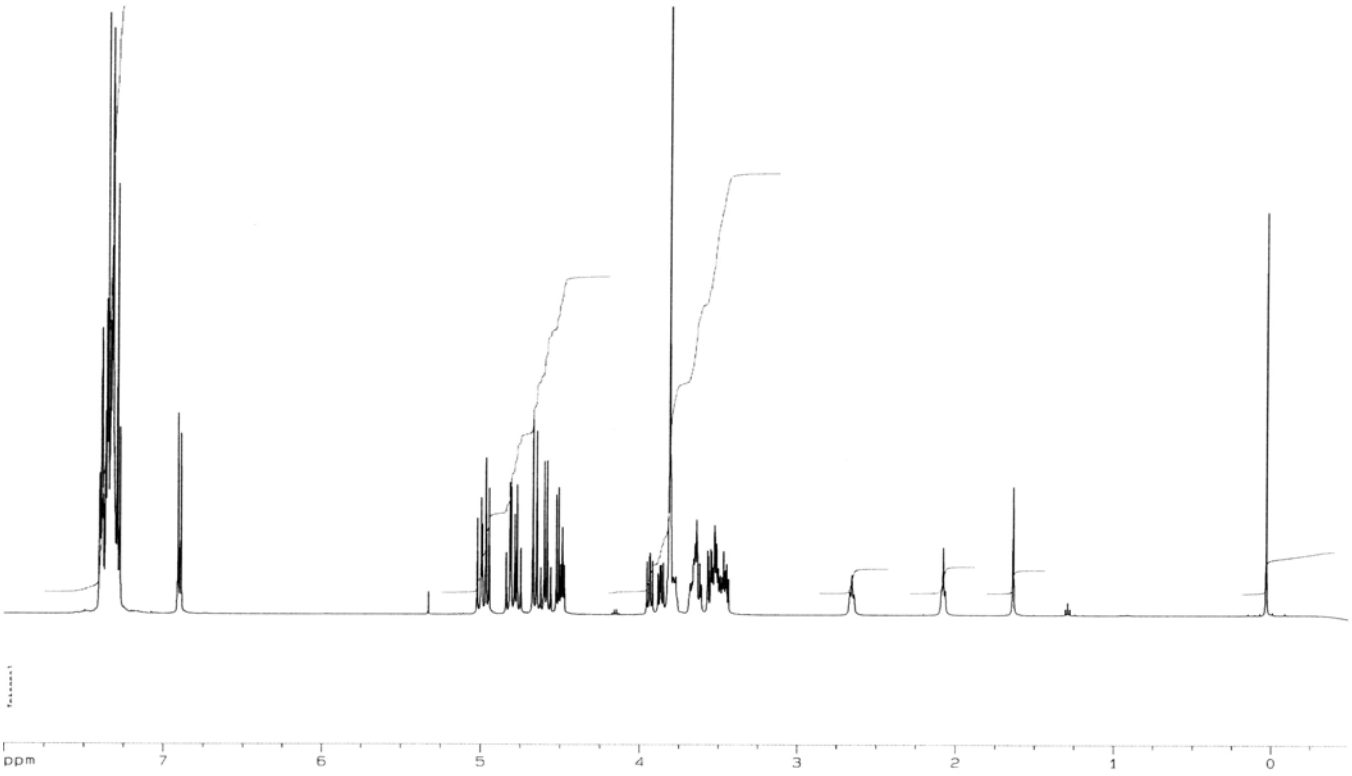
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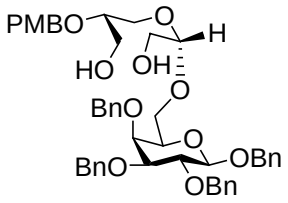
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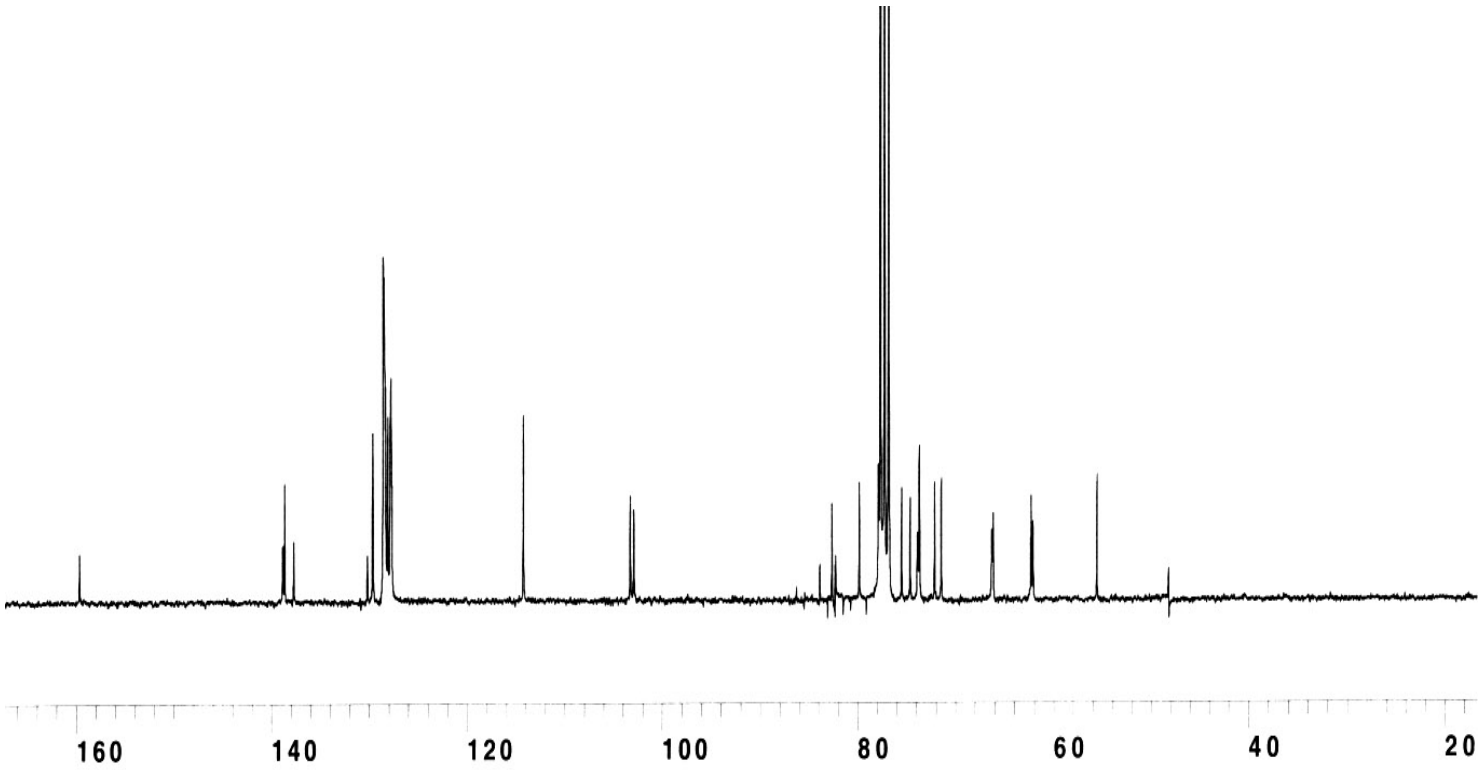
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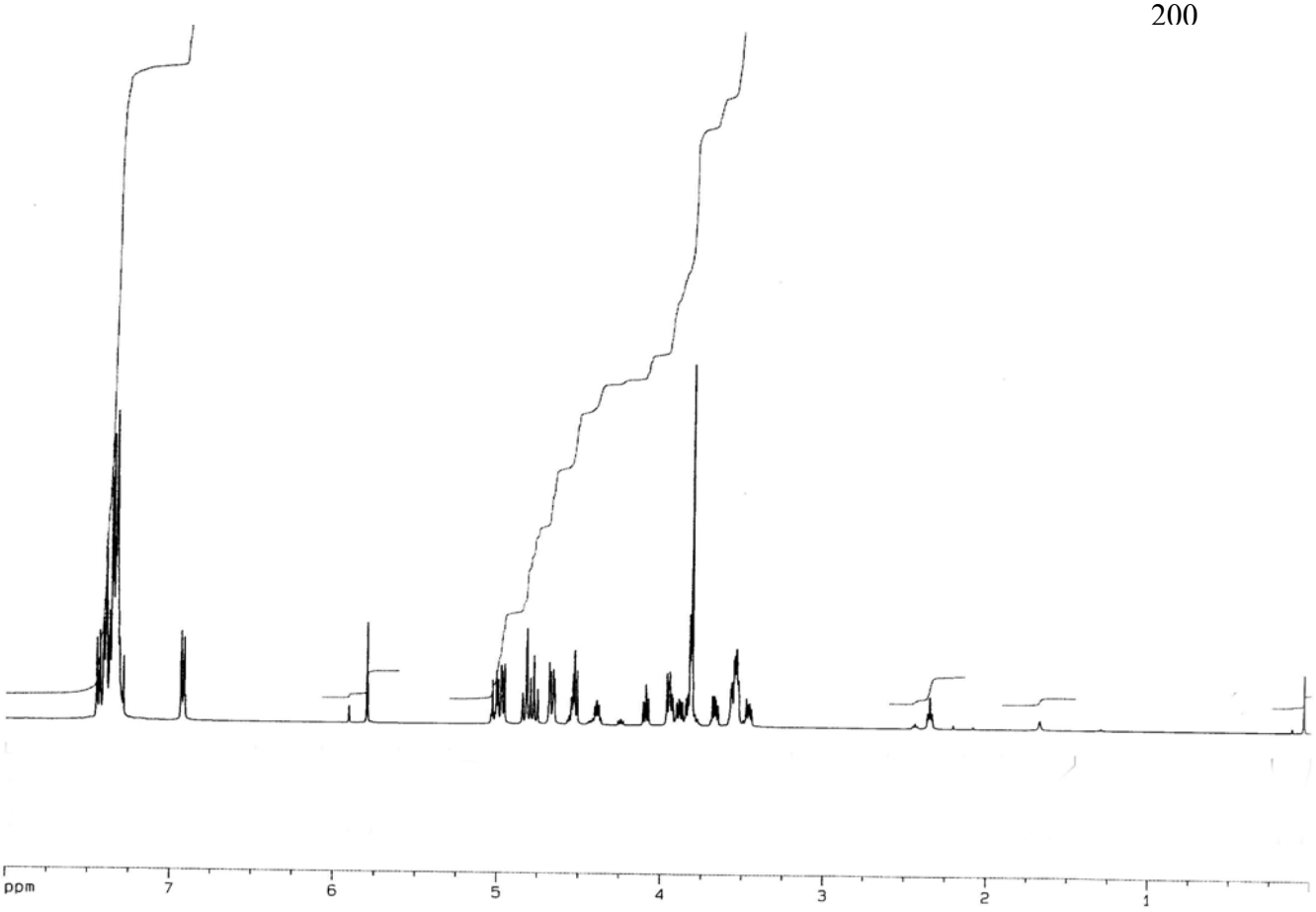
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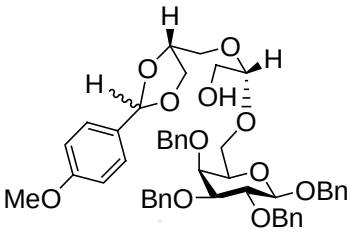
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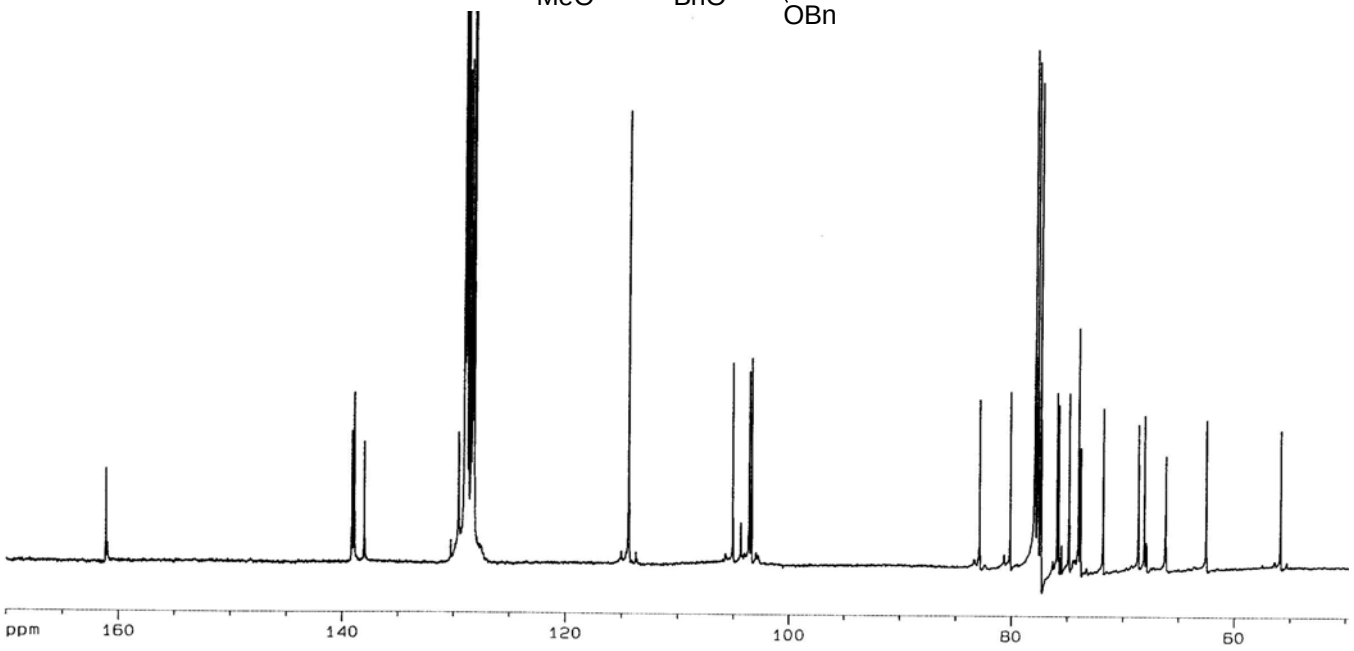
