CHEMISTRY OF INOSITOLS: NEIGHBORING GROUP EFFECTS IN THE REACTIONS OF *O*-SUBSTITUTED *MYO*-INOSITOL 1,3,5-ORTHOFORMATE DERIVATIVES

Thesis

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in Chemistry

by

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October-1999

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "**Chemistry of inositols: Neighboring group effects in the reactions of *O*-substituted *myo*-inositol orthoformate derivatives**" submitted by **Mr. PRAVEEN T.** was carried out by him 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.

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MSShash

(Dr. M. S. SHASHIDHAR)
Research guide

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15/10/99

Praveen T

DECLARATION

I here by declare that the thesis entitled "**Chemistry of inositols: Neighboring group effects in the reactions of *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: 15|10|99

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15/10/99

(T. **PRAVEEN**)

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
DEA	N,N-Diisopropylethylamine
DHP	Dihydropyran
Dia-	Diasteriomeric
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	Insoitol 1-phosphate
Ins (1,2,4) P_3	Inositol 1,2,4-triphosphate
Ins (1,2-cyclic) P	Inositol 1,2-cyclicphosphate

Ins (1,2-cyclic,4,5) P_3	Inositol 1,2-cyclic 4,5-triphosphate
Ins (1,3) P_2	Inositol 1,3-bisphosphate
Ins (1,3,4,5) P_4	Inositol 1,3,4,5-tetrakisphosphate
Ins (1,3,4,5,6) P_5	Inositol 1,3,4,5,6-pentakisphosphate
Ins (1,3,5) P_3	Inositol 1,3,5-triphosphate
Ins (1,4,5) P_3	Inositol 1,4,5-triphosphate
Ins (1,5) P_2	Inositol 1,5-bisphosphate
Ins (2) P	Insoitol 2-phosphate
Ins (4) P	Insoitol 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
P	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
TEA	Triethylamine
t-Bu	Tert-butyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
Thp	Tetrahydropyranyl
TMS	Tetramethyl silane
Tr	Trityl
Ts	p-Toluene sulfonyl

CHAPTER 1

Ester protecting groups in inositol chemistry

There has been an upsurge in interest in the chemistry of inositols in the last decade, mainly due to the establishment of the role of D-*myo*-inositol-1,4,5-trisphosphate as a second messenger in cellular signal transduction mechanisms. *Myo*-inositol also plays an important role in anchoring of certain proteins to cell membranes. The progress in understanding of the biological role played by *myo*-inositol derivatives depends on the availability of biologically relevant synthetic inositol derivatives. Key intermediates for the synthesis of biologically important derivatives are the corresponding *O*-protected inositols. Generally the first step during the preparation of a desired protected inositol derivative from *myo*-inositol is its conversion to a ketal or orthoformate. Further steps usually involve selective etherification or esterification of the remaining hydroxyl groups. Esters provide an inexpensive and efficient means of protecting hydroxyl groups and are amongst the oldest protecting groups known. An added advantage of using ester protecting groups is the scope of using enzymatic resolution methods or use of chiral esters to achieve chemical resolution to obtain optically pure products. However, problems associated with the use of ester protecting groups in polyhydroxy systems are (a) inter or intramolecular acyl migrations and (b) their instability towards acids as well as bases. However esters have been successfully used as protecting groups in the synthesis of several important inositol derivatives. This chapter presents an illustrative survey of the existing literature on the use of ester protecting groups in the chemistry of inositols.

CHAPTER 2

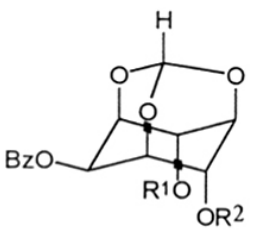
Silver (I) oxide mediated alkylation of (±)-2,4-di-*O*-acyl-*myo*-inositol 1,3,5-orthoformates: Effect of solvent and silver halides

Myo-inositol 1,3,5-orthoformate is an important intermediate for the synthesis of inositol phosphates, phosphatidyl inositols and their glycosylated derivatives. Recently a derivative of this orthoester viz., (±)-2,4-di-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate (**1**) was used as a versatile intermediate for the synthesis of several inositol derivatives. During this study it was observed that the silver (I) oxide mediated *O*-alkylation of the dibenzoate **1** in DMF gave the diether **2** as the major product instead of the expected monoether **3**. We have now carried out the alkylation of 2,4 -di-

Synopsis of the thesis

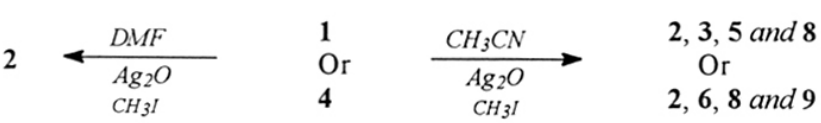
O-acyl derivatives **1** and **4** in order to understand the mechanism of this unusual *O*-alkylation. Silver (I) oxide mediated alkylation of the diesters **1** and **4** in acetonitrile gave different products depending on the alkyl halide used(**Scheme 1**). A systematic investigation of this reaction revealed that transesterification of the diacyl derivatives **1** and **4** to give the corresponding triacyl derivative **5** or **6** along with the diol **7** (which undergoes *O*-alkylation), was a competing reaction. The silver halides generated during *O*-alkylation were also found to augment the transesterification of **1** and **4**. These observations suggested the operation of several parallel reaction pathways resulting in the formation of several products. This work also lead to the discovery of an unusual and extremely facile intermolecular benzoyl transfer in the dibenzoate **1** in solid as well as solution states, which is detailed in the next two chapters.

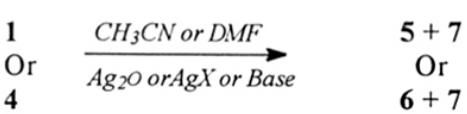
Scheme 1



Bz = C_6H_5CO-

1 R1 = H, R2 = Bz
2 R1 = R2 = CH_3
3 R1 = CH_3, R2 = Bz
4 R1 = H, R2 = Ac
5 R1 = R2 = Bz
6 R1 = R2 = Ac
7 R1 = R2 = OH
8 R1 = CH_3, R2 = OH
9 R1 = CH_3, R2 = Ac

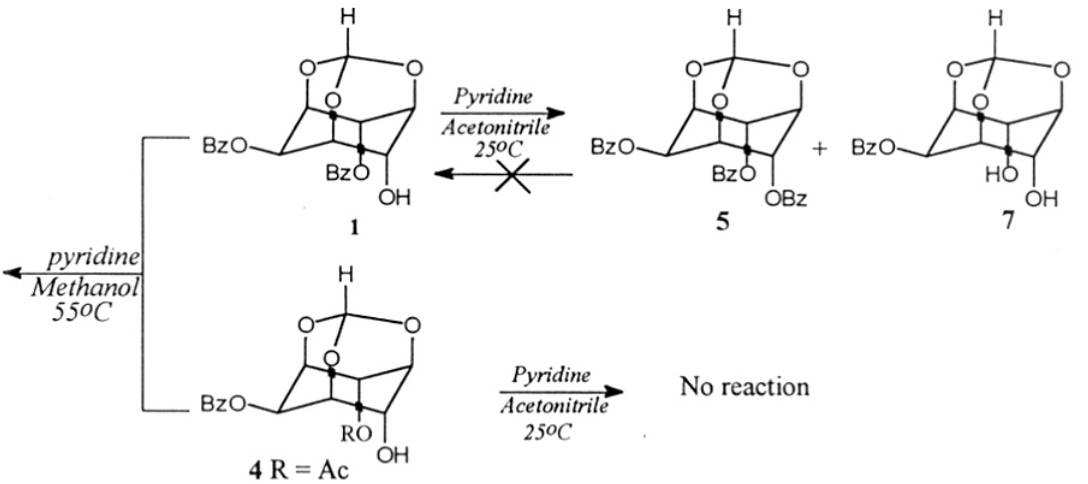




CHAPTER 3

Inter molecular acyl transfer in (±)-2,4-di-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate in the solid state

Crystals of the dibenzoate **1** on heating (140° C) in the presence of solid sodium carbonate underwent transesterification to give the tribenzoate **5** and the diol **7** (**Scheme 2**) in 46% and 49% yields respectively. The same reaction could be



Contrary to expectations, transesterification of the dibenzoate **1** in the presence of pyridine was more facile than that of its analogues, the acetate **4** and the p-nitrobenzoate **10** (**Scheme 3**). However the facility with which the three hydroxy esters underwent base catalyzed methanolysis was as expected viz., reactivity of the p-nitrobenzoate **10** > acetate **4** > dibenzoate **1**. Temperature dependent NMR spectroscopy of the three esters suggested stronger association between the molecules of the dibenzoate **1** as compared to the acetate **4** and the p-nitrobenzoate **10**. A mechanism for transesterification of the dibenzoate **1** involving its self assembly has been proposed taking cue from its crystal structure since it exhibits similar reactivity in the solid and solution states.

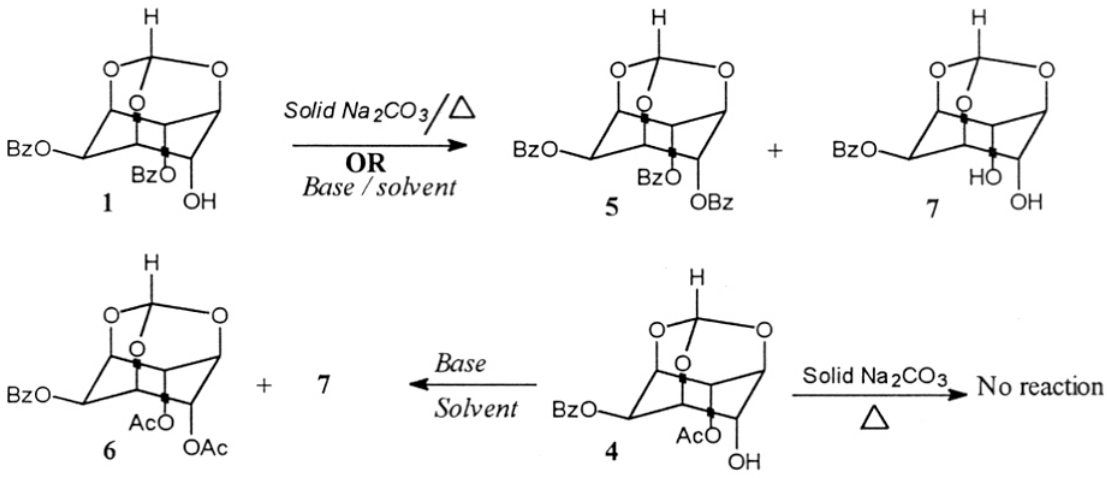
CHAPTER 5

Silver (I) oxide mediated methanolysis of (±) 2,4-di-*O*-benzoyl-6-*O*-sulfonyl-*myo*-inositol 1,3,5- orthoformates : An unusual participation by the sufonyl group

Influence of one functional group on the reactions of another in close proximity is well established in organic chemistry. There are many reports on the effect of hydroxyl, amino and carbonyl groups on the reactions of neighboring carboxylic acids and their derivatives. However reports on the effect of a sulfonyl group on the reactions of esters within the same molecule are scarce. The present chapter presents a systematic study on the effect of a sulfonyl group during the methanolysis of (±)-2,4-di-*O*-benzoyl-6-*O*-sulfonyl-*myo*-inositol 1,3,5- orthoformates. Methanolysis of the

performed by microwave irradiation. The corresponding acetate **4** was unreactive in the solid state under identical conditions. Both the hydroxyesters **1** and **4** underwent base catalyzed transesterification in solution. The facility with which the dibenzoate **1** undergoes transesterification as compared to the acetate **4** in the solid state was explained based on their single crystal X-ray structures. In crystals of the dibenzoate **1**, the screw axis related molecules have the carbonyl and the hydroxyl groups ideally oriented for the reaction; whereas crystals of the acetate **4** lack this geometry and hence are unreactive. A few other diacyl derivatives of *myo*-inositol 1,3,5-orthoformate were also prepared and examined for the solid state reactivity. But most of them were unreactive.

Scheme 2



CHAPTER 4

Intermolecular acyl migration in (±)-2,4-di-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate in solution: Is the reaction controlled by self-assembly?

This chapter presents a systematic investigation of the unusually facile transesterification of the dibenzoate **1** in solution. Transesterification of the dibenzoate **1** was strongly dependent on the nature of the solvent used and was irriversible in the presence of a weak base such as pyridine. Hydrogen bonding solvents retarded the reaction; however, isolable amount of the transesterification product, tribenzoate **5**, could be obtained even in the presence of 10-20 fold excess of methanol in acetonitrile.

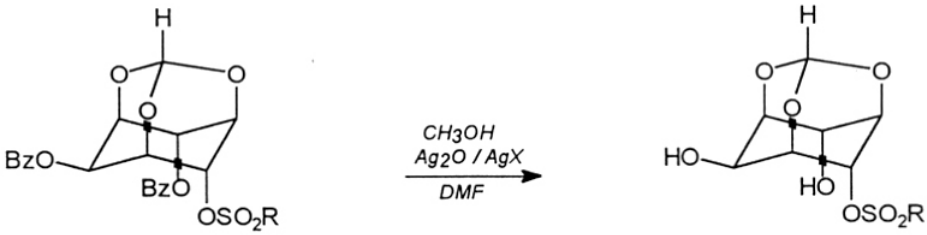
Scheme 3

CHAPTER 1

Ester protecting groups in inositol chemistry

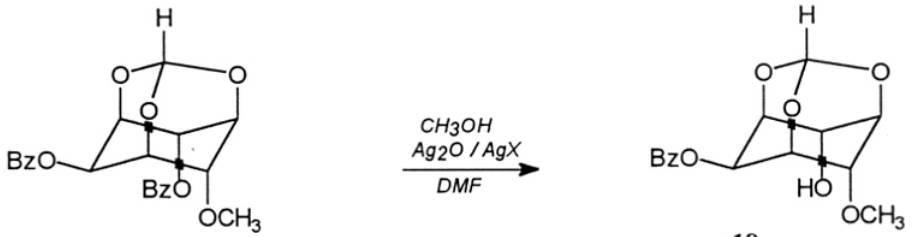
dibenzoates **11**, **12** and **13** (mixture of diastereomers) in the presence of silver (I) oxide / silver halide system gave the corresponding diols **14**, **15** and **16** respectively in excellent yields; whereas, methanolysis of the methyl ether **17** (which lacks a sulfonyl group) resulted in the formation of the corresponding hydroxy ester **18**. These results clearly showed that the sulfonyl group assists in the methanolysis of the equatorial benzoate group. A mechanism involving silver chelates (**19** or **20**) has been proposed for these reactions. Single crystal X-ray structure analysis of the diol **14** has also been presented.

Scheme 4



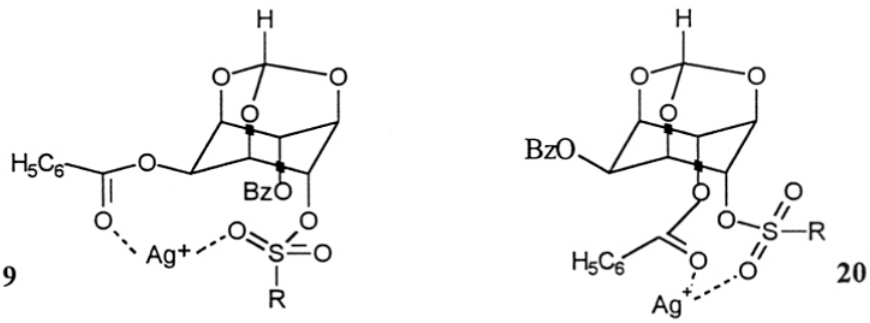
11 R = methyl
12 R = p-tolyl
13 R = camphoryl

14 R = methyl
15 R = p-tolyl
16 R = camphoryl



17

18



19

20

*An unusual transesterification of 2,4-di-*O*-benzoyl-myo-inositol-1,3,5-orthoformate: Is the hydroxyl group unusually reactive?*

T. Praveen, T. Das, U. Samanta, 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 structure of* O*-substituted myo inositols.*

U. Samanta, D. Pal, V.G. Puranik, P. Chakrabarti, **T. Praveen**, T. Das, M. S. Shashidhar.

XVII Congress of International Union of Crystallography, Seattle, Washington, USA 1996.

Base catalyzed transesterification of 2,4-di-O-acyl-myo-inositol-1,3,5-orthoformates: An unusual reversal of reactivity.

T. Praveen, K. A. P. Xavier, K. Pius, M. S. Shashidhar.

National symposium in chemistry, I. I. Sc., Bangalore, January 29-30, 1999.

Dedicated to my family members

List of Publications

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

Publications:

Reactivity controlled by lattice interaction in the 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, P. Chakrabarti, J. Am. Chem. Soc., **1998**, *120*, 3842-3845.

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 intermediates involved.

T. Das, **T. Praveen**. M.S. Shashidhar.
Carbohydr. Res., **1998**, *313*, 55-59.

Crystal structure of 2-O-benzoyl-myo-inositol 1,3,5-orthoformate.
U. Samanta, V.G. Puranik, P. Chakrabarti, P. Thoniyot, M.S. Shashidhar. *Acta Cryst. Sec C.*, **1998**, *54*, 1289-1291.

Inter molecular acyl transfer in (±)-2,4-Di-O-benzoyl-myo-inositol 1,3,5-Orthoformate in Solution:
Is the reaction controlled by molecular association?.
T. Praveen, Mysore S. Shashidhar, Pinak Chakrabarti, K.A.P. Xavier and Kuruvilla Pius. (Communicated)

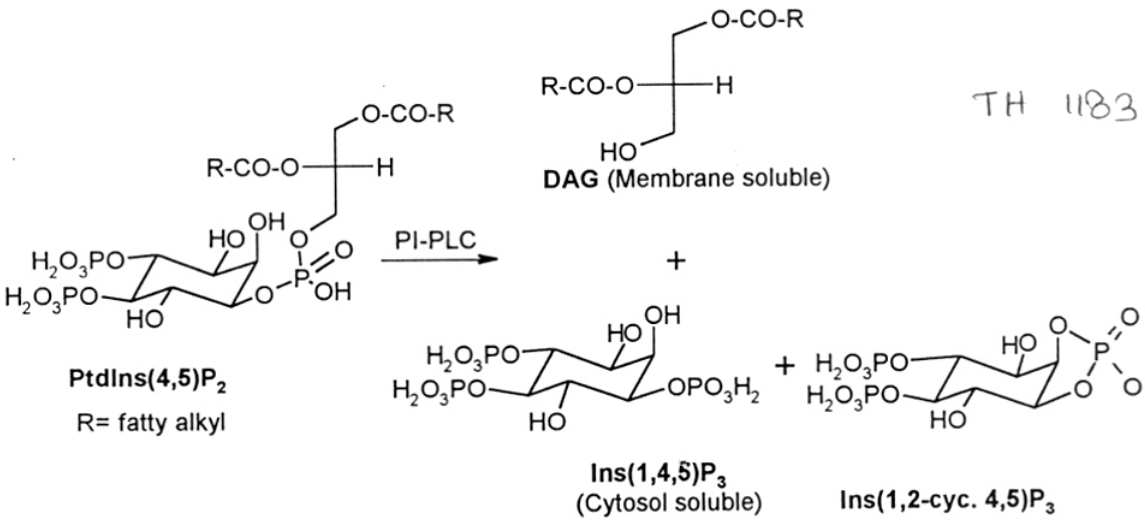
Papers presented in Symposia and Seminars

Electrochemical reduction of myo-inositol derivatives: Cyclic voltammetric behaviour of (dl) 2,4-di-O-benzoyl -6-oxo-myo-inositol 1,3,5- orthoformate and 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.

1.1 Introduction

The last decade witnessed a renaissance in the chemistry and biochemistry of inositols mainly due to the establishment of the role played by phosphorylated *myo*-inositol derivatives in important biological phenomena such as cellular signal transduction[1] and anchoring of certain proteins to cell membranes.[2] The phosphatidylinositol-specific phospholipase C (PI-PLC) mediated hydrolysis of phosphatidylinositol 4,5-bis phosphate [PtdIns(4,5)P_2] to give *myo*-inositol 1,4,5-trisphosphate [Ins(1,4,5)P_3], *myo*-inositol-1,2-cyclic,4,5-trisphosphate [Ins(1-2 cyc.4,5)P_3] and diacyl glycerol (DAG), through the activation of membrane bound receptors by neurotransmitters or hormones (**Scheme 1.1**) is now established as an important second messenger pathway for transmembrane signalling in eukariotic cells.[3]

Scheme 1.1

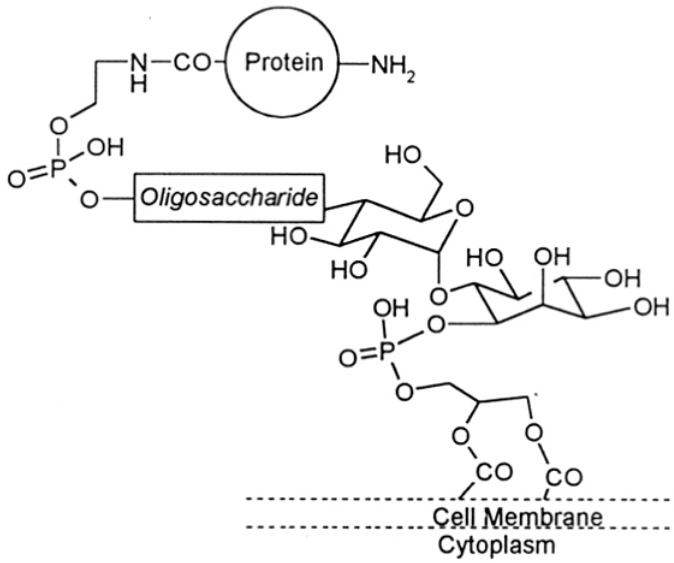


The hydrophilic Ins(1,4,5)P_3 diffuses into the cytosol and mobilizes calcium ions from endoplasmic reticulum, which ultimately leads to a cell response. Ins(1,4,5)P_3 then gets metabolized via the intermediacy of several *myo*-inositol phosphates to give *myo*-inositol, which is then recycled for the synthesis of PtdIns(4,5)P_2, thus completing the *myo*-inositol cycle. Apart from this well established process, there are other important pathways involving Ins (3,4,5) P_3[4,5] and Ins(1,3,4,5)P_4 which regulate influx of calcium ions in stimulated cells. A bewildering array of *myo*-inositol phosphates and their lipid

derivatives[6] have been identified and/or isolated from plant as well as animal cells; however, the biological role played by many of them is not yet clearly understood.

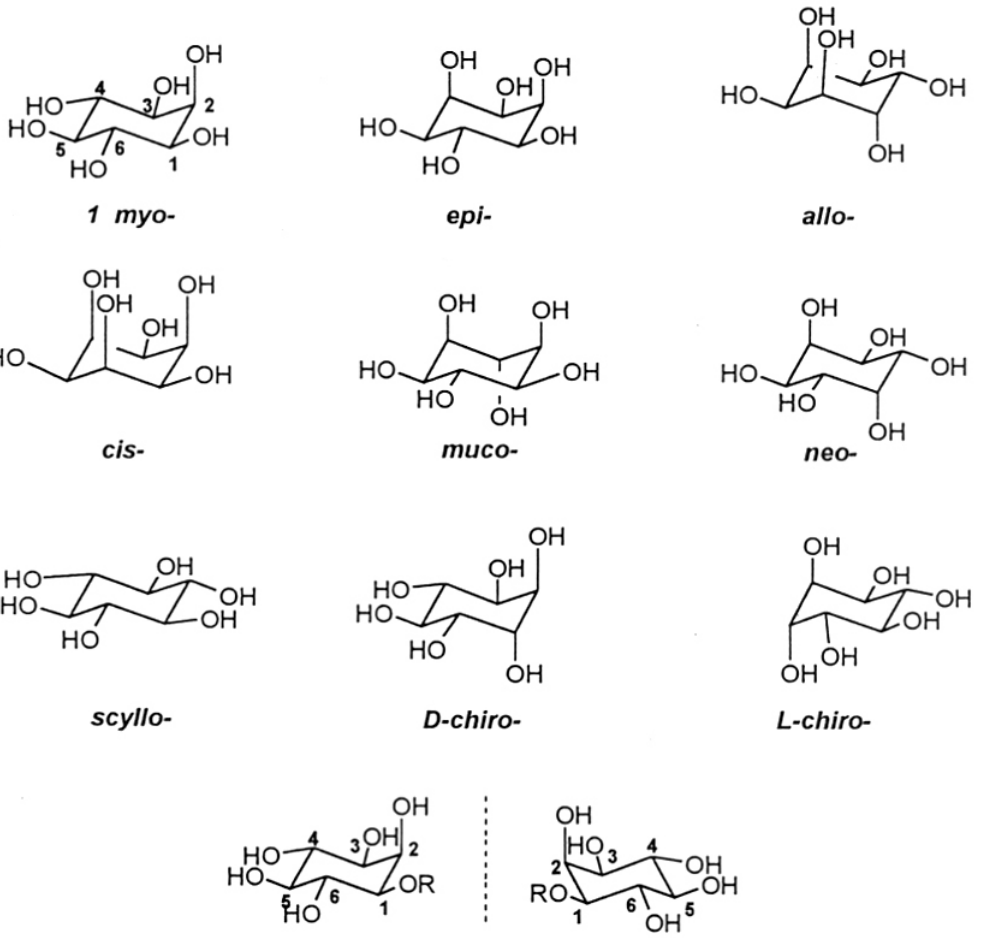
The role of Glycosyl phosphatidyl inositols (GPI) in cells have long been recognized.[7,8] They are involved in anchoring of certain proteins to cell membranes;[9] for example, variant surface glycoprotein of trypanosomes.[8] A typical structure of a GPI anchor is shown in **Scheme 1.2**; the cell surface proteins are linked through an oligosaccharide unit to the 6-position of the *myo*-inositol ring of phosphatidyl inositol.[10] Lipophosphoglycans and glycoinositol phospholipids, are thought to play an important role in parasite virulence.[9]

Scheme 1.2



Inositols are cyclohexane hexols; nine isomers are known including the enantiomers of chiroinositol (**Scheme 1.3**). *Myo*-inositol is a meso isomer with five equatorial hydroxyl groups and an axial hydroxyl group. There is a plane of symmetry passing through C-2 and C-5 atoms. The carbon bearing the axial hydroxyl group is designated as C-2 and the other ring carbons can be numbered from C-1 to C-6 starting from a C-1 atom and proceeding around the ring in clockwise or anticlockwise fashion. According to convention, an anti-clockwise numbering in asymmetrically substituted inositol leads to configurational D-prefix and clockwise numbering gives the substituted inositol an L-prefix.[11] An IUPAC nomenclature allowing all biologically relevant compounds to be denoted as D isomers has also been proposed.[12] Although all

Scheme 1.3



unsymmetrically substituted *myo*-inositol derivatives reported in this thesis are racemic, for clarity and simplicity only one enantiomer is shown in all the schemes.

Many of the phosphorylated derivatives of inositol are available only in small amounts from natural sources. Biologists need larger amounts of these compounds and their analogues to examine and understand various biological phenomena mediated by phosphoinositols. Consequently, many methodologies and techniques have been developed, for the synthesis and isolation of structurally well-defined phosphoinositols and their analogues. The key intermediates for the synthesis of biologically important derivatives of inositols are the corresponding hydroxyl group protected derivatives (having free hydroxyl group(s) at desired positions). Five different strategies have so

far been developed for the synthesis of protected *myo*-inositol derivatives and their analogues (**Scheme 1.4**).

(a) From commercially available *myo*-inositol (**1**)[1,13]

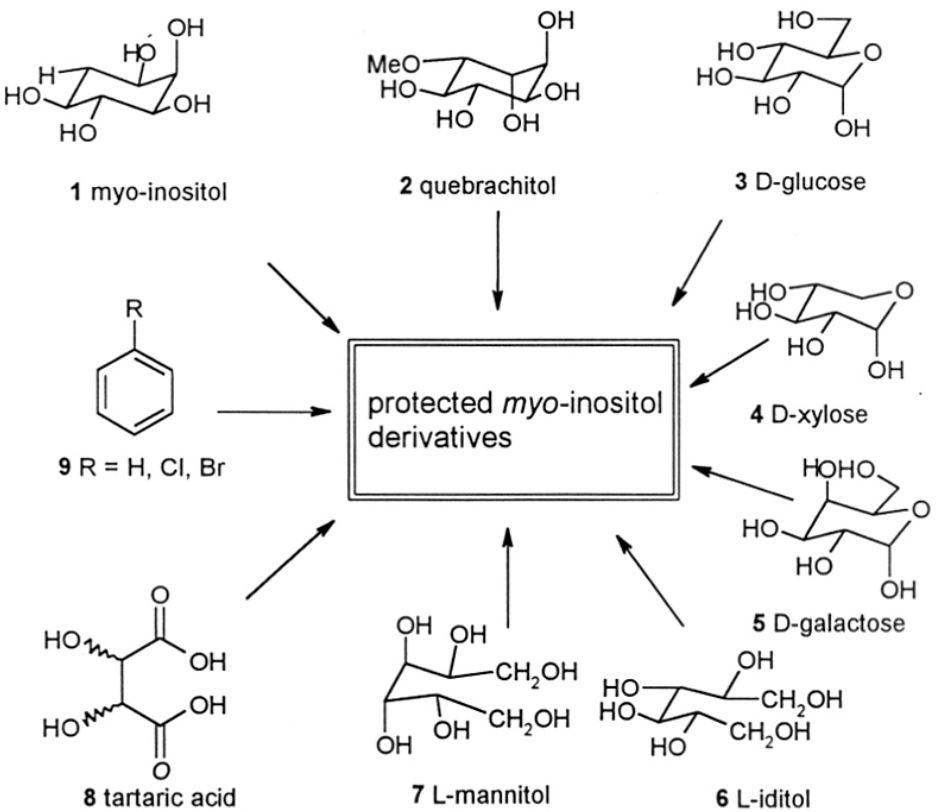
(b) From naturally occurring quebrachitol (**2**)[14-17]

(c) From carbohydrates, *e.g.* glucose (**3**),[18-25] D-xylose (**4**),[26-28] D-galactose (**5**),[29] *D*-mannitol (**6**),[30] and L-iditol (**7**)[31]

(d) From tartaric acid (**8**)[32,33]

(e) From benzene and its derivatives (**9**)[34-37]

Scheme 1.4

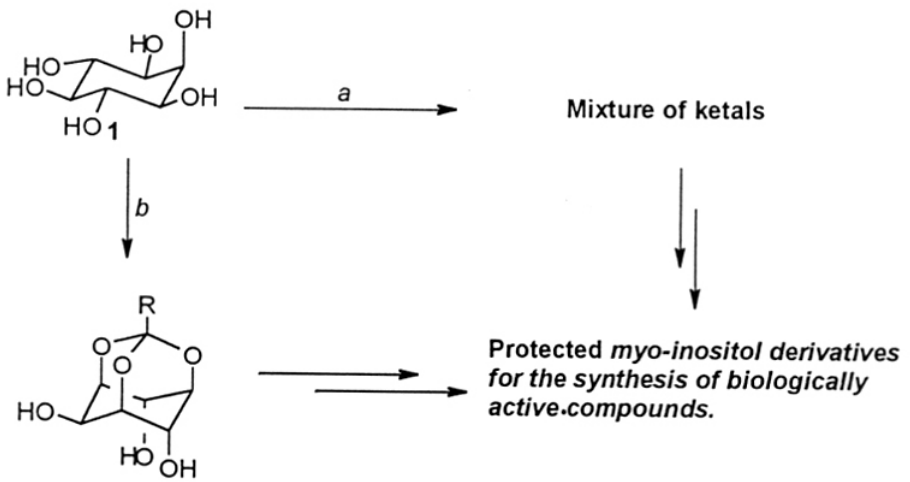


Route (a) necessarily involves several protection and deprotection steps and chemical or enzymatic resolution of intermediates to obtain the required enantiomerically pure protected *myo*-inositol. The next three routes (b, c and d) give access to optically pure intermediates since the starting materials **2-8** are chiral. The

synthesis from benzene or its derivatives (route e) involving its microbial oxidation by *pseudomonas putida* to cyclohexadiene diol has the advantage in that it can be used to generate isomeric inositols or their derivatives. Route (a) is widely used because of the 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.

Generally, the synthesis of a biologically active derivatives of *myo*-inositol (from commercially available *myo*-inositol **1**) starts with the protection of its hydroxyl groups as ketals [cyclohexylidene[38] isopropylidene[39] cyclopentylidene[40]] or an orthoester derivative (orthoformate,[41] orthoacetate[42]) (**Scheme 1.5**). The orthoformate derivative

Scheme 1.5



10 R = H
11 R = CH_3

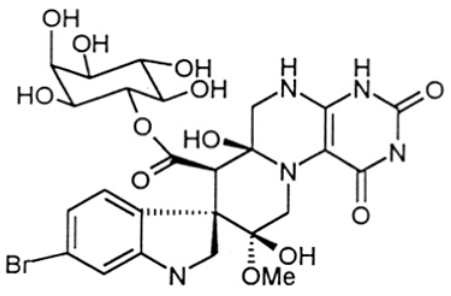
a) R^1-CO-R^2 or R^1-C$(OR^3)_2$-R^2, H^+
b) RC$(OR^3)_3$, H^+

10 obtained by the treatment of *myo*-inositol (**1**) with triethylorthoformate in the presence of an acid catalyst provides an interesting protected inositol in which 1,3 and 5 hydroxyl groups are protected simultaneously. In addition, the normal axial/equatorial relationship of the hydroxyl groups is reversed. Further manipulation of the protected *myo*-inositol involving protection-deprotection and/or functionalization of the hydroxyl groups lead to the desired inositol derivative.

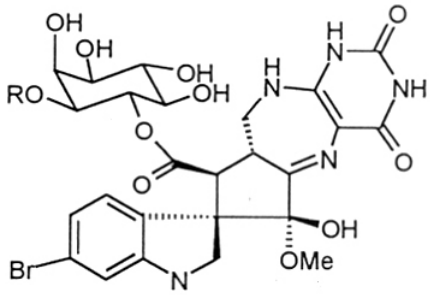
Esters are amongst the oldest class of protecting groups used in organic synthesis. They are easily prepared by standard methods using carboxylic acids or their activated

derivatives. The relative ease of hydrolysis (for the regeneration of parent alcohol) varies and can be tuned by taking advantage of electronic and steric factors. Ester groups have been extensively used in inositol chemistry for the selective protection, ease of isolation and chemical or enzymatic resolution of the inositol derivatives. Inositol esters have also been used as membrane permeant analogues for biological studies, since esters can be cleaved by intracellular esterases to generate the parent (often hydrophilic) inositol derivative inside the living cell. Also some *myo*-inositol esters such as surugatoxin (**12**), prosurugatoxin (**13**) and neosurugatoxin (**14**) are marine natural products[43-46] (**Scheme 1.6**). Since this thesis centers around the chemistry of ester derivatives of *myo*-inositol, rest of this chapter is devoted to an illustrative review on the use of ester groups during the synthesis of biologically active derivatives (and their analogues) of *myo*-inositol.

Scheme 1.6

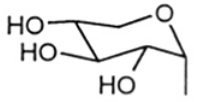


12 Surugatoxin 1



13 R = H Prosurugatoxin

14 R =



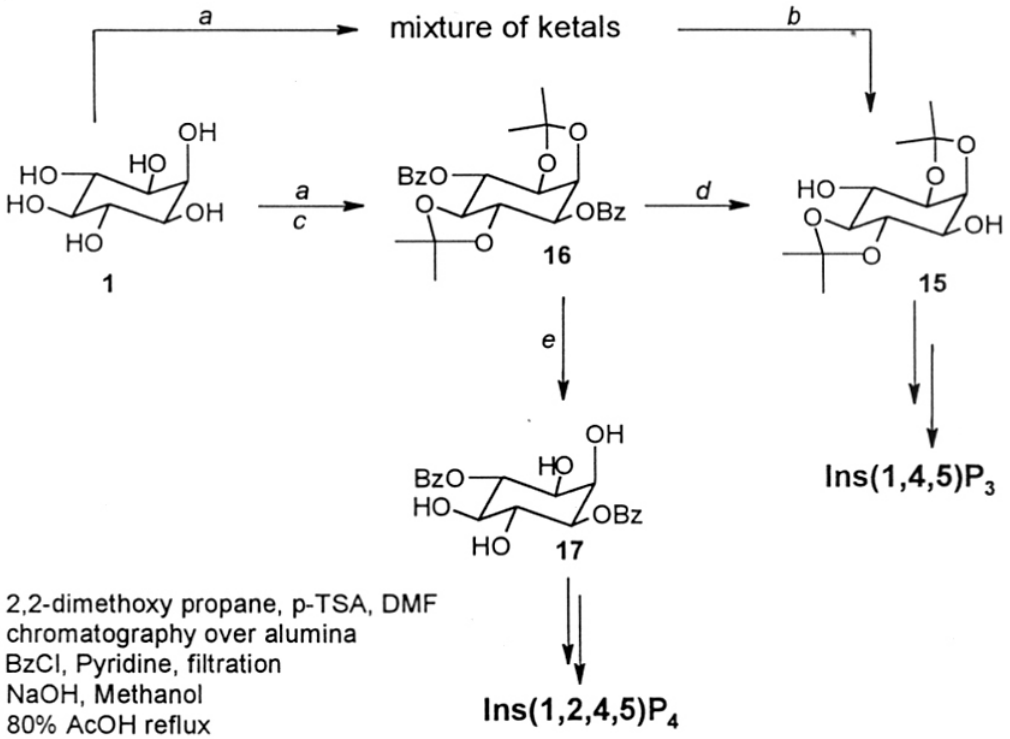
Neosurugatoxin

1.2 Use of esters to facilitate the isolation of *myo*-inositol derivatives

(±)-1,2:4,5-di-*O*-isopropylidine-*myo*-inositol (**15, Scheme 1.7**) has been used as an intermediate in the synthesis of various *myo*-inositol phosphates.[1] Initially this compound was obtained by ketalisation of *myo*-inositol with 2,2-dimethoxy propane followed by column chromatography in 21 % yield. Benzoylation of the mixture of isopropylidene derivatives followed by filtration afforded the crystalline dibenzoate **16**, due to its low solubility in DMF. Saponification of the dibenzoate **16** with methanolic

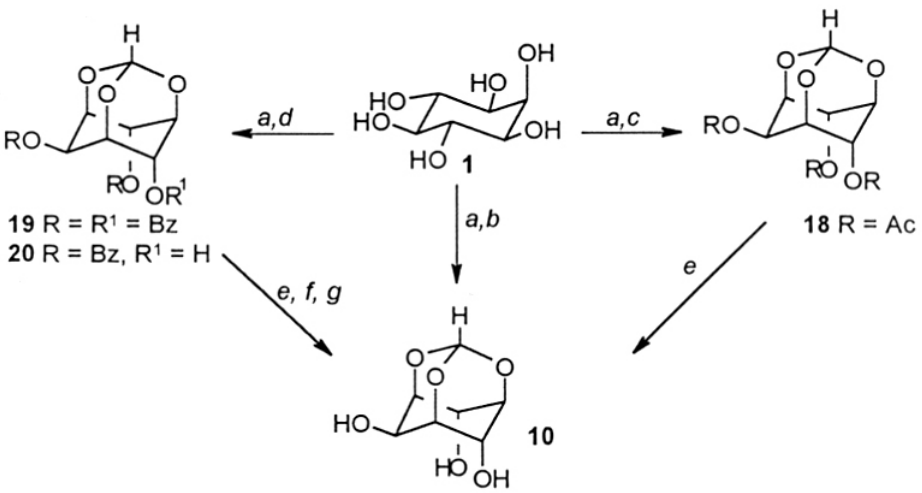
sodium hydroxide yielded the diol **15** in 30 % over all yield starting from *myo*-inositol, circumventing the tedious column chromatography.[39] Potter[47] *et al.* have used this intermediate for the synthesis of Ins(1,2,4,5)P_4 (**Scheme 1.7**).[16] Synthesis of this racemic tetraphosphate provides an example where ester groups are retained to avoid phosphate migration.

Scheme 1.7



Kishi[41] *et al.* in their first report, isolated *myo*-inositol 1,3,5-orthoformate **10** by column chromatography in 76 % yield. Andersch and Schneider[48] avoided tedious isolation procedure by acetylation of the triol **10**, followed by crystallization, to isolate the triacetate **18**. The triacetate **18** was hydrolyzed to obtain the crude triol **10** which on lyophilization gave the pure product (**10**) in 85% yield (**Scheme 1.8**). In our group, the orthoformate **10** was isolated as a mixture of dibenzoate **19** and tribenzoate **20** by precipitation with methanol. Aminolysis of the precipitate with tertiary butyl amine in methanol gave the triol **10**, in pure form in an over all yield of 90%.

Scheme 1.8

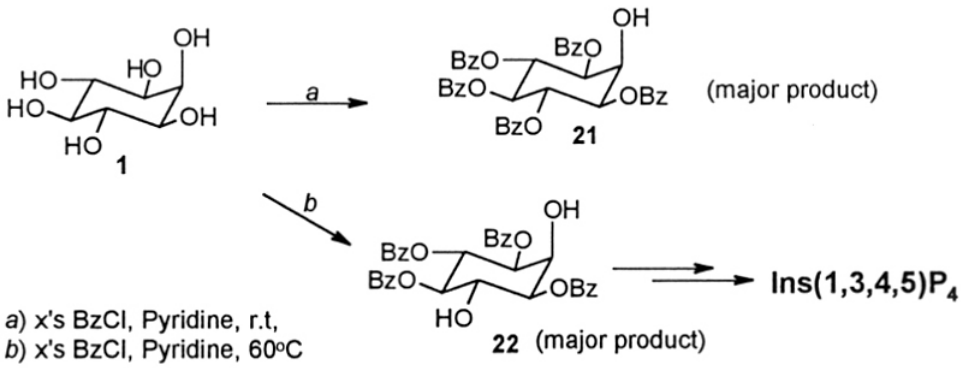


a) $CH(OEt)_3$, p-TSA, DMF *b*) Column chromatography over alumina
c) Ac_2O, Pyridine *d*) BzCl, Pyridine *e*) NaOH, MeOH,lyophililsation, Crystallization *f*) t-Butyl amine, MeOH g) Precipitation and washing with ether.

1.3 Regioselective esterification of *myo*-inositol derivatives:

Direct acylation of *myo*-inositol using excess benzoyl chloride in pyridine showed a moderate selectivity towards 1,3,4 and 5 positions depending on the temperature at which the reaction was carried out.[49] Reaction at ambient temperature yielded Ins(1,3,4,5,6)Bz_5 (**21**, **Scheme 1.9**) as the major product (48%); while above 60°C Ins(1,3,4,5)Bz_4 (**22**) was the major product (34%). The tetra benzoate **22** was converted to the racemic Ins(1,3,4,5)P_4. The racemeic Ins(1,3,4,5)P_4 has been resolved using chiral column chromatography.[49]

Scheme 1.9

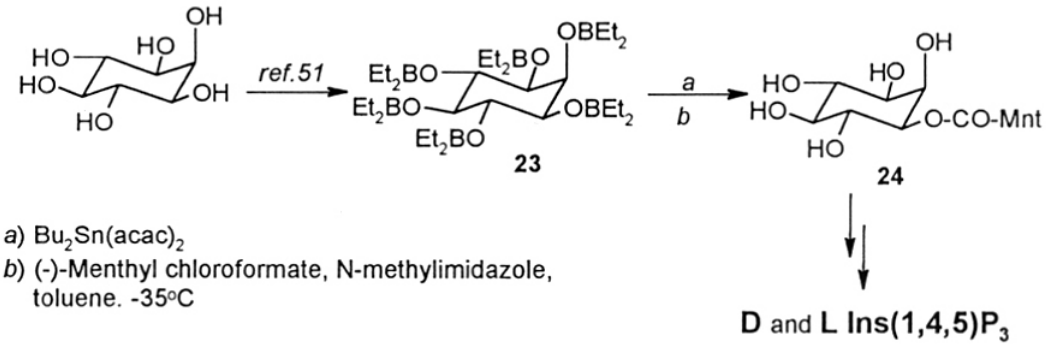


a) x's BzCl, Pyridine, r.t,
b) x's BzCl, Pyridine, 60°C

Regioselective 1-*O*-acylation of *myo*-inositol (**Scheme 1.10**) and simultaneous optical resolution has been achieved by perborylation, transmetallation using di-n-

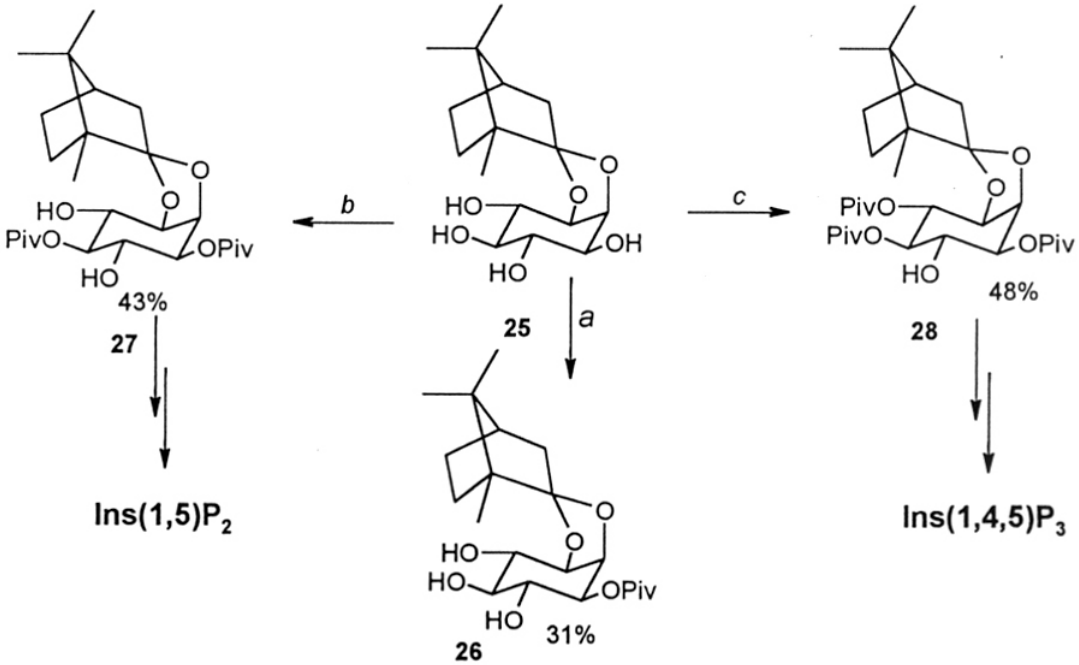
butyltin-bis-acetyl acetonate followed acylation with (-)-menthylchloroformate.[50] Diastereomerically pure 1-*O*-(-)-menthoxycarbonyl-*myo*-inositol **24** obtained was used for the synthesis of D and L Ins(1,4,5)P_3.

Scheme 1.10



Reaction of 2,3-*O*-(D-1,7,7-trimethyl[2.2.1]bicyclohept-2-ylidene)-*myo*-inositol (**25**, **Scheme 1.11**) with 1, 2 or 3 equivalents of pivaloyl chloride in pyridine resulted in *O*-acylation predominantly at 1-, 1,5- and 1,4,5- positions respectively to give **26**, **27** or **28**. The di and tripivaloyl derivatives (**27-28**) were converted to D-Ins(1,5)P_2 and D-Ins(1,4,5)P_3 respectively.[52]

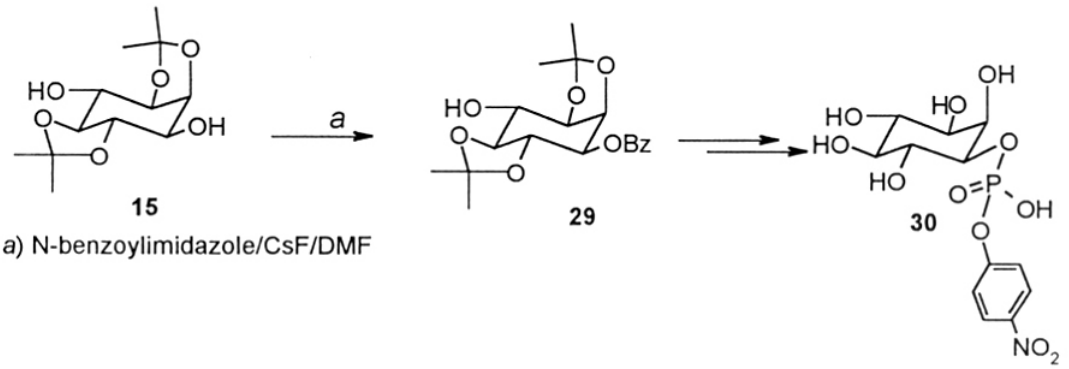
Scheme 1.11



a) 1 eq. PivCl/ Pyridine b) 2 eq. PivCl/Pyridine *c*) x'sPivCl/Pyridine

Racemic 1,2:4,5-di-*O*-isopropylidene-*myo*-inositol (**15**) has been selectively acylated at the *O*-3 position.[53] Best results were obtained by using N-benzoyl imidazole perhaps due to the low reactivity of benzoyl imidazole (which results in high selectivity). The 3-*O*-benzoyl derivative **29** was used for the synthesis of the *p*-nitrophenyl phosphate derivative **30** (**Scheme 1.12**).

Scheme 1.12



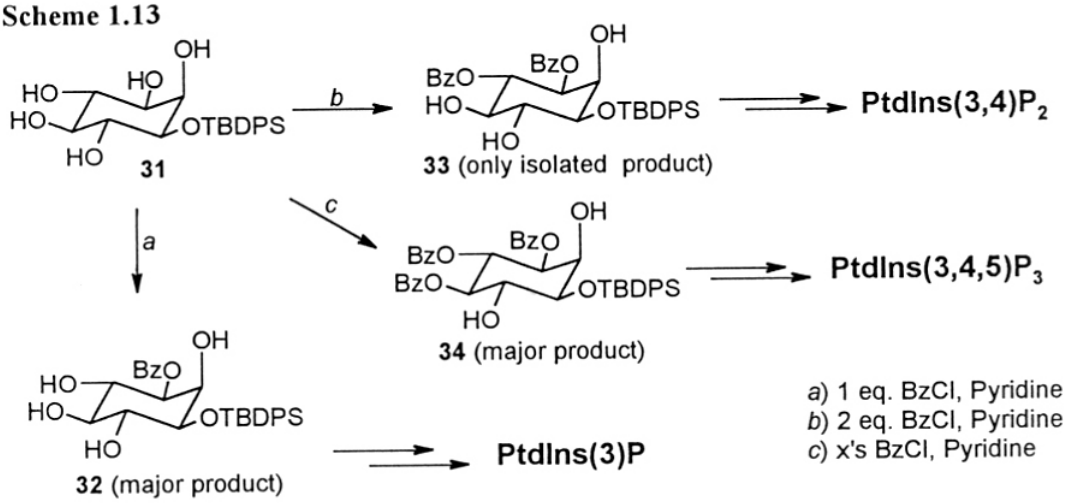
15 **29** **30**

a) N-benzoylimidazole/CsF/DMF

Two reasons were suggested for the observed selectivities at OH-3 group. (a) Kinetic acidity of the OH-3 group may be enhanced through its intramolecular hydrogen bonding with the cis-vicinal oxygen at C-2. (b) Nucleophilicity of the alkoxide may be enhanced due to its interaction with the cis vicinal oxygen in a manner similar to the through space α-effect.[54] Recently, higher reactivities of 3(1) position [rather than 6(4) position] of 1,2:4,5-di-*O*-isopropylidene-*myo*-inositol (**15**) has been evaluated using semiempirical[55] and quantum mechanical calculations.[56]

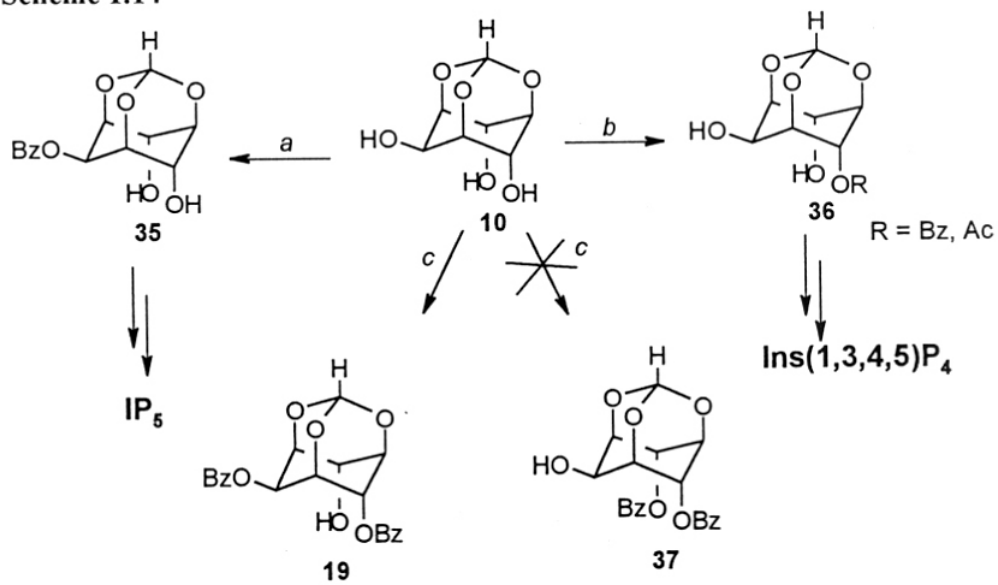
1-*O*-t-Butyldiisopropylsilyl-*myo*-inositol (**31**), on benzoylation with 1 or 3 equivalents of benzoyl chloride gave predominantly 3-*O*-, 3,4-di-*O*- or 3,4,5-tri-*O*-benzoylated products (**32-34**, **Scheme 1.13**) respectively.[57] The mono, di and tri benzoates **32-34** were converted to the racemic PtdIns(3)P, PtdIns(3,4)P_2 and PtdIns(3,4,5)P_3. Regioselectivity observed here were attributed to the higher reactivity of the OH-3 group along with the steric effect of the silyl and the benzoate groups.

Scheme 1.13



Conditions for the regioselective acylation of axial and equatorial hydroxyl groups in *myo*-inositol orthoformate **10**, has been investigated by various groups. The selectivity in the case of the triol **10** is better as compared to the other examples discussed above. For instance, acylation of the triol **10** with benzoyl chloride/triethyl amine or acetyl imidazole/triethyl amine yields the axial ester **36** exclusively[58,59] whereas the use of benzoyl chloride/pyridine results in the predominant benzoylation of the equatorial hydroxyl group to obtain **35** (**Scheme 1.14**).[60-63] Acetylation of the triol in the presence of lipases is reported to show selectivity towards axial or equatorial hydroxyl group depending on the enzyme used.[13]

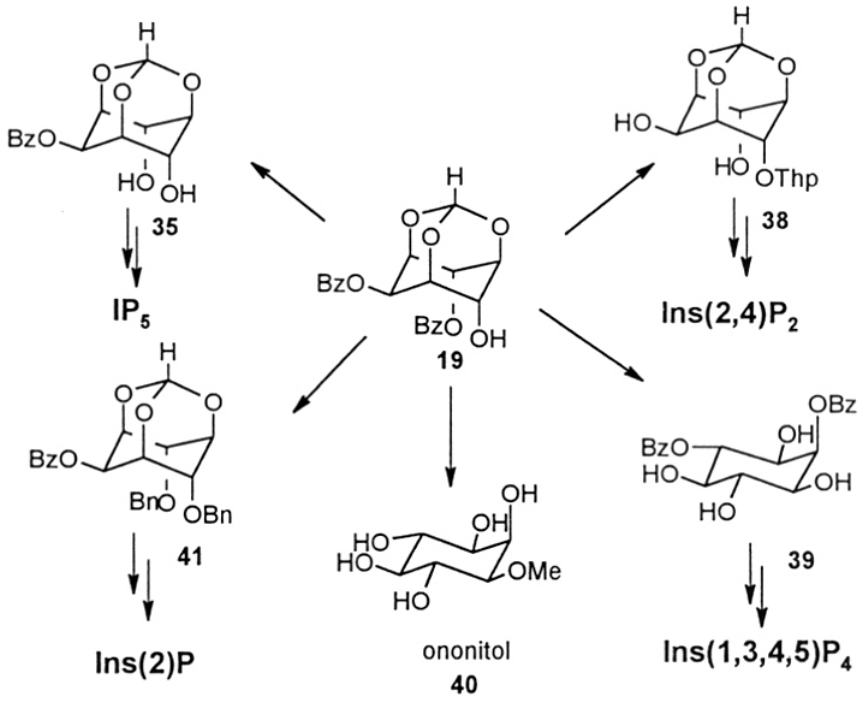
Scheme 1.14



Benzoylation of the orthoformate **10** in the presence of two equivalents of benzoyl chloride/pyridine yielded the unsymmetrical 2,4-dibenzoate **19** as the major product.[63] Formation of the symmetrical diaxial dibenzoate **37** was not observed. All the partially acylated derivatives of *myo*-inositol 1,3,5-orthoformate have been used for the synthesis of several *myo*-inositol phosphates.

The unsymmetrical dibenzoate **19** was found to be a versatile intermediate for the synthesis of various inositol derivatives including the naturally occurring ononitol **40**, **(Scheme 1.15)**.[64]

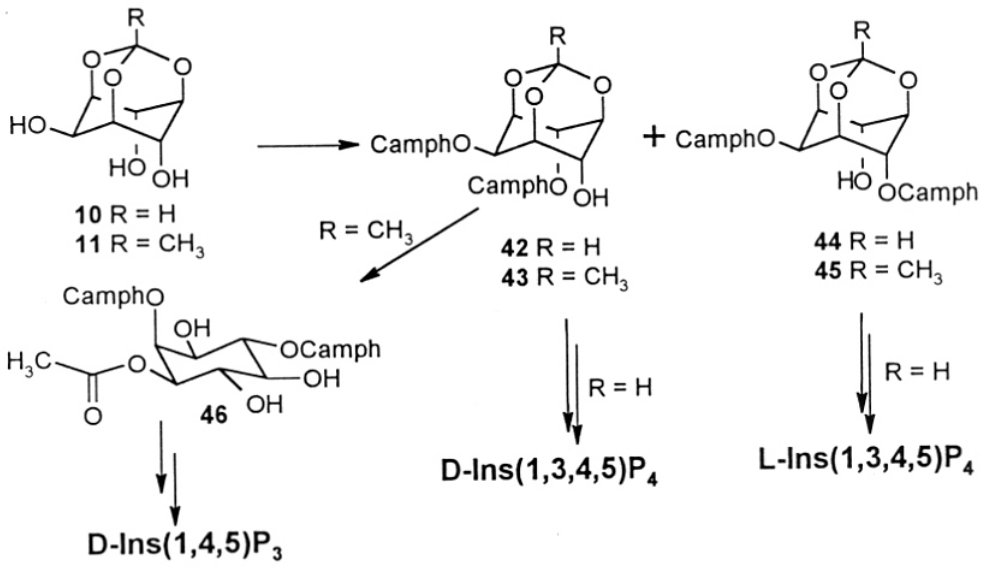
Scheme 1.15



Potter *et. al.* regioselectively acylated the triol **10** at 2 and 4 positions using (1S)-camphanic acid chloride and obtained diastereomeric diesters **42** and **44 (Scheme 1.16)**. The diesters **42** and **44** were converted to D- and L-Ins(1,3,4,5)P_4.[65] The same group synthesized D-Ins(1,4,5)P3 by regioselective diacylation and simultaneous optical resolution via chiral camphanate ester of *myo*-inositol orthoacetate **11**[42] **(Scheme 1.16)**. This synthesis involved conversion of the orthoacetate **11** into an acetate protecting group to obtain the intermediate **46**.

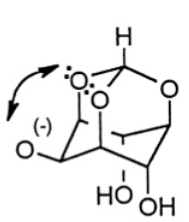
The regioselectivity observed for the acylation of the triols **10** and **11** has been attributed to the following factors: (a) The presence of intramolecular hydrogen

Scheme 1.16

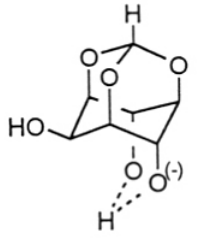


bonding between the two axial hydroxyl groups increases the acidity of one of them and stabilizes the anion formed in the presence of strong bases. This leads to the predominant 4-*O*-acylation of the axial hydroxyl group. Another reason could be the lesser probability of the formation of equatorial anion, due to electron pair repulsion with the lone pair of electron on the 1- and 3- oxygens (**Scheme 1.17**), (b) 1,3-diaxial steric interactions, especially during acylation with bulky reagents (*e.g.* pyridine/benzoylchloride where the acylating agent is the benzoyl pyridinium ion) precludes acylation at the axial positions and predominantly yields the 2-*O*-acylated derivatives. The observed selectivity in the presence of lipases cannot be rationalized with the existing data in the literature, since not much is known about the interaction between the concerned lipase and the substrate.

Scheme 1.17



Destabilization of the equatorial anion by electron pair repulsion

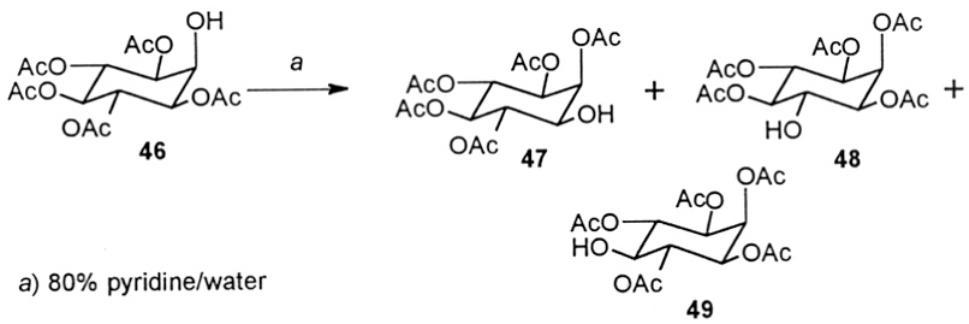


Stabilization of axial anion by hydrogen bonding

1.4 Acyl migration

One problem associated with the use of esters as protecting groups in poly functional systems, is their tendency to migrate (intermolecular or intramolecular) to other hydroxyl groups leading to loss of selectivity/specificity, during acylation or subsequent manipulations. Many instances of acyl migration have been reported in carbohydrate chemistry.[66] The review on the chemistry of *myo*-inositol by Shvets[67] states that acyl migration is almost equally probable in trans- and cis- directions, as exemplified by the acetyl migration during the silver (I) oxide mediated methylation of 1,3,4,5,6-penta-*O*-acetyl-*myo*-inositol (**46**)[68] to give a mixture of products. The same group showed that basic conditions as mild as aqueous pyridine in water was sufficient to affect both cis and trans migration in partially acetylated *myo*-inostiols(**47-49**)[69] (**Scheme 1.18**). Acetyl migration could however, be minimized by storing the

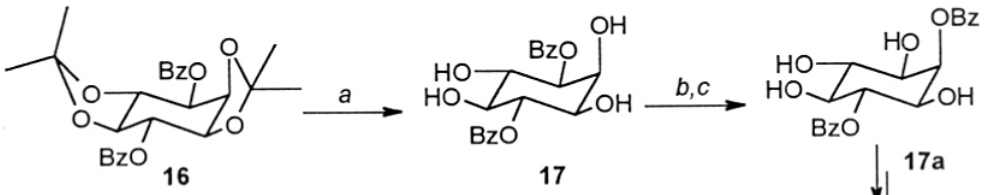
Scheme 1.18



acetylated derivatives in the presence of traces of acetic acid. Although acyl migration in polyhydroxy molecules is considered a nuisance by majority of chemists, reports on the exploitation of acyl migration as a key step in the synthesis of *myo*-inositol phosphates have appeared recently.

