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Silver (I) oxide assisted *O*-alkylation of 2,4-di-*O*-benzoyl-*myo*-inositol-1,3,5-orthoformate and its 6-*O*-substituted derivatives: transannular participation of oxygen [1]

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Abstract

The reaction of 2,4-di-*O*-benzoyl-*myo*-inositol-1,3,5-orthoformate and its 6-*O*-substituted derivatives with alkyl halides in the presence of silver (I) oxide has been studied systematically. The nature of the product obtained depends on the amount of silver (I) oxide and alkyl halides used as well as on the solvent employed for the reaction. By varying these parameters, the corresponding symmetrical 4,6-di-*O*-alkylated or 4-mono-*O*-alkylated *myo*-inositol-1,3,5-orthoformates can be obtained in good yields. These alkylations proceed by two different pathways which involve the transannular participation of the neighbouring oxygen. Results presented for the allylation of 2,4-di-*O*-benzoyl-*myo*-inositol-1,3,5-orthoformate suggest cleavage and allylation of the axial 4-benzoate moiety prior to allylation of the free C-6-hydroxyl group. Involvement of a *myo*-inositol orthoformate-silver complex during these alkylation reactions is suggested. © 1997 Elsevier Science Ltd.

Keywords: Cyclitols; Inositol; Alkylations; Neighbouring group effects

1. Introduction

Over the past few years, a great deal of attention has been focused on the chemistry and biochemistry of *myo*-inositol [1], due to the involvement of its phosphorylated derivatives in important biological phenomena such as cellular signal transduction and anchoring of certain proteins to cell membranes. A large number of *O*-protected *myo*-inositol derivatives have been prepared to suit the requirements of the synthesis of inositol phosphates, phosphatidylinositols, and their glycosyl conjugates. One of the strategies for the synthesis of phosphoinositols is via the *myo*-inositol-1,3,5-orthoformate **1**, originally prepared by Lee and Kishi [2]. Billington et al. [3] later employed **1** for the synthesis of several racemic *myo*-inositol phosphates through the regioselective *O*-alkylation of one of the axial hydroxy groups. Vasella et al. synthesized optically active *myo*-inositol derivatives [4] and also carried out selective glycosidation of **1** with diazirene derived glycosylidene carbenes [5]. Both reports are based on the enhanced reactivity of one of the hydroxyl groups

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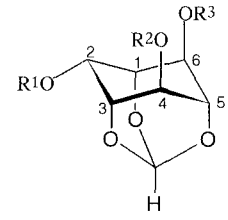
due to the presence of a 1,3-diaxial diol system [6,7]. We herein report an unusual silver (I) oxide mediated *O*-alkylation of the dibenzoate **2** and its 6-*O*-substituted derivatives. Silver (I) oxide as well as several silver salts have been used for the *O*-alkylation of alcohols [8] (Koenigs–Knorr and Purdie reactions) for several decades. A combination of silver (I) oxide and alkyl halides has been recommended for the *O*-alkylation of hydroxy esters [9]. However, the results presented in this paper show that, under certain conditions, esters are not stable to *O*-alkylation conditions in the presence of silver (I) oxide. A preliminary account of this work has earlier been published [10].

2. Results and discussion

The dibenzoate **2** (Scheme 1) was prepared in a one pot reaction from *myo*-inositol as reported earlier [2] [10]. Alkylation of **2** with an excess of allyl bromide, benzyl bromide or methyl iodide in the presence of an excess silver (I) oxide [3], in dry DMF gave the corresponding symmetrical 4,6-di-*O*-alkyl ethers **4–6** in good yields (Table 1), instead of the expected 6-*O*-alkylated derivatives **7–9** (Scheme 1). The equatorial benzoate at C-2 of the *myo*-inositol ring remained unaffected under these alkylation conditions. Initially, the formation of the di-ethers **4–6** via the diol **3** was suspected, which could arise from the hydrolysis of the axial benzoate in **2** due to adsorbed hydroxyl ions or water on the surface of silver (I) oxide. We previously reported [10] the preferential base catalyzed methanolysis of the axial 4-benzoate over that of the equatorial 2-benzoate in **2**. Treatment of the dibenzoate **2** with an excess of silver (I) oxide in dry DMF or aqueous DMF did not result in the formation of the diol **3**. The dibenzoate **2**



