Regioselective protection of *myo*-inositol orthoesters – recent developments

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Abstract

There has been a revival of interest in the chemistry of cyclitols in the recent past due to the discovery of phosphoinositol based signal transduction mechanisms in eukaryotic systems. Traditionally, synthesis of inositol derivatives involved the protection of its hydroxyl groups as the corresponding ketals. However, recently orthoesters of *myo*-inositol have emerged as convenient intermediates for the synthesis of inositol derivatives. The present account describes recent progress in the chemistry related to *myo*-inositol orthoesters.

Keywords: Inositol, signal transduction, cyclitol, protecting groups, second messenger

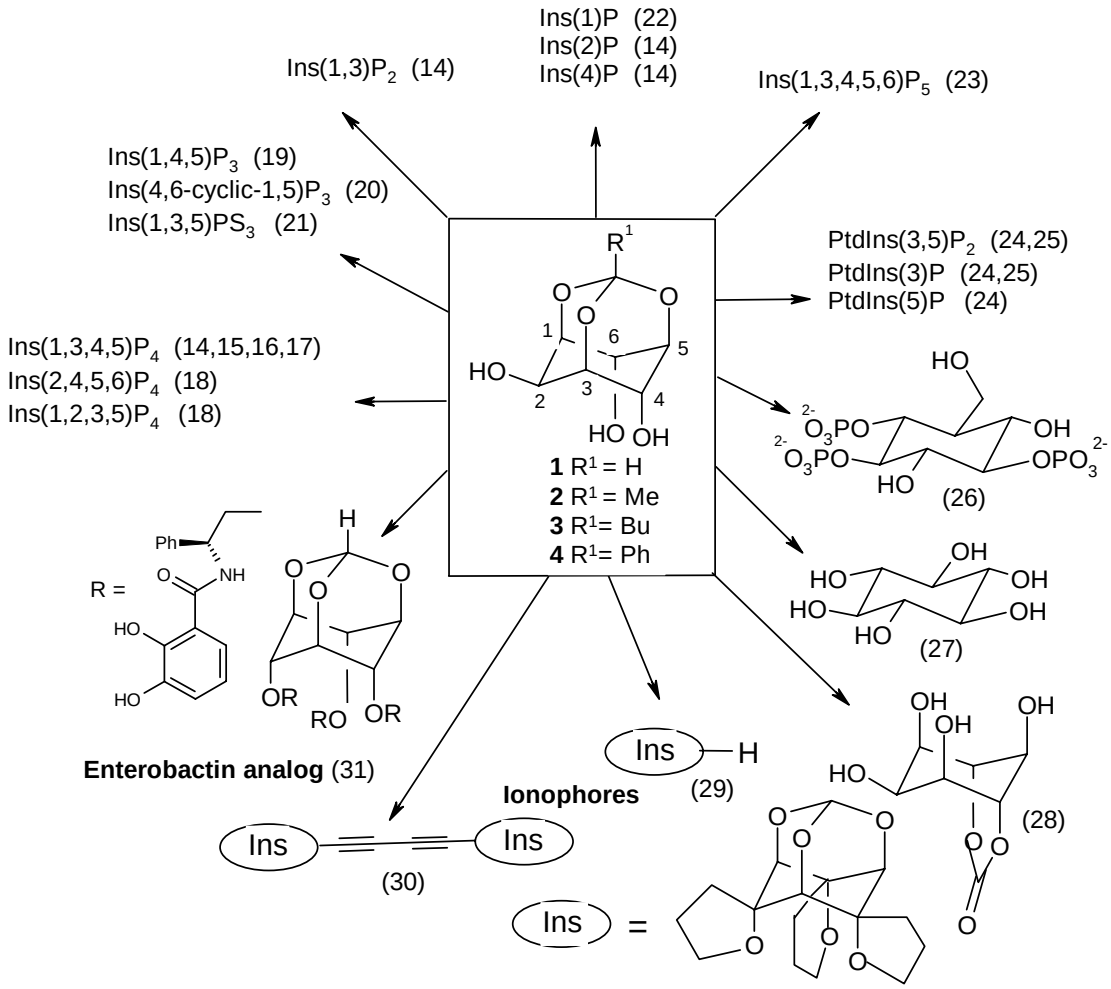
Introduction

Chemistry and biology of *myo*-inositol derivatives has been investigated extensively in the recent past due to the involvement of phosphoinositols in cellular signal transduction mechanisms[1] and anchoring of certain proteins to cell membranes.[2] Although a bewildering array of *myo*-inositol phosphates and their lipid derivatives have been identified and / or isolated from plant as well as animal sources, the biological roles played by many of them is not yet clearly understood. However, receptors and effectors involved in various stages of phosphoinositol based signal transduction pathways remain potential targets for pharmacological intervention in states of disease.[1c] These developments in biology and medicine have necessitated the efficient synthesis of naturally occurring phosphoinositols and their synthetic analogs. Consequently, many methodologies and techniques have been developed,[1c, 3] for the synthesis and isolation of phosphoinositols and their analogs.

