CHEMISTRY OF INOSITOLS: MECHANISTIC AND SYNTHETIC STUDIES WITH O-SUBSTITUTED *MYO* - INOSITOL ORTHOFORMATE DERIVATIVES

Thesis
submitted to the
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for the degree of
DOCTOR OF PHILOSOPHY
in CHEMISTRY

by

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December 1997

DEDICATED TO MY PARENTS AND HUSBAND

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "**Chemistry of Inositols: Mechanistic and Synthetic Studies with O-Substituted *myo*-Inositol Orthoformate Derivatives**" submitted by **Ms. TANYA DAS (neé BANERJEE)** was carried out by her under my supervision at National Chemical Laboratory, Pune, India. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

MS Shashidhar

Date: December 24, 1997
National Chemical Laboratory
Pune 411008

(Dr. M. S. SHASHIDHAR)
Research Guide

DECLARATION

I hereby declare that the thesis entitled "**Chemistry of Inositols: Mechanistic and Synthetic Studies with O-Substituted *myo*-Inositol Orthoformate Derivatives**" submitted for Ph. D. degree to the University of Pune has not been submitted by me for a degree to any other University.

Date: 24-12-97

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(**TANYA DAS**)

Acknowledgment

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Das

(TANYA DAS)

CONTENTS

ABBREVIATIONS

Ac	Acetyl
Ac_2O	Acetic anhydride
AcCl	Acetyl chloride
All	Allyl
Anal.	Analysis
B	Base
Bn	Benzyl
Bz	Benzoyl
Calcd.	Calculated
Camph	Camphanoyl
Carb	Carbamate
Concd.	Concentrated
D_2O	Deuterium oxide
DAG	Diacylglycerol
DHP	Dihydropyran
Dia-	Diastereomeric
DIBAL	Diisobutyl aluminium hydride
DMAP	4-Dimethyl aminopyridine
DMF	N, N-Dimethyl formamide
DMSO	Dimethyl sulphoxide
Ent	Enantiomeric
Eq.	Equivalent
EtOAc	Ethyl acetate
g	Grams
GPI	Glycosyl Phosphatidyl Inositol
h	Hours
Ins (1) P	Inositol 1-phosphate
Ins (1,2,4) P_3	Inositol 1,2,4-trisphosphate
Ins (1,2-cyclic) P	Inositol 1,2-cyclic phosphate
Ins (1,2-cyclic,4,5) P	Inositol 1,2-cyclic 4,5-trisphosphate

Ins (1,3) P_2	Inositol 1,3-bisphosphate
Ins (1,3,4,5) P_3	Inositol 1,3,4,5-tetrakisphosphate
Ins (1,3,4,5,6) P_3	Inositol 1,3,4,5,6-pentakisphosphate
Ins (1,3,5) P_3	Inositol 1,3,5-trisphosphate
Ins (1,4,5) P_3	Inositol 1,4,5-trisphosphate
Ins (1,5) P_2	Inositol 1,5-bisphosphate
Ins (2) P	Inositol 2-phosphate
Ins (4) P	Inositol 4-phosphate
IR	Infrared
LDA	Lithium diisopropylamide
LPL	Lipoprotein lipase
m.p.	Melting point
Me	Methyl
mM or mmol	Millimole
MPLC	Medium Pressure Liquid Chromatography
Ms	Methane sulfonyl
NMR	Nuclear Magnetic Resonance
Ⓟ	PO_3H_2
Ph	Phenyl
PI-PLC	Phosphatidylinositol specific Phospholipase C
PLE	Pig Liver Esterase
PMB	p-Methoxy benzyl
PNB	p-Nitrobenzoyl
PpTs	Pyridinium p-toluene sulfonate
Pr	Propyl
PtdIns	Phosphatidylinositol
PtdIns (4,5) P_2	Phosphatidylinositol 4,5-bisphosphate
pTSA	p-Toluene sulfonic acid
r.t.	Room temperature
Rac	Racemic
R_f	Retention Factor
RX	Alkyl halide
TBPP	Tetrabenzyl pyrophosphate

t-Bu	Tert-butyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
Thp	Tetrahtdropyranyl
TMS	Tetramethyl silane
Tr	Trityl
Ts	p-Toluene sulfonyl

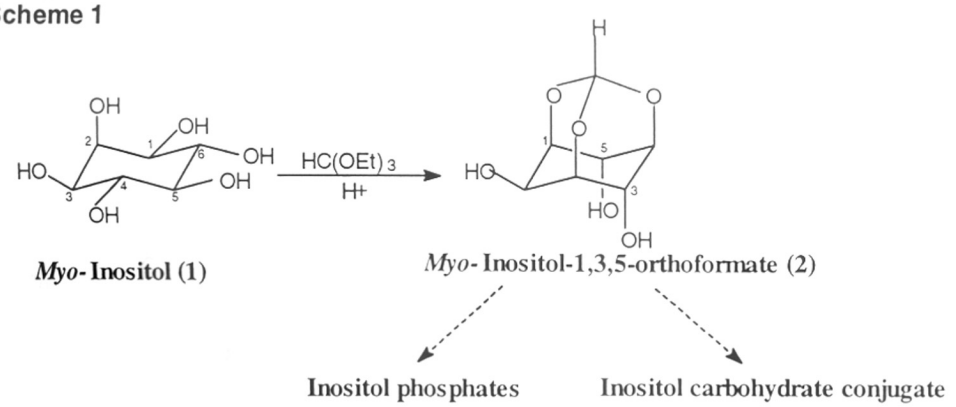
SYNOPSIS OF THE THESIS

CHAPTER 1

Myo-inositol-1,3,5-orthoformate: A Review

Inositols are hexahydroxycyclohexanes. Of the nine isomers known, *myo*-isomer **1** is the most abundant in nature. Phosphorylated derivatives of *myo*-inositol are involved in the cellular signal transduction mechanisms and regulation of Ca^{2+}. In particular, *myo*-inositol-1,4,5-triphosphate [Ins(1,4,5)P_3] is a second messenger in cellular signal transduction pathways. Glycosyl phosphatidylinositols are involved in the anchoring of proteins to cell membranes, for example, variant surface glycoprotein of trypanosomes. Availability of naturally occurring inositol derivatives as well as their synthetic analogues is essential to investigate and understand the different facets of these important biological processes. The recent upsurge in interest in the chemistry of inositol is evidenced by more than 5000 publications related to inositol in scientific journals. Syntheses of myo-inositol derivatives generally involve a large number of protections and deprotection steps owing to the presence of six hydroxy groups. *Myo*-inositol-1,3,5-orthoformate **2**, were first prepared in 1966 and its correct structure assigned in 1985. It is an important synthon since three of the six hydroxyl groups can be protected in a single step and the rest of the three hydroxyl groups can be protected and deprotected to obtain a large variety of intermediates for the synthesis of *myo*-inositol derivatives.In this chapter, a survey of the existing literature on *myo*-inositol-1,3,5-orthoformate is presented.

Scheme 1

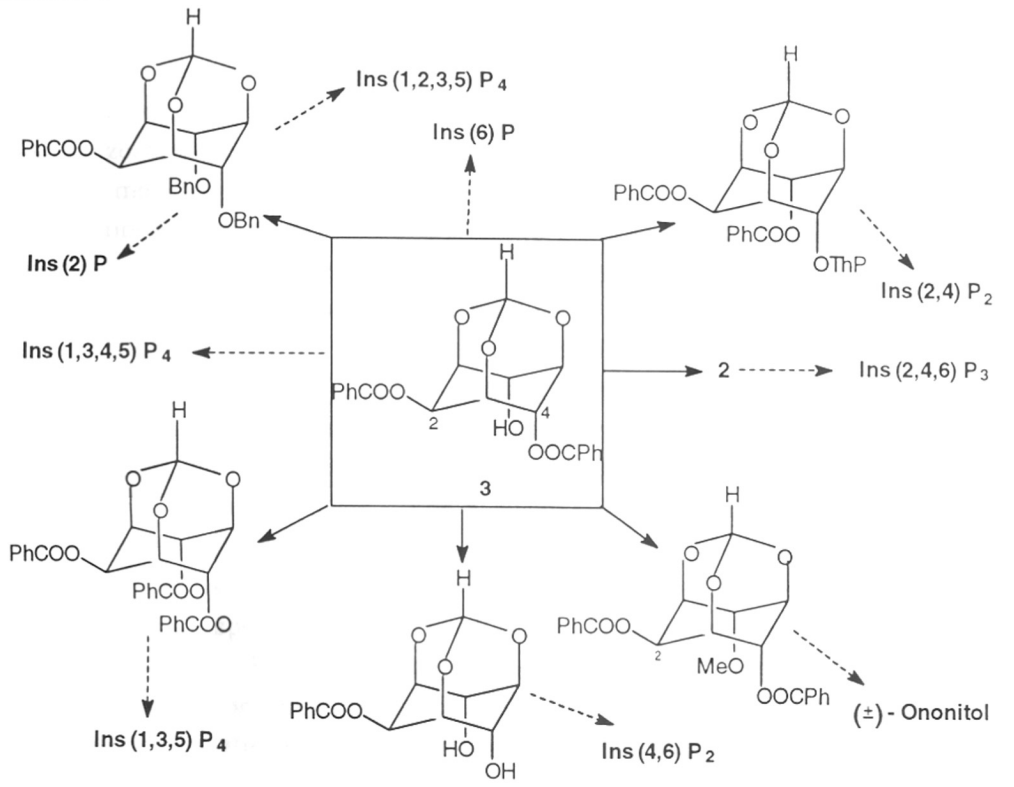


CHAPTER 2

2,4-Di-O-benzoyl-*myo*-inositol-1,3,5-orthoformate: A versatile intermediate for the synthesis of inositol derivatives

In this chapter we have discussed the multigram scale synthesis of the penta-protected *myo*-inositol derivative, 2,4-di-O-benzoyl-*myo*-inositol- 1,3,5 - orthoformate (**3**). The dibenzoate **3** was obtained by sequential reaction of *myo*-inositol (**1**) with triethylorthoformate/H^+ and benzoyl chloride/pyridine in a one pot procedure. The structure of this unsymmetrical diester was established by spectroscopy and single crystal X-ray analysis. The dibenzoate **3** can be easily converted to several protected *myo*-inositols which are important intermediates for the synthesis of *myo*-inositol derivatives. Some of the representative examples are shown below (**Scheme 2**).

Scheme 2



The axial 4-benzoate in **3** underwent base catalysed solvolysis with facility over the equatorial 2-benzoate to yield 2-O-benzoyl-*myo*-inositol-1,3,5-orthoformate (**4**). The reaction proceeds with the assistance of the axial hydroxyl group at the 6-position. This was established by the fact that the 6-O-protected derivatives of **3** were completely stable under identical solvolytic conditions.

* Note: All the *myo*-inositol derivatives prepared in the present work are racemic. However, for clarity, the nomenclature employed and the structures represented for these derivatives are that of the D-enantiomer, as recommended by the **IUPAC** (M. J. Berridge, R. F. Irvine, *Nature*, **1989**, *341*, 197.)

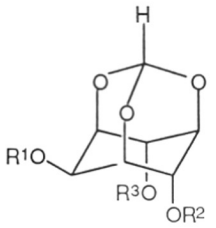
CHAPTER 3

Part A: Silver (I) oxide mediated alkylation of 2,4-Di-O-benzoyl-*myo*-inositol-1,3,5-orthoformate and its derivatives: A mechanistic study

As mentioned in **chapter 2** (see **Scheme 1**), benzylation of the dibenzoate **3** using excess benzylbromide in the presence of silver (I) oxide resulted in the cleavage of the axial 4-O-benzoate to yield the dibenzyl ether **5** in about 80% isolated yield, instead of the expected monobenzyl ether **8**. However, the equatorial ester group at the 2-position remained unaffected. Since esters are reported to be stable under these alkylation conditions, we suspected that the axial hydroxyl group at the 6-position might be assisting in the cleavage of the axial ester moiety at the 4-position. This result led us to investigate in detail the reaction of 2,4-di-O-benzoyl-*myo*-inositol-1,3,5-orthoformate **3** with alkyl halides in the presence of silver (I) oxide. This chapter presents a systematic study of the alkylation of O-substituted *myo*-inositol-1,3,5-orthoformate derivatives in the presence of silver (I) oxide in an attempt to delineate the mechanism involved. For a given substrate, nature of the product obtained in these alkylations depended on the amount of silver (I) oxide and alkyl halide used as well as on the solvent employed for the reaction. By varying these parameters the corresponding symmetrical 4,6-di-O-alkylated (**5-7**) or 4-mono-O-alkylated *myo*-inositol-1,3,5-orthoformates (**11-12**) could be obtained in good yields. Results presented for the allylation of 2,4-di-O-benzoyl-*myo*-inositol-1,3,5-orthoformate suggests the cleavage and allylation of the axial 4-benzoate moiety prior to the allylation of the free 6-hydroxy group. These alkylations perhaps proceed by

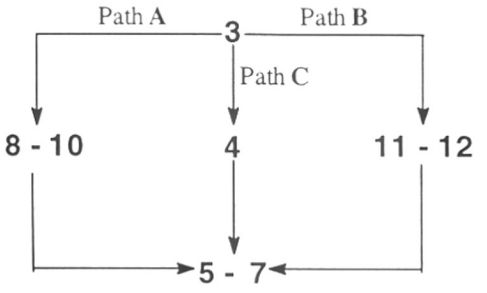
several parallel pathways which involve the transannular participation of the neighbouring axial oxygen (**Scheme 4**). Involvement of a *myo*-inositol orthoformate-silver complex during these alkylation reactions is suggested. The single crystal X-ray analysis of the tribenzoate **13** has also been presented.

Scheme 3



2	$R^1 = R^2 = R^3 = H$	**3**	$R^1 = R^2 = Bz, R^3 = H$
4	$R^1 = Bz, R^2 = R^3 = H$	**5**	$R^1 = Bz, R^2 = R^3 = Bn$
6	$R^1 = Bz, R^2 = R^3 = All$	**7**	$R^1 = Bz, R^2 = R^3 = Me$
8	$R^1 = R^2 = Bz, R^3 = Bn$	**9**	$R^1 = R^2 = Bz, R^3 = All$
10	$R^1 = R^2 = Bz, R^3 = Me$	**11**	$R^1 = Bz, R^2 = H, R^3 = All$
12	$R^1 = Bz, R^2 = H, R^3 = Me$	**13**	$R^1 = R^2 = R^3 = Bz$
14	$R^1 = R^2 = Bz, R^3 = Ac$	**15**	$R^1 = Bz, R^2 = R^3 = Ac$
16	$R^1 = R^2 = Bz, R^3 = Thp$	**17**	$R^1 = Bz, R^2 = Ac, R^3 = Me$

Scheme 4



CHAPTER 3

Part B: Silver (I) oxide mediated alkylation of 2-O-benzoyl-*myo*-inositol-1,3,5-orthoformate

To determine clearly whether 2-O-benzoyl-*myo*-inositol- 1,3,5-orthoformate **4** is one of the intermediates formed by hydrolysis of the axial 4-benzoate group during the reaction of 2,4-di-O-benzoyl-*myo*-inositol-1,3,5-orthoformate **3** with alkyl halides in the presence of silver (I) oxide, we subjected **4** to alkylation conditions as described in **Part A**. This was essential since the axial 4-benzoate in the diester **3** is prone to hydrolysis/solvolysis under mild alkaline conditions, as illustrated in **Chapter 2**. Alkylation of the diol **4** yielded the corresponding tri-O-alkyl-*myo*-inositol-orthoformates (**Scheme 5**) as the major product. Dialkyl ethers **5-7** (**Scheme 3**) were obtained as minor products. This was in contrast to the alkylation of the dibenzoate **3** which yielded dialkyl ethers **5-7** as the only isolable product. This observation ruled out the involvement of the diol **4** during the alkylation of the dibenzoate **3** (**Path C, Scheme 4**).

Scheme 5

When RX = MeI, $R^1 = R^2 = R^3 = Me$

When RX = Allyl bromide, (i) $R^1 = R^2 = R^3 = Allyl$ (major)

(ii) $R^1 = PhCOO$, $R^2 = R^3 = Allyl$ (minor)

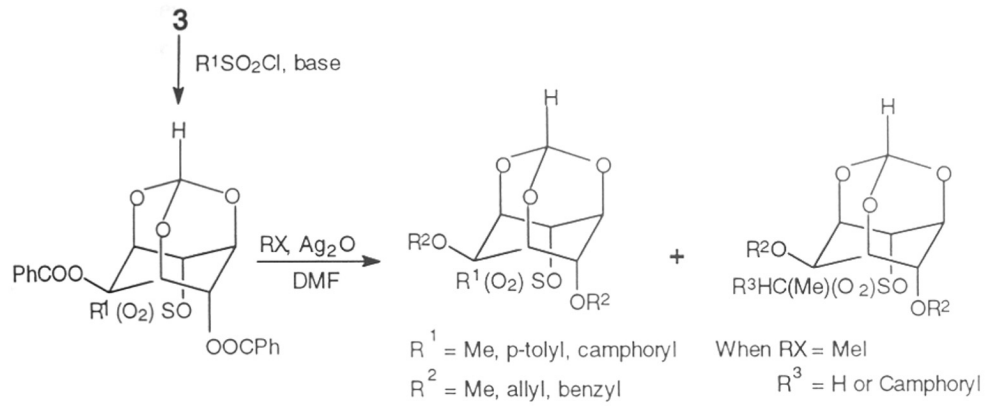
When RX = Allyl chloride, $R^1 = PhCOO$, $R^2 = Allyl$, $R^3 = H$

CHAPTER 4

Silver (I) oxide mediated alkylation of 6-O-sulfonylated derivatives of 2,4-di-O-benzoyl-*myo*-inositol-1,3,5-orthoformate

Since O-acylated derivatives of *myo*-inositol orthoformate showed unusual product formation on alkylation with silver (I) oxide / alkyl halides, we prepared several sulfonylated derivatives of inositol orthoformate and subjected them to alkylation as in **Chapter 3**. Reaction of the sulfonates with alkyl halides (**Scheme 6**) in the presence of silver (I) oxide gave the corresponding 2,4-dialkyl ethers. However when the aliphatic sulfonate derivatives was methylated with CH_3I/Ag_2O, some amount of C-methylation was also observed on the carbon bearing the sulfonyl group. Interestingly, in contrast to O-acyl-*myo*-inositol-orthoformates (**Chapter 3**) the sulfonylated derivatives (**Scheme 6**) undergo cleavage of both axial and equatorial 2,4-di-O-acyl groups. Structure of the 2,4-di-O-benzoyl-6-O-mesyl-*myo*-inositol-1,3,5-orthoformate was solved by single crystal X-ray analysis. An attempt was made to explain the observed unusual reactions by a comparison of X-ray structure data for several *myo*-inositol orthoformate derivatives.

Scheme 6



List of Publications and Patents

This thesis is based on the following publications. Some related unpublished results are also included in the thesis.

Publications:

"Neighbouring hydroxy group assisted O-alkylation and solvolysis of an unsymmetrical diester derivative of myo-inositol".
T.Das (neé Banerjee), M. S. Shashidhar
Tetrahedron Letters, 1994, *35*, 8053-8056.

Silver (I) oxide assisted O-alkylation of 2,4-di-O-benzoyl-myo-inositol-1,3,5-orthoformate and its 6-O-substituted derivatives: Transannular participation of oxygen.
T. Das, M. S. Shashidhar
Carbohydrate Research, 1997, *297*, 243-249.

Mechanism of silver (I) oxide mediated O-alkylation of 2,4-di-O-acyl-myo-inositol-1,3,5-orthoformate: Effect of solvent and silver halide on the nature of the intermediate involved.
T. Das, T. Praveen, M. S. Shashidhar
(Communicated).

Racemic 2,4-di-O-benzoyl-myo-inositol-1,3,5-orthoformate: A versatile intermediate for the preparation of myo-inositol phosphates.
Tanya Das and M.S. Shashidhar
(Communicated).

Reactivity Controlled by Lattice Interactions in Crystal: Intermolecular Acyl Transfer in (±)-2,4-di-O-benzoyl-myo-inositol-1,3,5-orthoformate.
T. Praveen, U. Samanta, T. Das, M. S. Shashidhar and P. Chakrabarti.
(Communicated).

Symposiums and seminars:

Electrochemical reduction of myo-inositol derivatives: Cyclic voltametric behaviour of (dl) 2,4-di-O-benzoyl-6-oxo-myo-inositol-1,3,5-orthoformate and (dl) 2,4-di-O-benzoyl-6-oxo-myo-inositol.
T. Praveen, T. Das, M. S. Shashidhar.
Frontier areas in Organic Chemistry, Department of Chemistry, University of Pune, February 14-15, 1997 (submitted).

An unusual transesterification reaction of 2,4-di-O-acyl -myo-inositol-1,3,5-orthoformate: Is the hydroxy group unusually reactive?
T. Praveen, T. Das, U. Samantha, V. G. Puranik, P. Chakrabarti, M. S. Shashidhar.
XI Carbohydrate Conference, IICB, Calcutta, November 21-22, 1996.

Aromatic – aromatic and CH...O interactions in the crystal structures of O-substituted myo-inositols.
U. Samantha, D. Pal, V. G. Puranik, P. Chakrabarti, T. Das, T. Praveen, M. S. Shashidhar.
XVII Congress of International Union of Crystallography, Seattle, Washington, USA, 1996.

Myo-inositol phosphates: Molecules involved in cell signalling.
M. S. Shashidhar, T. Das (neé Banerjee), U. Samantha, V. G. Puranik, P. Chakrabarti.
V National Bio-Organic Symposium, Kolhapur, India, 1995.

CH...O Hydrogen bonding in the crystal structures of myo-inositol-1,3,5-orthoformates.
U. Samantha, V. G. Puranik, P. Chakrabarti., T. Das (neé Banerjee), M. S. Shashidhar.
XXVI National Seminar on Crystallography, Mysore, India, 1995.

Patents:

A facile process for the preparation of 2,4(6)-di-O-alkyl-myo-inositol-1,3,5-orthoformate sulphonic acid esters.
T. Das, M. S. Shashidhar.
(Filed)

A process for the preparation of 2,4(6)-di-O-acyl-myo-inositol-1,3,5-orthoformate esters of sulphonic acids.
T. Das, M. S. Shashidhar.
(Filed)

A process for the preparation of 2,4(6)-di-O-acetyl-6(4)-O-tosyl myo-inositol-1,3,5-orthoformate.
T. Das, M. S. Shashidhar.
(Filed)

CHAPTER 1

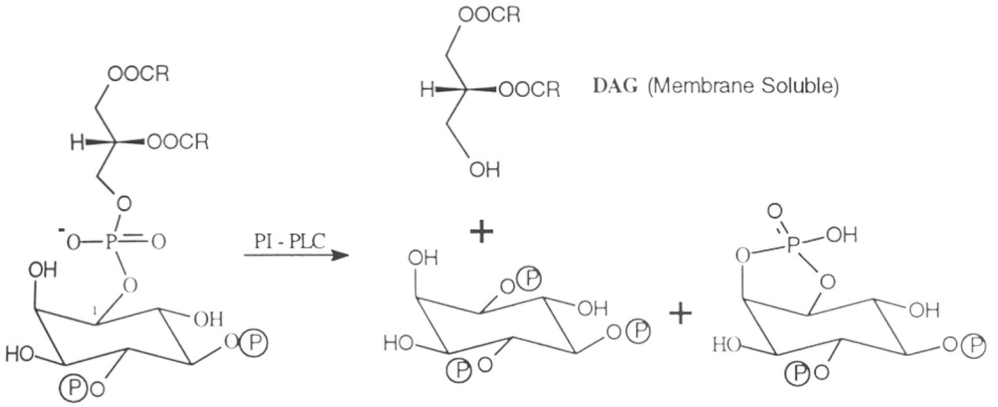
Myo-inositol-1,3,5-orthoformate: A Review

1.1 INTRODUCTION

Over the past few years, a great deal of attention has been focused on the chemistry and biochemistry of *myo*-inositol due to the involvement of its phosphorylated derivatives in important biological phenomena such as cellular signal transduction and anchoring of certain proteins to the cell membrane. The phosphatidylinositol - specific phospholipase C (PI-PLC) mediated hydrolysis of phosphatidylinositol 4,5-bisphosphate [PtdIns (4,5) P_2] to give inositol 1,4,5-trisphosphate [Ins (1,4,5) P_3], inositol 1,2-cyclic-4, 5-trisphosphate [Ins (1,2-cyclic, 4,5) P_3] and diacylglycerol (DAG) (**Scheme 1.1**) is now firmly established as an important second messenger pathway resulting from activation of membrane receptors by a number of neurotransmitters and hormones[1]. Both Ins (1,4,5) P_3 and DAG act as second messengers in the stimulated cell, the former mediating the release of calcium from an intracellular store and the latter activating protein kinase C in cell membrane. Further metabolism of Ins (1,4,5) P_3 then takes place with the intermediacy of several *myo*-inositol phosphates to give finally *myo*-inositol which is then recycled for the synthesis of PtdIns (4,5) P_2 thus completing the *myo*-inositol cycle. There is evidence for the existence of an important alternative pathway for rapid metabolism of Ins (1,4,5) P_3 *via* a 3-kinase to the Ins (1,3,4,5) P_4 which appears to be an important second messenger regulating influx of calcium ion in stimulated cells[2]. However, many facets of these fundamental signal transduction pathways are not clear.

Glycosyl phosphatidylinositols (GPI) are involved in the anchoring of proteins to cell membranes[3], for example, variant surface glycoprotein of trypanosomes. Certain cell surface proteins are linked through an oligosaccharide unit to the 6-position of *myo*-inositol ring of phosphatidylinositol (PtdIns) (**Scheme 1.1**). GPI anchors occur much more frequently in protozoans than in higher eukaryotes[4]. Glycoconjugates on the cell surface of protozoans frequently play a crucial role in determining parasite survival and infectivity. Recently a number of non-protein glycosyl phosphatidylinositol cell surface molecules[5], *viz.* lipophosphoglycans and glycoinositol phospholipids have been isolated, which play an important role in parasite virulence.

Scheme 1.1

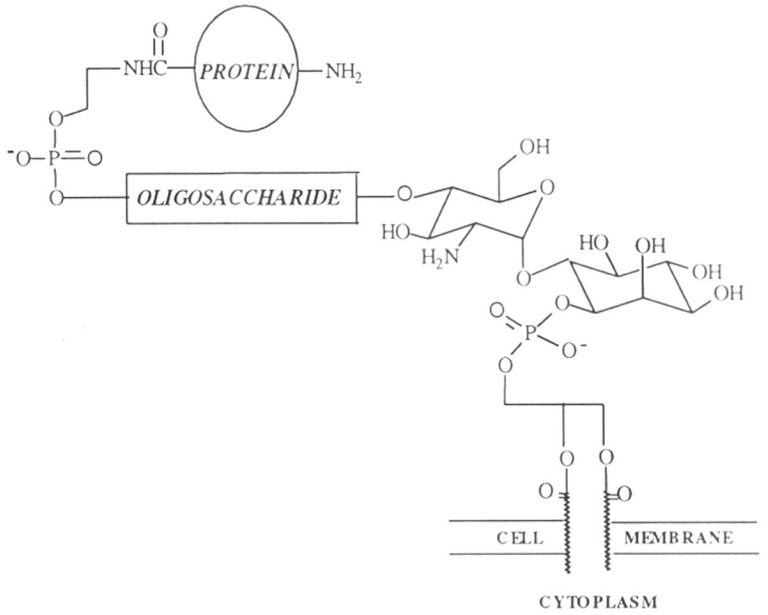


PtdIns (4,5) P_2

Ⓟ = PO_3H_2, R = Fatty alkyl

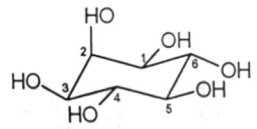
Ins (1,4,5) P_3
(Cytosol Soluble)

Ins (1,2-cyclic, 4,5) P_3

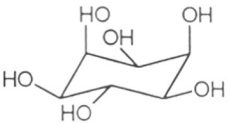


Inositols are cyclohexane hexols; of the nine isomers known (**Scheme 1.2**), two are chiral and others are optically inactive forms.

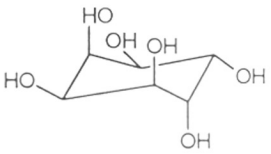
Scheme 1.2



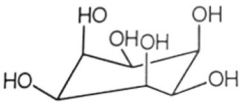
myo-



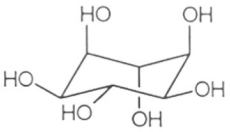
epi-



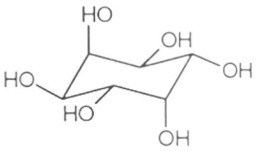
allo-



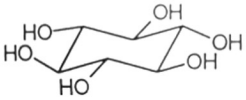
cis-



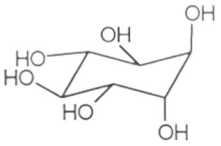
muco-



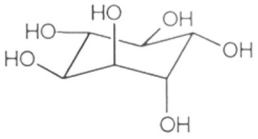
neo-



scyllo-



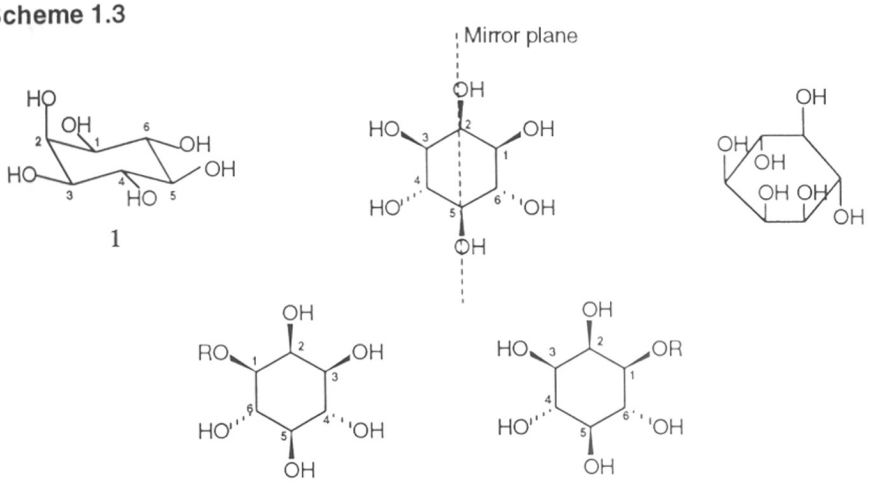
D-chiro (+)



L-chiro (-)

Myo-inositol (**1**), having five equatorial hydroxyl groups and one axial hydroxyl group, has the meso configuration. Different representations of *myo*-inositol ring used in the literature and the numbering of carbon atoms are shown in **Scheme 1.3**. Since the plane of symmetry in *myo*-inositol is through C-2 and C-5, substitution at C-1, C-3, C-4 or C-6 gives rise to chiral derivatives. According to the IUPAC recommendation[6], an anticlockwise numbering in an asymmetric derivative of *myo*-inositol is given the prefix D, and the clockwise numbering given the prefix L. However IUPAC recommendations allow all biologically relevant *myo*-inositol derivatives to be denoted with the D-configuration. **Accordingly, for clarity and simplicity in this thesis, although all the *myo*-inositol derivatives reported (Chapters 2 - 4) are racemic, they are represented using the D-configuration.**

Scheme 1.3



1

L 1 - Isomer
D 3 - Isomer

D 1 - Isomer
L 3 - Isomer

Availability of naturally occurring inositol derivatives as well as their synthetic analogues is essential to investigate and understand the different facets of the important biological processes mentioned above. Syntheses of *myo*-inositol derivatives generally involve a large number of protection and deprotection steps owing to the presence of six hydroxyl groups. Key intermediates for the synthesis of biologically important inositol derivatives are their hydroxyl group protected precursors. Four different strategies have so far been utilized for the synthesis of protected *myo*-inositol derivatives[7] (**Scheme 1.4**): -

(I) From commercially available *myo*-inositol[7-16]

(II) From naturally occurring Quebrachitol[17-27]

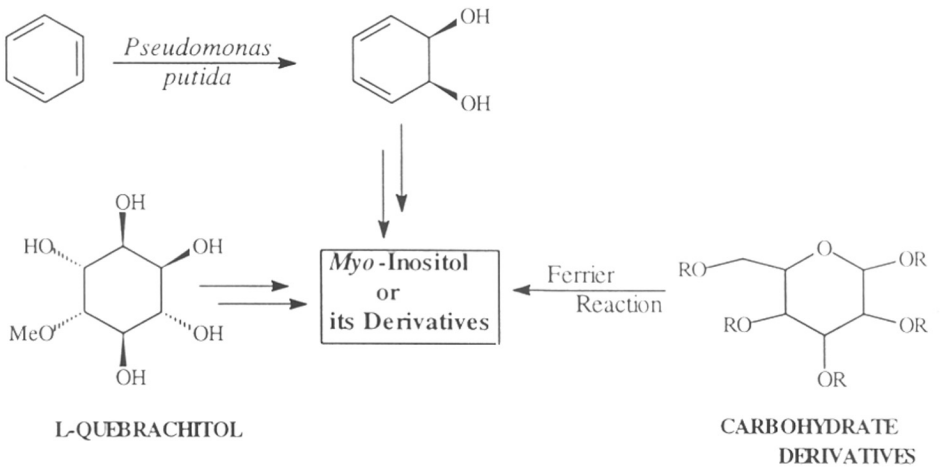
(III) From glucose or other carbohydrate precursors[28-35]

(IV) From benzene and it's derivatives[36-38]

The first route mentioned above (I), necessarily involves either chemical or enzymatic resolution of intermediates to obtain the required enantiomerically pure end product. The next two routes (II-III) give rise to one enantiomer, as the starting materials are chiral. The synthesis from benzene[36-38] (route IV) involves the oxidation of benzene by *Pseudomonas putida* to cyclohexadiene diol [36], which is subsequently

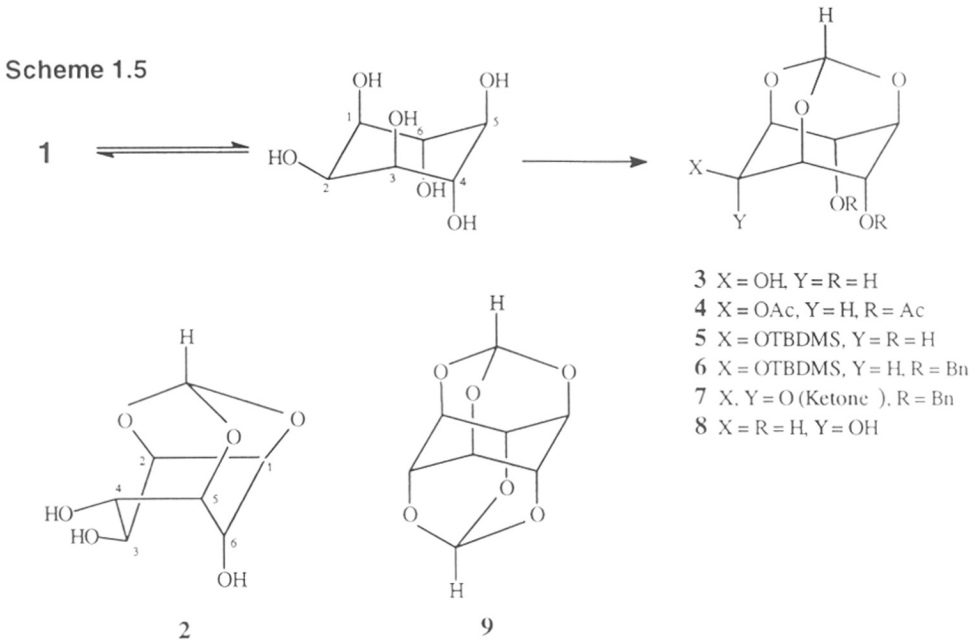
converted to inositol derivatives. This route has the advantage in that it can be used to generate isomeric inositols or their derivatives. Route (I) is widely used perhaps due to easy availability of *myo*-inositol in large quantities and its low cost. Also, efficient resolution methods are now available which provide enantiomerically pure *myo*-inositol derivatives in several gram quantities[39-40].

Scheme 1.4



Usually the first step for the synthesis of protected inositol is its conversion to a ketal or orthoformate derivative[7]. Isopropylidene and cyclohexylidene ketals of *myo*-inositol were synthesized and characterized several decades ago. However, *myo*-inositol orthoformate has been employed for the synthesis of biologically important inositol derivatives only recently. *Myo*-inositol-1,3,5-orthoformate (**3**) (**Scheme 1.5**) is an important synthon since three of the six hydroxyl groups can be protected in a single step and the rest of the three hydroxyl groups can be protected and deprotected to obtain a large number of intermediates. Accordingly, rest of this chapter consists of a literature review on *myo*-inositol-1,3,5-orthoformate (**3**).

Scheme 1.5



1.2 PREPARATION OF *MYO*-INOSITOL-1,3,5-ORTHOFORMATE (3)

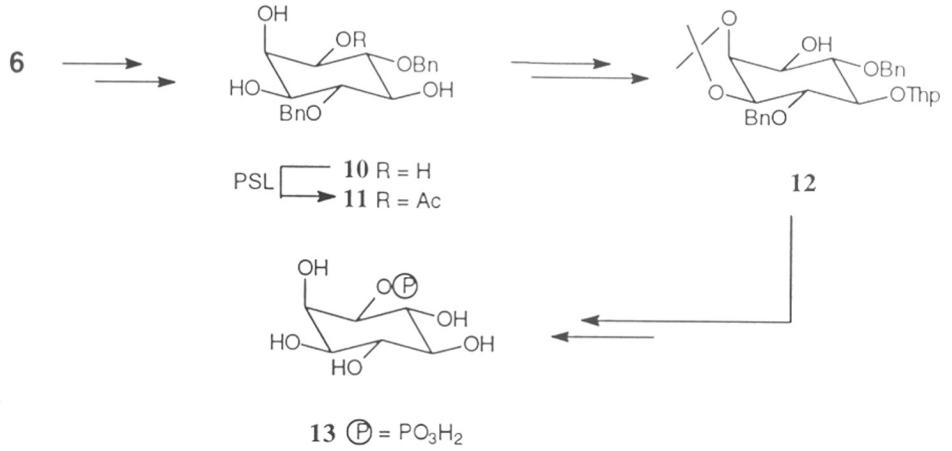
In 1966, Luk'yanov[41] first reacted *myo*-inositol with triethylorthoformate in toluene, and assigned structure **2** (**Scheme 1.5**) to the product obtained. Several years later, in 1985, Lee and Kishi[42] reexamined this reaction by using DMSO as a solvent instead of toluene and were able to isolate *myo*-inositol-1,3,5-orthoformate (**3**) in 76% yield. They also converted the orthoformate **3** to its triacetate derivative **4**. The ^{1}H NMR spectral data of both **3** and **4** showed the presence of a symmetry element, which allowed the assignment of the trioxa-adamantane structure to **3**. Unfortunately, no physical data was available from the previous report[41] which could be compared to conclude that this product was identical with the mono-orthoformate **2** reported by Luk'yanov. Thus was obtained a trioxaadamantane system (with its conformational rigidity) bearing two axially disposed hydroxyl groups at 4- and 6-positions, which later turned out to be an excellent intermediate for the preparation of inositol derivatives. Its potential as an intermediate for the preparation of several natural and unnatural *myo*-inositol derivatives with biological implications is evident by recent publications. Lee and Kishi were in fact interested in *scyllo*-inositol-1,3,5-orthoformate (**8**), which they prepared from **3** *via* the ketone **7**. *Scyllo*-inositol

orthoformate **8** could not be prepared directly from *scyllo*-inositol, as formation of the bis-orthoformate **9** was faster than formation of the mono-orthoformate **8**.

Billington et. al.[43, 44] as well as Vasella and coworkers[10] obtained a cleaner product **3** by using DMF instead of DMSO as the solvent for the reaction. Vasella et. al. avoided chromatographic purification of **3** by isolating it from the aqueous phase after lyophilisation and subsequent crystallization from methanol. Schneider and coworkers[14] were able to avoid chromatographic purification step by preparing the triacetate **4** *in situ*, which was separated by crystallization. This triacetate on treatment with sodium methoxide in methanol gave the orthoformate **3** in 70% yield on 250 grams scale.

1.3 SYNTHESIS OF *MYO*-INOSITOL MONOPHOSPHATES, CYCLIC PHOSPHATES AND THEIR ANALOGUES

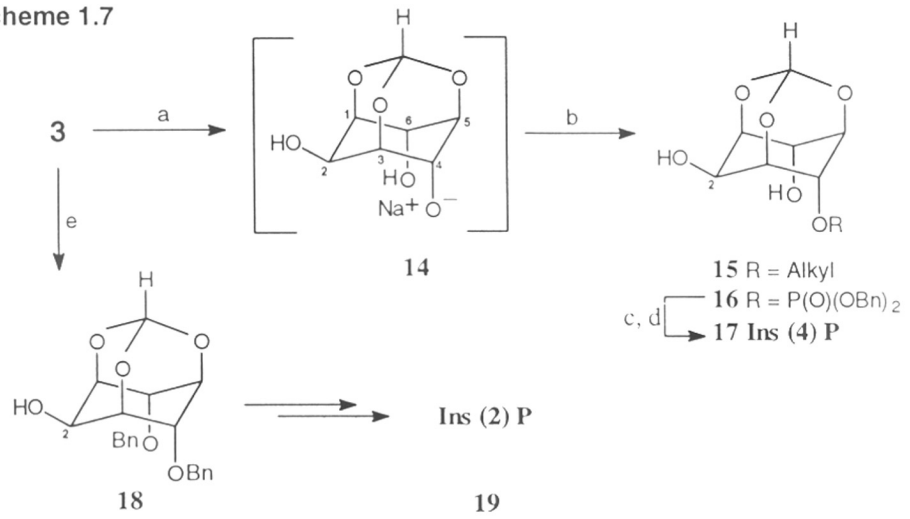
Scheme 1.6



Ghisalba et. al. reported a chemo-enzymatic synthesis of D-Ins (1) P (**13**) from **3**[45] (**Scheme 1.6**). The dibenzyl ether **6** prepared from **3** (**Scheme 1.5**) was converted to the meso-1,2,3,5-tetrol **10** which was selectively acetylated at the 1-position using lipase from *Pseudomonas species* to give the optically active (-)-1-monoacetate **11**. The pentaprotected *myo*-inositol derivative **12** obtained from **11** was phosphorylated by known methods to obtain (+)-D-*myo*-Ins (1) P (**13**).

Billington and coworkers[43, 44] discovered that treatment of **3** with one equivalent of sodium hydride in DMF at 25°C, followed by one equivalent of an alkyl halide resulted in the derivatization of one of the axial hydroxyl groups selectively to give **15** (**Scheme 1.7**).

Scheme 1.7



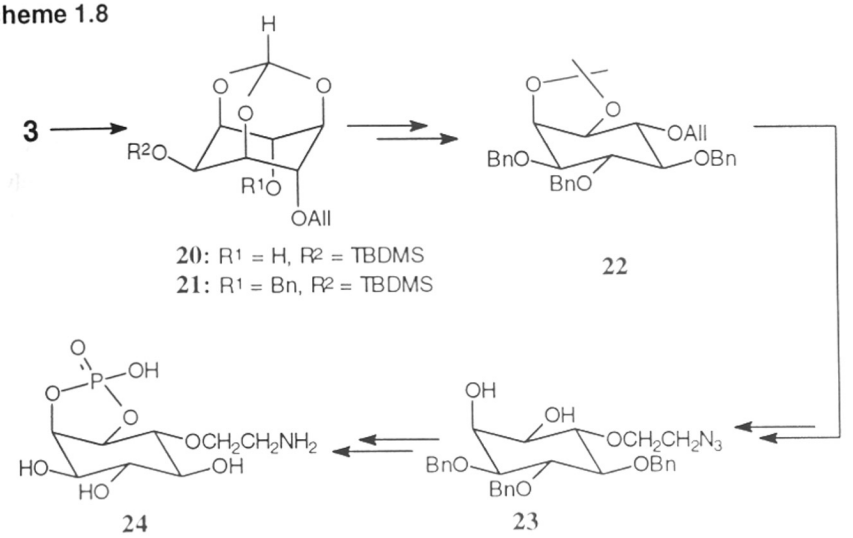
Reagents and conditions: (a) NaH (1 eq) (b) RX or TBPP (1 eq) (c) H_2, Pd-C (d) TFA-H_2O (e) NaH (2 eq), BnBr (2 eq).

They attributed this selectivity to CHELATION EFFECT and postulated the intermediacy of the anion **14**. Use of tetrabenzyl pyrophosphate instead of an alkyl halide provided the racemic phosphate **16**, which on deprotection gave racemic Ins (4) P (**17**). Reaction of the orthoformate **3** with two equivalents of sodium hydride and benzyl bromide resulted in a mixture of 2,4- and 4,6-dibenzyl ethers in the ratio of 5:1. The latter (**18**) on phosphorylation and deprotection afforded Ins (2) P (**19**).

To prepare a potential insulin mimetic second messenger 6-O- (2-aminoethyl)-D, L-*myo*-inositol-1, 2-cyclic phosphate **24** (**Scheme 1.8**), Cobb et. al.[45] regioselectively protected the equatorial 2-hydroxyl group of the allyl ether **15** (R = allyl) with TBDMS-chloride and benzylated the 6-hydroxyl group in **20** to obtain the fully protected *myo*-inositol derivative **21**. Deprotection of **21** with aqueous hydrochloric acid gave the corresponding 1,2,3,5-tetrol, which was converted to **22**. The allyl group in **22** was dihydroxylated and converted to the azide **23**, which on

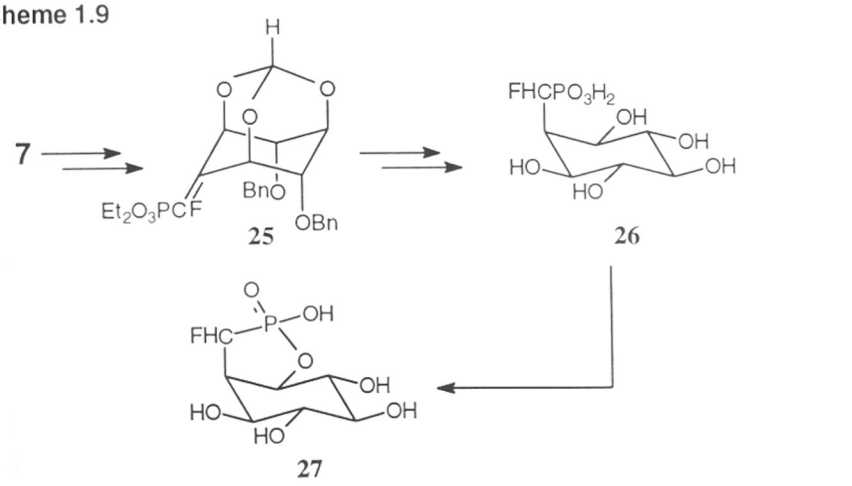
phosphorylation and hydrogenolysis afforded the 6-O- (2-aminoethyl) derivative **24** in 52% yield.

Scheme 1.8



To examine the mechanism of PI-PLC mediated hydrolysis of PtdIns, Thatcher et.al.[47, 48] synthesized a stable, isopolar, isosteric analogue **27** of Ins (1,2-cyclic) P (**Scheme 1.9**). The ketone **7** (**Scheme 1.5**) on reaction with the bisphosphonate $Et_2O_3PCHFPO_3Et_2$ in the presence of LDA gave the vinyl phosphonate **25**.

Scheme 1.9

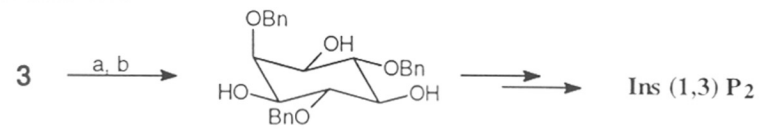


Deprotection of the orthoformate and phosphonate ester followed by hydrogenation of benzyl and vinyl groups gave **27** as the major product after column chromatography. Presumably the phosphonate **26** formed initially cyclised during chromatography on silica gel to afford **27**.

1.4 SYNTHESIS OF *MYO*-INOSITOL BISPHOSPHATES AND THEIR ANALOGUES

The 2,4,6-tri-O-benzyl-*myo*-inositol-1,3,5-orthoformate, prepared by the benzylation of **3** (**Scheme 1.10**) with excess sodium hydride and benzyl bromide, gave the triol **28**[43,44] on acid hydrolysis. Phosphorylation of the triol **28** gave 82:18 mixture of 1,3- and 1,5-bisphosphates. The desired 1,3-isomer was isolated by crystallization and deprotected to obtain Ins (1,3) P_2 (**29**).

Scheme 1.10

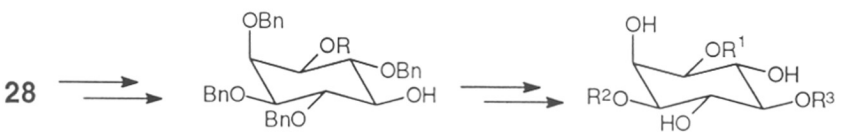


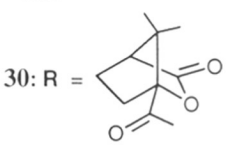
28 29

Reagents and conditions: (a) Excess NaH, BnBr (b) H^+, H_2O

To investigate the role of Ins (1,5) P_2 in mammalian cells, a convenient synthesis of D-*myo*-Ins (1,5) P_2 (**32**) and its analogues (**Scheme 1.11**) was developed by Westerduin et. al[49].

Scheme 1.11





31: R = H

32: $R^1 = R^3 = PO_3H_2$, $R^2 = H$
Ent-32: $R^1 = H$, $R^2 = R^3 = PO_3H_2$
33: $R^1 = R^3 = SO_3H$, $R^2 = H$
34: $R^1 = R^3 = SO_2NH_2$, $R^2 = H$

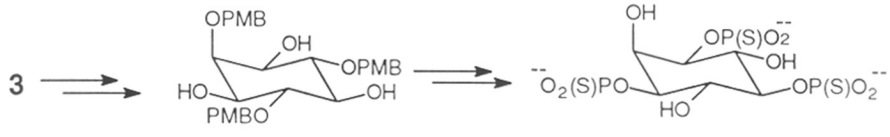
The 2,4,6-tribenzyl derivative **28** prepared as in **Scheme 1.10**, was selectively benzylated at O-3 position and resolved as the camphanate ester **30**. Diastereomers

30 and **Dia-30** were separated and converted to D-Ins (1,5) P_2 (**32**) and D-Ins (3,5) P_2 (**Ent-32**) respectively using standard methods. To obtain an analogue of **32** with reduced negative charge, the diol **31** was treated with triethylamine-sulfur trioxide complex and then debenzylated to give *myo*-inositol-1,5-bissulfate **33**. Sulfamoylation of **31** with sulfamoyl chloride (NH_2SO_2Cl) followed by hydrogenolysis of the benzyl groups, gave the bis-sulfamoyl derivative **34,** which is a neutral analogue of **32**.

1.5 SYNTHESIS OF *MYO*-INOSITOL TRISPHOSPHATES AND THEIR ANALOGUES

Myo-inositol-1,3,5-trisphosphate has been prepared from the triol **28** as in **Scheme 1.10** by phosphorylation followed by deprotection using standard protocols[41]. Potter and coworkers prepared phosphorothioate analog **36** of Ins (1,3,5) P_3 from **3**[50] and tested it as an inhibitor of Ins (1,4,5) P_3 5-phosphatase (**Scheme 1.12**). The triol **35** was prepared from **3** and phosphorylated using standard protocols. *p*-Methoxy benzyl group was used to protect the hydroxyl groups as it can be removed by oxidation. Phosphorothioates are not stable to hydrogenolysis conditions necessary to cleave benzyl ethers.

Scheme 1.12

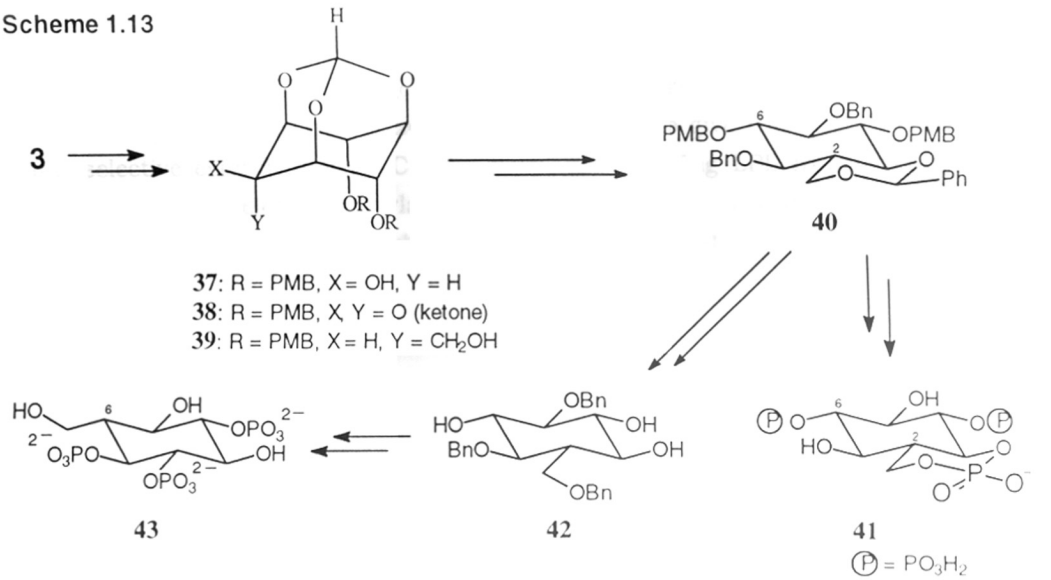


35 **36**

The synthesis of a conformationally restricted cyclic phosphate analogue **41** of Ins (1,4,5) P_3 has been reported by Potter et. al.[51] (**Scheme 1.13**). The triol **3** was reacted with sodium hydride and *p*-methoxybenzyl chloride (PMB-Cl) to give **37** as the major product. It was converted to the ketone **38** by Swern oxidation. Wittig methylenation of **38** afforded the corresponding alkene, which was hydroborated with 9-Borabicyclo[3.3.1]nonane to give **39** in 97% yield. **39** were converted to **41** as shown in **Scheme 1.13** *via* **40**. 6-Deoxy-6-hydroxymethyl-*scyllo*-inositol-1,2,4-trisphosphate **43** was synthesized[52] (**Scheme 1.13**) and its biological activity was compared with those of D-Ins (1,4,5) P_3 and DL-*scyllo*-Ins (1,2,4) P_3. The benzylidene acetal **40** was reduced regioselectively using borane-trimethylamine complex /

aluminium chloride and the *p*-methoxybenzyl group removed to give the triol **42**. This was phosphorylated and debenzylated to obtain **43** in 71% yield.

