SYNTHESIS OF CYCLITOLS AND THEIR ANALOGS FROM NATURALLY OCCURRING INOSITOLS

THESIS

SUBMITTED TO THE

UNIVERSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN
CHEMISTRY

By

RAJENDRA C. JAGDHANE

Research Supervisor

DR. M. S. SHASHIDHAR

DIVISION OF ORGANIC CHEMISTRY

NATIONAL CHEMICAL LABORATORY
PUNE 411 008, INDIA

DECEMBER 2010

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Dedicated to my Family……

National Chemical Laboratory, Pune (India).

DECLARATION

I hereby declare that the thesis entitled **"Synthesis of cyclitols and their analogs from naturally occurring inositols"** submitted for Ph. D. degree to the University of Pune has been carried out at National Chemical Laboratory, under the supervision of **Dr. M. S. Shashidhar**. This work is original and has not been submitted in part or full by me for any degree or diploma to any university.

Date: **(RAJENDRA C. JAGDHANE)**

Division of Organic Chemistry

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "**Synthesis of cyclitols and their analogs from naturally occurring inositols**" submitted by **Rajendra Jagdhane** 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.

Date:

(Dr. M. S. SHASHIDHAR)

Research Supervisor

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Dec 2010 *Rajendra*

CONTENTS

Chapter 4: Formal Synthesis of valiolamine from *myo*-inositol

Abbreviations.

Ac	Acetyl
Ac_2O	Acetic anhydride
AcCl	Acetyl chloride
AIBN	Azobisisobutyronitrile
All	Allyl
Anhy.	Anhydrous
aq.	Aqueous
Bn	Benzyl
BnBr	Benzyl bromide
Boc	*tert*-Butyloxycarbonyl
BuLi	Butyl lithium
Bz	Benzoyl
BzCl	Benzoyl chloride
Calcd.	Calculated
Cat.	Catalytic
CBz	Carbobenzyloxy
Conc.	Concentration
CSA	Camphorsulfonic acid
CsOAc	Cesium acetate
DAST	(Diethylamino) sulfur trifluoride
DCC	N,N'-Dicyclohexylcarbodiimide
D_2O	Dueterium Oxide
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

DIBAL-H	Diisobutyl aluminium Hydride
dil.	Dilute
DIPEA	Di-isopropyl ethyl amine
DMAP	*N, N*-dimethylamino pyridine
DMF	*N, N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
eq.	Equivalent
Et_3N	Triethylamine
EtOAc	Ethyl acetate
g	Gram
GPI	Glycophosphatidylinositol
h	Hour (s)
Hz	Hertz
i$BuNH_2$	*iso*-Butyl amine
IBX	2-Iodoxybenzoic acid
IR	Infrared
KOAc	Potassium acetate
KOBz	Potassium benzoate
LC-MS	Liquid chromatography-mass spectrometry
LDA	Lithium diisopropylamide
L-selectride	Lithium tri-*sec*-butylborohydride
*m*CPBA	3-Chloroperbenzoic acid
M.p.	Melting point
Me	Methyl
MeOH	Methanol
MeI	Methyliodide

Mes	Mesityl
mg	Milli gram
min.	Minute(s)
mL	Milliliter
mmol	Milli moles
MsCl	Methane sulfonyl chloride
$NiCl_2$(dppp)	[1,3-bis(diphenylphosphino)propane]dichloronickel(II)
NaOMe	Sodium methoxide
NMR	Nuclear magnetic Resonance
NMO	N-Methylmorpholine-N-oxide
ORTEP	Oak Ridge Thermal Ellipsoid Plot Program
$Pd(dba)_2$	Bis(dibenzylideneacetone) palladium(0)
Ph	Phenyl
PI-PLC	Phosphatidylinositol-specific phospholipase C
PMB	4-Methoxy benzyl
PCB	4-Chloro benzyl
PBB	4-Bromo benzyl
PPTS	Pyridinium para toluene sulfonate
PIP_3	Phosphatidylinositol-3,4,5-tris-phosphate
Py	Pyridine
rac-	Racemic
rt	Room temperature (23–30 ^oC)
TBHP	*tert*-Butyl hydroperoxide
TBS	*tert*-Butyldimethylsilyl
TMS	Trimethylsilyl
TFA	Trifluoroacetic acid

TFAA	Trifluroacetic anhydride
Tf_2O	Trifluoromethanesulfonic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TsCl	4-Toluene sulfonyl chloride
TsOH	4-Toluene sulfonic acid

Abstract of the Thesis

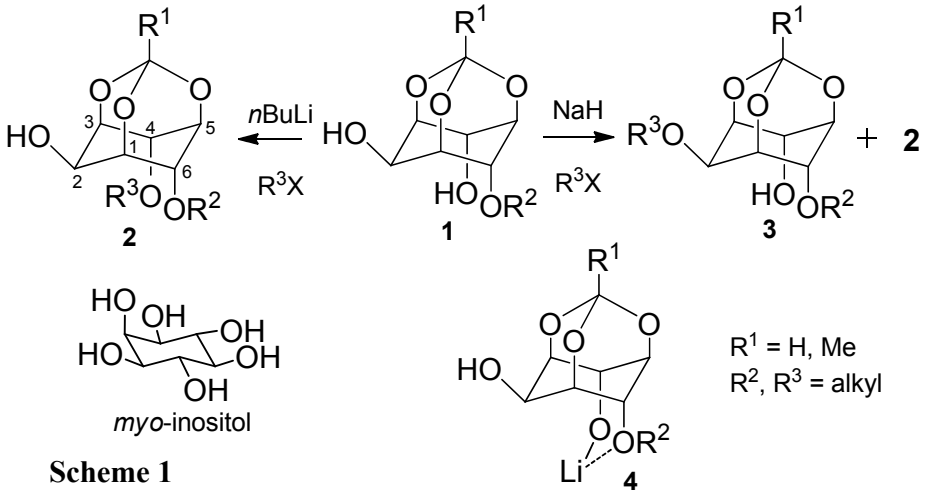
The thesis entitled '**Synthesis of cyclitols and their analogs from naturally occurring inositols**' consists of four chapters. The first chapter is a review of reactions wherein regioselectivity is affected by the influence of metal ions present in the reaction mixture. The second chapter describes the work done to study the effect of the alkali metal counter ion (sodium or lithium) in the base, on the regioselectivity during O-alkylation reactions of *myo*-inositol derivatives and the preparation of orthogonally protected *myo*-inositol orthoester derivatives. The third chapter illustrates of the use of orthogonally protected *myo*-inositol derivatives for the preparation of isomeric cyclitol derivatives. The fourth chapter presents the synthesis of valiolamine from *myo*-inositol, based on the results generated in the previous chapters.

Chapter 1: Metal ion assisted selective reactions in complex organic molecules.

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[(2)] such as cellular signal transduction, calcium mobilization, insulin stimulation, exocytosis and anchoring of certain proteins to cell membranes. These developments in biology, with wide applications in the field of medicine, necessitated simpler methods for the synthesis of various inositol derivatives. *myo*-Inositol (Scheme 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 a few natural products.[(3)]

myo-Inositol has six secondary hydroxyl groups which exhibit subtle differences in reactivity. There have been many attempts to devise methods for the selective reactions of the six hydroxyl groups of *myo*-inositol. Although regio and enantioselective reactions of *myo*-inositol hydroxyl groups are known to occur in living systems, there is no practical laboratory method for the exclusive regioselective O-substitution (or other reactions) of any one of the hydroxyl groups of *myo*-inositol and most of its partially protected derivatives. The present thesis is an attempt towards the development of methods for the preparation of synthetically useful O-substituted *myo*-inositol derivatives using reaction sequences in which each step is selective to one of the hydroxyl groups of *myo*-inositol derivatives.

Earlier work in our laboratory had revealed that alkylation of 4-O-substituted *myo*-inositol orthoester **1**, with butyl lithium and alkyl halides gives selectively the di-axial ether **2**, whereas the same reaction with sodium hydride gives a mixture of regioisomers **2** and **3** (Scheme 1).[4] Hence we were curious to see, if such instances of change in selectivity due to variation in the nature of metal ion is documented in the literature. Accordingly, the first chapter gives a brief account of such reactions reported in the



Scheme 1

literature, which illustrates the influence of metal ions in deciding the selectivity of reactions of complex organic molecules.[5]

Chapter 2: Relative reactivity of hydroxyl groups in inositol derivatives: role of metal ion chelation.

Previous work in our laboratory had shown that excellent selectivity could be achieved for the O-alkylation of the C6-hydroxyl group in C4-ethers of *myo*-inositol orthoesters (e.g. **1**), by using lithium derived bases such as lithium hydride and butyllithium. However, the selectivity observed for the O-alkylation of some inositol derivatives containing more than one hydroxyl group (but without the orthoester bridge) was not so impressive (Chart 2 shows the derivatives studied earlier).

In order to further probe the effect of metal ions on O-alkylation of *myo*-inositol derivatives containing more than one hydroxyl group but devoid of the rigid orthoester bridge, partially protected *myo*–inositol derivatives were prepared and subjected to O-alkylation conditions. O-Alkylation reactions of the triols **5**, **23** and diols **10**, **15**, **18** and

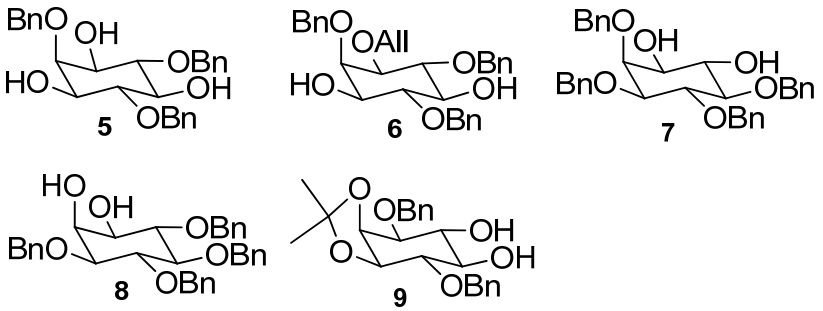
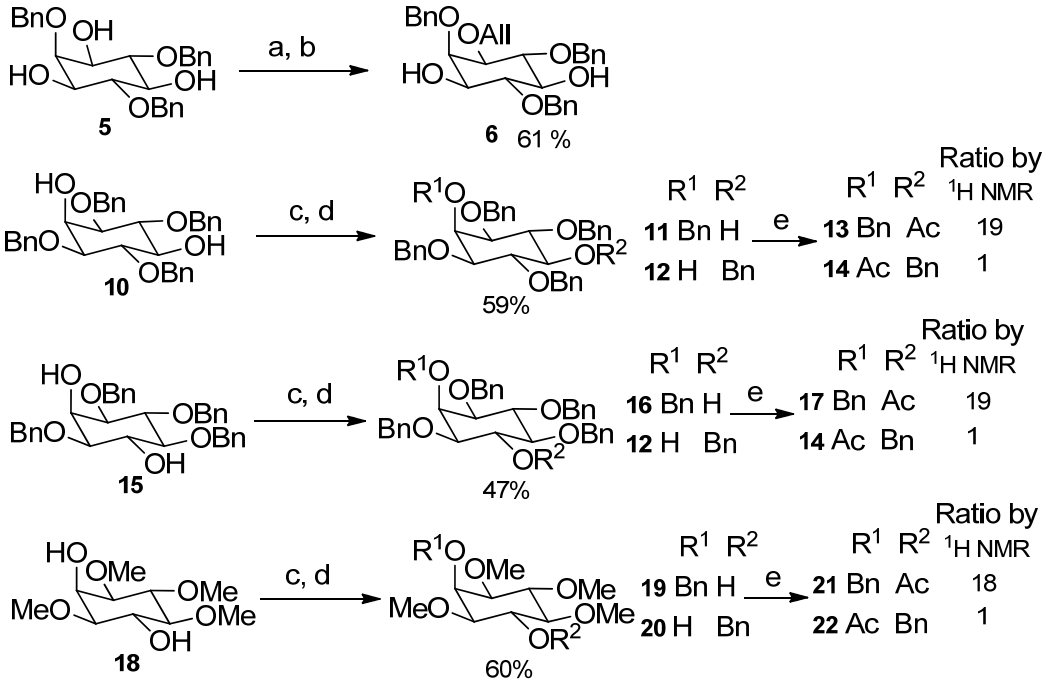


Chart 2

24 were studied using sodium and lithium bases. Allylation of the triol **5** with sodium hydride led to exclusive formation of allyl ether **6**.[6] Benzylation of diols (Scheme 2) having an axial and an equatorial hydroxyl group, gave predominantly axial benzyl ethers. These results suggest that (a) O-alkylation preferentially (but not exclusively) occurs at a hydroxyl group having a vicinal *cis*-oxygen atom; (b) chelation of metal ions by inositol derivatives plays a significant role in the observed regioselectivity,

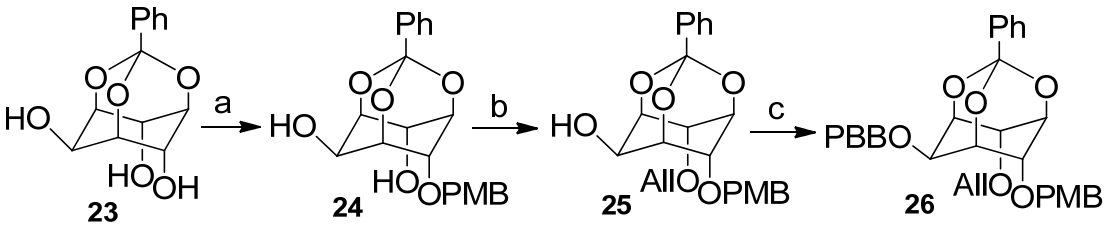


Scheme 2. (a) DMF, NaH; (b) AllBr, DMF; (c) THF, NaH; (d) BnBr, DMF; (e) Py, $(Ac)_2O$.

(c) steric factors associated with the axial or equatorial disposition of the reacting hydroxyl group do not contribute much to the outcome of these O-alkylation reactions.

The observed differences in reactivity of the hydroxyl groups were utilized for the preparation of orthogonally protected orthobenzoate derivative **26** (Scheme 3) from the

triol **23**. These results clearly show that the observed selectivity for the O-alkylation of *myo*-inositol orthoesters (*via* their sodium or lithium alkoxides) is independent of the alkyl halide used for alkylation. The presence of hetero atoms in the alkyl halides does not appear to disturb the regioselectivity during O-alkylation. Synthetic utility of the orthogonally protected *myo*-inositol derivatives (in Scheme 3) is illustrated in the next chapter.



23 **24** **25** **26**

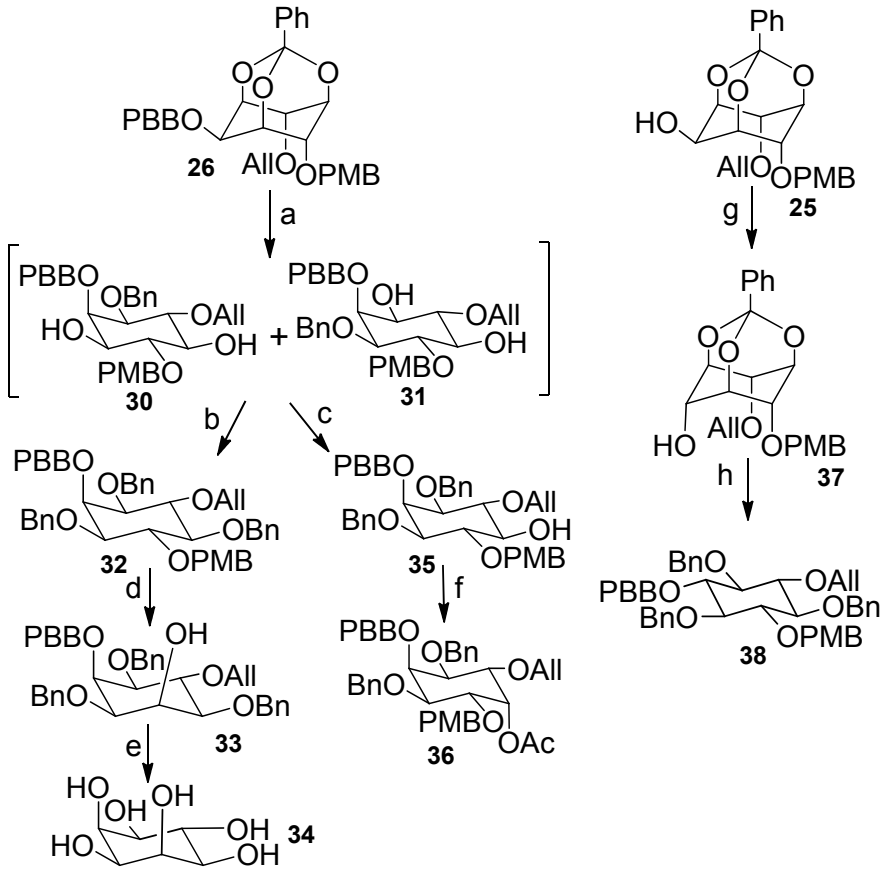
Scheme 3: a) DMF, NaH, PMBCl, 90%; b) THF, *n*BuLi, DMF, AllBr, 80%; c) DMF, NaH, PBBBr, 95%.

Chapter 3: Synthesis of orthogonally protected isomeric inositol derivatives from *myo*-inositol: illustration of the potential of chelation controlled O-alkylation of *myo*-inositol derivatives.

This chapter presents results on the conversion of differentially protected *myo*-inositol derivatives (such as **32**, **37** and **47** obtained *via* regioselective O-alkylation reactions), to six isomeric inositol derivatives carrying orthogonal hydroxyl protecting groups and other ring modified cyclitol derivatives. In most of these reactions we have obtained one product, which obviates the need for the separation of isomeric inositol derivatives. Wherever possible, we have compared the efficiency of our synthetic schemes with the earlier methods reported in the literature.

Preparation of *scyllo*-, *epi*-, and *neo*-inositol derivatives.[7]

Orthogonally protected *scyllo*-inositol orthobenzoate derivative **37** could be obtained (Scheme 4) by the sequential oxidation and reduction of the C2-hydroxyl group in **25** (described in the previous chapter) followed by O-alkylation with 4-bromobenzyl bromide. Reduction of the orthobenzoate moiety of *scyllo*-inositol orthobenzoate followed by benzylation provided a *scyllo*-inositol derivative **38** carrying three orthogonal protecting groups. Reduction of the orthobenzoate moiety in **26** (described in the previous chapter) with excess of DIBAL-H gave a mixture of isomeric diols **30** and **31** (Scheme 4). Selective benzylation at the C1(3)-hydroxyl group provided the

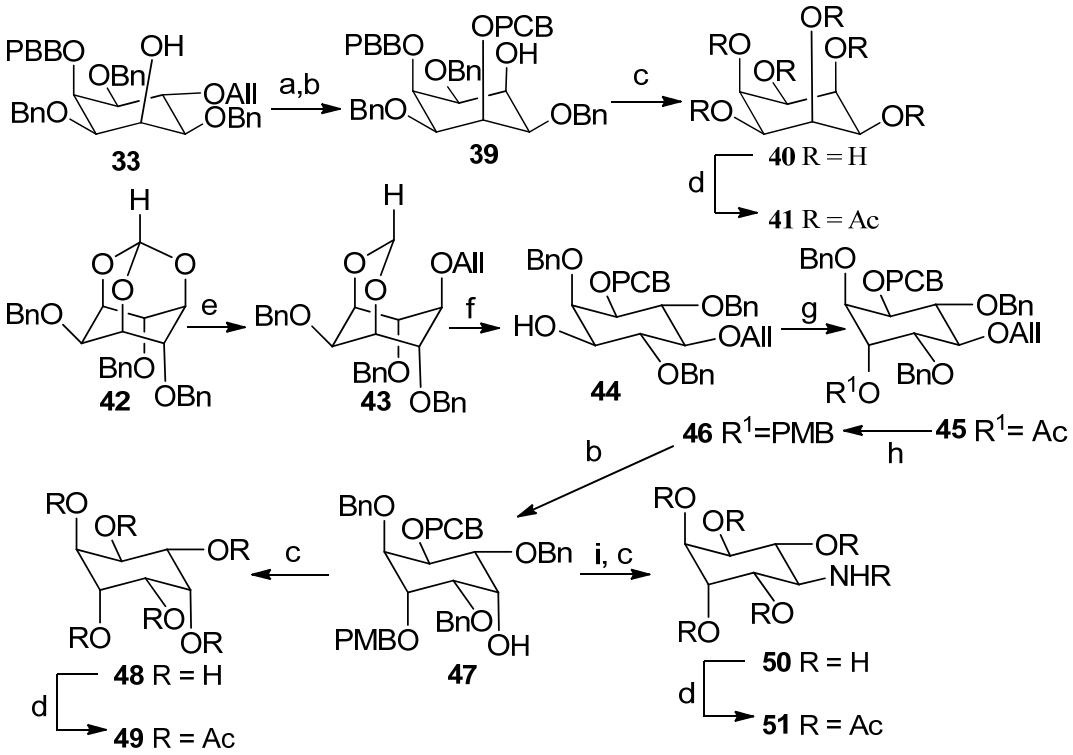


Scheme 4: (a) DIBAL-H, DCM, 78%; (b) NaH(x's), BnBr(x's), DMF, 92%; (c) NaH(1.1 eq.), BnBr (1.0 eq.), DMF, 57%; (d) i. DDQ, DCM:H_2O ii. IBX, EtOAc iii. $NaBH_4$, THF:MeOH; (e) i. Pd-C, MeOH:H_2O ii. $Pd(OH)_2$-C, H_2, EtOH, THF, H_2O, TFA, 75% (over 5 steps); (f) i. MsCl, pyridine ii. CsOAc, DMF, 86%; (g) i. Swern oxidation, ii. $NaBH_4$, THF:MeOH, 75%; (h) i. NaH, PBBBr, DMF, ii. DIBAL-H, DCM, iii. NaH, BnBr, DMF, 64% (over 3 steps).

corresponding dibenzyl ether **35**, while benzylation of the same mixture using excess of benzyl bromide gave the tribenzyl ether **32**. PMB group in the tribenzyl ether **32** was cleaved and the resulting hydroxyl group was inverted (by sequential oxidation - reduction), to obtain the *epi*-inositol derivative **33**. Global deprotection of this derivative gave *epi*-inositol (**34**) in an overall yield of 33% from *myo*-inositol. Yield of *epi*-inositol in methods reported earlier[7] was in the range 6–15% from *myo*-inositol and 1–21% from other starting materials. Inversion of the free hydroxyl group in the dibenzyl ether **35** *via* its mesylate gave the *neo*-inositol derivative **36**.

Preparation of *cis*-, *chiro*-, and *allo*-inositol derivatives.[7]

The *epi*-inositol derivative **33** (Scheme 4) could be transformed to a *cis*-inositol derivative **39** by protection of the axial hydroxyl group followed by cleavage of the allyl ether and inversion of the resulting hydroxyl group. Global deprotection of all the hydroxyl groups provided *cis*-inositol (**40**, isolated as its hexaacetate **41**) in an overall yield of 25% from *myo*-inositol (Scheme 5); yield in most of the methods reported earlier was less or required separation of isomeric inositols.



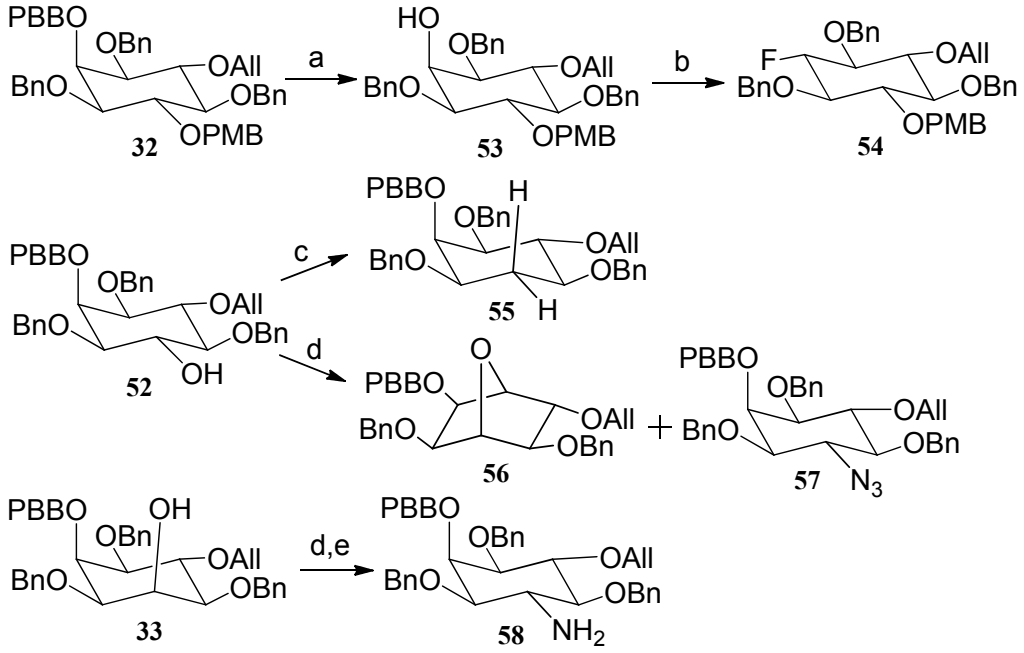
Scheme 5. (a) NaH, PCBBr, DMF; (b) i. DIBAL-H, $NiCl_2$(dppp), Ph-CH_3, ii. Swern oxidation iii. $NaBH_4$, THF:MeOH, 73% for **39**, 83 % for **47**; (c) $Pd(OH)_2$-C, H_2, EtOH, THF, H_2O, TFA; (d) $(Ac)_2O$, Py, 86% for **41**, 90% for **49,** 70% for **51**; (e) i. DIBAL-H, DCM ii. NaH, AllBr, DMF; (f) i. HCl, MeOH ii. NaH, PCBBr, DMF, 73% (from **42**); (g) i. Tf_2O, DCM:Py, ii. CsOAc, Ph-H, 63%; (h) i. *i*$BuNH_2$, MeOH, ii. NaH, PBMCl, DMF, 94%; (i) i. Tf_2O, DCM:Py, ii. NaN_3, DMF, 63%.

Since conversion of *myo*-inositol to *chiro*-inositol involves the inversion of the C1-hydroxyl group, it cannot be obtained from a derivative such as **26**. Hence, for the synthesis of the *chiro*-inositol derivative, we started from the tribenzyl ether **42** (Scheme 5). Regiospecific cleavage of the orthoformate moiety in the tribenzyl ether **42** followed by allyation gave the C5-allyl ether **43**. Hydrolysis of the acetal in **43** followed by selective O-alkylation of one of the hydroxyl groups gave the pentaprotected *myo*-inositol derivative **44**. Inversion of the free hydroxyl group in **44** *via* its triflate using cesium acetate provided

the racemic *chiro*-inositol derivative **45.** Aminolysis of the acetate followed by alkylation (with PMBCl) gave a differentially substituted *chiro*-inositol derivative **46**. An *allo*-inositol derivative **47** could be obtained by selective cleavage of the allyl ether (in **46**) followed by inversion of the hydroxyl group (by sequential oxidation and reduction). Global deprotection of **47** gave *allo*-inositol in an overall yield of 28% which was isolated as its hexaacetate **49.** Yields of *allo*-inositol in methods reported earlier was 15% from *myo*-inositol and 2–16% from other starting materials. None of the previously reported methods dealing with the preparation of isomeric inositols or their derivatives provide orthogonally protected inositol derivatives. From the *allo*-inositol derivative **47**, *chiro*-inosamine hexaacetate **51**[8] was prepared by nucleophilic displacement of triflate with azide followed by reduction and global deprotection of hydroxyl groups by hydrogenolysis.

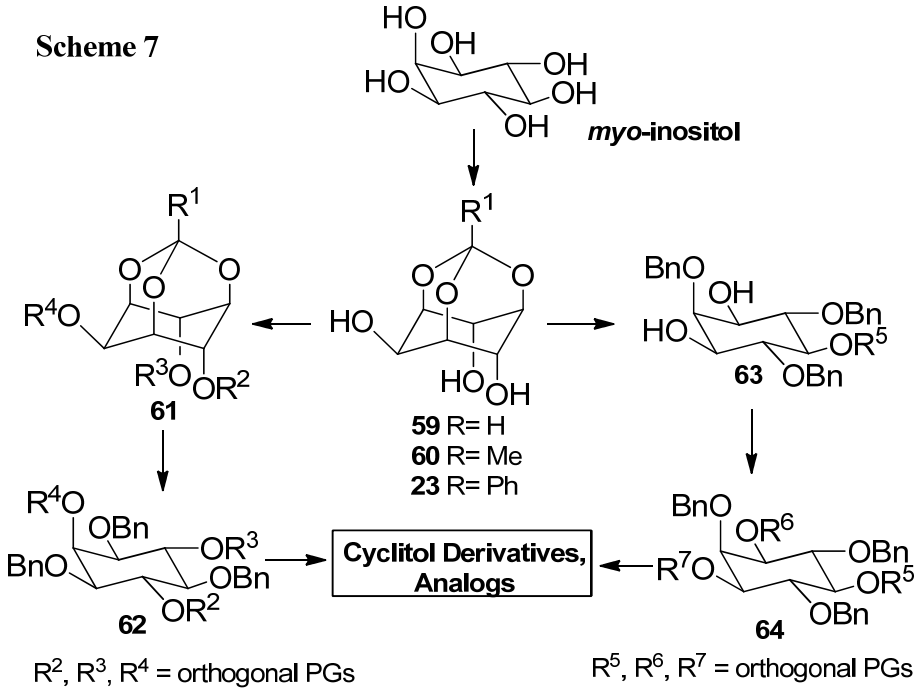
The reactions shown in scheme 6 leading to the synthesis of ring modified cyclitol derivatives, a deoxy-fluoro-inositol **54**, a deoxyinositol **55**, a deoxy azido inositol **57** and amino cyclitols **58** and **51** (Scheme 6) illustrate the synthetic potential and flexibility of orthogonally protected inositol derivatives prepared in the present work. The synthetic methodology presented in this chapter also shows that the orthogonally protected inositol derivatives can be used to obtain cyclitol derivatives modified at all the six positions of the carbocyclic ring.

Our primary objective in the work described so far was to devise methods to prepare orthogonally protected *myo*-inositol derivatives which could be extended to cyclitols and their analogs. Such an approach (Scheme 7) in principle will allow the regioselective O-substitution of all the six hydroxyl groups in *myo*-inositol and provide methods to prepare orthogonally protected *myo*-inositol derivatives such as **62** and **64**. The results presented in the next chapter consist of an attempt to use the chemistry developed in previous chapters to prepare useful cyclitol derivatives.



Scheme 6. (a) i. PhN(H)Me, $Pd(dba)_2$, (O-biph)$P(tBu)_2$, NaOtBu, Ph-CH_3 ii. $ZnCl_2$, CH_2Cl_2, 66%; (b) DAST, CH_2Cl_2, 80%; (c) i. THF, NaH, CS_2, MeI, ii. Ph-CH_3, $n$$Bu_3SnH$, AIBN, 65%; (d) i. Tf_2O, CH_2Cl_2, Py, ii. DMF, NaN_3, 61% for **56**, 17% for **57**; (e) PPh_3, THF:H_2O, 58% (3 steps).

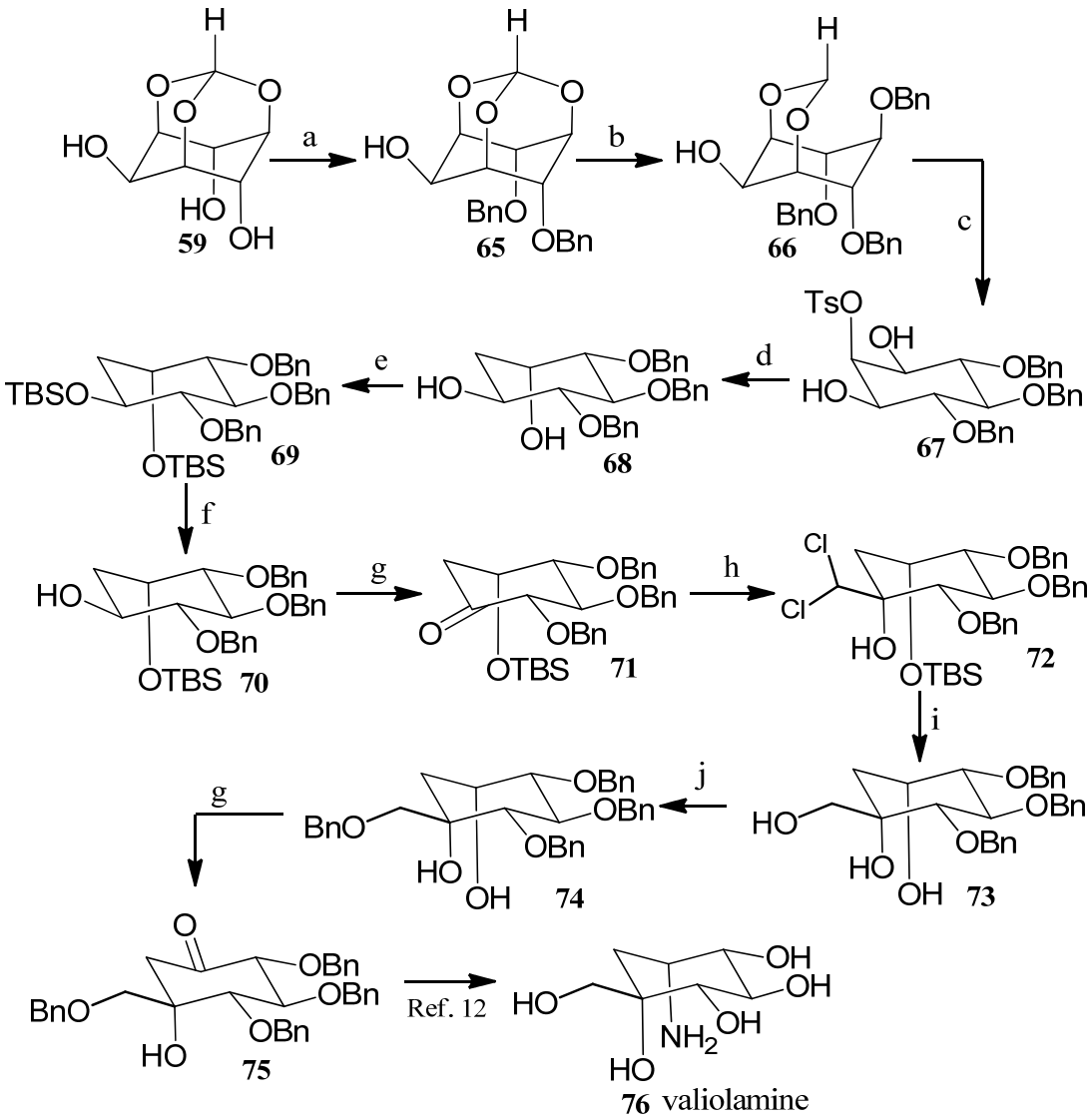
Scheme 7



Chapter 4: Formal Synthesis of valiolamine from *myo*-inositol.

Valiolamine is a pseudoamino sugar first isolated from the fermentation broth of *Streptomyces hygroscopicus* subsp. *limoneus*. Valiolamine and its N-substituted derivatives have potent α-D-glucosidase inhibitory activity, and one of its derivatives, *N*-[2-hydroxy-1-(hydroxymethy1)ethyl] valiolamine (AO-128) is an orally active antidiabetic medicine.[9] We envisioned a route to valiolamine from abundantly available *myo*-inositol. Our planned synthetic approach involved (i) lithium hydride mediated selective benzylation of the C4- and C6-hydroxyl groups of *myo*-inositol orthoformate **59**; (ii) a novel deoxygenation reaction of the tosylate **67**,[10] and (iii) nucleophilic addition of dichloromethyllithium to the inosose **71** (Scheme 8).[11] We have attempted the synthesis of racemic valiolamine, details of which are presented in this chapter.

First, the triol **59** was converted to the dibenzyl ether **65** by benzylation using lithium hydride as a base and the C2-hydroxyl group was protected as the PMB ether. Regiospecific cleavage of the orthoformate with DIBAL-H released the C5-hydroxyl group, which was benzylated; C2-hydroxyl group was deprotected with DDQ to obtain **66**. The free hydroxyl group in **66** was converted to tosylate and the methylidene acetal was cleaved to get the corresponding diol **67**. Reaction of the tosylate **67** with lithium tri- ethyl borohydride (Super-Hydride) resulted in the reduction of the tosylate and inversion of one of the hydroxyl groups to give **68**.[10] The diol **68** was converted into bis-silyl derivative **69**, which on selective deprotection of equatorial TBS group and subsequent oxidation led to the ketone **71**. For introduction of the equatorial hydroxymethyl group, inosose **71** was reacted with dichloromethyllithium (generated by reacting dichloromethane with lithium diisopropyl amide) to get a dichloromethyl derivative **72**. Single crystal X-ray analysis of **72** confirmed the formation of product with equatorial disposition of dichloromethyl group. The dichloromethyl derivative **72** was reacted with tetrabutylammonium hydroxide to obtain the triol **73**. The triol **73** was converted to known ketone **75**[12] by benzylation using dibutyltinoxide and benzyl bromide followed by oxidation. Synthesis of (+)-valiolamine from optically active **75** is reported in literature.[12]



Scheme 8. (a) DMF, LiH, BnBr, 65%; (b) i. DMF, NaH, PMBCl; ii. DCM, DIBAL-H; iii. DMF, NaH, BnBr; iv. DCM:H_2O, DDQ, 90%; (c) i. Py, TsCl, DMAP; ii. DCM, TFAA, AcOH then K_2CO_3, MeOH, 84 %; (d) THF, $LiEt_3BH$, 85%; (e) DCM, 2,6-lutidine, TBSOTf, 95%; (f) CSA, MeOH, 95%; (g) AcOEt, IBX, 95% for **72**, 65% for **75**; (h) THF, LDA, CH_2Cl_2, 82%; (i) DMSO, aq. $n(Bu)_4NOH$ then MeOH, $NaBH_4$, 51%; (j) Bu_2SnO, MeOH:toluene then BnBr, nBu_4NBr, 84%.

<u>Note:</u> Compound numbers in the synopsis are different from those in thesis and references are given separately for each chapter.

References.

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List of Publications.

1. 'Relative reactivity of hydroxyl groups in inositol derivatives: role of metal ion chelation', Devaraj, S. D.; **Jagdhane, R. C.** and Shashidhar, M. S. *Carbohydr. res*., **2009**, *344*, 1159–1166.
2. 'Orthogonally Protected Cyclohexanehexols by a One Reaction - One Product Approach: Efficient Access to Cyclitols and Their Analogs', **Jagdhane, R. C.** and Shashidhar, M. S. *Eur. J. Org. Chem*., **2010**, 2945–2953.
3. 'Formal synthesis of valiolamine from *myo*-inositol', **Jagdhane, R. C.** and Shashidhar, M. S. (Manuscript under preparation).
4. 'Crystal structure analysis of hexa-acetates of *cis*, *allo*-inositol and *chiro*-inosamine hexa-acetate', **Jagdhane, R. C.**; Shashidhar, M. S.: Gonnade, R. G.; Krishnaswamy, S. (To be communicated).
5. 'New polymorph of *epi*-inositol', **Jagdhane, R. C.**; Shashidhar, M. S.; Gonnade, R. G. (To be communicated).
6. 'Review: Metal ion assisted selective reactions in complex organic molecules' **Jagdhane, R. C.**; Shashidhar, M. S.; Devaraj, S. (Manuscript under preparation).

Presentations and Posters.

1. 'Synthesis of cyclitols and their analogs from *myo*-inositol', **Jagdhane, R. C.** Oral presentation at 3rd J-NOST symposium held at GNDU, Amritsar (Punjab) Nov 2007.
2. 'Regioselective O-alkylations of inositol derivatives: efficient access to isomeric cyclitols and their analogs', **Jagdhane, R. C.** and Shashidhar, M. S. Poster presentation at National Science Day Function at NCL, Feb 2009.

Chapter 1. Metal ion assisted selective reactions in complex organic molecules

1.1. Introduction.

Small polyfunctional organic compounds (such as amino acids, carbohydrates) occurring in nature in large amounts have been exploited as starting materials for the synthesis of a variety of organic compounds (including natural products) of specific or potential applications and utility, over the last century. These synthetic efforts led to the development of a large number of new organic reactions and efficient methods for the separation and isolation of small organic molecules. Development of the latter techniques implies that a majority of the reactions carried out by organic chemists resulted in the formation of undesired products which had to be removed before the next synthetic transformation could be performed on the desired intermediate. Formation of more than one product in any reaction also contributes to the reduction in yield and efficiency of the synthesis as well as appreciation in the labor, time and cost needed to synthesize the target molecule. One of the ways to make a synthesis efficient and reduce the labor and the time needed is to select individual reactions in a synthetic scheme that give a single product and hence circumvent the need for separation of products from a mixture. Other efforts towards developing efficient synthesis of small molecules include atom economy in synthesis,[1] protecting group-less synthesis,[2] cascade synthesis,[3] and diversity oriented synthesis.[4]

The realization of the involvement of phosphoinositols in cellular signal transduction pathways and efforts to exploit the *myo*-inositol (**1.1**, Figure 1.1) cycle for drug discovery[5] demanded an understanding of the chemistry and structure of inositols and their derivatives. The revival in interest in the chemistry of inositols also led to efforts to use naturally occurring inositols and their derivatives for the synthesis of a variety of organic compounds.[6] This demanded efficient methods to carry out selective reactions on the secondary hydroxyl groups of inositols and their derivatives. In particular, the chemistry of *myo*-inositol, the most abundantly available cyclitol in nature, was studied extensively in the last two decades.[5c, 7] In syntheses involving cyclitols and carbohydrates, hydroxyl group protection is unavoidable. New methodologies for the selective protection and deprotection of functional groups continue to appear in the literature regularly.[8] 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*). 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.[7c, 9] 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.[6, 10] 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 cyclohexane derived alcohols; (c) preferential hydrolysis of *trans* acetals over *cis* acetals of vicinal cyclic diols.[11] Hydrolysis or reduction of orthoesters of diols and triols are also reported[12] 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 bye products.

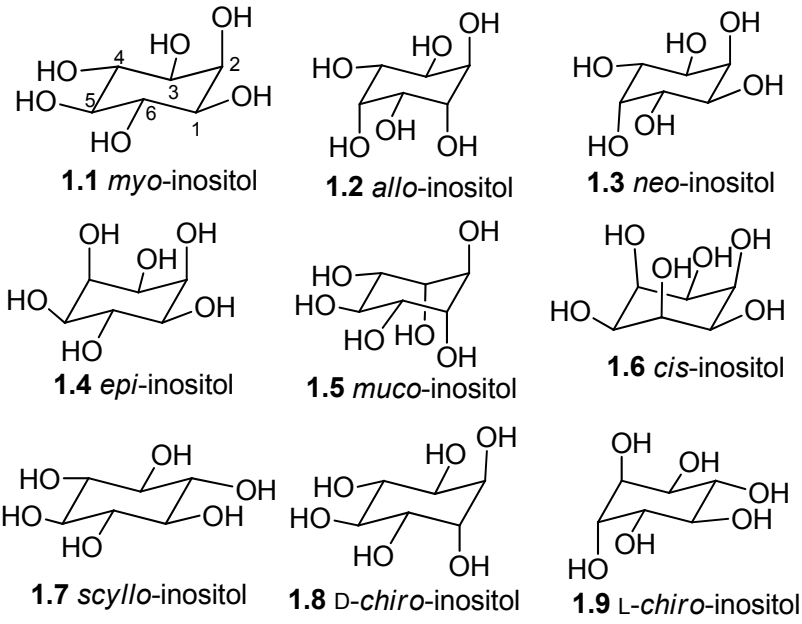
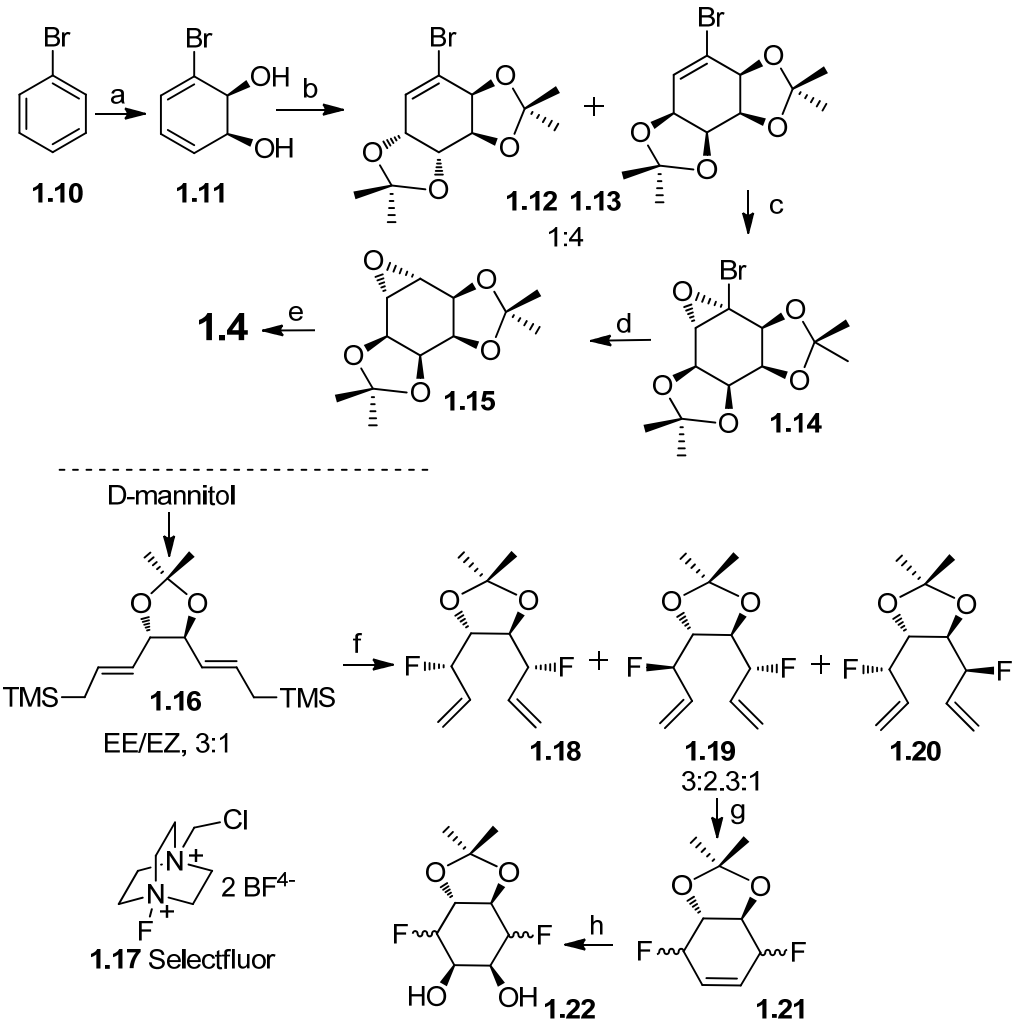


Figure 1.1. Structures of nine inositol isomers reported in the literature. All the inositols except *chiro*-inositols have the *meso* configuration.

We are interested in developing methods for the regioselective reactions in cyclitols (inositols) and their derivatives with the aim of getting selectively one product in each step

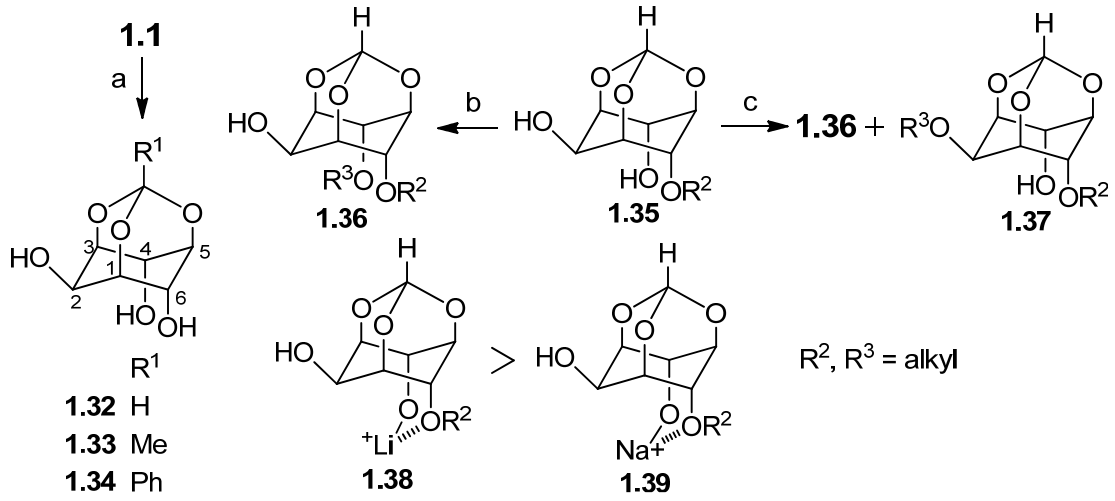
and be able to access a variety of cyclitol derivatives and analogs from a particular intermediate. Among the nine isomers of inositols (Figure 1.1), *myo*-, *scyllo*-, *neo*- and (D- and L-) *chiro*-inositols or their derivatives occur in nature; other four inositols (*muco*-, *allo*-, *epi*-, *cis*-) are unnatural synthetic products. Cyclitols and their analogs have been synthesized starting from small molecules, carbohydrates, inositol isomers *etc*. Few illustrative examples are shown in Scheme 1.1.[13] The main shortcomings of these methods are that most of these routes lead to a mixture of regioisomers and majority of these syntheses are targeted for a particular cyclitol derivative or analog.



Scheme 1.1. (a) toluene dioxygenase; (b) i. DCM, OsO_4, NMO; ii. acetone, 2,2-dimethoxypropane (DMP), TsOH, 75%; (c) DCM, $CHCl_3$, *m*CPBA, reflux, 70%; (d) THF, nBu_3SnH, dibenzoyl peroxide, reflux, 85%; (e) Dowex, H_2O, 100 °C, 90%; (f) **1.17**, 54%; (g) Grubb's II, 70–75%; (h) OsO_4, 10–20 days, 25–59%.

(i) i. Ph-H, TFA, Py, DMSO, DCC; ii. Et_3N, Ac_2O, DMAP, EDC, 100 °C, 2 h, 83%; (j) Dioxane, H_2O, $PdCl_2$ (cat.), 60 °C, 3 h; (k) MeOH, $NaBH_4$ (1.5 eq.); (l) i. 10 N NaOH, MeOH, ii. MeOH, H_2, $Pd(OH)_2/C$.

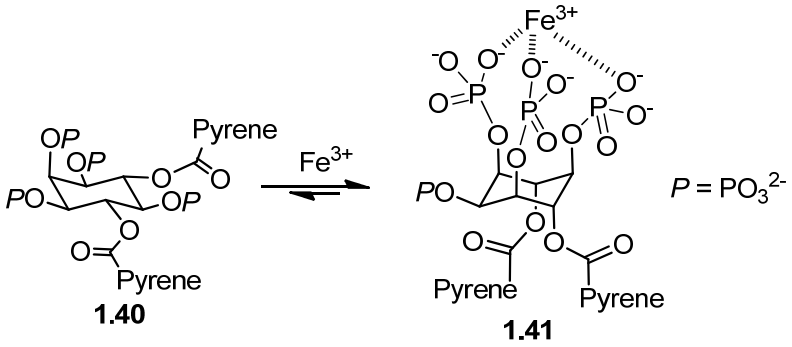
Previous work in our laboratory[14] explored methods for the selective protection of the three hydroxyl groups of *myo*-inositol orthoesters (**1.32**-**1.34**, Scheme 1.2); the latter



Scheme 1.2. (a) Ref. 15; (b) *n*BuLi, R^3X; (c) NaH, R^3X (R^3=Alkyl).

can be obtained as single products from *myo*-inositol in gram quantities.[15] Results of these explorations showed that judicious choice of bases derived from sodium and lithium can result in excellent selectivity for the O-alkylation of the three hydroxyl groups of *myo*-inositol orthoesters.[14] For instance, reaction of 4-O-substituted *myo*-inositol orthoesters **1.35**, with alkyl halides assisted by butyllithium gave selectively the di-axial ether **1.36**, whereas the same reaction assisted by sodium hydride gave a mixture of regioisomers **1.36** and **1.37**.[16] This was attributed to the differences in the relative stability of chelates **1.38** and **1.39**. The lithium chelate **1.38** is expected to be relatively more stable than the chelate **1.39**, because of the small size and better coordination capacity of lithium ion as compared to sodium ion (and hence leads to the formation of **1.36** exclusively). The work described in this thesis deals with the exploitation of such differences in reactivity for the synthesis of cyclitol derivatives. Hence we were curious to see similar instances of variation in the selectivity of products due to changes in the nature of metal ion present in a reaction mixture, reported in the literature. Accordingly, a brief account of reactions reported in the literature, which illustrates the influence of metal ions in deciding the selectivity of reactions of organic molecules is presented in the following pages of this chapter.

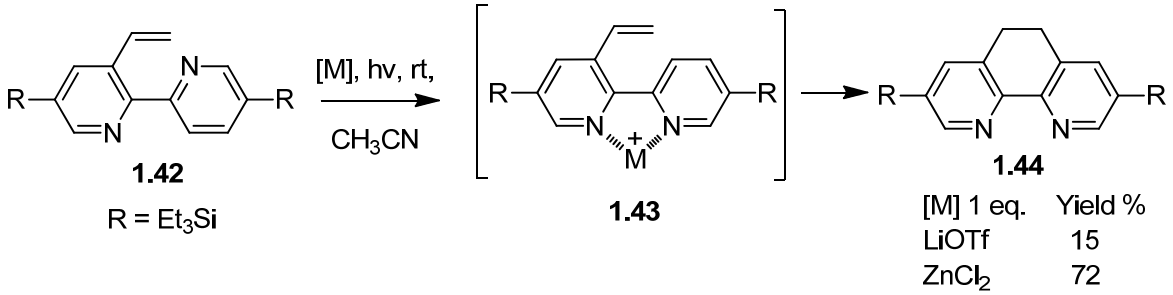
Metal ions play significant roles in organic chemical and biochemical systems. A host of reagents and a number of enzymes that are crucial for the success of organic synthesis and chemical transformations in living cells respectively, contain metal ions. Although many metals are known to cause damage to the environment above certain concentration, their use in laboratory organic chemical reactions and in industrial processes is essential and even appears un-avoidable for the existence of healthy urban colonies. There are a large number of instances of organic reactions wherein the metal ions play significant roles in achieving regio- or stereoselectivity as revealed by the variation in selectivities brought about by change of metal ions or their absence. These observed differences in reactivity and / or selectivity is often due to the differences in the ability of metal ions to form chelates with hetero atoms, present in the reacting molecule. Chelation can force the reacting molecules to adopt selected conformations, other than those present in the absence of metal ions, resulting in change in the nature of the product formed. Although effects due to chelation of metal ions appear to be subtle during a reaction, they can be strong enough to stabilize seemingly unstable conformations, under normal conditions. For instance, 1,2,3,5-tetrakis phosphate **1.40** of *myo*-inositol, which is a good model of natural *myo*-inositol phosphate antioxidants containing the 1,2,3-trisphosphate motif, binds ferric ions in the (normally) unstable penta-axial conformation but exists in the relatively stable penta-equatorial conformation in the absence of ferric ions (Scheme 1.3).[17]



Scheme 1.3.

This is analogous to the change in the molecular conformation sometimes observed for small molecules between the solution and the crystalline state, where in lattice interactions force the molecules to adopt different conformations (or isomeric structures),[18] which reflect in differences in chemical and physical properties of

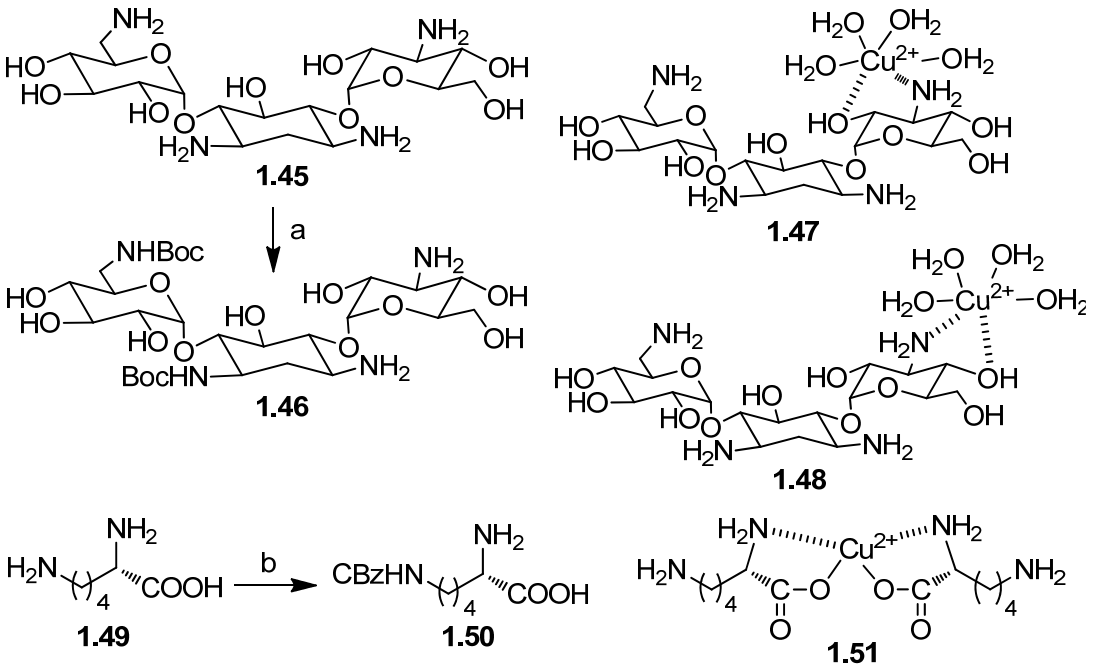
molecules in the two phases. Hence effects of chelation can be exploited to alter certain reactions to achieve higher yields and / or product selectivity. An efficient chelation-assisted photochemical electrocyclic reaction of 3-alkenyl-2,2'-bipyridines to yield 1,10-phenanthrolines is shown in scheme 1.4. The formation of zinc



Scheme 1.4.

chelate restricts the conformation of bipyridines so as to induce a significant bathochromic shift of the absorption band, which permits efficient excitation of the substrate and its cyclization.[19]

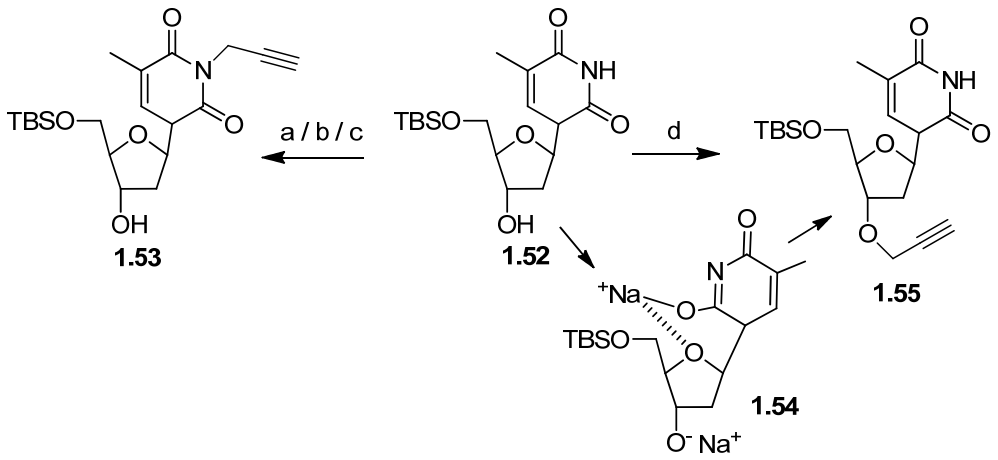
In contrast, complexation of metal ions with certain functional groups can also lead to hindrance of their reactivity, as exemplified by the acylation of amino groups (in the presence of cupric ions) in aminoglycoside antibiotics and amino acids (Scheme 1.5) as well as alkylation in a deoxynucleoside (Scheme 1.6). The selectivity observed was due to the protection provided for some of the amino groups by complexation with cupric ions (which prevented their acylation, Scheme 1.5).[20] L-Lysine (**1.49)** can be converted to its



Scheme 1.5. a) $(Boc)_2O$ (2.0 eq.), $Cu(OAc)_2$ (4.0 eq.), DMSO; b) i. $CuCO_3$, NaOH ii. CBzCl, NaOH, 80%.

N-CBz derivative **1.50**, by blocking the reaction at α–amino group using copper(II) ions which form the chelate **1.51**.[21]

Alkylation of pyrimidine nucleoside derivatives with sodium hydride and alkyl halide in DMF resulted in exclusive N-alkylation while the same reaction in THF resulted in predominant O-alkylation.[22] The differences in the observed selectivity were attributed to the formation of a sodium chelate **1.54** (Scheme 1.6) in THF. Use of potassium or lithium hydrides (instead of sodium hydride) for the same reaction did not show drastic changes in selectivity, although yields varied. Hence this reaction protocol allowed regioselective alkylation of pyrimidine deoxynucleosides, without the necessity of protection–deprotection steps.

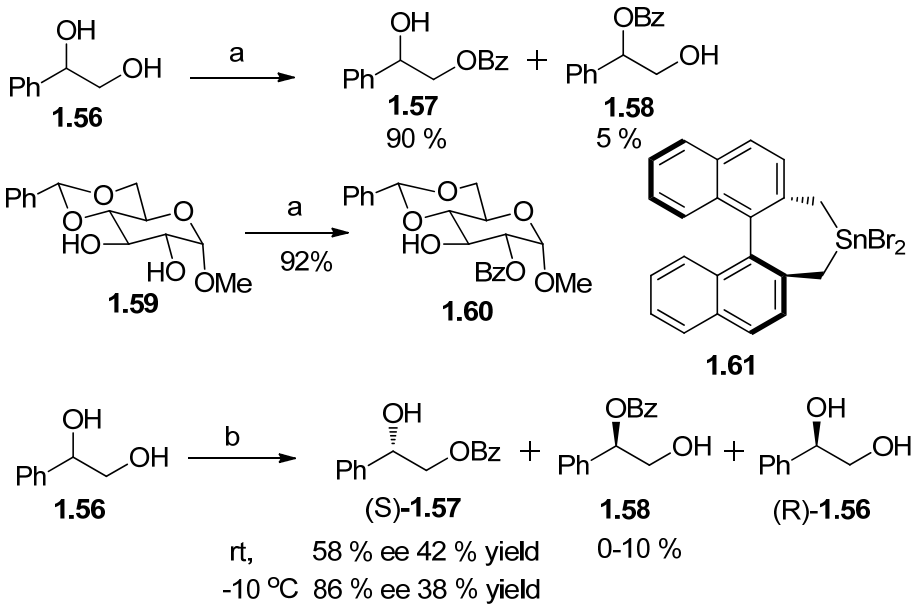


Scheme 1.6. (a) KH, propargyl bromide (1.2 eq.), DMF, 83 %; (b) LiH, propargyl bromide (1.2 eq.), DMF, 25 %; (c) NaH (1.2 eq.), propargyl bromide (1.2 eq.), DMF, 93%; (d) NaH (2.5 eq.), propargyl bromide (2.5 eq.), THF, 100 %.

The following three sections illustrate the potential of such effects brought about by chelation of metal ions mostly in small cyclic systems. Although such effects do prevail in certain acyclic systems, their occurrence is relatively less, perhaps due to the relatively higher conformational freedom in acyclic molecules.

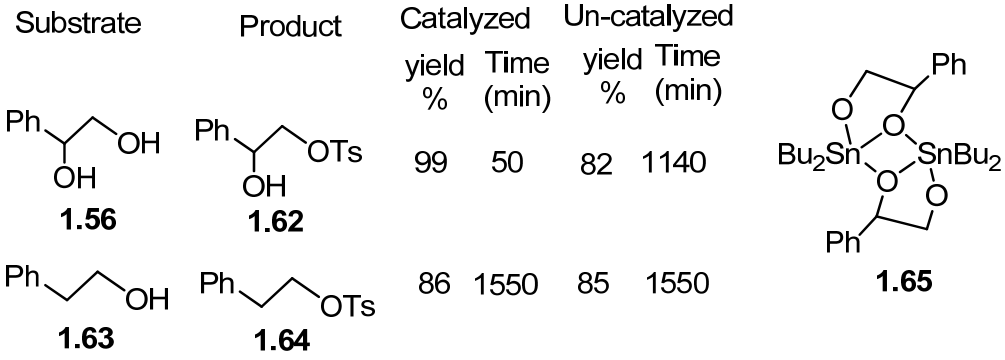
1.2. Regioselective reactions in polyols aided by metal ions.

Selective O-acylation, O-alklylation and O-sulfonylation of a hydroxyl group in diols and polyols can be effected with the aid of organotin compounds such as dimethyltin dichloride and dibutyltin oxide. A variety of cyclic and acyclic diols, in particular 1,2-diols, were selectively monobenzoylated in good yields by reaction with benzoyl chloride in the presence of catalytic amount of dimethyltin dichloride and inorganic bases such as potassium carbonate. This method was successfully applied to the kinetic resolution of racemic 1-phenyl-1,2-ethanediol (**1.56**) using a chiral organotin catalyst **1.61** (Scheme 1.7). The enantiomeric excess obtained was dependent on the kind of the base used, presence of water (as an additive) in the reaction mixture, and the reaction temperature.[23]



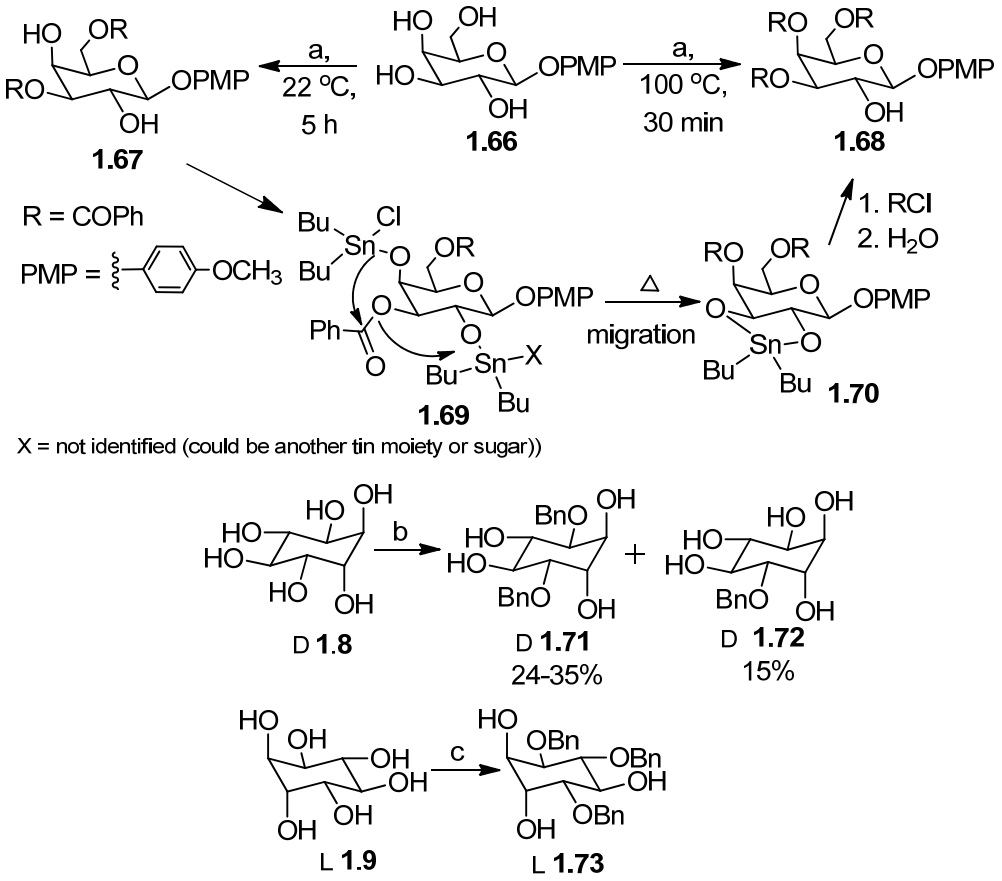
Scheme 1.7. (a) THF, BzCl, Me_2SnCl_2 (cat.), K_2CO_3, rt, 12 h; (b) THF, BzCl (0.5 eq.), **1.61** (0.25 mol %), Na_2CO_3, H_2O.

A convenient protocol for the regioselective sulfonylation of α-chelatable alcohols using catalytic amounts (2 mol %) of Bu_2SnO was described; these reactions are reported to be extremely rapid, highly selective and avoid the generation (and hence separation) of equimolar amounts of lipophilic tin waste (Scheme 1.8). Under similar conditions, tosylation of alcohols without an α-chelatable group proceeded with greatly reduced rates although yields were comparable. The observed reduction in rates for isolated hydroxyl groups was attributed to the lack of a neighboring chelatable group (for the tin compound). Good selectivity for the tosylation of a primary hydroxyl group which has a neighboring α-hydroxyl group over another primary hydroxyl group (which has no neighboring α-hydroxyl group), was observed. The fact that primary alcohols containing an α-chelatable hydroxyl group could be tosylated (to about 20%) in methanol solution showed the facility of the reaction induced by chelation. The reduction in the reaction time (for 99% conversion) for the dibutyltinoxide catalyzed tosylation of a hydroxyl group next to an α-chelatable hydroxyl group was about 30 fold. An investigation of the mechanistic details of this tin catalyzed reaction revealed that Bu_2SnO, $Bu_2Sn(OMe)_2$, Bu_2SnCl_2, and $Bu_2Sn(OAc)_2$ exhibit essentially similar catalytic activity and that the reaction proceeds with the intermediacy of the stannylene dimmer **1.65**.[(24)]



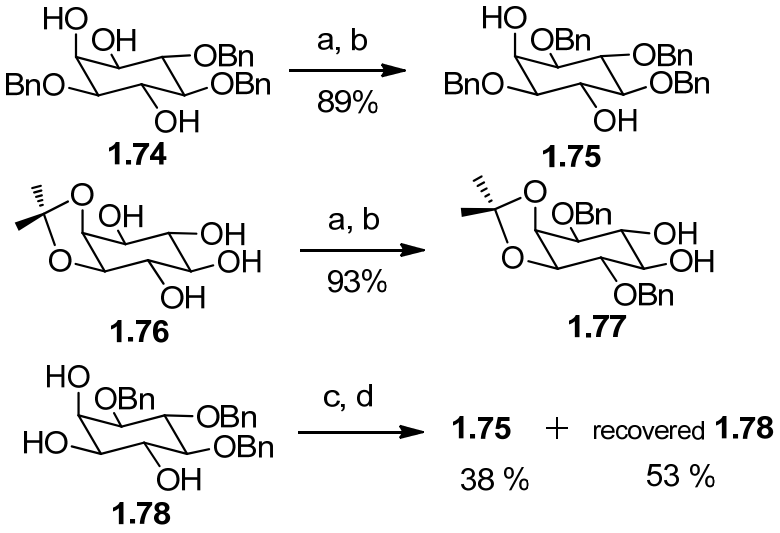
Scheme 1.8. CH_2Cl_2, Bu_2SnO (2 mol %), TsCl (1.0 eq.), Et_3N (1.0 eq.).

Different regioselectiviteis were observed for the dibutyltin oxide mediated benzoylation of carbohydrate derivatives, depending on the temperature at which the reaction (Scheme 1.9) was carried out. The difference in product formation at elevated temperatures was attributed to migration of the benzoyl group. These methods allowed the synthesis of several glycoside benzoates (including galactosides, glucosides, mannosides and lactosides) with one or two free hydroxyl groups, in high yields.[25] However, in view of the report[26] that selective O-benzylation of two or more hydroxyl groups in polyols is possible by an efficient turnover of dibutyltinoxide (to form two different stannylene acetals successively), multiple benzoylations observed in carbohydrates (Scheme 1.9) could also be due to direct benzoylation resulting from the turnover of excess dibutyltinoxide used.



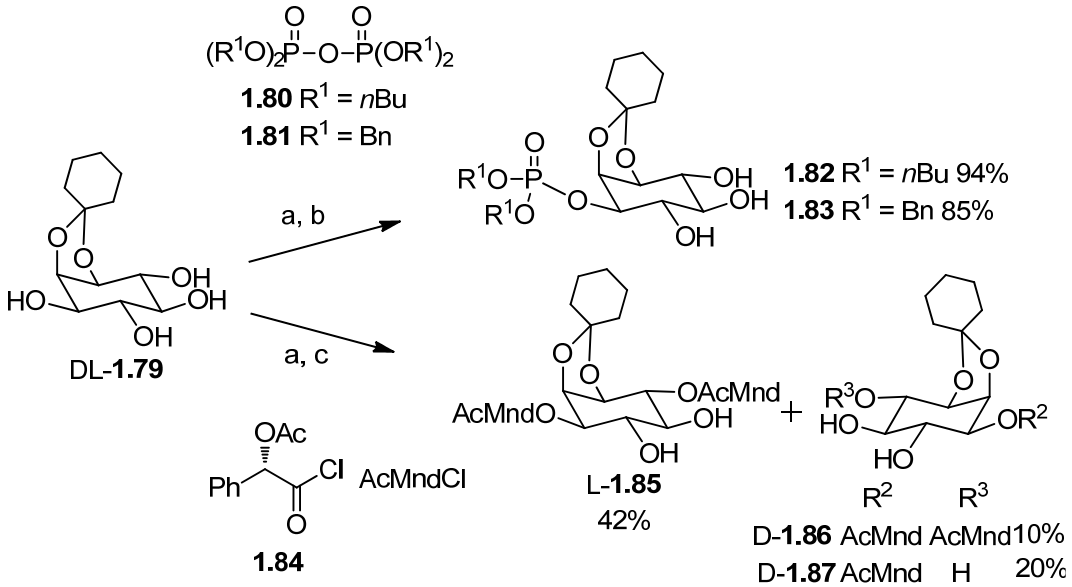
Scheme 1.9. (a) Bu_2SnO (3.0 eq.), BzCl (3.3 eq.), 93%; (b) Bu_2SnO, CH_3CN, CsF, BnBr, DMF; (c) Bu_2SnO, $n Bu_4NI$, BnCl, CH_3CN, 32%.

A consistent and economical protocol, with dibutyltin oxide / BnBr system has been described, for the mono-*O*-benzylation of vicinal *trans*-1,2-diol moieties on cyclohexane backbone, which are rather resistant to these transformations (**1.76**, Scheme 1.10). Such protocol has been successfully applied to *myo*-inositol derived diols. The selectivity could be greatly improved by using a 1:1 mixture of methanol and toluene as the solvent for the reaction.[27] 1,2-*cis*-Diol moieties on cyclohexane ring however undergo O-alkylation and acylation at the equatorial hydroxyl group relatively easily.[28]



Scheme 1.10. (a) Bu_2SnO, MeOH:Toluene, (1:1), 130 °C, 3h; (b) BnBr, nBu$_4$NBr, toluene; (c) Bu_2SnO (1.2 eq.), Ph-H, reflux, 20 h; (d) BnBr (3.0 eq.), nBu$_4$NI (1.0 eq.), 70 °C, 2 h.

Prior attempts at benzylation (or allylation) of the racemic tetrol **1.76** in the presence of an excess of dibutyltin oxide gave, a mixture of products.[29] Tin mediated regiospecific O-alkylation and phosphorylation of *myo*-inositol derived tetrol **1.79** (Scheme 1.11) paved the way for a concise synthesis of phosphatidylinositol with the natural configuration. Stannylene methodology was used for the optical resolution as well as regioselective

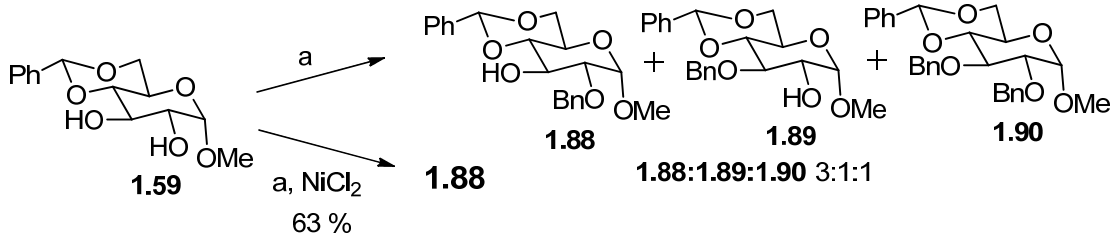


Scheme 1.11. (a) Bu_2SnO, toluene, reflux; (b) **1.80** or **1.81**, CH_2Cl_2, 0 °C; (c) **1.84**, CH_2Cl_2, –20 °C.

phosphorylation of the *myo*-inositol derived ketal **1.79**.[30] Advantages of the dibutyltin oxide / alkyl halide system for the conversion of alcohols to ethers include (a) reaction of stannylene acetals with alkyl halides under essentially neutral conditions; (b) preferential O-substitution of primary hydroxyl groups over those of secondary and tertiary ones; (c) preferential reaction of equatorial hydroxyl groups over that of axial ones; (d) possibility of mono *O*-substitution of 1,2-diol moieties even in the presence of other unprotected hydroxyl groups.

The available data in the literature on the tin mediated O-substitution of diols and polyols reveals mostly the selective reaction of vicinal diols; there appear to be no data on the O-alkylation of diols or polyols containing only non-vicinal hydroxyl groups. We were able to locate one reference[29a] which mentions that non-vicinal diols do not undergo tin mediated O-alkylaion. This is perhaps because formation of the stannylene acetal intermediate is expected to be facile only in the case of vicinal diols. Hence there is a need for the development of methods for the selective O-alkylation of polyols devoid of vicinal diols.

Regioselective monobenzylation and monobenzoylation of monosaccharide derived vicinal diols were carried out *via* their transition metal (Zn^{2+}, Pt^{2+}, and Ni^{2+}) chelates;[31] nickle(II) chloride performed best in terms of the reaction rate and yield (Scheme 1.12). It was observed that the substitution occurs exclusively at a position adjacent to the axially oriented substituent of the pyranose ring, for example, at C-2 of α-D-gluco and at C-3 of β-D-galacto sugars (Scheme 1.12). Benzoylation of the same sugars, with benzoyl chloride in

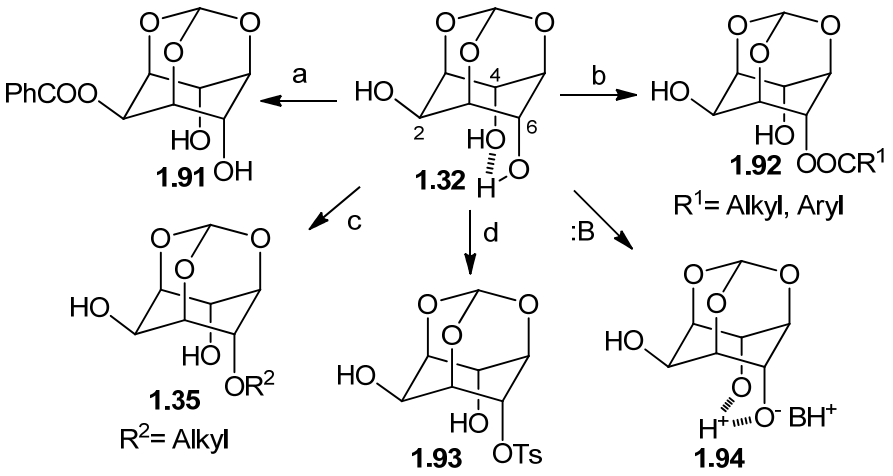


Scheme 1.12. (a) THF, DMF, BnBr, NaH.

the presence of either pyridine or NaH as a base and in the absence of a transition metal salt, proceeded with fair (pyridine as base) or no (NaH as base) regioselectivity, which indicated the necessity of a transition metal ion chelation to achieve good regioselectivity. Importance of chelation of metal ions for these reactions was also supported by the effect of the solvent on the efficiency of the reaction. Reactions in THF were regioselective, but

too sluggish to be of preparative value, while, in DMF, the rates were higher but the regioselectivity was significantly compromised. THF containing 10–20% DMF by volume was optimal in terms of rates, regioselectivity, and the yield.

The orthoesters of *myo*-inositol (eg., **1.32**, Scheme 1.13) constitute an interesting molecular system having a rigid conformation in which the relative orientation of the three hydroxyl groups is fixed, and two of the hydroxyl groups are strongly hydrogen bonded to each other. Hence the relative reactivity of the three secondary hydroxyl groups for nucleophilic substitution can be varied by the use of different reagents. Reaction of the orthoesters of *myo*-inositol with bases (metal hydrides, triethyl amine, potassium carbonate) which are strong enough to de-protonate one of the (C4- or C6-) axial hydroxyl groups result in exclusive O-alkylation or acylation or sulfonylation[16, 32] at the C4(6)-O-position. Deprotonation of one of the two axial hydroxyl groups (which are strongly hydrogen bonded) results in an anion which is stabilized by the other axial hydroxyl group due to intramolecular hydrogen bonding (**1.94**, chelation of H^+!) of the proton by the two axial oxygen atoms. Hence preferential O-substitution occurs at C4(6)-position, on reaction with electrophiles. Chelation of protons has also been observed during the opening of 1,2-epoxycyclohexanes (Scheme 1.19) in the gas-phase.[33]

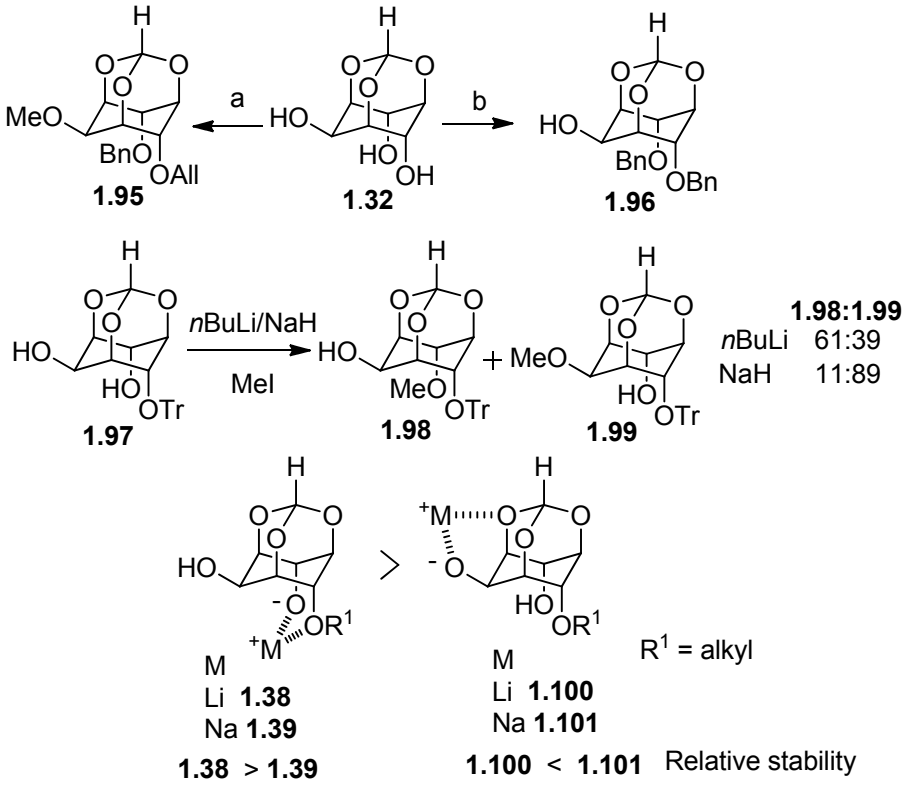


Scheme 1.13. (a) Pyridine, PhCOCl; (b) NaH (1.0 eq.), R^1COX (X = Cl or OOCR); (c) NaH (1.0 eq.), R^2X (1.0 eq.); (d) TsCl, Et_3N.

However, reaction of these orthoesters with electrpohiles in the presence of weaker bases (like pyridine) which cannot deprotonate any of the three hydroxyl groups, results in predominant reaction at the C-2 position due to (a) relatively higher nucleophilicity of the C2-OH and (b) relatively less steric hindrance (compared to diaxial C4(6)-hydroxyl

groups) for the C2-OH. The C4(6)-OH groups are relatively less nucleophilic due to intramolecular H-bonding between the C4- and C6-hydroxyl groups (which increases their acidity). In fact the intramolecular H-bonding between the C4- and C6-hydroxyl groups in *myo*-inositol orthoesters is strong enough to be observed in crystals of *myo*-inositol orthoesters as well as their 2-benzoyl derivatives.[15c, 34]

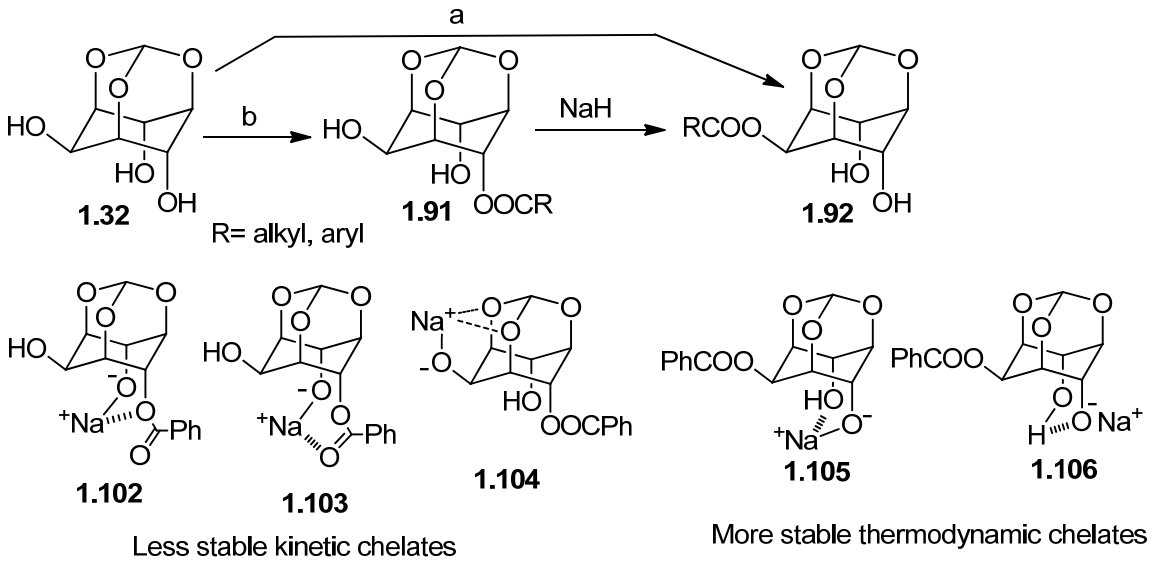
Previous work in our laboratory provided a general method for the completely regioselective protection of the three secondary hydroxyl groups of orthoester derivatives of *myo*-inositol, utilizing the subtle differences in reactivity exhibited by its alkali metal alkoxides due to differences in their ability to form chelates (Scheme 1.14). This method provides convenient access to orthogonally protected *myo*-inositol derivatives. A comparison of the methylation of racemic trityl ether **1.97** 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.[14]



Scheme 1.14. (a) i. DMF, NaH, BnBr, 89%; ii. THF, *n*BuLi, AllBr in DMF; iii. NaH, MeI, 80%; (b) DMF, LiH, BnBr, 80%.

O-alkylation of the *myo*-inositol orthoesters with alkyl halides (more than one equivalent) in most solvents and in the presence of sodium hydride proceeded with high rates but provided a mixture of products. The same reaction in the presence of lithium hydride (or butyllithium) was much slower in THF but the rate appreciated on addition of DMF to the reaction mixture. This was probably because, lithium alkoxides of inositol derivatives are present as aggregates in THF (hence lower rates of reaction with alkyl halides) and a dipolar aprotic solvent like DMF, breaks these aggregates (enabling them to react with alkyl halides and hence appreciation of rates). This line of thinking is supported by the fact that aggregates of dilithium enediolates of α-naphthylacetic acid in THF solution are broken by the addition of HMPA, as revealed by a bathochromic shift, in the UV spectrum of naphthylacetic acid dilithium enediolates.[35] A solution of naphthylacetic acid dilithium enediolates in THF containing 10% HMPA is much more reactive towards alkyl halides than a solution of naphthylacetic acid dilithium enediolates in THF alone. Similar trend in reactivity due to change of solvent was observed in the lithium base promoted O-alkylation of inositol orthoester derivatives.[14] Also, it is generally observed that lithium and magnesium enolates exhibit propensities for coordination with oxygenated functional groups (present in either the enolate or the aldehyde), which result in profound stereochemical consequences during aldol reactions.[36]

Product of acylation of *myo*-inositol orthoesters in the presence of metal hydrides depends on the amount of the base used (Scheme 1.15). While the use of 1 equiv of the base (sodium hydride or lithium hydride or potassium *tert*-butoxide) for the acylation of *myo*-inositol orthoesters gave the corresponding C4-ester **1.91** exclusively, the use of two or more equivalents of the same base for the acylation reaction gave the C2-ester **1.92** exclusively. Acylation at the C2-hydroxyl group is a result of migration of the acyl group from the C4-position to the C2-position in the presence of strong bases. This was established by the treatment of the racemic C4-ester with strong bases, which resulted in the formation of the C2-ester exclusively; the reverse reaction (in solution) is however, not feasible.[34c] The driving force for the isomerization of the C4-esters to the corresponding C2-esters was suggested to be the formation of a relatively stable alkoxide (such as **1.105**, **1.106**) of a 1,3-diaxial diol from the chelate (such as **1.102-1.104**) of a hydroxyl ester.[37]



Scheme 1.15. (a) DMF, NaH (2.0 eq.), ROCX (X = Cl or RCOO); (b) DMF, NaH (1.0 eq.), ROCX.

That the sites for the co-ordination of different metal ions is different in orthoesters of *myo*-inositol (Schemes 1.14 and 1.15), is supported by theoretical calculations as well as a comparison of the ability of *myo*-inositol derivatives to complex with metal salts. Calculations show that cations with radius less than 0.8 Å co-ordinate to the 1,3-*cis* diaxial oxygen atoms (**1.108**, Figure 1.2) whereas cations with radius more than 0.8 Å co-ordinate to the 1,2-*cis* oxygen atoms (**1.107**).[38]

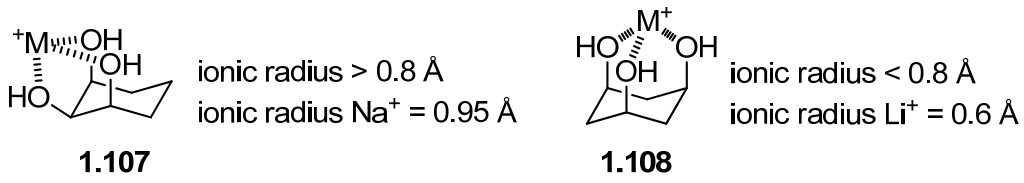
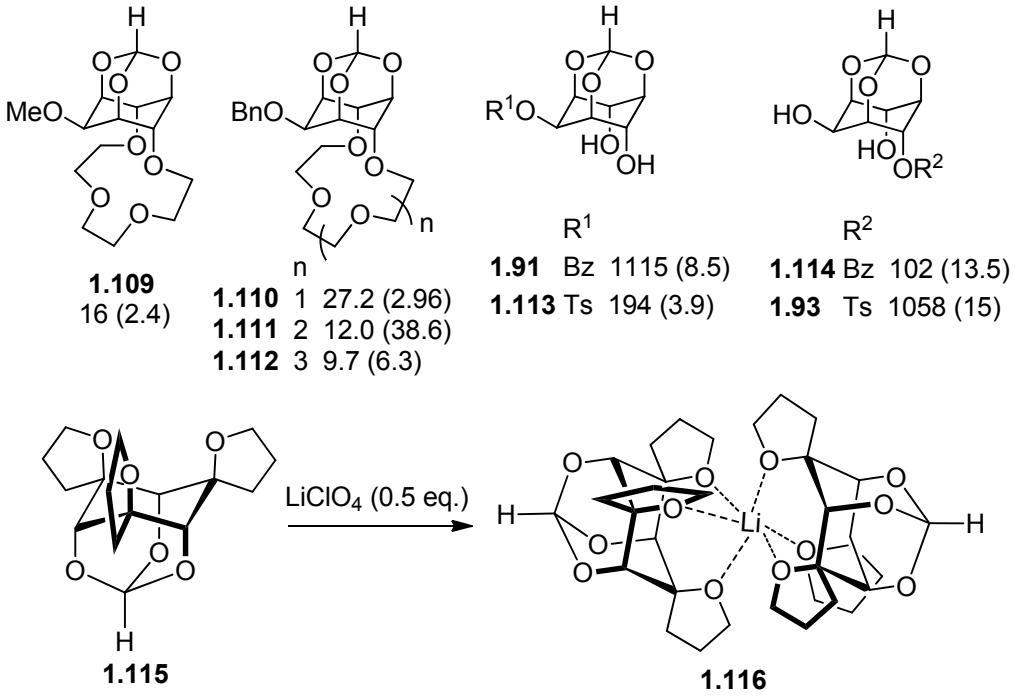


Figure 1.2.

Estimation of the relative binding constants for simple inositol derivatives as well as inositol based metal complexing agents show that ligands having 1,3-diaxial oxygen atoms exhibit better selectivity for the binding of lithium picrate compared to other alkali metal picrates (Scheme 1.16).[39] Lithium ion selective ligands have been built on *myo*-inositol orthoester platform which form stable crystalline complexes with lithium salts; their crystal structures (**1.116**) reveal the sites of co-ordination of the lithium ions.[40] These results are in accordance with the observed regioselectivity during the O-substitution reactions of *myo*-inositol orthoesters with the aid of sodium and lithium derived bases.



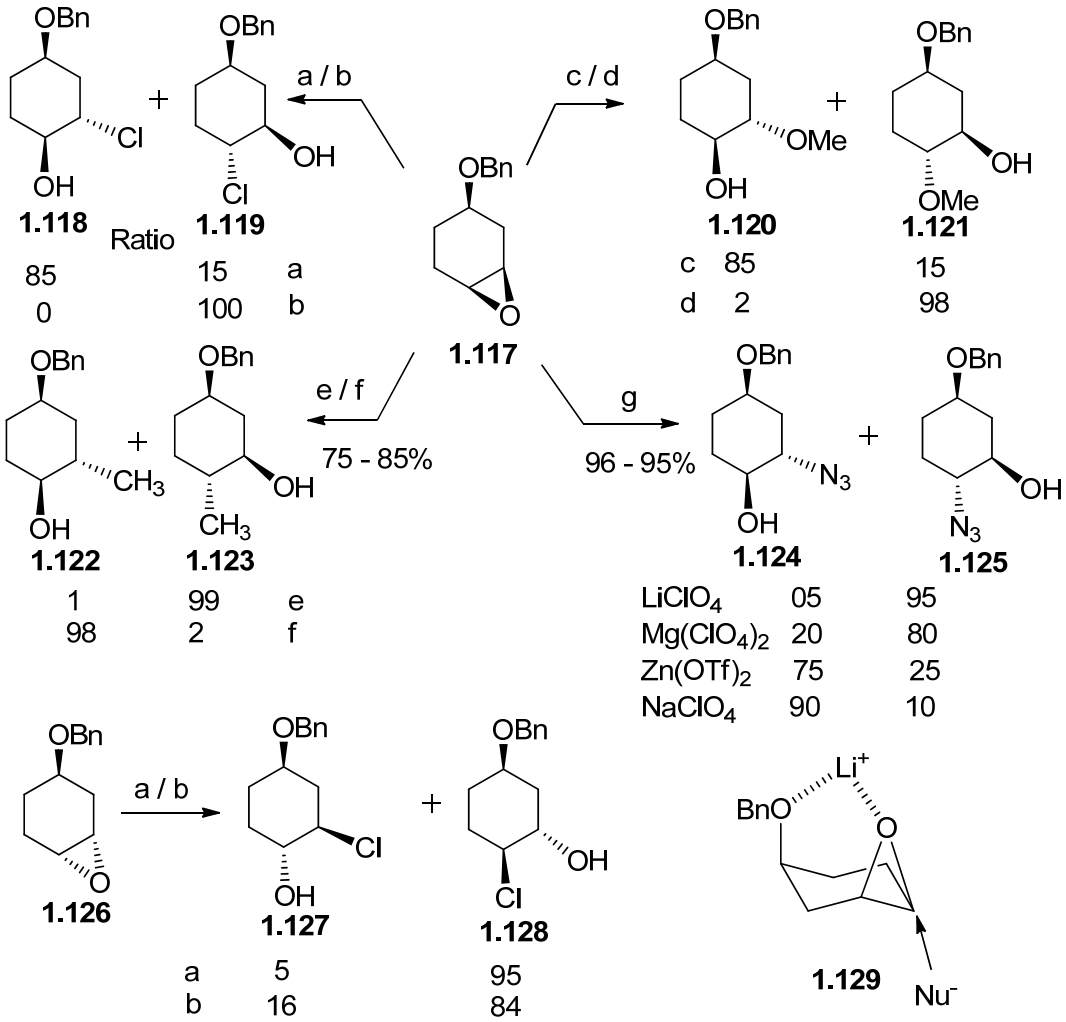
Scheme 1.16. Numbers below each structure represents Ka × 10^{-4} dm^3 mol^{-1} for lithium (sodium) picrate.