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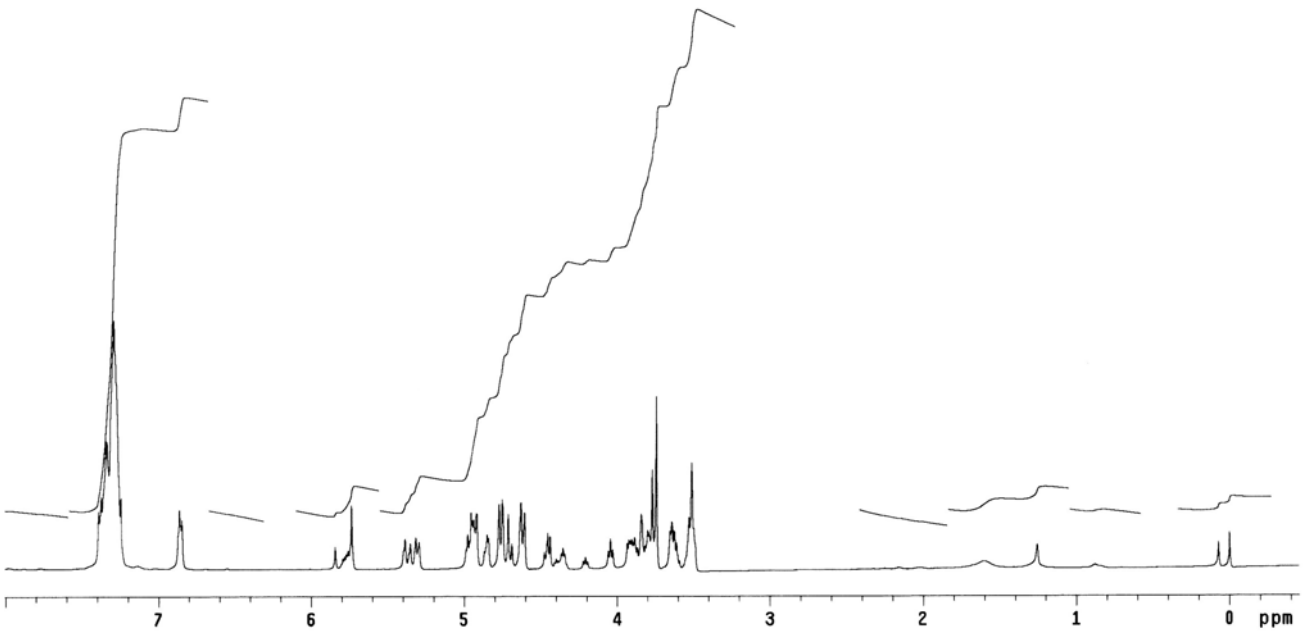
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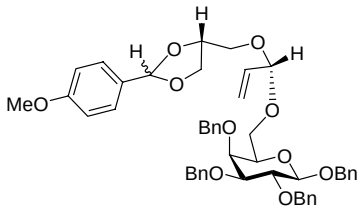
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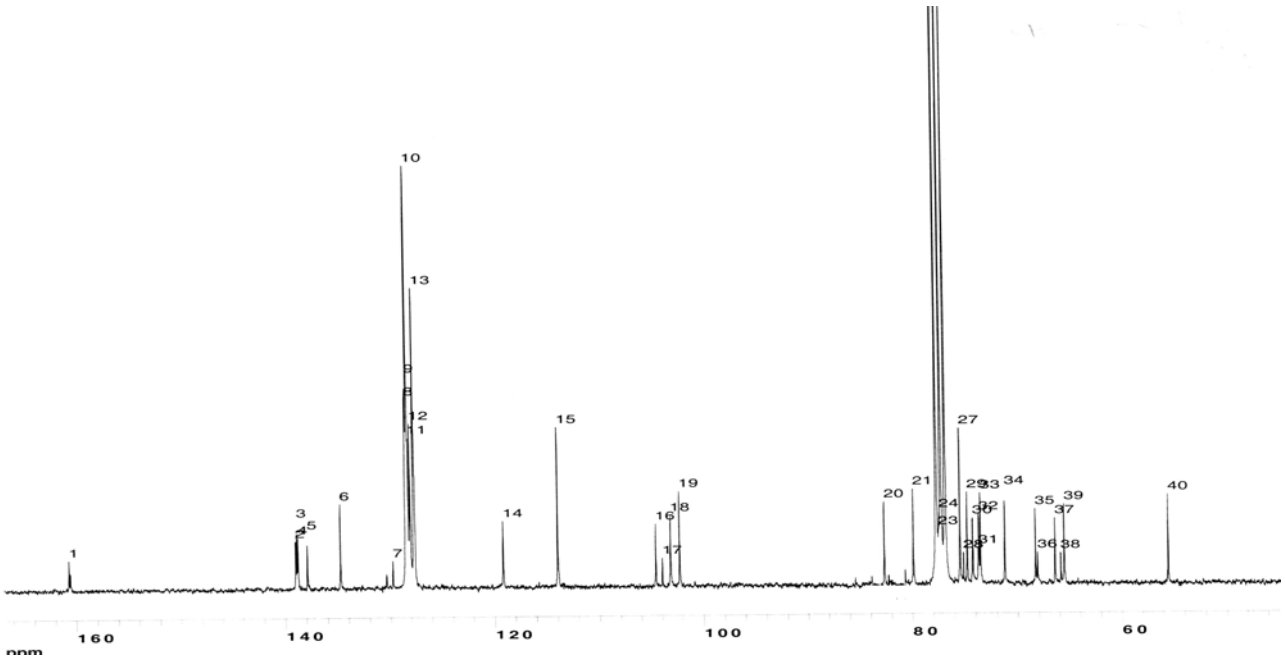
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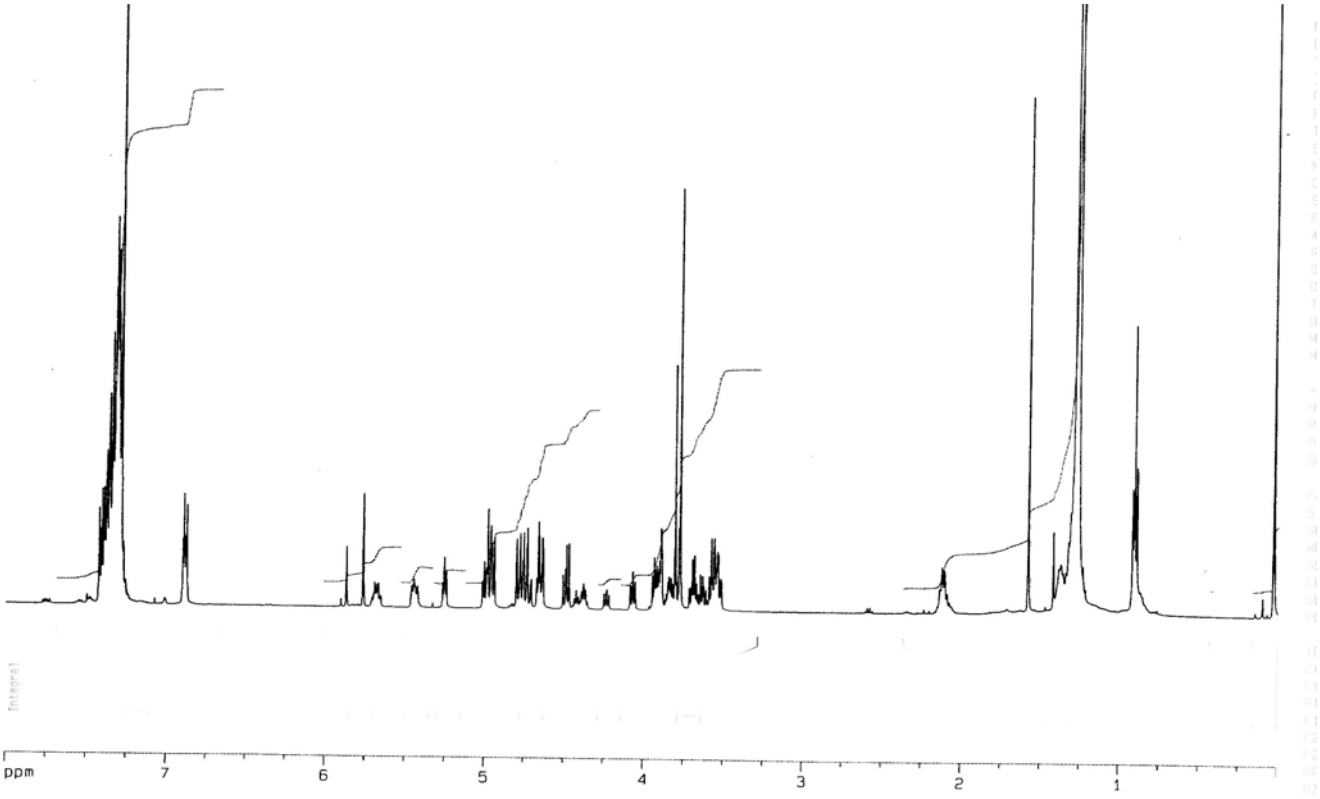
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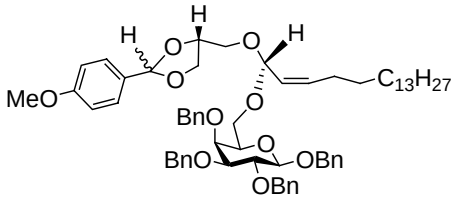
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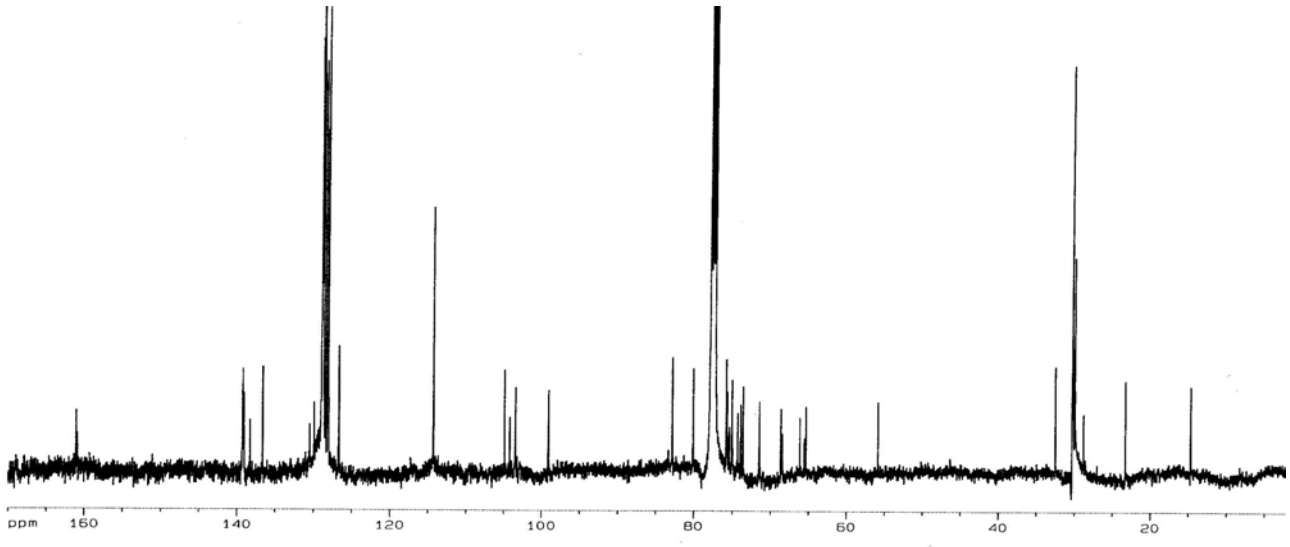
