Synthesis of isomeric cyclitols and their derivatives / analogs from *myo*-inositol and the associated structural studies

THESIS SUBMITTED TO THE

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IN

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BY

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Dedicated to my
Beloved Mummy
&
late Pappa…

NATIONAL CHEMICAL LABORATORY

(Council of Scientific and Industrial Research)

Dr. Homibhabha Road, Pune – 411008, INDIA.

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "**Synthesis of isomeric cyclitols and their derivatives / analogs from *myo*-inositol and the associated structural studies**" submitted by **Madhuri T. Patil** was carried out by her under my supervision at the National Chemical Laboratory, Pune, India. Such materials, obtained from other sources have been duly acknowledged in the thesis.

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DECLARATION

I hereby declare that the thesis entitled **"Synthesis of isomeric cyclitols and their derivatives / analogs from *myo*-inositol and the associated structural studies"** 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.

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(MADHURI T. PATIL)

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CONTENTS

Abbreviations

Ac	Acetyl
Ac_2O	Acetic anhydride
AcCl	Acetyl chloride
Anhd.	Anhydrous
aq.	Aqueous
Bn	Benzyl
BnBr	Benzyl bromide
Bz	Benzoyl
BzCl	Benzoyl chloride
Calcd	Calculated
Cat.	Catalytic
Concd	Concentration
CSA	Camphorsulfonic acid
COSY	Correlation Spectroscopy
D_2O	Deuterium Oxide
DCM	Dichloromethane
DIBAL-H	Diisobutyl aluminium Hydride
dil.	Dilute
DIPEA	Di-isopropyl ethyl amine
DMAP	*N,N*-dimethylamino pyridine
DMF	*N,N*-Dimethylformamide
DMP	2,2-dimethoxypropane
DMTST	Dimethyl(methylthio)sulfonium triflate
DMSO	Dimethyl sulfoxide
eq.	Equivalent
Et_3N	Triethylamine
g	Gram
GPI	Glycophosphatidylinositol
h	Hour (s)
Hz	Hertz
i$BuNH_2$	*iso*-Butyl amine

IBX	2-Iodoxybenzoic acid
IR	Infrared
LAH	Lithium aluminum hydride
LC-MS	Liquid chromatography-mass spectrometry
mp	Melting point
Me	Methyl
MeOH	Methanol
MeI	Methyliodide
Ms	Mesityl
mg	Milli gram
min.	Minute(s)
mL	Milliliter
mmol	Milli moles
MsCl	Methane sulfonyl chloride
NaDMDTC	Sodium *N,N'*-dimethyldithiocarbamate
NMO	*N*-Methylmorpholine-*N*-oxide
NaOMe	Sodium methoxide
NMR	Nuclear magnetic Resonance
ORTEP	Oak Ridge Thermal Ellipsoid Plot Program
PI-PLC	Phosphatidylinositol-specific phospholipase C
PMB	4-Methoxybenzyl
PIP_3	Phosphatidylinositol-3,4,5-tris-phosphate
Py	Pyridine
rac-	Racemic
rt	Room temperature (23–30 ^{o}C)
SBox	S-benzyloxazolyl
TBAF	Tetra-*n*-butylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
TBDMS triflate	Tert-butyldimethylsilyl trifluoromethanesulfonate
TFA	Trifluoroacetic acid
TFAA	Trifluroacetic anhydride
Tf_2O	Trifluoromethanesulfonic anhydride

THF	Tetrahydrofuran
TLC	Thin layer chromatography
TPAP	Tetrapropylammonium perruthenate
TPP	Triphenylphosphine
TsCl	*p*-Toluenesulfonyl chloride
PTSA	*p*-Toluenesulfonic acid

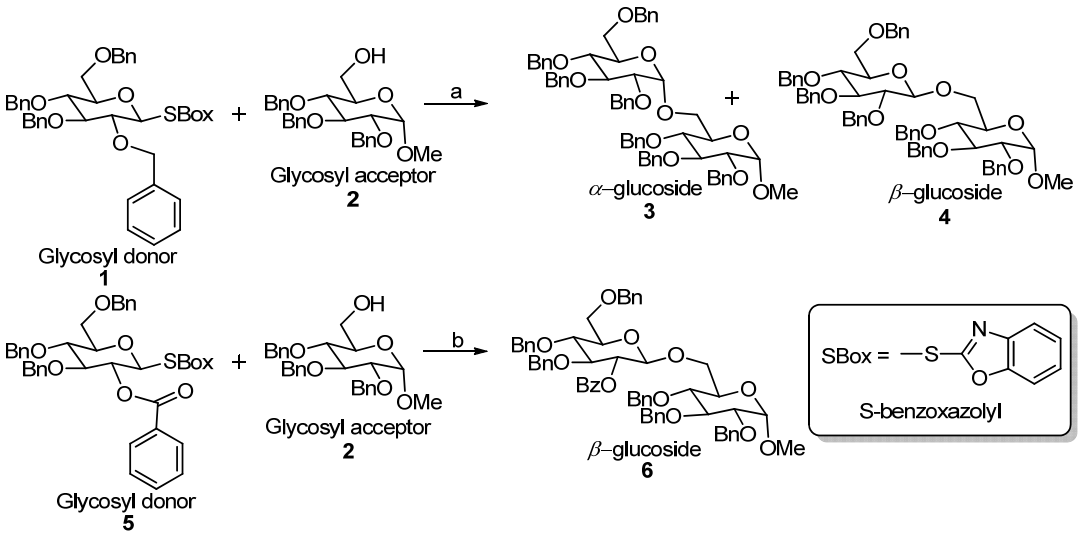
Synopsis of the thesis

The thesis entitled **"Synthesis of isomeric cyclitols and their derivatives / analogs from *myo*-inositol and the associated structural studies"** consists of four chapters. Chapter 1 is a brief account of the literature on the effect of protecting groups on the reactions of inositol derivatives. The subsequent chapters of this thesis represent an attempt to exploit this phenomenon for the efficient synthesis of inositol derivatives. Chapter 2 describes an attempt to exploit the effect of hydroxyl protecting groups to improve the selectivity during the addition of nucleophiles to carbonyl group of inososes. This chapter also investigates the effect of the orientation (axial or equatorial) of a neighboring (protected) hydroxyl group on the outcome of the stereoselectivity during the addition of nucleophiles to carbonyl group of inososes. This study revealed that stereoselectivity during the hydride reduction of *epi*-inosose is sensitive to the presence of other protecting groups in the molecule. Also the orientation of the *β*-hydroxyl group is crucial for the observed stereoselectivity during the hydride reduction as well as Grignard reactions of inososes. This work resulted in an efficient preparation of *epi*-inositol, and its *C*-methyl as well as *O*-methyl derivatives. Chapter 3 is an attempt to use preferential crystallization technique for the preparation of chiral inositol derivatives. In particular this chapter describes results on the resolution of racemic 4-*O*-benzyl-6-*O*-tosyl *myo*-inositol-1, 3, 5-orthoforamate by preferential crystallization. Chapter 4 describes an attempt towards the synthesis of orthoformate derivatives of 2-deoxy-2-mercapto *myo*-inositol and structural studies of mercapto-inositol and its S-S dimmer. This work was intended to develop molecular systems capable of acyl transfer reactions in the solid state. Chapters 2 – 4 also have detailed experimental procedures, spectroscopic, crystallographic and analytical data relevant to the new results described in the thesis.

Chapter 1. Effect of protecting groups on the reactions of inositol derivatives

Chemistry of inositols has been the subject of intense investigations in the recent past due to the ubiquitous presence of phsophoinositols in living cells and their implication in biological phenomena such as cellular signal transduction, calcium mobilization, insulin stimulation, exocytosis, cytoskeletal regulation, intracellular trafficking of vesicles and anchoring of certain proteins to cell membranes.[1] Derivatives of inositols other than phosphoinositols are also important since several of them occur in nature and some are essential constituents of our diet. Naturally occurring cyclitols or

inositols have also been used as starting materials for natural product synthesis and their derivatives are also interesting because of their structure and reactivity in the solid state.[2] Due to the presence of six secondary hydroxyl groups in *myo*-inositol, whose reactivities are not widely different, elaborate protection-deprotection steps are necessary during the execution of a synthetic sequence. Although an ideal protecting group is one which does not alter the reactivity of other functional groups in the same molecule, in reality, protecting groups do perturb the reactivity of other functional groups.[3] Hence, the reactivity and selectivity in reactions of small molecules containing several functional groups can to some extent be tuned by varying the protecting groups utilized during a synthetic sequence. Scheme 1 shows well known example of the effect of protecting groups on the outcome of glycosylation reaction.[4]

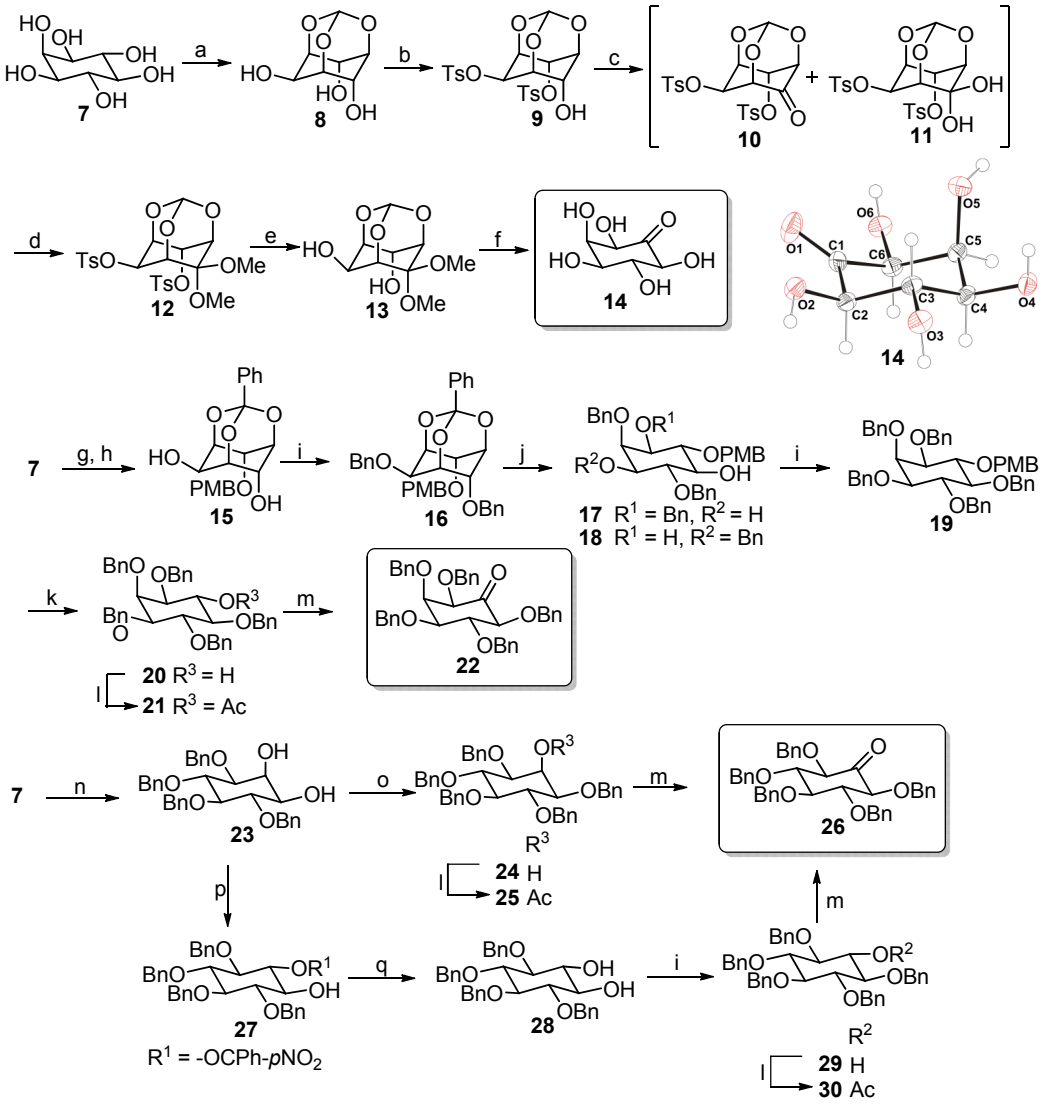


Scheme 1. (a) DCM, DMTST [dimethyl(methylthio)sulfonium triflate], 0 °C–RT, 2 h, 91% (**3**:**4** = 1.2:1); (b) DCM, DMTST, 0 °C, 5 min., 90%.

Although there is a large body of data in the literature pertaining to the use of various protecting groups during the synthesis of cyclitols and their derivatives, no attempt has been made to compare or catalog the effect of protecting groups on the reactivity of other functional groups present in the same molecule. In this chapter we have attempted to scrutinize the data available in the literature to see if protecting groups can be exploited to achieve the desired selectivity during synthesis involving inositol derivatives. The results of this compilation suggest that reactivity of some functional groups in an inositol derivative can be manipulated to our advantage by changing the groups used to mask inositol hydroxyl groups. This compilation of literature reports has been accepted for publication as a review in *Trends in carbohydrate chemistry.*

Chapter 2. Effect of protecting groups and the orientation of the *β*- hydroxyl / alkoxy group on hydride reduction and Grignard reactions of an inosose: efficient synthesis of *epi*-inositol and its *O*-methyl and *C*-methyl derivatives

As mentioned earlier, reactivity and selectivity in reactions of small molecules containing several functional groups such as inositol derivatives could be dependent on the protecting groups used to mask other groups in the same molecule. Conversely, it should be possible to alter the regio- and stereoselectivity of reactions of inositol derivatives to our advantage by manipulation of the protecting groups. But it is surprising that this conceptually simple approach has not been exploited to the extent possible for the preparation of analogs of *myo*-inositol. This chapter presents and compares results of (a) the hydride reduction of *epi*-inosose **14** and the corresponding pentabenzyl ether **22**; (b) the hydride reduction of pentabenzyl *epi*-inosose **22** and the corresponding *scyllo*-inosose derivative **26**; (c) Grignard reaction of pentabenzyl *epi*-inosose **22** and the corresponding *scyllo*-inosose **26**; (d) synthesis of *O*-methyl derivative **44** of *epi*-inositol. Syntheses of the inososes (**14**, **22** and **26**) are shown in Scheme 2.[5]



Scheme 2. (a) DMF, PTSA, $HC(OEt)_3$, 100 °C, 4 h, Et_3N, RT, 30 min., 94%; (b) pyridine, TsCl, 90 °C, 48 h, 80%; (c) DMSO, $(COCl)_2$, DCM, Et_3N, –78 °C, 82%; (d) DMF, Ag_2O, MeI, RT, 24 h, 92%; (e) NaOMe, MeOH, reflux, 12 h, 75%; (f) TFA–H_2O, RT, 24 h, 99%; (g) DMSO, CSA, $PhC(OMe)_3$, 100 °C, 4 h, Et_3N, RT, 30 min., 93%; (h) DMF, NaH, PMBCl, 86%; (i) DMF, NaH, BnBr, 16 h, (96%, for **16**), (81%, for **19** over two steps), (81%, for **28**); (j) DCM, DIBAL–H in toluene, 20 h; (k) DCM-MeOH, conc. HCl, reflux, 6 h, 93%; (l) pyridine, DMAP, Ac_2O, reflux, 18 h, 92-95%; (m) IBX, EtOAc, reflux, 6 h, 94–96%; (n) as in ref. 5; (o) benzene, NaH, BnBr, reflux, 1.5 h, 78%; (p) benzene, TPP, imidazole, *p*-NO_2BzOH, 30 min., 89%; (q) NaOH, THF-MeOH, reflux, 30 min., 98%.

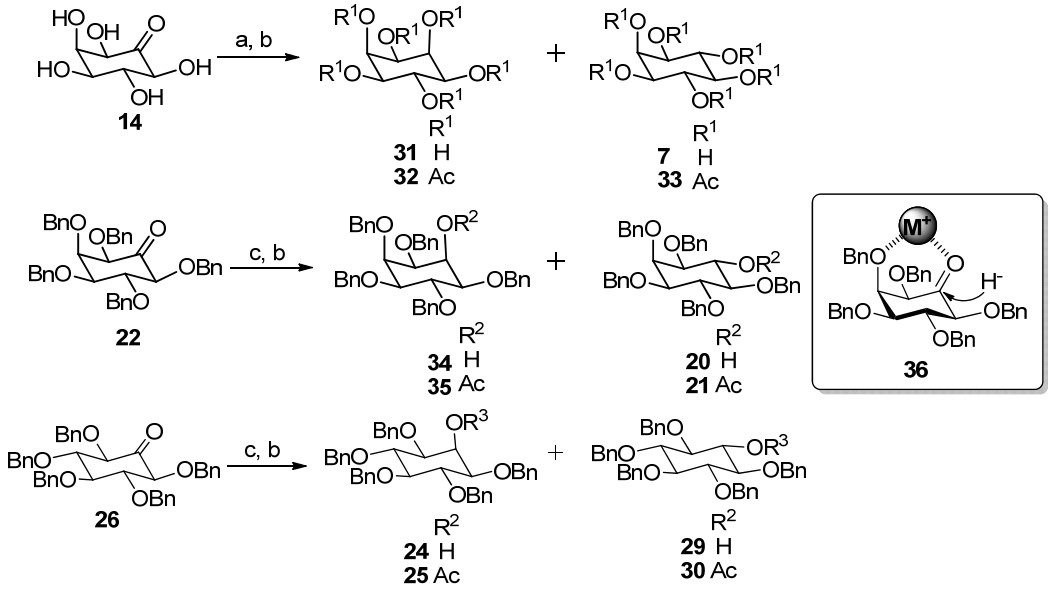
Crystal structure of racemic *epi*-inosose **14** was solved and compared with the previously reported crystal structure of (–)-*epi*-inosose (–)-**14**.[6] The overall molecular organization in the crystals of the racemic and chiral compounds is remarkably similar. This is primarily due to the fact that the second molecule in the asymmetric

unit of (–) *epi*-inososе ***L*-14** plays the role of the second enantiomer in the crystal packing. The compound also follows Wallach's rule,[7] in that the racemic crystals are denser than the optically active form.

Reduction of *epi*-inososе **14** with different reducing agents gave a mixture of *myo*- and *epi*-inositols. The ratio of *myo*-inositol to *epi*-inositol was estimated by ^{1}H NMR spectroscopy of the mixture of hexaacetates **33** and **32** (Scheme 3). The reduction of the protected *epi*-inososе **22** with sodium borohydride, was stereoselective to yield the corresponding *epi*-alcohol **34** with about 98% selectivity. The pentabenzyl *epi*-inositol **34** was isolated by column chromatography which on global deprotection by hydrogenolysis gave *epi*–inositol **31** as a colorless solid in an overall yield of 52% in 9 steps starting from *myo*-inositol. Hence protection of the hydroxyl groups improves the stereoselectivity of hydride reduction.

We are of the opinion that higher selectivity in hydride reduction of the fully protected *epi*-inososе **22** (in contrast to the reduction of **14**) arises due to its ability to form the complex with the metal ions of reducing agent, which forces the hydride to approach the carbonyl group as shown in **36** (Scheme 3) to yield the axial alcohol. Perhaps, the *epi*-inososе **14** gives a mixture of products since its chelation with metal ion is not expected to be strong enough in water (as compared to organic solvents) to facilitate the approach of the hydride from one face of the carbocylic ring.

The *epi*- and *scyllo*- inososes **22** and **26** differ only in the orientation of one benzyloxy group at the *β*-position with respect to the ketone. But this translates into a considerable difference in the outcome of the hydride reduction reaction. The presence of the axial benzyloxy substituent forces the hydride to approach from the equatorial direction and yields larger amount of the axial alcohol. This effect is also evident during the reduction of the unprotected inososе **14**.



Scheme 3. (a) $NaBH_4$, H_2O, RT; (b) pyridine, DMAP, Ac_2O, reflux, 18 h, 92-95%; (c) $NaBH_4$, DCM:MeOH (4 : 1), 30 min, 94%.

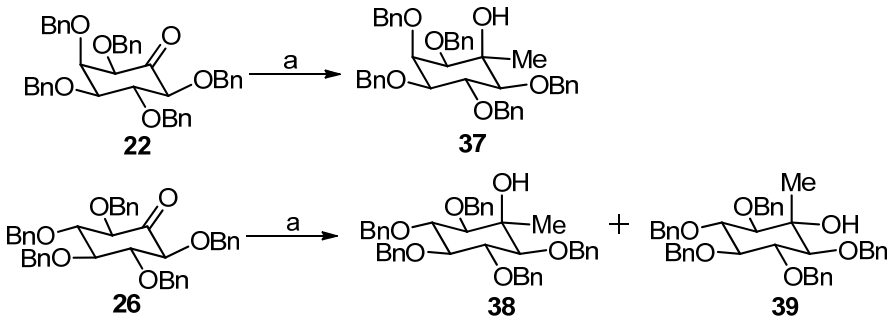
Table 1. Comparison of reduction of *epi*- and *scyllo*-inososse

Sr. No.	inosose	Reducing agent	Temperature	Products[a]
1	*epi* (**14**)	$NaBH_4$	0 ºC	Complex mixture
2	*epi* (**14**)	$NaBH_4$	ambient	**31**:**7** = 89:11
3	*epi* (**22**)	$NaBH_4$	0 ºC	**34**:**20** = 98:2
4	*scyllo* (**26**)	$NaBH_4$	0 ºC	**24**:**29** = 80:20
5	*scyllo* (**26**)	$NaBH_4$	– 55 ºC	**24**:**29** = 92:8

[a] The ratio of products was estimated by proton NMR spectroscopy after conversion to the corresponding acetates.

This observed trend in stereoselectivity for the hydride reduction of inososes (*epi*- **22** and *scyllo*- **26**) is maintained during their Grignard reaction as well. Addition of methyl magnesium iodide to **22** results in the formation of **37** exclusively while the corresponding reaction of **26** gives a mixture of both the possible products. That the effect of the orientation of the *β*-hydroxyl or alkyloxy group on the outcome of the addition of a nucleophile to the carbonyl group that we observed is not an isolated incident was ascertained by comparison of results reported in the literature on the reactions of structurally similar inositol derivatives. The *C*-methyl derivatives **38** and

39 were isolated in 76% and 18% yields respectively and their structures were confirmed using 2D NMR spectroscopy (Figure 1).



Scheme 4. (a) MeMgI, THF, 0 °C–RT, 93% (for **37**); 76% (for **38)** and 18% (for **39**).

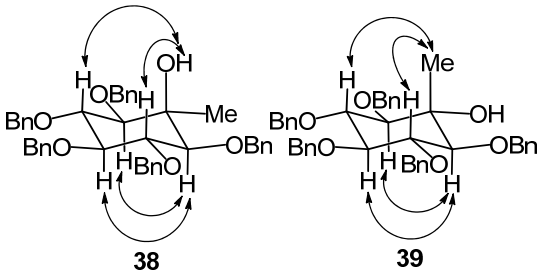
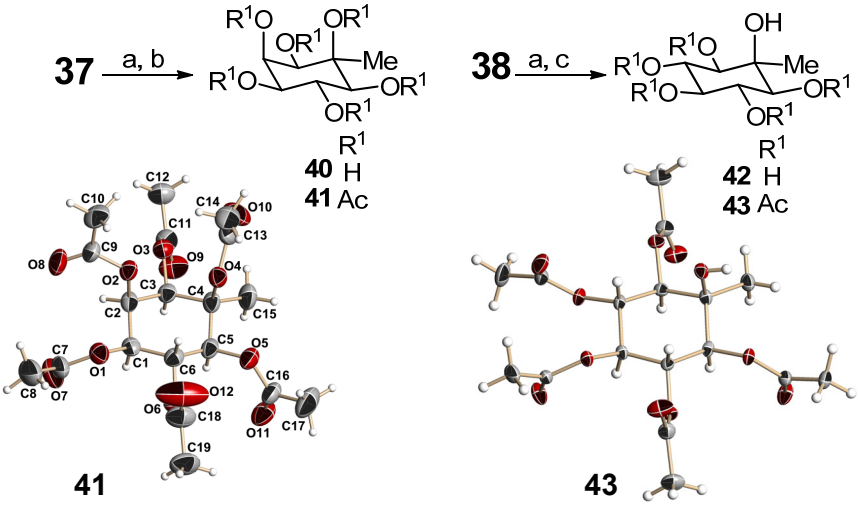


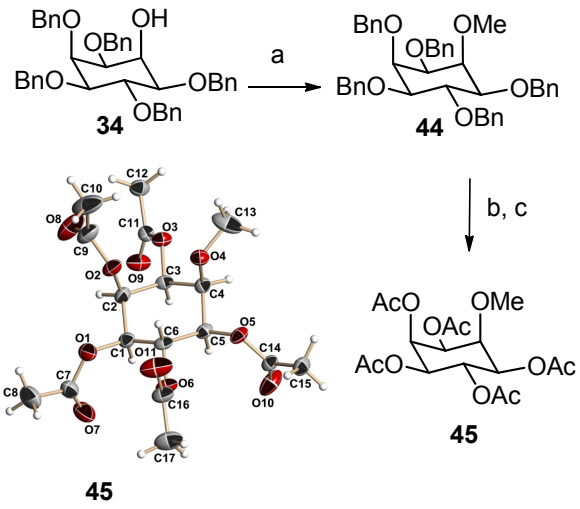
Figure 1. Summary of observed nOe for compounds **38** and **39**.

Incidentally these reactions provided synthetic routes to *iso*-laminitol **40** and *iso*-mytilitol **42** (Scheme 5). The structure of acetates **41** and **43** were confirmed by single crystal X-ray diffraction analysis.



Scheme 5. (a) H_2, 20% $Pd(OH)_2$ on C, 60 *psi*, THF:EtOH:H_2O:TFA, 20 h; (b) pyridine, DMAP, Ac_2O, reflux, 18 h, 86% over two steps; (c) pyridine, DMAP, Ac_2O, RT, 24 h, 88% over two steps.

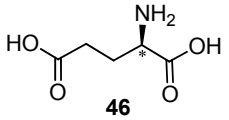
We utilized the racemic pentabenzyl *epi*-inositol **34** for the preparation of racemic 4-*O*-methyl *epi*-inositol (*iso*-ononitol, Scheme 6). The structure of **45** was confirmed by single crystal X-ray diffraction analysis. *iso*-Ononitol hexaactate was obtained in an overall yield of 43% in 10 steps starting from *myo*-inositol.



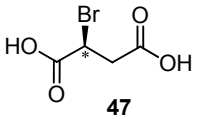
Scheme 6. (a) DMF, NaH, MeI, 96%; (b) H_2, $Pd(OH)_2$-C, 60 *psi*, THF:EtOH:H_2O:TFA, 20 h; (c) pyridine, Ac_2O, DMAP, reflux, 20 h, 83% over two steps.

Chapter 3. Access to chiral inositol derivatives by preferential crystallization of conglomerates

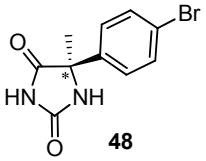
The upsurge in interest in the chemistry of inositols demands better methods for the synthesis of chiral inositol derivatives. Consequently several methods have been used for the preparation of chiral inositol derivatives. These methods can be broadly grouped under the following heads: (a) conventional resolution of racemic inositol derivatives; (b) desymmetrization of *meso*-derivatives of inositols; (c) synthesis of chiral inositol derivatives from chiral starting materials; (d) enzyme mediated preparation of chiral inositol derivatives. Each of these methods has its own advantages and limitations. For example use of naturally occurring chiral starting materials require maintenance of chirality throughout the synthesis and we can get only one enantiomeric end product. One of the oldest methods known for obtaining chiral organic compounds which has regained its importance in recent times viz., preferential crystallization of conglomerates (Chart 1) has not been explored for the preparation of chiral inositol derivatives.



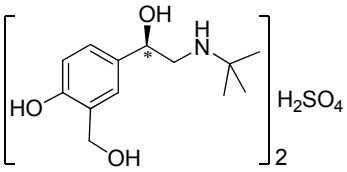
46
(*D*)-Glutamic acid
Bull. Chem. Soc. Jpn. **1965**, *38*, 9, 1552-1555



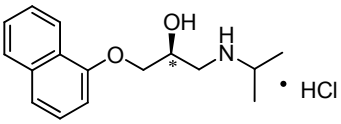
47
(*R*) Bromosuccinic acid
Bull. Chem. Soc. Jpn. **1998**, *71*, 3, 735-739



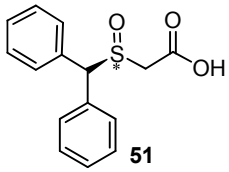
48
(*R*) 5-(4-bromophenyl)-5-methylhydantoin
Chem. Lett. **2001**, 364-365



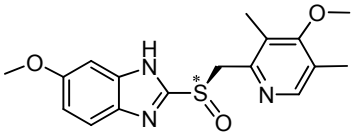
49
(*R*) Albuterol sulfate
Tetrahedron Asymm. **2007**, *18*, 1170–1175



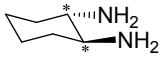
50
(*R*) Propranolol hydrochloride
CrystEngComm. **2007**, 7, 9, 1628-1634



51
(*R*) Modafinic acid
CrystEngComm. **2008**, *10*, 724-733



52
(*R*) Omeprazole
Worldwide Pat. WO2009027614, 2009



53
(1R, 2R) trans-1,2-diamino cyclohexane
Tetrahedron Asymm. **2010**, *21*, 2212–2217

Chart 1: Compounds which have been resolved by preferential crystallization.

We thought of exploring this possibility since we had prepared a large number of crystalline inositol derivatives and investigated their crystal structures.[8,2c] Conglomerates are defined as mechanical mixture of crystals of both the enantiomers. Preferential crystallization is an attractive method to obtain pure enantiomers due to practical considerations and the advantage of obtaining directly a chiral solid product. A CSD search for crystalline inositol derivatives resulted in 234 hits, out of which 64 crystals are in chiral space group. Of these 64 compounds, 28 are diastereomers, 27 are enantiomers, 6 are meso derivatives and 3 are racemic (conglomerates, chart 2)[9,8a,8b] We also identified **57** and **58** which exist as conglomerates, from our unpublished work.

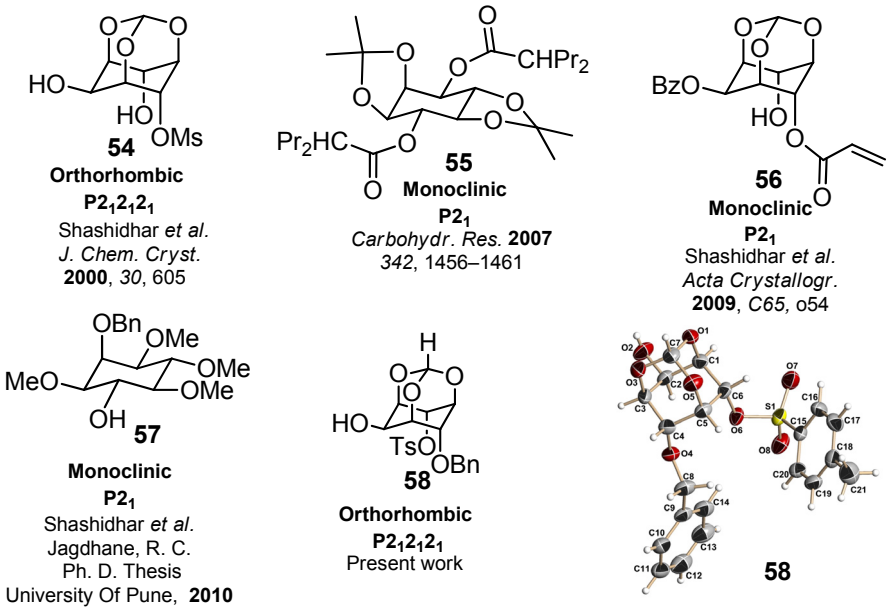
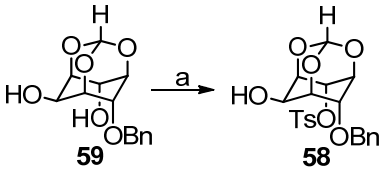


Chart 2. Racemic inositol derivatives that crystallize in chiral space group.

We decided to attempt the resolution of compound **58** as we had converted racemic **58** to many other derivatives of *myo*-inositol.[10] The compound **58** was synthesized by tosylation of racemic benzyl ether **59** by a known method (Scheme 7).[10a]



Scheme 7. (a) DMF, LiH, TsCl, 65%.

The summary of results of crystallization experiments with **58** are shown in Figure 2. We were able to attain 83% *ee* for one of the enantiomers. The enantiomeric excess was estimated by chiral HPLC. The results obtained in this work suggest that separation of enantiomers by preferential crystallization has good potential to provide chiral inositol derivatives.

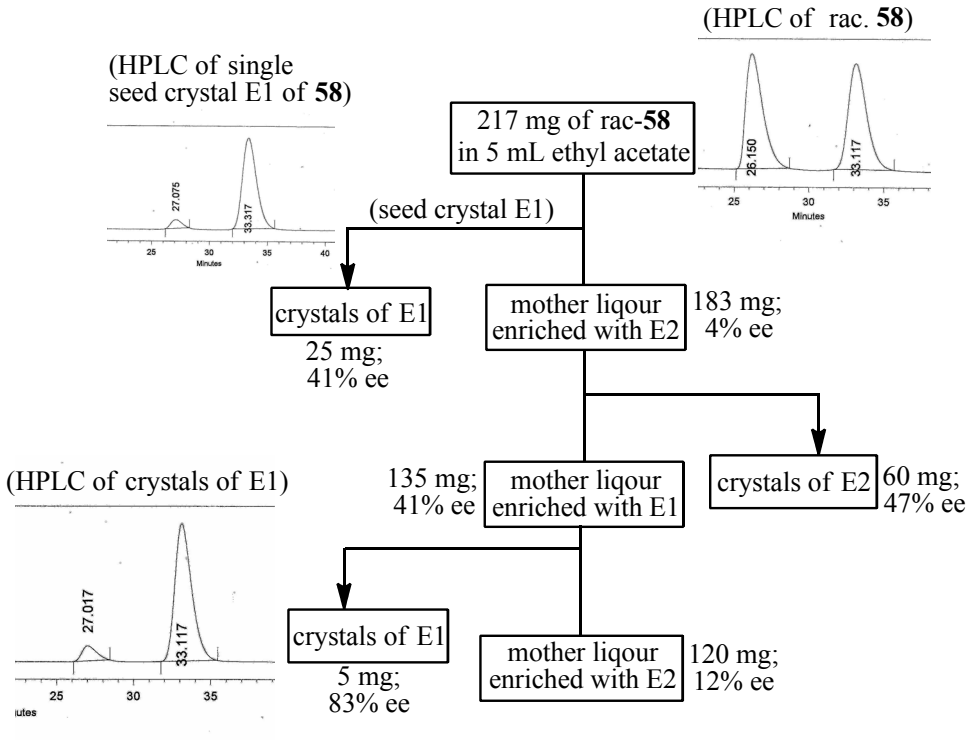


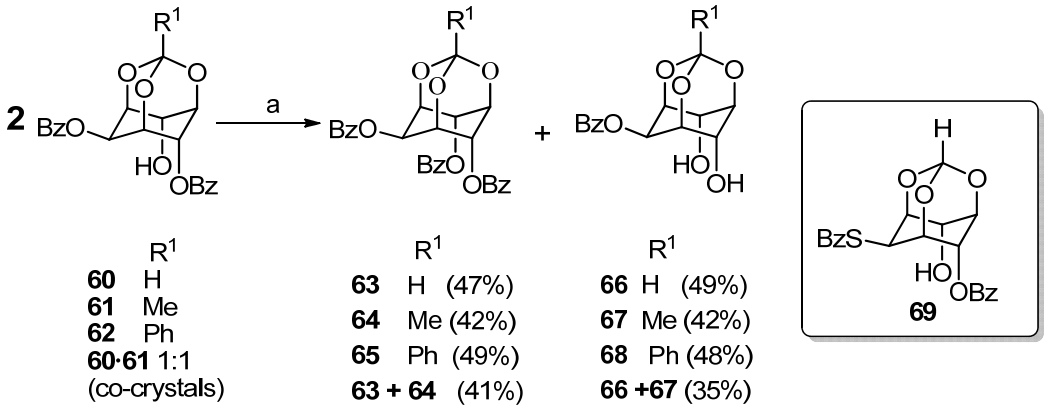
Figure 2. Results of preferential crystallization of a conglomerate **58**.

E1 and E2 are enantiomers of **58**.

Chapter 4. Synthesis and structural studies of 2-deoxy-2-mercapto *myo*-inositol 1,3,5-orthoformate derivatives

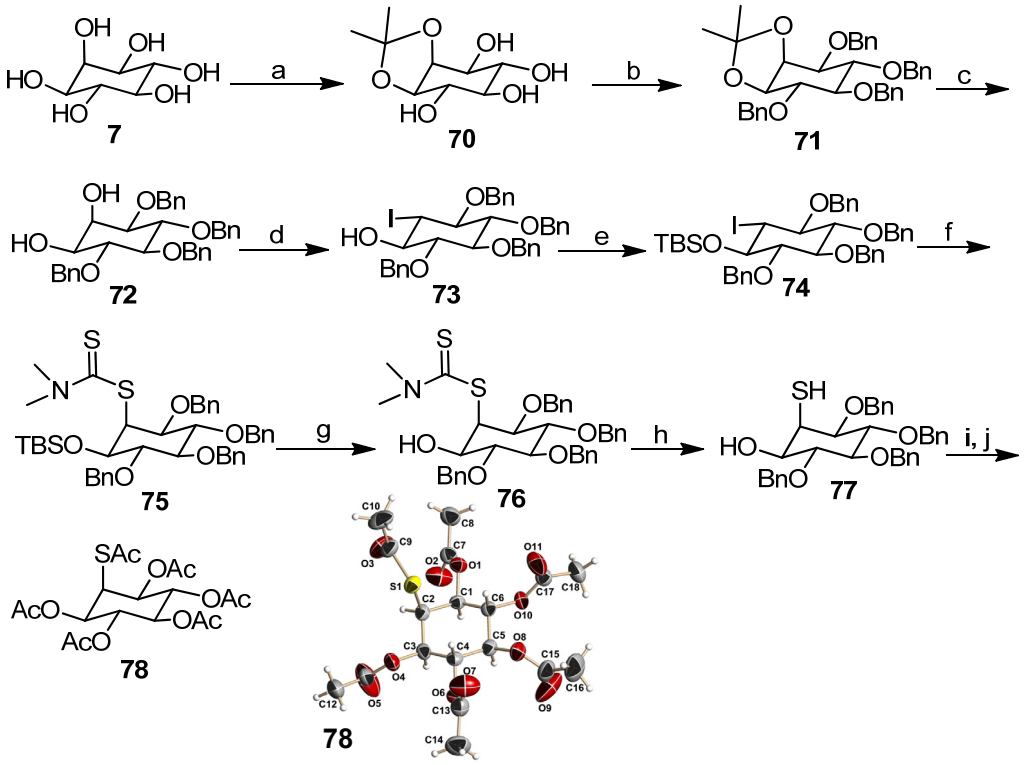
The study of organic reactions in molecular solids and crystals has emerged as a frontier area of research in the recent past. Although reactions in molecular crystals are less common than reactions in the gas phase or in solution, the degree of (regio- and/or stereo-) control exerted by the crystalline state is often comparable to that observed in enzyme mediated processes.[11] Transesterification reactions among the hydroxyl groups of partially acylated inositol derivatives in solution occur frequently and this has been exploited for the preparation of biologically relevant phosphorylated inositol derivatives.[12] Most of these acyl migration reactions however result in the formation of a mixture of isomeric hydroxy esters and consequently result in poor isolated yield of the required *O*-protected inositol derivative. Also isolation of each individual isomer resulting from indiscriminate acyl migration reactions requires efficient and laborious methods of separation.

Extremely facile and neat intermolecular benzoyl group transfer reactions in crystals of racemic 2,6-di-*O*-benzoyl *myo*-inositol 1,3,5-orthoesters (**60**–**62**) and their co-crystals **60•61** have been reported from our laboratory (Scheme 8).[2d]



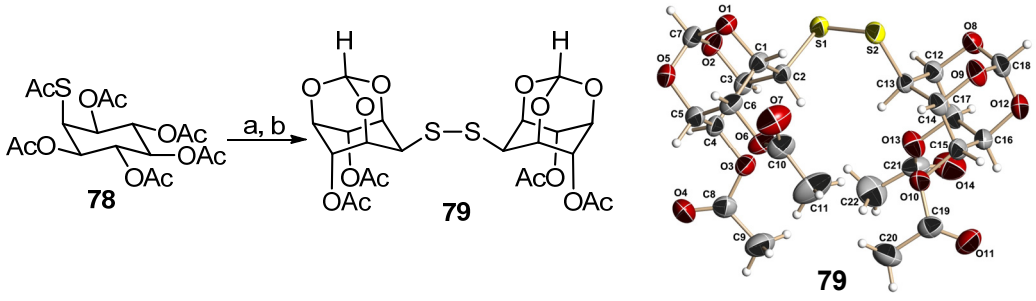
Scheme 8. (a) Na_2CO_3, heat.

Perturbations to the basic molecular framework of these orthoesters and the consequent changes in the acyl transfer reactivity of the resulting molecules in their crystals have been investigated. [2d] As a sequel to these studies and to see if the scope of acyl transfer reactions in molecular crystals can be widened, we under took the preparation of thio analogs of inositol orthoesters (such as **69**, Scheme 8) and examine the possibility of acyl transfer in their crystals. Accordingly, the results presented in this chapter pertain to our attempts towards the preparation orthoester derivatives of thio analogues of *myo*-inositol. A search of the literature revealed that preparation of a few thio-inositols is reported in literature.[13] However, there are no reports on the preparation of thio analogs of inositol orthoesters and their derivatives. To synthesize 2-deoxy 2-mercapto *myo*-inositol **69** we followed the route reported by Guidot *et al.*[13f] except that the thiol moiety was introduced using sodium dimethyldithiocabamate (NaDMDTC) instead of sodium benzyl mercaptide (Scheme 9). The structure of **78** was confirmed by single crystal X-ray diffraction analysis.



Scheme 9. (a) DMSO, PTSA, 2,2-dimethoxypropane, 110 °C, 70%; (b) DMF, NaH, BnBr, 16 h, 96%; (c) MeOH, HCl, reflux, 20 min, 98%; (d) TPP/imidazole/I_2, benzene, 80 °C, 20 min, 89%; (e) DCM, 2,6-lutidine, TBDMSOTf, 30 min., 98%; (f) DMF, NaDMDTC, 120 °C, 91%; (g) DCM-MeOH, AcCl, 30 min., 96%; (h) THF, LAH, reflux, 8 h, 95%; (i) liq. NH_3, Na metal, 1 h; (j) pyridine, DMAP, Ac_2O, reflux, 12 h, 88% over two steps.

The product obtained by aminolysis of the hexaacetate **78** using *iso*-butylamine in MeOH on treatment with triethylorthoformate in DMF using catalytic PTSA and subsequent acetylation using acetic anhydride, pyridine, DMAP gave the product **79** (Scheme 10), the structure of which was established by single crystal X-ray diffraction analysis. Efforts to obtain orthoformate derivative of **69** are in progress.



Scheme 10. (a) i) *iso*-butylamine, MeOH, reflux, 6 h; ii) $HC(OEt)_3$, PTSA, DMF, 100 ºC, 4 h, Et_3N, RT, 30 min.; (b) pyridine, Ac_2O, DMAP, 73% (over two steps).

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Note: Compound numbers in the synopsis are different from those in the thesis and references are included separately for each chapter.

List of Publications

1. "Protecting group directed stereoselective reduction of an *epi*-inososе: efficient synthesis of *epi*-inositol", **Patil, M. T.**; Shobhana, K.; Sarmah, M. P.; Shashidhar, M. S. *Tetrahedron Lett.* **2011**, *52*, 3756-3758.
2. "Comparison of racemic *epi*-inososе and (–)-*epi*-inososе", Shobhana, K.; **Patil, M. T.**; Shashidhar, M. S. *Acta Crystallogr.* **2011**, *C67*, o435-o438.
3. "Effect of protecting groups on the reactions of inositol derivatives", **Patil, M. T.**; Shashidhar, M. S. accepted in *Trends in carbohydrate chemistry.*
4. "Comparison of crystal structure of *myo*-inositol hexaacetate and corresponding 2-deoxy-2-mercapto *myo*-inositol analog. Shobhana, K.; **Patil, M. T.**; Shashidhar, M. S. manuscript under preparation.

Poster Presentations

1. **Patil, M. T.**; Shashidhar, M. S. Poster presentation, "Protecting group directed stereoselective reduction of an *epi*-inososе: efficient synthesis of *epi*-inositol" Science day held at NCL, Pune Feb. 2011.

Chapter 1

Effect of the protecting groups on the reactions of inositol derivatives

1.1. Introduction

Chemistry of cyclohexane polyols (inositols, cyclitols, Chart 1.1) has been the subject of intense investigations in the recent past due to the ubiquitous presence of their derivatives in living cells and implication of phsophoinositols in biological phenomena such as cellular signal transduction, calcium mobilization, insulin stimulation, exocytosis, cytoskeletal regulation, intracellular trafficking of vesicles and anchoring of certain proteins to cell membranes.[1] Derivatives of inositols other than phosphoinositols are also important since several of them occur in nature and some are essential constituents of our diet.[2] Amino derivatives of inositols are present in antibiotics[3] and some of them function as glycosidase inhibitors.[4] Key intermediates for the synthesis of biologically important derivatives of inositols are the corresponding hydroxyl group protected derivatives. Many of these intermediates have been synthesized from benzene, quinic acid, carbohydrates and naturally occurring inositols.[5] Cyclitols or inositols have also been used as starting materials for natural product synthesis[6] and their derivatives are also interesting because of their structure and reactivity in the solid state.[7] In particular, the chemistry of *myo*-inositol, the most abundantly available cyclitol, and its derivatives has been studied extensively in the last two decades.[1a,5d,8] *myo*-Inositol **1.1**, a hexahydroxy cyclohexane, is a meso isomer with five equatorial hydroxyl groups and an axial hydroxyl group. There is a plane of symmetry passing through two of its carbon atoms C2 and C5 (as shown in Chart 1.1).

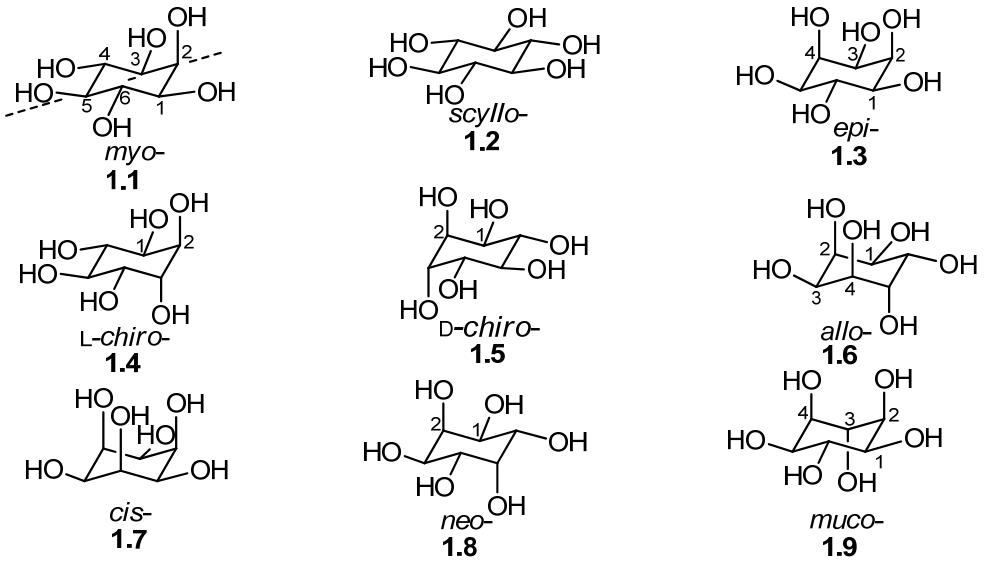


Chart 1.1. The nine known isomeric inositols.

The carbon bearing the axial hydroxyl group is designated as C2 and the other ring carbons can be numbered from C1 to C6 starting from a C1 atom and proceeding around the ring in anticlockwise **1.10** or clockwise **1.11** fashion (Chart 1.2). According to convention,[9] anti-clockwise numbering in an unsymmetrically substituted *myo*-inositol leads to the configurational D-prefix and clockwise numbering gives the substituted *myo*-inositol an L-prefix. An IUB recommendation allowing all biologically relevant *myo*-inositol derivatives to be denoted as D-isomers has also been proposed.[10] Although, many of the unsymmetrically substituted *myo*-inositol derivatives reported in this thesis are racemic, for clarity and simplicity they are represented in schemes by only one enantiomer. Optically inactive (racemic, *meso*) synthetic derivatives of inositol are numbered without prefixes, while optically active derivatives are numbered with a suitable prefix (D-, L, ent, dia).

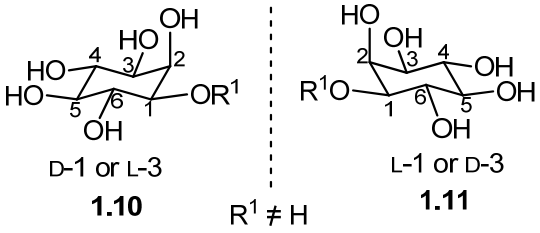
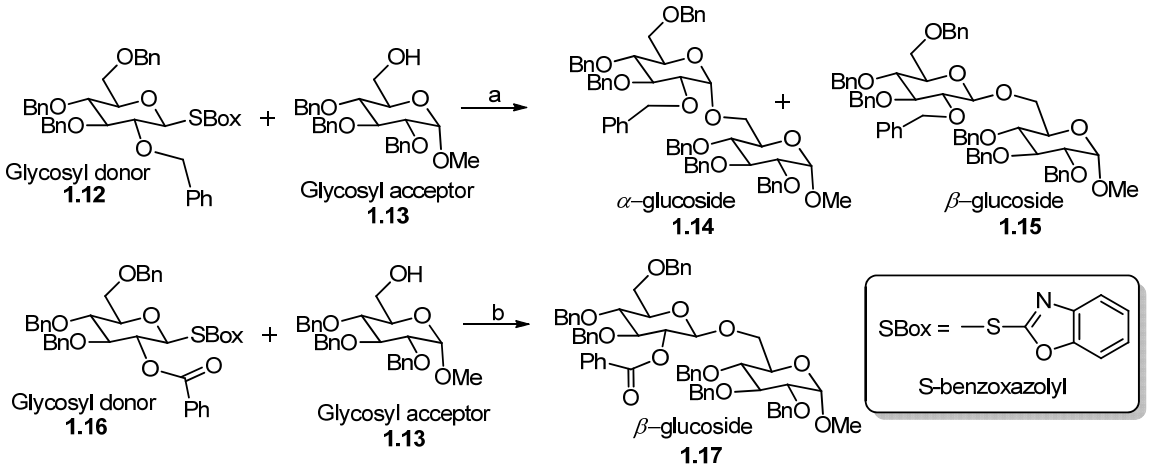


Chart 1.2. Numbering in unsymmetrical *myo*-inositol derivatives.

Although there are many reports on the utility of *myo*-inositol as a starting material for the synthesis of inositol derivatives, analogs and natural products, these suffer from lengthy routes and low yields. This is mainly due to the formation of regioisomeric products due to the presence of six secondary hydroxyl groups in *myo*-inositol, whose reactivities are not drastically different. This situation calls for elaborate protection-deprotection steps during the execution of a synthetic sequence. General characteristics of protecting groups used in polyhydroxy compounds including carbohydrates have been well described[11] and hence will not be further elaborated here. Although an ideal protecting group is one which does not alter the reactivity of other functional groups in the same molecule, in reality, protecting groups do perturb the reactivity of other functional groups.[11b,12] Hence, the reactivity and selectivity in reactions of small molecules containing several functional groups can to some extent be tuned by varying the protecting groups utilized during a synthetic sequence. Scheme 1.1 shows the effect of protecting groups on the outcome of glycosidation reaction.[13]



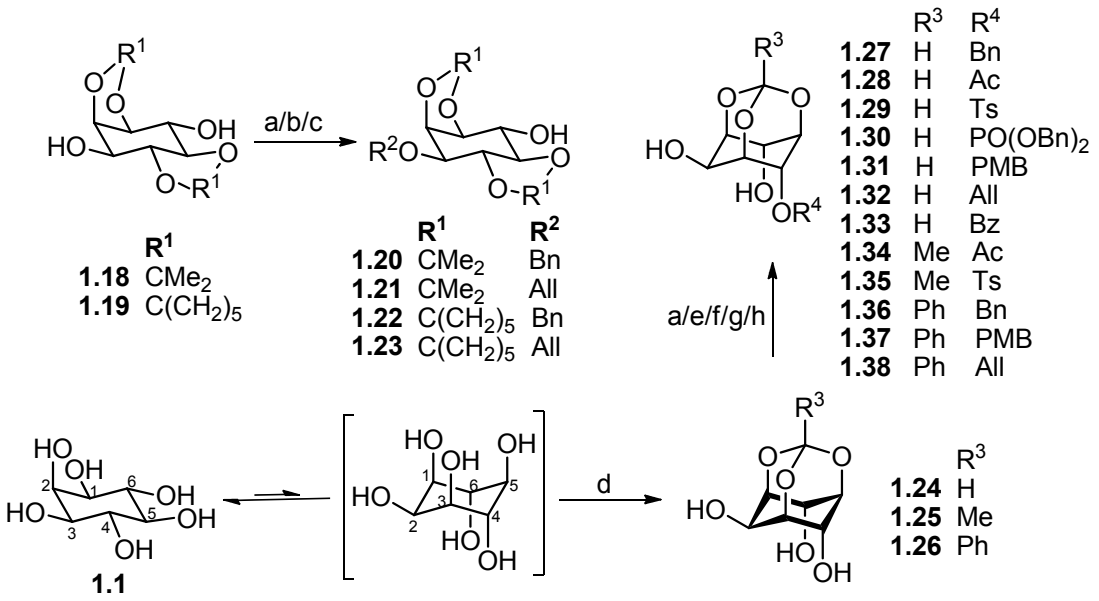
Scheme 1.1. (a) DCM, DMTST, 0 °C–rt, 2 h, 91% (**1.14**:**1.15** = 1.2:1); (b) DCM, DMTST, 0 °C, 5 min., 90%.

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.[14] 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. Although there is a large body of data in the literature pertaining to the use of various protecting groups during the synthesis of cyclitols and their derivatives, starting from inositols, no attempt has been made to compare or catalog the effect of protecting groups on the reactivity of other functional groups present in the same molecule. In the present chapter we have attempted to scrutinize the data available in the literature to see if protecting groups can be exploited to achieve the desired selectivity during syntheses involving inositol derivatives.

1.2. Effect of the protecting groups on the reactions of inositol derivatives

1.2.1. Reactivity of hydroxyl groups in partially *O*- protected inositol derivatives

Relative reactivity (and hence regioselectivity) of hydroxyl groups in majority of partially *O*-protected *myo*-inositol derivatives are not affected by the hydroxyl protecting groups used. This is illustrated in Scheme 1.2 with examples chosen from the literature.[15]



Scheme 1.2. (a) DMF, NaH, BnBr; (b) toluene, NaH, BnBr, reflux; (c) DMF, AllBr, BaO, $Ba(OH)_2$; (d) DMF/DMSO, PTSA/CSA, $R^3C(OEt)_3$, 100 °C, Et_3N, rt, 30 min.; (e) DMF, NaH, Ac_2O; (f) DMF, NaH, TsCl; (g) NaH, tetrabenzylpyrophosphate; (h) DMF, NaH, R^5X [R^5 = PMB, All, Bz; X = Cl, Br].

The reactivity of the hydroxyl groups in *myo*-inositol and its derivatives decreases in the order C-1 (C-3) > C-4 (C-6) > C-5 > C-2, except in *myo*-inositol 1,3,5-orthoesters, where the reactivity pattern is C-4 > C-2 ≈ C-6.[5d] However, the ratio of the isomeric products isolated in specific reactions can vary without drastic changes in the selectivity pattern. Protection of *myo*-inositol hydroxyl groups as the corresponding 1,3,5-orthoester results in an unusual pattern of reactivity of the C2, C4 and C6-hydroxyl groups since in these orthoesters, the *myo*-inositol ring undergoes inversion (from 'equatorial rich' to 'axial rich' conformation). Normal *myo*-inositol derivatives have only the C2-hydroxyl group in axial orientation while in *myo*-inositol-1,3,5-orthoesters (**1.24**–**1.26**), only the C2-hydroxyl group has the equatorial orientation (with respect to the inositol ring – bold in Scheme 1.2). Hence reactivity of inositol hydroxyl groups cannot be drastically altered by varying the protecting groups, as long as conformation of the inositol ring is conserved.

Examples of change in conformation of the inositol ring on increasing the bulk of hydroxyl protecting groups is shown in chart 1.3.[16] Scrutiny of the ring conformation of 3,4-di-*O*-substituted and 4,5-di-*O*-substituted *myo*-inositol derivatives revealed that *myo*-

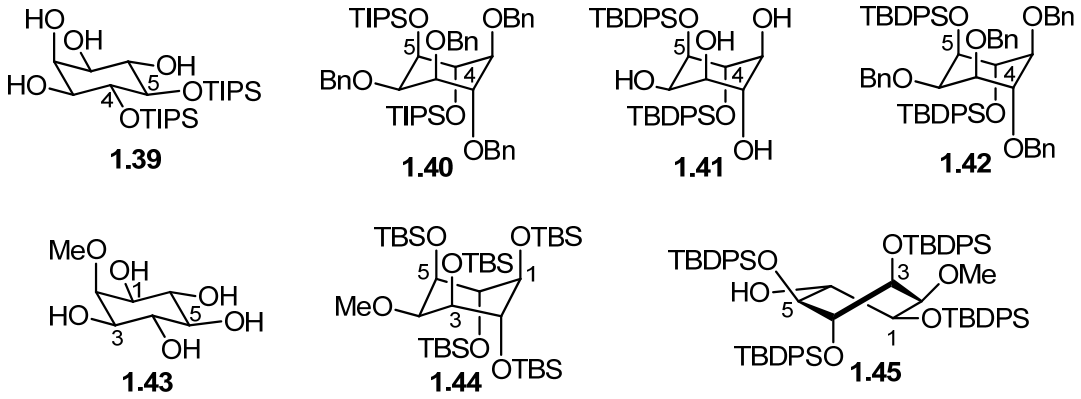
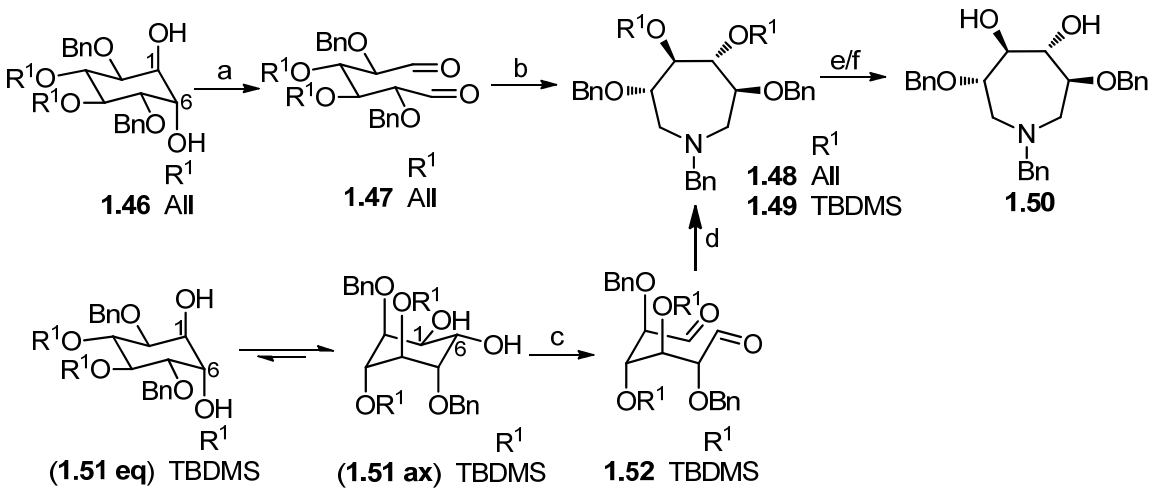


Chart 1.3. Ring conformation of *O*-silylated *myo*-inositol derivatives.

inositol ring flips into the 'axial-rich' chair form when TIPS or TBDPS groups were introduced on the C4- and C5-hydroxyl groups. Similarly, the ring conformation of 2-*O*-methyl-1,3,4,5-tetrakis-*O*-*tert*-butyldiphenylsilyl-*myo*-inositol (**1.45**) was found to be in a twist form both in solid state and in solution states.[17] However, reactivity patterns of the functional groups in these unusual conformations were not investigated.

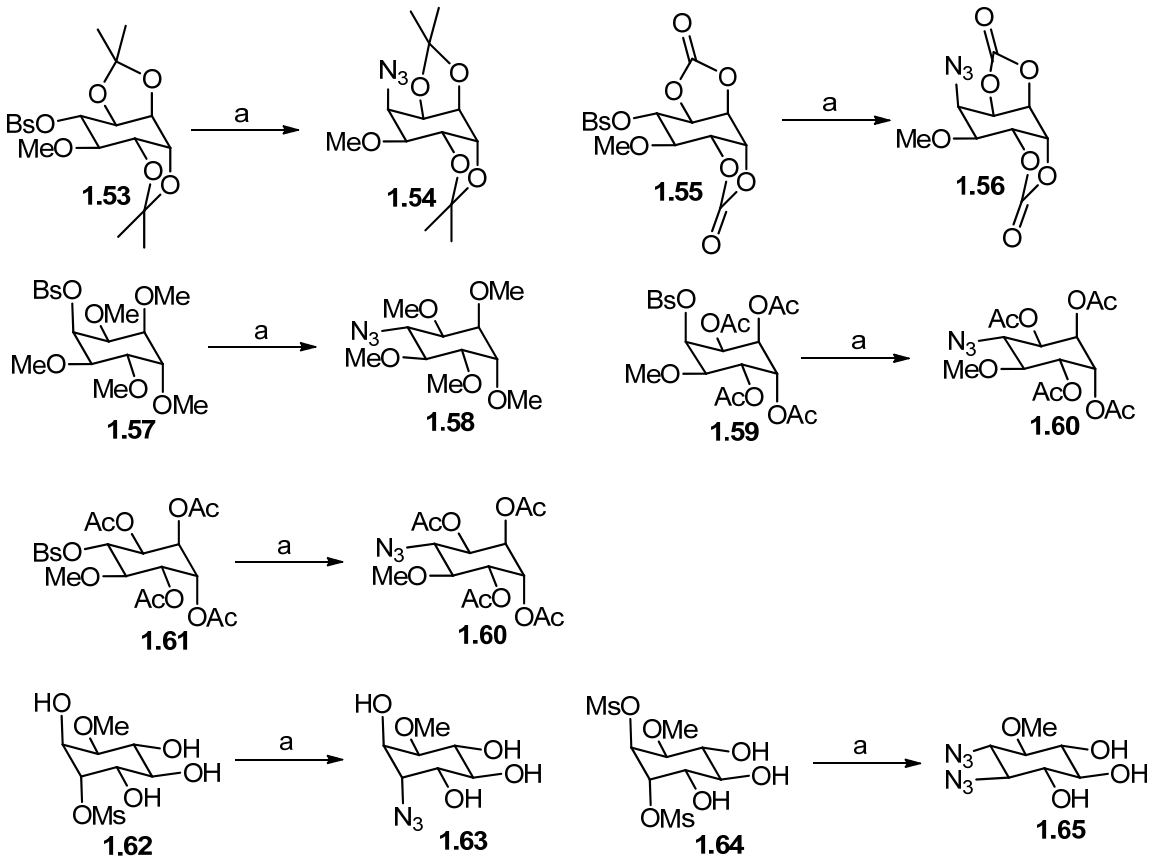
This phenomenon of the flipping of the inositol ring from equatorial rich chair form to axial rich chair form conformation because of presence of silyloxy group has also been utilized to improve the yield of trans diol cleavage reaction (Scheme 1.3).[18] Treatment of the *trans*-diaxial 1,6-diol of *chiro*-inositol derivative **1.46** carrying allyl group, with periodate gave the dialdehyde **1.47** in 35% yield, while *trans*-diequatorial 1,6-diol **1.51** carrying TBDMS groups on cleavage with periodate gave the dialdehyde **1.52** in 82% yield. The improvement in efficiency of the diol cleavage on changing the protecting groups from allyl to TBDMS is because of the change in conformation of the inositol ring from equatorial-rich chair form to axial-rich chair form due to the presence of the bulky silyl groups which converts 1,6-diaxial-trans diol (**1.51 eq**) to 1,6-diequatorial trans diol (**1.51 ax**). The dialdehyde **1.52** was used to prepare 3,6-di-*O*-benzyl-L-ido-tetrahydroxyazepane **1.50**.



Scheme 1.3. (a) $NaIO_4$, H_2O, CH_3CN, 90 °C, 20 h, 35%; (b) $BnNH_2$, $NaCNBH_3$, AcOH, 3 Å sieves, MeOH, –78 °C–rt, 14 h, 58%; (c) $NaIO_4$, H_2O, CH_3CN, 65 °C, 6 h, 82%; (d) $BnNH_2$, $NaCNBH_3$, AcOH, 3 Å sieves, MeOH, –78 °C–rt, 18 h, 59%; (e) Pd/C, PTSA, MeOH, 64 °C, 5 h, 50% (from **1.48**); (f) MeOH, concd. HCl, rt, 2 h, 93% (from **1.49**).

1.2.2. Nucleophilic displacement of sulfonate esters

Displacement of a sulfonate ester on the inositol framework has traditionally[19] been used for the preparation of ring modified inositol analogs such as inosamines, thioinositols. Organic moieties used to protect other hydroxyl groups are reported to have drastic effects on the outcome of such displacement reactions. Examples shown in Scheme 1.4 illustrate that the configuration of the azidoinositol obtained can be controlled by the choice of the protecting groups.[20]



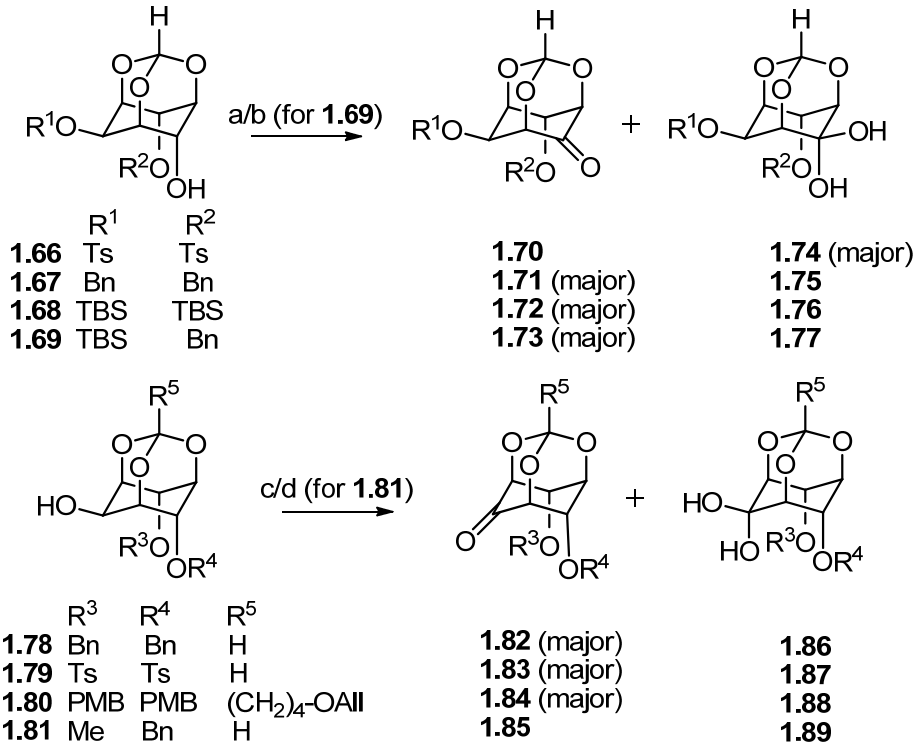
Scheme 1.4. (a) DMF, NaN_3, 110 °C (140 °C for **1.63** and **1.65**).

