Synopsis of the Thesis
The thesis entitled 'Chemistry of inositols: Investigation on the solid-state acyl transfer reactions of inositol derivatives and the use of sulfonate protecting groups for the synthesis of cyclitol derivatives' consists of two parts. Part A: Investigation on the acyl transfer reactions of inositol derivatives in the solid state. Part B: Use of sulfonate protecting groups for the synthesis of cyclitol derivatives. Part A consists of two sections; Section 1 gives an account of solid state group transfer reactions reported in the literature relevant to the work described in Section 2. The work done on the solid state acyl transfer reactions of inositol derivatives is presented in Section 2. Part B also consists of two sections; Section 1 is a review of the literature on the use of sulfonate protecting groups for the synthesis of various organic compounds. Section 2 presents the work done on the synthesis of cyclitol derivatives with the aid of sulfonate groups for the protection of hydroxyl groups. Both Part A and Part B also have experimental sections and appendices, which give detailed experimental procedures, spectroscopic, crystallographic and other analytical data on the compounds prepared during the course of this investigation.


Section 1. An illustrative review on the solid state group transfer reactions.

This section reviews the literature on organic group transfer reactions in the solid state. Reports on group transfer reactions of organic compounds are very common in solution, but are rare in the solid state. Solid-state reactions are gaining interest among organic chemists because the product selectivity of reactions in the solid state is often different from their selectivity in solution. In the solid state, the reactivity depends on steric packing factors in crystals and perhaps on electronic properties of molecules. While, in solution the reactivity is mainly dependent on the electronic and steric properties of the reactant molecules. Also, since solvents are not needed to carry out reactions in the solid state, such reactions have the potential to be developed as green reactions. Solid state reactions coupled with the X-ray crystal structure data (of reactants and / or products) can also provide valuable information on the mechanisms of reactions that cannot be obtained by observing the corresponding reactions in solution. For example, good understanding of the mechanisms of reactions like addition to C=C, S\textsubscript{N}2
displacement reactions and Chapman rearrangement-like reactions, have resulted because of studies conducted in the solid state. Although addition to C=C in the solid state is well investigated, these are not covered in the present review as they have been discussed extensively in the literature.

Section 2. Solid state acyl transfer reactions in inositol derivatives

Inositols and their derivatives have continued to attract the attention of chemists and biologists due to their ubiquitous presence in animals and plants as well as their involvement in several biological processes in eukaryotic cells. Solution state acyl migration reactions among the hydroxyl groups of inositol derivatives have been used for the preparation of phosphoinositols in the last two decades. Most of these acyl migration reactions however, resulted in the formation of a mixture of isomeric esters, which are not easy to separate and consequently in poor isolated yield of the required O-protected cyclitol intermediates. The first example of a facile acyl transfer reaction in the solid state (Scheme 1) was reported from our laboratory1 few years ago. Hydrogen bonding interaction between the carbonyl oxygen of the C-2-O-benzoyl group of one molecule of 1 and the hydrogen atom of C-6-hydroxyl group of another molecule in the same crystal, as well as electrophile (C=O) – nucleophile (OH) interactions between the two reacting molecules were thought to be responsible for the facile reaction in the solid state.

Scheme 1. Reagents and conditions: a) Na₂CO₃ (8 eq), 140 °C, 60 h; b) Na₂CO₃ (8 eq), microwave, 25 min.

Encouraged by the discovery of a clean solid-state acyl transfer reaction (Scheme 1) we sought out to explore such reactions further with the following objectives, (a) Can we find other inositol derivatives that exhibit solid-state acyl transfer reaction and if so could they be used for the preparation of protected myo-inositol derivatives? (b) How do minor modifications in the molecular structure reflect in their reactivity in the solid state? (c) Can we utilize the non-bonded intermolecular interaction parameters, similar to those observed in the crystals of the dibenzoate 1 that were used to rationalize its reactivity, to
predict the reactivity of other hydroxyl esters? Accordingly, this section describes preparation of several inositol based hydroxyl esters (Scheme 2) and study of their acyl transfer reactivity in the solid state. Acyl transfer reactions of some of the esters were carried out in the solution and molten states for comparison. Correlation of the observed reactivity in the solid state with the crystal structure of the reactants was also attempted. Since crystals of 1, 8 and 19 were found to be isostructural, we tried to crystallize them together from different solvents. We were able to obtain 1:1 molecular complex crystals of 1 and 8 (1.8) which also showed good acyl transfer reactivity in the solid state.

From the results obtained it was observed that structurally similar hydroxyl esters show widely different reactivity under similar conditions. An interesting observation was that minor modification in the molecular structure (for example changing from
orthoformate 1 to orthoacetate 8) resulted in considerable change in the solid state reactivity. Results of the solid state reactivity of the inositol derivatives and their crystal structures suggested that three types of intermolecular interactions in the crystals of myo-inositol orthoester derivatives played crucial role to decide the facility of acyl transfer. (a) Hydrogen bonding interaction between the carbonyl oxygen of C-2-O-benzoyl group of one molecule and the hydrogen atom of C-6-hydroxyl group of another molecule (b) electrophile – nucleophile interactions between the two reacting molecules (c) CH…π interaction between the phenyl ring of the migrating benzoyl group and a hydrogen of the inositol ring.