1.3. Selective cleavage of C-O bonds arising from metal ion chelation.

Selective cleavage of C-O bonds is of need and significance in small organic molecules as well as larger molecules containing many functional groups. In the former, selective cleavage aids in the construction of well defined larger molecules, as exemplified by the cleavage of epoxides by nucleophiles and in the latter, the selective cleavage helps to achieve regioselective reactions, as illustrated by the selective cleavage of ethers in polyols.

The regiochemical outcome of the ring opening of cyclohexene epoxides bearing polar remote functional group (ring oxygen or benzyloxy group) was dependent on the presence or absence of metal ions in the reaction mixture. These reactions proceed through the chelation of metal ions, which give a leverage for regiochemical control.[(41)] A remote benzyloxy group served as a good ligand for the chleation of metal ions which aided the regioselective nucleophilic addition to the cyclohexane epoxide ring (Scheme 1.17). The reaction of *cis*-epoxide **1.117** with titanium(IV) chloride in dichloromethane gave exclusively the chlorohydrin **1.119**, whereas the regioisomeric chlorohydrin **1.118** was obtained as the major product from its reaction with HCl. Similarly, the protic acid catalyzed methanolysis of **1.117** (to give the regioisomers **1.120**:**1.121** in the ratio 85:15)

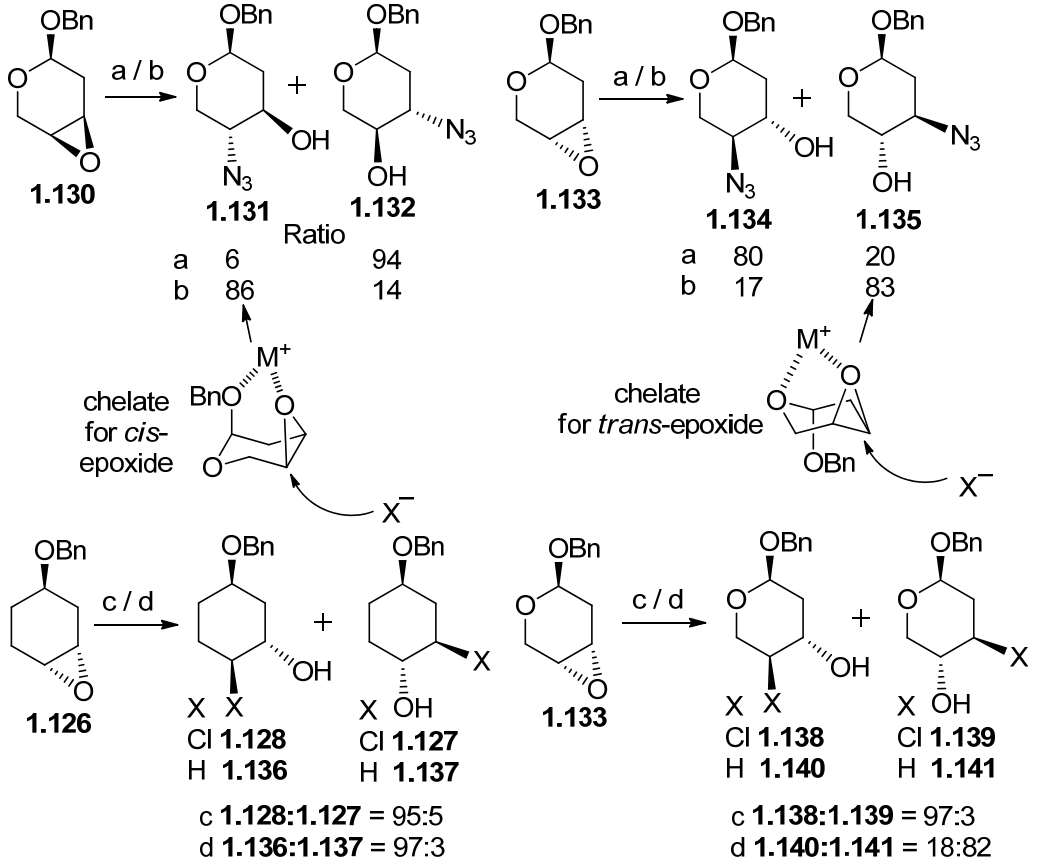
was completely inverted (2:98) when the solvolysis was carried out with concentrated methanolic lithium perchlorate. The regiochemical outcome of the ring-opening addition reactions with *trans*-epoxide **1.126** was independent of any bidentate chelation effects. In all of the addition reactions of **1.117** and **1.126** the ring-opened products were consistent with the well-known preference for diaxial nucleophilic ring-opening in cyclohexene oxide derivatives.[42] The control exerted by the remote oxygen atom on the regiochemistry of the methylating ring opening of oxiranes through metal chelating processes was supported by the fact that the addition of a crown ether to the reaction mixture reversed the regiochemical outcome of the reaction.[43] The ability of the metal ion to influence the regioselectivity of the reactions of **1.117** by the chelating process decreased in the order $Li^+ > Mg^{2+} > Zn^{2+} > Na^+$, but their effectiveness in catalyzing the nucleophilic oxirane ring-opening process decreased in the order $Zn^{2+} > Mg^{2+} > Li^+ >> Na^+$. It appears that the size of the metal ion affects the stability of the bidentate structure **1.129** since the smaller ions are the most effective in promoting the chelation-assisted addition pathway of epoxide **1.117**.[44] This was also evident for the reaction of the polyols and their derivatives with electrophilic reagents (Scheme 1.14).



Scheme 1.17. Ring opening reactions of *cis* and *trans* epoxides (**1.117** and **1.126**). (a) HCl, $CHCl_3$; (b) TBHP, $TiCl_4$; (c) H_2SO_4, MeOH; (d) $LiClO_4$, MeOH; (e) $AlMe_3$, BuLi, pentane; (f) $AlMe_3$, BuLi, 12-crown-4, pentane; (g) NaN_3, metal salt, CH_3CN.

Regiochemical ring opening of 1,2-epoxides in conformationally semi-rigid cyclic systems, bearing remote functionalities capable of chelating metal ions depended on the presence or absence of metal ions in the reaction mixture. Both the *cis*- **1.130** and *trans*-**1.133** epoxides (Scheme 1.18) exhibited marked change in regioselectivity on going from non-chelating to chelating reaction conditions. This allowed considerable control over the regioselectivity leading to a high degree of regioalteration.[45] A comparison of the oxirane ring opening in the carbocyclic and the corresponding heterocyclic systems (**1.126** and **1.133**, Scheme 1.18) reveals that the presence of the oxygen atom in the parent ring does not change the outcome of the oxirane ring opening while the selectivity is reversed in reactions which involve metal ions. This could indicate the preference of the ligating sites of the metal and supports the involvement of chelates during the reaction. If metal ions

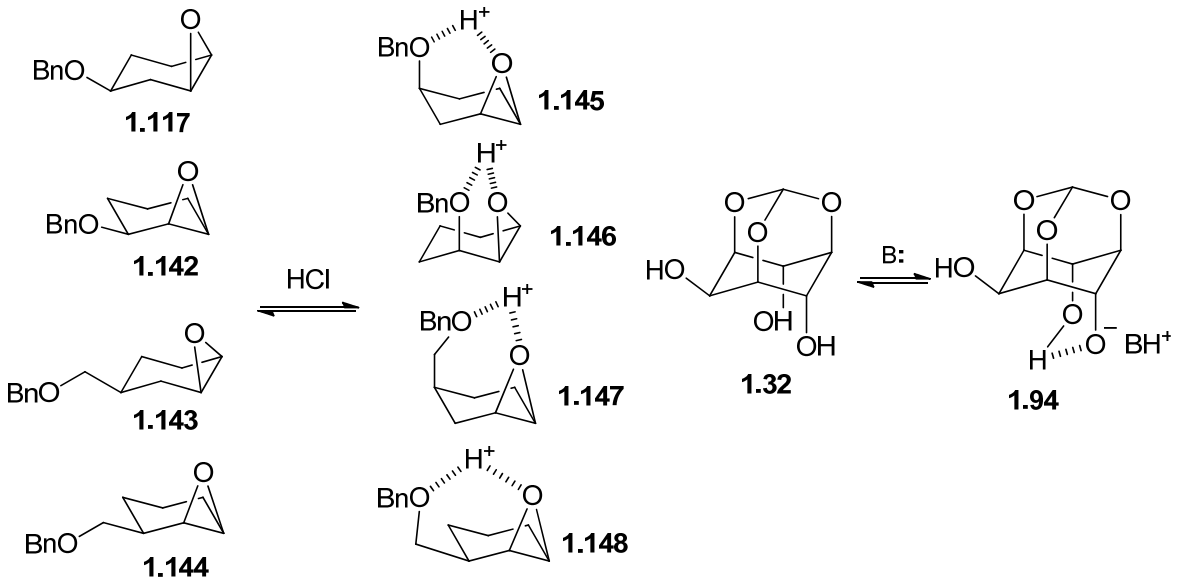
were inert, during the oxirane ring opening, the stereochemical outcome of these reactions would not have changed, as observed for the oxirane ring opening with HCl.



Scheme 1.18. Ring opening reactions of *cis*- and *trans*- epoxides (**1.130** and **1.133**) containing oxygen in the ring. (a) NaN_3, NH_4Cl; (b) NaN_3, $LiClO_4$; (c) HCl; (d) $LiAlH_4$, pentane.

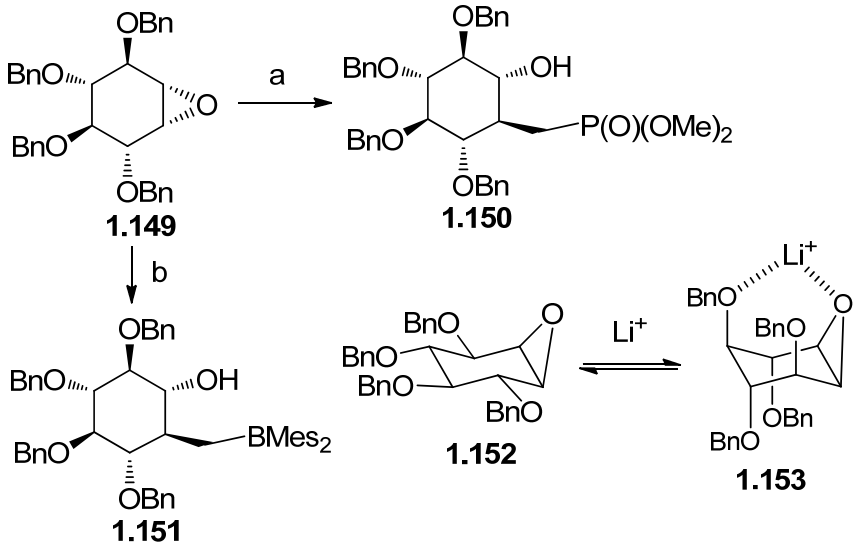
It is interesting to note that the regiochemical outcome of the acid catalyzed ring opening reaction of the *cis*-oxirane systems (epoxides **1.117**, **1.142**–**1.144**, Scheme 1.19) in the gas phase was similar to that observed in the solution phase in the presence of a metal salt such as lithium perchlorate. This implies that the proton functions as a chelating agent in the gas phase reactions; protons however, were ineffective as chelating agents in the solution phase.[46] This is perhaps because, the relatively large excess of the solvent (methanol) present in the solution phase reactions is better at co-ordinating with protons than the oxygen atoms in the substrate (epoxide) molecules. It is likely that the overall stabilization energy of the chelated species resulting from the chelation of protons is far less than that achieved by lithium ions due to smaller size of a proton. Chelation of proton has been observed during the regioselective O-alkylation of *myo*-inositol orthoesters in the

solution phase, wherein the distance between the two chelating oxygen atoms appears to be much less than that in epoxides **1.117**, **1.142-1.144**.



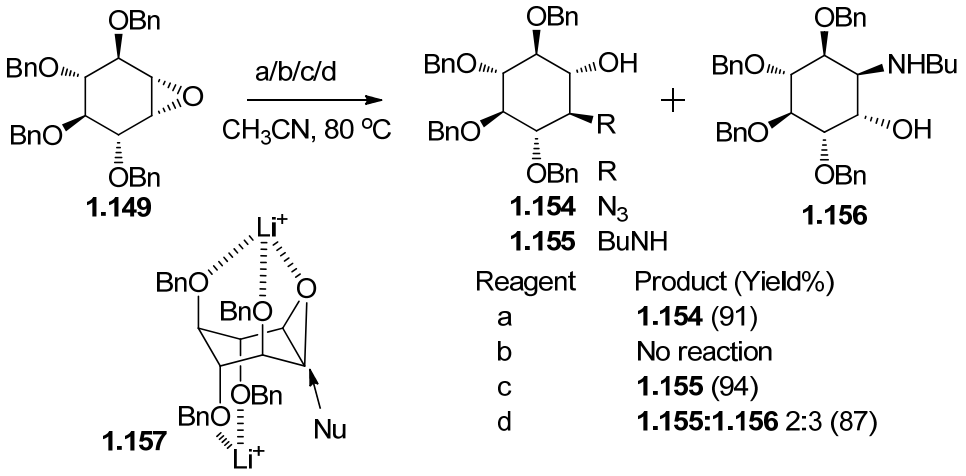
Scheme 1.19. Epoxide ring opening in the gas phase.

Oxirane ring opening with (lithiomethyl)-dimesitylborane in epoxides derived from quinic acid and *myo*-inositol, was regiospecific (Scheme 1.20). The observed regioselectivity suggested the involvement of a transition state where *trans*-diaxial nucleophilic attack occurred on the axial rich conformer **1.153** stabilized by chelation with lithium ion.[47]



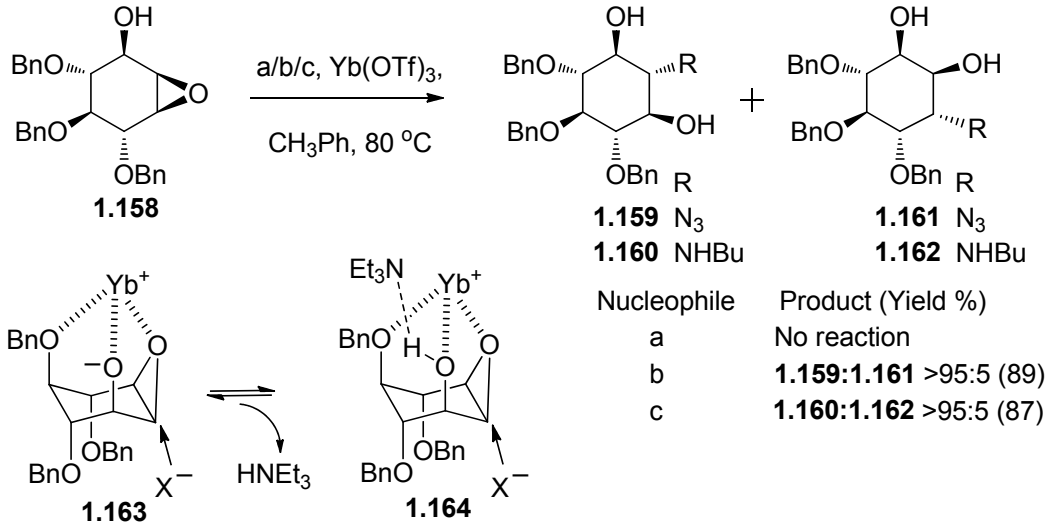
Scheme 1.20. (a) $(MeO)_2P(O)CH_2Li/BF_3$, 61%; (b) Mes_2BCH_2Li.

Opening of the epoxide ring in the inositol derived epoxide **1.149** with azide and amine nucleophiles was regiospecific in the presence of lithium perchlorate, but gave a mixture of products in the absence of lithium perchlorate (Scheme 1.21). These results were in accordance with theoretical models; the inclusion of two Li^+ ions in the chelated models favored the operation of a low populated "all axial" conformation **1.157** leading to the C1 adducts.(48)



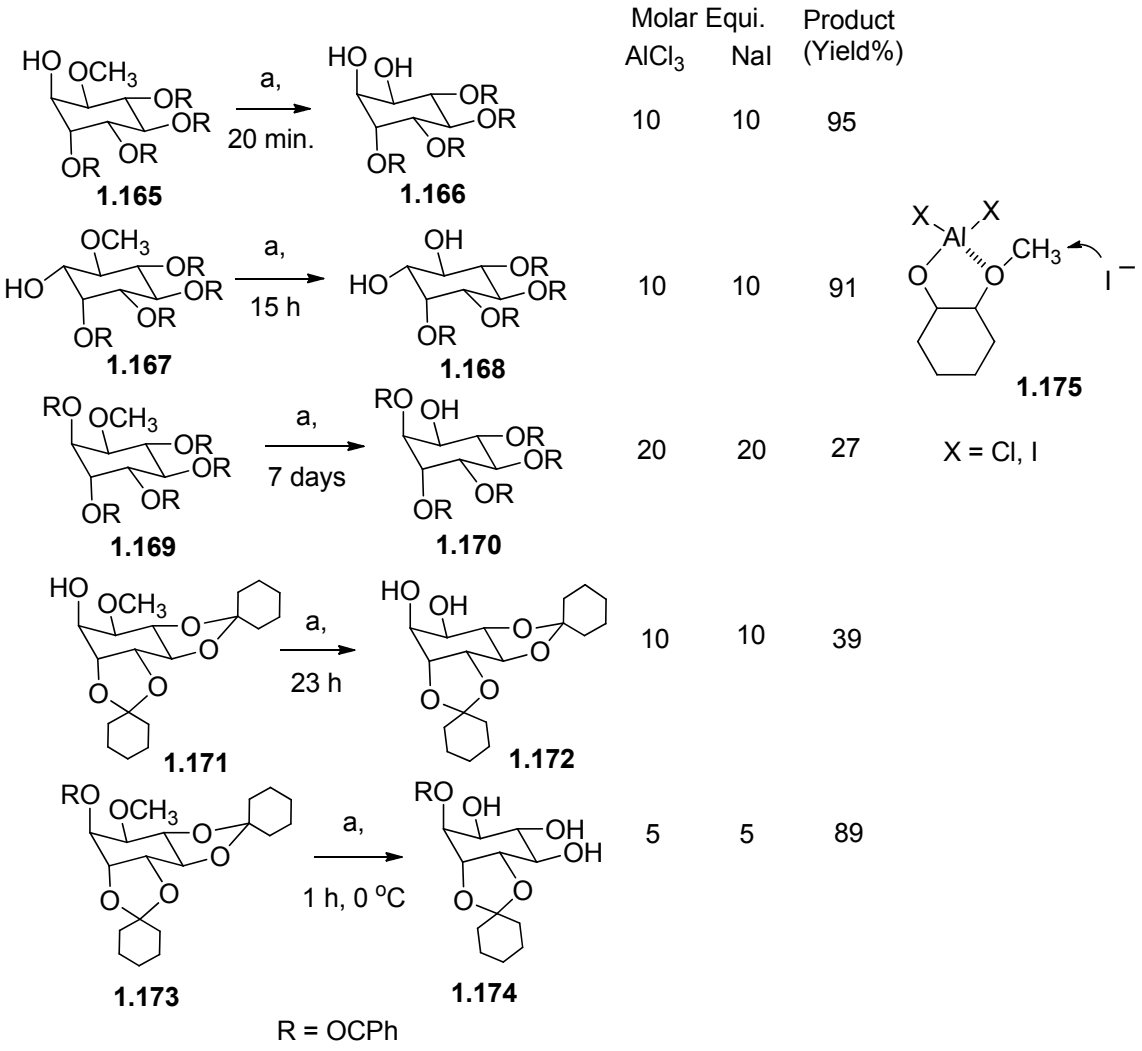
Scheme 1.21. (a) NaN_3, $LiClO_4$; (b) NaN_3; (c) $BuNH_2$, $LiClO_4$; (d) $BuNH_2$.

A chelation-controlled aminolysis and azidolysis of cyclitol epoxides (having a neighboring free hydroxyl group) proceeds with regiocontrol in the presence of $Yb(OTf)_3$ (Scheme 1.22). The presence of a free OH group was essential for the coordination with the ytterbium ion, which is responsible for the regio-control.(49)



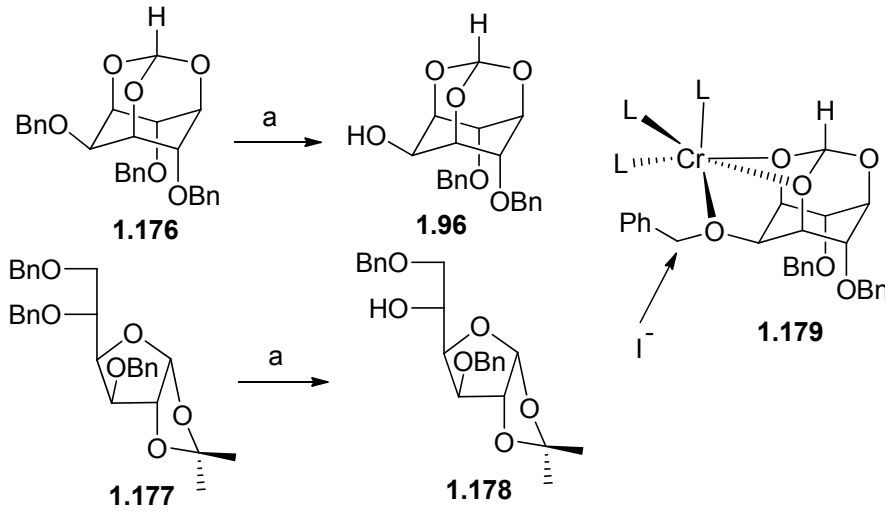
Scheme 1.22. (a) NaN_3; (b) NaN_3, Et_3N (0.15 eq.); (c) $BuNH_2$.

Normally ethers are relatively more resistant to cleavage compared to esters and acetals. An unusual example of facile cleavage of methyl ether in the presence of a *cis*-acetal or benzoate was observed in a *myo*-inositol derivative (Scheme 1.23). Cleavage of the methyl ether by $AlCl_3$-NaI system was facilitated by a vicinal hydroxyl group; a *cis* vicinal hydroxyl group was more efficient than a *trans* vicinal hydroxyl group, in bringing about the cleavage of the methyl ether.[50]



Scheme 1.23. (a) $AlCl_3$, NaI, CH_3CN.

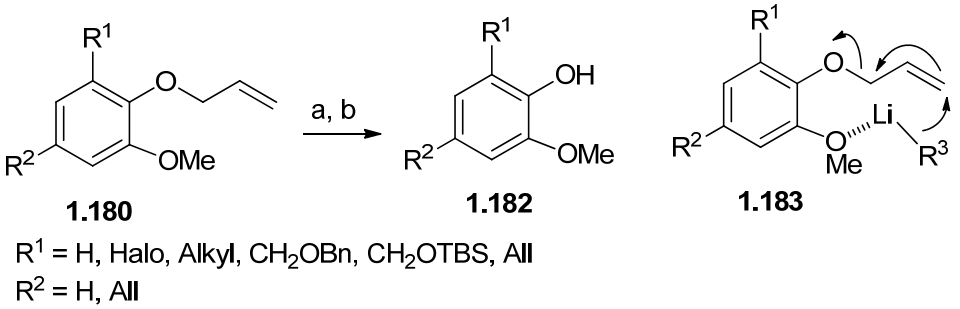
Poly-*O*-benzylated sugars could be regioselectively debenzylated using $CrCl_2$/LiI in moist ethyl acetate (Scheme 1.24). The regioselectivity of ether cleavage could be predicted with a three-point coordination model **1.179**. Dimethoxybenzyl ethers were cleaved in preference to benzyl ethers and acetals were stable under these ether cleavage conditions, involving metal ion chelation.[51] Cleavage of the C-2 benzyl ether in the



Scheme 1.24. (a) $CrCl_2$, LiI, moist EtOAc, 12 h, 55–75 °C, 81–83%.

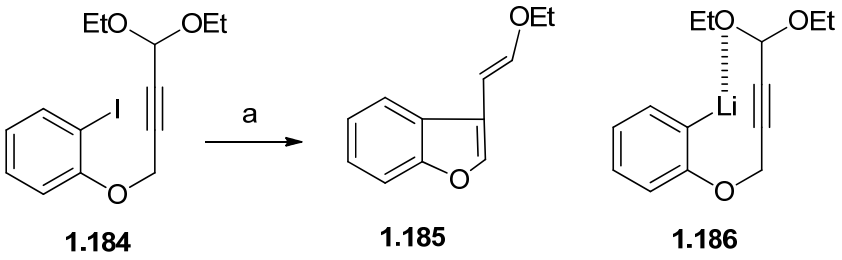
tribenzyl ether **1.176** substantiates the observation that metal ions of radius > 0.8 Å ligate with vicinal oxygen atoms in the axial-equatorial mode rather than the axial-axial mode (Fig. 1.2). If there was indeed considerable chelation of chromium ions in the axial-axial mode, we should have observed cleavage of the C4(6)-benzyl ethers as well.

Selective cleavage of allyl ether in *o*-allyloxy anisoles by *sec*- or *t*Bu-lithium due to chleation of the lithium ion by the methoxy group has also been reported (Scheme 1.25).[52]



Scheme 1.25. (a) *s*BuLi or *t*BuLi, Et_2O, –78 °C; (b) MeOH, –78 °C–20 °C, 80–95%.

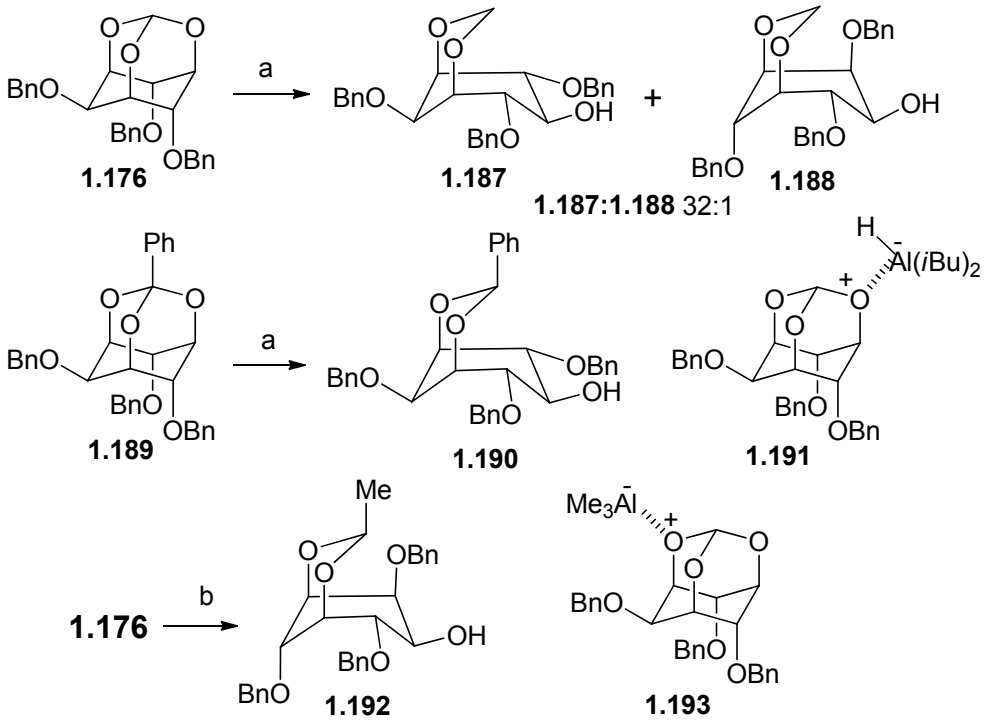
An instance of intramolecular coordination of lithium by an oxygen atom of the acetal appendage, which persists during the ring-closure process, and drives the cation to the E site of the final olefin formed has been reported (Scheme 1.26).[53] The treatment of **1.184** with one equivalent of butyllithium led to the formation of **1.186**. DFT calculations supported the intramolecular coordination of lithium by one oxygen atom of the terminal acetal appendage and also revealed that in the absence of lithium - oxygen coordination, the Z olefin must result from a classical *syn* addition of the aryllithium. The experimental results were in agreement with the outcome of theoretical calculations.



1.184 **1.185** **1.186**

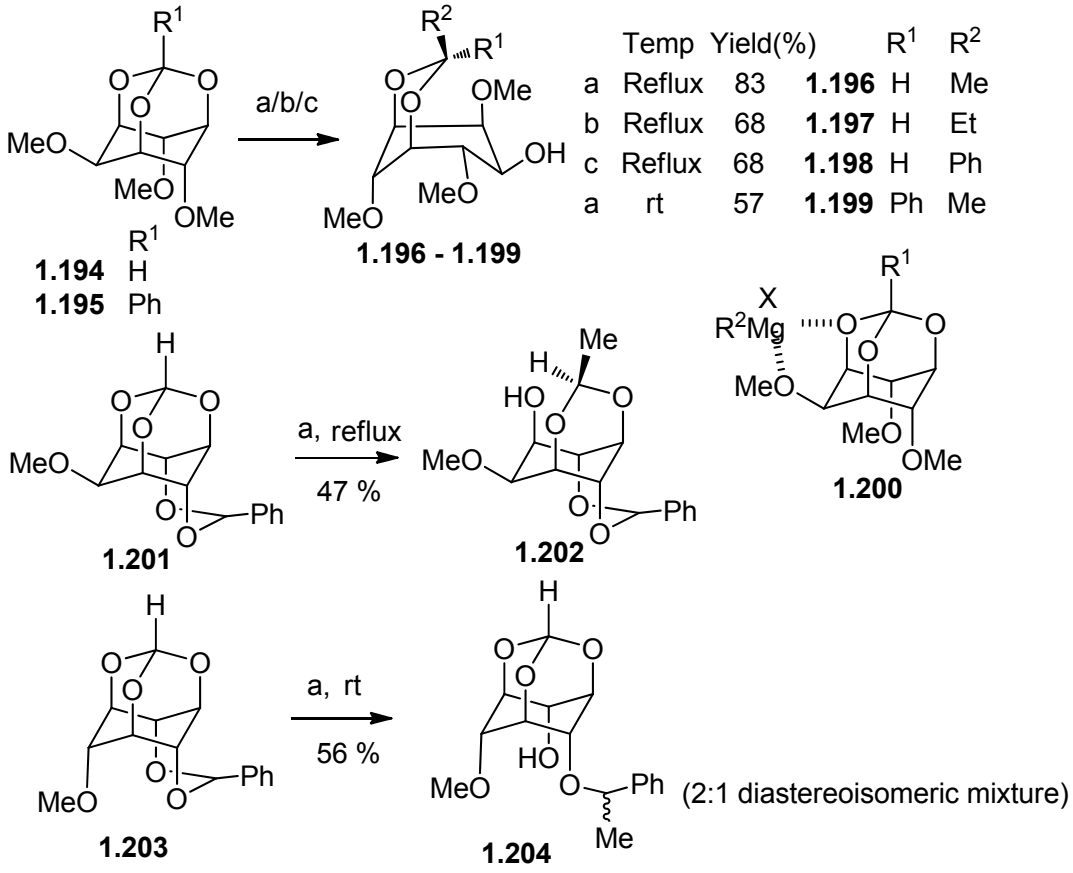
Scheme 1.26. (a) *n*BuLi (3.3), THF, –78 °C, 62%.

An interesting observation of the change in selectivity in the cleavage of a C-O bond, in *myo*-inositol orthoformate, depending on the size of the organometallic reagent was reported (scheme 1.27).[54] Reduction of the orthoester **1.176** with DIBAL-H at room temperature resulted in a highly stereoselective cleavage of the C5-O bond of the orthoester moiety to produce the 1,3-acetal **1.187** (with a trace of the isomeric **1.188**), while reaction of **1.176** with trimethylaluminium resulted in the predominant cleavage of the C1(3)-O bond to give the alkylated acetal **1.192**. Both the reactions were suggested to proceed through the initial complexation of aluminium with one of the orthoformate oxygen atoms.



Scheme 1.27. (a) DIBAL-H in toluene/hexane, DCM, 93–100%; (b) $AlMe_3$ in hexane, DCM, 84%.

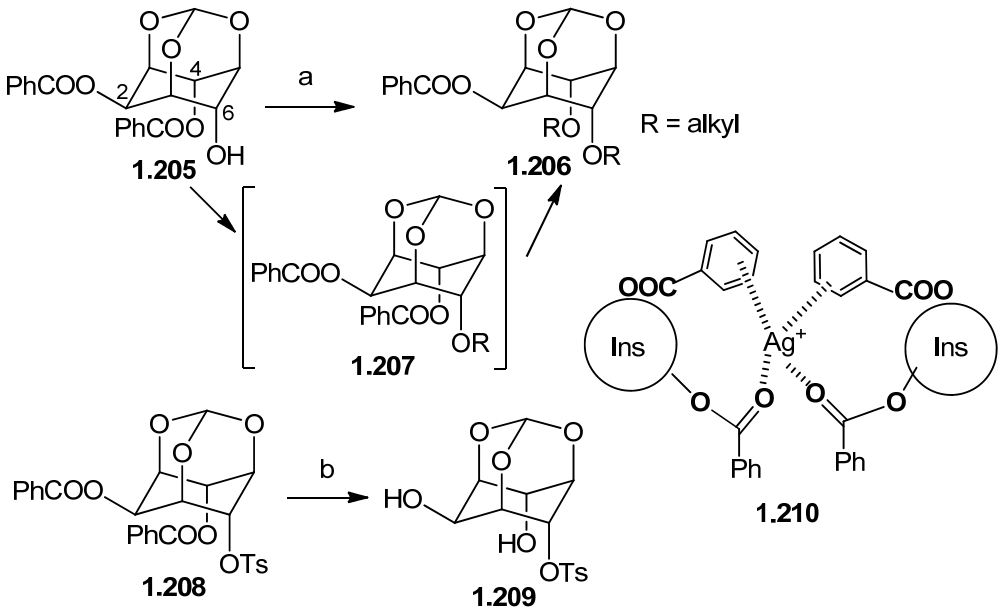
Selective cleavage of the orthoester moiety in *myo*-inositol orthoesters could also be effected with Grignard reagents (Scheme 1.28).[55] That these cleavage reactions proceed by the initial chelation (**1.200**) of magnesium with the C2-oxygen of the *myo*-inositol was suggested due to the inability of the Grignard reagent to cleave the orthoester moiety in the analogous *scyllo*-inositol orthoester derivative **1.203**. All these C-O bond cleavage reactions (Schemes 1.27, 1.28) are very useful for the efficient synthesis of cyclitol derivatives.



Scheme 1.28. (a) MeMgI, Ph-H, ether; (b) EtMgBr, Ph-H, ether; (c) PhMgBr, Ph-H, ether.

One of the classical methods for the O-alkylation of alcohols containing carboxylic acid esters is by using silver(I) oxide and alkyl halide, which leaves the ester group undisturbed;[56] most other bases bring about hydrolysis or transesterification of the ester. Unexpectedly, the reaction of racemic 2,4-di-*O*-benzoyl-*myo*-inositol-1,3,5-orthoformate (**1.205,** Scheme 1.29) with excess alkyl bromides or iodides, in the presence of excess silver(I) oxide resulted in the cleavage of the C4-benzoate, to give the symmetrical diether **1.206**. The reaction could however be controlled to give the monoether **1.207** and leave the C4-ester undisturbed (by varying the reaction time or the solvent or by the use of alkyl

chloride). Propensity for the formation of the diether decreased in the order, alkyl iodides > alkyl bromides > alkyl chlorides. Involvement of a *myo*-inositol orthoformate-silver complex (such as **1.210**) during these alkylation reactions was suggested.[57] It is likely that the silver halide generated during the O-alkylation of the hydroxyl group aided the cleavage of the ester (see below).



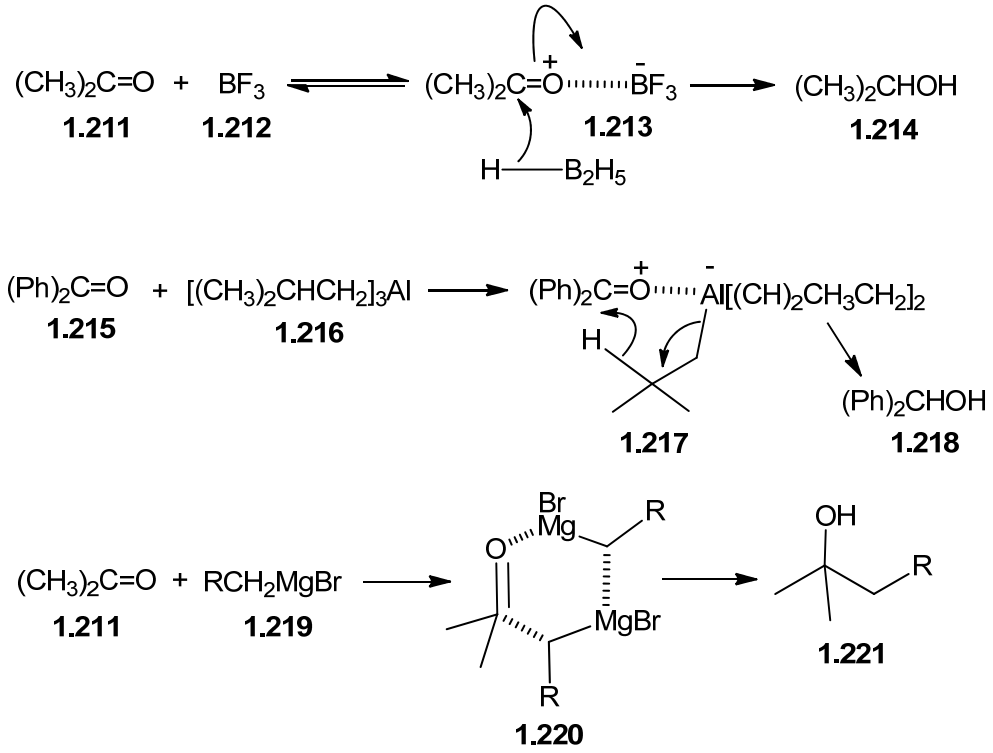
Scheme 1.29. (a) DMF, Ag_2O, RX (X = Br, I), 83%; (b) DMF, MeOH, Ag_2O, AgX (X = Br, I).

Only the C4-ester in the dibenzoate **1.205**, (or its 6-*O*-methyl derivative) could be solvolyzed in the presence of silver(I) oxide and silver halide, while in the 6-*O*-sulfonylated derivatives (**1.208**), under identical conditions, both the C4- and C2-esters underwent solvolysis.[58] Catalytic efficiency of the silver halides in bringing about solvolysis of the benzoates decreased in the order AgI > AgBr > AgCl. It is interesting to note that these unusual O-alkylation and solvolysis reactions complement each other. In these reactions, involvement of inositol derivative – silver halide aggregates (containing complexes such as **1.210**) rather than well defined silver – inositol derivatives complexes is postulated for reasons as below. Silver halides are known to be more covalent (compared to other metal halides such as alkali metal halides); silver ions are known to form linear complexes with ligands, rather than chelates;[59] silver is also known to complex with olefins, acetylenes and aromatic rings, which precludes precise defining of the sites of co-ordination on inositol derivatives with silver ions.[60] Nevertheless, these aggregates increase the electrophilicity of the ester carbonyl groups to cause their solvolysis in

methanol. Strongly complexed metal ions are known to facilitate nucleophilic reactions that occur at the carbonyl carbon of the ligands.[61] These unusual reactions involving silver – inositol aggregates were successfully utilized for the synthesis of D- and L-*myo*-inositol-1,3,4,5 tetrakisphosphate precursors.[62]

1.4. Addition of nucleophiles to carbonyl groups.

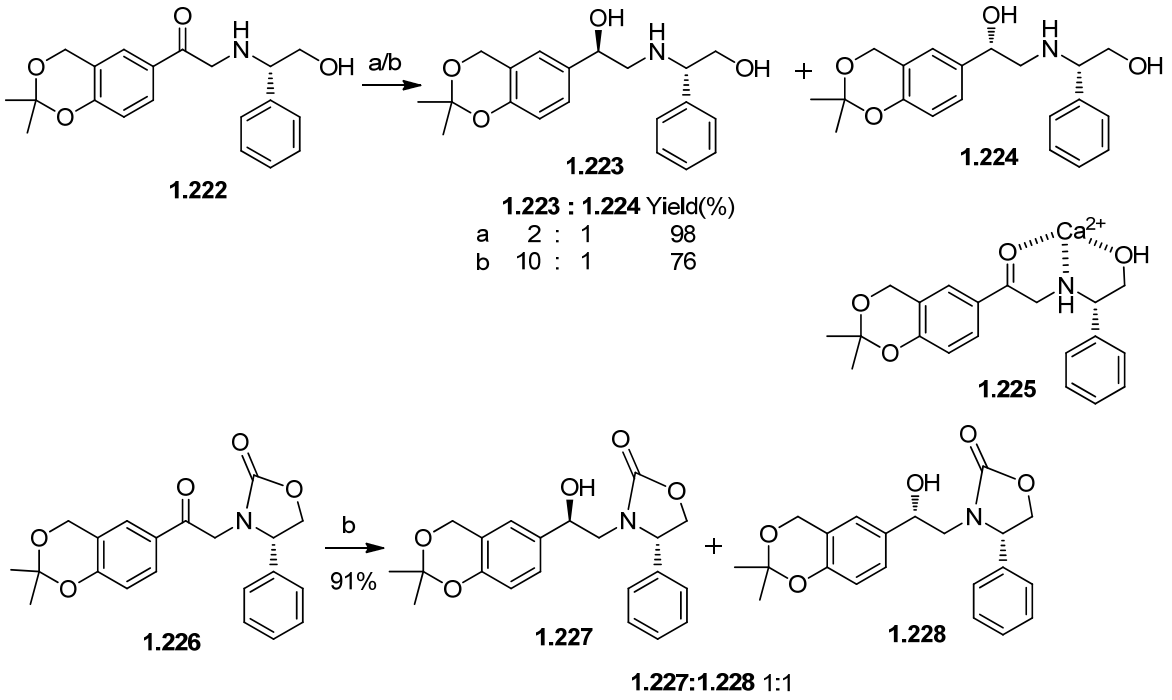
Nucleophilic addition to carbonyl groups, including hydride reduction, is one of the ubiquitous reactions in organic synthesis. Reactivity of a carbonyl group is susceptible to the presence of agents which can interact with the oxygen atom of the carbonyl group. For instance, one of the factors which facilitate the reaction of organometallic reagents with carbonyl compounds is the interaction of the carbonyl oxygen with metal ions. Lewis acids are known to aid reactions of carbonyl groups because of their ability to complex with the carbonyl group (Scheme 1.30). The focus in the present section however is on the chelation of metal ions with carbonyl groups which influences the product selectivity.



Scheme 1.30

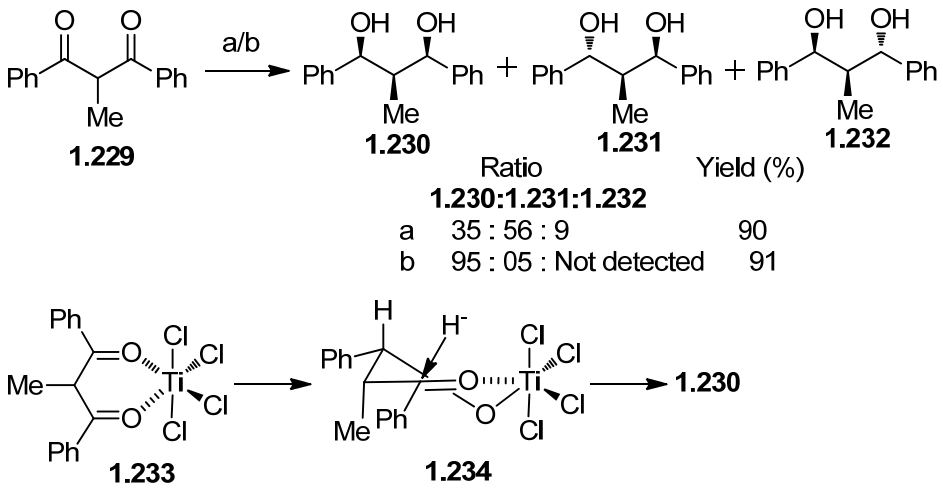
Chelation control has been effectively used in the asymmetric reduction of a prochiral ketone **1.222** (Scheme 1.31) using sodium borohydride by Bream *et al.* [63] in their synthesis of (*R*)-salmeterol. Calcium chloride enhanced the solubility of the ketone in methanol and allowed for selective reduction, yielding a 10:1 mixture of diastereomers

(**1.223** (*anti*) : **1.224** (*syn*). A marked downfield shift of one of the α-keto protons in the ^{1}H NMR spectrum of **1.222** was observed in the presence of one equivalent of $CaCl_2$, indicating strong complexation (**1.225**) between **1.222** and $CaCl_2$. The selectivity observed in the reduction of the ketone **1.222** is thought to arise *via* the complex **1.225**. In the case of ketone **1.226**, where neither a hydroxyl group nor amino group is available for complexation with $CaCl_2$, the ratio of the reduction products **1.227** and **1.228** was 1:1.



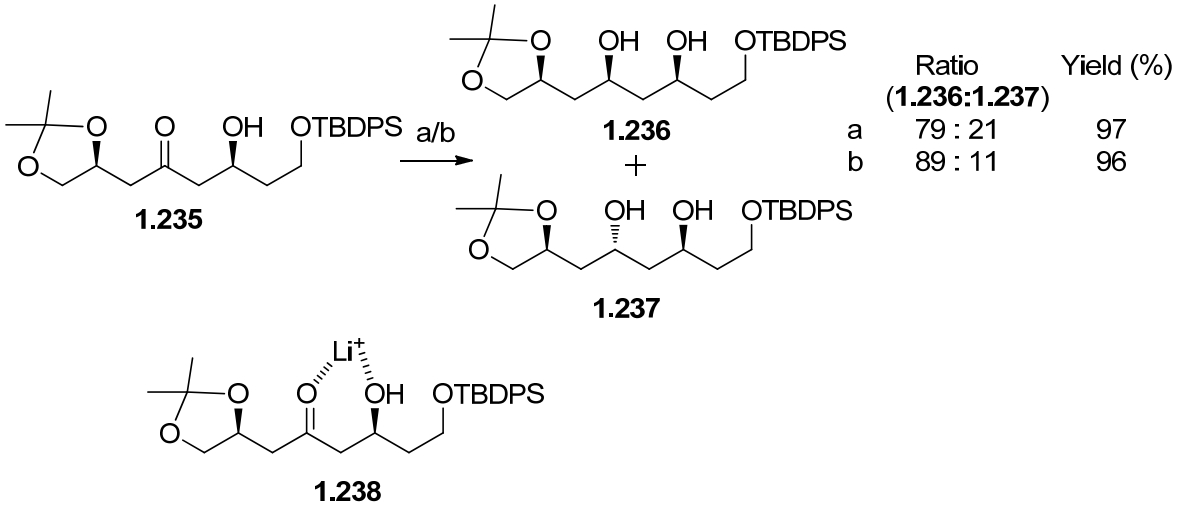
Scheme 1.31. (a) $NaBH_4$, THF, MeOH (3:5), 0 ^oC; (b) $NaBH_4$, $CaCl_2 \cdot 2H_2O$, MeOH, 0 ^oC.

1,3-Diols with three chiral centers are easily obtained, as a diastereoisomeric mixture, by the reduction of β-dicarbonyl compounds with lithium aluminum hydride and $TiCl_4$ (Scheme 1.32). The major isomer **1.230** was formed by the addition of hydride to both carbonyl groups of **1.229** from the less hindered side; the course of this reduction can be explained *via* the cyclic models **1.233** and **1.234**. Alternatively, a reduction pathway through boat conformations according to Maier's model[(64)] would also account for the formation of **1.230**.[(65)]



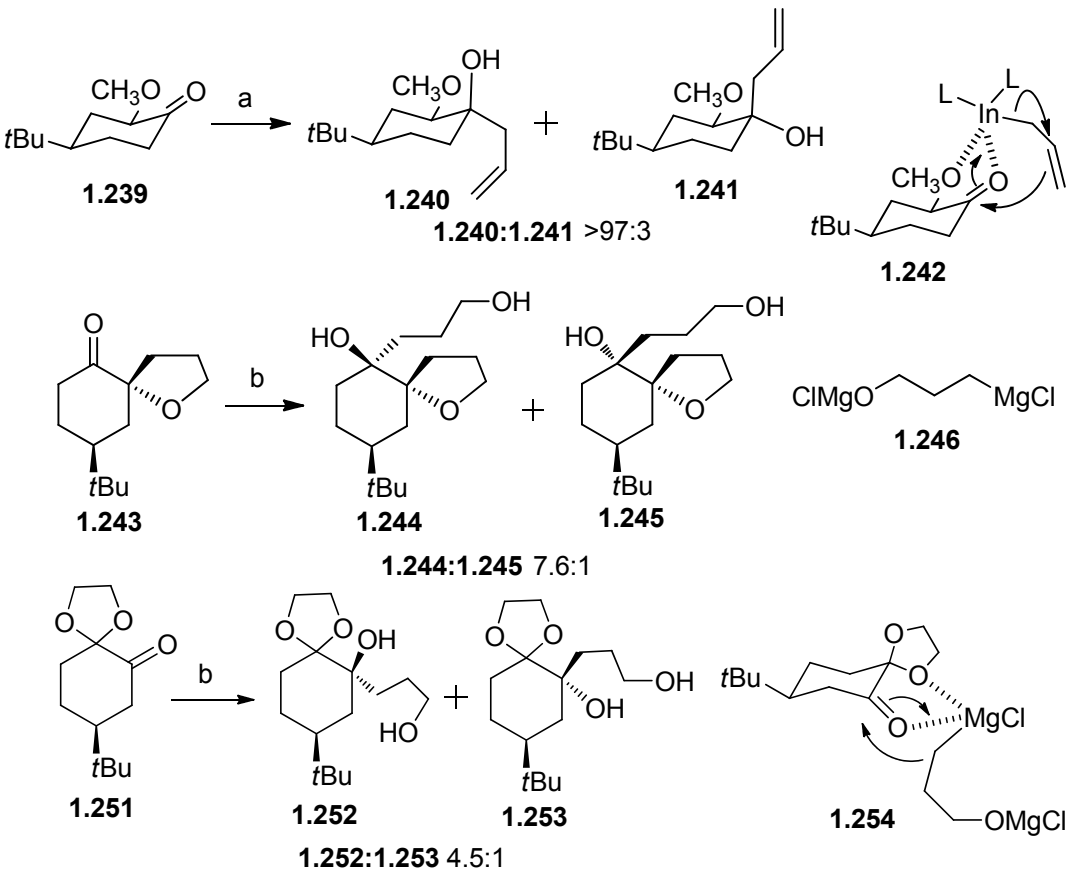
Scheme 1.32. (a) LAH, CH_2Cl_2; (b) LAH, $TiCl_4$, CH_2Cl_2.

The reduction of acyclic β-alkoxy ketones with lithium aluminum hydride in the presence of lithium iodide proceeds with high diastereoselection to provide *syn*-1,3-diols (Scheme 1.33). Decrease in the extent of diastereoselectivity for the same reaction in the absence of lithium iodide suggests the involvement of lithium chelates during reduction.[66] This methodology has been utilized in a short synthesis of the *δ*-lactone moiety of the HMG-CoA reductase inhibitors, compactin and mevinolin.[67]



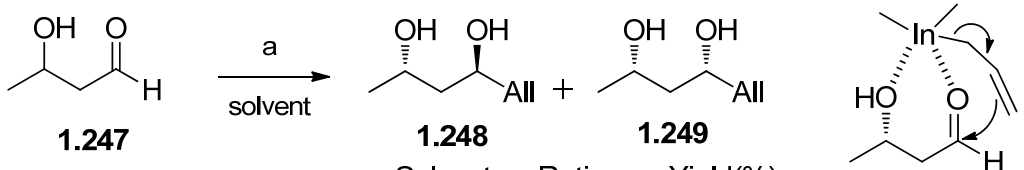
Scheme 1.33. (a) LAH, Et_2O, –78 °C; (b) LAH, LiI, Et_2O, –78 °C.

Similarly a neighboring methoxyl substituent has also been shown to be capable of engaging in chelation of the metal ion during the course of 1,2-addition of several allylmetal reagents and of the Normant Grignard (**1.246**) to cyclohexanones **1.239, 1.243** and **1.251** (Scheme 1.34).[68]



Scheme 1.34. (a) AllBr, Indium metal, THF, 76%; (b) **1.246**, THF, 0 °C, 84–88%.

The stereochemical course of the indium-promoted allylations to α- and *β*-oxy aldehydes were investigated in various solvents including water (Scheme 1.35). The free hydroxyl derivatives reacted with excellent diastereofacial control to give significantly heightened levels of *syn*-1,2-diols and *anti*-1,3-diols. An estimation of the relative reactivities of the α- oxy aldehydes, suggested that the selectivity arises due to chelated intermediates.[69] Investigation into the facial selectivity of the indium-promoted allylation

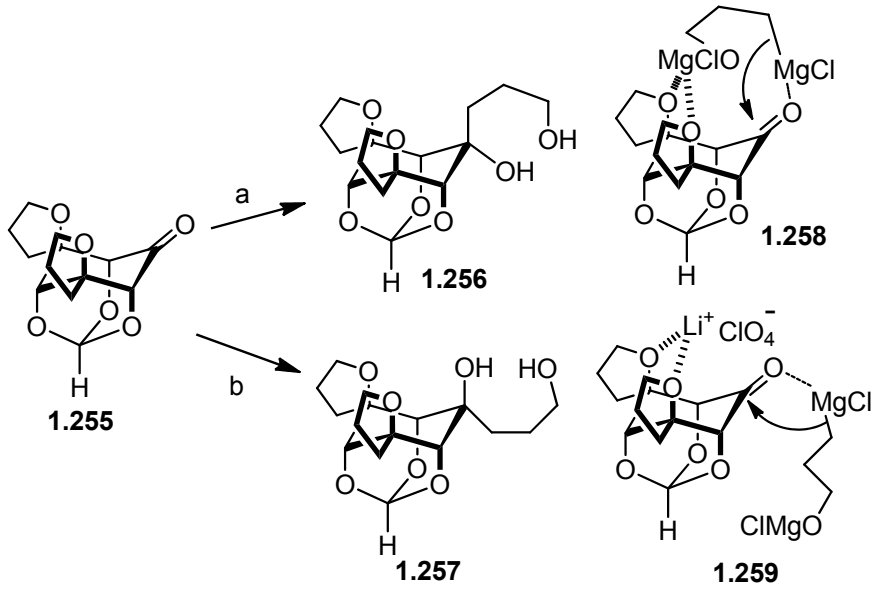


Solvent	Ratio 1.248:1.249	Yield(%)
H_2O	8.5:1	77
THF/H_2O	8.2:1	74
THF	-	(No reaction)

Scheme 1.35. (a) AllBr, Indium metal.

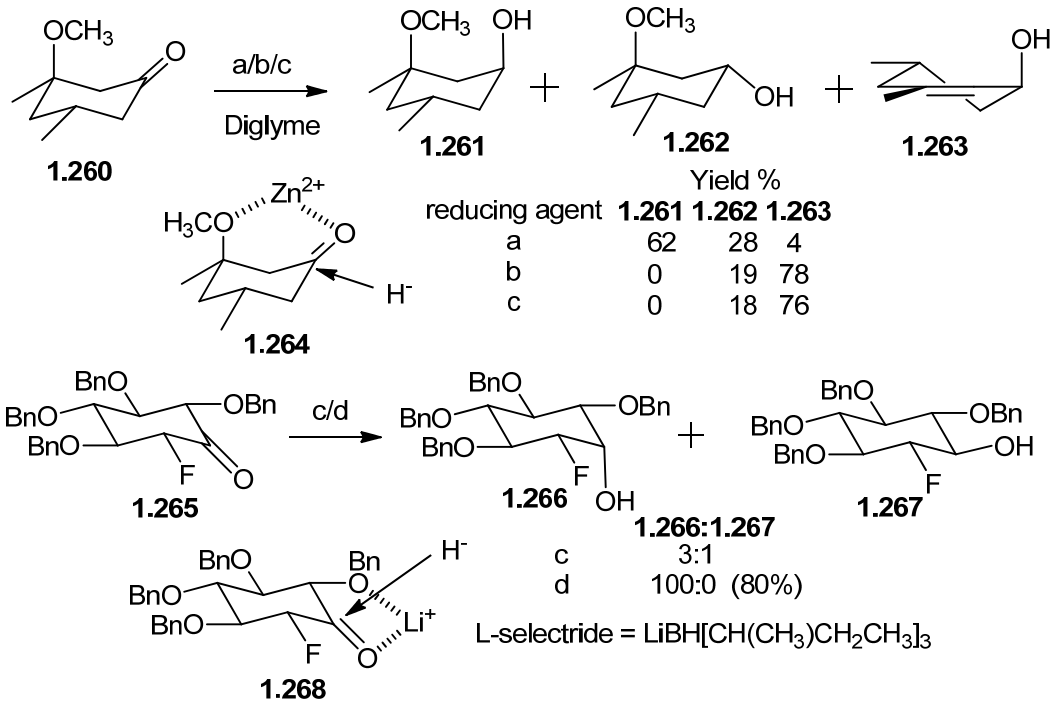
of 2-hydroxycyclohexanones in water, revealed evidence for possible chelation control in these carbonyl addition reactions.[70]

Reaction of the ketone **1.255** with Normant Grignard reagent **1.246** gave the isomeric diols **1.256** and **1.257** in the ratio 10:1 (Scheme 1.36). This reaction was postulated to proceed through the intermediacy of the magnesium complex **1.258**. The same reaction when conducted in the presence of excess of lithium perchlorate, yielded the diol **1.257** exclusively.[71] This was attributed to the intermediacy of the lithium chelate **1.259** during the addition of the Grignard reagent to the ketone **1.255**, since compounds like **1.255** are efficient chelators of lithium ions.[40a]



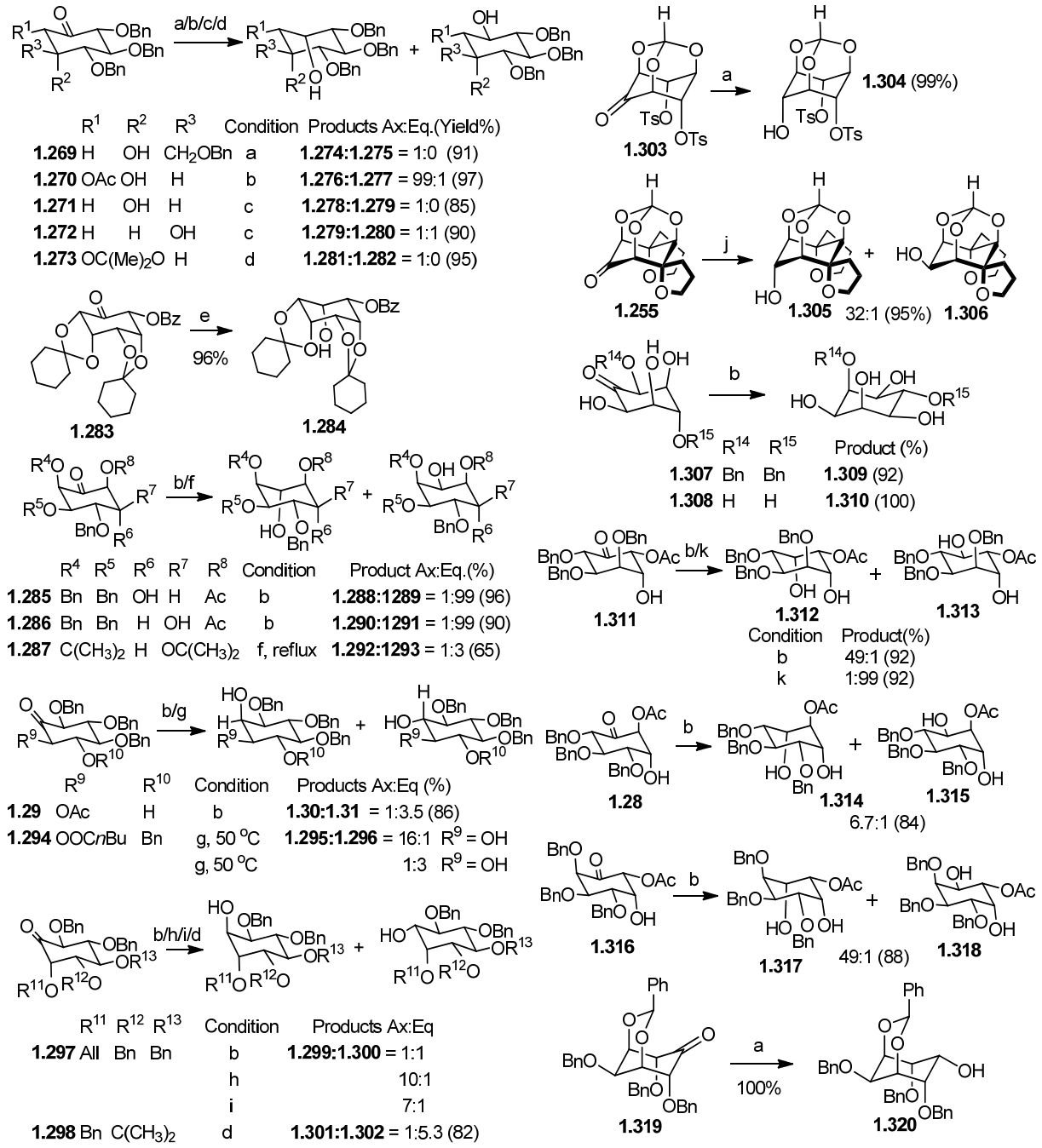
Scheme 1.36. (a) **1.246**, THF; (b) **1.246,** $LiClO_4$, THF.

The observed stereochemical course of hydride reduction of ketones, especially cyclic ketones have been explained or rationalized using different concepts such as orbital symmetry, orbital overlap, stabilization of the transition state *etc*.[72] However there are a few reports in the literature which attribute the observed stereochemistry during hydride reduction of ketones to chelation of metal ions. For instance, the stereochemistry of the zinc borohydride reduction of alkoxy substituted cyclohexanones has been investigated in detail and the formation of a zinc mediated cyclic intermediate (chelate complex **1.264**, Scheme 1.37) which includes the ether oxygen and the carbonyl oxygen has been suggested to be responsible for the selectivity observed.[73] This is reflected in the product distribution with different reducing agents, shown in scheme 1.37.

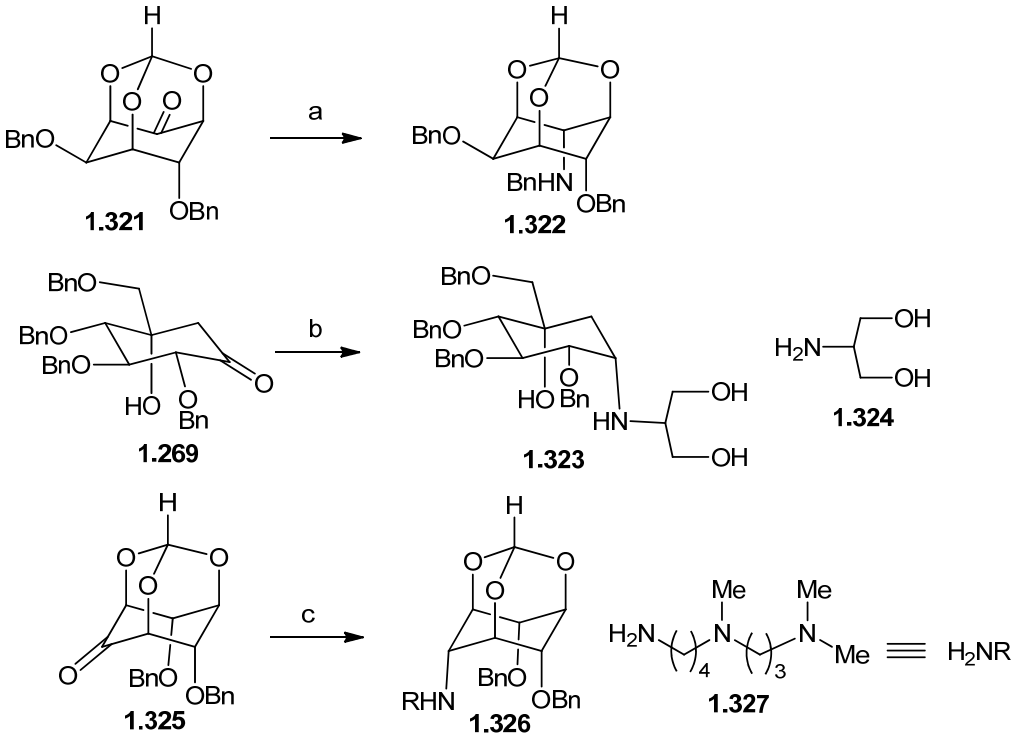


Scheme 1.37. (a) $Zn(BH_4)_2$; (b) LAH; (c) $NaBH_4$; (d) L-selectride. Zn chelate hinders the approach of the hydride which would yield the equatorial alcohol

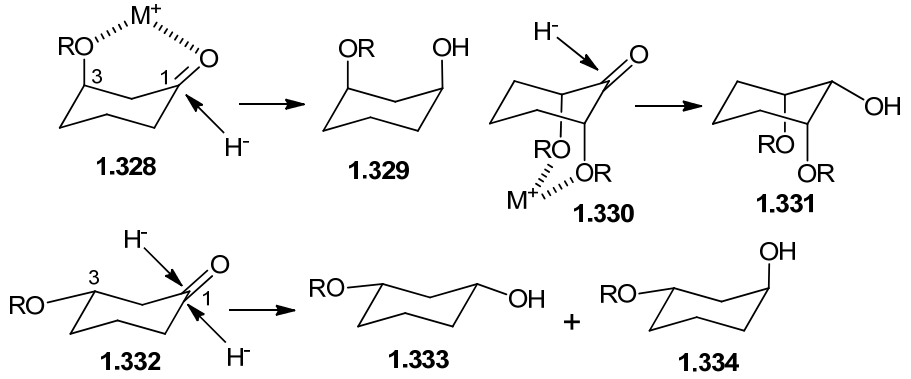
Such chelation effects could gain prominence during nucleophilic addition to cyclohexanones derived from cyclitols and their derivatives since they contain several hetero atoms. For instance, sodium borohydride reduction of (fluoro **1.265**)[74] favors the formation of the axial alcohol **1.266** despite the fact that sodium borohydride usually reduces cyclohexanones to equatorial alcohols.[75] Hence we compiled and compared the outcome of hydride reduction or reductive amination of several inositol derived ketones reported in the literature (Schemes 1.38).[13c, 71, 75b, 76] It is interesting to note that stereochemical outcome of these metal borohydride reductions depend on the orientation of the hydroxyl group (or the protected hydroxyl group) at the 3-position (considering ketone carbon as the 1-position). Presence of an axial hydroxyl group at the 3-position favors the formation of an axial alcohol (or the corresponding amine on reductive amination, Scheme 1.39),[76a, 76j, 76k] while the presence of an equatorial hydroxyl group at the 3-position favors the formation of the equatorial alcohol or does not show a great bias towards formation of any of the two possible isomeric alcohols. This generality (Scheme 1.40) has very few exceptions, which could be due to the steric crowding caused by other substituents in the ketone or in the reducing agent (as in L- selectride) or alternate sites for the chelation of the metal ion in the substrate (as in **1.285-1.287**, **1.297**, **1.319**).



Scheme 1.38. (a) $NaBH_4$, THF, MeOH; (b) $NaBH_4$, MeOH; (c) $NaBH_4$, dioxan; (d) $NaBH_4$, EtOH; (e) $NaBH_4$, $CHCl_3$, MeOH; (f) $NaBH_4$, *i*PrOH; (g) $NaBH_4$, CH_3CN; (h) L-selectride, THF; (i) $LiBH_4$, THF (j) $NaBH_4$, THF; (k) $Me_4NBH(OAc)_3$, CH_3CN, MeOH.

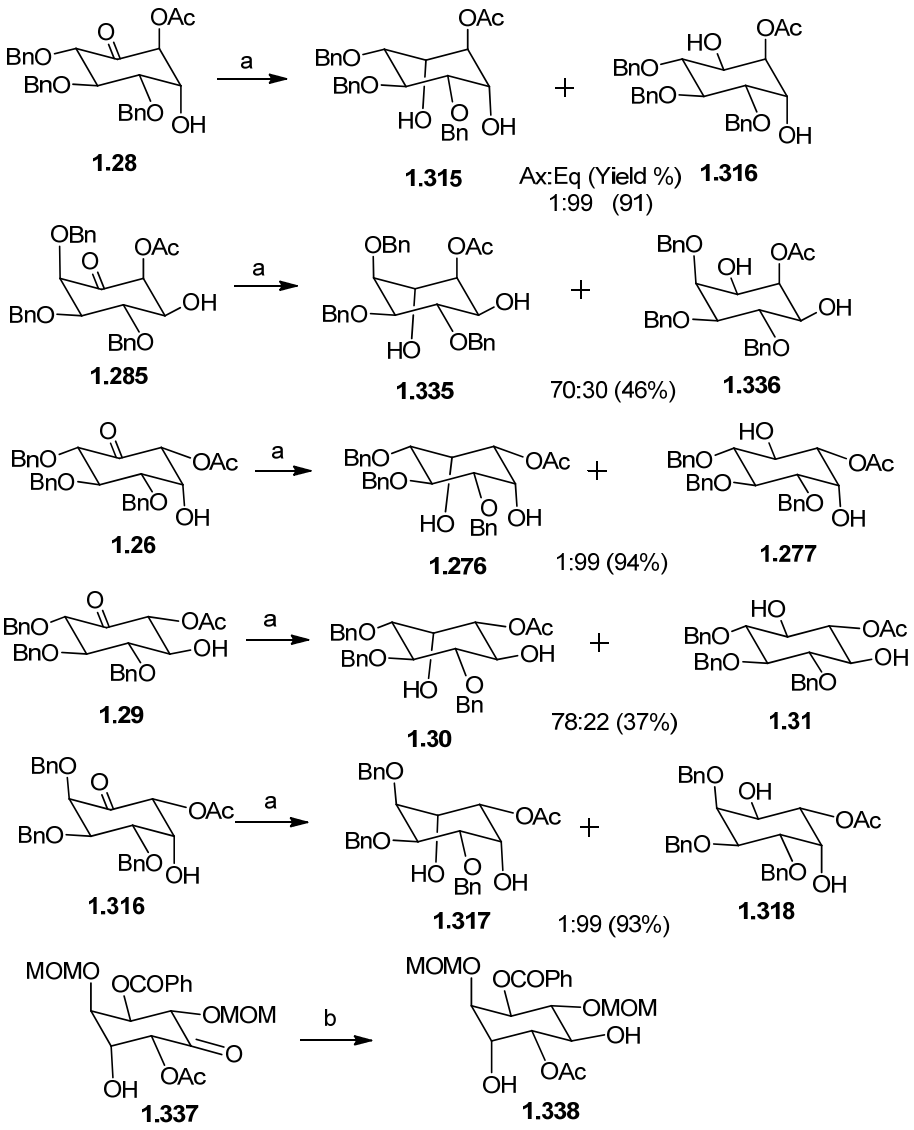


Scheme 1.39. (a) $BnNH_2$, MeOH, 50 ^oC, 3 h, $NaBH_3CN$, rt, 90%; (b) **1.324**, $NaBH_3CN$, MeOH, rt, 75%; (c) **1.327**, toluene, PPTS, reflux, 3 days, $NaBH_3CN$, MeOH, pH 4, 77%.



Scheme 1.40.

This line of thought is supported by the fact that hydride reducing agents devoid of metal ions give products arising out of opposite selectivity (Scheme 1.41)[13c, 76l] to that observed in reductions with hydride reagents containing metal ions.



Scheme 1.41. (a) $Me_4NBH(OAc)_3$, CAN, MeOH, 0 ^oC–r.t; (b) $NaBH(OAc)_3$, AcOH, ACN, 73%.

1.5. Conclusions.

The reactions presented in the three sections of this chapter clearly show that the ability of small organic molecules containing several functional groups capable of chelation with metal ions can be exploited to achieve regio- or stereoselectivity during chemical reactions. The extent of selectivity observed in these reactions depends on the stability of the chelate involved or the relative stability of the chelates, if more than one chelate is possible under the conditions of the reaction in progress. Hence the selectivity observed (especially in the latter situation) could depend on factors such as nature of the metal ion, nature of the solvent used for the reaction, temperature of the reaction and

nature of the substituents present in the reactant as well as the reagent. However, an understanding of the intricacies of the interactions of organic molecules with metal ions can be of help in fine tuning the reaction conditions to achieve the desired selectivity. The next three chapters of this thesis describe such attempts to achieve regioselective reactions in inositol derivatives.

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(76) for ketones **1.26**, **1.28**, **1.29**, **1.270**, **1.285**, **1.286**, **1.311**, **1.316** see Ref. 13(c); for ketone **1.255** Ref. 71; for **1.298** Ref. 75(b); (a) for ketone **1.269** Fukase, H.; Horii, S. *J. Org. Chem*. **1992**, *57*, 3642–3650; (b) for ketones **1.271** and **1.272** Semeria, D.; Philippe, M; Delaumeny, J-M.; Sepulchre, A-M.; Gero, S. D. *Synthesis*, **1983**, 710–713; (c) for ketone **1.283** Angyal S. J.; Hickman, R. J. *Carbohydr. Res*. **1971**, *20*, 97–104; (d) for ketone **1.287** Espelie, K. E.; Anderson, L. *Carbohydr. Res*. **1976**, *46*, 53–66; (e) for ketone **1.294** Roemer, S.; Stadler, C.; Rudolf, M. T.; Jastorff, B.; Schultz, C. *J. Chem. Soc., Perkin Trans*, *1*, **1996**, 1683–1694; (f) for ketone **1.297** Jaramillo, C.; Chiara, J.-L.; Martín-Lomas, M. *J. Org. Chem*., **1994**, *59*, 3135–3141; (g) for ketone **1.303** Sarmah, M. P.; Shashidhar, M. S. *Carbohydr. Res*. **2003**, *338*, 999–1001; (h) for ketones **1.307**, **1.308** Pistara, V.; Barili, P. L.; Catelani, G.; Coraso, A.; D'Andrea, F.; Fisichella, S. *Tetrahedron Lett.* **2000**, *4*, 3253–3256; (i) for ketone **1.319** Murali, C.; Gurale, B. P.; Shashidhar, M. S. *Eur. J. Org. Chem*., **2010**, 755–764; (j) for ketone**1.321** Sarmah, M. P. Ph. D. Thesis, University of Pune, 2005; (k) for ketone **1.325** Frontier, A. J.; Raghavan, S.;

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Chapter 2. Relative reactivity of hydroxyl groups in inositol derivatives: role of metal ion chelation

2.1. Introduction.

Selective protection and deprotection methods for functional groups are quite important in organic synthesis.[1] Although synthesis of organic compounds without the use of protecting groups[2] is being vigorously investigated by many researchers, and is one of the most desirable methods of synthesis, the use of protecting groups is inevitable when the starting material carries many functional groups, especially of the same kind (as in polyols, poly acids, poly amines etc). Although, methods for the selective protection and deprotection of different kinds of functional groups (e.g. protection of amines, in the presence of acids or alcohols and *vice-versa*) can be selected from the literature[1] and adopted easily to meet one's requirements, methods for the protection of a particular functional group in the presence of similar functional group in the same molecule (e.g. one hydroxyl group in the presence of others) are far more difficult to encounter. This is because such reactions or methods inherently demand regioselective reactions (in contrast to chemoselective reactions), designing of which needs an understanding of the relative reactivity of the functional groups in a molecule.

myo-Inositol is an attractive starting material for the synthesis of cyclitol derivatives and their analogs. Conventional methods for the protection of inositol hydroxyl groups are formation of ketals, ethers and esters. Most of these methods often give mixture of isomers from which the desired product must be separated, which translates to excessive labor and lower yields. There are very few reports in the literature which provide a single product in respectable yields, starting from *myo*-inositol or its derivatives containing two or more hydroxyl groups.[3] The reaction of the three hydroxyl groups of *myo*-inositol orthoesters with alkyl halides can be achieved with excellent selectivity (Chapter 1, Scheme 1.2) by the judicious choice of the base (derived from sodium or lithium).[3g] However, results of a similar strategy for the regioselective O-alkylation of a few inositol derivatives containing more than one hydroxyl group, but without the orthoester bridge, was not so impressive (Chart 2.1).[4]

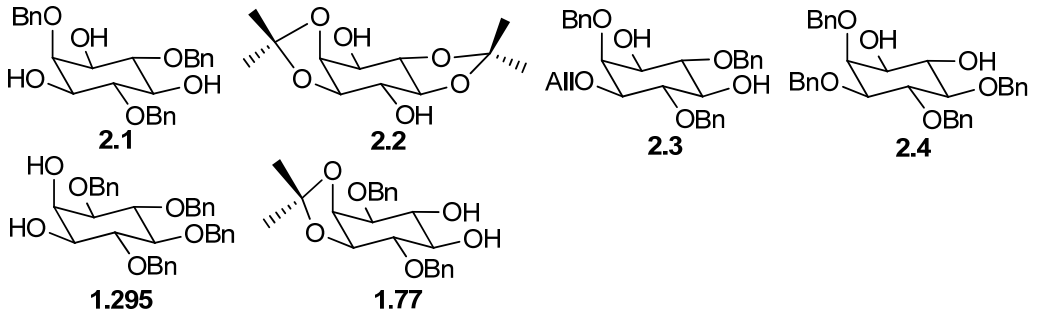


Chart 2.1. *myo*-Inositol derivatives studied earlier in our laboratory.

Hence, in order to further probe the effect of metal ions on O-alkylation of *myo*-inositol derivatives containing more than one hydroxyl group but devoid of the rigid orthoester bridge, some more partially protected *myo*–inositol derivatives were studied. Accordingly this chapter presents results on the O-alkylation reactions of the triol **1.34** and diols **2.5**, **1.75**, **2.6**, **1.279** (Chart 2.2). Also, earlier work on O-alkylation of *myo*-inositol orthoesters in our laboratory[3g] had provided access to methyl, allyl and benzyl ethers, the synthetic utility of which is limited. In the present work, O-alkylation of the triol **1.34** has been carried out using substituted benzyl halides, which provide inositol derivatives containing orthogonal protecting groups and hence are of good synthetic utility.

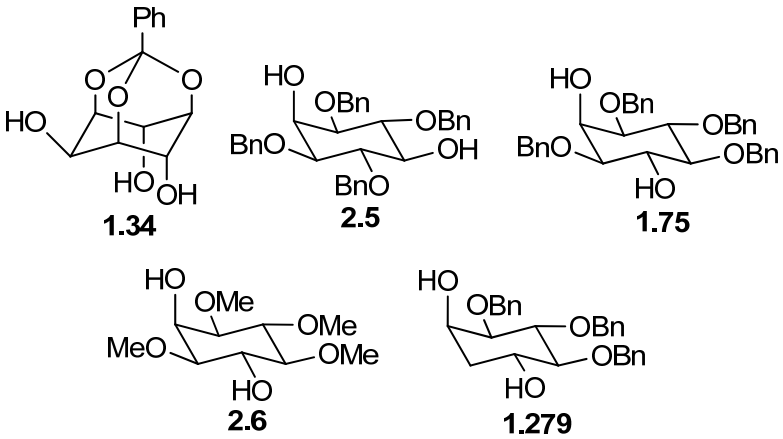


Chart 2.2.

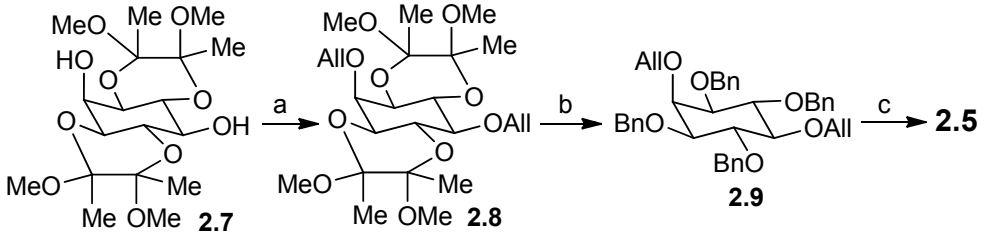
2.2. Results and discussion.

The substrates (partially protected *myo*-inositol derivatives) for O-alkylation reaction were chosen such that they have no vicinal diols (Chapter 1, see section 1.2). The diols **2.5**,[5] **1.75**[6] and **2.6** were prepared from *myo*-inositol as described in the sub-sections below. The preparation of the diol **1.279**[7] is given in chapter 4 (Scheme 4.1).

2.2.1. Preparation of *myo*-inositol derived diols **2.5**, **1.75**, **2.6 and 1.279.**

1,3,4,6-Tetra-*O*-benzyl-*myo*-inositol (2.5).

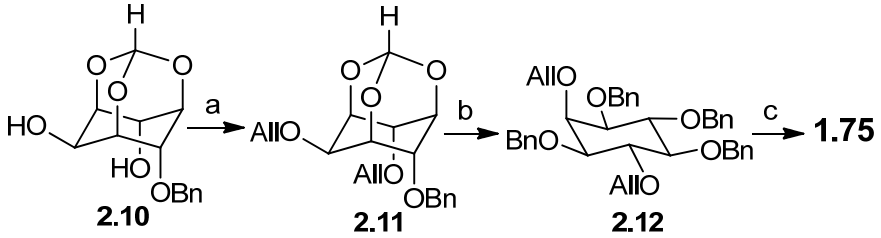
The 2,5-diol **2.5** having an axial hydroxyl group with two *cis* vicinal oxygen atoms and an equatorial hydroxyl group with two *trans* vicinal oxygen atoms, was prepared starting from the known bis(butane-2,3-diacetal) derivative of *myo*-inositol **2.7** (Scheme 2.1).[3d] The free hydroxyl groups in **2.7** were protected as allyl ethers and the acetal groups were cleaved using TFA. The resulting tetrol was perbenzylated to get the hexa-O-protected inositol derivative **2.9**. Isomerization of the allyl groups followed by acid hydrolysis using a known procedure[8] provided the desired diol **2.5**.



Scheme 2.1. (a) DMF, NaH, AllBr, 71%; (b) i. aq. TFA; ii. DMF, NaH, BnBr, 87%; (c) 10 % Pd-C, TsOH, MeOH, H_2O, 39%.

Racemic 1,3,4,5-tetra-*O*-benzyl-*myo*-inositol (1.75).

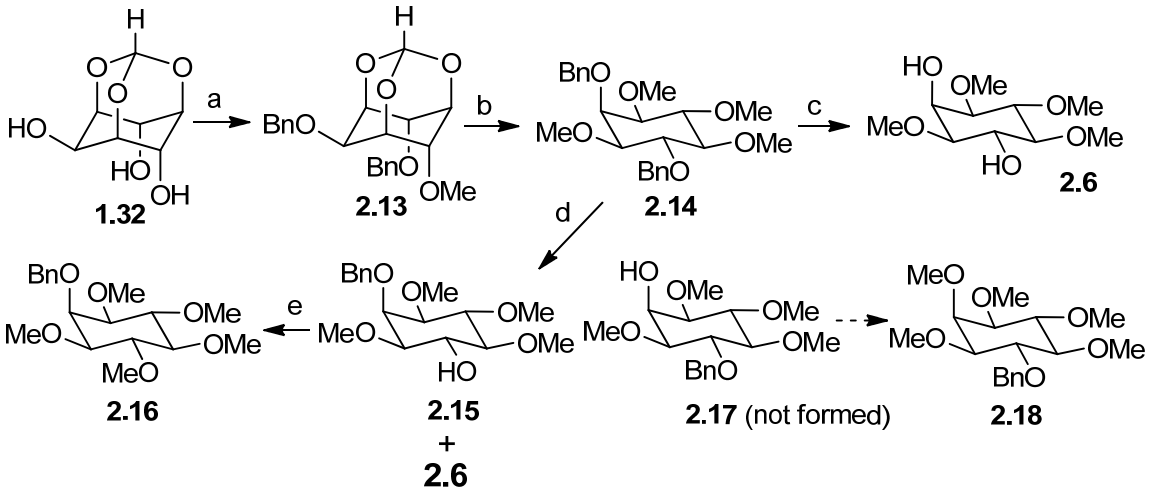
The 2,6 diol **1.75** (having an axial hydroxyl group with two *cis* vicinal oxygen atoms and an equatorial hydroxyl group with two *trans* vicinal oxygen atoms) was prepared from the known[3b] racemic 4-O-benzyl-*myo*-inositol-1,3,5-orthoformate (**2.10**, Scheme 2.2). The free hydroxyl groups in **2.10** were protected as allyl ethers and the orthoformate bridge was cleaved to obtain the corresponding triol which was benzylated to get the racemic hexa-O-protected *myo*-inositol derivative **2.12**. Cleavage of the allyl ethers in **2.10** afforded the required diol **1.75**.



Scheme 2.2. (a) DMF, NaH, AllBr, 86%; (b) i. MeOH, TsOH; ii. DMF, NaH, BnBr, 80%; (c) MeOH, H_2O, 10 % Pd-C, TsOH, 35%.

Racemic 1,3,4,5-tetra-*O*-methyl-*myo*-inositol (2.6).

The tetra-methyl ether **2.6** was prepared from *myo*-inositol orthoformate (**1.32**, Scheme 2.3). Selective mono-methylation of the triol **1.32** followed by benzylation gave racemic **2.13**. Cleavage of the orthoformate in **2.13** and methylation of the resulting triol with methyl iodide gave the fully protected *myo*-inositol **2.14**. Hydrogenolysis of the benzyl ethers in **2.14** in the presence of palladium (10% on carbon) was dependent on the solvent used for the reaction. Hydrogenolysis in ethyl acetate gave a mixture of the required diol **2.6**, and the racemic mono-benzyl ether **2.15** in the ratio 1:1, but the isomeric diol **2.17** was not observed. It is interesting to note that the axial C2-benzyl ether is relatively more stable to hydrogenolysis among the two benzyl ethers present in **2.14**. The structure of **2.15** was confirmed by converting it to the symmetric penta-methyl ether **2.16**. The ^{1}H NMR spectrum of **2.16** showed only three peaks for the five methyl groups and four peaks (ratio of integrals 1:2:2:1) for inositol ring hydrogens, as expected for a *meso*-derivative of *myo*-inositol. On O-methylation, the isomeric monobenzyl ether **2.17** would have resulted in the formation of (an unsymmetric) racemic pentamethyl ether **2.18** (which is expected to have an asymmetric ^{1}H NMR spectrum). But when the hydrogenolysis reaction was carried out using methanol as a solvent, only the required diol **2.6** was formed in good yield. Perhaps, the rate of cleavage of the two benzyl ethers of **2.14** in methanol is not very different as observed in ethyl acetate.

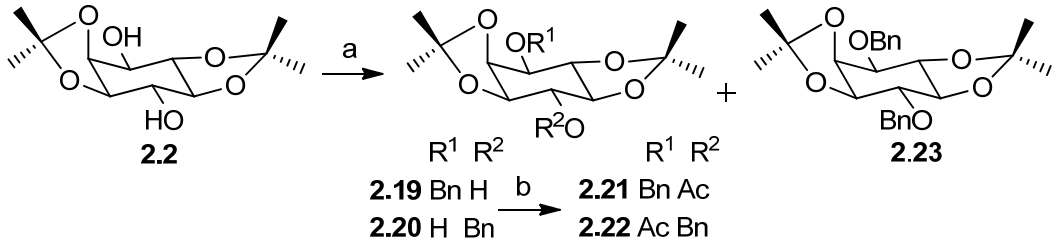


Scheme 2.3. (a) i. DMF, NaH (1 eq.), MeI (1 eq.); ii. DMF, NaH, BnBr, 70% (for 2 steps); (b) i. MeOH, TsOH; ii. DMF, NaH (x's), MeI (x's), 74% (for 2 steps); (c) MeOH, 10 % Pd-C, H_2, 85%; (d) EtOAc, 10 % Pd-C, H_2, 48% of **2.15**, 49% of **2.6**; (e) DMF, NaH, MeI.

2.2.2. O-Alkylation of the diols 2.2, 2.5, 1.75, 2.6 and 1.279.

O-Alkylation of racemic 1,2;4,5-di-*O*-isopropylidene-*myo*-inositol (2.2).

O-alkylation of the diol **2.2**[9] has earlier been investigated quite extensively[9b, 10] using different bases, alkyl halides and solvents at different temperatures. Although in most of the experiments the 3-O-substituted derivative was obtained as the major product, no information on the ratio of the two possible monoethers (Scheme 2. 4) formed is available. Also, most of these reports involve widely different experimental conditions



Reaction Conditions		Products obtained		
Addition	Reaction at	**2.19**:**2.20***	**2.23**	**2.2**
0 °C	rt (60 h.)	57 % (10:1)	25 %	5 %
Reflux	Reflux (4 h.)	32 % (10:1.5)	46 %	10 %
0 °C	0 °C–5 °C (3 days) 15 °C (4 days)	40 % (10:5)	22 %	26 %

* Ratio of the mono ethers was estimated by ^{1}H NMR spectroscopy, after conversion to their acetates.

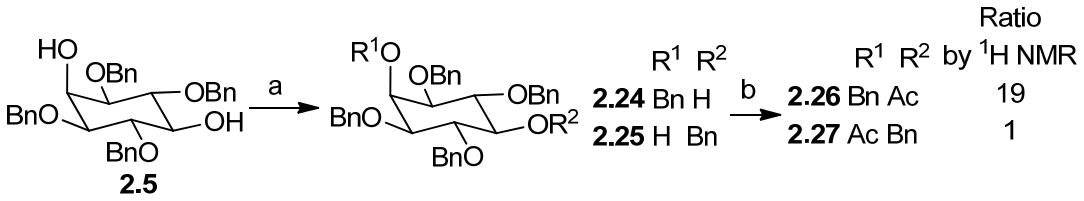
Scheme 2.4. (a) THF, *n*BuLi, BnBr, DMF; (b) Py, Ac_2O.

which preclude the comparison of the results published by different research groups. Earlier work[11] in our laboratory had suggested the formation of the C3-ether **2.19** exclusively on reaction of the diol **2.2** with butyllithium and benzyl bromide, but a mixture of products with lithium hydride and benzyl bromide (at 55 ºC). Hence the O-benzylation of the diol **2.2** was reinvestigated at different temperatures and the ratio of the monobenzyl ethers obtained, was estimated using ^{1}H NMR spectroscopy of their acetates **2.21**[12] and **2.22**.[12] The results summarized in Scheme 2.4 show that the C3-ether is formed in higher proportion, but not exclusively. Benzylation of the racemic 3,6-diol **2.2** with sodium hydride and benzyl bromide is known[9] to give a mixture of monobenzyl ethers (**2.19**, **2.20**) and the dibenzyl ether **2.23** (15%) from which the monobenzyl ether **2.19** (56%) was isolated by crystallization. A comparison of these results with the present work clearly shows that although better regioselectivity during O-substitution in the diol **2.2** can be achieved by generating the alkoxide with butyllithium, yield of the C3-ether is

compromised, perhaps due to the lower reactivity of the lithium alkoxides as compared to the corresponding sodium alkoxides.

O-Alkylation of 1,3,4,6-tetra-*O*-benzyl-*myo*-inositol (2.5).

The diol **2.5** on O-benzylation using one equivalent each of sodium hydride and benzyl bromide gave predominantly the C2-axial ether **2.24** (Scheme 2.5) and 22% of the starting diol **2.5** was recovered. The relative ratio of isomers (axial **2.24**/ equatorial **2.25**,[13] approx. 19/1) was estimated by ^{1}H NMR spectrum of the mixture of acetates of the isomeric monoethers. Predominant formation of the axial benzyl ether over the equatorial ether was unexpected (see below). However, similar instances have earlier been



Scheme 2.5. (a) THF, NaH, BnBr, DMF, 59 %; (b) Py, Ac_2O.

reported in the literature.[6] Since benzylation with sodium hydride / benzyl bromide gave very good selectivity, there was no need to carry out the corresponding reaction with butyllithium. The structure of the monobenzyl ether **2.24** was confirmed by X-ray crystallography (Figure 2.1).

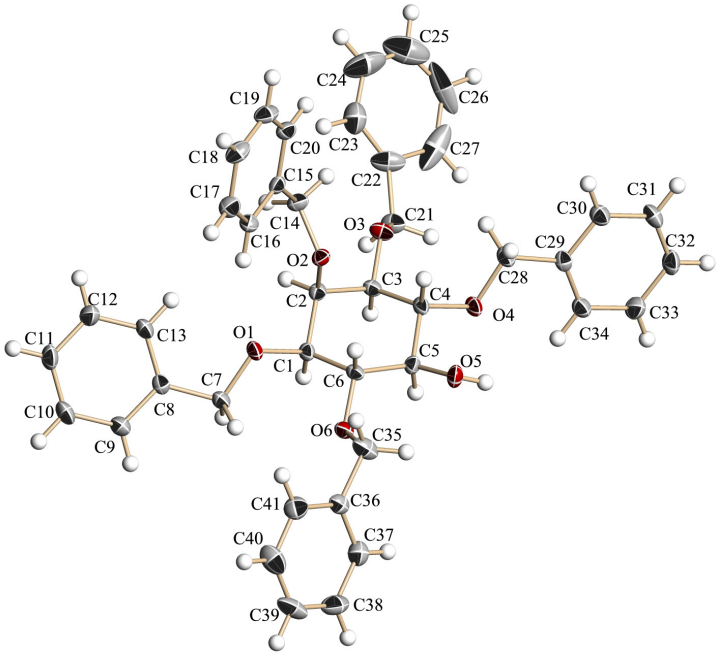
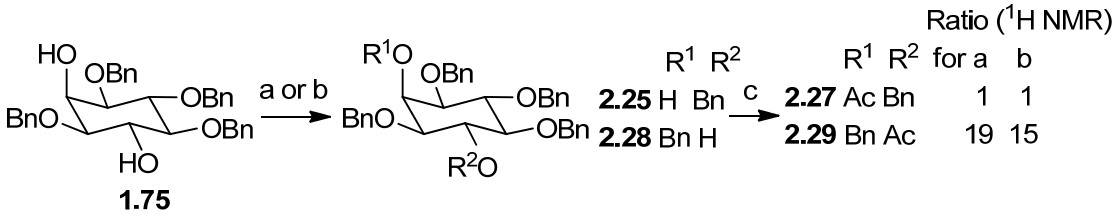


Figure 2.1. ORTEP of **2.24**.

O-Alkylation of racemic 1,3,4,5-tetra-*O*-benzyl-*myo*-inositol (1.75).

O-benzylation of **1.75** using one equivalent each of sodium hydride and benzyl bromide gave predominantly the axial substitution product **2.28** (Scheme 2.6) and 47% of the starting diol was recovered. The relative ratio of isomers (axial **2.28**/ equatorial **2.25**, appox. 19/1) was estimated by ^{1}H NMR spectrum of the mixture of acetates of the isomeric monoethers. We also carried out the benzylation of **1.75** using potassium hydroxide and benzyl chloride (in benzene as a solvent), since benzylation of the isomeric



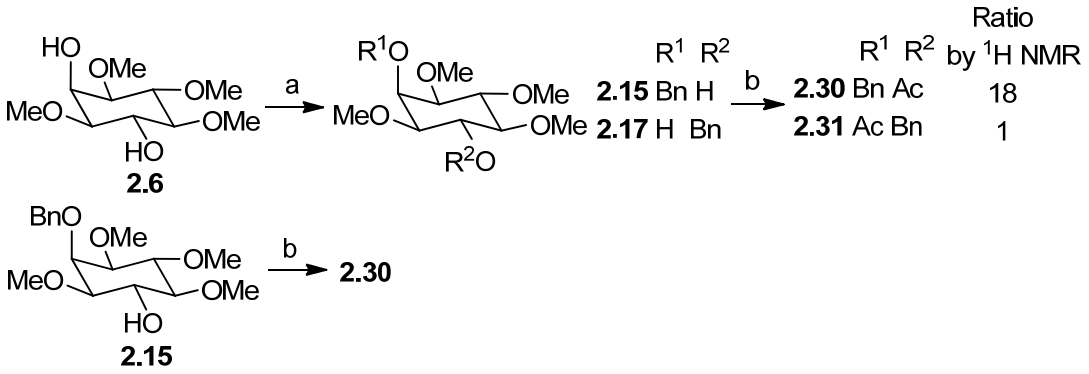
Scheme 2.6. (a) THF, NaH, BnBr, DMF, 47% (47 % Starting diol recovered); (b) Benzene, KOH, BnCl 49% (25 % **1.75** recovered); (c) Py, Ac_2O.

diol **2.5** using potassium hydroxide (excess) and benzyl chloride (1.1 eq.) in benzene is reported to give the equatorial ether **2.25**.[13] There was slight increase in the proportion of the equatorial isomer **2**.**25** (**2**.**28**/**2**.**25**, 15:1) as compared to the reaction with sodium hydride and benzyl bromide (**2**.**28**/**2**.**25**, 19:1). Again, since benzylation with sodium hydride gave very good selectivity, there was no need to carry out the corresponding reaction with butyllithium. Preferential reaction at the axial hydroxyl group during ether formation in the diol **1.75** has earlier been reported.[6] But we carried out the benzylation of **1.75** again since the earlier report mentioned reversal of selectivity for the acylation of **1.75** in the presence of sodium hydride. We did not carry out acylation (on any of the inositol derivatives) in the present study due to the potential of hydroxyl esters to undergo inter or intra molecular acyl migration in the presence of strong bases, which would hamper conclusions on the observed regioselectivity. Also, the outcome of O-alkylation and O-acylation of inositol derivatives may not be comparable since they could proceed by different mechanisms; the former by S_N1 / S_N2 and the latter by addition elimination (at the acyl carbonyl carbon).

