Silver(I) oxide–silver halide mediated alcoholysis of *O*-benzoyl-*myo*-inositol 1,3,5-orthoformates: intramolecular assistance by the sulfonyl group

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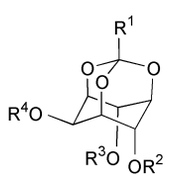
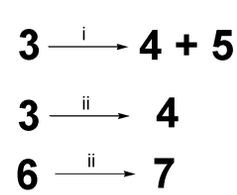
Silver(I) oxide–silver halide mediated alcoholyses of racemic 2,4-di-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate, and its 6-*O*-methyl and 6-*O*-sulfonylated derivatives, under identical conditions have been compared. While only the 4-*O*-benzoyl group undergoes solvolysis in the former two, to yield the corresponding 2-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate, both the 4-*O*- as well as the 2-*O*-benzoyl groups undergo solvolysis in the latter, to yield racemic 6-*O*-sulfonyl-*myo*-inositol 1,3,5-orthoformates. These results show that solvolysis of the 2-*O*-benzoyl group in sulfonates is a consequence of intramolecular assistance by the sulfonyl group. Catalytic efficiency of the silver halides in bringing about solvolysis of the benzoates decreased in the order AgI > AgBr > AgCl. A reaction mechanism involving silver–inositol derivative chelates has been proposed.

Introduction

The involvement of phosphoinositols in important biological phenomena such as cellular signal transduction[1] and protein anchoring to cell membranes[2] is now well established. In the past decade, organic chemists have developed methods for the synthesis of most of the *myo*-inositol phosphates and their lipid derivatives[1c,3] known to occur in nature, as well as many of their analogs useful in unraveling the intricacies of the complex *myo*-inositol cycle. Among the several protected *myo*-inositol derivatives used, *myo*-inositol orthoesters[4] (**1**, **2**, Scheme 1) have



1 $R^1 = R^2 = R^3 = R^4 = H$
2 R^1 = Me or n-Bu, $R^2 = R^3 = R^4 = H$
3 $R^1 = R^2 = H$, $R^3 = R^4$ = Bz
4 $R^1 = R^2 = R^3 = H$, R^4 = Bz
5 $R^1 = H$, $R^2 = R^3 = R^4$ = Bz
6 $R^1 = H$, R^2 = Me, $R^3 = R^4$ = Bz
7 $R^1 = R^3 = H$, R^2 = Me, R^4 = Bz



Scheme 1 *Reagents and conditions*: i, DMF, Ag_2O, AgX; ii, DMF–MeOH, Ag_2O, AgX.

recently emerged as key intermediates for the synthesis of several natural as well as unnatural *myo*-inositol phosphates. The orthoformate **1** has also served as a good starting material for the synthesis of metal ion complexing agents,[5] enterobactin analogs,[6] other cyclitols[7] and their derivatives.[8] Apart from their utility as important synthons, the chemistry of *myo*-inositol orthoformates is interesting due to their unusual trioxa-adamantane structure that is very rigid and has two 1,3-diaxial hydroxy groups. Due to these features, *myo*-inositol orthoesters and their derivatives exhibit reactivity and selectivity patterns not ordinarily encountered, during *O*-alkylation,[4n,9] *O*-acylation[10] and transesterification reactions.[11]

Intramolecular assistance by functional groups in small polyfunctional molecules leading to unexpected rates and/or product formation is well documented in the literature.[12] The effect of carbonyl and hydroxy groups on the reactions of neighboring functional groups such as carboxylic acids and their derivatives has been studied extensively.[12b] Often, studies of such unusual reactions exhibited by small organic molecules have helped in the understanding of the mechanisms of analogous complex enzyme catalyzed reactions.[13] But instances of unusual reactions due to juxtaposition of sulfonyl groups with other functional groups are scarce in the literature.[14] We herein describe an intramolecular sulfonyl group assisted alcoholysis of *O*-benzoyl groups, in the presence of silver(I) oxide and silver halides.

Results and discussion

We had observed earlier[11b] that the dibenzoate **3** (Scheme 1) undergoes transesterification with itself easily in the presence of silver(I) oxide and silver halides, to yield the diol **4** and the tribenzoate **5**. Hence, as expected, **3** underwent methanolysis in the presence of silver(I) oxide and silver halides to yield the corresponding diol **4** (Table 1). We initially attributed this enhanced susceptibility of the 4-*O*-benzoyl group towards methanolysis, to the intramolecular general base catalysis of the hydroxy group (1,3-*cis*), as was observed for the pyridine catalyzed methanolysis of the dibenzoate **3**.[15] During this work, we had observed that the same 4-*O*-benzoyl group in the methyl ether **6** was stable to methanolysis in the presence of pyridine.

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Table 1 Solvolysis of *myo*-inositol 1,3,5-orthoformate derivatives in the presence of silver(I) oxide and silver halides[a]