Meek *et al.*[70] subjected Ins(1,4)Bz_2 **17** (**Scheme 1.19**) to basic conditions under which it predominantly rearranged to Ins(2,4)Bz_2 **17a**. The dibenzoate was phosphorylated to obtain Ins(1,3,4,5)P_4. This constituted the first report of exploiting benzoate migration for the synthesis of *myo*-inositol phosphates.

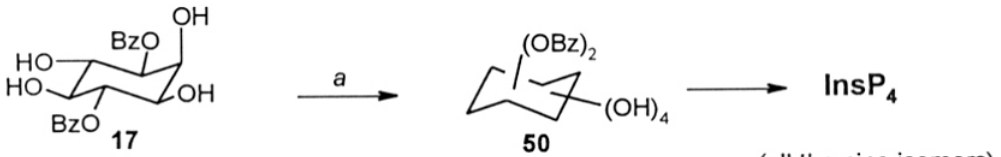
Scheme 1.19



a) AcOH, MeOH
b) 60% pyridine, water, 100°C
c) Crystallization

Chung and co-workers studied acyl migration in the dibenzoate **17**[71-73] and its 1,2-*O*-isopropylidine derivative and standardized conditions for the separation of all possible nine isomeric *myo*-inositol dibenzoates (**Scheme 1.20**). They also prepared isomeric $InsP_1$,[74] $InsP_2$,[75] $InsP_3$,[76] and $InsP_5$,[77] starting from the corresponding pentabenzoates, tetrabenzoates, tribenzoates and monobenzoates generated via acyl migration and separation of isomeric benzoates.

Scheme 1.20



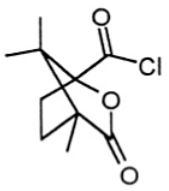
a) 60% pyridine, water, 100°C (all the nine isomers) (all the nine isomers)

1.5 Resolution of *myo*-inositol derivatives as esters.

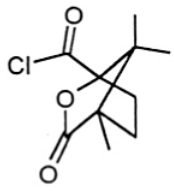
Most of the biologically active derivatives of *myo*-inositol occurring in nature are chiral and hence their synthesis (or synthesis of their analogues) in the laboratory requires resolution or desymmetrization of a protected *myo*-inositol derivative, since *myo*-inositol itself has the meso configuration. Both chemical and enzymatic methods have been developed for the preparation of chiral inositol derivatives.

1.5a Chemical resolution. Several optically active carboxylic acids or their derivatives have been used for the resolution of protected *myo*-inositol derivatives (**Scheme 1.21**). Optical resolution as camphanate esters seems to be the most widely

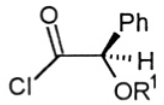
Scheme 1.21



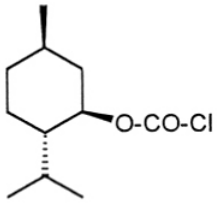
51 1S-(-)-camphanoyl chloride



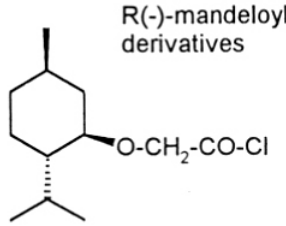
52 1R-(+)-camphanyl chloride



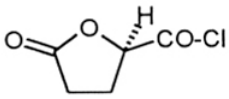
53 $R^1 = CH_3$
54 R^1 = TBDMS
R(-)-mandeloyl chloride derivatives



55 (-)-menthyl chloroformate



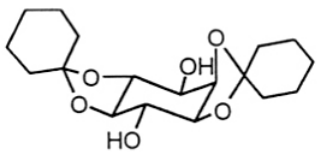
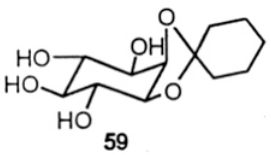
56 (-)-menthoxy acetyl chloride

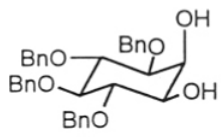


57 R-(-)-5-oxo-2-tetrahydrofuran carboxylic acid chloride

used method. In most of the cases the diastereomeric inositol esters were separable by chromatography or crystallization. Some examples of the resolution of *myo*-inositol derivatives (as corresponding esters) are tabulated in **Table 1.1.**

Table 1.1

myo-inositol derivative	*ester/reagent*	*final product prepared*	*ref.*
 **58**	a) 3,6-di-*O*-camphanate/**51**	D and L Ins(1,4,5)P_3 D and L Ins(1,4)P_2	78
	b) 3-*O*-menthyloxyacetate/**56**	D-Ins(1,4,5)P_3 D and L Ins(1,4,5)P_3	79
 **59**	3-*O*-mandalate/**54**	D and L Ins(1,4,5)P_3	80

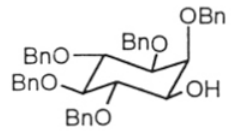


60

3-*O*-camphanate/ **51**and **56**

D and L Ins(3,4,5,6)P_4 and membrane permeant analogues

81

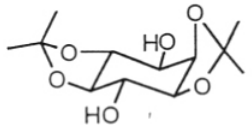


61

1-*O*-camphanate/**51**

D and L Ins(1)P

82

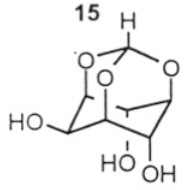


15

3,6-di-O-camphanate/**51**

D and L Ins(1,2,4,5)P_4

83

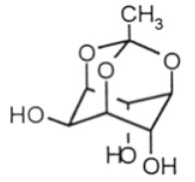


10

2,4-di-O-camphanate/**51**

D and L Ins(1,3,4,5)P_4

65

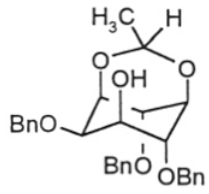


11

2,4-di-O-camphanate/**51**

D and L Ins(1,4,5)P_3

42

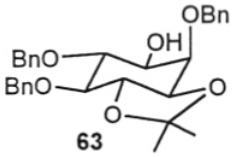


62

R-(-)-oxotetrahydrofuran carboxylate/**57**

L-PtdIns(3,5)P_2

84

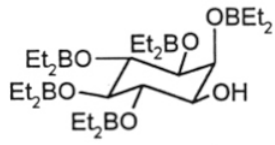


63

1-(S)-(-)-camphanate/**51**

D and L [^{3}H]-Ins(1,3,4)P_3

85



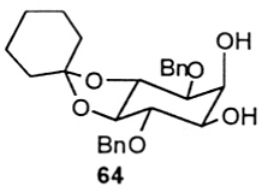
23

1-(*O*)-(-)-menthyloxy carbonate/**55**

D and L Ins(1,4,5)P_3

49

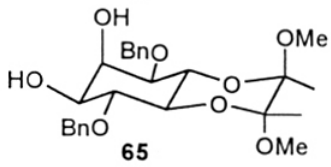
TH 1183



64

1-(*O*)-(-)-menthyloxy acetyate/**56**

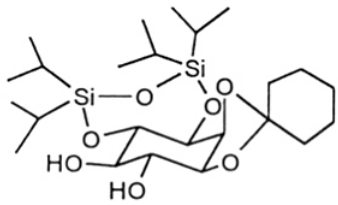
D and L Ins(1,2- cyclic,4,5)P_3 [86]
Ins(1,4,5)P_3, Ins(2,4,5)P_3



65

1-(*O*)-acetyl mandalate/**53**

Bicyclic anaogue of D and L Ins(1,4,5)P_3 [87]



66

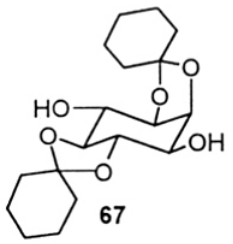
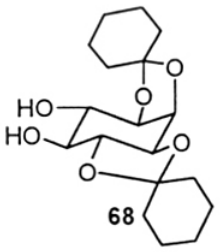
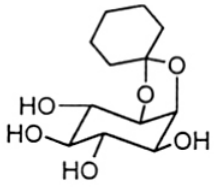
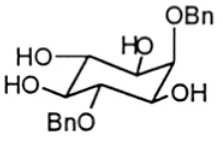
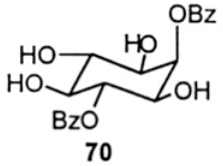
1-(*O*)-acetyl mandalate/**53**

D-PI Ins(3,4,5)P_3 [88]

1.5b Enzymatic methods.

Enzymatic methods of optical resolution of alcohols, usually involves enantioselective esterification/hydrolysis of a meso compound or the selective hydrolysis or esterifiction of one of the enantiomers in a racemic mixture, by an enzyme. The former method is more advantageous than the latter as all of the starting meso derivatives can be converted into one enantiomer. The reactions involving enzymes are generally conducted in aqueous media because of the prevalent notion that an aqueous environment is optimal for maintaining the active conformation of the enzyme for substrate binding and catalysis. Excellent reviews are available on the application of nonaqueous biocatalytic methods in the resolution of organic compounds in general and in the chemistry of inositol derivatives.[89,13] Enzyme catalyzed selective hydrolysis in aqueous media was used to resolve some *myo*-inositol derivatives.[90-92] However, many of the synthetically useful inositol derivatives are insoluble in water and hence the application of nonaqueous solvents like diethyl ether, acetonitrile, dioxane, ethyl acetate, benzene, THF, acetone etc. has become common for the enzymatic hydrolysis or esterification of inositol derivatives. **Table 1.2** lists some *myo*-inositol derivatives prepared using lipases.

Table 1.2

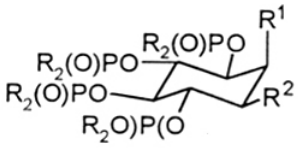
myo-inositol derivative	*method/enzyme*	*final product prepared*	*ref.*
 **67**	a) enantio and regioselective acetylation at *O*-3 / Amanolipase P from *pseudomonas Sp.*	D and L Ins(1,4,5)P_3	13
	b) enantio and regioselective acetylation at *O*-4 / Amanolipase AY from *Candida cyndidracea*		13
	c) enantioselective hydrolysis of 6-*O*-butyryl ester / PPL		13
 **68**	regio and enantioselective acetylation at *O-5 / Lipase AY*	D and L Ins(1,4,6)P_3	13
 **59**	a) regio and enantioselective acetylation at *O*-1 / Amanolipase P and Lipase CES from *Pseudomonas sp.*	Various Inositol phosphates	93-95
	b) regio and enantioselective acetylation at *O*-1 / Porcine pancreatic Lipase		96
 **69**	regio and enantioselective acetylation at *O*-1 /Lipase PS from *pseudomonas Sp.*		97
 **70**	transesterification using vinylbutyrate at *O*-1 / Lipo proteinlipase from *pseudomonas Sp.*		89

Attempts to desymmetrize *myo*-inositol 1,3,5-orthoformate by enzymatic esterification or hydrolysis have not been successful. In many cases high regiospecificity was observed but the product was found to be racemic.[13]

1.6 Use of esters to facilitate membrane permeability

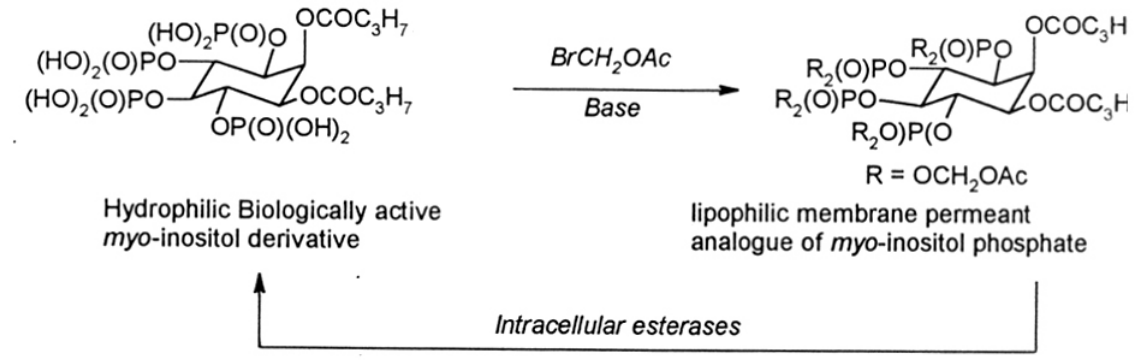
Esters are frequently used to mask the negative charge[99,100] of organic anions to increase their ability to cross biological membranes. Such ester derivatives have to be stable outside the cells, diffuse across the plasma membrane and undergo intracellular enzymatic hydrolysis inside the cell, generating the parent molecule. Most widely used esters are acetoxymethyl esters, which can be easily prepared using acetoxymethylbromide in the presence of a base. Schultz *et. al.* synthesized membrane-permeant analogues of various inositol phosphates for the biological evaluation.[101-104] Few of them are represented in **Scheme 1.22**. It was demonstrated that the octakis(acetoxymethyl)ester of DL-1,2-di-*O*-butyryl *myo*-inositol (3,4,5,6) tetrakis phosphate (**76**) was able to penetrate plasma membrane of T_{84} cells and result in

Scheme 1.22



R = OCH_2OAc

70 R^1 = OH, R^2 = $OCOC_3H_7$
71 R^1 = $OCOC_3H_7$, R^2 = OH
72 R^1 = H, R^2 = $OCOC_3H_7$
73 R^1 = $OCOC_3H_7$, R^2 = H
74 R^1 = H, R^2 = $OCOC_3H_7$
75 R^1 = $OCOC_3H_7$, R^2 = H
76 R^1 = $OCOC_3H_7$, R^2 = $OCOC_3H_7$
77 R^1 = CH_3 , R^2 = $OCOC_3H_7$
78 R^1 = $OCOC_3H_7$, R^2 = CH_3
79 R^1 = CH_3 , R^2 = CH_3
80 R^1 = Cl , R^2 = Cl



elevation of intracellular Ins(3,4,5,6)P_4. Also it was shown that the use of membrane permeant bioactivable derivative **76** was capable of uncoupling Cl^- secretion from the Ca^{2+} signal. Hence Ins(3,4,5,6)P_4 was considered to have intracellular messenger function. Biological activity of most of the derivatives reported is yet to be evaluated.

1.7 Conclusions

A survey of the existing literature shows that ester protecting groups have been efficiently used in inositol chemistry:

a) to enable convenient isolation of *myo*-inositol derivatives.

b) for the regioselective functionalization of various hydroxyl groups of *myo*-inositol and its derivatives

c) for the resolution of racemic *myo*-inositol derivatives

d) for the desymmetrization of *myo*-inositol derivatives having meso configuration.

e) to synthesize membrane permeant analogues of inositol phosphates.

Development of methodologies as above, has made available several phospho inositols and their analogues to study important biological phenomena. Although enzymatic esterification and hydrolysis of *myo*-inositol derivatives has contributed much for the total synthesis of inositol phosphates and related lipids, further investigation is necessary to understand and explain regioselectivities observed. Problems associated with ester protecting groups such as acyl migration have been and exploited for the synthesis of *myo*-inositol phosphates.

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CHAPTER 2

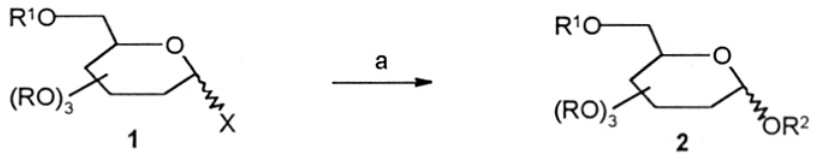
Silver (I) oxide mediated alkylation of (±)-2,4-di-*O*-acyl-*myo*-inositol 1,3,5-orthoformates: effect of solvent and silver halides.

2.1 Introduction

O-Alkylation of alcohols with alkyl halides in the presence of silver (I) oxide or other silver salts is known for many decades. The Köenigs-Knorr[1,2] and Purdie[3,4] reactions (**Scheme 2.1**) provide classical examples of silver (I) oxide assisted *O*-

Scheme 2.1

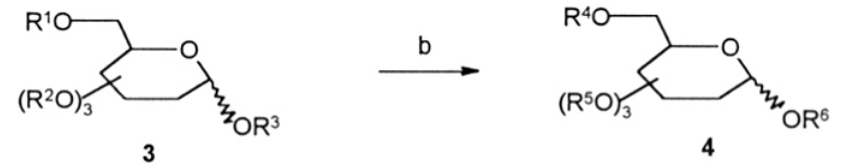
Koenigs-Knorr Reaction



R, R^1= H or protecting group, X = halo, R^2OH = Carbohydrate derivatives

a) R^2OH, Ag_2O or Ag salt

Purdie reaction

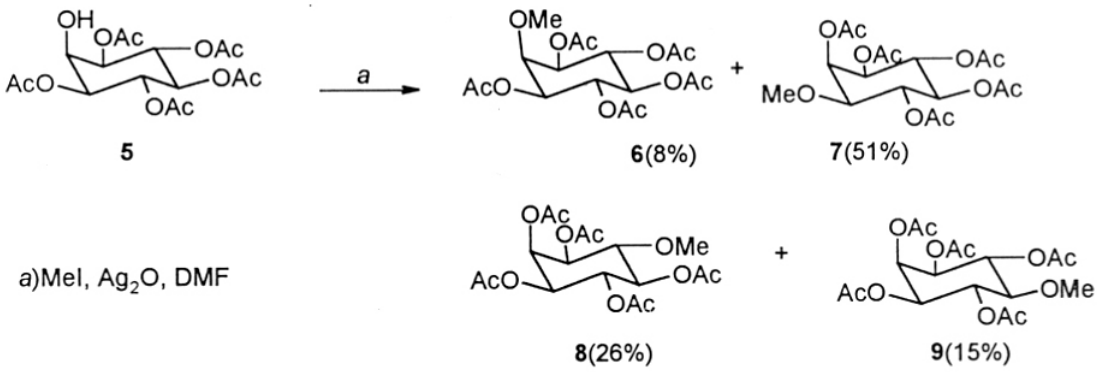


R^1, R^2, R^3 = H or protecting group
R^4, R^5, R^6 = methyl or protecting group

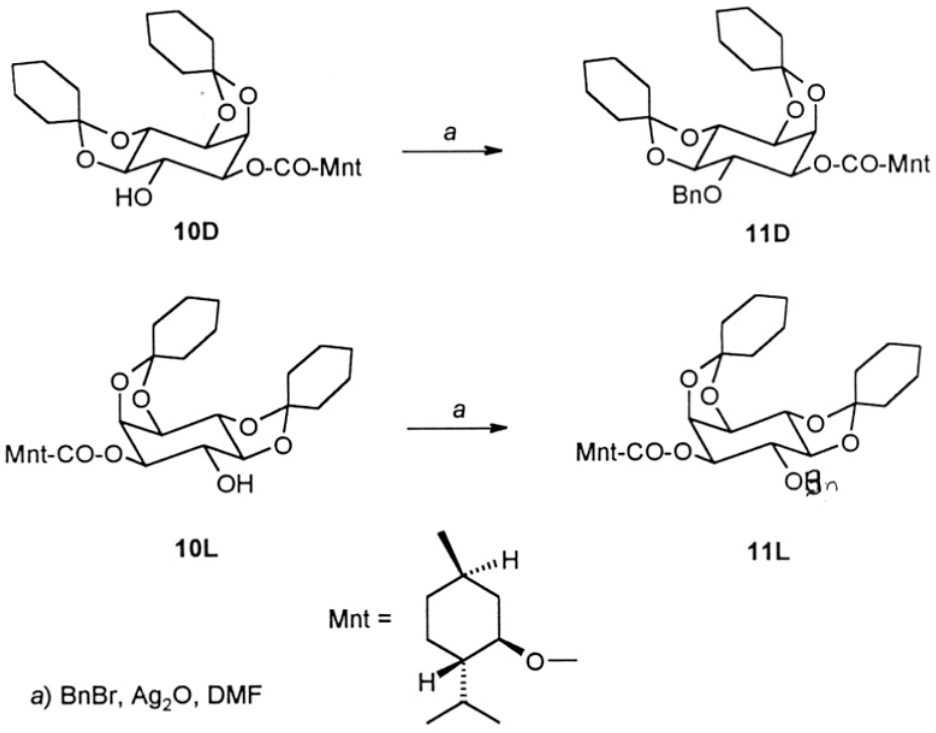
b) MeI/Ag_2O

alkylation reactions. Carboxylic acid esters are known to be stable under these alkylation conditions and hence this procedure has been extensively used for the alkylation of hydroxy esters[5,6,7] as well as for the preparation of glycosides.[8,9] Recently, silver (I) oxide has also been used for the monoalkylation of symmetric diols.[10] However, during the *O*-alkylation of esters of polyhydroxy alcohols (with one or more hydroxyl groups) acyl migration has been observed.[11,12] More relevant to the present work, acyl migration was observed during the methylation of 1,3,4,5,6-penta-*O*-acetyl myo-inositol **5** with methyl iodide in the presence of silver (I) oxide resulting in the formation of a mixture of methyl ethers **6-9**[13,14] (**Scheme 2.2**). But enantiomeric *myo*-inositol derivatives **10D** and **10L** were converted to the corresponding benzyl ethers **11D** and **11L** in the presence of silver (I) oxide without intramolecular migration of the carbonate moities[15] (**Scheme 2.3**).

Scheme 2.2



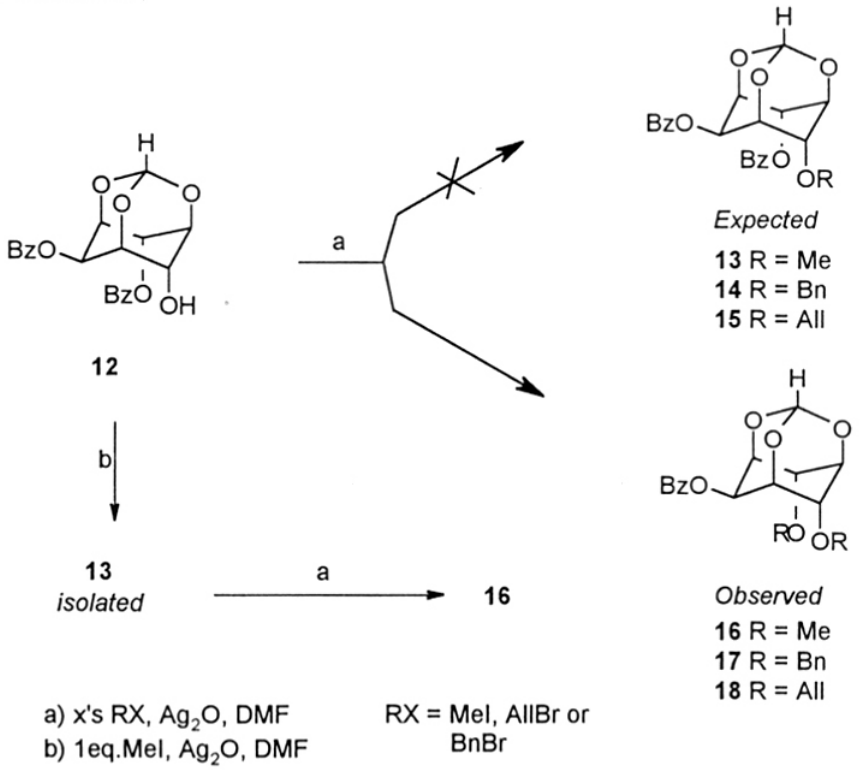
Scheme 2.3



Recently, (±)-2,4-di-*O*-benzoyl -*myo*-inositol 1,3,5-orthoformate (**12**) was shown to be a versatile intermediate for the preparation of a variety of orthogonally protected *myo*-inositol derivatives[16] (see **Chapter 1**), which are useful intermediates for the synthesis of various *myo*-inositol phosphates and *myo*-inositol glycoconjugates.

During this study it was found that the alkylation of the dibenzoate **12** with alkyl halides (*e.g.* benzyl bromide, methyl iodide. allyl bromide etc.) in the presence of silver (I) oxide in DMF gave the corresponding 4,6-diethers **16-18** instead of the expected 6-mono ethers **13-15**[17,18] **(Scheme 2.4)**. This reaction proceeded with transannular participation of 4,6-diaxial oxygens. It was further shown that methylation of the dibenzoate **12** in DMF with methyl iodide to give the dimethyl ether **16** proceeded exclusively through the intermediacy of the monoether **13 (Scheme 2.4)**. However, such

Scheme 2.4



clear-cut evidence (*i.e.* isolation of the monoethers **14** and **15**) for the exclusive intermediacy of the monethers could not be obtained for the reaction of the dibenzoate **12** with other alkyl halides such as BnBr and AllBr. However, based on the experimental results obtained, a mechanism involving several parallel reaction pathways leading to the formation of 4,6-diethers **16-18** was proposed for these alkyl halides.

From a synthetic point of view, although the methyl ether **13** could be obtained in good yields (from the dibenzoate **12**), its use as an intermediate for the preparation of biologically important inositol derivatives is limited since methyl ethers cannot be deprotected efficiently. Hence, we further investigated the silver (I) oxide assisted *O*-

alkylation of the dibenzoate **12** with alkyl halides in different solvents to see if an easily cleavable ether analogue (allyl or benzyl) of **13** (*i.e.* **14** or **15**) can be obtained in yields comparable to that of the methyl ether **13**. Further more, this could also help in clarifying the mechanism of the unusual *O*-alkylation reaction observed in the case of the dibenzoate **12**. Accordingly, this chapter presents results on the silver (I) oxide assisted *O*-alkylation reactions of the dibenzoate **12** with benzyl chloride, propyl bromide, 1,2-bis(iodoethoxy)ethane (**26**), and butyl chloride in DMF as well as methylation of the dibenzoate **12** and the corresponding acetate **33** in acetonitrile. We have also investigated the effect of silver halides on the transesterification reaction of the dibenzoate **12**, which was observed as a side reaction during its alkylation in acetonitrile. In fact, the observed transesterification of the dibenzoate **12** during its methylation prompted us to study the *O*-alkylation of the corresponding acetate **33** to examine the generality of the transesterification of 2,4-di-*O*-acyl myo-inositol orthoformates.

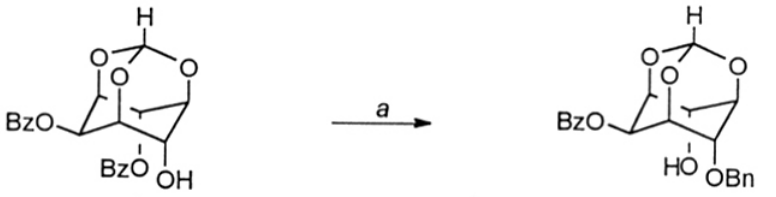
2.2.Results and Discussion.

2.2.1 Silver (I) oxide mediated *O*-alkylation of the dibenzoate 12 in DMF with

a) Benzyl chloride

Benzylation of the dibenzoate **12** with benzyl chloride gave the mono benzyl ether **19** in about 42 % yield (**Scheme 2.5**), unlike in its reaction with benzyl bromide

Scheme 2.5



12 **19**

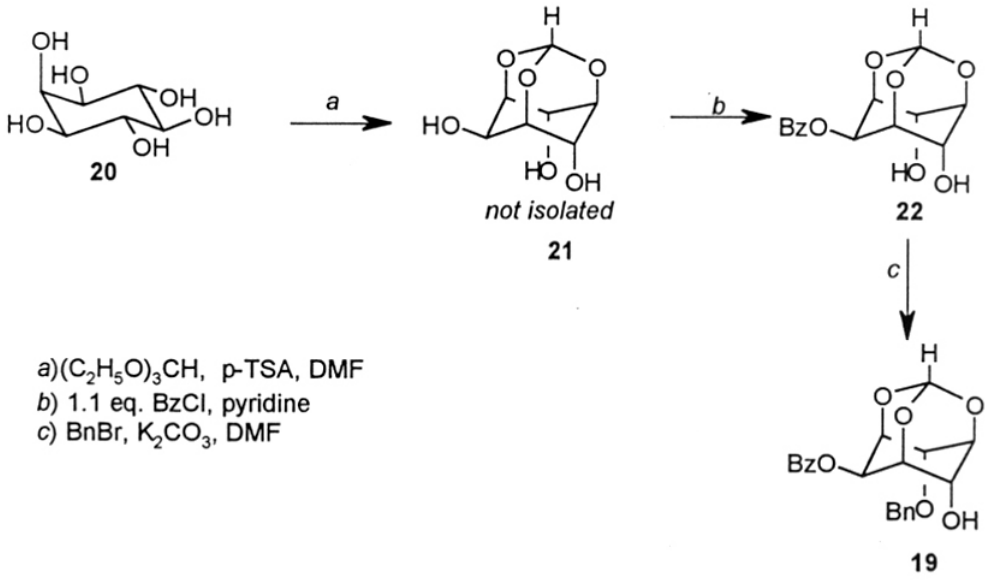
a)BnCl, Ag_2O, DMF

where in the dibenzyl ether **17** was the major product.[16] The monobenzyl ether **19** was characterized by IR and NMR spectroscopy as well as by unambiguous synthesis, starting from *myo*-inositol. (**Scheme 2.6**)

Infrared spectrum of **19** showed the presence of hydroxyl group (3442 cm^1) and carbonyl group (1710 cm^{-1}). The ^1H NMR spectrum of **19** (**Figure 1**) showed one hydroxyl proton at 3.90 δ (exchangeable with D_2O) and ten aromatic hydrogens with peak integration ratio of 8:2 (7.35 to 7.70 δ, 8H and 8.15 to 8.20 δ 2H). The benzylic protons appeared as a doublet of doublet between 4.65 and 4.90 δ. The six inostol ring hydrogens appeared as multiplets from 4.50 to 5.55 δ. The orthoformate proton appeared as a doublet at 5.55 δ overlapping with one of the ring protons of inositol. The long range coupling between protons make ^1H NMR spectrum of *myo*-inositol orthoformate derivatives complicated and hence the assignment of each signal is not straightforward based on coupling constants. The ^{13}C NMR spectrum of **19** (**Figure 2**) clearly showed six distinct inositol ring carbons, the benzylic carbon (63.7 to 74.1 δ), the orthoformate carbon (102.8 δ) aromatic carbons (128.40 to 136.0 δ) and the carbonyl carbon (166.3 δ).

The structure of **19** was unambiguously established by an alternate synthesis (**Scheme 2.6**) starting from *myo*-inositol. *Myo*-inositol (**20**) was converted to the

Scheme 2.6



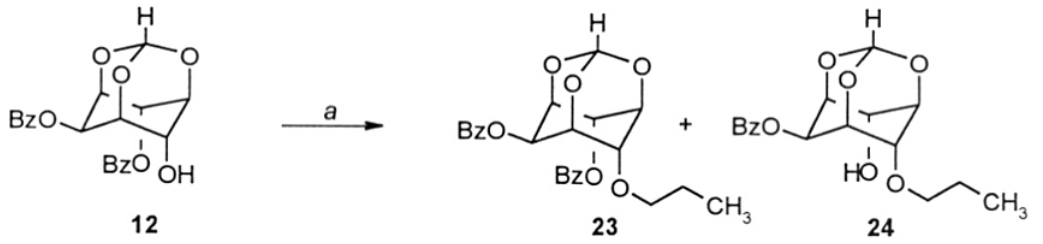
symmetric diol **22** in a one-pot reaction by successive treatment with triethyl orthoformate followed by benzoyl chloride and pyridine. The structure of the diol **22** was confirmed by comparing its ^1H NMR spectrum with that of an authentic sample[16]

and by X-ray crystallography (see Chapter III for details). The diol **22** was benzylated with benzyl bromide in the presence of anhd. potassium carbonate. The monobenzyl ether **19** obtained on benzylation of **22** was identical to the sample obtained by the silver (I) oxide mediated benzylation of the dibenzoate **12** with benzyl chloride.

b) n-propyl bromide

Reaction of the dibenzoate **12** with propyl bromide gave the mono alkylated products **23** and **24** **(Scheme 2.7)** as was observed in the case of allyl chloride[17]. The

Scheme 2.7



12 **23** **24**

a) n-propyl bromide, Ag_2O, DMF

IR spectrum of the compound **23** showed a peak due to both the carbonyl groups (1722 cm^{-1}). The ^1H NMR spectrum **(Figure 3)** showed a triplet corresponding to the methyl protons of the propyl group between 0.7 and 0.8 δ. The two methylene groups appeared between 1.35 and 1.4 δ (CH_3-CH_2) and 3.35 and 3.65 δ (O-CH_2). The six inositol ring hydrogens appeared as multiplets between 4.25 and 5.85 δ and the orthoformate hydrogen appeared at 5.6 δ along with one of the inositol ring protons. Ten aromatic protons appeared as three broad multiplets with three distinct peak integration ratio of 4:2:4.

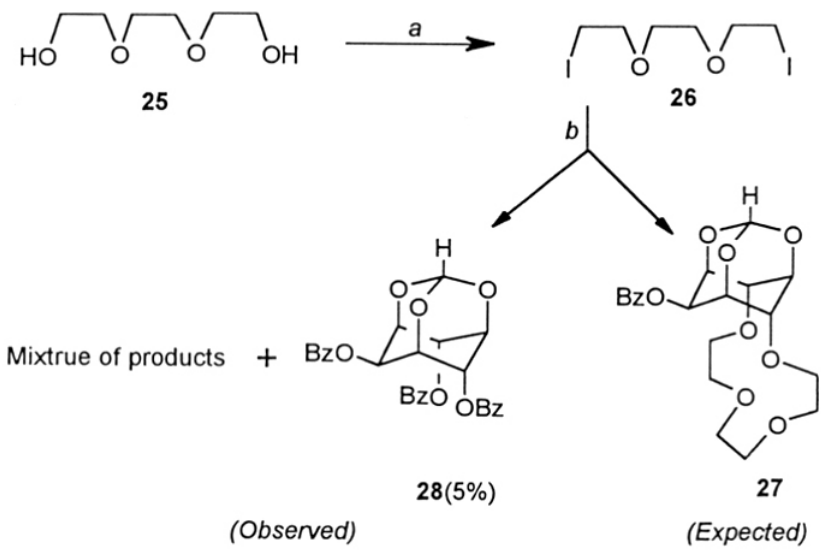
The IR spectrum of **24** showed the presence of hydroxyl group (3420 cm^{-1}) and a carbonyl group (1720 cm^{-1}). The ^1H NMR spectrum of **24** **(Figure 4)** was similar to that of the benzyl ether **19**, except that the signals due to the benzyl ether group were replaced by signals of the n-propyl group (see experimental section for details).

c) 1,2-bis (2-iodoethoxy) ethane (26)

Since *O*-methylation of the dibenzoate **12** with methyl iodide gave the corresponding dimethyl ether **16**,[18] we hoped that alkylation of **12** with **26** would yield

the hitherto unknown inositol based crown ether **27**. Hence we synthesized **26** by the reaction of triethylene glycol (**25**) with iodine and tirphenyl phosphine in the presence of imidazole in toluene[19] (**Scheme 2.8**). The structure of the bis iodide **26** was

Scheme 2.8



a) I_2, PPh_3, Imidazole, Toluene
b) **12**, Ag_2O, DMF

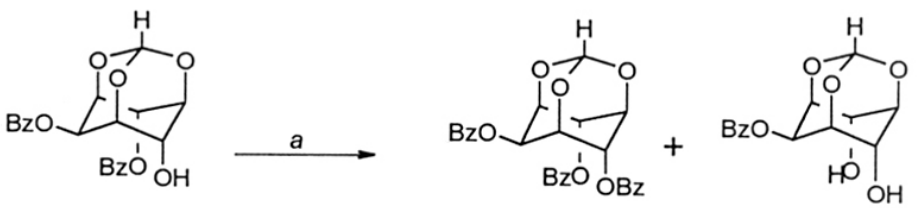
confirmed by comparing its ^1H NMR spectrum with the reported data.[20] Alkylation of the dibenzoate **12** with the diiodo compound **26** (**Scheme 2.8**), gave a mixture of products. TLC analysis of the products obtained suggested the formation of too many products with close R_f values. No attempt was made to separate the products, since this route did not appear to be a good method of preparation of inositol based crown ethers. However, the tribenzoate **28** (5%) could be isolated from the mixture of produtcs obtained. This clearly indicates that transesterification of the dibenzoate **12** is a side reaction during the silver (I) oxide assisted *O*-alkylation of the dibenzoate **12** (see below).

d) n-Butyl chloride.

n-Butyl chloride failed to alkylate the dibenzoate **12** in the presence of silver (I) oxide. The only observed reaction was the transesterification of **12** to give the tribenzoate **28** (14%) and the diol **22** (14%) (**Scheme 2.9**). About 72% of the unreacted

12 was recovered. The identity of **22** and **28** was established by comparison of their IR and ^{1}H NMR spectra as well as melting point with those of authentic samples.[17]

Scheme 2.9



12 **28** **22**

a) n-Butyl chloride,Ag_2O, DMF

The results described above along with the known data on the alkylation of the dibenzoate **12**[17,18] (**Table 2.1**) suggests that, higher the reactivity of the alkyl halide, the more facile is the ester cleavage and formation of the corresponding 4,6-diether (such as **16-18**) This is also evident from the reaction of tri-*O*-acyl-*myo*-inositol 1,3,5-orthoformates with methyl iodide, benzyl bromide or allyl bromide in the presence of silver (I) oxide where the corresponding 4,6-di-*O*-alkylated derivative is the sole isolated product.[17] When less reactive alkyl halide such as n-propyl bromide, benzyl chloride or butyl chloride is used (**Table 2.1**, Entries 8,9 and 11) for alkylation of **12** in DMF, formation of the dialkylated product is not observed.

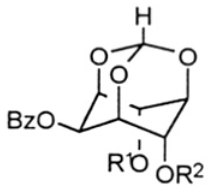
Table 2.1 Reaction of the dibenzoate **12** with alkyl halides in DMF in the presence of silver (I) oxide. [a]

Entry	**12** : Ag_2O	RX(eq.)	Products (yield %)
1.	1 : 5	MeI (10)	**16** (80)
2.	1 : 5	MeI (1)	**13** (80)
3.	1 : 5	BnBr (10)	**17** (80)
4.	1 : 5	AllBr (10)	**18** (74)
5.	1 : 5	AllBr (1)	**15** (4), **18** (17), **29** (40)
6.	1 : 2.5	AllBr (1)	**15** (50), **29** (18)

Table 2.1 (contd.)

7.	1 : 1	AllBr (1)	**15** (50), **29** (12)
8.	1 : 5	n-PrBr (10)	**23** (54), **24** (35)
9.	1 : 5	BnCl (10)	**19** (42)
10.	1 : 5	AllCl (14)	**15** (64), **29** (24)
11.	1 : 5	BuCl (10)	**22** (14), **28** (14)

[a] Entries 1-7 and 10 are from reference 17



12 R^1 = Bz, R^2 = H
13 R^1 = Bz, R^2 = Me
14 R^1 = Bz, R^2 = Bn
15 R^1 = Bz, R^2 = All
16 R^1 = Me, R^2 = Me
17 R^1 = Bn, R^2 = Bn
18 R^1 = All, R^2 = All
19 R^1 = H, R^2 = Bn
22 R^1 = R^2 = H
23 R^1 = Bz, R^2 = n-Prpyl
24 R^1 = H, R^2 = n-Prpyl
28 R^1 = R^2 = Bz
29 R^1 = All, R^2 = H

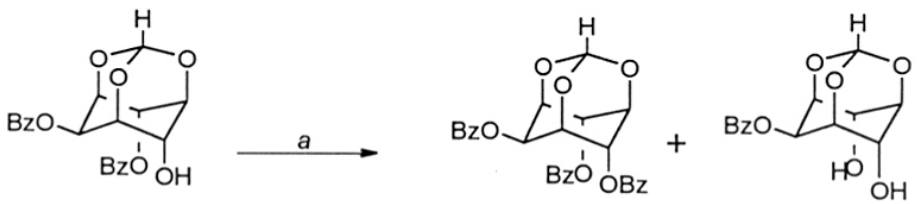
Formation of diethers **16-18** in the reactions presented above could also be governed by the autocatalysis of the silver halides generated during the alkylation of the dibenzoate **12**. It is known that catalytic efficiency of silver halides during silver (I) oxide assisted *O*-alkylation of alcohols decreases in the order AgI>AgBr>AgCl. As is evident from the table **2.1**, we could not arrive at conditions of alkylation to obtain monoethers (such as **14** or **15**, **Scheme 2.4**) of dibenzoate **12** exclusively by the *O*-alkylation of **12** in the presence of silver (I) oxide in DMF. Formation of the tribenzoate **28** during silver (I) oxide assisted *O*-alkylation of the dibenzoate **12** with n-butyl chloride or the diiodo compound **26** shows that the transesterification of **12** (with itself) is an important side reaction. Perhaps, transesterification of **12** was not observable during its reaction with more reactive alkyl halides (such as methyl iodide, benzyl bromide or allyl bromide) for the following reasons.

(a) Rate of *O*-alkylation of **12** could be faster than the rate at which **12** undergoes transesterification in DMF.

(b) The products of transesterification of **12** (viz., the diol **22** and the tribenzoate **28**) undergo alkylation to yield the 4,6-di ethers.[17]

This argument is supported by the fact that when the dibenzoate **12** was exposed to a mixture of silver (I) oxide and silver halide, it underwent transessterification to give isolable amount of the tirbenzoate **28** and the diol **22** (**Scheme 2.10**, **Table 2.2**). The catalytic efficiency of silver halides to bring about transesterification of the dibenzoate **12** decreased in the order AgI>AgBr>AgCl, as has been observed for the *O*-alkylation of alcohols.

Scheme 2.10



12 **28** **22**

a) AgX, Ag_2O, DMF
X = I, Br, Cl

Table 2.2: Transesterification of the dibenzoate **12** in the presence of silver (I) oxide[a]

Entry	AgX (2 eq.)	Products (%)
1	AgI	**12** (57), **22** (21), **28** (21)
2	AgBr	**12** (78), **22** (10), **28** (10)[b]
3	AgCl	**12** (90), **22** (4), **28** (4)[b]
4	None	No reaction

[a] 5 equivalents of silver (I) oxide was used in all the experiments.

[b] Yields were estimated from ^{1}H NMR spectroscopy of the mixture of products obtained based on the integration of the characteristic peaks at 2.70 δ (1H of **12**), 5.00 δ (1H of **28**) and 5.55-5.75 δ (2H of **12** and 1H of **28**). See Figures **5-8**.

2.2.2 Solvent Effects

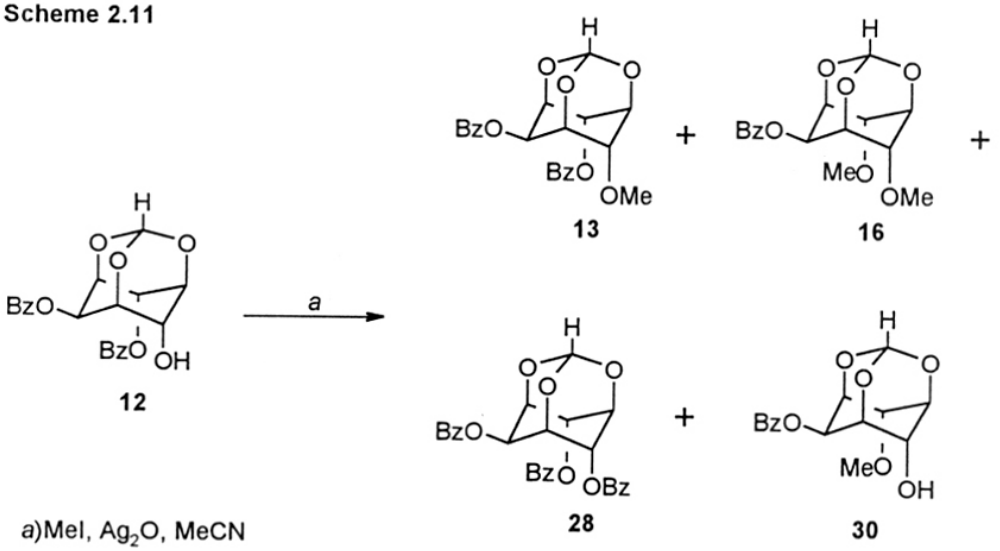
Reactivity of alkyl halides towards alcohols in the presence of silver (I) oxide is known to be solvent dependent.[21, 22] Etherification of alcohols with alkyl halides in the presence of silver (I) oxide in acetonitrile is generally sluggish, supposedly be due to the

complexation of silver ions by acetonitrile.[23,24] Hence we theorized that such reaction conditions might suppress the alkylation of the initially formed monoethers (**13**, **14**, **15** **Scheme 2.4**) to the corresponding diethers (**16**, **17**, **18**) during the *O*-alkylation of the dibenzoate **12**. If successful, this route would provide us a way for the monoalkylation of **12**. Accordingly we carried out the methylation of the dibenzoate **12** with methyl iodide in the presence of silver (I) oxide in acetonitrile and compared the results obtained with the corresponding reaction in DMF.

2.2.2a. Silver (I) oxide mediated methylation of the dibenzoate 12 with methyl iodide in acetonitrile.

Contrary to our expectation the dibenzoate **12** reacted with excess of methyl iodide to yield the corresponding dimethyl ether **16** (66%) along with three other minor products, **13** (5%), **28** (14%), and **30** (5%) (**Scheme 2.11**). The monoether **13** and **28**

Scheme 2.11

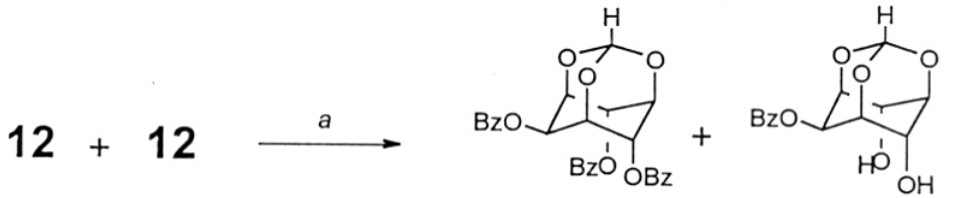


were obtained as an inseparable mixture after column chromatography. The yields of **13** and **28** were estimated from the ^{1}H NMR spectrum of the mixture based on the integrals of the peaks at 3.5 δ (OMe of **13**) and 5.0 δ (one of the ring protons of **28**, see **Figures 5-8**). The structures of **16** and **30** were established by the comparison of their ^{1}H NMR spectra with those of authentic samples.[17]

Isolation of appreciable amount of the tribenzoate **28**, shows that transesterification of the dibenzoate **12** (with itself) is a competing reaction to its *O*-methylation, as was observed during *O*-alkylation in DMF. It appears that due to

reduced rate of *O*-methylation of the dibenzoate **12** in acetonitrile, its relative rate of transesterification appreciates to yield a considerable amount of the tribenzoate. Yet another reason for the accumulation of **28** could be its lesser susceptibility to *O*-methylation (to yield **16** as was observed in DMF) in acetonitrile. A blank experiment in which only the dibenzoate **12** when treated with silver (I) oxide in acetonitrile for 80 hours gave the tribenzoate **28** (36%) and the diol **22** (36%) along with 26% of the unreacted dibenzoate **12** (**Scheme 2.12**).

Scheme 2.12



28 **22**

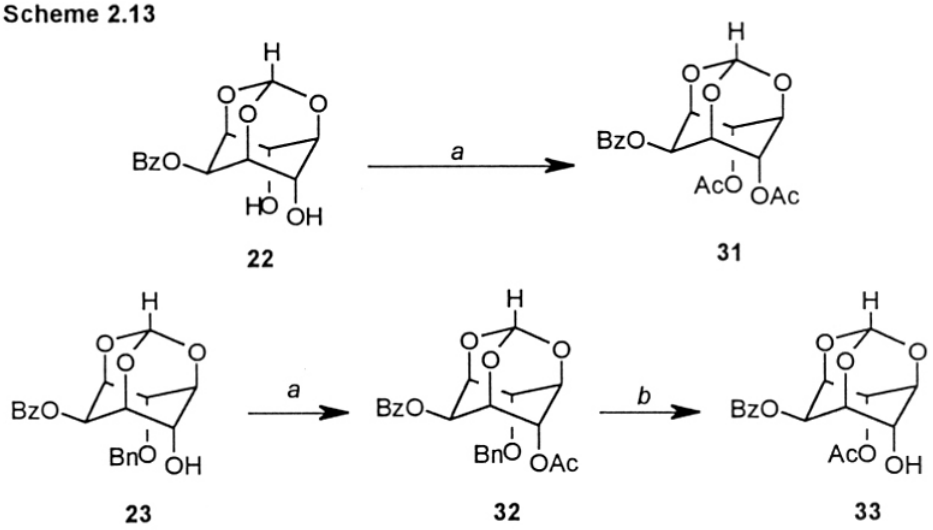
a) Ag_2O, MeCN

In order to test the generality of the transesterification reaction observed during the alkylation of the dibenzoate **12**, we synthesized the corresponding acetate **33** **(Scheme 2.13)** and carried out its alkylation in acetonitrile. Prior to this, alkylation of the acetate **33** was carried out in DMF to check whether it behaves in the same manner as the benzoate **12** towards methylation in DMF.

2.2.2b. Synthesis of (±)-2-O-benzoyl-4-*O*-acetyl-*myo*-inositol 1,3,5-orthoformate (33)

The acetate **33** was synthesized starting from the symmetric diol **22**. Initially we attempted the direct acylation of the diol **22** with 1.1 equivalent of acetyl chloride or acetic anhydride in pyridine. In both the reactions, the dicacetate **31**, (**Scheme 2.13**) was obtained as the major product. Hence we protected one of the axial hydroxyl groups of the diol **22** as the corresponding benzyl ether **19** (**Scheme 2.6**), which was acetylated using acetic anhydride in pyridine to obtain the corresponding acetate **32**. The benzyl ether in **32** was cleaved by hydrogenolysis to obtain the required acetate **33** in an overall yield of 68% starting from the diol **22.**

Scheme 2.13



22 **31** **23** **32** **33**

a) Ac_2O / pyridine, *b*) 10%Pd-C or $Pd(OH)_2$ in EtOAc

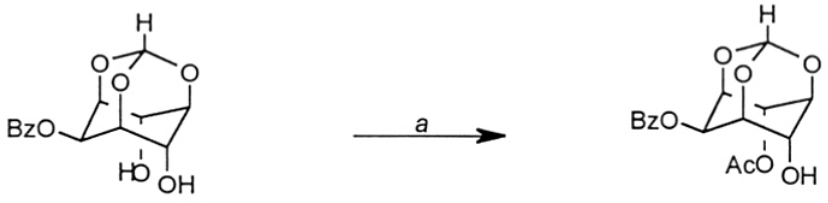
The charecterisation of the monobenzyl ether **19** was discussed in section **2.2.1a**. The acetate **32** showed a broad peak centered at 1730 cm^{-1} in the IR spectrum due the acetyl and benzoyl carbonyl groups. The ^1H NMR spectrum of the same compound (**Figure 9**) showed a singlet at 1.9 δ corresponding to the acetyl methyl group and six inositol ring hydrogens appeared as multiplets between 4.45 and 5.65 δ. The benzylic protons appeared as a doublet of doublet between 4.50 and 4.80 δ. The orthoformate proton appeared along with one of the inositol ring hydrogens at 5.6 δ. The aromatic hydrogens corresponding to the benzylether appeared from 7.3 to 7.4 δ as a multiplet and those corresponding to the benzoate group appeared as three multiplets with distinct peak integration ratio of 2:1:2 between 7.7 and 8.25 δ. In the ^{13}C NMR spectrum (**Figure 10**), the acetyl methyl carbon appeared at 20.4 δ, six inositol carbons as well as the benzylic carbon between 64.1 and 77.9 δ. The peak due to benzylic carbon (71.6 δ) was assigned based on the DEPT spectrum. The ^{13}C NMR spectrum of **32** also showed the presence of aromatic carbons (127.6 δ to 137.2 δ), the orthoformate carbon (103.1 δ) and two carbonyl carbons (189.8 and 166.0 δ).

The IR spectrum of the acetate **33** (nujol mull) showed the presence of hydroxyl group (3442 cm^{-1}) and carbonyl groups (1714 cm^{-1} in nujol). The signal due to the two carbonyl groups could be resolved into two separate signals in solution (1722 cm^{-1} and 1755 cm^{-1} in DCM). The ^1H NMR spectrum of the acetate **33** (**Figure 11**) showed one

hydroxyl proton at 2.1 δ (exchangeable with D_2O) and a sharp singlet (2.2 δ) for the acetyl methyl group. The six inostol ring hydrogens appeared as multiplets from 4.5 to 5.6 δ. The orthoformate proton appeared as a doublet at 5.60 δ merging with one of the ring protons of inositol. The five aromatic protons appeared between 7.45 δ and 8.25 δ with three distinct peak integration ratio of 2:1:2. The ^{13}C NMR spectrum of **33** (**Figure 12**) clearly showed six distinct inositol ring carbons (64.3 to 71.8 δ), the orthoformate carbon (102.6 δ), the two carbonyl carbons (165.6, 169.9 δ) and aromatic carbons (129.2 to 134.0 δ) as expected.

One main problem associated with the protection–deprotection sequence (**Scheme 2.13**) was the inconsistent yield in the hydrogenolysis step. We could however, overcome this by using Pearlmann's catalyst.[25] Later the entire scheme was replaced by a one step acetylation procedure of the diol **22** with N-acetyl imidazole[26,27] to obtain the acetate **33** in 85% yield (**Scheme 2.14**).

Scheme 2.14



22 **33**

a) N-Acetyl imidazole, $Et(i\text{-}Pr)_2N$, DMF

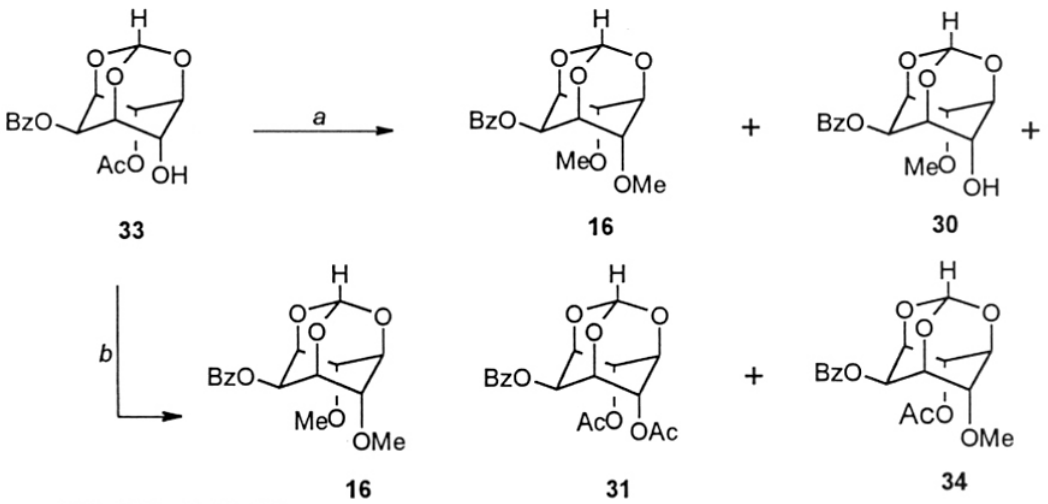
2.2.2c Silver (I) oxide mediated methylation of the acetate 33 with methyl iodide in DMF

Reaction of the acetate **33** with methyl iodide in the presence of excess of silver (I) oxide gave the dimethyl ether **16** in 90% yield (**Scheme 2.15**) as in the case of dibenzoate **12**. Structure of the symmetric dimethyl ether **16** was established by comparison of its ^1H NMR spectrum with that of an authentic sample.[17]

2.2.2d Silver (I) oxide mediated methylation of the acetate 33 with methyl iodide in acetonitrile

Reaction of the acetate **33** with excess of methyl iodide in acetonitrile gave similar product formation as was observed in the case of the dibenzoate **12**. The products obtained were **16** (30%), **30** (28%), **31** (5%) and **34** (30%) (**Scheme 2.15**).

Scheme 2.15



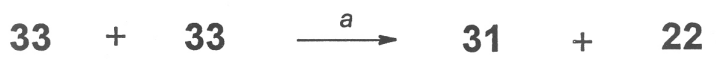
33 **16** **30** **16** **31** **34**

a) MeI / Ag_2O, MeCN
b) MeI, Ag_2O, DMF

Compounds **16** and **34** were obtained as an inseparable mixture after column chromatography. The yields of **16** and **34** were estimated from the ^1H NMR spectrum of the mixture based on the integrals of the signals due to the acetyl methyl groups (of **34** at 2.2 δ) and the O-CH_3 group (of **16** and **34** at 3.5 δ see **Figures 13** and **14**).

Isolation of the diacetate **31** suggests that transesterification of the acetate **33** (with itself) is a competing side reaction during methylation, as observed earlier in the case of the dibenzoate **12**. Quenching of the methylation at the end of 16 hours yielded 30% of the diacetate **31** along with **16** (20 %), **30** (14%), and **34** (36%). Increased yields of the diacetate **31** as well as the monomethyl ether **34**, with shorter reaction time shows that these intermediates undergo further methylation to yield the dimethyl ether **16**. In the absence of methyl iodide, the acetate **33** underwent silver (I) oxide assisted transesterification with facility to yield 40% of the diacetate **31**, at the end of 80 hours (**Scheme 2.16**).

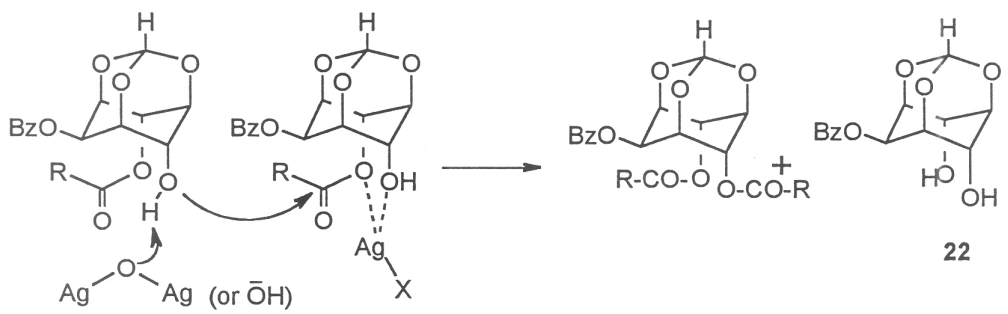
Scheme 2.16



a) Ag_2O, MeCN, 80h.

The results presented so far indicate that transesterification of 2,4-di-*O*-acyl-*myo*-inositol 1,3,5-orthoformates could be a general phenomenon. Perhaps silver halides function as Lewis acids and form a complex with diesters and facilitate their transesterification. Simultaneously, silver (I) oxide (or residual hydroxyl ions adsorbed on its surface) could function as a general base to promote the transesterification reaction observed. A plausible mechanism for the transesterification reaction discussed is shown in **Scheme 2.17**.

Scheme 2.17



R = C_6H_5, CH_3
X = I, Br, Cl

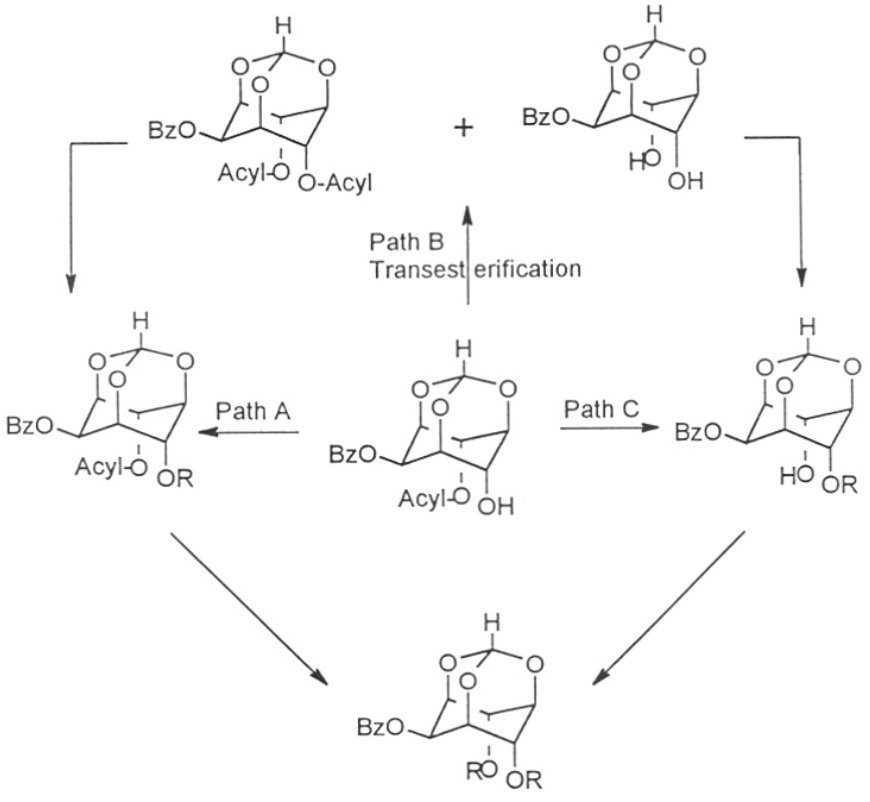
Results of the reaction of alkyl halides with the dibenzoate **12** and the acetate **33** in acetonitrile are summarized in **Table 2.3**.