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). *O*-protected *myo*-inositol derivatives and their analogues have been prepared from (a) commercially available *myo*-inositol,[3a, 3b] (b) naturally occurring quebrachitol,[4] (c) carbohydrates (glucose,[3c] D-xylose,[5] D-galactose,[6] D-mannitol,[7] and L-iditol,[8]) (d) tartaric acid[9] and (e)

benzene and its derivatives.[10] Among the different strategies developed for the synthesis of protected *myo*-inositol derivatives and their analogs, those starting from commercially available *myo*-inositol is many times preferred because of its low cost and convenience. Several efficient methods are now available for the desymmetrization or resolution of *myo*-inositol derivatives that can be used for the preparation of enantiomeric phosphoinositols and their analogs.

Traditionally, the first step in the preparation of *O*-protected *myo*-inositol derivatives was the ketalization of two or four hydroxyl groups of *myo*-inositol. These aspects have been extensively reviewed.[3a, 3b, 11]. However, in the last decade, protection of the C-1, C-3 and C-5 hydroxyl groups of *myo*-inositol as the corresponding orthoester has been frequently used.[12] This is mainly because, orthoesters of *myo*-inositol can be easily obtained in gram quantities as a single product.[13]. In contrast, ketalization of *myo*-inositol results in the formation of mixture of isomers, which require tedious chromatographic separation and/or the yield of individual isomers is seldom more than 30%. Phosphoinositols and other compounds with interesting properties that have been synthesized starting from *myo*-inositol orthoesters are shown in Scheme 1.

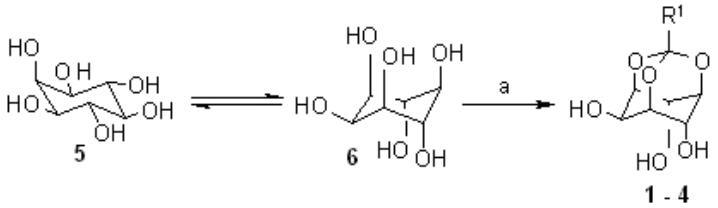


Scheme 1. Numbers in paranthesis indicate relevant references.

Billington[14] first reported the selective C-4-*O*-alkylation of the orthoformate **1** and its application for the preparation of a few *myo*-inositol phosphates. We have developed good methods for the selective functionalization of (a) only the C-2 or the C-4 hydroxyl group,[32] (b) C-2 and C-4 (or C-6) hydroxyl groups simultaneously[33] and (c) C-4 and C-6 hydroxyl groups simultaneously[34] in **1** and **2**. In the present account, results of our efforts towards the synthesis of *O*-protected inositol derivatives starting from orthoesters of *myo*-inositol is presented. In addition to being useful intermediates for the synthesis of phosphoinositols, orthoesters of *myo*-inositol exhibit interesting and unusual chemistry due to their rigid adamantane – like structure. These unusual chemical characteristics are also referred to, in relevant sections of this account.

2. Preparation of *myo*-inositol orthoesters

Although four orthoesters of *myo*-inositol (1-4, Scheme 1) are reported in the literature, most of the reports on the preparation of *O*-protected *myo*-inositol derivatives have utilized the orthoformate **1**. Orthoesters of *myo*-inositol are prepared by the reaction of *myo*-inositol (**5**, **Scheme 2**) with ethyl or methyl orthoester of the desired carboxylic acid. They can be isolated (in 90% yield or more) by column chromatography or as the corresponding triacetate or the tribenzoate, without the aid of chromatography. The orthoesters **1-4** can be obtained by the methanolysis or aminolysis of the corresponding triacetate or the tribenzoate. Using these procedures, the required orthoester may be obtained on tens of grams to hundred-gram scale in a short time.[13]



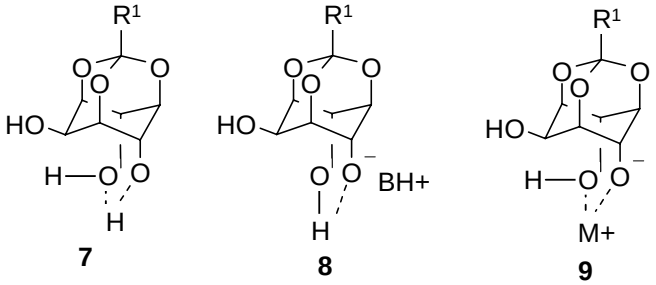
Scheme 2. (a) $(EtO)_3CR^1$, DMF, *p*-TsA, 100 ˚C