Examples shown in Scheme 1.4 suggest that, when participation by a neighboring *trans*-acetyl or hydroxyl group is possible, displacement usually proceeds by a neighboring group participation mechanism resulting in retention of configuration. Direct displacement results when neighboring groups do not participate in the reaction. The observation that these displacement reactions proceed with second-order kinetics supported this expectation.[20] Theoretical investigations aimed at better understanding of these reactions are also reported.[20] Interest in the synthesis of stereochemically well defined azidoinositols is because they are precursors for the preparation of inosamines which are present in several natural products and also have antiglycosidase activity.[21] Azido inositols are also known to exhibit antiproliferative activity.[22]

1.2.3. Oxidation of protected inositol derivatives

Regiospecific oxidation of inositol hydroxyl groups (often in penta-*O*-protected inositol derivatives) to the corresponding inosose is of significance since the latter

provide access to isomeric inositol derivatives (by hydride reduction), inosamines (by reductive amination) and C-alkyl inositols (eg. by Grignard reaction). In normal protected inositol derivatives, not much variation in reactivity is expected during oxidation other than the rate of formation and the yield of the inosose. However, in *myo*-inositol 1,3,5-orthoester derivatives, due to the rigidity of the molecular framework (which resembles adamantane), the ketone could exist in equilibrium with the corresponding gem-diol. This equilibrium is biased towards the ketone, except in **1.70** (Scheme 1.5) where tosylates are used for the protection of the hydroxyl groups.



	R^1	R^2
1.66	Ts	Ts
1.67	Bn	Bn
1.68	TBS	TBS
1.69	TBS	Bn

1.70
1.71 (major)
1.72 (major)
1.73 (major)

1.74 (major)
1.75
1.76
1.77

	R^3	R^4	R^5
1.78	Bn	Bn	H
1.79	Ts	Ts	H
1.80	PMB	PMB	$(CH_2)_4$-OAll
1.81	Me	Bn	H

1.82 (major)
1.83 (major)
1.84 (major)
1.85

1.86
1.87
1.88
1.89

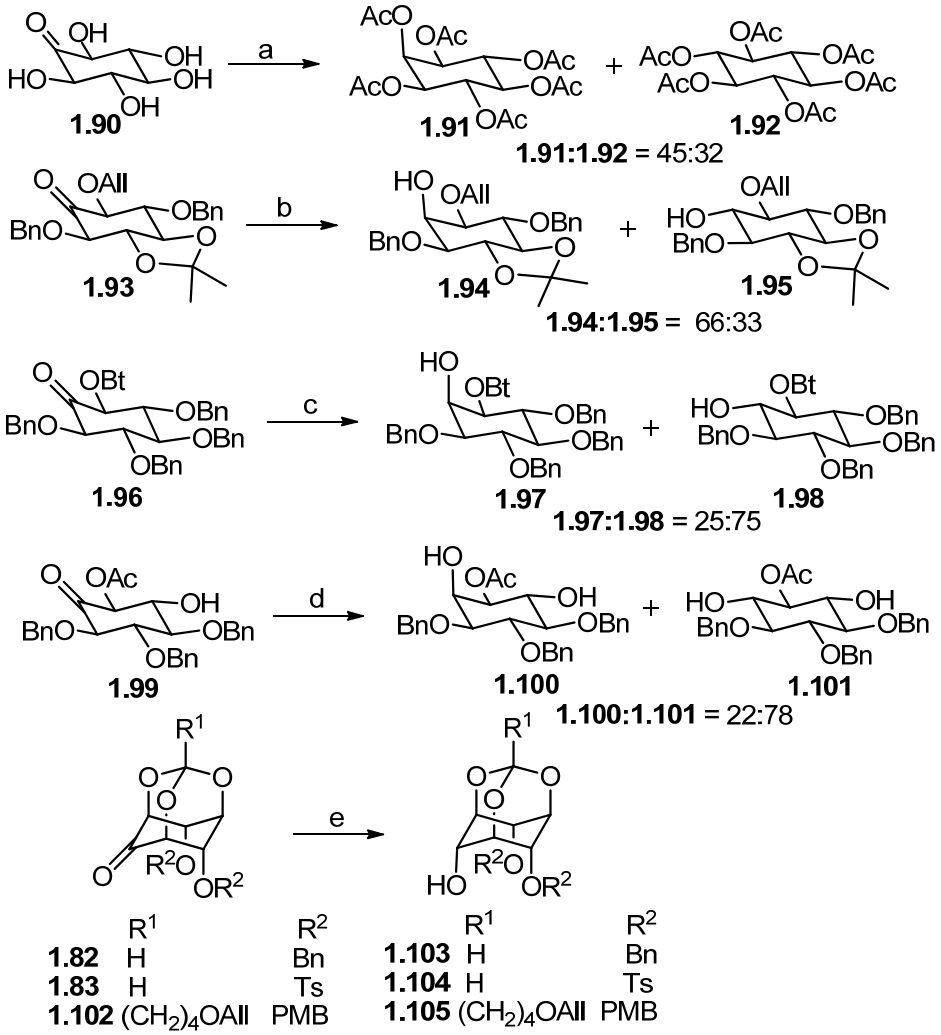
Scheme 1.5. (a) DMSO, $(COCl)_2$, DCM, –78 °C, 1 h then Et_3N, rt, 3 h, 82 %; (b) DCM, Dess-Martin periodinane, 15 h, rt, 86 %; (c) DMSO, Ac_2O, 40 h, 94 %; (d) 1.5 equiv., NMO, 0.2 equiv TPAP, DCM, molecular sieves.

It is interesting to note that the ketone **1.70** undergoes hydration with ease to give the *gem* diol **1.74**, but hydration of the ketone **1.83** was not facile, even though both the compounds have two tosylate groups situated three bonds away from the carbonyl group. The factors that could control the relative stability of a ketone and its *gem* diol (or the ease of hydration of a ketone) are electrophilicity of the carbonyl carbon and steric factors that could stabilize the ketone or the *gem* diol. If the electron withdrawing nature

of the tosylates solely decided the extent of hydration of the keto group, then the 2-ketone **1.83** should have existed as the corresponding *gem* diol **1.87**, since the tosylate groups are three bonds away from the carbonyl carbon as in the case of the isomeric 4-ketone **1.70**. However, hydration of the 2-ketone **1.83** would result in steric crowding due to the presence of three axial substituents (in the *gem* diol **1.87**). Hence perhaps, the steric crowding drives the equilibrium back towards the 2-ketone **1.83** in the symmetric ditosylate. Thus it appears that the relative stability of the ketone and the *gem* diol in these rigid trioxaadamantane systems depends on a balance between the electron withdrawing effect of the sulfonyl groups as well as 1,3-diaxial steric interactions (Scheme 1.5).[23]

1.2.4. Hydride reduction of inososes and solvolysis of esters

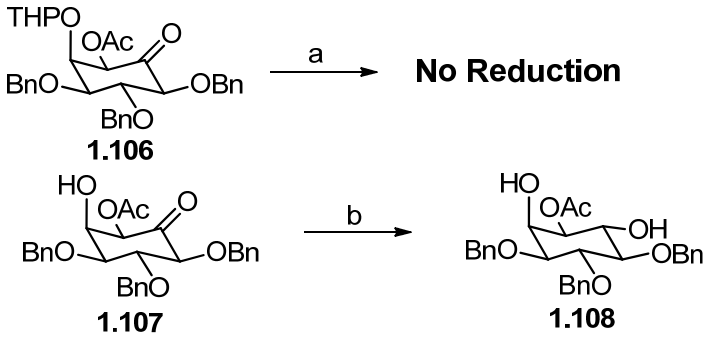
Oxidation - reduction sequence of inositol hydroxyl groups is frequently adopted for the inversion of configuration of the inositol ring carbons.[24] This two step process is a convenient way of generating diastereomeric inositols, provided stereoselectivity of the reduction process can be controlled to generate only one diastereomer, which circumvents the need for the separation of isomeric products. One of the ways often used to control the stereoselectivity during the reduction of inososes is to use different reducing agents which could result in different selectivities for the reduction of a carbonyl group.[25] A survey of the literature reveals that stereoselectivity during the reduction of inososes can also depend on the nature of the protecting groups used to protect other hydroxyl groups in these ketones. Scheme 1.6 and Scheme 1.7 illustrate the variation in the observed selectivity during the reduction of inososes due to variation in the hydroxyl protecting groups.



Scheme 1.6. (a) i) $NaBH_4$, H_2O, 0 °C–rt, 18 h; ii) conc. H_2SO_4, Ac_2O; (b) $NaBH_4$, EtOH; (c) $NaBH_4$, ^{i}PrOH, 50 °C; (d) $NaBH_4$, MeOH, 0 °C–rt; (e) $NaBH_4$, THF:MeOH, rt.

Hydride reduction of few *scyllo*-inososes carrying different protecting groups is compared in Scheme 1.6. Comparison of the ratio of the products (*myo*- to *scyllo*-) reveals that this diastereomeric ratio can be altered by the use of different hydroxyl protecting groups. Reduction of the inositol orthoester derivatives (**1.82**, **1.83** and **1.102**) constitutes an extreme situation since exclusively the *scyllo*-isomer can be obtained by the reduction of these inososes, which are conformationally rigid compared to other inososes.[23a,23f,24a,24b,25b,26]

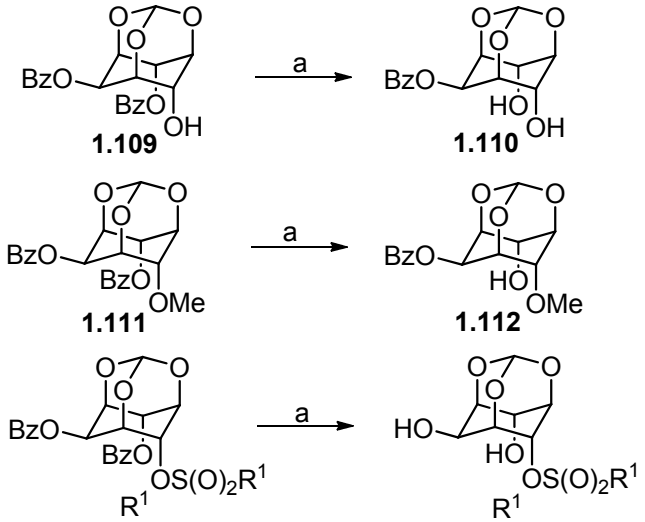
Yu *et al.* observed a dramatic change in susceptibility toward hydride reduction of the carbonyl group in the inosose **1.106** (Scheme 1.7).



Scheme 1.7. (a) Various conditions for reduction; (b) $NaBH(OAc)_3$, CH_3CN/AcOH, rt.

Although the inosose **1.107** could be reduced to the corresponding *myo*-inositol derivative **1.108** with $NaBH(OAc)_3$, all the attempts to reduce **1.106** under various conditions failed.[27]

A comparison of the methanolysis (in the presence of silver(I) oxide and silver halides) of the dibenzoate **1.109**, its methyl ether **1.111** and the corresponding sulfonates **1.113**, **1.114**, **1.115** (Scheme 1.8) showed that presence of the sulfonyl group brings about the methanolysis of both the C2 and C4-benzoates while its absence results in the solvolysis of the C4-benzoate alone.[28]

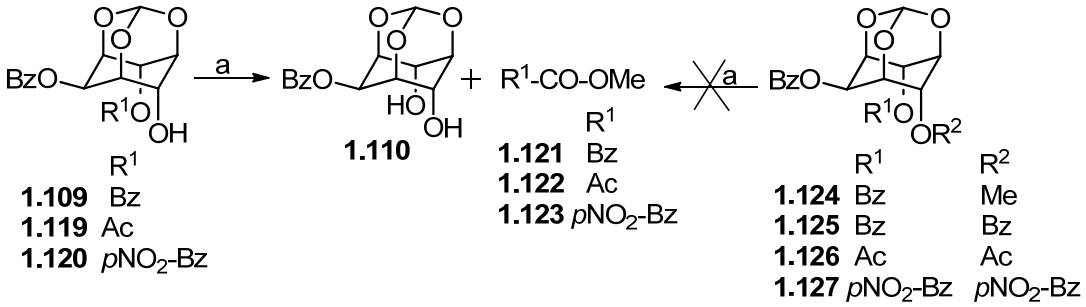


1.113 Me
1.114 *p*-tolyl
1.115 (1s)-(+)-10-camphonyl
mixture of diastereomers

1.116 Me
1.117 *p*-tolyl
1.118 (1s)-(+)-10-camphonyl
mixture of diastereomers

Scheme 1.8. (a) DMF-MeOH, Ag_2O, AgX (X = Br or I).

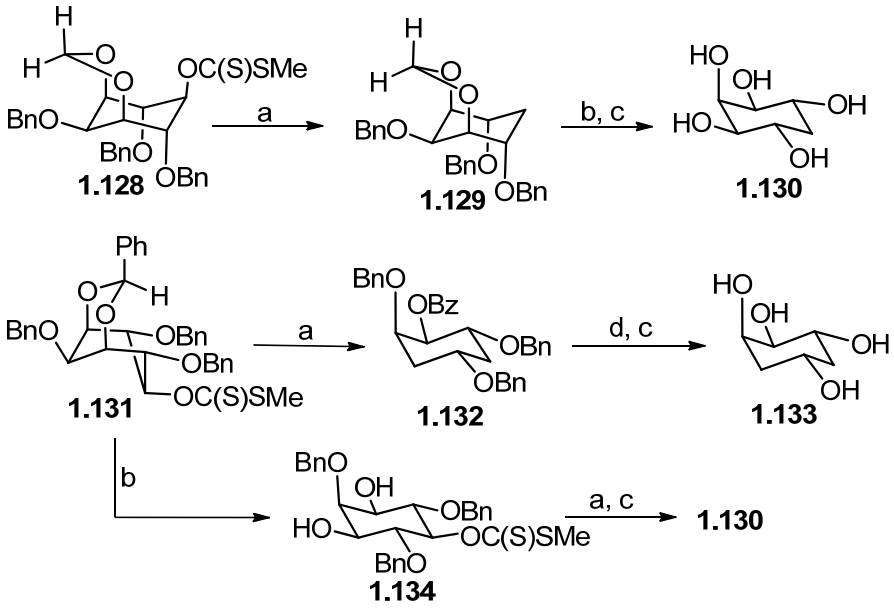
The Diesters **1.109**, **1.119** and **1.120** underwent methanolysis in the presence of pyridine to give the diol **1.110**. The corresponding *O*-protected derivatives **1.124**–**1.127** were stable to these solvolysis conditions. These results imply that the observed methanolysis in the diesters **1.109**, **1.119** and **1.120** is assisted by the free transannular hydroxyl group.[30]



Scheme 1.9. (a) pyridine, methanol, rt, 60 h for **1.109**; 56 h for **1.119** and 18 h for **1.120**.

1.2.5. Deoxygenation of inositol derivatives

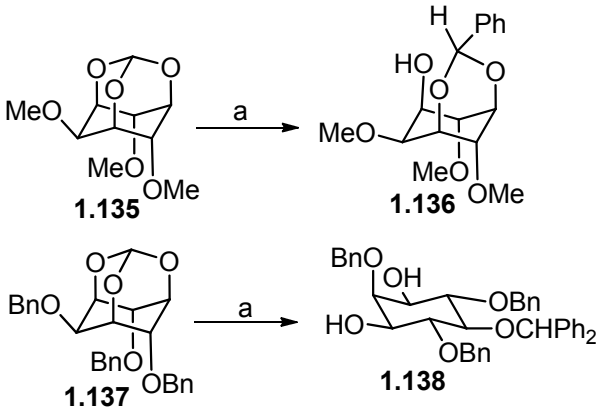
Barton - McCombie reaction is a classical method for the conversion of alcohols to the corresponding hydrocarbon;[31] the corresponding xanthate is an intermediate in this reaction sequence and deoxygenation occurs *via* a radical mechanism. An unusual dependence of the result of this deoxygenation reaction on the nature of the acetal present in certain protected inositol derivatives has been reported.[32] Deoxygenation of the C5-hydroxyl group *via* its xanthate **1.128** (Scheme 1.10) carrying a methylidene acetal gave the corresponding C5-deoxygenated product, **1.129** while the same reaction on an analog **1.131** carrying a benzylidene acetal resulted in the formation of the C3, C5-dideoxygenated product **1.132**. Hence this reaction could be used to prepare either a monodeoxy inositol **1.130** or a dideoxy inositol **1.133** by changing the protecting groups on the C1 and C3 hydroxyl groups from methylidene acetal to the corresponding benzylidene acetal. Monodeoxygenation could also be carried out by using the corresponding 1, 3-diol **1.134**.



Scheme 1.10. (a) *n*–Bu_3SnH, AIBN, toluene, reflux; (b) THF:H_2O, HCl, reflux; (c) MeOH, H_2 (60 psi), 20% $Pd(OH)_2$/C, rt; (d) MeOH, *iso*-butylamine, reflux.

1.2.6. Cleavage of inositol orthoesters with Grignard reagents

myo-Inositol 1,3,5-orthoformates can be cleaved using Grignard reagents. This reaction is strongly dependent on the groups used to protect the C2, C4 and C6 hydroxyl groups (Scheme 1.11).[32] Cleavage of the trimethyl ether **1.135** with phenylmagensium bromide gave the corresponding 3,5-benzylidene acetal **1.136** whereas the tribenzyl ether **1.137** gave the 1,3–diol **1.138** under identical conditions. Reason for this contrast in product formation brought about by remote protecting groups is not clear.



Scheme 1.11. (a) PhMgBr, THF, 0 ^oC–rt.

1.3. Conclusions

A comparison of similar reactions of inositol derivatives carrying different protecting groups shows that selectivity in reactions of inositol hydroxyl groups or its derivatives can be modified by varying the protecting groups utilized during a synthetic sequence. Hence the results presented here gives new insight into the effect of protecting groups on the outcome of reactions rather than merely looking at protecting groups as masking agents for functional groups exhibiting similar reactivity.

1.4. References

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Chapter 2

The effect of protecting groups and the orientation of the *β*-hydroxyl / alkoxyl group on the hydride reduction and the Grignard reaction of an inosose: efficient synthesis of *epi*-inositol, its *O*-methyl and *C*-methyl derivatives

2.1. Introduction

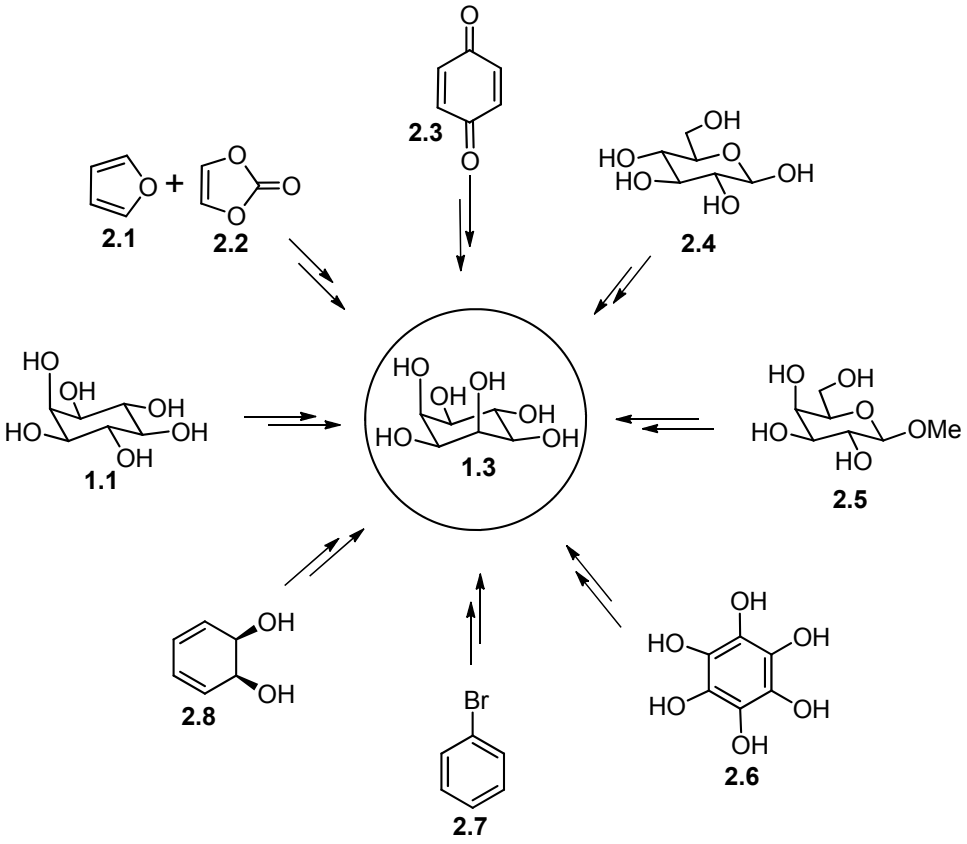
As elaborated in the first chapter, reactivity and selectivity in reactions of small molecules containing several functional groups such as inositols could be dependent on the protecting groups used to mask other groups in the same molecule. Conversely, it should be possible to alter the regio- and stereoselectivity of reactions of inositol derivatives to our advantage by manipulation of the protecting groups. But it is surprising to see that this conceptually simple approach has not been exploited to the extent possible for the preparation of analogs of *myo*-inositol. The present chapter describes a study of inososes in this perspective and its use in efficient synthesis of inositol isomers and their *O*-methyl and *C*-methyl derivatives from naturally abundant *myo*-inositol. It is seen that the hydride reduction of penta-protected *epi*-inosose to *epi*-inositol is far more selective than the corresponding un-protected inosose. Also presence of *β*-axial hydroxyl group (free or *O*-protected) relative to the keto group, in inososes enhances the selectivity towards the formation of the product containing 1,3-diaxial hydroxyl groups (or its *O*-protected derivative) during addition to the carbonyl group.

2.2. *epi*-Inositol: a historical perspective

epi-Inositol (**1.3**), a cyclohexane hexol having two axial and four equatorial hydroxyl groups is a member of the cyclitol family. *epi*-inositol (**1.3**) is unnatural and hence an expensive isomer. *epi*-Inositol is biologically active in its ability to affect the regulation of the *myo*-inositol biosynthetic pathway. *epi*-Inositol has also been evaluated as a potential antidepressant drug that could interact with lithium ion and *myo*-inositol receptors in the brain.[1] *epi*-Inositol **1.3** and racemic *epi*-inosose were tested for their ability to inhibit phospatidylinositol-specific phospholipase C (PI-PLC) from *Bacillus cereus*, (IC_{50} for *epi*-inositol, 2 mM; IC_{50} for racemic *epi*-inosose, 3 mM).[2] Also it was found that at a concentration of 0.1 mM *epi*-inositol could induce glucose uptake, indicating their significant insulin-mimetic activity.[3] Shaldubina and co-workers have shown that *epi*-inositol has the ability to modify the expression of the yeast *INO1* gene encoding the *myo*-inositol-3-phosphate synthatase.[4] Also L-*epi*-2-inosose provides beneficial effects in the treatment of Alzheimer's disease, dementia and mild cognitive impairment.[5]

2.3. Known methods for the synthesis of *epi*-inositol

Several synthetic routes for *epi*-inositol, starting from furan,[6] D-glucose,[7] *myo*-inositol,[8] *p*-benzoquinone,[9] and benzene derivatives[10,11] are reported in the literature. Some of the deficiencies of the methods shown in scheme 2.1 are noted below.



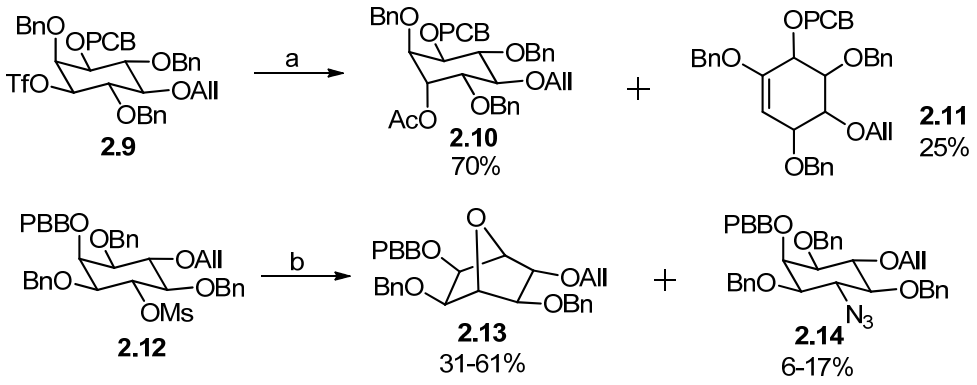
Scheme 2.1. Various starting materials used for the synthesis of *epi*-inositol.

Conversion of *myo*-inositol to *epi*-inositol was realized perhaps, first by Posternak,[8a] *via* hydrogenation of pentacetyl *epi*-inosose using platinum oxide as catalyst. During the early phase of the development of the chemistry of inositols, most of these polyols were handled as their acetates, which were later realized to undergo extensive migration among the hydroxyl groups[12] and the use of ester derivatives was discontinued. Reymond *et al.*[8b] converted *myo*-inositol to *epi*-inositol *via* the sodium borohydride reduction of *epi*-inosose[8a] in an overall yield of 10-12%. This method did not involve protection-deprotection sequence of the *myo*-inositol hydroxyl groups.[8b] The Diels-Alder reaction between **2.1** and **2.2** gave a mixture of both *endo*- (17%) and *exo*- (3%) adducts but only the minor *exo* adduct was useful for the preparation of *epi*-inositol. Also, most of the subsequent synthetic steps were low yielding.[7c] Synthesis

of *epi*-inositol from derivatives of glucose (**2.4**) and galactose by the Ferrier reaction led to a mixture of inososes, and the required isomer (52%) had to be separated by chromatography. Pistará and co-workers[7b] also synthesized *epi*-inositol from methyl-*β*-D-galactopyranoside (**2.5**). Although this synthesis starts from easily available **2.5**, this is not an efficient method as it is lengthy and initial steps of the synthesis are low yielding. Ferrier II reaction, which converts pyranose ring to a carbocyclic ring, gave a mixture of inososes; the major product (obtained in 60% yield) was utilized for the synthesis of *epi*-inositol.

Carless and co-workers[10] synthesized *epi*-inositol from *cis*-1,2-cyclohexadienediol **2.8**, which was obtained by microbial (*Pseudomonas putida*) oxidation of benzene. The method of Carless and co-workers also generated isomeric polyols during the hydroxylation reactions of C-C double bonds, which contributes to the reduction in overall yield of *epi*-inositol. Vitelio reported a comparatively good method for the synthesis of *epi*-inositol from bromo benzene (**2.7**) with 34% overall yield.[11b]

Synthesis of *epi*-inositol from *myo*-inositol (**1.1**) and inositol derivatives[8] requires the protection of inositol hydroxyl groups. This usually yields a mixture of isomeric *O*-protected inositol derivatives, which need to be separated. However previously reported synthesis of *epi*-inositol from *myo*-inositol from our laboratory (with 33% overall yield in 10 steps)[8f] has the potential to generate orthogonally protected *epi*-inositol derivatives. *epi*-Inositol can be obtained from *myo*-inositol by inverting the hydroxyl group at the C4 position. Inversion of hydroxyl group in inositols or their derivatives can be achieved either by nucleophilic substitution reaction or by oxidation-reduction sequence. Inversion with the help of nucleophilic substitution reaction is not convenient as it could lead to elimination or formation of bicyclic products along with the desired product.[8f,13] For example, the triflate **2.9** on reaction with cesium acetate gave the elimination product **2.11** along with the expected *chiro*-acetate **2.10** (Scheme 2.2). The mesylate **2.12** upon treatment with sodium azide gave the bicyclic compound **2.13** as the major product and the un-desired azide **2.14** as the minor product.



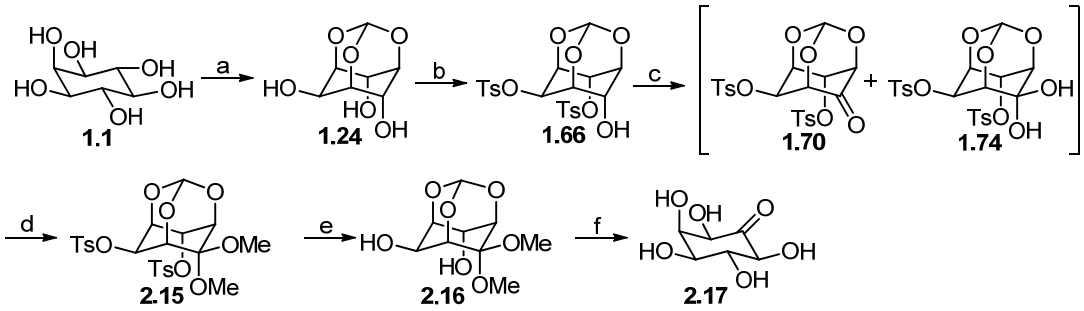
Scheme 2.2. (a) Benzene, CsOAc, 18-crown-6, reflux, 2 h; (b) DMF, NaN_3, rt.

Hence oxidation - reduction sequence of inositol hydroxyl groups is routinely adopted for the inversion of configuration of the inositol ring carbon atoms.[7b,8c,14] This two-step process is a convenient way of generating diastereomeric inositols, provided stereoselectivity of the reduction process can be controlled to generate only one diastereomer, which circumvents the need for separation of isomeric polyols or their *O*-protected derivatives.

2.4. Results and discussion

2.4.1. Synthesis of *epi*-inositol from racemic *epi*-inosose

Racemic *epi*-inosose (**2.17**) was synthesized in 42% overall yield in 6 steps, from *myo*-inositol (**1.1**) using orthoformate for the protection of C1, C3 and C5-hydroxyl groups (Scheme 2.3). Previous experience in our laboratory had shown that *myo*-inositol orthoesters and their derivatives can be obtained as single products in good yields.[8f,15]

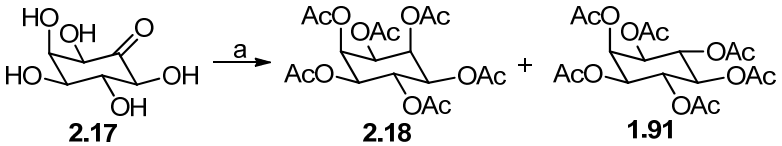


Scheme 2.3. (a) DMF, PTSA, $HC(OEt)_3$, 100 °C, 4 h, Et_3N, rt, 30 min., 94%; (b) py., TsCl, 90 °C, 48 h, 80%; (c) DMSO, $(COCl)_2$, DCM, Et_3N, –78 °C, 82%; (d) DMF, Ag_2O, MeI, rt, 24 h, 92%; (e) NaOMe, MeOH, reflux, 12 h, 75%; (f) TFA–H_2O, rt, 24 h, 99%.

Swern oxidation of **1.66**[16] gave a mixture of the ketone **1.70** and the gem-diol **1.74**. Methylation of a mixture of **1.70** and **1.74** gave the ketal **2.15** exclusively. We

solvolyzed the tosylates in **2.15** before the deprotection of the orthoformate, since cleavage of the orthoformate first would restore the normal chair conformation of the inositol ring, and the tosylates would then be amenable for elimination reactions and perhaps could lead to aromatization of the inositol ring as well.[17] Presence of the orthoformate moiety retains the rigidity of the adamantane type of structure and ensures clean solvolysis of the two tosylates in **2.15**. The ketal **2.16** on hydrolysis gave racemic *epi*-inososе (**2.17**).

Racemic *epi*-inososе (**2.17**) was reduced with different reducing agents under different conditions in water (Scheme 2.4) and the results are shown in Table 2.1. In all the experiments a mixture of *myo*- and *epi*-inositols was obtained. The ratio of *myo*-inositol to *epi*-inositol was estimated by ^{1}H NMR spectroscopy of the mixture of hexa acetates **1.91** and **2.18** since the *epi*-hexa acetate **2.18** and the *myo*-hexaacetate **1.91** show distinct peaks at δ2.17 and δ2.21 respectively.[8c,18]



2.17 **2.18** **1.91**

Scheme 2.4. (a) As mentioned in table 2.1.

Table 2.1. Reduction of racemic *epi*-inososе (**2.17**) with borohydride in water.

Sr. No.	Brohydride[a]	Temp ºC	*epi*-**2.18**:*myo*-**1.91** [b]
1	$NaBH_4$	0	Complex mixture
2	$NaBH_4$	Ambient	90:10
3	$NaBH_4$	55	89:11
4	$NaBH_4$	90	91:9
5	KBH_4	Ambient	91:9
6	KBH_4	55	90:10
7	$LiBH_4$	55	50:50
8	$NaCNBH_3$	90	53:47

[a]20 equiv. of the reducing agent was used, reaction time was 24 h; [b]the ratio of hexaacetates was estimated by ^{1}H-NMR spectroscopy; acetylation of the mixture of inositols obtained was carried out with acetic anhydride in dry pyridine.

All our attempts to improve the selectivity for the reduction of *epi*-inososе (**2.17**) to *epi*-inositol were unsuccessful. We could not use other solvents for the reduction of **2.17** due to its poor solubility in solvents other than water.

2.4.2. Comparison of the crystal structures of racemic-*epi*-inosose (2.17) and (-)-*epi*-inosose (*L*-2.17)

Good quality prism shaped crystals of racemic *epi*-inosose (**2.17**) were obtained by slow evaporation of a hot aqueous solution of **2.17**. The crystal structure was solved by single crystal X-ray diffraction method (Figure 2.1).

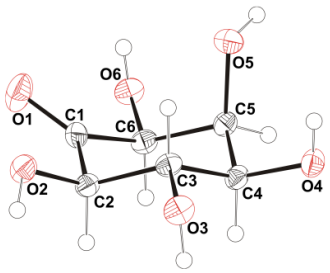


Figure 2.1. ORTEP of racemic *epi*-inosose (**2.17**). Displacement ellipsoids are drawn at 50% probability level and H atoms are shown as small spheres of arbitrary radii.

A Cambridge Structural Database search revealed that the structure of the optically active (-)-*epi*-inosose (***L*-2.17**) was reported earlier [CSD (version 5.31) reference code: XEGVUA].[19] We were thus presented with an opportunity for the comparison of the molecular assembly in the crystals of these racemic and chiral inososes. Single-crystal X-ray intensity measurements for crystals of racemic *epi*-inosose (**2.17**) were recorded at ambient temperature (297 K) as reported for optically active (-)-*epi*-inosose (**L-2.17**). Crystals of the racemic ketone **2.17** are orthorhombic, belonging to the space group $Pca2_1$, while the chiral ketone **L-2.17** crystallizes in the noncentrosymmetric space group $P2_1$, with two independent molecules in the asymmetric unit. The overlap of the molecules in the asymmetric unit of **L-2.17** and the corresponding enantiomer in racemic **2.17** reveals orientational differences in the hydroxyl hydrogen atoms at C3 and C4 (Figure 2.2).

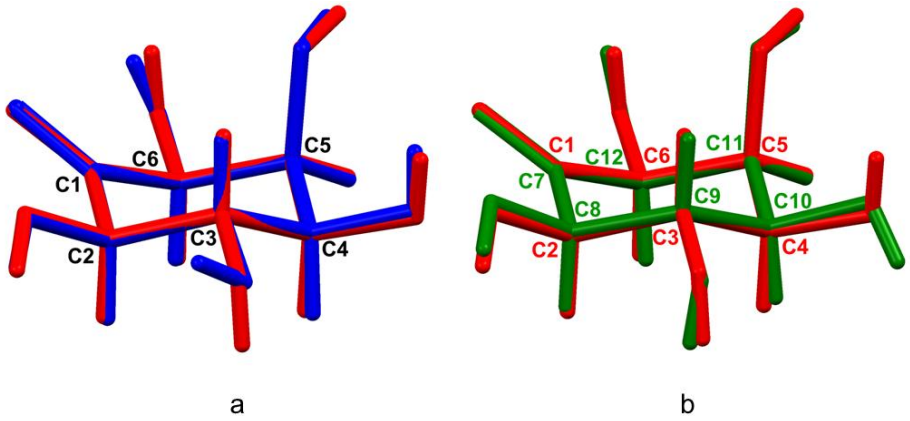


Figure 2.2. The overlap of the molecules in crystals of (-)-*epi*-inosose, (***L*-2.17**), and racemic *epi*-inosose, (**2.17**), showing the differences in the orientations of the hydroxy groups. In (a), one of the two independent molecules in the asymmetric unit of **L-2.17** (blue) and the corresponding enantiomer in **2.17** (red) is shown, while in (b) the second independent molecule in the asymmetric unit of **L-2.17** (green) and the corresponding enantiomer in **2.17** (red) is shown.

In accordance with Wallach's rule[20] the racemic crystal is 1.7% denser than the enantiomeric crystal. The unit cell of racemic **2.17** consists of four molecules *i.e.* two pairs of enantiomers, whereas that of **L-2.17** contains two pairs of the two symmetry independent molecules of the asymmetric unit. The presence of five hydroxyl groups and a ketone carbonyl results in extensive hydrogen bonding interactions in both the crystals.

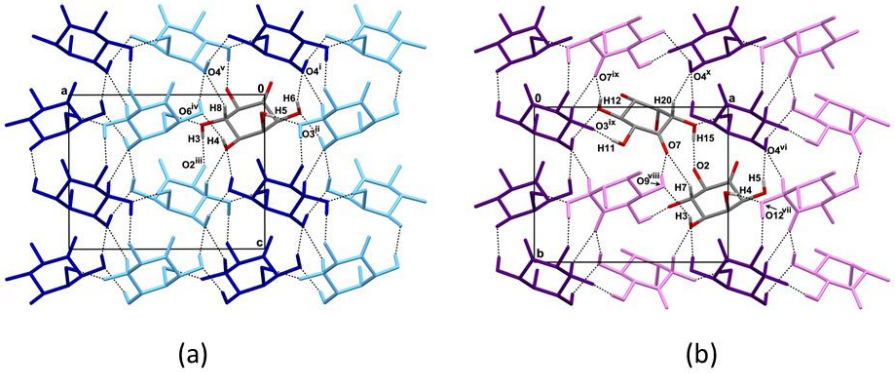


Figure 2.3. Chains of molecules linked through hydrogen-bonding interactions (dotted lines) in the crystal structures of (a) racemic *epi*-inosose (**2.17**) and (b) (-)-*epi*-inosose (***L*-2.17**). The different colors represent the enantiomers of **2.17** in (a) (dark blue and light blue) and the independent molecules in the asymmetric unit of **L-2.17** in (b) (purple and light pink). H atoms not involved in hydrogen bonding have been omitted. [Symmetry codes: (ii) -x + 1/2, y, z + 1/2; (iii) x + 1/2, -y, z; (iv) x-1/2, -y, z; (v) -x, -y, z-1/2; (vii) -x + 1/2, y, z -1/2; (viii) -x + 2, y -1/2, -z; (ix) -x + 2, y + 1/2, -z; (x) -x + 1, y + 1/2, -z; (xi) -x + 1, y -1/2, -z; (xii) x, y-1, z].

In the crystals of racemic **2.17**, each enantiomer forms a homochiral O6—H6···O4 hydrogen bonded chain along the *c*-axis with adjacent heterochiral molecular chains along the *a*-axis linked by short and linear O3—H3···O2, O4—H4···O6, O5—H5···O3 and C3—H8···O4 interactions (Figure 2.3a, see appendix I for H-bonding interaction parameters). In the case of **L-2.17**, each of the two molecules in the asymmetric unit, forms a similar O6—H5···O4 hydrogen bonded chain along the *b*-axis. Interestingly, the ketone carbonyl oxygen (O7) of only one of the molecules (molecule B) is involved in O—H···O hydrogen bonding (O9—H12···O7), because of the conformational differences in the hydroxyl groups of the two molecules in the asymmetric unit. The adjacent molecular chains along the *a*-axis are linked by a large number of hydrogen bonding interactions (Figure 2.3b).

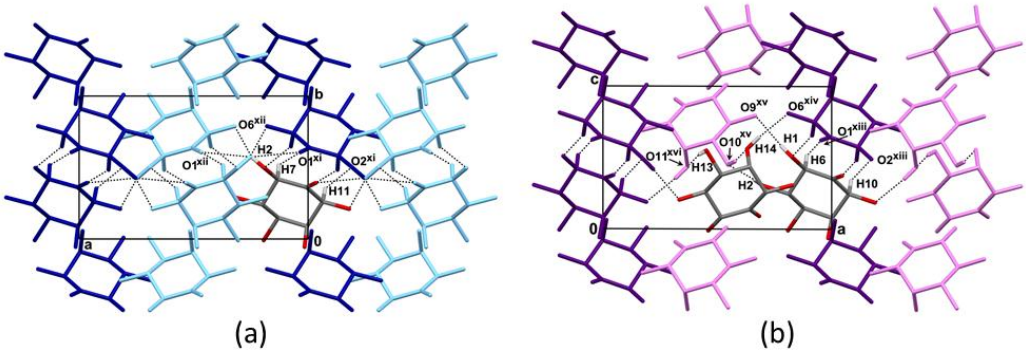


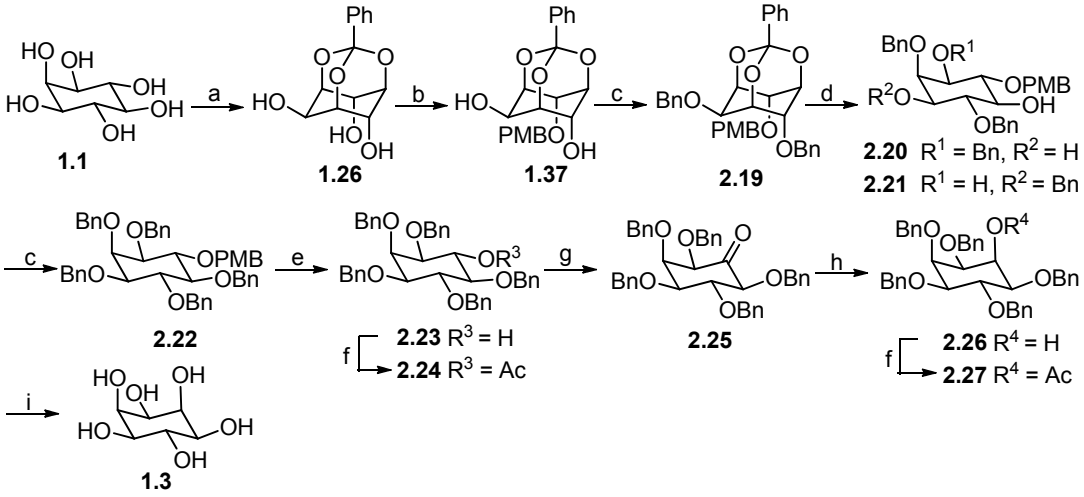
Figure 2.4. A view of the molecular packing (a) down the c axis in crystals of racemic *epi*-inosose (**2.17**) and (b) down the b axis in crystals of (-)-*epi*-inosose (**L-2.17**). Dotted lines represent hydrogen-bonding interactions, some of which (shown in Figure 2.3) have been omitted for clarity. [Symmetry codes: (i) x + 1/2, -y + 1, z; (vi) -x, -y + 1, z + 1/2; (xiii) x + 2, y + 1/2, -z + 1; (xiv) -x + 2, y-1/2, -z + 1; (xv) -x + 1, y + 1/2, -z + 1; (xvi) -x + 1, y-1/2, -z + 1].

A view of these molecular chains down the *c*-axis in racemic **2.17** and *b*-axis in **L-2.17** shows a corrugated sheet-like assembly (Figure 2.4). Thus, the overall molecular organization in the crystals of the racemic and chiral compounds is remarkably similar. This is primarily due to the fact that the second molecule in the asymmetric unit of **L-2.17** plays the role of the second enantiomer in the crystal packing in racemic **2.17**.

2.4.3. Synthesis of *epi*-inositol *via* a penta-*O*-protected inosose

We next attempted the conversion of *myo*-inositol to *epi*-inositol by using a completely protected derivative of inosose. We thought this could be advantageous since such a derivative would be soluble in organic solvents and hence amenable to

reduction in different solvents, thus widening the scope for improvement in selectivity during its reduction. Accordingly we prepared the penta *O*-protected *epi*-inososse **2.25** (Scheme 2.5) from the known racemic PMB ether **1.37**.[8f] The racemic PMB ether **1.37** on benzylation with excess sodium hydride and benzyl bromide afforded the corresponding dibenzyl ether **2.19**. The orthobenzoate moiety in **2.19** was reduced with DIBAL–H to obtain a mixture of diols **2.20** and **2.21**. Benzylation of this mixture of diols afforded the pentabenzyl ether **2.22**. The PMB ether in **2.22** was cleaved using HCl to afford the alcohol **2.23**; oxidation of **2.23** with IBX gave the protected *epi*-inososse **2.25**. Reduction of the *epi*-inososse **2.25** with sodium borohydride was stereoselective to yield the corresponding *epi*-alcohol **2.26** with about 98% selectivity. The pentabenzyl ether **2.26** was isolated by column chromatography. Global deprotection of **2.26** by hydrogenolysis afforded *epi*–inositol **1.3** as a colorless solid in an overall yield of 52% in 9 steps, starting from *myo*-inositol.

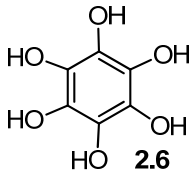
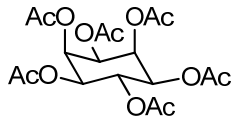
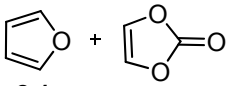
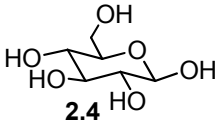
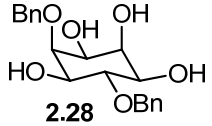
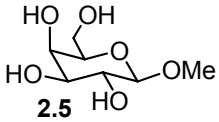
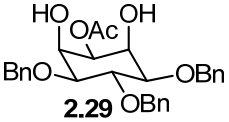
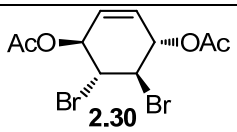
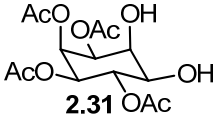
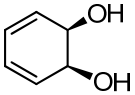
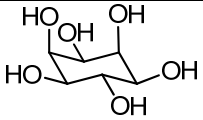
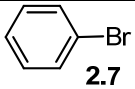
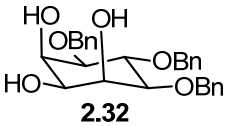


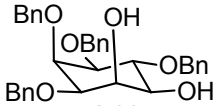
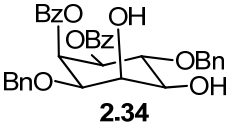
Scheme 2.5. (a) DMSO, CSA, $PhC(OMe)_3$, 100 °C, 4 h, Et_3N, rt, 30 min. 93%; (b) DMF, NaH, PMBCl, 86%; (c) DMF, NaH, BnBr, 16 h, 96% (for **2.19**); 81% (for **2.22**, over two steps); (d) DCM, 1M DIBAL–H in toluene, 20 h; (e) DCM-MeOH, conc. HCl, reflux, 6 h, 93%; (f) py., DMAP, Ac_2O, reflux, 18 h, 95% (for **2.24**); 92% (for **2.27**); (g) IBX, EtOAc, reflux, 6 h, 94%; (h) $NaBH_4$, DCM:MeOH (4 : 1), 30 min, 94%; (i) 20% $Pd(OH)_2/C$, THF-H_2O-TFA, H_2 (60 *psi*), rt, 20 h, 96%.

Selective reduction of the protected *epi*-inososse **2.25** to the *epi*-alcohol **2.26** with >98% selectivity was also confirmed by conversion of the crude product to the corresponding acetate and its scrutiny by ^{1}H NMR spectroscopy (the acetate methyl peak for the *epi*-isomer **2.27** appears at δ 2.09 while the corresponding peak for the *myo*-isomer **2.24** appears at δ 1.92, see appendix I for ^{1}H NMR spectra).

A comparison of the reported methods of synthesis of *epi*-inositol with the present work is shown in Table 2.2. Yield of *epi*-inositol in previously reported methods was in the range 6–33% from *myo*-inositol[8] and 1–34% from other starting materials.[6,7b,7c,10,11] Apart from the lesser overall yield, many of these procedures result in a mixture of isomeric products from which the *epi*-inositol derivative needs to be separated, thus making the procedure laborious.[6,7c,8d] The present method on the other hand yields *epi*-inositol in higher yield and precludes the need for separation of products in all the synthetic steps.

Table 2.2. Comparison of the present method of synthesis of *epi*-inositol (**1.3**) with the methods reported in the literature.

Sr. No.	Starting material	Steps	Yield ‡ (%)	*epi*-Inositol / derivative
1	 **2.6**	1	<6[11a]	**2.18** 
2	 **2.1** **2.2**	3	<1[6]	**2.18**
3	 **2.4**	8	13[7a,7c]	 **2.28**
4	 **2.5**	4	21[7b]	 **2.29**
5	 **2.30**	9	7[9]	 **2.31**
6	 **2.8**	3	<18[10]	 **1.3**
7	 **2.7**	6	34[11b]	*epi*-inositol (**1.3**)
8	*myo*-inositol (**1.1**)	5	<10[8a]	**2.18**
9	*myo*-inositol (**1.1**)	4	<10[8b]	**1.3**
10	*myo*-inositol (**1.1**)	12	15[8c]	 **2.32**

11	*myo*-inositol (**1.1**)	4	6[8d]	 **2.33**
12	*myo*-inositol (**1.1**)	9	6[8e]	 **2.34**
13	*myo*-inositol (**1.1**)	10	33[8f]	**1.3**
14	*myo*-inositol (**1.1**)	9	52[§]	**1.3**

[‡]Overall yield refers to the products shown in the last column; [§]Present work.

Perusal of the earlier reports[7,8c,8f] on the synthesis of *epi*-inositol revealed that the hydride reduction of the protected inososes **2.35**, **1.107** and **2.36** (Chart 2.1) were also selective to yield the corresponding *epi*-isomer.

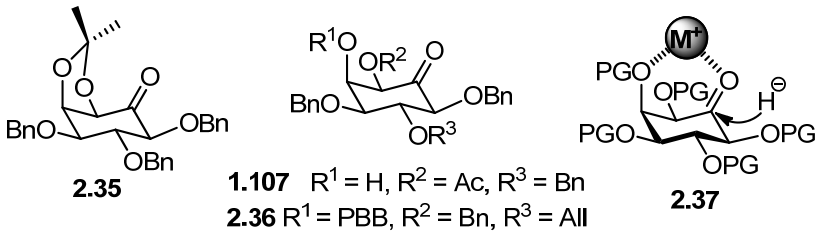


Chart 2.1. *O*-Protected *epi*-inososes that undergo stereoselective hydride reduction.

We are of the opinion that higher selectivity in hydride reduction of the fully protected *epi*-inososes (in contrast to the reduction of unprotected ketone **2.17**) arises due to their ability to complex the metal ions of the reducing agent which forces the hydride to approach the carbonyl group as shown in **2.37** (Chart 2.1) to yield the axial alcohol. Earlier reports also show that cyclitols which have a sequence of three hydroxyl groups in the axial-equatorial-axial arrangement (as in *epi*-inositol) form complexes with metal cations.[21] This supports our hypothesis (as shown in **2.37**). Also, the *epi*-inosose (**2.17**) gives a mixture of products perhaps because its chelation with metal ions is not expected to be strong enough in water (as compared to that in organic solvents) to facilitate the approach of the hydride from one face of the carbocyclic ring. A comparison of the ^{1}H NMR spectra of the mixture of products obtained by the reduction of *epi*-inosose (**2.17**) and the corresponding penta-protected derivative **2.25** reveals the effect of the hydroxyl group protection on the outcome of the hydride reduction of these ketones (Figure 2.5). A similar effect due to the protecting groups is also seen on comparison of the hydride reduction of *scyllo*-inosose and its penta benzyl ether. The ratio of axial (*myo*-): equatorial (*scyllo*-)

alcohols formed on reduction of the former (un-protected inosose **1.90**) was 45:32 (Table 2.3, entry 2, section 2.4.4) while on reduction of the latter (fully protected inosose **2.40**) was 80:20 or better (Table 2.3, entry 8).

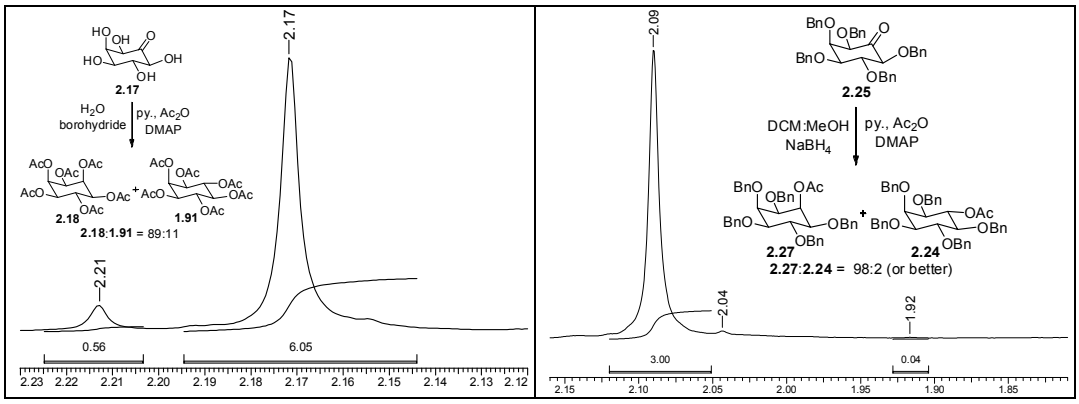


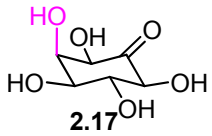
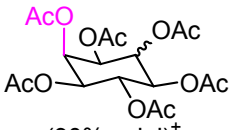
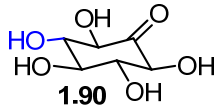
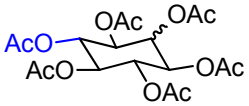
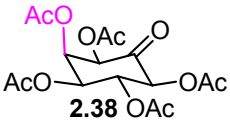
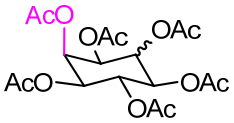
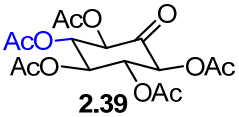
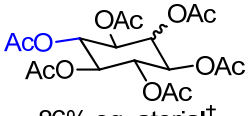
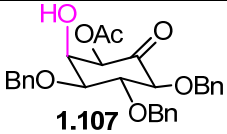
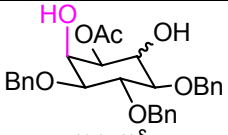
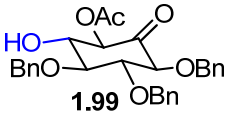
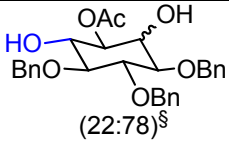
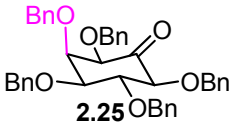
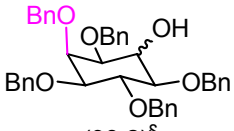
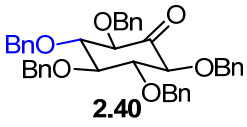
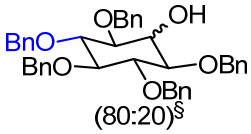
Figure 2.5. Relevant regions of the ^{1}H NMR spectra of the products of reduction of *epi*-inososes **2.17** and **2.25**.

The foregoing discussion also implies that the outcome of the hydride reduction of an inosose could be dependent on the orientation of the *β*-hydroxyl group with respect to the carbonyl group. This is because all the ketones (**2.25**, **2.35**, **1.107** and **2.36**) that were reduced with very high selectivity for the *epi*-isomer contain an axial *β*-hydroxyl group (*β*-hydroxy ketone). Hence we compared the outcome of the hydride reduction of cyclohexanones which have an axial *β*-hydroxyl group (or its protected derivative) with their epimeric derivatives (equatorial *β*-hydroxyl group or its protected derivative). We also carried out Grignard reaction on (*epi*- and *scyllo*-) inososes which differ in the orientation of the *β*-alkoxyl group (with respect to the carbonyl group).

2.4.4. Effect of the orientation of the *β*-hydroxyl group (or its protected derivative) on the hydride reduction of cyclohexanones

A comparison of the result of hydride reduction of inososes and other cyclohexanones containing a *β*-hydroxyl group (or its protected derivative) is shown in Tables 2.3 and 2.4. The inososes in the odd numbered entries (in Table 2.3) have a *β*-hydroxyl group (or its protected derivative) in the axial orientation while the inososes in the even numbered entries have a *β*-hydroxyl group (or its protected derivative) in the equatorial orientation. Results of hydride reduction of these pairs of inososes clearly show that the stereo selectivity of reduction (to yield the axial alcohol) is much better when the *β*-hydroxyl group (or its protected derivative) is in the axial orientation.

Table 2.3. Result of sodium borohydride reduction of inososes, which differ only in the orientation of the *β*-hydroxyl group (or its protected derivative).

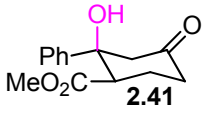
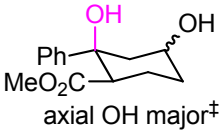
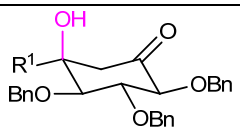
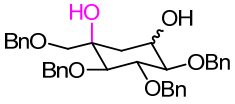
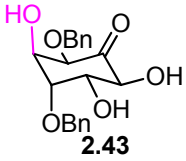
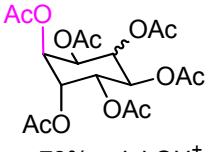
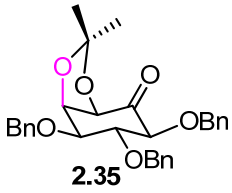
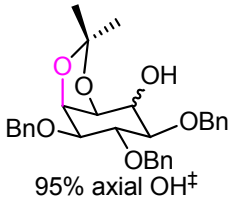
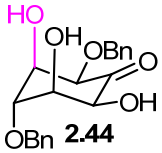
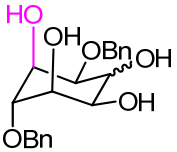
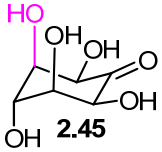
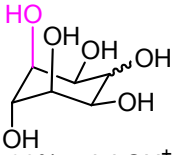
Sr. No.	Ketone	Conditions	Products (ax:eq)	Reference
1	 **2.17**	Reduction in absolute alcohol or water then acetylation	 (90% axial)‡ (89:11) §	8b **Present Work**
2	 **1.90**	Reduction in absolute alcohol then acetylation	 (45:32)‡	8b
3	 **2.38**	Reduction in absolute methanol (*p*H=3) then acetylation	 90% axial‡	8c
4	 **2.39**	Reduction in absolute methanol (*p*H=8) then acetylation	 86% equatorial‡	8c
5	 **1.107**	MeOH	 (99:1)§	7c
6	 **1.99**	MeOH	 (22:78)§	7c
7	 **2.25**	Reduction in DCM:MeOH (4:1) then acetylation	 (98:2)§	**Present work**
8	 **2.40**	Reduction in DCM:MeOH (4:1) then acetylation	 (80:20)§	see scheme 2.8 and figure 2.6

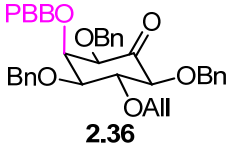
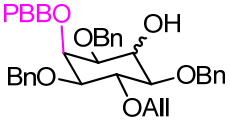
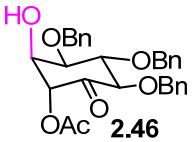
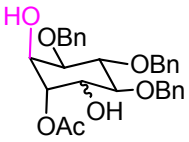
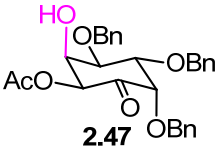
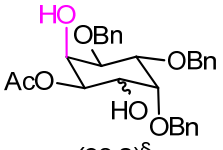
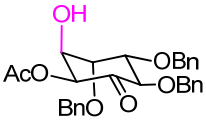
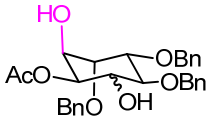
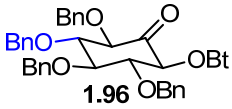
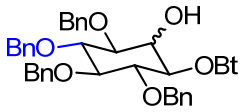
‡ Ratio determined by isolating products. § The ratio of the diastereomers was estimated by ^{1}H NMR spectroscopy.

Table 2.4 lists the results of the reduction of ketones having an axial *β*-hydroxyl group (or its protected derivative) for which exact comparison (as shown in Table 2.3) is not available. However these ketones also result in the formation of the

axial alcohol as the major product on hydride reduction[7b,7c,8c,8f,22] except the *scyllo*-inosose derivative (last entry, Table 2.4)[14b] which gives the equatorial alcohol as the major product (because both the alkyloxy groups *β*-to the keto group are in the equatorial orientation). From these results it is clear that the orientation of the *β*-hydroxyl group (or its protected derivative) plays a decisive role in the stereochemical outcome of the reduction of cyclohexanones.

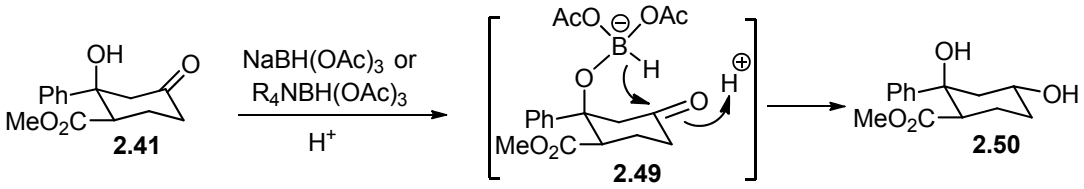
Table 2.4. Result of sodium borohydride reduction of cyclohexanones having a *β*-hydroxyl group (or its protected derivative).

Sr. No.	Ketone	Solvent	Products (ax:eq)	Reference
1	 **2.41**	^{i}PrOH or THF	 axial OH major‡	22a
2	 **2.42** $R^1 = CH_2OBn$	THF:MeOH (1:4)	 91% axial OH‡	22b
3	 **2.43**	EtOH	 78% axial OH‡	22c
4	 **2.35**	EtOH	 95% axial OH‡	8c
5	 **2.44**	MeOH	 90% axial OH‡	7b
6	 **2.45**	MeOH	 90% axial OH‡	7b

7	 **2.36**	THF:MeOH	 93% axial OH‡	8f
8	 **2.46**	MeOH	 (87:13)§	7c
9	 **2.47**	MeOH	 (98:2)§	7c
10	 **2.48**	MeOH	 (98:2)§	7c
11	 **1.96**	Ratio of the products formed depends on the solvent and temperature		14b

‡ Ratio determined by isolating products. § The ratio of the diastereomers was estimated by ^{1}H NMR spectroscopy.

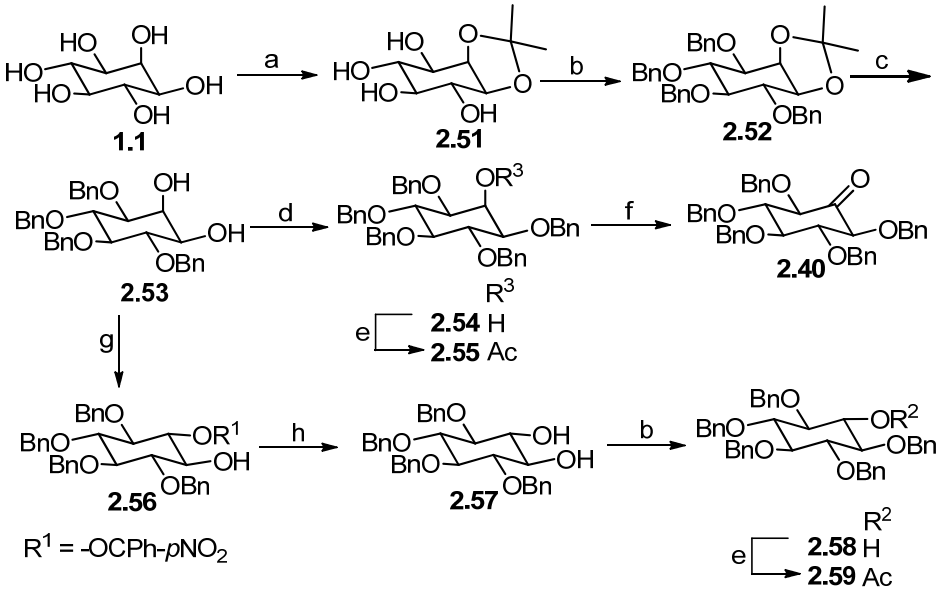
Use of bulky hydride reducing agents such as sodium triacetoxyborohydride for the reduction reverses the selectivity in most of the ketones listed in Tables 2.3 and 2.4. The course of this reaction is suggested to proceed as shown in Scheme 2.6[7a,7c,22,23]



Scheme 2.6. Reduction of *β*-hydroxy cyclohexanone using triacetoxyborohydride.

To confirm the effect of orientation of the *β*-hydroxyl group on the selectivity of reduction of inososes, we prepared (Scheme 2.7) and reduced penta-*O*-benzyl *scyllo*-inosose **2.40** (Scheme 2.8). For this purpose *myo*-inositol derived diol **2.53**[24] was converted to penta-*O*-benzyl-*myo*-inositol **2.54** by benzylation with sodium

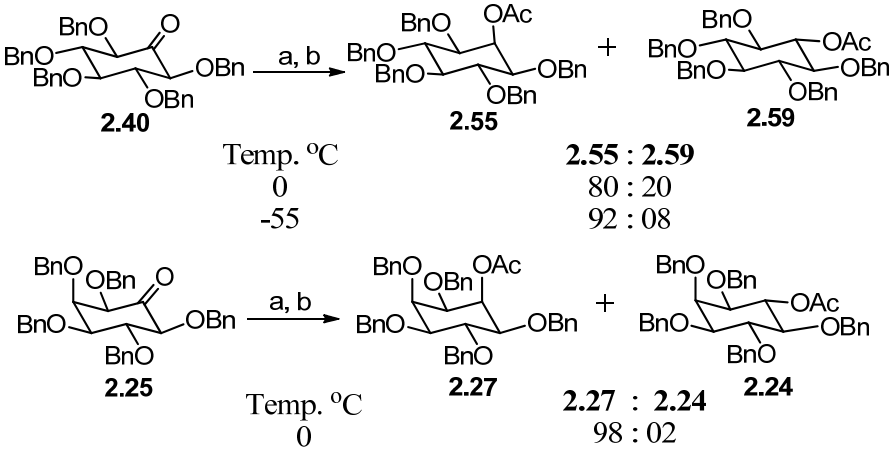
hydride and benzyl bromide in benzene.[25] The *myo*-alcohol **2.54** on oxidation with IBX in ethyl acetate gave the *scyllo*-inososе **2.40**. The *myo*-diol **2.53** was converted to the *scyllo*-inositol derivative **2.56** by Mitsunobu reaction (Scheme 2.7).[26] Hydrolysis of the benzoate in **2.56** afforded the *scyllo*-diol **2.57**, which on mono-*O*-benzylation gave the penta-*O*-benzyl *scyllo*-inositol **2.58**. The *myo*- and *scyllo*- inositol derivatives **2.54** and **2.58** were converted to their acetates **2.55** and **2.59** respectively. These acetates were useful for the estimation (by ^{1}H NMR spectroscopy) of the ratio of the diastereomeric inositols formed on reduction of the *scyllo*-inososе **2.40**, as the two acetates **2.55** and **2.59** exhibit characteristic peaks at δ 2.17 and 1.83 respectively, in their ^{1}H NMR spectra.