Table 2.3 Reaction of 2,4-di-*O*-acyl-*myo*-inositol 1,3,5-orthoformates with alkyl halides in acetonitrile.

Entry	Reactant	RX (reaction time h.)	Products (yield %)
1	**12**	MeI (80)	**16**(66) , **13**(5), **28**(14), **30** (5),
2	**33**	MeI (80)	**16** (30), **30** (28), **31** (5), **34**(30),
3	**33**	MeI (16)	**16** (20), **30** (14), **31** (30), **34**(36),
4	**12**	AllBr [ref. 17]	**15** (9), **18** (4), **28** (14), **29** (63)

In light of the results pertaining to the facile transesterification of 2,4-di-*O*-acyl-*myo*-inositol 1,3,5-orthoformates during their alkylation, routes for the formation of various *O*-alkylated products isolated from the reaction of diesters **12** and **33** with alkyl halides in acetonitrile can be summarized as in **Scheme 2.18**.

Scheme 2.18



2.3 Conclusions

A detailed investigation of the silver (I) oxide mediated *O*-alkylation of 2,4-di-*O*-acyl-*myo*-inositol 1,3,5-orthoformates in DMF and acetonitrile was carried out. Comparison of the results obtained with the data on the corresponding reaction in DMF helped us to arrive at conditions (see table **2.1** and **2.3**) to obtain a variety of *O*-alkylated *myo*-inositol orthofomates. These *O*-protected *myo*-inositol derivatives have potential use in the preparation of *myo*-inositol derivatives of biological interest. Results presented on the transesterification 2,4-di-*O*-acyl-*myo*-inositol orthoformates perhaps constitutes the first report on the silver halide catalyzed transesterification of hydroxy esters. A detailed investigation of the facile intermolecular acyl transfer reaction of 2,4-di-*O*-acyl-*myo*-inositol 1,3,5-orthoformates, discovered during this study is presented in the next two chapters.

2.4 Experimental Section

General: All the deuterated solvents, *myo*-inositol, triethyl orthoformate, benzyl bromide, N-N-di-isopropylethylamine, n-propyl bromide and palladium hydroxide were obtained from Aldrich Chemical Company, USA and were used as received. Benzoyl chloride, benzyl chloride, acetic anhydride, imidazole, acetonitrile, dimethylformamide, methanol, methyl iodide, anhyd. sodium sulfate, silver nitrate, pyridine, p-TsA, palladium-carbon and silica gel for column chromatography (60-120 mesh and 100-200 mesh) were obtained from SD Fine Chemicals, India. All the solvents used, benzoyl chloride, benzylchloride and p-TsA were purified according to the literature procedures.[28] Silver (I) oxide was prepared from silver nitrate as reported.[29] Silica gel for flash column chromatography (230 - 400 mesh) was obtained from Spectrochem India Ltd. The dibenzoate **12** was prepared as reported earlier.[17] Light petroleum refers to the 60-80° C boiling fraction of petroleum ether. TLC was performed on E-Merk pre-coated 60 F_{254} plates and the spots were rendered visible either by shining UV light or by charring the plates after spraying conc. sulfuric acid. Column chromatographic separations were carried out by gradient elution with light petroleum-ethyl acetate mixture, unless otherwise mentioned. IR spectra were recorded in the solid state as nujol mull or KBr pellets and in solution using an appropriate solvent (conc.1μM). NMR spectra were recorded either on Bruker ACF 200 (200 MHz for ^{1}H) or MSL 300 (300 MHz for ^{1}H) spectrometers. Chemical shifts (δ) reported are referred to internal tetramethyl silane. Microanalytical data were obtained using a Carlo-Erba CHNS-0 EA 1108 Elemental Analyser. All the melting points reported are uncorrected and were recorded using an electro-thermal melting point apparatus. 'Usual work-up' implies washing of the organic layer with water followed by brine, drying over anhd. sodium sulphate followed by removal of the solvent *in vacuo* using a rotavapor. All the compounds previously known in the literature were characterized by comparison of their R_f values on TLC, IR and H^1 NMR spectra as well as melting point (in case of solids) with authentic samples.

Silver (I) oxide mediated *O*-alkylation of *myo*-inositol orthoformate derivatives

General procedure: *Myo*-inositol 1,3,5-orthoformate derivative (0.1 to 1.25 mmol) and the alkyl halide were dissolved in dry DMF (0.5 to 7ml) or acetonitrile (2 to 6ml) and

freshly prepared silver (I) oxide was added with vigorous stirring at room temperature. Stirring was continued till the starting material disappeared (60-80 h). The reaction mixture was diluted with chloroform (20 ml) and filtered through a short bed of celite. The filtrate was washed with sodium cyanide solution (1%, 100 ml) and then worked up as usual. The products were separated by column chromatography over silica gel.

Silver (I) oxide mediated *O*-alkylation of (±)-2,4-di-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate (12) with:

a) benzyl chloride: The dibenzoate **12** (0.3g, 0.75 mmol), dry DMF (4.5 ml), silver (I) oxide (0.873 g, 3.77 mmol) and benzyl chloride (1.25g, 7.5 mmol) were used for the alkylation as in the general procedure above. The products were separated by column chromatography (Silica gel, 60-120 mesh, 18g). The fractions eluted with 8% EtOAc-light petroleum gave the mono benzyl ether **19** (0.120g, 42%). Unreacted dibenzoate **12** was obtained on eluting with 20% EtOAc-light petroleum (0.135g, 45%).

Data for **19** See p 51

b) n-Propyl bromide: The dibenzoate **12** (0.2g, 0.5 mmol), dry DMF (3 ml), silver (I) oxide (0.58 g, 2.5 mmol) and propyl bromide (0.615g, 5 mmol) were used for the alkylation. The products were separated by column chromatography (Silica gel, 100-200 mesh, 15g). The products obtained were **23** (0.1120g, 54%) and **24** (0.060g, 35%).

Data for **23**

gum

IR (cm^{-1}): 1722.

^1H NMR ($CDCl_3$) δ: 0.70-0.80 (t, 3H), 1.35-1.45 (m, 2H), 3.35-3.65 (m, 2H), 4.25-4.30 (m, 1H), 4.50-4.60 (m, 2H), 4.70-4.80 (m, 1H), 5.60-5.70 (m, 2H), 5.70-5.85 (m, 1H), 7.58-7.65(m, 4H), 8.05-8.20 (m, 6 H).

Data for **24**

m.p. 87 °C

IR (cm^{-1}): 3420, 1720.

^{1}H NMR ($CDCl_3$) δ: 1.00 (t, 3H), 1.60-1.75 (m, 2H), 3.55-3.65 (m, 1H), 3.70-3.80 (m, 1H), 3.98 (d, 1H; D_2O exchangeable), 4.35-4.66 (m, 5H), 5.45 (m, 1H), 5.60 (d, 1H), 7.45-7.55(m, 2H), 7.55-7.65 (m, 1H), 8.15-8.25 (m, 2H).

c) 1,2-bis(iodo ethoxy)ethane (26): The dibenzoate **12** (0.2g, 0.5 mmol), dry DMF (5 ml), silver (I) oxide (0.0.58g, 2.5 mmol) and **26** (0.844g, 2.5 mmol) were used for the alkylation. Only pure tribenzoate **28** (0.03g, 5%) was isolated after column chromatography (silica gel, 60-120 mesh). No attempt was made to isolate other products.

d) n-butyl chloride: The dibenzoate **12** (0.2g, 0.5 mmol), DMF (3 ml), silver (I) oxide (0.58 g, 2.5 mmol) and n-butyl chloride (0.463g, 5 mmol) were used for the alkylation (as above). Column chromatography (silica gel, 100-200 mesh, 10g) yielded the tribenzoate **28** (0.0.035g, 14%) the diol **22** (0.019g, 14%) and the starting material **12** (0.045 g, 45%).

Preparation of 1,2-bis(iodo ethoxy) ethane(26): Trigol **25** (1.2 g, 8 mmol) was dissolved in toluene (32 ml), iodine (8.112g, 32 mmol), triphenyl phosphine (6.292g, 24 mmol) and imidazole (1.142g, 16.8 mmol) were added and the mixture was refluxed for 4 h. The reaction mixture was cooled to room temperature diluted with EtOAc (50 ml) and insoluble materials were discarded. Usual workup gave a gummy residue (7g) which on column chromatography (silicagel, 60-120 mesh) yielded the diiodo derivative **26** (2.15g, 80%).

Data for **26**

gum

^{1}H NMR ($CDCl_3$) δ: 3.25-3.35 (t, 4 H), 3.7 (s, 4H), 3.75-3.85 (t, 4H).

General procedure for the silver (I) oxide/silver halide mediated transesterification

2,4-di-*O*-acyl-*myo*-inositol 1,3,5-orthoformate derivative (0.25-0.5 mmol) was dissolved in DMF (1-2 ml). To this solution, freshly prepared silver (I) oxide (5 eq.) and silver halide (2eq.) were added and stirred vigorously at room temperature for 80h. The work up and purification of the products were carried out as described in the general procedure for alkylation.

Transesterification of 2,4-di-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate (12) in DMF in the presence of:

a) Silver (I) oxide and Silver iodide.

The dibenzoate **12** (0.1g, 0.25 mmol) was dissolved in DMF. To this solution freshly prepared silver (I) oxide (0.289g, 1.25 mmol) and silver iodide (0.118g, 0.5 mmol) were added and stirred vigorously at room temperature for 80h. The work up and purification of the products were carried out as described in the general procedure for alkylation. The products were separated by column chromatography (silica gel, 60-120 mesh, 8g) to obtain the tribenzoate **28** (0.026g, 21%), the diol **22** (0.015g, 21%) and unreacted dibenzoate **12** (0.057g, 57%).

b) Silver (I) oxide and Silver bromide

The dibenzoate **12** (0.1g, 0.25 mmol), silver (I) oxide (0.289 g, 1.25 mmol), silver bromide (0.098g, 0.5 mmol) and DMF (1 ml) were used for the transesterification reaction as in (a) above. The products were separated by column chromatography (silica gel, 60-120 mesh, 8g) to obtain the tribenzoate **28** (0.012g, 10%), the diol **22** (0.007g, 10%) and unreacted dibenzoate **12** (0.078g, 78%).

c) Silver (I) oxide and Silver chloride

The dibenzoate **12** (0.1g, 0.25 mmol), silver (I) oxide (0.289 g, 1.25 mmol), silver chloride (0.143 g, 0.5 mmol) and DMF (1 ml) were used for the transesterification reaction. NMR spectra of the mixture obtained after work up showed that the products are the tribenzoate **28** (4%), the diol **22** (4%) and unreacted dibenzoate **12** (92 %). No attempt was made to isolate the products.

d) Silver (I) oxide

The dibenzoate **12** (0.1g, 0.25 mmol), silver (I) oxide (0.289 g, 1.25 mmol) and DMF (1 ml) were used for the transesterification reaction. NMR spectra of the product obtained after work up showed the presence of dibenzoate **12** (0.098g .98%) alone. Very faint spots corresponding to the tribenzoate **28** and the diol **22** were visible on the TLC.

Preparation of 2-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate (22): *Myo*-inositol **20** (2.7 g, 0.015 mol), trimethylorthoformate (2.39 g, o.225 mol), *p*-TsA.H_2O (0.25g, 1.31 mmol) and dry DMF (20 ml) were mixed and heated at 100 °C with stirring for 3h. The

clear solution obtained was cooled to room temperature, neutralized with triethyl amine (1 ml) and concentrated. The residue was co-evaporated with dry benzene in *vacuo* (2x5 ml). The residue was dissolved in pyridine (10ml), cooled to 0 °C, and benzoyl chloride (2.2015 g, 0.015 mol) was added over a period of 30 min. The reaction mixture was brought to room temperature and stirred for 8h. The solvents were then evaporated *in vacuo*. The gummy residue obtained was chromatographed over silica gel (60-120 mesh, 100 g) using 15 % ethyl acetate/light petroleum as eluent to obtain the diol **22** (2.5 g, 57%) as a solid. For crystallographic investigation the compound was recrystallized from chloroform (m.p. 209-210 °C, literature.[17] m.p. 210-213 °C).

Preparation of (±)-2-*O*-benzoyl-4-*O*-benzyl-*myo*- inositol 1,3,5-orthoformate (19): The diol **22** (1.00 g, 3.4 mmol) and benzyl bromide (1.064 g, 6.22 mmol) were dissolved in DMF (20 ml) and stirred after the addition of anhyd. potassium carbonate (2.86 g, 20 mmol) for 40 h at ambient temperature. The reaction mixture was then diluted with chloroform (40 ml) and worked up as usual to obtain a gummy residue (2 g) which on chromatography over silica gel (60-120 mesh, 20g) using 12% ethyl acetate-light petroleum as eluent, gave the mono benzyl ether **19** (0.92 g, 68%) as a gum. The pure monobenzyl ether **19** turned into a solid on storing at 0 °C.

m.p. 100 °C

IR (cm^{-1}): 1710, 3415.

^1H NMR ($CDCl_3$): 3.9 (d, 1H, D2O exchangeable), 4.35 (m, 1H), 4.5 (m, 2H) 4.65-4.9 (q, 4H), 5.55 (m, 2H), 7.3-7.65 (m, 8H), 8.12-8.25 (d, 2H).

^{13}C NMR ($CDCl_3$): 63.7, 68.1, 68.2, 69.6, 72.6, 72.8, 74.1, 102.8, 128.4, 128.6, 128.9, 129.0, 129.8, 130.1, 133.5, 136.0, 166.3.

Preparation of (±)-2-*O*-benzoyl-4-*O*-benzyl-6-*O*-acetyl-*myo*-inositol 1,3,5-ortho-formate (32): The monobenzyl ether **19** (0.5 g, 1.3 mmol) was treated with acetic anhydride (0.6 ml, 6.5 mmol) in pyridine (5 ml) at room temperature overnight. The reaction mixture was diluted with chloroform (50 ml) and worked up as usual to obtain the acetate **32** (0.55 g, 100%) as a gum.

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

^{1}H NMR ($CDCl_3$): 1.9 (s, 3 H), 4.45 (m, 2 H), 4.6 (m, 2 H), 4.70 (m, 2 H), 5.05-5.15 (m, 2H), 5.45 (m, 1H), 7.30-7.40 (m, 5H), 7.45-7.70 (m, 3H), 8.10-8.25(d, 2H).

^{13}C NMR ($CDCl_3$): 20.5, 64.1, 66.7, 68.3, 69.5, 71.6, 73.3, 77.9, 103.1, 127.6, 128.0, 128.4, 129.7, 129.9, 133.3, 137.2, 169.8, 166.0.

Elemental Analysis calcd. for $C_{23}H_{22}O_8$: C, 64.21, H, 5.16. Found: C, 64.78; H, 5.16.

Debenzylation of 32 using Pd-C (10%) to give (±)-2-*O*-benzoyl-4-*O*-acetyl-*myo*-inositol 1,3,5-orthoformate (33): The mono benzyl ether **32** (0.5g, 1.17 mmol) was dissolved in ethyl acetate (8 ml) and hydrogenated at 30 psi for 24 h. in the presence of 10% Pd-C (0.3 g). The reaction mixture was then filtered and the clear filtrate was evaporated under reduced pressure to obtain the acetate **33** (0.39 g, 99%) as a solid. For crystallographic investigation **33** was recrystallized from chloroform.

m.p. 198 °C

IR (cm^{-1}): 3442, 1714.

^{1}H NMR ($CDCl_3$): 2.1 (d, 1H, D_2O exchangeable), 2.20 (s, 3H), 4.50 (m, 3H), 4.15-4.20 (m, 1H), 5.50 (d, 1H), 5.60 (s, 2H), 7.10-7.15 (m, 1H), 7.45-7.55 (m, 2H), 8.15-8.25 (d, 2H).

^{13}C NMR (DMSO-d_6): 21.1, 64.3, 66.5, 68.5, 68.6, 69.4, 71.8, 102.6, 129.1, 129.7, 134.0, 165.6, 169.9.

Elemental Analysis calcd. for $C_{16}H_{16}O_8$: C, 57.14; H, 4.80. Found: C, 57.18; H, 4.76.

Note: The efficiency of debenzylation of **32** varied with different batches of catalyst (Pd-C) obtained from different suppliers. The yield reported above is the best obtained in several trials. Difficulties in the debenzylation of *myo*-inositol 1,3,5-orthoformate benzyl ethers have earlier been encountered.[25]

Debenzylation of 32 using $Pd(OH)_2$ to give (±)-2-*O*-benzoyl-4-*O*-acetyl-*myo*-inositol 1,3,5-orthoformate (33): The mono benzyl ether **32** (0.5g, 1.17 mmol) was dissolved in ethyl acetate (6 ml) and hydrogenated at 30 psi for 24 h. in the presence of $Pd(OH)_2$ (0.1g). The reaction mixture was then filtered through celite and the clear filtrate was evaporated under reduced pressure to obtain the acetate **33** (0.39 g, 99%) as a solid.

Preparation of (±)-2-*O*-benzoyl-4-*O*-acetyl-*myo*-inositol 1,3,5-orthoformate (33) using acetyl imidazole: The diol **22** (0.294 g, 1 mmol) and diisopropylethylamine (0.129 g, 1 mmol) were dissolved in DMF (3mL) and stirred for five minutes at room temperature. N-acetyl imidazole [26] (0.110 g, 1 mmol) was added and stirring continued for 1h at the end of which TLC showed monoacetate **33** as the major product. The reaction mixture was then diluted with chloroform and worked-up as usual and the product was crystallized from chloroform - light petroleum mixture to obtain **33** (0.220 g). The mother liquor was chromatographed over silica gel to obtain an additional amount of **33** (0.065 g, total yield 85%).

Silver (I) oxide mediated methylation of (±)-2-*O*-benzoyl-4-O-acetyl-myo-inositol 1,3,5-orthoformate (33) in DMF: The acetate **33** (0.168g, 0.5 mmol), dry DMF (3 ml), silver (I) oxide (0.58 g, 2.5 mmol) and methyl iodide (0.720g, 5 mmol) were used for the alkylation as in the general procedure (page 47). The products were separated by column chromatography (silica gel, 100-200 mesh, 15g). The dimethylether **16** (0.145 g, 90%) was isolated after column chromatography.

Silver (I) oxide mediated methylation of (±)-2,4-di-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate (12) in acetonirile: The dibenzoate **12** (0.3g, 0.75 mmol), dry acetonitrile (6 ml), silver (I) oxide (0.8 g, 3.75 mmol), and methyl iodide (1.07g, 7.5 mmol) were used for alkylation as in the general procedure (page 47). The products were separated by column chromatography (silica gel, 100-200 mesh, 10g). The fractions eluted with 5% EtOAc-light petroleum was found to be a mixture (0.070g, R_f = 0.7 in 20% EtOAc-light petroleum) of **13** (5%) and tribenzoate **28** (14%) as estimated from their ^{1}H NMR spectrum. Elution with 10% EtOAc-light petroleum gave the dimethyl ether **16** (0.160g, 66%, m.p. 145°C literature[17] 143-145 °C) and methyl hydroxy **30** (0.020g, 5%, m.p. 105 °C literature[17] 102-105 °C).

Silver (I) oxide mediated methylation of (±)-2-*O*-benzoyl-4-O-acetyl-*myo*-inositol 1,3,5-orthoformate (33) in acetonitrile (80h.): The acetate **33** (0.2g, 0.595 mmol), dry acetonitrile (4.5 ml), silver (I) oxide (0.844 g, 2.975 mmol) and methyl iodide (0.8448, 5.95mmol) were used for alkylation as above. The products were separated by column chromatography (silica gel, 100-200 mesh, 10g). The dimethyl ether **16** (30%) and methyl ether **34** (30%) were obtained as an inseparable mixture (0.120g, R_f = 0.7 in

25% ethyl acetate-light petorleum). Yields of which were calculated from its ^{1}H NMR spectrum. The other products obtained were the diacetate **31** (0.011g, 5%) and the methyl ether **30** (0.052g, 28%).

Silver (I) oxide mediated methylation of (±)-2-*O*-benzoyl-4-O-acetyl-*myo*-inositol 1,3,5-orthoformate (33) in acetonitrile (16h.): The acetate **33** (0.1g, 0.3 mmol), dry acetonitrile (4.5 ml), silver (I) oxide (0.345 g, 1.5 mmol) and methyl iodide (0.426g, 3.0 mmol) were used for the alkylation as above. The products were separated by column chromatography (silica gel, 100-200 mesh, 10g). The diacetate **31** (0.034g, 30%) and methyl ether **34** (36%) were obtained as an inseparable mixture (0.058g, R_f = 0.7 in 25% ethyl acetate-light petorleum). The yields of which were estimated from the ^{1}H NMR spectrum. The other products were **16** (21%) and methyl ether **30** (0.014g, 14%).

Silver (I) oxide mediated transesterification of 2-*O*-benzoyl-4-*O*-acetyl-myo-inositol 1,3,5-orthoformate (33) in acetonitrile:

The acetate **33** (0.15 g, 0.45 mmol), silver (I) oxide (0.522 g, 2.25 mmol) and acetonitrile (3 ml) were used for the transesterification as described in the general procedure (page 21). The products were separated by column chromatography (silica gel, 60-120 mesh, 8g) to obtain diacetate **31** (0.068g, 40 %), diol **22** (0.053g, 40%) and unreacted acetate **33** (0.030g, 20%).

2.5 References

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Figure 1

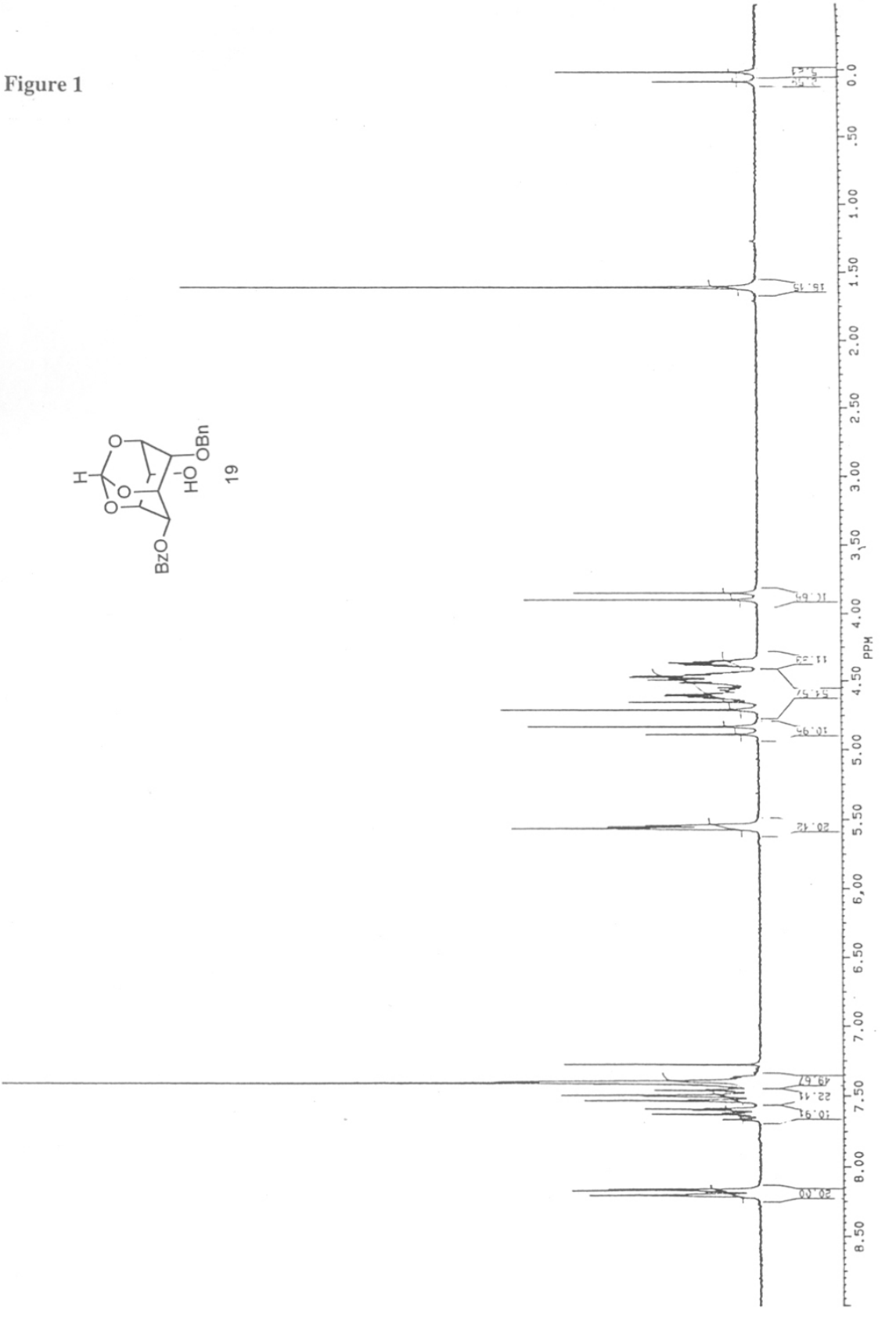
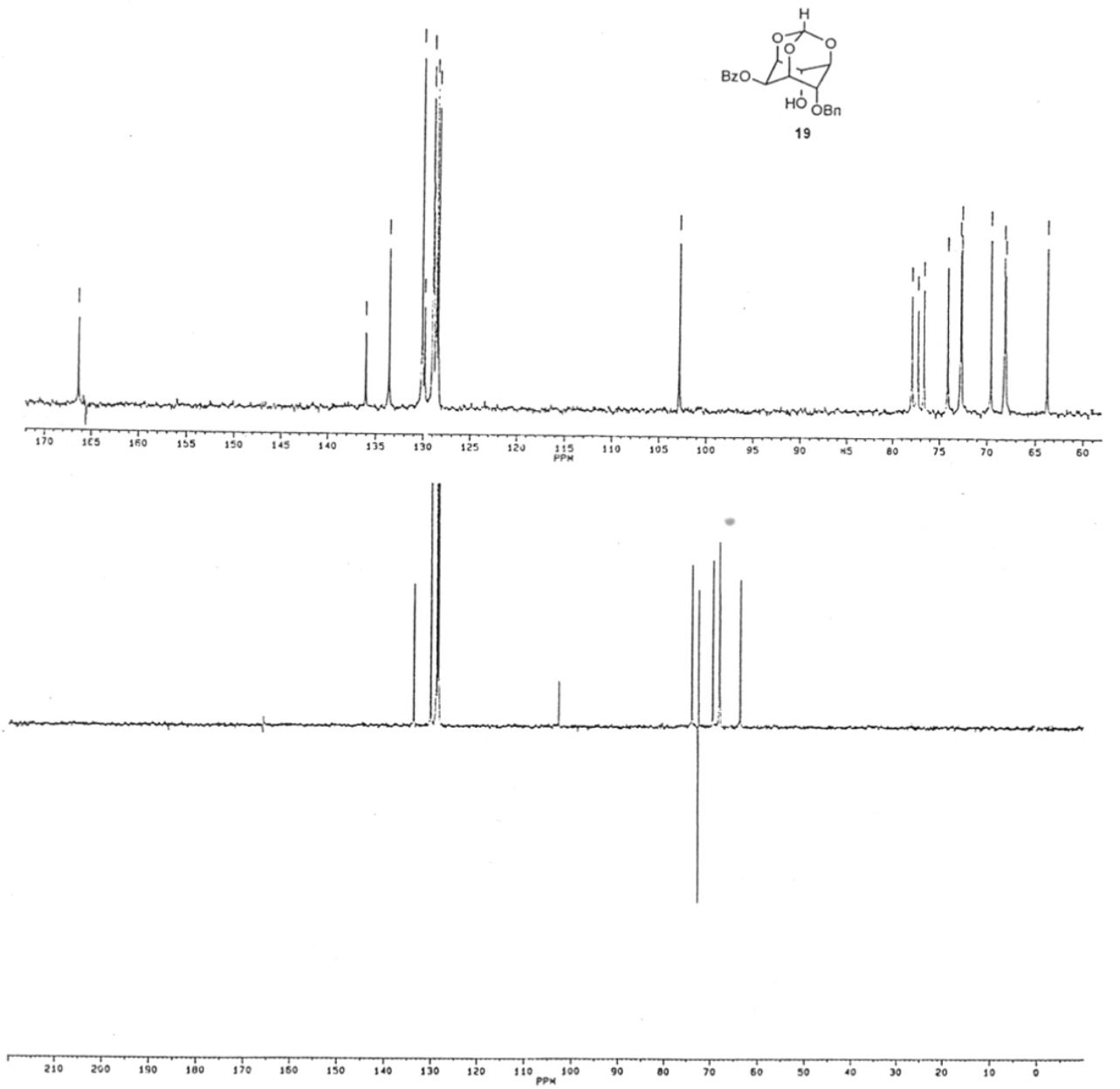


Figure 2



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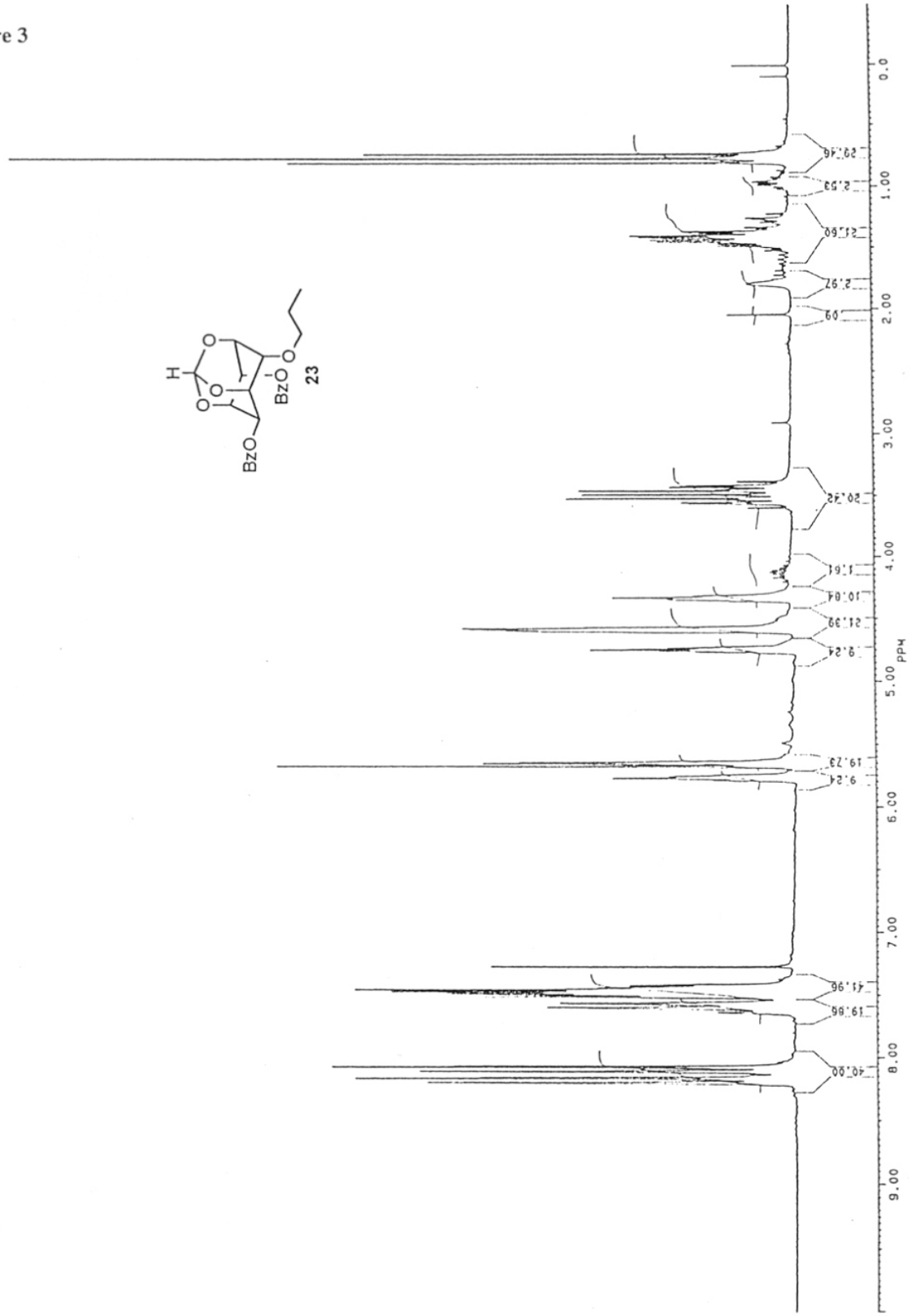

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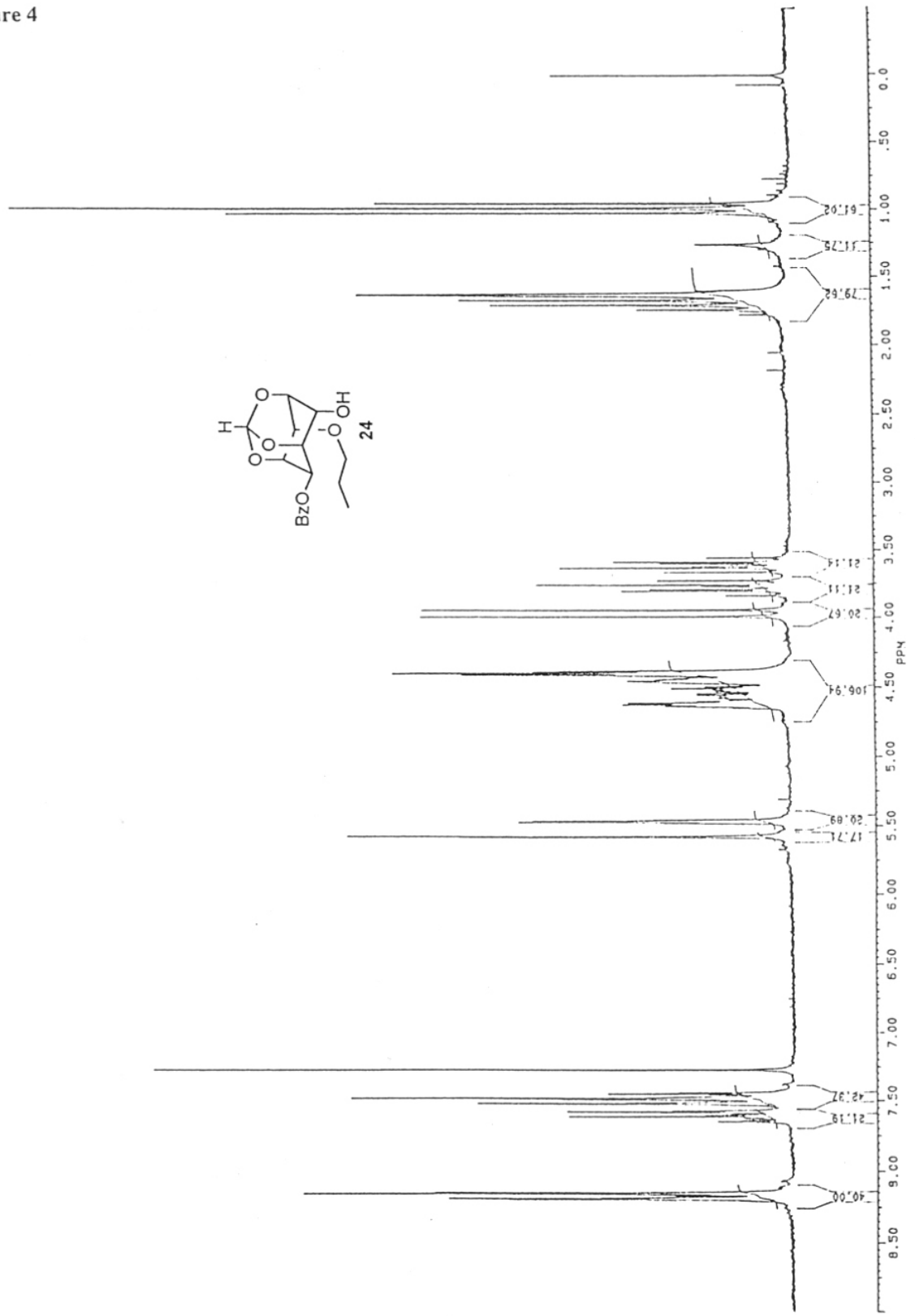
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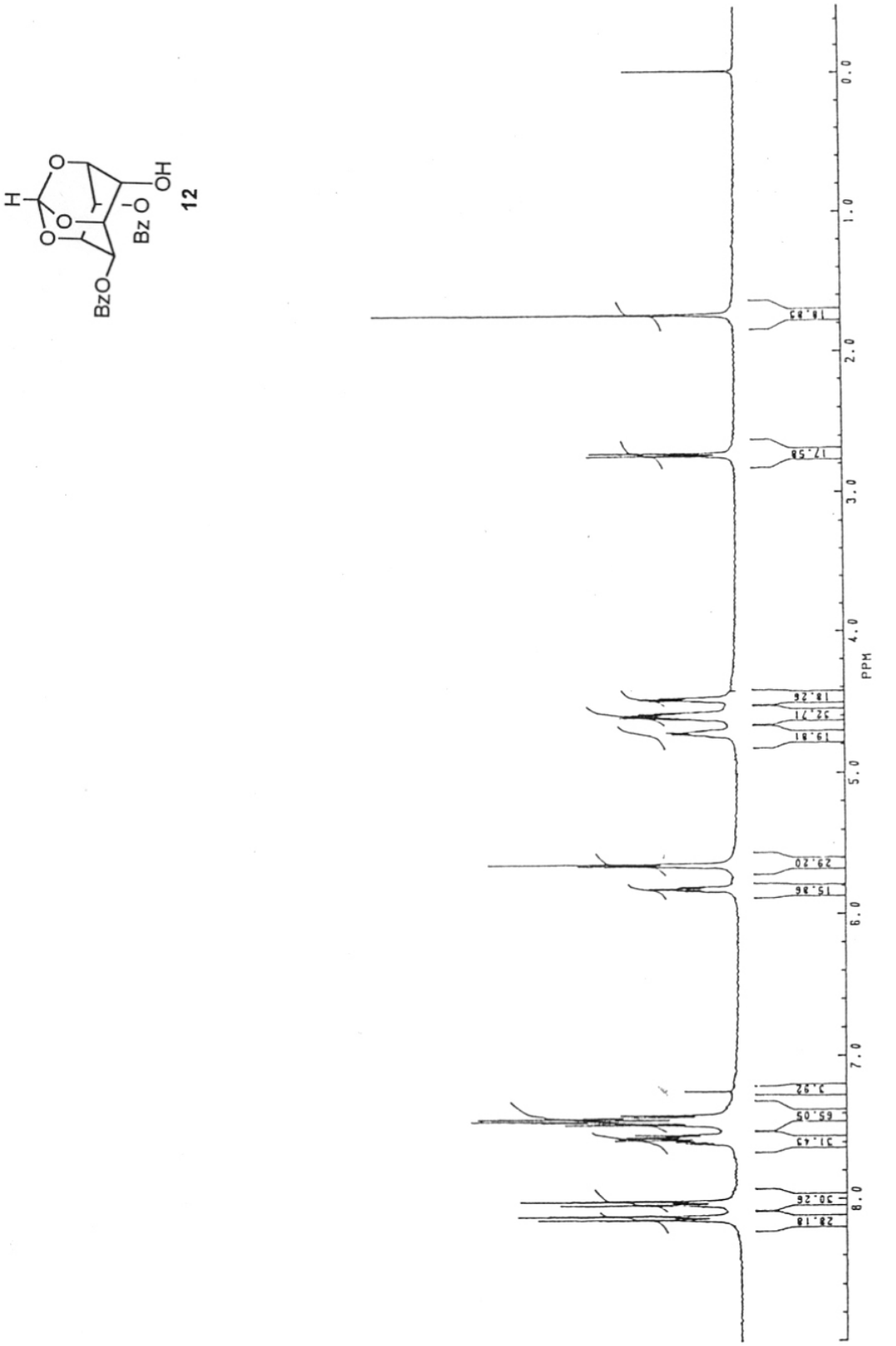
H
O
61.02
11.75
79.62
21.14
21.11
20.67
106.94
20.89
17.71
42.92
21.18
40.00
PPM

Figure 5


H
O
O
O
OH
Bz O
BzO
12
PPM
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1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
16.83
17.58
18.26
32.71
19.81
29.20
15.86
3.92
65.05
31.43
30.26
28.18

Figure 6

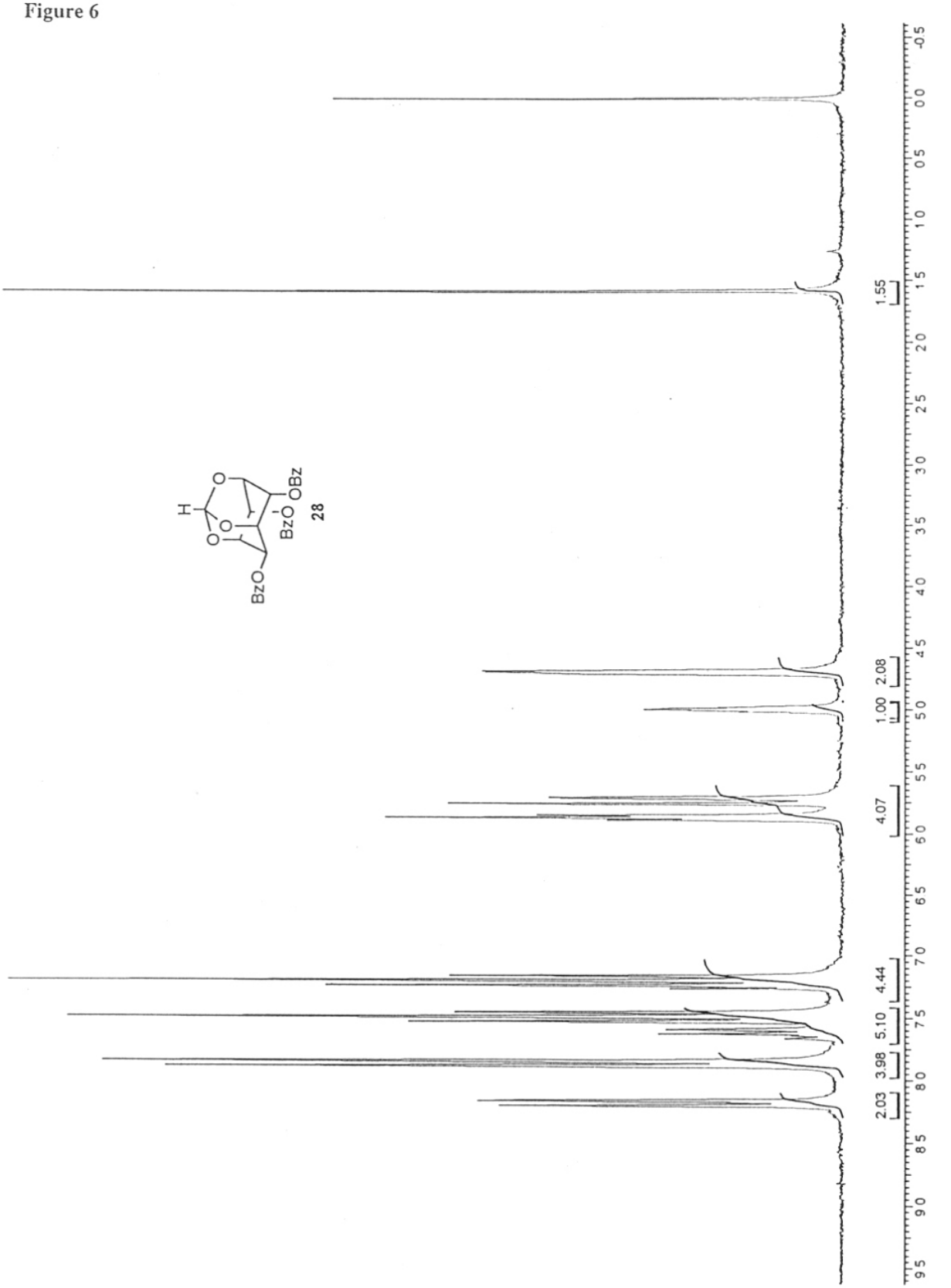
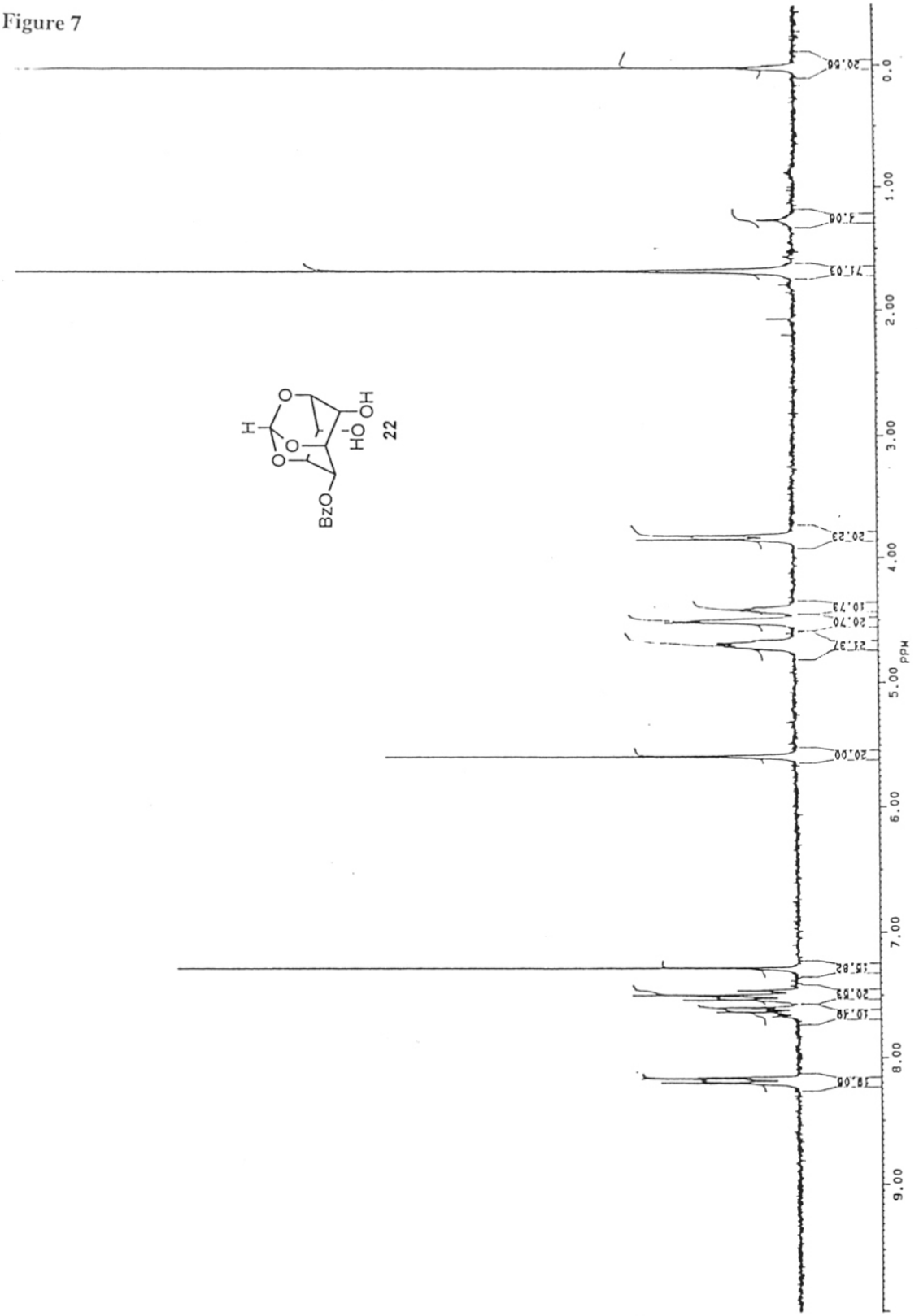


Figure 7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7.03
20.23
10.73
20.70
25.97
20.00
15.82
20.03
10.49
18.08
0.0
1.00
2.00
3.00
4.00
5.00
6.00
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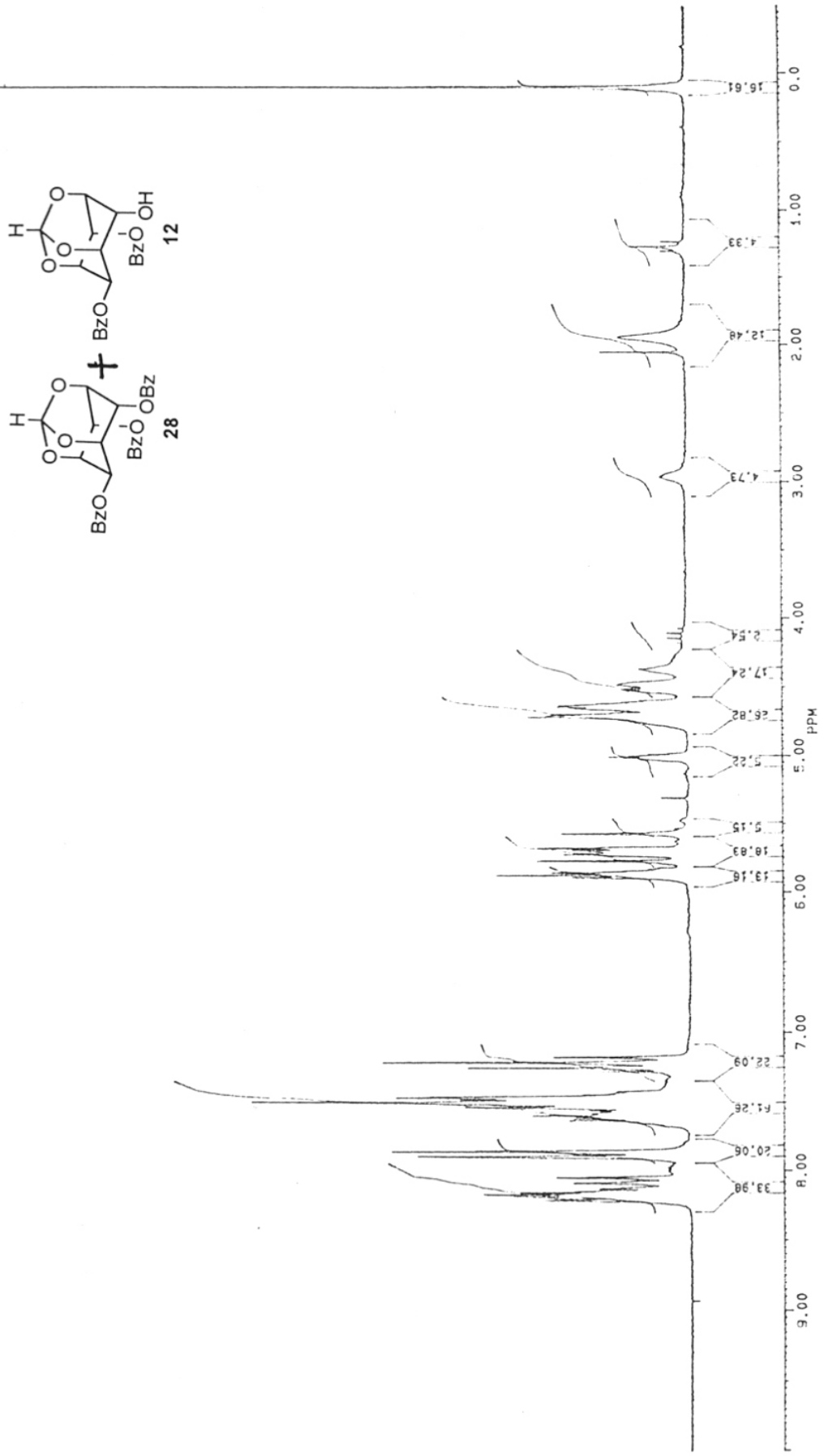
8.00
9.00
PPM
H
O
O
O
HO
OH
BzO
22

Figure 8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+
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OBz
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26.82
5.22
5.15
10.83
13.16
22.09
41.26
20.06
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7.00
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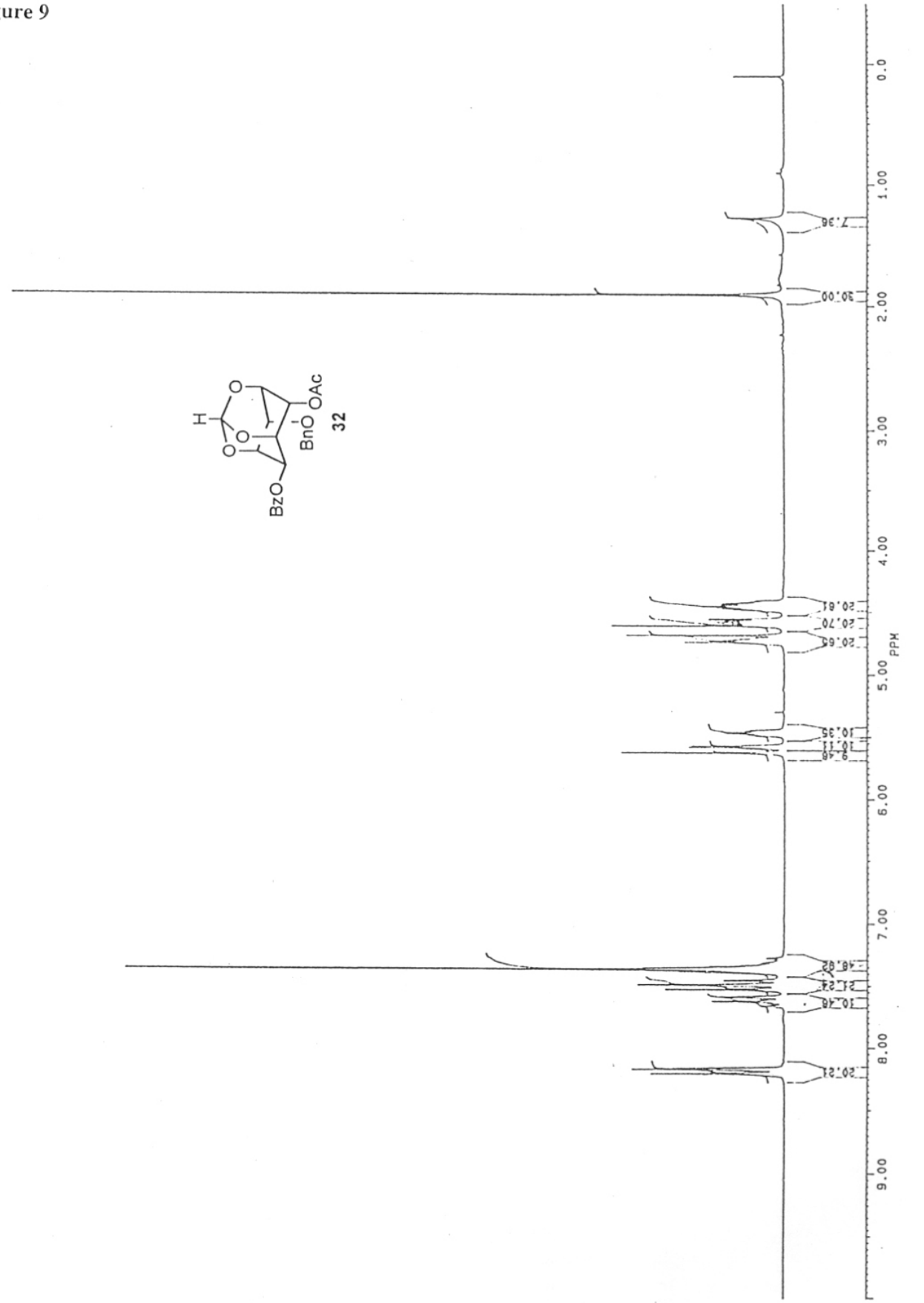
9.00
PPM

Figure 9



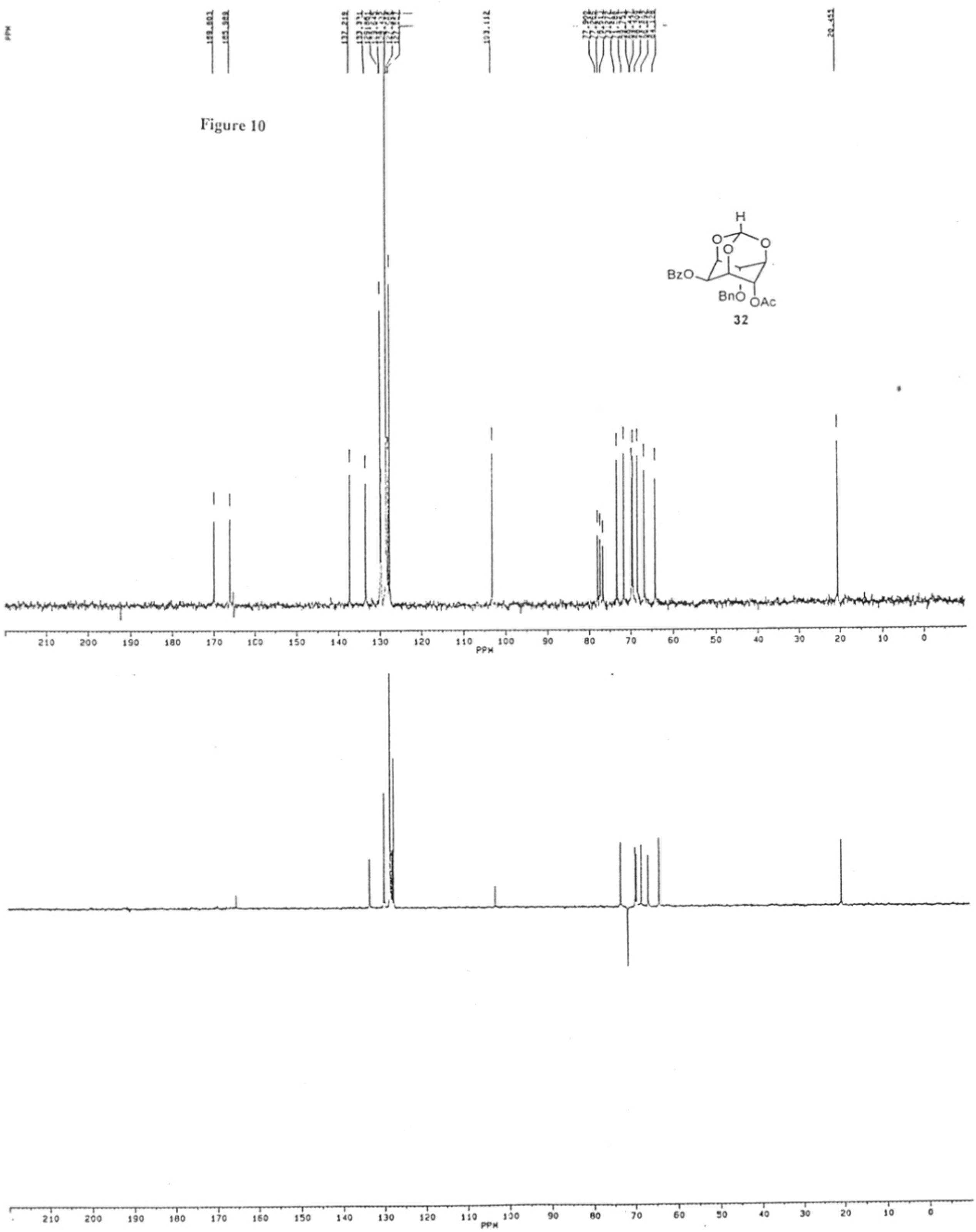
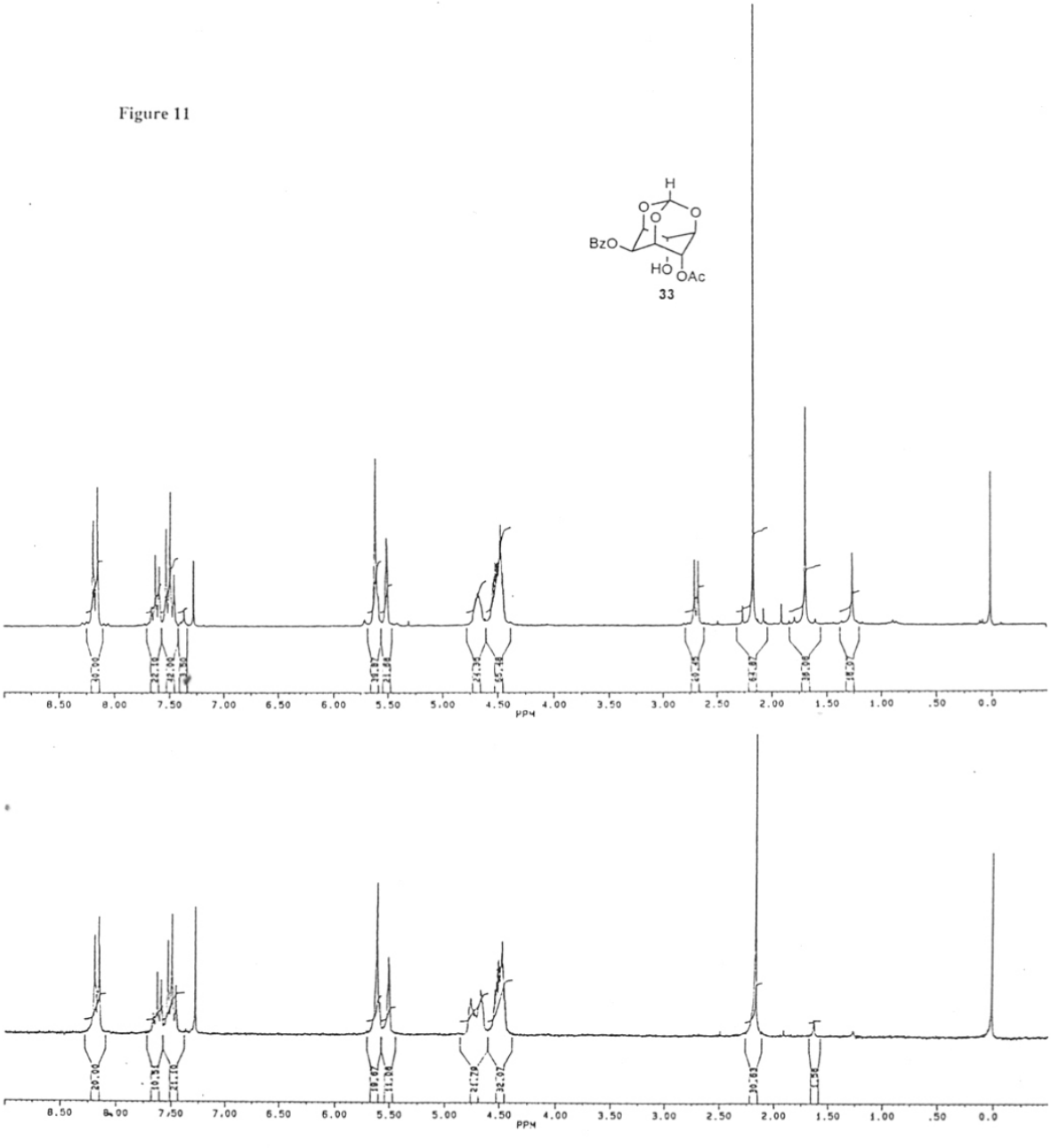


Figure 10

32

Figure 11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BzO
HO
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7.50
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6.00
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5.00
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3.50
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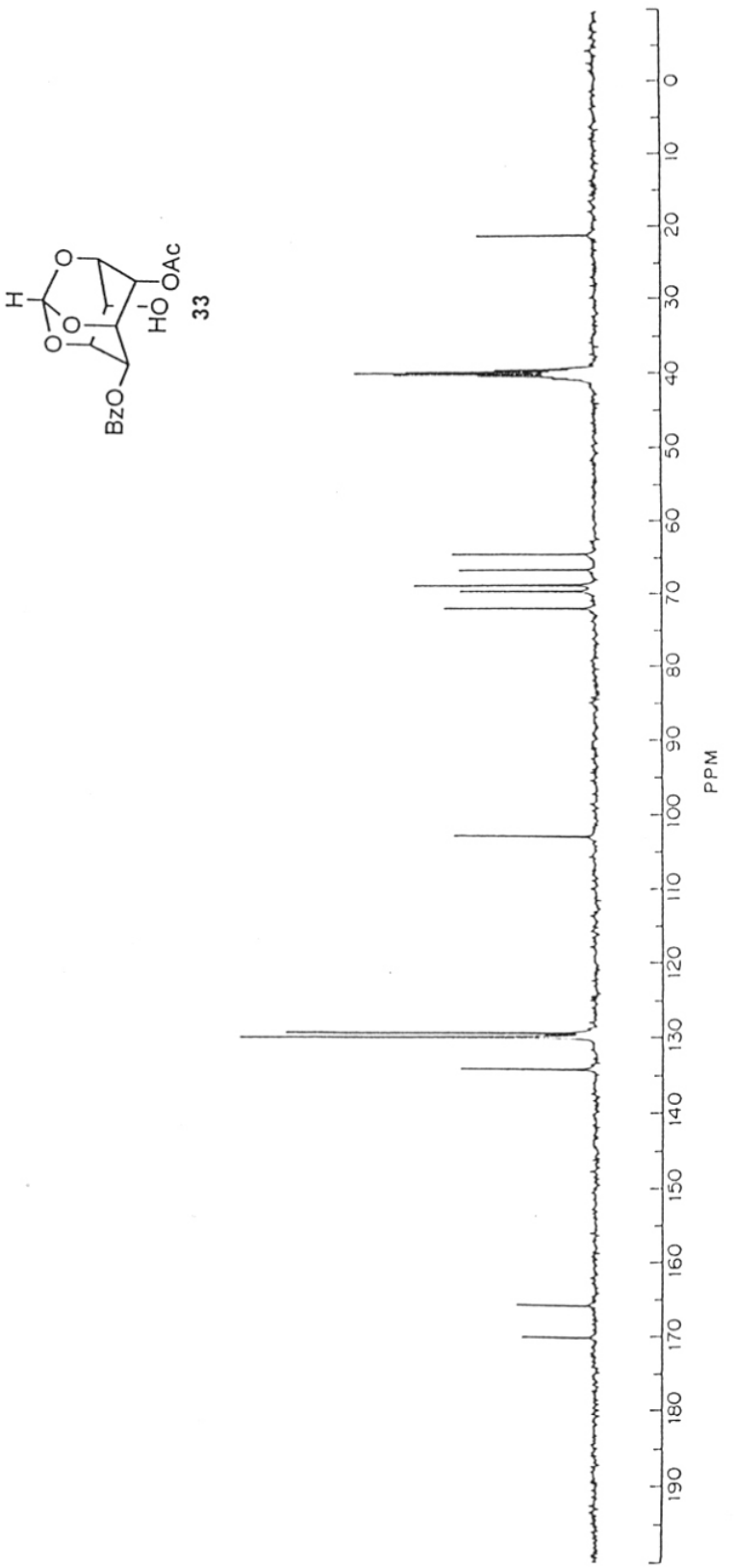
2.50
2.00
1.50
1.00
.50
0.0
PPM

Figure 12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O
O
O
HO
OAc
BzO
33
0
10
20
30
40
50
60
70
80
90
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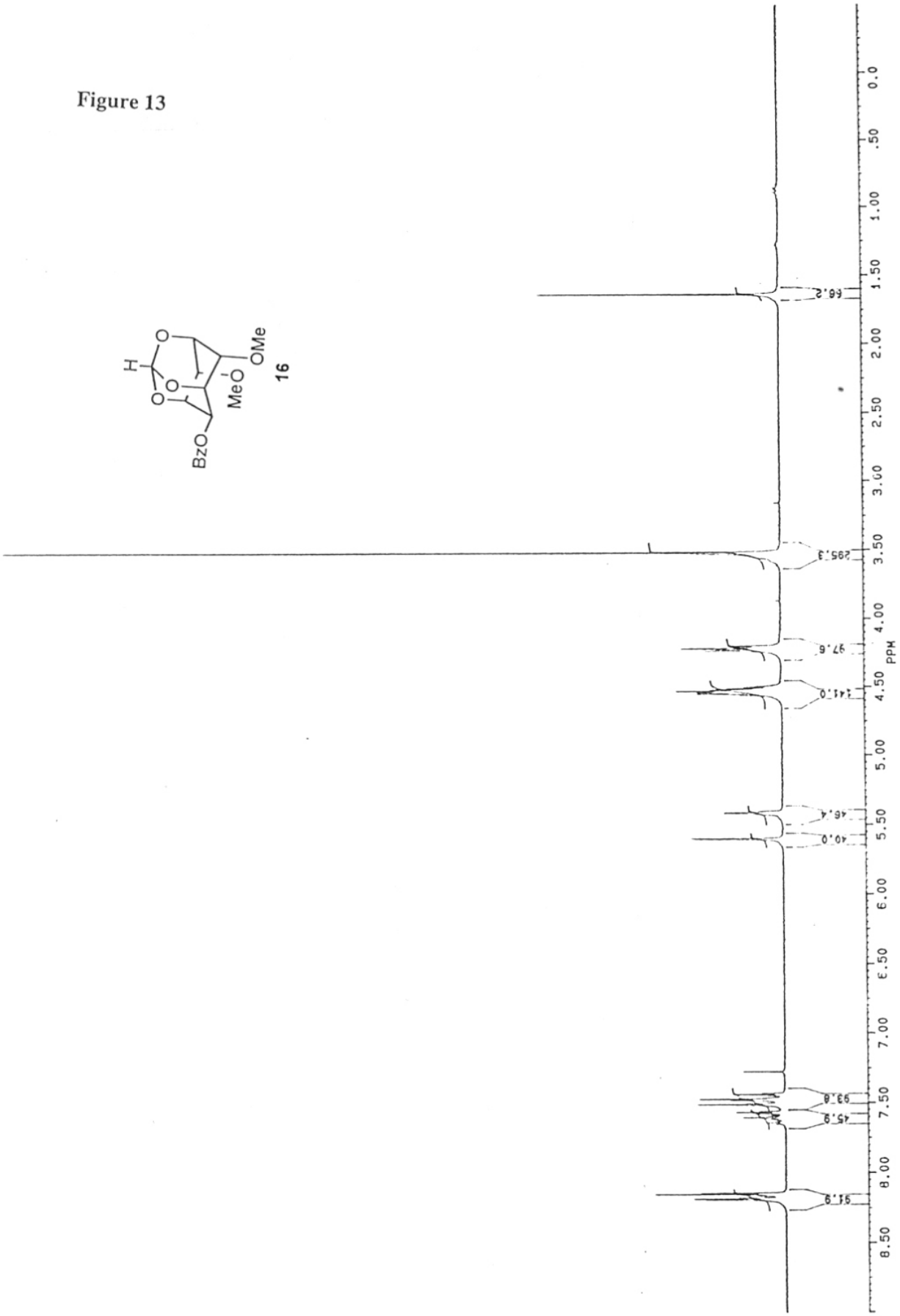
130
140
150
160
170
180
190
PPM

Figure 13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O
O
O
MeO
OMe
BzO
16
66.2
295.3
97.6
241.0
46.4
40.0
93.8
45.9
91.9
PPM
0.0
.50
1.00
1.50
2.00
2.50
3.00
3.50
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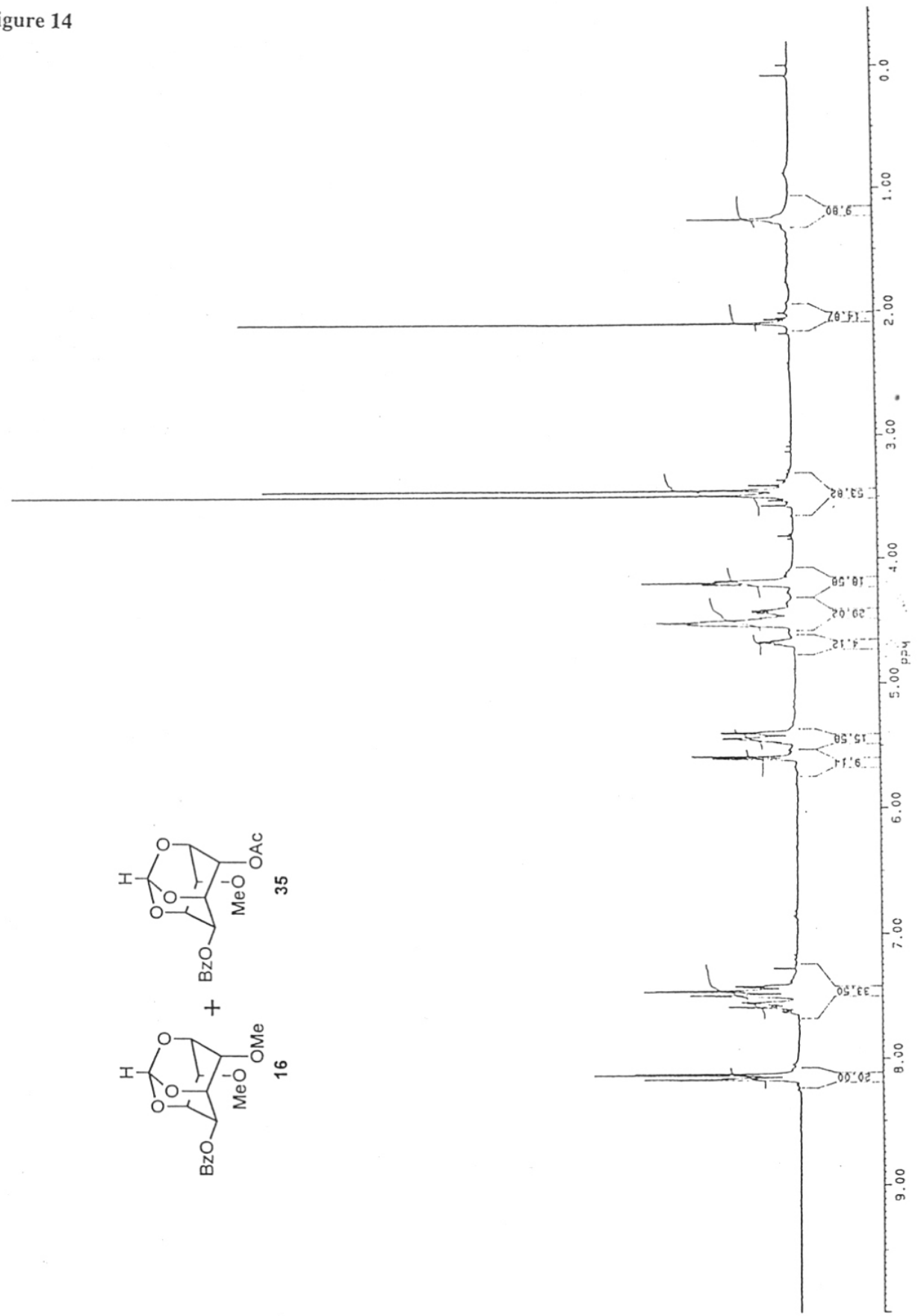
5.00
5.50
6.00
6.50
7.00
7.50
8.00
8.50

Figure 14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O
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BzO
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+
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O
O
BzO
MeO
OMe
16
9.80
14.07
53.82
18.58
29.02
4.12
15.58
9.14
33.50
20.00
0.0
1.00
2.00
3.00
4.00
5.00
6.00
7.00
8.00
9.00
ppm

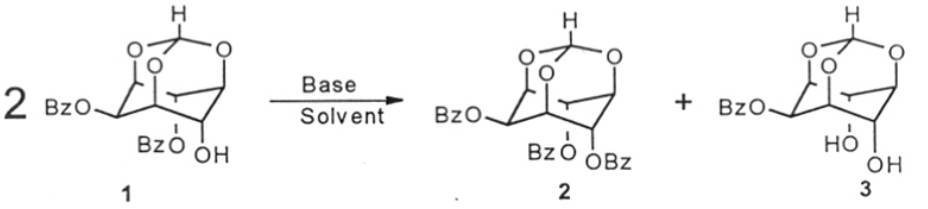
CHAPTER 3

Inter molecular acyl transfer in (±)-2,4-di-*O*-benzoyl-*myo*-inositol 1,3,5-Orthoformate in the solid state

3.1 Introduction

The transesterification reaction of the dibenzoate **1** observed during its alkylation in the presence of silver (I) oxide (**Chapter 2**) occurred with facility in the presence of a variety of bases including sodium carbonate, silver carbonate etc. which are insoluble in organic solvents (see **Chapter 4**). We had also observed that the dibenzoate **1** underwent transesterification in non-polar solvents (in which it was sparingly soluble) as well as a suspension in pyridine/DMF mixture. The latter was realized during the preparation of the dibenzoate **1** starting from *myo*-inositol where in the reaction mixture was stored for several hours for the precipitation of the dibenzoate **1**. We observed formation of the tribenzoate **2** and the diol **3** (by TLC) during concentration of the reaction mixture, which resulted in the precipitation of the dibenzoate **1** (**Scheme 3.1**). Hence we suspected that the dibenzoate **1** could be

Scheme 3.1



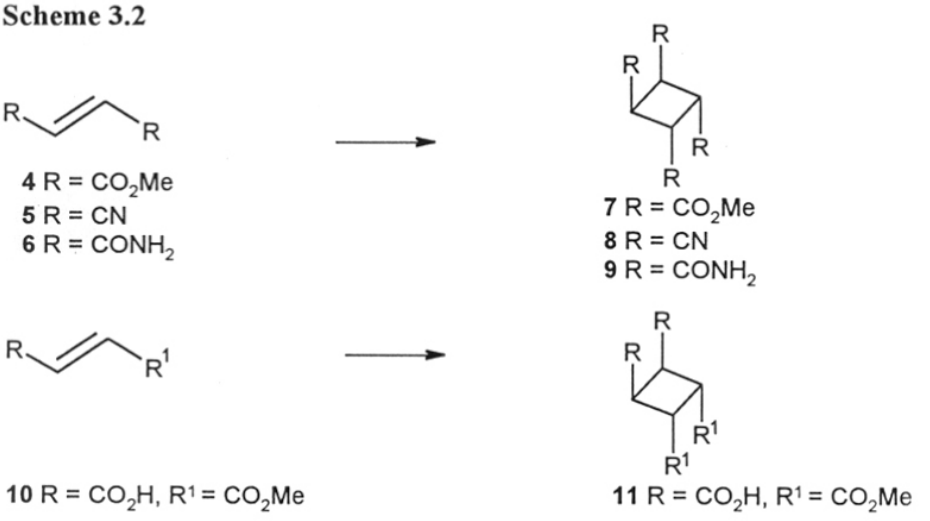
1 **2** **3**

undergoing transesterification to give the tribenzoate **2** and the diol **3** in the solid state (i.e. suspension in pyridine/DMF mixture). These experimental observations lead us to investigate the solid state reactivity of the dibenzoate **1**, especially since occurrence of organic reactions in the solid state are only rarely encountered (see below).

Some interesting and well studied examples of geometrically or topochemically controlled reactions are observed in the solid state where the crystal lattice serves to predispose the reactants in a favourable orientation for the reaction and thereby achieve selectivities often not possible in solution.[1-9] Crystal packing forces can lower the entropy of activation of a reaction by either constraining the molecular conformation leading to a unimolecular reaction or fixing the relative orientation of the sites in the crystal matrix facilitating intermolecular processes. However, most of the intermolecular reactions known in the literature involved the dimerisation of olefinic bonds, mainly because of the higher chances of observing the proper orientations of

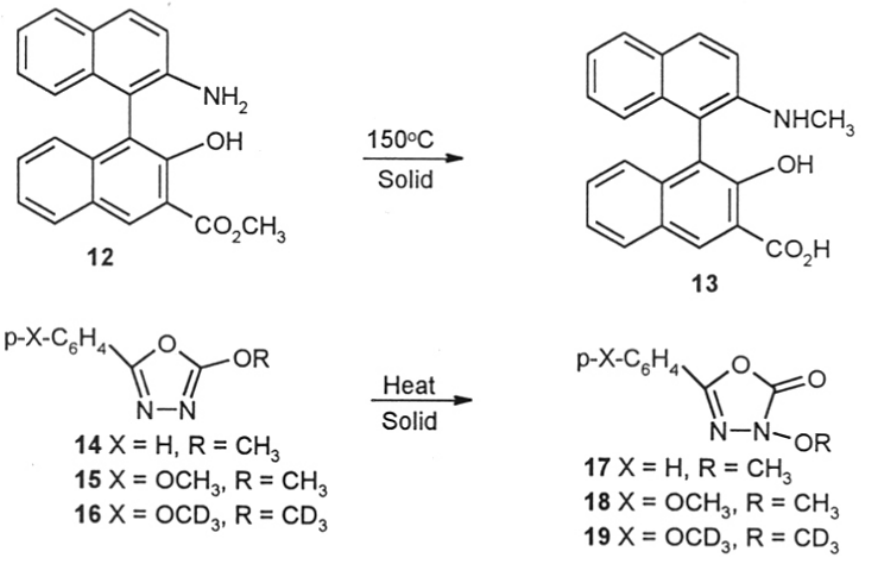
double bonds by stacking of the molecules.[10-11] Few examples from literature are shown in **Scheme 3.2**

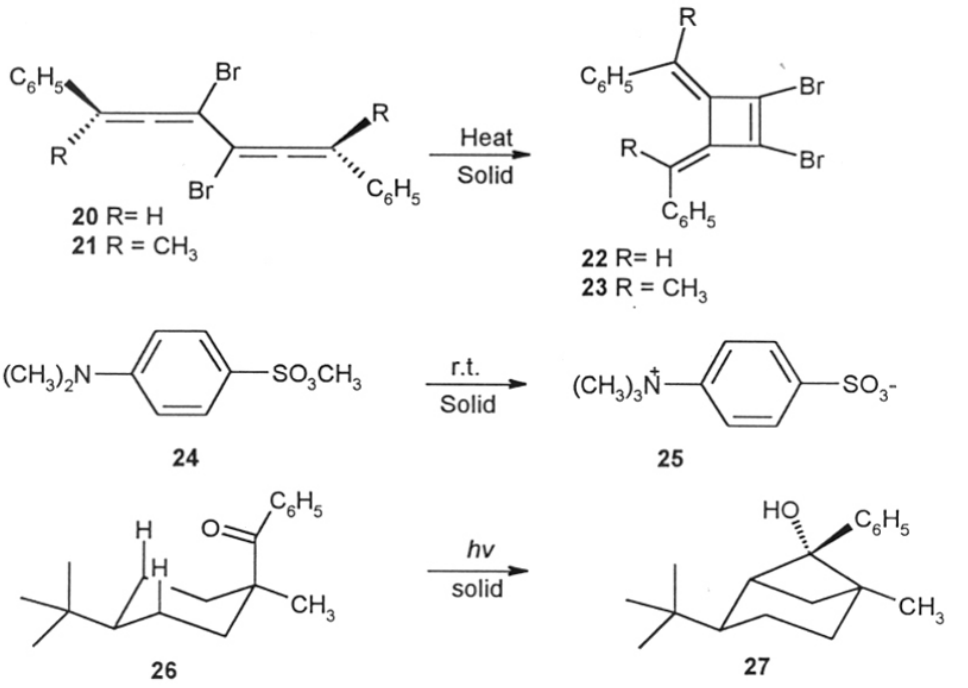
Scheme 3.2



Other types of reactions involving different chemical entities are rarely encountered[12-17] since weak interactions between prospective functional groups become overwhelmed by numerous other interactions (like hydrogen bonding) in the crystal lattice positioning them away from each other. Some examples of reactions occurring in the solid state are shown in **Scheme 3.3**. In most of the examples, the reactivity pattern observed in the solid state could be explained based on their crystal structures.

Scheme 3.3





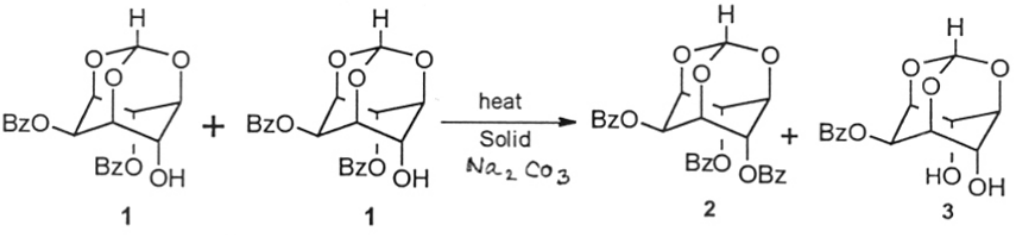
In all examples reactivity pattern observed in solution were completely different from that observed in the solid state.

3.2 Results and discussion

3.2.1Transesterification of the dibenzoate 1 in the solid state

The dibenzoate **1**, when heated with sodium carbonate at 140°C for 60 h gave the tribenzoate **2** and the diol **3** in 47% and 49% yields respectively which add to a total yield of 96% (**Scheme 3.4**). Both the products were characterized by comparison (TLC,

Scheme 3.4

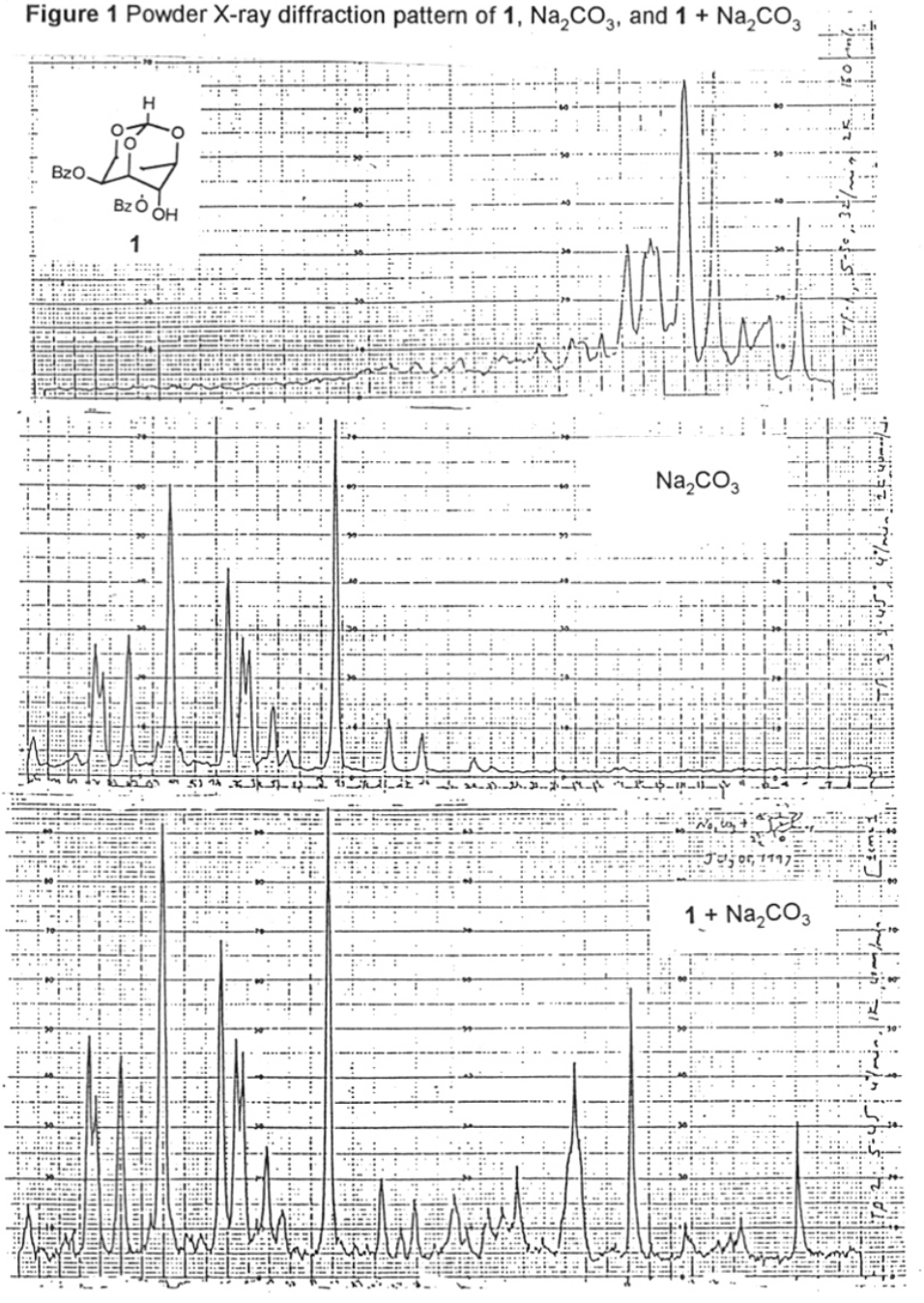


m.p. IR and NMR spectroscopy) with authentic samples.[18] Since this is a disproportionation reaction the maximum yield of **2** and **3** obtainable is 50% each. There was no reaction when the dibenzoate **1** was heated in the absence of sodium

carbonate, and **1** could be recovered quantitatively. This control reaction clearly showed that the transesterification of **1** in the solid state needs catalysis by a base.

The melting points of starting dibenzoate **1** and the products **2** and **3** are 163-164, 216-218, and 210-213 °C respectively. All these melting points are well above the reaction temperature (140 °C), which clearly rules out the occurrence of transesterification of **1** in the molten state. We recorded the X-ray powder diffraction pattern for **1** and sodium carbonate as well as for the reaction mixture (see **Figure 1**).

Figure 1 Powder X-ray diffraction pattern of **1**, Na_2CO_3, and **1** + Na_2CO_3



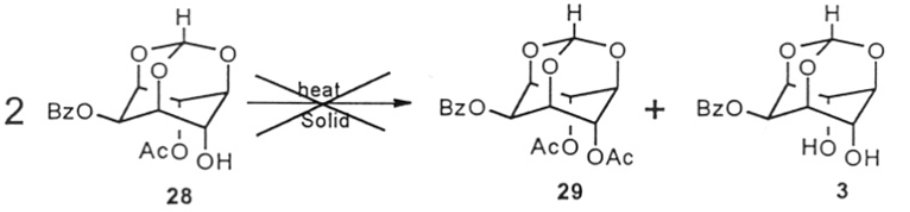
The diffraction pattern for the reaction mixture (**1** + Na_2CO_3) is just the superposition of the two reactants recorded separately. These results exclude the possibility of formation of a new phase on mixing and grinding **1** with sodium carbonate. Transesterification of **1** could also be carried out under microwave conditions where the reaction time was substantially reduced.[19-20] The dibenzoate **1** when mixed with sodium carbonate and irradiated with microwaves for 25 minutes, yielded the tribenzoate **2** in 46% yield along with the diol **3** (45%). Results of transesterification of the dibenzoate **1** in the solid state are summarized in **Table 3.1**.

Table 3.1 Transesterification of the dibenzoate **1** in the solid state

Entry	temperature	products(yield%)
1	140 °C	**2**(47), **3**(49), **1**(0)
2	120 °C	**2**(31), **3**(30), **1**(38)
3	100 °C	**2**(19), **3**(19), **1**(58)
4	80 °C	**2**(10), **3**(10), **1**(78)
5	microwave (25 min)	**2**(46), **3**(45), **1**(0)

Since we had observed the facile transesterification of the acetate **28** during its alkylation (**Chapter 2**) we were curious to see if it reacted in the solid state. The acetate **28** (m.p. 198 °C) decomposed on heating (at 140 °C) in the presence of sodium carbonate, and no transesterified product could be isolated (**Scheme 3.5**). Since the

Scheme 3.5



28 **29** **3**

expected product, diacetate **29**, has a melting point of 142-143 °C, to rule out the possibility of decomposition of **29** after the reaction, we carried out transesterification of **1** as well as **28** at lower temperatures. A comparison of the results presented in **Table**

3.1 and **Table 3.2** clearly show that the acetate **28** is unreactive in the solid state while the dibenzoate **1** undergoes facile transesterification. Acetate **28** on irradiation under microwaves also failed to undergo transesterification and 80% of the starting material could be recovered.

Table 3.2 Transesterification of the acetate **28** in solid state

Entry	temperature	products(yield%)
1	140 °C	Decomposed
2	120 °C	**28**(65)
3	100 °C	**28**(90)
4	80 °C	**28**(95)
5	microwave (25 min)	**28**(80)

The benzoate **1** as well as the acetate **2** underwent transesterification in refluxing acetonitrile solution (24 h), in the presence of diisopropylethylamine, to yield 26% and 29% of triesters **2** and **29**, respectively. This reaction in solution is likely to proceed by the intramolecular catalytic assistance provided by the axial hydroxyl group, as has been shown in the base catalyzed methanolysis of **1**.[21] In spite of both **1** and **28** having a free axial hydroxyl group it is only the benzoate **1** that undergoes the facile reaction in the solid state, suggesting that the proper orientation of the reacting functional moieties (reduction in the entropy of activation), rather than the catalytic assistance by the axial hydroxyl group that is important for the reaction in the solid state. An explanation for the difference in the reactivity in the solid state can be sought in terms of the crystal structures of the two compounds (**Figure 2** and **Figure 3**).

The principle of structure correlation[22-24] has been used to map the reaction pathway for the addition of a nucleophile, Nu (amino or hydroxyl) to a carbonyl group.[25-28] This method attempts the extraction of dynamics pertaining to a chemical reaction information from crystallographic data. A study on the molecules of the type **30-33**[28] (**Scheme 3.6**) where the electrophile (carbonyl group) and the nucleophile (amino group) have transannular relation helped to arrive at conditions for the addition of a nucleophile to an electrophile. The compounds **30** to **33** show N...C=O distances

Figure 2 ORTEP diagram of **1**

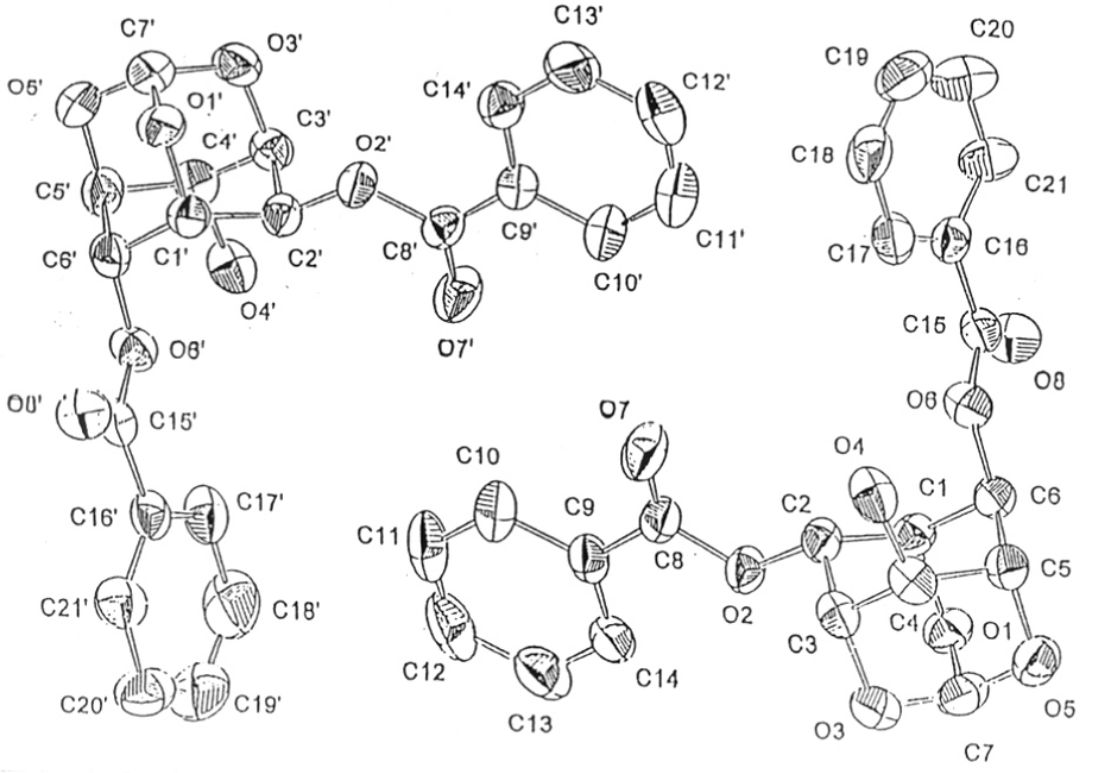
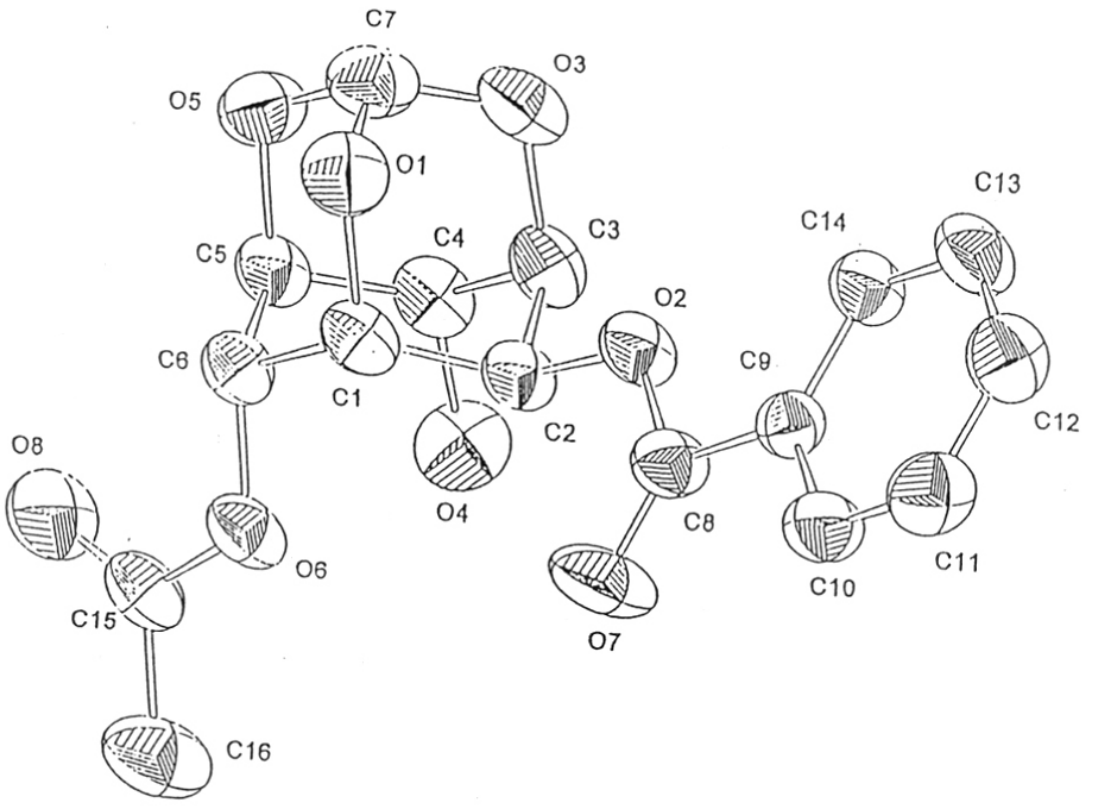
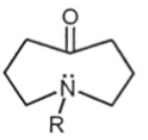


Figure 3 ORTEP diagram of **28**

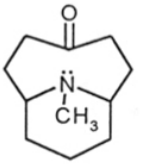


Scheme 3.6

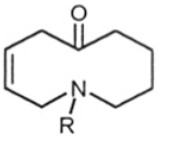


R = CH_3, *p*-CH_3-C_6H_4

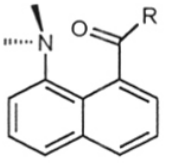
30



31



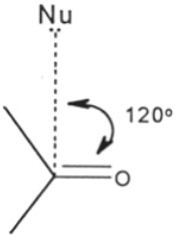
32



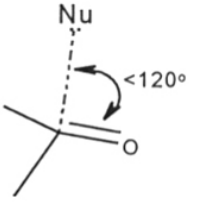
33

ranging from ~3A° to 15A° and a C=O group that deviates markedly from the usual coplanar geometry; a decrease in N...C=O distance was accompanied by an increase in the nonplanarity of the carbonyl carbon and slight lengthening of the C=O distance. Furthermore the approach of the nucleophile is not perpendicular to the C=O plane, but at an angle of about 105°. These data from the crystal structure can be extended to arrive at mechanism for the addition of a nucleophile to the carbonyl carbon. At distances close to or below the sum of the Van der Waals radii of Nu and C, the Nu...C=O angle was observed to be nearly constant at 110°. Hence the mechanism of addition of a nucleophile to carbonyl carbon (as predicted by the principle of structure correlation) can be shown as in **Scheme 3.7**

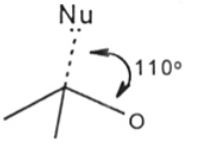
Scheme 3.7



Nucleophile at infinity
Planar sp^2 C
Angle Nu...C=O = 120°



Approach of Nu:, Deviation from planar sp^2 C, decrease in angle



Ideal situation for the addition of nucleophile to crbonyl carbon: Tetrahedral intermediate

In the crystal of **1** the hydroxyl group is at ~ 3.2 A° from the carbonyl carbon atom of the benzoyl group of a symmetry-related molecule, such that the O...C=O angle is ~ 90° (**Table 3.3** and **Figure 2**). Moreover, the X-O...C angles (involving the two atoms, X bonded to O4) are close to the tetrahedral value indicating that the sp^3 lone pair on the hydroxyl group is oriented close to being perpendicular to the carbonyl group. This relative orientation of the two groups 'frozen-in' along the reaction pathway

is facilitated by the attractive nature of the nucleophile-electrophile interaction and has also been observed in macromolecular structures.[29-30] An additional hydrogen bond between the two molecules (**Figure 4**), again reminiscent of what is observed between the protein and the substrate in the active site of enzymes [31,32] helps to maintain the right geometry. As a result, on heating the crystals of **1** with a base the reaction is driven to completion along the right pathway.

Figure 4: Two crystallographic symmetry related molecules of **1** held together by hydrogen bonding.

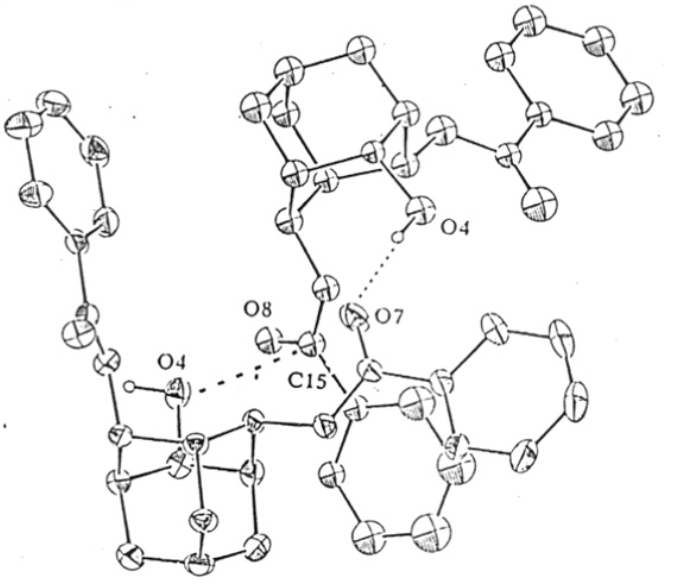


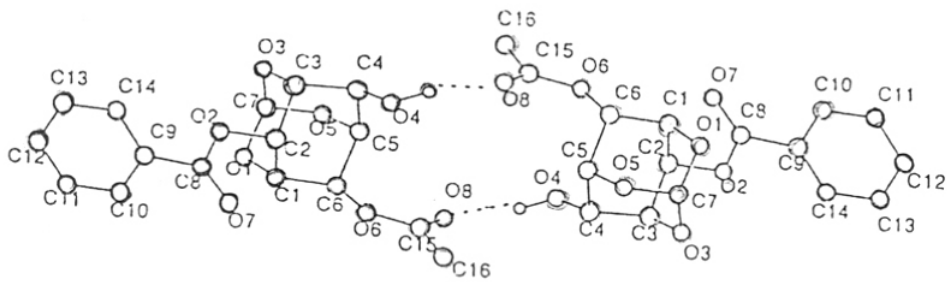
Table 3.3 Distances (A°) and angles (°) involving intermolecular O...C=O interactions in the crystal structures of **1** (both the molecules) and **28**[* **]

	1		**28**	**28***
O4...C15	3.226	3.249	3.748	3.320
O4...C15-O8	88.1	89.9	33.1	98.9
C4-O4...C15	117.5	113.1	96.0	96.8
H(O4)-O4...C15	113.1	110.0	13.7	91.0

** The hydroxyl group (O4) is provided by the molecule at x,y,z, and the carbonyl group [>C15=O8] comes from the positions 1 - x, 1/2 + y, 1/2 - z and 2 - x, -1/2 + y, 1/2 - z for the two molecules in the asymmetric unit for **1** and 2 - x, 1 - y, 2 - z for **2**. *Intramolecular interaction.

The hydroxyl and the carbonyl groups in a crystal of **28** are involved in intermolecular hydrogen bonding and the geometry is not conducive for an electrophile-nucleophile interaction (**Figure 5**). The large relative movement required to achieve the

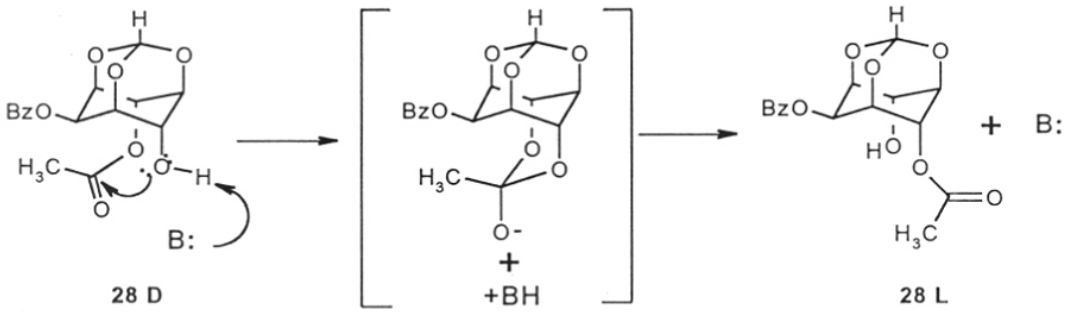
Figure 5: Two molecules of **28** related by a crystallographic inversion center and connected by hydrogen bonding (dashed lines) between the hydroxyl and the carbonyl groups.



proper orientation is opposed by various lattice contacts. Indeed, it is known since the pioneering work of Schmidt [33-35] that a solid state reaction is facile if it involves a minimum amount of atomic or molecular movement. Consequently, the transesterification reaction in crystals of **28** cannot proceed. However, the intramolecular O4...C15=O8 geometry in **28** is quite amenable for an elctrophile-nucleophile interaction; (see **Table 3.3**, column 5) nonetheless, since **28** is racemic this does not lead to a new product.

We attempted to examine this intramolecular acyl transfer in **28** (**Scheme 3.8**) by differential scanning calorimetry, since we thought that any heat change due to a reaction in the solid state would be detectable. However, preliminary results of such experiments (**Figure 6**, see experimental section) were inconclusive. It could however,

Scheme 3.8



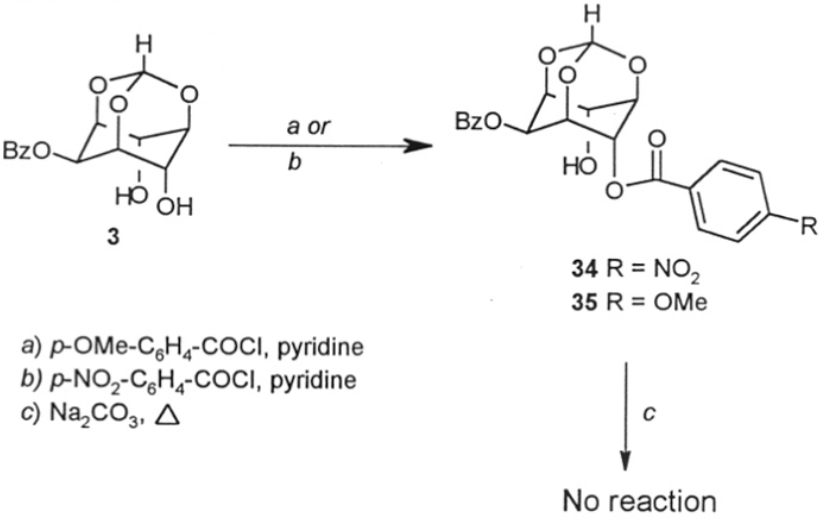
be suggested that occurrence of intramolecular acyl transfer in **28** may be demonstrated by using optically active (D or L) **28** as the starting material. In this case, intramolecular acyl transfer would result in the formation of its enantiomer, perhaps leading to racemization.

In most cases, solid state reactions do not proceed quantitatively, mainly due to the gradual collapse of the crystal lattice as the reaction progresses, which eventually destroys the favourable arrangement of reacting molecules. High yields are attained only if the product is isostructural with the starting material (so that the crystal lattice does not collapse) or due to kinetic factors, *i.e.* if the reaction occurs at high rate as a domino process in symmetry-related chains. To determine if any of these factors played a key role in the transesterification of **1** we compared the crystal structures of the products **2**[36] and **3**[37] (**Figure 7**, see experimental section) with that of the starting dibenzoate **1**. Summary of crystal data, data collection, structure solution and refinement details for **3** are given in the experimental section for comparison (**Table 3.4** and **Table 3.5**, see experimental section). It is obvious that products **2** and **3** have crystal structures quite different from that of the starting material **1**. Hence the high yield of the reaction observed may be due to the fact that the two molecules of **1** (providing the two reactive groups) are held together tightly (as discussed earlier) by nucleophile-electrophile interaction as well as hydrogen bonding.

3.2.2 Preparation and the attempted solid state transesterification of other 2,4-di-*O*-acyl *myo*-inositol 1,3,5-orthoformate derivatives.

A few other 2.4-di-*O*-acyl derivatives were prepared to examine the reactivity in the solid state. The p-nitro derivative **34,** and the p-methoxy derivative **35** could be prepared by the direct acylation of the diol[36] **3** (**Scheme 3.9**) using the corresponding acid chlorides (for details, see experimental section).

Scheme 3.9



34 and **35** on grinding and heating with sodium carbonate at 140°C, 120°C and 100°C did not under go transesterification and only the starting material could be isolated from the reaction mixture. The recovery of starting material was not quantitative which indicates that some amount of the compound may have decomposed.

3.3 Conclusions

There are only a few known examples of intermolecular reaction (usually methyl-transfer) brought about in the crystalline state.[12-16] Hence the results on the transesterification of the dibenzoate **1** in the solid state presented in this chapter adds valuable data to the library of organic solid state reactions. The reaction reported here involves the substrate **1** and the catalyst (Na_2CO_3) in two solid phases. This indicates that the catalysis occurs at or near the surface of the substrate crystals, and this provides an example showing how the crystal packing (i.e., the interactions in the bulk) can be a controlling factor for a reaction occurring at or near the solid surface. In the crystal, two screw-axis related neighbors of **1** are optimally arranged for the nucleophilic attack by a hydroxyl group to a carbonyl carbon. As the reaction (addition of a nucleophile to carbonyl carbon) is quite ubiquitous in nature - being used by serine proteases, lipases, as well as many hydrolases and transferases[38,39] - the geometry of alignment between the reactive groups found here provides a realistic model of what goes on in the enzyme active site.

3.4 Experimental section.

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

p-Nitrobenzoyl chloride, *p*-methoxy benzoic acid, TBDMSCl and p-bromo benzoic acid were obtained from Aldrich chemical Company, USA. Triethyl amine, sodium iodide and thionyl chloride were obtained from S.D. Fine Chemicals, India. The microwave reactions were carried out in BPL-Sanyo microwave oven at a power of 400 watts.

Transesterification of the dibenzoate 1 in the solid state. The dibenzoate **1** (0.100g, 0.25 mmol) and sodium carbonate (0.212g, 2.0 mmol) were ground together using a pestle and mortar and the resulting mixture was heated at 140° C in an atmosphere of argon for 60h. The solid obtained after the reaction was cooled to ambient temperature and extracted with chloroform followed by methanol. The combined organic extract was evaporated *in vacuo*, the products **2** (0.06g, 47%) and **3** (0.036g, 49%) were isolated by column chromatography over silica gel (eluent: ethyl acetate – light petroleum, gradient elution) and characterized by comparison (TLC, m.p., IR and NMR spectra) with authentic samples. mp.of **2** 216-218° C, lit.[8] 216-218° C. mp. of **3** 210-213° C, lit.[8] 210° C. IR and NMR spectra were identical to those reported in literature.

Transesterification of **1** was also carried out at 120° C (0.100g, 0.25 mmol), 100° C (0.100g, 0.25 mmol) and 80 ° C(0.100g, 0.25 mmol) as above. The yield of **2** and **3** obtained (after heating for 60h.) respectively were, at 120°C: 31% (0.039g) and 30% (0.022g); 100°C: 19% (0.024g) 19% (0.014g). 80°C: 10% (0.01g) and 10% (0.01g).

Transesterification of the dibenzoate 1 in the solid state by microwave irradiation. Transesterification of **1** was also carried out (as above) using **1** (0.100g, 0.25 mmol) and sodium carbonate (0.212g, 2.0 mmol) by irradiating the reaction mixture in a microwave oven. Yield of the tribenzoate **3** obtained after irradiation for 25 min. was 46% (0.058g).

Transesterification of the acetate 28 in the solid state. The acetate **28** (0.100g, 0.3 mmol) and sodium carbonate (0.254g, 2.4 mmol) were used for the reaction as described in the case of the dibenzoate **1**. Amount of starting material recovered at

140°C, 100 °C and 80 °C was 65% (0.065 g), 90% (0.090 g)and 95% ((0.095g) respectively.

Transesterification of the acetate 28 in the solid state by microwave irradiation.

Reaction of **28** (0.100g, 0.3 mmol) and sodium carbonate (0.254g, 2.4 mmol) by irradiation of microwave was carried out as in the case of dibenzoate **1**; 80% of the starting material was recovered

Transesterification in solution. The dibenzoate **1** (0.100g, 0.25 mmol) was dissolved in 1M diisopropylethylamine solution (2 ml) in dry acetonitrile and refluxed for 24h. The solvent was evaporated and the residue was chromatographed as above to obtain the tribenzoate **3** (0.033 g, 26%) and the diol **3** (0.019g, 26%).

Transesterification of the acetate **2** (0.129g, 0.37 mmol) in the presence of diisopropylethylamine was carried out as above (in 3ml solution) to obtain the diacetate **4** (0.040g, 29%) and the diol **3** (0.032g, 29%). The diacetate **4** was charaterized by comparison (TLC, m.p., IR and NMR spectra) with an authentic sample.[8]

(±)-2-*O*-benzoyl-4-*O*-(*p*-nitrobenzoyl)-*myo*-inositol 1,3,5-orthoformate (34). The diol **3** (0.5 g, 1.7 mmol) was taken in pyridine (4 mL) and cooled to 0 °C under argon atmosphere. A solution of p-nitrobenzoyl chloride (0.317 g, 1.7 mmol) in pyridine (6 mL) was added drop-wise over 30 min. and the reaction mixture was stirred overnight at ambient temperature. Pyridine was evaporated and the residue was taken in chloroform and worked up as usual. The solid obtained was purified by column chromatography over silica gel (24 g) using ethyl acetate - light petroleum as eluent. Fractions eluted with 20% ethyl acetate - light petroleum were combined and evaporated to obtain **34** (0.68 g, 90%).

m. p. 212 - 214 °C.

IR (cm^{-1}): 3420, 1700, 1725.

^1H NMR ($CDCl_3$+DMSO-d_6): δ 4.25 (m, 1H), 4.30 - 4.50 (m, 3H), 5.4 (d, 1H, D_2O exchangeable). 5.45 (d, 1H), 5.5 - 5.55 (m, 1H), 5.55 - 5.65 (m, 1 H), 7.25 - 7. 35 (m, 2H), 7.35 - 7.50 (m, 1H), 7.90 - 8.00 (m, 2H), 8.10 (s, 4H).

^{13}C NMR (DMSO-d_6): δ 64.29, 66.41, 68.57, 69.26, 69.44, 71.75, 102.58, 124.15, 129.07, 129.67, 131.16, 133.92, 135.02, 150.82, 163.58, 165.60.

Elemental Analysis calcd. for $C_{21}H_{17}O_{10}N$: C 56.88, H 3.84, N 3.16; Found: C 56.72, H 4.14, N 2.95.

(±)-2-*O*-benzoyl-4-*O*-(*p*-methoxy benzoyl)-*myo*-inositol 1,3,5-orthoformate (35). The diol **3** (0.294 g, 1mmol) was taken in pyridine (2 mL) and cooled to 0 °C under argon atmosphere. *p*-Methoxy benzoyl chloride (0.853g, 5 mmol) was added and the reaction mixture was stirred overnight at ambient temperature. Pyridine was evaporated and the residue was taken in chloroform and worked up as usual. The solid obtained was purified by column chromatography over silica gel (24 g) using ethyl acetate - light petroleum as eluent. Fractions eluted with 20% ethyl acetate - light petroleum were combined and evaporated to obtain **35** (0.340 g, 79%). .

m. p. 198 - 200 °C.

IR (cm^{-1}): 3420, 1705.

^1H NMR $CDCl_3$: δ 2.6 (d, 1H, D^2O exchangable), 3.9 (s, 3H), 4.45-4.8 (m, 4H), 5.7 (m, 2H), 5.8-5.9 (m, 1 H), 6.9-7.0 (m, 2H), 7.45-7.55 (m, 2H), 7.55–7.65 (m, 1H), 7.95-8.05 (2H, m) 8.15-8.25 (m, 2H).

Transesterification of the *p*-nitrobenzoate 34 in the solid state.

Transesterification of **34** (0.100g, 0.23 mmol) was carried out under identical conditions as described in the case of the dibenzoate **1**. Starting material was recovered (0.088g, 88%) after heating at 100 °C for 60 h.

Transesterification of **34** (0.100g, 0.23 mmol) was carried out under identical conditions as described in the case of the dibenzoate **1**. Starting material was recovered (0.092g, 92%) after heating at 80 °C for 60 h.

Transesterification of the *p*-methoxy benzoate 35 in the solid state.

Transesterification of **35** (0.100g, 0.24 mmol) was carried out under identical conditions as described in the case of the dibenzoate **1**. Starting material was recovered (0.090g, 90%) after heating at 80 °C for 60 h.

Transesterification of **35** (0.100g, 0.24 mmol) was carried out under identical conditions as described in the case of the dibenzoate **1**. Starting material was recovered (0.095g, 95%) after heating at 80 °C for 60 h.

X-ray crystallography. Crystal data for **1** and **2** are taken from ref. 37. **3** and **28** were crystallized from chloroform. Intensities of reflections to 2θ(Mo) = 47° were measured by $\omega/2\theta$ scan technique on a CAD-4 diffractometer. Structures were solved by using the program *SHELXS*86 and least-squares refinement on $|F^2|$ was carried out with *SHELXL*93. All the H atoms were located from the difference Fourier map and their isotropic temperature factors were kept fixed.

The crystal data for **3** and **28** are given in **Table 3.4** and **Table 3.5**.

Table 3.4. Summary of crystal data, data collection, structure solution, and refinement details.

	1	**28**
	(a) Crystal data	
formula	$C_{21}H_{18}O_8$	$C_{16}H_{16}O_8$
molar mass	398.36	336.29
colour, habit	colourless, prism	colourless, prism
crystal size, mm	0.30 x 0.30 x 0.70	0.83 x 0.75 x 0.40
crystal system	monoclinic	triclinic
a, Å	16.674(5)	8.370(2)
b, Å	9.822(2)	9.473(2)
c, Å	22.533(5)	9.755(3)
α, deg	90	101.29(2)
β, deg	90.70(2)	102.87(2)
γ, deg	90	90.46(2)
V, Å^3	3690(2)	738.4(3)
space group	$P2_1/c$	$P\,1$
Z	8	2
F(000)	1664	352
d_{calc}, g cm^{-3}	1.434	1.513
μ, mm^{-1}	0.111	0.123
	(b) Data acquisition	
temp. K	293(2)	293(2)
unit-cell reflecns	25(16.5-23)	25(14.3-21.8
(θ range, deg)		

max θ (deg) for reflcns	23.42	23.46
hkl range of reflcns	-18 18; 0 10; 0 25	-9 9; 0 10; -10 10
variation in three standard reflcns	< 1%	0.0%
reflcns measd	5432	2187
unique reflcns	5432	2187
reflcns with $I > 2\sigma(I)$	3423	1977

(c) Structure Solution and Refinement

refinement on	F^2	F^2
solution method	SHELXS-86	SHELXS-86
H-atom treatment	from Δ-map, not refined	from Δ-map, not refined
no. variables in L.S.	523	217
k in $w = 1/(\sigma^2 F_o^2 + k)$	$(0.0914P)^2 + 4.3008P$	$(0.0728P)^2 + 0.5070P$
$[P = (F_o^2 + 2F_c^2)/3]$	$4.3008P$	$0.5070P$
R, R_w, gof	0.060, 0.177, 1.068	0.047, 0.1296, 1.057
density range in final Δ-map, e Å^{-3}	-0.373, 0.327	-0.335, 0.225
final shift, error ratio	-0.001	-0.001
sec. extnct type	none	none

Table 3.5 Summary of crystal data, data collection, structure solution, and refinement details.