3. Selective protection of *myo*-inositol orthoester hydroxyl groups Synthesis of *O*-protected *myo*-inositol derivatives

3.1. Protection of one of the hydroxyl groups of *myo*-inositol orthoesters

Formation of 1,3,5-orthoesters of *myo*-inositol involves inversion of the inositol ring (**6**, Scheme 2). Consequently, these orthoesters have five oxygen atoms in axial position and an oxygen atom in the equatorial position with respect to the *myo*-inositol ring. *Myo*-inositol orthoesters are in fact highly functionalized adamantanes. Three of the carbon atoms in adamantane are replaced by three oxygen atoms (C-1, C-3 and C-5 oxygen atoms of the inositol ring) and three of the methylene groups of adamantane are hydroxylated (C-2, C-4 and C-6 of the inositol ring). This results in an analog of adamantane molecule, which has two pairs of 1,3-trans hydroxyl groups and one pair of 1,3-cis hydroxyl groups. The rigidity of the adamantane frame-work and the

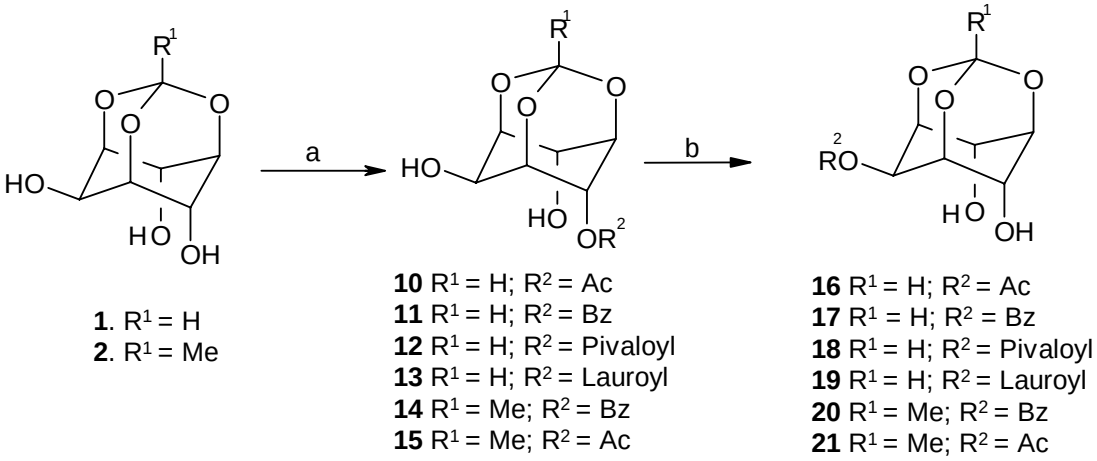
presence of six oxygen atoms in the molecule imparts unusual chemical and physical properties on *myo*-inositol orthoesters and its derivatives. All these orthoesters have the meso configuration and hence two of the hydroxyl groups (C-4 and C-6) are chemically equivalent. The C-4 and C-6 hydroxyl groups form a strong intramolecular hydrogen bond, [15,35] (Scheme 3) as a result of which, one of these hydroxyl groups is more acidic than the C-2 hydroxyl group.



Scheme 3

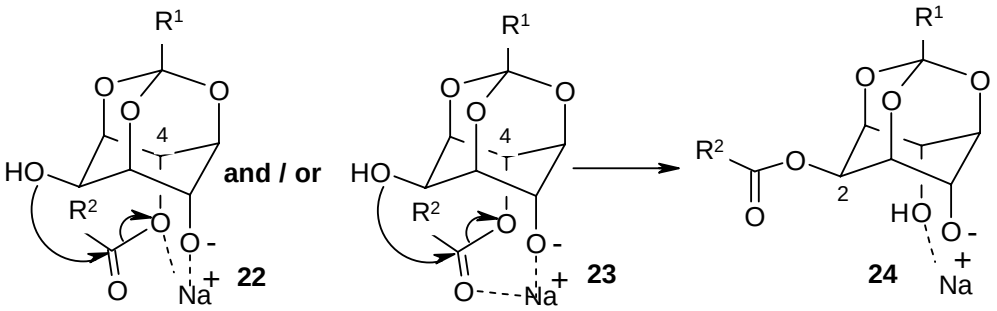
Hence bases that can de-protonate the more acidic hydroxyl group (C-4 or C-6) result in the formation of the corresponding anion (**8**) which is also stabilized by intramolecular hydrogen bonding with the other axial hydroxyl group. When metal hydrides are used as bases, the resulting alkoxide at the C-4 or the C-6 hydroxyl group is stabilized by chelation (**9**) with the *cis*-hydroxyl group. As a result of these intramolecular interactions, selective mono functionalization of one of the 1,3-*cis* hydroxyl groups or the C-2 hydroxyl group can be achieved.[14]