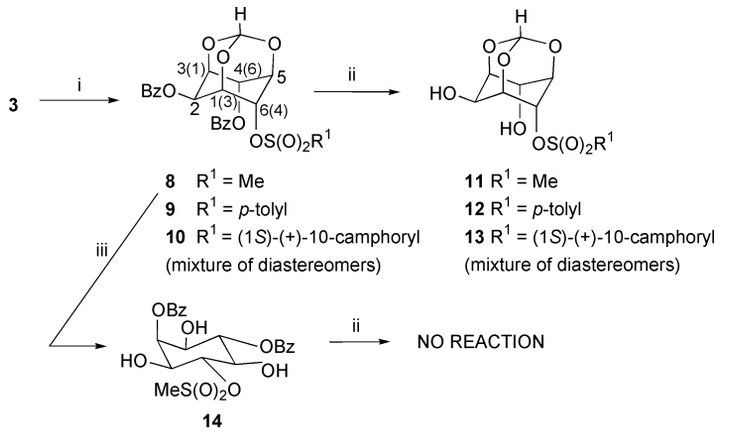
Entry	Substrate	AgX	Products (Yield %)
	Dibenzoate **3**		
1		AgI	**4** (94)
2		AgBr	**4** (68), **3** (30)
3		AgCl	**4** (20), **3** (79)
4		AgI[b]	**3** (100)
5		None	**3** (98)
6		AgI[c]	**4** (44)
	Methyl ether **6**		
7		AgI	**7** (26), **6** (70)
8		AgBr	**7** (13), **6** (70)
9		AgCl	**6** (95)
10		AgI[d]	**7** (80), **6** (16)
11		AgI[b]	**6** (100)
12		None	**6** (100)
	Mesylate **8**		
13		AgI	**11** (98), methyl benzoate (66)
14		AgI[e]	**11** (92), allyl benzoate (90)
15		AgBr	**17** (12), **11** (27), **8** (60)
16		AgBr[f]	**11** (65)
17		AgCl	**8** (92)
18		AgI[g]	**17** (29), **11** (30), **8** (40)
19		AgI[b]	**8** (100)
20		None	**8** (95)
21		AgI[h]	**8** (100)
	Tosylate **9**		
22		AgI	**12** (92)
	Camphorsulfonates **10**		
23		AgI	**13** (95)
	Mesylate **14**		
24		AgI[d]	**14** (95)

[a] All the reactions (except as indicated) were carried out as described in the general procedure. [b] In the absence of silver(I) oxide. [c] Hydrolysis using aqueous DMF. [d] Reaction time, 80 h. [e] Solvolysis with allyl alcohol. [f] Reaction time, six days. [g] Reaction time, 10 h. [h] In the absence of methanol.

However, a comparison of the methanolysis of the dibenzoate **3** and its methyl ether **6** in the presence of silver(I) oxide and silver(I) halides (Table 1) showed that the 4-*O*-benzoyl group in the methyl ether **6** is prone to methanolysis unlike in the case of the pyridine catalyzed reaction.[15] Although, under comparable conditions, the isolated yield of the corresponding alcohol **7** was lower, its yield could be increased by allowing the reaction to proceed for longer periods of time (Table 1, entry 10). These results clearly showed that the observed methanolysis of the 4-*O*-benzoyl group in the dibenzoate **3**, in the presence of silver(I) oxide and silver halide, was not due to the intramolecular general base catalysis by the hydroxy group. In all these reactions only the 4-*O*-benzoyl group (in **3** and **6**) underwent methanolysis while the 2-*O*-benzoyl group (1,3-*trans* with respect to -OH or -OMe) remained unaffected. The catalytic efficiency of silver halides in bringing about methanolysis of the 4-*O*-benzoyl group decreased in the order AgI > AgBr > AgCl. Similar catalytic efficiency had earlier been reported for the silver(I) oxide mediated *O*-alkylation of alcohols with alkyl halides.[16] These results are important, especially because silver(I) oxide has been used for several decades as a reagent for the *O*-alkylation of hydroxy groups in hydroxy esters, since it has been known to leave the esters undisturbed. But, we had shown[9] in the recent past that *O*-acyl-*myo*-inositol orthoformates are an exception to this rule since the 4-*O*-acyl group in them underwent cleavage and *O*-alkylation with alkyl halides in the presence of silver(I) oxide.

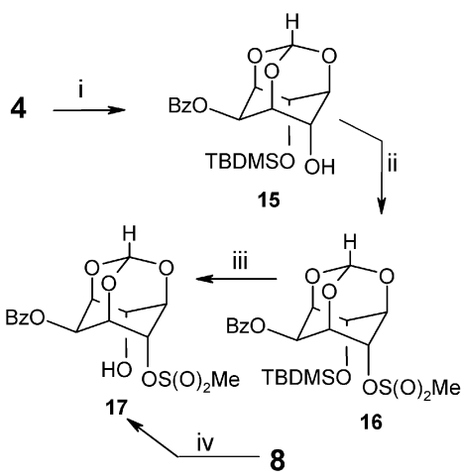
Since the 4-*O*-benzoyl group in the methyl ether **6** also underwent solvolysis in the presence of silver(I) oxide and silver halides, we subjected the sulfonates **8**–**10** (which also do not have a free hydroxy group), to methanolysis. The sulfonates **8**–**10** (Scheme 2) were prepared in good yields by the sulfonylation of the dibenzoate **3** with the required sulfonyl chloride in the presence of a base. The camphorsulfonate was obtained as a 1 : 1 mixture of diastereomers, as revealed by ^{1}H NMR spectroscopy. The mixture of diastereomers **10** was used in all the experiments. Methanolysis of the sulfonates **8**–**10** in the presence of silver(I) oxide and silver halide yielded the corresponding diols **11**–**13** (Table 1, entries 13–23). The observed methanolysis of the 2-*O*-benzoyl group in addition to the methanolysis of the 4-*O*-benzoyl group in **8**–**10** was unexpected. A comparison of the methanolysis of the benzoates **3** or **6** with the sulfonates **8**–**10** suggests that solvolysis of the 2-*O*-benzoyl group (1,3-*trans* with respect to R^1SO_2O-) in the sulfonates is due to the presence of the sulfonyl group. The sulfonate **14** (Scheme 2), which lacks the rigid trioxa-adamantane configuration of **8**–**10** (but in which the relative axial–equatorial configuration between the 2-*O*-benzoyl group and the 6-*O*-sulfonyl group is maintained) did not undergo methanolysis in the presence of silver(I) oxide and silver iodide (Table 1, entry 24). This showed that proximity of the ester and the sulfonyl groups due to the presence of the rigid orthoformate moiety is essential for the methanolysis of the 2-*O*-benzoyl group in **8**–**10**. Similar results were obtained for the solvolysis of the mesylate **8** with allyl alcohol (Table 1, entry 14). In some of the experiments methyl and allyl benzoates were also isolated (Table 1, entries 13, 14). In all these experiments the sulfonate esters did not undergo solvolysis (substitution at the ring carbon) due to the adamantane-like rigid framework of these molecules, which makes nucleophilic substitution on ring carbons difficult.