1	$R^1 = R^2 = R^3 = H$	**2**	$R^1 = R^2 = Bz$, $R^3 = H$
3	$R^1 = Bz$, $R^2 = R^3 = H$	**4**	$R^1 = Bz$, $R^2 = R^3 = Bn$
5	$R^1 = Bz$, $R^2 = R^3 = Allyl$	**6**	$R^1 = Bz$, $R^2 = R^3 = Me$
7	$R^1 = R^2 = Bz$, $R^3 = Bn$	**8**	$R^1 = R^2 = Bz$, $R^3 = Allyl$
9	$R^1 = R^2 = Bz$, $R^3 = Me$	**10**	$R^1 = Bz$, $R^2 = H$, $R^3 = Bn$
11	$R^1 = Bz$, $R^2 = H$, $R^3 = Allyl$	**12**	$R^1 = Bz$, $R^2 = H$, $R^3 = Me$
13	$R^1 = R^2 = R^3 = Bz$	**14**	$R^1 = R^2 = Bz$, $R^3 = Ac$
15	$R^1 = Bz$, $R^2 = R^3 = Ac$	**16**	$R^1 = R^2 = Bz$, $R^3 = THP$
17	$R^1 = Bz$, $R^2 = Ac$, $R^3 = Me$		

Scheme 1.

could be recovered quantitatively. The results described above clearly showed the non-involvement of **3** as well as the preferential cleavage and *O*-alkylation of the axial benzoate during the formation of diethers **4–6** from **2**.

Two pathways could be considered for the formation of diethers **4–6** from **2**, involving either cleavage of the axial 4-benzoate *subsequent* to the alkylation of the free 6-hydroxyl group (path **A**, **2** → **7–9** → **4–6**) or cleavage of the axial 4-benzoate is *prior* to the alkylation of the free 6-hydroxyl group (path **B**, **2** → **10–12** → **4–6**). In order to distinguish between both, the alkylation of the dibenzoate **2** (Table 1) as well as several tri-*O*-substituted *myo*-inositol-1,3,5-orthoformate derivatives (Table 2) was carried out under a variety of conditions.

From Table 1, it is clear that the formation of the mono allyl ether **8** (path **A**) is facilitated by decreasing the amount of silver (I) oxide [4], or conversely the formation of **11** (path **B**) is facilitated as the amount of silver (I) oxide is increased. The formation of **11** was also facilitated by changing the solvent from DMF to acetonitrile (Table 1, entry 10). Reaction of the dibenzoate **2** with allyl chloride resulted in the formation of **8** as the major product and the hydroxy ether **11** as a minor product. No diallyl ether **5** could

[2] Good quality crystals suitable for single crystal X-ray analysis were obtained. Details of the X-ray analysis and the unusual CH · · · O hydrogen bonding and aromatic–aromatic interactions exhibited by **2** and its 6-*O*-substituted derivatives (**9** and **13**) in their crystal structure will be published elsewhere [11,12].

[3] We also attempted the alkylation of the dibenzoate with allyl bromide in the presence of lead oxide, mercuric oxide, zinc oxide, copper oxide, magnesium oxide, and silver carbonate. The former five oxides did not bring about any reaction whereas silver carbonate gave a mixture of products, indicating that these alkylation reactions are specific to silver.

[4] Minor amounts of products arising from cleavage of the equatorial 2-benzoate were observed by ^{1}H NMR spectroscopy.

Table 1
Reaction of **2** with alkyl halides (RX) in DMF

Entry	2:Ag_2O	RX (mM)	Products (yield [a] %, mp °C)
1	1:5	BnBr (10)	**4** (80, 102–104)
2	1:5	MeI (10)	**6** (80, 143–145)
3	1:5	MeI (10)	**9** (80 [b], 229–230)
4	1:5	AllBr (10)	**5** (74, gum)
5	1:5	AllCl (14)	**8** (64, 112–115), **11** [c] (24)
6	1:5	MeI (1)	**9** (80) [b]
7	1:5	AllBr (1)	**5** (17) [d], **8** (4) [d], **11** (40)
8	1:2.5	AllBr (1)	**8** (50), **11** (18)
9	1:1	AllBr (1)	**8** (50), **11** (12)
10	1:5 [e]	AllBr (5)	**11** (63) [f]
11	1:10 [g]	AllBr (1)	**5** (7), **6** (> 80), **8** (26), **11** (26)