Scheme 1.13



37: R = PMB, X = OH, Y = H
38: R = PMB, X, Y = O (ketone)
39: R = PMB, X = H, Y = CH_2OH

40

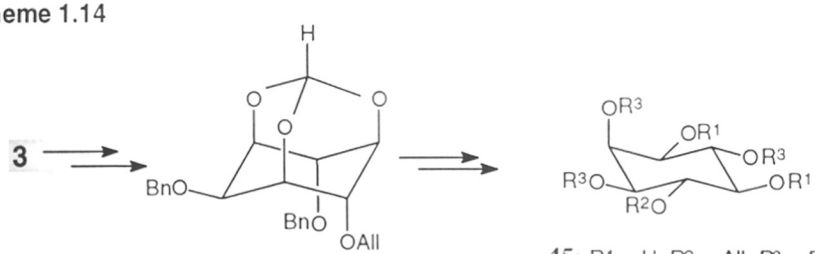
41
Ⓟ = PO_3H_2

42

43

In another attempt to prepare synthetic analogues of racemic Ins (1,4,5) P_3 containing carboxymethyl moieties as phosphate isosteric group, Westerduin et. al.[53] converted 4-O-allyl-2,6-di-O-benzyl derivative **44** (**Scheme 1.14**) to 2,3,6-tribenzyl ether **45** which gave the 1,5 diether **46** on treatment with *t*-butyl bromoacetate. Subsequent oxidation of allyl group and deprotection afforded the tricarboxylate **47**.

Scheme 1.14

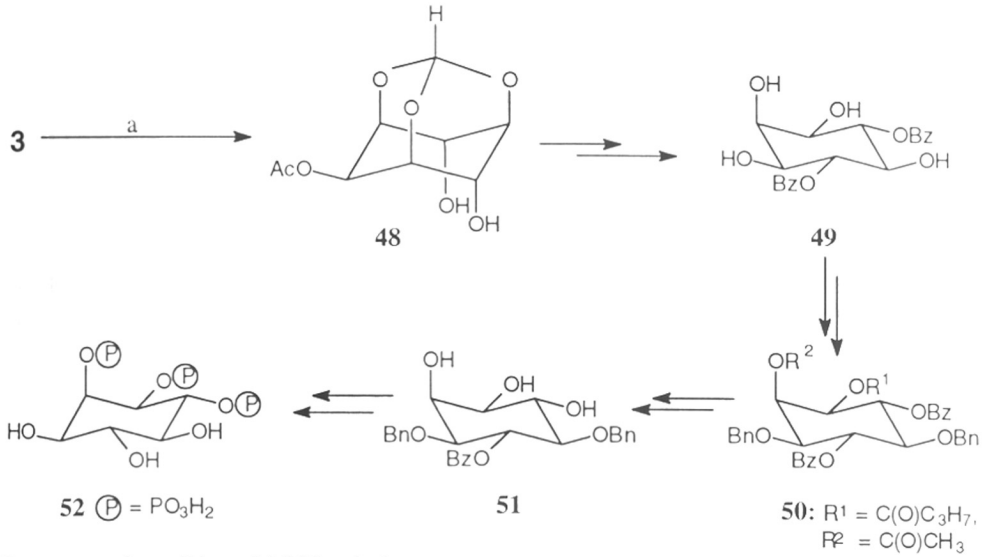


44

45: R^1 = H, R^2 = All, R^3 = Bn
46: R^1 = $CH_2C(O)OBut$, R^2 = All, R^3 = Bn
47: R^1 = R^2 = CH_2COOH, R^3 = H

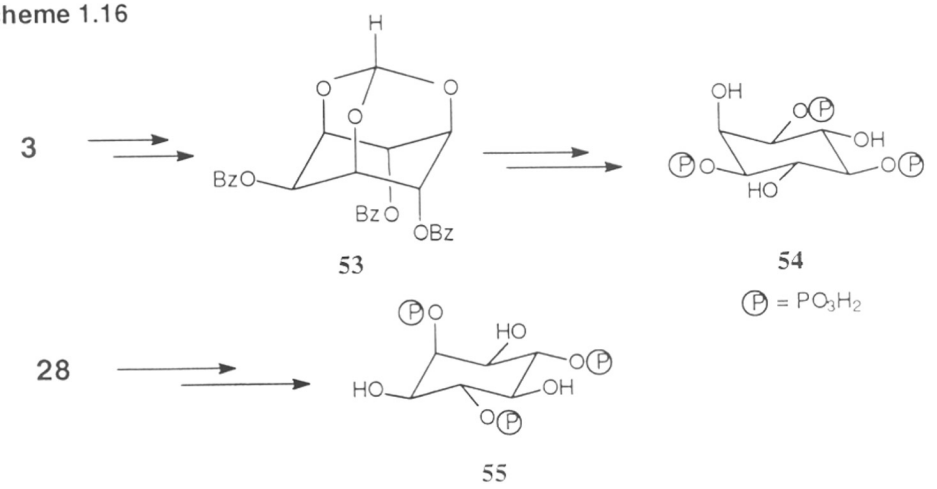
Schneider et. al. reported an enzyme-assisted synthesis[54] of D-*myo*-inositol-1,2,6-trisphosphate (α-trinositol) (**52**), which is an experimental drug used broadly in the treatment of several acute and chronic diseases. Treatment of **3** with vinyl acetate and lipoprotein lipase (LPL) gave the 2-acetate **48** exclusively (**Scheme 1.15**) which was then benzoylated to the 4,6-di-O-benzoyl derivative, and the acetate and orthoformate groups were hydrolyzed with HCl/MeOH to give the 1,2,3,5 - tetrol **49**. Enantioselective esterification of C-1 hydroxyl group using LPL from *Pseudomonas species* followed by selective acetylation of C-2 with $CH_3(OEt)_3$ and *p*TSA followed by benzylation gave **50** exclusively, which was converted to α-trinositol **52** *via* the triol **51**.

Scheme 1.15



Chung et. al. reported[55,56] a divergent synthesis of all the possible 12 regioisomers of *myo*-inositol trisphosphate *via* base catalyzed isomerisation of inositol tribenzoates. They synthesized the symmetrical 2,4,6- and 1,3,5-tribenzoates of *myo*-inositol from **3** (**Scheme 1.16**). The symmetrical triols on phosphorylation and deprotection yielded 1,3,5-trisphosphate **54** and 2,4,6-trisphosphate **55** respectively.

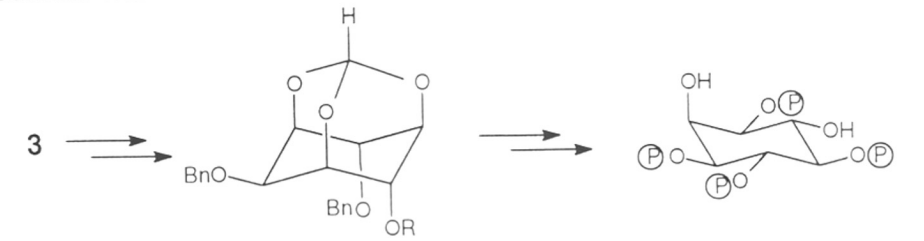
Scheme 1.16



1.6 SYNTHESIS OF *MYO*-INOSITOL TETRAKISPHOSPHATE AND THEIR ANALOGUES

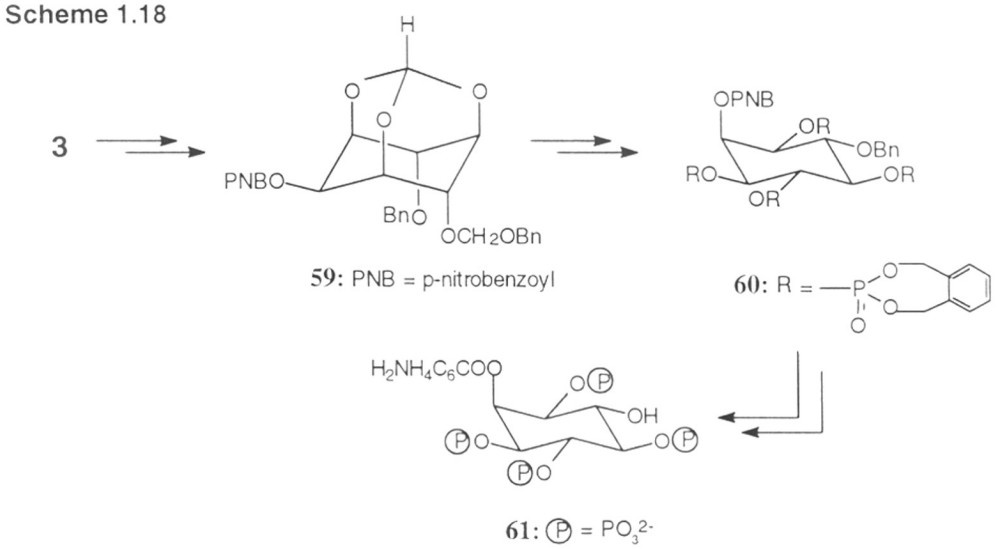
Vacca et al. prepared[57] racemic Ins (1,3,4,5) P_4 (**58**) from the triol **3**. One of the axial hydroxyl groups in **3** was protected as the corresponding benzyloxymethyl ether and the resulting 2,6-diol was benzylated to obtain **56** (**Scheme 1.17**), from which the tetraphosphate **58** was prepared using established procedures. The same tetraphosphate has also been prepared[43, 58] using allyl group to protect one of the axial hydroxyl groups in **3** instead of the benzyloxymethyl group.

Scheme 1.17



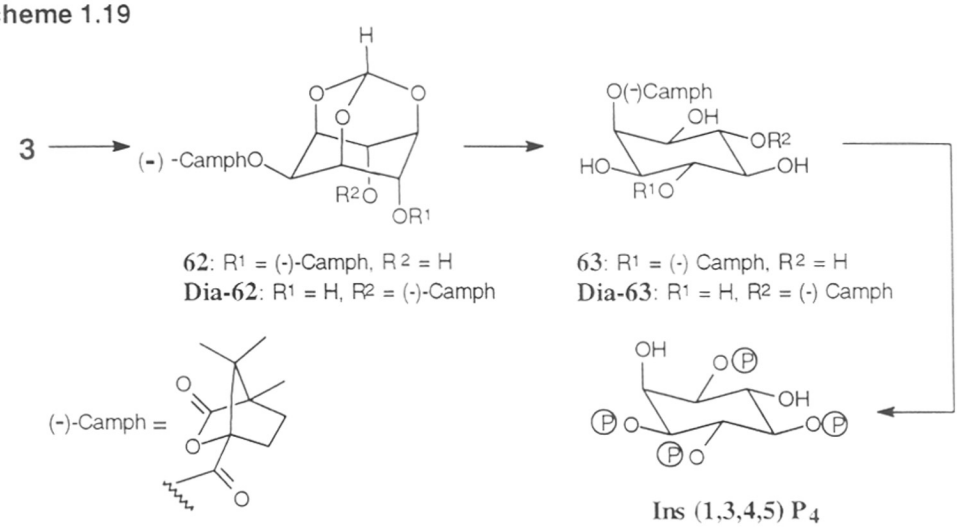
Ozaki et. al. prepared[59] Ins (1,3,4,5) P_4 analog **61** (**Scheme 1.18**) and used it for the isolation of Ins (1,3,4,5) P_4 binding proteins by affinity chromatography. They used a combination of reactions discussed in earlier sections to obtain the desired Ins (1,3,4,5) P_4 analog **61**, starting from **3** *via* the *p*-nitrobenzoate ester **59**.

Scheme 1.18



Recently, Potter et.al.[60] have reported the synthesis of optically active D- and L-Ins (1,3,4,5) P_4 from *myo*-inositol orthoformate **1** *via* the 2,6-di-O-[(-)-ω-camphanoyl]-*myo*-inositol-1,3,5-orthoformate (**62**) and the 2,4-di-O-[(-)-ω-camphanoyl]-*myo*-inositol-1,3,5-orthoformate (**Dia-62**) respectively (**Scheme 1.19**). The diastereomers were separated by flash chromatography and converted to the D- (**63**) and the L-tetrol (**Dia-63**) respectively. **63** and **Dia-63** were phosphorylated to the D- and L-Ins (1,3,4,5) P_4 respectively.

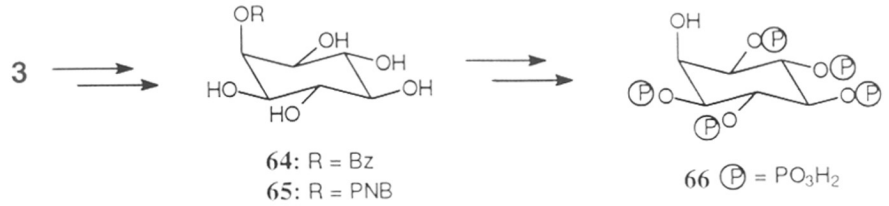
Scheme 1.19



1.7 SYNTHESIS OF *MYO*-INOSITOL PENTAKISPHOSPHATES

The Ins (1,3,4,5,6) P_5 (**66**) (**Scheme 1.20**) and its analogues were prepared from **3** by the selective protection of 2-hydroxyl group in **3** as the corresponding benzoate **64**[59, 61] using benzoyl chloride in pyridine, followed by deprotection of the orthoformate and phosphorylation. The *p*-nitrobenzoate analogue **65** was also prepared and converted to *p*-aminobenzoyl derivative of **66**.

Scheme 1.20

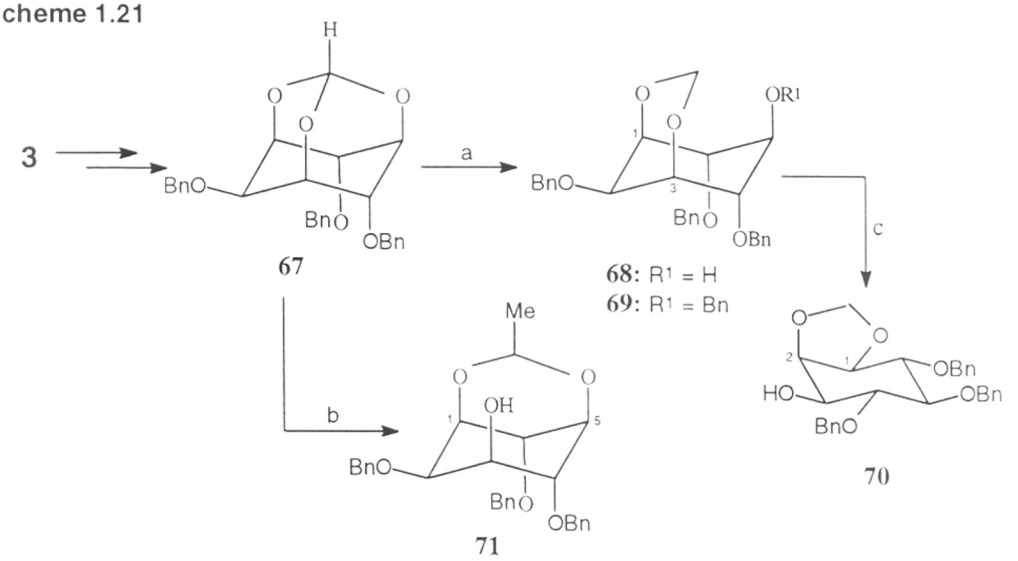


1.8 MISCELLANEOUS APPLICATIONS OF *MYO*-INOSITOL-1,3,5-ORTHOFORMATE (3)

An interesting method to synthesize protected *myo*-inositols, which may be further useful for inositol phosphate synthesis, was reported by Gilbert et al[62, 63]. They selectively cleaved the orthoformate moiety in **67** (**Scheme 1.21**), to obtain the corresponding 1,3- and 1,5-acetals. Use of DIBAL in a mixture of dichloromethane

and hexane at room temperature afforded the 1,3-acetal **68** while the use of trimethylaluminium gave the alkylated 1,5-acetal **71**. This difference in product formation is perhaps due to the increase in bulk of the reducing agent used. Benzylation of **68** gave the corresponding tetra-O-benzyl derivative **69** in which the 2-O-benzyl ether could be selectively removed with titanium (IV) chloride perhaps due to specific coordination of the Lewis acid with three ether oxygens in **69**. This however resulted in acetal migration to give **70**.

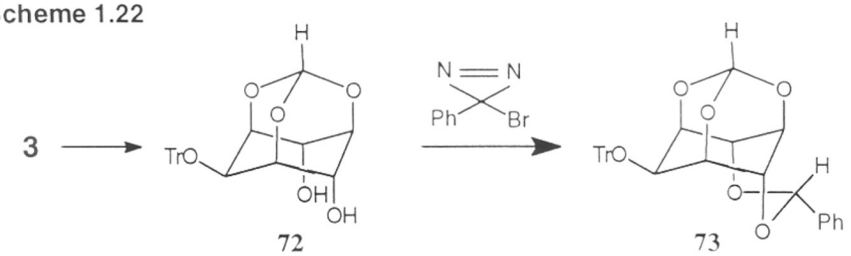
Scheme 1.21



Reagents and conditions: (a) DIBAL (b) Me_3Al (c) $TiCl_4$.

Vasella et al.[64] treated the 2-trityl derivative **72** (**Scheme 1.22**) with phenyl bromodiazirine under basic condition to obtain the benzylidene acetal **73** (93%), as a single diastereomer.

Scheme 1.22

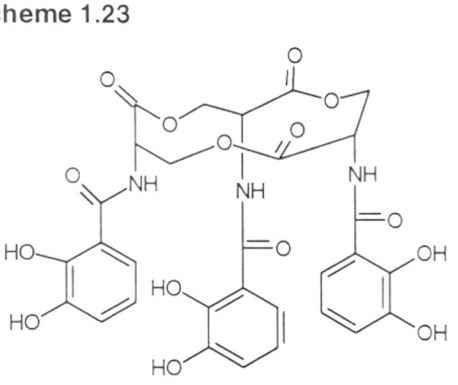


RR
DAS

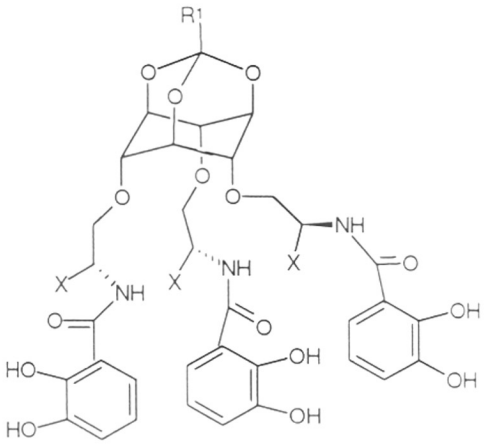
TH-1111

Kishi and Tse attempted to prepare[65] chiral analogues of Enterobactin **74** (**Scheme 1.23**), with hydrophilic and lypophilic properties, for potential medicinal applications.

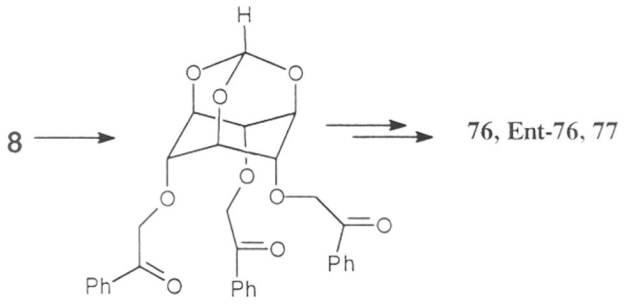
Scheme 1.23



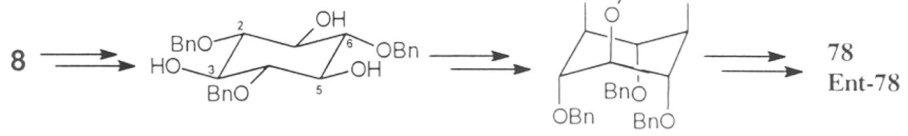
74



76: R^1 = H, X = Ph
Ent-76: Enantiomer of **76**
77: R^1 = X = H
78: R^1 = n-$C_{10}H_{21}$, X = Ph



75



79

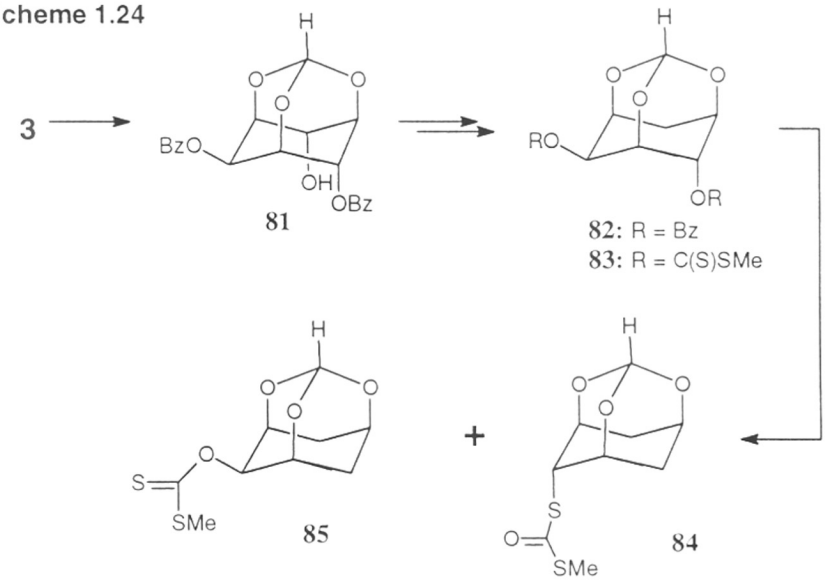
80: R^1 = n-$C_{10}H_{21}$

They converted *scyllo*-inositol-1,3,5-orthoformate (**8**) to the triketone **75**. Asymmetric reduction with Corey's (S)-oxazaborolidine reagent, (CBS), gave stereoselectively the

all- (S)-triol, which was converted to the corresponding chiral enterobactin analogue **76**. Use of (R)-CBS afforded the enantiomer **Ent-76**. They also synthesized the achiral analogue **77**. The lipophilic analog **78** was prepared by the hydrolysis of 1,3,5-tri-O-benzyl-*scyllo*-inositol-orthoformate to 1,3,5-tri-O-benzyl-*scyllo*-inositol **79**, followed by treatment with trimethyl orthoundecanoate to give **80**, which was converted as above to the chiral analogues **78** and **Ent-78**. Binding of ferric ion with **76**, **77** and **78** were studied and their lipophilicities compared.

While investigating the origin of β-oxygen effect in Barton deoxygenation reaction, Crich et. al.[66] required a rigid adamantane system for which **3** was a convenient starting point. The unsymmetrical dibenzoate **81**[67] (**Scheme 1.24**) was converted to the 6-deoxy derivative **82**, which was again converted to the bisxanthate **83**. Deoxygenation of **83** by Barton-McCombie procedure gave the 4,6-dideoxy derivatives **84** and **85** as major products.

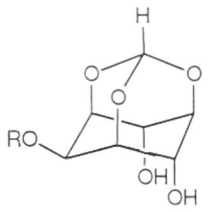
Scheme 1.24



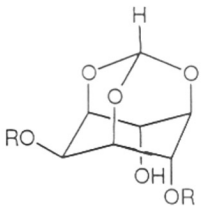
O'Leary et.al. did a systematic NMR spectroscopic study[68] of intramolecular H-bonding in several derivatives of **3** (**Scheme 1.25**). Oxidation of **86** with DMSO/Ac_2O gave the ketone **87**, which was converted to **88** by reaction with methyl magnesiumchloride. This resulted in concomitant loss of the axial TBDMS ether in **87**. **89** was prepared from **87**. The deuterium-isotope effects in ^1H NMR of the diols

and **89** in several solvents and varying temperature showed that the effect was much larger than those found in conformationally mobile systems.

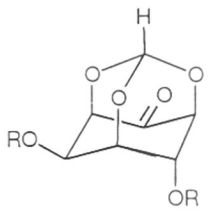
Scheme 1.25



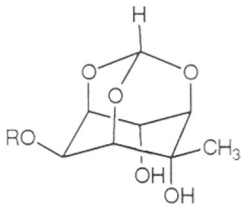
4



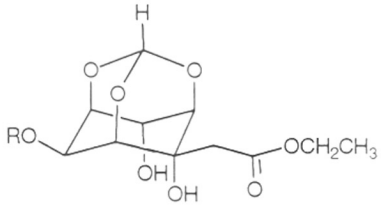
86



87



88



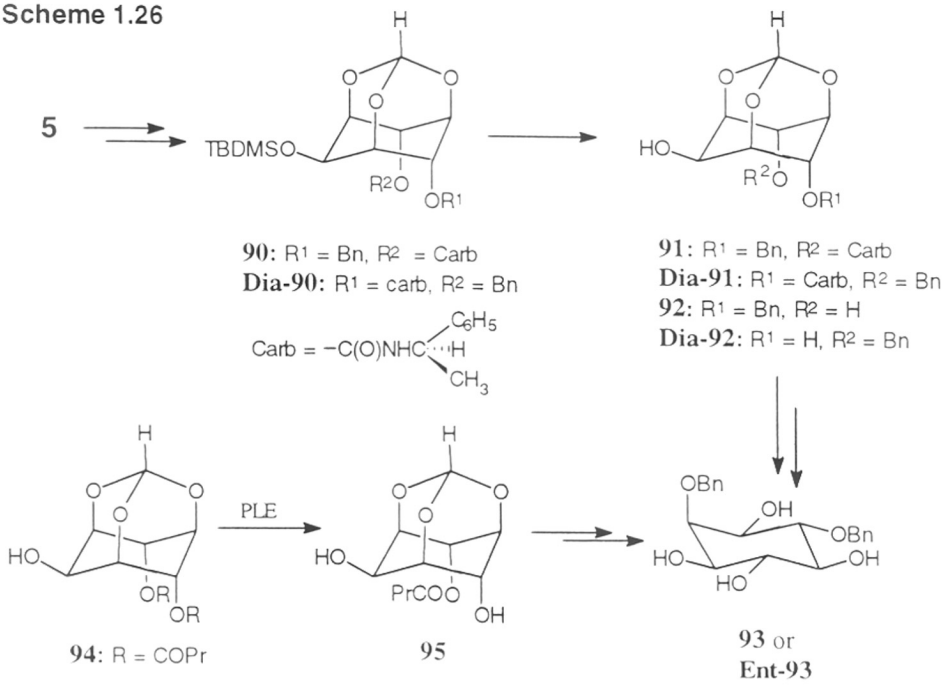
89

R = TBDMS

1.9 DESYMMETRIZATION / RESOLUTION OF *MYO*-INOSITOL-1,3,5-ORTHOFORMATE (3) DERIVATIVES

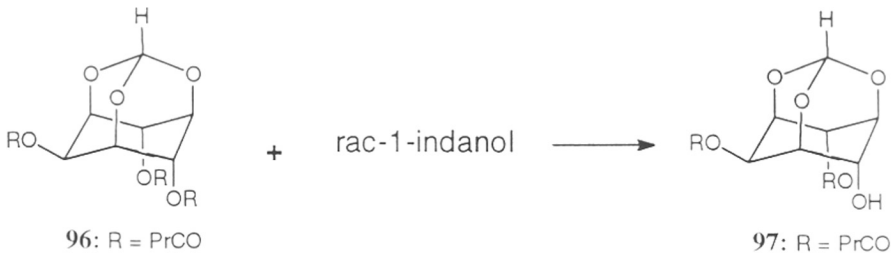
The first attempt to resolve a derivative of **3** was made in 1988 by Vasella and coworkers[10]. They prepared diastereomeric carbamates **90** and **Dia-90** from **5** (**Scheme 1.26**), which could not be separated. Desilylation of a mixture of **90** and **Dia-90** gave the diastereomers **91** and **Dia-91** in 33% and 36.5% yield respectively, which were separable by MPLC. **92** and **Dia-92** formed as a by-product during desilylation of **90** and **Dia-90** were recycled. Deprotection of orthoformate and carbamate groups afforded **93** and **Ent-93** from **92** and **Dia-92** respectively. Although enantiomeric inositol tetraphosphates were synthesized by this approach, this method does not seem to be efficient for the desymmetrization of **3**. They also attempted enantioselective deacylation of several derivatives of **3** by a range of enzymes. Hydrolysis of **94** with PLE gave (-)-butyrate **95** with good enantioselectively (e.e.>95%, 83% yield). Deacylation of **94** was carried out at a pH 6.8 to prevent 1,3-acyl migration between the axial hydroxyl groups. **95** could be converted to both **93** and **Ent-93** respectively.

Scheme 1.26



Another desymmetrization reaction[69], wherein the tributyrate **96** was enantioselectively converted to the 2,6-di-O-butyrate **97** (**Scheme 1.27**) using rac-1-indanol, was reported by Lin and coworkers.

Scheme 1.27

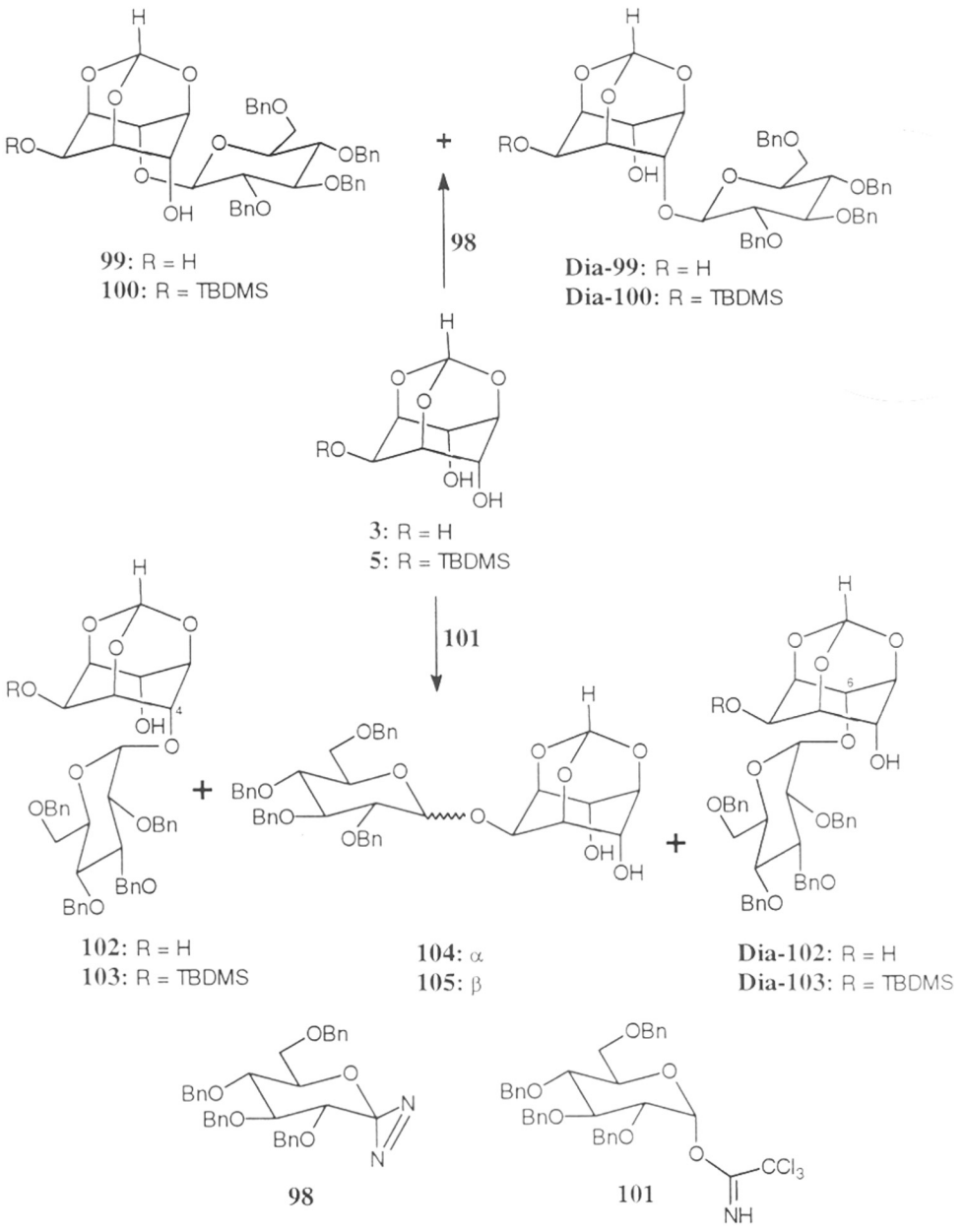


Servi and coworker's attempt[70] for the desymmetrization of **3** by enzymatic acylation with several enzymes failed.

Recently, Potter et.al.[60] have reported the synthesis of optically active D- and L-Ins (1,3,4,5) P_4 by reaction of *myo*-inositol orthoformate **3** with (-)-camphanic acid chloride (**Scheme 1.19**). The diastereomers could be separated by flash chromatography to give the optically pure 2,6- and 2,4-di-O-[(-)-ω-camphanoyl]-*myo*-

inositol-1,3,5-orthoformate (**62** and **Dia-62**). These were further converted to the optically pure D- and L- Ins (1,3,4,5) P_4.

Scheme 1.28



Vasella and coworkers have studied[10] and compared (**Scheme 1.28**) the glycosidation of the orthoformates **3** and **5**. The diol **5** reacted with azisugar **98** to give α-D-glycosides **100** and **Dia-100** in the ratio 1:1 in good yield. The triol **3** reacted with **98** to give 1:1 mixture of the α-D-glycosides **99** and **Dia-99** resulting exclusively from the monoglycosidation of the axial hydroxyl groups. Glycosidation of **5** with the trichloroacetimidate **101** gave four isomers (**102**, **Dia-102**; **103**, **Dia-103**) whereas the reaction of **3** with **101** afforded all six monoglycosilated products (**102**, **Dia-102**; **103**, **Dia-103**; **104**, **105**). The orthoformates **3** and **5** undergo glycosidation with azisugar **98** exclusively at the axial position due to intramolecular H-bonding between them[71]. This results in an increase in the acidity for one of the axial hydroxyl groups which results in diastereoselectivity during the glycosylation of the diol **5** and regioselectivity during the glycosylation of the triol **3**.

1.10 CONCLUSIONS

Myo-inositol orthoformate is a useful intermediate for the preparation of a variety of *myo*-inositol derivatives. *Myo*-inositol orthoformate exhibits interesting chemistry due to inherent conformational rigidity and the presence of 1,3-diaxial hydroxyl groups. Development of efficient methods for the desymmetrization of *myo*-inositol-orthoformate is necessary, which is essential for its conversion to enantiomerically pure *myo*-inositol derivatives of biological significance.

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CHAPTER 2

2,4-Di-O-benzoyl-*myo*-inositol-1,3,5-orthoformate: A versatile intermediate for the synthesis of inositol derivatives

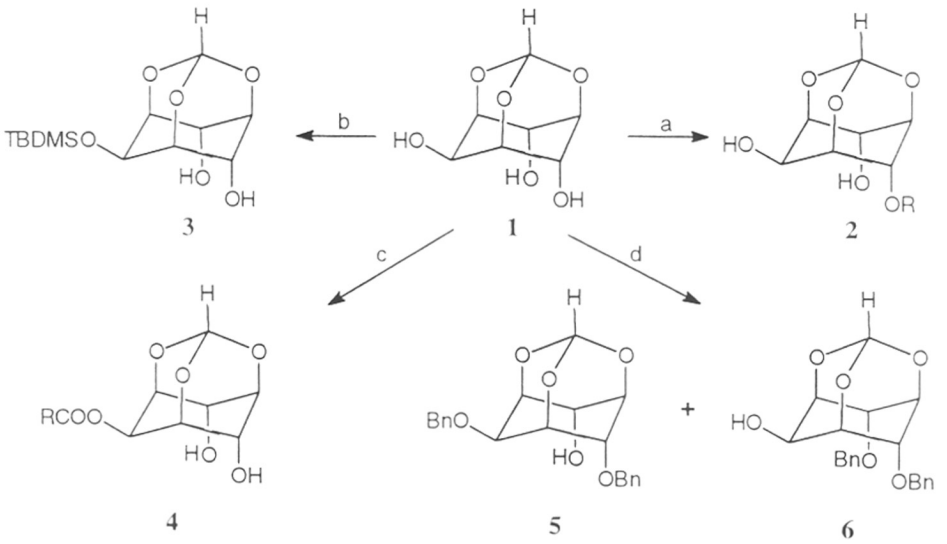
2.1 INTRODUCTION

A survey of the recent literature on *myo*-inositol-1,3,5-orthoformate (presented in **Chapter I**) shows that it is widely used for the preparation of phosphorylated inositol derivatives. Although *myo*-inositol orthoformate has been prepared in gram quantities and the differential reactivity of its axial and equatorial hydroxyl groups was known, there are no reports on the preparation of unsymmetrical O-substituted derivatives of *myo*-inositol orthoformate using simple procedures. This chapter presents a convenient one pot procedure for the preparation of racemic 2,4-di-O-benzoyl-*myo*-inositol-1,3,5-orthoformate in gram quantities and its conversion to key intermediates for the preparation of several *myo*-inositol phosphates and to racemic ononitol.

2.2 RESULTS AND DISCUSSION

The equatorial and axial hydroxyl groups of *myo*-inositol orthoformate **1** can be selectively functionalised under different reaction conditions.

Scheme 2.1

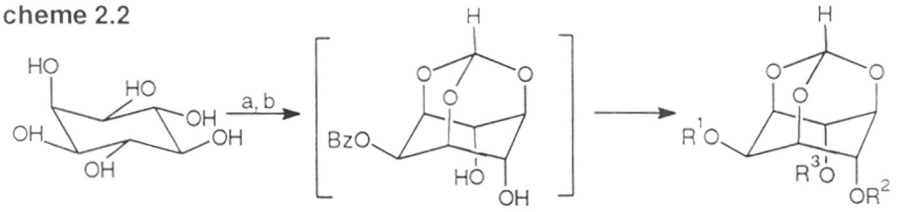


Reagents and conditions: (a) NaH, RX (1 eq.) (b) TBDMS-Cl, Imidazole (c) RCOCl, Pyr, DMAP (d) NaH, RX (2 eq.).

It had been observed that the reactivity of the 4,6-axial hydroxyl groups and 2-equatorial hydroxyl group towards O-acylation or O-alkylation depended on the base used to carry out the O-substitution. For instance, with one equivalent of alkyl halide in the presence of sodium hydride, alkylation of **1** took place exclusively at one of the axial hydroxyl groups[1] to give **2** (**Scheme 2.1**). In contrast, the reaction of one equivalent of TBDMS-Cl in the presence of a mild base like imidazole resulted in O-substitution at the equatorial hydroxyl group[2] predominantly to give **3** (48%). Similarly acylation of **1** with benzoyl chloride or *p*-nitrobenzoyl chloride in the presence of DMAP in pyridine[3] gave the corresponding 2-O-acyl derivative **4** (see **Section 1.9, Chapter 1**).

Dibenzylation of **1** with two equivalents of benzyl bromide in the presence of sodium hydride[1] gave a mixture of two dibenzylated products **5** and **6** from which the diaxial ether **6** was isolated in 30-40% yield. Hence, we theorized that the reaction of *myo*-inositol-1,3,5-orthoformate **1** with two equivalents of benzoyl chloride in the presence of pyridine should result in the formation of the unsymmetrical 2,4-di-O-benzoyl derivative **8** as shown in **Scheme 2.2**.

Scheme 2.2



7

8: $R^1 = R^2 = Bz$, $R^3 = H$ (major)
9: $R^1 = R^2 = R^3 = Bz$ (minor)
10: $R^1 = Bz$, $R^2 = R^3 = H$ (minor)
11: $R^1 = H$, $R^2 = R^3 = Bz$ (not formed)

Reagents and conditions: (a) $HC(OEt)_3$, DMF, pTSA, 100 °C, 3 h (b) BzCl (2.5 eq.), Pyr, 24 h, r.t.

Myo-inositol-1,3,5-orthoformate (**1**) prepared by the reaction of *myo*-inositol (**7**) with triethyl orthoformate in the presence of *p*-TSA in DMF was benzoylated *in situ* with 2.5 equivalents of benzoyl chloride in the presence of excess of pyridine. Analysis of the reaction mixture by TLC indicated the presence of a major product and two minor products. Neutralization with triethylamine, removal of DMF *in vacuo* followed by dilution with methanol and cooling gave crystals of the dibenzoate **8**. The

minor products, triester **9** and the diol **10** were isolated by column chromatography from the mother liquor.

IR spectrum of the major product showed the presence of hydroxyl group (3500 cm^{-1}) and two non-equivalent carbonyl groups (1726, 1711 cm^{-1}). The ^1H NMR spectrum of the same sample showed one hydroxyl proton (exchangeable with D_2O) and ten aromatic hydrogens along with five distinct peaks with peak integration ratios of 1: 2: 1: 2: 1 (**Figure 1**). The orthoformate proton appeared at δ 5.60 as a doublet (J = 1.1 Hz) as has been observed in other *myo*-inositol orthoformate derivatives[1,3]. The six inositol ring hydrogens appeared as five multiplets in the ratio 1: 2: 1: 1: 1 between δ 4.75 and δ 5.85. The long range couplings between protons make the ^1H NMR spectrum of *myo*-inositol orthoformate derivatives complicated and hence assignment of ring protons to each signal is not straightforward. However the ^1H NMR spectrum clearly showed that the major product obtained is a dibenzoate ester of *myo*-inositol orthoformate. The ^{13}C NMR spectrum of this dibenzoate clearly showed the presence of six distinct inositol ring carbons, the orthoformate carbon (103.6 ppm), the two carbonyl carbons (165.4, 166.5 ppm) and aromatic carbons (**Figure 2**). This is consistent with the unsymmetrical structure assigned to the dibenzoate **8**. If the major product had been the symmetrical 4,6-dibenzoate **11**, the only other isomeric dibenzoate derivative of the orthoformate **1** possible, then the ^{13}C NMR spectrum should have shown four inositol ring carbons and one carbonyl carbon since C_4, C_6 and C_1, C_3 would be equivalent due to the presence of a plane of symmetry passing through C_2 and C_5 of the *myo*-inositol ring (see **Scheme 1.3, Chapter I**). The unsymmetrical structure of the dibenzoate **8** was established beyond doubt by single crystal X-ray crystallography. Good quality crystals for X-ray diffraction studies could be obtained by crystallizing the dibenzoate **8** from a mixture of chloroform and petroleum ether.

The single crystal X-ray diffraction data of the dibenzoate **8** showed the presence of two molecules in the asymmetric unit which are related by pseudo-inversion centre (**Figure 3**). The two molecules form a compact dimer. The Van der waals contacts and edge-to-face interaction between two pairs of benzene rings are responsible for strong association between the molecules. The molecule of **8** is L-shaped so that there is snug fit between the two centrosymmetrically - related molecules. Besides, the molecules share two pairs of phenyl rings in the energetically favored edge-to-face orientation such that two C-H protons of one point towards electron rich central core of the other. Even the two central rings are parallel such

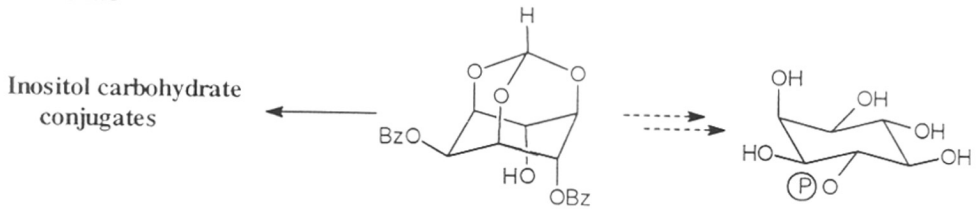
that their C-H and C=O bonds are stagerred with respect to each other, thus providing further electrostatic stabilization.

The minor product with higher R_f (0.7, eluent 20% ethyl acetate – light petroleum) was shown to be the tribenzoate **9** by IR, NMR and X-ray crystallography. The IR spectrum showed presence of a broad peak for two carbonyl groups (1750-1760 cm^{-1}) and the ^1H NMR spectrum showed the presence of one orthoformate proton (δ 5.80), six *myo*-inositol ring protons and fifteen aromatic protons (**Figure 4**). The six inositol ring protons appeared as four signals in the ratio 1: 2: 2: 1 indicating the symmetric nature of the tribenzoate **9**. The ^{13}C NMR spectrum showed only four signal for the six inositol ring carbons, one orthoformate carbon, two carbonyl carbons (165.4, 166.5 ppm) and aromatic carbons (**Figure 5**). The structure of **9** was also confirmed by single crystal X-ray analysis. The ORTEP diagram of the tribenzoate **9** is shown in **Figure 6**.

The other minor product with lower R_f (0.2, eluent 20% ethyl acetate - light petroleum) was the symmetrical diol **10** whose structure was established by IR and NMR spectroscopy. IR spectrum of **10** showed the presence of hydroxyl group (3400 cm^{-1}) and a carbonyl group (1720 cm^{-1}). ^1H NMR spectrum showed the presence of two hydroxyl protons δ 5.35 (D_2O exchangeable) and the orthoformate proton at δ 5.20, six inositol ring protons in the ratio 1:2:2:1 and five aromatic protons (**Figure 7**). The appearance of the hydroxyl protons at δ 5.35 suggests the presence of intramolecular hydrogen bonding between the axial hydroxyl groups as has been observed for *myo*-inositol orthoformate **1**[4]. The ^{13}C NMR spectrum showed an orthoformate carbon (101.8 ppm), aromatic carbons, four signals for inositol ring carbons and one carbonyl carbon at 165.2 ppm as is expected of the symmetrical monobenzoate **10** (**Figure 8**).

The synthetic utility of the dibenzoate **8** is demonstrated by its conversion to several protected *myo*-inositol derivatives, which are the key intermediates for the preparation of *myo*-inositol phosphates. We have not carried out phosphorylation of these derivatives as methods for the phosphorylation of protected inositol derivatives are well established. The dibenzoate **8** itself can be phosphorylated directly at the 6 (or 4)-hydroxyl group to give Ins (4) P (**Scheme 2.3**), which has been prepared by the direct phosphorylation of **1** at the 4-position using tetrabenzyl pyrophosphate and sodium hydride[1]. The dibenzoate **8** can also be glycosylated at C_6 position to prepare inositol – carbohydrate conjugates, which are part of GPI anchors of proteins to cell membranes[5].

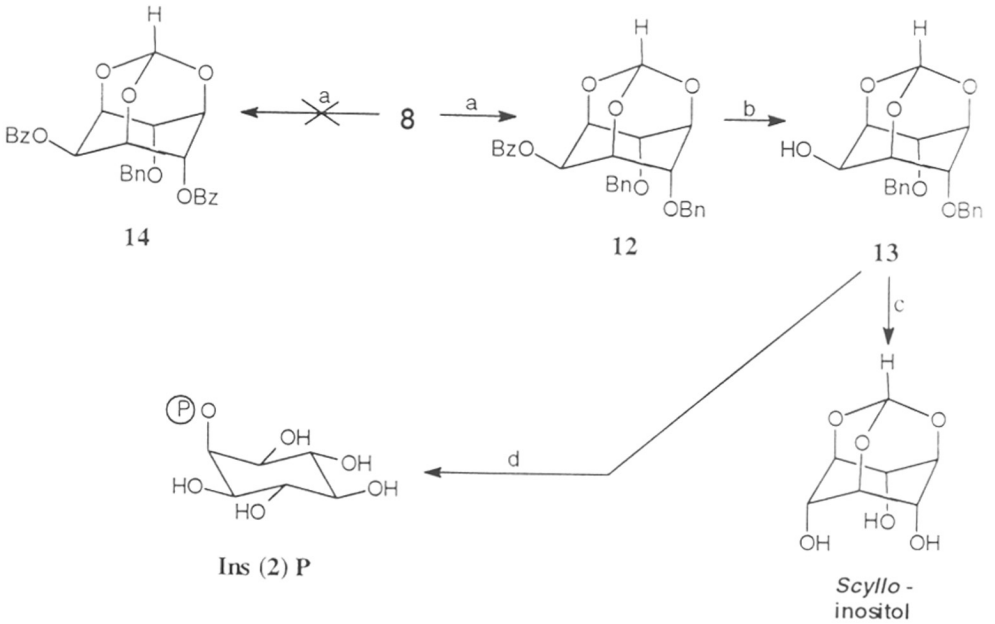
Scheme 2.3



8 Ins (4) P

Reaction of the dibenzoate **8** with excess benzyl bromide in the presence of excess silver (I) oxide yielded the symmetrical 4,6-dibenzyl ether **12** in 80% yield (**Scheme 2.4**) instead of the expected monobenzyl ether **14**.

Scheme 2.4



14 12 13

Ins (2) P

Scyllo - inositol

Reagents and conditions: (a)BnBr, Ag_2O, DMF, 66 h (b) t-Butyl amine, MeOH, reflux
(c) Oxidation - reduction as in reference 2 (d) As in reference 1.

This was unusual, since silver (I) oxide is a well known reagent used for the O-alkylation of hydroxy esters as it does not affect ester groups (a detailed investigation of this reaction is presented in subsequent chapters). Structure of the 4,6-di-O-benzyl ether **12** was established by IR and NMR spectroscopy as well as its conversion to the known **13**[1]. The IR spectrum of **12** showed one peak for the ester carbonyl group (1740 cm^{-1}). The ^1H NMR spectrum showed besides fifteen aromatic protons and the orthoformate proton (δ 5.70), four benzylic protons appearing as a singlet at δ 4.75 which indicated the symmetrical nature of the molecule (**Figure 9**). The ^{13}C NMR spectrum of **12** showed the presence of one carbonyl carbon (166.3 ppm), one orthoformate carbon (103.5 ppm) and four signals for inositol ring carbons and one benzylic carbon thereby indicating that the benzyl groups are present in the 4,6-diaxial position (**Figure 10**). The expected monobenzyl ether **14** would have shown two benzylic protons in the ^1H NMR spectrum and the ^{13}C NMR spectrum would have shown two carbonyl carbons and six distinct *myo*-inositol ring carbons besides one benzylic carbon. The dibenzyl ether **12** on aminolysis gave the known **13**. Preparation of **13** has been reported earlier[1], as an intermediate for the synthesis of Ins (2) P, by the direct benzylation of *myo*-inositol-orthoformate **1** in the presence of sodium hydride followed by chromatographic purification (see **Section 1.3, Chapter 1**). The yield of **13**, starting from *myo*-inositol-1,3,5-orthoformate (**1**) (**Scheme 2.1**) was 30-40%. In another report[2], **13** was prepared from **1** *via* the TBDMS ether **3** in two steps and in 40-50% overall yield. The present procedure gives the symmetrical diether **13** in an overall yield of 80% starting from the dibenzoate **8**. The dibenzyl ether **13** is also the key intermediate for the preparation of *scyllo*-inositol[2].

Heating the diester **8** in pyridine / methanol (1:5 v/v) at 50°C, resulted in the preferential solvolysis of the axial 4-benzoate (**Scheme 2.5**) to afford the diol **10** in 75% yield. The diol **10** can be phosphorylated to obtain Ins (4,6) P_2 or converted to Ins (1,3,4,5,6) P_5 using known procedures[3] (**Scheme 2.5**). The preferential base catalyzed methanolysis of the axial 4-benzoate in the dibenzoate **8** was observed, although the equatorial ester groups are known to undergo base catalyzed solvolysis (or hydrolysis) much more readily as compared to the corresponding axial ester groups. The steric requirement of the tetrahedral transition state being greater than that of the ground state, crowding around axial substituent produces steric hindrance and consequently the axial ester group undergoes hydrolysis or solvolysis at a slower rate than the corresponding equatorial ester group.

Scheme 2.5

Ins (4,6) P_2

Reagents and conditions: (a) MeOH, Pyr, 50 °C.

For instance, the equatorial benzoate **15** undergoes base catalyzed hydrolysis 2.5 times faster than the corresponding axial benzoate **16**[6] (**Scheme 2.6**).

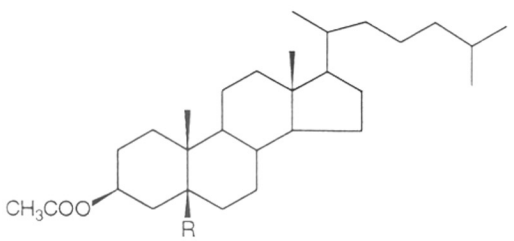
The reversal of reactivity observed for the methanolysis of the axial and the equatorial benzoate groups in case of the diester **8** point to the intramolecular assistance by the axial hydroxyl group at the 6-position for the base catalyzed solvolysis of the axial 4-benzoate. The acceleration of ester solvolysis or hydrolysis by a neighbouring hydroxyl group in coprostane-3β, 5β-diol 3-monoacetate **18** has been reported[7,8] (**Scheme 2.6**).

Scheme 2.6

15

16

$R = C_6H_4NO_2$-p, $k_{15}/k_{16} = 2.5$



Coprostane - 3β,5β - diol 3 - monoacetate

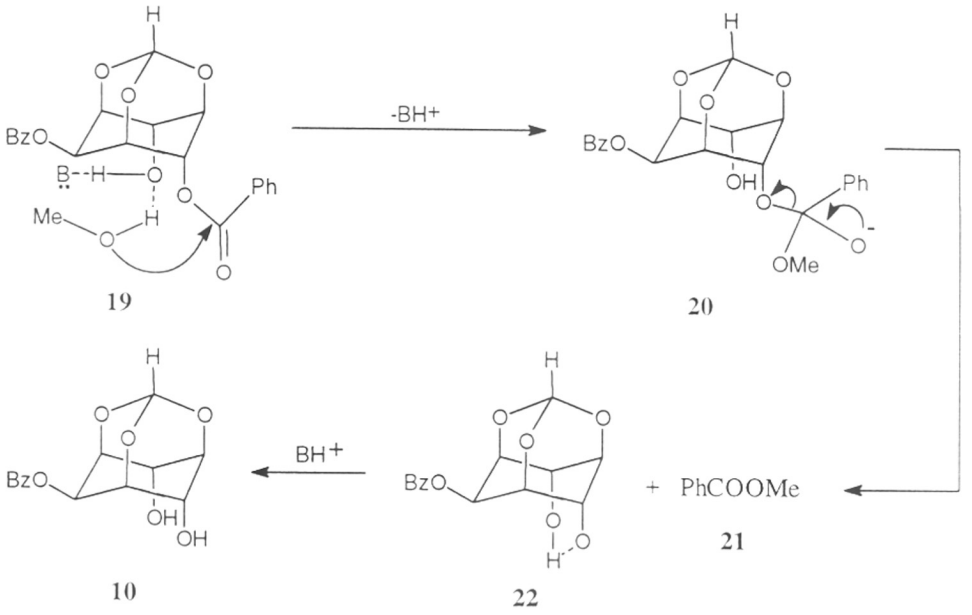
Relative rates **17** R = H : 1
18 R = OH : 300

The occurrence of intramolecular catalysis by the free axial hydroxyl group was established by the fact that derivatives of the dibenzoate **8** in which the axial 6-hydroxyl group is blocked (tribenzoate **9** and Thp-ether **23**) failed to undergo solvolysis under the condition used for the dibenzoate **8**. The tribenzoate **9** and the Thp-ether **23** could be recovered quantitatively after treatment with methanol /

pyridine at 50°C for 24 hrs. A possible mechanism for the base catalyzed methanolysis of the axial benzoate in **8**, with intramolecular assistance of the 6-hydroxyl group, is shown in **Scheme 2.7**.