Control experiments with the dibenzoate **3** and the mesylate **8** showed that a combination of silver(I) oxide and silver halide was essential for the methanolysis (Table 1, entries 4, 5, 19, 20). Treatment of the mesylate **8** with silver(I) oxide and silver iodide in the absence of methanol did not result in the formation of the diol **11** (Table 1, entry 21). This indicated that there is no hydrolysis of the *O*-benzoyl groups due to the residual hydroxy ions or water that could be present on the surface of silver(I) oxide. Use of water instead of methanol for the solvolysis of **3** under similar conditions resulted in greatly reduced yields of the products (Table 1, entry 6), suggesting the sensitivity of this reaction to the nature of the interface (solid–



Scheme 2 *Reagents and conditions*: i, R^1SO_2Cl–pyridine; ii, DMF–MeOH, Ag_2O, AgX; iii, CH_2Cl_2–MeOH, *p*-TsA, 80 h.

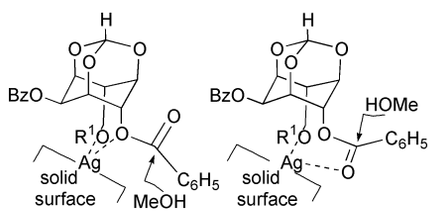
solution) present in the reaction mixture. The catalytic efficiency of the silver halides decreased in the order AgI > AgBr > AgCl as was observed for the methanolysis of the dibenzoates **3** and **6**. Methanolysis of **8** for a shorter period of time (Table 1, entry 18) showed that the two *O*-benzoyl groups in the sulfonate underwent methanolysis sequentially; first the 4-*O*-benzoyl group followed by the 2-*O*-benzoyl group. This conclusion is based on the fact that the product resulting from methanolysis of the 2-*O*-benzoyl group alone (in **8**) *viz.*, racemic 4-*O*-benzoyl-6-*O*-mesyl-*myo*-inositol 1,3,5-orthoformate, was not formed when the methanolysis was carried out for shorter periods of time or by using a less efficient catalyst (Table 1, entries 15, 18). The structure of the intermediate **17** (Scheme 3)

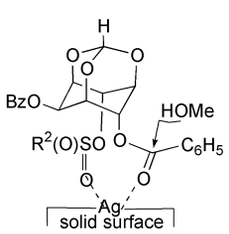


Scheme 3 *Reagents and conditions*: i, TBDMSCl–imidazole; ii, $MeSO_2$-Cl–pyridine; iii, Bu_4NF–THF; iv, DMF–MeOH, Ag_2O, AgBr, 24 h.

was established by its unambiguous synthesis starting from the symmetrical diol **4**.

A plausible mechanism for the methanolysis of the 4-*O*-benzoyl group in the dibenzoates **3** and **6** is through the intermediacy of a chelate **18** or **19** (Scheme 4) on the surface of a mixture of silver(I) oxide and silver halide. Such a chelate could arise by the complexation of the dibenzoates with silver ion or silver halide (which could function as a Lewis acid). Formation of such chelates would facilitate the attack of a nucleophile (methanol) on the 4-*O*-benzoyl carbonyl group. Comparison of the results in Table 1 shows that the hydroxy group (in **3**) is much more effective in assisting the methanolysis of the 4-*O*-benzoyl group, in the presence of silver(I) oxide and silver halide as compared to the corresponding methoxy group (in **6**). The observed difference in the relative ease of methanolysis of the dibenzoate **3** as compared to its methyl ether **6** could be due to the ability of the hydroxy group to chelate better with silver halide, as compared to the methoxy group.

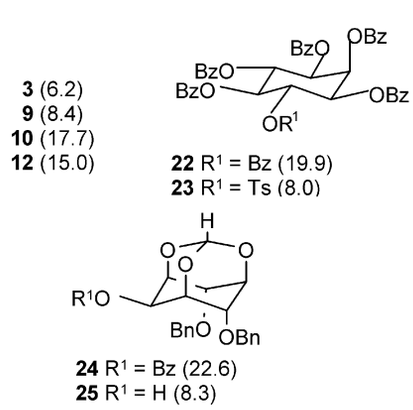




Scheme 4

Unexpected reaction patterns of *myo*-inositol orthoformate derivatives due to their chelation with metal ions had earlier been encountered.[4n,9–11] We performed silver picrate extraction experiments with several *myo*-inositol orthoformate derivatives to see if these compounds do really bind silver.

Scheme 5 shows the results of silver picrate extraction



Scheme 5 *myo*-Inositol derivative–silver picrate association constants ($K_a \times 10^{-4}$).

experiments with some *myo*-inositol derivatives. It is clear from these results that this class of compounds do bind silver picrate considerably. Although the binding constants have been calculated assuming the formation of 1 : 1 complexes, it is likely that the observed extractability of silver picrate by the inositol derivatives is due to aggregation of these poly-oxygenated compounds and silver ions. Carbohydrates are indeed known to form soluble complexes with many metal ions[17] and silver ions

form complexes with ligands containing oxygen and olefinic donors.[18] Association constants exhibited by the inositol derivatives under study are comparable to those of some of the crown ethers.[19] These observations support the involvement of silver–inositol derivative complexes during the solvolysis reactions presented above.

In order to explain the observed ease of solvolysis of both the *O*-benzoyl groups in sulfonates **8**–**10**, two factors should be considered: (a) the strong electron withdrawing ability (inductive effect) of the sulfonyl group could result in an increased electrophilicity of the benzoyl carbonyl carbons and (b) involvement of silver chelates (Scheme 4) which aid in the solvolysis of both the 4-*O*- and the 2-*O*-benzoyl groups, by a mechanism similar to that discussed for the solvolysis of the 4-*O*-benzoyl group in **3** and **6**. In order to gain insight into these possibilities we compared ^{1}H and ^{13}C NMR spectra and X-ray crystal structures of **3**,[11a] **6** (which has two independent molecules in the asymmetric unit of the crystal, only one of them is shown in Fig. 1) and **8** (Fig. 2). Crystal data for **6** and **8** are given in Table 2.

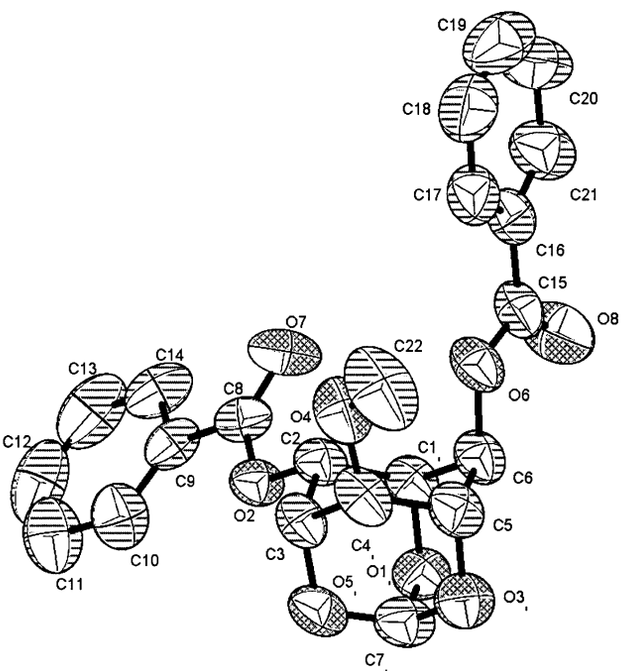


Fig. 1 ORTEP diagram of **6**. Hydrogen atoms are omitted. Ellipsoids are drawn at 50% probability level.

If the electron withdrawing inductive effect of the sulfonyl group is responsible for increasing the electrophilicity of the carbonyl carbons in **8**–**10**, this should be reflected in a considerable change in the chemical shifts of the inositol ring hydrogen (H-2) and the carbonyl carbons[20] as well as C=O bond lengths (as compared to those in the dibenzoates **3** and **6**). A comparison of these parameters reveals an insignificant variation (for compounds **3**, **6**, **8**–**10**, $\delta_{H\text{-}2}$ = 5.60 ± 0.05; $\delta_{C=O}$ = 165.75 ± 0.75; see Scheme 6 for C=O bond lengths), suggesting that the inductive effect of the sulfonyl group is not strong enough to influence the reactivity of the *O*-benzoyl groups in **8**–**10** towards solvolysis. That the inductive effect of the sulfonyl group does not enhance the electrophilicity of the carbonyl carbons in **8**–**10** is also revealed by the fact that both the *O*-benzoyl groups in the triol **14** are stable to solvolysis in the presence of silver(I) oxide and silver iodide. The inability of the sulfonyl group to influence the electrophilicity of carbonyl carbons *via* the inductive effect is not unexpected, since the carbonyl groups and the sulfonyl group are separated by five covalent bonds.

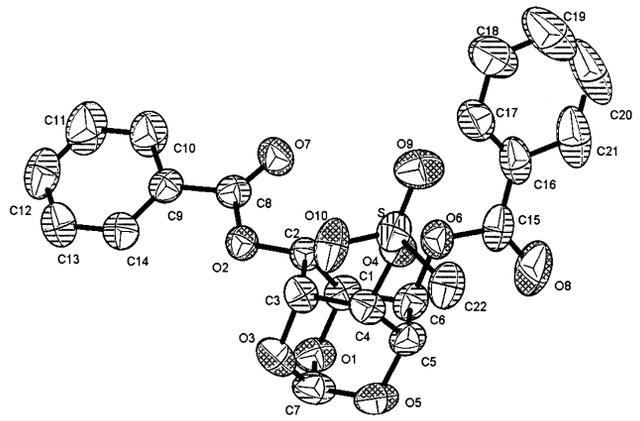
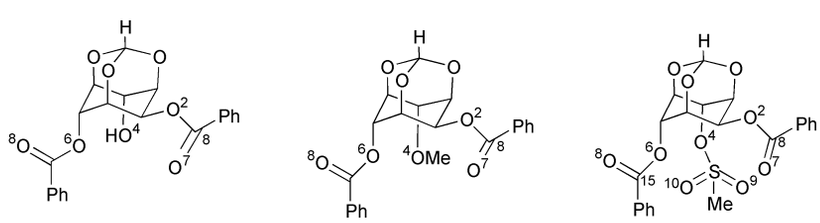


Fig. 2 ORTEP diagram of **8**. Hydrogen atoms are omitted. Ellipsoids are drawn at 50% probability level.

