CHAPTER 1
Ester protecting groups in inositol chemistry
1.1 Introduction

The last decade witnessed a renaissance in the chemistry and biochemistry of inositol 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.\(^3\)

\[\text{Scheme 1.1}\]

![Scheme 1.1](image)

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 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 inositol (GPI) in cells have long been recognized. They are involved in anchoring of certain proteins to cell membranes, for example, variant surface glycoprotein of trypanosomes. 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. Lipophosphoglycans and glycoinositol phospholipids, are thought to play an important role in parasite virulence.

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. An IUPAC nomenclature allowing all biologically relevant compounds to be denoted as D isomers has also been proposed. Although all
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 inositol 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)\textsuperscript{1,13}

(b) From naturally occurring quebrachitol (2)\textsuperscript{14-17}

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

(d) From tartaric acid (8)\textsuperscript{32,33}

(e) From benzene and its derivatives (9)\textsuperscript{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, isopropylidene cyclopentylidene] or an orthoester derivative (orthoformate, orthoacetate) (Scheme 1.5). The orthoformate derivative

**Scheme 1.5**

![Scheme 1.5](image)

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\(^3\)-\(^6\) (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 = HO

Neosurugatoxin

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

(±)-1,2:4,5-di-O-isopropylidene-my\(\text{a}^{\text{i}}\)no-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. Benzylation 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% overall yield starting from myo-inositol, circumventing the tedious column chromatography. Potter et al. have used this intermediate for the synthesis of Ins(1,2,4,5)P_4 (Scheme 1.7). Synthesis of this racemic tetraphosphate provides an example where ester groups are retained to avoid phosphate migration.

Scheme 1.7

Kishi et al. in their first report, isolated myo-inositol 1,3,5-orthoformate 10 by column chromatography in 76% yield. Andersch and Schneider 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 overall yield of 90%.
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. Reaction at ambient temperature yielded Ins(1,3,4,5,6)Bz₅ (21, Scheme 1.9) as the major product (48%); while above 60°C Ins(1,3,4,5)Bz₄ (22) was the major product (34%). The tetra benzoate 22 was converted to the racemic Ins(1,3,4,5)P₄. The racemic Ins(1,3,4,5)P₄ has been resolved using chiral column chromatography.

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 (-)-menthyl chloroformate.\textsuperscript{50} Diastereomerically pure 1-O-(-)-menthoxycarbonyl-\textit{myo}-inositol 24 obtained was used for the synthesis of D and L Ins(1,4,5)P\textsubscript{3}.

**Scheme 1.10**

![Scheme 1.10 diagram](image)

\textit{a)} Bu\textsubscript{2}Sn(acac\textsubscript{2})
\textit{b)} (-)-Menthyl chloroformate, N-methylimidazole, toluene. -35°C

D and L Ins(1,4,5)P\textsubscript{3}

Reaction of 2,3-\textit{O}-(D-1,7,7-trimethyl[2.2.1]bicyclohept-2-ylidene)-\textit{myo}-inositol (25, **Scheme 1.11**) with 1, 2 or 3 equivalents of pivaloyl chloride in pyridine resulted in \textit{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\textsubscript{2} and D-Ins(1,4,5)P\textsubscript{3} respectively.\textsuperscript{52}

**Scheme 1.11**

![Scheme 1.11 diagram](image)

\textit{a)} 1 eq. PivCl/ Pyridine  \textit{b)} 2 eq. PivCl/Pyridine  \textit{c)} x'sPivCl/Pyridine
Racemic 1,2:4,5-di-O-isopropylidene-\textit{myo}-inositol (15) has been selectively acylated at the O-3 position.\ citation{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 \textit{p}-nitrophenyl phosphate derivative 30 (Scheme 1.12).

