Synthesis of D-2-deoxy-*myo*-inositol 1,3,4,5-tetrakisphosphate from D-glucose

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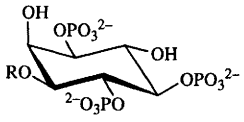
A route to a novel, structurally modified D-*myo*-inositol 1,3,4,5-tetrakisphosphate analogue, D-2-deoxy-*myo*-inositol 1,3,4,5-tetrakisphosphate 3, is described, involving as the key steps a selective protection of methyl α-D-glucopyranoside and subsequent catalytic Ferrier rearrangement to a deoxyinosose. Thus, methyl α-D-glucopyranoside was converted by an improved procedure into methyl 4,6-*O*-benzylidene-α-D-glucopyranoside 4 and thence into methyl 3-*O*-benzoyl-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside 7 without recourse to column chromatography. Compound 7 was converted into methyl 3,4-di-*O*-benzoyl-2-*O*-benzyl-6-deoxy-α-D-*xylo*-hex-5-enopyranoside 12 *via* methyl 3,4-di-*O*-benzoyl-2-*O*-benzyl-6-bromo-6-deoxy-α-D-glucopyranoside 8. Rearrangement of enol ether 12 with mercury(II) trifluoroacetate provided (2*S*,3*R*,4*S*,5*R*)-2,3-dibenzoyloxy-4-benzyloxy-5-hydroxycyclohexanone 13 and (2*S*,3*R*,4*S*,5*S*)-2,3-dibenzoyloxy-4-benzyloxy-5-hydroxycyclohexanone 14. Attempts to invert the configuration at position 5 of compound 14 were unsuccessful, but provided a number of discrete products. Reduction of compound 13 and saponification furnished L-1-*O*-benzyl-3-deoxy-*scyllo*-inositol 23, which was phosphorylated and deprotected to give the target 3.

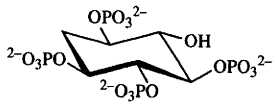
Introduction

Receptor-mediated phospholipase C-catalysed cleavage of phosphatidylinositol 4,5-bisphosphate releases D-*myo*-inositol 1,4,5-trisphosphate [Ins(1,4,5)P_3, **1**], which interacts with a family of Ins(1,4,5)P_3-receptor-operated Ca^{2+} channels to mobilise intracellular Ca^{2+} stores in many cell types.[1] Ins(1,4,5)P_3 is metabolised *via* two pathways:[2] deactivation by a 5-phosphatase to D-*myo*-inositol 1,4-bisphosphate [Ins(1,4)P_2] or phosphorylation by a 3-kinase to D-*myo*-inositol 1,3,4,5-tetrakisphosphate [Ins(1,3,4,5)P_4, **2**]. The function of the latter is controversial: it has been suggested to be a second messenger in its own right and may be involved in Ca^{2+} homeostasis at the plasma membrane, helping to control entry of extracellular Ca^{2+} into the cell.[3] In support of this hypothesis, an Ins(1,3,4,5)P_4-sensitive Ca^{2+}-permeable channel has been characterised from endothelial cells,[4] and Ins(1,3,4,5)P_4-binding proteins have been purified from pig[5] and rat[6,7] cerebellum and porcine platelets.[8] The last example has received particular recent interest: this protein has been tentatively proposed as an Ins(1,3,4,5)P_4 receptor,[8-10] has demonstrated a high specificity for Ins(1,3,4,5)P_4 over all other inositol tetrakis-[9] and various other polyphosphates,[8] and *in vitro* Ins(1,3,4,5)P_4-stimulated guanosine triphosphatase-activating protein (GAP) activity against *Ras* has been demonstrated.[10] The Ins(1,3,4,5)P_4-binding region of this protein has been identified.[10]