Scheme 2.7. (a) DMSO, DMP, PTSA, 73%; (b) DMF, NaH, BnBr, 90% (for **2.52**), 89% (for **2.58**); (c) DCM:MeOH, conc. HCl, reflux, 30 min., 82%; (d) benzene, NaH, BnBr, reflux, 1.5 h, 78%; (e) py., DMAP, Ac_2O, reflux, 18 h, (94%, for **2.55** and 96% for **2.59**); (f) IBX, ethyl acetate, reflux, 6 h, 95%; (g) benzene, TPP, imidazole, *p*-NO_2BzOH, 89%; (h) 1% aqueous NaOH, THF-MeOH, reflux, 98%.

Results of the reduction of *scyllo*-inososе **2.40** are shown in Scheme 2.8 and the result of the reduction of the *epi*-inososе **2.25** is also given for comparison. A comparison of these results clearly shows that the reduction of the inososе having a *β*-axial hydroxyl group is more selective than the corresponding inososе having a *β*-equatorial hydroxyl group. The ratio of the products (**2.55**:**2.59** = 80:20) was estimated by ^{1}H NMR spectroscopy of the mixture of acetates (Figure 2.6). The isolated yields of the products **2.55** and **2.59** were 79% and 16%. Hence these results

clearly establish the effect of the *β*-hydroxyl group on the outcome of the reduction of inososes.



Scheme 2.8. (a) $NaBH_4$, DCM: MeOH, 0 ºC-rt, 30 min.; (b) py., DMAP, Ac_2O, reflux, 18 h.

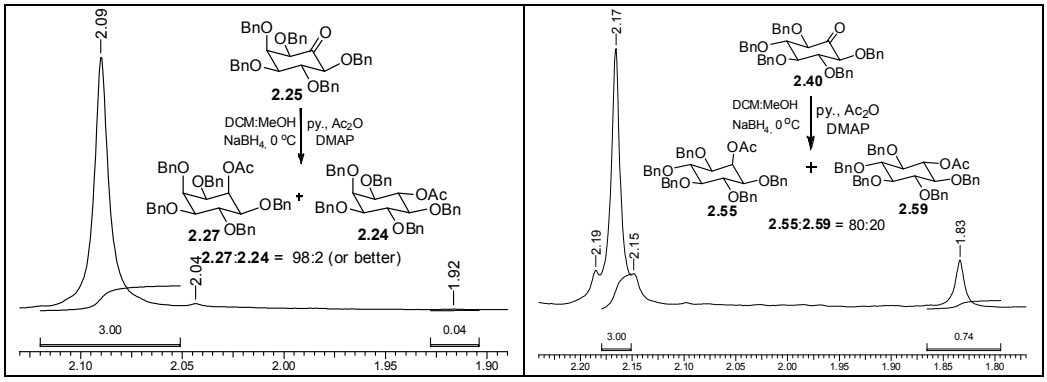
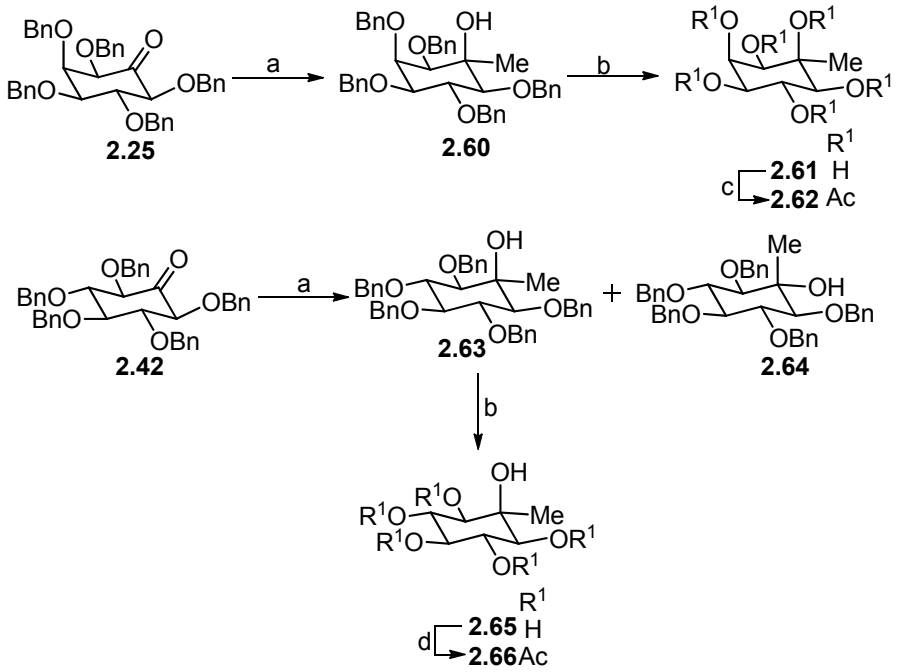


Figure 2.6. Relevant regions of the ^{1}H NMR spectra of *O*-acetylated products of the reduction of *epi*-inosose **2.25** and *scyllo*-inosose **2.40**.

2.4.5. Grignard reaction of *epi*- and *scyllo*-inososes

As expected, Grignard reaction of *epi*- and *scyllo*-inososes **2.25** and **2.40** with methyl magnesium iodide resulted in the formation of the *C*-methyl *epi*-inositol derivative **2.60** and a mixture of *C*-methyl inositol derivatives **2.63** (76%) and **2.64** (18%) respectively (Scheme 2.9). These results are similar to those obtained for the hydride reduction of the inososes **2.25** and **2.40** which suggest that the orientation of the *β*-hydroxyl group in inososes affect addition of nucleophiles to carbonyl group the same way.



Scheme 2.9. (a) MeMgI, THF, 0 °C-rt, 93% (for **2.60**); 76% (for **2.63**); 18% (for **2.64**); (b) THF:EtOH:H_2O:TFA, 20% $Pd(OH)_2$/C, H_2 (60 *psi*); (c) py., DMAP, Ac_2O, reflux, 18 h, 86%; (d) py., DMAP, Ac_2O, rt, 18 h, 88%, over two steps.

Global deprotection of **2.60** gave 2-*C* methyl *epi*-inositol (**2.61**, *iso*-laminitol) which was characterized as its hexaacetate **2.62** (43% overall yield in 8 steps starting from naturally abundant *myo*-inositol). Iso-mytilitol derivative **2.63** (76%) and mytilitol derivative **2.64** (18%) were separated by column chromatography. Global deprotection of **2.63** gave the 2-*C* methyl *myo*-inositol (**2.65**, *iso*-mytilitol) which was characterized as its pentaacetate **2.66** (27% overall yield in 8 steps starting from naturally abundant *myo*-inositol). The structure of the peracetyl derivatives **2.62** and **2.66** was confirmed by single crystal X-ray diffraction analysis (Figure 2.7).

Figure 2.7a

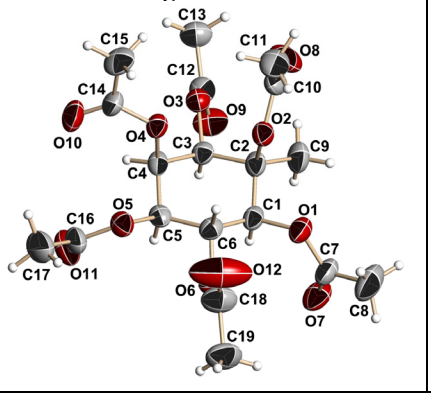


Figure 2.7b

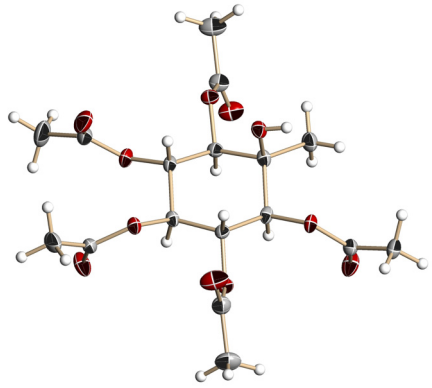
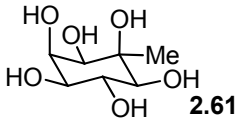
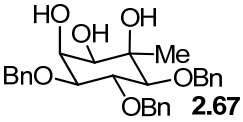
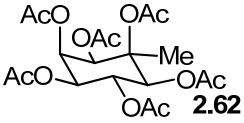
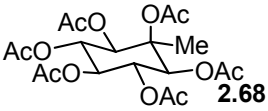
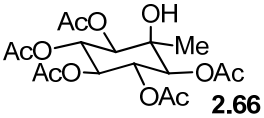


Figure 2.7. (a) ORTEP of **2.62**; (b) ORTEP of **2.66**. Displacement ellipsoids are drawn at 30% (for **2.62**) and at 50% (for **2.66**) probability level and H atoms are shown as small spheres of arbitrary radii.

Tables 2.6 compares the present methods of preparation of *C*-methyl inositols with the methods reported in the literature.[27]

Table 2.6. Comparison of the present method of synthesis of *iso*-laminitol and *iso*-mytilitol with the methods reported in the literature (starting material is *myo*-inositol).

Sr. No.	No. of Steps	Yield‡ (%)	Product	Reference
***iso*-laminitol**				
1	4	<12	 **2.61**	27b
2	9	<25	 **2.67**	8c
3	7	32	 **2.62**	**Present Work**
***iso*-mytilitol**				
1	4	<10	 **2.68**	27a
2	8	27	 **2.66**	**Present work**

‡Overall yield refers to the products shown.

iso-Laminitol (**2.61**) and *iso*-mytilitol (**2.65**) are synthetic analogs of naturally occurring *C*-methyl inositols, (–)-laminitol (**2.69**) and the symmetrical mytilitol (**2.70**) both isolated from algae (Chart 2.2).[28] Laminitol (**2.69**) inhibits the growth of *Neurospora crassa*.[29] Racemic as well as optically active laminitol[8c,30] and mytilitol,[30c,30d,31] have been synthesized.

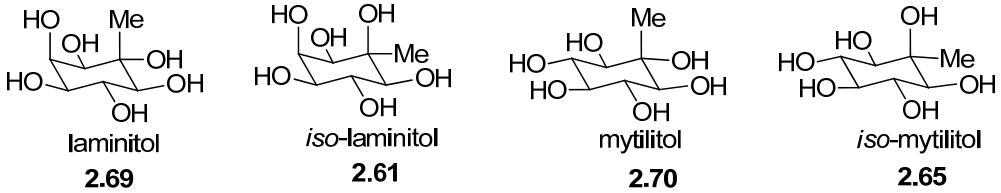


Chart 2.2. *C*-methyl derivatives of inositols.

2.4.6. Synthesis of racemic 2-*O*-methyl *epi*-inositol

Methylated inositols are abundant in grains and forage legumes.[32] Some of the known *O*-methylated inositols are shown in Chart 2.3.[33] The methyl ethers of *epi*-inositol known in the literature are 6-*O*-methyl-*epi*-inositol (**2.76**) and the hexamethyl ether **2.74**.[34] 6-*O*-Methyl-*epi*-inositol (**2.76**) was isolated from the aerial parts of *Canavalia rosea*.[35]

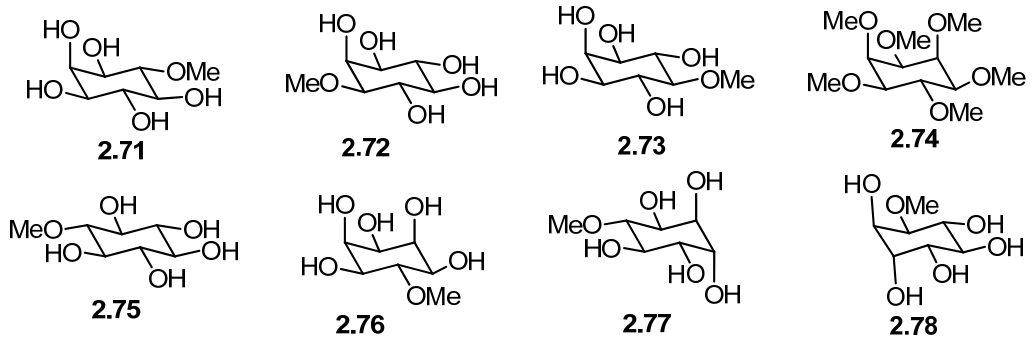
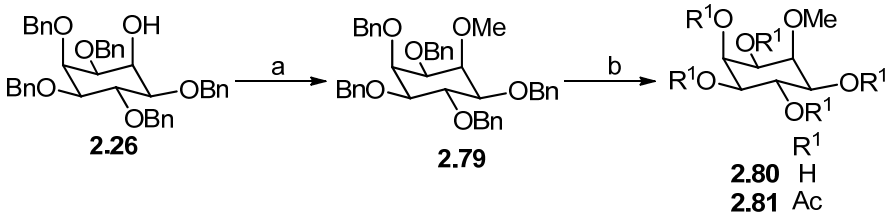


Chart 2.3. Known inositol methyl ethers.

We utilized the penta benzyl ether **2.26** of *epi*-inositol for the preparation of 2-*O*-methyl *epi*-inositol (**2.80**). The *epi*-inositol derivative **2.26** was treated with sodium hydride and methyl iodide to get the corresponding methyl ether **2.79**. Global deprotection of **2.79** by hydrogenolysis gave **2.80**, which was characterised as its penta acaetate derivative **2.81** (Scheme 2.10). Structure of the per acetyl derivative **2.81** was confirmed by a single crystal X-ray diffraction analysis (Figure 2.8). The synthesis described herein provided 2-*O*-methyl *epi*-inositol (**2.80**) in an overall yield of 41% in 9 steps starting from *myo*-inositol. This represents the first synthesis of 2-*O*-methyl *epi*-inositol (**2.80**, *iso*-ononitol).



Scheme 2.10. (a) DMF, NaH, MeI, 96%; (b) i) THF:EtOH:H_2O:TFA, $Pd(OH)_2/C$, H_2 (60 psi), 20 h; ii) py., Ac_2O, DMAP, reflux, 20 h, 83% over two steps.

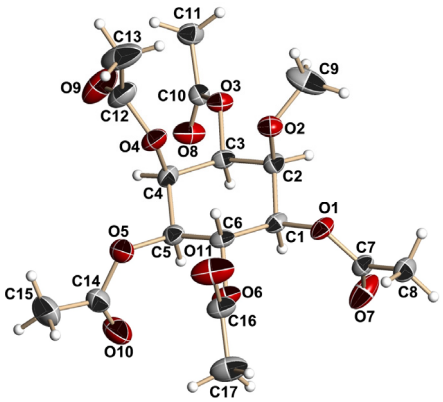


Figure 2.8. ORTEP of **2.81**. Displacement ellipsoids are drawn at 30% probability level and H atoms are shown as small spheres of arbitrary radii.

2.5. Conclusions

A comparative study of the hydride reduction and Grignard reaction of *epi*- and *scyllo*-inososes reveals the subtle role played by the hydroxyl protecting groups in the outcome of the stereoselectivity of these reactions. Since the hydroxyl protecting groups improve the selectivity of nucleophilic addition to the carbonyl groups, this could be exploited for a high yielding conversion of *myo*-inositol to *epi*-inositol. Significantly, this also results in developing a scheme for the conversion of *myo*-inositol to *epi*-inositol, wherein each step results in the formation of a single product. Similar synthetic approaches to other inositol derivatives *ie.,* synthetic schemes which provide one product in each step, had earlier been realized in our laboratory.[8f,36] Availability of such synthetic protocols greatly reduces on the labor, wastage and cost, and also reduces the time needed for achieving synthetic targets.

Another fall out of the results presented in this chapter is the effect of the orientation of the *β*-hydroxyl group or a *β*-alkoxyl group on the stereoselectivity of addition of a nucleophile to the carbonyl group, of an inosose. An axial orientation of this *β*-substituent results in better selectivity during the addition of a nucleophile to the carbonyl group. Knowledge of such effects is useful in planning a synthetic scheme and could help to avoid or minimize the formation of undesired isomeric products.

2.6. Experimental

2.6.1. 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).[37] All the data were corrected for Lorentzian and polarization effects using SAINT programs (Bruker, 2003).[37] A semi-empirical absorption correction (multiscan) based on symmetry equivalent reflections was applied by using the SADABS program (Bruker, 2003).[37] 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.[38] Molecular diagrams were generated using SHELXTL and ORTEP-32.[39]

2.6.2. General Experimental Methods

All the solvents were purified according to the literature procedure[40] before use. All air or moisture sensitive reactions were carried out in an atmosphere of argon or nitrogen. Dry DMF and dry THF were used as solvents in all the experiments involving metal hydrides. Sodium hydride used in experiments was 60% suspension in mineral oil. 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. '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, or 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 ^{1}H 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 for convenience and clarity. Compounds previously reported in the literature were characterized by comparison of their melting points and/or ^{1}H NMR spectra with the reported data.

Racemic-*epi*-inososse (2.17).

The dimethyl ketal **2.16**[41] (0.40 g, 1.70 mmol) was stirred with a mixture of trifluoroacetic acid (4 mL) and water (1 mL) at ambient temperature for 24 h. Evaporation of the solvents under reduced pressure followed by co-evaporation of the residue with toluene gave *epi*-inososse (**2.17**; 0.30 g, 99%); R_f = 0.5 (MeOH); **mp** 219–222 °C; **IR** (KBr): $\bar{\nu}$ 3176–3600, 1738 cm^{-1}; **^{1}H NMR** (200 MHz; $CDCl_3$): δ 3.72 (t, J = 9.8 Hz, 1H, Ins H), 3.84–4.05 (dd, J_1 = 2.6 Hz, J_2 = 9.8 Hz, 1H, Ins H), 4.24-4.34 (m, 2H, Ins H), 4.24–4.34 (dd, J_1 = 1.5 Hz, J_2 = 3.4 Hz, 1H, Ins H) ppm; **^{13}C NMR** (50 MHz; D_2O + MeOH): δ 71.2 (Ins C), 74.1 (Ins C), 74.7 (Ins C), 75.1 (Ins C), 76.7 (Ins C), 208.1 (Ins CO) ppm; elemental analysis calcd (%) for $C_6H_{10}O_6$: C, 40.45; H, 5.66; found C, 40.18; H, 5.44%.

Reduction of *epi*-inososse (2.17) and subsequent acetylation.

General procedure for the reduction of *epi*-inososse (2.17).

To a solution of *epi*-inososse **2.17** (0.010 g–0.05 g) in water (3 mL) borohydride (20 equiv.) was added in one portion at ambient temperature and the reaction mixture was stirred at a desired temperature for 24 h. The reaction mixture was cooled to ambient temperature and the reaction mixture was acidified with dil. HCl. The reaction mixture was concentrated under reduced pressure. The residue obtained was co-evaporated with absolute ethanol to get colorless solid which was dried *in vacuo*. This crude alcohol was suspended in dry pyridine (5 mL), DMAP (0.010 g) and acetic anhydride (1.00 mmol–5.00 mmol, 0.5 mL) were added and the mixture was refluxed for 24 h. The reaction mixture was cooled to ambient temperature and quenched by adding few pieces of ice, solvent was removed under reduced pressure and the residue

obtained was worked up with DCM or ethyl acetate to obtain a mixture of acetates (**2.18** and **1.91**), which was analyzed by ^{1}H-NMR spectroscopy.

Racemic-4-*O*-(*p*-methoxybenzyl)-2,6-di-*O*-benzyl-*myo*-inositol-1,3,5-orthobenzoate 2.19).

To a stirred solution of racemic ether **1.37** (3.86 g, 10.00 mmol) in dry DMF (30 mL) was added sodium hydride (1.00 g, 25.00 mmol) under argon at 0 ºC. The reaction mixture was stirred at 0 ºC for 10 min then at ambient temperature for 30 min. The reaction mixture was again cooled to 0 ºC and benzyl bromide (3.6 mL, 30 mmol) was added to the reaction mixture at 0 ºC and the reaction mixture was stirred at ambient temperature for 16 h. The reaction was quenched by adding few pieces of ice and the solvent was removed under reduced pressure. The residue was worked up with ethyl acetate. The crude product obtained was purified by flash column chromatography (230–400 mesh silica and eluent was 20% ethyl acetate/ light petroleum) to get racemic **2.19** (5.43 g, 96%) as a colorless solid; R_f = 0.26 (20% ethyl acetate/ light petroleum); **mp** 97–98 °C; **^{1}H NMR** (200 MHz; $CDCl_3$): δ 3.80 (s, 3H, CH_3), 4.09 (t, J = 1.5 Hz, 1H, Ins H), 4.38–4.51 (m, 6H, CH_2Ph), 4.51–4.57 (m, 2H, Ins H), 4.58–4.63 (m, 1H, Ins H), 4.67 (s, 2H, Ins H), 6.78–6.86 (m, 2H, Ar H), 7.10–7.42 (m, 15H, Ar H), 7.59–7.69 (m, 2H, Ar H) ppm; **^{13}C NMR** (50 MHz; $CDCl_3$): δ 55.3 (CH_3), 66.3 (Ins C), 69.2 (Ins C), 71.2 (CH_2) 71.4 (CH_2), 71.6 (CH_2), 72.0 (Ins C), 72.1 (Ins C), 73.9 (Ins C), 74.1 (Ins C), 107.9 (O_3CPh), 113.9 (Ar C), 125.5 (Ar C), 127.7 (Ar C), 127.8 (Ar C), 127.9 (Ar C), 128.0 (Ar C), 128.1 (Ar C), 128.5 (Ar C), 129.39 (Ar C), 129.44 (Ar C), 129.8 (Ar C), 137.3 (Ar C), 137.8 (Ar C), 138.2 (Ar C), 159.4 (Ar C) ppm; elemental analysis calcd (%) for $C_{35}H_{34}O_7$: C, 74.19; H, 6.05; found C, 73.92; H, 5.99%.

Racemic-1,2,3,4,5-penta-*O*-benzyl-6-*O*-(*p*-methoxybenzyl)-*myo*-inositol (2.22).

To a stirred solution of the orthobenzoate **2.19** (3.97 g, 7.00 mmol) in dry DCM (21 mL) under argon at 0 ºC was added DIBAL-H (28 mL, 1.0 *M* solution in toluene; 28.00 mmol) over 10 min. The solution was stirred at 0 ºC for 15 min then at ambient temperature for 20 h. The reaction mixture was poured into a vigorously stirred solution of sodium potassium tartarate in water (70 mL, 1*M*) and saturated ammonium chloride solution (70 mL) and stirring was continued at ambient temperature for 20 h. This mixture was transferred to a separating funnel and the product was extracted with ethyl acetate. The organic layer was dried over sodium sulphate and filtered. The

filtrate was concentrated under reduced pressure and the mixture of diols **2.20** and **2.21** (4.30 g) obtained was used for the next reaction without purification.

To a stirred solution of the mixture of diols **2.20** and **2.21** (4.30 g) in dry DMF (21 mL) at 0 ºC under argon was added sodium hydride (0.70 g, 17.50 mmol). The suspension was stirred at 0 ºC for 10 min and then at ambient temperature for 30 min. The resulting solution was cooled to 0 ºC again and benzyl bromide (2.50 mL, 21.00 mmol) was added drop-wise and the solution was stirred at ambient temperature for 16 h. The reaction was quenched by adding few pieces of ice and the solvent was evaporated under reduced pressure; the residue obtained was worked up with ethyl acetate. The crude product obtained was purified by column chromatography (230–400 mesh silica and eluent was 15% ethyl acetate/ light petroleum) to get **2.22** (4.24 g, 81%) as a colorless solid. R_f = 0.17 (10% ethyl acetate/ light petroleum); **mp** 76–78 °C; **^{1}H NMR** (200 MHz; $CDCl_3$): δ 3.32 (t, J = 1.7 Hz, 1H, Ins H), 3.37 (t, J = 1.7 Hz, 1H, Ins H), 3.46 (t, J = 9.3 Hz, 1H, Ins H), 3.78 (s, 3H, OCH_3), 4.01–4.15 (m, 3H, Ins H), 4.56–4.96 (m, 12H, CH_2Ph), 6.75–6.85 (m, 2H, Ar H), 7.15–7.46 (m, 27H, Ar H) ppm; **^{13}C NMR** (50 MHz; $CDCl_3$): δ 55.3 (CH_3), 72.9 (CH_2), 74.2 (CH_2), 74.5 (Ins C), 75.7 (CH_2), 76.0 (CH_2), 81.07 (Ins C), 81.10 (Ins C), 81.5 (Ins C), 81.8 (Ins C), 83.9 (Ins C), 113.8 (Ar C), 127.5 (Ar C), 127.58 (Ar C), 127.64 (Ar C), 127.67 (Ar C), 127.71(Ar C), 127.8 (Ar C), 127.9 (Ar C), 128.2 (Ar C), 128.3 (Ar C), 128.42 (Ar C), 128.46 (Ar C), 128.5 (Ar C), 129.9 (Ar C), 131.1 (Ar C), 138.5 (Ar C), 138.6 (Ar C), 138.9 (Ar C), 139.0 (Ar C), 139.1 (Ar C), 159.2 (Ar C) ppm; elemental analysis calcd (%) for $C_{49}H_{50}O_7$: C, 78.37; H, 6.71; found C, 78.01; H, 6.80%.

Racemic-1,2,3,4,5-penta-*O*-benzyl-*myo*-inositol (2.23).

To a stirred solution of the PMB ether **2.22** (3.76 g, 5.00 mmol) in DCM (5 mL) was added MeOH (15 mL) followed by concentrated HCl (5 mL). The reaction mixture was stirred at reflux temperature for 6 h. The reaction mixture was cooled to ambient temperature and neutralized by adding aqueous NH_3 solution and the solvent was evaporated under reduced pressure. The residue obtained was worked up with ethyl acetate. The crude product obtained was purified by flash column chromatography (230–400 mesh silica and eluent was 15% ethyl acetate/ light petroleum) to get **2.23** (2.92 g, 93%) as a colorless solid; R_f = 0.31 (20% ethyl acetate/ light petroleum); **mp** 72–74 °C; **IR** ($CHCl_3$): $\bar{\nu}$ 3200–3600 cm^{-1}; **^{1}H NMR** (200 MHz; $CDCl_3$): δ 2.51 (d, J = 2Hz, 1H, OH, D_2O exchangable), 3.19 (dd, J_1 = 2.2 Hz, J_2 = 9.8 Hz, 1H, Ins H),

3.31–3.45 (m, 2H, Ins H), 4.00–4.25 (m, 3H, Ins H), 4.47–4.97 (m, 10H, CH_2Ph), 7.21–7.41 (m, 25H, Ar H) ppm; **^{13}C NMR** (50 MHz; $CDCl_3$): δ 72.4 (CH_2), 72.9 (CH_2), 73.0 (Ins C), 73.7 (Ins C), 74.2 (CH_2), 75.5 (CH_2), 75.9 (CH_2), 80.2 (Ins C), 81.2 (Ins C), 81.5 (Ins C), 83.5 (Ins C), 127.5 (Ar C), 127.6 (Ar C), 127.70 (Ar C), 127.75 (Ar C),127.81 (Ar C), 127.84 (Ar C),128.0 (Ar C), 128.1 (Ar C), 128.3 (Ar C), 128.4 (Ar C), 128.5 (Ar C), 128.6 (Ar C), 138.0 (Ar C), 138.4 (Ar C), 138.9 (Ar C), 138.92 (Ar C) ppm; elemental analysis calcd (%) for $C_{41}H_{42}O_6$: C, 78.07; H, 6.71; found C, 77.93; H, 6.36%.

Racemic 1,2,3,4,5-penta-*O*-benzyl-6-*O*-acetyl-*myo*-inositol (2.24).

To a stirred solution of the alcohol **2.23** (0.63 g, 1.00 mmol) in dry pyridine (7 mL) were added DMAP (0.02 g) and acetic anhydride (0.20 mL, 2.00 mmol) and the reaction mixture refluxed for 18 h. The reaction mixture was allowed to cool to ambient temperature and quenched by adding few pieces of ice. The solvent was evaporated under reduced pressure and the residue obtained was worked up with ethyl acetate. The crude product obtained was purified by column chromatography (silica gel 100–200 mesh and eluent was 12% ethyl acetate/ light petroleum) to get **2.24** as a colorless solid (0.60 g, 95%) which was crystallized from ethyl acetate-light petroleum; R_f = 0.4 (20% ethyl acetate/ light petroleum); **mp** 121–122 ºC; **IR** (Nujol): $\bar{\nu}$ 1742 cm^{-1}; **^{1}H NMR** (200 MHz; $CDCl_3$): δ 1.92 (s, 3H, CH_3), 3.27 (dd, J_1 = 2.2 Hz, J_2 = 10.2 Hz, 1H, Ins H), 3.34 (dd, J_1 = 2.3 Hz, J_2 = 9.8 Hz, 1H, Ins H), 3.43 (t, J = 9.4 Hz, 1H, Ins H), 4.02 (t, J = 2.3 Hz, 1H, Ins H), 4.15 (t, J = 9.5 Hz, 1H, Ins H), 4.41 (d, J = 12.1 Hz, 1H, CH_2Ph), 4.54 (d, J = 8.9 Hz, 1H, CH_2Ph), 4.56–4.69 (m, 3H, CH_2Ph), 4.74–4.98 (m, 5H, CH_2Ph), 5.64 (t, J = 10 Hz, 1H, Ins H), 7.16–7.45 (m, 25H, Ar H) ppm; **^{13}C NMR** (50 MHz; $CDCl_3$): δ 21.2 (CH_3), 72.1 (CH_2), 72.8 (CH_2), 73.2 (Ins C), 73.3 (Ins C), 74.0 (CH_2), 75.3 (CH_2), 75.9 (CH_2), 78.3 (Ins C), 80.7 (Ins C), 81.6 (Ins C), 81.7 (Ins C), 127.5 (Ar C), 127.69 (Ar C), 127.74 (Ar C), 127.8 (Ar C), 127.9 (Ar C), 128.0 (Ar C), 128.2 (Ar C), 128.24 (Ar C), 128.4 (Ar C), 128.48 (Ar C), 128.5 (Ar C), 138.0 (Ar C), 138.3 (Ar C), 138.6 (Ar C), 138.7 (Ar C), 138.74 (Ar C), 170.1 (CO) ppm; elemental analysis calcd (%) for $C_{43}H_{44}O_7$: C, 76.76; H, 6.59; found C, 76.50; H 6.51%.

Racemic 1,2,3,4,5-penta-*O*-benzyl-6-*epi*-inosose (2.25).

To a solution of the alcohol **2.23** (1.58 g, 2.51 mmol) in ethyl acetate (12 mL) was added IBX (2.80 g, 10.00 mmol) and the resulting suspension stirred at reflux

temperature for 6 h. The reaction mixture was cooled to ambient temperature and filtered through Celite. The filtrate obtained was concentrated under reduced pressure and the residue was purified by flash column chromatography (silica gel 230–400 mesh, eluent 12% ethyl acetate/ light petroleum) to get the *epi*-inosose **2.25** (1.48 g, 94%) as a colorless solid; R_f = 0.3 (15% ethyl acetate/ light petroleum); **mp** 133–134 °C; **IR** (Nujol): $\bar{\nu}$ 1740 cm^{-1}; **^{1}H NMR** (200 MHz; $CDCl_3$): δ 3.70 (dd, J_1 = 2.3 Hz, J_2 = 9.4 Hz, 1H, Ins H), 3.90–4.03 (m, 2H, Ins H), 4.12 (t, J = 2.1 Hz, 1H, Ins H), 4.20 (t, J = 9.4 Hz, 1H, Ins H), 4.39–4.66 (m, 4H, CH_2Ph), 4.73–5.02 (m, 6H, CH_2Ph), 7.23–7. 35 (m, 25H, Ar H) ppm; **^{13}C NMR** (50 MHz; $CDCl_3$): δ 72.3 (CH_2), 72.8 (CH_2), 73.6 (CH_2), 73.7 (CH_2), 75.6 (Ins C), 76.1 (CH_2), 80.1 (Ins C), 81.4 (Ins C), 82.6 (Ins C), 84.0 (Ins C), 127.5 (Ar C), 127.7 (Ar C), 127.76 (Ar C), 127.84 (Ar C), 127.87 (Ar C), 127.91 (Ar C), 128.06 (Ar C), 128.14 (Ar C), 128.21 (Ar C), 128.24 (Ar C), 128.4 (Ar C), 128.5 (Ar C), 128.6 (Ar C), 137.4 (Ar C), 137.7 (Ar C), 138.0 (Ar C), 138.2 (Ar C), 138.6 (Ar C), 201.8 (CO) ppm; elemental analysis calcd (%) for $C_{41}H_{40}O_6$: C, 78.32; H, 6.41; found C, 78.22; H, 6.08%.

Racemic 1,2,3,5,6-penta-*O*-benzyl-*epi*-inositol (2.26).

To the solution of *epi*-inosose **2.25** (1.78 g, 2.83 mmol) in DCM (12 mL), methanol (3 mL) was added. This solution was cooled to 0 °C and sodium borohydride (0.21 g, 5.66 mmol) was added to it in one portion and the reaction mixture was stirred at 0 °C for 5 min then at ambient temperature for half an hour. The reaction was quenched by adding aqueous ammonium chloride solution. The resulting mixture was concentrated under reduced pressure and the residue obtained was worked up with ethyl acetate and purified by column chromatography (silica gel 230–400 mesh, eluent 15% ethyl acetate/ light petroleum) to get the the *epi*-alcohol **2.26** (1.68 g, 94%) as a colorless solid; R_f = 0.36 (20% ethyl acetate/ light petroleum); **mp** 141–142 ºC; **IR** (Nujol): $\bar{\nu}$ 3445 cm^{-1}; **^{1}H NMR** (200 MHz; $CDCl_3$): δ 3.18 (t, J = 2.6 Hz, 1H, Ins H), 3.22–3.36 (m, 2H, Ins H), 4.05–4.17 (m, 2H, Ins H, one D_2O exchangeable), 4.22 (t, J = 9.8 Hz, 1H, Ins H), 4.28–4.40 (m, 1H, Ins H), 4.41–4.98 (m, 10H, CH_2Ph), 7.18–7.46 (m, 25H, Ar H) ppm; **^{13}C NMR** (50 MHz; $CDCl_3$): δ 69.1 (Ins C), 70.3 (CH_2), 72.2 (CH_2), 73.1 (CH_2), 74.2 (Ins C), 75.6 (CH_2), 76.1 (CH_2), 78.9 (Ins C), 79.3 (Ins C), 80.5 (Ins C), 80.8 (Ins C), 127.6 (Ar C), 127.68 (Ar C), 127.7 (Ar C), 127.8 (Ar C), 127.9 (Ar C), 128.0 (Ar C), 128.2 (Ar C), 128.3 (Ar C), 128.37 (Ar C), 128.40 (Ar C), 128.41 (Ar C), 128.48 (Ar C), 128.54 (Ar C), 137.77 (Ar C), 137.82 (Ar C), 138.4 (Ar

C), 139.0 (Ar C) ppm; elemental analysis calcd (%) for $C_{41}H_{42}O_6$: C, 78.07; H, 6.71; found C, 77.82; H, 6.58%.

Racemic 1,2,3,5,6-penta-*O*-benzyl-4-*O*-acetyl *epi*-inositol (2.27).

To a stirred solution of the alcohol **2.26** (0.50 g, 0.79 mmol) in dry pyridine (5 mL) were added DMAP (0.015 g) and acetic anhydride (0.20 mL, 2.37 mmol) at ambient temperature and the reaction mixture was refluxed for 18 h. The reaction mixture was cooled to ambient temperature and quenched by adding few pieces of ice. The solvent was evaporated under reduced pressure and the residue obtained was worked up with ethyl acetate. The crude product obtained was purified by column chromatography (silica gel 230–400 mesh, eluent 12% ethyl acetate/ light petroleum) to get **2.27** (0.49 g, 92%) as a gum. R_f = 0.43 (20% ethyl acetate/ light petroleum); **IR** (Nujol): $\bar{\nu}$ 1736 cm^{-1}; **^{1}H NMR** (200 MHz; $CDCl_3$): δ 2.09 (s, 3H, CH_3), 3.23–3.35 (m, 2H, Ins H), 3.41 (dd, J_1 = 3.6 Hz, J_2 = 9.7 Hz , 1H, Ins H), 4.04–4.12 (m, 1H, Ins H), 4.24 (t, J = 9.8 Hz, 1H, Ins H), 4.36–4.96 (m, 10H, CH_2Ph), 5.87–5.96 (m, 1H, Ins H), 7.18–7.48 (m, 25H, Ar H) ppm; **^{13}C NMR** (50 MHz; $CDCl_3$): δ 21.3 (CH_3), 66.9 (Ins C), 71.2 (CH_2), 72.4 (CH_2), 72.6 (CH_2), 73.7 (CH_2), 75.7 (Ins C), 75.8 (Ins C), 75.9 (CH_2), 78.6 (Ins C), 79.0 (Ins C), 80.1 (Ins C), 127.1 (Ar C), 127.5 (Ar C), 127.6 (Ar C), 127.66 (Ar C), 127.7 (Ar C), 127.8 (Ar C), 128.0 (Ar C), 128.07 (Ar C), 128.14 (Ar C), 128.3 (Ar C), 128.36 (Ar C), 128.4 (Ar C), 128.5 (Ar C), 137.8 (Ar C), 138.0 (Ar C), 138.5 (Ar C), 139.1 (Ar C), 139.4 (Ar C), 171.4 (CO) ppm; elemental analysis calcd (%) for $C_{43}H_{44}O_7$: C, 76.76; H, 6.59; found C, 76.47; H, 6.64%.

***epi*-inositol (1.3).**

The pentabenzyl ether **2.26** (0.32g, 0.5 mmol), THF (2 mL), water (2 mL) and TFA (1 mL) were taken in a hydrogenation bottle and 20 % $Pd(OH)_2$ on carbon (0.15 g) was added in one portion. The reaction mixture was agitated in an atmosphere of hydrogen (60 *psi*) at ambient temperature for 20 h. The reaction mixture was then diluted with (1:1) ethanol-water (10 mL) and filtered through a bed of Celite. The Celite bed was washed with hot water (2 x 5 mL) and ethanol (2 x 5 mL) alternatively. The combined filtrate was evaporated under reduced pressure and the residue co-evaporated with absolute ethanol (2 x 5 mL) to get *epi*-inositol **1.3** (0.086 g, 96%) as a solid.

1,3,4,5,6-penta-*O*-benzyl-*myo*-inositol (2.54).

To a stirred solution of the diol **2.53**[24] (3.01 g, 5.58 mmol) in dry benzene (30 mL) was added sodium hydride (1.81 g, 45.20 mmol) and the mixture was stirred at RT for

30 min. To this mixture, a solution of benzyl bromide (0.7 mL, 5.86 mmol) in benzene (2 mL) was added and the reaction mixture refluxed for 1.5 h. The reaction mixture was then allowed to come to ambient temperature, a few pieces of ice were added and the solvent was removed under reduced pressure. The residue obtained was worked up with ethyl acetate. The filtrate was concentrated under reduced pressure and the crude product obtained was purified by flash column chromatography (230–400 mesh silica, eluent 15 % ethyl acetate/ light petroleum) to get 1,3,4,5,6-penta-*O*-benzyl-*myo*-inositol (**2.54**) (2.75 g, 78%) as a colorless solid; **mp** 125–128 ºC (Lit. mp. 125-127 ºC)[25]; **IR** (Nujol): $\bar{\nu}$ 3300-3600 cm^{-1}; **^{1}H NMR** (200 MHz; $CDCl_3$): δ 2.49 (s, 1H, OH, D_2O exchangeable), 3.40 (dd, J_1 = 2.4 Hz, J_2 = 9.6 Hz, 2H, Ins H), 3.48 (m, 1H, Ins H), 4.00 (t, J = 9.5 Hz, 2H, Ins H), 4.22 (t, J = 2.5 Hz, 1H, Ins H), 4.65–4.98 (m, 10H, CH_2Ph), 7.18–7.44 (m, 25H, Ar H) ppm; **^{13}C NMR** (50 MHz; $CDCl_3$): δ 67.5 (Ins C), 72.7 (CH_2), 75.9 (CH_2), 79.7 (Ins C), 81.2 (Ins C), 83.1 (Ins C), 127.5 (Ar C), 127.8 (Ar C), 128.0 (Ar C), 128.3 (Ar C), 128.4 (Ar C), 137.9 (Ar C), 138.6 (Ar C), 138.7 (Ar C) ppm.

1,3,4,5,6-penta-*O*-benzyl-2-*O*-acetyl-*myo*-inositol (2.55).

The pentabenzyl ether **2.54** (0.063 g, 0.01 mmol), dry pyridine (2 mL), DMAP (0.01 g, catalytic) and acetic anhydride (20 µL, 0.20 mmol) were refluxed for 18 h. The reaction mixture was cooled to ambient temperature and quenched by adding few pieces of ice. The solvent was evaporated under reduced pressure and the residue obtained was worked up with ethyl acetate. The crude product obtained was purified by column chromatography (silica gel 100-200 mesh, eluent 12 % ethyl acetate – light petroleum) to get **2.55** as a colorless solid (0.063 g, 94%); **mp** 107–110 °C (Lit. 110–111 °C)[17a]; **IR** (Nujol): $\bar{\nu}$ 1745 cm^{-1}; **^{1}H NMR** (200 MHz; $CDCl_3$): δ 2.17 (s, 3H, CH_3), 3.41–3.58 (m, 3H, Ins H), 3.90 (t, J = 9.6Hz, 2H, Ins H), 4.47–4.59 (d, J = 11.1 Hz, 2H, CH_2Ph), 4.68–4.97 (m, 8H, CH_2Ph), 5.87 (t, J = 2.53 Hz, 1H, Ins H), 7.13–7.38 (m, 25H, Ar H) ppm; **^{13}C NMR** (50 MHz; $CDCl_3$): δ 20.5 (CH_3), 66.0 (Ins C), 71.5 (CH_2), 75.2 (CH_2), 75.5 (CH_2), 75.7 (Ins C), 80.7 (Ins C), 82.3 (Ins C), 126.9 (Ar C), 127.0 (Ar C), 127.1 (Ar C), 127.28 (Ar C), 127.34 (Ar C), 127.5 (Ar C), 127.6 (Ar C), 127.7 (Ar C), 137.0 (Ar C), 137.8 (Ar C), 138.0 (Ar C), 169.7 (CO) ppm.

1,2,3,4,5-penta-*O*-benzyl *scyllo*-inosose (2.40).

To a solution of the penta-*O*-benzyl *myo*-inositol (**2.54**) (2.70 g, 4.28 mmol) in ethyl acetate (30 mL), IBX (3.60 g, 12.8 mmol) was added and the resulting suspension was

refluxed for 6 h. The reaction mixture was cooled to ambient temperature and filtered through a bed of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (silica gel 230–400 mesh, eluent 12% ethyl acetate/ light petroleum) to get the *scyllo*-inosose **2.40** (2.56 g, 95%) as a colorless solid; **mp** 159–162 °C (Lit. 163–164 °C)[25]; **IR** (Nujol) $\bar{\nu}$ 1729 cm^{-1}; **^{1}H NMR** (400 MHz; $CDCl_3$): δ 3.62 (t, J = 9.4 Hz, 2H, Ins H), 3.87 (t, J = 9.3 Hz, 1H, Ins H), 4.15 (d, J = 9.8 Hz, 2H, Ins H), 4.55 (d, J = 6 Hz, 2H, CH_2Ph), 4.77 (d, J = 10.8 Hz, 2H, CH_2Ph), 4.85–4.93 (m, 6H, CH_2Ph), 7.23–7. 36 (m, 21H, Ar H), 7.36–7.41 (m, 4H, Ar H) ppm; **^{13}C NMR** (50 MHz; $CDCl_3$): δ 73.3 (CH_2), 76.0 (CH_2), 76.1 (CH_2), 81.4 (Ins C), 82.1 (Ins C), 83.7 (Ins C), 127.7 (Ar C), 127.87 (Ar C), 127.95 (Ar C), 128.0 (Ar C), 128.1 (Ar C), 128.3 (Ar C), 128.4 (Ar C), 137.2 (Ar C), 138.0 (Ar C), 138.1 (Ar C), 202.1 (CO) ppm.

Racemic 1,2,3,4-tetra-*O*-benzyl *scyllo*-inositol (2.57).

To a stirred solution of **2.56**[26] (2.14 g, 3.10 mmol) in dry THF (3 mL) was added MeOH (9 mL) and 10% NaOH solution (1.5 mL). The reaction mixture was stirred at ambient temperature for 4 h. The solvent was removed under reduced pressure. The residue was worked up with ethyl acetate. The crude product was purified by column chromatography (60-120 mesh silica, eluent 35% ethyl acetate/ light petroleum) to get **2.57** (1.65 g, 98%) as a colorless solid; **mp** 164–168 °C; **IR** (Nujol): $\bar{\nu}$ 3200–3350 cm^{-1}; **^{1}H NMR** (400 MHz; $CDCl_3$): δ 2.77 (bs, 2 H, OH, D_2O exchangeable), 3.38–3.44 (m, 2H, Ins H), 3.47–3.52 (m, 2H, Ins H), 3.56–3.61 (m, 2H, Ins H), 4.80 (d, J= 6 Hz, 2H, CH_2Ph), 4.84–4.94 (m, 6H, CH_2Ph), 7.19–7.40 (m, 20H, Ar H) ppm; **^{13}C NMR** (100 MHz; $CDCl_3$): δ 73.8 (Ins C), 75.5 (CH_2), 75.8 (CH_2), 82.3 (Ins C), 83.0 (Ins C), 127.7 (Ar C), 127.8 (Ar C), 127.9 (Ar C), 128.4 (Ar C), 128.5 (Ar C), 138.3 (Ar C), 138.4 (Ar C); elemental analysis calcd for $C_{34}H_{36}O_6$: C 75.53, H 6.71; found C 75.36; H 6.81 %.

1,2,3,4,5-penta-*O*-benzyl *scyllo*-inositol (2.58).

To a stirred solution of the diol **2.57** (2.90 g, 5.37 mmol) in dry DMF (30 mL) was added sodium hydride (0.215 g, 5.37 mmol) at 0 ºC. The reaction mixture was stirred at 0 ºC for 10 min then at ambient temperature for 30 min. The reaction mixture was again cooled to 0 ºC and a solution of benzyl bromide (0.65 mL, 5.42 mmol) in DMF (2 mL) was added and the reaction mixture was allowed to come to ambient temperature and stirred for 1 h. The reaction was quenched by adding few pieces of

ice and the solvent was removed under reduced pressure. The residue obtained was worked up with ethyl acetate. The crude product obtained was purified by flash column chromatography (230-400 mesh silica, eluent 15% ethyl acetate/ light petroleum) to get **2.58** (3.03 g, 89%) as a colorless solid; **mp** 103–106 °C (Lit. 108–109 °C)[25]; **IR** (Nujol): $\bar{\nu}$ 3583 cm^{-1}; **^{1}H NMR** (400 MHz; $CDCl_3$): δ 2.50 (bs, 1H, OH, D_2O exchangeable), 3.34–3.52 (m, 2H, Ins H), 3.52–3.72 (m, 4H, Ins H), 4.67–4.96 (m, 10H, CH_2Ph), 7.20–7.42 (m, 25H, Ar H) ppm; **^{13}C NMR** (50 MHz; $CDCl_3$): δ 74.3 (Ins C), 75.5 (CH_2), 75.8 (CH_2), 75.9 (CH_2), 82.4 (Ins C), 82.7 (Ins C), 83.1 (Ins C), 127.6 (Ar C), 127.79 (Ar C), 127.85 (Ar C), 127.9 (Ar C), 128.4 (Ar C), 128.5 (Ar C), 138.3 (Ar C), 138.4 (Ar C) ppm.

1,2,3,4,5-penta-*O*-benzyl-6-*O*-acetyl-*scyllo*-inositol (2.59).

The pentabenzyl ether **2.58** (0.063 g, 0.10 mmol), dry pyridine (2 mL), DMAP (0.01 g, catalytic) and acetic anhydride (20 μL, 0.20 mmol) were refluxed together for 18 h. The reaction mixture was cooled to ambient temperature and quenched by adding few pieces of ice. The solvent was evaporated under reduced pressure and the residue obtained was worked up with ethyl acetate. The crude product obtained was purified by column chromatography (silica gel 100 – 200 mesh, eluent 12% ethyl acetate – light petroleum) to get **2.59** as a colorless solid (0.064 g, 96%); **mp** 118–122 °C; **IR** (Nujol): $\bar{\nu}$ 1741cm^{-1}; **^{1}H NMR** (200 MHz; $CDCl_3$): δ 1.83 (s, 3H, CH_3), 3.42–3.67 (m, 5H, Ins H), 4.63 (d, J = 11.4 Hz, 2H, CH_2Ph), 4.75–4.95 (m, 8H, CH_2Ph), 5.16 (t, J = 9.5 Hz, 1H, Ins H), 7.13–7.38 (m, 25H, Ar H) ppm; **^{13}C NMR** (50 MHz; $CDCl_3$): δ 20.9 (CH_3), 73.5 (Ins C), 75.5 (CH_2), 76.0 (CH_2), 80.6 (Ins C), 82.7 (Ins C), 82.8 (Ins C), 127.7 (Ar C), 127.8 (Ar C), 128.0 (Ar C), 128.4 (Ar C), 138.2 (Ar C), 138.3 (Ar C), 170.0 (CO) ppm; elemental analysis calcd (%) for $C_{43}H_{44}O_7$: C 76.76, H 6.59; found C 76.69; H 6.56%.

Reduction of 1,2,3,4,5-penta-*O*-benzyl-*scyllo*-inosose (2.40).

The penta–*O*–benzyl *scyllo*-inosose (**2.40**; 0.063 g, 0.01 mmol) was dissolved in DCM (4 mL) – methanol (1 mL) mixture. To this solution sodium borohydride (0.008 g, 0.02 mmol) was added in one portion at 0 °C and the reaction mixture stirred at 0 °C for 5 min then at ambient temperature for 30 min. The reaction was quenched by adding aqueous ammonium chloride solution. The resulting mixture was concentrated under reduced pressure and the residue was worked up with ethyl acetate and the product was purified by column chromatography (silica gel 230–400 mesh, eluent

12% ethyl acetate/ light petroleum) to get the penta-*O*-benzyl-*myo*-alcohol **2.54** (0.050 g, 79%) and penta-*O*-benzyl-*scyllo*-alcohol **2.58** (0.010 g, 16%).

General Procedure for the reduction of inosose and estimation of the products.

The inosose (0.01 mmol) was dissolved in DCM (4 mL) – methanol (1 mL) mixture. To this solution borohydride reagent (0.02 mmol) was added in one portion at 0 °C and the reaction mixture stirred at 0 °C for 5 min and then at ambient temperature for 30 min. The reaction was quenched by adding aqueous ammonium chloride solution (1 N HCl when tetrabutylammonium borohydride was used). The resulting mixture was concentrated under reduced pressure and the residue obtained was worked up with ethyl acetate. The crude product obtained was acetylated as below.

A mixture of the product obtained above, dry pyridine (2 mL), DMAP (0.01 g) and acetic anhydride (20 µL, 0.20 mmol) was refluxed for 18 h. The reaction mixture was cooled to ambient temperature and quenched by adding few pieces of ice. The solvent was evaporated under reduced pressure and the residue obtained was worked up with ethyl acetate and the diastereomeric products were estimated by ^{1}H NMR spectroscopy.

Sr. No.	inosose	Reducing agent	Temperature	Ratio of OH_{ax} : OH_{eq}
1	*epi* (**2.25**)	$NaBH_4$	0 ºC	98 : 2
2	*scyllo* (**2.40**)	$NaBH_4$	0 ºC	80 : 20
3	*scyllo* (**2.40**)	$NaBH_4$	-55 ºC	92 : 18

Racemic 1,3,4,5,6-penta-*O*-benzyl-2-*C*-methyl *epi*-inositol (2.60).

To a stirred solution of penta–*O*–benzyl *epi*-inosose **2.25** (0.63 g, 0.10 mmol) in THF (7 mL) was added methyl magnesium iodide (3M solution in ether, 50 µL, 0.15 mmol) at 0 °C and the reaction mixture stirred at 0 °C for 15 min then at ambient temperature for 2 h. The reaction mixture was cooled to 0 °C and quenched by adding ethyl acetate (0.5 mL) followed by aqueous ammonium chloride solution (1 mL). The resulting mixture was concentrated under reduced pressure and the residue obtained was worked up with ethyl acetate. The crude product was purified by column chromatography (silica gel 100-200 mesh, 12% ethyl acetate-pet ether) to get **2.60** as a colorless solid (0.600 g, 93%); **mp** 147–150 ºC; **IR** (Nujol): $\bar{\nu}$ 3500–3700 cm^{-1}; **^{1}H NMR** (200 MHz; $CDCl_3$): δ 1.21 (s, 3H, CH_3), 2.93 (d, J = 2.4 Hz, 1H, Ins H), 3.06 (d, J = 9.6 Hz, 1H, Ins H), 3.34 (dd, J_1 = 2.5 Hz, J_2 = 9.8 Hz, 1H, Ins H), 4.12 (t, J =

2.5 Hz, 1H, Ins H), 4.20 (t, J = 9.8 Hz, 1H, Ins H), 4.36–4.48 (m, 1H, CH_2Ph, 1H, OH; D_2O exchangeable), 4.58–5.03 (m, 8H, CH_2Ph, 1H, Ins H), 7.19–7.44 (m, 25H, Ar H) ppm; **^{13}C NMR** (50 MHz; $CDCl_3$): δ 22.3 (CH_3), 72.0 (CH_2), 73.0 (CH_2), 75.2 (CH_2), 75.8 (CH_2), 76.09 (CH_2), 76.14 (Ins C), 76.8 (Ins C), 77.3 (Ins C), 80.7 (Ins C), 84.2 (Ins C), 127.4 (Ar C), 127.5 (Ar C), 127.6 (Ar C), 127.7 (Ar C), 127.8 (Ar C), 128.0 (Ar C), 128.08 (Ar C), 128.15 (Ar C), 128.2 (Ar C), 128.3 (Ar C), 128.4 (Ar C), 137.3 (Ar C), 137.5 (Ar C), 138.2 (Ar C), 138.3 (Ar C), 138.7 (Ar C); elemental analysis calcd for $C_{42}H_{44}O_6$: C 78.23, H 6.88 ppm; found C 78.43; H 6.96%.

Racemic 1,2,3,4,5,6-hexa-*O*-acetyl-2-*C*-methyl *epi*-inositol (2.62).

Racemic 1,3,4,5,6-penta-*O*-benzyl-2-*C*-methyl *epi*-inositol **2.60** (0.100 g, 0.16 mmol), THF (2 mL), water (0.50 mL) and TFA (0.50 mL) were taken in a hydrogenation bottle and 20 % Pd–$(OH)_2$ on carbon (0.050 g) was added in one portion. The reaction mixture was kept in an atmosphere of hydrogen (60 *psi*) at ambient temperature for 20 h. The reaction mixture was then diluted with (1:1) ethanol–water (10 mL) and filtered through a small bed of Celite. The Celite bed was washed with hot water and ethanol (2 x 5 mL) alternately. The combined filtrate was evaporated under reduced pressure and the residue was co–evaporated with absolute ethanol (2 x 5 mL) to get crude racemic 2-*C*-methyl *epi*–inositol **2.61** (0.032 g) which was directly used in the next step without further purification.

A mixture of the crude product **2.61** (0.032 g, 0.16 mmol), pyridine (2 mL), DMAP (0.01 g, catalytic) and acetic anhydride (0.27 mL, 2.88 mmol) was refluxed for 18 h. The reaction mixture was cooled to ambient temperature and quenched by adding few pieces of ice. The solvent was evaporated under reduced pressure and the residue obtained was worked up with ethyl acetate. The crude product obtained was purified by column chromatography (silica gel 100-200 mesh, 35 % ethyl acetate – light petroleum) to get **2.62** as a colorless solid (0.061 g, 86%); **mp** 133–137 ºC (Crystals obtained by slow evaporation from hot MeOH solution); **IR** (Nujol): $\bar{\nu}$ 1748 cm^{-1}; **^{1}H NMR** (200 MHz; $CDCl_3$): δ 1.25 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 4.95–5.07 (m, 2H, Ins H), 5.68–5.18 (dd, J = 3.8 Hz, J_2 = 10.5 Hz, 1H, Ins H), 5.57 (t, J = 3.5 Hz, 1H, Ins H), 5.70 (t, J = 10.2 Hz, 1H, Ins H) ppm; **^{13}C NMR** (50 MHz; $CDCl_3$): δ 19.8 (CH_3), 20.4 (CH_3), 20.5 (CH_3), 20.7 (CH_3), 22.5 (CH_3), 67.9 (Ins C), 68.4 (Ins C), 70.1 (Ins C), 73.7 (Ins C), 82.8 (Ins C-4), 168.8 (CO), 169.4 (CO), 169.6

(CO), 169.7 (CO), 169.8 (CO), 170.0 (CO) ppm; elemental analysis calcd for $C_{19}H_{26}O_{12}$: C 51.12, H 5.87; found C 51.26; H 5.80%.

1,3,4,5,6-penta-*O*-benzyl-2-*C*-methyl *myo*-inositol (2.63) and 2,3,4,5,6-penta-*O*-benzyl-1-*C*-methyl *scyllo*-inositol (2.64).

To a stirred solution of penta–*O*–benzyl *scyllo*-inosose **2.40** (0.126 g, 0.02 mmol) in THF (3 mL) was added methyl magnesium iodide (3M solution in ether, 10 μL, 0.03 mmol) at 0 °C and the reaction mixture stirred at 0 °C for 15 min then at ambient temperature for 2 h. The reaction was cooled to 0 °C and quenched by adding ethyl acetate (1 mL) followed by aqueous ammonium chloride solution. The resulting mixture was concentrated under reduced pressure and the residue obtained was worked up with ethyl acetate. The crude product obtained was purified by column chromatography (silica gel 100–200 mesh, eluent: 12% ethyl acetate- light peroleum) to get racemic 2,3,4,5,6-penta-*O*-benzyl-1-*C*-methyl *scyllo*-inositol (**2.64**) (0.023 g, 18%) and racemic 1,3,4,5,6-penta-*O*-benzyl-2-*C*-methyl *myo*-inositol (**2.63**) (0.098 g, 76%) as a colorless solids.

Data for 2.64: **mp** 160–163 ºC; **IR** (Nujol): $\bar{\nu}$ 3500–3600cm^{-1}; **^{1}H NMR** (400 MHz; $CDCl_3$): δ 1.30 (s, 3H, CH_3), 2.18 (bs, 1H, D_2O exchangeable, OH), 3.46 (d, J = 9.8 Hz, 2H, Ins H), 3.53 (t, J = 9.2 Hz, 2H, Ins H), 3.62 (t, J = 9.1 Hz, 1H, Ins H), 4.79–4.94 (m, 10H, CH_2Ph), 7.23–7.38 (m, 25H, Ar H) ppm; **^{13}C NMR** (100 MHz; $CDCl_3$): δ 17.6 (CH_3), 75.78 (CH_2), 75.84 (CH_2), 76.0 (Ins C), 76.1 (CH_2), 82.8 (Ins C), 83.5 (Ins C), 84.8 (Ins C), 127.65 (Ar C), 127.69 (Ar C), 127.9 (Ar C), 128.40 (Ar C), 128.43 (Ar C), 138.4 (Ar C), 138.8 (Ar C) ppm; elemental analysis calcd for $C_{42}H_{44}O_6$: C 78.23, H 6.88; found C 77.94; H 6.93%.

Data for 2.63: mp 103–106 ºC; **IR** (Nujol): $\bar{\nu}$ 3557 cm^{-1}; **^{1}H NMR** (200 MHz; $CDCl_3$): δ 1.23 (s, 3H, CH_3), 2.12 (bs, 1H, D_2O exchangeable, OH), 3.21 (d, J = 9.60 Hz, 2H, Ins H), 3.54 (t, J = 9.60 Hz, 1H, Ins H), 3.99 (t, J = 9.48 Hz, 2H, Ins H), 4.64 (d, J = 10.86 Hz, 2H, CH_2Ph), 4.80–5.03 (m, 8H, CH_2Ph), 7.21–7.40 (m, 25H, Ar H) ppm; **^{13}C NMR** (100 MHz; $CDCl_3$): δ 23.0 (CH_3), 75.1 (Ins C-2), 75.78 (CH_2), 75.84 (CH_2), 76.1 (CH_2), 82.88 (Ins C), 82.93 (Ins C), 83.3 (Ins C), 127.52 (Ar C), 127.57 (Ar C), 127.7 (Ar C), 127.8 (Ar C), 128.3 (Ar C), 128.4 (Ar C), 137.9 (Ar C), 138.6 (Ar C) ppm; elemental analysis calcd for $C_{42}H_{44}O_6$: C 78.23, H 6.88; found C 77.81; H 6.97%.

1,3,4,5,6-penta-*O*-acetyl-2-*C*-methyl *myo*-inositol (2.66).

1,3,4,6,5–penta–*O*–benzyl–2-*C*-methyl *myo*–inositol **2.63** (0.925 g, 1.43 mmol), THF (6 mL), EtOH (3 mL) and TFA (1.50 mL) were taken in a hydrogenation bottle and 20 % Pd-$(OH)_2$ on carbon (0.75 g) was added in one portion. The reaction mixture was kept in an atmosphere of hydrogen (60 *psi*) at ambient temperature for 20 h. The reaction mixture was then diluted with (1:1) ethanol–water (10 mL) and filtered through a small bed of Celite. The Celite bed was washed with hot water and ethanol (2 x 5 mL) alternately. The combined filtrate was evaporated under reduced pressure and the residue was co–evaporated with absolute ethanol (2 x 5 mL) to get crude 1-*C*-methyl *myo*-inositol **2.65** (0.032 g) which was directly used in the next step without further purification.

A mixture of the crude product **2.65** (0.27 g), pyridine (5 mL), DMAP (0.01 g, catalytic) and acetic anhydride (2.43 mL, 25.74 mmol) was stirred at rt for 30 h. The reaction mixture was cooled to ambient temperature and quenched by adding few pieces of ice. The solvent was evaporated under reduced pressure and the residue obtained was worked up with ethyl acetate. The crude product obtained was purified by column chromatography (silica gel 100-200 mesh, 30% ethyl acetate – light petroleum) to get **2.66** as a colorless solid (0.51 g, 88%); **mp** 133–137 ºC (Crystals obtained by slow evaporation from hot MeOH solution); **IR** (Nujol): $\bar{\nu}$ 1746, 3200–3600 cm^{-1}; **^{1}H NMR** (400 MHz; $CDCl_3$): δ 1.14 (s, 3H, CH_3), 1.99 (s, 6H, CH_3), 2.01 (s, 3H, CH_3), 2.13 (s, 6H, CH_3), 2.15 (bs, 1H, OH, D_2O exchangeable), 5.45 (d, J = 10.0 Hz, 2H, Ins H), 5.22 (t, J = 9.8 Hz, 1H, Ins H), 5.53 (t, J = 9.9 Hz, 2H, Ins H) ppm; **^{13}C NMR** (100 MHz; $CDCl_3$): δ 20.49 (CH_3), 20.52 (CH_3), 22.1 (CH_3), 70.6 (Ins C), 70.7 (Ins C), 73.1 (Ins C), 73.4 (Ins C-2), 169.6 (CO), 169.73 (CO), 169.75 (CO) ppm; elemental analysis calcd for $C_{17}H_{24}O_{11}$: C 50.49, H 5.98; found C 50.26; H 5.66%.

Racemic 1,3,4,5,6-penta-*O*-benzyl-2-*O*-methyl *epi*-inositol (2.79).

To a solution of penta-*O*-benzyl *epi*-alcohol **2.26** (0.063 g, 0.1 mmol) in DMF was added NaH (0.005 g, 0.12 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and then at ambient temperature for 30 min. The reaction mixture was cooled again to 0 °C and methyl iodide (9 µL, 0.15 mmol) was added to it. The reaction mixture was allowed to come to ambient temperature and stirred for 2 h. The reaction was quenched by adding few pieces of ice, concentrated under reduced pressure and

the residue obtained was worked up with ethyl acetate. The crude product obtained was purified by column chromatography (100-200 mesh silica, 12 % ethyl acetate-light petroleum ether) to get the racemic 4-*O*-methyl penta-*O*-benzyl *epi*-alcohol **2.79** (0.062 g, 96%) as a gummy product; **^{1}H NMR** (200 MHz; $CDCl_3$): δ 3.13 (t, J = 2.3 Hz, 1H, Ins H), 3.20–3.35 (m, 2H, Ins H), 3.69 (s, 3H, OCH_3), 3.89 (bs, 1H, Ins H), 4.10 (bs, 1H, Ins H), 4.31 (t, J = 9.7 Hz, 1H, Ins H), 4.43–4.99 (m, 10H, CH_2Ph), 7.13–7.53 (m, 25H, Ar H) ppm; **^{13}C NMR** (50 MHz; $CDCl_3$): δ 61.3 (CH_3), 71.1 (CH_2), 72.6 (CH_2), 73.6 (CH_2), 74.8 (Ins C), 75.8 (CH_2), 78.1 (Ins C), 78.4 (Ins C), 79.2 (Ins C), 80.3 (Ins C), 80.7 (Ins C), 126.8 (Ar C), 127.1 (Ar C), 127.32 (Ar C), 127.35 (Ar C), 127.47 (Ar C), 127.54 (Ar C), 127.6 (Ar C), 127.7 (Ar C), 127.9 (Ar C), 128.1 (Ar C), 128.20 (Ar C), 128.24 (Ar C), 128.3 (Ar C), 137.9 (Ar C), 138.57 (Ar C), 138.63 (Ar C), 139.1(Ar C), 139.5 (Ar C) ppm; elemental analysis calcd for $C_{42}H_{44}O_6$: C 78.23, H 6.88; found C 78.36; H 7.21 %.

Racemic 1,3,4,5,6-penta-*O*-acetyl-2-*O*-methyl *epi*-inositol (2.81).

Racemic 1,3,4,5,6–penta–*O*–benzyl *epi*–inositol **2.79** (0.134 g, 0.21 mmol), THF (2 mL), water (0.50 mL) and TFA (0.50 mL) were taken in a hydrogenation bottle and 20 % $Pd(OH)_2$ on carbon (0.050 g) was added in one portion. The reaction mixture was kept in an atmosphere of hydrogen (60 *psi*) at ambient temperature for 20 h. The reaction mixture was then diluted with (1:1) ethanol–water (10 mL) and filtered through a bed of Celite. The Celite bed was washed with hot water and ethanol (2 x 5 mL) alternately. The combined filtrate was evaporated under reduced pressure and the residue was co-evaporated with absolute ethanol (2 x 5 mL) to get crude racemic 4-*O*-methyl *epi*-inositol **2.80** (0.039 g) which was used in the next step without further purification.