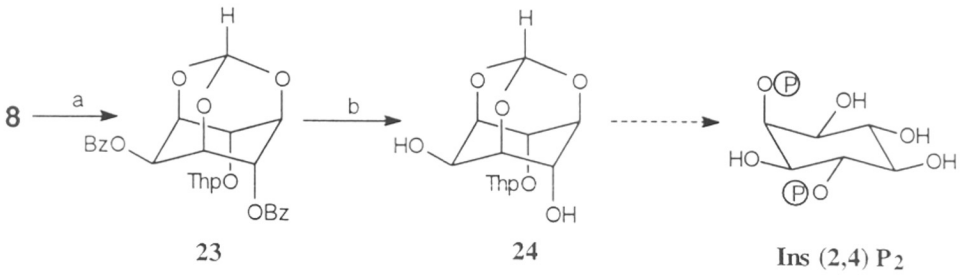
The dibenzoate **8** undergoes base catalyzed transesterification with facility (in the absence of hydroxylic solvent or water) in solid state as well as in solution, to give the triester **9** and the diol **10**[9]. This could be the reason for the formation of the triester **9** and the diol **10** in approximately 1:1 ratio during the preparation of the dibenzoate **8**.

Scheme 2.7



The free 6-hydroxyl group of the dibenzoate **8** could be protected as the tetrahydropyranyl ether to obtain **23** (**Figure 11**, **12**) as a mixture of diastereomers (**Scheme 2.8**) which on aminolysis with *t*-butylamine in methanol afforded the 2, 4-diol **24** (mixture of diastereomers) (**Figures 13**). The diol **24** is a precursor for the synthesis of Ins (2,4) P_2

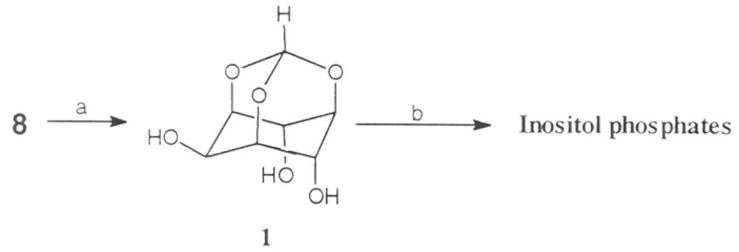
Scheme 2.8



Reagents and conditions: (a) DHP, PpTs, DCM (b) t-Butylamine, MeOH, reflux.

The diester **8** on refluxing with *t*-butyl amine in methanol affords *myo*-inositol-orthoformate **1** (**Scheme 2.9**) in quantitative yield. Hence this route is an alternative procedure for the preparation of the triol **1** in gram quantities, without the use of chromatography. Procedures for the preparation of several *myo*-inositol phosphates from **1** is available in the literature (see **Chapter 1**).

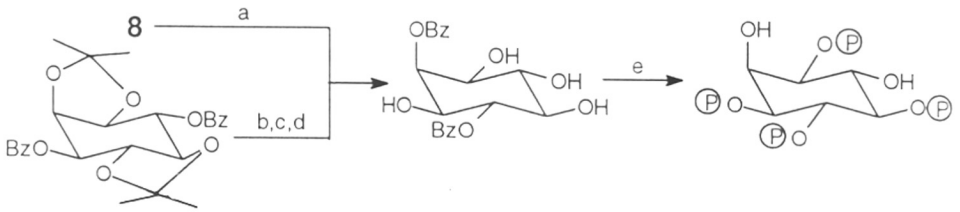
Scheme 2.9



Reagents and conditions: (a) t-Butylamine, MeOH, reflux (b) As in **Chapter 1.**

Methanolysis of the dibenzoate in the presence of *p*TSA gave the tetrol **25** **(Scheme 2.10)**. Neutralization of *p*TSA with triethyl amine resulted in migration of the benzoate groups to other hydroxyl groups and the pure tetrol **25** could not be isolated. Base catalyzed intramolecular migration of acyl group resulting in a mixture of all possible O-acyl *myo*-inositol derivatives is known in the literature[10-13]. Hence, in order to isolate the pure tetrol **25**, the residue obtained after removal of the solvent was filtered directly over silica gel to remove *p*TSA. Using this base free procedure, the tetrol **25** was isolated in quantitative yield. The purity of the sample was established by comparison of ^{1}H NMR spectrum and m.p. of **25** with those known in the literature[14]. The tetrol **25** is a precursor for the synthesis of Ins (1,3,4,5) P_4.

Scheme 2.10

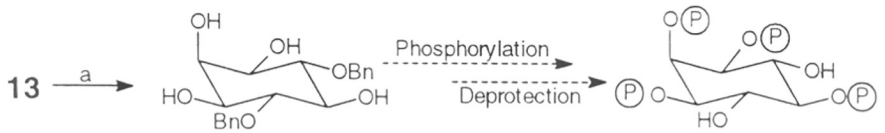


Reagents and conditions: (a) pTSA, MeOH, DCM (b) H^+, MeOH (c) Pyridine (d) Crystallization (e) As in reference 14 .

Meek et. al. have prepared[14] Ins (1,3,4,5) P_4 from the tetrol **25** which they obtained from 3,6-di-O-benzoyl-1,2:4,5-di-O-isopropylidene-*myo*-inositol (**26**) in two steps (overall yield 18%). They isomerised 1,4-di-O-benzoyl-*myo*-inositol to a mixture of benzoates using pyridine, and isolated the required tetrol **25** by crystallization. But the present method yields the tetrol **25** as a single isomer in quantitative yield from the dibenzoate **8**. None of the steps (starting from *myo*-inositol) involve column chromatography or any expensive reagents. Hence this sequence of reactions constitute the shortest formal synthesis of racemic Ins (1,3,4,5) P_4. Recently, Potter et.al.[15] have reported the synthesis of optically active D- and L-Ins (1,3,4,5) P_4 *via* the 2,6- and the 2,4-di-O-(-)-camphanate esters of *myo*-inositol orthoformate **1** respectively (see **Chapter 1, Section 1.6**).

Cleavage of the orthoformate moiety in the dibenzyl ether **13** affords the 1,2,3,5-tetrol **27** which can be phosphorylated to obtain Ins (1,2,3,5) P_4 (**Scheme 2.11**).

Scheme 2.11

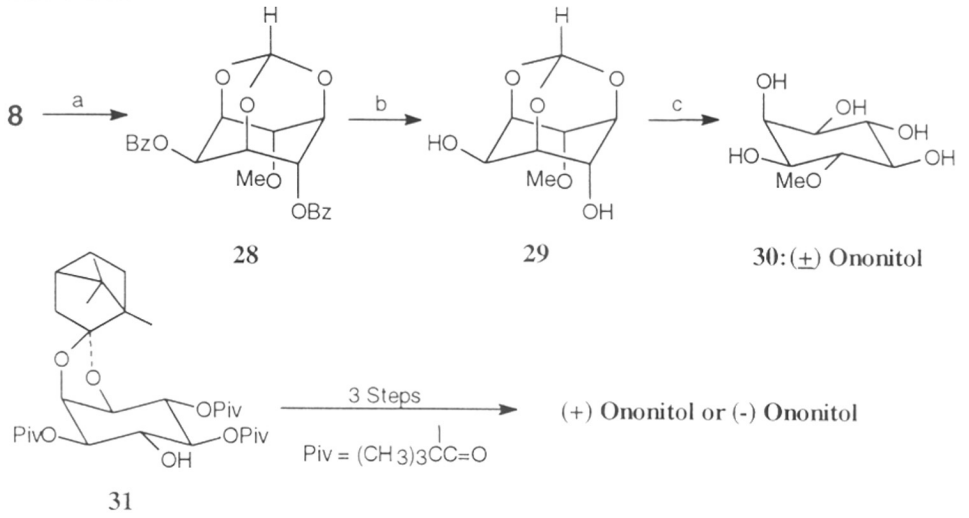


Reagents and conditions: (a) pTSA, MeOH

The 1,2,3,5-tetrol **27** has been prepared earlier[2.16] from *myo*-inositol orthoformate **1** in three steps *via* the TBDMS ether **3** (**Scheme 5 and 6, Chapter 1**) and was converted to D-Ins (1) P.

The dibenzoate **8** could be converted to the corresponding methyl ether **28** using methyl iodide and silver (I) oxide (**Scheme 2.12**) in 80% yield.

Scheme 2.12



Reagents and conditions: (a) MeI, Ag_2O, DMF, 2 h (b) t-Butyl amine, MeOH, reflux (c) pTSA, MeOH.

The IR spectrum of **28** showed a broad peak at 1730 cm^{-1}. The ^1H NMR spectrum showed one singlet for the methyl group (δ 3.40), five signals for the inositol ring protons in the ratio 1:2:1:1:1, one orthoformate proton (δ 5.70) and ten aromatic protons indicating the presence of two benzoate groups (**Figure 14**). The ^{13}C NMR spectrum of **28** showed the presence of one methyl carbon, one orthoformate carbon (103.4 ppm), six distinct ring carbons, two carbonyl carbons and aromatic carbons as expected for the monomethyl ether **28** (**Figure 15**). The benzoate groups of **28** were then removed by reaction with t-butyl amine. The orthoformate moiety in **29** (not isolated) was removed using *p*-TSA / methanol to obtain (±)-Ononitol **30**. Optically active (+) and (-)-ononitol have earlier been prepared[11] in five steps from *myo*-inositol by methylation of the key intermediate **31** with silver (I) oxide and methyl iodide followed by deprotection. Conditions for methylation of **31** had to be controlled carefully to avoid intramolecular migration of pivaloyl groups.

2.3 CONCLUSIONS

The dibenzoate **8** has been prepared in a simple one pot procedure in gram quantities starting from commercially available *myo*-inositol. This procedure allows the protection of five of the six hydroxyl groups present in *myo*-inositol in a single step. Since the 2,4-dibenzoate **8** has 6-hydroxyl group free, it is a useful intermediate for the preparation of inositol-carbohydrate conjugates, which form part of the GPI anchors. Versatility of racemic 2,4-di-O-benzoyl-*myo*-inositol-1,3,5-orthoformate (**8**) as an important synthon for the synthesis of several *myo*-inositol phosphates has been demonstrated by its conversion to several key intermediates known in the literature, using simple procedures. The results presented in this chapter constitutes formal synthesis of Ins (2) P, Ins (4) P, Ins (1,3,4,5) P_4 and Ins (1,3,4,5,6) P_5 starting from *myo*-inositol.

2.4 EXPERIMENTAL SECTION

Materials and methods:- Benzyl bromide, triethyl orthoformate and dihydropyran were obtained from Aldrich Chemical Company, USA and used as received. Benzoyl chloride, *t*-butyl amine, dimethyl formamide, methanol, methyl iodide, anhydrous sodium sulfate, silver nitrate, pyridine, triethyl amine, pTSA, and silica gel (60-120 mesh) for column chromatography were obtained from SD Fine Chemicals, India. All the solvents used, benzoyl chloride and pTSA were purified according to literature procedures[17]. Silver (I) oxide was prepared from silver nitrate as reported[18]. PpTs was prepared as reported[19]. Light petroleum refers to the 60-80°C boiling fraction of petroleum ether. TLC was performed on Merck pre-coated 60 F_{254} plates and the spots were rendered visible either by UV light or by spraying the plates with concentrated sulfuric acid followed by charring. "Usual workup" implies washing of the organic layer with water followed by brine, drying over anhydrous sodium sulfate and removal of solvent *in vacuo* using Buchi rotavapor.

Infrared spectra of solids were recorded as nujol mull and liquids / gums as neat (smear) or in chloroform solution unless otherwise stated. NMR spectra (200 MHz for ^1H) were recorded on Bruker ACF 200 spectrometer or Bruker MSL 300 NMR spectrometer in $CDCl_3$ solution (unless otherwise specified) at ambient temperature. Chemical shifts (δ) reported are referred to internal TMS. Microanalytical data were obtained from CHNS-O EA 1108 Elemental Analyzer. All the melting points reported are uncorrected and were recorded using an electrothermal melting point apparatus.

Preparation of racemic 2, 4-di-O-benzoyl-*myo*-inositol-1, 3, 5-orthoformate (8):

A mixture of *myo*-inositol (10.8 g, 0.06 mole), triethyl orthoformate (13.32 g, 15 ml, 0.09 mole), dry DMF (100 ml) and *p*TSA (1 g, 0.005 mole) was heated at 100°C for 3 h. The clear solution obtained was allowed to cool to room temperature and neutralized with dry triethyl amine (4 ml). Ethanol formed was removed by co-evaporation with dry benzene (2 x 10 ml). Pyridine (24 ml) was added and the solution cooled to 0°C, and benzoyl chloride (18 ml, 0.15mole) was added dropwise over a period of 30 mins. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was concentrated to a thick jelly and diluted with methanol (100 ml) and kept in the fridge for 24 h when a white solid precipitated out. It was filtered, washed with methanol and crystallized from chloroform – light petroleum mixture to obtain pure dibenzoate

8 (6.1 g, 25%). The mother liquor was concentrated, dissolved in chloroform (300 ml), washed successively with 0.1 N HCl solution (200 ml), water (2 x 200 ml), 1% sodium bicarbonate solution (200 ml) and water (2 x 200 ml) and the organic phase was dried over anhydrous sodium sulfate. The chloroform solution was evaporated to half its volume and light petroleum was added to it. Crystals of the dibenzoate **8** appeared which was separated and recrystallized from chloroform – light petroleum (4.74 g, 20%). The filtrate was concentrated, again triturated with methanol and stored in the fridge to obtain a further quantity of the dibenzoate **8** (1.1 g, 4.6%). The products in the mother liquor were separated by column chromatography to obtain **8** (2.5 g, 10%), triester **9** (3.2 g, 11%) and the diol **10** (2 g, 11%).

Data for 8:

m.p. 163-164°C.

IR (cm^{-1}): 3500, 1726, 1711.

^{1}H NMR: 2.70 (d, 1H, D_2O exchangeable), 4.50 (m, 1H), 4.65 (m, 2H), 4.75 (m, 1H), 5.65 (m, 2H), 5.85 (m, 1H), 7.45 (m, 4H), 7.65 (m, 2H), 8.05 (dd, 2H), 8.20 (dd, 2H).

^{13}C NMR: 64.1, 67.7, 68.8, 69.9, 72.1, 103.2, 128.7, 128.9, 129.2, 129.7, 130.2, 133.8, 133.9, 165.4, 166.5.

Elemental analysis calcd. for $C_{21}H_{18}O_8$: C, 63.31%, H, 4.55%.
Found: C, 62.79%, H, 4.79%.

Data for 9:

m.p. 216-218°C.

IR (cm^{-1}): 1740, 1750(s).

^{1}H NMR: 4.70 (m, 2H), 5.00 (m, 1H), 5.75 (t, 1H), 5.80 (d, 1H), 5.90 (t, 2H), 7.15-7.30 (m, 4H), 7.45-7.70 (m, 5H), 7.95-8.05 (m, 4H), 8.10-8.30 (m, 2H).

^{13}C NMR: 64.1, 67.4, 68.7, 69.7, 103.6, 128.7, 128.8, 129.6, 130.1, 130.2, 133.8, 165.4, 166.5.

Elemental analysis calcd for $C_{28}H_{22}O_9$: C, 66.93%, H, 4.38%.
Found: C, 66.58%, H, 4.82%.

Data for 10:

m.p. 210-213°C;

IR (cm^{-1}): 1720, 3400-3450.

^{1}H NMR ($CDCl_3$-DMSO-d_6): 3.92 (m, 1H), 4.05 (m, 2H), 4.20 (m, 2H), 5.20 (dd, 2H), 5.35 (d, 2H, D_2O-exchangeable), 7.15-7.30 (m, 3H), 7.80 (m, 2H).

^{13}C NMR ($CDCl_3$-DMSO-d_6): 63.3, 67.1, 68.4, 71.7, 101.8, 127.9, 129.2, 132.7, 165.2.
Elemental analysis calcd. for $C_{14}H_{14}O_7$: C, 57.16%, H, 4.76%.
Found: C, 57.17%, H, 5.16%.

Preparation of 2-O-benzoyl-*myo*-inositol-1,3,5-orthoformate (10):

The dibenzoate **8** (1.5 g, 3.8 mmol) was heated with pyridine (18 ml) in methanol (90 ml) for 24 h at 50°C. The reaction mixture was allowed to attain room temperature and the solvent evaporated. The residue was crystallized (methanol-chloroform) to obtain the diol **10** (0.58 g, 53%). A further quantity of **10** (0.24 g, 22%) could be obtained by column chromatography of the mother liquor (eluent: 30% ethyl acetate – light petroleum) along with some triol **1** (0.09 g, 13%).

Data for 1:
m.p. 300-301°C (Literature[2] m.p. 300-302°C).
IR (cm^{-1}): 3350.
^{1}H NMR (D_2O): 4.20 (m, 2H), 4.30 (m, 2H), 4.60 (t, 2H), 5.60 (d, 1H, J = 1Hz).

Preparation of *myo*-inositol-1, 3, 5-orthoformate (1):

The dibenzoate **8** (1.64 g, 4.1 mmol) was refluxed in methanol (44 ml) with t-butyl amine (2.2 ml, 20.5 mmol) for 3 h. The product was purified by crystallization from methanol (0.78 g, 100%).

Preparation of 2-O-benzoyl- 4,6-di-O-benzyl-*myo*-inositol-1, 3, 5-orthoformate (12):

The dibenzoate **8** (1.2 g, 3 mmol) and benzyl bromide (3.6 ml, 5.13 g, 30 mmol), were taken in dry DMF (12 ml) and freshly prepared silver (I) oxide (3.48 g, 15 mmol) was added in portions over a period of 10 minutes with vigorous stirring and external cooling with ice. Stirring was continued at room temperature till the starting material disappeared on TLC (66 h). The solid was allowed to settle and the supernatant liquid was decanted. The residue was washed successively with DMF (15 ml) and chloroform (3X40 ml). The organic extract was washed with sodium cyanide solution (1%, 500 ml) and the aqueous layer was extracted with chloroform (2X50 ml). The combined chloroform extract was washed with water (3X500 ml), dried over

anhydrous sodium sulfate and evaporated *in vacuo*. The product was purified by column chromatography (eluent: 5% ethyl acetate – light petroleum) (1.15 g, 81%).

Data for 12:

m.p. 102 -104°C.

IR (cm^{-1}): 1740.

^1H NMR: 4.50 (t, 2H), 4.60 (m, 3H), 4.75 (s, 4H), 5.67 (broad s, 1H), 5.71 (broad s, 1H), 7.30-7.70 (m, 13H), 8.25 (m, 2H).

^{13}C NMR: 64.8, 68.5, 70.5, 71.7, 74.0, 103.5, 128.0, 128.6, 130.1,133.4, 137.6, 166.3.

Elemental analysis calcd. for $C_{28}H_{26}O_7$: C, 70.90%, H, 5.48%.
Found: C, 70.75%, H, 5.73%.

Preparation of 4,6-di-O-benzyl-*myo*-inositol-1, 3, 5-orthoformate (13):

The dibenzyl ether **12** (0.47 g, 1 mmol) was refluxed with t-butyl amine (0.8 ml) and methanol (10 ml) for 20 h. The solvent was removed *in vacuo* and the residue was purified by crystallization from chloroform – light petroleum mixture (0.34 g, 92%).

Data for 13:

m.p.124 -125°C (Literature[1] m.p. 125°C).

IR (cm^{-1}): 3300.

^1H NMR: 3.00 (d, 1H, D_2O exchangeable), 4.20 (m, 3H), 4.40 (m, 3H), 4.60 (q, 4H), 5.50 (s, 1H), 7.30 (m, 10H).

Preparation of 2,4-di-O-benzoyl-6-O-tetrahydropyranyl-*myo*-inositol-1,3,5-orthoformate (23):

The dibenzoate **8** (0.87 g, 2.2 mmol) was dissolved in dichloromethane (8 ml) and 3,4-dihydro-2H-pyran (0.42 g, 5 mmol, 0.45ml) and PpTs (0.07 g, 0.28 mmol) were added and stirred at room temperature for 24 h. The reaction mixture was then diluted with dichloromethane, washed successively with 5% sodium carbonate solution (200 ml) and water (2 x 200 ml) and the organic phase was dried over anhydrous sodium sulfate. The solvent was evaporated and the product (mixture of

diastereomers) was purified by crystallization from chloroform – light petroleum mixture (0.92 g, 90%).

Data for 23:

m.p. 135 -139°C.

IR (cm^{-1}): 1730.

^{1}H NMR: 0.95-1.80 (m, 6H), 3.35-3.60 (m, 1H), 3.65-3.95 (m, 1H), 4.65 (m, 2H), 4.70 (m, 2H), 4.85 (m, 1H), 5.65 (m, 2H), 5.80 (m, 1H), 7.40-7.65 (m, 6H), 8.05-8.25 (m, 4H).

^{13}C NMR: 19.1, 19.3, 24.9, 25.2, 30.3, 30.5, 62.7, 63.0, 64.5, 67.4, 68.5, 68.6, 69.9, 70.0, 71.3, 71.8, 72.7, 98.8, 99.9, 103.4, 128.5, 128.6, 129.4, 129.7, 129.8, 130.1, 133.5, 165.3, 169.1.

Elemental analysis calcd. for $C_{26}H_{26}O_9$: C, 64.73%, H, 5.39%.

Found: C, 64.51%, H, 5.44%.

Methanolysis of 2,4-di-O-benzoyl-6-O-tetrahydropyranyl-1, 3, 5-orthoformate (23):

The tetrahydropyranyl ether **23** (0.16 g, 0.3 mmol) was heated with methanol (10 ml) and pyridine (3 ml) at 50°C for 24 h. TLC showed the presence of only the starting material, which could be recovered quantitatively after the usual work-up.

Preparation of 4-O-tetrahydropyranyl-*myo*-inositol-1,3,5-orthoformate (24):

The tetrahydropyranyl ether **23** (0.33 g, 0.7 mmol) was refluxed in methanol (8 ml) with t-butyl amine (0.6 ml) for 9 h. The product **24** was purified by column chromatography (50% ethyl acetate- light petroleum) (0.17 g, 91%).

Data for 24:

m.p. 201-203°C.

IR (cm^{-1}): 3160-3380.

^{1}H NMR: 1.50-1.90 (m, 6H), 3.15-3.40 (broad, D_2O exchangeable), 3.50-3.70 (m, 1H), 3.80 (d, 1H, D_2O exchangeable), 3.85-4.00 (m, 1H), 4.05-4.30 (m, 3H), 4.30-4.60 (m, 2H), 4.60-4.85 (m, 2H), 5.50 (d, 1H).

^{13}C NMR: 19.1, 19.3, 25.5, 30.6, 59.4, 62.7, 63.0, 67.8, 69.1, 74.8, 93.8, 102.4. (Better spectrum could not be obtained due to solubility problem of **24**).

Elemental analysis calcd. for $C_{12}H_{18}O_7$: C, 52.55%, H, 6.57%.
Found: C, 52.90%, H, 6.26%.

Preparation of 2,4-di-O-benzoyl-*myo*-inositol (25):

The dibenzoate **8** (0.4 g, 1.0 mmol) was dissolved in dichloromethane (4 ml) and methanol (4 ml) and anhydrous pTSA (0.04 g, 0.2 mmol) were added and the reaction mixture stirred for 40 h at room temperature. The solvent was then evaporated and the residue purified by filtration over a short silica gel column (50% ethyl acetate – light petroleum) to give the tetrol **25** (0.36 g, 93%).

Data for 25:
m.p. 193 -195°C (Literature[14] m.p. 198-201°C).
IR (nujol) (cm^{-1}): 1700, 2900 (broad), 3200-3500 (broad).
^1H NMR ($CDCl_3$-DMSO-d_6)**:** 3.40-3.90 (m, 4H), 4.70 (dd, 2H, D_2O exchangeable), 4.90 (d, 1H, D_2O exchangeable), 5.10 (d, 1H, D_2O exchangeable), 5.40 (t, 1H), 5.65 (t, 1H), 7.30-7.65 (m, 6H), 8.00 (t, 4H).

Preparation of 4,6-di-O-benzyl-*myo*-inositol (27):

The crude dibenzyl ether **13** (0.83 g, 2.32 mmol) prior to crystallization was dissolved in methanol (20 ml) and stirred at room temperature with pTSA (0.4 g) for 24 h. The pure product (0.75 g, 90%, based on **12**) was obtained by column chromatography (eluant:: ethyl acetate).

Data for 27:
m.p. 137 -138°C (Literature[16] m.p. 138.5-139°C).
IR(cm^{-1}): 3360-3550
^1H NMR: 2.50-2.55 (m, 3H, D_2O exchangeable), 2.80 (d, 1H, D_2O exchangeable), 3.50-3.70 (m, 5H), 4.10 (m, 1H), 4.80 (q, 4H, J = 10 Hz), 7.30-7.40 (m, 10H).

Preparation of 2,4-di-O-benzoyl-6-O-methyl-*myo*-inositol-1, 3, 5-orthoformate (28):

The dibenzoate **8** (0.5 g, 1.3 mmol) and methyl iodide (0.08 ml, 0.18 g, 1.3 mmol) were taken in dry DMF (5 ml) and freshly prepared silver (I) oxide (1.45 g, 6.3

mmol) was added in portions over 10 minutes with vigorous stirring and external cooling with ice. Stirring was continued at room temperature till the starting material disappeared on TLC (2 h). The solid was allowed to settle and the supernatant liquid was decanted. The residue was washed successively with DMF (7 ml) and chloroform (3X20 ml). The combined organic extract was washed with sodium cyanide solution (1%, 200 ml) and the aqueous layer was extracted with chloroform (2X20 ml). The combined chloroform extract was washed with water (3X200 ml), dried over anhydrous sodium sulfate and evaporated *in vacuo*. The product **28** was crystallized from chloroform - light petroleum mixture (0.44 g, 85%).

Data for 28:

m.p. 229-230°C.

IR (cm^{-1}): 1730

^{1}H NMR: 3.40 (s, 3H), 4.27 (m, 1H), 4.60 (m, 2H), 4.76 (m, 1H), 5.60 (m, 1H), 5.70 (d, 1H), 5.80 (m, 1H), 7.40-7.65 (m, 6H), 8.05-8.25 (m, 4H).

^{13}C NMR: 57.6, 64.3, 66.9, 68.4, 69.8, 70.0, 75.5, 103.4, 128.6, 128.7, 129.4, 129.8, 130.1, 133.6, 133.7, 165.5, 166.3.

Elemental analysis calcd. for $C_{22}H_{20}O_8$: C, 64.10%, H, 4.85%.
Found: C, 64.41%, H, 4.81%.

Preparation of racemic 4-O-methyl-*myo*-inositol (ononitol) (30):

The methyl ether **28** (0.42 g, 0.995 mmol) was treated with t-butyl amine (0.8 ml) in methanol (10 ml) at room temperature for 19 h to obtain the diol **29** (0.25 g). The crude diol **29** was treated with pTSA (0.14 g, 0.625 mmol) and methanol (8 ml) as in the preparation of the tetrol **25** to obtain racemic ononitol **30**, which was purified by column chromatography (10% methanol-ethyl acetate) (0.19 g, 98%).

Data for 30:

m.p. 165-168°C.

^{1}H NMR (D_2O): 3.30 (t, 1H), 3.40 (dd, 1H), 3.50 (dd, 1H), 3.60 (s, 3H), 3.60-4.00 (m, 2H), 4.05 (t, 1H).

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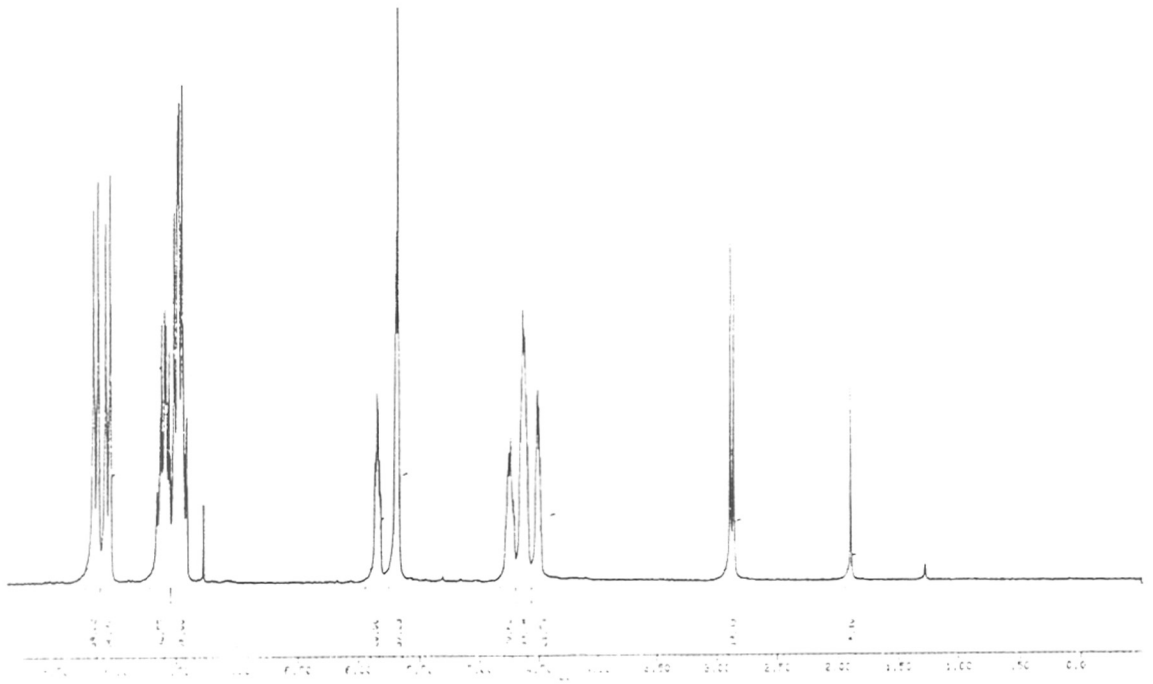
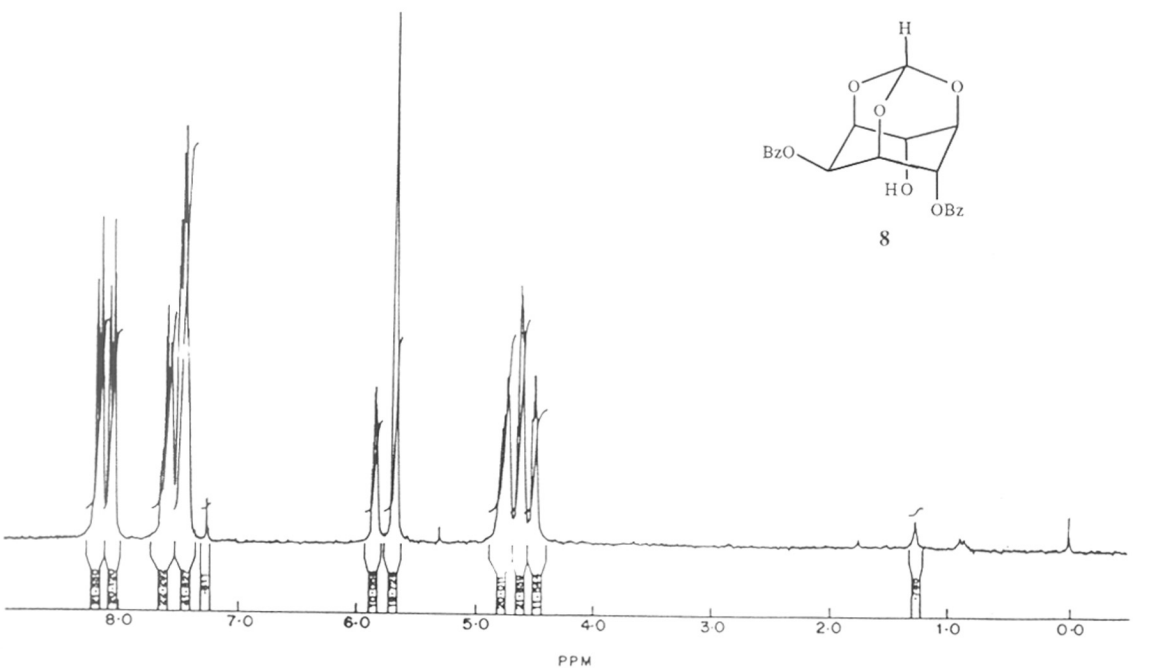
Figure 1





8

Figure 2

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O
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OBz
BzO
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10
20
30
40
50
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100
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120
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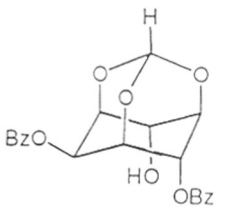
190
200
210
PPM

Figure 3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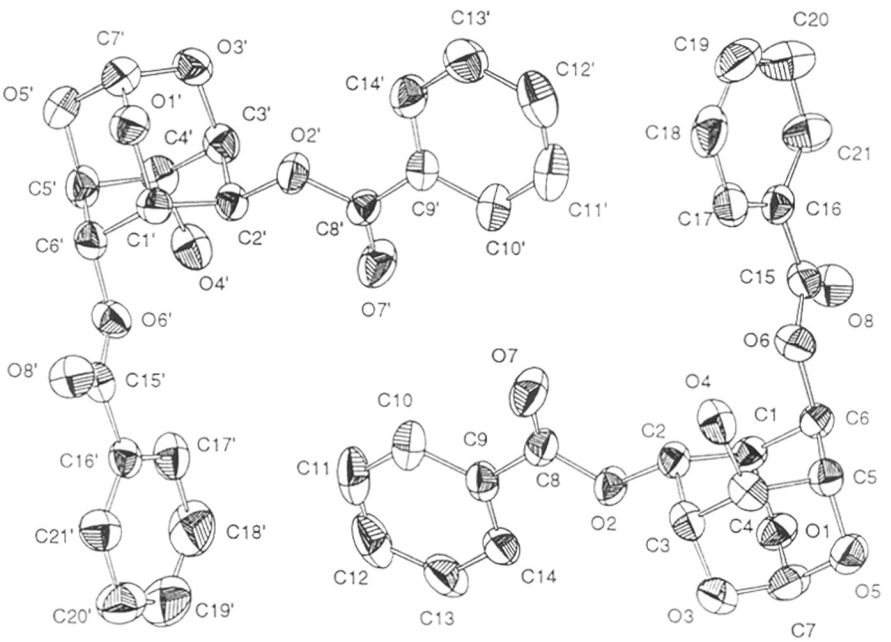
O
BzO
HO
OBz

8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C10
C1
C6
C9
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O1
C3
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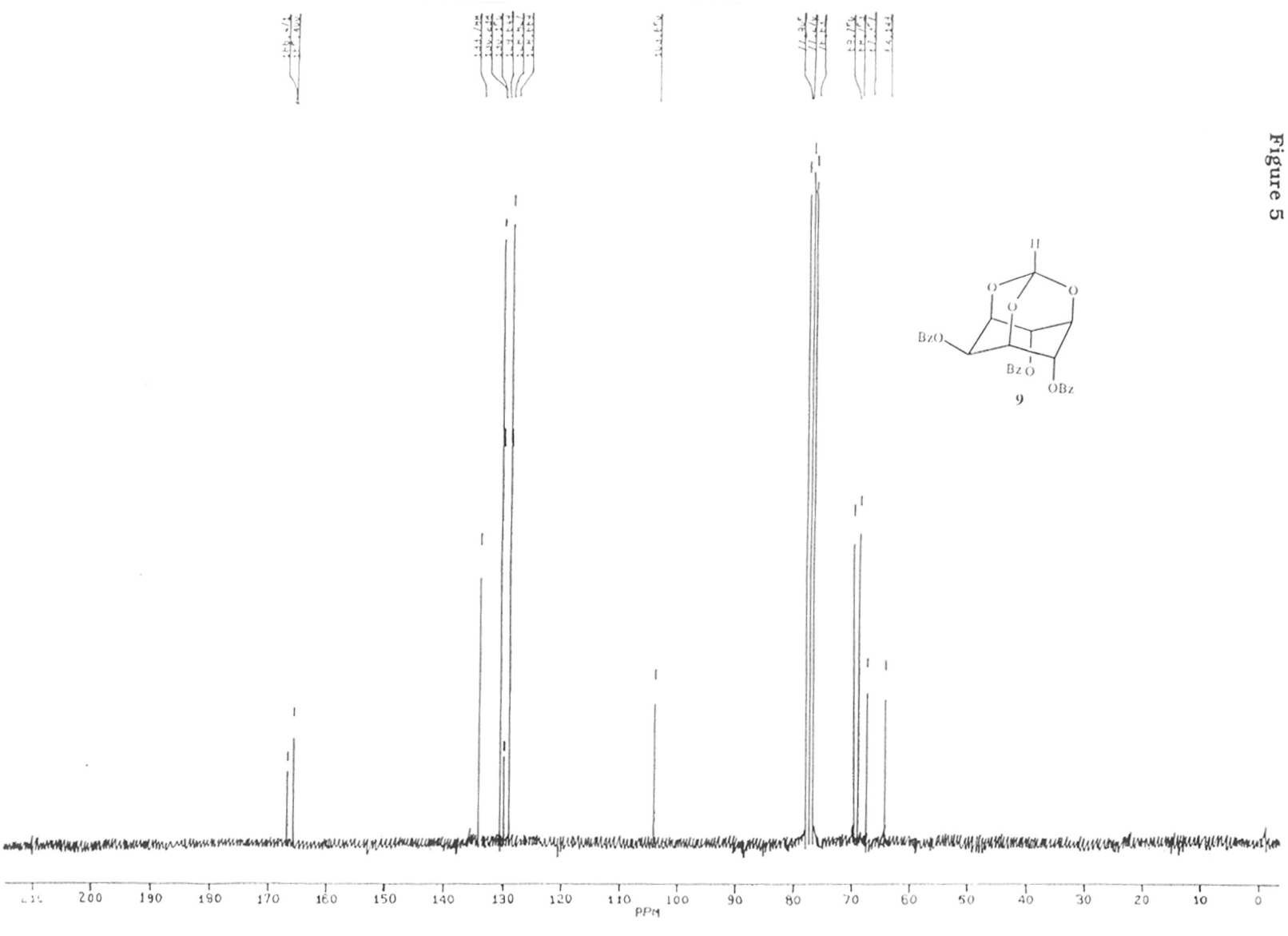
C14
O5
O3
C13
C7

Figure 4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O
BzO
Bz O
OBz
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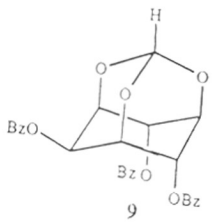
80
70
60
50
40
30
20
10
0
PPM

Figure 5

Figure 6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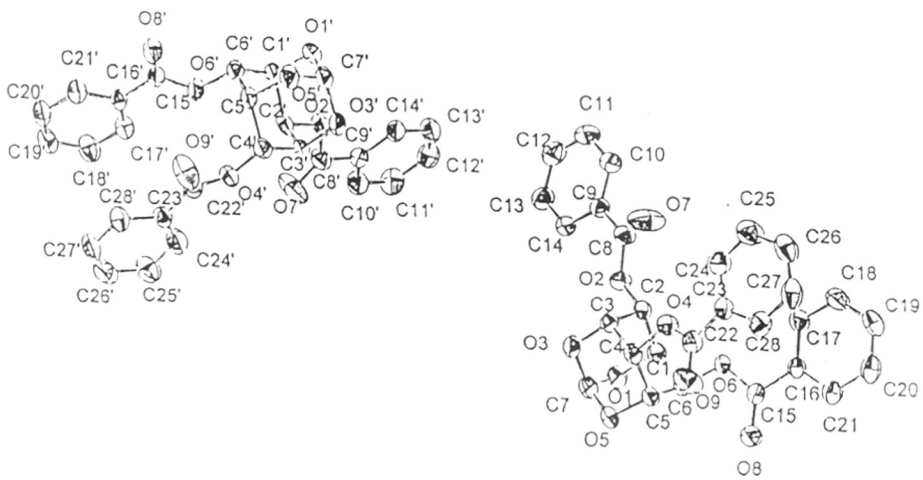
BzO
BzO
OBz

9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C15
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C25'
C11
C12
C10
C13
C9
O7
C25
C14
C8
C26
C24
C18
O2
C2
C23
C27
C3
O4
C19
O3
C4
C22
C28
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C16
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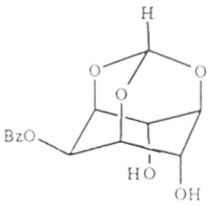
O5
O8

Figure 7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BzO
HO
OH

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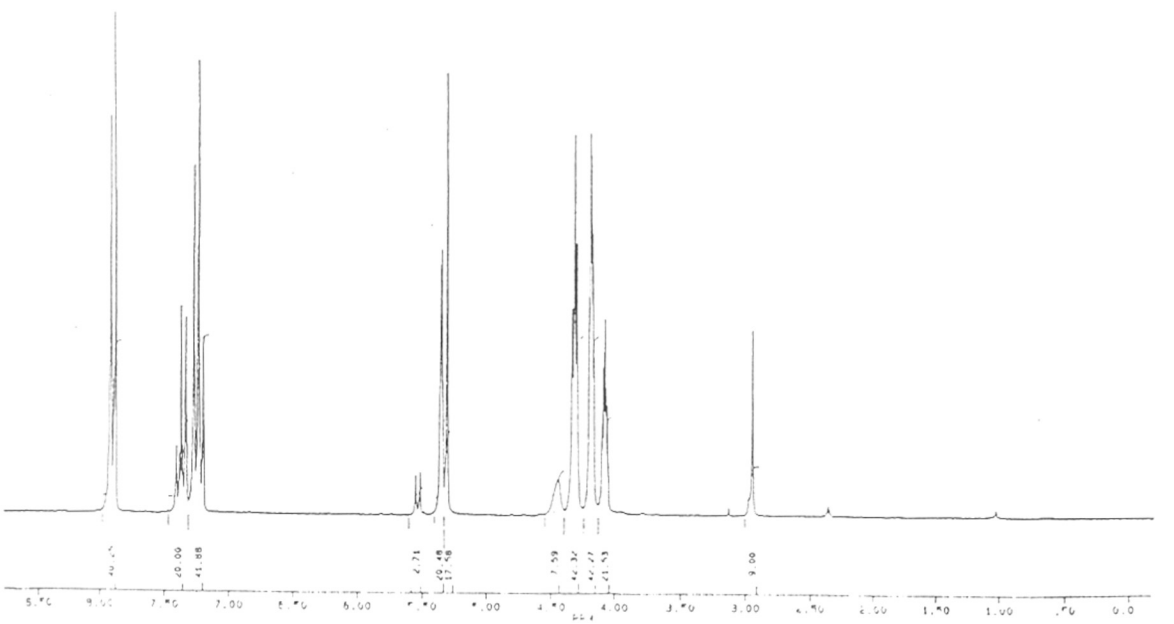
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Figure 8

10

Figure 9

OBn
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BzO
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103.64
10.84
8.26
43.64
33.81
20.98
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
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3.50
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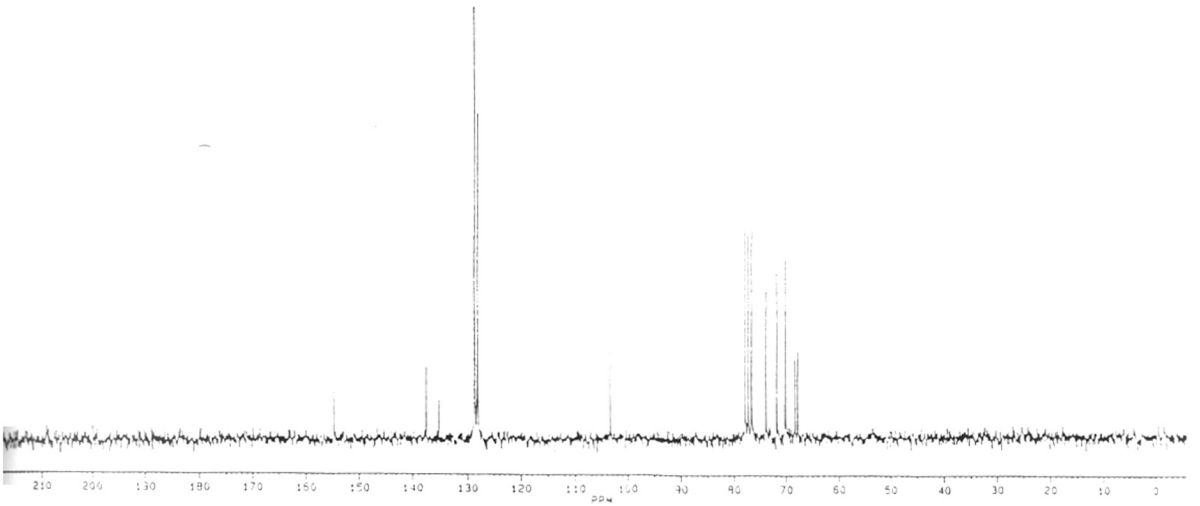
2.50
2.00
1.50
1.00
.50
0.0
PPM

Figure 10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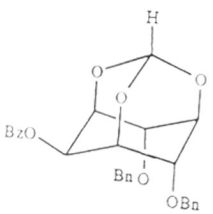
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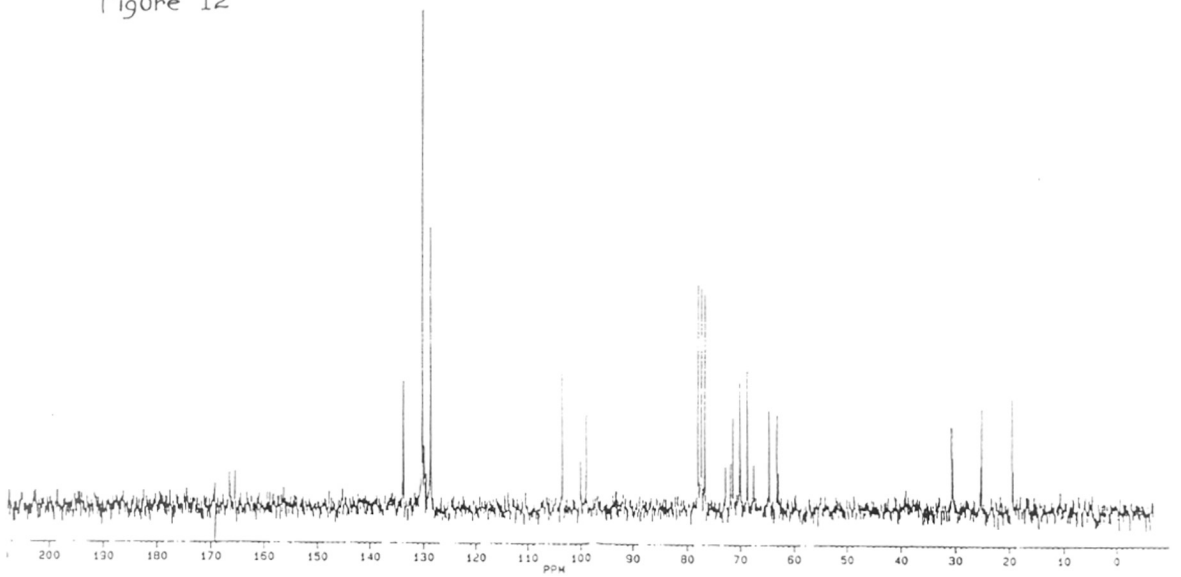
0

Figure 11

Figure 12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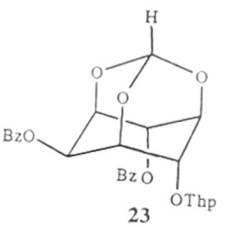
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BzO
Bz O
OThp

23

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50
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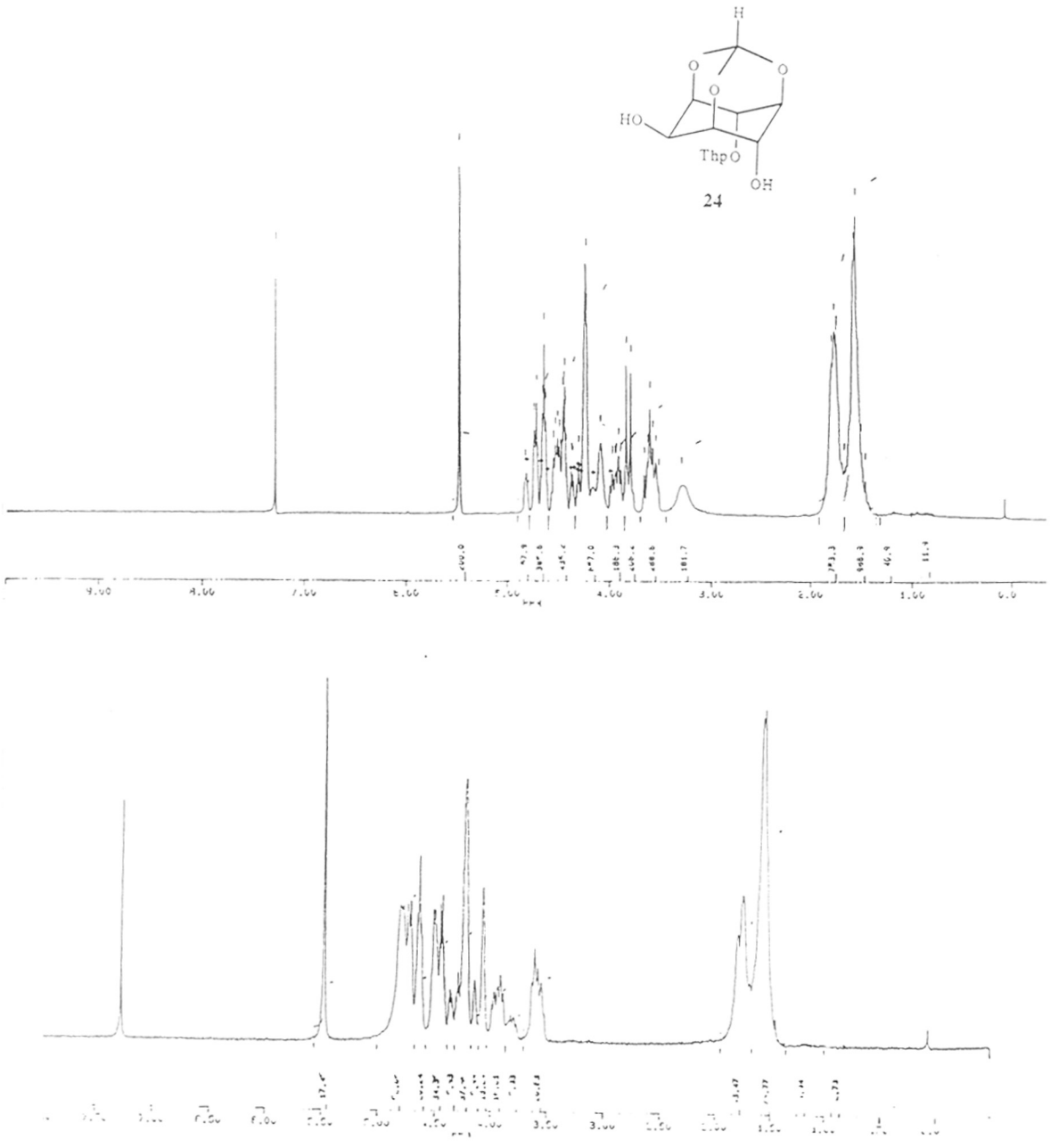
30
20
10
0
PPM

Figure 13



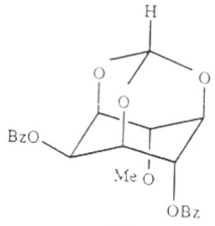
24

Figure 14

Figure 15

28

Figure 16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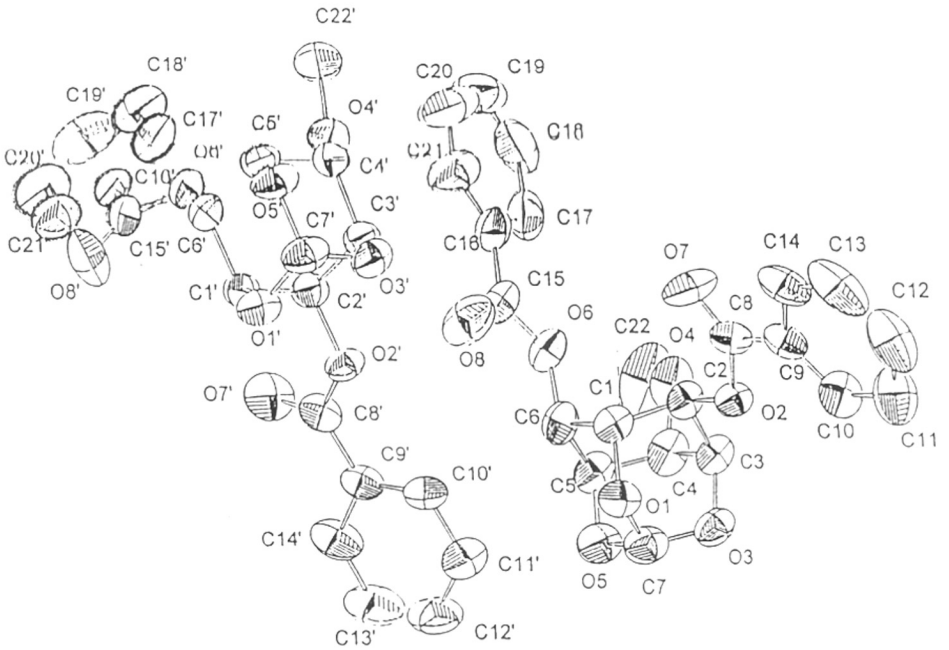
O
BzO
Me O
OBz

28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O6
C22
O4
C2
C9
C1
O2
C10
C11
C6
C3
C5
C4
O1
O3
O5
C7

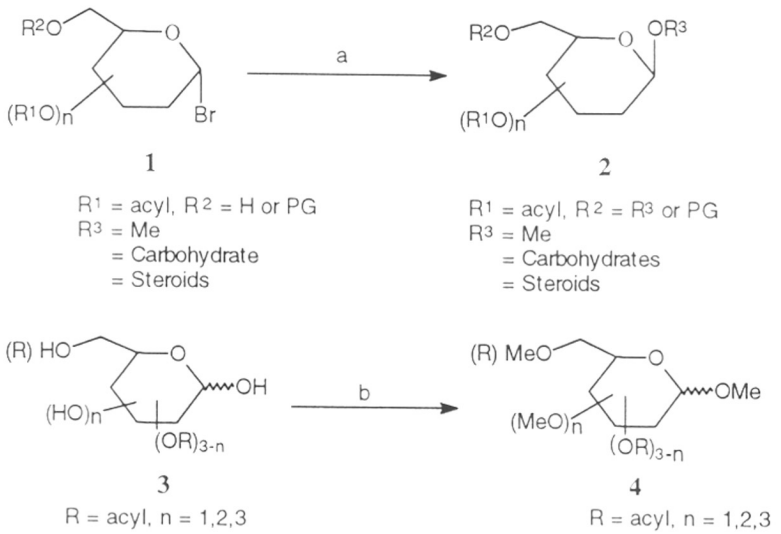
CHAPTER 3

Part A: Silver (I) oxide mediated alkylation of 2,4-Di-O-benzoyl-*myo*-inositol-1,3,5-orthoformate and its derivatives: A mechanistic study

3A.1 INTRODUCTION

Silver (I) oxide as well as several other silver salts have been used for O-alkylation of alcohols (Koenigs-Knorr and Purdie reactions)[1] for several decades and are specially recommended for the O-alkylation of hydroxy esters, since esters are known to be stable under these alkylation conditions[2] (**Scheme 3A.1**). Silver salts have also been extensively used for the glycosylation of carbohydrates[3].