	3
(a) Crystal data	
formula	$C_{14}H_{14}O_7$
molar mass	294.45
colour, habit	colourless, prism
crystal size, mm	0.70 x 0.55 x 0.40
crystal system	monoclinic
a, Å	6.184(2)
b, Å	17.787(4)
c, Å	11.746(2)
β, deg	91.65(2)
V, Å^3	1291.5(6)
space group	$P2_1/n$
Z	4
F(000)	1664
d_{calc}, g cm^{-3}	1.513
μ, mm^{-1}	0.123
(b) Data acquisition	
temp. K	293(2)
unit-cell reflcns	
(θ range, deg)	
max θ (deg) for reflcns	25
hkl range of reflcns	-7 7; 0 21; 0 13

variation in three standard reflcns	
reflcns measd	2284
unique reflcns	2284
reflcns with $I > 2\sigma(I)$	1846

(c) Structure Solution and Refinement

refinement on	F^2
solution method	SHELXS-86
H-atom treatment	from Δ-map, not refined
k in $w = 1/[\sigma^2 F_o^2 + (0.1710P)+(0.2638P)$	
no. variables in L.S.	523
$[P = (F_o^2 + 2\,F_c^2)/3]$	
R, R_w, gof	0.060, 0.177, 1.068
density range in final Δ-map, e Å^{-3}	-0.373, 0.327
final shift, error ratio	-0.001
sec. extnct type	none

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Figure 7.ORTEP diagram of **3**

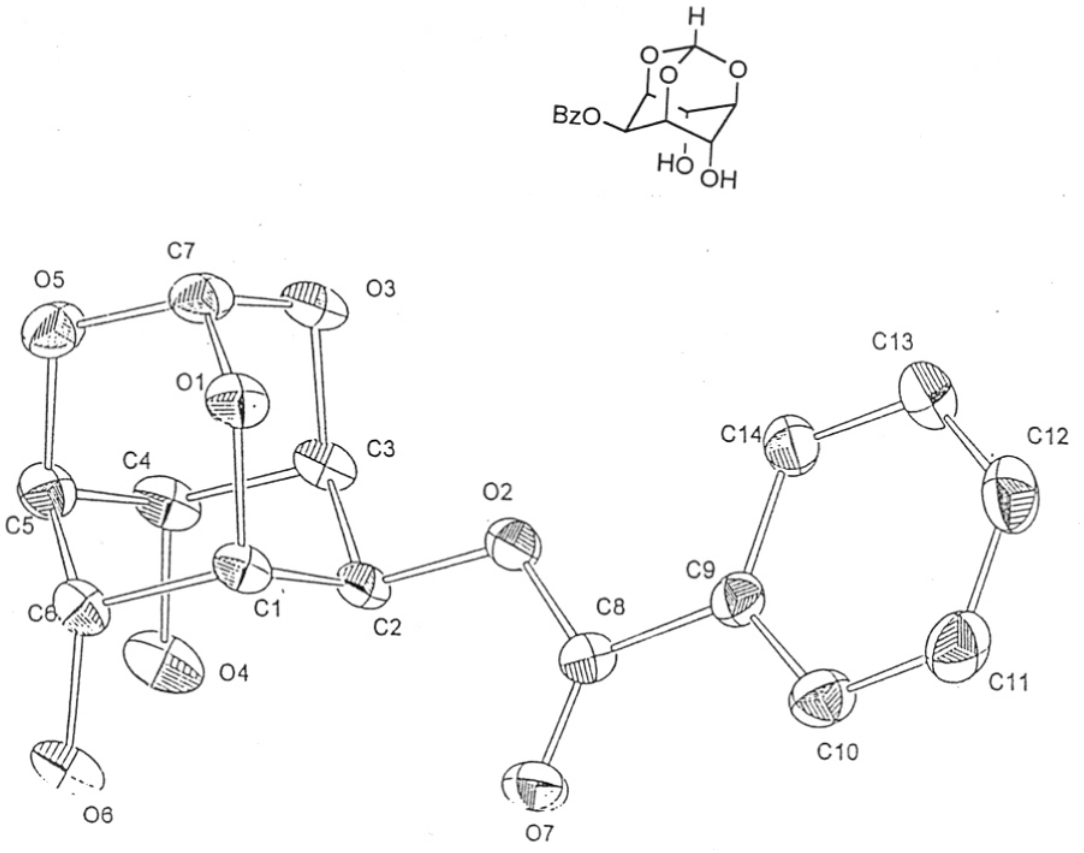


Figure 8

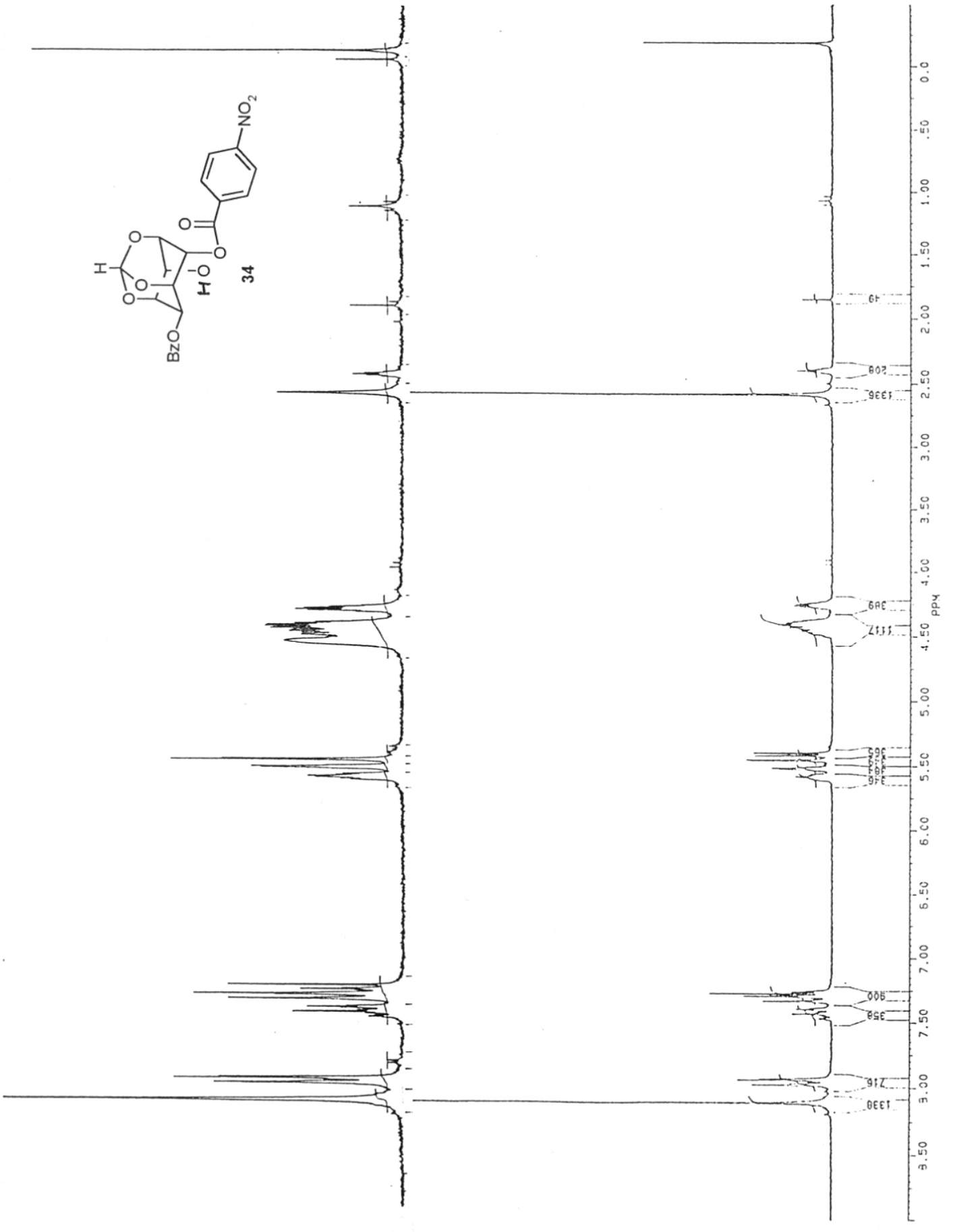


Figure 9

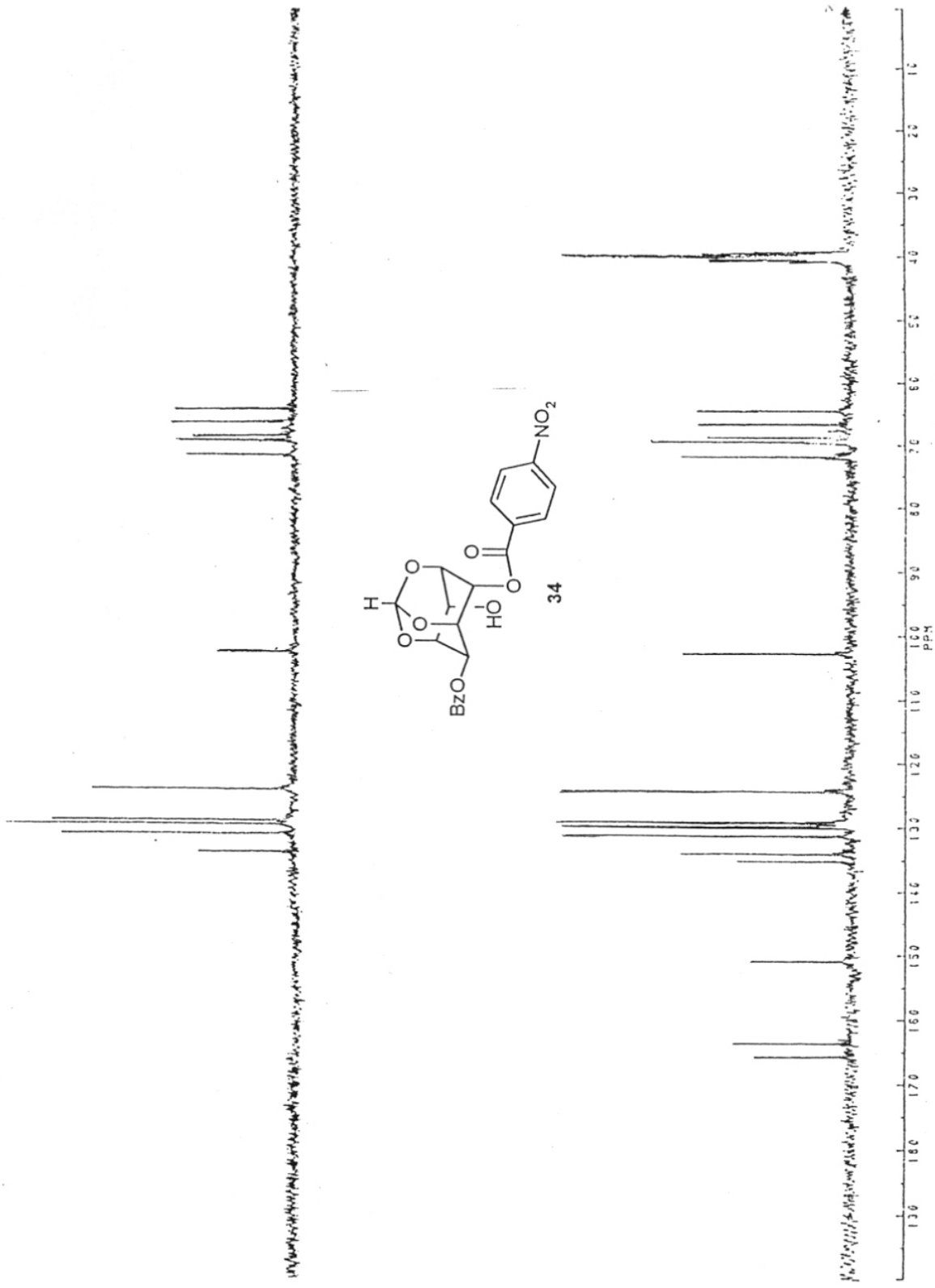
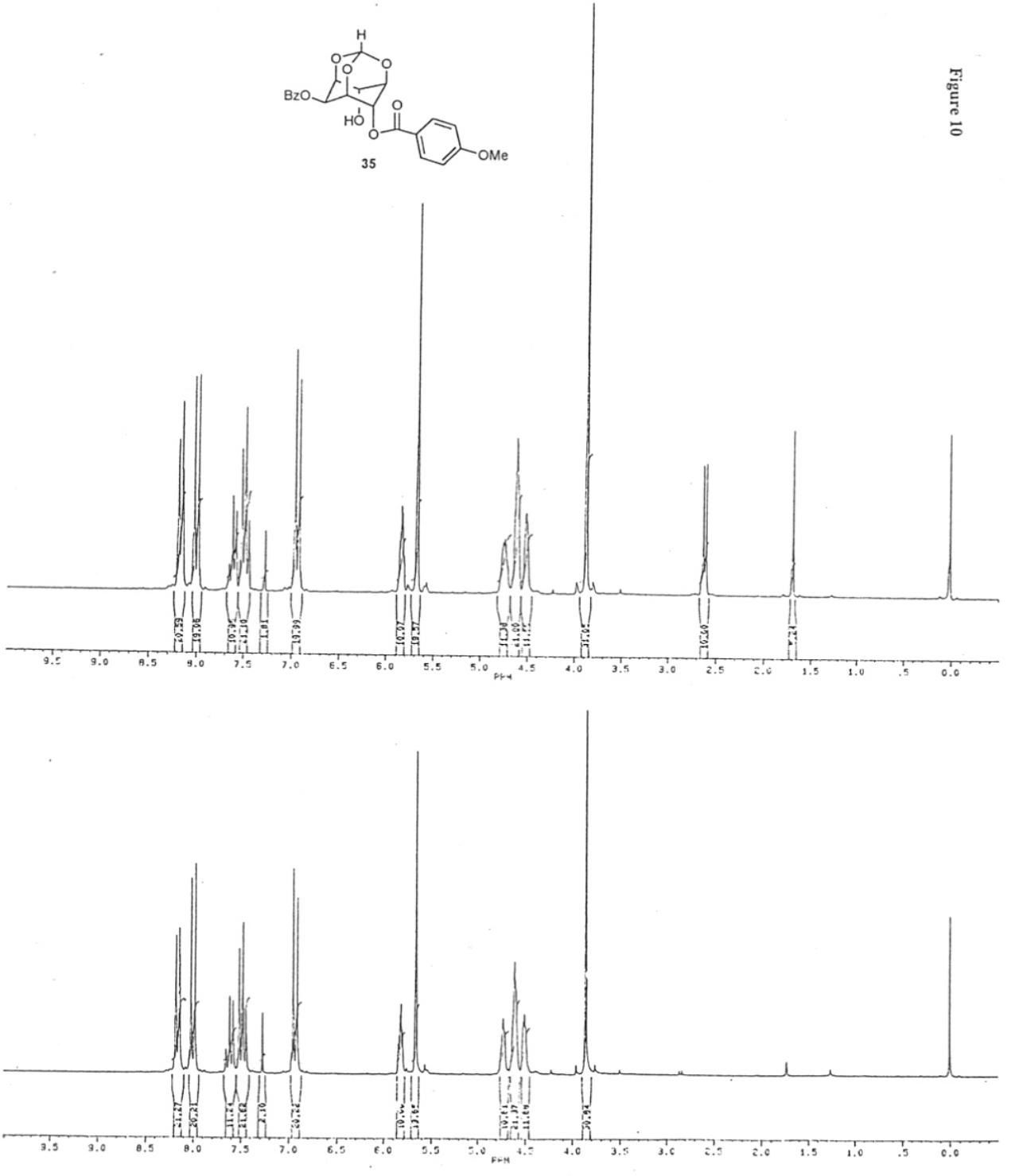


Figure 10



CHAPTER 4

Intermolecular acyl migration in (±)-2,4-di-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate in solution: Is the reaction controlled by self-assembly?

4.1 Introduction

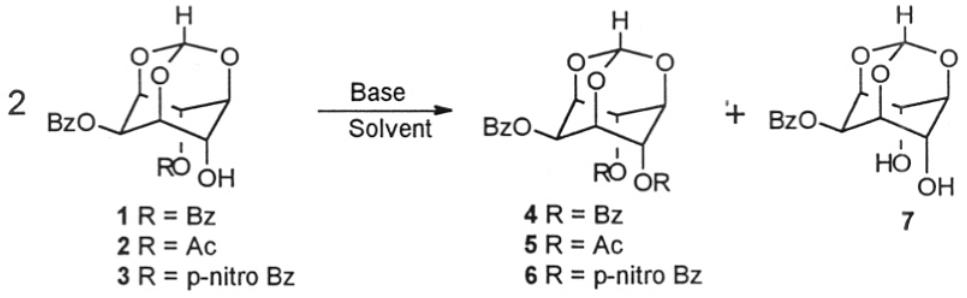
Previous chapter described a novel transesterification reaction of the dibenzoate **1** in the solid state. As evident from the examples cited in section **3.1**, **Chapter 3**, the observed characteristics of reactions in the solid state are seldom comparable to the corresponding reaction in solution. Hence we were curious to examine the transesterification of the diacyl *myo*-inositol orthoformates (**1,2** and **3**) in solution to see whether or not their relative reactivities as observed in the solid state is maintained in solution. In other words, we wondered whether we can arrive at reaction conditions in solution where in the dibenzoate **1** undergoes transesterification, but normally more reactive esters (based on electronic effects) viz., p-nitrobenzoate **3** and the acetate **2** remain unreactive. Yet another reason to study the transesterification of the dibenzoate **1** in solution (as well as in the solid state as described in **Chapter 3**) was to see how stable the dibenzoate **1** is. This is of considerable importance if the dibenzoate **1** (or any other (±) 2,4-di-*O*-acyl–*myo*-inositol 1,3,5-orthoformate) has to be resolved into its enantiomers. This is especially because the disproportionation of the dibenzoate **1** (racemic or enantiomeric) yields the tribenzoate **4** and the diol **7** which have meso configuration (which results in loss of optical activity). Accordingly, this chapter describes a detailed investigation on the transesterification and methanolysis of the diacyl derivatives **1,2** and **3** in solution.

4.2 Results and discussion

4.2.1 Transesterification of 2, 4-di-*O*-acyl *myo*-inositol 1,3,5-orthoformate derivatives in solution

All the three esters **1**, **2** and **3** underwent transesterification (**Scheme 4.1**) under a variety of conditions as shown in **Table 4.1**. The products were characterized based

Scheme 4.1



1 R = Bz
2 R = Ac
3 R = p-nitro Bz

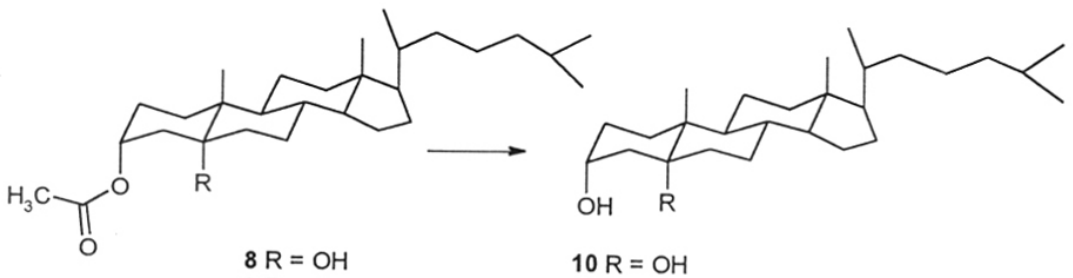
4 R = Bz
5 R = Ac
6 R = p-nitro Bz

7

on spectroscopy and elemental analysis[1]. These experimental results indicated that the intermolecular transesterification reaction is a general reaction for the (±)-2,4-di-*O*-acyl derivatives of *myo*-inositol orthoformate. However, the reaction of the dibenzoate **1** was found to be different from **2** and **3** in many respects (see following sections).

In all the reactions **(Table 4.1)**, transesterification involving the 2-equatorial benzoate was not observed. This is not unexpected since intermolecular acyl transfer of the axial acyl group in **1**, **2** and **3** could be catalyzed by the intramolelcular hydroxyl group as has been observed for the methanolysis of the dibenzoate **1** and the acetate **2** (see Section **4.2.7**) and also for the hydrolysis of 1,3-diaxial diol half ester **8**.[2] **(Scheme 4.2)**. In the reaction under investigation another molecule of the hydroxy ester functions as an acyl acceptor instead of a molecule of methanol (during the methanolysis of the dibenzoate **1**). Hence by analogy the mechanism for the transesterification of the hydroxy esters **1-3** (**Table 4.1**) may be represented as in **Scheme 4.3**.

Scheme 4.2



8 R = OH
9 R = H

10 R = OH
11 R = H

Hydrolysis of **8** *is 300 times faster than* **9** *due to transannular hydroxyl group participation*

Scheme 4.3

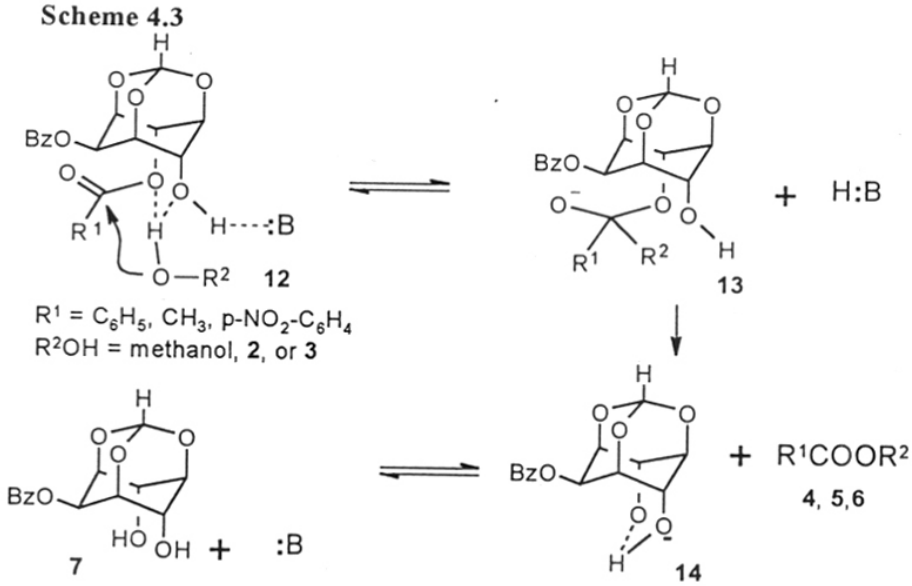


Table 4.1 Transesterifcation of (±)-2,4-di-*O*-acyl-*myo*-inositol 1,3,5-orthoformate derivatives in acetonitrile solution[a].

entry	Compound	Base	products (Yield %)
1	**1**	Ag_2O	**4**(30), 7(30), **1**(39)
2	**1**	Ag_2CO_3	**4**(22), 7(22), **1**(45)
3	**1**	Na_2CO_3	**4**(22), 7(22), **1**(45)
4	**1**	DEA[b]	**4** (40), 7(40), **1**(10)
5[d]	**1**	DEA[b]	**4**(27)[c]
6	**1**	TEA[e]	**4**(32)
7	**2**	Ag_2O	**5**(32), 7(31), **2**(44)
8	**2**	Ag_2CO_3	**5**(25), 7(25), **2**(50)
9	**2**	Na_2CO_3	**5**(23), 7(22), **2**(53)
10	**2**	DEA[b]	**5** (15), 7(14), **2**(68)
11[d]	**2**	DEA[b]	**5**(29)
12	**3**	DEA[b]	**6** (30)

[a] All the reactions were carried out with **1, 2, 3** (0.125 or 0.25 mmol) in acetonitrile (1 mL or 2 mL) in the presence of a base (10 – 20eq.) at ambient temperature for 80h. Products isolated by column chromatography.

[b]Diisopropyl ethylamine.

[c]Since equivalent amount of the triester (**4**, **5** or **6**) and the diol 7 were obtained in all the reactions, in some cases only the triester was isolated. No attempt was made to isolate the diol 7 or the starting material in some experiments. Entries 5, 6, 11 and 12.

[d]Refluxed for 24h.

[e]Triethylamine

4.2.2 Effect of base strength

Since all the three esters underwent transesterification in the presence of reasonably strong bases, we varied the strength of the base and the temperature of the reaction and carried out the transesterification of the dibenzoate **1**, to arrive at mildest

possible conditions for its transesterification. Results of such experiments are tabulated in **Table 4.2**.

Table 4.2 Homogeneous base catalyzed transesterification of (±)2,4-di-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate (**1**) in acetonitrile[a]

entry	Base	products (Yield %)
1	Diisopropylethylamine	**4**(40), 7(40), **1**(10)
2	Triethyl amine	**4**(32), 7(31), **1**(35)
3	Imidazole	**4**(28), 7(26), **1**(46)
4	Pyridine	**4**(25), 7(24), **1**(50)

[a] All the reactions were carried out with **1** (0.125 or 0.25 mmol) in acetonitrile (0.9 mL or 1.8 mL) in the presence of base (0.1 or 0.2 mL) at ambient temperature.

In the case of dibenzoate **1**, conditions as mild as 10% v/v mixture of pyridine and acetonitrile was sufficient to carry out its transesterification. But, the acetate **2** and the *p*-nitro benzoate **3**, both of which are expected to be more reactive then **1** failed to react at 25°C and starting materials could be recovered quantitatively. At 32°C, although the p-nitrobenzoate **3** underwent transesterification, the isolated yield (12%) of the triester **6** was much less than that obtained (23%) in the case of the dibenzoate **1**. It is important to note that in the case of the acetate **2** and *p*-nitrobenzoate **3** the amount of pyridine used was 2.5 times more than in the case of the dibenazoate **1** due to solubility reasons (**Table 4.3**). This indicates that the reaction mechanism of trasnesterification of the dibenzoate **1** may be different from that of the acetate **2** and the *p*-nitrobenzoate **3** in the presence of pyridine. Further more these results also show that the relative reactivities of **1**, **2** and **3** in acetonitrile/pyridine solution is similar to that observed in the solid state (**Chapter 3**) viz., the *p*-nitrobenzoate **3** and the acetate **2** are unreactive under the conditions wherein the dibenzoate undergoes transesterification.

Table 4.3 Transesterification of (±)-2,4-di-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate (**1**) in pyridine/acetonitrile system[a].

Entry	Substrate (% of pyridine)	Triester (Yield %)
1	**1** (10)[b]	**4** (23)
2	**2** (25)[b]	**5** (0)
3	**3** (25)[b]	**6** (12)
4	**1** (10)[c]	**4** (20)
5	**2** (25)[c]	**5** (0)
6	**3** (25)[c]	**6** (0)

[a] All the reactions were carried out with 1 (0.125 or 0.25 mmol) in acetonitrile (1 mL or 2 mL) in the presence of pyridine (10 eq.) for 80h.

[b] At 32°C

[c] At 25°C

4.2.3 Effect of Solvent

When a strong base such as N,N-diisopropylethylamine was used for the transesterification of the dibenzoate **1**, the reaction was found to be facile in almost all the common organic solvents as is evident from **Table 4.4**.

Table 4.4. Effect of solvent on the N,N-diisopropylethylamine catalyzed transesterification[a] of **1**.

Entry	Solvent	**4** (yield %)
1	Acetonitrile	40
2	DMF	35
3	Dichloromethane	40
4	Chloroform	35
5	THF	29

[a] All the reactions were carried out with **1** (0.125 or 0.25 mmol) in the required solvent (0.9 mL or 1.8 mL) and in the presence of diisopropyl ethyl amine (0.1 or 0.2 mL) at ambient temperature.

However, the yield of tribenzoate **4** changed drastically on changing the solvent for the pyridine catalyzed reaction (**Table 4.5**). Although small amounts of pyridine catalyzed the transesterification of **1**, use of pyridine as a solvent completely prevented the reaction. Normally transesterification reactions are unaffected by change of solvents, but in the present case, when a mild base such as pyridine is used, strongly hydrogen bonding solvents retarded or prevented the transesterification of **1**.

Table 4.5. Effect of solvent on the pyridine catalyzed transesterification[a] of **1**.

Entry	Solvent	**4** (yield %)
1	None[b]	47
2	Carbontetrachloride[c]	15
3	Acetonitrile	23
4	Dichloromethane	20
5	Chloroform	20[d]
6	DMF	<5[d]
7	THF	<5[d]
8	Acetonitrile-10% Methanol	0
9	Pyridine	0
10	DMSO	0

[a] All the reactions were carried out with **1** (0.125 or 0.25 mmol) in the required solvent (0.9 mL or 1.8 mL) in the presence of pyridine (0.1 or 0.2 mL) at ambient temperature.

[b] Reaction in the solid state (See **chapter 3**)

[c] The reaction mixture was slightly turbid due to low solubility of **1** (0.125 mmol) in carbontetrachloride (3.6 mL).

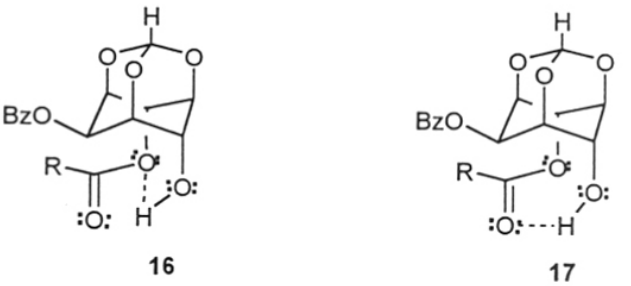
[d] Estimated by ^{1}H NMR spectroscopy as described in **Chapter 2**.

Another unusual feature observed was that, unlike normal transesterification reactions, it was found to be irreversible. The treatment of the diol **7** and the tribenzoate **3** in acetonitrile/pyridine for 80 h. did not result in the formation of the dibenzoate **1**. However, a stronger base viz., N,N-diisopropylethylamine was able to catalyze the reverse reaction. Treatment of the diol **7** and the tribenzoate **4** with N,N-diisopropylethylamine in acetonitrile for 80h yielded 10% of the dibenzoate **1**.

The results described so far indicate that transesterification of **1** (as compared to **2** and **3**) is unusually facile in solution and is very sensitive to the reaction conditions used. This is unexpected since acetates and *p*-nitrobenzoates usually undergo base catalyzed hydrolysis or alcoholysis (transesterification) faster than the corresponding benzoyl esters[3]. For instance, the rate constants for the basic hydrolysis of methyl benzoate, methyl acetate and methyl *p*-nitro benzoate at 25°C are 9×10^{-3}, 184×10^{-3} and 347×10^{-3} $M^{-1}sec^{-1}$ respectively. The increased facility of transesterification observed in the case of dibenzoate **1** as compared to **2** or **3** could be due to one or more of the following reasons.

(a) The hydroxyl group in **1** is more nucleophilic as compared to those in **2** or **3**, perhaps due to the intramolecular hydrogen bonding as shown in **Scheme 4.4**.

Scheme 4.4



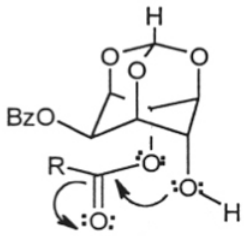
R = C_6H_5, R = CH_3, R = *p*-NO_2-C_6H_4

Possible intramolecularly hydrogen bonded structures for the diesters **1-3**

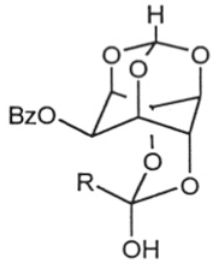
(b) The carbonyl carbon in **1** is more electrophilic as compared to those in **2** or **3**.

(c) The hydroxyl esters **2** and **3** exist as (or in equilibrium with) the corresponding ring-closed tautomers (**19-20**), which prevent them from undergoing transesterification under the conditions where **1** reacts. Based on the electronic effects,[4,5] a solution of esters **2**, and **3** should be expected to contain larger fraction of the ring form as compared to **1** in solution (**Scheme 4.5**).

Scheme 4.5



1 R = C_6H_5
2 R = CH_3
3 R = *p*-NO_2-C_6H_4



18 R = C_6H_5
19 R = CH_3
20 R = *p*-NO_2-C_6H_4

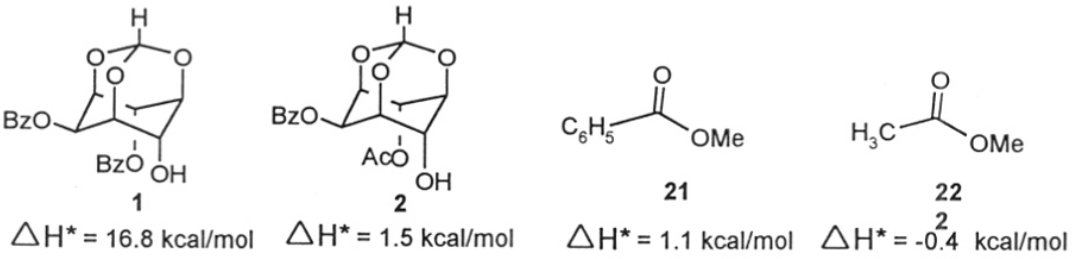
(d) Molecules of the dibenzoate **1** are present as aggregates in solution, the structure of which is similar to that in its crystal structure and consequently some of the adjacent molecules of **1** are properly oriented for the transesterification reaction even in solution. We have thought of this possibility, since relative reactivities of the esters **1-3** in the presence of pyridine is same as that observed in the solid state and also the transesterification of the dibenzoate **1** is quite sensitive to the reaction conditions used which implies susceptibility to environment of reacting molecules. This suggests a prior organization of the reacting molecules as observed in enzymatic reactions[6] (which, are affected by a change in pH, temperature, ionic strength etc.).

In order to examine the possibilities (a), (b), (c) or (d) above, we carried out theoretical, spectroscopic and experimental investigations on the diesters **1-3**, which are described below.

4.2.4 Theoretical methods[7]

We compared the eases of transesterification of **1** and **2** by computing the activation energies for nucleophilic attack on the axial ester carbonyls of **1** and **2** using LiH as the model nucleophile. The semi-empirical MO method MNDO[8] was used to obtain the transition states for the reactions of the diesters **1** and **2** with the model nucleophile LiH. The calculations reveal that nucleophilic attack on the 4-*O*-acyl carbonyl group of **1** would require greater activation energy as compared to the attack on the corresponding carbonyl group of **2** (**Scheme 4.6**). For the dibenzoate **1**, the enthalpy of activation at MNDO level has been computed to be 16.8 kcal/mol, whereas

Scheme 4.6 Activation energies for nucleophilic attack on axial ester carbonyls



for the acetate **2** the enthalpy of activation computed using the same theoretical method is 1.5 kcal/mol. These results may be compared with the enthalpies of activation computed for the attack of LiH on methyl benzoate and methyl acetate respectively of 1.1 and -0.4 kcal/mol. The enthalpies of activation in solution are positive even in the latter case, though for an isolated molecule the value is negative.

Therefore, the present calculations suggest that the acetyl carbonyl of **2** should be more electrophilic than the benzoyl carbonyl of **1** even to a greater degree than the well known greater electrophilicity of acetyl than benzoyl groups. There is no intrinsic preference for the axial benzoyl carbonyl of **1** in comparison with the axial acetyl carbonyl of **2** to be attacked by the nucleophile. The present theoretical study suggests that the difference in the susceptibility towards transesterification is not due to the variation in the electrophilicities of the two carbonyls. These calculations, however, do not take into account the medium effects. Lack of reversal in electrophilicities of the axial carbonyl groups in **1**, **2** and **3** is also shown by their relative susceptibility to base catalysed methanolysis (see section **4.2.7**). The foregoing discussion is therefore suggestive of some other factor being responsible for the enhanced reactivity of **1** as compared to **2** and **3**, since electronic effects cannot be implicated as the cause of the unexpected susceptibility.

The semi-empirical molecular orbital method AM1[9] has been used to obtain the structures of the diesters **1** and **2**. Fully optimized geometries of the diesters **1** and **2** are clearly indicative of the absence of O-H...O-C=O or O-H...O=C intramolecular hydrogen bonds (to form a six or an eight membered ring respectively) in these species, which could affect their reactivity.

4.2.5 Infrared spectroscopy

Infrared spectrum of the dibenzoate **1** in the solid state (nujol mull) showed hydrogen bonded OH stretch (3472 cm^{-1}) and two peaks for the carbonyl groups (1710 and 1728 cm^{-1}). The absorption at 1710 cm^{-1} may be attributed to the carbonyl group hydrogen bonded with the hydroxyl group. The infrared spectra of **1** in solution at an ambient temperature however showed only one peak due to both the carbonyl groups making it difficult to decipher any information regarding the association among the molecules of **1** in solution. The infrared spectrum of **1** in acetonitrile showed absorptions due to hydrogen bonded (3460 cm^{-1}) as well as non-bonded (3580-3620 cm^{-1}) hydroxyl groups. Similar results were obtained for the esters **2** and **3** (**Table 4.6**) and hence definitive conclusions on the structures of esters **1-3** in solution could not be arrived at from a comparison of their IR spectra.

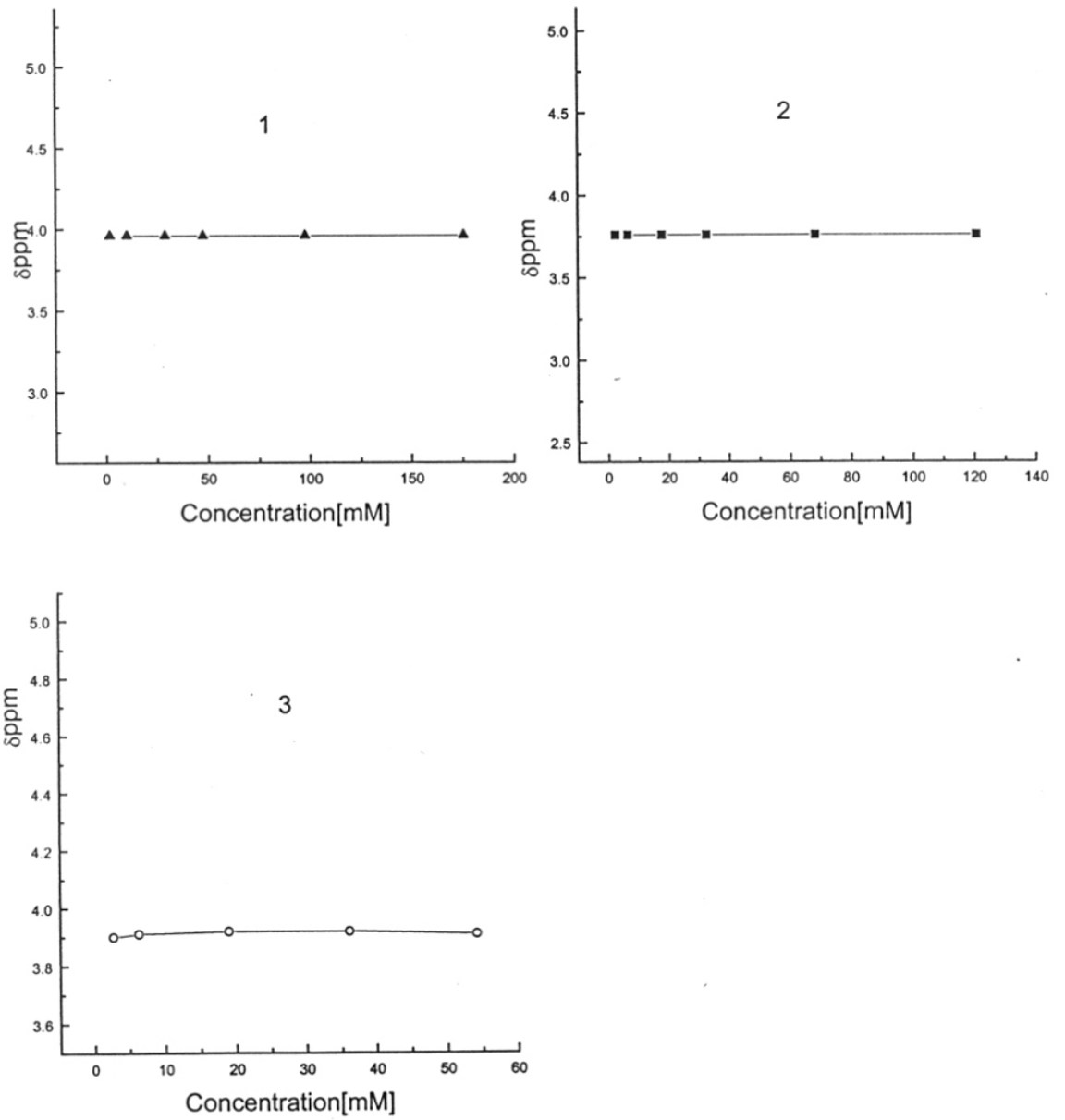
Table 4.6 Selected IR frequencies of **1**, **2** and **3** in different solvents.

Entry	Compound	Solvent	ν - OH (cm^{-1})	ν - C=O(cm^{-1})
1	**1**	Nujol	3472	1711, 1728
		MeCN	3460	1726
		DCM	3598	1724
		THF	3485-3365	1728
		Methanol/DCM (30% v/v)	-------	1724
2	**2**	Nujol	3445	1710
		MeCN	3430-3460	1747, 1724
		DCM	3600	1755, 1722
		THF	3490	1753, 1724
		Methanol/DCM (30% v/v)	-------	1724
3	**3**	Nujol	3445	1699, 1722
		MeCN	3440-3600	1734
		DCM	3520-3650	1738
		THF	3483	1755, 1724
		Methanol/DCM (30% v/v)	--------	1732

4.2.6 NMR spectroscopy

We attempted to study the variation of the chemical shift of the hydroxyl proton with concentration for the three esters **1-3** in non-polar solvents. However, we were unsuccessful due to their limited solubility in non-polar solvents such as carbontetrachloride. In polar solvents (chloroform-d and acetonitrile-d_3) variation of the chemical shift of the hydroxyl proton with concentration at 30 °C (**Figure 1**) were, for

Figure 1 Variation of the chemical shift of the hydroxyl proton in **1**, **2** and **3** with concentration (acetonitrile-d_3).



1, 0.04 ppm (0.003-0.176 M); for **2**, 0.03 ppm (0.003-0.121 M); and for **3**, 0.01 ppm (0.003-0.054 M). The negligible concentration dependence of the hydroxyl proton observed in the three esters could be due to an intramolecularly hydrogen bonded hydroxyl group in **1**, **2** or **3** either to the 6-oxygen atom of the inositol ring or to the carbonyl group of the axial ester moiety (**Scheme 4.4**). This can lead to an increase in nucleophilicity of the hydroxyl group as well as the electrophilicity of the carbonyl group. However, both of these effects cannot explain enhanced facility in the transesterification of **1** as compared to **2** and **3** since intramolecular hydrogen bonding if at all exists appears to be common to all the three esters (also see section **4.2.3**).

We also compared the ^{1}H NMR spectra of the three esters under study in acetonitrile-d_3 and chloroform-d (**Table 4.7**), as well as the spectra of **1** in different solvents (see **Table 4.8**). The dibenzoate **1** having a higher δ-OH is perhaps indicative of its higher reactivity, assisted by favourable intermolecular interactions in solution, similar to the interaction existing in the solid state (**Chapter 3**). This proposition is made from the fact that, if intramolecular factors play a major role in determining the reactivity, the esters **2** and **3** should have been more reactive.[3]

Table 4.7 Chemical shift of the hydroxyl proton of the esters **1**, **2** and **3** in Acetonitrile-d_3 and chloroform-d

Entry	Compound	Solvent	δ OH
1	**1**	Acetonitrile-d_3	4.07
2	**3**	Acetonitrile-d_3	3.97
3	**2**	Acetonitrile-d_3	3.76
4	**1**	chloroform-d	2.70
5	**3**	chloroform-d	2.37
6	**2**	chloroform-d	2.10

The chemical shift of the hydroxyl proton of **1**, in different solvents is shown in **Table 4.8** (see page 112). These results suggest a better hydrogen bonded hydroxyl group (higher δ value) in acetonitrile as compared to dichloromethane or chloroform, and hence better yield of the tribenzoate **4** in acetonitrile. Dimethylsulfoxide and

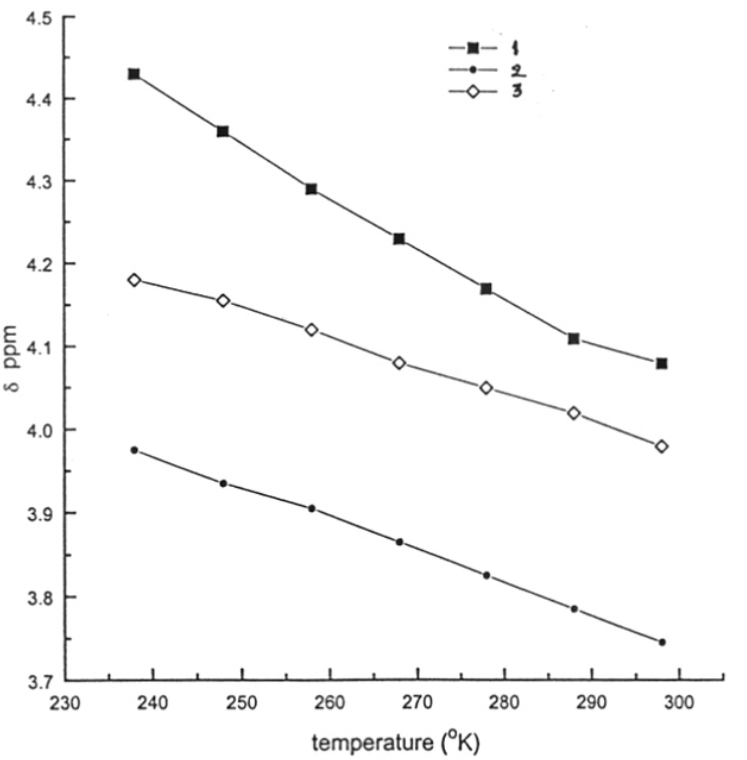
pyridine being good hydrogen bonding acceptors perhaps strongly hydrogen bond with the hydroxyl group of **1** (hence the larger deshielding of the hydroxyl proton) and disrupt the association among the molecules of **1**, thereby preventing its transesterification (entries 8-10, **Table 4.5**).

Table 4.8 Chemical shift of hydroxyl proton of **1** in different solvents

Entry	Solvent	δ OH
1	Acetonitrile-d_3	4.07
2	Chloroform-d	2.70
3	Dichloromethan-d_2	2.49
4	Dimethylsulfoxide-d_6	4.93
5	Pyridine-d_5	8.1

The observed variation in chemical shift with concentration in polar solvents, for the hydroxyl proton of **1** in acetonitrile-d_3 (**Figure 2**) perhaps indicates that the association between the molecules of **1** is not strong at higher temperatures, which is in

Figure 2 Variation of the chemical shift of the hydroxyl protons in **1**, **2** and **3** with temperature in acetonitrile-d_3



accordance with the relative reactivity pattern observed for the pyridine catalyzed methanolysis of **1-3** at 55 °C (see section **4.2.7**). Hence we studied the variation in the chemical shift of the hydroxyl proton with temperature for the esters **1-3** in acetonitrile. The change in chemical shift of the hydroxyl proton with decrease in temperature for the three esters showed that the association among the molecules of **1** is stronger ($\Delta\delta$ / $\Delta T = -6.15 \times 10^{-3}$) than those between the molecules of **2** or **3** (respective values of $\Delta\delta$ / ΔT being -3.62×10^{-3} and -3.98×10^{-3}). If the association of the three esters was with the solvent, then we should have observed similar values[10] of $\Delta\delta$ / ΔT for all of the three esters. We also observed a shift of about 0.1δ for one of the *myo*-inositol ring hydrogens at $\cong$ 5.6 δ, in the case of **1** and **3**, over the temperature range investigated. But, reason for this change is as yet unknown.

We also recorded the ^{13}C NMR spectra of the dibenzoate **1** and the acetate **2** in a mixture of pyridine-d_5 and acetonitrile-d_3 (1:9 v/v) to see if these esters exist as an equilibrium mixture of the open and cyclized forms under the conditions of transesterification (see section **4.2.3**, **Scheme 4.5**). Both the diesters clearly showed the presence of two carbonyl groups and absence of the quarternary carbon, which suggests the existence of **1** and **2** completely in hydroxy ester form under the conditions where the dibenzoate **1** undergoes transesterification. Hence these results rule out the ring chain tautomerism (i.e. intramolecular hydroxyl addition to axial ester carbonyl group) hindering the acetate from undergoing transesterification. It is known in the literature that the cyclic structures of the type **18-20** are not preferred[4,5] over the open chain isomers **1-3** (**Scheme 4.5**).

4.2.7 Base catalyzed methanolysis of (±)-2,4-di-*O*-acyl derivatives of *myo*-inositol 1,3,5-orthoformate

We carried out base catalyzed methanolysis of the esters **1-3** to see if their relative reactivity pattern is maintained when a different alcohol is used as the acyl acceptor, during transesterification. If the relative reactivity of **1-3** towards transesterification is due to the inherent reactivity of individual molecules (for any reason), their relative reactivity towards transesterification with themselves as well as towards methanol is expected to be similar.

Results on the base (pyridine) catalyzed methanolysis of **1-3** (**Table 4.9**) showed that the reactivity of the three hydroxyl esters towards methanolysis is as expected, the order being, *p*-nitro benzoate **3** > the acetate **2** > the benzoate **1** (**Table 4.9** entries 1-3). It is interesting to note that **1** showed an inherent tendency to undergo transesterification with itself to yield the tribenzoate **4** even in the presence of excess of methanol. This is evident by the fact that a ten fold excess of methanol was sufficient to solvolyze majority of the acetate **2** and the *p*-nitro benzoate **3** to the diol **7** (**Table 4.9** entries 7-9) without concomitant formation of the corresponding triesters **5** and **6**, where as the dibenzoate **1** yielded isolable amount of the corresponding tribenzoate **4** (due to transesterification with itself) in addition to the diol **7** under solvolytic conditions (**Table 4.9** entries 4-6). The triacyl derivatives **5** and **6** were found to be stable to the methanolysis conditions (**Table 4.9** entries 10-11).

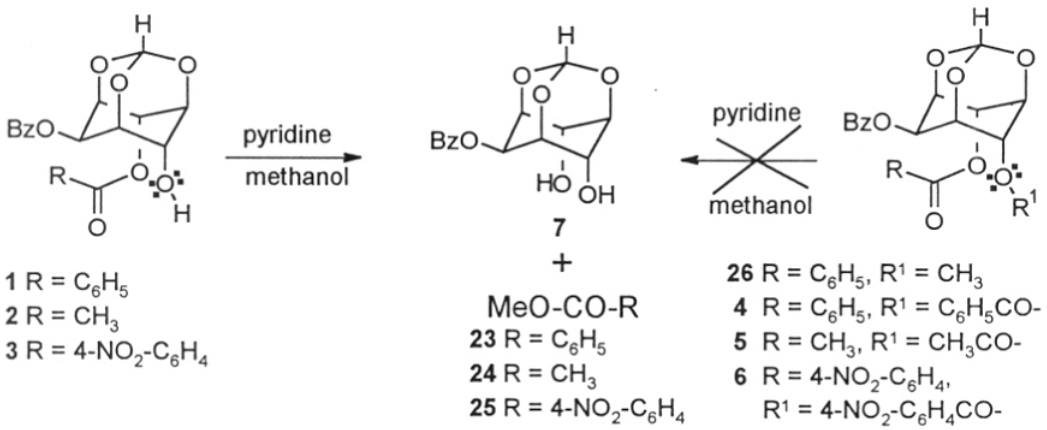
Table 4.9. Base catalyzed methanolysis [a] of hydroxy esters **1**, **2** and **3**.

Entry	Substrate	Solvent	Products (yield %)
1	**1**	Methanol	**7**(80) **3**(0) **1**(0)
2	**2**	Methanol	**7**(95) **4**(0) **2**(0)
3	**3**	Methanol	**7**(100) **5**(0) **3**(0)
4	**1**	20% Methanol-DMF	**7**(60) **4**(8) **1**(20)
5	**1**	10% Methanol-DMF	**7**(30) **4**(14) **1**(40)
6	**1**	10% Methanol-Acetonitrile	**7**(35) **4**(18) **1**(30)
7	**2**	10% Methanol-DMF	**7**(70) **5**(0) **2**(19)
8	**2**	10% Methanol-Acetonitrile	**7**(65) **5**(0) **2**(20)
9	**3**	10% Methanol-Acetonitrile	**7**(100) **6**(0) **3**(0)
10	**5**	20% Methanol-Acetonitrile	**5**(95)
11	**6**	20% Methanol-acetonitrile	**6**(90)

[a] Entries 1-3: Pyridine, 4-11 diisopropylethylamine. Reaction times for the completion of methanolysis at 55 °C were: for **1**, 60 h.; for **2**, 56 h.; for **3**, 18 h. See experimental section for details. Entries 4-9: reaction at ambient temperature for 24 h. Ratio of concentration of substrate: methanol: N,N-diisopropylethylamine = 1:10:10 except for entry 4, where the ratio was 1:20:10.

Base catalysed methanolysis of **1**, **2** and **3** is assisted by the free transannular hydroxyl group.[11] This is evidenced by the fact that the corresponding *O*-protected derivatives **26**, **4**, **5** and **6** do not undergo base catalyzed methanolysis (in the present case pyridine) under the conditions used for the methanolysis of **1**, **2** and **3** (**Scheme 4.7**). A consequence of intramolecular assistance is the reversal of reactivity of the two

Scheme 4.7



1 R = C_6H_5
2 R = CH_3
3 R = 4-NO_2-C_6H_4

7
+
MeO-CO-R
23 R = C_6H_5
24 R = CH_3
25 R = 4-NO_2-C_6H_4

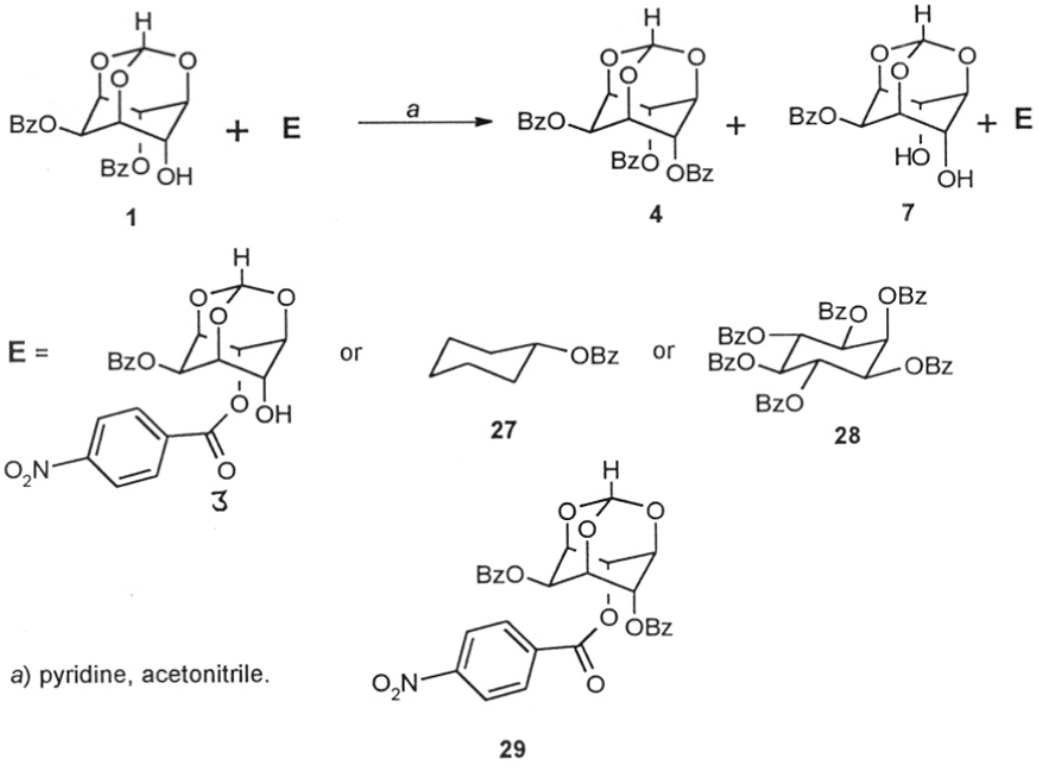
26 R = C_6H_5, R^1 = CH_3
4 R = C_6H_5, R^1 = C_6H_5CO-
5 R = CH_3, R^1 = CH_3CO-
6 R = 4-NO_2-C_6H_4,
R^1 = 4-NO_2-C_6H_4CO-

benzoate groups in **1**. In the dibenzoate **1**, the benzoate at the equatorial 2-position of the *myo*-inositol ring is expected to be more prone to the addition of a nuclephile as compared to the axial benzoate based on steric effects[12]; however the opposite is observed (i.e. the nucleophilic addition to the axial 4-*O*-benzoate) during methanolysis.

4.2.8 Transesterification of the dibenzoate 1 in the presence of other acyl donors

Results presented in the previous section showed that the relative reactivity of the dienzoate **1** (as compared to **2** and **3**) is as expected in the presence of methanol (as acyl acceptor) (Table **4.9** entries 1-3). Hence we wondered if the dibenzoate **1** behaved normally in the presence of other acyl donors (i.e. other esters). Hence we carried out transesterification of **1** in the presence of cyclohexyl benzoate **27**, *myo*-inositol hexabenzoate **28** and the *p*-nitrobenzoate **3** and the results are shown in **Scheme 4.8**. In all these reactions (**Scheme 4.8**) the dibenzoate **1** preferred to react with itself to yield the tribenzoate **4** and the diol **7** and the other acyl donors (**3**, **27** and **28**) were recovered quantitatively. Formation of neither cyclohexanol, nor a *myo*-inositol pentabenzoate (or

Scheme 4.8



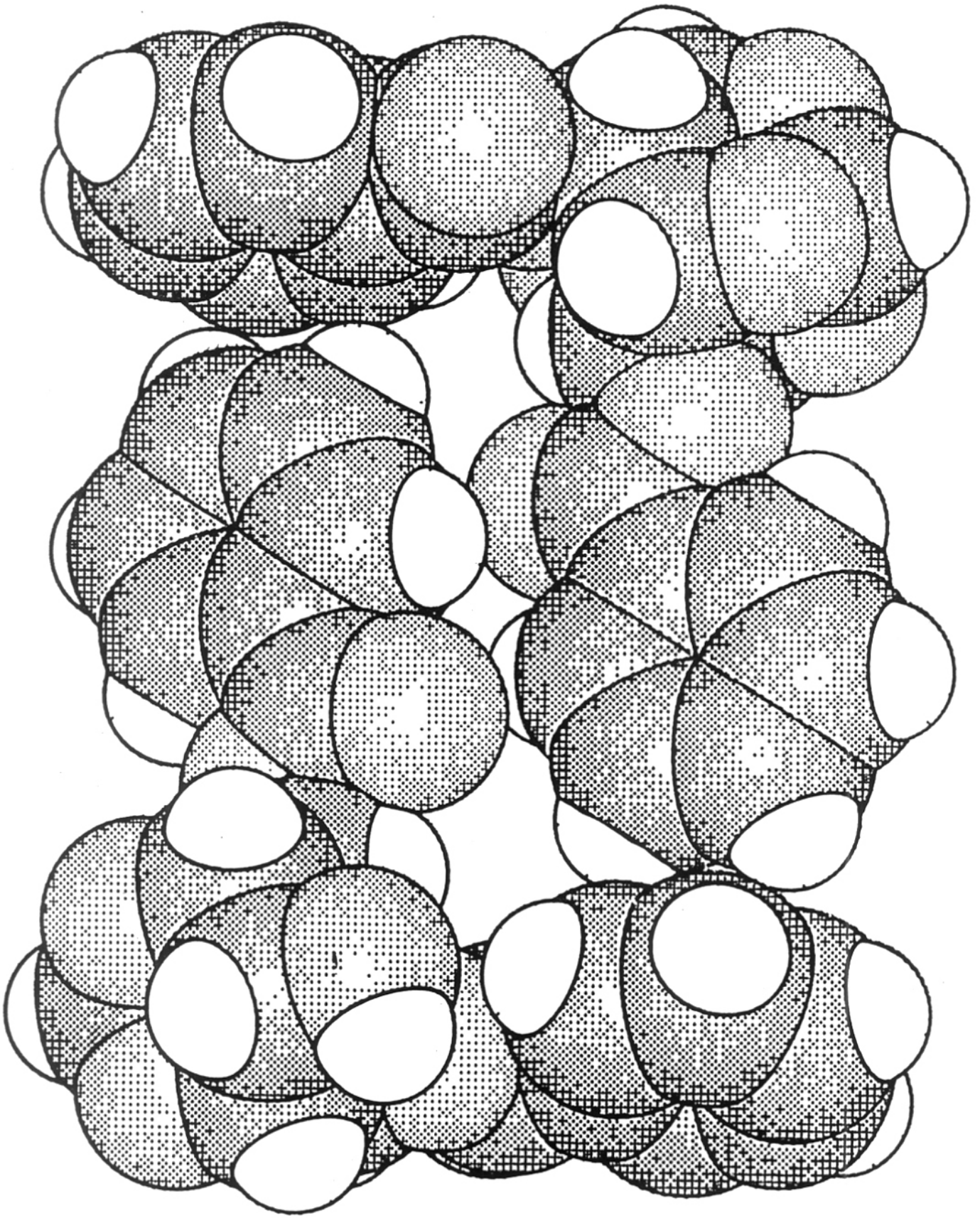
a mixture of isomeric *myo*-inositol pentabenzoates) nor the cross product **29** could be detected (**Scheme 4.8**).

These results clearly establish that the dibenzoate **1** prefers to function as an acyl donor as well as an acyl acceptor even in the presence of esters that are more reactive than itself (e.g. **3**). This suggests that the involvement of intermolecular interactions between molecules of **1** in solution might be playing a role in its reactivity towards itself rather than electronic factors intrinsic to each molecule.

The reaction of **1** in solution is thus clearly analogous to its reaction in the solid state (see **Chapter 3**) where the reaction is extremely facile due to the proper juxtaposition of the reacting functional groups in the two screw-axis-related molecules (held by a hydrogen bond) in its crystal. An idea of the supramolecular assembly that may exist in solution and lead to facile transesterification **1** as has been observed in the solid state, can be obtained from the crystal structure which shows the molecules packed in two distinct layers perpendicular to the *c* axis. Within these layers there are strong

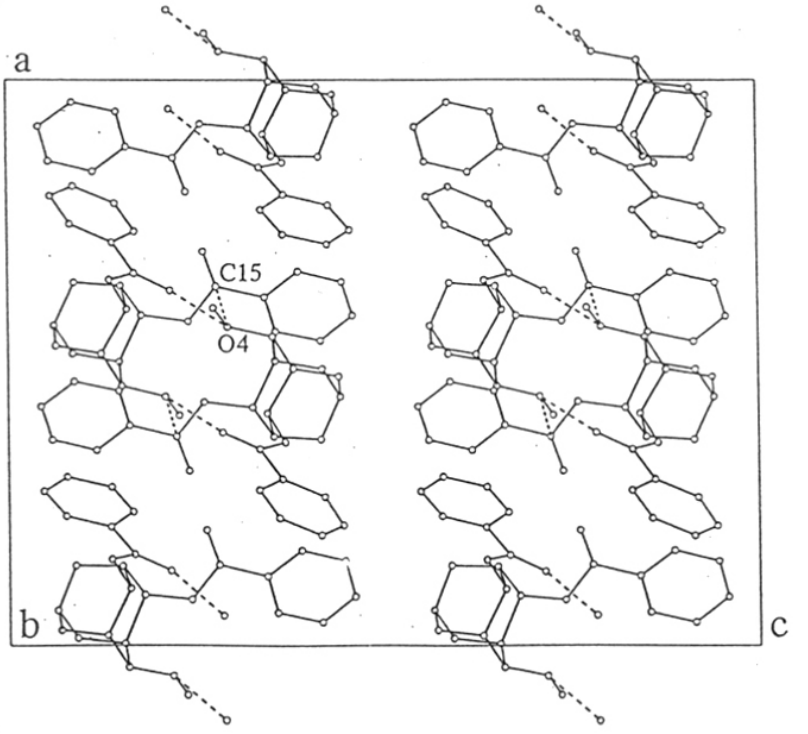
interactions. The crystal asymmetric unit of **1** has two molecules (related by a pseudo center of symmetry) which form a tight dimer (**Figure 3**) with favourable geometry for

Figure 3



aromatic-aromatic interactions.[13-19] There are two edge - to - face interactions (with angles 81° and 78° between the ring planes, and distance between their centroids being 5.18 and 5.15Å respectively) and one stacking interaction (10° and 6.52Å). Simultaneous occurrence of such interactions have been found in oligocatenanes.[20] In the former type of interaction two C-H protons of one benzene ring point to the π electron cloud of the second ring (at distances 3.11 and 2.88 Å, 3.07 and 2.93 Å). Such aromatic interactions play key role in molecular recognition processes.[21-32] That L-shaped molecules like **1** can form stable dimer is not unprecedented. To cite an example,[33] in an inorganic complex of a dibutyl substituted planar ligand; one of the alkyl side chains is bent so as to give the molecule an L-shape that can form a tightly bound dimeric structure. The calculation of non-bonded energy for the two molecules of **1** individually (153.4, 155.1 kcal/mol) and taken together (294.5 kcal/mol) provide a binding energy of 14.0 kcal/mol, thus indicating a snug fitting between the two molecules. In the crystal, each of these molecules interact through hydrogen bonding (donor-acceptor distances for the two cases: 2.871 and 2.849 Å) and nucleophile - electrophile interactions (hydroxyl O atom to ester carbonyl C atom distances 3.226 and 3.249 Å) to a 2_1 - screw axis related molecule, providing a very closely packed arrangement of molecules along this axis (**Figure 4**).

