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Lewis acid-catalysed rearrangements of *myo*-inositol orthoformate derivatives

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ABSTRACT

Reduction of 2,4,6-tri-*O*-benzyl-DL-*myo*-inositol 1,3,5-orthoformate (**1**) with di-isobutylaluminium hydride gave 2,4,6-tri-*O*-benzyl-1,3-*O*-methylene-DL-*myo*-inositol (**2**), whereas reaction with trimethylaluminium gave 2,4,6-tri-*O*-benzyl-1,5-*O*-ethylidene-DL-*myo*-inositol (**6**). 2,4,5,6-Tetra-*O*-benzyl-1,3-*O*-methylene-DL-*myo*-inositol (**16**) reacted with allyltrimethylsilane in the presence of Lewis acids to give 2,4,5,6-tetra-*O*-benzyl-1-*O*-(3-butenyl)-DL-*myo*-inositol [(±)-**17**] or rearranged to give 4,5,6-tri-*O*-benzyl-1,2-*O*-methylene-DL-*myo*-inositol [±)-**18**].

INTRODUCTION

Inositol phospholipid metabolism is involved in a wide variety of cellular processes, the control of which may be beneficial in the treatment of disease[1]. As a result, there has been an enormous interest in the synthesis of phosphorylated derivatives of *myo*-inositol and related phospholipids[2–4]. A phosphatidylinositol 3-kinase has been reported to catalyse the phosphorylation of phosphatidylinositol to phosphatidylinositol 3-phosphate[5], which is implicated in the regulation of cell growth[6]. We now report the syntheses of differentially protected *myo*-inositol derivatives with a view to preparing unsymmetrical 1,3-substituted examples.

RESULTS AND DISCUSSION

The starting material for this work was 2,4,6-tri-*O*-benzyl-*myo*-inositol 1,3,5-orthoformate (**1**), first synthesised by Billington and Baker[7] using a discovery by Lee

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and Kishi[8]. The ortho ester already has the 2-, 4-, and 6-positions differentiated from the 1- and 3-positions, and requires differentiation of the 1- and 3-positions from the 5-position.

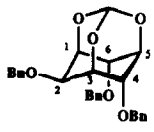
The reductive cleavage of axially substituted 2-alkoxy-1,3-dioxane ortho esters with lithium aluminium hydride is highly diastereoselective[9–11], and the related reduction with di-isobutylaluminium hydride (DIBAL) has been used[12] for the monoprotection of 1,n-diols. On this basis, we decided to investigate whether such a process would allow differentiation of the 1-, 3- and 5-positions of the ortho ester **1**, and a preliminary report has been published[13].

Lithium aluminium hydride failed to react with **1**, even in refluxing tetrahydrofuran. However, treatment of **1** with DIBAL (2 equiv) in dichloromethane at room temperature gave the 1,3-acetal **2** (93–100%). The symmetry of the ^1H and ^{13}C NMR spectra of **2** confirmed the 1,3-acetal structure rather than the 1,5-acetal **3**. Thus, there are benzyl groups in only two different environments and signals for only four inositol-ring carbons. In the ^1H NMR spectrum of **2**, the signals of the inositol-ring protons are poorly resolved, but they are visible in the spectrum of the 5-acetate **4**.

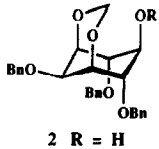
None of the 1,5-acetal (**3**) was isolated at this stage, although, after acetylation, the ^1H NMR spectrum of the crude product contained singlets for OAc at δ 2.05 (for **4**) and δ 2.12 (provisionally assigned to **5**) in the ratio 32:1 (see below).

The ^1H NMR spectrum of **4** contained signals for inositol-ring protons that reflected only four different environments and they could be assigned. These spectra contrast with those of the asymmetrically substituted inositols (see below).

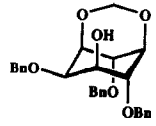
Treatment of **1** with 2 equiv of DIBAL at room temperature led to complete reduction in < 2.5 h, whereas reaction with 1.14 equiv for 54 h at room temperature gave a 47% yield of the product and 25% of **1** was recovered.



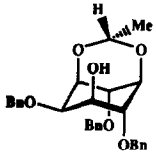
1



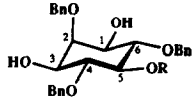
2 R = H
4 R = Ac



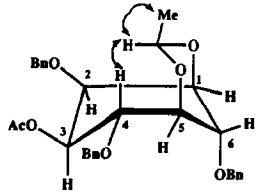
3 R = H
5 R = Ac



6



7 R = $CHMe_2$
8 R = H



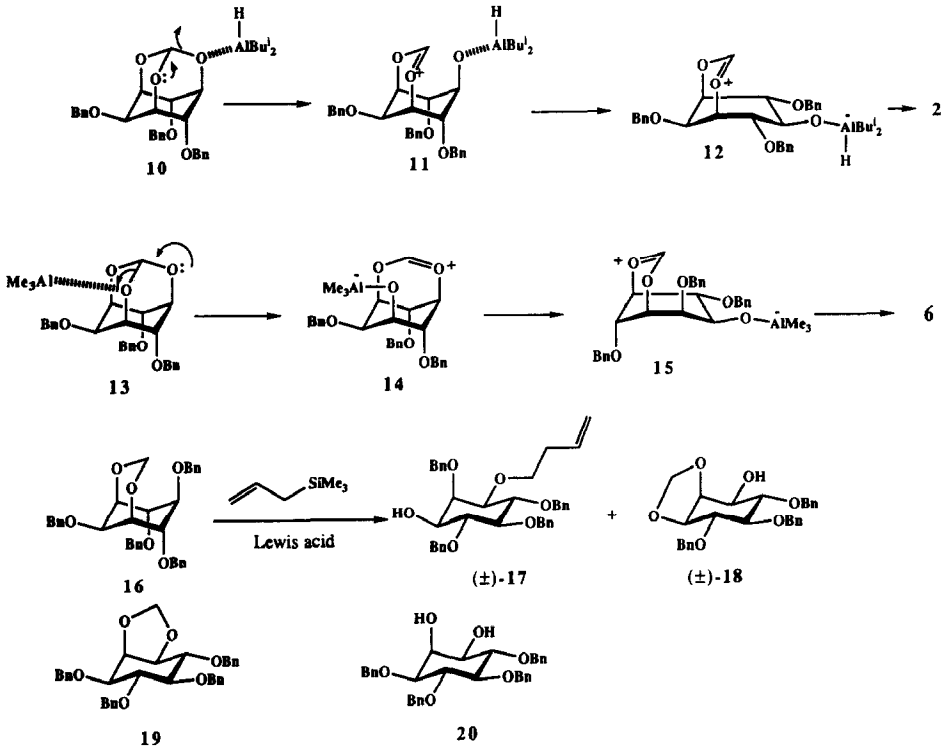
9

Although the cleavage of cyclic acetals with trimethylaluminium is not particularly diastereoselective[14], treatment of **1** with trimethylaluminium in dichloromethane at room temperature gave the 1,5-acetal **6** (84–86%) together with the 5-isopropyl ether **7**, formed presumably by attack of trimethylaluminium on **6**. Trace amounts of the analogous 1-isomer were also present, but they were characterised incompletely. Incomplete reaction was observed with an equimolar proportion of trimethylaluminium, thus an excess was always employed.