A mixture of crude **2.80** (0.039 g, 0.16mmol), pyridine (2 mL), DMAP (0.01 g, catalytic) and acetic anhydride (0.3 mL, 3.15 mmol) was refluxed for 18 h. The reaction mixture was cooled to ambient temperature and quenched by adding few pieces of ice. The solvent was evaporated under reduced pressure and the residue obtained was worked up with ethyl acetate. The crude product obtained was purified by column chromatography (silica gel 100–200 mesh, 35 % ethyl acetate – light petroleum) to get **2.81** as a colorless solid (0.071 g, 83%); **mp** 131–133 ºC (Crystals obtained by slow evaporation from hot MeOH solution); **IR** (Nujol): $\bar{\nu}$ 1747 cm^{-1}; **^{1}H NMR** (400 MHz; $CDCl_3$): δ 2.00 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.07 (s, 3H,

CH_3), 2.09 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 3.50 (s, 3H, OCH_3), 3.92 (bs, 1H, Ins H), 4.89-4.95 (dd, J_1 = 3.3 Hz, J_2 = 10. 3 Hz, 1H, Ins H), 4.98–5.05 (m, 2H, Ins H), 5.54–5.58 (m, 1H, Ins H), 5.72 (t, J = 10.3 Hz, 1H, Ins H) ppm; **^{13}C NMR** (100 MHz; $CDCl_3$): δ 20.5 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 61.3 (OCH_3), 67.4 (Ins C), 68.4 (Ins C), 68.5 (Ins C), 68.8 (Ins C), 71.3 (Ins C), 77.9 (Ins C), 169.5 (CO), 169.6 (CO), 169.7 (CO), 169.9 (CO), 170.6 (CO) ppm; elemental analysis calcd for $C_{17}H_{24}O_{11}$: C 50.49, H 5.98; found C 50.36; H 5.81 %.

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Appendix I

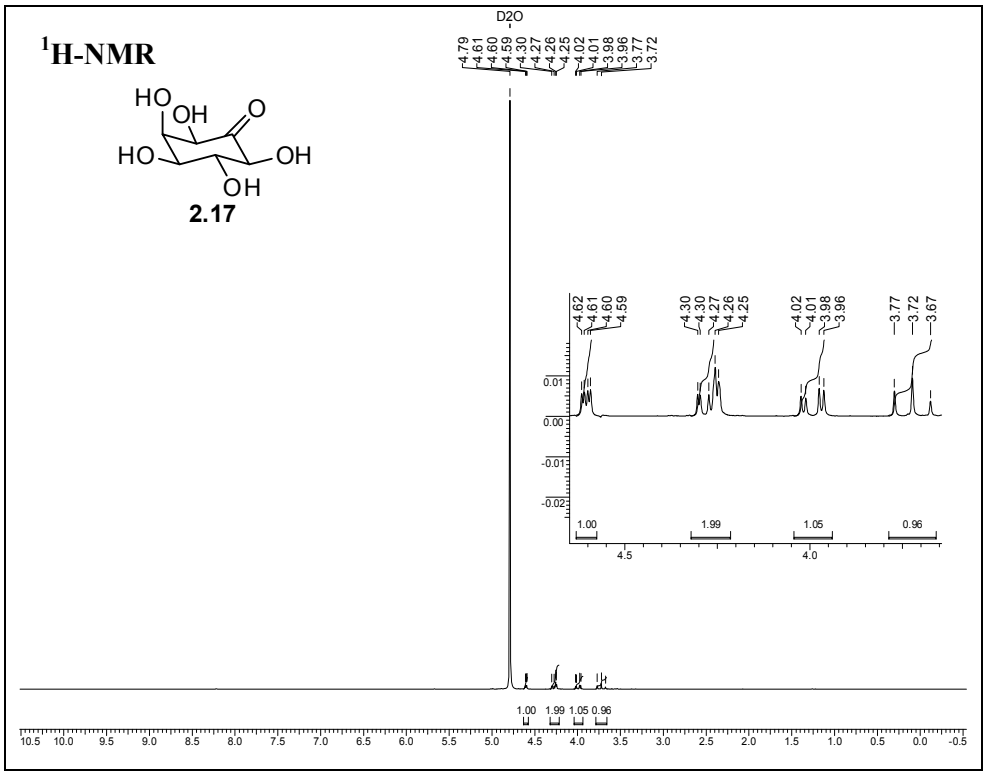
Appendix I Index

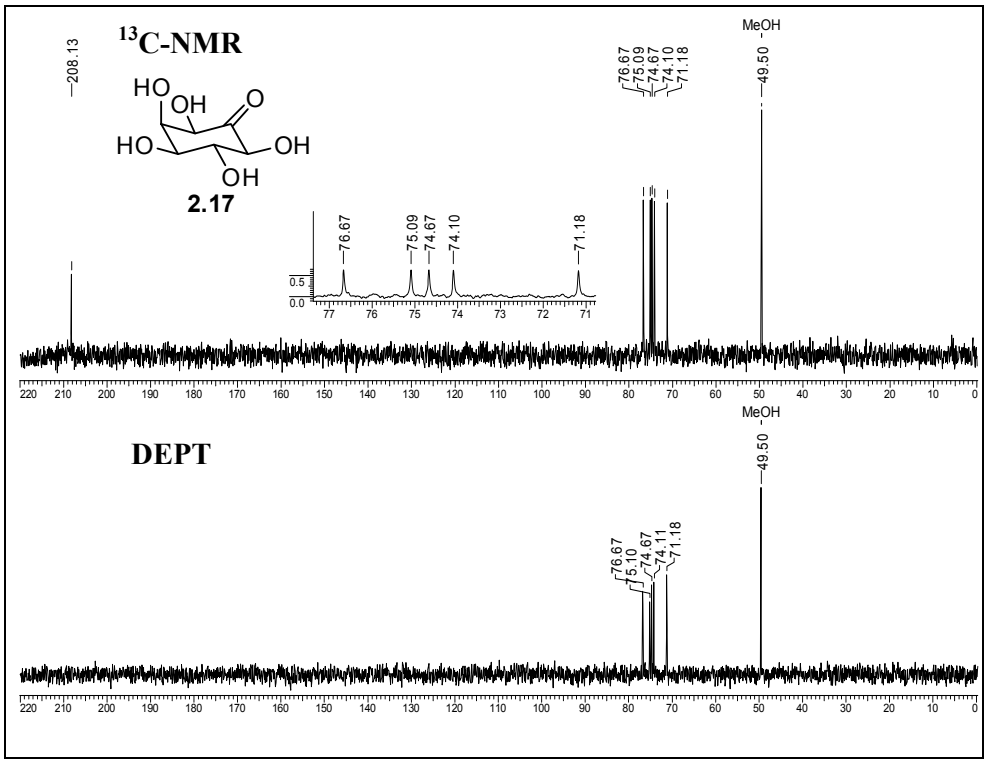
Crystal Data Table

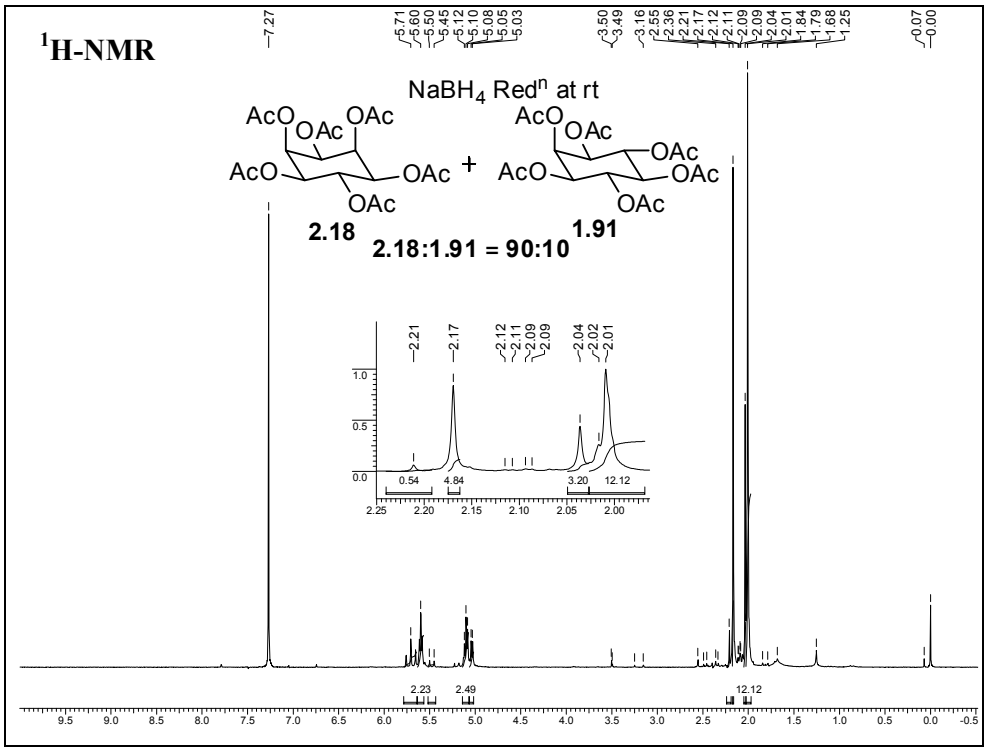
Compund No.	**rac-2.17**	**1.37**	**2.24**	**2.56**
Chemical formula	$C_6H_{10}O_6$	$C_{21}H_{22}O_7$	$C_{43}H_{44}O_7$	$C_{41}H_{39}O_9N$
M_r	178.14	386.39	672.78	689.73
Temperature (K)	297(2)	297(2)	297(2)	297(2)
Morphology	prism	plate	rectangular plates	plate
Crystal size	0.29 × 0.28 × 0.17	0.16×0.13 ×0.08	0.53 × 0.25 × 0.16	0.32×0.06 ×0.05
Crystal system Space group	orthorhombic $Pca2_1$	monoclinic $P2_1/c$	monoclinic $P2_1/c$	monoclinic $P2_1/c$
a (Å) b (Å) c (Å) α (°) β (°) γ (°)	11.1825(18) 6.9752(12) 8.7930(15) 90 90 90	13.776(15) 12.532(14) 10.999(13) 90 104.34(2) 90	14.216(2) 10.3165(17) 27.948(4) 111.242(6)	18.144(4) 7.9967(19) 25.775(6) 90 100.167(4) 90
V (Å^3)	685.9(2)	1840(4)	3820.4(10)	3681.0(15)
Z	4	4	4	4
D_{calc} (g cm^{-3})	1.725	1.395	1.170	1.245
μ (mm^{-1})	0.158	0.105	0.078	0.088
F(000)	376	816	1432	1456
Absorption correction T_{min} / T_{max}	Multi-scan 0.956 / 0.974	Multi-scan 0.983 / 0.992	Multi-scan 0.959 / 0.987	0.973 / 0.996
h, k, l (min, max)	(-10, 13), (-8, 8), (-10, 10)	(-16, 13), (-14, 14), (-10, 13)	(-16,16), (-12,12), (-33,33)	(-21, 21), (-9, 9), (-30, 30)
Reflns collected	3225	8877	36075	34554
Unique reflns Observed reflns	1189 1176	3225 2254	6717 4195	6497 4908
R_{int}	0.0152	0.0509	0.0340	0.0590
No. of parameters	129	262	452	464
GoF	1.059	1.024	1.030	1.299
$R_1[I > 2\sigma(I)]$ $wR_2[I > 2\sigma(I)]$	0.0268 0.0689	0.0481 0.1131	0.0824 0.2239	0.1030 0.2066
R_1_all data wR_2_all data	0.0270 0.0691	0.0725 0.1269	0.1221 0.2565	0.1369 0.2260
$\Delta\rho_{max}$, $\Delta\rho_{min}$(e Å^{-3})	0.24, -0.13	0.17, -0.18	0.47, -0.18	0.25, -0.25
CCDC No.	-	-	816954	-

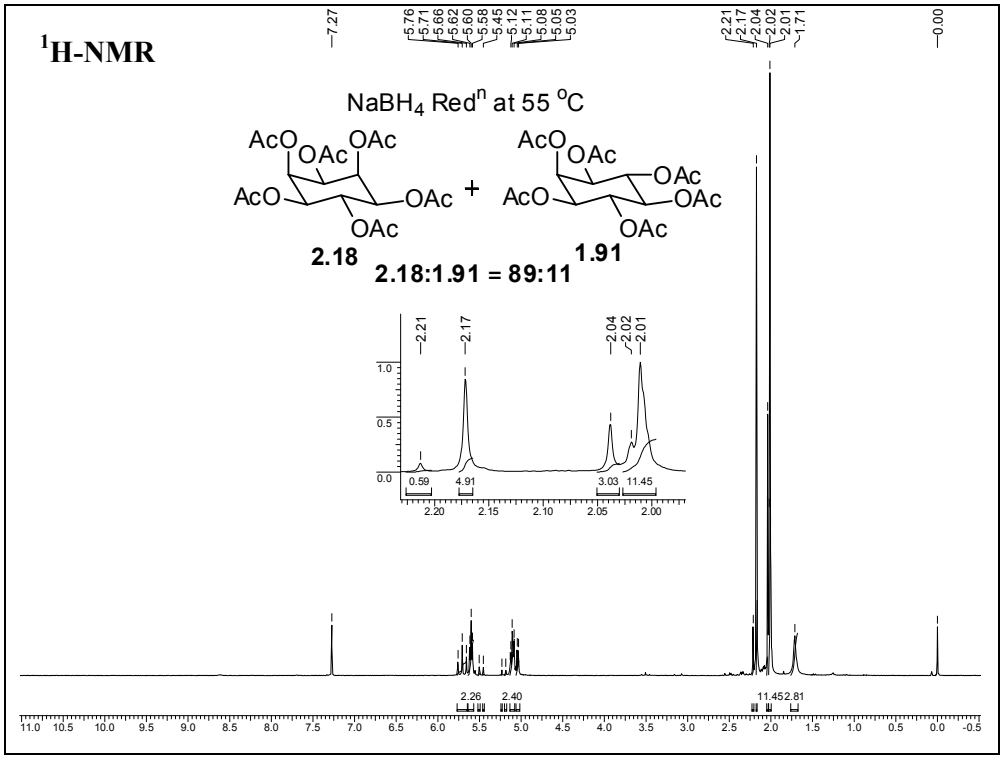
Crystal Data Table

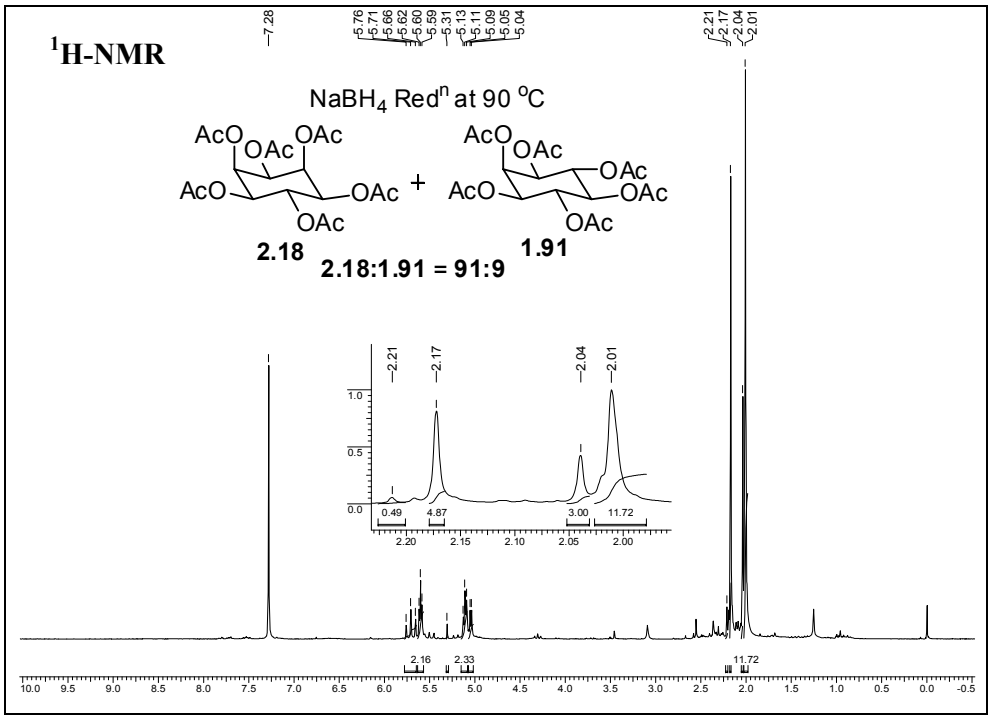
Compund No.	**2.62**	**2.66**	**2.81**
Chemical formula	$C_{19}H_{26}O_{12}$	$C_{17}H_{24}O_{11}\cdot 0.25(H_2O)$	$C_{17}H_{24}O_{11}$
M_r	446.40	408.36	404.36
Temperature (K)	297(2)	297(2)	297(2)
Morphology	plate	prism	thick plate
Crystal size	0.37×0.27 ×0.19	0.46×0.41 ×0.27	0.33×0.26 ×0.19
Crystal system Space group	monoclinic $P2_1/c$	triclinic P-1	triclinic P-1
a (Å) b (Å) c (Å) α (°) β (°) γ (°)	10.983(7) 32.95(2) 14.886(7) 90 112.22(4) 90	8.5062(7) 9.5170(8) 26.338(2) 98.029(4) 93.690(4) 100.574(4)	10.4171(14) 13.5098(18) 15.498(2) 77.756(2) 79.661(2) 88.350(2)
V (Å^3)	4987(5)	2066.6(3)	2096.8(5)
Z	8	4	4
D_{calc} (g cm^{-3})	1.189	1.313	1.281
μ (mm^{-1})	0.100	0.112	0.108
F(000)	1888	864	856
Absorption correction T_{min} / T_{max}	Multi-scan 0.964 / 0.981	Multi-scan 0.951/0.971	Multi-scan 0.965 / 0.980
h, k, l (min, max)	(-13, 13), (-39, 39), (-17, 17)	(-10, 10), (-11, 11), (-31, 31)	(-12, 12), (-16, 16), (-18, 18)
Reflns collected	28962	46382	20206
Unique reflns Observed reflns	8746 4606	7276 6277	7363 5391
R_{int}	0.0955	0.045	0.0328
No. of parameters	601	529	517
GoF	1.064	1.106	1.066
$R_1[I > 2\sigma(I)]$ $wR_2[I > 2\sigma(I)]$	0.1035 0.2701	0.0491 0.1281	0.1026 0.2626
R_1_all data wR_2_all data	0.1737 0.3159	0.0568 0.1327	0.1203 0.2828
$\Delta\rho_{max}$, $\Delta\rho_{min}$(e Å^{-3})	0.21, -0.25	0.59, -0.12	0.95, -0.27
CCDC No.	-	-	-

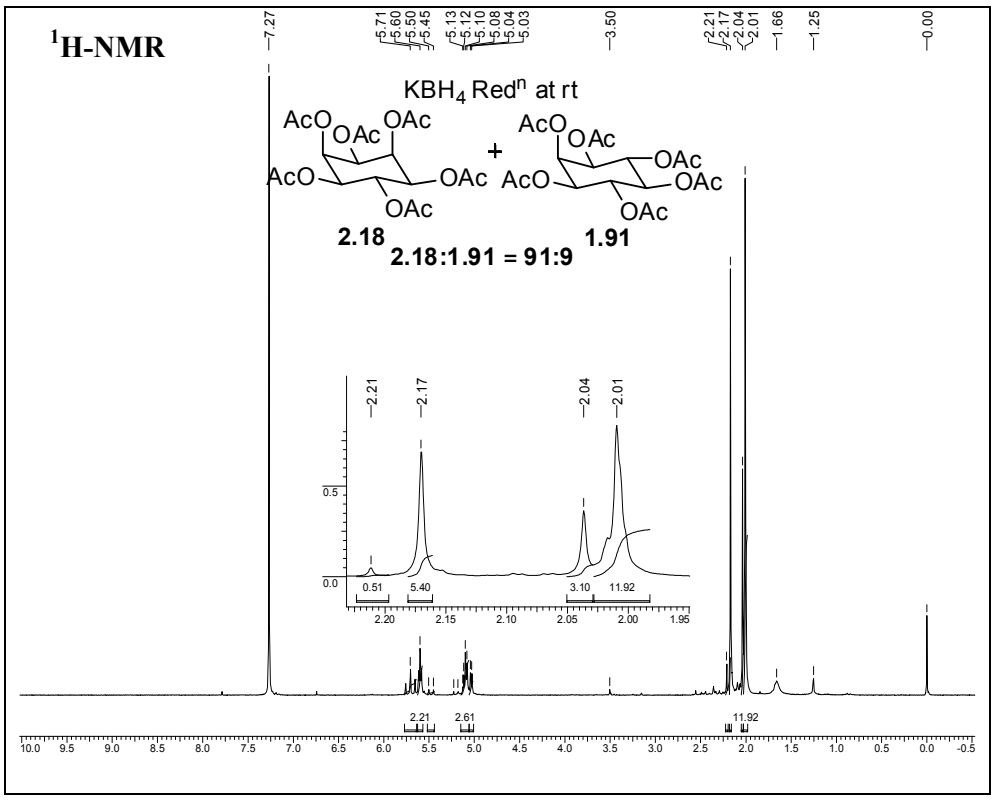

^{1}H-NMR
D2O
HO
OH
O
HO
OH
OH
2.17
4.79
4.61
4.60
4.59
4.30
4.27
4.26
4.25
4.02
4.01
3.98
3.96
3.77
3.72
1.00
1.99
1.05
0.96

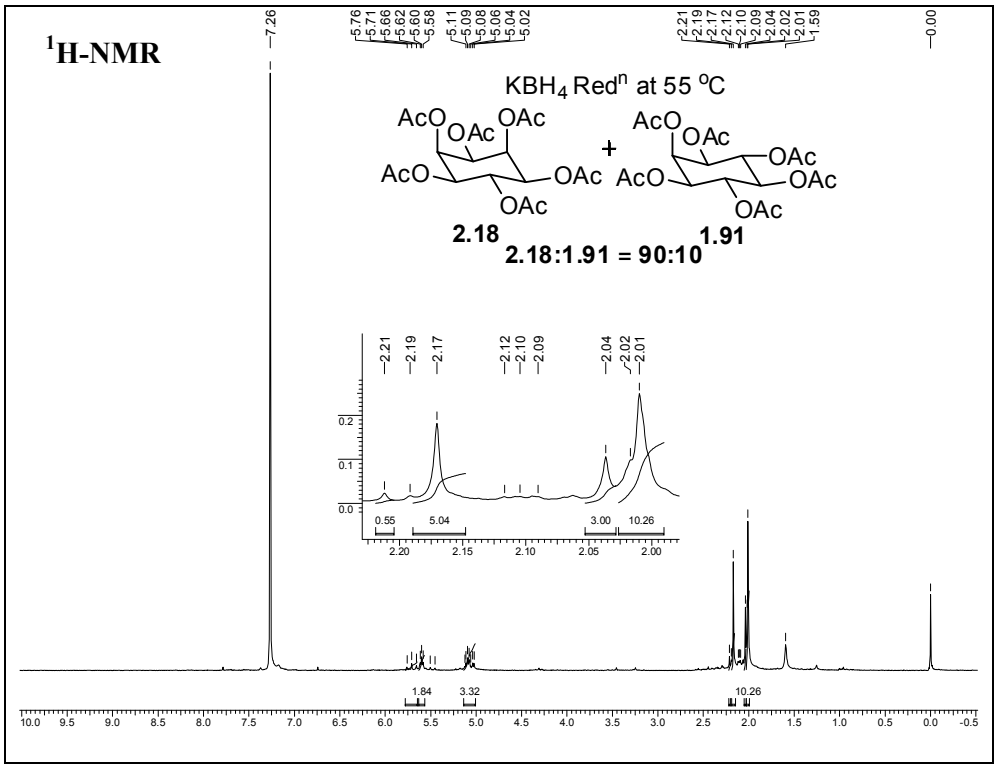

^{13}C-NMR
208.13
HO
OH
O
HO
OH
OH
2.17
76.67
75.09
74.67
74.10
71.18
MeOH
49.50
DEPT
76.67
75.10
74.67
74.11
71.18
MeOH
49.50

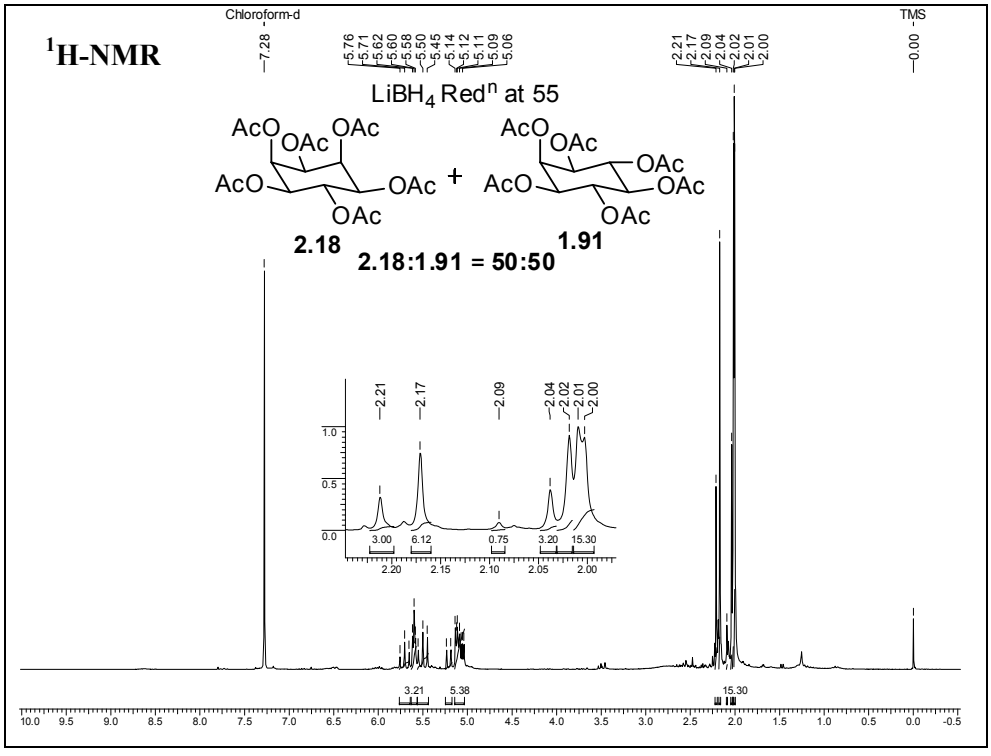

1H-NMR
NaBH4 Redn at rt
2.18
1.91
2.18:1.91 = 90:10

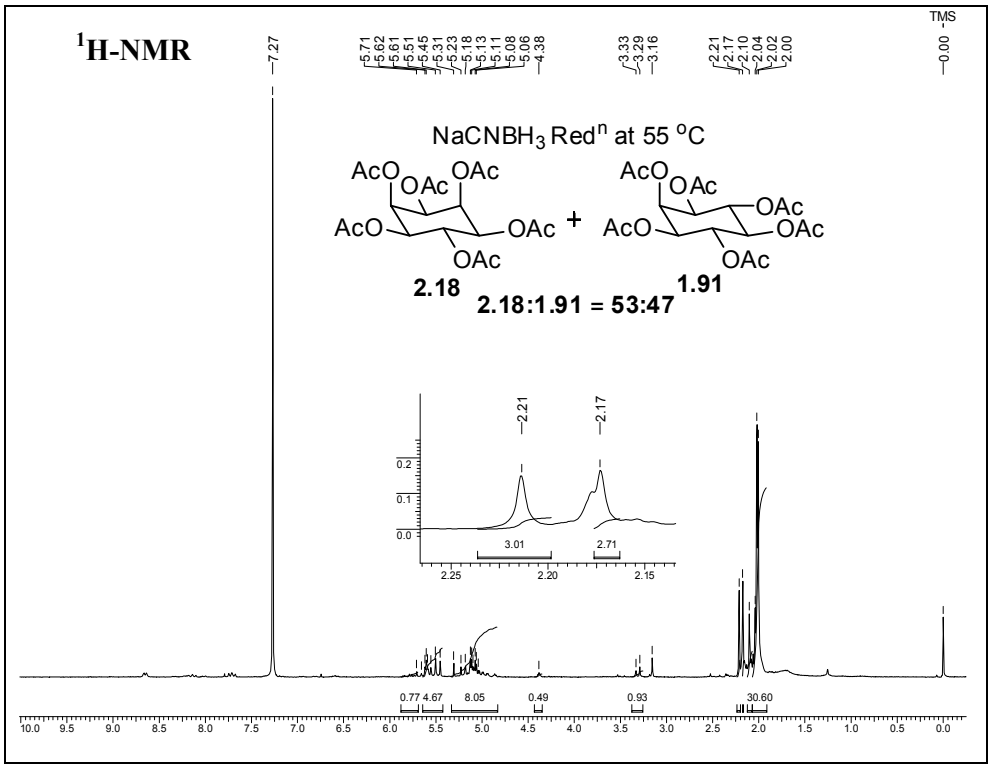

1H-NMR
NaBH4 Redn at 55 °C
2.18
1.91
2.18:1.91 = 89:11

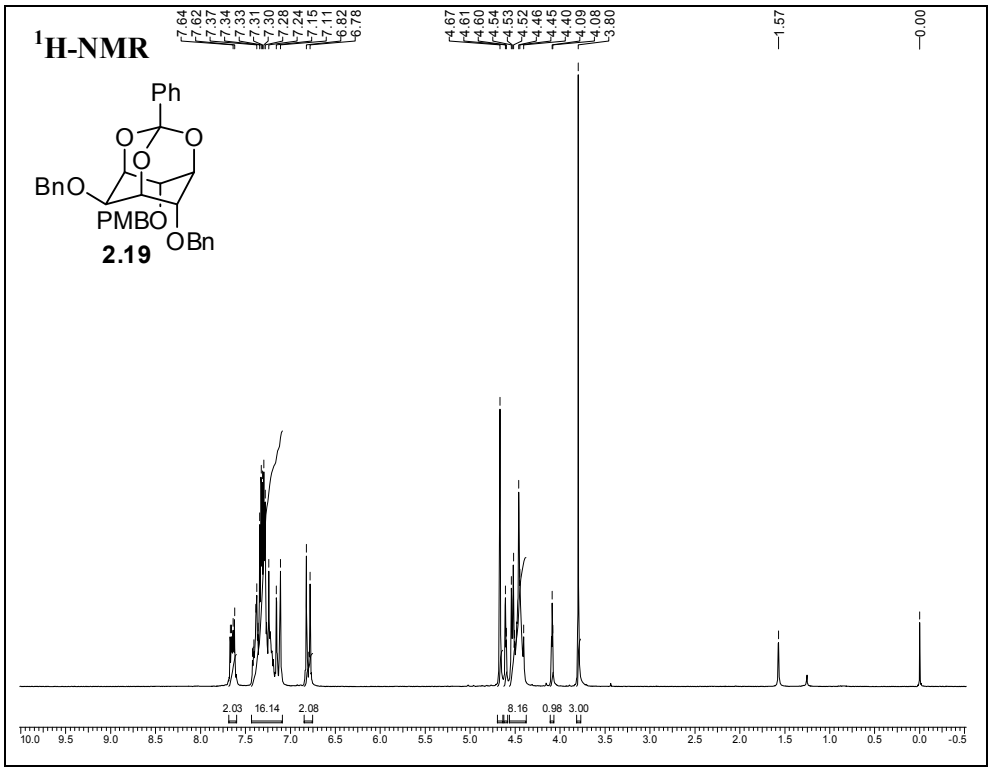

^{1}H-NMR
NaBH$_4$ Red^n at 90 ^{o}C
AcO
OAc
2.18
1.91
2.18:1.91 = 91:9

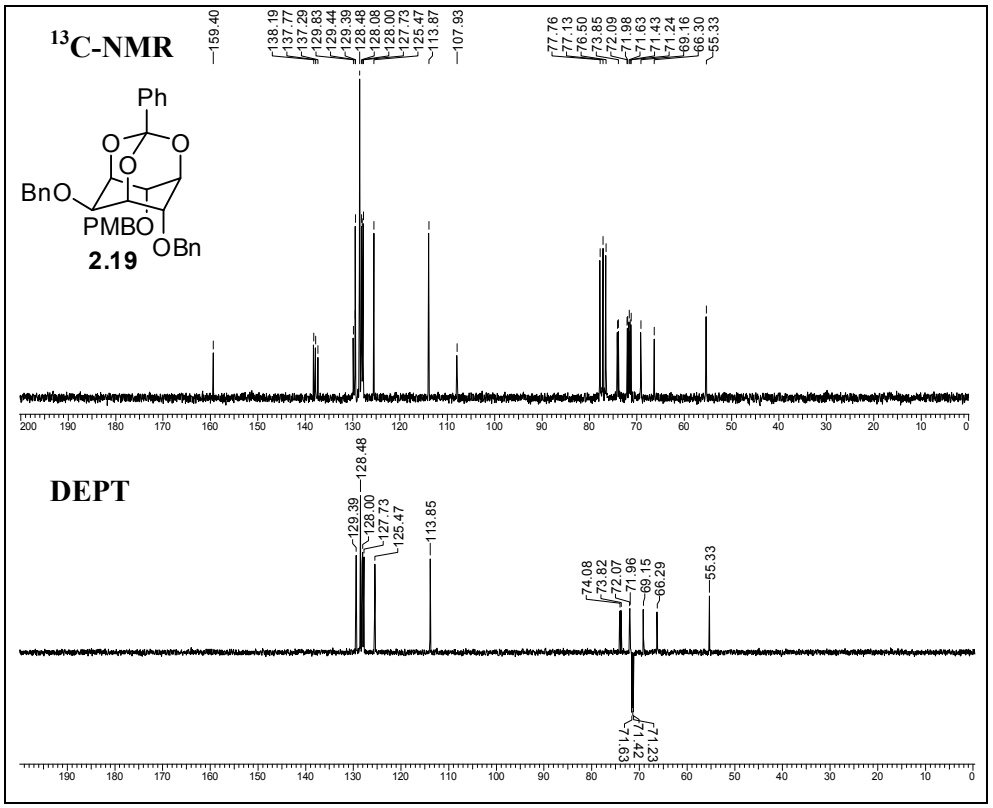

^{1}H-NMR
KBH$_4$ Red^n at rt
AcO
OAc
2.18
1.91
2.18:1.91 = 91:9

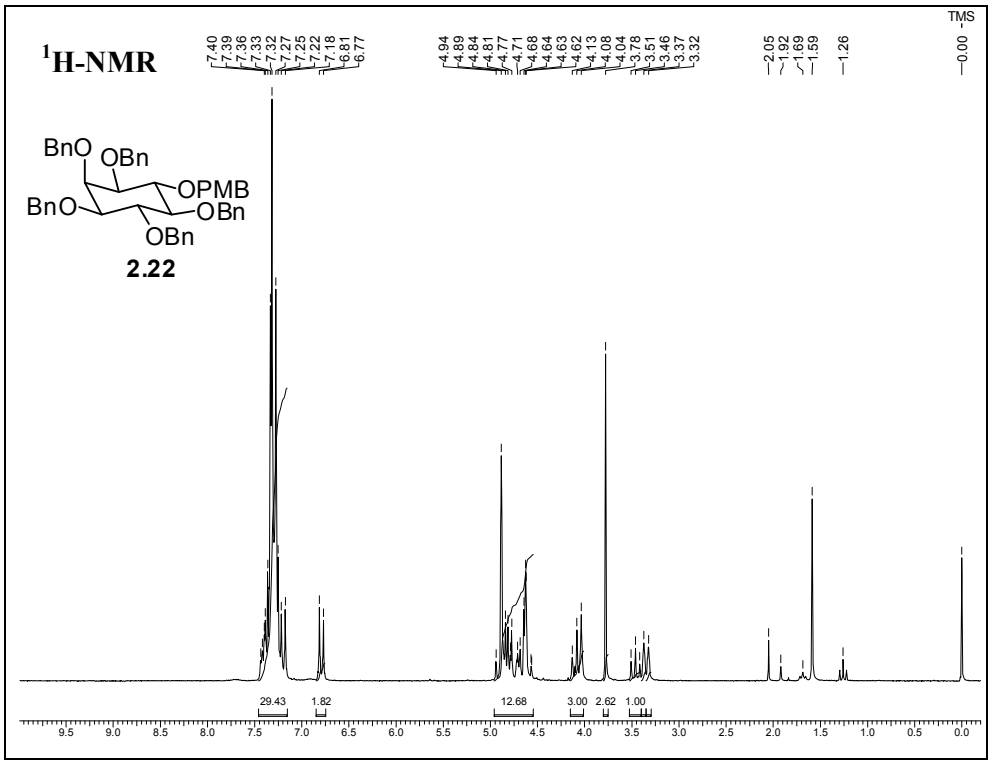

^{1}H-NMR
KBH$_4$ Red^n at 55 ^{o}C
2.18
1.91
2.18:1.91 = 90:10

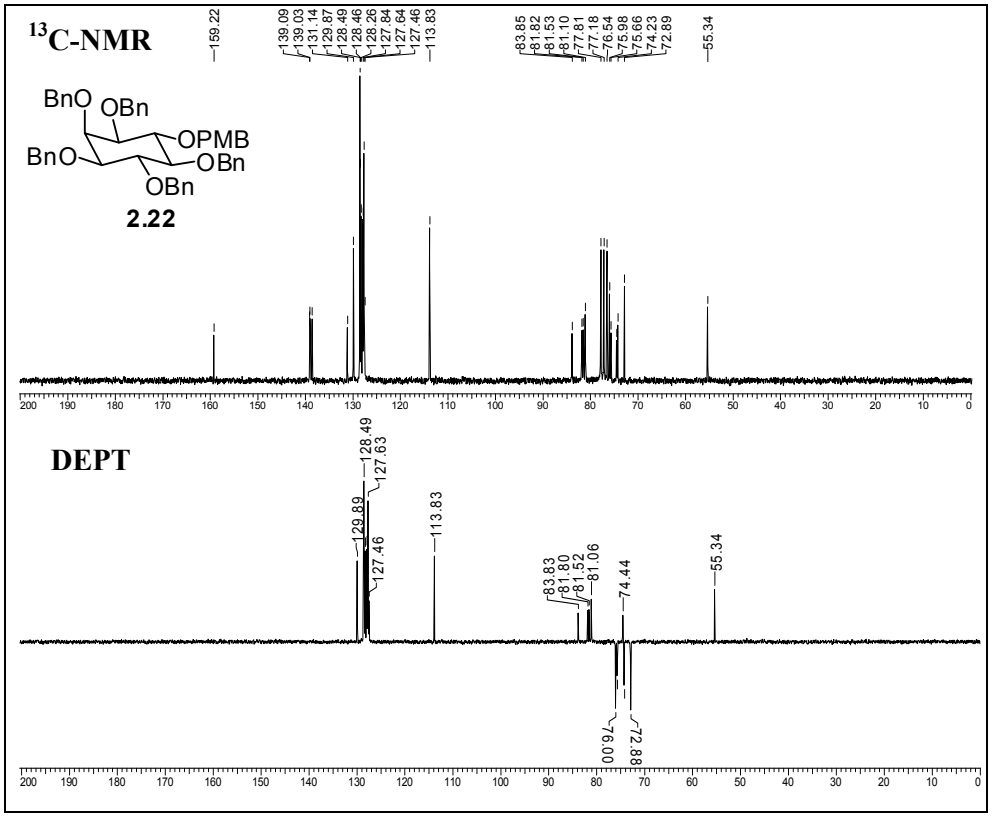

^{1}H-NMR
LiBH$_4$ Red^n at 55
2.18
1.91
2.18:1.91 = 50:50

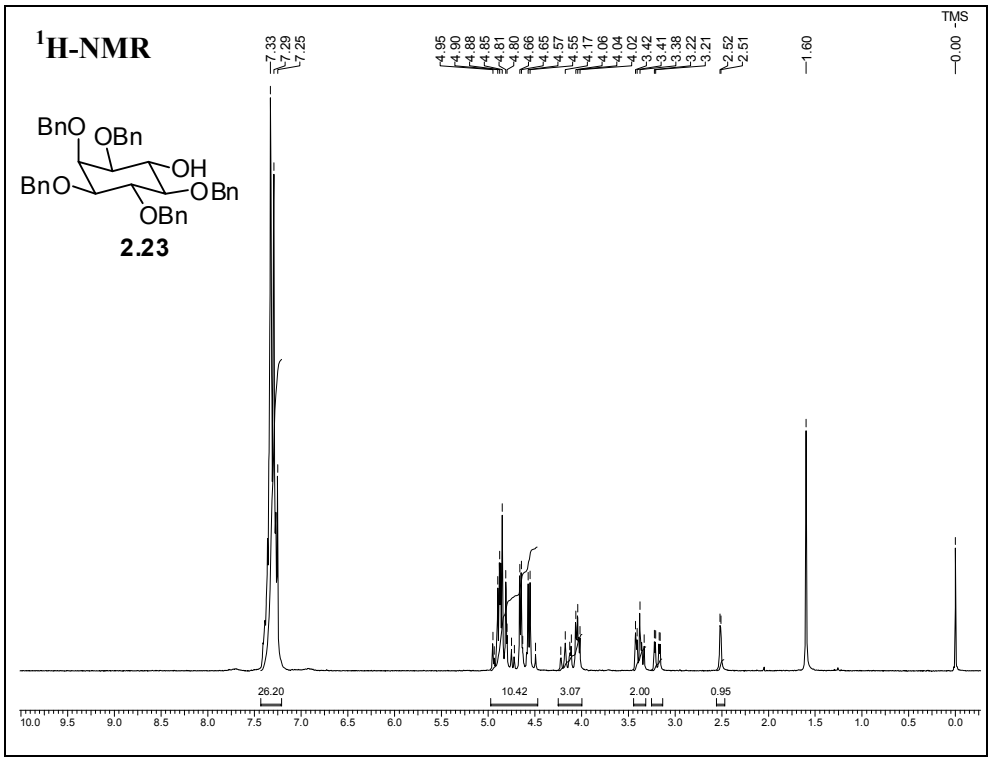

^{1}H-NMR
NaCNBH$_3$ Red^n at 55 ^{o}C
2.18
1.91
2.18:1.91 = 53:47

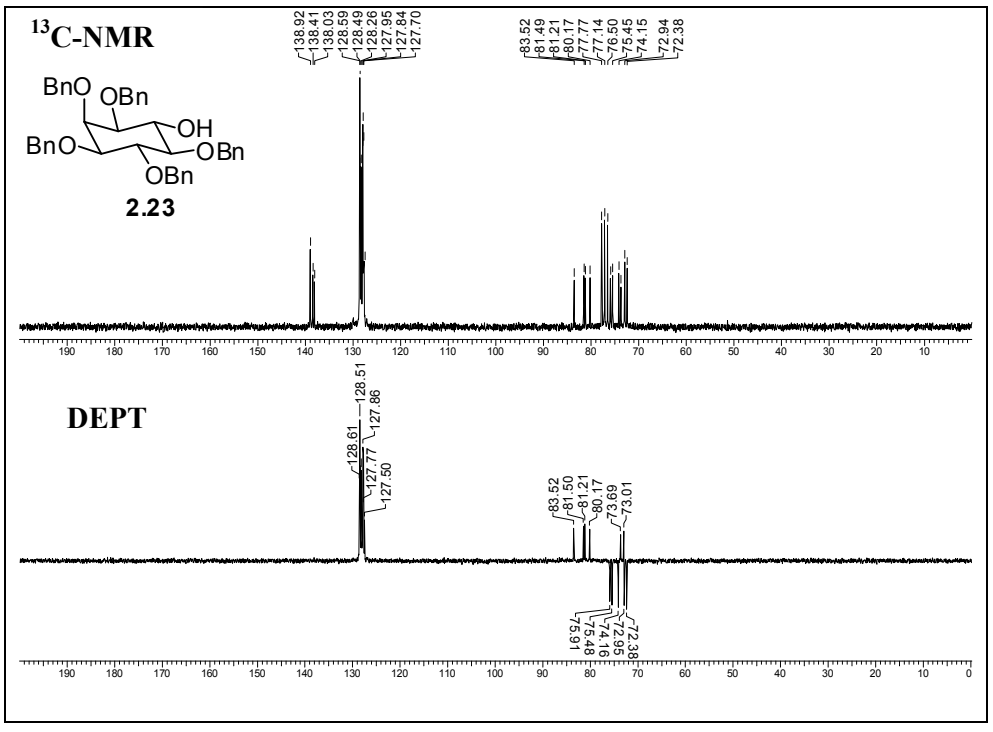

^{1}H-NMR
Ph
O
O
O
BnO
PMBO
OBn
2.19
7.64
7.62
7.37
7.34
7.33
7.31
7.30
7.28
7.24
7.15
7.11
6.82
6.78
4.67
4.61
4.60
4.54
4.53
4.52
4.46
4.45
4.40
4.09
4.08
3.80
1.57
0.00
2.03
16.14
2.08
8.16
0.98
3.00

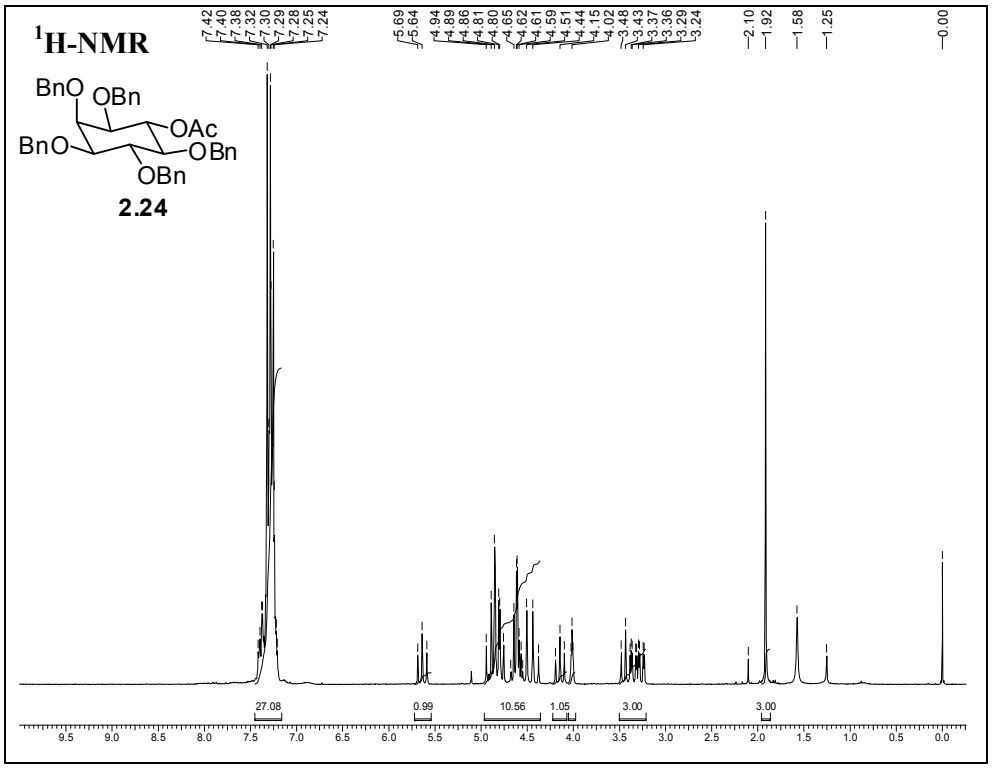

^{13}C-NMR
Ph
O
O
O
BnO
PMBO
OBn
2.19
159.40
138.19
137.77
137.29
129.83
129.44
129.39
128.48
128.08
128.00
127.73
125.47
113.87
107.93
77.76
77.13
76.50
73.85
72.09
71.98
71.63
71.43
71.24
69.16
66.30
55.33
DEPT
128.48
129.39
128.00
127.73
125.47
113.85
74.08
73.82
72.07
71.96
69.15
66.29
55.33
71.63
71.42
71.23

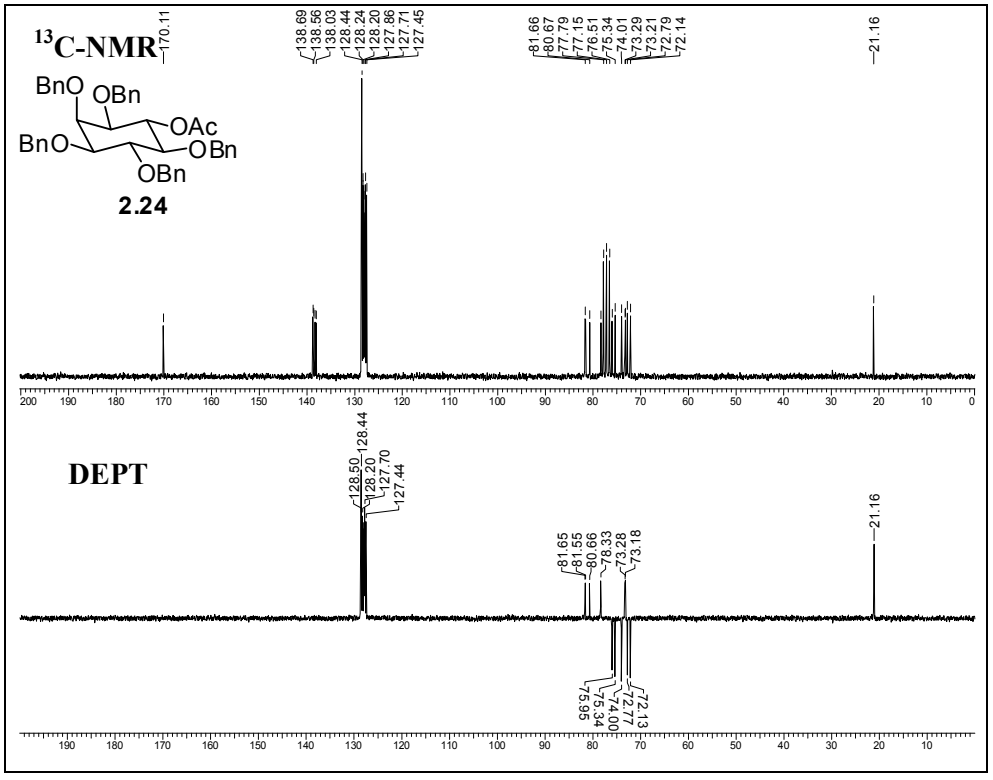

^{1}H-NMR
BnO
OBn
OPMB
BnO
OBn
OBn
2.22
TMS
7.40
7.39
7.36
7.33
7.32
7.27
7.25
7.22
7.18
6.81
6.77
4.94
4.89
4.84
4.81
4.77
4.71
4.68
4.64
4.63
4.62
4.13
4.08
4.04
3.78
3.51
3.46
3.37
3.32
2.05
1.92
1.69
1.59
1.26
0.00
29.43
1.82
12.68
3.00
2.62
1.00

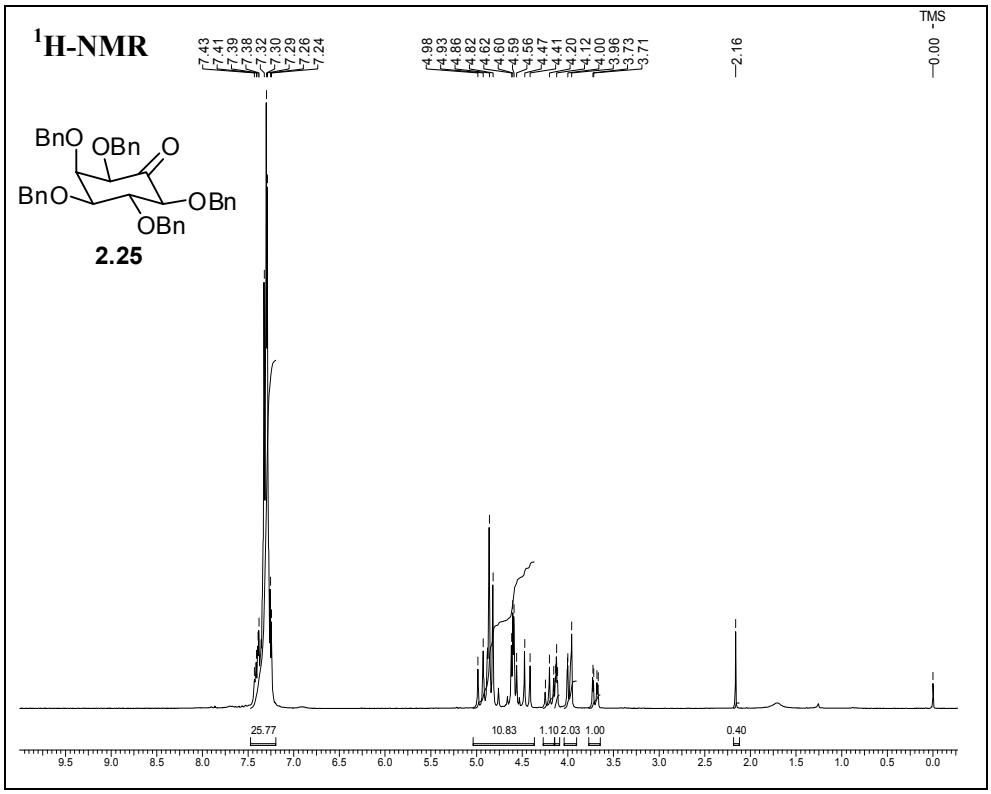

^{13}C-NMR
BnO
OBn
OPMB
BnO
OBn
OBn
2.22
159.22
139.09
139.03
131.14
129.87
128.49
128.46
128.26
127.84
127.64
127.46
113.83
83.85
81.82
81.53
81.10
77.81
77.18
76.54
75.98
75.66
74.23
72.89
55.34
DEPT
128.49
127.63
129.89
127.46
113.83
83.83
81.80
81.52
81.06
74.44
55.34
76.00
72.88

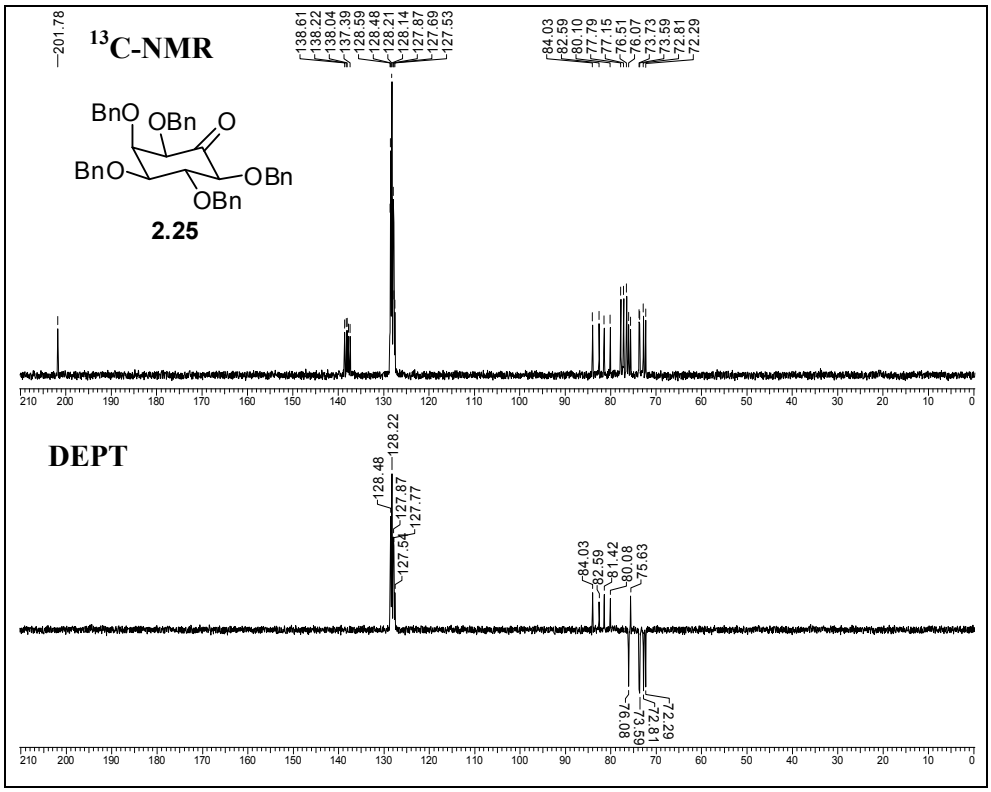

^{1}H-NMR
BnO
OBn
OH
BnO
OBn
OBn
2.23
TMS
7.33
7.29
7.25
4.95
4.90
4.88
4.85
4.81
4.80
4.66
4.65
4.57
4.55
4.17
4.06
4.04
4.02
3.42
3.41
3.38
3.22
3.21
2.52
2.51
1.60
0.00
26.20
10.42
3.07
2.00
0.95

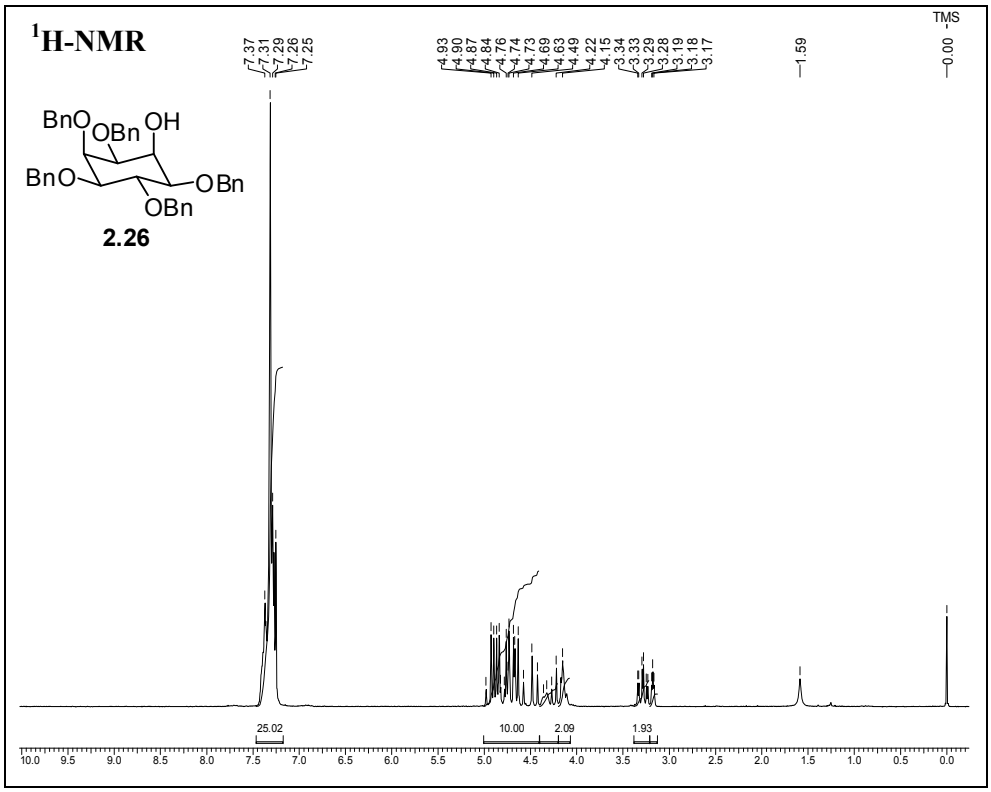

^{13}C-NMR
BnO
OBn
OH
BnO
OBn
OBn
2.23
138.92
138.41
138.03
128.59
128.49
128.26
127.95
127.84
127.70
83.52
81.49
81.21
80.17
77.77
77.14
76.50
75.45
74.15
72.94
72.38
DEPT
128.51
128.61
127.86
127.77
127.50
83.52
81.50
81.21
80.17
73.69
73.01
75.91
75.48
74.16
72.95
72.38

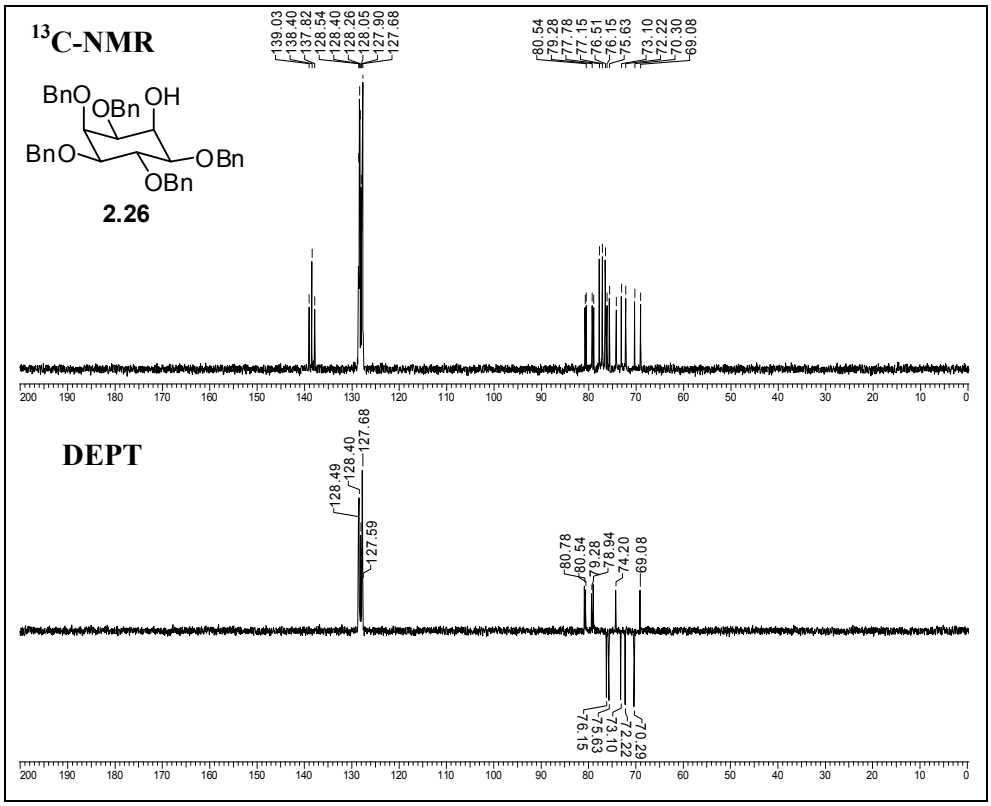

^{1}H-NMR
BnO
OBn
OAc
BnO
OBn
OBn
2.24

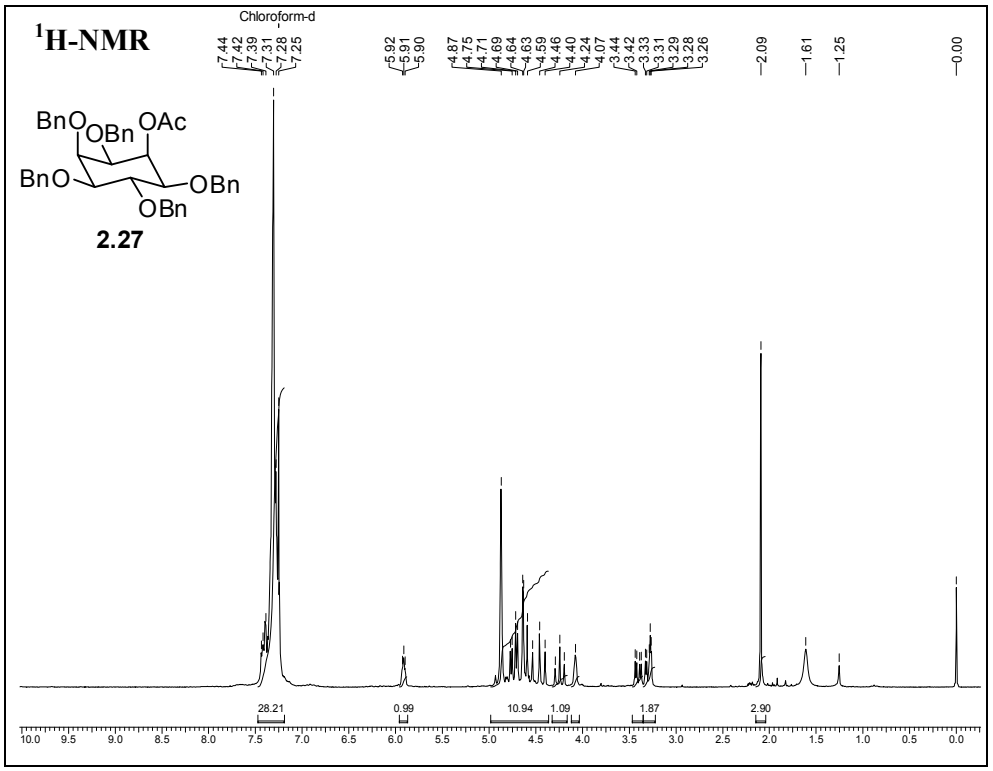

^{13}C-NMR
BnO
OBn
OAc
BnO
OBn
OBn
2.24
DEPT

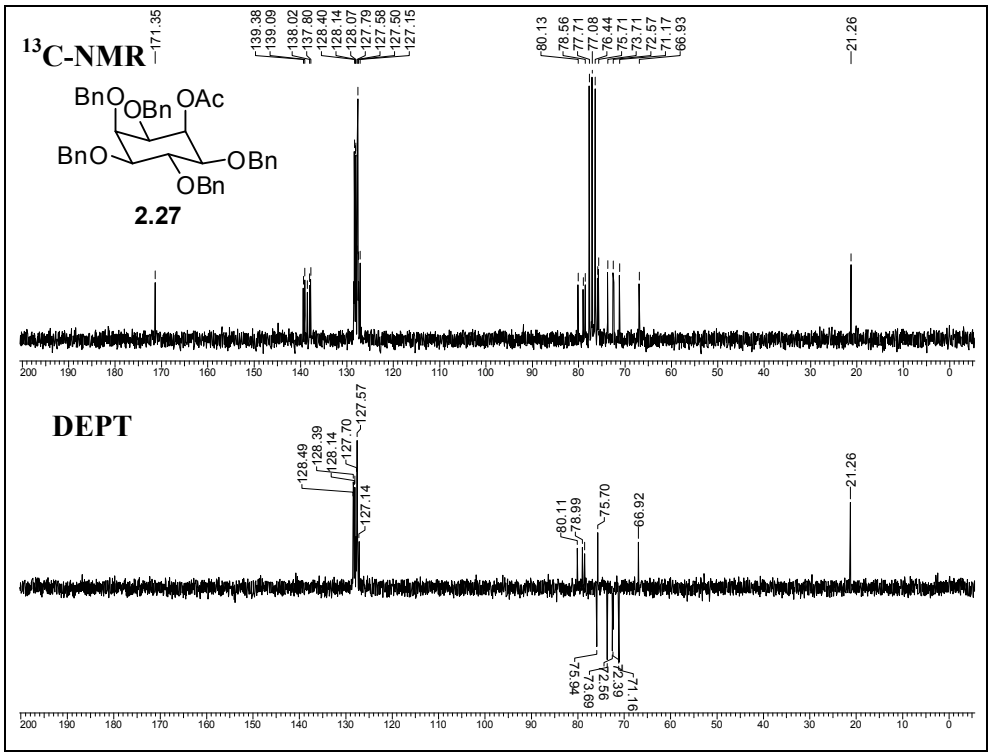

^{1}H-NMR
BnO
OBn
O
BnO
OBn
OBn
2.25
TMS
7.43
7.41
7.39
7.38
7.32
7.30
7.29
7.26
7.24
4.98
4.93
4.86
4.82
4.62
4.60
4.59
4.56
4.47
4.41
4.20
4.12
4.00
3.96
3.73
3.71
2.16
0.00
25.77
10.83
1.10
2.03
1.00
0.40