To study structure–activity relationships in inositol tris- and tetrakis-phosphates, we have prepared inositol phosphates and analogues as potential enzyme inhibitors and receptor antagonists.[2] Although the role of position 2 of Ins(1,4,5)P_3 in binding to its recognition proteins has been investigated,[11] a similar study has not been performed for Ins(1,3,4,5)P_4. We therefore required D-2-deoxy-*myo*-inositol 1,3,4,5-tetrakisphosphate **3** † in which the hydroxy group at this position is deleted. Deletion of hydroxy groups adjacent to phosphomonoesters can also engender inhibitory activity against phosphatases; for example D-2-deoxy-Ins(1)P and D-6-deoxy-Ins(1,4,5)P_3 inhibit inositol monophosphatase[12] and Ins(1,4,5)P_3-5-phosphatase[13] respectively. The phosphorothioate analogue of D-6-deoxy-Ins(1,4,5)P_3 is a partial agonist at the Ins(1,4,5)P_3 receptor.[14] Tetrakisphosphate **3** is therefore also a potential inhibitor of the enzyme Ins(1,3,4,5)P_4-3-phosphatase.[15] We report here the synthesis of compound **3** from methyl α-D-glucopyranoside, involving a Ferrier rearrangement[16] as the central reaction. This rearrangement has previously been used to provide Ins(1,3,4,5)P_4 affinity labels[17] and a chiral phosphorylation precursor of Ins(1,4,5)P_3.[18] While the present work was in progress, preliminary accounts of its use in the preparation of several other deoxy[19] and non-deoxy[20] inositol phosphates, including D-6-deoxy-Ins(1,3,4,5)P_4,[19b] have been described.



1 R = H
2 R = PO_3^{2-}

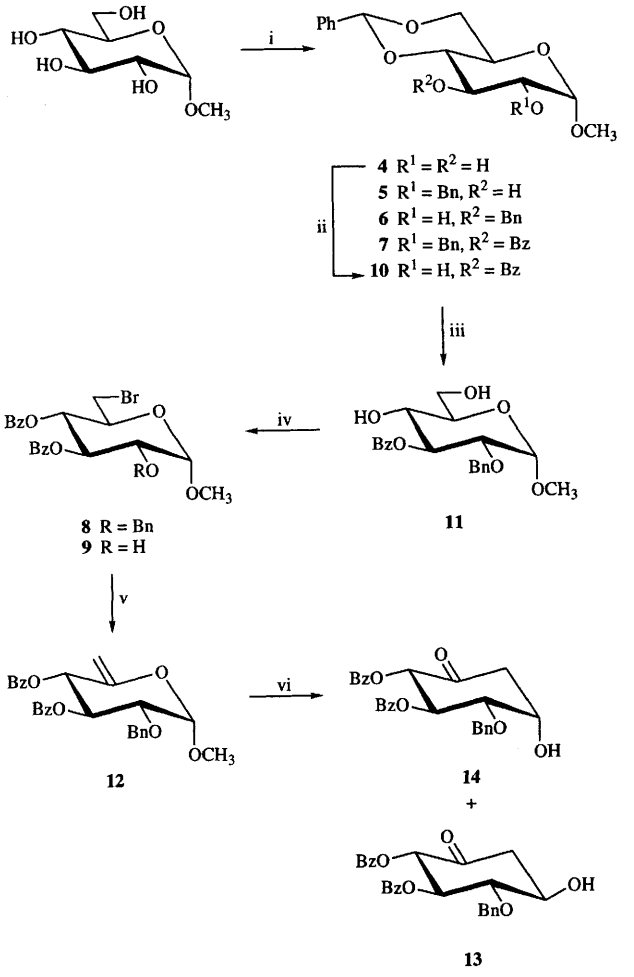


3

Results and discussion

Many methods have been described for the preparation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **4** (Scheme 1), including the reaction of methyl α-D-glucopyranoside with zinc chloride–benzaldehyde[21] (and note an important modification[22]); with benzaldehyde dimethyl acetal in dimethylformamide (DMF) in the presence of toluene-*p*-sulfonic acid (PTSA),[23,24] pyridinium toluene-*p*-sulfonate (PPTS)[24] or tetrafluoroboric acid;[25] with benzaldehyde dimethyl acetal in 10% methanolic H_2SO_4;[26] and with benzaldehyde diethyl acetal in DMF in the presence of HCl,[27] or in 1,4-dioxane in the presence of a strong cation-exchange resin,[28] or in chloroform in the presence of camphor-10-sulfonic acid.[29] Although excellent yields are reported for most of these techniques, suitability for large-scale preparation (*i.e.* 0.5 mol or more) is rarely discussed.

† Compound **3** could be named as L-4-deoxy-*scyllo*-inositol 1,2,3,5-tetrakisphosphate, but is named here as a derivative of *myo*-inositol for clarity in relation to biochemical nomenclature; intermediates in this paper are, however, named as derivatives of *scyllo*-inositol.