From the foregoing discussion, a mechanism invoking the involvement of silver chelates can be proposed for the solvolysis of both the *O*-benzoyl groups in the sulfonates **8**–**10**. Solvolysis of the 4-*O*-benzoyl group in the sulfonates **8**–**10** can proceed through the intermediacy of chelates (Scheme 4, **18**, **19** R^1 = R^2SO_2) similar to those involved during the solvolysis of the 4-*O*-benzoyl group in the methyl ether **6**. However, the possibility of the involvement of silver chelates **20**, where the metal chelates with one of the sulfonyl oxygens and the 4-*O*-benzoyl group, due to the proximity of the two di-axial functionalities cannot be ruled out. The possibility of the formation of such a silver chelate is supported by the fact that the complexation of silver ions with sulfonyl oxygens in silver salts of methanesulfonic acid and *p*-bromobenzenesulfonic acid is known in the literature.[21]

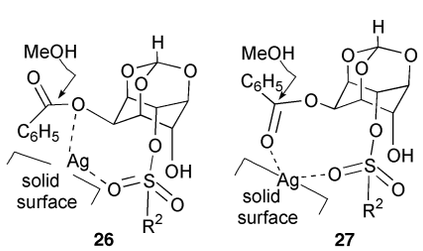


C8=O7	1.199(4)	1.192(4), 1.210(4)	1.201(2)
C15=O8	1.196(4)	1.204(3), 1.195(4)	1.196(3)
O4 - O6	2.816(4)	2.851(4), 2.853(4)	2.793(2)
O4 - O8	5.031(4)	5.058(5), 5.054(5)	4.467(3)
O2 - O9			5.951(3)
O2 - O10			5.124(2)
O7 - O9			6.271(3)
O7 - O10			6.279(3)

Scheme 6 C=O bond lengths and selected inter-oxygen distances (both in Å) in the dibenzoates. Two sets of values for **6** are for two independent molecules in the asymmetric unit. Numbers in parentheses represent esds.

Table 2 Crystal data for compounds **6** and **8**

	6	**8**
Formula	$C_{22}H_{20}O_8$	$C_{22}H_{20}O_{10}S$
Molar mass	412.38	476.44
Colour, habit	Colorless, prism	Colorless, prism
Crystal size/mm	0.35 × 0.30 × 0.25	0.51 × 0.44 × 0.13
Crystal system	Triclinic	Triclinic
a/Å	10.442(4)	8.860(3)
b/Å	14.706(6)	11.530(4)
c/Å	14.775(6)	12.0794)
α/degree	118.14(4)	109.20(5)
β/degree	90.39(7)	105.28(5)
γ/degree	90.06(3)	102.01(5)
V/Å^3	2000.8(13)	1063.5(6)
Space group	$P\bar{1}$	$P\bar{1}$
Z	4	2
F(000)	864	496
d_{calc}/g cm^{-3}	1.369	1.488
μ/mm^{-1}	0.105	0.211
	Data Acquisition	
Temperature/K	293(2)	293(2)
Unit-cell reflections (θ range/degree)	6498 (1.57 25.09)	6921 (1.91 27.78)
Max. θ (deg) for reflections	25.09	27.78
hkl range of reflections	−11 12; −17 17; −17 17	−10 11; −14 14; −15 15
Reflections measured	14191	11503
Unique reflections	7019	4533
Reflections with $I > 2\sigma(I)$	4650	3863
Absorption correction	Multiscan	Multiscan
Max. and Min.	1.000000	1.000000
Transmission	0.639309	0.774924
Refinement on	F^2	F^2
Solution method	SHELXTL	SHELXTL
H-atom treatment	Geometric—not refined	Geometric—not refined
No. variables in L.S.	544	300
k in $w = 1/(\sigma^2 F_o^2 + k)$ [$P = (F_o^2 + 2F_c^2)/3$]	$(0.0598P)^2 + 0.65P$	$(0.0892P)^2 + 0.26P$
R, R_w, gof	0.064, 0.159, 1.109	0.053, 0.149, 1.064
Density range in final Δ-map/eÅ^{-3}	0.182, −0.170	0.381, −0.440
Final shift, error ratio	0.000	0.000
Sec. extinction type	0.0008(8)	0.003(4)



Scheme 7

Formation of chelates **26** and **27** (Scheme 7), involving the *trans*-oriented sulfonyl group and the 2-*O*-benzoyl group, appears to be difficult. In order to examine this possibility we compared the relevant inter-oxygen distances in the dibenzoates **3**, **6** and **8** (Scheme 6). Our attempts to obtain crystals of the intermediate hydroxy ester **17** suitable for single crystal X-ray structure determination were not successful. These inter-oxygen distances indicate that O4–O6 and perhaps O4–O8 in all the dibenzoates are close enough to allow the formation of silver chelates (involving the two axial functional groups and silver ion or silver halide) which could augment the solvolysis of the 4-*O*-benzoyl group. Chelation between O4 (or O6) and one of the oxygens in the 2-*O*-benzoyl group (O2 or O7) is not possible due to the rigidity of the orthoformate derivatives **3** and **6** and hence the observed resistance of the 2-*O*-benzoyl group in them, towards solvolysis. Larger inter-oxygen distances O7–O9(O10) and O2–O9(O10) in **8** also do not appear to be suitable for the formation of chelates in the molecular conformation as present in the crystal. However, the possibility of the mesylate **8** getting into a suitable conformation (by rotation of single bonds C2–O2, C4–O4, C6–O6 and O4–S) for the formation of reactive chelates on the surface of a mixture of silver(I) oxide and silver halide cannot be ruled out. This is especially so since the O9 and O10 atoms are three bonds away from the carbocyclic ring and hence are not spatially constrained unlike O4 and O6. It is well recognised that the structures of some metal complexes in solution differ from those in the solid state owing to different kinds of intermolecular interactions present in the crystalline and solution states (lattice interactions, solvation *etc.*).[22]

Conclusions

Results on the methanolysis of *myo*-inositol orthoformate derivatives presented here show that a suitably placed sulfonyl group in the vicinity of a carboxylic acid ester can enhance the electrophilicity of the carbonyl carbon, in the presence of silver(I) oxide and silver halides. This is perhaps the first report on the intramolecular assistance by a sulfonyl group for the nucleophilic addition to a neighboring carbonyl group. Also for the first time we have observed silver halide catalysis for the transesterification of the carboxylic acid esters, although under special conditions. These results indicate that simple *myo*-inositol derivatives have the ability to form complexes with metal ions and result in unusual reactivity and selectivity during chemical reactions, which could be of potential use to design

better methods for the preparation of biologically relevant cyclitols and their derivatives. Work towards the application of the results presented here for the synthesis of phosphoinositols is in progress, which will be reported in due course.