Usually chemical reactions in crystals lead to distortion of the crystal lattice due to appearance of products, only exceptions to this being single crystal to single crystal transformations. Distortion of the crystal structure is usually high enough to cause a collapse which result in rather low conversion to the product due to loss of topochemical control. However, if the reaction proceeds in a domino fashion along an axis in the crystal of the reactant, higher conversion and better yield of the products can be expected. The transesterification of 1 and 1.8 having very good facility of the heterogeneous reaction that proceeds to high conversion to products could be categorized in the above class. Based on their crystal structure a mechanism for the reaction was suggested. A part of this work has been communicated for publication.

**Part B: Use of sulfonate protecting groups for the synthesis of cyclitol derivatives.**

**Section 1. A review on the use of sulfonates as hydroxyl protecting groups**

This section reviews the literature on the use of alkyl / aryl sulfonyl groups for the protection of alcohols with a bias towards cyclitol hydroxyl groups. Protection and deprotection of functional groups like OH, NH₂, C=O are very common in organic synthesis. Protection of alcohols as their carboxylic acid esters, ethers etc. are encountered very often in the literature; but reports on their protection as sulfonates are very rare (Scheme 3). The main reason behind this is that sulfonates function as good leaving groups and result in nucleophilic substitution at the carbon carrying the sulfonate group (which could result in inversion or racemization in optically active alcohols) or elimination to form unsaturated compounds (Scheme 4). Hence deprotection of
sulfonates to regenerate the parent alcohol is not easily achievable or needs conditions that could affect other functional groups in the same molecule.

![Chemical structures](attachment:image.png)

**Scheme 3.** Reagents and conditions: a) reference 5; b) NaOMe, MeOH, reflux, 12 h, 99%; c) reference 6; d) LiAlH₄ (3 eq), THF, 0 °C-rt, 2 h, 63%; e) reference 7; f) reference 8; g) NaBH₄, DMSO, 150 °C, 24 h, 71%.

Although there are many reports in the literature on the sulfonates (mesylates, tosylates, camphorsulfonates) of cyclitols, most of them were used for the further

![Chemical structures](attachment:image.png)

**Scheme 4.** Reagents and conditions: a) R³SO₂Cl, base; b) NaOMe (1 eq), MeOH, reflux, 15 min, 91%; c) KCN (4 eq), 2-methoxyethanol, 100 °C, 42%.
functionalization of the cyclitol moiety by nucleophilic substitution or deoxygenation. Accordingly this section provides a survey of the literature (that is relevant to the work described in the next section) illustrating the points mentioned above.

Section 2. Synthesis of cyclitol derivatives with the aid of sulfonyl groups for the protection of myo-inositol hydroxyl groups.

Previous work in our laboratory\(^5\) had shown that the three hydroxyl groups of myo-inositol orthoesters (6, 7) can be sulfonlated with very good regioselectivity and the resulting sulfonates can be cleaved efficiently with retention of configuration of the myo-inositol ring. This is mainly because these orthoesters are trioxaadamantanes. In the present work, we have used sulfonate protection in myo-inositol orthoesters for the synthesis of isomeric cyclitols, their methylated derivatives and aminocyclitols. Some of the cyclitol derivatives synthesized in the present work are shown in Scheme 5.

![Scheme 5](image)

**Scheme 5**

Synthesis of methylated derivatives of cyclitols. O-methylated derivatives of inositols are present in grains and forage legumes and are known to take part in many biological phenomena in the plant kingdom. Natural O-methyl ethers of myo-inositol such as (+)-bornesitol (1D-3-O-methyl-my o-inositol), (+)-ononitol (1D-4-O-methyl-my o-inositol), sequoyitol (5-O-methyl-my o-inositol) are all present, albeit in small amount, in many plants and frequently in combination with one another, which makes it difficult to isolate them from plant sources. O-methyl-scyllo-inositol was isolated from the seeds of *Phaseolus vidissimus* (mung bean). Among the O-methylated inositols (-)-quebrachitol (1L-2-O-methyl-chiro-inositol) and (+)-pinitol (1D-3-O-methyl-chiro-inositol) are commercially available but most of the other inositol methyl ethers are scarce. Laminitol and mytilitol are the two known naturally occurring C-methyl inositols, mostly found in algae. Synthesis of (+)- & (-)-ononitol, racemic & (-)-laminitol and mytilitol are reported
in the literature; but in all of the literature procedures the isolated yields were very low (3-18%). There is no report in the literature on the synthesis of the unnatural isomer, (+)-laminitol, till date. We have developed high yielding procedures (overall yield in parenthesis) for the synthesis of both (+)- & (-)-ononitol (32%), scylo-inositol methyl ether (60%), mytilitol (48%), racemic laminitol (63%), (-) & (+) laminitol (30%) and scylo-inositol (64%) from myo-inositol using sulfonate (tosylate) as protecting group. The synthetic route for (+)- and (-)-ononitol (D-46 & L-46) is shown in Scheme 6. Configuration of D-53 and L-53 were established by X-ray crystallography. Synthetic route for mytilitol (47) and scylo-inositol methyl ether (48) are shown in the Scheme 7. Configuration of 61 and 66 were established by X-ray crystallography.