O-Alkylation of 1,3,4,5-tetra-*O*-methyl-*myo*-inositol (2.6).

Although equatorial hydroxyl groups normally undergo O-substitution with better facility than the axial hydroxyl groups in cyclohexanols, benzylation of the **2.5** and **1.75**

gave the corresponding C2-axial benzyl ether as the major product. However, such reasoning may not be accurate in reactions under discussion since inositols have many (protected) hydroxyl groups which could influence the reactivity of each other. We wondered whether this could be an outcome of several benzyl groups present in the tetrabenzyl ethers **2.5** and



Scheme 2.7. (a) THF, NaH, BnBr, DMF, 60%; (b) Py, Ac_2O.

1.75 and hence we carried out benzylation of the corresponding tetramethyl ether **2.6**. The diol **2.6** on benzylation using sodium hydride and benzyl bromide gave the C2-axial ether **2.15** predominantly (Scheme 2.7). The structure of the monobenzyl ether **2.15** was confirmed by X-ray crystallography (Figure 2.2).

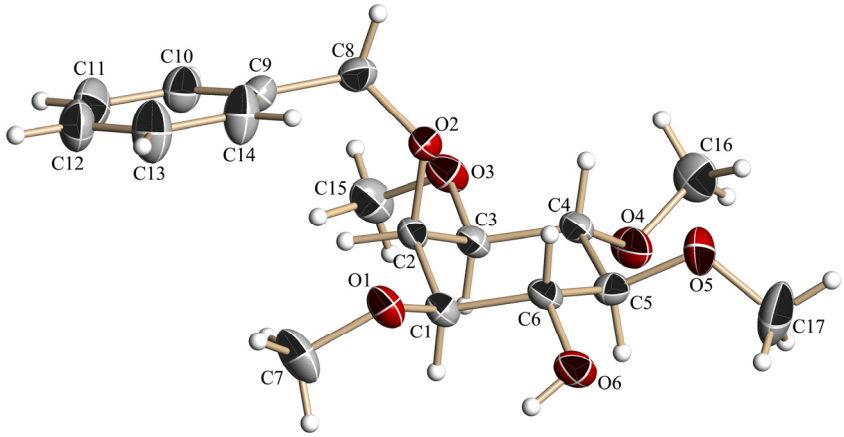


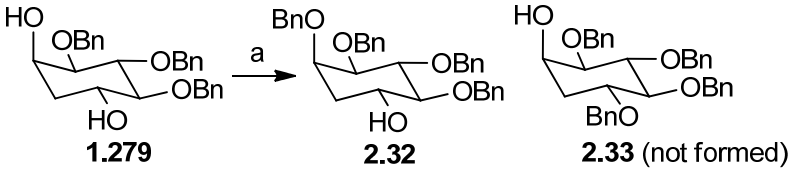
Figure 2.2. ORTEP of **2.15.**

The relative ratio of isomers (axial **2.15**/ equatorial **2.17**, 18/1) was estimated by ^{1}H NMR spectrum of the mixture of acetates of the isomeric monoethers. An authentic sample of the acetate **2.30** was also prepared by acetylation of **2.15** obtained by partial hydrogenolysis of the dibenyl ether **2.14** (Scheme 2.3). These results clearly showed that the observed

regioselectivity for the O-alkylation of the diols **2.5** and **1.75** was not dependent on the hydroxyl protecting groups.

O-Alkylation of racemic 3-deoxy-1,5,6-tri-*O*-benzyl-*myo*-inositol (1.279).

To examine the effect of vicinal *cis*-oxygen atoms on the observed selectivity in O-alkylation reactions described above, we decided to subject the deoxy-inositol **1.279** (for preparation see chapter 4, Scheme 4.1), to O-alkylation reaction. The diol **1.279** on reaction with one equivalent each of sodium hydride and benzyl bromide, gave predominantly the C2-axial ether **2.32** (Scheme 2.8). Formation of **2.32** was suggested by a comparison of its physical and spectral data with that of **2.33**,[14] the only other tetrabenzyl ether possible in this reaction.



Scheme 2.8. (a) THF, NaH, BnBr, DMF, 60%.

Since high regioselectivity was observed for the O-alkylation of the diols **2.5**, **1.75**, **2.6**, **1.279**, on using sodium hydride as the base, there was no need to carry out the corresponding reactions with butyllithium. X-ray crystal structures (see Appendix 2.6) of diols **2.5**, **1.75**, **2.6** did not show any unusual feature in their molecular structures that could provide clues for the unexpected observed regioselectivity.

Before attempting to arrive at any conclusions from the results of O-alkylation reactions carried out in the present work, we compiled results of similar instances of O-alkylation reported in the literature. We also wished to compare the effect of change in the metal ion (sodium and lithium) in the base used on the outcome of O-alkylation reactions.[4] The data obtained from the literature as well as from our laboratory are shown in Chart 2.3 and Table 2.2.

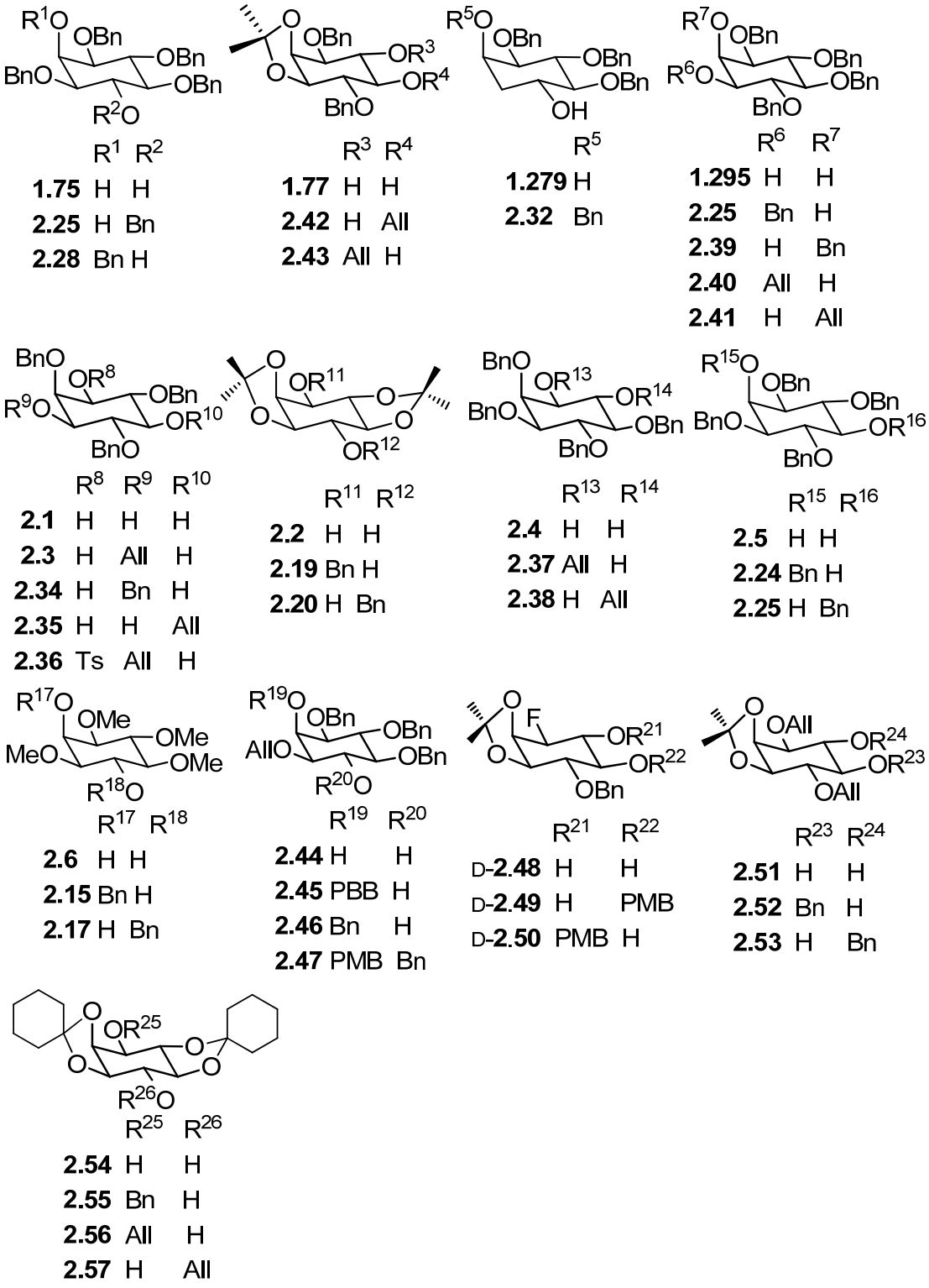


Chart 2.3. Structures of the compounds appearing in Table 2.2.

Table 2.2. A compilation of the data on O-alkylation of partially protected *myo*-inositol derivatives carried out under comparable conditions.[4]

Entry	Diol/ triol	Reaction conditions	Products (ratio; % yield)
1	**1.75**	THF, NaH, DMF, BnBr*	**2.25:2.28** (1:19, 47)
2	**1.75**	DMF, NaH, BnBr, TBAI[6]	**2.28** (78)
3	**1.75**	Benzene, KOH, BnCl*	**2.25:2.28** (1:15, 49)
4	**1.77**	THF, *n*BuLi, DMF, AllBr[4]	**2.42:2.43** (1:1; 76)
5	**1.279**	THF, NaH, DMF, BnBr*	**2.32** (60)
6	**1.295**	THF, *n*BuLi, DMF, BnBr, –78 ºC[4]	**2.25:2.39** (45:55; 69)
7	**1.295**	THF, *n*BuLi, DMF, BnBr, 0 ºC[4]	**2.25:2.39** (52:48; 70)
8	**1.295**	THF, *n*BuLi, DMF, AllBr, 0 ºC[4]	**2.40:2.41** (67:33; 66)
9	**1.295**	THF, *n*BuLi, DMF, BnBr, 76 ºC[4]	**2.25:2.39** (71:29; 74)
10	**1.295**	THF, NaH, DMF, BnBr, 0 ºC[4]	**2.25:2.39** (64:36; 76)
11	**1.295**	Benzene, KOH, BnCl, reflux[13]	**2.25:2.39** (98:2, 65)
12	**2.1**	DMF, NaH, BnBr[15]	(±)-**2.34** (63)
13	**2.1**	THF, *n*BuLi, DMF, AllBr[4]	(±)-**2.3** (71)
14	**2.1**	THF, NaH, DMF, AllBr[4]	**2.3**:**2.35** (1:1, 95)
15	**2.1**	NaH, DMF, AllBr,[15]	**2.3** (61)
16	**2.2**	DMF, NaH, BnBr[16]	**2.19:2.20** (9:1, 45)
17	**2.2**	THF, *n*BuLi, DMF, BnBr, rt*	**2.19:2.20** (10:1, 57)
18	**2.2**	THF, *n*BuLi, DMF, BnBr, reflux*	**2.19:2.20** (10:1.5, 32)
19	**2.2**	THF, *n*BuLi, DMF, BnBr, 0 ºC–15 ºC*	**2.19:2.20** (10:5, 40)
20	(±)-**2.3**	THF, *n*BuLi, DMF, TsCl[4]	**2.36** (53)
21	**2.4**	THF, *n*BuLi, DMF, AllBr[4]	**2.37**:**2.38** (4:1; 67)
22	**2.4**	THF, NaH, DMF, AllBr[4]	**2.37:2.38** (2:1; 75)
23	**D-2.4**	THF, NaH, AllBr[3e]	**D-2.37:D-2.38** (7:1, 56)
24	**2.5**	THF, NaH, DMF, BnBr*	**2.24:2.25** (19:1, 59)
25	**2.6**	THF, NaH, DMF, BnBr*	**2.15:2.17** (18:1, 60)
26	**2.44**	DMF, NaH, PBBBr, TBAI[17]	**2.45** (81)
27	**2.44**	DMF, NaH, BnBr, TBAI, –5–0 °C[18]	**2.46** (66)
28	**2.44**	DMF, NaH, TBAI, PMBCl 0 °C then BnBr[18]	**2.47** (51)
29	**D-2.48**	DMF, NaH, PMBCl, 0 °C[19]	**D-2.49:D-2.50**(1:2; 60)
30	**2.51**	DMF, NaH, BnBr[10a]	**2.52: 2.53** (1:1.3; 56)
31	**2.54**	Toluene, NaH, BnBr, reflux[20]	**2.55** (60)
32	**2.54**	Benzene, NaH, AllBr, reflux[21]	**2.56**:**2.57** (5:1, 61)

* Present Work.

From the data in Table 2.2, it is clear that, O-alkylation of inositol based diols and triol, *via* their alkali metal alkoxides (sodium or lithium) preferentially occurs at a hydroxyl group having *cis* adjacent oxygen over the hydroxyl group that has *trans* adjacent oxygen. This is similar to the observed regioselectivity during the O-alkylation of carbohydrate pyranoses in the presence of transition metal salts[22] (Chapter 1, Scheme 1.12). The diols **2.5**, **1.75**, **2.6** and **1.279** which predominantly give the axial ether on mono-O-alkylation are no exception to this since the axial hydroxyl group has one or two adjacent *cis* oxygen atoms while the equatorial hydroxyl group in these molecules, has two adjacent *trans* oxygen atoms. Hence, we believe that this apparent 'unexpected' result (based solely on steric disposition - axial or equatorial - of the hydroxyl groups) is not so surprising. It is conceivable that in reactions involving sodium or lithium alkoxides, the chelation of the metal ion by a vicinal *cis*-oxygen atom is better than the chelation by a vicinal *trans*-oxygen atom. As a result the O-substitution (in **2.5**, **1.75**, **2.6** and **1.279**) preferentially takes place at the axial hydroxyl group, since the axial alkoxide is expected to be relatively more stable than the equatorial alkoxide.

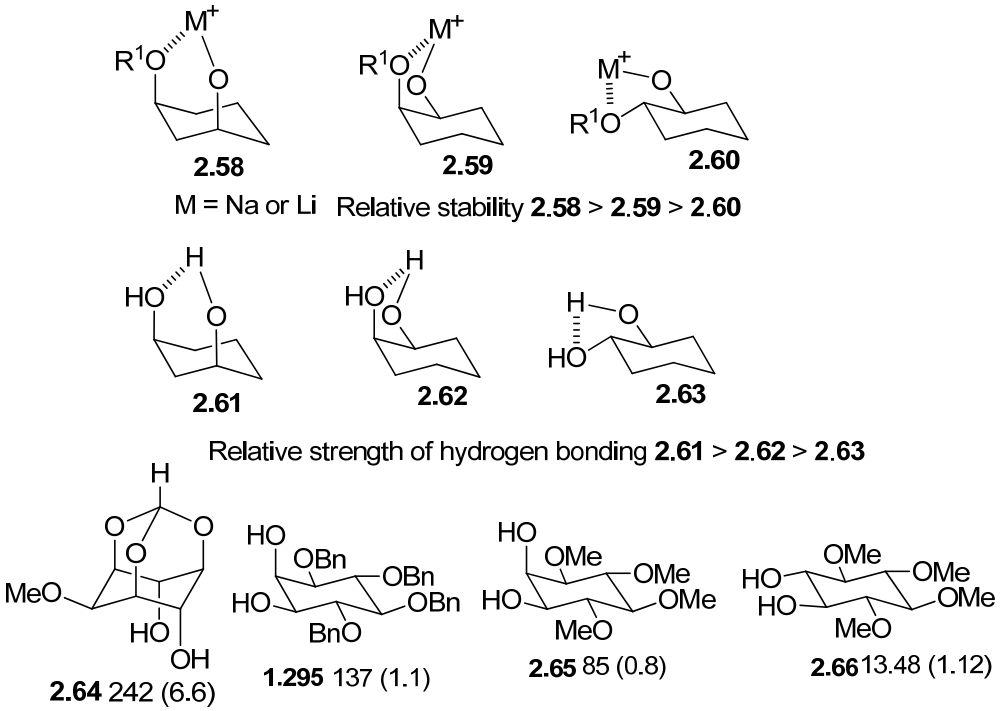


Chart 2.4. Numbers below the diols **2.64**, **1.295**, **2.65** and **2.66** represents Ka×10^{-4} dm^3 mol^{-1} for the binding of Li (Na) picrates in $CDCl_3$ at 27 °C.

This is analogous to the relative strength of intramolecular hydrogen bonding in polyhydroxy cyclohexanes which is known to decrease in the order 1,3-diaxial diols > 1,2-*cis* diols > 1,2-*trans* diols. Intramolecular hydrogen bonds in *cis*-1,3 (diaxial) diols have

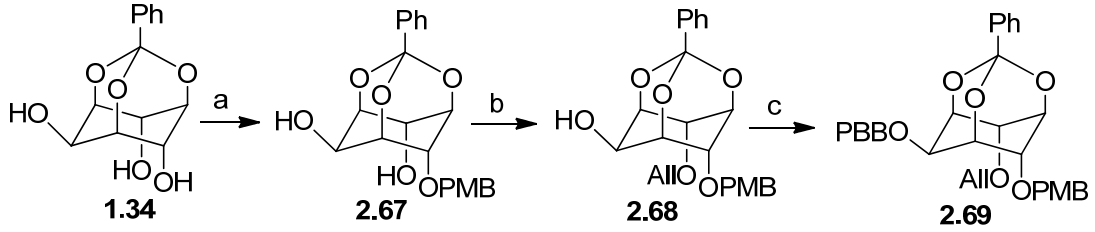
been observed in their crystals.[23] Hence the relative stability of alkali metal chelates is expected to decrease in the order **2.58** > **2.59** > **2.60** (Chart 2.4**)**. This line of thought is also supported by the fact that O-alkylation of a substrate *via* its lithium alkoxides shows relatively better regioselectivity than the corresponding reaction *via* the sodium alkoxide, since the ability of lithium ion for forming chelates is better than that of sodium ion. The picrate extraction study of inositol derived diols is in agreement with the statement made above since the ability of diols to bind with sodium and lithium picrates decreases in the order 1,3-*cis*-diol > 1,2-*cis*-diol > 1,2-*trans*-diol.[3g, 24] Solution and solid-state studies on carbohydrate-lanthanide complexes clearly indicate that most stable carbohydrate-metal complexes form where the carbohydrate has three adjacent hydroxyl groups that are in an *ax-eq-ax* conformation in the pyranose form.[25] The *ax-eq-ax* arrangement of hydroxyl groups results in adjacent hydroxyl groups having the *cis* orientation which is most favourable for mono O-substitution to occur through the formation of a chelate.

2.2.3. Preparation of an orthogonally protected *myo*-inositol orthobenzoate derivative, racemic 2.69.

As seen in previous sections, O-alkylation of partially protected *myo*-inositol derivatives preferentially occurs at a hydroxyl group having one or more vicinal *cis*-oxygen atoms. However this conclusion is based on data generated mostly from alkylation with allyl and benzyl halides and the synthetic utility of resulting ethers is limited since the inositol derivatives obtained do not have many orthogonal protecting groups. Hence in order to broaden the generality of these selective reactions and to prepare inositol derivatives of synthetic utility, we carried out alkylation of *myo*-inositol orthoesters with ring substituted benzyl halides which provide inositol derivatives carrying orthogonal protecting groups.

The reaction of *myo*-inositol orthobenzoate **1.34** with 4-methoxybenzyl chloride (assisted by sodium hydride), allyl bromide (assisted by butyllithium) and 4-bromobenzyl bromide (assisted by sodium hydride) in that sequence provided an orthogonally protected *myo*-inositol orthobenzoate **2.69** (Scheme 2.10). These results clearly show that the observed selectivity for the O-alkylation of *myo*-inositol orthoesters (*via* their sodium or lithium alkoxides) is independent of the alkyl halide used for alkylation. The presence of hetero atoms in the alkyl halides does not appear to disturb the regioselectivity during O-

alkylation. Synthetic utility of the orthogonally protected *myo*-inositol derivatives (in Scheme 2.10) is illustrated in the next chapter.



Scheme 2.10. (a) DMF, NaH, PMBCl, 90%; (b) THF, *n*BuLi, DMF, AllBr, 80%; (c) DMF, NaH, PBBBr, 95%.

2.3 Conclusions.

Results on O-alkylation of partially protected *myo*-inositol derivatives having hydroxyl groups in different relative orientations, using bases derived from different alkali metals suggest that (a) O-alkylation preferentially (but may not exclusively) occurs at a hydroxyl group having a vicinal *cis*-oxygen atom; (b) chelation of metal ions by inositol derivatives plays a significant role in the observed regioselectivity, (c) steric factors associated with the axial or equatorial disposition of the reacting hydroxyl group do not contribute much to the outcome of these O-alkylation reactions. These results could serve as guidelines in planning synthetic strategies with other polyols and their derivatives as well as molecules containing polyol moieties.

2.4. Experimental.

2.4.1. General methods.

All the solvents were purified according to the literature procedure[26] before use. All air or moisture sensitive reactions were carried out an atmosphere of argon or nitrogen. 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. Sodium hydride, butyllithium (1.62 M) in dry hexanes, DIBAL-H (1.0 M) in toluene, LDA (2.0 M) in THF/heptane/ethyl benzene, Super-hydride (1.0 M) in THF, were purchased from sigma-aldrich chemical Co. 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 chromic acid solution. 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. For column chromatographic separation of compounds containing the PMB/TBS group or triflate, the silica gel used was pre-eluted with a triethylamine/light petroleum (1:49, 3–5 mL/g) mixture. '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. IR spectra were recorded (in $CHCl_3$ solution, as a Nujol mull or as a neat film) with a Shimadzu FTIR-8400 or Perkin–Elmer spectrophotometer. NMR spectra (200 MHz for ^1H and 50.3 MHz for ^{13}C) were recorded with a Bruker ACF 200 spectrometer unless otherwise mentioned. Chemical shifts (δ, ppm) reported are referred to internal tetramethylsilane (0 ppm) for ^1H NMR and $CDCl_3$ (77 ppm) for ^{13}C NMR. 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. Yields refer to chromatographically and spectroscopically pure compounds. All the asymmetrically substituted myo-inositol derivatives reported are racemic; however only one of the enantiomers is shown in all the schemes. Compounds previously reported in the literature were characterized by comparison of their melting points and/or ^1H NMR spectra with the reported data.

Compounds **2.7**,[3d] the benzyl ether **2.10**[3b] and *myo*-inositol 1,3,5-orthobenzoate (**1.34**)[23b, c] were prepared as reported in the literature.

2.4.2. X-ray Data (Collection, Structure Solution and Refinement).

Single crystal X-ray studies were carried out on a Bruker SMART APEX single crystal X-ray CCD diffractometer with graphite-monochromatized (Mo K_α= 0.71073Å) radiation. The X-ray generator was operated at 50 kV and 30 mA. Diffraction data were collected with ω scan width of 0.3° at different settings of φ (0°, 90°, 180° and 270°) keeping the sample-to-detector distance fixed at 6.145 cm and the detector position (2θ) fixed at -28°. The X-ray data acquisition was monitored by SMART program (Bruker, 2003).[27] All the data were corrected for Lorentzian and polarization effects using SAINT programs (Bruker, 2003).[27] A semi-empirical absorption correction based on symmetry equivalent reflections was applied by using the SADABS program (Bruker, 2003).[27] Lattice parameters were determined from least squares analysis of all reflections. The structure was solved by direct method and refined by full matrix least-squares, based on

F^2, using SHELX-97 software package.[28] Molecular diagrams were generated using ORTEP-32.[29]

1,6:3,4-Bis-[*O*-(2,3-dimethoxybutane-2,3-diyl)]-2,5-di-*O*-allyl-*myo*-inositol (2.8).

To an ice-cooled solution of **2.7**[3d] (2.478 g, 6.07 mmol) in dry DMF (40 mL), sodium hydride (2.50 g, 62.5 mmol) was added followed by allyl bromide (7.34 g, 60.6 mmol) and the mixture was stirred at room temperature for 24 h. Excess of sodium hydride was quenched by the addition of ice and the solvents were removed under reduced pressure. The residue was worked up 'as usual' with dichloromethane; the crude product was purified by flash column chromatography to afford **2.8** (2.10 g, 71%) as a gum.

Data for 2.8: **^{1}H NMR** (200 MHz, $CDCl_3$): δ 6.08–5.84 (m, 2H), 5.36 (q, J = 1.7 Hz, 1H), 5.27 (q, J = 1.63, 2.05 Hz, 1H), 5.2–5.0 (m, 2H), 4.36–4.26 (m, 4H), 4.06 (t, J = 9.4 Hz, 2H), 3.74 (t, J = 2.3 Hz, 1H), 3.50 (dd, J = 2.4, 9.4 Hz, 2H), 3.38 (t, J = 9.3 Hz, 1H), 3.27 (s, 6H), 3.23 (s, 6H), 1.28 (s, 12H) ppm.**^{13}C NMR** (50.3, $CDCl_3$): δ 136.0, 135.7, 115.7, 115.2, 99.4, 98.9, 78.3, 75.4, 73.4, 72.4, 69.7, 69.2, 47.8, 47.6, 17.8, 17.5. **Elemental Analysis** Calcd for $C_{24}H_{40}O_{10}$ (488.57): C, 58.99; H, 8.24; found C, 58.65; H, 8.46%.

2,5-Di-*O*-allyl-1,3,4,6-tetra-*O*-benzyl-*myo*-inositol (2.9).

A solution of **2.8** (2.10 g, 4.30 mmol) in TFA–H_2O (9:1, 40 mL), was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the residue co-evaporated with toluene to get crude 2,5-di-*O*-allyl-*myo*-inositol (1.25 g) as a white solid. The tetraol so obtained was suspended in dry DMF (30 mL), cooled with ice, sodium hydride (2.80 g, 70 mmol) was added, followed by benzyl bromide (7.97 g, 46.6 mmol); the mixture was stirred at room temperature for 48 h. Excess of sodium hydride was quenched by the addition of ice, the solvents were removed under reduced pressure and the residue was worked up 'as usual' with ethyl acetate. The crude product was purified by flash column chromatography to obtain the tetrabenzyl ether **2.9** (2.319 g, 87%) as a white solid.

Data for 2.9: **Mp**. = 83–84 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.40–7.27 (m, 20H), 6.10–5.86 (m, 2H), 5.34–5.12 (m, 4H), 4.87 (d, J = 10.5 Hz, 2H), 4.80 (d, J = 10.5 Hz, 2H), 4.66 (s, 4H), 4.36–4.32 (m, 4H), 4.01–3.92 (m, 3H), 3.34–3.24 (m, 3H) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 138.8, 138.3, 135.7, 135.3, 128.2, 128.0, 127.5, 116.7, 116.5, 83.3, 81.6,

80.5, 75.8, 74.6, 73.8, 73.3, 72.7 ppm; **Elemental Analysis** calcd for $C_{40}H_{44}O_6$ (620.77): C, 77.39; H, 7.14; found C, 76.98; H, 6.91%.

1,3,4,6-Tetra-*O*-benzyl-*myo*-inositol (2.5).

A mixture of the diallyl ether **2.9** (0.500 g, 0.806 mmol), 10% Pd/ C (0.051 g), *p*-toluenesulfonic acid (0.023 g, 0.13 mmol), methanol (13 mL), and water (1.6 mL) was heated (75–80 °C) for 24 h. Excess of 10% Pd/C (0.010 g) was added and the mixture was stirred at room temperature for 2 days. The reaction mixture was then diluted with methanol and passed through Celite to remove Pd/C. The filtrate was concentrated under reduced pressure; the residue was diluted with ethyl acetate, washed with saturated sodium bicarbonate solution, and then worked up 'as usual'. The crude product was purified by flash column chromatography to obtain **2.5** (0.170 g, 39%) as a white solid. In several trials the yield of **2.5** varied; the best yield obtained was 39%. **Mp**. = 129–131 °C (crystals from warm light petroleum–dichloromethane), Lit.[5] **Mp.** = 125 °C.

Racemic 1,3,4,5-tetra-*O*-benzyl-2,6-di-*O*-allyl-*myo*-inositol (2.12).

To an ice-cooled solution of the benzyl ether **2.10**[3b] (1.085 g, 3.88 mmol) in dry DMF (10 mL), sodium hydride (0.465 g, 11.6 mmol) was added, followed by the addition of a solution of allyl bromide (1.641 g, 13.6 mmol) in dry DMF (5 mL). The reaction mixture was stirred at room temperature for 90 min. The reaction was quenched by the addition of ice to the reaction mixture, solvents were removed under reduced pressure and then worked up 'as usual' with ethyl acetate to afford the crude product, which was purified by flash column chromatography to obtain **2.11** as a gum (1.203 g, 86%).

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.33 (m, 5H), 6.09–5.77 (m, 2H), 5.52 (d, J = 1.3 Hz, 1H), 5.37–5.17 (m, 4H), 4.69 (d, J = 11.9 Hz, 1H), 4.57 (d, J = 11.9 Hz, 1H), 4.45–4.40 (m, 1H), 4.35–4.28 (m, 4H), 4.16–4.06 (m, 4H), 3.93–3.98 (m, 1H) ppm.

A mixture of **2.11** (1.125 g, 3.12 mmol), *p*-toluenesulfonic acid monohydrate (1.781 g, 9.36 mmol), and methanol (15 mL) was stirred at room temperature overnight. Solvents were removed under reduced pressure; the residue was taken in ethyl acetate, washed with saturated sodium bicarbonate solution, and worked up 'as usual' to afford crude racemic 2,4-di-O-allyl-6-O-benzyl-*myo*-inositol (1.050 g) as a pale yellow gum. To an ice-cooled solution of the crude triol (1.050 g) obtained above in dry DMF (20 mL), sodium hydride (0.980 g, 24.5 mmol) was added followed by a solution of benzyl bromide (4.190 g, 24.5

mmol) in dry DMF (5 mL). The reaction mixture was stirred at room temperature for 40 h. Excess of sodium hydride was quenched with ice, solvents were removed under reduced pressure, and worked up 'as usual' with ethyl acetate to afford the crude product, which was purified by flash column chromatography to obtain the tetrabenzyl ether **2.12**[6] as a colorless solid (1.549 g, 80%). **Mp**. 62–64 °C (crystals from methanol).

Racemic 1,3,4,5-tetra-*O*-benzyl-*myo*-inositol (1.75).

A mixture of **2.12** (0.420 g, 0.68 mmol), 10% Pd/C (0.126 g), *p*-toluenesulfonic acid (0.126 g, 0.732 mmol), methanol (12 mL), and water (2.5 mL) was heated (70–80 °C) for 30 h. The reaction mixture was diluted with methanol and passed through Celite to remove Pd/C. The filtrate was concentrated under reduced pressure and the residue was taken in ethyl acetate, washed with saturated sodium bicarbonate solution, and worked up 'as usual'. The crude product was purified by flash column chromatography to obtain **1.75** (0.130 g, 35%) as a colorless solid. In several trials the yield of **1.75** varied; maximum yield obtained was 35%; **Mp**. 111–113 °C (crystals obtained by slow evaporation of methanol solution, at ambient temperature). Lit.[30] **Mp**. 116–118 °C (from ethyl acetate–light petroleum).

Racemic 2,4-di-*O*-benzyl-6-*O*-methyl-*myo*-inositol 1,3,5 orthoformate (2.13).

To an ice-cooled solution of **1.32** (0.380 g, 2.00 mmol) in dry DMF (5 mL), sodium hydride (0.088 g, 2.20 mmol) was added followed by a solution of methyl iodide (0.312 g, 2.20 mmol) in dry DMF (1 mL) and the mixture was stirred at room temperature for 2 h. The reaction mixture was cooled with ice, sodium hydride (0.500 g, 12.5 mmol) was added followed by benzyl bromide (1.725 g, 10.0 mmol). The resulting mixture was stirred at room temperature overnight. Excess sodium hydride was quenched by adding ice, the solvents were removed under reduced pressure and the residue was worked up with ethyl acetate 'as usual'. The crude product obtained was purified by flash column chromatography to obtain the dibenzyl ether **2.13** (0.540 g, 70%) as a gum.

Data for 2.13: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.43–7.28 (m, 10H), 5.52 (d, J = 1.3 Hz, 1H), 4.67 (s, 2H), 4.62 (d, J = 12 Hz, 1H), 4.49 (d, J = 12 Hz, 1H), 4.44–4.39 (m, 1H), 4.36–4.27 (m, 2H), 4.24–4.19 (m, 1H), 4.16–4.11 (m, 1H), 3.97–3.92 (m, 1H), 3.38 (s, 3H) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 137.7, 137.5, 128.18, 128.21, 127.7,127.56, 127.64,

127.2, 102.9, 75.7, 73.6, 71.3, 70.2, 70.0, 67.4, 67.2, 57.0 ppm; **Elemental Analysis** calcd for $C_{22}H_{24}O_6$ (384.42): C, 68.73; H, 6.29; found: C, 69.11; H, 6.24 %.

Racemic 1,3,4,5-tetra-*O*-methyl-2,6-di-*O*-benzyl-*myo*-inositol (2.14).

A mixture of **2.13** (0.500 g, 1.30 mmol), *p*-toluenesulfonic acid monohydrate (0.740 g, 3.89 mmol), and methanol (10 mL) was stirred at room temperature for 10 h, the solvent was removed under reduced pressure. The residue was taken in ethyl acetate, washed with a saturated solution of sodium carbonate, and then worked up 'as usual' to obtain the crude triol as a gum (0.540 g). To an ice-cooled solution of the triol (0.540 g) obtained above, in dry DMF (8 mL), sodium hydride (0.577 g, 14.4 mmol) was added followed by a solution of methyl iodide (2.0 g, 14.1 mmol) in dry DMF (2 mL) and the mixture was stirred at room temperature for 24 h. The reaction was quenched by the addition of ice to the reaction mixture, solvents were removed under reduced pressure, and the residue was worked up 'as usual' using ethyl acetate. The product was subjected to flash column chromatography to isolate **2.14** (0.400 g, 74%) as gum which turned into a solid on storing at room temperature.

Data for 2.14: Mp. 66–67 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.44–7.27 (m, 10H), 4.84 (s, 2H), 4.85 (d, J = 10.7 Hz, 1H), 4.76 (d, J = 10.7 Hz, 1H), 4.08 (t, J = 2.3 Hz, 1H), 3.83 (t, J = 9.4 Hz, 1H), 3.65–3.53 (m, 1H), 3.64 (s, 3H), 3.62 (s, 3H), 3.44 (s, 3H), 3.42 (s, 3H), 3.11–3.02 (m, 2H), 2.96 (dd, J = 2.2, 9.8 Hz, 1H) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 138.88, 138.78, 128.17, 127.93, 127.50, 127.38, 127.16, 85.37, 83.04, 82.72, 82.38, 81.46, 75.48, 73.79, 72.41, 61.04, 60.78, 58.34, 58.17 ppm; **Elemental Analysis** calcd for $C_{24}H_{32}O_6$ (416.51): C, 69.21; H, 7.74; found: C, 69.07; H, 7.76 %.

Racemic 2-*O*-benzyl-1,3,4,5-tetra-*O*-methyl-*myo*-inositol (2.15).

A mixture of **2.14** (0.344 g, 0.82 mmol), 10% Pd/C (0.026 g), and ethyl acetate (5 mL), was stirred under hydrogen atmosphere at room temperature for 48 h. Analysis of the reaction mixture by TLC showed the presence of the starting material **2.14**. Excess of 10% Pd/C (0.050 g) and methanol (3 mL) were added and the mixture was stirred under hydrogen atmosphere at room temperature for another 3 h. The catalyst was removed by passing the reaction mixture through a bed of Celite. The filtrate was evaporated under reduced pressure and the residue was flash chromatographed on a column of silica gel to

afford the monobenzyl ether **2.15** (0.130 g, 48%) as a gum (which turned into a solid on storing at room temperature) and the diol **2.6** (0.096 g, 49%) as a colorless solid.

Data for 2.15: **Mp**. = 55–57 °C; **IR** ($CHCl_3$) 3250–3550 (OH) cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.42–7.27 (m, 5H), 4.84 (d, *J* = 12 Hz, 1H), 4.77 (d, *J* = 12 Hz, 1H), 4.12 (t, *J* = 2.2 Hz, 1H), 3.95 (t, *J* = 9.5 Hz, 1H), 3.64 (s, 3H), 3.62–3.54 (m, 4H, Ins H), 3.46 (s, 3H), 3.37 (s, 3H), 3.04–2.90 (m, 3H), 2.59 (bs, OH) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 138.8, 128.2, 127.7, 127.4, 84.84, 83.1, 83.0, 82.1, 74.0, 72.1, 71.5, 60.8, 60.7, 58.4, 57.7 ppm; **Elemental Analysis** calcd for $C_{17}H_{26}O_6$ (326.38): C, 62.56; H, 8.03; found: C, 62.86; H, 8.34 %.

Racemic 2-*O*-benzyl-1,3,4,5,6-penta-*O*-methyl-*myo*-inositol (2.16).

To an solution of **2.15** (0.03 g, 0.1 mmol) in DMF (0.5 mL) was added sodium hydride (0.01 g, 0.25 mmol) followed by methyl iodide (0.05 mL, 0.8 mmol) and stirred at ambient temperature for 3 h. Ice was added to reaction mixture, solvents removed under reduced pressure and residue worked up 'as usual' to afford **2.16** as a gum.

Data for 2.16: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.45–7.22 (m, 5H), 4.82 (s, 2H), 4.06 (t, *J* = 2.4 Hz, 1H), 3.62 (s, 3H, OCH_3), 3.61 (s, 6H, 2×OCH_3), 3.55 (t, *J* = 9.5 Hz, 2H), 3.42 (s, 6H, 2×OCH_3), 3.04–2.90 (m, 3H) ppm.

Racemic 1,3,4,5-tetra-*O*-methyl-*myo*-inositol (2.6).

A mixture of **2.15** (1.15 g, 2.76 mmol), 10% Pd/C (0.064 g), and methanol (15 mL) was stirred at room temperature under H_2 atmosphere for 24 h. The catalyst was removed by passing the reaction mixture through Celite. The filtrate was evaporated under reduced pressure to obtain the diol **2.6** (0.550 g, 85%) as a colorless solid.

Data for 2.6: Mp. 137–138 °C (crystals obtained by cooling a warm solution of ethyl acetate to room temperature); Lit.[31] **Mp**. 130–132 °C; **IR** ($CHCl_3$) 3300–3550 (OH) cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.36 (t, *J* = 2.7 Hz, 1H), 3.86 (t, *J* = 9.6, 1H), 3.65 (s, 3H), 3.62 (s, 3H), 3.55–3.45 (2s and m, 7H), 3.09–2.93 (m, 3H), 2.69 (br s, OH), 2.41 (br s, OH) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 84.4, 82.5, 82.0, 81.3, 71.6, 65.2, 60.8, 58.3, 57.8 ppm; **Elemental Analysis** calcd for $C_{10}H_{20}O_6$ (236.26): C, 50.83; H, 8.53. Found: C, 50.98; H, 8.89 %.

O-Alkylation of *myo*-inositol-derived triol and diols.

General procedure

The required *myo*-inositol-derived triol or diol (0.5–1 mmol) was dissolved in dry THF (2–6 mL) and cooled to 0 °C sodium hydride or butyllithium (1.0–1.2 mmol) was added followed by a solution of the required alkyl halide (1.2–1.5 mmol) in DMF (0.5–1 mL) at 0 °C. The reaction mixture was stirred for 20–30 h at room temperature and worked up as usual with ethyl acetate. The products were separated by flash column chromatography using 10–20% ethyl acetate–light petroleum (80% for mixture of monobenzyl ethers **48** and **49**) mixture as eluent. In some experiments, the ratio of the mixture of ethers formed was estimated by ^{1}H NMR spectroscopy of their acetate derivatives.

Benzylation of racemic 1,2;4,5-di-*O*-isopropylidene-*myo*-inositol (2.2).

Procedure A: The racemic diol **2.2**[9] (0.13 g, 0.5 mmol) was benzylated as in general procedure (reaction time 60 h, ambient temp.), using buytllithium (0.92 mL, 0.60 mmol) and benzyl bromide (0.07 mL, 0.6 mmol) to obtain a mixture of monobenzyl ethers **2.19** and **2.20** (0.1 g, 57%), the diether **2.23** (0.054 g, 25%) and starting diol **2.2** (0.02, 5%) was recovered. The mixture of benzyl ethers **2.19** and **2.20** (0.072 g) was acetylated using acetic anhydride (0.5 mL) and pyridine (1.0 mL) overnight at ambient temperature. Usual work-up of the reaction mixture with ethyl acetate gave a mixture of acetates **2.21**[12] and **2.22**[12] (0.074 g). The ^{1}H NMR spectrum of the mixture showed that **2.21** and **2.22** are present in the ratio 10:1.

Procedure B: The racemic diol **2.2** (0.13 g, 0.5 mmol) was benzylated as in general procedure (reaction time 4 h, reflux), using buytllithium (0.36 mL, 0.60 mmol) and benzyl bromide (added at reflux) (0.07 mL, 0.6 mmol) to obtain a mixture of monobenzyl ethers **2.19** and **2.20** (0.055 g, 32%), the diether **2.23** (0.08 g, 46%) and starting diol **2.2** (0.012, 10%) was recovered. The mixture of benzyl ethers **2.19** and **2.20** (0.036 g) was acetylated using acetic anhydride (0.2 mL) and pyridine (1.0 mL) overnight at ambient temperature. Usual work-up of the reaction mixture with ethyl acetate gave a mixture of acetates **2.21** and **2.22** (0.038 g). The ^{1}H NMR spectrum of the mixture showed that **2.21** and **2.22** are present in the ratio 10:1.5.

Procedure C: The racemic diol **2.2** (0.13 g, 0.5 mmol) was benzylated as in general procedure (reaction time 0 $^\circ$C–5 $^\circ$C for 3 days, 15 $^\circ$C for 4 days), using buytllithium (0.92

mL, 0.60 mmol) and benzyl bromide (0.07 mL, 0.6 mmol) to obtain a mixture of monobenzyl ethers **2.19** and **2.20** (0.07 g, 40%), the diether **2.23** (0.05 g, 22%) and starting diol **2.2** (0.034 g, 26%) was recovered. The mixture of benzyl ethers **2.19** and **2.20** (0.031 g) was acetylated using acetic anhydride (0.25 mL) and pyridine (0.5 mL) overnight at ambient temperature. Usual work-up of the reaction mixture with ethyl acetate gave a mixture of acetates **2.21** and **2.22** (0.056 g). The ^{1}H NMR spectrum of the mixture showed that **2.21** and **2.22** are present in the ratio 10:5.

Benzylation of 1,3,4,6-tetra-*O*-benzyl-*myo*-inositol (2.5).

The racemic diol **2.5** (0.075 g, 0.138 mmol) was benzylated as in the general procedure (reaction time 18 h, rt) using sodium hydride (0.006 g, 0.165 mmol) and benzyl bromide (0.026 g, 0.15 mmol) to obtain a mixture of penta-*O*-benzyl *myo*-inositols **2.24** and **2.25** (0.051 g, 59%) as a colorless solid, the starting diol **2.5** (0.016 g, 22%), and hexa-*O*-benzyl-*myo*-inositol (0.011 g, 11%). The mixture of benzyl ethers (0.025 g) was acetylated using acetic anhydride (0.05 mL) and pyridine (1 mL) overnight at room temperature. Usual work-up of the reaction mixture with ethyl acetate gave a mixture of acetates **2.26** and **2.27**[13] (0.024 g). The ^{1}H NMR spectrum of the mixture showed that major product is **2.26** (>95%).

Benzylation of racemic 1,3,4,5 tetra-*O*-benzyl-*myo*-inositol (1.75).

The racemic diol **1.75** (0.1 g, 0.19 mmol) was benzylated as in the general procedure (reaction time 16 h, rt) using sodium hydride (0.008 g, 0.20 mmol) and benzyl bromide (0.035 g, 0.20 mmol) to obtain a mixture of penta-*O*-benzyl *myo*-inositols **2.25**[13] and **2.28** (0.054 g, 47%) and the starting diol **1.75** (0.047 g, 47%). The mixture of benzyl ethers (0.02 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 **2.27** and **2.29** (0.021 g). The ^{1}H NMR spectrum of the mixture showed that major product is **2.29** (>95%).

Benzylation of racemic 1,3,4,5-tetra-*O*-methyl-*myo*-inositol (2.6).

The racemic diol **2.6** (0.1 g, 0.42 mmol) was benzylated as in the general procedure (reaction time 24 h, rt) using sodium hydride (0.021 g, 0.50 mmol) and benzyl bromide (0.08 g, 0.46 mmol) to obtain a mixture of monobenzyl ethers **2.15** and **2.17** (0.083 g, 60%), the 2,4-di-*O*-benzyl-1,3,5,6-tetra-*O*-methyl-*myo*-inositol (0.04 g, 23%), and the

starting diol **2.6** (0.01 g, 10%). The mixture of benzyl ethers (0.035 g) was acetylated using acetic anhydride (0.05 mL) and pyridine (1 mL) overnight at room temperature. Usual work-up of the reaction mixture with ethyl acetate gave a mixture of acetates **2.30** and **2.31** (0.034 g). The ^{1}H NMR spectrum of the mixture showed that **2.30** and **2.31** were present in the ratio 18:1. The acetate **2.30** was made from **2.15** (see above) for comparison with the ^{1}H NMR spectrum of the mixture of **2.15** and **2.17**.

Preparation of racemic 1-deoxy 2,3,4,5 tetra-*O*-Bn-*myo*-inositol (1.279).

To an ice-cooled solution of the diol **1.279** [7] (chapter 4, scheme 4.1) (0.23 g, 0.53 mmol) in THF (3 mL), was added sodium hydride (0.023 g, 0.58 mmol) followed by a of solution of benzyl bromide (0.07 mL, 0.58 mmol) in DMF (0.7 mL). The reaction mixture was stirred at ambient temperature for 17 h. The reaction was quenched by the addition of ice and the reaction mixture was concentrated under reduced pressure. The residue was taken in ethyl acetate and worked up as usual. The crude product was purified by flash column chromatography (eluent: ethyl acetate / light petroleum, 1:3) to afford the tetrabenzyl ether **2.32** (0.17, 60 %) as a colorless solid; the starting diol **1.279** (0.05 g, 22%) was also recovered.

Data for 2.32: **Mp**. = 133–135 ^{o}C; **IR** (Nujol): $\bar{\nu}$ 3400–3100 (OH) cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.45–7.26 (m, 20H), 5.10–4.95 (m, 2H), 4.81 (d, *J*=10.7 Hz, 1H), 4.73–4.60 (m, 5H), 4.02 (t, *J*=9.5 Hz, 1H), 4.00– 3.80 (m, 2H), 3.46 (dd, *J*= 9.6 and 2.9 Hz, 1H), 3.29 (t, *J*=9.2 Hz, 1H), 2.40–2.18 (br s and dt, *J*= 13.9 and 4.3 Hz, OH and Ins H, 2H), 1.33–1.15 (m, 1H) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 138.8 (C_{ipso}), 138.7 (C_{ipso}), 138.4 (C_{ipso}), 128.6 (C_{arom}), 128.2 (C_{arom}), 128.29 (C_{arom}), 128.0 (C_{arom}), 127.8 (C_{arom}), 127.6 (C_{arom}), 127.56 (C_{arom}), 127.52 (C_{arom}), 86.4 (CH), 83.4 (CH), 81.8 (CH), 75.6 (CH_2), 75.3 (CH_2), 72.5 (CH_2), 72.1 (CH), 71.5 (CH_2), 68.1 (CH), 31.9 (Ring CH_2), ppm; **Elemental Analysis** calcd for $C_{34}H_{36}O_5$ (524.65); C, 77.84; H, 6.92; found C, 78.09; H, 7.16 %.

Preparation of racemic 4-*O*-(4-methoxybenzyl)-*myo*-inositol 1,3,5-orthobenzoate (2.67).

To an ice cooled solution of *myo*-inositol 1,3,5-orthobenzoate (**1.34**)[23b, c] (10 g, 37.59 mmol) in DMF (80 mL), sodium hydride (1.50 g, 37.59 mmol) was added followed by a solution of 4-methoxybenzyl chloride (5.09 g, 37.59 mmol) in DMF (20 mL). The reaction mixture was stirred at room temperature for 4 h. The reaction mixture was then

decomposed by the addition of ice, solvents were removed under reduced pressure and the residue worked up as usual with dichloromethane as solvent. The crude product obtained was purified by flash column chromatography (eluent, ethyl acetate/light petroleum 2:3) on silica gel to obtain **2.67** (13.0 g, 90 %) as a colorless solid.

Data for 2.67: **Mp**. 126–128 ^{o}C; **IR** ($CHCl_3$) $\bar{\nu}$: 3600–3550, 3550–3400 (OH) cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.70–7.55 (m, 2H, Ar-H), 7.45–7.32 (m, 3H, Ar-H), 7.31–7.20 (m, 2H, Ar-H), 7.00–6.80 (m, 2H, Ar-H), 4.64 (q, *J*=11.5 Hz, 2H, CH_2Ph(OCH_3)) 4.61–4.48 (m, 2H), 4.44–4.32 (m, 3H), 4.14 (m, 1H), 3.82 (s, 3H, OCH_3) 3.80 (d, 1H, D_2O exchangeable, OH), 3.15 (d, *J*=12 Hz, 1H, D_2O exchangeable, OH) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 159.8 (C_{ipso}), 136.5 (C_{ipso}), 129.7 (C_{arom}), 129.5 (C_{arom}), 127.9 (C_{arom}), 127.8 (C_{ipso}), 125.1 (C_{arom}), 114.1 (C_{arom}), 107.2 (PhCO_3), 75.9 (Ins C), 73.4 (Ins C), 72.5 (CH_2), 68.0 (Ins C), 67.6 (Ins C), 59.7 (Ins C), 55.1 (OCH_3) ppm; **Elemental analysis** calcd for $C_{21}H_{22}O_7$ (386.4): C, 65.28; H, 5.74; found: C, 64.92; H, 5.62 %.

Preparation of racemic 4-*O*-(4-methoxybenzyl)-6-*O*-allyl-*myo*-inositol 1,3,5-orthobenzoate (2.68).

To a cooled (0 to –5 ^{o}C) solution of **2.67** (4.03 g, 10.44 mmol) in dry THF (40 mL) was added *n*BuLi (7.83 mL, 12.53 mmol, 1.6 M solution. in cyclohexane) followed by a solution of allyl bromide (0.95 mL, 10.96 mmol) in dry DMF (20 mL). The reaction mixture was stirred at room temperature for 30 h and then decomposed by the addition of ice. The solvents were removed under reduced pressure and the residue worked up as usual with dichloromethane. The crude product obtained was purified by flash column chromatography (eluent, ethyl acetate/light petroleum 5:17) on silica gel to obtain **2.68** (3.55 g, 80 %) as a gum.

Data for 2.68: **IR** (Nujol): $\bar{\nu}$ 3584–3320 (OH) cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.70–7.55 (m, 2H, Ar-H), 7.44–7.23 (m, 5H, Ar-H), 6.94–6.82 (m, 2H, Ar-H), 6.02–5.80 (m, 1H, *CH*=CH_2), 5.38–5.14 (m, 2H, CH=*CH_2*), 4.70–4.31 (m, 7H), 4.25–4.05 (m, 3H), 3.81 (s, 3H, Ph-OCH_3), 3.10 (d, *J*=12 Hz, 1H, D_2O exchangeable, OH) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 159.2 (C_{ipso}), 136.9 (C_{ipso}),134.0, 129.6 (C_{ipso}), 129.4, 129.1, 127.9, 125.1, 117.5 (C=*CH_2*), 113.7, 107.8 (PhCO_3), 74.2 (Ins C), 74.2 (Ins C), 73.4 (Ins C), 73.0 (Ins C), 71.1 (CH_2), 70.7 (CH_2), 68.5 (Ins C), 60.4 (Ins C), 55.1 (OCH_3) ppm; **Elemental analysis** calcd for $C_{24}H_{26}O_7$ (426.46): C, 67.59; H, 6.15; found C, 67.40; H, 5.80 %.

Preparation of racemic 2-*O*-(4-bromobenzyl)-4-*O*-(4-methoxybenzyl)-6-*O*-allyl-*myo*-inositol 1,3,5-orthobenzoate (2.69).

To an ice cooled solution of **2.68** (7.90 g, 18.54 mmol) in dry DMF (50 mL) was added sodium hydride (1.48 g, 37.09 mmol) followed by a solution of 4-bromobenzyl bromide (5.10 g, 20.40 mmol) in DMF (20 mL), and the reaction mixture was stirred at room temperature for 12 h. Excess of sodium hydride was destroyed by adding ice to the reaction mixture, solvents were removed under reduced pressure and the residue worked up as usual with dichloromethane. The crude product was purified by flash column chromatography (eluent, ethyl acetate/light petroleum 1:4) on silica gel to obtain **2.69** (10.5 g, 95 %) as a gum.

Data for 2.69: **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.70–7.59 (m, 2H, Ar-H), 7.50–7.43 (m, 2H, Ar-H), 7.37–7.18 (m, 7H, Ar-H), 6.91–6.84 (m, 2H, Ar-H), 5.95–5.76 (m, 1H, *CH*=CH_2), 5.31–5.16 (m, 2H, CH=*CH_2*), 4.64 (s, 2H) 4.59–4.35 (m, 7H), 4.17–3.97 (m, 3H), 3.82 (s, 3H, Ph-O*CH_3*) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ = 159.2 (C_{ipso}), 137.1 (C_{ipso}),134.0 (C_{arom}), 131.3 (C_{arom}), 129.6 (C_{ipso}), 129.3 (C_{arom}), 129.2 (C_{arom}), 129.0 (C_{arom}), 127.8 (C_{arom}), 125.2 (C_{arom}), 121.4 (C_{ipso}), 117.4 (C=*CH_2*), 113.7 (*CH*=C), 107.7 (Ph*C*O_3), 73.6 (Ins CH), 73.4 (Ins CH), 71.8 (Ins CH), 71.7 (Ins CH), 71.1 (CH_2), 70.5 (CH_2), 70.2 (CH_2), 68.8 (Ins CH), 66.5 (Ins CH), 55.1 (OCH_3) ppm; **Elemental analysis** calcd for $C_{31}H_{31}BrO_7$ (594.13): C, 62.53; H, 5.25; found C, 62.29; H, 4.86 %.

2.5. References.

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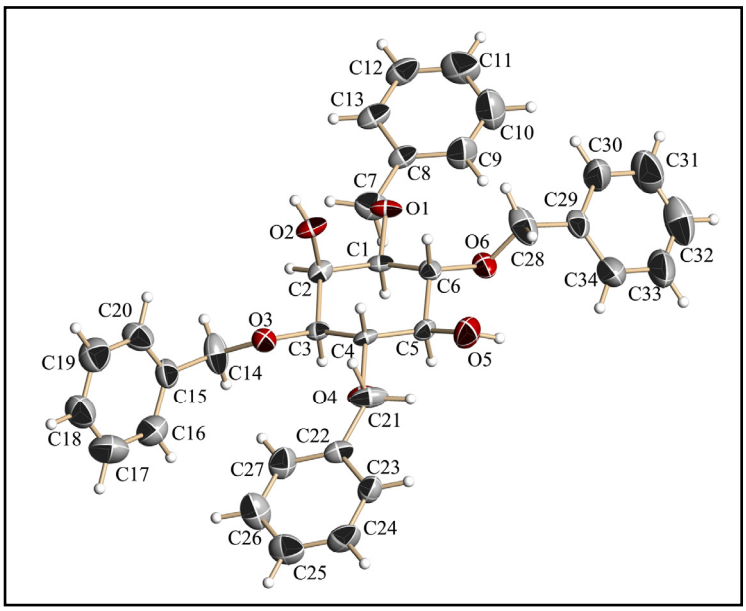
2.6. Appendix.

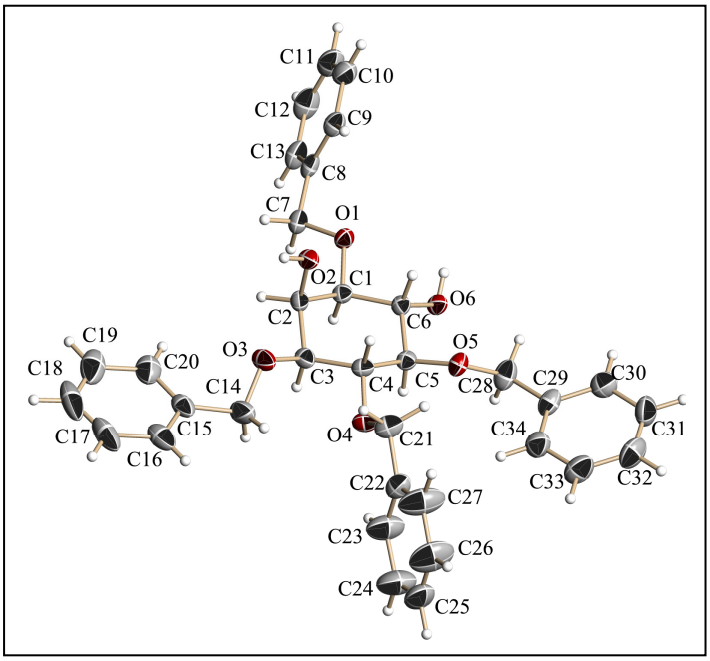
2.6.1. Appendix Index.



ORTEP diagram of **2.5**

Crystal data table of **2.5**

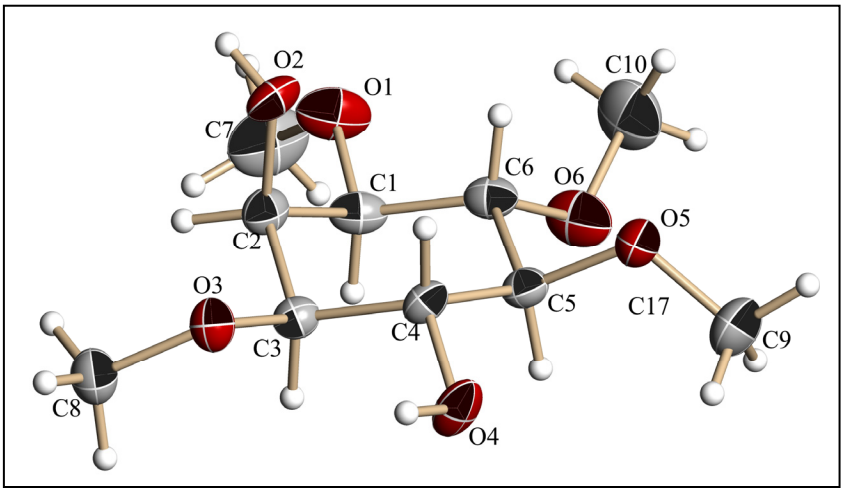
Identification code	**2.5** (crystals from light petroleum-DCM)
Empirical formula	$C_{34}H_{36}O_6$
Formula weight	540.63
Temperature (K)	297 (2) K
Wavelength (Å)	0.71073 A
Crystal system, Space group	Monoclinic, *Cc*
Unit cell dimensions	a = 32.890 (19) Å α = 90° b = 7.631(4) Å β = 108.602 (10) ° c = 12.414 (7) Å γ = 90°
Volume	2953 (3) $Å^3$
Z, Calculated density	4, 1.216 g/cm^3
Absorption coefficient	0.082 mm^{-1}
F(000)	1152
Crystal size	0.56 x 0.44 x 0.34 mm^3
Index ranges	-38<=h<=38, -9<=k<=9, -14<=l<=14
Reflections collected / unique	9414 / 4841[R(int) = 0.0490]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9725 and 0.9553
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4841 / 2 / 363
Goodness-of-fit on F^2	1.025
Final R indices [I>2σ(I)]	R1 = 0.0674, wR2 = 0.1419
R indices (all data)	R1 = 0.1241, wR2 = 0.1669
Largest diff. peak and hole	0.266 and -0.165 $Å^{-3}$
CCDC Nos	CCDC 699532



ORTEP diagram of **1.75**

Crystal data table of **1.75**

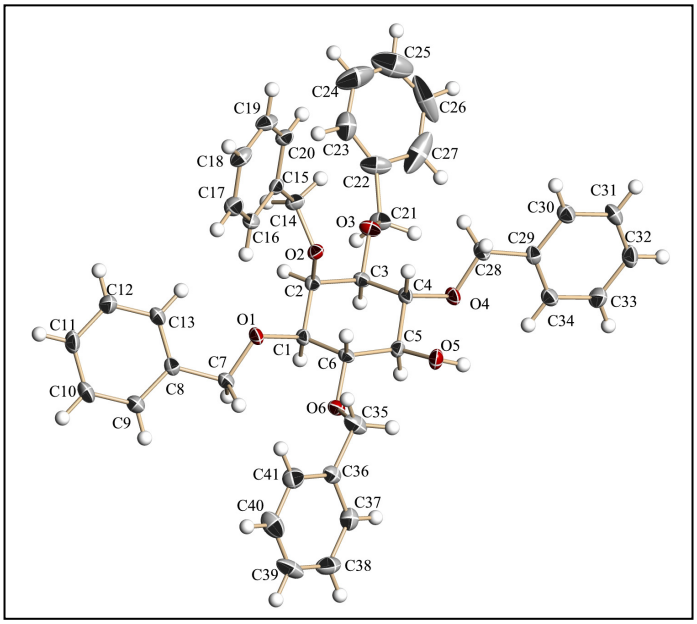
Identification code	**1.75** (crystals from methanol)
Empirical formula	$C_{34}H_{36}O_6$
Formula weight	540.63
Temperature (K)	133 (2) K
Wavelength (Å)	0.71073 A
Crystal system, Space group	Monoclinic, $P2_1/c$
Unit cell dimensions	a = 24.935 (3) Å α = 90° b = 16.295 (2) Å β = 95.909(2) ° c = 7.1993 (9) Å γ = 90°
Volume	2909.7 (6) $Å^3$
Z, Calculated density	4, 1.234 g/cm^3
Absorption coefficient	0.084 mm^{-1}
F(000)	1152
Crystal size	0.29 x 0.19 x 0.14 mm^3
Index ranges	-21<=h<=30, -18<=k<=20, -8<=l<=8
Reflections collected / unique	15539 / 5672 [R(int) = 0.0294]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9884 and 0.9765
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5672 / 0 / 369
Goodness-of-fit on F^2	1.063
Final R indices [I>2σ(I)]	R1 = 0.0544, wR2 = 0.1356
R indices (all data)	R1 = 0.0641, wR2 = 0.1413
Largest diff. peak and hole	0.393 and -0.257 $Å^{-3}$
CCDC Nos	CCDC 699530



ORTEP diagram of **2.6**

Crystal data table of **2.6**

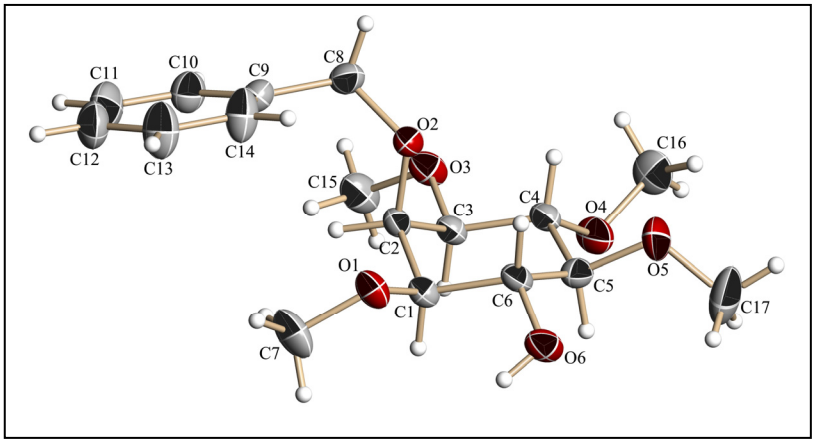
Identification code	**2.6** (crystals from ethyl acetate)
Empirical formula	$C_{10}H_{20}O_6$
Formula weight	236.26
Temperature (K)	297 (2)
Wavelength (Å)	0.71073
Crystal system, Space group	Orthorhombic, *Pbca*
Unit cell dimensions	a = 6.9753 (7) Å α = 90° b = 13.1180 (14) Å β = 90 (2)° c = 26.415 (3) Å γ = 90°
Volume	2417.0 (4) $Å^3$
Z, Calculated density	8, 1.299 g/cm^3
Absorption coefficient	0.107 mm^{-1}
F(000)	1024
Crystal size	0.68 x 0.26 x 0.10 mm^3
Index ranges	-8<=h<=8, -14<=k<=15, -29<=l<=31
Reflections collected / unique	11258 / 2125 [R(int) = 0.0256]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9894 and 0.9310
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2125 / 0 / 181
Goodness-of-fit on F^2	1.063
Final R indices [I>2σ(I)]	R1 = 0.0403, wR2 = 0.1049
R indices (all data)	R1 = 0.0513, wR2 = 0.1124
Largest diff. peak and hole	0.170 and -0.160 $Å^{-3}$
CCDC Nos	CCDC 699531



ORTEP diagram of **2.24**

Crystal data table of **2.24**

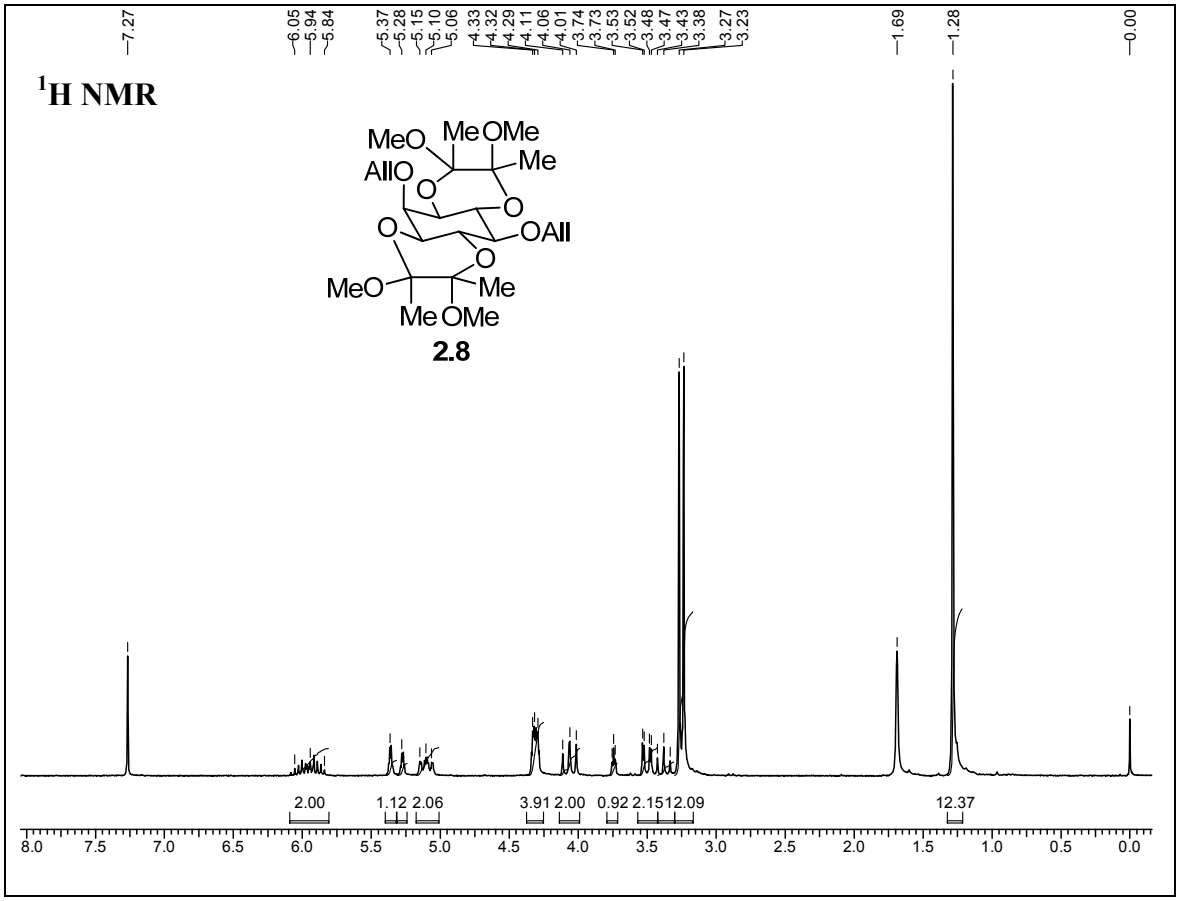
Identification code	**2.24** (crystals from methanol-DCM)
Empirical formula	$C_{41}H_{42}O_6$
Formula weight	630.75
Temperature	297 (2) K
Wavelength	0.71073 Å
Crystal system, Space group	Monoclinic, *P2₁/c*
Unit cell dimensions	a = 15.8257 (11) Å α = 90° b = 8.7184 (6) Å β = 96.4930 (10)° c = 24.1053 (17) Å γ = 90°
Volume	3304.6 (4) $Å^3$
Z, Calculated density	4, 1.268 g/cm^3
Absorption coefficient	0.084 mm^{-1}
F(000)	1344
Crystal size	0.82 × 0.18 × 0.11 mm^3
θ range for data collection	2.59 to 25.00 °
Limiting indices	-18<=h<=18, -10<=k<=10, -28<=l<=28
Reflections collected / unique	30783 / 5812 [R(int) = 0.0528]
Completeness to θ = 25.00	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9908 and 0.9344
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5812 / 0 / 431
Goodness-of-fit on F^2	1.043
Final R indices [I>2σ(I)]	R1 = 0.0482, wR2 = 0.1170
R indices (all data)	R1 = 0.0553, wR2 = 0.1232
Largest diff. peak and hole	0.572 and -0.348 $Å^{-3}$

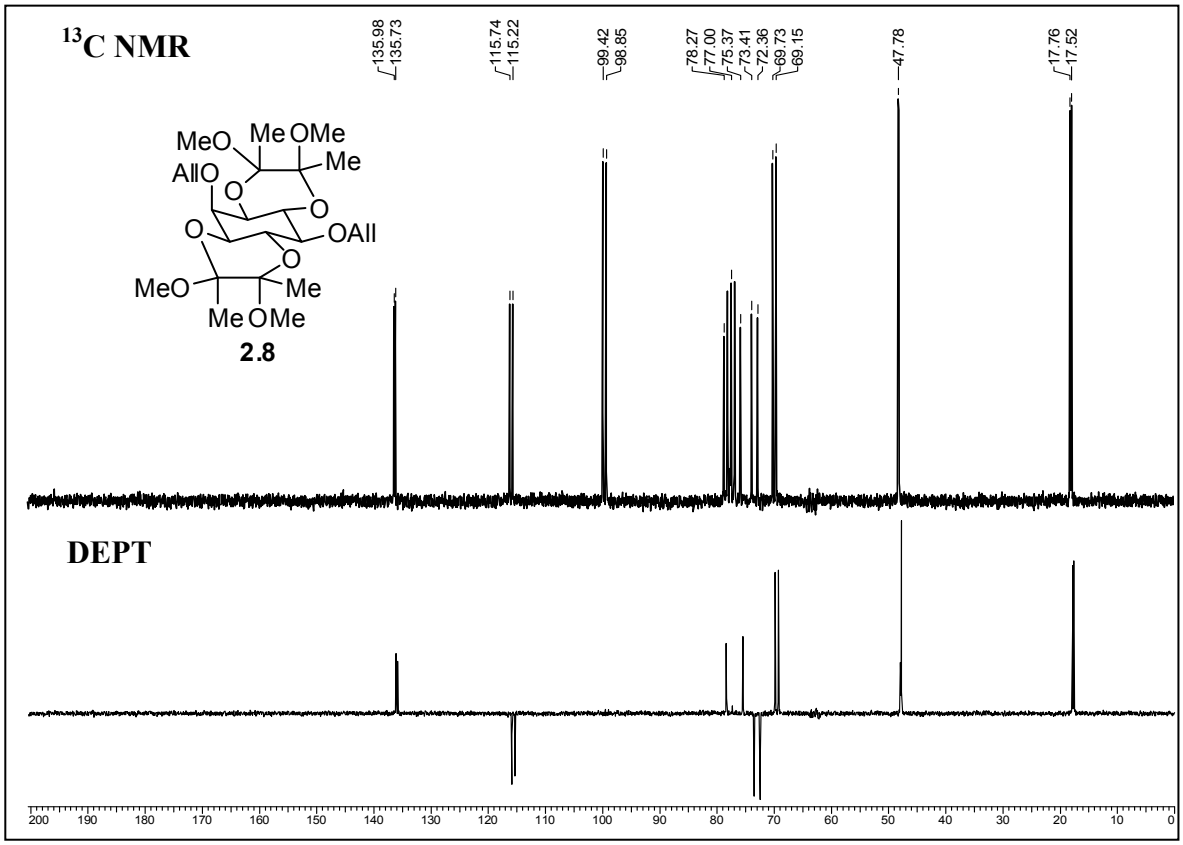


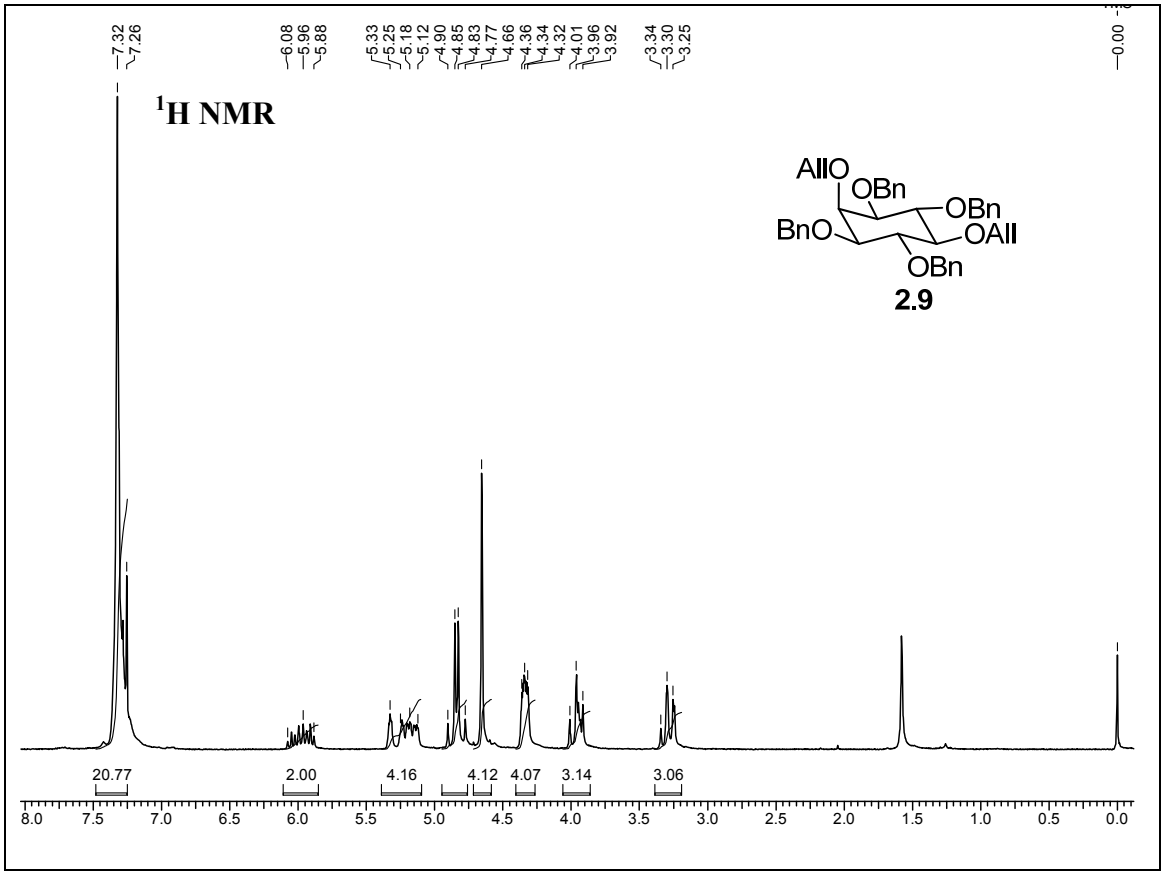
ORTEP diagram of **2.15**

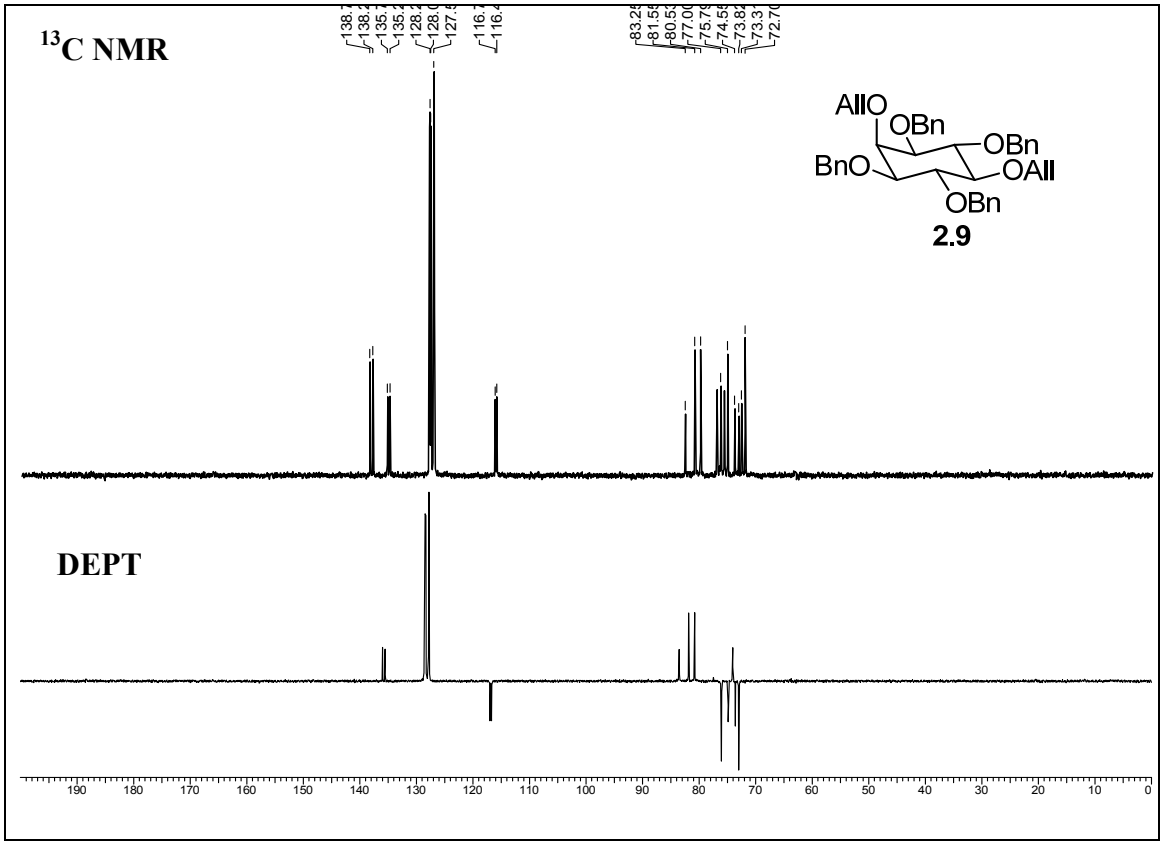
Crystal data table of **2.15**

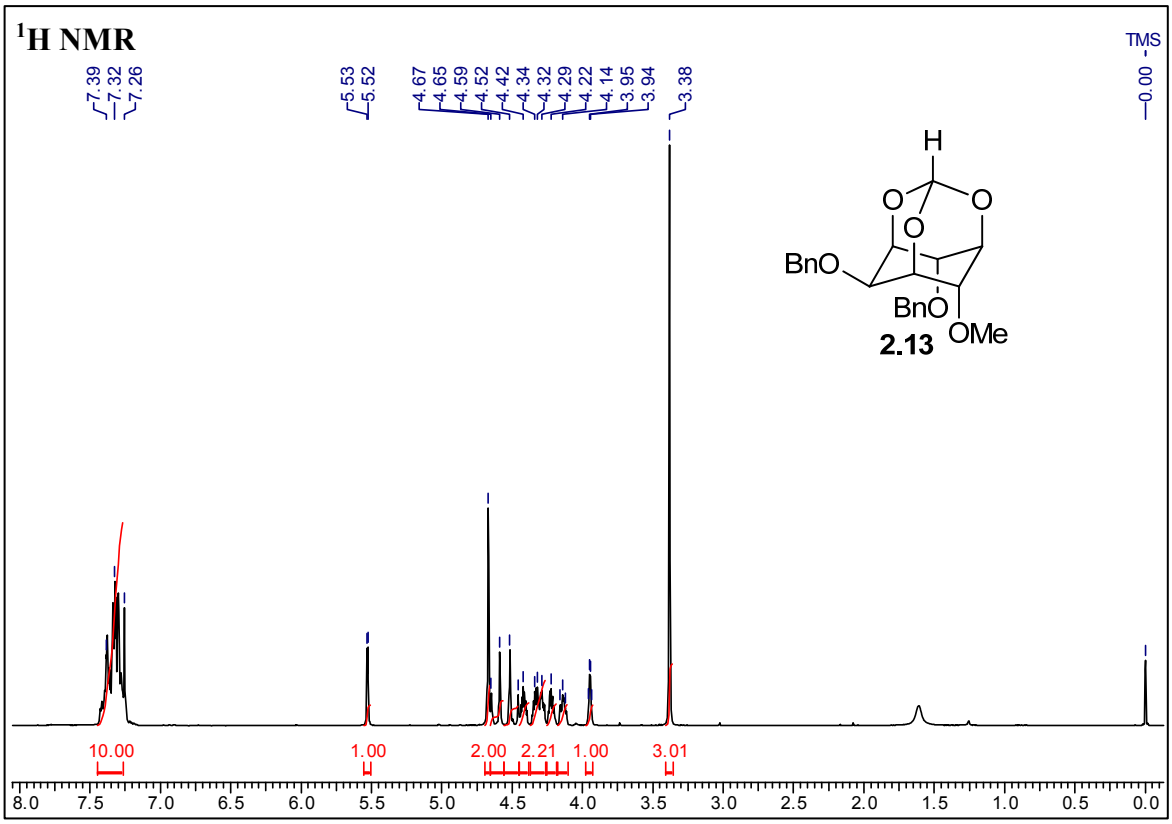
Identification code	**2.15** (crystals from ethyl acetate-DCM)
Empirical formula	$C_{17}H_{26}O_6$
Formula weight	326.38
Temperature	297(2) K
Wavelength	0.71073 Å
Crystal system, Space group	Monoclinic, *P2₁*
Unit cell dimensions	a = 9.807 (2) Å α = 90° b = 5.1666 (11) Å β = 96.266 (4)° c = 17.057 (4) Å γ = 90°
Volume	859.1 (3) $Å^3$
Z, Calculated density	2, 1.262 g/cm^3
Absorption coefficient	0.095 mm^{-1}
F(000)	352
Crystal size	0.54 × 0.21 × 0.14 mm^3
θ range for data collection	2.09 to 25.00 °
Limiting indices	-11<=h<=11, -6<=k<=6, -20<=l<=16
Reflections collected / unique	4280 / 2764 [R(int) = 0.0172]
Completeness to θ = 25.00	98.4 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9869 and 0.9506
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2764 / 1 / 212
Goodness-of-fit on F^2	1.065
Final R indices [I>2σ(I)]	R1 = 0.0619, wR2 = 0.1683
R indices (all data)	R1 = 0.0641, wR2 = 0.1700
Absolute structure parameter	-1 (2)
Largest diff. peak and hole	0.282 and -0.189 $Å^{-3}$

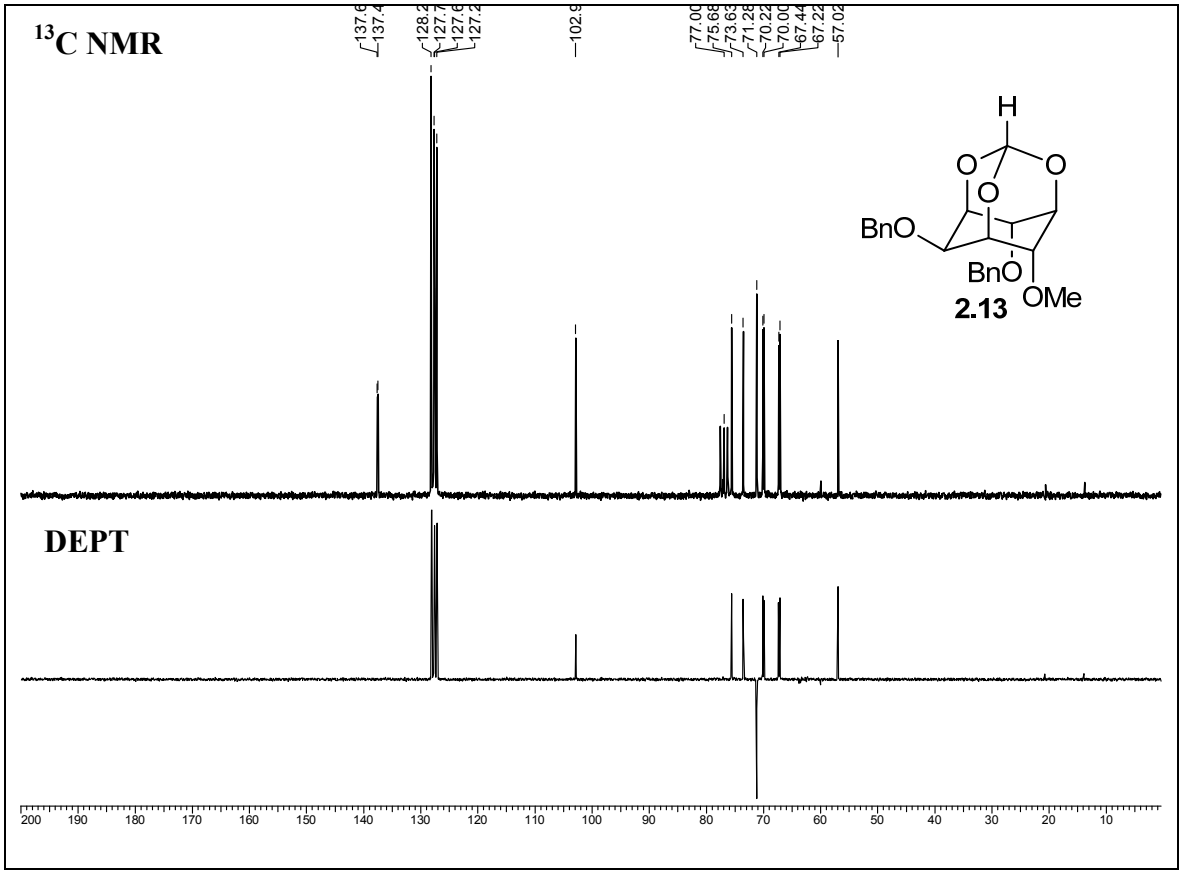

^{1}H NMR
MeO
Me OMe
Me
AllO
O
O
OAll
O
O
MeO
Me
Me OMe
2.8
7.27
6.05
5.94
5.84
5.37
5.28
5.15
5.10
5.06
4.33
4.32
4.29
4.11
4.06
4.01
3.74
3.73
3.53
3.52
3.48
3.47
3.43
3.38
3.27
3.23
1.69
1.28
0.00
2.00
1.12
2.06
3.91
2.00
0.92
2.15
12.09
12.37

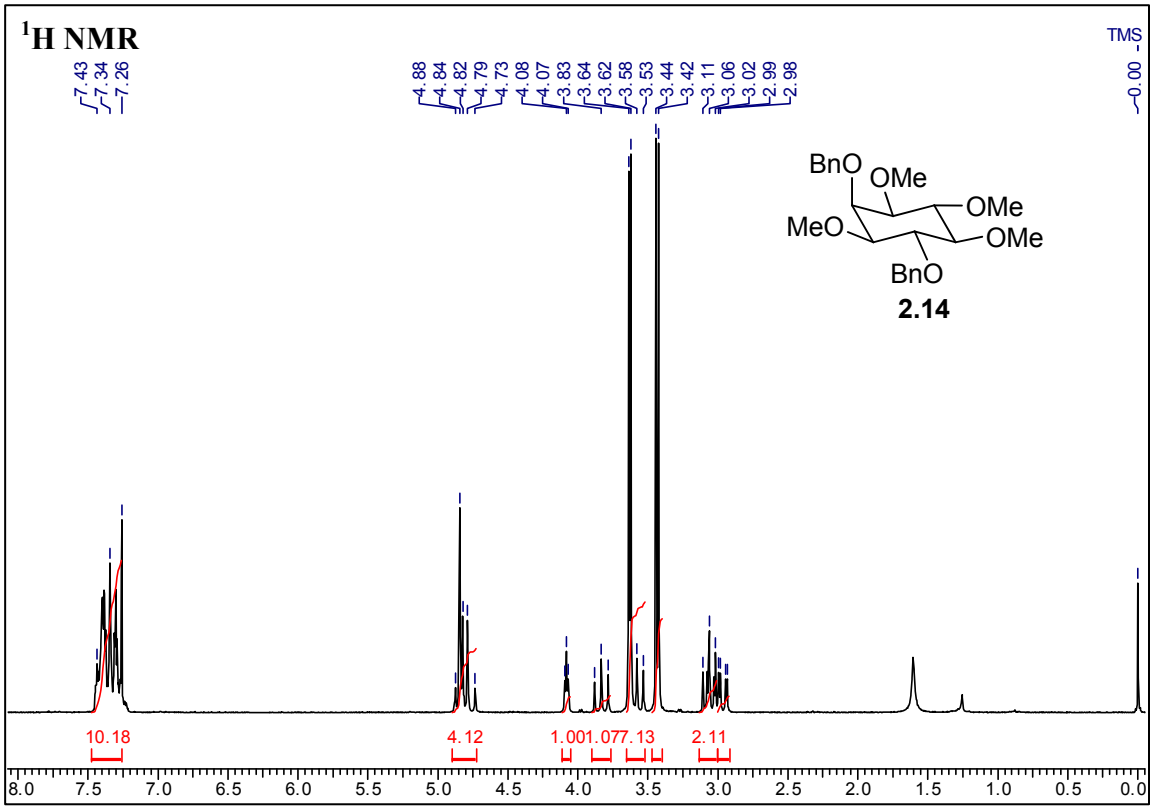

^{13}C NMR
MeO
Me OMe
Me
AllO
O
O
O
OAll
O
MeO
Me
Me OMe
2.8
135.98
135.73
115.74
115.22
99.42
98.85
78.27
77.00
75.37
73.41
72.36
69.73
69.15
47.78
17.76
17.52
DEPT

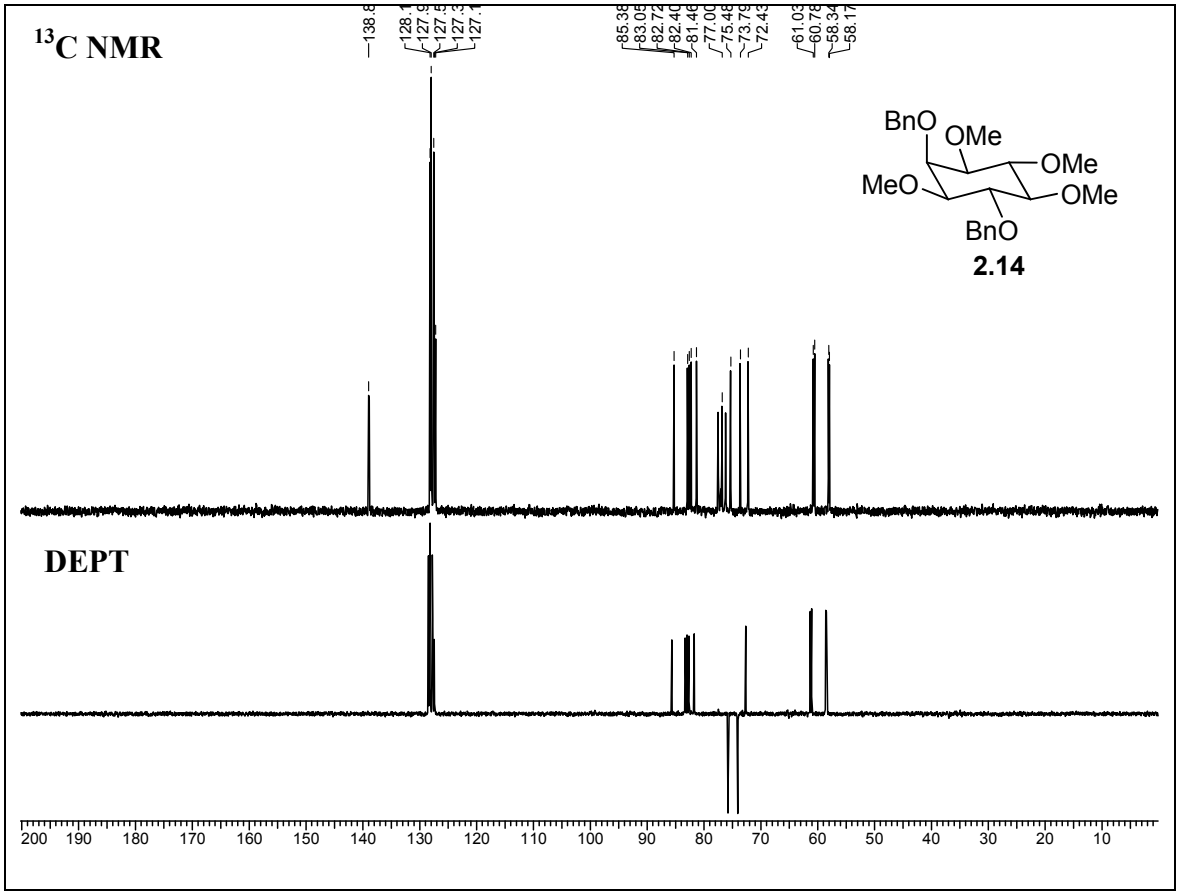

7.32
7.26
6.08
5.96
5.88
5.33
5.25
5.18
5.12
4.90
4.85
4.83
4.77
4.66
4.36
4.34
4.32
4.01
3.96
3.92
3.34
3.30
3.25
0.00
^{1}H NMR
AllO
OBn
OBn
BnO
OAll
OBn
2.9
20.77
2.00
4.16
4.12
4.07
3.14
3.06
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

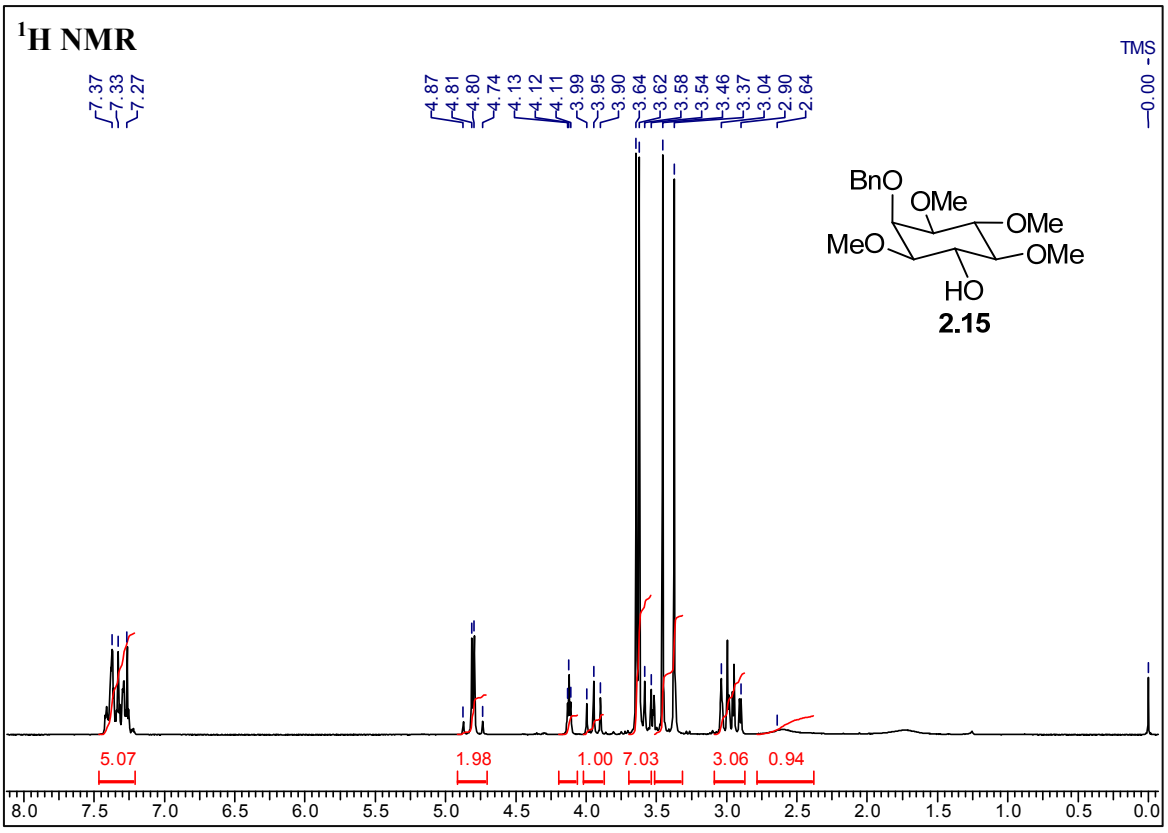

^{13}C NMR
AllO
OBn
OBn
BnO
OAll
OBn
2.9
DEPT
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