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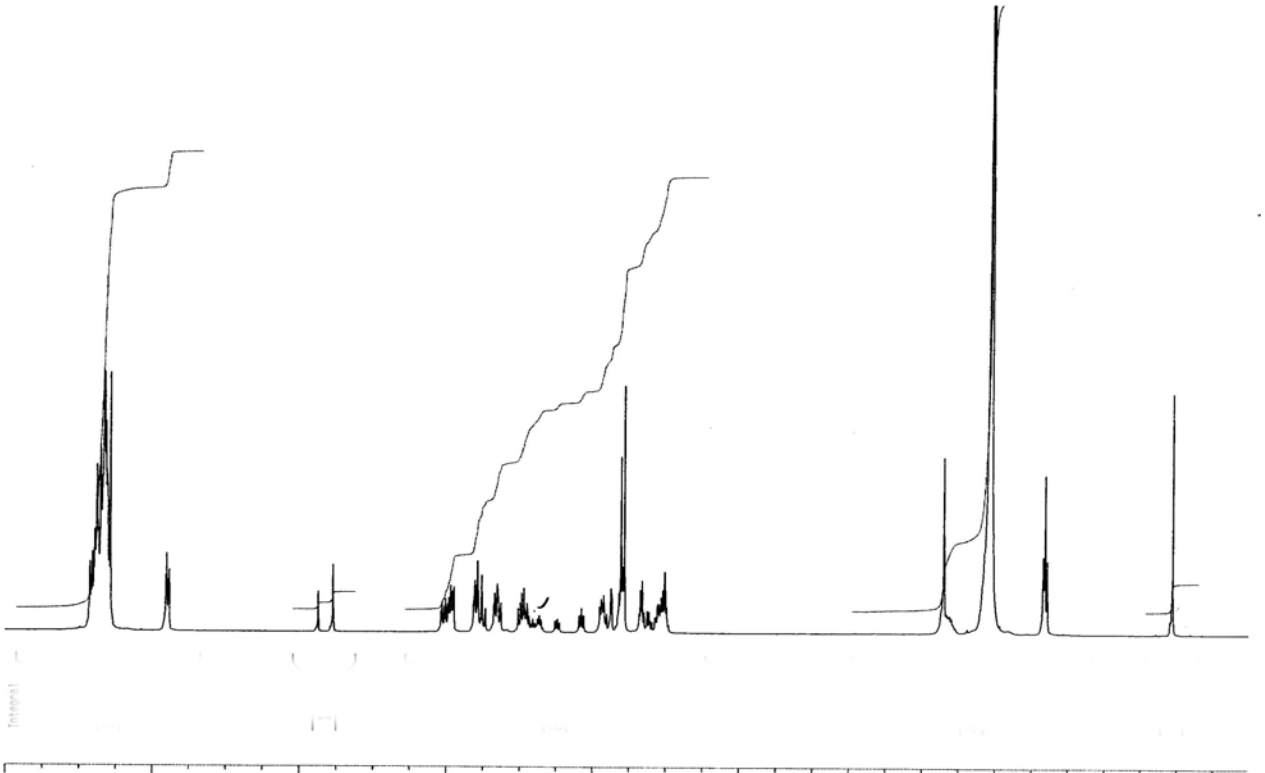
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$C_{13}H_{27}$
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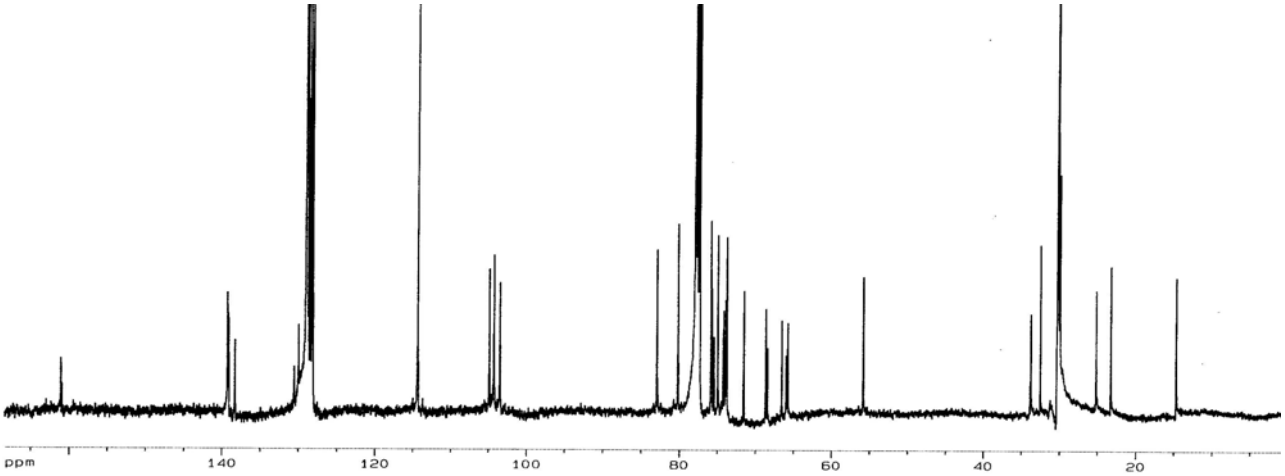
OBn
OBn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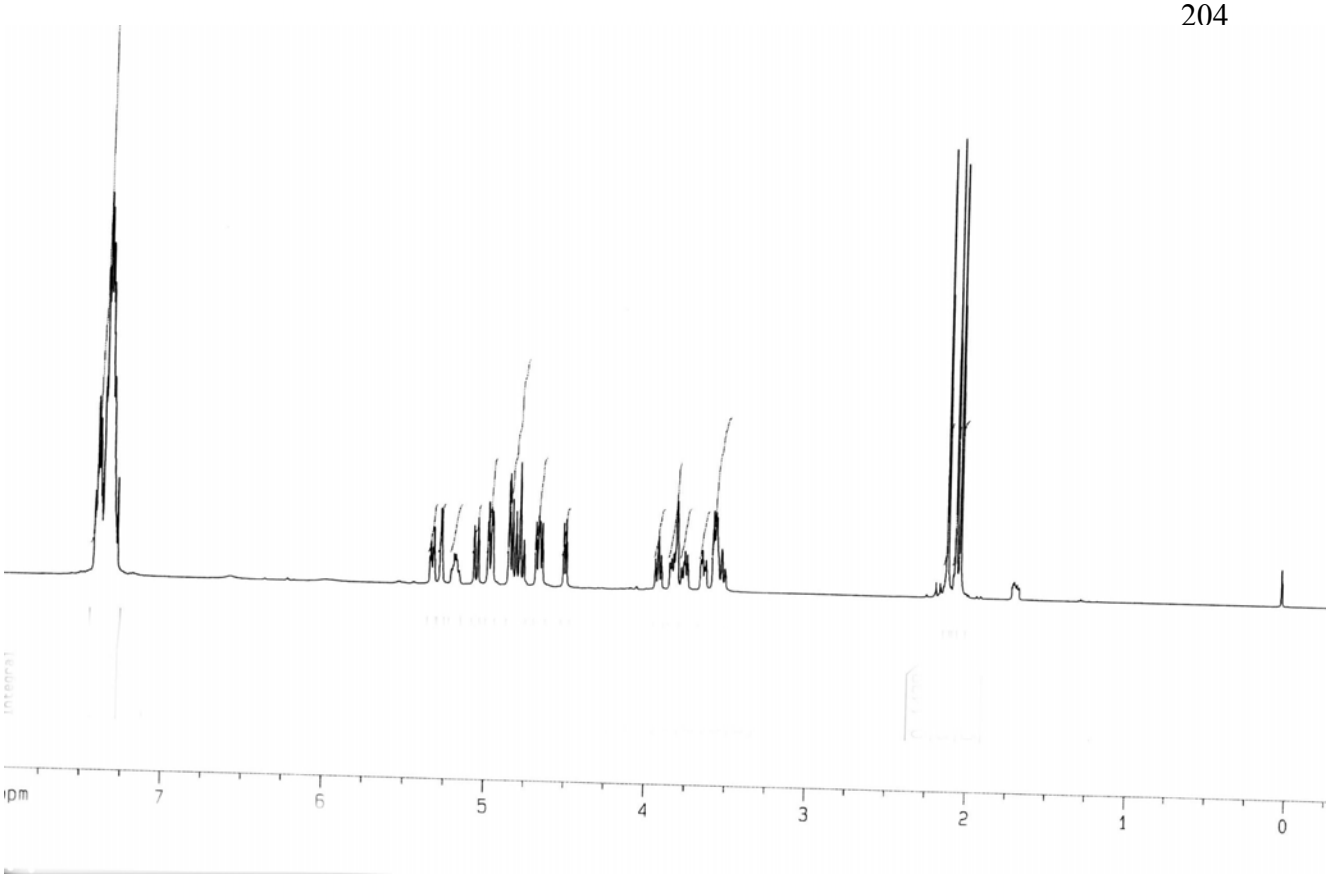
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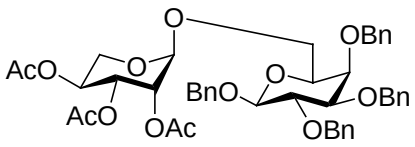