Acylation of *myo*-inositol orthoesters (Scheme 4) with one equivalent of an acylating agent in the presence of a strong base such as triethylamine or sodium hydride (one equivalent) results in the formation of the corresponding C-4 (or C-6) ester. The use of excess of sodium hydride for mono acylation leads to the formation of the C-2 ester. This method for the acylation of the C-2 hydroxyl group gives the corresponding C-2-ester exclusively in excellent yields.[32]



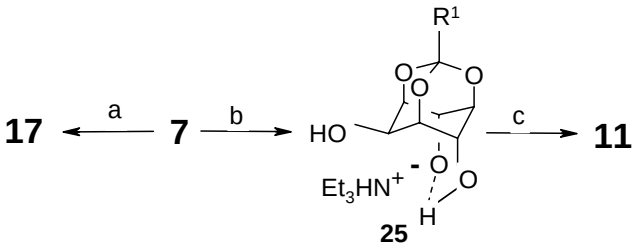
Scheme 4. (a) DMF, NaH (1 eq), R^2X, rt. (R^2X=acyl chloride or anhydride).
(b) DMF, Nah, rt, 5 min.

The different regioselectivities observed for the acylation of the orthoesters in the presence of one equivalent and excess of sodium hydride is due to an intramolecular acyl migration from C-4-*O*-position to the C-2-*O*-position (**Scheme 5**). That this migration is intramolecular was suggested by carrying out the acyl migration in a mixture (equimolar) of the acetate **10** and the benzoate **14**, which did not result in the formation of any cross products (**17** or **21**). It appears this migration takes place since the chelate **24** of the C-2 ester is expected to be more stable than the chelates **22, 23** of the C-4 ester. It is interesting to note that this 1,3-*trans* acyl migration is quite facile in spite of the fact that formation of a tetrahedral intermediate is not possible due to rigidity of these molecules. It is likely that this migration proceeds in an S_N2 like mechanism wherein bond formation (C2-O...C=O) and bond breakage (C4-O — C=O) are simultaneous.



Scheme 5

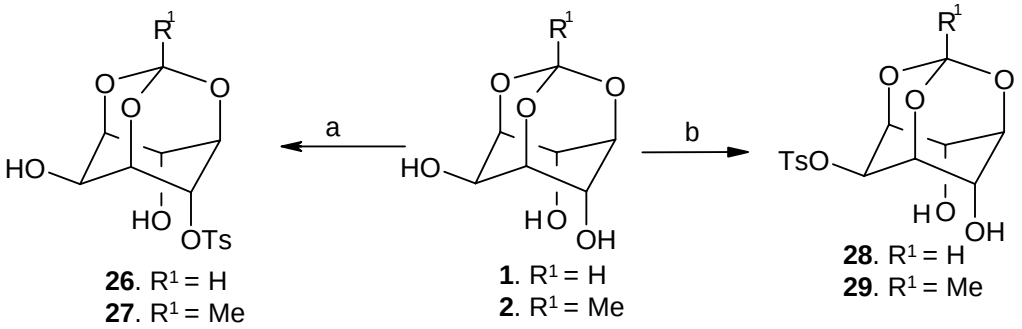
It is important to note that regioselectivity observed during acylation of orthoesters of *myo*-inositol in the presence of sodium hydride is the same irrespective of the acylating agent used. In contrast, regioselectivity for the acylation of these orthoesters in the presence of organic bases varies with the acylating agent.[36] For instance, benzoylation of the triol **1** with benzoyl chloride, in the presence of pyridine (pK_a = 5.58) and triethylamine (pK_a = 11.01) yield the C-2-benzoate **17** and the C-4-benzoate **11** respectively. Triethylamine being a stronger base can perhaps deprotonate one of the axial hydroxyl groups, whose acidity is higher than that of normal alcohols (and the C-2-hydroxyl group) due to a very strong intramolecular hydrogen bond[35] (**Scheme 6**). The resulting anion **25** is also stabilized by intramolecular hydrogen bonding and hence benzoyl chloride preferentially reacts at the C-4(6)-*O* position. Pyridine being a weaker base, cannot deprotonate the C-4(6) hydroxyl group; and hence the reactivity among the



Scheme 6. (a) Pyridine, BzCl; (b) Net_3; (c) BzCl.

