SYNTHETIC AND MECHANISTIC STUDIES RELATED TO RIGID DERIVATIVES OF CYCLITOLS

THESIS

SUBMITTED TO THE

UNIVERSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

BY

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Dedicated to my parents

sister, brothers

and uncles

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "**Synthetic and mechanistic studies related to rigid derivatives of cyclitols**" submitted by **S. Devaraj** was carried out by him under my supervision at the National Chemical Laboratory, Pune, India. Such materials obtained from other sources have been duly acknowledged in the thesis.

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(**Dr. M. S. SHASHIDHAR**)
Research guide

DECLARATION

I hereby declare that the thesis entitled "**Synthetic and mechanistic studies related to rigid derivatives of cyclitols"** submitted for Ph. D. degree to the University of Pune has not been submitted by me for a degree to any other University.

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CONTENTS

CHAPTER 2: SECTION A

Chelation controlled regiospecific O-substitution of *myo*-inositol orthoesters: convenient access to orthogonally protected *myo*-inositol derivatives

CHAPTER2: SECTION B

Chelation controlled regioselective O-substitution in *myo*-inositol derived 1,3,5-triol and diols

CHAPTER 3

Attempted synthesis of rigid, *myo*-inositol derived, triaxial 1,3,5-triols

Chapter 1

General observations on the known methodologies for the O-substitution in *myo*-inositol, its triol and diol derivatives

Chapter 2: Section A

Chelation controlled regiospecific O-substitution of *myo*-inositol orthoesters: convenient access to orthogonally protected *myo*-inositol derivatives

Chapter 2: Section B

Chelation controlled regioselective O-substitution in *myo*-inositol derived 1,3,5-triol and diols

Chapter 3

Attempted synthesis of rigid, *myo*-inositol derived, triaxial 1,3,5-triols

ABBREVIATIONS

Ac	Acetyl
Ac_2O	Acetic anhydride
AIBN	Azoisobutryonitrile
All	Allyl
AMOH	Acetylmandelic acid
anhyd	Anhydrous
Bn	Benzyl
BOC	*tert*-Butoxycarbonyl
BOM	Benzyloxymethyl
Bt	Butyryl
n-Bu	Normal Butyl
t-Bu	*tert*-Butyl
Bz	Benzoyl
Calcd.	Calculated
Cat.	Catalytic
Conc	Concentrated
m-CPBA	*m*-Chloroperbenzoic acid
CSA	Camphorsulfonic acid
DAG	Diacylglycerol
DBU	1,8-Diazabicyclo[5,4,0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DIBAL-H	Diisobutylaluminium hydride
DIPEA	Diisopropylethylamine

DMAP	4-*N*,*N*-Dimethylaminopyridine
DMF	*N*,*N*-Dimethyl formamide
DMSO	Dimethyl sulfoxide
DSC	Differential scanning calorimetry
ee	Enantiomeric excess
eq	Equivalent
Et	Ethyl
EtOAc	Ethyl acetate
g	Gram
GPI	Glycosyl phosphatidyl inositol
h	Hour(s)
HPLC	High performance liquid chromatography
Hz	Hertz
Ins(1,4,5)P_3	D-*myo*-inositol-1,4,5-trisphosphate
Ins(1,2-cyc,4,5)P_3	D-myo-inositol-1,2-cyclic,4,5-trisphosphate
IR	Infrared
M	Molar
Me	Methyl
MeCN	Acetonitrile
MEM	2-Methoxyethoxymethyl
MHz	Mega Hertz
min.	Minute(s)
mL	Milli liter
mmol	Milli Mole
mnt	Menthyl

mp.	Melting point
NIS	*N*-Iodosuccinimide
NMR	Nuclear Magnetic Resonance
ORTEP	Oak Ridge thermal ellipsoid plot
Ph	Phenyl
PMB	*p*-Methoxybenzyl
PNB	*p*-Nitrobenzyl
i-Pr	*iso*-propyl
psi	Per square inch
Pyr	Pyridine
R_f	Retention factor
rt	Room temperature (23-30 ºC)
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPDS	1,3-(1,1,3,3-Tetraisopropyldisiloxanylidene)
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
Tr	Trityl (or) triphenylmethyl
Ts	*p*-Toluenesulfonyl
TsOH	*p*-Toluenesulfonic acid
UV	Ultraviolet

Synopsis of the Thesis

The thesis entitled '**Synthetic and mechanistic studies related to rigid derivatives of cyclitols**' is divided in to three chapters. The first chapter consists of a review of the relevant literature pertaining to the chemistry of *myo*-inositol necessary to place the work described in the subsequent chapters in proper context. The second chapter consists of the experimental work done to develop a general methodology useful for the preparation of *myo*-inositol derivatives. The third chapter describes the attempts towards the preparation of rigid derivatives of *myo*-inositol to achieve the goal mentioned above.

Chapter 1: General observations on the known methodologies for the O-substitution in *myo*-inositol, its triol and diol derivatives.

In the past two decades a large amount of research has been carried out on the chemistry and biochemistry related to inositols[1], mainly due to the realization of the role played by phosphorylated *myo*-inositol derivatives in important biological phenomena such as cellular signal transduction, calcium mobilization, insulin stimulation, exocytosis and anchoring of certain proteins to the cell membranes.[2] These developments in biology, with wide implications in the field of medicine, necessitated simpler methods for the synthesis of various inositol derivatives. *myo*-Inositol **1** being inexpensive and naturally abundant has served as a good starting material for the preparation of phosphoinositols, their derivatives and analogs as well as some natural products (for example polyoxin J, Nojirimycin, Sphingofungin D).[3] Hence this chapter gives a survey of the literature pertaining to the reactions of *myo*-inositol (hydroxyl groups) and its partially protected derivatives. Results presented in this chapter emphasize on the observed regioselectivity during the O-substitution reactions of *myo*-inositol as well as triols and diols derived from it (Chart 1).

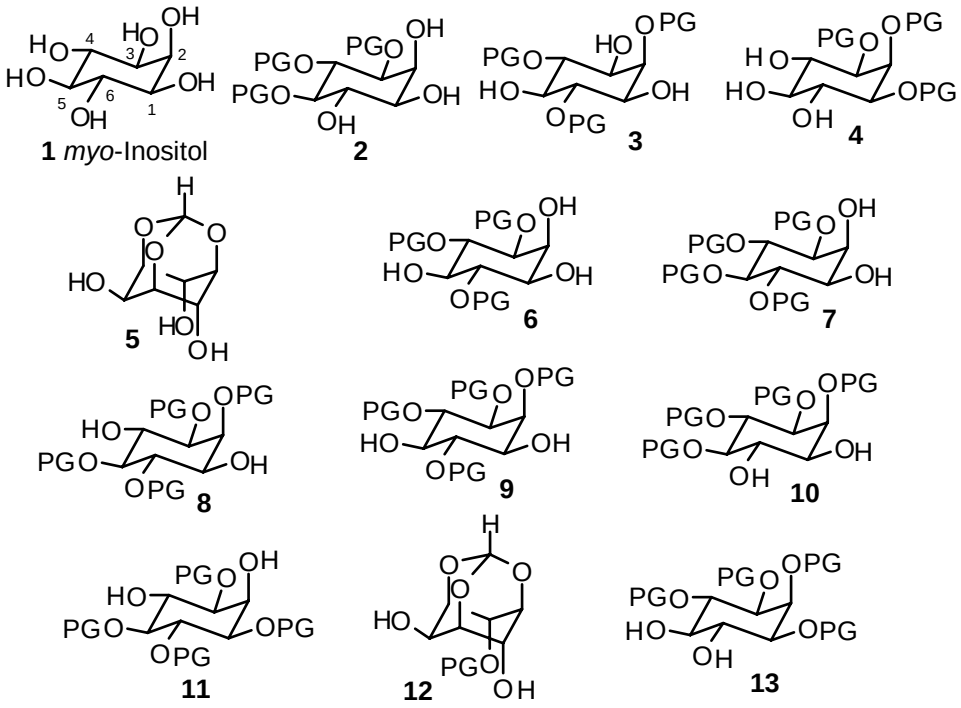
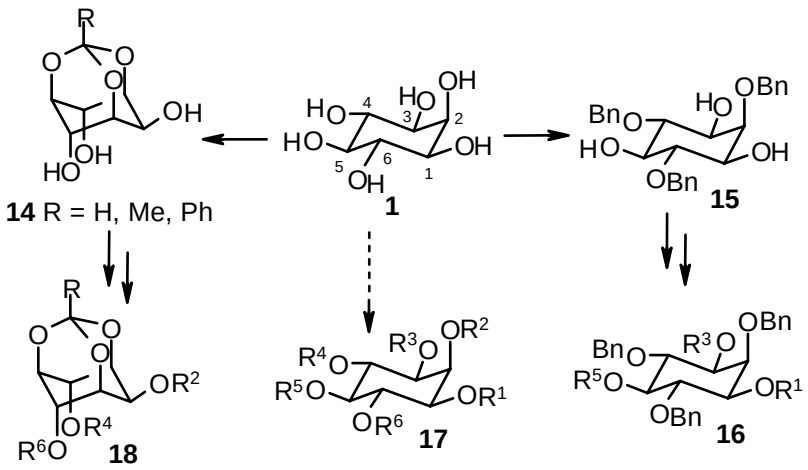


Chart 1 PG = protecting group

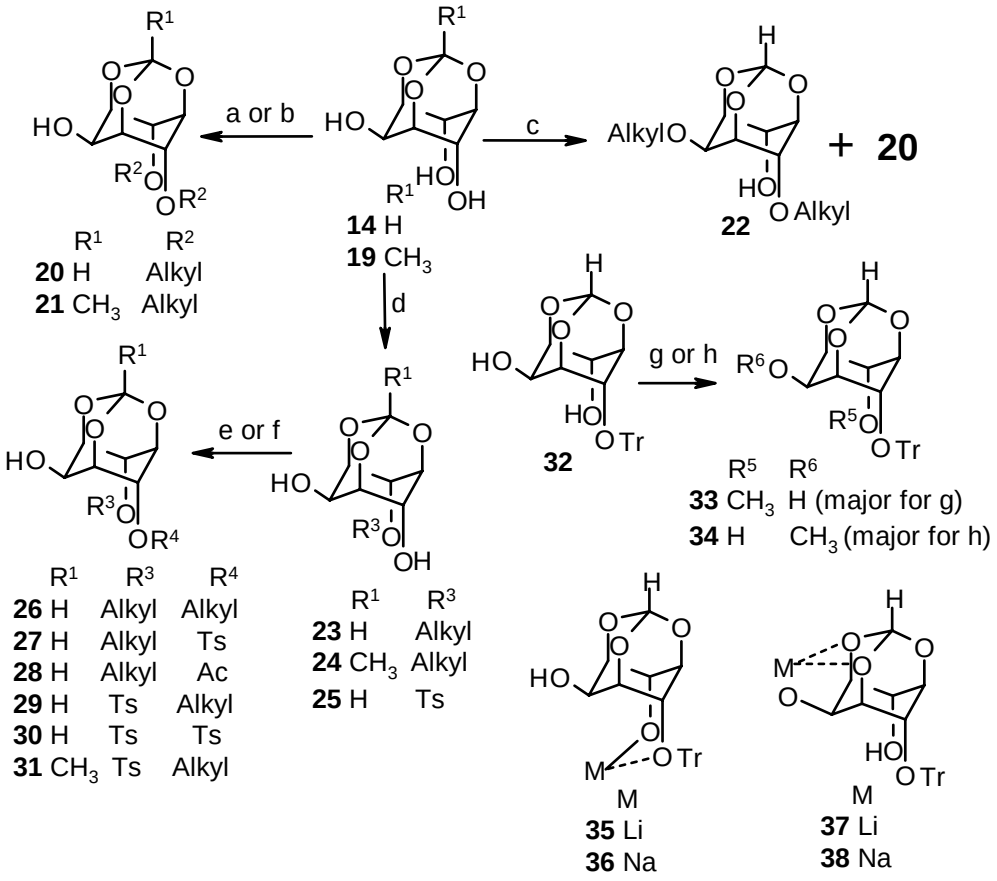
Although, regio- and enantioselective reactions of *myo*-inositol hydroxyl groups are known to occur in living systems, there is no method for the regioselective O-substitution of any one of the six hydroxyl groups (of *myo*-inositol) exclusively and perhaps it is not easy to achieve this in the laboratory. Hence our approach was to prepare two *myo*-inositol based triols (**14** and **15**) and develop methods for the regioselective O-substitution in them in such a way that each step is regioselective to one of the hydroxyl groups. Such an approach in principle would allow regioselective O-substitution of all the six *myo*-inositol hydroxyl groups (**17**, Scheme 1). Since the triols, *myo*-inositol 1,3,5-orthoformate (**14**) and 2,4,6-tri-O-benzyl-*myo*-inositol (**15**) can be obtained easily in high yields,[4] we have studied the relative reactivity of hydroxyl groups in these two triols and developed methods for the regioselective protection in these *myo*-inositol derivatives.



Scheme 1

Chapter 2: Section A: Chelation controlled regiospecific O-substitution of *myo*-inositol orthoesters: convenient access to orthogonally protected *myo*-inositol derivatives.

This section describes the work that led to the development of a general method for the sequential regiospecific O-substitution of all the three hydroxyl groups present in *myo*-inositol 1,3,5-orthoesters. This could be achieved utilizing the subtle differences in reactivity exhibited by alkali metal alkoxides of *myo*-inositol 1,3,5-orthoesters, due to differences in their ability to form chelates. This method provides convenient access to orthogonally protected *myo*-inositol derivatives (Scheme 2). A comparison of the methylation of racemic 4-*O*-trityl-*myo*-inositol 1,3,5-orthoformate (**32**) in the presence of sodium or lithium ions showed that stabilization of the C4-alkoxide by chelation with lithium overrides steric hindrance offered by the C6-axial substituent in deciding the regioselectivity during the nucleophilic O-substitution. Scheme 2 shows the summary of the results presented and discussed in this section which were rationalized based on the difference in the abilities of sodium and lithium ions to form chelates (**35-38**) with oxygen atoms in *myo*-inositol-1,3,5- orthoformate derivatives.

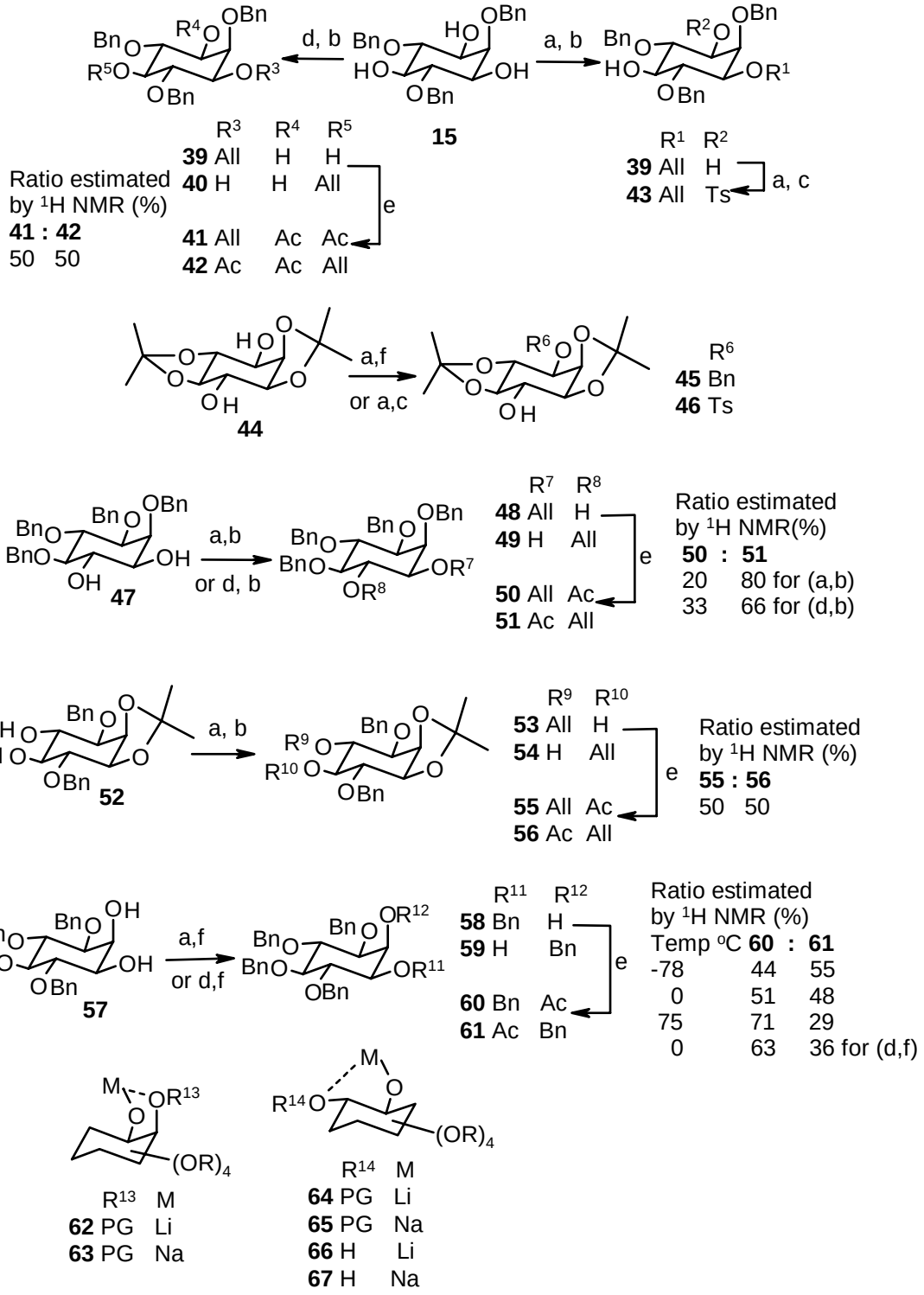


Scheme 2. a) (i) n-BuLi (2eq) / THF; (ii) alkyl halide (2eq) / DMF; b) LiH, alkyl halide, DMF; c) NaH (2eq), alkyl halide (2eq), DMF; d) NaH (1eq), alkyl halide or TsCl, DMF; e) (i) n-BuLi (1eq) / THF; (ii) alkyl halide or TsCl / DMF; f) LiH, alkyl halide or TsCl or Ac_2O, DMF; g) n-BuLi / THF, MeI / DMF; h) NaH / THF, MeI / DMF.

Chapter 2: Section B: Chelation controlled regioselective O-substitution in *myo*-inositol derived 1,3,5-triol and diols.

This section describes a study on the O-substitution in a *myo*-insoitol derived 1,3,5-triol **15** and a few *myo*-inositol derived diols (**39**, **44**, **47**, **52** and **57**) via their alkoxides generated using either n-butyllithium or sodium hydirde. All the diols and triol studied in this section (Scheme 3) do not posess the orthoformate moiety and hence are not rigid. O-substitution in lithium alkoxides of the 1,3,5-triol **15** occurred exclusively at the C-1(3) hydroxyl group which has a vicinal *cis*-ether oxygen. As a result, both the C1 and C3 hydroxyl groups in **15** could be protected sequentially without disturbing the C5-

hydroxyl group. However the same reactions carried out using the sodium alkoxide resulted in a mixture of products (**39** and **40**). Similar trend (O-substitution in lithium



Scheme 3. a) n-BuLi / THF, (b) AllBr / DMF; c) TsCl / DMF; d) NaH / THF; e) Ac_2O, pyridine; f) BnBr / DMF.

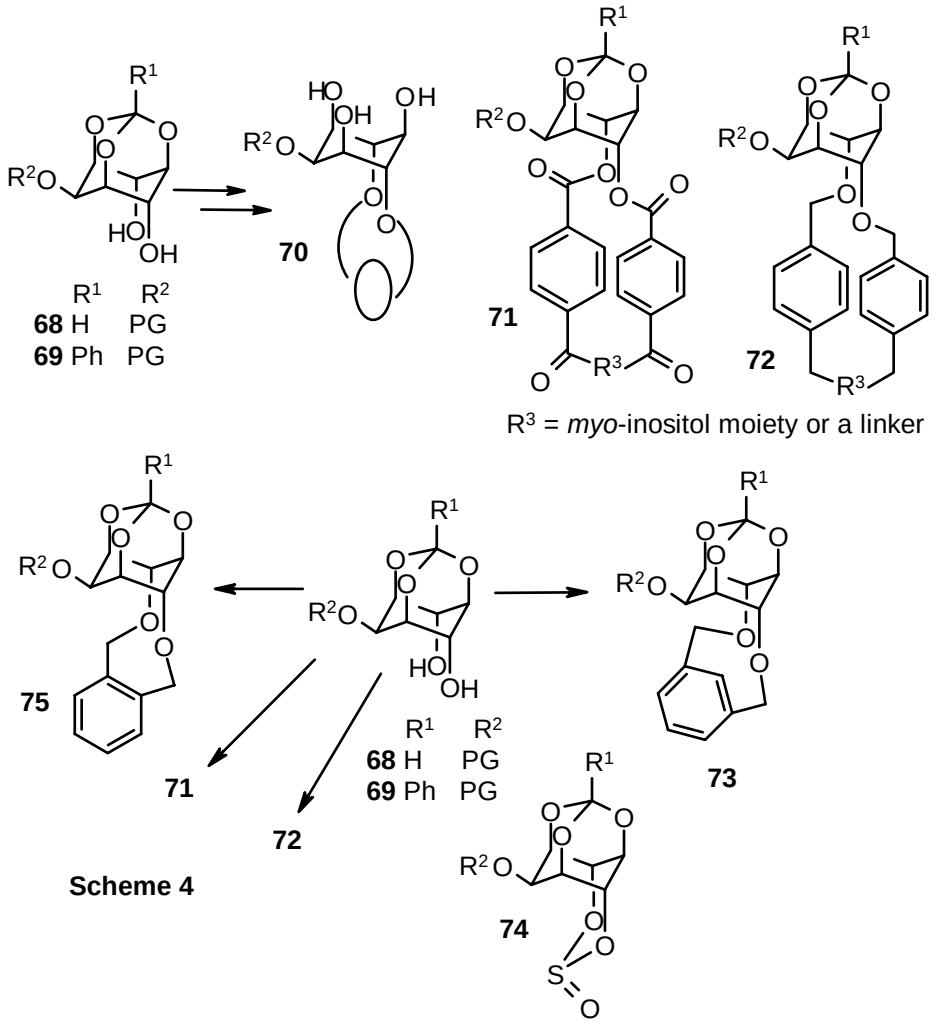
alkoxides exclusively at the hydroxyl group which has a vicinal *cis*-ether oxygen) was observed for the O-substitution of *myo*-inositol based non-vicinal diols **39** and **44**.

In the case of vicinal diols (**47**, **52** and **57**), reaction of lithium and sodium alkoxides with alkyl halides gave a mixture of products. The observed regioselectivity (for the O-substitution at a hydroxyl group next to a *cis*-oxygen) was much better in reactions where the alkoxide was generated with butyllithium as compared to the reaction where the alkoxide was generated with sodium hydride. Variation of temperature for the benzylation of the 1,2-diol **57** revealed that at lower temperatures O-substitution at the axial C2-O-position was preferred. These results suggest that the reaction of inositol derived diols and triol with alkyl halides or sulfonly chloride can be directed to a hydroxyl group having a vicinal *cis*-oxygen atom, in the presence of lithium ions. The results show that the observed regioselectivity during the O-substitution in *myo*-inositol derivatives is sensitive to reactions conditions such as the presence of the metal ion (sodium or lithium), reaction temperature and the solvent used for the reaction, which support the involvement of chelates (**62**-**67**).

Chapter 3: Attempted synthesis of rigid, *myo*-inositol derived, triaxial 1,3,5-triols.

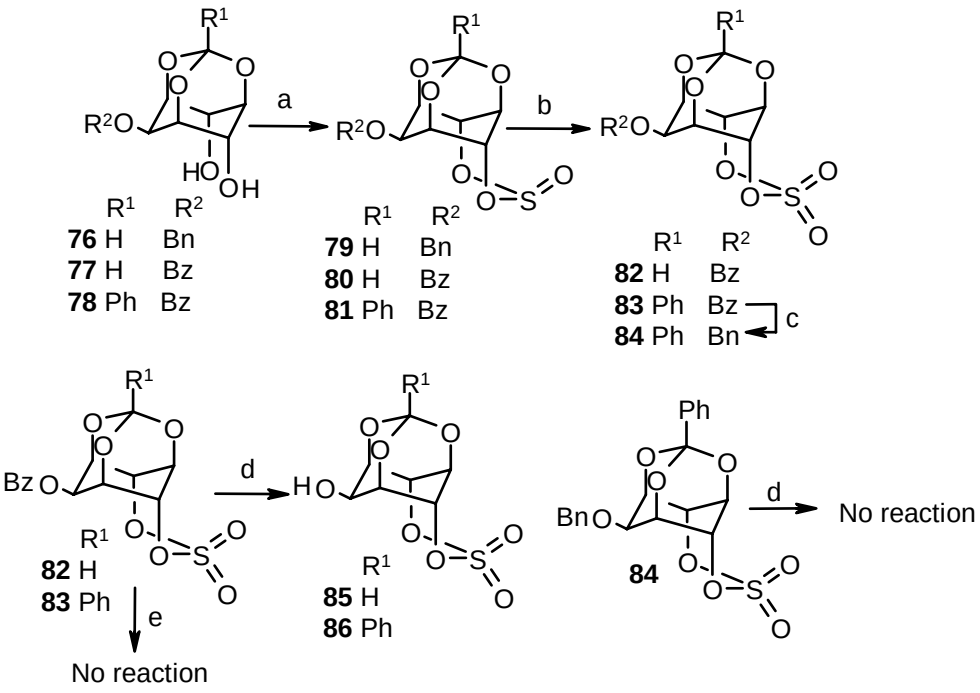
This chapter describes our attempts toward the synthesis of rigid *myo*-inositol derived triaxial 1,3,5-triols **70**. Very few cyclohexane based triaxial 1,3,5-triols are known in the literature.[5] These triols are known to complex metal ions and hence could have potential applications in separation and detection of metal ions. Also, pertaining to the chemistry of *myo*-inositol and its derivatives described in previous chapters, it was of interest to examine the regioselectivity of O-substitution reactions among the three axial hydroxyl groups in the 'axial-rich' configuration of *myo*-inositol (as in **70**). Hence we attempted to prepare *myo*-inositol derivatives locked

with a bridge between the C4 and C6 hydroxyl groups in the configuration having five axially disposed hydroxyl groups. The bridges we attempted to make are shown in Scheme 4.



Scheme 4

We succeeded in making the bridge with a sulfite or a sulfate moiety (Scheme 5), but we were unable to cleave the orthoester without disturbing the sulfur-oxygen linkage. Structures of all the sulfur-bridged compounds (**79**-**84**) were established by single crystal X-ray diffraction method. The sulfite and the sulfate moiety were sensitive to acid hydrolysis (in the case of orthoformates **79**, **80**, **82**) or prevented hydrogenolysis (in the case of orthobenzoates **81**, **83**, **84**) or hydride reduction of the orthoester moiety. Reaction of *myo*-inositol orthoester derivatives with appropriate alkyl or acyl halides for the preparation of other bridged derivatives (**71, 72, 73** and **75**) resulted in mixture of products and there was no evidence for the formation of the desired products.



Scheme 5. a) $SOCl_2$, pyridine, DCM; b) $RuCl_3.H_2O$, $NaIO_4$, CH_3CN, H_2O, DCM.
c) (i) *iso*-$BuNH_2$, MeOH; (ii) NaH, BnBr, DMF; d) DIBAL, DCM;
e) $Pd(OH)_2$ / H_2, MeOH or EtOAc.

1.1. Introduction

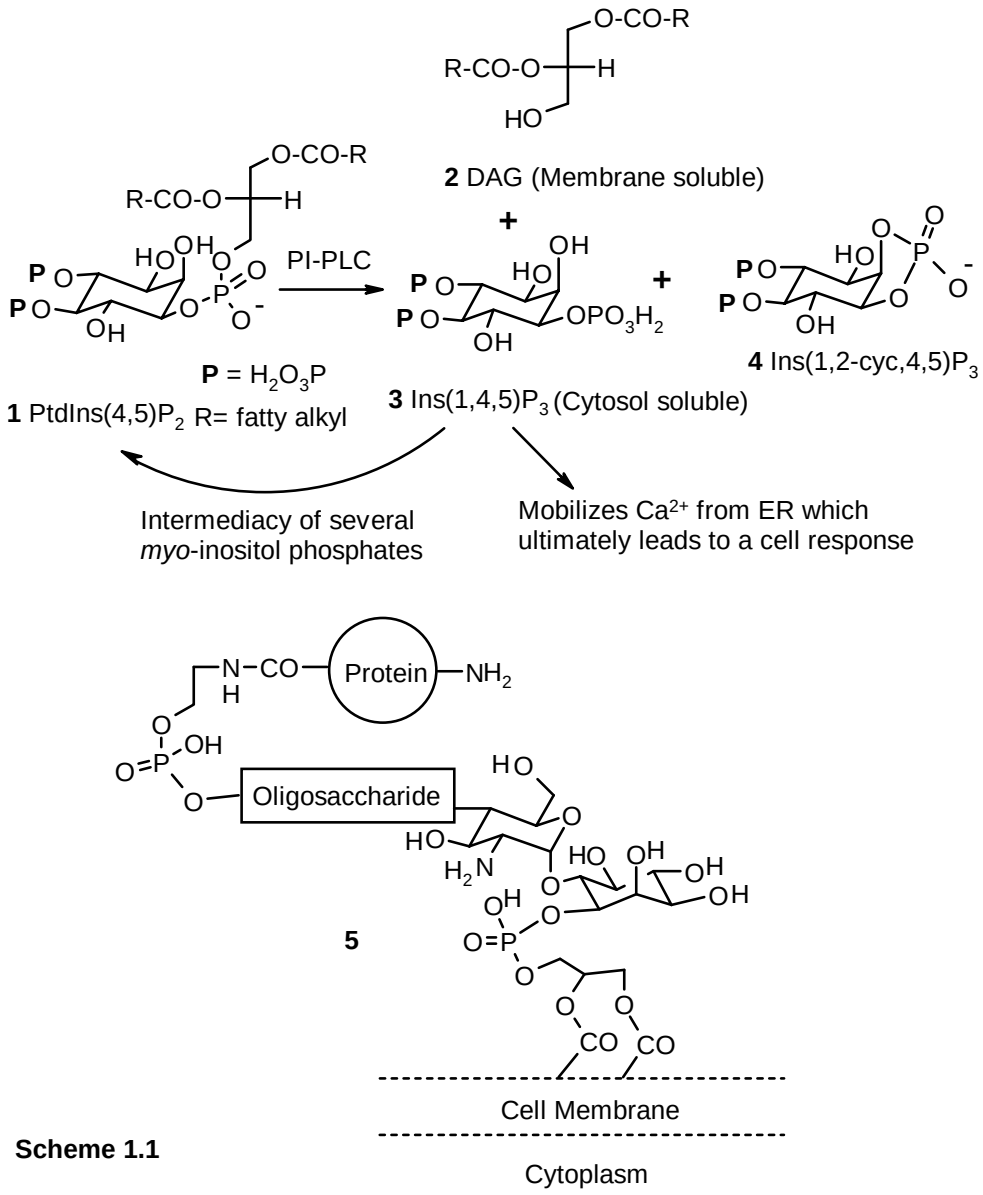
Centuries of research in chemistry resulted in an understanding of the chemical behavior of small organic molecules and enabled their characterization and classification depending on the functional groups present in them. This is essentially due to the exclusive reactions that each functional group undergoes in the presence of other functional groups in a small molecule. When several functional groups are present in the same molecule it is often difficult to carry out the desired reaction on a particular functional group due to interference from others. This led to the development of protecting groups, which aid in masking one functional group from a reagent or reaction condition while exposing the other functional groups present in the same molecule for the same reagent and hence bring about a functional group transformation, which forms the basis of organic synthesis. However, in molecules with the same kind of functional groups e.g., polyols (carbohydrates, cyclitols), polyamines, polyacids *etc.* bringing about a reaction at a particular site is an inordinate task. This is achieved in living systems with the help of enzymes, but understanding of organic reactions has not yet reached a point where this is possible in laboratory reactors.

New methodologies for the selective protection and deprotection of functional groups continue to appear in the literature regularly.[1] Understanding the reasons that govern differences in the reactivity of different functional groups in the same molecule is the key for successful regioselective functionalization of complex organic molecules. Such an understanding becomes crucial while working with molecules having non-equivalent functional groups of the same kind (polyols, polyamines,

polyacids, *etc*). In syntheses involving cyclitols and carbohydrates, hydroxyl group protection is unavoidable.

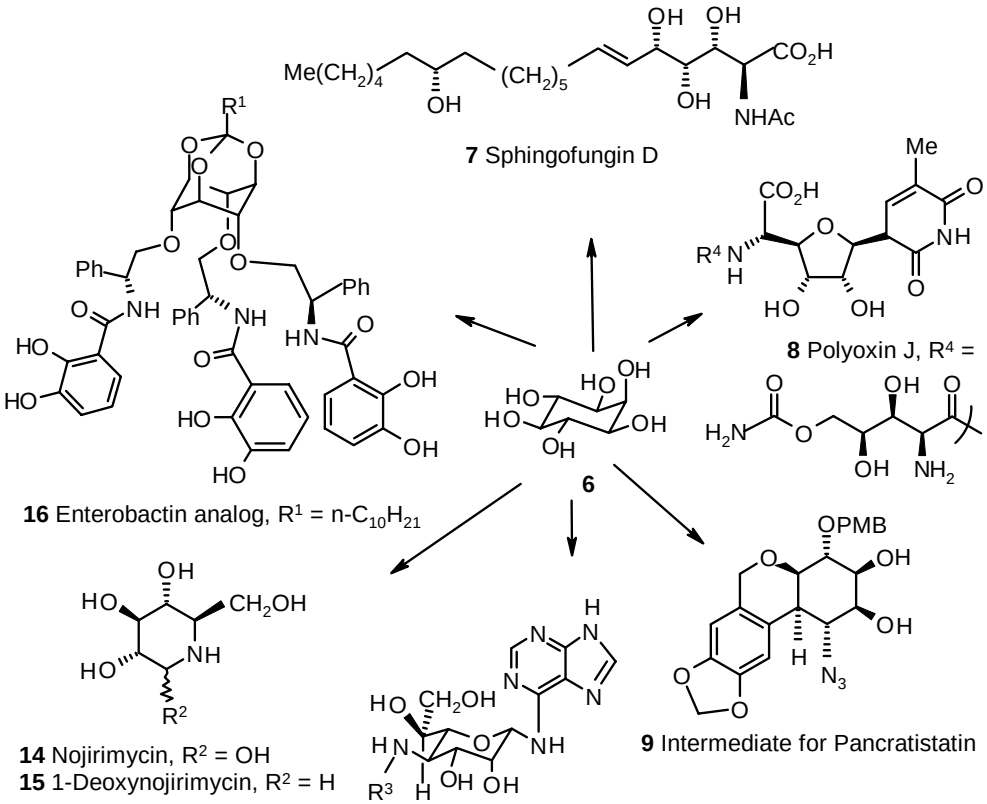
Achieving selective reaction at one hydroxyl group in polyhydroxy compounds such as carbohydrates and cyclitols or their partially protected derivatives is a challenge and a topic of current research interest.[2] This has implications for the synthesis of several classes of biologically or medicinally important compounds as exemplified by carbohydrates, oligosaccharides, inositols and their derivatives as well as natural products that can be synthesized from these polyols.[3] Classical methods for the discrimination of hydroxyl groups in a polyol include (a) selective reaction of primary alcohols, in the presence of secondary and tertiary alcohols, with electrophiles; (b) preferential O-substitution of an equatorial hydroxyl group over that of an axial hydroxyl group in cyclic alcohols; (c) preferential hydrolysis of *trans* acetals over *cis* acetals of vicinal cyclic diols.[4] Hydrolysis or reduction of orthoesters of diols and triols are also reported[5] to be specific although their use in synthesis is restricted to certain category of compounds. However, when all the nonequivalent hydroxyl groups in a molecule are secondary or tertiary in nature, obtaining selectively derivatized products is a formidable task, due to various reasons including subtle differences in their reactivity and / or difficulty in separation of isomeric products and by-products.

Phosphorylated cyclitols and their analogs have attracted the attention of chemists and biologists in the last two decades due to their involvement in various biological phenomena such as cellular signal transduction, calcium mobilization, insulin stimulation, exocytosis, cytoskeletal regulation, intracellular trafficking of vesicles and anchoring of certain proteins to cell membranes (Scheme 1.1).[3, 6]

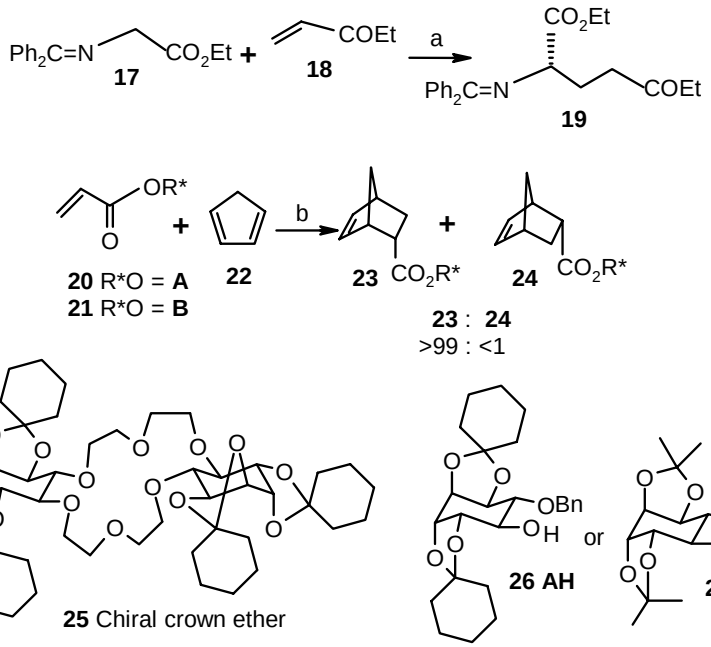


Scheme 1.1

Cyclitols have also been used as starting materials for the synthesis of natural products and their analogs having interesting biological and medicinal properties,[3d, 7] as chiral auxiliary or catalyst in asymmetric synthesis[8] (Scheme 1.2).

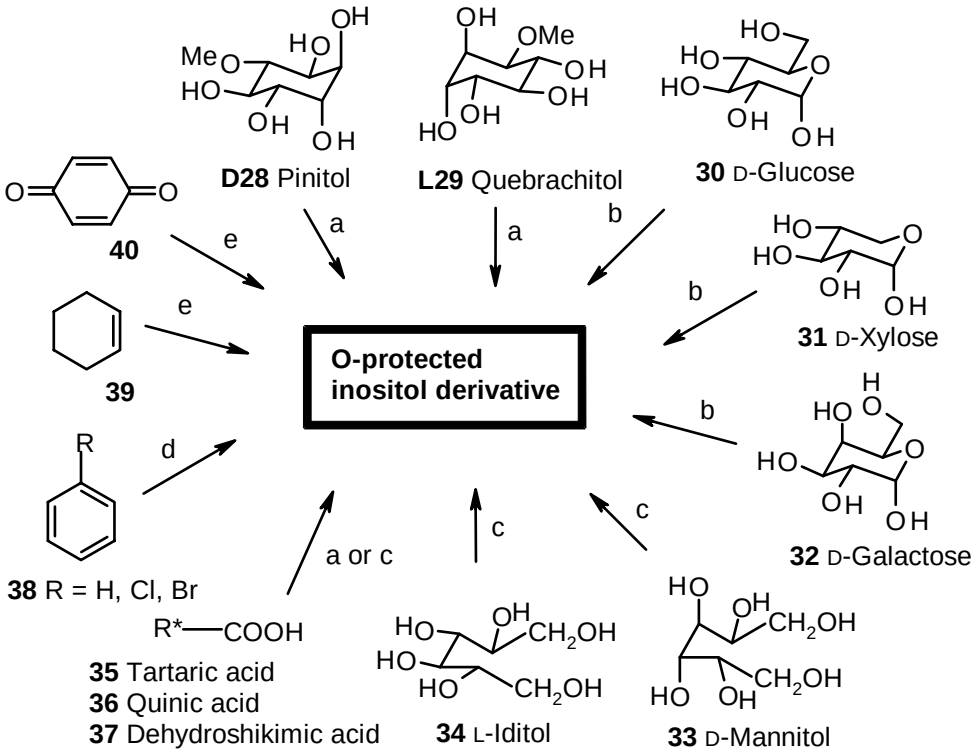


10 Spicamycin, $R^3 = Me_2CH(CH_2)_nCONHCH_2CO-$ or $MeCH_2CH_2(CH_2)_nCONHCH_2CO-$ (n = 8-14):
11 Spicamycin Amino Nucleoside(SAN), R^3 = H
12 SPM Vlll, $R^3 = Me(CH_2)_{10}CONHCH_2CO-$
13 KRN 5500, $R^3 = ME(CH_2)_8CH=CHCH=CHCONHCH_2CO-$



Scheme 1.2. a) **25**, t-BuOK (0.2 eq), DCM, -78 °C, 15 min, 65% (96% ee);
b) $TiCl_4$, Et_2O, -78 °C, 2 h, 80-90%.

Consequently, different methodologies have been developed for the regioselective protection and deprotection of inositol hydroxyl groups. Partially protected inositol derivatives can also be obtained from starting materials other than inositols (Scheme 1.3).



Scheme 1.3. a) Hydroxyl groups protection / deprotection; b) Ferrier reaction; c) SmI_2-mediated cyclization; d) *Pseudomonas putida*-mediated hydroxylation followed by dihydroxylation reactions; e) Hydroxylation.

Since the rest of this thesis deals with the reactions of *myo*-inositol and its derivatives a brief description of its nomenclature is given below. Inositols are cyclohexane hexols. Nine isomers are known in the literature (Chart 1.1), among these isomers *myo*-, *scyllo*- and *chiro*- occur in nature, the *myo*-isomer being the most abundant. *myo*-Inositol has one axial and five equatorial hydroxyl groups. The carbon bearing the axial hydroxyl group is designated as C2 and the other ring carbons can be numbered from C1 to C2 starting from a C1 atom and proceeding around the ring in clockwise or anticlockwise fashion. According to convention, an anticlockwise

numbering in asymmetrically substituted *myo*-inositol leads to the configuration with D-prefix and the clockwise numbering gives the substituted *myo*-inositol an L-prefix (Chart 1.1). An IUB nomenclature[9] allowing all biologically relevant compounds to be denoted as D-isomers has also been proposed.

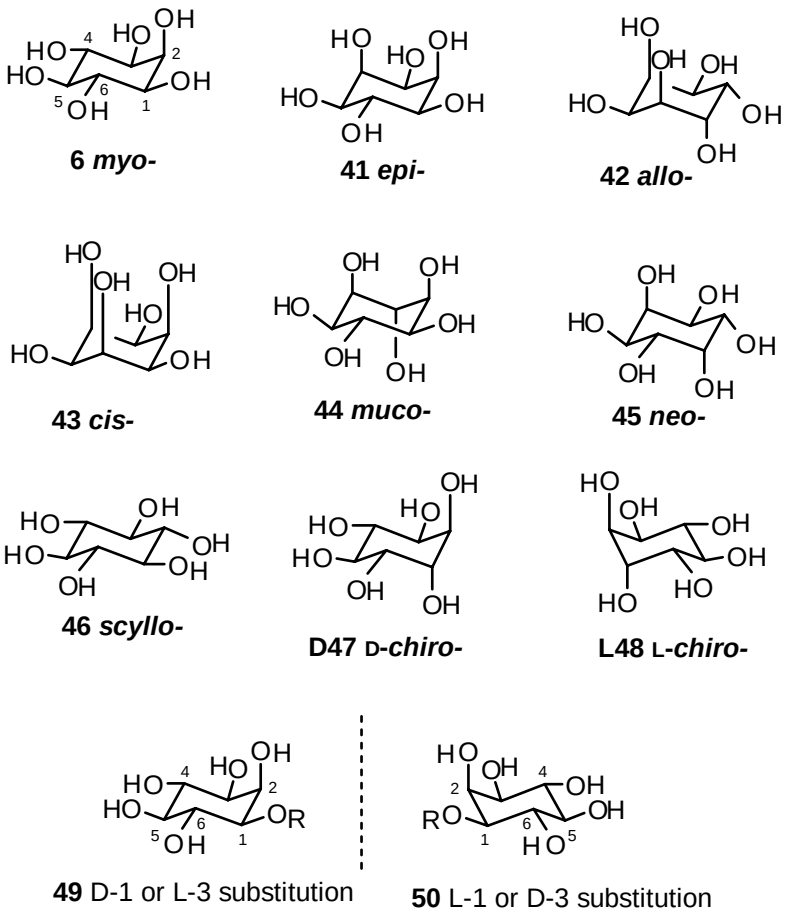
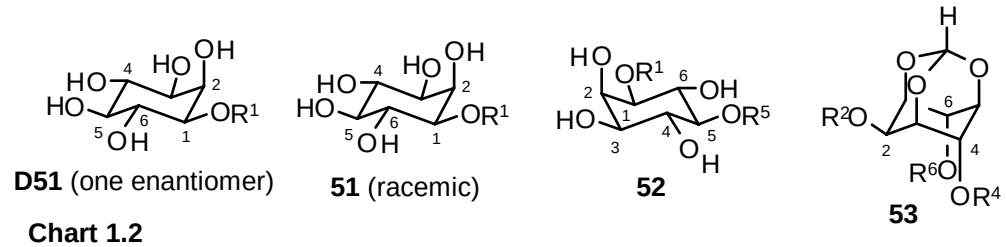


Chart 1.1

For convenience, in the rest of this thesis, numbering for the O-substituents (R groups) in *myo*-inositol derivatives have been given superscript numbers corresponding to the carbon bearing that particular R-group, irrespective of the number of R groups present in the structure (for examples see Chart 1.2). All the structures of *myo*-inositol derivatives which represent a single enantiomer or a diastereomer have been numbered with D- or L-prefix to distinguish the other structures of *myo*-inositol derivatives which represent a racemic mixture.

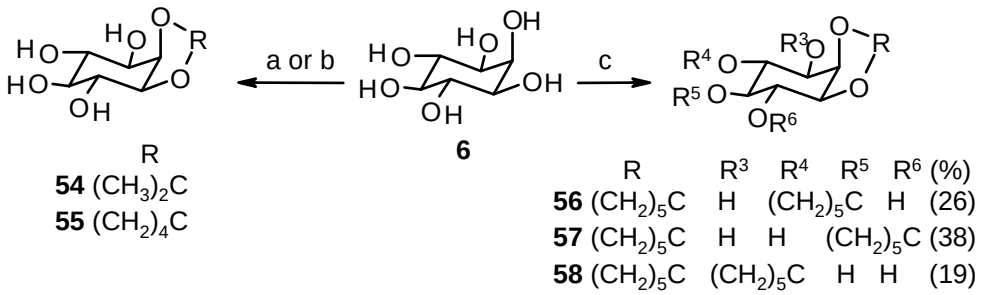


D51 (one enantiomer) **51** (racemic) **52** **53**

Chart 1.2

Interest in the chemistry of inositols was revived in the past two decades due to the involvement of its phosphorylated derivatives in various cellular processes (Scheme 1.1). There are continued efforts towards the synthesis of naturally occurring phosphoinositols, their analogs, new cyclitol derivatives and other natural products with interesting biological and physical properties. Central to these efforts is the regioselective derivatization of inositol hydroxyl groups. The rest of this chapter gives a survey of the literature pertaining to selective reactions of *myo*-inositol and its partially protected derivatives necessary to put the work described in the following chapters in proper context.

Classical approach for the protection of *myo*-inositol hydroxyl groups involved the use of acetals of acetone, cyclohexanone, cyclopentanone, benzaldehyde, camphor etc.[10] These methods of derivatization resulted in the formation of a mixture of products from which the desired ketal had to be separated (Scheme 1.4).



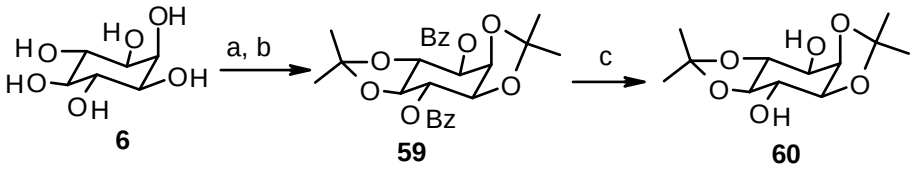
R
54 $(CH_3)_2C$
55 $(CH_2)_4C$

6

	R	R^3	R^4	R^5	R^6	(%)
56	$(CH_2)_5C$	H	$(CH_2)_5C$	H		(26)
57	$(CH_2)_5C$	H	H	$(CH_2)_5C$		(38)
58	$(CH_2)_5C$	$(CH_2)_5C$	H	H		(19)

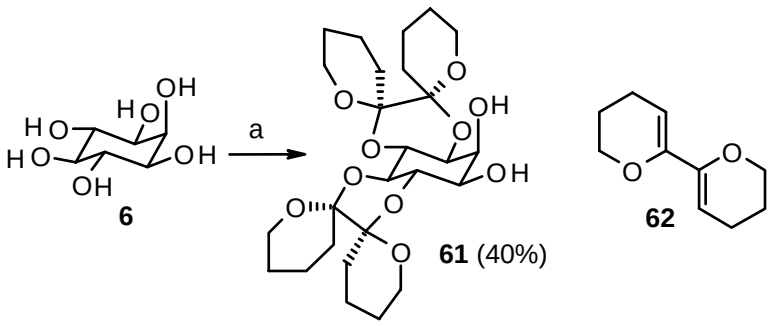
Scheme 1.4. a) (i) Dry acetone, anhyd $ZnCl_2$, acetic acid, reflux, 9 h; Ac_2O, Pyr; (ii) alcoholysis; b) cyclopentanone, TsOH, benzene, reflux, 6 h, 29%.
c) 1-ethoxy cyclohexene, TsOH (cat), DMF (or DMSO).

Gigg *et al*[11] discovered that the dibenzoate **59** (Scheme 1.5) had very low solubility in organic solvents and exploited this property for the easy isolation of **59** from a mixture of isomeric ketal dibenzoates. The 3,6-diol **60** was obtained by hydrolysis of the dibenzoate **59**. This procedure for the isolation of the diisopropylidene diol did not require chromatography.



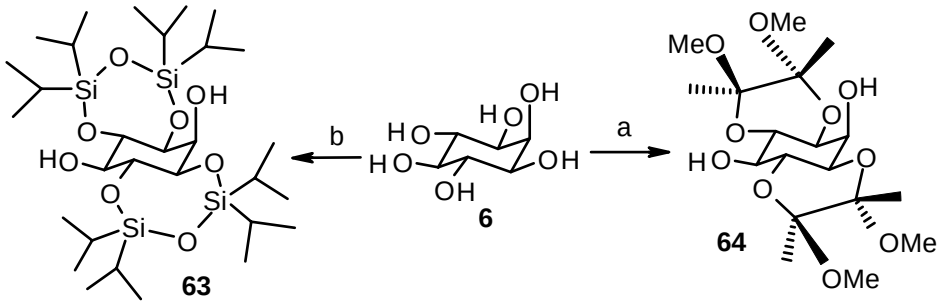
Scheme 1.5. a) 2,2-Dimethoxy propane, TsOH (cat), DMSO, 110 °C; b) BzCl, Pyr, filtration; c) NaOH, MeOH, reflux.

More recently, Bruzik *et al*[12] prepared diastereomeric D-camphor ketals. This method also achieved the resolution of *myo*-inositol derivatives in addition to the protection of its hydroxyl groups. Ley *et al*[13] reported a highly regioselective formation of bis dispoke acetal **61** in modest yields, on treatment of *myo*-inositol with bisdihydropyran (**62**) in the presence of CSA in DMF (Scheme 1.6).



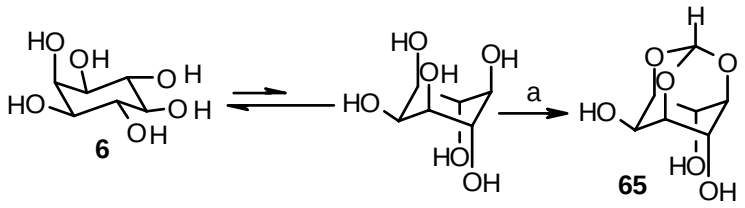
Scheme 1.6. a) **62**, CSA, DMF, 100 °C

Frost *et al*[14] reported the protection of vicinal *trans* hydroxyl groups in *myo*-inositol with 2,2,3,3,-tetramethoxybutane to obtain the 2,5-diol **64** in very good yield. Similar regioselective protection of the 1,3,4,6-hydroxyl groups can be achieved (**63**) using TIPDSCl although in lower yields (Scheme 1.7).[15]



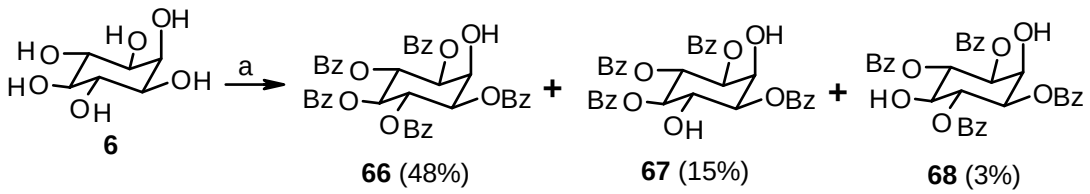
Scheme 1.7. a) 2,2,3,3-Tetramethoxybutane, $(MeO)_3CH$, CSA, MeOH, reflux, 79%; b) TIPDSCl (2.5 eq), Pyr, rt.

Lee and Kishi reported[16] the protection of C1-, C3- and C5-hydroxyl groups in *myo*-inositol as the orthoformate. The orthoformate **65** was obtained as a single product in good yield (Scheme 1.8).



Scheme 1.8. a) $(EtO)_3CH$, DMSO, TsOH, 100 °C

Attempts have also been made to achieve selective reaction at one or a few hydroxyl groups of *myo*-inositol by acylation. Benzoylation[17] of *myo*-inositol with benzoyl chloride in pyridine at room temperature yielded the pentabenzoate **66** as the major product (Scheme 1.9). However, such approaches are of little use since chemically distinguishing the benzoates in subsequent synthetic steps becomes difficult.



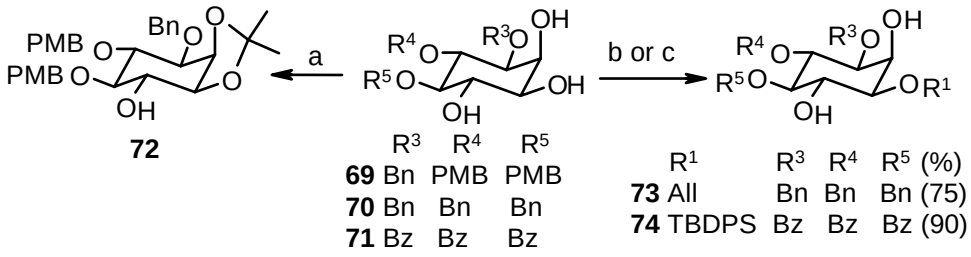
Scheme 1.9. a) BzCl (3.5 eq), Pyr, 2 h.

The reactions of *myo*-inositol described so far show that derivatization of *myo*-inositol hydroxyl groups often lead to mixture of products and hence the yield of the desired *myo*-inositol derivative becomes poor. One of the exceptions is the formation of the orthoester **65** which can be obtained as a single product in more than 90% yield.[16] However the consequence of the initial protection of *myo*-inositol hydroxyl groups as ketals is that further regioselective protection needs to be achieved among diols and triols which is easier than handling all the six hydroxyl groups (in inositol) at a time. After this is achieved, hydroxyl groups protected as ketals can be released to give diols, which can be selectively protected. This scheme of reactions although provides a route for the protection of the hydroxyl groups of *myo*-inositol, it often makes a synthetic scheme quite elaborate and low yielding. Also usually the method of preparation is specific to one or a small set of *myo*-inositol derivatives.

1.2. Protection of myo-*inositol derived triols*

1.2.1. Protection of myo-*inositol derived 1,2,6-triols*

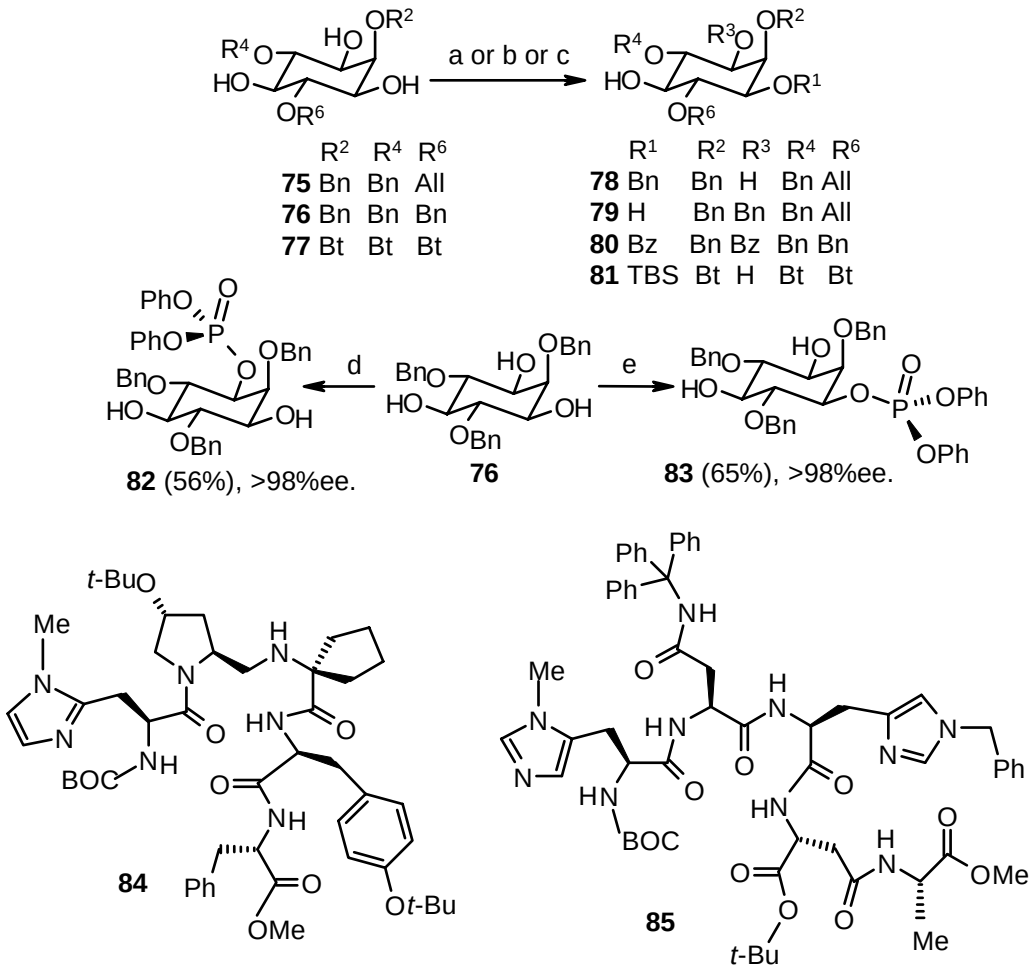
Since these triols possess vicinal hydroxyl groups, the *cis*-diol moiety can be protected selectively as the corresponding ketal[18] (**72**, Scheme 1.10) owing to its thermodynamic stability. Alkylation[19] and silylation[20] on these triols resulted in the preferential formation of the corresponding C1-hydroxyl group protected derivatives **73** and **74**. These results show that C1-hydroxyl group can be protected selectively in 1,2,6-triols.



Scheme 1.10. a) 2,2-Dimethoxypropane, TsOH, acetone (dry), rt, 2 h; b) (i) Bu_2SnO, benzene, reflux, 20 h, (ii) Bu_4NI, AllBr, 70 ^oC, 2 h; c) TBDPSCl, imidazole, DMF.

1.2.2. Protection of *myo*-inositol derived 1,3,5-triols

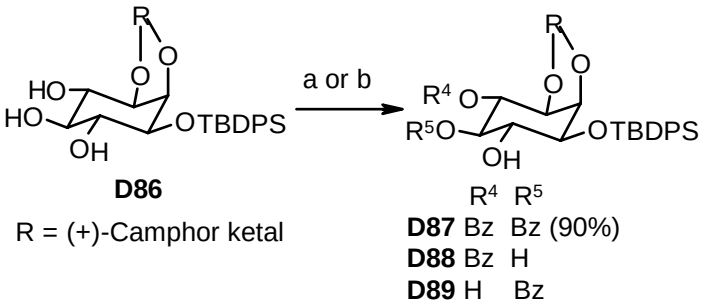
Alkylation,[21] acylation[22] and silylation[23] of these triols result in predominant reaction at the C1(3)-hydroxyl group (Scheme 1.11). When the R groups at C4 and C6 positions are different, a mixture of products is obtained. Miller *et al*[24] reported regio and enantioselective monophosphorylation of C1- or C3-hydroxyl groups (>98% ee) of the triol **76** using low-molecular weight peptide-based catalysts. This reaction gives an easy access to enantiomeric *myo*-inositol-1-phosphates. The reactions in scheme 1.11 show that C5-hydroxyl group is the least reactive among the three hydroxyl groups in 1,3,5-triols.



Scheme 1.11. a) BnBr, Bu_4NBr, 2M NaOH, DCM; b) BzCl, Pyr; c) TBSCl, imidazole, DMF; d) $ClPO(OPh)_2$, 2.5 mol% **84**, Et_3N, toluene, 0 ^oC; e) $ClPO(OPh)_2$, 2 mol% **85**, Et_3N, toluene, 0 ^oC.

1.2.3. Protection of *myo*-inositol derived 4,5,6-triol

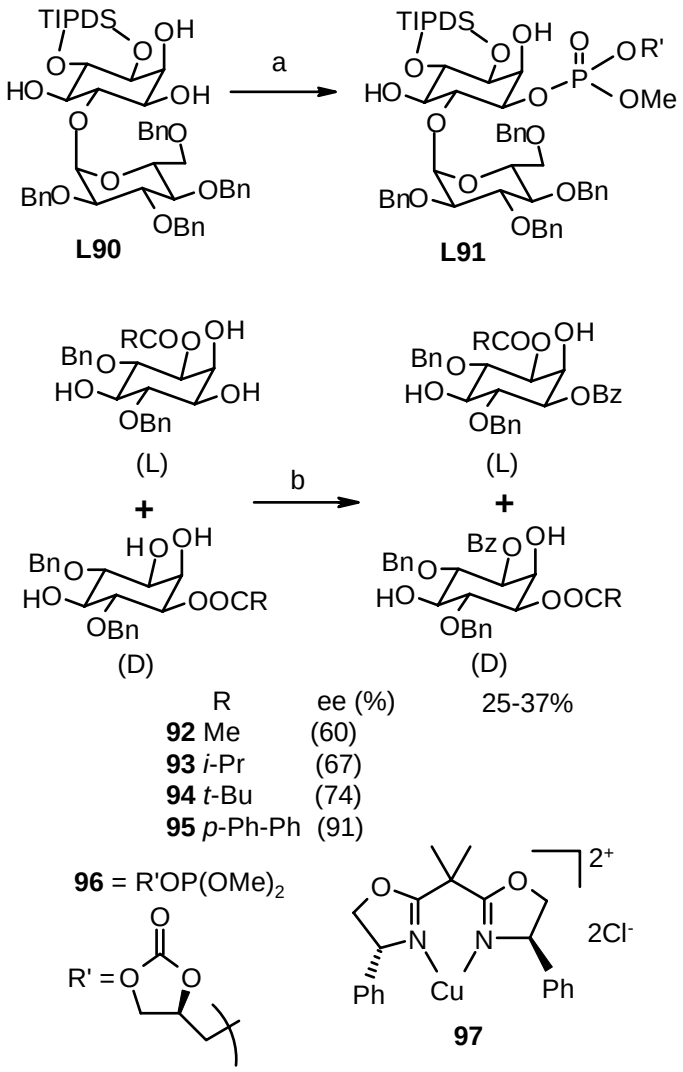
Relative configurations of the three hydroxyl groups in these triols are all *trans* and hence ketalization of these triols could lead to the formation of a mixture of ketals, unlike in the case of 1,2,6-triols (Scheme 1.10). Diacylation[25] of the triol **D86** (Scheme 1.12) with benzoyl chloride gave the 4,5-dibenzoate **D87** while monobenzoylation gave a mixture of 4- and 5-benzoates **D88** and **D89**. This is in contrast to the reactions of other triols and diols having the C5-hydroxyl group free where C5-hydroxyl group is the least reactive.



Scheme 1.12. a) BzCl (2 eq), Pyr; b) BzCl (1.3 eq), Pyr.

1.2.4. Protection of *myo*-inositol derived 1,2,5-triols

Phosphorylation[26] of the triol **L90** (Scheme 1.13) resulted in predominant phosphorylation at the C1-hydroxyl group, perhaps due to the steric hindrance for the reaction at C2- and C5-hydroxyl groups. Attempts at kinetic resolution of racemic *myo*-inositol derivatives **92-95** by benzoylation[27] in the presence of chiral Cu(II) complex **97** resulted in moderate to good enantiomeric excess depending on the R group in the ester at the C1(3)-position (Scheme 1.13).

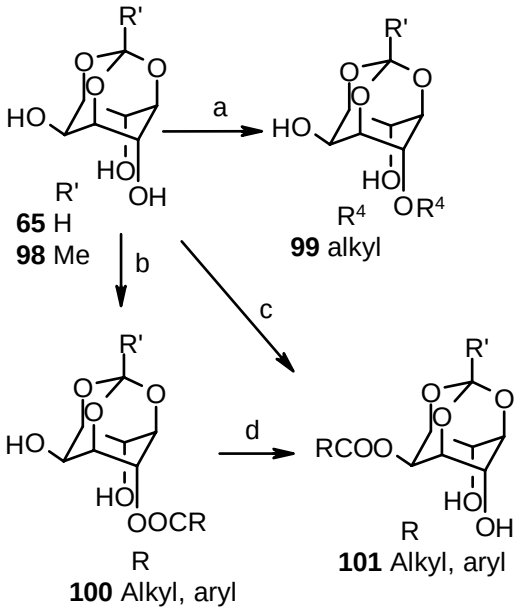


Scheme 1.13. a) **96**, Pyr-HBr_3, Et_3N, DCM; b) **97**, BzCl, DIPEA, 0 °C

1.2.5. Protection of myo-*inositol derived 2,4,6-triols*

myo-Inositol 1,3,5-orthoesters are a group of 2,4,6-triols which are frequently used for the preparation of inositol derivatives. They can be obtained exclusively in several gram quantities from *myo*-inositol. Literature reports show that one of the axial hydroxyl groups or the equatorial C2-hydroxyl group in orthoesters (**65**, **98**) can be derivatized with moderate to good selectivity by varying the reaction conditions. For example, monoacylation[28] of these triols in the presence of pyridine resulted in the formation of C2-esters as the major products while the use of triethylamine or sodium hydride as a base resulted in the formation of C4-esters (Scheme 1.14).

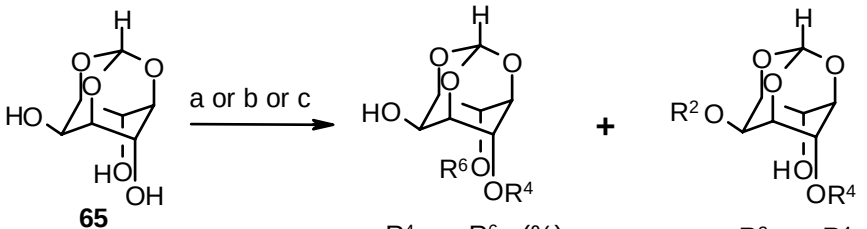
Exclusive acylation of the C2-hydroxyl group can also be effected *via* intramolecular acyl migration[28a] in C4-esters (**100** → **101**). Similarly, alkylation[29] of these triols in the presence of sodium hydride leads to the formation of the C4-ether **99** as the only product.



Scheme 1.14. a) NaH, alkyl halide, DMF; b) NaH (1 eq) or Et_3N, acyl halide, DMF; c) NaH (2 eq), acyl halide (1 eq), DMF; d) NaH, DMF.

Dialkylation[29a,30] of the triol **65** with two equivalents of alkyl halide and two equivalents of a base like sodium hydride gave a mixture of products (Scheme 1.15) with symmetrical diether being the major product, but the isolated yields were poor. The unsymmetrical dibenzyl ether **106** could be obtained in good yields by benzylation[31] of the monoether **99** (R^4 = Bn) under acidic conditions with benzyltrichloroacetamidate (see section 1.3.6, Scheme 1.27). Acylation[32] or sulfonylation[33] of *myo*-inositol orthoesters with two equivalents of acyl chloride or sulfonyl chloride in the presence of pyridine also resulted in the formation of unsymmetrical diesters. Symmetrical ditosylate **105** could be obtained as the major product by tosylation[33] of **65** using sodium hydride as the base. These literature reports show that regiospecific alkylation or acylation of these 2,4,6-triols can be

carried out with modest to good yields, but dialkylation or diesterification leads to a mixture of products.

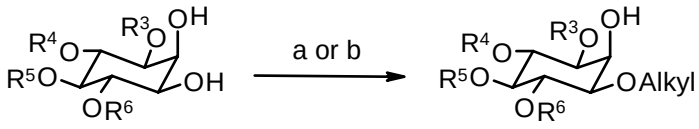


Scheme 1.15. a) NaH (2 eq), alkyl halide (2 eq), DMF; b) Acyl halide (2 eq) or TsCl (2 eq), Pyr; c) NaH (2 eq), TsCl (2 eq), DMF.

1.3. Protection of *myo*-inositol derived diols

1.3.1. Protection of *myo*-inositol derived 1,2-diols

Alkylation,[18,34] acylation,[34a,b,35] silylation,[36] phosphorylation[37] and tosylation[35b,38] of 1,2-diols resulted in major reaction at the C1-hydroxyl group, as expected (Schemes 1.16 – 1.18). Acylation[39] with chiral acids was used for the resolution of racemic *myo*-inositol derived diols. Dibutyltin oxide was the reagent most frequently used for the selective functionalization of the C1-hydroxyl group in 1,2-diols. Use of potassium hydroxide or sodium hydroxide for benzylation[34a] of **111** (Scheme 1.16) in benzene resulted in exclusive reaction at the C1-hydroxyl group. The above methodologies show that equatorially disposed C1-hydroxyl group is more reactive than the axially disposed C2-hydroxyl group as expected.

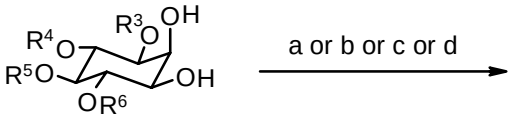


	R^3	R^4	R^5	R^6
111	Bn	Bn	Bn	Bn
112	Bn	PMB	PMB	Bn
113	All	All	All	Bn
114	PMB	Bn	Bn	Bn
115	Bn	Bn	PMB	PMB
116	All	All	Bn	Bn
117	Bn	Bn	Bn	All
118	Bn	$(CH_3O(CH_3)C)_2$		Bn

119

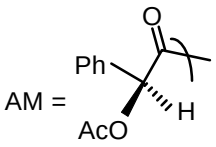
Alkyl = Bn or All or PMB or Me

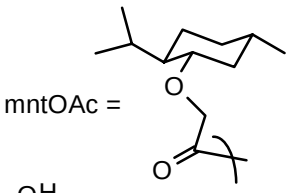
Scheme 1.16. a) Alkyl halide, KOH or NaOH, benzene, reflux, 50-52%; b) Bu_2SnO, alkyl halide, 72-96%.

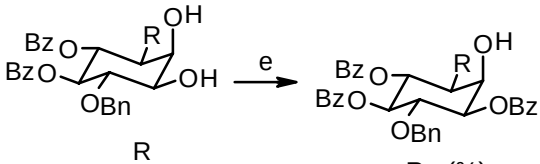


	R^3	R^4	R^5	R^6
111	Bn	Bn	Bn	Bn
112	Bn	PMB	PMB	Bn
115	Bn	Bn	PMB	PMB
118	Bn	$(CH_3O(CH_3)C)_2$		Bn
120	Me	Me	Me	Me
121	Ac	Ac	Ac	Ac
122	All	PMB	Bn	All
123	Bz	Bz	Bz	Bn
124	Bn	All	All	Bn

	R^1	R^3	R^4	R^5	R^6	(%)
125	Bz	Bn	Bn	Bn	Bn	(68)
126	Ac	Bn	Bn	Bn	Bn	(76)
127	Ts	Bn	Bn	Bn	Bn	(79)
D128	(+)-AM	Bn	PMB	PMB	Bn	
D129	(+)-AM	Bn	Bn	PMB	PMB	
D130	(+)-AM	Bn	$(CH_3O(CH_3)C)_2$		Bn	
131	Ac	Me	Me	Me	Me	(47)
132	Ts	Ac	Ac	Ac	Ac	(55)
D133	(+)-AM	All	PMB	Bn	All	
D134	mntOAc	Bz	Bz	Bz	Bn	
135	TBS	Bn	All	All	Bn	(87)



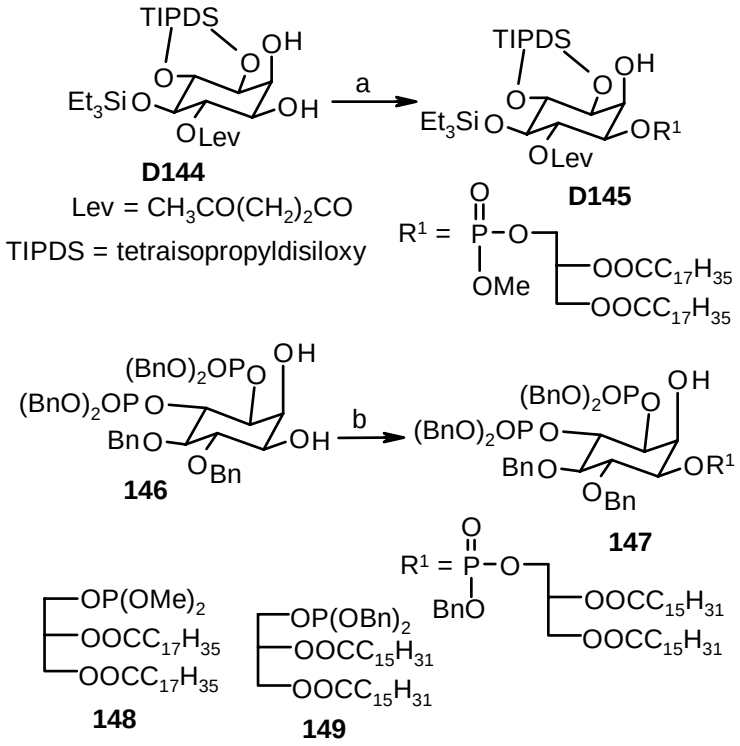




	R
136	Cl
137	Br
138	OMe
139	H

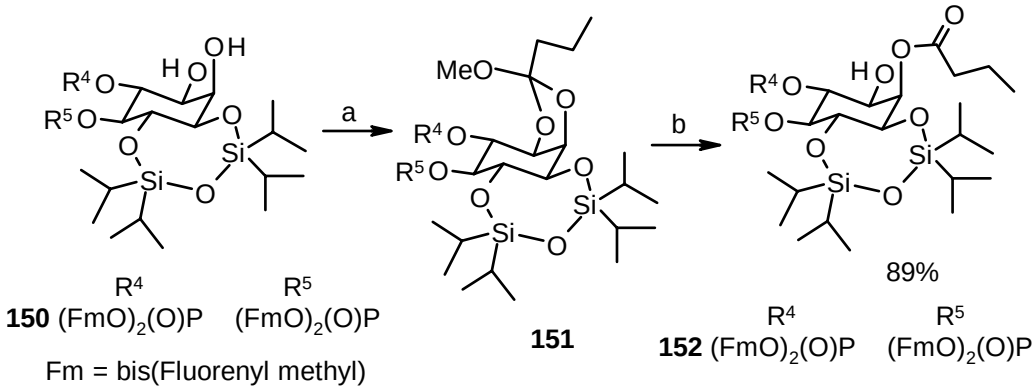
	R	(%)
140	Cl	(93)
141	Br	(77)
142	OMe	(72)
143	H	(91)

Scheme 1.17. a) Acyl chloride or TsCl, Pyr; b) (+)-AMOH, DCC, DMAP, DCM, -15 °C c) mntOAcCl, Pyr, 0 °C; d) TBSCl, 2,6-Lutidine; e) BzCl, Pyr, rt, 16-40 h.



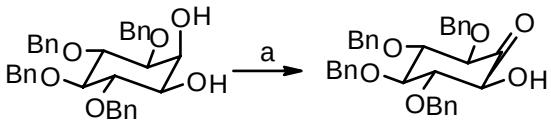
Scheme 1.18. a) **148**, Pyr-HBr_3.Et_3N; b) **149**, Pyr-HBr_3, DCM / Pyr / Et_3N (1:0.1:0.05), -20 °C, 2 h, 0 °C, 0.5 h.

However, acylation at the C2-hydroxyl group could be achieved using orthoesters.[5a, 23, 40] Recently Schultz *et al*[40b] reported the regioselective acylation of 1,2-diol at C2-position *via* orthoester intermediate (Scheme 1.19).



Scheme 1.19. a) $(MeO)_3CCH_2CH_2Me$, CSA, toluene, rt, 30 min; b) MeOH (wet), rt, 2 h.

Frost *et al*[41] reported the regioselective oxidation of the 1,2-diol **111** at C2-position to get the inosose **153**.

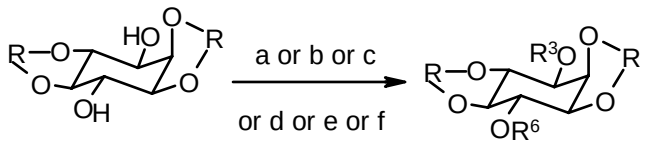


111 **153**

Scheme 1.20. a) (i)Bu_2SnO, MeOH, reflux; (ii) Br_2, DCM, Bu_3SnOMe, 50%.

1.3.2. Protection of *myo*-inositol derived 3(1),6(4)-diols

Most of the diols belonging to this category consist of diacetals of *myo*-inositol. Alkylation[42] and acylation[39e] of 3,6-diols usually result in a mixture of products, the C3-O-substituted derivative being the major constituent (Scheme 1.21). Alkylation of dicyclohexylidene diol **56** exclusively at the C3-hydroxyl group could be carried out using barium oxide-barium hydroxide octahydrate as the base[43] or by the gradual addition of sodium hydride[44] at 0-5 °C to provide kinetic control. Yield for the tosylation[45] of the diol **60** was reported to be quite low. These examples illustrate that the C3-hydroxyl group in 3,6-diols is more reactive and can be functionalized with electrophiles in preference to the C6-hydroxyl group.



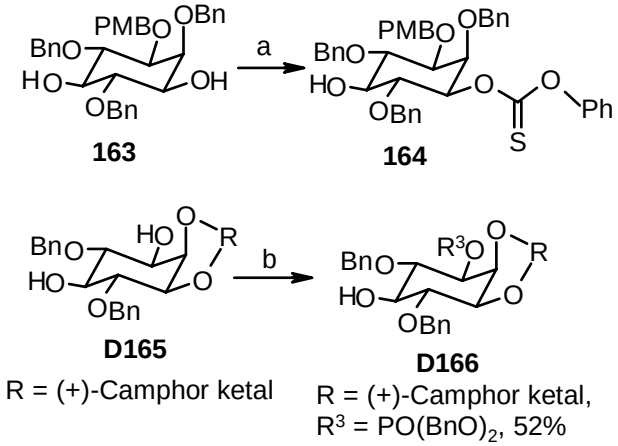
	R
56	$(CH_2)_5C$
60	$(CH_3)_2C$

	R	R^3	R^6
154	$(CH_3)_2C$	Bn	H
155	$(CH_3)_2C$	H	Bn
156	$(CH_3)_2C$	Bn	Bn
157	$(CH_2)_5C$	Bn	H
158	$(CH_2)_5C$	H	Bn
159	$(CH_2)_5C$	Bn	Bn
160	$(CH_3)_2C$	All	H
161	$(CH_3)_2C$	Ts	H
162	$(CH_2)_5C$	Bz	H

Scheme 1.21. a) NaH, BnBr, DMF, 45% (**154**); b) NaH, BnBr, toluene, reflux, 60% (**157**); c) BaO, $Ba(OH)_2.8H_2O$, BnBr, 70% (**157**); d) BaO, $Ba(OH)_2.8H_2O$, AllBr, DMF; e) TsCl, Pyr, 30% (**161**); f) Benzoylimidazole, CsF, DMF, rt, 2 h, 65% (**162**).

1.3.3. Protection of *myo*-inositol derived 1(3),5-diols

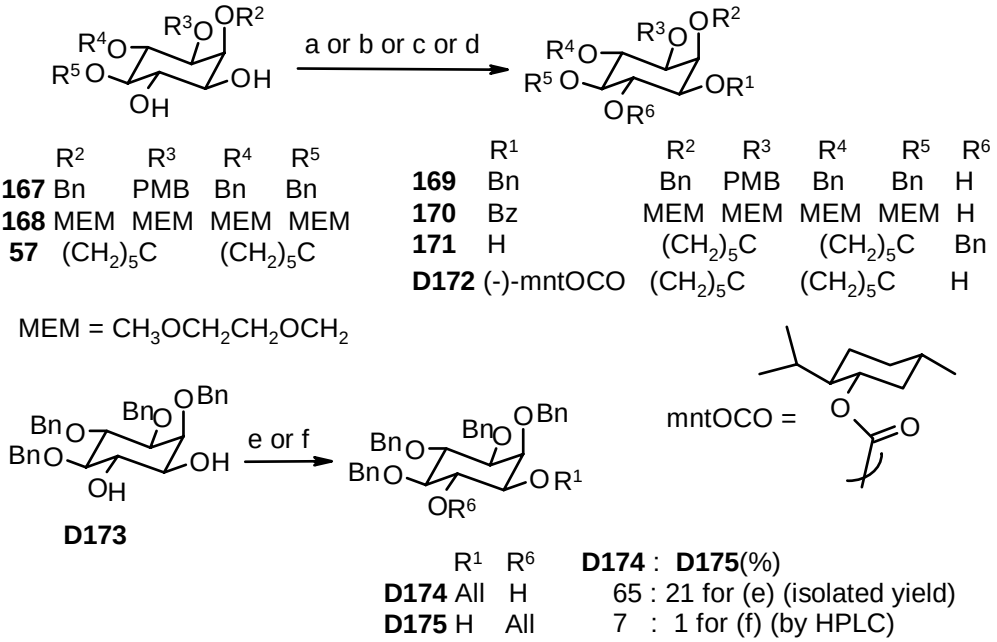
C1-Hydroxyl group appears to be more reactive than the C5-hydroxyl group in 1,5-diols as acylation[46] and phosphorylation[47] result in the formation of the corresponding C1-O-derivative (Scheme 1.22).



Scheme 1.22. a) PhOCSCl, DMAP, MeCN, benzene, 0 °C, 20 h;
b) $(iPr)_2NP(OBn)_2$ (1eq), 1H-tetrazole, DCM, 23 °C, 2 h, *m*-CPBA, -40 °C, 1 h.

1.3.4. Protection of *myo*-inositol derived 1,6-diols

The observed regioselectivity for the O-alkylation of 1,6-diols appears to be dependent on the reagents used. Dibutyltin oxide mediated benzylation[48] of **167** (Scheme 1.23) is reported to occur exclusively at the C1-position in the presence of cesium fluoride while benzylation[49] in the absence of cesium fluoride afforded minor amounts of the C6-ether along with the C1-ether. Allylation[50] of the optically pure 1,6-diol **D173** *via* the stannylene derivative gave the C1- and C6-allyl ethers in the ratio 3:1 while the same products were obtained in the ratio 7:1 (estimated by HPLC, total yield 56%) on using sodium hydride as the base. Acylation[51] of 1,6-diols in the presence of tertiary amines occurred predominantly at the C1-position.



	R^2	R^3	R^4	R^5
167	Bn	PMB	Bn	Bn
168	MEM	MEM	MEM	MEM
57	$(CH_2)_5C$		$(CH_2)_5C$	

	R^1	R^2	R^3	R^4	R^5	R^6
169	Bn	Bn	PMB	Bn	Bn	H
170	Bz	MEM	MEM	MEM	MEM	H
171	H	$(CH_2)_5C$		$(CH_2)_5C$		Bn
D172	(-)-mntOCO	$(CH_2)_5C$		$(CH_2)_5C$		H

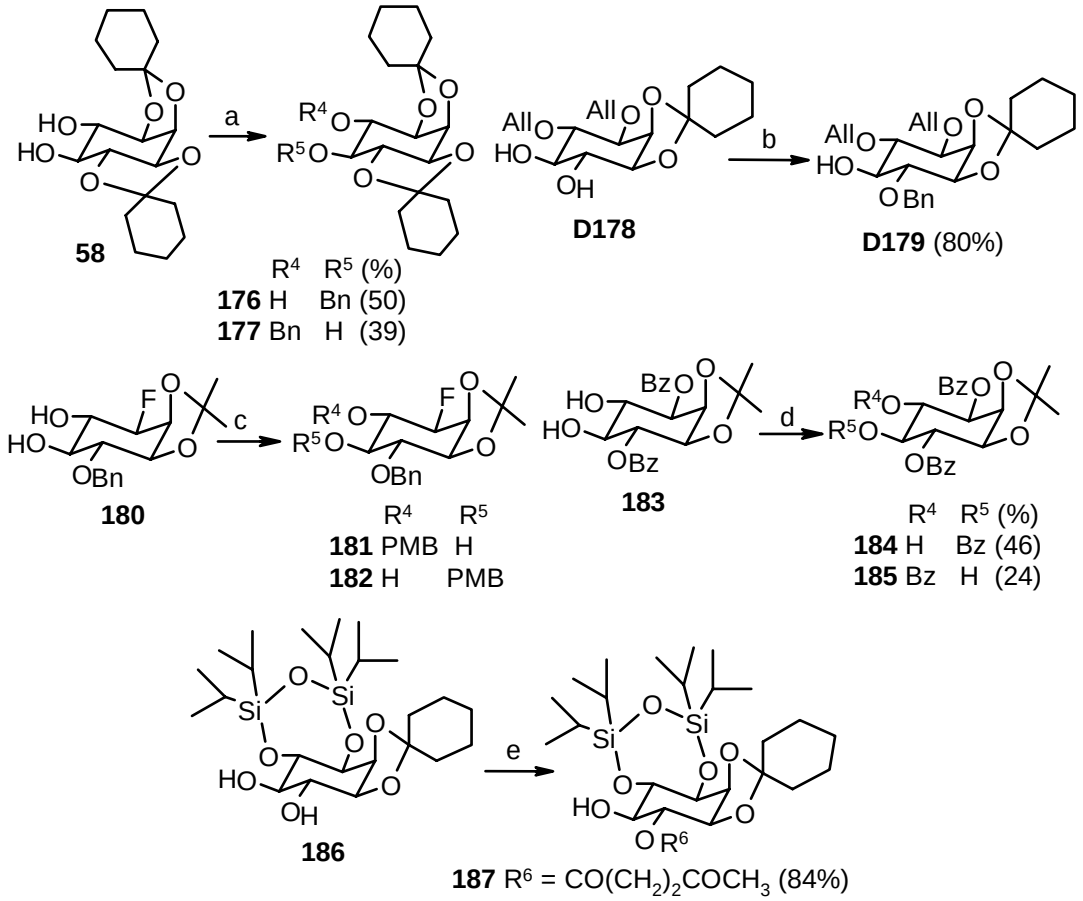
D173

	R^1	R^6	**D174** : **D175**(%)
D174	All	H	65 : 21 for (e) (isolated yield)
D175	H	All	7 : 1 for (f) (by HPLC)

Scheme 1.23. a) Bu_2SnO, BnBr, toluene, 80% (**169**); b) BzCl, Pyr, -30 ^oC; c) Bu_2SnO, BnBr, CsF, 91-97% (**171**); d) $(Bu_3Sn)_2O$, toluene, (-)-MntO-COCl, $NaHCO_3$, 70%; e) Bu_2SnO, AllBr, toluene; f) NaH, AllBr, THF.