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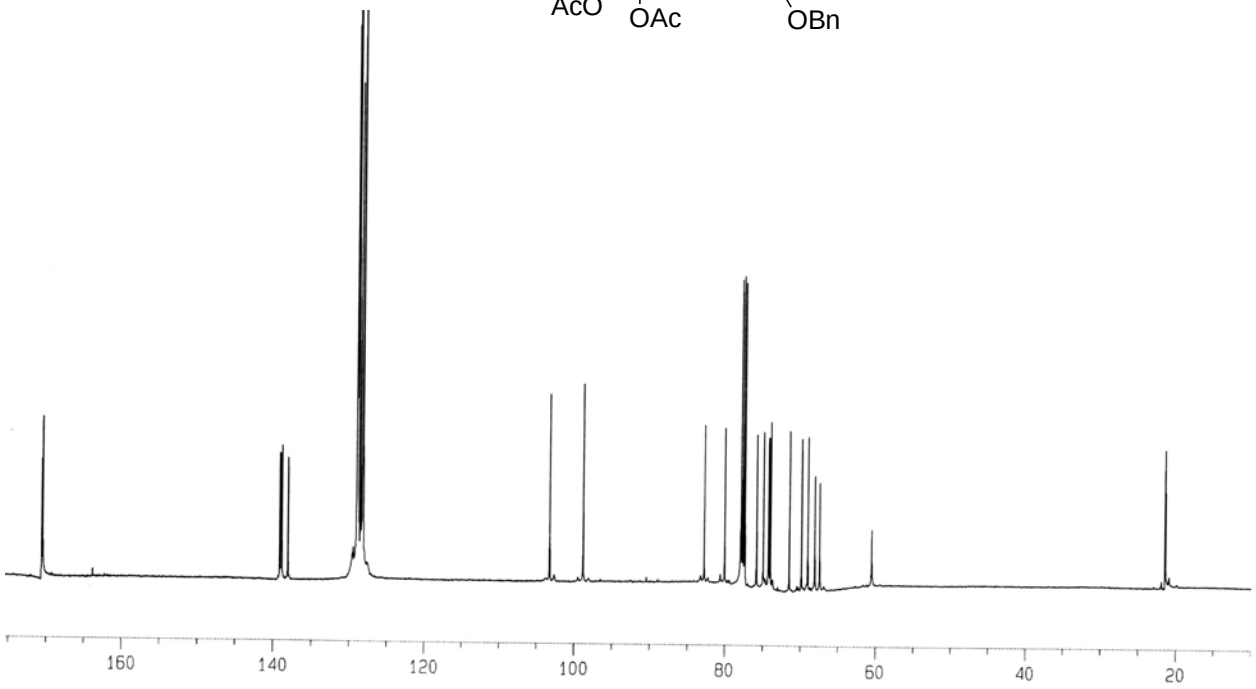
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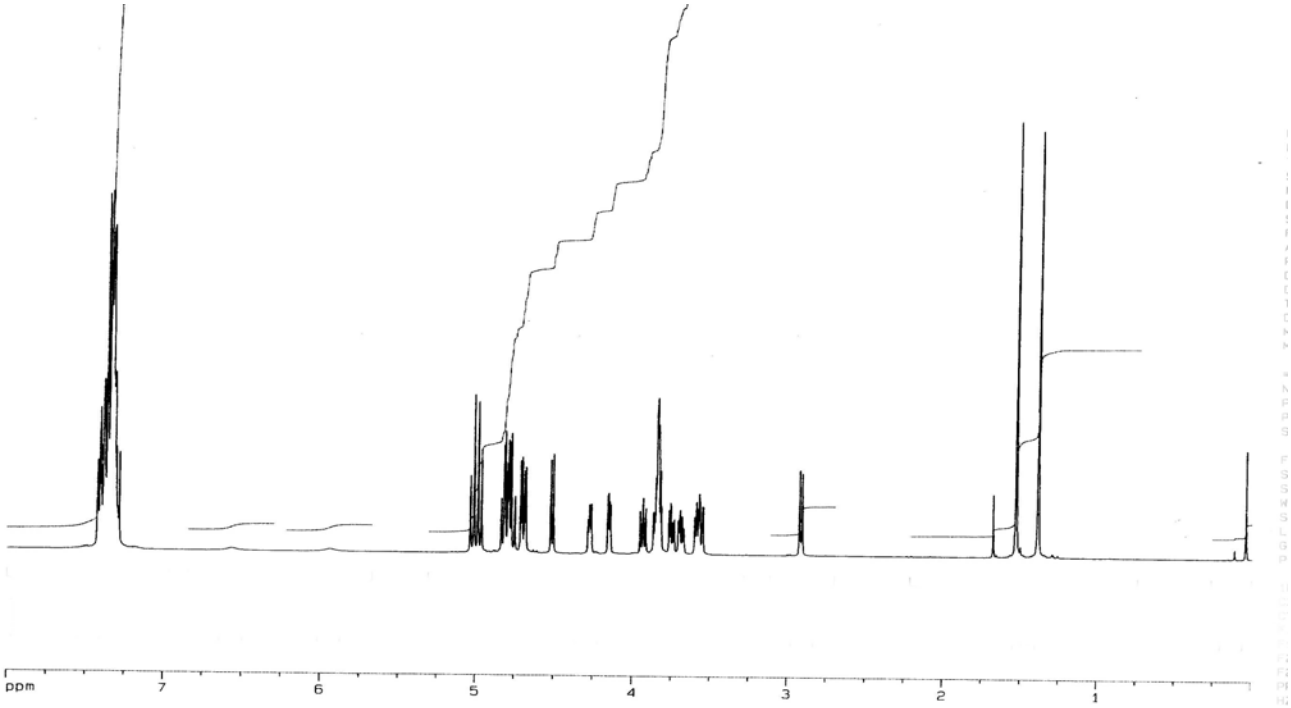
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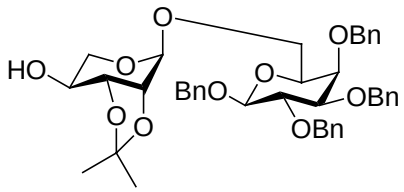
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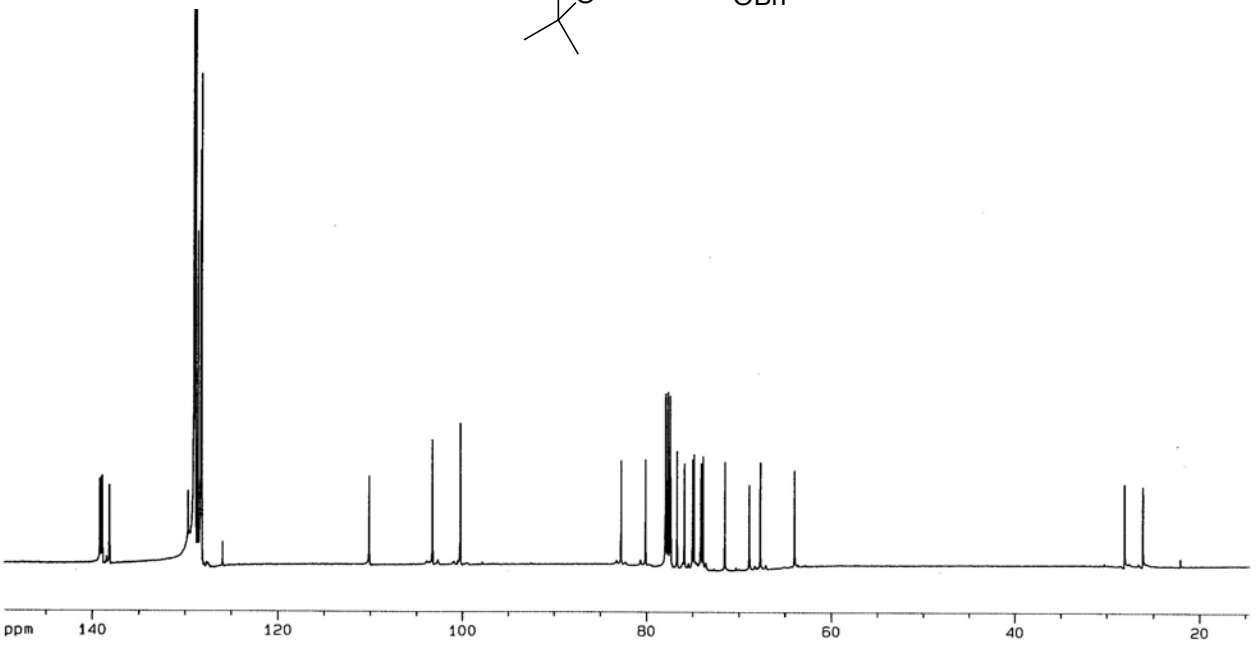
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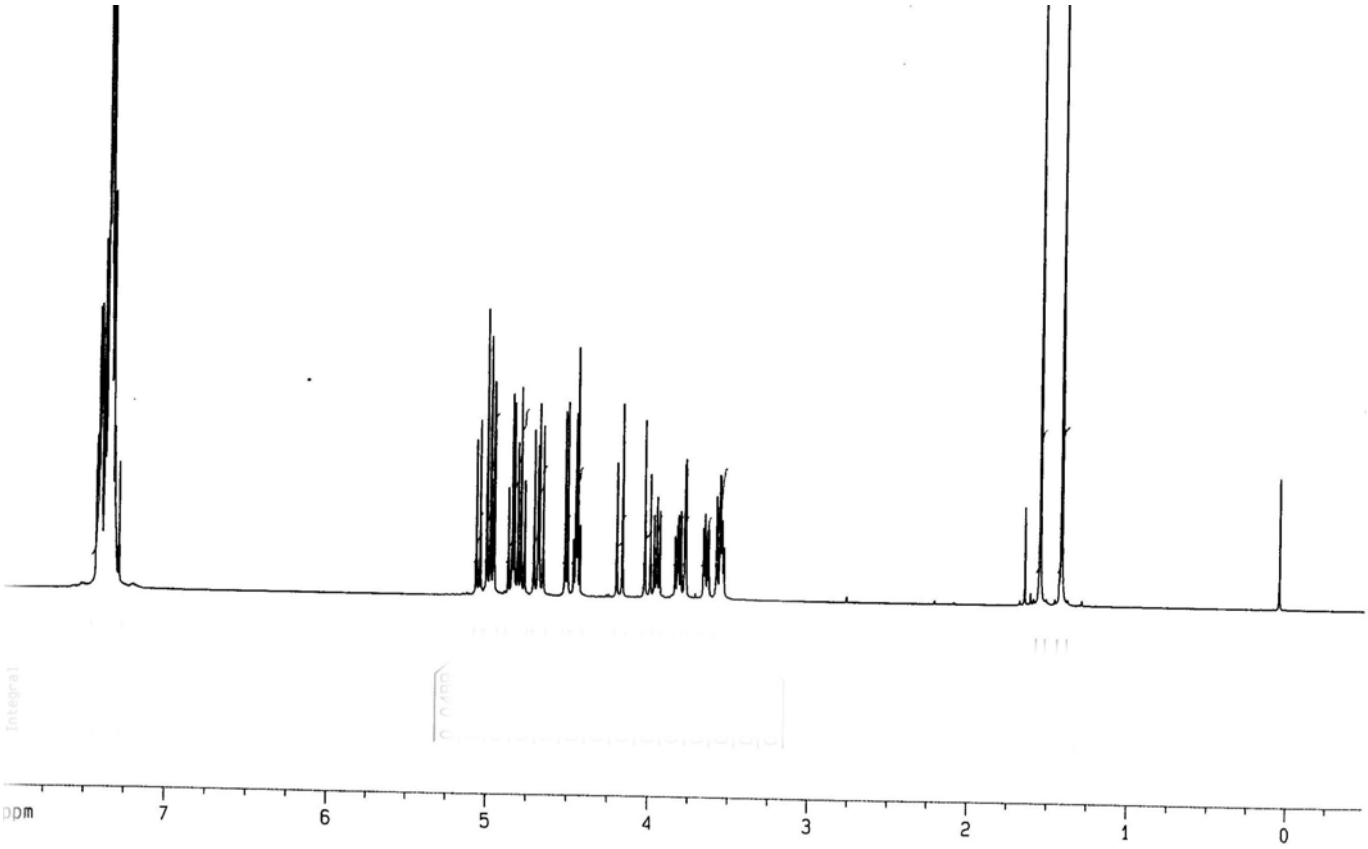
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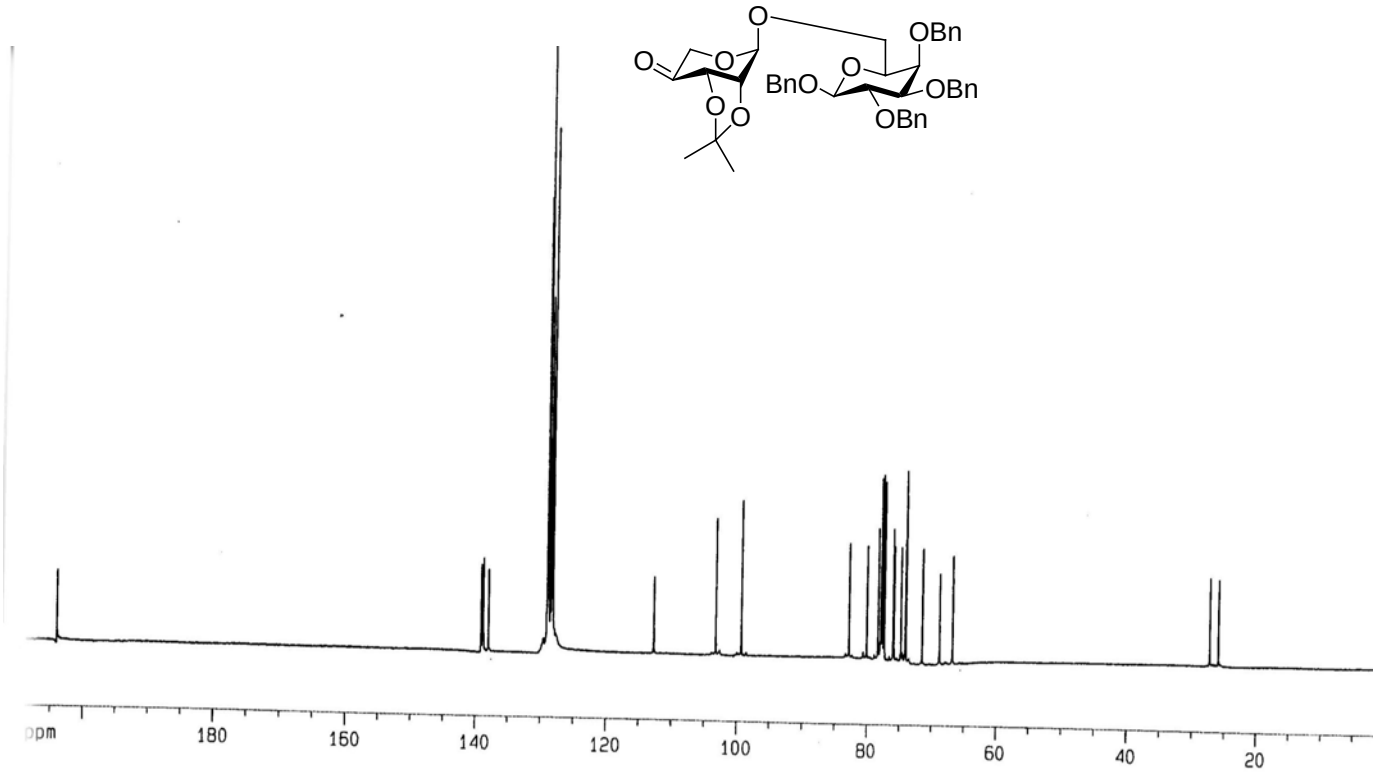