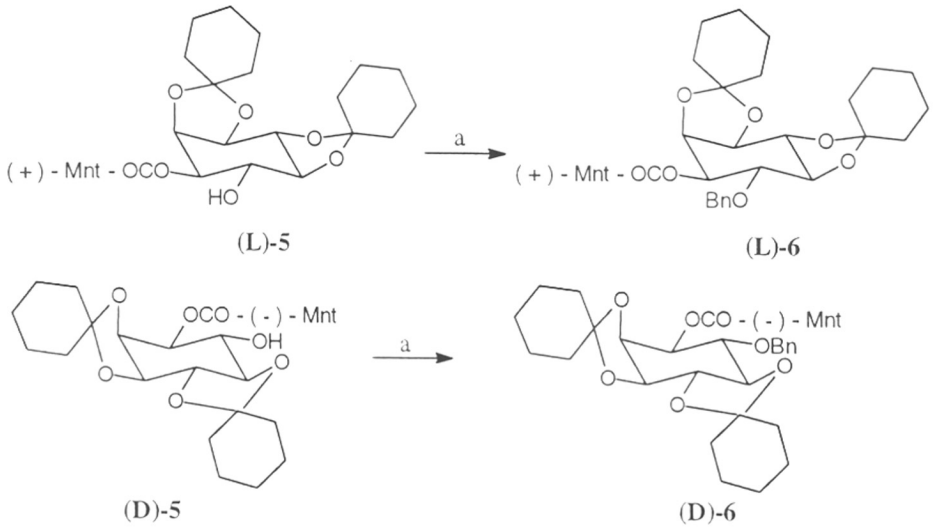
Scheme 3A.1



Reagents and conditions: (a) R 3OH, Ag_2O (b) MeI, Ag_2O.
PG = Protecting Group

More relevant to the present work, enantiomeric *myo*-inositol derivatives **L-5** and **D-5** (**Scheme 3A.2**) were converted to the corresponding benzyl ethers **L-6** and **D-6** respectively using benzyl bromide in the presence of silver (I) oxide, to avoid intramolecular migration of the carbonate moities[4].

Scheme 3A.2

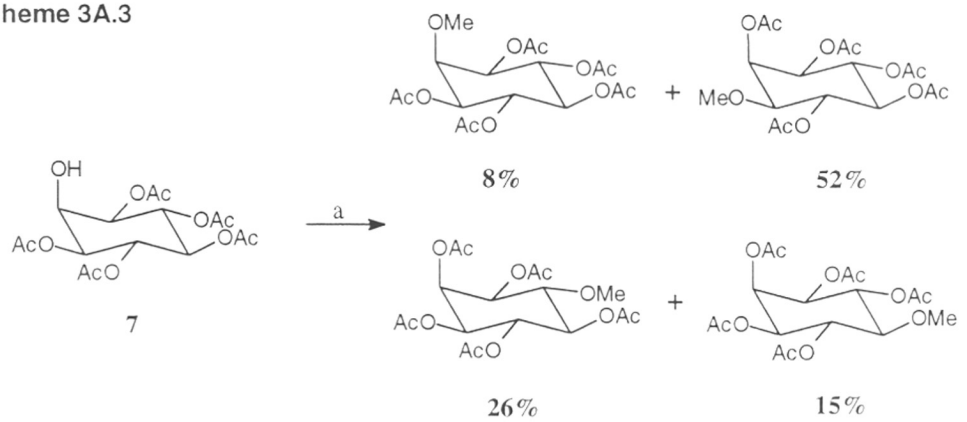


Reagents and conditions: (a) BnBr, Ag_2O, DMF

Mnt = Menthyl

However, intramolecular acyl migration was observed during the methylation of certain O-acetyl-*myo*-inositol derivatives like **7** with methyl iodide (**Scheme 3A.3**) in the presence of silver (I) oxide, resulting in the formation of a mixture of O-methylated products[5].

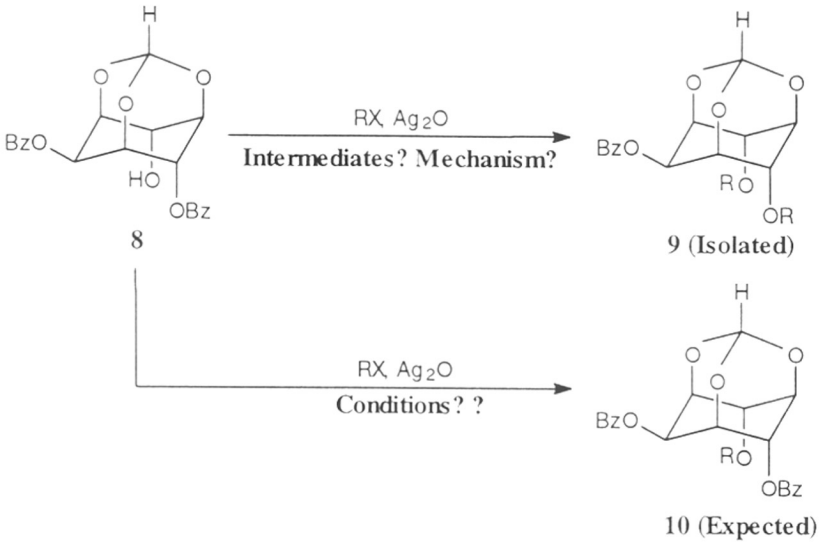
Scheme 3A.3



Reagents and conditions: (a) MeI, Ag_2O, DMF

Racemic 2,4-di-O-benzoyl-*myo*-inositol-1,3,5-orthoformate (**8**), which could be prepared in gram quantities (see **Chapter 2**) appeared to be a useful intermediate for the preparation of inositol - carbohydrate conjugates. But, as mentioned in **Chapter 2**, reaction of the dibenzoate **8** with benzyl bromide in the presence of silver (I) oxide gave the corresponding 4,6-dibenzyl ether **9** (R = Bn) instead of the expected 6-monobenzyl ether **10** (R = Bn) (**Scheme 3A.4**).

Scheme 3A.4



Hence we undertook a detailed investigation of the reaction of the dibenzoate **8** with alkyl halides in the presence of silver (I) oxide with the following objectives:

(a) To examine the mechanism of formation of 4,6-di-O-alkyl-*myo*-inositol orthoformates **9** from the dibenzoate **8**.

(b) To arrive at experimental conditions which provide the expected 6-O-alkylated products **10** in good yields.

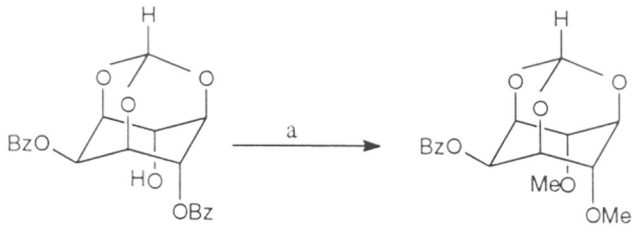
Accordingly, this chapter presents results on O-alkylation of the dibenzoate **8** and its 6-O-substituted derivatives with several alkyl halides under a variety of conditions.

3A.2 RESULTS AND DISCUSSION

3A.2.1 Reaction of racemic 2,4-di-O-benzoyl-*myo*-inositol-1,3,5-orthoformate (8) with methyl iodide in DMF:

Reaction of the dibenzoate **8** with excess methyl iodide in the presence of excess silver (I) oxide gave the dimethyl ether **11** in 80% yield instead of the expected 6-O-methyl ether (**Scheme 3A.5**).

Scheme 3A.5



8 11

Reagents and conditions: (a) Excess MeI, Ag_2O, DMF, 60h

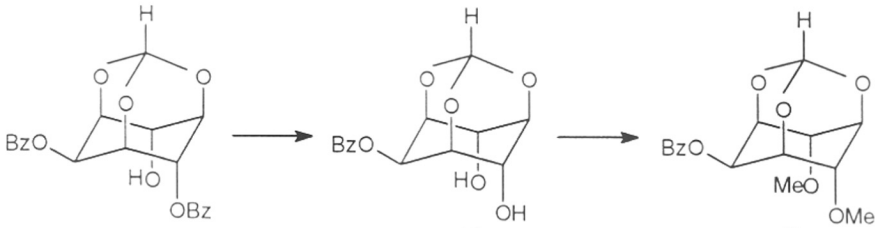
The structure of the symmetrical dimethyl ether **11** was established by IR, ^{1}H NMR and ^{13}C NMR spectroscopy. The IR spectrum of **11** showed the presence of a single carbonyl group (1720 cm^{-1}). The ^{1}H NMR spectrum showed, besides one orthoformate proton at δ 5.60 (doublet), five aromatic hydrogens indicating the presence of one benzoate group, a singlet for six methyl hydrogens at δ 3.55 and six inositol ring hydrogens between δ 4.22 and 5.40. A singlet for the two methyl groups is consistent with the symmetrical structure assigned to the dimethyl ether **11** (**Figure 1**). The ^{13}C NMR spectrum of **11** showed the presence of the orthoformate carbon (103.4 ppm), aromatic carbons, one signal for the methyl carbons (57.7 ppm), four signals for the six inositol ring carbons and one carbonyl carbon (**Figure 2**). Methyl benzoate (2 equivalents) was formed as a by-product during methylation*.

We initially suspected the formation of the dimethyl ether **11** *via* the diol **12** which could arise by the hydrolysis of the axial benzoate in the dibenzoate **8** due to hydroxyl ions or water adsorbed on the surface of silver (I) oxide (**Scheme 3A.6**). As discussed in **Chapter 2, Section 2.2**, the axial benzoate moiety in the dibenzoate **8** is

* In all the alkylation reactions reported in this thesis, the corresponding alkyl benzoate was obtained.

susceptible to intramolecular hydroxyl group assisted basic hydrolysis (or solvolysis) to yield the diol **12** under mild conditions.

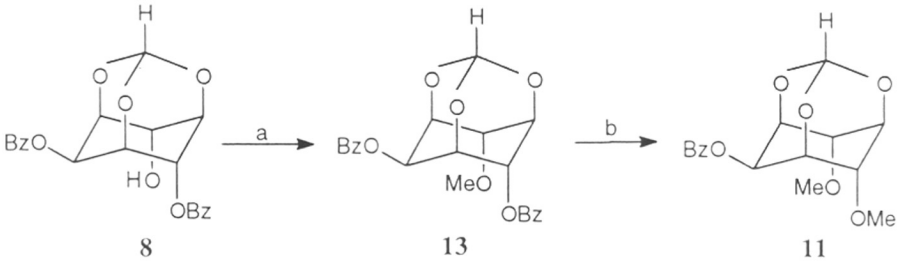
Scheme 3A.6



Hence we carried out a control experiment to see if the diol is being formed by the hydrolysis of the axial benzoate in the dibenzoate **8** during the alkylation. Stirring the dibenzoate **8** with silver (I) oxide in aqueous or dry DMF for 66 hrs did not result in the formation of the diol **12** (TLC) and the dibenzoate **8** could be recovered quantitatively. These control experiments showed that the benzoate esters in **8** do not undergo hydrolysis in the presence of silver (I) oxide.

A careful monitoring of the progress of methylation of the dibenzoate **8** by TLC revealed the formation of an intermediate (R_f = 0.7: eluant 20% ethyl acetate-light petroleum) which further reacted with methyl iodide to give the dimethyl ether **11** (R_f = 0.5) (**Scheme 3A.7**).

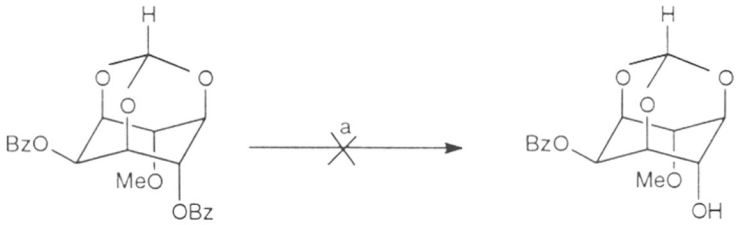
Scheme 3A.7



Reagents and conditions: (a) MeI (1 eq.), Ag_2O, DMF, 2h (b) Excess MeI, Ag_2O, DMF, 48h

This intermediate could be isolated in 80% yield by quenching the reaction at the end of 2h. IR, ^{1}H NMR and ^{13}C NMR spectra of this intermediate showed it to be the expected monomethyl ether **13** (see **Chapter 2, Section 2.4** for details). The monomethyl ether **13** could also be prepared in good yield by reacting the dibenzoate **8** with one equivalent of methyl iodide in the presence of silver (I) oxide for 2 hrs. The methyl ether **13** smoothly reacted with an excess of methyl iodide in the presence of silver (I) oxide to give the symmetrical dimethyl ether **11** in excellent yield (**Scheme 3A.7**). These reactions clearly showed the sequence of reactions (**8** → **13** → **11**) which result in the formation of the dimethyl ether **11** on methylation of the dibenzoate **8** with methyl iodide. Again, the possibility of hydrolysis of the monomethyl ether **13** to the corresponding hydroxy derivative **14** could be ruled out by a control reaction (**Scheme 3A.8**).

Scheme 3A.8



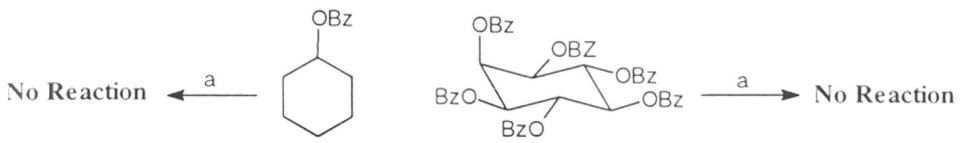
13 14

Reagents and conditions : (a) Ag_2O, DMF, 60h

Treatment of the monomethyl ether **13** with silver (I) oxide in DMF did not result in the formation of the corresponding hydroxyl derivative **14**. Furthermore, in absence of the intramolecular assistance by the 6-axial hydroxyl group for the hydrolysis of the 4-axial benzoate, preferential hydrolysis of the 2-equatorial benzoate would be expected based on steric grounds (see **Chapter 2, Section2.2**). This should result in the formation of the 2-equatorial methyl ether as well. Hence from the foregoing we can conclude that the axial benzoate in **13** undergoes alkylative cleavage with methyl iodide in the presence of silver (I) oxide. Since the 2-equatorial benzoate remains unaffected during methylation of the dibenzoate **8**, this reaction perhaps involves the transannular participation of the diaxial oxygens. To test this hypothesis, we subjected cyclohexyl benzoate **15** (which lacks other oxygens) and *myo*-inositol hexabenzoate[6] **16** in which, none of the *myo*-inositol ring oxygens are present in 1,3-diaxial orientation, to methylation conditions as in the case of the

dibenzoate **8** (**Scheme 3A.9**). In both the reactions the starting materials were recovered quantitatively.

Scheme 3A.9



15 16

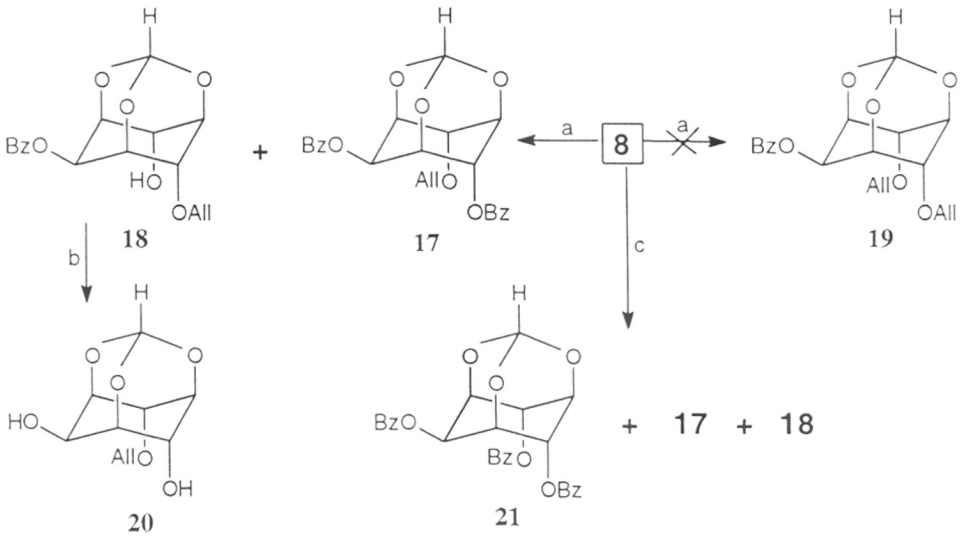
Reagents and conditions: (a) MeI, Ag_2O, DMF, 66h

These results show that proper orientation of the two oxygens is necessary for the cleavage and alkylation of the axial ester moiety. Also, the observed unusual methylation could be due to the rigidity of *myo*-inositol orthoformate molecule.

3A.2.2 Reaction of racemic 2,4-di-O-benzoyl-*myo*-inositol-1,3,5-orthoformate (8) with allyl chloride in DMF:

The dibenzoate **8** reacted with excess allyl chloride in the presence of silver (I) oxide to give the expected monoallyl ether **17** (R_f = 0.7; 20% EtOAc – light petroleum) as the major product (60%) and hydroxy ether **18** (R_f = 0.4; 20% EtOAc – light petroleum, 2 runs) as the minor product (24%) (**Scheme 3A.10**). No diallyl ether **19** could be detected. Use of lesser amount of allyl chloride (10 equivalents) resulted in the formation of a small amount of the tribenzoate **21** as a side product (detected by ^{1}H NMR spectroscopy), probably due to the lower reactivity of allyl chloride as compared to those of methyl iodide and allyl bromide, and enhanced rate of transesterification of the dibenzoate **8** (see **Section 3A.2.7**). Hence 14 equivalents of allyl chloride had to be used in order to suppress the formation of the tribenzoate **21**. The monoallyl ethers **17** and **18** were identified by their IR, ^{1}H NMR and ^{13}C NMR spectroscopic data. The IR spectrum of **17** showed two carbonyl peaks (1720, 1710 cm^{-1}). The ^{1}H NMR spectrum showed six inositol ring protons, five allylic protons and one orthoformate proton in the region between δ 4.10 and δ 5.85. The signals between δ 7.40 and 8.30 integrated to ten aromatic hydrogens indicating the presence of two benzoate groups (**Figure 3**).

Scheme 3A.10



Reagents and conditions: (a) AlCl (14 eq.), Ag $_2$O, DMF, 66h (b) *i*-Butyl amine, MeOH, reflux (c) AlCl (10 eq.), Ag $_2$O, DMF, 66h.

The ^{13}C NMR spectrum confirmed the structure with spectroscopic characteristics similar to that of the monomethyl ether **11** except that instead of the methyl carbons, two carbons belonging to allyl group were present, along with the olefinic carbon (O-C-C=C) appearing at δ 118.2 (**Figure 4**).

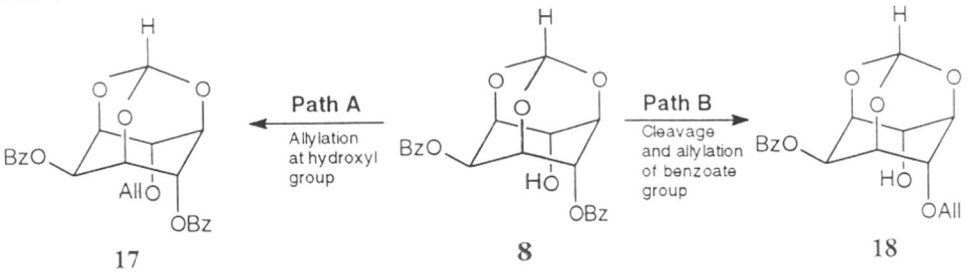
The IR spectrum of **18** showed the presence of carbonyl group (1720 cm^{-1}) and hydroxyl group (3300-3600 cm^{-1}). The ^{1}H NMR spectrum of **18** showed a D_2O exchangeable proton at δ 3.87 appearing as a doublet. The olefinic proton of the allyl group (O-C-C(H)=C) appeared as a broad multiplet (δ 5.85-6.05). The methylene protons of the allyl group and the inositol ring protons appeared between δ 4.15 and δ 5.50 and the orthoformate proton appeared at δ 5.60 as a doublet. The signals in the aromatic region integrated to five protons indicating the presence of one benzoate group (**Figure 5**). ^{13}C NMR spectrum of **18** showed one orthoformate carbon (102.9 ppm), one carbonyl carbon (166.4 ppm), seven signals for inositol ring carbons and one of the three allyl carbons (**Figure 6**). The olefinic carbon of the allyl group (O-C-C=C) appeared at 119.8 ppm. **18** was converted to the known diol **20** by aminolysis with iso-butyl amine in methanol. The ^{1}H NMR spectrum compared with that

available in the literature[7] showed **20** to be the 4-O-allyl-*myo*-inositol-1,3,5-orthoformate.

In contrast to its reaction with methyl iodide and allyl bromide (see below) the dibenzoate **8** was unreactive when one equivalent of allyl chloride was used for allylation and it could be recovered at the end of 66 hours.

Although reaction of the dibenzoate **8** with allyl chloride gave the expected allyl ether **17** as the major product, it is of interest to examine the origin of the minor product **18**, both from synthetic as well as mechanistic points of view. We could envisage two paths (**Scheme 3A.11**) for the formation of hydroxy ether **18** from the dibenzoate **8** since we had already ruled out the possibility of hydrolysis of the dibenzoate (under the conditions of alkylation, see **Section 3A.2.1**) to the diol followed by its allylation (also see **Chapter 3B, Section 3B.2.B**).

Scheme 3A.11



17 **8** 18

Also the possibility of hydrolysis of the axial benzoate in the monoallyl ether **17** to generate the corresponding hydroxy ether **18** can be ruled out based on the results discussed in **Section 3A.2.1** (**Scheme 3A.8**). Hence it is likely that the axial benzoate group in the dibenzoate **8** undergoes cleavage, followed by allylation prior to the O-allylation of the free 6-axial hydroxyl group to yield the hydroxy ether **18** as a minor product. This reaction is similar to the cleavage and methylation of the axial benzoate in **13** (**Scheme 3A.7**) except that the axial hydroxyl group participates instead of an axial methoxy group. The product **18** does not undergo further allylation to yield the diallyl ether **19** probably due to the lower reactivity of allyl chloride (see **Chapter 3B**).

3A.2.3 Reaction of racemic 2,4-di-O-benzoyl-*myo*-inositol-1,3,5-orthoformate (8) with allyl bromide in DMF:

Reaction of the dibenzoate **8** with excess allyl bromide in the presence of silver (I) oxide resulted in the formation of the diallyl ether **19** in 74% yield as the only isolable product (**Scheme 3A.12**).

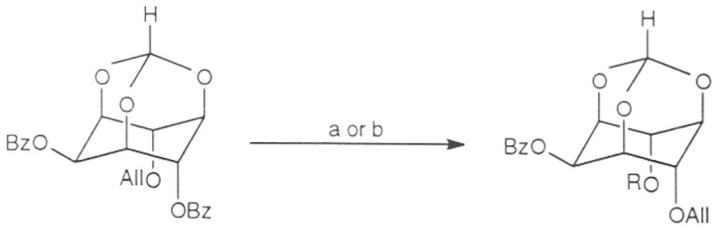
Scheme 3A.12

Reagents and conditions: (a) AllBr (excess), DMF, Ag_2O, 66h (b) AllBr (1 eq. Ag_2O, DMF, 66h.

The product was characterized as the symmetrical diallyl ether by IR, ^{1}H NMR and ^{13}C NMR spectroscopic data. The IR spectrum of **19** showed the presence of a single carbonyl peak (1720 cm^{-1}). The ^{1}H NMR spectrum of **19** showed one orthoformate proton, five aromatic hydrogens indicating the presence of one benzoate group and six signals with proton ratio 4:2:3:4:1:2 pertaining to inositol ring protons and allyl group protons (**Figure 7**). The ^{13}C NMR spectrum confirmed the structure further with spectroscopic characteristics similar to that of the dibenzyl ether **9** (R = Bn) as described in **Chapter 2** except that **19** has allyl carbons instead of the benzylic carbons (**Figure 8**). In order to see if allylation of the dibenzoate **8** proceeded through a sequence of reactions similar to that observed during its methylation with methyl iodide (**Scheme 3A.7**), we carried out allylation of the dibenzoate **8** with one equivalent of allyl bromide and isolated the products formed (**Scheme 3A.12**). TLC analysis of the reaction mixture showed two distinct spots (R_f = 0.7 and 0.4; eluent: 20% ethyl acetate-light petroleum). The spot with higher R_f value was a mixture of two products, *viz.*,the diallyl ether **19** (17%) and the monoallyl ether **17** (4%) as revealed by ^{1}H NMR spectroscopy. The major product (R_f = 0.4; 20% EtOAc – light petroleum, 2 runs) was the hydroxy allyl ether **18** (40%), the structure of which was established by ^{1}H NMR, ^{13}C NMR and IR spectroscopy and comparison with authentic samples from the reaction of the dibenzoate **8** with allyl chloride (**Section 3A.2.2**). The monoallyl ether **17** reacted with excess of allyl bromide in the presence of silver

(I) oxide to yield the corresponding diallyl ether **19**. The monoallyl ether **17** also reacted with methyl iodide to give the methyl ether **22** in 62% yield (**Scheme 3A.13**).

Scheme 3A.13



17

19: R = All
22: R = Me

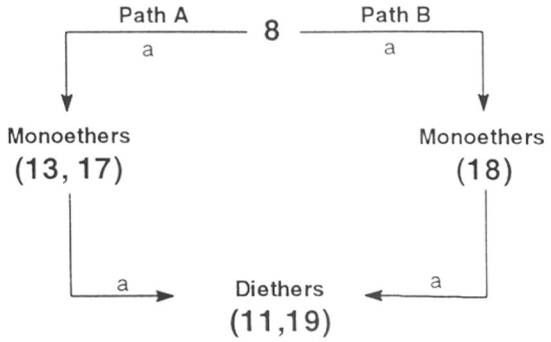
Reagents and conditions: (a) MeI, Ag_2O, DMF, 60h (b) AllBr, Ag_2O, DMF, 60h.

The product **22** was characterized by ^1H spectroscopy. The ^1H NMR spectrum of **22** showed a singlet for the three protons of the methyl group at δ 3.50. Four protons of allyl group (O-C$\underline{H_2}$-CH=C$\underline{H_2}$) and six inositol ring protons appeared between δ 4.15 and δ 5.50. The orthoformate proton appeared at δ 5.60 as a doublet and the olefinic proton of allyl group [O-C-C($\underline{H}$)=C] appeared as a broad multiplet between δ 5.85 and 6.05. The aromatic region integrated to five protons indicating the presence of one benzoate group (**Figure 9**).

The isolation of two intermediates, monoallyl ether **17** and hydroxy ether **18** suggests the operation of two different pathways for the formation of the diallyl ether **19** from the dibenzoate **8** as shown in **Scheme 3A.11**. In path **A**, cleavage of the axial 4-benzoate is subsequent to the allylation of the free 6-hydroxy group (**8** → **17** → **19**) and in path **B**, cleavage of the axial 4-benzoate is prior to the allylation of the free 6-hydroxy group (**8** → **18** → **19**). Hence the reaction of the dibenzoate **8** with allyl bromide is similar to its reaction with allyl chloride, except that the monoallyl ethers **17** and **18** formed, undergo further allylation to yield the diallyl ether **19**.

From the results presented so far, it can be concluded that the dibenzoate **8** reacts with methyl iodide *via* Path **A** while allyl chloride and allyl bromide react *via* paths **A** and **B** (**Scheme3A.14**).

Scheme 3A.14



Reagents and conditions: (a) RX, Ag_2O, DMF.

3A.2.4 Reaction of racemic 2,4-di-O-benzoyl-*myo*-inositol-1,3,5-orthoformate (8) with benzyl bromide in DMF:

The dibenzoate **8** reacted with excess of benzyl bromide in the presence of silver (I) oxide to yield the corresponding dibenzyl ether **9** (R = Bn) (**Scheme 3A.4**) in 80% yield (see **Chapter 2, Section 2** for details). Isolation of the dibenzyl ether **9** (R = Bn) was quite tedious due to the presence of excess of benzyl bromide and other low polar products resulting from benzyl bromide. Hence reaction wherein the amount of benzyl bromide was varied (as in the case of methyl iodide and allyl bromide) was not carried out.

3A.2.5 Reaction of the dibenzoate 8 with alkyl halides in the presence of other silver salts and metal oxides:

The dibenzoate **8** was allowed to react with alkyl halides in the presence of other silver salts like silver (I) acetate, silver benzoate and silver carbonate. The dibenzoate **8** did not react with methyl iodide in the presence of silver acetate and silver benzoate and the starting material was recovered quantitatively. We attempted the reaction in the presence of silver acetate and silver benzoate to see if these salts influence the alkylation of the dibenzoate **8** as they are formed as by-products during the alkylation reactions under discussion.

A mixture of products was obtained when the dibenzoate **8** was treated with allyl bromide in the presence of silver carbonate. It underwent transesterification as

well as alkylation to give the tribenzoate **21** and diol **12** along with some amount of the monoallyl ether **17** and diallyl ether **19** (detected by ^{1}H NMR spectroscopy).

The dibenzoate **8** did not react with allyl bromide in the presence of mercuric oxide or zinc oxide or lead (IV) oxide, and it was recovered quantitatively in all the experiments. We attempted these reactions to examine the specificity of the metal salts/oxides used. Glycosylation of certain carbohydrates in the presence of mercuric oxide is known in the literature[3].

3A.2.6 Effect of the amount of silver (I) oxide and products on the reaction of racemic 2,4-di-O-benzoyl-*myo*-inositol-1,3,5-orthoformate (8) with alkyl halides:

We carried out the allylation of the dibenzoate **8** by varying the amount of silver (I) oxide (see **Table I**) since we suspected the involvement of a silver – inositol orthoformate complex during the alkylation of **8**. We also carried out allylation of the dibenzoate **8** with allyl bromide in the presence of the dimethyl ether **11** and monomethyl ether **13**, to see if the products formed had any effect on the alkylation reaction. The results are tabulated in **Table II**. Methyl ethers were used in these reactions, since the use of the corresponding allyl ethers would make the interpretation of results ambiguous.

Table I: Reaction of **8** with one equivalent of allyl bromide with varying amounts of silver (I) oxide.

Entry	Ag_2O (eq.)	Products (%)
1	5	**17** (4)[1], **18** (40), **19** (17)[1]
2	2.5	**17** (50), **18** (18)
3	1	**17** (50), **18** (12)

[1]Detected and yield calculated by ^{1}H NMR spectroscopy since **17** and **19** have same R_f values on TLC (R_f = 0.7: 20% EtOAc – light petroleum) and they could not be separated by column chromatography.

Table II: Effect of products on the reaction of dibenzoate **8** with one equivalent of allyl bromide and excess silver (I) oxide.

Entry	Compd.No.	Products (%)
1	**8**	**17** (4), **18** (40), **19** (17)
2	**8** + **11**[1]	**11** (>80), **17** (26), **18** (26), **19** (7)[2]
3	**8** + **13**[1]	**13** (52), **14** (22), **17** (75), **18** (13)

[1] **8** and **11** (or **13**) were used in the ratio of 1:1 mmol.
[2] Minor amounts of products arising from cleavage of equatorial benzoate was observed by ^{1}H NMR spectrum.

Formation of the mono allyl ether **17** (path **A**) is facilitated by decreasing the amount of silver (I) oxide (**Scheme 3A.11**), or conversely the formation of allyl hydroxy monoester **18** (path **B**) is facilitated as the amount of silver (I) oxide is increased.

Decrease in the formation of hydroxy ether **18** and increase in the formation of monoallyl ether **17**, was also observed when an equimolar mixture of the dibenzoate **8** and the dimethyl ether **11** was subjected to allylation with one equivalent of allyl bromide (**Table II**). The monoallyl ether **17** (26%) and the hydroxy ether **18** (26%) were obtained along with a small amount of the diallyl ether **19** (7%) and about 80% of the dimethyl ether **11** was recovered unchanged. Similar reactions using equimolar mixture of **8** and **13** yielded the monoallyl ether **17** (75%). Although the major part of **13** could be recovered unchanged, material balance with respect to **13** could not be established. Neither the diallyl ether **19** nor products arising out of allylation of **13** could be isolated. These experiments show that the cleavage of the axial benzoate in dibenzoate **8** is inhibited by the presence of 4,6-di-O-substituted derivatives of the diol **12**. Hence, it is likely that the predominant pathway for the formation of diallyl ether **19** from the dibenzoate **8** on its reaction with allyl bromide is *via* path **B** (**Scheme 3A.14**), at least in the initial stages of the reaction when little tri-O-substituted *myo*-inositol orthoformate derivatives are present. The results discussed so far support the operation of path **A** as well as path **B** during the allylation of the dibenzoate **8**.

3A.2.7 Solvent effects:

Since the reactivity of alcohols with alkyl halides in the presence of silver (I) oxide is known to be dependent on the solvent used for the reaction[8], we carried out allylation of the dibenzoate **1** in solvents other than DMF (**Table III**).

Table III: Effect of solvent on alkylation with excess alkyl halide (RX) and silver (I) oxide.

Entry	Compd. No.	RX[1]	Solvent	Products (%)
1	**8**	MeI	DMF	**11** (80)
2	**8**	MeI	CH_3CN	**11** (66), **13** (5), **14** (5), **21** (15)[2]
3	**8**	MeI	THF	No Reaction
4	**8**	AllBr	DMF	**19** (74)
5	**8**	AllBr	CH_3CN	**17** (9)[3], **18** (63), **19** (4)[3], **21** (11)[3]
6	**13**	AllBr	CH_3CN	No Reaction

[1] 10 Eq. of RX and 5 eq. of silver (I) oxide were used in all the experiments.

[2] From Reference 9.

[3] Detected and yield calculated by ^1H NMR spectroscopy since **17**, **19** and **21** have the same R_f value on TLC and they could not be separated by column chromatography.

As mentioned earlier (**Section 3A.2.1**), reaction of the dibenzoate **8** with methyl iodide or allyl bromide in DMF gave the corresponding 4,6-diethers, but the same reaction in acetonitrile gave mixture of products (**Table III**). Reaction of the dibenzoate **8** with excess allyl bromide in acetonitrile afforded the hydroxy ether **18** in 63% yield. Minor amount of diallyl ether **19**, monoallyl ether **17** and tribenzoate **21** could be detected by ^1H NMR spectroscopy. Similar results were obtained for the reaction of the dibenzoate **8** with methyl iodide[9]. Formation of the hydroxy ether **18** (or **14**) was facilitated by changing the solvent from DMF to acetonitrile. The dibenzoate **8** failed to react with methyl iodide in THF and the starting material could

be recovered quantitatively. Isolation of the tribenzoate **21** shows that transesterification of **8** is a side reaction to generate the diol **12**. Allylation of **21** could not be carried out under identical conditions used for the allylation of **8**, due to its limited solubility in acetonitrile. Hence to check if tri-O-substituted *myo*-inositol-1,3,5-orthoformates undergo allylation in acetonitrile, we subjected the dibenzoate **13** (which has one axial benzoate) to allylation in acetonitrile with allyl bromide. The benzoate **13** remained unaffected and could be recovered quantitatively. This is in contrast to our earlier observation that tri-O- substituted *myo*-inositol orthoformates undergo silver (I) oxide assisted allylation in DMF to yield the corresponding diallyl ethers. These experiments showed that alkylation of dibenzoate **8** in acetonitrile[7] proceeds by a combination of several reaction pathways and that the formation of the diol **12** *via* transesterification *is a competing reaction.*

A blank experiment in which the dibenzoate **8** was treated with silver (I) oxide in acetonitrile gave the tribenzoate **21** and the diol **12** in 36% yields respectively[7] along with some unreacted dibenzoate (27%). Later work in our laboratory has shown that the dibenzoate **1** undergoes base catalyzed transesterification in solid[10] and solution states[9] with facility and that this reaction is also strongly dependent on solvents[9]. Hence we carried out few more control experiments to see if the dibenzoate **8** undergoes transesterification in DMF. As mentioned earlier (page 69), the dibenzoate **8** was stable to silver (I) oxide in DMF. However, **8** underwent transesterification in DMF in the presence of a silver halide and the efficiency of transesterification decreased in the order AgI > AgBr > AgCl (**Table IV**). These results also point to the involvement of a dibenzoate – silver complex during the reaction. A plausible machanism for transesterification is shown in **Scheme 3A.15.**

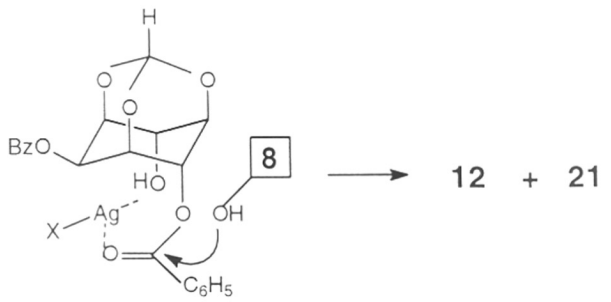
Table IV: Transesterification of **8** in the presence of silver (I) oxide[1] and silver halides (AgX) in DMF.

Entry	AgX (2 eq.)	Products (%)
1	AgI	**8** (31), **12** (21), **21** (21)
2	AgBr[2]	**8** (78), **12** (10), **21** (10)
3	AgCl[2]	**8** (90), **12** (4), **21** (4)
4	None	No Reaction

[1] 5 Eq. silver (I) oxide were used in all the experiments.

[2] From reference 9, yield by ^{1}H NMR spectroscopy.

Scheme 3A.15



The transesterification of **8** in DMF was prominent only in the absence of an alkyl halide, since the reaction of the dibenzoate **8** with one equivalent of methyl iodide or allyl bromide did not yield the tribenzoate **21**. It is important to note that the amount of silver halide used in these experiments (**Table IV, entries 1,2,3**) is the stoichiometric amount that would be generated after the completion of the corresponding alkylation reaction. The concentrations of the dibenzoate **8** and that of the silver halide vary inversely during the course of alkylation. Consequently, the transesterification reactions used as controls (**Table IV, entries 1,2,3**) give an over estimate of the amount of the diol **12** and the tribenzoate **21** if at all generated during the corresponding alkylation of the dibenzoate **8**. The occurrence of transesterification of **8** in absence of alkyl halides further support the fact that the ester moieties in **8** do not undergo hydrolysis under the conditions of alkylation, as transesterification could not have occurred in the presence of hydroxide ion, which is essential for hydrolysis of esters. The amount of the diol **12** formed *via* transesterification of **8** cannot account for the high yields of the diethers obtained by its alkylation, if diethers had formed exclusively by alkylation of the diol generated *via* transesterification of **8**. Furthermore, if diol **12** is the intermediate during formation of diethers from the dibenzoate **8**, then products and the corresponding yields obtained from alkylation of both the dibenzoate **8** and the diol **12** should be comparable. Hence we carried out alkylation of the diol **12** with alkyl halides under the conditions used for the dibenzoate **8** (see **Chapter 3B**).

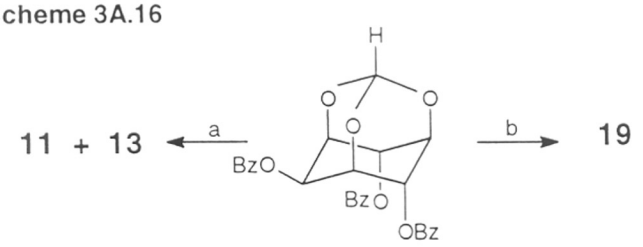
3A.2.8 Reaction of tri-O-substituted *myo*-inositol orthoformate derivatives with alkyl halides:

Since the two tri-O-substituted derivatives of *myo*-inositol orthoformate *viz.* **13** and **17** reacted with excess alkyl halide to give the diethers **11** and **19** respectively, we reacted several tri-O-substituted orthoformates with alkyl halides in DMF in the presence of excess silver (I) oxide to see how the reaction proceeds with tri-O-substituted orthoformates.

(i) Alkylation of the tribenzoate 21:

The tribenzoate **21** reacted with allyl bromide or methyl iodide to afford the corresponding diethers **11** or **19** in 80% yield. Methylation of **21** also gave some amount of the monomethyl ether **13**, which shows that the diether **11** is formed by sequential cleavage of the axial ester moieties (**Scheme 3A.16**).

Scheme 3A.16



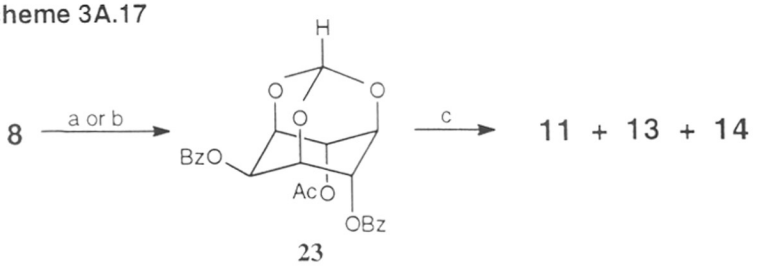
21

Reagents and conditions: (a) MeI, Ag_2O, DMF, 66h (b) AllBr, DMF. Ag_2O, 66h.

(ii) Reaction of the monoacetate 23 with methyl iodide:

The monoacetate **23** was prepared from **8** by reaction with acetic anhydride in pyridine (**Scheme 3A.17**) (**Figure 10, 11**). It could also be prepared by the reaction of the dibenzoate **8** with acetyl chloride in the presence of silver (I) oxide. No diacetate **24** could be detected during acetylation with acetyl chloride. Treatment of **23** with methyl iodide in the presence of silver (I) oxide resulted in the formation of the dimethyl ether **11** as the major product along with some monomethyl ether **13** and **14**.

Scheme 3A.17

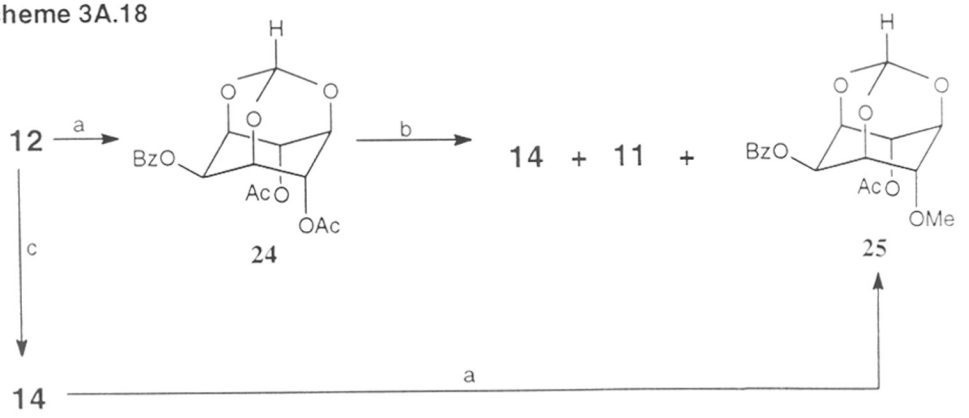


Reagents and conditions: (a) Ac $_2$O, Pyr (b) AcCl, Ag $_2$O, DMF (c) MeI Ag$_2$O, DMF, 66h

(iii) Reaction of the diacetate 24 with methyl iodide:

The diacetate **24**, prepared by the acetylation of the diol **12** with acetic anhydride in pyridine (**Scheme 3A.18**), also reacted with methyl iodide to afford dimethyl ether **11** as the major product and **27** as minor product along with the methyl ether **14** detected by TLC and ^{1}H NMR (< 10%). In order to establish the structure of **14** (**Figure 14, 15**) and the acetate **25** (**Figure 16, 17**), they were also prepared from the diol **12**. Partial methylation of the diol **12** with methyl iodide in the presence of anhydrous potassium carbonate gave **14**, which on acetylation yielded **25**.

Scheme 3A.18

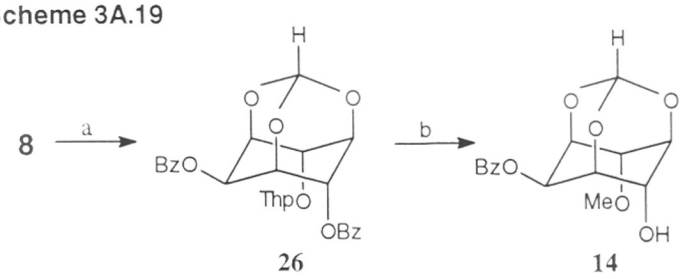


Reagents and conditions: (a) Ac $_2$O, Pyr (b) MeI, Ag $_2$O, DMF, 66h (c) MeI, K $_2$CO$_3$, DMF.

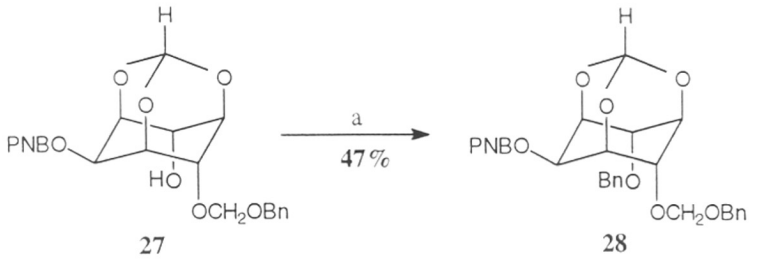
(iv) Reaction of the tetrahydropyranyl ether 26 with methyl iodide:

When the tetrahydropyranyl ether **26** (prepared as in **Chapter 2**) was subjected to methylation with methyl iodide in the presence of silver (I) oxide, the monohydroxy derivative **14** was obtained as the major product (**Scheme 3A.19**). The reaction of **26** with allyl bromide resulted in approximately 50% cleavage of the Thp-ether **26** (based on the starting material recovered).

Scheme 3A.19



Reagents and conditions: (a) DHP, PpTs, DCM (b) MeI, Ag_2O, DMF, 66l



Reagents and conditions: (a) Excess BnBr, Ag_2O, DMF.

It is pertinent to point out the results on benzylation of a *myo*-inositol orthoformate derivative **27**, in the presence of silver (I) oxide, reported by Ozaki and coworkers[11]. Benzylation of 2-O-*p*-nitrobenzoyl-4-O-benzyloxymethyl *myo*-inositol orthoformate **27** with benzyl bromide in the presence of silver (I) oxide yielded only 47% of the 6-O-benzyl ether **28**. Better yield of the benzyl ether was not obtained probably due to the cleavage of the benzyloxymethyl group (formaldehyde acetal) as we have observed in the case of methylation of tetrahydropyranyl ether **26**.

Results of the alkylation reactions presented in this section are summarized in **Table V**.

Table V: Reaction of tri-O-substituted orthoformates with alkyl halides (RX) in DMF.

Entry	Compd. No.	RX	Products[1] (%)
1.	**17**	MeI	**22** (62)
2.	**17**	AllBr	**19** (83)
3.	**13**	MeI	**11** (89)
4.	**21**	MeI	**11** (79), **13** (10)
5.	**21**	AllBr	**19** (80)
6.	**23**	MeI	**11** (76), **13** (5), **14**[2]
7.	**24**	MeI	**11** (58), **14** (9%), **25** (26)[2,3]
8.	**26**	MeI	**14** (61)

[1] All the reactions were carried out in 7 ml DMF for 66h at ambient temperature. The ratio of the orthoformate : Ag_2O : RX was 1:5:10 in all the experiments. Yields reported are isolated unless otherwise stated.

[2] Detected by TLC and ^{1}H NMR spectroscopy.

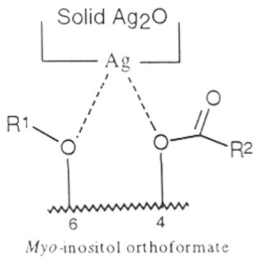
[3] Yields of all the products were calculated by ^{1}H NMR spectroscopy as **11** and **25** have the same R_f values on TLC.

All the tri-O-substituted orthoformates, except the THP ether **26** (mixture of diastereomers), reacted with methyl iodide or allyl bromide to yield the corresponding diether as the major product. In some cases (**21, 23, 24**) monomethyl ethers (**13, 25**) were obtained as minor products, which indicated the sequential cleavage of the axial ester moieties. It is important to note that the equatorial benzoate in *myo*-inositol orthoformate derivatives discussed so far remained unaffected during alkylation.

In the alkylation reactions discussed in this Chapter, it is likely that a silver-inositol orthoformate complex is involved which facilitates the cleavage and alkylation of the ester moieties (**Scheme 3A.20**). Although the complex **29** appears to be more plausible as compared to **30** (complexation with silver results in a six membered ring in **29** where as an eight membered ring in **30**), the reverse is suggested by the fact

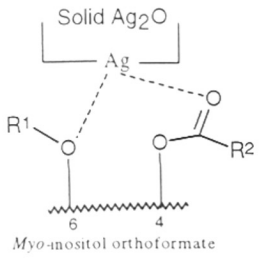
that the dibenzoate **8** undergoes transesterification in the presence of silver halides to give the triester **21** and the diol **12**.

Scheme 3A.20



Myo-inositol orthoformate

29



Myo-inositol orthoformate

30

Silver complexes of rigid molecules (calixarenes) through ether oxygens have been isolated[12] and the involvement of an alkali metal chelate during selective O-alkylation of *myo*-inositol orthoformate has earlier been suggested[7]. The isolation of a free hydroxy derivative **14** during the methylation of tri-O-substituted orthoformates (**Table V**) is of particular importance. It is relevant to note that the yield of the free hydroxy derivative **14** increases on going from benzoate **21** (**21** → **23** → **24**) to the Thp-ether **26**. This product could arise from a silver complex that breaks down to yield **14** during aqueous work-up. Methylation of the Thp-ether **26** supports this view, since the methylation of the corresponding complex (**30**, R_2CO = Thp) would be extremely difficult and thus results in larger yield of the hydroxy derivative **14**. This is supported by the fact that **14** was not visible on TLC analysis of the reaction mixture (unlike **18** which could be detected before work-up in the reaction of the dibenzoate **8** with allyl halides) (**Section 3A.2.3**) but appeared only after working up the reaction mixture (see experimental section for details). It is known in the literature[13] that tetrahydrothiopyranyl ethers can be cleaved under neutral conditions with silver nitrate in good yields. It is likely that the silver halide generated plays a role in the cleavage of the ester function (path **A**) since allyl bromide and methyl iodide react with tri-O-substituted orthoformates to yield the corresponding di-ethers but not allyl chloride. This is consistent with the fact that efficiency of transesterification of the dibenzoate **8** in the presence of silver halides decreases in the order AgI>AgBr>AgCl. It is also known that silver (I) oxide mediated etherification of alkyl halides could be autocatalytic due to silver halide generated during the reaction and that the catalytic efficiency decreases in the order AgI>AgBr>AgCl[14].

However, more work is necessary to establish the precise nature of the silver complex involved in the alkylation reactions discussed in the present chapter.

3A.3 CONCLUSIONS

The reaction of 2,4-di-O-benzoyl-*myo*-inositol-1,3,5-orthoformate (**8**) and its 6-O-substituted derivatives with alkyl halides in the presence of silver (I) oxide has been studied systematically. Nature of the product obtained depends on the amount of silver (I) oxide and alkyl halides used as well as on the solvent employed for the reaction. By varying these parameters the corresponding symmetrical 4,6-di-O-alkylated or 4-mono-O-alkylated *myo*-inositol-1,3,5-orthoformates can be obtained in good yields. These alkylations proceed by two different pathways which involve the transannular participation of the neighboring oxygen. Results presented for the allylation of 2,4-di-O-benzoyl-*myo*-inositol-1,3,5-orthoformate (**8**) suggests the cleavage and allylation of the axial 4-benzoate moiety prior to the allylation of the free 6-hydroxy group. Results presented in this chapter point to the involvement of a *myo*-inositol orthoformate-silver complex during these alkylation reactions. This work constitutes the first illustration of alkylative cleavage of esters in the presence of silver, although under specific conditions.

3A.3 EXPERIMENTAL SECTION

Materials and methods:- General experimental conditions, materials and methods are same as mentioned in **Chapter 2**, except for the following:

Allyl bromide was obtained from Aldrich Chemical Company, USA and was used as received. Acetic anhydride, pyridine, allyl chloride, acetyl chloride, cyclohexanol and potassium carbonate were obtained from SD Fine Chemicals, India and purified according to literature procedures[15]. The dibenzoate **8**, diol **12**, monomethyl ether **13**, tribenzoate **21**, dibenzyl ether **9** (R = Bn), tetrahydropyranyl ether **28** and silver (I) oxide were prepared as discribed in **Chapter 2**.

Alkylation of *myo*-inositol 1,3,5-orthoformate derivatives.

General procedure:- *Myo*-inositol 1,3,5-orthoformate derivative and the alkyl halide were dissolved in dry DMF and freshly prepared silver (I) oxide was added in portions over 10 min. with vigorous stirring and external cooling with ice. Stirring was continued at room temperature till the starting material disappeared (60-66h). The residue was allowed to settle and the supernatant liquid was decanted. The solid was washed successively with DMF (7 ml) and chloroform (2 X 10 ml). The organic extract was washed with sodium cyanide solution (1%, 100 ml) and the aqueous layer was extracted with chloroform (3 X 30 ml). The combined chloroform extract was washed with water (3 X 50 ml), dried over anhydrous sodium sulfate and evaporated in vacuo. The products were separated by column chromatography and then crystallized (EtOAc - light petroleum or DCM - light petroleum). Column chromatography was performed using silica gel (60-120 mesh) and light petroleum-ethyl acetate as eluant (gradient elution upto 20:1) unless otherwise specified.

Reaction of racemic 2,4-di-O-benzoyl-*myo*-inositol-1,3,5-orthoformate (8) with:

Excess methyl iodide:

The dibenzoate **8** (0.2 g, 0.5mmol) was allowed to react with methyl iodide (0.71 g, 5 mmol) and freshly prepared silver (I) oxide (0.58 g, 2.5 mmol) in dry DMF (2 ml) as above. The residue after workup was purified by column chromatography to give dimethyl ether **11** as a white solid (0.13 g, 80%).

Data for 11:

m.p. 143-145°C

IR (cm^{-1}): 1720

^1H NMR: 3.55 (s, 6H), 4.22 (t, 2H), 4.55 (m, 3H), 5.40 (m, 1H), 5.60 (d, 1H), 7.40-7.65 (m, 3H), 8.10-8.30 (m, 2H).

^{13}C NMR: 57.7, 64.5, 68.2, 70.0, 76.1, 103.4, 128.6, 130.0, 133.4, 166.2.

Elemental anal. calcd for $C_{16}H_{18}O_7$: C, 59.64; H, 5.59.

Found: C, 59.90; H, 5.76.