Scheme 1 *Reagents and conditions:* i, $PhCH(OMe)_2$, PTSA, DMF, 70 °C, 4 h, −MeOH (90%); ii, (*a*) Bu_2SnO, toluene, reflux, 3 h, $-H_2O$; (*b*) BnBr, Bu_4NBr, MeCN, 4 Å sieves, reflux, 2 days; (*c*) BzCl, DMAP, pyridine, room temp., 2 h; (*d*) fractional crystallisation (EtOH) (34%); iii, 80% AcOH in water, reflux, 1.75 h (98%); iv, (*a*) Ph_3P, CBr_4, THF, N_2, room temp., 16 h; (*b*) BzCl, DMAP, pyridine, room temp., 2 h, (63%); v, (*a*) NaI, Bu_4NI, DMSO, 4 Å sieves, N_2, 100 °C, 2 h; (*b*) DBU, 2 h, (62%); vi, $Hg(CF_3CO_2)_2$, 1% AcOH in acetone–water (5:2), 30 h (83%)

In our hands a modification of Evans' method,[23] previously used to prepare methyl 2,3:4,6-di-*O*-benzylidene-α-D-mannopyranoside,[30] in which methyl α-D-glucopyranoside, benzaldehyde dimethyl acetal and PTSA were stirred in DMF at 70 °C with removal of liberated methanol *via* an air condenser gave an excellent yield of crystalline product on a 100 g (or larger) scale. This preparation did not require dried solvent, or purified reagents.

Benzylation of the 2,3-*O*-dibutylstannanediyl derivative of compound **4** with benzyl bromide in acetonitrile in the presence of quaternary ammonium salts gave a ~4:1 mixture of the chromatographically separable 2- and 3-*O*-benzyl ethers **5** and **6** respectively.[31] Attempts to isolate compound **5** by crystallisation met with little success, but after benzoylation of the mixture the corresponding 3-benzoate **7** was isolated by fractional crystallisation from ethanol.

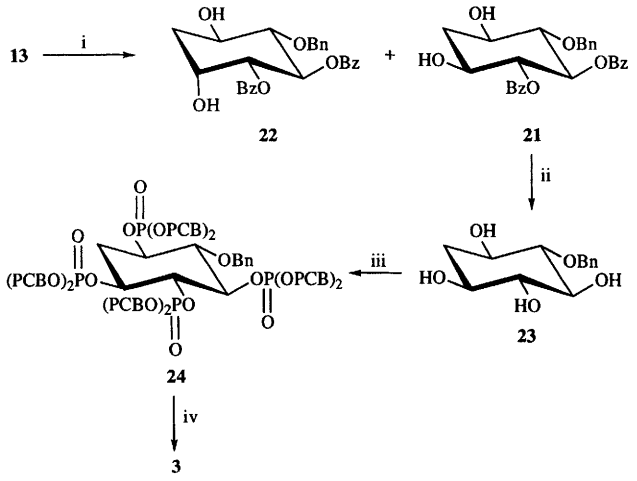
Reaction of the benzyl ether **7** with *N*-bromosuccinimide (NBS) in carbon tetrachloride[32] gave only 28% of the required bromide **8**, together with significant quantities of debenzylated products **9** and **10**, a not entirely unexpected side-reaction.[33] A more efficient route from compound **7** to bromide **8** required acidic hydrolysis to methyl 3-*O*-benzoyl-2-*O*-benzyl-α-D-glucopyranoside **11** followed by bromination with triphenylphosphine–carbon tetrabromide and conventional benzoylation.

The highly crystalline olefin **12** was readily available by iodide exchange in dimethyl sulfoxide (DMSO) at 100 °C followed by addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),[34] a superior method in this case to silver(I) fluoride–pyridine,[35] which gave only a 31% yield of compound **12** after crystallisation.