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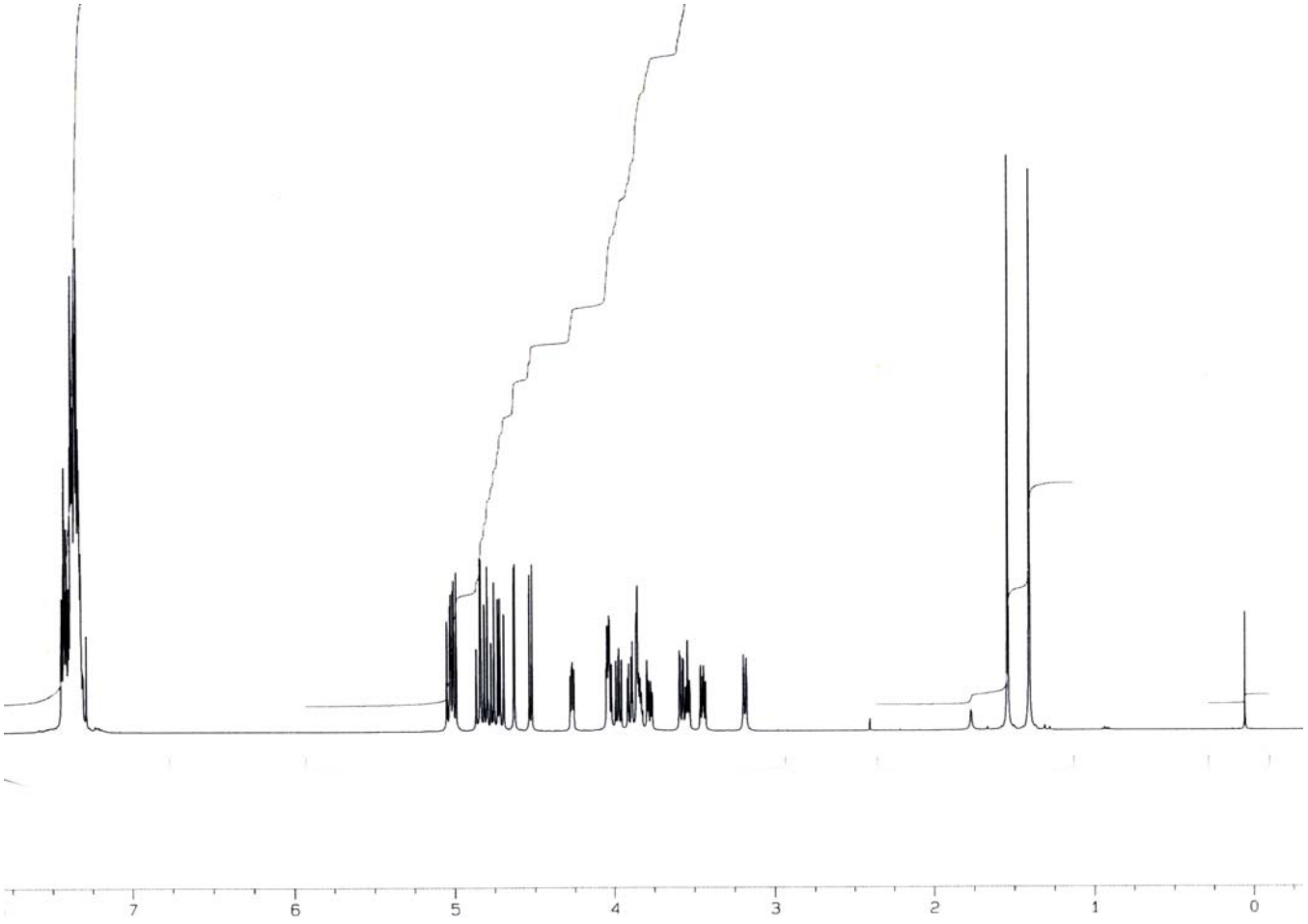
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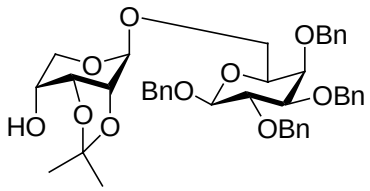
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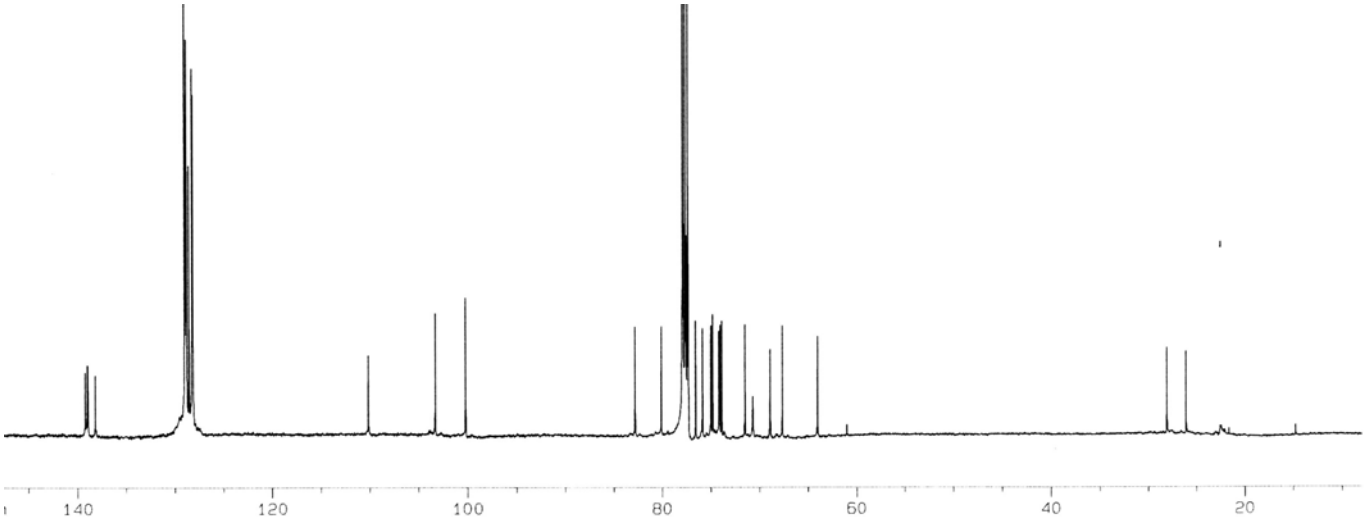
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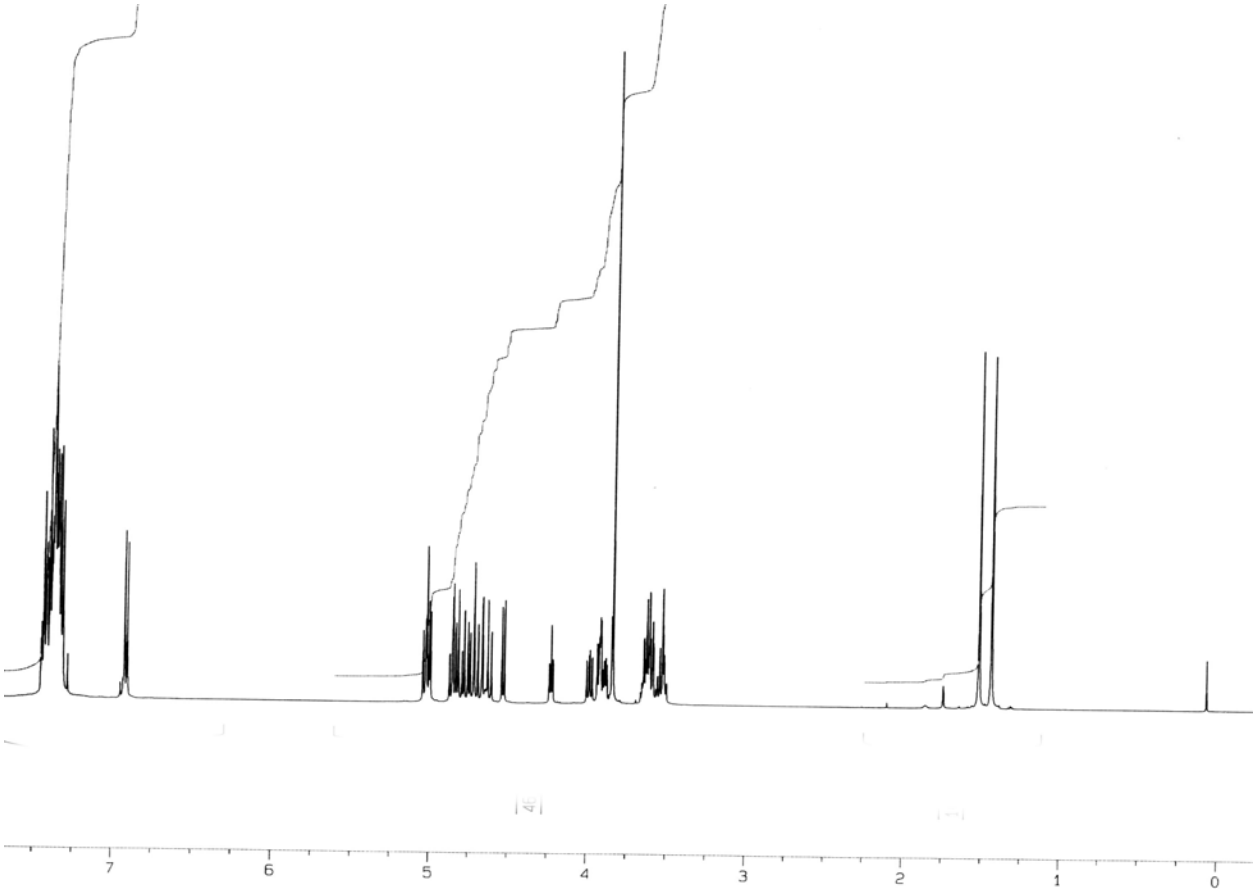
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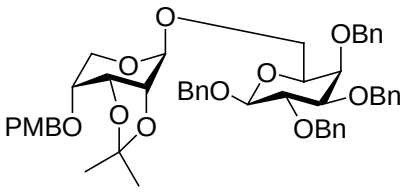