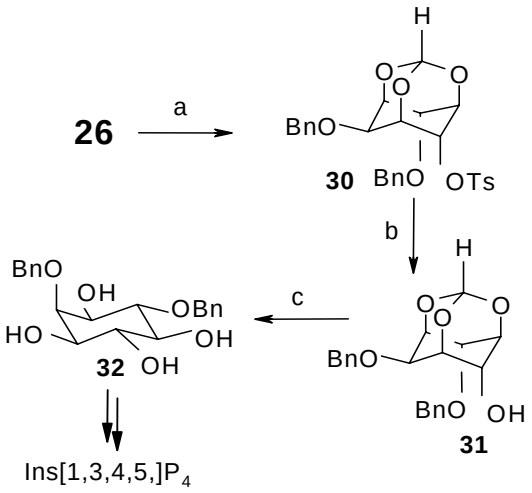
three hydroxyl groups of **1** is determined by the relative nucleophilicity and steric factors. Since the axial C-4(6) hydroxyl groups are more acidic than the C-2-hydroxyl group, they are expected to be less nucleophilic than the C-2-hydroxyl group, and as a result, benzoylation takes place at the C-2-*O* position, in pyridine. Steric hindrance for *O*-substitution at the axial C-4(6)-*O*-position may also contribute to the observed selectivity for the reaction in pyridine, since the benzoylating species in pyridine is thought to be the bulky benzoyl pyridinium ion.[36]

Regioselectivity observed for the sulfonylation of the orthoesters **1** and **2** (Scheme 7) is similar to that observed during their acylation. Use of stronger bases (sodium hydride,



Scheme 7. (a) DMF, NaH (or Net_3), TsCl, rt. (b) Pyridine, TsCl, rt.

triethylamine) results in the formation of the C-4 sulfonate (**26** or **27**) while the use of pyridine results in the formation of the C-2 sulfonate (**28** or **29**). However, the C-4 sulfonates (**26** or **27**) cannot be converted to the corresponding C-2 sulfonates (**28** or **29**) by treatment with excess sodium hydride, as in the case of carboxylic acid esters (Scheme 4). We have demonstrated[34] that *myo*-inositol orthoester hydroxyl groups can be selectively protected as alkyl or aryl sulfonates and these sulfonates can be deprotected by cleavage with magnesium in methanol or sodium methoxide in methanol.



Scheme 8. (a) NaH, BnBr; (b) Mg / MeOH; (c) Aq. TFA.

Table 1. A comparison of the overall yield of racemic (**32**) as well as D- and L-2,4-di-*O*-benzyl-*myo*-inositol reported in the literature

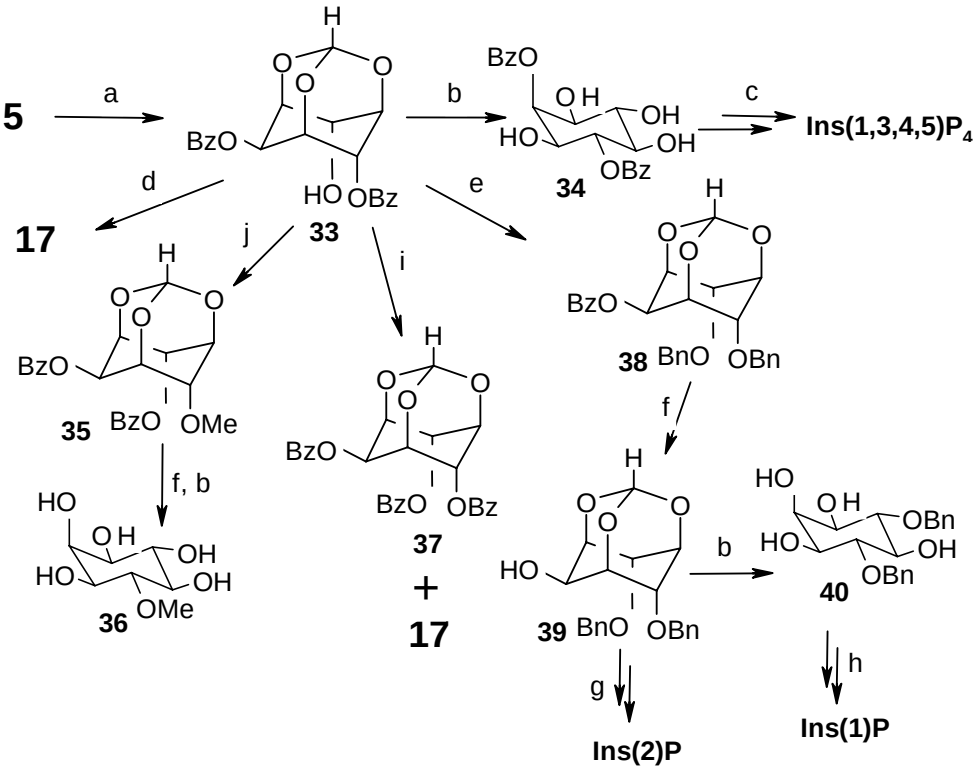
Entry	Key intermediate	Yield(%)[a]	Ref
1	*Myo*-inositol 1,3,5-orthoformate	33.3[b]	38
2	1,3,4,5-tetra-*O*-benzoyl-*myo*-inositol	17	39
3	*Myo*-inositol 1,3,5-orthoformate	35	40
4	***Myo*-inositol 1,3,5-orthoformate**	**75**	**37**
5	*Myo*-inositol 1,3,5-orthoformate	27 (27)[c]	17
6	*Myo*-inositol 1,3,5-orthoformate	12 (13)	15
7	*Myo*-inositol 1,3,5-orthoformate	15 (14)	15
8	1,2;4,5-di-*O*-cyclohexylidene *myo*-inositol	3[d]	41
9	1,3,5-tri-*O*-benzoyl-*myo*-inositol	8	42
10	(-)-2,3;4,5-di-*O*-cyclohexylidene-*myo*-inositol	7	43
11	***Myo*-inositol 1,3,5-orthoformate**	**37 (39)**	**37**