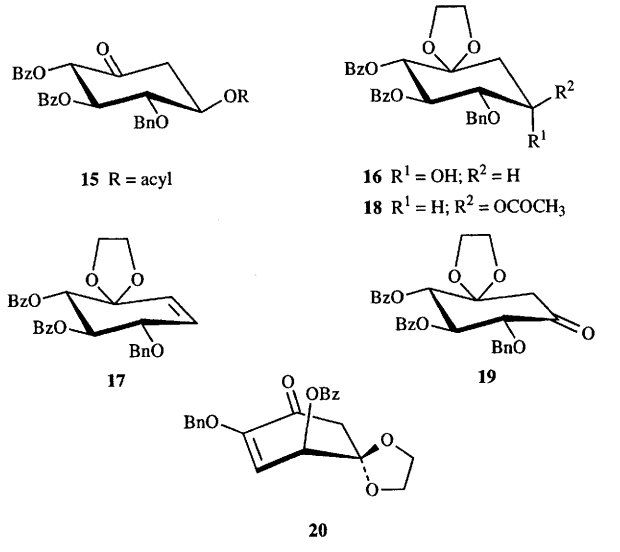
Treatment of olefin **12** with 0.1 mol equiv. of mercury(II) trifluoroacetate gave a mixture of cyclohexanones **13** and **14**, respectively, in the ratio ~1:10. The structures of products **13**, and **14** were assigned mainly on the basis of their ^1H and ^{13}C NMR spectra. The isomers were easily distinguishable by comparing the coupling constants for the newly generated axial methylene proton at position 6. In compound **13** this proton experiences a geminal (AB) coupling of 14.5 Hz, as well as a vicinal axial–axial coupling of 11.2 Hz with the position 5 methine; in epimer **14** the geminal coupling (12 Hz) is accompanied by the much smaller (vicinal) axial–equatorial coupling of 3.7 Hz. The proportion of minor product **13** in this case was considerably lower than in examples where the hydroxy groups at positions 3 and 4 of D-*xylo*-olefin precursors have been protected with ethers,[19,36] *e.g.* methyl 2,3,4-tri-*O*-benzyl-α-D-*xylo*-hex-5-enopyranoside gave 5α- and 5β-hydroxy epimers in the ratio 3:1. It is noteworthy that lower proportions of minor product (if any) have been isolated in all previous examples in which esters, rather than ethers, have been employed at both positions 3 and 4.[37] This may indicate a subtle influence of protecting groups on the stereochemical outcome of the mercury(II)-catalysed rearrangement. In the present case, the proportion of **13** could not be increased by using different mercury salts[16b] or palladium(II) chloride,[38] which had increased the amount of minor product in a previous example.[38b]

Attention now turned to inversion of stereochemistry at position 5 of compound **14**; esterification of the inverted product would provide a versatile intermediate **15** with potentially the required regiochemical protection for preparation of other chiral Ins(1,4,5)P_3 derivatives in addition to compound **3**. In an attempt to avoid competing β-elimination,[16,39] compound **14** was protected as the ethylene ketal **16**. The optimum method of Ferrier and Haines[40] provided the best yield of ketal **16**, albeit with a significant quantity of the eliminated product **17**, clearly identifiable by its olefinic protons. Mitsunobu conditions[41] failed, in keeping with previous inositol examples.[42,43] Attempted S_N2 inversions of the 5-*O*-triflate with caesium acetate in DMF,[44] or the 5-*O*-mesyl derivative with caesium acetate in refluxing toluene in the presence of crown ethers[45] provided only a 12–18% yield of the required acetate **18**, together with a 50–55% yield of olefin **17**. An oxidation–reduction approach was attempted next. Oxidation of compound **16** with oxalyl chloride and DMSO[46] provided a highly crystalline, strongly dextrorotatory product which was not, however, the required compound **19** but rather enone **20**. The ^{13}C NMR spectrum of compound **20** was particularly useful in assigning its structure: signals corresponding to only one benzoyl group were present together with signals characteristic of a ketone (δ_C 189), an ethylene ketal (methylenes at δ_C 65 and quaternary carbon at δ_C 107, an enol ether (methine at δ_C 111 and quaternary carbon at δ_C 152), a saturated methylene (δ_C 46) and a methine geminal to a benzoate (δ_C 70). Ketone **19** was eventually obtained by oxidation with acidic pyridinium chlorochromate (PCC),[47] but sodium borohydride, sodium borohydride–cerium trichloride and even the Alpine–Hydrides which furnished equatorial products in an inosose derived from D-*chiro*-inositol,[43] all gave exclusively the axial alcohol **16**. At this stage inversion attempts were not pursued further and the route was continued with the other product from the Ferrier rearrangement compound **13**.