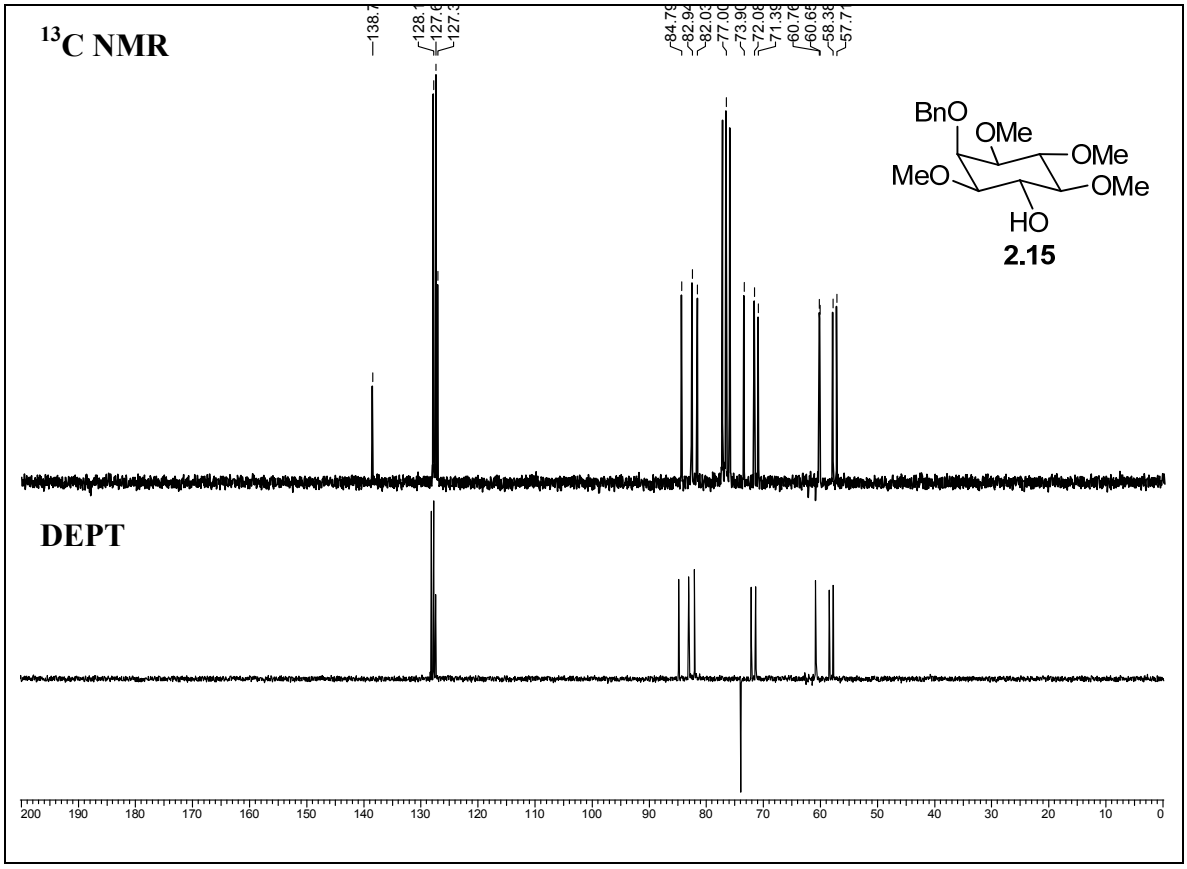

^{1}H NMR
TMS
7.39
7.32
7.26
5.53
5.52
4.67
4.65
4.59
4.52
4.42
4.34
4.32
4.29
4.22
4.14
3.95
3.94
3.38
0.00
H
O
O
O
BnO
BnO
OMe
2.13
10.00
1.00
2.00
2.21
1.00
3.01
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

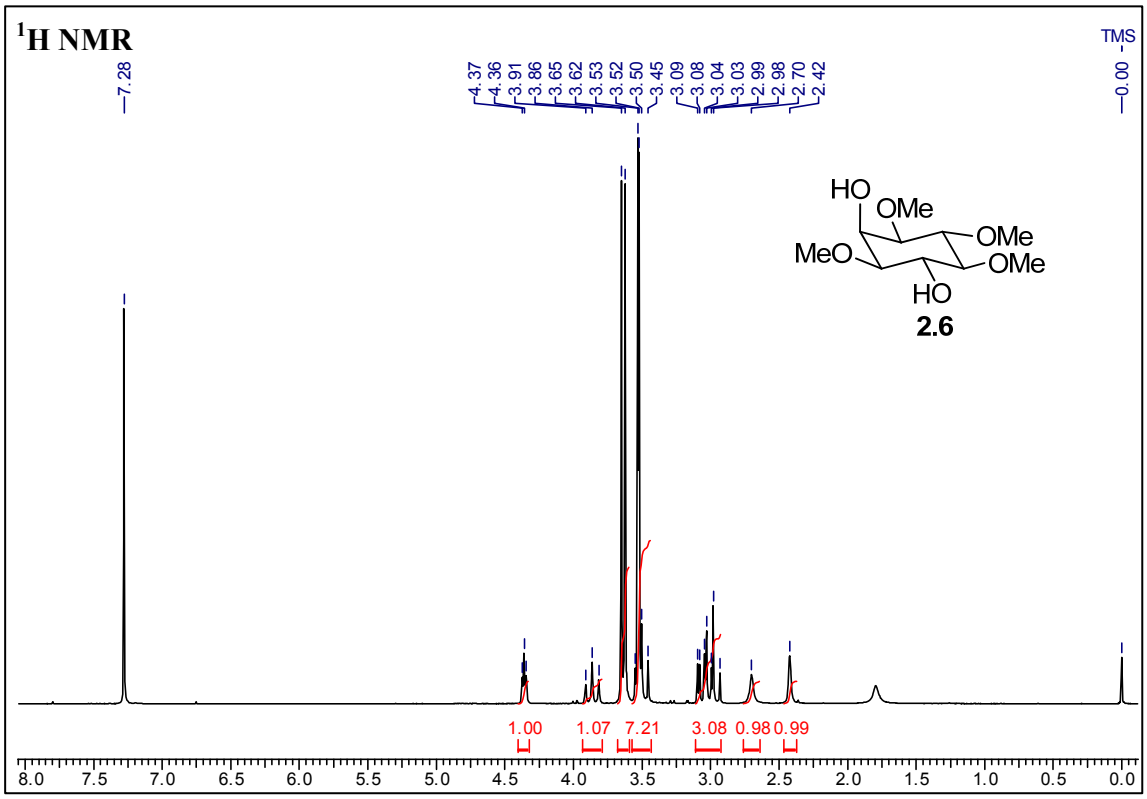

^{13}C NMR
137.6
137.4
128.2
127.7
127.6
127.2
102.9
77.00
75.68
73.63
71.28
70.22
70.00
67.44
67.22
57.02
H
O
O
O
BnO
BnO
OMe
2.13
DEPT
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

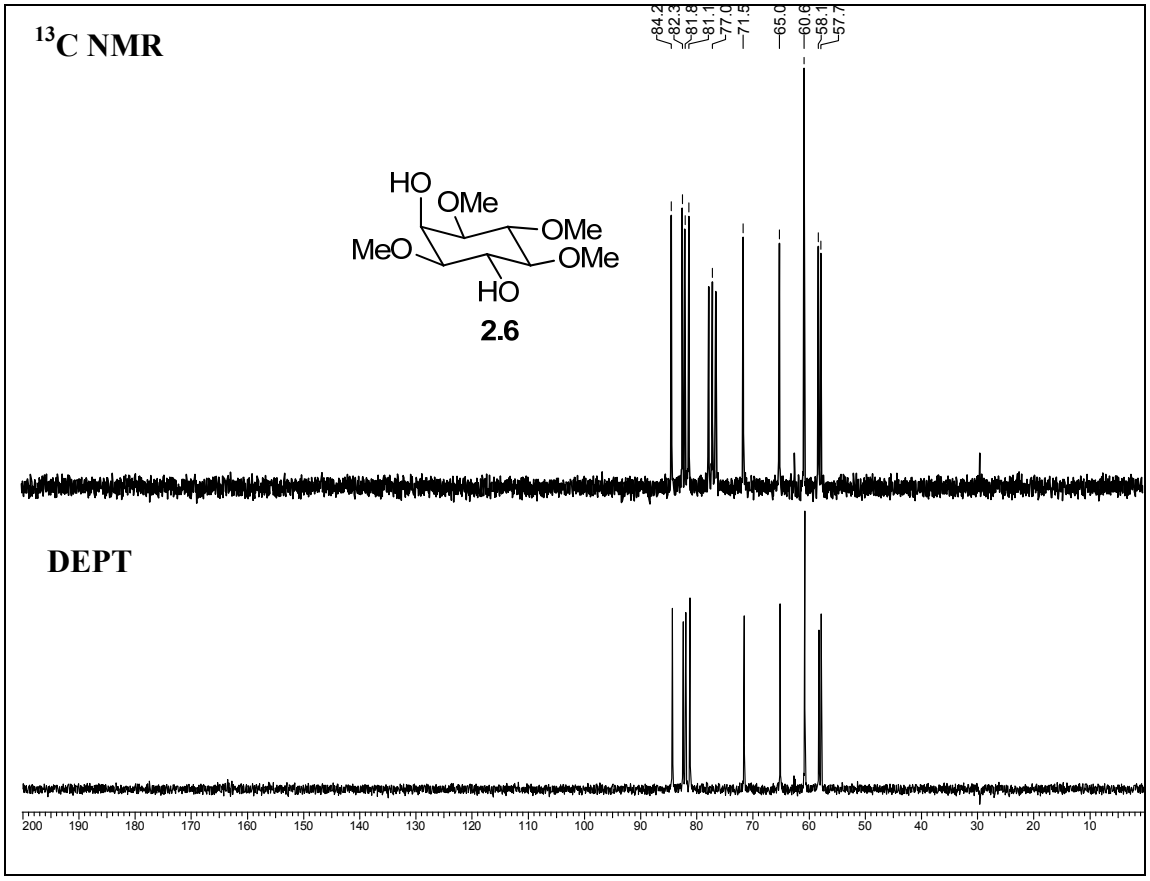

^{1}H NMR
TMS
7.43
7.34
7.26
4.88
4.84
4.82
4.79
4.73
4.08
4.07
3.83
3.64
3.62
3.58
3.53
3.44
3.42
3.11
3.06
3.02
2.99
2.98
0.00
BnO
OMe
OMe
MeO
OMe
BnO
2.14
10.18
4.12
1.00
1.07
7.13
2.11
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

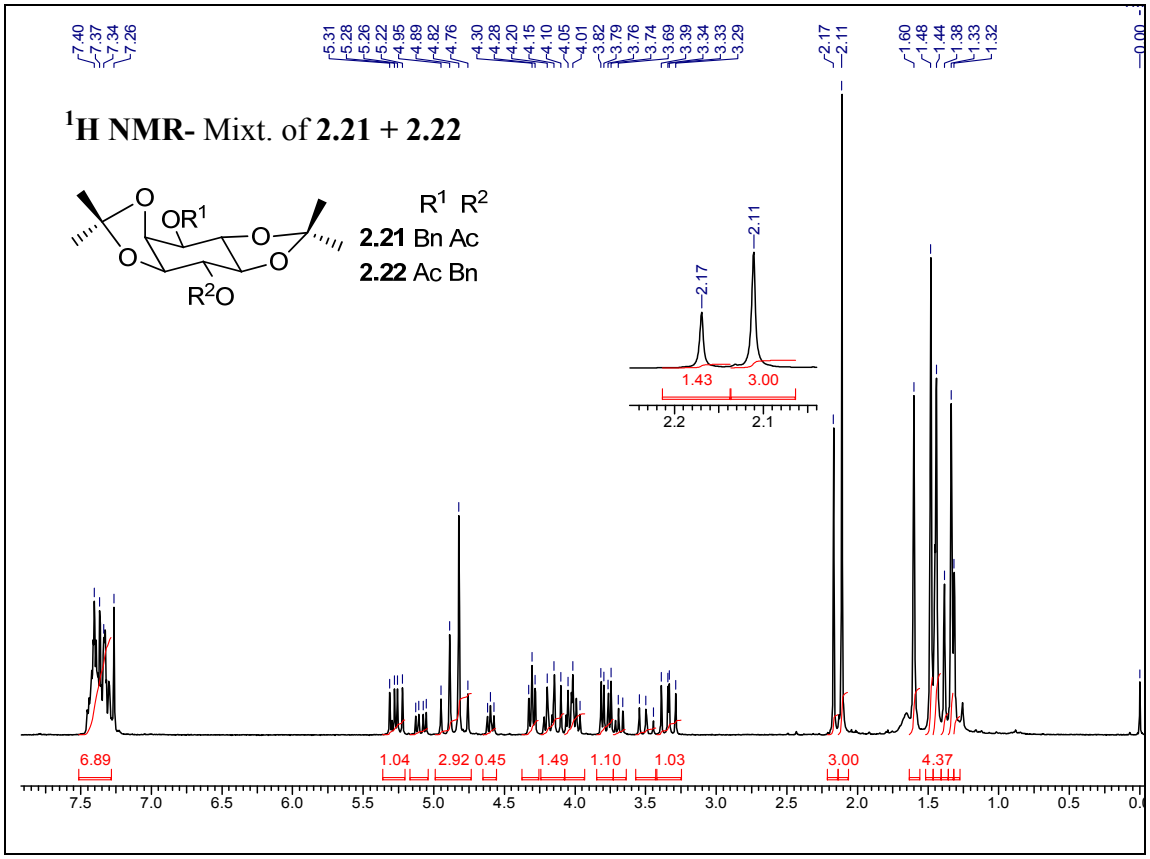

^{13}C NMR
138.8
128.1
127.9
127.5
127.3
127.1
85.38
83.05
82.72
82.40
81.46
77.00
75.48
73.79
72.43
61.03
60.78
58.34
58.17
BnO
OMe
OMe
MeO
OMe
BnO
2.14
DEPT
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

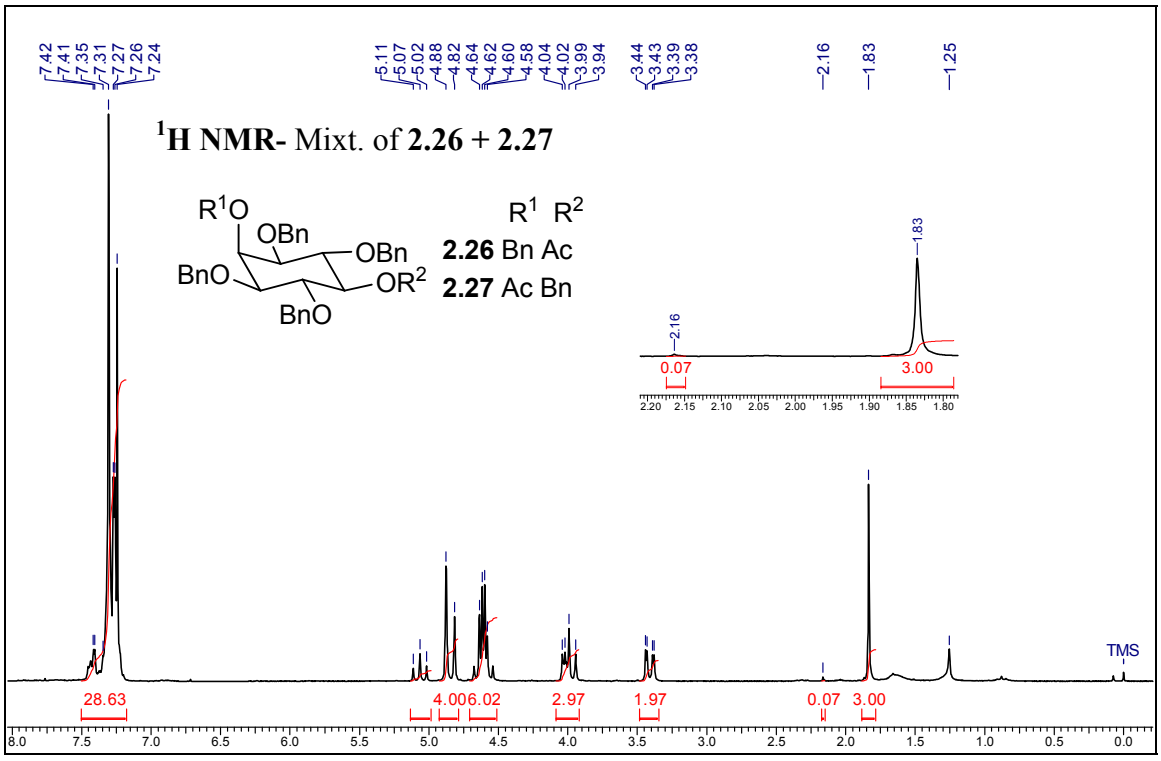

^{1}H NMR
TMS
7.37
7.33
7.27
4.87
4.81
4.80
4.74
4.13
4.12
4.11
3.99
3.95
3.90
3.64
3.62
3.58
3.54
3.46
3.37
3.04
2.90
2.64
0.00
BnO
OMe
OMe
MeO
OMe
HO
2.15
5.07
1.98
1.00
7.03
3.06
0.94
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

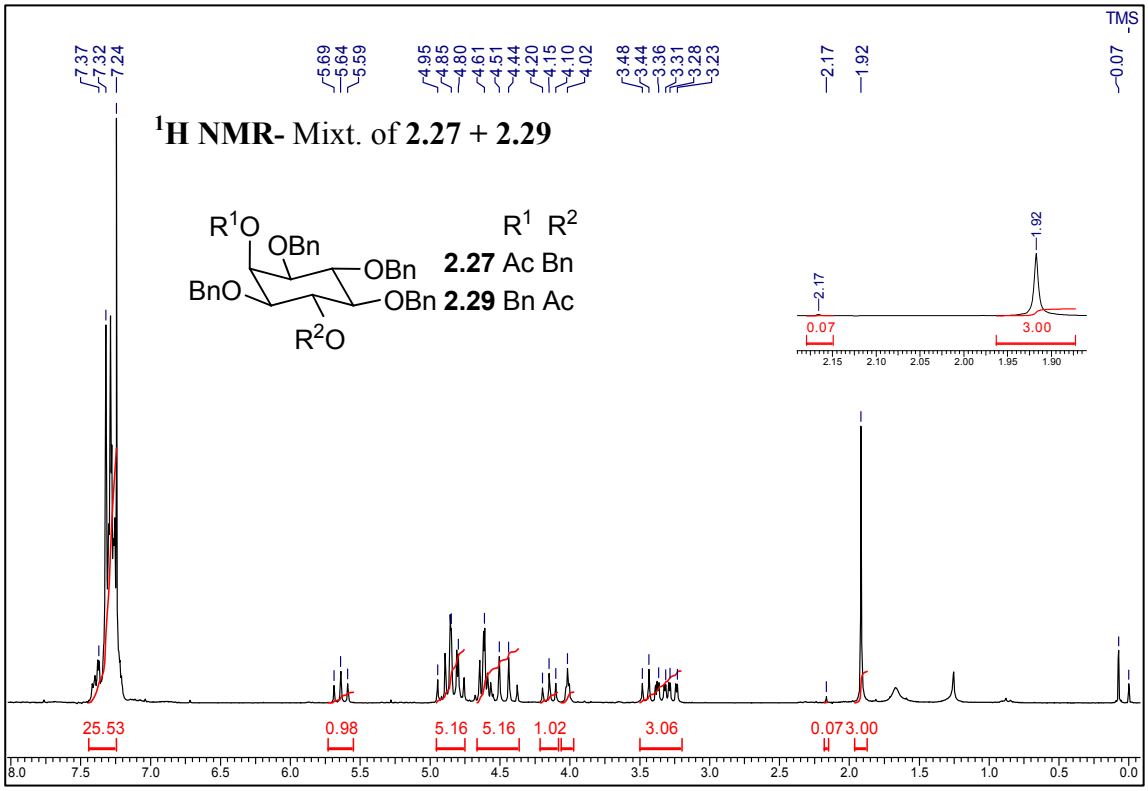

^{13}C NMR
138.7
128.1
127.6
127.3
84.79
82.94
82.03
77.00
73.90
72.08
71.39
60.76
60.65
58.38
57.77
BnO
OMe
OMe
MeO
OMe
HO
2.15
DEPT
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


^{1}H NMR
TMS
7.28
4.37
4.36
3.91
3.86
3.65
3.62
3.53
3.52
3.50
3.45
3.09
3.08
3.04
3.03
2.99
2.98
2.70
2.42
0.00
HO
OMe
OMe
MeO
OMe
HO
2.6
1.00
1.07
7.21
3.08
0.98
0.99


^{13}C NMR
84.2
82.3
81.8
81.1
77.0
71.5
65.0
60.6
58.1
57.7
HO
OMe
OMe
MeO
OMe
HO
2.6
DEPT


7.40
7.37
7.34
7.26
5.31
5.28
5.26
5.22
4.95
4.89
4.82
4.76
4.30
4.28
4.20
4.15
4.10
4.05
4.01
3.82
3.79
3.76
3.74
3.69
3.39
3.34
3.33
3.29
2.17
2.11
1.60
1.48
1.44
1.38
1.33
1.32
0.00
1H NMR- Mixt. of 2.21 + 2.22
OR1
O
O
O
O
R2O
R1 R2
2.21 Bn Ac
2.22 Ac Bn
2.17
2.11
1.43
3.00
2.2
2.1
6.89
1.04
2.92
0.45
1.49
1.10
1.03
3.00
4.37
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


7.42
7.41
7.35
7.31
7.27
7.26
7.24
5.11
5.07
5.02
4.88
4.82
4.64
4.62
4.60
4.58
4.04
4.02
3.99
3.94
3.44
3.43
3.39
3.38
2.16
1.83
1.25
1H NMR- Mixt. of 2.26 + 2.27
R1O
OBn
OBn
BnO
OR2
BnO
R1 R2
2.26 Bn Ac
2.27 Ac Bn
1.83
2.16
0.07
3.00
2.20
2.15
2.10
2.05
2.00
1.95
1.90
1.85
1.80
TMS
28.63
4.00
6.02
2.97
1.97
0.07
3.00
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


TMS
7.37
7.32
7.24
5.69
5.64
5.59
4.95
4.85
4.80
4.61
4.51
4.44
4.20
4.15
4.10
4.02
3.48
3.44
3.36
3.31
3.28
3.23
2.17
1.92
0.07
1H NMR- Mixt. of 2.27 + 2.29
R1O
OBn
OBn
BnO
OBn
R2O
R1 R2
2.27 Ac Bn
2.29 Bn Ac
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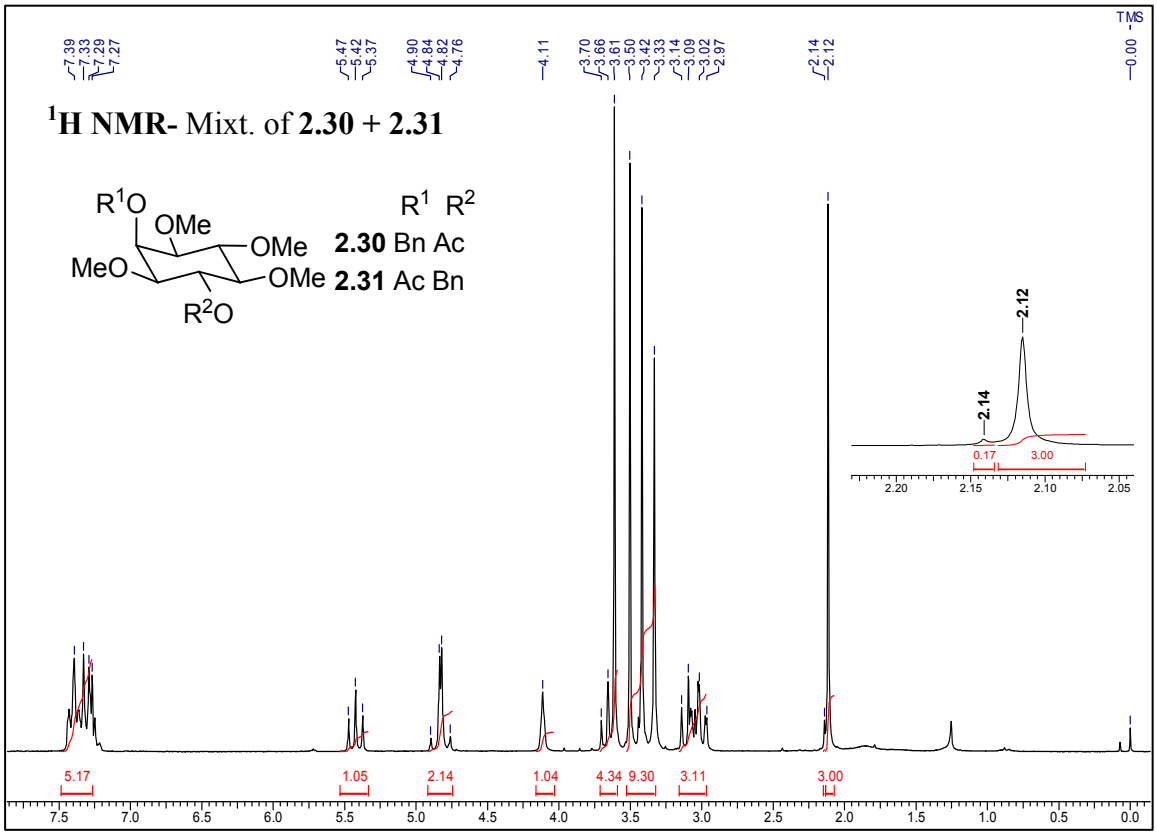
0.98
5.16
5.16
1.02
3.06
0.07
3.00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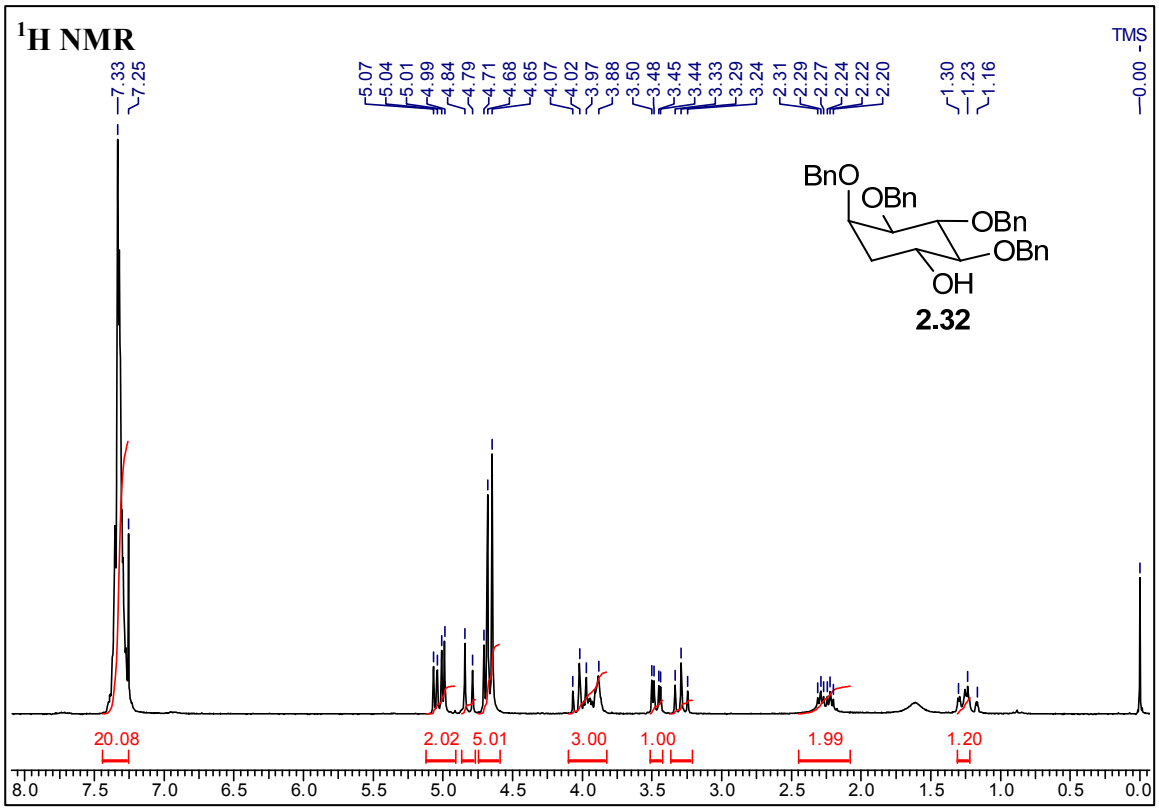
7.29
7.27
5.47
5.42
5.37
4.90
4.84
4.82
4.76
4.11
3.70
3.66
3.61
3.50
3.42
3.33
3.14
3.09
3.02
2.97
2.14
2.12
0.00
1H NMR- Mixt. of 2.30 + 2.31
R1O
OMe
OMe
MeO
OMe
R2O
R1 R2
2.30 Bn Ac
2.31 Ac Bn
5.17
1.05
2.14
1.04
4.34
9.30
3.11
3.00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5.04
5.01
4.99
4.84
4.79
4.71
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4.65
4.07
4.02
3.97
3.88
3.50
3.48
3.45
3.44
3.33
3.29
3.24
2.31
2.29
2.27
2.24
2.22
2.20
1.30
1.23
1.16
0.00
BnO
OBn
OBn
OBn
OH
2.32
20.08
2.02
5.01
3.00
1.00
1.99
1.20
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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3.0
2.5
2.0
1.5
1.0
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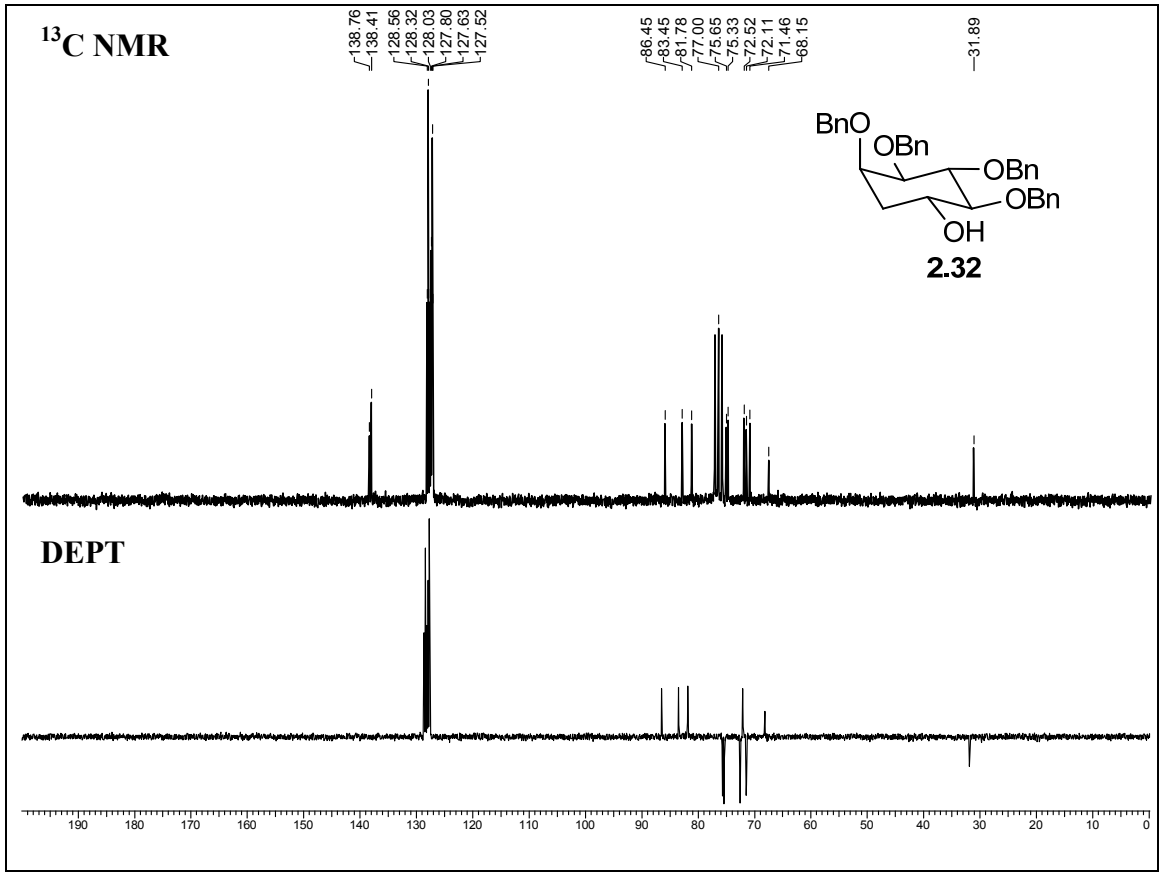
0.0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127.63
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81.78
77.00
75.65
75.33
72.52
72.11
71.46
68.15
31.89
BnO
OBn
OBn
OBn
OH
2.32
DEPT
190
180
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160
150
140
130
120
110
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70
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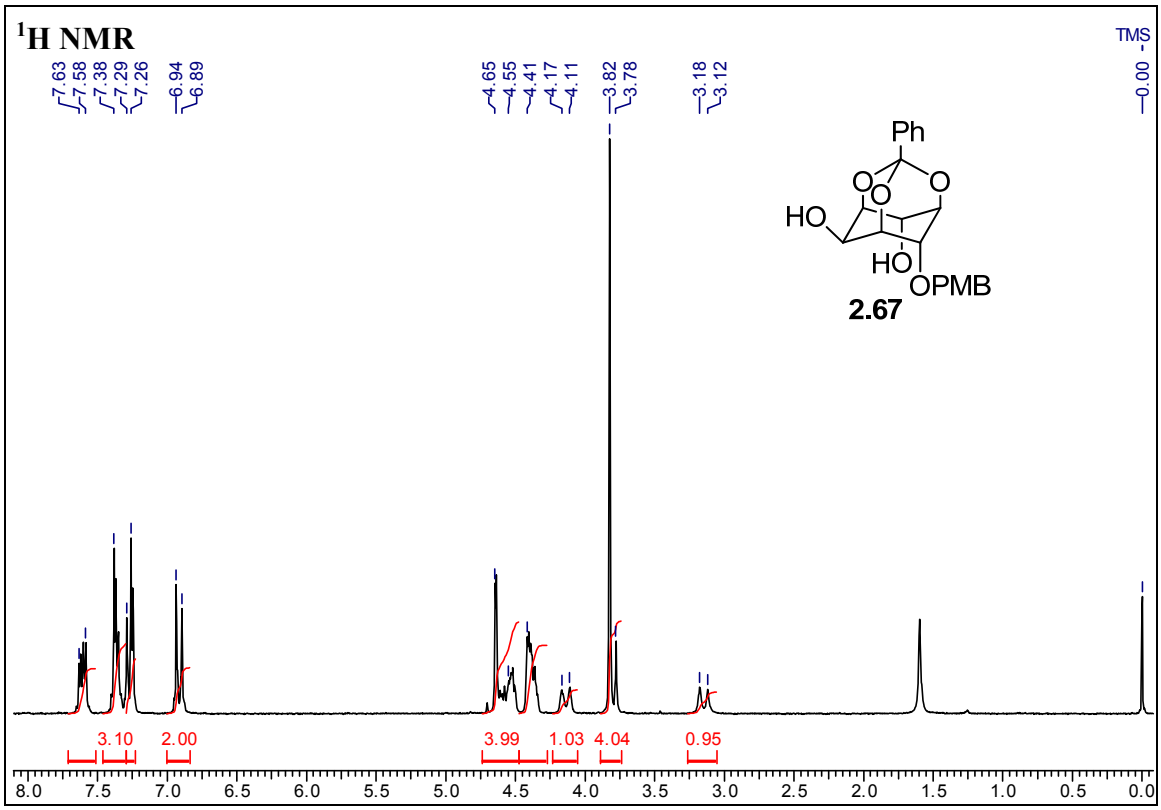
40
30
20
10
0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4.17
4.11
3.82
3.78
3.18
3.12
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Ph
O
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O
HO
HO
OPMB
2.67
3.10
2.00
3.99
1.03
4.04
0.95
8.0
7.5
7.0
6.5
6.0
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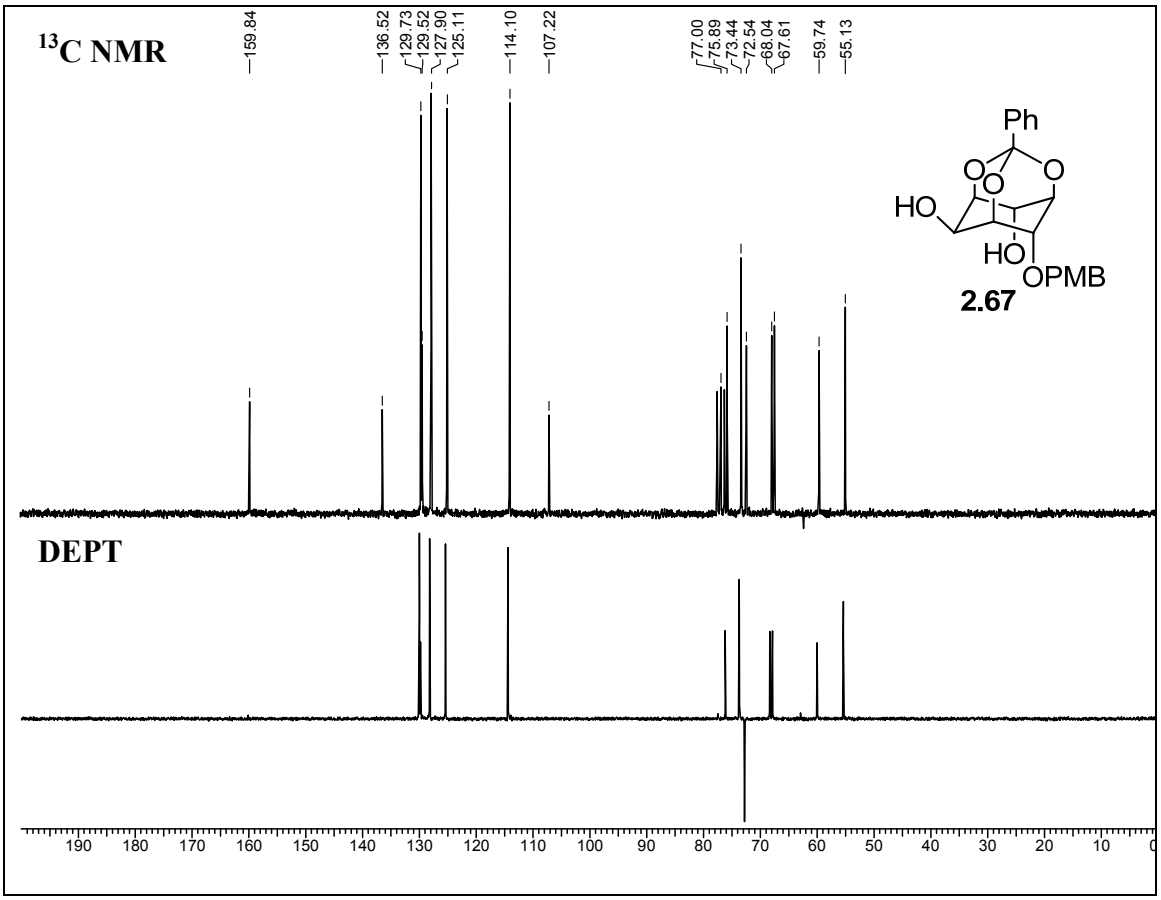
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129.52
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114.10
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72.54
68.04
67.61
59.74
55.13
Ph
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O
O
HO
HO
OPMB
2.67
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20
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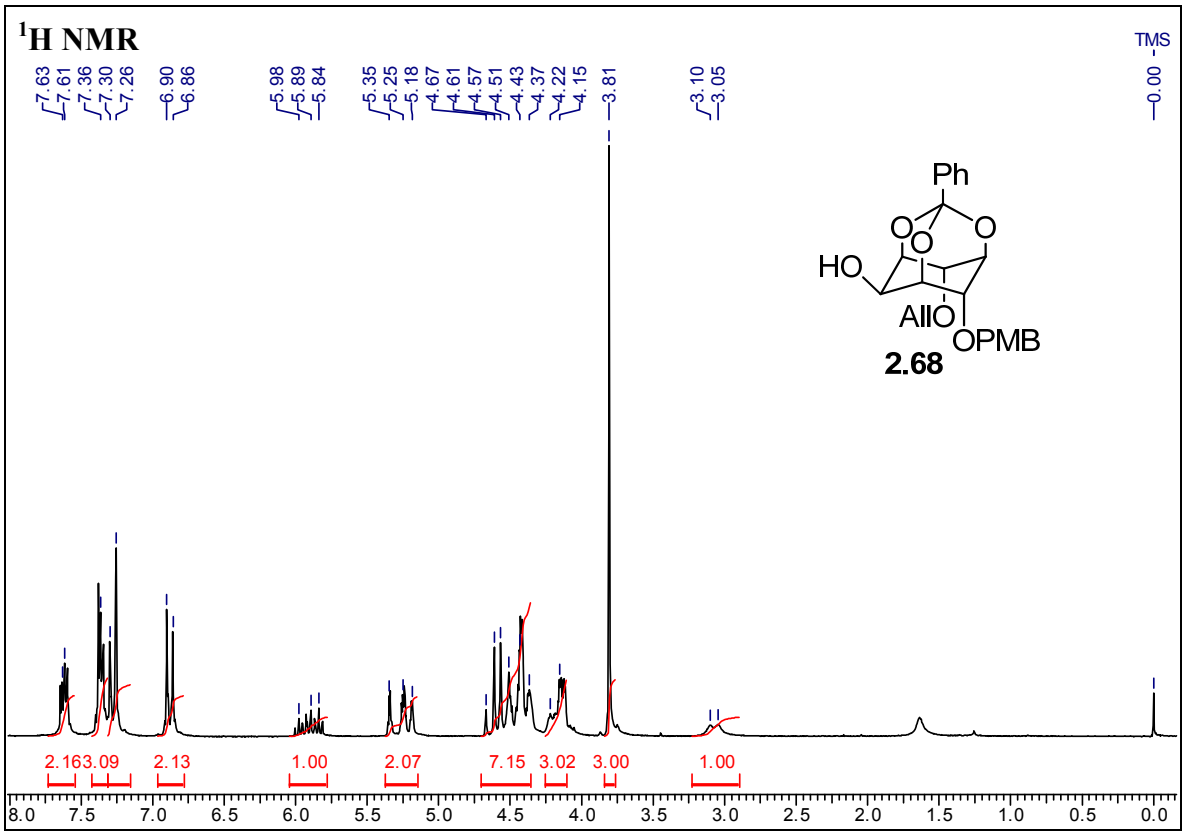
1H NMR
TMS
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7.61
7.36
7.30
7.26
6.90
6.86
5.98
5.89
5.84
5.35
5.25
5.18
4.67
4.61
4.57
4.51
4.43
4.37
4.22
4.15
3.81
3.10
3.05
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Ph
O
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O
HO
AllO
OPMB
2.68
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3.09
2.13
1.00
2.07
7.15
3.02
3.00
1.00
8.0
7.5
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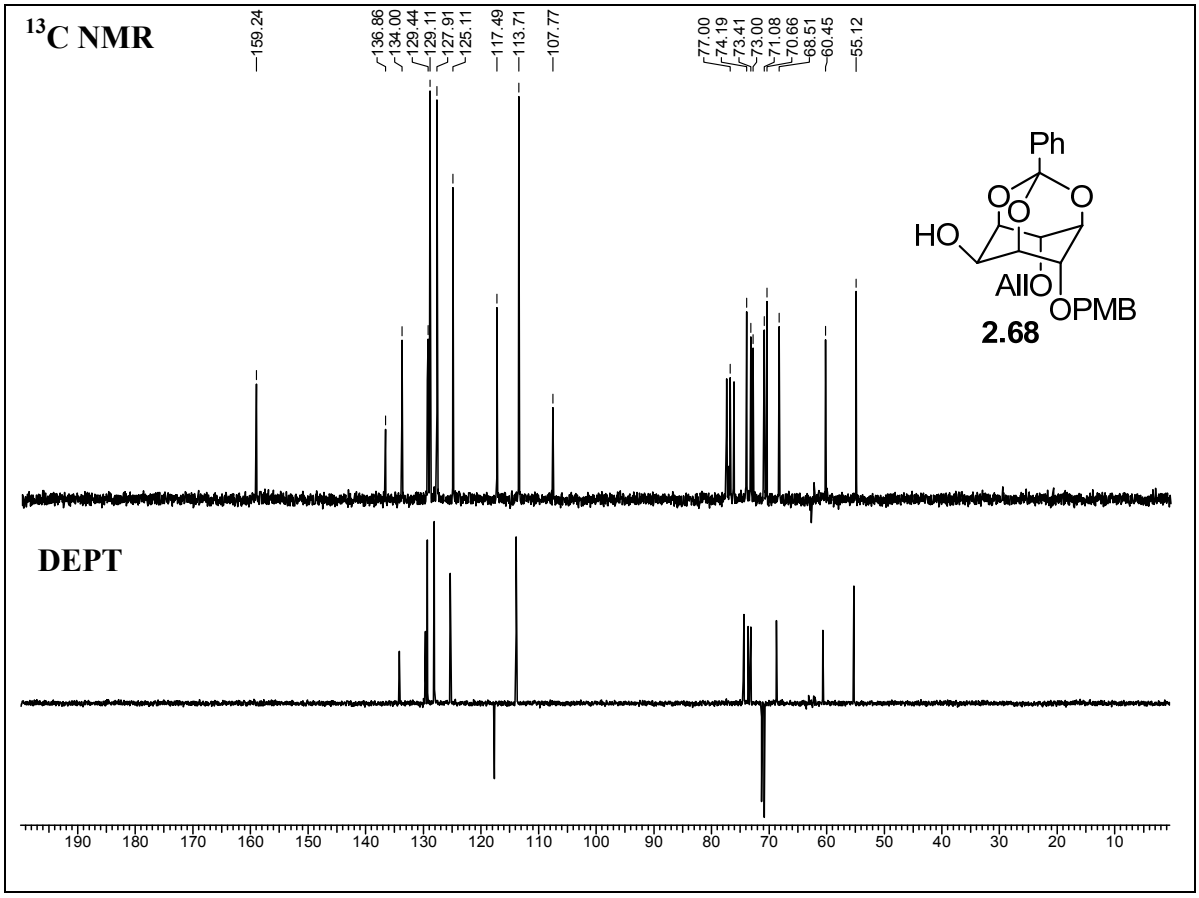
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134.00
129.44
129.11
127.91
125.11
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113.71
107.77
77.00
74.19
73.41
73.00
71.08
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68.51
60.45
55.12
Ph
O
O
O
HO
AllO
OPMB
2.68
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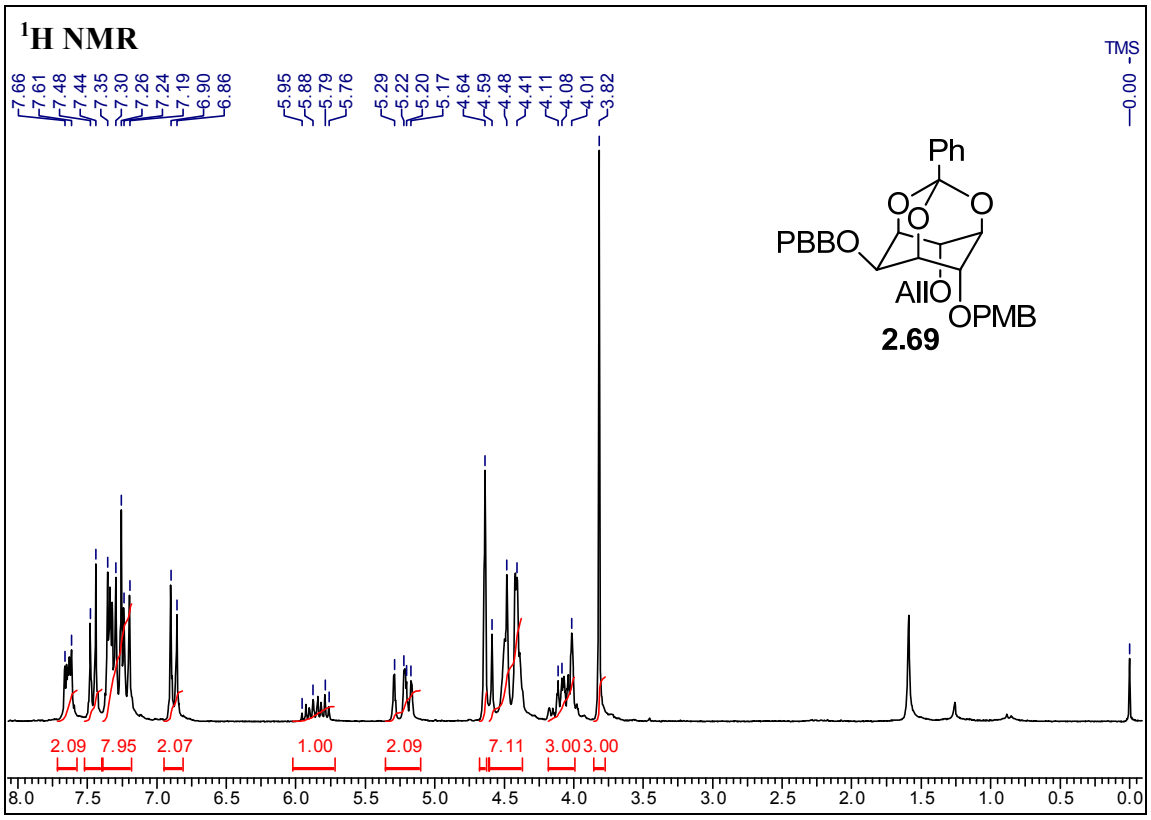
20
10


^{1}H NMR
TMS
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7.48
7.44
7.35
7.30
7.26
7.24
7.19
6.90
6.86
5.95
5.88
5.79
5.76
5.29
5.22
5.20
5.17
4.64
4.59
4.48
4.41
4.11
4.08
4.01
3.82
0.00
Ph
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O
O
PBBO
AllO
OPMB
2.69
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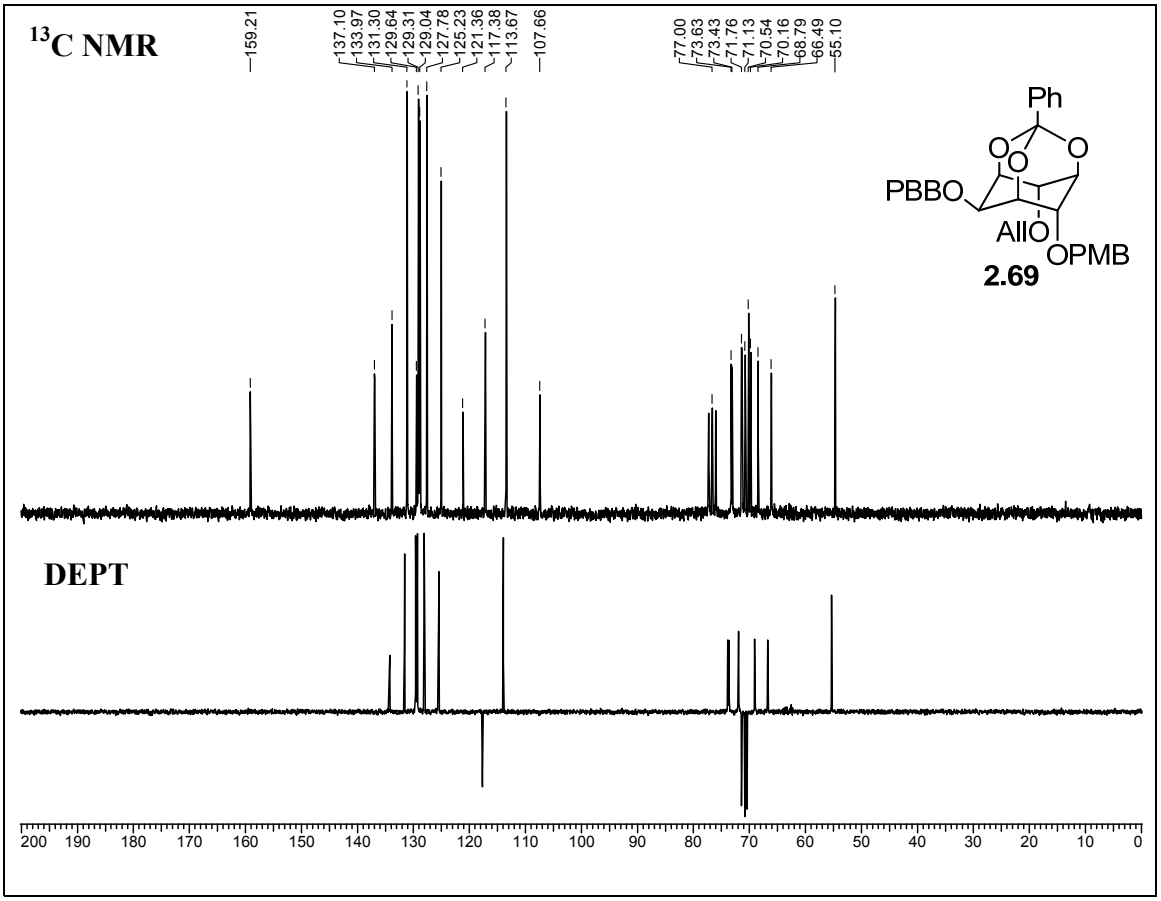
^{13}C NMR
159.21
137.10
133.97
131.30
129.64
129.31
129.04
127.78
125.23
121.36
117.38
113.67
107.66
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73.63
73.43
71.76
71.13
70.54
70.16
68.79
66.49
55.10
Ph
O
O
O
PBBO
AllO
OPMB
2.69
DEPT
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180
170
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150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

Chapter 3. Synthesis of orthogonally protected isomeric inositol derivatives from *myo*-inositol: Illustration of the potential of chelation controlled O-alkylation of *myo*-inositol derivatives

3.1. Introduction.

Realization of the importance of phosphoinositols in fundamental cellular processes[1] drove chemists to devise novel methods for the synthesis of cyclitol derivatives.[1,2] Cyclitols and their derivatives have been synthesized from different kinds of starting materials, such as naturally occurring inositols (*myo*- and *chiro*-inositols and their derivatives),[3] sugars (glucose, galactose, xylose etc.),[4] benzene and its derivatives (toluene, naphthalene, benzoquinone),[5] and norbornyl derivatives[6] (Chart 3.1). However,

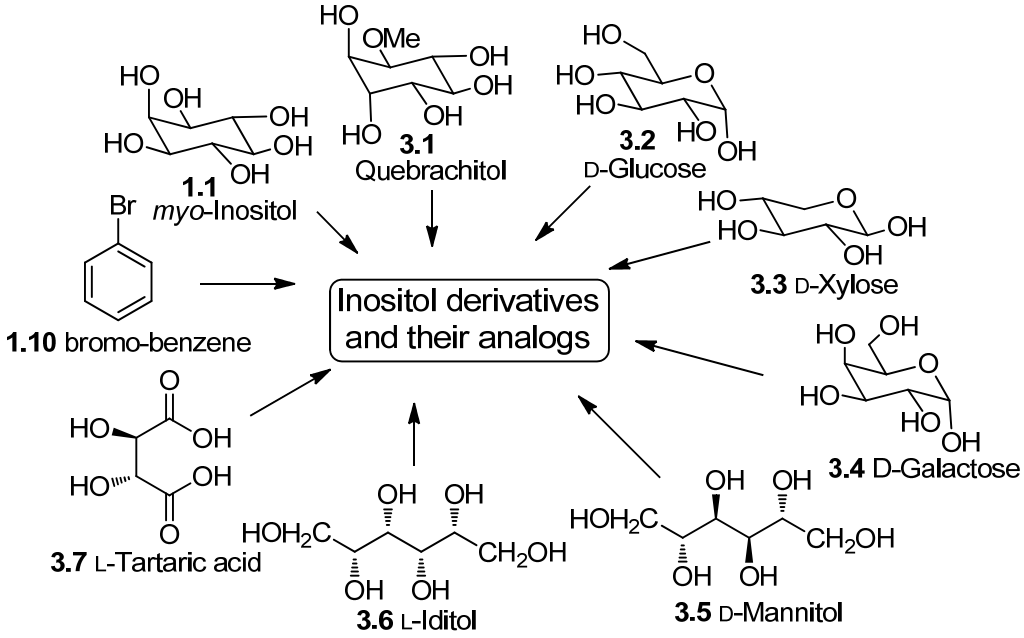
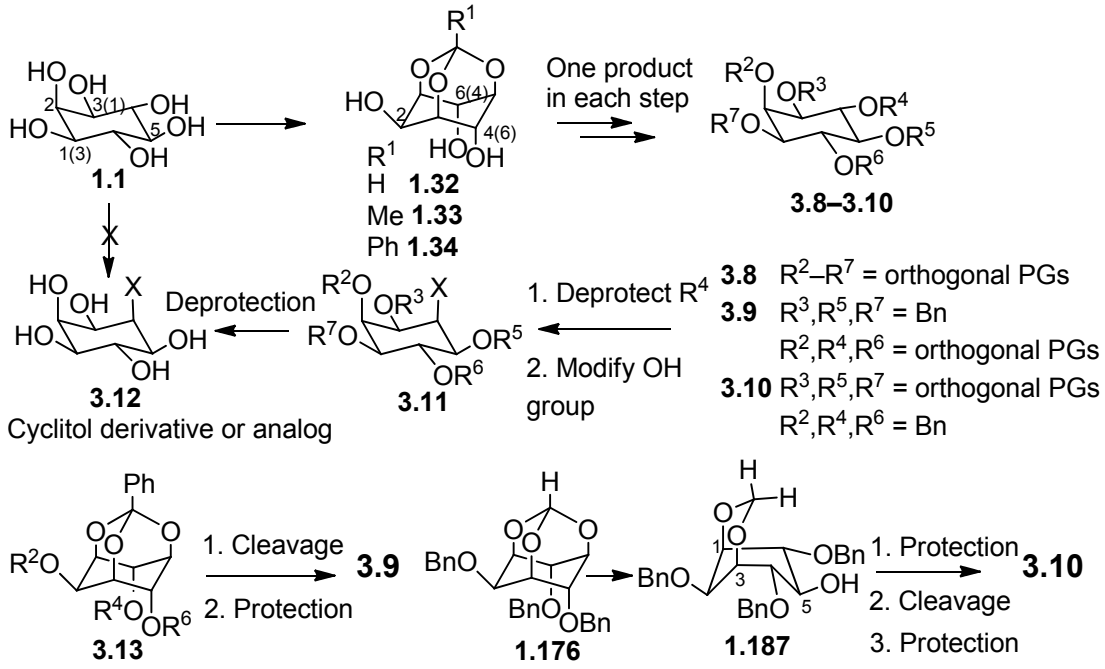


Chart 3.1.

scope of most of these methods are narrow as they were developed for the preparation of one or a few inositol derivatives (predominantly phosphoinositols) and hence are not flexible enough to provide a large number of isomeric cyclitol derivatives. Research efforts in chemistry and biology over the last two decades have resulted in a fairly good understanding of the role of *myo*-inositol and its phosphorylated derivatives[7] in cellular processes. However, access to isomeric inositol derivatives is needed to unravel the intricate details such as ligand structure recognition parameters, identification of specific inositol binding proteins, receptors[8] and their subunits.[9]

Efficient synthesis of cyclitol derivatives starting from naturally occurring *myo*-inositol largely depends on ones's ability to carry out selective reactions on its hydroxyl groups. As seen in previous chapters, considerable efforts have been made to understand the observed regioselectivity for the O-alkylation of *myo*-inositol derivatives with alkyl halides leading to the formation of ethers with the intention of devising better methods for the selective O-alkylation of partially protected inositol derivatives.[10] Due to subtle differences in the reactivity between the secondary hydroxyl groups in *myo*-inositol (or its derivatives), most of the reactions used for the protection of its hydroxyl groups result in the formation of isomeric products, and there are few exceptions to this rule.[11]

Although investigations on the chemistry of *myo*-inositol (and its derivatives) helped to qualitatively understand the relative reactivity of their hydroxy groups,[2] actual reaction conditions required to react any one of their hydroxyl groups exclusively were seldom realized in the laboratory. Enzyme-mediated regio and enantiospecific reactions of *myo*-inositol (or its derivatives)[12] are known, but they are not yet viable for organic synthesis, because most of these involve acylation or phosphorylation reactions, both of which are prone to migration among the hydroxyl groups. The availability of methods for exclusive reaction at any one hydroxyl group (Scheme 3.1) in *myo*-inositol and its



Scheme 3.1. Orthogonally protected inositol derivatives. Structural modification shown in the derivative **3.12** is for illustration.

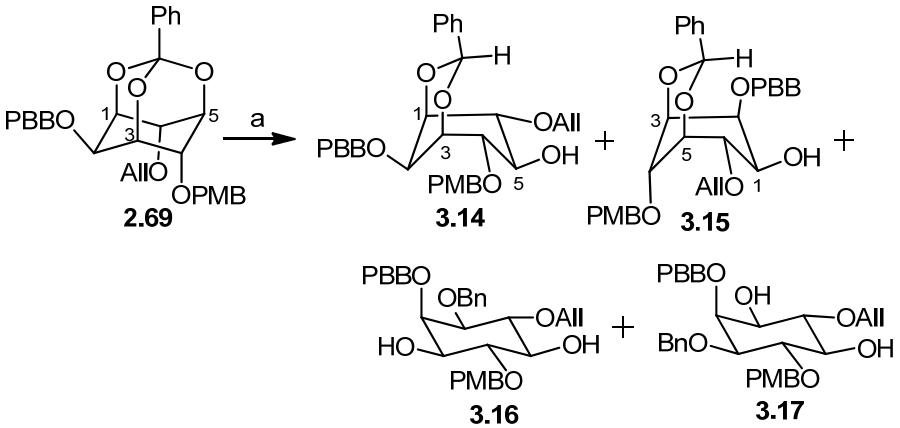
derivatives would be of immense utility to access cyclitol derivatives and many other kinds of compounds that can be obtained from cyclitols. The shortcomings mentioned above can be addressed if orthogonally protected isomeric inositol derivatives, such as **3.8**–**3.10** (Scheme 3.1), can be synthesized in a few steps, avoiding the formation of isomers during the reaction of the six hydroxyl groups of *myo*-inositol.

We envisioned that if we can devise an efficient method for the preparation of **3.9** and **3.10** and demonstrate the orthogonality of the protecting groups in these derivatives, we would achieve the goal of being able to manipulate all the six hydroxyl groups in *myo*-inositol and generate isomeric inositol derivatives and analogs. An inositol derivative such as **3.9**, can be prepared from orthogonally protected orthobenzoate **3.13** (eg. **2.69,** chapter 2, Scheme 2.10) whereas for accessing compound such as **3.10**, *myo*-inositol orthoformate can be used as shown in the scheme 3.1. Accordingly, this chapter describes efforts on the preparation of orthogonally protected *myo*-inositol derivatives such as **3.9** and **3.10** and their conversion to other isomeric cyclitols as well as the synthesis of a few cyclitol derivatives. The hydroxyl protecting groups in **3.9** and **3.10** were so chosen as to allow their deprotection, one at a time.

3.2. Results and Discussion.

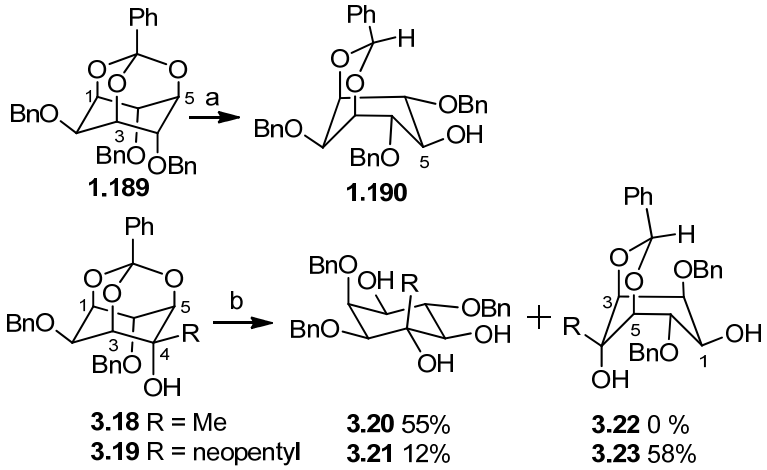
3.2.1. Preparation of a O-alkylated *myo*-inositol derivative suitable for the manipulation of C2-, C4- and C6-hydroxyl groups.

The preparation of *myo*-inositol orthobenzoate **2.69** carrying three orthogonal protecting groups at C2-, C4- and C6-positions was described in the second chapter (Section 2.2.3). We first attempted to release the C5-hydroxyl group in the orthobenzoate **2.69** by its reduction with limited quantity of DIBAL-H. This reaction resulted in the formation of a mixture of products from which the required benzylidene acetal **3.14** (Scheme 3.2) could be isolated in 60% yield. Other minor products were isomeric benzylidene acetal (probably **3.15**) and mixture of diastereoisomeric diols **3.16** and **3.17** (14%).We attempted the reduction of **2.69** since the reduction of the orthobenzoate moiety in the symmetric tribenzyl ether **1.189** (Scheme 3.3) with DIBAL-H is known to result in the release of the C5-hydroxyl group exclusively.[13] Recent reports on the cleavage of the orthoester moiety in *myo*-inositol orthoesters suggest that the extent of selectivity during



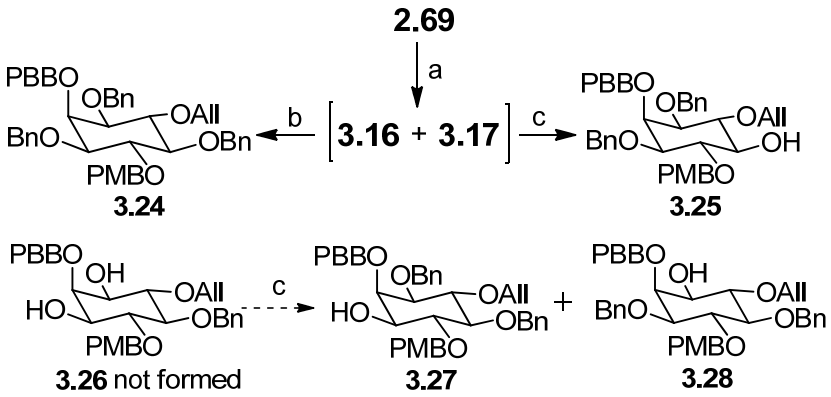
Scheme 3.2. (a) CH_2Cl_2, DIBAL-H (2.2 eq.), –10 °C–rt, 60% (for **3.14**).

cleavage with DIBAL-H is sensitive to the groups present in the molecule (Scheme 3.3).[14]



Scheme 3.3. (a) CH_2Cl_2, DIBAL-H (2.0 eq.), 97%; (b) CH_2Cl_2, DIBAL-H (3.5 eq.), rt, 12 h.

Reduction of the orthobenzoate moiety in **2.69** with an excess of diisobutylaluminium hydride (DIBAL-H) gave a mixture of isomeric diols **3.16** and **3.17** (Scheme 3.4). This was confirmed by benzylation of the mixture of diols **3.16** and **3.17** using one equivalent of benzyl bromide and sodium hydride which resulted in a single product **3.25** (resulting from selective benzylation at the 1(3)-hydroxy group). Had the isomeric diol **3.26** formed during the cleavage of the orthobenzoate **2.69** with DIBAL-H (due to C1/3-O cleavage), subsequent O-benzylation would have resulted in the formation of two isomeric dibenzyl ethers (**3.27** and **3.28**). Benzylation of the mixture of **3.16** and **3.17** using an excess of benzyl bromide gave the tribenzyl ether **3.24** carrying orthogonal

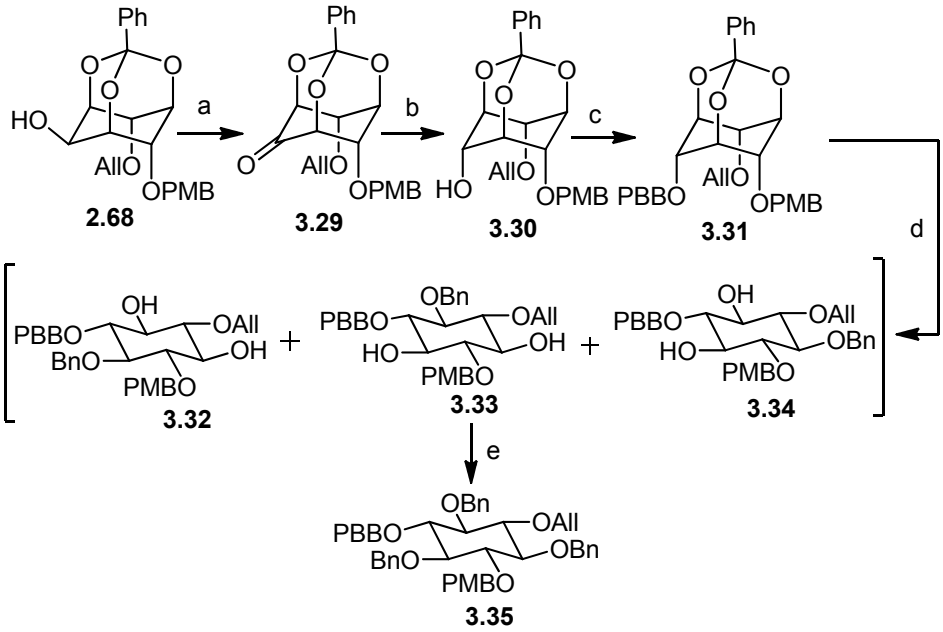


Scheme 3.4. (a) CH_2Cl_2, DIBAL-H (5.5 eq.), 78%; (b) DMF, NaH (x's), BnBr (x's), 92%; (c) DMF, NaH (1.1 eq.), BnBr (1.0 eq.), 57% (**3.25**).

protecting groups at the C2-, C4- and C6-positions of *myo*-inositol. The protected hydroxyl groups at these positions could now be released and the resulting hydroxyl group modified as desired.

3.2.2. Preparation of a *scyllo*-inositol derivative carrying orthogonal protecting groups.

Obtaining a *scyllo*-inositol derivative starting from a *myo*-inositol derivative requires inversion of the C2-hydroxyl group to generate an all *trans*-configuration on the cyclohexane ring. This was achieved by inverting the hydroxyl group in the *myo*-inositol orthobenzoate derivative **2.68** (Chapter 2, Scheme 2.10), which was an intermediate during the preparation of **2.69**. The C2-hydroxyl group in **2.68** was oxidized using Swern oxidation condition and the resulting ketone was reduced using sodium borohydride to get exclusively the *scyllo*-inositol orthobenzoate derivative **3.30** (Scheme 3.5). A *scyllo*-inositol derivative **3.35** containing three orthogonal protecting groups could be obtained by (a) *O*-alkylation (of the orthobenzoate **3.30**) with 4-bromobenzyl bromide; (b) reduction of the orthobenzoate moiety in **3.31** with excess DIBAL-H [theoretically three diols are possible **3.32–3.34**; but we believe only two diols formed in the reaction, as indicated by TLC analysis of reaction mixture and similar observation in scheme 3.4)]; and (c) benzylation of the diols obtained in (b).



Scheme 3.5. (a) CH_2Cl_2, $(COCl)_2$, DMSO, NEt_3,–78 °C–rt, 83%; (b) THF, MeOH, $NaBH_4$, 90%; (c) DMF, NaH, PBBBr, 94%; (d) CH_2Cl_2, DIBAL-H (5.5 eq.); (e) DMF, NaH, BnBr, 68%.

myo-Inositol derivatives have earlier been converted into *scyllo*-inositol derivatives,[15] but none of these provided a versatile derivative that allowed further manipulation of their hydroxyl groups. Most of the *scyllo*-inositol derivatives reported in the literature were intermediates during the synthesis of particular targeted cyclitol derivatives and often were separated from mixture of products, resulting in low yields (Chart 3.2 shows some of the protected *scyllo*-inositol derivatives reported in the literature).

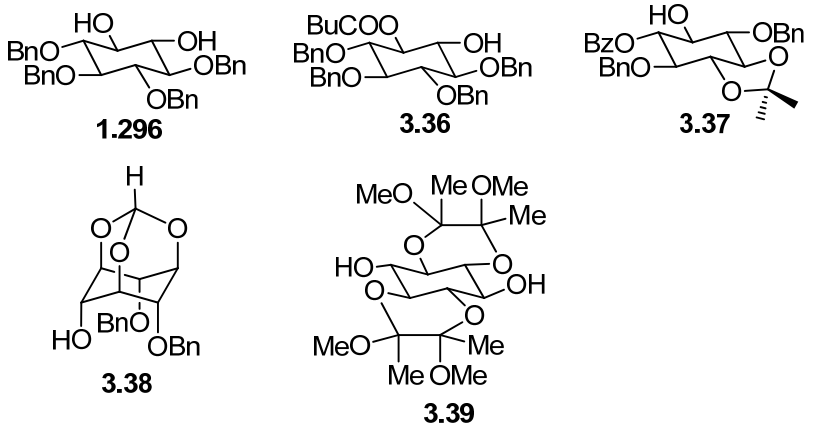
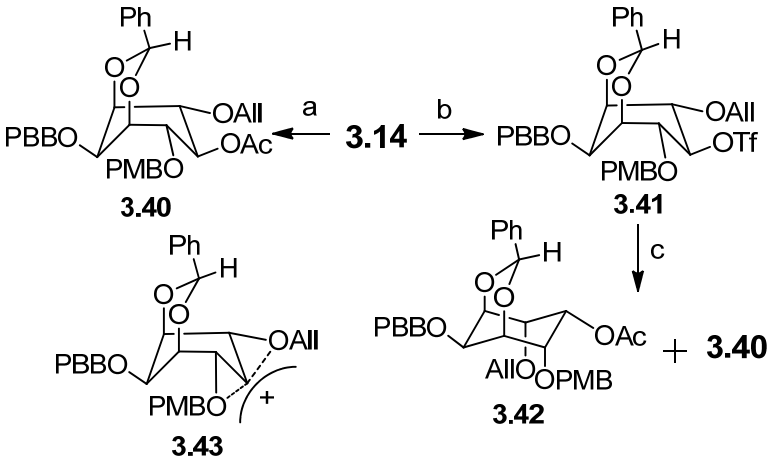


Chart 3.2.

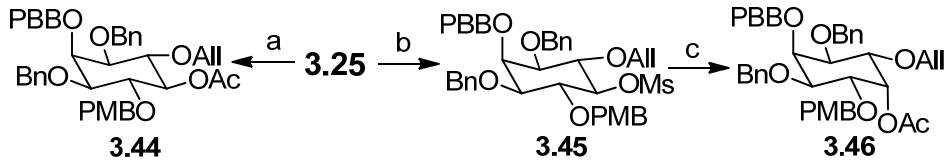
3.2.3. Preparation of a *neo*-inositol derivative carrying orthogonal protecting groups.

We first attempted to prepare a *neo*-inositol derivative by inversion of the C5-hydroxy group in the benzylidene acetal **3.14** by S_N2 substitution on its triflate **3.41** with cesium acetate (Scheme 3.6). This however, resulted in a mixture of products consisting of *neo*- and *myo*- isomers. A comparison of the NMR spectrum of an authentic sample of the *myo*-acetate **3.40**, with that of the mixture of acetates obtained established the poor selectivity (**3.42**:**3.40,** 1:0.45) of this nucleophilic substitution reaction. Reason for the formation of a mixture of products could be the sterically demanding approach of the nucleophile, acetate ion, as the leaving group (triflate) is flanked by substituents on both sides, in addition to the inherent rigidity of the molecule because of the presence of the benzylidene acetal. Also C4- and C6- substituents can help stabilize the carbocation formed (**3.43**) and thus lead to S_N1 reaction, giving both the possible diastereomers.



Scheme 3.6. (a) Py, Ac_2O, 93%; (b) CH_2Cl_2, Py, Tf_2O, –40 °C–rt, 2 h, 95% (c) DMF, CsOAc, 50 °C for 24 h then 100 °C for 4 h, 87%.

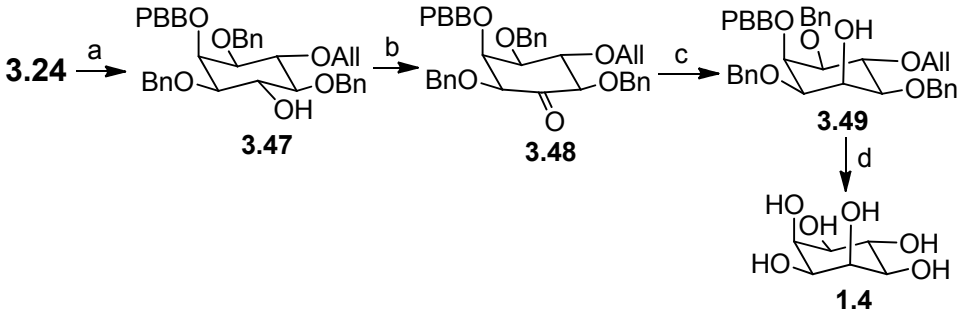
Although the bicyclic *myo*-inositol derivative **3.14** could not provide the corresponding *neo*-inositol derivative exclusively, the dibenzyl ether **3.25** could be converted to the desired *neo*-inositol derivative **3.46** exclusively, *via* its mesylate **3.45** as in scheme 3.7. Although, *neo*-inositol has been prepared from various starting materials, (1,2:5,6-di-O-isopropylidene-*chiro*-inositol,[16] furan, *myo*-inositol, D-mannitol, bromobenzene, *p*-benzoquinone) none of these are suitable for the manipulation of its hydroxyl groups since they don't carry orthogonal protecting groups as in **3.46**.



Scheme 3.7. (a) Py, Ac_2O, 92%; (b) Py, MsCl, 95%; (c) DMF, CsOAc, 18-crown-6, 140 °C, 90%.

3.2.4. Preparation of an *epi*-inositol derivative carrying orthogonal protecting groups.

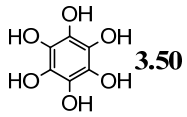
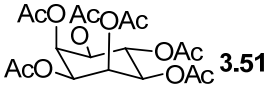
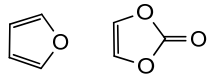
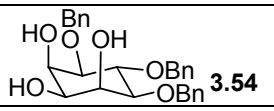
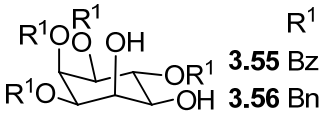
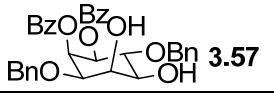
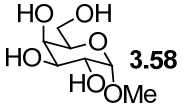
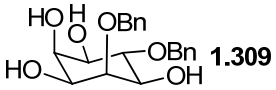
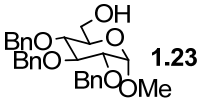
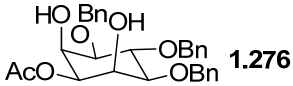
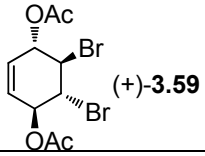
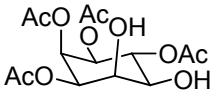
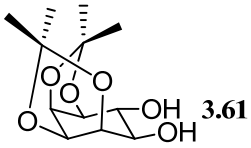
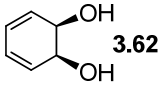
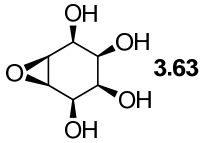
The *epi*-inositol derivative **3.49** was prepared from the *myo*-inositol derivative **3.24** as shown in scheme 3.8. Cleavage of the 4-methoxybenzyl (PMB) ether in **3.24**, followed by IBX oxidation afforded the ketone **3.48**. Sodium borohydride reduction of the ketone **3.48** was stereoselective to give the *epi*-inositol derivative **3.49** exclusively. Global deprotection of **3.49** gave *epi*-inositol (**1.4**) in an overall yield of 33% from *myo*-inositol.



Scheme 3.8. (a) CH_2Cl_2, H_2O, DDQ, 93%; (b) AcOEt, IBX, reflux; (c) THF, MeOH, $NaBH_4$, 93%; (d) i. MeOH, H_2O, Pd-C, TsOH, reflux, 92%; ii. EtOH, THF, TFA, Pd-$(OH)_2$/C, H_2, rt, 94%.

A comparison of the reported methods with the present work is shown in table 3.1. Yield of *epi*-inositol in previously developed methods was in the range 6–15% from *myo*-inositol [3a,3b,3d] and 1–21% from other starting materials.[4a,4b,5a,5b,5c,5g,6a,17] Apart from the lesser overall yield, many of these procedures result in a mixture of isomeric products from which the desired product needs to be separated thus making the procedure laborious. Some of these reported methods[3b, 4b, 6a] are outlined in scheme 3.9 for illustration. Attempts at the synthesis of *epi*-inositol were made perhaps because of its ability to affect the regulation of the *myo*-inositol biosynthetic pathway.[18] *epi*-Inositol has also been evaluated as a potential antidepressant drug that could interact with lithium and *myo*-inositol receptors in the brain.[18, 19]

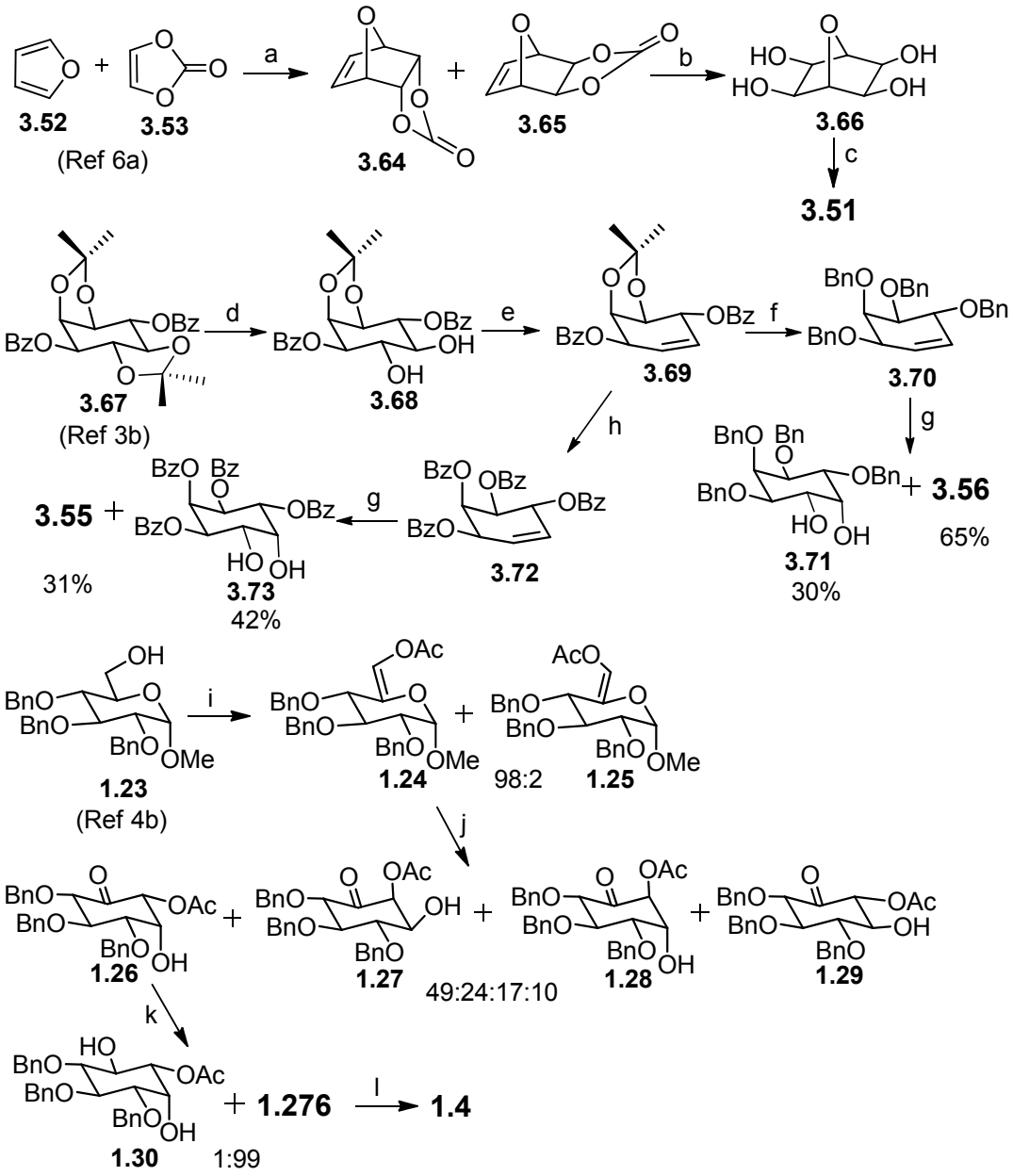
Table 3.1. Synthesis of *epi*-inositol (**1.4**); comparison with methods reported in the literature.

Entry	Starting material	Steps	Overall Yield[a] (%)	*epi*-Inositol derivative obtained[b]
1	 **3.50**	1	<6[5a]	 **3.51**
2	 **3.52** **3.53**	3	<1[6a]	**3.51**
3	**1.1**	12	15[3a]	 **3.54**
4	**1.1**	4	6[3b]	 **3.55** Bz **3.56** Bn
5	**1.1**	9	6[3d]	 **3.57**
6	 **3.58**	8	13[4a]	 **1.309**
7	 **1.23**	4	21[4b]	 **1.276**
8	 (+)-**3.59**	9	7[17]	 (-)-**3.60**
9	**1.10**	6	1[5g]	 **3.61**
10	 **3.62**	4	8[5c]	 **3.63**
11	**1.1**	**10**	**33**[c]	**3.49**

[a] Overall yield refers to *epi*-inositol or its hexa-acetate (except entry 4 and 5 where the yield is for **3.55**, **3.56** and **3.57**).

[b] In all the cases the protected *epi*-inositol derivative has been converted to *epi*-inositol (**1.4**) or its hexa-acetate **3.51** (except entry 4 and 5).

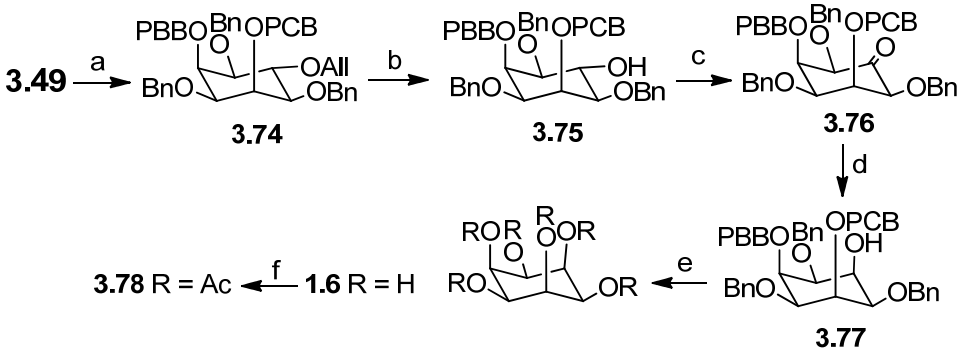
[c] Present work.



Scheme 3.9. (a) sealed tube, 120 °C, 12 h, 17% (**3.64**), 4% (**3.65**); (b) i. EtOAc, Py, OsO_4; ii. NaOH, 6.6%; (c) i. AcOH, H_2O, H_2SO_4, heated on water bath for 14 h; ii. Ac_2O, H_2SO_4, 40 °C, 24 h. paper chromatography for identifying the *epi*-inositol; (d) CH_2Cl_2, MeOH, AcCl (cat.), 75%; (e) Toluene, PPh_3, imidazole, I_2, reflux, 77%; (f) i. AcOH, H_2O, 100 °C; ii. MeOH, NaOMe, reflux; iii. DMF, NaH, BnBr, 87%; (g) Acetone, H_2O, OsO_4, NMO; (h) i. AcOH, H_2O, 100 °C; ii. Py, BzCl, 91%; (i) i. Ph-H, TFA, Py, DMSO, DCC; ii. Et_3N, Ac_2O, DMAP, 1,2-dichloroethane, 100 °C, 2 h, 83%; (j) Dioxane, H_2O, $PdCl_2$ (cat.), 60 °C, 3 h, 81%; (k) MeOH, $NaBH_4$(1.5 eq.), 97%; (l) i. 10 N NaOH, MeOH, ii. MeOH, H_2, $Pd(OH)_2$/C, 73%.

3.2.5. Preparation of a *cis*-inositol derivative carrying orthogonal protecting groups.

The *epi*-inositol derivative **3.49** could be transformed into the *cis*-inositol derivative **3.77** (Scheme 3.10) by (a) protection of the axial hydroxy group; (b) cleavage of the allyl ether[20] to release the required equatorial hydroxyl group; (c) oxidation of the free hydroxyl group in **3.75** to obtain the corresponding keotne; and (d) stereoselective hydride reduction of the inosose **3.76** (resulting in overall inversion of the C4(6)-hydroxyl group in *myo*-inositol) to afford the *cis*-inositol derivative **3.77**. Global deprotection of all the hydroxyl groups by hydrogenolysis gave *cis*-inositol, which was isolated as its hexaacetate **3.78** for convenience. The overall yield of the hexaacetate **3.78** from *myo*-inositol was 25%; free *cis*-inositol (**1.6**) can be generated by aminolysis of the acetates in **3.78**.[21]

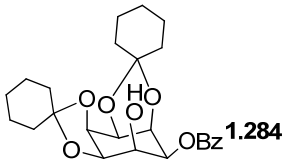
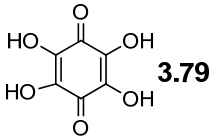
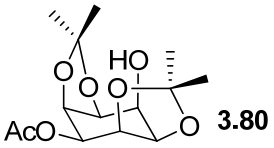
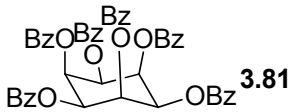


Scheme 3.10. (a) DMF, NaH, PCBBr, 96%; (b) Ph-CH_3, $NiCl_2$(dppp), DIBAL-H, 83%, (c) CH_2Cl_2, $(COCl)_2$, DMSO, Et_3N, –78 °C–rt; (d) THF, MeOH, $NaBH_4$, 91%; (e) EtOH, THF, TFA, $Pd(OH)_2/C$, H_2, rt; (f) Py, Ac_2O, 110 °C, 86%.

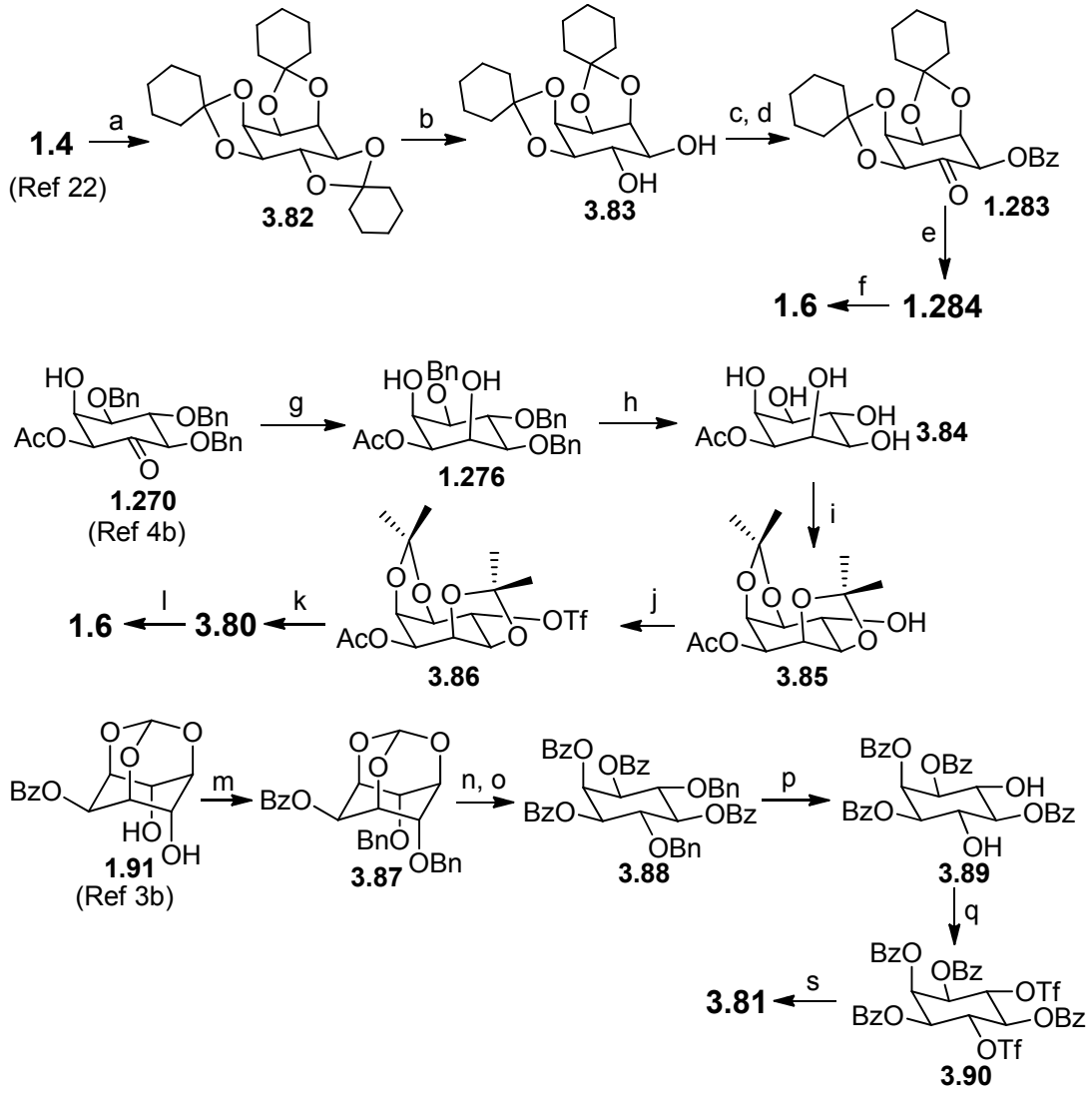
A comparison of the method described here with the procedures previously reported (Table 3.2) for the preparation of *cis*-inositol,[3b, 4b, 5b, 22, 23] clearly reveals the efficiency of our method. Synthetic sequences pertaining to entry 1, 4 and 5 in table 3.2 are summarized in scheme 3.11. Methods in entries 2 and 3 (Table 3.2) involve single step since *cis*-inositol was obtained as one of the products of hydrogenation of tetrahydroxy *p*-benzoquinone[23] or hexahydroxybenzene.[5b] It is pertinent to mention that the number of steps in our method (Entry 6, Table 3.2) are more than other methods, since our aim was to obtain a *cis*-inositol derivative carrying orthogonal protecting groups that would allow further manipulation of the inositol skeleton and hence the preparation of *cis*-inositol itself is incidental. *cis*-Inositol (**1.6**) is an interesting compound as it readily forms strong complexes with metal ions and oxyacid anions,[24] (e.g., borate) because of the three syn-

axial hydroxyl groups. *cis*-Inositol was first isolated as one of the many products formed in the high-pressure hydrogenation of tetrahydroxyquinone over Raney nickel.[5a]

Table 3.2. Synthesis of *cis*-inositol (**1.6**); comparison with methods reported in the literature.

Entry	Starting Material	No. of steps	Overall Yield[a] (%)	*cis*-Inositol derivative obtained[b]
1	**1.4**	7	25[22]	 **1.284**
2	 **3.79**	1	31[23]	**1.6**
3	**3.50**	1	20[5b]	**1.6**
4	**1.23**	9	16[4b]	 **3.80**
5	**1.1**	7	9[3b]	 **3.81**
6	**1.1**	**12**	**25**[c]	**3.77**

[a] Overall yield refers to that of *cis*-inositol (except entry 5).
[b] In all the cases the protected *cis*-inositol derivative shown was converted to *cis*-inositol (**1.6**) (except entry 5).
[c] Present work.