Experimental

General

All the compounds are racemic; (1*S*)-(+)-10-camphorsulfonates **10** and **13** are mixture of diastereomers. However, in all the schemes only one enantiomer or diastereomer is shown for brevity and simplicity. Accordingly, numbering of inositol ring carbons may be clockwise or anti-clockwise (Scheme 2). For general experimental conditions, preparation of the methyl ether **6**, dibenzyl ethers **24** and **25** see ref. 9. The dibenzoate **3**,[15] camphorsulfonyl chloride[23] (from (1*S*)-(+)-10-camphorsulfonic acid), *myo*-inositol hexabenzoate **22**[24] and silver(I) oxide[25] were prepared using literature procedures. Silver picrate[19a]–inositol derivative binding constants were estimated by the method of Cram.[26] NMR spectra (200 MHz for ^{1}H) were recorded at ambient temperature and chemical shifts are reported with reference to internal tetramethylsilane.

Silver(I) oxide–silver halide mediated solvolysis of racemic 2,4-di-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate derivatives. General procedure

The required dibenzoyl derivative (0.25 to 1 mmol) was dissolved in alcohol–DMF mixture (1 : 9 v/v, 1 mL). Freshly prepared silver(I) oxide (5 mmol) and silver halide (2 mmol) were added with vigorous stirring at ambient temperature. Stirring was continued for 24 h, at the end of which the reaction mixture was diluted with chloroform (10–20 mL) and filtered through a short column of Celite. The filtrate was washed with sodium cyanide solution (1%, 100 mL) followed by water and brine. The chloroform layer was dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. The products were separated by column chromatography over silica gel. Yields of the products obtained and any deviations from the procedure described here are as shown in Table 1.

Preparation of sulfonates 8–10. General procedure

The dibenzoate **3** (2–5 mmol) was dissolved in pyridine (10–15 mL) and a solution of the appropriate sulfonyl chloride (10–20 mmol) in pyridine (3–10 mL) was added dropwise (15 min) with cooling (ice) and the reaction was allowed to proceed at 0–5 °C (overnight for **8**), or at reflux (29 h for **9**) or at ambient temperature (70 h for **10**). Pyridine was then evaporated under reduced pressure and the gummy residue was dissolved in chloroform (30–50 mL), washed with dilute hydrochloric acid followed by water and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The product was purified by crystallization (from a mixture of chloroform–petroleum ether in the case of **8**) or by column chromatography (in the case of **9** and **10**) by gradient elution with ethyl acetate–light petroleum mixture.

Racemic 2,4-di-*O*-benzoyl-6-*O*-mesyl-*myo*-inositol 1,3,5-orthoformate (8). The mesylate **8** was prepared as above in 95% yield, mp 181–182 °C. ν_{max} 1690, 1710 cm^{-1}. δ_H ($CDCl_3$) 2.90 (s, 3H), 4.70 (m, 2H), 4.85 (m, 1H), 5.45–5.55 (m, 1H), 5.65 (q, 1H), 5.70 (d, 1H), 5.85 (m, 1H), 7.45–7.70 (m, 6H), 8.05–8.20 (m, 4H). δ_C ($CDCl_3$) 38.5, 63.3, 67.4, 67.7, 69.4, 69.8, 71.9, 103.2, 128.8, 128.9, 129.4, 130.2, 133.9, 134.1, 165.1, 166.2. Anal. calcd for $C_{22}H_{20}O_{10}S$: C, 55.42; H, 4.23. Found: C, 55.58; H, 4.03%.

Racemic 2,4-di-*O*-benzoyl-6-*O*-*p*-tolylsulfonyl-*myo*-inositol 1,3,5-orthoformate (9). The tosylate **9** was prepared as above in 92% yield, mp 163–164 °C. ν_{max} 1710, 1720 cm^{-1}. δ_H ($CDCl_3$) 2.40 (s, 3H), 4.45–4.65 (m, 3H), 5.30 (m, 1H), 5.55 (m, 1H), 5.65 (d, 1H), 5.80–5.85 (m, 1H), 7.15–7.30 (d, 2H), 7.35–7.75 (m, 8H), 8.00–8.20 (m, 4H). δ_C ($CDCl_3$) 21.8, 63.3, 67.3, 67.5, 69.3, 69.8, 72.2, 103.2, 128.1, 128.8, 129.5, 129.7, 130.1, 130.2, 130.3, 132.4, 133.8, 145.9, 165.1, 165.9. Anal. calcd for $C_{28}H_{24}O_{10}S$: C, 60.86; H, 4.38. Found: C, 60.68; H, 4.65%.

2,4(6)-Di-*O*-benzoyl-6(4)-*O*-(1(*S*)-camphorsulfonyl)-*myo*-inositol 1,3,5-orthoformate (10, mixture of diastereomers). The camphorsulfonate **10** was prepared as above in 99% yield, mp 71–74 °C. ν_{max} 1720–1740 cm^{-1}. δ_H ($CDCl_3$) 0.75 (2s, 3H), 0.95–1.00 (2s, 3H), 1.20–2.45 (m, 7H), 2.85–3.00 (2d, 1H), 3.50–3.60 (2d, 1H), 4.60–4.80 (m, 2H), 4.8–4.9 (m, 1H), 5.50–5.65 (m, 2H), 5.70 (d, 1H), 5.80–5.90 (m, 1H), 7.40–7.65 (m, 6H), 8.10–8.20 (m, 4H). δ_C ($CDCl_3$) 19.5, 24.9, 26.8, 26.9, 42.3, 42.7, 48.1, 48.3, 57.9, 63.3, 67.4, 67.6, 69.2, 69.5, 69.9, 72.4, 72.6, 76.6, 93.4, 96.4, 103.1, 128.6, 128.7, 128.9, 129.4, 130.0, 130.1, 133.6, 133.8, 165.0, 165.1, 165.9, 187.5, 213.8, 213.9. Anal. calcd for $C_{31}H_{32}O_{11}S$: C, 60.78; H, 5.26. Found: C, 60.56; H, 5.21%.