1.3.5. Protection of *myo*-inositol derived 4(6),5-diols

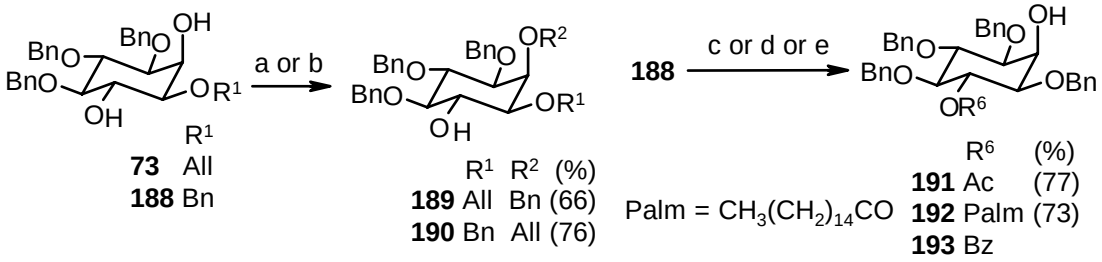
Alkylation[5b,52] of 4,5-diols results in the formation of a mixture of products, the C4-ether being the major constituent (Scheme 1.24). However, as observed in the case of 1,6-diols, the use of cesium fluoride resulted in the formation of C4(6)-ether (**D179**) exclusively.[53] Benzoylation[54] of the diol **183** gave a mixture of products but acylation[37a] of the silyl protected diol **186** gave the C4-ester **187** in 84% yield. The better regioselectivity observed for the acylation of the silyl ether **186** could be due to the steric hindrance of the bulky silyl ether for the reaction at the C5-hydroxyl group.



Scheme 1.24. a) Bu_2SnO, toluene, BnBr, Bu_4NBr, 70 °C; b) (i) Bu_2SnO, toluene; (ii) BnBr, CsF, DMF, -41 to 23 °C; c) NaH, PMBCl, DMF; d) BzCl, Pyr; e) $CH_3CO(CH_2)_2COOH$, DCC, DMAP.

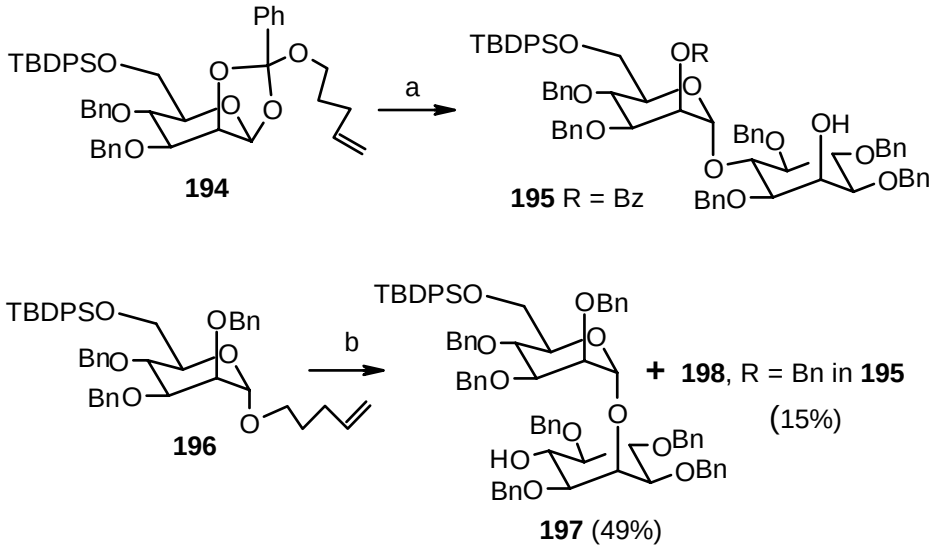
1.3.6. Protection of *myo*-inositol derived 2,6(4)-diols

Fraser-reid *et al* reported an extensive study on the alkylation[19,55] and acylation[55] of the 2,6(4)-diols **73** and **188** (Scheme 1.25). Benzylation and allylation on the diols **73** and **188** resulted in predominant alkylation at the C2-hydroxyl group along with minor amount of dialkylated products. Acylation in the presence of pyridine however resulted in the formation of the C6-ester.



Scheme 1.25. a) NaH, BnBr, Bu_4NI, DMF, -5 to 0 °C, 1-2 h; b) NaH, AllBr, Bu_4NI, DMF,0 °C, 1 h; c) Ac_2O (3.5 eq), DMAP, Pyr, 0 °C, 30 min; d) PalmCl (3 eq), DMAP, Pyr, 0 °C, 1 h; e) BzCl (3 eq), DMAP, Pyr, 0 °C, 1 h.

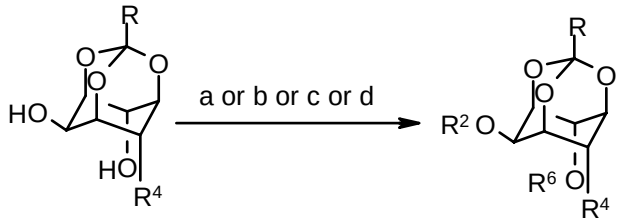
They also carried out glycosidation[56] of 2,6(4) diols (Scheme 1.26), since C2- and / or C6-mono and diglycosylated inositols occur in inositides of glycosylphosphatidylinositols (GPIs) and lipoarabinomannans (LAMs), the biological "warheads" of malaria and tuberculosis cell surface oligosaccharides, respectively. Reaction of the diol **188** with n-pentenyl glycoside (NPG) **196** occurred at the C2-hydroxyl group to give α-mannosides **197** and **198** in the ratio 3:1 (65% overall yield). In contrast when n-pentenyl orthoester **194** was used for glycosylation of the diol **188** the reaction occurred at the C6-hydroxyl group.



Scheme 1. 26. a) **188**, NIS (1.3 eq), TBSOTf (cat), DCM, 0 °C, 20 min; b) **188**, NIS (1.3 eq), TBSOTf (cat), DCM, rt, 10 min.

In *myo*-inositol-1,3,5-orthoester derived 2,6(4)-diols (Scheme 1.27), due to inversion of the inositol ring, C2-hydroxyl group is present in the equatorial

orientation and the C6(4)-hydroxyl group is present in the axial orientation (with respect to the *myo*-inositol ring). Benzylation[29a] of the 2,6(4)-diol **199** with sodium hydride resulted in the formation of a mixture of products (**102**, **106**) in the ratio 5:1. Acid catalyzed benzylation[31] of the 2,6(4)-diol **199** with benzyltrichloroacetimidate resulted in the formation of the C2-ether **106**. Similar results were obtained on acylation[28b] of 2,4-diol **200** and silylation[57] of the deoxy derivatives **201** and **202**.



	R	R^4
199	H	OBn
200	H	OBOM
201	Bu	F
202	Bu	H

	R	R^2	R^4	R^6
102	H	H	OBn	Bn
106	H	Bn	OBn	H
203	H	PNB	OBOM	H
204	Bu	TBS	F	H
205	Bu	TBS	H	H

Scheme 1. 27. a) Benzyl trichloroacetimidate, TfOH, DCM, cyclohexane, 81% (**106**); b) PNBCl, Pyr, DMAP, 0 ^{o}C, 12 h, 78% (**203**); c) TBSOTf, Pyr, DCM, 0 to 23 ^{o}C, 75-100% (**204**); d) TBSOTf, 2,6-lutidine, DMF, 81% (**205**).

1.4. Conclusions

The literature available on the synthetic chemistry of *myo*-inositol and its derivatives suggests that there are no methods available for derivatizing a particular hydroxyl group selectively. There are only a few instances (listed below) of obtaining exclusively a single product on the reaction of *myo*-inositol or its partially protected derivatives. (a) protection of *myo*-inositol with 2,2,3,3,-tetramethoxybutane[14] or TIPDS chloride[15] (Scheme 1.7); (b) Formation of *myo*-inositol orthoesters[16] from *myo*-inositol (Scheme 1.8); (c) enantioselective phosphorylation[24] of the 1,3,5-triol **76** in the presence of certain low molecular weight peptides (Scheme 1.11); (d) mono acylation[28a] of *myo*-inositol orthoesters (Scheme 1.14); (e) mono alkylation[29] of *myo*-

inositol orthoesters (Scheme 1.14); (f) alkylation[48] of the 1,6-diol **167** using dibutyltin oxide in the presence of cesium fluoride (Scheme 1.23). The general trend of reactivity among hydroxyl groups observed in *myo*-inositol (or its derivatives) is C1(C3)> C4(C6)> C5> C2 except in *myo*-inositol 1,3,5-orthoesters, where the reactivity pattern is C4 > C2 ~ C6. Although a general pattern of selectivity is observed in the reactivity of *myo*-inositol hydroxyl groups, the selectivity could be altered in some derivatives by manipulating the protecting groups. Differences in reactivity between axial and equatorial hydroxyl groups are reasonably well understood in terms of conformation and steric hindrance, but there are several exceptions to this. However, it is clear that relative reactivities of the inositol hydroxyl groups are often dependent on factors such as intramolecular and intermolecular interactions, especially hydrogen bonding and metal ion chelation effects which are influenced by reaction conditions and other reagents / solvents present in the reaction mixture. Furthermore, a chemical modification at a given position on the inositol ring could induce reactivity changes in other functional groups in the ring due to charge distributions, hydrogen bonding, conformational change, chelation, steric bulk, *etc*. which could result in change of relative reactivities of the hydroxyl groups. Hence it appears that there is a need for the development of a methodology for the efficient protection of *myo*-inositol hydroxyl groups wherein each step provides a single regioisomer. Such a method would provide easy and short routes for the protection of desired inositol hydroxyl groups and provide precursors for the synthesis of inositol derivatives. Such attempts carried out in our laboratory are described in the rest of this thesis.

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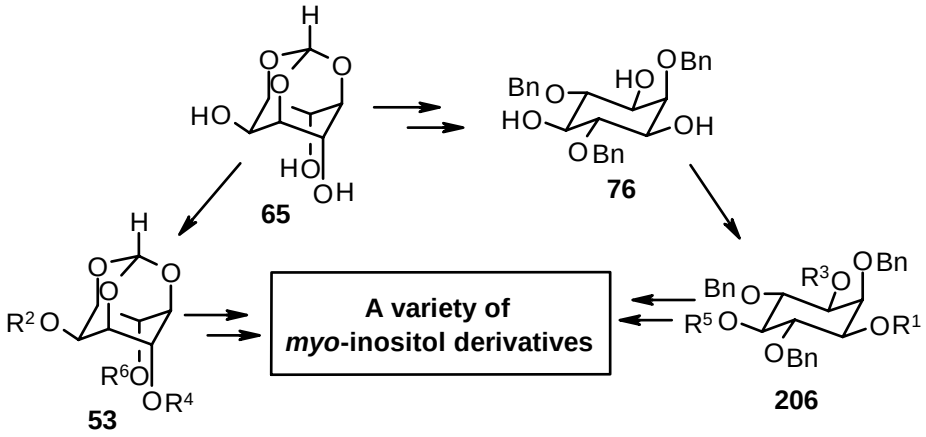
2A.1. Introduction

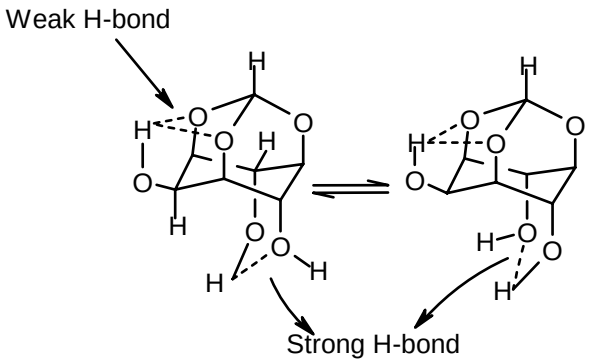
A survey of the literature (Chapter 1) revealed that although many *myo*-inositol derivatives have been synthesized, there is no general method that is flexible enough to be adopted for the preparation of a variety of inositol derivatives. Also, most of the procedures used for the derivatization of inositol hydroxyl groups yield mixture of products from which the desired product is separated.[1] The overall yield of the required O-protected *myo*-inositol derivative is usually not good due to: (a) formation of isomeric *myo*-inositol derivatives and / or (b) use of transient protecting groups (esters, sulfonates, allyl ether, *etc*.) which increase the number of steps and decrease the overall yield. Hence we have attempted to devise a methodology for the convenient preparation of inositol derivatives with the formation of minimum number of products. In other words, we set out to device methods for the regioselective derivatization of inositol hydroxyl groups. From previous experience in our laboratory as well as those reported in the literature, it was clear that regioselective derivatization of any one of the six hydroxyl groups in *myo*-inositol is not easy to achieve in the laboratory, although such reactions do occur in living cells.[2] Hence we envisaged regioselective derivatization of two *myo*-inositol derived triols obtainable easily from *myo*-inositol that would allow us to investigate regioselective derivatization of all the *myo*-inositol hydroxyl groups. We chose *myo*-inositol-1,3,5-orthoformate (**65,** a 2,4,6-triol) and 2,4,6-tri-*O*-benzyl-*myo*-inositol (**76,** a 1,3,5-triol) for our investigations. Development of methods for the regioselective derivatization of the hydroxyl groups in these two triols would in principle allow convenient access to a variety of O-protected *myo*-inositol derivatives (Scheme 2A.1). Regioselective functionalization of *myo*-inositol orthoesters are being attempted[3] and appear to show

promise for the synthesis of biologically relevant molecules. The present section deals with the regioselective O-substitution in *myo*-inositol orthoesters.



Scheme 2A.1

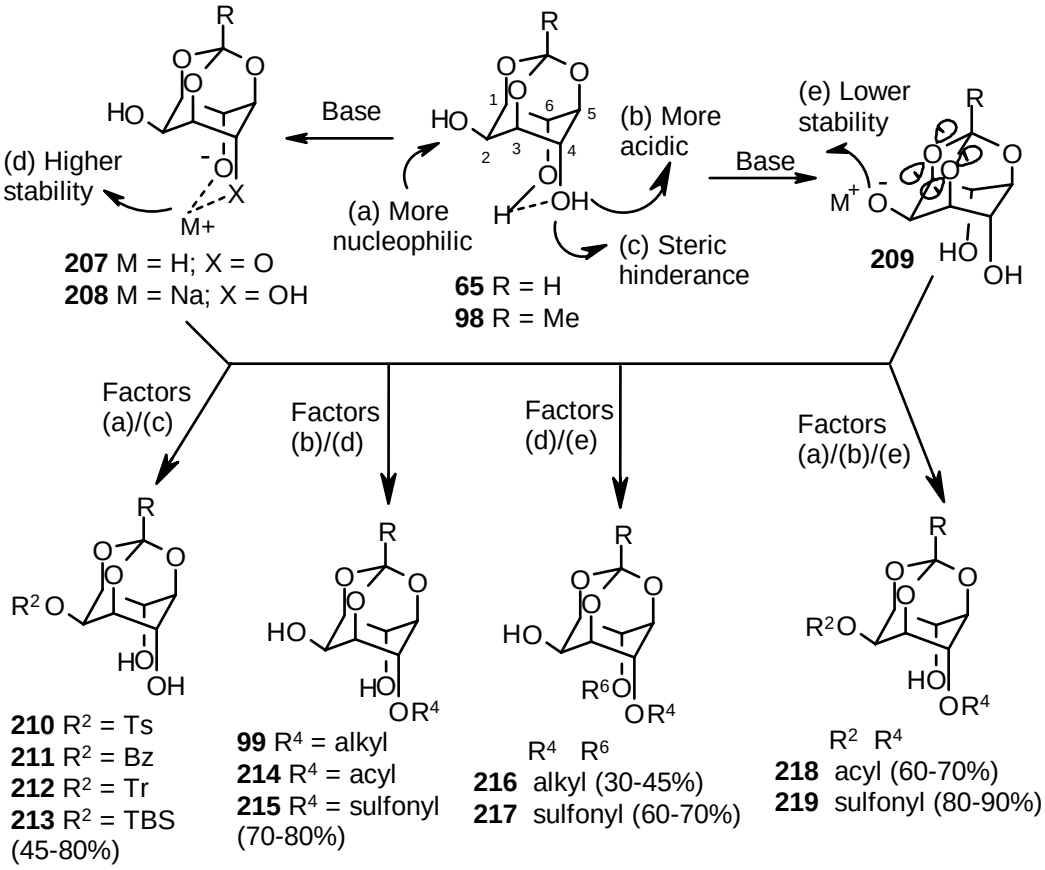
Formation of orthoesters of *myo*-inositol involves inversion of the carbocyclic ring. This results in five axial and one equatorial oxygen atoms on the carbocyclic ring. These orthoesters are in fact trioxa analogs of adamantane and hence have very rigid molecular frame. Due to the presence of two 1,3-diaxial hydroxyl groups which are strongly hydrogen bonded to each other, acidity of the C4- and C6-hydroxyl groups is higher than that of the equatorial C2-hydroxyl group (Scheme 2A.2).



Scheme 2A.2

This difference in acidity of the hydroxyl groups of *myo*-inositol orthoesters can be exploited for their regioselective derivatization. The existence of hydrogen bond between the C4- and C6-hydroxyl groups in *myo*-inositol orthoesters was

established by NMR spectroscopy as well as X-ray crystal structures of *myo*-inositol orthoesters.[4]



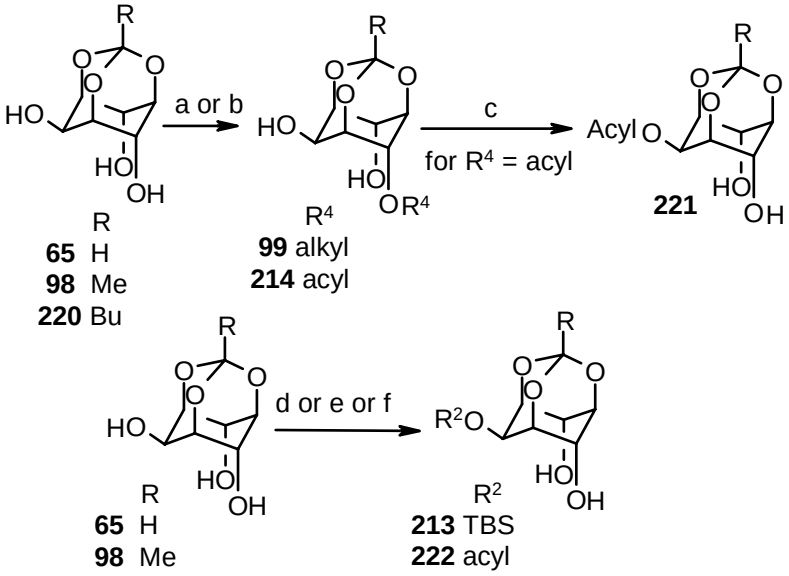
Scheme 2A.3

The differences in the observed reactivity of the three hydroxyl groups (and hence the observed regioselectivity) of *myo*-inositol orthoesters have been attributed to various factors[3] shown in Scheme 2A.3 and other parameters such as nature of the electrophile,[3a] strength of the base used,[3a,b, 5] solvent used for the reaction,[3b,c] presence or absence of metal ions,[3c,d] steric bulk of the reagent[3a,e] and the catalyst used.[6] These variations were utilized to obtain either mono-O-substituted derivatives (**99, 210-215**, Scheme 2A.3) or di-O-substituted derivatives (**216-219**) in poor to good isolated yields. However, there is no general method for the orthogonal protection of the three hydroxyl groups of *myo*-inositol orthoesters (especially as ethers) which generates

only one regioisomer in each step, in respectable yields. Such a method would provide orthogonally protected *myo*-inositol orthoesters, which are the key intermediates for the synthesis of biologically important inositol derivatives. The following section describes a general method for the completely regioselective protection of the three secondary hydroxyl groups of *myo*-inositol orthoesters, utilizing the subtle differences in reactivity exhibited by its alkali metal alkoxides.

2A.2. Results and Discussion

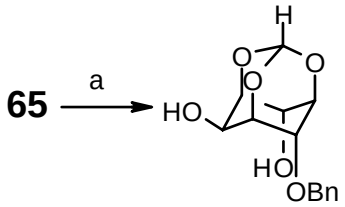
Mono O-substitution of the axial C4-hydroxyl group in *myo*-inositol orthoesters can be achieved with very high regioselectivity. Mono O-alkylation[3c] and O-acylation[3d] of *myo*-inositol orthoesters **65** and **98** in the presence of sodium hydride was thought to be due to the involvement of chelates such as **208** (Scheme 2A.3).[4c, 7] However, acylation with acyl halides in the presence of tertiary amines (e.g. triethylamine, pKa_H = 10.8[8]) is also known[3a,5] to give the corresponding C4-O-acylated derivatives (Scheme 2A.4).



Scheme 2A.4. a) NaH, alkyl halide or acyl halide, DMF; b) Et_3N, acyl halide, DMF; c) NaH, DMF; d) NaH (2 eq), acyl halide (1 eq), DMF; e) TBSCl, imidazole, DMF; f) acyl halide, Pyr.

Weaker bases bring about substitution at the C2-O-position as exemplified by the benzoylation[3a] of **65** in the presence of pyridine (pKa_H = 5.2[8]). Similarly, alkylation of **65** under phase transfer catalytic conditions[9] and silylation[3f] of **65** in the presence of imidazole also result in the formation of the corresponding C2-O-substituted derivative as the major product. The predominant formation of the C2-O-substituted derivatives in the presence of weaker bases could be due to the relatively higher nucleophilicity of the C2-OH as compared to the C4(6)-OH under unionized conditions, due to the involvement of the latter in intramolecular H-bonding (Scheme 2A.2). Hence it was of interest to examine the regioselectivity observed (exclusive reaction at the C4-O-position) during the mono-O-substitution[3c] of the triol (**65** or **98**) in the presence of other bases.

The triol **65** did not undergo alkylation with benzyl bromide in the presence of DBU. Benzylation of **65** in the presence of potassium carbonate resulted in exclusive alkylation at the C4-O-position to yield the benzyl ether **199** in 72% isolated yield (Scheme 2A.5).

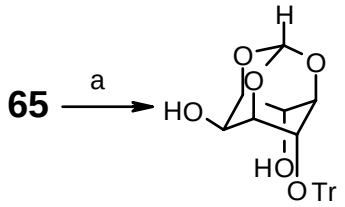


199 (72%)

Scheme 2A.5. a) DMF, K_2CO_3, BnBr.

This result along with the formation of C4-esters **214** in the absence of metal ions[3a] imply that chelation with metal ions is not a necessary condition for the mono-O-substitution at the C4-O-position in the triol **65**. The observed regioselectivity can be rationalized by considering the intramolecular hydrogen bonding that is present[4] in these triols, which results in an increase of the acidity of the C4(6)-hydroxyl group.[3g,10] If the base used is strong enough to form even minor amounts of the anion

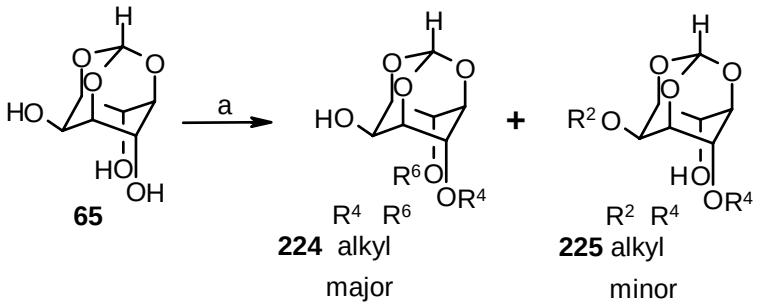
at the C4-O-position, which is also stabilized by intramolecular hydrogen bonding (**207**, Scheme 2A.3), reaction brought about by such bases result in substitution at the C4-O-position. Hence, during the mono-O-substitution of these triols (**65** and **98**), in our opinion, there is no need to invoke either chelation (Scheme 2A.3, **208**) with metal ions or steric effect of the two axial hydroxyl groups[3a] to rationalize the experimental observations, since hydrogen present in the *cis*-axial hydroxyl group is a good acceptor of hydrogen bond which could stabilize the anion (Scheme 2A.3, **207**). That the steric bulk of the electrophile does not contribute much to the observed regioslectivity for the reaction with orthoesters was evident by the fact that the C4-trityl ether **223** could be obtained by tritylation of the triol **65** using sodium hydride as the base (Scheme 2A.6).



223 (40%)

Scheme 2A.6. a) NaH, TrCl, DMF.

Although O-alkylation[3c] of *myo*-inositol orthoesters (such as **65** or **98**) with alkyl halides in the presence of one equivalent of sodium hydride resulted in exclusive reaction at the C4(6)-O-position,[3c,10] reaction of these triols with two equivalents of alkyl halide[3c,h,i] in the presence of two equivalents of sodium hydride resulted in the formation of a mixture of 2,4- and 4,6-diethers. However, isolated yield of the major product, the 4,6-diether **224** was poor (Scheme 2A.7).

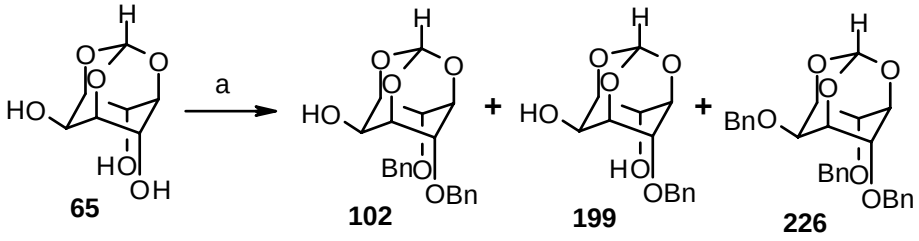


Scheme 2A.7. a) NaH (2 eq), alkyl halide (2 eq), DMF.

Reaction of the C4-monoether (such as **99**, Scheme 2A.4) with alkyl halide in the absence of metal ions provided the unsymmetrical diether (such as **225**) as the major product.[9] These results give credence to the postulated chelation[3c] of the metal ion with 4,6-diaxial oxygens, during O-substitution of the axial monoether **99**, since acidity of the two hydroxyl groups in this monoether is expected to be comparable in the absence of the strong intramolecular hydrogen bond[4] as present in the corresponding triols (**65** and **98**). Vasella[4a] has reported that the axial hydroxyl group in C4-monobenzyl ether **199** does form intramolecular hydrogen bond with the axial hydroxyl group, but this is not as strong as the intramolecular hydrogen bond between the two axial hydroxyl groups in the triol **65**. Similarly crystal structure of C4-esters (such as **214**, Scheme 2A.4) showed that the axial hydroxyl group is involved in intermolecular hydrogen bonding rather than in intramolecular hydrogen bonding.[11]

We postulated that if chelation of the metal ions was indeed operational during O-substitution reactions of C4-ethers (such as **199**), the use of lithium alkoxides instead of sodium alkoxides must result in better regioselectivity, resulting in the formation of greater amounts of the 4,6-di-O-substituted derivatives **224** as compared to the 2,4-di-O-substituted derivatives **225** (Scheme 2A.7). This is expected since lithium, being smaller and a better ion for co-ordination[12] with oxygen atoms, would stabilize the oxyanion at the C6(4)-O-position in axial C4(6)-O-monosubstituted *myo*-inositol orthoesters (such as **99,** Scheme 2A.4).

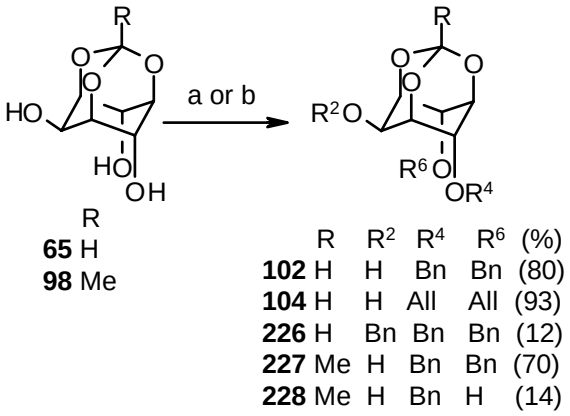
Reaction of the triol **65** with two equivalents of butyl lithium and benzyl bromide (2 eq) in THF resulted in the formation of the C4-benzyl ether **199**, the 4,6-dibenzyl ether **102** and a trace of the tribenzyl ether **226** (Scheme 2A.8).



Scheme 2A.8. a) THF, n-BuLi, BnBr.

TLC analysis of the reaction mixture during the progress of the reaction revealed that the monobenzyl ether **199** did not get completely converted to the 4,6-dibenzyl ether **102** even under reflux; however, formation of the 2,4-dibenzyl ether **106** (Scheme 1.15, Chapter 1) was not observed. Incomplete conversion of **199** to **102** could have been due to the formation of lithium-inositol derivative aggregates in THF which could retard further reaction. Literature reports show that lithium enolates do form aggregates in THF and the rate of the reaction of these aggregates with the alkyl halides is sluggish.[13] Hence in future experiments DMF was used as a co-solvent to break the purported lithium-inositol derivative aggregates and increase the rate of the alkylation reaction.

Reaction of the triol **65** with two equivalents of butyl lithium and benzyl bromide (2 eq) in a mixture of THF and DMF resulted in the formation of the symmetrical diether **102** (Scheme 2A.9) and traces of the tribenzyl ether **226**. Since we isolated the tri-O-benzyl ether **226** but no 2,4-di-O-benzyl derivative **106**, it appears that **226** resulted from benzylation of the initially formed 4,6-dibenzyl ether **102**.



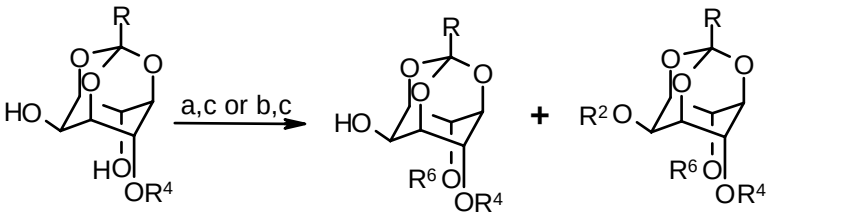
Scheme 2A.9. a) n-BuLi (2 eq), THF, BnBr or AllBr in DMF; b) DMF, LiH (4 eq), BnBr or AllBr.

Dibenzylation of the triol **65** with two equivalents of lithium hydride in DMF resulted in the formation of the C4-monobenzyl ether **199** and the 4,6-dibenzyl ether **102** but the reaction did not go to completion (as revealed by TLC analysis of the reaction mixture). But again, formation of the 2,4-dibenzyl ether **106** was not observed. When benzylation of **65** was carried out using four equivalents of lithium hydride in DMF, the symmetrical 4,6-dibenzyl ether **102** was obtained exclusively. Hence use of BuLi or lithium hydride for the benzylation of the triol **65** resulted in O-substitution at the C4-hydroxyl group first followed by O-substitution at the C6-hydroxyl group; O-substitution at the C2-hydroxyl group was not observed.

The 4,6-di-O-benzyl orthoacetate **227** and the di-O-allyl orthoformate **104** could also be obtained in good yields using BuLi or lithium hydride as a base for the alkylation of the corresponding triols (Scheme 2A.9). The structure of the dibenzyl orthoacetate **227** was confirmed by comparing its ^{1}H NMR spectrum with that of the dibenzyl orthoformate **102**. The only difference observed between the ^{1}H NMR spectra of these two ethers was the presence of the orthoacetate methyl peak instead of the orthoformate proton peak. The diallyl ether **104** was characterized by comparison of its ^{1}H NMR spectrum with that reported[3i] in the literature. The literature method of preparation of **104** consisted of allylation of the triol **65** using

sodium hydride as the base, which resulted mixture of allyl ethers, from which the 4,6-diallylether **104** was isolated in 44%yield. In general, known methods[3c,h,i] for the preparation of 4,6-di-O-substituted derivatives of triols **65** or **98** either resulted in a mixture of products or were restricted to the preparation of disulfonates[3b] or the dibenzyl ether **102** *via* a circuitous route.[3f, 14]

Having obtained this interesting result on the di-O-substitution of the diaxial diols directly from a triol, we carried out O-alkylation of the C4-mono substituted derivatives of *myo*-inositol orthoesters using butyllithium or lithium hydride as a base, to investigate the generality of this reaction. In all such experiments only one regioisomer *viz*., the C4- and C6-di-O-substituted product was obtained. The results obtained for the regioselective C6-O substitution in a few C4-monosubstituted derivatives of *myo*-inositol orthoesters are listed in Scheme 2A.10.



	R	R^4
198	H	Bn
229	H	Ts
230	Me	Ts

	R	R^4	R^6	(%)
102	H	Bn	Bn	(89)
105	H	Ts	Ts	(57)
231	H	Bn	All	(80)
232	H	Bn	Ac	(70)
233	H	Bn	Ts	(65)
234	H	Ts	All	(72)
235	Me	Ts	All	(62)

	R	R^2	R^4	R^6	(%)
226	H	Bn	Bn	Bn	(8)
236	H	All	Bn	All	(10)
237	H	Ac	Bn	Ac	(15)
238	H	Ts	Bn	Ts	(10)
239	H	All	Ts	All	(6)
240	H	Ts	Ts	Ts	(30)
241	Me	All	Ts	All	(9)

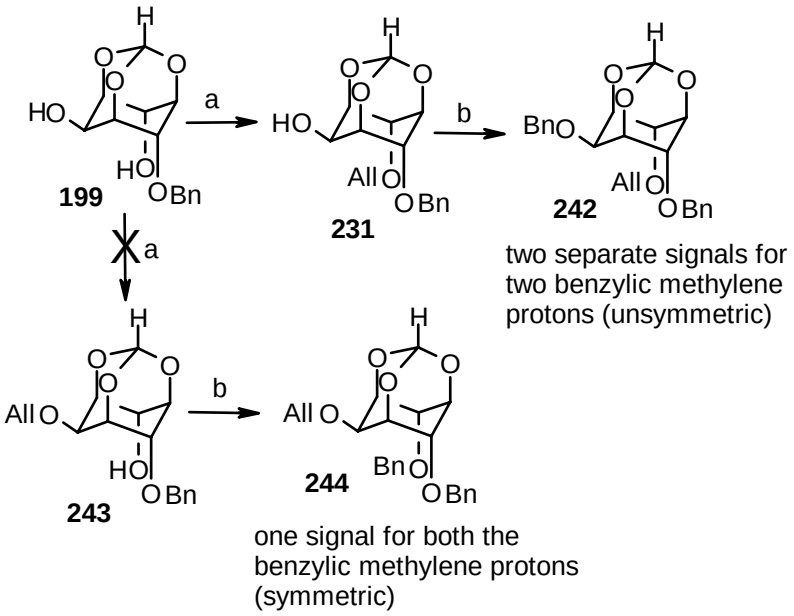
Scheme 2A.10. a) n-BuLi / THF; b) DMF, LiH;
c) Alkyl halide or Ac_2O or TsCl, DMF or TsCl / THF.

A comparison of the yield of symmetrical 4,6-di-O-substituted derivatives reveals that tosylation of the unsymmetrical diols **199** and **230** are low yielding compared to their alkylation and acylation reactions. However, in all the tosylation reactions carried out, the unsymmetrical 2,4-ditosylate **110** (Scheme 1.15, Chapter 1) was not formed. The low yield of symmetric ditosylates was perhaps due to the lesser polarity

(compared to DMF) of the solvent used for the reaction (THF). The use of a mixture of THF and DMF for the tosylation reactions resulted in the formation of the tritosylate **240**. Reasons for these observations are not clearly understood.

Among the 4,6-di-O-substituted derivatives obtained, the dibenzyl ether **102**[3c] and the ditosylate **105**[15] are previously reported in the literature and hence their structure could be established by comparison of the physical and spectroscopic data available in the literature. The NMR spectra of symmetrically C4- and C6-di-O-substituted derivatives of *myo*-inositol orthoesters are quite characteristic due to the presence of a mirror plane in the molecule.

Structure of the allyl ether **231** was confirmed by converting it to the known[3c] 2,4-dibenzyl ether **242** (Scheme 2A.11) and comparison of its (**242**) ^{1}H NMR spectrum with that reported in the literature. One of the characteristics of unsymmetrical benzyl ethers derived from *myo*-inositol orthoformate is that the two benzylic methylene protons of the axial benzyl ether appear as AB quartet and the benzylic methylene protons of the equatorial benzyl ether appears as a singlet in their ^{1}H NMR spectra. In the case of symmetrical 4,6-dibenzyl ether, benzylic protons of both the benzyl ether groups appear as AB quartet with the same chemical shift.



Scheme 2A.11. a) n-BuLi / THF, AllBr / DMF; b) NaH, BnBr, DMF.

The structure of the orthoformate 6-acetate **232** was confirmed by comparing the chemical shift of the acetate methyl peak in its ^{1}H NMR spectrum with the chemical shifts for the acetate methyl groups in the ^{1}H NMR spectra of known orthoester acetates **245-251** (Chart 2A.1). In the case of C2-acetates (equatorial), the acetate methyl peak appears in the range δ 2.20-2.26 while in the case of C4(6)-acetates, acetate methyl peak appears in the range δ 1.88-2.11. Since in the ^{1}H NMR spectrum of the acetate **232** the acetate methyl peak appeared at δ 1.86 we concluded that the acetylation had occurred at the C6-hydroxyl group and not at the C2-hydroxyl group.

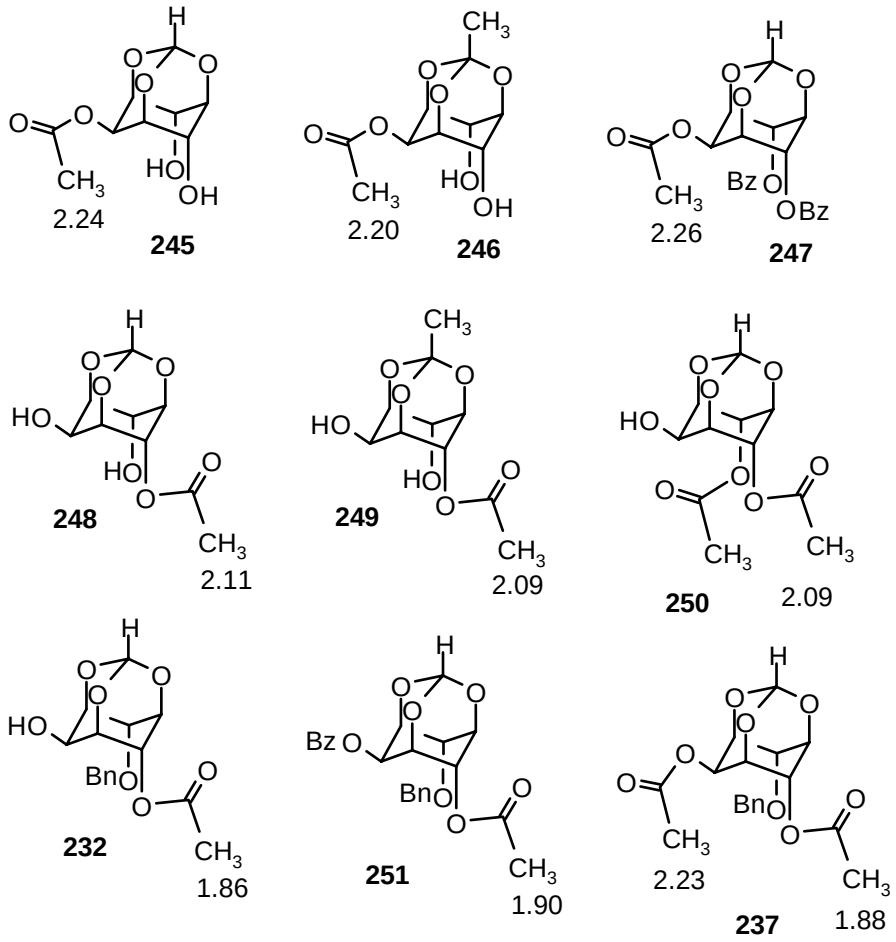


Chart 2A.1. Chemical shift of acetate methyl groups in the ^{1}H NMR spectra of acetate derivatives of *myo*-inositol orthoesters.

The structure of the 6-tosylate **233** was arrived at by comparing the chemical shift of the C6-ring proton (attached to the carbon bearing the tosylate group) in its ^{1}H NMR spectrum with the spectra of its analogs (Chart 2A.2). In the ^{1}H NMR spectra of C4- and / or C6-tosylate derivatives of *myo*-inositol orthoesters the signal due to the (equatorial) hydrogen attached to C4 and / or C6 always appeared at $\delta > 5.00$ whereas for the C2-tosylate the signal due to the (axial) hydrogen attached to C2 appeared at $\delta < 5.00$. The appearance of a signal in the ^{1}H NMR spectrum of the tosylate **233** at δ 5.19 showed that tosylation had occurred at the C6-hydroxyl group in **199**. This is further supported by the ^{1}H NMR spectrum of the by-product ditosylate **238** in which one ring proton appears at δ 5.09 and another proton appears at δ 4.93. In the ^{1}H NMR spectra of all these tosylate derivatives the most de-shielded

signals can be attributed to the hydrogen attached to the carbon carrying the tosylate group.

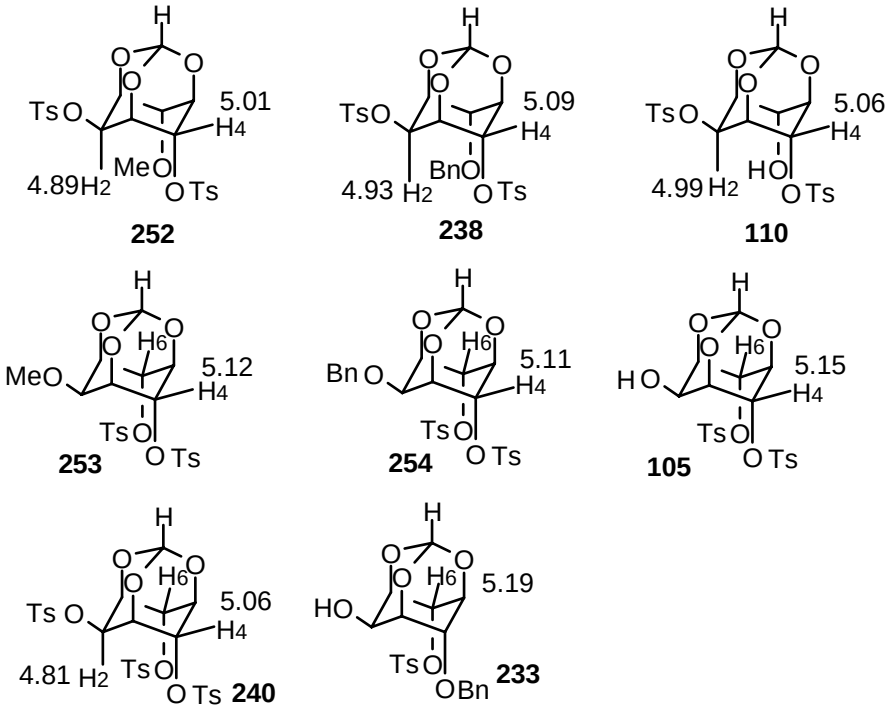
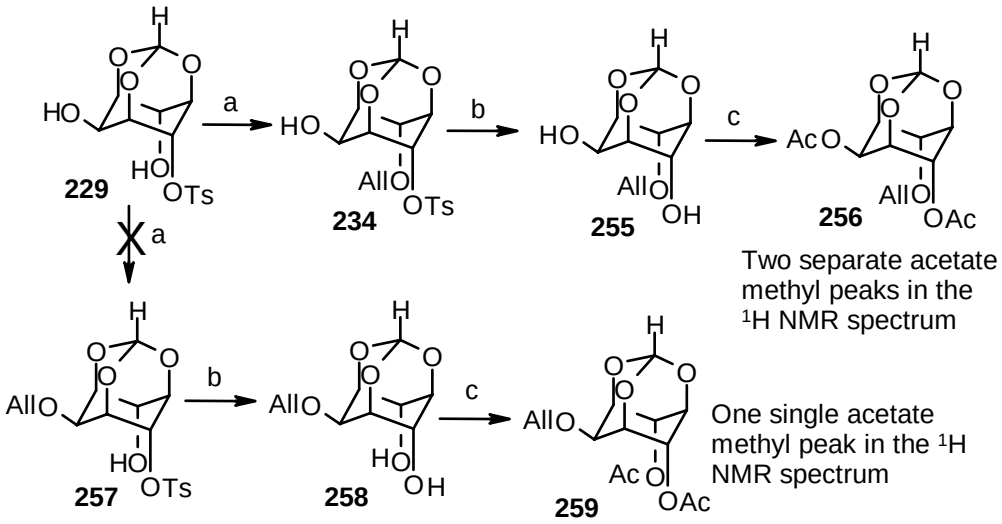


Chart 2A.2. Chemical shift of the C2-H and C6(4)-H in the ^{1}H NMR spectra of tosyltate derivatives of *myo*-inositol orthoformates.

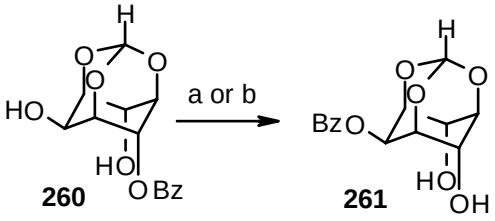
The structure of the C6-allyl ether **234** was confirmed by solvolysis of the tosylate followed by acetylation, which gave the racemic 2,4-diacetate **256** (Scheme 2A.12). The structure of the unsymmetrical diacetate **256** was established by its ^{1}H NMR spectrum which showed two separate singlets for the acetyl methyl groups. If the product of allylation of the racemic 4-tosylate **229** was the corresponding 2-allyl ether, solvolysis of the tosylate followed by acetylation would have resulted in the formation of the symmetric diacetate **259** which would exhibit a single peak for the two acetyl methyl groups in its ^{1}H NMR spectrum.



Scheme 2A.12. a) AllBr, LiH, DMF; b) NaOMe, MeOH, reflux; c) Ac_2O, Pyr.

The structure of the orthoacetate allyl ether **235** was confirmed by comparison of its ^{1}H NMR spectrum with the orthoformate analog **234**. The two ^{1}H NMR spectra were similar except that the orthoacetate methyl peak appeared (at δ 1.42) in the spectrum of **235** instead of the peak for the orthoformate proton (at δ 5.44) in the spectrum of **234**.

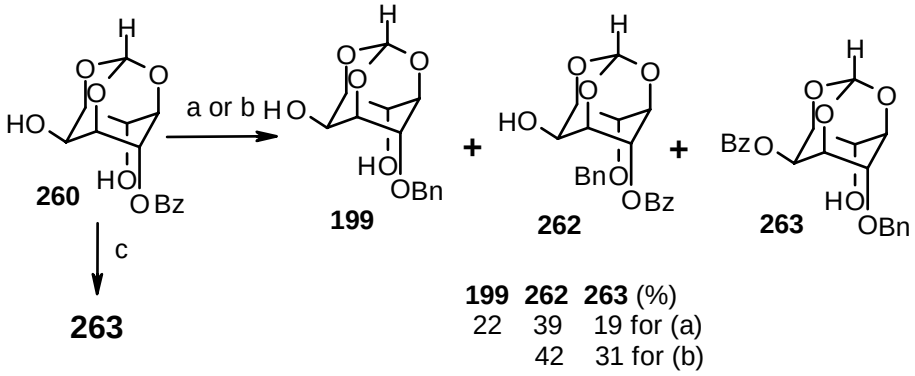
We also tested the possibility of carrying out the O-substitution of the unsymmetrical 2,4-diol having an ester group at the C4-position (such as **260**, Scheme 2A.13). Earlier work[3d] in our laboratory had shown that C4-esters undergo facile isomerization to the corresponding C2-esters when treated with sodium hydride in DMF.



Scheme 2A.13. a) NaH, DMF, 5 min; b) LiH, DMF, 30 min.

Since lithium alkoxides are less reactive as compared to the corresponding sodium alkoxides (through which the isomerization of the C4-ester to the C2-ester

proceeds), we wondered whether this would allow us to obtain good yield of the axial C6-ethers on alkylation of the racemic C4-benzoate **260** in the presence of lithium hydride. The fact that the lithium alkoxide is less reactive than the corresponding sodium alkoxide was indicated by the experimental observation that the C4-benzoate **260** underwent complete isomerization to the corresponding C2-benzoate **261** in 5 min (or less) on treatment with sodium hydride while the reaction time was about 30 min in the presence of lithium hydride (Scheme 2A.13). However, the weaker basicity of lithium hydride (as compared to that of sodium hydride) as a reason for the slower rate of conversion (of the C4-benzoate **260** to the C2-benzoate **261**) observed cannot be ruled out. In any case, irrespective of the cause for the difference in rates observed, slower isomerization of the C4-benzoate **260** in the presence of lithium hydride prompted us to attempt its benzylation. Butyllithium could not be used for this reaction to generate the required lithium alkoxide since alkyllithium is known[16] to react with esters to give the corresponding alkyl ketone.



Scheme 2A.14. a) DMF, BnBr, LiH; b) DMF, BnBr, NaH; c) DMF, NaH, BnBr.

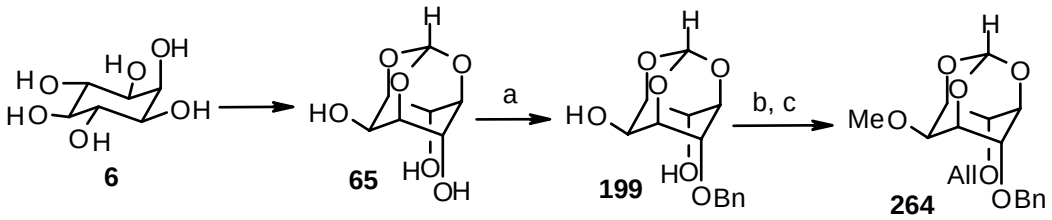
Benzylation of the C4-benzoate **260** using sodium hydride as a base is known[11] to yield a mixture of benzyl ethers **262** and **263** in the ratio 1.3:1 (based on isolated yields), provided sodium hydride was added to a solution of **260** and benzyl bromide in DMF (Scheme 2A.14). Addition of benzyl bromide to a mixture of **260** and sodium hydride results in the exclusive formation of the benzyl ether **263**.

Reaction of benzyl bromide with the C4-benzoate **260** using lithium hydride as the base yielded **262** and **263** in the ratio 2:1 (based on isolated yields). Although formation of the undesired product **263** was suppressed on using lithium hydride instead of sodium hydride, the isolated yield of the desired product **262** remained same. It is interesting to see that benzylation at the C2-O-position did not occur; this is perhaps because, formation of the C2-alkoxide results in immediate migration of the C4-O-benzoyl group (which is an intramolecular reaction) to the C2-O-position rather than its benzylation (which is an intermolecular reaction). These results also seem to support our contention that in the presence of metal ions, C4-alkoxide is formed preferentially due to their stabilization by chelate formation.

In a separate experiment, we also observed hydrolysis of the benzoate during work-up of the reaction mixture (by quenching lithium hydride with ice and evaporation of DMF at higher temperature 75-80 ºC) and isolated **263** (12%) and **199** (73%). The product **199** can arise directly by the hydrolysis of the benzoate in **262** or **263** and in principle also by hydrolysis of the axial benzoate in **260** to generate the triol **65** followed by its benzylation. The latter route for the formation of **199** can be ruled out since this is possible only during the reaction (before quenching with ice) and if so, we should have obtained comparable yield of **199** in all the experiments irrespective of the work-up procedure. However, these results clearly showed that the use of lithium hydride as a base to bring about C6-O-substitution in C4-esters of *myo*-inositol orthoesters is not of much synthetic utility.

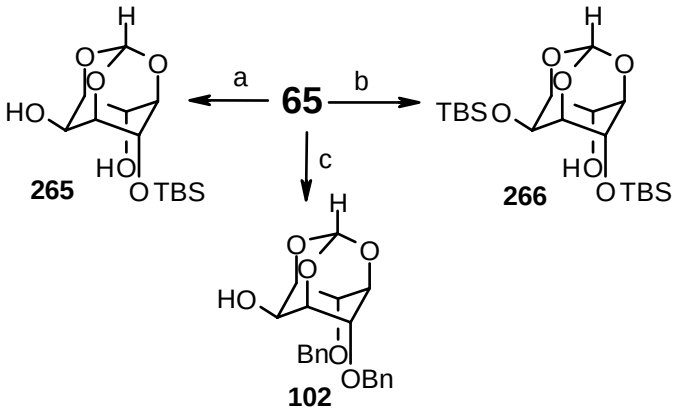
A perusal of the results described in this section shows that, the experimental protocol for best results for the C6-O-substitution in C4-O-protected *myo*-inositol 1,3,5-orthoester derivatives is the generation of the lithium alkoxide in dry THF followed by the addition of a solution of the appropriate electrophile in dry DMF.

This method is sufficiently flexible to allow the preparation of 4,6-diethers and any combination of ether, ester (alkylation followed by acylation – see preparation of the acetate **232**, Scheme 2A.10) and sulfonate derivatives. This method is not suitable for the preparation of 4,6-diesters since alkoxides of C4(6)-monoesters (**214**, Scheme 2A.4) undergo isomerization to the corresponding C2-esters[3d] faster than substitution at the C6-O-position. The versatility of this method was demonstrated by the rapid and efficient preparation of an unsymmetrical tri-O-substituted derivative **264** (Scheme 2A.15) from the racemic C4-benzyl ether **199** in a one pot reaction. Hence starting from *myo*-inositol, an orthogonally protected 2,4,6-tri-O-substituted derivative can be obtained in four steps, wherein each step gives only one product / regioisomer. This method should allow modification of the hydroxyl groups at C2, C4 and C6 positions to obtain other inositol derivatives.



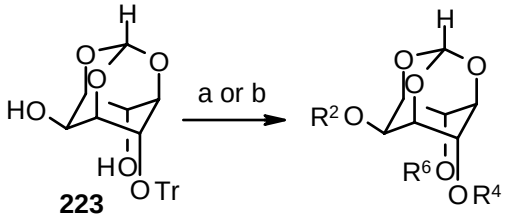
Scheme 2A.15. a) DMF, NaH, BnBr; b) n-BuLi / THF, AllBr / DMF; c) NaH, MeI.

We also investigated the extent to which steric hindrance due to the presence of 4,6-diaxial substituents (in **65**, **98** and their derivatives) dictate the course of the reaction and contribute to the observed regioselectivity. To understand this, we carried out (a) reaction of the triol **65** with bulky electrophiles (TBSCl) and (b) O-substitution of *myo*-inositol orthoester derivatives carrying a bulky protecting group (trityl) at the C4-O-position, with a small electrophile (methyl iodide).



Scheme 2A.16. a) n-BuLi, TBSCl, THF; b) LiH (4eq), TBSCl (2eq), DMF; c) n-BuLi / THF, BnBr / DMF.

Reaction of the triol **65** with TBSCl (1 eq.) / BuLi led to the formation of the C4-O-protected derivative **265** as the major product (Scheme 2A.16), and the corresponding C2-silyl ether was not formed. Silylation of **65** in the presence of metals (palladium)[17] those are not basic enough to form the C4-oxyanion result in a mixture of products consisting of different regioisomeric silyl ethers. Reaction of the triol **65** with two equivalents of TBSCl / LiH led to the formation of the racemic 2,4-di-O-silyl derivative **266**. This is in contrast to the corresponding reaction of the triol **65** with alkyl halides (not having bulky alkyl groups), which afforded the 4,6-diethers as the major product (Scheme 2A.9). The difference in the observed regioselectivity in these two reactions can be attributed to the steric hindrance offered by the C4-O-TBS group for the entry of another bulky TBS group at the C6-O-position.

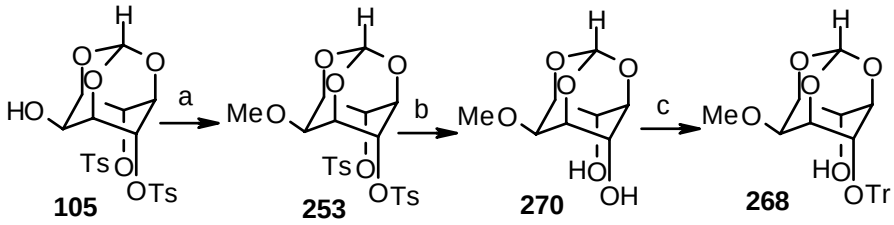


	R^2	R^4	R^6
267	H	Tr	Me
268	Me	Tr	H
269	Me	Tr	Me

Scheme 2A.17. a) n-BuLi / THF, MeI / DMF; b) NaH / THF, MeI / DMF.

Reaction of the racemic trityl ether **223** (Scheme 2A.17) with butyllithium followed by methyl iodide gave a mixture of products consisting of isomeric monomethyl ethers **267** and **268** as well as the dimethyl ether **269**. The racemic C6-ether **267** was formed in higher proportion compared to the corresponding C2-methyl ether **268** (**267**:**268** = 61:39). The use of sodium hydride for the same reaction also resulted in a mixture of products (**267**-**269**) but **268** was present in larger proportion as compared to **267** (**267**:**268** = 11:89).

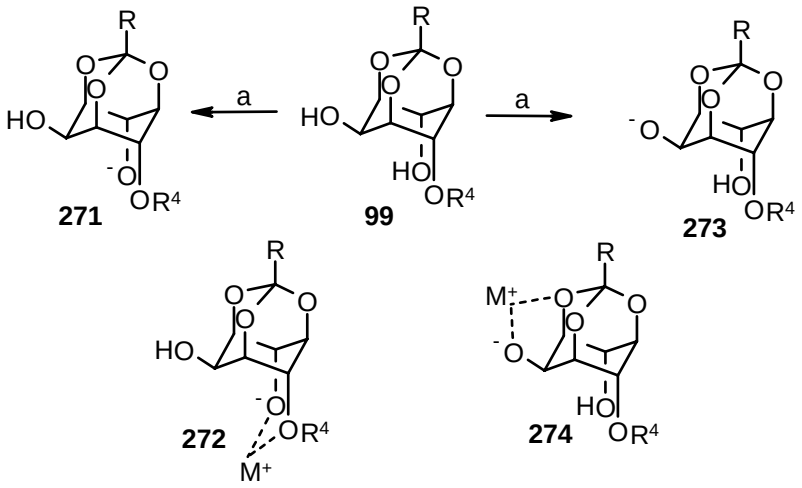
The structure of the two monomethyl ethers **267** and **268** were established by unambiguous synthesis of **268** starting from the known ditosylate **105** (Scheme 2A.18).[15] The ditosylate **105** was methylated using sodium hydride and methyl iodide and the tosyl groups in **253** were cleaved with sodium methoxide in methanol under reflux. The diol **270** so obtained was tritylated to give **268**.



Scheme 2A.18. a) NaH, MeI, DMF; b) NaOMe, MeOH, reflux; c) NaH, TrCl, DMF.

In principle, reaction of *myo*-inositol orthoester derived 2,4-diols (such as **99**, Scheme 2A.4) with butyllithium or sodium hydride can result in the formation of two anions **271** and **273** (Scheme 2A.19). Higher isolated yields of the 4,6-disubstituted products on the reaction of *myo*-inositol orthoester derived 2,4-diols with electrophiles in the presence of metal hydrides (Scheme 2A.10) suggest that **271** is preferentially formed (see results on alkylation of the C4-benzoate Scheme 2A.14). This could be a result of greater stabilization of the anion **271** by metal ions due to chelation (**272**) with two diaxially oriented oxygen atoms as compared to the

stabilization of the anion **273** due to chelation (**274**) with the oxygen atoms in axial – equatorial orientation.



Scheme 2A.19. a) NaH or LiH or n-BuLi.

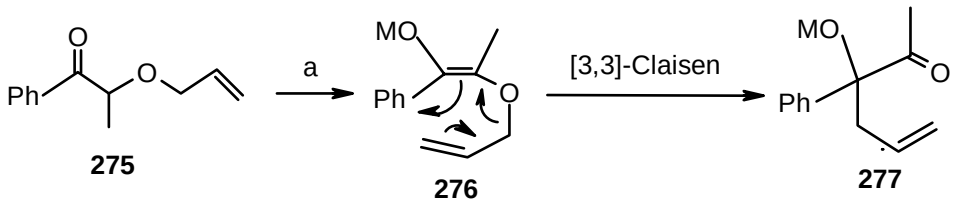
This is analogous to the formation of a strong intramolecular hydrogen bond between the 4,6-diaxial hydroxyl groups in *myo*-inositol orthoesters (e.g. **65**) which has been observed in their crystals,[4a,b] while the *cis*-1,2-hydroxyl groups result in a comparatively weaker intramolecular hydrogen bond.[4a,c] Increase in the yield of the 4,6-di-O-substituted derivatives and non formation of the 2,4-di-O-substituted derivatives (Scheme 2A.10 and Scheme 2A.17) in the BuLi assisted reaction as compared to the NaH assisted reaction suggests that Li^+ stabilizes the anion **271** better than Na^+ does.

It is of relevance to compare the results of alkylation of the C4-trityl ether **223** (Scheme 2A.17) and the corresponding benzyl ether **199** in the presence of Na^+ and Li^+, which could shed light on the relative ease of formation / stabilization of anions **271** and **273** under the conditions of alkylation. Since monobenzylation of the triol **65** with NaH / BnBr yields **199** exclusively, it can be inferred that dibenzylation of the triol **65** proceeds exclusively *via* the 4-benzyl ether **199** to yield a mixture of products consisting of 2,4 and 4,6 diethers (Scheme 2A.7) in the ratio 1:5 and minor amount of the tribenzyl ether **226**.[3c] On increasing the steric bulk of the alkyl group at the C4-O-

position with a trityl group, predominant methylation (using sodium hydride as the base) took place at the C2-O-position (to give **268**, Scheme 2A.17) which reflects the steric crowding at the C6 position. Alkylation of the benzyl ether **199** with BuLi / BnBr on the other hand provided the 4,6-diether **102** exclusively while methylation of the trityl ether **223** with MeI / BuLi gave the C6-methylether **267** as the major product (unlike in the reaction assisted by Na^+). These results give credence to our postulate that in Li^+ assisted reactions stabilization of the anion **271** by chelation plays a dominant role over steric effect of the trityl group. However, yet another possibility which cannot be ruled out is the inability of the larger Na^+ to chelate at the 4,6-positions (in **223**) due to the presence of bulky trityl group while the smaller Li^+ can still form a chelate at the 4,6 positions due to its smaller size. These results strongly suggest that stabilization of the oxyanion by chelation with lithium (**272**) overrides steric hindrance offered by the *cis*-axial substituent in deciding the regioselectivity during the nucleophilic O-substitution in *myo*-inositol orthoesters. Hence it appears that the major factor that controls regioselectivity during the di-O-substitution of *myo*-inositol orthoesters in the presence of metal ions is the extent of chelation that exists between the metal ion and the two di-axial oxygen atoms. It is also interesting to note that *myo*-inositol derivatives were indeed found to bind lithium ions better than sodium ions as postulated above, by the picrate extraction experiments.[18] Several *myo*-inositol derivatives tested bound lithium picrate 10-100 times better than sodium picrate. These results support our suggestion that the extent of chelation of metal ions by inositol derivatives is a major factor in deciding the observed regioselectivity for the O-substitution reactions shown in Scheme 2A.10.

We also carried out a search of the literature to see if any systematic study had been carried out to investigate the effect of counter ions on organic reactions.

Although butyllithium had been used as a base to generate lithium alkoxides from the corresponding alcohols[19] their reaction with alkyl halides has not been investigated in detail. However, retardation of the rate of anionic oxy-Claisen rearrangement of α-allyloxy ketones due to the nature of counter ion is reported.[20] This study showed that rate of oxy-Claisen rearrangement was dependent on the strength of the metal oxygen bond in enolates **276**; lithium enolate was the least reactive and the potassium enolate was the most reactive (Scheme 2A.20).



Metal ion(M)	Temperature (^oC)	Half-life($t_{1/2}$), h
K	-23	3.3
Na	0	2.6
Li	96.5	1.1

Scheme 2A.20. a) Metal hydride, toluene.

2A.3 Conclusions

We have developed a general method for the orthogonal O-substitution of the three hydroxyl groups of *myo*-inositol orthoesters wherein each step in the scheme of reactions proceed with very high regioselectivity. We have also shown that chelation of the metal ions with inositol orthoester derivatives play a major role in deciding the regioselectivity in these reactions. These results coupled with other regioselective reactions reported in the literature provide convenient access to any O-substituted *myo*-inositol orthoester derivative.

2A.4. Experimental section

General. All the solvents used were purified according to literature procedures.[21] All the reactions were carried out in an atmosphere of argon. Dry DMF and dry THF were used as solvents in all the experiments involving metal hydrides or n-butyllithium. Sodium hydride used in experiments was 60% suspension in mineral oil. A stock solution of n-butyllithium (1.4-1.7 M) in dry hexanes was prepared and used in all the experiments. *myo*-Inositol derivatives **65**,[3f] **98**,[22] **199**,[3c] **229**[3b] were prepared according to literature procedures. Thin layer chromatography was performed on E. Merck pre-coated 60 F_{254} plates and the spots were rendered visible either by shining UV light or by charring the plates with concd H_2SO_4 or chromic acid. Column chromatographic separations (silica gel, 100-200 mesh) and flash column chromatographic separations (silica gel, 230-400 mesh) were carried out with light petroleum-ethyl acetate mixtures as eluent. 'Usual work-up' implies washing of the organic layer with water followed by brine, drying over anhydrous sodium sulfate and removal of the solvent under reduced pressure using a rotary evaporator. Compounds previously reported in the literature were characterized by comparison of their melting points and / or ^{1}H NMR spectra with the reported data. IR spectra were recorded in $CHCl_3$ solution or as nujol mull or as neat on a Shimadzu FTIR-8400 or Perkin Elmer 16 spectrophotometer. NMR spectra were recorded on Bruker ACF 200 spectrometer (at 200 MHz for ^{1}H and 50.3 MHz for ^{13}C) unless otherwise mentioned. Chemical shifts (δ) reported are referred to internal tetramethylsilane. Microanalytical data were obtained using a Carlo-Erba CHNS-0 EA 1108 elemental analyzer. All the melting points reported are uncorrected and were recorded using a Büchi B-540 electro-thermal melting point apparatus. All the asymmetrically substituted *myo*-inositol

derivatives reported are racemic; however, only one of the enantiomers is shown in all the schemes.

Racemic 4-*O*-benzyl-*myo*-inositol 1,3,5-orthoformate (199). The triol **65** (0.100 g, 0.53 mmol) and benzyl bromide (0.63 mL, 5.26 mmol) were dissolved in DMF (4 mL) and stirred with potassium carbonate (0.727 g, 5.26 mmol) at 106 °C for 26 h. The reaction mixture was cooled to ambient temperature, diluted with ethyl acetate and worked up as usual. The known[3c] benzyl ether **199** (0.106 g, 72%) was isolated as a gum after filtration of the crude product on a short column of silica gel.

Racemic 4-*O*-trityl-*myo*-inositol 1,3,5-orthoformate (223). To a solution of the triol **65** (1.00 g, 5.30 mmol) in DMF (15 mL) was added sodium hydride (0.233 g, 5.83 mmol) and stirred for 0.5 h. A solution of trityl chloride (1.630 g, 5.83 mmol) in DMF (8 mL) was added drop-wise and the mixture stirred for 1 h. The reaction mixture was worked up with ethyl acetate and the crude product was purified by filtration over a short column of silica gel to obtain **223** (0.900 g, 40%) as a solid.

Data for 223:

mp. 217-218 °C.

IR (ν, $CHCl_3$): 3350-3700 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 7.20-7.60 (m, 15H), 5.28 (s, 1H), 4.53-4.62 (m, 1H), 4.16-4.40 (m, 3H), 3.87 (d, 1H, J = 9.8 Hz, D_2O exchangeable), 3.69-3.77 (m, 1H), 3.02-3.20 (m, 2H, 1H, D_2O exchangeable).

^{13}C NMR ($CDCl_3$): δ 142.6, 128.4, 128.2, 128.0, 102.3, 89.8, 74.1, 73.1, 70.1, 67.7, 67.4, 60.9.

Elemental analysis calcd for $C_{26}H_{24}O_6$: C, 72.21; H, 5.59. Found: C, 72.19; H, 5.73.

Racemic 4-*O*-(*p*-toluenesulfonyl)-*myo*-inositol 1,3,5-orthoacetate (230). To a solution of the triol **98**[22] (0.650 g, 3.20 mmol) in dry DMF (6 mL) sodium hydride

(0.154 g, 3.84 mmol) was added and stirred for 0.5 h. Then a solution of tosyl chloride (0.730 g, 3.84 mmol) in DMF (6 mL) was added in one lot and stirred for 0.5 h. The reaction mixture was worked up with ethyl acetate as usual and the solid obtained was filtered through a short column of silica gel to get **230** (0.837 g, 73%) as a colorless solid.

Data for 230:

mp. 137-139 °C.

IR (ν, nujol): 3078-3533 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 7.83 (d, 2H, J = 7.8 Hz), 7.40 (d, 2H, J = 7.8 Hz), 5.06-5.18 (m, 1H), 4.47-4.60 (m, 1H), 4.15-4.31 (m, 2H), 3.96-4.13 (m, 2H), 2.90-3.15 (broad s, 1H, D_2O exchangeable), 2.30-2.80 (br, 1H, D_2O exchangeable), 2.48 (s, 3H), 1.42 (s, 3H).

^{13}C NMR ($(CD_3)_2CO$): δ 145.8, 133.7, 130.4, 128.1, 108.9, 75.1, 74.4, 73.2, 69.7, 66.8, 58.7, 23.8, 20.9.

Elemental analysis calcd for $C_{15}H_{18}O_8S$: C, 50.27; H, 5.06. Found: C, 50.08; H, 5.06.

Synthesis of 4,6-di-O-substituted-*myo*-inositol 1,3,5-orthoesters.

Procedure A. The required triol **65** or **98** (1 mmol) was taken in THF (5 mL) and n-butyllithium (2.3 mmol) was added at 0 °C. A solution of the appropriate alkyl halide (2.2 mmol) in DMF (1 mL) was added and the mixture stirred for 36-45 h. The resulting mixture was then worked up with ethyl acetate. The products were separated by column chromatography using 10-20% ethyl acetate – light petroleum as the eluent.

Procedure B. The required triol **65** or **98** (1 mmol) was taken in DMF (2-3 mL) and lithium hydride (4 mmol) was added at ambient temperature. A solution of the appropriate alkyl halide (2.2 mmol) in DMF (1 mL) was added and the mixture was

stirred for 36-45 h. The reaction mixture was then worked up with ethyl acetate and the products were separated as in procedure A.

Procedure C. The required 4-O-substituted *myo*-inositol orthoester (1 mmol) was taken in dry THF (4 mL) and cooled to 0 °C. n-Butyllithium (1.5 mmol) was added drop-wise using a syringe followed by a solution of the required alkyl halide, acyl halide or sulfonyl halide (1.2 mmol) in DMF (2 mL). The reaction mixture was stirred for 22-28 h and worked up with ethyl acetate and the products were separated as in procedure A.

Procedure D. The required 4-O-substituted *myo*-inositol orthoester (1 mmol) was taken in DMF (3-4 mL) and stirred for 2 h with lithium hydride (2 mmol). A solution of the alkyl halide in DMF (2 mL) was added and the mixture stirred for 36-40 h. The reaction mixture was then worked up with ethyl acetate and the products were separated as in procedure A.

4,6-Di-*O*-benzyl-*myo*-inositol 1,3,5-orthoformate (102). The triol **65** (0.190 g, 1 mmol) was benzylated using benzyl bromide (0.376 g, 2.20 mmol) and n-butyllithium (Procedure A) to obtain the known **102**[3c] (0.296 g, 80%) and tribenzyl ether **226**[3c] (0.055 g, 12%).

mp. (for **102**) 118-120 °C, (Lit.[3c] mp. 124-125 °C).

mp. (for **226**) 103-105 °C, (Lit.[3c] mp. 102-104 °C).

4,6-Di-*O*-allyl-*myo*-inositol 1,3,5-orthoformate (104). The triol **65** (0.190 g, 1 mmol) was allylated using allyl bromide (0.278 g, 2.30 mmol) and lithium hydride (Procedure B) to obtain **104** (0.251 g, 93%) as a gum.

Data for 104:

IR (ν, $CHCl_3$): 3250-3700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.82-5.93 (m, 2H), 5.48 (s, 1H), 5.30 (dd, 2H, J = 1.4, 17.0 Hz), 5.20 (dd, 2H, J = 1.4, 10.0 Hz), 4.39-4.44 (m, 1H), 4.29 (t, 2H, J = 3.2 Hz), 4.18-4.23 (m, 2H), 4.03-4.15 (m, 5H), 3.14 (d, 1H, J = 10 Hz, D_2O exchangeable).

^{13}C NMR ($CDCl_3$): δ 134.3, 117.5, 103.5, 73.8, 73.2, 70.7, 68.0, 61.5.

Elemental analysis Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.60; H, 7.04.

4,6-Di-*O*-(*p*-toluenesulfonyl)-*myo*-inositol 1,3,5-orthoformate (105). The racemic 4-tosylate **229** (0.500 g, 1.45 mmol) was taken in THF (8 mL) and n-butyllithium (1.60 mmol) was added at -78 °C. A solution of tosyl chloride (0.332 g, 1.75 mmol) in THF (2 mL) was added and the mixture stirred for 2 h during which the reaction temperature was allowed to come to ambient temperature. The resulting mixture was then worked up with ethyl acetate. The known ditosylate **105** (0.412 g, 57%) and tritosylate **240** (0.284 g, 30%) were separated by column chromatography.

mp. (for **105**) 181-182 °C, (Lit.[15] mp. 183-185 °C).

mp. (for **240**)102-104 °C, (Lit.[15] mp. 103-105 °C).

4,6-Di-*O*-benzyl-*myo*-inositol 1,3,5-orthoacetate (227). The triol **98** (0.204 g, 1 mmol) was benzylated using benzyl bromide (0.359 g, 2.20 mmol) and n-butyllithium (Procedure A) to obtain **227** (0.268 g, 70%) as a solid and the monobenzyl ether **228** (0.040 g, 14%) as a gum.

Data for 227:

mp. 88-90 °C.

IR (ν, $CHCl_3$): 3300-3600 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 7.28 (s, 10H), 4.62 (AB q, 4H, J = 11.7 Hz), 4.08-4.46 (m, 6H), 3.04 (d, 1H, J = 11.7 Hz, D_2O exchangeable), 1.44 (s, 3H).

^{13}C NMR ($CDCl_3$): δ 137.7, 128.5, 127.9, 127.7, 109.3, 73.8, 73.6, 71.7, 67.9, 60.4, 24.4.

Elemental analysis calcd for $C_{22}H_{24}O_6$: C, 68.74; H, 6.29. Found: C, 68.97; H, 6.14.

Data for 228:

^{1}H NMR ($CDCl_3$): δ 7.15-7.53 (m, 5H), 4.66 (d, 2H, J = 2 Hz), 4.34-4.50 (m, 2H), 4.15-4.31 (m, 3H), 3.96-4.10 (m, 1H), 3.67 (d, 1H, J = 9.7 Hz, D_2O exchangeable), 3.00-3.35 (broad s, 1H, D_2O exchangeable), 1.43 (s, 3H).

4,6-Di-*O*-benzyl-*myo*-inositol 1,3,5-orthoformate (102). The monobenzyl ether **199** (0.283 g, 1 mmol) was benzylated by procedure C to obtain the known[3c] dibenzyl ether **102** (0.328 g, 89%) and the tribenzyl ether **226** (0.037 g, 8%).

mp. (for **102**) 118-120 °C.

Racemic 4-*O*-benzyl-6-*O*-allyl-*myo*-inositol 1,3,5-orthoformate (231). The monobenzyl ether **199** (0.283 g, 1 mmol) was allylated by procedure C to obtain the 6-allyl ether **231** (0.256 g, 80%) and the diallyl ether **236** (0.036g, 10%) as gums.

Data for 231:

IR (ν, $CHCl_3$): 3220-3600 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 7.33 (s, 5H), 5.75-6.00 (m, 1H), 5.47 (s, 1H), 5.16-5.35 (m, 2H), 4.62 (AB q, 2H, J = 11.8 Hz), 4.38-4.49 (m, 1H), 4.26-4.37 (m, 2H), 3.95-4.25 (m, 5H), 3.22 (d, 1H, J = 11.2 Hz, D_2O exchangeable).

^{13}C NMR ($CDCl_3$): δ 137.9, 134.3, 128.7, 128.1, 127.8, 117.8, 103.6, 73.9, 73.3, 71.7, 71.0, 68.0, 61.7.

Elemental analysis Calcd for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29. Found: C, 63.83; H, 6.47.

Data for 236:

^{1}H NMR ($CDCl_3$): δ 7.30 (s, 5H), 5.75-6.10 (m, 2H), 5.50 (s, 1H), 5.10-5.40 (m, 4H), 4.58 (AB q, 2H, J = 11.7 Hz), 4.20-4.45 (m, 5H), 3.90-4.20 (m, 5H).

The monoallyl ether **231** obtained above was converted to the known[3c] racemic dibenzyl ether **242** as follows: To a solution of **231** (0.050 g, 0.20 mmol) in DMF (1

mL), sodium hydride (0.016 g, 0.40 mmol) was added and stirred for 5 min. Benzyl bromide (0.068 g, 0.40 mmol) was added and the mixture stirred for 0.5 h and worked up as usual to obtain **242** (0.062 g, 97%).

Racemic 4-*O*-benzyl-6-*O*-acetyl-*myo*-inositol 1,3,5-orthoformate (232). The monobenzyl ether **199** (0.286 g, 1 mmol) was acetylated (Procedure D, reaction time 4 h), with acetic anhydride (0.125 g, 1.20 mmol) to obtain the racemic **232** (0.230 g, 70%) and the diacetate **237** (0.057 g, 15%) as white solids.

Data for 232:

mp. 102-104 °C.

IR (ν, $CHCl_3$): 3300-3570, 1737 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 7.16-7.45 (m, 5H), 5.51 (s, 1H), 5.35-5.46 (m, 1H), 4.62-4.72 (m, 1H), 4.57 (s, 2H), 4.05-4.43 (m, 4H), 3.31 (d, 1H, J = 11.8 Hz, D_2O exchangeable), 1.86 (s, 3H).

^{13}C NMR ($CDCl_3$): δ 170.2, 137.5, 128.8, 128.4, 127.7, 103.5, 73.6, 72.8, 72.2, 68.6, 66.6, 61.6, 20.9.

Elemental analysis Calcd for $C_{16}H_{18}O_7$: C, 59.62; H, 5.63. Found: C, 59.91; H, 5.65.

Data for 237:

mp. 116-118 °C

^{1}H NMR ($CDCl_3$): δ 7.30-7.45 (m, 5H), 5.58 (s, 1H), 5.40 (td, 1H, J = 1.5, 3.9 Hz), 5.31-5.36 (m, 1H), 4.65-4.72 (m, 1H), 4.59 (AB q, 2H, J = 11.3 Hz), 4.40-4.46 (m, 1H), 4.29-4.39 (m, 2H), 2.23 (s, 3H), 1.88 (s, 3H).

Racemic 4-*O*-benzyl-6-*O*-(*p*-toluenesulfonyl)-*myo*-inositol 1,3,5-orthoformate (233). The monobenzyl ether **199** (0.278 g, 1 mmol) was sulfonylated (Procedure D, reaction time 4 h), with *p*-toluenesulfonyl chloride (0.228 g, 1.20 mmol) to obtain the 6-tosylate **233** as a solid (0.283 g, 65%) and the ditosylate **238** (0.060 g, 10%) as gum.

Data for 233:

mp. 160-162 °C.

IR (ν, $CHCl_3$): 3300-3600 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 7.75 (d, 2H, J = 8.3 Hz), 7.20-7.40 (m, 7H), 5.43 (s, 1H), 5.13-5.25 (m, 1H), 4.59 (AB q, 2H, J = 11.7 Hz), 4.40-4.47 (m, 1H), 4.27-4.39 (m, 1H), 4.15-4.24 (m, 1H), 3.96-4.14 (m, 2H), 3.11 (d, 1H, J = 11.7 Hz, D_2O exchangeable), 2.44 (s, 3H).

^{13}C NMR ($CDCl_3$): δ 145.7, 137.4, 133.1, 130.3, 128.7, 128.1, 127.9, 103.3, 73.0, 72.9, 72.8, 72.3, 71.8, 67.5, 60.9, 21.9.

Elemental analysis Calcd for $C_{21}H_{22}O_8S$: C, 58.06; H, 5.10. Found: C, 58.10; H, 4.80.

Data for 238:

^{1}H NMR ($CDCl_3$): δ 7.79 (d, 2H, J = 8.3 Hz), 7.73 (d, 2H, J = 8.3 Hz), 5.44 (d, 1H, J = 1.4 Hz), 5.09 (td, 1H, J = 1.5, 3.9 Hz), 4.90-4.96 (m, 1H), 4.53 (AB q, 2H, J = 11.8 Hz), 4.35-4.41 (m, 1H), 4.25 (td, 1H, J = 1.5, 3.4 Hz), 4.13-4.20 (m, 1H), 4.04-4.11 (m, 1H), 2.46 (s, 3H), 2.43 (s, 3H).

Racemic 4-*O*-(*p*-toluenesulfonyl)-6-*O*-allyl-*myo*-inositol 1,3,5-orthoformate (234). The racemic 4-tosylate **229**[3b] (0.344 g, 1 mmol) was allylated (Procedure D), with allyl bromide (0.145 g, 1.20 mmol) to obtain **234** (0.278 g, 72%) and the diallyl ether **239** (0.026 g, 6%) as gums.

Data for 234:

IR (ν, $CHCl_3$): 3200-3600 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 7.81 (d, 2H, J = 8.3 Hz), 7.37 (d, 2H, J = 8.3 Hz), 5.75-6.00 (m, 1H), 5.44 (s, 1H), 5.05-5.38 (m, 3H), 4.35-4.50 (m, 1H), 3.95-4.34 (m, 6H), 3.18 (d, 1H, J = 10.3 Hz, D_2O exchangeable), 2.47 (s, 3H).

^{13}C NMR ($CDCl_3$): δ 145.8, 133.9, 130.3, 128.2, 118.1, 103.3, 72.8, 72.3, 70.8, 67.5, 60.9, 21.9.

Data for 239:

^{1}H NMR ($CDCl_3$): δ 7.82 (d, 2H, J = 8.6 Hz), 7.38 (d, 2H, J = 8.2 Hz), 5.75-6.10 (m, 2H), 5.49 (s, 1H), 5.05-5.40 (m, 5H), 3.80-4.45 (m, 9H), 2.47 (s, 3H).

The monoallyl ether **234** obtained above was converted to the known[3c] 4-allyl ether **255** as follows: The racemic **234** (0.050 g, 0.13 mmol) and sodium methoxide (0.070 g, 1.30 mmol) were refluxed in dry methanol (2 mL) for 2 h. The reaction mixture was cooled to ambient temperature and worked up as usual to obtain racemic **255** (0.026 g, 87%) as a gum. The monoallyl ether **255** (0.026 g) was characterized as its diacetate **256** (0.031 g, 89%) obtained by acetylation with acetic anhydride (0.046 g, 0.45 mmol) in pyridine (1 mL) for 12 h.

Data for 256:

mp. 87-89 °C (colorless solid).

IR (ν, $CHCl_3$): 1742 cm^{-1}.

^{1}H NMR (300MHz, $CDCl_3$): δ 5.79-5.94 (m, 1H), 5.57 (d, 1H, J = 1.0 Hz), 5.38-5.43 (m, 1H), 5.31-5.35 (m, 1H), 5.19-5.29 (m, 2H), 4.61-4.66 (m, 1H), 4.35-4.40 (m, 1H), 4.27-4.33 (m, 2H), 4.03-4.10 (m, 2H), 2.22 (s, 3H), 2.06 (s, 3H).

Elemental analysis Calcd for $C_{14}H_{18}O_8$: C, 53.50; H, 5.77. Found: C, 53.70; H, 5.73.

Racemic 4-*O*-(*p*-toluenesulfonyl)-6-*O*-allyl-*myo*-inositol 1,3,5-orthoacetate (235). The racemic 4-tosylate **230** (0.358 g, 1 mmol) was allylated (Procedure D), with allyl bromide (0.146 g, 1.20 mmol) to obtain **235** (0.246 g, 62%) and diallyl ether **241** (0.039 g, 9%) as gums.

Data for 235:

IR (ν, $CHCl_3$): 3300-3590 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 7.82 (d, 2H, J = 8.3 Hz). 7.38 (d, 2H, J = 8.3 Hz), 5.75-6.00 (m, 1H), 5.15-5.40 (m, 2H), 5.00-5.12 (m, 1H), 4.34-4.39 (m, 1H), 3.94-4.28 (m, 6H), 2.89-3.10 (broad s, 1H, D_2O exchangeable), 2.47 (s, 3H), 1.42 (s, 3H).

^{13}C NMR ($CDCl_3$): δ 145.6, 134.0, 133.4, 130.3, 128.2, 117.9, 109.4, 73.5, 73.2, 72.9, 72.7, 70.8, 67.5, 60.0, 24.3, 21.8.

Elemental analysis calcd for $C_{18}H_{22}O_8S$: C, 54.26; H, 5.57. Found: C, 54.12; H, 5.55.

Data for 241:

^{1}H NMR ($CDCl_3$): δ 7.82 (d, 2H, J = 8.3 Hz), 7.38 (d, 2H, J = 7.8 Hz), 5.75-6.10 (m, 2H), 5.15-5.40 (m, 4H), 4.95-5.10 (m, 1H), 3.95-4.35 (m, 8H), 3.75-3.85 (m, 1H), 2.47 (s, 3H), 1.43 (s, 3H).

Reaction of racemic 4-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate with lithium hydride and benzyl bromide.

Procedure E. To a solution of the diol **260** (0.294 g, 1 mmol) and benzyl bromide (0.13 mL, 1.10 mmol) in DMF (3 mL) lithium hydride (0.016 g, 2.00 mmol) was added and the mixture stirred for 24 h at ambient temperature. The reaction mixture was worked up with ethyl acetate as the solvent and the products were separated by column chromatography **263** (0.073 g, 19%), **262** (0.151 g, 39%) and **199** (0.062 g, 22%).

Procedure F. To a solution of the diol **260** (0.250 g, 0.85 mmol) and benzyl bromide (0.11 mL, 0.94 mmol) in DMF (3 mL) lithium hydride (0.014 g, 1.70 mmol) was added and the mixture stirred for 24 h at ambient temperature. The reaction mixture was quenched with ice and DMF was evaporated at 75-80 °C under reduced pressure and worked up as usual with ethyl acetate. The products were separated by column chromatography to obtain **263** (0.039 g, 12%) and **199** (0.174 g, 73%).

Data for 262:

mp. 104-106 °C.

^{1}H NMR ($CDCl_3$): δ 7.88 (d, 2H, J = 7.1 Hz), 7.45-7.56 (m, 1H), 7.10-7.31 (m, 7H), 5.71-5.79 (m, 1H), 5.57 (d, 1H, J = 1.1 Hz), 4.62-4.71 (m, 1H), 4.54 (s, 2H), 4.31-4.46 (m, 3H), 4.20-4.28 (m, 1H), 3.10-3.50 (broad s, 1H, D_2O exchangeable).

Data for 263:

mp. 98-100 °C.