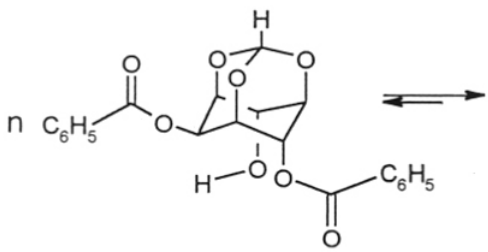
Figure 4



An association phenomenon, similar to the one described as above, could be responsible for arresting the reactants' relative motion in solution and properly orient them for the intermolecular acyl transfer and thereby enhance the reactivity of **1** in solution. Crystallization from solution occurs via aggregation of the solute molecules through the energy minimum path leading to close intermolecular interactions and the final separation of the solid phase. In this process the energy factor outweighs the entropy factor. Hence it is reasonable to deduce that a more favourable transition state possible for the dibenzoate **1** via aggregation (self-assembly?) makes it more reactive than **2** or **3**.

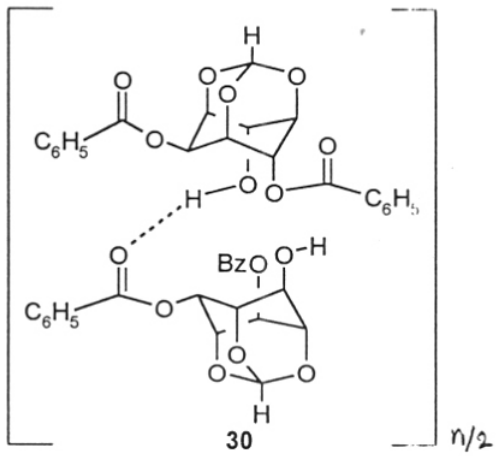
Association among the molecules of **1** in solution is in fact indicated by the solvent dependent reactivity of **1** (see p-104) and variable temperature NMR spectroscopic studies (see section **4.2.6**). Such aggregates are more likely to be present in acetonitrile, since it can be considered as an extremely small surfactant (a hydrophobic methyl group and a hydrophilic cyano group connected by a covalent bond) wherein formation of macromolecular structures are possible, as postulated in solvent heterogeneity theories.[34]. Acetonitrile was found to be the best solvent for the reaction as is evident from yield of the tribenzoate **4** obtained in pyridine catalyzed transesterification of **1** (**Table 4.1** entry 4). Hence the mechanism for the transesterification of **1** in solution may be represented as in **Scheme 4.9**.

Scheme 4.9



1

Association based on the crystal structure considering only one molecule in the asymetric unit



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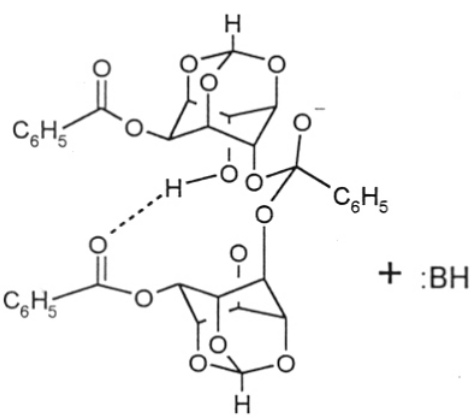

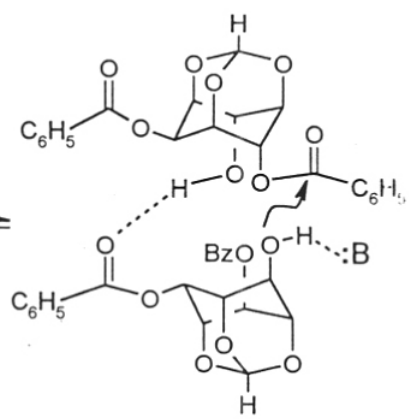

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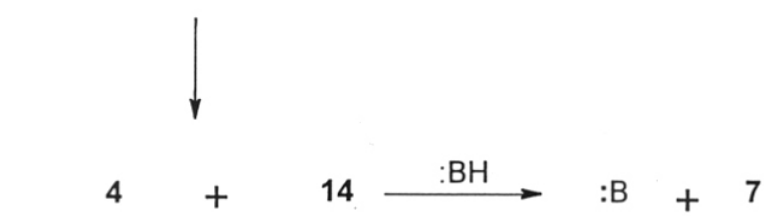

4.3 Conclusions

This chapter presented a novel and unusual transesterification reaction of the dibenzoate **1**. This reaction has similar characteristics in solid state as well as in solution due to favourable intermolecular interactions. This reaction is also analogus to enzyme catalyzed reactions with respect to specificity, sensitivity to the reaction condition used and perhaps pre-organization of the reacting functional groups. Perhaps this is the first report on a reaction between small molecules, wherein the rates are enhanced due to self-assembly. Also this is an example of an intermolecular reaction where favourable orientation between the functional groups due to aggregation takes precedence over electronic effects in deciding the facility with which the reaction occurs. Catalysis by enzymes is as facile when carried out in the crystalline state as in solution.[35] By analogy one may wonder if the chemical reactivity shown by a small organic molecule in the crystalline state can also be retained in solution, although such a behaviour would be very improbable as the weak intermolecular interactions that hold the supramolecular assembly in the crystal are likely to break in solution. Although results presented in sections **4.2.4** to **4.2.7** rules out the possibilities (a), (b), and (c) as being reasons for the facility with which the dibenzoate **1** undergoes transesterification with itself, and suggest the possibility of molecular aggregation leading to the increased reactivity among the molecules of **1** in solution, further experiments with analogus compounds and an estimation of rate constants is necessary to conclude unambiguously about the phenomenon of aggregation among the molecules of **1**.

4.4 Experimental section.

Materials and methods:- General experimental conditions, materials and methods are same as mentioned in **Chapter 2**. Silver (I) oxide mediated transesterification of **1** and **2** in acetonitrile was carried out as described in **Chapter 2.** A similar procedure was used for the transesterification of **1** and **2** using silver carbonate and sodium carbonate in acetonitrile.

Computations: The AM1 and MNDO calculations were carried out using MOPAC version 6.0.[36] Non-bonded energy calculations were performed on a Silicon Graphics Indigo Workstation using the CVFF force-field in vacuum (dielectric of 1.0) as implemented in the DISCOVER program.[37]

2-*O*-benzoyl-4,6-di-*O*-(p-nitrobenzoyl)-*myo*-inositol 1,3,5-orthoformate (6). The diol 7 (0.294 g, 1 mmol) and p-nitrobenzoyl chloride (0.475 g, 2.5 mmol) were stirred in pyridine (6 mL) at room temperature overnight. The reaction mixture was then diluted with chloroform (20 mL), washed with saturated sodium bicarbonate solution and worked up as usual. The crude product obtained was purified by crystallization from chloroform - light petroleum mixture to give **6** (0.580 g, 98 %).

m. p. 246 - 247 °C.

IR (cm^{-1}): 1720, 1732, 1751.

^1H NMR ($CDCl_3$): δ 4.70 - 4.75 (m, 2H), 5.1 (m, 1H), 5.70 - 5.80 (m, 2H), 5. 85- 5.95 (t, 2H), 7.45 - 7.55 (m, 2H), 7.60 - 7.70 (m, 1H), 7.90-8.10 (m, 8H), 8.15-8.25 (m, 2H). Elemental Analysis calcd. for $C_{28}H_{20}O_{13}N_2$: C 56.76, H 3.38, N 4.73; Found: C 56.68, H 3.24, N 4.58.

Transesterification of 1, 2 and 3 in acetonitrile - diisopropylethylamine The dibenzoate **1** (0.1 g, 0.25 mmol) was dissolved in a mixture of acetonitrile (1.8 mL) and diisopropylethylamine (0.2 mL) and stirred at ambient temperature. After 80 h. the solvents were evaporated at room temperature *in vacuo* and the products were separated by flash chromatography (eluent 10 % ethyl acetate - light petroleum) to isolate **4** (0.050 g, 40%).

The transesterification of **2** and **3** was carried out under identical conditions and the yields of the triesters **5** and **6** are tabulated in **Table 4.1**.

The transesterification of **1** using triethylamine (0.2 ml) imidazole (2.5 mmol), pyridine (0.2 ml) was also carried out under identical conditions and the yield of the triester **4** are tabulated in **Table 4.2**

Transesterification of 1, 2 and 3 in acetonitrile - pyridine at 25 °C. The dibenzoate **1** (0.1 g, 0.25 mmol) was dissolved in a mixture of acetonitrile (1.8 mL) and pyridine (0.2 mL, 2.5 mmol) and stirred in a constant temperature bath at 25 °C. After 80 h. the solvents were evaporated at room temperature *in vacuo* and the products were separated by flash chromatography (eluent 10 % ethyl acetate - light petroleum) to obtain **1** (0.020 g, 20%), **4** (0.020 g, 20 %) and **7** (0.014 g, 20 %).

In the case of **2** (0.084g, 0.25 mmol) and **3** (0.111g, 0.25 mmol), slight excess of pyridine (0.3 mL) and acetonitrile (1.7 mL) were used to solubilize the esters completely, starting materials were recovered quantitatively and at the end of 80h.

Identical conditions were used for the transesterification of **1** in DMF, dichloromethane, chloroform, THF, 10% acetonitrile/ methanol, pyridine and DMSO. The yield of the tribenzoate **4** obtained are given in **Table 4.5**.

Transesterification of 1 in the presence of methanol.

The dibenzoate **1** (0.200 g, 0.5 mmol) was dissolved in a mixture of DMF (1.8 mL), methanol (0.2 mL, 4.9 mmol) and N,N-diisopropylethylamine (0.645 g, 5 mmol) and stirred at room temperature for 24 hours. The reaction mixture was then diluted with chloroform (20 mL) and worked up as usual. The products were separated by flash chromatography (eluent 10% ethyl acetate - light petroleum) to obtain **1** (0.080 g, 40%), **4** (0.035 g, 14%), 7 (0.060 g, 30%) and methyl benzoate (0.018 g, 26%).

Identical conditions were used for the transesterification of the dibenzoate **1** in acetonitrile–methanol system. The yield of the products are given in **Table 4.9**

Transesterification of 1 in the presence of acyl donors 3, 27 or 28

The dibenzoate **1** (0.100 g, 0.25 mmol) and the *p*-nitrobenzoate **3** (0.111 g, 0.25 mmol) were dissolved in pyridine (0.8 mL) - acetonitrile (3.2 mL) mixture and stirred at room temperature for 80 hours. The solvents were evaporated *in vacuo* at room temperature

and the products were separated by flash chromatography (eluent 10% ethyl acetate - light petroleum) to obtain **1** (0.019 g, 19%), **4** (0.055 g, 22%), 7 (0.028 g, 20%) and **3** (0.110 g, 99%).

A similar procedure was used for the transesterification of **1**(0.100g, 0.25 mmol) in the presence of cyclohexyl benzoate **27** (0.051g, 0.25 mmol). Flash chromatographic purification of the reaction mixture yielded **1** (0.020g, 20%), **4** (0.052g, 22%), 7 (0.028g, 20%) and **27** (0.050g, 98%).

Use of *myo*-inositol hexabenzoate **28** (0.183g, 0.25 mmol) for transesterification of **1** (0.100g, 0.25 mol) also gave the same product distribution along with the recovery of **28** (0.180g, 98%).

Methanolysis of the hydroxy esters in the presence of pyridine. The dibenzoate **1** (0.1 g, 0.25 mmol) was suspended in methanol (1.6 mL) and pyridine (0.4 mL) and stirred at 55 °C in a constant temperature bath. The reaction was monitored carefully by TLC, which showed the absence of the starting material at the end of 60 h. The solvents were evaporated *in vacuo* at room temperature and the residue was purified by flash column chromatography (eluent 20 % ethyl acetate - light petroleum) to obtain the diol 7 (0.030 g, 80 %).

Under identical conditions, complete methanolysis of the acetate **2** (0.084g, 0.25 mmol) and the p-nitrobenzoate **3** (0.111g, o.25 mmol) took 56 h. and 18 h. respectively. The isolated yields of the diol 7 were (070g, 95%) and (0.0735g, 100%) respectively.

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36. Biosym Technologies, Inc. 9685 Scranton Road, San Diego, CA 92121-2777, USA.

37. Stewart, J.J.P. QCPE # 455.

Figure 5. Variation of the chemical shift of hydroxyl groups of **1** with concentration

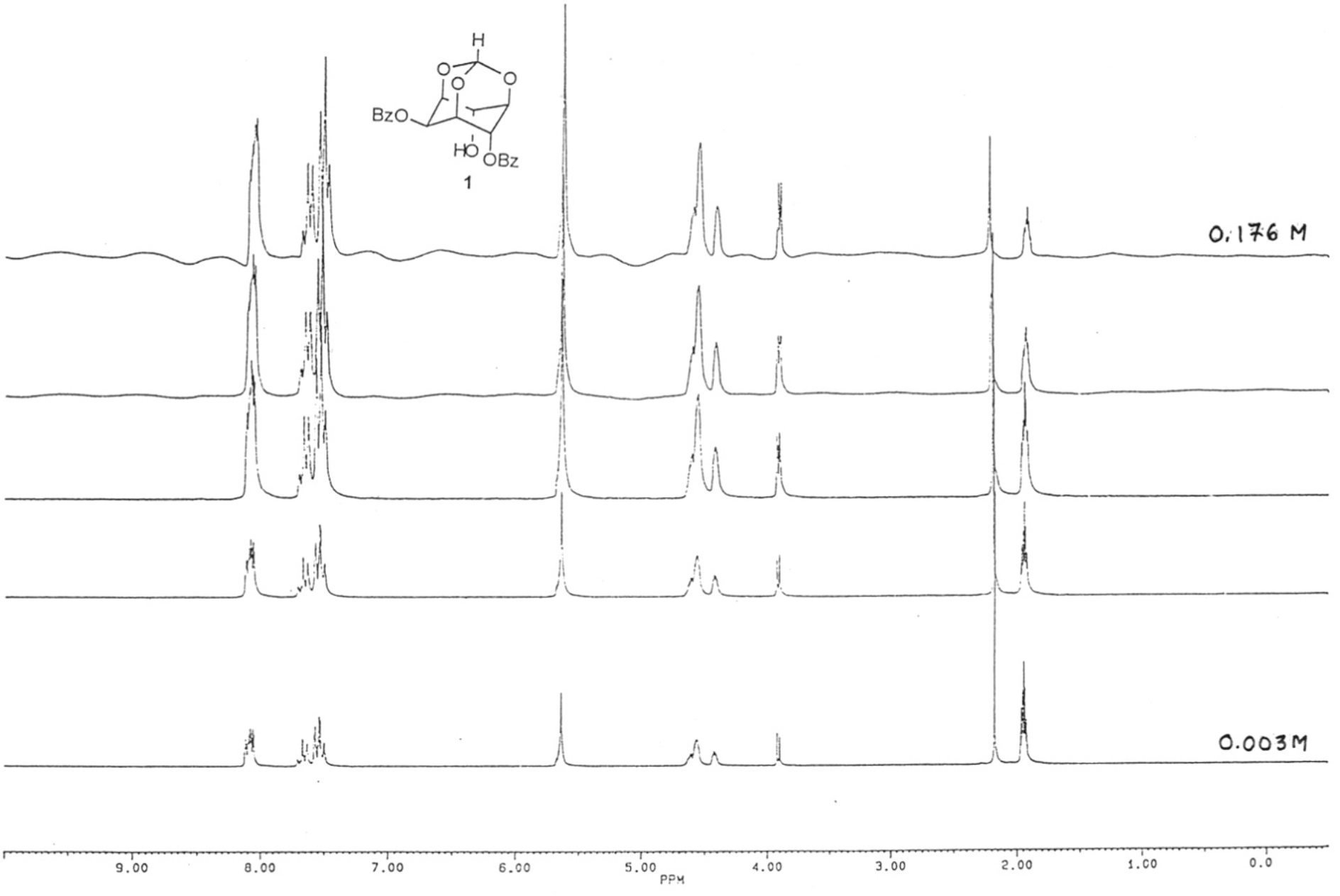

Figure 6. Variation of the chemical shift of hydroxyl groups of **2** with concentration

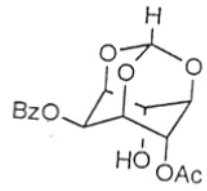

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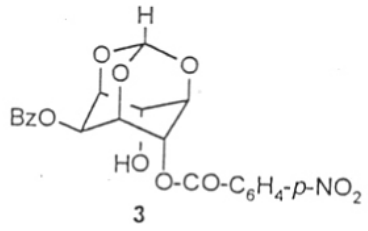
Figure 7. Variation of the chemical shift of hydroxyl groups of **3** with concentration



3

Figure 8. Variation of the chemical shift of hydroxyl groups of **1** with temperature

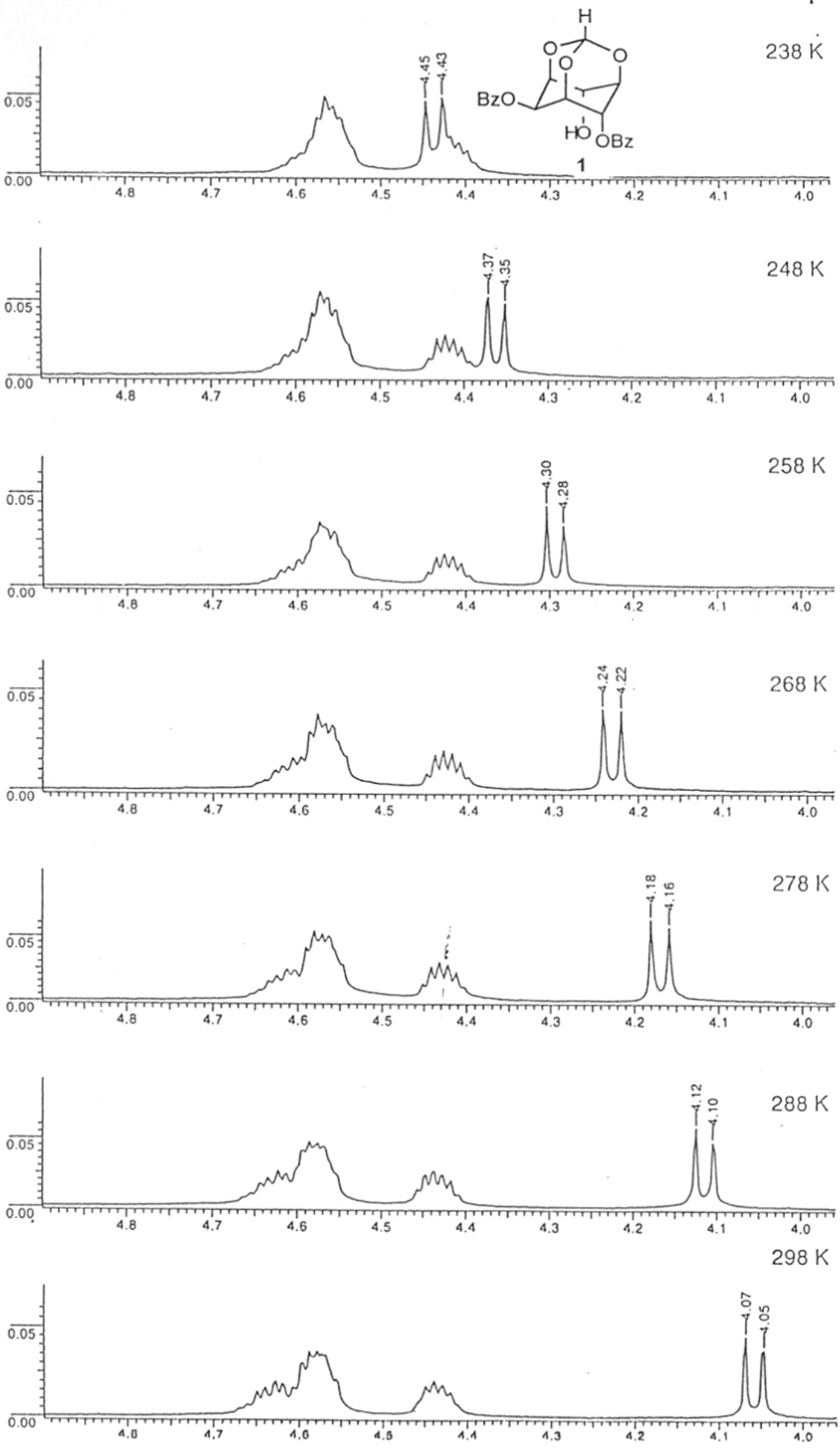


Figure 9. Variation of the chemical shift of hydroxyl groups of **2** with temperature

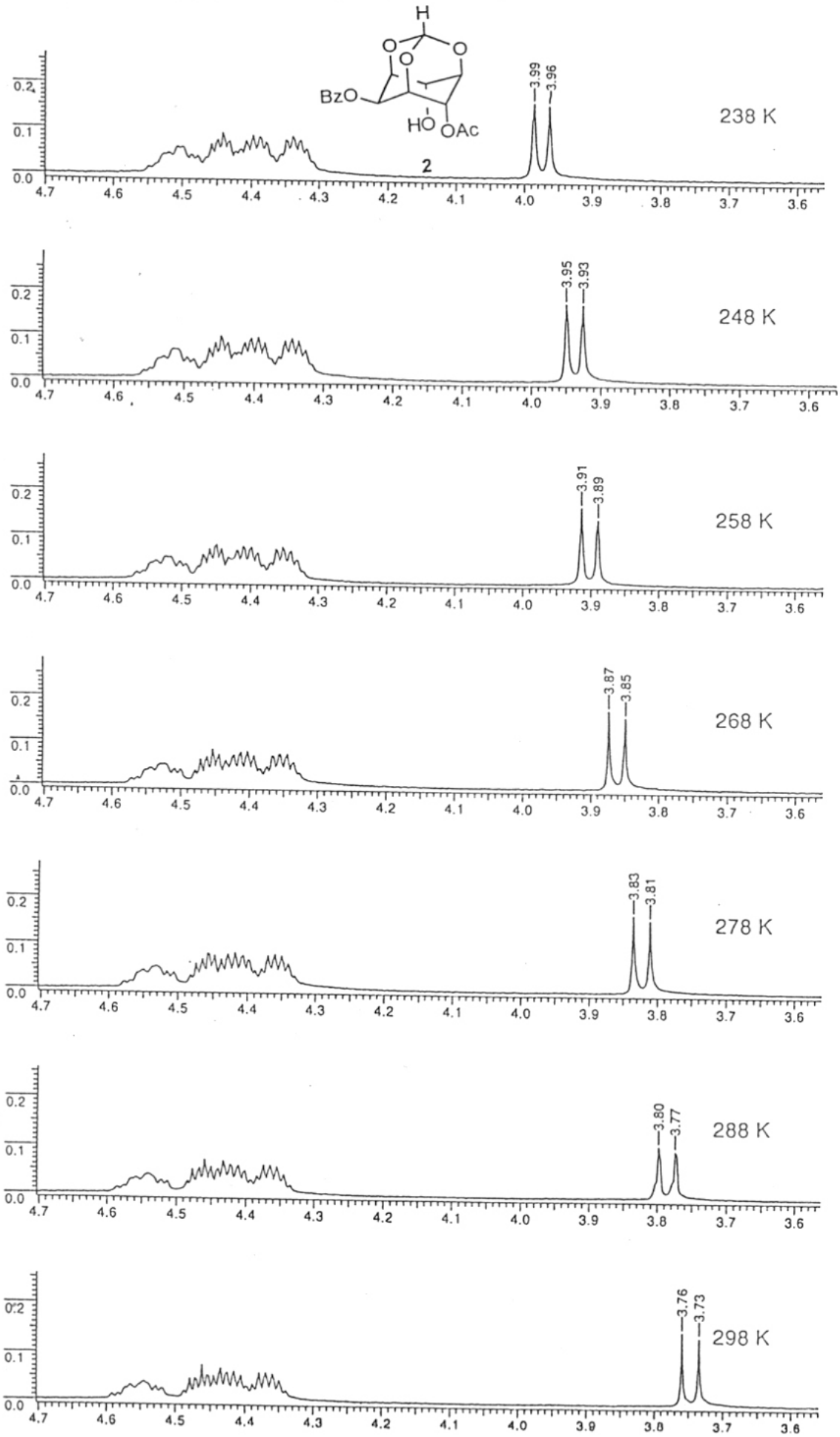


Figure 10. Variation of the chemical shift of hydroxyl groups of **3** with temperature

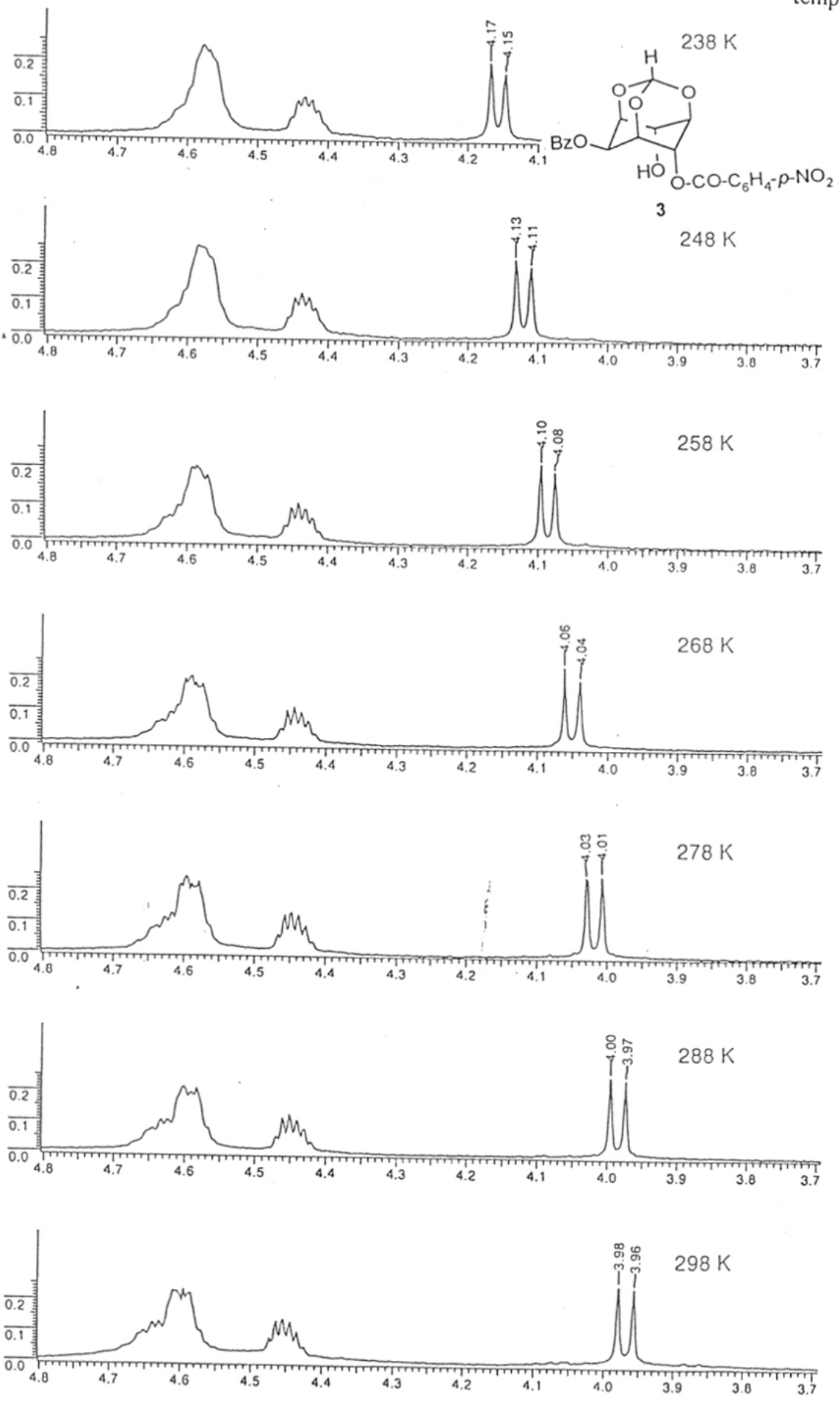


Figure 11. Variation of the chemical shift of hydroxyl groups of **1** with temperature

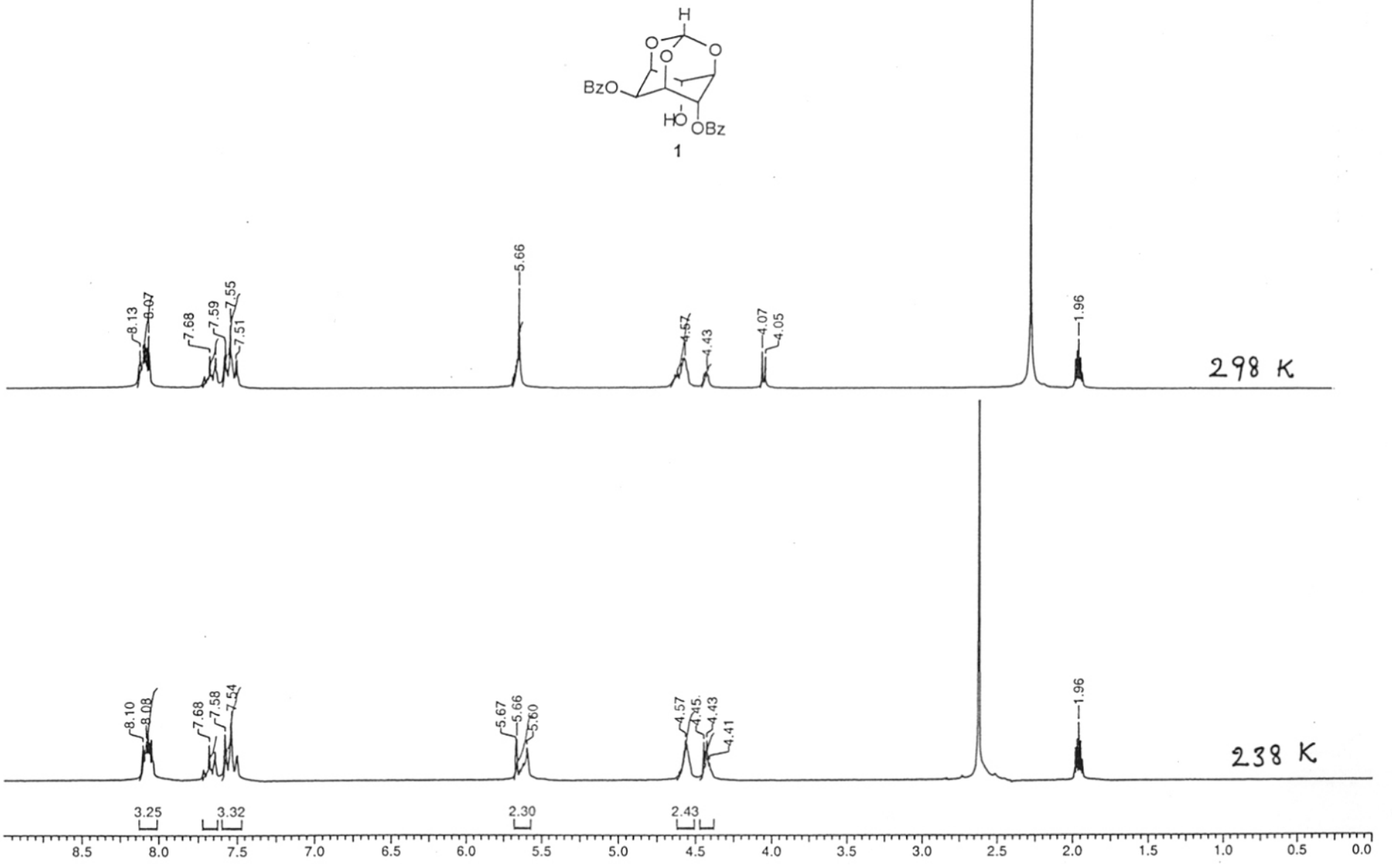
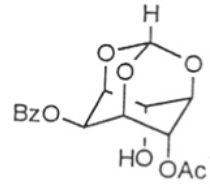
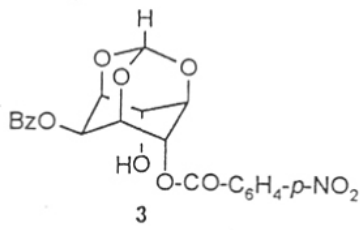


Figure 12. Variation of the chemical shift of hydroxyl groups of **2** with temperature



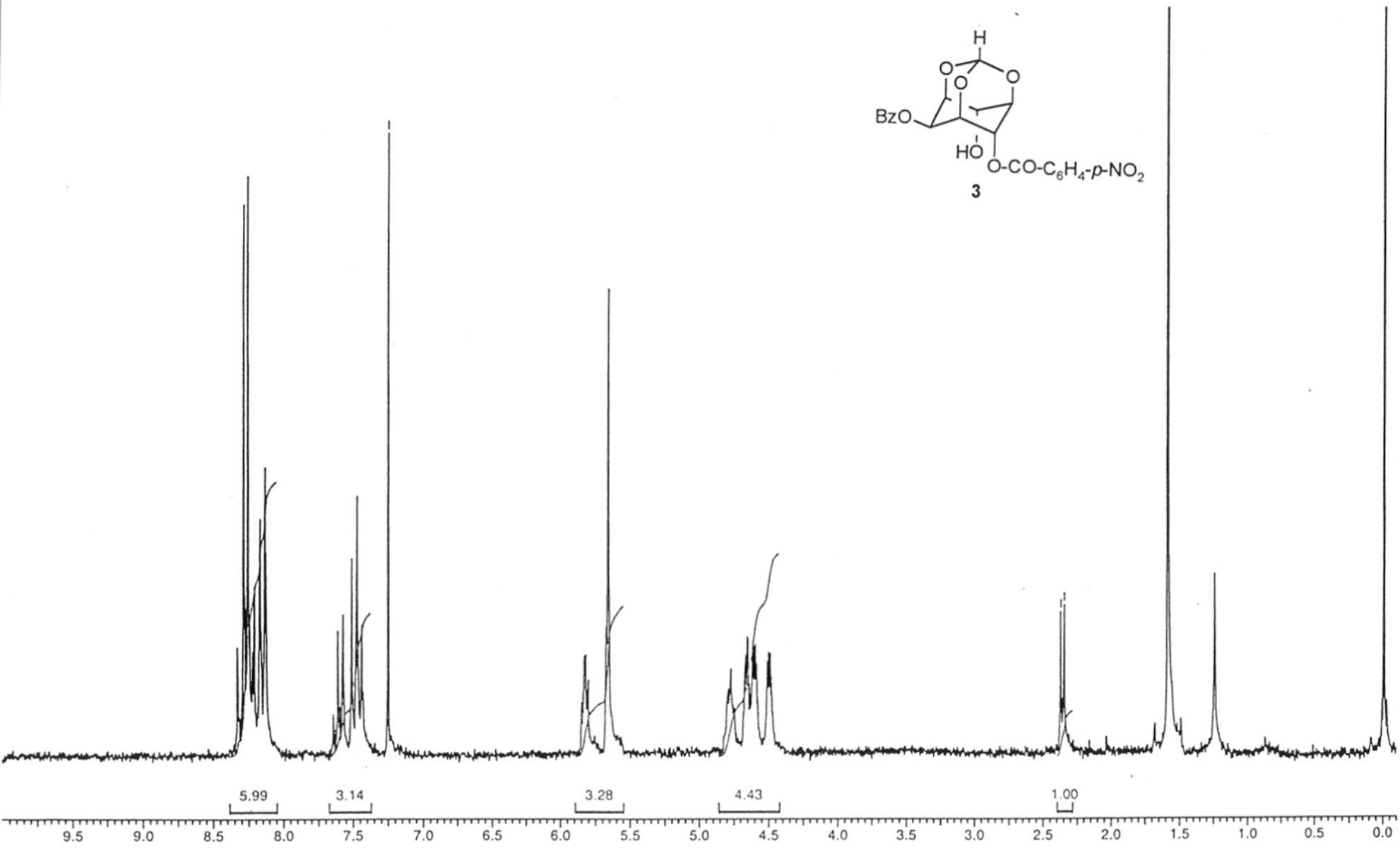
2

Figure 13. Variation of the chemical shift of hydroxyl groups of **3** with temperature



3

Figure 14. **3** in chlorofom-d



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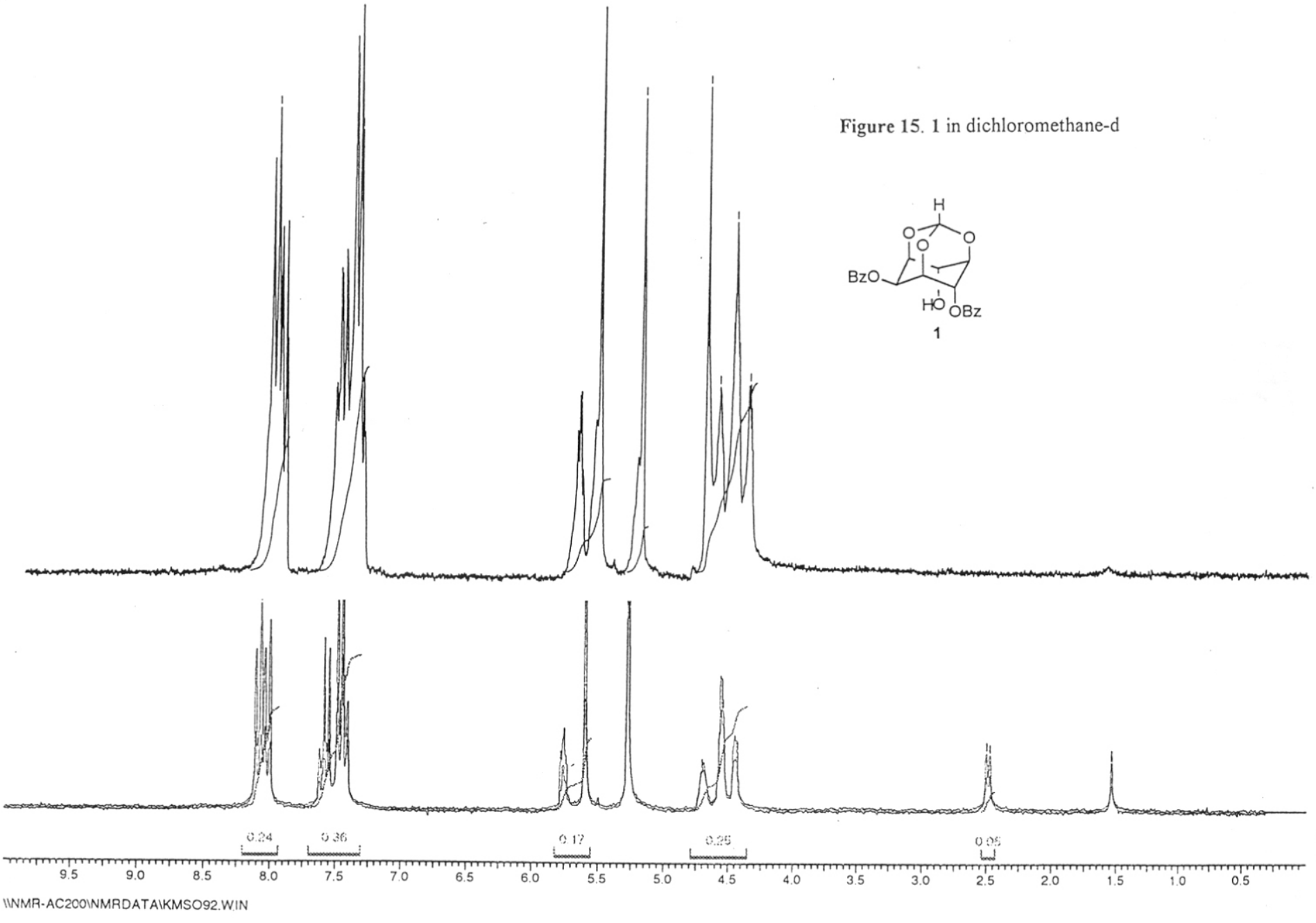
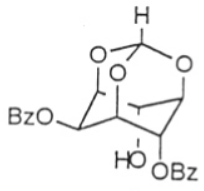


Figure 15. 1 in dichloromethane-d

1

Figure 16. 1 in pyridine-d_5



1

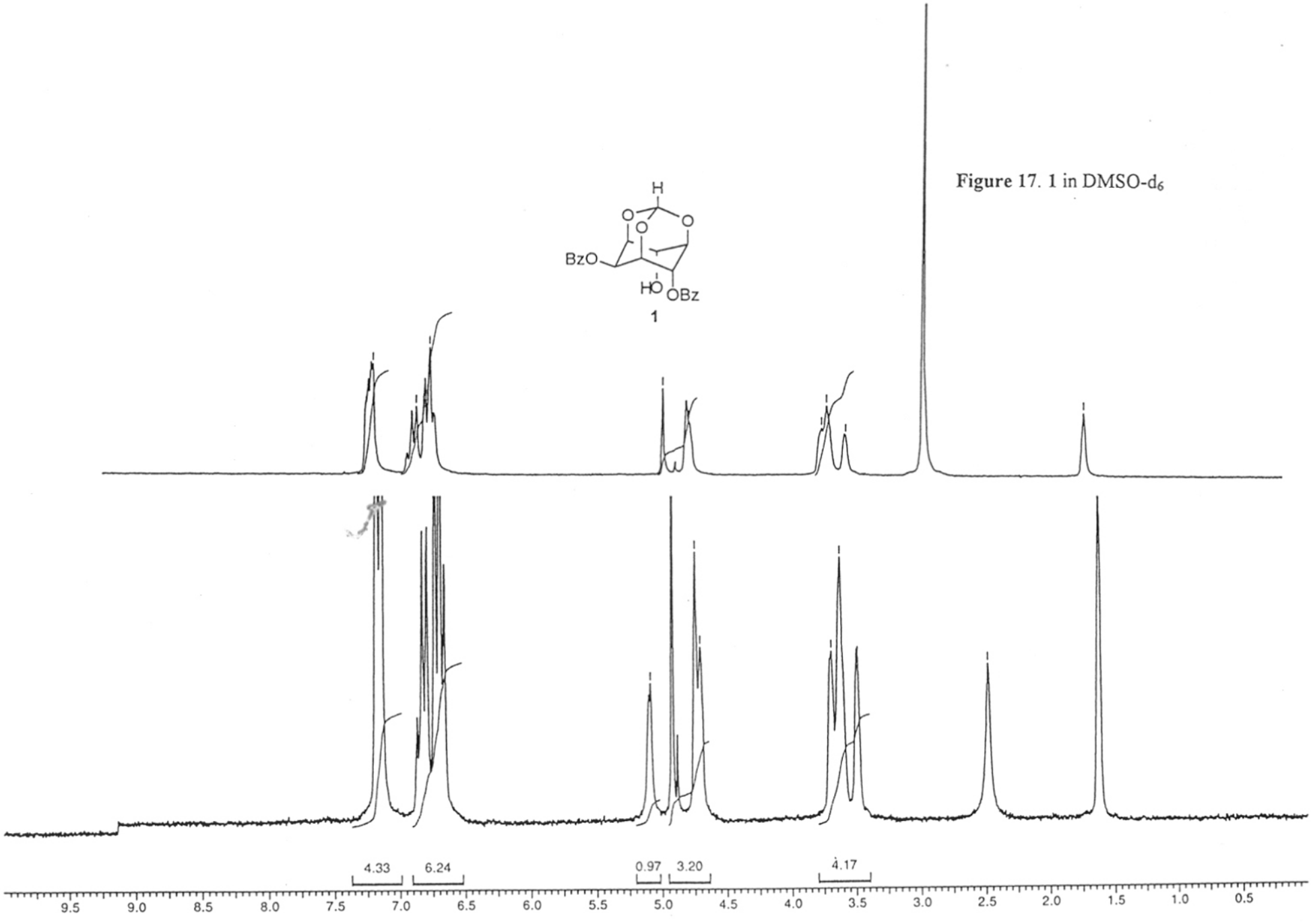


Figure 17. 1 in DMSO-d_6

Figure 18. 1 in acetonitrile-d_3 + pyridine-d_5

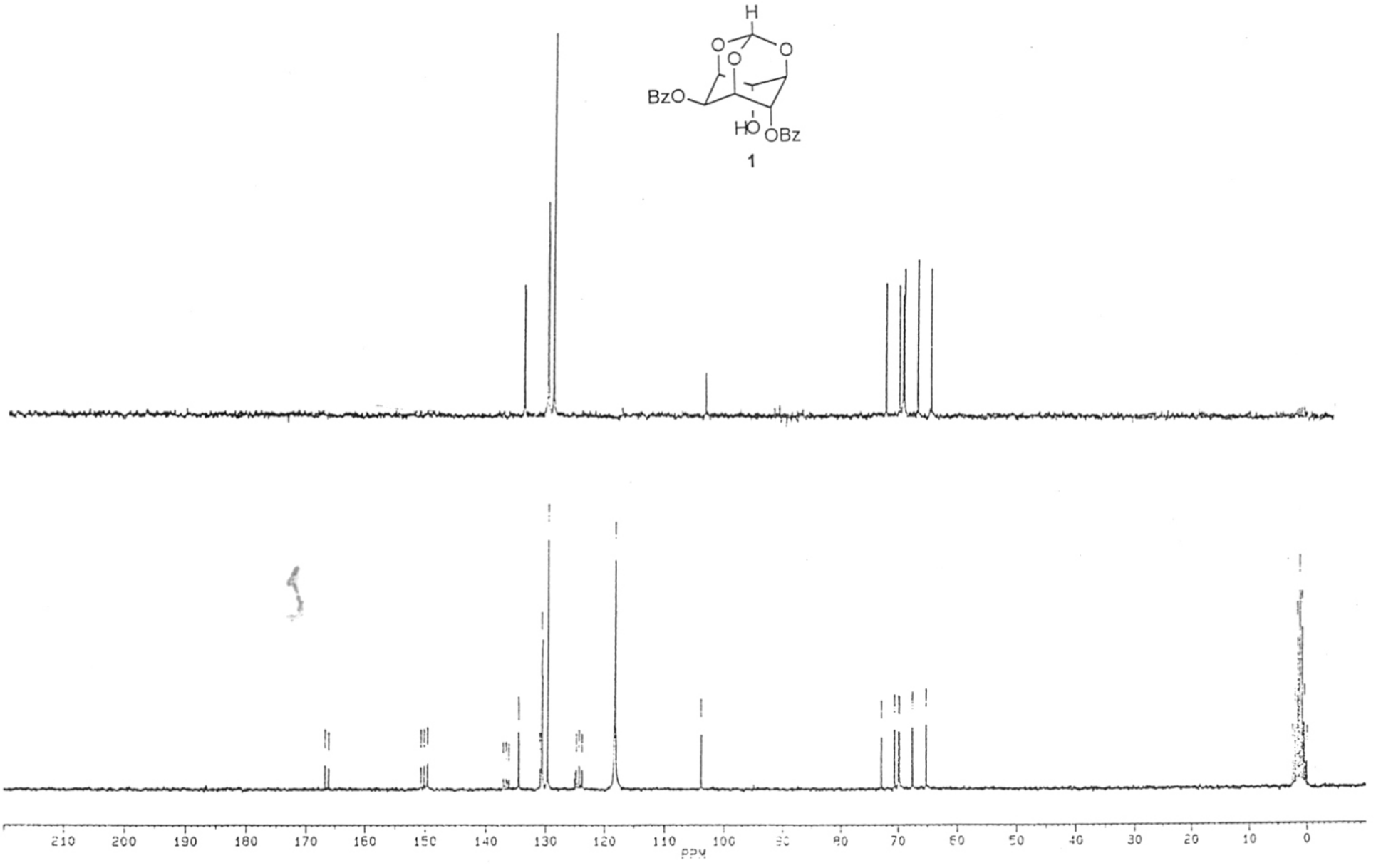


Figure 19

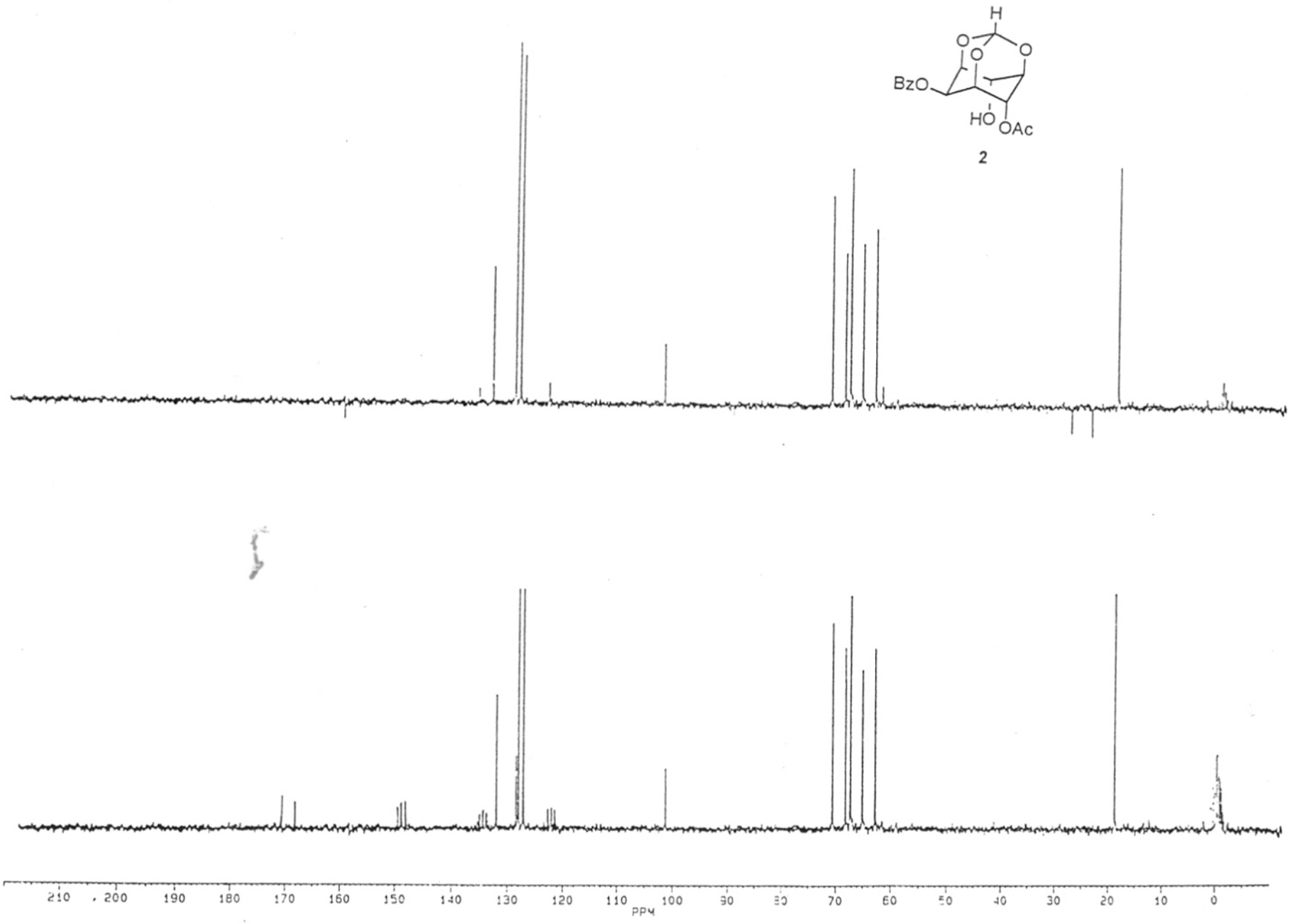
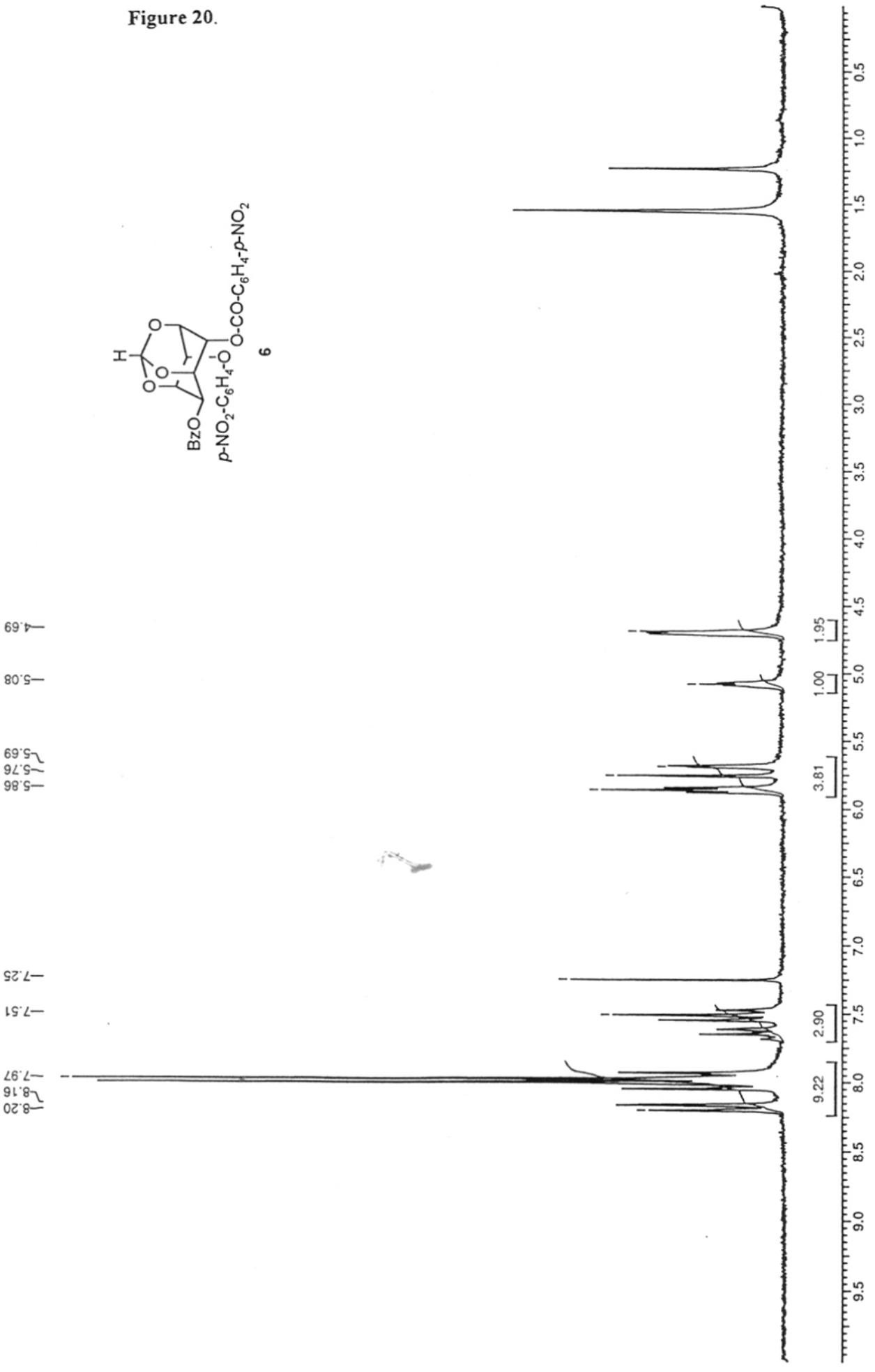

H
O
O
O
BzO
HO
OAc
2
210
200
190
180
170
160
150
140
130
120
110
PPM
100
90
80
70
60
50
40
30
20
10
0

Figure 20.


BzO
p-NO2-C6H4-O
O-CO-C6H4-p-NO2
6
8.20
8.16
7.97
7.51
7.25
5.86
5.76
5.69
5.08
4.69
9.22
2.90
3.81
1.00
1.95

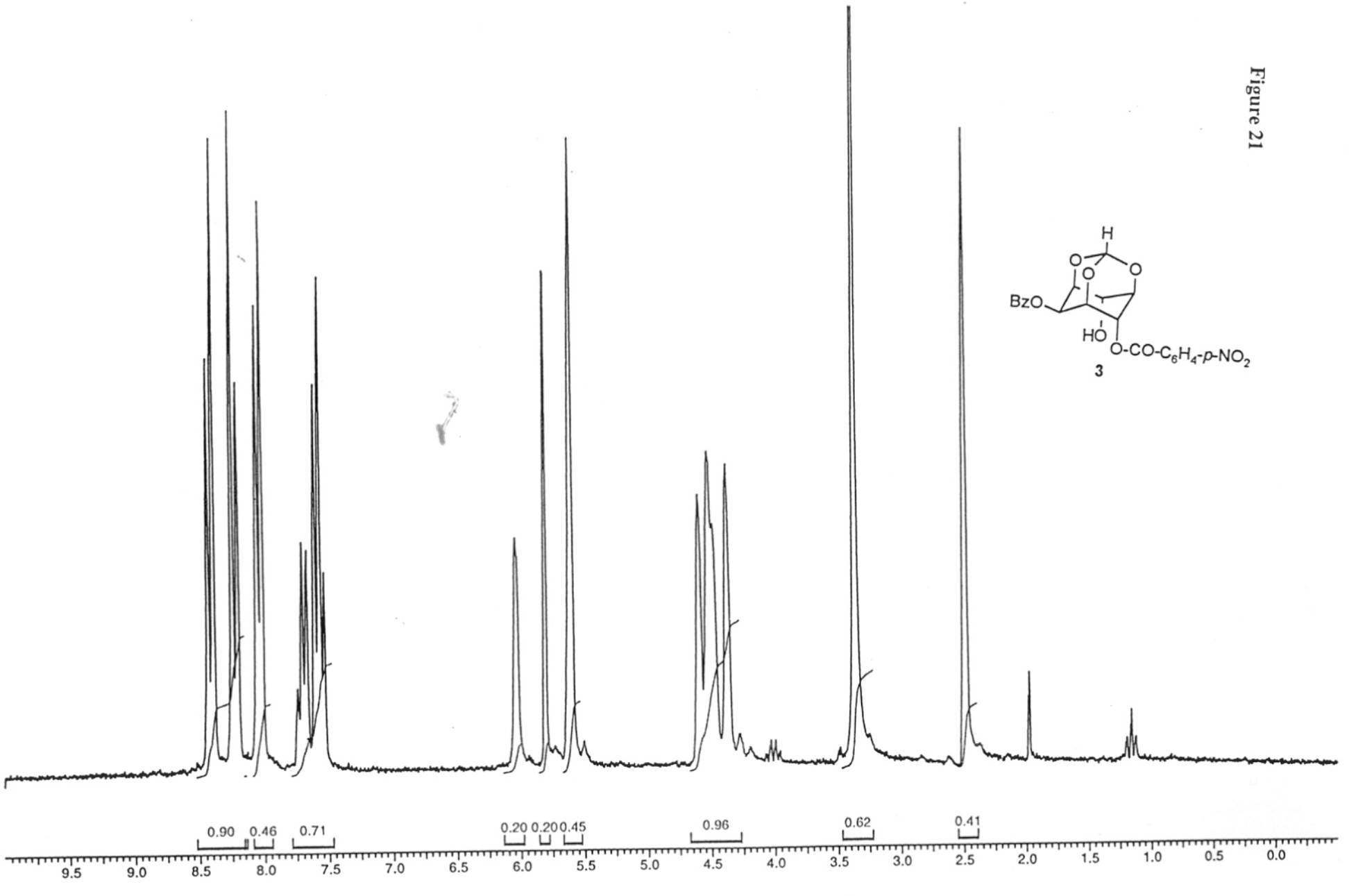

1H, DMSOD6,
BzO
HO
O-CO-C6H4-p-NO2
3
0.90
0.46
0.71
0.20
0.20
0.45
0.96
0.62
0.41
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

Figure 21

Figure 22

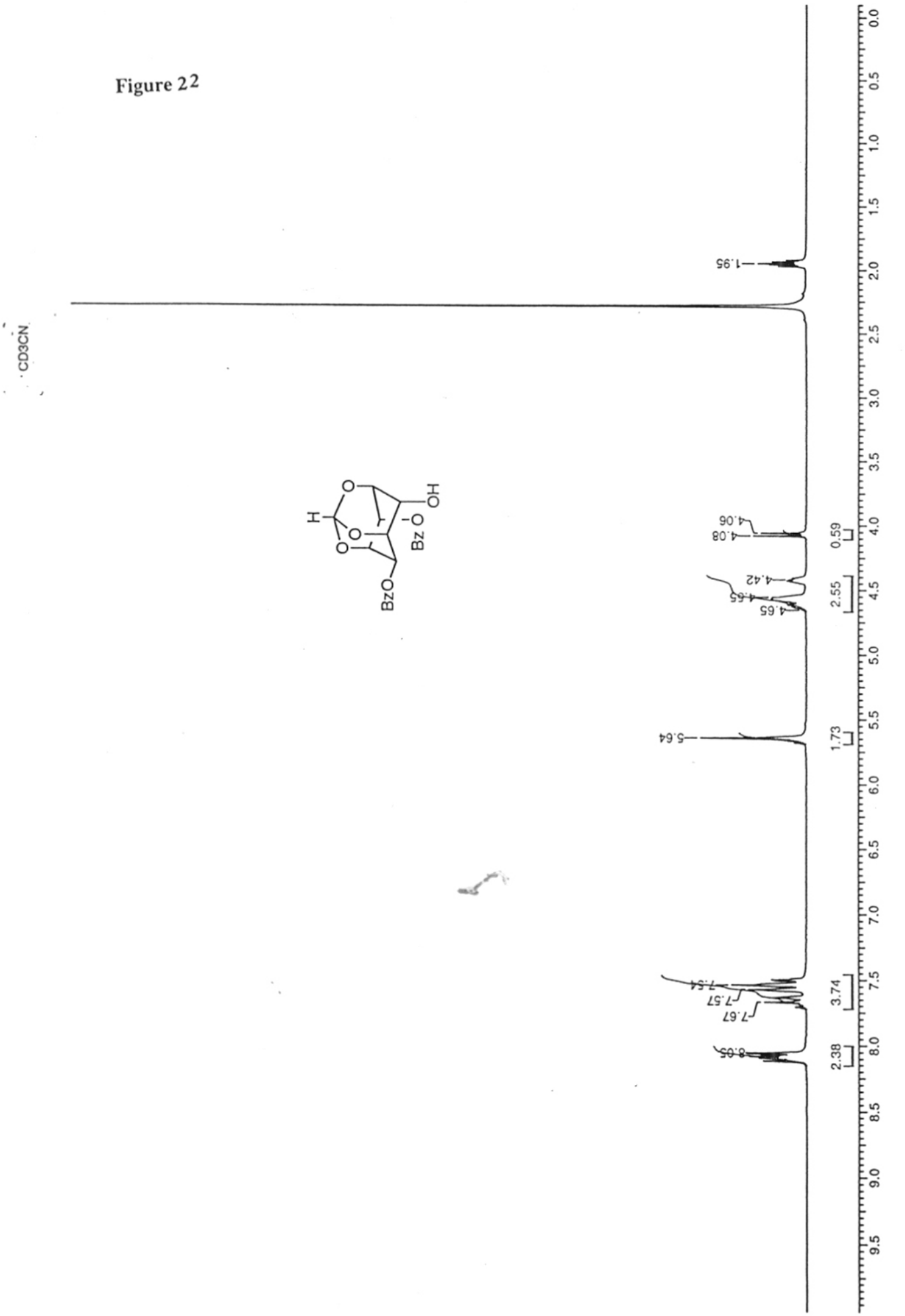

CD3CN
1.95
4.08
4.06
4.42
4.65
4.65
5.64
7.54
7.57
7.67
8.05
0.59
2.55
1.73
3.74
2.38
H
O
O
O
O
Bz O
OH
BzO

Figure 23

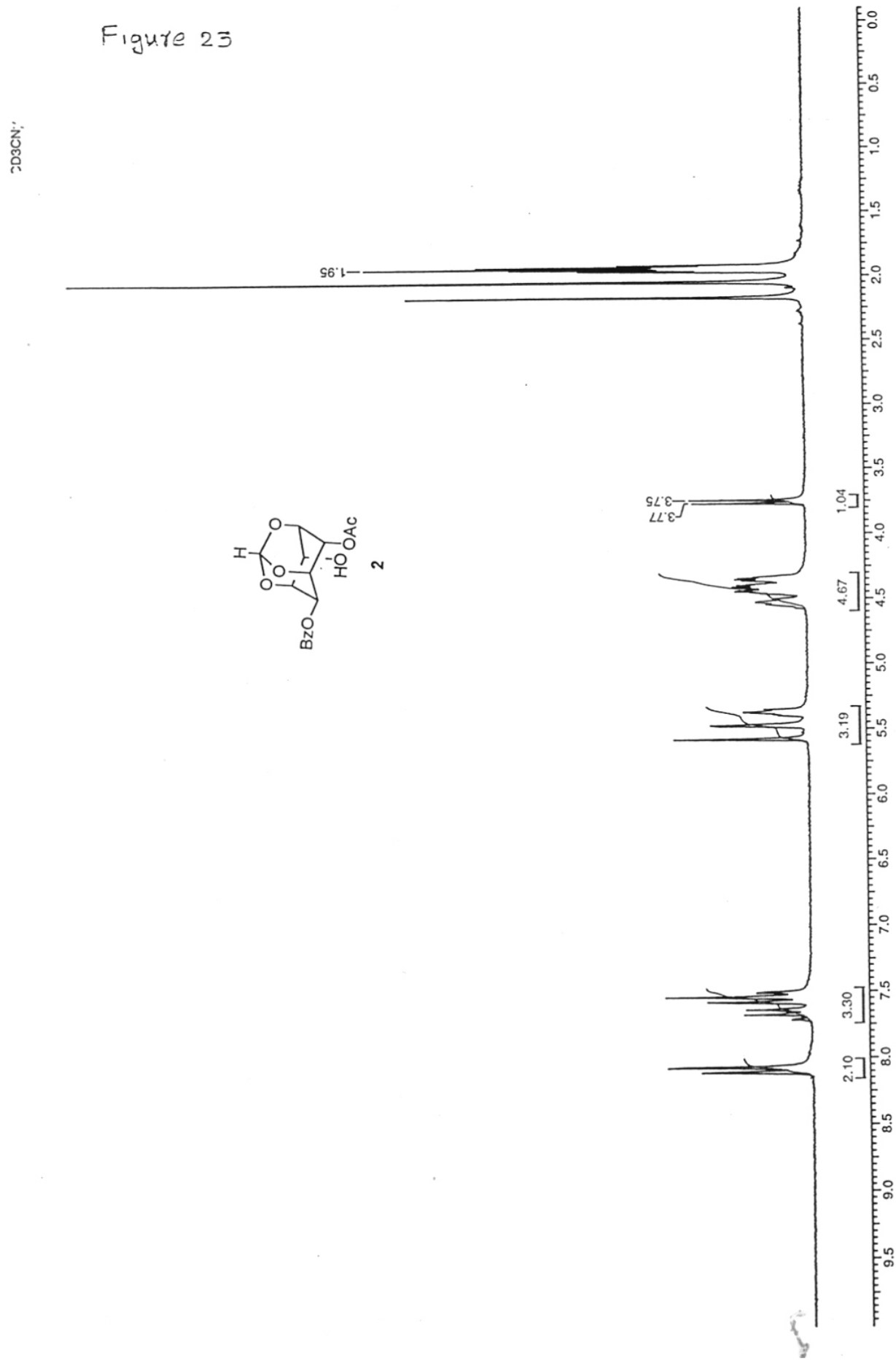
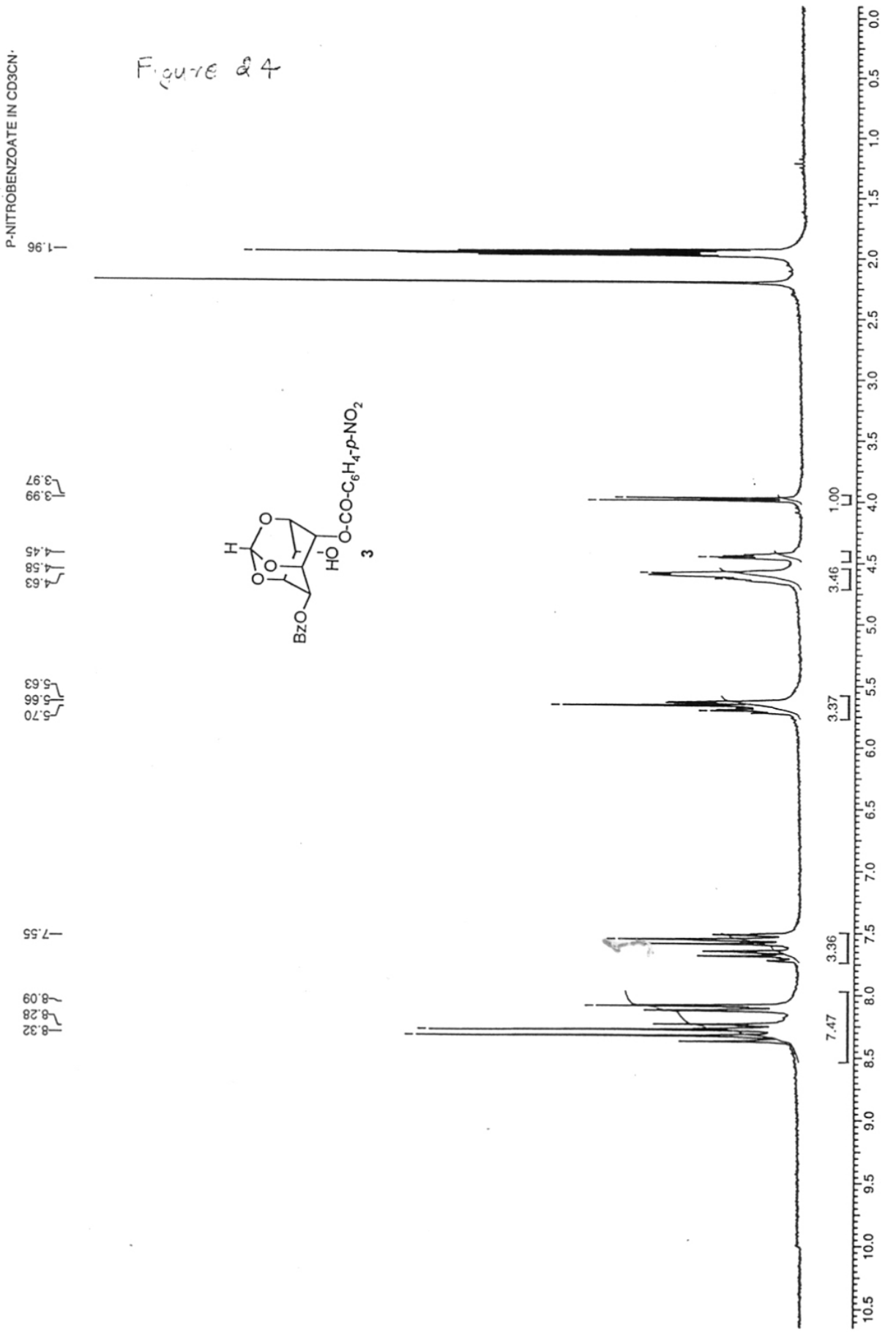


Figure 24


P-NITROBENZOATE IN CD3CN
1.96
3.97
3.99
4.45
4.58
4.63
5.63
5.66
5.70
7.55
8.09
8.28
8.32
1.00
3.46
3.37
3.36
7.47
BzO
HO
O-CO-C6H4-p-NO2
3

CHAPTER 5

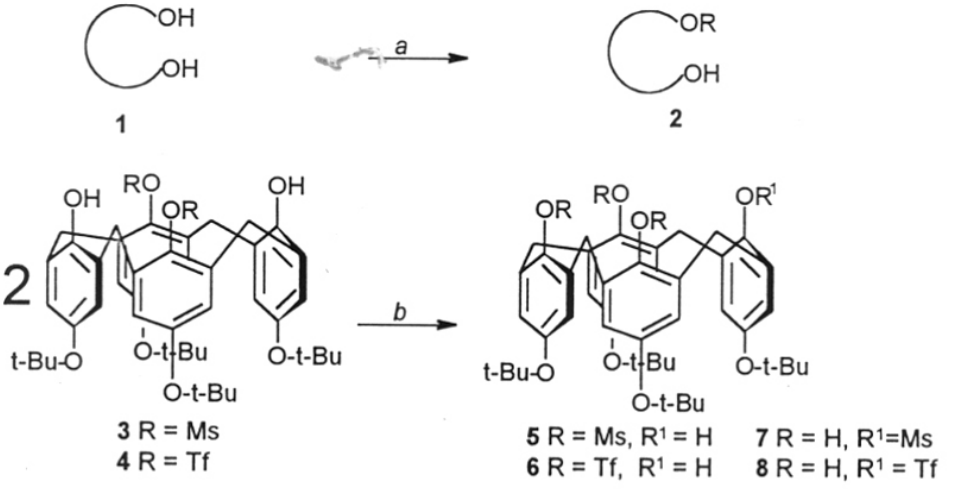
Silver (I) oxide mediated methanolysis of (±) 2,4-di-*O*-benzoyl-6-*O*-sulfonyl-*myo*-inositol 1,3,5- orthoformates: An unusual participation by the sufonyl group

5.1 Introduction

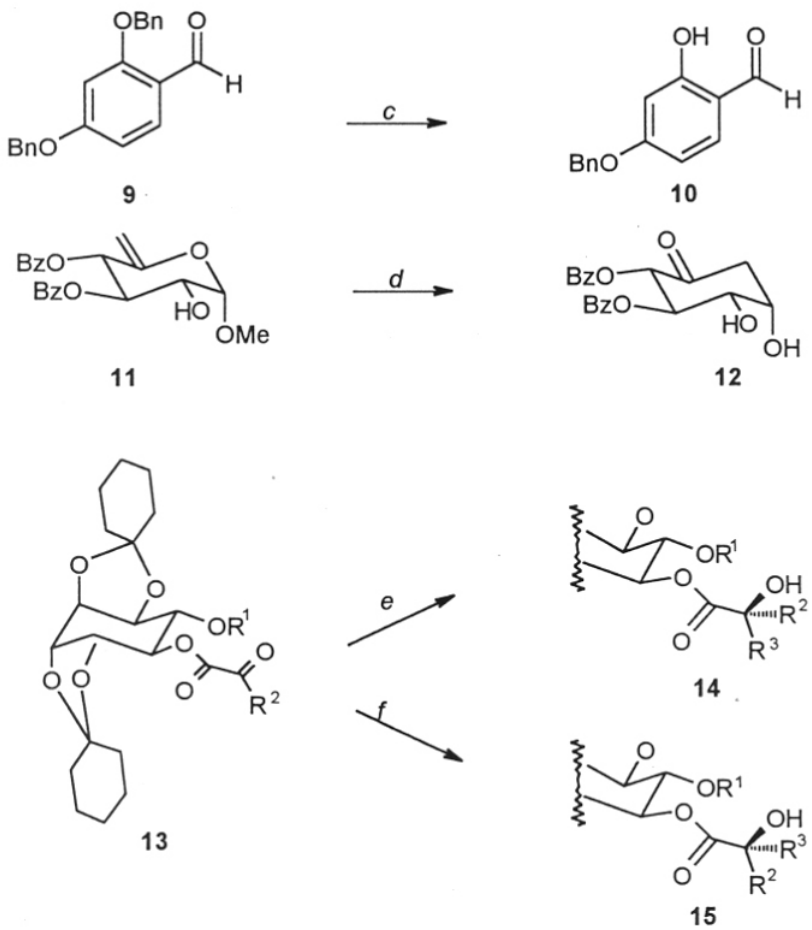
Many instances of unusual organic chemical reactions of small molecules due to the presence of two or more functional groups in close proximity are reported in the literature.[1,2] Effect of hydroxyl groups and carbonyl groups on the reaction of neighboring functional groups have been well studied and some of these systems have been used to model analogous enzyme catalyzed reactions.[3,4,5] Of particular interest to synthetic chemists are reactions where in the presence of metal ions in the reaction medium leads to unexpected and sometimes beneficial product formation. Some examples of such reactions reported in the literature are shown in **Scheme 5.1**.

Symmetric diols of the type **1** could be mono alkylated in high yields in presence of silver (I) oxide[6] and an alkyl halide in DCM or toluene to obtain synthetically important monoprotected symmetric diols **2**. The trisubstituted calixarenes **5** and **6** (otherwise difficult to synthesize) were easily obtained by the Palladium mediated inter molecular transesterification of the corresponding disubstituted derivatives **3** and **4**.[7] Exclusive cleavage of the benzyl group located ortho to the carbonyl group in aromatic benzyl ethers like **9** could be achieved in the presence of magnesium bromide to obtain **10**.[8] In the palladium mediated Ferrier rearrangement of **11** to **12**, the stereoselecctivity of the newly formed chiral center was controlled by the complexation of the hydroxyl protecting groups with Palladium.[9] The nucleophilic addition of organometallics to the α-ketoesterester **13** derived from chiro-inositol gave the corresponding α-hydroxy ester of high diastereomeric excess. Grignard reagents attacked from *re*-face to give **14** while organolithium reagents preferred *si*-face attack to give **15**.[10]

Scheme 5.1



Scheme 5.1(contd.)

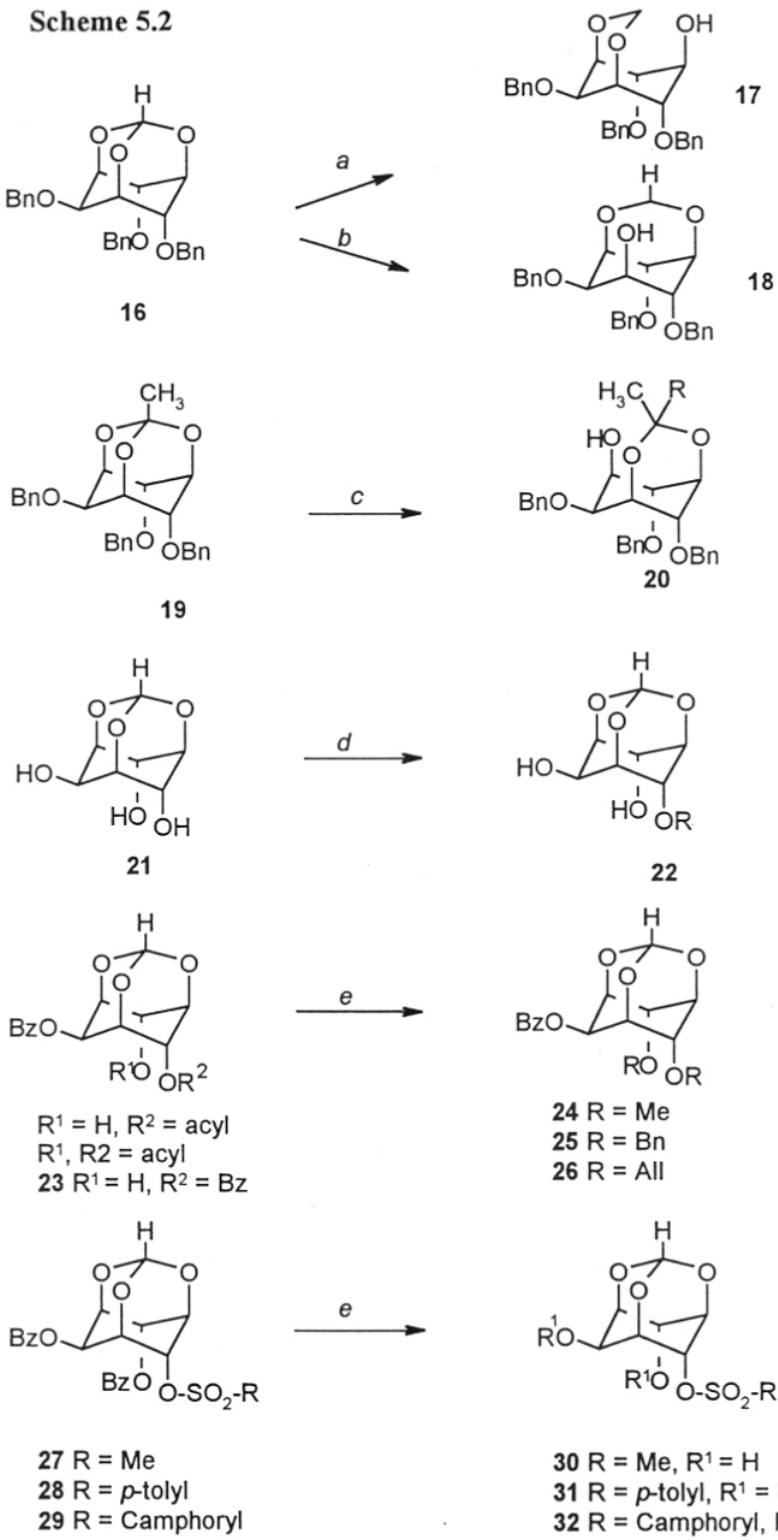


a) RX, Ag_2O, dichloromethane *b*) $Pd(Pph)_3Cl_2$, LiCl, dichloromethane *c*) $MgBr_2$, benzene *d*) Pd(II)salt, dioxane/water (2:1 v/v) *e*) R^3MgX, Ether or toluene *f*) R^3Li, ether or toluene

More relevant to the present work, regioselective reactions of *myo*-inositol derivatives observed due to the presence of metal ions in the reaction medium are shown in **Scheme 5.2**. In most of these reports, involvement of metal ion chelates with *myo*-inositol derivatives has been postulated. Chelation assisted C-O bond cleavage has been reported in the case of several *myo*-inositol 1,3,5-orthoformate derivatives. Reduction of the orthoformate derivative **16** with DIBAL resulted in the regiospecific cleavage of the orthoester bond at O-5 (**17**) while the reaction with trimethyl aluminium[11,12] resulted in the cleavage of the ester bond at O-1/3 to yield **18**. In a similar manner, **19** on treatment with Grignard reagent affected cleavage at O-1 position yielding the ether**20**[13]

(**Scheme 5.2**). One of the axial hydroxyl groups of the triol **21** could be selectively monoalkylated in presence of sodium hydride and an alkyl halide in DMF.[14]

Scheme 5.2



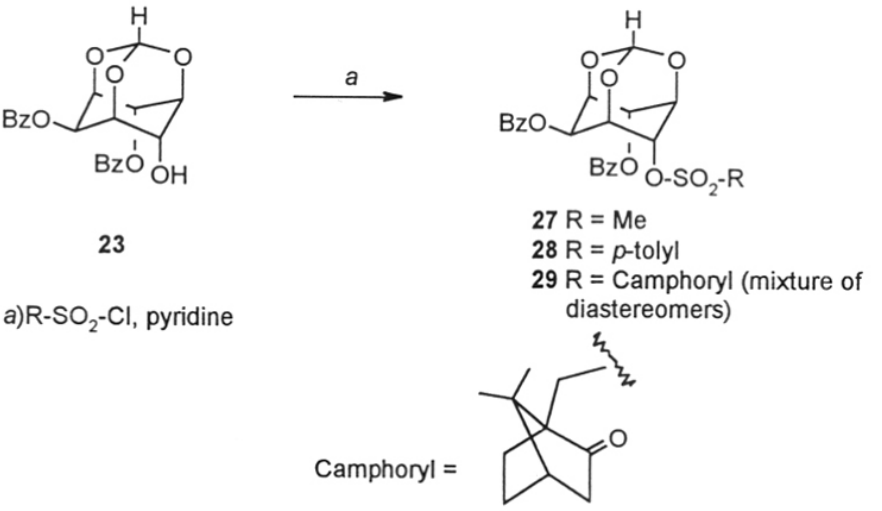
In our laboratory, the silver (I) oxide mediated alkylation of di- or tri-*O*-acyl-*myo*-inositol 1,3,5-orthoformate derivatives (eg. **23**) yielded 4,6-di-*O*-alkylated products (**24-26**) instead of the expected 6-*O*-monoalkylated products.[15,16] A detailed study on the mechanism on this reaction suggested the involvement of a silver complex during the reaction (see **Chapter 2**). Similarly, the reaction of sulfonate esters **27-29** with alkyl halides in the presence of silver (I) oxide resulted in the formation of diethers **30-32**.[17] It is interesting to note that silver (I) oxide mediated alkylation of the di- or tri-*O*-acyl *myo*-inositol orthoformates resulted in the cleavage and alkylation of axial esters exclusively, while in the case of sulfonates **27-29** cleavage and alkylation of axial as well as equatorial esters was observed. If indeed this reaction involved the chelation of *O*-acyl *myo*-inositol orthoformate derivatives with silver (I) oxide or silver halide generated during the alkylation reaction, we thought that the treatment of esters (**27-29**) with methanol (instead of alkyl halide) should result in their transesterification leading to the formation of the corresponding diols. Accordingly, this chapter presents an investigation on the methanolysis of O-acyl *myo*-inositol orthoformates in the presence of silver oxide and silver halides.

5.2 Results and discussion

5.2.1 Methanolysis of (±)2,4-di-*O*-benzoyl-6-*O*-sulfonyl-*myo*-inositol 1,3,5-orthoformate derivatives in presence of silver (I) oxide and silver halide

Sulfonates **27-29** were prepared by slightly modifying the reported procedure[17] (**Scheme 5.3**) and were characterized by comparison of the melting points and ^{1}H NMR

Scheme 5.3



spectra with those of the authentic samples. Sulfonates **27-29** underwent methanolysis with ease (**Scheme 5.4**) in 10% methanol-DMF in the presence of silver (I) oxide and silver iodide to the corresponding diols **33-35**. In all the three cases excellent yields (92%-97%) of the diols (**33-35**) were obtained. The mesylate **27** underwent complete methanolysis in 24 hours while the sulfonates **28** and **29** took 28 and 35 hours respectively for the complete reaction under identical conditions.

Scheme 5.4

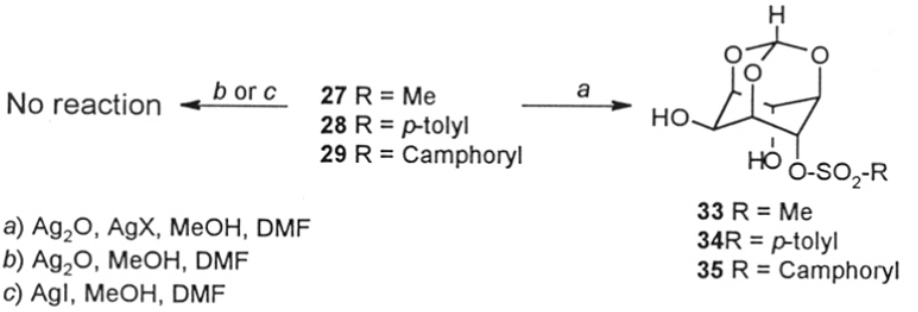


Table 5.1 Methanolysis of (±)2,4-di-*O*-benzoyl-6-*O*-mesyl-*myo*-inositol 1,3,5-orthoformate derivative **27** in presence of silver (I) oxide and silver halides[a]

Entry	Silver halide	Products (isolated yield %)
1	AgI	**33** (98)
2	AgBr	**33**(12), **36**(27), **27**(60)
3	AgCl	**33**[b](0) ,**27**(95)
4	AgI[c]	**33**(12), **36**(29), **27**(40)
5	AgI[d]	**33**(0),**27**(100)
6	None	**33**(0), **27**(100)

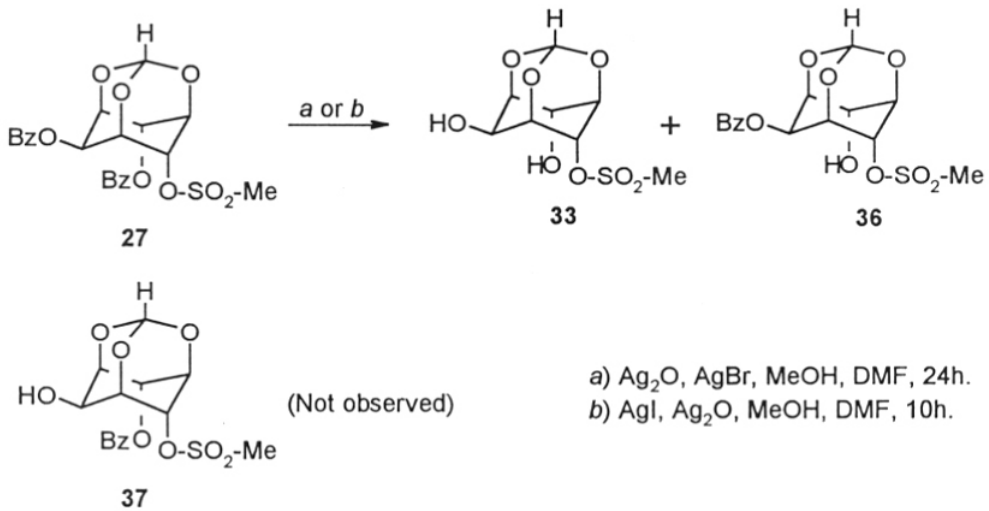
[a] All the reactions were carried out using 0.25 mmol of **27** in 1ml of methanol/DMF mixture (10%v/v) for 24 hours in presence of 1.25 mmol of silver (I) oxide and 0.5 mmol of silver halide.

[b] Detectable by TLC

[c] for 10 h.

[d] Reaction done in the absence of silver (I) oxide

Scheme 5.5



No methanolysis was observed on treatment of **27** with silver (I) oxide or silver iodide alone separately under the same conditions as above. More than 90% of the starting material **27** could be recovered at the end of 24 hours. This showed that a combination of silver (I) oxide and silver iodide is crucial for the methanolysis of **27-29**. Results of methanolysis of the sulfonates **27-29** under various conditions are shown in **Table 5.1**.

The diols **33-35** were characterized based on their spectroscopic and analytical data. Infrared spectrum of **33** showed the presence of hydroxyl group (3325-3500 cm^{-1}). The ^{1}H NMR spectrum of **33** showed two hydroxyl protons at 5.53 δ and 5.68 δ (exchangeable with D_2O) and six inostol ring hydrogens between 3.94 δ and 5.15 δ. The orthoformate proton appeared as a doublet at 5.56 δ and the protons corresponding to the methyl group of the mesylate appeared as a sharp singlet at 3.28 δ. The ^{13}C NMR spectrum of **33** clearly showed six distinct inositol ring carbons (58.84 δ to 73.32 δ), the methyl carbon of the mesyl group (38.38 δ) and the orthoformate carbon (102.57 δ). The spectral characteristics of the diols **34** and **35** were similar to that of **33** except for the signals corresponding to the tosyl and camphoryl groups (see experimental section for details).

We studied the concentration dependence of the chemical shift of the hydroxyl protons in the ^{1}H NMR spectrum of the diols **34** and **35**. Chemical shift of both the hydroxyl groups in **34** and **35** increased gradually with concentration in chloroform-d as

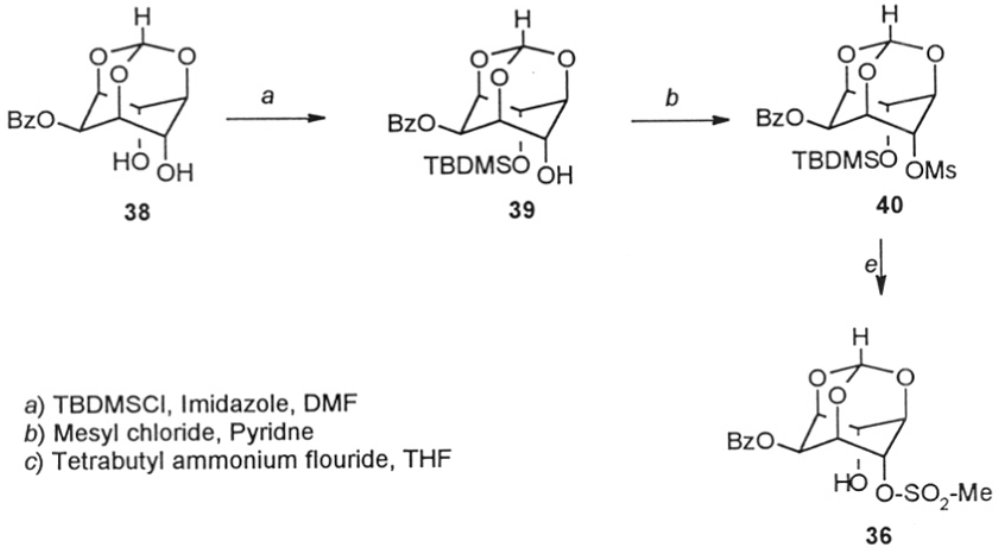
shown in **Figure 1**. The concentration dependence indicates that both the hydroxyl groups in **34** and **35** take part in intermolecular hydrogen bonding in solution. We could not carry out a similar study with **33** in non-polar solvents due to its limited solubility. However, in the solid state as shown by X-ray diffraction studies (**Figure 15**), the axial 4-hydroxyl group of **33** is hydrogen bonded to the axial 6-oxygen.

Methanolysis of the mesylate **27** in the presence of silver bromide and silver (I) oxide gave the diol **33** (27%) and the hydroxy ester **36** (**Table 5.1**, entry-2 **Scheme 5.5**). A mixture of the diol **33** and the hydroxy ester **36** was obtained on decreasing the reaction time (10 h.) for the silver iodide catalyzed methanolysis of **27**, we could isolate 29% of **36**, 12% of the diol **33** and 40% of the starting material **27**. These results show that **36** is an intermediate during the methanolysis of **27** in the presence of silver (I) oxide and silver halide. Isolation of **36** implies that the axial benzoate undergoes methanolysis faster than the equatorial benzoate group in **27**. Silver chloride failed to bring about the methanolysis of the benzoates in **27** as was evidenced by the recovery of the starting material (92%) at the end of 24h. These results indicate that nature of the silver halide plays a major role during the methanolysis, as was observed during the transesterification of the dibenzoate **23** with itself (**Chapter 2**).

The IR spectrum of **36** showed the presence of a carbonyl (1722 cm^{-1}) and hydroxyl group (3400 cm^{-1}). The ^1H NMR spectrum of **36** showed protons of the mesyl group as a sharp singlet at 3.2 δ. The six inositol ring hydrogens appeared between 4.3 and 5.5 δ. The hydroxyl proton appeared at 4.5 δ along with one of the *myo*-inositol ring hydrogens and the orthoformate proton appeared at 5.6 δ as a doublet. The five aromatic hydrogens appeared between 7.2 and 8.3 δ as multiplets with a peak integration ratio of 2:1:2. Since there are two isomeric hydroxy esters possible on partial methanolysis of **27** (**36** and **37**), the structure of **36** was unambiguously established by alternate synthesis (**Scheme 5.6**).

The hydroxy ester **36** was prepared starting from the diol **38** (**Scheme 5.6**). Silylation of **38** with TBDMSCl in DMF using imidazole as a base gave the monosilyl ether **39** which was mesylated using mesyl chloride/pyridine to obtain the protected mesylate **40**. The silyl ether in **40** was cleaved using tetrabutyl ammonium fluoride to obtain **36** (**Scheme 5.6**).

Scheme 5.6

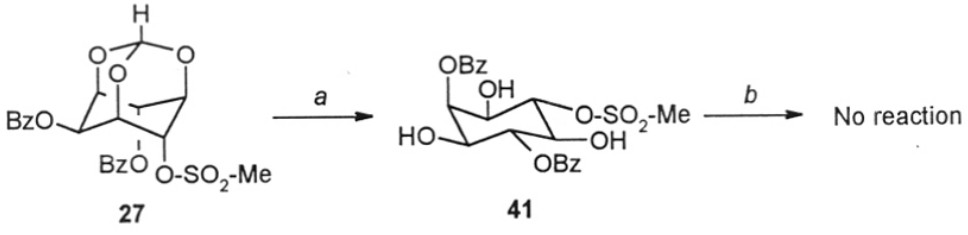


^{1}H NMR spectrum of the product obtained via this route was identical to that of the product obtained on methanolysis of **27** in the presence of silver (I) oxide and silver bromide.

In order to see whether the ease of methanolysis of the benzoates in **27-29** is due to: (a) the relative spatial orientation of the ester and the sulfonyl groups in **27-29** (which could facilitate formation of a chelate due to the proximity of oxygen atoms. (see **Scheme 5.10**) or (b) due to the electron withdrawing effect of the sulfonyl group, we studied the methanolysis of the triol **41**; which lacks the rigid orthoformate backbone as in **27**.

The triol **41** was prepared by the acid catalyzed methanolysis of the mesyl derivative **27** using *p*TSA in methanol (**Scheme 5.7**). The triol **41** was characterized by

Scheme 5.7



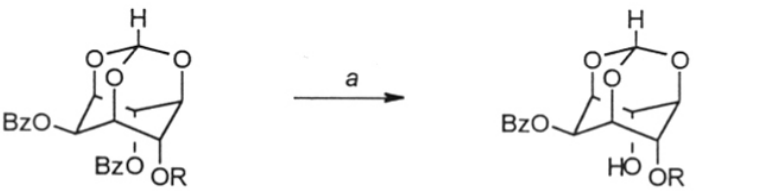
spectroscopy and elemental analysis. The IR spectrum of **41** showed absorptions corresponding to two carbonyl groups (1680 and 1695 cm^{-1}) and the hydroxyl groups (3460-3540 cm^{-1}). In the ^1H NMR spectrum (in DMSO-d_6) the mesyl group appeared at 3.15 δ as a sharp singlet. The six inositol ring hydrogens appeared as multiplets from 3.2 to 5.6 δ. Three hydroxyl protons appeared as three distinct doublets at 5.45, 5.55 and 5.65 δ. The aromatic region of the ^1H NMR spectrum contained multiplets corresponding to the ten aromatic hydrogens (7.4-8.1 δ) with a peak integration ratio of 4:6. The ^{13}C NMR spectrum (DMSO-d_6) of **41** showed two carbonyl carbons (165.77 and 161.45 δ), aromatic carbons (128.98-133.79 δ), six inositol ring carbons (67.63 to 85.41 δ) and the methyl carbon of the mesyl group (38.73 δ).

The mesyl triol **41** when subjected to methanolysis in the presence of silver (I) oxide and silver iodide remained unchanged and it was recovered quantitatively (**Scheme 5.7**). This experiment showed that the spatial orientation of the sulfonyl group and ester groups and not the electronic effect of the sulfonyl group that is responsible for the methanolysis of the benzoates in **27-29**.

5.2.2 Methanolysis of (±)-2,4-di-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate 23 and its methyl ether 42 in the presence of silver (I) oxide and silver halides

To establish that the sulfonyl group did play a role (as was observed during their alkylation with alkyl halides in the presence of silver (I) oxide) we carried out the methanolysis of the dibenzoate **23** and the methyl ether **42** (**Scheme 5.8**). The results of such experiments are shown in **Table 5.2** and **Table 5.3**.

Scheme 5.8



23 R = H
42 R = Me

38 R = H (20-94%)
43 R = Me (0-80%)

a) Ag_2O, AgX, MeOH, DMF

Table 5.2 Methanolysis of (±)-2,4-di-*O*-benzoyl-*myo*-inositol- 1,3,5-orthoformate (**23**) in the presence of silver (I) oxide and silver halides[a]

Entry	Silver halide	Products (isolated yield %)
1	AgI	**38**(94), **23**(0)
2	AgBr	**38**(68), **23**(30)
3	AgCl	**38**(20), **23**(80)
4	AgI[b]	**38**(0), **23**(100)
5	None	**38**(0), **23**(100)

[a] All the reactions were carried out using 0.25 mmol of **23** in 1ml of methanol/DMF mixture (10%v/v) for 24 hours in the presence of 1.25 mmol of silver (I) oxide and 0.5 mmol of silver halide.

[b] In the absence of silver (I) oxide

The dibenzoate **23** underwent methanolysis in the presence of silver (I) oxide and silver halides to yield the diol **38**. In all the experiments methanolysis of only the axial benzoate was observed while the equatorial benzoate remained intact. These results are comparable with the results on *O*-alkylation of di- and tri-*O*-substituted *myo*-inositol orthoformates with alkyl halides in the presence of silver (I) oxide where, only the axial benzoate group underwent cleavage and alkylation, to yield the corresponding diaxial diethers (**Chapter 2, Scheme 2.3**).[17] The relative efficiencies of the silver halides in bringing about the methanolysis of the axial benzoate in **23** was in the same order as observed for the methanolysis of the sulfonates **27-29**, viz.; AgI > AgBr > AgCl.

Table 5.3 Methanolysis of (±)-2,4-di-*O*-benzoyl-6-*O*-methyl-*myo*-inositol 1,3,5-orthoformate **42** in presence of silver (I) oxide and silver halide[a]

Entry	Silver halide	Products (isolated yield %)
1	AgI	**43**(26), **42**(70)
2	AgBr	**43**(13), **42**(86)
3	AgCl	**43**[b](0), **42**(95)
4	AgI[c]	**43**(80), **42**(16)

Table 5.3 (Contd.)

5	AgI	**34**(0), **42**(100)
6	None	**34**(0), **42**(100)

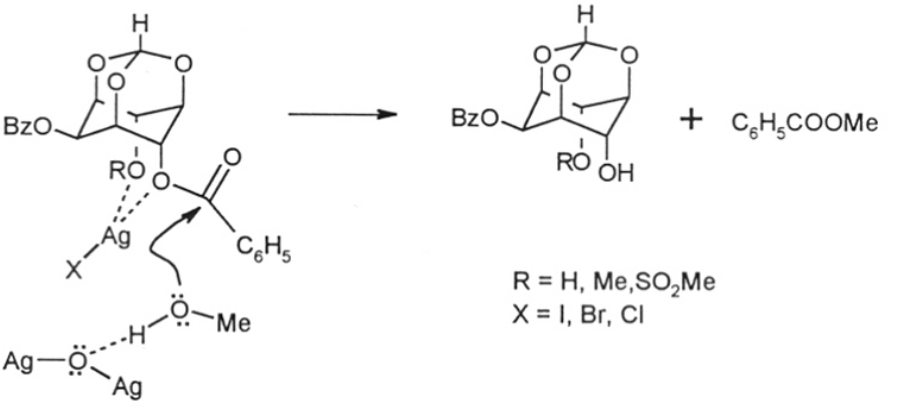
[a] All the reactions were carried out using 0.25 mmol of**42** in 1ml of methanol/DMF mixture (10%v/v) for 24 hours in presence of 1.25 mmol silver (I) oxide and 0.5 mmol of silver halide.

[b] Detectable by TLC

[c] for 80 h.

Similar results were obtained for the methanolysis of the axial benzoate in the methyl ether **42**. But, the yields of the hydroxy ether **43** obtained (entries 1-3 **Table 5.3**) for the 24h. reaction was much less than those obtained in the case of the dibenzoate **23**. However, the yield of **43** could be increased to 80% by allowing the reaction to continue for 80h (entry 4, **Table 5.3**). Comparison of the results in **Table 5.2** and **Table 5.3** show that the axial hydroxyl group is much more effective in intramolecularly assisting the methanolysis of the axial benzoate, in the presence of silver (I) oxide and silver halide as compared to the corresponding methoxy group. A mechanism similar to the one proposed for the transesterification of the dibenzoate **23** (**Chapter 2**) may be operating during the methanolysis of the axial benzoate in **23**, **27**, and **42** (**Scheme 5.9**). The observed difference in the relative rates of methanolysis of **23** and **42** could be due to the ability of the hydroxyl group to chelate better with silver halide, as compared to the methoxy group.

Scheme 5.9

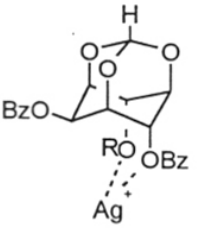


A comparison of the results on the methanolysis experiments of the mesylate **27** with that of the methyl ether **42** and the dibenzoate **23** (**Section 5.2.2**) clearly shows that

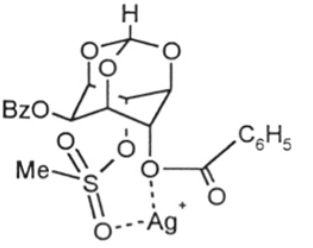
the cleavage of the equatorial benzoate group is due to the sulfonate group at the 4(6)-position. Also the dependence of the relative ease of methanolysis on the silver halide used suggests the involvement of a silver chelate during the methanolysis of the sulfonates **27-29**. To see if any other metal could bring about the methanolysis of any of the diesters **27**, **23** or **42** we treated them with $MgBr_2$ under methanolysis conditions used in the presence of silver halide. In all the cases starting materials were recovered quantitatively.

Based on the results presented so far, the structures of the chelates (formed on the surface a mixture of silver (I) oxide and silver halide) that might be responsible for the methanolysis of the benzoates in **27-29** are shown in **Scheme 5.10**. The possibility

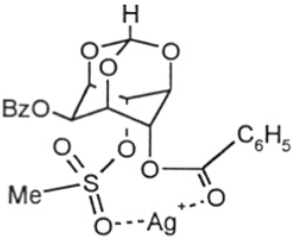
Scheme 5.10



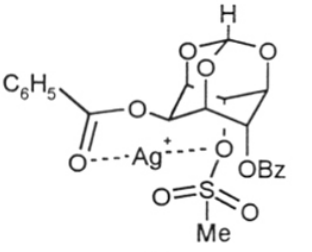
44 R = H, Me, Ms



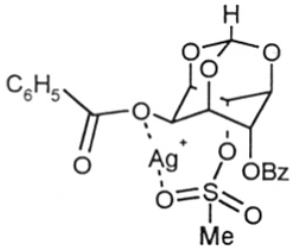
45



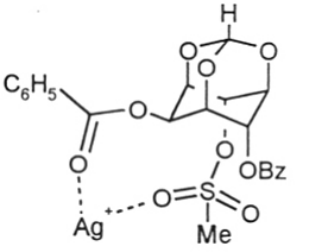
46



47



48

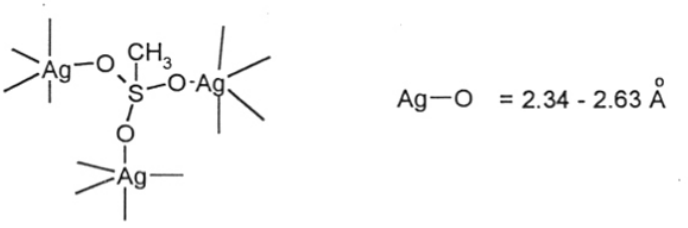


49

of formation of silver chelates is supported by the fact that the complexation of silver ions with sulfonyl oxygens in silver salts of methane sulfonic acid and p-bromomethane

sulfonic acid are known in the literature[18, 19] (**Scheme 5.11**). In the former case, there is no distinct molecule; the methane sulfonyl groups act as penta-coordinating ligands. Thus, each silver atom is surrounded by a very distorted trigonal bipyramid with Ag-O bond distance in the range of 2.34-2.63 Å.

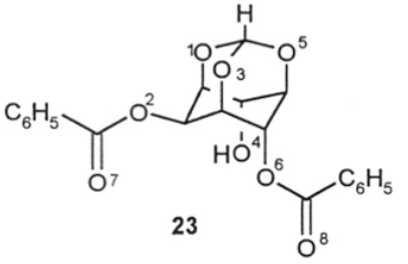
Scheme 5.11



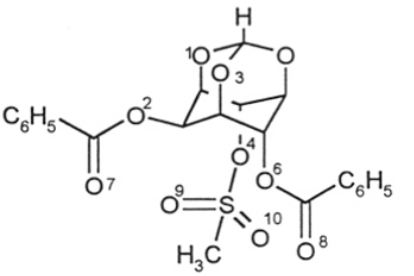
Although formation of chelates **44**, **45** and **46** involving the sulfonate group and the axial benzoate group appears to be possible (which facilitates the methanolysis of the axial benzoate group in **27-29**, **23** and **42**), due to the proximity of the two diaxial functionalities, the formation of the corresponding chelates **47-49** involving the axial sulfonyl group and the equatorial benzoate group appears to be remote, since they are disposed in 1,3-axial-equatorial configuration. It is evident that a chelate such as **47** is not involved during the methanolysis of **27-29**, since in the dibenzoate **23** and the methyl ether **42** only the axial ester undergoes methanolysis.

We calculated the relevant inter oxygen distances in compounds **23**, **27**, **38** and **42** obtained from their single crystal X-ray diffraction data.[17] (**Table 5.4**) The inter oxygen distances in **27** indicate that O_4-O_6 and perhaps O_4-O_8 are close enough to allow the formation of silver chelates (involving axial functional groups, **Scheme 5.12**). However, larger inter oxygen distances (O_7-O_9 and O_7-O_{10}) in **27** may not be suitable for the formation of chelates such as **48** or **49**, in the molecular conformation present in the crystal. A computation of the minimum distance possible between O_7 and O_9 interactively using the molecular modeling program NEMESIS (version 1.1 Oxford Molecular Ltd.1992) showed it to be about 4Å. The corresponding conformation of **27** is reproduced in **Scheme 5.13** Formation of a chelate **49** as shown in **Scheme 5.10** appears to be possible in this conformation and hence the mechanism for the cleavage of the equatorial ester group can be represented as in **Scheme 5.14**.

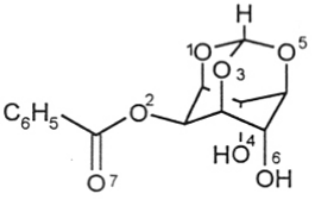
Scheme 5.12



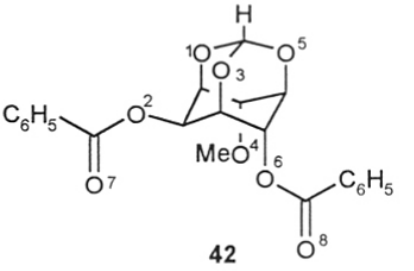
23



27



38

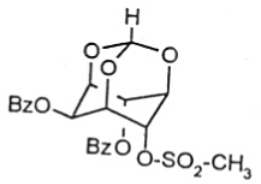


42

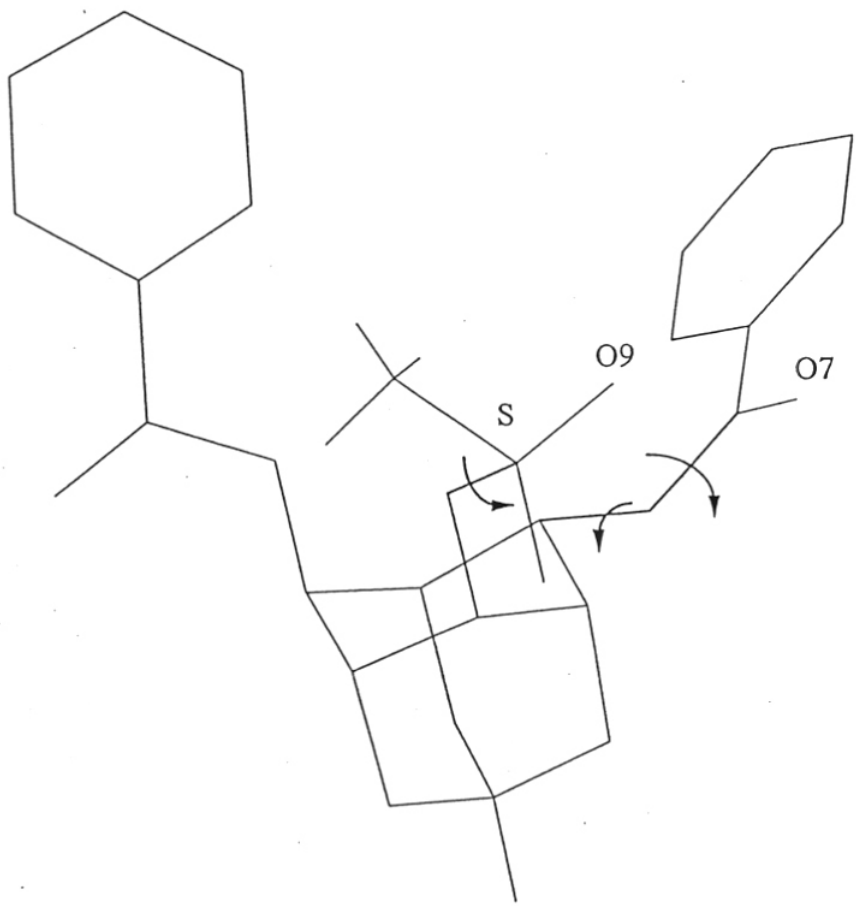
Table 5.4 Comparison of inter-oxygen distances (Å) in **23**, **27**, **38** and **42**

Mol/asym. unit	**23**	**27**	**38**	**42**
O_4-O_6	2.8165	2.7929	2.7185	2.8330
O_4-O_8	5.0314	4.4511	----------	5.0373
O_7-O_9	----------	6.2662	----------	----------
O_7-O_{10}	----------	6.2782	----------	----------

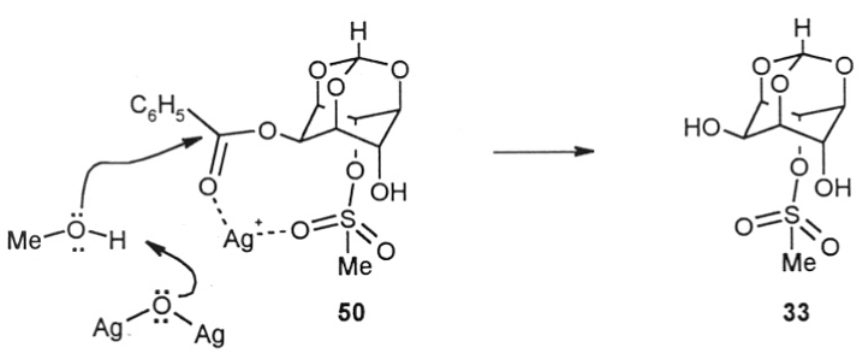
Scheme 5.13



27



Scheme 5.14



50 33

5.3 Conclusions

Interaction of different functional groups in a small organic molecule leading to unusual reactions is well precedented in the literature. Results on the methanolysis of *myo*-inositol orthoformate derivatives presented in this chapter show that a suitably placed sulfonyl group in the vicinity of a carboxylic acid ester can enhance the electrophilicity of the carbonyl carbon, in the presence of silver (I) oxide and silver halides. This is perhaps the first report on the intramolecular assistance by a sulfonyl group for the nucleophilic addition to a neighboring carbonyl group. Also for the first time we have observed silver halide catalysis for the transesterification of the carboxylic acid esters, although under very specific conditions. Some of the sulfonates prepared here could be useful in the synthesis of biologically important inositol derivatives.

5.4 Experimental section.

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

Mesyl chloride, tosyl chloride, and camphor sulfonic acid were obtained from Aldrich Chemical Company., USA. Camphor sulfonyl chloride was prepared using the procedure of Davis, et. al.[20] The camphor sulfonate **29** (mixture of diastereomers), the dibenzoate **23**, the diol **38** and the methyl ether **42** were prepared as reported earlier.[15,17] THF solution of magnesium bromide was prepared as in ref. 8.

Preparation of (±)-2,4-di-*O*-benzoyl-6-*O*-mesyl-*myo*-inositol 1,3,5-orthoformate (27) The dibenzoate **23** (1.2 g, 3 mmol) was dissolved in pyridine (10 ml) and a solution of mesyl chloride (2.291g, 15 mmol) in pyridine (3 ml) was added dropwise (15 min.) with cooling (ice) and the reaction mixture was stored in the fridge overnight. Pyridine was then evaporated in vacuo and the residue was dissolved in chloroform (30 ml) washed with hydrochloric acid, water and brine. The organic solution was dried over anhd. sodium sulfate and evaporated. The residue was crystallized from a mixture of chloroform and light petroleum to obtain **27** (1.36 g, 95%).

Data for **27**

m.p. 181-182 °C Lit.[17] m.p.179-182 °C

^{1}H NMR ($CDCl_3$): 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).

Elemental Analysis calcd. for $C_{22}H_{20}O_{10}S$: C 55.46, H 4.20, S 6.72; Found: C 55.58, H 4.03, S 6.69.

Preparation of (±)-2,4-di-*O*-benzoyl-6-*O*-Tosyl-*myo*-inositol 1,3,5-orthoformate (28) The dibenzoate **23** (0.800 g, 2 m mol) was dissolved in pyridine (8 ml) and tosyl chloride (1.14g, 6 m mol) was added at room temperature. The reaction mixture was then stirred at 55 °C for 24 h. Pyridine was evaporated in vacuo and the reaction mixture was dissolved in chloroform (30 ml) washed with hydrochloric acid and worked up as usual. The residue obtained was purified by flash chromatography to obtain the pure tosylate **28** (0.900 g, 81%) m.p. 164 °C Lit.[17] m.p.163-164 °C.

Silver (I) oxide/silver halide mediated methanolysis of (±)-2,4-di-*O*-benzoyl-*myo*-inositol orthoformate derivatives. General procedure: The dibenzoyl derivative (0.25 to 1 mmol) was dissolved in methanol/DMF mixture (10 % v/v, 1 to 5 ml). Freshly prepared silver (I) oxide (5 eq.) and silver halide (2 eq.) were added with vigorous stirring at room temperature. Stirring was continued for 24h, at the end of which the reaction mixture was diluted with chloroform (10-20 ml) and filtered through a short bed of celite. The filtrate was washed with sodium cyanide solution (1%, 100 ml) and then worked up as usual. The products were separated by column chromatography over silica gel.

Methanolysis of (±)-2,4-di-*O*-benzoyl-6-*O*-mesyl-*myo*-inositol 1,3,5-orthoformate (27) in the presence of

a) Silver (I) oxide and silver iodide for 24 hours: The mesyl derivative **27** (0.476g, 1 mmol), silver (I) oxide (1.147g, 5 mmol), silver iodide (0.471g, 2 mmol) and methanol/DMF mixture (10% v/v, 1ml) were used for methanolysis. The reaction mixture was diluted with methanol and filtered through celite. The filtrate on column chromatography yielded the diol **33** (0.260g, 97%) as the only product.

Data for **33**

m. p. 246 - 247 °C.

IR (cm^{-1}): 3325-3500

^1H NMR ($CDCl_3$): δ 3.28 (s, 3H), 3.94 (m, 2H), 4.13 (m, 1H), 4.31 (m, 2H), 5.15 (m, 1H), 5.53(d, 1H, D_2O exchangeable), 5.56 (d, 1H), 5.68 (d, 1H, D_2O exchangeable).

^{13}C NMR (DMSO-d_6): δ 38.38, 58.84, 66.64, 69.54, 72.45, 74.13, 74.32, 102.57

Elemental Analysis calcd. for $C_8H_{12}O_8S$: C 35.82, H 4.47, S 11.94; Found: C 35.91, H 4.46, S 12.35.

b) Silver (I) oxide and silver iodide for 10 hours: The mesyl derivative **27** (0.100g, 0.21 mmol), silver (I) oxide (0.242g, 1.05 mmol), silver iodide (0.099g, 0.42 mmol) and methanol/DMF mixture (10% v/v, 1 ml) were used for methanolysis. The reaction mixture was diluted with methanol/chloroform mixture and filtered through celite. The

filtrate on column chromatography yielded the monohydroxy derivative **36** (0.023g, 29%), the diol **33** (0.017g, 30%), and the starting material **27** (0.040g, 40%).

Data for **36**

m. p. 175-176 °C.

IR (cm^{-1}): 3442, 3351, 1726.

^1H NMR ($CDCl_3$): δ 2.83 (d, 1H, D_2O exchangeable), 3.22 (s, 3H), 4.49-4.74 (m, 4H), 5.4-5.55 (m, 3H), 7.40-7.70 (m, 3H), 8.05-8.3 (m, 2H).

Elemental Analysis calcd. for $C_{15}H_{16}O_9S$: C 48.39, H 4.30, S 8.60; Found: C 48.03, H 4.28, S 8.54.

c) Silver (I) oxide and silver bromide: The mesyl derivative **27** (0.100g, 0.21 mmol), silver (I) oxide (0.242g, 1.05 mmol), silver bromide (0.079g, 0.42 mmol) and methanol/DMF mixture (10% v/v, 1 ml) were used for methanolysis. The reaction mixture was diluted with methanol/chloroform mixture and filtered through celite. The filtrate on column chromatography yielded the monohydroxy derivative **36** (0.009g, 12%), the diol **33** (0.015g, 27%), and the starting material **27** (0.060g, 60%).

d) Silver (I) oxide and silver chloride: The mesyl derivative **27** (0.100g, 0.21 mmol), silver (I) oxide (0.242g, 1.05 mmol), silver chloride (0.06g, 0.42 mmol) and methanol/DMF mixture (10% v/v, 1 ml) were used for methanolysis as described in the general procedure. TLC indicated no reaction. Starting material **27** (0.092g, 92%) was recovered after work up.

e) Silver (I) oxide: The mesyl derivative **27** (0.100g, 0.21 mmol), silver (I) oxide (0.242g, 1.05 mmol), and methanol/DMF mixture (10% v/v, 1 ml) were used for methanolysis. TLC indicated no reaction. Starting material **27** (0.095g, 95%) was recovered after work up.

f) Silver iodide: The mesyl derivative **27** (0.100g, 0.21 mmol), silver iodide (0.117g, 0.502 mmol) and 10% v/v methanol/DMF mixture (1 ml) were used for methanolysis. TLC indicated no reaction. Starting material **27** (0.100g, 100%) was isolated after work up.

g) Magnesium bromide: The mesyl derivative **27** (0.100g, 0.21 mmol), 1 mm solution

of magnesium bromide (0.764ml, 0.42 mmol) and methanol/DMF mixture (10% v/v, 1 ml) were used for methanolysis. TLC indicated no reaction. Starting material **27** (0.100g, 100%) was recovered after work up.

Methanolysis of (±)-2,4-di-*O*-benzoyl-6-*O*-tosyl-*myo*-inositol 1,3,5-orthoformate (28) in the presence of

a) silver (I) oxide and silver iodide. The tosyl derivative **28** (0.120, 0.22 mmol), silver (I) oxide (250g, 1.1 mmol), silver iodide (0.104g, 0.44 mmol) and methanol/DMF mixture (10% v/v, 1 ml) were used for methanolysis. The reaction was continued till the disappearance of the starting material on TLC (28h.). The work up and chromatography was carried out as described in the general procedure to obtain the diol **34** (0.070g, 92%) as the only product.

Data for **34**

m. p. 159 - 162 °C.

IR (cm^{-1}): 3442, 3351.

^1H NMR ($CDCl_3$): δ 2.49 (s, 3H), 2.50 (d, 1H D_2O exchangeable), 3.05 (d, 1H D_2O exchangeable), 4.00-4.10 (m, 2H), 4.15-4.25 (m, 1H), 4.35-4.45 (m, 1H), 4.50-4.65 (m, 1H), 5.10-5.20 (m, 1H), 5.45 (d, 1H). 7.30-7.50 (m, 2H), 7.75-7.95 (d, 2H)

Elemental Analysis calcd. for $C_{14}H_{16}O_8S$: C 48.84, H 4.65, S 9.30; Found: C 48.76, H 4.95, S 9.46.

b) Magnesium bromide: The tosyl derivative **28** (0.100g, 0.18 mmol), 1 mm solution of magnesium bromide (0.36ml, 0.36 mmol) and methanol/DMF mixture (10% v/v, 1 ml) were used for methanolysis. TLC indicated no reaction. Starting material **28** (0.100g, 100%) was recovered after work up as in the general procedure.

Methanolysis of (±)-2,4-di-*O*-benzoyl-6-*O*-camphorsulfonyl-*myo*-inositol 1,3,5-orthoformate (29) in the presence of

a) Silver (I) oxide and silver iodide. The camphor sulfonyl derivative **29** (0.150, 0.25 mmol), silver (I) oxide (0.283g, 1.225 mmol), silver iodide (0.117g, 0.5 mmol) and methanol/DMF mixture (10% v/v, 1 ml) were used for methanolysis. The reaction mixture was worked up and chromatographed as in the general procedure to obtain the

diol **35** (0.094g, 95%) as the only product (mixture of diastereomers).

Data for **35**

m. p. 137 - 138 °C.

IR (cm^{-1}): 3453,3122.

^1H NMR ($CDCl_3$): δ 0.86 (s, 3H), 1.05 (s, 3H), 1.20-2.50 (m, 7H), 2.9-3.40 (m, 3H, two of them are D_2O exchangeable), 3.5-3.75 (m, 1H), 4.00-4,75 (m, 7H).

^{13}C NMR (DMSO-d_6): δ 24.89, 30.44, 31.99, 53.19, 53.31, 53.57, 63.23, 64.10, 71.92, 75.00, 77.85, 77.95, 79.40, 79.63, 107.86, 134.04, 219.41.

b) magnesium bromide

The camphor sulfonyl derivative **29** (0.100g, 0.16 mmol), 1 mm solution of magnesium bromide in THF (0.32ml, 0.32 mmol) and methanol/DMF mixture (10% v/v, 1 ml) were used for methanolysis. TLC indicated no reaction. Workup as described in the general procedure yielded the starting material **29** (0.98g, 98%).