[a] All the reactions were carried out in DMF (4 mL/1 mM of **2**). Yields reported are isolated unless otherwise stated. Analytical data for **4**, calcd for $C_{28}H_{26}O_7$: C, 70.90; H, 5.48. Found: C, 70.75; H, 5.73; **6**, calcd for $C_{16}H_{18}O_7$: C, 59.64; H, 5.59. Found: C, 59.90; H, 5.76; **8**, calcd for $C_{24}H_{22}O_8$: C, 65.81; H, 5.02. Found: C, 66.13; H, 5.12.; **9**, calcd for $C_{22}H_{20}O_8$: C, 64.09; H, 4.85. Found: C, 64.41; H, 4.81.
[b] Reaction time 2 h.
[c] Converted to the known [3] 4-*O*-allyl-*myo*-inositol-1,3,5-orthoformate by aminolysis.
[d] By ^{1}H NMR since **5**, **8**, **9**, and **13** have same R_f values on TLC.
[e] CH_3CN, 24 h.
[f] Minor quantities of **5**, **8**, and **13** could be detected by ^{1}H NMR spectroscopy.
[g] Alkylation of a mixture of **2** (0.35 mM) and **6** (0.34 mM) in 3 mL DMF.

be isolated from this reaction. It appears that the formation of the hydroxy derivative **11** is facilitated by increasing the reactivity of the alkyl halide, since allyl bromide, and allyl chloride, respectively, yield 40% and 24% of **11**, whereas methyl iodide does not give **12** (see below). The same effect, viz decrease in the formation of **11** and increase in the formation of **8**, was also observed when an equimolar mixture of the dibenzoate **2** and the dimethyl ether **6** was subjected to allylation with one equivalent of allyl bromide (Table 1, entry 11). The monoallyl ether **8** (26%) and the hydroxy ether **11** (26%) were obtained along with a small amount of the diallyl ether **5** (7%) and about 80% of **6** was recovered unchanged [5].

[5] Although the major part of the methyl ether **9** was recovered in these experiments, material balance with respect to **9** could not be established.

Table 2
Reaction of tri-*O*-substituted orthoformates with alkyl halides (RX) in DMF

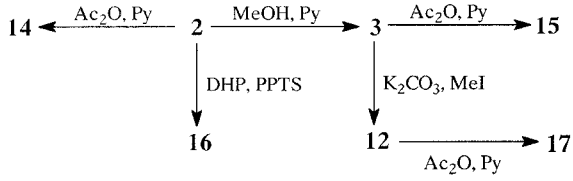
Entry	Compd. # (mM)	RX	Products [a] (yield %)
1	**8** (0.16)	AllBr	**5** (83)
2	**9** (0.14)	MeI	**6** (89)
3	**13** (0.73)	MeI	**6** (79), **9** (10)
4	**13** (0.5)	AllBr	**5** (80)
5	**14** (0.45)	MeI	**6** (76), **9** (5), **12** [b]
6	**15** (0.5)	MeI	**6** (59) [c], **12** [b], **17** (26%) [c]
7	**16** (0.4)	MeI	**12** (61)

[a] All the reactions were carried out in 7 mL DMF (1 mL and 0.5 mL, respectively, in the case of **8** and **9**) for 66 h at ambient temperature. The ratio of the orthoformate: Ag_2O: RX was 1:5:10 in all the experiments. Yields reported are isolated unless otherwise stated.
[b] Detected by TLC and ^{1}H NMR (< 10%)
[c] Yields by ^{1}H NMR.

Similar reactions using equimolar mixtures of **2** and **9** yielded the monoallyl ether **8** as the major product (90%). Neither the diallyl ether **5**, nor products arising out of allylation of **9**, could be isolated. These experiments show that the cleavage of the axial benzoate in **2** is inhibited by the presence of 4,6-di-*O*-substituted derivatives of **3**. Hence, it is likely that the predominant pathway for the formation of the diallyl ether **5** is via path **B**, at least in the initial stages of the reaction when little tri-*O*-substituted derivatives are present. The results presented so far show that path **A** as well as path **B** are operative during the allylation of the dibenzoate **2** [6].