^{1}H NMR ($CDCl_3$): δ 8.17 (d, 2H, J = 6.9 Hz), 7.55-7.67 (m, 1H), 7.43-7.54 (m, 2H), 7.38 (s, 5H), 5.50-5.58 (m, 2H), 4.75 (AB q, 2H, J = 11.4 Hz), 4.56-4.63 (m, 1H), 4.41-4.55 (m, 3H), 4.31-4.39 (m, 1H), 3.86 (d, 1H, J = 9.9 Hz, D_2O exchangeable).

Racemic 2-*O*-methyl-4-*O*-benzyl-6-*O*-allyl-*myo*-inositol 1,3,5-orthoformate (264). Racemic **199** (0.281 g, 1 mmol) was taken in THF (4 mL) and cooled to 0 °C. n-Butyllithium (1.1 mL, 1.50 mmol) was added slowly followed by allyl bromide (0.145 g, 1.20 mmol) in dry DMF (2 mL) and the mixture stirred for 22 h. Then excess sodium hydride (0.100 g, 2.50 mmol) and methyl iodide (0.355 g, 2.50 mmol) were added and the mixture stirred for 4 h and worked up with ethyl acetate. The triether **264** (0.267 g, 80%) was separated (as gum) by flash column chromatography.

Data for 264:

^{1}H NMR ($CDCl_3$): δ 7.20-7.50 (m, 5H), 5.75-6.05 (m, 1H), 5.51 (s, 1H), 5.14-5.40 (m, 2H), 4.63 (AB q, 2H, J = 11.7 Hz), 4.24-4.50 (m, 5H), 4.00-4.23 (m, 2H), 3.78 (s, 1H), 3.48 (s, 3H).

^{13}C NMR ($CDCl_3$): δ 137.9, 134.4, 128.7, 128.1, 127.8, 117.9, 103.4, 74.2, 74.0, 71.9, 71.1, 70.2, 70.0, 69.6, 68.3, 56.9.

Elemental analysis Calcd for $C_{18}H_{22}O_6$: C, 64.66; H, 6.63. Found: C, 64.76; H, 6.89.

Racemic 4-*O*-(*t*-butyldimethylsilyl)-*myo*-inositol 1,3,5-orthoformate (265). The triol **65** (0.500 g, 2.63 mmol) was silylated (Procedure A) in THF (25 mL) using n-butyllithium (1.7 mL, 2.63 mmol) and a solution of *t*-butyldimethylsilyl chloride (0.476 g, 3.15 mmol) in THF (5 mL). The known racemic **265** (0.584 g, 73%) was isolated by column chromatography.

mp. 74-76 °C, (Lit.[17] mp. 73-74 °C).

Racemic 2,4-di-*O*-(*t*-butyldimethylsilyl)-*myo*-inositol 1,3,5-orthoformate (266). The triol **65** (0.150 g, 0.80 mmol) was silylated (Procedure B) in dry DMF (2 mL) using lithium hydride (0.260 g, 3.20 mmol) and *t*-butyldimethylsilyl chloride (0.253 g, 1.68 mmol) to obtain the known racemic **266** (0.174 g, 52%) as a solid.

mp. 79-81 °C, (Lit.[3n] mp. 75-78 °C).

Methylation of racemic 4-*O*-trityl-*myo*-inositol 1,3,5-orthoformate (223). Racemic **223** (0.600 g, 1.40 mmol) was methylated (Procedure C) in THF (6 mL) using n-butyllithium (1 mL, 1.68 mmol) and methyl iodide (0.12 mL, 1.68 mmol) in DMF (1 mL) to obtain the 6-methyl ether **267** (0.147 g, 24%), the 2-methyl ether **268** (0.036 g, 6%) and the dimethyl ether **269** (0.183 g, 29%).

Data for 267:

mp. 165-166 °C.

IR (ν, nujol): 3323-3541 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 7.43-7.55 (m, 6H), 7.23-7.40 (m, 9H), 5.29 (s, 1H), 4.43-4.52 (m, 1H), 4.14-4.24 (m, 2H), 4.02-4.10 (m, 1H), 3.72-3.83 (m, 1H), 3.46 (s, 3H), 3.08-3.18 (m, 1H), 2.77-2.94 (broad s, 1H, D_2O exchangeable).

^{13}C NMR ($CDCl_3$): δ 143.8, 128.6, 128.0, 127.5, 102.8, 88.0, 75.8, 73.7, 72.4, 69.0, 68.0, 61.3, 57.6.

Elemental analysis calcd for $C_{27}H_{26}O_6$: C, 72.63; H, 5.87. Found: C, 72.30; H, 6.10.

Data for 268:

mp. 191-193 °C.

IR (ν, nujol): 3304-3541 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 7.25-7.50 (m, 15H), 5.32 (d, 1H, J = 1.1 Hz), 4.54-4.62 (m, 1H), 4.31-4.45 (m, 2H), 3.79-3.89 (m, 2H, 1H, D_2O exchangeable), 3.57-3.65 (m, 1H), 3.48 (s, 3H), 3.41-3.51 (m, 1H).

^{13}C NMR ($CDCl_3$): δ 142.7, 128.5, 128.2, 128.1, 102.3, 89.9, 71.1, 70.3, 69.9, 69.0, 68.1, 67.8, 56.9.

Elemental analysis calcd for $C_{27}H_{26}O_6$: C, 72.63; H, 5.87. Found: C, 72.43; H, 5.44.

Data for 269:

mp. 251-253 °C.

^{1}H NMR ($CDCl_3$): δ 7.45-7.55 (m, 5H), 7.20-7.40 (m, 10H), 5.34 (s, 1H), 4.44-4.52 (m, 1H), 4.28-4.36 (m, 1H), 4.08-4.15 (m, 1H), 3.99-4.07 (m, 1H), 3.74-3.80 (m, 1H), 3.53 (s, 3H), 3.31 (s, 3H), 3.07-3.14 (m, 1H).

^{13}C NMR ($CDCl_3$): δ 143.9, 128.6, 128.1, 127.5, 102.8, 88.0, 75.9, 70.1, 69.7, 69.4, 69.2, 68.5, 57.7, 56.7.

Elemental analysis calcd for $C_{28}H_{28}O_6$: C, 73.03; H, 6.13. Found: C, 72.99; H, 6.10.

The proportion of **267** and **268** formed on using butyllithium and sodium hydride for the methylation of **223** were estimated as follows: Racemic **223** (0.100 g, 0.23 mmol) was methylated (Procedure C) in THF (1 mL) using n-butyllithium (0.15 mL, 0.25 mmol) and methyl iodide (0.02 mL, 0.25 mmol) in DMF (0.18 mL). The mixture of monoethers **267** and **268** (0.042 g) was separated by column chromatography and their proportion (**267**:**268** = 61:39) estimated by ^{1}H NMR spectroscopy. Use of sodium hydride (0.010 g, 0.25 mmol) instead of butyllithium in the above experiment

provided a mixture of the two ethers (0.053 g) in the ratio **267**:**268** = 11:89 and the dimethyl ether **269** (0.030 g. 28%).

Racemic 2-*O*-methyl-4-*O*-trityl-*myo*-inositol 1,3,5-orthoformate (268). To a solution of the ditosylate **105** (0.300 g, 0.60 mmol) in DMF, sodium hydride (0.036 g, 0.90 mmol) was added followed by methyl iodide (0.06 mL, 0.90 mmol). The reaction mixture was stirred for 15 min and worked up with ethyl acetate as usual to get 2-*O*-methyl-4,6-di-*O*-(*p*-toluenesulfonyl)-*myo*-inositol 1,3,5-orthoformate (**253**, 0.287 g, 93%).

Data for 253:

mp. 141-143 °C.

^{1}H NMR ($CDCl_3$): δ 7.84 (d, 4H, J = 8.2 Hz), 7.39 (d, 4H, J = 8.2 Hz), 5.44 (d, 1H, J = 1.6 Hz), 5.12 (t, 2H, J = 4 Hz), 4.26-4.37 (m, 2H), 4.13-4.22 (m, 1H), 3.59-3.68 (m, 1H), 3.42 (s, 3H), 2.48 (s, 6H).

The methyl ether **253** (0.450 g, 0.90 mmol) and sodium methoxide (0.486 g, 9 mmol) were refluxed in dry methanol : THF (4:1) for 6 h. The solvents were evaporated and the solid obtained was chromatographed over silica gel using 1:1 ethyl acetate – light petroleum as eluent to obtain 2-*O*-methyl-*myo*-inositol 1,3,5-orthoformate (**270**, 0.124 g, 69%).

Data for 270:

mp. 179-181 °C.

^{1}H NMR ($(CD_3)_2CO$): δ 5.38 (d, 1H, J = 1.2 Hz), 4.98-5.10 (broad s, 2H, D_2O exchangeable), 4.39-4.52 (m, 2H), 4.24-4.31 (m, 2H), 4.15-4.23 (m, 1H), 3.75-3.82 (m, 1H), 3.46 (s, 3H).

To a solution of the diol **270** obtained above (0.080 g, 0.40 mmol) in DMF was added sodium hydride (0.024 g, 0.60 mmol) and trityl chloride (0.167 g, 0.60 mmol) and the

reaction mixture stirred at ambient temperature for 1 h and worked up as usual with ethyl acetate. Column chromatography over silica gel gave the trityl ether **268** (0.054 g, 31%).

mp. 191-193 °C.

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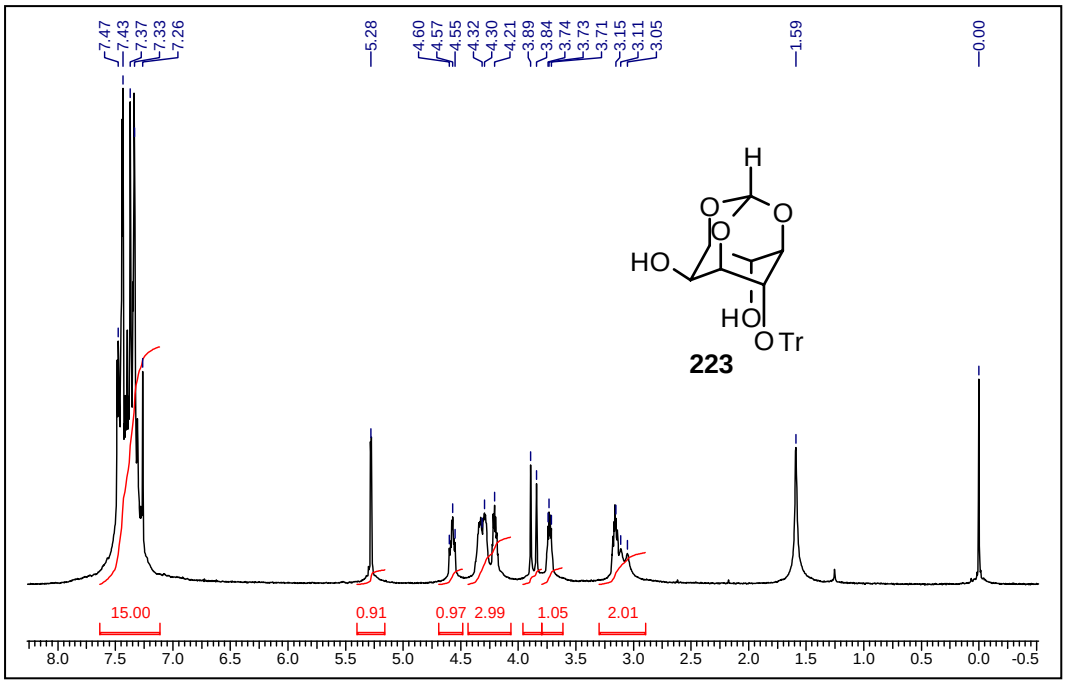
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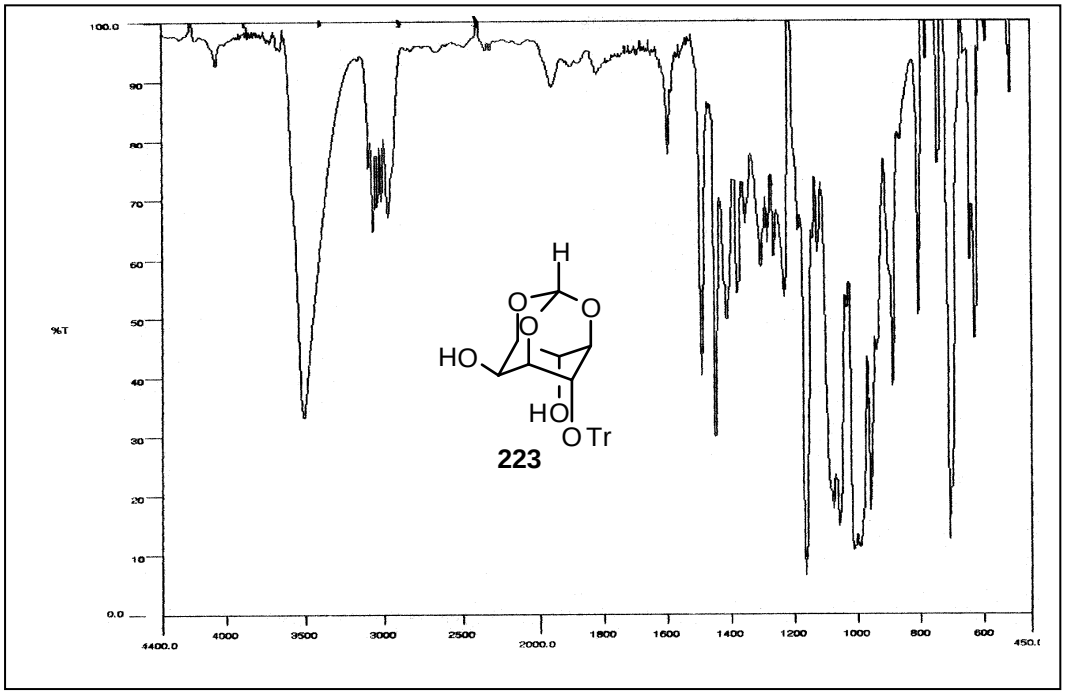
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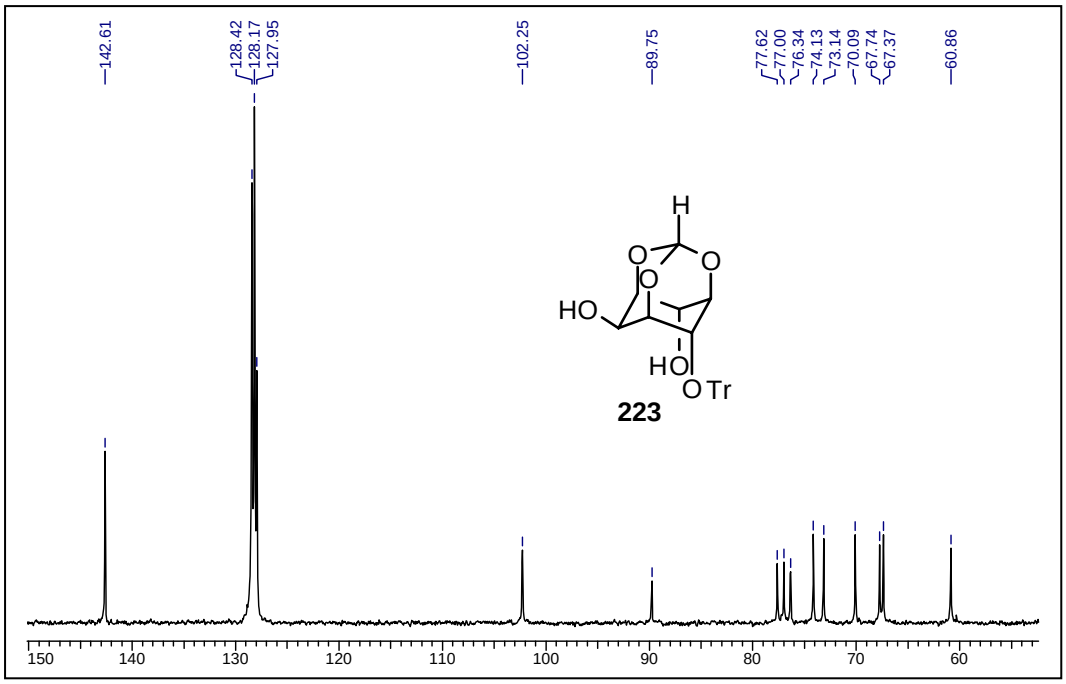
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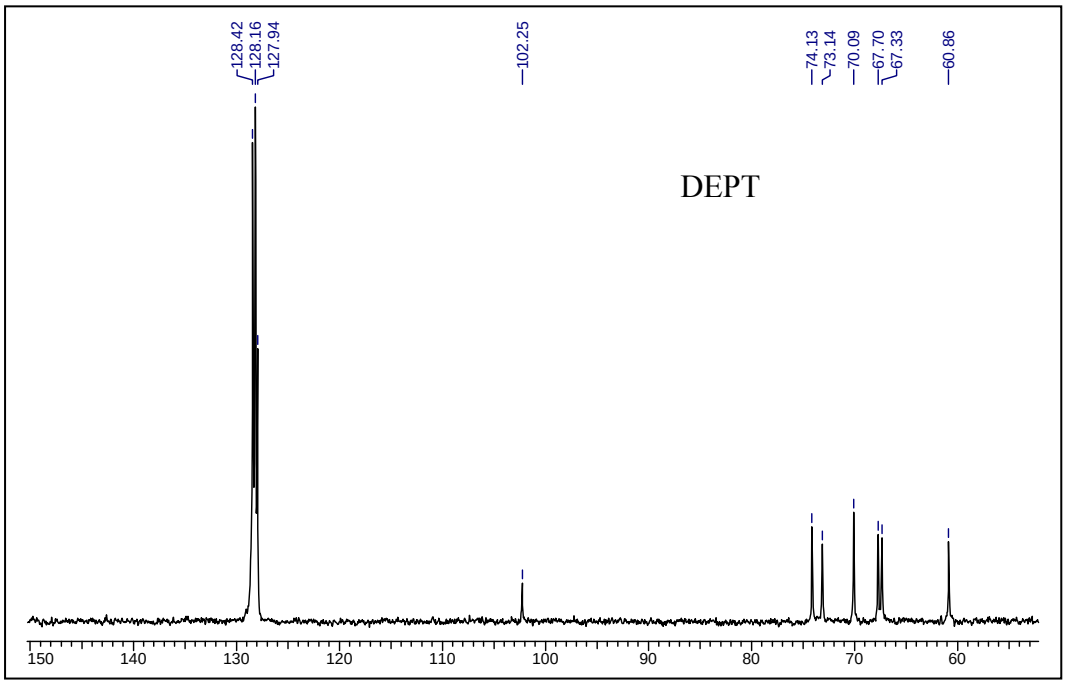
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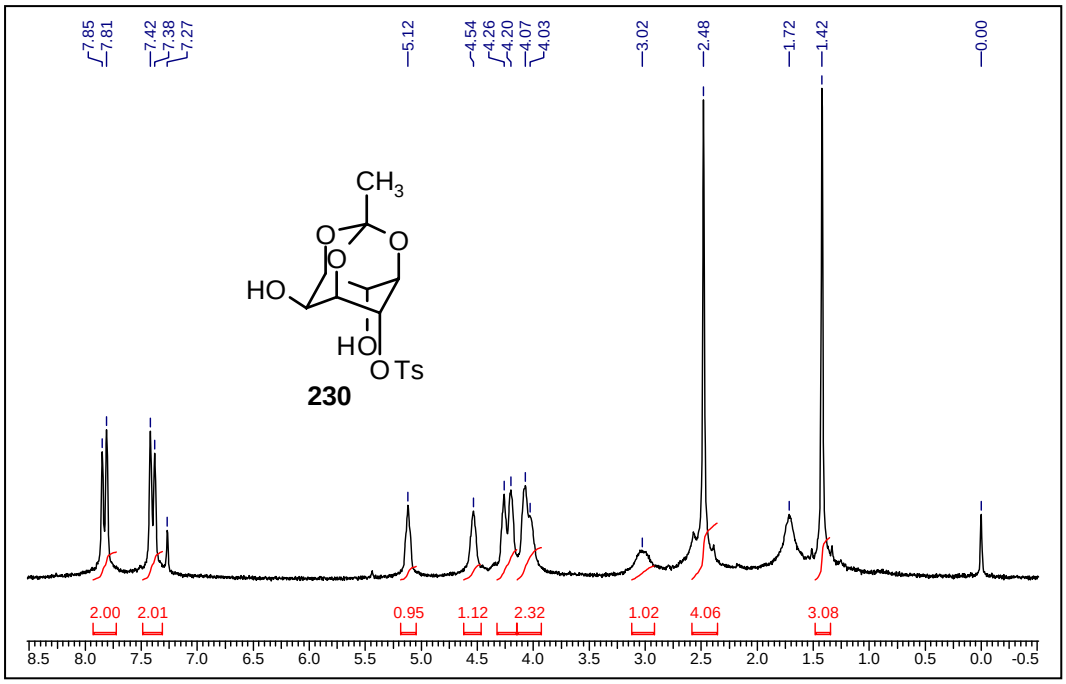
60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7.81
7.42
7.38
7.27
5.12
4.54
4.26
4.20
4.07
4.03
3.02
2.48
1.72
1.42
0.00
CH3
O
O
O
HO
HO
O Ts
230
2.00
2.01
0.95
1.12
2.32
1.02
4.06
3.08
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
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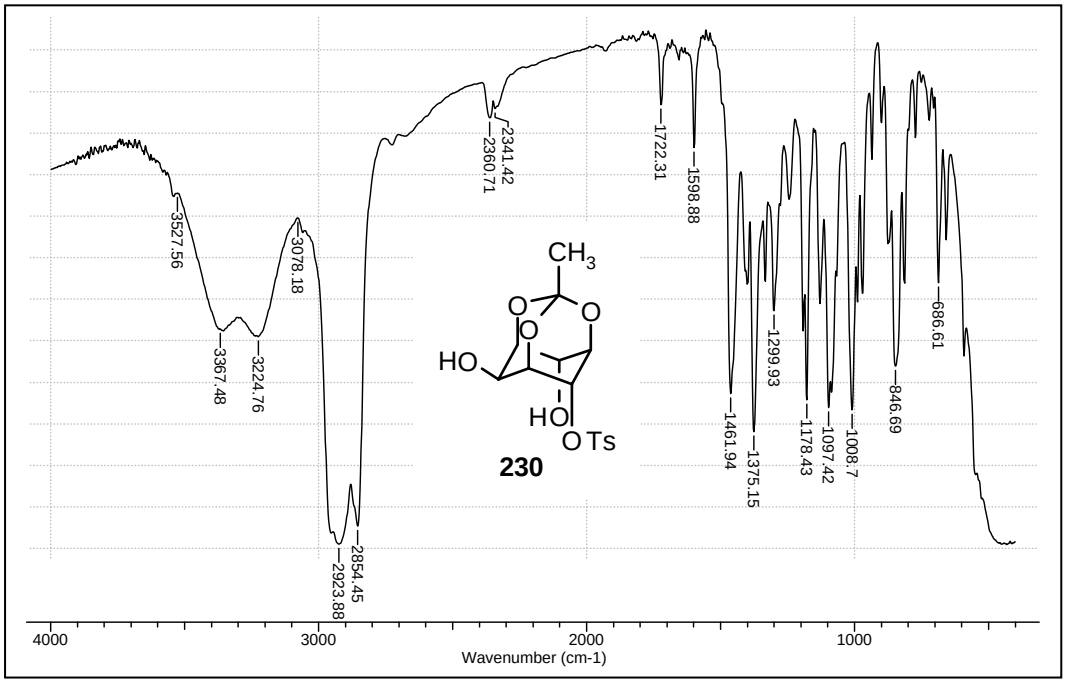
0.0
-0.5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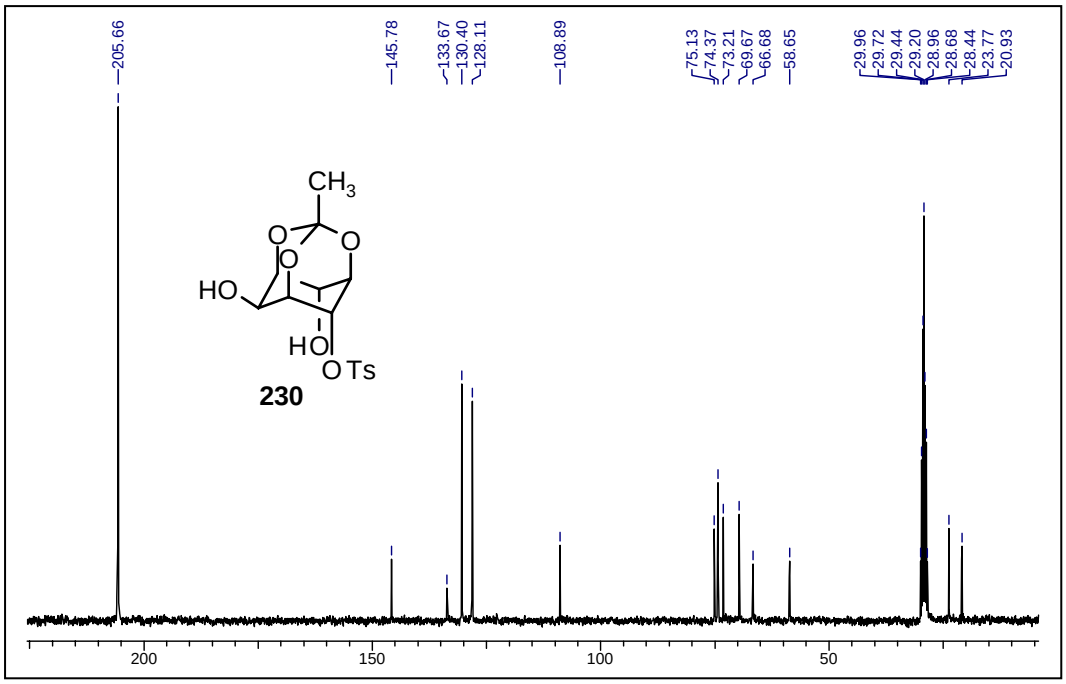
2923.88
2854.45
2360.71
2341.42
1722.31
1598.88
1461.94
1375.15
1299.93
1178.43
1097.42
1008.7
846.69
686.61
CH3
O
O
O
HO
HO
O Ts
230
4000
3000
2000
1000
Wavenumber (cm-1)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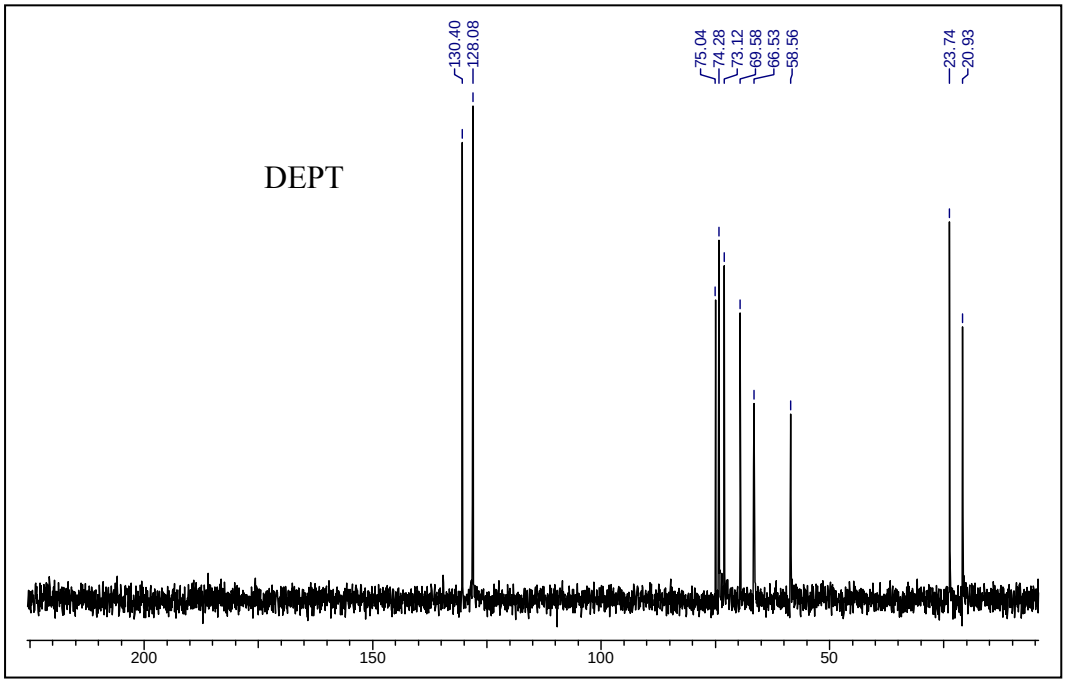
133.67
130.40
128.11
108.89
75.13
74.37
73.21
69.67
66.68
58.65
29.96
29.72
29.44
29.20
28.96
28.68
28.44
23.77
20.93
CH3
O
O
O
HO
HO
O Ts
230
200
150
100
50


DEPT
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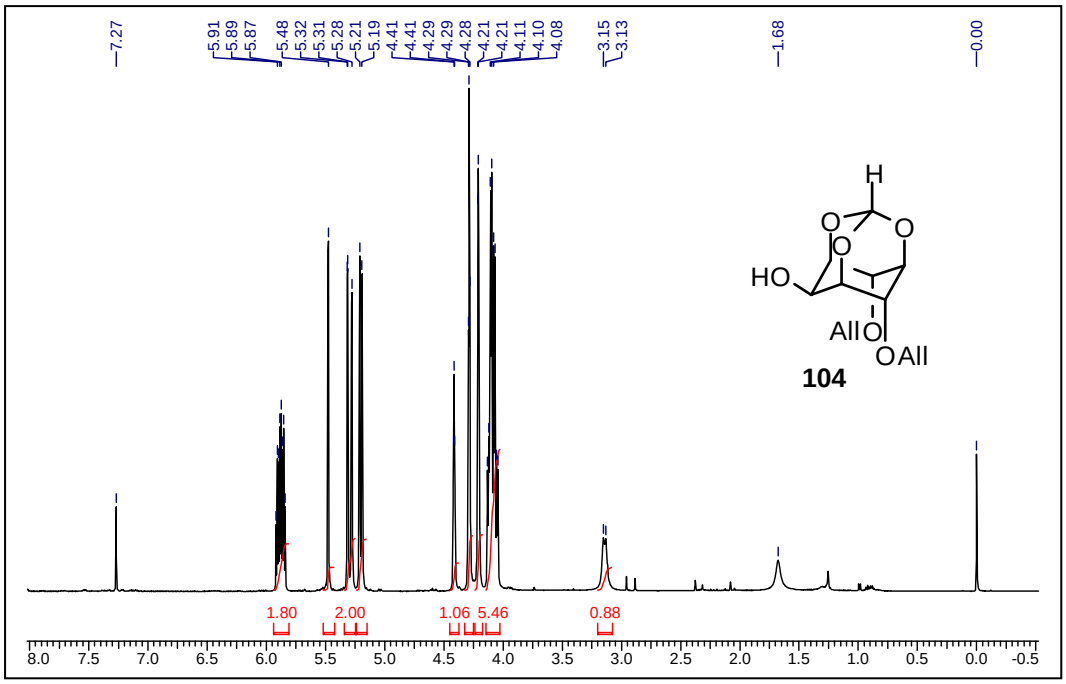
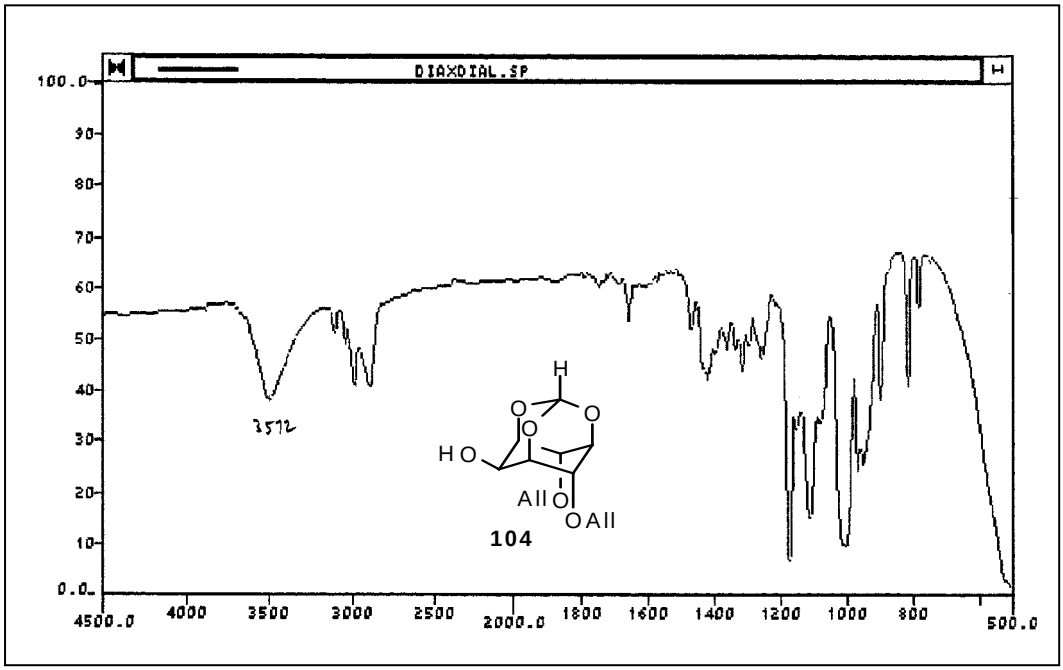
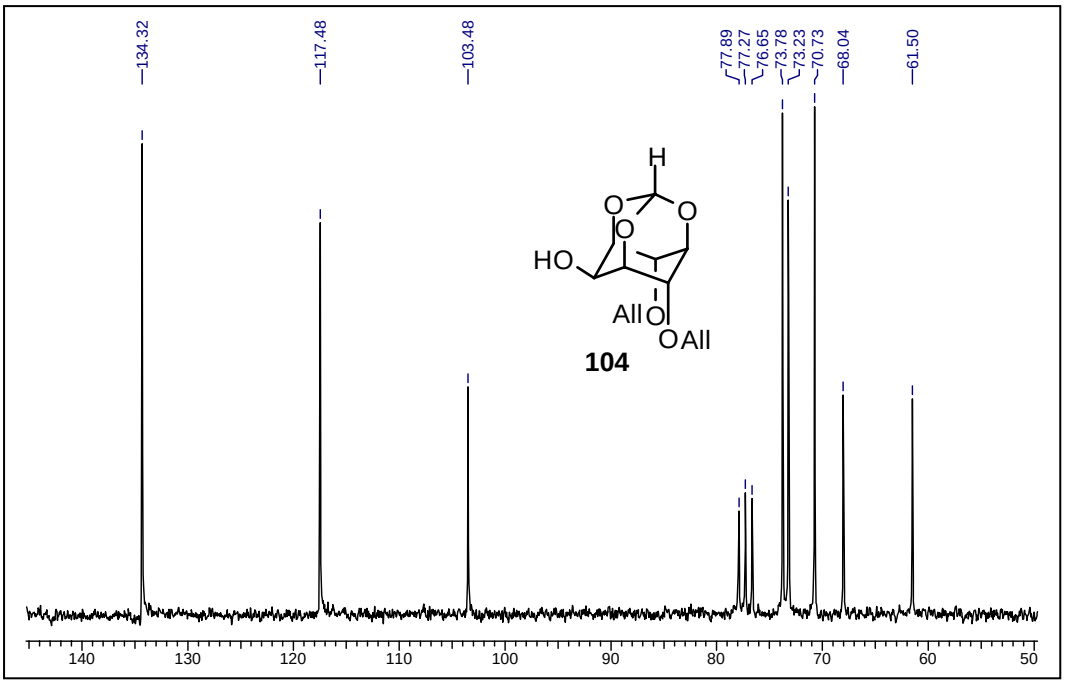
128.08
75.04
74.28
73.12
69.58
66.53
58.56
23.74
20.93
200
150
100
50


7.27
5.91
5.89
5.87
5.48
5.32
5.31
5.28
5.21
5.19
4.41
4.41
4.29
4.29
4.28
4.21
4.21
4.11
4.10
4.08
3.15
3.13
1.68
0.00
1.80
2.00
1.06
5.46
0.88
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
H
O
O
O
HO
AllO
OAll
104


DIAXDIAL.SP
H
100.0
90
80
70
60
50
40
30
20
10
0.0
3572
4500.0 4000 3500 3000 2500 2000.0 1800 1600 1400 1200 1000 800 500.0
H
O
O
O
HO
AllO
OAll
104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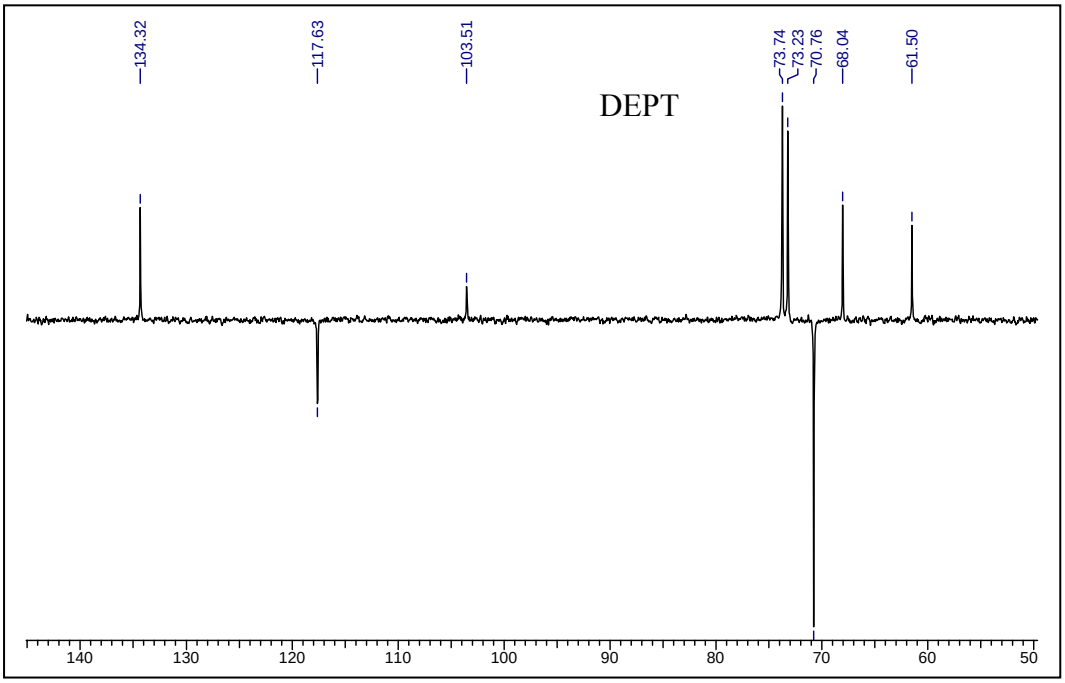
117.48
103.48
77.89
77.27
76.65
73.78
73.23
70.73
68.04
61.50
H
O
O
O
HO
All
O
O All
104
140
130
120
110
100
90
80
70
60
50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117.63
103.51
73.74
73.23
70.76
68.04
61.50
DEPT
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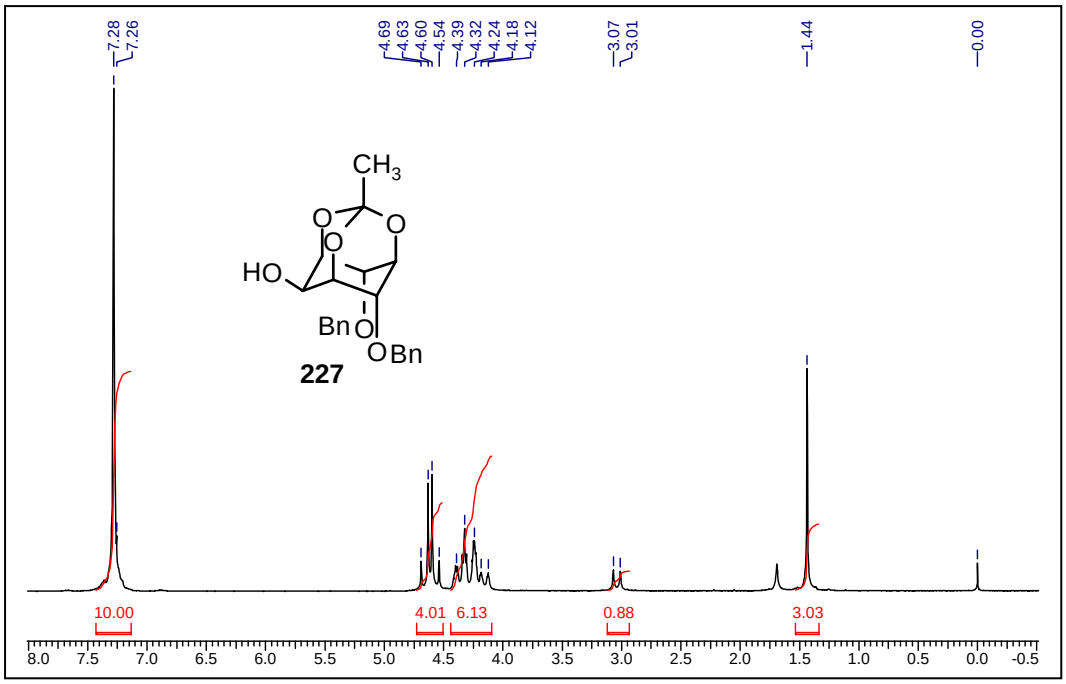
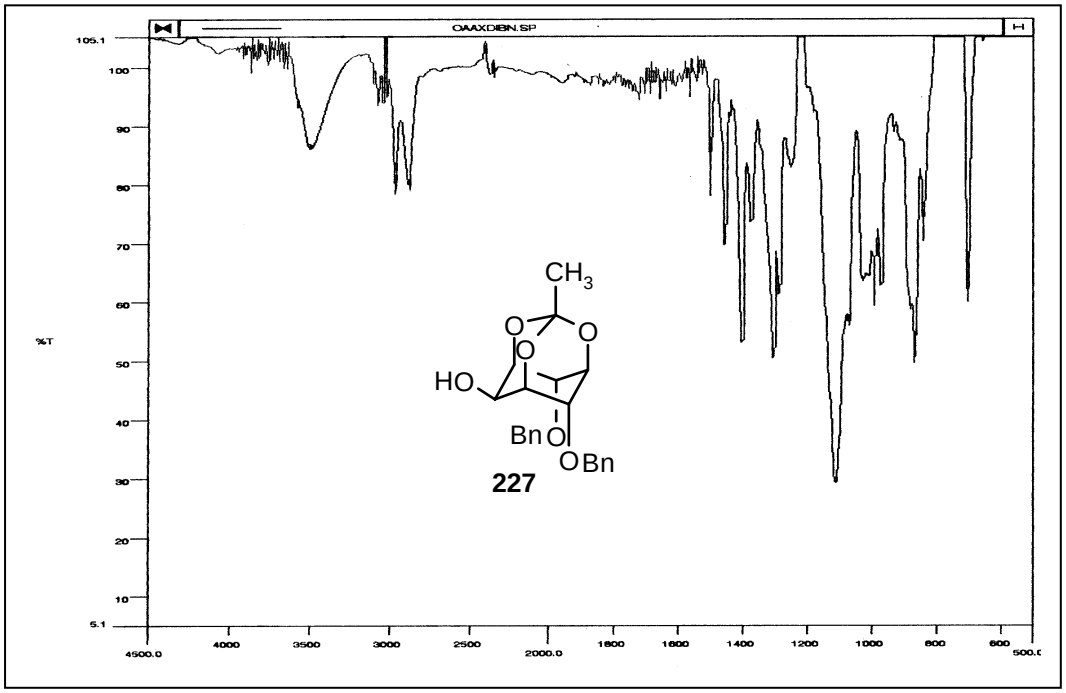
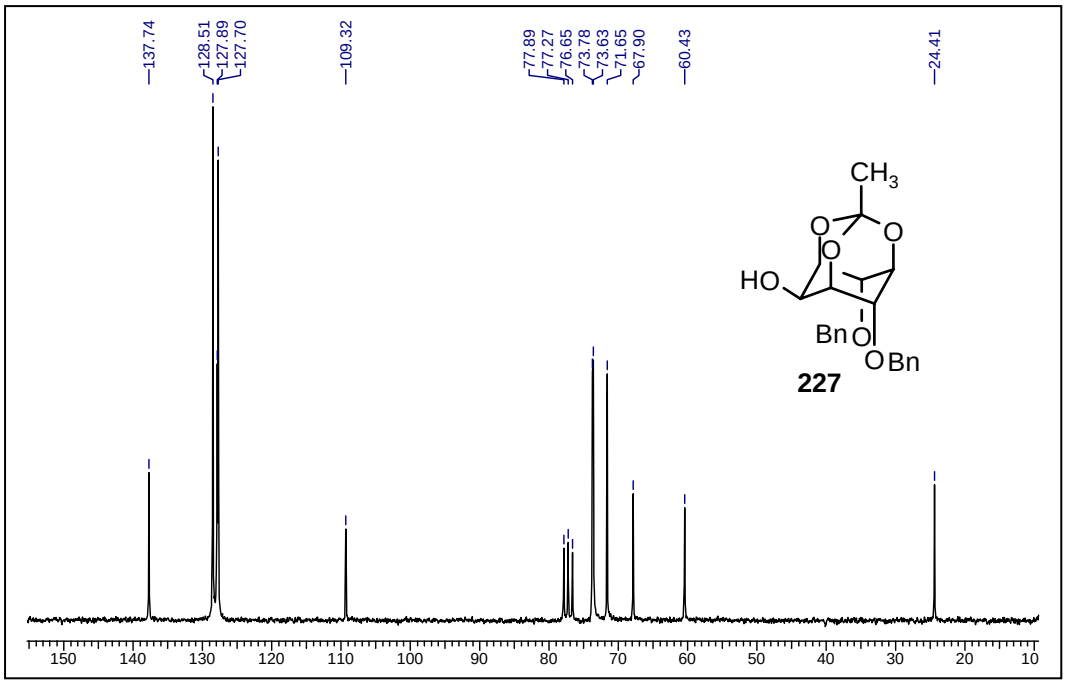
130
120
110
100
90
80
70
60
50


7.28
7.26
4.69
4.63
4.60
4.54
4.39
4.32
4.24
4.18
4.12
3.07
3.01
1.44
0.00
CH3
O
O
O
HO
Bn O
O Bn
227
10.00
4.01
6.13
0.88
3.03
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


OMXDIBN.SP
H
105.1
100
90
80
70
60
50
40
30
20
10
5.1
%T
CH3
O
O
O
HO
Bn O
O Bn
227
4500.0
4000
3500
3000
2500
2000.0
1800
1600
1400
1200
1000
800
600
500.0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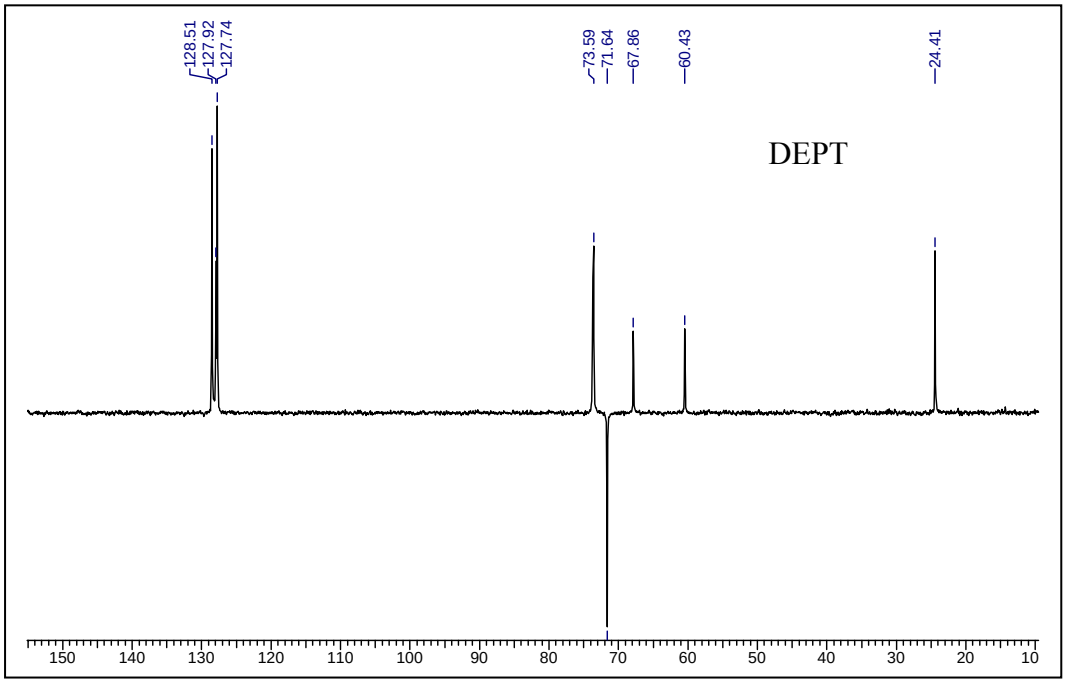
127.89
127.70
109.32
77.89
77.27
76.65
73.78
73.63
71.65
67.90
60.43
24.41
CH3
O
O
O
HO
Bn O
O Bn
227
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10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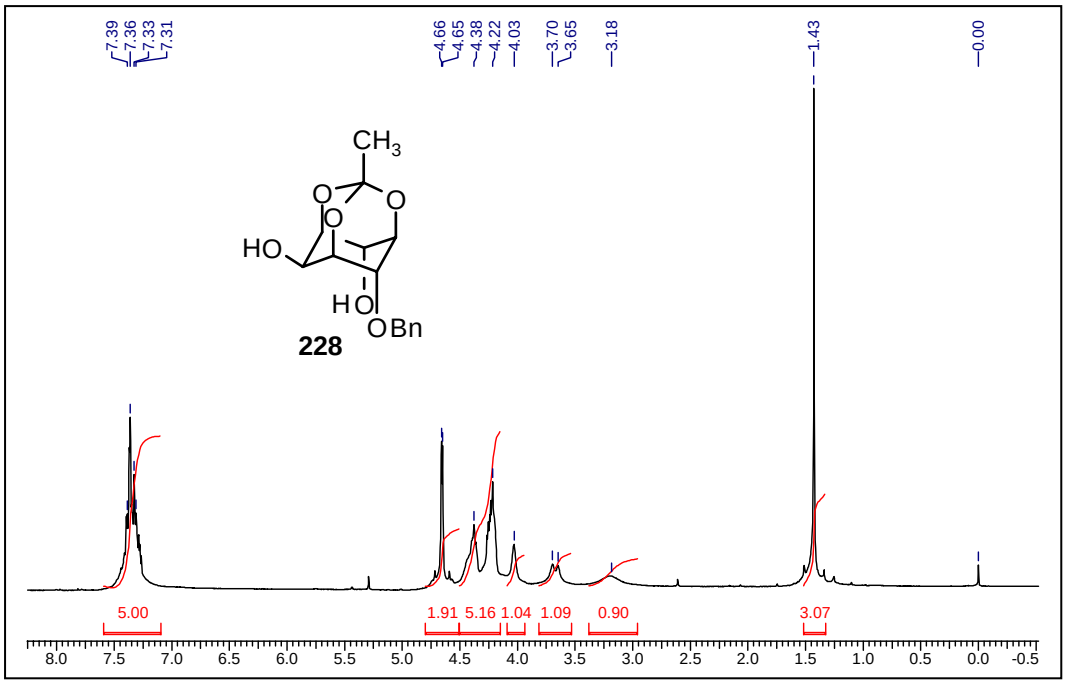
127.74
73.59
71.64
67.86
60.43
24.41
DEPT
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10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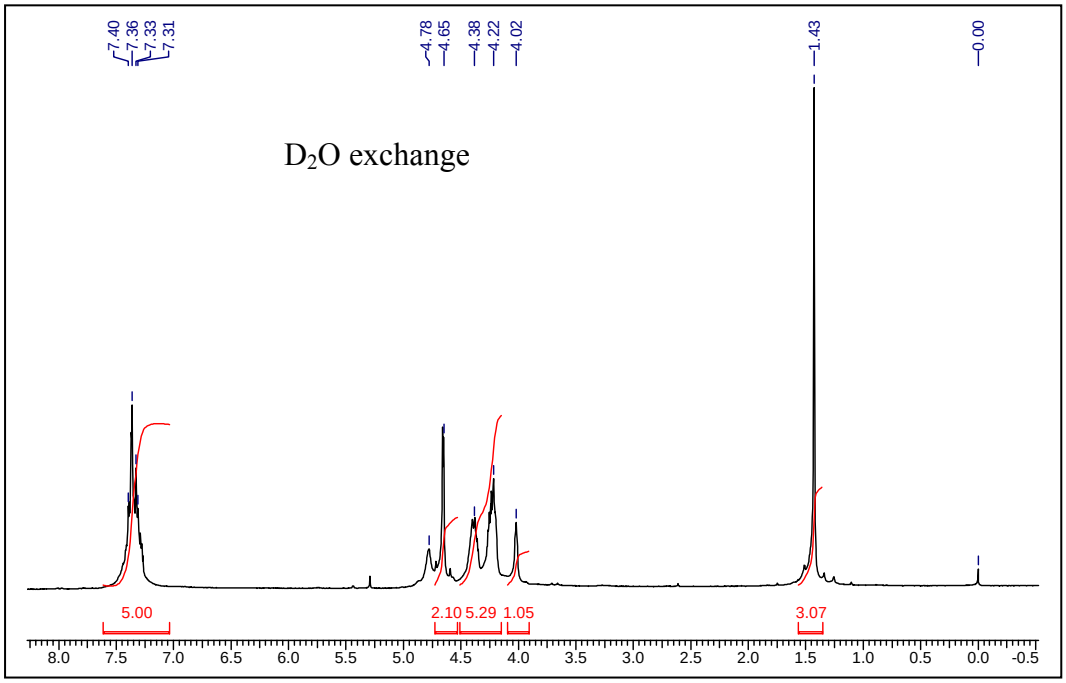
7.36
7.33
7.31
4.66
4.65
4.38
4.22
4.03
3.70
3.65
3.18
1.43
0.00
CH3
O
O
O
HO
HO
OBn
228
5.00
1.91
5.16
1.04
1.09
0.90
3.07
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5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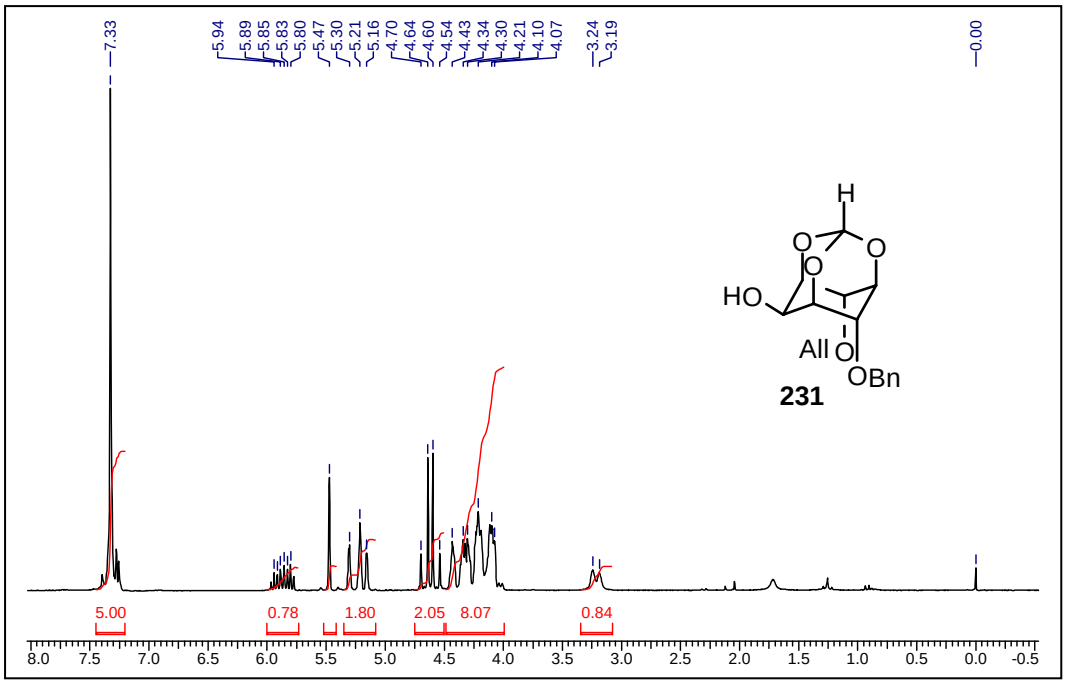
7.36
7.33
7.31
4.78
4.65
4.38
4.22
4.02
1.43
0.00
D2O exchange
5.00
2.10
5.29
1.05
3.07
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5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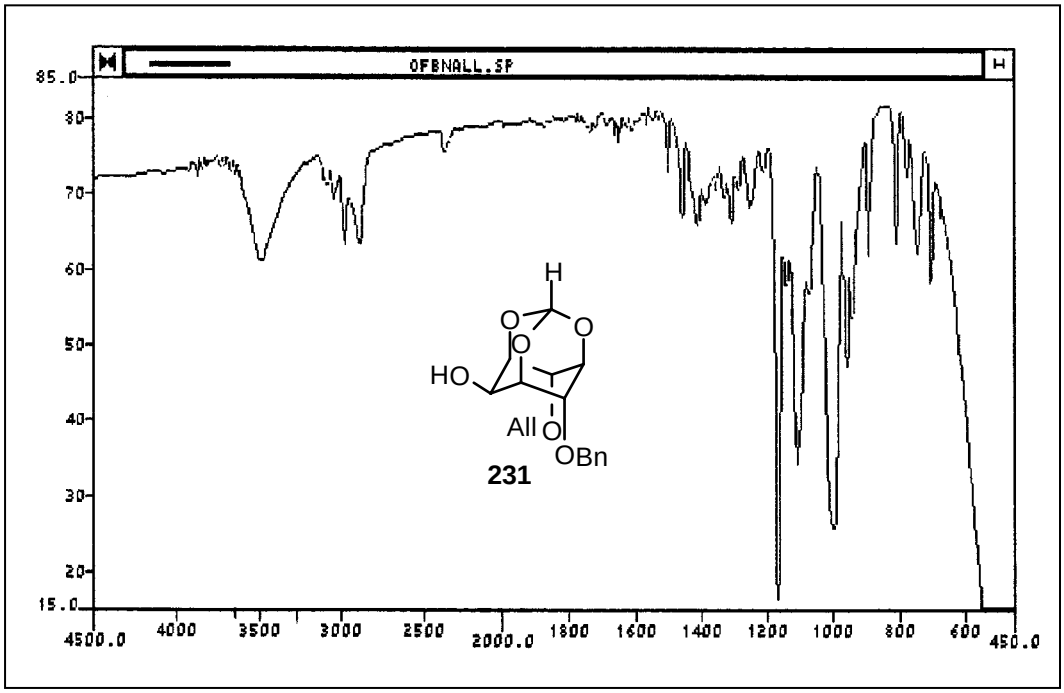
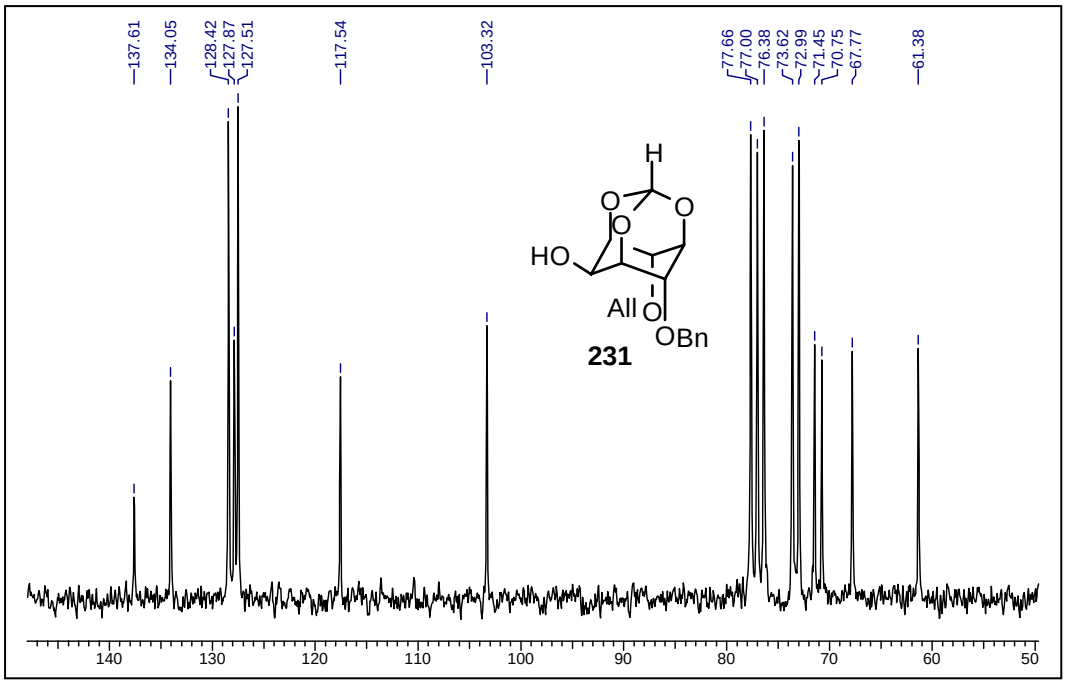
5.89
5.85
5.83
5.80
5.47
5.30
5.21
5.16
4.70
4.64
4.60
4.54
4.43
4.34
4.30
4.21
4.10
4.07
3.24
3.19
0.00
5.00
0.78
1.80
2.05
8.07
0.84
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
H
O
O
O
HO
All O
OBn
231


OFBNALL.SP
H
85.0
80
70
60
50
40
30
20
15.0
4500.0 4000 3500 3000 2500 2000.0 1800 1600 1400 1200 1000 800 600 450.0
H
O
O
O
HO
All O
OBn
231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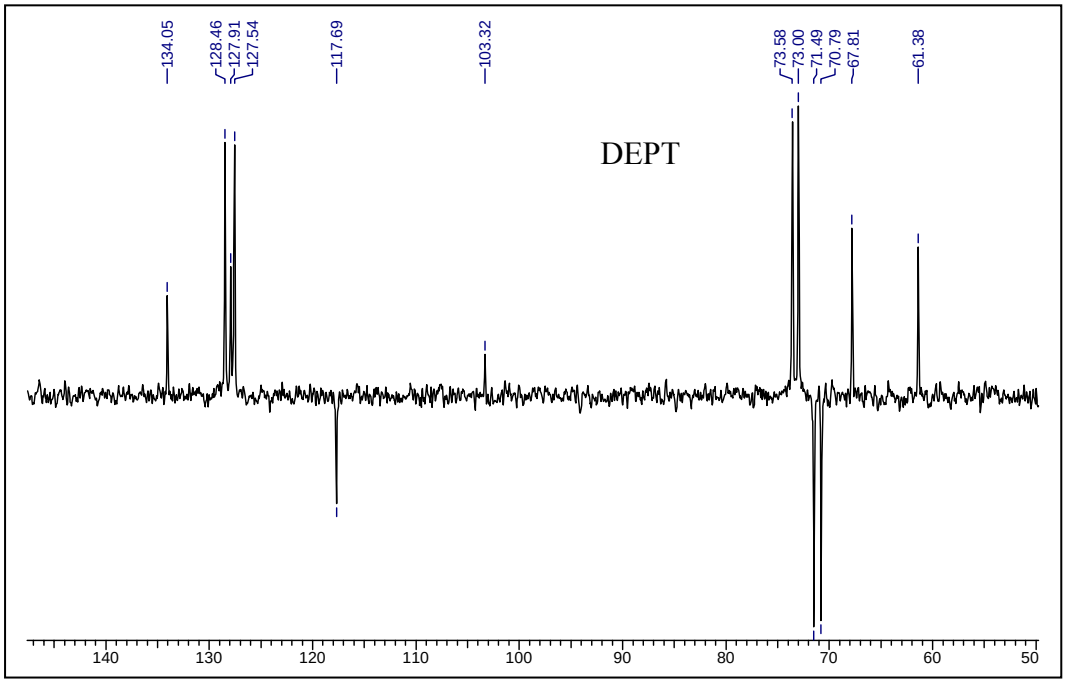
134.05
128.42
127.87
127.51
117.54
103.32
77.66
77.00
76.38
73.62
72.99
71.45
70.75
67.77
61.38
H
O
O
O
HO
All
O
OBn
231
140
130
120
110
100
90
80
70
60
50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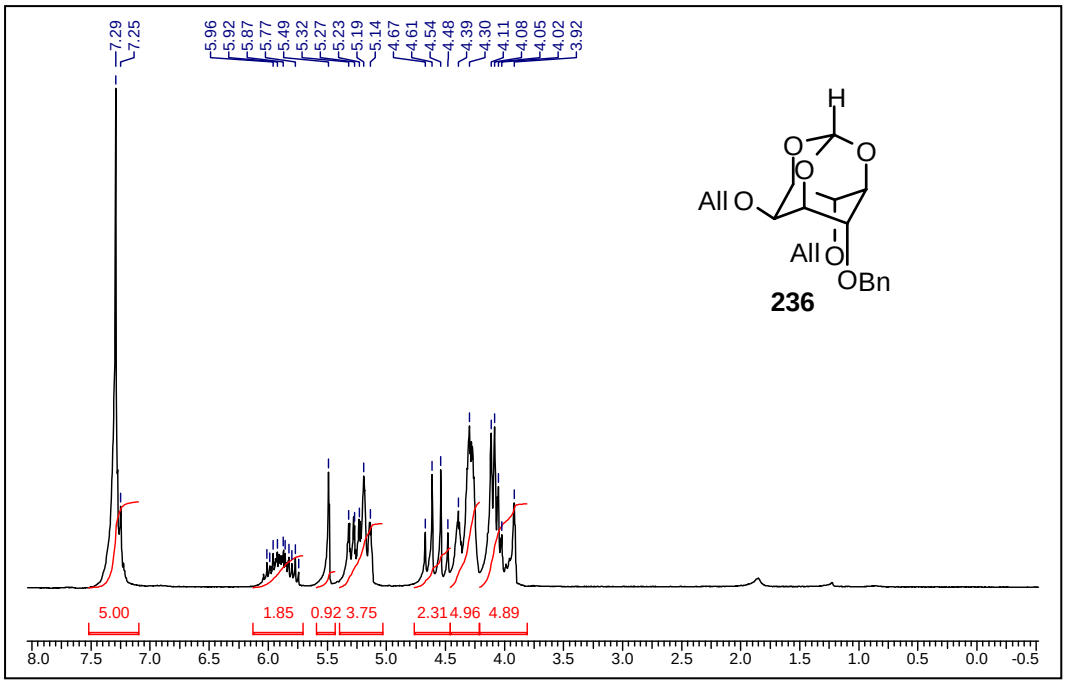
127.91
127.54
117.69
103.32
73.58
73.00
71.49
70.79
67.81
61.38
DEPT
140
130
120
110
100
90
80
70
60
50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7.25
5.96
5.92
5.87
5.77
5.49
5.32
5.27
5.23
5.19
5.14
4.67
4.61
4.54
4.48
4.39
4.30
4.11
4.08
4.05
4.02
3.92
H
O
O
O
All O
All O
OBn
236
5.00
1.85
0.92
3.75
2.31
4.96
4.89
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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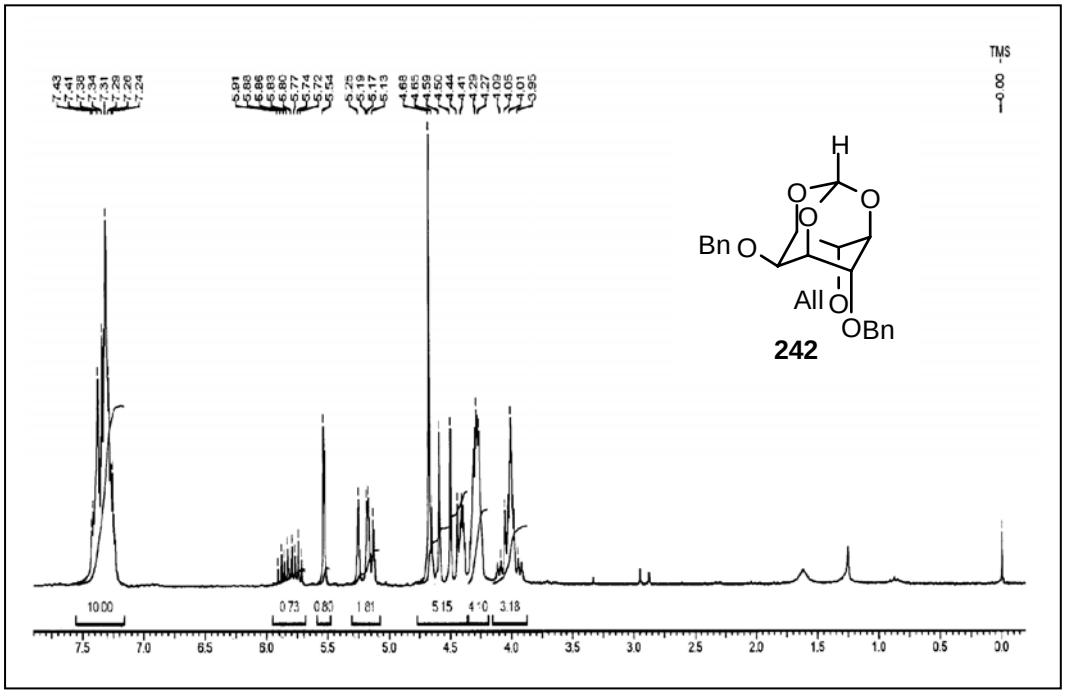
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


TMS
H
O
O
O
Bn O
All O
OBn
242
10.00
0.73
0.80
1.81
5.15
4.10
3.18
7.5
7.0
6.5
6.0
5.5
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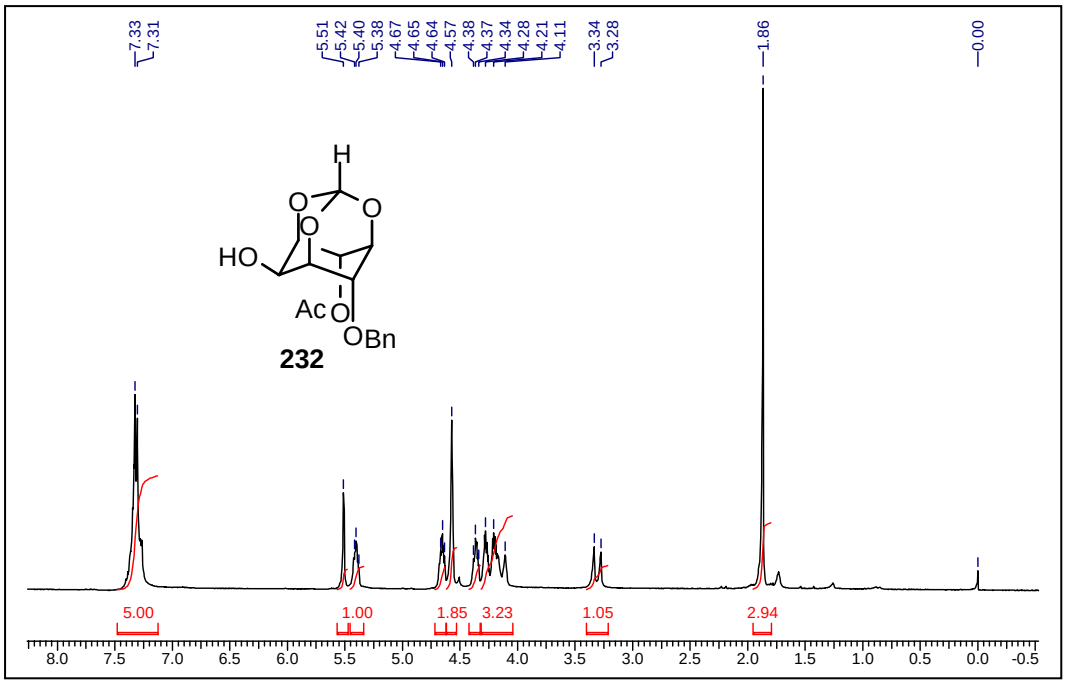
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0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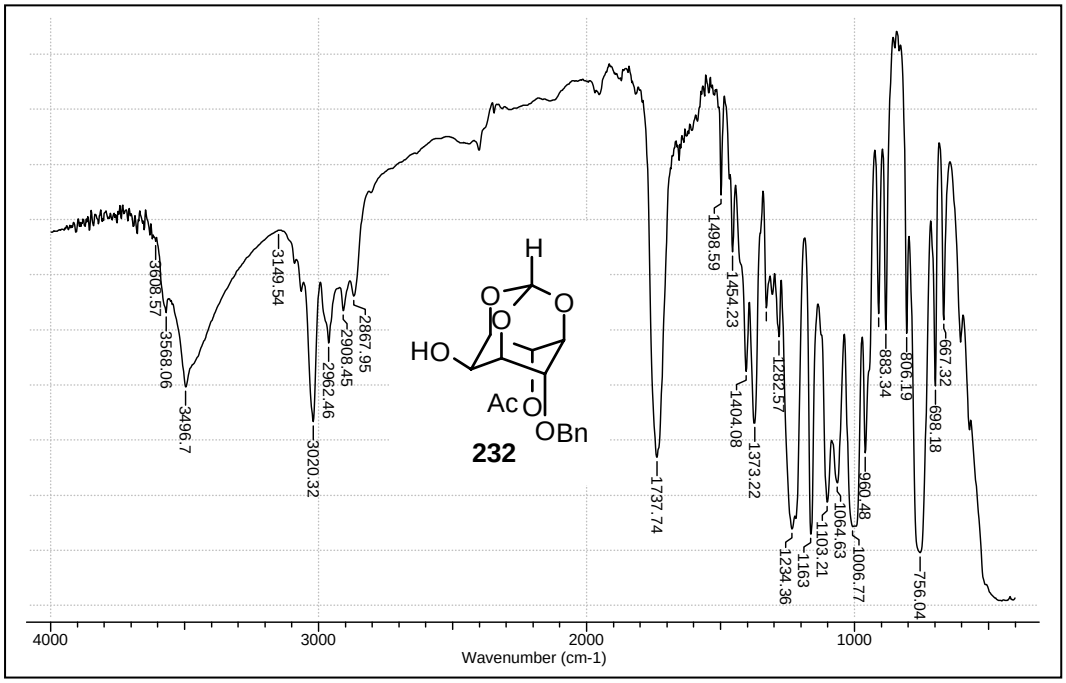
7.31
5.51
5.42
5.40
5.38
4.67
4.65
4.64
4.57
4.38
4.37
4.34
4.28
4.21
4.11
3.34
3.28
1.86
0.00
H
O
O
O
HO
Ac
O
OBn
232
5.00
1.00
1.85
3.23
1.05
2.94
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5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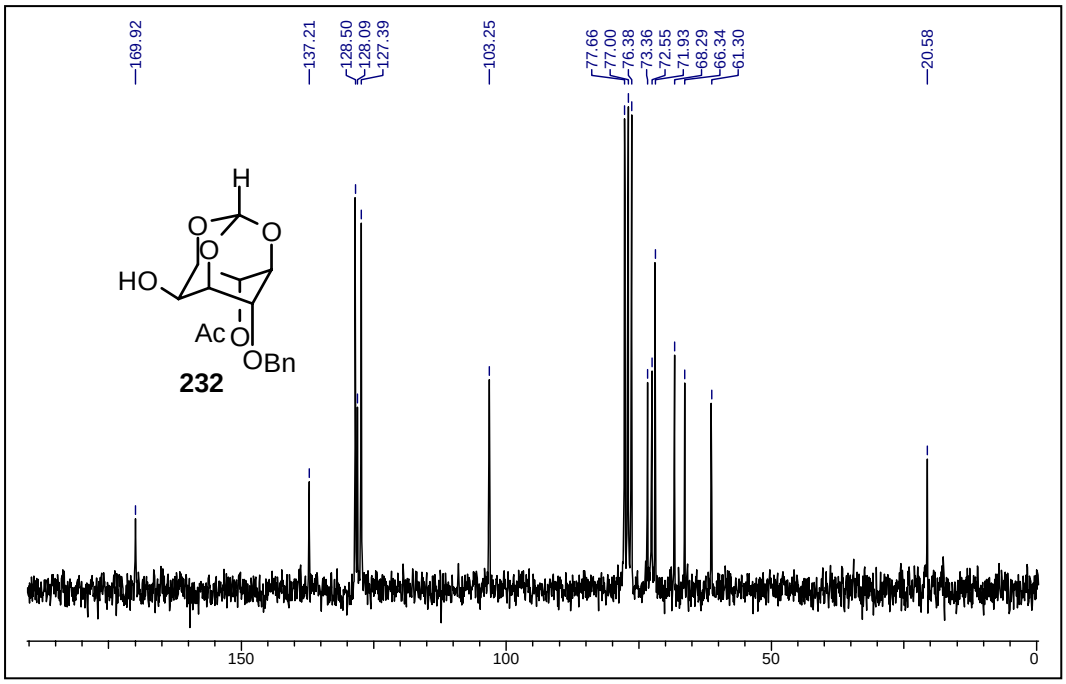
3496.7
3149.54
3020.32
2962.46
2908.45
2867.95
1737.74
1498.59
1454.23
1404.08
1373.22
1282.57
1234.36
1163
1103.21
1064.63
1006.77
960.48
883.34
806.19
756.04
698.18
667.32
H
O
O
O
HO
Ac
O
OBn
232
4000
3000
2000
1000
Wavenumber (cm-1)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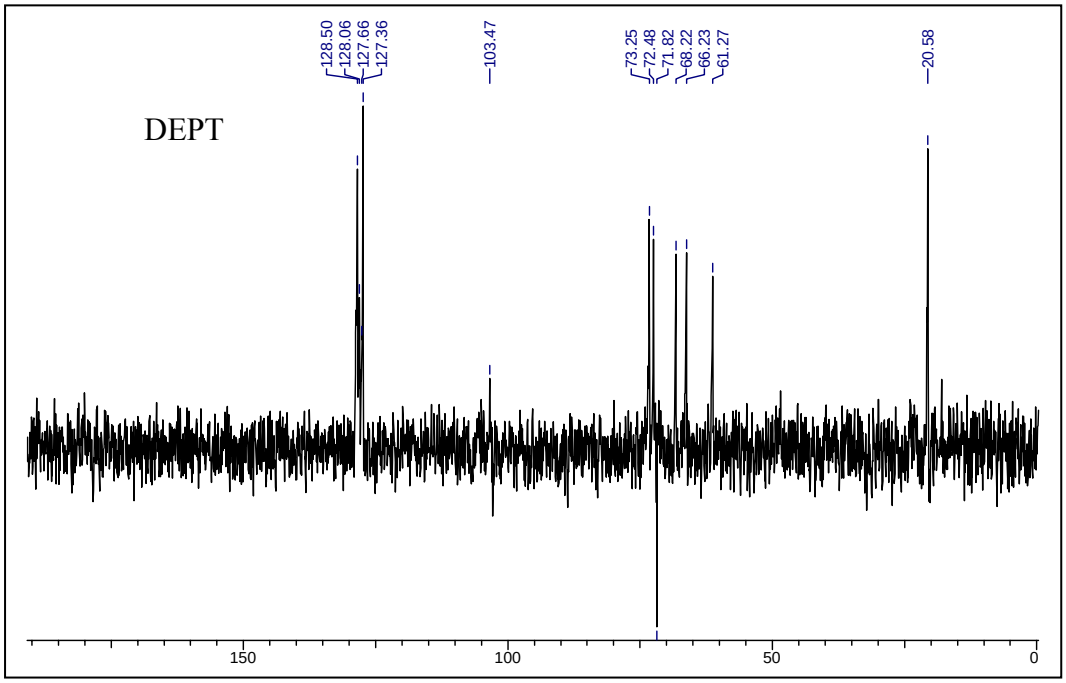
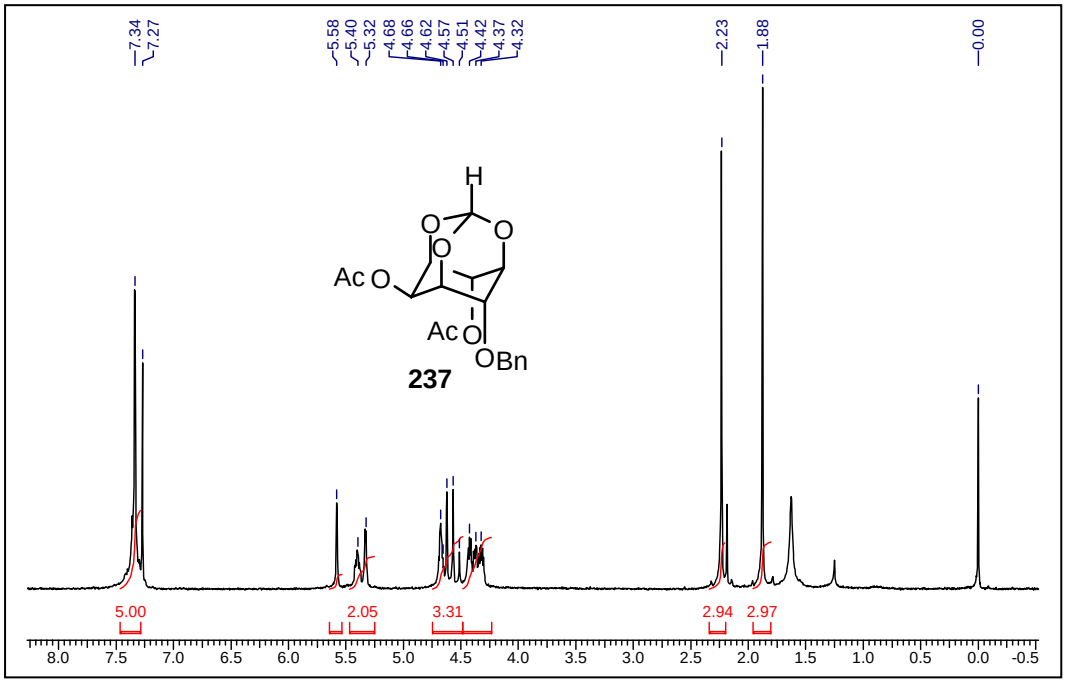
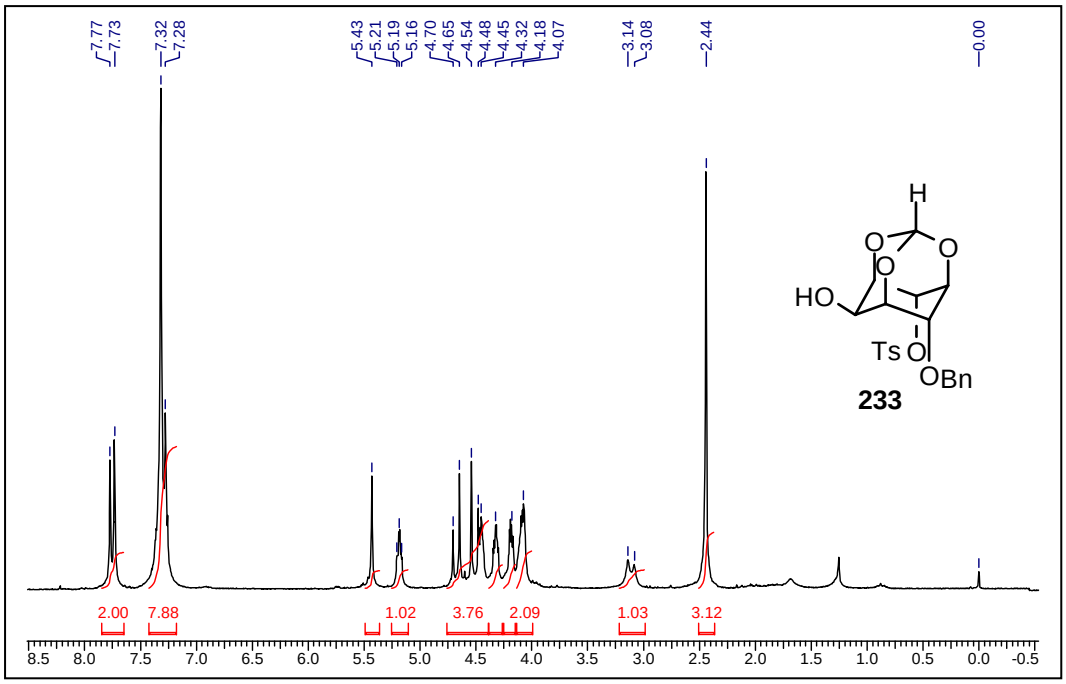
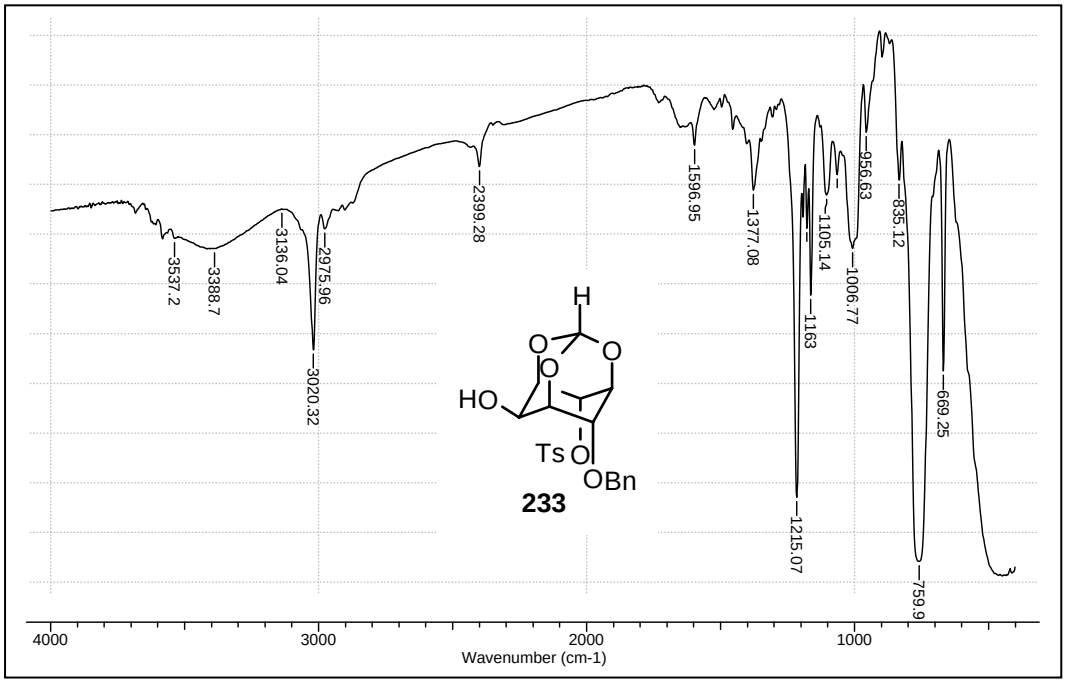
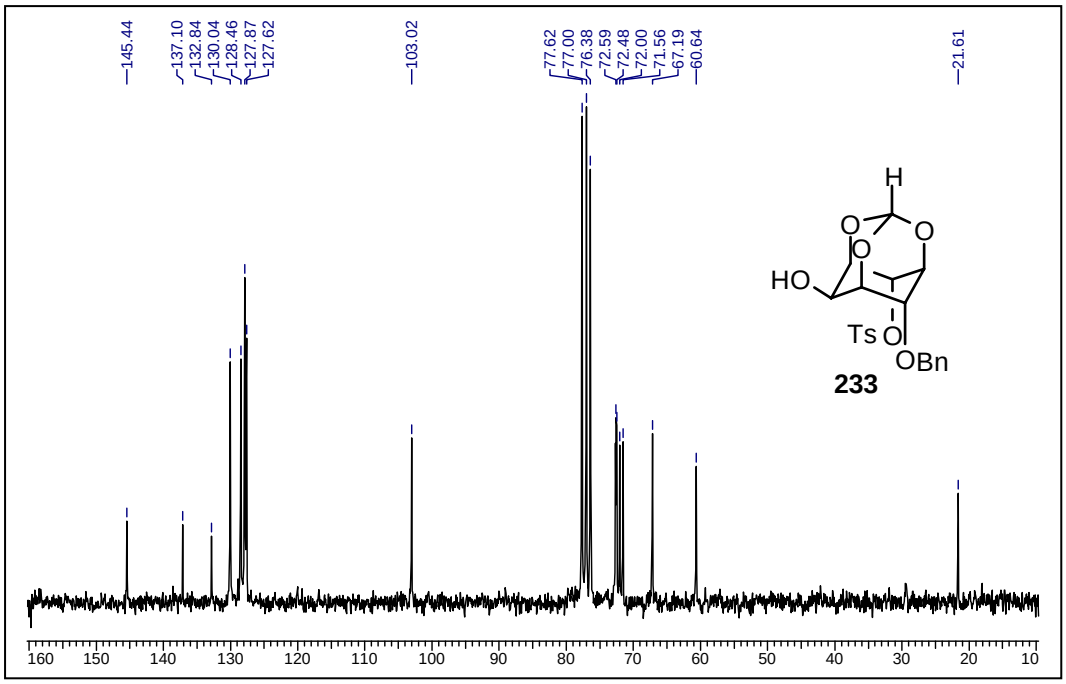
128.09
127.39
103.25
77.66
77.00
76.38
73.36
72.55
71.93
68.29
66.34
61.30
20.58
H
O
O
O
HO
Ac
O
OBn
232
150
100
50
0