[a] From *myo*-inositol. [b] Entries 1-4 for racemic dibenzyl ether **32**. [c] For L- and (D-) isomers respectively. [d] L- enantiomer obtained by enzyme mediated enantio-selective acylation.

Using this method of protection – deprotection (Scheme 8) we could obtain the 2,4-dibenzyl ether in better yield[37] than the previously reported methods. The racemic dibenzyl ether **31** can be resolved as camphanate esters to prepare enantiomeric dibenzyl ethers **32** which are precursors for the preparation of D- and L-Ins(1,3,4,5)P_4. The yields obtained by using sulfonate protection and other methods of protection reported in the literature are compared in Table 1.

3.2. Simultaneous protection of C-2 and C-4 hydroxyl groups of *myo*-inositol orthoesters

The C-2 and C-4 hydroxyl groups of *myo*-inositol orthoesters can be protected simultaneously by benzoylation in the presence of pyridine.[33] As mentioned in the previous section, the first acylation takes place at the C-2-hydroxyl group resulting in the formation of the symmetric diol **17**, which undergoes further acylation to yield the corresponding unsymmetrical racemic dibenzoate **33**. We have shown[13, 44] that the racemic dibenzoate **33** can be used for the preparation of several useful *O*-protected *myo*-inositol derivatives (Scheme 9). The orthoformate moiety in the dibenzoate **33** can be cleaved to obtain the tetrol **34** which is an intermediate for the preparation of racemic Ins(1,3,4,5)P_4. The yield of the tetrol **34** obtained from **33** is about 60% (from *myo*-inositol) which is much better than the previous report[45] (18%) that used diisopropylidene-*myo*-inositol as an intermediate. The dibenzoate **33** can be converted to the dibenzyl ether **38** by benzylation with benzyl bromide in the presence of silver(I) oxide. This alkylation reaction can be effected with any alkyl bromide or iodide.[46] The conversion of **33** to the corresponding diether proceeds through the intermediacy of the corresponding monoalkyl ether (such as **35**).[46, 47] This was exploited for the synthesis of racemic ononitol (**36**).[44] Detailed investigation of this alkylation reaction revealed the catalytic role of silver halides (generated during alkylation) in bringing about the cleavage of the C-4 benzoate.[12]



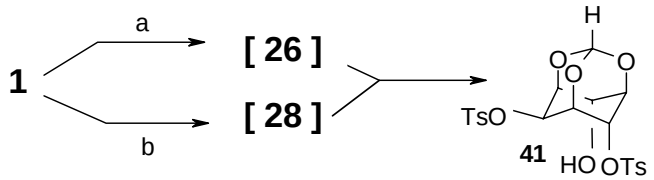
Scheme 9. (a) i. $HC(OEt)_3$, H+; ii. Pyridine, BzCl; (b) Aq. TFA; (c) As in ref. 45; (d) MeOH, pyridine; (e) DMF, Ag_2O, BnBr, (f) lsobutylamine, MeOH; (g) As in ref. 14; (h) As in ref. 22; (i) Na_2CO_3, 140 ˚C ; (j) DMF, Ag_2O, MeI, 1h.

The dibenzyl ether **40** which is the key intermediate for the preparation of Ins(1)P could be obtained in an overall yield of 67% (from *myo*-inositol) without the use of chromatography via benzylation of the dibenzoate **33**.[13] Yield (from *myo*-inositol) by literature methods[14, 22, 48] for the preparation of **40** does not exceed 45% and involve chromatographic methods of separation. This approach (*i.e.*, diacylation of **1** and **2**) has also been used by others for the efficient synthesis of *myo*-inositol-1,3,4,5-tetraphosphate[16] and *myo*-inositol-1,4,5-triphosphate.[49]

The C-4 benzoate in **33** can be selectively solvolyzed to obtain the diol **17**. The preferential solvolysis of the C-4 benzoate over the C-2 benzoate is due to the intramolecular general base catalysis of the C-6 hydroxyl group.[33] The dibenzoate **33** undergoes facile transesterification reaction to give the corresponding tribenzoate **37** and the diol **17** in solution[47] as well as solid states.[50] The facile reaction in the solid state is due to the packing of the molecules in crystals of the dibenzoate **33**, which orients the two reacting molecules in a manner that is most suitable for

the intermolecular acyl transfer reaction.[50] This reaction constitutes the first example of nucleophilic addition to a carbonyl group in the solid state.

Disulfonylation of *myo*-inositol orthoester **1** in the presence of pyridine or triethylamine also results in the formation of the corresponding racemic 2,4-disulfonate **41**.[37] However the intermediate monosulfonates involved in the triethylamine and pyridine catalyzed reactions are respectively the 4-sulfonate **26** and the 2-sulfonate **28** (Scheme 10).



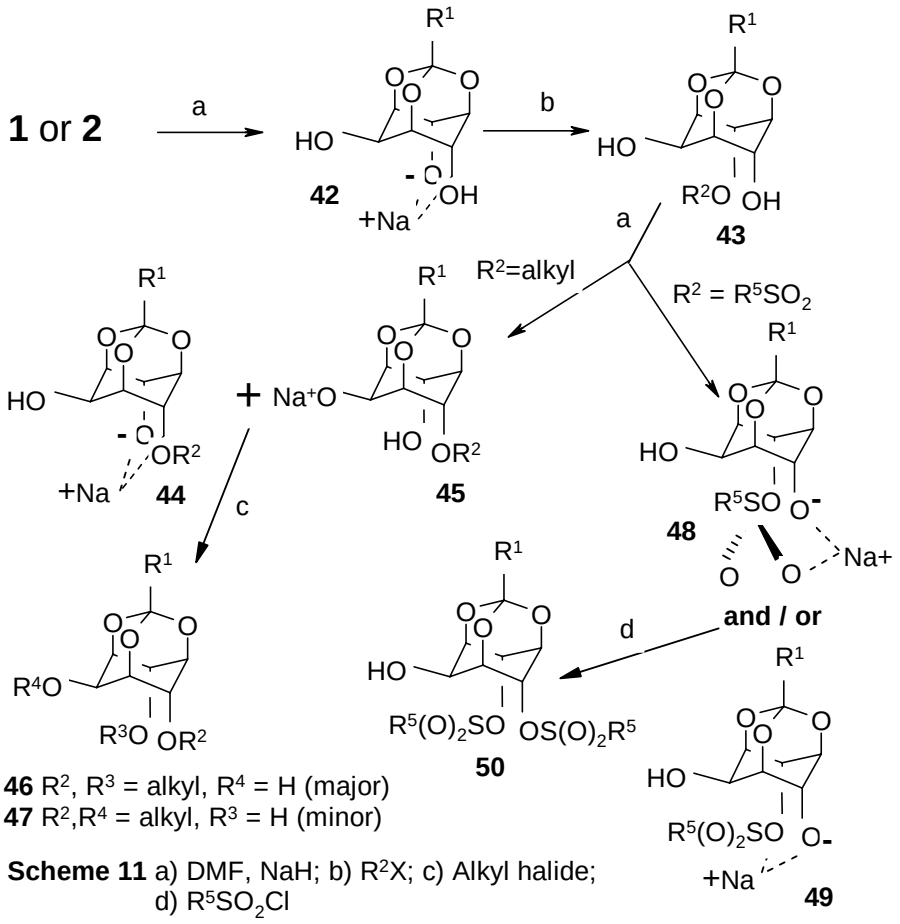
Scheme 10. (a) TsCl, Et_3N; (b) TsCl, pyridine.