Methanolysis of 8. Methanolysis of **8** was carried out as in the case of **3** to obtain the diol **11**, mp 246–247 °C. ν_{max} 3325–3500 cm^{-1}. δ_H ($CDCl_3$) 3.28 (s, 3H), 3.94 (m, 2H), 4.13 (m, 1H), 4.31 (m, 2H), 5.15 (m, 1H), 5.53 (d, 1H, D_2O exchangeable), 5.56 (d, 1H), 5.68 (d, 1H, D_2O exchangeable). δ_C (DMSO-d_6) 38.4, 58.8, 66.6, 69.5, 72.5, 74.1, 74.3, 102.6. Anal. calcd for $C_8H_{12}O_8S$: C, 35.82; H, 4.51. Found: C, 35.91; H, 4.46%.

Methanolysis of 9. Methanolysis of **9** was carried out as above to obtain the diol **12**, mp 159–162 °C. ν_{max} 3351, 3442 cm^{-1}. δ_H ($CDCl_3$) 2.49 (s, 3H), 2.50 (d, 1H, D_2O exchangeable), 3.05 (d, 1H, D_2O exchangeable), 4.00–4.10 (m, 2H), 4.15–4.25 (m, 1H), 4.35–4.45 (m, 1H), 4.50–4.65 (m, 1H), 5.10–5.20 (m, 1H), 5.45 (d, 1H), 7.30–7.50 (d, 2H), 7.75–7.95 (d, 2H). δ_C (CH_3OH, D_2O as external lock): δ 20.6, 59.7, 66.8, 69.7, 72.5, 74.0, 74.4, 103.1, 128.0, 130.2, 133.3, 146.0. Anal. calcd for $C_{14}H_{16}O_8S$: C, 48.83; H, 4.68. Found: C, 48.76; H, 4.95%.

Methanolysis of 10. Methanolysis of the camphorsulfonate **10** was carried out as above to obtain the diol **13** (mixture of diastereomers), mp 137–138 °C. ν_{max} 3122, 3453 cm^{-1}. δ_H ($CDCl_3$) 0.86 (s, 3H), 1.05 (s, 3H), 1.20–2.50 (m, 7H), 2.9–3.40 (m, 3H, 2H, D_2O exchangeable), 3.5–3.75 (dd, 1H), 4.00–4.75 (m, 5H), 5.40–5.60 (m, 2H). δ_H ($CDCl_3$ + D_2O): δ 0.86 (s, 3H), 1.05 (s, 3H), 1.20–2.50 (m, 7H), 2.9–3.20 (m, 1H), 3.5–3.75 (m, 1H), 4.00–4.75 (m, 5H), 5.40–5.60 (m, 2H). δ_C (DMSO-d_6) 24.9, 30.4, 32.0, 53.2, 53.3, 53.6, 63.2, 64.1, 71.9, 75.0, 77.9, 78.0, 79.4, 79.6, 107.9, 134.0, 219.4. Anal. calcd for $C_{17}H_{24}O_9S$: C, 50.49; H, 5.98. Found: C, 50.91; H, 6.28%.

Racemic 2,4-di-*O*-benzoyl-6-*O*-mesyl-*myo*-inositol (14). The mesylate **8** (1.000 g, 2.1 mmol) was dissolved in dichloromethane–methanol mixture (1 : 1 v/v, 30 mL) and *p*-TsA (0.328 g, 2.1 mmol) was added and stirred at ambient temperature for 80 h. The solvents were then evaporated and the residue was purified by flash chromatography to obtain the triol **14** (0.587 g, 61%), mp 176–177 °C. ν_{max} 1680, 1700, 3300–3500 cm^{-1}. δ_H ($CDCl_3$) 3.15 (s, 3H), 3.70–3.80 (m, 1H), 3.95–4.05 (t, 2H), 4.55–4.65 (t, 1H), 5.20–5.40 (t, 1H), 5.40–5.55 (d, 1H, D_2O exchangeable), 5.55–5.60 (m, 1H), 5.65–5.75 (d, 1H, D_2O exchangeable), 5.80–5.90 (d, 1H, D_2O exchangeable), 7.40–7.75 (m, 6H), 7.90–8.10 (m, 4H). δ_C (acetone-d_6) 39.4, 69.3, 71.9, 76.0, 76.8, 86.0, 129.1, 130.5, 131.5, 133.8, 166.4. Anal. calcd. for $C_{21}H_{22}O_{10}S\cdot0.25H_2O$: C, 53.55; H, 4.82. Found: C, 53.53; H, 5.03%.

Racemic 2-*O*-benzoyl-4-*O*-*tert*-butyldimethylsilyl-*myo*-inositol 1,3,5-orthoformate (15). The diol **4** (0.600 g, 2.04 mmol) was dissolved in DMF (6 mL). Imidazole (0.138 g, 2.04 mmol) and

TBDMSCl (0.307 g, 2.04 mmol) were added successively and stirred overnight at ambient temperature. The reaction mixture was diluted with chloroform, washed with water followed by brine, dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. The silyl ether **15** was isolated by chromatography over silica gel (0.600 g, 72%), mp 84 °C. ν_{max} 1710, 3420–3500 cm^{-1}. δ_H ($CDCl_3$) 0.25 (2s, 6H), 1.0 (s, 9H), 4.10 (d, 1H), 4.25–4.30 (m, 1H), 4.35–4.50 (m, 2H), 4.50–4.60 (m, 1H), 4.70 (m, 1H), 5.55 (m, 2H), 7.45–7.65 (m, 3H), 8.20 (m, 2H). δ_C ($CDCl_3$) −5.8, −5.4, 17.4, 25.2, 63.0, 67.9, 68.6, 68.8, 71.1, 72.3, 102.1, 128.0, 129.4, 129.6, 132.9, 165.5. Anal. calcd. for $C_{20}H_{28}O_7Si$: C, 58.80; H, 6.91. Found: C, 58.64; H, 7.17%.