The structure of the 1,5-acetal **6** was confirmed as follows. Hydrolysis of **6** gave 2,4,6-tri-*O*-benzyl-*myo*-inositol (**8**) which could also be obtained by hydrolysis of **1**[7,15]. Thus, no benzyl migration had occurred during the reaction of **1** with trimethylaluminium. The asymmetry of the NMR spectra confirmed that **6** had been formed in preference to the 1,3-acetal **2** and, in contrast to the 1,3-acetal, it was possible to distinguish benzyl groups in three environments. Signals for all six inositol-ring carbon atoms and ring protons were visible, although they could not be assigned completely. However, the relevant ^{1}H signals for the 3-acetate **9** were assigned.

The stereochemistry of the ring-opening reaction which gave **6** was deduced from the NOE between the acetal C*H*Me (δ 5.25, q, J 4.8 Hz) and H-4 (δ 3.80, d, J 6.3 Hz) in **6**. There was no NOE between the methyl group and any ring proton. Likewise, for **9**, there was a NOE between C*H*Me (δ 5.2, q, J 5 Hz) and H-4 (δ 4.0, d, J 7.9 Hz) and H-4 was coupled to the deshielded H-3 (δ 5.41, t, J 7.9 Hz), which was both coupled and connected by a NOE to H-2 (δ 4.4, d, J 7.9 Hz). The foregoing data suggest that the cyclitol ring in **9** adopts a distorted boat conformation ($J_{3,2} = J_{3,4}$), whereas the acetal ring remains in a chair conformation. Models indicate that the acetal ring and the inositol ring cannot both be in chair conformations as there is severe steric interaction of the acetal carbon and the 3-substituent.

The trimethylaluminium-mediated ring opening of **1** takes place with inversion of configuration, whereas the stereochemical outcome of the DIBAL reduction is unknown. The stereoelectronic factors that govern the opening of ortho esters have been discussed[9,16,17], but no such effects are obvious for **1**. Alternative arguments based on steric effects[11,12] may be more relevant. The control of diastereoselectivity in the opening of cyclic acetals has been investigated extensively[18] and is dependent on the substrate (steric and electronic effects)[19], the nature of the cleaving reagent[10–12,14,20–24], and the Lewis acid employed. The mechanistic details have recently been classified[25,26] according to the type of intermediate involved. Cleavages with DIBAL and related hydride reagents occur with retention of configuration, whereas trimethylaluminium shows much lower selectivity unless the reactivity is enhanced with halophenyl ligands when retention of configuration is observed[24]. Thus, the highly chemoselective cleavage of **1** simply by changing the reagent is quite remarkable. The difference in selectivity is ascribed to steric effects. The bulky DIBAL probably coordinates to O-5 (which is more accessible) in **1** to give **10**, thus resulting in cleavage to give **11**. The inositol



ring can relieve crowding by flipping into the boat conformation **12**. The aluminate species is now remote from the oxacarbenium ion. Should the alternative cleavage occur via coordination at the sterically less accessible O-1 or O-3, then there would not be such a relief from crowding on changing the inositol ring into a boat conformation. The oxacarbenium ion **12** could then be reduced by another equivalent of DIBAL. The stereochemistry of this reduction is unknown.

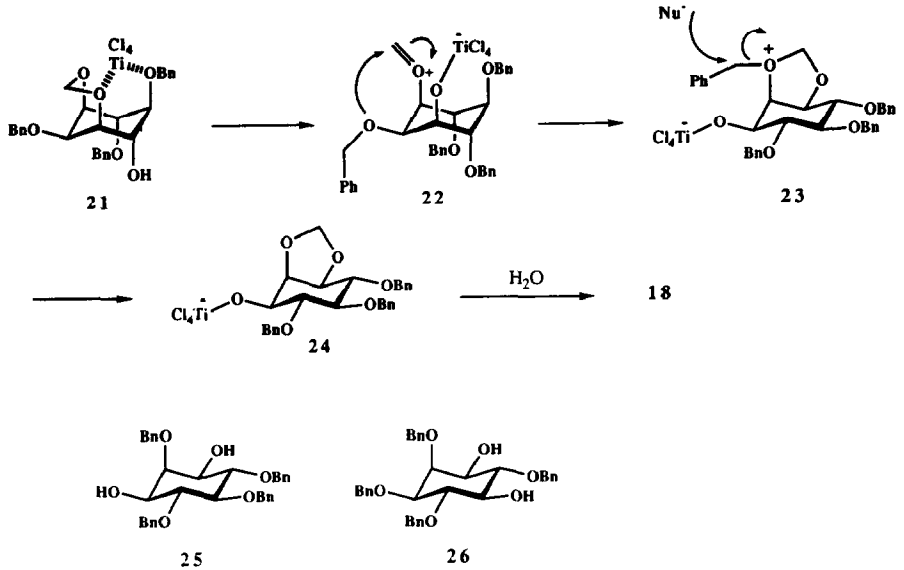
Trimethylaluminium is smaller than DIBAL and may be able to coordinate first to O-2 in **1** and then transfer to O-1 or O-3 (**13**) that are equivalent, one of which will be the preferred site of cleavage. The resulting intermediate **14** would be partially stabilised by the inositol ring flipping into the boat conformation **15**. The dioxalenium ion could then be attacked intermolecularly by another molecule of trimethylaluminium, with inversion of configuration representing by far the less-hindered trajectory of approach.

The 1,3-acetal **2** was benzylated at HO-5 to give the protected acetal **16** (97–99%). Differentiation of the 1- from the 3-position was then required and it was planned to open the acetal with a nucleophile in the presence of a Lewis acid. By choosing a suitable nucleophile, a protecting group could be introduced directly at the 1-position.