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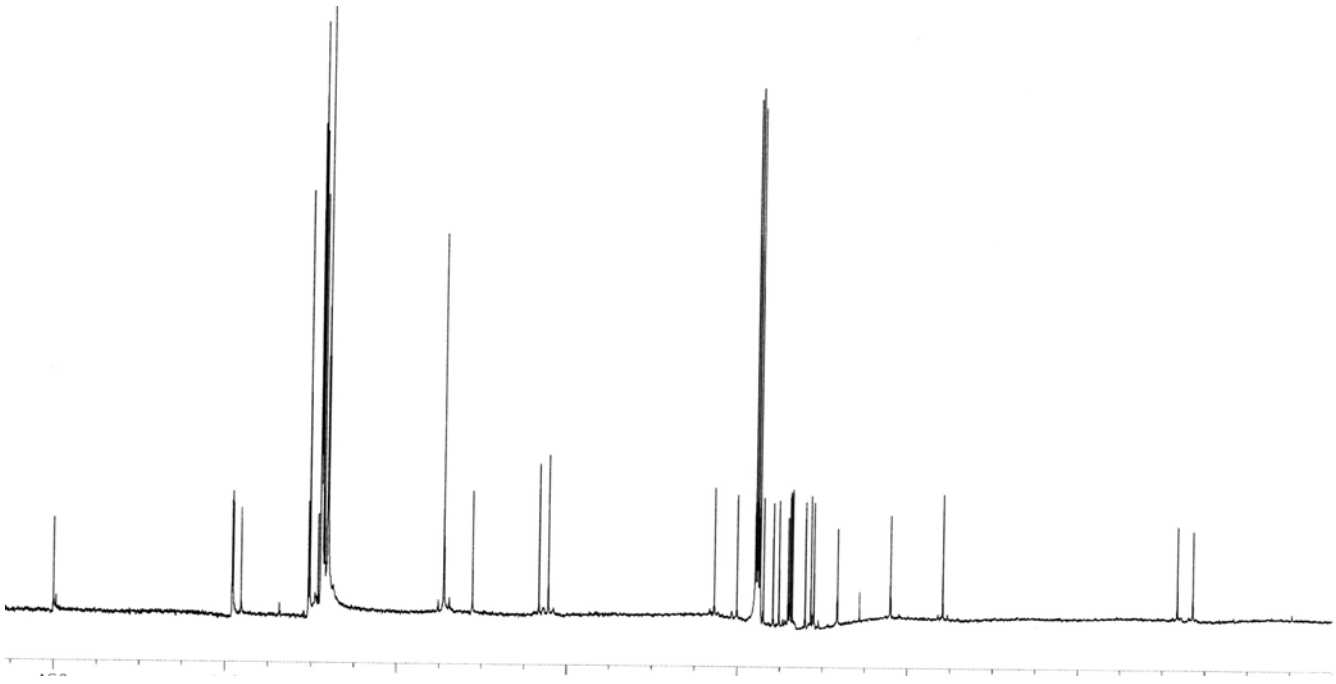

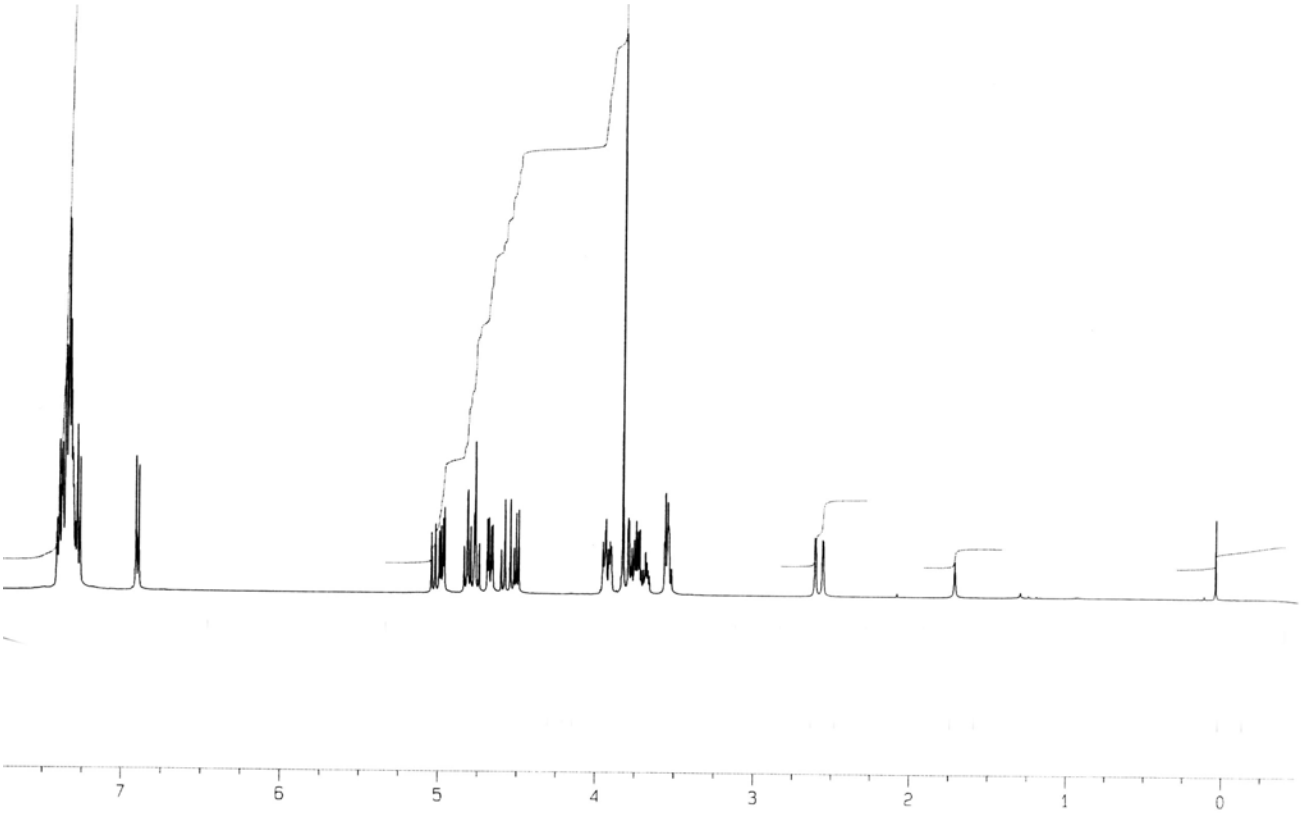
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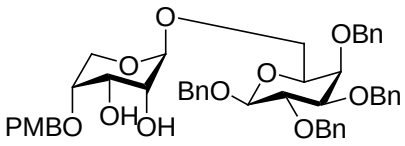
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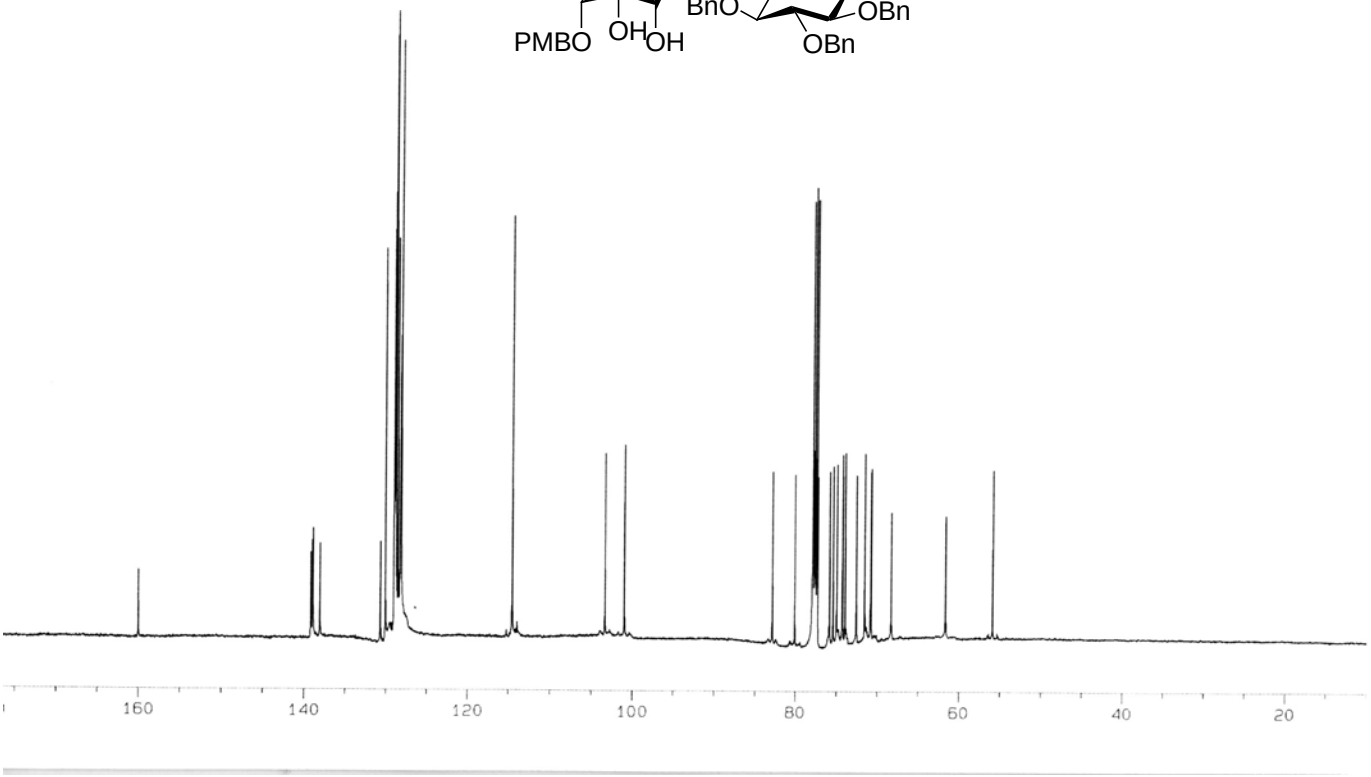
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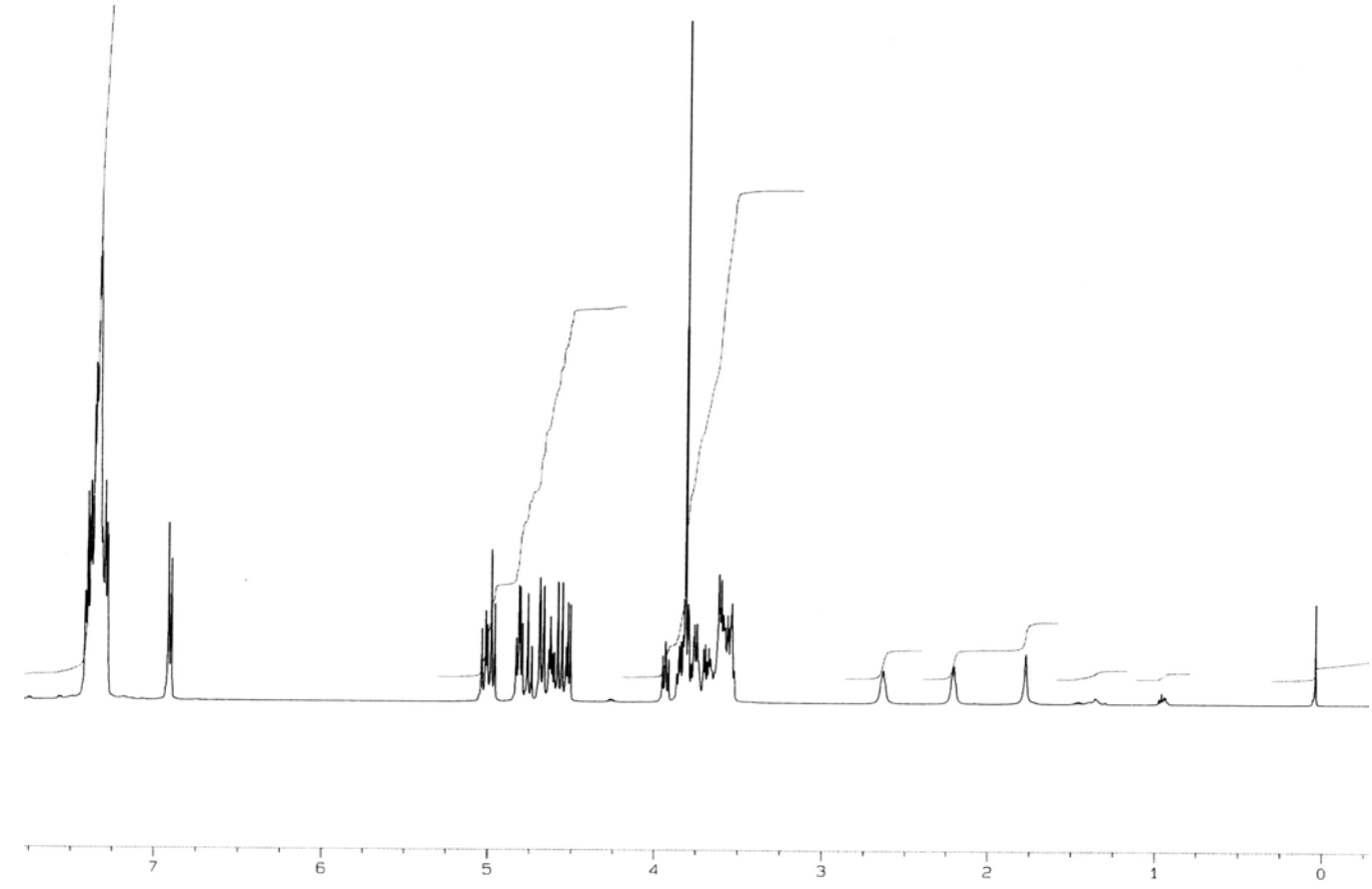
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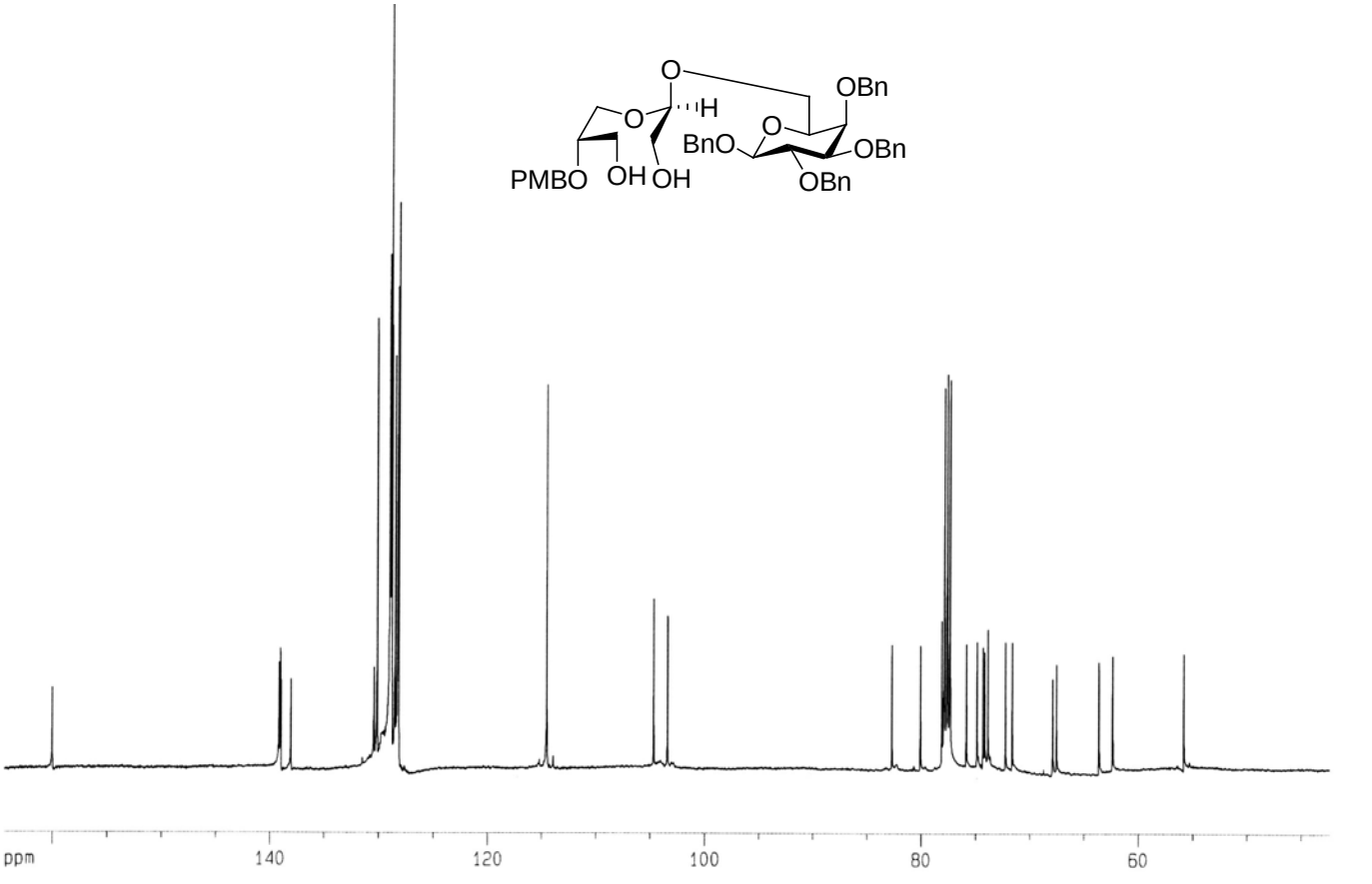
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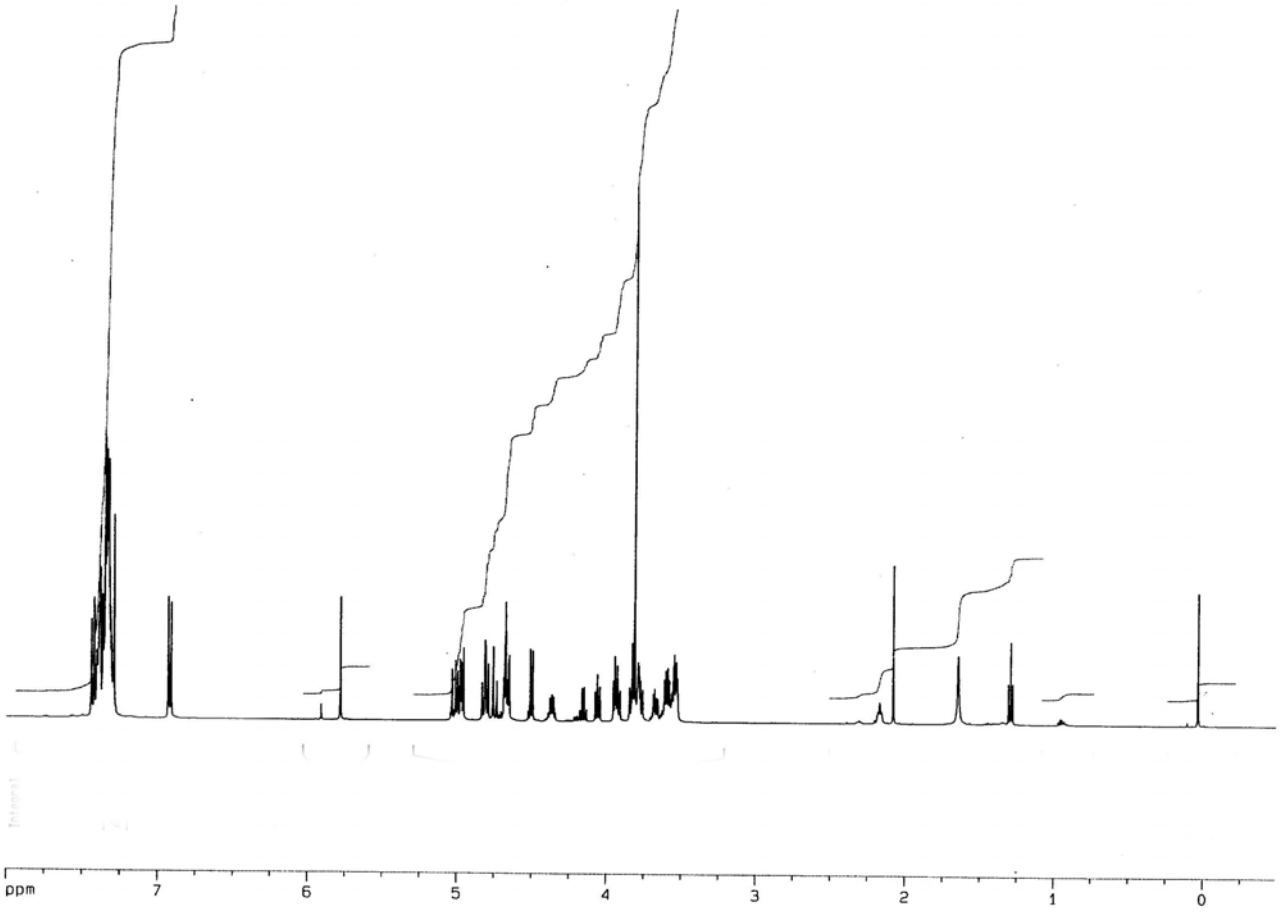