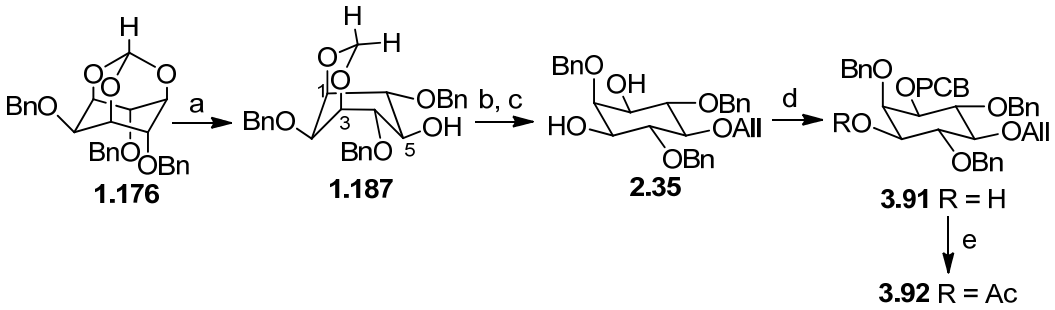


Scheme 3.11. (a) Ph-H, cyclohexanone, TsOH, 60%; (b) i. light petroleum, Ph-H, EtOH, reflux; ii. TsOH, EtOH, 71%; (c) Py, BzCl, 51%; (d) Ph-H, DMSO, Ac_2O, reflux, 50%; (e) $CHCl_3$, MeOH, $NaBH_4$, 96%; (f) i. MeOH, Na metal, 99%; ii. H_2O, AcOH, steam bath, 2 h, 76%; (g) $NaBH_4$, MeOH, 97%; (h) H_2, $Pd(OH)_2/C$, MeOH, 100%; (i) concd. H_2SO_4, acetone, 83%; (j) Tf_2O, Py, CH_2Cl_2, 89%; (k) i. CF_3COOCs, 18-crown-6, toluene, DMF, 80 °C; ii. satd. $NaHCO_3$, 78%; (l) TFA, MeOH, 60 °C; (m) BnBr, NaH, mol. sieve (4Å), DMF, 82%; (n) TsOH, MeOH, reflux; (o) BzCl, Py, 91%; (p) Pd(OH)/C, MeOH, H_2 (50 psi), 96%; (q) Tf_2O, CH_2Cl_2, Py, –42 °C–rt, 89%; (s) KOBz, DMSO, 100 °C, 32%.

3.2.6. Preparation of a O-alkylated *myo*-inositol derivative suitable for the manipulation of C1-, C3- and C5-hydroxyl groups.

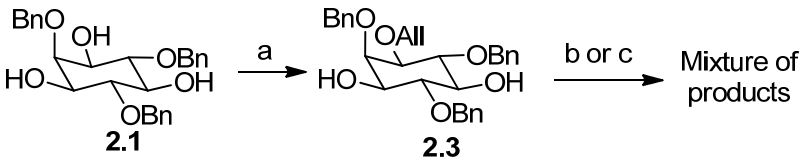
A partially protected *myo*-inositol, which allows modification of C1-, C3- and C5-hydroxyl groups, was prepared starting from the tribenzyl ether of *myo*-inositol orthoformate (Scheme 3.12). The C5-hydroxyl group in **1.176** was released by cleavage with DIBAL-H to obtain **1.187**.[13a] O-allylation of **1.187** followed by hydrolysis of the acetal gave the symmetric 1,3-diol **2.35**. Alkylation of one of the hydroxyl groups in **2.35**

with (4-chloro)benzyl bromide, provided **3.91** which allows modification at the C1-, C3- and C5-hydroxyl groups of *myo*-inositol.



Scheme 3.12. (a) DIBAL-H, DCM, 100%; (b) DMF, NaH, AllBr; (c) MeOH, concd. HCl, reflux, 94%; (d) DMF, NaH, PCBBr, 48%; (e) Py, Ac_2O.

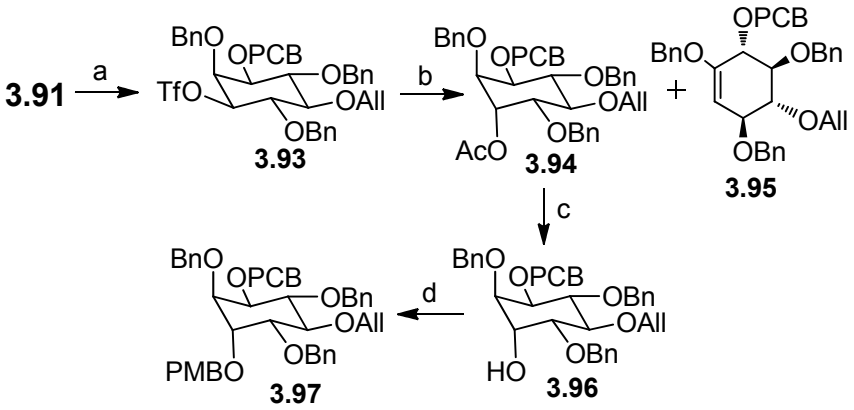
We initially attempted the preparation of a *myo*-inositol derivative like **3.10** (see scheme 3.1), from the triol **2.1** (Scheme 3.13).[11b] Allylation of the of the triol **2.1** with one equivalent sodium hydride and allyl bromide led to exclusive formation of the corresponding allyl ether **2.3**.[25] However, attempts at selective O-alkylation of the C3-hydroxyl group with sodium hydride (or butyllithium) and 4-methoxybenzyl chloride resulted in a mixture of products. No attempt was made to separate and identify these products since this reaction did not appear to be synthetically viable.



Scheme 3.13. (a) DMF, NaH, AllBr, 61%; (b) *n*BuLi, THF, PMBCl, DMF; (c) DMF, NaH, PMBCl.

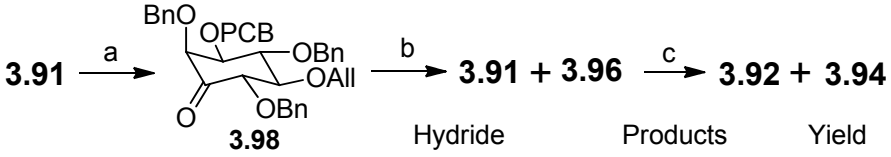
3.2.7. Preparation of a *chiro*-inositol derivative carrying orthogonal protecting groups.

A racemic *chiro*-inositol derivative **3.94** was obtained by the nucleophilic displacement reaction on the triflate **3.93** with cesium acetate (Scheme 3.14). The cyclohexene derivative **3.95** was also generated as a minor product in this reaction. The acetate **3.94** on aminolysis followed by alkylation with 4-methoxybenzyl chloride led to an orthogonally protected racemic *chiro*-inositol derivative **3.97**.



Scheme 3.14. (a) CH_2Cl_2, Py, Tf_2O, –15 °C–rt, 90%; (b) Ph-H, CsOAc, 18-crown-6, reflux, 70%; (c) MeOH, *i*$BuNH_2$, reflux; (d) DMF, NaH, PMBCl, 0 °C–rt, 94%.

We also attempted inversion of the C1(3)-hydroxyl group by sequential oxidation and hydride reduction, since this procedure had given a single isomer during the synthesis of the *epi*-inositol derivative (section 3.2.4). Swern oxidation of the *myo*-inositol derivative **3.91** proceeded smoothly to afford the corresponding inosose in very good yield (Scheme 3.15). However, hydride reduction of the inosose **3.98** using various reducing agents was not selective and gave a mixture of *myo*- and *chiro*- inositol derivatives. The ratio of the



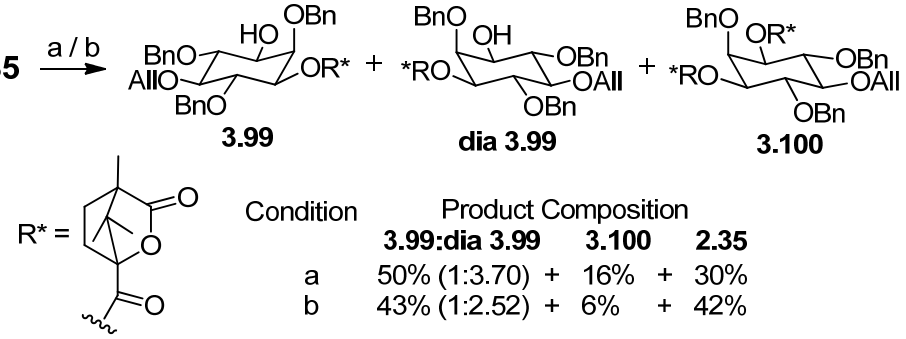
Hydride	Products *myo*:*chiro* Ratio	Yield (%)
DIBAL-H	**3.92:3.94** = 2.6:1	89
KBH_4	**3.92:3.94** = 0.94:1	95
Red-Al	**3.92:3.94** = 0.5:1	95
$NaBH_4$	**3.91:3.96** = 1:1	90
$LiBH_4$	**3.91** major (TLC)	

Scheme 3.15. (a) $(COCl)_2$ (2.4 eq.), DMSO (3.3 eq.), Et_3N (5.5 eq.), CH_2Cl_2, –78 °C–rt, 89%; (b) THF, reducing agent (hydride), 0 ^oC–rt, 30 min; (c) Py, Ac_2O.

two isomers present in the mixture of products (except in the case of reduction with lithium borohydride and sodium borohydride) was estimated by ^1H NMR spectrum of the mixture of acetates. No attempt was made to separate the two isomeric inositol derivatives since the inversion of the C1(3)-hydroxyl group in **3.91**, *via* its triflate gave better yield of the *chiro*-inositol derivative **3.94**. A perusal of the earlier reports[3c,3e] reveals that much time and effort has been invested in attempts to prepare protected *chiro*-inositol derivatives such as **3.97** (starting from *chiro*-inositol), with little success.

Since we could synthesize the racemic *chiro*-inositol derivative **3.97** from the *myo*-inositol derivative **2.35** (Scheme 3.12) in respectable yield, we attempted the

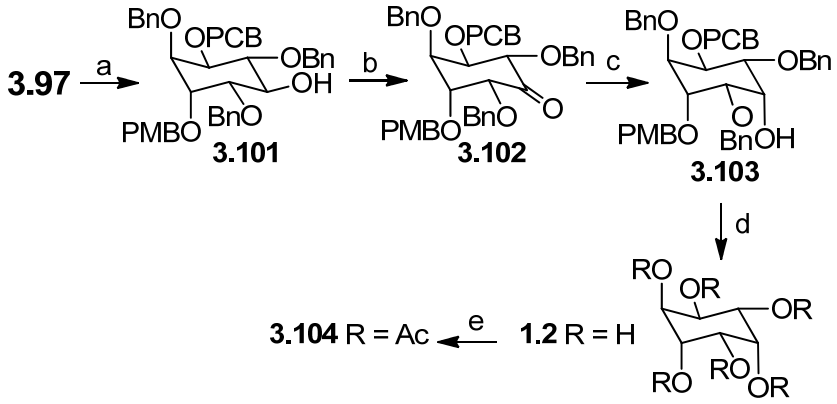
desymmetrization of the diol **2.35**, which would give access to a chiral derivative of *chiro*-inositol. Accordingly, the diol **2.35** was reacted with camphanic acid chloride in the presence of a base (pyridine or triethyl amine) which resulted in the formation of a mixture of diastereoisomers (Scheme 3.16). Since the diastereoselectivity was not impressive, this was not pursued further.



Scheme 3.16. (a) Et_3N, (–)-(1S)-R*Cl, DMAP, CH_2Cl_2; (b) Py, (–)-(1S)-R*Cl, DMAP, DCM.

3.2.8. Preparation of a *allo*-inositol derivative carrying orthogonal protecting groups.

The *allo*-inositol derivative **3.103** could be obtained from the racemic *chiro*-inositol derivative **3.97**, by a sequence of three high yielding reactions (Scheme 3.17). The allyl

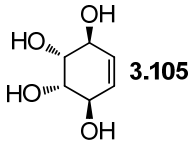
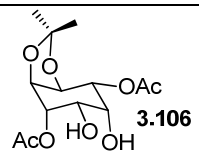
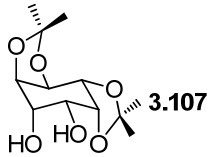
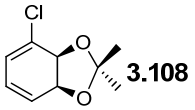
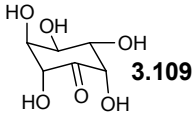
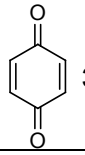
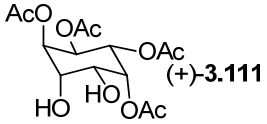
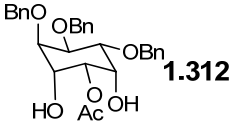
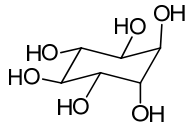
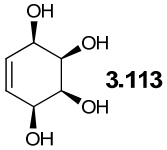
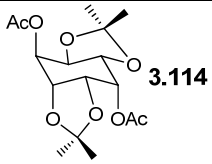


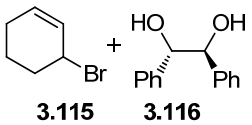
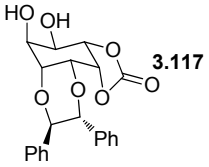
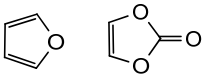
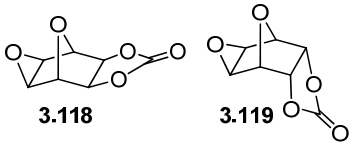
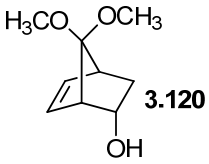
Scheme 3.17. (a) Ph-CH_3, $NiCl_2$(dppp), DIBAL-H, 86%; (b) i. CH_2Cl_2, $(COCl)_2$, DMSO, Et_3N, –78 °C–rt; (c) THF, MeOH, $NaBH_4$, 96% (from **3.101**); (d) EtOH, THF, TFA, $Pd(OH)_2/C$, H_2, rt; (e) Py, Ac_2O, 80 °C, 90% (from **3.103**).

ether in **3.97** was cleaved and the resulting free hydroxyl group was oxidized (Swern's method); the inosose so obtained was reduced with sodium borohydride leading to the *allo*-inositol derivative **3.103**. *allo*-Inositol (isolated as its hexaacetate **3.104**) was prepared by global deprotection of the hydroxyl groups (in **3.103**) in an overall yield of 28% from *myo*-inositol. Free *allo*-inositol (**1.2**) can be generated by aminolysis of the hexaacetate

3.104.[21] For comparison (Table 3.3), the yield of *allo*-inositol obtained in methods reported earlier was 15% from *myo*-inositol[3g] and 1–16% from other starting materials.[3b,5c, 5d, 5e, 6a, 6b, 17, 26]

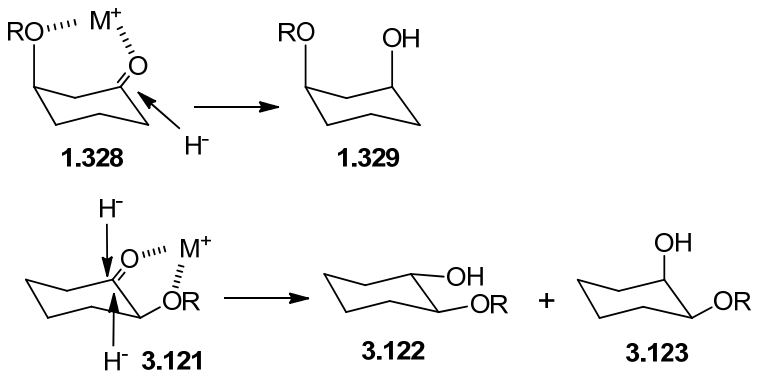
Table 3.3. Synthesis of *allo*-inositol (**1.2**); comparison with methods reported in the literature.

Sr. No.	Starting Material	No. of steps	Overall yield[a] (%)	*allo*-Inositol derivative obtained[b]
1	 **3.105**	5	4[26b]	 **3.106**
2	**1.10**	8	3[5e]	 **3.107**
3	 **3.108**	4	2[5d]	 **3.109**
4	 **3.110**	8	9[17]	 **(+)-3.111**
5	**1.23**	5	16[4b]	 **1.312**
6	 D-*chiro*-inositol **1.8**	4	4[26a]	**3.105**
7	 **3.112**	4	7[5c]	 **3.113**
8	**1.1**	6	15[3g]	 **3.114**

9	 **3.115** **3.116**	15	1[26c]	 **3.117**
10	 **3.52** **3.53**	3	3[6a]	 **3.118** **3.119**
11	 **3.120**	13	5[6b]	**3.107**
12	**1.1**	**12**	**28**[c]	**3.103**

[a] Overall yield refers to *allo*-inositol or its hexaacetate.
[b] In all the entries the protected *allo*-inositol derivative was converted to *allo*-inositol (**1.2**) or its hexa-acetate (**3.104**).
[c] Present work.

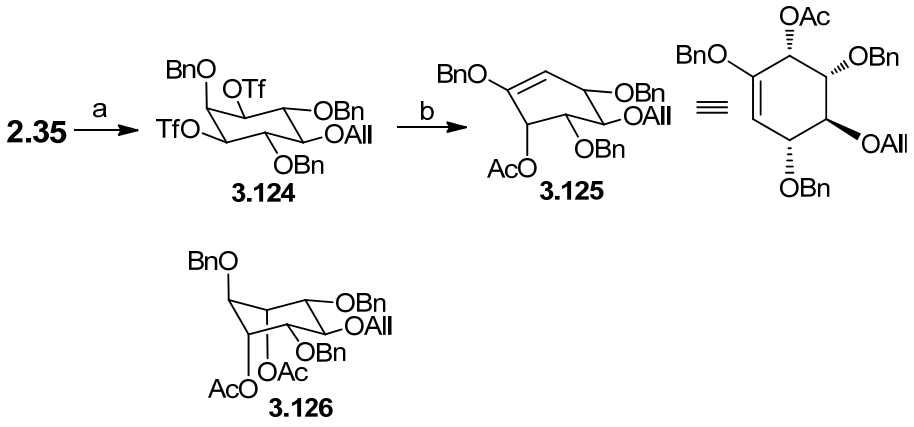
An important feature in our synthetic strategy for differentially protected isomeric inositol derivatives is the stereoselective hydride reduction of inososes **3.29**, **3.48**, **3.76** and **3.102**; but, reduction of the ketone **3.98** was not selective. A comparison of the structure of these ketones and the outcome of their hydride reduction reveals that the carbonyl group in the ketones which undergo reduction to give one single diastereomer is flanked by an axial alkoxy group at the 3-positon (relative to the carbonyl carbon), while the carbonyl group in the ketone which gives mixture of products lacks this axial hydroxyl group. This is consistent with the observations made in the first chapter (section 1.4) pertaining to the reduction of cyclohexanones. Hence it appears that chelation of the metal ion (scheme 3.18) blocks one side of the ketones resulting in stereoselective delivery of the hydride to the carbonyl group. In case of the ketone which lacks the axial alkoxy group, chelation with the neighboring equatorial alkoxyl group does not result in efficient blocking of either of the sides of the carbonyl group and hence the delivery of the hydride in not selective.



Scheme 3.18. Chelation assited stereoselective reduction of ketones.

3.2.9. Attempted preparation of a *muco*-inositol derivative carrying orthogonal protecting groups.

We attempted the synthesis of a *muco*-inositol derivative starting from the symmetric diol **2.35** by inversion of both the hydroxyl groups together *via* nucleophilic displacement reaction. The reaction of the bis-triflate derived from **2.35**, with potassium acetate resulted in elimination of one of the hydroxyl groups, leading to the formation of the cyclohexene derivative **3.125**; no di-axial diacetate of *muco*-configuration (**3.126**) was obtained. Nucleophilic displacement of two hydroxyl groups in an inositol derivative has earlier been reported (Scheme 3.11).[(3b)]



Scheme 3.19. (a) Py, CH_2Cl_2, Tf_2O, 78 %; (b) DMA, KOAc, 74 %.

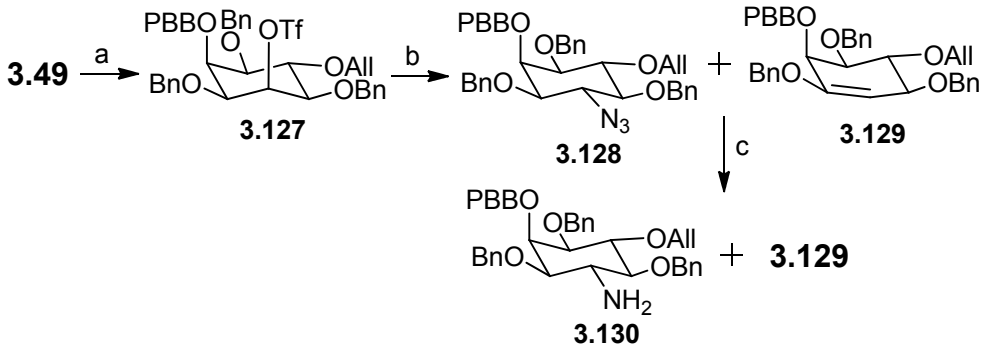
The synthetic approach described so far in this chapter provided seven isomeric inositol derivatives (**3.24**, **3.35**, **3.46**, **3.49**, **3.77**, **3.97**, **3.103**) that are amenable to manipulation to obtain a variety of cyclitol derivatives. Inositol isomers (Chapter 1, Figure 1.1) other than the *myo*-isomer are not readily available (or relatively expensive if commercially available) in quantities large enough to be used as starting materials for the

preparation of differentially protected derivatives. Furthermore, such an approach[19] would require standardizing the reaction conditions for selective reactions of the six hydroxyl groups in each of these isomeric cyclohexanehexols and their partially protected derivatives. Illustration of the utility of the isomeric inositol derivatives carrying orthogonal protecting groups to prepare ring modified derivatives is provided in the remaining part of this chapter.

3.2.10. Preparation of inosamines.

Aminocyclitols are a group of natural products of significant relevance in medicinal and biological chemistry, as they are structural components of a variety of antibiotics,[27] glycosidase inhibitors,[28] and other families of biologically active compounds.[29] Amino cyclitols have been synthesized from inositol derivatives by displacement of the hydroxyl group by nitrogen nucleophiles, reductive amination of inososes, ring opening of cyclitol epoxides and aziridines with suitable nucleophiles. We planned to use some of the orthogonally protected inositol derivatives prepared in the present work for accessing inosamines of *myo*- and *chiro*- configurations.

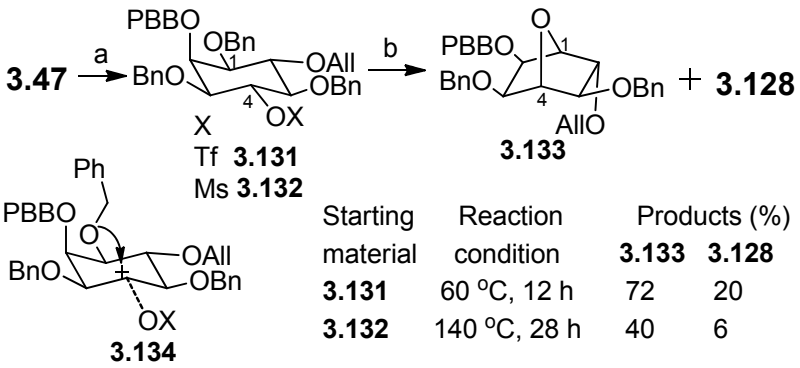
The inosamine derivative **3.130** could be obtained starting from the *epi*-inositol derivative **3.49**. The triflate of **3.49** on reaction with sodium azide gave the azide **3.128** along with the cyclohexene **3.129**. The mixture of products obtained was reduced with triphenylphosphine to convert the azide to the corresponding amine, which was subsequently separated from the cyclohexene **3.129**.



Scheme 3.20. (a) Py, DCM, Tf_2O; (b) DMF, NaN_3; (c) THF, H_2O, PPh_3, reflux, 58% (for **3.130**), 20% (for **3.129**).

Reaction of the *myo*-triflate **3.131** with sodium azide (Scheme 3.21) which was expected to provide an epimer of the azide **3.128**, however resulted in the formation of the

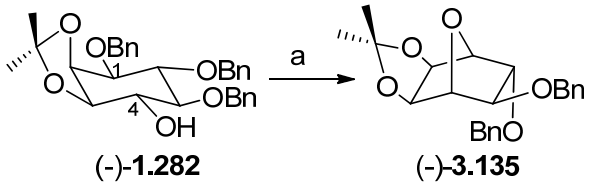
bicyclo derivative **3.133** as the major product; the azide **3.128**, was obtained as a minor product. Reaction of the mesylate **3.132** also resulted in the formation of the same products, but in lower yield.



Starting material	Reaction condition	Products (%) 3.133	3.128
3.131	60 °C, 12 h	72	20
3.132	140 °C, 28 h	40	6

Scheme 3.21. (a) CH_2Cl_2, Py, Tf_2O (–40 °C–rt), 95% or Py, MsCl (0 °C–rt), 92%; (b) DMF, NaN_3.

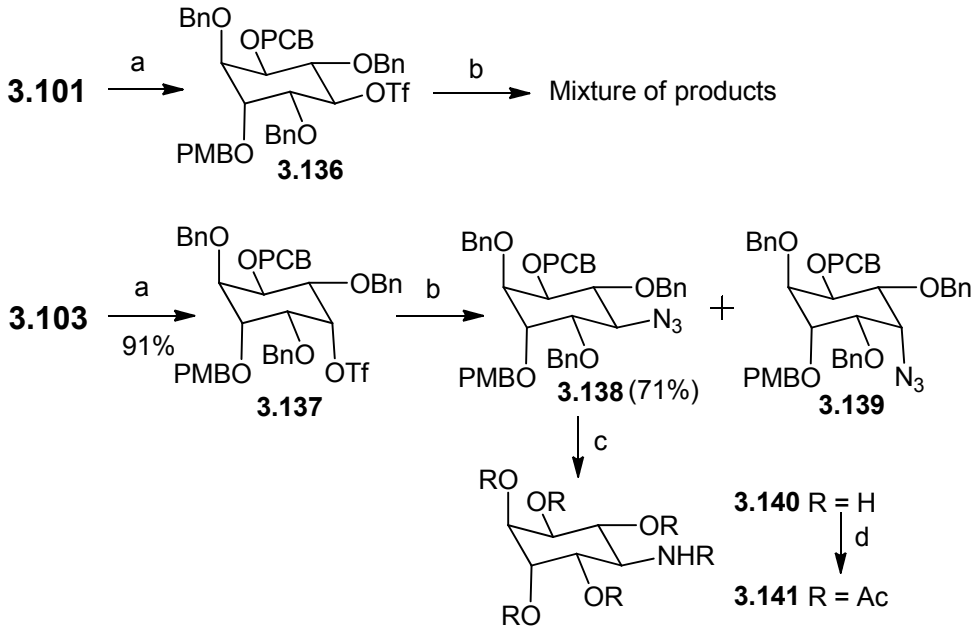
Formation of bicyclo derivatives (similar to **3.133**) does have precedence in the literature; fluorination of **1.282** with diethylaminosulphur trifluoride (DAST) is reported to give **3.135** (Scheme 3.22).[30] The bicyclo derivative **3.133** arises perhaps because the oxygen atom located at the C1-position participates in the reaction (as shown in **3.134**). This results in an increase in the susceptibility of the benzylic carbon for nucleophilic substitution, which leads to the formation of **3.133**. It is likely that the substitution of the triflate in **3.131** proceeds via an S_N1 pathway. This view is supported by the observed retention of configuration at C-4 upon formation of the azide **3.128**. Here, inversion at C-4 is prevented by participation of the 1-benzyloxy group (formation of **3.128**).



Scheme 3.22. (a) CH_2Cl_2, DAST, –78 °C–rt, 1 h, 94%.

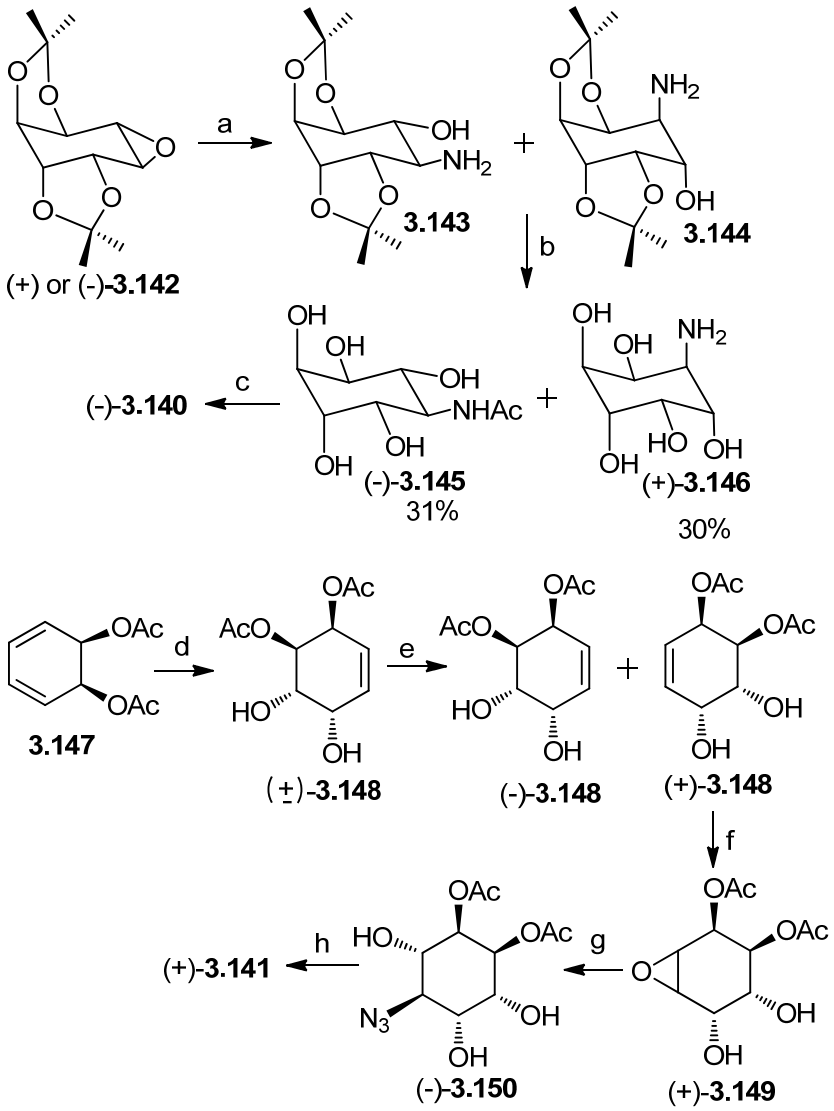
Initially, for the preparation of the inosamine **3.140** (Scheme 3.23), nucleophilic displacement (with sodium azide) of the triflate derived from the *chiro*-alcohol **3.101** was attempted. But this reaction was sluggish and gave a mixture of products (elimination product being major). Displacement of the triflate of the *allo*-inositol **3.103** with sodium azide led to mixture of regioisomeric azides **3.138** (major) and **3.139** (minor), (indicated by LC-MS of the mixture of two isomeric azides) from which the *chiro*-azide **3.138** was

separated by column chromatography. The *chiro*-azide **3.138** was subjected to hydrogenation, to reduce the azide to the corresponding amine and to regenerate all the hydroxyl groups. The racemic *chiro*-inosamine was isolated and characterized as its hexaacetate **3.141**.[31]



Scheme 3.23. (a) Py, CH_2Cl_2, Tf_2O; (b) DMF, NaN_3, rt, 3 h; (c) EtOH, THF, TFA, H_2, 20 % $Pd(OH)_2$; (d) Py, Ac_2O, 70 %.

Reported methods[31, 32] for the synthesis of the *chiro*-amine **3.140** from a cyclitol epoxide and cyclohexadiene diol **3.147** are summarized in scheme 3.24. As is evident, unlike the present method, none of these routes allow further manipulation of the hydroxyl groups in the amino cyclitol obtained.

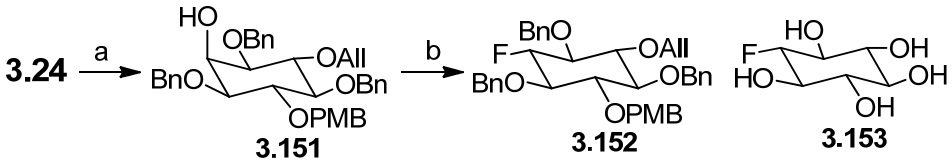


Scheme 3.24. (a) MeOH satd. with NH_3, 100 °C, 88 h, 87% for mixture; (b) i. 0.1 N H_2SO_4, steam-bath, 3 h; ii. NaOAc, Ac_2O, reflux, 2 h; (c) 0.1 N H_2SO_4, reflux, 2 h, Amberlite IRA-400 (OH) resin, 77%; (d) CH_2Cl_2, OsO_4, NMO, 83%; (e) Lipase from *mucor miehei* (Lypozyme IM), vinyl acetate, *t*butylmethyl ether, 45 °C, 6 h, 48% [(+)-**3.148**, *ee* 92%], 44 % [(–)-**3.148**, *ee* 95%]; (f) CH_2Cl_2, *m*CPBA, 86%; (g) NH_4Cl, DMF, NaN_3, 50 °C, 36 h, 79%; (h) i. EtOH, H_2, Pd/C, 98%; ii. Py, Ac_2O.

3.2.11 Preparation of the fluoro-inositol 3.152.

For preparing the substituted fluoro-inositol **3.152** (Scheme 3.25), the C2 hydroxyl group in **3.24** was deprotected by converting the 4-bromobenzyl group to 4-N(Ph)(Me)benzyl group and subsequent exposure to Lewis acid ($ZnCl_2$). The alcohol so obtained was reacted with DAST to give selectively the fluoro-*scyllo*-inositol derivative **3.152**. The advantage with the current synthetic approach is that either compound **3.153** can be prepared by global deprotection of **3.152**, or orthogonal protection in **3.152** can be

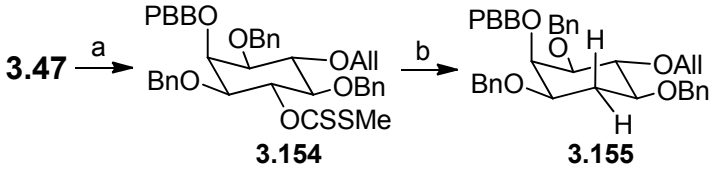
exploited to generate other cyclitol derivatives from **3.152**. Compound **3.153** has shown promise as a potential therapeutic agent for Alzheimer's disease, by significantly inhibiting the formation of amyloid $\beta_{1\text{-}42}$ peptides.[33] A recent report suggests that compound [^{18}F]**3.153** has promise for breast cancer imaging in rodent tumour models.[34]



Scheme 3.25. (a) i. PhN(H)Me, $Pd(dba)_2$, (*O*-biph)P(*t*Bu)$_2$, NaO*t*Bu, Ph-CH_3, 100 °C ii. CH_2Cl_2, $ZnCl_2$, 0 °C–rt, 66%; (b) CH_2Cl_2, DAST, 0 °C–rt, 80%.

3.2.12 Preparation of the protected quercitol 3.155.

The deoxy inositol derivative **3.155** was prepared by the Barton-McCombie deoxygenation protocol on **3.47**.



Scheme 3.26. (a) THF, NaH, CS_2, MeI, 0 °C–reflux, 92%; (b) Ph-CH_3, *n*Bu$_3$SnH, AIBN, 100 °C, 70%.

The reactions shown in schemes above (Schemes 3.20, 3.23, 3.25, 3.26) leading to the synthesis of ring-modified cyclitol derivatives, an azidoinositol, an aminocyclitol, a deoxyinositol and a deoxyfluoroinositol, illustrate the synthetic potential and flexibility of orthogonally protected inositol derivatives. These newly synthesized cyclitol derivatives carry protecting groups that can be cleaved in the presence of each other to release the desired hydroxy group, which can be further modified to give second-generation (with two modifications) cyclitol derivatives. Hence, this methodology can be used to prepare a large number of cyclitols and their derivatives starting from commercially available *myo*-inositol. In addition, phosphorylation and glycosylation reactions can be carried out on orthogonally protected cyclitol derivatives (since all the protecting groups can be cleaved by hydrogenolysis) to obtain the corresponding cyclitol phosphate or glycoside conjugates.

3.3. Conclusions.

An understanding of the relative reactivities of the *myo*-inositol hydroxy groups[2,10,13b] and differences in their ability to chelate with metal ions[35] helped us to develop reaction conditions for the selective derivatization of these hydroxy groups. Judicious choice of alkyl halides[36] for the preparation of *myo*-inositol ethers provided *myo*-inositol derivatives carrying orthogonal protecting groups. Since any of these ethers could be cleaved in the presence of other ethers present in the same derivative, the desired *myo*-inositol hydroxyl group can be released and inverted to obtain six (of the eight possible isomers) isomeric inositol derivatives carrying orthogonal protecting groups. Also, since most of the ethers used are (substituted) benzyl ethers, they can all be cleaved simultaneously by hydrogenation to release all the hydroxy groups in one step, if necessary. These compounds can now be used for the preparation of a variety of cyclitol derivatives. Although, methods for the preparation of isomeric inositols have been reported in the literature, none of these approaches provide access to differentially protected isomeric inositol derivatives. Chiral cyclitol derivatives can be obtained by resolution of the intermediates.

3.4. Experimental.

General Methods: General experimental methods are same as in the sub-section 2.4.1 (Chapter 2).

X-ray Data (Collection, Structure Solution and Refinement): Same as in the sub-section 2.4.2 (Chapter 2).

Racemic 1,3-benzylidene-2-*O*-(4-bromobenzyl)-4-*O*-(4-methoxybenzyl)-6-*O*-allyl-*myo*-inositol (3.14).

To a cooled (ice and salt mixture) solution of the orthobenzoate **2.69** (1.06 g, 1.78 mmol) in dichloromethane (20 mL), was added DIBAL-H (3.92 mL, 1 M solution in toluene) and stirred at the same temperature for 5 min and then at ambient temperature for 150 min. The reaction mixture was diluted with dichloromethane (60 mL) and poured into solution of saturated sodium potassium tartarate and saturated ammonium chloride (25 mL each) and rapidly stirred for 12 h. The organic layer was separated; the aqueous layer was washed with dichloromethane (30 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure. The product was purified by column chromatography (eluent: ethyl acetate/light petroleum,

2:5) on silica gel to obtain the *myo*-alcohol **3.14** (0.65 g, 60%) as a gum. Other minor products were isomeric benzylidene acetal **3.15** (0.065 g, 10%) and mixture of diastereoisomeric diols **3.16** and **3.17** (0.15 g, 14%).

Data for 3.14: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.60–7.24 (m, 11H, Ar-H), 6.95–6.85 (m, 2H, Ar-H), 6.03–5.82 (m, 1H, *CH*=CH_2), 5.73 (s, 1H, Ph(OR)$_2$C-*H*), 5.40-5.18 (m, 2H, CH=*CH*$_2$), 4.75–4.50 (m, 2H), 4.65 (s, 2H), 4.38 (t, *J*=2.3 Hz, 1H), 4.29 (t, *J*=2.3 Hz, 1H), 4.27–4.05 (m, 2H), 3.97 (t, *J*= 8.7 Hz, 2H), 3.81 (s, 3H, Ph-O*CH*$_3$), 3.73 (t, *J*=8.5 Hz, 1H), 3.57 (t, *J*=2.40 Hz, 1H) 2.54 (br s, D_2O exchangeable, 1H, OH) ppm.

Racemic 6-*O*-allyl-1,3,5-tri-*O*-benzyl-2-*O*-(4-bromobenzyl)-4-*O*-(4-methoxybenzyl)-*myo*-inositol (3.24).

To an ice-cooled solution of the orthobenzoate **2.69** (4.5 g, 7.56 mmol) in dichloromethane (50 mL), DIBAL-H (42 mL, 42 mmol, 1 M in toluene) was added, and the reaction mixture was stirred at ambient temperature for 4 h. The reaction mixture was diluted with dichloromethane (150 mL) and rapidly poured into a mixture of saturated solutions of ammonium chloride (90 mL) and sodium potassium tartarate (120 mL) with stirring and cooling. The stirring was continued at ambient temperature until two layers separated. The aqueous layer was washed with dichloromethane (2×60 mL), and the combined organic layers were washed with brine, dried with anhydrous sodium sulfate, and the solvent was removed under reduced pressure to afford the crude product, which was purified by flash column chromatography (ethyl acetate/light petroleum, 7:15) on silica gel to obtain a mixture of diastereomeric diols **3.16** and **3.17** (3.3 g, 73%) as a gum. To an ice-cooled solution of **3.16** and **3.17** (3.3 g, 5.51 mmol) in dry DMF (30 mL), sodium hydride (1.10 g, 27.55 mmol) was added, followed by benzyl bromide (3.27 mL, 27.55 mmol), and the reaction mixture was stirred at ambient temperature for 12 h. Excess of sodium hydride was destroyed by adding ice to the reaction mixture, solvents were removed under reduced pressure, and the residue was worked up as usual with dichloromethane. The crude product was purified by flash column chromatography (ethyl acetate/light petroleum, 1:9) on silica gel to obtain **3.24** (4.15 g, 97%) as a colorless solid.

Data for 3.24: Mp. = 66–68 °C. **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.40–7.17 (m, 21 H, Ar-H), 6.84–6.77 (m, 2 H, Ar-H), 6.07–5.88 (m, 1H, C*H*=CH_2), 5.33–5.09 (m, 2 H, CH=C*H*$_2$), 4.86 (s, 2 H), 4.79–4.53 (m, 8 H), 4.44–4.26 (m, 2 H), 4.06–3.83 (m, 3 H), 3.78 (s, 3 H, Ar-OC*H*$_3$), 3.47–3.23 (m, 3 H) ppm. **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 158.9 (C_{ipso}), 138.7

(C_{ipso}), 138.2 (C_{ipso}), 138.1 (C_{ipso}), 137.8 (C_{ipso}), 135.3, 131.0, 130.8 (C_{ipso}), 129.5, 129.2, 128.2, 128.1, 127.7, 127.5, 127.3, 120.9 (C_{ipso}), 116.3 (C=*C*H_2), 113.5, 83.5 (Ins C), 81.2 (Ins C), 81.1 (Ins C), 80.6 (Ins C), 80.5 (Ins C), 75.7 (CH_2), 75.3 (CH_2), 74.8 (Ins CH), 74.3 (CH_2), 73.2 (CH_2), 72.75 (CH_2), 72.69 (CH_2), 55.0 (CH_3) ppm. **Elemental Anal**. $C_{45}H_{47}BrO_7$ (779.75): calcd. C, 69.31; H, 6.08 found C, 69.18; H, 6.10 %.

Racemic 6-*O*-allyl-1,3-di-*O*-benzyl-2-*O*-(4-bromobenzyl)-4-*O*-(4-methoxybenzyl)-*myo*-inositol (3.25).

To an ice-cooled solution of a mixture of diastereomeric diols **3.16** and **3.17** (1.16 g, 1.94 mmol) in DMF (12 mL), was added sodium hydride (0.086 g, 2.13 mmol) followed by benzyl bromide (0.23 mL, 1.94 mmol), and the mixture was stirred at ambient temperature for 20 min. The reaction was quenched by the addition of ice, solvents were removed under reduced pressure, and the residue was taken into dichloromethane and worked up as usual. The products were separated by flash column chromatography (ethyl acetate/light petroleum, 1:3) on silica gel to obtain *myo*-alcohol **3.25** (0.75 g, 57%) as a gum, which turned into a colorless solid on storing at ambient temperature. The triether **3.24** (0.15 g, 20%) and the starting diols **3.16** and **3.17** (0.11 g, 10%) were also obtained.

Data for 3.25: Mp. = 66–69 °C; **IR** (Nujol): $\bar{\nu}$ 3603–3344 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.46–7.28 (m, 13 H, Ar-H), 7.25–7.19 (m, 3 H, Ar-H), 6.88–6.78 (m, 2 H, Ar-H), 6.07–5.88 (m, 1 H, C*H*=CH_2), 5.33–5.12 (m, 2 H, CH=CH_2), 4.90–4.50 (m, 8 H), 4.45–4.23 (m, 2 H), 3.96 (t, *J* = 2.4 Hz, 1 H), 3.87 (t, *J* = 9.5 Hz, 1 H), 3.79 (s, 3 H, Ar-OCH_3), 3.80–3.70 (m, 1 H), 3.44 (t, *J* = 9.2 Hz, 1 H), 3.36–3.26 (m, 2 H), 2.52 (br. s, 1 H, D_2O exchangeable, OH) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 159.1 (C_{ipso}), 138.2 (C_{ipso}), 138.1(C_{ipso}), 137.9 (C_{ipso}), 135.2, 131.1, 130.9 (C_{ipso}), 129.6, 129.3, 128.3, 127.6, 127.4, 127.38, 121.0 (C_{ipso}), 116.7 (C=*C*H2), 113.7, 80.63 (Ins C), 80.6 (Ins C), 80.5 (Ins C), 80.4 (Ins C), 75.0 (Ins C), 74.9 (CH2), 74.8 (Ins C), 74.1 (CH_2), 73.3 (CH_2), 72.7 (CH_2), 72.6 (CH_2) ppm; **Elemental Anal.** $C_{38}H_{41}BrO_7$ (689.63): calcd. C, 66.18; H, 5.99 found C, 66.16; H, 6.35 %.

Racemic 2-*O*-allyl-4-*O*-(4-methoxybenzyl)-*scyllo*-inositol 1,3,5-orthobenzoate (3.31). Dichloromethane (3 mL) and oxalyl chloride (1.06 mL, 12.22 mmol) were taken in a two-necked round bottom flask (50 mL) and cooled to –78 ^oC. A solution of dimethylsulphoxide (1.11 mL, 16.79 mmol) in dichloromethane (3 mL) was added and stirred at –78 ^oC for 20 min. A solution of the orthobenzoate **2.68** (2.17 g, 5.09 mmol) in

dichloromethane (10 mL) was added drop-wise to the reaction mixture and stirring continued at –78 ^{o}C for 2 h. Triethylamine (3.90 mL, 27.99 mmol) was added to the reaction mixture at –78 ^{o}C and stirred for 2 h during which the reaction mixture was allowed to warm up to ambient temperature. The reaction mixture was diluted with dichloromethane and worked up as usual. The crude product was purified by flash column chromatography (eluent: ethyl acetate/light petroleum 1:4) on silica gel to obtain the corresponding ketone **3.29** (1.80 g, 83%) as a gum. To an ice cooled solution of the *myo*-inososе **3.29** (2.0 g, 4.72 mmol) in methanol (20 mL), sodium borohydride (0.87 g, 23.58 mmol) was added and stirred at room temperature for 30 min. The reaction mixture was quenched by adding saturated solution of ammonium chloride, the solvents removed under reduced pressure and the residue worked up with ethyl acetate. The crude product was purified by flash column chromatography (eluent: ethyl acetate/light petroleum 9:41) on silica gel to afford **3.30** (1.80 g, 90%) as a gum, which turned into a solid on storing at ambient temperature.

Data for 3.30:**Mp.** = 93–95 ^{o}C; **IR** (Neat): $\bar{\nu}$ 3506 (OH) cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.65–7.55 (m, 2H, Ar-H), 7.40–7.24 (m, 5H, Ar-H), 6.91–6.83 (m, 2H, Ar-H), 5.99–5.79 (m, 1H, *CH*=CH_2), 5.32–5.16 (m, 2H, CH=*CH_2*), 4.72–4.50 (m, 6H), 4.50–4.42 (m, 2H), 4.19 (t, *J*=1.4 Hz, 1H), 4.16 (t, *J*=1.4 Hz, 1H), 4.11 (d, *J*=12 Hz, 1H, D_2O exchangeable, OH), 3.81 (s, 3H, Ph-O*CH_3*) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 159.3 (C_{ipso}), 136.4 (C_{ipso}), 133.5, 129.4, 129.3, 128.9, 127.9, 125.2, 117.6 (C=*CH_2*), 113.7, 107.3 (PhCO3), 72.8 (Ins CH), 72.4 (Ins CH), 71.2 (CH_2) 70.5 (CH_2), 69.9 (Ins CH), 68.8 (Ins CH), 66.6 (Ins CH), 55.1 (OCH_3) ppm; **Elemental Anal.**$C_{24}H_{26}O_7$ (426.46): calcd. C, 67.59; H, 6.15 found C, 67.51; H, 6.44 %.

Racemic 1,3,5-tri-*O*-benzyl-2-*O*-(4-bromobenzyl)-4-*O*-(4-methoxybenzyl)-6- *O*-allyl-*scyllo*-inositol (3.35).

To an ice cooled solution of the *scyllo*-alcohol **3.30** (1.56 g, 3.67 mmol) in dry DMF (12 mL), sodium hydride (0.44 g, 1.10 mmol) was added followed by a solution of 4-bromobenzyl bromide (1.38 g, 5.50 mmol) in DMF (8 mL), and the reaction mixture stirred at room temperature for 12 h. Excess of sodium hydride was destroyed by the addition of ice to the reaction mixture, solvents were removed under reduced pressure and the residue was worked up with dichloromethane, as usual. The crude product was purified

by flash column chromatography (eluent: ethyl acetate/light petroleum 1:9) on silica gel to obtain fully protected orthobenzoate **3.31** (2.05 g, 94 %) as a colorless solid.

Data for 3.31: **Mp.** = 78–80 ^{o}C; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.66–7.55 (m, 2H, Ar-H), 7.40–7.31 (m, 5H, Ar-H), 7.25–7.18 (m, 4H, Ar-H), 6.82–6.75 (m, 2H, Ar-H), 6.00-5.80 (m, 1H, *CH*=CH_2), 5.31–5.12 (m, 2H, CH=*CH_2*), 4.68–4.56 (m, 7H) 4.46–4.37 (m, 3H), 4.17 (t, *J*=1.4 Hz, 1H), 4.14 (t, *J*=1.4 Hz, 1H), 3.81 (s, 3H, Ph-O*CH_3*) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 158.9 (C_{ipso}), 137.0 (C_{ipso}), 136.6 (C_{ipso}), 134.3, 131.0, 129.9 (C_{ipso}), 129.3, 129.1, 127.9, 125.2, 120.9 (C_{ipso}), 117.2 (C=*CH_2*), 113.3, 108.0 (Ph*C*O_3), 72.3 (Ins CH), 72.2 (Ins CH), 71.9 (Ins CH), 70.8 (CH_2), 70.5 (CH_2), 69.9 (CH_2), 69.2 (Ins CH), 69.1 (Ins CH), 55.0 (OCH_3) ppm; **Elemental Anal.** $C_{31}H_{31}BrO_7$ (594.13): calcd. C, 62.53; H, 5.25 found C, 62.71; H, 5.07 %.

To an ice cooled solution of the protected orthobenzoate **3.31**(1.37 g, 2.29 mmol) in dichloromethane (20 mL), DIBAL-H (12.6 mL, 12.6 mmol, 1 M solution in toluene) was added and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with dichloromethane (120 mL), poured into a cold mixture of saturated ammonium chloride (60 mL) and saturated sodium potassium tartarate (50 mL) solutions, and stirred vigorously at room temperature till two layers separated. The aqueous layer was washed with dichloromethane (2×30 mL), and the combined organic layer washed with brine, dried over anhydrous sodium sulphate and the solvent removed under reduced pressure. The product was purified by flash column chromatography (eluent: ethyl acetate/light petroleum 2.5:7.5) on silica gel to obtain a mixture of diastereoisomeric diols (1.1 g, 81 %) as a gum.To an ice cooled solution of the mixture of diols (1.1 g, 1.85 mmol) obtained above, in dry DMF (12 mL), sodium hydride (0.29 g, 7.35 mmol) was added followed by addition of benzyl bromide (0.87 mL, 7.35 mmol) and the reaction mixture was stirred at room temperature for 12 h. Excess of sodium hydride was destroyed by the addition of ice, the solvents were removed under reduced pressure and the residue was worked up with dichloromethane as usual. The crude product was purified by flash column chromatography (eluent: ethyl acetate/light petroleum 1:9) on silica gel to obtain **3.35** (1.3 g, 84%) as a colorless solid.

Data for 3.35: Mp. = 118–119 ^{o}C; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.41–7.28 (m, 17H, Ar-H), 7.23–7.05 (m, 4H, Ar-H), 6.84–6.77 (m, 2H, Ar-H), 6.06–5.87 (m, 1H, *CH*=CH_2), 5.34–5.12 (m, 2H, CH=*CH_2*), 4.94–4.72 (m, 10H), 4.35 (d, *J*=5.7 Hz, 2H), 3.78 (s, 3H, Ph-

O*CH*$_3$), 3.54–3.36 (m, 6H) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 159.1 (C_{ipso}), 138.4 (C_{ipso}), 138.32 (C_{ipso}), 138.3 (C_{ipso}), 137.4 (C_{ipso}), 134.9 (C_{arom}), 131.3 (C_{arom}), 130.4 (C_{ipso}), 129.4 (C_{arom}), 129.3 (C_{arom}), 128.3 (C_{arom}), 127.8 (C_{arom}), 127.76 (C_{arom}), 127.6 (C_{arom}), 127.56 (C_{arom}), 127.5 (C_{arom}), 121.3 (C_{ipso}), 116.8 (C=*CH*$_2$), 113.7 (*CH*=C), 82.73 (Ins CH), 82.68 (Ins CH), 82.5 (Ins CH), 82.4 (Ins CH), 75.8 (CH_2), 75.7 (CH_2), 75.5 (CH_2), 74.8 (CH_2), 74.5 (CH_2), 55.0 (CH_3) ppm; **Elemental Anal.** $C_{45}H_{47}BrO_7$ (779.75): calcd. C, 69.31; H, 6.08 found C, 69.46; H, 6.37 %.

Racemic 1,3-di-*O*-benzyl-2-*O*-(4-bromobenzyl)-4-*O*-(4-methoxybenzyl)-5-*O*-aceyl-6-*O*-allyl-*neo*-inositol (3.46).

To an ice cooled solution of *myo*-alcohol **3.25** (0.40 g, 0.58 mmol) in pyridine (4 mL), was added methanesulfonyl chloride (0.089 mL, 1.16 mmol) and stirred for 12 h at ambient temperature. The reaction mixture was decomposed by the addition of ice, solvents were removed under reduced pressure, the residue was taken in dichloromethane and worked up as usual. The product was purified by flash column chromatography (eluent: ethyl acetate/light petroleum 1:4) on silica gel to obtain the mesylate **3.45** (0.43 g, 95 %) as a gum. A mixture of DMF (4 mL), the mesylate **3.45** (0.20 g, 0.26 mmol), cesium acetate (0.15 g, 0.78 mmol) and 18-crown-6 (0.14 g, 0.52 mmol) was stirred at 140 ^{o}C for 8 h. The reaction mixture was decomposed by the addition of ice, solvents were removed under reduced pressure, the residue taken in dichloromethane and worked up as usual. The product was purified by flash column chromatography (eluent: ethyl acetate/light petroleum 17:83) on silica gel to obtain the *neo*-acetate **3.46** (0.17 g, 90 %) as a gum.

Data for 3.46: IR (Nujol): $\bar{\nu}$ 1742 (C=O) cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.41–7.17 (m, 16H, Ar-H), 6.88–6.79 (m, 2H, Ar-H), 6.01–5.84 (m, 1H, *CH*=CH_2), 5.79 (t, *J*=3.2 Hz, 1H, H-5), 5.37–5.11 (m, 2H, CH=*CH*$_2$), 4.85–4.72 (m, 4H), 4.70–4.45 (m, 4H), 4.25–4.02 (m, 3H), 3.94 (dd, *J*=3.1 and 10.0 Hz, 1H), 3.86 (dd, *J*=3.1 and 10.0 Hz, 1H), 3.80 (s, 3H), 3.68 (t, *J*=1.9 Hz, 1H), 3.63 (t, *J*=1.9 Hz, 1H), 2.10 (s, 3H, OC-*CH*$_3$) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 170.3 (C=O), 159.1 (C_{ipso}), 138.7 (C_{ipso}), 138.0 (C_{ipso}), 134.7, 131.1, 130.2 (C_{ipso}), 129.5, 129.4, 128.24, 128.2, 127.41,127.4, 127.31, 127.3, 121.1 (C_{ipso}), 116.7 (C=*CH*$_2$), 113.6, 78.5 (Ins C), 76.4 (Ins C), 76.3 (Ins C), 76.2 (Ins C), 73.9 (CH_2), 73.19 (CH_2), 73.16 (CH_2), 71.8 (CH_2), 71.3 (CH_2), 67.3 (Ins CH), 55.1 (OCH_3), 21.1 (CH_3) ppm; **Elemental Anal.** $C_{40}H_{43}BrO_8$ (731.67): calcd. C, 65.66; H, 5.92 found C, 65.57; H, 6.30 %.

Racemic 1,3,5-tri-*O*-benzyl-2-*O*-(4-bromobenzyl)-4-*O*-allyl-*myo*-inositol (3.47).

To an ice cooled solution of the PMB ether **3.24** (4.35 g, 5.58 mmol) in dichloromethane:water (100:1 mL), DDQ (1.52 g, 6.70 mmol) was added and stirred at room temperature for 2 h. The reaction mixture was washed with 40% aq. sodium hydrogencarbonate solution (2×70 mL), followed by brine and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (eluent: ethyl acetate/light petroleum 3:17) to afford **3.47** (3.4 g, 93%) as a gum.

Data for 3.47: IR (Neat): $\bar{\nu}$ 3601–3279 (OH) cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.42–7.14 (m, 19H, Ar-H), 6.09–5.87 (m, 1H, *CH*=CH_2), 5.33–5.11 (m, 2H, CH=*CH_2*), 4.86 (q, J=11.1 Hz, 2H), 4.85–4.55 (m, 6H), 4.45–4.26 (m, 2H), 4.08 (t, J=9.6 Hz, 1H), 3.95 (t, *J*=2.3 Hz, 1H), 3.88 (t, *J*=9.5 Hz, 1H), 3.38–3.26 (m, 2H), 3.18 (dd, *J*=2.3 and 9.9 Hz, 1H) 2.48 (br s, D_2O exchangable, 1H, OH) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 138.7 (C_{ipso}), 138.3 (C_{ipso}), 137.8 (C_{ipso}), 135.3, 131.1, 129.2, 128.4, 128.3, 127.9, 127.8, 127.6, 127.5, 121.1 (C_{ipso}), 116.5 (C=*C*H_2), 83.2 (Ins C), 81.1(Ins C), 80.8 (Ins C), 79.9 (Ins C), 75.3 (CH_2), 74.4 (CH_2), 74.3 (Ins C), 73.3 (CH_2), 72.9 (CH_2), 72.7 (Ins CH), 72.4 (CH_2), ppm; **Elemental Anal.** $C_{37}H_{39}BrO_6$ (659.61): calcd. C, 67.37; H, 5.96 found C, 67.13; H,6.26 %.

Racemic 1,3,5-tri-*O*-benzyl-2-*O*-(4-bromobenzyl)-6-*O*-allyl-*epi*-inositol (3.49).

To an ice cooled solution of **3.47** (2.2 g, 3.34 mmol) in ethyl acetate (25 mL), IBX (1.87 g, 6.68 mmol) was added and refluxed for 7 h. The reaction mixture was brought to room temperature and passed through a bed of Celite, the latter was washed with ethyl acetate, and the combined ethyl acetate solution was concentrated to get the crude ketone (2.3 g). A small portion (0.10 g) was purified by flash column chromatography (eluent: 60:39:1 light petroleum/dichloromethane/ethyl acetate) to obtain the *myo*-inosose **3.48** (0.09 g) as a colorless solid.

Data for 3.48: Mp. = 122–124 ^oC; **IR** (Nujol): $\bar{\nu}$ 1732 (C=O) cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.45–7.26 (m, 17H, Ar-H), 7.22–7.14 (m, 2H, Ar-H), 6.06–5.87 (m, 1H, *CH*=CH_2), 5.33–5.13 (m, 2H, CH=*CH_2*), 4.98–4.51 (m, 7H) 4.46–4.26 (m, 3H), 4.08–3.87 (m, 4H), 3.64 (dd, *J*=2.2 and 9.1 Hz, 1H) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 201.5 (C=O), 137.8 (C_{ipso}), 137.5 (C_{ipso}), 137.1 (C_{ipso}), 134.9 (C_{arom}), 131.0 (C_{arom}), 129.5 (C_{arom}), 128.4 (C_{arom}), 128.3 (C_{arom}), 128.2 (C_{arom}), 127.9 (C_{arom}), 127.7 (C_{arom}), 127.6 (C_{arom}), 127.4 (C_{arom}), 121.1 (C_{ipso}), 116.4 (C=*CH_2*), 83.6 (Ins CH), 82.0 (Ins CH), 81.1 (Ins CH), 79.6

(Ins CH), 76.2 (Ins CH), 74.4 (CH_2), 73.3 (CH_2), 72.8 (CH_2), 72.1 (CH_2) ppm; **Elemental Anal.** $C_{37}H_{37}BrO_6$ (657.59): calcd C, 67.58; H, 5.67 found C, 67.27; H, 5.57 %.

To an ice cooled solution of the crude ketone **3.48** (2.2 g) in THF:methanol (20:4 mL) mixture, sodium borohydride (0.62 g, 16.7 mmol) was added and stirred at room temperature for 30 min. The reaction mixture was quenched by adding saturated solution of ammonium chloride and the solvents were removed under reduced pressure. The residue was taken in ethyl acetate and worked up as usual. The crude product obtained was purified by flash column chromatography (eluent: ethyl acetate/light petroleum 3:17) to afford **3.49** (2.05 g, 93%) as a gum.

Data for 3.49: IR (Nujol): $\bar{\nu}$ 3504–3403 (OH) cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.45–7.26 (m, 17H, Ar-H), 7.25–7.17 (m, 2H, Ar-H), 6.12–5.90 (m, 1H, *CH*=CH_2), 5.34–5.12 (m, 2H, CH=*CH_2*), 4.83–4.50 (m, 8H), 4.48–4.28 (m, 3H), 4.12–4.01 (m, 2H), 3.94 (d, *J*=8.9 Hz, D_2O exchangeable, 1H, OH) 3.29–3.14 (m, 3H) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 138.3 (C_{ipso}), 138.2 (C_{ipso}), 137.5 (C_{ipso}), 136.7 (C_{ipso}), 135.4, 131.3, 129.6, 128.4, 128.3, 128.2,127.8, 127.62, 127.55, 127.5, 127.4, 121.6 (C_{ipso}), 116.3 (C=*CH_2*), 80.3 (Ins C), 80.2 (Ins C), 79.3 (Ins C), 78.8 (Ins C), 74.6 (CH_2), 74.5 (CH_2), 74.0 (Ins C), 73.2 (CH_2), 72.1 (CH_2), 70.2 (CH_2), 68.9 (Ins CH) ppm. **Elemental Anal.** $C_{37}H_{39}BrO_6$ (659.61): calcd. C, 67.37; H, 5.96 found C, 67.15; H, 5.91 %.

***epi*-Inositol (1.4).**

A mixture of methanol (5 mL), water (0.5 mL), *epi*-alcohol **3.49** (0.3 g, mmol), 10 % Pd-C (0.020 g) and TsOH (0.025 g), were refluxed for 24 h. TLC analysis showed the presence of **3.49**; hence excess of 10 % Pd-C (0.020 g) was added to the reaction mixture and refluxed for 20 h. The reaction mixture was cooled to room temperature and filtered through a bed of Celite. The filtrate was evaporated to dryness in vacuo, and the residue taken in ethyl acetate, washed with saturated solution of sodium hydrogen carbonate and then with brine. The organic layer was dried over anhydrous sodium sulphate and the solvent removed under reduced pressure to get the crude product. The crude product was purified by flash column chromatography (eluent: ethyl acetate/light petroleum 1:3) to afford the *epi*-diol (0.260 g) as a colorless solid. A mixture of the *epi*-diol (0.125 g), THF (2 mL), ethanol (7 mL), deionized water (0.5 mL), trifluoroacetic acid (1.0 mL), and 20 % Pd-$(OH)_2$ (0.05 g) were taken in a hydrogenation bottle and stirred under an atmosphere of hydrogen (60 psi) for 40 h. The reaction mixture was filtered through a bed of Celite, the

latter was washed successively with ethanol and hot water. The combined filtrate was evaporated under reduced pressure to afford *epi*-inositol **1.4** (0.34 g, 94%) as a glassy solid.

Data for 1.4: Mp. = 274–276 ^{o}C (Crystals obtained from the reaction mixture), (Lit[5g] **Mp.** = 270 ^{o}C); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.05 (t, *J*=2.6 Hz, 2H), 3.81 (t, *J*=10.0 Hz, 1H) 3.77 (t, *J*=2.7 Hz, 1H), 3.45 (dd, *J*=2.5 and 9.9 Hz, 2H) ppm.

Racemic 1,3,5-tri-*O*-benzyl-2-*O*-(4-bromobenzyl)-4-*O*-(4-chlorobenzyl)-*epi*-inositol (3.75).

To an ice cooled solution of the *epi*-alcohol **3.49** (2.02 g, 3.06 mmol) in DMF (20 mL), was added sodium hydride (0.368 g, 9.19 mmol) followed by a solution of 4-chlorobenzyl bromide (1.26 g, 6.13 mmol) in DMF (10 mL) and stirred at room temperature for 12 h. Excess of sodium hydride was destroyed by adding ice to the reaction mixture, solvents were removed under reduced pressure and the residue worked up as usual with ethyl acetate. The crude product was purified by flash column chromatography (eluent: ethyl acetate/petroleum ether 3:22) on silica gel to obtain the fully protected *epi*-inositol **3.74** (2.3 g, 96%) as a gum.

Data for 3.74: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40–7.17 (m, 21H, Ar-H), 7.16–7.08 (m, 2H, Ar-H), 6.10–5.90 (m, 1H, *CH*=CH_2), 5.33–5.08 (m, 2H, CH=*CH_2*), 4.90–4.59 (m, 8H) 4.45–4.36 (m, 4H), 4.21 (t, *J*=9.8 Hz, 1H), 4.08 (t, *J*=2.4 Hz, 2H), 3.24 (dd, *J*=2.9 and 9.7 Hz, 2H), 3.16 (t, *J*= 2.5 Hz, 1H) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 138.6 (C_{ipso}),138.4 (C_{ipso}), 137.9 (C_{ipso}), 137.7 (C_{ipso}), 135.5 (C_{arom}), 132.6 (C_{ipso}), 130.9 (C_{arom}), 129.3 (C_{arom}), 128.9 (C_{arom}), 128.4 (C_{arom}), 128.3 (C_{arom}), 128.0 (C_{arom}), 127.7 (C_{arom}),127.5 (C_{arom}),127.5 (C_{arom}), 127.4 (C_{arom}), 120.7 (C_{ipso}), 116.3 (C=*CH_2*), 80.6 (Ins C), 79.2 (Ins C), 78.1 (Ins C), 75.8 (Ins C), 75.78 (Ins C), 74.5 (CH_2), 73.3 (CH_2), 72.9 (CH_2), 71.3 (CH_2) ppm; **Elemental Anal.** $C_{44}H_{44}BrClO_6$ (784.17): cald. C, 67.39; H, 5.66 found C, 67.68; H, 5.34 %.

To an ice cooled solution of the **3.74** (0.960 g, 1.22 mmol), and $NiCl_2$(dppp) (0.013 g, 0.024 mmol) in toluene (8 mL), DIBAL-H (3.67 mL, 3.67 mmol, 1 M solution in toluene) was added and stirred at room temperature for 3 h. The reaction mixture was diluted with dichloromethane, 10% hydrochloric acid (10 mL) was added and stirred at room temperature for 3 h. The organic layer was separated and washed successively with sodium hydrogen carbonate solution, water, brine and then dried over anhydrous sodium sulphate.

Solvents were removed under reduced pressure and the crude product obtained was purified by column chromatography (eluent: ethyl acetate/light petroleum 1:3) to afford the *epi*-alcohol **3.75** (0.750 g, 83%) as a colorless solid.

Data for 3.75: IR (Nujol): $\bar{\nu}$ 3500–3380 (OH) cm^{-1}; **Mp.** = 99–102 ^{o}C (crystals from dichloromethane-light petroleum); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.40–7.17 (m, 20H, Ar-H), 7.15–7.09 (m, 3H, Ar-H), 4.77 (d, *J*=3.03 Hz, 4H), 4.66 (s, 4H), 4.57–4.43 (m, 3H), 4.12 (t, *J*=2.3 Hz, 2H), 3.25–3.15 (m, 3H), 2.64 (bs, 1H, D_2O exchangeable, OH) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 138.3 (C_{ipso}),138.1 (C_{ipso}), 137.75 (C_{ipso}), 137.7 (C_{ipso}), 132.6 (C_{ipso}), 131.0 (C_{arom}), 129.2 (C_{arom}), 128.8 (C_{arom}), 128.5 (C_{arom}), 128.4 (C_{arom}), 128.0 (C_{arom}), 127.8 (C_{arom}), 127.7 (C_{arom}), 127.6 (C_{arom}), 127.1 (C_{arom}), 120.7 (C_{ipso}), 80.1 (Ins CH), 78.5 (Ins CH), 75.1 (Ins CH), 73.3 (CH_2), 72.2 (CH_2), 71.3 (CH_2), 70.0 (Ins CH) ppm; **Elemental Anal.** $C_{41}H_{40}BrClO_6$ (744.11): calcd. C, 66.18; H, 5.42 found C, 66.15; H, 5.60 %.

Racemic 1,3,5-tri-*O*-benzyl-2-*O*-(4-bromobenzyl)-4-*O*-(4-chlorobenzyl)-*cis*-inositol (3.77).

Dichloromethane (1.5 mL) and oxalyl chloride (0.10 mL, 1.15 mmol) were taken in a two-necked 50 mL round bottom flask and cooled to –78 ^{o}C. A solution of DMSO (0.10 mL, 1.52 mmol) in dichloromethane (1.5 mL) was added and stirred at –78 ^{o}C for 20 min. To this mixture, a solution of the *epi*-alcohol **3.75** (0.34 g, 0.46 mmol) in dichloromethane (5.0 mL) was added drop-wise and stirred at –78 ^{o}C for 2 h. Triethylamine (0.35 mL, 2.53 mmol) was added to the reaction mixture at –78 ^{o}C and the reaction mixture was allowed to warm up to ambient temperature over 2 h. The reaction mixture was diluted with dichloromethane and worked up as usual to get the crude ketone **3.76** (0.383 g). To an ice cooled solution of the ketone **3.76** (0.38 g) in THF:methanol (4:1 mL), sodium borohydride (0.08 g, 2.3 mmol) was added and stirred at room temperature for 30 min. The reaction mixture was quenched by adding a saturated solution of ammonium chloride (1 mL); the solvents were removed under reduced pressure, the residue was taken in ethyl acetate and worked up as usual. The crude product was purified by flash column chromatography (eluent: ethyl acetate/light petroleum 6:19) on a small bed of silica, to afford the *cis*-alcohol **3.77** (0.31 g, 91%) as a gum.

Data for 3.77: IR (Nujol): $\bar{\nu}$ 3600–3450 (OH) cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.40–7.19 (m, 20H, Ar-H), 7.18–7.09 (m, 3H, Ar-H), 4.96–4.50 (m, 8H) 4.48 (s, 2H), 4.34

(br s, 1H), 4.22 (s, 2H), 3.90 (bs, 1H, D_2O exchangeable, OH) 3.18 (t, *J*=2.6 Hz, 1H) 3.11 (t, *J*=2.6 Hz, 2H) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 137.8 (C_{ipso}), 137.5 (C_{ipso}), 137.3 (C_{ipso}), 132.7 (C_{ipso}), 131.0 (C_{arom}), 129.2 (C_{arom}), 128.8 (C_{arom}), 128.4 (C_{arom}), 128.3 (C_{arom}), 128.0 (C_{arom}), 127.7 (C_{arom}), 127.6 (C_{arom}), 127.5 (C_{arom}), 127.1 (C_{arom}), 120.8 (C_{ipso}), 78.1 (Ins C), 77.0 (Ins C), 75.9 (Ins C), 73.7 (CH_2), 70.9 (CH_2), 70.2 (CH_2), 69.8 (Ins C) ppm; **Elemental Anal.** $C_{41}H_{40}BrClO_6$ (744.11): calcd. C, 66.18; H, 5.42 found C, 66.48; H, 5.56 %.

Hexa-*O*-acetyl-*cis*-inositol (3.78).

The *cis*-alcohol **3.77** (0.100 g, 0.13 mmol), THF (2 mL), ethanol (7 mL), deionized water (0.5 mL), trifluoroacetic acid (0.5 mL), 20% $Pd(OH)_2/C$ (0.03 g) were taken in a hydrogenation bottle and stirred under an atmosphere of hydrogen (60 psi) for 30 h. The reaction mixture was passed through a bed of Celite, the latter was washed successively with ethanol (20 mL) and hot water (30 mL). The combined filtrate and washings was evaporated under reduced pressure to afford *cis*-inositol **1.6** (0.03 g) as a glassy solid. The product **1.6** (0.03 g), pyridine (2 mL) and acetic anhydride (1.5 mL) were heated at 110 ^oC for 2.5 h. The reaction mixture was cooled to room temperature, ice was added and stirred for 15 min. The solvents were removed under reduced pressure, the residue was taken in ethyl acetate and washed successively with saturated sodium hydrogen carbonate solution, water and brine. The organic layer was dried over anhydrous sodium sulphate and the solvents were removed under reduced pressure and the residue (0.080 g), purified by flash column chromatography (eluent: ethyl acetate/light petroleum 3:7) to afford the hexaacetate **3.78** as a solid (0.05 g, 86%).

Data for 3.78: Mp. = 203–205 ^oC (crystals obtained from ethanol-water at room temperature); Lit.[23] **Mp.** = 206 ^oC; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.56 (bs, 3H, Ins H) 5.08 (bs, 3H, Ins H), 2.16 (s, 9H, OC-*CH_3*), 2.03 (s, 9H, OC-*CH_3*) ppm.

Racemic 5-*O*-allyl-1-*O*-(4-chlorobenzyl)-2,4,6-tri-*O*-benzyl-*myo*-inositol (3.91).

To an ice-cooled solution of **1.187**[13a] (8.50 g, 18.39 mmol) in DMF (50 mL), was added sodium hydride (2.20 g, 55.17 mmol) followed by allyl bromide (3.18 mL, 36.78 mmol), and the mixture was stirred at ambient temperature for 4 h. Excess of sodium hydride was destroyed by the addition of ice, the solvents were removed under reduced pressure, and the residue was worked up with ethyl acetate as usual to obtain the crude product (10.2 g). To the crude allyl ether (10.2 g), methanol (25 mL) and concd. HCl (5 mL) were added,

and the mixture was refluxed for 5 h. The reaction mixture was cooled to ambient temperature, acid was neutralized by the addition of solid sodium hydrogen carbonate, and the mixture was filtered through a bed of Celite. The filtrate was concentrated under reduced pressure and worked up with ethyl acetate as usual. The product was purified by flash column chromatography (ethyl acetate/light petroleum, 1:3) to afford the 1,3-diol **2.35** (8.5 g, 94%) as a gum. To an ice-cooled solution of **2.35** (6.00 g, 12.24 mmol) in dry DMF (30 mL), was added sodium hydride (0.54 g, 13.47 mmol) followed by a solution of 4-chlorobenzyl bromide (2.64 g, 12.86 mmol) in DMF (20 mL), and the reaction mixture was stirred at room temp. for 12 h. Excess of sodium hydride was destroyed by the addition of ice, solvents were removed under reduced pressure, and the residue was worked up with ethyl acetate as usual. The product was separated by flash column chromatography (ethyl acetate/light petroleum, 1:4) on silica gel to obtain **3.91** (3.6 g, 48%; 78% based on recovered **2.35**) as a gum, which turned into a sticky solid on cooling under light petroleum (in a refrigerator); unreacted starting diol **2.35** (2.3 g, 38%) was recovered.

Data for 3.91: IR ($CHCl_3$): $\bar{\nu}$ 3559, 3455 (OH) cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.40–7.28 (m, 15 H, Ar-H), 7.24–7.18 (m, 4 H, Ar-H), 6.08–5.89 (m, 1 H, C*H*=CH_2), 5.35–5.14 (m, 2H, CH=C*H*$_2$), 5.00–4.87 (m, 2H), 4.84 (s, 2 H), 4.78–4.69 (dd, *J* = 2.5, 11.0 Hz, 2H), 4.61 (s, 2H), 4.44–4.27 (m, 2H), 4.05–3.94 (m, 2H), 3.77 (t, *J* = 9.5 Hz, 1H), 3.48–3.28 (m, 3H), 2.24 (br. s, 1H, D_2O exchangeable, OH) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 138.43 (C_{ipso}), 138.4 (C_{ipso}), 136.6 (C_{ipso}), 134.9, 133.0 (C_{ipso}), 128.5, 128.3, 128.1, 127.83, 127.8, 127.5, 127.39, 127.36, 116.4 (CH=*C*H_2), 83.0 (Ins C), 81.6 (Ins C), 81.5 (Ins C), 80.5 (Ins C), 76.6 (Ins C), 75.6 (CH_2), 75.2 (CH_2), 74.4 (CH_2), 74.2 (CH_2), 71.9 (Ins C), 71.6 (CH_2) ppm; **Elemental Anal.** $C_{37}H_{39}ClO_6$ (615.15): calcd. C, 72.24; H 6.39 found C, 72.58; H, 6.55 %.

Racemic 1-*O*-allyl-2,4,6-tri-*O*-benzyl-*myo*-inositol (2.3).

To an ice-cooled soln. of triol **2.1** (0.225 g, 0.5 mmol) in DMF (4.0 mL) was added sodium hydride (0.022 g, 0.55 mmol), followed by addition of allyl bromide (0.043 mL, 0.5 mmol). Reaction mixture was stirred for 15 min. at ambient temperature. Ice was added to reaction mixture solvent removed under reduced pressure and residue worked up as usual with ethyl acetate. Crude product was purified by flash column chromatography to obtain

allyl ether **2.3**[10b] (0.15 g, 61%) as a gum. A small amount of di-allyl ether (0.027 g, 10%) and starting triol **2.1** (0.05 g, 20%) was obtained.

Racemic 6-*O*-acetyl-4-*O*-allyl-1,3,5-tri-*O*-benzyl-2-*O*-(4-chlorobenzyl)-*chiro*-inositol (3.94).

To a cooled solution (–15 °C) of **3.91** (1.43 g, 2.32 mmol) in pyridine/dichloromethane (5:15 mL) was added trifluoromethanesulfonic anhydride (0.58 mL, 3.49 mmol), and the reaction mixture was stirred for 2 h, during which time the mixture was allowed to warm to ambient temperature. The reaction mixture was decomposed by the addition of ice, then solvents were removed under reduced pressure, and the residue was worked up with dichloromethane as usual. The product was purified by column chromatography on silica gel to obtain the corresponding triflate **3.93** (1.6 g, 90%) as a gum. The triflate **3.93** (1.6 g), benzene (12 mL), cesium acetate (1.23 g, 6.43 mmol) and 18-crown-6 (1.13 g, 4.28 mmol), were refluxed for 2 h. The reaction mixture was cooled to ambient temperature and decomposed by the addition of ice, then diluted with dichloromethane and worked up as usual. The product was purified by flash column chromatography (ethyl acetate/light petroleum, 1.5:8.5) to afford the *chiro*-acetate **3.94** (0.98 g, 70%) as a gum and 4-*O*-allyl-1,3,5-tri-*O*-benzyl-2-*O*-(4-chlorobenzyl)cyclohex-1(6)-ene-1,2,3,4,5-pentol (**3.95**) (ethyl acetate/light petroleum, 1:13) as a colorless solid (0.32 g, 25%).

Data for 3.94: IR (neat): $\bar{\nu}$ 1747(C=O) cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.39–7.27 (m, 17H, Ar-H), 7.24–7.17 (m, 2H, Ar-H), 6.10–5.90 (m, 1H, C*H*=CH2), 5.36–5.14 (m, 3H, CH=CH_2, 1H), 4.84 (q, *J* = 12.8 Hz, 2H), 4.74–4.47 (m, 6H), 4.45–4.23 (m, 2H), 3.95–3.79 (m, 2H), 3.73 (t, *J* = 3.6 Hz, 1H), 3.66–3.55 (m, 2H), 1.99 (s, 3H, OC-C*H*3) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 169.6 (C=O), 138.6 (C_{ipso}), 137.9 (C_{ipso}), 137.7 (C_{ipso}), 136.7 (C_{ipso}), 135.2, 133.2 (C_{ipso}), 128.9, 128.34, 128.29, 128.27, 128.2, 128.1, 127.8, 127.63, 127.6, 116.4 (CH=*C*H_2), 81.5 (Ins C), 81.3 (Ins C), 79.2 (Ins C), 77.3 (Ins C), 76.0 (CH_2), 74.5 (CH_2), 74.0 (Ins CH), 73.1 (CH_2), 72.6 (CH_2), 72.1 (CH_2), 67.8 (Ins C), 20.8 (OC-*C*H_3) ppm; **Elemental Anal.** $C_{39}H_{41}ClO_7$ (657.19): calcd. C, 71.28; H, 6.29 found C, 71.32; H, 6.49 %.

Data for 3.95: Mp. = 87–89 °C. **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.45–7.28 (m, 15H, Ar-H), 7.24–7.15 (m, 4H, Ar-H), 6.10–5.90 (m, 1H), 5.37–5.30 (m, 2H), 5.00–4.57 (m, H), 4.50–4.30 (m, 2H), 4.28–4.16 (m, 2H), 3.72 (dd, *J* = 7.3, 7.5 Hz, 1H), 3.56 (dd, *J* = 7.3, 7.2 Hz, 1H) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 153.7 (C_{ipso}), 138.52 (C_{ipso}), 138.46 (C_{ipso}),

136.9 (C_{ipso}), 136.4 (C_{ipso}), 135.1, 133.2 (C_{ipso}), 129.5, 128.5, 128.4, 128.34, 128.30, 128.1, 127.9, 127.8, 127.7, 127.6, 116.8 (CH=*C*H_2), 96.9 (Ins C), 83.2 (Ins C), 82.5 (Ins C), 80.2 (Ins C), 78.4 (Ins C), 75.6 (CH_2), 74.12 (CH_2), 74.06 (CH_2), 72.4 (CH_2), 69.7 (CH_2) ppm; **Elemental Anal.** $C_{37}H_{37}ClO_5$ (597.14): calcd. C, 74.42; H, 6.25 found C, 74.46; H, 5.86 %.

Preparation of racemic 4-*O*-allyl-1,3,5-tri-*O*-benzyl-2-*O*-(4-chlorobenzyl)-6-*O*-(4-methoxybenzyl)-*chiro*-inositol (3.97).

A mixture of *chiro*-acetate **3.94** (1.75 g, 2.66 mmol), isobutylamine (2 mL) and methanol (12 mL) was refluxed for 4 h. The solvent was removed under reduced pressure, and the residue was worked up with ethyl acetate as usual, to afford the corresponding crude alcohol (1.65 g). To an ice-cooled solution of the alcohol (1.65 g) and tetrabutylammonium iodide (0.02 g) in DMF (15 mL), sodium hydride (0.32 g, 7.98 mmol) was added followed by PMBCl (0.90 g, 6.65 mmol). The mixture was stirred at ambient temperature for 4 h, then the reaction mixture was decomposed by the addition of ice, the solvent was removed under reduced pressure, and the residue was worked up with dichloromethane as usual. The product was purified by column chromatography (ethyl acetate/light petroleum, 2:23) on silica gel to obtain the racemic *chiro*-PMB ether **3.97** (1.85 g, 95% yield) as a gum.

Data for 3.97: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40–7.17 (m, 17 H, Ar-H), 7.16–7.10 (m, 2 H, Ar-H), 7.05–7.00 (m, 2H, Ar-H), 6.82–6.77 (m, 2H, Ar-H), 6.06–5.96 (m, 1 H), 5.32–5.25 (m, 1H), 5.18–5.13 (m, 1H), 4.84 (q, *J* = 10.7 Hz, 2H), 4.69 (d, *J* =11.9 Hz, 1 H), 4.60–4.31 (m, 8 H), 4.25 (d, *J* = 11.9 Hz, 1H), 3.85–3.77 (m, 1H), 3.79 (s, 3 H, Ar-OC*H*3), 3.75–3.68 (m, 3H), 3.61–3.58 (m, 1H), 3.51 (t, *J* = 3.36 Hz, 1H) ppm; **^{13}C NMR** (125.6 MHz, $CDCl_3$): δ 159.1 (C_{ipso}), 139.0 (C_{ipso}), 138.8 (C_{ipso}), 138.2 (C_{ipso}), 137.3 (C_{ipso}), 135.6, 133.2 (C_{ipso}), 130.5 (C_{ipso}), 128.3, 129.1, 128.4, 128.3, 128.0, 127.9, 127.7, 127.6, 127.5, 116.4 (CH=*C*H_2), 113.7, 82.0 (Ins C), 81.9 (Ins C), 79.6 (Ins C), 79.5 (Ins C), 75.9 (CH_2), 74.9 (Ins C), 74.6 (CH_2), 74.5 (Ins C), 73.3 (CH_2), 72.9 (CH_2), 72.8 (CH_2), 72.3 (CH_2), 55.2 (OCH_3) ppm; **Elemental Anal.** $C_{45}H_{47}ClO_7$ (735.30): calcd. C, 73.50; H, 6.44 found C, 73.64; H, 6.58 %.

Preparation of racemic 1-*O*-(4-chlorobenzyl)-2,4,6,-tri-*O*-benzyl-3-Oxo-5-*O*-allyl-m*yo*-inositol (3.98).

Dichloromethane (2.0 mL) and oxalyl chloride (0.24 mL, 2.73 mmol) were taken in a two-necked round bottom flask (50 mL) and cooled to -78 ^{o}C. A solution of dimethyl

sulphoxide (0.25 mL, 3.75 mmol) in dichloromethane (2.0 mL) was added, and stirred at -78 ^{o}C for 20 min. To the resulting mixture, a solution of the *myo*-alcohol **3.91** (0.70 g, 1.14 mmol) in dichloromethane (7.0 mL) was added dropwise and strirring continued at -78 ^{o}C for 2 h. Triethylamine (0.87mL, 6.27 mmol) was added to the reaction mixture at -78 ^{o}C and then stirred for 2 h at ambient temperature. The reaction mixture was diluted with dichloromethane and worked up as usual and the residue was purified by flash column chromatography to afford the ketone **3.98** (0.62 g, 89%) as a gum.

Data for 3.98: IR (Nujol): $\bar{\nu}$ 1738 (C=O) cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.40–7.28 (m, 14H, Ar), 7.25–7.13 (m, 5H, Ar), 6.06–5.86 (m, 1H), 5.35–5.13 (m, 2H), 4.86 (s, 2H), 4.65 (s, 1H), 4.60 (d, *J* = 1.6 Hz, 1H), 4.53-4.16 (m, 8H), 3.94 (d, *J*=2.8 Hz, 1H), 3.43-3.32 (m, 2H) ppm.

Reduction of 1-*O*-(4-chlorobenzyl)-2,4,6,-tri-*O*-benzyl-3-Oxo-5-*O*-allyl-*myo*-inositol (3.98).

General procedure: To an ice cooled solution of the inosose **3.98** (0.4-0.06 mmol), in solvent was added the hydride reducing agent (1.98-0.3 mmol) and stirred for 30 min. To the reaction mixture, saturated solution of ammonium chloride was added, solvents removed under reduced pressure and the residue worked up as usual with ethyl acetate. The crude product was taken in pyridine (1.5 mL) and stirred for 12 h after the addition of acetic anhydride (0.5 mL). The reaction mixture was decomposed by the addition of ice, solvents were removed under reduced pressure and the residue worked up as usual with ethyl acetate to get a mixture of isomeric acetates **3.92:3.94** (0.04–0.05 g), from which ratio of isomers was estimated by ^{1}H NMR spectroscopy.

Reduction with sodium borohydride in THF:MeOH: Procedure A: The *myo*-inosose **3.98** (0.24 g, 0.39 mmol) was reduced in THF:methanol (3.6:1.0 mL), with sodium borohydride (0.74 g, 1.98 mmol) as in the general procedure to afford *chiro*-alcohol **3.96** [0.08 g, 33% (eluent: 17 % ethyl acetate:light petroleum)], *myo*-alcohol **3.91** (0.06 g, 25%) and a mixture of **3.91**:**3.96** (0.08 g, 33%) after column chromatography, *myo*-alcohol **3.91** was acetylated using acetic anhydride and pyridine to get the *myo*-acetate **3.92**.

Data for 3.92: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.38–7.20 (m, 19H, Ar), 6.07–5.86 (m, 1H), 5.35–5.10 (m, 2H), 4.90–4.55 (m, 9H), 4.34 (d, *J* = 5.55 Hz, 2H) 4.10–3.95 (m, 3H), 3.50–3.30 (m, 2H), 1.93 (s, 3H) ppm.

Reduction with potassium borohydride in THF:MeOH: Procedure B: The *myo*-inosose **3.98** (0.04 g, 0.06 mmol) was reduced in THF:methanol (1.0:0.5 mL), with potassium borohydride (0.03 g, 0.55 mmol) as in the general procedure to obtain a mixture of **3.92**:**3.94** (0.04 g, 95%).

Reduction with DIBAL-H in THF: Procedure C: The *myo*-inosose **3.98** (0.05 g, 0.08 mmol) was reduced in THF (1.0 mL), with DIBAL-H (1.0 M soln. in toluene) (0.3 ml, 0.3 mmol) as in the general procedure to obtain mixture of **3.92**:**3.94** (0.04 g, 89%).

Reduction with Red-Al (sodium bis(2-methoxyethoxy)aluminium hydride) in THF: Procedure D: The *myo*-inosose **3.98** (0.05 g, 0.08 mmol) was reduced in THF (1.0 mL), with sodium bis(2-methoxyethoxy)aluminium hydride, Red-al (1.58 M soln. in toluene) (0.08 ml, 0.13 mmol) as in the general procedure to obtain a mixture of **3.92**:**3.94** (0.05 g, 95%).

Reaction of symmetric diol 2.35 with (–)-(1S)-Camphanic chloride.

Procedure A: To an ice cooled solution of diol **2.35** (0.20 g, 0.41 mmol) , DMAP (0.01 mg) in DCM (4 mL) tri-ethylamine (0.063 mL, 0.45 mmol) was added followed by addition of (–)-(1S)-camphanic chloride (0.09 g, 0.42 mmol) in DCM stirred at 0 °C and then at rt 4 h. Ice was added to reaction mixture, diluted with DCM and worked up 'as usual'. Crude product was purified by flash column chromatography to afford mixture of **3.99** and **dia 3.99** (0.14 g, 50%) along with di-ester **3.100** (0.06 g, 16%) and starting diol **2.35** (0.06 g, 30%) to give. Ratio of **3.99** and **dia 3.99** (1:3.7) was estimated from ^{1}H NMR of the mixture.

Procedure B: To an ice cooled solution of diol **2.35** (0.115 g, 0.23 mmol) , DMAP (5 mg) in DCM (2 mL) pyridine (0.095 mL, 1.17 mmol) was added followed by addition of camphanic acid chloride (0.053 g, 0.246 mmol) in DCM stirred at 0 °C and then at rt 4 h. To the reaction mixture ice was added, diluted with DCM and worked up 'as usual'. Crude product was purified by flash column chromatography to afford mixture of **3.99** and **dia 3.99** (0.07 g, 43%) along with di-ester **3.100** (0.012 g, 6%) and starting diol **2.35** (0.05 g, 42%) to give. Ratio of **3.99** and **dia 3.99** (1:2.52) was estimated from ^{1}H NMR of the mixture.

Racemic 1,3,5-tri-*O*-benzyl-2-*O*-(4-chlorobenzyl)-6-*O*-(4-methoxybenzyl)-*chiro*-inositol (3.101).

To an ice-cooled solution of the *chiro*-allyl ether **3.97** (1.85 g, 2.51 mmol) in toluene (20 mL), (dppp)$NiCl_2$ (0.07 g, 0.12 mmol) and DIBAL-H (7.55 mL, 7.55 mmol, 1 M in toluene) were added, and the mixture was stirred at room temp. for 3 h. The reaction mixture was diluted with dichloromethane (80 mL), cooled to 0 °C and methanol (4 mL) and 10% HCl (5 mL) were added. The mixture was stirred at room temp. for 3 h, and the precipitate formed was filtered by passing through a bed of Celite and washed with dichloromethane. The filtrate was concentrated under reduced pressure, and the residue was taken up in dichloromethane, washed successively with aq. sodium hydrogen carbonate, water, brine and dried with anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the product was purified by column chromatography (ethyl acetate/light petroleum, 1:4) to afford the racemic *chiro*-alcohol **3.101**(1.50 g, 86%) as a gum.

Data for 3.101: IR ($CHCl_3$): $\bar{\nu}$ 3609–3322 (OH) cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.40–7.27 (m, 13H, Ar-H), 7.25–7.12 (m, 6H, Ar-H), 7.08–6.99 (m, 2H, Ar-H), 6.85–6.76 (m, 2H, Ar-H), 4.86 (q, *J* = 12.5 Hz, 2H), 4.65–4.35 (m, 7H), 4.23 (d, *J* = 11.7 Hz, 1H), 3.98 (t, *J* = 8.5 Hz, 1H), 3.83–3.72 (m, 2H), 3.80 (s, 3H, Ar-OC*H*3), 3.71–3.57 (m, 3H), 2.53 (br. s, 1H, D2O exchangeable, OH) ppm;**^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 159.1 (C_{ipso}), 138.9 (C_{ipso}), 138.3 (C_{ipso}), 138.1 (C_{ipso}), 137.1 (C_{ipso}), 133.1 (C_{ipso}), 130.2 (C_{ipso}), 129.2 (C_{arom}), 129.0 (C_{arom}), 128.4 (C_{arom}), 128.3 (C_{arom}), 127.9 (C_{arom}), 127.74 (C_{arom}), 127.7 (C_{arom}), 127.4 (C_{arom}), 113.6 (C_{arom}), 81.6 (InsC), 79.2 (InsC), 79.1 (InsC), 75.3 (CH_2), 74.8 (InsC), 73.6 (InsC), 73.0 (InsC), 72.9 (CH_2), 72.7 (CH_2), 72.1 (CH_2), 55.1 (OCH_3) ppm; **Elemental Anal.** $C_{42}H_{43}ClO_7$ (695.24): calcd. C 72.56, H 6.23; found C 72.83, H 6.08 %.

Racemic 1,3,5-tri-*O*-benzyl-2-*O*-(4-chlorobenzyl)-6-*O*-(4-methoxybenzyl)-*allo*-inositol (3.103).

Dichloromethane (1.5 mL) and oxalyl chloride (0.18 mL, 2.07 mmol) were taken in a twonecked round-bottomed flask (50 mL) and cooled to –78 °C. A solution of dimethyl sulfoxide (0.18 mL, 2.84 mmol) in dichloromethane (1.5 mL) was added, and the reaction mixture was stirred at –78 °C for 20 min. To the resulting mixture, a solution of the *chiro*-alcohol **3.101** (0.60 g, 0.86 mmol) in dichloromethane (5.0 mL) was added dropwise, and

the mixture was stirred at –78 °C for 2 h.Triethylamine (0.66 mL, 4.73 mmol) was added at –78 °C, and the mixture was stirred at ambient temperature for 2 h. The reaction mixture was diluted with dichloromethane and worked up as usual to obtain the ketone **3.102** (0.70 g). To an ice-cooled solution of the crude ketone **3.102** (0.70 g) in a THF/methanol (8:2 mL) mixture, sodium borohydride (0.16 mL, 4.3 mmol) was added, and the mixture was stirred at ambient temperature for 30 min. Saturated ammonium chloride solution was added to the reaction mixture, solvents were removed under reduced pressure, and the residue was worked up as usual with dichloromethane. The product was purified by flash column chromatography (ethyl acetate/light petroleum, 1:4) to afford racemic *allo*-alcohol **3.103** as a gum (0.58 g, 96%).

Data for 3.103: IR (Neat): $\bar{\nu}$ 3505 (OH) cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.45–7.27 (m, 15 H, Ar-H), 7.24–7.02 (m, 6H, Ar-H), 6.85–6.77 (m, 2H, Ar-H), 4.81–4.30 (m, 11H), 4.05–3.63 (m, 5H), 3.80 (s, 3 H, Ar-OCH_3), 3.56 (br. s, OH, 1 H, D_2O exchangeable) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 159.3 (C_{ipso}), 138.5 (C_{ipso}), 138.1 (C_{ipso}), 137.4 (C_{ipso}), 133.0 (C_{ipso}), 129.4 (C_{arom}), 129.0 (C_{arom}), 128.30 (C_{arom}), 129.27 (C_{arom}), 128.2 (C_{arom}), 127.7 (C_{arom}), 127.5 (C_{arom}), 127.4 (C_{arom}), 113.7 (C_{arom}), 78.4 (InsC), 77.8 (InsC), 76.0 (InsC), 75.3 (InsC), 73.6 (CH_2), 73.2 (CH_2), 72.7 (CH_2), 72.2 (CH_2), 55.2 (OCH_3) ppm; **Elemental Anal.** $C_{42}H_{43}ClO_7$ (695.24): calcd. C, 72.56; H, 6.23 found C, 72.87; H, 6.42 %.

Hexa-*O*-acetyl-*allo*-inositol (3.104).

A mixture of the *allo*-inositol derivative **3.103** (0.100 g, 0.13 mmol), THF (2 mL), ethanol (6 mL), deionized water (0.5 mL), trifluoroacetic acid (1.0 mL) and 20% Pd-$(OH)_2$ (0.04 g) was hydrogenated at 60 psi for 40 h. The reaction mixture was passed through a bed of Celite, and the latter washed successively with ethanol and hot water. The combined filtrate was evaporated under reduced pressure to afford *allo*-inositol **1.2** (0.03 g) as a glassy solid. *allo*-Inositol **1.2** (0.03 g), pyridine (2 mL) and acetic anhydride (0.5 mL) were heated at 80 ^oC for 8 h. The reaction mixture was cooled to room temperature and stirred with ice for 15 min. The solvents were removed under reduced pressure, the residue was taken in ethyl acetate and washed sequentially with saturated sodium hydrogen carbonate solution, water and brine. The organic layer was dried over anhydrous sodium sulphate and the solvents removed under reduced pressure. The residue (0.080 g) was purified by flash

column chromatography to afford *allo*-inositol hexaacetate **3.104** (eluent: ethyl acetate/light petroleum 7:13) as a solid (0.055 g, 90%).

Data for 3.104: Mp. = 137–139 ^{o}C (crystals obtained from ethanol at room temperature), Lit.[26b] **Mp.** = 142–143 ^{o}C; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.52–5.42 (m, 3H, Ins H) 5.37–5.28 (m, 3H, Ins H), 2.09 (bs, 18H, OC-*CH_3*) ppm.

Reaction of bis-triflate of diol 2.35 with potassium acetate.

To a cooled (ice and salt mixture) solution of the diol **2.35** (0.25 g, 0.51 mmol), in pyridine :dichloromethane (1:3.5 mL) was added trifluoromethane sulphonic anhydride (0.21 mL, 1.27 mmol) and stirred at ambient temperature for 2 h. Ice was added to the reaction mixture, and concentrated under reduced pressure; the residue was worked up as usual with dichloromethane. The crude product was purified by column chromatography (eluent: ethyl acetate / light petroleum, 1:19) to afford the bis-triflate **3.124** (0.3 g, 78%) as a colorless solid.

Data for 3.124: Mp. = 88–90 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.50–7.28 (m, 15H), 5.98–5.77 (m, 1H), 5.35–5.10 (m, 2H), 4.79 (s, 4H), 4.76 (s, 2H), 4.67 (dd, *J*=10.0 and 2.4 Hz, 2H), 4.35 (t, *J*=2.4 Hz, 1H), 4.32–4.24 (m, 2H), 4.07 (t, *J*= 9.5 Hz, 2H), 3.30 (t, *J*= 9.4 Hz, 1H) ppm.

The bis-triflate **3.124** (0.10 g, 0.13 mmol) obtained above, potassium acetate (0.06 g, 0.61 mmol) and dimethyl acetamide (2.0 mL) were heated at 80 °C for 12 h. The reaction mixture was cooled to ambient temperature and ice was added, and the mixture was concentrated under reduced pressure; the residue was worked up as usual with ethyl acetate. The crude product was purified by flash column chromatography (eluent: ethyl acetate / light petroleum, 1:4) to obtain the mono acetate **3.125** (0.050 g, 74 %) as a gum.

Data for 3.125: IR (Neat): $\bar{\nu}$ 1745 (C=O), 1672 (C=C) cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.45–7.26 (m, 15H), 6.11–5.89 (m, 1H), 5.84 (d, *J*=3.8 Hz, 1H), 5.36–5.13 (m, 2H), 4.87 (d, *J*= 2.5 Hz, 1H), 4.81–4.51 (m, 6H), 4.51–4.20 (m, 2H), 4.15 (dd, *J*=6.9 and 2.8 Hz, 1H), 3.83 (dd, *J*= 10.5 and 6.9 Hz, 1H), 3.59 (dd, *J*= 10.5 and 3.9 Hz, 1H), 2.10 (s, CH_3, 3H) ppm.**^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 170.3 (C=O), 151.3 (Ring C), 138.6 (C_{ipso}), 138.0 (C_{ipso}), 136.2 (C_{ipso}), 135.3 (C_{arom}), 128.4 (C_{arom}), 128.3 (C_{arom}), 127.95 (C_{arom}), 127.87 (C_{arom}), 127.8 (C_{arom}), 127.7 (C_{arom}), 127.60 (C_{arom}), 127.57 (C_{arom}), 127.1 (C_{arom}), 116.5 (C=*C*H_2) 100.4 (Ring CH) 79.9 (CH), 78.3 (CH), 77.3 (CH), 73.9 (CH_2),

72.3 (CH_2), 71.9 (CH_2), 69.5 (CH_2), 67.7 (CH), 21.0 (OC-*C*H_3) ppm; **Elemental Anal.** $C_{32}H_{34}O_6$ (514.61): calcd. C, 74.69; H, 6.66 found C, 74.83; H, 7.01 %.

Racemic 4-amino-4-deoxy-1,3,5-tri-*O*-benzyl-2-*O*-(4-bromobenzyl)-6-*O*-allyl *myo*-inositol (3.130).

To a cooled (–40 ^oC) solution of the *epi*-alcohol **3.49** (0.42 g, 0.63 mmol) in dichloromethane (4 mL), pyridine (2 mL) and trifluoromethanesulphonic anhydride (0.16 mL, 0.95 mmol) were added and stirred at ambient temperature for 1 h. The reaction mixture was decomposed by the addition of ice. The solvents were removed under reduced pressure; the residue was taken in dichloromethane and worked up as usual. The product was purified by column chromatography on silica gel to obtain the *epi*-triflate **3.127** (0.46 g, 92 %) as a gum. To an ice cooled solution of the *epi*-triflate **3.127** (0.25 g, 0.32 mmol) in DMF (3.5 mL), sodium azide (0.04 g, 0.64 mmol) was added and stirred at ambient temperature for 1 h. The reaction mixture was decomposed by the addition of ice and solvents removed under reduced pressure. The residue was taken in ethyl acetate and worked up as usual to afford a (0.19 g) mixture of *myo*-azide **3.128** and the cyclohexene **3.129**.The mixture of products obtained above (0.19 g), THF (10 mL), deionised water (0.5 mL) and triphenyl phosphine (0.12 g, 0.46 mmol) were refluxed for 12 h. The reaction mixture was cooled to ambient temperature and decomposed by the addition of ice. The solvents were removed under reduced pressure, the residue taken in ethyl acetate and worked up as usual. The products were separated by flash column chromatography (eluent: ethyl acetate/light petroleum, 11:39) to obtain the cyclohexene **3.129** as a gum (0.04 g, 22%) and the *myo*-amine **3.130** (eluent: ethyl acetate/light petroleum, 4:1) as a colorless solid (0.13 g, 63%).

Data for 3.130: Mp. = 56–58 ^oC; **IR** (Neat): $\bar{\nu}$ 3362, 3295 (NH_2) cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.41–7.28 (m, 17H, Ar-H), 7.23–7.17 (m, 2H, Ar-H), 6.09–5.89 (m, 1H, *CH*=CH_2), 5.33–5.12 (m, 2H, CH=*CH_2*), 5.00 (d, *J*=10.8 Hz, 1H), 4.82–4.55 (m, 6H), 4.52–4.25 (m, 4H), 4.00 (t, *J*=2.1 Hz, 1H), 3.91 (t, *J*=9.4 Hz, 1H), 3.48–3.30 (m, 2H), 3.27–3.08 (m, 2H) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 138.6 (C_{ipso}), 138.3 (C_{ipso}), 137.9 (C_{ipso}), 137.7 (C_{ipso}), 135.2, 131.1, 129.1, 128.4, 128.5, 128.3, 127.8, 127.7, 127.63, 127.59, 127.4, 83.7 (Ins C), 81.8 (Ins C), 81.2 (Ins C), 80.7 (Ins C), 75.5 (CH_2), 74.2 (CH_2), 73.8 (Ins CH), 73.2 (CH_2), 73.0 (CH_2), 72.1 (CH_2), 52.8 (Ins C) ppm; **HRMS** $C_{37}H_{41}NO_5Br$ (M+1) calcd 658.2168 found 658.2168.

Data for 3.129: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.48–7.26 (m, 17H, Ar-H), 7.23–7.14 (m, 2H, Ar-H), 6.12–5.92 (m, 1H, *CH*=CH_2), 5.38–5.12 (m, 2H, CH=*CH_2*), 4.80–4.56 (m, 9H), 4.54–4.30 (m, 2H), 4.22–4.00 (m, 3H), 3.52 (dd, *J*=3.4 and 10 Hz, 1H) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 154.4 (C_{ipso}), 138.8 (C_{ipso}), 138.4 (C_{ipso}), 137.7 (C_{ipso}), 136.2 (C_{ipso}), 135.4, 131.1, 129.6, 128.5, 128.3, 128.0, 127.7, 127.6, 127.5, 127.4, 121.1 (C_{ipso}), 116.5 (C=*CH_2*), 98.2 (Ins C), 80.1 (Ins C), 79.3 (Ins C), 78.8 (Ins C), 74.5 (Ins C), 73.8 (CH_2), 72.5 (CH_2), 72.2 (CH_2), 71.0 (CH_2), 69.6 (CH_2) ppm; **Elemental Anal.** $C_{37}H_{37}BrO_5$ (641.59): calcd C, 69.26; H, 5.81 found C, 69.36; H, 5.95 %.

Reaction of the triflate of 3.47 with sodium azide (to give bicyclo compound 3.133 and the *myo*-azide 3.128).

To a cooled (–40 ^{o}C) solution of the *myo*-alcohol **3.47** (0.56 g, 0.85 mmol) in dichloromethane (4 mL), pyridine (2 mL) and trifluoromethanesulphonic anhydride (0.21 mL, 1.27 mmol) were added and stirred at ambient temperature for 1 h. The reaction mixture was decomposed by the addition of ice. The solvents were removed under reduced pressure; the residue was taken in dichloromethane and worked up as usual. The product was purified by column chromatography (eluent: ethyl acetate/light petroleum 3:22) on silica gel to obtain the *myo*-triflate **3.131** (0.64 g, 95 %) as a gum. To the *myo*-triflate **3.131** (0.28 g, 0.35 mmol) in DMF (4 mL), sodium azide (0.12 g, 1.80 mmol) was added and stirred at 60 ^{o}C for 12 h. The reaction mixture was decomposed by the addition of ice and the solvents were removed under reduced pressure. The residue was taken in dichloromethane and worked up as usual. The product was purified by column chromatography (eluent: ethyl acetate/light petroleum, 3:17) on silica gel to obtain the bicyclic product **3.133** as a colorless solid, (0.14 g, 72 %) and the *myo*-azide **3.128** (eluent: ethyl acetate/light petroleum, 3:22) as a gum (0.05 g, 20%).

Data for 3.133: Mp. = 91–90 ^{o}C; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.46–7.38 (m, 2H, Ar-H), 7.37–7.28 (m, 10H, Ar-H), 7.24–7.17 (m, 2H, Ar-H), 5.89–5.70 (m, 1H, *CH*=CH_2), 5.24–5.13 (m, 2H, CH=*CH_2*), 4.68–4.60 (m, 3H), 4.55–4.47 (m, 4H), 4.42 (t, *J*=1.4 Hz, 1H), 4.16 (d, *J*=6.1 Hz, 1H), 3.90–3.83 (m, 2H) 3.78 (dt, *J*=1.5, 5.3 Hz, 1H), 3.72 (d, *J*= 6.1 Hz, 1H), 3.28 (d, *J*= 1.7 Hz, 1H) ppm; **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 137.7 (C_{ipso}), 137.4 (C_{ipso}), 137.1 (C_{ipso}), 133.7, 131.4, 129.6, 128.42, 128.4, 128.0, 127.9, 127.85, 127.8, 121.5 (C_{ipso}), 117.7 (C=*CH_2*), 84.1 (CH), 83.4 (CH), 83.1 (CH), 79.9 (CH),78.6 (CH), 76.7

(CH), 72.7 (CH_2), 72.1 (CH_2), 71.4 (CH_2), 71.2 (CH_2) ppm; **Elemental Anal.** $C_{30}H_{31}BrO_5$ (551.47): calcd. C, 65.34; H, 5.67 found C, 65.34; H, 5.94 %.

Data for 3.128: IR (Neat): $\bar{\nu}$ = 2110 (N_3) cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.45–7.28 (m, 17H, Ar-H), 7.23–7.15 (m, 2H, Ar-H), 6.07–5.87 (m, 1H, *CH*=CH_2), 5.34–5.12 (m, 2H, CH=*CH_2*), 4.82 (q, *J*=12.2 Hz, 2H), 4.75–4.48 (m, 6H), 4.45–4.22 (m, 2H), 4.00–3.83 (m, 3H), 3.25–3.06 (m, 3H) ppm; **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 138.1 (C_{ipso}), 138.0 (C_{ipso}), 137.6 (C_{ipso}), 137.5 (C_{ipso}), 135.2, 131.2, 129.4, 128.5, 128.4, 128.37, 128.2, 127.9, 127.8, 127.7, 127.5, 121.2 (C_{ipso}), 116.6 (C=*CH_2*), 81.8 (Ins C), 81.2 (Ins C), 80.3 (Ins C), 78.7 (Ins C), 75.8 (CH_2), 74.5 (CH_2), 74.2 (Ins C) 73.3 (CH_2), 72.9 (CH_2), 72.6 (CH_2), 65.2 (Ins C) ppm; **Elemental Anal.** $C_{37}H_{38}BrN_3O_5$ (684.62): calcd. C, 64.91; H, 5.59; N, 6.14 found C, 65.07; H, 5.24; N, 6.27 %.

Reaction of the mesylate of 3.47 with sodium azide (to give bicyclo compound 51 and the *myo*-azide 52).

To an ice cooled solution of the *myo*-alcohol **3.47** (0.62 g, 0.94 mmol) in pyridine (6 mL), was added methanesulphonyl chloride (0.14 mL, 1.87 mmol) and stirred for 12 h at ambient temperature. The reaction mixture was decomposed by the addition of ice and the solvents removed under reduced pressure. The residue was taken in ethyl acetate and worked up as usual. The product was purified by flash column chromatography (eluent: ethyl acetate/light petroleum 4:21) on silica gel to obtain the *myo*-mesylate **3.132** (0.64 g, 92 %) as a solid. The *myo*-mesylate (0.10 g, 0.14 mmol**)**, DMF (3 mL) and sodium azide (0.05, g 0.68 mmol) were heated at 140 ^oC for 28 h under argon atmosphere. The reaction mixture was decomposed by adding ice, solvents were evaporated under reduced pressure and worked up as usual. Flash column chromatography of the crude product yielded the bicyclo compound **3.133** (0.03 g, 40%), the *myo*-azide **3.128** (5.4 mg, 6%) and the starting mesylate (0.035 g, 35%).

Racemic 4-azido-4-deoxy-1,3,5-tri-*O*-benzyl-2-*O*-(4-chlorobenzyl)-6-*O*-(4-methoxybenzyl)-*chiro*-inositol (3.138).

To a cooled (ice and salt mixture) solution of the *allo*-alcohol **3.103** (0.60 g, 0.86 mmol) in dichloromethane (4 mL), pyridine (2 mL) and trifluoromethanesulphonic anhydride (0.22 mL, 1.29 mmol) were added and stirred at ambient temperature for 2 h. The reaction mixture was decomposed by the addition of ice. The solvents were removed under reduced pressure; the residue was taken in dichloromethane and worked up as usual. The product

was purified by column chromatography to obtain the *allo*-triflate **3.137** (0.65 g, 91%) (eluent: ethyl acetate / light petroleum, 1:9) as a gum. A mixture of *allo*-triflate **3.137** (0.6 g, 0.72 mmol), sodium azide (0.24 g, 3.62 mmol), and DMF (4 mL) was stirred at ambient temperature for 3 h. Ice was added to the reaction mixture and concentrated under reduced pressure. The residue was worked up as usual with ethyl acetate. Crude product obtained was purified by flash column chromatography (eluent: ethyl acetate / light petroleum, 1:9) to afford *chiro* azide **3.138** (0.37, 71%) as a gum and mixture of **3.138** and *allo* azide **3.139** (major **3.138** and minor **3.139**, 0.10 g, 19%).

Data for 3.138: IR (Neat): $\bar{\nu}$ 2106 (N_3) cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.43–7.27 (m, 14H), 7.26–7.05 (m, 5H), 7.05–6.95 (m, 2H), 6.86–6.75 (m, 2H), 4.83 (s, 2H), 4.72–4.17 (m, 8H), 3.91–3.47 (m, 6H) 3.80 (s, 3H) ppm; **^{13}C NMR** (100.6 MHz, $CDCl_3$) : δ 159.2 (C_{ipso}), 138.3 (C_{ipso}), 137.9 (C_{ipso}), 136.9 (C_{ipso}), 133.3 (C_{ipso}), 130.0 (C_{ipso}), 129.3 (C_{arom}), 129.1 (C_{arom}), 128.43 (C_{arom}), 128.38 (C_{arom}), 128.34 (C_{arom}), 128.32 (C_{arom}), 128.1 (C_{arom}), 127.79 (C_{arom}), 127.77 (C_{arom}), 127.7 (C_{arom}), 127.6 (C_{arom}), 80.2 (Ins CH), 79.3(Ins CH), 77.6 (Ins CH), 75.7 (CH_2), 74.5 (Ins CH), 73.7 (Ins CH), 72.92 (CH_2), 72.89 (CH_2), 72.85 (CH_2), 72.2 (CH_2), 65.5 (Ins CH), 55.2 (OCH_3) ppm; **Elemental Anal.** $C_{42}H_{42}ClN_3O_6$ (720.25): calcd. C, 70.04; H, 5.88; N, 5.83 found C, 69.72; H, 5.88; N, 5.44 %.

Racemic 1,2,3,5,6-penta-*O*-acetyl-4-acetylamino-4-deoxy-*chiro*-inositol (3.141).

A mixture of the *chiro* azide **3.138** (0.27 g, 0.37 mmol), THF (4 mL), ethanol (5 mL), trifluoroacetic acid (0.5 mL) and 20% Pd-$(OH)_2$ (0.04 g) was hydrogenated at 60 psi for 40 h. The reaction mixture was passed through a bed of Celite, and the latter washed successively with ethanol and hot water. The combined filtrate was evaporated under reduced pressure to afford *chiro*-inosamine **3.140** (0.12 g) as a glassy solid. Crude *chiro*-inosamine **3.140** (0.12 g), pyridine (3 mL) and acetic anhydride (2.5 mL) were stirred at ambient temperature for 40 h. Ice was added to the reaction mixture and stirred for 15 min. The solvents were removed under reduced pressure; the residue was taken in ethyl acetate and washed sequentially with saturated sodium hydrogen carbonate solution, water and brine. The organic layer was dried over anhydrous sodium sulphate and the solvents removed under reduced pressure. The residue (0.17 g) was purified by flash column chromatography (eluent: ethyl acetate/dichloromethane, 7:3) to afford *chiro*-inosamine hexaacetate **3.141**[31] as a solid (0.11 g, 70%).

Data for 3.141: Mp. = 184–186 ^{o}C (crystals obtained from ethyl acetate at room temperature); **IR** ($CHCl_3$) $\bar{\nu}$: 3300–3450 (NH), 1757 (broad peak C=O), 1678 (HNC=O) cm^{-1}; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 5.50 (d, *J*=10 Hz, D_2O exchangeable, NH, 1H), 5.40 (t, *J*= 3.3 Hz, 1H), 5.36–5.14 (m, 4H), 4.62 (q, *J*= 10 Hz, 1H), 2.21 (s, 3H), 2.17 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 1.99 (s, 3H), 1.92 (s, 3H), ppm; ^{13}**C NMR** (100.6 MHz, $CDCl_3$): δ 170.8 (C=O), 170.5 (C=O), 170.1 (C=O), 169.5 (C=O), 169.0 (C=O), 168.7 (C=O), 69.9 (Ins CH), 69.0 (Ins CH), 68.6 (Ins CH), 67.5 (Ins CH), 67.2 (Ins CH), 50.1 (Ins CH), 23.0 (CH_3), 20.7 (CH_3), 20.6 (CH_3), 20.5 (CH_3), 20.4 (CH_3) ppm; **Elemental Anal.** $C_{18}H_{25}NO_{11}$ (431.39): calcd. C, 50.12; H, 5.84; N, 3.25 found C, 50.11; H, 6.01; N, 3.01%.

Racemic 1,3,5-tri-*O*-benzyl-4-*O*-(4-methoxybenzyl)-6-*O*-allyl-*myo*-inositol (3.151).

A solution of N-methyl aniline (0.06 mL, 0.54 mmol) and 4-bromobenzyl ether **3.24** (0.35 g, 0.45 mmol) in toluene (4 mL), was added into a flask containing $Pd(dba)_2$ (0.005 g, 0.009 mmol), (O-biph)$P(t\text{-}Bu)_2$ (0.005 g, 0.018 mmol), sodium *tert*-butoxide (0.06 g, 0.63 mmol) and toluene (1 mL) and heated at 100 ^{o}C for 6 h.[36] The reaction mixture was cooled to ambient temperature, diluted with dichloromethane and passed through a bed of Celite. The filtrate was evaporated under reduced pressure and the residue was flash column chromatographed (eluent: ethyl acetate/light petroleum 1:9) on silica gel to get a mixture (0.29 g) of 2-(4-N-methyl-N-phenyl) benzyl ether and the starting material **3.24**. To an ice cooled solution of the mixture obtained above (0.29 g) in dichloromethane (4 mL), zinc chloride (0.06 g, 0.45 mmol) was added and stirred for 2 h. The reaction mixture was diluted with dichloromethane and washed successively with water, saturated solution of sodium hydrogen carbonate, brine and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the product was purified by flash column chromatography (eluent: ethyl acetate/light petroleum 1:4) on silica gel to obtain the starting material **3.24** (0.05 g 14%) and **3.151** (0.18 g, 66 %) as a gum.

Data for 3.151: IR (Neat): $\bar{\nu}$ 3603–3308 (OH) cm^{-1}; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 7.40–7.17 (m, 17H, Ar-H), 6.86–6.77 (m, 2H, Ar-H), 6.08–5.88 (m, 1H, *CH*=CH_2), 5.34–5.11 (m, 2H, CH=*CH_2*), 4.85 (s, 2H), 4.78 (d, *J*=2.4 Hz, 2H), 4.71 (s, 4H), 4.44–4.26 (m, 2H), 4.19 (t, *J*=2.6 Hz, 1H), 4.00-3.77 (m, 2H), 3.79 (s, 3H, Ph-O*CH_3*), 3.44–3.27 (m, 3H), 2.44 (bs, D_2O exchangeable, 1H) ppm; ^{13}**C NMR** (100.6 MHz, $CDCl_3$): δ 159.0 (C_{ipso}), 138.7 (C_{ipso}), 137.94 (C_{ipso}), 137.9 (C_{ipso}), 135.2, 130.9 (C_{ipso}), 129.5, 128.3, 128.2, 127.8, 127.7, 127.4, 116.5 (C=*CH_2*), 113.6, 83.1 (Ins C), 80.7 (Ins C), 79.7 (Ins C), 79.5 (Ins C),

75.8 (CH_2), 75.5 (CH_2), 74.5 (CH_2), 72.64 (CH_2), 72.6 (CH_2), 67.5 (Ins C), 55.1 (OCH_3) ppm; **Elemental Anal.** $C_{38}H_{42}O_7$ (610.74): calcd. C, 74.73; H, 6.93 found C, 74.80; H, 7.18 %.

Racemic 1,3,5-tri-*O*-benzyl-2-deoxy-2-fluoro-4-*O*-(4-methoxybenzyl)-6-*O*-allyl-*scyllo*-inositol (3.152).

A solution of **3.151** (0.10 g, 0.16 mmol) in dichloromethane (1.5 mL) was added to a solution of (diethylamino)-sulphurtrifluoride (0.08 mL, 0.61 mmol) in dichloromethane (1 mL) at 0 ^oC and maintained at the same temperature under stirring for 2 h, then at ambient temperature for 1 h. The reaction mixture was decomposed by the addition of ice and extracted with dichloromethane. The organic layer was washed with saturated sodium hydrogen carbonate followed by brine and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to get the crude product which was purified by flash column chromatography (eluent: ethyl acetate/light petroleum 1:9) on silica gel to obtain the fluoro *scyllo*-inositol **3.152** (0.08 g, 80 %) as a colorless solid.

Data for 3.152: Mp. = 57–59 ^oC; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.45–7.28 (m, 15H, Ar-H), 7.23–7.14 (m, 2H, Ar-H), 6.86–6.77 (m, 2H, Ar-H), 6.05–5.85 (m, 1H, *CH*=CH_2), 5.34–5.11 (m, 2H, CH=*CH_2*), 4.91–4.70 (m, 8H), 4.51 (dt, $^2J_{H,\,F}$=51.4 and $^3J_{H,H}$ =9.1 Hz, 1H, H-2), 4.37–4.30 (m, 2H), 3.79 (s, 3H, Ph-O*CH_3*), 3.70–3.31 (m, 5H) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 159.2 (C_{ipso}), 138.4 (C_{ipso}), 138.2 (C_{ipso}), 134.9, 130.5 (C_{ipso}), 129.5, 128.3, 128.05, 128.0, 127.9, 127.8, 127.73, 127.7, 116.8 (C

=*CH_2*), 113.8, 96.1 (d, *J*=183.3 Hz, Ins C), 82.4 (Ins C), 81.1 (Ins C), 80.8 (Ins C), 80.7 (Ins CH), 75.9 (CH_2), 75.7 (CH_2), 75.4 (CH_2), 74.7 (CH_2), 55.2 (OCH_3) ppm; **^{19}F NMR** (188.31 MHz, $CDCl_3$, hexafluoro benzene as internal reference δ –164.71): δ –196.6 (dt, *J*=12.7 and 51.6 Hz) ppm; **Elemental Anal.** $C_{38}H_{41}FO_6$ (612.73): calcd. C, 74.49; H, 6.74 found C, 74.15; H, 6.92 %.

Racemic 1,3,5-tri-*O*-benzyl-2-*O*-(4-bromobenzyl)-4-deoxy-6-*O*-allyl-*myo*-inositol (3.155).

To an ice cooled solution of **3.154** (0.91 g, 1.38 mmol) in THF (15 mL), sodium hydride (0.28 g, 6.90 mmol) was added and stirred at ambient temperature for 20 min. Carbon disulphide (1.24 mL, 20.70 mmol) was added to the reaction mixture and stirred for 20 min. at ambient temperature, and then refluxed for 90 min. The reaction mixture was cooled to ambient temperature, methyl iodide (0.43 mL, 6.90 mmol) was added and stirred

for 16 h at ambient temperature. The reaction mixture was then diluted with ethyl acetate and washed successively with water:ethanol (100:2 mL), saturated ammonium chloride solution and brine. The organic layer was dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure. The product was purified by flash column chromatography (eluent: ethyl acetate/light petroleum 2:13) to afford the *myo*-xanthate (0.95 g, 92 %) as a gum. The *myo*-xanthate (0.58 g, 0.77 mmol), toluene (10 mL), tributyltin hydride (0.83 mL, 3.09 mmol) and AIBN (0.02 g, cat.) were heated at 100 ^{o}C for 135 min. The reaction mixture was cooled to ambient temperature, solvents were removed under reduced pressure and the crude product was flash chromatographed (eluent: light petroleum: dichloromethane:ethyl acetate, 35:14:1) to obtain a mixture of **3.155** and bis-tri-*n*-butyl stannane. This mixture was extracted with dry light petroleum (3×5 mL). The light petroleum extract was evaporated in vacuo to afford **3.155** (0.35 g, 70 %) as a gum.

Data for 3.155: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.45–7.22 (m, 19H, Ar-H), 6.10–5.91 (m, 1H, *CH*=CH_2), 5.34–5.11 (m, 2H, CH=*CH_2*), 4.87–4.53 (m, 6H), 4.45 (d, *J*= 1.9 Hz, 2H), 4.36 (d, *J*=5.7 Hz, 2H), 3.99 (s, 1H), 3.83 (t, *J*=9.2 Hz, 1H), 3.41–3.15 (m, 3H), 2.26–1.96 (m, 2H, H-6) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 138.7 (C_{ipso}), 138.6 (C_{ipso}), 138.3 (C_{ipso}), 138.1 (C_{ipso}), 135.6, 131.1, 129.3, 128.4, 128.3, 128.0, 127.62, 127.59, 127.52, 127.5, 127.3, 120.9 (C_{ipso}),116.3 (C=*CH_2*), 82.6 (Ins CH), 81.0 (Ins CH), 77.8 (Ins CH), 75.6 (Ins CH), 75.2 (Ins CH), 74.4 (CH_2), 73.0 (CH_2), 72.9 (CH_2), 72.3 (CH_2), 70.8 (CH_2), 30.5 (CH_2) ppm; **Elemental Anal.** $C_{37}H_{39}BrO_5$ (643.61): calcd C, 69.05; H, 6.11 found C, 68.99; H, 6.41%.

3.5. References.

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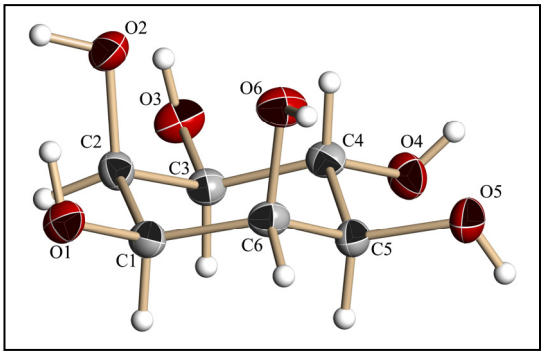
3.6. Appendix.

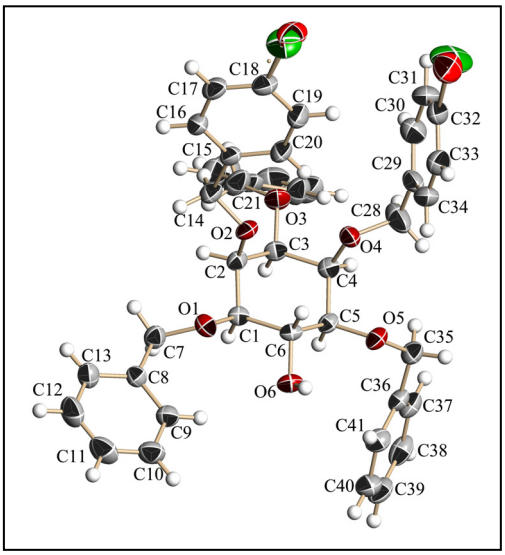
3.6.1. Appendix Index.



ORTEP diagram of **1.4**

Crystal data table of **1.4**

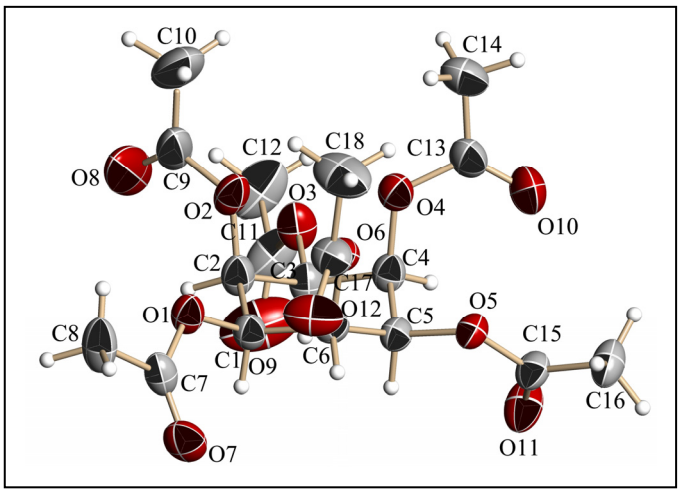
Identification code	**1.4** (crystals from EtOH-TFA-H_2O-THF)
Empirical formula	$C_6H_{12}O_6$
Formula weight	180.16
Temperature (K)	297 (2) K
Wavelength (Å)	0.71073 A
Crystal system, Space group	Monoclinic, P 21/n
Unit cell dimensions	a = 4.8412 (5) Å α = 90° b = 14.7339 (16) Å β = 90.365 (2) ° c = 10.1052 (11) Å γ = 90°
Volume	720.79 (13) $Å^3$
Z, Calculated density	4, 1.660 Mg/m^3
Absorption coefficient	0.151 mm^{-1}
F(000)	384
Crystal size	0.43 x 0.09 x 0.05 mm^3
θ range for data collection	2.44 to 25.00°
Index ranges	-5<=h<=5, -17<=k<=17, -11<=l<=12
Reflections collected / unique	5118 / 1267 [R(int) = 0.0186]
Completeness to θ = 25.00	99.9%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9925 and 0.9380
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1267 / 0 / 157
Goodness-of-fit on F^2	1.090
Final R indices [I>2σ(I)]	R1 = 0.0398, wR2 = 0.0979
R indices (all data)	R1 = 0.0431, wR2 = 0.0998
Largest diff. peak and hole	0.280 and -0.144 $Å^{-3}$



ORTEP diagram of **3.75**

Crystal data table of **3.75**

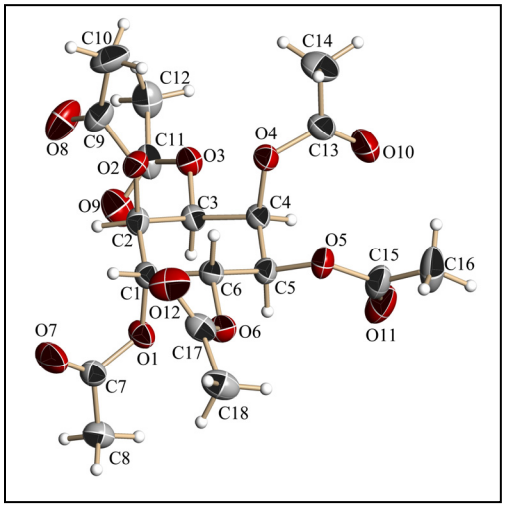
Identification code	**3.75** (crystals from dichloromethane-light petroleum)
Empirical formula	$C_{41}H_{40}BrClO_6$
Formula weight	744.09
Temperature (K)	297 (2) K
Wavelength (Å)	0.71073 A
Crystal system, Space group	Triclinic, P-1
Unit cell dimensions	a = 10.4924 (8) Å α = 88.1430 (10)° b = 11.0232 (9) Å β = 77.7860 (10) ° c = 16.1800 (13) Å γ = 86.099 (2)°
Volume	1824.5 (3) $Å^3$
Z, Calculated density	2, 1.354 Mg/m^3
Absorption coefficient	1.246 mm^{-1}
F(000)	772
Crystal size	0.37 x 0.29 x 0.09 mm^3
θ range for data collection	1.29 to 25.00°
Index ranges	-12<=h<=12, -13<=k<=13, -19<=l<=19
Reflections collected / unique	17771 / 6417 [R(int) = 0.0254]
Completeness to θ = 25.00	99.8%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.8972 and 0.6563
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6417 / 0 / 461
Goodness-of-fit on F^2	1.019
Final R indices [I>2σ(I)]	R1 = 0.0461, wR2 = 0.1142
R indices (all data)	R1 = 0.0773, wR2 = 0.1309
Largest diff. peak and hole	0.326 and -0.217 $Å^{-3}$



ORTEP diagram of **3.78**

Crystal data table of **3.78**

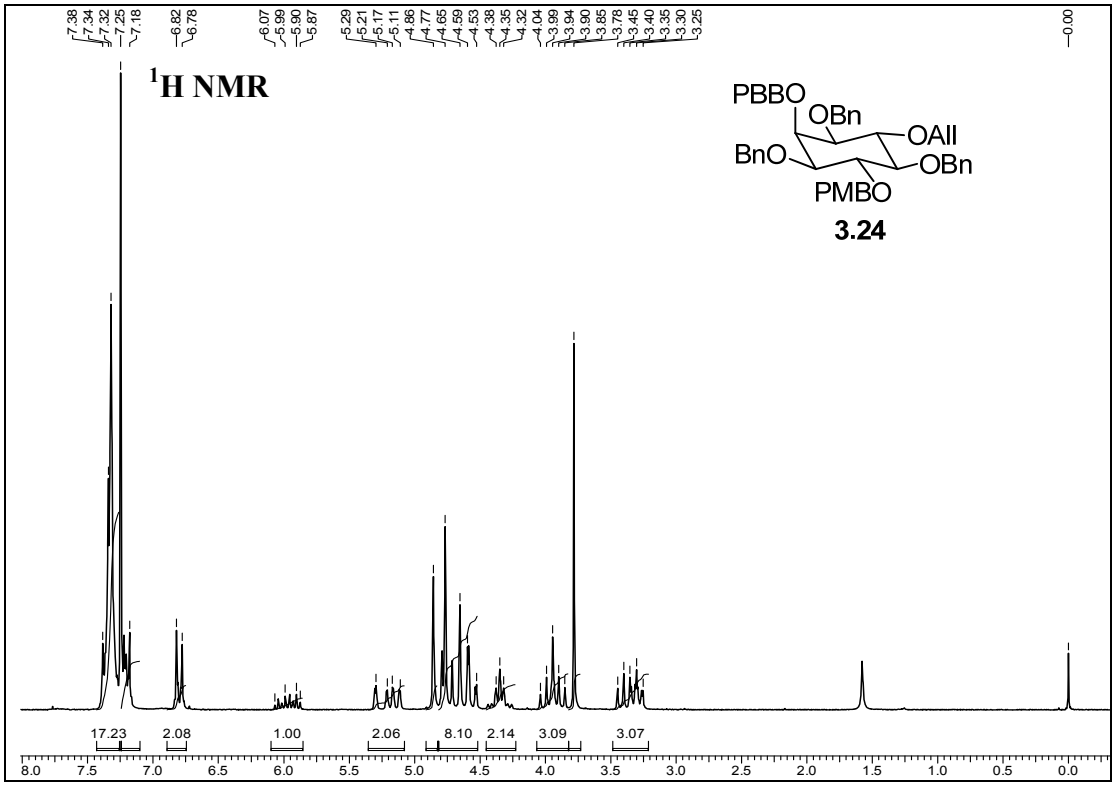
Identification code	**3.78** (crystals from ethanol-water)
Empirical formula	$C_{18}H_{24}O_{12}$
Formula weight	432.37
Temperature (K)	297 (2) K
Wavelength (Å)	0.71073 A
Crystal system, Space group	Triclinic, P-1
Unit cell dimensions	a = 10.2791 (11) Å α = 80.504 (2)° b = 14.7360 (16) Å β = 72.282 (2) ° c = 15.5923 (17) Å γ = 80.391 (2)°
Volume	2201.8 (4) $Å^3$
Z, Calculated density	4, 1.304 Mg/m^3
Absorption coefficient	0.111 mm^{-1}
F(000)	912
Crystal size	0.29 x 0.21 x 0.12 mm^3
θ range for data collection	1.85 to 25.00°
Index ranges	-12<=h<=12, -17<=k<=17, -18<=l<=18
Reflections collected / unique	21473 / 7745 [R(int) = 0.0226]
Completeness to θ = 25.00	99.8%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9868 and 0.9685
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7745 / 0 / 553
Goodness-of-fit on F^2	1.025
Final R indices [I>2σ(I)]	R1 = 0.0671, wR2 = 0.1745
R indices (all data)	R1 = 0.0979, wR2 = 0.1971
Largest diff. peak and hole	0.469 and -0.393 $Å^{-3}$

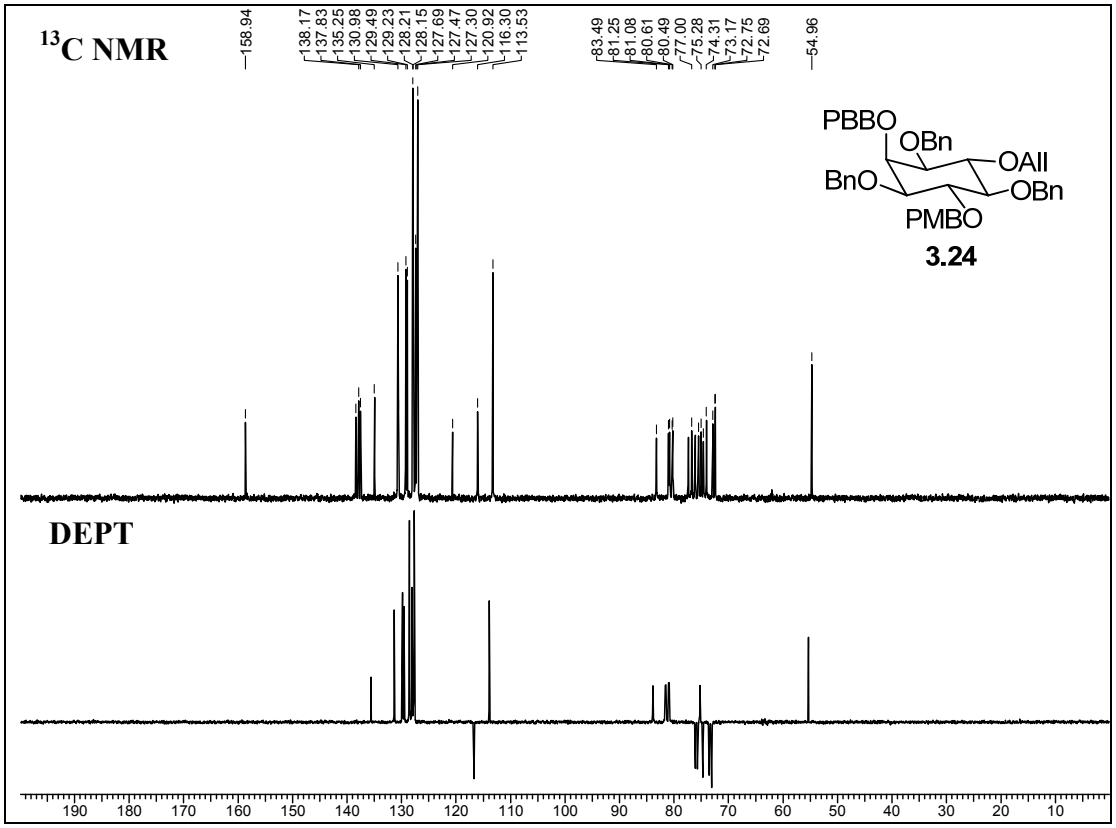


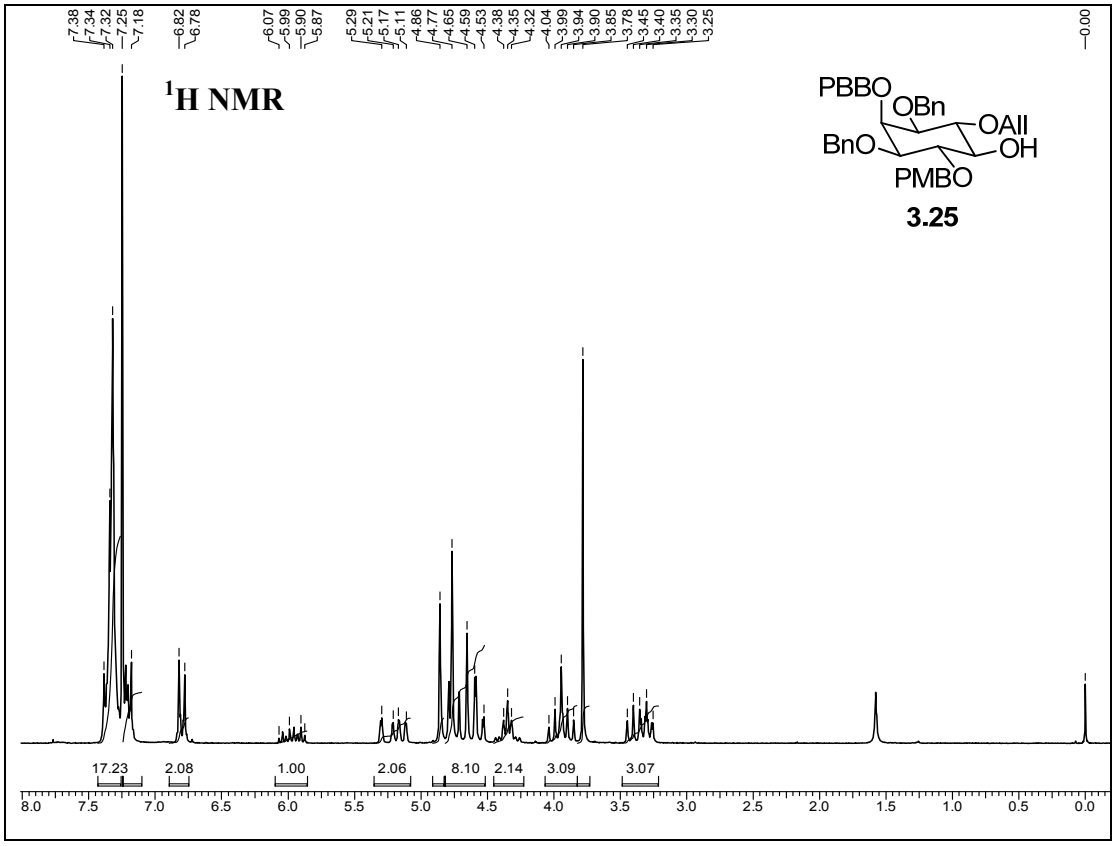
ORTEP diagram of **3.104**

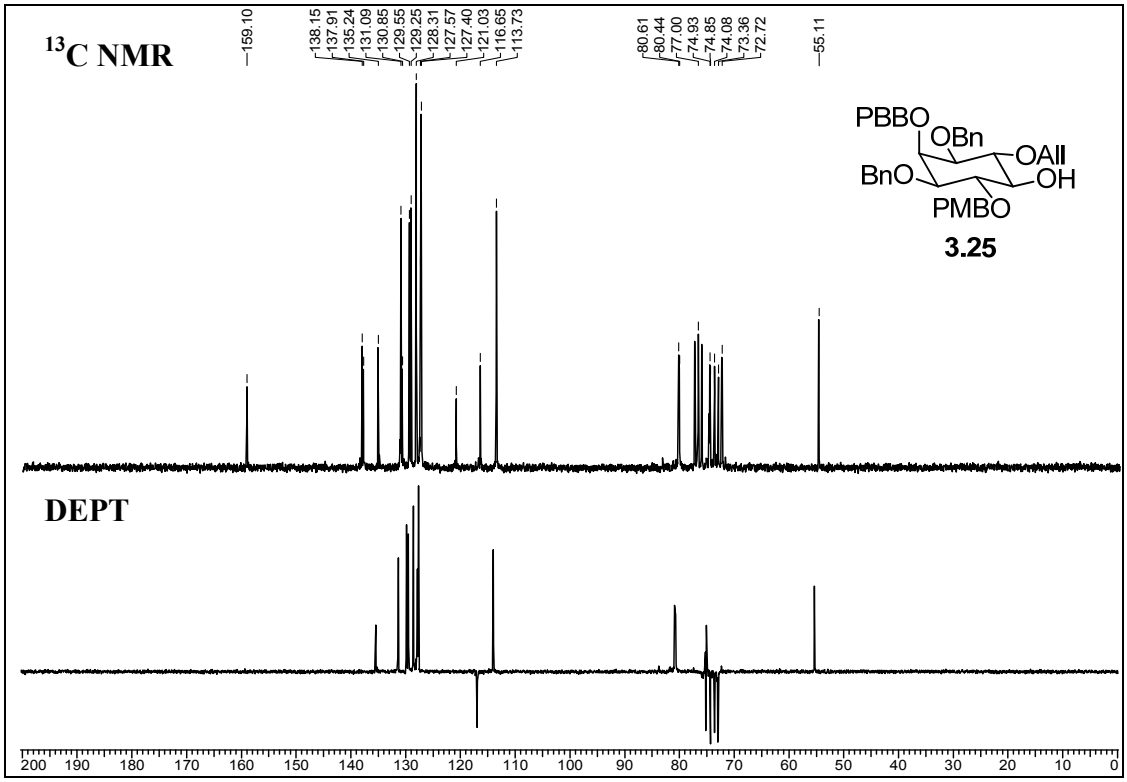
Crystal data table of **3.104**

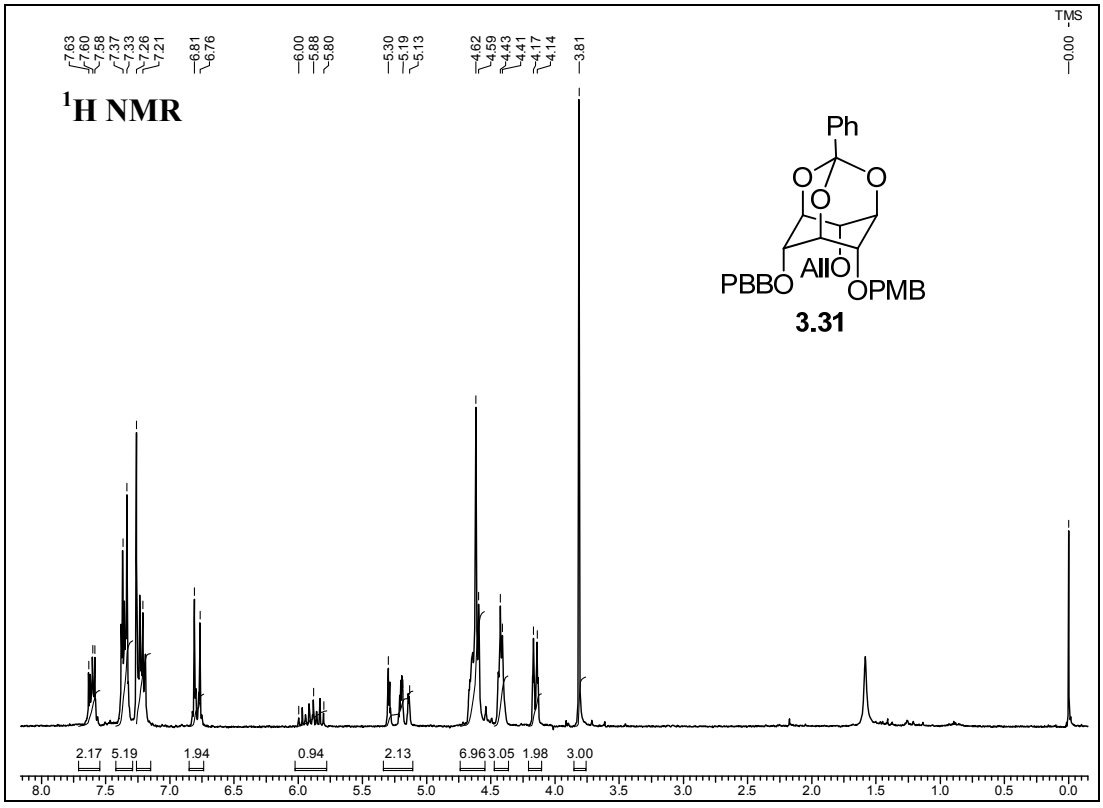
Identification code	**3.104** (crystals from ethanol)
Empirical formula	$C_{18}H_{24}O_{12}$
Formula weight	432.37
Temperature (K)	297 (2) K
Wavelength (Å)	0.71073 A
Crystal system, Space group	Orthorhombic, Pbca
Unit cell dimensions	a = 11.454 (8) Å α = 90 ° b = 12.974 (9) Å β = 90 ° c = 29.76 (2) Å γ = 90 °
Volume	4422 (5) $Å^3$
Z, Calculated density	8, 1.299 Mg/m^3
Absorption coefficient	0.111 mm^{-1}
F(000)	1824
Crystal size	0.41 x 0.28 x 0.27 mm^3
θ range for data collection	2.24 to 25.00°
Index ranges	-13<=h<=13, -15<=k<=15, -17<=l<=35
Reflections collected / unique	20688 / 3888 [R(int) = 0.0447]
Completeness to θ = 25.00	99.8%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9707 and 0.9560
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3888 / 0 / 277
Goodness-of-fit on F^2	1.044
Final R indices [I>2σ(I)]	R1 = 0.0468, wR2 = 0.1254
R indices (all data)	R1 = 0.0637, wR2 = 0.1373
Largest diff. peak and hole	0.265 and -0.203 $Å^{-3}$


^{1}H NMR
PBBO
OBn
OAll
BnO
OBn
PMBO
3.24


^{13}C NMR
PBBO
OBn
OAll
BnO
OBn
PMBO
3.24
DEPT


^{1}H NMR
PBBO
OBn
OAll
BnO
OH
PMBO
3.25
17.23
2.08
1.00
2.06
8.10
2.14
3.09
3.07


^{13}C NMR
PBBO
OBn
OAll
BnO
OH
PMBO
3.25
DEPT


TMS
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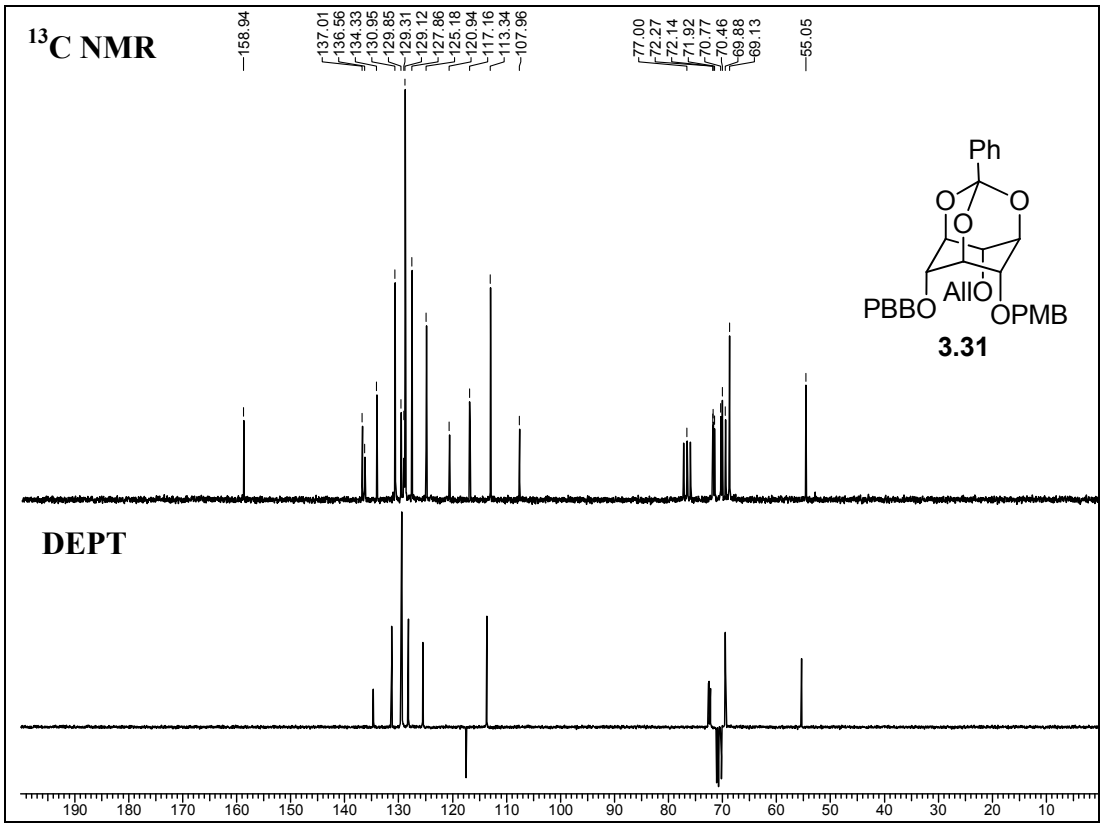
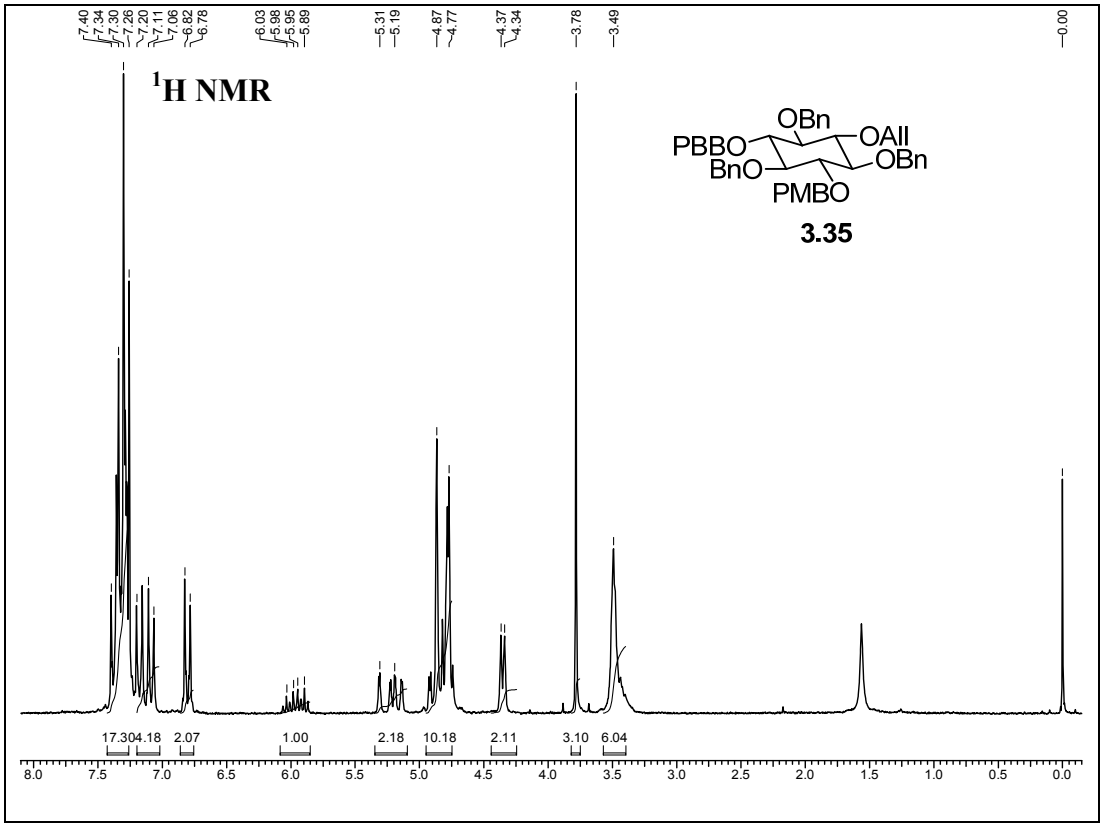
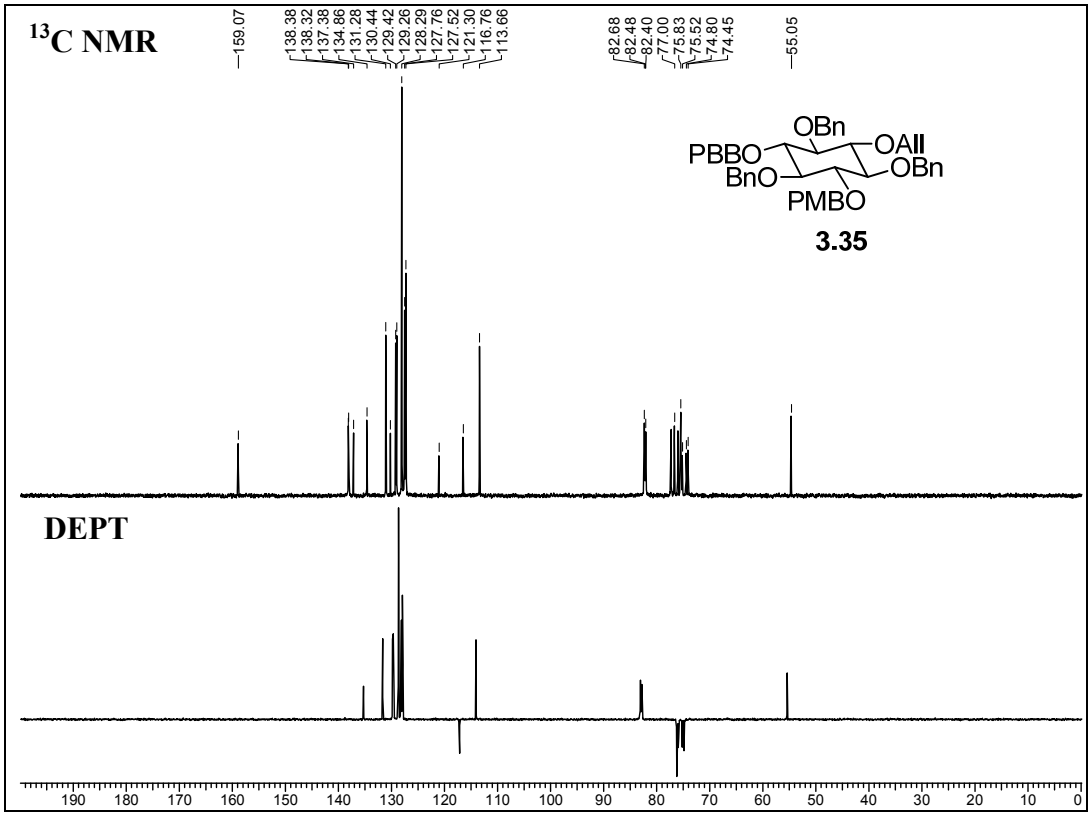
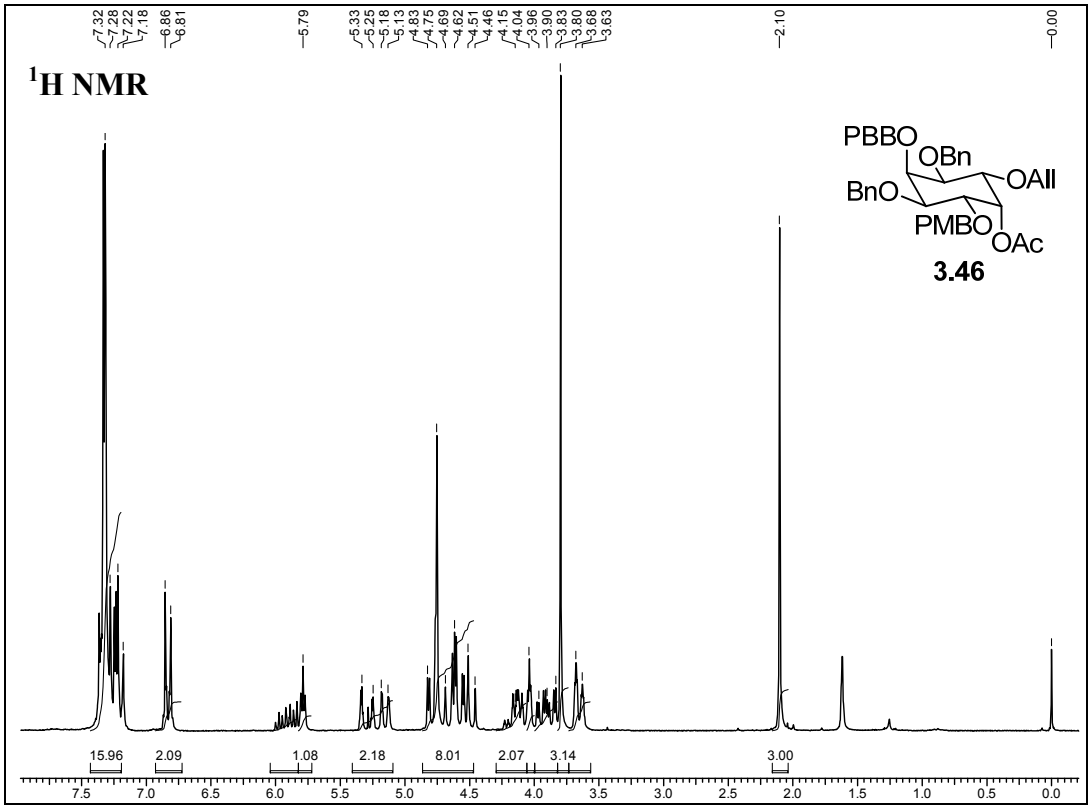
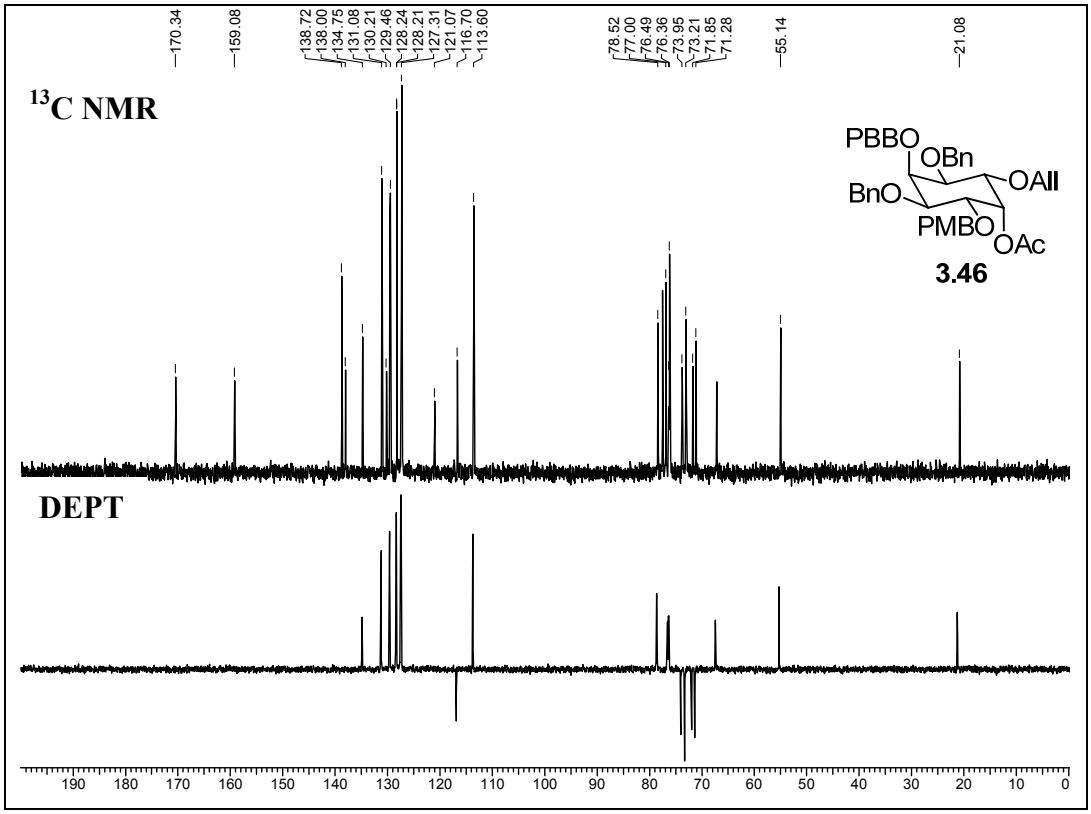
7.60
7.58
7.37
7.33
7.26
7.21
6.81
6.76
6.00
5.88
5.80
5.30
5.19
5.13
4.62
4.59
4.43
4.41
4.17
4.14
3.81
0.00
1H NMR
Ph
O
O
O
PBBO
AllO
OPMB
3.31
2.17
5.19
1.94
0.94
2.13
6.96
3.05
1.98
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

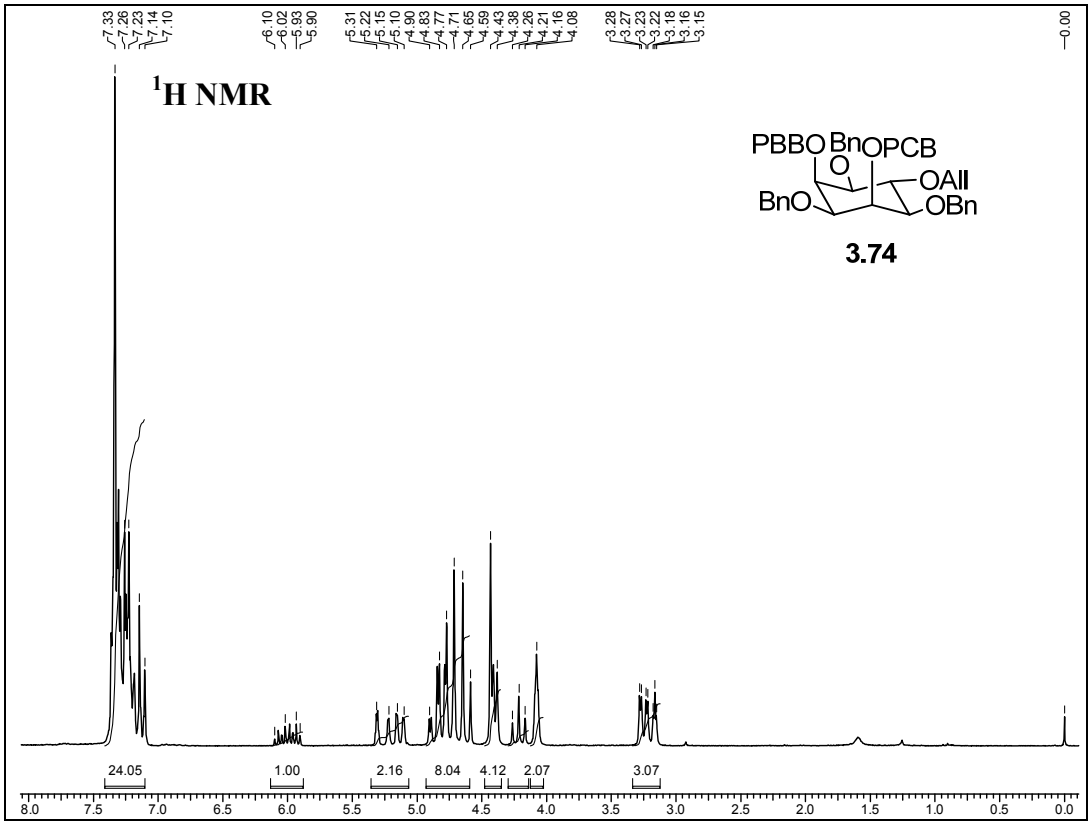

13C NMR
158.94
137.01
136.56
134.33
130.95
129.85
129.31
129.12
127.86
125.18
120.94
117.16
113.34
107.96
77.00
72.27
72.14
71.92
70.77
70.46
69.88
69.13
55.05
Ph
O
O
O
PBBO
AllO
OPMB
3.31
DEPT
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

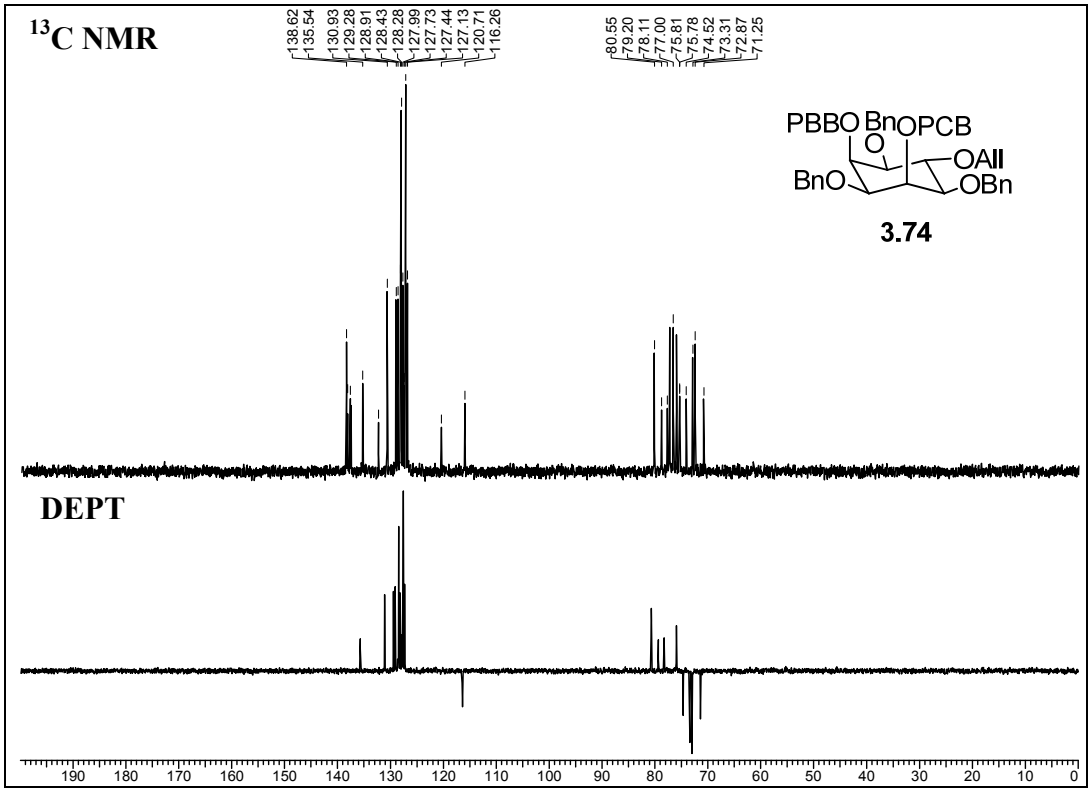

7.40
7.34
7.30
7.26
7.20
7.11
7.06
6.82
6.78
6.03
5.98
5.95
5.89
5.31
5.19
4.87
4.77
4.37
4.34
3.78
3.49
0.00
^{1}H NMR
OBn
OAll
PBBO
BnO
OBn
PMBO
3.35
17.30
4.18
2.07
1.00
2.18
10.18
2.11
3.10
6.04
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

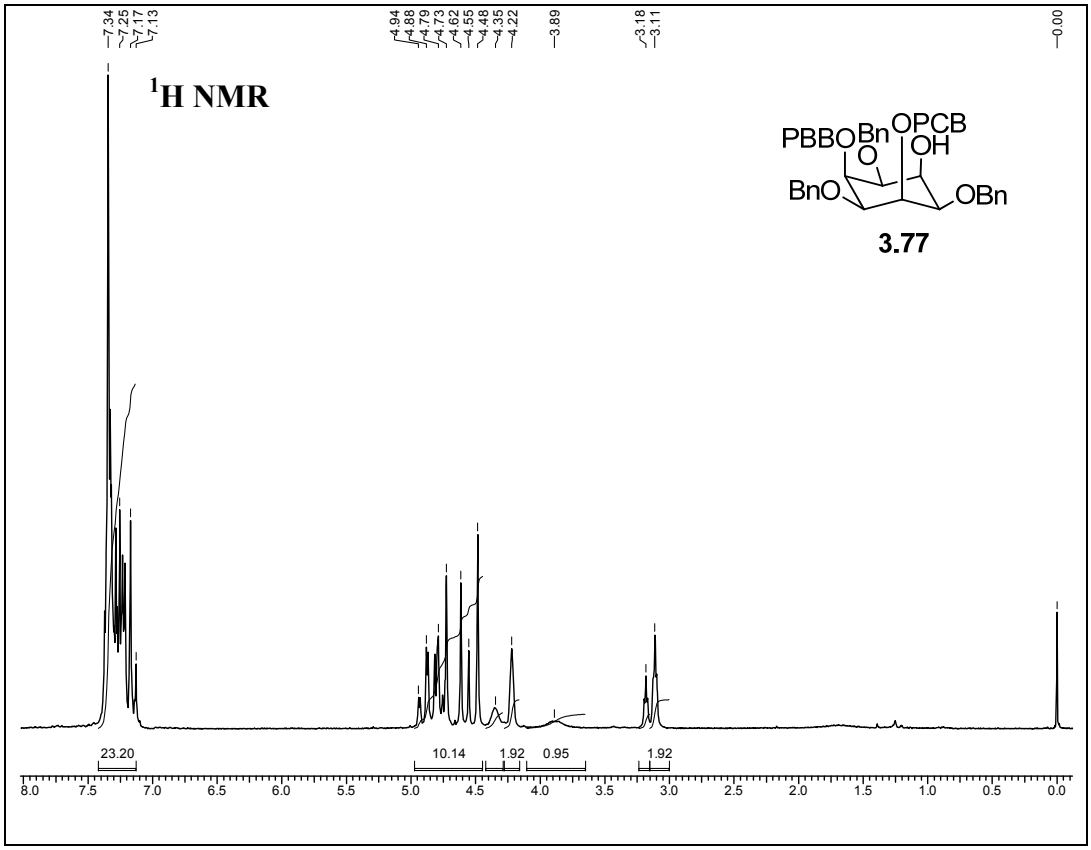

^{13}C NMR
159.07
138.38
138.32
137.38
134.86
131.28
130.44
129.42
129.26
128.29
127.76
127.52
121.30
116.76
113.66
82.68
82.48
82.40
77.00
75.83
75.52
74.80
74.45
55.05
OBn
OAll
PBBO
BnO
OBn
PMBO
3.35
DEPT
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

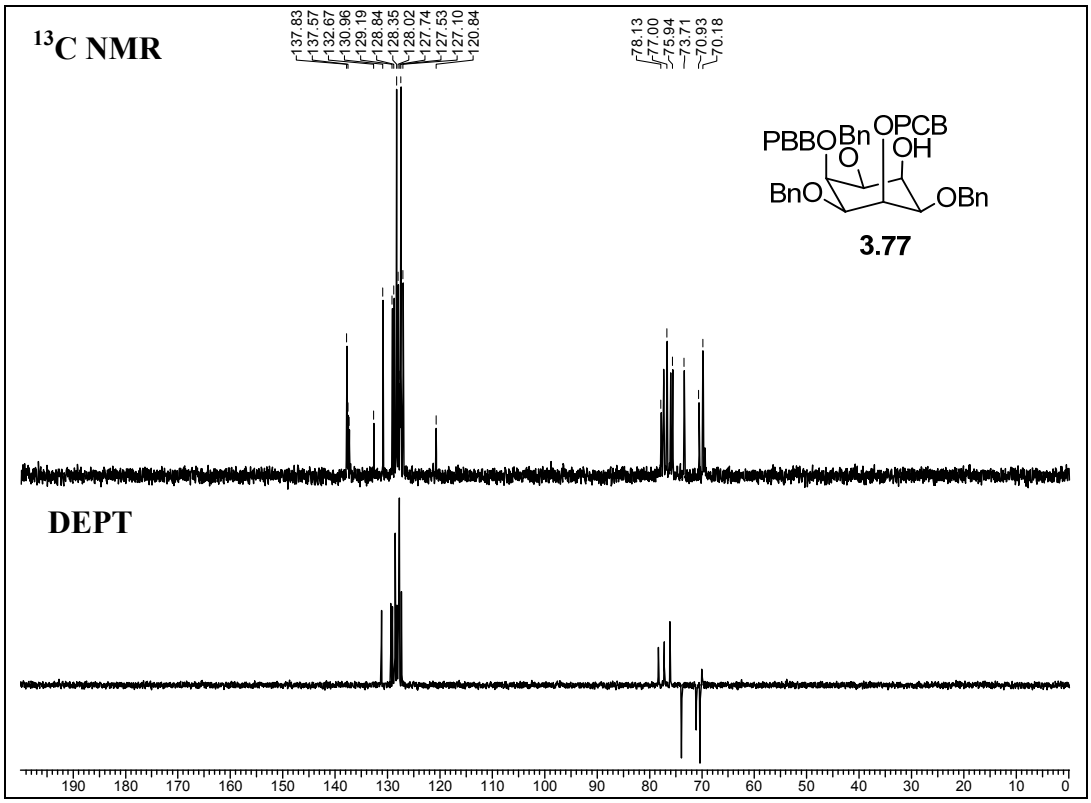

7.32
7.28
7.22
7.18
6.86
6.81
5.79
5.33
5.25
5.18
5.13
4.83
4.75
4.69
4.62
4.51
4.46
4.15
4.04
3.96
3.90
3.83
3.80
3.68
3.63
2.10
0.00
1H NMR
PBBO
OBn
OAll
BnO
PMBO
OAc
3.46
15.96
2.09
1.08
2.18
8.01
2.07
3.14
3.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

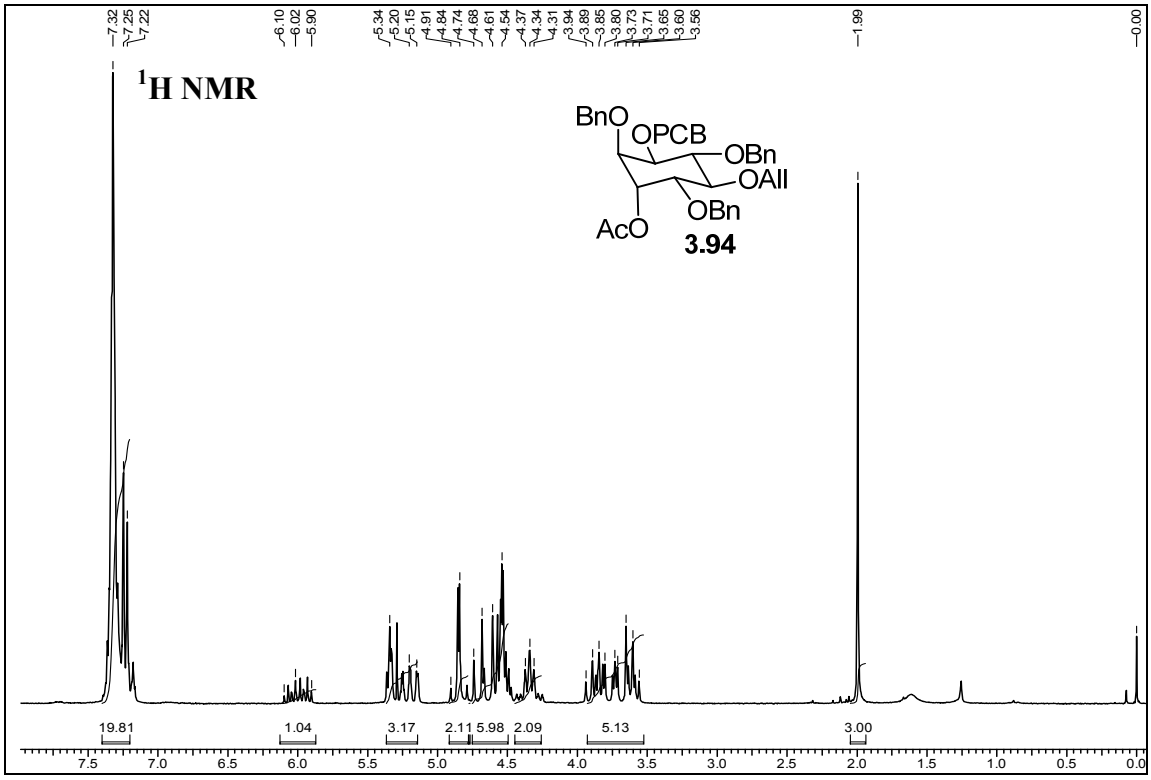

170.34
159.08
138.72
138.00
134.75
131.08
130.21
129.46
128.24
128.21
127.31
121.07
116.70
113.60
78.52
77.00
76.49
76.36
73.95
73.21
71.85
71.28
55.14
21.08
13C NMR
PBBO
OBn
OAll
BnO
PMBO
OAc
3.46
DEPT
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

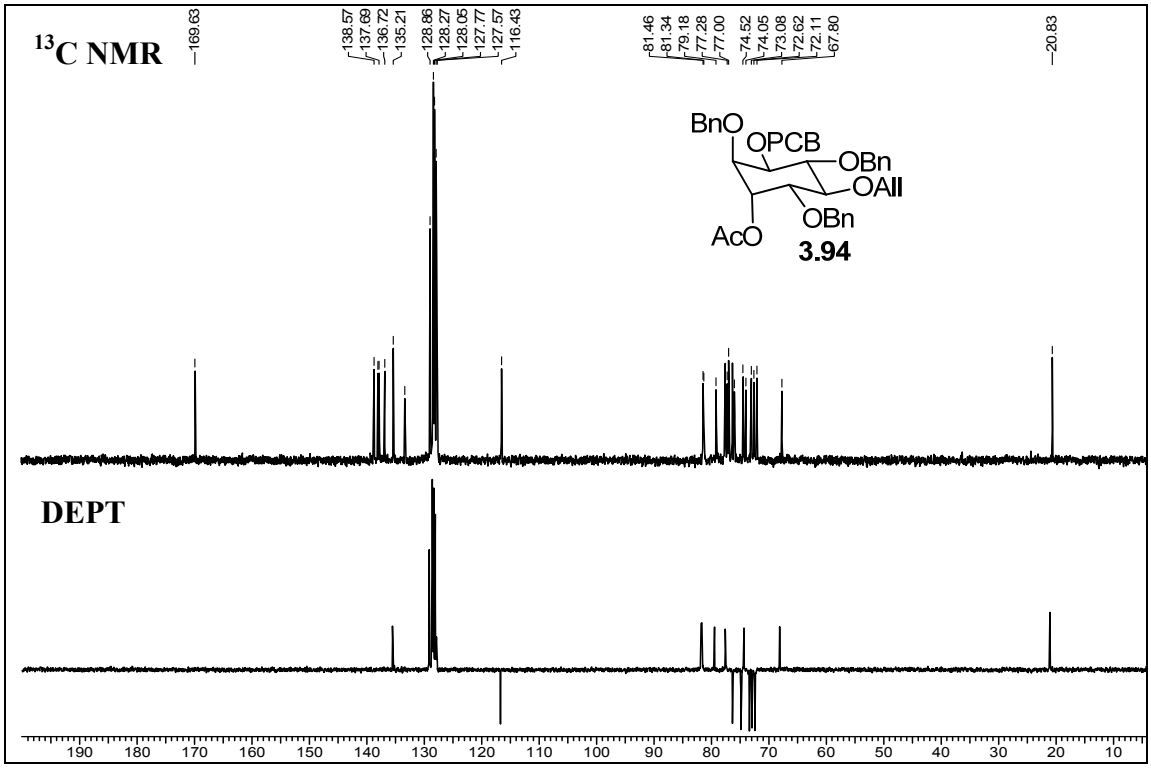

7.33
7.26
7.23
7.14
7.10
6.10
6.02
5.93
5.90
5.31
5.22
5.15
5.10
4.90
4.83
4.77
4.71
4.65
4.59
4.43
4.38
4.26
4.21
4.16
4.08
3.28
3.27
3.23
3.22
3.18
3.16
3.15
0.00
1H NMR
PBBO BnO OPCB
O
OAll
BnO
OBn
3.74
24.05
1.00
2.16
8.04
4.12
2.07
3.07
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


13C NMR
138.62
135.54
130.93
129.28
128.91
128.43
128.28
127.99
127.73
127.44
127.13
120.71
116.26
80.55
79.20
78.11
77.00
75.81
75.78
74.52
73.31
72.87
71.25
PBBO BnO OPCB
O
OAll
BnO
OBn
3.74
DEPT
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


7.34
7.25
7.17
7.13
4.94
4.88
4.79
4.73
4.62
4.55
4.48
4.35
4.22
3.89
3.18
3.11
0.00
^{1}H NMR
PBBO
Bn
O
OPCB
OH
BnO
OBn
3.77
23.20
10.14
1.92
0.95
1.92
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


^{13}C NMR
137.83
137.67
132.67
130.96
129.19
128.84
128.35
128.02
127.74
127.53
127.10
120.84
78.13
77.00
75.94
73.71
70.93
70.18
PBBO
Bn
O
OPCB
OH
BnO
OBn
3.77
DEPT
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


7.32
7.25
7.22
6.10
6.02
5.90
5.34
5.20
5.15
4.91
4.84
4.74
4.68
4.61
4.54
4.37
4.34
4.31
3.94
3.89
3.85
3.80
3.73
3.71
3.65
3.60
3.56
1.99
0.00
^{1}H NMR
BnO
OPCB
OBn
OAll
AcO
OBn
3.94
19.81
1.04
3.17
2.11
5.98
2.09
5.13
3.00


169.63
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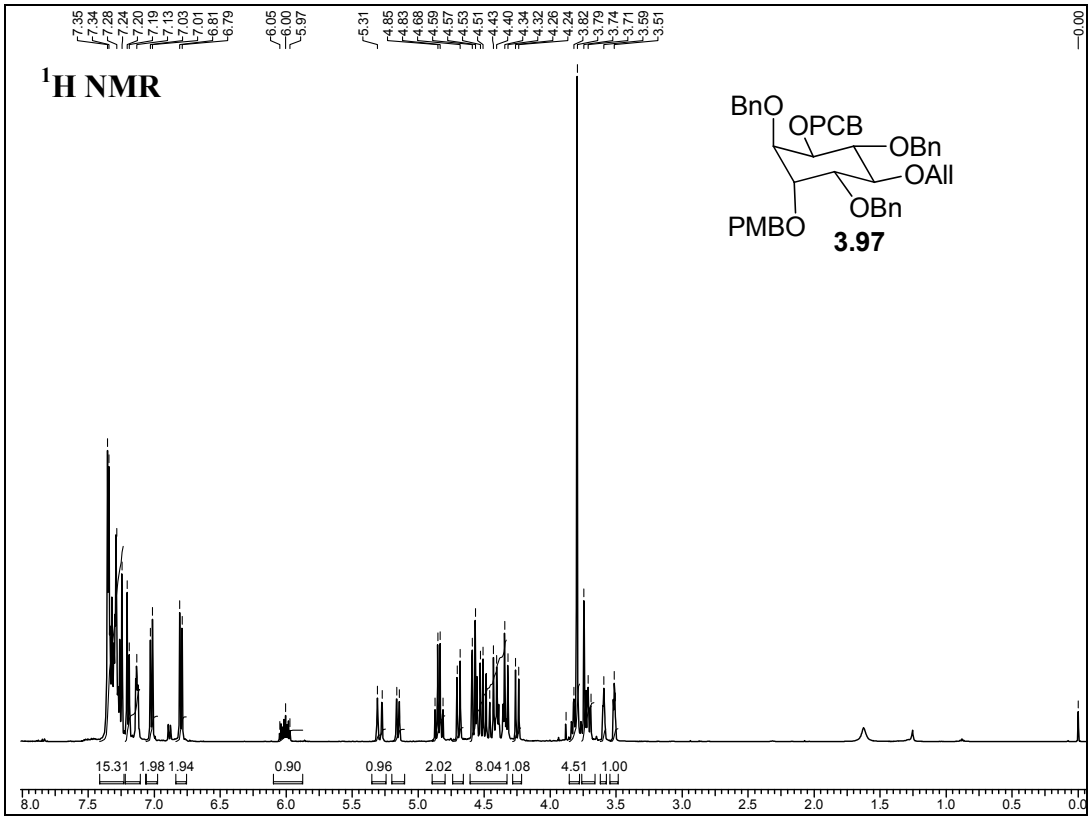
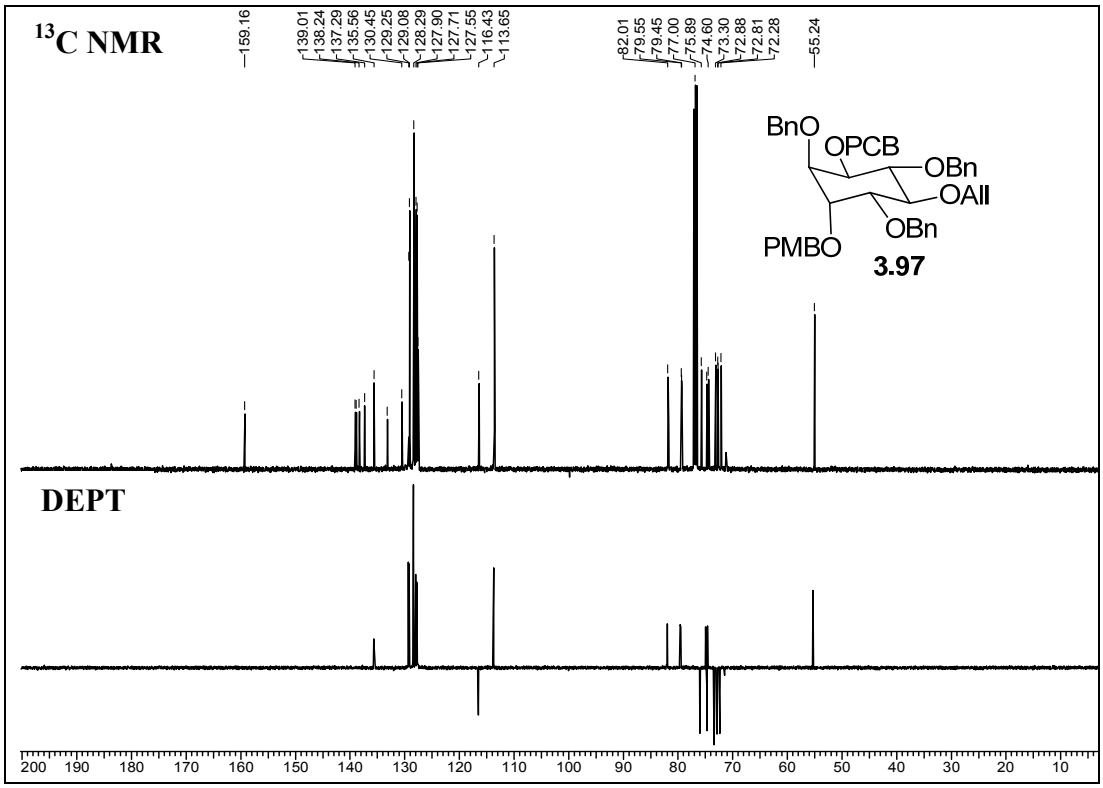
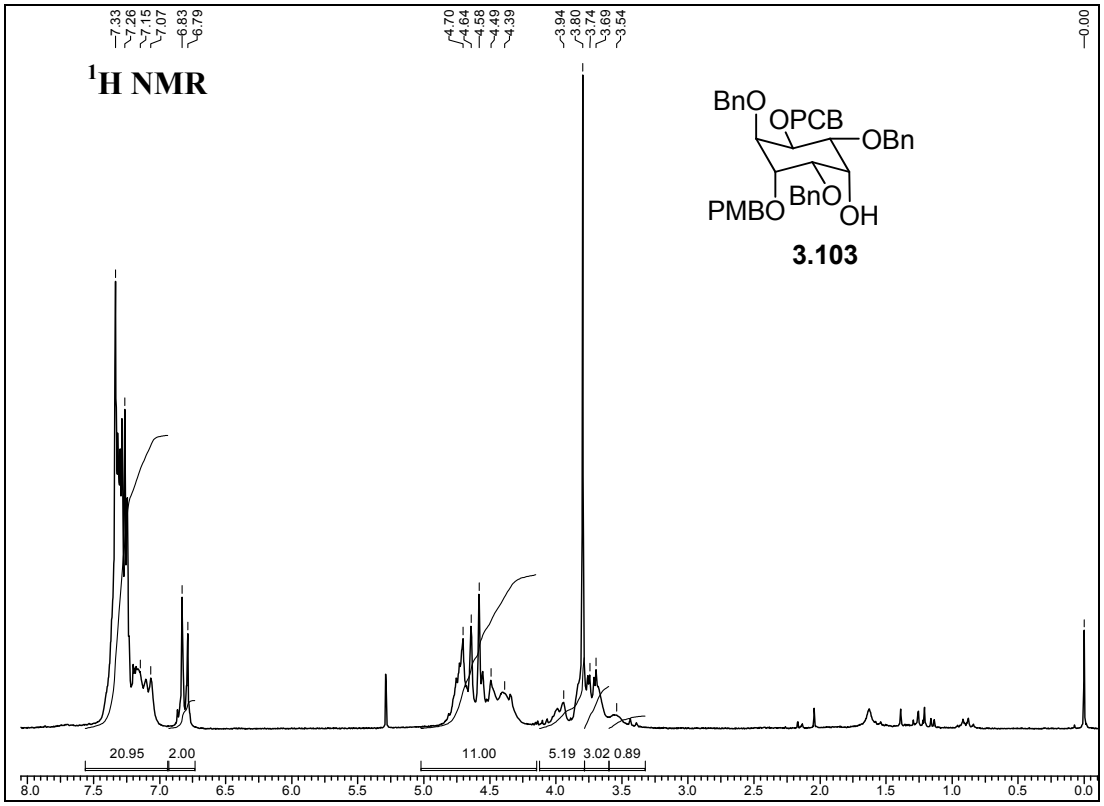
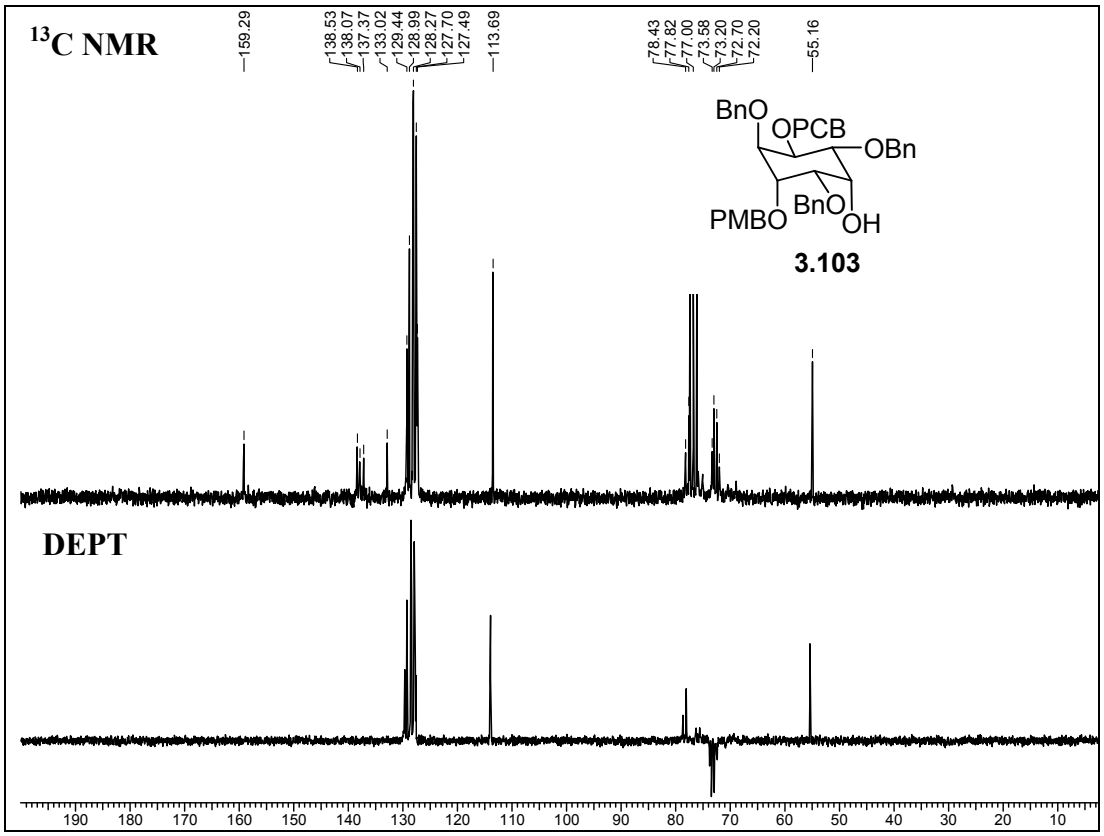
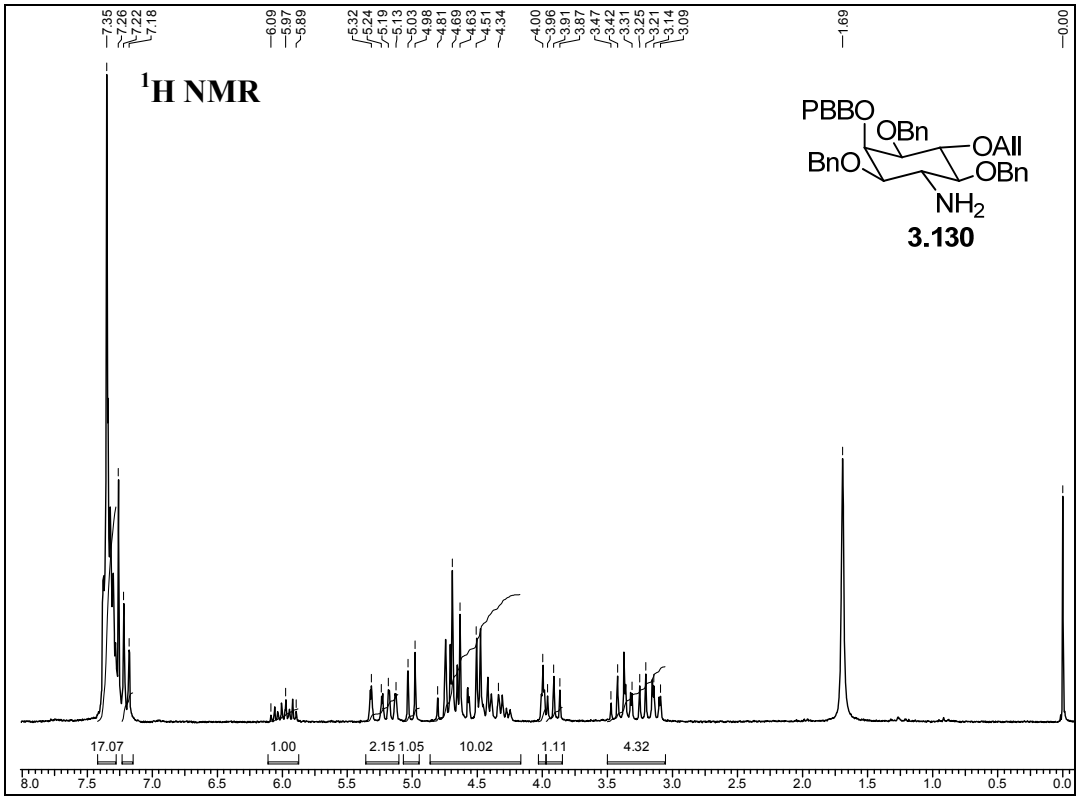
136.72
135.21
128.86
128.27
128.05
127.77
127.57
116.43
81.46
81.34
79.18
77.28
77.00
74.52
74.05
73.08
72.62
72.11
67.80
20.83
^{13}C NMR
BnO
OPCB
OBn
OAll
AcO
OBn
3.94
DEPT

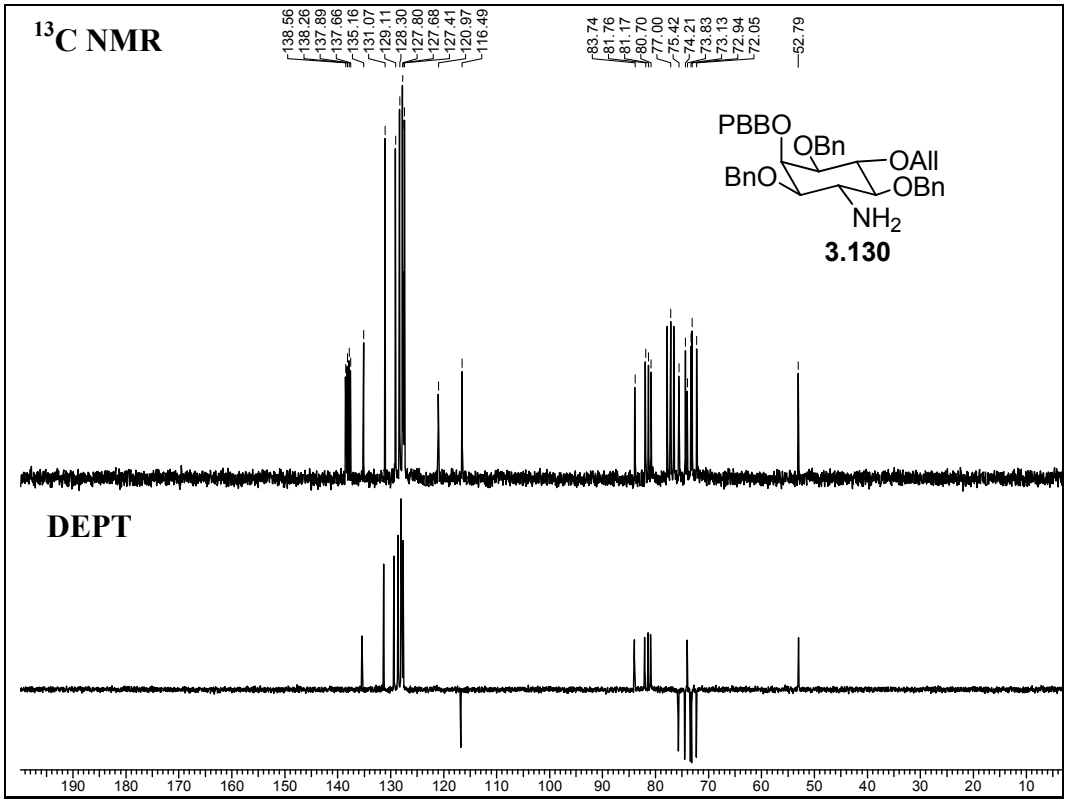

1H NMR
BnO
OPCB
OBn
OAll
OBn
PMBO
3.97


13C NMR
BnO
OPCB
OBn
OAll
OBn
PMBO
3.97
DEPT


7.33
7.26
7.15
7.07
6.83
6.79
4.70
4.64
4.58
4.49
4.39
3.94
3.80
3.74
3.69
3.54
0.00
1H NMR
BnO
OPCB
OBn
PMBO
BnO
OH
3.103
20.95
2.00
11.00
5.19
3.02
0.89


13C NMR
159.29
138.53
138.07
137.37
133.02
129.44
128.99
128.27
127.70
127.49
113.69
78.43
77.82
77.00
73.58
73.20
72.70
72.20
55.16
BnO
OPCB
OBn
PMBO
BnO
OH
3.103
DEPT


7.35
7.26
7.22
7.18
6.09
5.97
5.89
5.32
5.24
5.19
5.13
5.03
4.98
4.81
4.69
4.63
4.51
4.34
4.00
3.96
3.91
3.87
3.47
3.42
3.31
3.25
3.21
3.14
3.09
1.69
0.00
^{1}H NMR
PBBO
OBn
OAll
BnO
OBn
NH2
3.130
17.07
1.00
2.15
1.05
10.02
1.11
4.32
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


^{13}C NMR
138.56
138.26
137.89
137.66
135.16
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129.11
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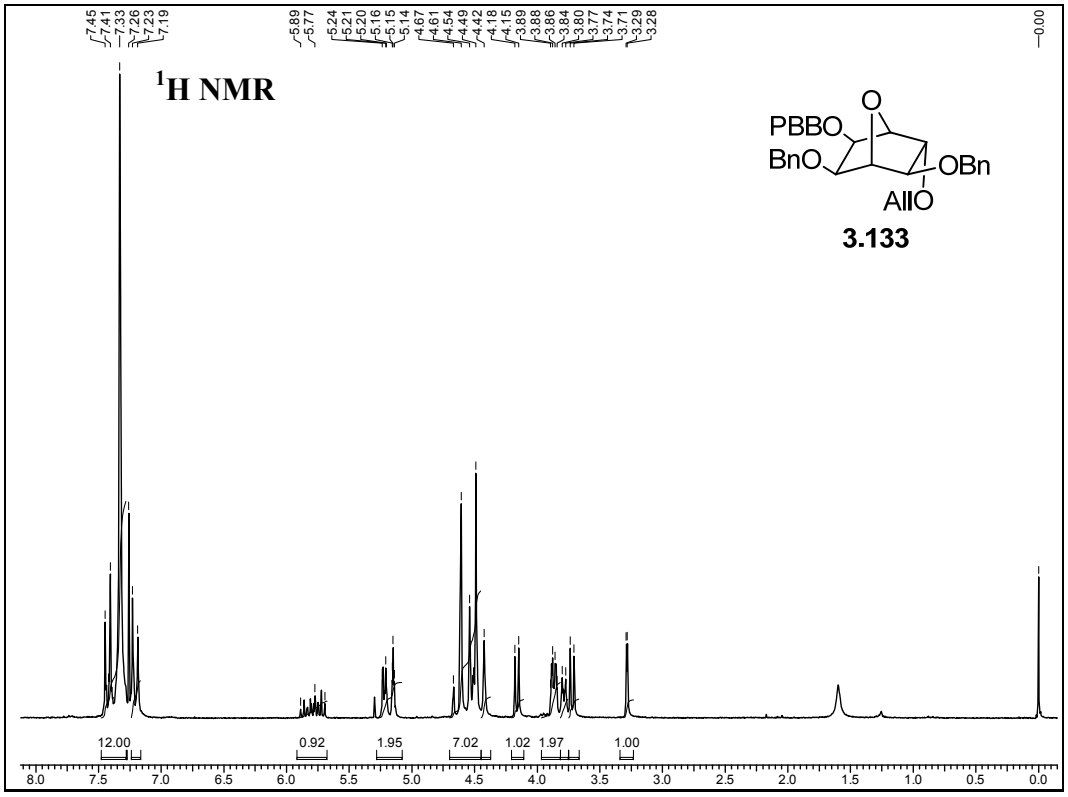
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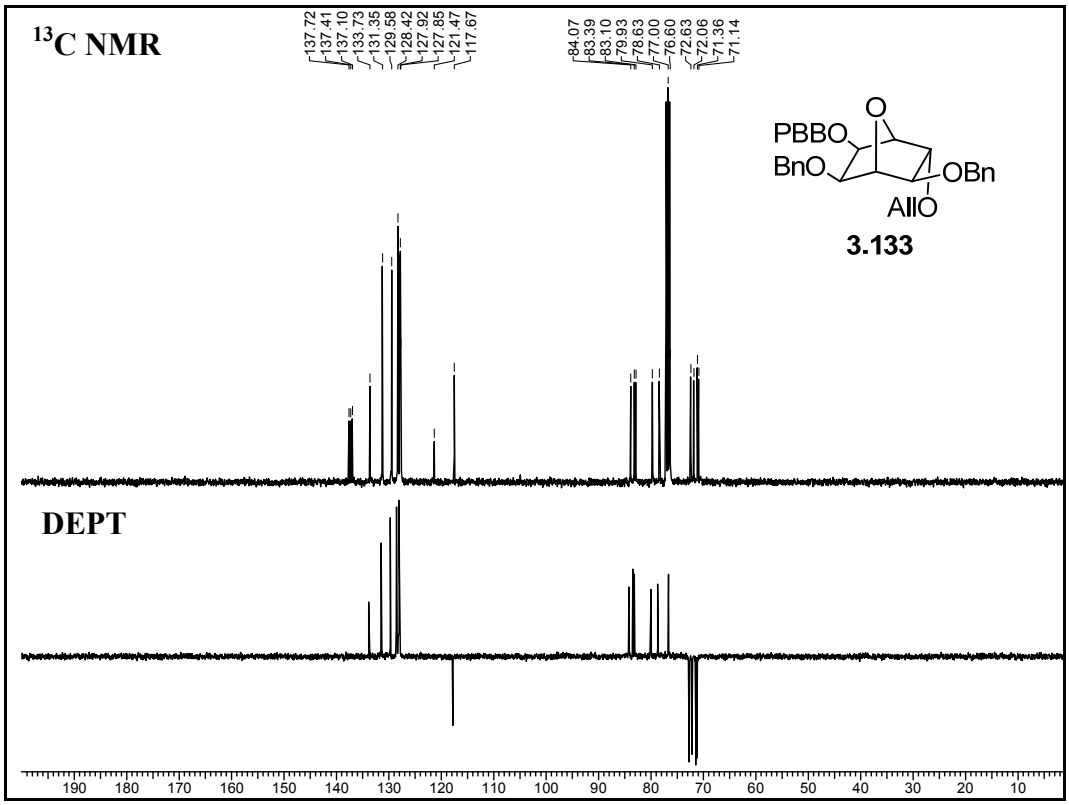
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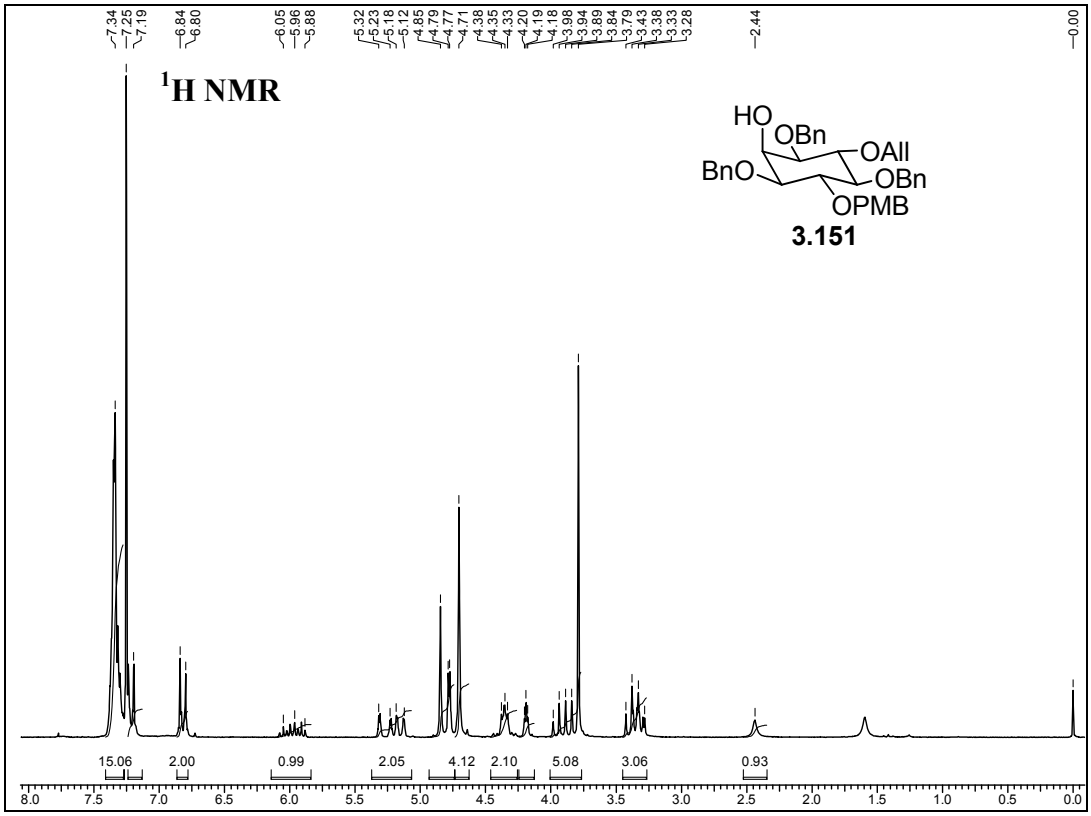
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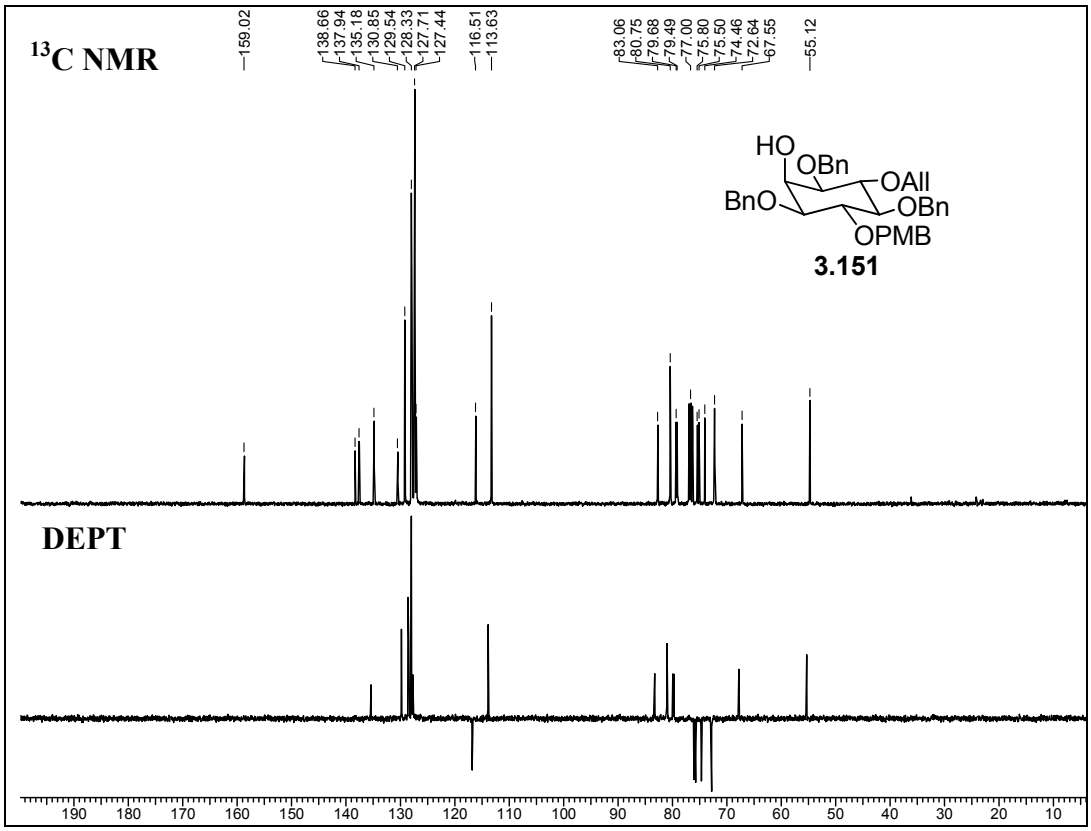
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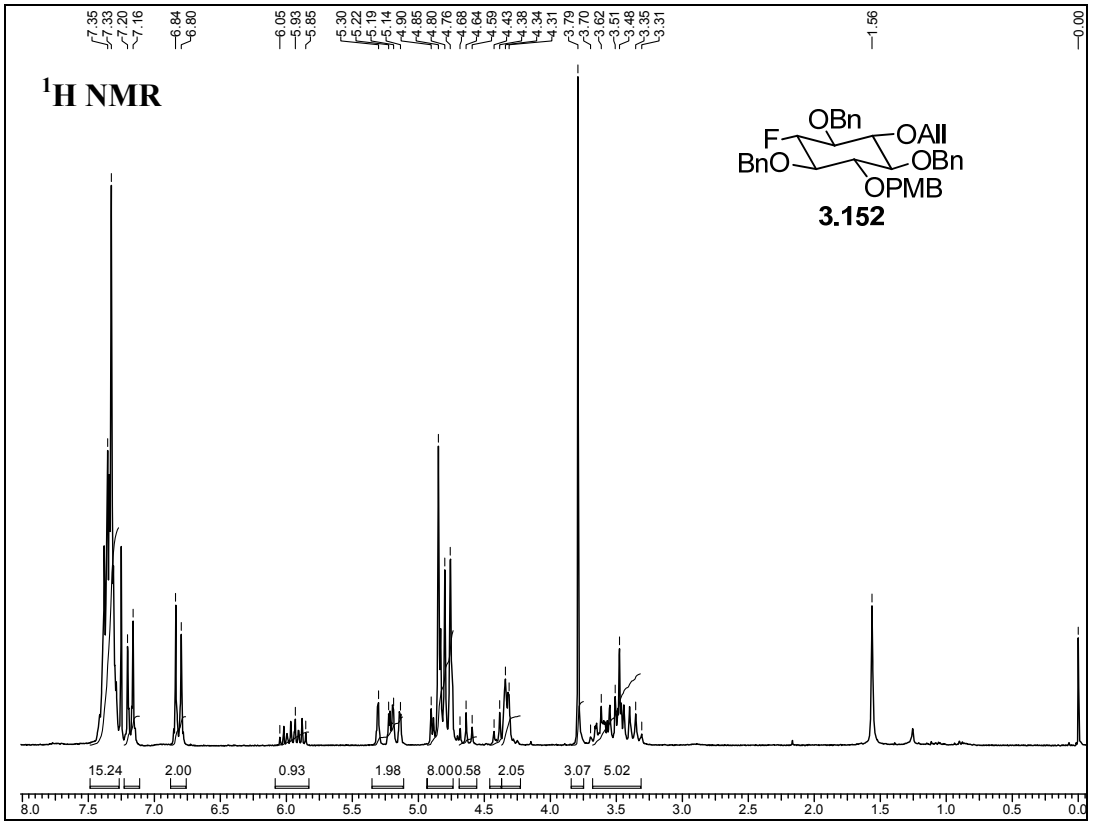
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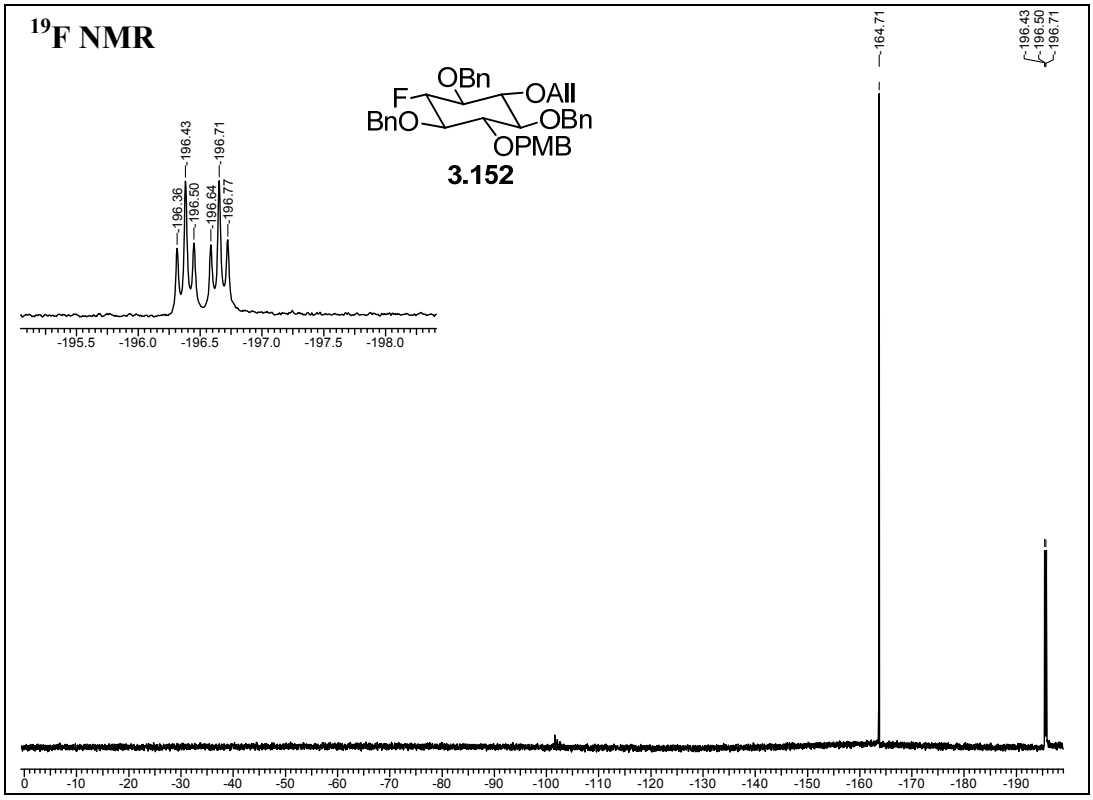
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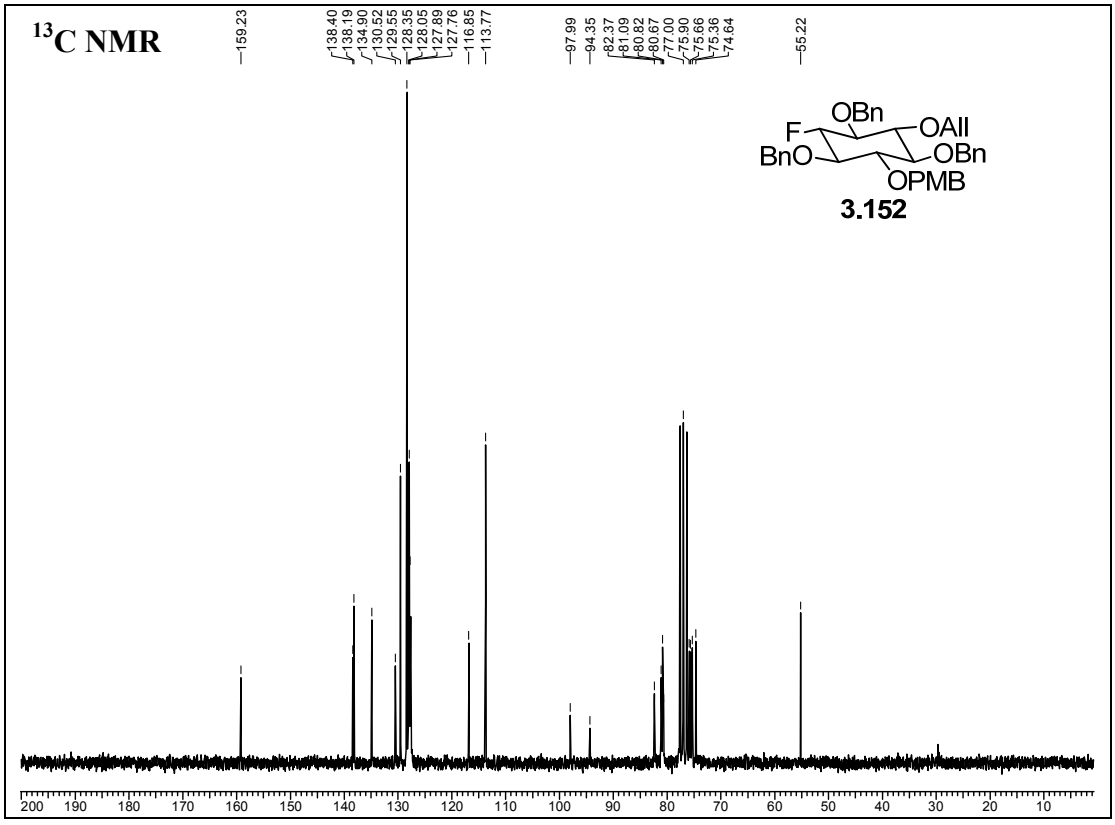
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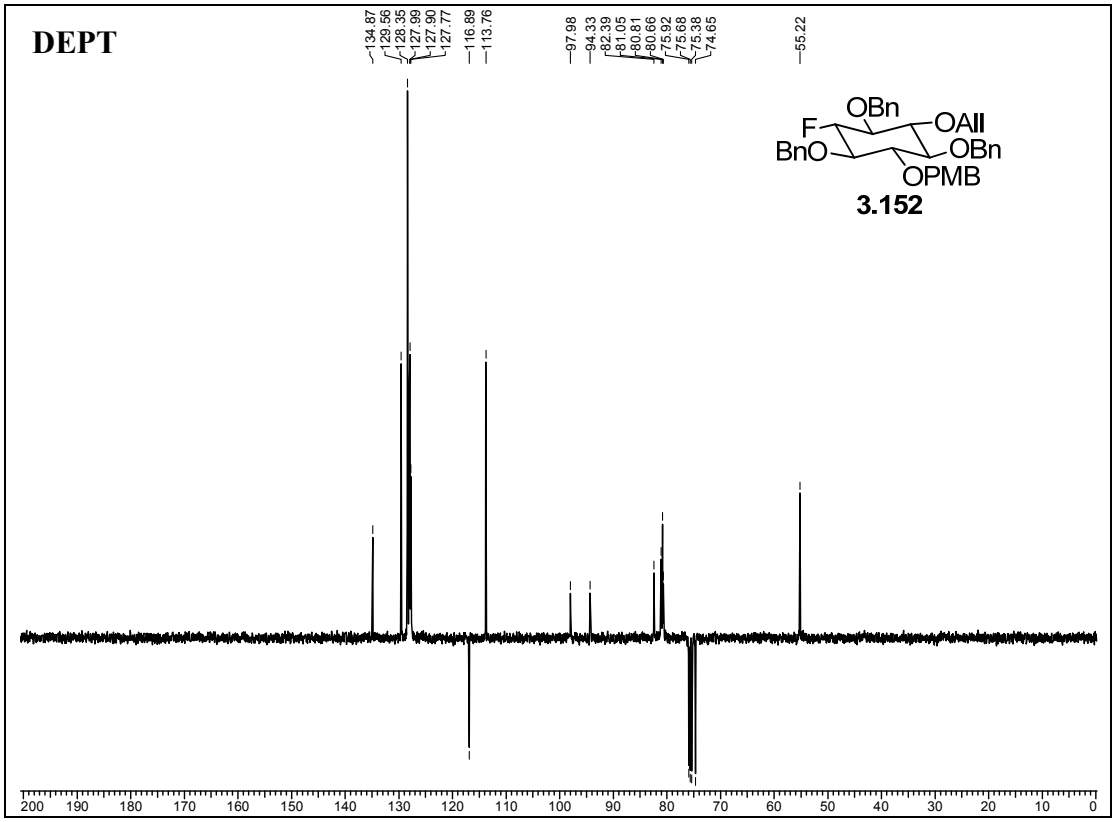
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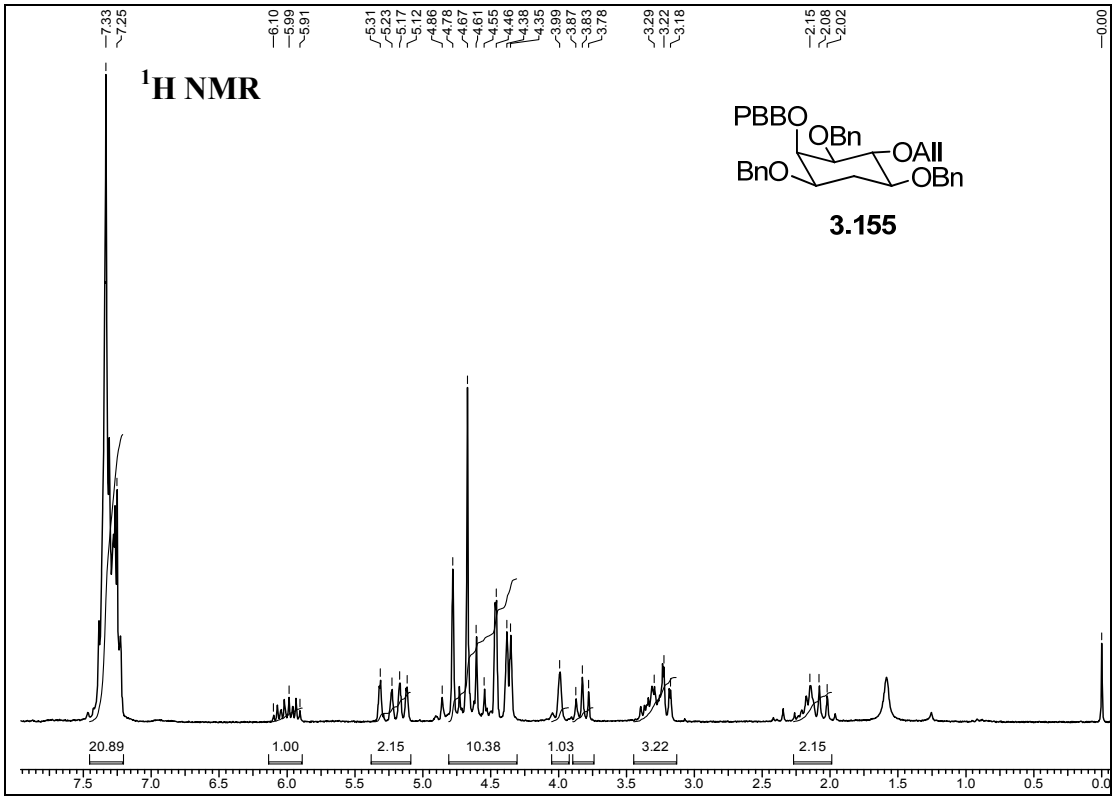
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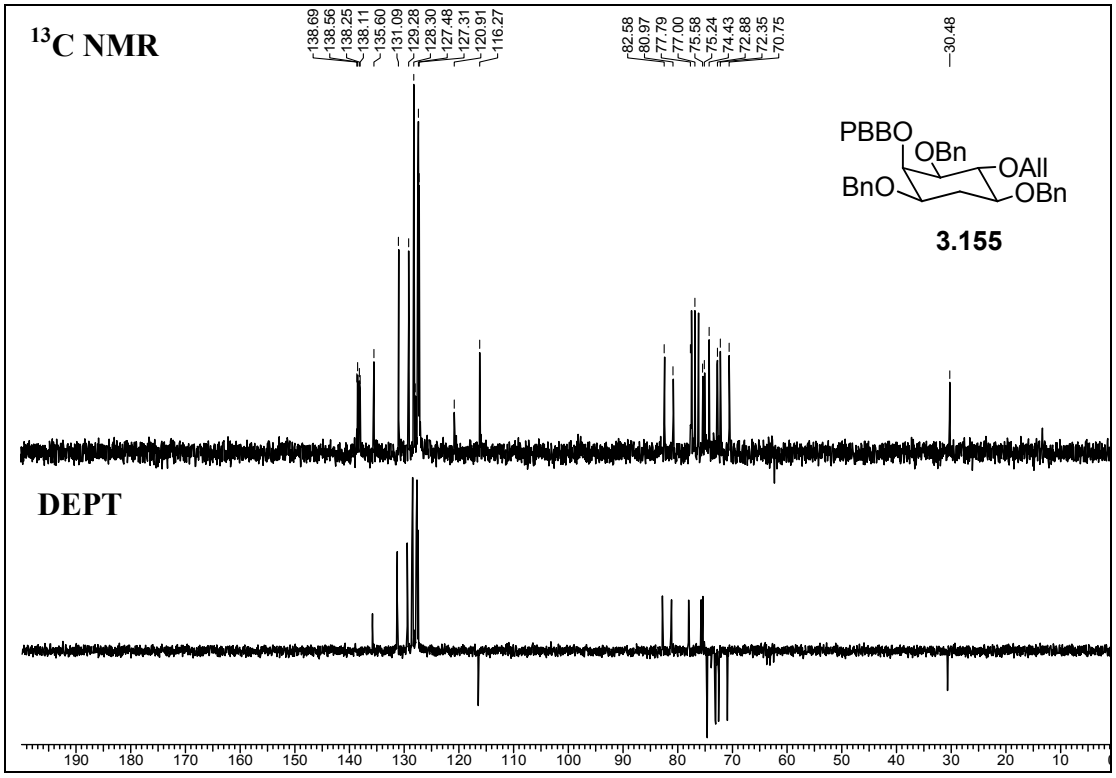
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Chapter 4. Formal Synthesis of valiolamine from *myo*-inositol

4.1. Introduction.

The previous chapter presented a methodology for the synthesis of orthogonally substituted *myo*-inositol derivatives which are suitable for the preparation of various isomeric cyclitols and their derivatives. The present chapter describes the utility of selective O-alkylation reactions for the target oriented synthesis of valiolamine from *myo*-inositol. The aim of this work is to illustrate the flexibility and adaptability of the reactions and synthetic methods presented in previous chapters rather than just to achieve the synthesis of valiolamine. Having selected this target to demonstrate the utility of our synthetic methodology, it is appropriate to briefly mention the contemporary significance of valiolamine and its derivatives.

There has been increasing interest in the chemistry and biochemistry of glycosidase inhibitors[(1)] because of their potential use as chemotherapeutic agents,[(2)] which are being actively investigated.[(3)] Glycosidases are enzymes that cleave glycosidic bonds and are responsible for glycoprotein processing on the surface of the cell wall and for carbohydrate digestion in animals. Inhibition of these enzymes has significant implications for both antiviral and antidiabetic chemotherapy.[(4)] Valiolamine (**4.1**, Figure 4.1) is a pseudoamino sugar first isolated from the fermentation broth of *Streptomyces hygroscopicus* subsp. *limoneus*.[(5)] The absolute structure of valiolamine was established by comparison[(6)] with that of validamine (**4.2**).[(7)] Valiolamine has been shown to be the most potent α-glucosidase inhibitor among the pseudoaminosugars (carbaaminosugars) validamine (**4.2**), hydroxyvalidamine (**4.3**)[(7)] and valienamine (**4.4**)[(8)] (Fig. 4.1) obtained from chemical or microbial degradation of validamycin.[(9)] Since valiolamine very strongly inhibits α-glucosidase and maltase,[(5)] its chemical modification has been extensively investigated, leading to the preparation of the *N*-(1,3-dihydroxyprop-2-yl) derivative, voglibose (**4.5**, coded as AO-128),[(10)] a clinically very useful agent for the control of diabetes.

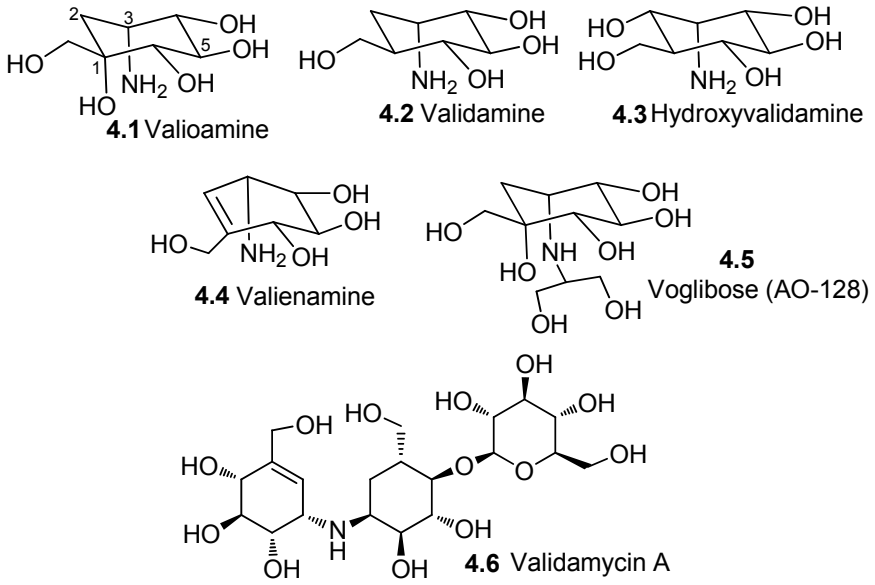


Figure 4.1.

Several syntheses of valiolamine **4.1** have been accomplished, starting from a Diels–Alder *endo*-adduct[11] of furan and acrylic acid, D- glucose,[12] L-quinic acid,[13] D-arabinose,[14] and *myo*-inositol (Chart 4.1).[15]

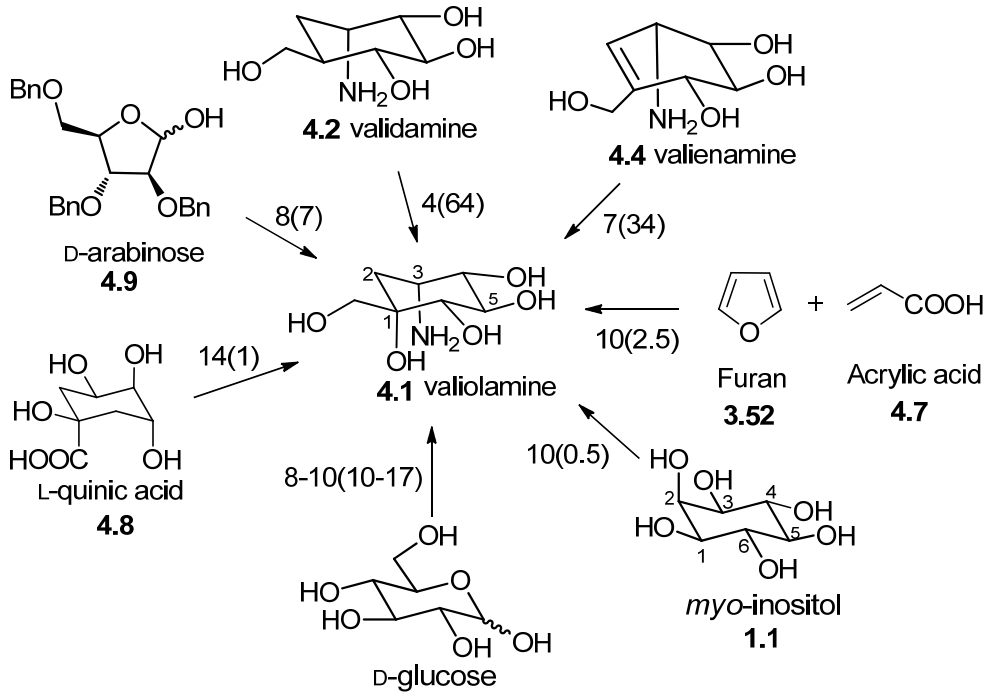


Chart 4.1. Literature reported syntheses of valiolamine. Numbers on the arrow indicate number of steps (% overall yield).

We envisioned a route to valiolamine from abundantly available *myo*-inositol based on the chemistry described in previous chapters. *myo*-Inositol has earlier been used as a starting material for the synthesis of natural products other than valiolamine (Chart 4.2).[16]

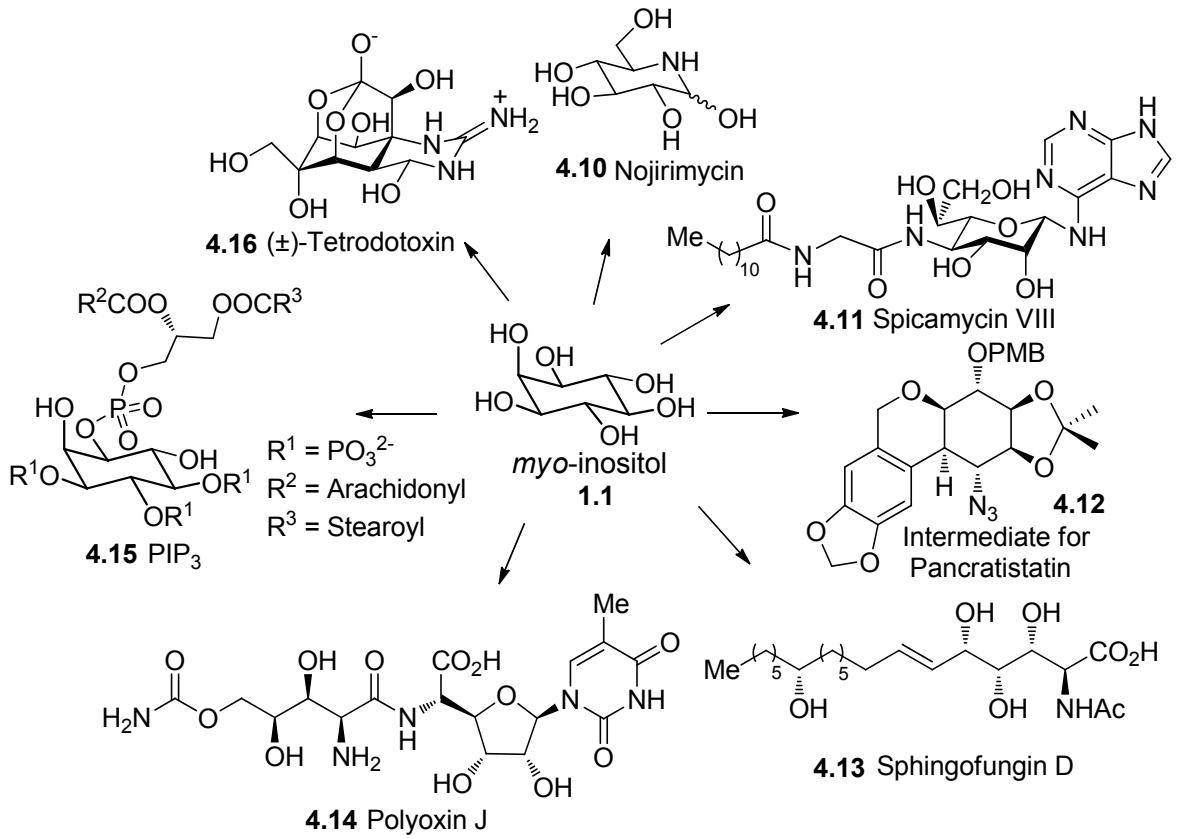
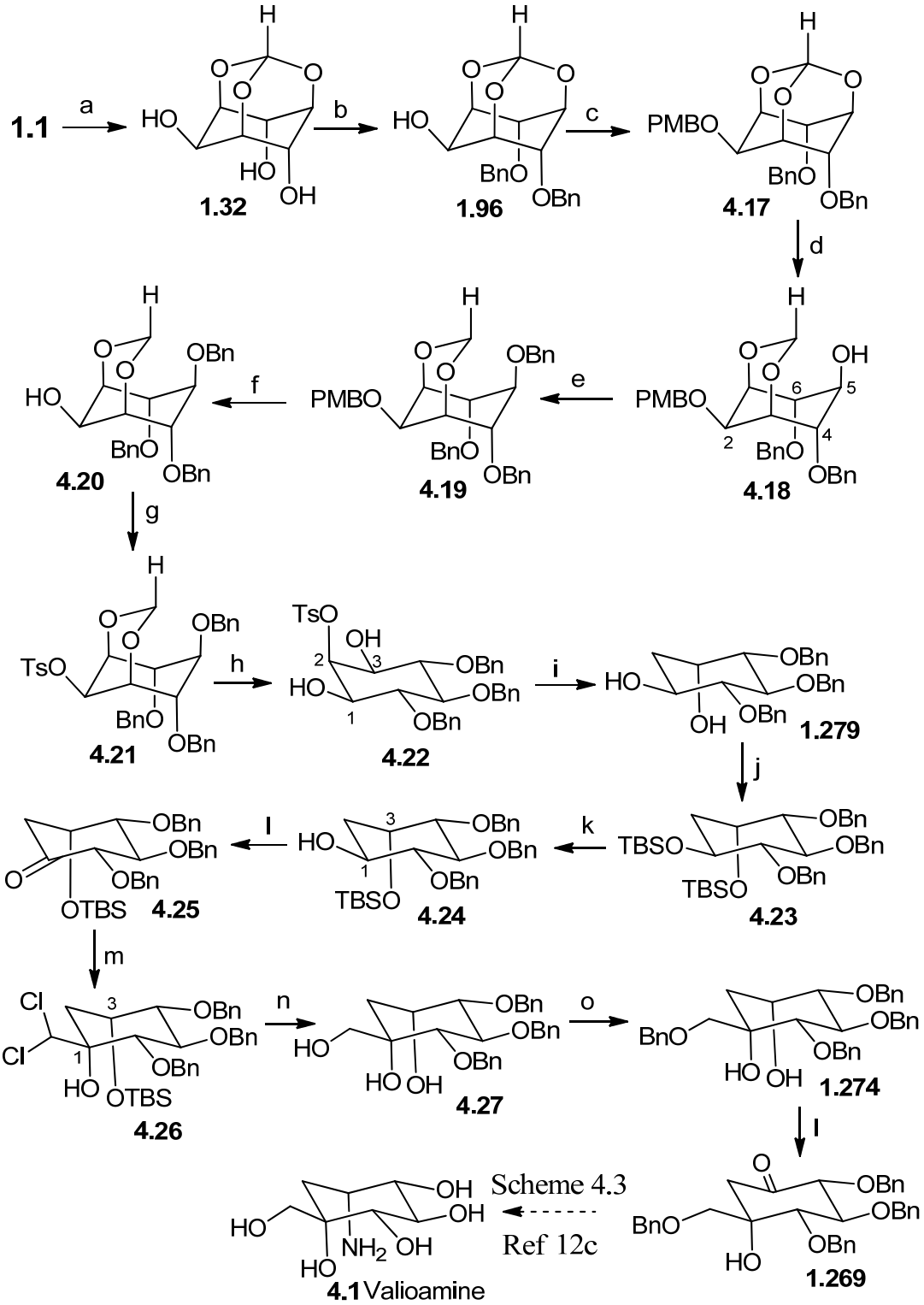


Chart 4.2. Natural products synthesized from *myo*-inositol.

A comparison of the structure of valiolamine and *myo*-inositol reveals that the relative orientation of the C4, C5 and C6 hydroxyl groups is same in both the molecules. To convert *myo*-inositol to valiolamine, (a) the C2-hydroxyl group has to be replaced by a hydrogen; (b) C1(3)-hydroxyl group must be converted to an amino group with inversion of configuration at the C1(3)-carbon; (c) the C3(1)-hydroxyl group must be replaced by a hydroxymethyl group; and (d) the C3(1)-hydrogen must be replaced by a hydroxyl group. Key reactions in our synthetic approach to achieve these changes in *myo*-inositol were (i) lithium hydride mediated selective benzylation of the C4- and C6-hydroxyl groups of *myo*-inositol orthoformate **1.32**; (ii) a novel deoxygenation reaction of the tosylate **4.22**,[17] and (iii) stereospecific nucleophilic addition of dichloromethyllithium to the inosose **4.25** (scheme 4.1).[16e]

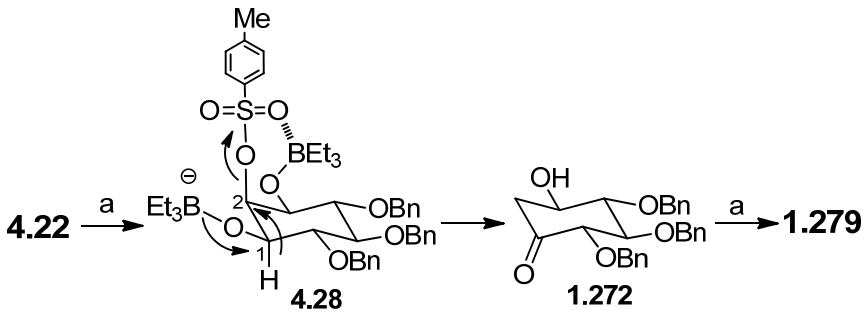
4.2. Results and discussion.

4.2.1. Synthesis of racemic ketone 1.269 from *myo*-inositol.



Scheme 4.1. (a) DMF, TsOH, $CH(OEt)_3$; (b) DMF, LiH, BnBr, 65%; (c) DMF, NaH, PMBCl; (d) DCM, DIBAL-H; (e) DMF, NaH, BnBr; (f) DCM:H_2O, DDQ, 90% (over 4 steps); (g) Py, TsCl, DMAP, 80 °C, 93%; (h) i. DCM, TFAA, AcOH ii. K_2CO_3, MeOH, 90%; (i) THF, $LiEt_3BH$, 85%;(j) DCM, 2,6-lutidine, TBSOTf, 95%; (k) CSA, MeOH, 95%; (l) AcOEt, IBX, 95% for **4.25**, 65% for **1.269**; (m) THF, LDA (2.0 eq.), CH_2Cl_2, 82%; (n) DMSO, aq. $n(Bu)_4NOH$ then MeOH, $NaBH_4$, 51%; (o) i. Bu_2SnO, MeOH, toluene ii. BnBr, $n Bu_4NBr$, 84%.

The complete synthetic scheme for the conversion of *myo*-inositol to racemic ketone **1.269** is shown in scheme 4.1; conversion of the ketone **1.269** to valiolamine is reported in the literature.[12c] *myo*-Inositol orthoformate (**1.32**) was obtained from *myo*-inositol using a known procedure;[18] the C4- and C6-hydroxyl groups were selectively benzylated using lithium hydride and benzyl bromide by a procedure developed earlier in our laboratory.[19] However, we had to optimize the procedure, to obtain the dibenzyl ether **1.96** on 10 g scale consistently. The free hydroxyl group in **1.96** was alkylated with PMBCl (on 10 g scale) and the crude **4.17** obtained was used in the next step without purification. The orthoformate moiety in **4.17** was reduced partially and selectively using DIBAL-H to get the C5-alcohol **4.18**. O-benzylation of crude **4.18** with benzyl bromide and sodium hydride followed by oxidative cleavage of the PMB ether with DDQ and column chromatographic purification afforded **4.20** in excellent yield (90 % over 4 steps from **1.96**). Cleavage of the PMB ether in **4.19** could not be performed on larger than 9 g (crude) scale due to the difficulties faced in the work-up procedure. The free hydroxyl group in **4.20** was converted to the corresponding tosylate **4.21**, by heating with tosyl chloride in pyridine (93% yield). It is generally observed that the sixth O-substitution in *myo*-inositol requires harsh reaction conditions to drive the reaction to completion. Although tosylates of secondary alcohols are known to undergo quarternization with ease, in the presence of pyridine, the tosylate **4.21** was stable at elevated temperatures, perhaps because of the rigidity imparted by the 1,3-acetal bridge on the molecule. Subjecting **4.21** to acetolysis using trifluoroacetic anhydride and acetic acid[20] resulted in cleavage of the methylidene acetal (with concomitant inversion of the carbocyclic ring) to furnish the diol **4.22** in good yield. Reaction of the tosylate **4.22** with excess lithium tri-ethyl borohydride (Super-Hydride)[17] in THF resulted in the reduction of the tosylate and inversion of one of the hydroxyl group (probably through **1.272** scheme 4.2) to give the key intermediate **1.279**.[21]



Scheme 4.2. (a) THF, $LiEt_3BH$.

In order to gain access to axial TBS protected ketone **4.25**, the diol **1.279** was converted into the bis-silyl derivative **4.23** in quantitative yield using excess of TBSOTf and 2,6-lutidine in dichloromethane. Then **4.23** was subjected to regioselective deprotection of the equatorial TBS using equimolar amount of camphorsulphonic acid in methanol, leaving axial TBS ether unaffected. Reaction of **1.279** with one equivalent of TBSOTf resulted in the protection of the equatorial hydroxyl group exclusively (see scheme 4.10). The free hydroxyl group in **4.24** was oxidized using IBX (2-iodoxy benzoic acid)[(22)] in refluxing ethyl acetate to give the desired ketone **4.25** in excellent yield.

For the introduction of the equatorial hydroxymethyl group, the ketone **4.25** was reacted with dichloromethyllithium (generated by reacting lithium di-isopropylamide with dichloromethane in THF at –78 °C) [(16e, 23)] to get exclusively a dichloromethyl derivative **4.26**. The dichloromethyl derivative is quite non-polar and is eluted in 2–3% ethyl acetate and light petroleum mixture from column. This non-polar nature of the compound **4.26** was made use of in crystallizing it from pentane. Single crystal X-ray analysis of **4.26** (Fig. 4.2) confirmed the formation of product with equatorial disposition of dichloromethyl group and axial tertiary hydroxyl group.

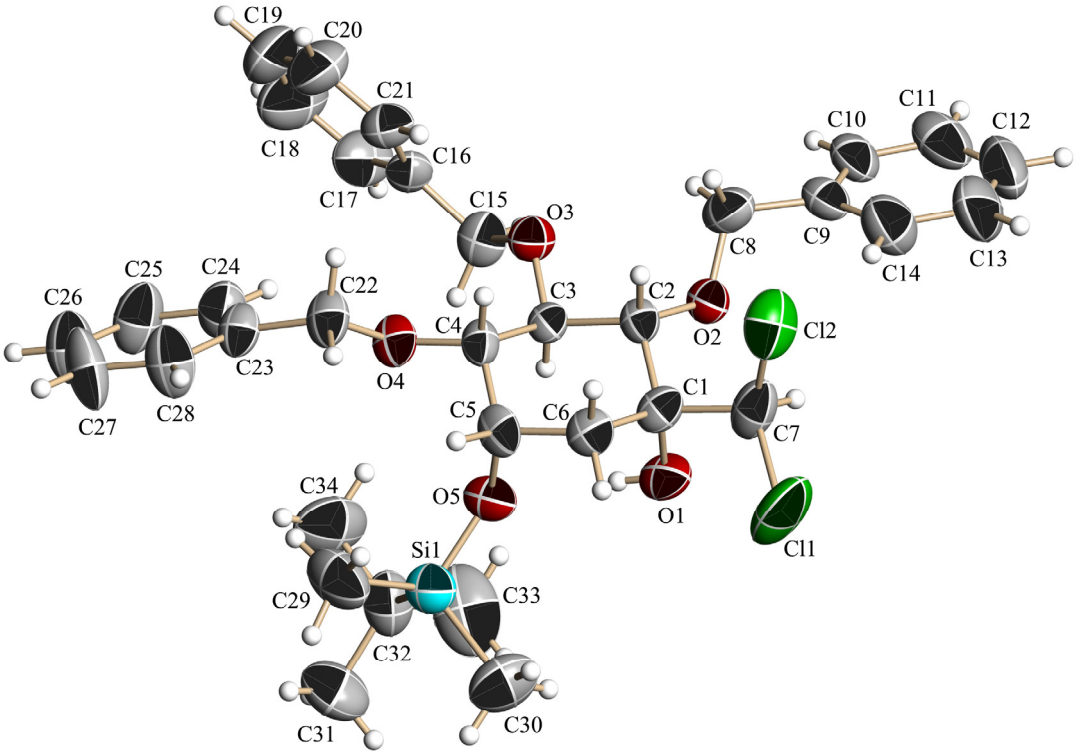
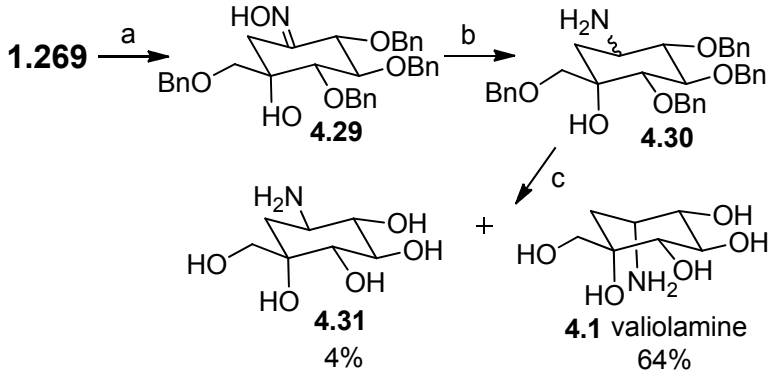


Figure 4.2. ORTEP diagram of dichloromethyl derivative **4.26**.

The selectivity observed for the addition of dichloromethyllithium to the ketone **4.25**, is perhaps due to the presence of the bulky axial silyl ether, which restricts the approach of the nucleophile to one face of the ketone. It is also possible that the lithium ion chleates between the axial oxygen (of the TBS ether) and the carbonyl oxygen to aid in the formation of the product carrying an equatorial dichloromethyl group. This is similar to the hydride reduction of inososes having an axial hydroxyl group in the 3-position (considering carbonyl carbon as the 1-position) discussed in chapter 1 (section 1.4). This line of thought is supported by the fact that addition of dichloromethyllithium to the epimer of **4.25** (**4.57** scheme 4.11), which has an equatorial TBS ether results in the formation of mixture of isomeric chloro-oxiranes.

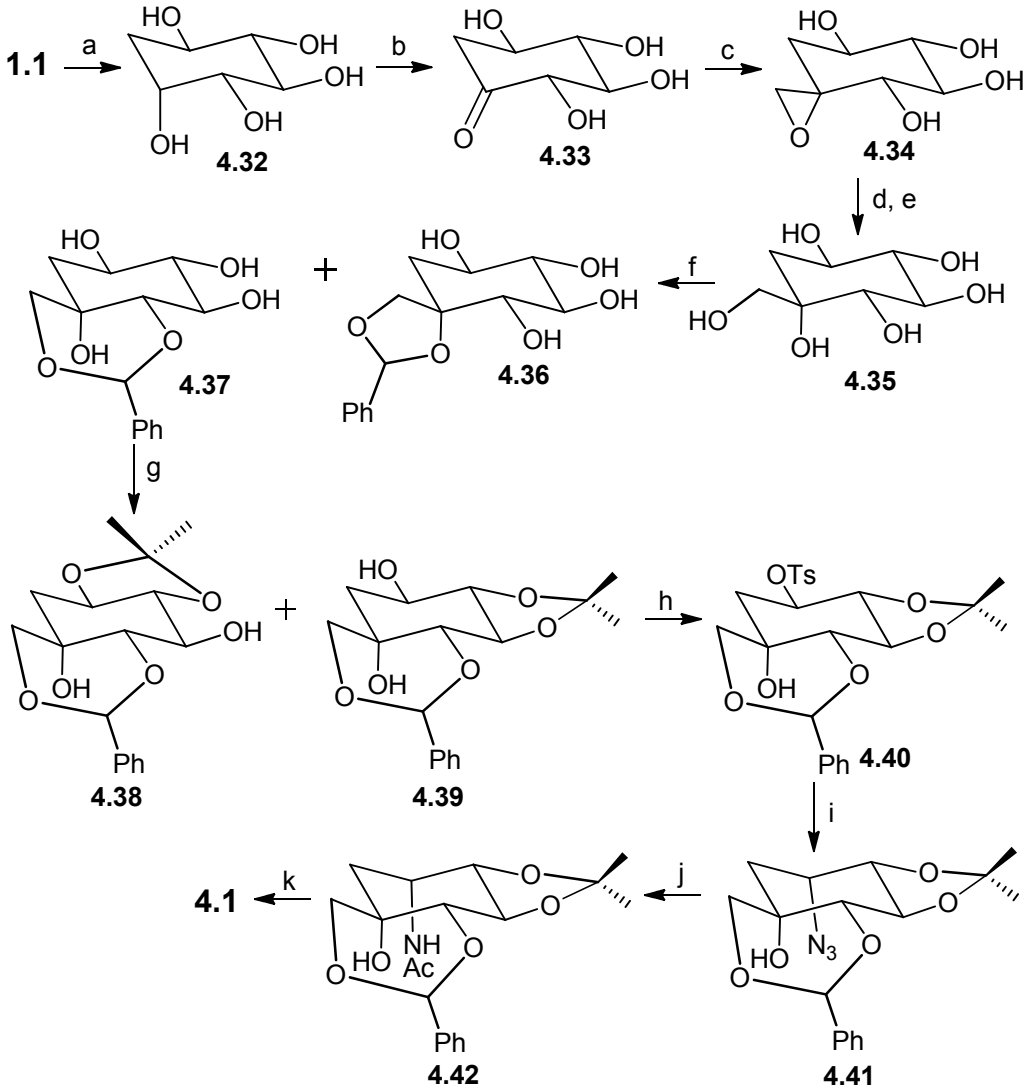
The dichloromethyl derivative **4.26** was reacted with aqueous tetrabutylammonium hydroxide[16e, 23] in DMSO as a solvent to obtain the hydroxymethyl derivative **4.27** with concomitant cleavage of the TBS group. Oxidation of the secondary hydroxyl group in **4.27** requires the protection of the primary hydroxyl group. Selective protection of the primary hydroxyl group in the triol **4.27** was achieved by its reaction with dibutyltin oxide

(MeOH:Toulene) followed by benzyl bromide. The secondary hydroxyl group in **1.274**[12b] was oxidized with IBX to obtain the known racemic ketone **1.269**.[12b] Synthesis of (+)-valiolamine (Scheme 4.3) as well as voglibose (AO-128) from an enantiomer of **1.269** is reported in the literature.[12c]



Scheme 4.3. (a) MeOH, $NH_2OH.HCl$, NaOAc, 94%; (b) MeOH, Raney-Ni; (c) HCOOH, MeOH, Pd-C.

Although there are several reports on the synthesis of valiolamine (Chart 4.1), only one report uses *myo*-inositol as the starting material.[15] This synthesis (Scheme 4.4) involves bio-deoxygenation of *myo*-inositol employing bacterial strains to produce mainly (–)-*vibo*-quercitol (**4.32**),[24] together with (–)-*epi* and (–)-*proto*-quercitol. These quercitols, or deoxyinositols, are then separated and purified by a combination of chromatography on ion-exchange-resin columns and subsequent recrystallization to get (–)-*vibo*-quercitol. (–)-*vibo*-Quercitol is then biochemically oxidized under the influence of *Gluconobacter* sp. AB10277. Apart from these drawbacks the synthesis also leads to formation of unwanted regioisomers during the protection of hydroxyl groups as acetal/ketal.



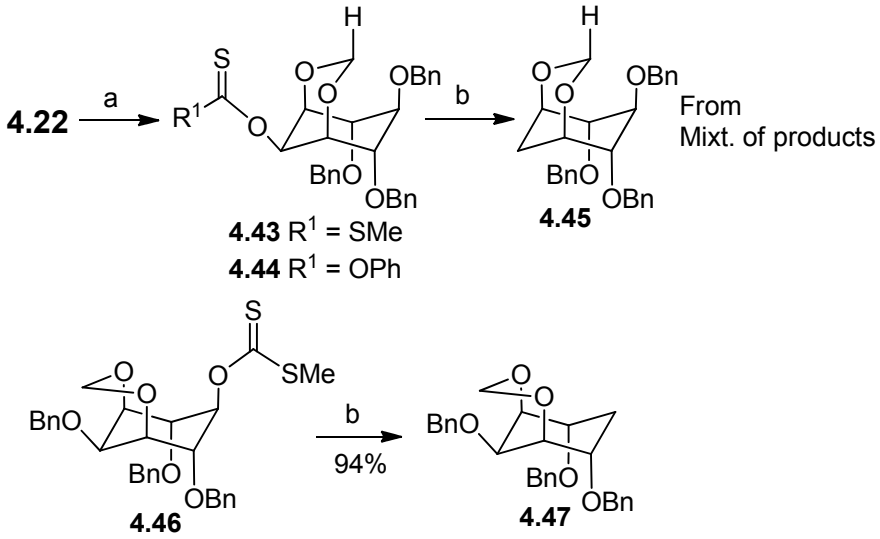
Scheme 4.4. (a) Bioconversion;[24] (b) *Gluconobacter* sp. AB 10277, 80% (for **4.33** and its hydrate); (c) MeOH, CH_2N_2, Et_2O, 44%; (d) 3 M aq. KOH, 100 °C; (e) NaOAc, DMF, H_2O, 120 °C, MeOH, NaOMe, 32%; (f) DMF, TsOH, $PhCH(OMe)_2$, 26% (**4.36**), 59% (**4.37**); (g) DMF, 2-methoxypropene, TsOH, 36% (**4.38**), 41% (**4.39**); (h) Py, TsCl, quant. (i) DMF, NaN_3, 120 °C, 88%; (j) EtOH, Raney-Ni, H_2, Ac_2O, 76%; (k) 2 M HCl, Dowex 50W × 2 (H^+) resin, aq. 1% NH_3, 90%.

Our synthetic approach has the flexibility of using different protecting groups at C4, C5 and C6 hydroxyl groups by using the reaction conditions developed in the earlier chapters of this thesis. In addition our approach avoids formation of regioisomers ('one reaction-one product' in all the steps except for **4.27**), yield in most of the steps is good to excellent and relatively cheap reagents and starting materials are used. These benefits compensates for a relatively longer synthetic protocol.

4.2.2. Hurdles / hitches circumvented during the synthesis of the ketone 1.269 from *myo*-inositol.

Attempted deoxygenation at C2 position of 4.22.

Earlier during the synthesis (Scheme 4.1) we attempted the Barton-McCombie deoxygenation of **4.43** and **4.44** in order to gain access to the deoxy inositol derivative **4.45** (Scheme 4.5). When the xanthate ester **4.43** was reacted with tributyltinhydride in the



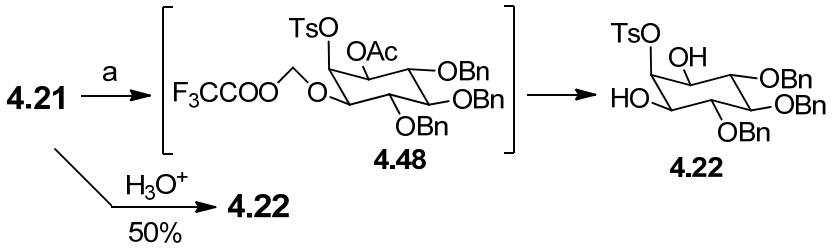
Scheme 4.5. (a) THF, NaH, CS_2, MeI, 82% or DCM, Py, DMAP, PhOC(S)Cl, 80%; (b) Toluene or Benzene, nBu$_3$SnH, AIBN.

presence of AIBN, a mixture of products was formed, from which a small amount of the deoxy-derivative **4.45** was isolated. Similar was the outcome of the reaction of the phenyl thionoformate derivative **4.44** with tributyltinhydride. In contrast, we had observed earlier in our laboratory[25] that the deoxygenation of the C5-hydroxyl group (*via* its xanthate) in the *myo*-inositol derivative **4.46** proceeded smoothly to afford the corresponding deoxy derivative **4.47** in excellent yield.

Hydrolysis of the acetal in 4.21.

Acid catalyzed solvolysis or hydrolysis of the acetal **4.21** (with HCl or TsOH in MeOH or THF) was very sluggish and resulted in about 50% conversion (to the corresponding diol **4.22**) after boiling for 4–5 days. This indicated that protic acids are not strong enough to bring about cleavage of the acetal. Hence we had to use a stronger (Lewis) acid, acylium ion, to cleave the methylidene acetal in **4.21** Reaction of the acetal **4.21** with an equimolar mixture of TFAA and acetic acid[20] resulted in the complete conversion of the acetal to the corresponding diol. Initially, acetic acid reacts with TFAA to generate the mixed anhydride which acts as a source of acylium ion; the latter opens the

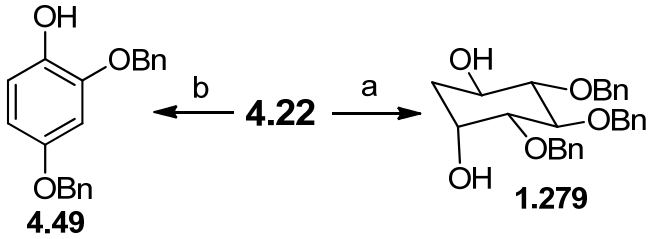
acetal ring to afford an intermediate of type **4.48**, which on methanolysis (with MeOH / K_2CO_3) *in situ* gives the diol **4.22** (Scheme 4.6).



Scheme 4.6. (a) i. DCM, TFAA, AcOH; ii. K_2CO_3, MeOH, 90 %.

Reaction of the tosylate 4.22 with super hydride.

The reduction of the tosylate **4.22** with super hydride resulting in the formation of **1.279** involves the complexation of lithium tri-ethyl borohydride with the hydroxyl groups in **4.22**. Subsequent 1, 2 hydride shift (from C1 to C2 position, Scheme 4.2) followed by reduction of the intermediate ketone **1.272** formed, (with lithium tri-ethylborohydride, Scheme 4.2) provides the diol **1.279**. This deoxygenation reaction required the use of fresh lithium tri-ethyl borohydride solution. The use of old samples of super hydride solution (which were turbid) resulted in the formation of the aromatized product **4.49**[17] exclusively (Scheme 4.7). Hence we suspected that the basic impurities present in turbid samples of super



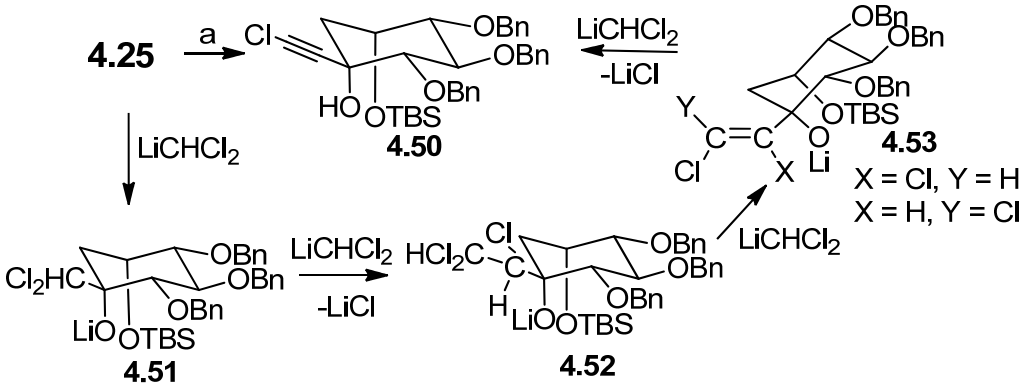
Scheme 4.7. (a) THF, $LiEt_3BH$, (fresh bottle) 85%; (b) THF, $LiEt_3BH$ (old bottle) or THF, NaH, 69%.

hydride solution could be triggering the aromatization of tosylate diol **4.22** or the intermediate ketone **1.272**. This suspicion was substantiated by the fact that treatment of the diol **4.22** with sodium hydride (4.0 eq.) in THF, resulted in the formation of the aromatized product **4.49**. Hence it took several attempts for us to standardize the conversion of **4.22** to **1.279** and obtain the yield of **1.279** consistently.

Addition of dichloromethyllithium to the ketone 4.25.

Initially, we carried out addition of dichloromethyllithium to the ketone **4.25** using 3 equivalents of LDA. However results of these experiments were not consistent and in some trials we observed the formation of the alkyne **4.50** (29%), while major amount of **4.25** remained unreacted (Scheme 4.8). To circumvent this problem, amount of LDA was lowered to 2 molar equivalents which produced the dichloromethyl derivative **4.26** consistently in good yield.

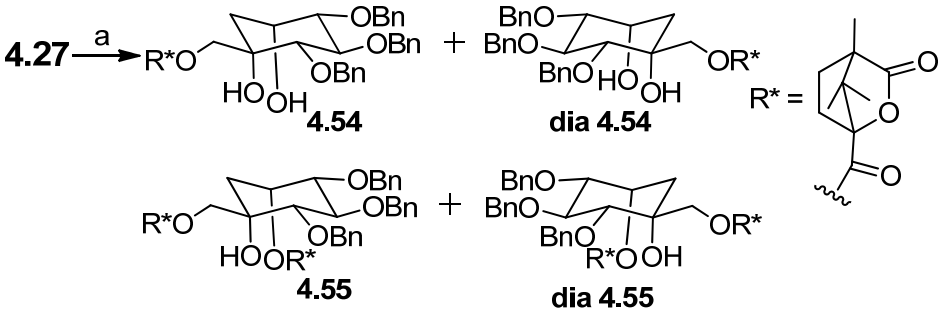
Formation of the chloro-alkyne **4.50** (from **4.25** and dichloromethyl lithium) is quite surprising and to the best of our knowledge this seems unprecedented in the literature. We are suggesting a plausible mechanism for the formation of the alkyne **4.50** based on the known electrophilic nature of dichloromethyl lithium[26] and organolithium mediated elimination of halo-alkenes.[27] Thus dichloromethyl lithium reacts with the initially formed **4.51** to give **4.52** which undergoes dehydrochlorination (twice), mediated by dichloromethyl lithium to form the chloroalkyne **4.50**.



Scheme 4.8. (a) THF, LDA (3.0 eq.), CH_2Cl_2, 29% **4.50**.

Attempted resolution of the intermediates 4.27 and 1.274.

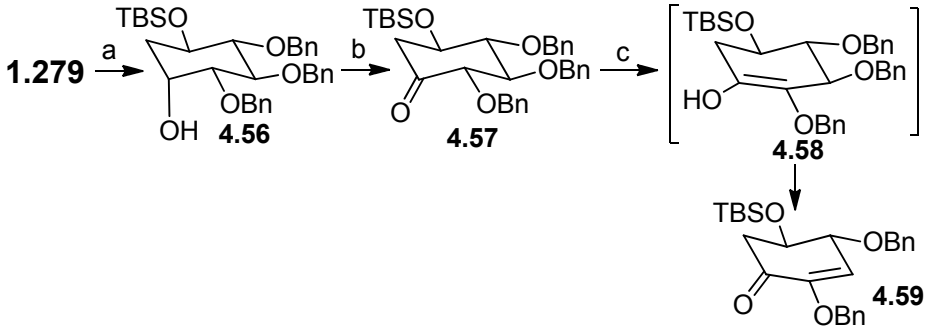
We attempted to resolve the triol **4.27** as its camphanate esters, in order to achieve the synthesis of enantiomeric valiolamine. Reaction of the triol **4.27** with (1S)-camphanic acid chloride in pyridine gave a mixture of **4.54** and its diastereoisomer as the major product. Although we could separate small amounts of the diastereomeric camphanates (as revealed by their ^{1}H NMR spectra) by column chromatography, this procedure did not appear to be synthetically viable. The diol **1.274** did not react with (1S)-camphanic chloride in pyridine (in the presence of DMAP, at rt as well as at 90 ºC).



Scheme 4.9. (a) Py, (–)-(1S)-R*Cl (1.2 eq.).

Addition of dichloromethyllithium to the ketone 4.57.

We also performed nucleophilic addition of dichloromethyllithium on the ketone **4.57**, hoping to convert the resulting product (**4.62**) to **1.269** (Scheme 4.1). The ketone **4.57** is an epimer of **4.25**, as it has an equatorial TBS ether (as against an axial TBS ether in **4.25**, Scheme 4.1). The ketone **4.57** was obtained by the regioselective silylation of the diol **1.279** with TBSOTf (1.5 molar eq.) followed by oxidation using IBX (Scheme 4.10). The

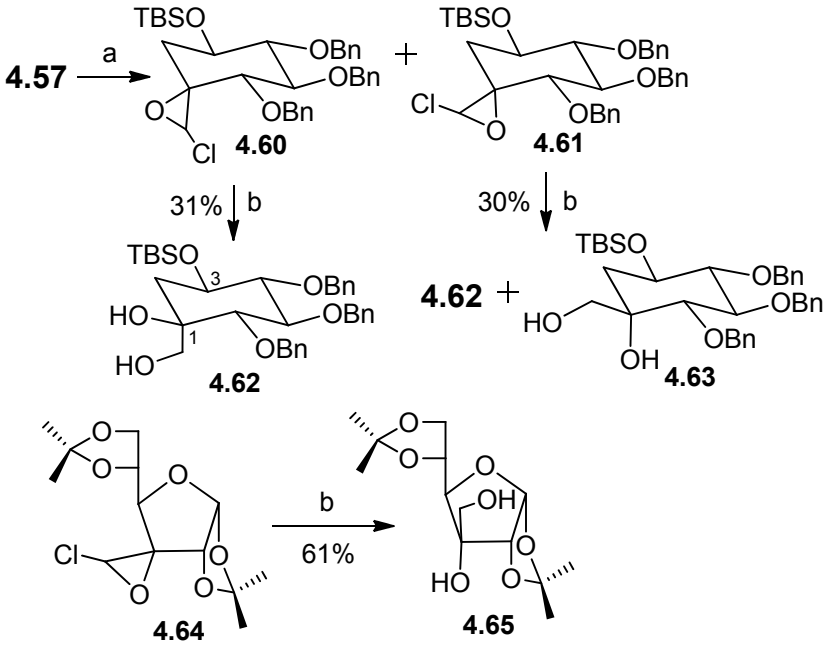


Scheme 4.10. (a) DCM, 2,6-lutidine, TBSOTf, 83%; (b) AcOEt, IBX, 85%; (c) silica gel pre-treated with tri-ethyl amine, 79%.

ketone **4.57** was purified by passing it through a small bed of silica gel (in less than 2 h). Initially, for the column chromatographic purification of the ketone **4.57**, we used silica gel pre-treated with triethylamine, since we were concerned that the acidity of the silica gel used, could cleave the TBS ether in **4.57**. However, this procedure resulted in the

formation of the α, β-unsaturated ketone **4.59** (IR absorption for carbonyl group 1697 cm^{-1}) probably through the enol **4.58** (the ketone **4.25** shows strong absorption at1732 cm^{-1} in its IR spectrum). However, it was interesting to see that the ketone **4.59** is not easily aromatized unlike the tosylate diol **4.22**.

Reaction of the ketone **4.57** with dichloromethyllithium resulted in the formation of two isomeric chlorooxiranes **4.60** and **4.61** (in the ratio 4.66:1) which were separable by column chromatography. Their structures were inferred from their spectroscopic and mass spectrometric data. The minor product, chlorooxirane **4.61**, could be crystallized from



Scheme 4.11. (a) THF, LDA, CH_2Cl_2, 70% (**4.60**), 15% (**4.61**); (b) i. DMSO, aq. $n(Bu)_4NOH$ ii. MeOH, $NaBH_4$.

acetonitrile at room temperature. Single crystal X-ray diffraction analysis of these crystals revealed the axial disposition of oxirane oxygen in **4.61** (Figure 4.3). The oxirane ring in the chlorooxiranes **4.60** and **4.61** were opened by reaction with aqueous tetrabutylammonium hydroxide in DMSO (reaction time 30 sec) leading to the

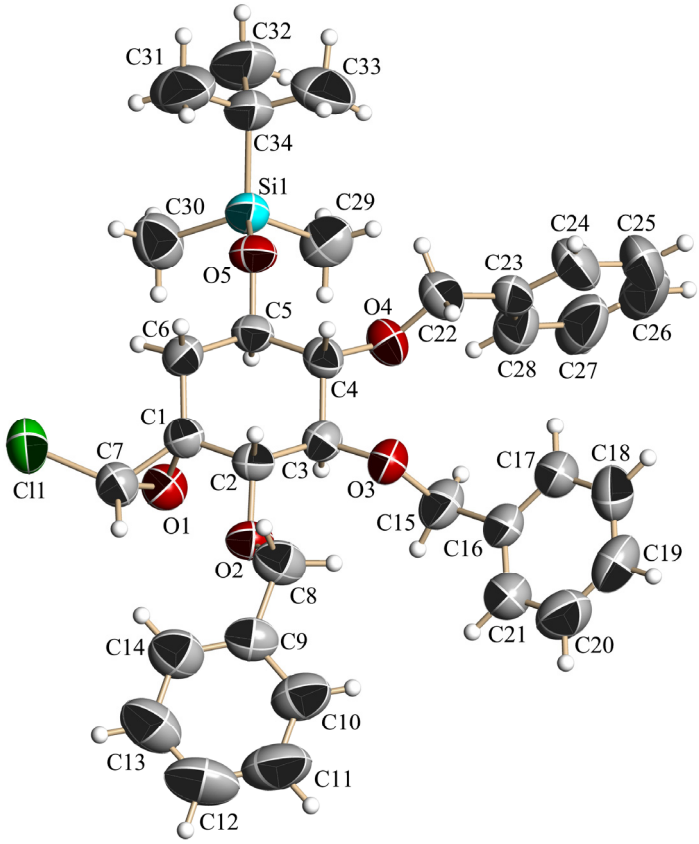


Figure 4.3. ORTEP diagram of chlorooxirane **4.61**.

hydroxymethyl derivative **4.62** and a mixture of hydroxymethyl derivatives **4.62** and **4.63** (2:1) respectively. Use of longer reaction times led to the formation of several products as revealed by TLC. These reactions implied that the major product chlorooxirane **4.60** is the undesired isomer (has an equatorial oxirane oxygen atom) for the synthesis of valiolamine, because valiolamine has the tertiary hydroxyl group in axial orientation. An instance of opening of chlorooxirane ring in a sugar derivative **4.64** to give the hydroxymethyl derivative **4.65** is reported.[23b]

4.3. Conclusions.

A formal synthesis of racemic valiolamine from *myo*-inositol presented in this chapter demonstrates the utility and potential of the synthetic methods presented in previous chapters, for the targeted synthesis of cyclitol derivatives. Although we have used one type of protecting group (benzyl) at C4, C5, C6 hydroxyl groups (see **4.20**, scheme 4.1), one can use orthogonal protection at these positions based on the chemistry developed in the earlier part of this thesis. Use of orthogonal protection could in principle give access to a variety of derivatives or analogs of natural product which has implications from

structure-activity relationship point of view. The main drawback with this strategy, since *myo*-inositol is a *meso* compound, is requirement of desymmetrization or optical resolution at some point in the synthesis to get access to optically active end products.

4.4. Experimental Section.

General Methods: General experimental methods are same as in the sub-section 2.4.1 (Chapter 2).

X-ray Data (Collection, Structure Solution and Refinement): Same as in the sub-section 2.4.2 (Chapter 2).

4,6-Di-*O*-benzyl-*myo*-inositol-1,3,5-orthoformate (1.96): To a solution of orthoformate **1.32** (10.0 g, 52.63 mmol) in DMF (500 mL) was added lithium hydride (1.68 g, 210.52 mmol) at ambient temperature and stirred for 1 h 30 min. To the above solution (thick slurry) benzyl bromide (13.77 mL, 115.78 mmol) was added and stirred for 24 h. Ice was added to reaction mixture and stirred for 5 h, solvents were removed under reduced pressure and the residue worked up 'as usual' with ethyl acetate. The crude product was crystallized from ethyl acetate to afford the dibenzyl ether **1.96** (12.7 g, 65%). **Mp.** = 122–124 ^{o}C (Lit.[18c] **Mp.** = 124–125 ^{o}C).

4,5,6-Tri-*O*-benzyl-1,3-methylidene-*myo*-inositol (4.20): To an ice cooled solution of the dibenzyl ether **1.96** (10.1 g, 27.27 mmol) in DMF (100 mL) was added sodium hydride (2.18 g, 54.53 mmol) followed by addition of 4-methoxybenzyl bromide (5.55 mL, 40.9 mmol) and the reaction mixture was stirred for 3 h at ambient temperature. Ice was added to reaction mixture and solvents were removed under reduced pressure and the residue worked up 'as usual' with ethyl acetate to obtain crude 4-methoxybenzyl ether **4.17** (16 g). This crude product **4.17** (16 g) was taken in dichloromethane (70 mL), cooled using ice bath and DIBAL-H (68.2 mL, 1.0 M soln. in toluene) was added and the resulting mixture was stirred at ambient temperature for 4 h. The reaction mixture was poured onto a rapidly stirred, cooled solution of saturated aq. ammonium chloride (200 mL) and sodium potassium tartarate (150 g in 250 mL of water). Ethyl acetate (400 mL) was added to it and stirred for 12 h at ambient temperature. The two layers were separated and the aqueous layer was extracted with ethyl acetate (3×300 mL); the combined organic layers was washed with brine, dried over anhydrous sodium sulphate, solvent was evaporated under reduced pressure to afford the crude benzylidene acetal **4.18** (17 g). The crude product **4.18** (17 g) was taken in DMF (100 mL) cooled using an ice bath and sodium hydride (2.18 g,

54.53 mmol) was added followed by addition of benzyl bromide (4.86 mL, 40.9 mmol), and the mixture was stirred for 1 h at ambient temperature. Ice was added to the reaction mixture, solvents were removed under reduced pressure; the residue obtained was taken in ethyl acetate and worked up 'as usual' to afford the crude tri-benzyl ether **4.19** (18 g). To an ice cooled solution of the tribenzyl ether **4.19** (9 g) in DCM:H_2O (300:3 mL), DDQ (4.64 g, 20.45 mmol) was added and stirred at ambient temperature for 5 h. The reaction mixture was diluted with DCM (200 mL) and washed with 40% aq. sodium hydrogen carbonate solution (2×400 mL), followed by brine and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (gradient elution: ethyl acetate/light petroleum 2:8 to 3:7) to afford **4.20** (5.68 g) as a solid. The last step was repeated on remaining 9 g crude tri-benzyl ether to get another 5.66 g of **4.20** (total yield 90%).

Data for 4.20: Mp. = 76–78 °C; **IR** ($CHCl_3$): $\bar{\nu}$ 3250–3550 (OH) cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 7.40–7.26 (m, 15H), 4.92 (d, J = 7.0 Hz, 1H, CH_AH$_B$Ph), 4.84 (d, J = 7.0 Hz, 1H, CH$_A$$H_B$Ph), 4.77 (s, 2H), 4.71 (d, J = 11.6 Hz, 2H, 2×CH_AH$_B$Ph), 4.57 (d, J = 11.6 Hz, 2H, 2×CH$_A$$H_B$Ph), 4.09 (d, J = 2.5 Hz, 2H), 3.97 (d, J = 7.6 Hz, 2H), 3.83 (d, J = 9.7 Hz, 1H), 3.68 (t, J = 7.7 Hz, 1H), 3.21 (d, J = 10.7 Hz, OH, 1H) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$) δ: 138.2 (C_{ipso}), 137.2 (C_{ipso}), 128.4 (C_{arom}), 128.2 (C_{arom}), 127.89 (C_{arom}), 127.86 (C_{arom}), 127.8 (C_{arom}), 127.6 (C_{arom}), 127.5 (C_{arom}), 85.2 (CH_2), 81.3 (CH), 75.2 (CH), 74.5 (CH_2), 71.5 (CH_2), 62.9 (CH) ppm; **Elemental Anal**. $C_{28}H_{30}O_6$ (462.53) calcd. C, 72.71; H, 6.54 found C, 72.74; H, 6.65 %.

4,5,6-Tri-*O*-benzyl-1,3-methylidene-2-*O*-tosyl-*myo*-inositol (4.21): The *myo*-alcohol **4.20** (9.5 g, 20.54 mmol), pyridine (25 mL), tosyl chloride (9.79 g, 51.35 mmol) and DMAP (0.1 g) were heated at 80 ^oC for 9 h. Ice was added to the reaction mixture, solvent was removed under reduced pressure, the residue was taken in ethyl acetate and worked up as usual. The crude product was purified by flash column chromatography (eluent: ethyl acetate / light petroleum 1:4) to afford the tosylate **4.21** (11.8 g, 93%) as a gum.

Data for 4.21: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.87–7.73 (m, 2H), 7.40–7.15 (m, 17H), 5.03 (d, J = 6.0 Hz, 1H), 4.92–4.83 (m, 2H), 4.58 (s, 2H), 4.50 (d, J = 11.7 Hz, 2H, CH_AH$_B$Ph), 4.41 (d, J = 11.7 Hz, 2H, CH$_A$$H_B$Ph), 4.15 (br s, 2H), 3.90 (br d, J = 4.4 Hz, 2H), 3.63 (t, J = 4.5 Hz, 1H) 2.36 (s, CH_3, 3H) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 145.0 (C_{ipso}), 137.8 (C_{ipso}), 137.2 (C_{ipso}), 133.4 (C_{ipso}), 129.8 (C_{arom}), 128.3 (C_{arom}), 127.9

(C_{arom}), 127.8 (C_{arom}), 127.72 (C_{arom}), 127.67 (C_{arom}), 85.3 (CH_2), 80.8 (CH), 78.7 (CH), 73.0 (CH_2), 72.6 (CH), 71.7 (CH), 71.4 (CH_2), 21.5 (CH_3) ppm; **Elemental Anal**. $C_{35}H_{36}O_8S$ (616.72) : calcd. C, 68.16; H, 5.88 found C, 67.80; H, 5.86 %.

4,5,6-Tri-*O*-benzyl-2-*O*-tosyl-*myo*-inositol (4.22): To an ice cooled solution of the tosylate **4.21** (7.0 g, 11.35 mmol) in dichloromethane (15 mL), trifluoroacetic anhydride (6.31 mL, 45.40 mmol) was added followed by glacial acetic acid (2.6 mL, 45.40 mmol) and stirred at ambient temperature for 12 h. Potassium carbonate was added to the ice cooled reaction mixture and stirred for 4 h (till the pH was neutral, as indicated by pH paper). The reaction mixture was passed through a bed of Celite and the filtrate was concentrated. The residue obtained (10 g) was taken in THF:MeOH (1:1, 20 mL) and Potassium carbonate (6.3 g, 45.40 mmol) was added, stirred for 8 h. Ice was added to the reaction mixture, solvents were removed under reduced pressure and the residue was worked up as usual with ethyl acetate. The crude product was flash column chromatoghraphed (eluent: ethyl acetate / light petroleum, 2:3) to afford the diol **4.22** (6.17 g, 90 %) as a colorless solid.

Data for 4.22: Mp. = 133.5–135.5 ^oC; **IR** ($CHCl_3$): $\bar{\nu}$ 3550–3500, 3500–3400 (OH) cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.85–7.75 (m, 2H), 7.40–7.27 (m, 17H), 5.08 (t, *J* =2.0 Hz, 1H), 4.86 (s, 2H), 4.87 (d, *J* =11.1 Hz, 2H), 4.72 (d, *J* =11.1 Hz, 2H), 3.75–3.60 (m, 4H), 3.55–3.43 (m, 1H), 2.45 (s, CH_3, 3H), 2.40 (d, *J* =2.0 Hz, OH, 2H) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 144.5 (C_{ipso}), 138.1 (C_{ipso}), 133.6 (C_{ipso}), 129.4 (C_{arom}), 128.4(C_{arom}), 128.3 (C_{arom}), 128.1 (C_{arom}), 127.9 (C_{arom}), 127.8 (C_{arom}), 127.7 (C_{arom}), 127.6 (C_{arom}), 82.8 (CH), 82.1 (CH), 81.4 (CH), 75.5 (CH_2), 75.4 (CH_2), 69.9 (CH), 21.6 (CH_3) ppm; **Elemental Anal**. $C_{34}H_{36}O_8S$ (604.71): calcd. C, 67.53; H, 6.00 found C, 67.28; H, 6.04 %.

Racemic (1)3,4,5-Tri-*O*-benzyl-(3)1-deoxy-*myo*-inositol or 2,3,4-Tri-*O*-benzyl-*vibo*-quercitol (1.279): To an ice cooled solution of the tosylate **4.22** (3.0 g, 4.96 mmol), in THF (20 mL) was added lithium triethylborohydride (19.8 mL, 1.0 M soln. in THF, 19.8 mmol) and stirred at ambient temperature for 4 h. Ice was added to the reaction mixture and the solvent evaporated under reduced pressure; the residue obtained was worked up as usual with ethyl acetate. The crude product was purified by flash column chromatography (eluent: ethyl acetate/light petroleum, 2:3) to afford the racemic diol **1.279**[21] (1.83 g, 85%) as a colorless solid.

Data for 1.279: Mp. = 100.5–102.5 °C (lit[21] 115–118 °C for (–)-**6**); **IR** (Neat): $\bar{\nu}$ 3600–3200 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.45–7.27 (m, 15 H), 5.01 (d, *J* =11.4 Hz, 1H), 4.92 (d, *J* =10.7 Hz, 1H), 4.82 (d, *J* = 10.7 Hz, 1H), 4.78–4.63 (m, 3H), 4.17–4.08 (m, 1H), 4.05–3.90 (m, 1H), 3.84 (t, *J* =9.3 Hz, 1H), 3.50 (dd, *J* = 9.3 and 3.1 Hz, 1H), 3.27 (t, *J* = 9.3 Hz, 1H), 2.48 (br s, OH, 1H), 2.40–2.17 (m, 1 OH, 2H), 1.48–1.28 (m, 1H) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 138.5 (C_{ipso}), 137.8 (C_{ipso}), 128.4 (C_{arom}), 128.3 (C_{arom}), 127.8 (C_{arom}), 127.7 (C_{arom}), 127.5 (C_{arom}), 86.1 (CH), 83.1 (CH), 81.4 (CH), 75.6 (CH_2), 75.3 (CH_2), 72.6 (CH_2), 67.8 (CH), 65.8 (CH), 33.7 (CH_2) ppm; **Elemental Anal**. $C_{27}H_{30}O_5$ (434.52): calcd. C, 74.63; H, 6.96 found C, 74.29; H, 6.71 %.

Preparation of bis-TBS ether 4.23: To an ice cooled solution of the diol **1.279** (3.0 g, 6.90 mmol) in dichloromethane (10 mL) 2,6-lutidine (2.0 mL, 17.26 mmol) was added followed by addition of TBSOTf (3.65 mL, 15.88 mmol). Resulting reaction mixture was stirred at room temperature for 1 h 30 min. Ice was added to reaction mixture, diluted with dichloromethane and worked up as usual. The crude product was purified by column chromatography (eluent: ethyl acetate/light petroleum, 1:9) to afford racemic bis-TBS ether **4.23** (4.34 g, 95%) as a gum. The silica gel (100–200 mesh) used was pre-eluted with triethyl amine/ light petroleum (1:49, 3–5 mL/g).

Data for 4.23: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40–7.20 (m, 15H), 4.92–4.72 (m, 4H), 4.68 (s, 2H), 4.20–4.00 (m, 2H), 3.86 (t, *J*=9.5 Hz, 1H), 3.38–3.24 (m, 2H), 2.05–1.87 (m, 1H), 1.50–1.30 (m, 1H), 0.89 (s, 18H) 0.08 (s, 3H), 0.06 (s, 6H), 0.04 (s, 3H) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 139.1 (C_{ipso}), 139.0 (C_{ipso}), 138.6 (C_{ipso}), 128.2 (C_{arom}), 128.1 (C_{arom}), 127.9 (C_{arom}), 127.7 (C_{arom}), 127.5 (C_{arom}), 127.3 (C_{arom}), 127.2 (C_{arom}), 87.0 (CH), 83.3 (CH), 81.4 (CH), 75.8 (CH_2), 75.7 (CH_2), 72.9 (CH_2), 70.4 (CH), 67.6 (CH), 38.4 (CH_2), 25.9 [SiC(CH_3)$_3$], 25.8 [SiC(CH_3)$_3$], 18.1 [SiC(CH_3)$_3$], 18.0 [SiC(CH_3)$_3$], -4.4 (SiCH_3), -4.5 (SiCH_3), -4.6 (SiCH_3), -5.2 (SiCH_3), ppm; **Elemental Anal**. cacld $C_{39}H_{58}O_5Si_2$ (663.05) C, 70.65; H, 8.82 found C, 70.58; H, 8.66 %.

Preparation of TBS ether 4.24: To an ice cooled solution of the diTBS ether **4.23** (1.54 g, 2.32 mmol) in methanol (16 mL) was added camphor sulphonic acid (0.54 g, 2.32 mmol) and stirred at ambient temperature for 35 min. The acid was neutralized by the addition of triethyl amine (0.5 mL), the reaction mixture was concentrated under reduced pressure and the residue was worked up as usual with ethyl acetate. The crude product was purified by column chromatography (eluent: ethyl acetate / light petroleum, 1:6) to afford the racemic

TBS ether **4.24** (1.21 g, 95%) as a gum. The silica gel (100–200 mesh) used was pre-eluted with triethyl amine/ light petroleum (1:49, 3–5 mL/g).

Data for 4.24: IR ($CHCl_3$): $\bar{\nu}$ 3300–3600 (OH) cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.41–7.23 (m, 15H), 5.08–4.90 (m, 2H), 4.85–4.57 (m, 4H), 4.25–4.15 (m, 1H), 4.05–3.85 (m, 2H), 3.43–3.20 (m, 2H), 2.26 (br s, D_2O exchangeable, OH, 1H), 2.15–1.95 (m, 1H), 1.45–1.22 (m, 1H), 0.88 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H) ppm; **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 138.71 (C_{ipso}), 138.67 (C_{ipso}), 138.5 (C_{ipso}), 128.6 (C_{arom}), 128.3 (C_{arom}), 128.2 (C_{arom}), 128.1 (C_{arom}), 128.0 (C_{arom}), 127.9 (C_{arom}), 127.5 (C_{arom}), 127.4 (C_{arom}), 86.6 (CH), 83.6 (CH), 81.4 (CH), 75.5 (CH_2), 72.6 (CH_2), 68.4 (CH), 67.2 (CH), 35.9 (CH_2), 25.8 [SiC(CH_3)$_3$], 18.1 [SiC(CH_3)$_3$], -4.6 (SiCH_3), -5.0 (SiCH_3) ppm; **Elemental Anal**. calcd for $C_{33}H_{44}O_5Si$ (548.78) C, 72.22; H, 8.08 found C, 71.93; H, 7.79 %.

Preparation of ketone 4.25: The TBS ether **4.24** (1.1 g, 2.00 mmol), ethyl acetate (15 mL) and IBX (1.68 g, 6.00 mmol) were refluxed for 8 h. The reaction mixture was cooled to room temperature and passed through a bed of Celite. The bed of Celite was washed with ethyl acetate (2×50 mL), and the combined filtrate was evaporated under reduced pressure. The residue was purified by passing through a short column of silica gel (100–200 mesh) (eluent: ethyl acetate / light petroleum, 1:9) to afford the racemic ketone **4.25** (1.05 g, 95 %) as a gum.

Data for 4.25: IR ($CHCl_3$): $\bar{\nu}$ 1737 (C=O) cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.45–7.20 (m, 15H), 5.00–4.78 (m, 3H), 4.74 (s, 2H), 4.57 (d, J = 11.7 Hz, 1H) 4.32–4.25 (m, 1H) 4.15–3.95 (m, 2H), 3.68 (dd, J= 2.0 and 8.3 Hz, 1H) 2.55–2.35 (m, 2H) 0.86 (s, 9H), 0.05 (s, 6H) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 203.7 (C=O), 138.4 (C_{ipso}), 138.1 (C_{ipso}), 137.8 (C_{ipso}), 128.3 (C_{arom}), 128.2 (C_{arom}), 128.05 (C_{arom}), 128.03 (C_{arom}), 127.64 (C_{arom}), 127.59 (C_{arom}), 127.5 (C_{arom}), 85.6 (CH), 82.1 (CH), 81.7 (CH), 75.7 (CH_2), 73.3 (CH_2), 72.9 (CH_2), 67.7 (CH), 45.0 (CH_2), 25.6 [SiC(CH_3)$_3$], 18.0 [SiC(CH_3)$_3$], -4.62 (SiCH_3), -5.16 (SiCH_3) ppm; **Elemental Anal**. $C_{33}H_{42}O_5Si$ (546.77): calcd. C, 72.49; H, 7.74 found C, 72.15; H, 8.12%.

Preparation of dichloromethyl derivative 4.26: To a cooled (dry ice, acetone -78 ^oC) solution of LDA (1.17 mL, 2.0 M soln. in THF / heptanes / ethyl benzene, 2.34 mmol) in THF (4.0 mL), was added dichloromethane (0.75 mL, 11.7 mmol) followed by (after 5 min) the ketone **4.25** (0.64 g, 1.17 mmol) in THF (4.0 mL).The reaction mixture was stirred at -78 ^oC for 2 h and then at O °C for 2 h. To the reaction mixture, a saturated

solution of aq. ammonium chloride (3.0 mL) was added, and concentrated under reduced pressure; the residue was worked up as usual with ethyl acetate. The crude product was purified by flash column chromatography (eluent: ethyl acetate / light petroleum, 1:33) to afford racemic **4.26** (0.60 g, 82%) as a gum converting into solid on keeping in the fridge. The silica gel used was pre-eluted with triethyl amine/ light petroleum (1:49, 3–5 mL/g) mixture).

Data for 4.26: Mp. = 59–60 °C (Crystallized from pentane at rt); **IR** ($CHCl_3$): $\bar{\nu}$ 3500–3200 (OH) cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.45–7.15 (m, 15H), 5.94 (s, 1H), 5.08 (s, D_2O exchangeable, OH, 1H), 5.04 (d, *J*=11Hz, 1H), 4.97 (d, *J*= 10.7 Hz, 1H), 4.86 (d, *J*= 10.7 Hz, 1H), 4.83–4.62 (m, 3H), 4.44–4.36 (m, 1H), 4.21 (t, *J*=9.6 Hz, 1H), 3.84 (d, *J*= 9.5 Hz, 1H), 3.42 (dd, *J*=9.6 and 2.8 Hz, 1H), 2.27 (dd, *J*=14.9 and 3.7 Hz, 1H), 1.79 (dd, *J*=14.9 and 2.4 Hz, 1H), 0.90 (s, 9H) 0.11 (s, 6H) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 138.3 (C_{ipso}), 138.1 (C_{ipso}), 138.0 (C_{ipso}), 128.32 (C_{arom}), 128.27 (C_{arom}), 127.89 (C_{arom}), 127.86 (C_{arom}), 127.7 (C_{arom}), 127.63 (C_{arom}), 127.59 (C_{arom}), 127.56 (C_{arom}), 82.6 (CH), 81.9 (CH), 81.1 (CH), 79.5 (C), 75.9 (CH), 75.7 (CH_2), 73.5 (CH_2), 70.1 (CH), 30.2 (CH_2), 25.7 [SiC(CH_3)$_3$], 18.1 [SiC(CH_3)$_3$], -4.5 (SiCH_3), -5.5 (SiCH_3) ppm; **Mass** calcd M (+Na) 653.23 found 653.26; **Elemental Anal**. calcd for $C_{34}H_{44}Cl_2O_5Si$ (630.23) C, 64.65; H, 7.02 found C, 64.59; H, 6.74%.

Preparation of triol 4.27: To a solution of the dichloromethyl derivative **4.26** (0.23 g, 0.36 mmol) in DMSO (3 mL), was added *n*-tetrabutylammonium hydroxide (1.3 mL, 35 % solution in H_2O, 1.82 mmol), at ambient temperature and stirred for 8 min. The reaction mixture was poured into a saturated solution (20 mL) of aq. ammonium chloride, diluted with ethyl acetate, and worked up as usual with ethyl acetate. The residue obtained was taken in methanol (60 mL), cooled using ice bath and a solution of sodium borohydride (0.016 g, 0.44 mmol) in H_2O (12 mL) was added and stirred at 0 °C to 5 °C for 20 min. Acetone (2.0 mL) was added to the reaction mixture, stirred for 10 min and concentrated under reduced pressure. The residue was worked up as usual with ethyl acetate. The crude product was purified by column chromatography (eluent: ethyl acetate / light petroleum, 4:1) to afford the racemic triol **4.27** (0.09 g, 51 %) as a thick gum. The silica gel (100–200 mesh) used was pre-eluted with triethyl amine/ light petroleum (1:49, 3–5 mL/g) mixture).

Data for 4.27: IR ($CHCl_3$): $\bar{\nu}$ 3600–3200 (OH) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.40–7.27 (m, 15H), 5.01 (d, *J*= 10.6 Hz, 1H), 4.96 (d, *J*= 11.3 Hz, 1H), 4.87 (d, *J*= 10.7

Hz, 1H), 4.74 (s, 2H), 4.67 (d, *J*=11.3 Hz, 1H), 4.23-4.14 (m, 2H), 3.79 (s, D_2O exchangeable, OH, 1H), 3.46 (dd, *J*= 9.6 and 3.2 Hz, 1H), 3.43–3.38 (m, 2H), 3.35–3.25 (m, OH and CH, 2H), 2.11 (dd, *J*=15.4 and 3.3 Hz, 1H), 1.53 (dd, *J*=15.4 and 2.7 Hz, 1H), 1.44 (br s, D_2O exchangeable, OH, 1H) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 138.6 (C_{ipso}), 137.93 (C_{ipso}), 137.87 (C_{ipso}), 128.55(C_{arom}), 128.53 (C_{arom}), 128.46 (C_{arom}), 128.4 (C_{arom}), 128.1 (C_{arom}), 127.93 (C_{arom}), 127.88 (C_{arom}), 127.6 (C_{arom}), 82.7 (CH), 80.7 (CH), 80.4 (CH), 76.1 (C), 76.0 (CH_2), 75.2 (CH_2), 72.5 (CH_2), 67.9 (CH), 66.4 (CH_2), 33.2 (CH_2) ppm; **Mass** calcd M (+Na) 487.22 observed 487.20.

Preparation of diol 1.274: A mixture of the triol **4.27** (0.075 g, 0.16 mmol), dibutyltin oxide (0.046 g, 0.19 mmol), toluene (1 mL), methanol (1 mL) was refluxed for 24 h. The reaction mixture was cooled to ambient temperature, concentrated under reduced pressure and the residue co-evaporated with toluene (2 × 3 mL). To the residue toluene (2.0 mL), benzyl bromide (0.038 mL, 0.32 mmol) and *n*-tetrabutylammonium bromide (0.01 g, 0.032 mmol) were added and refluxed for 5 h. The reaction mixture was cooled to ambient temperature, concentrated under reduced pressure and the residue was purified by column chromatography (100–200 mesh silica gel, eluent: ethyl acetate/light petroleum, 3:7) to afford the racemic tetrabenzyl ether **1.274**[(12b)] (0.075 g, 84 %) as a low melting solid.

Data for 1.274: IR ($CHCl_3$): 3650–3150 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.45–7.15 (m, 20 H), 4.99 (d, *J*= 10.6 Hz, 1H), 4.92 (d, *J*= 11 Hz, 1H), 4.84 (d, *J*= 10.6 Hz, 1H), 4.75 (s, 2H) 4.55 (d, *J*= 11 Hz, 1H), 4.45 (d, *J* = 11.9 Hz, 1H), 4.38 (d, *J* = 11.9 Hz, 1H), 4.25–4.05 (m, 2H), 3.67 (d, *J* = 9.6 Hz, 1H), 3.57–3.37 (m, D_2O exchangeable, 2×OH, 4H), 3.19 (d, *J* = 8.6 Hz, 1H), 2.05 (dd, *J* = 3.2 and 15.4 Hz, 1H), 1.85 (dd, *J* = 2.8 and 15.4 Hz, 1H) ppm.

Preparation of ketone 1.269: The mixture of diol **1.274** (0.016 g, 0.029 mmol), IBX (0.024 g, 0.087 mmol), ethyl acetate (3 mL) was refluxed for 7 h. The reaction mixture cooled to ambient temperature and passed through a bed of celite and washed with ethyl acetate (2×15 mL), concentrated under reduced pressure. The crude residue was purified by column chromatography (100-200 silica gel, eluent: ethyl acetate/light petroleum, 1:3) to afford racemic ketone **1.269**[(12b)] (0.01 g, 65 %) as a solid.

Data for 1.269: Mp. = 91–92 °C (crystals from Et_2O/light petroleum (1:2) at rt) (Lit[(12b)] **Mp.** 84–85 °C for (+)-**13**); **IR** ($CHCl_3$): $\bar{\nu}$ 3600-3250 (OH), 1738 (C=O) cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.50–7.27 (m, 18H), 7.23–7.13 (m, 2H), 5.05–4.90 (m, 3H), 4.74 (d,

J = 10.7 Hz, 1H), 4.61–4.52 (m, 2H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.40 (d, *J* = 11.7 Hz, 1H), 4.19–4.10 (m, 1H), 4.10–3.99 (m, 2H), 3.53 (d, *J* = 8.6 Hz, 1H), 3.15 (d, *J* = 8.6 Hz, 1H), 2.84 (d, *J* = 14.5 Hz, 1H), 2.46 (d, *J* = 14.5 Hz, 1H), 2.41 (br s, D_2O exchangeable, OH, 1H) ppm.

Racemic 2,4-bis(benzyloxy)-phenol (4.49): To an ice-cooled solution of tosylate diol **4.22** (0.1 g, 0.16 mmol) in THF (2 mL) was added sodium hydride (0.03 g, 0.66 mmol) and stirred at ambient temperature for 48 h. Ice was added to reaction mixture, evaporated under reduced pressure, residue taken in ethyl acetate and worked up as usual. Crude product was purified by flash column chromatography to afford substituted phenol **4.49**[17] (0.035 g, 69 %) as a colorless solid.

Data for 4.49: Mp. = 79–81 ^{o}C; **IR** ($CHCl_3$): $\bar{\nu}$ 3300–3550 (OH), 1610, 1504 (C=C ring) cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.50–7.27 (m, 10H), 6.84 (d, *J*=8.6 Hz, 1H), 6.64 (d, *J*=2.6 Hz, 1H), 6.48 (dd, *J*=8.7 and 2.8 Hz, 1H), 5.30 (s, OH, 1H), 5.05 (s, 2H), 4.98 (s, 2H) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 152.4 (C_{ipso}), 146.0 (C_{ipso}), 140.0 (C_{ipso}), 137.0 (C_{ipso}), 136.0 (C_{ipso}), 128.5 (C_{arom}), 128.4 (C_{arom}), 128.2 (C_{arom}), 127.7 (C_{arom}), 127.6 (C_{arom}), 127.4 (C_{arom}), 114.3 (C_{arom}), 105.9 (C_{arom}), 101.6 (C_{arom}), 70.7 (CH_2), 70.5 (CH_2) ppm; **Elemental Anal**. $C_{20}H_{18}O_3$ (306.36): calcd C, 78.41; H, 5.92 found C, 78.72; H, 6.22 %.

Preparation of alkyne 4.50: To a cooled (dry ice, acetone -78 ^{o}C) solution of LDA (2.88 mL, 2.0 M soln. in THF / heptanes / ethyl benzene, 5.76 mmol) in THF (6.0 mL), was added dichloromethane (1.23 mL, 19.2 mmol) followed by (after 5 min) the ketone **4.25** (1.05 g, 1.92 mmol) in THF (6.0 mL).The reaction mixture was stirred at -78 ^{o}C for 4 h. The reaction was quenched with a saturated solution of aq. ammonium chloride (8.0 mL) was added, and concentrated under reduced pressure; the residue was worked up as usual with ethyl acetate. The crude product was purified by flash column chromatography (eluent: ethyl acetate / light petroleum, 1:33) to afford racemic **4.50** (0.37 g, 29%) as a solid and the starting ketone **4.25** (0.63 g, 60%). The silica gel used was pre-eluted with triethyl amine/ light petroleum (1:49, 3–5 mL/g) mixture).

Data for 4.50: Mp. = 93–95 °C (crystals from light petroleum at rt); **IR** (Nujol): $\bar{\nu}$ 3500–3250 (OH), 2229 (C≡C) cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.50–7.27 (m, 15H), 4.92 (s, 2H), 4.89 (s, 2H), 4.84 (s, D_2O exchangeable, OH, 1H) 4.79 (d, *J* = 11.6 Hz, CH_AH_BPh, 1H), 4.69 (d, *J* = 11.6 Hz, CH_AH_BPh, 1H), 4.30–4.20 (m, 1H), 4.07 (t, *J* = 9.6 Hz, 1H),

3.50 (d, *J* = 9.5 Hz, 1H), 3.36 (dd, *J* = 9.7 and 2.7 Hz, 1H), 2.32 (dd, *J* = 15.0 and 3.6 Hz, 1H), 1.75 (dd, *J* = 15.0 and 2.2 Hz, 1H), 0.88 (s, 9H), 0.08 (s, 6H) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 138.6 (C_{ipso}), 138.1 (C_{ipso}), 138.0 (C_{ipso}), 128.5 (C_{arom}), 128.3 (C_{arom}), 128.2 (C_{arom}), 127.9 (C_{arom}), 127.7 (C_{arom}), 127.6 (C_{arom}), 127.53 (C_{arom}), 127.49 (C_{arom}), 86.2 (CH), 82.2 (CH), 79.6 (CH), 76.2 (CH_2), 75.9 (CH_2), 73.6 (CH_2), 71.6 (C), 70.9 (C), 70.6 (CH), 62.3 (C), 39.7 (CH_2), 25.6 [SiC(CH_3)$_3$], 18.0 [SiC(CH_3)$_3$], -4.5 [SiCH_3], -5.5 [SiCH_3] ppm; **Mass** calcd M (+Na) 629.26; observed 629.25; **Elemental Anal**. $C_{35}H_{43}ClO_5Si$ (606.26): calcd. C, 69.23; H, 7.14 found C, 69.15; H, 6.90 %.

Reaction of triol 4.27 with (–)-(1S)-camphanic chloride: To a solution of triol **4.27** (0.05 g, 0.1 mmol) in pyridine was added (–)-(1S)-Camphanic chloride (26 mg, 0.12 mmol) and stirred at ambient temperature for 2.5 h. Reaction mixture was diluted with ethyl acetate and worked up 'as usual'. The flash column chromatography of the crude product afforded five fractions; i. mixture of di-esters **4.55** and **dia-4.55** (10 mg, 11%) eluted in 32–35% ethyl acetate:light petroleum; ii. pure **4.54** (5 mg, 7%); iii. mixture of **4.54** and **dia-4.54** (14 mg, 20%); iv. pure **dia-4.54** (5 mg, 7%) fractions ii–iv were eluted in 35% ethyl acetate:light petroleum; v. starting triol **4.27** (20 mg, 40%).

Data for 4.54: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.50–7.25 (m, 15H), 5.10–4.70 (m, 5H), 4.52 (d, *J* = 10.8 Hz, 1H), 4.27–4.02 (m, 4H), 3.81 (br s, D_2O exchangeable, OH, 1H), 3.61–3.43 (m, 2H), 3.22 (br s, D_2O exchangeable, OH, 1H), 2.48–2.29 (m, 1H), 2.14 (dd, *J* = 15.3 and 3.3 Hz, 1H), 2.05–1.82 (m, 1H), 1.77–1.55 (m, 1H), 1.11 (s, CH_3, 3H), 1.04 (s, CH_3, 3H), 0.96 (m, CH_3, 3H) ppm.

Data for Dia-4.54: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.45–7.22 (m, 15H), 5.05–4.67 (m, 5H), 4.55 (d, *J* = 10.9 Hz, 1H), 4.25–4.05 (m, 4H), 3.83 (br s, D_2O exchangeable, OH, 1H), 3.60–3.40 (m, 2H), 3.23 (br s, D_2O exchangeable, OH, 1H), 2.50–2.30 (m, 1H), 2.15 (dd, *J* = 15.3 and 3.3 Hz, 1H), 2.05–1.83 (m, 2H), 1.80–1.55 (m, 2H), 1.11 (s, CH_3, 3H), 1.05 (s, CH_3, 3H), 0.91 (s, CH_3, 3H) ppm.

Preparation of TBS ether 4.56: To a cooled (ice and salt mixture) mixture of the diol **1.279** (1.02 g, 2.35 mmol), dichloromethane (5 mL) and 2,6-lutidine (0.68 mL, 5.86 mmol) was added TBSOTf (0.8 mL, 3.52 mmol) and the reaction mixture was allowed to warm upto 10 ^oC over 1 h and then stirred at ambient temperature for 2 h. Ice was added to the reaction mixture, diluted with dichloromethane and worked up as usual. The crude product was purified by flash column chromatography (eluent: ethyl acetate / light petroleum, 1:4)

to obtain the racemic TBS ether **4.56** (1.07 g, 83 %) as a gum. Silica gel used was pre-eluted with triethyl amine / light petroleum (1:49, 3–5 mL/g) mixture.

Data for 4.56: IR (Neat): $\bar{\nu}$ 3300–3600 (OH) cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.40–7.20 (m, 15H), 4.90 (d, *J*= 11.1 Hz, 1H), 4.81 (d, *J*= 11.1 Hz, 1H), 4.82 (s, 2H), 4.73 (d, *J*= 11.5 Hz, 1H), 4.65 (d, *J*= 11.5 Hz, 1H), 4.16–4.00 (m, 2H), 3.79 (t, *J*= 9.5 Hz, 1H), 3.46 (dd, *J*= 9.5 and 3.1 Hz, 1H), 3.30 (t, *J*= 9.2 Hz, 1H), 2.42 (br s, OH, 1H), 2.22–2.07 (m, 1H), 1.50-1.30 (m, 1H) 0.89 (s, SiC(CH_3)$_3$, 9H), 0.10 (s, SiCH_3, 3H), 0.06 (s, SiCH_3, 3H) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 139.1 (C_{ipso}), 138.8 (C_{ipso}), 138.0 (C_{ipso}), 128.4 (C_{arom}), 128.2 (C_{arom}), 128.1 (C_{arom}), 127.89 (C_{arom}), 127.86 (C_{arom}), 127.7 (C_{arom}), 127.4 (C_{arom}), 127.1 (C_{arom}), 86.5 (CH), 82.9 (CH), 81.4 (CH), 75.9 (CH_2), 75.5 (CH_2), 72.8 (CH_2), 69.7 (CH), 66.1 (CH), 36.0 (CH_2), 25.8 [SiC(CH_3)$_3$], 17.9 [SiC(CH_3)$_3$], -4.5 (SiCH_3), -4.64 (SiCH_3), ppm; **Elemental Anal**. $C_{33}H_{44}O_5Si$ (548.78): calcd. C, 72.22; H, 8.08 found C, 72.29; H, 7.92 %.

Preparation of ketone 4.57: The TBS ether **4.56** (1.0 g, 1.82 mmol), ethyl acetate (13 mL) and IBX (1.53 g, 5.46 mmol) were refluxed for 8 h. The reaction mixture was cooled to room temperature and passed through a bed of Celite. The bed of Celite was washed with ethyl acetate (2×40 mL), and the combined filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (100–200 mesh silica gel, eluent: ethyl acetate / light petroleum, 1:6) to afford the racemic ketone **4.57** (0.85 g, 85 %) as a colorless solid.

Data for 4.57: Mp. = 53–55 °C; **IR** ($CHCl_3$): $\bar{\nu}$ 1732 (C=O) cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.45–7.20 (m, 15H), 5.00–4.67 (m, 5H), 4.56 (d, *J*= 11.5 Hz, 1H), 4.25 (d, *J*= 9.5 Hz, 1H), 3.90–3.55 (m, 3H), 2.70–2.45 (m, 2H), 0.86 (s, SiC(CH_3)$_3$, 9H), 0.06 (s, SiCH_3, 3H), 0.04 (s, SiCH_3, 3H) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 204.2 (C=O), 138.3 (C_{ipso}), 138.2 (C_{ipso}), 137.5 (C_{ipso}), 128.3 (C_{arom}), 128.2 (C_{arom}), 128.1 (C_{arom}), 127.9 (C_{arom}), 127.8 (C_{arom}), 127.6 (C_{arom}), 127.5 (C_{arom}), 85.06 (CH), 85.04 (CH), 81.8 (CH), 75.4 (CH_2), 74.9 (CH_2), 73.5 (CH_2), 69.5 (CH), 45.9 (CH_2), 25.7 [SiC(CH_3)$_3$], 17.8 [SiC(CH_3)$_3$], -4.7 ($SiCH_3$), -4.9 ($SiCH_3$) ppm; **Elemental Anal**. $C_{33}H_{42}O_5Si$ (546.77): calcd. C, 72.49; H, 7.74 found C, 72.28; H, 7.82 %.

Preparation of α,β-unsaturated ketone 4.59: TBS ether **4.56** (1.22 g, 2.22 mmol), ethyl acetate (15 mL), IBX (1.87 g, 6.67 mmol) were refluxed for 8 h. Reaction mixture was cooled to room temperature and passed through a bed of Celite, successively washed with

ethyl acetate, evaporated under reduced pressure. Crude product was purified by flash column chromatography (eluent: ethyl acetate/light petroleum, 1:9) to afford α,β-unsaturated ketone **4.59** (instead of ketone **4.57**) (0.85 g, 79%) as a colorless solid. The silica gel used was pre-eluted with triethyl amine/ light petroleum (1:49, 3–5 mL/g) mixture.

Data for 4.59: Mp.= 72–74 °C; **IR** ($CHCl_3$): $\bar{\nu}$ 1697 (C=O) cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.40–7.27 (m, 10H), 5.68 (d, *J*=3.3 Hz, 1H), 4.83 (q, *J*= 12.4 Hz, 2H), 4.67 (q, *J*= 11.9 Hz, 2H), 4.20–4.05 (m, 2H), 2.96–2.81 (m, 1H), 2.60–2.43 (m, 1H), 0.87 (s, $SiC(CH_3)_3$, 9H), 0.07 (s, $Si(CH_3)_2$, 6H) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 191.8 (C_{ipso}), 150.3 (C_{ipso}), 137.9 (C_{ipso}), 135.7 (C_{ipso}),128.5 (C_{arom}), 128.4 (C_{arom}), 128.0 (C_{arom}), 127.8 (C_{arom}), 127.7 (C_{arom}), 127.3 (C_{arom}), 115.0 (C=*C*H), 78.3 (CH), 72.6 (CH_2), 71.3 (CH), 69.7 (CH_2), 44.7 (Ring CH_2), 25.6 ($SiC(CH_3)_3$), 17.9 ($SiC(CH_3)_3$), -4.8 ($SiCH_3$), -4.9 ($SiCH_3$) ppm; **Elemental Anal**. $C_{26}H_{34}O_4Si$ (438.63): calcd C, 71.19; H, 7.81, found C, 71.17; H, 7.98 %.

Preparation of chloro-oxiranes 4.60 and 4.61: To a cooled (dry ice, acetone –78 °C) solution of LDA (0.82 mL, 2.0 M soln. in THF / heptanes / ethyl benzene, 1.64 mmol) in THF (1.0 mL), was added dichloromethane (0.35 mL, 5.49 mmol) followed by (after 5 min) the ketone **4.57** (0.30 g, 0.55 mmol). Resulting reaction mixture was stirred at –78 °C for 1 h 30 min, at 0 °C for 1 h and then at ambient temperature for 2 h. To the reaction mixture, a saturated solution (1.0 mL) of aq. ammonium chloride was added, and the volatiles were evaporated under reduced pressure; the residue was worked up as usual with ethyl acetate. The crude product was purified by flash column chromatography (eluent: ethyl acetate / light petroleum 1:32) to afford racemic **4.60** (0.24 g, 70 %) as a gum and racemic **4.61** (0.05 g, 15 %) as a colorless solid. The silica gel used was pre-eluted with triethyl amine/ light petroleum (1:49, 3–5 mL/g) mixture.

Data for 4.60: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.17 (m, 15 H), 5.39 (s, ClOC*H*, 1H), 4.92 (d, *J*= 11 Hz, 1H, CH_AH_BPh), 4.85 (d, *J*= 11 Hz, 1H, CH_AH_BPh), 4.79 (s, 2H), 4.64 (d, *J*= 10.5 Hz, 1H), 4.58 (d, *J*= 10.5 Hz, 1H), 3.83–373 (m, 2H), 3.51–3.42 (m, 2H), 2.09 (dd, *J*= 13.3 and 5.0 Hz, 1H), 1.99 (t, *J*= 12.8 Hz, 1H) 0.9 (s, CMe_3, 9H), 0.11 (s, CH_3, 3H), 0.07 (s, CH_3, 3H) ppm; **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 138.6 (C_{ipso}), 138.3 (C_{ipso}), 137.7 (C_{ipso}), 128.4 (C_{arom}), 128.3 (C_{arom}), 128.2 (C_{arom}), 128.0 (C_{arom}), 127.9 (C_{arom}), 127.8 (C_{arom}), 127.6 (C_{arom}), 127.5 (C_{arom}), 127.4 (C_{arom}), 85.9 (CH), 83.1 (CH), 79.2 (CH), 76.1

(CH_2), 75.8 (CH_2), 75.4 (CH_2), 70.5 (CH), 70.0 (CH), 62.0 (CH), 34.1 (CH_2), 25.8 [SiC(CH_3)$_3$], 17.9 [SiC(CH_3)$_3$], -4.64 ($SiCH_3$), -4.74 ($SiCH_3$) ppm; **Mass** calcd. M (+Na), 617.25; observed 617.30; **Elemental anal**. $C_{34}H_{43}ClO_5Si$ (594.26): calcd. C, 68.60; H, 7.28 found C, 68.95; H, 7.38 %.

Data for 4.61: Mp.: 106–108 °C (Crystals obtained from acetonitrile at room temperature); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.40–7.15 (m, 15 H), 5.17 (s, ClOCH, 1H), 5.00–4.70 (m, 5 H) 4.54 (d, J= 11.5 Hz, 1H), 4.01–3.86 (m, 1H), 3.77-3.61 (m, 2H), 3.54–3.42 (m, 1H), 2.01 (dd, J=14.1, 5.3 Hz, 1H), 1.81 (dd, J= 14.0, 11.2 Hz, 1H), 0.89 (s, CMe_3, 9H), 0.08 (s, CH_3, 3H), 0.06 (s, CH_3, 3H) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 138.7 (C_{ipso}), 138.3 (C_{ipso}), 137.2 (C_{ipso}), 128.6 (C_{arom}), 128.3 (C_{arom}), 128.2 (C_{arom}), 128.1 (C_{arom}), 127.9 (C_{arom}), 127.6 (C_{arom}), 127.4 (C_{arom}), 127.3 (C_{arom}), 86.3 (CH), 83.1 (CH), 77.3 (CH), 76.0 (CH_2), 75.6 (CH_2), 75.1 (CH_2), 71.2 (CH), 70.5 (CH), 62.3 (C), 33.8 (CH_2), 25.8 [SiC(CH$_3$)$_3$], 17.9 [SiC(CH_3)$_3$], -4.6(SiCH$_3$), -4.7 (SiCH$_3$) ppm; **Mass**: calcd. M (+Na), 617.25; observed 617.32; **Elemental Anal**. $C_{34}H_{43}ClO_5Si$ (594.26): calcd. C, 68.60; H, 7.28 found C, 68.62; H, 7.65 %.

Preparation of diol 4.62: To a solution of the chloroepoxide **4.60** (0.10 g, 0.17 mmol) in DMSO (4 mL), was added aq. *n*-tetrabutylammonium hydroxide (0.63 mL, 0.85 mmol, 36 % soln. in water), at ambient temperature and stirred for 30 sec. The reaction mixture was poured into a saturated solution (15 mL) of aq. ammonium chloride, diluted with ethyl acetate, and worked up as usual with ethyl acetate. The residue obtained was taken in methanol (4 mL), cooled using ice bath; sodium borohydride (0.06 g, 1.7 mmol) was added and stirred at ambient temperature for 2 h. Saturated aq. ammonium chloride solution (1.0 mL) was added to the reaction mixture, and volatiles were evaporated under reduced pressure. The residue was worked up as usual with ethyl acetate. The crude product was purified by flash column chromatography (eluent: ethyl acetate/light petroleum, 1:4), to afford the racemic diol **4.62** (0.03 g, 31 %) as a colorless solid.

Data for 4.62: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.45–7.15 (m, 15H), 4.95–4.70 (m, 5 H), 4.69 (d, J=11.0 Hz, 1H), 3.96 (d, J= 11.5 Hz, 1H), 3.80–3.20 (m, OH, 6H), 2.73 (d, J=10.0 Hz, OH, 1H), 1.93 (dd, J= 13.5 and 4.7 Hz, 1H), 1.75–1.55 (m, 1H), 0.89 (s, SiC(CH_3)$_3$, 9H), 0.07 (s, SiCH_3, 3H), 0.05 (s, SiCH_3, 3H) ppm. **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 138.5 (C_{ipso}), 138.3 (C_{ipso}), 137.9 (C_{ipso}), 128.7 (C_{arom}), 128.4 (C_{arom}), 128.3(C_{arom}), 128.1(C_{arom}), 128.0 (C_{arom}), 127.7 (C_{arom}), 127.6 (C_{arom}), 127.4 (C_{arom}), 88.0 (CH), 86.4

(CH), 82.4 (CH), 76.4 (CH_2), 75.6 (CH_2), 75.5 (CH_2), 71.8 (C), 69.8 (CH), 66.6 (CH_2), 39.8 (CH_2), 25.7 [SiC(CH_3)$_3$], 17.9 [SiC(CH_3)$_3$], -4.6 (SiCH_3), -4.7 (SiCH_3) ppm.

Hydrolysis of chlorooxirane 4.61: To a solution of the chlorooxirane **4.61** (0.06 g, 0.1 mmol) in DMSO (2 mL), was added aq. *n*-tetrabutylammonium hydroxide (0.37 mL, 0.5 mmol, 36 % soln. in water), at ambient temperature and stirred for 30 sec. The reaction mixture was poured into a saturated solution (15 mL) of aq. ammonium chloride, diluted with ethyl acetate, and worked up as usual with ethyl acetate. The residue obtained was taken in methanol (10 mL) cooled using ice bath, and a solution of sodium borohydride (0.006 g, 0.15 mmol) in water (2.0 mL) was added and stirred at ambient temperature for 2 h. Saturated aq. ammonium chloride solution (1.0 mL) was added to the reaction mixture, and volatiles were evaporated under reduced pressure. The residue was worked up as usual with ethyl acetate. The crude product was purified by flash column chromatography (eluent: ethyl acetate/light petroleum, 1:4), to get the mixture of racemic diols **4.62** and **4.63** (0.017 g, 30%). The ratio of diols **4.62** and **4.63** (1:2) was determined from the ^{1}H nmr.

4.5. References.

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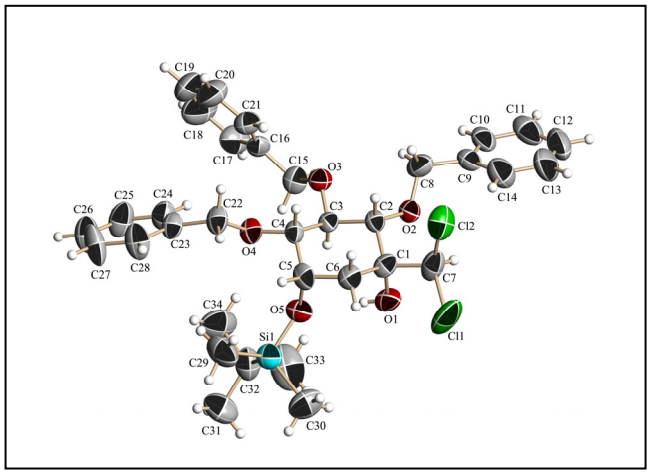
4.6. Appendix.

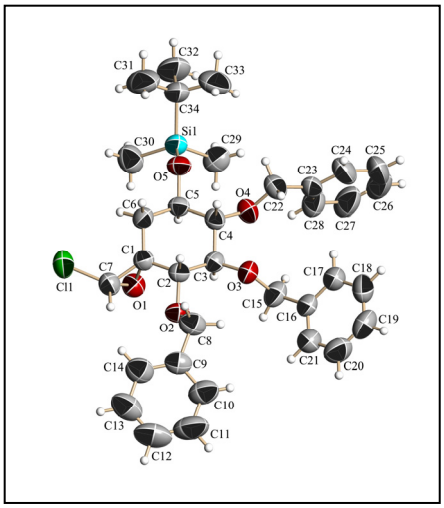
4.6.1 Appendix Index



ORTEP diagram of **4.26**

Crystal data table of **4.26**

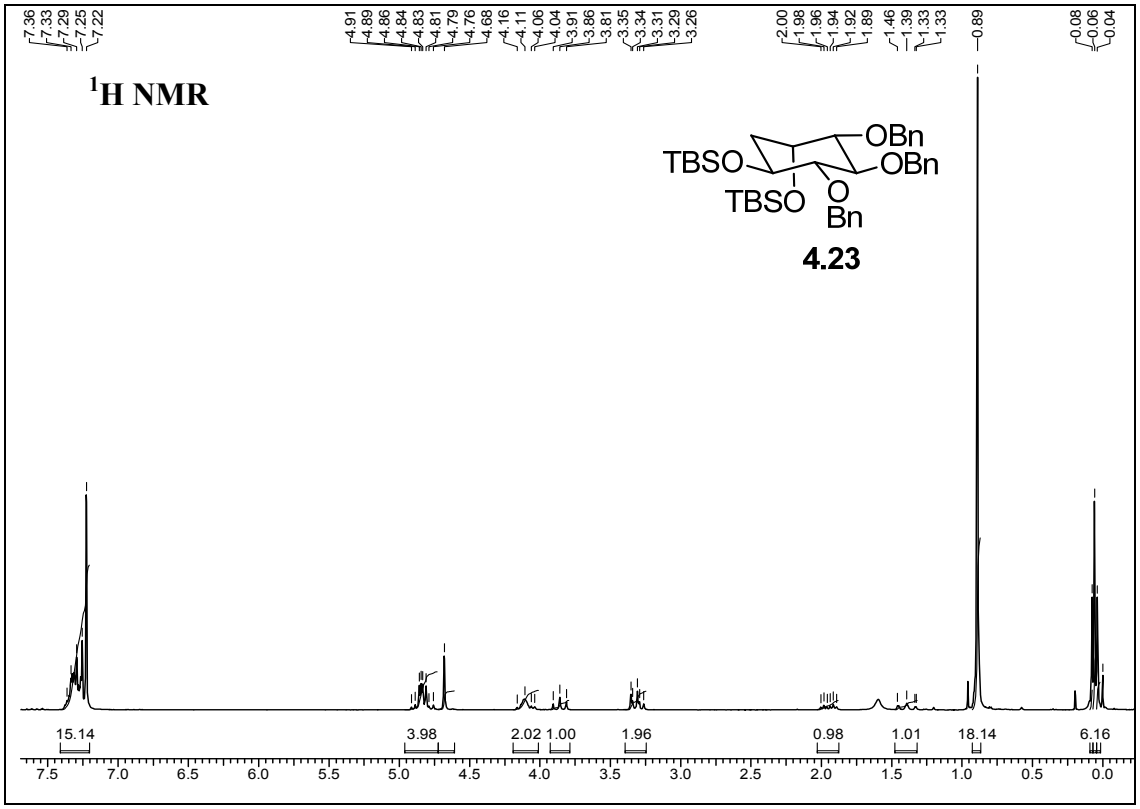
Identification code	**4.26** (crystals from pentane)
Empirical formula	$C_{34}H_{44}Cl_2O_5Si$
Formula weight	631.68
Temperature	297(2) K
Wavelength	0.71073 Å
Crystal system, Space group	Orthorhobmic, *Pbca*
Unit cell dimensions	a = 13.842 (5) Å α = 90° b = 12.035 (4) Å β = 90° c = 41.092 (14) Å γ = 90°
Volume	6845 (4) $Å^3$
Z, Calculated density	8, 1.226 g/cm^3
Absorption coefficient	0.263 mm^{-1}
F(000)	2688
Crystal size	0.40 × 0.10 × 0.05 mm^3
θ range for data collection	0.99 to 25.00 °
Limiting indices	-14<=h<=16, -14<=k<=13, -48<=l<=48
Reflections collected / unique	32751 / 6027 [R(int) = 0.1496]
Completeness to θ = 25.00	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9867 and 0.9034
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6027/ 0 / 384
Goodness-of-fit on F^2	1.086
Final R indices [I>2σ(I)]	R1 = 0.1082, wR2 = 0.2226
R indices (all data)	R1 = 0.2121, wR2 = 0.2761
Largest diff. peak and hole	0.989 and -0.360 $Å^{-3}$



ORTEP diagram of **4.61**

Crystal data table of **4.61**

Identification code	**4.61** (crystals from acetonitrile)
Empirical formula	$C_{34}H_{43}ClO_5Si$
Formula weight	595.22
Temperature	297(2) K
Wavelength	0.71073 Å
Crystal system, Space group	Monoclinic, *P2₁/c*
Unit cell dimensions	a = 11.143 (3) Å α = 90° b = 21.539 (6) Å β = 115.363 (14)° c = 15.866 (3) Å γ = 90°
Volume	3440.9(15) Å^3
Z, Calculated density	4, 1.149 g/cm^3
Absorption coefficient	0.182 mm^{-1}
F(000)	1272
Crystal size	0.61 × 0.25 × 0.22 mm^3
θ range for data collection	1.71 to 25.00 °
Limiting indices	-12<=h<=13, -16<=k<=25, -18<=l<=18
Reflections collected / unique	17155 / 6059 [R(int) = 0.0244]
Completeness to θ = 25.00	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9601 and 0.8977
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6059/ 0 / 375
Goodness-of-fit on F^2	1.028
Final R indices [I>2σ(I)]	R1 = 0.0481, wR2 = 0.1240
R indices (all data)	R1 = 0.0679, wR2 = 0.1361
Largest diff. peak and hole	0.251 and -0.157 Å^{-3}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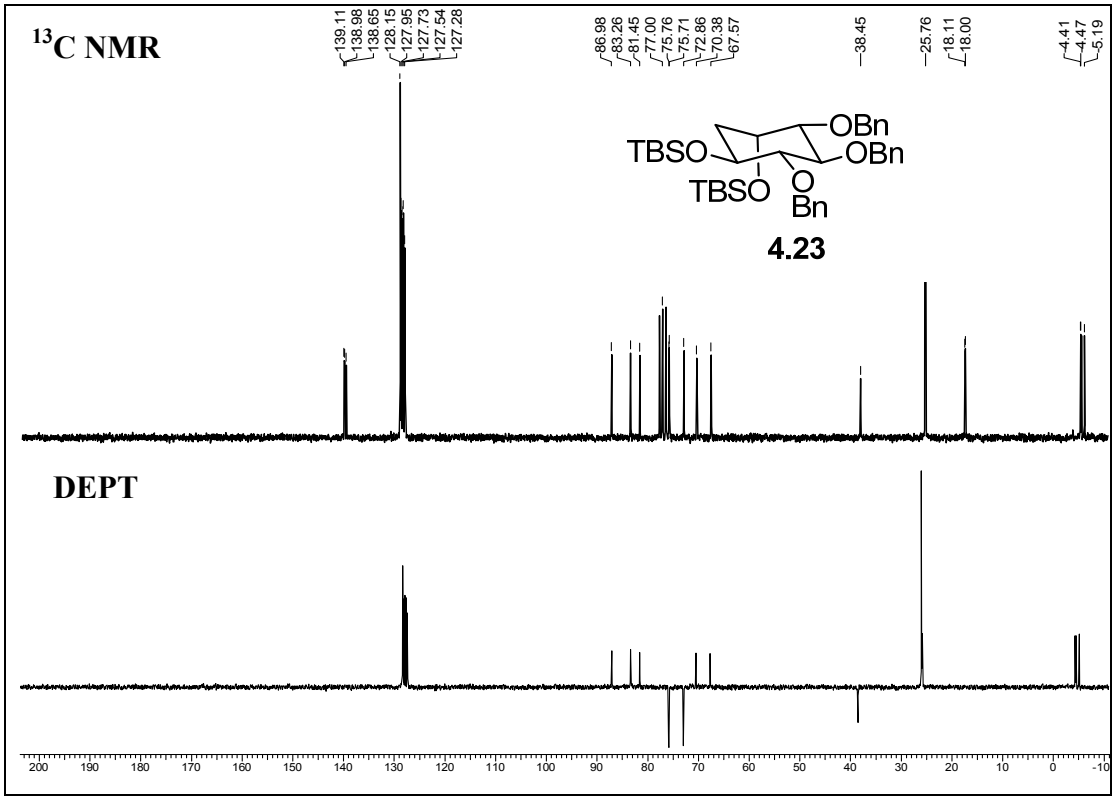
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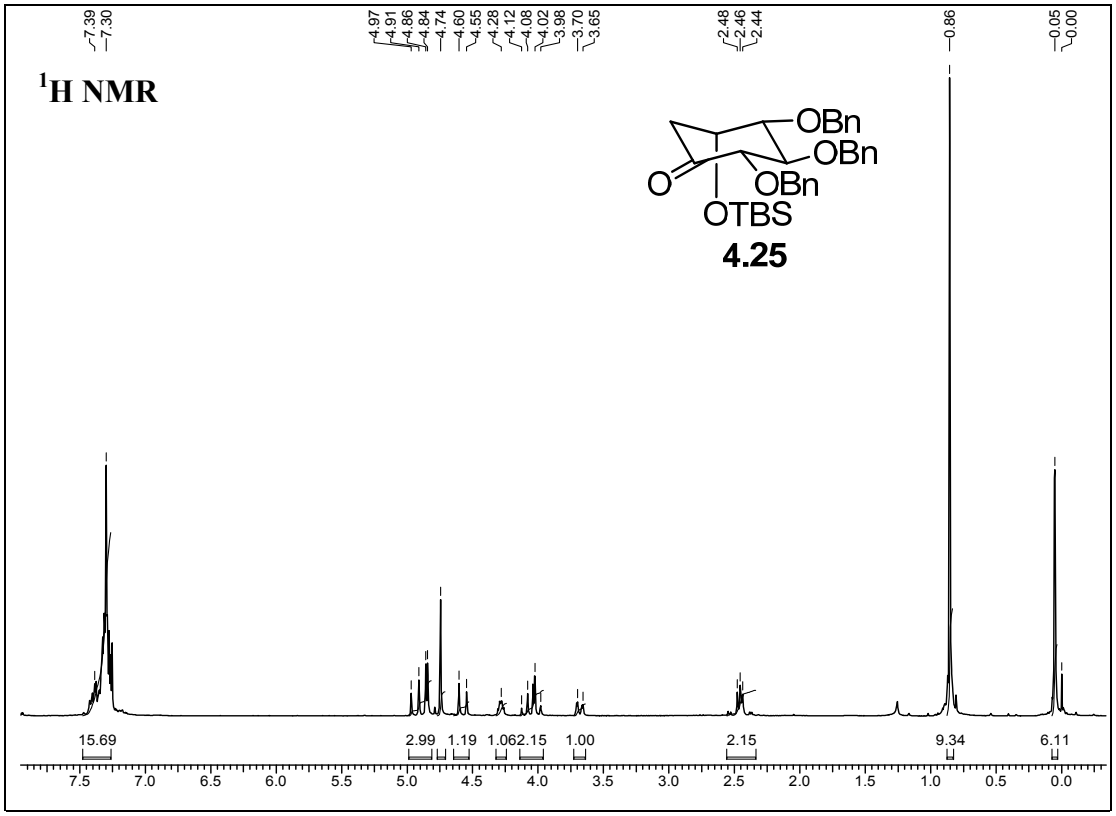
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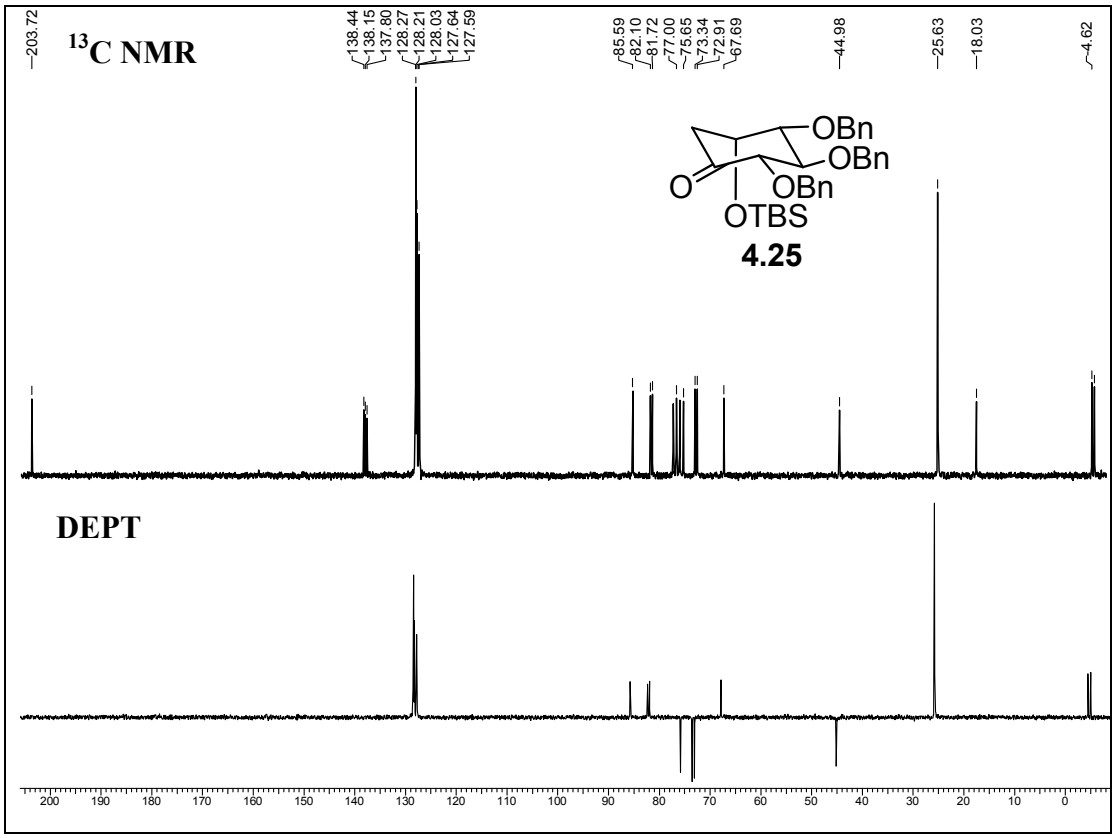
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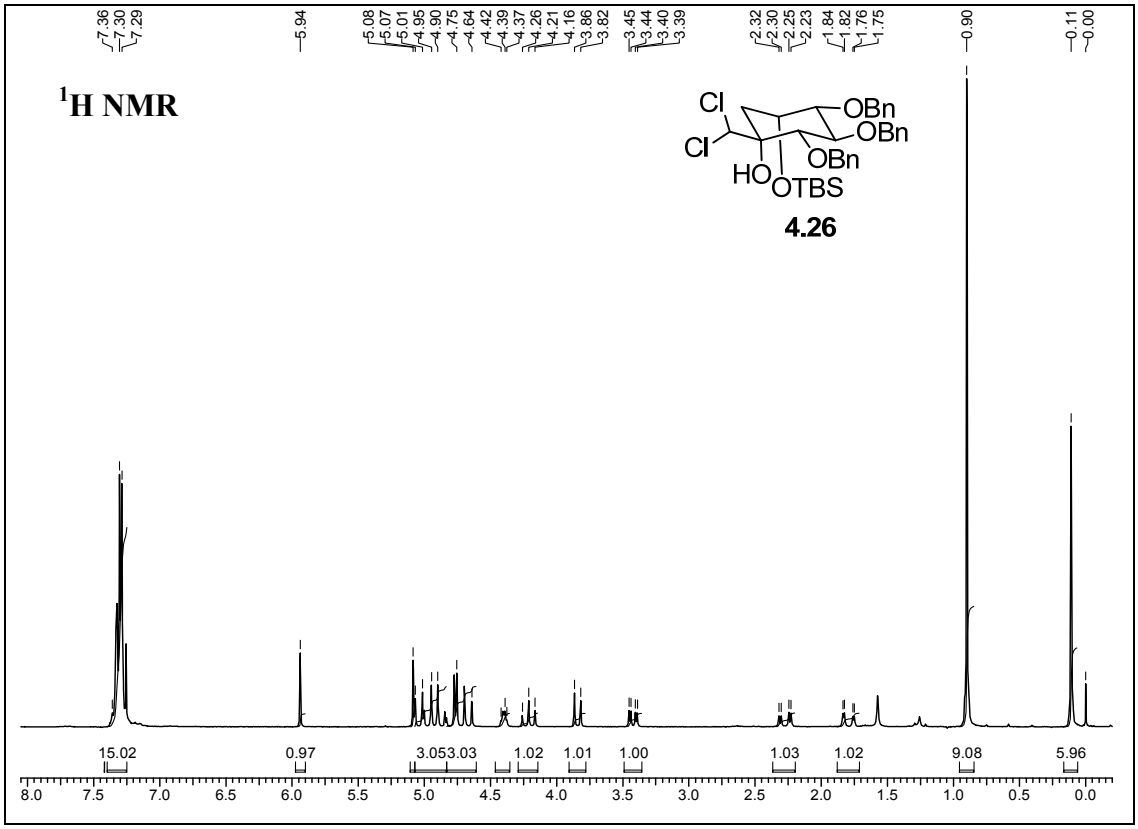
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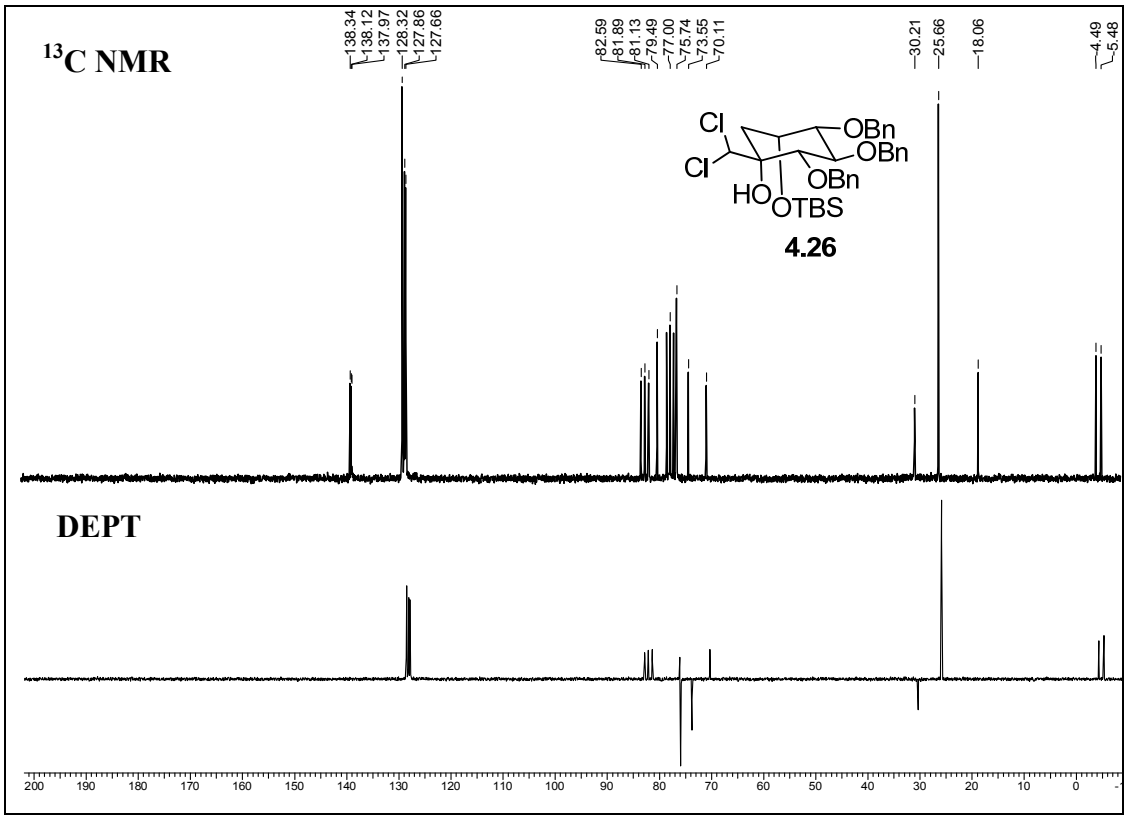
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138.12
137.97
128.32
127.86
127.66
82.59
81.89
81.13
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77.00
75.74
73.55
70.11
30.21
25.66
18.06
4.49
5.48
Cl
Cl
OBn
OBn
OBn
HO
OTBS
4.26
DEPT
200
190
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150
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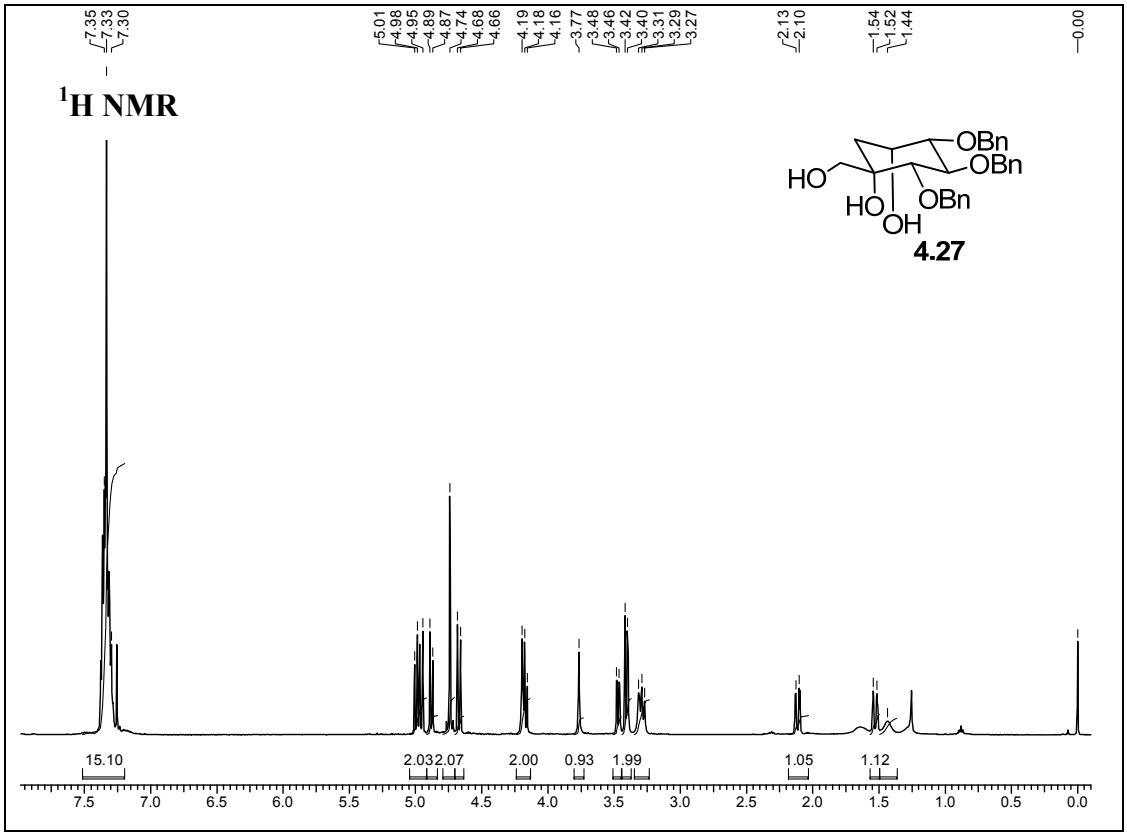
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7.33
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4.87
4.74
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4.66
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4.18
4.16
3.77
3.48
3.46
3.42
3.40
3.31
3.29
3.27
2.13
2.10
1.54
1.52
1.44
0.00
1H NMR
OBn
OBn
HO
HO
OBn
OH
4.27
15.10
2.03
2.07
2.00
0.93
1.99
1.05
1.12
7.5
7.0
6.5
6.0
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3.0
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2.0
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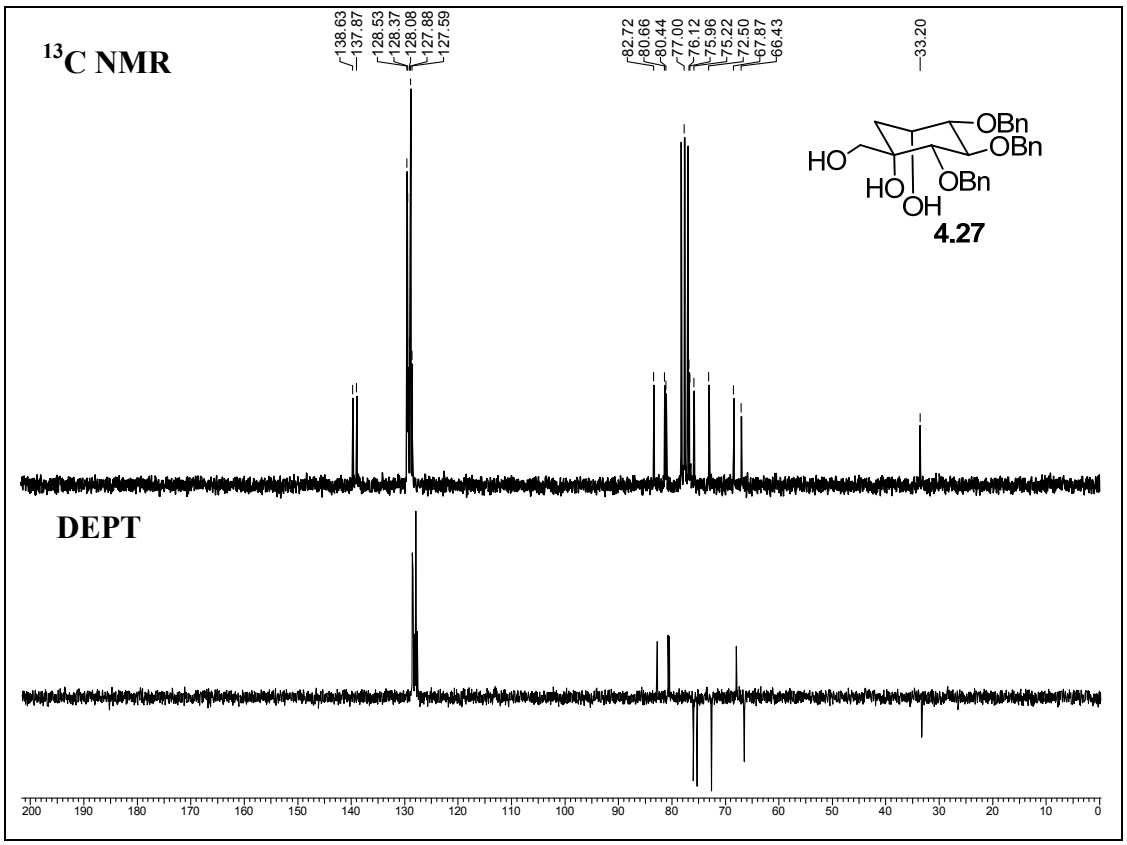
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127.59
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76.12
75.96
75.22
72.50
67.87
66.43
33.20
OBn
OBn
HO
HO
OBn
OH
4.27
DEPT
200
190
180
170
160
150
140
130
120
110
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30
20
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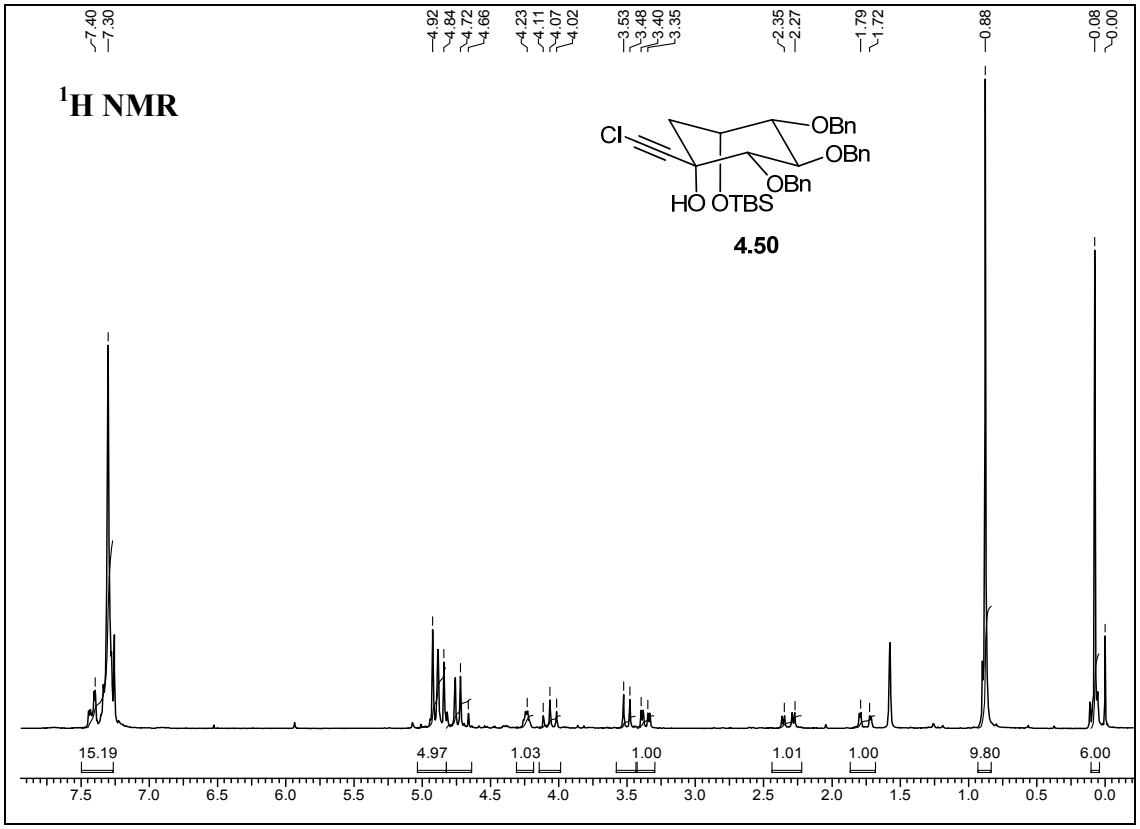
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4.11
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4.02
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3.40
3.35
2.35
2.27
1.79
1.72
0.88
0.08
0.00
1H NMR
Cl
OBn
OBn
OBn
HO OTBS
4.50
15.19
4.97
1.03
1.00
1.01
1.00
9.80
6.00
7.5
7.0
6.5
6.0
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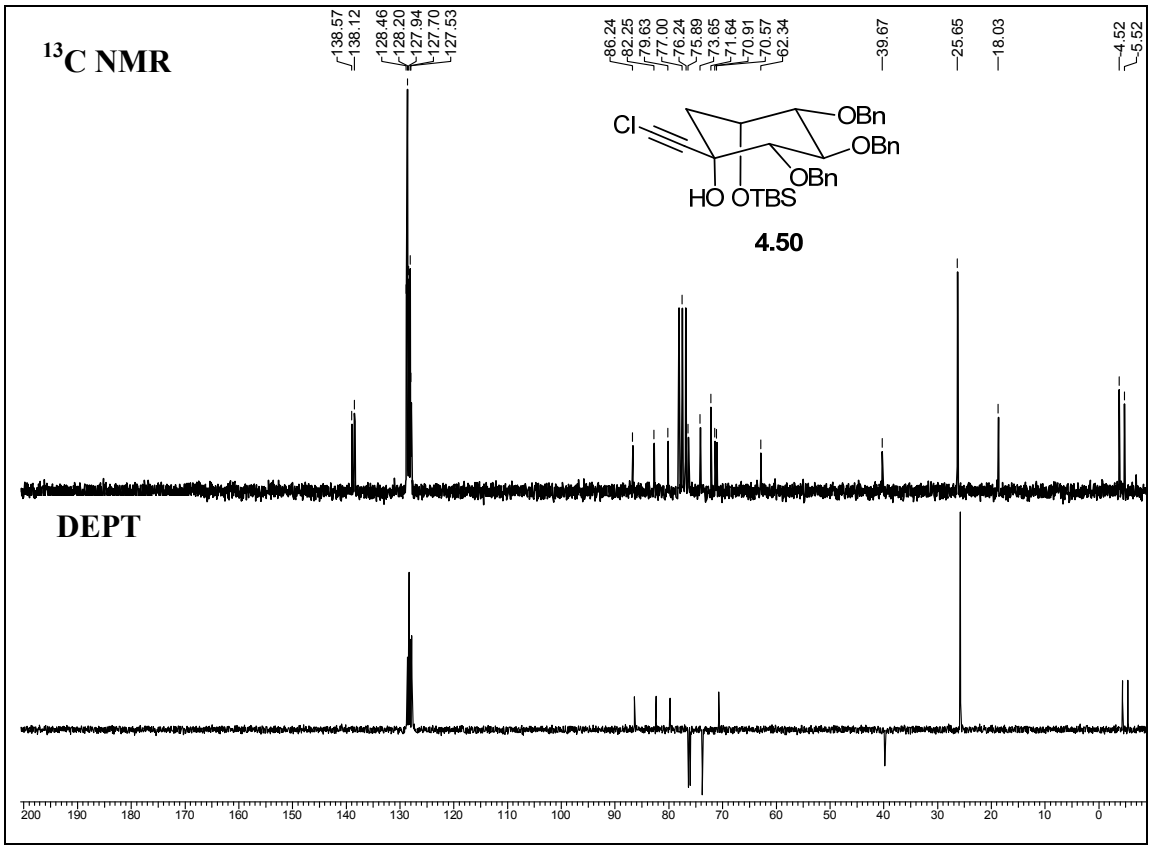
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75.89
73.65
71.64
70.91
70.57
62.34
39.67
25.65
18.03
4.52
5.52
13C NMR
Cl
OBn
OBn
OBn
HO OTBS
4.50
DEPT
200
190
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120
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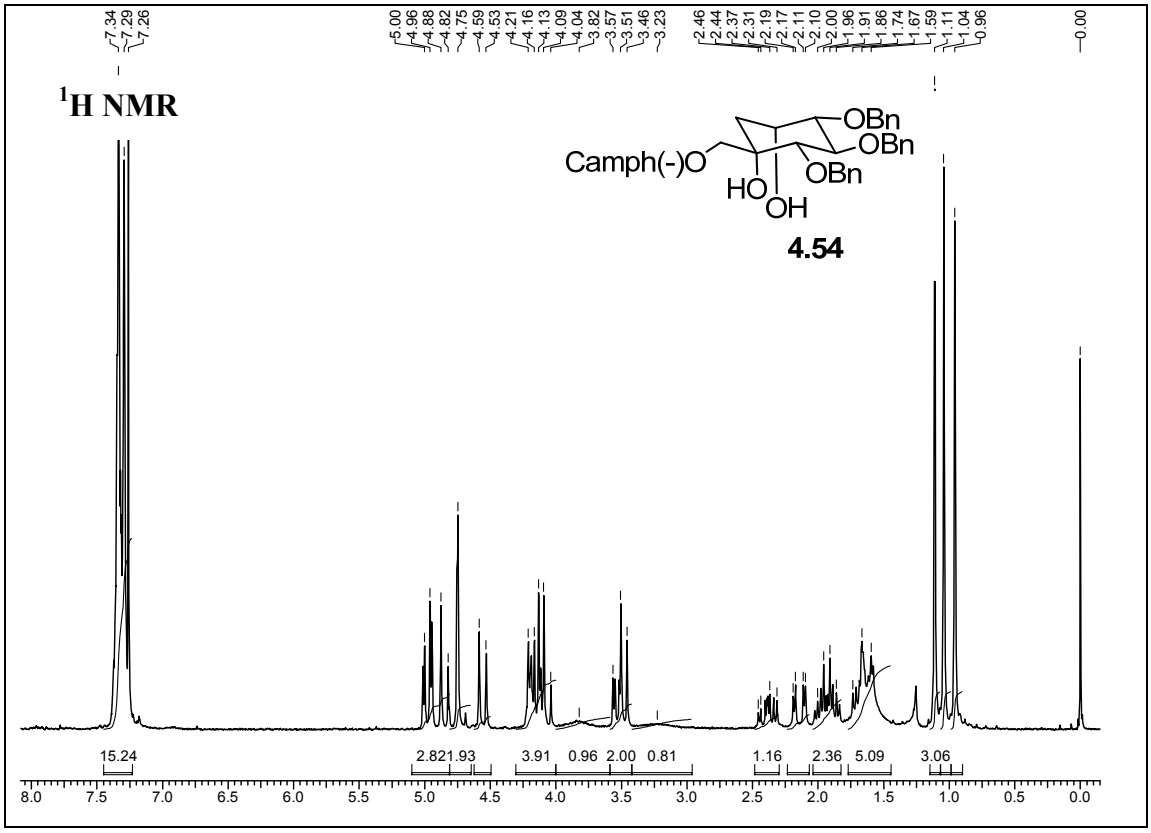
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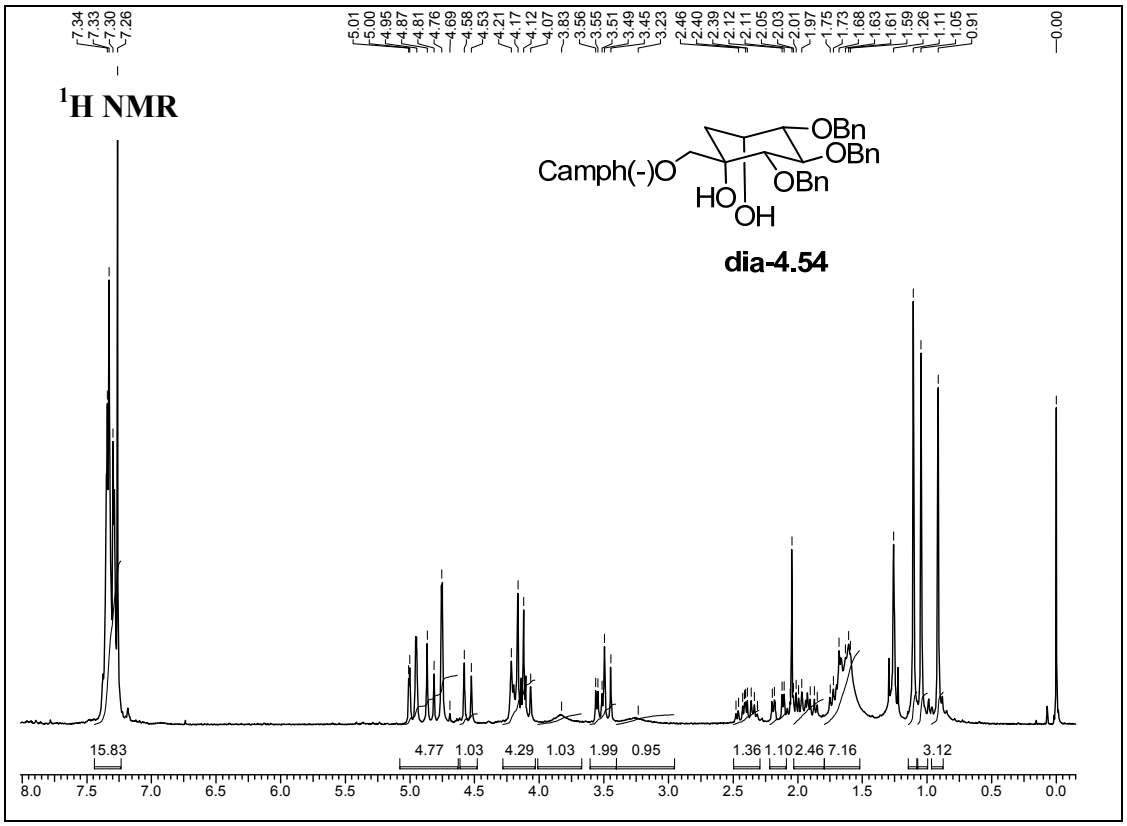
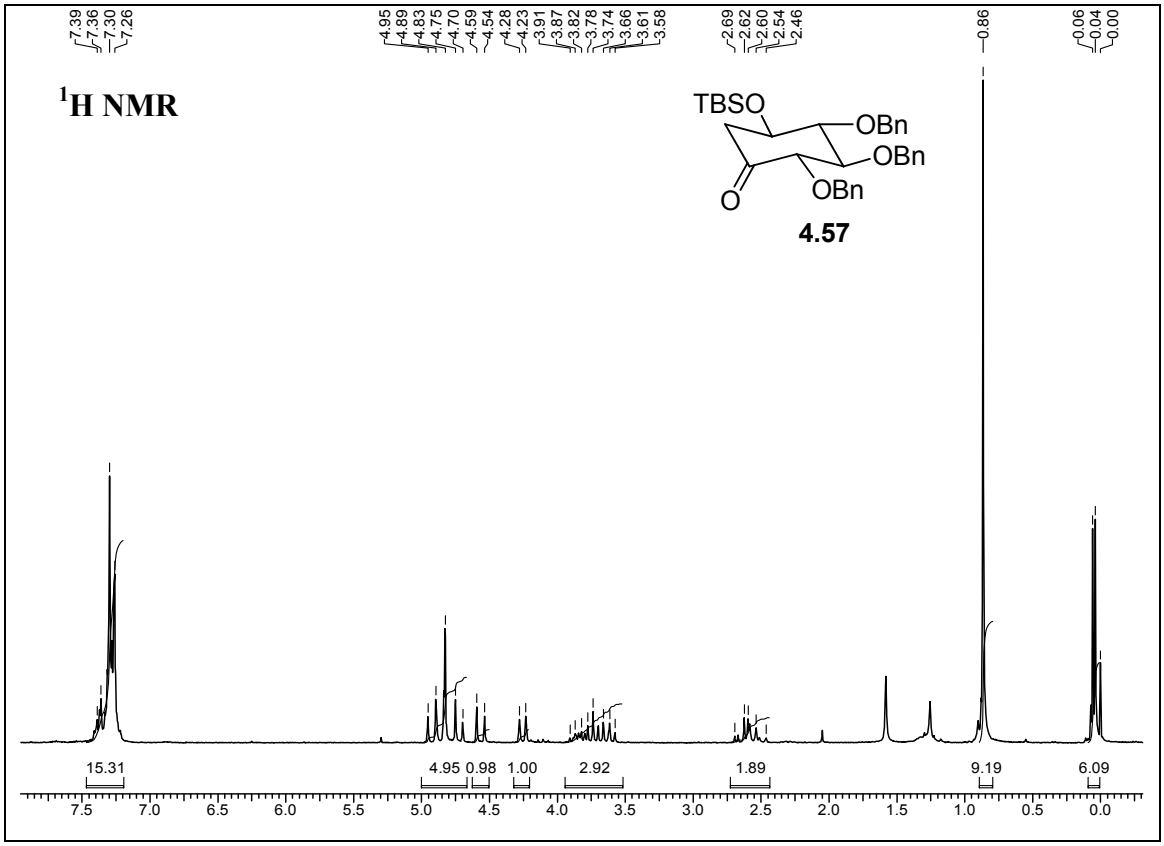
Camph(-)O
OBn
HO
OH
4.54


^{1}H NMR
OBn
OBn
Camph(-)O
OBn
HO
OH
dia-4.54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7.26
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4.89
4.83
4.75
4.70
4.59
4.54
4.28
4.23
3.91
3.87
3.82
3.78
3.74
3.66
3.61
3.58
2.69
2.62
2.60
2.54
2.46
0.86
0.06
0.04
0.00
^{1}H NMR
TBSO
OBn
OBn
OBn
O
4.57
15.31
4.95
0.98
1.00
2.92
1.89
9.19
6.09
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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3.0
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2.0
1.5
1.0
0.5
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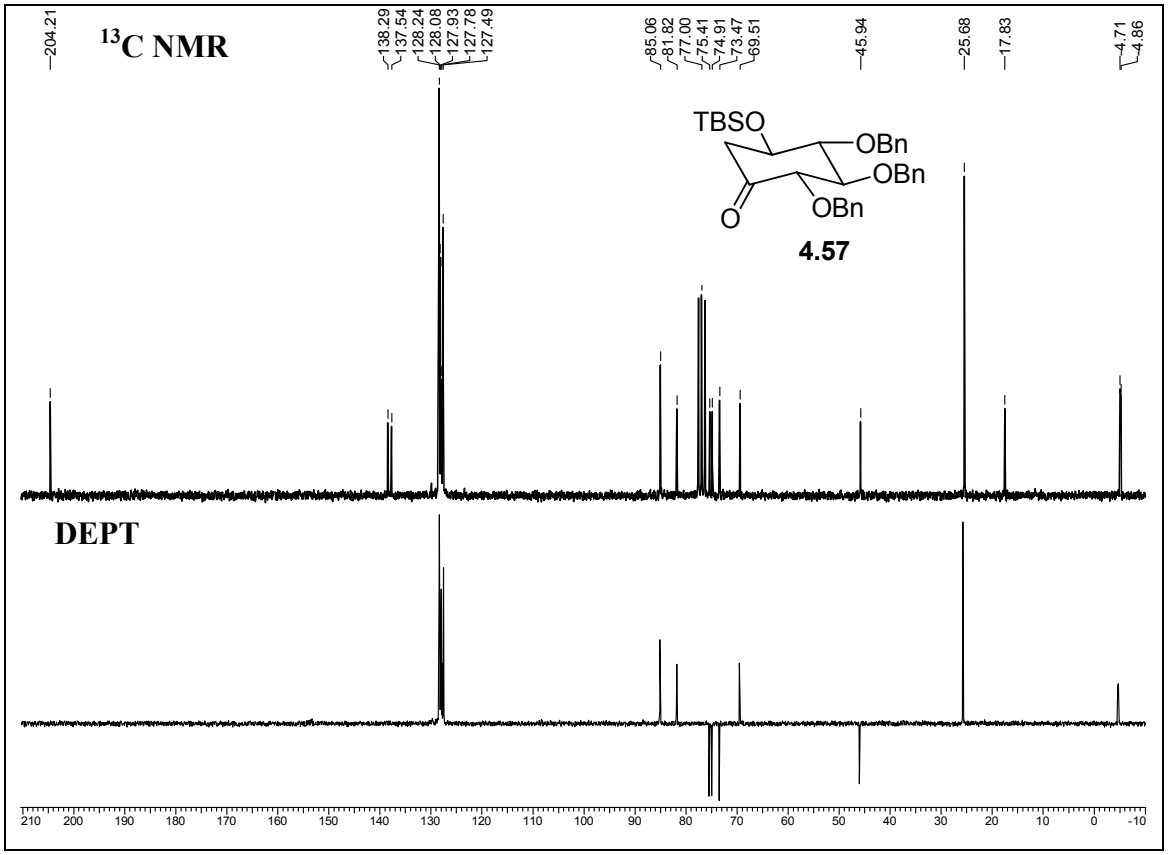
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127.49
85.06
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74.91
73.47
69.51
45.94
25.68
17.83
4.71
4.86
TBSO
OBn
OBn
OBn
O
4.57
DEPT
210
200
190
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130
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100
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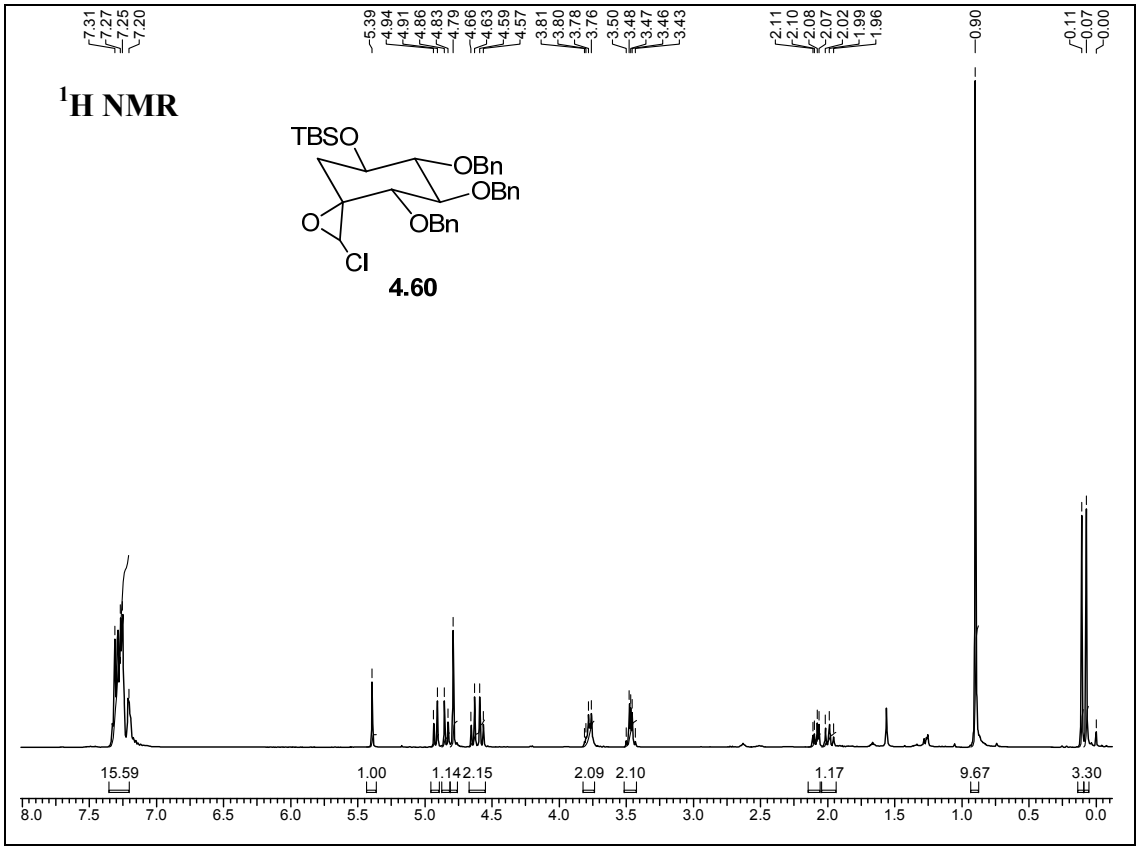
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4.94
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4.86
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4.79
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4.63
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4.57
3.81
3.80
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3.50
3.48
3.47
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3.43
2.11
2.10
2.08
2.07
2.02
1.99
1.96
0.90
0.11
0.07
0.00
^{1}H NMR
TBSO
OBn
OBn
O
OBn
Cl
4.60
15.59
1.00
1.14
2.15
2.09
2.10
1.17
9.67
3.30
8.0
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6.5
6.0
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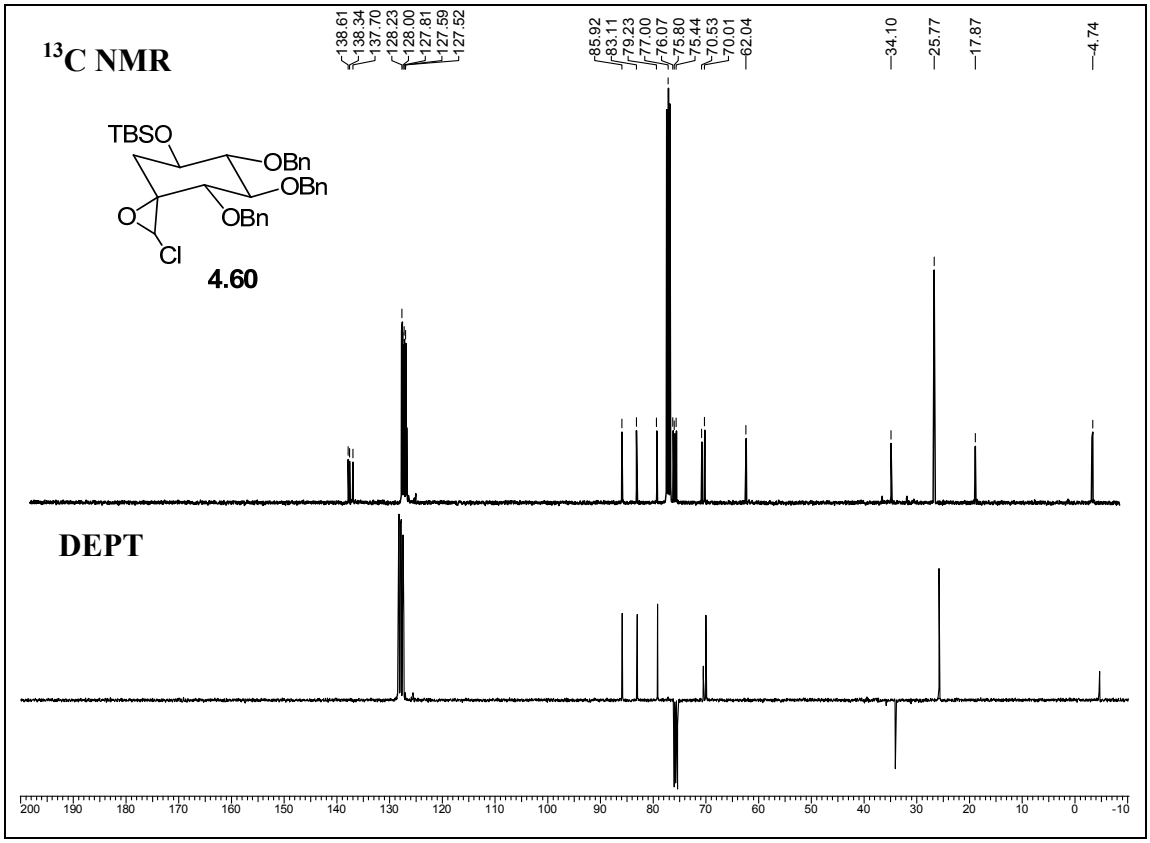
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77.00
76.07
75.80
75.44
70.53
70.01
62.04
34.10
25.77
17.87
4.74
^{13}C NMR
TBSO
OBn
OBn
O
OBn
Cl
4.60
DEPT
200
190
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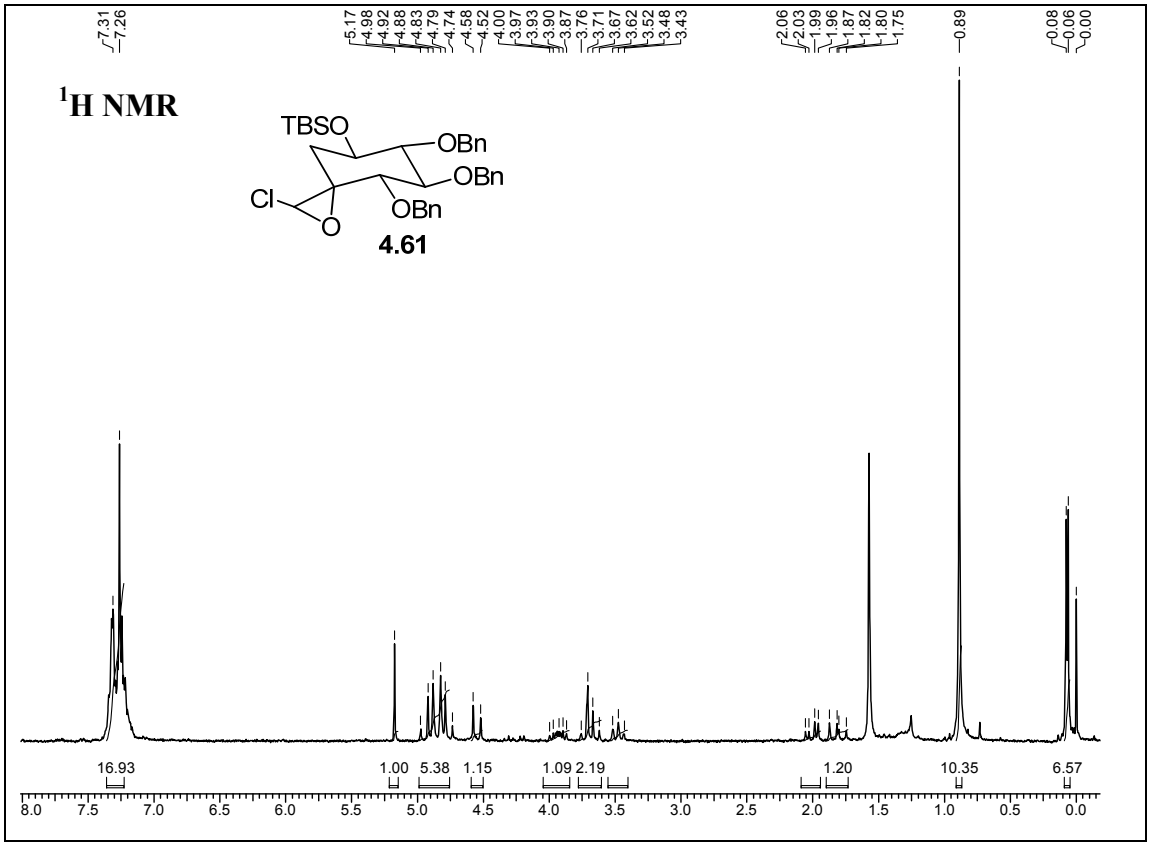
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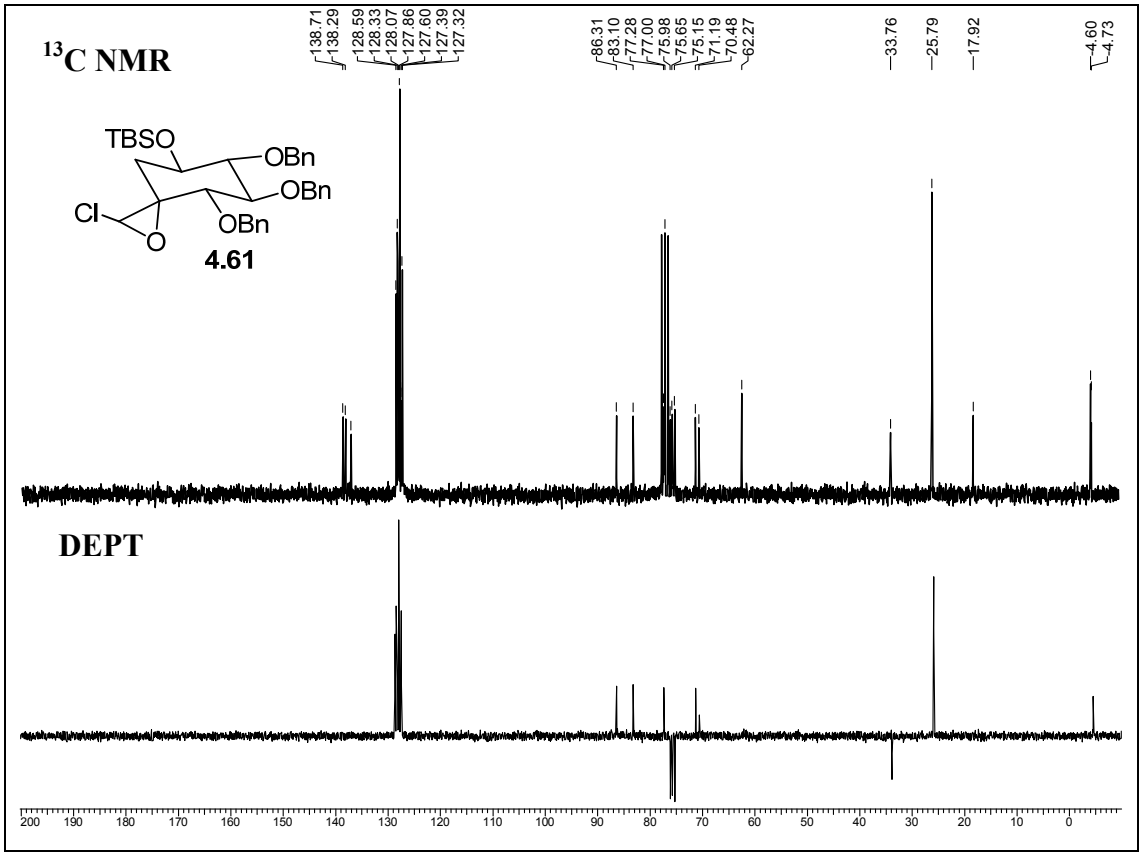
TBSO
OBn
OBn
OBn
Cl
O
4.61


13C NMR
TBSO
OBn
OBn
OBn
Cl
O
4.61
DEPT