Titanium tetrachloride-mediated reactions of acetals with allylsilanes are well known[27–29], and treatment of **16** and allyltrimethylsilane with titanium tetrachlo-

ride at −78° gave the homoallylic ether alcohol **17** (14–25%) together with **18** (7–49%). Addition of titanium tetrachloride prior to addition of allyltrimethylsilane gave the by-product **18** (65–75%) but no **17**. The use of aluminium trichloride (at room temperature) as the Lewis acid in the allylsilane reaction gave an improved yield (38%) of **17** and only 16% of **18**. The NMR spectra of **18** showed a lack of symmetry and the mass spectrum showed that one benzyl group had been lost. The ^{13}C NMR spectrum of **18** contained signals for six inositol carbon atoms, three different benzyl groups, and an acetal group. The structure **18** was confirmed by benzylation to give 3,4,5,6-tetra-*O*-benzyl-1,2-*O*-methylene-*myo*-inositol (**19**), hydrolysis of which gave known[30] 3,4,5,6-tetra-*O*-benzyl-*myo*-inositol (**20**). The acetal **18** could also be hydrolysed to 4,5,6-tri-*O*-benzyl-*myo*-inositol in boiling concd hydrochloric acid.

As mentioned above, the rearranged debenzylation product **18** could be formed from **16** in the absence of an added nucleophile such as allyltrimethylsilane. Thus, **16** reacted with a stoichiometric quantity of titanium tetrachloride to give **18** (63–71%) and similarly (55%, unoptimised) with tin tetrachloride. Presumably, complexation with the Lewis acid is very favourable (e.g. → **21**). Molecular models indicate that steric congestion can be relieved if the acetal ring assumes a boat conformation. Thus, cleavage of **21** would form the intermediate oxacarbenium ion **22** which is suitably positioned to be trapped by O-5 to give the oxonium species **23**. Chloride ions then act as the nucleophile to cleave the benzyl group to give **24**, hydrolysis of which yields **18**. There is a large thermodynamic advantage in undergoing this rearrangement, as there is a significant reduction in crowding.



Hydrolysis of **16** in refluxing acidic methanol gave 2,4,5,6-tetra-*O*-benzyl-*myo*-inositol (**25**, 80–82%). When this reaction was carried out on a large scale, 3% of another product, possibly 2,3,4,6-tetra-*O*-benzyl-*myo*-inositol (**26**), was obtained. The NMR spectra showed the asymmetry of **26**; the four benzyl groups were in different environments and there was no acetal group. This product could have been produced from the 3-*O*-benzyl derivative of the 1,5-acetal **3** present as an impurity in the 1,3-acetal **2** arising from the DIBAL reduction of **1**. The ratio obtained for the products **25** and **26** was at least 27–32:1, indicative of the marked selective formation of the 1,3-acetal **2** over the alternative 1,5-isomer **3**.

Thus, the various Lewis acid-mediated substitutions of the orthoformate **1** make it a versatile precursor which will allow the 1,2-, 1,3-, or 1,5-positions to be protected differently from the remaining four positions.

EXPERIMENTAL

NMR spectra were recorded with a Bruker WM-250 (250 MHz for ^1H and 62.5 MHz for ^{13}C) or WM-400 (400 MHz for ^1H and 62.5 MHz for ^{13}C) instrument, using either $CHCl_3$ as the reference or internal deuterium lock. ^{13}C NMR spectra were recorded as proton-decoupled spectra and the multiplicites were determined using Applied Proton Test (APT) experiments. IR spectra were recorded with a Perkin–Elmer 1310 spectrometer. EI-mass spectra were recorded with an MS 30 instrument. High-resolution CI (ammonia) and FAB (thioglycerol or 3-nitrobenzyl alcohol as the matrix) mass spectra were obtained with a VG ZAB-E instrument at the S.E.R.C. Mass Spectrometry Centre (Dr. J. Ballantine, University College, Swansea). Melting points were determined with either a Büchi 510 or a Koffler hotplate melting-point apparatus and are uncorrected. TLC was carried out on Silica Gel 60 F_{254} (Merck) with detection by UV light, or by spraying with either basic potassium permanganate solution or ethanolic phosphomolybdic acid solution followed by heating. Flash-column chromatography was carried out on Kieselgel 60 Merck (230–400 mesh). Reagents were purified and dried where necessary by standard techniques[31]. Tetrahydrofuran was distilled from potassium. All compounds described are either meso or racemic.

*2,4,6-Tri-*O*-benzyl-1,3-*O*-methylene-*DL*-myo-inositol* (**2**).—(*a*) Di-isobutylaluminium hydride (DIBAL) (60 mL of a M solution in hexane, 60 mmol) was added to a solution of **1**[7,8,15] (11.41 g, 24.8 mmol) in dry CH_2Cl_2 (150 mL) at 0° under N_2. The mixture was stirred at room temperature for 2.5 h, then poured into a rapidly stirred, cooled solution of sodium potassium tartrate (150 g in 250 mL of H_2O) and satd aq NH_4Cl (200 mL). Ethyl acetate (600 mL) was added, the mixture was stirred for 1 h at room temperature, the aqueous layer was extracted with EtOAc (3 × 600 mL), and organic layers were combined, dried ($MgSO_4$), and concentrated under reduced pressure. Flash-column chromatography (15 → 40% EtOAc in hexane) of the residue gave **2**, isolated as an oil (11.45 g, 100%), R_F 0.1 (20% EtOAc in hexane); ν_{max}^{film} 3560, 3090, 3065, 3035, 2920, 1960, 1880, 1815, 1750, 1607,

1588, 1496, 1454, 1400, 1372, 1305, 1209, 1180, 1142, 1075, 1030, 885, 846, 740, and 700 cm^{-1}. NMR data ($CDCl_3$): ^1H (250 MHz), δ 7.38–7.25 (m, 15 H, 3 Ph), 5.59 (d, 1 H, J 4.9 Hz, $H_AH_BCO_2$), 4.70 (d, 1 H, J 4.9 Hz, $H_AH_BCO_2$), 4.69 (d, 2 H, J 11.9 Hz $PhCH_AH_B$ of BnO-4,6), 4.63 (s, 2 H, $PhCH_2$ of BnO-2), 4.58 (d, 2 H, J 11.9 Hz, $PhCH_ACH_B$ of BnO-4,6), 4.49–4.45 (m, 2 H, ring CHO), 4.34–4.32 (m, 1 H, ring CHO), 4.05 (t, 2 H, J 2.8 Hz, ring CHO), 4.00 (bs, 1 H, ring CHO), and 2.91 (bs, 1 H, OH); ^{13}C (100 MHz), δ 137.81 (s), 137.50 (s), 128.35 (d), 128.28 (d), 127.77 (d), 127.61 (d), 127.42 (d), 85.52 (t, H_2CO_2), 80.98 (d, ring CHO), 72.52 (d, ring CHO), 71.90 (t, $PhCH_2O$), 70.58 (t, $PhCH_2O$), 70.03 (d, ring CHO), and 69.27 (d, ring CHO). EI-mass spectrum: m/z 462 (M^+, 1%), 371 [($M^+ - PhCH_2$), 2], 253 (15), 173 (10), and 91 ($PhCH_2^+$, 100) (Found: C, 72.60; H, 6.60; M^+, 462.2056. $C_{28}H_{30}O_6$ calcd: C, 72.71; H, 6.54%, M^+, 462.2043).

(*b*) To a solution of **1** (321.6 mg, 0.70 mmol) in dry CH_2Cl_2 (4 mL) under N_2 at room temperature was added DIBAL (0.80 mL of a M solution in hexane, 0.80 mmol). The mixture was stirred for 24 h, when TLC (20% EtOAc in hexane) revealed unreacted **1**. After 54 h, the reaction was quenched with satd aq NH_4Cl (10 mL) and aq 25% sodium potassium tartrate (25 mL), then extracted with EtOAc (4 × 25 mL), and the extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure. Flash-column chromatography (10 → 25% EtOAc in hexane) of the residue gave **2** (152.4 mg, 47%) and **1** (79.2 mg, 25%).

5-O-Acetyl-2,4,6-tri-O-benzyl-1,3-O-methylene-DL-myo-*inositol* (**4**).—To a solution of **2** (0.113 g, 0.24 mmol) in dry CH_2Cl_2 (1 mL) under N_2 were added dry triethylamine (0.145 g, 1.43 mmol), acetic anhydride (0.05 mL, 0.054 g, 0.53 mmol), and 4-dimethylaminopyridine (catalytic quantity). The mixture was stirred for 1 h at room temperature, MeOH (a few drops) was added, and the solution was stirred for a further 30 min. The mixture was diluted with CH_2Cl_2 (25 mL), washed with 2 M NaOH (2 × 20 mL), M HCl (2 × 20 mL), satd aq $NaHCO_3$ (2 × 20 mL), and brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Flash-column chromatography (20% EtOAc in hexane) gave **4** (0.122 g, 99%), mp 90–92° (from EtOAc–hexane), R_F 0.25; $\nu_{max}^{CHCl_3}$ 2910–2870 (C–H), 1730 (C=O), 1370, 1145, 1092–1025 (C–O), and 890 cm^{-1}. NMR data ($CDCl_3$): ^1H (250 MHz), 7.39–7.25 δ (m, 15 H, 3 Ph), 5.47 (d, 1 H, J 4.5 Hz, $H_AH_BCO_2$), 5.17 (bs, 1 H, H-5), 4.71 (d, 2 H, J 12 Hz, $PhCH_AH_B$ of BnO-4,6), 4.68 (d, 1 H, J 4.5 Hz, $H_AH_BCO_2$), 4.64 (s, 2 H, $PhCH_2$ of BnO-2), 4.60 (d, 2 H, J 12 Hz, $PhCH_AH_B$ of BnO-4,6), 4.34 (bs, 2 H, H-1 and H-3), 4.22 (bs, 1 H, H-2), 3.85–3.82 (m, 2 H, H-4 and H-6), and 2.05 (s, 3 H, Ac); ^{13}C (62.5 MHz), δ 170.32 (s, C=O), 137.78 (s), 137.72 (s), 128.53, 128.43, 127.93, 127.90, 127.82, 127.72 (d, aromatic CH), 85.47 (t, H_2CO_2), 79.58 (d, ring CHO), 71.86 (t, $PhCH_2O$), 71.16 (d, ring CHO), 70.78 (t, $PhCH_2O$), 70.17 (d, ring CHO), 69.76 (d, ring CHO), and 21.19 (q, CH_3CO), EI-mass spectrum: m/z 504 (M^+, 5%), 215 (15), 181 (20), 91 ($PhCH_2^+$, 100) (Found: C, 71.60; H, 6.45; M^+, 504.2188. $C_{30}H_{32}O_7$ calcd: C, 71.41; H, 6.59%; M^+ 504.2148).

2,4,6-Tri-O-benzyl-1,5-O-ethylidene-DL-myo-*inositol* (**6**).—Trimethylaluminium (1.11 mL of a 2.0 M solution in hexane, 2.22 mmol) was added to a solution of **1**

(0.410 g, 0.89 mmol) in dry CH_2Cl_2 (4 mL) under N_2 at 0°. The mixture was stirred at room temperature for 5.5 h, then poured into a solution of sodium potassium tartrate (10 g) in H_2O (20 mL) and satd aq NH_4Cl (20 mL), and stirred vigorously for 1 h at room temperature. The product was extracted into CH_2Cl_2 (100 mL, and 2×50 mL), and the extract were combined dried ($MgSO_4$), and concentrated under reduced pressure. Flash-column chromatography (25 → 100% ether in hexane) of the residue gave **6**, isolated as an oil (357.8 mg, 84%), R_F 0.28 (40% ether in hexane); $\nu_{max}^{CCl_4}$ 3540, 3075, 3040, 3000, 2945, 2880, 1950, 1878, 1810, 1730, 1495, 1455, 1415, 1400, 1370, 1330, 1205, 1162, 1100, 1030, 913, and 888 cm^{-1}. NMR data ($CDCl_3$): ^1H (400 MHz), δ 7.38–7.25 (m, 15 H, 3 Ph), 5.25 (q, 1 H, J 4.8 Hz, C*H*Me), 4.80–4.71 (m, 3 H, 1.5 PhCH_2O), 4.69 (d, 1 H, J_{AB} 11 Hz), 4.49 (d, 1 H, J_{AB} 11 Hz), 4.43–4.40 (m, 3 H, 2 ring CHO and PhCH_AH_B), 4.33–4.32 (m, 1 H, ring CHO), 4.16–4.12 (m, 1 H, ring CHO), 3.97 (t, 1 H, J 3.8 Hz, ring CHO), 3.80 (d, 1 H, J 6.3 Hz, H-4), 3.2 (bs, 1 H, OH), 1.23 (d, 3 H, J 4.8 Hz, CHCH_3); ^{13}C (100 MHz), δ 138.43 (s), 137.64 (s), 137.32 (s), 128.62, 128.50, 128.37, 128.30, 128.25, 127.95, 127.64, 127.54 (d, aromatic CH), 90.81 (d, *C*HMe), 82.33 (d, ring CHO), 73.03 (d, ring CHO), 72.82 (t, Ph*C*H_2O), 72.54 (d, ring CHO), 71.91 (d, ring CHO), 71.87 (t, Ph*C*H_2O), 71.24 (t, Ph*C*H_2O), 68.82 (d, ring CHO), 68.38 (d, ring CHO), and 21.04 (q, CH*C*H_3). CI-mass spectrum: m/z 494.25426 ([$M^+ + NH_4$], 45%, $C_{29}H_{36}NO_6$), 385.3 (20), 314.3 (15), 288.3 (25), 224.2 (30), 198.3 (25), 179.2 (20), 108.1 (100), and 91.1 (20).

Treatment of **6** with acetic anhydride in the presence of triethylamine and 4-dimethylaminopyridine in CH_2Cl_2, as described for the preparation of **4**, gave the 3-acetate **9**, mp 75.5–77.5° (from EtOAc–hexane); $\nu_{max}^{CCl_4}$ 3080, 3050, 1750, and 1500 cm^{-1}. NMR data ($CDCl_3$): ^1H (400 MHz), δ 7.34–7.25 (m, 15 H, 3 Ph), 5.41 (t, 1 H, J 7.8 Hz, H-3), 5.14 (q, 1 H, J 4.7 Hz, C*H*Me), 4.73 (d, 1 H, J 12.2 Hz, PhCH_AH_B of OBn′), 4.71 (d, 1 H, J 11.7 Hz, PhCH_AH_B of OBn″), 4.64 (d, 1 H, J 10.7 Hz, PhCH_AH_B of OBn‴), 4.60 (d, 1 H, J 12.2 Hz, PhCH_AH_B of OBn′), 4.48 (d, 1 H, J 11.7 Hz, PhCH_AH_B of OBn″), 4.41 (bs, 1 H, H-5), 4.40 (d, 1 H, J 6.4 Hz, H-2), 4.33 (bd, 1 H, J 3.4 Hz, H-6), 4.30 (d, 1 H, J 10.7 Hz PhCH_AH_B of OBn‴), 4.0 (d, 1 H, J 8.3 Hz, H-4), 3.98 (t, 1 H, J 3.6 Hz, H-1), 2.04 (s, 3 H, Ac), and 1.24 (d, 3 H, J 4.8 Hz, CH*Me*); ^{13}C (100 MHz), 170.44 (s, C=O), 138.03 (s), 137.88 (s), 137.49 (s), 128.52, 128.34, 128.20, 127.99, 127.91, 127.87, 127.65, 127.59 (d, aromatic CH), 90.61 (d, *C*HMe), 78.83 (d, ring CHO), 72.88 (t, *C*H_2Ph), 72.72 (d, ring CHO), 72.43 (d, ring CHO), 71.63 (t, *C*H_2Ph), 71.43 (t, *C*H_2Ph), 70.01 (d, ring CHO), 68.03 (d, ring CHO), 20.95 (q, OCO*Me*), and 20.79 (CH*Me*) (Found: C, 71.75; H, 6.60. $C_{31}H_{34}O_7$ calcd: C, 71.73; H, 6.57%).

Also contained was 2,4,6-tri-*O*-benzyl-5-*O*-isopropyl-DL-*myo*-inositol (**7**) isolated as an oil (9.2 mg, 2%), R_F 0.18 (30% EtOAc in hexane); $\nu_{max}^{CCl_4}$ 3575, 3070, 3040, 2980, 2935, 1945, 1875, 1805, 1455, 1385, 1370, 1160, 1125, 1065, 1030, 930, and 695 cm^{-1}. NMR data ($CDCl_3$): ^1H (400 MHz), δ 7.38–7.24 (m, 15 H, 3 Ph), 4.93 (d, 2 H, J_{AB} 11.2 Hz, 2 PhCH_AH_B), 4.77 (s, 2 H, PhCH_2O), 4.74 (d, 2 H, J_{AB} 11.2 Hz, 2 PhCH_AH_B), 4.13–4.07 (m, 1 H, C*H*Me_2), 3.97 (t, 1 H, J 2.6 Hz, ring CHO), 3.68

(t, 2 H, *J* 9.5 Hz, ring CHO), 3.50 (dd, 2 H, *J* 9.7 and 2.4 Hz, ring CHO), 3.36 (t, 1 H, *J* 9.2 Hz, ring CHO), 1.22 (d, 6 H, *J* 6.1 Hz, $CHMe_2$); ^{13}C (100 MHz), δ 138.60 (s), 138.51 (s), 128.54, 128.38, 128.00, 127.82, 127.69 (d, aromatic CH), 82.30 (d), 79.57 (d), 78.82 (d), 75.76 (t, $PhCH_2O$), 75.14 (t, $PhCH_2O$), 73.10 (d), 72.63 (d), 22.74 [q, $CH(CH_3)_2$]. CI-mass spectrum: *m/z* 511 [$(M^+ + 1 + NH_4)$, 8%], 510 [$(M^+ + NH_4)$, 29], 494 [$(M^+ + 1 + H)$, 20], 493.25901 [$(M^+ + H)$, 65, $C_{30}H_{37}O_6$], 403 (4), 402 (7), 401 (7), 385 (3), 313 (2), 312 (5), 311 (7), 288 (12), 240 (3), 198 (28), 181 (14), 179 (12), 109 (7), 108 (100), 106 (17), 91 (33).

*2,4,6-Tri-O-benzyl-*DL*-myo-inositol* (**8**).—(*a*) A solution of **1** (6.14 g, 13.3 mmol) in MeOH (300 mL) was boiled under reflux with satd methanolic HCl (15 mL) for 30 min, then concentrated in vacuo. Flash chromatography (30 → 50% EtOAc in hexane) of the residue gave **8** (5.44 g, 91%), mp 80–81.5°, lit.[7,15] mp 83–84.5°. NMR data ($CDCl_3$): ^1H (250 MHz), δ 7.38–7.25 (m, 15 H, 3 pH), 4.86 (s, 4 H, 2 $PhCH_2O$ equatorial), 4.84 (s, 2 H, $PhCH_2O$ axial), 4.00 (t, 1 H, *J* 2.6 Hz, ring CHO), 3.71–3.53 (m, 5 H, 5 ring CHO), 2.9–2.1 (bs, 3 H, 3 OH); ^{13}C (62.5 MHz), δ 138.33 (s), 128.48, 128.40, 127.94, 127.82, 127.76 (d, aromatic CH), 81.84 (d, ring CHO), 79.22 (d ring CHO), 75.22 (t, $PhCH_2O$), 74.95 (t, $PhCH_2O$), 74.82 (d ring CHO), and 72.38 (d ring CHO). EI-mass spectrum: *m/z* 359 [$(M^+ - PhCH_2)$, 80%], 91 ($PhCH_2^+$, 100).

(*b*) A solution of **6** (87.0 mg, 0.18 mmol) in MeOH (3 mL) and concd. HCl (0.4 mL) was boiled under reflux under N_2 for 45 min, then cooled, and neutralised with solid $NaHCO_3$. Ether was added, and the mixture was filtered and concentrated under reduced pressure. Flash-column chromatography (50% EtOAc in hexane) of the residue gave **8**, isolated as an oil (74.8 mg, 91%), which was identical (NMR data) with the product in (*a*).

*2,4,5,6-Tetra-O-benzyl-1,3-O-methylene-*DL*-myo-inositol* (**16**).—Sodium hydride (1.81 g of a 50% suspension in oil, 37.7 mmol) was washed with sodium-dried hexane (2 × 20 mL, then 10 ml) under N_2. A solution of **2** (11.43 g, 24.8 mmol) in dry DMF (70 mL) was added at 0°. The mixture was stirred at room temperature for 1 h, benzyl bromide (4.42 mL, 38.2 mmol) was added, and stirring was continued at room temperature for 18 h. The reaction was quenched with H_2O and the solvent was removed under reduced pressure. Flash-column chromatography (10 → 20% EtOAc in hexane) of the residue gave **16**, isolated as an oil (13.57 g, 99%), R_F 0.5 (25% EtOAc in hexane); ν_{max}^{film} 3090, 3065, 3030, 2910, 2870, 1608, 1586, 1495, 1455, 1370, 1310, 1208, 1178, 1150, 1100, 1070, 1030, 1015, 890, 815, 740, and 700 cm^{-1}. NMR data ($CDCl_3$): ^1H (250 MHz), δ 7.38–7.25 (m, 20 H, 4 Ph), 5.20 (d, 1 H, *J* 5.5 Hz, HCO_2), 4.85 (d, 1 H, *J* 5.5 Hz, HCO_2), 4.66 (s, 4 H, 2 $PhCH_2O$), 4.61 (d, 2 H, J_{AB} 12.3 Hz, 2 $PhCH_AH_BO$), 4.54 (d, 2 H, J_{AB} 11.8 Hz, 2 $PhCH_AH_B$), 4.27 (bs, 2 H, ring CHO), 3.97 (d, 2 H, *J* 5.5 Hz, ring CHO), 3.85 (t, 1 H, *J* 2 Hz, ring CHO), and 3.63 (t, 1 H, *J* 5.5 Hz, ring CHO); ^{13}C (62.5 MHz), δ 138.40 (s), 137.8 (s, 2 peaks), 128.59 (d), 128.55 (d), 128.46 (d), 128.00 (d), 127.95 (d), 127.79 (d), 85.48 (t, H_2CO_2), 82.00 (d, ring CHO), 80.01 (d, ring CHO), 73.45 (t, $PhCH_2O$), 71.95 (d, ring CHO), 71.69 (t, $PhCH_2O$), 70.97 (t, $PhCH_2O$), and

70.19 (d, ring CHO). EI-mass spectrum: *m/z* 461 [(M^+ – $PhCH_2$), 1%], 263 (5), 253 (8), 181 (11), and 91 ($PhCH_2^+$, 100) (Found: C, 76.10; H, 6.60. $C_{35}H_{36}O_6$ calcd: C, 76.06; H, 6.57%).

*2,3,5,6-Tetra-O-benzyl-1-O-(3-butenyl)-*DL-myo-*inositol* (**17**).—Allyltrimethylsilane (0.23 mL, 0.165 g, 1.4 mmol) and then M $TiCl_4$ in CH_2Cl_2 (0.5 mL) were added to a solution of **16** (199.5 mg, 0.36 mmol) in dry CH_2Cl_2 (3.5 mL) at −78° under Ar. After 10 min, no **16** could be detected by TLC. After 25 min, MeOH (0.5 mL) was added, and the solution was allowed to warm to room temperature, then poured into M HCl (25 mL), and extracted with CH_2Cl_2 (25 mL). The extract was dried (Na_2SO_4) and concentrated under reduced pressure. Flash-column chromatography (15 → 65% EtOAc in hexane) of the residue gave **17**, isolated as an oil (53 mg, 25%), R_F 0.51 (45% EtOAc in hexane); ν_{max}^{film} 3560, 3450, 3070, 3035, 2910, 2870, 1955, 1880, 1815, 1730, 1642, 1608, 1588, 1498, 1455, 1398, 1360, 1310, 1210, 1125, 1085, 1025, 915, 825, 735, and 700 cm^{-1}. NMR data ($CDCl_3$): ^1H (250 MHz), δ 7.37–7.24 (m, 20 H, 4 Ph), 5.91–5.74 (m, 1 H, C*H*=CH_2), 5.13–4.65 (m, 10 H, 4 PhCH_2O and CH=CH_2), 4.03 (t, 1 H, *J* 1.5 Hz, ring CHO), 3.97 (t, 1 H, *J* 9.5 Hz, ring CHO), 3.78 (t, 1 H, *J* 9.5 Hz, ring CHO), 3.65 (td, 2 H, *J* 6.7 and 2.0 Hz, ring CHO), 3.51–3.41 (m, 2 H, OC$H_2$$CH_2$), 3.30 (dd, 1 H, *J* 9.8 and 2.4 Hz, ring CHO), and 2.36 (bq, 2 H, *J* 6.7 Hz, OCH_2CH_2); ^{13}C (100 MHz), δ 138.74 (s), 138.60 (s), 138.53 (s), 135.16 (d, *C*H=CH_2), 128.44, 128.32, 128.29, 128.05, 127.96, 127.80, 127.71, 127.51 (d, aromatic CH), 116.62 (t, C=*C*H_2), 83.43 (d, ring CHO), 82.15 (d, ring CHO), 81.82 (d, ring CHO), 81.69 (d, ring CHO), 76.7 (d, ring CHO), 75.75 (t, CH_2), 75.70 (t, CH_2), 75.52 (t, CH_2), 74.69 (t, CH_2), 72.29 (d, ring CHO), 70.49 (t, CH_2), and 34.72 (t, CH_2). EI-mass spectrum: *m/z* 503 [(M^+ – $PhCH_2$), 2%], 397 (1), 182 (1), 181 (4), 179 (1), 147 (2), 145 (3), 143 (1), 133 (1), 131 (1), 129 (1), 128 (1), 127 (2), 117 (3), 111 (1), 109 (3), 108 (1), 107 (3), 106 (6), 105 (8), 92 (10), 91 (100), and 77 (10) (Found: C, 76.70; H, 7.31. $C_{38}H_{42}O_6$ calcd: C, 76.74; H, 7.12%).

Also obtained was 4,5,6-tri-*O*-benzyl-1,2-*O*-methylene-DL-*myo*-inositol (**18**; 87.0 mg, 52%), R_F 0.25 (45% EtOAc in hexane), mp 105–106.5° (from EtOAc–hexane); $\nu_{max}^{CHCl_3}$ 3580, 2870, 1950, 1875, 1814, 1720, 1590, 1450, 1360, 1085, 997, 965, 910, and 875 cm^{-1}. NMR data ($CDCl_3$): ^1H (250 MHz), δ 7.38–7.25 (m, 15 H, 3 Ph), 5.22 (s, 1 H, OC$H_A$$H_B$O), 4.95 (s, 1 H, $OCH_A$$H_B$O), 4.86–4.64 (m, 6 H, 3 PhCH_2O), 4.28–4.20 (m, 2 H, 2 ring CHO), 3.97 (dd, 1 H, *J* 7.9 and 3.4 Hz, ring CHO), 3.87–3.78 (m, 2 H, 2 ring CHO), 3.58–3.51 (m, 1 H, ring CHO); ^{13}C (100 MHz), δ 138.33 (s), 138.16 (s), 128.55, 128.39, 128.37, 127.98, 127.94, 127.91, 127.70 (d, aromatic CH), 95.12 (t, H_2CO_2), 82.34 (d, ring CHO), 80.92 (d, ring CHO), 80.84 (d, ring CHO), 78.56 (d, ring CHO), 75.86 (d, ring CHO), 74.59 (t, PhCH_2O), 74.50 (t, PhCH_2O), 73.80 (t, PhCH_2O), and 69.43 (d, ring CHO); EI-mass spectrum: *m/z* 462 (M^+, 2%), 372 (3), 371 (10), 107 (7), 106 (2), 105 (4), 92 (15), 91 (100) (Found: C, 72.6; H, 6.50; M^+, 462.2068. $C_{28}H_{30}O_6$ calcd: C, 72.71; H, 6.54; M^+, 462.2042).

Compound **18** was also prepared by the following methods.

(*a*) To a solution of **16** (141.5 mg, 0.26 mmol) in dry CH_2Cl_2 (2 mL) at −78° under Ar was added M $TiCl_4$ (0.35 mmol) in CH_2Cl_2 (0.35 mL). The mixture was stirred at −78° for 30 min, H_2O (0.5 mL) was added, and the mixture was allowed to warm to room temperature, then poured into 2 M HCl (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL), and the organic layers were combined, dried (Na_2SO_4), and concentrated under reduced pressure. Flash-column chromatography (40 → 90% ether in hexane) of the residue gave **18** as a white solid (84.3 mg, 71%).

(*b*) To a solution of **16** (188.7 mg, 0.34 mmol) in dry CH_2Cl_2 (1 mL) under Ar at 0° was added M $SnCl_4$ (0.4 mmol) in CH_2Cl_2 (0.4 mL). The mixture was stirred at 0° for 4 h, then cooled to −78°, and the reaction was quenched with H_2O (0.5 mL). The mixture was warmed to room temperature, poured into 2 M HCl (20 mL), extracted with CH_2Cl_2 (3 × 25 mL), and the extracts were combined, dried (Na_2SO_4), and concentrated under reduced pressure. Flash-column chromatography (40 → 90% ether in hexane) of the residue gave **18** as a white solid (86.2 mg, 55%).

*4,5,6-Tri-*O*-benzyl-*DL-myo-*inositol.*—A solution of **18** (78.6 mg, 0.17 mmol) in dry MeOH (2 mL) and concd HCl (0.4 mL) was boiled under reflux for 3 h under N_2, when there was no sign of reaction by TLC. More concd HCl (0.5 mL) was added, and boiling under reflux was continued for 75 min, when no **18** remained (TLC). The solution was neutralised with solid $NaHCO_3$, filtered, and concentrated under reduced pressure. The residue was extracted with EtOAc, and the extract was dried ($MgSO_4$) and concentrated. Flash-column chromatography (70% EtOAc in hexane, then 4% MeOH in EtOAc) gave the title compound (28.9 mg, 38%), R_F 0.35 (EtOAc); $\nu_{max}^{CHCl_3}$ 3570, 2870, 1955, 1880, 1725, 1600, 1362, 1120, 1060, and 935 cm^{-1}. NMR data ($CDCl_3$): ^1H (250 MHz), δ 7.38–7.25 (m, 15 H, Ph), 4.94 (d, 2 H, J_{AB} 11.2 Hz, 0.5 PhCH_2O-4,6), 4.89 (s, 2 H, PhCH_2O-5), 4.76 (d, 2 H, *J* 11.2 Hz, 0.5 PhCH_2O-4,6), 4.07 (bs, 1 H, ring CHO), 3.84–3.76 (m, 2 H, 2 ring CHO), and 3.52–3.44 (m, 3 H, 3 ring CHO); ^{13}C (100 MHz), δ 138.45 (s), 138.36 (s), 128.61, 128.45, 127.95, 127.92, 127.79, 127.69 (d, aromatic CH), 83.34 (d, ring CHO), 81.80 (d, ring CHO), 75.60 (t, PhCH_2O), 75.53 (t, PhCH_2O), 71.89 (d, ring CHO), and 71.08 (d, ring CHO). CI-mass spectrum: *m/z* 468.2386 [(M^+ + NH_4), 100%, $C_{27}H_{34}NO_6$], 389 (4) 359 (6), 315 (9), 288 (10), 271 (6), 269 (10), 217 (6), 201 (5), 199 (5).