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.\ citation{54} Recently, higher reactivities of 3(1) position [rather than 6(4) position] of 1,2:4,5-di-O-isopropylidene-\textit{myo}-inositol (15) has been evaluated using semiempirical\ citation{55} and quantum mechanical calculations.\ citation{56}

1-\textit{O}-t-Butyldiisopropylsilyl-\textit{myo}-inositol (31), on benzylation with 1 or 3 equivalents of benzoic chloride gave predominantly 3-\textit{O}-, 3,4-di-\textit{O}- or 3,4,5-tri-\textit{O}-benzoylated products (32-34, Scheme 1.13) respectively.\ citation{57} The mono, di and tri benzoates 32-34 were converted to the racemic PtdIns(3)P, PtdIns(3,4)P\textsubscript{2} and PtdIns(3,4,5)P\textsubscript{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.
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.\(^{13}\)
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. 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)P₄. 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 (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
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 4-0-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 2-0-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.
1.4 Acyl migration

One problem associated with the use of esters as protecting groups in polyfunctional 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. The review on the chemistry of myo-inositol by Shvets 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-myoinositol (46) 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-inositiols (47-49) (Scheme 1.18). Acetyl migration could however, be minimized by storing the 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. subjected Ins(1,4)Bz₂ 17 (Scheme 1.19) to basic conditions under which it predominantly rearranged to Ins(2,4)Bz₂ 17a. The dibenzoate was phosphorylated to obtain Ins(1,3,4,5)P₄. This constituted the first report of exploiting benzoate migration for the synthesis of myo-inositol phosphates.
Chung and co-workers studied acyl migration in the dibenzoate 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 InsP₁, InsP₂, InsP₃, and InsP₅ starting from the corresponding pentabenzoates, tetrabenzoates, tribenzoates and monobenzoates generated via acyl migration and separation of isomeric benzoates.

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
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

<table>
<thead>
<tr>
<th>myo-inositol derivative</th>
<th>ester/reagent</th>
<th>final product prepared</th>
<th>ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>3,6-di-O-camphanate/51</td>
<td>a) 3,6-di-O-camphanate/51</td>
<td>D and L Ins(1,4,5)P₃</td>
<td>78</td>
</tr>
<tr>
<td>3-O-menthoxyacetate/56</td>
<td>b) 3-O-menthoxyacetate/56</td>
<td>D and L Ins(1,4,5)P₂</td>
<td>79</td>
</tr>
<tr>
<td>3-O-mandalate/54</td>
<td>c) 3-O-mandalate/54</td>
<td>D and L Ins(1,4,5)P₃</td>
<td>80</td>
</tr>
</tbody>
</table>
3-O-camphanate/51 and 56
D and L Ins(3,4,5,6)P₄
and membrane permeant analogues

1-O-camphanate/51
D and L Ins(1)P

3,6-di-O-camphanate/51
D and L Ins(1,2,4,5)P₄

2,4-di-O-camphanate/51
D and L Ins(1,3,4,5)P₄

2,4-di-O-camphanate/51
D and L Ins(1,4,5)P₃

R-(-)-oxotetrahydrofuran carboxylate/57
L-PtdIns(3,5)P₂

1-(S)-(-)-camphanate/51
D and L [³H]-Ins(1,3,4)P₃

1-(O)-(-)-menthloxy carbonate/55
D and L Ins(1,4,5)P₃
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 esterification 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.\textsuperscript{89,11} Enzyme catalyzed selective hydrolysis in aqueous media was used to resolve some \textit{myo}-inositol derivatives.\textsuperscript{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 \textit{myo}-inositol derivatives prepared using lipases.
Table 1.2