Moist silver (I) oxide:

The dibenzoate **8** (0.05 g, 0.125 mmol) in DMF (0.5 ml) was stirred at room temperature with silver (I) oxide (0.15 g, 0.67 mmol) and 0.05 ml of water for 66 h. After filtering the reaction mixture over a celite column (one inch) and washing the residue with $CHCl_3$, the organic layer was washed with water to remove DMF and concentrated after drying over anhydrous sodium sulphate. The dibenzoate **8** was recovered quantitatively.

One equivalent methyl iodide: (see **Chapter 2**).

Reaction of racemic 2,4-di-O-benzoyl-4-O-methyl-*myo*-inositol-1,3,5-orthoformate (13) with excess methyl iodide:

The monomethyl ether **13** (0.06 g, 0.14 mmol) and excess methyl iodide (0.198 g, 1.4 mmol) were taken in dry DMF (0.5 ml) and stirred with freshly prepared silver (I) oxide (0.16 g, 0.7 mmol) at room temperature for 66 hours, and worked up as usual. The dimethyl ether **11** (0.04 g, 89%) was obtained by column chromatography.

Reaction of racemic 2,4-di-O-benzoyl-4-O-methyl-*myo*-inositol-1,3,5-orthoformate (13) with silver (I) oxide:

The monomethyl dibenzoate **13** (0.05 g, 0.121 mmol) was stirred with freshly prepared silver (I) oxide (0.14 g, 0.6 mmol) in dry DMF (1 ml) and at room temperature for 66 hours. After filtering the reaction mixture over a celite column (one inch) and washing the residue with $CHCl_3$, the organic layer was washed with water to remove DMF and concentrated after drying over anhydrous sodium sulfate. The monomethyl ether **13** was recovered quantitatively.

Preparation of cyclohexylbenzoate (15):

Cyclohexanol (1.0 g, 10 mmol) was taken in dry pyridine (1 ml) and a solution of benzoyl chloride (2.1 g, 15 mmol) in dry pyridine (2 ml) was added dropwise at 0°C. After the addition was complete, the reaction mixture was stirred at room temperature for 22 hours. The reaction mixture was then quenched with ice water and extracted with chloroform (250 ml), and the organic layer was washed successively with 1N HCl (200ml), water (200 ml), 20% sodium bicarbonate solution (200 ml) and water (250ml X 3) and dried over anhydrous sodium sulphate. The organic layer was evaporated and the residue was purified by column chromatography (light petroleum) to give **15** as a colourless liquid (1.90 g, 90%).

Data for 15:

^{1}**H NMR**: 1.25-2.10 (m, 10H), 5.05 (m, 1H), 7.40-7.60 (m, 3H), 8.00-8.15 (m, 2H).

Reaction of cyclohexyl benzoate (15) with methyl iodide:

Cyclohexyl benzoate **(15)** (0.2 g, 1 mmol) and methyl iodide (0.6 ml, 10 mmol) was stirred in DMF (4 ml) with silver (I) oxide (1.16 g, 5 mmol) at room temperature for 60 h. The reaction mixture was worked up as usual and purified by column chromatography to recover the starting material **15** quantitatively.

Preparation of *myo*-inositol hexabenzoate (16):

Myo-Inositol (0.9 g, 5 mmol) was taken in dry pyridine (10 ml) and a solution of benzoyl chloride (8.4 g, 60 mmol) in dry pyridine (10 ml) was added dropwise at 0°C. After the addition was complete, the reaction mixture was stirred at room temperature for 72 hours. The reaction mixture was then quenched with ice-water, and the white precipitate formed was dissolved in chloroform (250 ml), washed successively with 1N HCl (200ml), water (200 ml), 20% sodium bicarbonate solution (200 ml) and water (250ml X 3) and dried over anhydrous sodium sulphate. The organic layer was evaporated and the residue was purified by crystallisation (DCM – light petroleum) to give the pure **16** as a white solid (3.5 g, 87%).

Data for 16:

m.p. 260-263°C (Literature[6] m.p. 266°C).

^{1}**H NMR**: 5.90 (dd, 2H), 6.15 (t, 1H, J=10 Hz), 6.35-6.50 (m, 3H), 7.20-7.75 (m, 18H), 7.85-8.00 (m, 10H), 8.15-8.25 (dd, 2H).

Reaction of *myo*-inositol hexabenzoate (16) with methyl iodide:

A solution of *myo*-inositol hexabenzoate **16** (0.2 g, 0.25 mmol) and methyl iodide (0.2 ml, 3.3 mmol) in DMF (1 ml) was stirred with silver (I) oxide (0.29 g, 1.25 mmol) at room temperature for 60 h. The reaction mixture was worked up as usual and the product purified by column chromatography to recover the starting material **16** quantitatively.

Reaction of racemic 2,4-di-O-benzoyl-*myo*-inositol-1,3,5-orthoformate (8) with:

Excess allyl chloride:

The dibenzoate **8** (0.2 g, 0.5 mmol) was allowed to react with allyl chloride (0.53 g, 7 mmol) and freshly prepared silver (I) oxide (0.58 g, 2.5 mmol) in dry DMF (2 ml) as on Page 89. The products were separated by column chromatography to obtain the monoallyl ethers **17** and **18** (0.04 g, 24%) as gums. Allyl ether **17** was crystallised (EtOAc – light petroleum) to give a white solid (0.14 g, 64%).

Data for 17:

m.p. 112-115°C

IR (cm^{-1}): 1710, 1720

^{1}H NMR: 4.10 (m, 2H), 4.42 (t, 1H), 4.57 (m, 2H), 4.75 (m, 1H), 5.10-5.32 (m, 2H), 5.65-5.85 (m, 4H), 7.40-7.65 (m, 6H), 8.05-8.30 (m, 4H).

^{13}C NMR: 64.5, 67.4, 68.4, 69.9, 70.4, 71.3, 73.7, 103.4, 118.2, 128.6, 129.4, 129.8, 130.1, 130.2, 133.6, 133.8, 165.5, 166.3.

Elemental anal. calcd for $C_{24}H_{22}O_8$: C, 65.81; H, 5.02.

Found: C, 66.13; H, 5.12.

Data for 18:

IR (cm^{-1}): 1720, 3300-3600.

^{1}H NMR: 3.87 (d, 1H, D_2O exchangeable), 4.15-4.65 (m, 7H), 5.30-5.45 (m, 2H), 5.50 (d, 1H), 5.60 (d, 1H), 5.85-6.05 (m, 1H), 7.45-7.70 (m, 3H), 8.15-8.30 (m, 2H).

^{13}C NMR: 63.7, 68.1, 68.3, 69.7, 72.0, 72.7, 74.3, 102.9, 119.8, 128.7, 129.8, 130.1, 132.9, 133.6, 166.4.

Allyl chloride (1 eq):

The dibenzoate **8** (0.2 g, 0.5 mmol) was allowed to react with allyl chloride (0.038 g, 0.5 mmol) and freshly prepared silver (I) oxide (0.58 g, 2.5 mmol) in dry

DMF (2 ml) as above. The residue after workup was purified by column chromatography to give back the starting material (0.19 g, 95%).

Reaction of racemic 2-O-benzoyl-4-O-allyl-*myo*-inositol-1,3,5-orthoformate (18) with excess allyl chloride:

The allyl ether **18** (0.08 g, 0.24 mmol) and excess allyl chloride (0.18 g, 2.4 mmol) were taken in dry DMF (1 ml) and stirred with freshly prepared silver (I) oxide (0.28 g, 1.2 mmol), at room temperature for 66 hours, and worked up as usual. The starting material **18** was recovered quantitatively.

Conversion of racemic 2-O-benzoyl-4-O-allyl-*myo*-inositol-1,3,5-orthoformate (18) to the known 4-O-allyl-*myo*-inositol-1,3,5-orthoformate (20)[7]:

The allyl ether **18** (0.15 g, 0.45 mmol) was refluxed with iso-butyl amine (0.2 ml, 2.1 mmol) in methanol (4 ml) for 48 h. After evaporation of solvent, the pure product **20** was obtained by column chromatography (0.09 g, 87%).

Data for 20:

^{1}H NMR: 3.40 (d, 1H, D_2O exchangeable, J = 10 Hz), 3.75 (d, 1H, D_2O exchangeable, J = 10 Hz), 4.00-4.55 (m, 8H), 5.25 (s, 1H), 5.35 (dd, 1H), 5.45 (s, 1H), 5.75-6.00 (m, 1H).

Reaction of racemic 2,4-di-O-benzoyl-*myo*-inositol-1,3,5-orthoformate (8) with:

Excess allyl bromide:

The dibenzoate **8** (0.2 g, 0.5 mmol) was dissolved in dry DMF (2 ml) and allyl bromide (0.6 g, 5 mmol) and silver (I) oxide (0.58 g, 2.5 mmol) were added to it. The reaction was carried out as described on Page 89. The diallyl ether **19** was obtained by column chromatography as a gum (0.14 g, 74%).

Data for 19:

IR (cm^{-1}): 1730

^{1}H NMR: 4.15 (m, 4H), 4.35 (t, 2H), 4.50 (m, 3H), 5.20-5.40 (m, 4H), 5.50 (broad s, 1H), 5.60 (d, 2H), 5.85-6.05 (m, 2H), 7.40-7.65 (m, 3H), 8.15 (m, 2H).

^{13}C NMR: 64.9, 68.6, 70.6, 70.7, 73.8, 103.5, 117.7, 128.6, 130.1, 133.5, 134.3, 166.3.

Elemental anal. calcd for $C_{20}H_{22}O_7$: C, 64.19; H,5.88.
Found: C,65.45; H,5.19.

Allyl bromide (1 eq):

The dibenzoate **8** (0.2 g, 0.5 mmol) and allyl bromide (0.06 g, 0.5 mmol) were dissolved in dry DMF (2 ml) and freshly prepared silver (I) oxide (0.58 g, 2.5 mmol) was added to it. After 60 hours the reaction mixture was worked up as above and the products separated by column chromatography. The product with higher R_f (0.7; 20% EtOAc – light petroleum) was found to be a mixture of the diallyl ether **19** and the monoallyl ether **17** in the ratio 1:4.25 (by ^{1}H NMR spectroscopy). The product with lower R_f was pure and characterised to be the allyl ether **18** (0.07 g, 41%).

Reaction of racemic 2,4-di-O-benzoyl-6-O-allyl-*myo*-inositol-1,3,5-orthoformate (17) with excess allyl bromide:

The monoallyl ether **17** (0.07 g, 0.16 mmol) and excess allyl bromide (0.19 g, 1.6 mmol) were dissolved in dry DMF (1 ml) and stirred with freshly prepared solid silver (I) oxide (0.19 g, 0.8 mmol) at room temperature for 66 hours, and worked up as usual. The pure diallyl ether **19** (0.05 g, 83.3%) was obtained by column chromatography.

Reaction of racemic 2,4-di-O-benzoyl-6-O-allyl-*myo*-inositol-1,3,5-orthoformate (17) with excess methyl iodide:

The monoallyl ether **17** (0.11 g, 0.23 mmol) and methyl iodide (0.33 g, 2.3 mmol) were dissolved in dry DMF (1 ml) and cooled to 0°C and freshly prepared solid silver (I) oxide (0.27 g, 1.15 mmol) was added to it. The reaction mixture was stirred at room temperature for 66 hours, and worked up as usual. The pure methyl ether **22** (0.05 g, 62.5%) was obtained by column chromatography as a gum.

Data for 22:

^{1}H NMR: 3.50 (s, 3H), 4.15-4.22 (m, 3H), 4.35 (m, 1H), 4.52 (m, 3H), 5.20-5.50 (m, 3H), 5.60 (d, 1H), 5.85-6.05 (m, 1H), 7.45-7.65 (m, 3H), 8.17 (dd, 2H).

Reaction of racemic 2,4-di-O-benzoyl-*myo*-inositol-1,3,5-orthoformate (8) with:

Excess benzyl bromide: see **Chapter 2**.

Allyl bromide in the presence of silver carbonate:

The dibenzoate **8** (0.09 g, 0.22 mmol) and allyl bromide (0.2 ml, 2.5 mmol) were dissolved in DMF (1 ml) and stirred with silver carbonate (0.31 g, 1.12 mmol) for 66 h at r. t. The products obtained were separated by column chromatography. The major product with R_f = 0.7 (20% EtOAc – petroleum ether) was found to be an inseparable mixture (detected by ^{1}H NMR spectroscopy) of the tribenzoate **21**, monoallyl ether **17** and the diallyl ether **19.** The product with R_f = 0.5 was identified as the dibenzoate **8** (0.01 g, 11%) and the product with R_f = 0.4 was the diol **12** (0.01 g, 15%).

Allyl bromide (1 eq) and silver (I) oxide (2.5 eq):

The dibenzoate **8** (0.2 g, 0.5 mmol) and allyl bromide (0.06 g, 0.5 mmol) were dissolved in dry DMF (2 ml) and freshly prepared silver (I) oxide (0.29 g, 1.25 mmol) was added to it. The reaction mixture was stirred at room temperature for 66 hours and worked up as usual. The products were separated by column chromatography to give monoallyl ethers **17** (0.11 g, 50%) and **18** (0.03 g, 18%).

Allyl bromide (1 eq) and silver (I) oxide (1 eq):

The dibenzoate **8** (0.2 g, 0.5 mmol) and allyl bromide (0.06 g, 0.5 mmol) were dissolved in dry DMF (2 ml) and freshly prepared silver (I) oxide (0.12 g, 0.5 mmol) was added to it. The reaction mixture was stirred at room temperature for 66 hours and worked up as usual. The pure allyl ethers **17** (0.11 g, 50%) and **18** (0.02 g, 12%) were obtained by column chromatography.

Allylation of racemic 2,4-di-O-benzoyl-*myo*-inositol-1,3,5-orthoformate (8) in the presence of racemic 2,4-di-O-benzoyl-6-O-methyl-*myo*-inositol-1,3,5-orthoformate (13):

The dibenzoate **8** (0.18 g, 0.45 mmol), the monomethyl ether **13** (0.185 g, 0.453 mmol) and allyl bromide (0.054 g, 0.45 mmol) were dissolved in dry DMF (3 ml) and stirred with freshly prepared silver (I) oxide (1.04 g, 4.5 mmol) at room temperature for 62 hours and worked up as usual. The products were separated by column chromatography to obtain the unreacted monomethyl ether **13** (0.09 g, 52%), the methyl ether **14** (0.02 g, 22%), the monoallyl ether **17** (0.14 g, 74%) and also the allyl ether **18** (0.04 g, 26%).

Allylation of racemic 2,4-di-O-benzoyl-*myo*-inositol-1,3,5-orthoformate (8) in the presence of 2-O-benzoyl-4,6-di-O-methyl-*myo*-inositol-1,3,5-orthoformate (11):

The dibenzoate **8** (0.14 g, 0.35 mmol), the dimethyl ether **11** (0.11 g, 0.34 mmol) and allyl bromide (0.03 g, 0.35 mmol) were dissolved in dry DMF (3 ml) and stirred with freshly prepared silver (I) oxide (0.8 g, 3.4 mmol) at room temperature for 62 hours and worked up as usual. The products were separated by column chromatography to obtain the unreacted dimethyl ether **11** (0.085 g, 76%), the monoallyl ether **17** (0.04 g, 26%), the diallyl ether **19** (0.01 g, 7%) (yields by ^{1}H NMR spectroscopy) and also the allyl ether **18** (0.03 g, 26%).

Reaction of racemic 2,4-di-O-benzoyl-*myo*-inositol-1,3,5-orthoformate (8) with:

Methyl iodide in THF:

The dibenzoate **8** (0.09 g, 0.23 mmol) and methyl iodide (0.15 ml, 2.3 mmol) were dissolved in THF (2 ml) and stirred with silver (I) oxide (0.26 g, 1.13 mmol) at r.t. for 82 h and worked up as usual. The starting material was obtained quantitatively after column chromatography.

Allyl bromide in acetonitrile;

The dibenzoate **8** (0.2 g, 0.5 mmol) and allyl bromide (0.5 ml, 5 mmol) were dissolved in acetonitrile (2 ml) and stirred with silver (I) oxide (0.57 g, 2.5 mmol) at r.t. for 60 h and worked up as usual. The products were separated by column chromatography. The product with R_f = 0.7 (20% EtOAc – light petroleum, 2 runs) was found to be a mixture of monoallyl ether **17** (9%), diallyl ether **19** (4%) and tribenzoate **21** (11%) (yields by ^{1}H NMR spectroscopy), and the major product with R_f = 0.4 (20% EtOAc – light petroleum, 2 runs) was the pure allyl ether **18** (0.11 g, 63%).

Silver iodide:

The dibenzoate **8** (0.19 g, 0.47 mmol) was dissolved in DMF (2 ml) and stirred with silver (I) oxide (0.58 g, 2.5 mmol) and silver iodide (0.24 g, 1 mmol) at r.t. for 66 h and worked up as usual. The products were separated by column chromatography. The product with R_f = 0.7 (20% EtOAc – light petroleum, 2 runs) was found to be the tribenzoate **21** (0.05 g, 21%) and the product with R_f = 0.2 (20% EtOAc – light petroleum, 2 runs) was the diol **12** (0.03 g, 21%). Some amount of dibenzoate **8** was also recovered (0.06 g, 31%).

Reaction of 2,4,6-tri-O-benzoate-*myo*-inositol-1,3,5-orthoformate (21) with:

Excess allyl bromide:

The tribenzoate **21** (0.1 g, 0.2 mmol) and allyl bromide (0.2 ml, 2 mmol) were dissolved in dry DMF (2 ml) and freshly prepared silver (I) oxide (0.23 g, 1 mmol) was added to it. The reaction mixture was stirred at room temperature for another 72 hours and worked up as usual. The product was purified by column chromatography to obtain the diallyl ether **19** (0.6 g, 80%).

Excess methyl iodide:

The triester **21** (0.37 g, 0.73 mmol) and methyl iodide (1.04 g, 7.3 mmol) were dissolved in dry DMF (7 ml) and stirred with freshly prepared silver (I) oxide (0.87 g, 3.75 mmol) at room temperature for 66 hours, and worked up as usual. The products were separated by column chromatography to give the monomethyl ether **13** (0.02 g, 10%) and the dimethyl ether **11** (0.19 g, 79%).

Preparation of racemic 2,4-di-O-benzoyl-6-O-acetyl-*myo*-inositol-1,3,5-orthoformate (23):

The dibenzoate **8** (1.2 g, 3 mmol) was dissolved in dry pyridine (20 ml) and a solution of acetic anhydride (3.06 g, 30 mmol) in dry pyridine (10 ml) was added drop-wise at 0°C. After the addition was complete, the reaction mixture was stirred at room temperature for 26h. The reaction mixture was then added to ice cold sodium chloride solution, and the white precipitate formed was filtered, washed twice with water and extracted with chloroform (200 ml). The chloroform solution was washed successively with 0.1 N hydrochloric acid (200 ml), water (200 ml), 20% sodium bicarbonate solution (50 ml X 2) and water (200 ml X 3) till the washings were neutral and finally dried over sodium sulfate and evaporated in vacuo. The residue was crystallized (DCM - light petroleum) to obtain **23** as a white solid (1.13 g, 89%).

Data for 23:

m.p. 155-156°C

IR (cm^{-1}): 1750, 1720.

^{1}H NMR: 1.80 (s, 3H), 4.55 (m, 1H), 4.62 (m, 1H), 4.77 (m, 1H), 5.65 (m, 2H), 5.70 (d, 1H), 5.80, (m, 1H), 7.40-7.65 (m, 6H), 8.05-8.20 (m, 4H)

^{13}C NMR: 20.6, 64.0, 66.7, 67.9, 68.1, 69.4, 69.5, 103.4, 128.7, 128.8, 129.1, 129.5, 130.0, 130.1, 133.8, 134.0, 164.9, 166.3, 169.3.

Elemental anal. calcd for $C_{23}H_{20}O_9$: C, 62.73; H, 4.54.

Found: C, 62.58; H, 4.20.

Preparation of racemic 2,4-di-O-benzoyl-6-O-acetyl-*myo*-inositol-1,3,5-orthoformate (23) from 2,4-di-O-benzoyl-*myo*-inositol-1,3,5-orthoformate (8):

The diester **8** (0.2 g, 0.5 mmol) and acetyl chloride (0.35 ml, 5 mmol) were dissolved in dry DMF (2 ml) and stirred with freshly prepared silver (I) oxide (0.58 g, 2.5 mmol) at room temperature for 60 hours, and worked up as usual. The product was purified by column chromatography to obtain the monoacetate **23** (0.16 g, 72%).

Reaction of racemic 2,4-di-O-benzoyl-6-O-acetyl-*myo*-inositol-1,3,5-orthoformate (23) with methyl iodide:

The triester **23** (0.2 g, 0.45 mmol) and methyl iodide (0.71 g, 5 mmol) were dissolved in dry DMF (7 ml) and stirred with freshly prepared silver (I) oxide (0.58 g, 2.5 mmol) at room temperature for 66 hours, and worked up as usual. The products were separated by column chromatography to obtain the 4,6-dimethyl ether **11** (0.11 g, 76%) and the mono-methyl ether **13** (0.01 g, 5%). A small amount of **14** (0.02 g, ~14%) could also be detected by ^{1}H-NMR spectroscopy.

Preparation of 2-O-benzoyl-4,6-di-O-acetyl-*myo*-inositol-1,3,5-orthoformate (24):

The diol **12** (0.6 g, 2 mmol) in dry pyridine (10 ml) was acetylated using a solution of acetic anhydride (2.04 g, 20 mmol) in dry pyridine (10 ml) as above, except that the reaction time was 9h. The product was purified by column chromatography to obtain **24** as a solid (0.65 g, 86%).

Data for 24:

m.p. 142-143°C

IR (cm^{-1}): 1750, 1715.

^{1}H NMR: 2.07 (s, 6H), 4.45 (m, 2H), 4.60 (m, 1H), 5.37 (d, 1H), 5.50 (t, 2H), 5.60 (d, 1H), 7.40-7.60 (m, 3H), 8.05-8.15 (m, 2H).

^{13}C NMR: 20.6, 63.7, 66.4, 67.8, 69.1, 103.2, 128.5, 129.4, 129.9, 133.6, 166.0, 169.1.

Elemental Anal. Calcd for $C_{18}H_{18}O_9$: C, 57.14; H, 4.76.
Found: C, 56.81; H, 4.83.

Reaction of 2-O-benzoyl-4,6-di-O-acetyl-*myo*-inositol-1,3,5-orthoformate (24) with excess methyl iodide:

The diacetate **24** (0.19 g, 0.5 mmol) and excess methyl iodide (0.71 g, 5 mmol) were dissolved in dry DMF (7 ml) and stirred with freshly prepared silver (I) oxide (0.58 g, 2.5 mmol) at room temperature for 66 hours, and worked up as usual. The products were separated by column chromatography to obtain the dimethyl ether **11**(0.09 g, 58%), the monoacetate **25** (0.05 g, 26%) and a trace of the hydroxy ether **14** (0.014 g, 9%) (**11, 25** and **14** detected and yield calculated by ^{1}H NMR spectroscopy).

Preparation of 2,4-Di-O-benzoyl-6-O-tetrahydropyranyl-*myo*-inositol-1,3,5-orthoformate (26) (mixture of diastereomers): See **Chapter 2.**

Reaction of 2,4-di-O-benzoyl-6-O-tetrahydropyranyl-*myo*-inositol-1,3,5-orthoformate (26) (mixture of diastereomer) **with methyl iodide:**

The Thp-ether **26** (0.2 g, 0.415 mmol) and excess methyl iodide (0.57 g, 4mmol) were dissolved in dry DMF (7 ml) and stirred with freshly prepared silver (I) oxide (0.5 g, 2.0 mmol) at room temperature for 66 hours, and worked up as usual. The products were separated by column chromatography to obtain the methyl ether **14** (0.08 g, 61%) and a trace of the monomethyl ether **13** (0.01 g, 2.4%).

Preparation of racemic 2-O-benzoyl-4-O-methyl-*myo*-inositol-1,3,5-orthoformate (14):

The diol **12** (0.29 g, 1 mmol), methyl iodide (1.42 g, 10 mmol) and anhydrous potassium carbonate (0.7 g, 5 mmol) were stirred in dry DMF (4 ml) at room temperature for 13h. The reaction mixture was filtered through a short silica gel column, and the filtrate was diluted with chloroform, washed with water, dried over anhydrous sodium sulphate and the solvent was evaporated. The products were separated by column chromatography to obtain the dimethyl ether **11** (0.03 g, 10%) and the monomethyl ether **14** as a white solid (0.23 g, 83%).

Data for 14:

m.p. 102-105°C

IR (cm^{-1}): 1720, 3360, 3500.

^{1}H NMR: 3.57 (s, 3H), 3.82 (d, D_2O exchangeable, 1H), 4.27 (m, 1H), 4.35-4.50 (m, 2H), 4.52 (m, 1H), 4.65 (m, 1H), 5.45 (d, 1H), 5.55 (d, 1H), 7.40-7.65 (m, 3H), 8.10-8.30 (m, 2H).

^{13}C NMR: 58.3, 63.6, 67.8, 68.2, 69.2, 72.6, 76.5, 102.8, 128.6, 129.7, 130.1, 133.6, 166.3.

Elemental anal. calcd for $C_{15}H_{16}O_7$: C, 58.44; H, 5.19.

Found: C, 58.52; H, 4.95.

Preparation of racemic 2-O-benzoyl-4-O-acetyl-6-O-methyl-*myo*-inositol-1,3,5-orthoformate (25):

The monomethyl ether **14** (0.11 g, 0.36 mmol) was acetylated as in the case of **15** in dry pyridine (1 ml) using a solution of acetic anhydride (0.42 ml, 4.1 mmol) in dry pyridine (1 ml) except that the reaction time was 17h. The product was filtered through a short column of silica gel to obtain **25** as a white solid (0.12 g, 99%).

Data for 25:

m.p. 135-138°C

IR (cm^{-1}): 1750, 1735.

^{1}H NMR: 2.12 (s, 3H), 3.45 (s, 3H), 4.22 (m, 1H), 4.45 (m, 1H), 4.55 (m, 1H), 4.65 (m, 1H), 5.45 (m, 2H), 5.62 (s, 1H), 7.35-7.65 (m, 3H), 8.10-8.25 (m, 2H).

^{13}C NMR: 20.8, 57.5, 64.2, 66.6, 68.4, 69.6, 69.7, 75.5, 103.3, 128.6, 129.8, 130.0, 133.5, 166.2, 170.0.

Elemental anal. calcd for $C_{17}H_{18}O_8$: C, 58.33; H, 5.14.

Found: C, 58.28; H,4.92.

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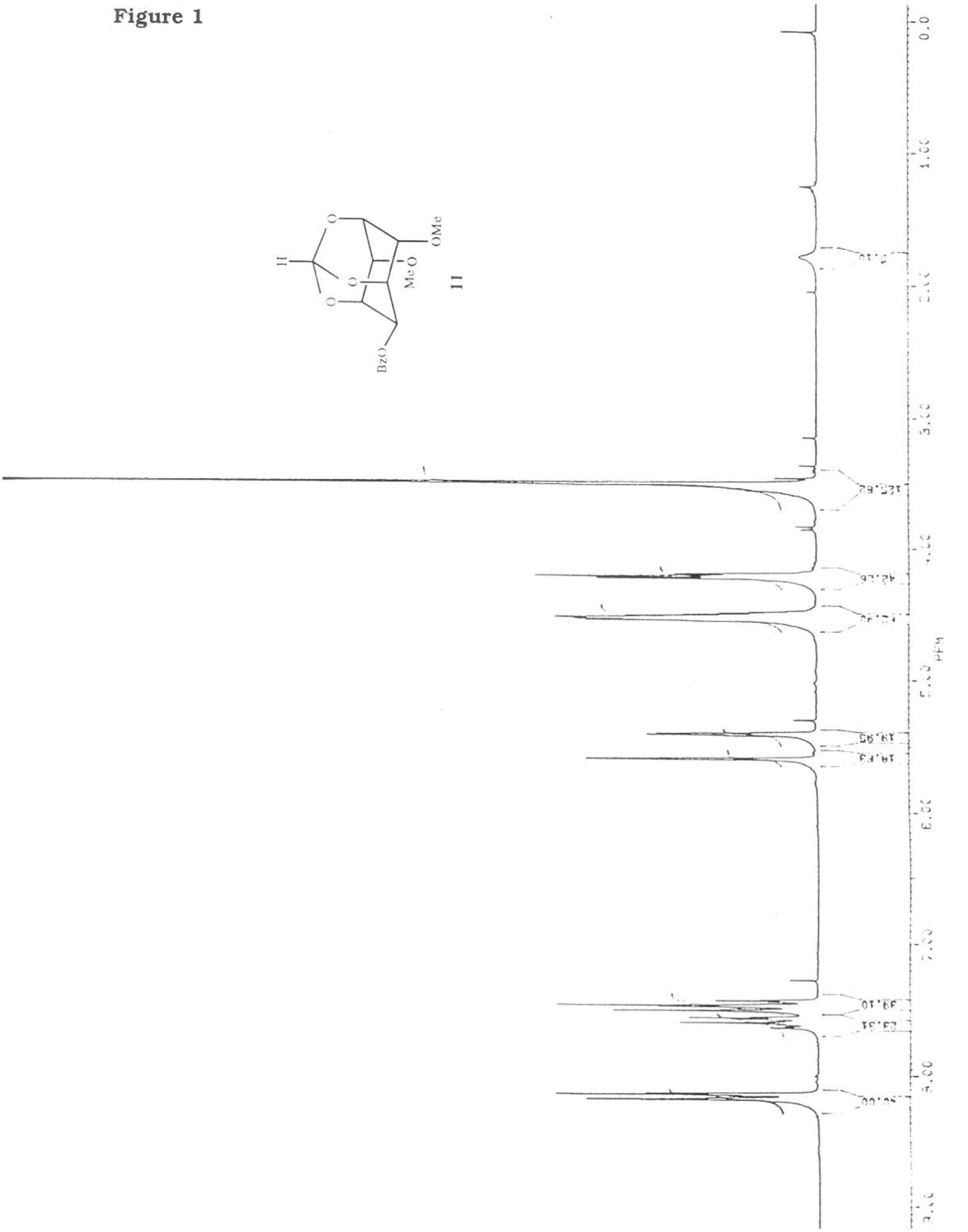
Figure 1



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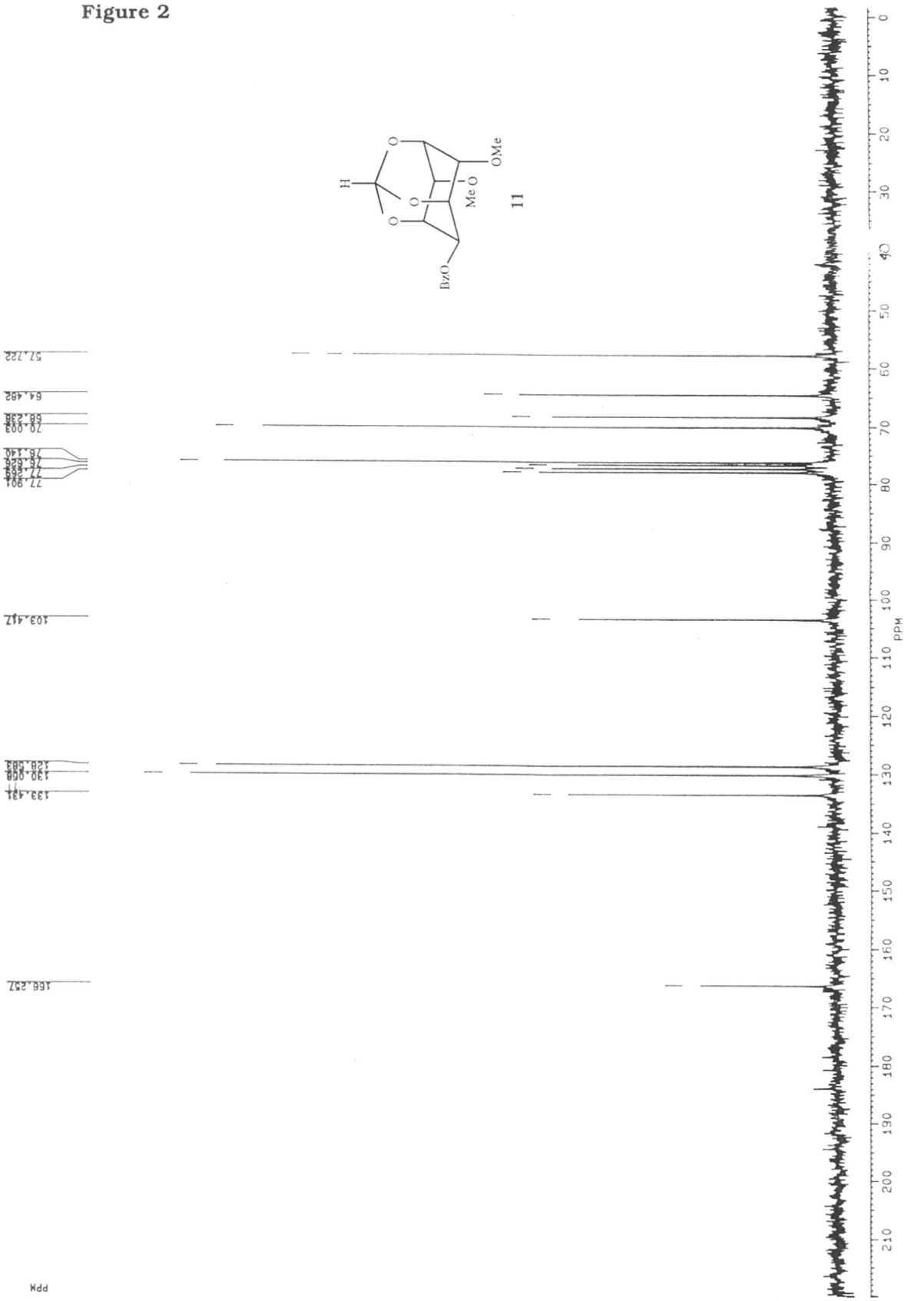
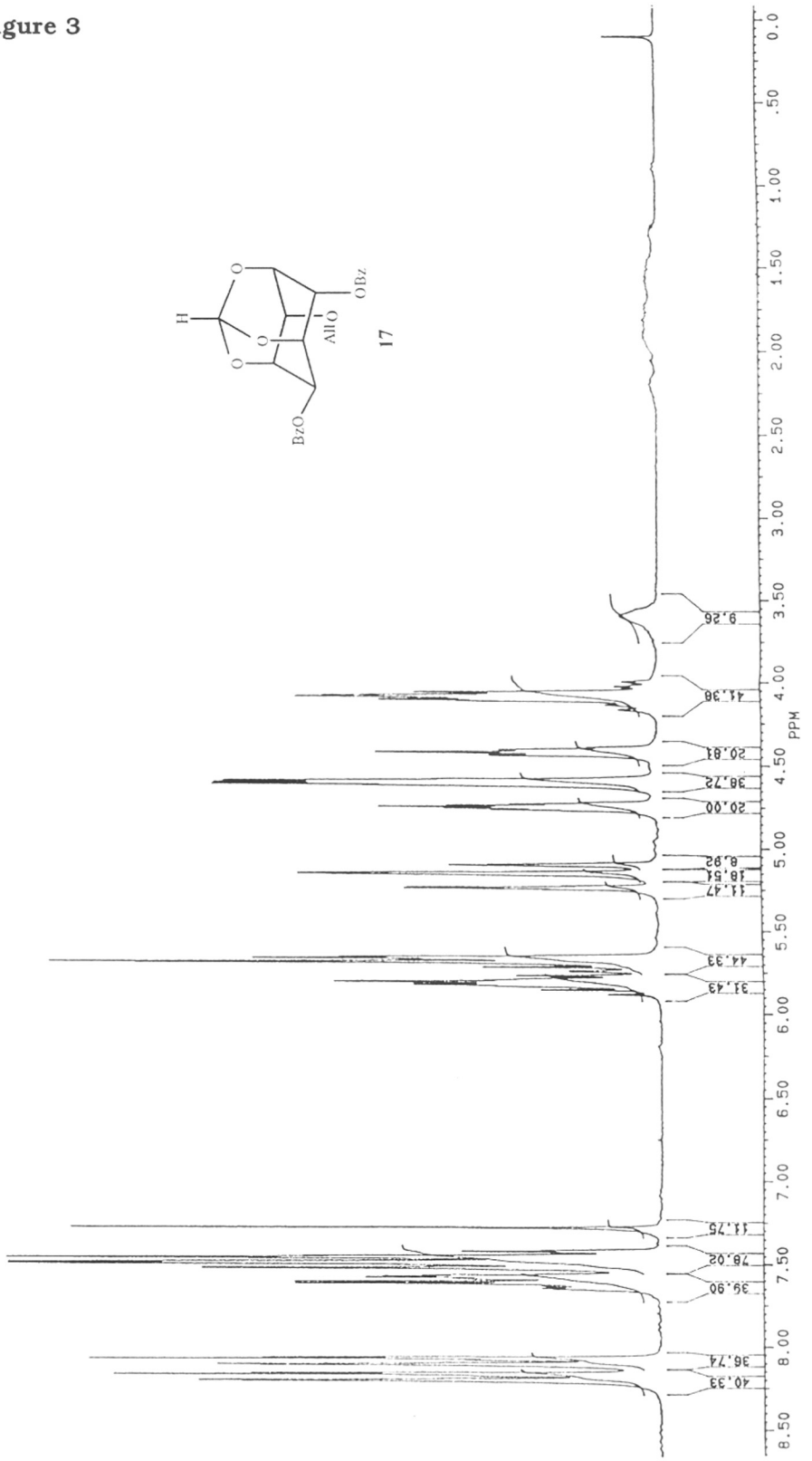


Figure 3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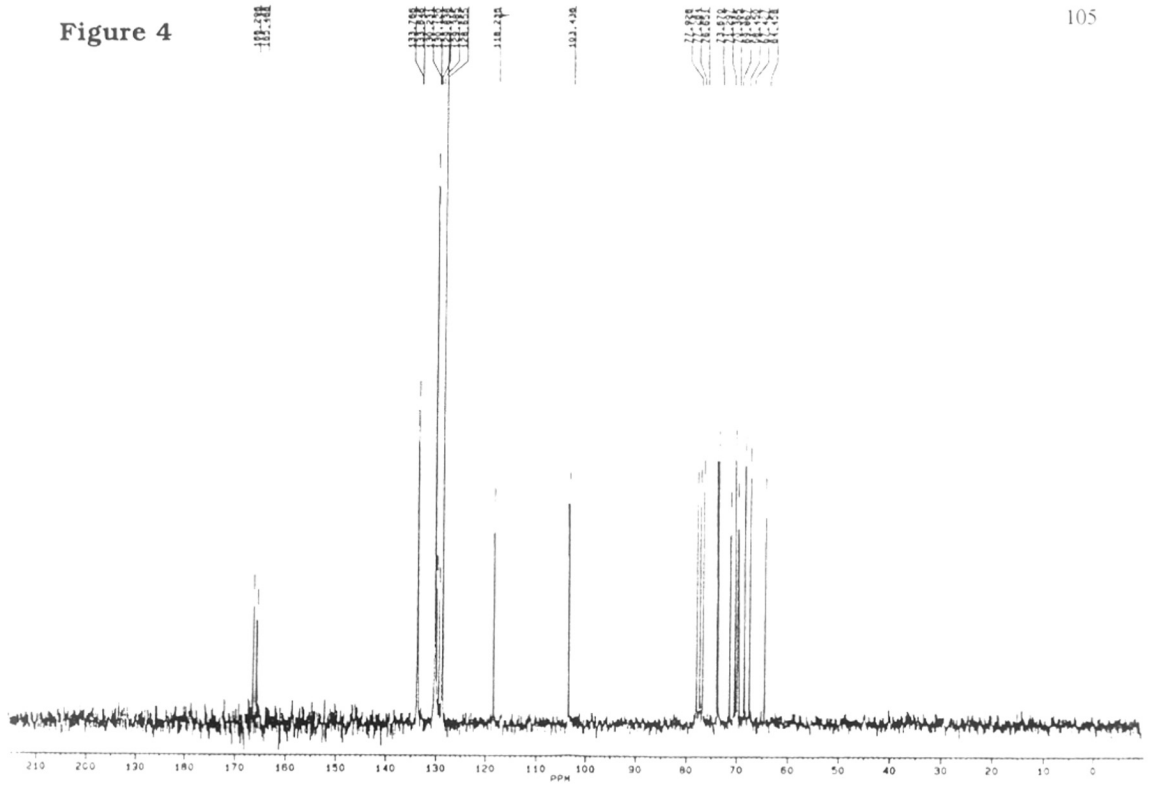
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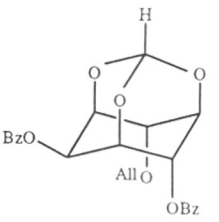
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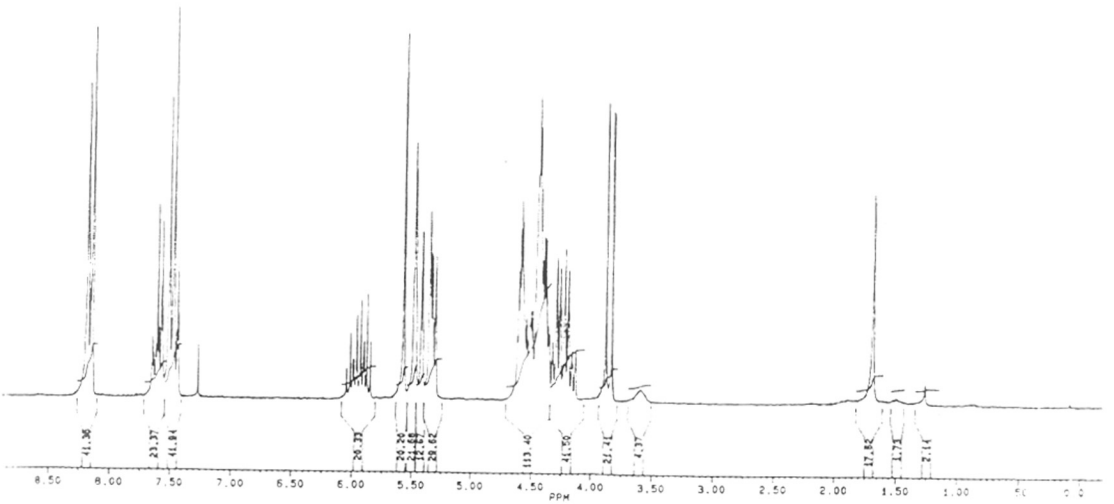
Figure 5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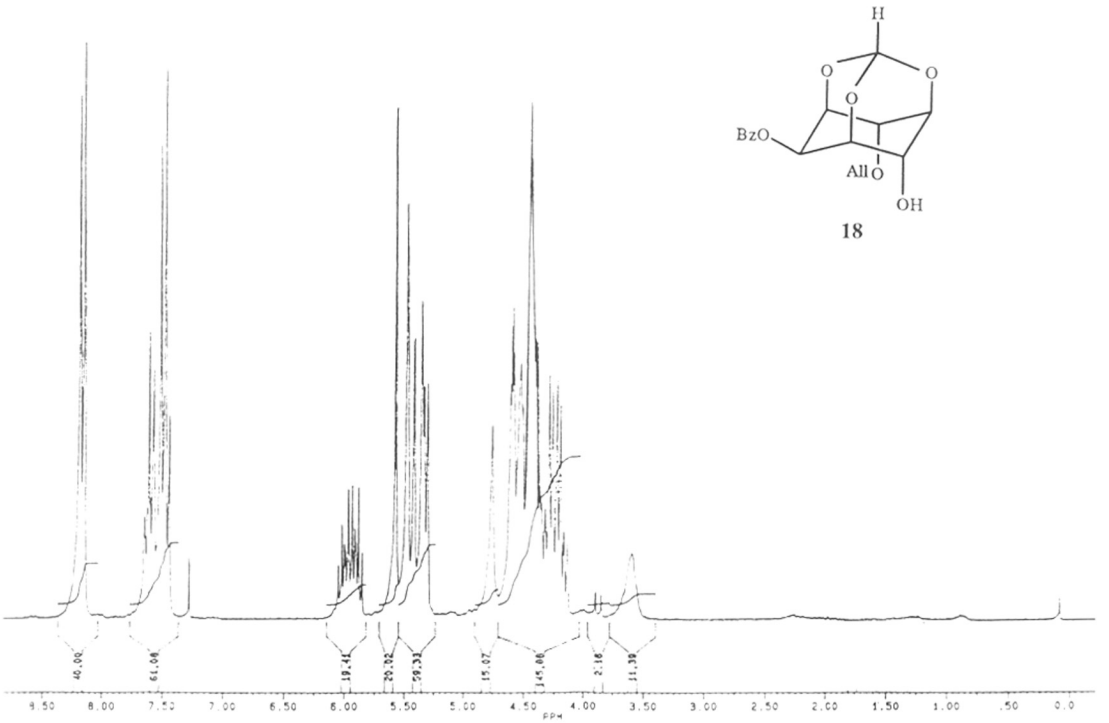
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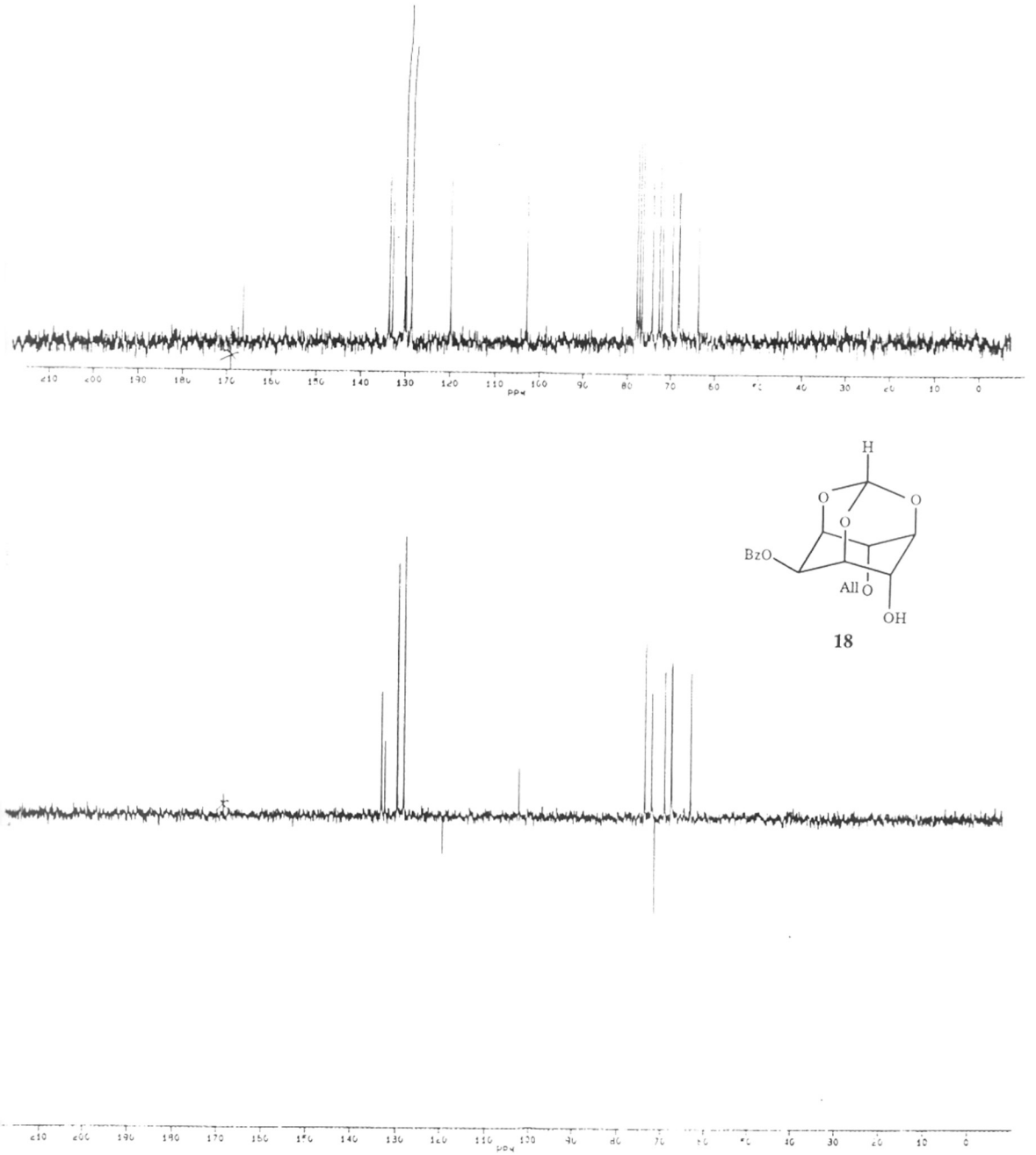

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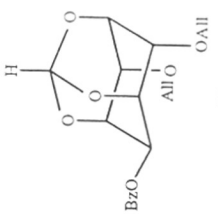
Figure 7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19

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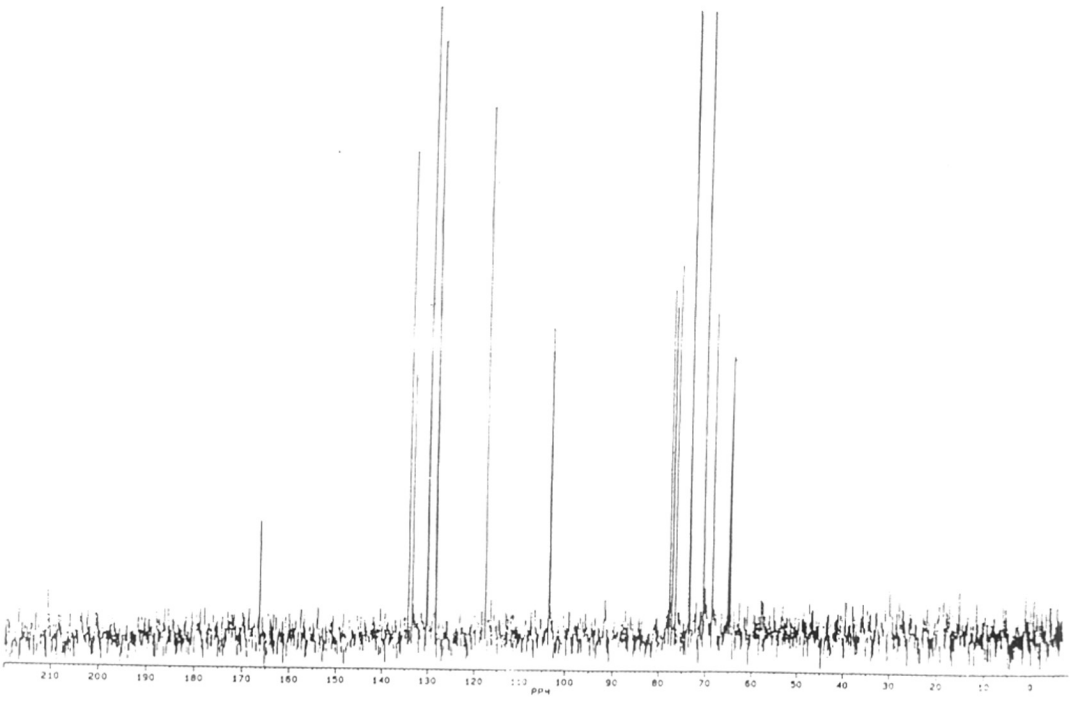
Figure 8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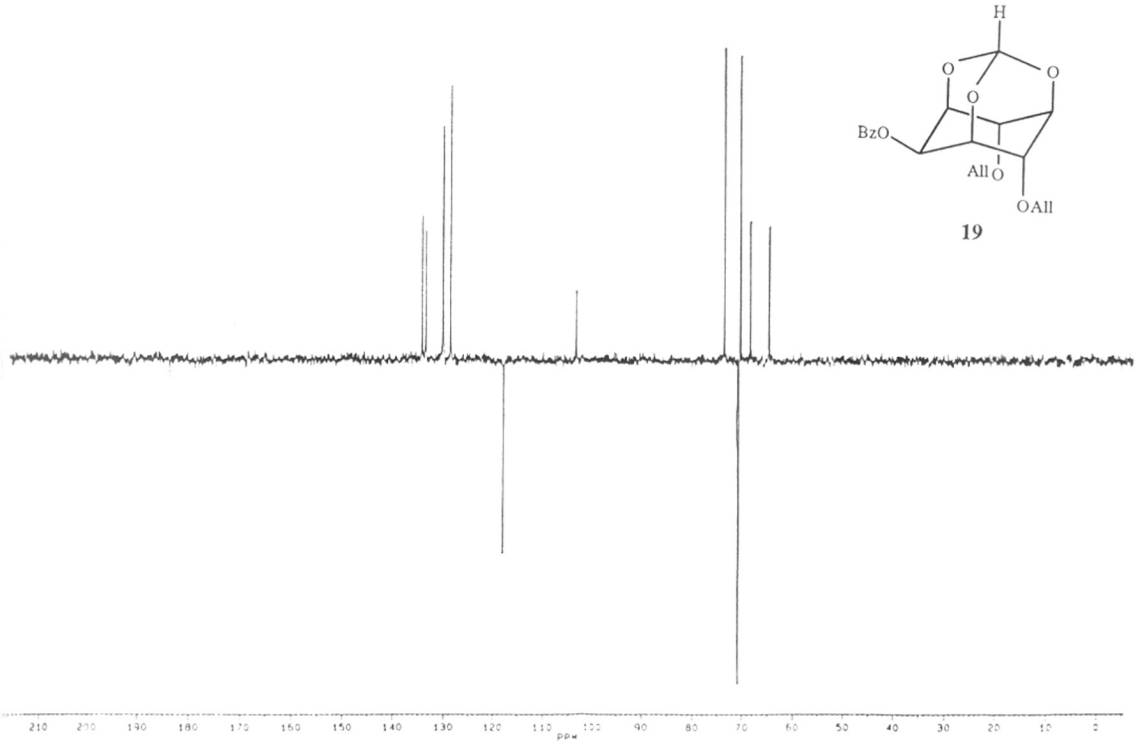
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10
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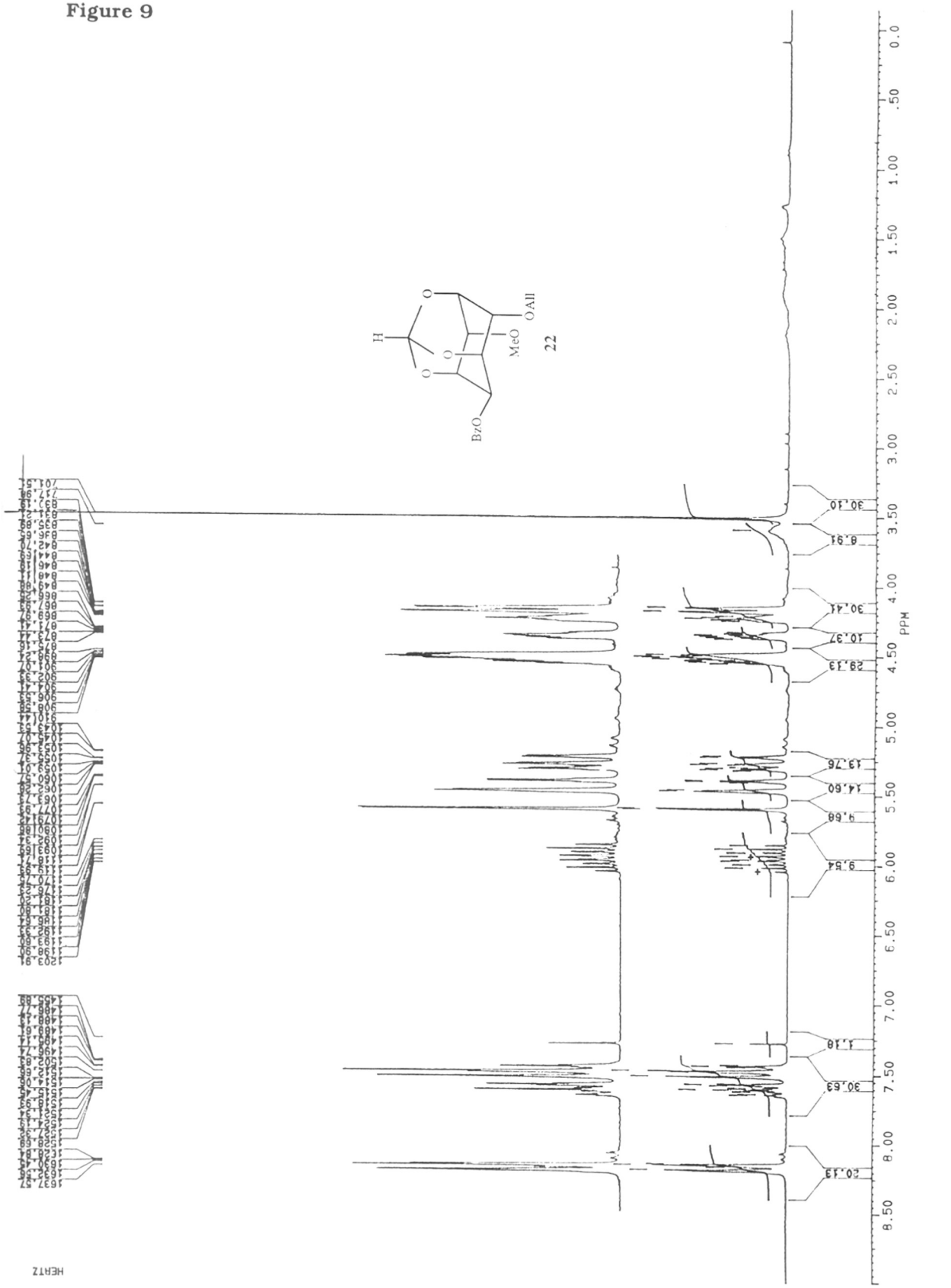
ppm