Reduction of compound **13** with sodium borohydride in 1,4-dioxane furnished deoxyinositols **21** and **22** in a ~3:1 ratio (Scheme 2). The structures of products **21** and **22** were



Scheme 2 *Reagents and conditions:* i, $NaBH_4$, 1,4-dioxane (92%); ii, NaOH, MeOH, reflux, 90 min, (86%); iii, (*a*) $(PCBO)_2PNPr^i_2$, 1*H*-tetrazole, room temp., 30 min; (*b*) MCPBA, −78 °C to room temp., 10 min, (54%); iv, Na/liquid NH_3



established by considering the coupling constants of the deshielded methine proton vicinal to the newly created hydroxy group. In compound **22** this signal presented as a doublet of doublets having an axial–axial coupling (10 Hz) and an axial–equatorial coupling (2.8 Hz); in complex **21** this proton experiences two axial–axial couplings (each 9.8 Hz) and presented as a pseudo-triplet. The observation that, contrary to the case in compound **19**, the equatorial alcohol was the major product in this case was interesting, but not unprecedented.[36] The benzoate esters of diol **21** were cleaved using methanolic sodium hydroxide to provide L-1-*O*-benzyl-3-deoxy-*scyllo*-inositol **23**. Phosphitylation of tetraol **23** with tetrazole-activated bis(*p*-chlorobenzyl)(diisopropylamino)phosphine[48] followed by oxidation of the intermediate tetrakisphosphite with *m*-chloroperbenzoic acid (MCPBA), provided fully protected compound **24**. Deprotection using sodium in liquid ammonia[49] afforded, after purification by ion-exchange chromatography, the target tetrakisphosphate **3**, which was isolated as its triethylammonium salt. The biological characterisation of compound **3** is in progress and will be reported elsewhere.

Experimental

Materials and methods

TLC was performed on precoated plates (Merck aluminium sheets silica 60 F_{254}, Art. no. 5554). Products were visualised by being sprayed with phosphomolybdic acid in methanol followed by heating. Flash chromatography refers to the method of Still *et al.*[50] and was carried out using Sorbsil C60 silica gel.

IR spectra were recorded on a Perkin-Elmer 782 spectrophotometer as KBr discs. ^1H and ^{13}C NMR spectra were recorded on JEOL JNM GX-270 or GX-400 NMR spectrometers. Unless otherwise stated, chemical shifts were measured in ppm relative to internal tetramethylsilane. ^{31}P NMR spectra were recorded on JEOL FX-90Q or GX-400 NMR spectrometers, and ^{31}P NMR chemical shifts were measured in ppm relative to external 85% H_3PO_4. *J* Values are given in Hz. Mps (uncorrected) were determined using a Reichert-Jung Thermo Galen Kofler block. Microanalysis was carried out at the University of Bath Microanalysis Service. Mass spectra were recorded at the University of Bath Mass Spectrometry service. Optical rotations were measured at ambient temperature using an Optical Activity Ltd. AA-10 polarimeter, and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Ion-exchange chromatography was performed on an LKB-Pharmacia Medium-Pressure Ion-Exchange Chromatograph using Sepharose Q Fast Flow resin and gradients of triethylammonium hydrogen carbonate (TEAB) as eluent. Compounds containing phosphates were assayed quantitatively by the Briggs phosphate test.[51]

Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside 4

A 1 litre flask containing methyl α-D-glucopyranoside (112 g, 0.58 mmol), PTSA (2 g), benzaldehyde dimethyl acetal (91 cm^3, 0.61 mol) and DMF (500 cm^3) was fitted with an air condenser, attached to a water-pump *via* a 3-way tap and evacuated. The system was stirred at 70 °C until methanol ceased to condense (4 h). The solution was cooled and concentrated to give a waxy residue. Crystallisation from 2% (w/v) aq. $NaHCO_3$ solution (1200 cm^3) gave the title compound as fine needles (147 g, 90%), mp 167–168 °C [lit.,[23a] 167.5–168.5 °C]; $[\alpha]_D$ +92.0 (*c* 5.0, $CHCl_3$) [lit.,[23a] +105].