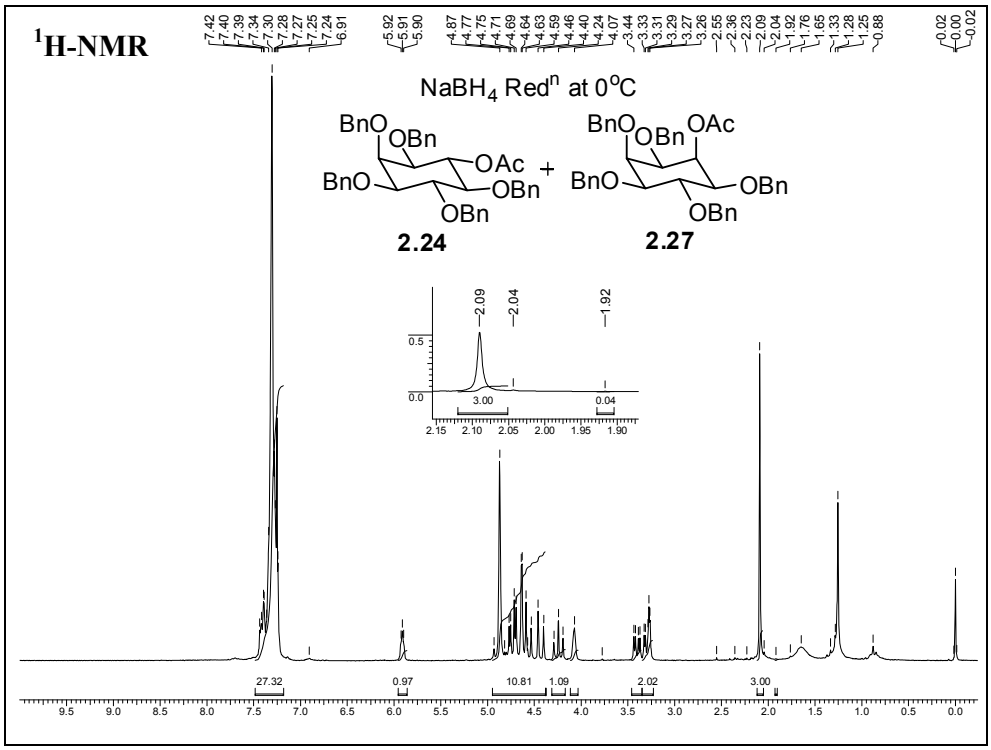

201.78
^{13}C-NMR
138.61
138.22
138.04
137.39
128.59
128.48
128.21
128.14
127.87
127.69
127.53
84.03
82.59
80.10
77.79
77.15
76.51
76.07
73.73
73.59
72.81
72.29
BnO
OBn
O
BnO
OBn
OBn
2.25
DEPT
128.48
128.22
127.87
127.77
127.54
84.03
82.59
81.42
80.08
75.63
80.08
73.59
72.81
72.29

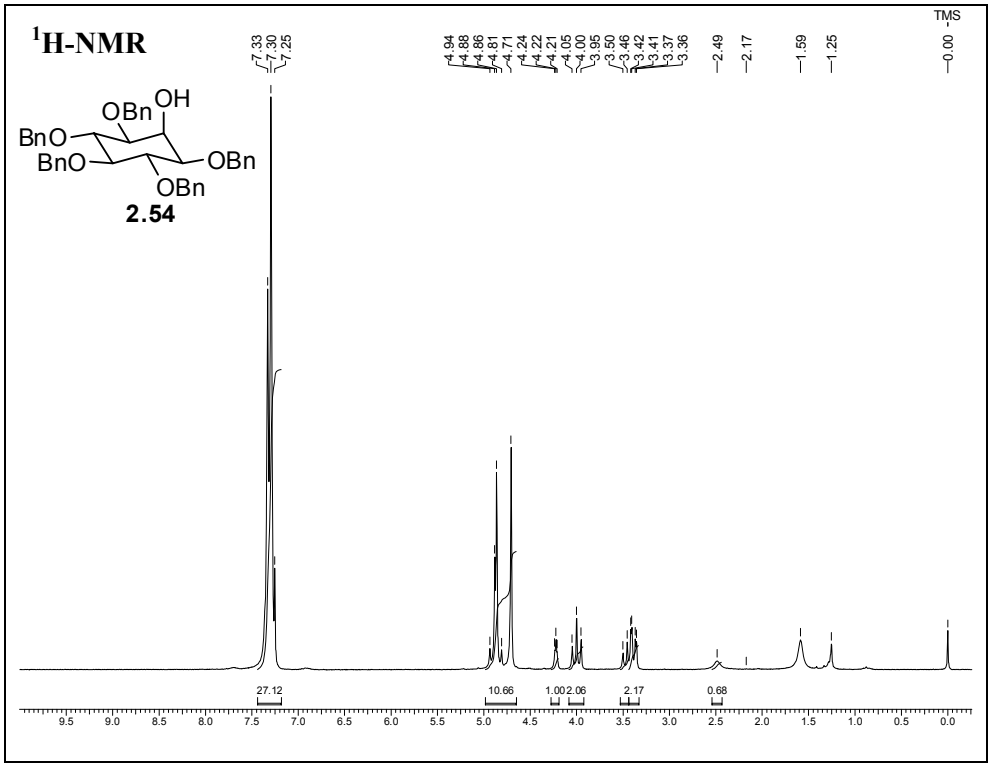

^{1}H-NMR
BnO
OBn
OH
BnO
OBn
OBn
2.26
TMS
7.37
7.31
7.29
7.26
7.25
4.93
4.90
4.87
4.84
4.76
4.74
4.73
4.69
4.63
4.49
4.22
4.15
3.34
3.33
3.29
3.28
3.19
3.18
3.17
1.59
0.00
25.02
10.00
2.09
1.93

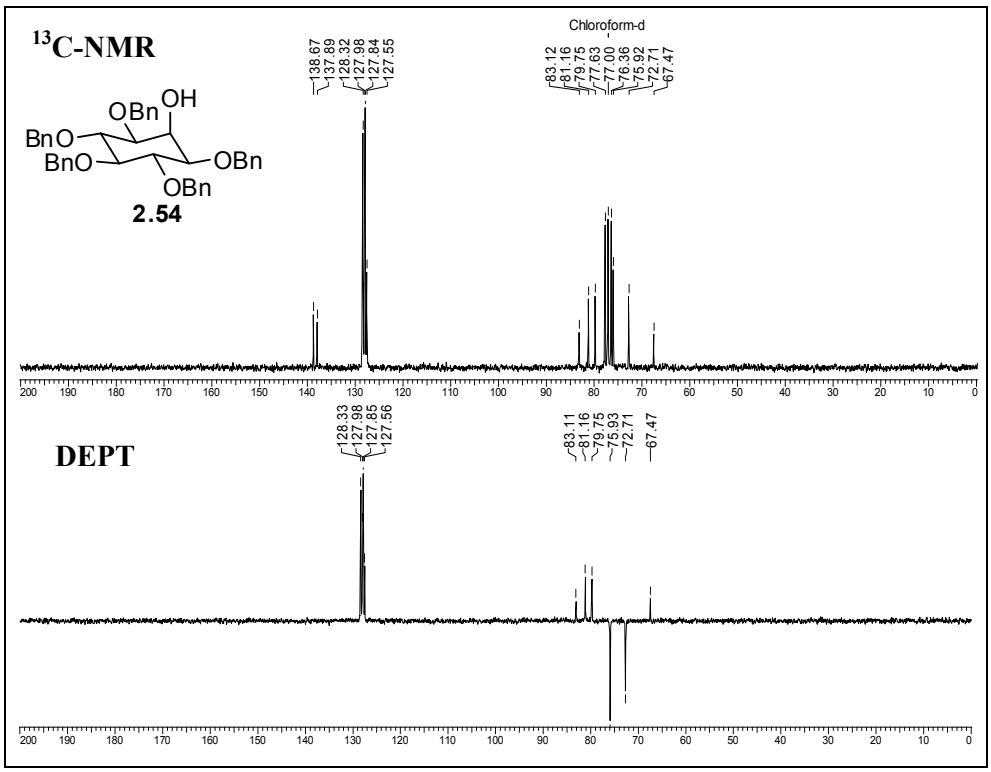

^{13}C-NMR
BnO
OBn
OH
BnO
OBn
OBn
2.26
139.03
138.40
137.82
128.54
128.40
128.26
128.05
127.90
127.68
80.54
79.28
77.78
77.15
76.51
76.15
75.63
73.10
72.22
70.30
69.08
DEPT
128.49
128.40
127.68
127.59
80.78
80.54
79.28
78.94
74.20
69.08
76.15
75.63
73.10
72.22
70.29

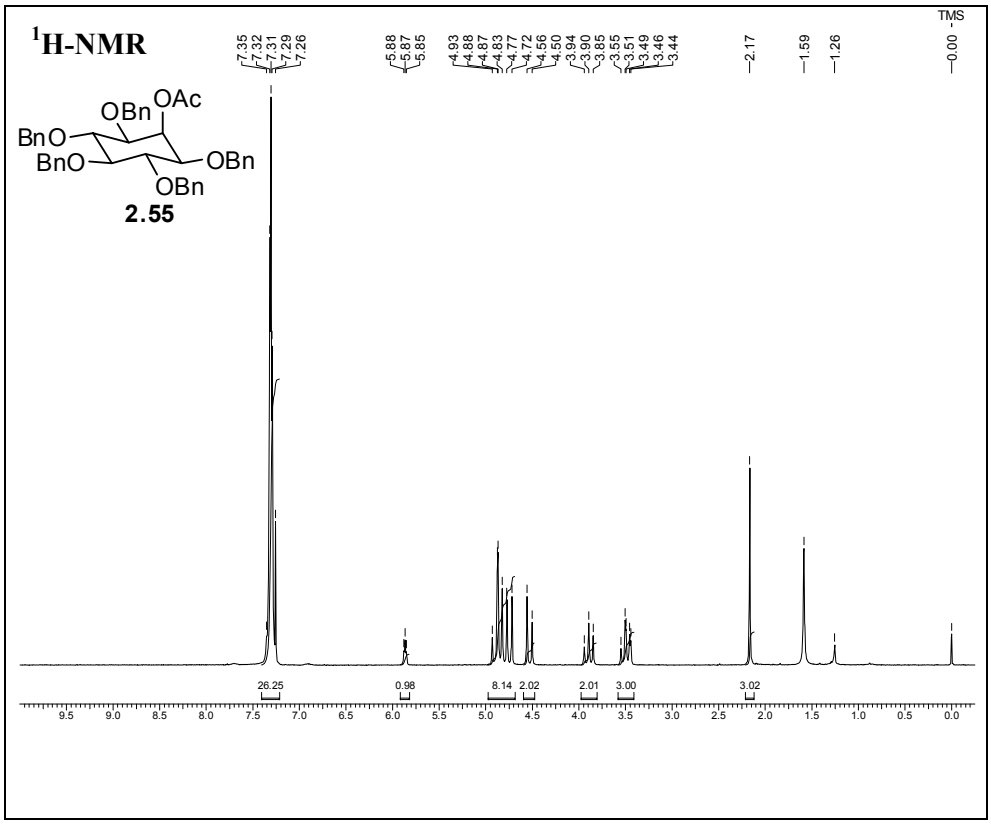

^{1}H-NMR
Chloroform-d
7.44
7.42
7.39
7.31
7.28
7.25
5.92
5.91
5.90
4.87
4.75
4.71
4.69
4.64
4.63
4.59
4.46
4.40
4.24
4.07
3.44
3.42
3.33
3.31
3.29
3.28
3.26
2.09
1.61
1.25
0.00
BnO
OBn
OAc
BnO
OBn
OBn
2.27
28.21
0.99
10.94
1.09
1.87
2.90


^{13}C-NMR
171.35
139.38
139.09
138.02
137.60
128.40
128.14
128.07
127.79
127.58
127.50
127.15
80.13
78.56
77.71
77.08
76.44
75.71
73.71
72.57
71.17
66.93
21.26
BnO
OBn
OAc
BnO
OBn
OBn
2.27
DEPT
127.57
128.49
128.39
128.14
127.70
127.14
80.11
78.99
75.70
66.92
21.26
75.94
73.69
72.63
72.56
71.16


^{1}H-NMR
NaBH$_4$ Red^n at 0^{o}C
BnO
OBn
OAc
OBn
OBn
2.24
BnO
OBn
OAc
BnO
OBn
OBn
2.27
2.09
2.04
1.92
27.32
0.97
10.81
1.09
2.02
3.00


^{1}H-NMR
OBn
OH
BnO
BnO
OBn
OBn
2.54
TMS
27.12
10.66
1.00
2.06
2.17
0.68


^{13}C-NMR
OBn
OH
BnO
BnO
OBn
OBn
2.54
Chloroform-d
DEPT


^{1}H-NMR
TMS
OBn
OAc
BnO
BnO
OBn
OBn
2.55
7.35
7.32
7.31
7.29
7.26
5.88
5.87
5.85
4.93
4.88
4.87
4.83
4.77
4.72
4.56
4.50
3.94
3.90
3.85
3.55
3.51
3.49
3.46
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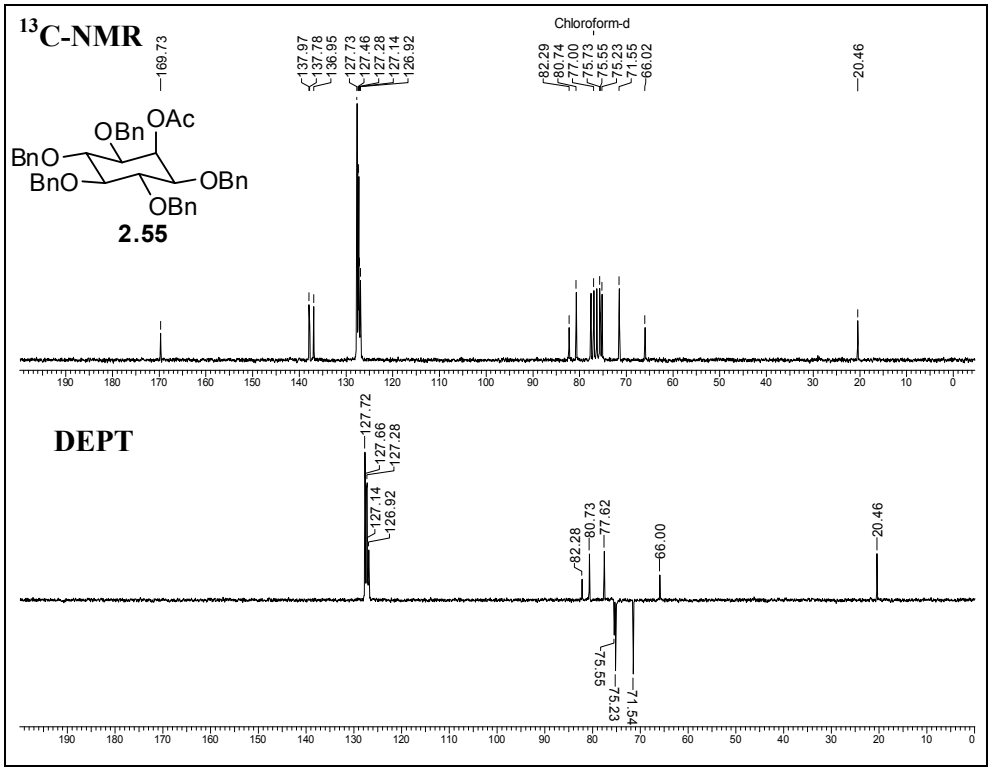
2.01
3.00
3.02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OAc
BnO
BnO
OBn
OBn
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136.95
127.73
127.46
127.28
127.14
126.92
82.29
80.74
77.00
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75.55
75.23
71.55
66.02
20.46
DEPT
127.72
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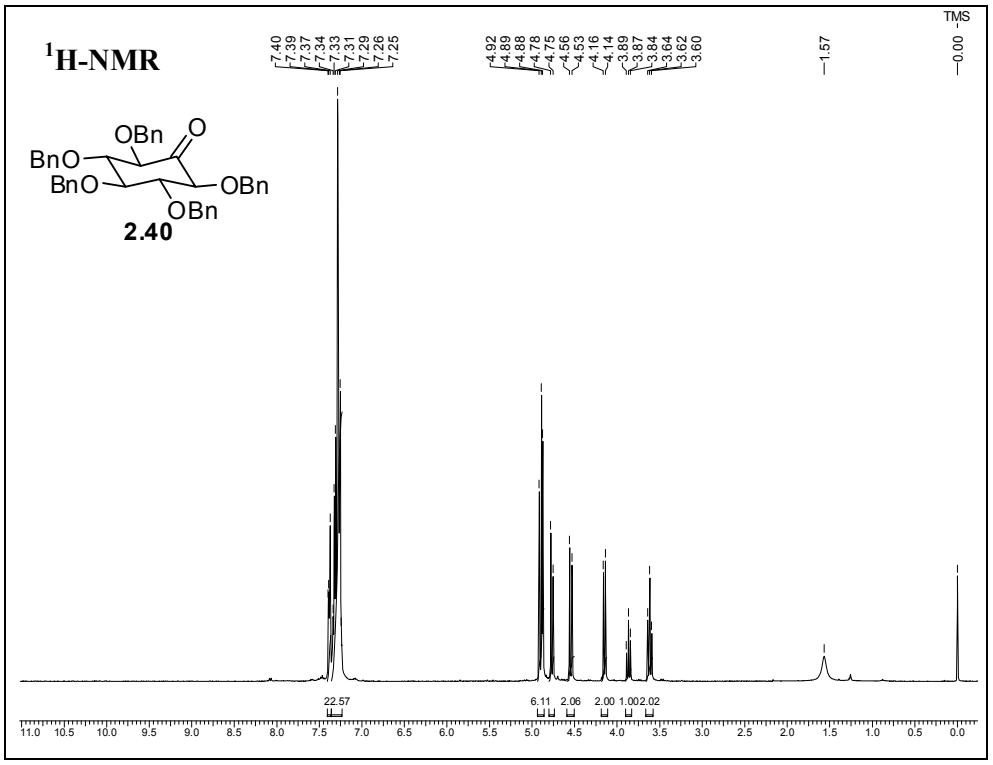
126.92
82.28
80.73
77.62
66.00
20.46
75.55
75.23
71.54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TMS
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7.39
7.37
7.34
7.33
7.31
7.29
7.26
7.25
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4.89
4.88
4.78
4.75
4.56
4.53
4.16
4.14
3.89
3.87
3.84
3.64
3.62
3.60
1.57
0.00
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O
BnO
BnO
OBn
OBn
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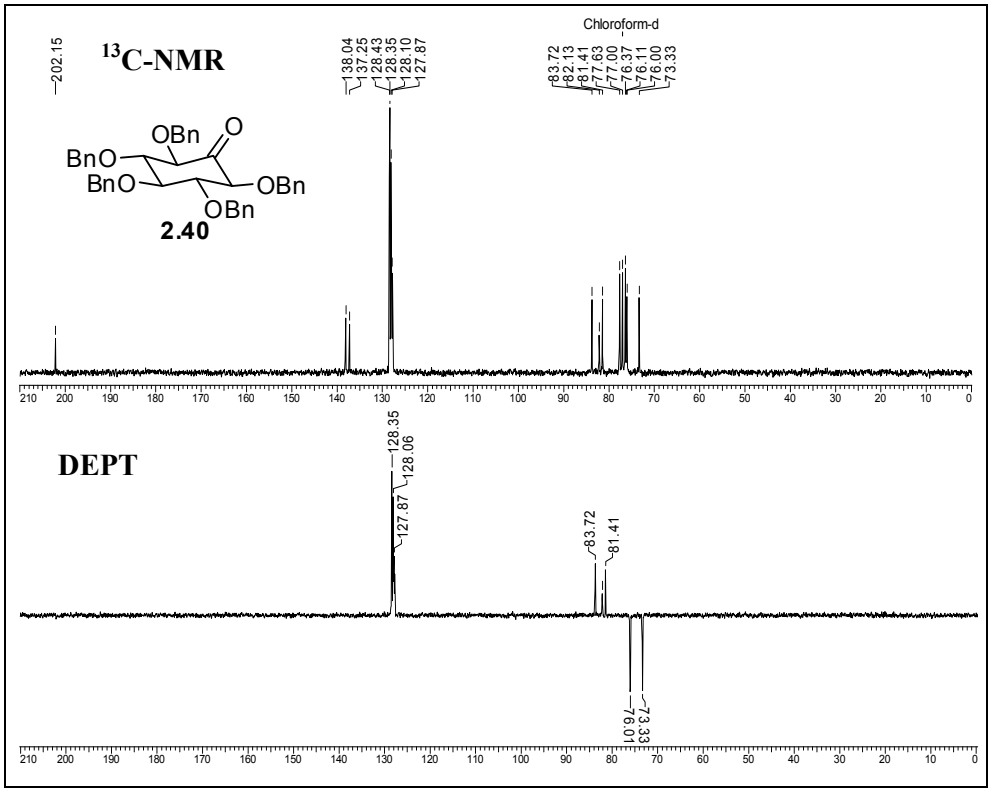
22.57
6.11
2.06
2.00
1.00
2.02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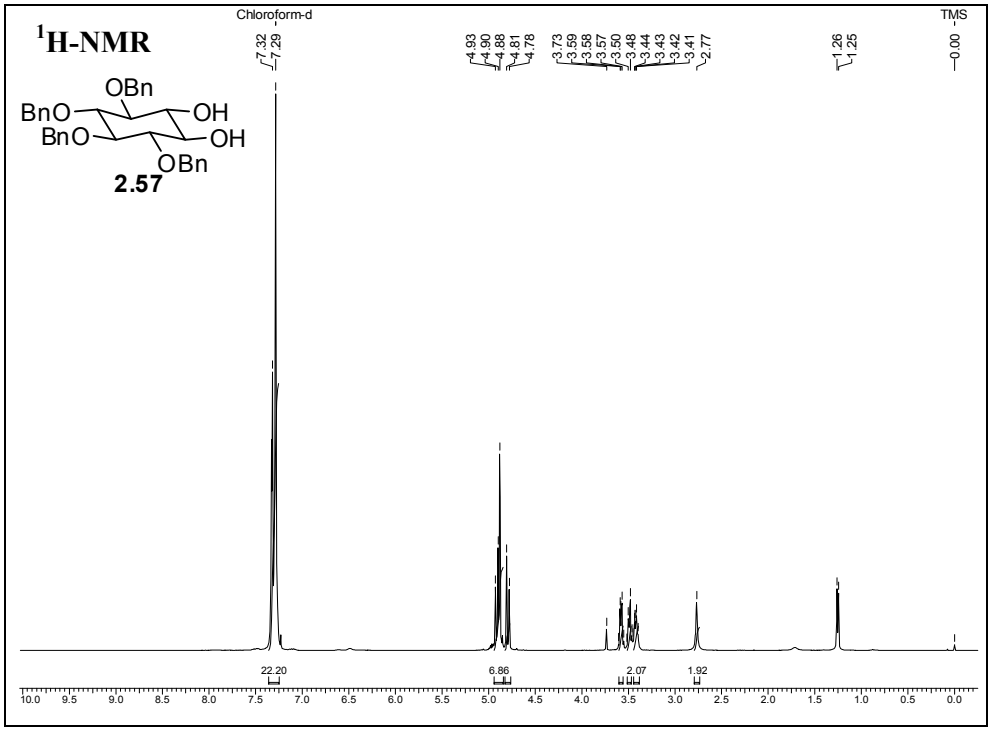
81.41
77.63
77.00
76.37
76.11
76.00
73.33
OBn
O
BnO
BnO
OBn
OBn
2.40
DEPT
128.35
128.06
127.87
83.72
81.41
76.01
73.33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OH
BnO
OH
OBn
2.57
Chloroform-d
TMS
7.32
7.29
4.93
4.90
4.88
4.81
4.78
3.73
3.59
3.58
3.57
3.50
3.48
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3.42
3.41
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1.25
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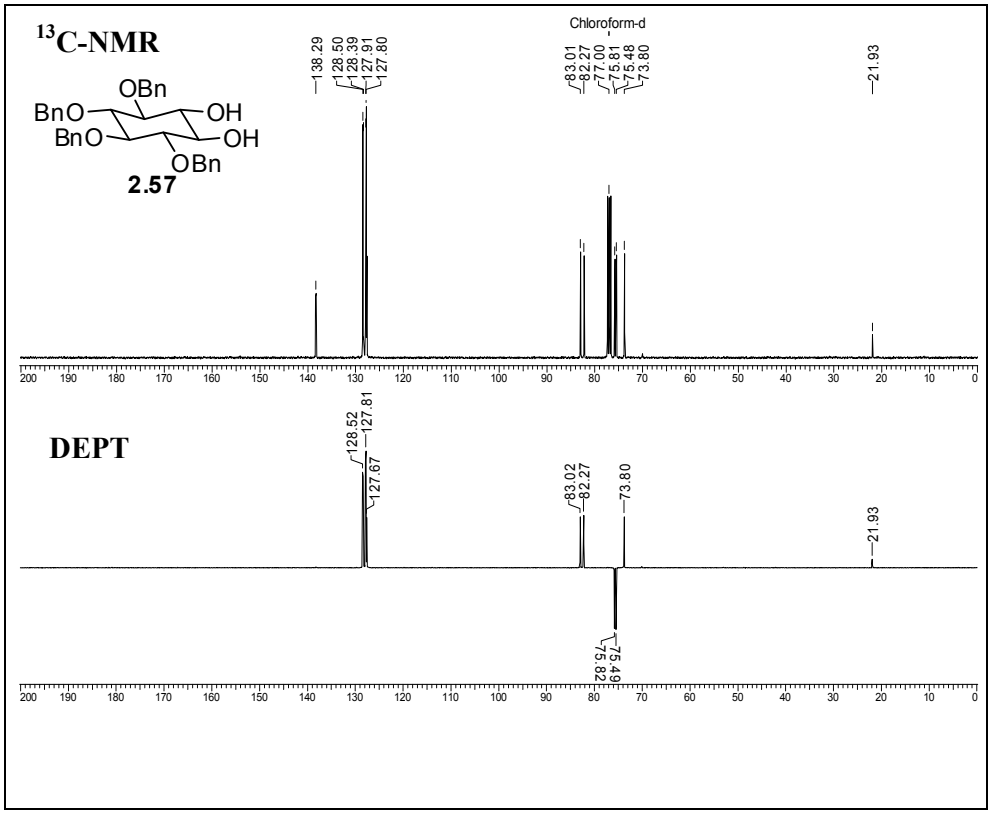
2.07
1.92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BnO
OH
BnO
OH
OBn
2.57
Chloroform-d
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128.39
127.91
127.80
83.01
82.27
77.00
75.61
75.48
73.80
21.93
DEPT
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127.67
83.02
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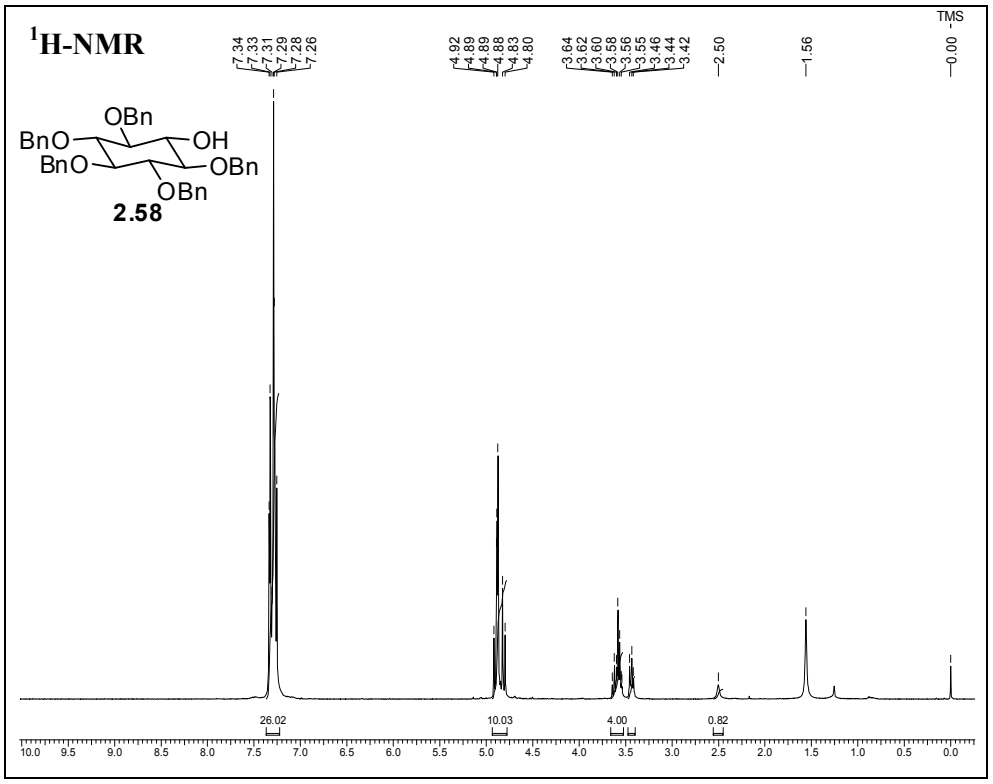
73.80
21.93
76.49
75.82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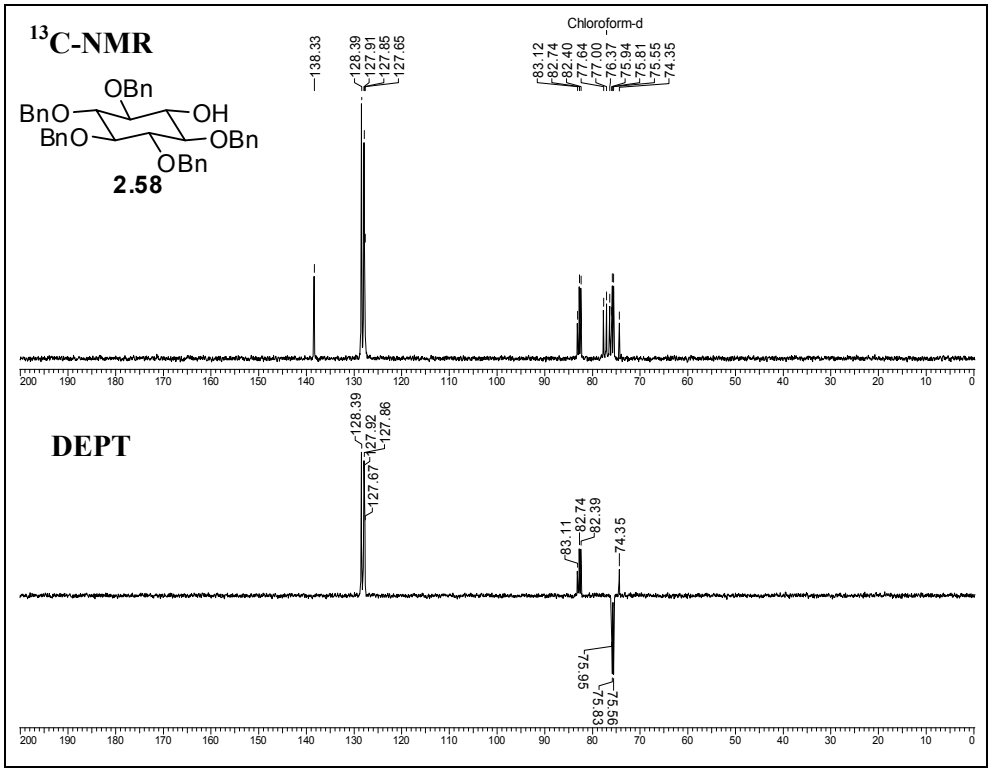
BnO
OH
BnO
OBn
OBn
2.58
TMS
26.02
10.03
4.00
0.82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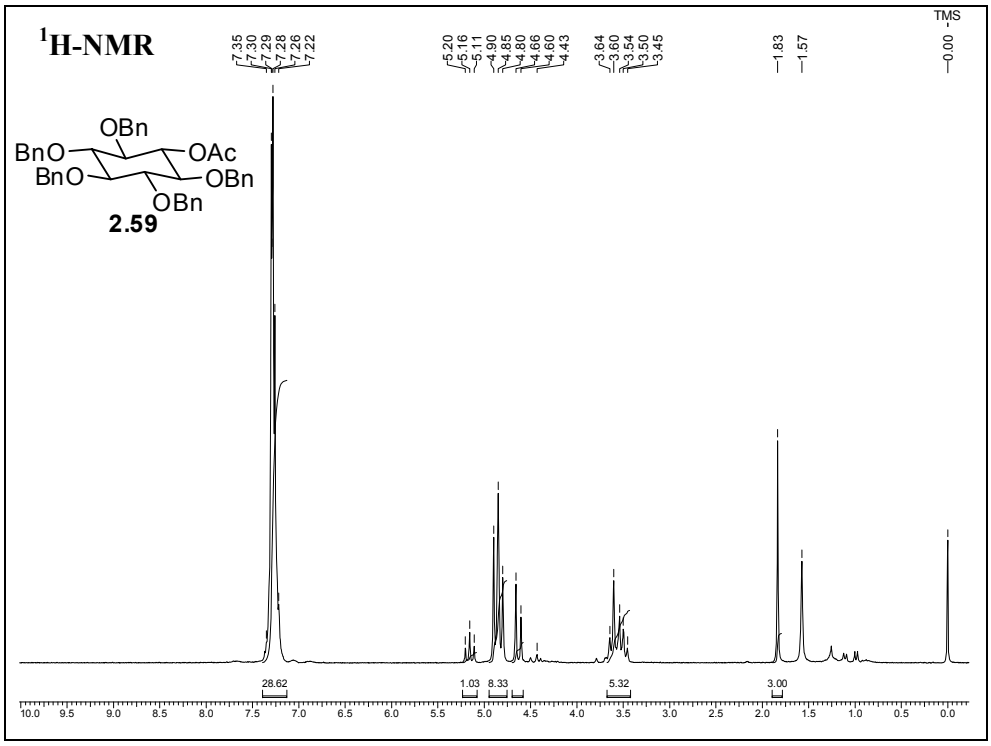
OBn
BnO
OH
BnO
OBn
OBn
2.58
Chloroform-d
DEPT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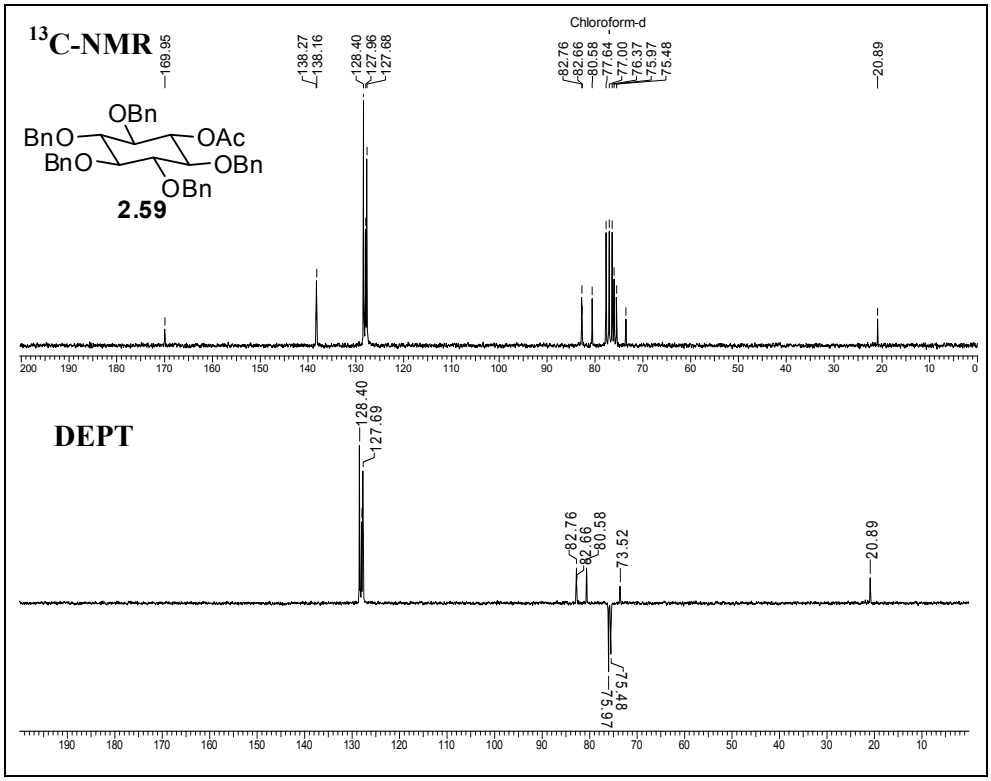
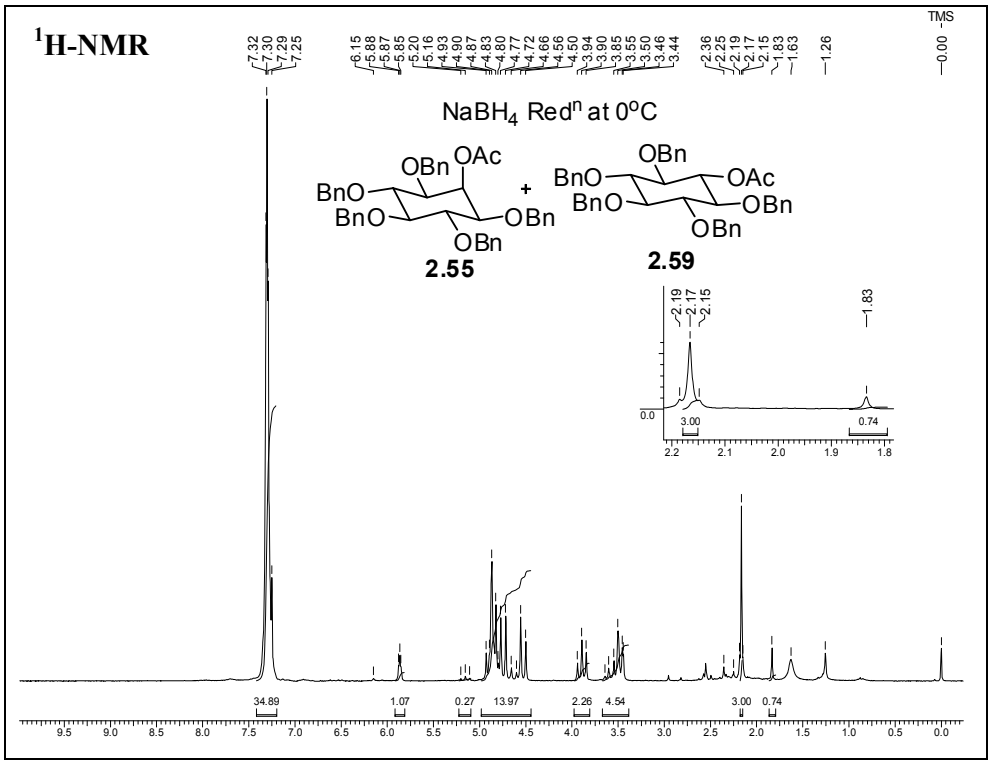
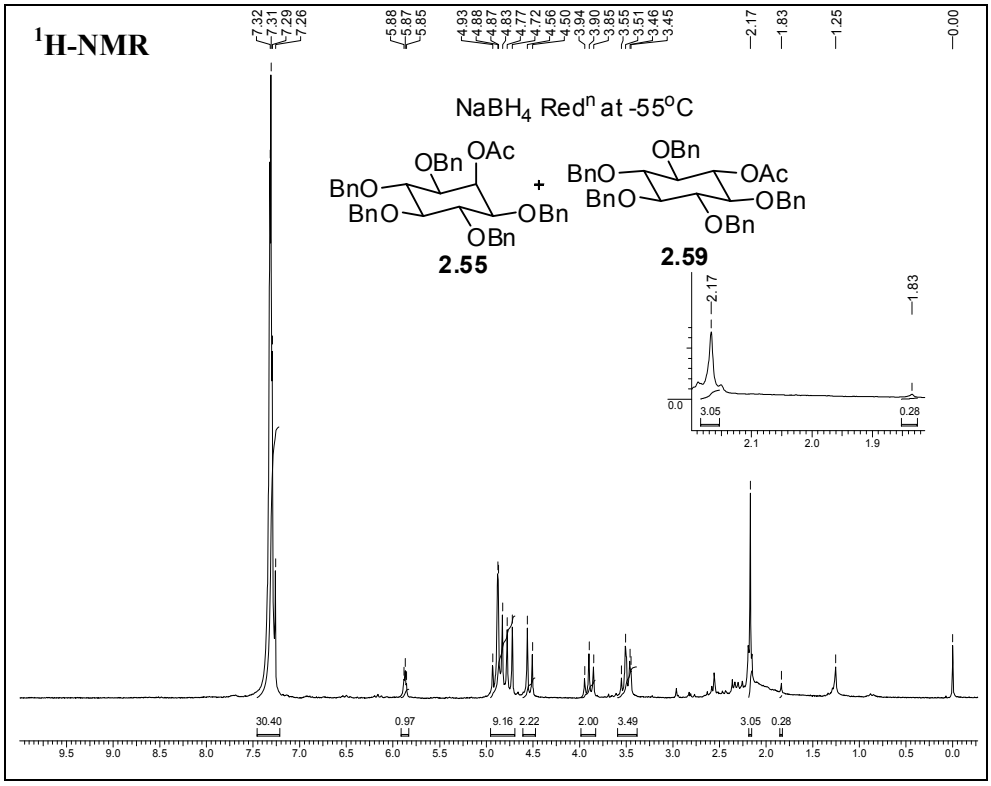
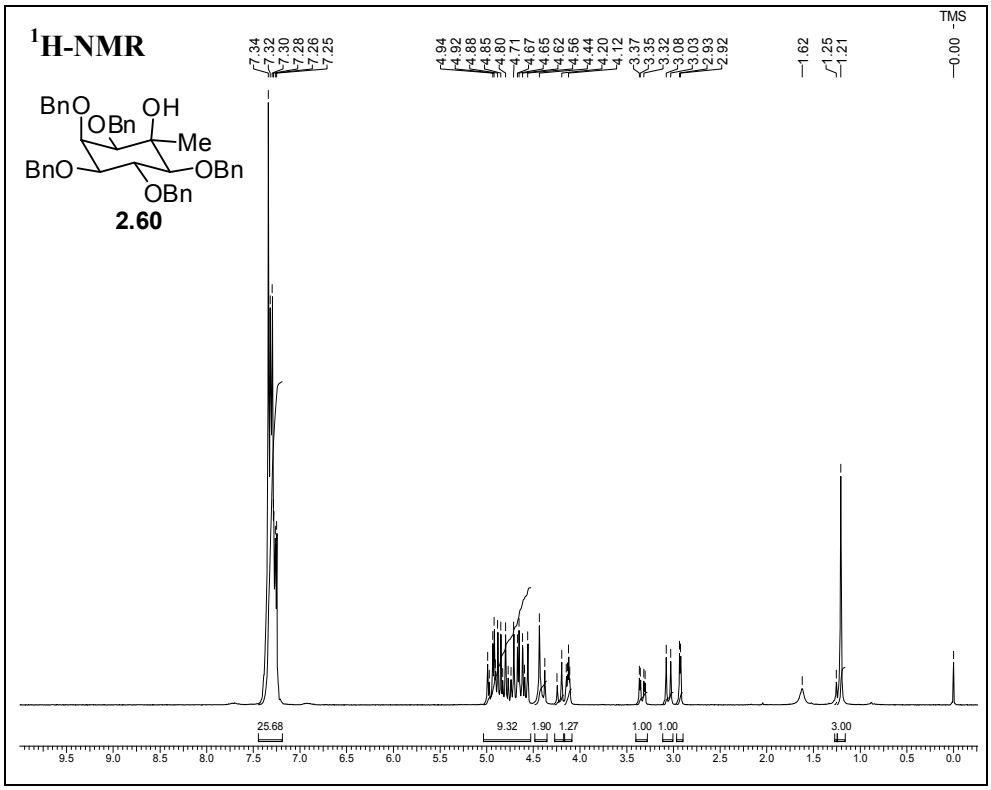
OBn
BnO
OAc
BnO
OBn
OBn
2.59
TMS


^{13}C-NMR
Chloroform-d
OBn
BnO
OAc
BnO
OBn
OBn
2.59
DEPT


^{1}H-NMR
NaBH$_4$ Red^n at 0^{o}C
2.55
2.59


^{1}H-NMR
NaBH$_4$ Red^n at -55^{o}C
2.55
2.59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BnO
OBn
OH
Me
BnO
OBn
OBn
2.60
TMS
7.34
7.32
7.30
7.28
7.26
7.25
4.94
4.92
4.88
4.85
4.80
4.71
4.67
4.65
4.62
4.56
4.44
4.20
4.12
3.37
3.35
3.32
3.08
3.03
2.93
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1.25
1.21
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9.32
1.90
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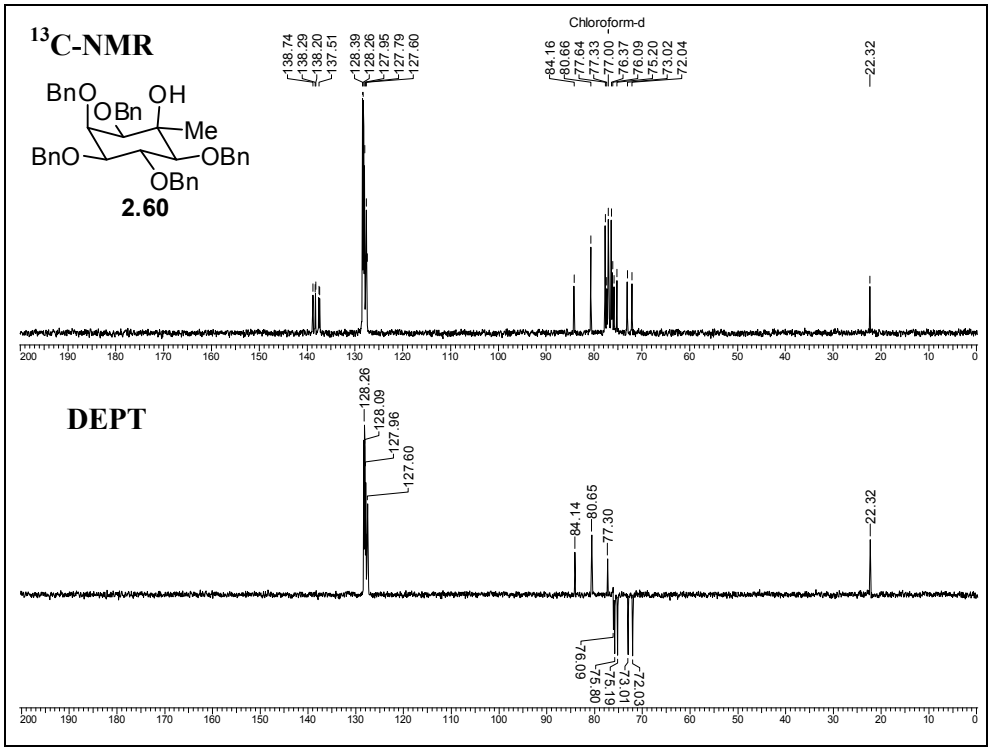
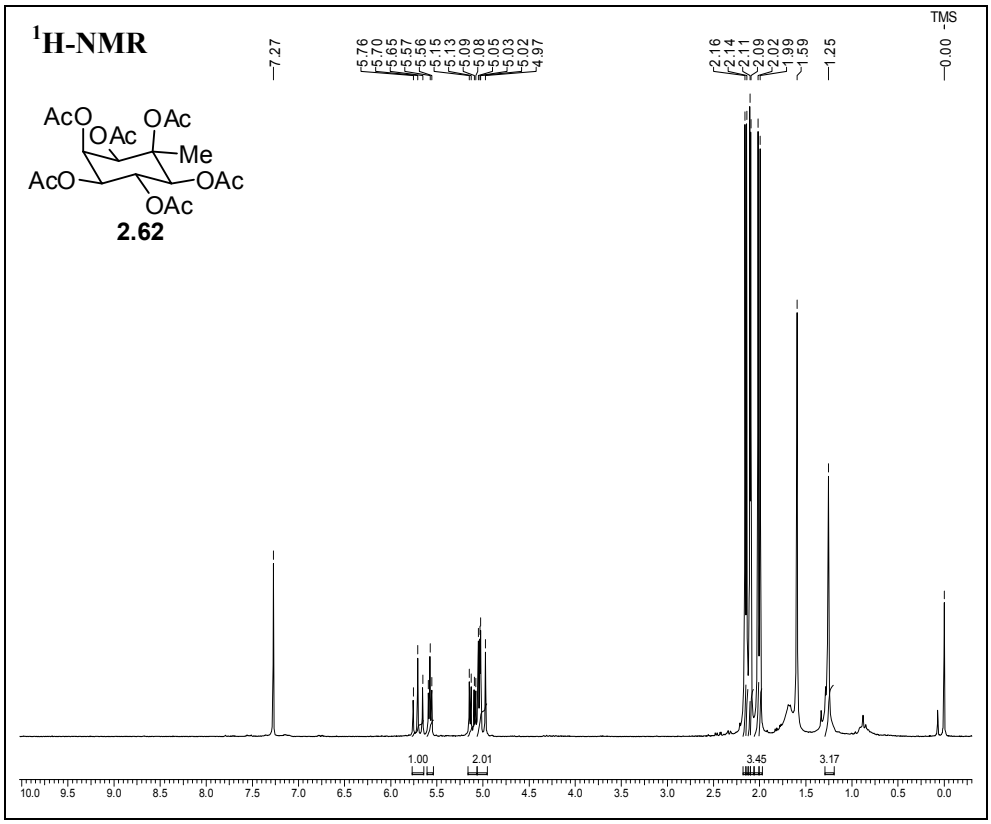
3.00


^{13}C-NMR
BnO
OBn
OH
Me
BnO
OBn
OBn
2.60
Chloroform-d
138.74
138.29
138.20
137.51
128.39
128.26
127.95
127.79
127.60
84.16
80.66
77.64
77.33
77.00
76.37
76.09
75.20
73.02
72.04
22.32
DEPT
128.26
128.09
127.96
127.60
84.14
80.65
77.30
22.32
76.09
75.80
75.19
73.01
72.05


1H-NMR
TMS
7.27
5.76
5.70
5.65
5.57
5.56
5.15
5.13
5.09
5.08
5.05
5.03
5.02
4.97
2.16
2.14
2.11
2.09
2.02
1.99
1.59
1.25
0.00
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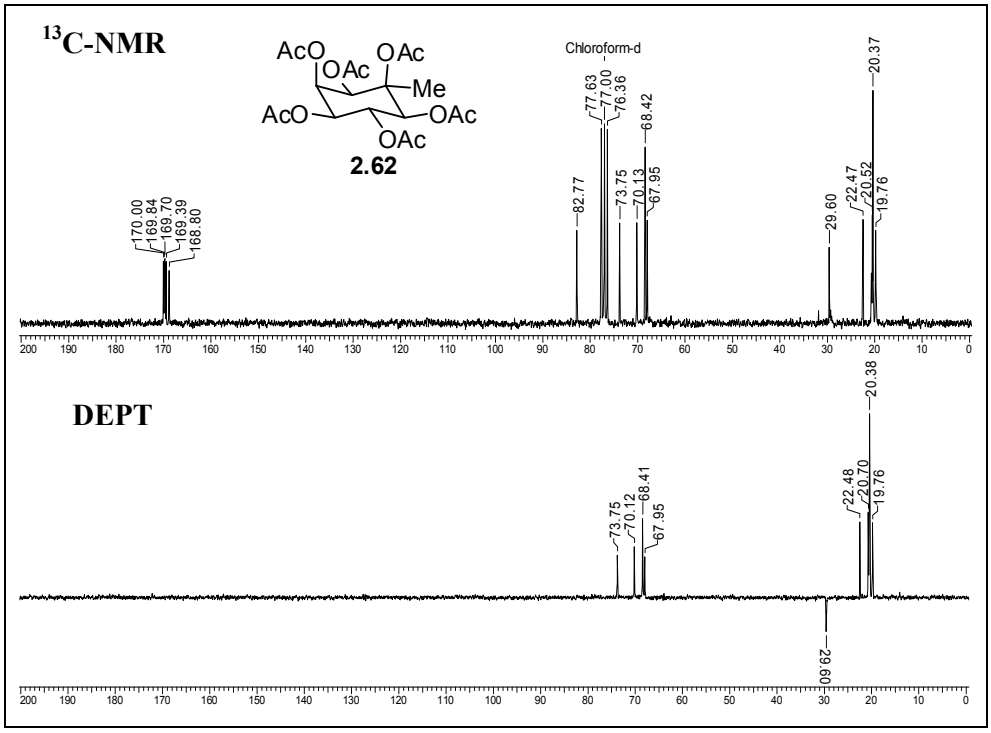
OAc
OAc
Me
AcO
OAc
OAc
2.62
1.00
2.01
3.45
3.17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AcO
OAc
OAc
Me
AcO
OAc
OAc
2.62
Chloroform-d
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77.00
76.36
68.42
82.77
73.75
70.13
67.95
20.37
29.60
22.47
20.52
19.76
170.00
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169.70
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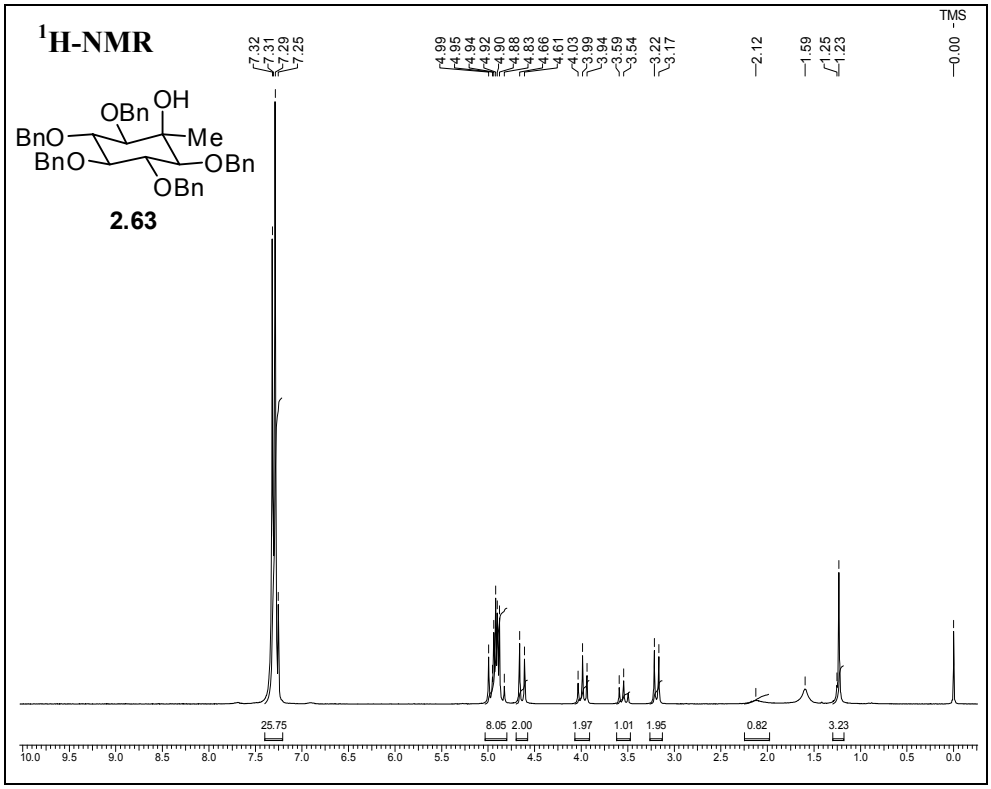
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OBn
OH
BnO
Me
BnO
OBn
OBn
2.63
TMS
7.32
7.31
7.29
7.25
4.99
4.95
4.94
4.92
4.90
4.88
4.83
4.66
4.61
4.03
3.99
3.94
3.59
3.54
3.22
3.17
2.12
1.59
1.25
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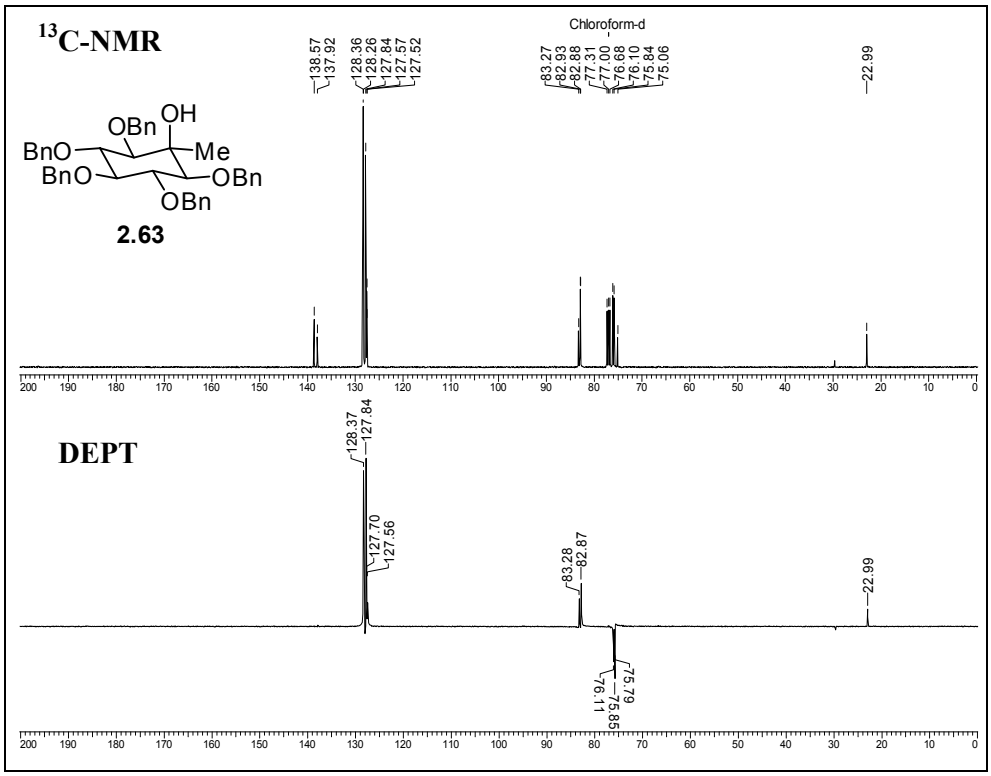
0.00
25.75
8.05
2.00
1.97
1.01
1.95
0.82
3.23


^{13}C-NMR
OBn
OH
BnO
Me
BnO
OBn
OBn
2.63
Chloroform-d
138.57
137.92
128.36
128.26
127.84
127.57
127.52
83.27
82.93
82.88
77.31
77.00
76.68
76.10
75.84
75.06
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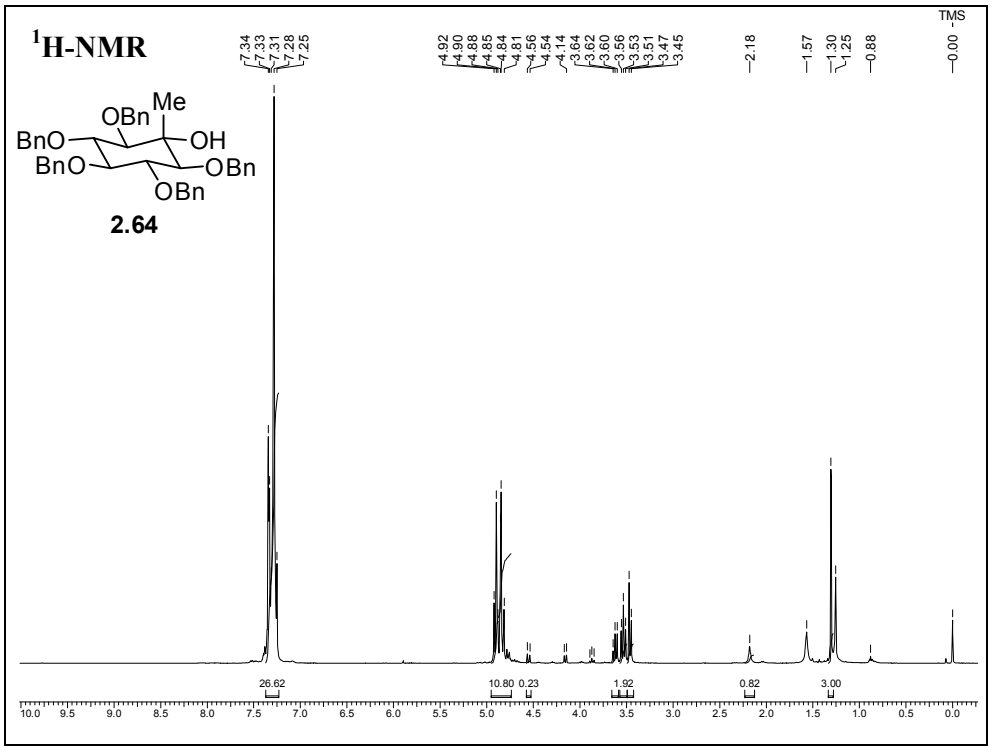
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Me
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OH
BnO
OBn
OBn
2.64
TMS
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3.62
3.60
3.56
3.53
3.51
3.47
3.45
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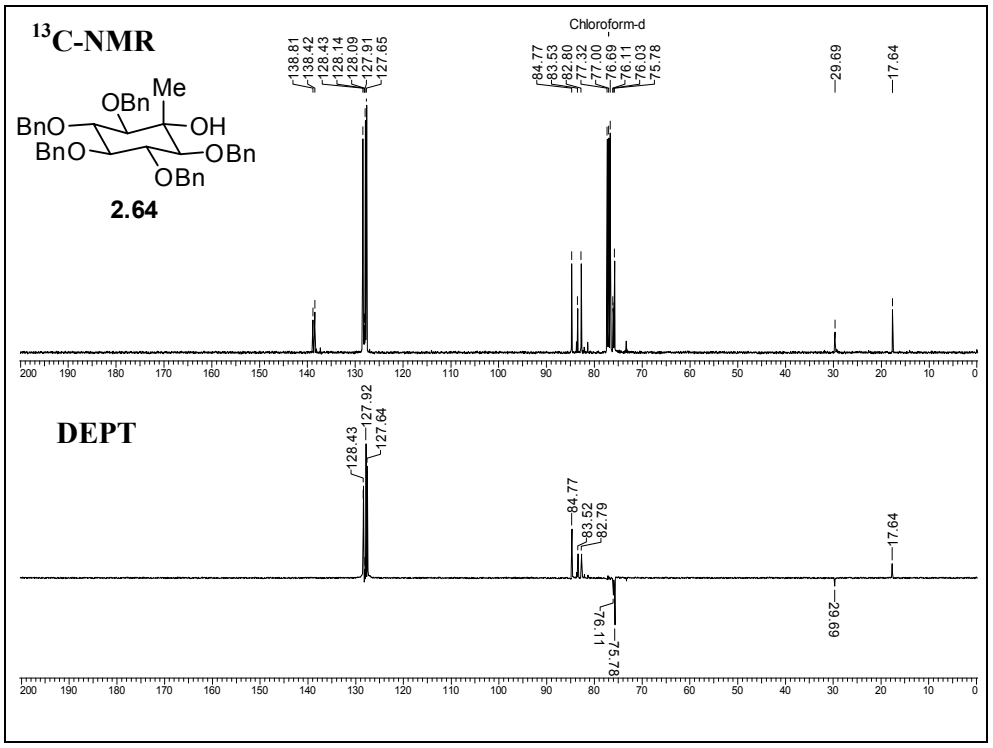
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OH
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2.64
Chloroform-d
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128.14
128.09
127.91
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84.77
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77.32
77.00
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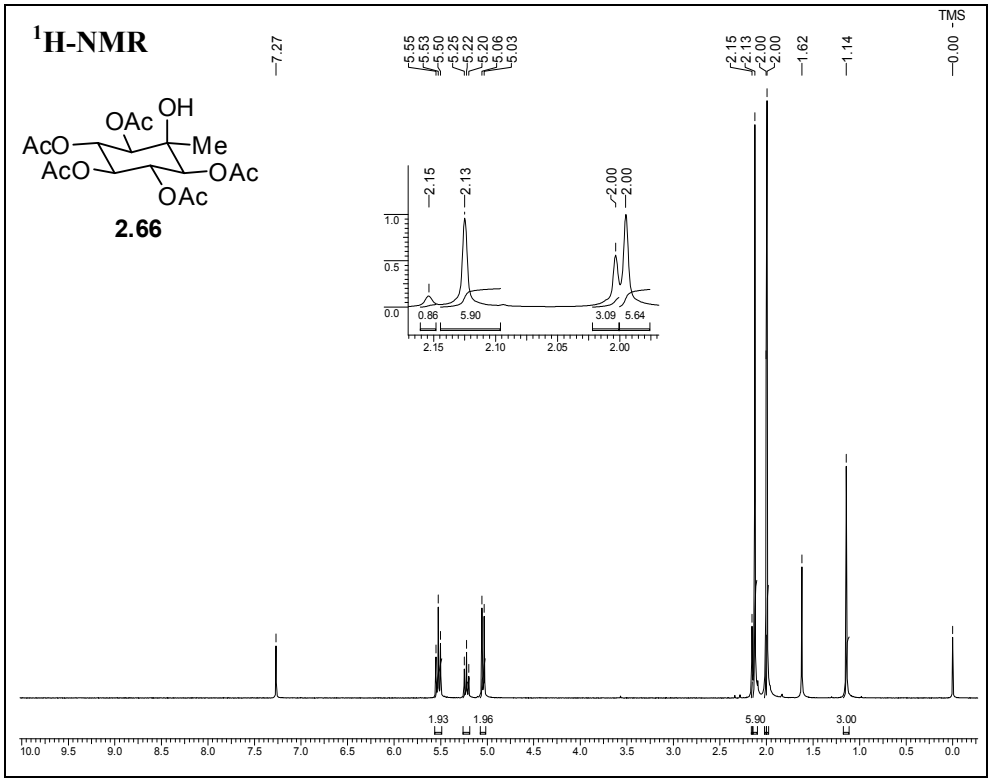
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TMS
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2.00
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AcO
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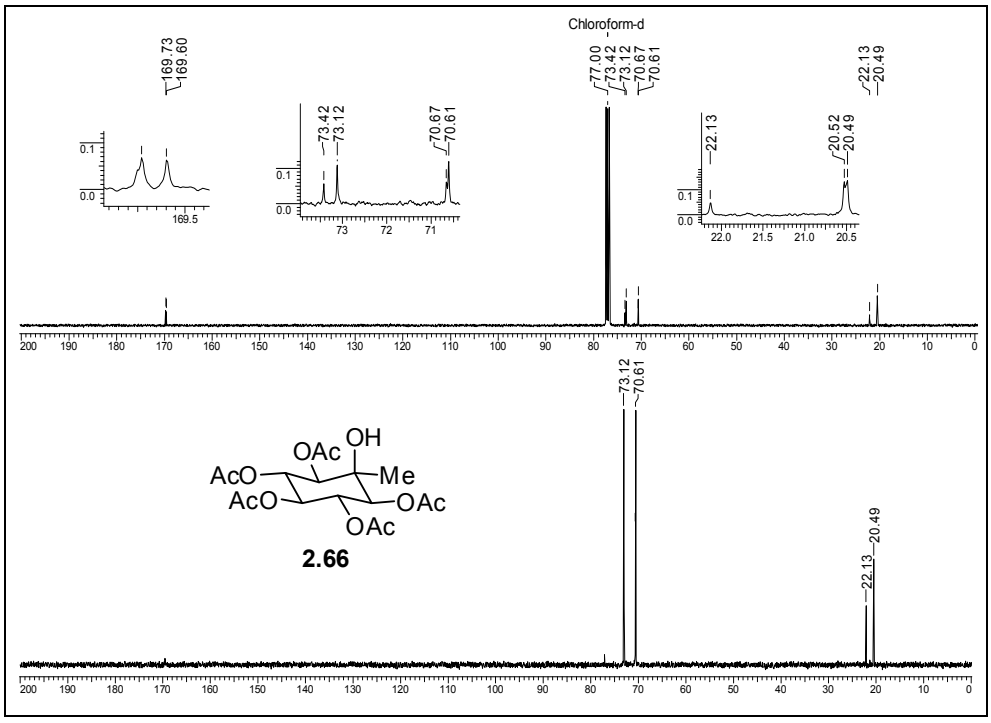
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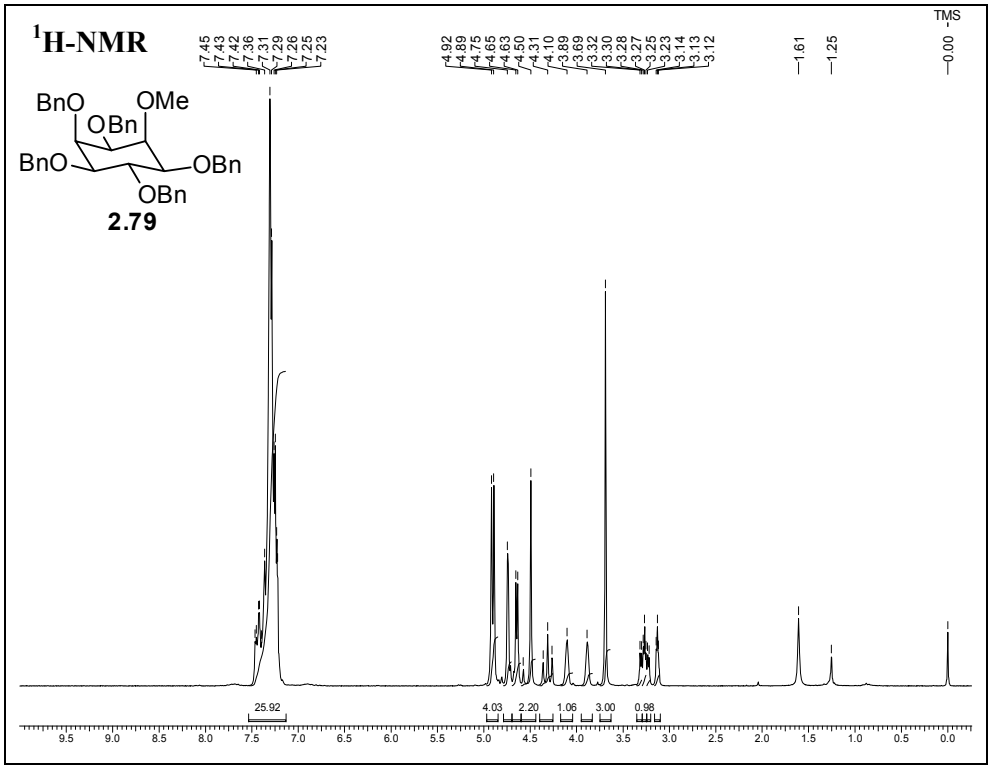
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OMe
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BnO
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OBn
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TMS
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7.26
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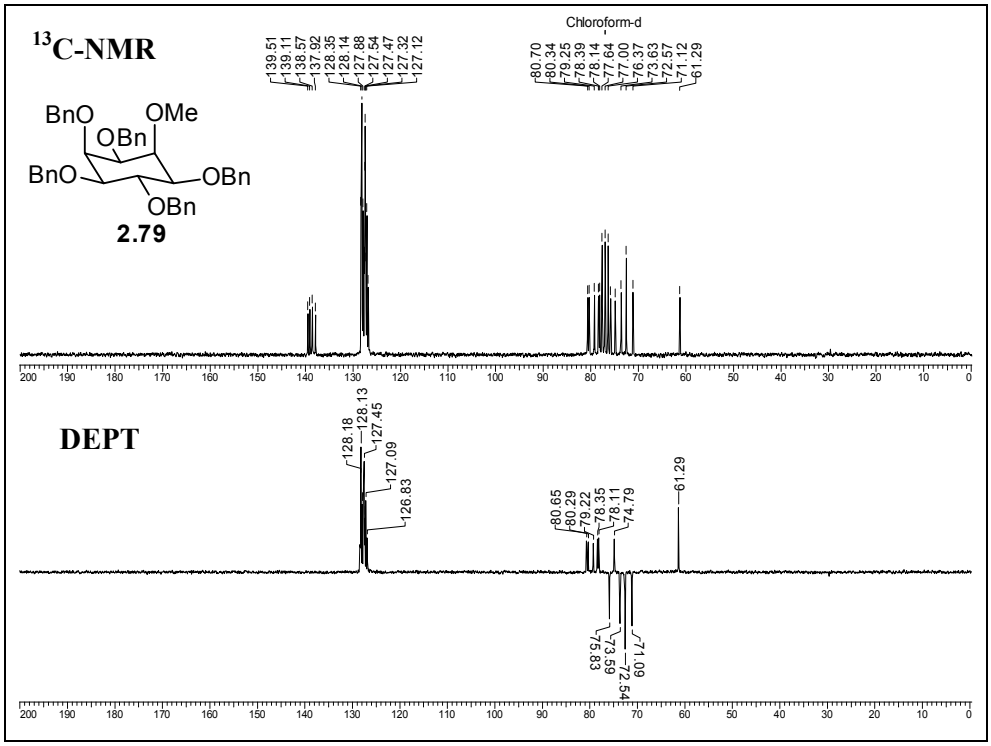
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BnO
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2.79
Chloroform-d
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128.35
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127.88
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127.47
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127.12
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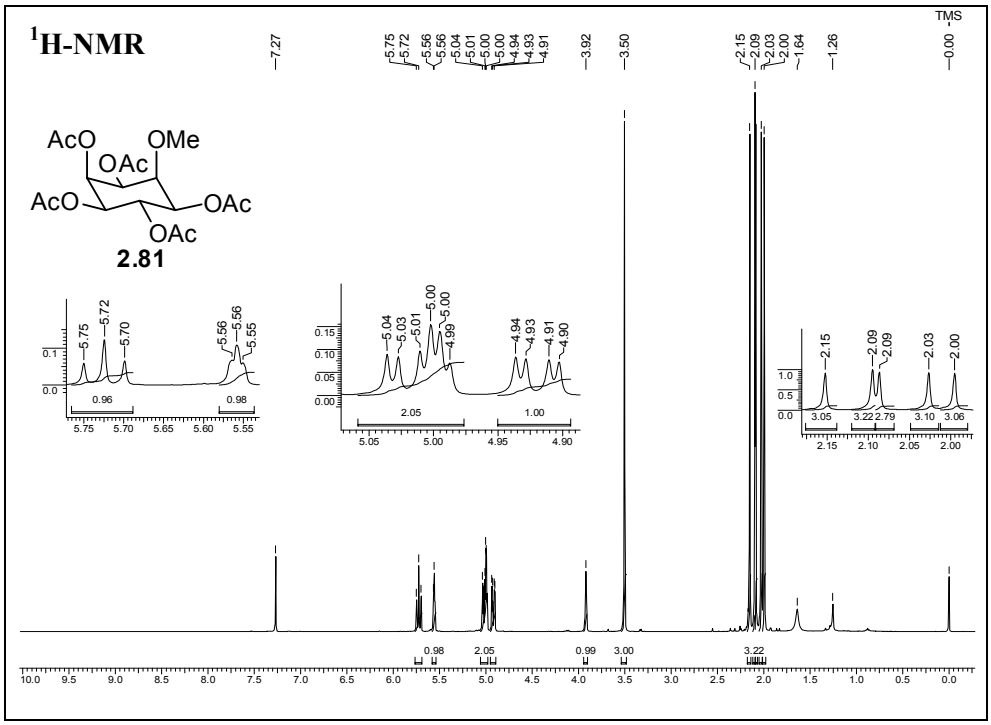
71.09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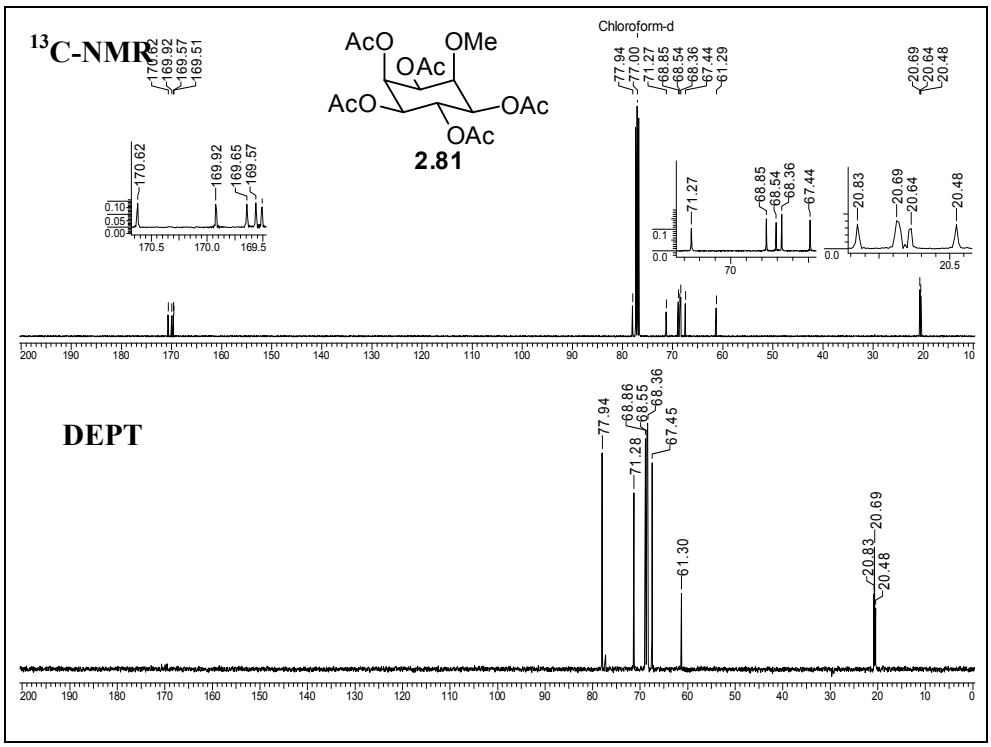
OMe
OAc
AcO
OAc
OAc
2.81