Since allyl chloride and allyl bromide differed in their reaction with the dibenzoate **2** (i.e., the extent to which path **A** and path **B** operate, as reflected by the yields of **8** and **11**, respectively), a careful investigation of the reaction of the dibenzoate **2** with an excess of methyl iodide in the presence of an excess of silver (I) oxide was carried out. Careful monitoring of the progress of the reaction by TLC revealed the formation of an intermediate which further reacted to give the dimethyl ether **6** after 66 h. Quenching the reaction after 2 h yielded the monomethyl ether **9** as the major product (80%). The same intermediate **9** could also be prepared in good yield by using one equivalent of methyl iodide (Table 1, entry 6) in the

[6] One of the referees has suggested that the diallyl ether can also form via the reaction pathway, **2** → **8** → **11** → **5**. However, it is likely that these alkylation reactions proceed by several parallel reactions, the importance of which could depend on the conditions used for alkylation.

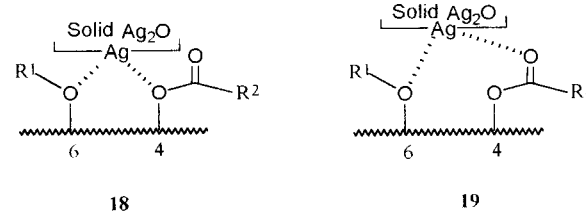


Scheme 2. Preparation of orthoformates **14–17**.

above reaction. The methyl ether **9** smoothly reacted with an excess of methyl iodide in the presence of silver (I) oxide to give the symmetrical dimethyl ether **6** in excellent yield. These reactions clearly showed that *only* path **A** is operative for the reaction of methyl iodide with the dibenzoate **2**.

Results of the silver (I) oxide mediated alkylation of tri-*O*-substituted *myo*-inositol orthoformates [7] are shown in Table 2 and the preparation of orthoformates **14–17** are shown in Scheme 2. All the tri-*O*-substituted orthoformates, except the tetrahydropyranyl ether **16** (mixture of diastereomers), reacted with methyl iodide or allyl bromide to yield the corresponding diether as the major product. In some cases (**13–15**), monomethyl ethers (**9**, **17**) were obtained as minor products, which indicated the sequential cleavage of the ester moieties. The tetrahydropyranyl ether **16** gave the monohydroxy derivative **12** as the major product [8]. In order to establish the structure of **12** and the acetate **17**, they were also prepared from **3**. Partial methylation of the diol **3** with methyl iodide in the presence of anhydrous potassium carbonate gave **12**, which on acetylation yielded **17**. It is important to note that the equatorial benzoate in *myo*-inositol orthoformate derivatives discussed so far remained unaffected during methylation. 1,2,3,4,5,6-Hexa-*O*-benzoyl-*myo*-inositol [13] as well as cyclohexyl benzoate were also subjected to methylation in the presence of silver (I) oxide. In both the experiments, starting materials were recovered completely. Thus, these results imply that the presence of oxygens in proper orientation is necessary for the alkylation to take place. These unusual alkylations could also be due to the rigidity of the *myo*-inositol orthoformate molecule.

In alkylation reactions discussed above, it is likely that a silver-inositol orthoformate complex is involved which facilitates the cleavage and alkylation of the ester moieties (Scheme 3). The complex **18** is more plausible than **19**, since silver forms a six membered ring in **18**, where as an eight membered ring in **19** and silver complexes of rigid molecules (calixarenes) through ether oxygens have been isolated [14]. The involvement of an alkali metal chelate during selective *O*-alkylation of *myo*-inositol orthoformate has earlier been suggested [3]. The isolation of a free hydroxy derivative **12** during the methylation of tri-*O*-substituted orthoformates (Table 2) is of particular importance. It is noteworthy that the yield of the free hydroxy derivative **12** increases on going from benzoate **13** to the tetrahydropyranyl ether **16**. This product could arise from a silver complex that breaks down to yield **12** during aqueous work-up. Methylation of **16** supports this view, since the methylation of the corresponding complex (**18**, R^2CO = THP) would be extremely difficult and thus results in a larger yield of the hydroxy derivative **12**. This is supported by the fact that **12** was not visible on TLC analysis of the reaction mixture (unlike **11** which could be detected before work-up in the reaction of the dibenzoate **2** with allyl halides) but appeared only after working up the reaction mixture (see experimental section for details). It is known in the literature [15] that tetrahydrothiopyranyl ethers can be cleaved under neutral conditions with silver nitrate in good yields. It is likely that the generated silver halide plays a role in the cleavage of the ester function (path **A**) since allyl bromide and methyl iodide react with tri-*O*-substituted orthoformates to yield the corresponding di-ethers but not allyl chloride (Table 1, entry 5), even though allyl chloride is more reactive than methyl iodide under normal solvolytic conditions [16,17]. It is known that silver (I) oxide medi-