Preparation of (±)-2-*O*-benzoyl-4-*O*-t-butyldimethylsilyl-*myo*-inositol 1,3,5-orthoformate (39) The diol **38** (0.600 g, 2.04 mmol) was dissolved in DMF (6 ml). Imidazole (0.138g, 2.04 mmol) and TBDMSCl (0.307g, 2.04 mmol) were added successively and stirred over night. The reaction mixture was worked up as usual and the product was chromatographed to obtain the pure silyl derivative **39** (0.600g, 72%).

Data for **39**

m. p. 84 °C

IR (cm^{-1}): 3480-3500, 1710

^1H NMR ($CDCl_3$): δ 0.5 (s, 6H), 1.0 (s, 9H), 4.10 (d, 1H, D_2O exchangeable), 4.25-4.30 (m, 1H), 4.40-4.45 (m, 2H), 4.55 (m, 1H), 4.70 (m, 1H), 5.55 (m, 2H), 7.45-7.65 (m, 3H), 8.20 (m, 2H).

^{13}C NMR ($CDCl_3$): δ -5.76, -5.43, 17.43, 25.19, 62.97, 67.93, 68.63, 68.81, 71.13, 72.27, 102.08, 128.02, 129.42, 129.60, 132.91, 165.51.

Elemental Analysis calcd. for $C_{20}H_{28}O_7Si$: C 58.82, H 6.86; Found: C 58.64, H 7.17.

Preparation of (±)-2-*O*-benzoyl-4-*O*-t-butyldimethylsilyl--6-O-mesyl-*myo*-inositol 1,3,5-orthoformate (40). The silyl ether **39** (0.408 g, 1 mmol) was dissolved in pyridine (3 ml) and a solution of mesyl chloride (1.1455g, 10 mmol) in pyridine (1 ml) was added dropwise at 0 °C over a period of 30 minutes. The reaction mixture was kept overnight in the refrigerator; pyridine was then removed under reduced pressure. The residue was dissolved in chloroform (10 ml) and worked up as usual. The organic solution was dried over anhd. sodium sulfate and passed over a short bed of silicagel to obtain the pure product **40** (0.440g, 90%).

Data for **40**

m. p. 115-116 °C.

IR (cm^{-1}): 1700

^1H NMR ($CDCl_3$): δ 0.17-0.18 (d, 6H), 1.0 (s, 9H), 3.15 (s, 3H), 4.30-4.40 (m, 2H), 4.55-4.65 (m, 2H), 5.5-5.6 (m, 3H), 7.45-7.65 (m, 3H), 8.15-8.20 (m, 2H).

Elemental Analysis calcd. for $C_{21}H_{30}O_9SSi$: C 51.85, H 6.17, S 6.58; Found: C 51.79, 6.25, S 6.75.

Preparation of (±)-2-*O*-benzoyl-6-*O*-mesyl-*myo*-inositol 1,3,5-orthoformate (36). The silyl ether **40** (0.250g, 0.514 mmol) was dissolved in THF (3 ml) and stirred at ambient temperature for 10 minutes with tetrabutyl ammonium fluoride (0.148g, 0.568 mmol). The reaction mixture was then diluted with chloroform (20 ml) and worked up as usual. The residue on flash chromatography yielded the pure mesyl derivative **36** (0.180g, 94%).

Data for the **36**

m. p. 175-176 °C.

IR (cm^{-1}): 1726, 3469-3564

^1H NMR ($CDCl_3$): δ 2.83 (d, 1H, D_2O exchangeable), 3.22 (s, 3H), 4.49-4.74 (m, 4H), 5.4-5.55 (m, 2H), 5.60 (d, 1H), 7.40-7.70 (m, 3H), 8.05-8.3 (m, 2H).

Elemental Analysis calcd. for $C_{15}H_{16}O_9S$: C 48.39, H 4.30, S 8.60; Found: C 48.03, H 4.28, S 8.54.

Preparation of (±)-2,4-di-*O*-benzoyl-6-*O*-mesyl-*myo*-inositol (41) The mesylate **27** (1.000g, 2.1 mmol) was dissolved in dichloromethane/methanol mixture (1:1 v/v, 30 ml) and pTSA (0.328g, 2.1 mmol) was added and stirred at ambient temperature. At the end of 80h. solvents were evaporated and the residue was purified by flash chromatography to obtain the pure triol **41** (0.587g, 61%).

Data for **41**

m. p. 176-177 °C.

IR (cm^{-1}): 1680, 1700, 3564, 3469.

^1H NMR ($CDCl_3$): δ 3.15 (s, 3H), 3.70-3.80 (m, 1 H), 3.95-4.05 (t, 2H), 4.55-4.65 (t, 1H), 5.20-5.40 (t, 1H), 5.40-5.55 (d, 1H, D_2O exchangeable) 5.55-5.60 (m, 1H), 5.65-5.75 (d, 1H, D_2O exchangeable), 5.75-5.85 (d, 1H, D_2O exchangeable), 7.40-7.75 (m, 6H), 7.90-8.10 (m, 4H).

Elemental Analysis calcd. for $C_{21}H_{22}O_{10}S$: C 53.53, H 5.03, S 6.57; Found: C 54.07, H 4.72, S 6.86

Methanolysis of (±)-2,4-di-*O*-benzoyl-6-*O*-mesyl-*myo*-inositol in the presence of silver (I) oxide and silver iodide. The triol **41** (0.100g, 0.215mmol), silver (I) oxide (0.248, 1.075 mmol), silver iodide (0.101g, 0.43 mmol) and methanol/DMF mixture (10% v/v, 1 ml) were used for methanolysis. TLC showed no reaction at the end of 80 hours. The reaction mixture was work up as described in the general procedure to recover the starting material **41** (0.095 g, 95%).

Methanolysis of (±)-2,4-di-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate (23) in the presence of

a)Silver (I) oxide and silver iodide: The dibenzoate **23** (0.100g, 0.25 mmol), silver (I) oxide (0.290g, 1.25 mmol), silver iodide (0.117g, 0.5 mmol) and methanol/DMF (10% v/v,1 ml) mixture were used for methanolysis. The reaction mixture was worked up as described in the general procedure and the product was purified by flash chromatography to obtain the diol **38** (0.069g, 94%).

b) Silver (I) oxide and silver bromide: The dibenzoate **23** (0.100g, 0.25 mmol), silver (I) oxide (0.290g, 1.25 mmol), silver bromide (0.094g, 0.5 mmol) and methanol/DMF mixture (10% v/v, 1 ml) were used for methanolysis. Work up as described in the

general procedure followed by column chromatography yielded the diol **38** (0.050g, 68%) and the starting material **23** (0.030g, 30%)

c) Silver (I) oxide and silver chloride: The dibenzoate **23** (0.100g, 0.25 mmol), silver (I) oxide (0.290g, 1.25 mmol), silver chloride (0.072g, 0.5 mmol) and methanol/DMF mixture (10% v/v, 1 ml) were used for methanolysis. Work up as described in the general procedure followed by column chromatography yielded the diol **38** (0.015g, 20%) and the starting material **23** (0.079g, 79%)

d) Silver (I) oxide: The dibenzoate **23** (0.100g, 0.25 mmol), silver (I) oxide (0.290g, 1.25 mmol) and methanol/DMF mixture (10% v/v, 1 ml) were used for methanolysis. The reaction mixture was worked up as described in the general procedure to obtain the starting material **23** (0.098g, 98%)

e) Silver iodide: The dibenzoate **23** (0.100g, 0.25 mmol), silver iodide (0.117g, 0.5 mmol) and methanol/DMF mixture (10% v/v, 1 ml) were used for methanolysis. The reaction mixture was worked up as described in the general procedure to obtain the starting material **23** (0.100g, 100%).

f) Magnesium bromide: The dibenzoate **23** (0.100g, 0.25 mmol), 1 mm solution of magnesium bromide in THF (0.5 ml, 0.5 mmol) and methanol/DMF mixture (10% v/v, 1 ml) were used for methanolysis. The reaction mixture was worked up as usual to obtain the starting material **23** (0.100g, 100%).

Methanolysis of (±)-2,4-di-*O*-benzoyl-6-*O*-methyl-*myo*-inositol 1,3,5-orthoformate (42) in the presence of

a) Silver (I) oxide and silver iodide: The methyl ether **42** (0.100g, 0.24 mmol), silver (I) oxide (0.277g, 1.2 mmol), silver iodide (0.113g, 0.48 mmol) and methanol/DMF mixture (10% v/v, 1 ml) were used for methanolysis. The reaction mixture was worked up as described in the general procedure and the products were isolated by flash chromatography to obtain **43** (0.019g, 26%) and the starting material **42** (0.070 g, 70%).

b) Silver (I) oxide and silver bromide: The methyl ether **42** (0.100g, 0.24mmol), silver (I) oxide (0.277g, 1.2 mmol), silver bromide (0.090g, 0.48 mmol) and methanol/DMF mixture (10% v/v 1 ml) were used for methanolysis. The reaction mixture was worked up as described in the general procedure and the products were isolated by flash

chromatography to obtain **43** (0.010g, 13%) and the starting material **42** (0.086 g, 70%).

c) Silver (I) oxide and silver chloride: The methyl ether **42** (0.100g, 0.24mmol), silver (I) oxide (0.277g, 1.2 mmol), silver chloride (0.069g, 0.48 mmol) and methanol/DMF mixture (10% v/v, 1 ml) were used for methanolysis. The reaction mixture was worked up as described in the general procedure and the starting material **42** (0.95 g, 95%) was recovered.

d) Silver (I) oxide: The methyl ether **42** (0.100g, 0.24mmol), Silver (I) oxide (0.277g, 1.2 mmol) and methanol/DMF mixture (10% v/v 1 ml) were used for methanolysis. The reaction mixture was worked up as described in the general procedure and the starting material **42** (0.100 g, 100%) was recovered.

e) Silver iodide: The methyl ether **42** (0.100g, 0.24mmol), silver iodide (0.113g, 1.2 mmol) and methanol/DMF mixture (10% v/v, 1 ml) were used for methanolysis. The reaction mixture was worked up as described in the general procedure and the starting material **42** (0.100 g, 100%) was recovered.

f) Magnesium bromide: The methyl ether **42** (0.100g, 0.24 mmol), 1 mm solution of magnesium bromide in THF (0.5 ml, 0.5 mmol) and methanol/DMF mixture (10% v/v, 1 ml) were used for methanolysis. The reaction mixture was worked as usual to obtain the starting material **42** (0.100g, 100%).

X-ray crystallography: The general methods used are described in **Chapter 3**. Summary of crystal data, data collection, structure solution, and refinement details are shown in **Table 5.5**

Table 5.5 Crystal data and structure refinement for 33

Empirical formula	$C_8 H_{10} O_8 S$
Formula weight	266.22
T	293(2) K
λ	0.70930 Å
Crystal system	Orthorhombic

Space group	P212121
Unit cell dimensions	a = 6.0940(10) Å α= 90 b = 6.502(2) Å β = 90 γ c =25.947(3) Å γ (= 90
Volume	1028.1(4) A-3
Z	4
Density (calculated)	.1.720 mg/m-3
Absorption coefficient	0.346 mm^{-1}
F(000)	552
Crystal size	? x ? x ? mm
θ range for data collection	1.57 to 24.96 °
Index ranges	0<=h<=7 0<=k<=7 0<=l<=30
Reflections collected	1089
Refinement method	Full-matrix least-squares on F^{-2}
Data / restraints / parameters	1089 / 0 / 155
Goodness-of-fit on F-2	1.119
Final R indices [I>2((I)]	R^1 = 0.0613 wR^2 = 0.1904
R indices (all data)	
R^1 = 0.0715	wR^2 = 0.2390
Absolute structure parameter	0.0(3)
Extinction coefficient	0.023(11)
Largest diff. peak and hole	0.536 and -0.568 e.A^{-3}

5.5 References

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Figure 1a. Variation of the chemical shift of hydroxyl group with concn. in **34**

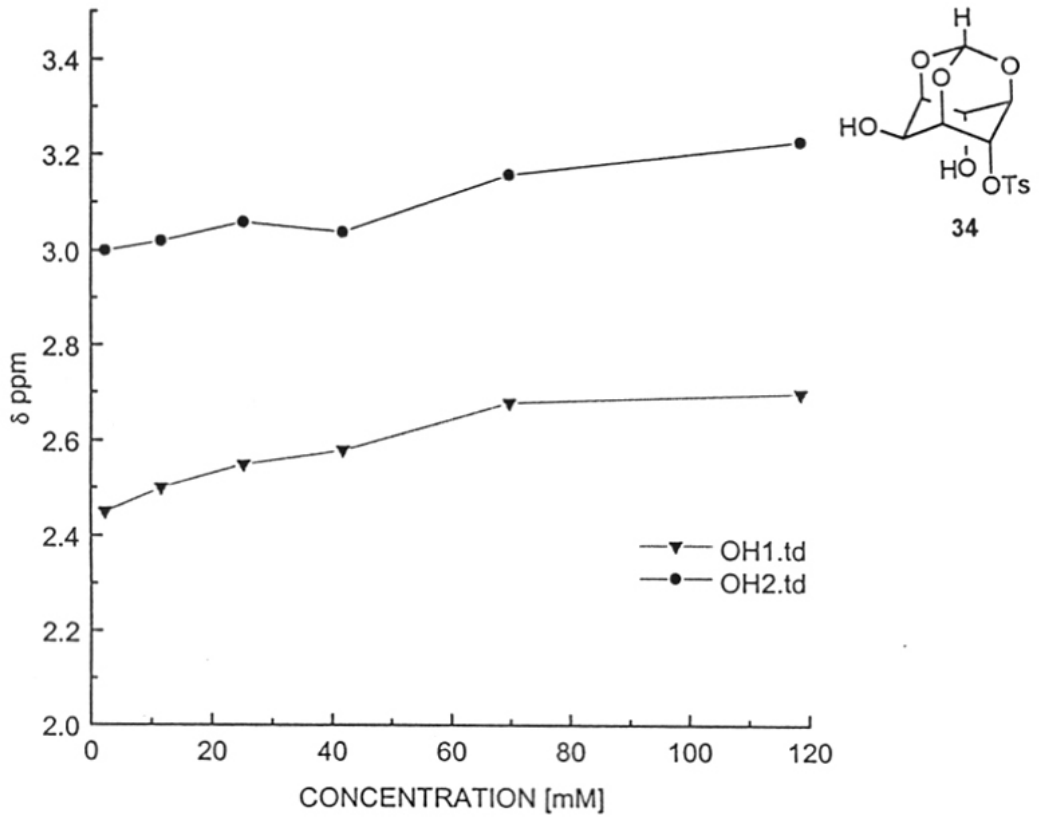


Figure 1b. Variation of the chemical shift of hydroxyl group with concn. in **35**

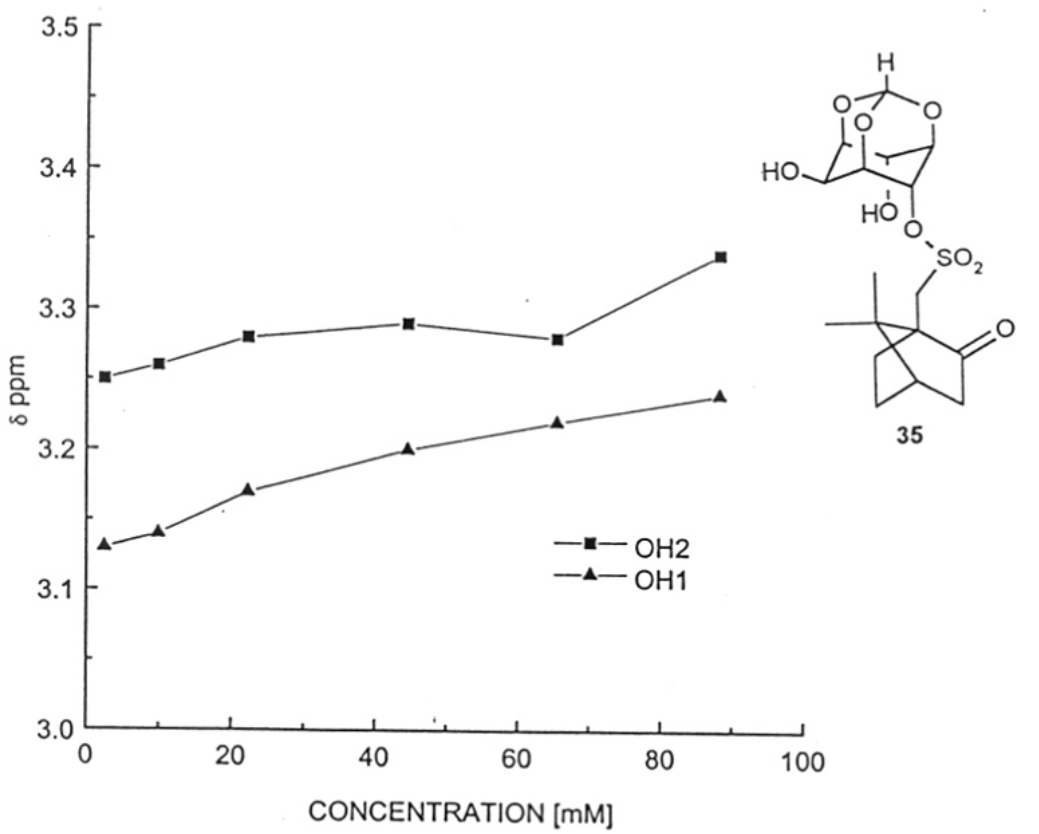


Figure 2

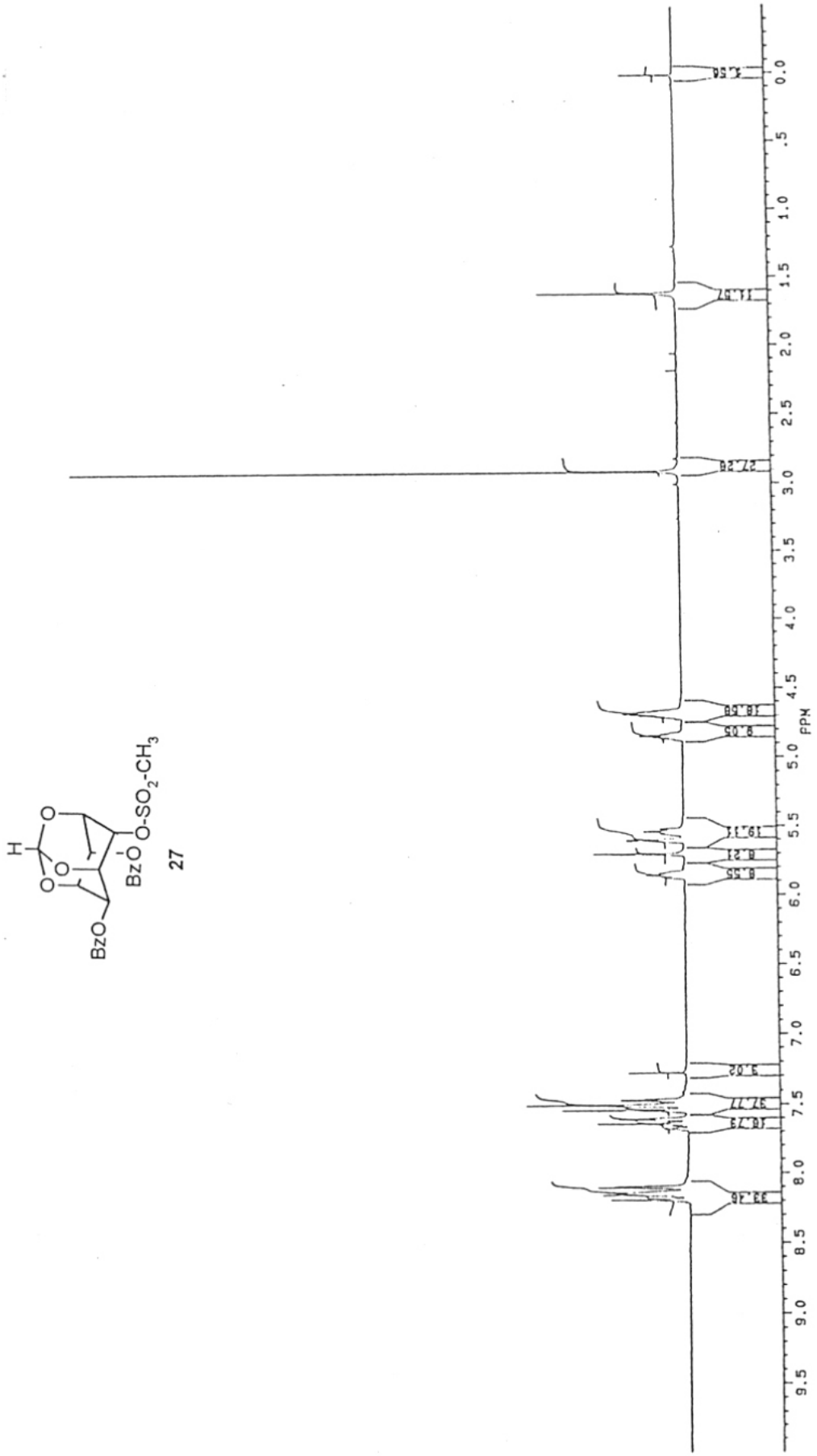
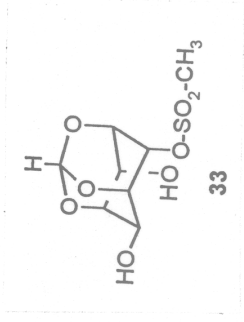


Figure 3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O
O
HO
HO
O-SO2-CH3

33

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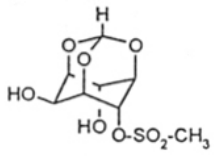
20.74
10.24
20.91
10.20
19.64
10.67
0.0
.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
PPM

Figure 4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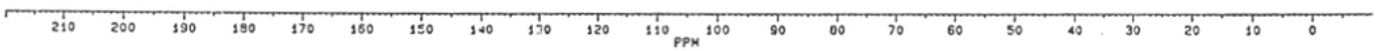
O
O
O
HO
HO
O-SO2-CH3

33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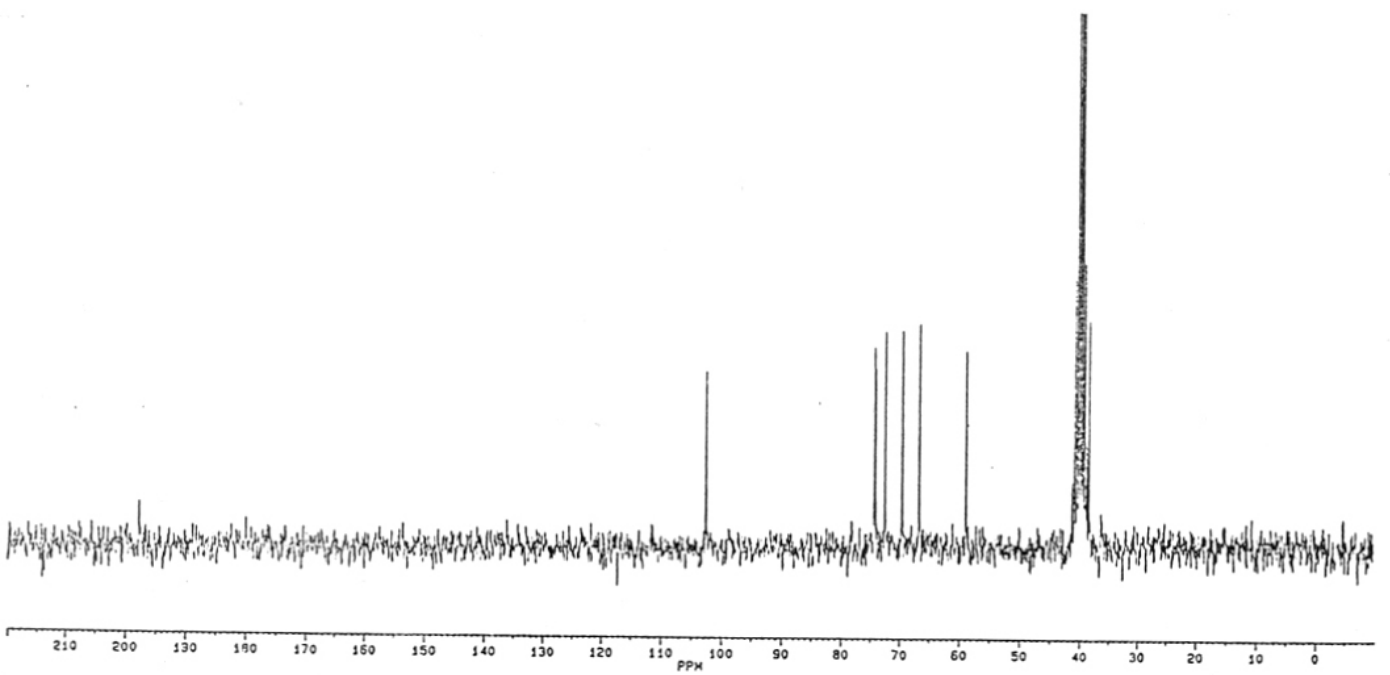
PPM



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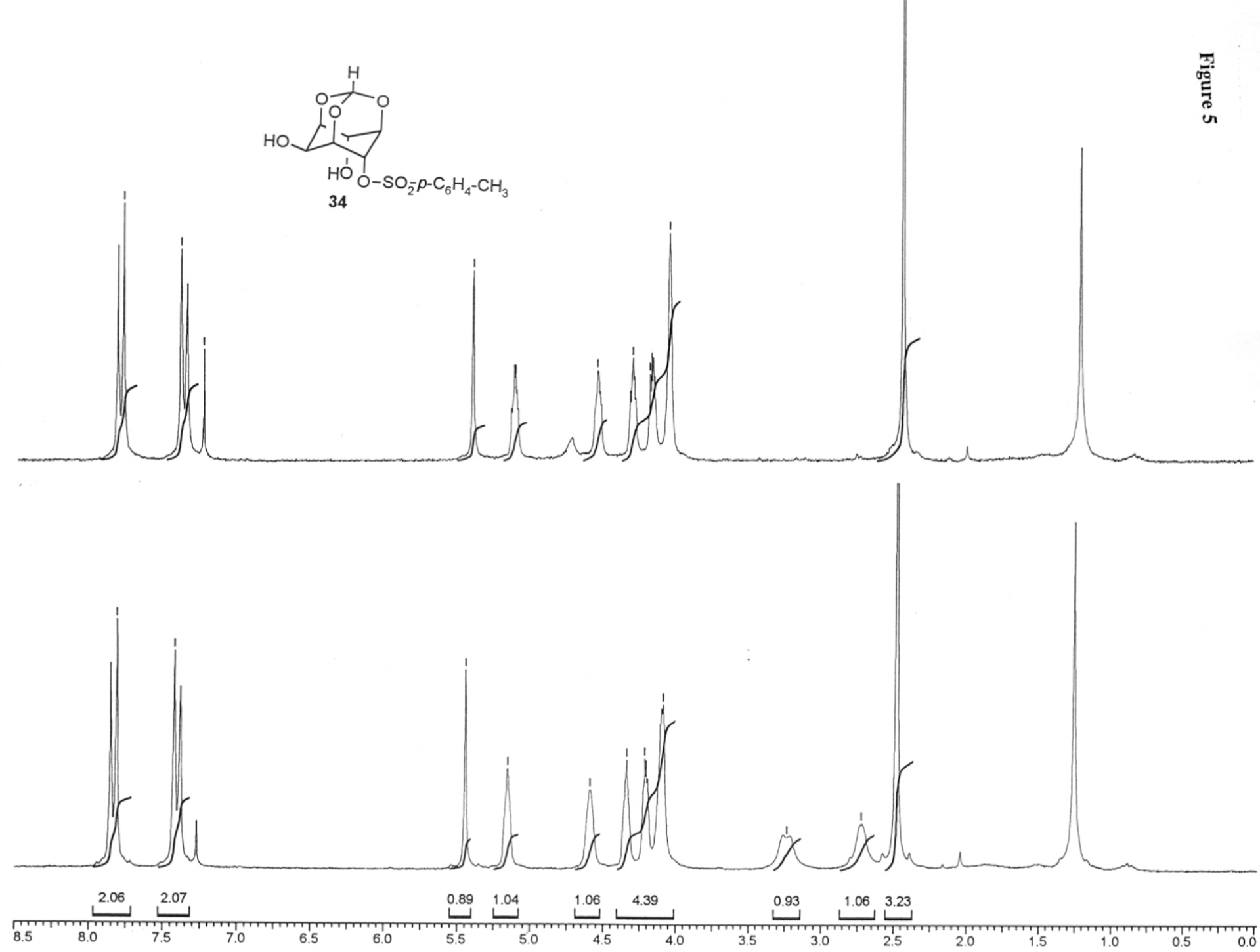
PPM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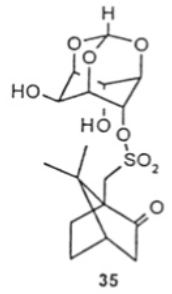
O
O
O
HO
HO
O–SO2-p-C6H4-CH3
34
2.06
2.07
0.89
1.04
1.06
4.39
0.93
1.06
3.23
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

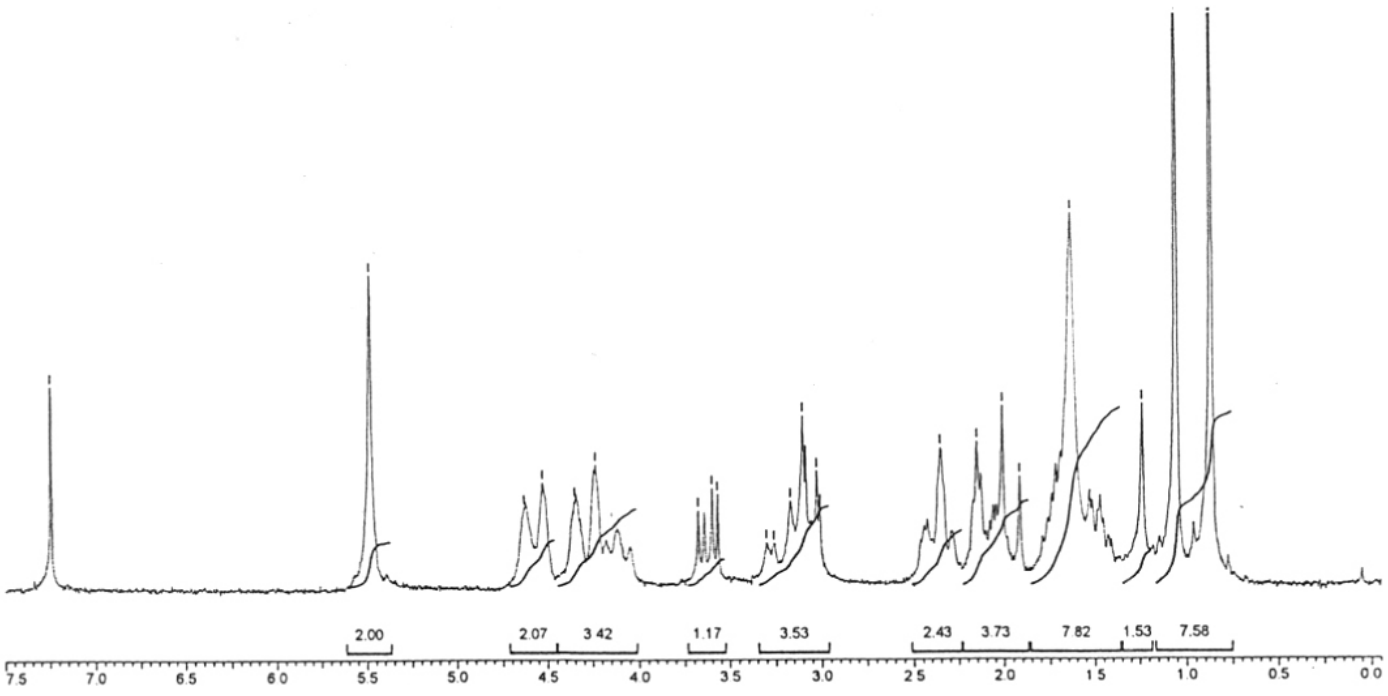
Figure 5

Figure 6


H
O
O
O
O
HO
HO
O
SO2
O

35

7.25
5.48
4.80
4.60
4.52
4.34
4.23
4.14
4.07
3.68
3.65
3.57
3.10
3.02
2.44
2.35
2.28
2.15
2.01
1.91
1.72
1.52
1.47
1.41
1.23
1.05
0.86
2.00
2.27
3.39
1.10
1.09
2.35
3.45
1.79
1.30
1.25
6.89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3.42
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2.43
3.73
7.82
1.53
7.58

Figure 7

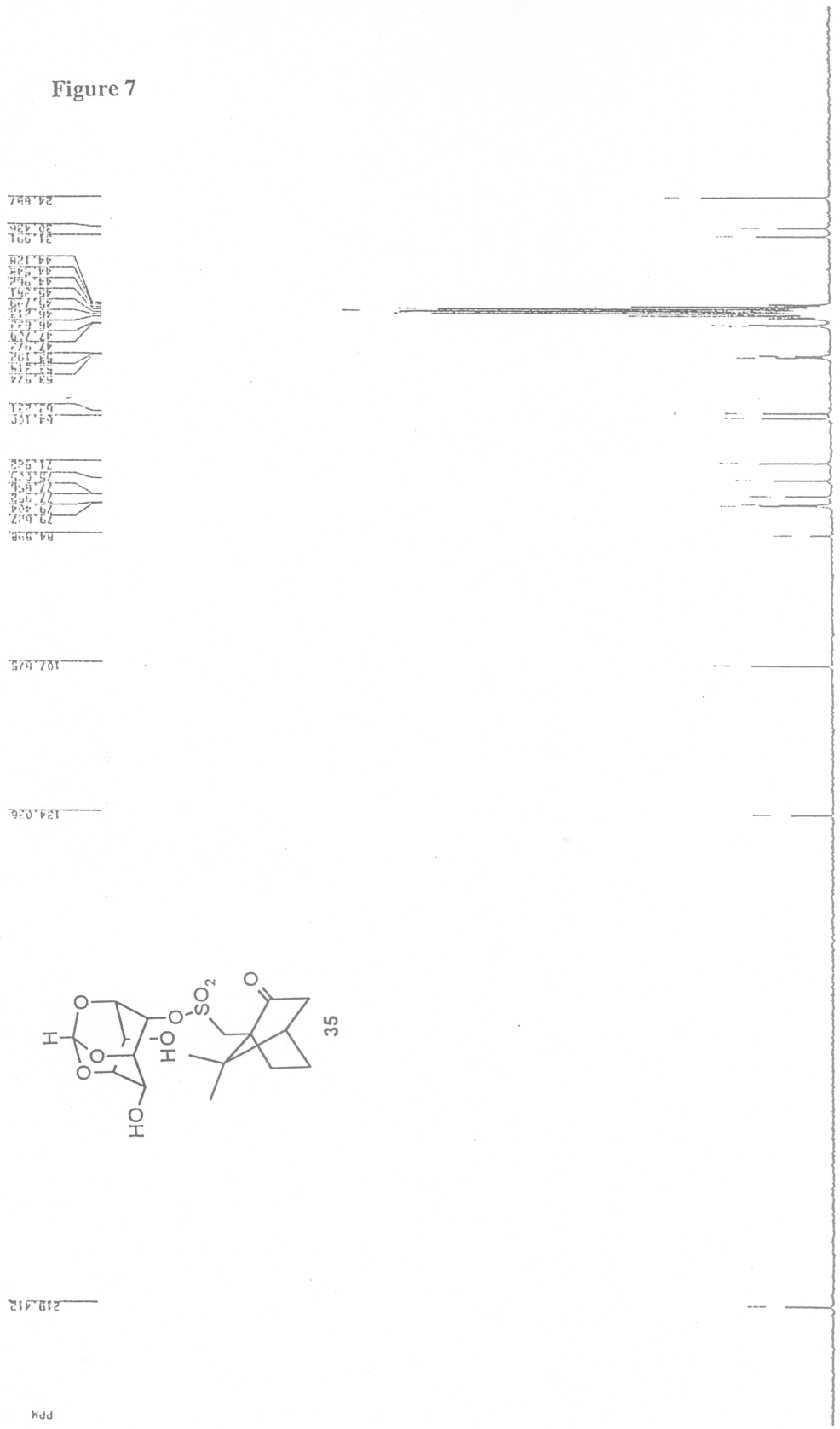
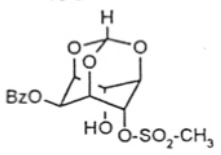


Figure 8


H
O
O
O
BzO
HO
O-SO2-CH3

36

8.14
7.49
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5.52
4.78
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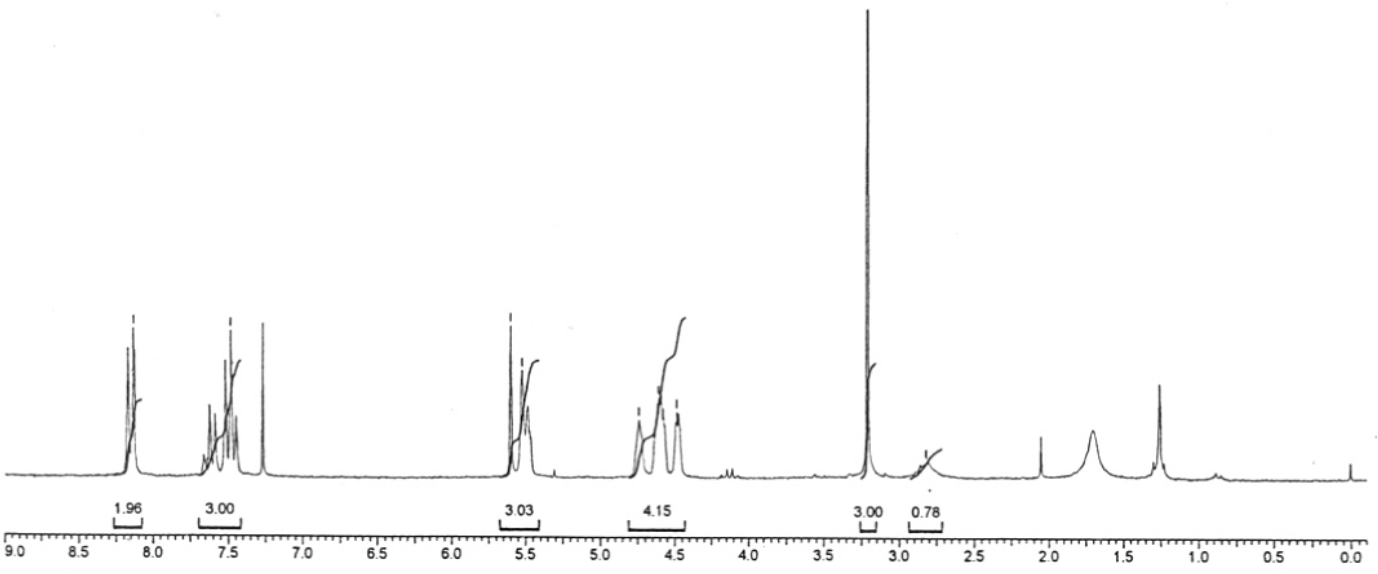
3.22
2.00
3.18
3.01
6.48
3.17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3.00
3.03
4.15
3.00
0.78

Figure 9

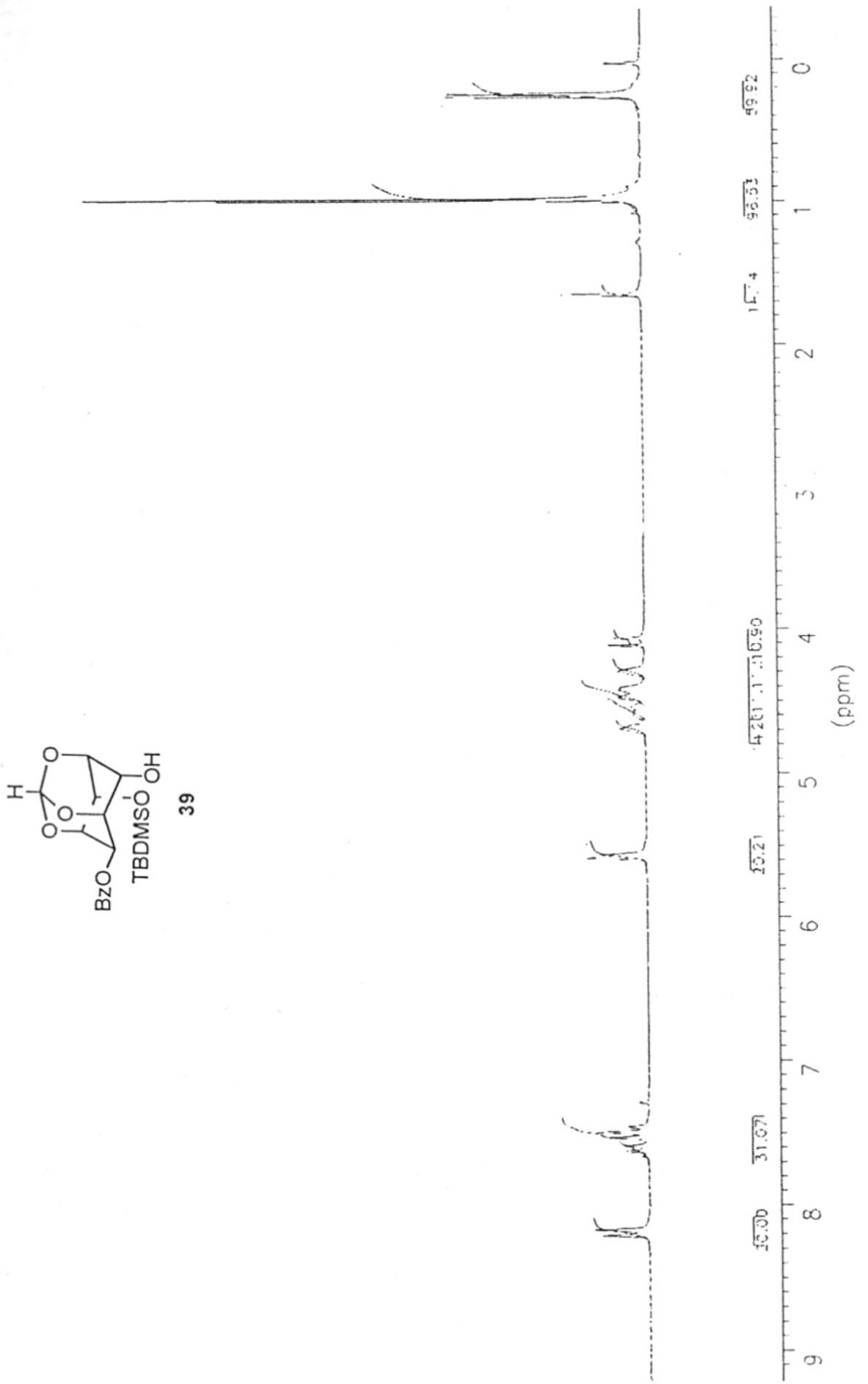
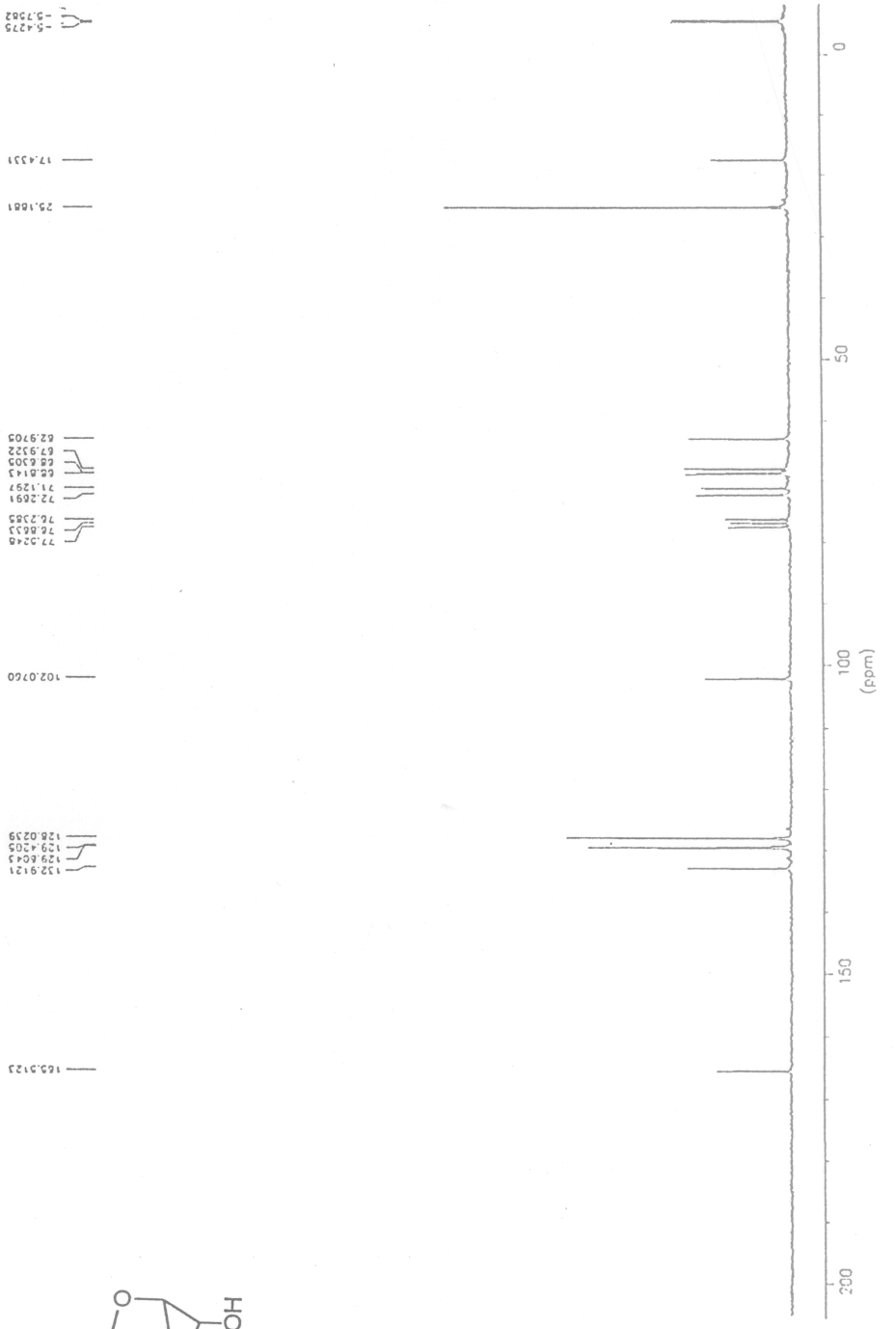


Figure 10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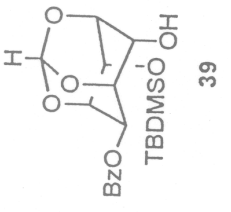
17.4331
25.1881
62.9705
63.8143
68.6305
67.9322
71.1297
72.2691
76.2365
76.8633
77.3248
102.0760
126.0239
129.4205
129.8043
132.9121
165.9123
0
50
100
150
200
(ppm)


H
O
O
O
OH
TBDMSO
BzO

39

Figure 11

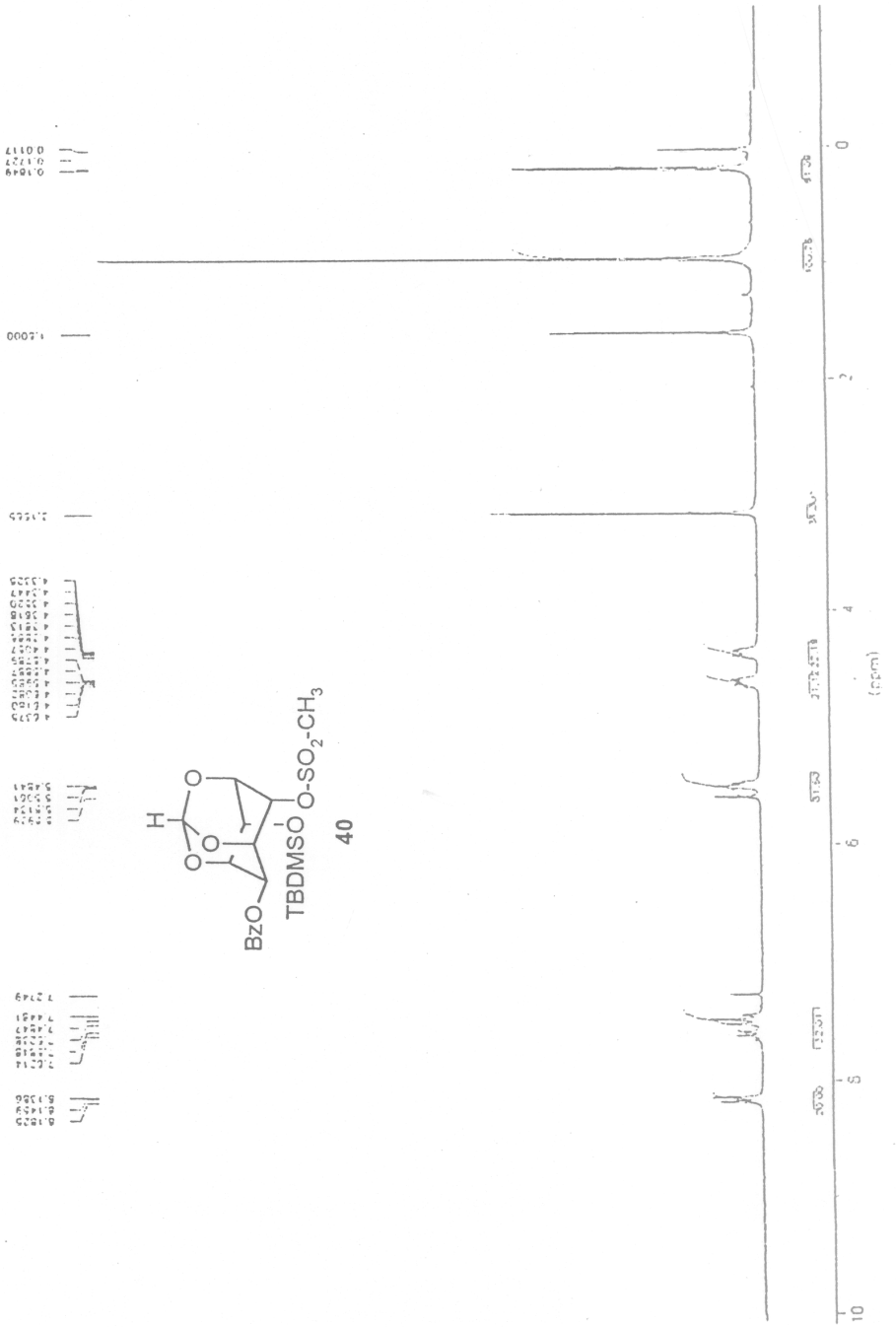
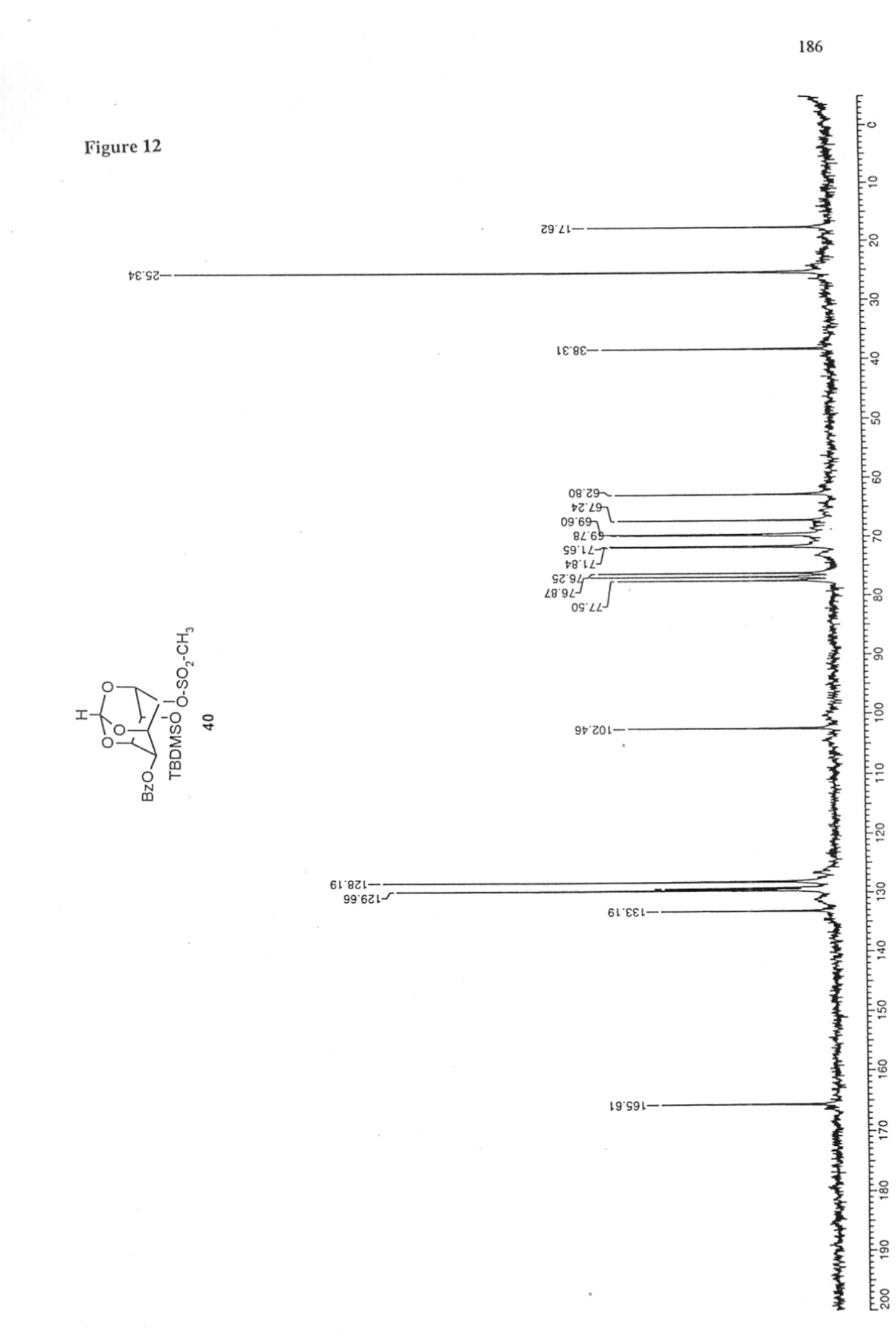


Figure 12


17.62
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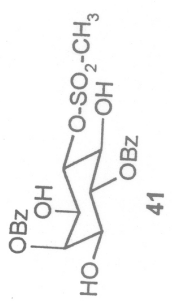
62.80
67.24
69.60
69.78
71.65
71.84
76.25
76.87
77.50
102.46
128.19
129.66
133.19
165.61
BzO
TBDMSO
O-SO2-CH3
40

Figure 13



41

Figure 14

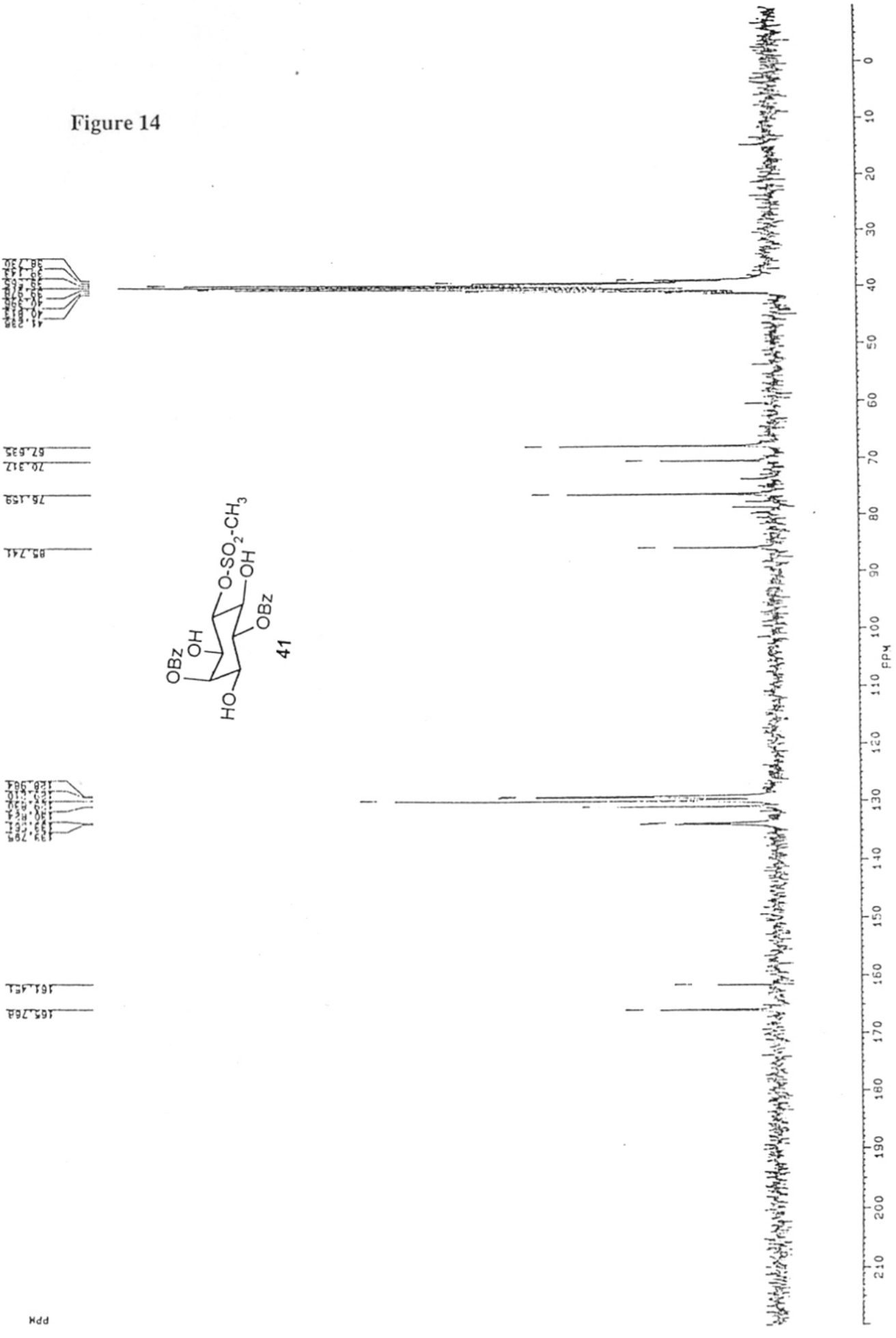
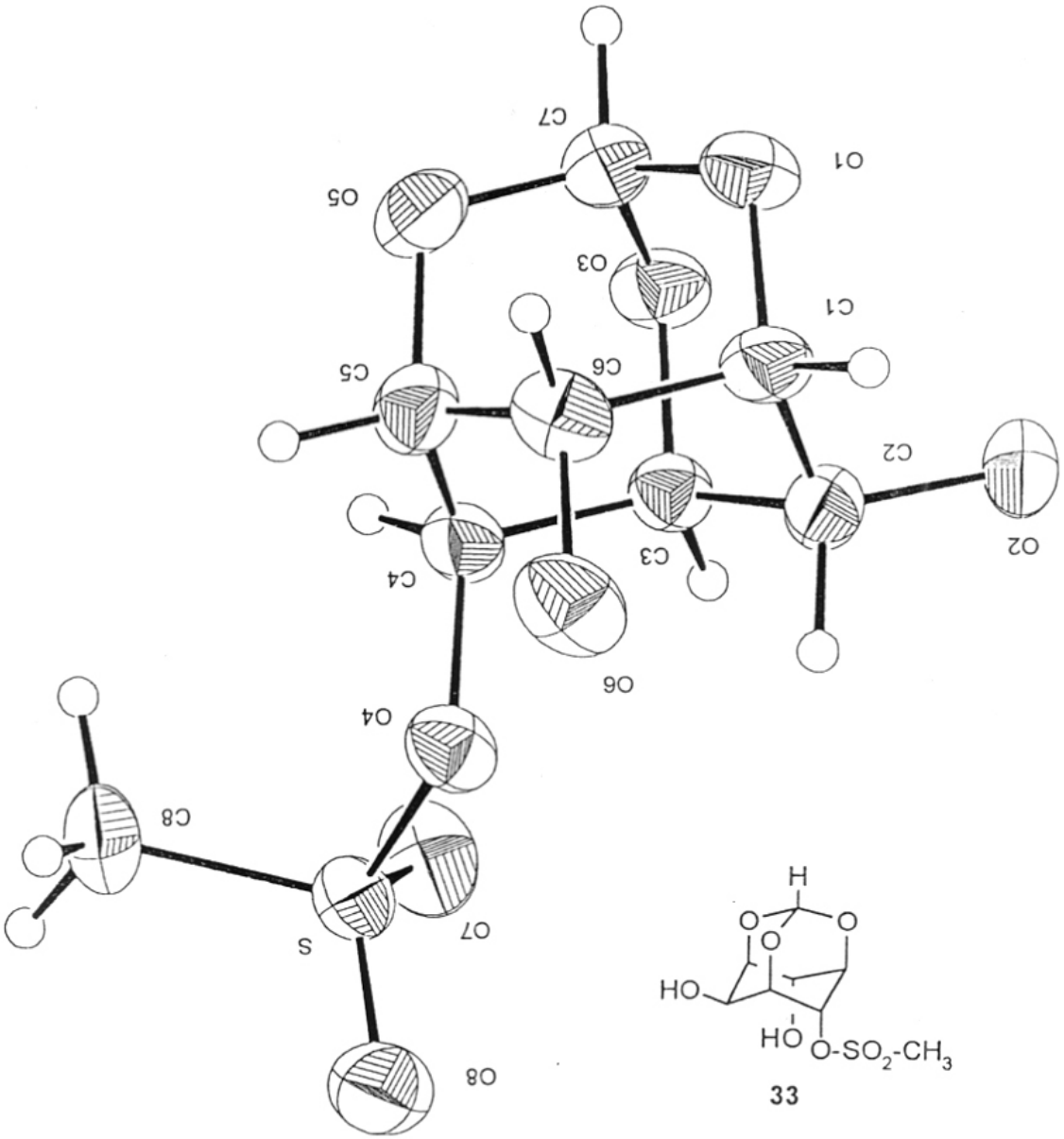


Figure 15



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