DEPT
128.50
128.06
127.66
127.36
103.47
73.25
72.48
71.82
68.22
66.23
61.27
20.58
150
100
50
0


7.34
7.27
5.58
5.40
5.32
4.68
4.66
4.62
4.57
4.51
4.42
4.37
4.32
2.23
1.88
0.00
H
O
O
O
Ac O
Ac O
OBn
237
5.00
2.05
3.31
2.94
2.97
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


7.77
7.73
7.32
7.28
5.43
5.21
5.19
5.16
4.70
4.65
4.54
4.48
4.45
4.32
4.18
4.07
3.14
3.08
2.44
0.00
2.00
7.88
1.02
3.76
2.09
1.03
3.12
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
H
O
O
O
HO
Ts O
OBn
233


3537.2
3388.7
3136.04
2975.96
3020.32
2399.28
1596.95
1377.08
1215.07
1163
1105.14
1006.77
956.63
835.12
759.9
669.25
4000
3000
2000
1000
Wavenumber (cm-1)
H
O
O
O
HO
Ts O
OBn
233


145.44
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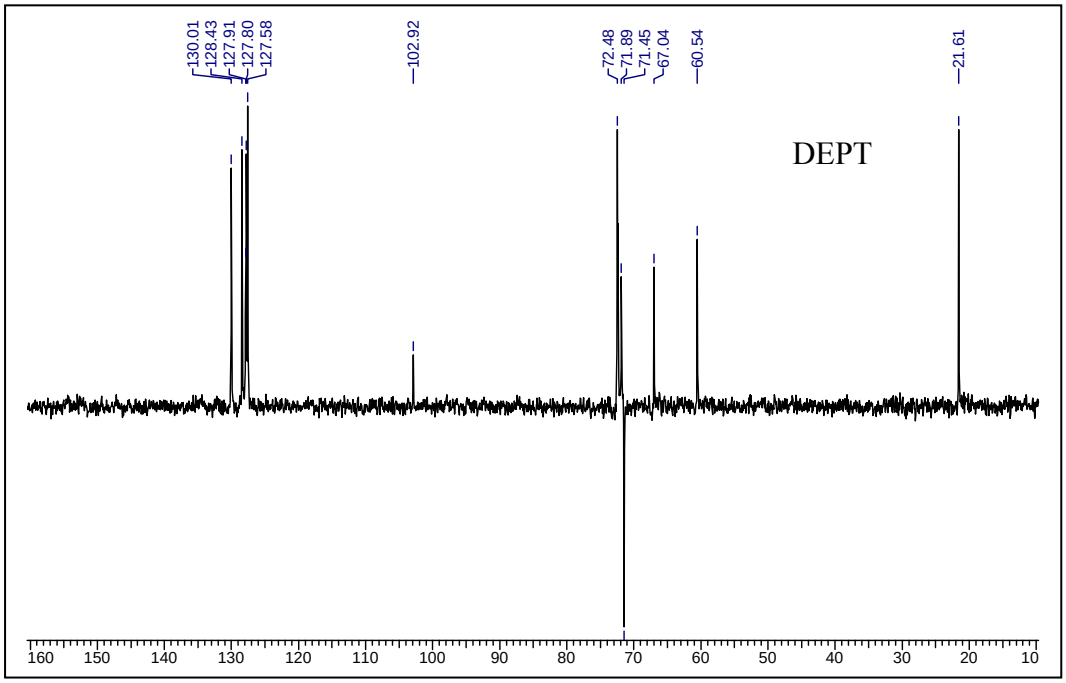
130.04
128.46
127.87
127.62
103.02
77.62
77.00
76.38
72.59
72.48
72.00
71.56
67.19
60.64
21.61
H
O
O
O
HO
Ts O
OBn
233
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10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71.89
71.45
67.04
60.54
21.61
DEPT
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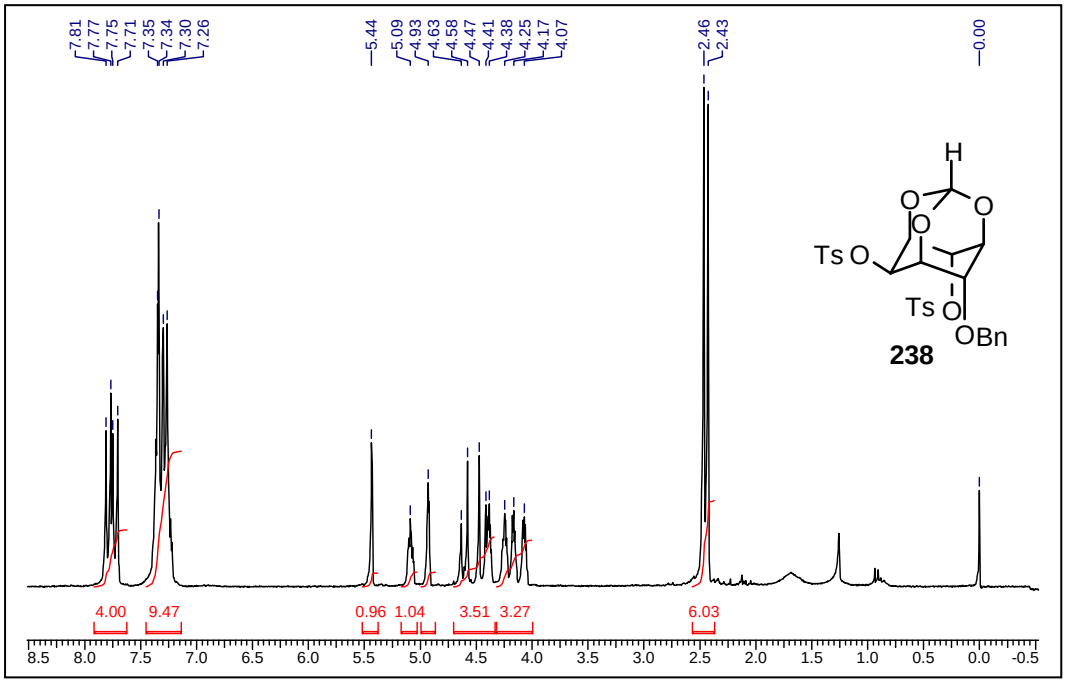
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7.77
7.75
7.71
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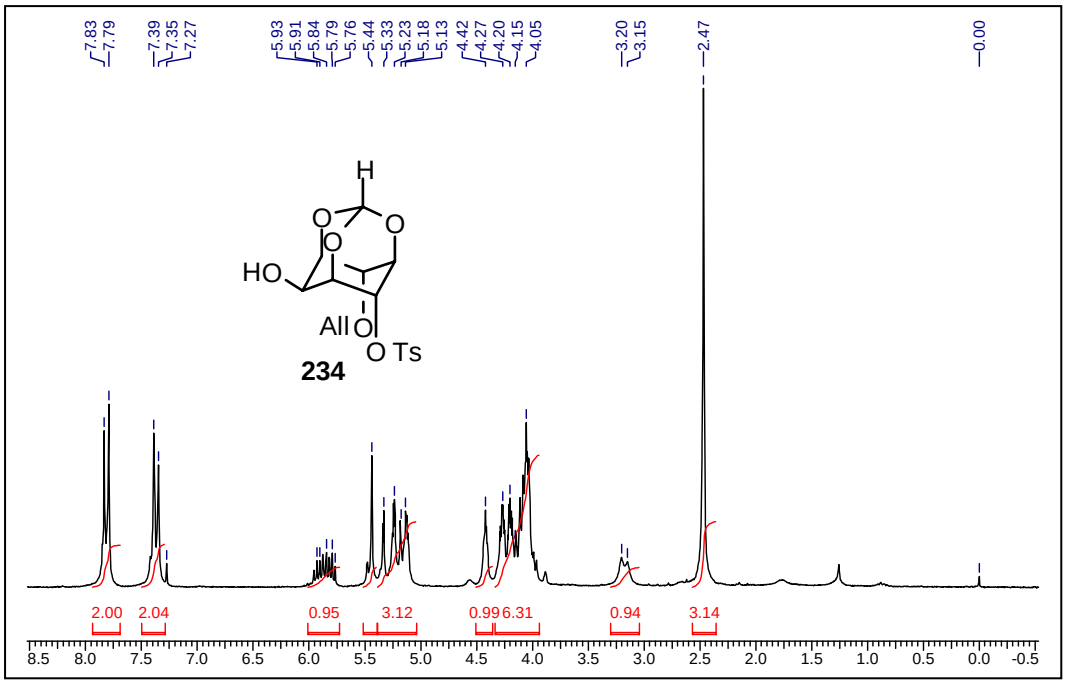
7.34
7.30
7.26
5.44
5.09
4.93
4.63
4.58
4.47
4.41
4.38
4.25
4.17
4.07
2.46
2.43
0.00
4.00
9.47
0.96
1.04
3.51
3.27
6.03
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
H
O
O
O
Ts O
Ts O
OBn
238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7.39
7.35
7.27
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5.91
5.84
5.79
5.76
5.44
5.33
5.23
5.18
5.13
4.42
4.27
4.20
4.15
4.05
3.20
3.15
2.47
0.00
H
O
O
O
HO
All O
O Ts
234
2.00
2.04
0.95
3.12
0.99
6.31
0.94
3.14
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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2.0
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0.0
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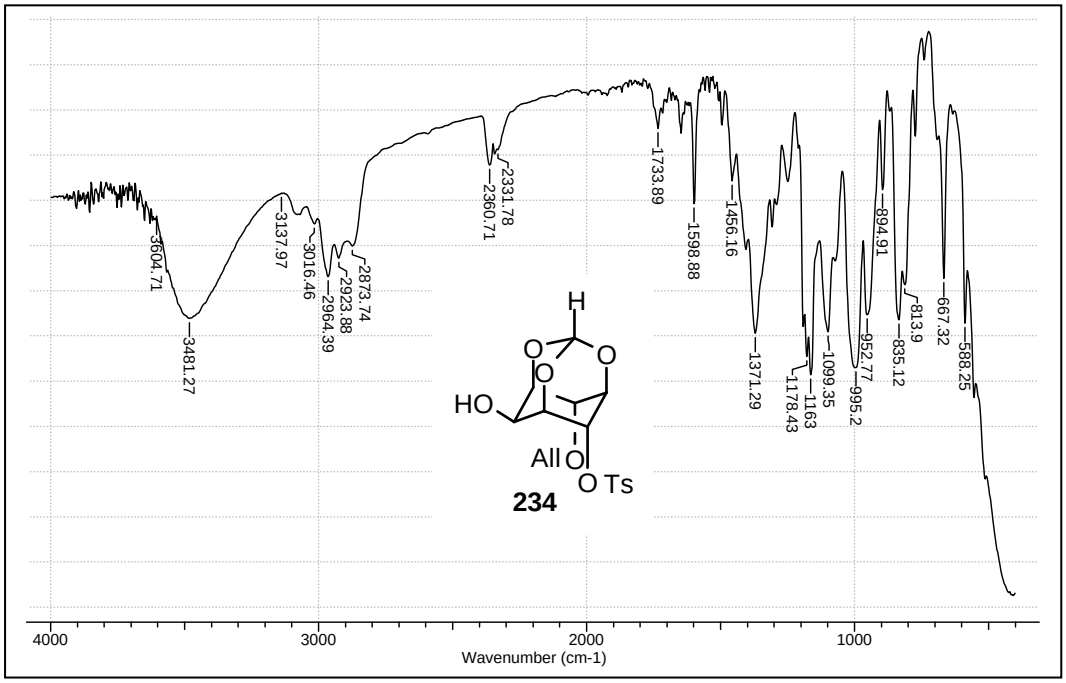
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2873.74
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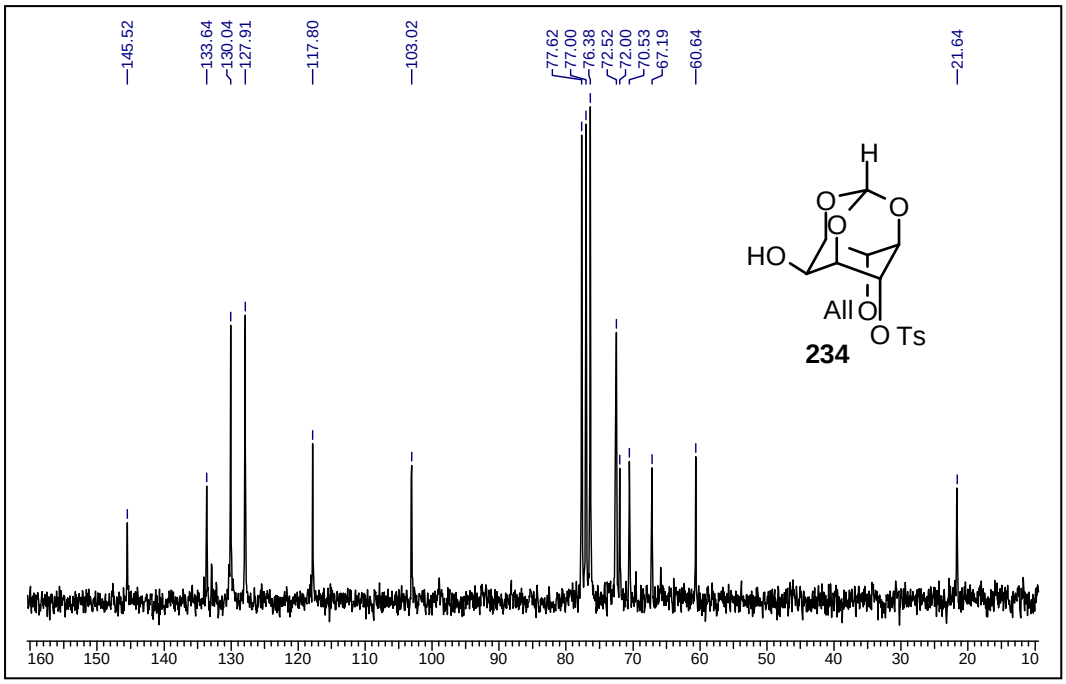
1456.16
1371.29
1178.43
1163
1099.35
995.2
952.77
894.91
835.12
813.9
667.32
588.25
H
O
O
O
HO
All O
O Ts
234
4000
3000
2000
1000
Wavenumber (cm-1)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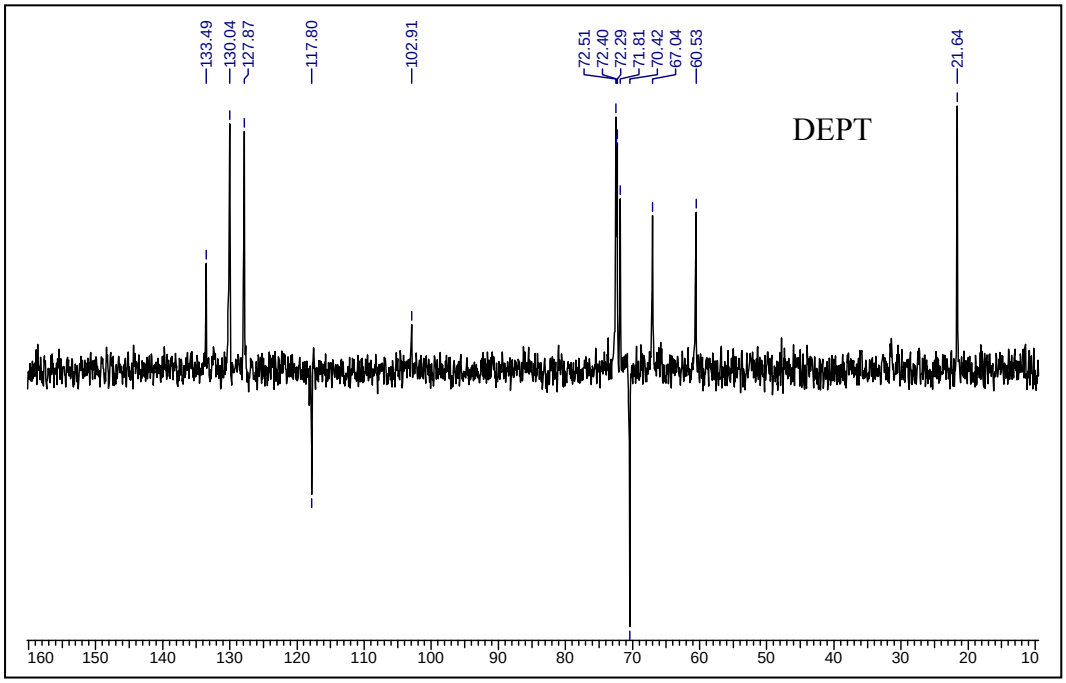
103.02
77.62
77.00
76.38
72.52
72.00
70.53
67.19
60.64
21.64
H
O
O
O
HO
All O
O Ts
234
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10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72.29
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67.04
60.53
21.64
DEPT
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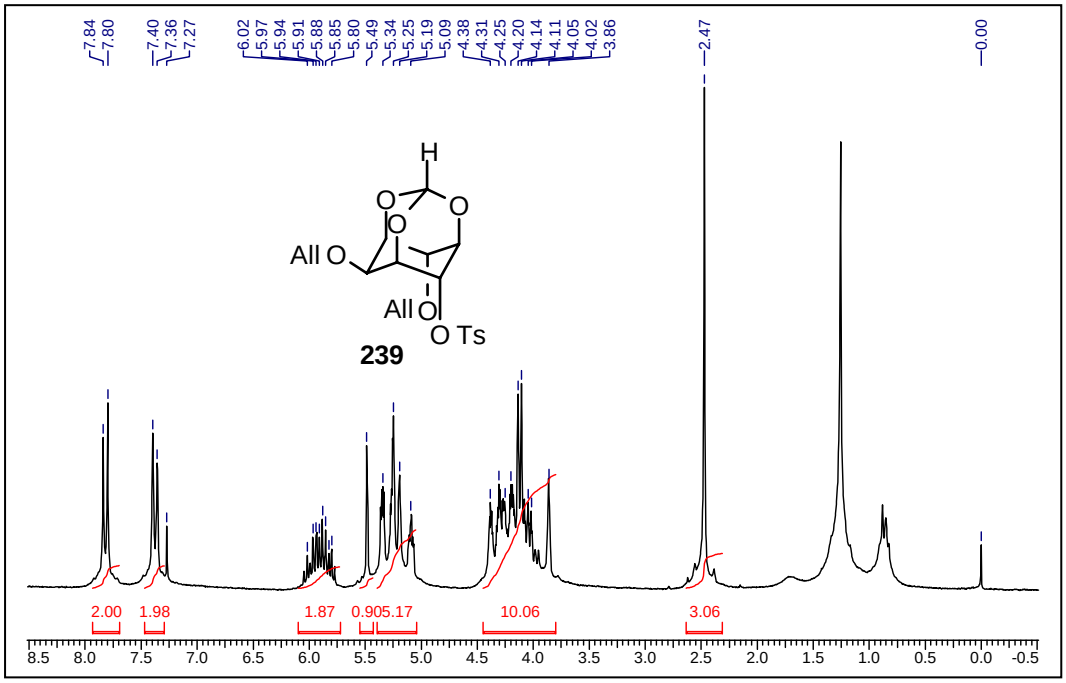
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7.40
7.36
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6.02
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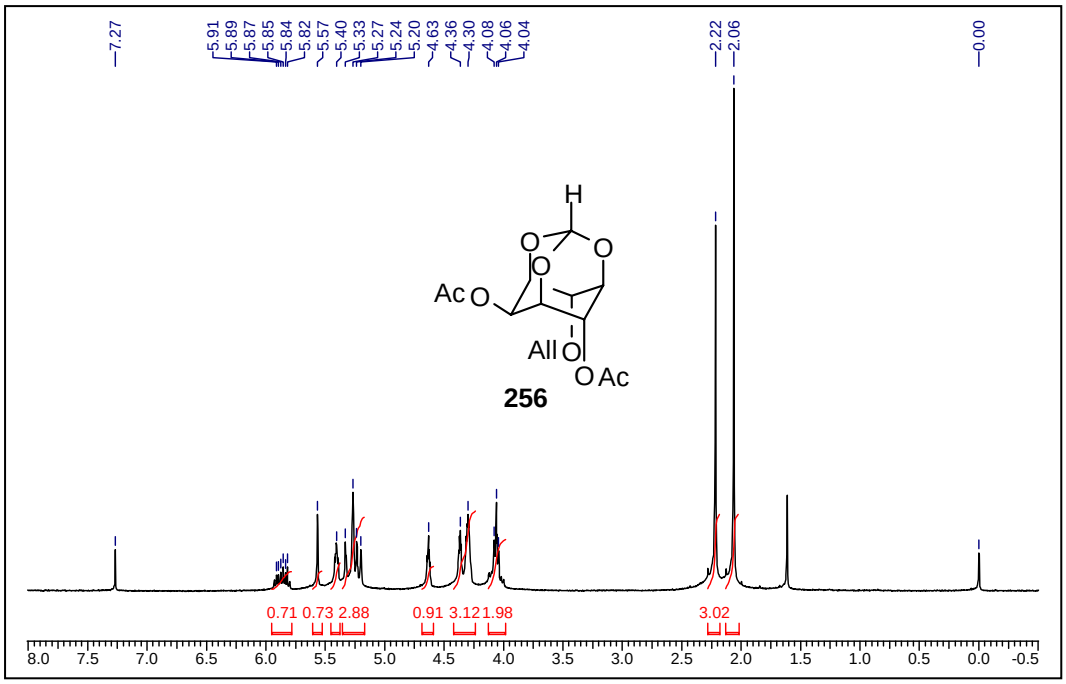
5.94
5.91
5.88
5.85
5.80
5.49
5.34
5.25
5.19
5.09
4.38
4.31
4.25
4.20
4.14
4.11
4.05
4.02
3.86
2.47
0.00
H
O
O
O
All O
All O
O Ts
239
2.00
1.98
1.87
0.90
5.17
10.06
3.06
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5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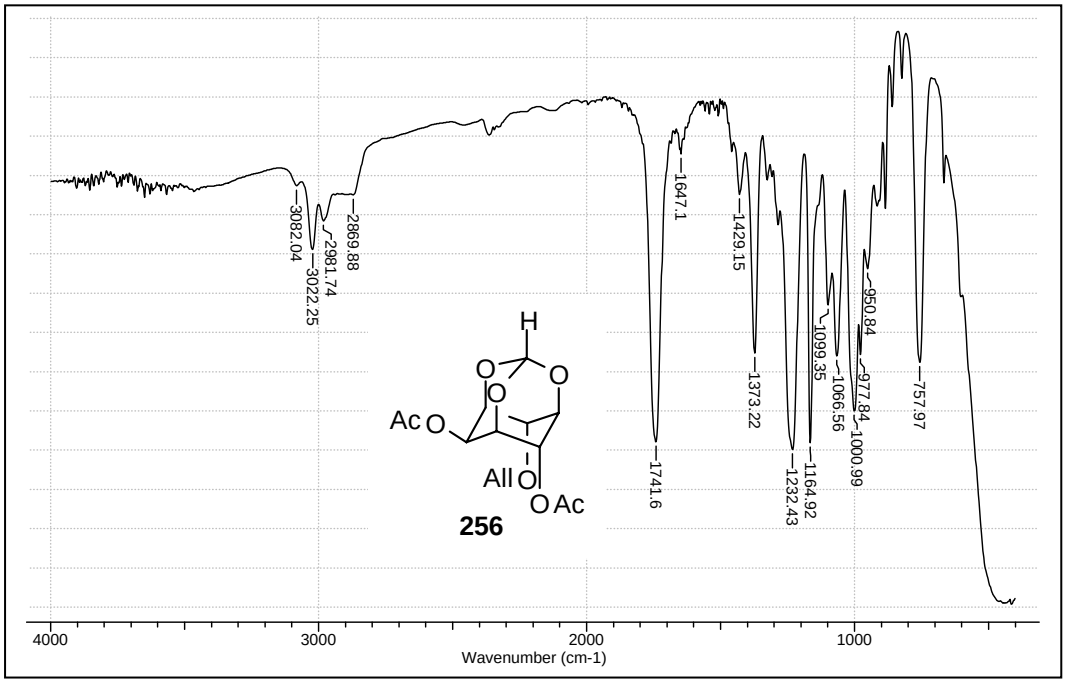
5.89
5.87
5.85
5.84
5.82
5.57
5.40
5.33
5.27
5.24
5.20
4.63
4.36
4.30
4.08
4.06
4.04
2.22
2.06
0.00
H
O
O
O
Ac O
All O
O Ac
256
0.71 0.73 2.88
0.91 3.12 1.98
3.02
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5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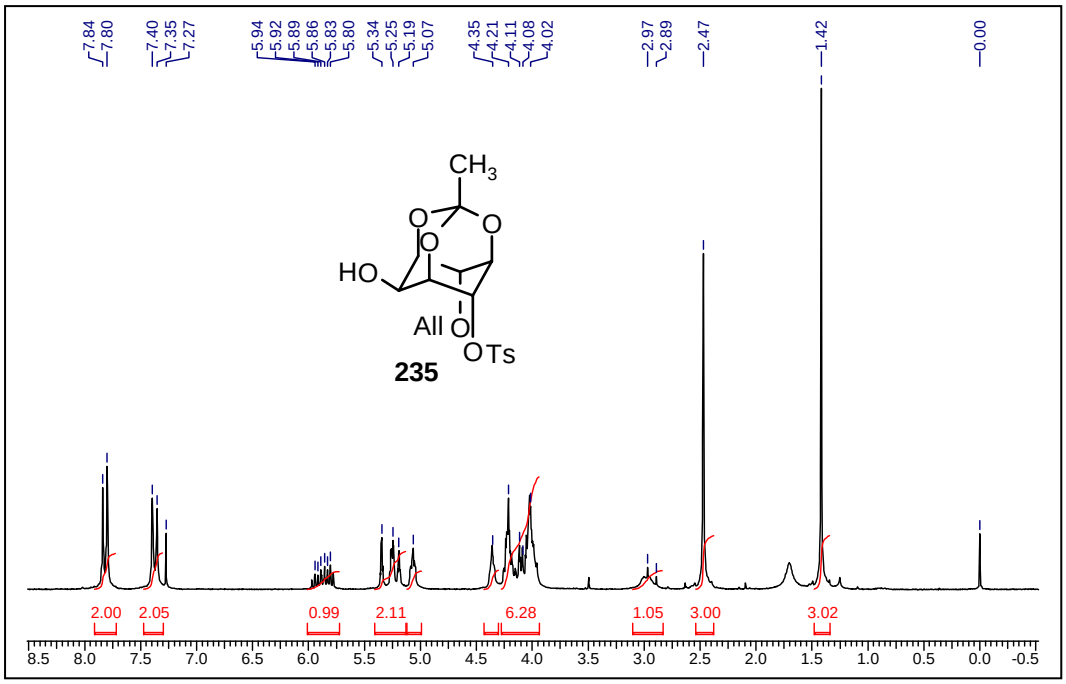
3022.25
2981.74
2869.88
1647.1
1429.15
1373.22
1741.6
1232.43
1164.92
1099.35
1066.56
1000.99
977.84
950.84
757.97
H
O
O
O
Ac O
All O
O Ac
256
4000
3000
2000
1000
Wavenumber (cm-1)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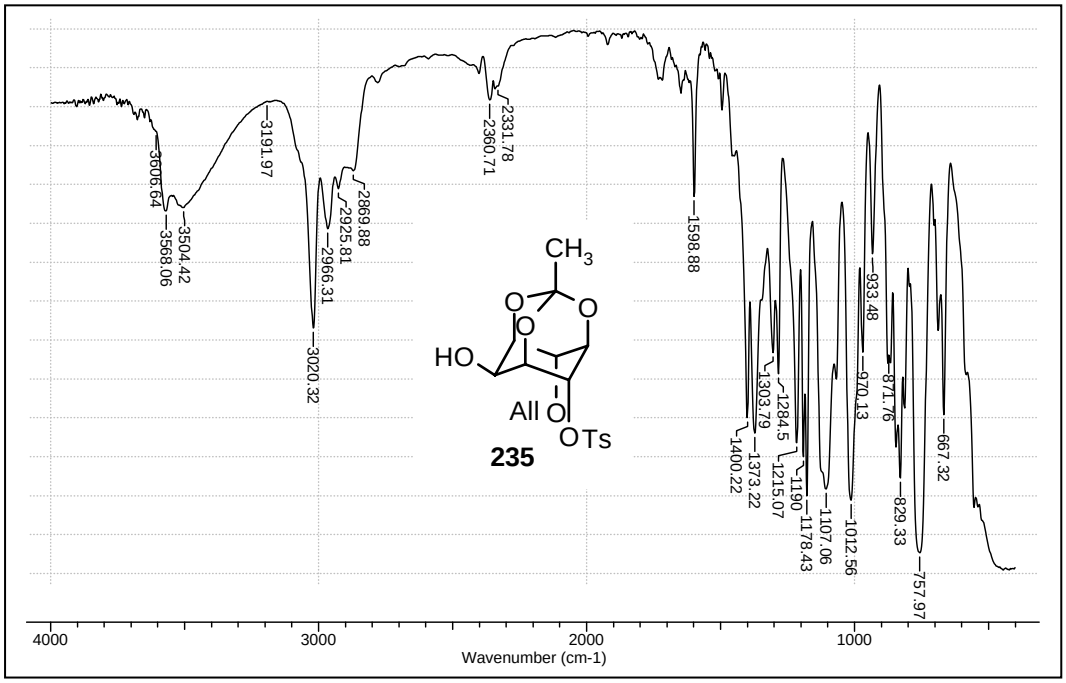
7.80
7.40
7.35
7.27
5.94
5.92
5.89
5.86
5.83
5.80
5.34
5.25
5.19
5.07
4.35
4.21
4.11
4.08
4.02
2.97
2.89
2.47
1.42
0.00
CH3
O
O
O
HO
All O
OTs
235
2.00
2.05
0.99
2.11
6.28
1.05
3.00
3.02
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5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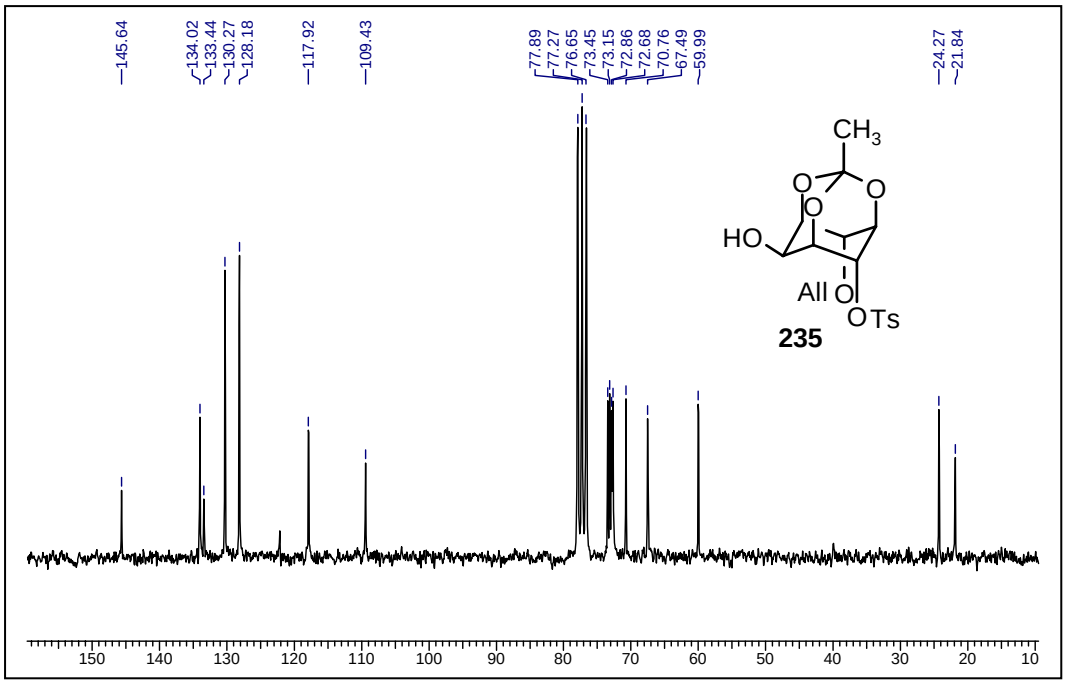
3504.42
3191.97
3020.32
2966.31
2925.81
2869.88
2360.71
2331.78
1598.88
1400.22
1373.22
1303.79
1284.5
1215.07
1190
1178.43
1107.06
1012.56
970.13
933.48
871.76
829.33
757.97
667.32
CH3
O
O
O
HO
All O
OTs
235
4000
3000
2000
1000
Wavenumber (cm-1)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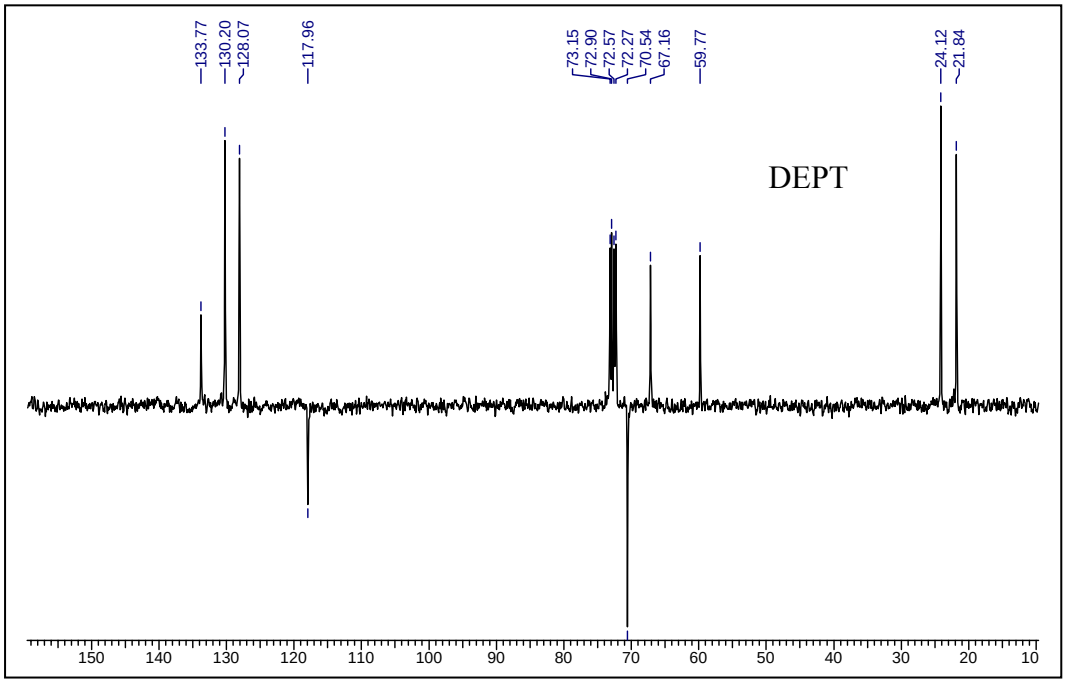
134.02
133.44
130.27
128.18
117.92
109.43
77.89
77.27
76.65
73.45
73.15
72.86
72.68
70.76
67.49
59.99
24.27
21.84
CH3
O
O
O
HO
All O
OTs
235
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10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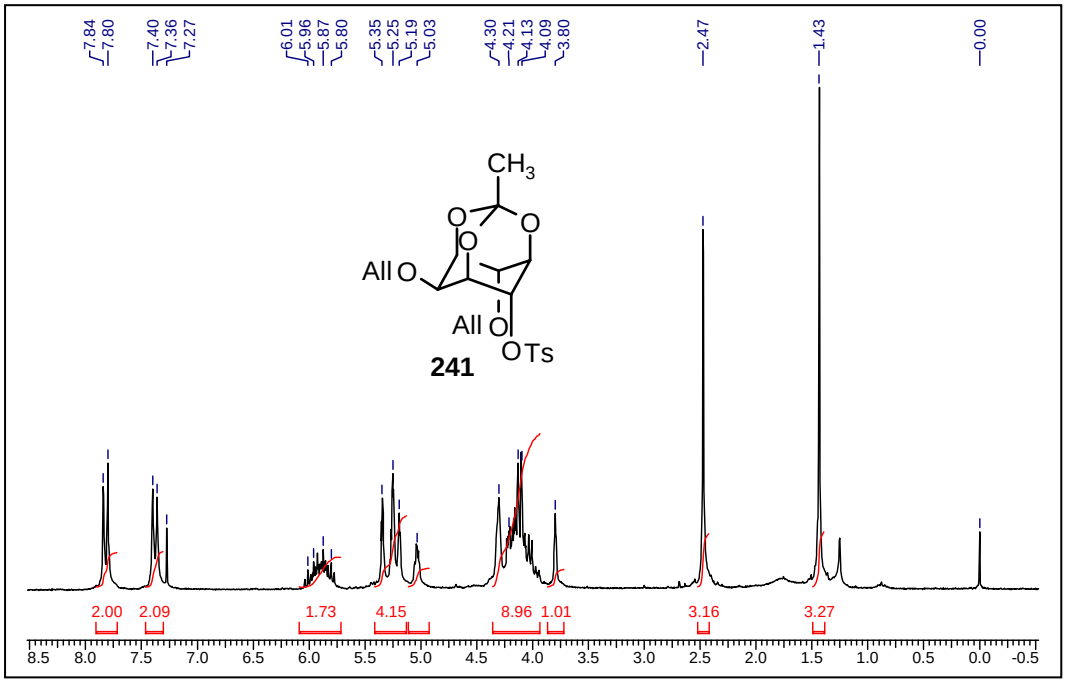
130.20
128.07
117.96
73.15
72.90
72.57
72.27
70.54
67.16
59.77
24.12
21.84
DEPT
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10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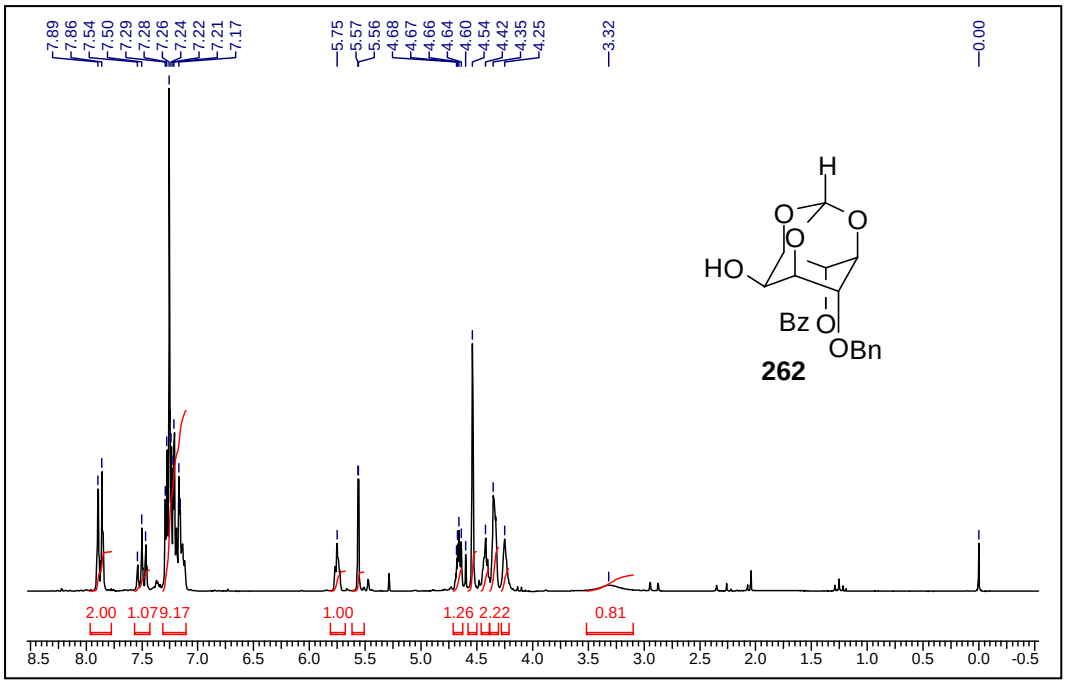
7.80
7.40
7.36
7.27
6.01
5.96
5.87
5.80
5.35
5.25
5.19
5.03
4.30
4.21
4.13
4.09
3.80
2.47
1.43
0.00
CH3
O
O
O
All O
All O
OTs
241
2.00
2.09
1.73
4.15
8.96
1.01
3.16
3.27
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5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7.86
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7.50
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7.28
7.26
7.24
7.22
7.21
7.17
5.75
5.57
5.56
4.68
4.67
4.66
4.64
4.60
4.54
4.42
4.35
4.25
3.32
0.00
H
O
O
O
HO
Bz O
OBn
262
2.00
1.07
9.17
1.00
1.26
2.22
0.81
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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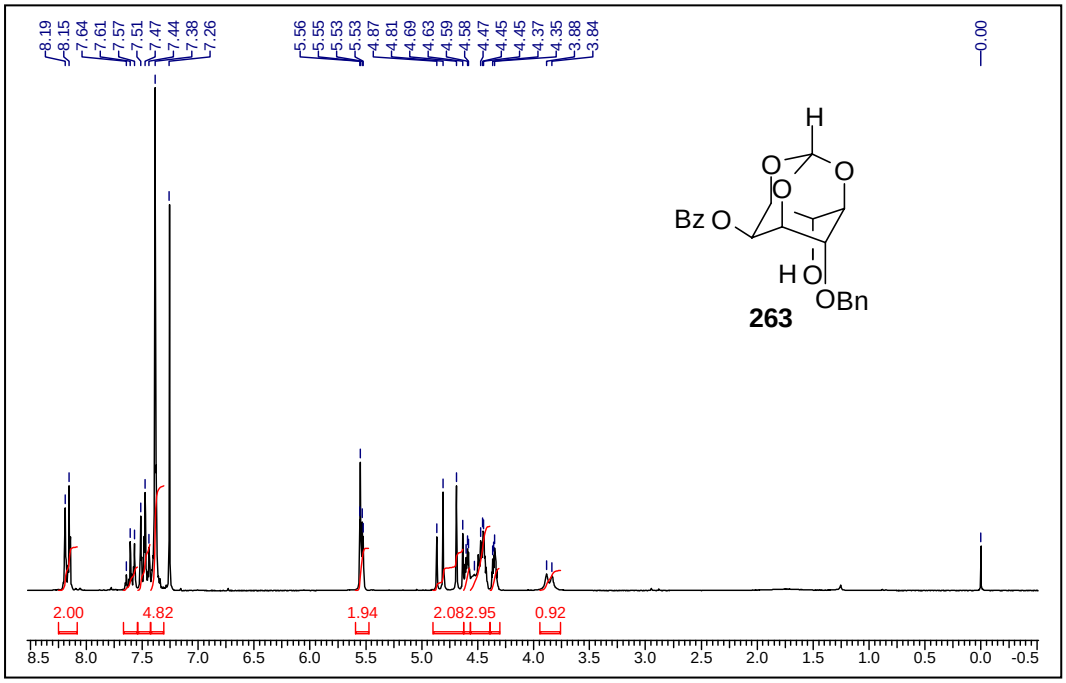
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5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8.15
7.64
7.61
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7.51
7.47
7.44
7.38
7.26
5.56
5.55
5.53
5.53
4.87
4.81
4.69
4.63
4.59
4.58
4.47
4.45
4.45
4.37
4.35
3.88
3.84
0.00
H
O
O
O
Bz O
H O
OBn
263
2.00
4.82
1.94
2.08
2.95
0.92
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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4.0
3.5
3.0
2.5
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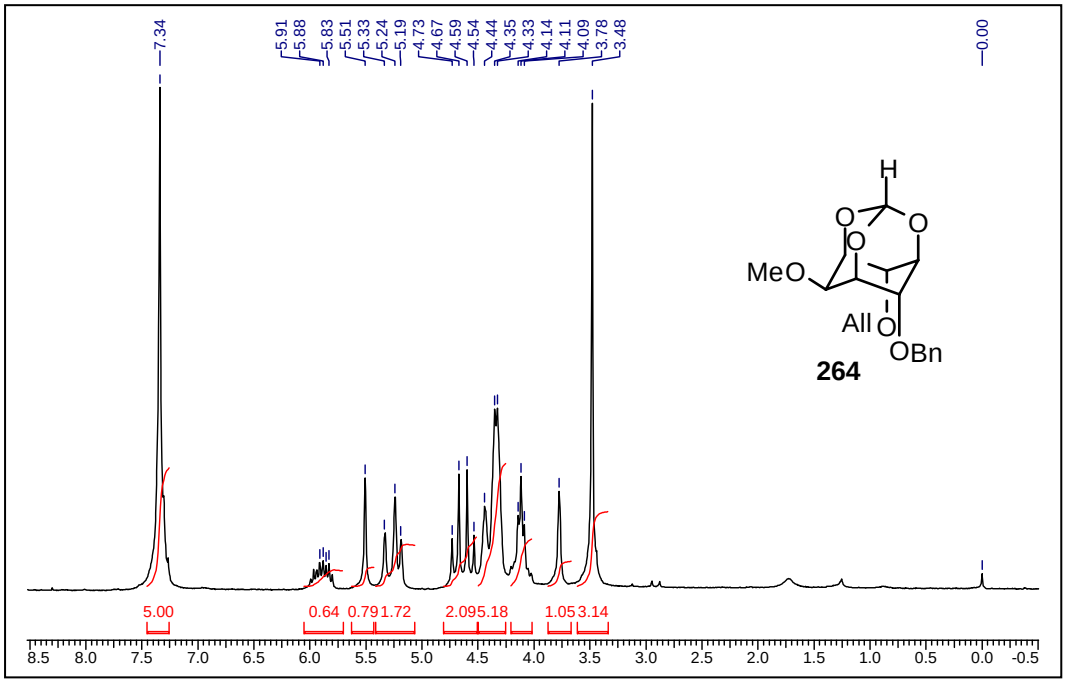
1.5
1.0
0.5
0.0
-0.5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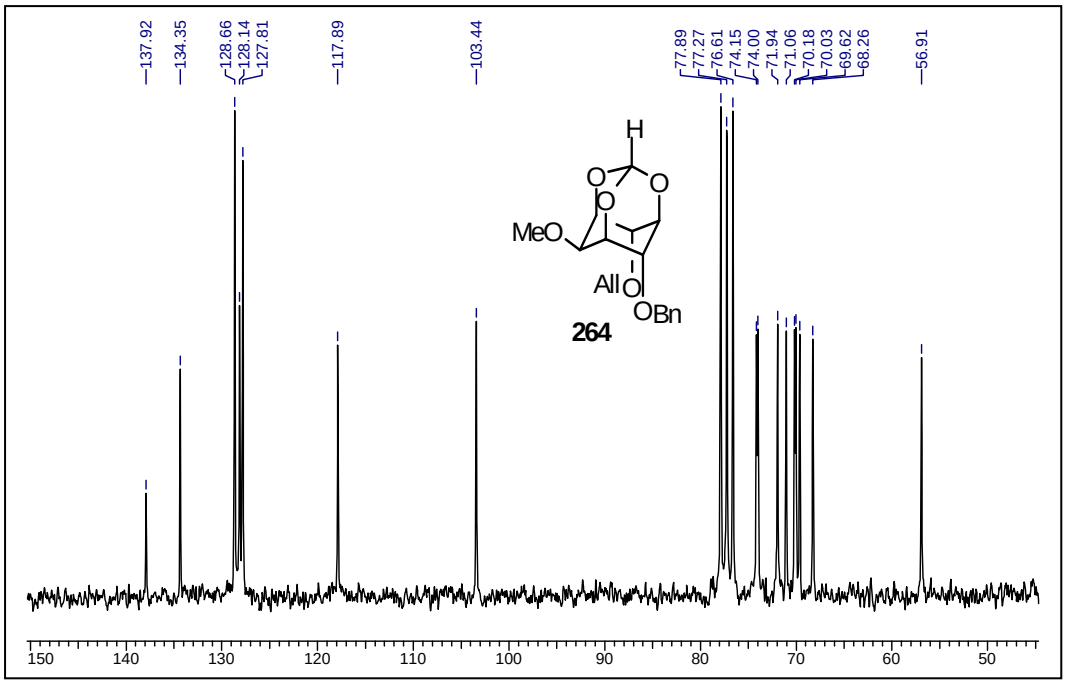
5.19
4.73
4.67
4.59
4.54
4.44
4.35
4.33
4.14
4.11
4.09
3.78
3.48
0.00
5.00
0.64
0.79
1.72
2.09
5.18
1.05
3.14
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
H
O
O
O
MeO
All
O
OBn
264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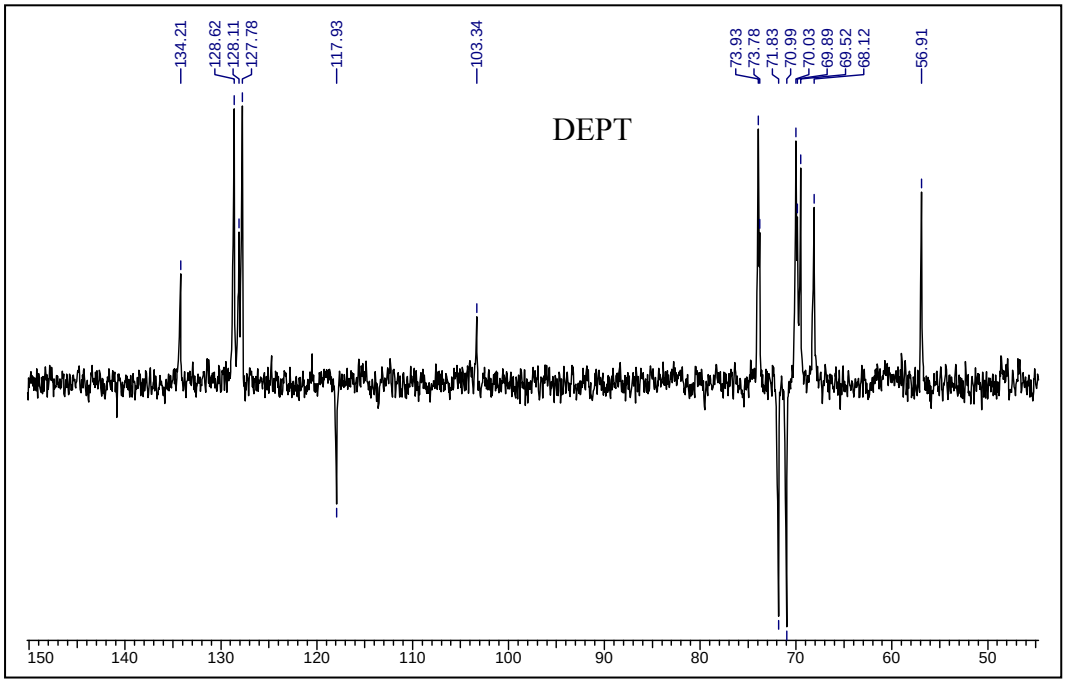
117.89
103.44
77.89
77.27
76.61
74.15
74.00
71.94
71.06
70.18
70.03
69.62
68.26
56.91
H
O
O
O
MeO
All
O
OBn
264
150
140
130
120
110
100
90
80
70
60
50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73.78
71.83
70.99
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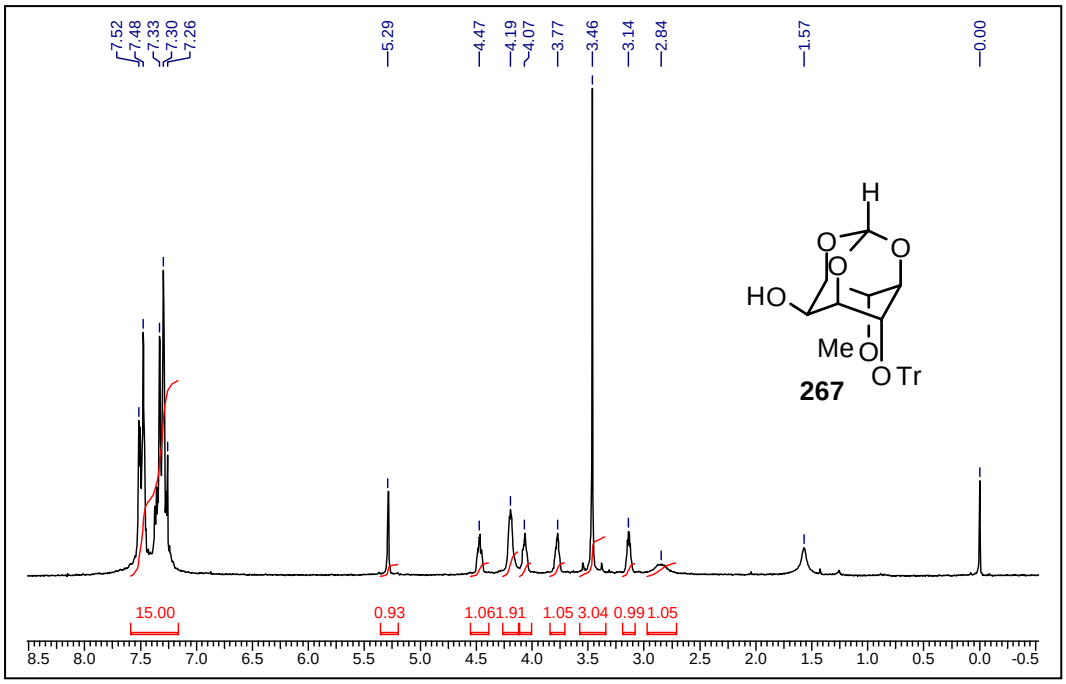
68.12
56.91
DEPT
150
140
130
120
110
100
90
80
70
60
50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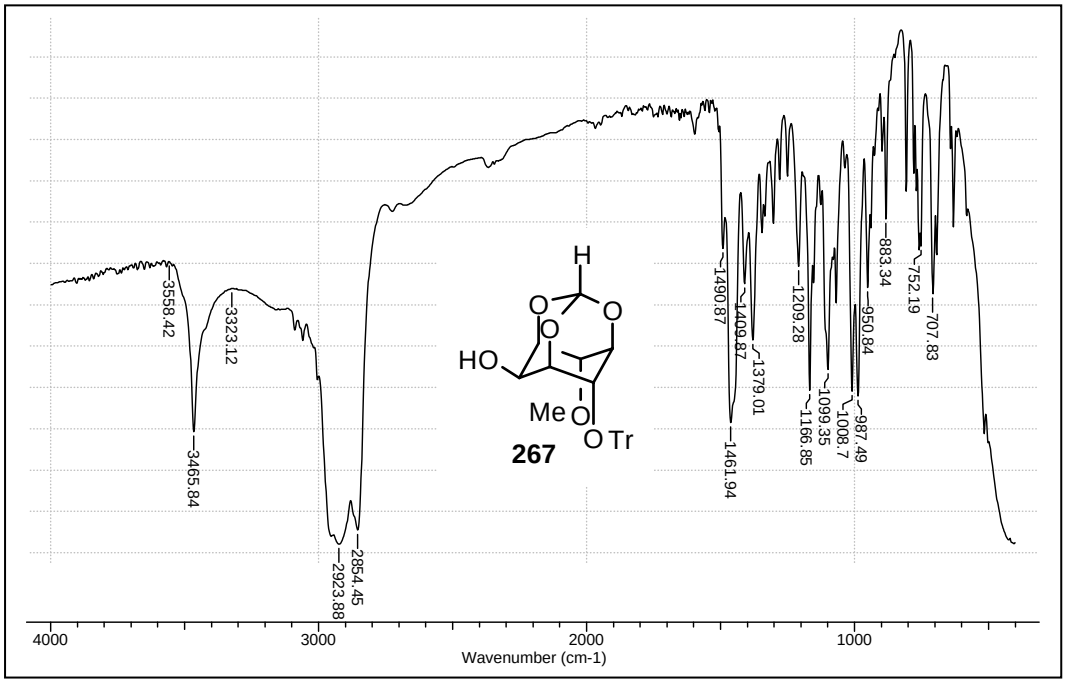
7.26
5.29
4.47
4.19
4.07
3.77
3.46
3.14
2.84
1.57
0.00
15.00
0.93
1.06
1.91
1.05
3.04
0.99
1.05
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
H
O
O
O
HO
Me
O
O Tr
267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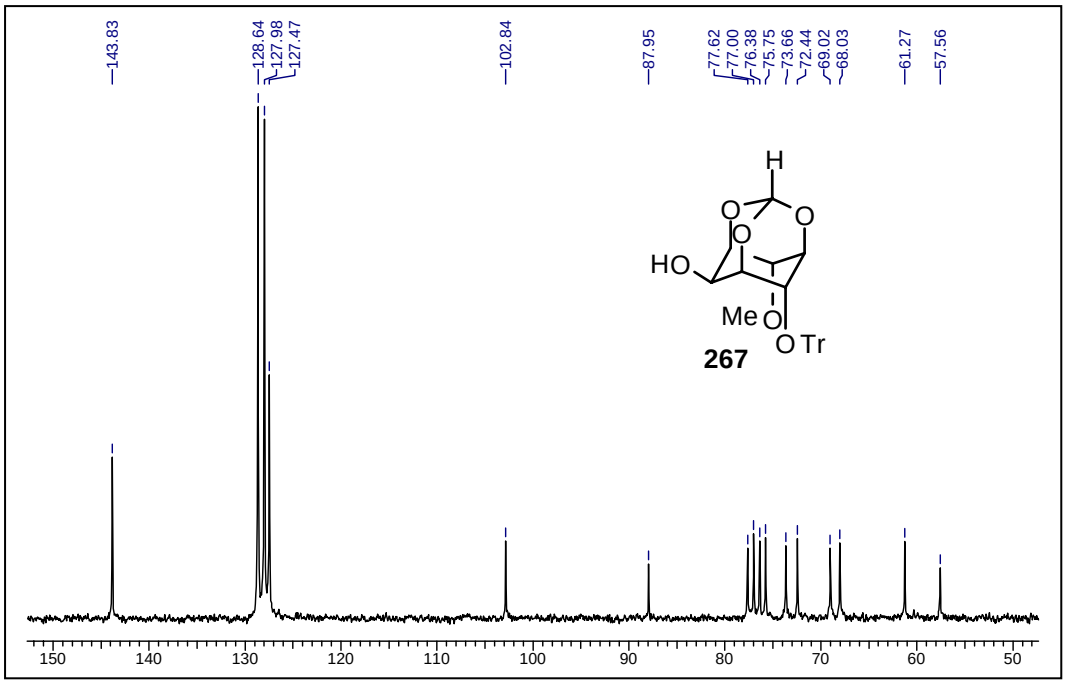
2854.45
1490.87
1461.94
1409.87
1379.01
1209.28
1166.85
1099.35
1008.7
987.49
950.84
883.34
752.19
707.83
4000
3000
2000
1000
Wavenumber (cm-1)
H
O
O
O
HO
Me
O
O Tr
267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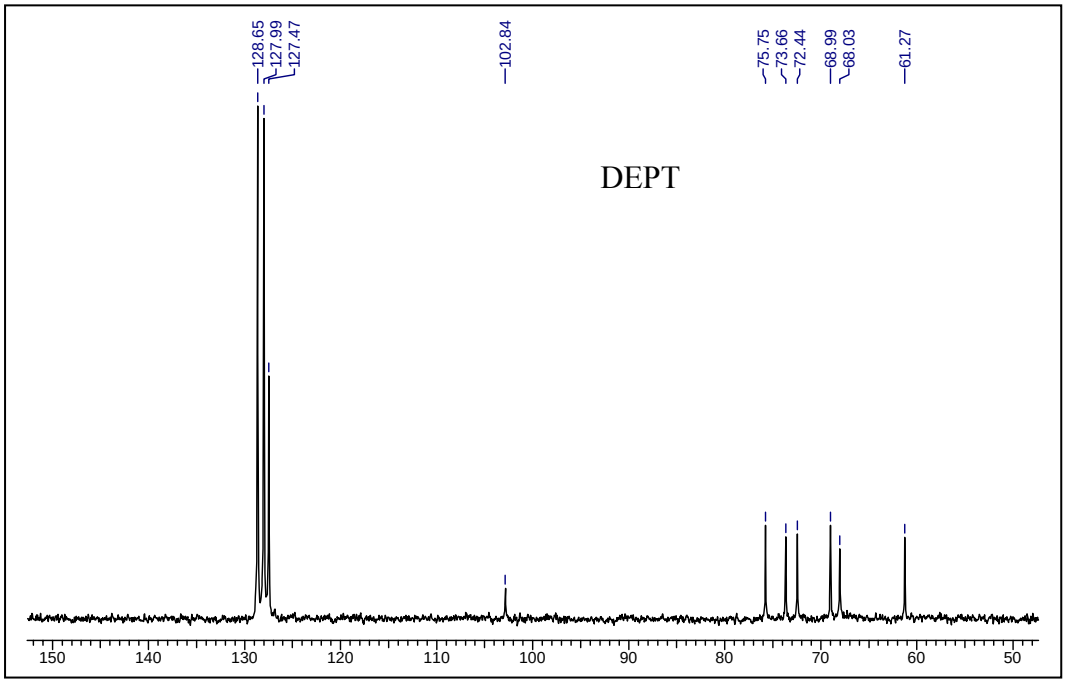
127.47
102.84
87.95
77.62
77.00
76.38
75.75
73.66
72.44
69.02
68.03
61.27
57.56
H
O
O
O
HO
Me
O
O Tr
267
150
140
130
120
110
100
90
80
70
60
50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127.47
102.84
75.75
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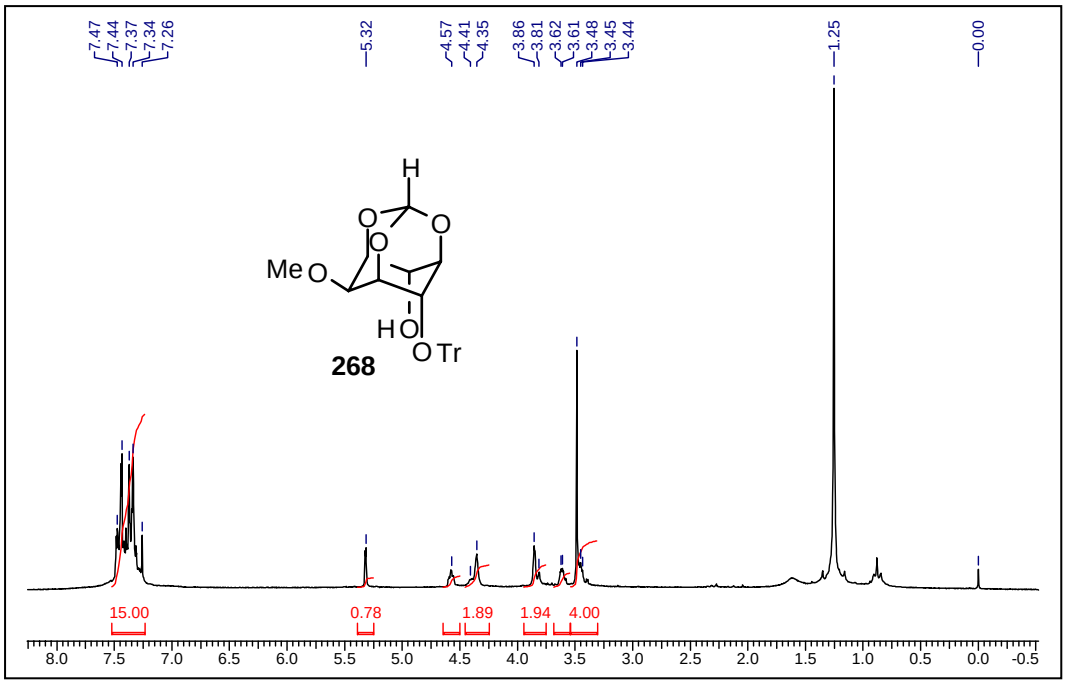
68.99
68.03
61.27
DEPT
150
140
130
120
110
100
90
80
70
60
50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7.44
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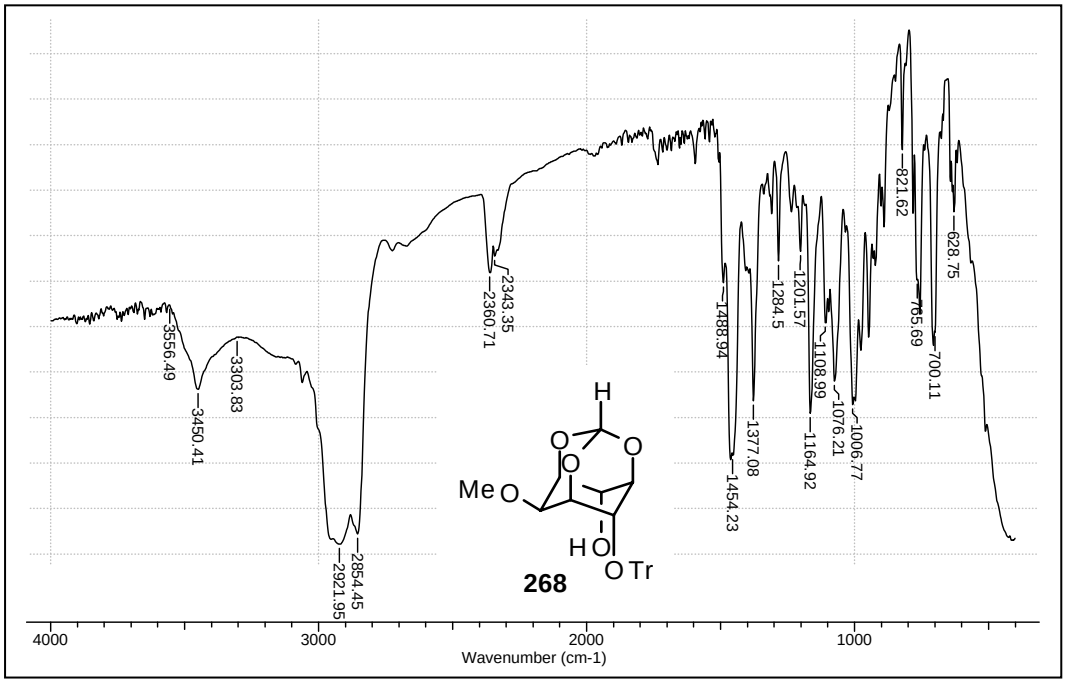
7.34
7.26
5.32
4.57
4.41
4.35
3.86
3.81
3.62
3.61
3.48
3.45
3.44
1.25
0.00
H
O
O
O
Me O
H O
O Tr
268
15.00
0.78
1.89
1.94
4.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5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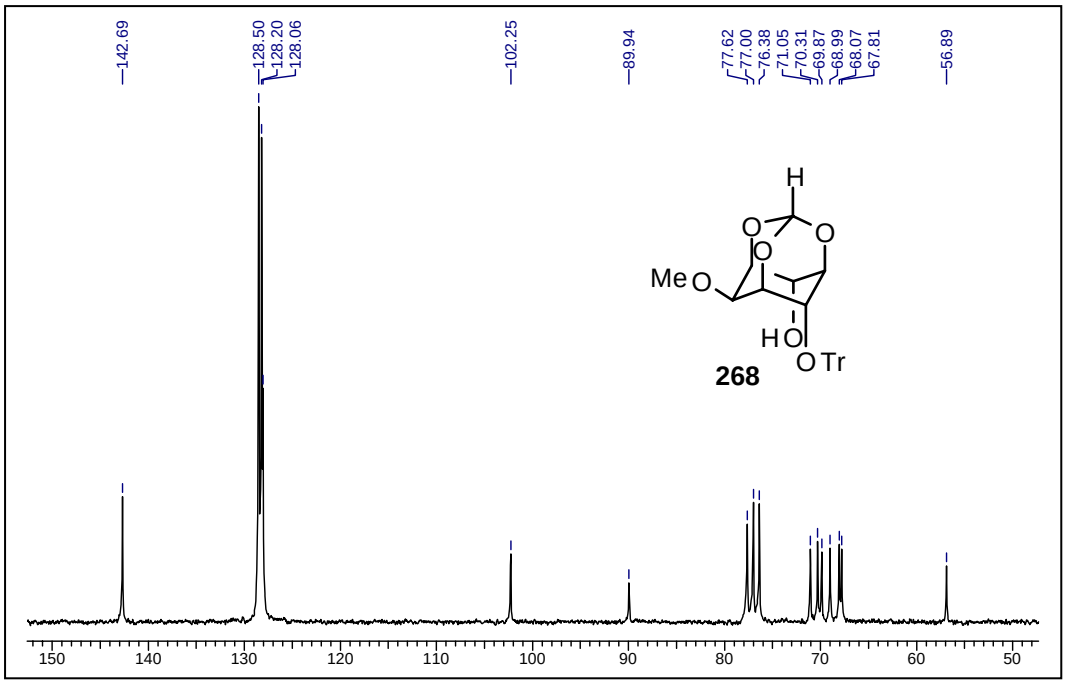
3450.41
3303.83
2921.95
2854.45
2360.71
2343.35
1488.94
1454.23
1377.08
1284.5
1201.57
1164.92
1108.99
1076.21
1006.77
821.62
795.69
700.11
628.75
H
O
O
O
Me O
H O
O Tr
268
4000
3000
2000
1000
Wavenumber (cm-1)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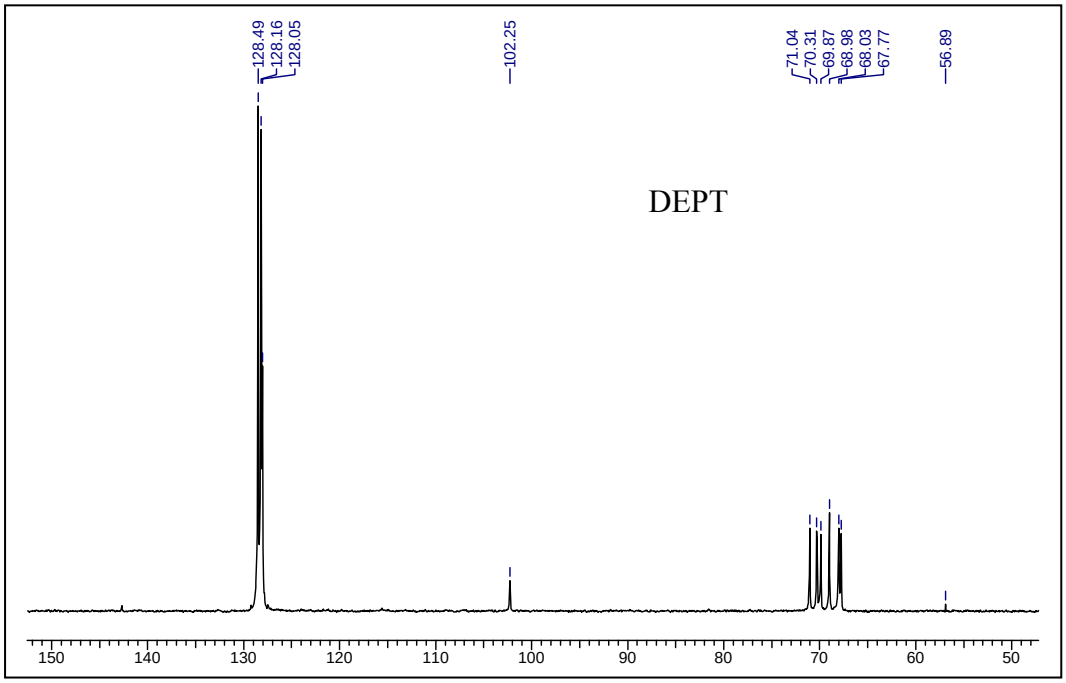
128.20
128.06
102.25
89.94
77.62
77.00
76.38
71.05
70.31
69.87
68.99
68.07
67.81
56.89
H
O
O
O
Me O
H O
O Tr
150
140
130
120
110
100
90
80
70
60
50

268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71.04
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67.77
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120
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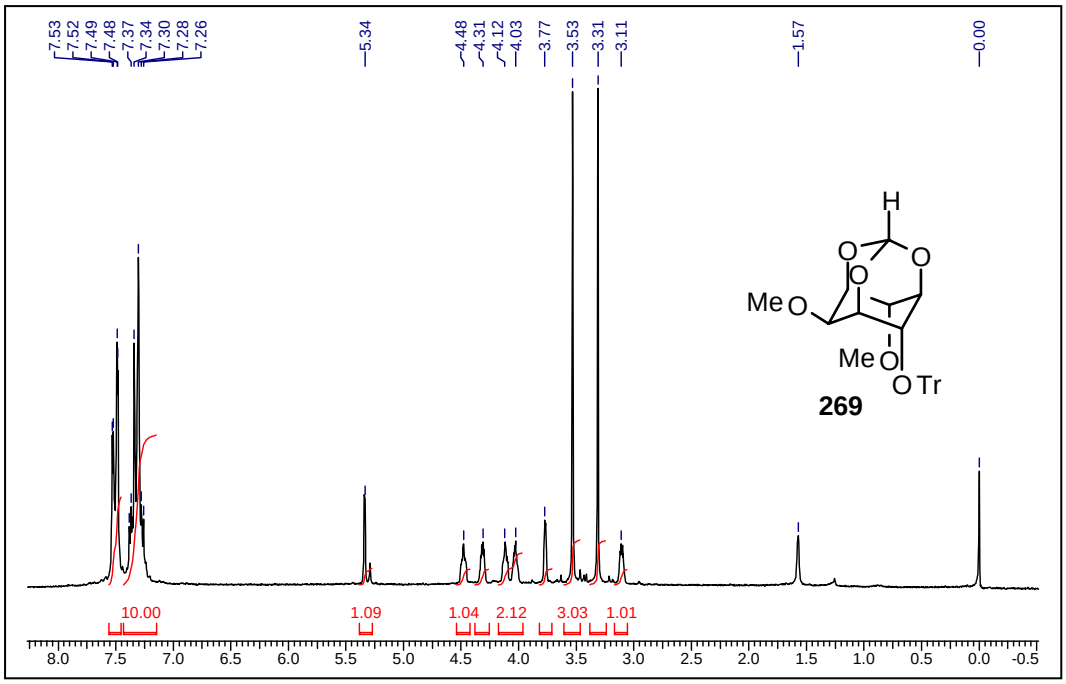
80
70
60
50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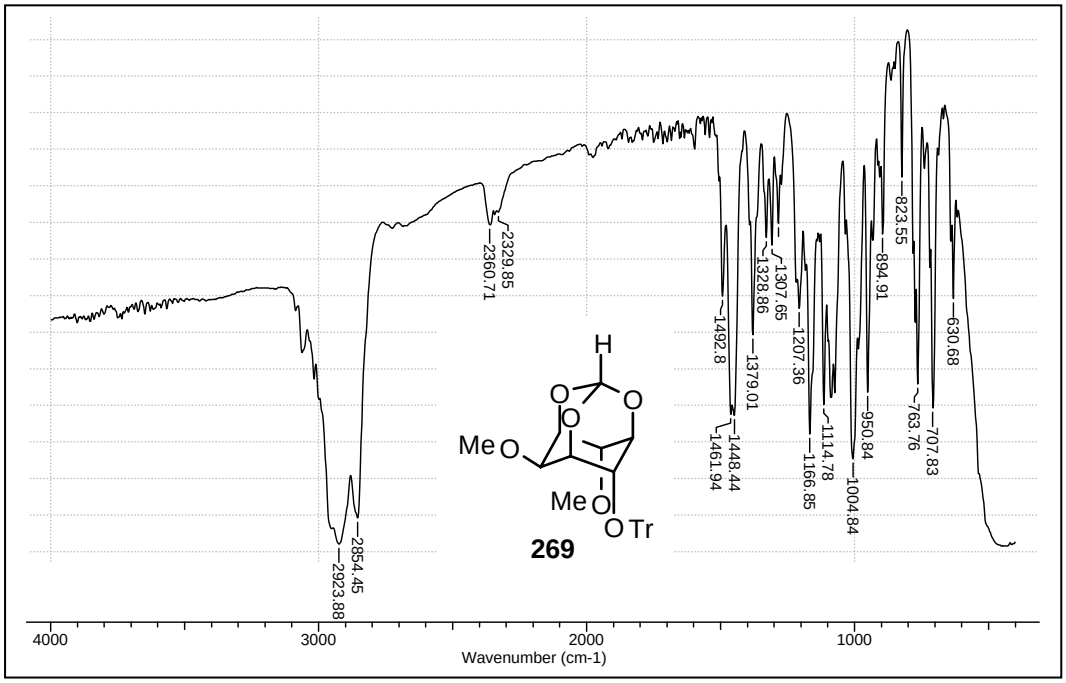
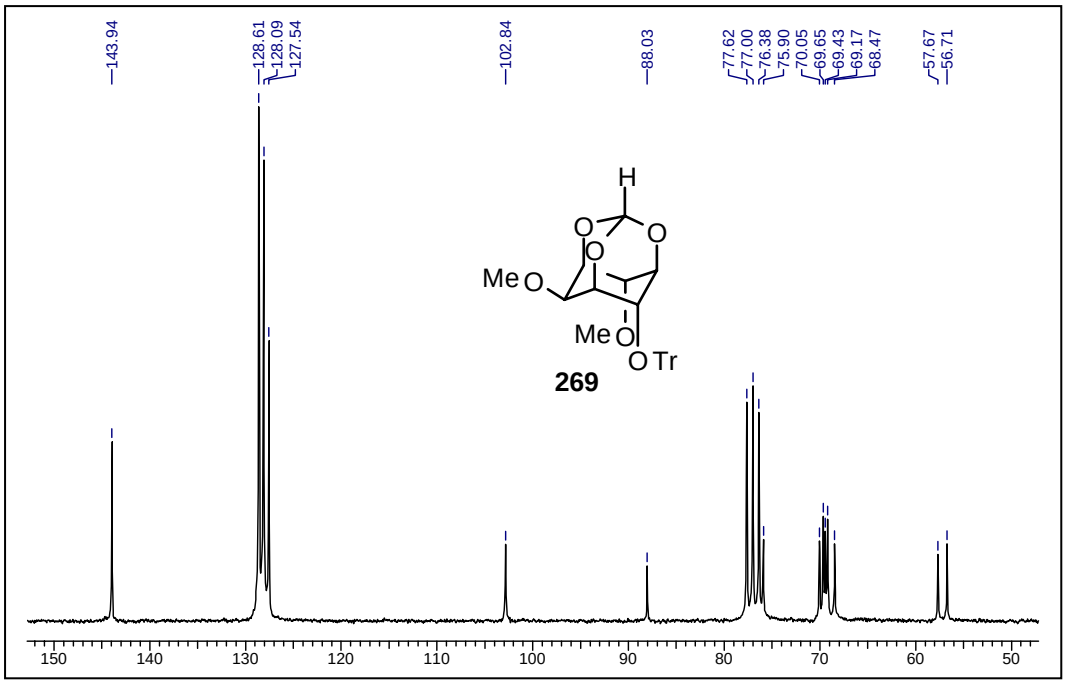
7.52
7.49
7.48
7.37
7.34
7.30
7.28
7.26
5.34
4.48
4.31
4.12
4.03
3.77
3.53
3.31
3.11
1.57
0.00
10.00
1.09
1.04
2.12
3.03
1.01
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
H
O
O
O
Me O
Me O
O Tr
269


2923.88
2854.45
2360.71
2329.85
1492.8
1461.94
1448.44
1379.01
1328.86
1307.65
1207.36
1166.85
1114.78
1004.84
950.84
894.91
823.55
763.76
707.83
630.68
4000
3000
2000
1000
Wavenumber (cm-1)
H
O
O
O
Me O
Me O
O Tr
269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102.84
88.03
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77.00
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70.05
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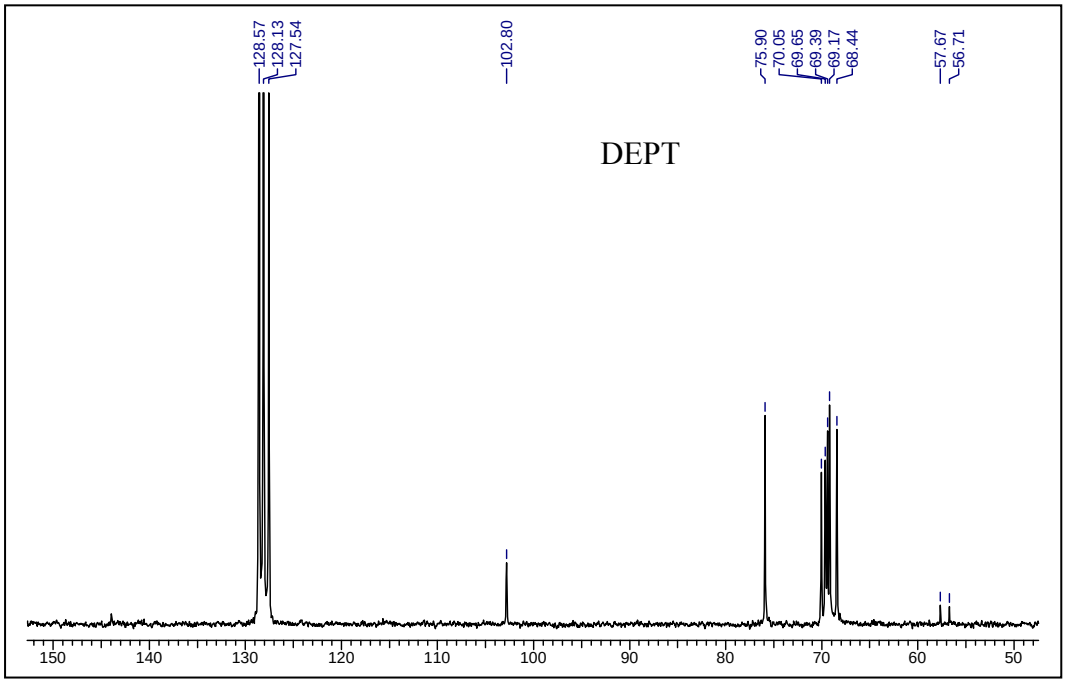
69.43
69.17
68.47
57.67
56.71
H
O
O
O
Me O
Me O
O Tr
150
140
130
120
110
100
90
80
70
60
50

269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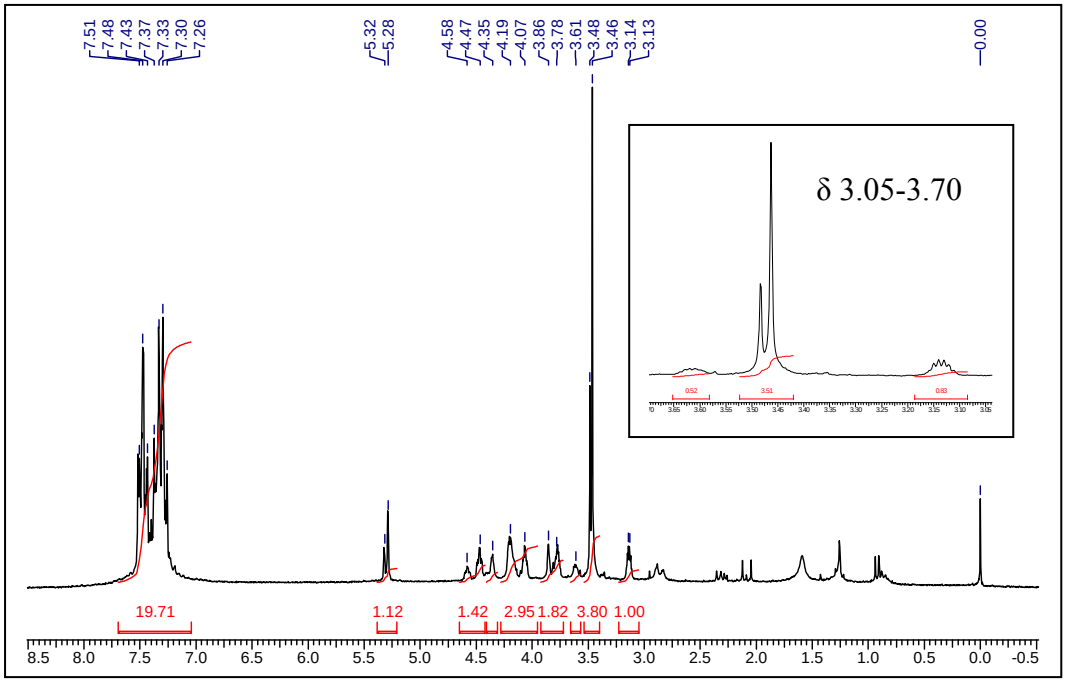
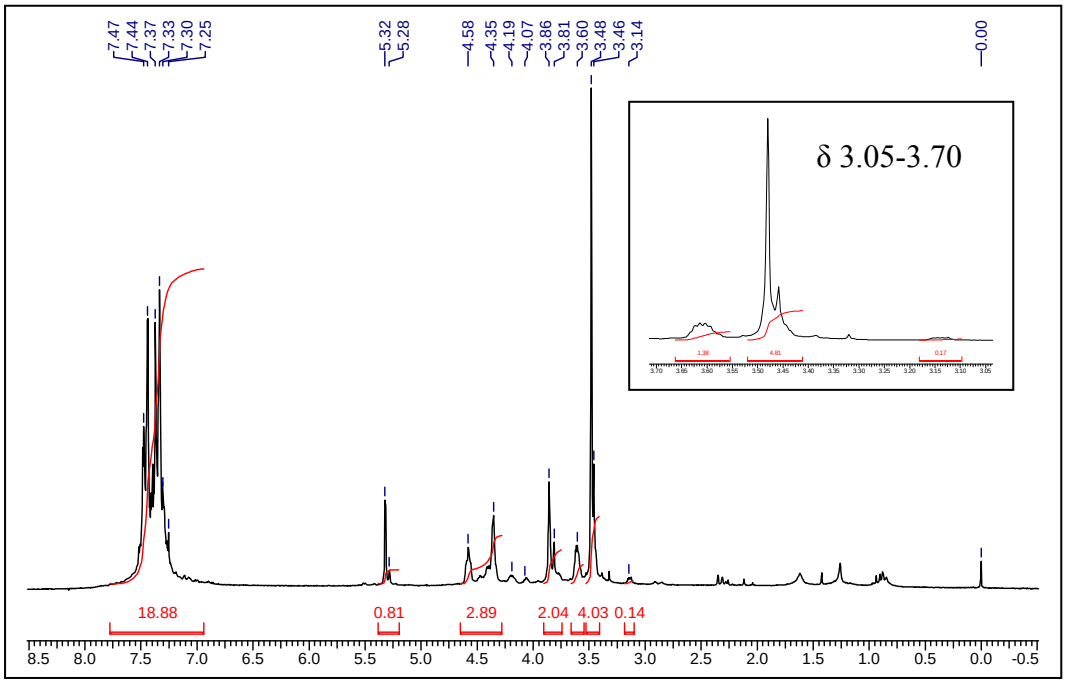
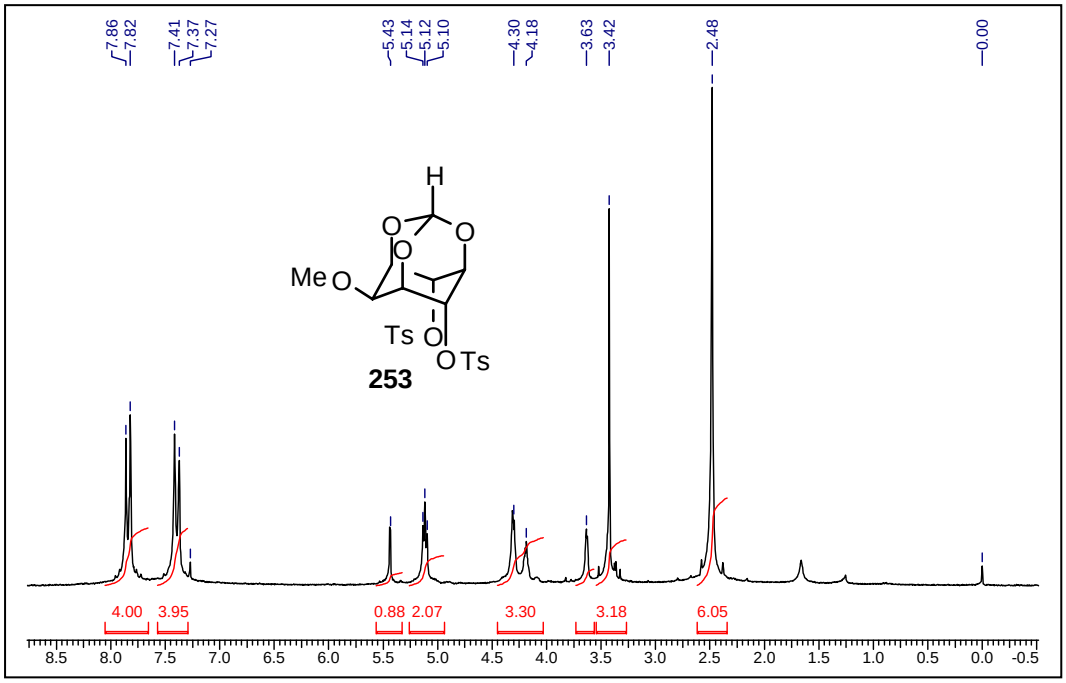
128.13
127.54
102.80
75.90
70.05
69.65
69.39
69.17
68.44
57.67
56.71
DEPT
150
140
130
120
110
100
90
80
70
60
50

^{1}H NMR spectra for the mixture of products **267** and **268** obtained on methylation of the racemic diol **223** with
a) butyllithium and methyl iodide.



b) sodium hydride and methyl iodide.

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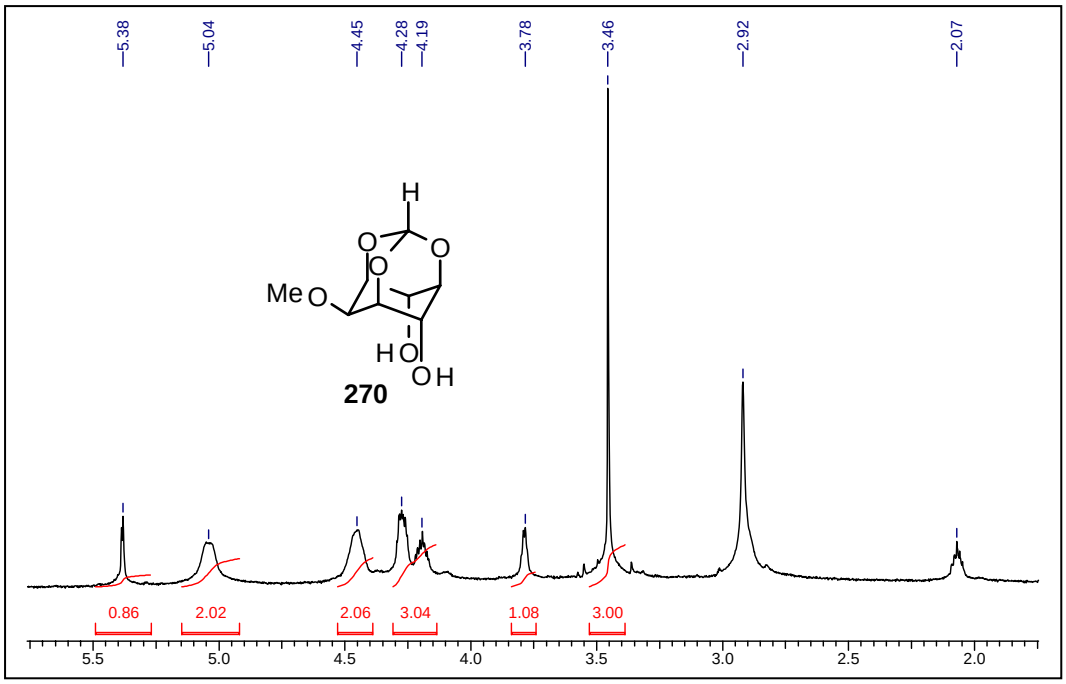
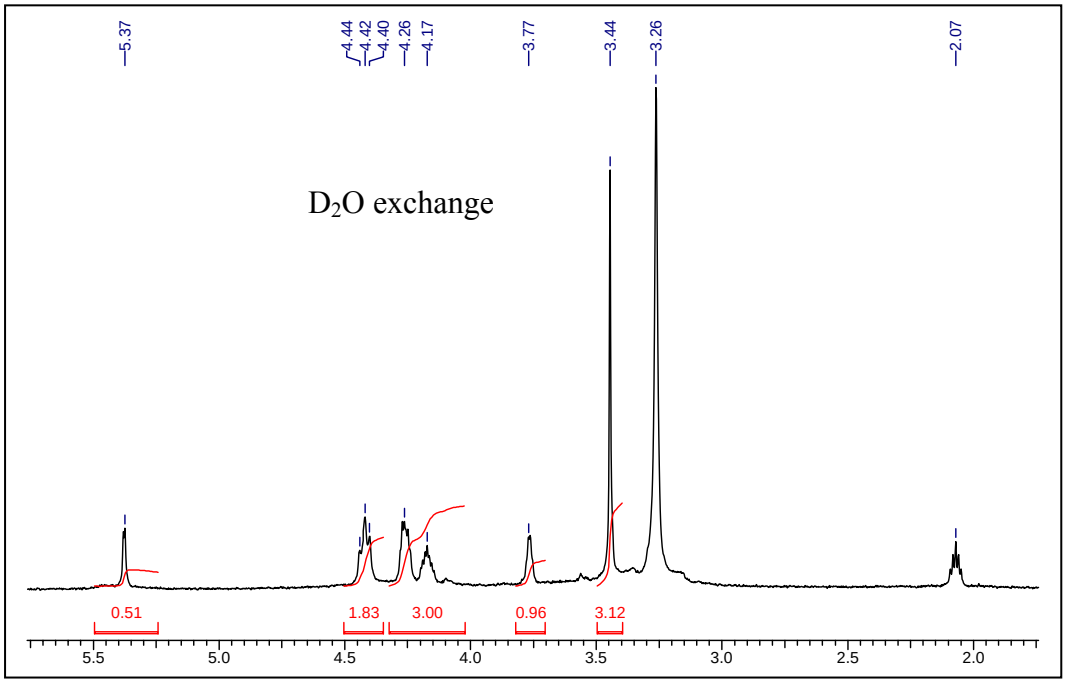
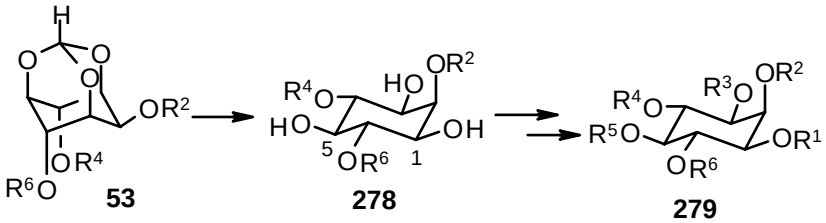
7.82
7.41
7.37
7.27
5.43
5.14
5.12
5.10
4.30
4.18
3.63
3.42
2.48
0.00
H
O
O
O
Me O
Ts O
O Ts
253
4.00
3.95
0.88
2.07
3.30
3.18
6.05
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


5.38
5.04
4.45
4.28
4.19
3.78
3.46
2.92
2.07
H
O
O
O
Me O
H O
O H
270
0.86
2.02
2.06
3.04
1.08
3.00
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0


5.37
4.44
4.42
4.40
4.26
4.17
3.77
3.44
3.26
2.07
D2O exchange
0.51
1.83
3.00
0.96
3.12
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0

2B.1. Introduction

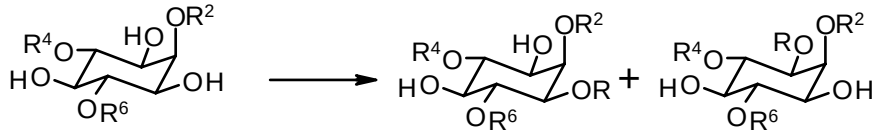
In the previous section a novel methodology for the orthogonal protection of the three hydroxyl groups of *myo*-inositol 1,3,5-orthoesters was described. Although it is likely that good regioselectivity observed was due to the inherent rigidity of the trioxaadamantane frame work of these orthoesters, it was curious to see if the regioselectivity of O-substitution reactions would get affected in partially protected *myo*-inositol derivatives in the absence of the orthoester moiety, on using sodium and lithium alkoxides. Hence we carried out O-substitution reactions of partially protected *myo*-inositol derivatives by generating their alkoxides using butyllithium and compared the results with the coresponding reaction where sodium hydride was used to generate the alkoxides. Discovery of reagents and reaction conditions to obtain good regioselectivity in O-substitution reactions of partially protected *myo*-inositol derivatives would be very useful, as seen in the chapter 1 of this thesis. This is especially appropriate since the work described in the previous section allowed sequential regioselective protection of C2-, C4- and C6-hydroxyl groups of *myo*-inositol and the availability of a general method for the regioselective protection of C1-, C3- and C5-hydroxyl groups would allow modification of all the six hydroxyl groups of *myo*-inositol at will (Scheme 2B.1).



Scheme 2B.1

In *myo*-inositol derived 1,3,5-triols (**278**), C1- and C3-hydroxyl groups have one *cis* and one *trans* vicinal oxygen atom, whereas the C5-hydroxyl group has both *trans* vicinal oxygen atoms. This difference is known to lead to some regioselectivity in the

reactions of these hydroxyl groups (Section 1.2.2, Chapter 1) but the known methods are not good enough. Hence we chose a symmetric 1,3,5-triol (**278**, $R^2 = R^4 = R^6 = Bn$) for our investigation since the regioselective monosubstitution at C1- as well as C3-positions would lead to a single racemic product. A similar reaction of the *myo*-inositol derived 1,3,5-triols carrying different substituents at C4- and C6-positions would lead to two different diastereomeric products (Scheme 2B.2).



Scheme 2B.2

Single racemic product when R^4, R^6 are same. Two racemic products when R^4, R^6 are different.

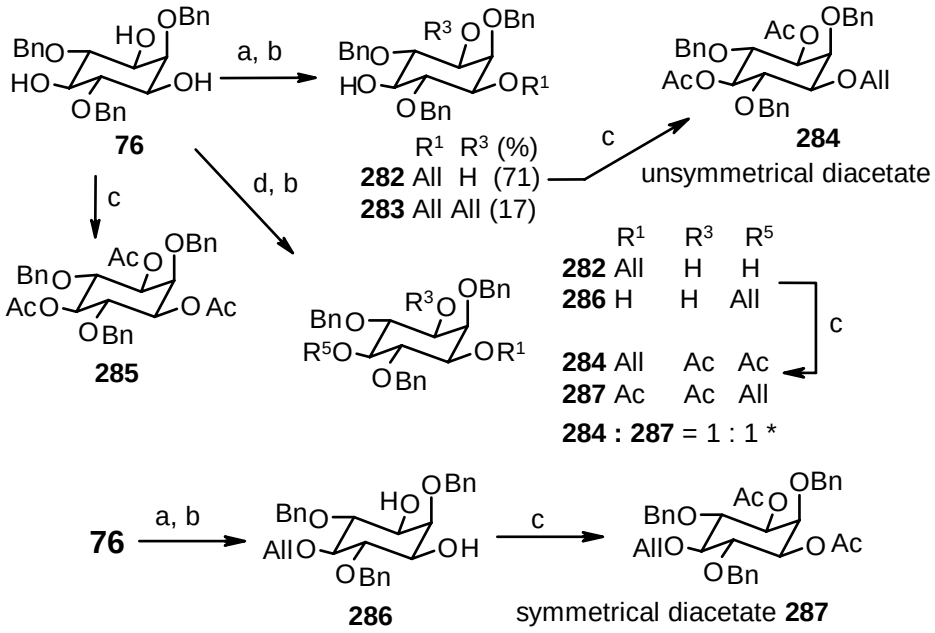
The following section deals with the orthogonal protection of the triol **76** (Scheme 2B.3) and the regioselective protection of some diols derived from *myo*-inositol, using butyllithium as well as sodium hydride as base under identical conditions. We have carried out O-substitution in a few *myo*-inositol derived diols to see the generality as well as to provide better method for the regiospecific protection of diols known to be useful for the preparation of inositol derivatives. We have chosen vicinal as well as non-vicinal diols having hydroxyl groups with different relative orientations.

2B.2. Results and discussion

2B.2.1. O-Alkylation of 2,4,6-tri-*O*-benzyl-*myo*-inositol

Reaction of the triol **76**[1] with one equivalent of butyllithium followed by one equivalent of allyl bromide resulted in mono allylation at the C1-hydroxyl group. This was confirmed by the ^{1}H NMR spectrum of the diacetate derivative **284** obtained by the acetylation of the monoallyl ether **282**. The ^{1}H NMR spectrum of the diacetate **284** showed two distinct acetate methyl peaks at δ1.93 and 1.85 in the ratio 1:1 because of

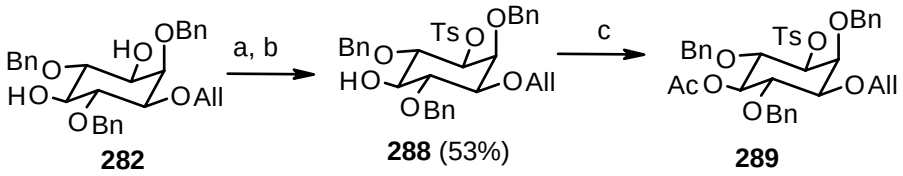
its unsymmetrical nature. The ^{1}H NMR spectrum of the tribenzyl triacetate **285** showed two peaks at δ1.94 and 1.87 in the ratio 2:1 because of the symmetry of the molecule. This clearly showed that allylation had taken place at the C1(3)-hydroxyl group. Had the allylation of the triol **76** taken place at the C5-hydroxyl group, the resulting diacetate **287** would have shown only one peak for the acetate methyl hydrogens. Presence of a mixture of C1- and C5-allyl ethers (**282** and **286**) would have been indicated by unequal integral ratios for the acetate methyl group signals in the ^{1}H NMR spectrum of a mixture of acetates **284** and **287**.



Scheme 2B.3. a) n-BuLi, THF; (b) AllBr, DMF; c) Ac_2O, Pyr; d) NaH, THF.
* Estimated by ^{1}H NMR spectroscopy.

Allylation of the triol **76** with one equivalent of sodium hydride and allyl bromide resulted in a mixture of products which was further acetylated. The ratio of the two allyl ethers **284** and **287** in the mixture was estimated to be 1:1 by comparing the integrals of the acetate methyl peaks in its ^{1}H NMR spectrum.

2B.2.2. O-Alkylation / tosylation of diols. O-Tosylation of racemic 1-*O*-allyl-2,4,6-tri-*O*-benzyl-*myo*-inositol

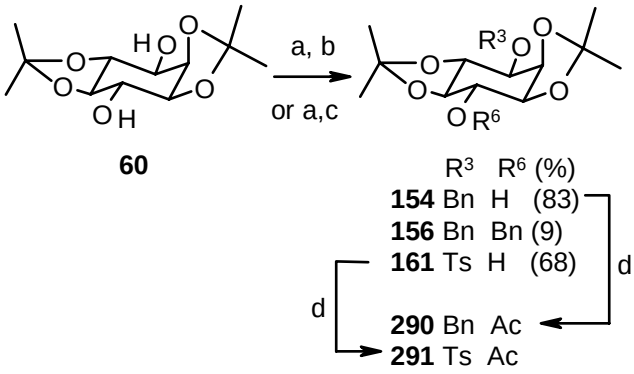


Scheme 2B.4. a) n-BuLi, THF; (b) TsCl, DMF; c) Ac_2O, Pyr.

Reaction of the racemic 3,5-diol **282** with one equivalent of butyllithium followed by one equivalent of tosyl chloride resulted in the corresponding C3-tosylate **288**. The ^1H NMR spectrum of the acetate obtained from the tosylate **288** showed a single acetate methyl peak at δ1.75. This confirmed that tosylation in **282** had occurred selectively at the C3-hydroxyl group. Hence O-substitution in lithium alkoxides of the triol **76** allows the sequential substitution of both C1- and C3-hydroxyl groups that are *cis* to the C2-oxygen leaving the C5-hydroxyl group undisturbed.

2B.2.3. O-Alkylation of racemic 1,2:4,5-di-*O*-isopropylidene-*myo*-inositol

Benzylation of the racemic 3,6-diol **60**[2] with one equivalent of butyllithium and one equivalent of benzyl bromide (or sulfonylation with tosyl chloride) resulted in the corresponding C3-O-substituted derivative in good yield (Scheme 2B.5). No reaction was observed at the C6-hydroxyl group of **60**.

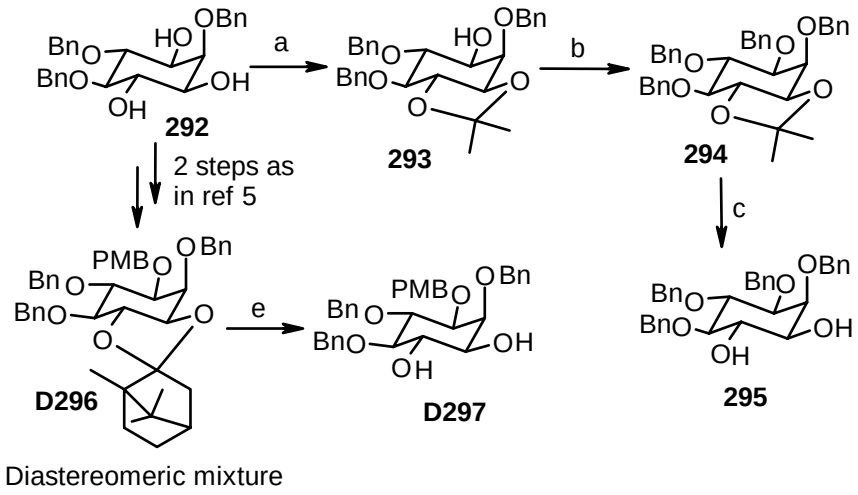


Scheme 2B.5. a) n-BuLi, THF; b) BnBr, DMF; c) TsCl, DMF; d) Ac_2O, Pyr.

Reaction of the racemic 3,6-diol **60** with electrophiles (alkyl halides, sulfonyl halides, acyl halides) under a variety of reaction conditions is reported[3] to give a mixture of products. Benzylation of the racemic 3,6-diol **60** with sodium hydride and benzyl bromide is known[3] to give a mixture of monobenzyl ethers (**154**, **155**) and the dibenzyl ether **156** (15%) from which the monobenzyl ether **154** (56%) was isolated by crystallization. Reaction of the racemic 3,6-diol **60** with tosyl chloride is reported[4] to give the 3-tosylate **161** in 30% yield. A comparison of these results with the present work clearly shows that better regioselectivity during O-substitution in the diol **60** can be achieved by generating the alkoxide with butyllithium. Use of lithium hydride as a base for the benzylation of the racemic 3,6-diol **60** gave a mixture of products (as indicated by TLC). This reaction was carried out at a higher temperatue (55 ºC) due to the low basicity of lithium hydride.

2B.2.4. O-Alkylation of racemic 2,3,4,5-tetra-*O*-benzyl-*myo*-inositol

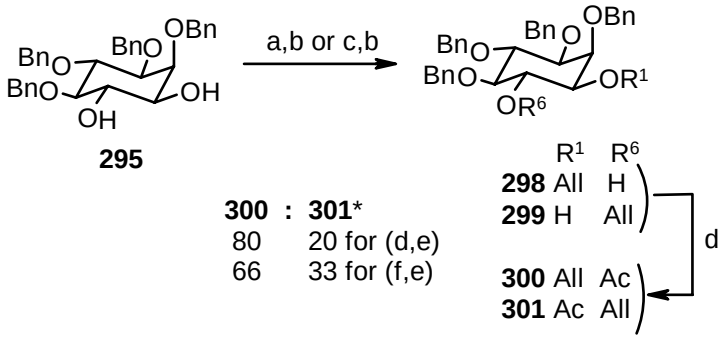
The racemic 1,6-diol **295** was prepared by a slightly modified procedure reported[5] for the preparation of an enantiomer **D297** of the 1,6-diol (Scheme 2B.6, **292** →→ **D297**). The racemic diol **295** was prepared from the triol **292** by first protecting the vicinal diols as the corresponding isopropylidene derivative. The ketal **293** was prepared by the reaction of the triol **292** with 2,2-dimethoxypropane in the presence of CSA. Our initial attempt to obtain this ketal[5] by using TsOH failed. The resulting isopropylidene derivative **293** was benzylated at the C3-hydroxyl group using sodium hydride and benzyl bromide. The isopropylidene group in the crude product **294** was cleaved by acid hydrolysis which afforded the racemic 1,6-diol **295**.



Scheme 2B.6. a) 2,2-Dimethoxypropane, CSA, DCM, reflux; b) NaH, BnBr, DMF; c) HCl, MeOH, DCM; e) AcCl, DCM, MeOH.

Preparation of racemic 1,6-diol **295** from the dicyclohexylidene derivative of *myo*-inositol is reported.[6] We did not follow this route due to practical difficulties in this method and the lower overall yield of **295**.

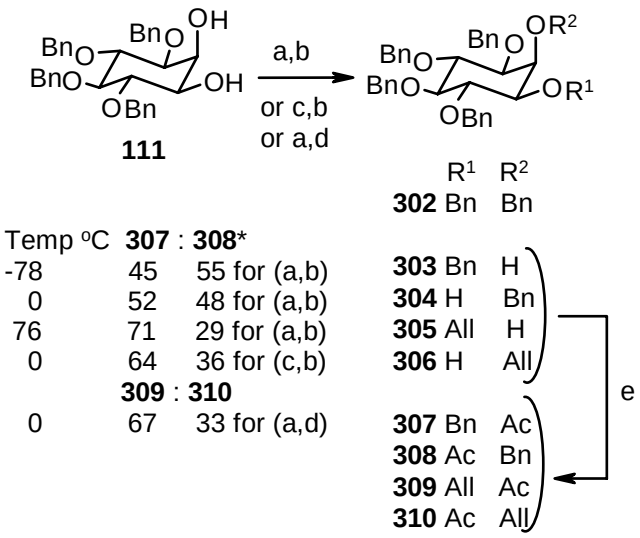
Allylation of the racemic 1,6-diol **295** using butyllithium as the base to generate the alkoxide yielded the corresponding C1-allyl ether **298** as the major product (Scheme 2B.7). The mixture of monoallyl ethers **298** and **299** was converted to the mixture of the corresponding acetates and their ratio (**300** : **301** = 80 : 20) was estimated by ^{1}H NMR spectroscopy. Use of sodium hydride to generate the alkoxide for allylation of the 1,6-diol **295** gave a mixture of monoethers in the ratio 2 : 1. This was revealed by the ^{1}H NMR spectrum of the mixture of acetates (**300**:**301** = 66 : 33). These results show that the regioselectivity for the allylation at the C1-hydroxyl group in 1,6-diol (using DMF as the solvent) is better when lithium alkoxide is used for the reaction. Allylation of one of the enatiomers of the 1,6-diol **D297** (Chapter 1, section 1.3.4) in the presence of sodium hydride in THF is reported[7] to give a mixture of C1- and C6-ethers in the ratio 7:1 in an overall yield of 56%.



Scheme 2B.7. a) n-BuLi, THF; b) AllBr, DMF; c) NaH, THF; d) Ac_2O, Pyr.
* Estimated by ^{1}H NMR spectroscopy.

2B.2.5. O-Alkylation of racemic 3,4,5,6-tetra-*O*-benzyl-*myo*-inositol

Benzylation of the racemic 1,2-diol **111**[8] (Scheme 2B.8) in DMF at 0 ºC, using butyllithium to generate the alkoxide, gave the pentabenzyl ethers **303** and **304** as the major product along with a small amount of the hexabenzyl ether **302**. The mixture of isomeric pentabenzyl ethers **303** and **304** was seperated by column chromatography and a portion of this mixture was acetylated to obtain a mixture of acetates **307** and **308**. ^{1}H NMR spectrum of the mixture of acetates **307** and **308** showed that the two pentabenzyl ethers **303** and **304** were present in more or less equal amounts. This was revealed by a comparison of the integrals of the acetate methyl group peaks in the ^{1}H NMR spectrum of the mixture of acetates **307** and **308**. The peak corresponding to the C2-acetate was identified by comparison with the ^{1}H NMR spectrum of the pentabenzyl-2-acetate **307** (acetate methyl peak at δ 2.17) synthesized following a literature procedure.[8]



Scheme 2B.8. a) n-BuLi, THF; b) BnBr, DMF; c) NaH, THF; d) AllBr, DMF; e) Ac_2O, Pyr.
* Estimated by 1H NMR spectroscopy.

Since the pentabenzyl ethers **303** and **304** had the same R_f value on TLC (eluent: 15% ethyl acetate / petroleum ether) we initially thought that it was a single isomer and obtained good quality crystals by crystallization from a mixture of ethyl acetate and light petroleum. Analysis of one of the crystals revealed it to be the C2-benzyl ether **304** (Figure 2B.1). However, as explained above, the product actually consisted of a mixture of two isomeric pentabenzyl ethers.

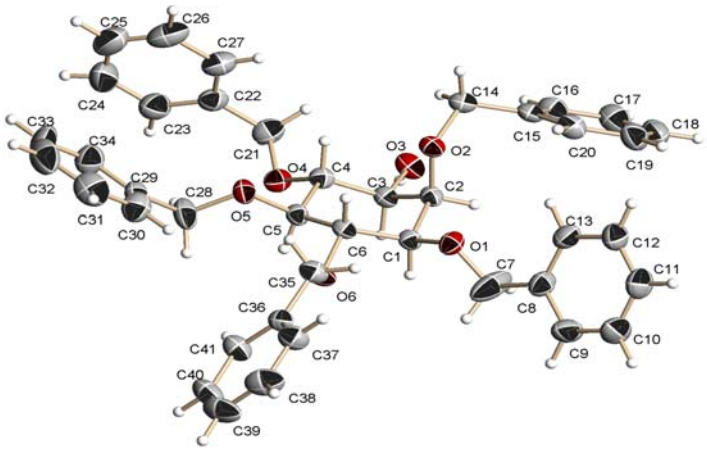
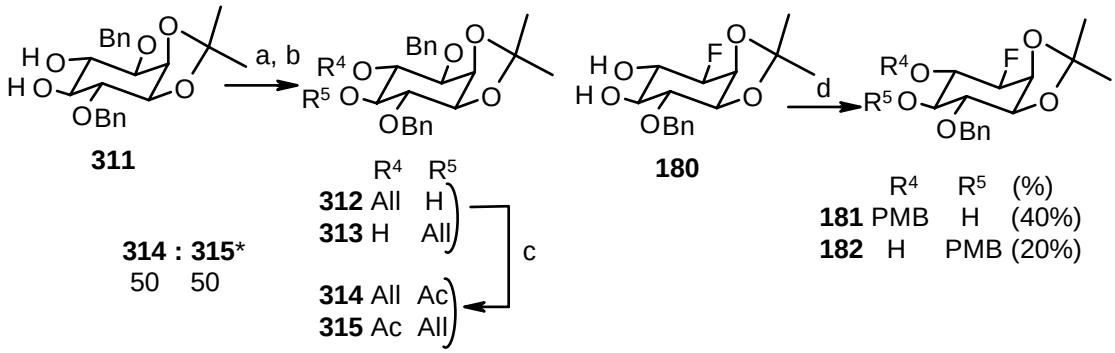


Figure 2B.1. ORTEP of **304**

Benzylation of the racemic 1,2-diol **111** was also carried out at -78 ºC and 75 ºC using BuLi to generate the alkoxide. These reactions also gave a mixture of pentabenzyl ethers **303** and **304** but the relative proportion of the equatorial C1-benzyl ether increased at higher temperatures (Scheme 2B.8). Benzylation of the racemic 1,2-diol **111** using sodium hydride as the base at 0 °C followed by acetylation gave a mixture of acetates **307** and **308** in the ratio 64:36. This experiment showed that benzylation was predominant at the C1-hydroxyl group in contrast to the benzylation when butyllithium was used as the base. We also carried out the allylation on the racemic diol **111** (using butyllithium as the base) at 0 °C and estimated the ratio of products (67:33) (after acetylation of the mixture of monoallyl ethers **305** and **306**) by ^{1}H NMR spectroscopy.

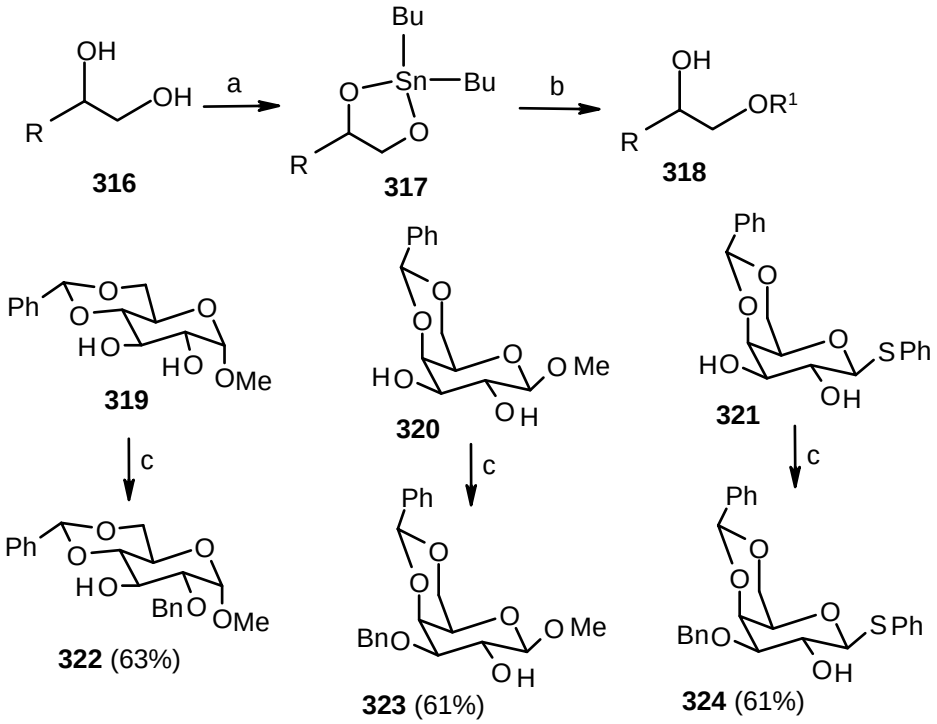
2B.2.6. O-Alkylation of racemic 1,2-*O*-isopropylidene-3,6-di-*O*-benzyl-*myo*-inositol

Allylation of the racemic 4,5-diol **311**[3a] (Scheme 2B.9) by sequential reaction with butyllithium and allyl bromide resulted in a mixture of products. The mixture of monoethers **312** and **313** was converted to the corresponding acetates **314** and **315** and their ratio (**314**:**315** = 50:50) was estimated by ^{1}H NMR spectroscopy. We did not carry out the alkylation of the racemic diol **311** using the corresponding sodium alkoxide since the reaction of its lithium alkoxide yielded a 1:1 mixture of products. Also alkylation of a diol **180** (1-deoxy-1-fluoro-2,3-isopropylidene-4-*O*-benzyl-*myo*-inositol) which is similar to **311** using sodium hydride is reported[9] to give a mixture of both the possible isomeric ethers.



Scheme 2B.9. a) n-BuLi, THF; b) AllBr, DMF; c) Ac_2O, Pyr; d) PMBCl, NaH, DMF.
* Estimated by ^1H NMR spectroscopy.

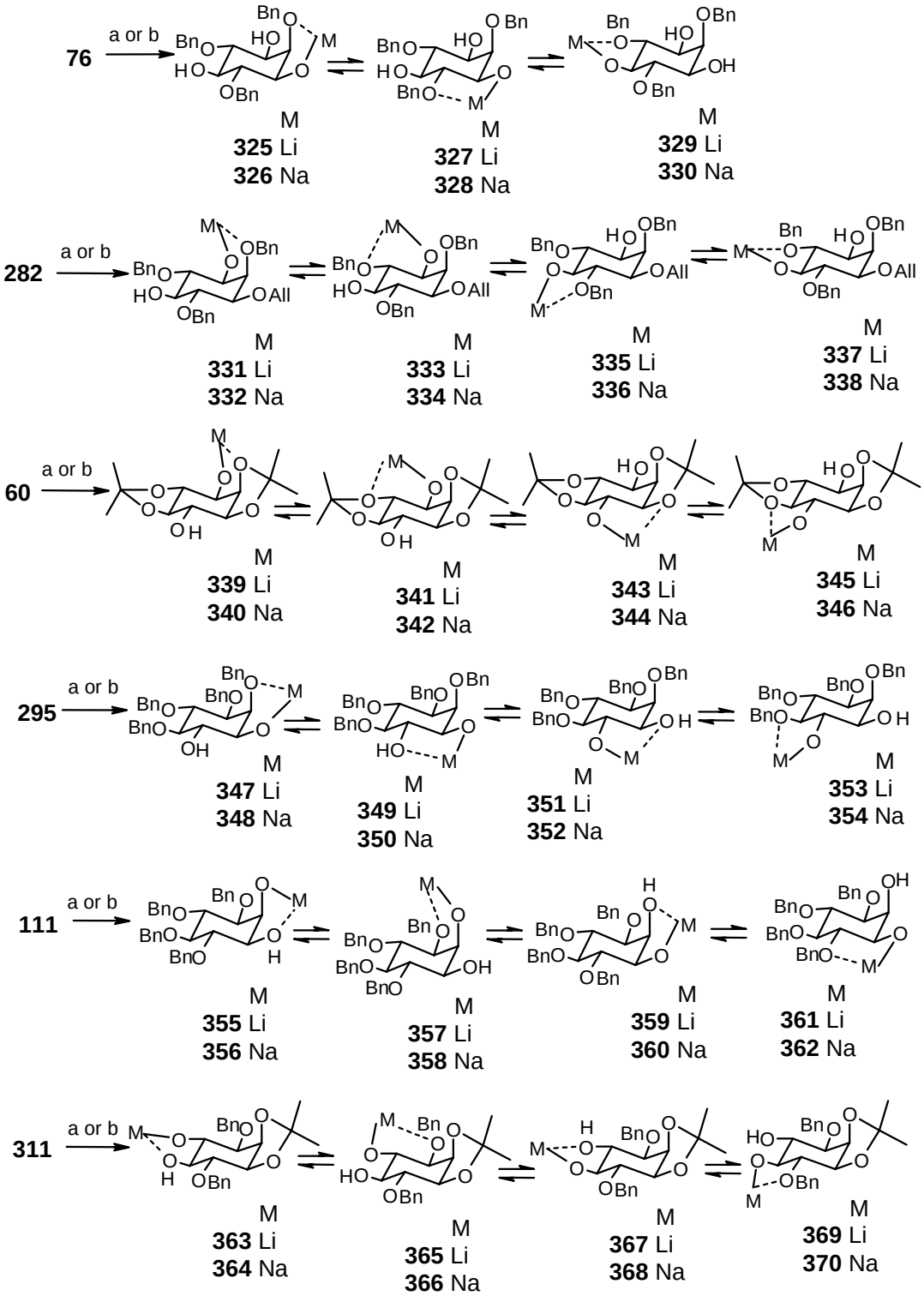
A comparison of the results on O-substitution of the triol **76** and the diols **60, 111, 282, 295** and **311** clearly shows that O-substitution in their lithium alkoxides preferentially takes place at a hydroxyl group that has a neighbouring *cis*-oxygen atom while the same reactions using sodium alkoxides are not that selective. This is supported by the fact that alkylation of the racemic 4,5-diol **311** (with butyllithium and allyl bromide) in which there is no adjacent *cis*-oxygen to either of the hydroxyl groups result in equal amounts of both the possible allyl ethers. Chelation assisted regioselective O-substitution of vicinal diols (using heavier metals)[10] have earlier been reported (Scheme 2B.10).



Scheme 2B.10. a) Bu_2SnO (or) $Bu_2Sn(OMe)_2$; b) (i) R^1X, (ii) H_2O; c) NaH, $NiCl_2$, BnBr, THF, DMF.

The results presented in Schemes 2B.3 - 2B.5 and 2B.7 - 2B.9 can be rationalized based on the relative stability of the alkoxides (Scheme 2B.11) generated by the reaction of the *myo*-inositol derived diols and triol with butyllithium or sodium hydride.

Scheme 2B.11 shows all the possible alkoxides that can be generated by the reaction of the *myo*-inositol derived triol (**76**) and the diols (**60, 111, 282, 295** and **311**) with butyllithium or sodium hydride. We can presume that the metal ions in all these alkoxides are chelated to neighboring oxygen atoms present in the molecule. As seen in Section A of this chapter, the alkoxides of these diols and triols would be present as an equilibrium mixture of the possible chelates. The relative proportion of individual chelates present in a reaction mixture at a given temperature would depend on their relative stability.



Scheme 2B.11. a) DMF, n-BuLi; b) DMF, NaH

We can assume that the O-substitution reaction takes place principally through these single molecular entities and the amount of the molecular aggregates present in the reaction mixture is negligible. This is because the O-substitution reaction in THF was

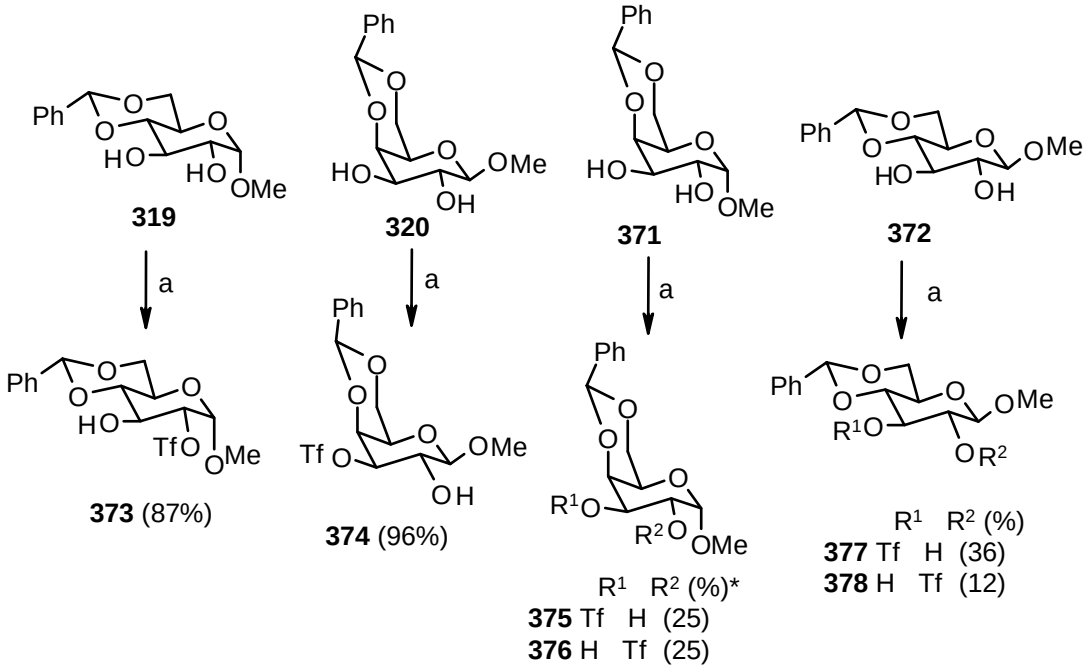
very sluggish while the same reaction in DMF – THF mixture proceeded smoothly (Section 2A.2 of this chapter).

The factors that could contribute to the relative stability of the alkoxides **325-370** are (a) the nature of the metal ion involved and (b) the relative orientation of the vicinal oxygen atoms in a *myo*-inositol derivative, which can chelate with the metal ion. In reactions involving lithium alkoxides, it is conceivable that the chelation from a vicinal *cis*-oxygen atom is better than the chelation from a vicinal *trans*-oxygen atom.[11] Hence the relative stability of lithium chelates is expected to decrease in the order **325**>**327~329** for **76**; **331**>**333~335~337** for **282**; **339**>**341~343~345** for **60**; **347**>**349~351~353** for **295**; **355**~**357**~**359**>**361** for **111**; **363**~**365**~**367**~**369** for **311**. This implies larger proportion of the O-substitution reaction proceeding through the chelates **325**, **331**, **339**, **347**, **355**, **357** or **359** and hence formation of the products resulting from O-substitution at a hydroxyl group which has a vicinal *cis*-oxygen atom. The relative stability of the chelates formed from sodium alkoxide is not expected to be very different since sodium ion is not as good a chelator as lithium ion. Hence reaction of sodium alkoxide with alkyl halides result in poorer regioselectivity.

In the case of the racemic 1,2-diol **111**, the alkoxide at the C2-position is stabilized by two vicinal *cis*-oxygen atoms (**355** and **357**) , whereas the C1-alkoxide is stabilized by chelation due to one vicinal *cis*-oxygen atom (**359**) and one vicinal *trans*-oxygen atom (**361**). This could be the reason for the formation of larger amounts of the C2-ether from lithium alkoxides. Perhaps with increase in temperature the difference in the stability of lithium chelates become narrower leading to the formation of relatively larger amounts of the C1-ether at higher temperatures. As discussed above, the relative stability of the chelates formed from sodium alkoxide is not expected to be very different and this results in the formation of larger amounts of the C1-ether due to steric

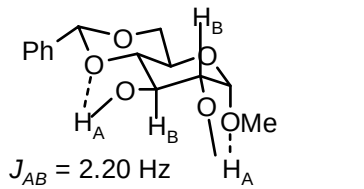
reasons (reaction at an axial hydroxyl group versus reaction at an equatorial hydroxyl group). These results seem to suggest that the O-substitution reaction in the diol **111** does depend on the realtive stability of the chelates since reducing the relative stability of chelates either by increasing the temperature (in the case of lithium chelates) or by changing the metal ion (sodium chelates) leads to similar trend (more reaction at the equatorial C1-hydroxyl group) in observed regioselectivity (Scheme 2B.8).

The relative stability of chelates (or the strength of chelation) depicted in Scheme 2B.11 is analogous to the relative strength of intramolecular hydrogen bonding in polyhydroxy cyclohexanes which is known[11a,b] to decrease as we go from 1,2-*cis* diols to 1,2-*trans* diols. Regioselectivity in the reactions of vicinal diols have earlier been correlated with the strength of intramolecular hydrogen bonding in carbohydrate derivatives. Knapp and coworkers reported[12] the regioselective triflation of carbohydrate derived vicinal diols **319, 320, 371** and **372** (Scheme 2B.12) having hydroxyl groups in different relative orientations. Among the two vicinal hydroxyl groups, exclusive triflation took place regioselectively at the hydroxyl group which was *cis* to the vicinal ether oxygen (**319** and **320**). When both the hydroxyl groups were either *cis* or *trans* to the vicinal ether oxygen (**371** and **372**), then the triflation gave a mixture of products.



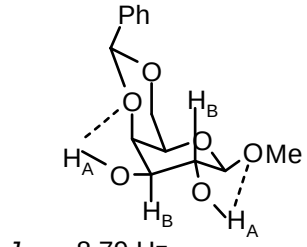
Scheme 2B.12. a) Tf_2O, Pyr, DCM, -20 ^oC. * Estimated by ^1H NMR specrtrpscopy

They also investigated hydrogen bonding interactions between the hydroxyl groups in compounds (**319, 320, 371** and **372**) subjected to triflation, by ^1H NMR spectroscopy (Chart 2B.1). The carbohydrate derived vicinal diols **319, 320, 371** and **372** with a neighbouring *cis* oxygen atom showed larger coupling constant (7-10 Hz, implying stronger hydrogen bond) than those that did not have a neighboring *cis* oxygen atom (coupling constant 1-3 Hz implying weaker hydrogen bond). Hence they were able to correlate the observed regioselectivity (for triflation) among the carbohydrate derived vicinal diols with the strength of the intramolecular hydrogen bonding interaction in carbohydrate derived diols **319, 320, 371** and **372**.



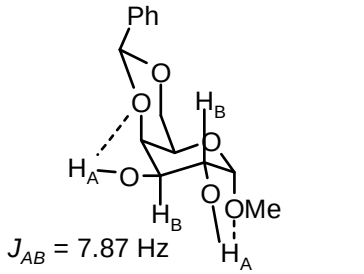
J_{AB} = 2.20 Hz J_{AB} = 9.52 Hz

319



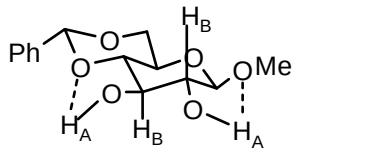
J_{AB} = 8.79 Hz J_{AB} = 1.52 Hz

320



J_{AB} = 7.87 Hz J_{AB} = 8.95 Hz

371



J_{AB} = 2.36 Hz J_{AB} = 2.25 Hz

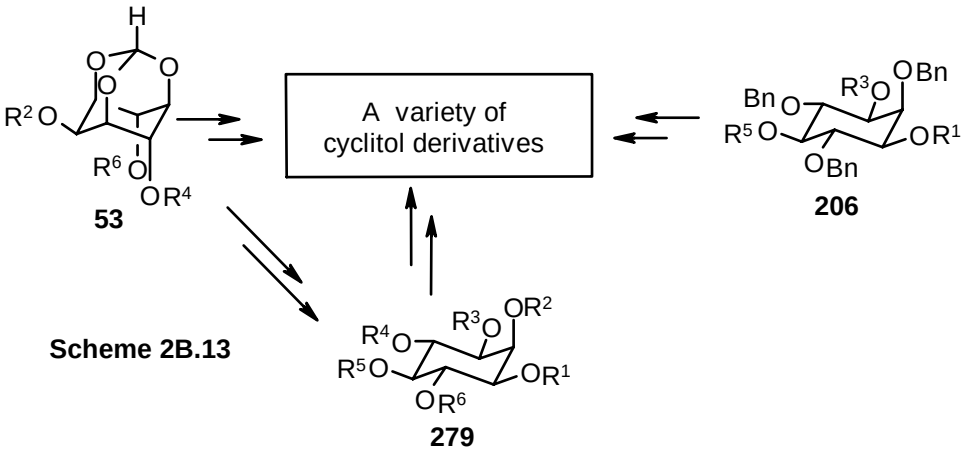
372

Chart 2B.1

A comparison of the regioselectivity observed in the reactions of *myo*-inositol orthoester derivatives (Section 2A) and the less rigid derivatives discussed in this section reveals that the orthoester derivatives exhibited better regioselectivity in their O-substitution reactions. This can again be explained based on the differences in the strength of chelation of lithium ions by 1,3-diaxial oxygen atoms (in *myo*-inositol orthoesters) as against 1,2-*cis* or 1,2-*trans* oxygen atoms in *myo*-inositol derivatives. Again, this correlates with the relative strength of the intramolecular hydrogen bonding between the 1,3-diaxial diol in *myo*-inositol orthoesters[11b,c] and the diols investigated in the present section.

2B.3. Conclusions

We have developed a method for the preferential O-substitution of hydroxyl groups that have an adjacent *cis* oxygen atom in *myo*-inositol derived triol and diols. This methodology has the potential to be useful for the selective derivatization of hydroxyl groups in polyols and their derivatives. We did not carry out acylation in the present study (Section B) due to the potential of hydroxyl esters to undergo inter or intra molecular acyl migration with ease,[13] which would hamper conclusions on the observed regioselectivity. The results described in this section in principle, should provide a convenient method for the preparation of *myo*-inositol derivatives carrying orthogonal protecting groups at C1-, C3- and C5-positions and hence allow their modification. The results presented in both the sections of this chapter provide convenient methods for the modification of all the six hydroxyl groups of *myo*-inositol and hence aid in the preparation of a variety of cyclitol derivatives (Scheme 2B.13).



Scheme 2B.13

2B.4. Experimental section

General: General experimental procedures are same as in section A of this chapter except for the following: A stock solution of n-butyllithium (0.82-1.62 M) in dry hexanes was prepared and used in all the experiments. *myo*-Inositol derivatives **60**,[2a,b] **76**,[1] **111**,[8] **307**,[8] **310**[3a] were prepared according to literature procedures. Compounds **284**, **285**, **290**, **291** were not characterized rigorously since they were not used further in any experiment.

General procedure for the O-alkylation and O-sulfonylation of *myo*-inositol derived triol and diols.

The required *myo*-inositol derived triol or diol (0.5-1 mmol) was dissolved in dry THF (3-6 mL) and cooled to 0 °C. n-Butyllithium (1.0-1.2 mmol) was added drop-wise using a syringe followed by a solution of the required alkyl halide or sulfonyl halide (1.2-1.5 mmol) in DMF (0.5-1 mL) at 0 ºC. The reaction mixture was stirred for 20-56 h at room temperature and worked up as usual with ethyl acetate. The products were separated by column chromatography using 10-20% ethyl acetate – light petroleum or light petroleum - DCM mixtures as eluents. In some experiments, the ratio of the mixture of ethers formed was estimated by ^{1}H NMR spectroscopy.

The same procedure was followed for the reactions where sodium hydride was used to generate the alkoxides, but the ratio of the products was estimated by ^{1}H NMR spectroscopy.

Racemic 1-*O*-allyl-2,4,6-tri-*O*-benzyl-*myo*-inositol (282).

The 1,3,5-triol **76** (0.450 g, 1 mmol) was allylated as in the general procedure (reaction time 28 h), using butyllithium (1.46 mL, 1.20 mmol) and allyl bromide (0.182 g, 1.50 mmol) to obtain the racemic 1-allyl ether **282** (0.351 g, 71%) as a gum and the diallyl ether **283** (0.089 g, 17%) as solid, after column chromatography.

Data For 282:

IR (ν, neat): 3196-3641 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 7.20-7.45 (m, 15H), 5.80-6.05 (m, 1H), 5.26-5.39 (m, 1H), 5.14-5.24 (m, 1H), 4.68-5.04 (m, 6H), 4.10-4.18 (m, 2H), 4.04 (t, 1H, J = 2.4 Hz), 3.85 (t, 1H, J = 9.4 Hz), 3.68 (t, 1H, J = 9.4 Hz), 3.51 (t, 2H, J = 9.0 Hz), 3.35 (dd, 1H, J = 2.4, 9.8 Hz), 2.52 (s, 1H, D_2O exchangeable), 3.33 (d, 1H, J = 5.9 Hz, D_2O exchangeable).

^{13}C NMR ($CDCl_3$): δ 134.6, 130.5, 124.3, 124.2, 123.9, 123.6, 123.5, 112.8, 73.5, 72.9, 72.3, 71.3, 70.8, 68.0, 67.3.

Elemental analysis calcd for $C_{30}H_{34}O_6$: C, 73.45; H, 6.99. Found: C, 73.07; H, 6.89.

Data for 283:

mp. 93-95 ºC.

^{1}H NMR ($CDCl_3$): δ 7.26-7.50 (m, 15H), 5.81-6.03 (m, 2H), 5.33-5.38 (m, 1H), 5.25-5.30 (m, 1H), 5.18-5.23 (m, 1H), 5.13-5.17 (m, 1H), 4.72-4.97 (m, 6H), 4.10 (dt, 4H, J = 1.5, 5.3 Hz), 4.02-4.06 (m, 1H), 3.82-3.95 (m, 2H), 3.42-3.55 (m, 1H), 3.25 (dd, 2H, J = 2.4, 9.7 Hz), 2.43-2.53 (broad s, 1H).

Racemic 1-*O*-allyl-2,4,6-tri-*O*-benzyl-3,5-di-*O*-acetyl-*myo*-inositol (284).

The racemic allyl ether **282** (0.030 g, 0.06 mmol) was acetylated using acetic anhydride (0.06 mL, 0.60 mmol) and pyridine (1 mL) overnight at room temperature. Usual work up of the reaction mixture with ethyl acetate gave the diacetate **284** (0.034 g, 98%) as a gum.

Data for 284:

IR (ν, $CHCl_3$): 1745 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 7.20-7.43 (m, 15H), 5.81-6.03 (m, 1H), 5.26-5.31 (m, 1H), 5.16-5.26 (m, 1H), 5.09 (t, 1H, J = 9.6 Hz), 4.81-4.93 (m, 2H), 4.74 (dd, 1H, J = 2.5, 10.2

Hz), 4.52-4.70 (m, 4H), 4.15 (dt, 2H, J = 1.4, 5.5 Hz), 4.05-4.11 (m, 1H), 3.88-4.03 (m, 2H), 3.48 (dd, 1H, J = 2.2, 9.8 Hz), 1.93 (s, 3H), 1.85 (s, 3H).

1,3,5-tri-*O*-acetyl-2,4,6-tri-*O*-benzyl-*myo*-inositol (285).

The 1,3,5-triol **76** (0.050 g, 0.11 mmol) was acetylated using acetic anhydride (0.3 mL, 3.30 mmol) and pyridine (1 mL) overnight at room temperature. Usual work up of the reaction mixture with ethyl acetate gave the triacetate **285** (0.063 g, 98%).

Data for 285:

mp. 117-119 ºC.

IR (ν, $CHCl_3$): 1749 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 7.19-7.44 (m, 15H), 5.19 (t, 1H, J = 9.6 Hz), 4.94 (dd, 2H, J = 2.5, 10.2 Hz), 4.53-4.71 (m, 6H), 4.11 (t, 1H, J = 2.5 Hz), 4.03 (t, 2H, J = 10 Hz), 1.94 (s, 6H), 1.87 (s, 3H).

Racemic 1-*O*-allyl-2,4,6-tri-*O*-benzyl-3-*O*-(*p*-toluenesulfonyl)-*myo*-inositol (288).

The racemic allyl ether **282** (0.254 g, 0.52 mmol) was sulfonylated as in the general procedure (reaction time 15 h), using butyllithium (0.76 mL, 0.62 mmol) and *p*-toluenesulfonyl chloride (0.148 g, 0.78 mmol) to obtain the racemic 3-tosylate **288** (0.179 g, 53%) as a gum, after column chromatography.

Data for 288:

IR (ν, neat): 3216-3630 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 7.73 (d, 2H, J = 8 Hz), 7.05-7.48 (m, 17H), 5.75-6.01 (m, 1H), 5.24-5.37 (m, 1H), 5.13-5.23 (m, 1H), 4.66-4.96 (m, 4H), 4.55 (AB q, 2H, J = 11.4 Hz), 4.37 (dd, 1H, J = 2.3, 10.2 Hz), 4.25 (t, 1H, J = 2.4 Hz), 4.08 (dt, 2H, J = 1.5, 5.5 Hz), 3.84 (AB q, 2H, J = 9.3 Hz), 3.44 (t, 1H, J = 9.4 Hz), 3.32 (dd, 1H, J = 2.3, 9.8 Hz), 2.43 (s, 1H, D_2O exchangeable), 2.34 (s, 3H).

^{13}C NMR ($CDCl_3$): δ 141.3, 136.3, 135.1, 131.1, 130.4, 126.3, 125.0, 124.8, 124.4, 124.2, 124.1, 113.5, 75.3, 74.0, 73.6, 73.3, 73.2, 71.9, 71.8, 71.6, 71.3, 68.1, 18.1.

Elemental analysis calcd for $C_{37}H_{40}O_8S.2.3H_2O$: C, 64.76; H, 6.55. Found: C, 64.38; H, 6.07.

Racemic 1-*O*-allyl-2,4,6-tri-*O*-benzyl-3-*O*-(*p*-toluenesulfonyl)-5-*O*-acetyl-*myo*-inositol (289).

The racemic 3-tosylate **288** (0.020 g, 0.03 mmol) was acetylated using acetic anhydride (0.04 mL, 0.46 mmol) and pyridine (0.7 mL) overnight at room temperature. Usual work up of the reaction mixture with ethyl acetate gave the acetate **289** (0.021 g, 99%) as gum.

Data for 289:

IR (ν, neat): 3193-3520, 1747 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, 2H, J = 8.4 Hz), 7.02-7.54 (m, 17H), 5.82-6.01 (m, 1H), 5.29-5.41 (m, 1H), 5.19-5.28 (m, 1H), 4.80-5.06 (m, 4H), 4.56-4.65 (m, 1H), 4.32-4.46 (m, 4H), 4.14 (dt, 2H, J = 1.5, 5.5 Hz), 3.93 (AB q, 2H, J = 9.9 Hz), 3.44 (dd, 1H, J = 2.2, 9.6 Hz), 2.34 (s, 3H), 1.75 (s, 3H).

Elemental analysis calcd for $C_{39}H_{42}O_9S.H_2O$: C, 66.46; H, 6.29. Found: C, 66.78; H, 6.04.

Reaction of 2,4,6-tri-*O*-benzyl-*myo*-inositol (76) with sodium hydride / allyl bromide.

The 1,3,5-triol **76** (0.100 g, 0.22 mmol) was allylated as in the general procedure (reaction time 2 h), using sodium hydride (0.011 g, 0.27 mmol) and allyl bromide (0.040 g, 0.33 mmol) to obtain a mixture of allyl ethers. This mixture was acetylated using acetic anhydride (0.3 mL) and pyridine (0.6 mL) overnight at room temperature. The mixture of acetates **284** and **287** was obtained (0.121 g) after usual work up with

ethyl acetate. Ratio of the peak integrals at 1.93 and 1.85 in ^{1}H NMR spectrum showed that the isomers **284** and **287** were present in the ratio 50:50.

Racemic 1,2:4,5-di-*O*-isopropylidene-3-*O*-benzyl-*myo*-inositol (154).

The racemic 1,4-diol **60** (0.260 g, 1 mmol) was benzylated as in the general procedure (reaction time 38 h) using butyllithium (1.34 mL, 1.10 mmol) and benzyl bromide (0.205 g, 1.20 mmol) to obtain the racemic 3-benzyl ether **154** (0.292 g, 83%) and the dibenzyl ether **156** (0.038 g, 9%), after column chromatography.

mp. (for **154)** 159-161 ºC (Lit.[2c] mp. 162-163 °C).

mp. (for **156)** 146-148 ºC (Lit.[2c] mp. 150-153 °C).

Racemic 1,2:4,5-di-*O*-isopropylidene-3-*O*-benzyl-6-*O*-acetyl-*myo*-inositol (290).

The racemic benzyl ether **154** (0.020 g, 0.06 mmol) was acetylated using acetic anhydride (0.03 mL, 0.30 mmol) and pyridine (0.7 mL) at room temperature (12 h). The acetate **290** (0.022 g, 98%) was obtained after usual work up with ethyl acetate.

Data for 290:

mp. 170-172 ºC (Lit.[14] mp. 183-185 °C).

^{1}H NMR ($CDCl_3$): δ 7.20-7.55 (m, 5H), 5.27 (dd, 1H, J = 6.8, 11.2 Hz), 4.86 (AB q, 2H, J = 12.2 Hz), 4.30 (t, 1H, J = 4.4 Hz), 4.15 (t, 1H, J = 9.3 Hz), 4.02 (dd, 1H, J = 4.8, 7.3 Hz), 3.78 (dd, 1H, J = 4.4, 10.3 Hz), 3.34 (dd, 1H, J = 9.3, 11.2 Hz), 2.12 (s, 3H), 1.60 (s, 3H), 1.49 (s, 3H), 1.44 (s, 3H), 1.34 (s, 3H).

Racemic 1,2:4,5-di-*O*-isopropylidene-3-*O*-(*p*-toluenesulfonyl)-*myo*-inositol (161).

The racemic 1,4-diol **60** (0.261 g, 1 mmol) was sulfonylated as in the general procedure (reaction time 2 h) using butyllithium (1.34 mL, 1.10 mmol) and *p*-toluenesulfonyl chloride (0.209 g, 1.10 mmol). The tosylate **161** (0.283 g, 68%) was isolated as white solid by column chromatography using DCM as eluent. Since spectral data for the tosyl derivative **161** is not reported in the literature,[4] we have characterised **161** completely.

Data for 161:

mp. 164-165 ºC (lit.[4] mp. 170-173 ºC).

IR (ν, nujol): 3539 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 7.86 (d, 2H, J = 8.1 Hz), 7.33 (d, 2H, J = 8.1 Hz), 4.81 (dd, 1H, J = 4.3, 10.3 Hz), 4.41 (t, 1H, J = 4.4Hz), 3.92-4.05 (m, 2H), 3.85 (dd, 1H, J = 6.6, 10.3 Hz), 3.29 (t, 1H, J = 9.5 Hz), 2.59 (broad s, 1H, D_2O exchangeable), 2.44 (s, 3H), 1.50 (s, 3H), 1.36 (s, 3H), 1.31 (s, 3H), 1.22 (s, 3H).

^{13}C NMR ($CDCl_3$): δ 145.7, 134.1, 130.0, 128.4, 113.1, 110.8, 82.2, 78.4, 77.6, 76.0, 74.7, 74.3, 28.0, 26.8, 26.7, 25.8, 21.7.

Elemental analysis calcd for $C_{19}H_{26}O_8S$: C, 55.06; H, 6.32. Found: C, 55.06; H, 6.26.

Racemic 1,2:4,5-di-*O*-isopropylidene-3-*O*-(*p*-toluenesulfonyl)-6-*O*-acetyl-*myo*-inositol (291).

The racemic tosylate **161** (0.030 g, 0.07 mmol) was acetylated using acetic anhydride (0.07 mL, 0.72 mmol) and pyridine (0.8 mL) at room temperature (12 h). The acetate **291** (0.031 g, 94%) was obtained after usual work up with ethyl acetate.

Data for 291:

mp. 214-216 ºC.

IR (ν, nujol): 1747 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 7.85 (d, 2H, J = 8.3 Hz), 7.32 (d, 2H, J = 8.0 Hz), 5.22 (dd, 1H, J = 6.8, 11.1 Hz), 4.83 (dd, 1H, J = 4.2, 10.4 Hz), 4.42 (t, 1H, J = 4.5 Hz), 4.11 (dd, 1H, J = 2.5, 4.7 Hz), 4.04-4.07 (m, 1H), 3.36 (dd, 1H, J = 9.4, 11.2 Hz), 2.44 (s, 3H), 2.11 (s, 3H), 1.55 (s, 3H), 1.35 (s, 3H), 1.29 (s, 3H), 1.21 (s, 3H).

Racemic 1,6-*O*-isopropylidene-2,4,5-tri-*O*-benzyl-*myo*-inositol (293).

The racemic tribenzyl triol **292** (2.00 g, 4.44 mmol), 2,2-dimethoxypropane (1.3 mL, 10.21 mmol) and CSA (0.516 g, 0.22 mmol) were refluxed in DCM (60 mL) for 3 h.

The resulting solution was cooled to room temperature and neutralized with triethyl amine. Solvents were evaporated and the solid obtained was purified by column chromatography to obtain the racemic isopropylidene derivative **293** (1.784 g, 75%).

Data for 293:

mp. 78-80 °C

IR (ν, nujol): 3115-3489 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 7.20-7.45 (m, 15H), 4.60-5.10 (m, 6H), 4.15-4.30 (m, 2H), 3.56-3.74 (m, 3H), 3.49 (dd, 1H, J = 2, 10 Hz), 2.40-2.50 (broad s, 1H, D_2O exchangeable), 1.49 (s, 3H), 1.47 (s, 3H).

^{13}C NMR ($CDCl_3$): δ 138.6, 138.5, 138.0, 128.4, 128.3, 128.2, 128.0, 127.8, 127.6, 127.4, 111.8, 84.0, 80.2, 77.8, 76.9, 75.9, 74.4, 74.2, 73.5, 72.9, 27.1, 26.7.

Elemental analysis calcd for $C_{30}H_{34}O_6.1.2\ H_2O$: C, 70.34; H, 7.16. Found: C, 70.03; H, 7.33.

Racemic 2,3,4,5-tetra-*O*-benzyl-*myo*-inositol (295).

To a solution of the racemic ketal **293** (1.500 g, 3.06 mmol) in DMF (15 mL) sodium hydride (0.184 g, 4.59 mmol) was added and stirred for 20 min. The reaction mixture was cooled to 0 °C and benzyl bromide (1.047 g, 6.12 mmol) was added drop-wise and the mixture stirred for 1h. The reaction was quenched by the addition of ice and worked up as usual with ethyl acetate. The crude product obtained (1.020 g) was dissolved in DCM (16 mL) and methanol (8 mL) and stirred with conc HCl (0.25 mL) for 4 h. Triethylamine was added to the reaction mixture and the solvents were evaporated under reduced pressure. The solid residue was purified by column chromatography to get the racemic 1,6-diol **295** (0.761 g, 74%) as a white solid.

Data for 295:

mp. 167-169 °C (lit.[6a] mp. 162-164 ºC).

^{1}H NMR ($CDCl_3$): δ 7.20-7.40 (m, 20H), 4.63-5.10 (m, 8H), 3.96-4.10 (m, 2H), 3.76-3.91 (m, 1H), 3.48 (dd, 1H, J = 2, 10 Hz), 3.25-3.39 (m, 2H), 2.47 (broad s, 1H, D_2O exchangeable), 2.30 (d, 1H, J = 8 Hz, D_2O exchangeable).

Elemental analysis calcd for $C_{34}H_{36}O_6$: C, 75.53; H, 6.71. Found: C, 75.55; H, 6.59.

Reaction of racemic 2,3,4,5-tetra-*O*-benzyl-*myo*-inositol (295) with butyllithium / allyl bromide.

To a solution of the racemic diol **295** (0.280 g, 0.52 mmol) in THF (3 mL) at 0 °C butyllithium (0.41 mL, 0.57 mmol) followed by a solution of allyl bromide (0.082 g, 0.68 mmol) in DMF (0.8 mL) were added and the mixture stirred for 56 h. The reaction mixture was worked up with ethyl acetate. The mixture of monoethers **298** and **299** (0.194 g, 67%) was separated by column chromatography using 10% ethyl acetate – light petroleum as eluent. This mixture (0.194 g) was acetylated using acetic anhydride (0.6 mL) in pyridine (2 mL) overnight at room temperature. Usual work up of the reaction mixture with ethyl acetate gave a mixture of acetates **300** and **301** (0.203 g). Ratio of the peak integrals at 1.95 and 2.02 in the ^{1}H NMR spectrum showed that the isomers **300** and **301** were present in the ratio 80:20.

Reaction of racemic 2,3,4,5-tetra-*O*-benzyl-*myo*-inositol (295) with sodium hydride / allyl bromide.

A solution of the racemic diol **295** (0.100 g, 0.19 mmol) in THF (1 mL) was cooled to 0 °C, sodium hydride (0.008 g, 0.21 mmol) and a solution of allyl bromide (0.030 g, 0.25 mmol) in DMF (0.3 mL) were added and stirred at room temperature for 56 h. The reaction mixture was worked up with ethyl acetate and the mixture of monoethers (**298** and **299**, 0.083 g, 75%) was separated by column chromatography using 10% ethyl acetate - light petroleum as eluent. The mixture of monoethers (0.083 g) was acetylated using acetic anhydride (0.2 mL) and pyridine (1 mL) at room temperature

overnight. Usual work up of the reaction mixture with ethyl acetate gave the mixture of acetates (**300** and **301**, 0.086 g). Ratio of the peak integrals at 1.95 and 2.02 in its ^{1}H NMR spectrum showed that the isomers **300** and **301** were present in the ratio 66:33.

Benzylation of racemic 3,4,5,6-tetra-*O*-benzyl-*myo*-inositol (111) with butyllithium / benzyl bromide.

Procedure A. The racemic diol **111** (0.200 g, 0.37 mmol) was benzylated as in the general procedure (reaction time 26 h, -78 ºC), using butyllithium (0.23 mL, 0.37 mmol) and benzyl bromide (0.076 g, 0.44 mmol) to obtain a mixture of pentabenzyl ethers **303** and **304** (0.161 g, 69%) and the hexaether **302** (0.048 g, 18%). The mixture of pentaethers (0.040 g) was acetylated using acetic anhydride (0.03 mL) and pyridine (1 mL) overnight at room temperature. Usual work up of the reaction mixture with ethyl acetate gave a mixture of acetates **307** and **308** (0.041 g). Ratio of the peak integrals at 2.16 and 1.91 in its ^{1}H NMR spectrum showed that the isomers **307** and **308** were present in the ratio 45:55.

Data for 302:

mp. 110-112 °C (lit.[8] mp. 109-110 °C).

^{1}H NMR ($CDCl_3$): δ 7.12-7.39 (m, 30H), 4.70-4.90 (m, 8H), 4.56 (AB q, 4H, J = 11.7 Hz), 3.92-4.09 (m, 3H), 3.41 (t, 1H, J = 9.3 Hz), 3.29 (dd, 2H, J = 2.4, 9.7 Hz).

Procedure B. The racemic diol **111** (0.100 g, 0.19 mmol) was benzylated as in the general procedure (reaction time 26 h, 0 ºC-rt), using butyllithium (0.12 mL, 0.20 mmol) and benzyl bromide (0.076 g, 0.44 mmol) to obtain the mixture of pentabenzyl ethers **303** and **304** (0.084 g, 70%) and the hexaether **302** (0.020 g, 15%). The mixture of pentaethers (0.050 g) was acetylated using acetic anhydride (0.04 mL) and pyridine (1 mL) overnight at room temperature. Usual work up of the reaction

mixture with ethyl acetate gave a mixture of acetates **307** and **308** (0.053 g). Ratio of the peak integrals at 2.17 and 1.92 in its ^{1}H NMR spectrum showed that the isomers **307** and **308** were present in the ratio 52:48.

Procedure C. The racemic diol **111** (0.200 g, 0.37 mmol) was benzylated as in the general procedure (reaction time 26 h at reflux ~76 °C), using butyllithium (0.45 mL, 0.37 mmol, added at 0 °C) and benzyl bromide (0.076 g, 0.44 mmol, added at reflux temperature) to obtain a mixture of pentabenzyl ethers **303** and **304** (0.172 g, 74%) and the hexaether **302** (0.051 g, 19%). The mixture of pentaethers (0.100 g) was acetylated using acetic anhydride (0.15 mL) and pyridine (2 mL) overnight at room temperature. Usual work up of the reaction mixture with ethyl acetate gave a mixture of acetates **307** and **308** (0.103 g). Ratio of the peak integrals at 2.16 and 1.91 in its ^{1}H NMR spectrum showed that the isomers **307** and **308** were present in the ratio71:29.

Benzylation of racemic 3,4,5,6-tetra-*O*-benzyl-*myo*-inositol (111) with sodium hydride / benzyl bromide.

Procedure B. The racemic diol **111** (0.200 g, 0.37 mmol) was benzylated as in the general procedure (reaction time 26 h, 0 ºC), using sodium hydride (0.015 g, 0.37 mmol) and benzyl bromide (0.076 g, 0.44 mmol) to obtain the mixture of pentabenzyl ethers **303** and **304** (0.177 g, 76%) and the hexaether **302** (0.058 g, 22%). The mixture of pentaethers (0.100 g) was acetylated using acetic anhydride (0.15 mL) and pyridine (2 mL) overnight at room temperature. Usual work up of the reaction mixture with ethyl acetate gave the mixture of acetates **307** and **308** (0.105 g). Ratio of the peak integrals at 2.16 and 1.91 in its ^{1}H NMR spectrum showed that the isomers **307** and **308** were present in the ratio 64:36.

Allylation of racemic 3,4,5,6-tetra-*O*-benzyl-*myo*-inositol (111) with butyllithium / allyl bromide.

Procedure B. The racemic diol **111** (0.150 g, 0.28 mmol) was allylated as in the general procedure (reaction time 20 h, 0 ºC), using butyllithium (0.19 mL, 0.28 mmol) and allyl bromide (0.044 g, 0.36 mmol) to obtain a mixture of allyl ethers **305** and **306** (0.107 g, 66%). The mixture of allyl ethers (0.032 g) was acetylated using acetic anhydride (0.03 ml) and pyridine (1 mL) overnight at room temperature. Usual work up of the reaction mixture with ethyl acetate gave a mixture of acetates **309** and **310** (0.034 g). Ratio of the peak integrals at 2.15 and 2.01 in its ^{1}H NMR spectrum showed that the isomers **309** and **310** were present in the ratio 67:33.

Reaction of racemic 1,2-*O*-isopropylidene-3,6-di-*O*-benzyl-*myo*-inositol (311) with butyllithium / allyl bromide.

The racemic diol **311** (0.200 g, 0.50 mmol) was allylated as in the general procedure (reaction time 52 h, 0 ºC), using butyllithium (0.67 mL, 0.55 mmol) and allyl bromide (0.091 g, 0.75 mmol) to obtain a mixture of mono allyl ethers **312** and **313** (0.166 g, 76%). The mixture of monoallyl ethers (0.166 g) was acetylated using acetic anhydride (0.4 mL) and pyridine (3 mL) overnight at room temperature. Usual work up of the reaction mixture with ethyl acetate gave a mixture of acetates **314** and **315** (0.181 g). Ratio of the peak integrals at 2.06 and 2.04 in its ^{1}H NMR spectrum showed that the isomers **314** and **315** were present in the ratio 50:50.

2B.5. References

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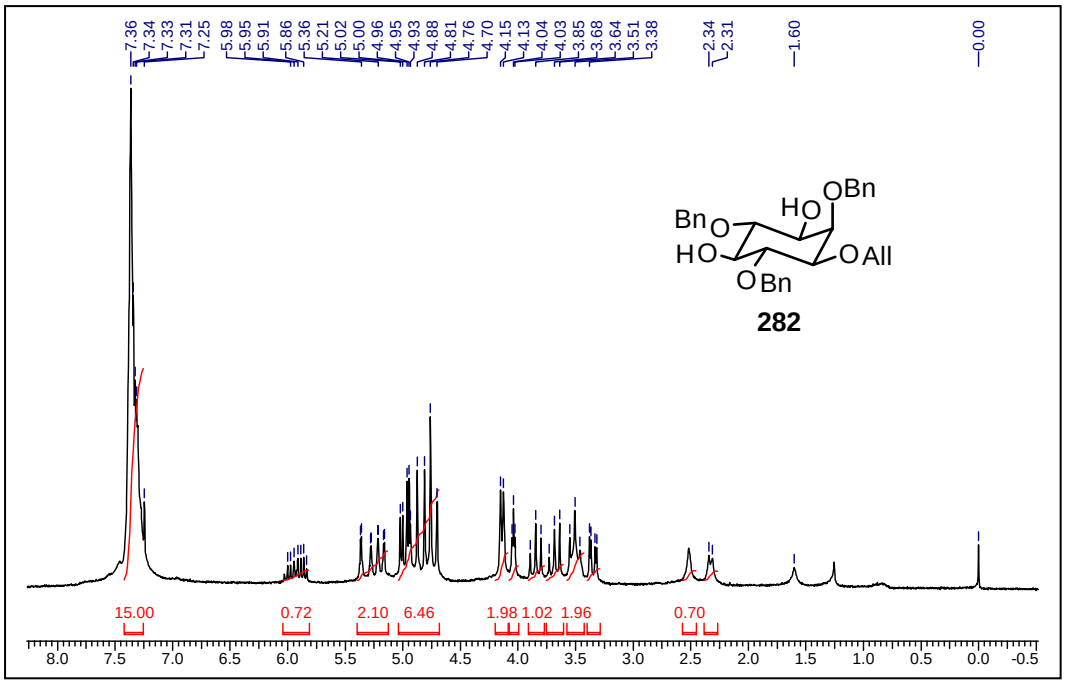
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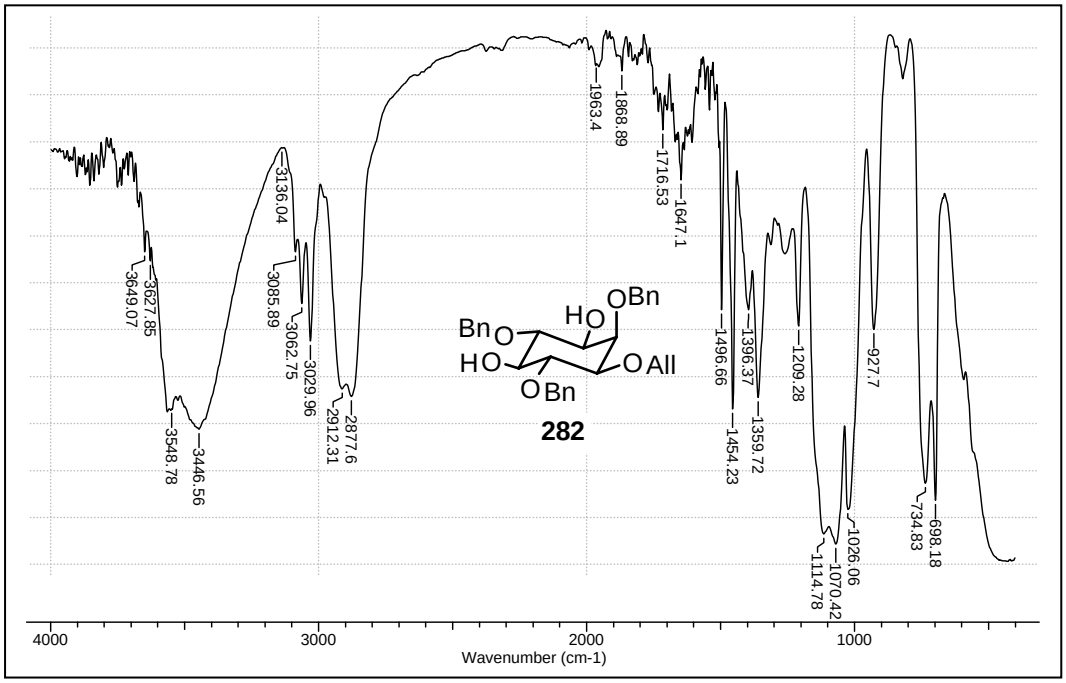
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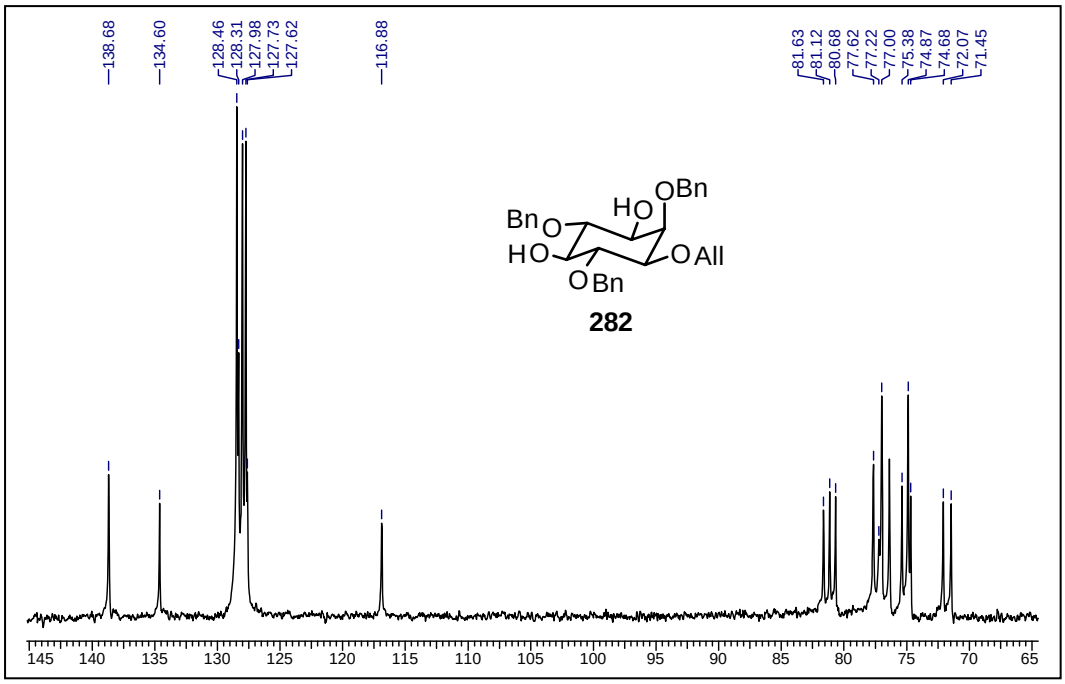
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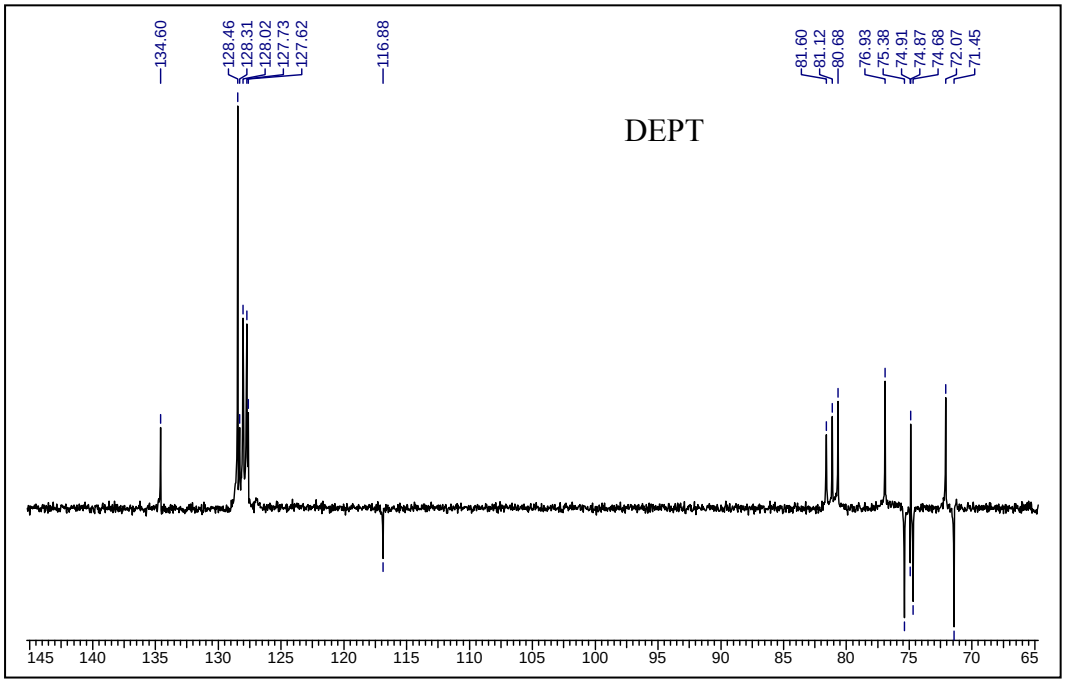
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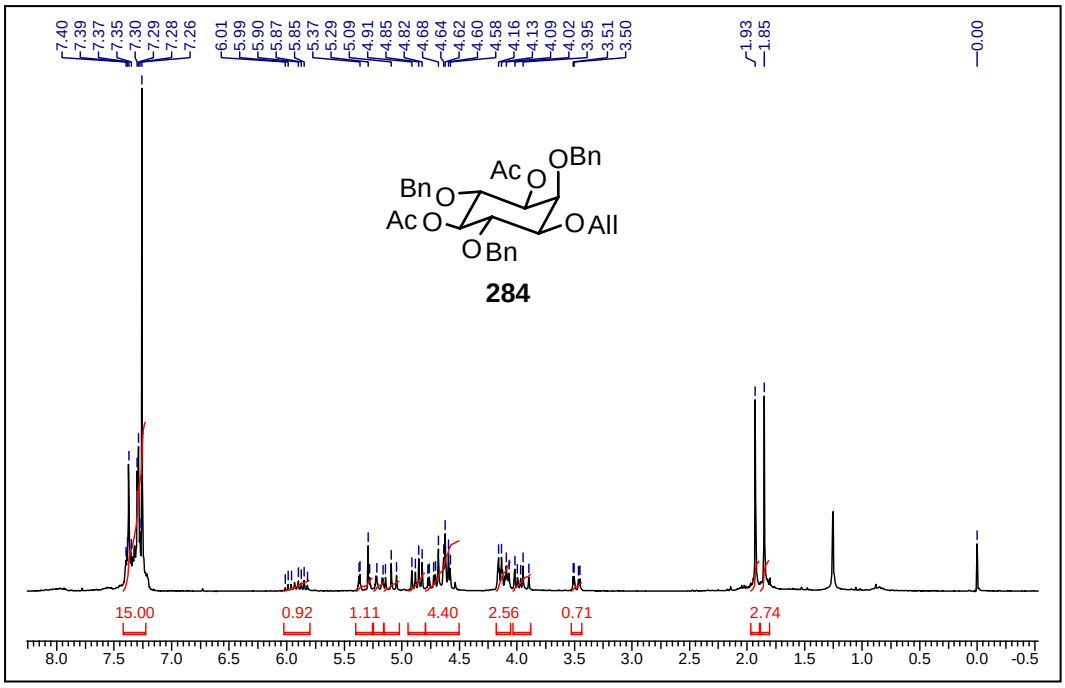
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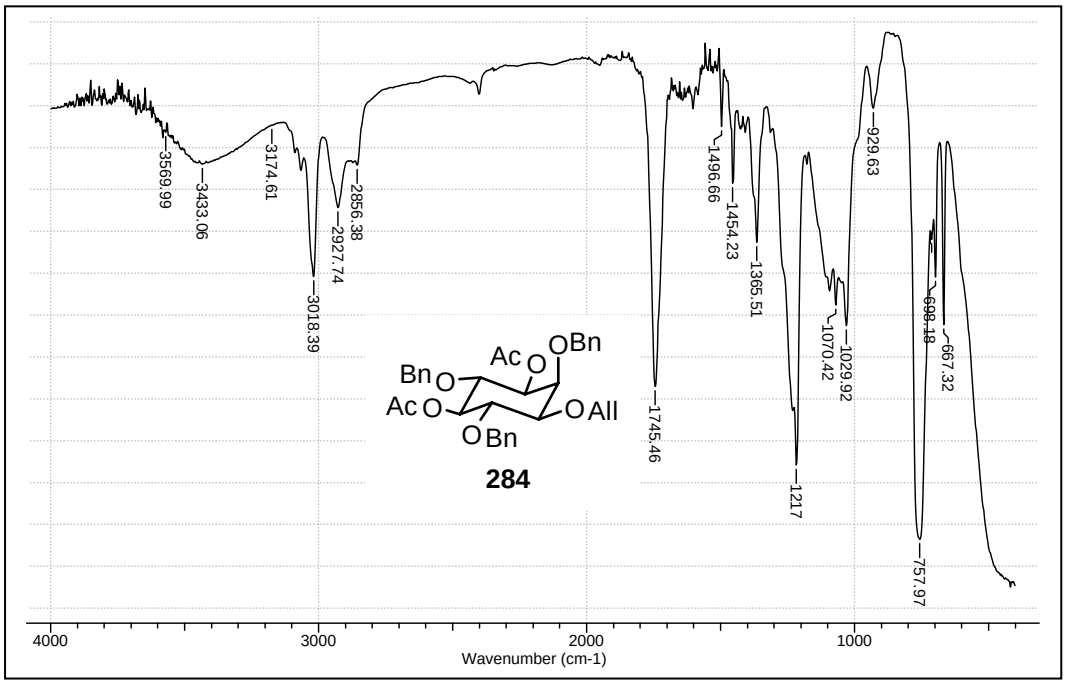
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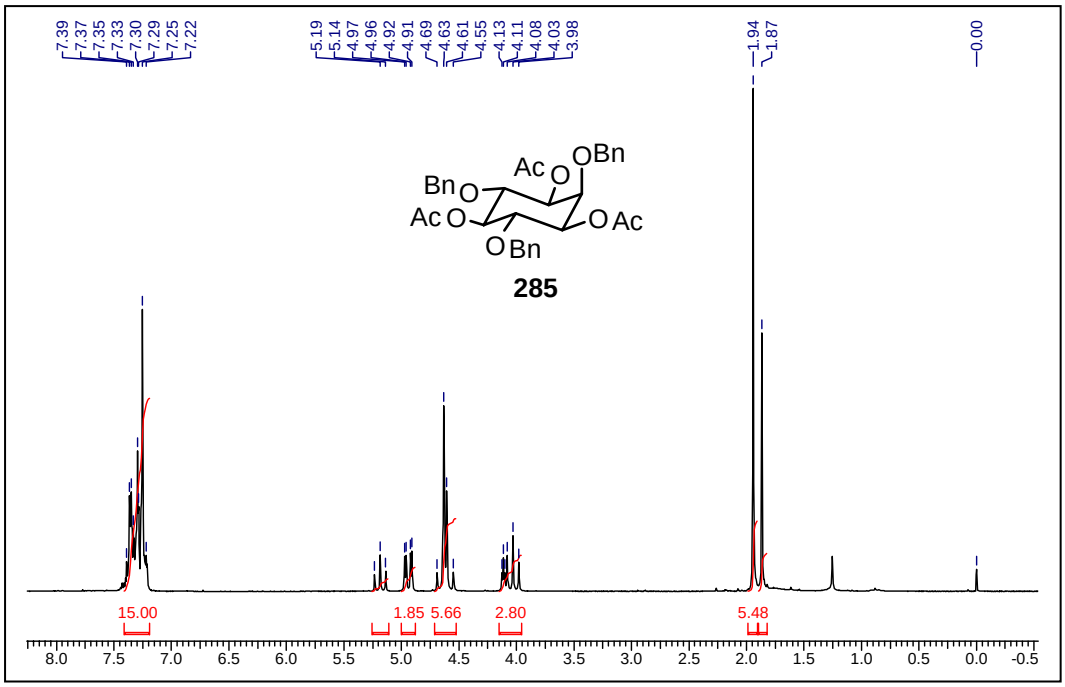
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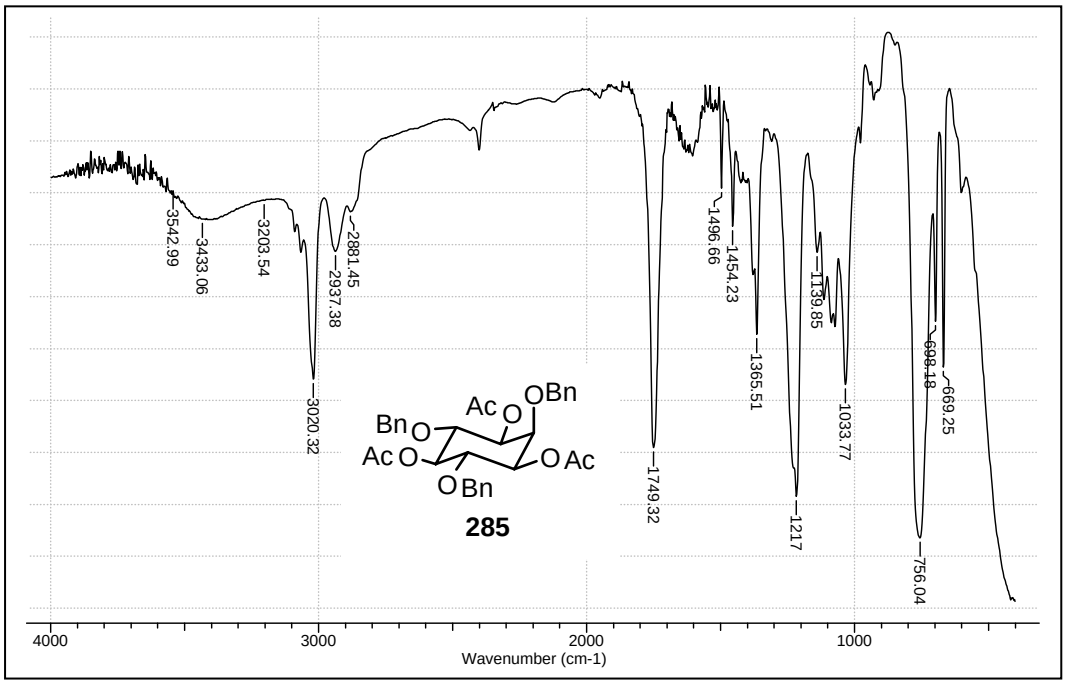
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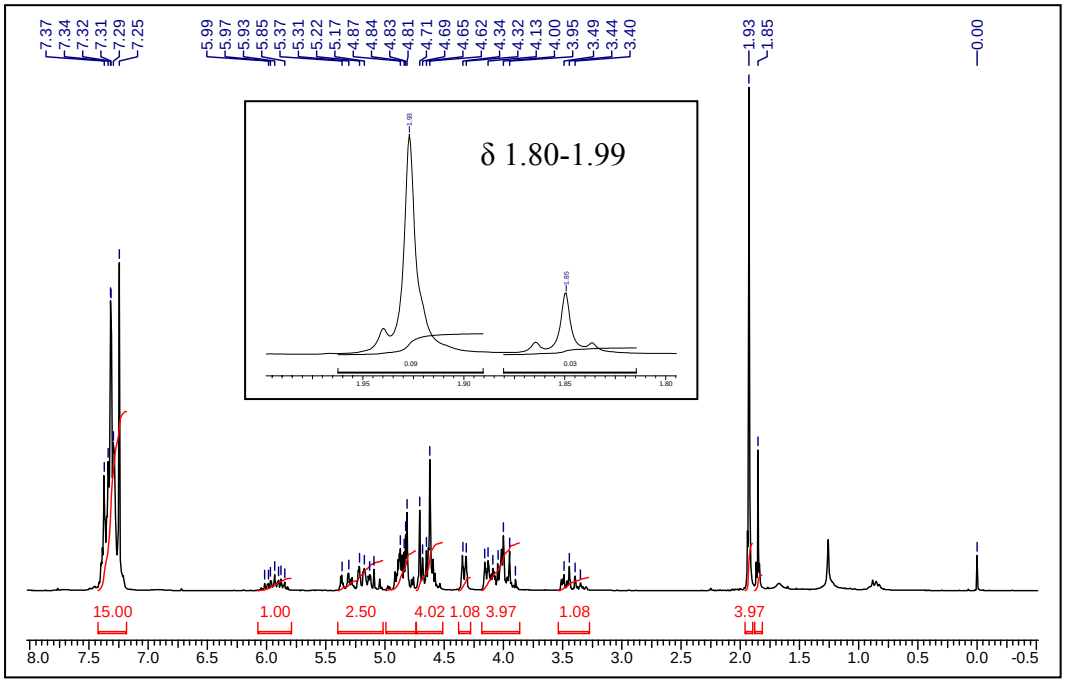
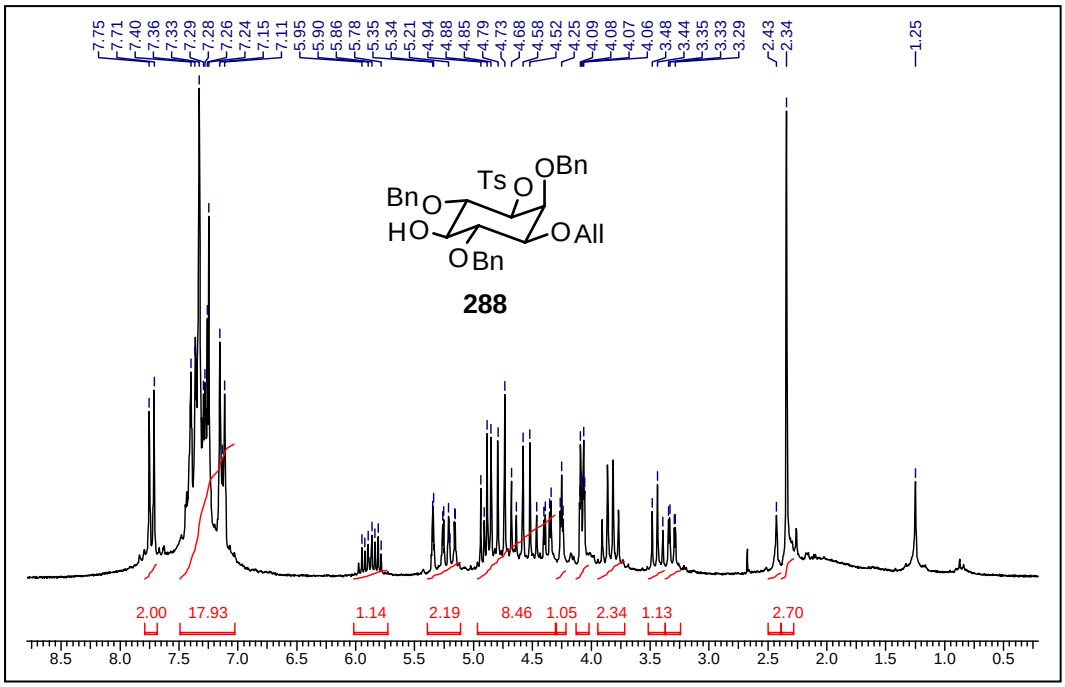
^{1}H NMR spectrum for the acetylated mixture of products **284** and **287** obtained on allylation of the triol **76** with sodium hydride / allyl bromide at 0 ºC**.**

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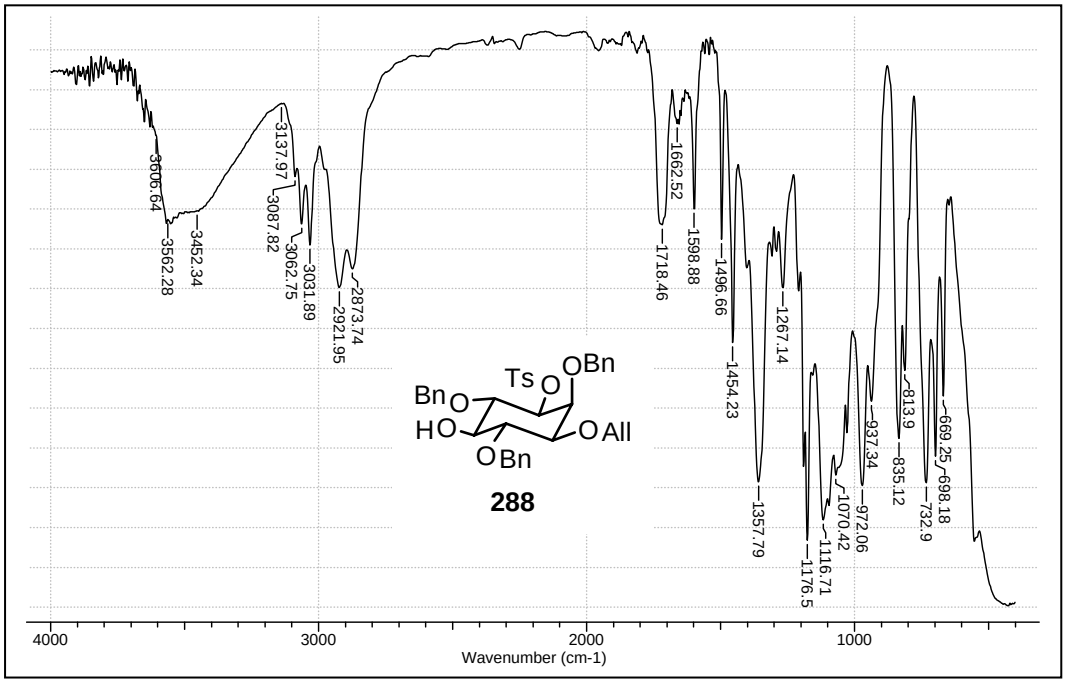
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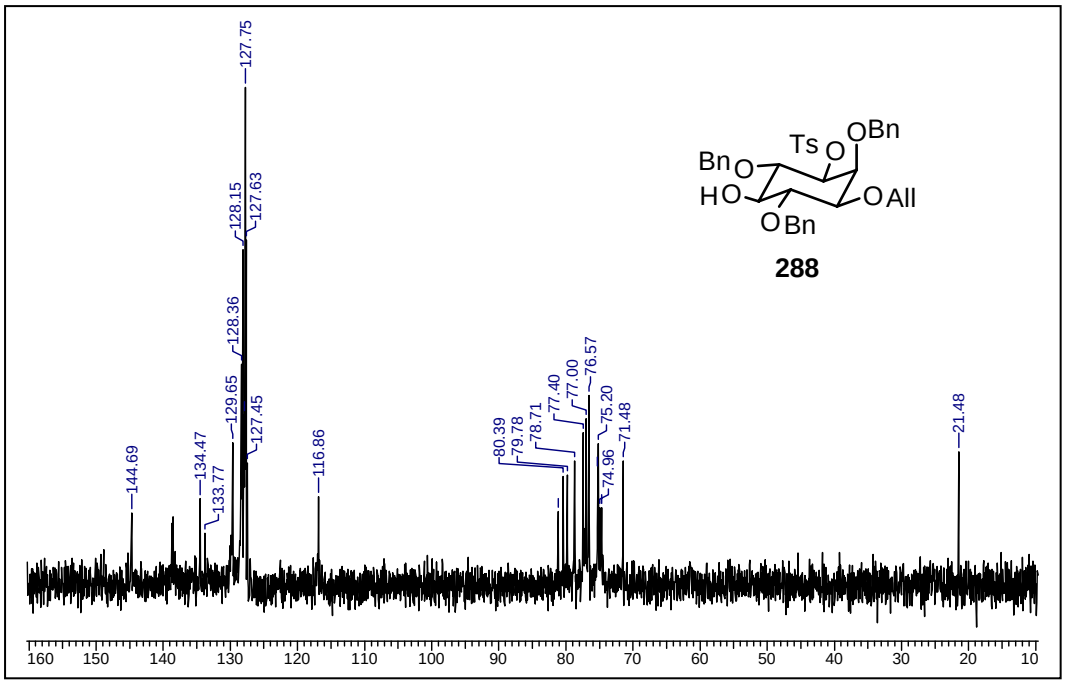
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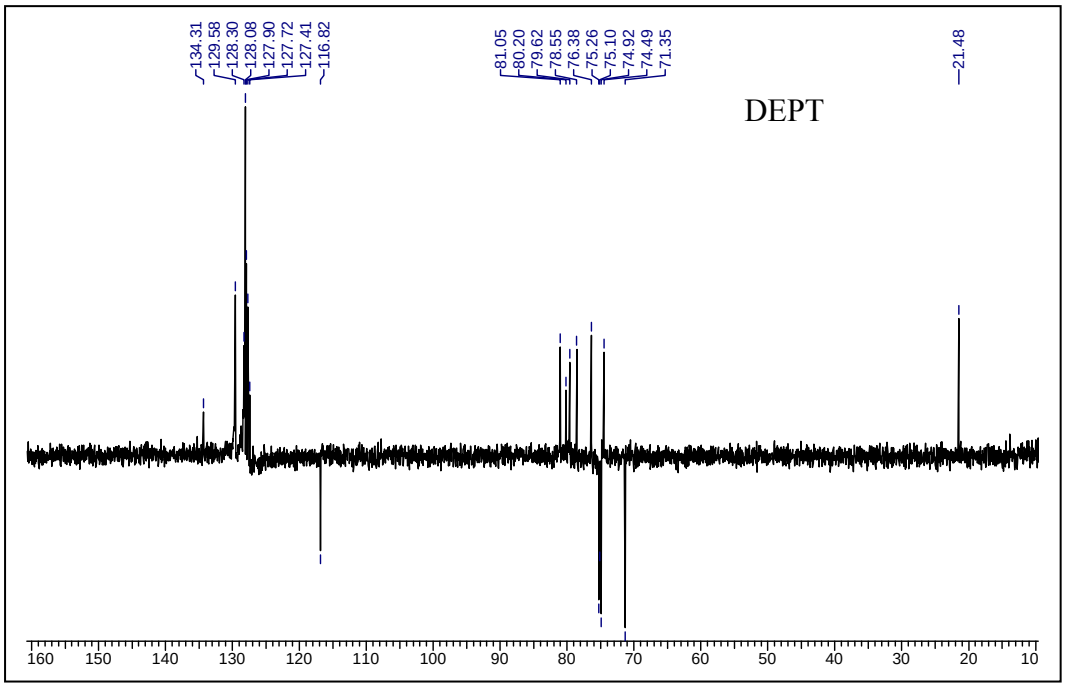
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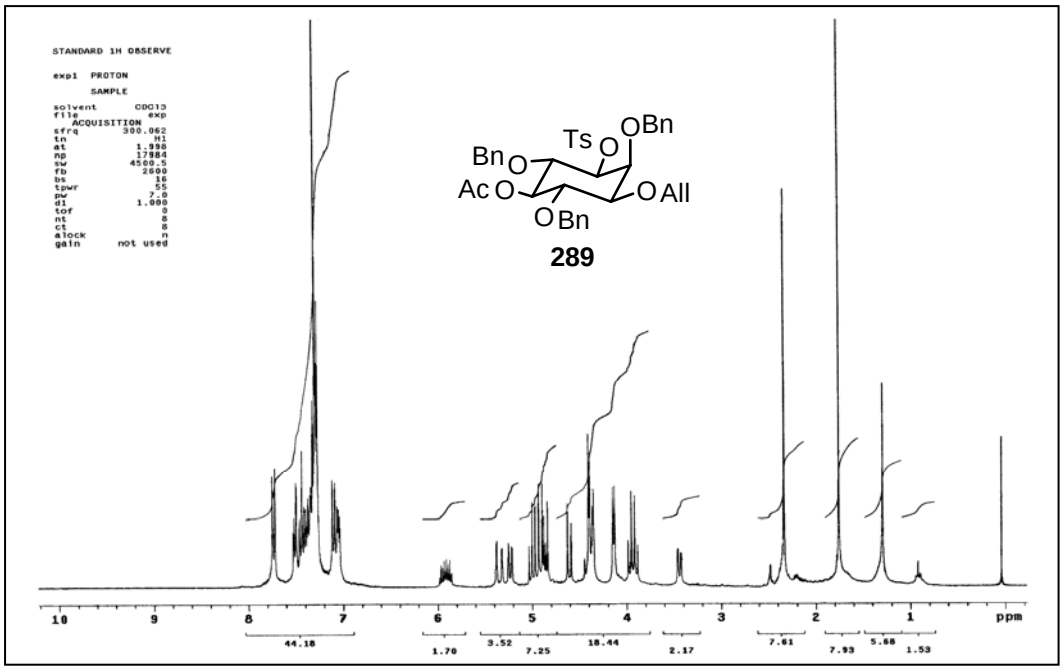
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ct 8
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gain not used
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O All
O Bn
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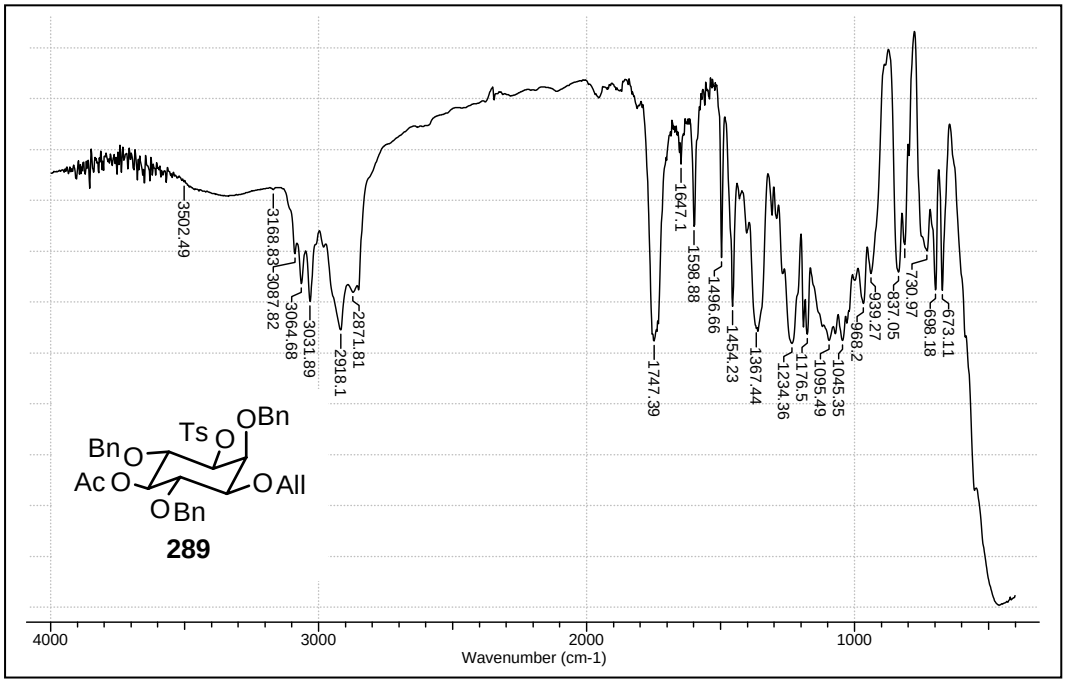
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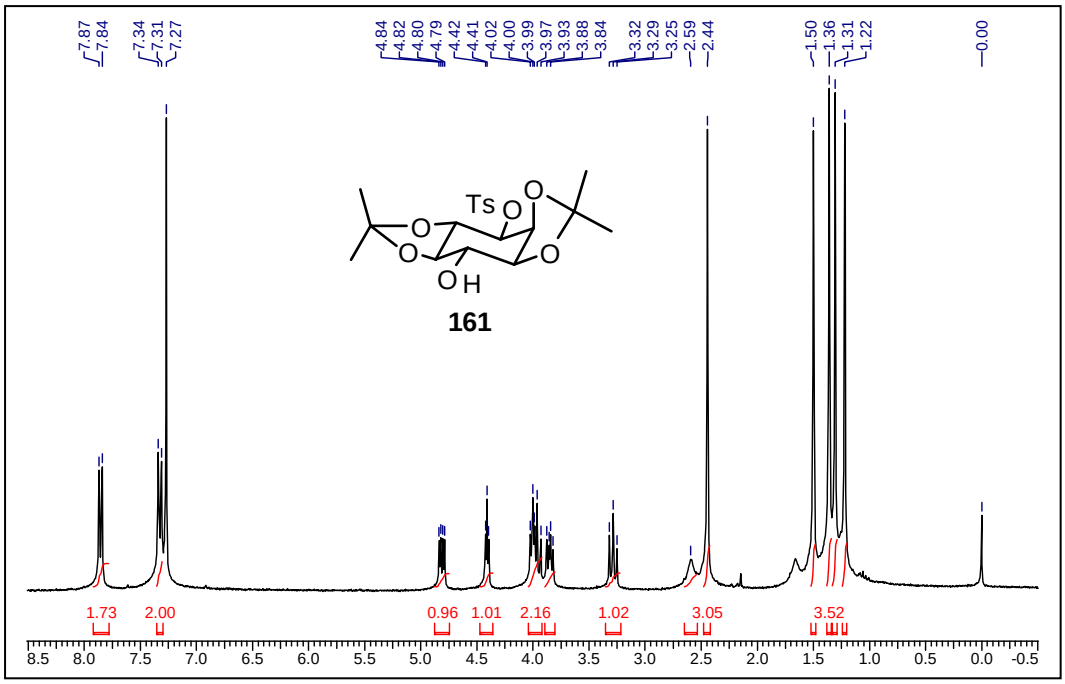
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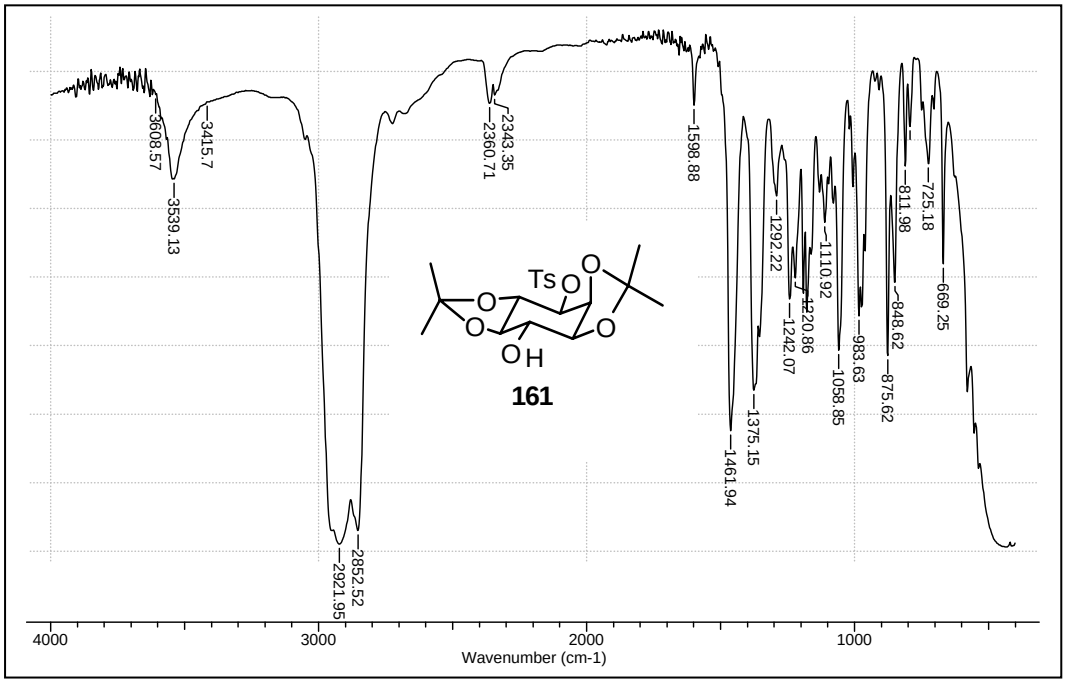
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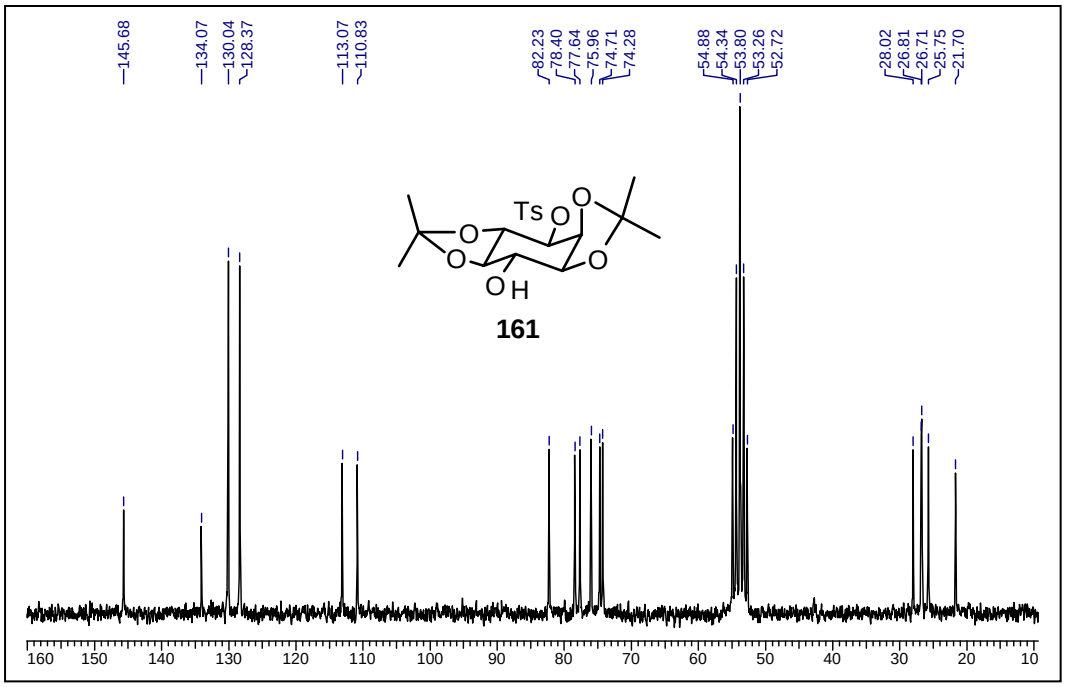
Wavenumber (cm-1)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26.71
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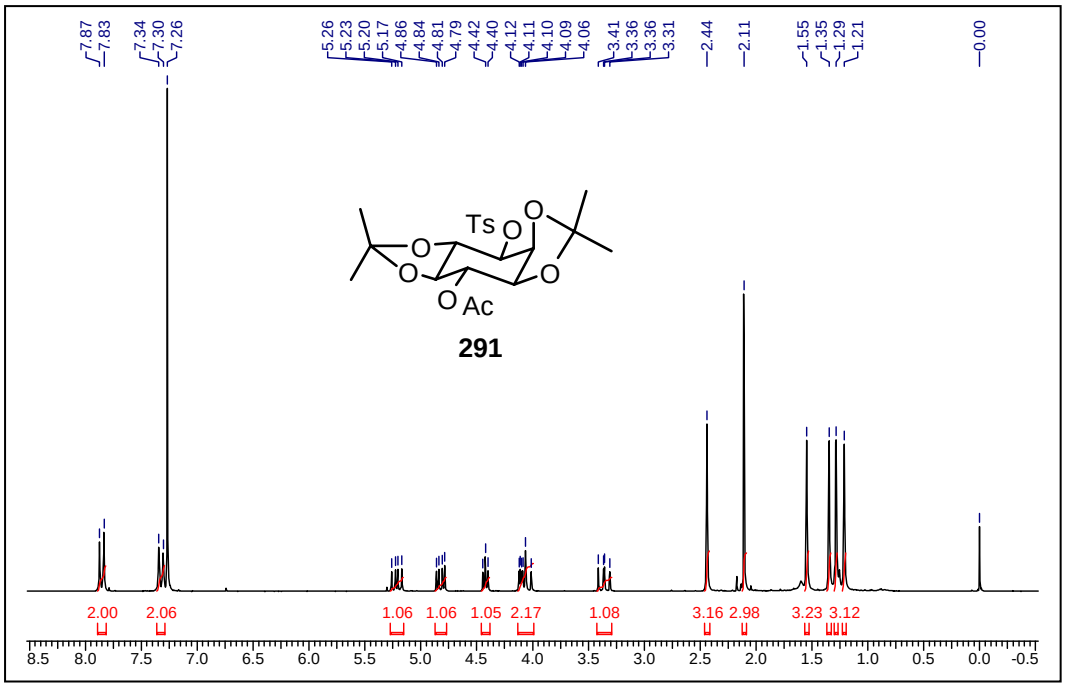
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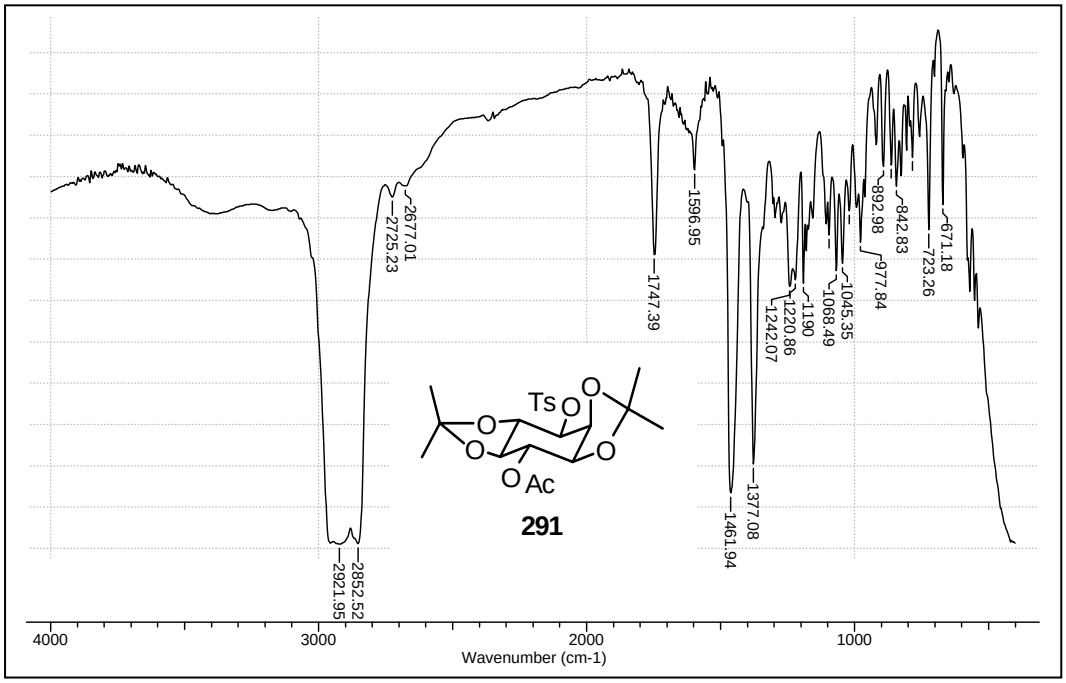
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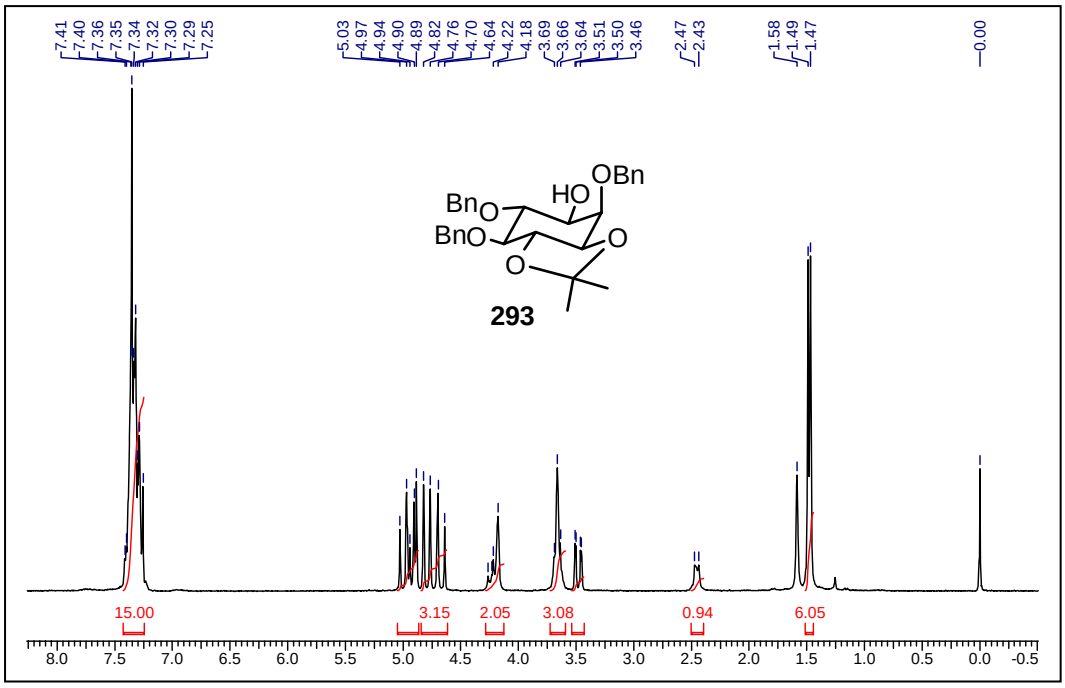
Wavenumber (cm-1)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BnO
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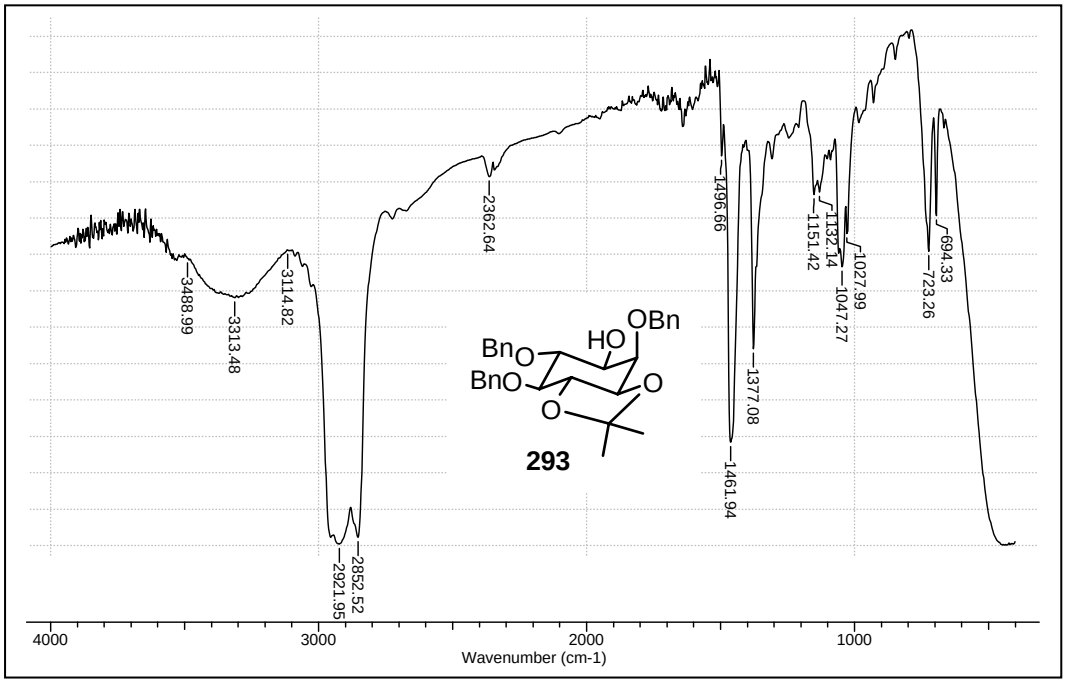
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2000
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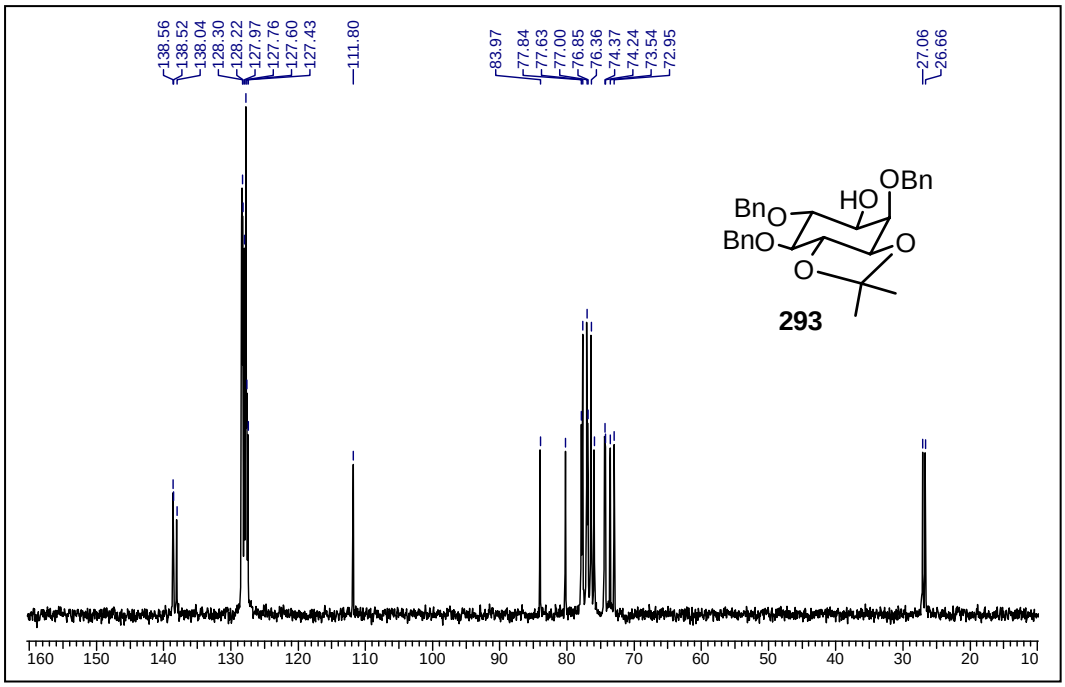
Wavenumber (cm-1)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73.54
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BnO
O
O
293
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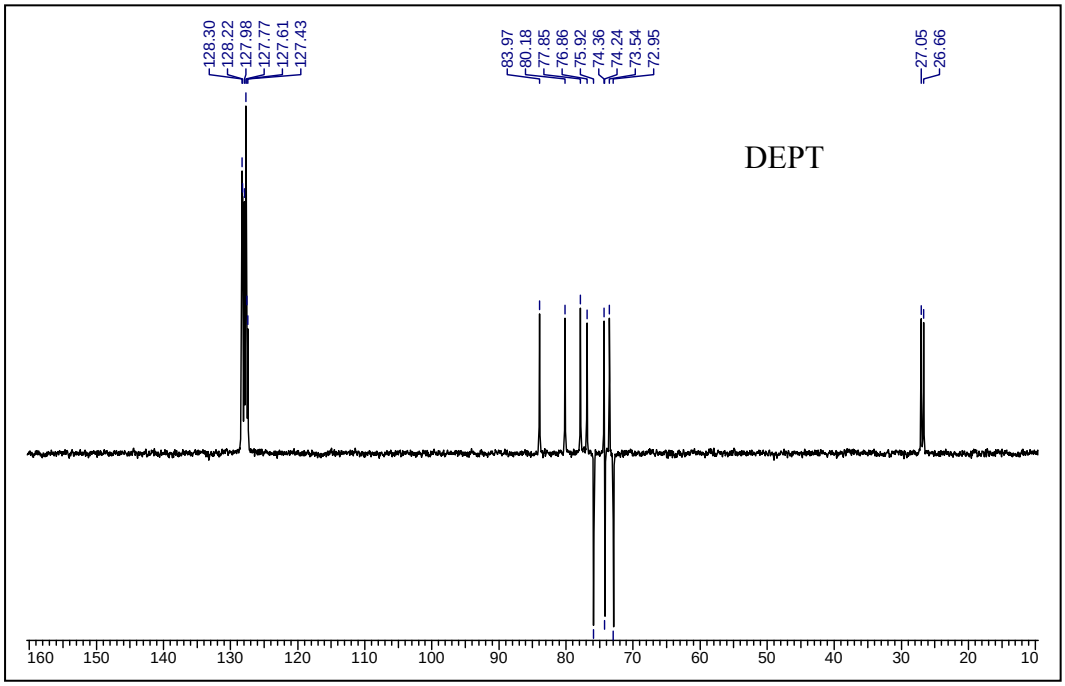
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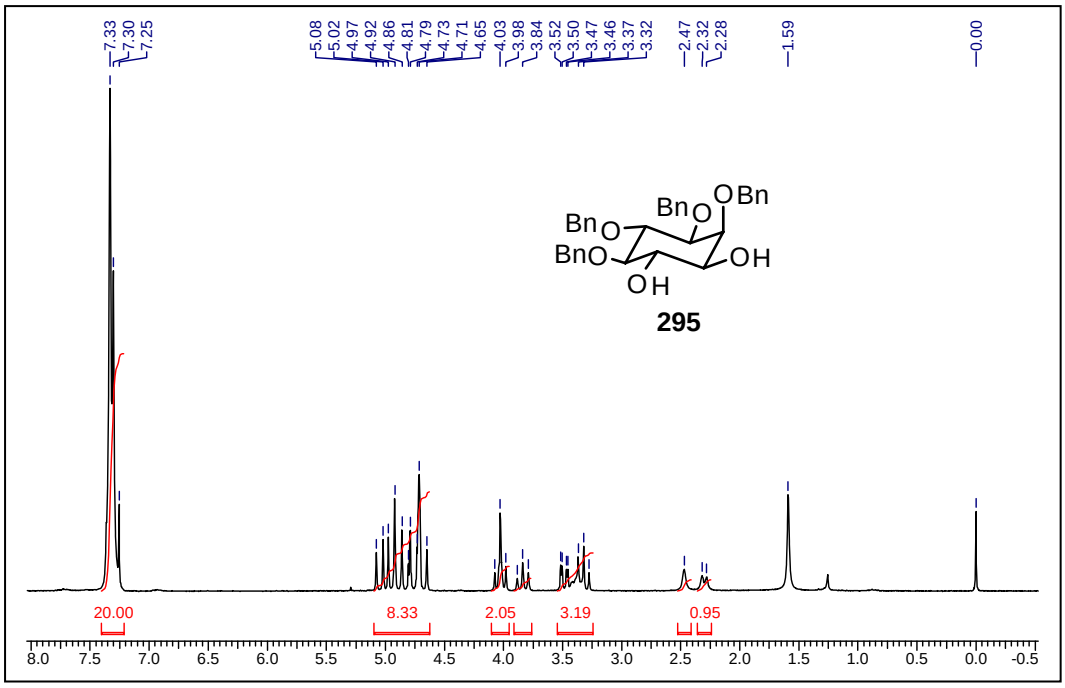
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3.37
3.32
2.47
2.32
2.28
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2.05
3.19
0.95
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
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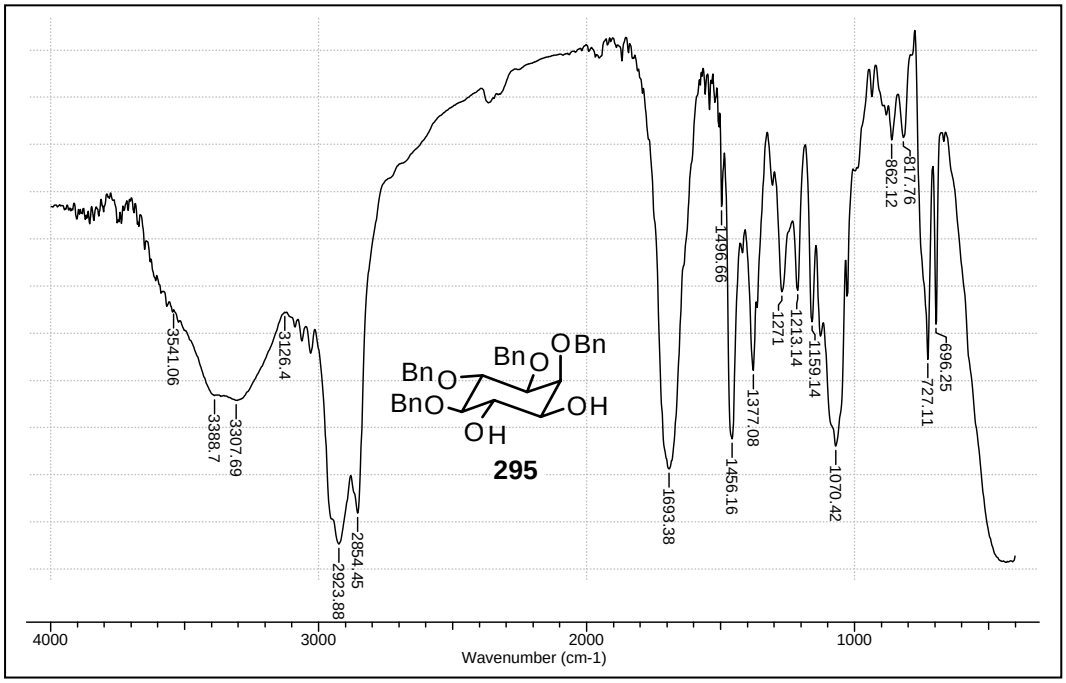
Bn O
BnO
OH
O H
295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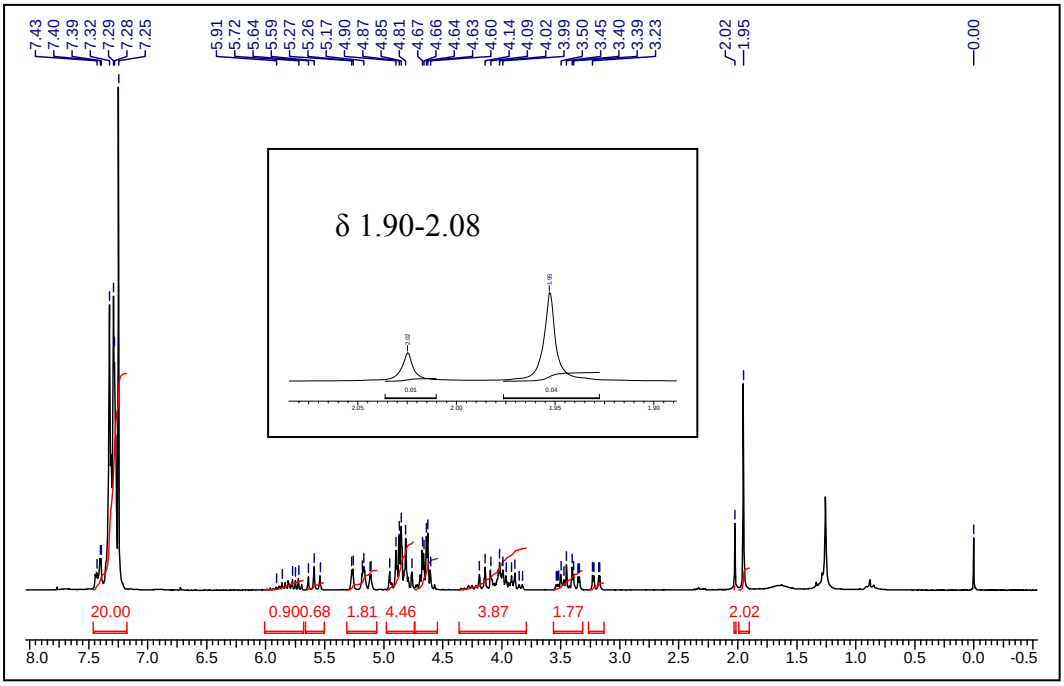
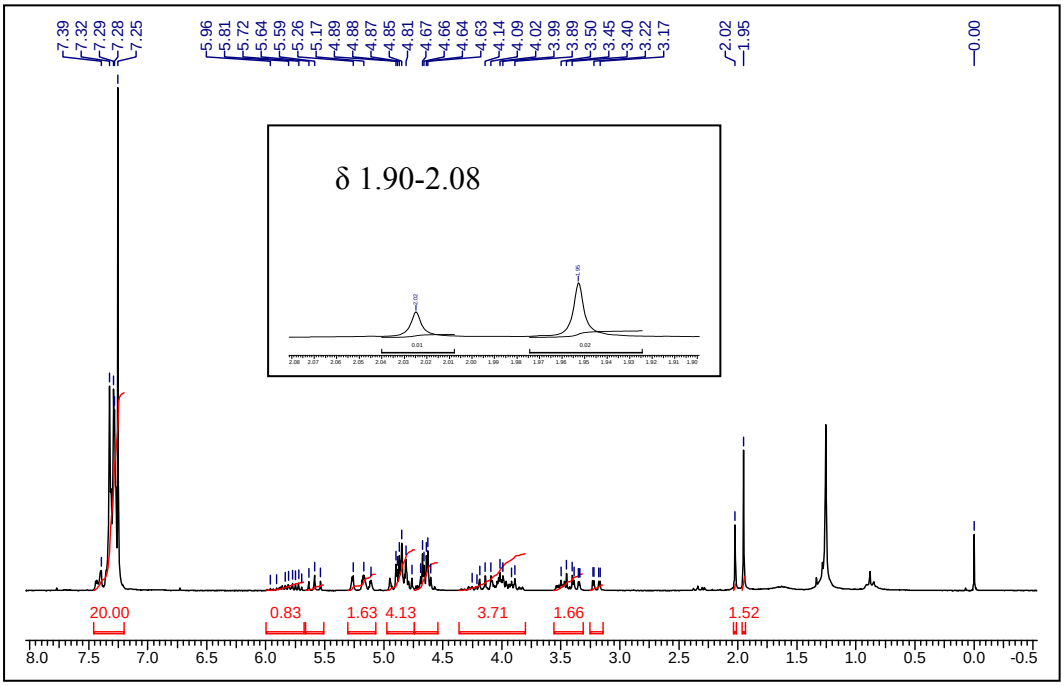
1159.14
1070.42
862.12
817.76
727.11
696.25
4000
3000
2000
1000
Wavenumber (cm-1)
Bn O OBn
Bn O
BnO
OH
O H
295

^{1}H NMR spectrum for the acetylated mixture of products **300** and **301** obtained on allylation of the racemic diol **295** with butyllithium / allyl bromide at 0 ºC**.**

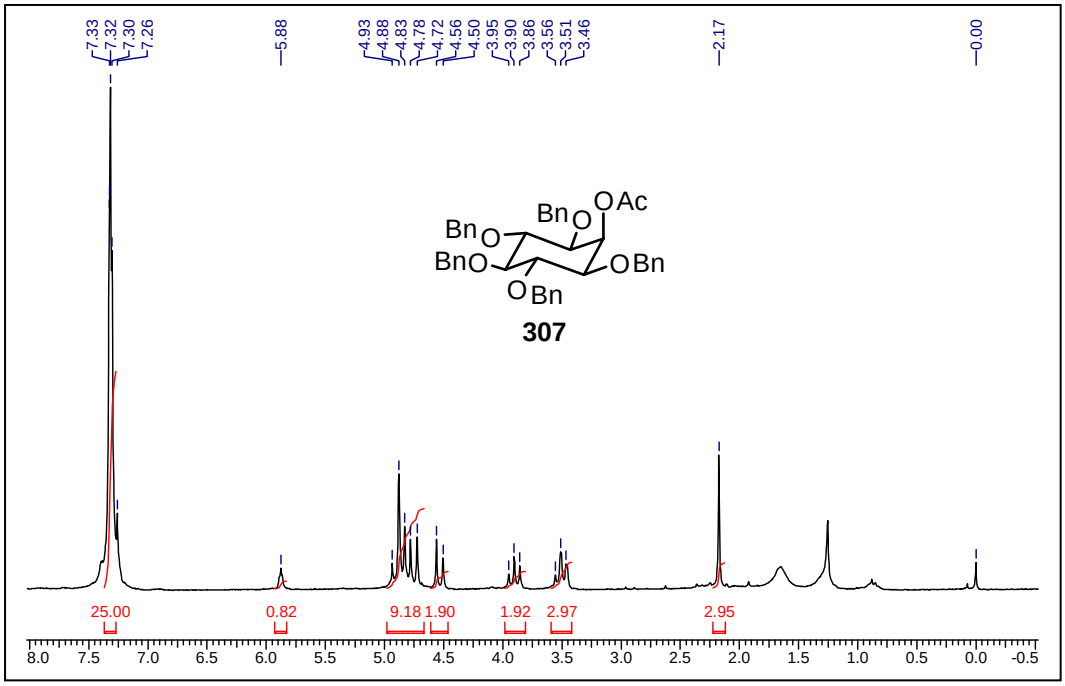


^{1}H NMR spectrum for the acetylated mixture of products **300** and **301** obtained on allylation of the racemic diol **295** with sodium hydride / allyl bromide at 0 ºC**.**



Crystal Data Table for **304**

Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P21/c
Unit cell dimensions	a = 5.968(2) Å alpha = 90° b = 19.946(8) Å beta = 92.375(10)° c = 28.736(10) Å gamma = 90°
Volume	3418(2) $Å^3$
Z, Calculated density	4, 1.226 Mg/m^3
Absorption coefficient	0.081 mm^{-1}
Crystal size	0.242 x 0.202 x 0.070 mm
Theta range for data collection	1.24 to 25.00 deg.
Reflections collected / unique	32577 / 6014 [R(int) = 0.0808]
Completeness to theta = 25.00	100.0 %
Refinement method	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.021
Final R indices [I>2sigma(I)]	R1 = 0.0625, wR2 = 0.1556
R indices (all data)	R1 = 0.1218, wR2 = 0.1849
Largest diff. peak and hole	0.263 and -0.192 e. $Å^{-3}$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3.56
3.51
3.46
2.17
0.00
Bn
O
OAc
BnO
OBn
OBn
307
25.00
0.82
9.18
1.90
1.92
2.97
2.95
8.0
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6.0
5.5
5.0
4.5
4.0
3.5
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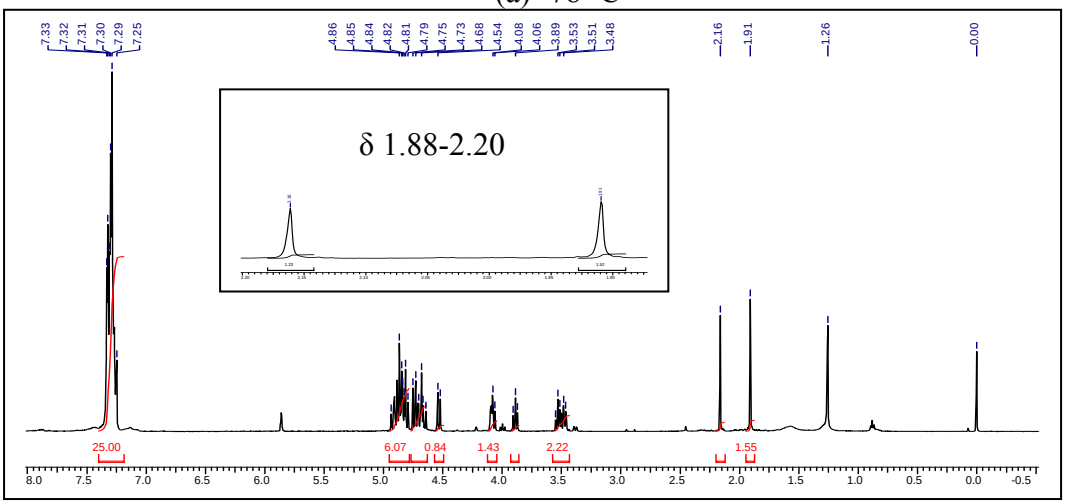
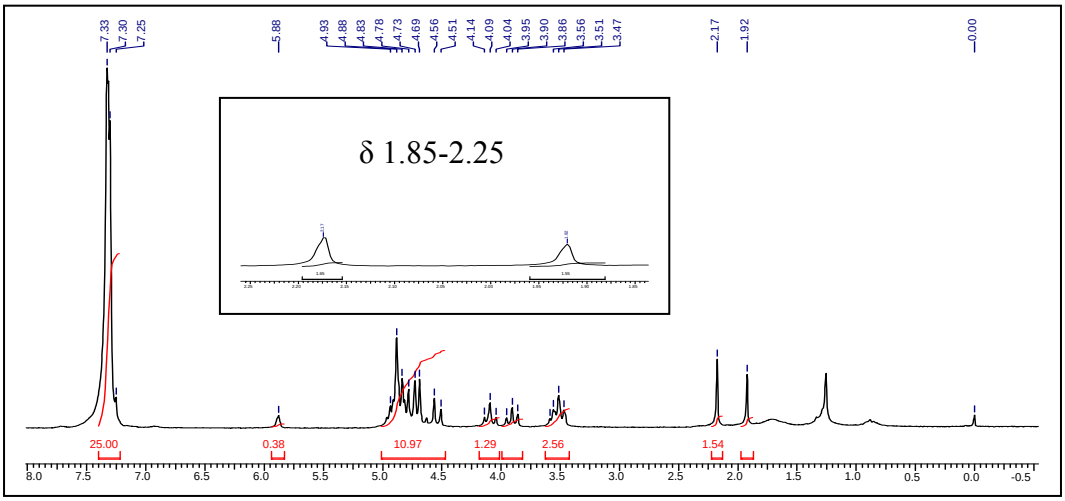
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

^{1}H NMR spectra for the acetylated mixture of products **307** and **308** obtained on benzylation of the racemic diol **111** with butyllithium / benzyl bromide.

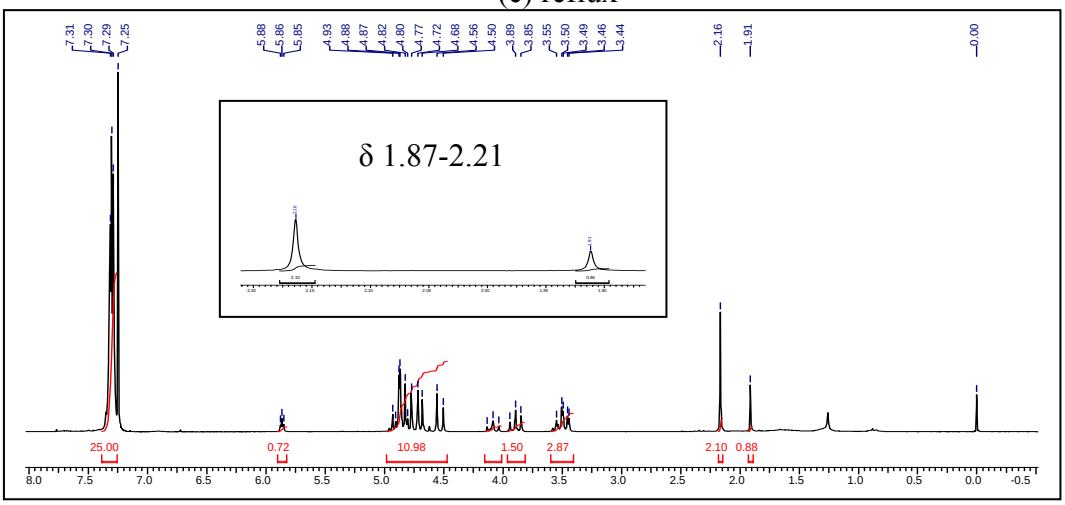
(a) -78 ºC



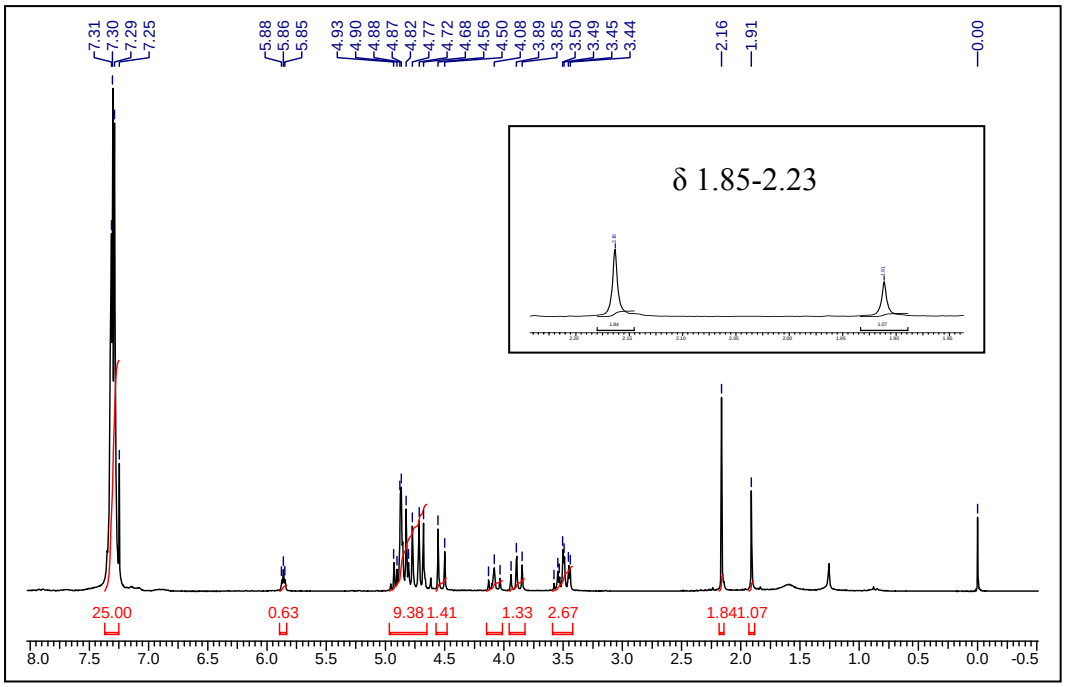
(b) 0 ºC



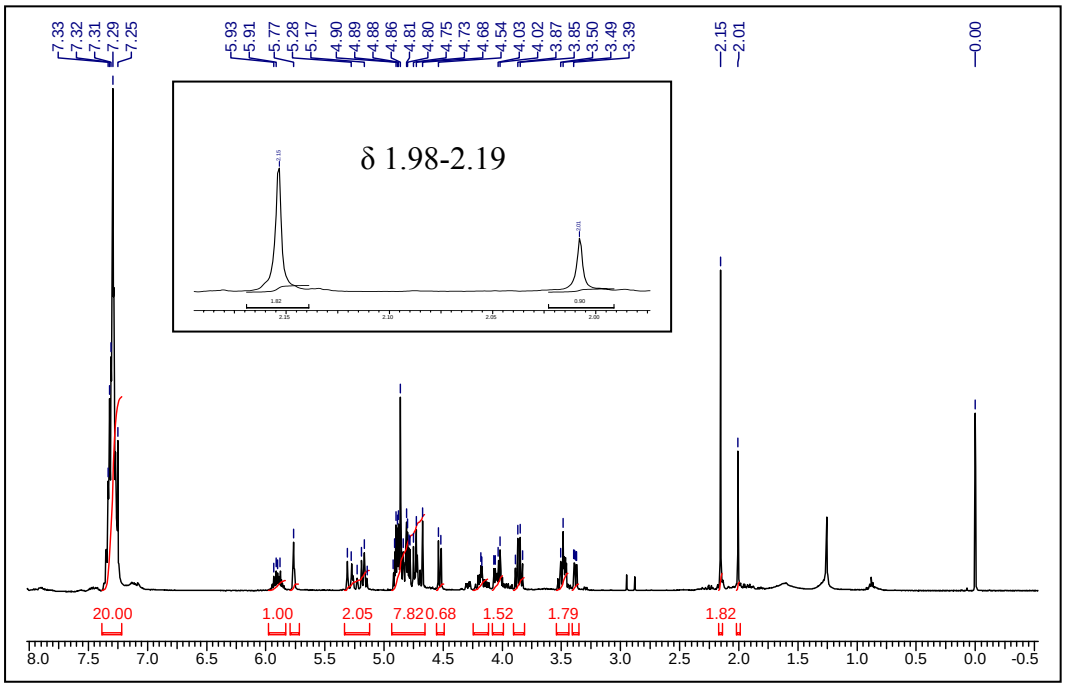
(c) reflux



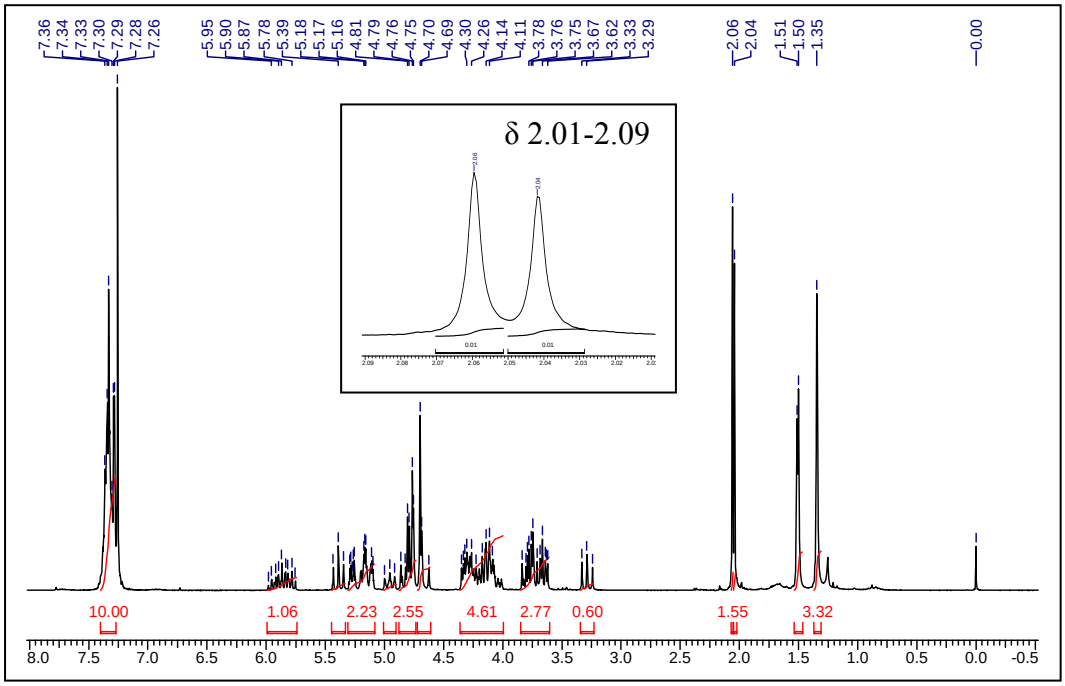
^{1}H NMR spectrum for the acetylated mixture of products **307** and **308** obtained on benzylation of the racemic diol **111** with sodium hydride / benzyl bromide at 0 ºC.



^{1}H NMR spectrum for the acetylated mixture of products **309** and **310** obtained on allylation of the racemic diol **111** with butyllithium / allyl bromide at 0 ºC**.**

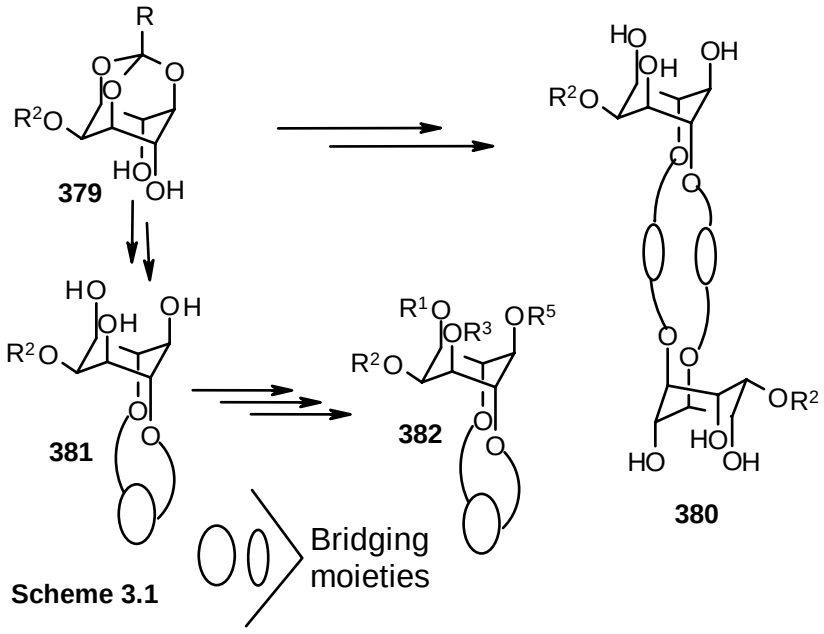


^{1}H NMR spectrum for the acetylated mixture of products **314** and **315** obtained on allylation of the racemic diol **311** with butyllithium / allyl bromide at 0 ºC.



3.1. Introduction

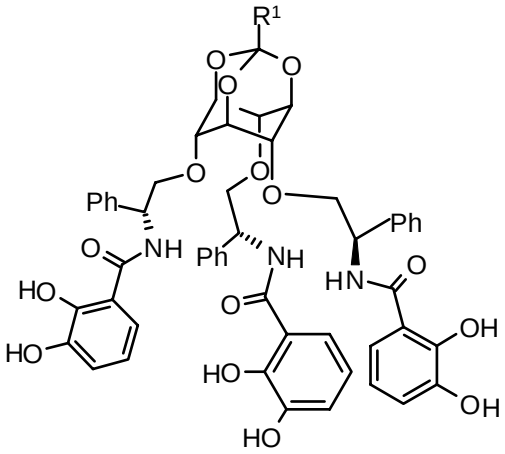
Previous chapters described methods for the orthogonal protection of *myo*-inositol orthoesters (2,4,6-triols) and a *myo*-inositol-1,3,5-triol. Another strategy that we thought of for the protection of C1-, C3- and C5-hydroxyl groups of *myo*-inositol was to see if the chair conformation of the *myo*-inositol ring as in its orthoesters could be locked by bridging the C4- and C6-hydroxyl groups and subsequently cleave the orthoester moiety to generate a 1,3,5-triaxial triol (Scheme 3.1). Two ways in which this can be achieved are, either by preparing the dimeric structure **380** or by preparing the monomeric structure **381**. Availability of such triols would allow a study of the relative reactivity of the three axially disposed C1-, C3- and C5-hydroxyl groups and perhaps the preparation of orthogonally protected *myo*-inositol derivatives.



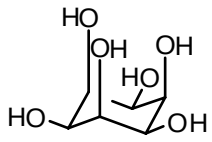
Scheme 3.1

Apart from this synthetic interest, axially disposed 1,3,5-cyclohexane triols have other properties like metal complexing ability[1] and can serve as ionophores.[2] Also, natural products like muellitol (**383**, Chart 3.1) and other unnatural products like *cis*-inositol[3] (**43**) contain triaxially disposed hydroxyl groups in a cyclohexane ring.

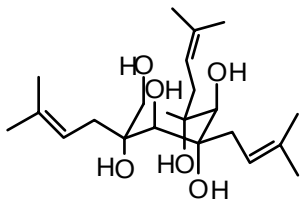
scyllo-Inositol orthoformate which is another molecule containing triaxial triol has been used for the preparation of enterobactin analog **16**.[4]



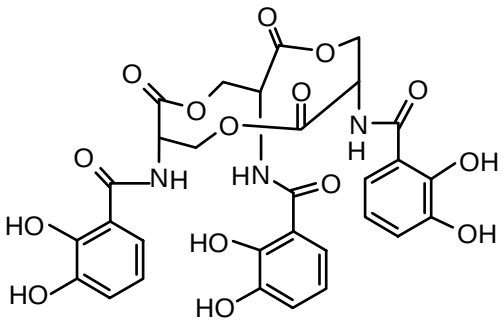
16 Enterobactin analog, R^1 = n-$C_{10}H_{21}$



43 *cis* -Inositol



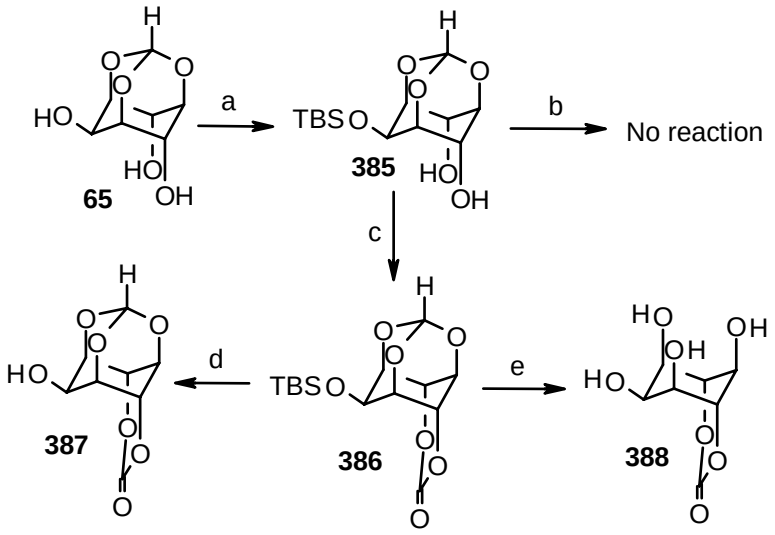
383 Muellitol



384 Enterobactin

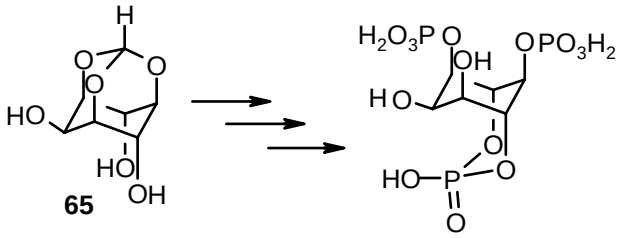
Chart 3.1

Angyal reported[1] the synthesis of the 1,3,5-triol **388** from *myo*-inositol orthoformate as shown in Scheme 3.2. Angyal also found that the methylene bridged derivative (formaldehyde acetal of **385**) cannot be prepared by the cyclization of the diol **385** with dihalomethanes. These results seem to suggest that the bridging of the C4- and C6-hydroxyl groups in *myo*-inositol orthoesters is not feasible with an acetal moiety. The carbonate moiety in the triol **388** was quite labile and underwent hydrolysis in boiling water.



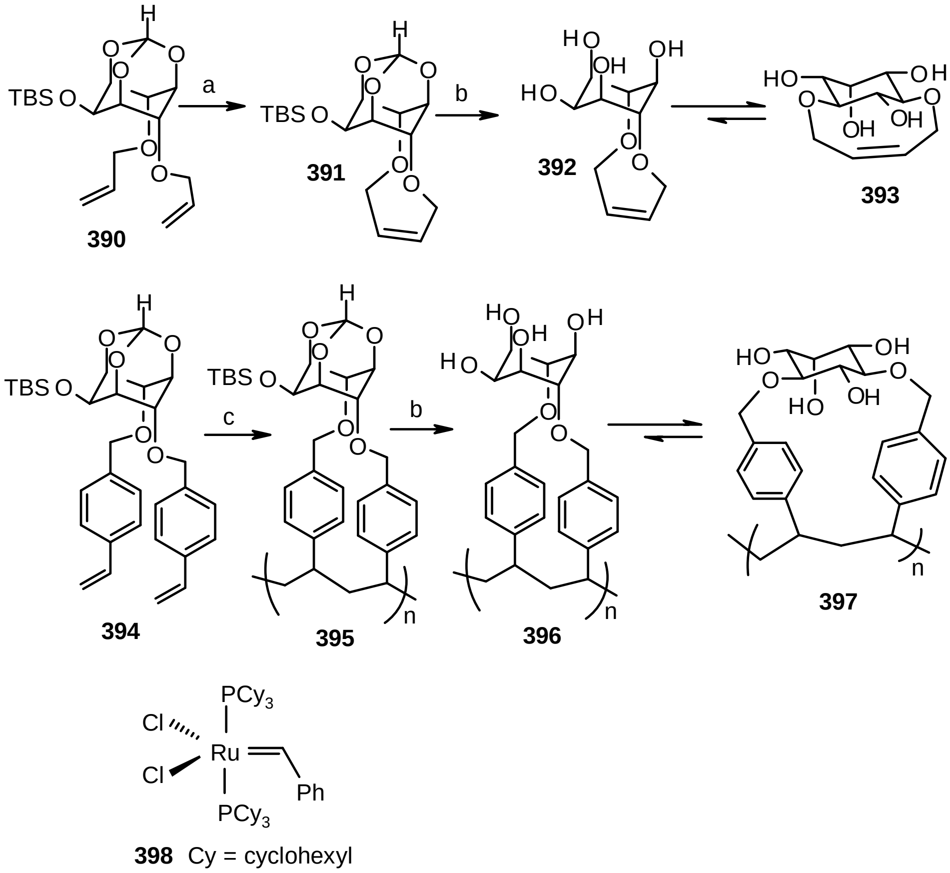
Scheme 3.2. a) TBSCl, 2,6-lutidine, DMF; b) CH_2Br_2 or CH_2I_2, NaH, DMF; c) 1,1-O-carbonylimidazole, THF, 70 ^oC; d) TFA, H_2O (4:1); e) TFA, H_2O (8:1).

Schlewer *et al* has reported[5] the synthesis of 4,6-cyclic phosphate **389** (an analog of *myo*-inositol 1,4,5-trisphosphate) from the triol **65** to investigate the biological activity of C4- and C6- bridged *myo*-inositol phosphates (Scheme 3.3).



Scheme 3.3

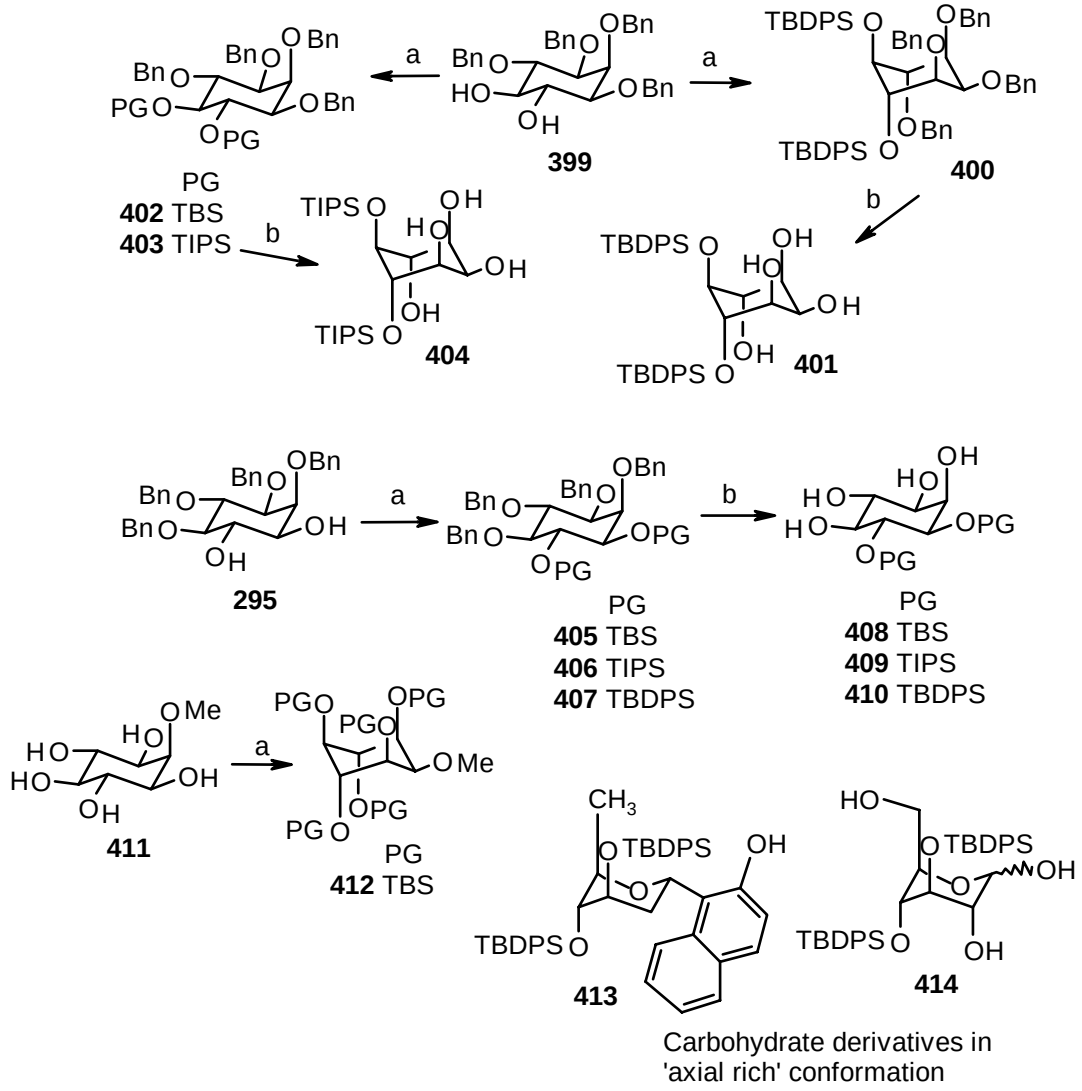
Cyclization of the diallyl ether **390**[6] (Scheme 3.4) by ring closing metathesis resulted in the formation of the corresponding cyclic ether derivative in moderate to good yields. However, cleavage of the orthoformate moiety in **391** resulted in inversion of the inositol ring back to the normal form and hence the tetrol **392** could not be obtained. Similar result was obtained for the polymerization of the styrene derivative **394**. From this report it is clear that larger bridges between C4- and C6-oxygen atoms, perhaps more than three carbon atoms, do not induce the required rigidity to keep the *myo*-inositol ring in the 'axial rich' (see below) conformation.



Scheme 3.4. a) **398**, DCM; b) TsOH, MeOH, THF; c) AIBN, toluene, heat, 90%.

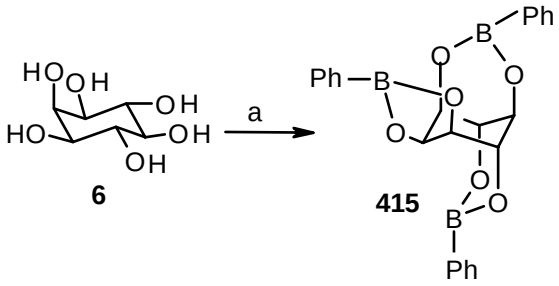
Yamada *et al* reported[7] the ring inversion of *myo*-inositol derivatives from the 'equatorial rich' conformation (e.g. **399**) to the 'axial rich' conformation (e.g. **400**) by introducing bulky silyl protecting groups in the vicinal *trans* hydroxyl groups (Scheme 3.5). Protection of the C5- and C6-hydroxyl groups in *myo*-inositol as the corresponding silyl ethers brought about a change in the conformation of the *myo*-inositol ring (from the 'equatorial rich' conformation to the 'axial rich' conformation) depending upon the bulkiness of the silyl protecting group. Use of TBDPS protection on C5- and C6-hydroxyl groups inverted the *myo*-inositol ring to the 'axial rich' conformation irrespective of the substituents present on the other hydroxyl groups. However, introduction of bulky silyl protecting group at C1- and C6-hydroxyl groups (**405**-**410**) did not bring about inversion of the *myo*-inositol ring. But there appears to be no way of predicting as to which groups can bring about a change in conformation

of the inositol ring. Ring inversion of carbohydrate derivatives by introducing bulky silyl protecting groups in vicinal *trans* diols (e.g. **413**, **414**) has also been reported.[8]



Scheme 3.5. a) R_3SiOTf, 2,6-lutidine, DMF, 100 °C; b) $Pd(OH)_2/C$, H_2, THF.

Kaup *et al*[9] obtained the phenyl boronate **415** by the reaction of *myo*-inositol with phenyl boronic acid in the solid state (Scheme 3.6). Although the inositol ring in the boronate **415** is flipped, it may not be possible to obtain the 1,3,5-triaxial triol or its derivatives starting from the boronate **415**. Such boronate esters are known to be quite labile to the action of water.[10]



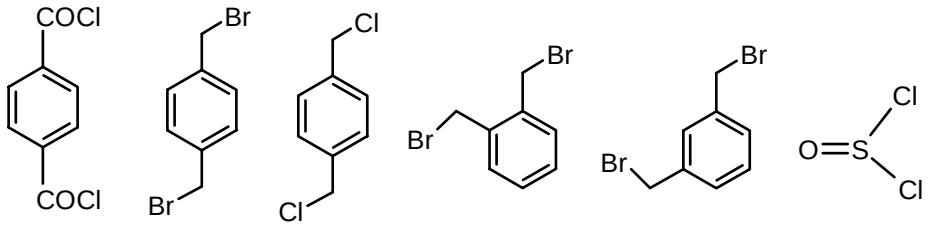
6 **415**

Scheme 3.6. a) $PhB(OH)_2$, 95 °C, 100%.

The following section describes our attempts to make rigid *myo*-inositol derivatives with triaxially disposed hydroxyl groups by bridging the C4- and C6-hydroxyl groups through a suitable linker.