*3,4,5,6-Tetra-*O*-benzyl-1,2-*O*-methylene-*DL-myo-*inositol* (**19**).—A solution of **18** (108.4 mg, 0.24 mmol) in dry DMF (1.1 mL) was added to NaH (0.019 g of 50% dispersion, 0.40 mmol) under N_2 at room temperature. The mixture was stirred for 2 h, benzyl bromide (0.05 mL, 0.07 g, 0.40 mmol) was added, stirring was continued for 17 h, the reaction was quenched with H_2O, and the mixture was concentrated under reduced pressure. Flash-column chromatography (10 → 25% EtOAc in hexane) of the residue gave **19**, isolated as an oil (112.3 mg, 87%), R_F 0.41 (25% EtOAc in hexane); ν_{max}^{film} 3065, 3035, 2870, 2060, 1955, 1880, 1810, 1725, 1605, 1587,

1495, 1450, 1360, 1310, 1210, 1085, 1028, 995, 930, 880, 820, 735, and 700 cm^{-1}. NMR data ($CDCl_3$): ^1H (400 MHz), δ 7.41–7.25 (m, 20 H, 4 Ph), 5.23 (s, 1 H, OCH_AH_BO), 5.03 (s, 1 H, OCH_AH_BO), 4.88–4.74 (m, 8 H, 4 $PhCH_2O$), 4.25–4.20 (m, 2 H, 2 ring CHO), 3.97–3.93 (m, 1 H, ring CHO), 3.86–3.81 (m, 2 H, 2 ring CHO), 3.54 (bt, 1 H, *J* 8.5 Hz, ring CHO); ^{13}C (100 MHz), δ 138.44 (s), 138.34 (s), 138.29 (s), 137.98 (s), 128.92, 128.32, 128.25, 127.90, 127.87, 127.80, 127.69, 127.62, 127.54 (d, aromatic CH), 95.16 (t, OCH_2O), 82.06 (d, ring CHO), 80.68 (d, ring CHO), 80.39 (d, ring CHO), 78.55 (d, ring CHO), 76.89 (d, ring CHO), 74.93 (d, ring CHO), 74.84 (t, $PhCH_2O$), 74.68 (t, $PhCH_2O$), 73.81 (t, $PhCH_2O$), and 73.00 (t, $PhCH_2O$). EI-mass spectrum: *m/z* 462 [(M^+ – $PhCH_2$), 2%], 461 (7), 355 (1), 263 (4), 182 (2), 181 (12), 107 (2), 105 (2), 92 (10), 91 (100) (Found: C, 76.20; H, 6.80. $C_{35}H_{36}O_6$ calcd: C, 76.06; H, 6.57%).

3,4,5,6-Tetra-O-*benzyl*-DL-myo-*inositol* (**20**).—A solution of **19** (31.4 mg, 57 μmol) in MeOH (2 mL) and concd HCl (0.4 mL) was boiled under reflux under N_2 for 6 h, then neutralised with solid $NaHCO_3$, filtered, and concentrated. The residue was extracted with EtOAc, and the extract was dried ($MgSO_4$) and concentrated under reduced pressure. Flash-column chromatography (25 → 70% EtOAc in hexane) of the residue gave **20** (22.3 mg, 73%), mp 113–115°, which was identical (NMR data) with an authentic sample prepared as described by Gigg and Warren[30].

2,4,5,6-Tetra-O-*benzyl*-DL-myo-*inositol* (**25**).—A solution of **16** (9.10 g, 16.5 mmol) in concd HCl (20 mL) and MeOH (150 mL) was boiled under reflux for 3 h, then cooled, neutralised with solid $NaHCO_3$, filtered, and concentrated under reduced pressure. The residue was extracted with EtOAc, and the extract was dried ($MgSO_4$) and concentrated in vacuo. Flash-column chromatography (0 → 40% EtOAc in hexane) of the residue gave **25** (7.32 g, 82%), mp 80–82° (from EtOAc–hexane); ν_{max}^{film} 3560, 3450, 3090, 3060, 3030, 2880, 1965, 1880, 1810, 1605, 1590, 1495, 1455, 1400, 1360, 1210, 1125, 1065, 1030, 935, 740, and 700 cm^{-1}. NMR data $CDCl_3$): ^1H (250 MHz), δ 7.39–7.24 (m, 20 H, 4 Ph), 4.94–4.70 (m, 8 H, 4 $PhCH_2O$), 4.00 (t, 1 H, *J* 2.6 Hz, ring CHO), 3.80 (t, 2 H, *J* 9.4 Hz, 2 ring CHO), 3.61–3.53 (m, 2 H, 2 ring CHO), 3.49 (t, 1 H, *J* 9 Hz, ring CHO), and 2.29 (d, 2 H, *J* 5.6 Hz, 2 OH); ^{13}C (62.5 MHz), δ 138.47 (s), 138.36 (s), 138.81 (s), 128.49 (d), 128.38 (d), 127.99 (d), 127.80 (d), 127.75 (d), 127.69 (d), 127.62 (d), 83.48 (d, ring CHO), 82.23 (d, ring CHO), 78.92 (d, ring CHO), 75.54 (t, $PhCH_2O$), 75.16 (t, $PhCH_2O$), and 72.57 (d, ring CHO); EI-mass spectrum: *m/z* 449 [(M^+ – $PhCH_2$), 23%], 271 (18), 269 (19), 182 (35), 181 (100), 179 (33), 127 (17), 92 (60), 91 ($PhCH_2^+$, 100), and 65 (35) (Found: C, 75.5; H, 6.5. $C_{34}H_{36}O_6$ calcd: C, 75.53; H, 6.71%).

Another compound was also isolated and thought to be 1,2,4,6-tetra-*O*-benzyl-DL-*myo*-inositol (**26**; 0.229 g, 3%), R_F 0.47 (50% EtOAc in hexane); $\nu_{max}^{CCl_4}$ 3580, 3080, 3045, 2920, 2880, 1950, 1878, 1812, 1740, 1495, 1455, 1390, 1365, 1310, 1208, 1105, 1070, 1025, 932, 915, and 700 cm^{-1}. NMR data ($CDCl_3$): ^1H (250 MHz), 7.38–7.25 (m, 20 H, 4 Ph), 5.01–4.68 (m, 8 H, 4 $PhCH_2O$), 4.06 (t, H, *J* 2.5 Hz, ring CHO), 3.90 (t, 1 H, *J* 9.4 Hz, ring CHO), 3.69 (t, 1 H, *J* 9.3 Hz, ring CHO),

3.52 (t, 1 H, *J* 9.0 Hz, ring CHO), 3.47 (td, 2 H, *J* 9.7 and 2.4 Hz, 2 ring CHO); ^{13}C (100 MHz), δ 138.71 (s), 138.13 (s), 128.54, 128.50, 128.42, 128.08, 128.05, 127.82, 127.69, 127.65 (d, aromatic CH), 81.70 (d, ring CHO), 81.31 (d, ring CHO), 80.92 (d, ring CHO), 77.30 (d, ring CHO), 75.51 (t, Ph*C*H_2O), 75.05 (d, ring CHO), 74.97 (t, Ph*C*H_2O), 74.81 (t, Ph*C*H_2O), 72.73 (t, Ph*C*H_2O), and 72.23 (d, ring CHO). CI-mass spectrum: *m/z* 558.28556 [($M^+ + NH_4$), 20%, $C_{34}H_{40}NO_6$], 359 (8), 288 (12), 269 (15), 198 (30), 179 (18), 108 (100), and 91 (25).

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