^{13}C-NMR
Chloroform-d
AcO
OMe
OAc
AcO
OAc
OAc
2.81
DEPT

Chapter 3

Access to chiral inositol derivatives by preferential crystallization of conglomerates

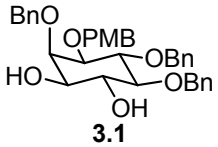
3.1. Introduction

As mentioned in the first chapter of this thesis, the last few decades have witnessed a renaissance in the chemistry and biology of inositols due to the involvement of phosphorylated inositols in various biological phenomena. Chiral derivatives of *myo*-inositol are among the most important central intermediates for the synthesis of biologically active inositol polyphosphates. The upsurge in interest in the chemistry of inositols demands efficient methods for the synthesis of chiral inositol derivatives. Consequently several methods have been used for the preparation of optically pure inositol derivatives. These methods can be broadly grouped under the following heads: (a) resolution of racemic inositol derivatives; (b) desymmetrization of *meso*-derivatives of inositols; (c) enzyme mediated preparation of chiral inositol derivatives; (d) synthesis of chiral inositol derivatives from chiral starting materials.

(a) Resolution of racemic inositol derivatives

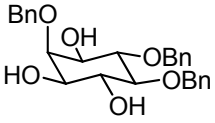
myo-Inositol, an accessible achiral substance, is the most used precursor for the preparation of its chiral derivatives. This involves the conversion of a racemic inositol derivative into a pair of diastereomeric isomers, followed by separation of the diastereomers. Chart 3.1 shows examples of a few inositol derivatives which are resolved by converting into diastereomers.

(I) Resolution of racemic inositol derivatives using camphor and its derivatives.



3.1

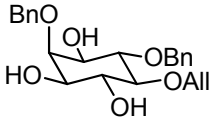
Org. Biomol. Chem. **2010**, *8*, 66–76



3.2

J. Chem. Soc. Perkin Trans. 1 **1999**, 923–935

Chem. Commun., **1997**, 1633–1634



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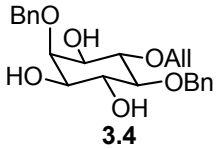
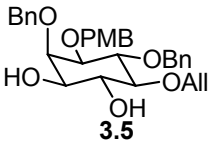


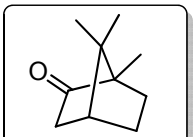
3.4

Tetrahedron Asymm. **2009**, *20*, 2809–2813



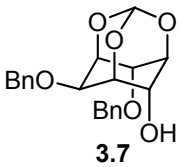
3.5

Org. Biomol. Chem. **2010**, *8*, 66–76



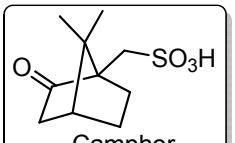
Camphor

3.6



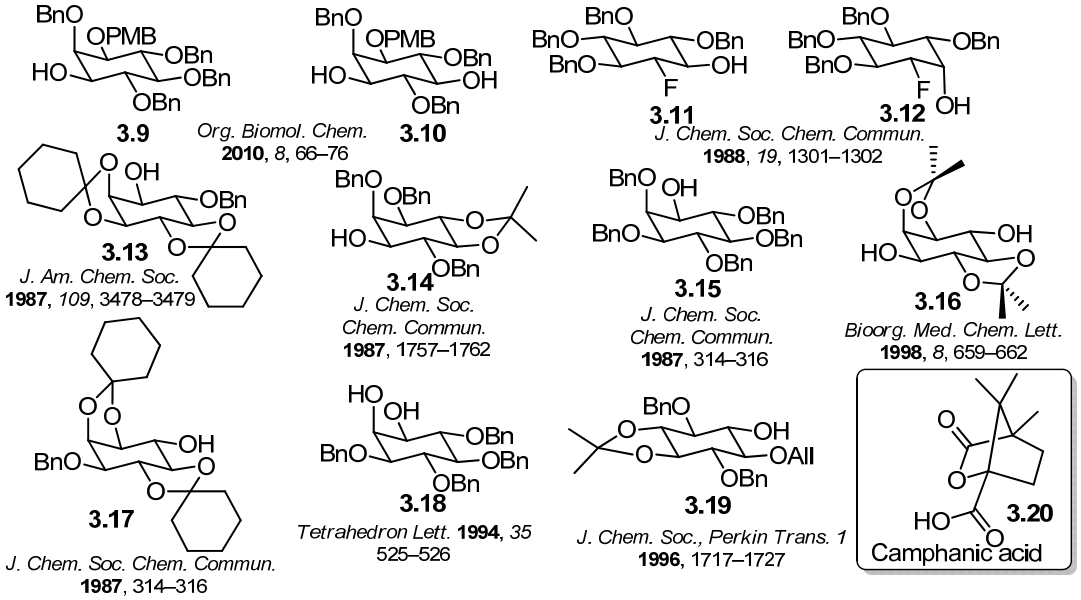
3.7

Carbohydr. Res. **2002**, *337*, 2399–2410

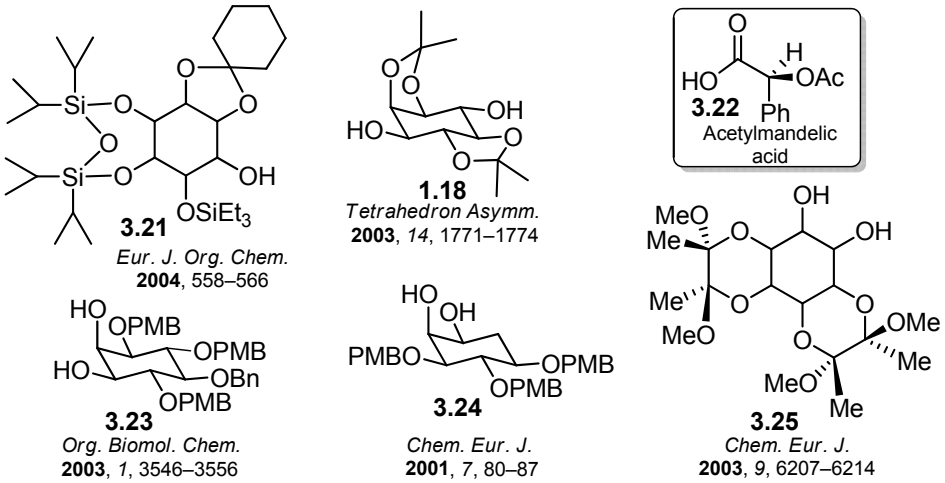


Camphor sulfonic acid

3.8



(II) Resolution of racemic inositol derivatives using acetylmandelic acid.



(III) Resolution of racemic inositol derivatives using menthoxyacetic acid.

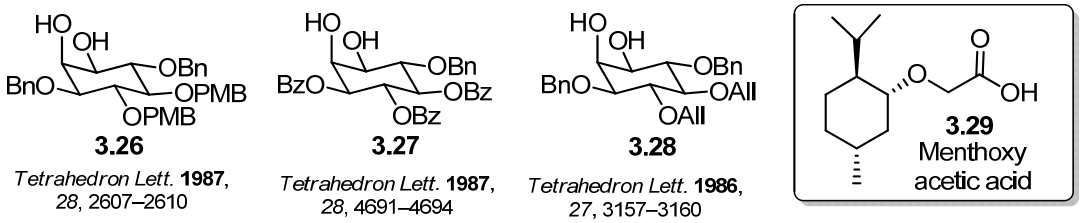
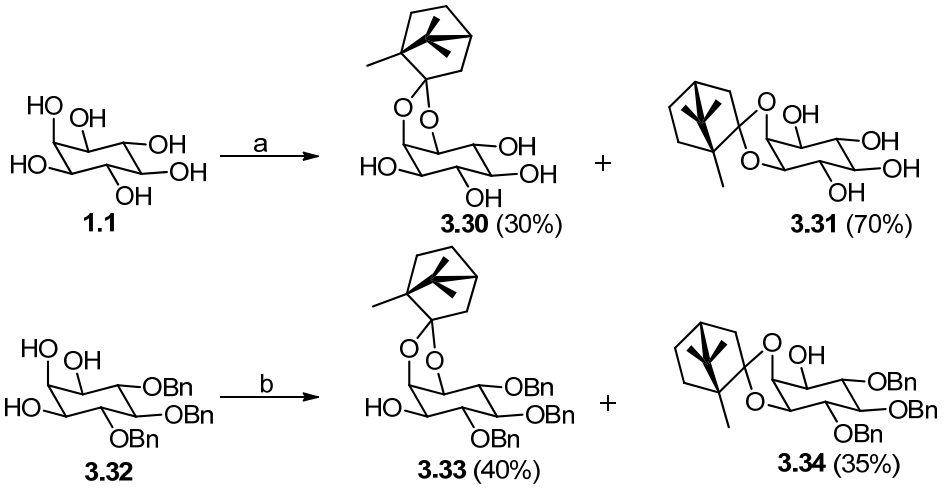


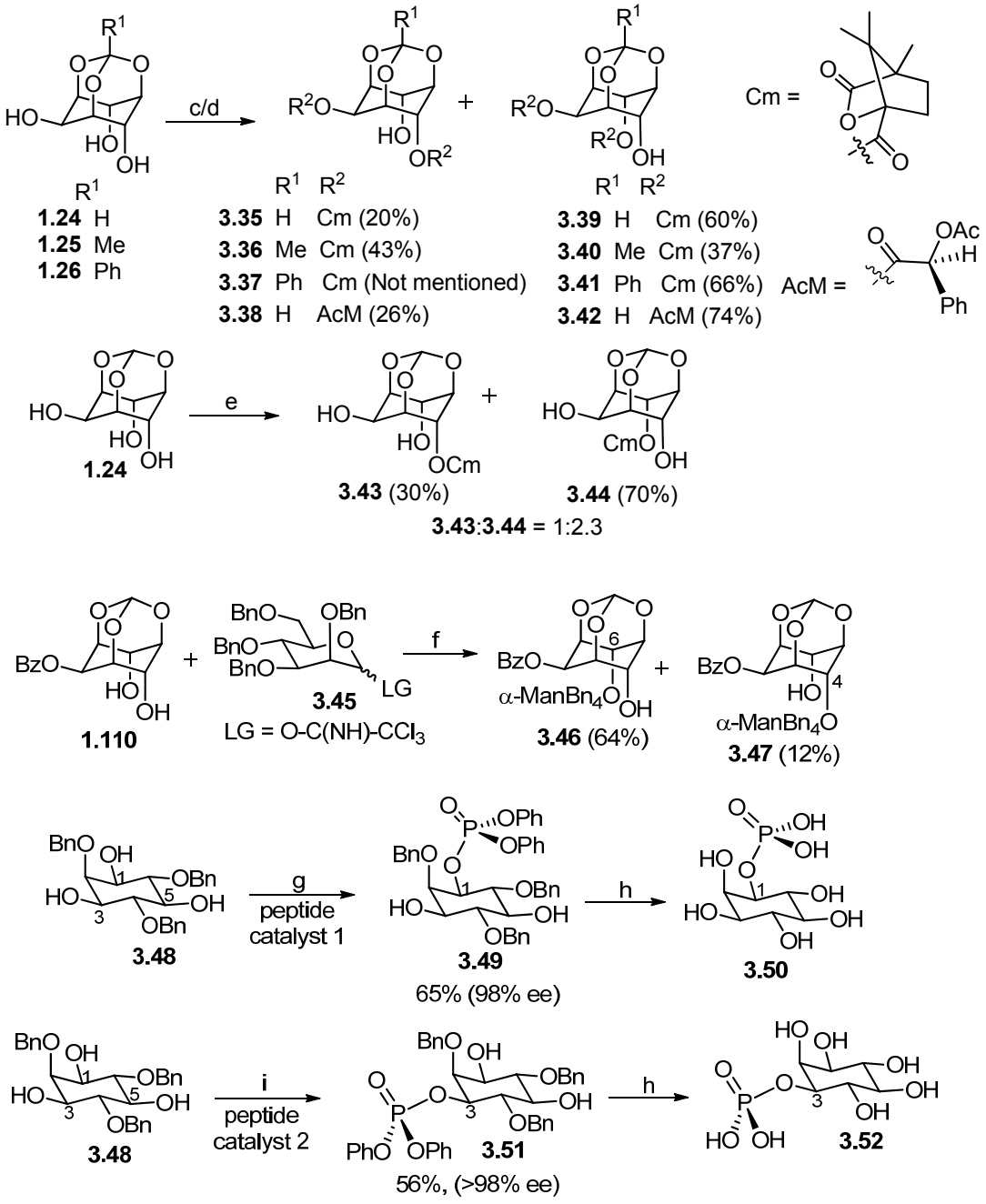
Chart 3.1. Racemic inositol derivatives which have been resolved by conversion to diastereomers. Resolution using camphor[1] (compounds **3.1** to **3.5**); resolution using camphor sulfonic acid[2] (compound **3.7**); resolution using camphanic acid[3, 1d] (compounds **3.9** to **3.19**) resolution using acetylmandelic acid[4]; resolution using menthoxyacetic acid.[5]

Although several resolving agents have been used for the resolution of inositol derivatives there are very few or no practical methods for the resolution on a large scale. In some cases, the resolution was carried out after a low yielding initial protection followed by tedious column chromatographic[6] or HPLC[7] separation of the diastereomers. Advantage of resolving a racemate is that both the enantiomers are accessible. However, if only one of the two enantiomers is required, the maximum yield is 50%. Another disadvantage of this method is that the synthetic strategy needs two extra steps, for the introduction and removal of the chiral auxiliary. Hence this could add to increase in labor, time and cost of the synthesis.

(b) Desymmetrization of symmetric inositol derivatives

myo-Inositol and its derivatives having the *meso*-configuration can in principle be converted to chiral derivatives by desymmetrization using chiral reagents or auxiliaries. Scheme 3.1 shows desymmetrization reactions of *myo*-inositol,[8] *myo*-inositol orthoformate **1.24**,[9] *myo*-inositol orthoacetate **1.25**,[10] *myo*-inositol orthobenzoate **1.26**,[11] 4,5,6-tri-*O*-benzyl-*myo*-inositol **3.32**,[12] the diol **1.110**,[13] and 2,4,6-tri-*O*-benzyl-*myo*-inositol **3.48**,[14] all of which provide access to chiral inositol derivatives.





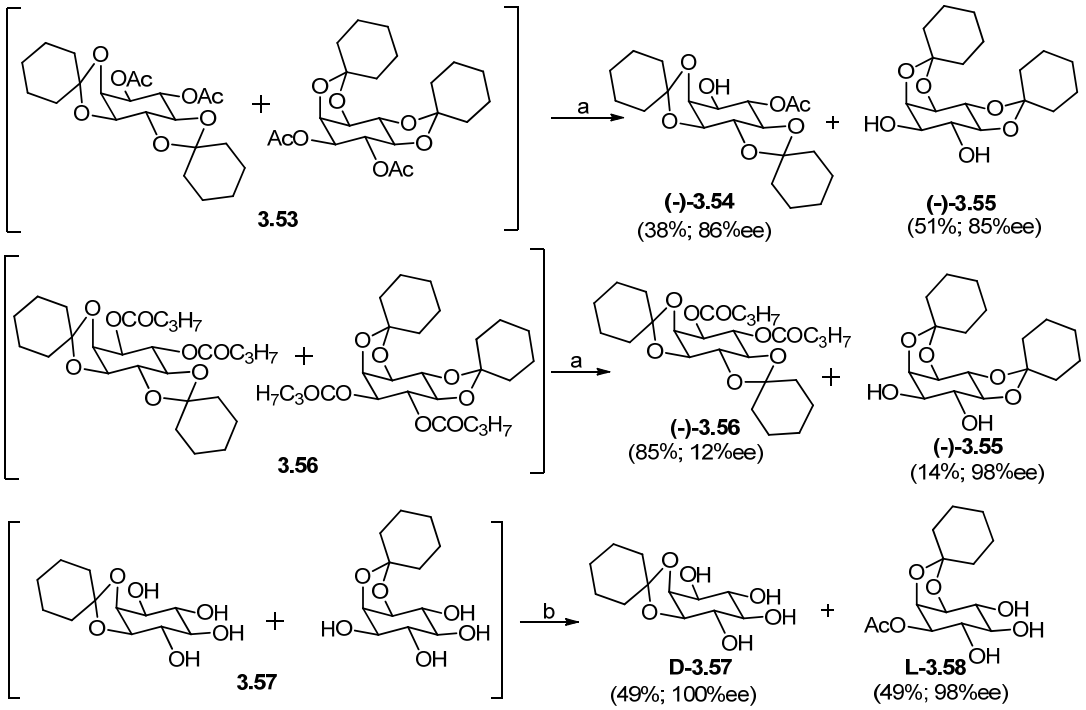
Scheme 3.1. (a) i) DMSO, D-camphor dimethyl ketal, H_2SO_4, 50–55 °C, Et_3N; ii) sonication, PTSA, rt, 12 h, Et_3N; (b) D-camphor dimethyl ketal, PTSA.H_2O, CH_2Cl_2, reflux, 100 min; (c) (1s)-(-)-camphanic acid chloride (2.0 equiv), CH_2Cl_2, Et_3N, DMAP, 0 °C to rt; (d) (S)-(+)-*O*-acetylmandeloyl chloride (2.1 equiv), py., 0 °C, 2 h; (e) 1 mol% $Yb(OTf)_3$, 1,4-dioxane, 40 °C, 3 days, 78%; (f) THF: DCM (1:5), –78 to –20 °C, $BF_3.OEt_2$; (g) Cl-P=O$(OPh)_2$, peptide catalyst 1 (2 mol%), Et_3N, toluene, 0 °C, 65%, (98% ee); (h) Li, liq. NH_3, THF, 96%; (i) Cl-P=O$(OPh)_2$, peptide catalyst 2 (2.5 mol%), Et_3N, toluene, 0 °C, 56%, (>98% ee).

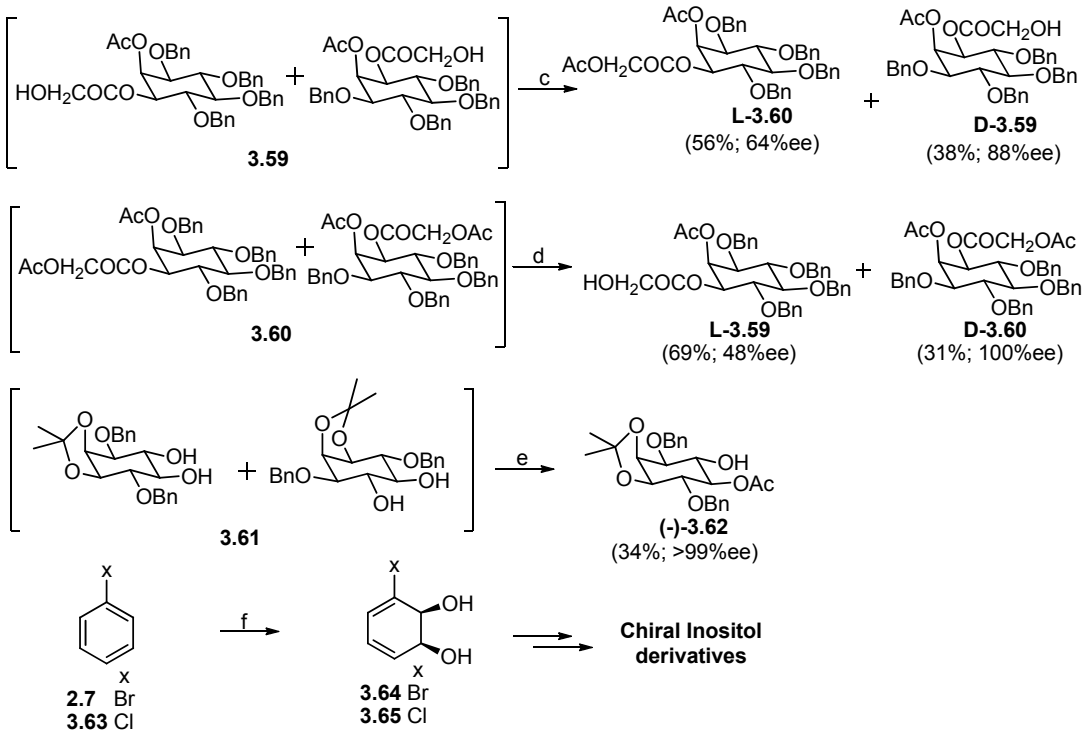
Desymmetrization of *meso*-derivatives can be advantageous if the two diastereomers are formed in unequal amounts. The maximum bias in the ratio during

the formation of the two diastereomeric inositol derivatives, reported to date is 12:64 for the desymmetrization of the diol **1.110**.[13] The meso-diol **1.110** can be D-mannosylated at the *O*-6 position to yield the corresponding chiral disaccharide **3.46** in high regioselectivity and stereoselectivity (Scheme 3.1).[13] Although the method of Sculimbrene[14] provided the chiral phosphates **3.49** and **3.51** in 98% ee, the peptide catalysts had to be synthesized. The peptide catalysts **1** and **2** were identified by screening a library of hundreds of peptides.

(c) Enzyme mediated preparation of chiral inositol derivatives

The use of enzymes in synthesis of optically active inositol derivatives seems attractive due to the possibility of high selectivity and efficiency of reactions catalyzed by these biocatalysts, under mild conditions.[15] The chiral cyclohexadienediol obtained by the microbial conversion of halobenzene[16] has been used for the synthesis of various inositols and their derivatives. Different approaches to obtain chiral inositol derivatives with the help of enzymes are shown in Scheme 3.2. As evident from these examples, yields as well as enantiomeric purity of the resulting chiral inositol derivatives vary.

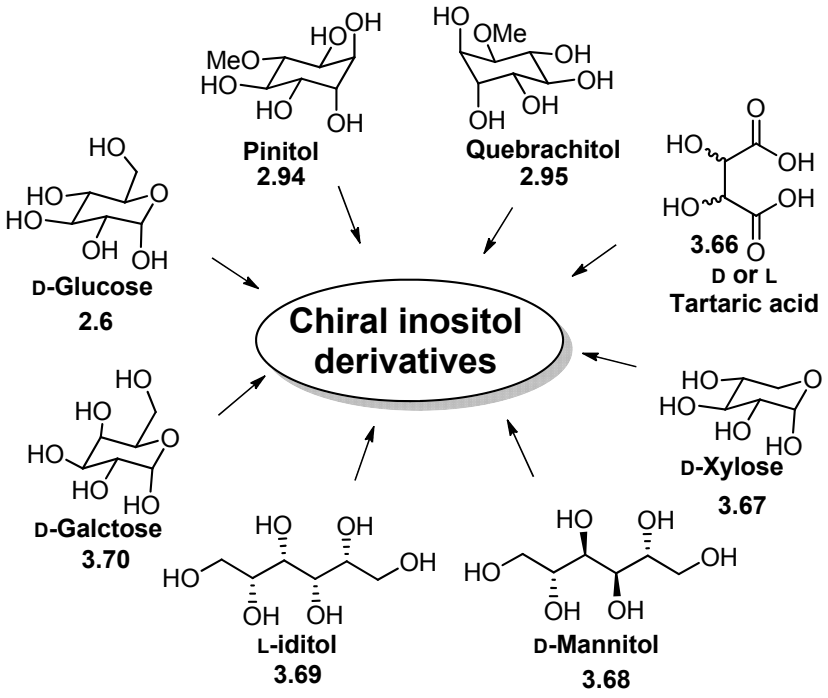




Scheme 3.2: (a) Cholesterol esterase;[15a] (b) acyl donor, ether, enzyme lipase AY;[15c,15e] (c) Ac_2O, ether, SP-435;[15f] (d) H_2O, *iso*-propyl ether, SP-435;[15f] (e) vinyl acetate, Novozym 435;[15g,15h] (f) Pseudomonas putida[16]

(d) Preparation of chiral inositol derivatives from chiral starting materials

Use of naturally occurring chiral molecules as the starting material has the obvious advantage of obtaining one single enantiomer of the desired product. Scheme 3.3 presents chiral starting materials used in the synthesis of chiral inositol derivatives. Use of sugars as starting materials necessarily involves carbocyclization step such as the Ferrier carbocyclization (or Ferrier II reaction),[17] which can generate a mixture of diastereomeric inositol derivatives. The use of naturally occurring chiral starting materials requires maintenance of chirality throughout the synthesis and we can get only one enantiomeric end product.



Scheme 3.3: Chiral compounds used for the synthesis of chiral inositol derivatives.[18-24]

From the foregoing discussion it is clear that one of the oldest methods known for obtaining chiral organic compounds which has regained its importance in recent times viz., preferential crystallization of conglomerates[25] has not been explored for the preparation of chiral inositol derivatives. Chart 3.2 lists compounds from recent literature, which have been resolved by preferential crystallization of conglomerates.

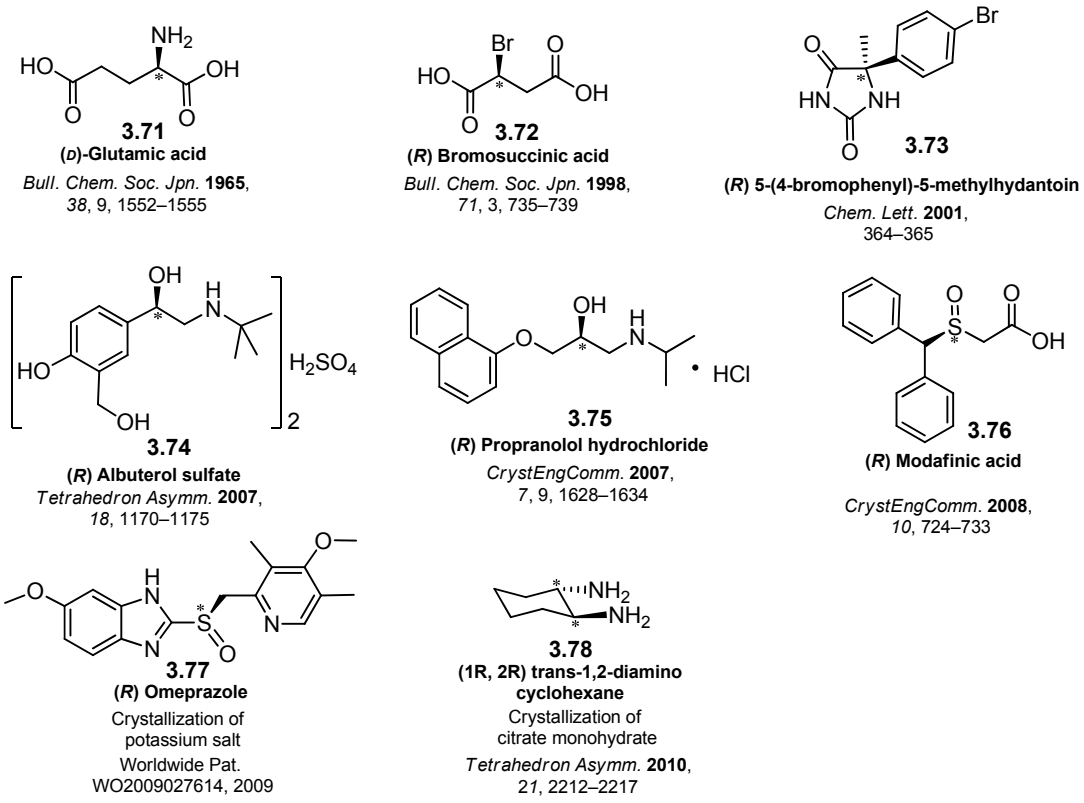


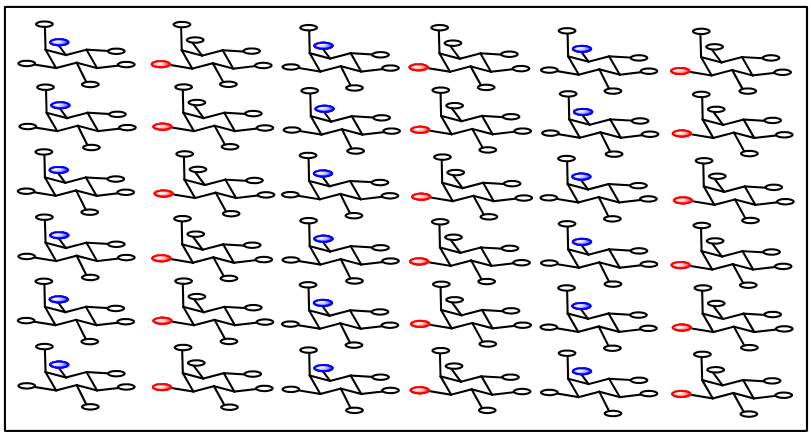
Chart 3.2. Compounds resolved by preferential crystallization of conglomerates.

We thought of exploring this possibility since we had prepared a large number of crystalline inositol derivatives and investigated their crystal structures.[26] The following sections of this chapter describe our attempts to identify crystalline inositol derivatives that have the potential to provide access to chiral inositol derivatives by preferential crystallization. Before giving the details of this effort, a short introduction to various aspects of preferential crystallization technique is included.

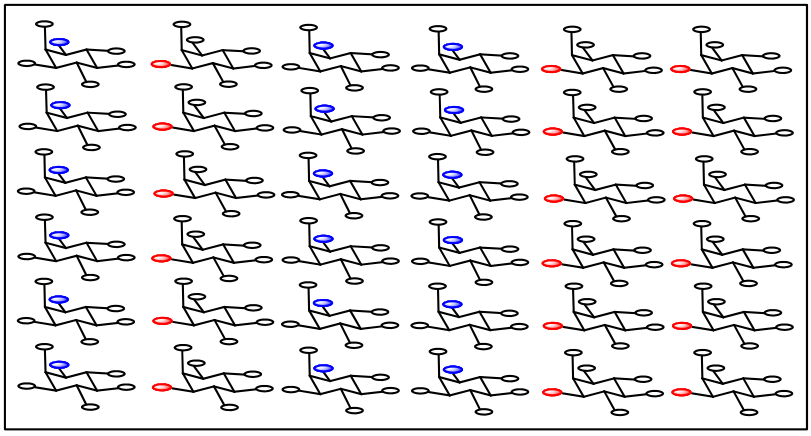
3.2. Salient features of preferential crystallization of conglomerates

3.2.1. Chiral molecules and their racemates

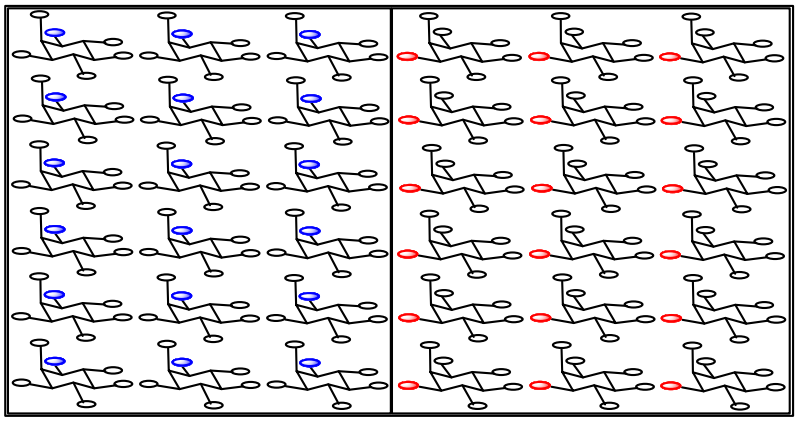
Three most common types of solid phases (Figure 3.1) obtained from a solution of a racemic substance are racemic compound, conglomerate, and solid solution (pseudoracemate)[27] The racemic compound is the most frequently observed racemic species (90-95% occurrence). A crystal of a racemic compound consists of an even ratio of both the enantiomers in a regularly structured array. A conglomerate is a physical mixture of single crystals containing homochiral molecules only, but the overall mixture is racemic.



(a)



(b)



(c)

Figure 3.1. Schematic representation of (a) racemates, (b) pseudoracemates, (c) conglomerates. Molecules with blue and red substituents represent the two enantiomers.

In other words, conglomerate is an equimolar mechanical mixture of crystals, each crystal containing only a single enantiomer. Statistically (based on crystal structure data base), conglomerates represent only 5 to 10% of the racemates.[27b] In terms of intermolecular interactions in the crystal lattice, in racemic conglomerates, each

enantiomer has a greater affinity for the same enantiomer than for the opposite enantiomer, while in racemic compounds, each enantiomer has a greater affinity for the opposite enantiomer than for the same enantiomer. A solid solution contains an equal number of molecules of each enantiomer but (contrary to the racemic compound), the arrangement of enantiomeric molecules is random. A solid solution (or a pseudoracemate) forms when both enantiomers compete for the same position in the crystal lattice. The racemic solid solution has lower occurrence than conglomerates. The three possibilities are schematically shown in figure 3.1.

The relative stability of the three solid forms (racemic crystals, enantiopure crystals, or a solid solution) at ambient pressure depends on the nature of the chiral compound, the system composition, and the temperature. The binary phase diagrams give important information on the possibility of chiral resolution through crystallization and hence enable chiral separation methods to be identified and designed. Typical temperature-composition binary phase diagrams are shown in figure 3.2. The upper lines (blue) in Figure 3.2a and 3.2b indicate the melting temperature for R and S enantiomers and their fractions whereas the lower line (pink) indicates the eutectic temperature.

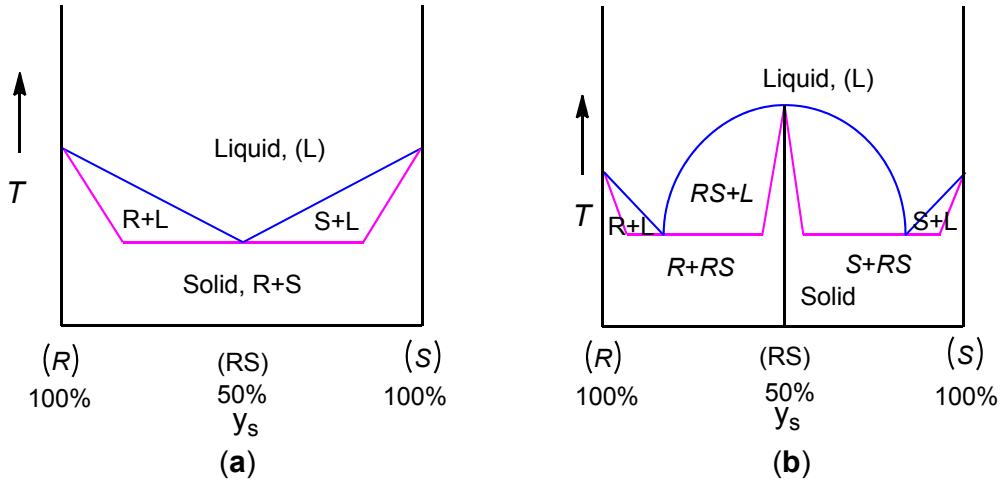


Figure 3.2. Typical binary melting-point phase diagrams of two enantiomers in (a) a racemic conglomerate and (b) a racemic compound.

Figure 3.2a shows the phase behavior of a conglomerate system when the enantiopure crystalline compounds *R* and *S* are stable compounds in the entire compositional range $0 \leq y_s \leq 1$ below the melting temperature. At the extreme ends (for $y_s = 0$ and 1), the melting temperatures are those of the pure crystalline enantiomers, which are equal. Decreasing enantiomer purity toward a racemic mixture

shows a decrease of the melting temperature (of enantiopure *S* or *R*) down to the eutectic temperature. Below the eutectic temperature, a mixture of enantiopure crystals *R* and *S* exists. Consequently, the melting point of the racemic conglomerate is always lower than that of the pure enantiomer. The more the difference between melting point of racemic compound and the enantiomer, easier is the resolution of racemic conglomerate to two individual enantiomers via preferential crystallization. Figure 3.2b shows the phase behavior of racemic compound. At the extreme ends (for y_s = 0 and 1), the melting temperature is that of the pure enantiomeric crystalline compounds *R* and *S*. Slightly decreasing enantiomer purity decreases the melting temperature. However, for compositions around y_s = 0.5 the racemic compound *RS* rather than the enantiopure compound *R* or *S* is more stable, which causes the melting temperature to rise as y_s approaches 0.5.

Pasteur manually separated left-handed and right-handed crystals of sodium ammonium tartrate (from its racemic conglomerate), for the first time[28] Besides the Pasteurian method, the resolution can be performed by "preferential crystallization" also called "crystallization by entrainment". Preferential crystallization is a stereoselective process in which, alternatively, for a given period of time, only one enantiomer crystallizes although both enantiomers are supersaturated in the mother liquor. In 1866, Gernez[29] was the first to observe that a saturated solution of racemic conglomerate slightly enriched (2-5 % ee) with one enantiomer when seeded by the crystal of the enriched enantiomer, allows the preferential crystallization of the same enriched enantiomer. The main advantage of preferential crystallization technique is that it does not require any resolving agent. However it suffers from a serious limitation: the compound to be resolved must crystallize as a conglomerate. The existence of a conglomerate is an absolute requirement to apply the 'classical' preferential crystallization (i.e. alternate and successive crystallizations of the two individual enantiomers) technique for the resolution of racemates.[28] Even though the requirement of a conglomerate is an important restriction to the application of preferential crystallization due to the low occurrence of conglomerates among molecular crystals,[27b] preferential crystallization is an attractive technology to produce pure enantiomers due to economic considerations and the advantage of obtaining directly a solid enantiomeric product.[27b,30] Preferential crystallization means, selective crystallization of the desired enantiomer from a solution containing both enantiomers using seed crystals of the desired enantiomer. It is implied that the two

enantiomers crystallize separately from a supersaturated solution. In other words, one of the two enantiomers can be crystallized out from a solution containing both the enantiomers, by a careful control of the crystallization conditions, which leads to the transfer of a single enantiomer from the solution to the solid phase.

A typical flow diagram for the separation of the two enantiomers present in a conglomerate is shown in figure 3.3. Preferential crystallization can be realized at the laboratory scale (mg) as well as at the industrial scale (tons).[31]

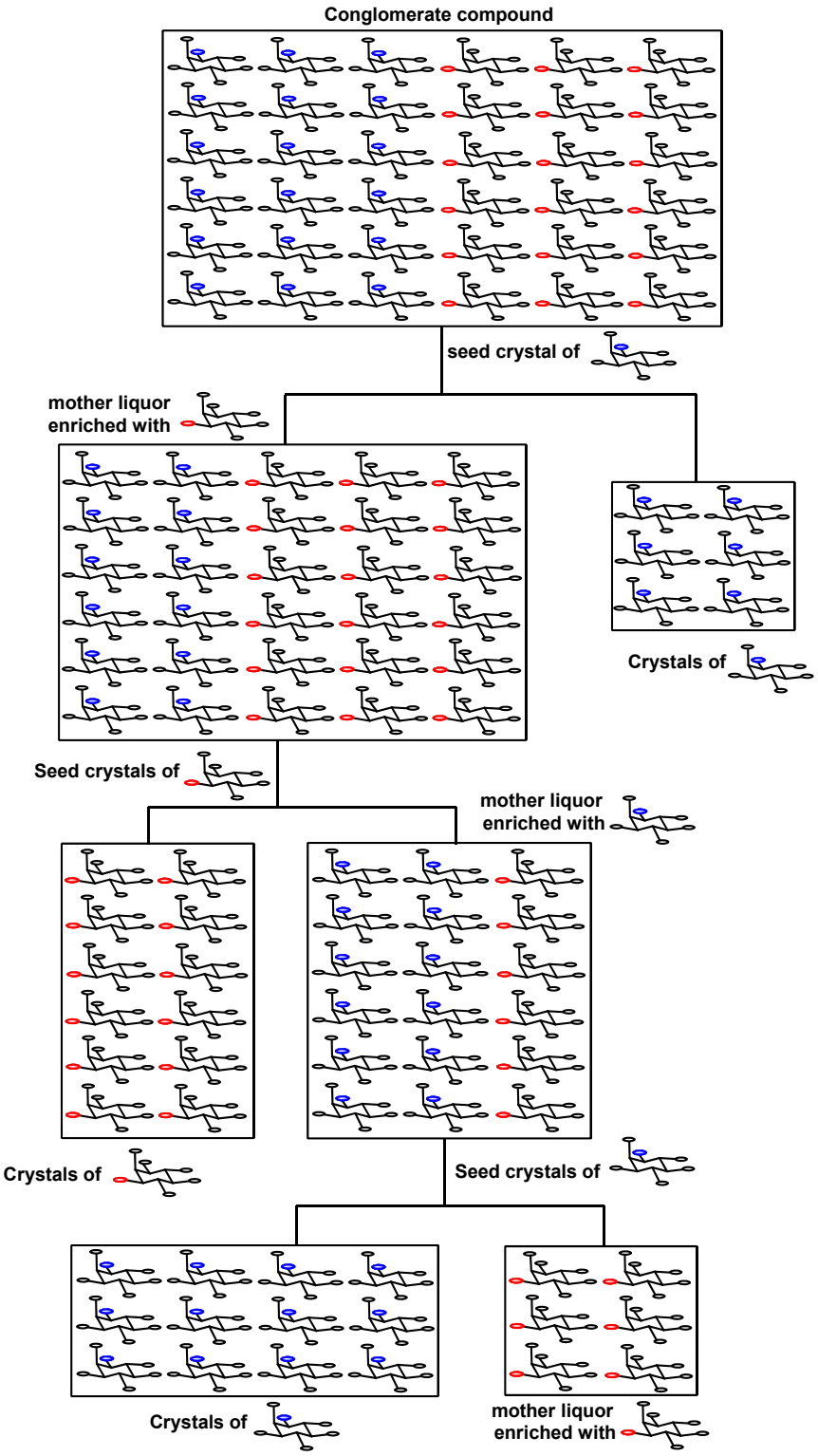


Figure 3.3. Schematic representation of preferential crystallization of conglomerates. Molecules with blue and red substituent represent the two enantiomers.

3.2.2. Chirality, crystal structure and space group

The nature of the crystal structure formed by chiral molecules is of major importance while considering the crystallization processes. There is significant difference between the chirality of the molecules and the chirality of crystals, since chiral crystals can result from achiral molecules also. The chiral crystals belong to space groups that contain only symmetry operation of the first kind (rotation, translation). It excludes the symmetry operations of the second kind (roto-inversion) which are allowed in non-centrosymmetric structures. Crystalline structures can then be classified into three categories.

- Centrosymmetric (achiral) structures (type CA) which corresponds to point groups -1, 2/m, mmm, 4/m, 4/mmm, -3, 3m, 6/m, 6/mmm, m3 and m3m.
- Non centrosymmetric achiral structures (type NA) for point groups m, mm2, -4, 4mm, -42m, 3m, -6 , 6mm, -6m2 and -43m.
- Non centrosymmetric chiral structures (type NC) associated with point groups 1, 2, 222, 4, 422, 3, 32, 6, 622, 23 and 432.

Racemic compounds can theoretically be part of any space group (CA, NA or NC) but 95% of the known racemic compounds crystallize in centrosymmetric space groups (CA). The predominant space groups are: $P2_1/c$, $C2/c$, $Pbca$ and $P\text{-}1$[32] Non-centrosymmetric racemic compounds (NA) represent a proportion of 4-5%, mainly placed in space groups $Pna2_1$, $Pca2_1$, Cc and Pc. Rare cases of racemic compounds (ortho-thyrosine, α-methylsuccinic acid or camphoroxime) crystallizing in chiral space groups (mainly $P2_12_12_1$ and $P2_1$) have been reported;[27b] their occurrence is estimated to be only about 0.02%.[27b] In case of conglomerate, the chirality of the molecules prohibits the formation achiral crystals during crystallization[27b,33] Consequently, conglomerates crystallize only in one of the 65 chiral space groups; space groups $P2_12_12_1$, $P2_1$, $C2$ and $P1$ represent 95 % of the known conglomerates.[34]

3.3. Results and Discussion

A Cambridge Structural Database (CSD, Version 5.33; Allen, 2012) search for crystalline inositol derivatives resulted in 234 hits, out of which 64 inositol derivatives had crystallized in chiral space groups. Of these 64 inositol derivatives, 28 are diastereomers, 27 are enantiomers, 6 are *meso* derivatives (Chart 3.3)[26f,35] and 3 are racemic (conglomerates, **3.87**, **3.88**, **3.89**, Chart 3.4) [26a,26b,36] We also identified **3.90** and **3.91** which exist as conglomerates, from our unpublished work.

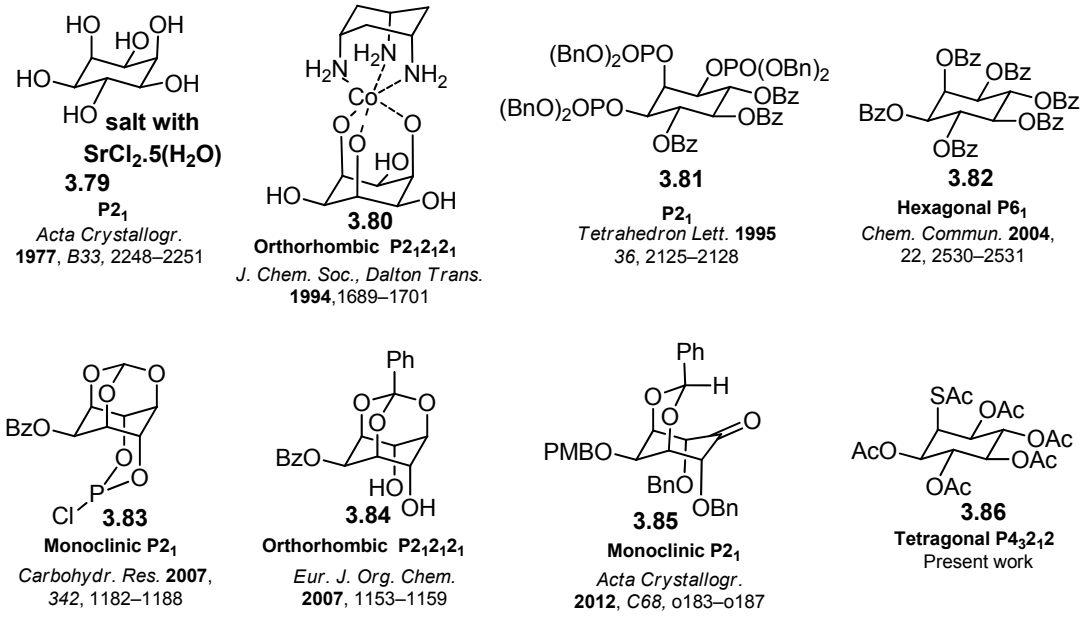


Chart 3.3. *meso* Inositol derivatives which crystallize in chiral space group.

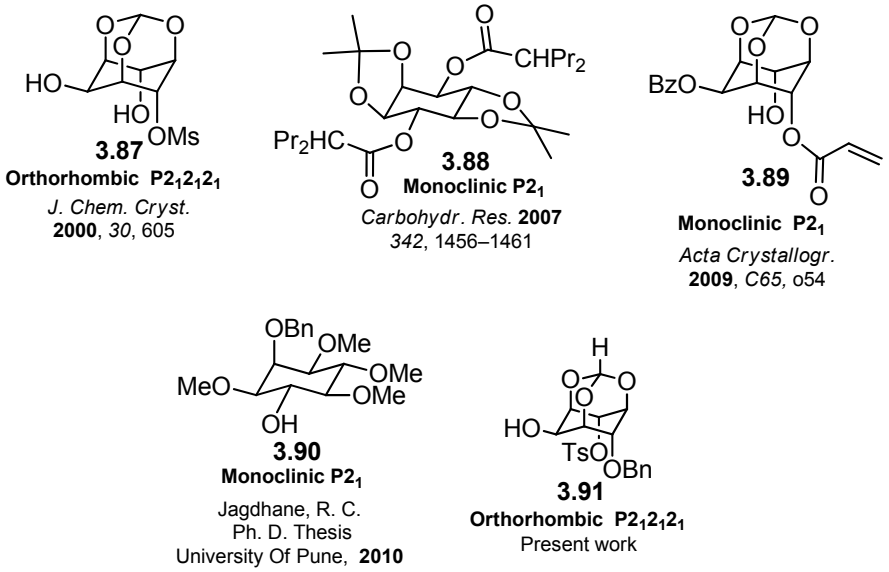


Chart 3.4. Racemic inositol derivatives that crystallize in chiral space group.

The tosylate **3.91** was initially obtained as a minor product during the *O*-benzylation of the racemic 4-*O*-tosylate **1.29** (Scheme 3.4), when we were attempting the preparation of tosylated inositol orthoester derivatives as precursors for amino cyclitols. Benzylation of the tosylate **1.29** yielded a mixture of products from which **3.91** was obtained as a crystalline solid, during chromatographic separation of the products.

Scheme 3.4: (a) DMF, 3.0 equivalent NaH, 3.5 equivalent BnBr; (b) column chromatography.

The crystal structure of **3.91** was solved in order to establish its molecular structure. On solving the crystal structure of **3.91** we realized that it crystallizes (Figure 3.4, Table 3.1) in a chiral space group ($P2_12_12_1$). Furthermore, we observed that a single crystal of **3.91** melted at a higher temperature (182–185 °C) compared to a random sample of racemic **3.91** (151-154 °C). These results suggested that racemic **3.91** crystallizes as conglomerates, i.e. **3.91** is a racemic mixture comprising of separate crystals of the two enantiomers. Crystallization of racemic **3.91** was attempted from different solvents viz. ethyl acetate, chloroform, acetonitrile, isopropanol; all the trials yielded needle shaped crystals weighing 2-5 mg each.

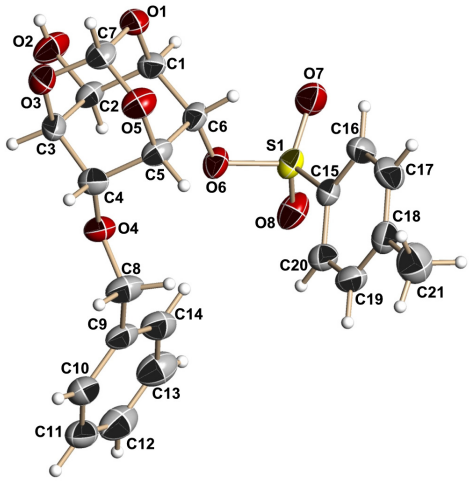


Figure 3.4. ORTEP of the tosylate **3.91**. Displacement ellipsoids are drawn at 50% probability level and H atoms are shown as small spheres of arbitrary radii.

Table 3.1. Crystal Data for the tosylate **3.91**

Chemical formula	$C_{21}H_{22}O_8S$
M_r	434.45
Temperature/K	293(2)
Morphology	Needle, colorless
Crystal size	0.74 × 0.15 × 0.12
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a (Å)	6.2125(10)
b (Å)	17.438(3)
c (Å)	18.315(3)
α (°)	90
β (°)	90
γ (°)	90
V(Å^3)	1984.1(5)
Z	4
D_{calc} (g cm^{-3})	1.454
μ (mm^{-1})	0.211
F(000)	912
Ab. correction T_{min} / T_{max}	Multi-scan 0.859 / 0.975
θ_{max} (°)	25
h, k, l (min, max)	(–7,7), (–16,20), (–21,20)
Reflns collected	10003
Unique reflns	3491
Observed reflns	3240
No. of parameters	278
GoF	1.051
R_obs	0.0322
wR_2_obs	0.0757
R_all	0.0358
wR_2_all	0.0776
$\Delta\rho_{max}$,$\Delta\rho_{min}$(eÅ^{-3})	0.25, –0.13

The crystal structure determination of **3.91** revealed that it belongs to the orthorhombic non-centrosymmetric chiral space group $P2_12_12_1$ and only one enantiomer is present in its crystals. The conformation of the molecule of **3.91** as observed in the crystal structure reveals regular chair conformation of the central inositol ring. The benzyloxy group at the C4 position takes an extended conformation pointing downwards and the tosyloxy group at the C6 position acquired folded conformation with respect to the orthoformate bridge.

Molecules of **3.91** form a helical assembly (figure 3.5) across the crystallographic two fold screw axis (*b*-axis) *via* O-H...O hydrogen bonding interactions involving OH group at the C2 position and one of the oxygen atom (O8) of the tosyl group to form O2-H2A…O8 interaction, the geometry being moderate (H2A…O8 = 2.252 Å, O2…O8 = 2.987 Å and ∠O2-H2A…O8 = 149°). Additionally, molecules form another helical assembly across the same crystallographic two-fold screw axis (*b*-axis) *via* linear C-H…π interactions involving H7 proton of the orthoformate bridge carbon atom C7 and the center of the π-cloud of the benzene ring (C9-C14) of the benzyl group at C4 position (C7-H7…Cg5, H7…Cg5 = 2.47 Å, C7…Cg5 = 3.444 Å and ∠C7-H7…Cg5 = 174°; Cg5 is the centroid of the benzene ring C9-C14). This arrangement also brings the ring carbon C20—H20 of the tosyl group closer to the orthoformate bridge oxygen O3 in the next molecule of the helical chain generating rather long and non-linear C-H…O interaction (C20-H20…O3, H20…O3 = 2.61 Å, C20…O3 = 3.307 Å and ∠C20-H20…O3 = 132°). These two helical assemblies run in parallel fashion and are stitched together by two C-H…O interactions, namely C1-H1…O5 and C5-H5…O7 along the *a*-axis. The latter contact is shorter than the former whereas the angle of approach for former is more linear compared to the latter. (C1-H1…O5, H1…O5 = 2.71 Å, C1…O5 = 3.670 Å and ∠C1-H1…O5 = 167°; C5-H5…O7, H5…O7 = 2.48 Å, C5…O7 = 3.370 Å and ∠C5-H5…O7 = 153°).

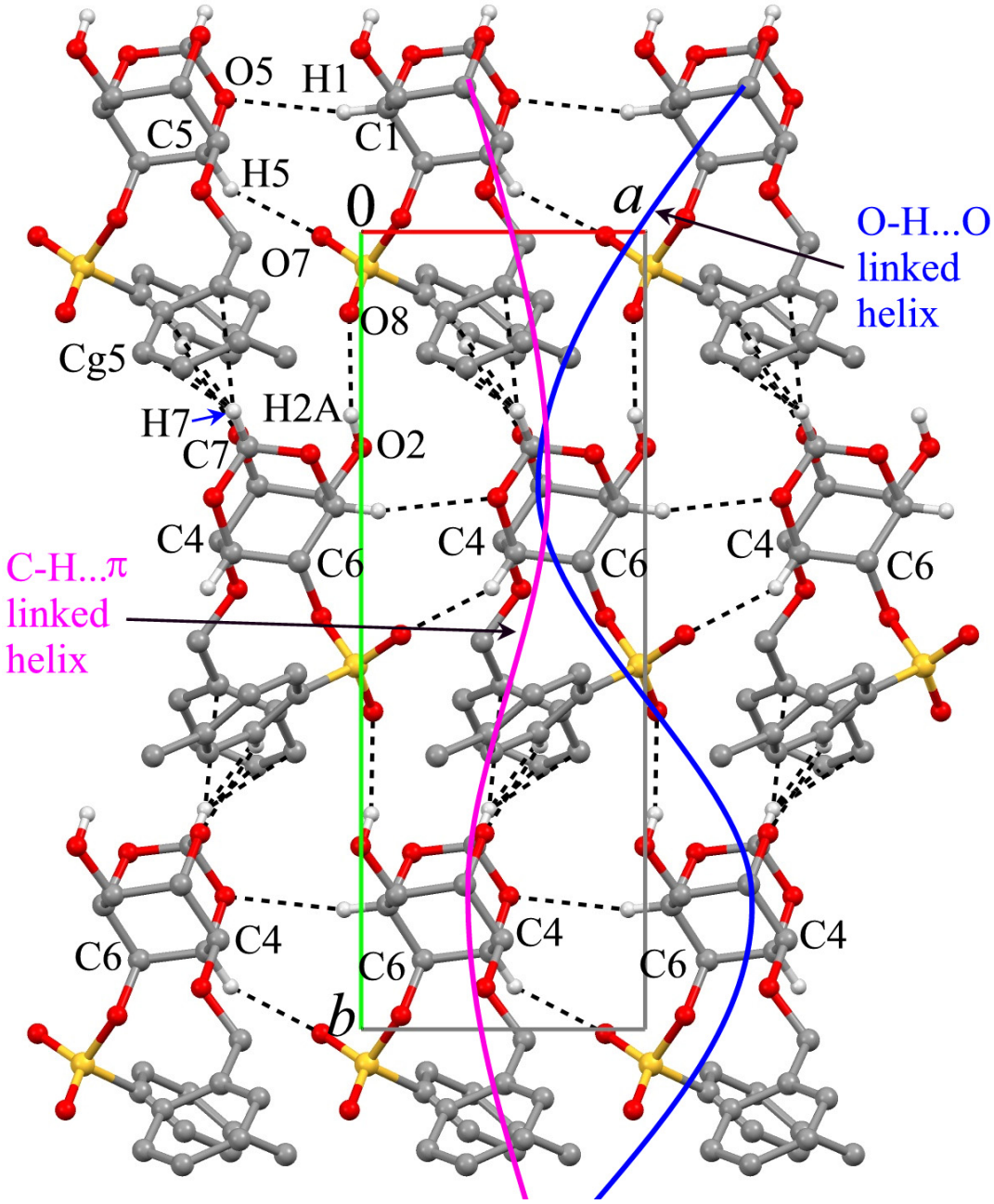


Figure 3.5. Interlinking of two different helices *via* C-H…O contacts. Hydrogen atoms which are not involved in any interaction have been omitted for clarity.

Molecular packing viewed down the *a*-axis (figure 3.6) revealed bridging of adjacent anti parallel C-H…π helices along the crystallographic two-fold screw axis (*c*-axis) *via* C12-H12…O1 and C21-H21A…O2 interactions (figure 3.6). The geometry of the latter is better compared to the former interactions (C12-H12…O1, H12…O1 = 2.65 Å, C12…O1 = 3.426 Å and ∠C12-H12…O1 = 141°; C21-H21…O2, H21…O2 = 2.52 Å, C21…O2 = 3.415 Å and ∠C21-H21…O2 = 156°).

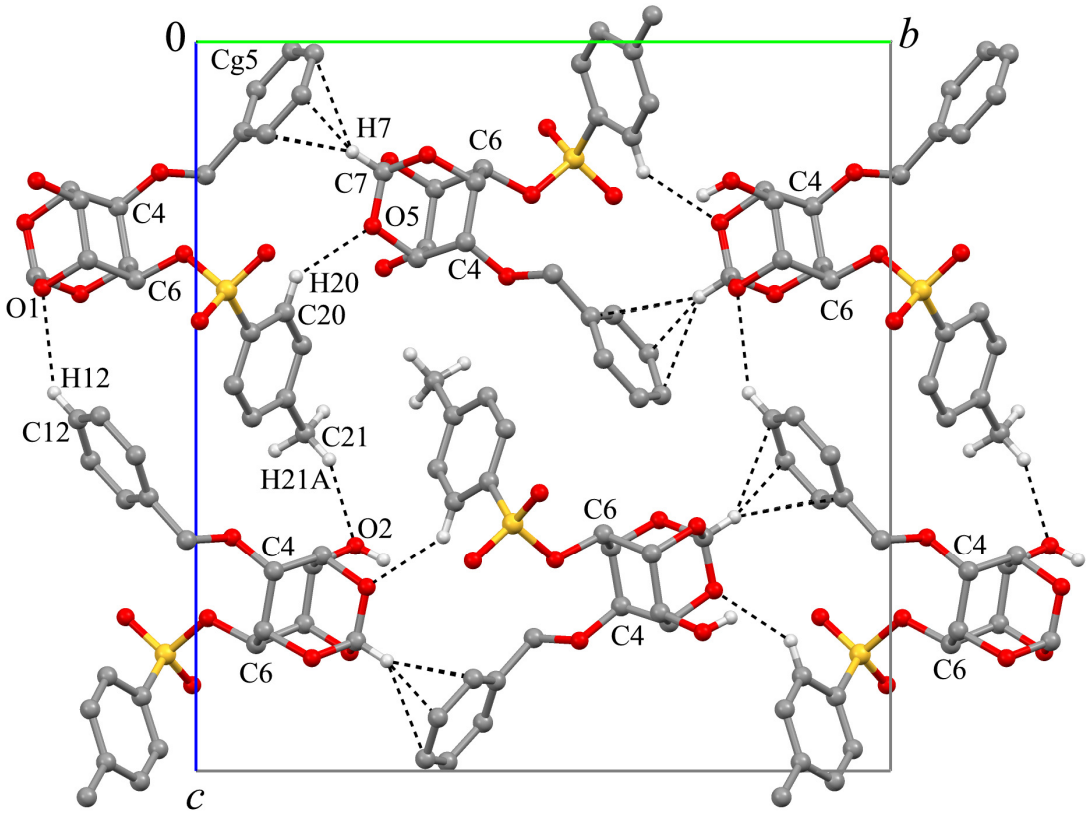


Figure 3.6. Packing of C-H…π helices along the *c*-axis via C-H…O interactions. Hydrogen atoms which are not involved in any interaction have been omitted for clarity.

Packing of the molecules of **3.91** along the third dimension, i.e. down the *b*-axis (figure 3.7) again showed the helical assembly of the molecules running along the *c*-axis. Molecules along the helical axis are connected by C21-H21A…O2 and C12-H12…O1 contacts. This arrangement also brings the ring atom C16—H16 of the tosyl group closer to the edge atoms C9, C10 and C11 of the C9–C14 phenyl ring of the benzyl group along the chain, rather than pointing towards the centre of the π-cloud, generating an off-centered C—H…π contact (C16—H16…Cg5, H16…Cg5 = 2.89 Å, C7…Cg5 = 3.687 Å and ∠C7-H7…Cg5 = 144°; Cg5 is the centroid of the benzene ring C9-C14). These

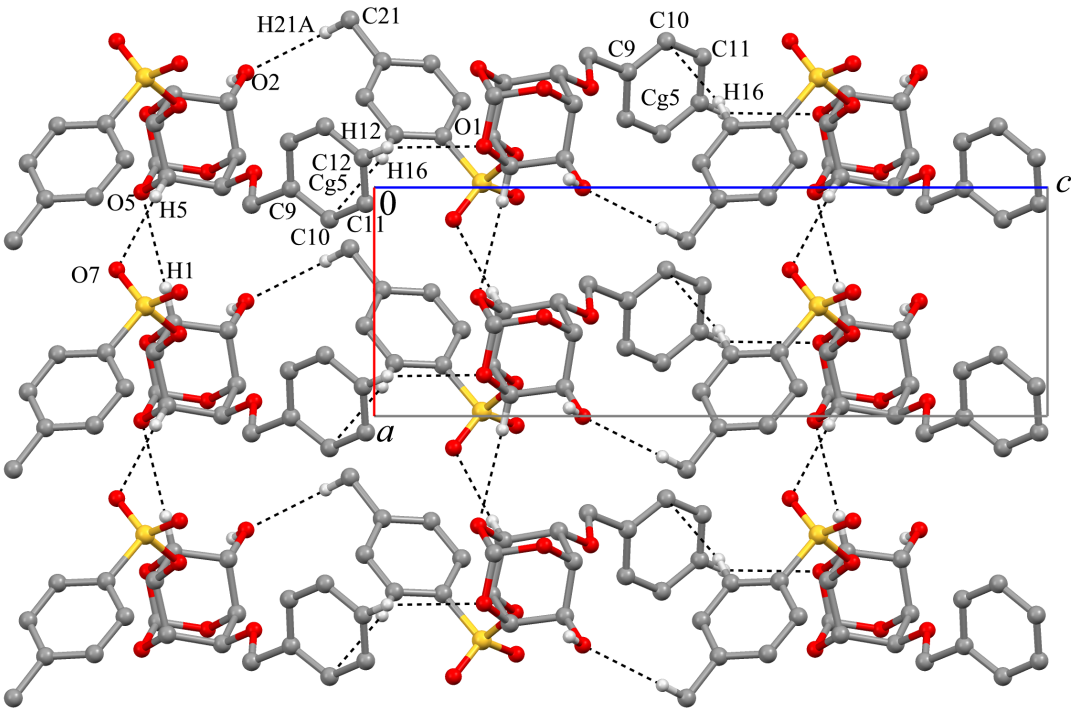


Figure 3.7. Molecular packing viewed down the *b*-axis. Hydrogen atoms which are not involved in any interaction have been omitted for clarity.

adjacent helices are connected along the a-axis via unit translated two C-H…O interactions, C1-H1…O5 and C5-H5…O7.

Above discussion on crystal packing indicates that, molecules in conglomerate crystals of **3.91** are tightly packed *via* various strong and weak intermolecular interactions. The notable one is the involvement of C-H…π contact. Surprisingly, the same benzene ring (of the benzyl group) is involved in making of C-H…π contact, the π-cloud of which accepts proton from C7 and C16 atoms, thus engaged from both the sides to have an extended conformation. The tight packing of the same enantiomers indicates strong affinity towards each other. This could be the reason for the formation of conglomerates during crystallization.

To quantify intermolecular interactions and packing arrangements in the crystal structures, we performed UNI force-field calculations using the PIXEL method as implemented in the program Mercury of the CCDC Mercury CSD 3.0 (Build RC5). This method allows the calculation of lattice energies which are in good agreement with crystal sublimation enthalpies for a wide selection of organic compounds.[37] Intermolecular potentials given are the sum of Columbic, polarization, dispersion and repulsion terms, as defined in the PIXEL method. The crystal structures were used as input, but hydrogen atom positions were normalized prior to

the calculations *viz.* O-H distances to 0.993 Å and C-H distances to 1.089 Å (standard values obtained by neutron diffraction). The calculation yielded a total packing energy of -216.0 kJ mol^{-1}. Furthermore, using the UNI force-field calculations, approximate energies of the intermolecular potential were also estimated. Surprisingly, the intermolecular potentials associated with the two neighboring molecules which are involved in helical chain formation *via* O2-H2A…O8 hydrogen bond have least value of -27.2 kJ/mol and the major contribution of -64.6 kJ/mol towards intermolecular potential comes from the association of the two neighboring molecules via unit translated two C-H...O interactions namely, C1-H1…O5 and C5-H5…O7. The second major contribution to the intermolecular potential (-44.3 kJ/mol) is between the neighboring molecules which are associated via 2_1-screw relation through C21-H21A…O2, C12-H12…O1 and off-centered C-H…π interactions (C16-H16…Cg5) whereas the molecule along the helical chain generated *via* excellent C-H…π interactions (C7-H7…Cg5) have value of intermolecular potential -29.9 kJ/mol. The estimation of intermolecular potentials suggest that, molecules of **3.91** are first associated along the shortest axis (*a*-axis) via unit translated C1-H1…O5 and C5-H5…O7 interactions to form one-dimensional molecular chain (figure 3.8) revealing it to be perhaps, the fastest growing face leading to the formation of needle shaped crystals. The subsequent crystal growth along the other two dimensions via O2-H2A…O8 and C7-H7…Cg5 results in the helical assembly and eventually the chiral crystal.

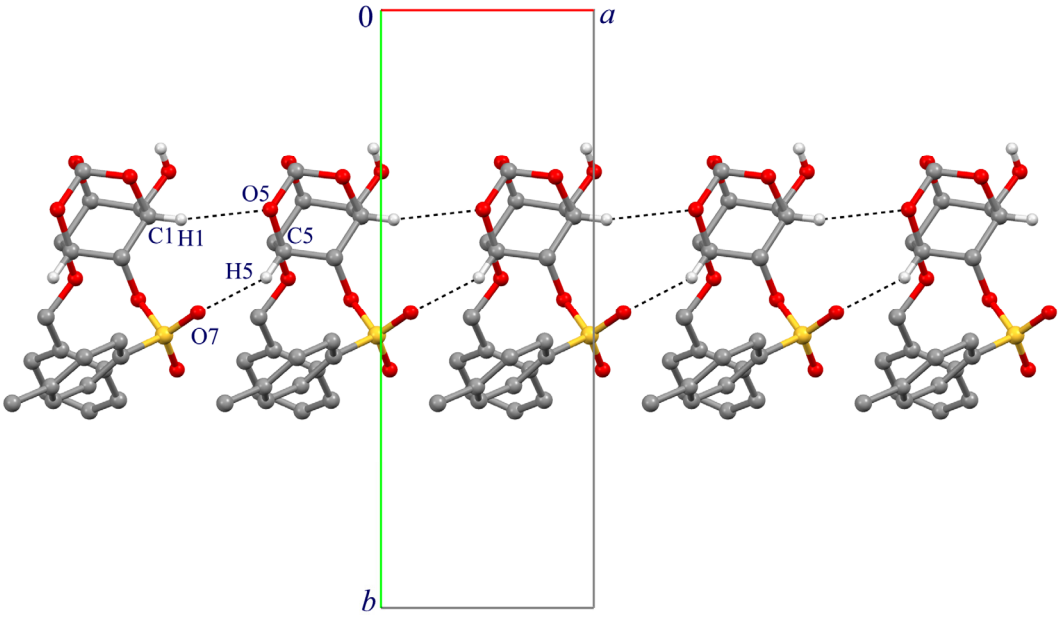


Figure 3.8. One dimensional molecular chain formed by two C-H…O interactions. Hydrogen atoms which are not involved in any interaction have been omitted for clarity.

Figure 3.9 shows the overlap of simulated powder XRD pattern obtained from single crystal X-ray data for a crystal of **3.91** with the experimental powder XRD pattern of the solid sample (powder) obtained by purification after column chromatography. The figure shows excellent match revealing conglomerate crystallization occurred even during the purification of **3.91**.

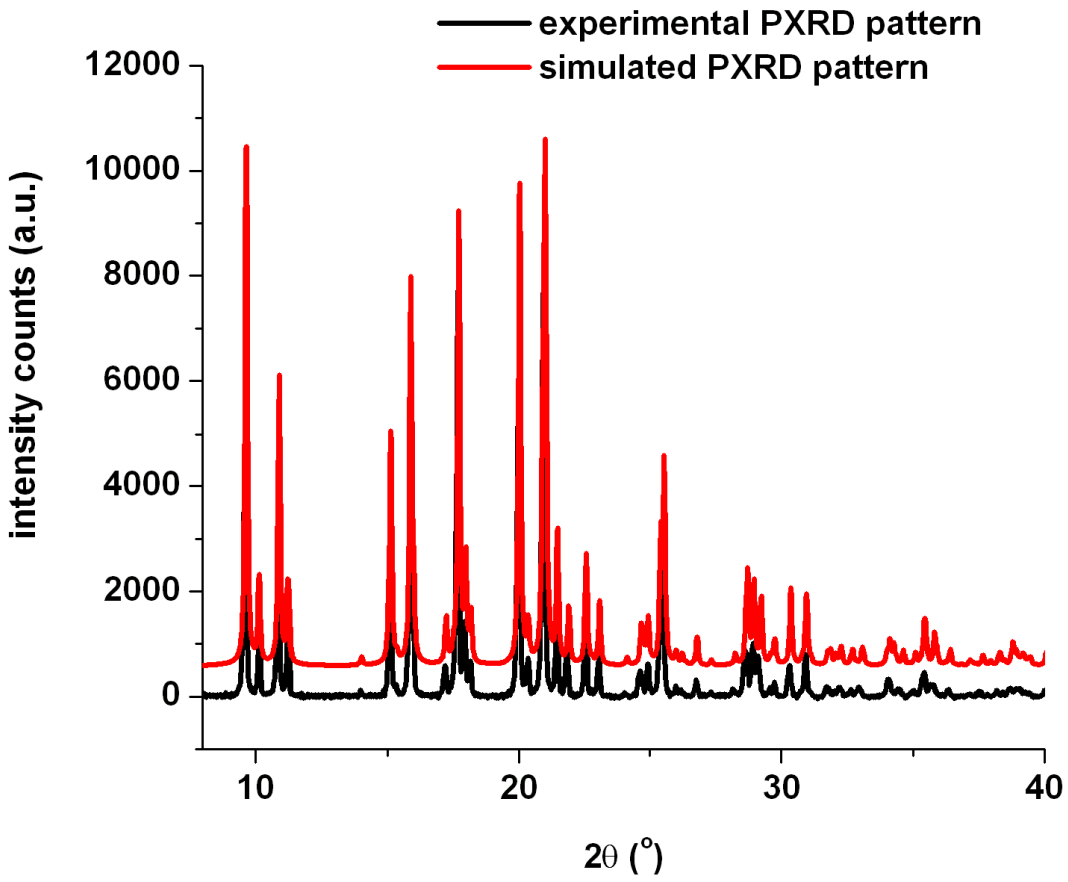
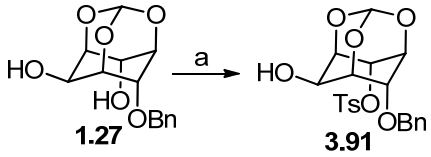


Figure 3.9. Overlap of powder XRD data; (a) Simulated powder X-ray data from a single crystal (red); (b) recorded powder XRD data of racemic **3.91** (black).

We decided to attempt the resolution of the tosylate **3.91** as we had previously used *O*-sulfonylated *myo*-inositol orthoformates to prepare many other useful derivatives of *myo*-inositol.[38] The tosylate **3.91** was synthesized by the tosylation of racemic benzyl ether **1.27** (Scheme 3.5), as this method gave better yield of **3.91**[39] compared to benzylation of the tosylate (Scheme 3.4). The products formed in the latter reaction (Scheme 3.4) and their yield were susceptible to factors such as sequence of addition of reagents, mode of addition of reagents and hence did not appear to be amenable for standardization. Previous work in our laboratory had shown that *O*-substitution reaction of the diols such as **1.27** in the presence of lithium hydride preferentially occurs at the C6-axial position.[39]



Scheme 3.5: (a) DMF, LiH, TsCl, 65%.

In order to choose a suitable solvent for the preferential crystallization of enantiomers, solubility of the racemic tosylate **3.91** was determined in different solvents (Table 3.2).

Table 3.2. Solubility of the racemic tosylate **3.91** in different solvents at ambient temperature.

Sr. No.	Solvent	Solubility (mg /mL)
1	Acetonitrile	22
2	Carbontetrachloride	3
3	Chloroform	69
4	Dichloromethane	75
5	Ethyl acetate	14
6	Methanol	5
7	Toluene	3

Racemic **3.91** is sparingly soluble in carbon tetrachloride, methanol and toluene; highly soluble in dichloromethane and chloroform and has moderate solubility in acetonitrile and ethyl acetate. Hence ethyl acetate was chosen as the solvent for crystallization experiments and the racemic tosylate **3.91** was crystallized once. One of the crystals was selected (hand picked) and analyzed by HPLC over a chiral column (Figure 3.10b) to determine the enantiomeric excess in single crystals. A random sample of crystals of **3.91** was also analyzed for comparison (Figure 3.10a).

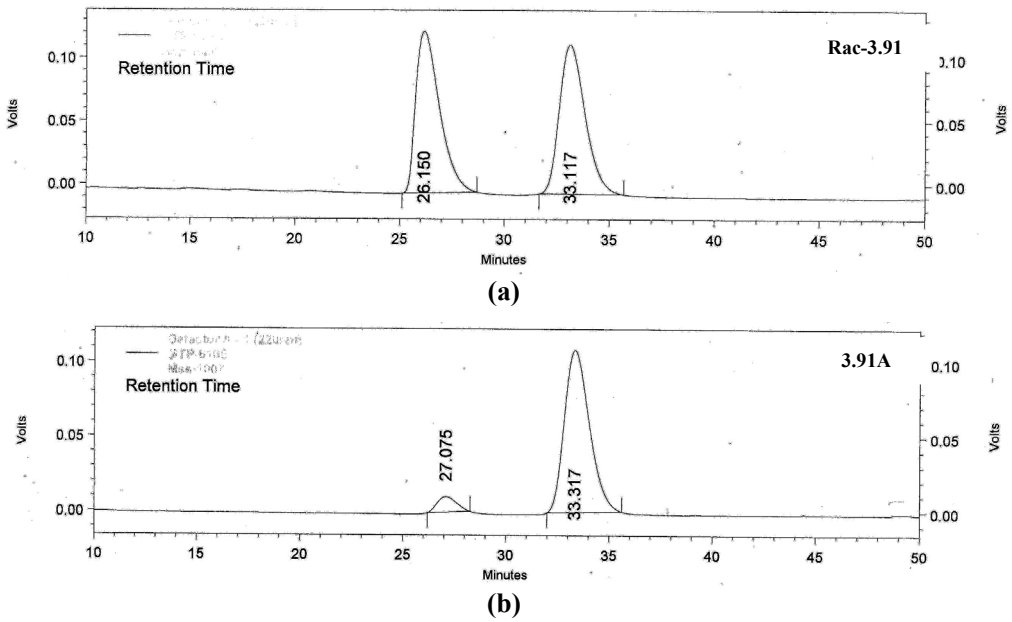


Figure 3.10. Chiral HPLC of (a) racemic **3.91**; (b) a single crystal of **3.91**. Column, chiracel OD-H (250 x 4.6 mm); mobile phase, *iso*-propanol:light petroleum (40:60).

The results of the HPLC analysis clearly show that the random sample of **3.91** is racemic while a single crystal of **3.91** has an ee of 87%. Ideally, a single crystal should consist of only one enantiomer, as suggested by X-ray diffraction analysis. However, HPLC analysis reveals the presence of both the enantiomers, probably because of the microcrystals of one enantiomer sticking to the larger crystal of the other enantiomer, which cannot be separated by mechanical separation.

The summary of results of crystallization experiments with **3.91** are shown in Figure 3.11. Starting from racemic **3.91** and using one single crystal as a seed crystal, we were able to attain 83% *ee* for one of the enantiomers (E1), in three crystallizations. Crystals of the other enantiomer (E2) was enriched to 47% ee. In the last step both crystals (3.100E) and mother liquor (3.100F) are enriched with the same enantiomer E1. This could be because of incomplete crystallization of the enantiomer E1 (we obtained only 5 mg of the crystals from 135 mg in solution).

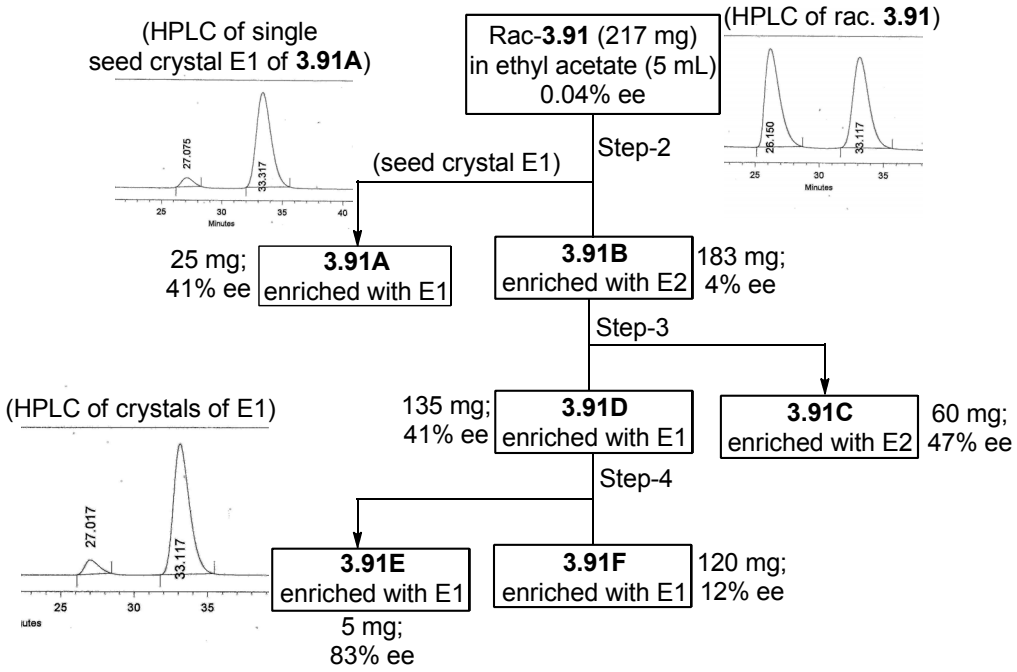


Figure 3.11. Results of preferential crystallization of racemic **3.91** from ethyl acetate. E1 and E2 are enantiomers of **3.91**. **3.91A**, **3.91C** and **3.91E** represent crystalline solids that crystallized out of the solution; E1 and E2 are the two enantiomers of **3.91**. See experimental section for details.

3.4. Conclusion

The results of preferential crystallization experiments of the racemic tosylate **3.91** suggest that separation of enantiomers by preferential crystallization has good potential to provide chiral inositol derivatives. However, further refinement of the crystallization experiments is needed to obtain larger quantities of the individual enantiomers of the tosylate **3.91** for these enantiomers to be synthetically viable.

3.5. Experimental

3.5.1. X-ray Data (Collection, Structure Solution and Refinement): Same as in the subsection 2.7.1 (Chapter 2).

3.5.2 General Experimental Methods: General experimental methods are same as in the subsection 2.7.2 (Chapter 2).

Racemic 4-*O*-benzyl-6-*O*-tosyl *myo*-inositol-1,3,5-orthoformate (3.91).

Method A: from racemic 6-*O*-tosyl *myo*-inositol-1,3,5-orthoformate (1.29).

To a solution of the racemic tosylate **1.29** (0.52 g, 1.5 mmol) in dry DMF (5 mL) was added sodium hydride (0.30 g, 7.5 mmol) at 0 °C and the reaction mixture stirred at ambient temperature for 30 min. The reaction mixture was cooled again to 0 °C and to this reaction mixture, a solution of benzyl bromide (0.45 mL, 3.75 mmol) in DMF (1 mL) was added slowly at 0 °C and the resulting reaction mixture was stirred at ambient temperature for 30 min. A few pieces of ice were then added and the mixture was concentrated under reduced pressure. The residue obtained was worked up with ethyl acetate which gave a mixture of three products. Racemic benzyl ether **3.91** (0.057 g, 9 %) was obtained as needle shaped crystals while separating the products by column chromatography (230-400 mesh silica gel; eluent: 15% ethyl acetate – light petroleum) mp. 151–154 °C; Lit. mp. 160 °C.[39] **^{1}H NMR** (200 MHz; $CDCl_3$): δ 2.45 (s, 3H, CH_3), 2.99 (d, 1H, J = 12 Hz, OH D_2O exchangeable), 4.02–4.15 (m, 2H, Ins H), 4.15–4.24 (m, 1H, Ins H), 4.27–4.38 (m, 1H, Ins H), 4.41–4.48 (m, 1H, Ins H), 4.68 (d, J = 11.6 Hz, 1H, CH_2Ph), 4.68 (d, J = 11.5 Hz, 1H, CH_2Ph), 5.13–5.25 (m, 1H, Ins H), 5.43 (s, 1H, O_3CH), 7.23–7.43 (m, 7H, Ar H), 7.69–7.83 (m, 2H, Ar H) ppm.

Method B: from racemic 4-*O*-benzyl *myo*-inositol-1,3,5-orthoformate (1.27)

To a solution of the racemic benzyl ether **1.27** (1.40 g, 5.0 mmol) in dry DMF (30 mL) was added lithium hydride (0.24 g, 30.0 mmol) at 0 °C and the reaction mixture stirred at ambient temperature for 2 h. To this reaction mixture, a solution of tosyl chloride (1.14 g, 6.0 mmol) in DMF (7 mL) was added slowly at 0 °C and stirred for 40 h. A few pieces of ice were then added and the mixture was concentrated under reduced pressure. The residue obtained was worked up with ethyl acetate and the product obtained was purified by column chromatography (230-400 mesh silica gel; eluent 20% ethyl acetate – light petroleum) to get racemic **3.91** (1.42 g, 65%); mp. 151-154 °C; Lit. mp. 160 °C.[39] mp. of a single crystal of **3.91**, 182–185 °C.

Determination of solubility of racemic 3.91 in different solvents.

A mixture of racemic **3.91** (0.026 g) and ethyl acetate (2 mL) was stirred at ambient temperature for 10 min. To the clear solution obtained excess of racemic **3.91** (0.004 g) was added and the mixture stirred at ambient temperature for 10 min, when some of the solid remained undissolved. A portion of the supernatant clear solution (1 mL) was evaporated to dryness to get racemic **3.91** (0.0137 g).

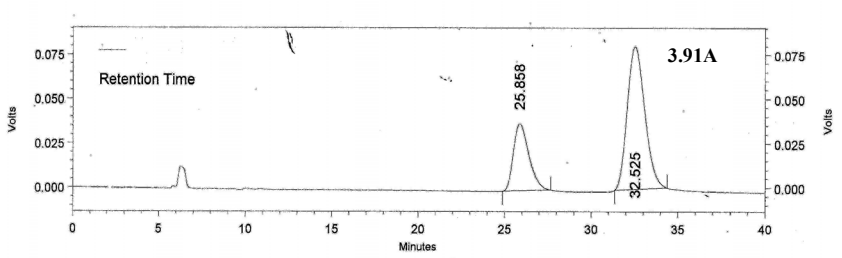
Similar procedure was followed to determine the solubility of racemic **3.91** in other solvents shown in Table 3.2.

Preferential crystallization of racemic 4-*O*-benzyl-6-*O*-tosyl-*myo*-inositol-1,3,5-orthoformate (3.91).

Step 1. Racemic **3.91** was crystallized from ethyl acetate to get well defined crystals of **3.91**. One single crystal was powdered to obtain micro-crystals (**3.91-E1**) of one enantiomer which could be used as seed crystals in future crystallization experiments.

Step 2. A mixture of the racemic tosylate **3.91** (0.217 g, **3.91**) and ethyl acetate (5 mL) was heated (using a hot air gun) in a closed glass vial (crystallization chamber) with stirring, till a clear solution was obtained. To this clear solution racemic **3.91** (0.007 g) was added and the mixture was heated to get a clear solution. Heating was stopped for a few minutes when a solid began to appear (indicating that the solution of **3.91** was supersaturated). The solution was heated again to re-dissolve the precipitated solid and micro crystals **3.91-E1** (obtained in Step 1) was added. The resulting mixture in the closed crystallization chamber was allowed to cool, with stirring, to ambient temperature (7-10 min). The precipitated crystals were filtered out by vacuum filtration and the crystalline solid obtained was dried under reduced pressure to get enantiomerically enriched **3.91A** (0.025 g, 41 % ee). The mother liquor was evaporated to get enantiomerically enriched **3.91B** (0.183 mg; 4% ee). The crystals **3.91A** and **3.91B** are enriched with opposite enantiomers, say enantiomers E1 and E2 respectively (as indicated in Figure 3.11).

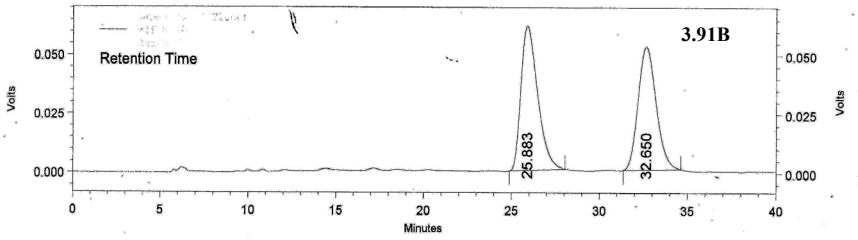
HPLC of **3.91A** enriched with E1 (41% ee)



Detector A - 1 (220nm)

Retention Time	C Area	Area %
25.858	2367536	29.391
32.525	5687825	70.609
Totals	8055361	100.000

HPLC of **3.91B** enriched with E2 (4% ee)



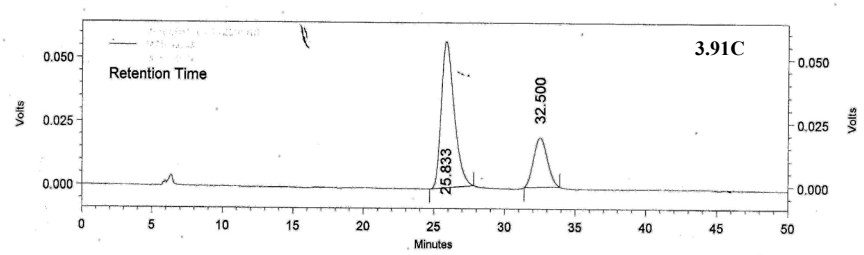
Detector A - 1 (220nm)

Retention Time	C Area	Area %
25.883	4075965	52.167
32.650	3737348	47.833
Totals	7813313	100.000

Step 3. A mixture of the crystals **3.91B** (0.183 g, 4% ee), racemic **3.91** (0.025 g) and ethyl acetate (5 mL) were heated in a closed glass vial (crystallization chamber) to get a clear solution. Excess racemic **3.91** was added to make up the total mass of **3.91** to approximately three times the solubility of **3.91** in ethyl acetate, (i.e. 0.21 g). The clear solution obtained was allowed to attain ambient temperature, with stirring (7-10 min). The solid precipitated was filtered out by vacuum filtration and the solid obtained was dried under reduced pressure to get **3.91C** (0.060 g, 47% ee) enriched

with E2. The mother liquor was evaporated to dryness to get **3.91D** enriched with E1 (0.135 g; 10% ee).

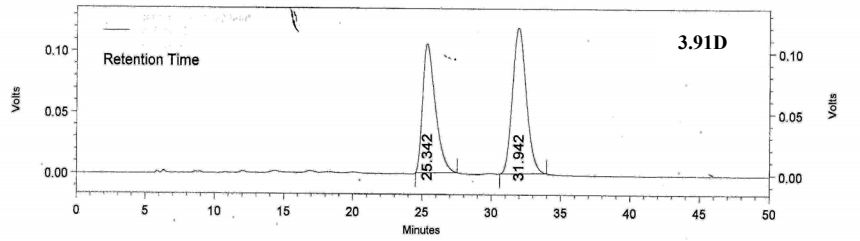
HPLC of **3.91C** enriched with E2 (47% ee)



Detector A - 1 (220nm)

Retention Time	C Area	Area %
25.833	3671262	73.507
32.500	1323199	26.493
Totals	4994461	100.000

HPLC of **3.91D** enriched with E1 (10% ee)

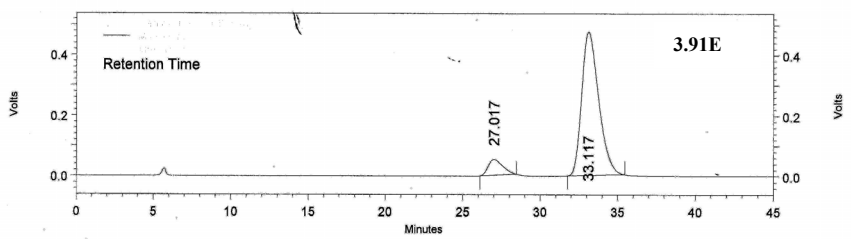


Detector A - 1 (220nm)

Retention Time	C Area	Area %
25.342	6731163	44.785
31.942	8298937	55.215
Totals	15030100	100.000

Step 4. A mixture of the solid **3.91D** enriched with E1 (0.135 mg; 10% ee) and ethyl acetate (3 mL) was heated in a closed vial (crystallization chamber), with stirring. The clear solution obtained was allowed to cool to ambient temperature (7-10 min). The crystalline solid precipitated was filtered out by vacuum filtration and the solid obtained **(3.91E)** was dried under reduced pressure (0.005 g, 83% ee). The mother liquor was evaporated to get **3.91F** enriched with E1 (0.12 mg; 12% ee).

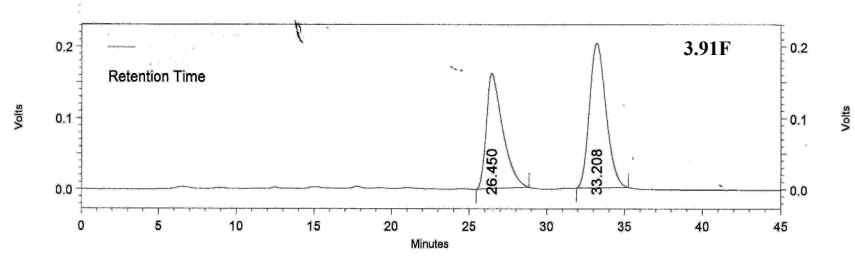
HPLC of **3.91E** enriched with E1 (83% ee)



Detector A - 1 (220nm)

Retention Time	C Area	Area %
27.017	3401265	8.574
33.117	36267671	91.426
Totals	39668936	100.000

HPLC of **3.91F** enriched with E1 (12% *ee*)



Detector A - 1 (220nm)

Retention Time	C Area	Area %
26.450	11819573	44.014
33.208	15034674	55.986
Totals	26854247	100.000

3.6. References

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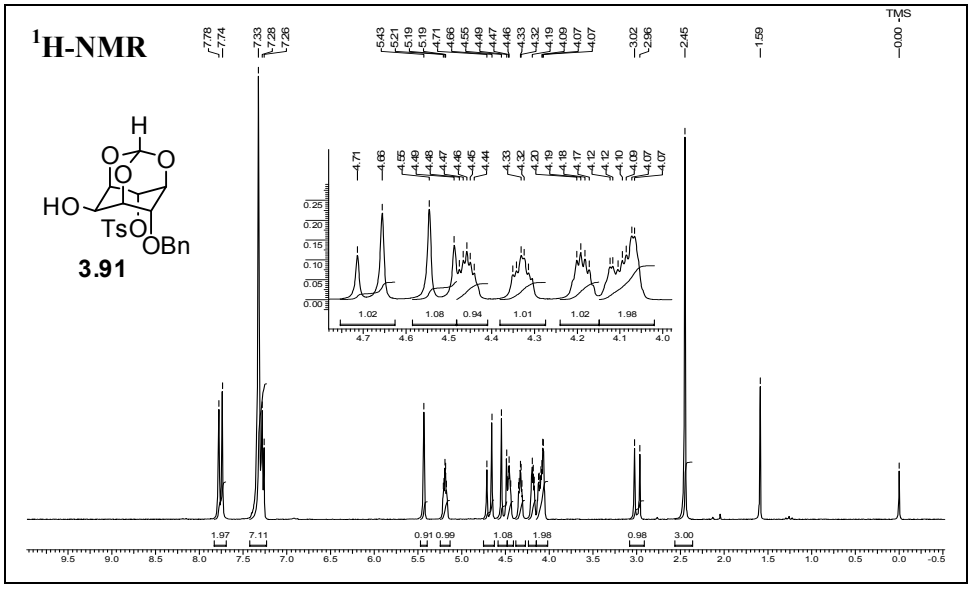
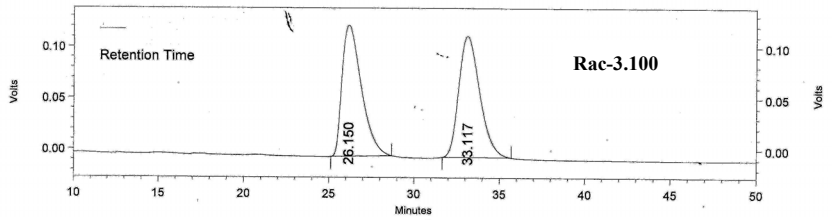
Appendix II

Appendix II Index



HPLC of racemic **3.91**

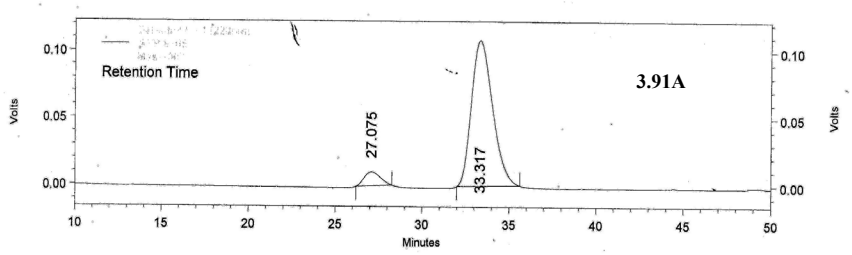


Detector A - 1 (220nm)

Retention Time	C Area	Area %
26.150	10113824	49.982
33.117	10121117	50.018
Totals	20234941	100.000

Project Leader : Dr.Shashidhar M S
Column :Chiralcel OD-H (250x4.6mm)
Mobile Phase :IPA:PE (40:60)
Wavelength : 220nm
Flow Rate : 0.5 ml/min 430psi
conc. : 0.5mg/1.0ml
Inj vol- : 10ul
Kunte

HPLC of single crystal **3.91A-E1** (87% ee)



Detector A - 1 (220nm)

Retention Time	C Area	Area %
27.075	663052	6.730
33.317	9189457	93.270
Totals	9852509	100.000

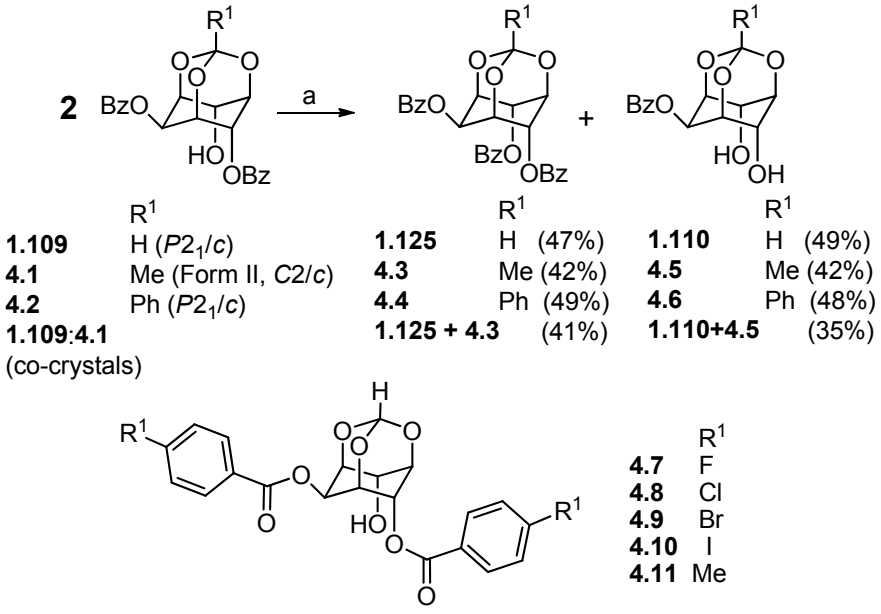
Chapter 4

Synthesis and structural studies of 2-deoxy-2-mercapto *myo*-inositol derivatives

4.1. Introduction

The study of organic reactions in molecular solids and crystals has emerged as a frontier area of research in the recent past. Although reactions in molecular crystals are less common than reactions in the gas phase or in solution, the degree of (regio- and/or stereo-) control exerted by the crystalline state is often comparable to that observed in enzymatic processes.[1] Transesterification reactions among the hydroxyl groups of partially acylated inositol derivatives in solution occur frequently[2] and this has been exploited for the preparation of biologically relevant phosphorylated inositol derivatives.[3] Most of these acyl migration reactions however result in the formation of a mixture of isomeric hydroxy esters and consequently result in poor isolated yield of the required *O*-protected inositol derivative. Also, isolation of each individual isomer resulting from indiscriminate acyl migration reactions requires efficient and laborious methods of separation.

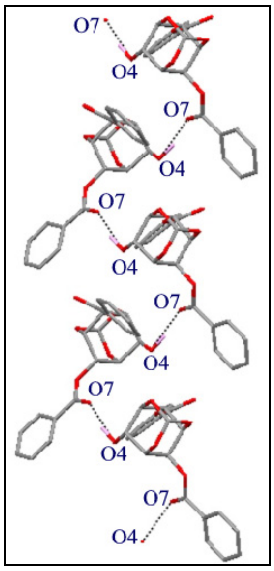
Extremely facile and neat intermolecular benzoyl group transfer reactions in crystals of racemic 2,6-di-*O*-benzoyl *myo*-inositol 1,3,5-orthoesters and their co-crystals have been reported from our laboratory (Scheme 4.1).[4]

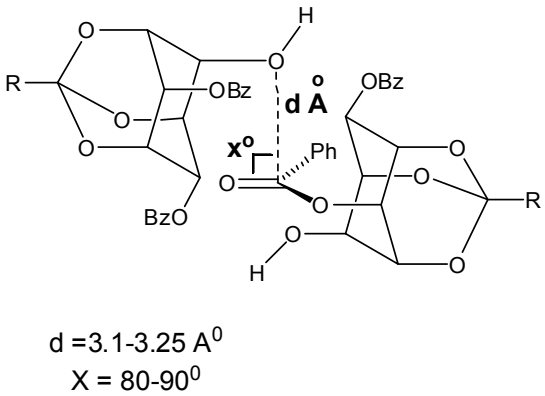


Scheme 4.1. (a) Na_2CO_3, heat. (All the compounds are racemic).

Minor perturbations to the basic molecular framework of these orthoesters (Scheme 4.1) and the consequent changes in the acyl transfer reactivity of the resulting molecules (**4.7**–**4.11**) in their crystals[5] helped in arriving at necessary

conditions for observing efficient acyl transfer in crystals, which are listed below. (i) The arrangement of molecules in crystals in which clean acyl transfer reaction takes place, must allow a domino type of process. For instance this arrangement can be helical as shown in figure 4.1(A); (ii) the hydroxyl group and the carbonyl group between which the acyl transfer takes place must be oriented as shown in Figure 4.1(B).





A **B**

Figure 4.1. Geometrical parameters that determine the facility of intermolecular acyl group transfer in crystals: (A) helical molecular packing in crystals of racemic **1.109** and (B) relative orientation of the reacting molecules.

As a sequel to these studies and to see if the scope of acyl transfer reactions in molecular crystals can be widened, we undertook the preparation of thio analogs of inositol orthoesters (Chart 4.1) to examine the possibility of acyl transfer in their crystals. Accordingly, the results presented in this chapter pertain to our attempts towards the preparation of orthoester derivatives of thio analogues of *myo*-inositol.

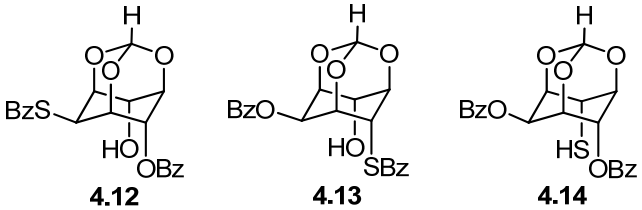


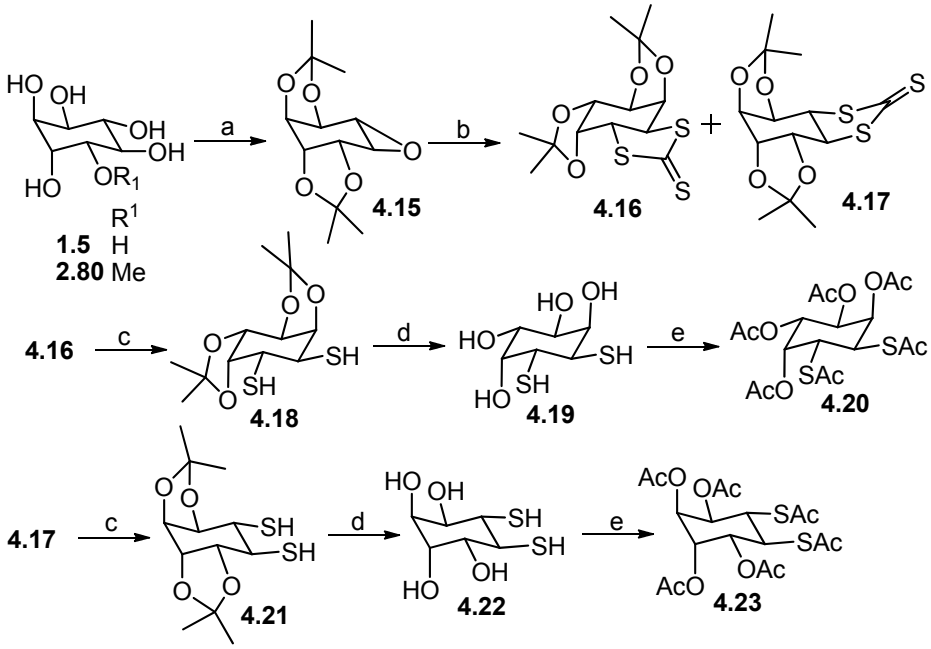
Chart 4.1. Compounds proposed to be investigated; all the compounds are racemic.

A search of the literature revealed that preparation of a few thio-inositols are reported in the literature.[6] However, there are no reports on the preparation of thio

analogs of inositol orthoesters and their derivatives. Known methods for the introduction of the thiol group in inositols are outlined below.

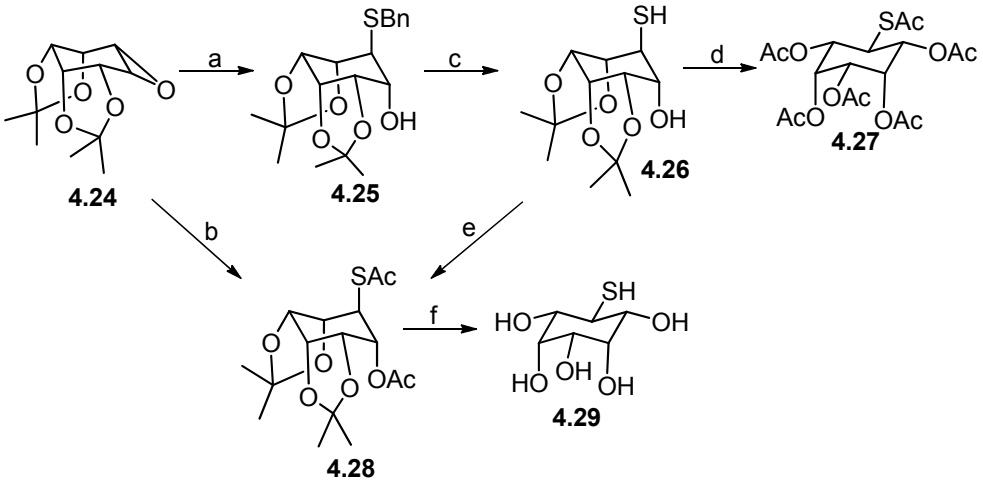
4.2. Known methods for the synthesis of thio analogs of inositols

McCastland and coworker's synthesis of 1,6-dideoxy-1,6-dimercapto-*neo*-inositol **4.19**, 5,6-dideoxy-5,6-dimercapto-*chiro*-inositol **4.22** (Scheme 4.2) constitutes the first report on the synthesis of sulfur analogs of inositol.[6a] This synthesis used the classical approach of using the ketals to protect the inositol hydroxyl groups. The thiol groups were introduced *via* the corresponding thiocarbonates. Diastereomeric thio carbonates were reduced to obtain the dithio analogs of *neo*- and *chiro*-inositols.



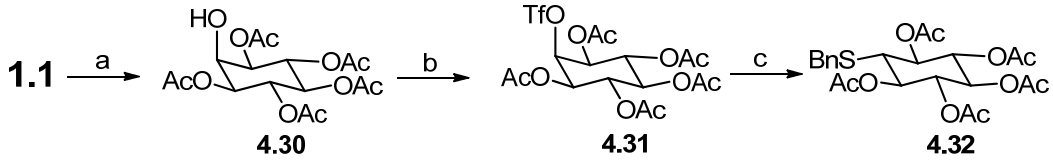
Scheme 4.2. (a) as in reference 7; (b) KOH, CS_2, MeOH, reflux, 24 h; (c) Et_2O, LAH, 12 h, rt; (d) 1:1 aqueous AcOH, reflux, 4 h; (e) AcONa, Ac_2O, reflux, 4 h.

Same authors also reported the synthesis of 6-deoxy-6-mercapto-*epi*-inositol (**4.29**, Scheme 4.3). The thiol moiety in this case was introduced using sodium benzylmercaptide.[6b]



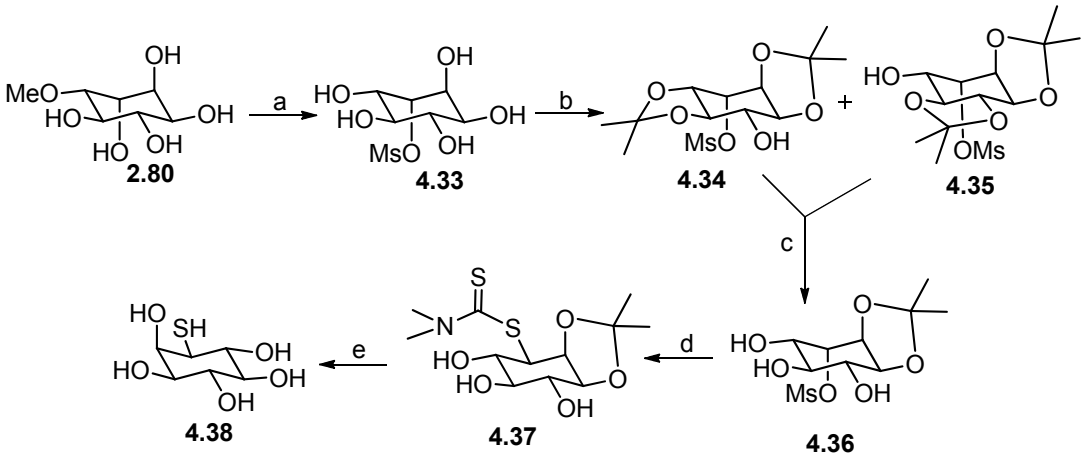
Scheme 4.3. (a) BnSH, Na metal, absolute EtOH, reflux, 2 h, 75%; (b) py., thioacetic acid, reflux, 4 h; (c) liq. NH_3, Na metal, 87%; (d) aqueous AcOH, heating then Ac_2O and heating again; (e) py., Ac_2O, 3 days, 83%; (f) 1N HCl, EtOH, reflux, 4 h, 65%.

The synthesis of 1-deoxy-1-mercapto *scyllo*-inositol derivative **4.32** (Scheme 4.4) from *myo*-inositol (**1.1**) was reported by Kohne and co-workers.[6c] The thiol moiety was introduced by the nucleophilic substitution of the triflate in **4.31** with sodium benzyl mercaptide.



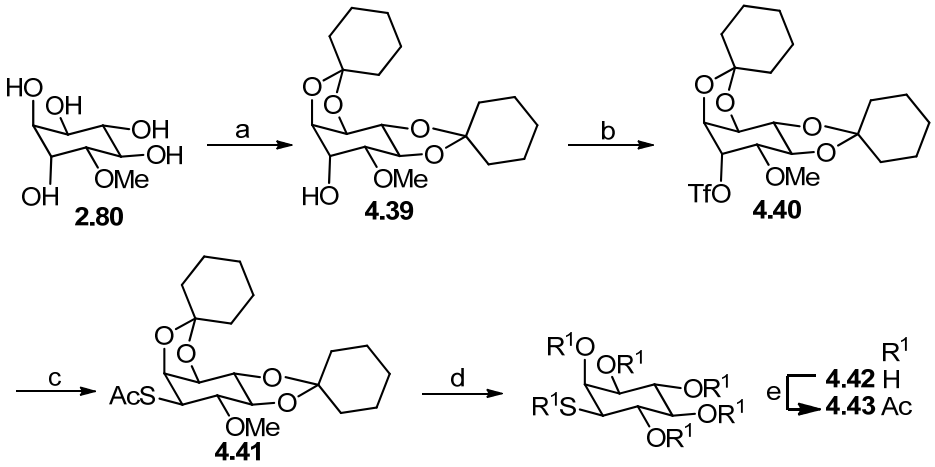
Scheme 4.4. (a) as in reference 8; (b) py., Tf_2O, 0 ºC–rt, 5 h; (c) BnSNa.

Powis and coworkers prepared D-3-deoxy-3-mercapto-*myo*-inositol from L-quebrachitol (**2.80**, Scheme 4.5).[6d] Substitution of the mesylate in **4.36** with dimethyldithiocarbamate followed by LAH reduction gave the thio analog of *myo*-inositol.



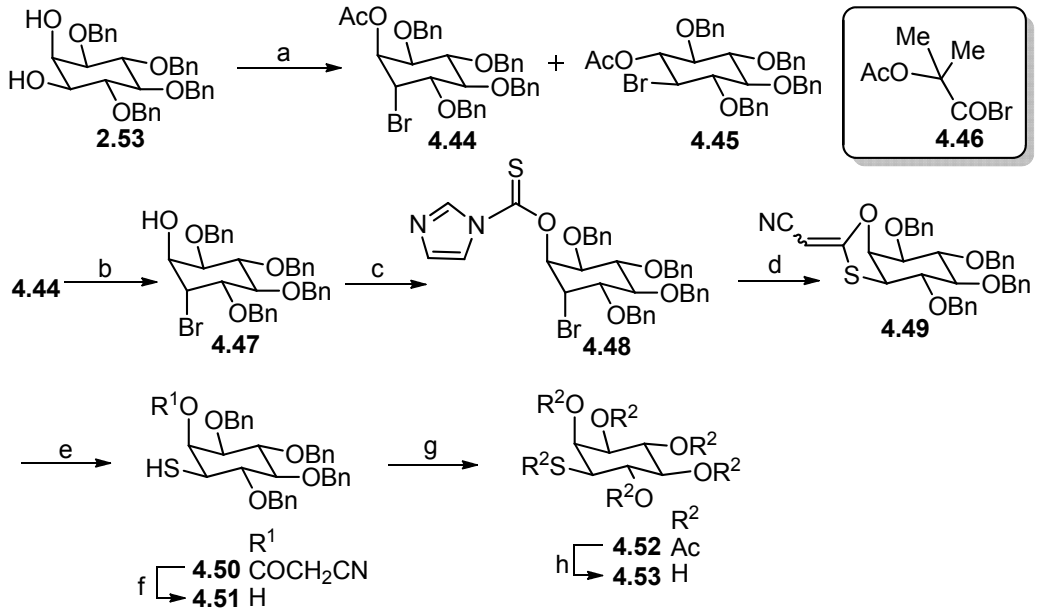
Scheme 4.5. (a) i) $H_2C{=}C(OCH_3)CH_3$, CSA, DMF, 65 ºC, 6 h, 75%; ii) $MeSO_2C1$, Et_3N, CH_2C1_2, 0 ºC, 98%; iii) BBr_3, DCM, rt, 86%; (b) $H_2C = C(OCH_3)CH_3$, CSA, DMF, 60 ºC, 90%, **4.34**:**4.35** = 1:1; (c) aqueous AcOH, rt, 18 h, 91%; (d) $(CH_3)_2NC(S)SNa$, H_2O, HMPA, 80 ºC, 10 h, 93%; (e) i) $LiAlH_4$, Et_2O, 23 ºC, 88%; (ii) TFA, H_2O, 1 h, 99%.

Johnson and coworkers[6e] also prepared D-3-deoxy-3-mercapto *myo*-inositol **4.42** (Scheme 4.6) using an approach similar to that of Powis *et al*.[6d]



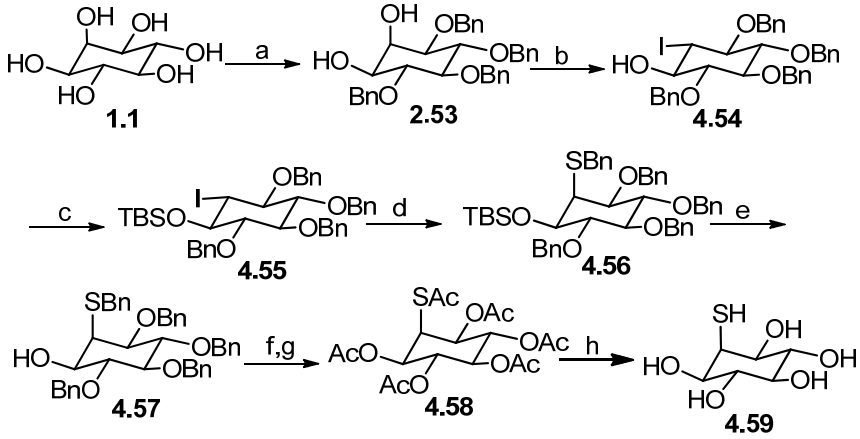
Scheme 4.6. (a) l-ethoxycyclohexene, DMF, PTSA; (b) Tf_2O, py., DCM; (c) KSAc, CH_3CN; (d) i) TFA–H_2O; ii) BBr_3, DCM; MeOH; (e) py., Ac_2O.

Guidot and coworkers presented the synthesis of racemic 1-deoxy-1-mercapto-*myo*-inositol (**4.52**)[6f] from the known diol **2.53** (Scheme 4.7).[9] The synthetic sequence involved two steps (a and d) in which configuration at the C1-position was inverted in order to retain the *myo*-configuration of the thiol **4.52**.



Scheme 4.7. (a) α-acetoxyisobutyryl bromide **4.46**, CH_3CN, 1 h, 80% for **4.44** and 10% for **4.45**; (b) AcCl, MeOH-$CHCl_3$, reflux, 16 h, 89%; (c) 1,l'-thiocarbonyldiimidazole, THF, rt, 4 h, 90%; (d) Li metal, CH_3CN, THF, –78 ºC, 4 h, then rt, 20 h, 65%; (e) 3:l THF:1N HCl, reflux, 3 h, 90%; (f) K_2CO_3, THF-MeOH, rt, 20 h, 89%; (g) Na metal, liq. NH_3-THF, –78 ºC, then 1:1 Ac_2O-py., rt, 20 h, 89%; (h) liq. NH_3, MeOH, rt, 18 h, 89%.

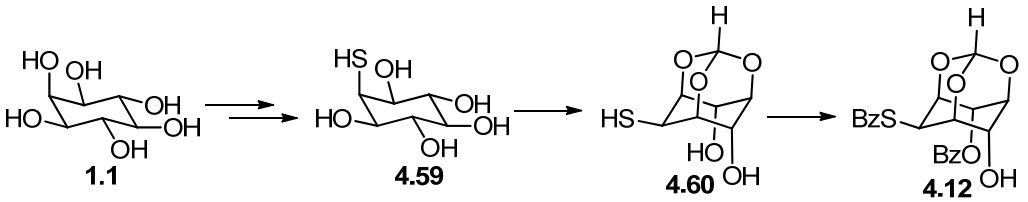
Same authors have also presented a route for the synthesis of 2-deoxy-2-mercapto-*myo*-inositol[6g] from the tetrabenzyl diol derivative **2.53**[9] (Scheme 4.8) in 6 steps with 41% overall yield.



Scheme 4.8. (a) as in the reference 9 (b) TPP, imidazole, I_2, benzene, 80 °C, 30 min., 70%; (c) DCM, 2,6-lutidine, TBSOTf, 98%; (d) BnSNa, DMF, 120 °C, 2 h, 84%; (e) TBAF, THF, rt, l h, 99%: (f) Na, liq. NH_3, THF, 30 min.; (g) py., Ac_2O, rt, 16 h, 85%; (h) liq., NH_3, MeOH, rt, 18 h, 91%.

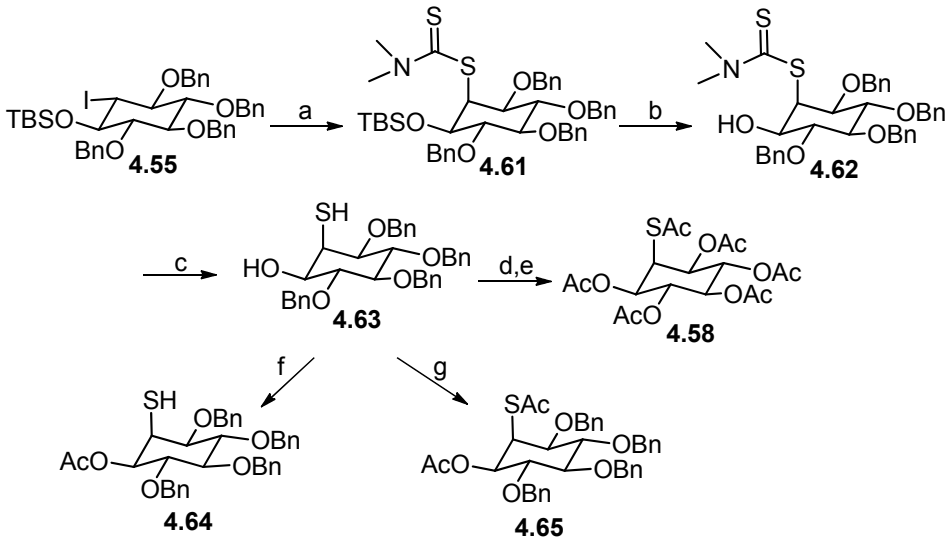
4.3. Present work

Having compared different approaches for the synthesis of thio derivatives of *myo*-inositol reported in the literature, we chose to prepare 2-deoxy-2-mercapto *myo*-inositol (**4.59**) as a precursor for the thiobenzoate **4.12** (Scheme 4.9).



Scheme 4.9. A proposed route for the preparation of orthoester derivatives of thio inositol useful for the study of solid state acyl transfer reactions

To synthesize 2-deoxy-2-mercapto *myo*-inositol we followed the same sequence of reactions reported by Guidot and Gall[6g] but used sodium *N,N′*-dimethyldithiocarbamate to replace the C2-oxygen atom with a sulfur atom on the inositol ring (Scheme 4.10). We preferred to use sodium *N,N′*-dimethyldithiocarbamate, instead of sodium salt of benzyl mercaptide since the former reagent is odorless while the latter has a foul smell.



Scheme 4.10. (a) DMF, NaDMDTC, 120 °C, 91%; (b) DCM-MeOH, AcCl, 96%; (c) THF, LAH, reflux, 8 h, 95%; (d) liq. NH_3, Na, 20 min.; (e) py., DMAP, Ac_2O (18 equivalent), rt, 12 h, 88% over two steps; (f) py., DMAP, Ac_2O (1.5 equivalent), rt, 1 h, 84%; (g) py., DMAP, Ac_2O (3 equivalent), rt, 12 h, 95%.

Thus compound **4.55** on heating with sodium dimethyldithiocarbamate in DMF yielded dithiocarbamate **4.61**. This reaction takes place by S_N2 mechanism and

the stereochemical outcome was confirmed by single crystal X-ray structure analysis of the product **4.61** (Figure 4.2).

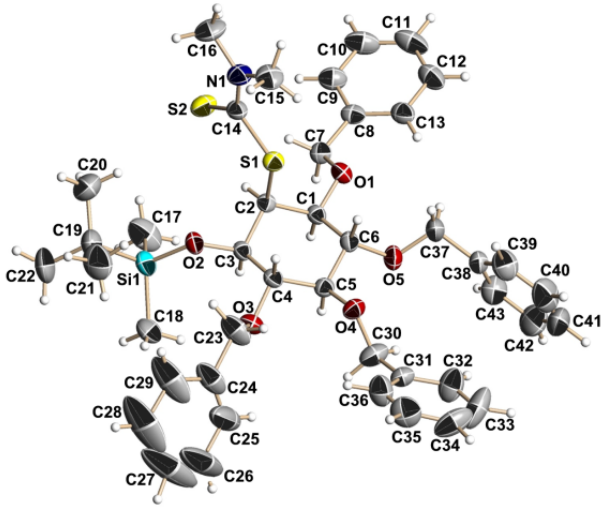


Figure 4.2. ORTEP of **4.61**. Displacement ellipsoids are drawn at 30% probability level and H atoms are shown as small spheres of arbitrary radii.

Deprotection of the TBS ether in **4.61** using TBAF always led to a mixture of products. Hence we tried to reduce the dithiocarbamate to the corresponding thiol prior to deprotection of the TBS ether. However all our attempts to reduce the dithiocarbamate using hydrazine hydrate and LAH in the presence of TBS ether failed. Hence the TBS ether in **4.61** was deprotected by using acetyl chloride in DCM-MeOH mixture. The dithiocarbamate **4.62** obtained was reduced with LAH to get tetra-*O*-benzyl-2-deoxy-2-thio-inositol **4.63**. The benzyl ethers in **4.63** were cleaved by treatment with sodium metal in liquid ammonia. The crude product was acetylated using Ac_2O in pyridine, to get the hexaacetate **4.58**, which was purified by chromatography. The structure of **4.58** was confirmed by single crystal X-ray diffraction analysis (Figure 4.3).

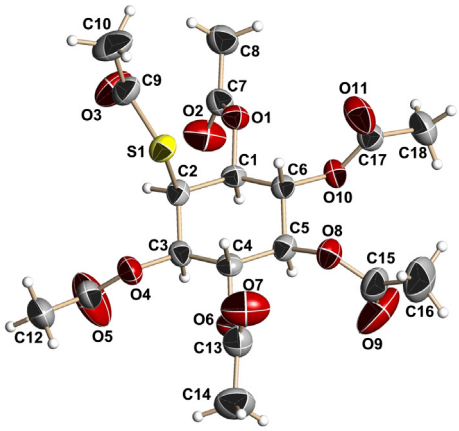
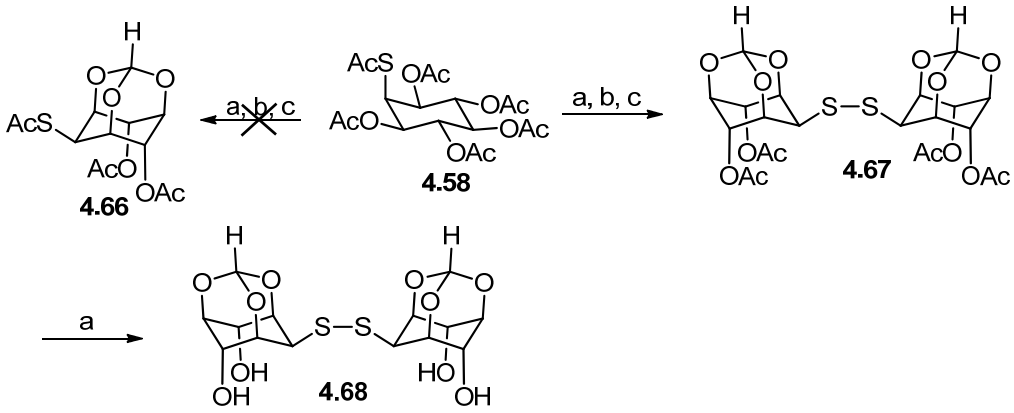


Figure 4.3. ORTEP of **4.58**. Displacement ellipsoids are drawn at 50% probability level and H atoms are shown as small spheres of arbitrary radii.