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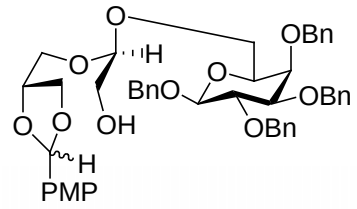
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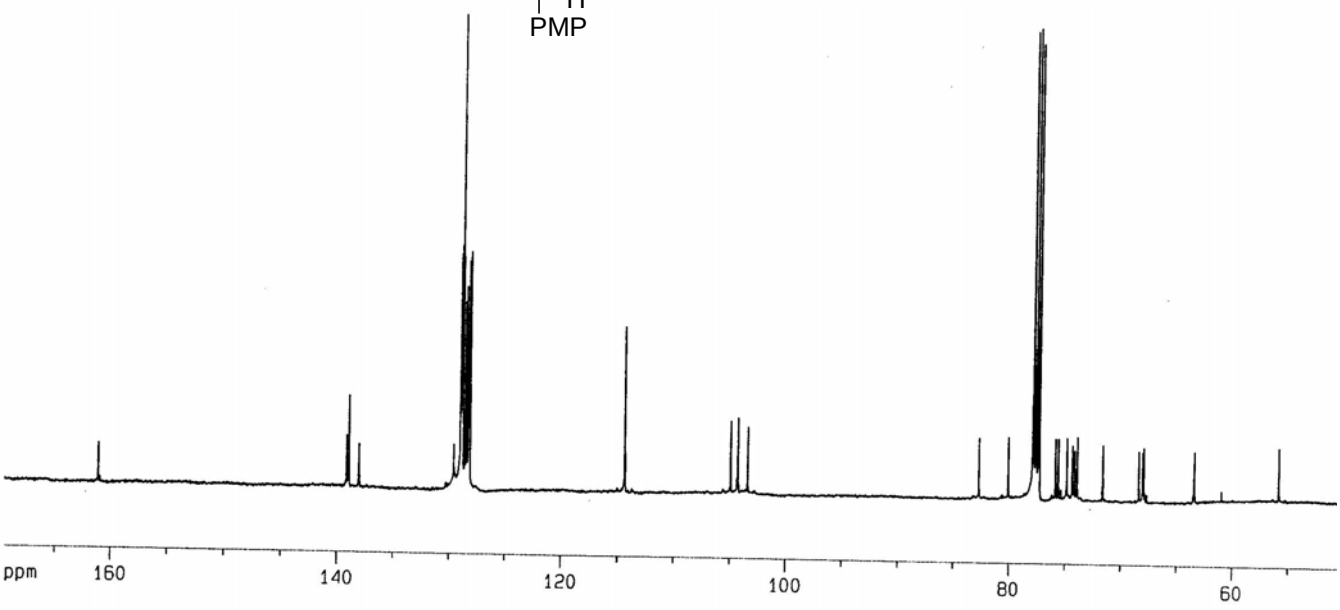
PMP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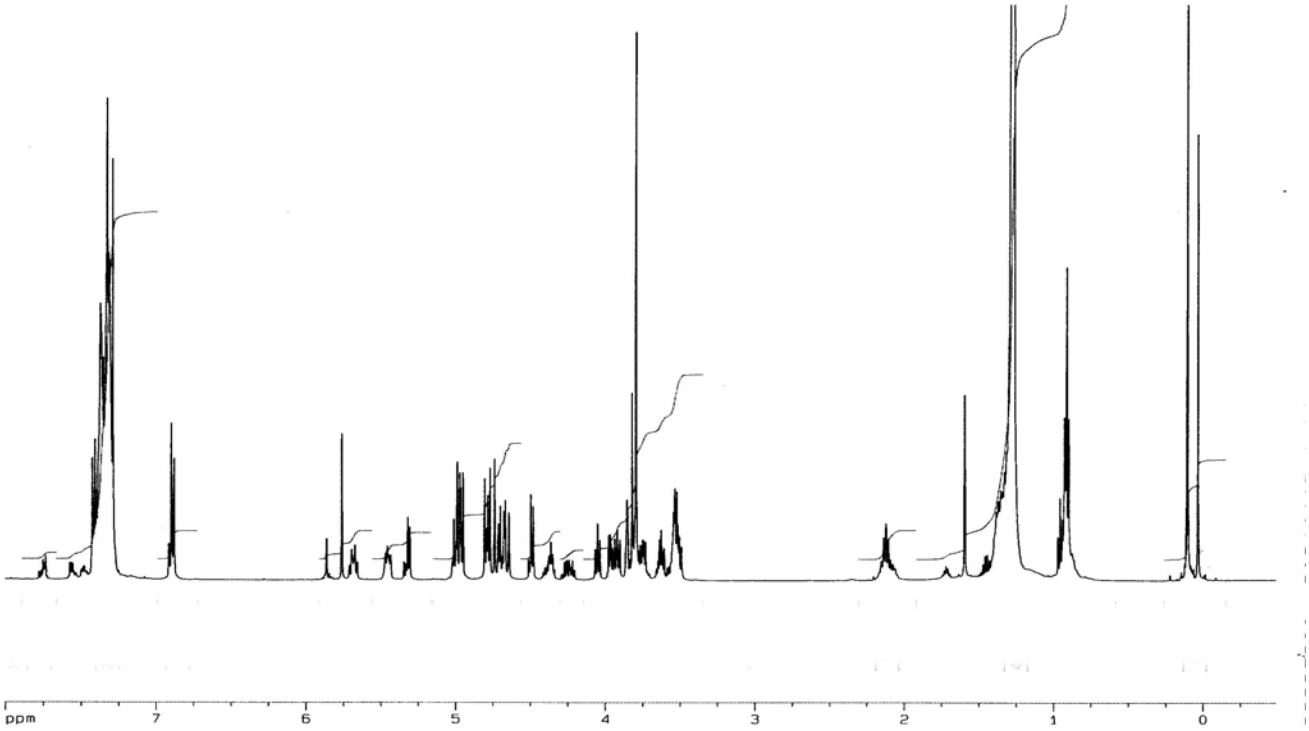
ppm
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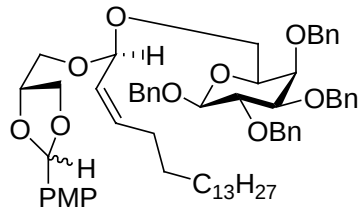
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OBn
OBn