Scheme 3. Possible mechanism for alkylation of inositol esters.

[7] Initial attempts [10] to react **13** with allyl bromide under identical conditions used for **2** (2 mL DMF) resulted in the recovery of the major part of the starting material. This was due to the low solubility of **13** in DMF. Use of an excess of solvent (7 mL) yielded the corresponding diallyl ether.

[8] Reaction of **16** with allyl bromide resulted in about 50% cleavage of the tetrahydropyranyl ether, based on the starting material recovered.

ated etherification of alkyl halides could be autocatalytic, due to silver halide generated during the reaction, and that the catalytic efficiency decreases in the order AgI > AgBr > AgCl [18].

In conclusion, an unusual silver (I) oxide mediated conversion of *O*-acyl *myo*-inositol orthoformate derivatives to the corresponding ethers has been found. This reaction proceeds through the transannular participation of oxygen atoms. This represents the first illustration of alkylative cleavage of esters in the presence of silver, although under specific conditions. Results reported in this paper also provide convenient access to several protected *myo*-inositol derivatives which are useful for the preparation of phosphoinositols and inositol carbohydrate conjugates.

3. Experimental

General methods.—All the solvents, benzoyl chloride, and acetic anhydride used were purified according to literature procedures [19]. Light petroleum refers to the 60–80 °C boiling fraction of petroleum ether. Benzyl bromide, allyl bromide, and dihydropyran were obtained from Aldrich Chemical Company, USA, and were used as received. Benzoyl chloride, acetic anhydride, methyl iodide, and silver nitrate were obtained from SD Fine Chemicals, India. Silver (I) oxide was prepared from silver nitrate [20]. The dibenzoate **2** was prepared as reported earlier [10]. All the compounds reported are racemic, however, nomenclature used for *myo*-inositol derivatives is that of the D-enantiomer in accordance with international conventions. TLC was performed on E. Merck precoated 60 F_{254} plates and the spots were detected either by UV light or by charring the plates with concd H_2SO_4. Infrared spectra of solids were recorded as nujol mull and liquids/gums in $CHCl_3$ or neat unless otherwise stated. NMR spectra (200 MHz for ^1H) were recorded in $CDCl_3$ (unless otherwise specified) at ambient temperature. Chemical shifts reported are referred to internal Me_4Si. All melting points reported are uncorrected and were recorded using an electrothermal melting point apparatus.

*2-O-Benzoyl-*myo*-inositol-1,3,5-orthoformate* (**3**).—The dibenzoate **2** (1.5 g, 3.75 mmol) was dissolved in a mixture of dry MeOH (90 mL) and dry pyridine (18 mL) and stirred for 24 h at 40 °C. The soln was allowed to cool to room temperature, and the solvent was evaporated in vacuo. The residue was chromatographed over a column of Silica Gel (5:1 light petroleum/EtOAc) to obtain **3** as a white solid (0.77 g, 70%) and **1** [2] (0.09 g, 13%). Data for **3**: mp 210–213 °C; IR 1720 3400–3450 cm^{-1}; ^1H NMR ($CDCl_3$–Me_2SO-d_6): δ 3.92 (m, 1 H), 4.05 (m, 2 H), 4.20 (m, 2 H), 5.20 (dd, 2 H), 5.35 (d, 2 H, D_2O-exchangeable), 7.15–7.30 (m, 3 H), 7.80 (m, 2 H); ^{13}C NMR: δ 63.3, 67.1, 68.4, 71.7, 101.8, 127.9, 129.2, 132.7, 165.2. Anal. Calcd for $C_{14}H_{14}O_7$: C, 57.16; H, 4.76. Found: C, 57.17; H, 5.16.