<table>
<thead>
<tr>
<th>myo-inositol derivative</th>
<th>method/enzyme</th>
<th>final product prepared</th>
<th>ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td></td>
<td>D and (L) (\text{Ins}(1,4))P (_3)</td>
<td>13</td>
</tr>
<tr>
<td>F</td>
<td></td>
<td>D and (L) (\text{Ins}(1,4,5))P (_3)</td>
<td>13</td>
</tr>
<tr>
<td>67</td>
<td></td>
<td>D and (L) (\text{Ins}(1,4,5))P (_3)</td>
<td>13</td>
</tr>
<tr>
<td>68</td>
<td></td>
<td>D and (L) (\text{Ins}(1,4,6))P (_3)</td>
<td>13</td>
</tr>
<tr>
<td>59</td>
<td></td>
<td>D and (L) (\text{Ins}(1,4,6))P (_3)</td>
<td>13</td>
</tr>
<tr>
<td>69</td>
<td></td>
<td>D and (L) (\text{Ins}(1,4,6))P (_3)</td>
<td>13</td>
</tr>
<tr>
<td>70</td>
<td></td>
<td>D and (L) (\text{Ins}(1,4,6))P (_3)</td>
<td>13</td>
</tr>
</tbody>
</table>

* a) enantio and regioselective acetylation at O-3 / Amanolipase P from *Pseudomonas* *Sp.*

* b) enantio and regioselective acetylation at O-4 / Amanolipase AY from *Candida cyndidracea*

* c) enantioselective hydrolysis of 6-O-butyryl ester / PPL

* regio and enantioselective acetylation at O-5 / Lipase AY

* a) regio and enantioselective acetylation at O-1 / Amanolipase P and Lipase CES from *Pseudomonas* *sp.*

* b) regio and enantioselective acetylation at O-1 / Porcine pancreatic Lipase

* regio and enantioselective acetylation at O-1 / Lipase PS from *Pseudomonas* *Sp.*

* transesterification using vinylbutyrate at O-1 / Lip proteinlipase from *Pseudomonas* *Sp.*
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.\textsuperscript{13}

1.6 Use of esters to facilitate membrane permeability

Esters are frequently used to mask the negative charge\textsuperscript{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 \textit{et. al.} synthesized membrane-permeant analogues of various inositol phosphates for the biological evaluation.\textsuperscript{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 T84 cells and result in Scheme 1.22

\begin{align*}
70 & \text{R}^1 = \text{OH}, \text{R}^2 = \text{OCCOC}_3\text{H}_7 \\
71 & \text{R}^1 = \text{OCOC}_3\text{H}_7, \text{R}^2 = \text{OH} \\
72 & \text{R}^1 = \text{H}, \text{R}^2 = \text{OCCOC}_3\text{H}_7 \\
73 & \text{R}^1 = \text{OCOC}_3\text{H}_7, \text{R}^2 = \text{H} \\
74 & \text{R}^1 = \text{H}, \text{R}^2 = \text{OCOC}_3\text{H}_7 \\
75 & \text{R}^1 = \text{OCOC}_3\text{H}_7, \text{R}^2 = \text{H} \\
76 & \text{R}^1 = \text{OCOC}_3\text{H}_7, \text{R}^2 = \text{OCCOC}_3\text{H}_7 \\
77 & \text{R}^1 = \text{CH}_3, \text{R}^2 = \text{OCCOC}_3\text{H}_7 \\
78 & \text{R}^1 = \text{OCOC}_3\text{H}_7, \text{R}^2 = \text{CH}_3 \\
79 & \text{R}^1 = \text{CH}_3, \text{R}^2 = \text{CH}_3 \\
80 & \text{R}^1 = \text{Cl}, \text{R}^2 = \text{Cl}
\end{align*}

\begin{align*}
\text{Hydrophilic Biologically active myo-inositol derivative} & \quad \text{lipophilic membrane permeant analogue of myo-inositol phosphate} \\
\text{Intracellular esterases}
\end{align*}
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 \textit{myo}-inositol derivatives.

b) for the regioselective functionalization of various hydroxyl groups of \textit{myo}-inositol and its derivatives.

c) for the resolution of racemic \textit{myo}-inositol derivatives.

d) for the desymmetrization of \textit{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 \textit{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 \textit{myo}-inositol phosphates.
1.8 References