We tried to execute the synthesis of racemic laminitol from the ditosylate 52. Oxidation of 52 gave a mixture of ketone 56 and gem diol 57, where gem diol was found
to be the major product. Unfortunately, our efforts to convert 57 to 56 and Grignard reaction on a mixture of 56 and 57 failed (Scheme 6).

Since the reaction of 56 + 57 with methyl magnesium iodide failed, we synthesized racemic laminitol (Scheme 8) from unsymmetrical dibenzyl ether 30. Structure of 69 was established by X-ray crystallography. After successful synthesis of racemic laminitol (49), both (-)- and (+)- laminitol (D-49 & L-49) were synthesized, by using same reaction sequence (as shown in Scheme 8) on enantiomeric dibenzyl ethers D-30 & L-30. For this purpose, the dibenzyl ether 30 was resolved by converting it to its diastereomeric 1S(-)-camphanoate esters according to procedure previously developed in our laboratory. Part of this work has been published in Trends in Carbohydrate Chemistry.
Synthesis of isomeric cyclitols from *myo*-inositol. *scyllo*-Inositol (50), the inositol having six equatorial hydroxyl groups, is found in many plants and animals. It has been suggested that certain human diseases are associated with *scyllo*-inositol depletion. Among the nine isomers of inositols known, the *myo*-isomer, having five equatorial and one axial hydroxyl group is the most abundant in nature and hence there have been efforts to convert *myo*-inositol to other isomers. Isomeric inositols have also been synthesized from carbohydrates as well as from benzene and its derivatives. There are reports on the conversion of *myo*-inositol to *scyllo*-inositol or its derivatives in overall yields of 10-40%. In the present work, *scyllo*-inositol was prepared from the ditosylate 64 without the involvement of chromatography (Scheme 9). Configuration of 71 was established by X-ray crystallography. This work was published in *Carbohydr. Res.* 2003, 338, 999-1001.


diagram

**Scheme 9.** Reagents and conditions: a) NaOMe, MeOH, reflux, 12 h; b) Ac₂O, pyr, rt, 12 h, 96% in two steps; c) iso-But-NH₂, MeOH, reflux, 12 h, 98%; d) TFA-H₂O (4:1), rt, 1 h, 98%.

*epi*-Inositol (76, Scheme 10) is one of the members of the cyclitol family having two axial and four equatorial hydroxyl groups. Several synthetic routes for *epi*-inositol, starting from different starting materials like D-glucose, D-galactose, *myo*-inositol and benzene are known in the literature. We investigated the possibility of obtaining *epi*-inositol from the ketone 67 and the gem-diol 57. The ketone 67 was subjected to acid hydrolysis in a mixture of trifluoroacetic acid and water to obtain the *epi*-inosose
derivative 72. Since 72 was unstable, we attempted to prepare its tribenzoate derivative. But benzoylation of 72 in pyridine gave a mixture of products that could not be separated by flash chromatography. One of the products 73 (yield 23%) could be isolated by crystallization from dichloromethane - light petroleum mixture. Structure of 73 was confirmed by X-ray crystallography. After our approach to synthesize epi-inositol from ketone 67 met with failure, we attempted synthesis of epi-inositol from gem diol 57 (Scheme 10). Attempts for the conversion of 51 to 76 are in progress.

Synthesis of aminocyclitols. Free and conjugated amino derivatives of inositols are capable of inhibiting glycosidases and also play an active role in antibiotic action. Azido- and amino-myoinositol derivatives are known to inhibit cell growth. To study biological and physical properties of isomeric inositols and aminocyclitols, sufficient supply of these compounds is required. However, only a few syntheses of amino derivatives of myo-inositol are reported in the literature till date. After successful synthesis of isomeric cyclitols and some O- and C-methylated cyclitol derivatives in high yield by using sulfonate protecting groups, we took up the synthesis of aminocyclitols from myo-inositol. Racemic 4-deoxy-4-amino-myoinositol (isolated as hexaacetate, 78) was prepared from the ketone 67, with an overall yield of 50% from myo-inositol (Scheme 11). The myo- configuration of racemic 78 was established by X-ray crystallography. Following the same sequence but starting from the enantiomeric ketones D-67 and L-67, enantiomers D-78 and L-78, were prepared, with overall yields 25% from myo-inositol.
Scheme 11. Reagents and conditions: a) BnNH$_2$ (3 eq), MeOH, 50 °C, 3 h followed by NaBH$_4$CN (3 eq), rt, 1 h 90%; b) Pd(OH)$_2$ (50 mol%), TFA-MeOH (1 : 1), H$_2$ / 60 psi, 8 h; c) Ac$_2$O, pyr., DMAP, rt, 12 h, 81% in two steps.

References: