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Sulfonate protecting groups. Regioselective sulfonylation of *myo*-inositol orthoesters—improved synthesis of precursors of D- and L-*myo*-inositol 1,3,4,5-tetrakisphosphate, *myo*-inositol 1,3,4,5,6-pentakisphosphate and related derivatives

Kana M. Sureshan,[a] Mysore S. Shashidhar,[a,*] Thoniyot Praveen,[a] Rajesh G. Gonnade,[b] Mohan M. Bhadbhade[b]

[a]*Division of Organic Synthesis, National Chemical Laboratory, Pune 411 008, India*
[b]*Division of Physical Chemistry, National Chemical Laboratory, Pune 411 008, India*

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Abstract

The regioselectivity of sulfonylation of *myo*-inositol orthoesters was controlled by the use of different bases to obtain the desired sulfonate. Monosulfonylation of *myo*-inositol orthoesters in the presence of one equivalent of sodium hydride or triethylamine resulted in the sulfonylation of the 4-hydroxyl group. The use of pyridine as a base for the same reaction resulted in sulfonylation of the 2-hydroxyl group. Disulfonylation of these orthoesters in the presence of excess sodium hydride yielded the 4,6-di-*O*-sulfonylated orthoesters. However, the use of triethylamine or pyridine instead of sodium hydride yielded the 2,4-di-*O*-sulfonylated orthoester. Sulfonylated derivatives of *myo*-inositol orthoesters were stable to conditions of *O*-alkylation but were cleaved using magnesium/methanol or sodium methoxide in methanol to regenerate the corresponding *myo*-inositol orthoester derivative. These new methods of protection–deprotection have been used: (i) for the efficient synthesis of enantiomers of 2,4-di-*O*-benzyl-*myo*-inositol, which are precursors for the synthesis of D- and L-*myo*-inositol 1,3,4,5-tetrakisphosphate; (ii) for the preparation of 2-*O*-benzyl-*myo*-inositol which is a precursor for the preparation of *myo*-inositol 1,3,4,5,6-pentakisphosphate.

Keywords: Cyclitol; Inositol; Inositol phosphate; Orthoesters; Sulfonates; Signal transduction

1. Introduction

Chemistry and biology of phosphorylated derivatives of *myo*-inositol have been extensively investigated in the recent past due to their involvement in cellular signal transduction mechanisms[1–3] and anchoring of certain proteins to cell membranes.[4] In particular, D-*myo*-inositol 1,4,5-trisphosphate [Ins(1,4,5)P_3] is known to function as a second messenger in eukaryotic cells. D-*myo*-Inositol 1,3,4,5-tetrakisphosphate [Ins(1,3,4,5)-P_4] is produced by phosphorylation of Ins(1,4,5)P_3 and has recently been shown[5] to inhibit Ins(1,4,5)P_3 metabolism, thereby facilitating the activation of the store operated calcium current. At higher concentrations, Ins(1,3,4,5)P_4 functions as an inhibitor of Ins(1,4,5)P_3 receptor, which provides both facilitatory and inhibitory feedback on calcium signaling. Although these findings have generated an intense interest in the biological functions of Ins(1,3,4,5)P_4, its precise physiological function in eukaryotic cells is not 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.[2] These developments in biology and medicine have necessitated the efficient synthesis of naturally occurring phosphoinositols and their synthetic analogs. Systematic biological investigation of the *myo*-inositol cycle requires a good supply of the naturally occurring phosphoinosi-

* Corresponding author. Tel.: +91-20-5893153; fax: 91-20-589-3153
E-mail address: shashi@dalton.ncl.res.in (M.S. Shashidhar).

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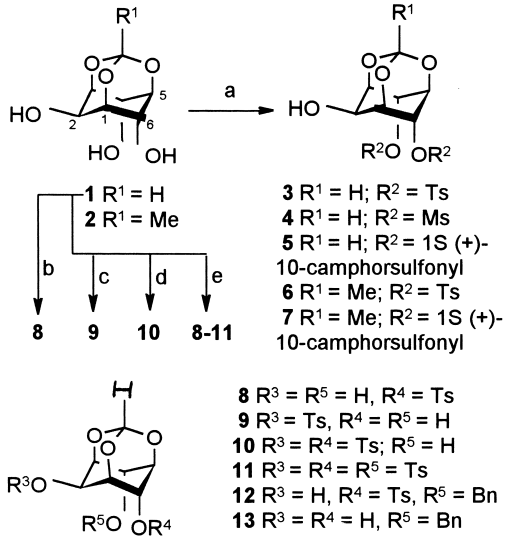
tols (and their enantiomers), which can only be isolated in minute amounts from natural sources (enantiomers may not occur in nature at all). As a result, several syntheses of phosphoinositols have been reported in the literature.[2,6]

In the past decade, there have been efforts to selectively protect the three hydroxyl groups of orthoesters (**1** and **2**) of *myo*-inositol which are easily obtainable in gram quantities[7,8] and serve as convenient starting materials for the preparation of important *O*-protected *myo*-inositol derivatives.[9,10] Methods for the selective protection of: (i) the C-4 (or C-6) hydroxyl group;[11] (ii) the C-2 hydroxyl group[7,12,13] and; (iii) C-2 and C-4 (or C-6) hydroxyl groups[14–16] simultaneously, in **1** and **2**, have been developed. Although attempts were made[11,17–19] to protect C-4 and C-6 hydroxyl groups in **1** simultaneously, the isolated yield of 4,6-di-*O*-substituted derivatives was about 40% or less. Majority of these methods (i, ii, iii, above) involved *O*-acylation or *O*-silylation reactions. Acyl groups for the protection of hydroxyl groups in polyhydroxy compounds are not desirable since they migrate among the hydroxyl groups easily.[12] To overcome this problem, we have used alkyl/aryl sulfonyl groups for the protection of *myo*-inositol hydroxyl groups. A preliminary communication on sulfonylation of **1** and **2** has appeared.[20]

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 undergo elimination to form olefins. In the case of cyclitols, they can also give rise to epoxides[21] or lead to aromatization.[22] Even if hydrolysis of the sulfonate of an optically active alcohol can be realized, it could result in inversion or racemization of the carbon carrying the sulfonate group. Many sulfonates (mesylates, tosylates) of cyclitols have previously been synthesized.[21–24] However, in all the previous reports, sulfonates were used for further functionalization of cyclitols by nucleophilic substitution or deoxygenation[25] (to obtain the corresponding deoxy-inositol derivative), but not as hydroxyl protecting groups. During nucleophilic substitution of cyclitol sulfonates, both inversion[26] and retention[26–28] of configuration have been observed. We herein report a systematic investigation of sulfonylation of *myo*-inositol orthoesters and the application of these new methods for the efficient synthesis of 2-*O*-benzyl-*myo*-inositol and, D- and L-2,4-di-*O*-benzyl-*myo*-inositol, which are precursors for the preparation of *myo*-inositol 1,3,4,5,6-pentakisphosphate [Ins(1,3,4,5,6)P_5] and L- and D-Ins(1,3,4,5)P_4, respectively.

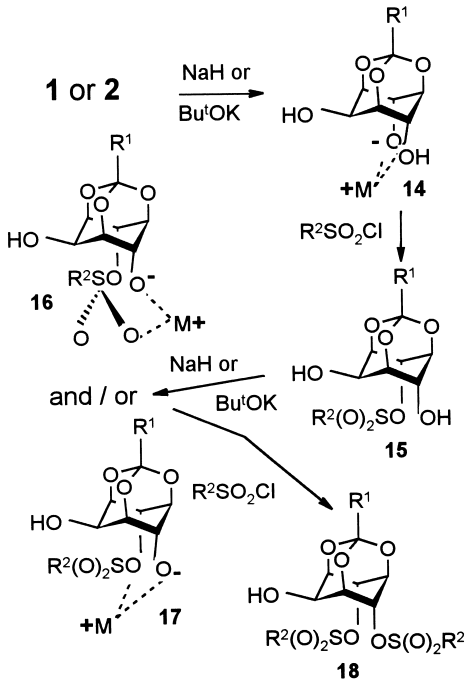


Scheme 1. Reagents and conditions: (a) R^2Cl (2 equiv), NaH or Bu^tOK (2 equiv); (b) TsCl (1 equiv), Et_3N; (c) TsCl (1 equiv), pyridine; (d) TsCl (2 equiv), Et_3N or pyridine; (e) TsCl (2 equiv), NaH (2 equiv), 18-crown-6.

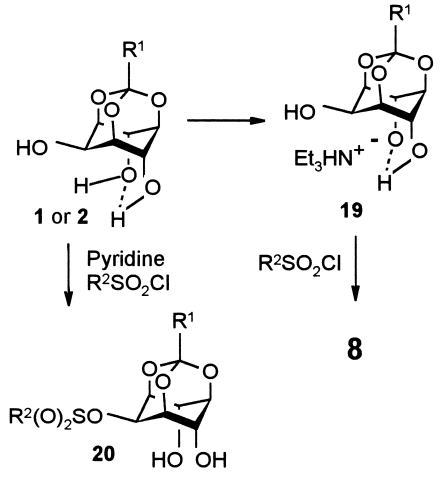
2. Results and discussion

Sulfonylation of triol **1** with one equivalent of tosyl chloride and one equivalent of sodium hydride in DMF, gave the racemic 4-tosylate **8** as expected[11] (Scheme 1). Ditosylation of triol **1** in DMF, with two equivalents of tosyl chloride and excess of sodium hydride yielded the 4,6-ditosylate **3** in good yield. Use of potassium *tert*-butoxide instead of sodium hydride also gave similar results. For these reactions, tosyl chloride was added in one portion; but slow addition of tosyl chloride over a period of ten minutes yielded a mixture of products, one of them being the 4,6-ditosylate **3**. To examine the generality of this regiospecific disulfonylation, the triol **1** was sulfonylated with mesyl chloride and camphorsulfonyl chloride under the conditions of ditosylation. In both experiments, the corresponding 4,6-disulfonates (**4** and **5**) were obtained in good yields. Similarly the orthoacetate **2** could also be sulfonylated with tosyl chloride and (1*S*)-(+)-10-camphorsulfonyl chloride to obtain the corresponding 4,6-di-*O*-sulfonyl derivatives **6** and **7**.

Change of solvent from DMF to THF while using sodium hydride as the base for sulfonylation of **1**, slowed down the reaction considerably and a mixture of products consisting of the 4-tosylate **8**, the 2,4-ditosylate **10**, the symmetrical ditosylate **3** and the tritosylate **11** resulted. Tosylation of triols **1** and **2** in the presence of sodium hydride and a crown ether in DMF, resulted in the loss of regio-selectivity and a mixture of products resulted. In this case, all possible monotosylates (**8**, **9**), ditosylates (**3**, **10**) and the tritosylate **11** were formed. Also, tosylation of the 4-tosylate **8** with



Scheme 2.



Scheme 3.

tosyl chloride and sodium hydride in DMF in the presence of a crown ether gave results similar to that observed for the reaction in THF. These facts suggest the possibility of involvement of *myo*-inositol derivative-sodium chelates (**16**, **17**, Scheme 2) under the conditions of ditosylation in DMF. Preferential alkylation at C-4 of triol **1** has been suggested[11] to be due to the involvement of chelate **14** and we had earlier reported[12] a facile chelation assisted intramolecular acyl migration in 4-*O*-acyl-*myo*-inositol 1,3,5-orthoesters.

It was clear from the formation of 4,6-disulfonates of **1** and **2** on sulfonylation in the presence of sodium hydride (Scheme 1) that, alkoxide formation in the second step is preferential at C-6. Formation of the alkoxide at the 2-*O*-position was not preferred since stabilization of this alkoxide by chelation is not possible. This preference could also be used for the protection of the C-6-hydroxyl group (in **8**) as the corresponding ether. Triol **1** on reaction with tosyl chloride followed sequentially by benzyl bromide, in the presence of sodium hydride, gave the benzyl ether **12** in good yield. Benzylation at C-4 was confirmed by methanolysis (see below) of **12**, which yielded the known[11] benzyl ether **13**.

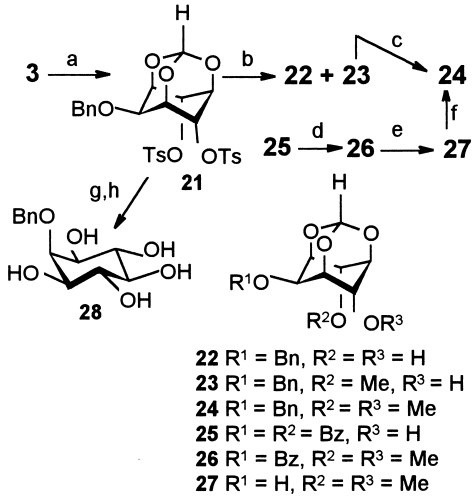
Earlier studies[29] on acylation of orthoesters **1** and **2** had shown that the regioselectivity observed during acylation is dependent on the reaction conditions. Hence, we wondered whether different regioselectivity could be observed for sulfonylation of triols **1** and **2** by changing the reaction conditions. Tosylation of triol **1** with one equivalent of tosyl chloride in the presence of triethylamine in DMF gave the 4-tosylate **8** (Scheme 1), while the use of pyridine instead of triethylamine yielded the 2-tosylate **9**. Ditosylation of triol **1** in the presence of pyridine or triethylamine gave the racemic 2,4-ditosylate **10** in good yield. Comparison of these results reveals that, although ditosylation of **1** in the presence of pyridine or triethylamine gives the same ditosylate **10**, it is formed through different intermediates. This is evident since initial tosylation of triol **1** in the presence of triethylamine takes place at C-4 while in the presence of pyridine, first tosylation is at the C-2 position. Regioselectivity observed for the tosylation of **1** is similar to the regioselectivity observed for its benzoylation.[14,29] The monotosylates **8** and **9** could also be prepared in good yield from *myo*-inositol, in one-pot procedures, by successive treatment with triethyl orthoformate and tosyl chloride.

The different regioselectivity observed for the sulfonylation of triol **1** in the presence of pyridine (pK_a 5.58) and triethylamine (pK_a 11.01) could be due to the difference in their basicity. 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[9] (Scheme 3). The resulting anion **19** is also stabilized by hydrogen bonding and hence tosyl chloride preferentially reacts at the 4-*O* position. Pyridine, being a weaker base, cannot deprotonate the 4-hydroxyl group, and hence the reactivity among the three hydroxyl groups of **1** is determined by the relative nucleophilicity and steric factors. Since the axial 4-hydroxyl groups are more acidic than the 2-hydroxyl group, they are expected to be less nucleophilic than the 2-hydroxyl group, and as a result, sulfonylation takes place at the 2-position, in pyridine. Steric hindrance for *O*-substitution at the axial 4-position[29] as well as the difference in polarity of the solvents used for tosylation (see Section 3: preparation of **8** and **9** by different procedures) may also

contribute to the observed selectivity for the reaction, in pyridine.

We utilized the different regioselectivities observed for the sulfonylation of *myo*-inositol orthoesters under different conditions, for the preparation of the benzyl ethers which are precursors for the synthesis of Ins(1,3,4,5,6)P_5 and both the enantiomers of Ins(1,3,4,5)P_4. Although sulfonate derivatives of cyclitols have been synthesized earlier, 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 atom carrying the sulfonate group is difficult. It is known in the literature[30] 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 increase the extent of retention of configuration during solvolysis.[31] 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.

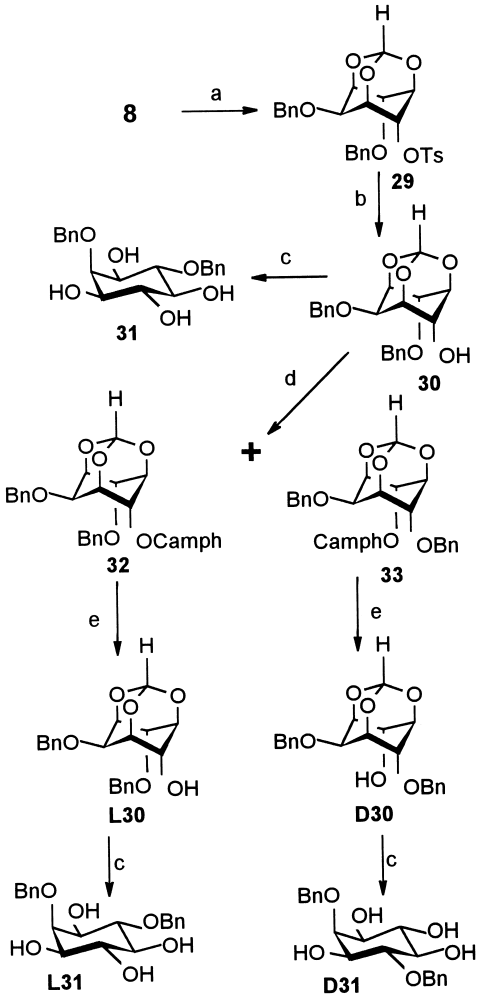
Alkylation of ditosylate **3** with benzyl bromide in the presence of sodium hydride in DMF or THF gave the corresponding benzyl ether **21** (Scheme 4). The benzyl ether **21** could also be prepared in a one pot procedure (from triol **1**) without isolation of the ditosylate **3**. The tosylate functionality in **21** could be cleaved either by refluxing with sodium methoxide in methanol or by stirring with magnesium in methanol[32] to obtain the benzyl ether **22**. The orthoformate moiety in **22** was hydrolyzed with aqueous acid to get the known 2-*O*-benzyl-*myo*-inositol (**28**). We could obtain the pentol **28** in 58% yield in seven steps from *myo*-inositol, which is much better than the reported[33] yield of 10% in seven steps. The diol **22** could also be prepared from triol **1** in a one-pot procedure by successive ditosylation and benzylation followed by methanolysis (yield for three steps 67%). As alkyl ethers are stable to methanolysis, any alkyl ether at C-2 of *myo*-inositol can be prepared by this method. It is of interest to mention that compounds having long chain alkyl ether at C-2 of *myo*-inositol show liquid crystal properties[34] and 2-*O*-substituted phosphatidylinositols are inhibitors of phosphatidylinositol-specific phospholipase C.[35,36] A two step preparation of a 2-THP ether of *myo*-inositol in about 56% yield (from *myo*-inositol) has recently been reported.[37]



Scheme 4. (a) NaH, BnBr; (b) NaOMe, MeOH; (c) NaH, MeI; (d) Ag_2O, MeI; (e) NaOH, MeOH; (f) NaH, BnBr; (g) Mg, MeOH; (h) TFA, water.

Although detosylation of **21** by methanolysis with sodium methoxide in methanol gave a good yield of the diol **22** on small scale (2 mmol), on larger scale (5 mmol), a small amount of the racemic methyl ether **23** was also obtained (Scheme 4). The structure of **23** was established by converting it to the dimethyl ether **24** and comparison of its ^{1}H NMR spectrum and melting point with an unambiguously synthesized sample of **24** from the dibenzoate **25**. Silver(I) oxide mediated methylation[38] of the dibenzoate **25** followed by aminolysis of the C-2-benzoate and subsequent benzylation of the dimethyl ether **27** with benzyl bromide in DMF gave **24**, which was identical to the dimethyl ether obtained on methanolysis of ditosylate **21** followed by methylation. Even though the amount of unwanted methyl ether **23** formed during the deprotection of the tosylates in **21** was less, the required diol **22** had to be purified by chromatography before further use. Hence we cleaved the tosyl groups in **21** using Mg/methanol, to obtain the diol **22**. The rate of deprotection of the camphorsulfonate **5** with magnesium in methanol was slow compared to that of the tosylate **3**.

The tosylate **8** on benzylation with benzyl bromide gave the dibenzyl ether **29** (Scheme 5). The tosyl group in **29** was cleaved by treatment with magnesium in methanol at room temperature, to get racemic **30**. Sodium methoxide in methanol at reflux could also be used to deprotect the tosylate without formation of any side product. The orthoformate in **30** was cleaved with aqueous acid to get the known[11] racemic **31**. Although synthesis of racemic **31** is reported in the literature, a comparison of the literature methods[11,39–42] with that described here reveals that the present method is better in terms of yield and also involves fewer steps. The overall yield of racemic **31** (from *myo*-inositol) was 74% and involved seven steps, while yield in previously reported procedures was 17–60%.



Scheme 5. (a) NaH, BnBr; (b) Mg, MeOH; (c) TFA, water; (d) (1*S*)-(−)-Camphanoyl chloride, pyridine, DMAP; (e) NaOMe, MeOH.

In order to prepare individual enantiomers of the dibenzyl ether **31**, which are precursors for the synthesis of enantiomers of Ins(1,3,4,5)P_4, we resolved the racemic orthoformate **30**. At first, we attempted to use the 10-camphorsulfonyl group for the resolution; but the diastereomeric camphorsulfonates **34** (of **30**) could not be separated by column chromatography. Hence, **30** was converted to chromatographically separable diastereomeric camphanate esters **32** and **33** by acylation with (1*S*)-(−)-camphanoyl chloride. The camphanate of lower polarity was D-2,4-di-*O*-benzyl-6-*O*-[(1*S*)-camphanoyl]-*myo*-inositol 1,3,5-orthoformate (**33**) and the higher polarity diastereomer was D-2,6-di-*O*-benzyl-4-[(1*S*)-*O*-camphanoyl]-*myo*-inositol 1,3,5-orthoformate (**32**). Their absolute configurations were established by solving their crystal structures (Figs. 1 and 2, Table 1) which also revealed the presence of chloroform in their crystals.

The camphanate esters in both the diastereomers **32** and **33** were removed by methanolysis with sodium methoxide in methanol to obtain the enantiomeric dibenzyl ethers[43] **D30** and **L30**. The orthoformate moiety in **D30** and **L30** was cleaved by acid hydrolysis to get the individual enantiomers of 2,4-di-*O*-benzyl-*myo*-inositol (**D31** and **L31**). The overall yield of **D31** and **L31** starting from *myo*-inositol were 36 and 34%, respectively. Again, a comparison of these yields with those reported in the literature shows that the present method is superior to other methods. Yields by previously reported[42–46] methods for the preparation of **D31** and **L31** were between 3 and 27%. Enantiomeric Ins(1,3,4,5)P_4 have also been synthesized by using acyl,[15] *p*-methoxybenzyl[47] or silyl groups[48] for the protection of C-2 and C-4(6) hydroxyl groups of *myo*-inositol. Although one of these methods[15] provides the precursor for the preparation of the D-tetrakisphosphate in comparable yield (42% from **1**) to the method described here, yield of the precursor for the unnatural L-isomer is much less (14% from **1**). An advantage of using the benzyl ether protecting groups for the synthesis of inositol phosphates is that the yield on phosphorylation and deprotection by hydrogenolysis is quantitative, while the use of other protecting groups (acyl and silyl) results in reduction of yields for these two steps.

In conclusion, the utility of sulfonyl groups for the protection of hydroxyl groups in *myo*-inositol has been successfully demonstrated. Reaction conditions and the nature of the base used for the sulfonylation of *myo*-inositol orthoesters can be tailored to protect either only the C-2 hydroxyl group, or only the C-4 hydroxyl group, or both C-2 and C-4 hydroxyl groups simultaneously or both C-4 and C-6 hydroxyl groups simultaneously. Procedures for the deprotection of sulfonates have been optimized to regenerate the *myo*-inositol hydroxyl groups. Newer methods of protection–deprotection have been used: (i) for the efficient synthesis of enantiomers of 2,4(6)-di-*O*-benzyl-*myo*-inositol which are precursors for the synthesis of D- and L-Ins(1,3,4,5)P_4; (ii) for the preparation of 2-*O*-benzyl-*myo*-inositol which is a precursor for the preparation of Ins(1,3,4,5,6)P_5. This is the first report on all the possible regioselective protection of the three hydroxyl groups of *myo*-inositol orthoesters by using the same reagent under different experimental conditions. Methods reported earlier to achieve different regioselectivities required the use of different protecting groups. We are presently working on the synthesis of other derivatives of phosphoinositols using sulfonate protection, which will be reported in due course.

3. Experimental

General methods.—For details on general experimental conditions, see Refs. 38 and 49. Orthoformate **1**,[8]

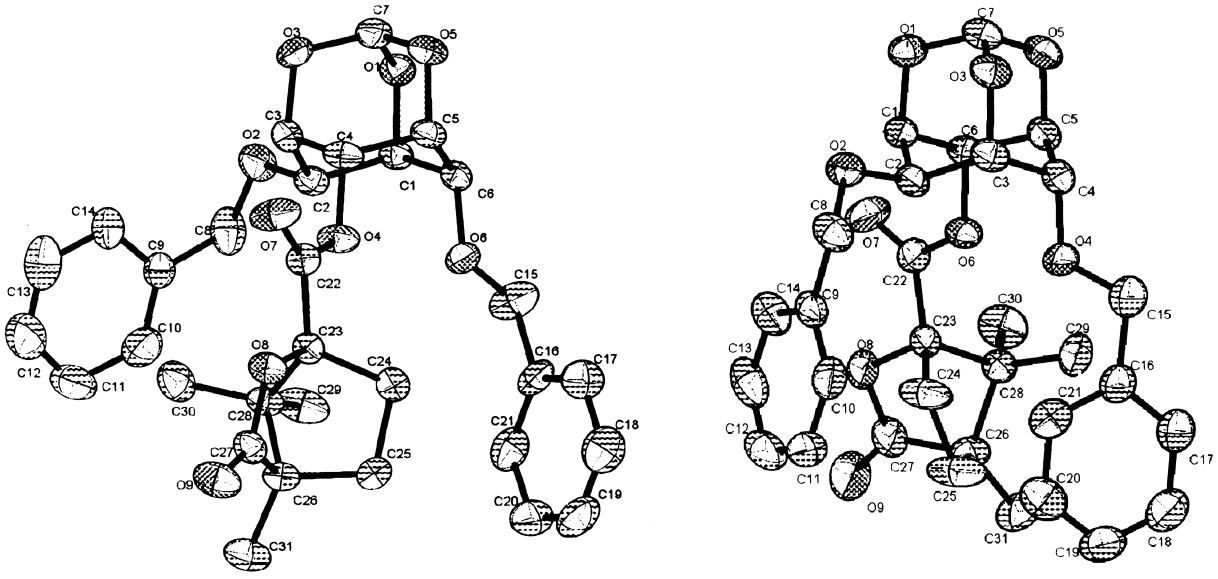


Figure 1. ORTEP diagram of **32** (left) and **33** (right). Ellipsoids are drawn at 30% probability level and hydrogen atoms are omitted for clarity.

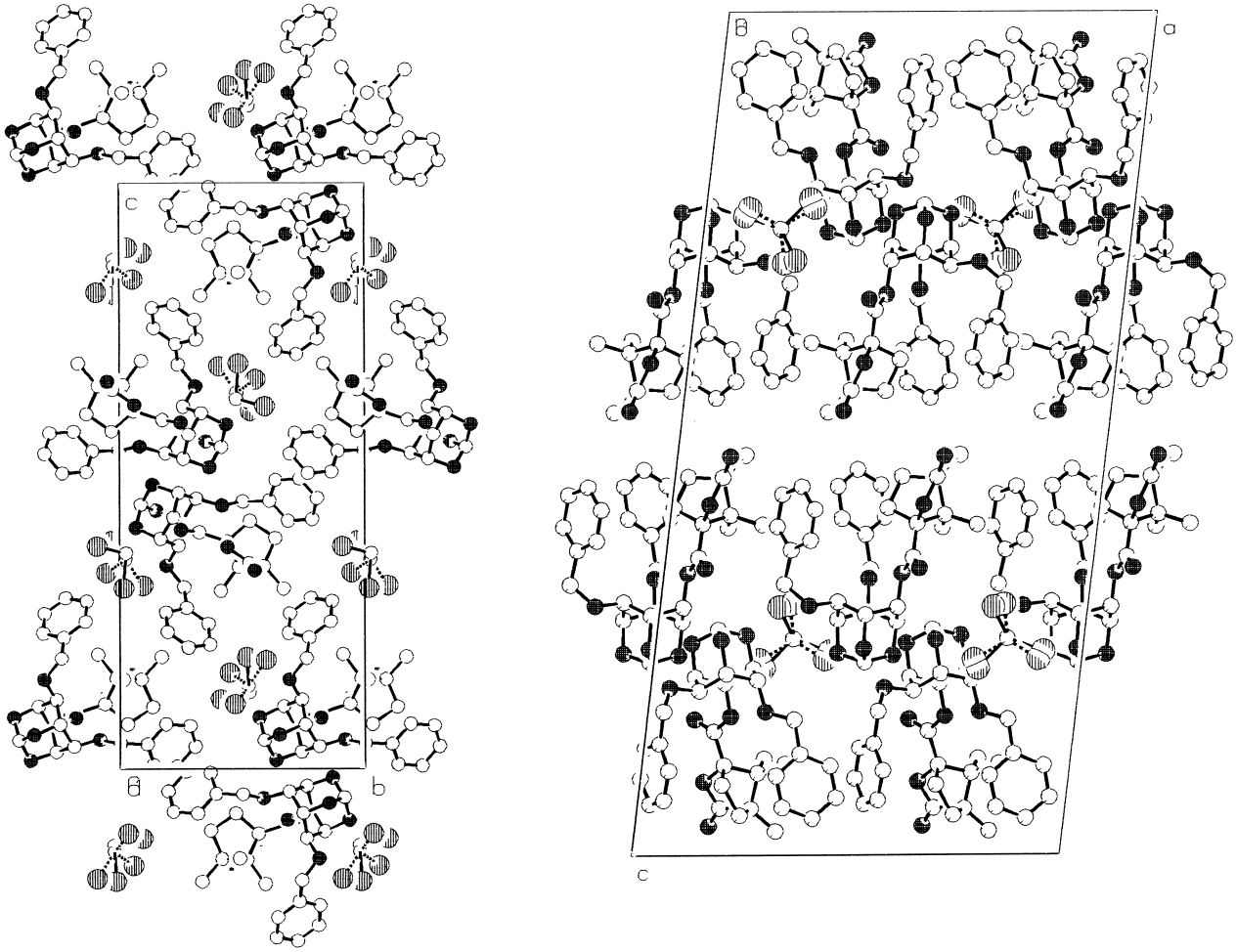


Figure 2. Packing diagram of **32** (left) and **33** (right). In both the structures chloroform is disordered over two sites. Occupancy of chloroform in **32** is full and that in **33** is half. Hydrogen atoms are omitted for clarity. Filled circles: oxygen; empty circles: carbon; shaded circles: chlorine.

Table 1
Crystal data for **32**·$CHCl_3$ and **33**·$CHCl_3$

Parameters	**32**·$CHCl_3$	**33**·$CHCl_3$
Empirical formula	$C_{31}H_{33}O_9$·$CHCl_3$	$C_{31}H_{33}O_9$·0.5 $CHCl_3$
Formula weight	668.97	609.28
Color, habit	colorless, thin needle	colorless, rectangular
Crystal size (mm)	$0.87\times0.16\times0.14$	$0.65\times0.61\times0.25$
Crystal system	orthorhombic	monoclinic
a (Å)	8.871(3)	17.994(5)
b (Å)	12.202(4)	9.460(2)
c (Å)	29.500(9)	35.985(9)
α (°)	90	90
β (°)	90	96.766(4)
γ (°)	90	90
V (Å^3)	3193.2(16)	6083(3)
Space group	$P2_12_12_1$	$C2$
Z	4	8
$F(000)$	1396	2564
d_{calc} (mg/m^3)	1.391	1.332
μ (mm^{-1})	0.340	0.223
	Data acquisition	
Temperature (K)	293(2)	293(2)
Unit-cell reflections (θ range (°))	2717 (2.80–20.234)	7268 (2.28–26.80)
Max. θ (°) for reflections	25.000	25.000
hkl range of reflections	$-11\le h\le11,\ -15\le k\le15,\ -32\le l\le37$	$-21\le h\le16,\ -11\le k\le10,\ -42\le l\le42$
Reflections measured	17969	15277
Unique reflections	6811	8963
Reflections with $I>2\sigma(I)$	3668	7344
Absorption correction	Multi scan	Multi scan
Max. and min. transmission	0.9539 and 0.7562	0.9464 and 0.8688
Refinement on	$\lvert F\rvert^2$	$\lvert F\rvert^2$
H-atom treatment	Riding model	Riding model
No. of variables in L.S.	437	800
k in $w=1/(\sigma^2F_o^2+k)$ [$P=(F_o^2+2F_o^2)/3$]	k in $w=1/[\sigma^2F_o^2+(0.0313\times P)^2+0.00\times P]$	k in $w=1/[\sigma^2F_o^2+(0.1150\times P)^2+0.05\times P]$
R, R_w, gof	0.0507, 0.0782, 0.878	0.0569, 0.1529, 1.027
Density range in final Δ-map (e Å^{-3})	0.208 and −0.158	0.305 and −0.264
Final shift, error ratio	0.003	0.001
Sec. extinction type	not applied	not applied

dibenzoate **25**,[14] dimethylether **26**,[38] (1*S*)-(+)-10-camphorsulfonyl chloride[50] and (1*S*)-(−)-camphanoyl chloride[51] were prepared using literature procedures. Column chromatographic separations were carried out by flash chromatography with light petroleum ether–ethyl acetate mixtures. 'Usual work-up' implies washing of the organic layer with water followed by brine, drying over Na_2SO_4 followed by removal of the solvent under reduced pressure using a rotary evaporator.

4,6-Di-O-*sulfonyl*-myo-*inositol 1,3,5-orthoesters: General procedure*.—Sodium hydride (5 mmol) was washed with dry light petroleum ether and then dried under reduced pressure. Clean NaH so obtained was suspended in dry DMF (5 mL) and triol, **1** or **2** (1 mmol) were added and stirred at ambient temperature under nitrogen atmosphere for 1–2 min. A solution of the required sulfonyl chloride (~2 mmol) in DMF (4 mL) was added in one portion with stirring. After 5 min, the reaction mixture was diluted with $CHCl_3$ and washed with water. The combined aq layer was acidified (dil HCl) and again extracted with $CHCl_3$. The combined $CHCl_3$ extract was washed successively with cold dil HCl, satd $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and the solvent was evaporated under diminished pressure. The crude product thus obtained was either crystallized or chromatographed to get the corresponding 4,6-di-*O*-sulfonyl-*myo*-inositol 1,3,5-orthoester.

4,6-Di-O-*tosyl*-myo-*inositol 1,3,5-orthoformate* (**3**).—Ditosylate **3** was prepared as in the general procedure using triol **1** (0.190 g, 1 mmol) and tosyl chloride (0.400 g, 2.1 mmol). The crude product obtained was

crystallized from $CHCl_3$ to get **3** (0.350 g, 70%). The same product could be obtained (72%) using potassium *tert*-butoxide instead of NaH; mp 183–185 °C. IR: 3533 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.45 (s, 6 H), 3.05 (d, 1 H, D_2O exchangeable), 4.00 (d, 1 H, *J* 4), 4.05–4.20 (m, 2 H), 4.20–4.30 (m, 1 H), 5.15 (t, 2 H, *J* 4), 5.43 (s, 1 H), 7.40 (d, 4 H, *J* 10), 7.85 (d, 4 H, *J* 9). ^{13}C NMR (Me_2SO-d_6): δ 21.3, 57.9, 66.7, 71.0, 72.4, 102.1, 127.9, 130.6, 132.1, 145.9. Anal. Calcd for $C_{21}H_{22}O_{10}S_2$: C, 50.58; H, 4.45. Found: C, 50.18; H, 4.43.

4,6-Di-O-*mesyl*-myo-*inositol 1,3,5-orthoformate* (**4**).—Dimesylate **4** was prepared as in the general procedure using triol **1** (0.190 g, 1 mmol) and mesyl chloride (0.16 mL, 2 mmol) and isolated by chromatography (0.290 g, 84%); mp 194–196 °C. IR: 3502 cm^{-1}. ^1H NMR (200 MHz, Me_2SO-d_6): δ 3.35 (s, 6 H), 3.90 (m, 1 H), 4.25 (m, 2 H), 4.65 (m, 1 H), 5.30 (m, 2 H), 5.70 (s, 1 H), 5.80 (d, 1 H, D_2O exchangeable, *J* 6). ^{13}C NMR (Me_2SO-d_6): δ 37.9, 58.2, 67.0, 71.3, 72.4, 102.2. Anal. Calcd for $C_9H_{14}O_{10}S_2$: C, 31.20; H, 4.08. Found: C, 31.13; H, 4.00.

4,6-Di-O-*[(1S)-10-camphorsulfonyl]*-myo-*inositol 1,3,5-orthoformate* (**5**).—Dicamphorsulfonate **5** was prepared using triol **1** (0.190 g, 1 mmol) and (1*S*)-(+)-10-camphorsulfonyl chloride (0.510 g, 2.04 mmol); **5** was isolated by chromatography, (0.430 g, 70%); mp 83–84 °C. IR: 3463 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.85 (s, 6 H), 1.07 (s, 6 H), 1.35–1.55 (m, 2 H), 1.60–1.85 (m, 2 H), 1.90–2.10 (m, 4 H), 2.10–2.20 (m, 3 H, 1 H, D_2O exchangeable), 2.25–2.50 (m, 4 H), 3.10–3.25 (dd, 2 H, *J* 14, 6), 3.60–3.75 (dd, 2 H, *J* 15, 6), 4.05–4.15 (m, 1 H), 4.45 (m, 2 H), 4.75 (m, 1 H), 5.45 (t, 2 H, *J* 4), 5.55 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 19.4, 24.8, 26.7, 42.3, 42.5, 48.1, 48.3, 57.8, 59.8, 67.3, 71.2, 71.4, 71.7, 71.9, 102.6, 213.9. Anal. Calcd for $C_{27}H_{38}O_{12}S_2$: C, 52.40; H, 6.19. Found: C, 52.02; H, 5.93.

4,6-Di-O-*tosyl*-myo-*inositol 1,3,5-orthoacetate* (**6**).—Ditosylate **6** was prepared using triol **2** (0.204 g, 1 mmol) and tosyl chloride (0.400 g, 2.1 mmol); the product was crystallized from $CHCl_3$ (0.400 g, 78%); mp 161–163 °C. IR: 3440 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.40 (s, 3 H), 2.45 (s, 6 H), 3.00 (d, 1 H, D_2O exchangeable, *J* 12), 3.90 (d, 1 H, *J* 12), 4.15 (m, 3 H), 5.10 (t, 2 H, *J* 4), 7.40 (d, 4 H, *J* 8), 7.85 (d, 4 H, *J* 8). ^{13}C NMR ($CDCl_3$): δ 21.5, 23.5, 58.7, 66.9, 71.5, 71.9, 109.0, 127.9, 130.0, 132.4, 145.6. Anal. Calcd for $C_{22}H_{24}O_{10}$ S_2: C, 51.54; H, 4.72. Found: C, 51.15; H, 4.59.

4,6-Di-O-[(1S)-10-camphorsulfonyl]-myo-*inositol 1,3,5-orthoacetate* (**7**).—Dicamphorsulfonate **7** was prepared using the triol **2** (0.204 g, 1 mmol), and (1*S*)-(+)-10-camphorsulfonyl chloride (0.500 g, 2 mmol); the product was isolated by chromatography (0.436 g, 69%); mp 99–102 °C. IR: 3460 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.70–0.90 (s, 6 H), 1.0–1.15 (s, 6 H), 1.50 (s, 3 H), 1.55–1.80 (m, 2 H), 1.80–2.20 (m, 8 H), 2.25–2.50 (m, 4 H), 2.95–3.35 (m, 3 H, 1 H is D_2O exchangeable), 3.50–3.80 (dd, 2 H, *J* 13, 8), 3.90–4.15 (m, 1 H), 4.25–4.50 (m, 2 H), 4.65–4.75 (m, 1 H), 5.30–5.55 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 19.4, 23.7, 24.8, 26.7, 42.3, 42.6, 48.1, 57.8, 58.9, 67.4, 71.4, 72.1, 72.3, 109.1, 159.5, 213.9, 214.0. Anal. Calcd for $C_{28}H_{40}O_{12}S_2$: C, 53.14; H, 6.38. Found: C, 53.36; H, 6.88.

Racemic 4-O-*tosyl*-myo-*inositol 1,3,5-orthoformate* (**8**)*: Procedure A.*—Triol **1** (0.190 g, 1 mmol) was stirred with NaH (0.024 g, 1 mmol) in DMF (3 mL) at rt for 1 min. Tosyl chloride (0.191 g, 1 mmol) was added in one portion with stirring. The reaction mixture was worked up after 5 min and the product was crystallized from $CHCl_3$ to get the 4-tosylate **8**[10] (0.320 g, 93%).

Procedure B.—Triol **1** (0.190 g, 1 mmol) was stirred with triethylamine (2 mL) in DMF (2 mL) at rt for 2 min. Tosyl chloride (0.200 g, 1.01 mmol) was then added with stirring. The reaction mixture was worked up after 24 h and the product chromatographed to get racemic **8**[10] (0.280 g, 81%).

Procedure C.—*myo*-Inositol (2.700 g, 15 mmol) was suspended in DMF (22 mL) and heated with triethyl orthoformate (4 mL) and *p*-TsA (0.500 g) at 100 °C for 1 h. The reaction mixture was cooled to rt and triethylamine (4 mL) was added. The reaction mixture was concentrated to a syrup and dissolved in DMF (15 mL). To this solution was added triethylamine (15 mL) and tosyl chloride (3.140 g, 16.5 mmol) and the reaction mixture was stirred at rt for 24 h. The reaction mixture was then worked up as usual and the product chromatographed to get the racemic **8**[10] (3.720 g, 72%).

2-O-*Tosyl*-myo-*inositol 1,3,5-orthoformate* (**9**)*: Procedure A.*—Triol **1** (0.190 g, 1 mmol) and tosyl chloride (0.200 g, 1.01 mmol) were dissolved in pyridine (10 mL) and heated at 80 °C for 48 h. After the usual work up followed by column chromatography **9** (0.300 g, 87%) was obtained; mp 117–119 °C. IR: 3100–3500 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.45 (s, 3 H), 3.90–4.05 (m, 2 H), 4.20–4.35 (m, 3 H), 4.45–4.65 (m, 2 H), 5.10 (s, 1 H), 5.50 (s, 1 H), 7.40 (d, 2 H, *J* 8), 7.85 (d, 2 H, *J* 8). ^{13}C NMR ($CDCl_3$): δ 21.4, 67.8, 68.2, 69.9, 72.0, 102.0, 127.6, 130.1, 133.1, 145.5. Anal. Calcd for $C_{14}H_{16}O_8S$: C, 48.82; H, 4.69. Found, C 48.61; H, 4.90.

Procedure B.—*myo*-Inositol (0.900 g, 5 mmol), triethyl orthoformate (1.5 mL) and *p*-TsA (0.150 g) were mixed in DMF (7 mL) and heated at 100 °C for 1 h. The resulting solution was cooled to ambient temperature and triethylamine (1.5 mL) was added. Volatiles were evaporated under reduced pressure. To the syrup obtained was added pyridine (10 mL) and tosyl chloride

(1.050 g, 5.5 mmol), and the mixture was stirred at rt for 24 h. The reaction mixture was worked up as usual and the product chromatographed to get **9** (1.260 g, 73%).

Racemic 2,4-di-O-*tosyl*-myo-*inositol 1,3,5-orthoformate* (**10**).—Triol **1** (0.400 g, 2.1 mmol) and tosyl chloride (0.860 g, 4.5 mmol) were dissolved in pyridine (10 mL) and heated at 80 °C for 48 h. Usual work up of the reaction mixture followed by column chromatography yielded racemic 2,4-ditosylate **10** (0.944 g, 90%); mp 114–115 °C. IR: 3498 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.45 (s, 3 H), 2.50 (s, 3 H), 2.75–2.90 (br d, 1 H, D_2O exchangeable), 4.00 (q, 1 H, *J* 4, 2), 4.20 (m, 1 H), 4.35 (m, 1 H), 4.50–4.65 (m, 1 H), 4.95 (s, 1 H), 5.05 (m, 1 H), 5.45 (s, 1 H), 7.30–7.45 (t, 4 H, *J* 8), 7.75–7.90 (dd, 4 H, *J* 6, 2). ^{13}C NMR ($CDCl_3$): δ 21.4, 66.4, 68.4, 68.5, 69.4, 71.3, 72.7, 102.1, 127.7, 129.9, 130.1, 131.7, 132.8, 145.3, 145.9. Anal. Calcd for $C_{21}H_{22}O_{10}S_2$: C, 50.58; H, 4.45. Found: C, 50.77; H, 4.39.

Procedure B.—Triol **1** (0.190 g, 1 mmol), tosyl chloride (0.400 g, 2.1 mmol) and Et_3N (2 mL) were dissolved in DMF (10 mL) and the reaction mixture was stirred at rt for 48 h. Usual work up of the reaction mixture followed by column chromatography yielded racemic **10** (0.400 g, 80%).

Tosylation of myo-*inositol 1,3,5-orthoformate* (**1**) *in the presence of 18-crown-6.*—A solution of triol **1** (0.095 g, 0.5 mmol), NaH (0.030 g, 1.25 mmol) and 18-crown-6 (0.265 g, 1 mmol) in DMF (3 mL) were stirred at rt for 2 min. A solution of tosyl chloride (0.195 g, 1.02 mmol) in DMF (2 mL) was added in one portion with stirring. The reaction mixture was worked up as usual after 10 min. The products were separated by chromatography to get the 4,6-ditosylate **3** (0.065 g, 26%), racemic 4-tosylate **8** (0.010 g, 6%), 2-tosylate **9** (0.014 g, 8%), the racemic 2,4-ditosylate **10** (0.092 g, 37%) and tritosylate **11** (0.061 g, 19%). Data for **11**: mp 103–105 °C. ^1H NMR (200 MHz, $CDCl_3$): δ 2.45–2.55 (2s, 9 H), 4.05–4.15 (m, 2 H), 4.15–4.30 (m, 1 H), 4.80 (m, 1 H), 5.10 (t, 2 H, *J* 4), 5.40–5.45 (s, 1 H), 7.30–7.50 (2d, 6 H, *J* 9), 7.75–7.90 (2d, 6 H, *J* 8). ^{13}C NMR ($CDCl_3$): δ 21.5, 67.0, 67.2, 69.1, 70.9, 102.1, 127.6, 127.8, 130.1, 131.9, 145.5, 145.8. Anal. Calcd for $C_{28}H_{28}O_{12}S_3$: C, 51.52; H, 4.33. Found: C, 51.43; H, 4.66.

Racemic 4-O-*benzyl-6*-O-*tosyl*-myo-*inositol 1,3,5-orthoformate* (**12**).—Triol **1** (0.380 g, 2 mmol) was dissolved in DMF (10 mL) and stirred with NaH (0.200 g, 8.3 mmol) at rt for 1 min. A solution of tosyl chloride (0.390 g, 2 mmol) in DMF (5 mL) was added in one portion and stirred for another 2 min. Benzyl bromide (0.24 mL, 2 mmol) was then added and stirring was continued for another 5 min. The reaction mixture was worked up as usual and the product chromatographed to get the racemic benzyl ether **12** (0.610 g, 70%); mp 159–161 °C. ^1H NMR (200 MHz, $CDCl_3 + D_2O$): δ 2.45 (s, 3 H), 4.10 (s, 2 H), 4.20 (m, 1 H), 4.30–4.35 (m, 1 H), 4.40–4.45 (m, 1 H), 4.45–4.70 (q, 2 H, *J* 10, 20), 5.20 (m, 1 H), 5.45 (s, 1 H), 7.25–7.45 (m, 7 H), 7.75 (d, 2 H, *J* 8). ^{13}C NMR ($CDCl_3$): δ 21.5, 60.5, 67.0, 71.4, 71.9, 72.4, 102.9, 127.5, 127.7, 128.4, 129.9, 132.6, 136.9, 145.3. The structure of **12** was confirmed by its conversion to the known racemic **13**[11] as follows: the tosylate **12** (0.100 g, 0.23 mmol) was stirred with Mg (0.100 g) in MeOH (5 mL) at 60 °C for 24h. Usual work up gave racemic **13** (0.064 g, 99%).

2-O-*Benzyl-4,6-di*-O-*tosyl*-myo-*inositol 1,3,5-orthoformate* (**21**)*: Procedure A.*—4,6-Ditosylate **3** (0.400 g, 0.8 mmol) was stirred with NaH (0.048 g, 2 mmol) in DMF (5 mL) at rt for 2 min. Benzyl bromide (0.1 mL, 0.83 mmol) was then added and stirring continued for 5 min. Usual work-up of the reaction mixture followed by chromatography gave benzyl ether **21** as colorless crystals (0.460 g, 97%); mp 140–141 °C. ^1H NMR (200 MHz, $CDCl_3$): δ 2.45 (s, 6 H), 3.85 (m, 1 H), 4.15–4.20 (m, 1 H), 4.25 (m, 2 H), 4.60 (s, 2 H), 5.1 (t, 2 H, *J* 4), 5.45 (s, 1 H), 7.25–7.50 (m, 9 H), 7.80 (d, 4 H, *J* 8). ^{13}C NMR ($CDCl_3$): δ 21.3, 65.4, 66.9, 68.9, 71.2, 71.5, 102.3, 127.6, 128.1, 129.8, 132.2, 136.7, 145.3, 159.3. Anal. Calcd for $C_{28}H_{28}O_{10}S_2$: C, 57.12; H, 4.80. Found: C, 57.15; H, 4.88.

Procedure B.—4,6-Ditosylate **3** (3.000 g, 6.02 mmol) was dissolved in THF (30 mL) and stirred with NaH (0.288 g, 12 mmol) at rt for 2 min. Benzyl bromide (0.85 mL, 7 mmol) was added and stirring was continued for 4 h. The reaction mixture was worked up as usual and the product obtained was washed several times with light petroleum ether to obtain crystalline **21** (3.100 g, 88%). The washings were evaporated and chromatographed to get an additional amount of **21** (0.260 g, 7%, total yield 3.360 g, 95%).

2-O-*Benzyl*-myo-*inositol 1,3,5-orthoformate* (**22**)*: Procedure A.*—Ditosylate **21** (0.588 g, 1 mmol) was stirred with Mg (0.150 g) in dry MeOH (4 mL) at ambient temperature. The reaction mixture was worked-up as usual after 48 h and the product crystallized from a mixture of CH_2Cl_2 and light petroleum ether to get diol **22** (0.265 g, 95%); mp 153–155 °C. IR: 3100–3600 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 3.95 (d, 3 H, *J* 8, 2 H D_2O exchangeable), 4.15 (m, 1 H), 4.25 (m, 2 H), 4.45 (m, 2 H), 4.70 (s, 2 H), 5.45 (d, 1 H, *J* 2), 7.25–7.50 (m, 5 H). ^{13}C NMR ($CDCl_3$): δ 66.6, 67.5, 68.3, 71.4, 71.6, 102.1, 127.9, 128.1, 128.4, 136.8. Anal. Calcd for $C_{14}H_{16}O_6$: C, 59.97; H, 5.75. Found: C, 59.74; H, 5.92.

Procedure B.—Benzyl ether **21** (0.460 g, 0.78 mmol) was refluxed with NaOMe (0.540 g, 10 mmol) in dry MeOH (4 mL). After 72 h, MeOH was evaporated and the residue was suspended in $CHCl_3$, washed successively with water, cold dil HCl, satd $NaHCO_3$ and brine

and finally dried over Na_2SO_4. The solvent was removed under diminished pressure and the product was crystallized from a mixture of $CHCl_3$ and light petroleum ether to obtain the **22** (0.200 g, 91%) as the only product. The same experiment on 5 mmol scale yielded, after column chromatography, **22** (89%) and the racemic methyl ether **23** (7%); mp 123–124 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.35 (s, 3 H), 3.55 (d, 1 H, *J* 10, D_2O exchangeable), 3.80 (m, 1 H), 4.17 (m, 1 H), 4.25–4.50 (m, 4 H), 4.75 (q, 2 H, *J* 12, 10), 5.55 (s, 1 H), 7.25–7.50 (m, 5 H). ^{13}C NMR ($CDCl_3$): δ 57.8, 66.1, 67.1, 67.7, 69.3, 71.1, 71.9, 76.3, 102.4, 127.7, 128.3, 137.4.

2-O-*Benzyl*-*4,6*-*di*-O-*methyl*-myo-*inositol* *1,3,5*-*orthoformate* (**24**)*: Procedure A.*—Methyl ether **23** (0.030 g, 0.1 mmol) was methylated with methyl iodide (0.5 mL) and NaH (0.010 g, 0.4 mmol) in DMF (1 mL) at rt. Usual work-up after 1 h gave the dimethyl ether **24** (0.030 g, 97%); mp 98–100 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.35–3.40 (s, 6 H), 3.80–3.90 (m, 1 H), 4.05–4.15 (m, 2 H), 4.25–4.35 (m, 2 H), 4.35–4.45 (m, 1 H), 4.75 (s, 2 H), 5.55 (d, 1 H, *J* 1), 7.20–7.50 (m, 5 H). ^{13}C NMR ($CDCl_3$): δ 57.4, 64.3, 67.6, 68.0, 69.9, 70.2, 103.2, 127.7, 128.3, 129.8, 133.1.

Procedure B.—Racemic dibenzoate **25** (200 g, 0.5 mmol) was methylated with methyl iodide (0.31 mL, 5 mmol) and silver(I) oxide (0.580 g, 2.5 mmol) in DMF (2 mL) at rt. The reaction was followed by TLC. When the starting material had disappeared (24 h), the reaction mixture was worked up as reported,[38] to get a gummy product. The gum was stirred with NaOH (0.060 g, 1.5 mmol) in MeOH (3 mL) for 24 h (to obtain **27**). Methanol was then evaporated and to the residue obtained was added DMF (2 mL), NaH (0.120 g, 5 mmol) and benzyl bromide (0.5 mL, 4.2 mmol) and stirred at ambient temperature for 0.5 h. The reaction mixture was worked up with $CHCl_3$ and benzyl ether **24** (0.110 g, 72%) was isolated by column chromatography; mp 98–100 °C.

2-O-*Benzyl*-myo-*inositol* (**28**).—Diol **22** (0.280 g, 1 mmol) was treated with a mixture of TFA and water (1 mL, 5:1 v/v) at rt for 24 h. The liquids were evaporated under reduced pressure to get **28** (0.270 g, 100%) as a white crystalline solid; mp 250–251 °C; lit.[33] mp 248–250 °C.

Racemic *2,4*-*di*-O-*benzyl*-*6*-O-*tosyl*-myo-*inositol* *1,3,5*-*orthoformate* (**29**).—Racemic 4-tosylate **8** (0.344 g, 1 mmol) was stirred with NaH (0.120 g, 5 mmol) in DMF (3 mL) at rt for 2 min. Benzyl bromide (0.3 mL, 2.5 mmol) was then added with stirring. The reaction mixture was worked up after 10 min with $CHCl_3$. Chloroform was removed under reduced pressure and the residue was washed with light petroleum ether and the crude product thus obtained was crystallized from a mixture of CH_2Cl_2 and light petroleum ether to get racemic **29** (0.500 g, 95%) as colorless crystals; mp 104–106 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.45 (s, 3 H), 3.95 (d, 1 H, *J* 2), 4.15–4.35 (m, 3 H), 4.35–4.45 (m, 2 H), 4.50–4.70 (m, 3 H), 5.15 (t, 1 H, *J* 4), 5.55 (s, 1 H), 7.10–7.50 (m, 12 H), 7.75 (d, 2 H, *J* 9). ^{13}C NMR ($CDCl_3$): δ 21.5, 66.4, 66.8, 67.3, 69.5, 70.0, 71.2, 71.5, 72.8, 102.8, 127.4, 127.7, 127.8, 127.9, 128.3, 129.7, 129.9, 132.6, 137.0, 137.3, 145.3. Anal. Calcd for $C_{28}H_{28}O_8S$: C, 64.09; H, 5.38. Found: C, 63.71; H, 5.76.

Racemic *2,4*-*di*-O-*benzyl*-myo-*inositol* *1,3,5*-*orthoformate* (**30**)*: Procedure A.*—Racemic **29** (0.524 g, 1 mmol) was refluxed with NaOMe (0.800 g) in MeOH (10 mL). After 48 h, MeOH was evaporated and the residue was extracted several times with $CHCl_3$. The combined $CHCl_3$ extract was washed successively with water, cold dil HCl, a satd $NaHCO_3$ soln and brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to get racemic **30** (0.350 g, 95%) as a gum which was converted to the known[11] racemic **31** (see below). ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.60–3.70 (d, 1 H, *J* 10, D_2O exchangeable), 3.90 (m, 1 H), 4.20–4.35 (m, 2 H), 4.35–4.45 (m, 3 H), 4.45–4.60 (q, 2 H, *J* 11), 4.60–4.85 (q, 2 H, *J* 12), 5.53 (d, 1 H, *J* 1), 7.20–7.50 (m, 10 H).

Procedure B.—Racemic **29** (1.570 g, 3 mmol) was stirred with Mg metal turnings (0.660 g, 27 mmol) in MeOH (20 mL). After 24 h, MeOH was evaporated and the residue was extracted several times with CH_2Cl_2 and worked-up as in procedure A to get racemic **30** (1.110 g, 100%) as a gum.

Racemic *2,4*-*di*-O-*benzyl*-myo-*inositol* (**31**).—Racemic dibenzyl ether **30** (0.185 g, 0.5 mmol) was hydrolyzed in 4:1 TFA–water (0.5 mL) at rt for 24 h. The solvents were evaporated under diminished pressure and the residue was washed with light petroleum ether and crystallized from a mixture of $CHCl_3$ and light petroleum ether to get racemic **31** (0.178 g, 99%); mp 119–120 °C; lit.[11] mp 119–120.5 °C.

*1*L-*2,4*-*Di*-O-*benzyl*-*6*-O-*[(1*S*)-camphanoyl]*-myo-*inositol* *1,3,5*-*orthoformate* (**32**) *and* *1*D-*2,4*-*di*-O-*benzyl*-*6*-O-*[(1*S*)-camphanoyl]*-myo-*inositol* *1,3,5*-*orthoformate* (**33**).—Racemic dibenzyl ether **30** (0.925 g, 2.5 mmol), Et_3N (2 mL) and DMAP (0.080 g) were dissolved in CH_2Cl_2 (15 mL). To this solution was added (1*S*)-(−)-camphanoyl chloride (0.550 g, 2.54 mmol) and the reaction mixture was stirred at ambient temperature for 12 h. Usual work up and chromatographic separation afforded **32** (0.675 g, 49%) and **33** (0.670 g, 49%). Data for **32**: $[\alpha]_D^{25}$ +24° (*c* 2, $CHCl_3$); mp 168–170 °C. IR 1789, 1759 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.70 (s, 3 H), 0.85 (s, 3 H), 1.05 (s, 3 H), 1.40–1.65 (m, 3 H), 1.70–1.90 (m, 1 H), 3.85–3.90 (d, 1 H, *J* 2), 4.25–4.30 (m, 1 H), 4.30–4.40 (m, 2 H), 4.40–4.55 (q, 2 H, *J* 12, 6), 4.55–4.65 (m, 1 H), 4.70 (s, 2 H), 5.45–5.55 (t, 1 H, *J* 4), 5.55–5.60 (d, 1 H, *J* 2), 7.15–7.25 (m, 2 H), 7.30 (s, 1 H, $CHCl_3$), 7.30–7.50 (m, 8 H). ^{13}C NMR ($CDCl_3$): δ 9.3, 16.3, 28.5, 29.9, 53.5, 54.4, 65.6, 67.0,

69.1, 69.3, 70.7, 72.3, 73.4, 77.1, 90.4, 102.9, 127.8, 128.0, 128.4, 136.6, 137.2, 165.8, 177.3. Anal. Calcd for $C_{31}H_{34}O_9 \cdot 0.85\ CHCl_3$: C, 58.63; H, 5.39. Found: C, 58.89; H, 5.07. Data for **33**: $[\alpha]_D^{25}$ −15.3° (*c* 2.75, $CHCl_3$); mp 121–122 °C. IR 1790, 1759 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.65 (s, 6 H), 1.10 (s, 3 H), 1.40–1.55 (m, 2 H), 1.60–1.75 (m, 1 H), 1.85–2.05 (q, 1 H, *J* 16, 8), 3.95 (s, 1 H), 4.25–4.40 (m, 3 H), 4.40–4.50 (q, 2 H, *J* 8, 4), 4.55–4.65 (m, 1 H), 4.75 (s, 2 H), 5.40–5.50 (m, 1 H), 5.60 (d, 1 H, *J* 2), 7.15–7.60 (m, 10 H). ^{13}C NMR ($CDCl_3$): δ 9.3, 16.1, 16.3, 28.6, 30.1, 53.7, 54.4, 65.8, 67.3, 69.1, 69.4, 69.8, 71.1, 72.2, 73.8, 77.1, 90.2, 103.0, 128.0, 128.3, 128.4, 136.9, 137.3, 166.2, 177.4. Anal. Calcd for $C_{31}H_{34}O_9$: C, 67.60; H, 6.23. Found: C, 67.40; H, 6.32.

*1*L-*(−)-2,4-Di*-O-*benzyl*-myo-*inositol* (**L31**).—Camphanate **32** (0.550 g, 1 mmol) was stirred with NaOMe (0.250 g, 4.63 mmol) in MeOH (5 mL) at rt for 6 h. Usual work up gave **L30** (0.350 g, 95%). $[\alpha]_D^{25}$ −8.3° (*c* 1, EtOH); lit.[43] $[\alpha]_D^{25}$ −8.4° (*c* 1, EtOH). The orthoformate **L30** (0.300 g, 0.81 mmol) was stirred in 4:1 TFA–water (1 mL) at rt for 24 h. Evaporation of TFA and water under reduced pressure gave **L31** (0.290 g, 100%); mp 144–145 °C; lit.[42] mp 145–146 °C; $[\alpha]_D^{25}$ −29.4° (*c* 1, EtOH); lit.[42] $[\alpha]_D^{25}$ −29.3° (*c* 1.3, EtOH).

*1*D-*(+)-2,4-Di*-O-*benzyl*-myo-*inositol* (**D31**).—Camphanate **33** (0.550 g, 1 mmol) was stirred with NaOMe (0.250 g, 4.63 mmol) in MeOH (5 mL) at ambient temperature for 6 h. Usual work up with CH_2Cl_2 gave **D30** as a colorless oil (0.370 g, 100%); $[\alpha]_D^{25}$ +8.2° (*c* 1, EtOH). ^1H NMR (200 MHz, $CDCl_3$): δ 3.60–3.70 (d, 1 H, *J* 10, D_2O exchangeable), 3.90 (m, 1 H), 4.20–4.35 (m, 2 H), 4.35–4.45 (m, 3 H), 4.45–4.60 (q, 2 H, *J* 11), 4.60–4.85 (q, 2 H, *J* 12), 5.53 (d, 1 H, *J* 1), 7.20–7.50 (m, 10 H). The orthoformate **D30** (0.350 g, 0.95 mmol) was stirred in 4:1 TFA–water (1 mL) at rt for 24 h. Evaporation of TFA and water under diminished pressure gave **D31** (0.340 g, 100%); mp 144–145 °C; lit.[43] mp 145–146 °C; $[\alpha]_D^{25}$ +29.3° (*c* 1.3, EtOH); lit.[43] $[\alpha]_D^{25}$ +29.5° (*c* 1.3, EtOH).

*1*D- *and 1*L-*2,4-Di*-O-*benzyl-6*-O-*[(1*S*)-10-camphorsulfonyl]*-myo-*inositol 1,3,5-orthoacetate (***34***, mixture of diastereomers).*—Triol **2** (0.612 g, 3 mmol) was dissolved in DMF (12 mL) and stirred with NaH (0.078 g, 3.25 mmol) at rt for 1 min. (1*S*)-(+)-10-Camphorsulfonyl chloride (0.775 g, 3.1 mmol) was then added and the mixture was stirred at rt for 5 min. Sodium hydride (0.216 g, 9 mmol) and benzyl bromide (1 mL, 8.33 mmol) were added into the resulting solution and the mixture was stirred for another 20 min. Usual work up gave a gum which was chromatographed to get tri-*O*-benzyl-*myo*-inositol 1,3,5-orthoacetate (gum, 0.400 g, 28%) and **34** (mixture of diastereomers) as colorless gum (1.200 g, 67%). Data for tribenzyl ether: ^1H NMR (200 MHz, $CDCl_3$): δ 1.50 (s, 3 H), 4.00 (m, 1 H), 4.25–4.35 (m, 4 H), 4.35–4.45 (m, 1 H), 4.45–4.65 (m, 4 H), 4.70 (s, 2 H), 7.15–7.45 (m, 15 H). Data for **34**: ^1H NMR (200 MHz, $CDCl_3$): δ 0.65–0.80 (2s, 3 H), 0.90–1.05 (2s, 3 H), 1.15–1.40 (m, 1 H), 1.45 (s, 3 H), 1.70–2.10 (m, 4 H), 2.15–2.45 (m, 2 H), 2.80–2.95 (d, 1 H, *J* 16), 3.40–3.60 (dd, 1 H, *J* 15, 6), 3.80–3.95 (d, 1 H, *J* 9), 4.00 (s, 2 H), 4.35–4.85 (m, 6 H), 5.30–5.45 (m, 1 H), 7.10–7.50 (m, 10 H). ^{13}C NMR ($CDCl_3$): δ 18.8, 23.5, 24.3, 26.1, 41.7, 42.1, 47.2, 47.6, 57.2, 64.5, 64.7, 67.3, 69.8, 70.3, 70.4, 70.8, 72.1, 72.7, 108.4, 126.7, 127.2, 127.8, 137.0, 137.3, 212.8. Anal. Calcd for $C_{32}H_{38}O_9S$: C, 64.18; H, 6.40. Found: C, 63.95; H, 6.76.

Crystallography.—Crystals of **32**·$CHCl_3$ and **33**·$CHCl_3$ suitable for X-ray diffraction analysis, were obtained by slow evaporation of a saturated solution (of **32** or **33** in $CHCl_3$) at ambient temperature. Single-crystal X-ray data were collected on Bruker SMART APEX Area Detector with graphite-monochromatized (Mo $K_\alpha = 0.71073$ Å) radiation. Cell refinement, data reduction and structure solutions were carried out with SAINT program. The empirical absorption corrections were applied using the program SADABS. The structure solution and least-squares refinement were performed using SHELXTL.[52] Hydrogen atoms were fixed stereochemically and refined using the riding model option for both **32** and **33**. Crystal data are presented in Table 1.

4. Supplementary material

Full crystallographic details, excluding structure factors, have been deposited with the Cambridge Crystallographic Data Center (Nos. 186415 and 186416). These data may be obtained, on request, from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Tel.: +44 1223 336408, fax: +44 1223 336033, e-mail deposit@ccdc.cam.ac.uk.

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