3.3. Simultaneous protection of C-4 and C-6 hydroxyl groups of *myo*-inositol orthoesters

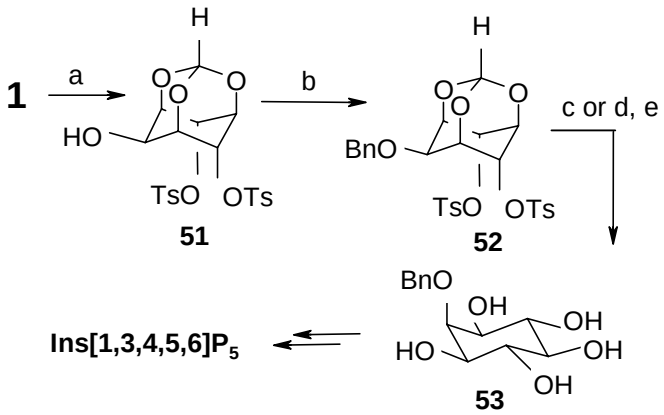
As seen in section 3.1, monoalkylation of the *myo*-inositol orthoesters exclusively results in the formation of the C-4(6)-monoethers (**43** R^2 = alkyl, Scheme 11). In these monoethers (**43**), the two hydroxyl groups are more or less of equal acidity and hence their reaction with sodium hydride leads to the formation of both the possible alkoxides **44** and **45**. As a result, dialkylation of the triol **1** results in the formation of both the possible diethers **46** and **47**. Although, the 4,6-diether **46** is formed in larger amounts as compared to the 2,4-diether **47** (due to the stabilization of the axial alkoxide **44** due to chelation) the isolated yield of 4,6-di-*O*-substituted derivative **46** was about 40% or less.[14, 20, 26, 28] We have reported[13] a method for the protection of C-4 and C-6 hydroxyl groups in **1** via the dibenzoate **33** (Scheme 9) in better yields (60-65%).

Diacylation of the triols **1** or **2** to obtain the symmetrical diesters is also not a facile process, since the regiospecificity of this reaction is dependent on the nature of the acylating agent, reaction conditions, nature of the base used and the possibility of inter- or intramolecular acyl migration. (see previous sections). We theorized that since sulfonyl groups are less prone to migration among hydroxyl groups (as compared to acyl groups), and also posses two oxygen atoms which could aid in the stabilization of the C-4 alkoxide, disulfonylation of the triols **1** and **2** would result in the formation of the corresponding symmetrical 4,6-disulfonates **50**. Indeed, disulfonylation of the triols **1** and **2** in the presence of excess of sodium hydride resulted in the formation of the corresponding symmetrical disulfonates **50** in good yields (Scheme 11).[34]

Detailed investigation of the ditosylation of the orthoformate **1** under a variety of conditions suggested the possibility of involvement of *myo*-inositol derivative-sodium chelates (**48**, **49**, Scheme 11) which could be responsible for the preferential formation of symmetrical 4,6-disulfonates **50**. This method provides a short route for the preparation of 2-*O*-substituted *myo*-inositol derivatives as well as *myo*-inositol-1,3,4,5,6-pentaphosphate. Using this approach, we could obtain 2-*O*-benzyl-*myo*-inositol (**53,** Scheme 12) in an overall yield of 58% in five steps from *myo*-inositol, which is much better than the reported[51] yield of 10% in seven steps.



Scheme 11. (a) DMF, NaH; (b) R^2X; (c) Alkyl halide; (d) R^5SO_2Cl.



Scheme 12. (a) DMF, NaH, TsCl; (b) DMF, NaH, BnBr; (c) NaOMe, MeOH; (d) Mg / MeOH; (e) Aq. TFA.

It is pertinent to mention that the use of sulfonate groups for the protection of alcohols is not usually encountered during organic synthesis because of the difficulties in their deprotection.

The sulfonate groups function as good leaving groups and result in nucleophilic substitution at the carbon carrying the sulfonate group or elimination to form olefins. Although sulfonate derivatives of cyclitols have been synthesized earlier,[52-58] they have not been used for the protection of hydroxyl groups, since the parent hydroxyl group could not be regenerated easily. However, *myo*-inositol orthoesters being trioxa analogs of adamantane, nucleophilic substitution at the carbon carrying the sulfonate group in them is difficult. It is known in the literature[59] that solvolysis of adamantan-2-ol tosylate or 2-bromoadamantane proceeds predominantly with retention of configuration. Furthermore, replacement of a methylene group in adamantane by an oxygen atom is known to appreciate the extent of retention of configuration during solvolysis.[60]

Because of the structural resemblance of orthoesters of *myo*-inositol with adamantane, we expected *O*-sulfonylated *myo*-inositol orthoester derivatives to undergo solvolysis with retention of configuration. Also, the presence of three endocyclic oxygen atoms in *myo*-inositol orthoesters (trioxaadamantane) should favor retention of configuration during solvolysis of their sulfonate derivatives. The examples presented in this account show that sulfonate groups can be successfully used as efficient protecting groups for *myo*-inositol hydroxyl groups.

In conclusion, we have developed methods for the selective protection of any of the three hydroxyl groups of *myo*-inositol orthoesters as the corresponding carboxylic acid esters, sulfonate esters and ethers. These newer methods of protection and / or deprotection can be used to prepare important *O*-protected *myo*-inositol derivatives in better yields as compared to those reported in the literature.

Acknowledgements

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