H
O
O
O
BzO
All
O
OAll

19

Figure 9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O
O
O
MeO
OAll
BzO
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8.91
30.44
10.37
28.13
13.76
14.60
9.68
9.64
1.18
30.63
20.13
PPM
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.50
1.00
1.50
2.00
2.50
3.00
3.50
4.00
4.50
5.00
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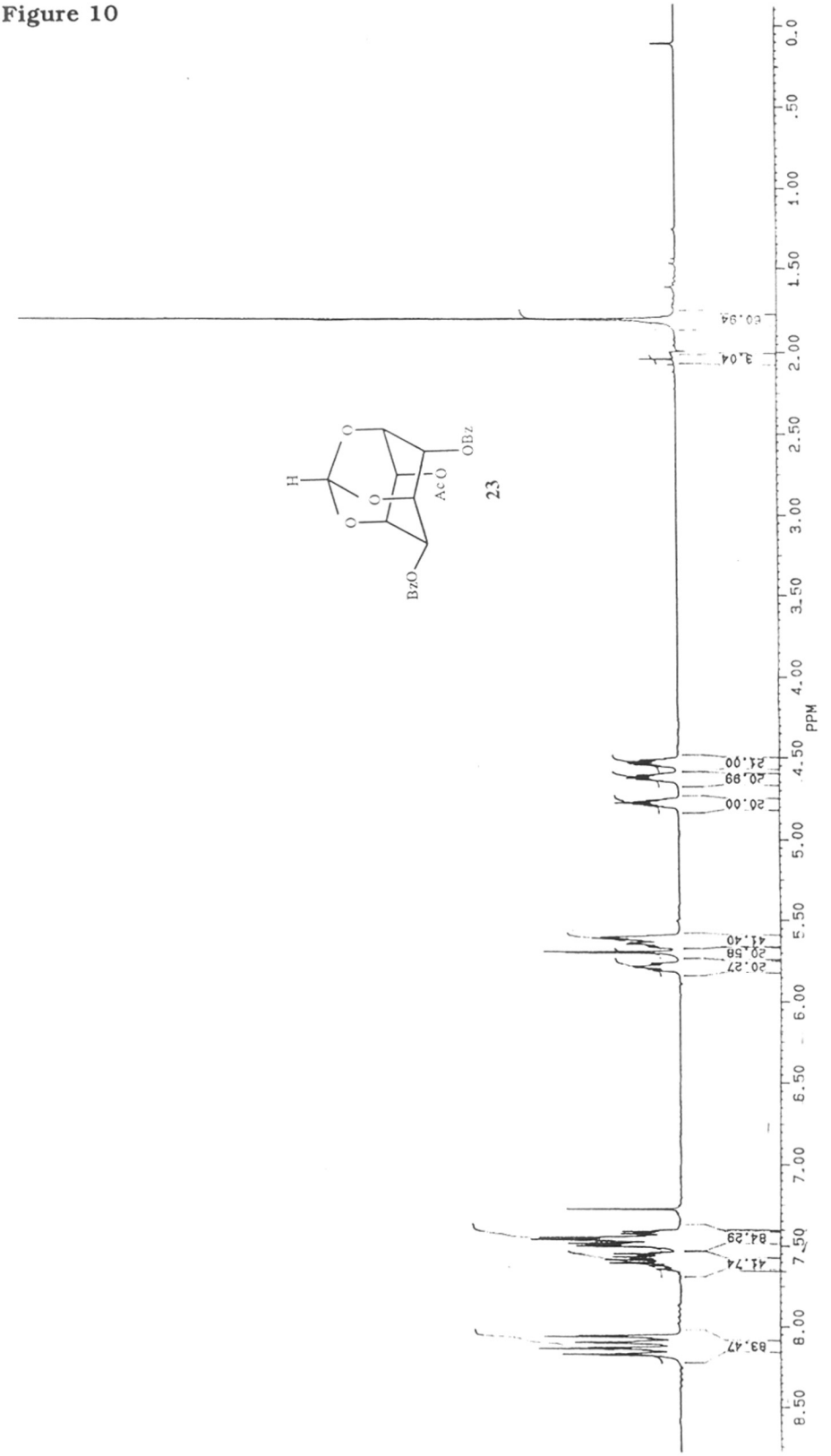
6.00
6.50
7.00
7.50
8.00
8.50

Figure 10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20.00
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20.27
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1.50
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3.50
4.00
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5.50
6.00
6.50
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8.00
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H
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O
O
O
AcO
OBz
BzO

23

Figure 11

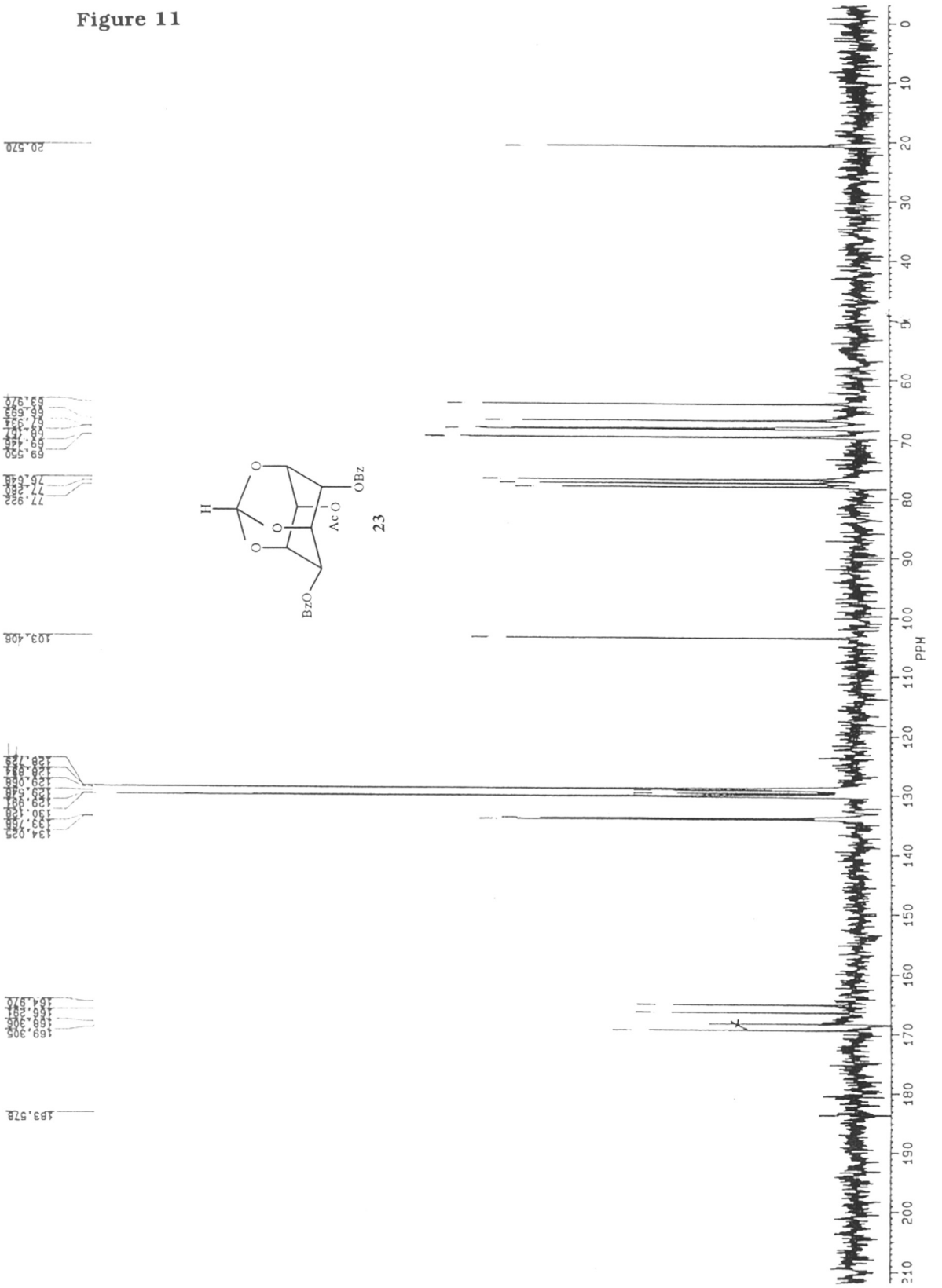
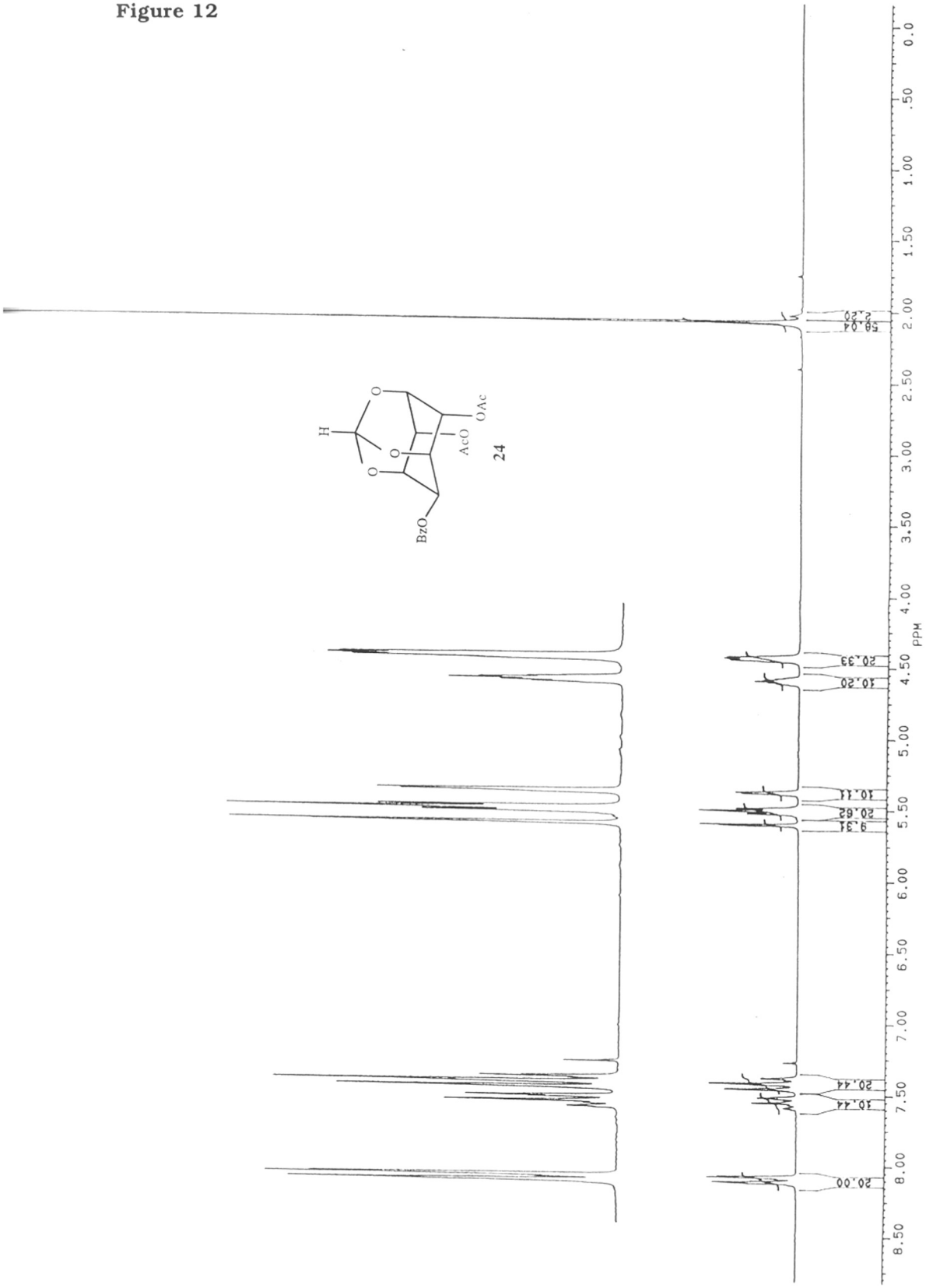


Figure 12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AcO
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BzO
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2.20
20.33
10.20
10.11
20.82
9.31
20.44
10.44
20.00
0.0
.50
1.00
1.50
2.00
2.50
3.00
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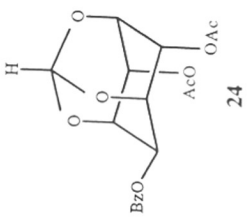
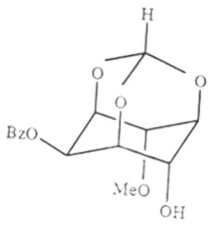
7.50
8.00
8.50
PPM

Figure 13



24

Figure 14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BzO
MeO
OH

14

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7.50
7.00
6.50
6.00
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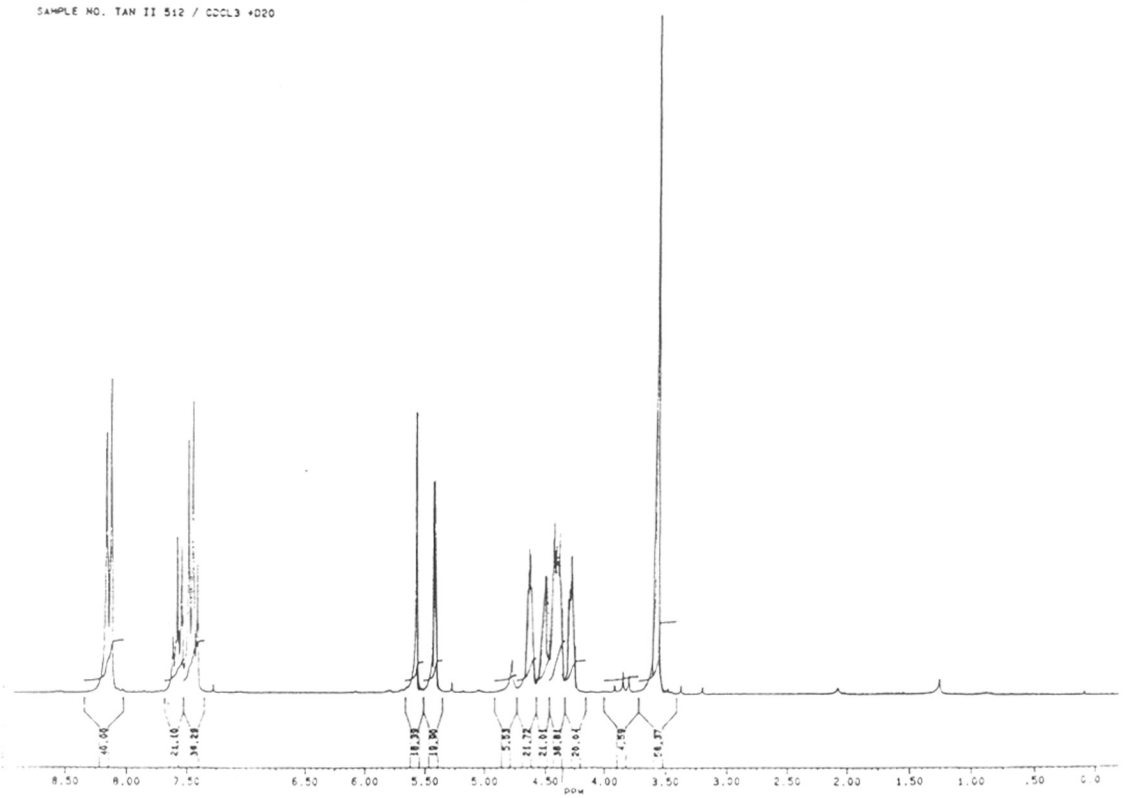
PPM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7.50
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2.50
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0.0
PPM

Figure 15

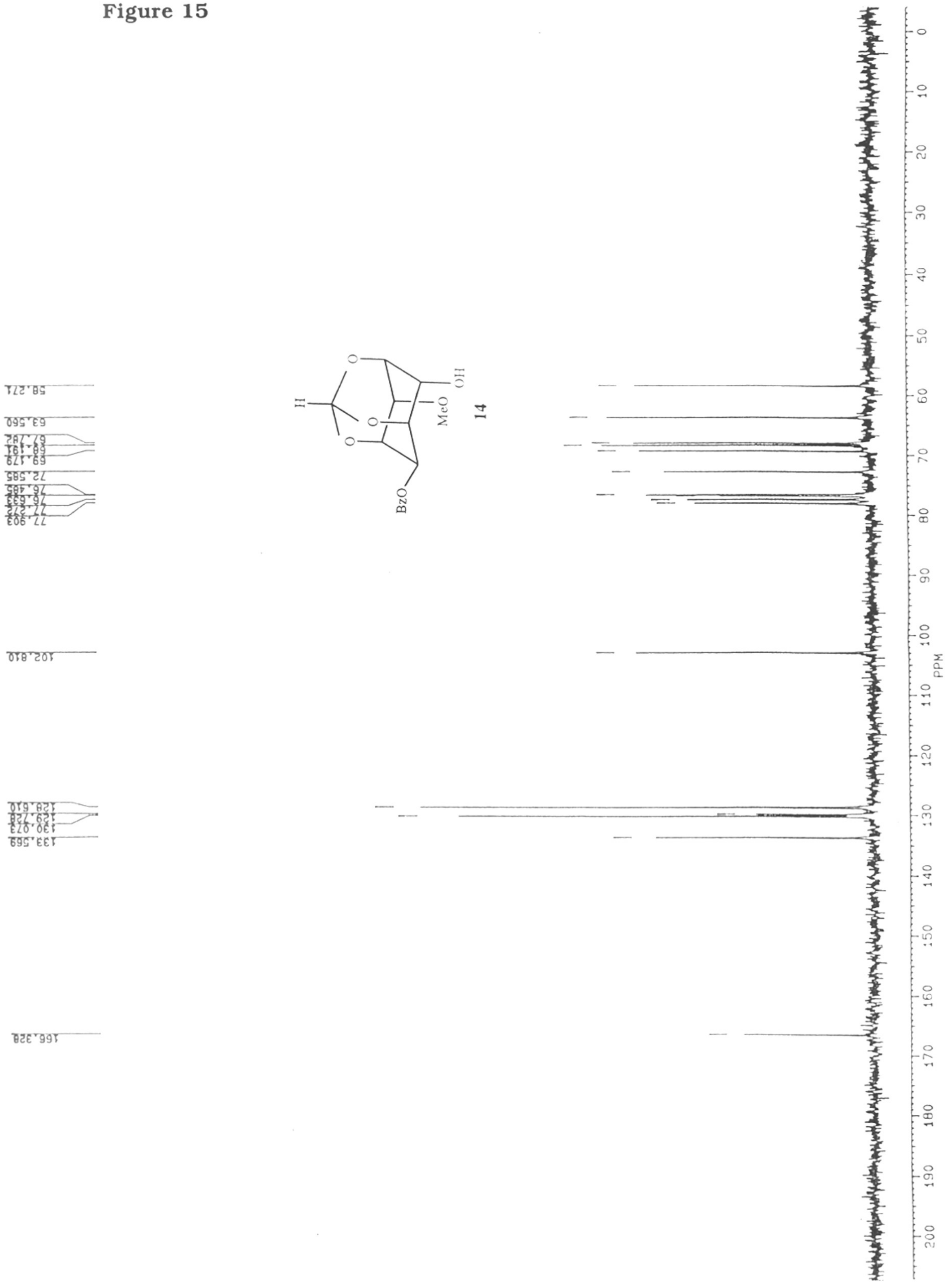
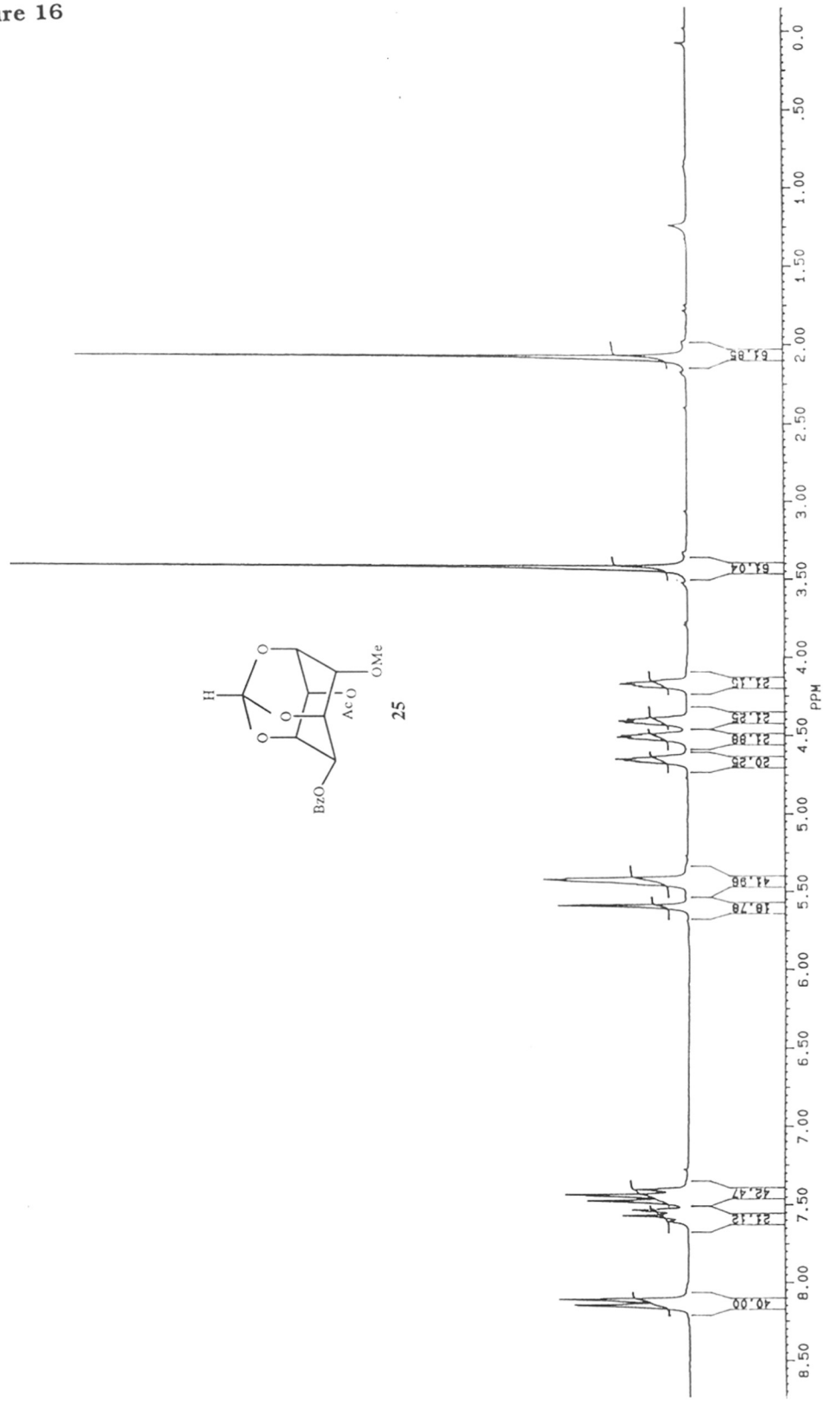


Figure 16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18.78
42.47
21.12
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4.50
5.00
5.50
6.00
6.50
7.00
7.50
8.00
8.50
PPM

H
O
O
O
AcO
OMe
BzO

25

Figure 17

20.823
57.907
64.162
66.677
69.634
69.736
75.468
76.648
77.279
77.913
103.298
133.511
166.176
168.962
H
O
O
O
AcO
OMe
BzO
25
ppm

CHAPTER 3

Part B: Silver (I) oxide mediated alkylation of 2-O-benzoyl-*myo*-inositol-1,3,5-orthoformate

3B.1 INTRODUCTION

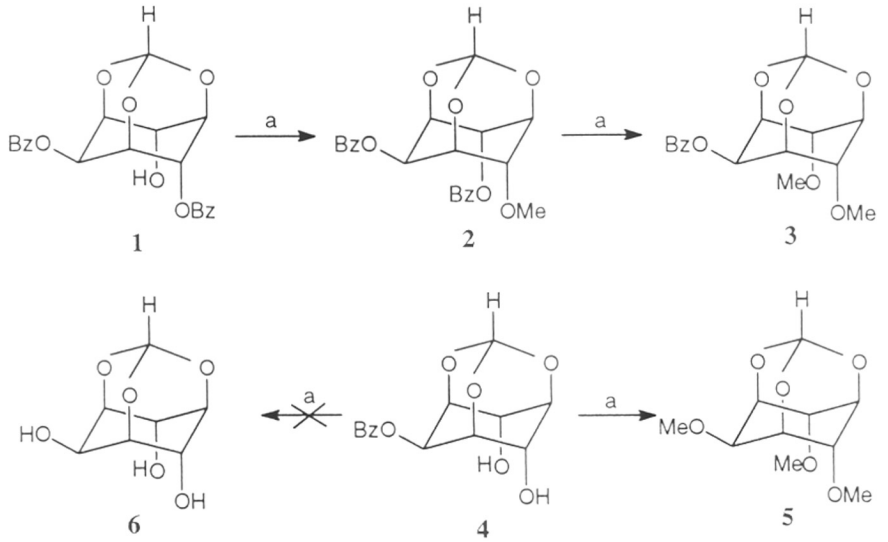
In **Chapter 3A**, an unusual silver (I) oxide mediated O-alkylation of the dibenzoate **1** and its derivatives to the corresponding 4,6-diethers which proceeds with transannular participation of 4,6-diaxial oxygens, was discussed. Methylation of the dibenzoate **1** in DMF with methyl iodide gave the dimethyl ether **3** and the reaction was found to proceed exclusively through the intermediacy of the monomethyl ether **2** (**Scheme 3B.1**). However, such clear cut evidence could not be obtained for the reaction of O-acyl-*myo*-inositol-1,3,5-orthoformates with other alkyl halides and several parallel reaction pathways leading to the formation of 4,6-diethers were suggested. Although hydrolysis of the axial 4-benzoate in **1** could be ruled out under the conditions of alkylation, its transesterification to generate the diol **4** seemed a remote possibility. If the diol is indeed an intermediate during the alkylation of the dibenzoate **1** in the presence of silver (I) oxide, products obtained by the alkylation of the dibenzoate **1** and the diol **4** under similar conditions, must be the same. In order to test this, we carried out alkylation of the diol **4** under the conditions used for the alkylation of the dibenzoate **1** (**Chapter 3A**). Accordingly, this Chapter presents a comparative study on the O-alkylation of the dibenzoate **1** and the diol **4** under a variety of conditions.

3B.2. RESULTS AND DISCUSSION

3B.2.A Reaction of diol 4 with methyl iodide in DMF:

Reaction of the diol **4** with methyl iodide yielded 2,4,6-tri-O-methyl-*myo*-inositol-1,3,5-orthoformate (**5**) as the major product (**Scheme 3B.1**) which was identified by ^{1}H and ^{13}C NMR spectroscopy (**Figure 1**). The ^{1}H NMR spectrum of **5** showed two singlets for methyl groups in the ratio 1:2 (δ 3.45 and 3.55), four signals for the inositol ring hydrogens and the orthoformate proton appeared as a doublet at δ 5.55. There were no signals in the aromatic region indiacting the absence of benzoate groups. The ^{13}C NMR spectrum further confirmed the structure showing one orthoformate carbon (102.7 ppm), four signals for inositol ring carbons and two signals for the methyl carbons (56.1 and 57.1 ppm) indicating the symmetrical nature of the molecule. Control experiments in which the diol **4** was treated with silver (I) oxide alone showed that there was no hydrolysis of the equatorial 2-benzoate in **4** to generate the corresponding triol **6**, under the conditions of alkylation (**Scheme 3B.1**).

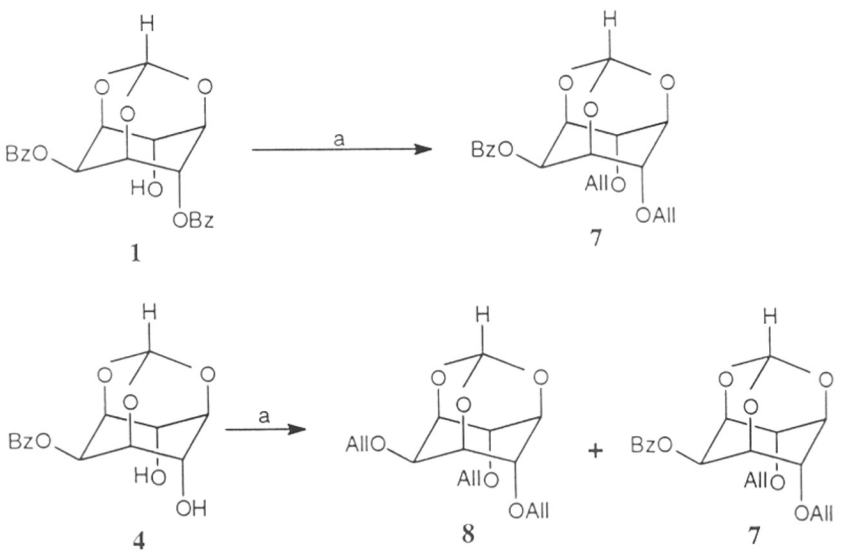
Scheme 3B.1



Reagents and conditions: (a) MeI, Ag_2O, DMF (b) Ag_2O, DMF.

3B.2.B Reaction of diol 4 with allyl bromide in DMF:

Scheme 3B.2

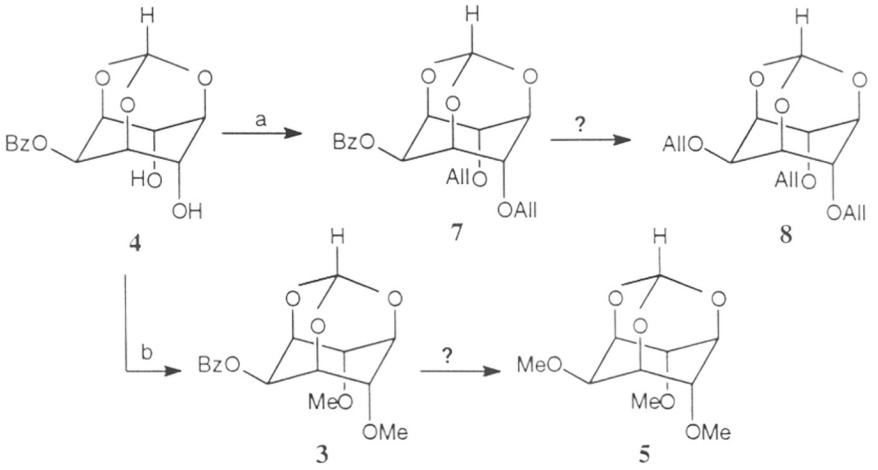


Reagents and conditions: (a) AllBr, Ag_2O, DMF.

The diol **4** reacted with allyl bromide to give the triallyl ether **8** in 53% yield (**Scheme 3B.2**) along with some diallyl ether **7**. The product **8** was characterized

by ^{1}H (**Figure 2**) and ^{13}C NMR spectroscopy (**Figure 3**). The spectral characteristics were similar to that of the trimethyl ether **5** except that the signals due to allyl groups were present instead of those due to the methyl groups (see **Experimental section** for details). Since alkylation of the diol **4** in DMF yielded the corresponding triethers **5** or **8**, the diethers **3** and **7** were subjected to methylation and allylation respectively to see if triethers **5** and **8** formed exclusively *via* the corresponding diethers (**Scheme 3B.3**).

Scheme 3B.3



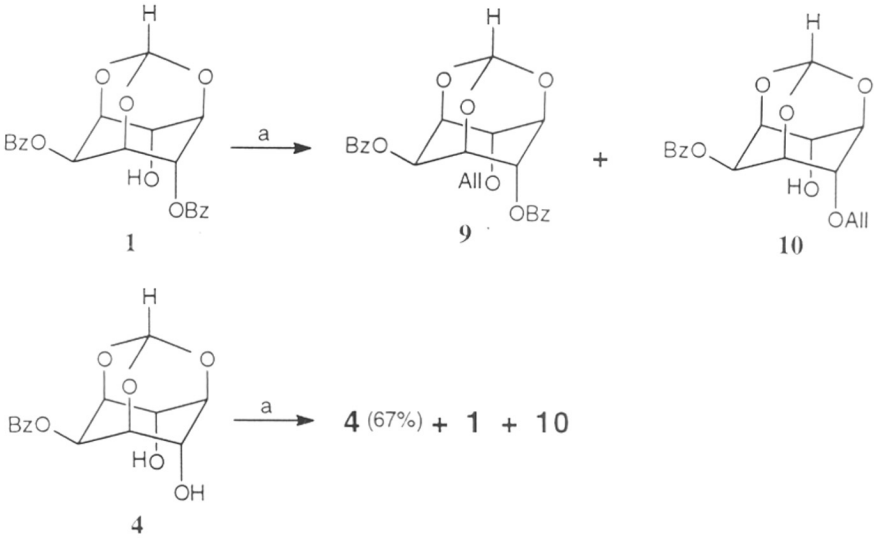
Reagents and conditions: (a) AllBr, Ag_2O, DMF (b) MeI, Ag_2O, DMF.

In all such experiments, at least 50% of diethers **3** and **7** could be recovered unchanged (**Table I, entries 7,8**). Hence, formation of larger amounts of triethers **5** and **8** from the diol **4**, as compared to that from diethers **3** and **7**, suggests operation of pathways other than those mentioned above. This is not surprising considering the biphasic nature of the reaction under study, where interfacial effects at the surface of the solid are also important.

3B.2.C Reaction of diol 4 with allyl chloride in DMF:

As mentioned earlier, reaction of the dibenzoate **1** with allyl chloride [**Chapter 3A, Section 3A.2.2**] in DMF gave a mixture of monoallyl ethers **9** and **10** (**Scheme 3B.4**).

Scheme 3B.4



Reagents and conditions: (a) AllCl (14 eq.), Ag_2O, DMF.

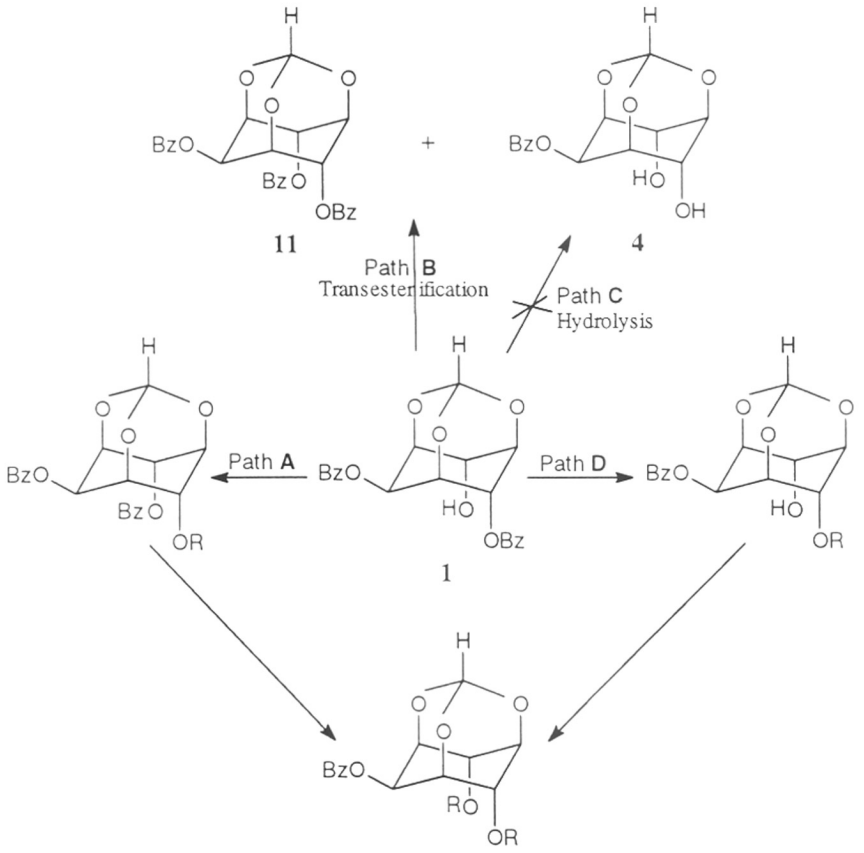
As discussed earlier (**Chapter 3A, Section 3A.2.3**), there are two paths (**Scheme 3B.5**) by which the minor product **10** can form from the dibenzoate **1**:

(a) By allylation of diol **4** formed *via* the transesterification of the dibenzoate **1** (Path **B**) and

(b) By cleavage and allylation of the benzoate ester prior to allylation of the free hydroxyl group (Path **D**).

Hence to check if the monoallyl ether **10** is formed exclusively through the intermediacy of the diol **4** (path **B**), we carried out reaction of the diol **4** with allyl chloride, but majority of the diol **4** (67%) was recovered unchanged. We could however isolate small amounts of the monoallyl ether **10** and the dibenzoate **1** (which results from transesterification of **4**). It is likely that the silver halide generated enhances the rate of transesterification of **4** in DMF as observed for the transesterification of the dibenzoate **1**. Results on alkylation of the dibenzoate **1** and the diol **4** with different alkyl halides in DMF as well as relevant control experiments are summarized in **Table I**.

Scheme 3B.5



From these results it is clear that the products obtained by the allylation of the dibenzoate **1** and the diol **4** with allyl bromide under similar conditions are different, *viz.*, the dibenzoate **1** afforded the corresponding 4,6-diallyl ether **7**as the major product whereas the diol **4** yields the 2,4,6-triallyl ether **8** as the major product. Hence it is unlikely that the allylation of the dibenzoate **1** with allyl bromide proceeds with the intermediacy of the diol **4**.

Similarly, considering the yield of the monoallyl ether **10** obtained from the two reactions (**Table I**, **entries 5,6**) and the amount of the diol **4** formed *via* transesterification in the presence of silver chloride (**Chapter 3A, Table V, Entry 3**) under comparable conditions, it is unlikely that the monoallyl ether **10** is formed *via* the path **B** during allylation of the dibenzoate **1** with allyl chloride. Furthermore, if **10** is formed *via* the diol **4** generated through path **B**, then we should have isolated an equivalent amount of the tribenzoate **11** as a by product, since we had shown earlier [**Chapter 3A, Section 3A.2.8**] that tri-O-substituted

myo-inositol-1,3,5-orthoformates do not undergo allylation with allyl chloride in the presence of silver (I) oxide in DMF.

Table I: Reaction of *myo*-inositol orthoformate derivatives with alkyl halides[a] in DMF.

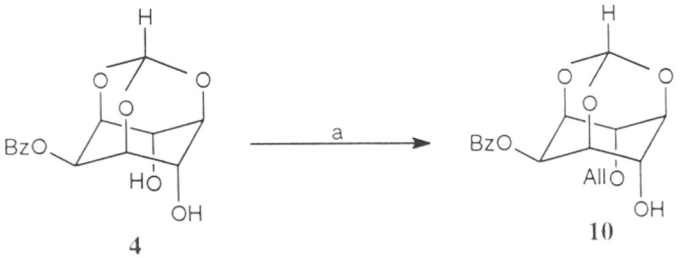
Entry	Reactant	RX	Products (yield %[b])
1	**1**	MeI	**3** (80)
2	**4**	MeI	**5** (76)
3	**1**	AllBr	**7** (74)
4	**4**	AllBr	**7** (14), **8** (53)[c]
5	**1**	AllCl	**9** (64), **10** (24)
6	**4**	AllCl	**1** (15), **4** (67), **10** (10)
7	**3**	MeI	**3** (50), **5** (41)
8	**7**	AllBr	**7** (57), **8** (24)

[a] All the reactions were carried out at ambient temperature (66h) using a ratio of the reactant : Ag_2O : RX = 1 : 5 : 10, except in the case of allyl chloride where it was 1 : 5 : 14.
[b] Isolated, unless otherwise specified.
[c] Other uncharacterized products, 25%.

3B.2.D Reaction of diol 4 with alkyl halides in acetonitrile:

Silver (I) oxide mediated allylation of the diol **4** in acetonitrile yielded the monoallyl ether **10** as the only isolable product, which was characterized as discussed in **Chapter 3A** (**Scheme 3B.6**).

Scheme 3B.6



4 **10**

Reagents and conditions: (a) AllBr, Ag_2O, CH_3CN.

The results of alkylation of the orthoformates **1**, **2** and **4** in acetonitrile are tabulated in **Table II**.

Table II: Reaction of *myo*-inositol orthoformate derivatives with alkyl halides[a] in acetonitrile.

Entry	Reactant	RX	Products (yield %[b])
1	**1**	AllBr	**9** (9), **7** (4), **10** (63), **11** (11)
2	**4**	AllBr	**10** (86)
3	**2**	AllBr	No reaction
4	**4**	None	No reaction[c]

[a] All the reactions were carried out at ambient temperature (80 h for MeI, 66 h for AllBr) using a ratio of the reactant : Ag_2O : RX = 1 : 5 : 10.
[b] Isolated
[c] by ^1H NMR spectroscopy, however a very faint spot corresponding to the dibenzoate **1** was visible in TLC.

Unlike the corresponding reaction in DMF neither the diallyl ether **7** nor the triallyl ether **8** was isolated. Since the product of allylation of the dibenzoate **1** as well as that from the diol **4** in acetonitrile is the same, in order to establish the contribution of path **B** (**Scheme 3B.5**) to the overall reaction, we had to rely upon the yields of the isolated products and the control reactions. Since transesterification of **1** is a disproportionation reaction, the maximum yield of the diol **4** and the tribenzoate **11** obtainable is 50% each. Accordingly, if **10** is formed exclusively by allylation of the diol **4** generated through transesterification of **1**, maximum yield of **11** can only be 50%. Furthermore, this sequence of reaction should yield 50% of the tribenzoate **11** as well (or a 1:1 yield of tribenzoate **11** and the monoallyl ether **10**). In order to see if the O-substituted derivatives of the dibenzoate **1** undergo allylation with allyl bromide in acetonitrile, we carried out the reaction of **2** with allyl bromide. However, the methyl ether **2** did not react with allyl bromide in the presence of silver (I) oxide, showing that tri-O-substituted *myo*-inositol orthoformate derivatives are stable to alkylation in acetonitrile. Reaction of the tribenzoate **11** (the actual product generated by transesterification of **1**) with allyl bromide in acetonitrile could not be carried out due to the very low solubility of the tribenzoate **11** in acetonitrile. These results clearly show that the intermediacy of the diol **4** formed by transesterification of the dibenzoate **1** during its allylation with allyl bromide is at best a minor side reaction. The contribution of path **B** to the overall reaction (**Table II, entry 1**) is about 11% as reflected by the yield of the tribenzoate **11**.

3B.3 CONCLUSIONS

A comparison of the results of alkylation of the dibenzoate **1** and the diol **4** under similar conditions shows that they give rise to different products. These results exclude the intermediacy of the diol **4** during the formation of the 4,6-diethers from the dibenzoate **1** or its derivatives. However, further work is necessary to understand the intricacies of this interesting heterogeneous reaction of *myo*-inositol orthoformate derivatives on the surface of silver (I) oxide and to see if this occurs in other conformationally constrained molecules.

3B.4 EXPERIMENTAL SECTION

Materials and methods:— For general methods and procedure for the alkylation of *myo*-inositol orthoformate derivatives see **Chapter 3A**. The diol **4** was prepared as discussed in **Chapter 2**.

Reaction of 2-O-benzoyl-*myo*-inositol-1,3,5-orthoformate (4) with:

Excess methyl iodide:

The diol **4** (0.15 g, 0.51 mmol) and methyl iodide (0.32 ml, 5 mmol) were dissolved in DMF (2 ml) and stirred with silver (I) oxide (0.59 g, 2.55 mmol) at r.t. for 66 h. The reaction mixture was worked up as described in **Chapter 3A** and the single product formed was purified by column chromatography to yield the trimethyl ether **5** (0.09 g, 76%).

Data for 5:

^{1}H NMR: 3.45 (s, 6H), 3.55 (s, 3H), 3.60 (s, 1H), 4.15 (m, 2H), 4.40 (m, 2H), 4.50 (m, 1H), 5.55 (d, 1H).

^{13}C NMR: 56.1, 57.1, 66.9, 68.7, 68.8, 75.5, 102.7.

Elemental anal. calcd. for $C_{10}H_{16}O_6$: C, 51.72; H, 6.90.

Found: C, 51.88; H, 6.88.

Excess allyl bromide:

The diol **4** (0.15 g, 0.51 mmol) and allyl bromide (0.4 ml, 5 mmol) were dissolved in DMF (2 ml) and stirred with silver (I) oxide (0.59 g, 2.55 mmol) at r.t. for 66 h. The reaction mixture was worked up as described in **Chapter 3A** and the products were purified by column chromatography to yield the diallyl ether **7** (0.026 g, 14%) and the triallyl ether **8** (0.085 g, 53%).

Data for 7:

See **Chapter 3A, Experimental section** for detail.

Data for 8:

^{1}H NMR: 3.90 (m, 1H), 4.00-4.20 (m, 11H), 5.10-5.50 (m, 7H), 5.80-6.05 (m, 3H).

^{13}C NMR: 67.5, 68.5, 70.5, 74.0, 103.5, 117.0, 117.5, 134.0, 135.0.

Excess allyl chloride:

The diol **4** (0.15 g, 0.51 mmol) and allyl chloride (0.4 ml, 5 mmol) were dissolved in DMF (2 ml) and stirred with silver (I) oxide (0.59 g, 2.55 mmol) at r.t. for 66 h. The reaction mixture was worked up as described in **Chapter 3A** and the

products were purified by column chromatography to yield the dibenzoate **1** (0.03 g, 15%), allyl ether **10** (0.01 g, 10%) and the starting material **4** (0.10 g, 67%).

Silver (I) oxide:

The diol **4** (0.08 g, 0.27 mmol) was dissolved in DMF (1 ml) and stirred with silver (I) oxide (0.31 g, 1.35 mmol) at r.t. for 66 h. The reaction mixture was worked up as described in **Chapter 3A** and the starting material was recovered by column chromatography (0.07 g, 87%).

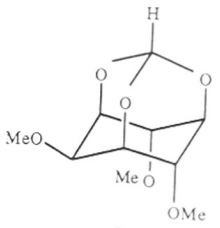
Allyl bromide in acetonitrile:

The diol **4** (0.15 g, 0.51 mmol) and allyl bromide (0.4 ml, 5 mmol) were dissolved in acetonitrile (2 ml) and stirred with silver (I) oxide (0.59 g, 2.55 mmol) at r.t. for 66 h. The reaction mixture was worked up as described in **Chapter 3A** and the single product formed was purified by column chromatography to yield the allyl ether **10** (0.16 g, 86%).

Silver (I) oxide in acetonitrile:

The diol **4** (0.04 g, 0.14 mmol) was dissolved in acetonitrile (0.7 ml) and stirred with silver (I) oxide (0.16 g, 0.68 mmol) at r.t. for 66 h. The reaction mixture was worked up as described in **Chapter 3A** to recover the starting material **4** quantitatively.

Figure 1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OMe

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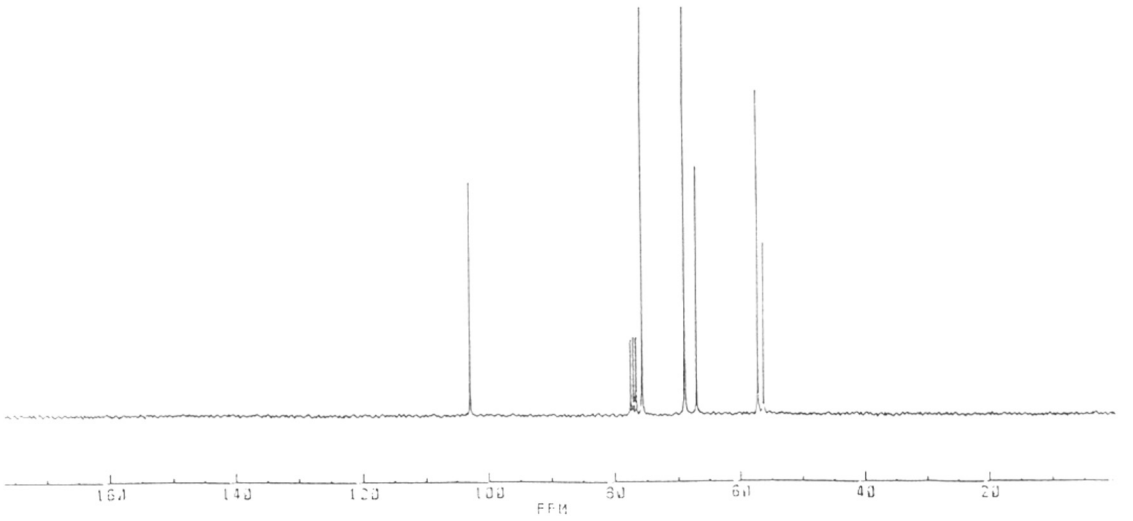
PPM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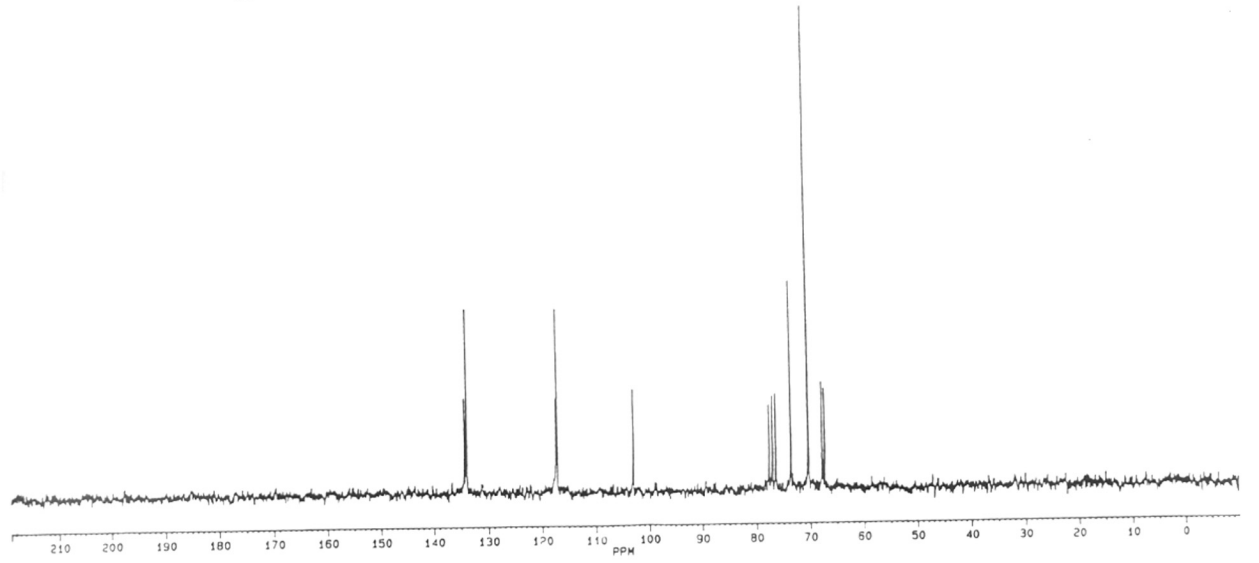
120
100
80
60
40
20
PPM

Figure 2

Figure 3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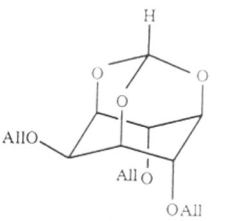
PPM


H
O
O
O
AllO
All O
OAll

8

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
PPM

CHAPTER 4

Silver (I) oxide mediated alkylation of 6-O-sulfonylated derivatives of 2,4-di-O-benzoyl-*myo*-inositol-1,3,5-orthoformate

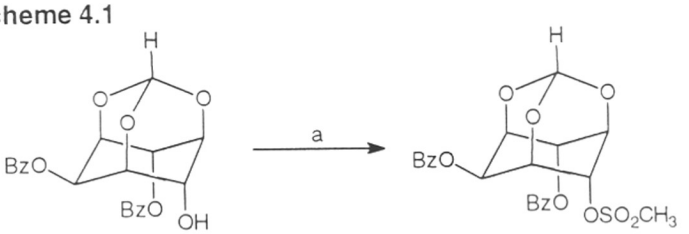
4.1 INTRODUCTION

Results on the alkylation of variously O-substituted *myo*-inositol-1,3,5-orthoformate derivatives presented in **Chapter 3** showed that carboxylic acid esters present in axial 4- and 6- positions of *myo*-inositol orthoformate undergo cleavage with alkyl halides in the presence of silver (I) oxide, to yield the corresponding diethers. Hence, in order to examine the reactivity of sulphonate esters of *myo*-inositol orthoformate and to study the effect of sulfonate group on the cleavage of carboxylic acid esters in the presence of silver (I) oxide, we prepared racemic 2,4-di-O-acyl-6-O-sulfonyl-*myo*-inositol-1,3,5-orthoformates and subjected them to alkylation in the presence of silver (I) oxide under the conditions described in **Chapter 3A**.