3.2. Results and discussion

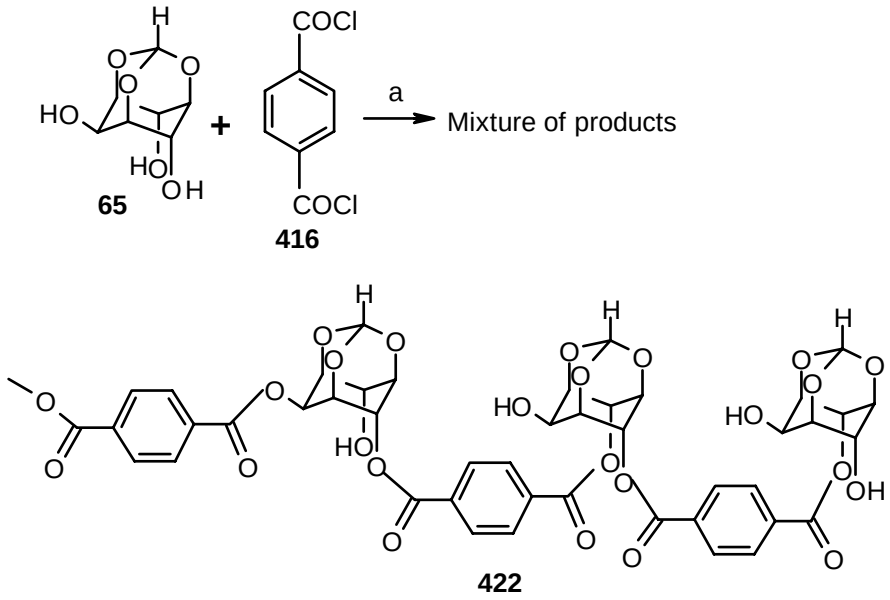
In order to prepare a derivative of *myo*-inositol orthoformate, bridged between the C4- and the C6-oxygen atoms, we attempted the reaction of *myo*-inositol orthoformate and its 2-O-protected derivatives with the reagents shown in Chart 3.2.



416 **417** **418** **419** **420** **421**

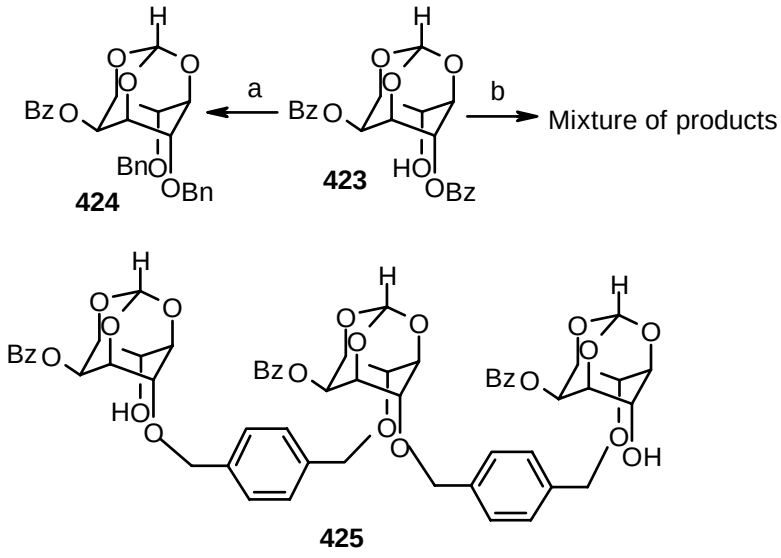
Chart 3.2

Reaction of the triol **65** with *tere*-phthaloyl chloride (**416**) using sodium hydride or triethylamine as a base resulted in a mixture of products (Scheme 3.7). No attempt was made to separate and identify the products since the TLC analysis of the mixture of products obtained suggested this to be impractical. It is likely that this reaction resulted in the formation of oligomers such as **422** consisting of phthaloyl and *myo*-inositol orthoformate units.



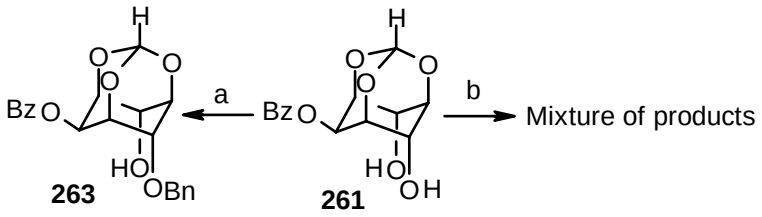
Scheme 3.7. a) NaH or Et_3N, DMF.

Reaction of the racemic dibenzoate **423** with dibromo-*p*-xylene **417** (whether 1eq or excess) in the presence of silver(I) oxide also resulted in a mixture of products, separation of which did not appear to be practical (Scheme 3.8). Earlier work[11] in our laboratory had shown that reaction of the racemic dibenzoate **423** with alkyl halides yields the corresponding 4,6-diether (e.g. **424**) in good yields. It is likely that this reaction resulted in the formation of oligomers such as **425** consisting of *p*-xylene and *myo*-inositol orthoformate units.



Scheme 3.8. a) Ag_2O, DMF, BnBr; b) Ag_2O, DMF, **417**.

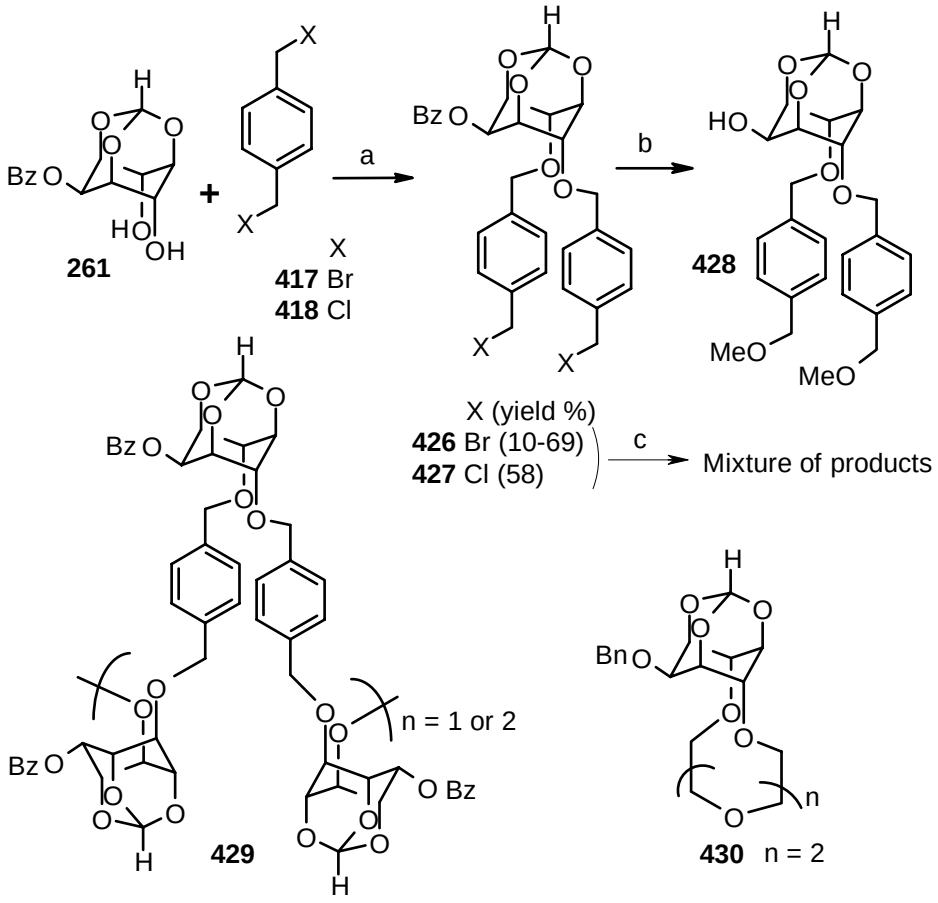
Reaction of the diol **261** with **417** in the presence of potassium carbonate or sodium hydride resulted in a mixture of products (Scheme 3.9). Again, this could be because of the formation of oligomers **425** (Scheme 3.8). Previous work[12] in our laboratory had shown that the reaction of the diol **261** with benzyl bromide gave the corresponding C4-ether **263** in good yield.



Scheme 3.9. a) K_2CO_3, DMF, BnBr; b) K_2CO_3 or NaH, DMF, **417**.

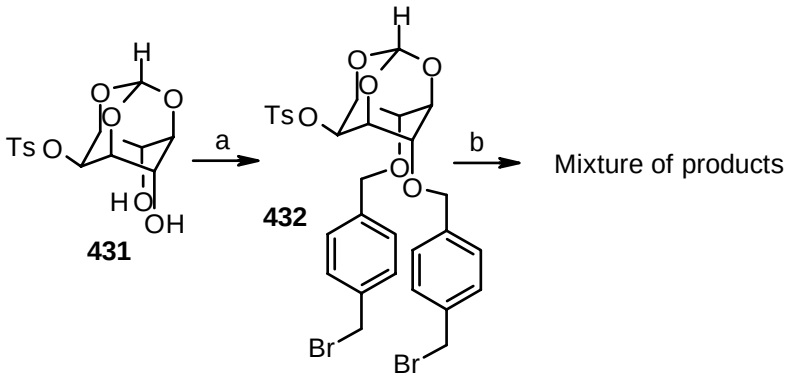
In all the experiments mentioned above, all the reactants were mixed in DMF and stirred at ambient temperature. But, when the reaction of the diol **261** with the dibromide **417** was carried out by the addition of sodium hydride (1.2 equivalents) to a solution of the diol **261** and the dibromide **417** in DMF, although a mixture of products resulted, the diether **426** could be isolated in 10% yield (Scheme 3.10). Increasing the amount of sodium hydride to 3.5 equivalents improved the yield of the diether **426** to 33%. Yield of the diether **426** could further be improved to 69% by the sequential addition of sodium hydride (5 equivalents) and the diol **261** to a solution of the dibromide **417** in DMF. The presence of the two bromomethyl groups in the diether **426** was confirmed by converting the dibromide **426** to the corresponding dimethyl ether **428** (Scheme 3.10). Reaction of the dibromo dixylylether **426** with the benzoate diol **261** resulted in a mixture of products (Scheme 3.10). Similar result was obtained on using the dichloride **427** as well. The dichloro derivative **427** was obtained by the reaction of **261** with dichloro-*p*-xylene **418** under similar conditions used for the preparation of the dibromide **426** (Scheme 3.10). The reaction conditions for the cyclization reaction shown in scheme 3.10 (condition c) were used since

earlier work[13] in our laboratory had shown this condition to be good for the preparation of *myo*-inositol orthoformate derived crown ethers like **430**.



Scheme 3.10. a) NaH (1-5 eq), **417** or **418** (6 eq), DMF; b) NaOMe, MeOH, THF (reaction with **426**); c) **261**, NaH, THF, 75 °C.

In order to rule out the possibility of hydrolysis of the C2-benzoate in the diol **261** and in the dixylyl ether **426** and the consequential formation of oligomers **429** and a mixture of products (Scheme 3.10), we also prepared the dixylylether **432** with tosylate at the C2-position (Scheme 3.11). Previous work[14] in our laboratory had shown that the tosylate at the C2-position in *myo*-inositol orthoformate derivatives was stable to alkylation conditions in the presence of sodium hydride. However, the attempted cyclization reaction of **432** with the diol **431** also resulted in a mixture of products.



Scheme 3.11. a) NaH (5 eq), **417** (6 eq), DMF; b) **431**, NaH, THF, 75 ^{o}C.

Since our attempts to obtain a C4-C6 bridged cyclic ether by the reaction of *myo*-inositol orthoformate or its derivatives with dihalo-*p*-xylenes failed, we investigated the crystal structure of the dibenzyl ether **102** which could give us information on the relative orientation of the two axial benzyl groups. The ORTEP plot for the dibenzyl ether **102** is shown in Figure 3.1.

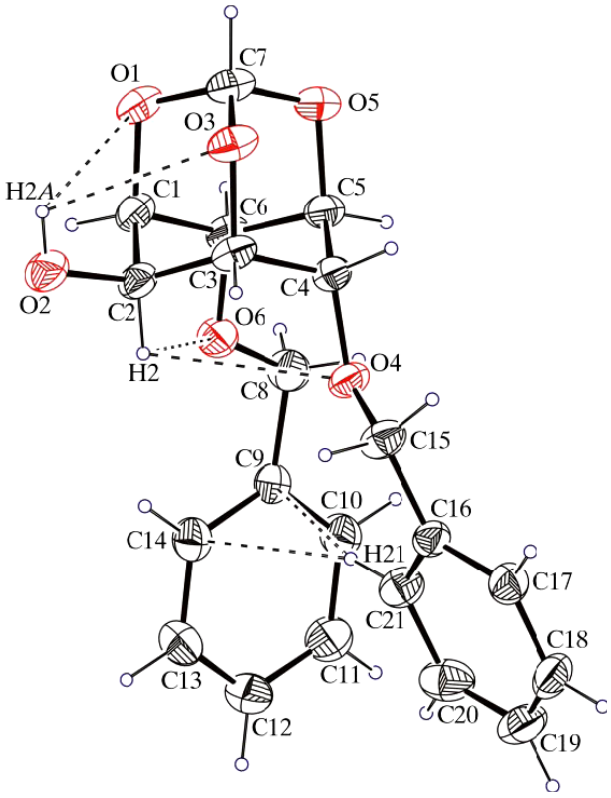
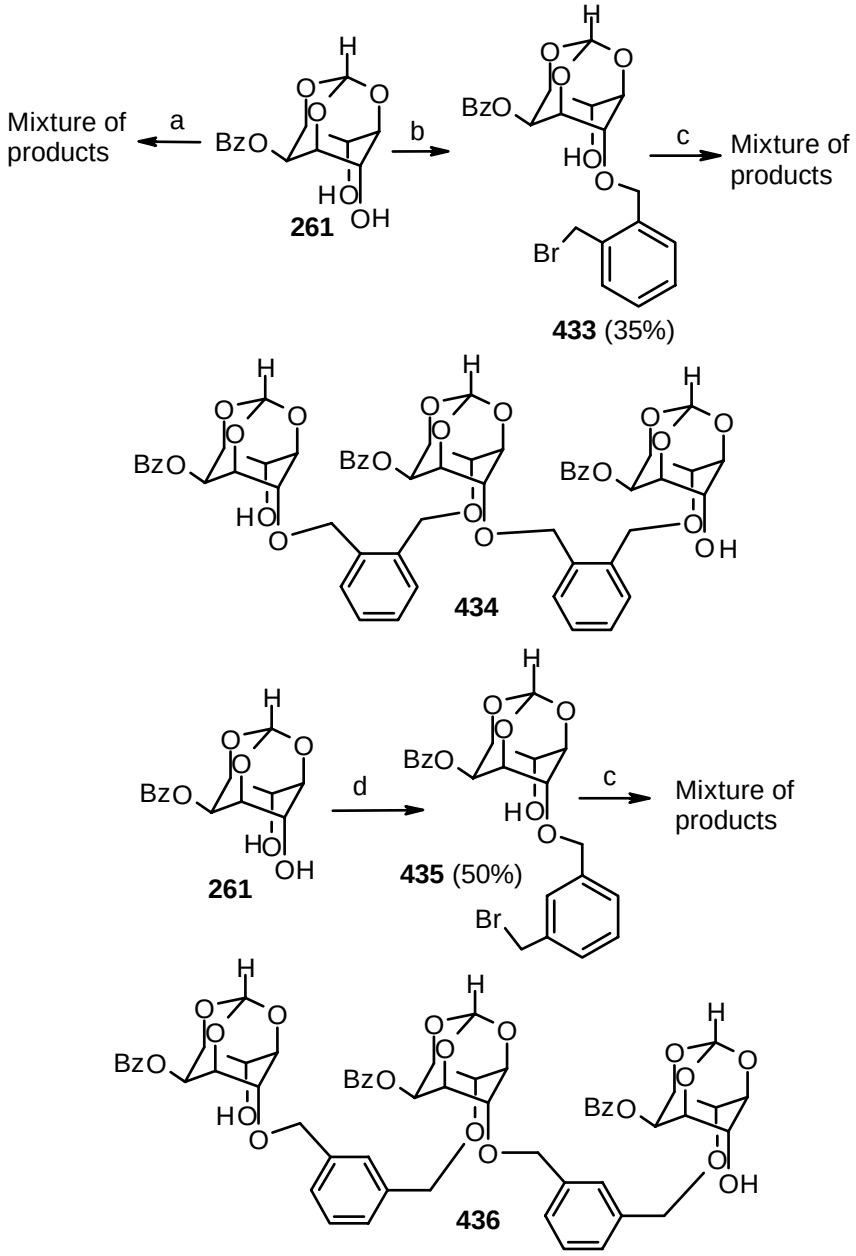


Figure 3.1. ORTEP of **102**

The three axial positions at C1, C3 and C5 constitute the orthoformate bridge. The conformation of the molecule as observed in the crystal shows three rather weak intramolecular interactions. The equatorial hydroxyl group O2-H2A makes bifurcated OH…O contacts with the orthoformate bridge atoms O1 and O3. Another bifurcated contact of the CH…O type is made by the C2-H2 group with ether atoms O4 and O6 (Table 3.4, page no. 196). An almost perpendicular orientation of the phenyl rings (the dihedral angle between the rings is 83.35°) facilitates the somewhat off-centred C21-H21…π interaction (H21…C9 = 2.85 Å and H21…C14 = 2.83 Å). The distance between the *para* carbons (C12 and C19) of phenyl rings was found to be 5.3 Å. The distance between the two axial oxygen atoms O4 and O6 in the diol **261** was 2.71 Å.[15] These interatomic distances and the orientation of the two axial benzyl groups do not appear to be conducive for the cyclization reaction between diols like **261** and dibenzyl ethers such as **426** (also see discussion on crystal structures, pages 175-178).

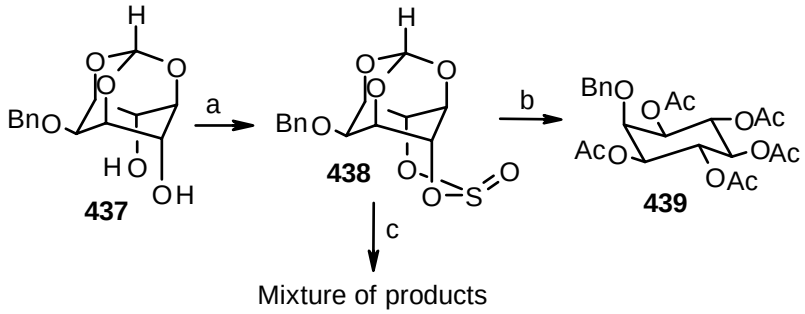
Reaction of the diol **261** with dibromo-*o*-xylene **419** in the presence of potassium carbonate gave a mixture of products. The same reaction when carried out using sodium hydride as the base gave the corresponding monoether **433** in reasonably good yield (Scheme 3.12). Attempted intramolecular cyclization of this bromide **433** however resulted in a mixture of products. This could again be because of the formation of oligomers such as **434**. Similar results were obtained with the *m*-xylyl ether **435**.



Scheme 3.12. a) K_2CO_3, DMF, **419**; b) DMF, NaH (1 eq), **419** (1.2 eq) in DMF; c) DMF, NaH; d) DMF, NaH (1 eq), **420** (1.2 eq) in DMF.

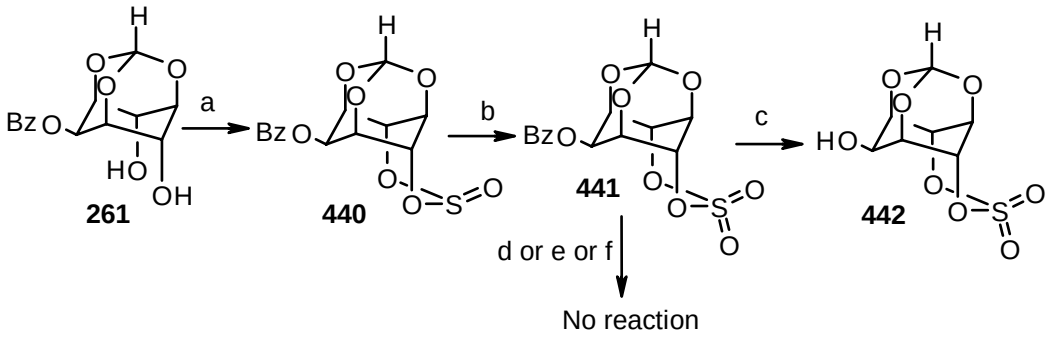
Reaction of the diol **437** with thionyl chloride gave the corresponding cyclic sulfite **438** (Scheme 3.13). Treatment of the cyclic sulfite with TFA to cleave the orthoformate resulted in complete cleavage of the sulfite moiety as well. Acetylation of the product of acid hydrolysis of the sulfite **438** gave the pentaacetate **439**. Oxidation[16, 17] of the sulfite **438** with ruthenium chloride / sodium periodate or ruthenium chloride / OXONE® gave a mixture of products. This was perhaps because

of the concomitant oxidation of the C2-benzyl group. Reports on the oxidation of *myo*-inositol orthoformate derivatives containing benzyl ethers giving rise to mixture of products have appeared earlier.[18]



Scheme 3.13. a) $SOCl_2$, Pyr, DCM; b) (i) TFA / H_2O; (ii) Ac_2O / Pyr; c) $RuCl_3.H_2O$, OXONE or $NaIO_4$.

The cyclic sulfite **440** of the diol **261** could also be prepared in good yield and oxidized to the corresponding cyclic sulfate **441** (Scheme 3.14). This supports our view that the formation of a mixture of products during the oxidation of the sulfite **438** was due to the presence of the benzyl ether in **438** (Scheme 3.13). But the orthoformate moiety in the sulfate **441** was resistant to hydrolysis under reaction conditions normally used to cleave the orthoformate moiety of other *myo*-inositol orthoester derivatives (for details see experimental section 3.4). In all these reactions the cyclic sulfate **441** was recovered quantitatively.

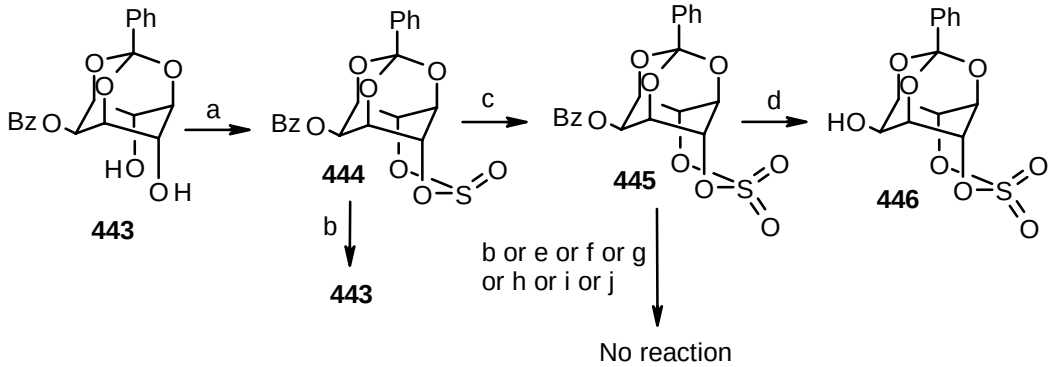


Scheme 3.14. a) $SOCl_2$, Pyr, DCM; b) $RuCl_3.H_2O$, $NaIO_4$, CH_3CN, DCM, H_2O (10:2:1); c) DIBAL-H, DCM; d) TFA, H_2O; e) TFA, H_2O, THF; f) TsOH, MeOH.

Attempted reduction of the orthoformate moiety in **441** with DIBAL-H resulted in exclusive cleavage of the C2-benzoate (Scheme 3.14) since benzoate

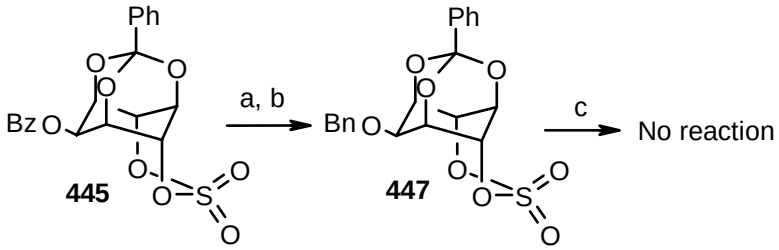
carbonyl group is more electrophilic than the orthoformate carbon. An interesting observation during the determination of the melting point of the cyclic sulfate **441** was that the crystals begin to jump to heights of several centimeters when heated to 208-215 ºC (well before the melting point, 230-232 ºC). Further investigations are being carried out in our laboratory to understand this phenomenon. Earlier instances of 'jumping crystals' of inositol derivatives have been reported.[19]

We next attempted the preparation of the cyclic sulfite from *myo*-inositol orthobenzoate derived diol **443** (Scheme 3.15) since the orthobenzoate moiety is amenable to cleavage under hydrogenolysis conditions. The cyclic sulfite derivative **444** of the orthobenzoate **443** was prepared easily, but its hydrogenolysis resulted in cleavage of the cyclic sulfite moiety rather than the orthobenzoate to give the C2-benzoate **443**. We also oxidized the cyclic sulfite **444** to the corresponding cyclic sulfate **445** but all our attempts to cleave the orthobenzoate moiety either under hydrogenolytic conditions or under acid hydrolytic conditions failed. Reduction of the cyclic sulfate **445** with DIBAL-H resulted in cleavage of the benzoate group as earlier (Scheme 3.14).



Scheme 3.15. a) $SOCl_2$, Pyr, DCM; b) $Pd(OH)_2/C$, H_2, EtOAc; c) $RuCl_3.H_2O$, $NaIO_4$, CH_3CN, DCM, H_2O (10:2:1); d) DIBAL-H, DCM; e) $Pd(OH)_2/C$, H_2, MeOH; f) $Pd(OH)_2/C$, H_2, EtOAc, MeOH; g) $Pd(OH)_2/C$, H_2, MeOH, Et_3N; h) $Pd(OH)_2/C$, H_2, MeOH, CH_3COOH; i) TFA, H_2O; j) TFA, MeOH.

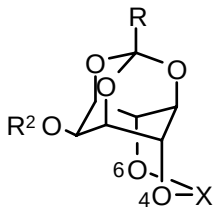
Subsequently, we converted the benzoate **445** to the corresponding benzyl ether **447** by aminolysis with isobutylamine followed by benzylation with sodium hydride and benzyl bromide (Scheme 3.16). The orthobenzoate moiety in the benzyl ether **447** resisted reduction with DIBAL-H.



Scheme 3.16. a) *i*-Butylamine, MeOH; b) NaH, BnBr, DMF; c) DIBAL-H, DCM.

We solved the crystal structure of cyclic sulfite and cyclic sulfate derivatives of *myo*-inositol orthoesters (see experimental section for details, pages 199, 203, 206, 210, 213, 216, 220) and compared them with the structure of cyclic carbonate[1] hoping to find a clue for understanding the experimental observations described in this chapter. The relevant ORTEP diagrams are shown in the experimental section (pages 199, 203, 206, 210, 213, 216, 220) and the relevant bond lengths, bond angles and inter atomic distances are given in Tables 3.1-3.2.

Table 3.1. Selected bond lengths, bond angles and interatomic distance for *myo*-inositol orthoester derivatives.

	**Bond length (Å)**			**Bond Angle (º)**
	O4-S	**O6-S**	**O4-O6**	**O4-S-O6**
438 R = H, R^2 = Bn, X = SO	1.611	1.620	2.464	99.84
440 R = H, R^2 = Bz, X = SO	1.620	1.628	2.476	99.35
444 R = Ph, R^2 = Bz, X = SO	1.632	1.619	2.467	98.74
441 R = H, R^2 = Bz, X = SO_2	1.561	1.563	2.445	103.02
445 R = Ph, R^2 = Bz, X = SO_2	1.572	1.567	2.445	102.33
447 R = Ph, R^2 = Bn, X = SO_2	1.562	1.560	2.437	102.64
442 R = H, R^2 = H, X = SO_2	1.562	1.564	2.439	102.57
387 R = H, R^2 = H, X = CO	1.343[a]	1.332[b]	2.312	119.67[c]
65[20]	--	--	2.768	--

[a] O4-C; [b] O6-C; [c] O4-C-O6

A comparison of the bond lengths and bond angles (involved in the formation of O4-O6 bridge, Table 3.1) for *myo*-inositol orthoester derivatives (cyclic sulfite, cyclic sulfate and cyclic carbonate) show that the bond lengths O4-S and O6-S do not vary much but the bond angle of O4-S-O6 increases by a few degrees after oxidation of the sulfites to corresponding sulfates. More significantly, the distance between O4 and O6 progressively decreases on going from *myo*-inositol orthoformate (**65**) to its cyclic sulfite (or sulfate) to its carbonate derivatives. This implies an increase in the deformation of the carbocyclic ring and strain in these molecules on forming O4-O6 bridged derivatives. Hence it is likely that the formation of O4-O6 bridge with a

tetrahedral carbon atom (as in a cyclic acetal) could result in an increase in the strain to such an extent that formation of such a bridge might not be feasible and stable.

Table 3.2. Selected bond lengths and bond angles for *myo*-inositol orthoester derivatives.

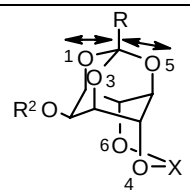
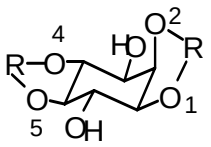
	**Bond lengths (Å)**			**Bond angles (°)**		
	C-O1	**C-O3**	**C-O5**	**O1-C-O3**	**O3-C-O5**	**O1-C-O5**
438, R = H, R^2 = Bn, X = SO	1.403	1.401	1.406	112.42	110.58	110.55
440, R = H, R^2 = Bz, X = SO	1.401	1.405	1.406	112.34	110.69	110.96
444, R = Ph, R^2 = Bz, X = SO	1.408	1.414	1.412	111.22	109.13	109.90
441, R = H, R^2 = Bz, X = SO_2	1.395	1.393	1.412	112.56	110.32	110.53
445, R = Ph, R^2 = Bz, X = SO_2	1.407	1.407	1.406	111.60	109.46	109.33
447, R = Ph, R^2 = Bn, X = SO_2	1.402	1.401	1.425	112.19	109.10	108.83
442, R = H, R^2 = H, X = SO_2	1.393	1.396	1.402	112.25	111.08	110.46
65[20]	1.401	1.407	1.404	111.13	111.21	111.47

Table 3.3. Selected bond lengths and bond angles for *myo*-inositol derived ketals (values taken from refs 21, 22).

	**Bond lengths (Å)**				**Bond angles (°)**	
	C-O1	**C-O2**	**C-O4**	**C-O5**	**O1-C-O2**	**O4-C-O5**
56, R = $(CH_2)_5C$	1.439	1.425	1.446	1.441	105.40	105.66
60, R = $(CH_3)_2C$	1.441	1.425	1.452	1.442	105.79	105.96

Similarly a comparison of the C-O bond lengths and the corresponding bond angles for *myo*-inositol orthoesters and their derivatives (Tables 3.1-3.2) with the

ketal derivatives (Table 3.3) show that C-O bond lengths decrease where as bond angles increase on going from ketals to orthoesters indicating an increase in strain. Hence the orthoester moiety being very rigid may not allow introduction of rings containing a tetrahedral carbon atom on the opposite face of the carbocyclic (inositol) ring which further increases the strain in the molecule. These reasons could be responsible for the non formation of O4-O6 bridged *myo*-inositol orthoester derivatives shown in Schemes 3.7-3.12.

3.3. Conclusions

We attempted to prepare O4-O6 bridged *myo*-inositol orthoester derivatives that could be potentially useful for the preparation of cyclitol derivatives and also serve as metal complexing agents. Although we were successful in preparing *myo*-inositol orthoester derivatives containing O4-O6 bridge (with sulfur) we were unable to cleave the orthoester moiety to release the 1,3,5-*cis* triaxial hydroxyl groups. A comparison of the crystal structures of various *myo*-inositol orthoester derivatives suggests that bridging of O4 and O6 atoms (as ethers or ketals) may not be feasible on these trioxa adamantane derivatives.

3.4. Experimental section

General: General experimental procedures are same as in Chapter 2, Section A except for the following: Dry DCM was used as solvent in all the experiments. Palladium hydroxide on charcoal (20 wt.%) was used for all the hydrogenolysis reactions. *myo*-Inositol derivatives **261**,[23] **423**,[24] **431**,[25] and **437**[25] were prepared according to literature procedures. The diol **443** was obtained as a gift from Mr. C. Murali.[26] Compounds **426-428, 432, 433, 435, 439, 442, 446** were not characterized rigorously since they were not used further in any experiment. ^{1}H NMR spectra reported for the compounds **426-428, 432, 433** and **435** are for crude products**.**

Reaction of 2-*O*-benzoyl *myo*-inositol 1,3,5-orthoformate (261) with α, α'-dibromo-*p*-xylene (417). Method A. To a solution of the diol **261** (0.147 g, 0.50 mmol) in DMF (4 mL) sodium hydride (0.012 g, 0.50 mmol) was added and stirred for 15 min. α, α'-Dibromo-*p*-xylene **417** (0.066 g, 0.25 mmol) was then added and the reaction mixture was stirred for 30 min at ambient temperature. TLC analysis of the reaction mixture showed a mixture of products. No attempt was made to isolate the products.

Method B. To a solution of the diol **261** (0.147 g, 0.50 mmol) and α, α'-dibromo-*p*-xylene **417** (0.792 g, 3 mmol) in DMF (8 mL) sodium hydride (0.024 g, 0.60 mmol) was added and stirred for 20 min. The reaction mixture was worked up by adding ethyl acetate saturated with water. The organic layer was washed with water followed by brine and dried over anhydrous sodium sulfate. The products were separated by column chromatography (100-200 mesh silica gel) using 15% ethyl acetate / petroleum ether as eluent to get the diether **426** (0.035 g, 10%).

Data for 426:

mp. 109-110 °C.

^{1}H NMR ($CDCl_3$): δ 8.15 (d, 2H, J = 7.3 Hz), 7.40-7.66 (m, 3H), 7.19-7.35 (m, 8H), 5.55-5.63 (m, 2H), 4.66 (s, 4H), 4.39-4.60 (m, 9H).

Elemental analysis calcd for $C_{30}H_{28}O_7Br_2$: C, 54.56; H, 4.27. Found: C, 54.48; H, 4.39.

Method C. To a solution of the diol **261** (0.147 g, 0.50 mmol) and α, α'-dibromo-*p*-xylene **417** (0.792 g, 3 mmol) in DMF (10 mL), sodium hydride (0.070 g, 1.75 mmol) was added and the mixture stirred at ambient temperature for 35 min. The reaction mixture was processed as above to obtain the diether **426** (0.110 g, 33%).

Method D. To a solution of α, α'-dibromo-*p*-xylene **417** (2.100 g, 8 mmol) in DMF (16 mL), sodium hydride (0.200 g, 5 mmol) and the diol **261** (0.294 g, 1 mmol) were added sequentially and the mixture stirred vigorously for 40 min and worked up as above to obtain the diether **426** (0.456 g, 69%).

Reaction of 2-*O*-benzoyl-4,6-di-*O*-(*p*-bromomethylbenzyl) *myo*-inositol 1,3,5-orthoformate (426) with sodium methoxide. To a solution of the dibromodiether **426** (0.100 g, 0.15 mmol) in THF (2 mL) and methanol (3 mL), sodium methoxide (0.082 g, 1.52 mmol) was added and the mixture refluxed for 1.5 h. The reaction mixture was worked up with ethyl acetate to get the dimethylether **428** (0.064 g, 75%). ^{1}H NMR spectrum of **428** suggested the presence of a small amount **426** in the product.

^{1}H NMR ($CDCl_3$): δ 7.25 (s, 8H), 5.45 (s, 1H), 4.15-4.70 (m, 15H), 3.38 (s, 6H), 2.18 (broad s, 1H).

Reaction of 2-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate (261) with α, α'-dichloro-*p*-xylene (418). To a solution of α, α'-dichloro-*p*-xylene **418** (0.462 g, 2.64 mmol) in DMF (6 mL) sodium hydride (0.070 g, 1.76 mmol) was added immediately followed by the diol **261** (0.130 g, 0.44 mmol) and the mixture stirred vigorously for

40 min at ambient temperature. Work up and purification as above gave the dichloro diether **427** (0.145 g, 58%).

Data for 427:

mp. 115-117 °C.

^{1}H NMR ($CDCl_3$): δ 8.15 (d, 2H, J = 7.3 Hz), 7.40-7.67 (m, 3H), 7.28 (s, 8H), 5.55-5.68 (m, 2H), 4.35-4.80 (m, 13H).

Elemental analysis calcd for $C_{30}H_{28}O_7Cl_2$: C, 63.10; H, 4.94. Found: C, 63.60; H, 5.40.

Reaction of 2-*O*-tosyl-*myo*-inositol 1,3,5-orthoformate (431) with α, α'-dibromo-*p*-xylene (417). To a solution of α, α'-dibromo-*p*-xylene **417** (0.650 g, 2.46 mmol) in DMF (6 mL) sodium hydride (0.066 g, 1.64 mmol) was added immediately followed by the tosylate diol **431** (0.140 g, 0.41 mmol) and the mixture stirred vigorously for 40 min at ambient temperature. Usual work up with ethyl acetate and column chromatography as in the method B (preparation of **426**) gave the diether **432** (0.181 g, 62%) as a light green gummy solid.

^{1}H NMR ($CDCl_3$): δ 7.76 (d, 2H, J = 8.8 Hz), 7.05-7.45 (m, 10H), 5.52 (s, 1H), 4.95-5.05 (m, 1H), 4.20-4.62 (m, 13H), 2.35 (s, 3H).

Reaction of 2-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate (261) with α, α'-dibromo-*o*-xylene (419). To a solution of the diol **261** (0.294 g, 1 mmol) in DMF (4 mL) sodium hydride (0.044 g, 1.10 mmol) was added and stirred for 15 min at ambient temperature. A solution of **419** (0.290 g, 1.10 mmol) in DMF (2 mL) was then added in one lot and the mixture stirred for 1 h at ambient temperature. Work up of the reaction mixture as above followed by column chromatography (10% ethyl acetate / petroleum ether) gave the crude monoether **433** (0.167 g, 35%) as a gum.

^{1}H NMR ($CDCl_3$): δ 8.01-8.26 (m, 2H), 7.20-7.70 (m, 7H), 5.43-5.65 (m, 2H), 4.79-5.05 (m, 2H), 4.35-4.75 (m, 7H), 3.71 (d, 1H, J = 9.8 Hz).

Reaction of 2-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate (261) with α, α'-dibromo-*m*-xylene (420). To a solution of the diol **261** (0.294 g, 1 mmol) in DMF (4 mL) sodium hydride (0.044 g, 1.10 mmol) was added and the mixture stirred for 15 min at ambient temperature. A solution of **420** (0.264 g, 1 mmol) in DMF (2 mL) was added in one lot and stirred for 1 h. Work up and purification as above gave the monoether **435** (0.237 g, 50%) as a gum.

^{1}H NMR ($CDCl_3$): δ 8.01 (d, 2H, J = 8.8 Hz), 7.17-7.60 (m, 7H), 5.48 (s, 1H), 5.43-5.47 (m, 1H), 4.68 (AB q, 2H, J = 11.8 Hz), 4.47-4.55 (m, 2H), 4.44 (s, 2H), 4.35-4.42 (m, 2H), 4.26-4.34 (m, 1H), 3.74 (d, 1H, J = 9.7 Hz).

Preparation of *myo*-inositol derived cyclic sulfites. General procedure. The required *myo*-inositol orthoester derivative and dry pyridine were taken in dry DCM and cooled to 0 °C. Thionyl chloride (**421**) was added drop-wise using a syringe at 0 °C over a period of 2-3 min. The reaction mixture was stirred for 3-4 h, diluted with DCM and washed with sodium bicarbonate solution followed by water and brine. The organic layer was dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure followed by column chromatography (using 10-20% ethyl acetate – light petroleum as the eluent) gave the cyclic sulfite.

2-*O*-benzyl-*myo*-inositol 1,3,5-orthoformate-4,6-cyclic sulfite (438). The cyclic sulfite **438** was prepared as above using the 2-benzyl ether **437** (0.500 g, 1.80 mmol), pyridine (2.20 mL), DCM (6 mL) and thionyl chloride (0.47 mL, 5.40 mmol). The cyclic sulfite **438** was obtained as a colorless solid (0.380g, 65%).

Data for 438:

mp. 129-131 °C.

^{1}H NMR ($CDCl_3$): δ 7.30-7.45 (m, 5H), 5.72-5.80 (m, 1H), 5.54-5.58 (m, 1H), 5.11-5.20 (m, 2H), 4.76 (s, 2H), 4.37-4.45 (m, 2H), 3.91-3.97 (m, 1H).

^{13}C NMR ($CDCl_3$): δ 137.2, 128.6, 128.2, 127.9, 102.4, 71.9, 69.0, 68.7, 66.8, 59.7.

Elemental analysis Calcd for $C_{14}H_{14}O_7S$: C, 51.53; H, 4.32. Found: C, 51.87; H, 4.19.

2-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate-4,6-cyclic sulfite (440). The cyclic sulfite **440** was prepared as above using the diol **261** (0.600 g, 2.04 mmol), pyridine (2.5 mL), DCM (12 mL) and thionyl chloride (0.53 mL, 6.12 mmol). The cyclic sulfite **440** was obtained as a colorless solid (0.403 g, 58%).

Data for 440:

mp. 178-180 °C.

IR (ν, nujol): 1720 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 8.10-8.25 (m, 2H), 7.40-7.70 (m, 3H), 5.80-5.92 (m, 1H), 5.60 (d, 1H, J = 1.3 Hz), 5.45-5.55 (m, 1H), 5.23 (t, 2H, J = 4 Hz), 4.55-4.65 (m, 2H).

^{13}C NMR ($CDCl_3$): δ 165.7, 133.7, 130.0, 129.1, 128.5, 102.3, 68.6, 63.2, 59.7.

Elemental analysis Calcd for $C_{14}H_{12}O_8S$: C, 49 41; H, 3.55. Found: C, 49.32; H, 3.25.

2-*O*-benzoyl-*myo*-inositol 1,3,5-orthobenzoate-4,6-cyclic sulfite (444). The cyclic sulfite **444** was prepared as above using the diol **443** (0.400 g, 1.08 mmol), pyridine (1.3 mL), DCM (6 mL) and thionyl chloride (0.28 mL, 3.24 mmol). The cyclic sulfite **444** was obtained as a colorless solid (0.337 g, 75%).

Data for 444:

mp. 162-164 °C.

IR (ν, nujol): 1711 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 8.16 (d, 2H, J = 8 Hz), 7.30-7.75 (m, 8H), 5.98-6.08 (m, 1H), 5.59 (t, 1H, J = 2 Hz), 5.32 (t, 2H, J = 4 Hz), 4.73-4.83 (m, 2H).

^{13}C NMR ($CDCl_3$): δ 165.7, 135.8, 133.6, 130.0, 129.9, 129.3, 128.6, 128.2, 125.3, 107.3, 70.2, 68.5, 62.6, 60.9.

Elemental analysis calcd for $C_{20}H_{16}O_8S$: C, 57.69; H, 3.87. Found: C, 57.57; H, 3.83.

Hydrolysis of 2-*O*-benzyl-*myo*-inositol 1,3,5-orthoformate-4,6-cyclic sulfite (438) with aqueous TFA. The cyclic sulfite **438** (0.017 g, 0.05 mmol) was stirred in distilled water (0.2 mL) and trifluoroacetic acid (0.8 mL) for 12 h. The solid obtained on evaporation of the solvent under reduced pressure was acetylated with acetic anhydride (0.5 mL) in pyridine (1 mL) overnight at room temperature, which gave the pentaacetate **439** (0.026 g, 100%).

Data for 439:

mp. 217-219 ºC.

IR (ν, nujol): 1744 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 7.32 (s, 5H), 5.61 (t, 2H, J = 10.1 Hz), 5.12 (t, 1H, J = 9.4 Hz), 4.95 (dd, 2H, J = 2.4, 10.6 Hz), 4.67 (s, 2H), 4.07-4.14 (m, 1H), 1.98 (s, 9H), 1.96 (s, 6H).

Hydrogenolysis of 2-*O*-benzoyl-*myo*-inositol 1,3,5-orthobenzoate-4,6-cyclic sulfite (444). A solution of the orthobenzoate **444** (0.100 g, 0.24 mmol) in ethyl acetate (1.5 mL) was hydrogenolyzed in the presence of palladium hydroxide on charcoal (0.100 g) at 65 psi for 7 h. The catalyst was removed by filtration through a small bed of Celite and evaporation of the filtrate gave the diol **443** (0.084 g, 95%).

mp. 183-185 ºC (Lit.[26] mp. 185-187 °C).

Preparation of *myo*-inositol cyclic sulfates. General procedure. The required *myo*-inositol orthoester cyclic sulfite was taken in a mixture of acetonitrile, dichloromethane and water (10:2:1 v/v 18-25 mL). Sodium periodate (4 eq) and ruthenium chloride monohydrate (7 mol%) were added and the mixture stirred for 2-3 h at room temperature. The reaction mixture was filtered through a small bed of Celite using DCM as solvent. Evaporation of the filtrate under reduced pressure gave the cyclic sulfate.

2-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate-4,6-cyclic sulfate (441). The cyclic sulfite **440** (0.520 g, 1.53 mmol) was oxidized using sodium periodate (1.300 g, 6.12 mmol) and ruthenium chloride monohydrate (0.023 g, 0.11 mmol) as in the general procedure to get cyclic sulfate **441** as a colorless solid (0.524 g, 96%).

Data for 441:

mp. 230-232 °C.

IR (ν, nujol): 1726 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 8.12-8.20 (m, 2H), 7.58-7.69 (m, 1H), 7.44-7.55 (m, 2H), 5.55-5.70 (m, 3H), 5.30-5.45 (m, 2H), 4.70-4.85 (m, 2H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 165.4, 133.8, 130.0, 128.9, 128.6, 101.8, 73.8, 68.6, 62.4, 59.1.

Elemental analysis Calcd for $C_{14}H_{12}O_9S$: C, 47.19; H, 3.40. Found: C, 47.06; H, 3.72.

2-*O*-benzoyl-*myo*-inositol 1,3,5-orthobenzoate-4,6-cyclic sulfate (445). The cyclic sulfite **444** (0.850 g, 2.04 mmol) was oxidized using sodium periodate (1.750 g, 8.16 mmol) and ruthenium chloride monohydrate (0.030 g, 0.14 mmol) as in the general procedure to get the cyclic sulfate **445** (0.865 g, 98%).

Data for 445:

mp. 80-82 °C.

IR (ν, $CHCl_3$): 1728 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 8.16 (d, 2H, J = 7 Hz), 7.57-7.71 (m, 3H), 7.34-7.55 (m, 5H), 5.70-5.82 (m, 2H), 5.43-5.54 (m, 2H), 4.92-5.02 (m, 2H).

^{13}C NMR ($CDCl_3$): δ 165.4, 134.7, 133.8, 130.4, 130.0, 128.9, 128.6, 128.3, 125.3, 107.0, 73.8, 70.0, 61.8, 60.3.

Elemental analysis calcd for $C_{20}H_{16}O_9S$: C, 55.55; H, 3.73. Found: C, 55.85; H, 3.66.

Attempted hydrolysis of 2-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate-4,6-cyclic sulfate (441). The orthoformate **441** was stirred with reagents shown below for 20-24 h. There was no reaction and the starting material was recovered after evaporation of the solvent.

a) Cyclic sulfate **441** (0.200 g, 0.56 mmol or 0.100 g, 0.28 mmol), distilled water (0.8 mL or 0.2 mL) and trifluoroacetic acid (1.2 mL or 0.8 mL) at room temperature.
b) Cyclic sulfate **441** (0.100 g, 0.28 mmol), THF (0.4 mL), distilled water (0.2 mL) and trifluoroacetic acid (0.4 mL) at room temperature.
c) as in (b) at 60 ºC.
d) Cyclic sulfate **441** (0.100 g, 0.28 mmol) and TsOH (0.004 g, 0.02 mmol) in methanol (1 mL) at room temperature.

Reduction of 2-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate-4,6-cyclic sulfate (441) with DIBAL-H. A solution of the cyclic sulfate **441** (0.200 g, 0.56 mmol) in DCM (5 mL) was cooled to 0 °C and a 1M solution of DIBAL-H in toluene (5.62 mL, 5.62 mmol) was added and stirred for 12 h at room temperature. The reaction mixture was worked up[27] by stirring with a solution of sodium potassium tartrate and saturated

ammonium chloride solution and extracted with DCM. The organic layer was washed with water, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure to get the product **442** (0.098 g, 70%).

Data for 442:

mp. 179-181 °C.

^{1}H NMR ($CDCl_3$): δ 5.57 (d, 1H, J = 1.2 Hz), 5.50-5.55 (m, 1H), 5.29-5.40 (m, 2H), 4.46-4.55 (m, 2H), 4.32-4.45 (m, 1H), 3.22 (d, 1H, J = 12 Hz).

Attempted hydrogenolysis of 2-*O*-benzoyl-*myo*-inositol 1,3,5-orthobenzoate-4,6-cyclic sulfate (445). A solution of the orthobenzoate **445** in methanol or ethyl acetate was hydrogenolyzed (various conditions as below) in the presence of palladium hydroxide on charcoal at 60 psi for 30 h. There was no reaction and the starting material was recovered by filtering through a small bed of Celite and evaporation of the solvent from the filtrate.

a) Cyclic sulfate **445** (0.250 g, 0.578 mmol) and palladium hydroxide on charcoal (0.250 g) in methanol (2 mL).
b) Cyclic sulfate **445** (0.200 g, 0.46 mmol) and palladium hydroxide on charcoal (0.200 g) in ethyl acetate (2 mL).
c) Cyclic sulfate **445** (0.250 g, 0.58 mmol) and palladium hydroxide on charcoal (0.250 g) in ethyl acetate (1 mL), methanol (1mL).
d) Cyclic sulfate **445** (0.200 g, 0.46 mmol), triethylamine (0.04 mL) and palladium hydroxide on charcoal (0.200 g) in methanol (2 mL).
e) Cyclic sulfate **445** (0.200 g, 0.46 mmol), acetic acid (0.04 mL) and palladium hydroxide on charcoal (0.200 g) in methanol (2 mL).

Attempted solvolysis of 2-*O*-benzoyl-*myo*-inositol 1,3,5-orthobenzoate-4,6-cyclic sulfate (445) with aqueous TFA. The orthobenzoate **445** (0.100 g, 0.23 mmol) was stirred in distilled water (0.2 mL) and trifluoroacetic acid (0.8 mL) for 20 h. There was no reaction; the starting material was recovered after evaporation of the solvent. Similar result was obtained on using methanol (0.2 mL or 0.8 mL) and trifluoroacetic acid (0.8 mL or 0.2 mL).

Reduction of 2-*O*-benzoyl-*myo*-inositol 1,3,5-orthobenzoate-4,6-cyclic sulfate (445) with DIBAL-H. To a solution of the orthobenzoate **445** (0.250 g, 0.58 mmol) in DCM (6 mL) cooled to 0 °C, a solution of DIBAL-H in toluene (5.8 mL, 5.78 mmol) was added and stirred for 12 h at room temperature. The reaction mixture was worked up[27] by stirring with a solution of sodium potassium tartrate and saturated ammonium chloride solution and extracted with DCM. The organic layer was washed with water, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure to get the product **446** (0.173 g, 91%).

^{1}H NMR ($CDCl_3$): δ 7.55-7.67 (m, 2H), 7.34-7.51 (m, 3H), 5.59-5.70 (m, 1H), 5.44 (t, 2H, J = 4.5 Hz), 4.62-4.74 (m, 2H), 4.35-4.51 (m, 1H), 3.30 (d, 1H, J = 11.4 Hz, D_2O exchangeable).

Preparation of 2-*O*-benzyl-*myo*-inositol 1,3,5-orthobenzoate-4,6-cyclic sulfate (447). A solution of the benzoate **445** (0.600 g, 1.40 mmol) and *iso*-butylamine (1.4 mL) in methanol (5.6 mL) was refluxed for 6 h. The solvents were evaporated and the residue was chromatographed to obtain the sulfate **446** (0.446 g). A portion of the crude sulfate **446** (0.400 g, 1.22 mmol) and benzyl bromide (0.626 g, 0.44 mL, 3.66 mmol) were dissolved in DMF (5 mL), sodium hydride (0.976 g, 2.44 mmol) was added and the mixture stirred for 1 h at room temperature. The reaction mixture was worked up as usual with ethyl acetate and the product **447** (0.490 g, 96%) was

separated by column chromatography using 10% ethyl acetate - petroleum ether as eluent.

Data for 447:

mp. 151-153 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.69 (m, 2H), 7.31-7.48 (m, 8H), 5.59-5.68 (m, 1H), 5.34-5.42 (m, 2H), 4.80 (s, 2H), 4.68-4.76 (m, 2H), 4.18-4.23 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.0, 134.9, 130.1, 128.6, 128.2, 128.1, 127.9, 125.4, 106.9, 74.2, 72.0, 70.1, 65.4, 60.3.

Elemental analysis calcd for $C_{20}H_{18}O_8S$: C, 57.41; H, 4.34. Found: C, 57.23; H, 4.28.

Reduction of 2-*O*-benzyl-*myo*-inositol 1,3,5-orthobenzoate-4,6-cyclic sulfate (447) with DIBAL-H. A solution of the orthobenzoate **447** (0.200 g, 0.48 mmol) in DCM (6 mL) was cooled to 0 °C and a solution of DIBAL-H (4.8 mL, 4.80 mmol) in toluene was added and the mixture was stirred for 12 h at room temperature. The reaction mixture was then worked up[27] by stirring with a solution of sodium potassium tartrate and saturated ammonium chloride solution and extracted with DCM. The organic layer was washed with water, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure to get the starting material (0.187 g, 94%).

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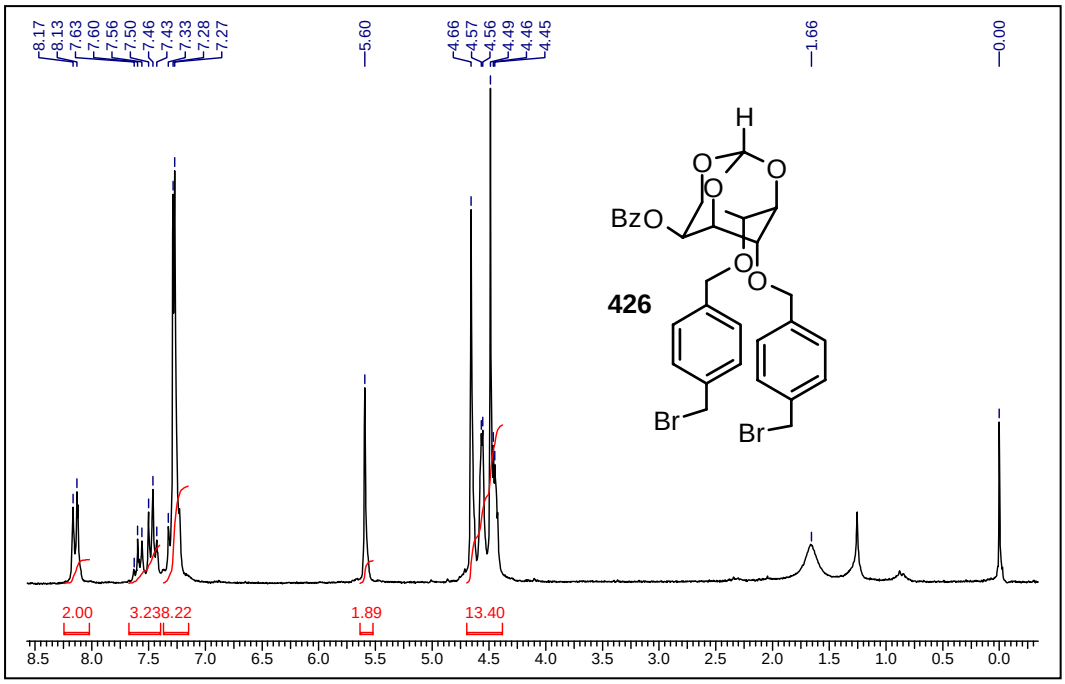
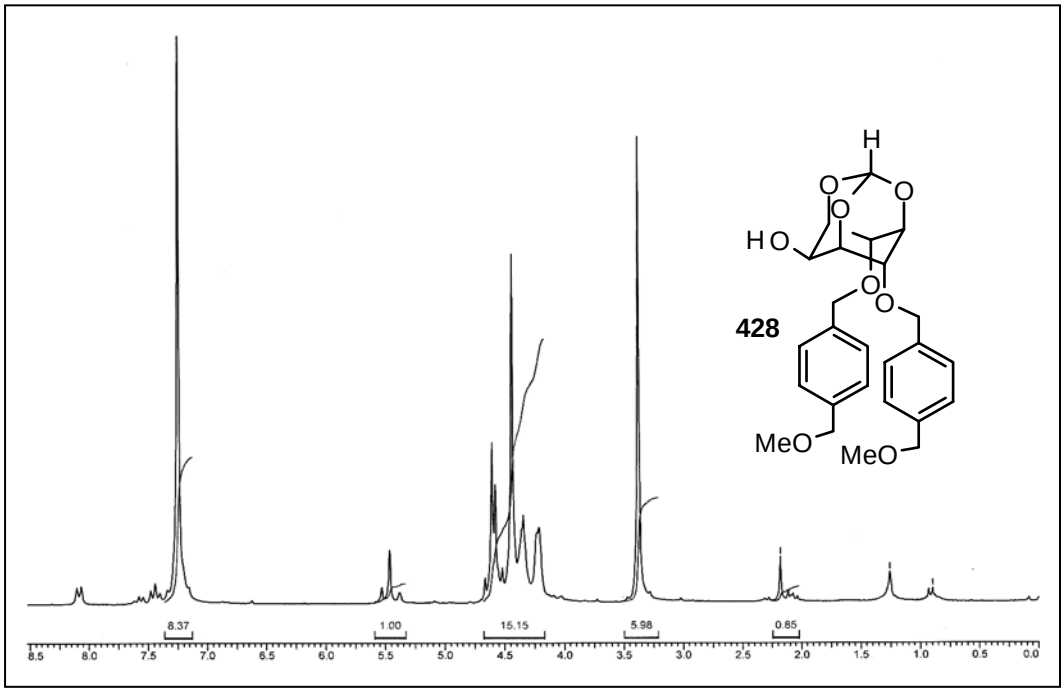
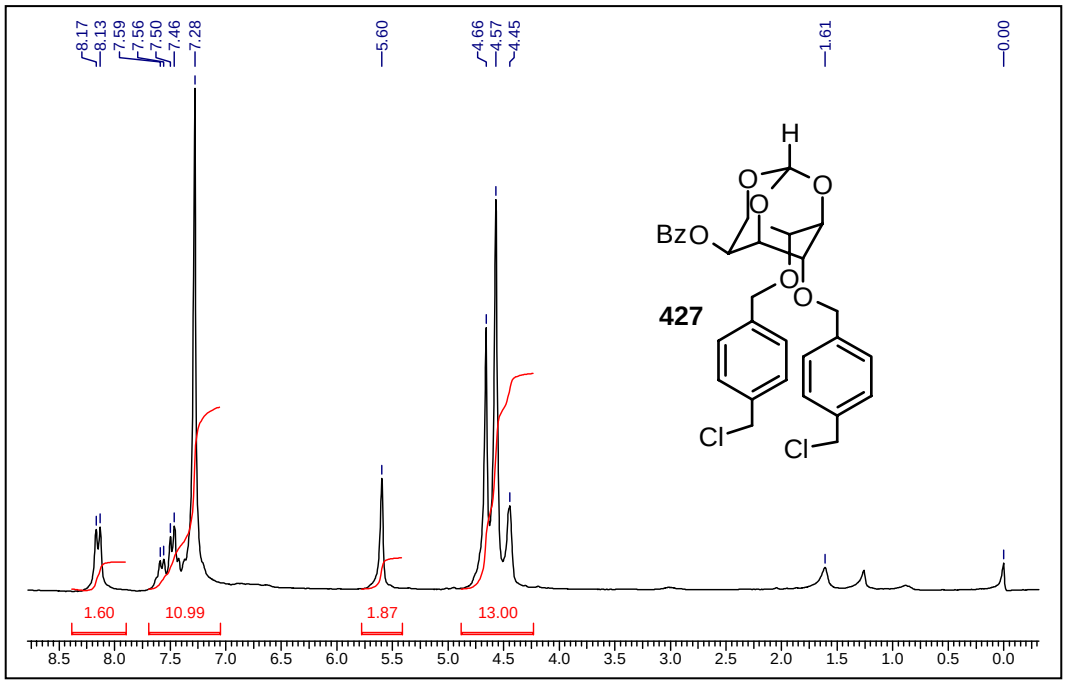

8.17
8.13
7.63
7.60
7.56
7.50
7.46
7.43
7.33
7.28
7.27
5.60
4.66
4.57
4.56
4.49
4.46
4.45
1.66
0.00
H
O
O
O
BzO
O
O
426
Br
Br
2.00
3.23
8.22
1.89
13.40
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


H
O
O
O
HO
O
O
428
MeO
MeO
8.37
1.00
15.15
5.98
0.85
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0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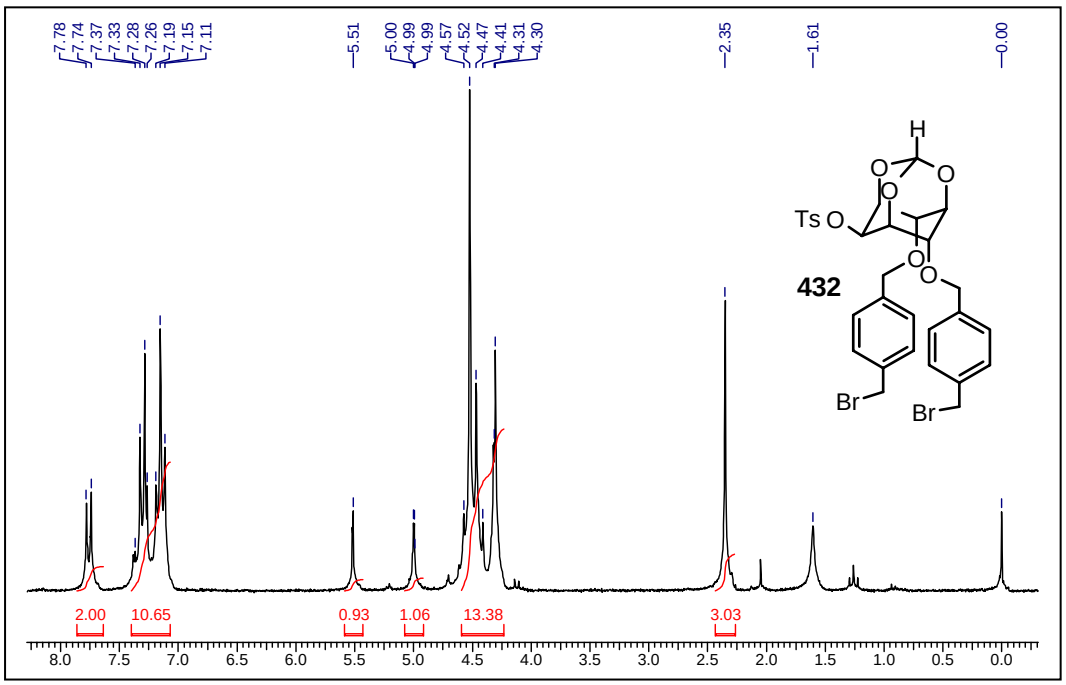
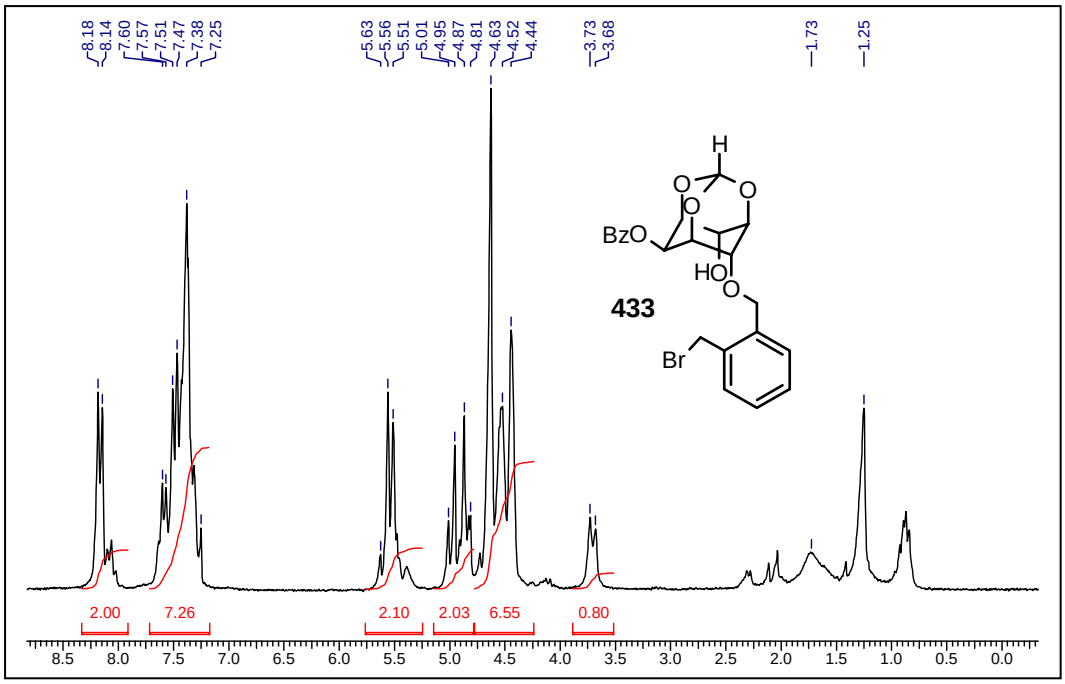
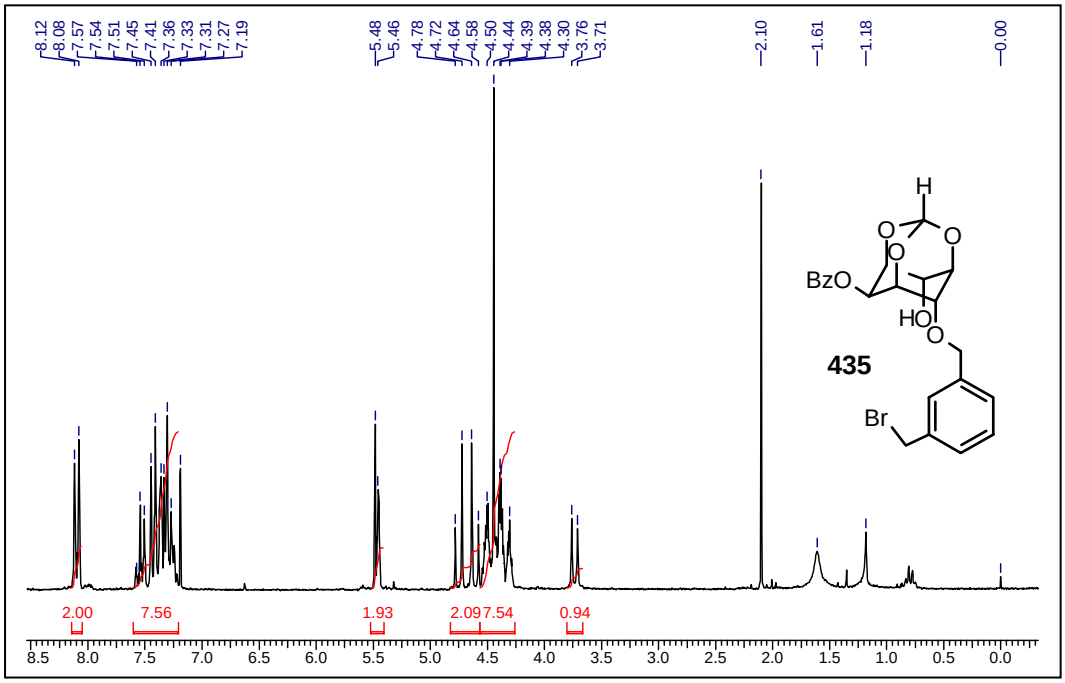
8.13
7.59
7.56
7.50
7.46
7.28
5.60
4.66
4.57
4.45
1.61
0.00
H
O
O
O
BzO
O
O
427
Cl
Cl
1.60
10.99
1.87
13.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


7.78
7.74
7.37
7.33
7.28
7.26
7.19
7.15
7.11
5.51
5.00
4.99
4.99
4.57
4.52
4.47
4.41
4.31
4.30
2.35
1.61
0.00
H
O
O
O
Ts O
O
O
432
Br
Br
2.00
10.65
0.93
1.06
13.38
3.03
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


8.18
8.14
7.60
7.57
7.51
7.47
7.38
7.25
5.63
5.56
5.51
5.01
4.95
4.87
4.81
4.63
4.52
4.44
3.73
3.68
1.73
1.25
H
O
O
O
BzO
HO
O
433
Br
2.00
7.26
2.10
2.03
6.55
0.80
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


8.12
8.08
7.57
7.54
7.51
7.45
7.41
7.36
7.33
7.31
7.27
7.19
5.48
5.46
4.78
4.72
4.64
4.58
4.50
4.44
4.39
4.38
4.30
3.76
3.71
2.10
1.61
1.18
0.00
H
O
O
O
BzO
HO
O
435
Br
2.00
7.56
1.93
2.09
7.54
0.94
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

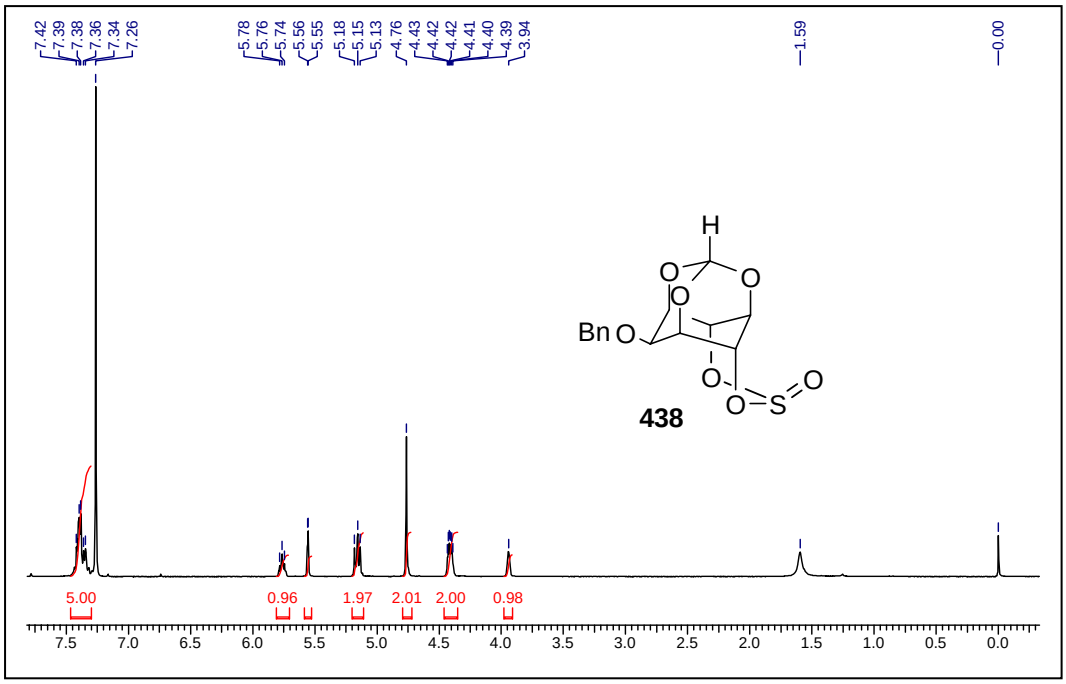
Crystal Data Table for **102**

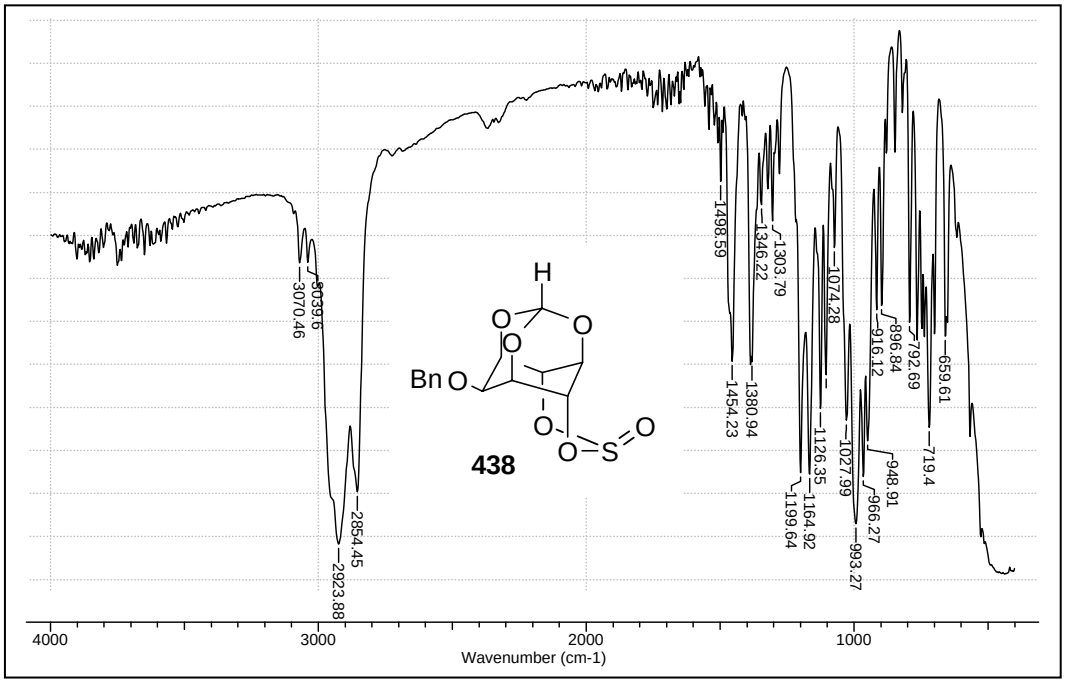
Wavelength	0.71073 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 9.0511(11) Å alpha = 68.849(2)° b = 10.0953(12) Å beta = 81.453(2)° c = 10.6586(13) Å gamma = 87.433(2)º
Volume	898.18(19) $Å^3$
Z, Calculated density	2, 1.370 Mg/m^3
Absorption coefficient	0.100 mm^{-1}
Crystal size	0.29 x 0.22 x 0.13 mm
Theta range for data collection	2.07 to 25.50 deg.
Reflections collected / unique	13398 / 3328 [R(int) = 0.0252]
Completeness to theta = 25.00	99.6 %
Refinement method	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.086
Final R indices [I>2sigma(I)]	R1 = 0.0448, wR2 = 0.1081
R indices (all data)	R1 = 0.0518, wR2 = 0.1126
Largest diff. peak and hole	0.185 and -0.184 e. $Å^{-3}$

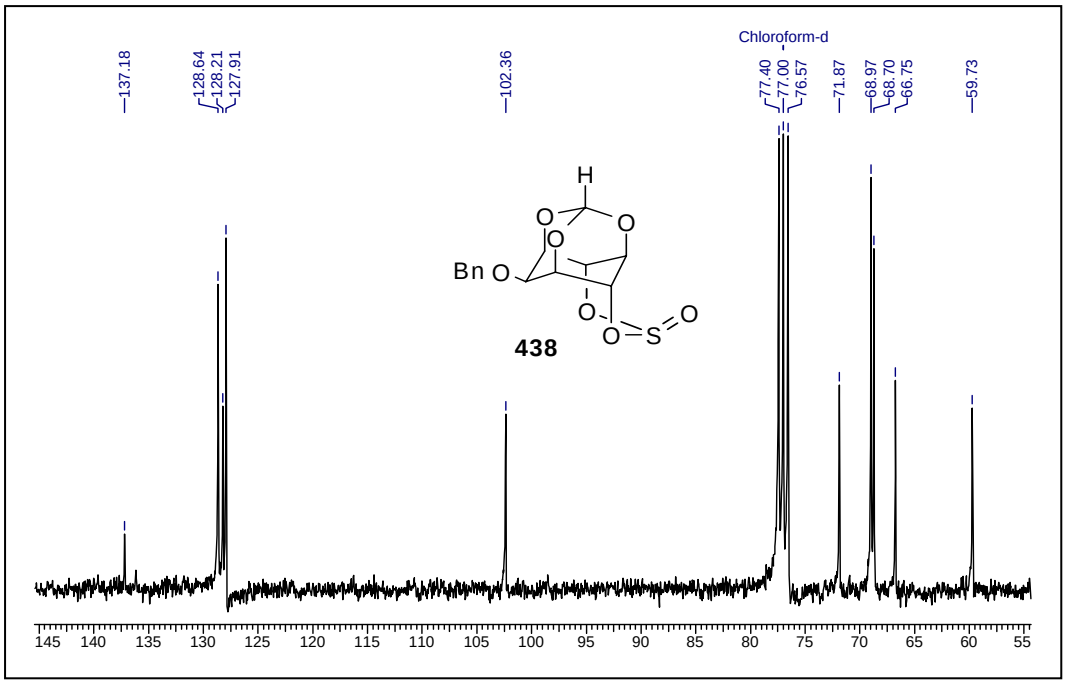
Table 3.4. Cg1 is the centroid of the C16-C21 ring

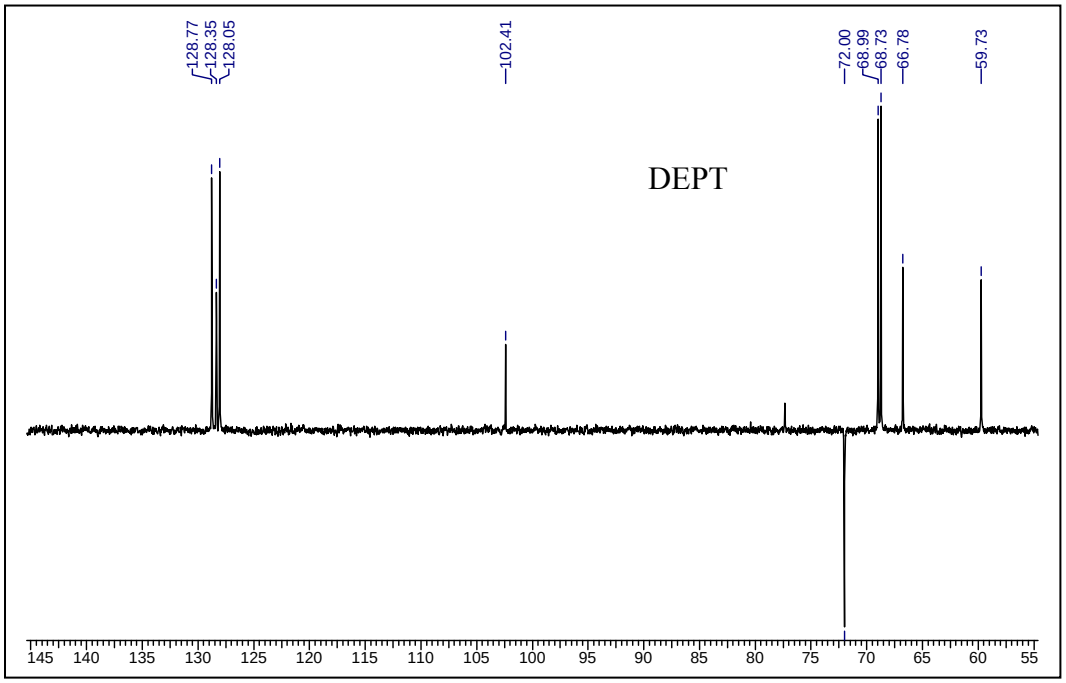
D-H···*A*	*D*-H	H···*A*	*D*···*A*	*D*-H···*A*
C2-H2···O6	0.98	2.47	2.8550 (19)	103
C2-H2···O4	0.98	2.69	3.0463 (18)	102
O2-H2*A*···O3	0.82	2.63	2.9385 (18)	104
O2-H2*A*···O1	0.82	2.66	2.9408 (18)	102
C10-H10···O4^{iii}	0.93	2.67	3.517 (2)	152
C15-H15*B*···O3^{ii}	0.97	2.64	3.514 (2)	150
C4-H4···O3^{ii}	0.98	2.62	3.466 (2)	145
O2-H2*A*···O1^{i}	0.82	2.15	2.8558 (16)	144
C15-H15*A*···*Cg*1^{iv}	0.97	2.69	3.602	158

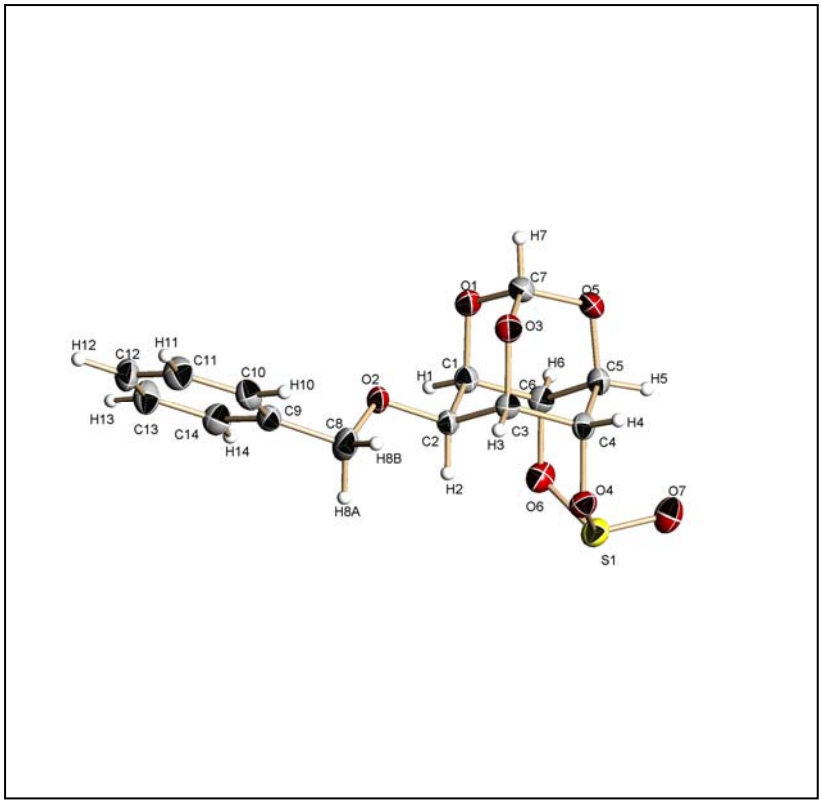
Symmetry codes: (i) –x, -y+2, -z+1; (ii) –x+1, -y+2, -z+1; (iii) –x+1, -y+1, -z+2; (iv) –x+1, -y, -z.