Methyl 3-*O*-benzoyl-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside 7

A mixture of diol **4** (129 g, 0.46 mol) and dibutyltin oxide (125 g, 0.50 mol) was heated under reflux in toluene (1500 cm^3) for 3 h with continuous azeotropic removal of water (Dean–Stark trap). The solution was cooled and the solvents were evaporated off to give a solid, to which were added acetonitrile (1200 cm^3), tetrabutylammonium bromide (100 g, 0.31 mol) and benzyl bromide (60 cm^3, 0.50 mol). This mixture was heated under reflux for 2 days *via* a Soxhlet thimble containing 4 Å molecular sieves. The solution was cooled, triethylamine (100 cm^3) was added, and the mixture was stirred for 3 h. The solvents were evaporated off and to the residue were added diethyl ether (2000 cm^3) and saturated aq. $NaHCO_3$ (700 cm^3). The mixture was vigorously stirred for 1 h and the resultant suspension was filtered through Celite. The residue was well washed with diethyl ether (250 cm^3) and the combined organic fraction was dried ($MgSO_4$), filtered, and concentrated. This crude mixture of monobenzyl ethers was dissolved in pyridine (500 cm^3) containing 4-(dimethylamino)pyridine (DMAP) (1 g). Benzoyl chloride (100 cm^3, 0.86 mol) was added dropwise at 0 °C and the system was stirred at room temperature for 3 h. Methanol (200 cm^3) was added and the mixture was stirred for a further 30 min. The solvents were evaporated off and the residue was co-evaporated with toluene (3 × 500 cm^3). The orange residue thus obtained was triturated with diethyl ether (3 × 500 cm^3) and the combined organic extracts were washed successively with 5 mol dm^{-3} HCl (2 × 250 cm^3) and water (4 × 250 cm^3), dried ($MgSO_4$), filtered and concentrated to give a pale yellow syrup. The *title compound* was obtained by fractional crystallisation from ethanol (74 g, 34%); R_f 0.57 (hexane–ethyl acetate 3:2); mp 136–137 °C (from EtOH); $[\alpha]_D$ −6.3 (*c* 4.4, $CHCl_3$) (Found: C, 70.3; H, 5.82. $C_{28}H_{28}O_7$ requires C, 70.56; H, 5.93%); δ_H($CDCl_3$; 270 MHz) 3.43 (3 H, s, OCH_3), 3.66–3.79 (3 H, m, 2- and 4-H, 6-H^{ax}), 3.97 (1 H, td, $J_{5\text{-H},6\text{-H}^{ax}}$ =

$J_{5\text{-H},4\text{-H}}$ 9, $J_{5\text{-H},6\text{-H}^{eq}}$ 4.5, 5-H), 4.30 (1 H, dd, J 4.5 and 10.5, 6-H^{eq}), 4.61 and 4.61 (2 H, AB, J_{AB} 12.7, PhCH_2), 4.75 (1 H, d, J 3.8, 1-H), 5.46 (1 H, s, 7-H), 5.85 (1 H, t, J 9, 3-H), 7.16–7.61 (13 H, m, ArH) and 8.02–8.07 (2 H, m, *o*-H of benzoyl ring); δ_C($CDCl_3$; 67.8 MHz) 55.45 (OCH_3), 62.44 (CH), 69.01 (C-6), 71.23 (CH), 72.90 (PhCH_2), 79.69 (C-2), 98.81 (C-1), 101.44 (C-7), 126.14, 127.91, 127.96, 128.10, 128.28, 128.40, 128.88 and 129.81 (arom CH), 130.26 (C-1 of benzoyl ring), 132.87 (C-4 of benzoyl ring), 137.04 and 137.64 (2 × C-1 of phenyl rings) and 165.37 (PhCO_2); m/z (CI) 477 [(M + 1)$^+$, 10%], 89 (100); ν_{max} 1730 cm^{-1}.