4.2 RESULTS AND DISCUSSION

The sulfonates **2-5** were prepared from the dibenzoate **1** by its reaction with the corresponding sulfonyl chloride in the presence of a mild base. The 6-O-mesyl derivative **2** was obtained in good yield (92%) from **1** using pyridine and mesyl chloride (**Scheme 4.1**).

Scheme 4.1



1 2

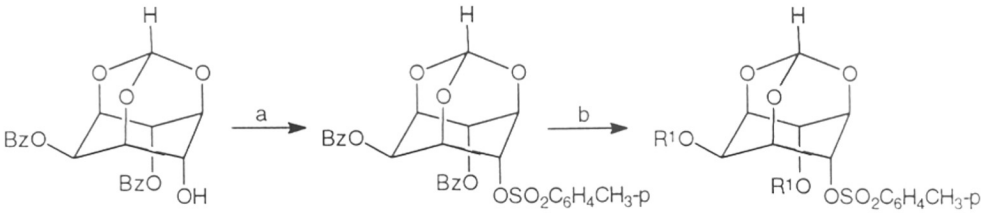
Reagents and conditions: (a) MsCl, Pyr, 0 °C.

The structure of the mesylate **2** was confirmed by IR, ^{1}H NMR (**Figure 1**) and ^{13}C NMR spectroscopy (**Figure 2**). The IR spectrum of **2** showed the presence of two carbonyl groups. The ^{1}H NMR spectrum showed a singlet at δ 2.90 corresponding to the methyl sulfonyl group, five signals for the inositol ring protons and the orthoformate proton appeared as a doublet at δ 5.70. The aromatic region showed ten protons indicating presence of two benzoate groups. The ^{13}C NMR spectrum showed, besides one orthoformate carbon and two carbonyl carbons, one methyl carbon at 38.5 ppm along with six inositol ring carbons and the aromatic carbons. The structure of the mesylate **2** was also solved by single

crystal X-ray analysis (**Figure 3**). Good quality crystals were obtained by crystallisation from a mixture of chloroform and light petroleum.

The reaction of the dibenzoate **1** with tosyl chloride at 0°C was sluggish and the tosylate **3** was obtained in 40-50% yield (**Scheme 4.2**). The reaction required a large excess of tosyl chloride and a mixture of pyridine and triethyl amine was used as base. The unreacted dibenzoate **1** could be recovered by column chromatography and recycled.

Scheme 4.2



1 3

Reagents and conditions: (a) TsCl, Et_3N, Pyr, 0°C (b) t-Butyl amine, MeOH (c) Ac_2O, Pyr, r.t.

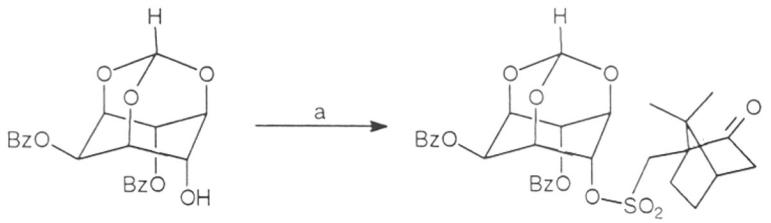
The structure of the tosylate **3** was confirmed by IR, ^1H NMR and ^{13}C NMR spectroscopy. The IR spectrum of **3** showed the presence of two carbonyl groups. The ^1H NMR spectrum showed the methyl peak of the tosyl group at δ 2.40 as a singlet, four signals for the inositol ring protons in the ratio 3:1:1:1 and the orthoformate proton appeared as a doublet at δ 5.65. The aromatic region showed fourteen protons consistent with the presence of two benzoate groups and one tosyl group. The ^{13}C NMR spectrum of **3** showed one orthoformate carbon and two carbonyl carbons, one methyl carbon at 21.8 ppm as well as six inositol ring carbons and the aromatic carbons. The difficulty in sulfonation with tosyl chloride could be due to the lesser reactivity of aryl sulfonyl chlorides as compared to alkyl sulfonyl chlorides[1].

The tosylate **3** on aminolysis with t-butyl amine gave the corresponding diol **4** (not isolated) which was acetylated with acetic anhydride and pyridine (in the same pot) to obtain the diacetate **5** (**Scheme 4.2**). The axial sulfonate remained unaffected during aminolysis of **3** perhaps due to the rigidity of *myo*-inositol orthoformate ring. Nucleophilic substitution at C4- and C6-positions of the inositol ring in the orthoformate **1** is difficult due to the rigidity of the *myo*-inositol orthoformate moiety. The structure of the diacetate **5** was confirmed by IR, ^1H NMR and ^{13}C NMR spectroscopy. The IR spectrum of **5** showed the presence of two carbonyl groups. The ^1H NMR spectrum was similar to that of the tosylate **3**

except for the presence of three singlets at δ 2.10, 2.25 and 2.50 (one for the aromatic methyl group and two for the acetate groups). The inositol ring protons appeared as six separate signals and the orthoformate proton appeared at δ 5.55 as a doublet. Signals in the aromatic region integrated to four protons indicating presence of only the tosyl group. The ^{13}C NMR spectrum showed the presence of three methyl carbons and two carbonyl carbons (indicating the unsymmetrical nature of the diacetate **5**), six inositol ring carbons and one orthoformate carbon.

Reaction of the dibenzoate **1** with camphor sulfonylchloride was carried out using excess sulfonyl chloride in pyridine at room temperature to obtain the camphorsulfonate **6** in 90% yield, as a mixture of diastereomers (**Scheme 4.3**).

Scheme 4.3



1 **6 and Dia-6**

Reagents and conditions: (a) Camphor sulfonyl chloride, Pyr, r. t.

The IR spectrum of **6** showed a broad peak in the region 1720-1740 cm^{-1}. The ^{1}H NMR spectrum showed four methyl groups as four singlets, the corresponding integrals were in the ratio of 1:1, indicating presence of the two diastereomers in the ratio 1:1. The camphor sulfonate ring protons (seven) appeared between δ 1.20 and 2.45. The two methylene protons appeared as two quartets (δ 2.85-3.00 and 3.50-3.60). The six inositol ring protons and the orthoformate proton appeared as five signals with integral ratio 4 :2 :4 :2 :2. The signals in the aromatic region indicated the presence of two benzoate groups (**Figure 4**). The ^{13}C NMR spectrum of **6** also indicated the presence of diastereomers. The two geminal methyl carbons of camphoryl group appeared as four peaks at 19.5, 24.9, 26.8 and 26.9 ppm. The methylene carbon of the camphorsulfonyl group appeared as two signals at δ 48.1 and 48.3. The other carbons of the camphoryl group and the inositol ring carbons (total fourteen carbons) appeared as nineteen signals indicating the presence of diastereomers. The orthoformate carbon appeared at 103.1 ppm and the aromatic carbons appeared in the region between 128.6 and 133.8 ppm. There were six signals for carbonyl carbons (165.0, 165.1, 165.9, 187.5, 213.8, 213.9 ppm) as expected for a mixture of diastereomers (**Figure 5**). The presence a mixture of diastereomers **6** and **Dia-6** in the ratio 1:1 is thereby clearly evident although **6** appeared as a

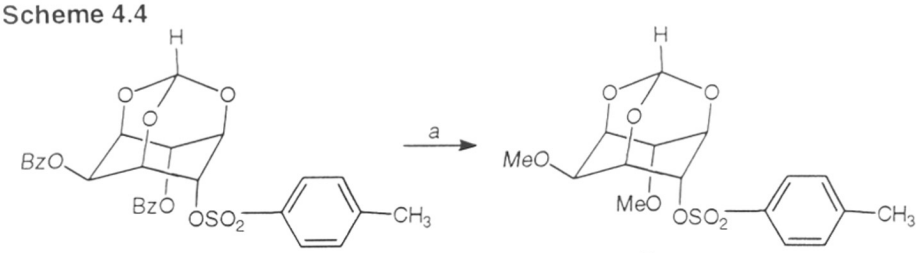
single spot on TLC and could not be separated either by crystallisation or by column chromatography.

4.2.1 Reaction of the sulfonates 2 - 5 with alkyl halides in the presence of excess silver (I) oxide:

Reaction with methyl iodide:

Reaction of the tosylate **3** with methyl iodide gave exclusively the dimethyl ether **7** (**Scheme 4.4**).

Scheme 4.4



3 7

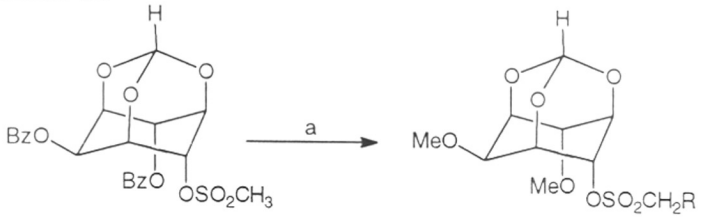
Reagents and conditions: (a) MeI, Ag_2O, DMF, 66h.

The structure of **7** was determined by ^1H NMR and ^{13}C NMR spectroscopy. The ^1H NMR spectrum (**Figure 6**) showed the tosylate methyl group at δ 2.50 and two singlets for methoxy groups (δ 3.40 and 3.50). The six inositol ring protons appeared between δ 3.65 and 5.10 as five peaks in the ratio 1:2:1:1:1 and the orthoformate proton appeared at δ 5.45 as a doublet. The aromatic region showed two doublets integrating to four protons characteristic of the tosyl group. The structure of **7** was further confirmed by ^{13}C NMR spectrum (**Figure 7**), which showed the presence of the tosylate methyl group at 21.5 ppm, two methoxy carbons at 56.7 and 57.0 ppm, and six inositol ring carbons between 66.8 and 74.7 ppm. The orthoformate carbon appeared at 102.8 ppm and there were four peaks for aromatic carbons. In order to make sure that the methylation did not take place by ester hydrolysis (by the water or hydroxyl ions adsorbed on silver (I) oxide surface) followed by methylation, the tosyl derivative **3** was stirred with silver (I) oxide and DMF. The starting material could be recovered quantitatively which indicated that the benzoates did not undergo hydrolysis in the presence of silver (I) oxide.

Reaction of the mesyl derivative **2** with methyl iodide in the presence of silver (I) oxide gave a mixture of products (TLC) (**Scheme 4.5**). The major products

were isolated by column chromatography. The product with higher R_f (0.4; 30% EtOAc – light petroleum, 2 runs) was shown to be the ethyl sulfonate derivative **8**.

Scheme 4.5



2

8: R = CH_3
9: R = H

Reagents and conditions: (a) MeI, Ag_2O, DMF, 66h.

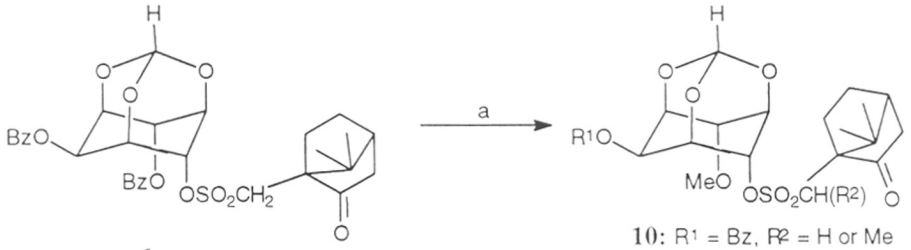
The structure of **8** was determined by ^{1}H NMR (**Figure 8**) and ^{13}C NMR spectroscopy (**Figure 9**). In the ^{1}H NMR spectrum, the two methoxy groups appeared at δ 3.45 and 3.55. It also showed a triplet for three protons at δ 1.45 and a quartet of two protons at δ 3.20 indicating the presence of an ethyl group. The six inositol ring protons appeared between δ 3.65 and 5.35 and the orthoformate proton appeared at δ 5.55 as a doublet. No signals were present in the aromatic region indicating the absence of any benzoate groups. C-methylation in the presence of silver (I) oxide is known in the literature[2]. The product with lower R_f (0.3; 30% EtOAc – light petroleum, 2 runs), **9**, was also characterised by ^{1}H NMR spectroscopy (**Figure 10**). There were three singlets integrating to three protons each (δ 3.10, 3.50 and 3.55) indicating the presence of one mesyl and two unsymmetrical methoxy groups. The six inositol ring protons appeared in the region δ 3.70-4.65. The orthoformate proton appeared as a doublet at δ 5.35. The absence of any peak in the aromatic region again showed clearly that the equatorial as well as the axial benzoates have undergone cleavage. In order to rule out the possibility of hydrolysis of **2**, it was stirred with silver (I) oxide in DMF as in the case with **3**, and the starting material was recovered.

The camphor sulfonate derivative **6** reacted with methyl iodide to give two products (by TLC). They were separated by column chromatography and each was found to be a mixture of compounds. The fraction with higher R_f (0.6; 30% EtOAc – light petroleum, 2 runs) was found to be a mixture of monomethyl ethers **10** (**Scheme 4.6**) and the fraction with lower R_f (0.5; EtOAC – light petroleum, 2 runs) was a mixture of dimethyl ethers **11** as revealed by ^{1}H NMR spectroscopy. There were six singlets between δ 1.05-1.20 instead of the expected four singlets for a mixture of diastereomers of **10** (R^1 = Bz, R^2 = H) or **11** (R^1 = Me, R^2 = H). There

were no peaks in the aromatic region (δ 7.00-9.00) for **11**, indicating that both the equatorial and axial benzoates have undergone cleavage.

The mixture of products was a result of C-methylation of the methylene carbon of the sulfonate group as shown by the ^{1}H NMR spectroscopy. The ^{13}C NMR spectrum of **11** supports this observation as it showed six methyl peaks between 13.2 and 20.8 ppm . This is not unexpected considering the similarity in structure of the mesylate **2** and camphorsulfonate **6**. The C-methylation in both cases is due to the increased acidity of the methylene protons due to the presence of strongly electron withdrawing sulfonyl group.

Scheme 4.6



6

(mixture of diastereomers)

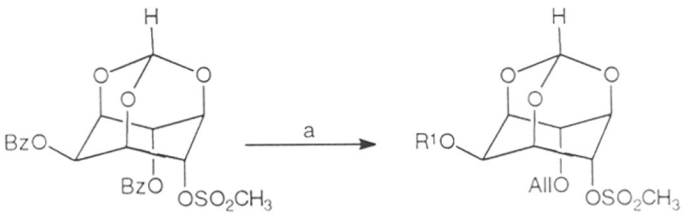
10: R^1 = Bz, R^2 = H or Me
11: R^1 = Me, R^2 = H or Me
(mixture of diastereomers)

Reagents and conditions: (a) MeI, Ag_2O, DMF, 66h.

Reaction with allyl bromide:

Reaction of the mesyl derivative **2** with allyl bromide (10 eq.) gave the diallyl ether **13** as the major product (**Scheme 4.7**).

Scheme 4.7



2

a → **12**: R^1 = Bz
a → **13**: R^1 = All

Reagents and conditions: (a) AllBr, Ag_2O, DMF, 66h.

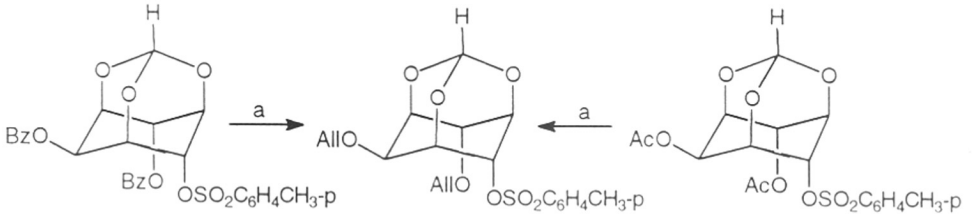
Some amount (10%) of the monoallyl ether **12** could also be isolated which could be identified by ^{1}H NMR spectroscopy. No C-allylated product was obtained as in the case of corresponding methylation reaction. The structure of **13** was determined by ^{1}H NMR and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum (**Figure 11**) showed the presence of one singlet for the mesyl group at δ 3.10. The six inositol ring protons and eight protons of the allyl groups (O-C$\underline{H}_2$-CH=C$\underline{H}_2$) appeared in the region δ 3.90-5.40 as five multiplets in the ratio 1: 4: 3: 1: 5. The orthoformate proton appeared as a doublet at δ 5.55. The two olefinic protons of the allyl groups (O-C-C($\underline{H}$)=C) appeared as a broad multiplet between δ 5.75 and 6.10. The absence of any peak in the aromatic region showed clearly that the equatorial as well as the axial benzoates have undergone cleavage. The structure of **13** was further confirmed by ^{13}C NMR spectrum (**Figure 12**), which showed the presence of the mesyl group (38.4 ppm), six inositol ring carbons and the allyl carbons between 66.4 and 117.9 ppm. The orthoformate carbon (102.8 ppm) and two signals for olefinic carbon (O-C-$\underline{C}$(H)=C) of the allyl groups appeared at 133.7 and 134.1 ppm indicating non-equivalence of the two allyl groups. The structure of **12** was determined by ^{1}H NMR spectroscopy (**Figure 13**), which showed one singlet for the methyl group of mesyl moeity at δ 3.15. The six inositol ring protons and four allyl protons (O-C$\underline{H}_2$-CH=C$\underline{H}_2$) appeared between δ 4.15 and 5.55 in the ratio 2: 1: 2: 1: 4. The orthoformate proton appeared as a doublet at δ 5.60. The olefinic proton of the allyl group (O-C-C($\underline{H}$)=C) appeared as a broad multiplet between δ 5.85 and 6.05. The signals in the aromatic region integrated to five protons indicating presence of one benzoate group. The structure **12** was assigned to the minor product since the axial benzoate in **2** is expected to undergo cleavage and alkylation preferentially due to its proximity with the sulfonyl group. Further work is necessary to unambiguously assign the structure **12** to the minor product (also see **Section 4.2.2**).

The diallyl ether **13** was obtained as the only product when the amount of allyl bromide (20 equivalents) and silver (I) oxide (10 equivalents) were doubled. This suggests the sequential cleavage of the axial and equatorial benzoate groups. No C-allylation was observed even under these vigorous conditions. This is perhaps due to the lower reactivity of allyl bromide as compared to methyl iodide in the preesnce of silver (I) oxide.

The tosyl derivative **3** on reaction with allyl bromide afforded exclusively the diallyl ether **14** (**Scheme 4.8**). The structure of **14** was determined by ^{1}H NMR and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum (**Figure 14**) showed the tosylate methyl group at δ 2.40. The six inositol ring protons and eight protons belonging to the non-equivalent allyl groups (O-C$\underline{H}_2$-CH=C$\underline{H}_2$) appeared between δ 3.80 and 5.35 as three multiplets in the ratio 1: 8: 5 and the orthoformate proton appeared

at δ 5.45 as a doublet. The two olefinic protons of the allyl groups (O-C-C(H)=C) appeared as a broad multiplet between δ 5.70 and 6.00. The aromatic region showed two doublets integrating to four protons characteristic of the tosylate group.

Scheme 4.8



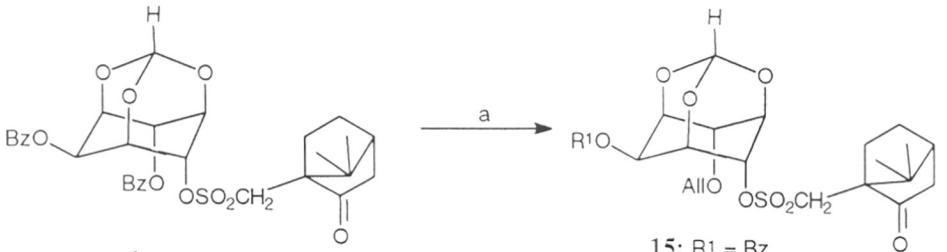
3 **14** **5**

Reagents and conditions: (a) AllBr, Ag_2O, DMF, 66h.

The structure was further confirmed by ^{13}C NMR spectrum (**Figure 15**), which showed the presence of the tosylate methyl group at 21.6 ppm, six inositol ring carbons and methylene carbons of two non-equivalent allyl groups between 66.6 and 117.8 ppm. The orthoformate carbon appeared at 102.9 ppm. The signals in the aromatic region showed presence of four carbons of the tosylate group and two peaks for the two olefinic carbons (O-C-C(H)=C) of allyl groups. Reaction of the diacetate **5** with allyl bromide was similar to that of the tosylate **3** and the diallyl ether **14** was obtained as the major product (55%). The TLC showed the presence of several other products which were not characterised.

The camphor sulfonyl derivative 6 (Scheme 4.9) gave a mixture of monoallyl ether 15 (35%) and the diallyl ether 16 (20%) and the ratio could not be altered even by using excess allyl bromide and silver (I) oxide as in the case of 2.

Scheme 4.9



6
(mixture of diastereomers)

15: R^1 = Bz
16: R^1 = All

Reagents and conditions: (a) AllBr, Ag_2O, DMF, 66h.

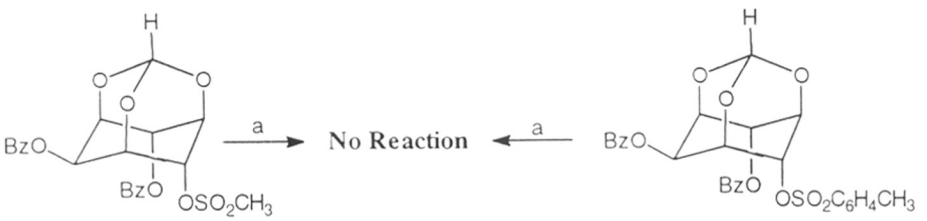
Again the diastereomers were inseparable, both by TLC and column chromatography. As in the case of the mesylate **2**, no C-allylation was observed. The structures of **15** and **16** were determined by ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum of **15** showed the presence of four singlets (δ 0.75-1.10) integrating to twelve protons for two methyl groups. The six inositol ring protons, nine protons belonging to the camphorsulfonyl group, four protons belonging to the allyl group (O-C$\underline{H}_2$-CH=C$\underline{H}_2$) and the orthoformate proton appeared between δ 1.25-5.65 as seven multiplets. The single olefinic proton of the allyl group (O-C-C($\underline{H}$)=C) appeared as a broad multiplet at δ 5.85. The aromatic region integral showed the presence of five protons indicating a benzoate group in the molecule.

The ^{1}H NMR spectrum of **16** showed the presence of four singlets (δ 0.85-1.10) integrating to twelve protons for two methyl groups. The nine protons belonging to the camphorsulfonyl group appeared as a multiplet of 18 protons (δ 1.40-2.55) and the two methylene protons appeared as a doublet (δ 3.05) and a quartet (δ 3.60-3.70). The six inositol ring protons, eight protons belonging to two allyl groups (O-C$\underline{H}_2$-CH=C$\underline{H}_2$) and the orthoformate proton appeared between δ 3.85 and 5.65. The two olefinic protons of the allyl groups (O-C-C($\underline{H}$)=C) appeared as a broad multiplet between δ 5.70 and 6.15. There were no signals in the aromatic region indicating the absence of both the benzoate groups in **16**.

Reaction with allyl chloride:

Both the mesyl derivative **2** and the tosyl derivative **3** did not react with allyl chloride and the starting material could be recovered (90 - 100%) (**Scheme 4.10**). But in the case of the camphor sulphonyl derivative **6**, about 70% of the starting material could be recovered. These results are consistent with earlier observation that allyl chloride does not react with tri-O-substituted derivatives of *myo*-inositol orthoformate.

Scheme 4.10



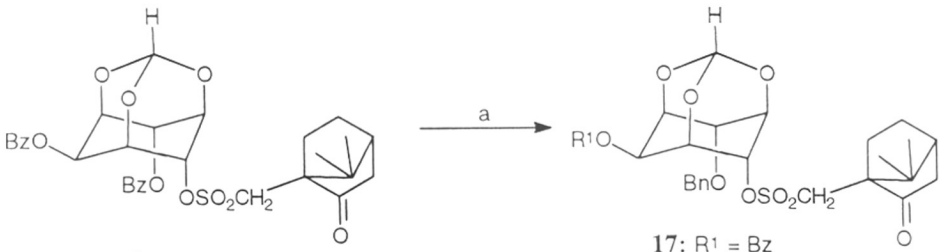
2 **3**

Reagents and conditions: (a) AllCl, Ag_2 O, DMF, 66h.

4.2.2 Reaction of 6 with benzyl bromide:

Reaction of the camphor sulfonyl derivative **6** with excess benzyl bromide in the presence of silver (I) oxide also gave a mixture of the dibenzyl ether **18** (major) and the monobenzyl ether **17** (**Scheme 4.11**), the structures of which were determined by IR and ^{1}H NMR spectroscopy.

Scheme 4.11



6
(mixture of diastereomers)

17: R^1 = Bz
18: R^1 = Bn

Reagents and conditions: (a) BnBr, Ag_2 O, DMF, 66h.

The ^{1}H NMR spectrum of **18** (**Figure 16**) showed four singlets at δ 0.75 and δ 1.00. The seven camphoryl ring protons appeared as a multiplet between δ 1.15 and 2.45. The six inositol ring protons and four benzylic protons appeared between δ 2.85 and 5.50. The two methylene protons of camphor sulfonyl group (-SO_2-C$\underline{H}_2$) appeared as a pair of double doublets at δ 3.45-3.65 and 3.95-4.05. The orthoformate proton appeared at δ 5.60 as a doublet. The ^{13}C NMR spectrum of **18** showed besides the orthoformate carbon at δ 103.2, the aromatic carbons in the expected region, nineteen other peaks corresponding to the camphor sulfonyl group, inositol ring and benzylic carbons.

The IR spectrum of **17** showed two carbonyl peaks at 1710 and 1730 cm^{-1}. The ^{1}H NMR spectrum of **17** showed, like **18**, four singlets between δ 0.75 and δ 1.10. The seven camphoryl ring protons appeared as multiplets between δ 1.15 and 2.50. The two methylene protons of camphor sulfonyl group (-SO_2-C$\underline{H}_2$) appeared as a pair of doublet of doublets at δ 3.00-3.15 and 3.60-3.75. The six inositol ring protons and two benzylic protons appeared between δ 4.40-5.60. The orthoformate proton appeared at δ 5.60 as a doublet. The ^{13}C NMR spectrum of **17** showed (**Figure 17**) besides the orthoformate carbon at 103.2 ppm and the aromatic carbons in the expected region, four peaks for two camphoryl methyl groups and fifteen other peaks corresponding to the camphoryl group, inositol ring and the benzylic carbon. One carbonyl peak corresponding to the benzoate group appeared at 165.8 ppm. In order to find out which of the axial and equatorial

and equatorial benzoates was undergoing cleavage preferentially, we attempted a comparison of the ^{13}C chemical shift values of benzoate carbonyl carbons in several *myo*-inositol orthoformate derivatives. The results are presented in **Table I**.

Table I: Comparison of ^{13}C chemical shift values (in $CDCl_3$) of benzoate carbonyl carbons in O-substituted *myo*-inositol orthoformate derivatives.

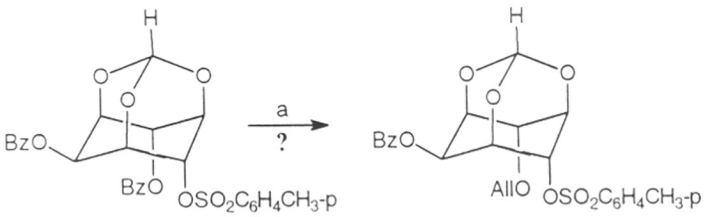
Entry	Name of compound	Chemical shift (ppm)
1.	2-O-benzoyl-4-O-methyl-*myo*-inositol-1,3,5-orthoformate	166.3
2.	2-O-benzoyl-4-O-allyl-*myo*-inositol-1,3,5-orthoformate	166.4
3.	2-O-benzoyl-4,6-di-O-methyl-*myo*-inositol-1,3,5-orthoformate	166.2
4.	2-O-benzoyl-4,6-di-O-allyl-*myo*-inositol-1,3,5-orthoformate	166.3
5.	2-O-benzoyl-4,6-di-O-benzyl-*myo*-inositol-1,3,5-orthoformate	166.3
6.	2-O-benzoyl-4-O-benzyl-6-O-camphorsulfonyl-*myo*-inositol-1,3,5-orthoformate	165.8
7.	2,4-di-O-benzoyl-6-O-allyl-*myo*-inositol-1,3,5-orthoformate	165.5, 166.3
8.	2,4-di-O-benzoyl-6-O-methyl-*myo*-inositol-1,3,5-orthoformate	165.5, 166.3
9.	2,4-di-O-benzoyl-6-O-mesyl-*myo*-inositol-1,3,5-orthoformate	165.1, 166.2
10.	2,4-di-O-benzoyl-6-O-tosyl-*myo*-inositol-1,3,5-orthoformate	165.1, 165.9
11.	2,4,6-tri-O-benzoyl-*myo*-inositol-1,3,5-orthoformate	165.4, 166.5
12.	2,4-di-O-benzoyl-*myo*-inositol-1,3,5-orthoformate	165.0, 167.0
13.	2,4-di-O-benzoyl-6-O-tetrahydropyranyl-*myo*-inositol-1,3,5-orthoformate	165.3, 169.1

Results in **Table I** suggests that the ^{13}C chemical shift values for the equatorial benzoate carbonyl carbon (entries 1-5) is close to 166 ppm. Comparison of this values with the chemical shift values of the benzoate carbonyl carbons of the compounds containing both the equatorial and the axial benzoate groups (entries 7-13) suggests that the ^{13}C chemical shift values for the axial benzoate is close to 165 ppm. Hence the observed chemical shift value for the carbonyl carbon (165.8 ppm) in the monobenzyl ether **17** (entry 6) suggests it to be the equatorial benzoate group.

4.2.3 Reaction of 3 with allyl bromide in the presence of excess silver (I) oxide in acetonitrile:

We attempted allylation of the tosylate **3** in acetonitrile with the view of isolating the intermediate axial monoallyl ether **19** (**Scheme 4.12**). Acetonitrile was chosen as a solvent since we had earlier found (**Chapter 3A. Section 3A.2.7**) that the reactivity of alkyl halide/silver (I) oxide system in acetonitrile is much lesser than in DMF. But this attempt was not successful due to the low solubility of sulfonates in acetonitrile. In all such experiments, about 80% of the starting material could be recovered and no useful product could be isolated.

Scheme 4.12



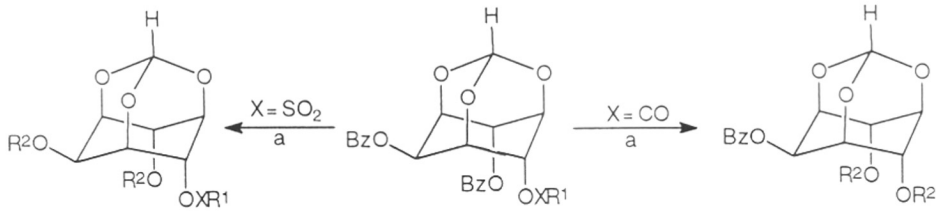
3 **19**

Reagents and conditions: (a) AllBr, Ag_2O, CH_3CN.

We had earlier observed that the dibenzoate **1** and its O-acyl derivatives undergo alkylation with alkyl halides in the presence of silver (I) oxide to yield the corresponding symmetrical diethers in good yields (see **Chapter 3A** for details). In all those experiments cleavage and alkylation of only the 4,6-diaxial ester moieties was observed and the ester at the equatorial 2-position remained unaffected. But in the case of sulfonates (**2, 3, 5 and 6**) under study, we see the cleavage and alkylation of the equatorial ester moieties also (**Scheme 4.13**). A comparison of alkylation of the tribenzoate **20** and the tosylate **3** under study suggests that the cleavage of the 2-equatorial ester group is due to participation by the sulfonyl group. Whereas reaction of the tribenzoate **20** with alkyl halides afforded the

corresponding diaxial ether **21** in good yields, the tosylate **3** under similar conditions of alkylation results in the cleavage of both the axial and equatorial esters giving the corresponding unsymmetrical diethers **22**.

Scheme 4.13



22

R^1 = Alkyl or aryl,
R^2 = alkyl

3: R^1 = p - Tolyl
X = SO_2
20: R^1 = Phenyl
X = CO

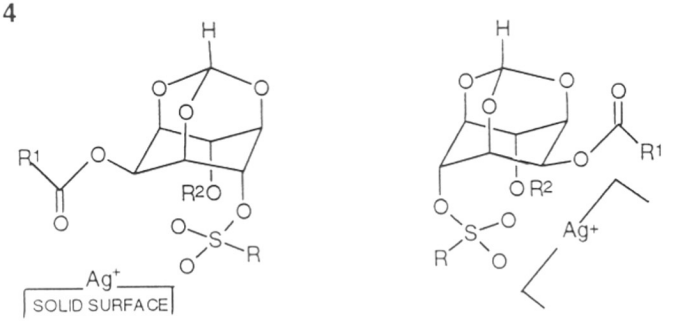
21

R^2 = alkyl

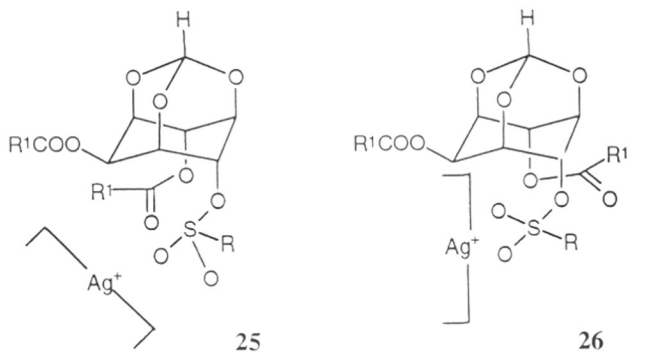
Reagents and conditions: (a) R 2X, Ag_2O, DMF.

Hence we postulated that on the surface of silver (I) oxide the sulfonates could form a chelate (**23**, **24**, **25 or 26**) (**Scheme 4.14**) which facilitate the cleavage and alkylation of the axial as well as the equatorial ester groups.

Scheme 4.14



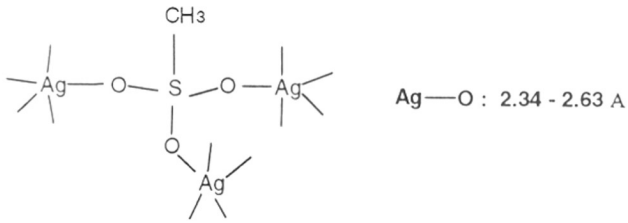
23 **24**



25 **26**

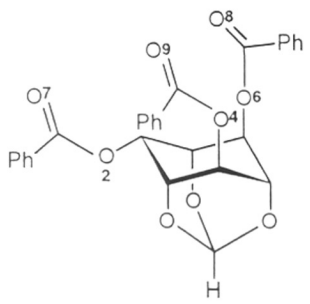
This is supported by the fact that complexation of silver ions with sulfonyl oxygens in silver salts of methane sulfonic acid and p-bromomethane sulfonic acid are known in the literature[3,4] (**Scheme 4.15**). In the former case, there is no distinct molecule; the methane sulfonyl groups act as pentacoordinating ligands. Thus, each silver atom is surrounded by a very distorted trigonal bipyramid with Ag-O bond distance in the range 2.34-2.63 Å.

Scheme 4.15

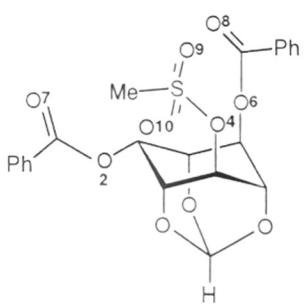


Although formation of a chelate **25 and/or 26** (**Scheme 4.14**) involving the sulfonate group and the axial benzoate group appears possible, due to the proximity of the two diaxial functionalities, the possibility of formation of the corresponding chelate involving the equatorial benzoate group **23 and/or 24** appears remote since they are disposed in 1,3-axial-equatorial configuration. Hence we compared the inter oxygen distances in **20** and **2** (**Scheme 4.16**), for which the X-ray crystal structure data were available. The relevent interatomic distances are tabulated in **Table II**.

Scheme 4.16



20



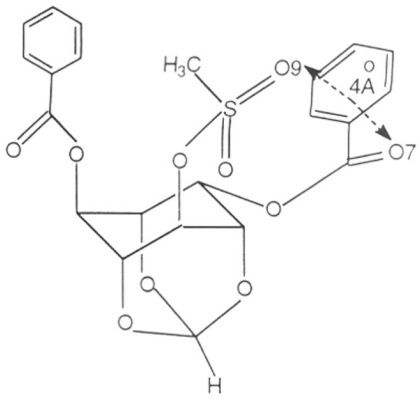
2

Table II: Comparison of inter - oxygen distances (Å) in triester **20** and mesylate **2**.

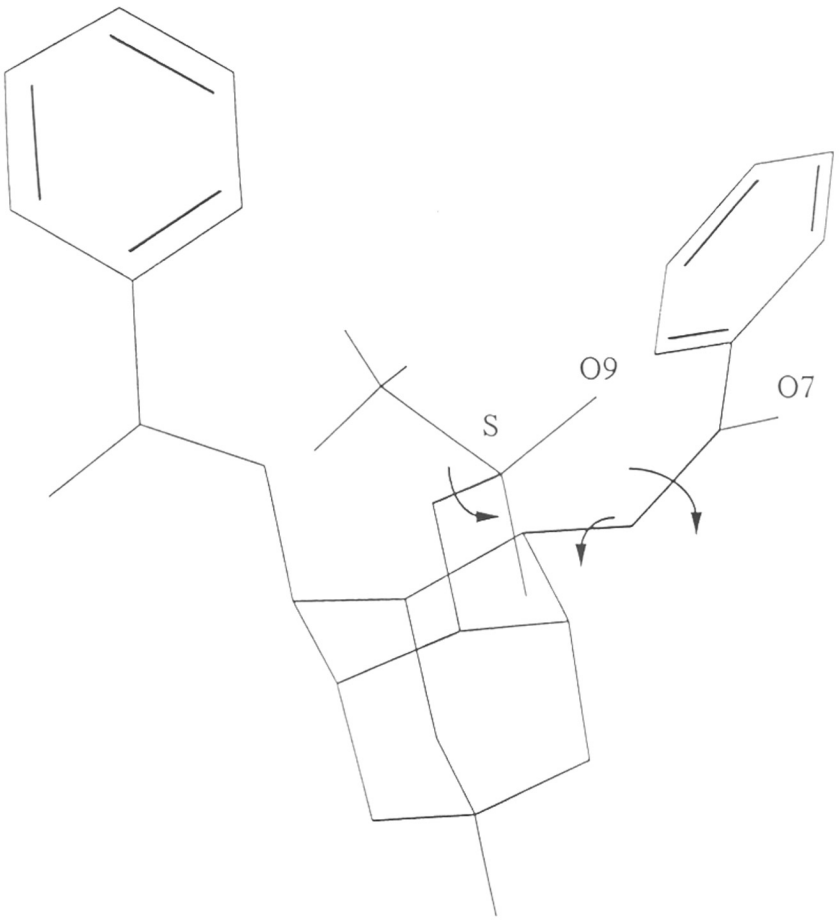
Mol/asymm. Unit	**20**	**2**
$O_9 - O_7$	6.2860	6.2662
$O_4 - O_6$	2.8551	2.7929
$O_2 - O_9$	6.2020	5.9360
$O_2 - O_8$	6.2530	6.1482
$O_6 - O_{10}$	–	5.1640
$O_7 - O_{10}$	–	6.2782
$O_9 - O_6$	3.6998	4.5354

Comparison of inter – oxygen distances in both the tribenzoate **20** and the mesylate **2** shows that $O_4 - O_6$ and $O_9 - O_6$ are close enough to allow formation of a silver chelate, which could result in the cleavage of the axial ester moieties. However, the larger inter - oxygen distances, $O_2 - O_8$, $O_7 - O_9$, $O_2 - O_9$ and $O_7 - O_{10}$ may not allow the formation of a chelate, in the molecular conformation present in the crystal of **2**. Hence we computed the minimum distance possible between O_7 and O_9 interactively using the molecular modelling program NEMESIS (version 1.1 Oxford Molecular Limited., 1992). The minimum distance possible between O_7 and O_9 was found to be about 4 Å. The corresponding conformation of the mesylate **2** is shown in **Scheme 4.17**. Formation of a chelate **23** as shown in **Scheme 4.14** appears to be possible in this conformation, which could result in the cleavage of the equatorial benzoate moiety.

Scheme 4.17



26



4.3 CONCLUSIONS

We have reported an unusual sulfonyl group assisted alkylation of *myo*-inositol orthoformate esters in the presence of silver (I) oxide. Perhaps this is the first report on the neighboring sulfonyl group assisted alkylation of esters to the corresponding ethers in the presence of silver (I) oxide.

4.4 EXPERIMENTAL SECTION

Materials and methods: General experimental conditions, materials and methods are same as mentioned in **Chapter 3A**, except for the following:
Mesyl chloride and camphor sulfonic acid were obtained from Aldrich Chemical Co., USA. Tosyl chloride was obtained from SD Fine Chemicals, India. Camphorsulphonyl chloride was prepared using the procedure of Davis, et al.[5]

Preparation of racemic 2,4-di-O-benzoyl-6-O-mesyl-*myo*-inositol-1,3,5-orthoformate (2)

The dibenzoate **1** (0.60g, 1.5 mmol) was dissolved in pyridine (14 ml) and a solution of mesyl chloride (0.9 ml) in pyridine (7 ml) was added dropwise with ice cooling and the reaction mixture was stored in a fridge overnight. The reaction mixture was then poured into ice cold solution of sodium bicarbonate and the precipitated solid was filtered and washed with water. The solid obtained was dissolved in ethyl acetate and washed successively with hydrochloric acid solution (0.1N), water and brine. The organic solution was dried over anhydrous sodium sulphate and evaporated. The residue was crystallised from a mixture of chloroform and light petroleum (0.66g, 92%).

Data for 2:
m.p. 179-182°C.
IR (cm^{-1}): 1690, 1710.
^{1}**H NMR**: δ 2.90 (s, 3H), 4.70 (m, 2H), 4.85 (m, 1H), 5.45-5.55 (m, 1H), 5.65 (q, 1H), 5.70 (d, 1H), 5.85 (m, 1H), 7.45-7.70 (m, 6H), 8.05-8.20 (m, 4H).
^{13}**C NMR:** 38.5, 63.3, 67.4, 67.7, 69.4, 69.8, 71.9, 103.2, 128.8, 128.9, 129.4, 130.2, 133.9, 134.1, 165.1, 166.2.

Preparation of racemic 2,4-di-O-benzoyl-6-O-p-toluenesulphonyl-*myo*-inositol-1,3,5-orthoformate (3)

The tosylate was prepared as above using the dibenzoate **1** (1.35g, mmol) in pyridine (14 ml) and triethyl amine (6 ml), and tosyl chloride (3.2 g, mmol) in pyridine (14 ml). The pure product **3** was obtained by column chromatography over silica gel (0.75g, 40%).

Data for 3:
m.p. 163-164°C.
IR (cm^{-1}): 1710, 1720.

^{1}H NMR: δ 2.40 (s, 3H), 4.45-4.65 (m, 3H), 5.30 (m, 1H), 5.55 (m, 1H), 5.65 (d, 1H), 5.80-5.85 (m, 1H), 7.20-7.75 (m, 10H), 8.00-8.20 (m, 4H).

^{13}C NMR: 21.8, 63.3, 67.3, 67.5, 69.3, 69.8, 72.2, 103.2, 128.1, 128.8, 129.5, 129.7, 130.1, 130.2, 130.3, 132.4, 133.8, 145.9, 165.1, 165.9.

Elemental anal. calcd. for $C_{28}H_{24}O_{10}S$: C, 60.87%; H, 4.35%; S, 5.79%.
Found: C, 60.68%; H,4.65%; S, 6.67%.

Preparation of racemic 2,4-di-O-acetyl-6-O-tosyl-*myo*-inositol-1,3,5-orthoformate (5)

The dibenzoate **3** (0.18 g, 0.34 mmol) was refluxed with t-butyl amine in methanol for 5h. The residue obtained after removal of volatile liquids was dissolved in pyridine (1 ml) and acetic anhydride (0.43 g, 4.2 mmol) in pyridine (1 ml) was added dropwise at 0°C for 24 h. The reaction mixture was then poured into ice cold solution of sodium bicarbonate and the precipitated solid was filtered and washed with water. The solid obtained was dissolved in ethyl acetate and washed successively with hydrochloric acid solution, water and brine. The organic solution was dried over anhydrous sodium sulphate and evaporated. The residue was purified by column chromatography (0.14g, 96%) to obtain pure **5**.

Data for 5:

m.p. 116°C.

IR (cm^{-1}): 1700, 1720.

^{1}H NMR: δ 2.10 (s, 3H), 2.25 (s, 3H), 2.50 (s, 3H), 4.20 (m, 1H), 4.35 (m, 1H), 4.60 (m, 1H), 5.05 (m, 1H) 5.25 (m, 1H), 5.45 (m, 1H), 5.55 (d, 1H), 7.40 (d, 2H), 7.85 (d, 2H).

^{13}C NMR: 20.3, 20.6, 21.4, 62.3, 66.2, 66.7, 68.6, 68.8, 71.8, 102.5, 127.6, 129.9, 132.0, 145.5, 169.2, 169.8.

Elemental anal. calcd. for $C_{18}H_{20}O_{10}S$: C, 50.47%; H, 4.67%; S, 7.48%.
Found: C, 50.43%; H,4.40%; S, 7.57%.

Preparation of 2,4-di-O-benzoyl-6-O-camphorsulphonyl-*myo*-inositol-1,3,5-orthoformate (6) (mixture of diastereomers)

The camphorsulphonate was prepared as in the case of **2** using the dibenzoate **1** (0.80 g, 2 mmol) in pyridine (16 ml) and camphorsulphonyl chloride (2.5 g, 10 mmol), except that the reaction was carried out at room temperature for 70 h. The residue was purified by column chromatography (1.21 g, 99%) to obtain pure **6** as 1:1 diastereomeric mixture.

Data for 6:

m.p. 71-74°C.

IR (cm^{-1}): 1720-1740, 2820-2920.

^{1}H NMR: 0.75 (2s, 6H), 0.95 (s, 3H), 1.00 (s, 3H), 1.20-2.45 (m, 14H), 2.85-3.00 (dd, 2H), 3.50 (d, 1H), 3.60 (d, 1H), 4.60-4.80 (m, 4H), 4.85 (m, 2H), 5.50-5.65 (m, 4H), 5.70 (d, 2H), 5.80-5.90 (m, 2H), 7.40-7.65 (m, 12H), 8.10-8.20 (m, 8H).

^{13}C NMR: 19.5, 24.9, 26.8, 26.9, 42.3, 42.7, 48.1, 48.3, 57.9, 63.3, 67.4, 67.6, 69.2, 69.5, 69.9, 72.4, 72.6, 76.6, 93.4, 96.4, 103.1, 128.6, 128.7, 128.9, 129.4, 130.0, 130.1, 133.6, 133.8, 165.0, 165.1, 165.9, 187.5, 213.8, 213.9.

Elemental anal. calcd. for $C_{31}H_{32}O_{11}S$: C, 60.78%; H, 5.23%.

Found: C, 60.56%; H, 5.21%.

Reaction of racemic 2,4-di-O-benzoyl-6-O-tosyl-*myo*-inositol-1,3,5-orthoformate (3) with methyl iodide

The tosylate **3** (0.28g, 0.51 mmol) and methyl iodide (0.30 ml, 5 mmol) were dissolved in 2 ml DMF and cooled (0-5°C). Silver (I) oxide (0.59g, 2.5 mmol) was added to this solution and stirred for 66 h. The reaction mixture was filtered over one inch column of celite, which was again washed with chloroform (10 ml X 3). The filtrate was washed with 1% solution of sodium cyanide followed by water and then dried over anhydrous sodium sulphate. The residue obtained after the evaporation of chloroform was purified by column chromatography over silica gel.. The dimethyl ether **7** formed as gum was the only isolated product (0.12 g, 64%).

Data for 7:

^{1}H NMR: δ 2.50 (s, 3H), 3.40 (s, 3H), 3.50 (s, 3H), 3.65 (q, 1H), 4.10-4.20 (m, 2H), 4.35 (m, 1H), 4.45 (m, 1H), 5.10 (m, 1H,) 5.45 (d, 1H), 7.40 (d, 2H), 7.85 (d, 2H).

^{13}C NMR: 21.5, 56.7, 57.0, 66.8, 68.4, 68.9, 69.0, 72.9, 74.7, 102.8, 127.8, 130.0, 132.7, 145.4.

Reaction of racemic 2,4-di-O-benzoyl-6-O-mesyl-*myo*-inositol-1,3,5-orthoformate (2) with methyl iodide

The mesylate **2** (0.20g, 0.42 mmol) was reacted with methyl iodide (0.25 ml, 4.2 mmol) as above using silver (I) oxide (0.59 g, 2.5 mmol) in DMF (2 ml) and two products were formed which had very close R_f values (0.4 and 0.3; 30% EtOAc – light petroleum, 2 runs). They were separated by column chromatography. The product with higher R_f was identified as the C-methylated product **8** (0.06 g, 46%) and the product with lower R_f was identified as the dimethyl ether **9** (0.04 g, 32%).

Data for 8:

^{1}H NMR: 1.45 (t, 3H), 3.20 (q, 2H), 3.45 (s, 3H), 3.55 (s, 3H), 3.65 (m, 1H), 4.20 (m, 1H), 4.40-4.50 (m, 2H), 4.60 (m, 1H), 5.35 (m, 1H), 5.55 (d, 1H).

^{13}C NMR: 7.8, 45.6, 56.6, 57.2, 66.9, 68.3, 68.9, 71.5, 74.7, 76.4, 102.7.

Data for 9:

^{1}H NMR: δ 3.10 (s, 3H), 3.50 (s, 3H), 3.55 (s, 3H), 3.70 (q, 1H), 4.20 (m, 1H), 4.40-4.50 (m, 2H) 4.55-4.65 (m, 1H), 5.30-5.40 (d, 1H).

Reaction of 2,4(6)-di-O-benzoyl-6(4)-O-camphorsulphonyl-*myo*-inositol-1,3,5-orthoformate (6) with methyl iodide

The camphorsulphonate **6** (0.21 g, 0.34 mmol) was reacted with methyl iodide (0.2 ml, 3.4 mmol) and silver oxide (0.4 g, 1.71 mmol) in DMF (2 ml). The products were obtained as gum by column chromatography over silica gel (eluant 5% EtOAc - light petroleum). The product with higher R_f (0.6; 20% EtOAc - light petroleum, two runs) was identified as the monomethyl ether **10** (0.09 g, 51%) and the product with lower R_f (0.3; 20% EtOAc - light petroleum, two runs) was the dimethyl ether **11** (0.07 g, 47%), both obtained as a mixture of diastereomers.

Data for 10:

^{1}H NMR: 1.05-2.20 (m, 16H), 2.35-2.55 (m, 2H), 3.55 (d, 3H), 4.25 (m, 1H), 4.50-4.70 (m, 3H), 5.40-5.55 (m, 2H), 5.60 (d, 1H), 7.45-7.65 (m, 3H), 8.15 (m, 2H).

^{13}C NMR: 13.9, 20.6, 21.6, 25.1, 25.3, 26.1, 26.3, 42.6, 45.1, 48.5, 57.1, 57.4, 57.5, 63.3, 67.6, 69.4, 69.6, 71.1, 71.4, 74.9, 102.9, 128.3, 129.4, 129.8, 133.3, 165.8, 214.4.

Data for 11:

^{1}H NMR: 1.05-2.00 (m, 20H), 2.30-2.40 (m, 2H), 3.40-3.65 (m, 9H), 4.10 (m, 1H), 4.30-4.60 (m, 3H), 5.35 (m, 1H), 5.50 (s, 1H).

Reaction of racemic 2,4-di-O-benzoyl-6-O-mesyl-*myo*-inositol-1,3,5-orthoformate (2) with allyl bromide

The mesylate **2** (0.23g, 0.5 mmol) was reacted with allyl bromide (0.5 ml, 5 mmol) and silver oxide (0.58 g, 2.5 mmol) in DMF (2 ml). The residue obtained was purified by column chromatography. The product with higher R_f (0.6; 30% EtOAc – light petroleum, 2 runs) was the monoallyl ether **12** obtained as a gum (0.02 g, 10%) and the product with lower R_f (0.4; 30% EtOAc – light petroleum, 2 runs) was the diallyl ether **13** obtained as a gum (0.11 g, 63%).

Data for 12:

IR (cm^{-1}): 1730.

^{1}H NMR: δ 3.15 (s, 3H), 4.15 (dd, 2H), 4.40 (m, 1H), 4.55 (m, 2H), 4.65 (m, 1H), 5.20-5.55 (m, 4H), 5.60 (d, 1H), 5.85-6.05 (m, 1H), 7.40-7.65 (m, 3H), 8.10-8.20 (m, 2H).

Data for 13:

^{1}H NMR: δ 3.10 (s, 3H), 3.90 (q, 1H), 4.00-4.25 (m, 4H), 4.30-4.50 (m, 3H), 4.55-4.60 (m, 1H), 5.20-5.40 (m, 5H) 5.55 (d, 1H), 5.75-6.10 (m, 2H).

^{13}C NMR: 38.4, 66.4, 67.4, 69.6, 70.0, 70.1, 70.5, 72.9, 102.8, 117.6, 117.9, 133.7, 134.1.

Reaction of racemic 2,4-di-O-benzoyl-6-O-mesyl-*myo*-inositol-1,3,5-orthoformate (2) with 20 eq. allyl bromide

The mesylate **2** (0.10 g, 0.21 mmol) was reacted with allyl bromide (0.5 ml, 5 mmol) and silver oxide (0.58 g, 2.5 mmol) in DMF (1 ml). The residue obtained was purified by column chromatography. The diallyl ether **13** (0.06 g, 82%) was obtained (gum) as the only product.

Reaction of racemic 2,4-di-O-benzoyl-6-O-tosyl-*myo*-inositol-1,3,5-orthoformate (3) with allyl bromide

The tosylate **3** (0.25 g, 0.45 mmol) was reacted with allyl bromide (0.40 ml, mmol) and silver oxide (0.52 g, 2.25 mmol) in DMF (2 ml). The diallyl ether **14** was obtained as gum by column chromatography over silica gel (eluant 5% EtOAc - light petroleum) as the only product (0.18 g, 94%).

Data for 14:

^{1}H NMR: δ 2.40 (s, 3H), 3.80 (q, 1H), 3.90-4.35 (m, 8H), 5.00-5.35 (m, 5H) 5.45 (d, 1H), 5.70-6.00 (m, 2H), 7.30 (d, 2H), 7.80 (d, 2H).