Alkylation of myo*-inositol 1, 3, 5-orthoformate derivatives. General procedure.*—The *myo*-inositol 1,3,5-orthoformate derivative (0.1 to 1.25 mmol) and the alkyl halide were dissolved in dry DMF (0.5 to 7 mL) and freshly prepared silver (I) oxide was added in portions over 10 min with vigorous stirring and external cooling with ice. Stirring was continued at room temperature till the starting material disappeared (60–66 h). The solid was allowed to settle and the supernatant liquid was decanted. The solid was washed successively with DMF (7 mL) and $CHCl_3$ (2 × 10 mL). The organic extract was washed with NaCN soln (1%, 100 mL) and the aq layer was extracted with $CHCl_3$ (3 × 30 mL). The combined chloroform extract was washed with water (3 × 50 mL), dried over anhyd Na_2SO_4 and evaporated in vacuo. The products were separated by column chromatography and then crystallized (EtOAc – light petroleum or CH_2Cl_2 – light petroleum). Column chromatography was performed using Silica Gel (60–120 mesh) and light petroleum–EtOAc as eluant (gradient elution up to 20:1) unless otherwise specified. See Tables 2 and 3 for specific experimental conditions, yields, analytical and spectroscopic data.

*2-O-Benzoyl-4-O-methyl-*myo*-inositol-1,3,5-orthoformate* (**12**).—The diol **3** (0.29 g, 1 mmol), methyl iodide (1.42 g, 10 mmol), and anhyd K_2CO_3 (0.7 g, 5 mmol) were stirred in dry DMF (4 mL) at room temperature for 13 h. The reaction mixture was filtered through a short Silica Gel column, and the filtrate was diluted with $CHCl_3$, washed with water, dried, and the solvent was evaporated. The products were separated by column chromatography to give the dimethyl ether **6** (0.03 g, 10%) and **12** as a white solid (0.23 g, 83%): mp 102–105 °C; IR 1720, 3360, 3500 cm^{-1}; ^1H NMR: δ 3.57 (s, 3 H), 3.82 (d, D_2O exchangeable, 1 H), 4.27 (m, 1 H), 4.35–4.50 (m, 2 H), 4.52 (m, 1 H), 4.65 (m, 1 H), 5.45 (d, 1 H), 5.55 (d, 1 H), 7.40–7.65 (m, 3 H), 8.10–8.30 (m, 2 H); ^{13}C NMR: δ 58.3, 63.6, 67.8, 68.2, 69.2, 72.6, 76.5, 102.8, 128.6, 129.7, 130.1, 133.6, 166.3. Anal. Calcd for $C_{15}H_{16}O_7$: C, 58.44; H, 5.19. Found: C, 58.52; H, 4.95.