7.42
7.39
7.38
7.36
7.34
7.26
5.78
5.76
5.74
5.56
5.55
5.18
5.15
5.13
4.76
4.43
4.42
4.42
4.41
4.40
4.39
3.94
1.59
0.00
H
O
O
O
Bn O
O
O=S=O
438
5.00
0.96
1.97
2.01
2.00
0.98
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


3070.46
3039.6
2923.88
2854.45
1498.59
1454.23
1380.94
1346.22
1303.79
1199.64
1164.92
1126.35
1074.28
1027.99
993.27
966.27
948.91
916.12
896.84
792.69
719.4
659.61
H
O
O
O
Bn O
O
O=S=O
438
4000
3000
2000
1000
Wavenumber (cm-1)


Chloroform-d
137.18
128.64
128.21
127.91
102.36
77.40
77.00
76.57
71.87
68.97
68.70
66.75
59.73
H
O
O
O
Bn O
O
O S O
438
145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55

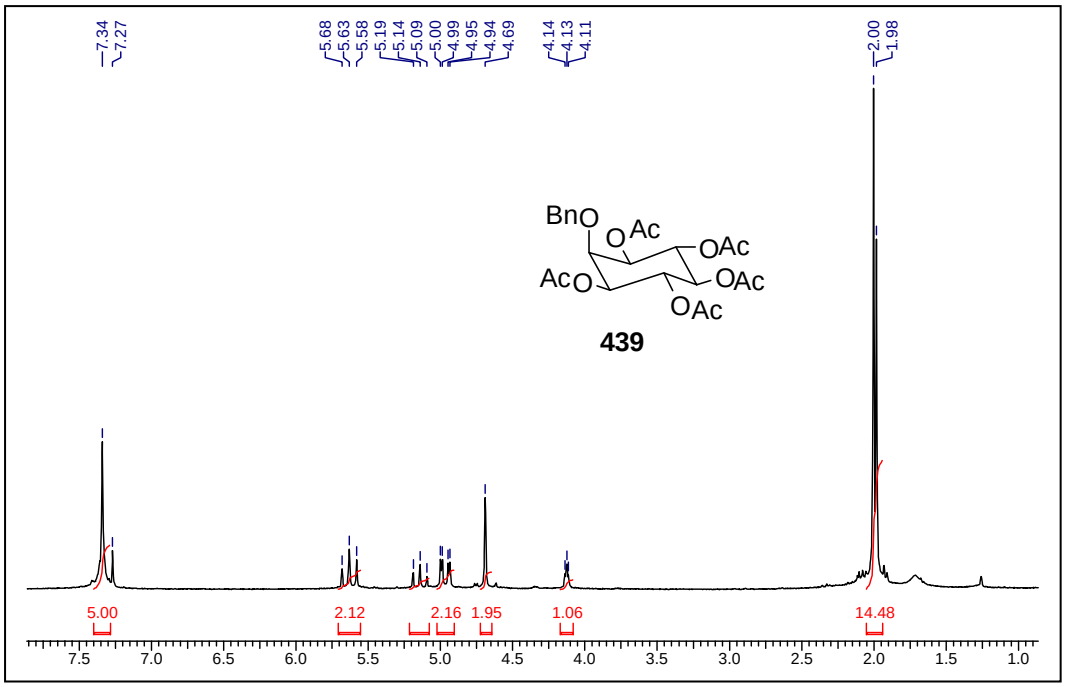

128.77
128.35
128.05
102.41
72.00
68.99
68.73
66.78
59.73
DEPT
145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55

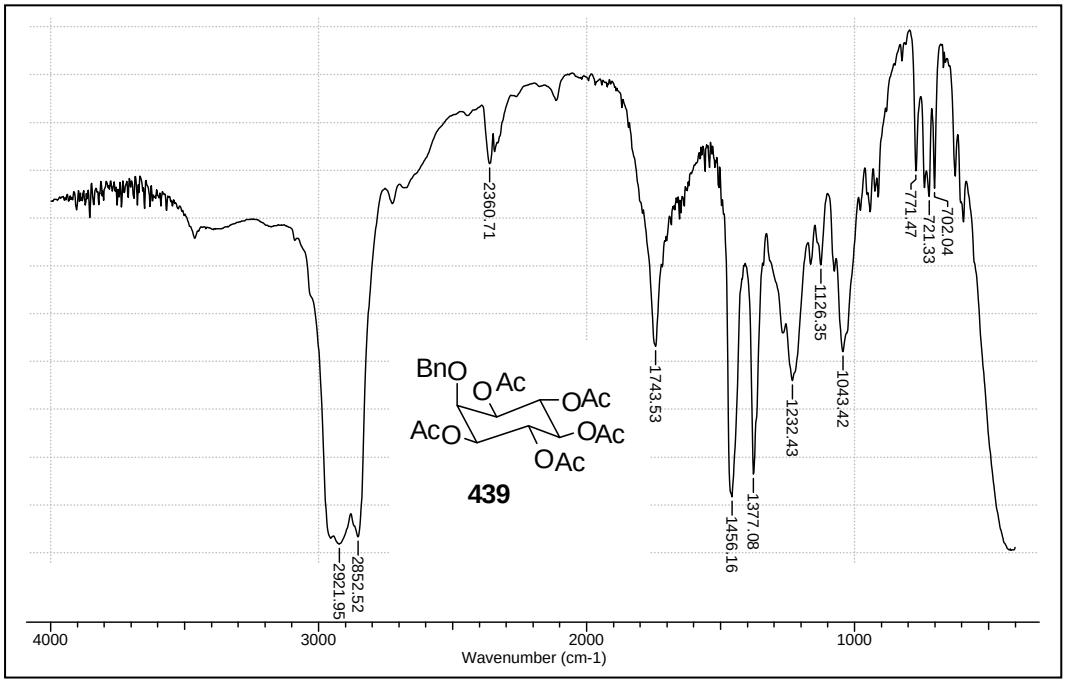


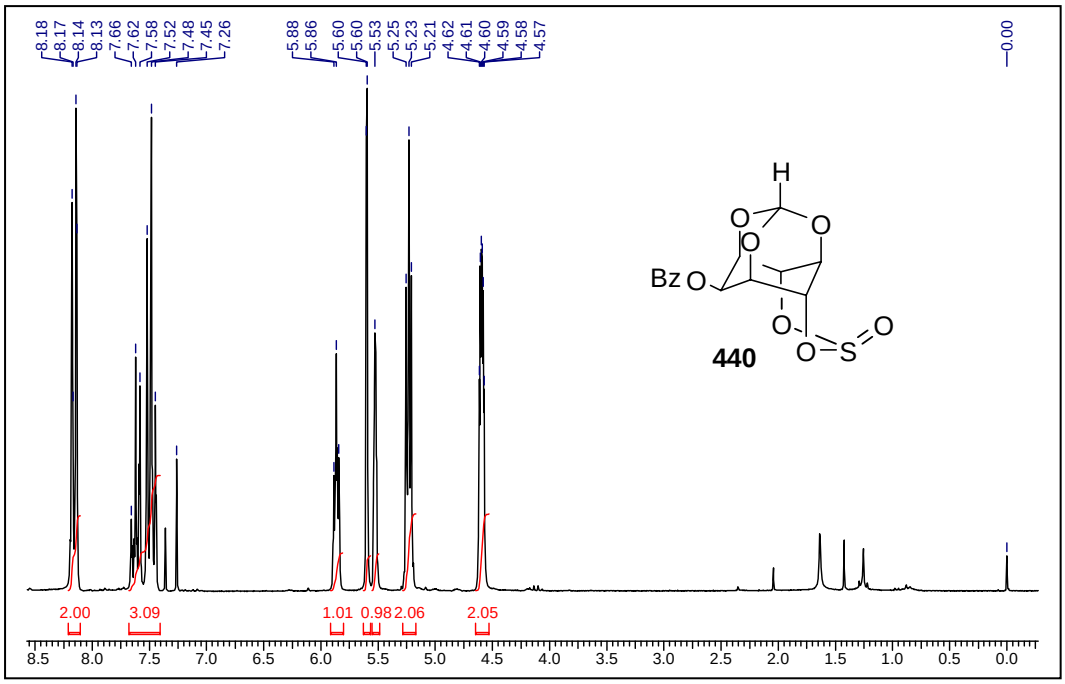
ORTEP of **438**

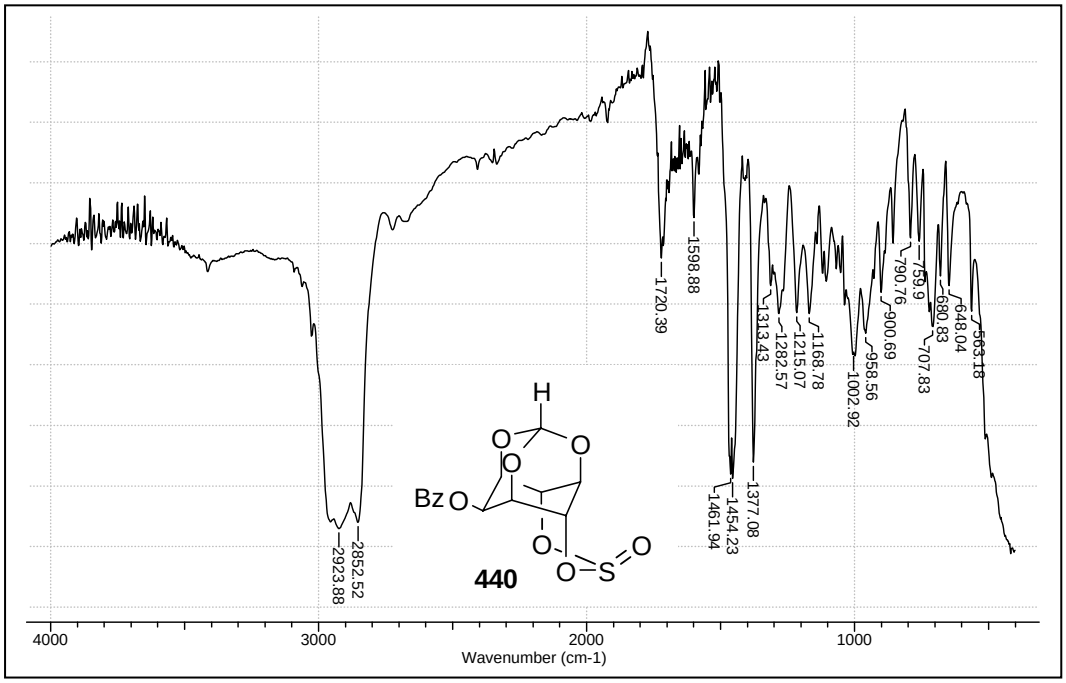
Crystal Data Table for **438**

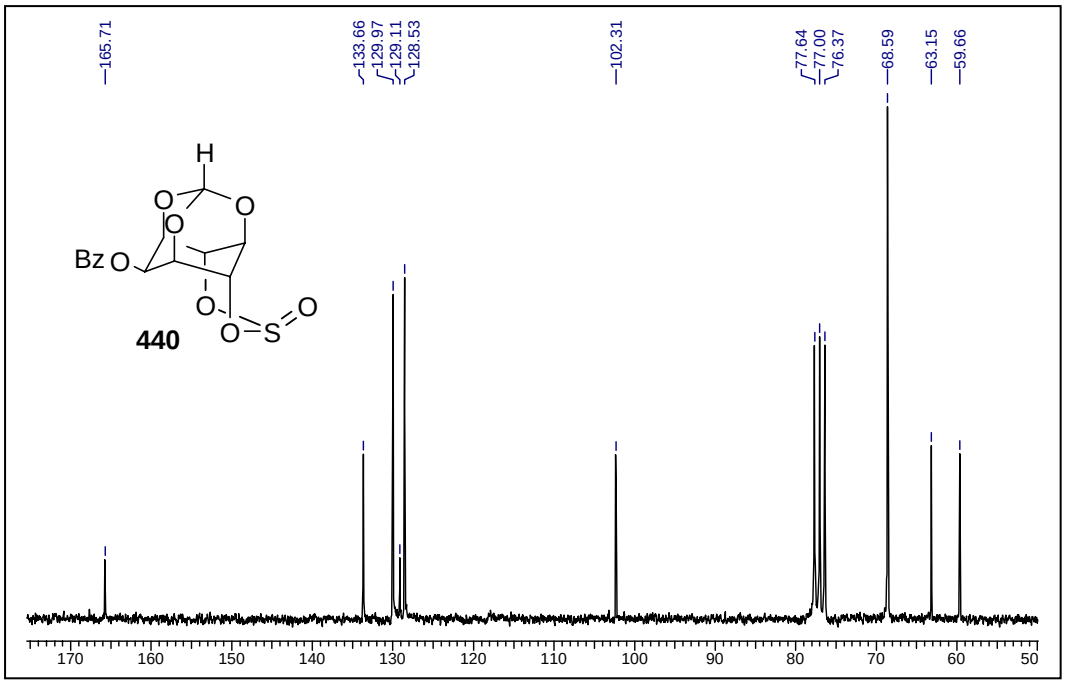
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, $P2_1/n$
Unit cell dimensions	a = 8.549(2) Å alpha = 90°. b = 11.112(3) Å beta = 99.109(7)°. c = 14.775(4) Å gamma = 90°
Volume	1386.0(7) $Å^3$
Z, Calculated density	4, 1.564 Mg/m^3
Absorption coefficient	0.268 mm^{-1}
Crystal size	0.28 x 0.26 x 0.21 mm
Theta range for data collection	2.30 to 25.00 deg.
Reflections collected / unique	6625 / 2432 [R(int) = 0.0254]
Completeness to theta = 25.00	99.8 %
Refinement method	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.044
Final R indices [I>2sigma(I)]	R1 = 0.0342, wR2 = 0.0888
R indices (all data)	R1 = 0.0404, wR2 = 0.0933
Largest diff. peak and hole	0.244 and -0.279 e. $Å^{-3}$

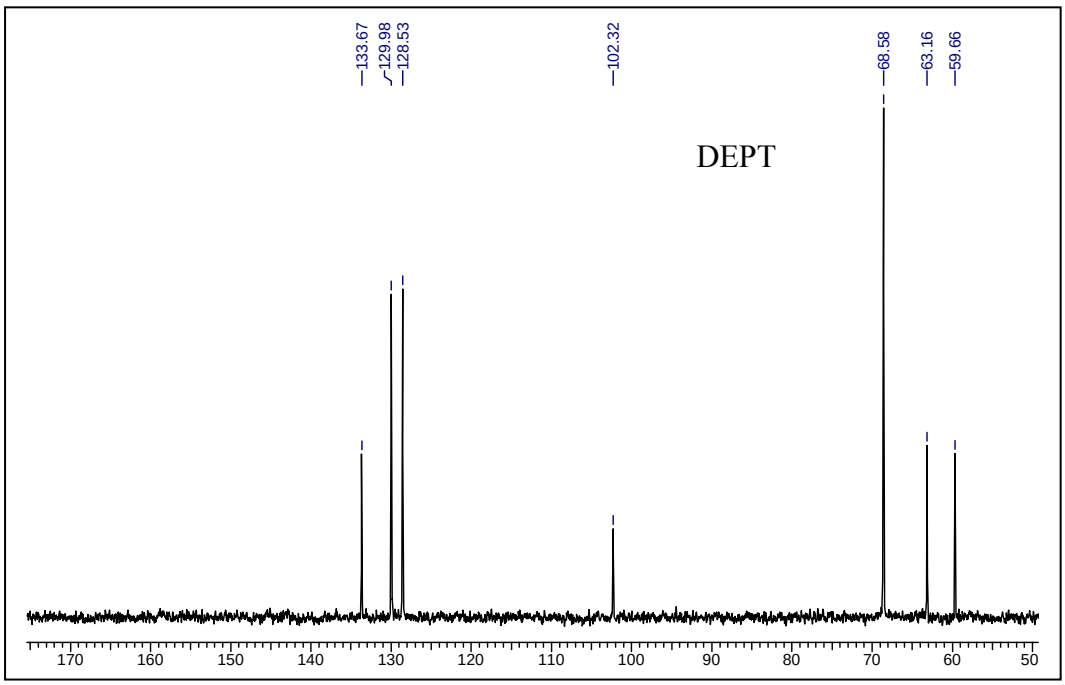

7.34
7.27
5.68
5.63
5.58
5.19
5.14
5.09
5.00
4.99
4.95
4.94
4.69
4.14
4.13
4.11
2.00
1.98
BnO
O
Ac
OAc
AcO
OAc
OAc
439
5.00
2.12
2.16
1.95
1.06
14.48
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

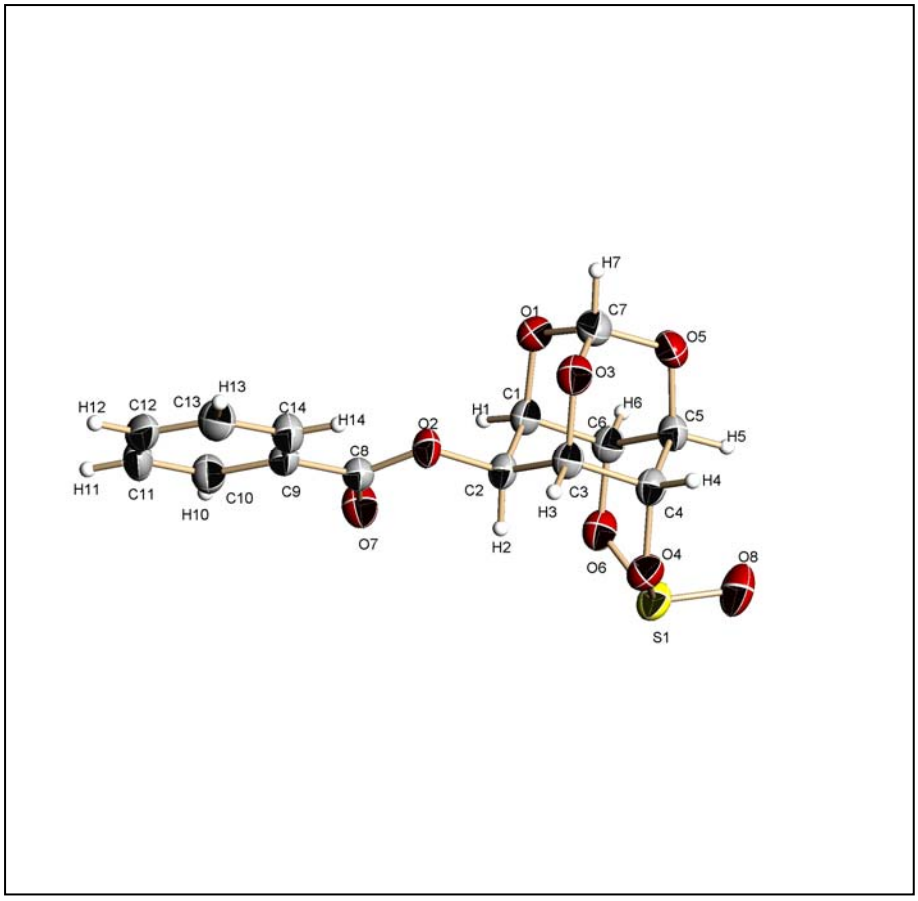

2360.71
2921.95
2852.52
1743.53
1456.16
1377.08
1232.43
1126.35
1043.42
771.47
721.33
702.04
BnO
O
Ac
OAc
AcO
OAc
OAc
439
4000
3000
2000
1000
Wavenumber (cm-1)


8.18
8.17
8.14
8.13
7.66
7.62
7.58
7.52
7.48
7.45
7.26
5.88
5.86
5.60
5.60
5.53
5.25
5.23
5.21
4.62
4.61
4.60
4.59
4.58
4.57
0.00
2.00
3.09
1.01
0.98
2.06
2.05
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
H
O
O
O
Bz O
O
O
O
S
O
440


2923.88
2852.52
1720.39
1598.88
1461.94
1454.23
1377.08
1313.43
1282.57
1215.07
1168.78
1002.92
968.56
900.69
790.76
759.9
707.83
680.83
648.04
563.18
4000
3000
2000
1000
Wavenumber (cm-1)
H
O
O
O
Bz O
O
O
O
S
O
440


165.71
133.66
129.97
129.11
128.53
102.31
77.64
77.00
76.37
68.59
63.15
59.66
H
O
O
O
Bz O
O
O
S
O
440
170
160
150
140
130
120
110
100
90
80
70
60
50

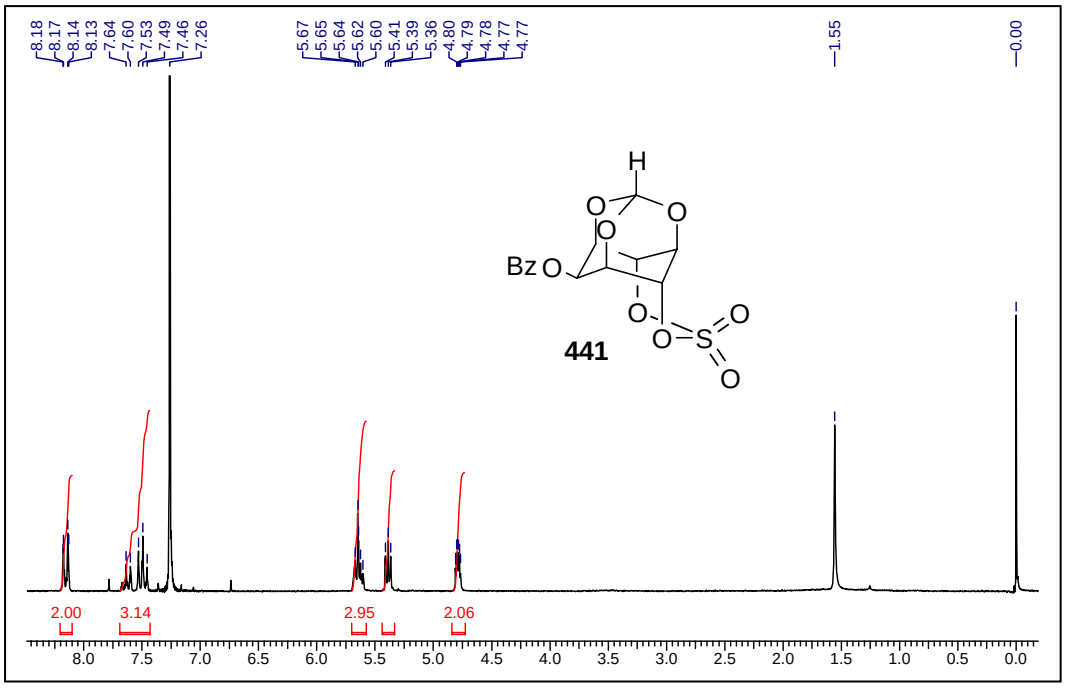

133.67
129.98
128.53
102.32
68.58
63.16
59.66
DEPT
170
160
150
140
130
120
110
100
90
80
70
60
50

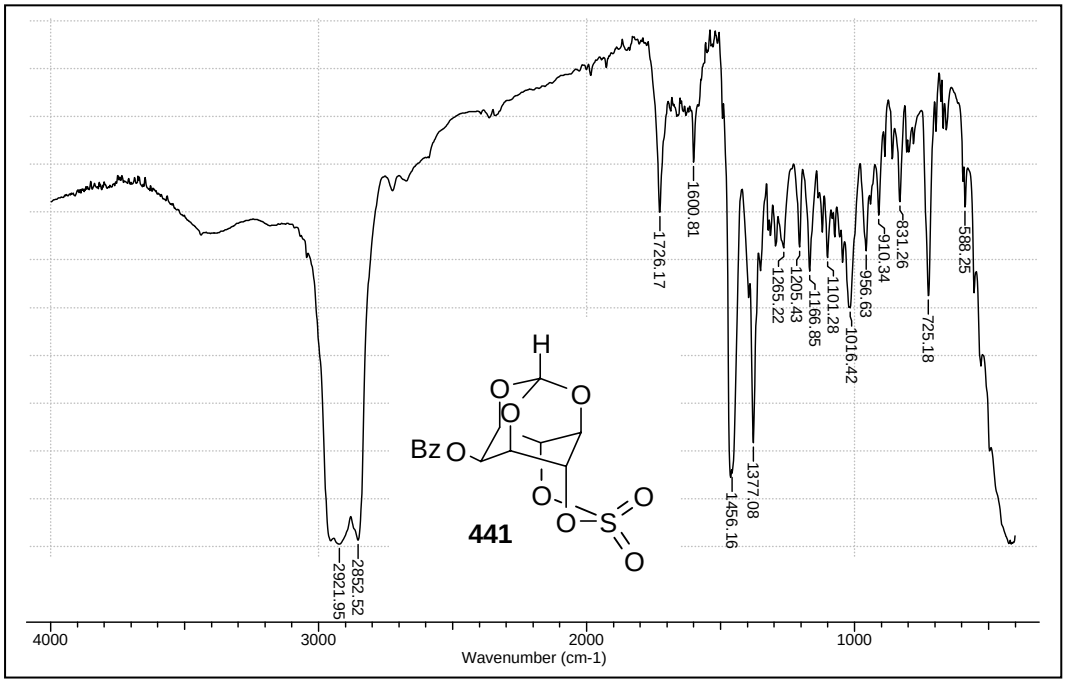


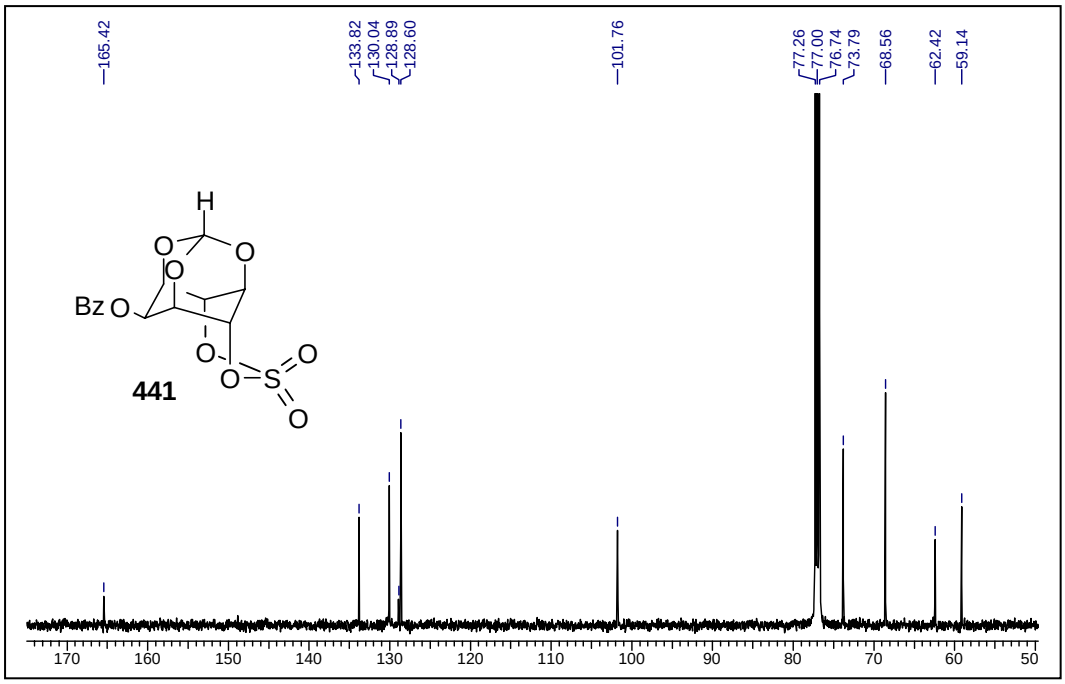
ORTEP of **440**

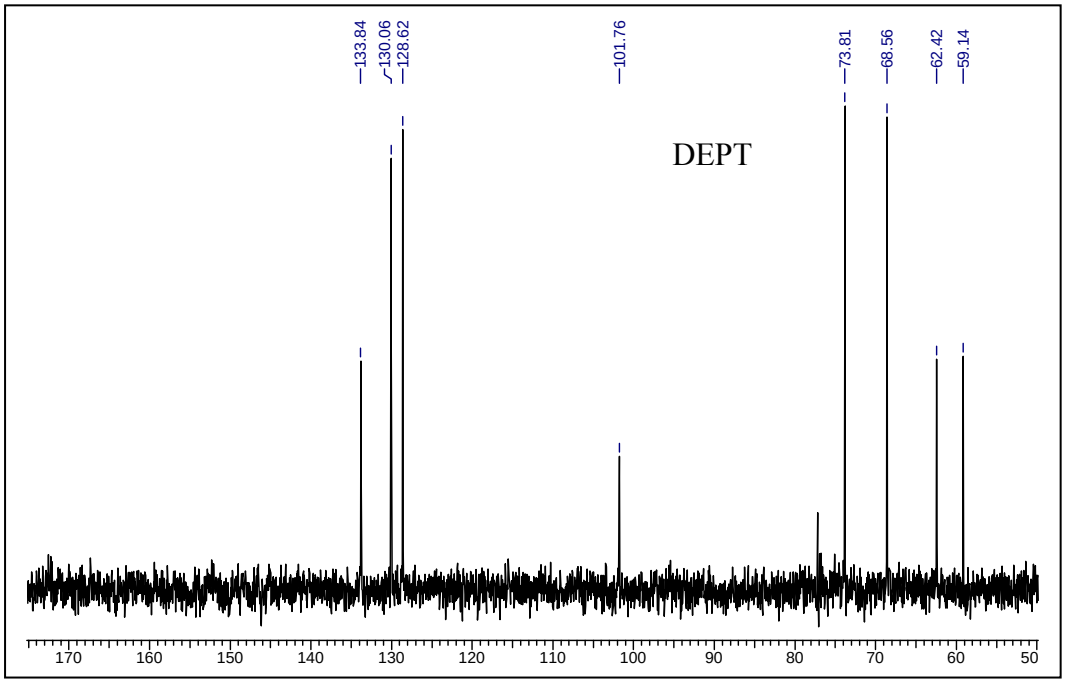
Crystal Data Table for **440**

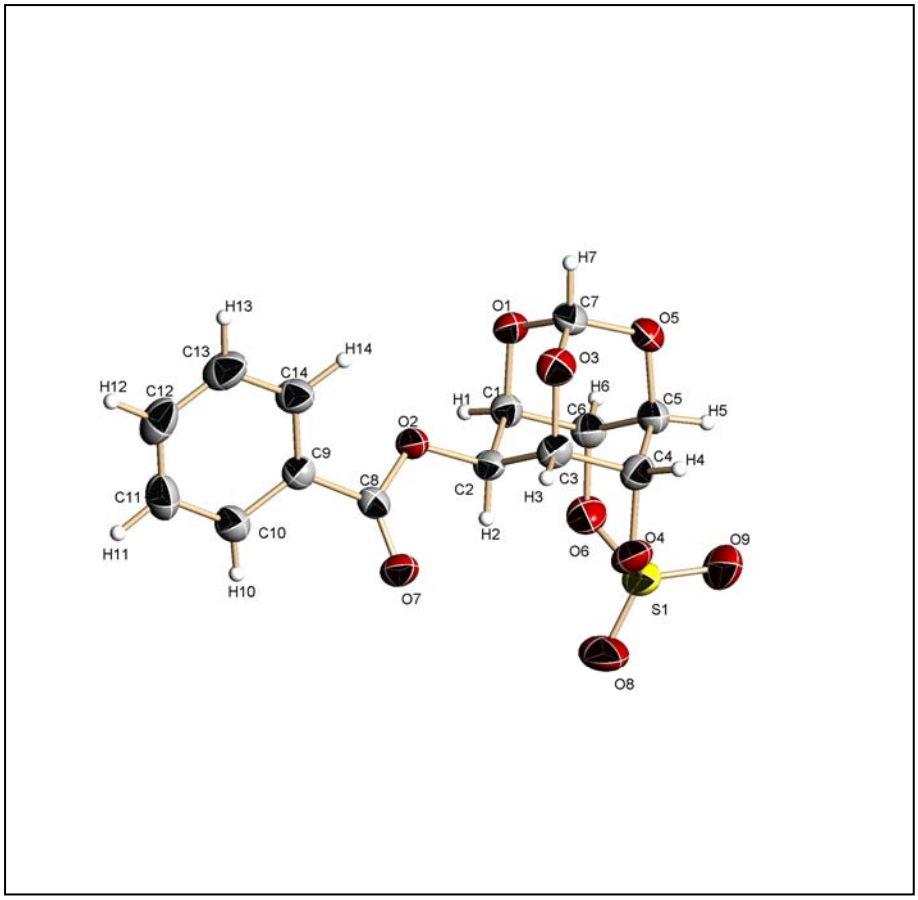
Wavelength	0.71073 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 6.225(2) Å alpha = 93.169(5)°. b = 7.268(3) Å beta = 97.104(5)°. c = 16.151(6) Å gamma = 109.801(5)°.
Volume	678.5(4) $Å^3$
Z, Calculated density	2, 1.666 Mg/m^3
Absorption coefficient	0.283 mm^{-1}
Crystal size	0.64 x 0.55 x 0.11 mm
Theta range for data collection	2.56 to 25.00 deg.
Reflections collected / unique	6506 / 2392 [R(int) = 0.0236]
Completeness to theta = 25.00	99.6 %
Refinement method	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.067
Final R indices [I>2sigma(I)]	R1 = 0.0344, wR2 = 0.0960
R indices (all data)	R1 = 0.0356, wR2 = 0.0970
Largest diff. peak and hole	0.263 and -0.332 e. $Å^{-3}$


8.18
8.17
8.14
8.13
7.64
7.60
7.53
7.49
7.46
7.26
5.67
5.65
5.64
5.62
5.60
5.41
5.39
5.36
4.80
4.79
4.78
4.77
4.77
1.55
0.00
Bz O
441
2.00
3.14
2.95
2.06
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


2921.95
2852.52
1726.17
1600.81
1456.16
1377.08
1265.22
1205.43
1166.85
1101.28
1016.42
956.63
910.34
831.26
725.18
588.25
Bz O
441
4000
3000
2000
1000
Wavenumber (cm-1)


165.42
133.82
130.04
128.89
128.60
101.76
77.26
77.00
76.74
73.79
68.56
62.42
59.14
H
O
O
O
Bz O
O
O
O
S
O
441
170
160
150
140
130
120
110
100
90
80
70
60
50


133.84
130.06
128.62
101.76
73.81
68.56
62.42
59.14
DEPT
170
160
150
140
130
120
110
100
90
80
70
60
50

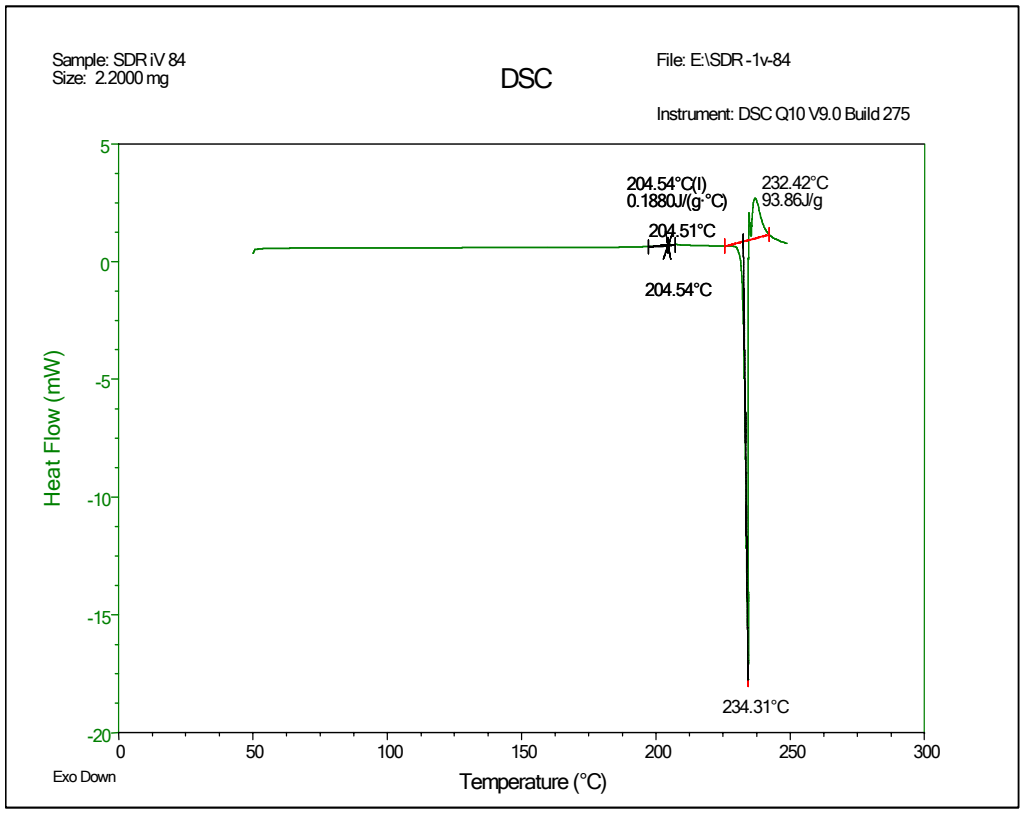


ORTEP of **441**

Crystal Data Table for **441**

Wavelength	0.71073 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 5.9115(8) Å alpha = 101.408(2)º. b = 10.0414(14) Å beta = 92.553(2)°. c = 12.5917(17) Å gamma =103.111(2)°
Volume	710.44(17) $Å^3$
Z, Calculated density	2, 1.666 Mg/m^3
Absorption coefficient	0.280 mm^{-1}
Crystal size	1.06 x 0.28 x 0.17 mm
Theta range for data collection	2.13 to 25.00 deg.
Reflections collected / unique	6824 / 2465 [R(int) = 0.0209]
Completeness to theta = 25.00	99.4 %
Refinement method	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.069
Final R indices [I>2sigma(I)]	R1 = 0.0322, wR2 = 0.0867
R indices (all data)	R1 = 0.0345, wR2 = 0.0886
Largest diff. peak and hole	0.205 and -0.349 e. $Å^{-3}$

DSC of **441**



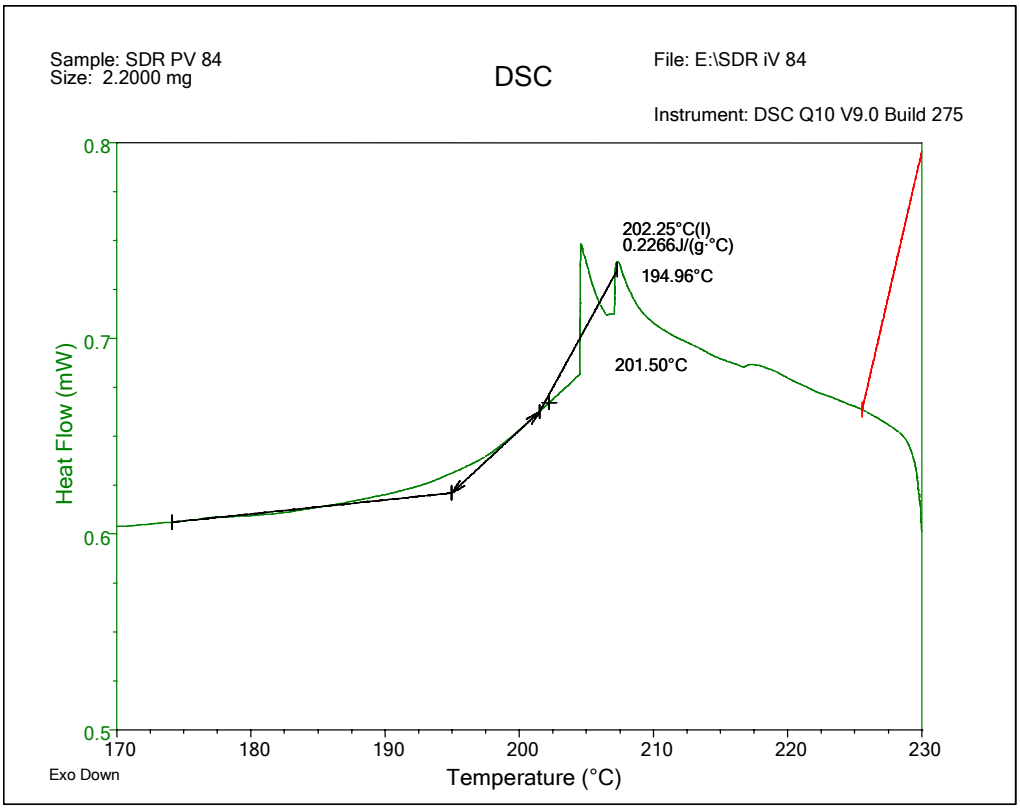
Peak Integration

Start	Onset	Maximum	Stop	Area
°C	°C	°C	°C	J/g
225.56	232.42	234.31	242.11	93.86

Glass Transition

Onset	Midpoint (I)	End	Height	Delta Cp
°C	°C	°C	mW	J/(g·°C)
204.51	204.54	204.54	0.03447	0.1880

Enlarged region (170-230 ºC) in DSC of **441**

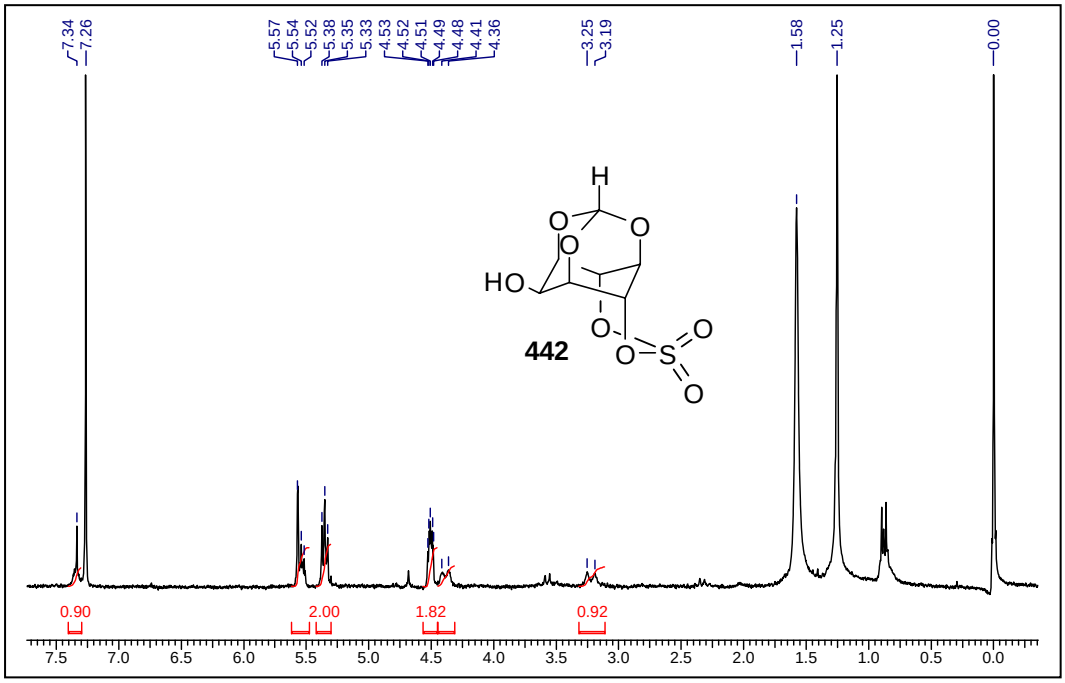


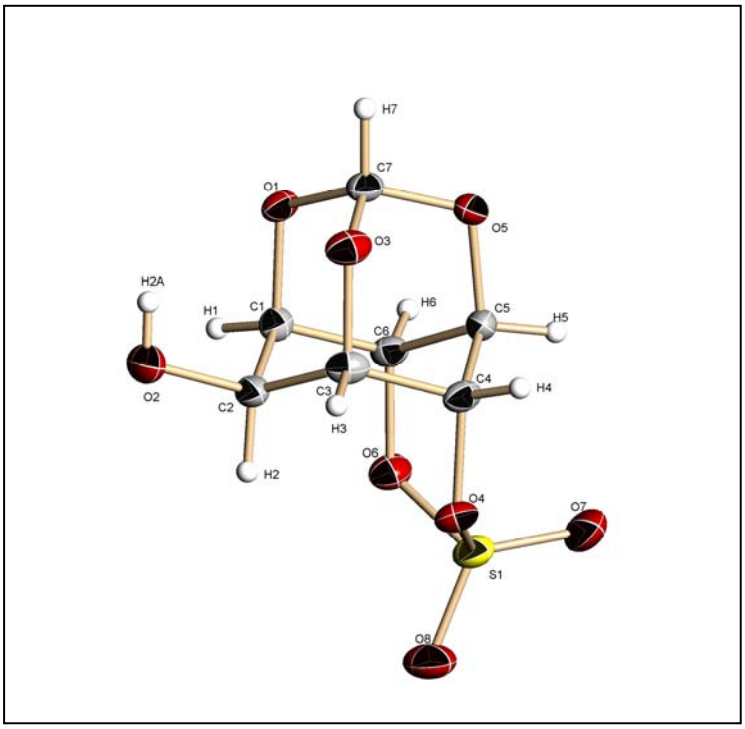
Peak Integration

Start	Onset	Maximum	Stop	Area
°C	°C	°C	°C	J/g
225.56	232.42	234.31	242.11	93.86

Glass Transition

Onset	Midpoint (I)	End	Height	Delta Cp
°C	°C	°C	mW	J/(g·°C)
194.96	202.25	201.50	0.04154	0.2266

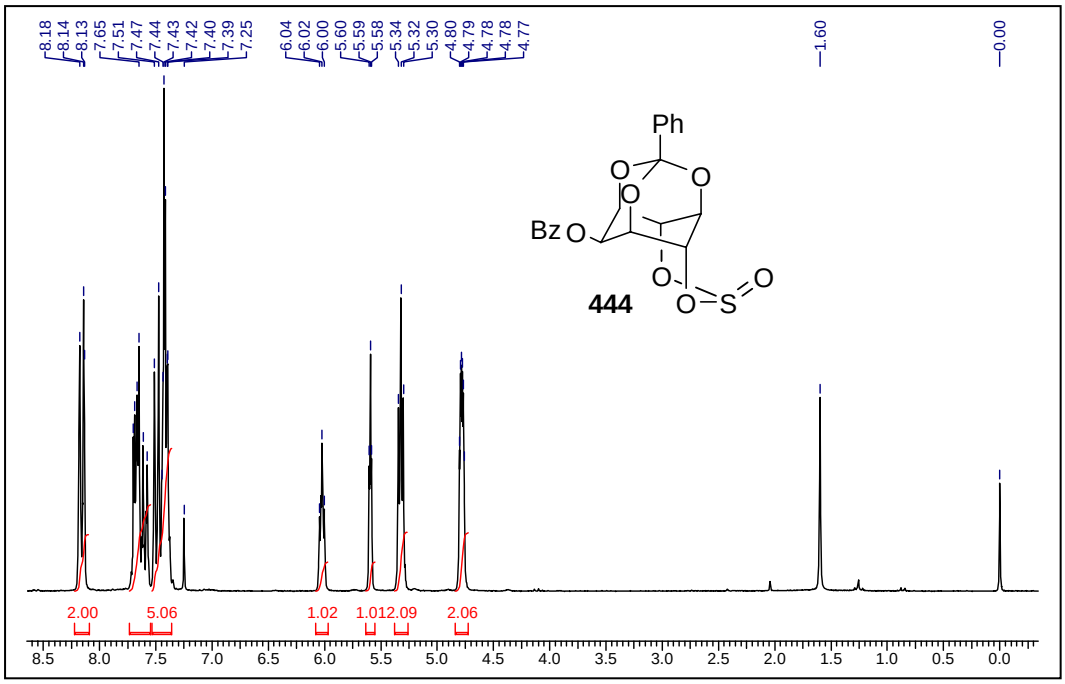

7.34
7.26
5.57
5.54
5.52
5.38
5.35
5.33
4.53
4.52
4.51
4.49
4.48
4.41
4.36
3.25
3.19
1.58
1.25
0.00
H
O
O
O
HO
O
O
S
O
O
442
0.90
2.00
1.82
0.92
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

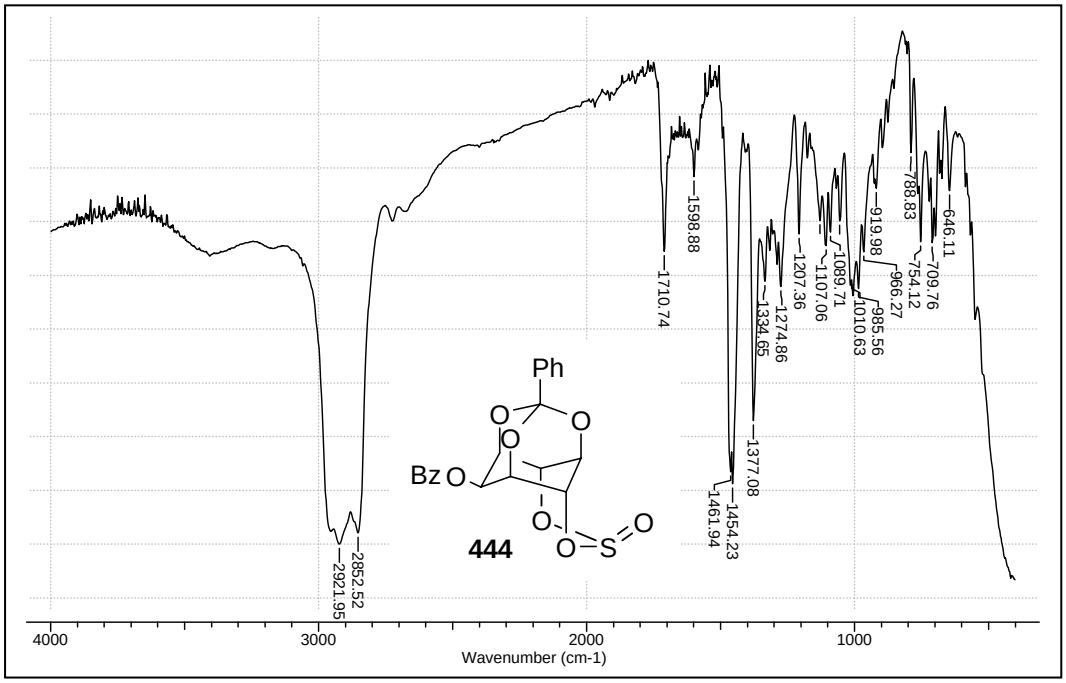


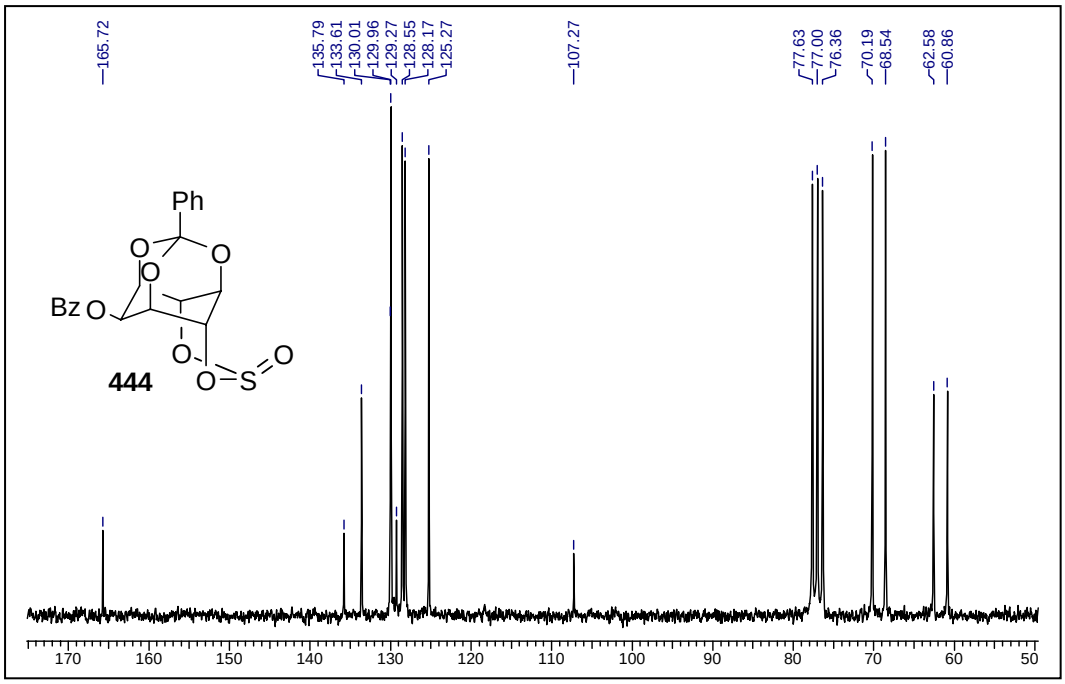
ORTEP of **442**

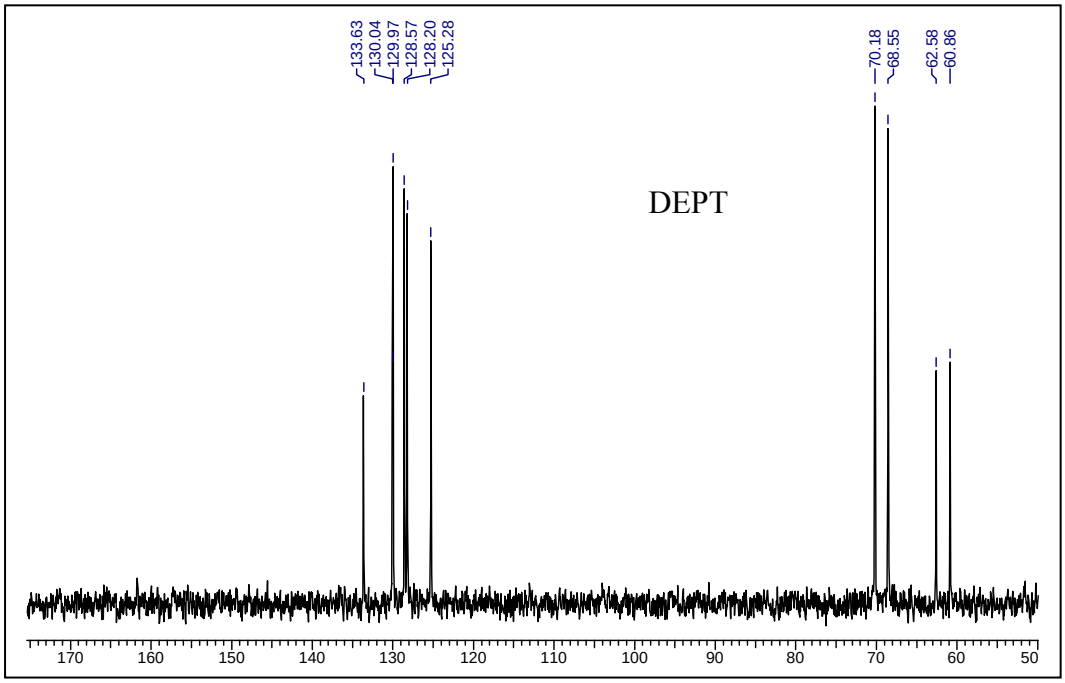
Crystal Data Table for **442**

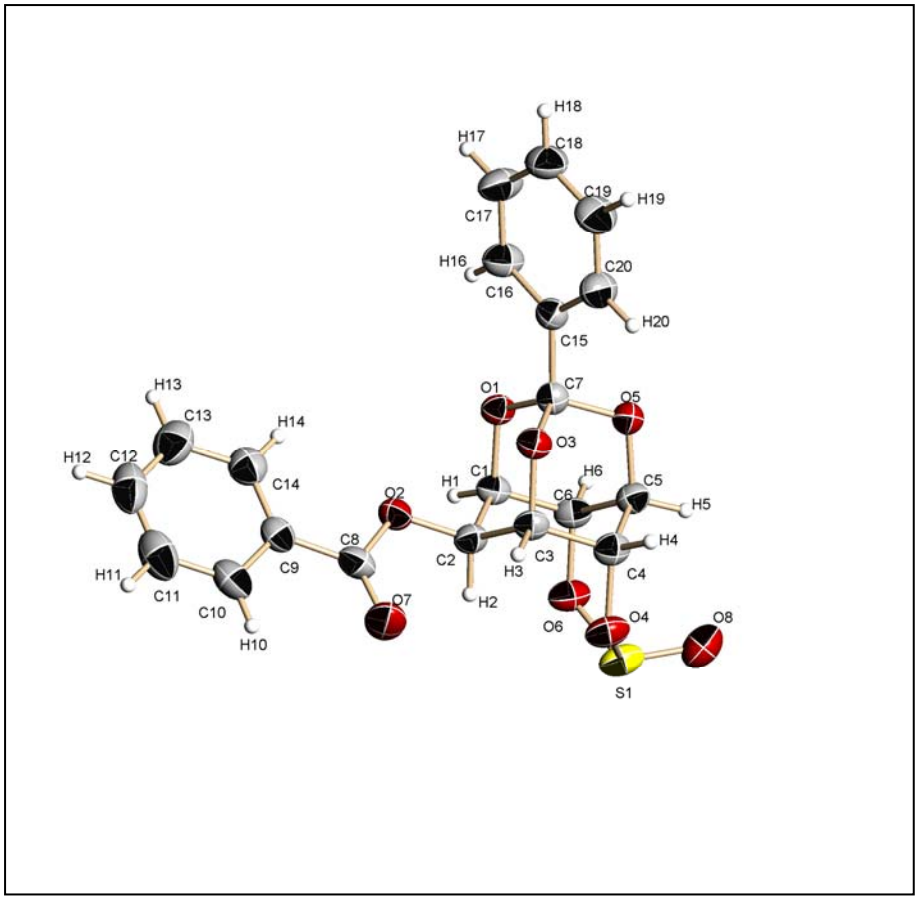
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, $Pna2_1$
Unit cell dimensions	a = 11.999(2) Å alpha = 90°. b = 8.3099(15) Å beta = 90°. c = 8.8995(16) Å gamma = 90°.
Volume	887.4(3) $Å^3$
Z, Calculated density	4, 1.888 Mg/m^3
Absorption coefficient	0.396 mm^{-1}
Crystal size	0.17 x 0.15 x 0.09 mm
Theta range for data collection	2.98 to 25.00 deg.
Reflections collected / unique	5988 / 1566 [R(int) = 0.0242]
Completeness to theta = 25.00	100.0 %
Refinement method	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.131
Final R indices [I>2sigma(I)]	R1 = 0.0310, wR2 = 0.0727
R indices (all data)	R1 = 0.0331, wR2 = 0.0737
Largest diff. peak and hole	0.150 and -0.265 e. $Å^{-3}$


8.18
8.14
8.13
7.65
7.51
7.47
7.44
7.43
7.42
7.40
7.39
7.25
6.04
6.02
6.00
5.60
5.59
5.58
5.34
5.32
5.30
4.80
4.79
4.78
4.78
4.77
1.60
0.00
Ph
O
O
O
Bz O
O
O
O
S
O
444
2.00
5.06
1.02
1.01
2.09
2.06
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


1710.74
1598.88
1461.94
1454.23
1377.08
1334.65
1274.86
1207.36
1107.06
1089.71
1010.63
985.56
966.27
919.98
788.83
754.12
709.76
646.11
2921.95
2852.52
Ph
O
O
O
Bz O
O
O
O
S
O
444
4000
3000
2000
1000
Wavenumber (cm-1)


165.72
135.79
133.61
130.01
129.96
129.27
128.55
128.17
125.27
107.27
77.63
77.00
76.36
70.19
68.54
62.58
60.86
Ph
O
O
O
Bz O
O
O
S
O
444
170
160
150
140
130
120
110
100
90
80
70
60
50

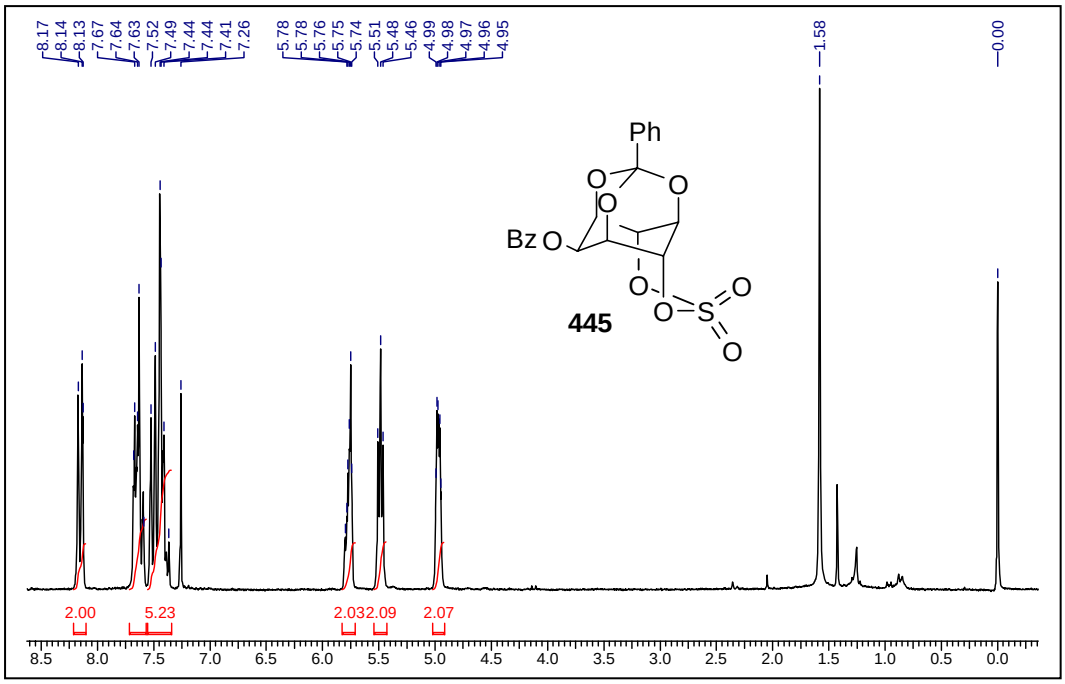

133.63
130.04
129.97
128.57
128.20
125.28
70.18
68.55
62.58
60.86
DEPT
170
160
150
140
130
120
110
100
90
80
70
60
50

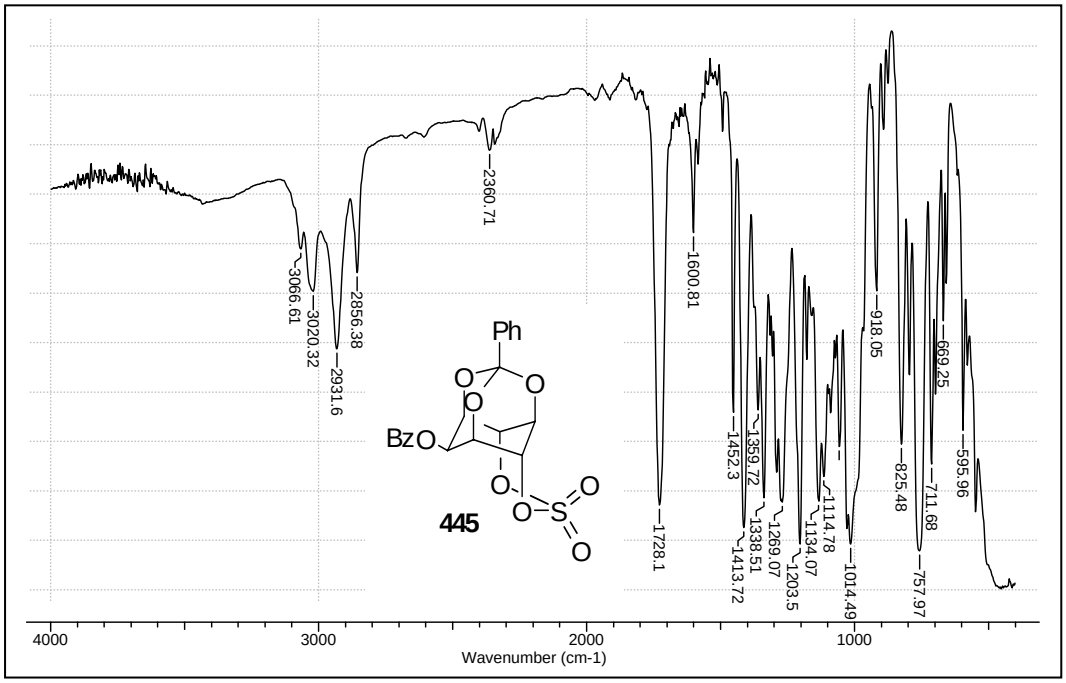


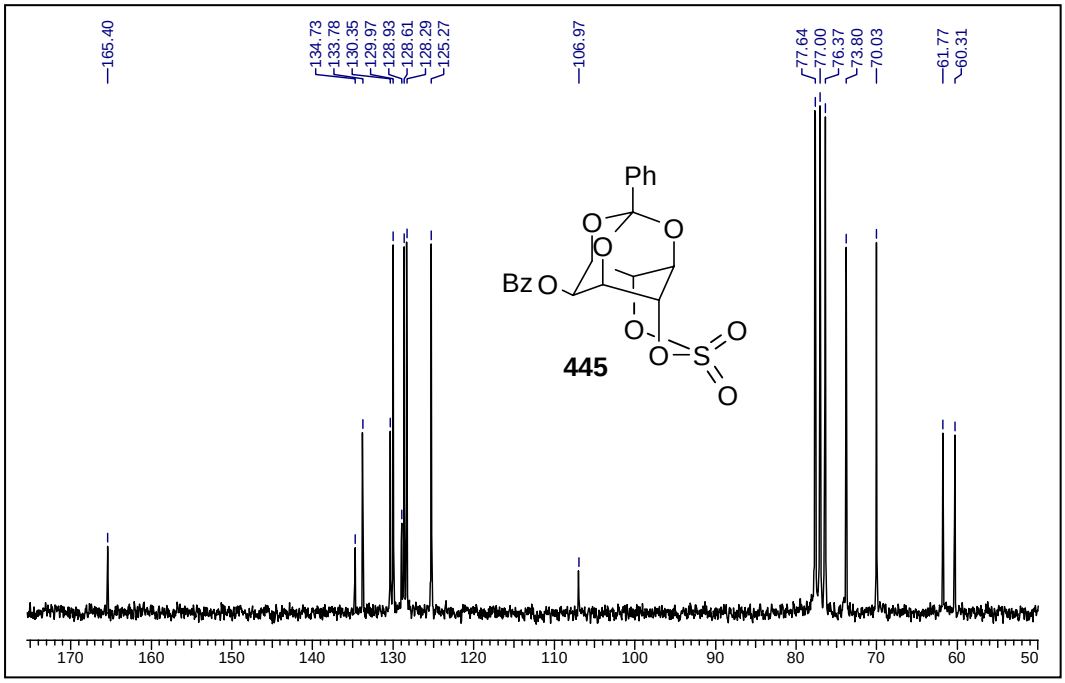
ORTEP of **444**

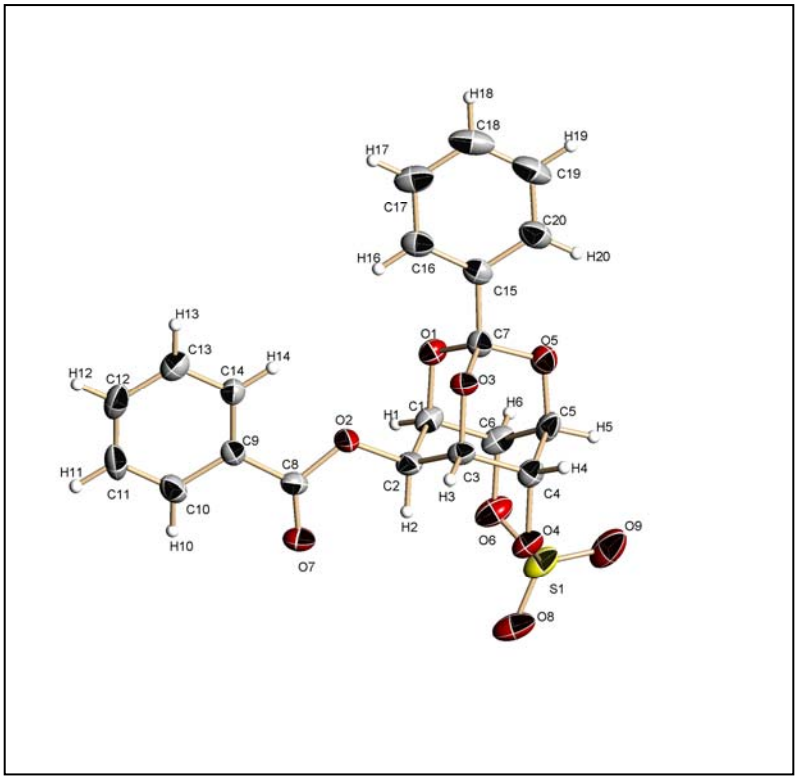
Crystal Data Table for **444**

Wavelength	0.71073 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 6.150(3) Å alpha = 97.946(11)°. b = 12.327(6) Å beta = 100.537(9)°. c = 12.441(6) Å gamma = 96.257(9)°.
Volume	909.6(8) $Å^3$
Z, Calculated density	2, 1.520 Mg/m^3
Absorption coefficient	0.227 mm^{-1}
Crystal size	0.45 x 0.33 x 0.31 mm
Theta range for data collection	2.18 to 25.00 deg.
Reflections collected / unique	4626 / 3166 [R(int) = 0.0265]
Completeness to theta = 25.00	98.6 %
Refinement method	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.318
Final R indices [I>2sigma(I)]	R1 = 0.0741, wR2 = 0.1756
R indices (all data)	R1 = 0.1123, wR2 = 0.1875
Largest diff. peak and hole	0.182 and -0.216 e. $Å^{-3}$


8.17
8.14
8.13
7.67
7.64
7.63
7.52
7.49
7.44
7.44
7.41
7.26
5.78
5.78
5.76
5.75
5.74
5.51
5.48
5.46
4.99
4.98
4.97
4.96
4.95
1.58
0.00
Ph
O
O
O
O
Bz O
O
O S O
O
445
2.00
5.23
2.03
2.09
2.07
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


3066.61
3020.32
2931.6
2856.38
2360.71
1600.81
1728.1
1452.3
1413.72
1359.72
1338.51
1269.07
1203.5
1134.07
1114.78
1014.49
918.05
825.48
757.97
711.68
669.25
595.96
Ph
O
O
O
O
BzO
O
O S O
O
445
4000
3000
2000
1000
Wavenumber (cm-1)

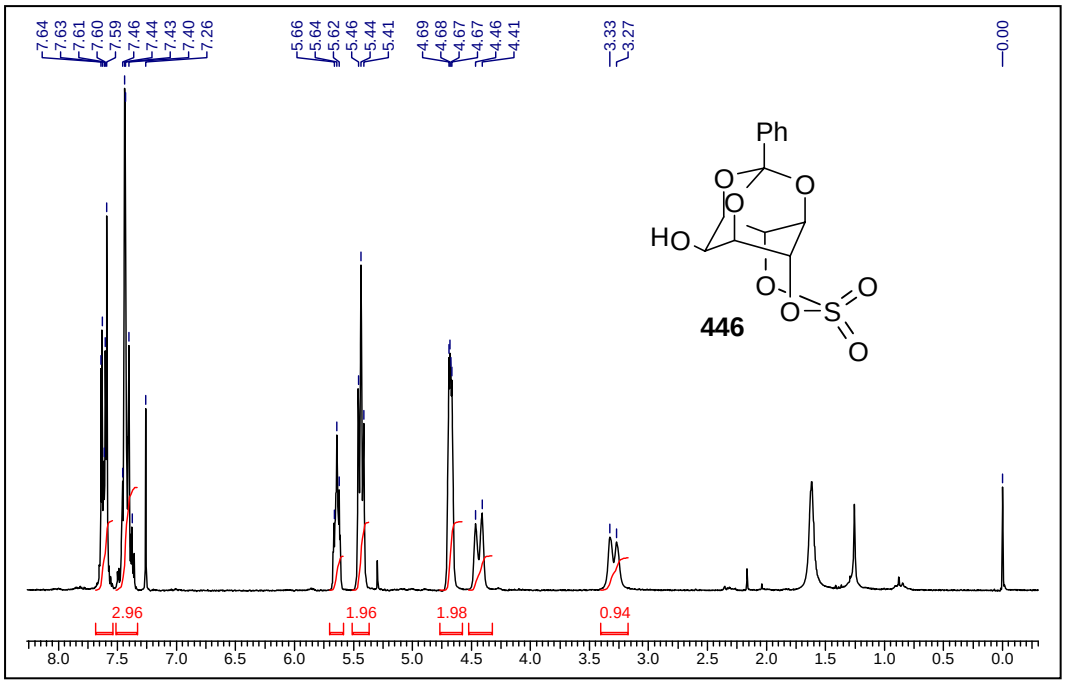

165.40
134.73
133.78
130.35
129.97
128.93
128.61
128.29
125.27
106.97
77.64
77.00
76.37
73.80
70.03
61.77
60.31
Ph
O
O
O
Bz O
O
O
S
O
O
445
170
160
150
140
130
120
110
100
90
80
70
60
50

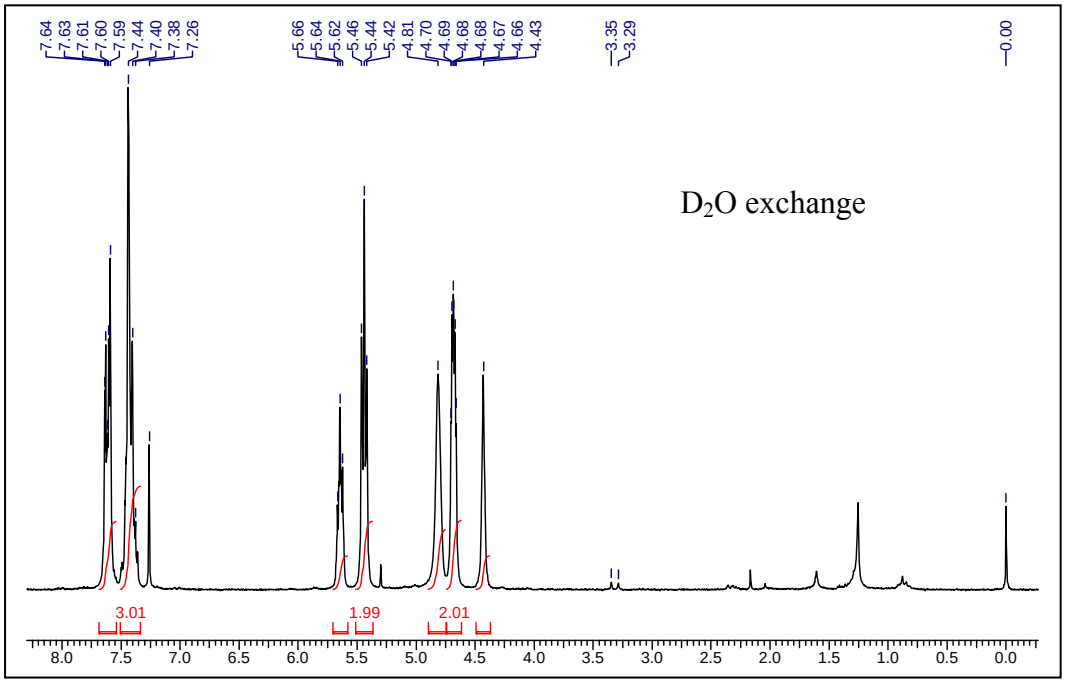


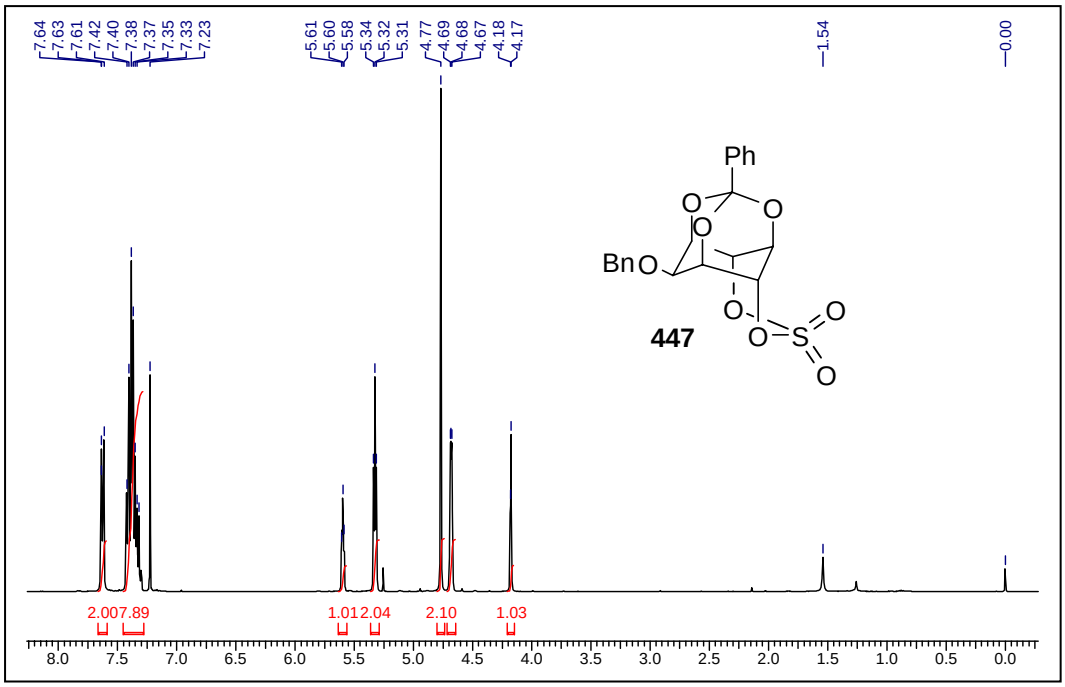
ORTEP of **445**

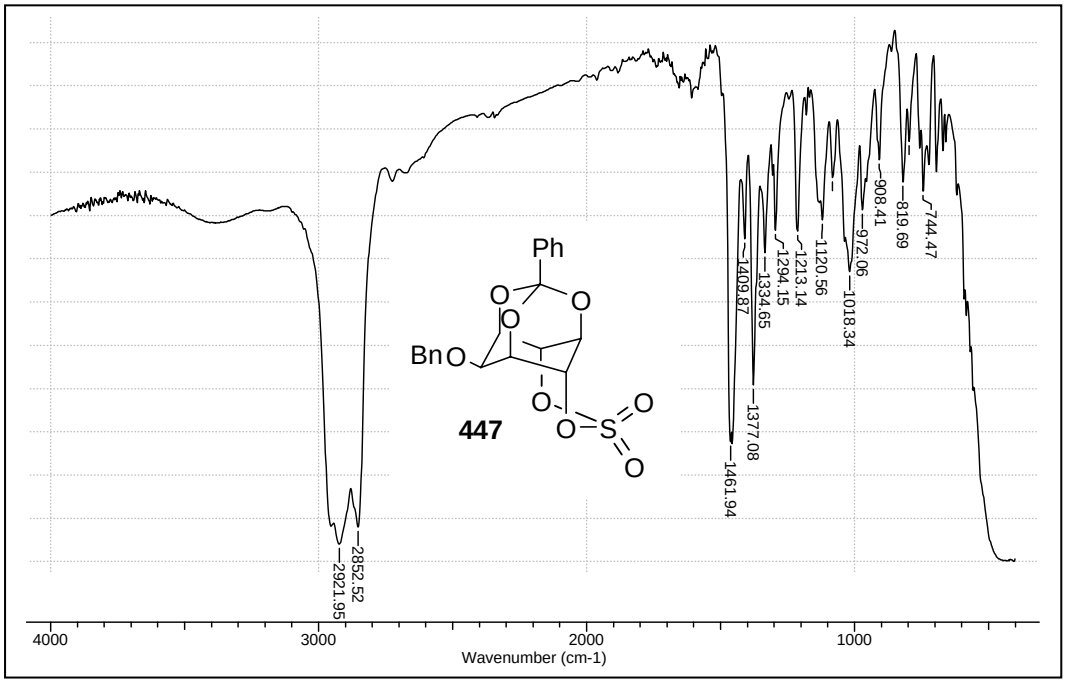
Crystal Data Table for **445**

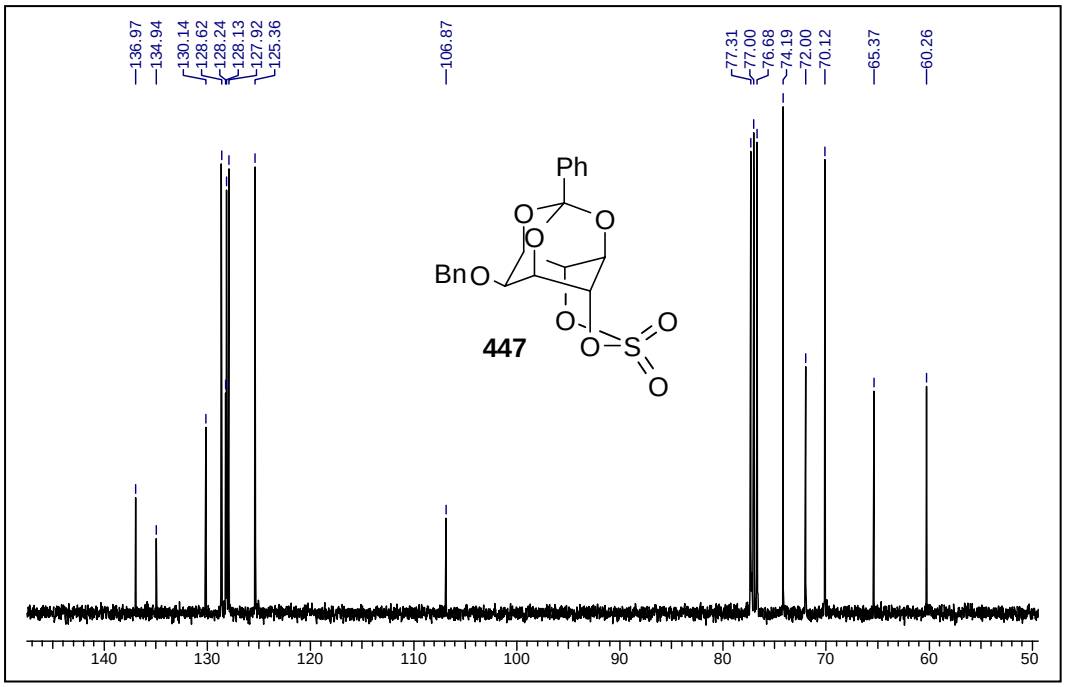
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, $P2_1\backslash N$
Unit cell dimensions	a = 8.549(2) Å alpha = 90°. b = 11.112(3) Å beta = 99.109(7)°. c = 14.775(4) Å gamma = 90°.
Volume	1386.0(7) $Å^3$
Z, Calculated density	8, 1.529 Mg/m^3
Absorption coefficient	0.227 mm^{-1}
Crystal size	0.28 x 0.26 x 0.21 mm
Theta range for data collection	2.30 to 25.00 deg.
Reflections collected / unique	6625 / 2432 [R(int) = 0.0254]
Completeness to theta = 25.00	99.8 %
Refinement method	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.044
Final R indices [I>2sigma(I)]	R1 = 0.0342, wR2 = 0.0888
R indices (all data)	R1 = 0.0404, wR2 = 0.0933
Largest diff. peak and hole	0.244 and -0.279 e. $Å^{-3}$

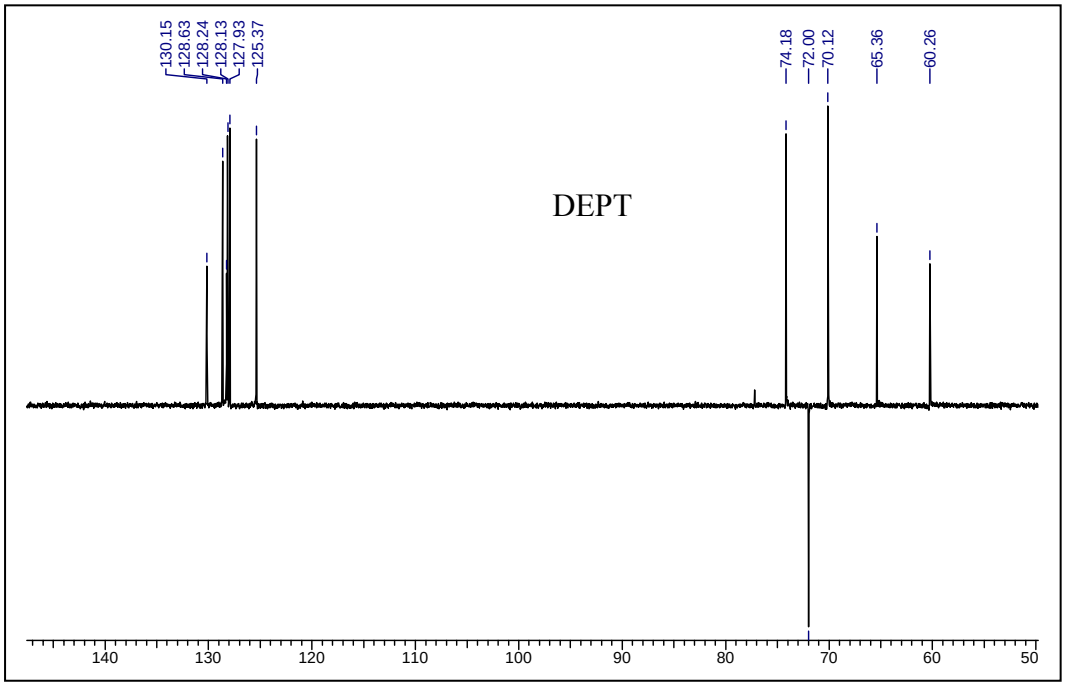

7.64
7.63
7.61
7.60
7.59
7.46
7.44
7.43
7.40
7.26
5.66
5.64
5.62
5.46
5.44
5.41
4.69
4.68
4.67
4.67
4.46
4.41
3.33
3.27
0.00
Ph
O
O
O
HO
O
O
O
S
O
O
446
2.96
1.96
1.98
0.94
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

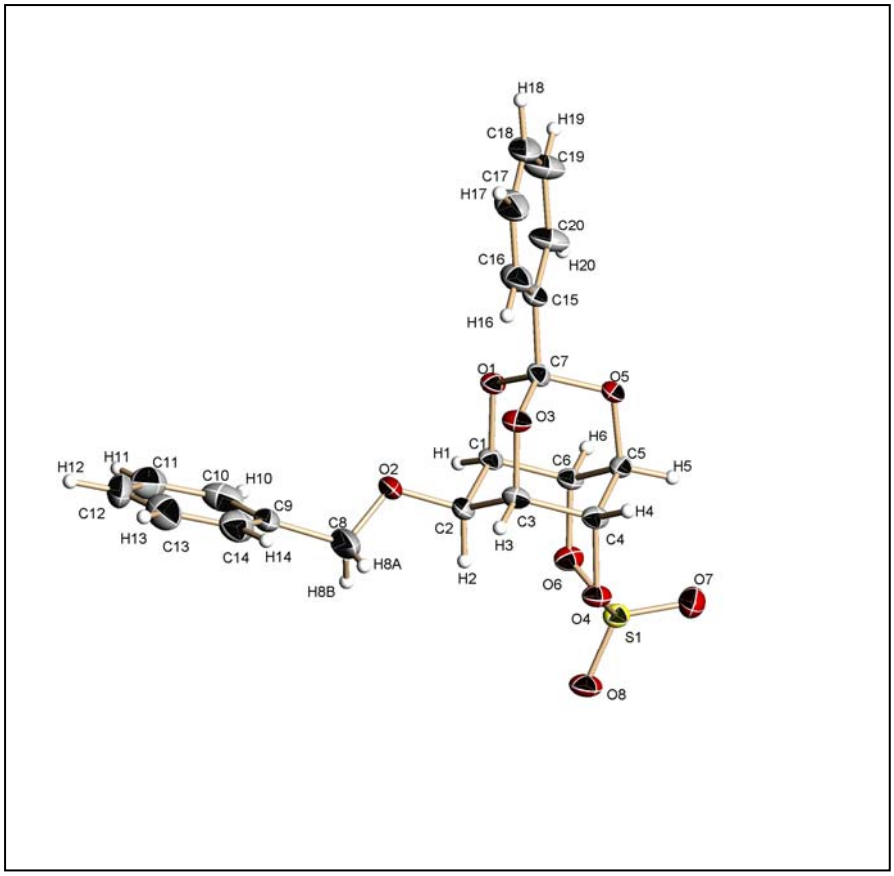

7.64
7.63
7.61
7.60
7.59
7.44
7.40
7.38
7.26
5.66
5.64
5.62
5.46
5.44
5.42
4.81
4.70
4.69
4.68
4.67
4.66
4.43
3.35
3.29
0.00
D2O exchange
3.01
1.99
2.01
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


7.64
7.63
7.61
7.42
7.40
7.38
7.37
7.35
7.33
7.23
5.61
5.60
5.58
5.34
5.32
5.31
4.77
4.69
4.68
4.67
4.18
4.17
1.54
0.00
Ph
O
O
O
BnO
O
O
S
O
O
447
2.00
7.89
1.01
2.04
2.10
1.03
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


2921.95
2852.52
1461.94
1409.87
1377.08
1334.65
1294.15
1213.14
1120.56
1018.34
972.06
908.41
819.69
744.47
Ph
O
O
O
BnO
O
O
S
O
O
447
4000
3000
2000
1000
Wavenumber (cm-1)


136.97
134.94
130.14
128.62
128.24
128.13
127.92
125.36
106.87
77.31
77.00
76.68
74.19
72.00
70.12
65.37
60.26
Ph
O
O
O
BnO
O
O
S
O
O
447
140
130
120
110
100
90
80
70
60
50


130.15
128.63
128.24
128.13
127.93
125.37
74.18
72.00
70.12
65.36
60.26
DEPT
140
130
120
110
100
90
80
70
60
50



ORTEP of **447**

Crystal Data Table for **447**

Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, C2/c
Unit cell dimensions	a = 22.887(12) Å alpha = 90°. b = 6.109(3) Å beta = 99.784(8)°. c = 26.752(14) Å gamma = 90°.
Volume	3686(3) $Å^3$
Z, Calculated density	8, 1.508 Mg/m^3
Absorption coefficient	0.224 mm^{-1}
Crystal size	0.99 x 0.105 x 0.061 mm
Theta range for data collection	2.17 to 25.00 deg.
Reflections collected / unique	8574 / 3235 [R(int) = 0.0456]
Completeness to theta = 25.00	99.7 %
Refinement method	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.045
Final R indices [I>2sigma(I)]	R1 = 0.0646, wR2 = 0.1629
R indices (all data)	R1 = 0.0917, wR2 = 0.1774
Largest diff. peak and hole	0.653 and -0.449 e. $Å^{-3}$

References:

1 (a) Thomas, J. R.; Dwek, R. A.; Rademacher, T. W. *Biochemistry*, **1990**, *29*, 5413. (b) Potter, B. V. L.; Lampe, D. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1933. (c) Hinchliffe, K.; Irvine, R. *Nature*, **1997**, *390*, 123.

2 (a) *The Inositol Phosphates. Chemical Synthesis and Biological Significance*, Billington, D. C. VCH, New York, N.Y. 1993. (b) *Phosphoinositides: Chemistry, Biochemistry and Biomedical Applications*, Bruzik, K. S. Ed.; ACS Symposium Series 718. American Chemical Society, Washington D. C. USA, 1999.

3 Suzuki, T.; Suzuki, S. T.; Yamada, I.; Koashi, Y.; Yamada, K. and Chida, N. *J. Org. Chem.*, **2002**, *67*, 2874. (b) Chida, N.; Ogawa, S. *Chem. Commun.*, **1997**, 807.

4 Sureshan, K. M.; Shashidhar, M. S.; Praveen, T.; Das, T. *Chem. Rev.* **2003,** *103*, 4477.

5 Angyal, S. *J. Carbohydr. Res.*, **2000**, *325*, 313 and the references cited therein.

List of publications:

1. Chelation controlled regiospecific O-substitution of *myo*-inositol orthoesters: Convenient access to orthogonally protected *myo*-inositol derivatives.

   S. Devaraj, M. S. Shashidhar and S. S. Dixit, *Tetrahedron* **2005**, *61*, 529.

2. OH….O bridge dimmers link *via* CH….O and CH…. π interaction in the crystal structure of 4,6-di-O-benzyl myo-inositol 1,3,5-orthoformate.

   K. Manoj, **S. Devaraj**, Rajesh Gonnade, M. M. Bhadbhade, M. S. Shashidhar, *Acta Crystallographica C*. **2005**, *61*, 628.

3. Cyclitol based metal complexing agents. Preference for the extraction of lithium by *myo*-inositol based crown-4-ethers depends on the relative orientation of crown ether oxygen atoms.

   S. S. Dixit, M. S. Shashidhar and **S. Devaraj**, *Tetrahedron* **2006**, *62*, 4360.

4. Chelation controlled regioselective O-substitution in cyclohexanepolyols.

   S. Devaraj and M. S. Shashidhar (Manuscript under preparation).

5. Intramolecular acyl migration in trioxaadamantane derivatives (*myo*-inositol 1,3,5-orthoesters): transesterification reaction without the involvement of the tetrahedral intermediate.

   K. M. Sureshan, **S. Devaraj** and M. S. Shashidhar (Manuscript under preparation).

Posters presented in conferences:

1. Effect of metal ion on regioselective alkylation and acylation of *myo*-inositol orthoesters.

   S. Devaraj and M. S. Shashidhar.

   Poster presented at the Fourth National Symposium in Chemistry, Feb. 1-3, 2002 (Organized by Chemical Research Society of India); National Chemical Laboratory; Pune-411 008; Maharashtra, India.

Oral presentations in conferences:

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   Presented at the first RSC-West India section students symposium, 2003, National Chemical Laboratory, Pune, India.