^{13}C NMR: 21.6, 66.6, 67.4, 69.6, 70.2, 70.4, 70.5, 72.7, 73.1, 76.6, 102.9, 117.6, 117.8, 127.9, 130.1, 132.9, 133.8, 134.2, 145.5.

Reaction of racemic 2,4-di-O-acetyl-6-O-p-toluenesulphonyl-*myo*-inositol-1,3,5-orthoformate (5) with allyl bromide

The tosylate **5** (0.13 g, 0.3 mmol) was reacted with allyl bromide (0.3 ml, 3.5 mmol) and silver oxide (0.35 g, 1.5 mmol) in DMF (2 ml). The diallyl ether **14** was obtained as gum by column chromatography over silica gel (eluant 5% EtOAc - light petroleum) as the major product (0.07 g, 55%) (R_f value and ^{1}H NMR spectrum were same as **14** obtained from **3**).

Reaction of 2,4(6)-di-O-benzoyl-6(4)-O-camphorsulphonyl-*myo*-inositol-1,3,5-orthoformate (6) with allyl bromide

The camphorsulphonate **6** (0.24 g, 0.39 mmol) was reacted with allyl bromide (0.70 ml, 7.8 mmol) and silver oxide (0.90 g, 3.9 mmol) in DMF (2 ml). The products were obtained as gum by column chromatography over silica gel (eluant 5% EtOAc - light petroleum). The product with higher R_f (0.6; 20% EtOAc - light petroleum, two runs) was identified as the monoallyl ether **15** (0.07 g, 32%) and the product with lower R_f (0.3; 20% EtOAc - light petroleum, two runs) was the diallyl ether **16** (0.08 g, 42%), both obtained as a gum and as a mixture of diastereomers.

Data for 15:

^{1}H NMR: 0.75 (s, 2H), 0.90 (s, 5H), 0.95 (s, 1H), 1.10 (s, 4H), 1.25-2.50 (m, 20 H), 2.65-3.90 (m, 8H), 4.15-4.35 (m, 1H), 4.40-4.75 (m, 6H), 4.82 (m, 1H), 5.40 (m, 1H), 5.50-5.65 (m, 4H), 5.85 (m, 1H), 7.45-7.65 (m, 6H), 8.00-8.20 (m, 4H).

Data for 16:

^{1}H NMR: δ 0.85 (2s, 6H), 1.10 (2s, 6H), 1.40-2.55 (m, 18H), 3.05 (d, 2H), 3.60-3.70 (dd, 2H), 3.85-4.75 (m, 18H), 5.15-5.65 (m, 12H), 5.70-6.15 (m, 2H).

Reaction of racemic 2,4-di-O-benzoyl-6-O-mesyl-*myo*-inositol-1,3,5-orthoformate (2) with allyl chloride

The mesylate **2** (0.24 g, 0.5 mmol) and allyl chloride (0.6 ml, 7.6 mmol) were dissolved in DMF (2. ml) and stirred with silver (I) oxide (0.58 g, 2.5 mmol) at r.t. for 66 h. The residue was purified by column chromatography over silica gel to obtain the starting material **2** quantitatively.

Reaction of racemic 2,4-di-O-benzoyl-6-O-p-toluenesulphonyl-*myo*-inositol-1,3,5-orthoformate (3) with allyl chloride

The tosylate **3** (0.28 g, 0.51 mmol) and allyl chloride (0.6 ml, 7.6 mmol) were dissolved in DMF (2. ml) and stirred with silver (I) oxide (0.59 g, 2.5 mmol) at r.t. for 66 h. The residue was purified by column chromatography over silica gel to obtain the starting material **3** quantitatively.

Reaction of 2,4(6)-di-O-benzoyl-6(4)-O-camphorsulphonyl-*myo*-inositol-1,3,5-orthoformate (6) with allyl chloride

The camphorsulfonate **6** (0.33 g, 0.54 mmol) and allyl chloride (0.6 ml, 7.6 mmol) were dissolved in DMF (2.5 ml) and stirred with silver (I) oxide (0.63 g, 2.69 mmol) at r.t. for 66 h. The residue was purified by column chromatography over silica gel to obtain the starting material **6** (0.23 g, 70%).

Reaction of 2,4(6)-di-O-benzoyl-6(4)-O-camphorsulphonyl-*myo*-inositol-1,3,5-orthoformate (6) with benzyl bromide

The camphorsulphonate **6** (0.25 g, 0.41 mmol) was reacted with benzyl bromide (1 ml, 8.2 mmol) and silver oxide (0.95 g, 4.1 mmol) in DMF (2 ml). The products were obtained as gum by column chromatography over silica gel (eluant 5% EtOAc - light petroleum). The product with higher R_f (0.6; 20% EtOAc - light petroleum, two runs) was identified as the monobenzyl ether **17** (0.08 g, 32%) and the product with lower R_f (0.2; 20% EtOAc - light petroleum, two runs) was the dibenzyl ether **18** (0.06 g, 25%) (both obtained as a mixture of diastereomers).

Data for 17:

IR (cm^{-1}): 1710, 1730.

^{1}H NMR: 0.75-0.90 (2s, 6H), 1.00-1.10 (2s, 6H), 1.15-2.50 (m, 14H), 3.00-3.15 (dd, 2H), 3.60-3.75 (dd, 2H), 4.40-4.85 (m, 12H), 5.45-5.60 (m, 4H), 5.60 (d, 2H), 7.25-7.70 (m, 16H), 8.15 (m, 4H).

^{13}C NMR: 19.4, 24.6, 25.0, 26.8, 42.3, 42.6, 42.7, 48.0, 48.3, 48.5, 57.8, 63.4, 67.8, 69.5, 69.8, 71.6, 71.9, 72.7, 102.9, 127.7, 128.0, 128.4, 128.5, 129.4, 129.9, 133.4, 137.0, 165.8, 213.9.

Data for 18:

^{1}H NMR: δ 0.75 (2s, 6H), 1.00 (2s, 6H), 1.15-2.45 (m, 14H), 2.85-3.00 (d, 2H), 3.45-3.65 (dd, 2H), 3.95-4.05 (dd, 2H), 4.25-4.85 (m, 16H), 5.40-5.50 (m, 2H), 7.10-7.60 (m, 20H).

^{13}C NMR: 19.8, 25.0, 27.0, 42.6, 42.9, 48.1, 48.3, 48.5, 58.0, 66.3, 67.9, 70.0, 70.1, 70.4, 71.7, 72.6, 72.7, 73.4, 103.2, 127.5, 127.7, 128.1, 128.2, 128.4, 128.7, 137.5, 214.0.

Reaction of racemic 2,4-di-O-benzoyl-6-O-mesyl-*myo*-inositol-1,3,5-orthoformate (2) with silver (I) oxide

The mesylate **2** (0.05 g, 0.1 mmol) was stirred with silver oxide (0.12 g, 0.5 mmol) in DMF (0.5 ml). There was no reaction by TLC and the starting material could be recovered quantitatively.

Reaction of racemic 2,4-di-O-benzoyl-6-O-p-toluenesulphonyl-*myo*-inositol-1,3,5-orthoformate (3) with silver (I) oxide

The tosylate **3** (0.05 g, 0.09 mmol) was stirred with silver oxide (0.1 g, 0.45 mmol) in DMF (1 ml). There was no reaction by TLC and the starting material could be recovered quantitatively.

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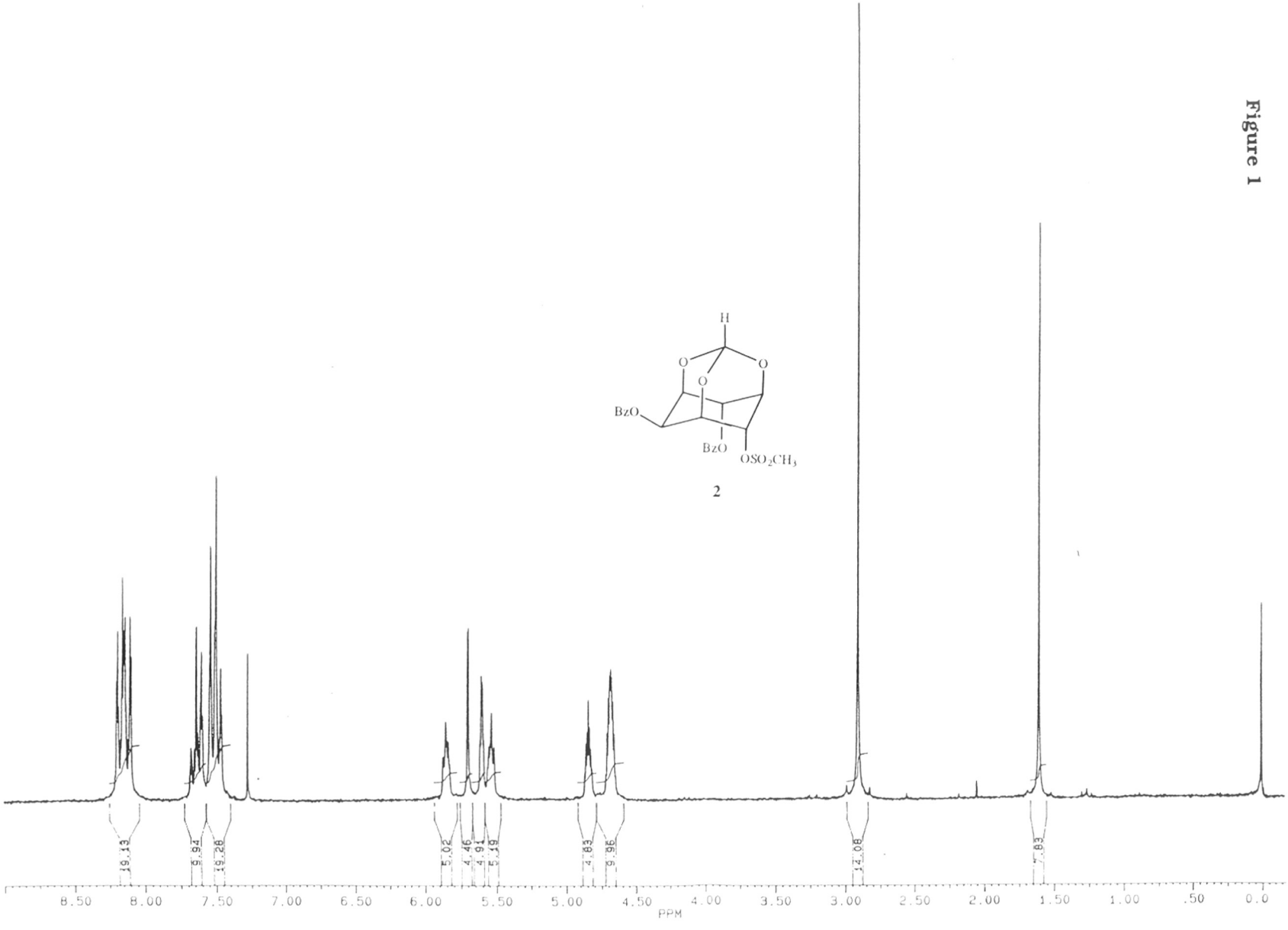
1. Feiser and Feiser, *Reagents for Organic Synthesis*, **1966**, Vol.1, P 662.
2. H. Taguchi, S. Y. Wang, *J. Org. Chem.*, **1977**, *42*, 3321-3323.
3. F. Charbonnier, R. Faure, H. Loiseleur, *Acta. Cryst.*, **1977**, *B33*, 2824-2826.
4. F. Charbonnier, R. Faure, H. Loiseleur, *Acta. Cryst.*, **1978**, *B34*, 3598-3601.
5. F. A. Davis, R. H. Jenkins, Jr., S. B. Awad, O. D. Stringer, W. H. Watson, J. Galloy, *J. Am. Chem. Soc.*, **1982**, *104*, 5412.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4.46
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14.08
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8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
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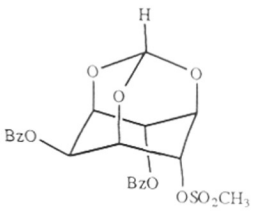
2.00
1.50
1.00
.50
0.0
PPM

2

Figure 1

Figure 2

Figure 3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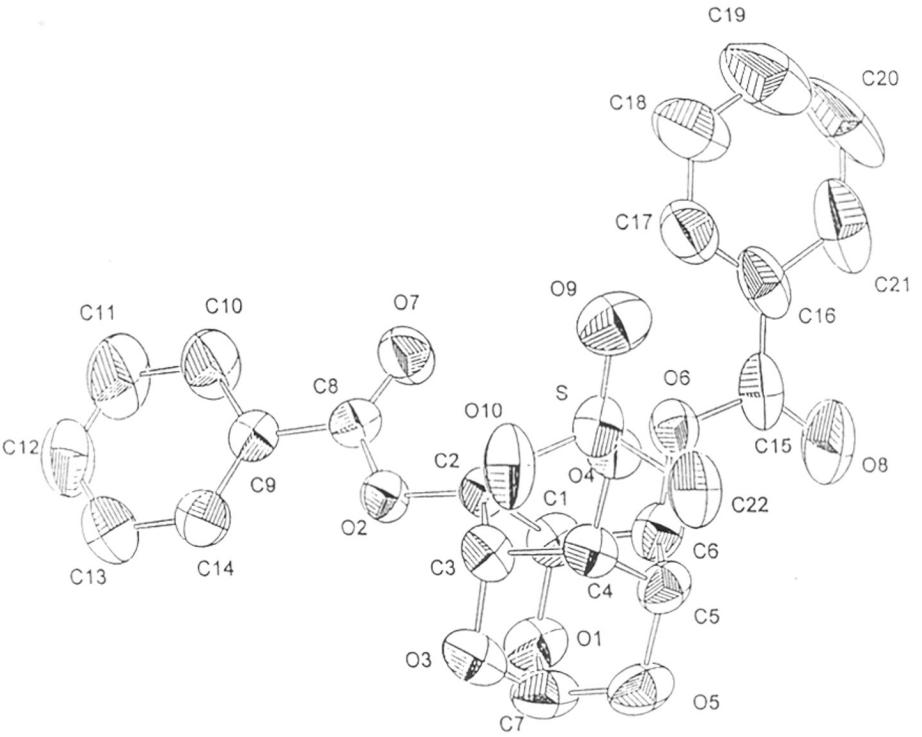
O
BzO
BzO
OSO_2CH_3

2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C18
C17
C21
C16
O9
O7
C11
C10
C8
S
O6
O10
C12
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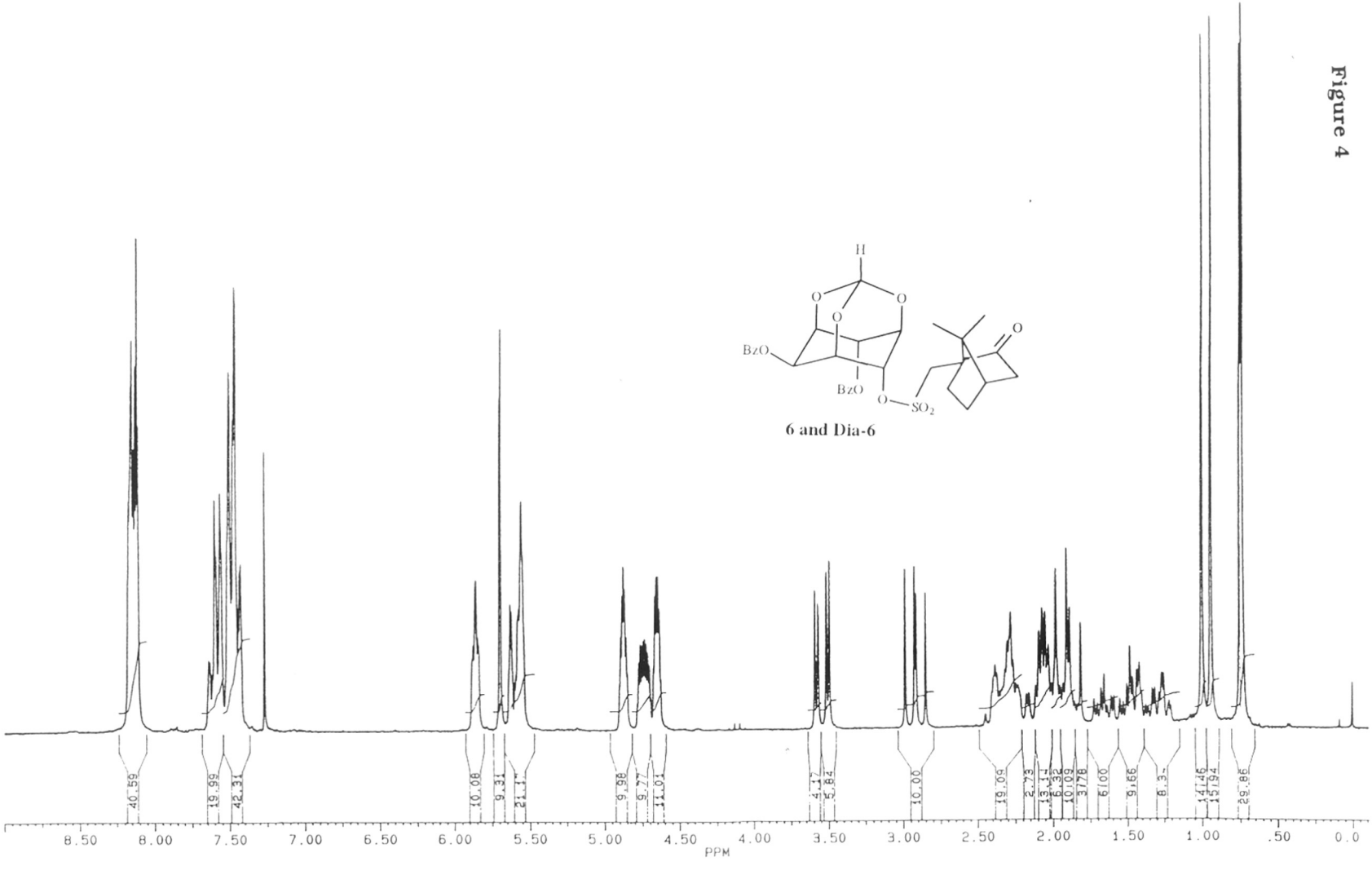
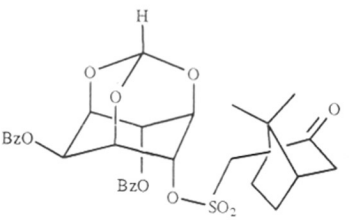
C15
O8
C9
O4
C1
C22
O2
C6
C3
C4
C13
C14
C5
O1
O3
O5
C7



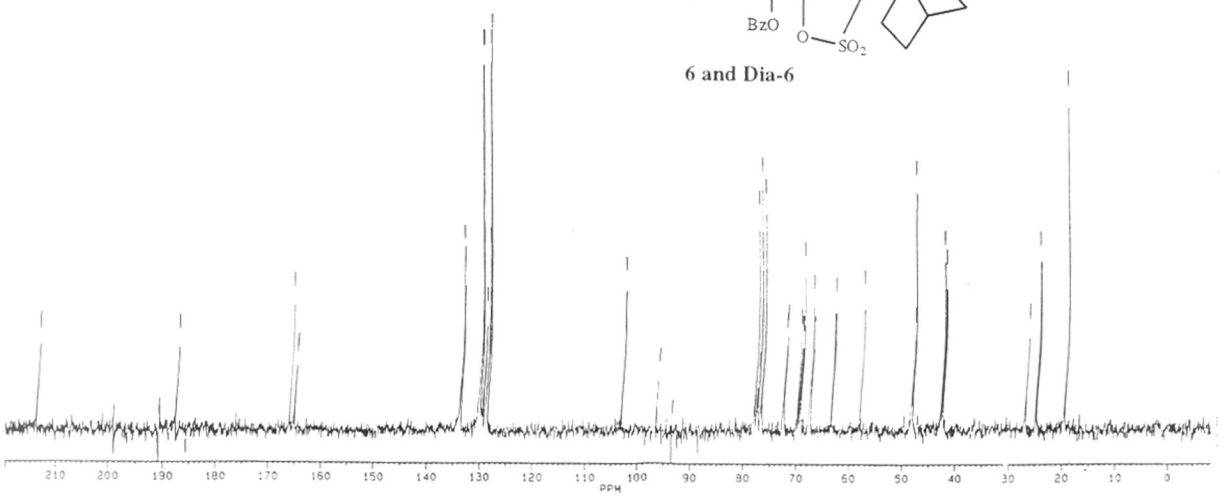
6 and Dia-6

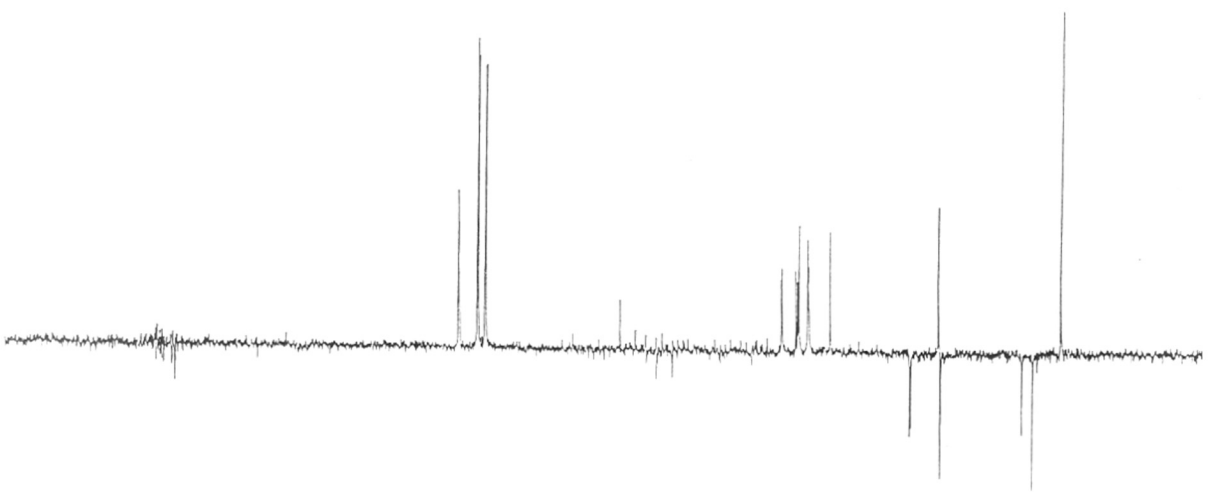
Figure 4

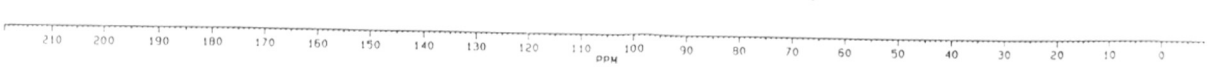
Figure 5

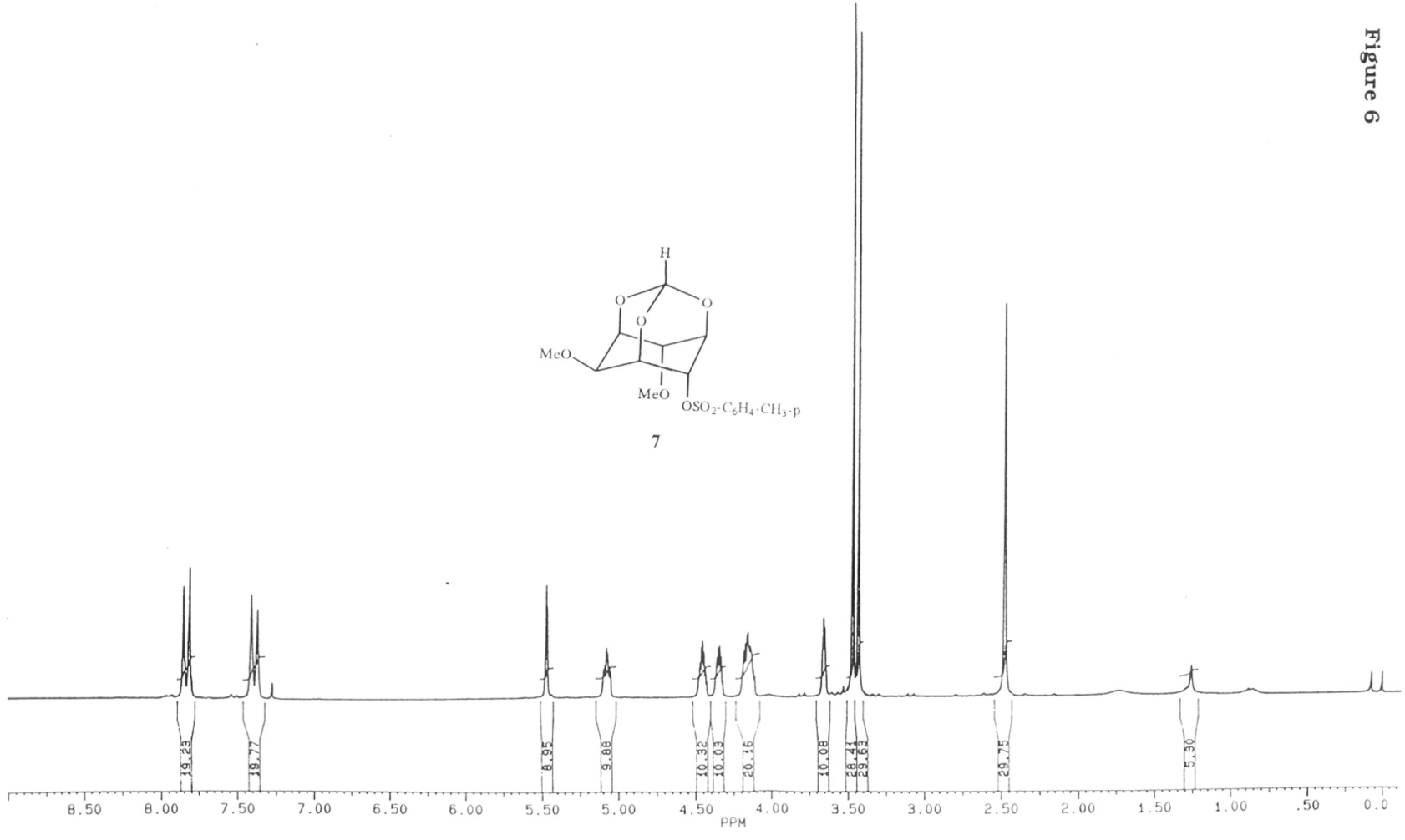


6 and Dia-6





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20.16
10.08
28.41
29.63
29.75
5.30
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6.00
5.50
5.00
4.50
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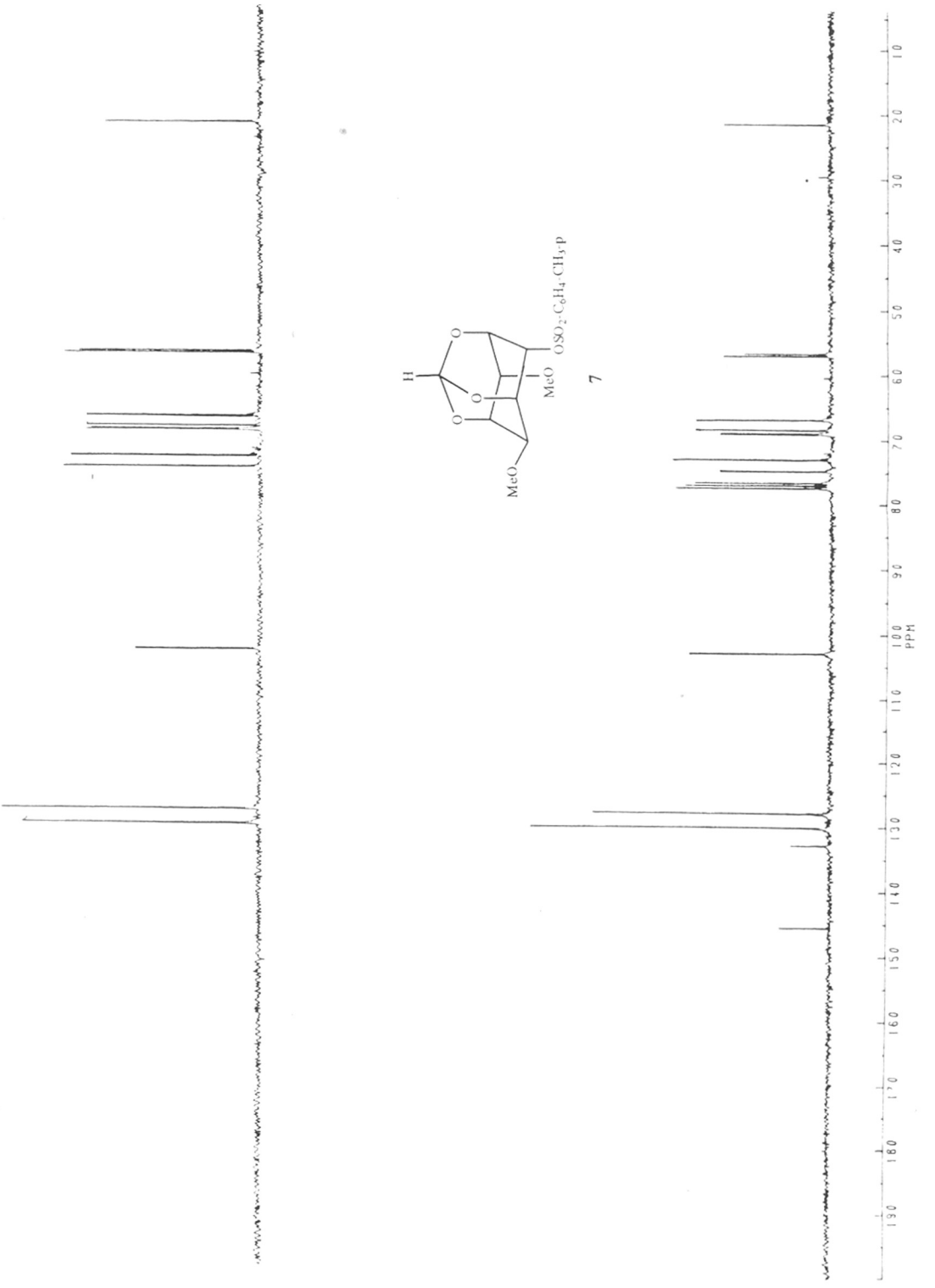
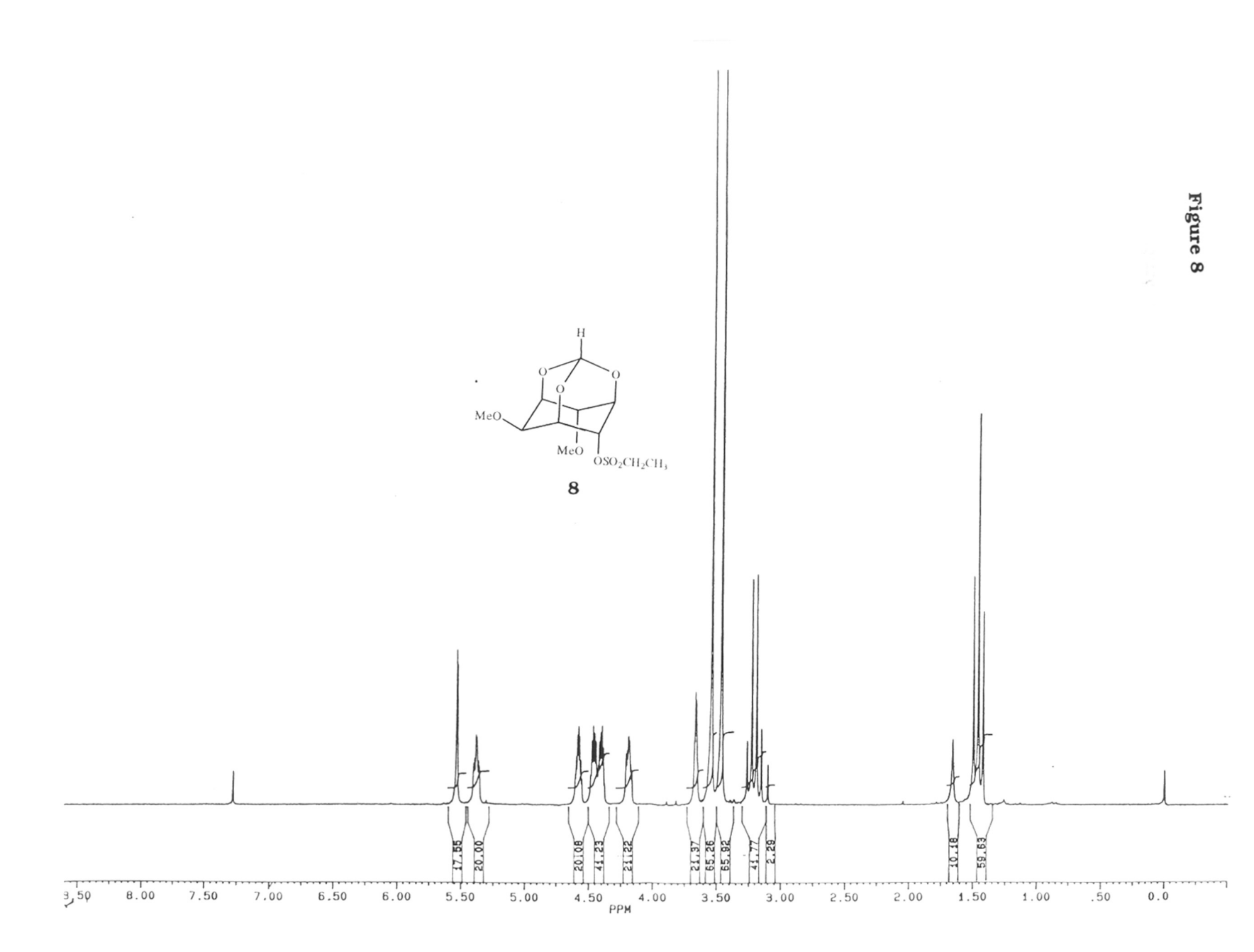
PPM

7

Figure 6

Figure 7

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41.23
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65.26
65.82
41.77
2.29
10.18
59.63
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
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1.00
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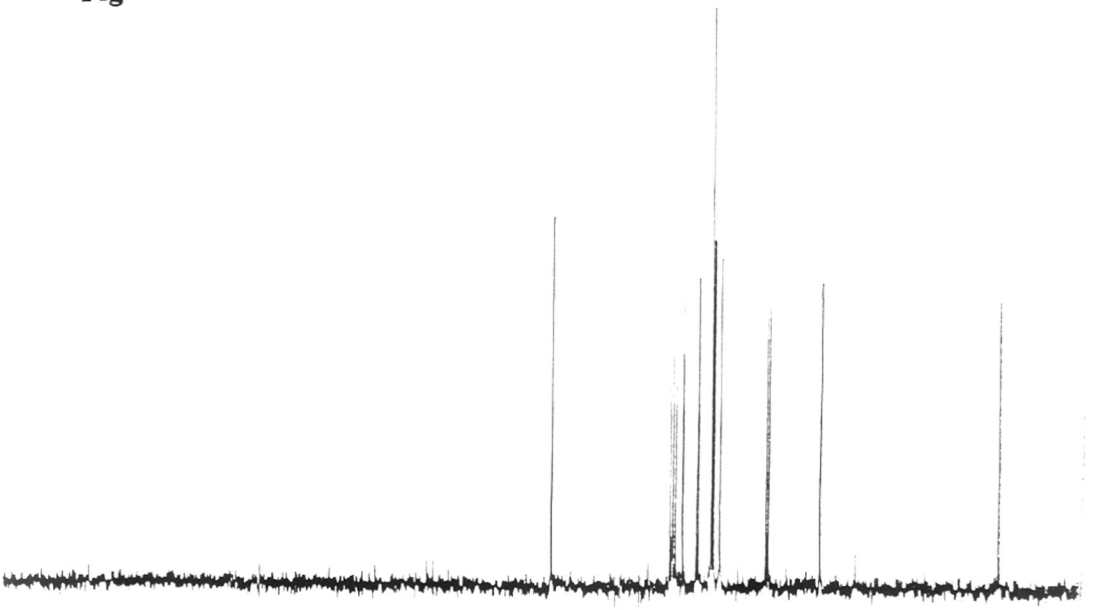
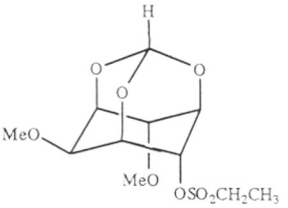
0.0
PPM

Figure 8

Figure 9





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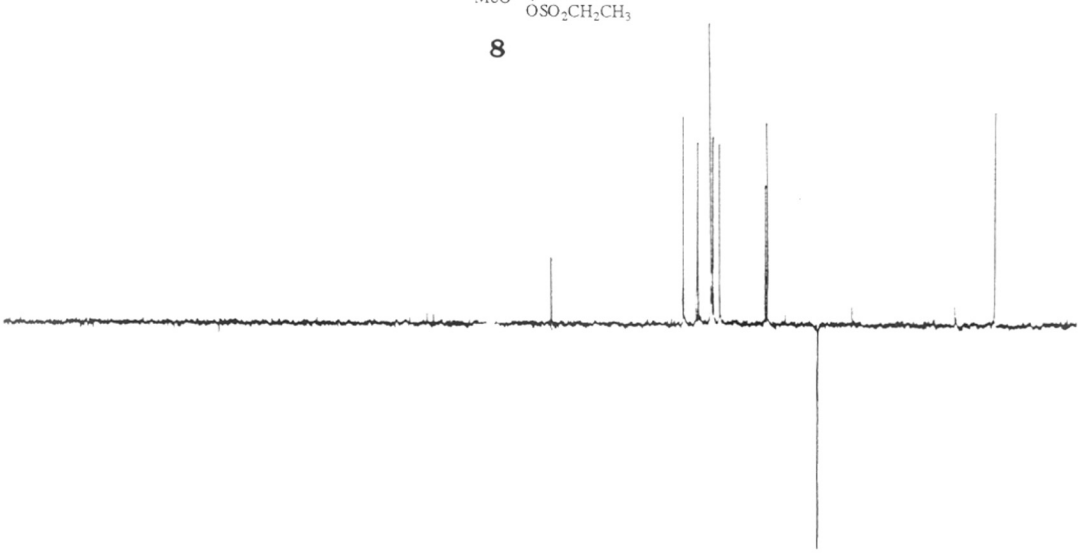

Figure 10

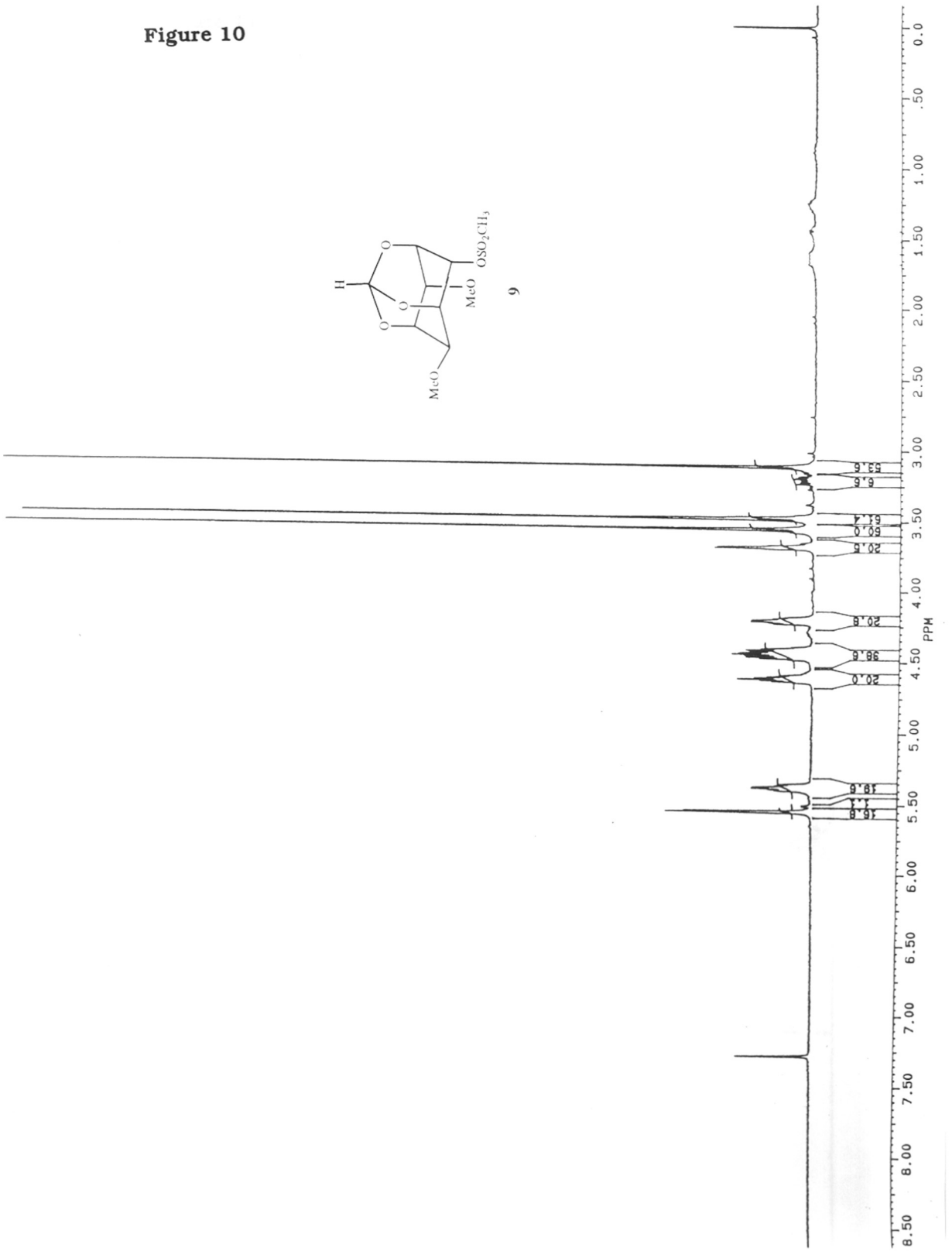

Figure 11

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2.02
7.50
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10.10
5.38
5.67
14.07
11.17
5.18
10.00
1455.98
HER12

Figure 12

Figure 13

H
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O
AllO
BzO
OSO2CH3
12
2.00
5.44
32.12
2.88
26.07
15.64
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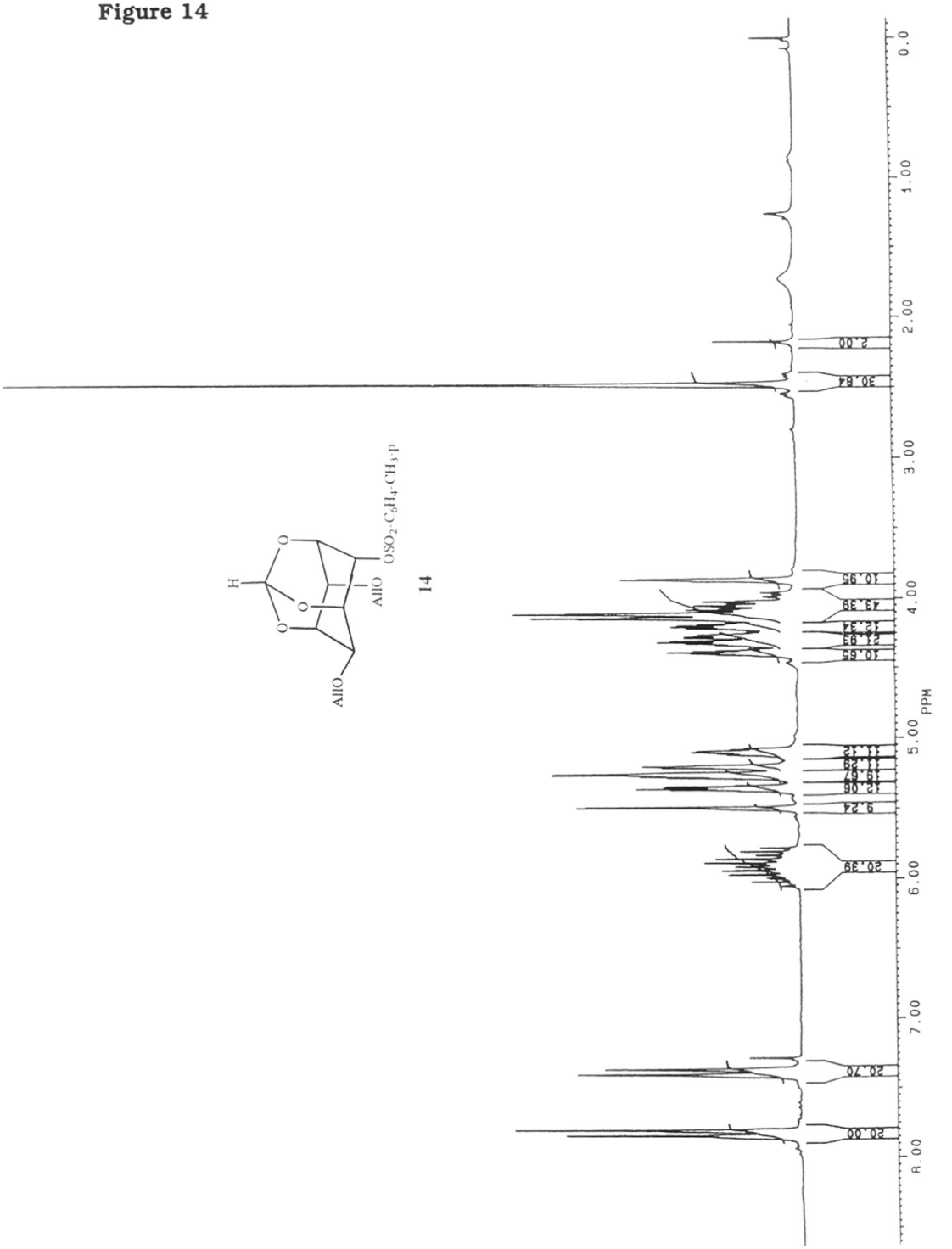
20.00
PPM

Figure 14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21.93
10.85
12.08
9.24
20.39
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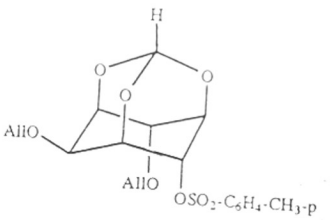
5.00
6.00
7.00
8.00
PPM

Figure 15



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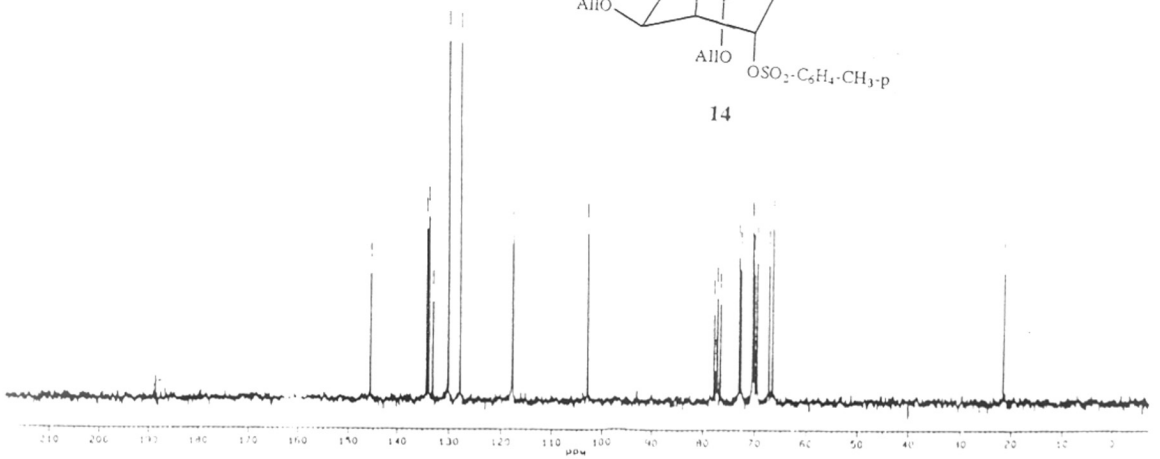

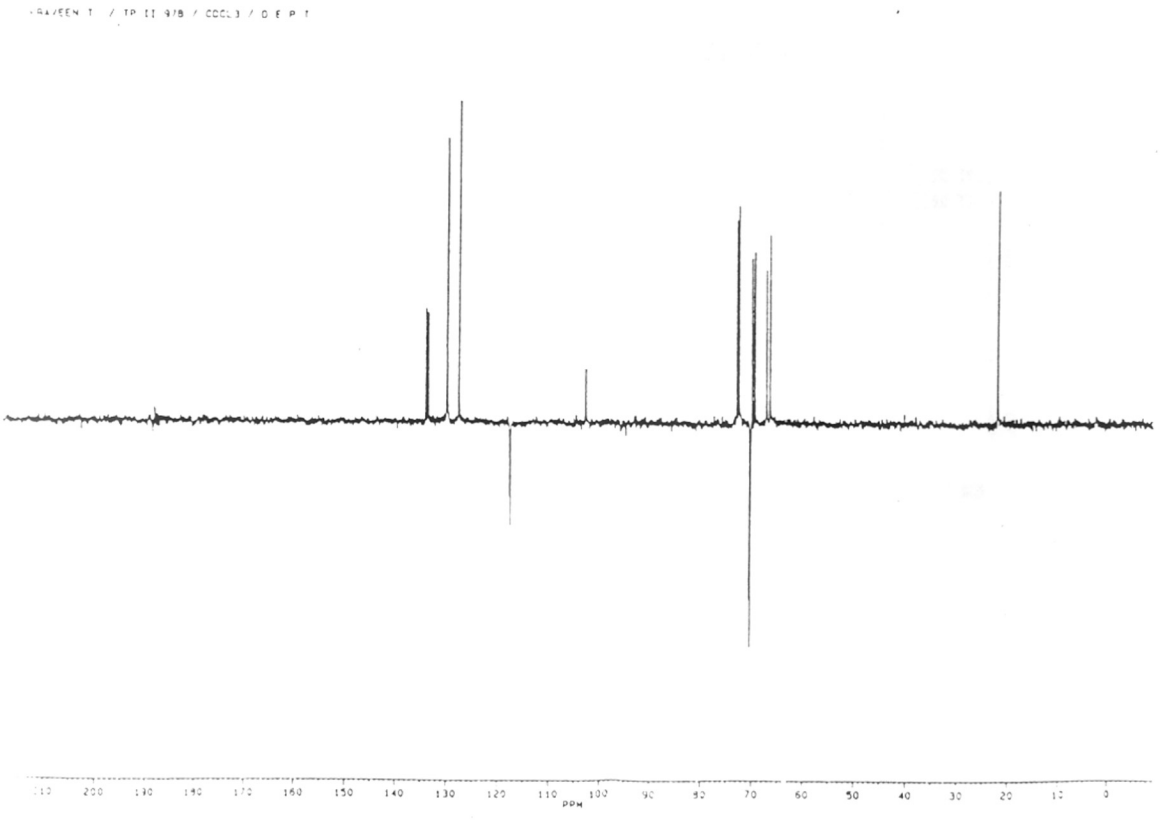

Figure 16

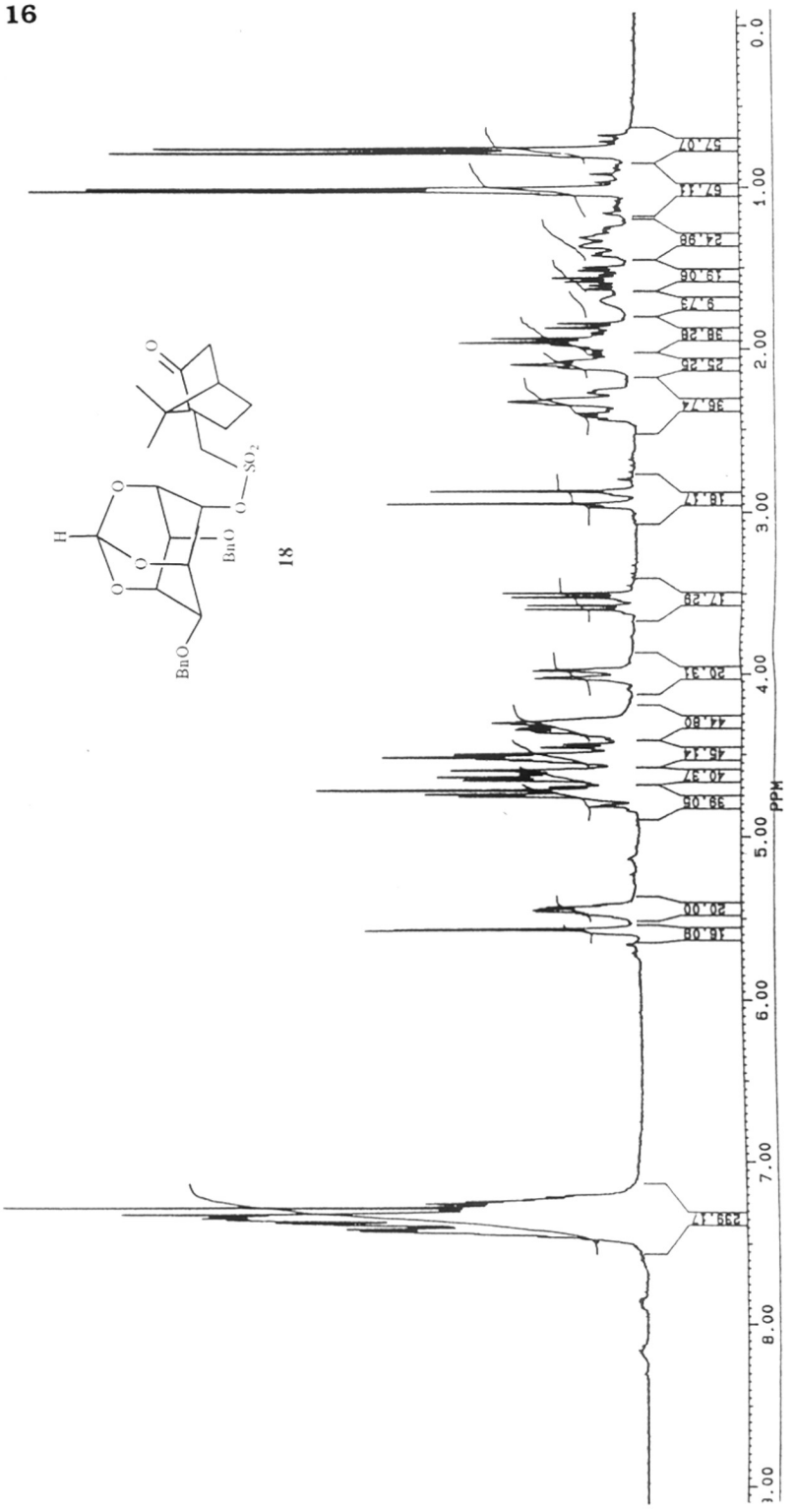

Figure 17