Methyl 3-*O*-benzoyl-2-*O*-benzyl-α-D-glucopyranoside 11

A solution of compound **7** (12.9 g, 27.2 mmol) in 80% (v/v) aq. acetic acid (100 cm^3) was heated under reflux for 1.75 h. The solution was cooled, the solvents evaporated off, and the residue was co-evaporated with toluene (3 × 60 cm^3). The residue thus obtained was extracted with ethyl acetate (3 × 100 cm^3). The combined extracts were washed with water (50 cm^3), dried ($MgSO_4$), filtered and concentrated to give the *title compound* as a solid of sufficient purity to be used for the next step (10.4 g, 98%). A sample was crystallised twice from propan-2-ol to provide an analytically pure sample; R_f 0.17 (hexane–ethyl acetate 2:3); mp 114–115 °C; [α]$_D$ +97.7 (*c* 1.1, $CHCl_3$) (Found: C, 64.6; H, 6.2. $C_{21}H_{24}O_7$ requires C, 64.92; H, 6.23%); δ_H($CDCl_3$; 270 MHz) 2.60 (1 H, t, J 5.6, exch. D_2O, 6-OH), 3.39 (3 H, s, OCH_3), 3.54 (1 H, d, J 4.6, exch. D_2O, 4-OH), 3.61 (1 H, dd, J 3.7 and 9.6, 2-H), 3.69–3.75 (2 H, m, 4- and 5-H), 3.83 (2 H, br s, 6-H_2), 4.60 and 4.60 (2 H, AB, J_{AB} 12.2, PhCH_2), 4.72 (1 H, d, J 3.7, 1-H), 5.50 (1 H, br t, J 9.3, 3-H), 7.23–7.62 (8 H, m, ArH) and 7.98–8.01 (2 H, m, 2 × *o*-H of benzoyl ring); δ_C($CDCl_3$; 67.8 MHz) 55.25 (OCH_3), 61.71 (C-6), 69.67 and 71.22 (CH), 72.77 (PhCH_2), 75.75 and 76.66 (CH), 97.73 (C-1), 127.86 and 128.33 (aromatic CH), 129.69 (C-1 of benzoyl ring), 129.82 (arom CH), 133.21 (C-4 of benzoyl ring), 137.57 (C-1 of benzyl ring) and 167.35 (PhCO_2); m/z (FAB$^-$) 387 [(M − 1)$^-$, 30%], 91 (100).

Methyl 3,4-di-*O*-benzoyl-2-*O*-benzyl-6-bromo-6-deoxy-α-D-glucopyranoside 8, methyl 3,4-di-*O*-benzoyl-6-bromo-6-deoxy-α-D-glucopyranoside 9 and methyl 3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside 10

(a). A mixture of compound **7** (2.00 g, 4.2 mmol), barium carbonate (1.2 g, 6.3 mmol; dried *in vacuo* over P_2O_5 at 75 °C for 16 h), *N*-bromosuccinimide (897 mg, 5.0 mmol; dried as for barium carbonate) and dry carbon tetrachloride (50 cm^3) was heated under reflux under nitrogen for 1 h, when TLC indicated three major products and unchanged starting material. The suspension was cooled, then filtered and the residue was well washed with methylene dichloride (100 cm^3). The combined filtrates were washed successively with 5% (w/v) aq. $Na_2S_2O_3$ (100 cm^3) and water (100 cm^3), dried ($MgSO_4$), filtered, and concentrated to give an oil, which was subjected to flash chromatography (eluent hexane–ethyl acetate 7:3) to give compound **8** (653 mg, 28%); R_f 0.69 (hexane–ethyl acetate 2:3); mp 111 °C (from EtOH); [α]$_D$ −26.0 (*c* 2.5, $CHCl_3$) (Found: C, 60.7; H, 4.8. $C_{28}H_{27}BrO_7$ requires C, 60.64; H, 4.91%); δ_H($CDCl_3$; 400 MHz) 3.43 (1 H, ABX, $^2J_{AB}$ 11.3, ^3J 7.6, 6-H), 3.51 (3 H, s, OCH_3), 3.51 (1 H, ABX, $^2J_{AB}$ 11.3, ^3J 2.7, 6-H′), 3.76 (1 H, dd, J 3.7 and 10.0, 2-H), 4.18 (1 H, ddd, J 2.4, 7.3 and 9.8, 5-H), 4.59 and 4.63 (2 H, AB, J_{AB} 12.5, PhCH_2), 4.81 (1 H, d, J 3.7, 1-H), 5.28 (1 H, t, J 9.8, 4-H), 5.94 (1 H, t, J 9.8, 3-H), 7.20–7.61 (11 H, m, ArH) and 7.89–7.93 (4 H, m, 2 × *o*-H of benzoyl rings); δ_C($CDCl_3$; 100.4 MHz) 31.71 (C-6), 55.74 (OCH_3), 69.04, 71.73 and 71.76 (CH), 73.10 (PhCH_2), 76.90 (CH), 97.91 (C-1), 128.00, 128.29 and 128.46 (arom CH), 128.77 (C-1 of benzoyl ring), 129.63 and 129.74 (aromatic CH), 129.90 (C-1 of benzoyl ring), 133.03 and 133.52 (2 × C-4 of benzoyl rings), 137.42 (C-1 of benzyl ring) and 165.53 (PhCO_2); m/z (FAB$^+$) 555 and 557 [(M + 1)$^+$, 35%], 121 (100).