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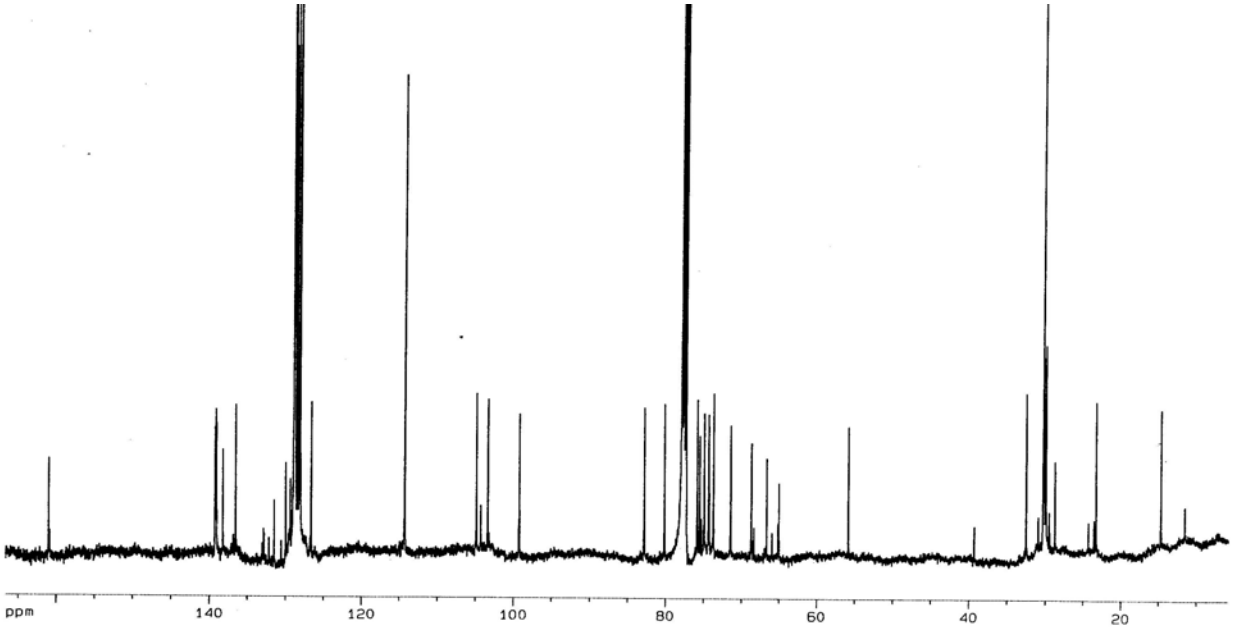
O
H
PMP
C13H27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80
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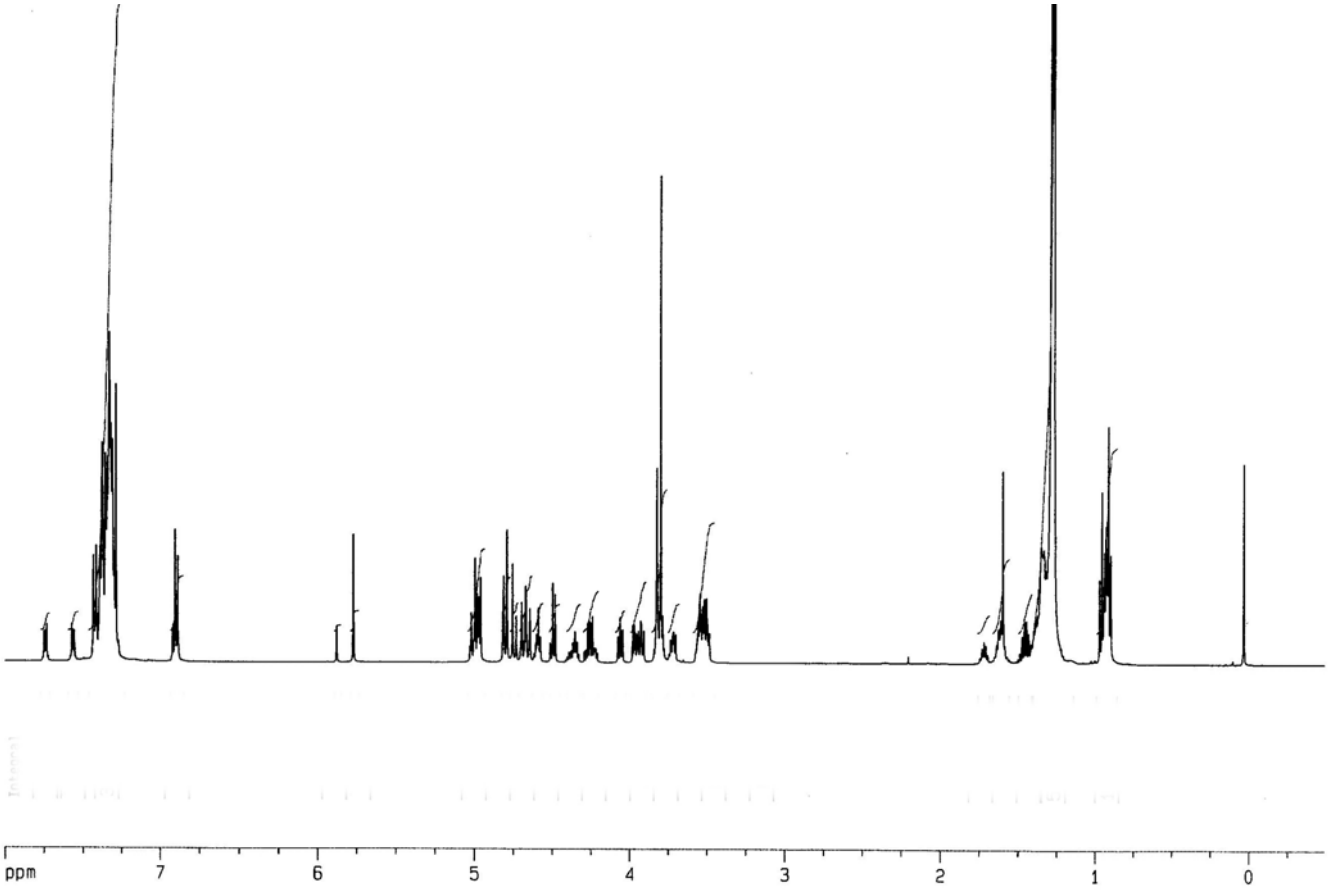
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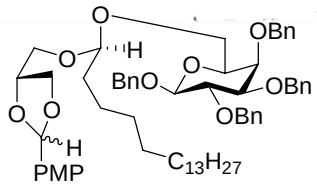
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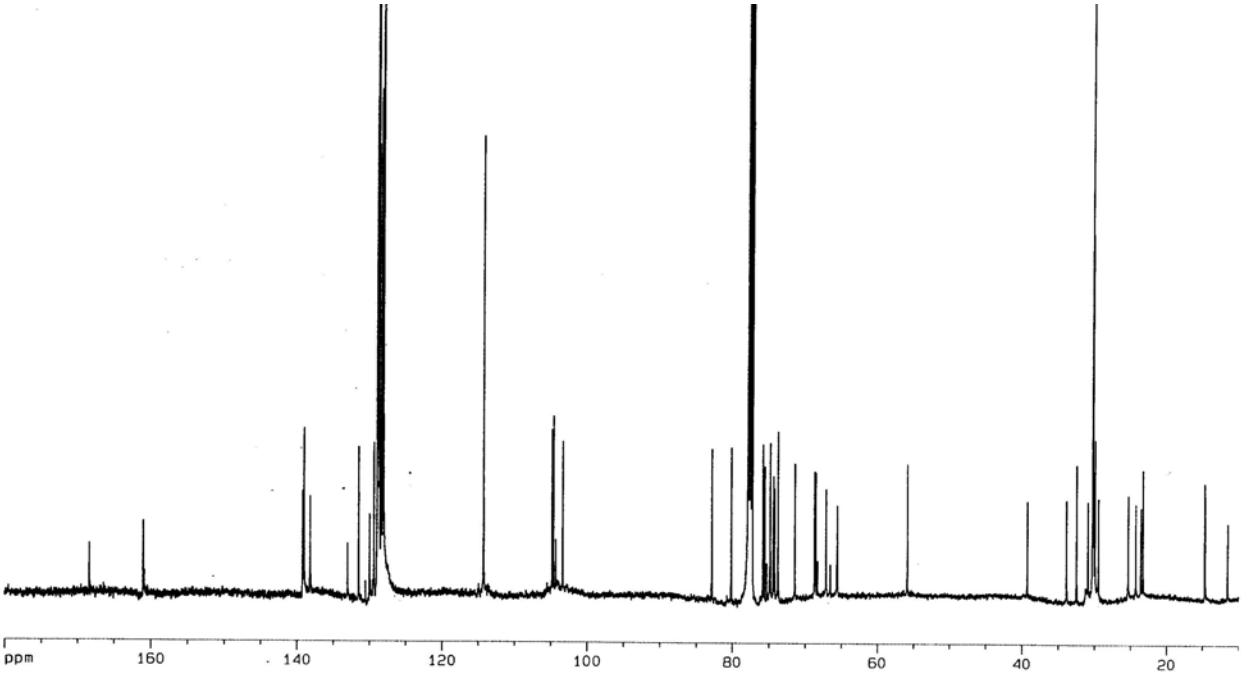
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20

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