Table 3
Spectroscopic data for some *myo*-inositol orthoformate derivatives

Compd. #	IR (cm^{-1})	^1H NMR (δ)	^{13}C NMR (δ)
4	1740	4.50 (t, 2 H), 4.60 (m, 3 H), 4.75 (s, 4 H), 5.67 (broad s, 1 H), 5.71 (broad s, 1 H), 7.30–7.70 (m, 13 H), 8.25 (m, 2 H)	64.8, 68.5, 70.5, 71.7, 74.0, 103.5, 128.0, 128.6, 130.1, 133.4, 137.6, 166.3
5	1730	4.15 (m, 4 H), 4.35 (t, 2 H), 4.50 (m, 3 H), 5.20–5.40 (m, 4 H), 5.50 (broad s, 1 H), 5.60 (d, 2 H), 5.85–6.05 (m, 2 H), 7.40–7.65 (m, 3 H), 8.15 (m, 2 H)	64.9, 68.6, 70.6, 70.7, 73.8, 103.5, 117.7, 128.6, 130.1, 133.5, 134.3, 166.3
6	1720	3.55 (s, 6 H), 4.22 (t, 2 H), 4.55 (m, 3 H), 5.40 (m, 1 H), 5.60 (d, 1 H), 7.40–7.65 (m, 3 H), 8.10–8.30 (m, 2 H)	57.7, 64.5, 68.2, 70.0, 76.1, 103.4, 128.6, 130.0, 133.4, 166.2
8	1710 1720	4.10 (m, 2 H), 4.42 (t, 1 H), 4.57 (m, 2 H), 4.75 (m, 1 H), 5.10–5.32 (m, 2 H), 5.65–5.85 (m, 4 H), 7.40–7.65 (m, 6 H), 8.05–8.30 (m, 4 H)	64.5, 67.4, 68.4, 69.9, 70.4, 71.3, 73.7, 103.4, 118.2, 128.6, 129.4, 129.8, 130.1, 130.2, 133.6, 133.8, 165.5, 166.3
9	1730	3.40 (s, 3 H), 4.27 (m, 1 H), 4.60 (m, 2 H), 4.76 (m, 1 H), 5.60 (m, 1 H), 5.70 (d, 1 H), 5.80 (m, 1 H), 7.40–7.65 (m, 6 H), 8.05–8.25 (m, 4 H)	57.6, 64.3, 66.9, 68.4, 69.8, 70.0, 75.5, 103.4, 128.6, 128.7, 129.4, 129.8, 130.1, 133.6, 133.7, 165.5, 166.3
11	1720 3300–3600	3.87 (d, 1 H, D_2O exchangeable), 4.15–4.65 (m, 7 H), 5.30–5.45 (m, 2 H), 5.50 (d, 1 H), 5.60 (d, 1 H), 5.85–6.05 (m, 1 H), 7.45–7.70 (m, 3 H), 8.15–8.30 (m, 2 H)	63.7, 68.1, 68.3, 69.7, 72.0, 72.7, 74.3, 102.9, 119.8, 128.7, 129.8, 130.1, 132.9, 133.6, 166.4

*2,4,6-Tri-O-benzoyl-*myo*-inositol-1,3,5-orthoformate* (**13**).—The tribenzoate **13** was prepared as reported earlier [10] and crystallized from CH_2Cl_2–light petroleum, mp 216–218 °C; IR 1740, 1750(s) cm^{-1}; ^1H NMR: δ 4.70 (m, 2 H), 5.00 (m, 1 H), 5.75 (t, 1 H), 5.80 (d, 1 H), 5.90 (t, 2 H), 7.15–7.30 (m, 4 H), 7.45–7.70 (m, 5 H), 7.95–8.05 (m, 4 H), 8.10–8.30 (m, 2 H); ^{13}C NMR: δ 64.1, 67.4, 68.7, 69.7, 103.6, 128.7, 128.8, 129.6, 130.1, 130.2, 133.8, 165.4, 166.5. Anal. Calcd for $C_{28}H_{22}O_9$: C, 66.93; H, 4.38. Found: C, 66.58; H, 4.82.

*2,4-Di-O-benzoyl-6-O-acetyl-*myo*-inositol-1,3,5-orthoformate* (**14**).—To the dibenzoate **2** (1.2 g, 3 mmol) in dry pyridine (20 mL) was added drop-wise at 0 °C a soln of Ac_2O (3.06 g, 30 mmol) in dry pyridine (10 mL). After the addition was complete, the reaction mixture was stirred at room temperature for 26 h. The reaction mixture was then added to ice cold NaCl soln, and the white precipitate formed was filtered, washed twice with water, and extracted with $CHCl_3$ (200 mL). The organic layer was washed successively with 0.1 N HCl (200 mL), water (200 mL), 20% $NaHCO_3$ (50 mL × 2), and water (200 mL × 3) till the washings were neutral, and finally dried over Na_2SO_4 and evaporated in vacuo. The residue was crystallized (CH_2Cl_2–light petroleum) to give **14** as a white solid (1.13 g, 89%): mp 155–156 °C; IR 1750(s), 1720 cm^{-1}; ^1H NMR: δ 1.80 (s, 3 H), 4.55 (m, 1 H), 4.62 (m, 1 H), 4.77 (m, 1 H), 5.65 (m, 2 H), 5.70 (d, 1 H), 5.80, (m, 1 H), 7.40–7.65 (m, 6 H), 8.05–8.20 (m, 4 H); ^{13}C NMR: δ 20.6, 64.0, 66.7, 67.9, 68.1, 69.4, 69.5, 103.4, 128.7, 128.8, 129.1, 129.5, 130.0, 130.1, 133.8, 134.0, 164.9, 166.3, 169.3. Anal. Calcd for $C_{23}H_{20}O_9$: C, 62.73; H, 4.54. Found: C, 62.58; H, 4.20.