Aminolysis of the hexaacetate **4.58** using *iso*-butylamine in MeOH gave a product, which was used for the preparation of the orthoformate derivative **4.60**. However, the actual product obtained was the dimer **4.67** (Scheme 4.11). The structure of **4.67** was established by single crystal X-ray diffraction analysis (Figure 4.4). This tetraacetate derivative **4.67** on aminolysis gave the corresponding tetrol **4.68.**



Scheme 4.11. (a) MeOH, *iso*-butyl amine, reflux, 6 h; (b) $HC(OEt)_3$, PTSA, DMF, 100 ºC, 4 h, Et_3N, rt, 30 min; (c) py., Ac_2O, DMAP, 73% (over three steps).

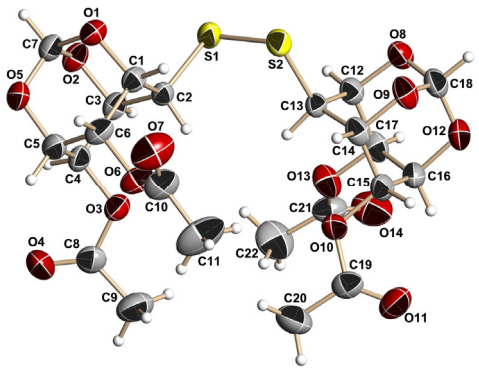
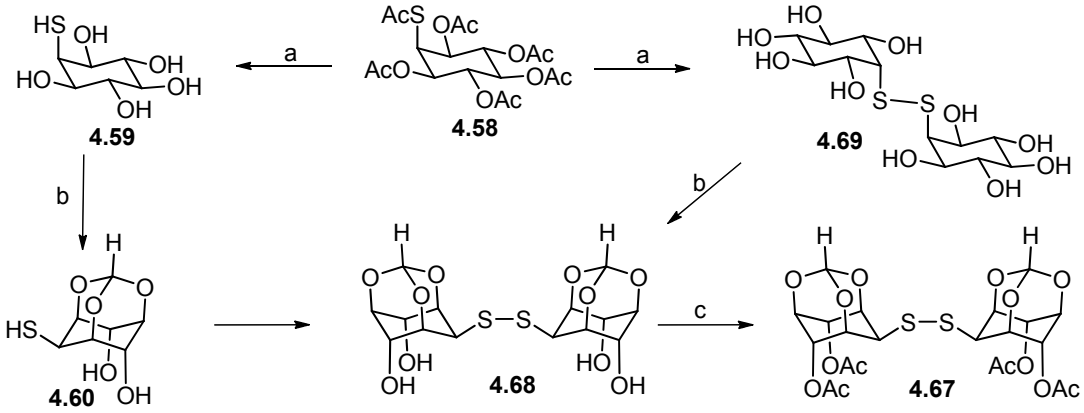


Figure 4.4. ORTEP of **4.67**. Displacement ellipsoids are drawn at 50% probability level and H atoms are shown as small spheres of arbitrary radii.

It was unexpected to see the formation of **4.67** as the major product. Since acetylation of **4.63** (Scheme 4.10) gave either the mono acetate **4.64** or the diacetate, **4.65** in good yield and no dimerized product was detected, we believe that dimerization during the preparation of the thioinositol orthoformate **4.60** did not occur during the acetyaltion stage. It is likely that dimerization of the free thioinositol **4.59** and/or its orthoformate derivative **4.60** took place either during the aminolysis step (step a) or during the formation of the orthoformate (step b) as shown in Scheme 4.12.



Scheme 4.12. (a) MeOH, *iso*-butyl amine, reflux, 6 h; (b) $HC(OEt)_3$, PTSA, DMF, 100 ºC, 4 h, Et_3N, rt, 30 min; (c) py., Ac_2O, DMAP, 73%.

This possibility was also suggested by isolation of a minor amount of the dimer **4.69** during attempts at crystallization of the product obtained on aminolysis of the hexa acetate **4.58**. The structure of the minor product **4.69** was established by X-ray crystallography (Figure 4.5).

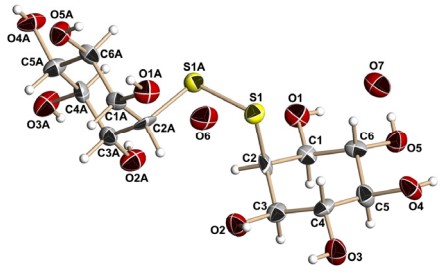


Figure 4.5. ORTEP of **4.69**. Displacement ellipsoids are drawn at 50% probability level and H atoms are shown as small spheres of arbitrary radii.

4.4. Conclusions

2-Deoxy-2-mercapto *myo*-inositol was prepared in nine steps starting from commercially available *myo*-inositol and was isolated as its hexa acetate. Experimental evidence suggests that conditions used either to carry out aminolysis of the acetates (to geneare the free thio-inositol) or formation of the orthoformate (of thio-inositol) brings about dimerization of 2-deoxy-2-mercapto *myo*-inositol. As a result, only the S-S dimer of thio-inositol orthoformate could be isolated. Further work is necessary to standardize the conditions for the formation and isolation of the orthoformate of 2-deoxy-2-mercapto *myo*-inositol, which do not facilitate the dimerization of the thiol.

4.5. Experimental

4.5.1. X-ray Data (Collection, Structure Solution and Refinement): Same as in the subsection 2.7.1 (Chapter 2).

4.5.2 General Experimental Methods: General experimental methods are same as in the subsection 2.7.2 (Chapter 2).

Racemic 1-*O*-*t*-butyldimethylsilyl-2-deoxy-2-N,N-dimethyldithiocarbamoyl-3,4,5,6-tetra-*O*-benzyl *myo*-inositol (4.61): The iodo derivative **4.55** (7.65 g, 10.00 mmol) of *myo*-inositol, dry DMF (30 mL) and sodium *N,N′*-dimethyldithiocarbamate (4.30 g, 30.00 mmol) were heated at 100 °C for 20 h. The reaction mixture was then allowed to come to ambient temperature and a few pieces of ice were added. The solvent was removed under reduced pressure and the residue obtained was worked up with ethyl acetate. The crude product obtained was purified by flash column chromatography (silica gel 230-400 mesh, eluent 10% ethyl acetate – light petroleum) to get racemic **4.61** (6.93 g, 91%) as a colorless solid. Crystals of **4.61** were obtained by slow evaporation of a hot ethyl acetate solution; $R_f = 0.33$ (10% ethyl acetate/ light petroleum); **mp** 128–130 °C; **IR** (Nujol): $\bar{\nu}$ 1247 cm^{-1}; **^{1}H NMR** (200 MHz; $CDCl_3$): δ 0.04 (s, 3H, CH_3), 0.20 (s, 3H, CH_3), 0.85 (s, 9H, CH_3), 3.39–3.57 (m, 6H, CH_3, 2H, Ins H), 3.63 (t, J = 9.3 Hz, 1H, Ins H), 3.70–3.81 (dd, J_1 = 3.9 Hz, J_2 = 9.4 Hz, 1H, Ins H), 3.83–3.94 (m, 1H, Ins H), 4.55–5.05 (m, 8H, $PhCH_2$), 5.32 (t, J = 4.1 Hz, 1H, Ins H), 7.09–7.46 (m, 20H, Ar H) ppm; **^{13}C NMR** (50 MHz; $CDCl_3$): δ – 4.63 (CH_3), – 4.58 (CH_3), 17.9 (CMe_3); 25.8 (CH_3), 41.6 (CH_3), 46.0 (CH_3), 58.6 (Ins C), 71.3 (Ins C), 73.3 (CH_2), 75.5 (CH_2), 75.6 (CH_2), 76.1 (CH_2), 78.1 (Ins C), 83.0 (Ins C), 83.6 (Ins C), 84.6 (Ins C), 127.2 (Ar C), 127.4 (Ar C), 127.5 (Ar C), 127.6 (Ar C), 127.8 (Ar C), 127.9 (Ar C), 128.1 (Ar C), 128.21 (Ar C), 128.25 (Ar C), 128.7 (Ar C), 137.9 (Ar C), 138.4 (Ar C), 138.8 (Ar C), 196.0 (OCSS) ppm; elemental analysis calcd (%) for $C_{43}H_{55}NO_5S_2Si$: C, 68.12; H, 7.31, N, 1.85; found C, 68.17, H, 7.30, N, 1.84%.

Racemic 2-deoxy-2-*N,N′*-dimethyldithiocarbamoyl-3,4,5,6-tetra-*O*-benzyl *myo*-inositol (4.62): To a solution of **4.61** (7.58 g, 10.00 mmol) in dry DCM (10 mL) and methanol (30 mL), freshly distilled acetyl chloride (5.00 mL, 71.43 mmol) was added slowly and stirred at ambient temperature for 1 h. The reaction mixture was then diluted with DCM, neutralized by adding saturated solution of $NaHCO_3$ and worked up with DCM. The product obtained was purified by flash column chromatography

(silica gel 230-400 mesh, eluent 30% ethyl acetate – light petroleum) to get racemic **4.62** (6.18 g, 96%) as a gum; R_f = 0.3 (30% ethyl acetate/ light petroleum); **IR** (Nujol): $\bar{\nu}$ 3300–3500 cm^{-1}; **^{1}H NMR** (200 MHz; $CDCl_3$): δ 3.24 (s, 1H, OH, D_2O exchangeable), 3.46 (s, 3H, CH_3), 3.57 (s, 3H, CH_3), 3.42–3.74 (m, 3H, Ins H), 3.83–3.95 (dd, J_1 = 4.6 Hz, J_2 = 10.0 Hz, 1H, Ins H), 4.00–4.19 (m, 1H, Ins H), 4.51 (d, 1H, J = 11.5 Hz, $PhCH_2$), 4.67–5.02 (m, 7H, CH_2Ph), 5.49 (t, 1H, J = 4.4 Hz, Ins H), 7.19–7.43 (m, 20H, Ar H) ppm; **^{13}C NMR** (50 MHz; $CDCl_3$): δ 42.0 (CH_3), 46.4 (CH_3), 56.4 (Ins C), 71.8 (Ins C), 72.1 (CH_2) 75.6 (CH_2), 75.8 (CH_2), 76.1 (CH_2), 77.6 (Ins C), 82.7 (Ins C), 83.7 (Ins C), 127.7 (Ar C), 127.8 (Ar C), 127.9 (Ar C), 128.0 (Ar C), 128.07 (Ar C), 128.11 (Ar C), 128.2 (Ar C), 128.5 (Ar C), 137.6 (Ar C), 138.5 (Ar C), 138.7 (Ar C), 138.8 (Ar C), 196.9 (OCSS) ppm; elemental analysis calcd for $C_{37}H_{41}NO_5S_2$: C, 69.02; H, 6.42, N, 2.18; found C, 68.84, H, 6.23, N, 2.29 %.

Racemic 2-deoxy-2-mercapto-3,4,5,6-tetra-*O*-benzyl *myo*-inositol (4.63): A solution of **4.62** (6.44 g, 10.00 mmol) in dry THF (70 mL) was cooled to 0 °C and LAH (1.14 g, 30.00 mmol) was added; the reaction mixture stirred at 0 °C for 10 min and then refluxed for 8 h. The reaction mixture was cooled to 0 °C and ethyl acetate (2 mL) was added followed by saturated sodium sulfate solution and stirred at 0 °C for 10 min then at ambient temperature for 30 min. The reaction mixture was filtered through Celite bed and worked up with ethyl acetate. The product obtained was purified by flash column chromatography (silica gel 230-400 mesh, eluent 25% ethyl acetate – light petroleum) to get racemic **4.63** (5.31 g, 95%) as a colorless solid; R_f = 0.4 (30% ethyl acetate/ light petroleum); **mp** 104–108 °C; **IR** (Nujol): $\bar{\nu}$ 3100–3500 cm^{-1}; **^{1}H NMR** (200 MHz; $CDCl_3$): δ 2.03 (d, J = 2.90 Hz, 1H, SH, D_2O exchangable), 2.57 (bs, 1H, OH, D_2O exchangable), 3.50 (t, J = 9.1 Hz, 1H, Ins H), 3.58–3.73 (m, 2H, Ins H), 3.90–4.00 (m, 2H, Ins H), 4.08 (t, 1H, J = 9.4 Hz, Ins H), 4.52–5.02 (m, 8H, CH_2Ph), 7.20–7.42 (m, 20H, Ar H) ppm; **^{13}C NMR** (50 MHz; $CDCl_3$): δ 42.8 (Ins C), 70.4 (Ins C), 71.9 (CH_2) 75.5 (CH_2), 75.7 (CH_2), 75.9 (CH_2), 79.0 (Ins C), 81.1 (Ins C), 81.7 (Ins C), 83.4 (Ins C) 127.7 (Ar C), 127.8 (Ar C), 127.9 (Ar C), 128.0 (Ar C), 128.06 (Ar C), 128.11 (Ar C), 128.4 (Ar C), 128.52 (Ar C), 128.55 (Ar C), 128.7 (Ar C), 137.7 (Ar C), 138.3 (Ar C), 138.4 (Ar C), 138.6 (Ar C) ppm; elemental analysis calcd for $C_{34}H_{36}O_5S$: C, 73.35%; H, 6.52%; found C, 73.08%; H 6.59%.

2-Deoxy-2-mercapto-*myo*-inositol hexacetate (4.58): A solution of **4.63** (3.73 g, 6.70 mmol) in dry THF (18 mL) was cooled to –78 °C and ammonia was condensed till the volume increased to about 54 mL. To this reaction mixture, sodium metal was added till blue color persisted and stirred for 1 h. The reaction was quenched with solid ammonium chloride (addition till the reaction mixture turned colorless), liquid ammonia was allowed to evaporte and the reaction mixture was evaporated under reduced pressure. The solid obtained was dried under reduced pressure. A mixture of the colorless solid obtained, pyridine (30 mL), DMAP (50 g) and Ac_2O (12 mL, 120.00 mmol) was refluxed for 12 h. The reaction mixture was allowed to come to ambient temperature and a few pieces of ice were added and the solvent was removed under reduced pressure. The residue obtained was worked up with ethyl acetate. The crude product obtained was purified by flash column chromatography (silica gel 230-400 mesh, eluent 12% ethyl acetate – light petroleum) to get **4.58** (2.63 g, 88%) as a colorless solid. It was crystallized from ethyl acetate. R_f = 0.3 (45% ethyl acetate/ light petroleum); **mp** 206–209 °C; (Lit mp 210 °C)[6g] **IR** (Nujol): $\bar{\nu}$ 1759 (OCO), 1708 (SCO) cm^{-1}; **^{1}H NMR** (200 MHz; $CDCl_3$): δ 1.98 (s, 6H, CH_3), 2.00 (s, 3H, CH_3), 2.01 (s, 6H, CH_3), 2.42 (s, 3H, CH_3), 4.54 (t, J = 2.8 Hz, 1H, Ins H), 5.05–5.20 (m, 1H, Ins H), 5.21–5.29 (m, 4H, Ins H) ppm; **^{13}C NMR** (125 MHz; $CDCl_3$): δ 20.41 (CH_3), 20.44 (CH_3), 20.5 (CH_3), 30.7 (CH_3), 44.7 (Ins C), 67.9 (Ins C), 70.6 (Ins C), 70.9 (Ins C), 169.2 (CO), 169.5 (CO), 169.6 (CO), 192.3 (CO) ppm; elemental analysis calcd (%) for $C_{18}H_{24}O_{11}S$: C, 48.21; H, 5.39; found C, 48.50; H 5.65%.

Racemic 1-*O*-acetyl-2-deoxy-2-mercapto *myo*-inositol (4.64): Tetra-*O*-benzyl *myo*-inositol **4.63** (0.56 g, 1.00 mmol), dry pyridine (5 mL), DMAP (0.020 g, catalytic), Ac_2O (0.10 mL, 1.10 mmol) were stirred at ambient temperature for 30 min and then a few pieces of ice were added. The solvent was removed under reduced pressure and the residue obtained was worked up with ethyl acetate. The crude product obtained was purified by column chromatography (silica gel 230-400 mesh, eluent 12% ethyl acetate – light petroleum) to get racemic **4.64** (0.50 g, 84%) as a gum. R_f = 0.5 (15% ethyl acetate/ light petroleum); **IR** ($CHCl_3$): $\bar{\nu}$ 1741 (OCO) cm^{-1}; **^{1}H NMR** (200 MHz; $CDCl_3$): δ 1.98 (d, J = 2.3 Hz, 1H, SH, D_2O exchangable), 2.03 (s, 3H, CH_3), 3.52 (t, J = 9.4 Hz, 1H, Ins H), 3.65–3.78 (dd, J_1 = 4.3 Hz, J_2 = 9.7 Hz, 1H, Ins H), 4.01–4.23 (m, 3H, Ins H), 4.56 (d, J = 11.4 Hz, 1H, $PhCH_2$), 4.67 (d, J = 7.0 Hz, 1H, CH_2Ph), 4.70–5.02 (m, 7H, CH_2Ph, 1H, Ins H), 7.21–7.40 (m, 20H, Ar H) ppm; **^{13}C**

NMR (50 MHz; $CDCl_3$): δ 20.8 (CH_3), 41.0 (Ins C), 71.9 (CH_2), 72.3 (Ins C), 75.6 (CH_2), 75.9 (CH_2), 76.0 (CH_2), 78.4 (InsC), 79.4 (CH_2), 81.0 (Ins C), 83.2 (Ins C), 127.6 (Ar C), 127.8 (Ar C), 127.9 (Ar C), 128.0 (Ar C), 128.3 (Ar C), 128.4 (Ar C), 137.4 (Ar C), 138.3 (Ar C), 138.4 (Ar C), 170.0 (OCO) ppm; HRMS calcd for $C_{36}H_{38}O_6SNa$ (M + Na+) 621.2281, found 621.2240.

Racemic 1-*O*-2-*S*-diacetyl- 3,4,5,6-tetra-*O*-benzyl 2-mercapto *myo*-inositol (4.65): The thiol **4.63** (0.56 g, 1mmol), dry pyridine (5 mL), DMAP (0.020 g, catalytic) and Ac_2O (0.42 mL, 3 mmol) were stirred at ambient temperature for 6 h and then a few pieces of ice were added. The solvent was removed under reduced pressure and the residue obtained was worked up with ethyl acetate. The crude product obtained was purified by column chromatography (silica gel 230-400 mesh, eluent 12% ethyl acetate – light petroleum) to get racemic **4.65** (0.61 g, 95%) as a gum. R_f = 0.3 (20% ethyl acetate/ light petroleum); **IR** ($CHCl_3$): $\bar{\nu}$ 1743 (OCO), 1700 (SCO) cm^{-1}; **^{1}H NMR** (200 MHz; $CDCl_3$): δ 1.94 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.42–3.60 (m, 2H, Ins H), 3.62–3.76 (m, 1H, Ins H), 3.78–3.92 (m, 1H, Ins H), 4.49 (d, J = 11.2 Hz, 1H, CH_2Ph), 4.57–4.97 (m, 7H, CH_2Ph, 1H, Ins H), 4.59–5.20 (dd, J = 4.2 Hz, J = 10.1 Hz, 1H, Ins H), 7.20–7.36, (m, 20H, Ar H) ppm; **^{13}C NMR** (50 MHz; $CDCl_3$): δ 20.9 ($SCOCH_3$), 30.9 ($OCOCH_3$), 44.9 (Ins C), 71.0 (Ins C), 72.2 (CH_2), 75.7 (CH_2), 76.0 (CH_2), 76.4 (CH_2), 77.3 (Ins C), 81.1 (InsC), 82.8 (Ins C), 83.1 (Ins C), 127.6 (Ar C), 127.7 (Ar C), 127.8 (Ar C), 127.9 (Ar C), 128.06 (Ar C), 128.12 (Ar C), 128.4 (Ar C), 128.5 (Ar C), 137.4 (Ar C), 138.3 (Ar C), 138.40 (Ar C), 138.45 (Ar C), 170.1 (OCO), 193.6 (SCO) ppm; elemental analysis calcd (%) for $C_{38}H_{40}O_7S$: C, 71.23; H, 6.29; found C, 71.50; H 6.45%.

S-S dimmer of 4,6-di-*O*-acetyl-2-deoxy-2-mercapto-*myo*-inositol-1,3,5-orthoformate (4.67): Hexaacetyl *myo*-inositol **4.58** (0.45 g, 1.00 mmol), *iso*-butyl amine (1.80 mL, 18.00 mmol) and dry MeOH (6 mL) were refluxed for 4 h. Reaction mixture was cooled to ambient temperature and the solvent was removed under reduced pressure. The colorless solid obtained was washed with diethyl ether (3 x 4 mL) and dried under reduced pressure.

The solid obtained above (0.20 g), DMF (4 mL), PTSA (0.019 g) and triethylorthoformate (0.25 mL, 1.50 mmol) were heated at 100 °C for 5 h. The reaction mixture was allowed to cool to ambient temperature and dry triethylamine (0.014 mL, 0.10 mmol) was added. The solvent was removed under reduced pressure.

The residue obtained (0.30 g), dry pyridine (5 mL), acetic anhydride (0.85 mL, 9.00 mmol) and DMAP (10 mg) were refluxed for 20 h. The reaction mixture was allowed to cool to ambient temperature and a few pieces of ice were added. The solvent was removed under reduced pressure and residue obtained was worked up with ethyl acetate. The crude product obtained was purified by column chromatography to get a colorless solid **4.67** (0.22 g; 76%); R_f = 0.3 (40% ethyl acetate/ light petroleum); It was crystallized from ethyl acetate to get good quality crystals; **mp** 184–188 °C; **IR** (Nujol): $\bar{\nu}$ 1748 cm^{-1}; **^{1}H NMR** (200 MHz; $CDCl_3$): δ 2.10 (s, 12H, CH_3), 3.49–3.55 (m, 2H, Ins H), 4.36–4.46 (m, 4H, Ins H), 4.58–4.66 (m, 2H, Ins H), 5.40–5.48 (m, 4H, Ins H), 5.56 (d, J = 1.4 Hz, 2H, O_3CH) ppm; **^{13}C NMR** (50 MHz; $CDCl_3$): δ 20.6 (CH_3), 44.6 (Ins C), 66.1 (Ins C), 67.2 (Ins C), 69.3 (Ins C), 103.2 (O_3C), 169.1 (CO) ppm; elemental analysis calcd (%) for $C_{22}H_{26}O_{14}S_2$: C, 45.67; H, 4.53; found C, 45.77; H 4.45%.

S-S dimmer of 2-deoxy-2-mercapto *myo*-inositol-1,3,5-orthoformate (4.68): Tetra-*O*-acetyl S-S dimmer **4.67** (0.29 g, 0.50 mmol), *iso*-butyl amine (0.60 mL, 6.00 mmol) and dry MeOH (6 mL) were refluxed for 4 h. The reaction mixture was then allowed to come to ambient temperature and the solvent was removed under reduced pressure. The colorless solid obtained was washed with diethyl ether (4 x 3 mL) and dried under reduced pressure to get **4.68** as a colorless solid in nearly quantitative yield (0.20 g, 98%); R_f = 0.5 (ethyl acetate); **mp** 252–255°C; **IR** (Nujol): $\bar{\nu}$ 3200–3600 cm^{-1}; **^{1}H NMR** (500 MHz; $CDCl_3$): δ 3.63 (d, J = 1.22 Hz, 2H, Ins H), 4.11–4.15 (m, 2H, Ins H), 4.16–4.21 (m, 4H, Ins H), 4.26–4.33 (m, 4H, Ins H), 5.58 (d, J = 1.23 Hz, 2H, O_3CH), 5.68 (d, J = 6.10 Hz, 4H, OH, D_2O exchangable) ppm; **^{13}C NMR** (125 MHz; $CDCl_3$): δ 45.2 (Ins C), 66.6 (Ins C), 69.2 (Ins C), 72.4 (Ins C), 101.9 (O_3C) ppm; elemental analysis calcd (%) for $C_{14}H_{18}O_{10}S_2$: C, 40.97; H, 4.42%; found C, 40.97, ; H, 4.65%.

S-S dimmer of 2-deoxy-2-mercapto *myo*-inositol (4.69)

Hexaacetyl *myo*-inositol **4.58** (0.45 g, 1.00 mmol), *iso*-butyl amine (1.80 mL, 18.00 mmol) and dry MeOH (6 mL) were refluxed for 4 h. Reaction mixture was cooled to ambient temperature and the solvent was removed under reduced pressure. The colorless solid obtained was washed with diethyl ether (3 x 4 mL) and dried under reduced pressure. The product obtained was crystallized by cooling its hot aqueous

solution to obtain (0.16 g, 82%). The crystal structure obtained was the S-S dimmer of of 2-deoxy-2-mercapto-*myo*-inositol.

4.6. References

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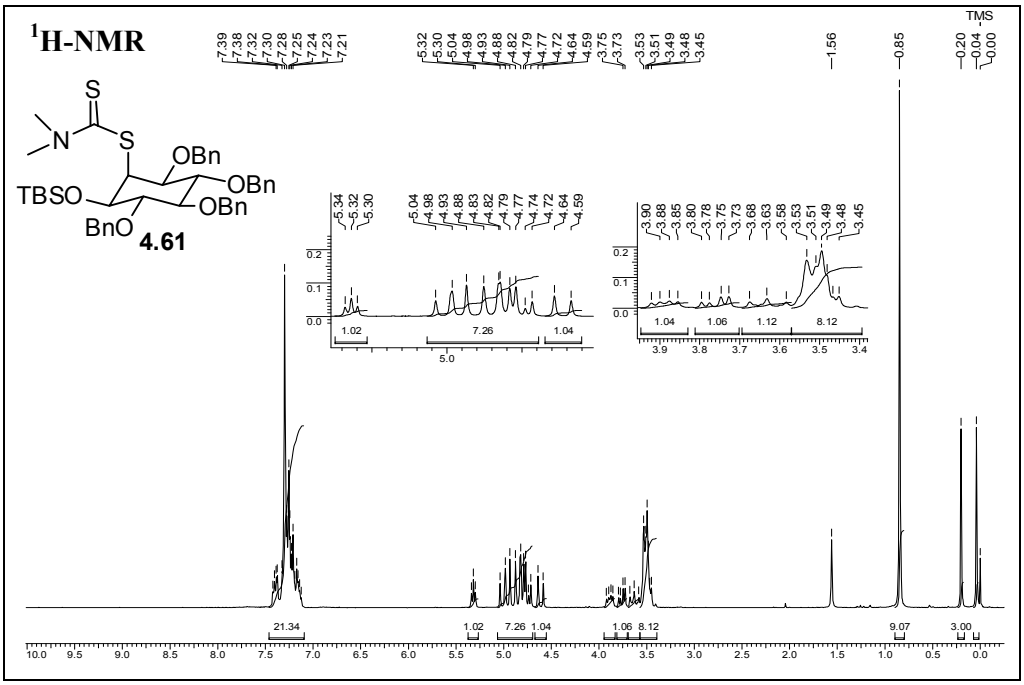
Appendix III

Appendix III Index

Crystal Data Table

Compund No.	**4.58**	**4.61**	**4.67**	**4.69**
Chemical formula	$C_{18}H_{24}O_{11}S$	$C_{43}H_{55}NO_5S_2Si$	$C_{22}H_{26}O_{14}S_2$	$C_{12}H_{22}O_{14}S_2$
M_r	448.43	758.09	578.55	454.42
Temperature (K)	297(2)	297(2)	297(2)	297(2)
Morphology	prism	plate	plate	plate
Crystal size	0.26×0.19 ×0.16	0.38×0.27 ×0.15	0.54×0.25 ×0.07	0.09×0.06 ×0.04
Crystal system Space group	tetragonal P_{43212}	triclinic *P*-1	monoclinic $P2_1/n$	monoclinic *C*2/*c*
a (Å) *b* (Å) *c* (Å) α (°) β (°) γ (°)	9.3374(11) 9.3374(11) 51.471(6) 90 90 90	15.140(3) 16.256(3) 18.739(4) 80.289(3) 82.674(3) 73.084(3)	11.288(3) 16.310(4) 14.933(4) 90 108.010(4) 90	20.528(13) 10.749(7) 9.737(6) 90 117.718(15) 90
V (Å^3)	4487.6(9)	4334.1(15)	2614.6(12)	1902(2)
Z	8	4	4	4
D_{calc} (g cm^{-3})	1.327	1.162	1.470	1.587
μ (mm^{-1})	0.198	0.192	0.274	0.351
F(000)	1888	1624	1208	952
Absorption correction T_{min} / T_{max}	0.950 / 0.969	0.931/ 0.972	0.867 / 0.982	0.969 / 0.986
h, k, l (min, max)	(-11, 11), (-11, 11), (-60, 61)	(-18, 18), (-19, 19), (-22, 22)	(-13, 13), (-16, 19), (-17, 17)	(-24, 24), (-12, 12), (-11, 11)
Reflns collected	32719	42190	13089	8764
Unique reflns Observed reflns	3948 3738	15219 11976	4608 3587	1678 1108
R_{int}	0.0458	0.0202	0.0331	0.1771
No. of parameters	277	951	347	127
GoF	1.310	1.044	1.087	1.714
$R_1[I > 2\sigma(I)]$ $wR_2[I > 2\sigma(I)]$	0.0635 0.1371	0.0654 0.1785	0.0552 0.1202	0.1845 0.4794
R_1_all data wR_2_all data	0.0674 0.1391	0.0780 0.1947	0.0753 0.1286	0.2292 0.4963
$\Delta\rho_{max}$, $\Delta\rho_{min}$(e Å^{-3})	0.32, -0.22	1.09, -0.54	0.38, -0.22	0.99, -1.47
CCDC No.	-	-	-	-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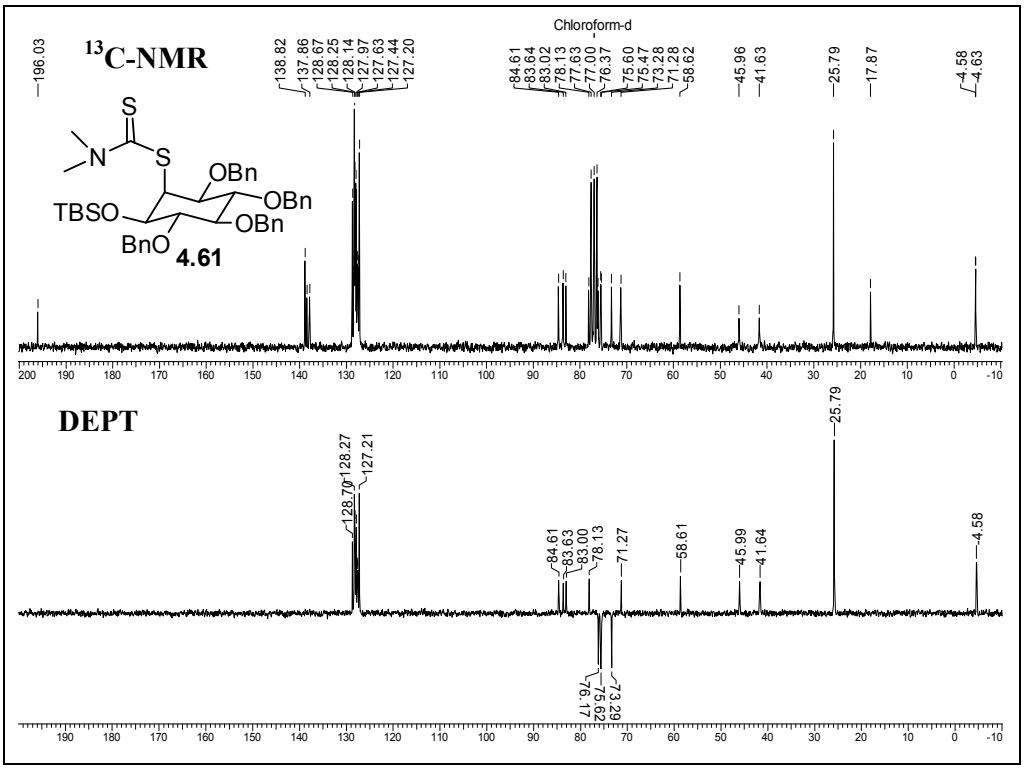
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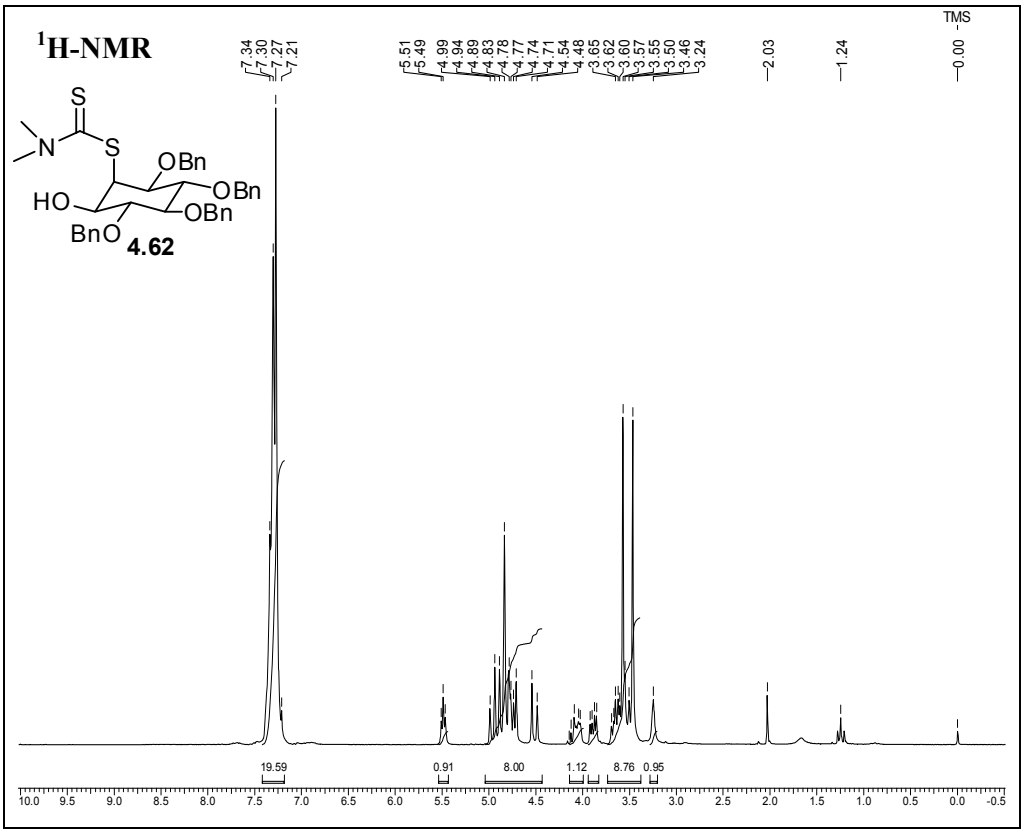
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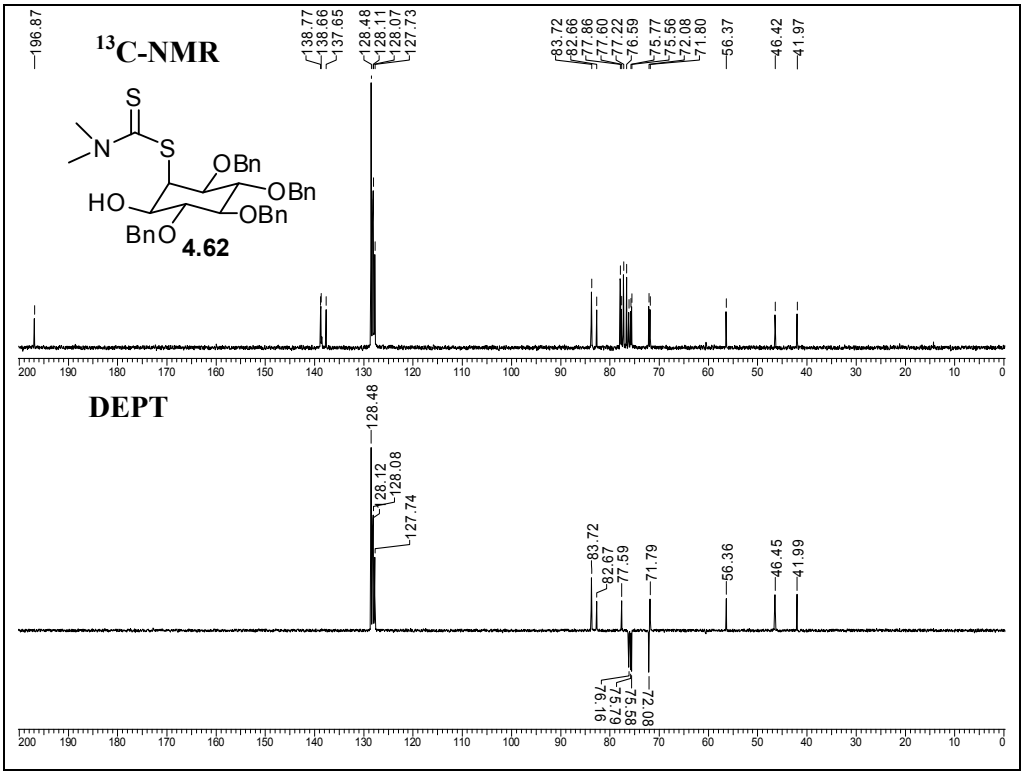
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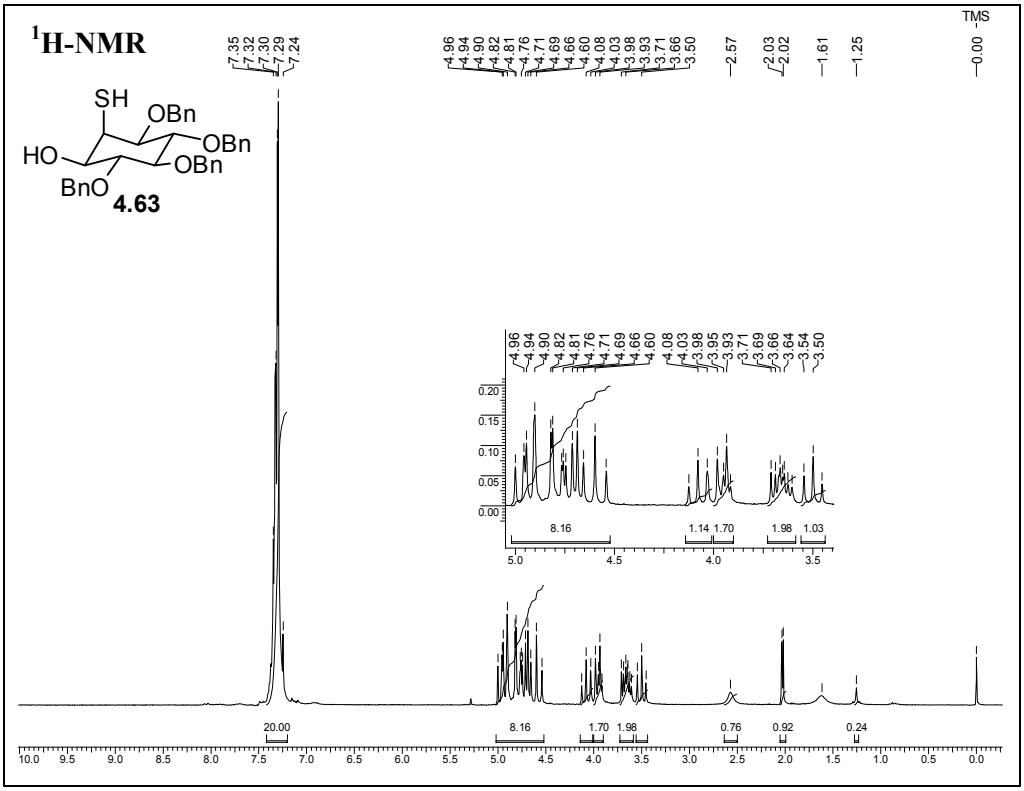
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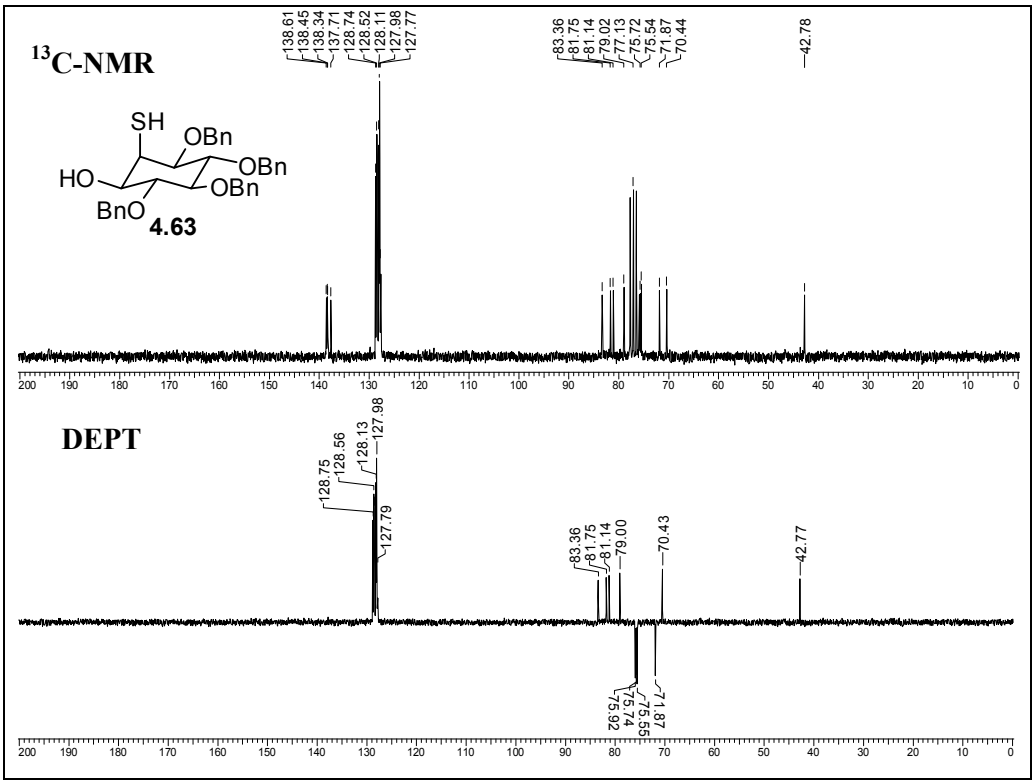
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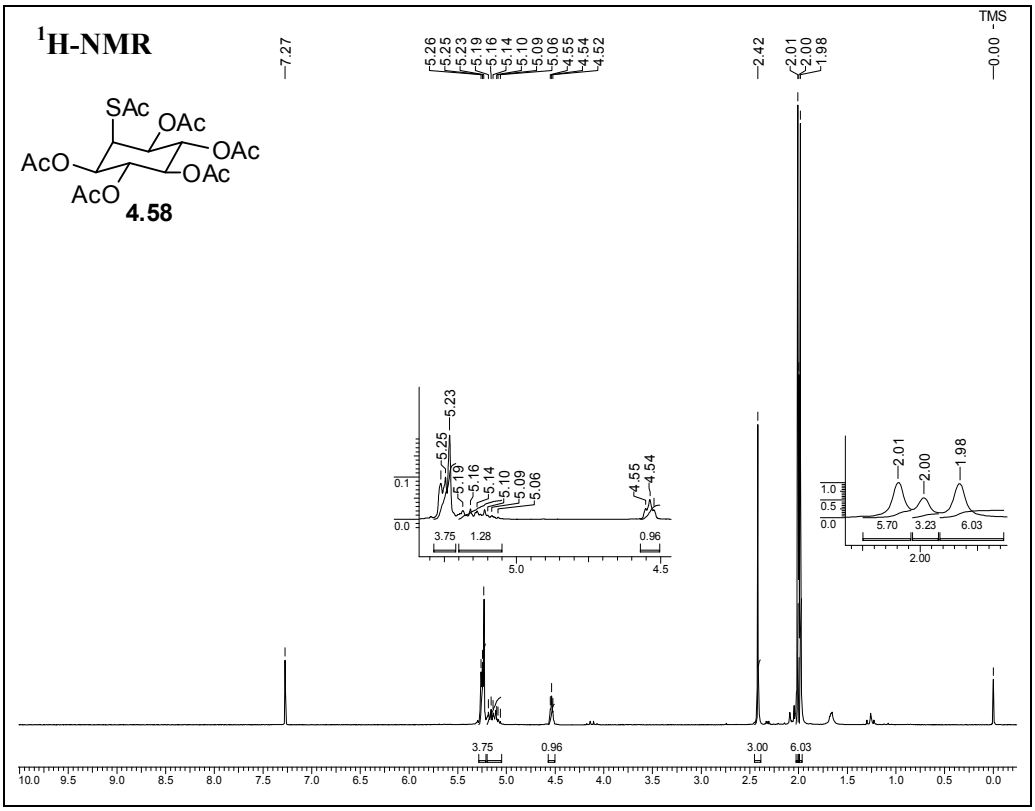
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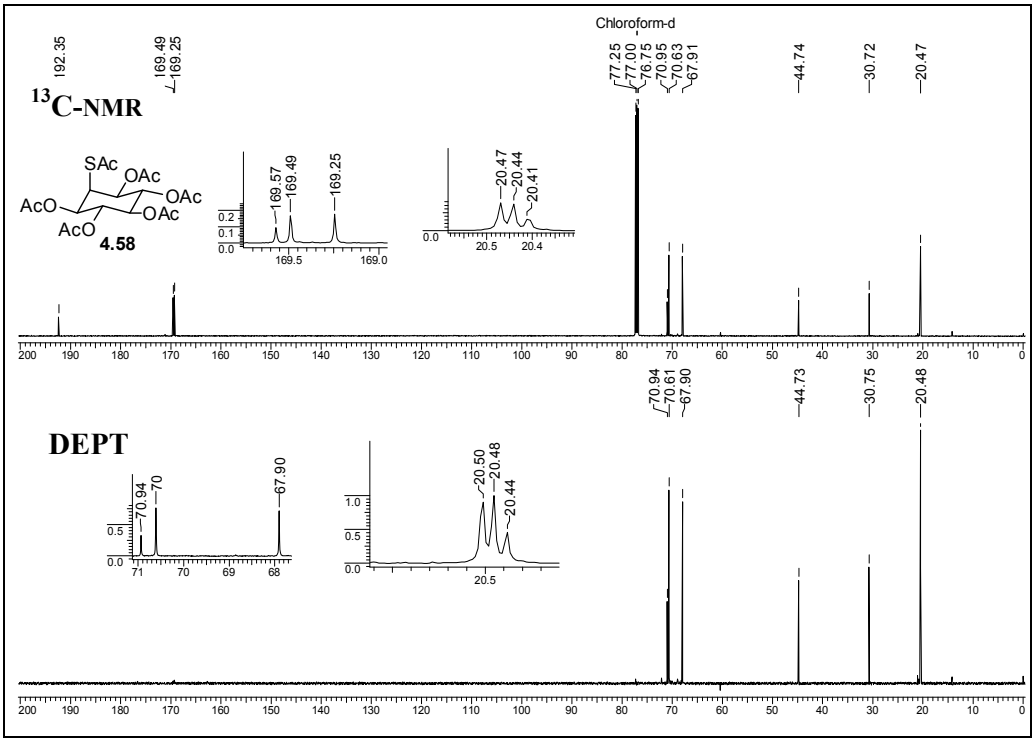
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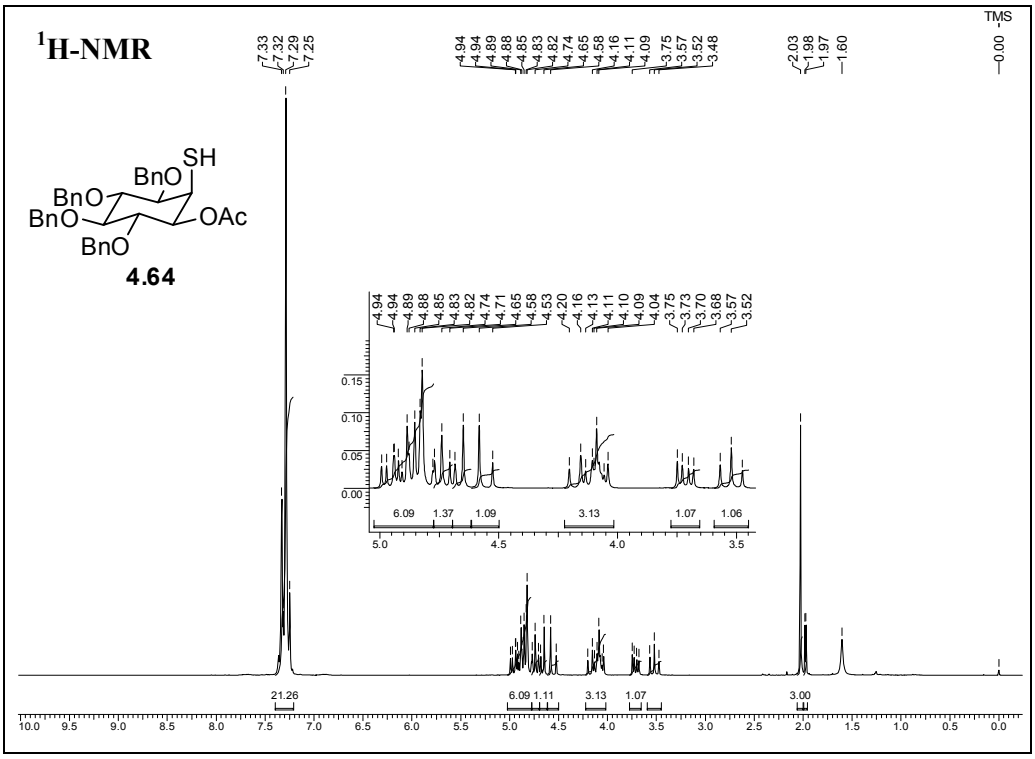
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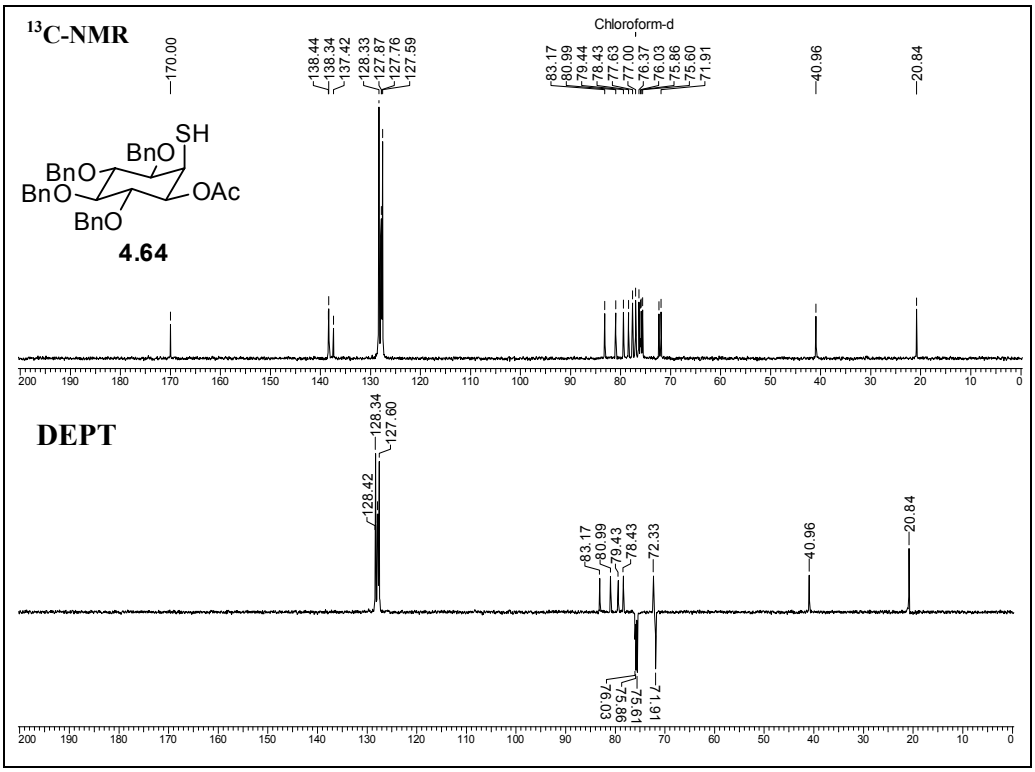
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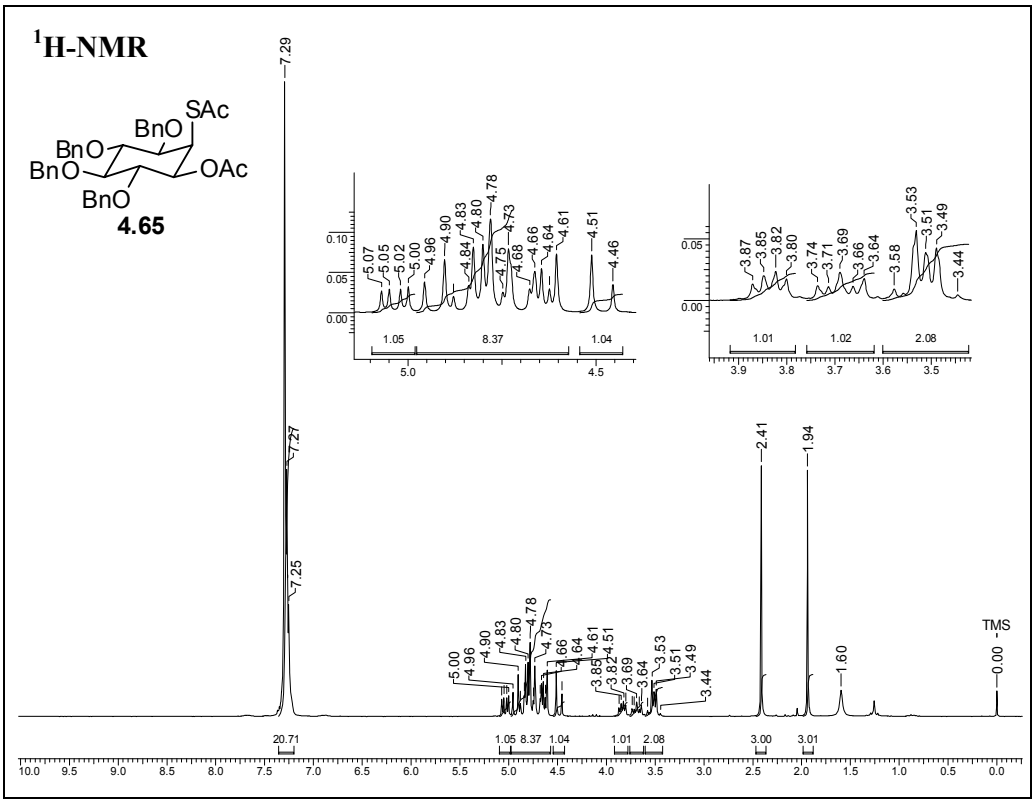
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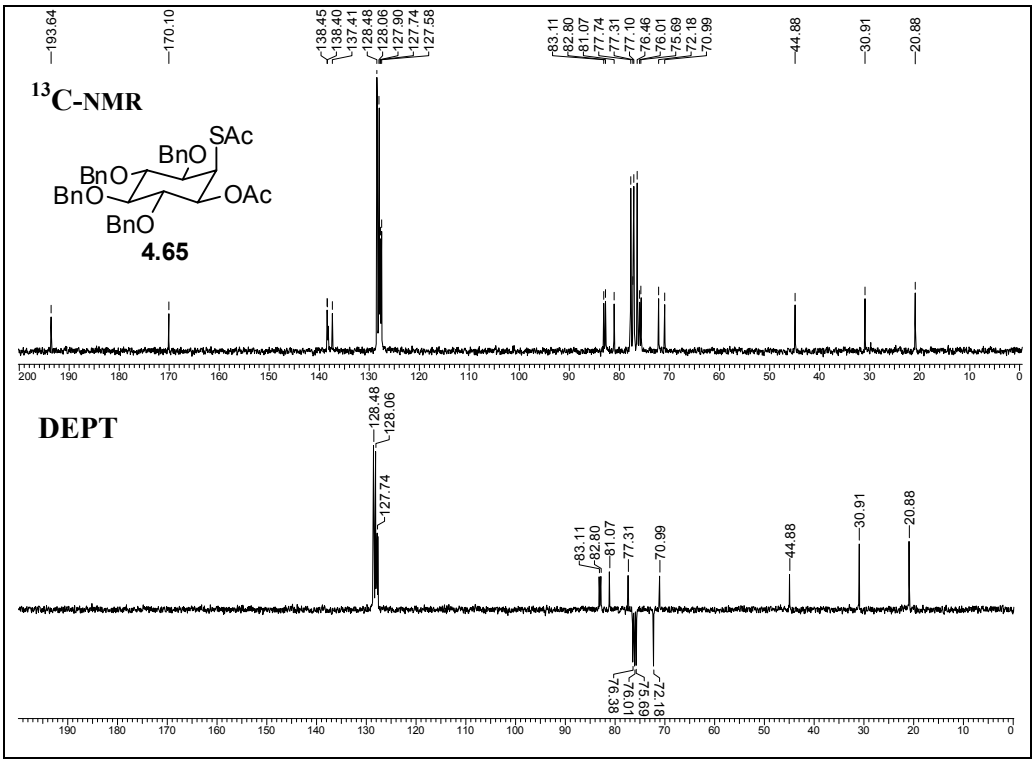
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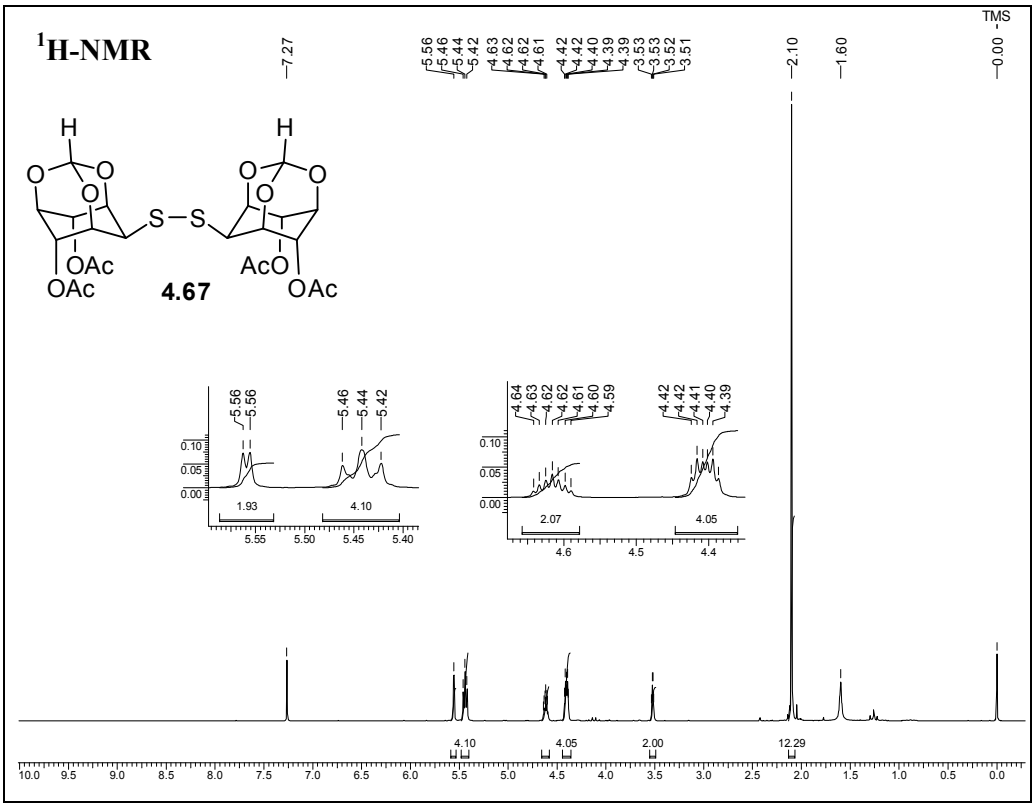
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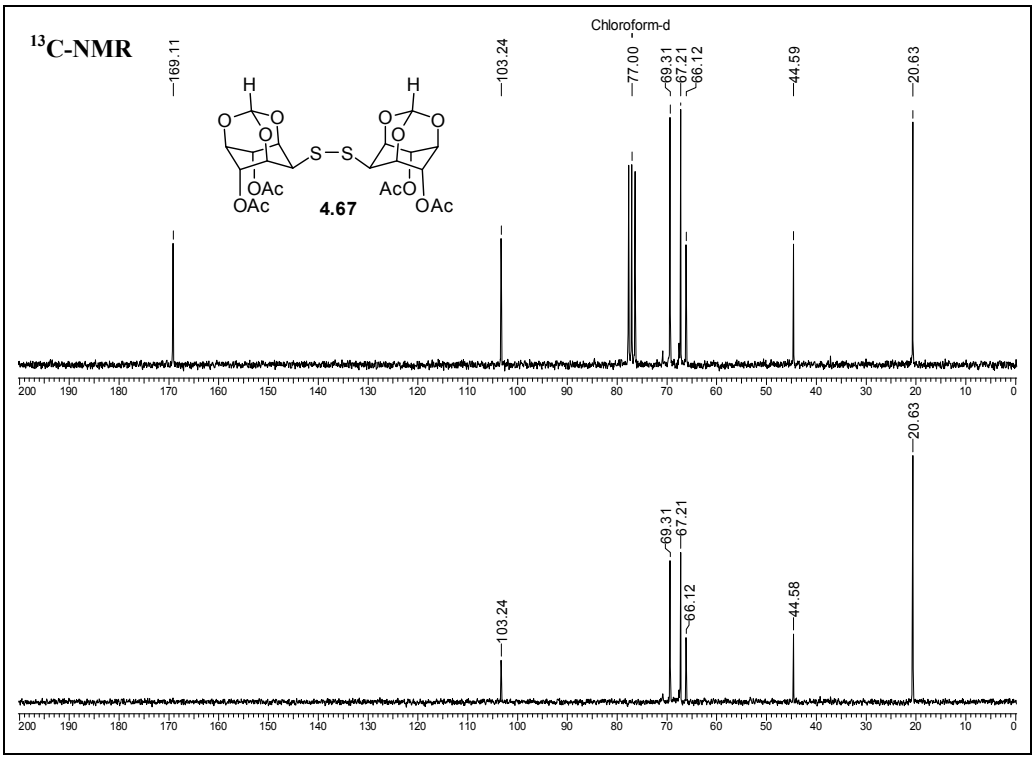
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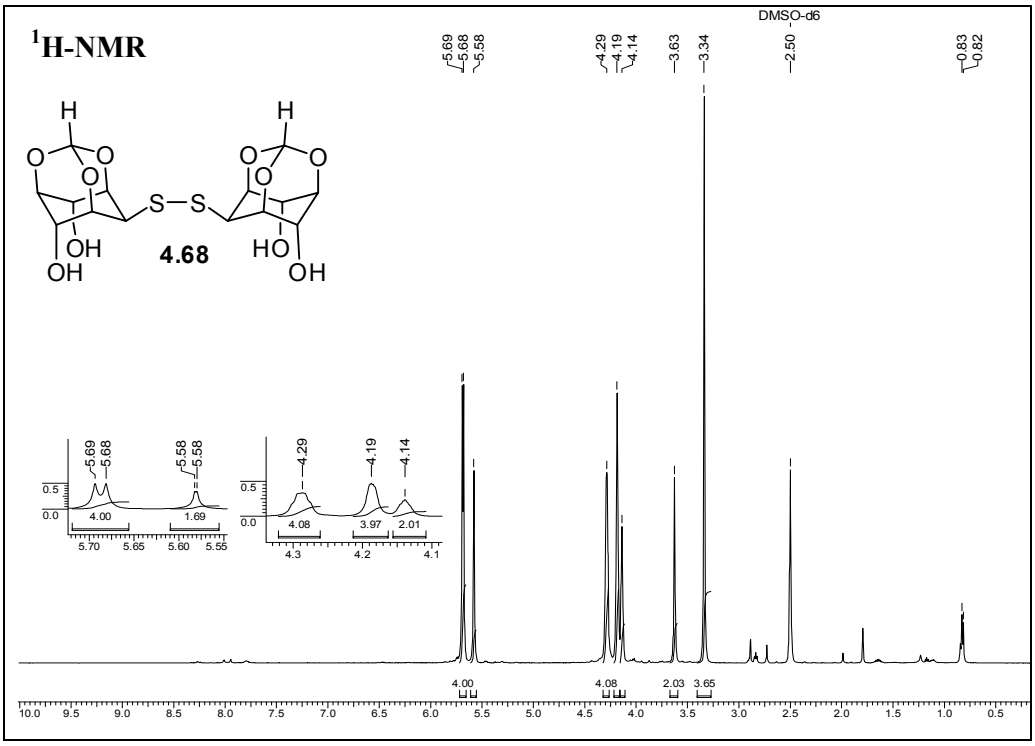
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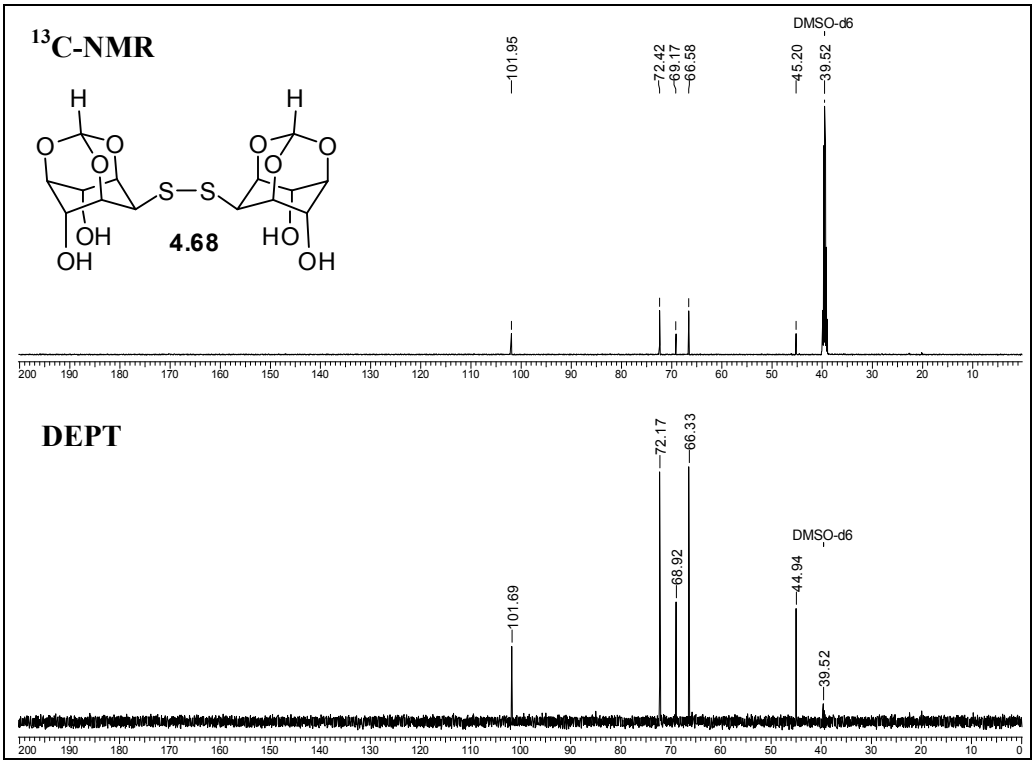
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