Racemic 2-*O*-benzoyl-4-*O*-*tert*-butyldimethylsilyl-6-*O*-mesyl-*myo*-inositol 1,3,5-orthoformate (16). The silyl ether **15** (0.408 g, 1 mmol) was mesylated as in the case of the dibenzoate **3** to obtain the mesylate **16** (0.440 g, 90%), mp 115–116 °C. ν_{max} 1700 cm^{-1}. δ_H ($CDCl_3$) 0.17–0.18 (2s, 6H), 1.0 (s, 9H), 3.16 (s, 3H), 4.30–4.40 (m, 2H), 4.55–4.65 (m, 2H), 5.48–5.55 (m, 2H), 5.59 (s, 1H), 7.45–7.65 (m, 3H), 8.15–8.20 (m, 2H). δ_C ($CDCl_3$) −5.2, −4.9, 17.9, 25.6, 38.7, 63.1, 67.6, 69.9, 70.1, 72.0, 102.8, 128.5, 129.9, 133.5, 166.0. Anal calcd for $C_{21}H_{30}O_9SSi$: C, 51.83; H 6.21. Found: C, 51.79; H, 6.25%.

Racemic 2-*O*-benzoyl-6-*O*-mesyl-*myo*-inositol 1,3,5-orthoformate (17). The silyl ether **16** (0.250 g, 0.514 mmol) was dissolved in THF (3 mL) and stirred at ambient temperature for 10 min after the addition of tetrabutylammonium fluoride (0.148 g, 0.568 mmol). The reaction mixture was then diluted with chloroform (20 mL) and worked up as in the preparation of **15**. The residue on flash chromatography yielded the mesyl derivative **17** (0.180 g, 94%), mp 175–176 °C. ν_{max} 1726, 3469–3564 cm^{-1}. δ_H ($CDCl_3$) 2.83 (br s, 1H, D_2O exchangeable), 3.22 (s, 3H), 4.40–4.50 (m, 1H), 4.55–4.65 (m, 2H), 4.65–4.75 (m, 1H), 5.4–5.55 (m, 2H), 5.65 (s, 1H), 7.40–7.70 (m, 3H), 8.05–8.3 (m, 2H). δ_C (DMSO, D_2O as external lock) 37.6, 62.9, 65.5, 68.8, 69.1, 71.0, 72.8, 100.8, 128.5, 129.2, 133.5, 163.9. Anal. calcd. for $C_{15}H_{16}O_9S$: C, 48.39; H, 4.33. Found: C, 48.03; H, 4.28%.

Racemic 1,2,3,5,6-penta-*O*-benzoyl-4-*O*-tosyl-*myo*-inositol (23). The tosylate **9** (1.104 g, 2 mmol) was stirred with *p*-TsA·H_2O (1.14 g, 6 mmol) in dry methanol (10 mL) at 60 °C for 24 h. Methanol was evaporated under reduced pressure and the residue was dissolved in dry pyridine (25 mL) and cooled to 0 °C. To the stirred solution, benzoyl chloride (7.2 mL, 60 mmol) was added dropwise over a period of 1 h and stirring was continued for 24 h at room temperature. Pyridine was then evaporated under reduced pressure; the residue was suspended in chloroform and washed successively with water, cold dilute HCl, saturated solution of $NaHCO_3$ and brine. The chloroform solution was dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. The residue was chromatographed over silica gel by gradient elution with ethyl acetate–petroleum ether to obtain **23** (1.655 g, 96%), mp 232–235 °C. ν_{max} 1735 cm^{-1}. δ_H ($CDCl_3$) 2.07 (s, 3H), 5.65–5.80 (m, 3H), 5.85–6.00 (m, 1H), 6.20–6.35 (m, 2H), 6.74 (d, 2H), 7.15–7.95 (m, 25H), 8.15 (d, 2H). δ_C ($CDCl_3$) 21.2, 69.0, 69.4, 69.8, 70.1, 77.3, 126.8, 128.1, 128.3, 128.5, 128.7, 129.2, 129.4, 129.6, 129.8, 133.2, 133.6, 144.2, 164.7, 164.9, 165.3. Anal. calcd for $C_{43}H_{38}O_{13}S$: C, 67.44. H, 4.45. Found: C, 67.06; H, 4.23%.

X-Ray crystallography

Single crystal X-ray data † were collected on a Bruker SMART APEX Area Detector with graphite monochromatized (MoKα = 0.71073 Å) radiation. Cell refinement, data reduction and structure solutions were carried out with the SAINT program. The empirical absorption corrections were applied using the program SADABS. The structure solution and least squares refinement were performed using SHELXTL. Hydrogen atoms were fixed stereochemically and refined using the riding model option for both **6** and **8**. There is approximate $P2_1/c$ symmetry in **6**; but based on data processing and refinement statistics the space group was retained as $P\bar{1}$. Except for some torsion angles in the aryl rings the two independent molecules in **6** are not significantly different. For details on the single crystal X-ray structure of the dibenzoate **3**, see reference 11(*a*).

† CCDC reference numbers 158621 and 158622. See http://www.rsc.org/suppdata/p2/b1/b101476p/ for crystallographic files in .cif or other electronic format.

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