*2-O-Benzoyl-4,6-di-O-acetyl-*myo*-inositol-1,3,5-orthoformate* (**15**).—The monobenzoate **3** (0.6 g, 2 mmol) was acetylated in dry pyridine (10 mL), using a soln of Ac_2O (2.04 g, 20 mmol) in dry pyridine (10 mL) as above, except that the reaction time was 9 h. The product was purified by column chromatography to give **15** as a solid (0.65 g, 86%) mp 142–143 °C; IR 1750, 1715 cm^{-1}; ^1H NMR: δ 2.07 (s, 6 H), 4.45 (m, 2 H), 4.60 (m, 1 H), 5.37 (d, 1 H), 5.50 (t, 2 H), 5.60 (d, 1 H), 7.40–7.60 (m, 3 H), 8.05–8.15 (m, 2 H); ^{13}C NMR: δ 20.6, 63.7, 66.4, 67.8, 69.1, 103.2, 128.5, 129.4, 129.9, 133.6, 166.0, 169.1. Anal. Calcd for $C_{18}H_{18}O_9$: C, 57.14; H, 4.76. Found: C, 56.81; H, 4.83.

*2,4-Di-O-benzoyl-6-tetrahydropyranyloxy-*myo*-inositol-1,3,5-orthoformate* (**16**).—The dibenzoate **2** (0.87 g, 2.2 mmol) was dissolved in dry CH_2Cl_2 (8 mL) and stirred with dihydropyran (0.42 g, 5 mmol) and pyridinium *p*-toluenesulfonate (0.07 g, 0.32 mmol) at room temperature for 24 h. The soln was then diluted with diethyl ether (50 mL) and washed

with 5% sodium carbonate solution (100 mL) followed by water till the aq layer was neutral. The organic layer was dried and concd in vacuo. The residue was purified by crystallization (light petroleum/CH_2Cl_2) to give **16** as a white solid (mixture of diastereomers, 0.92 g, 90%): mp 135–139 °C; IR 1730 cm^{-1}; ^1H NMR: δ 0.95–1.80 (m, 6 H), 3.35–3.60 (m, 1 H), 3.65–3.95 (m, 1 H), 4.65 (m, 2 H), 4.70 (m, 2 H), 4.85 (m, 1 H), 5.65 (m, 2 H), 5.80 (dt, 1 H), 7.40–7.65 (m, 6 H), 8.05–8.25 (m, 4 H); ^{13}C NMR: δ 19.1, 19.3, 24.9, 25.2, 30.3, 30.5, 62.7, 63.0, 64.5, 67.4, 68.5, 68.6, 69.9, 70.0, 71.3, 71.8, 72.7, 98.8, 99.9, 103.4, 128.5, 128.6, 129.4, 129.7, 129.8, 130.1, 133.5, 165.3, 169.1. Anal. Calcd for $C_{26}H_{26}O_9$: C, 64.73; H, 5.39. Found: C, 64.51; H, 5.44.

2-O-Benzoyl-4-O-acetyl-6-O-methyl-myo-*inositol-1,3,5-orthoformate* (**17**).—The monomethyl ether **12** (0.11 g, 0.36 mmol) was acetylated, as for **15**, in dry pyridine (1 mL) using a solution of Ac_2O (0.42 mL, 4.1 mmol) in dry pyridine (1 mL) except that the reaction time was 17 h. The product was filtered through a short column of Silica Gel to give **17** as a white solid (0.12 g, 99%): mp 135–138 °C; IR 1750, 1735 cm^{-1}; ^1H NMR: δ 2.12 (s, 3 H), 3.45 (s, 3 H), 4.22 (m, 1 H), 4.45 (m, 1 H), 4.55 (m, 1 H), 4.65 (m, 1 H), 5.45 (m, 2 H), 5.62 (s, 1 H), 7.35–7.65 (m, 3 H), 8.10–8.25 (m, 2 H); ^{13}C NMR: δ 20.8, 57.5, 64.2, 66.6, 68.4, 69.6, 69.7, 75.5, 103.3, 128.6, 129.8, 130.0, 133.5, 166.2, 170.0. Anal. Calcd for $C_{17}H_{18}O_8$: C, 58.33; H, 5.14. Found: C, 58.28; H,4.92.

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