Further elution gave starting material (326 mg, 16% recovery).

Further elution gave compound **9** as a pale yellow oil (310 mg, 16%); R_f 0.48 (hexane–ethyl acetate 2:3); [α]$_D$ +30.9 (*c* 1.4, $CHCl_3$) [lit.,[52] +32.8 and +34.4]; δ_H($CDCl_3$; 270 MHz) 2.48 (1 H, br s, exch. D_2O, 2-OH), 3.43–3.54 (2 H, m, 6-H_2), 3.57 (3 H, s, OCH_3), 3.91 (1 H, br dd, sharpens D_2O exch., J 3.7 and 9.7, 2-H), 4.19 (1 H, ddd, J 3.7, 9.7 and 10.6, 5-H), 4.95 (1 H, d, J 3.7, 1-H), 4.96 (1 H, t, J 9.7, 4-H), 5.36 (1 H, t, J 9.7, 3-H) and 7.26–7.95 (10 H, m, ArH); m/z FAB$^+$ 465 and 467 [(M + 1)$^+$, 5%], 105 (100).

Further elution gave compound **10** (158 mg, 10%); R_f 0.40 (hexane–ethyl acetate 2:3); mp 215–220 °C (from EtOH) [lit.,[53] 217–218 °C]; [α]$_D$ +19.5 (*c* 1.3, $CHCl_3$) [lit.,[53] +33.5].

(b). A solution of compound **11** (15.4 g, 39.7 mmol) in freshly distilled, dry tetrahydrofuran (THF) (250 cm^3) at 0 °C under nitrogen was sequentially treated with triphenylphosphine (10.9 g, 41.7 mmol) and freshly sublimed carbon tetrabromide (15.8 g, 47.6 mmol). The mixture was stirred for 1 h at 0 °C and for 16 h at room temperature, when TLC (ethyl acetate) indicated consumption of starting material (R_f 0.38) to give a product (R_f 0.73). The solvent was evaporated off and the residue was subjected to flash chromatography (eluent hexane–ethyl acetate 1:1) to remove triphenylphosphine oxide (R_f 0.30 in ethyl acetate). The crude product was dissolved in dry pyridine (150 cm^3) and stirred with DMAP (250 mg) and benzoyl chloride (5.0 cm^3, 43.1 mmol) for 2 h. Methanol (5 cm^3) was added and the mixture was stirred for 5 min. The solvents were evaporated off and the residue was co-evaporated with toluene (3 × 200 cm^3). The residue thus obtained was vigorously shaken with diethyl ether (500 cm^3) and the resulting suspension was filtered. The filtrate was washed with water (200 cm^3), dried ($MgSO_4$), filtered, and concentrated to give a pale yellow oil. Crystallisation from ethanol gave compound **8** (13.9 g, 63%).

Methyl 3,4-di-*O*-benzoyl-2-*O*-benzyl-6-deoxy-α-D-*xylo*-hex-5-enopyranoside 12

A mixture of compound **8** (20.9 g, 37.7 mmol), sodium iodide (23.2 g, 154.8 mmol; dried *in vacuo* over P_2O_5 at 75 °C for 2 h), tetrabutylammonium iodide (5.8 g, 15.7 mmol; dried as for sodium iodide) and dry DMSO (90 cm^3) was stirred at 100 °C under a stream of nitrogen for 2 h in the presence of 4 Å sieves (about 50 pieces). DBU (11.2 cm^3, 75.3 mmol) was added to the orange solution, which rapidly turned dark brown. The mixture was vigorously stirred for 2 h, then was cooled. The resultant dark brown semi-solid mass was extracted with diethyl ether (3 × 500 cm^3) and the combined extracts were washed successively with 5% (w/v) aq. $Na_2S_2O_3$ (300 cm^3) and saturated aq. KCl (500 cm^3), dried ($MgSO_4$), filtered and concentrated. The concentrate was purified by flash chromatography (hexane–ethyl acetate 4:1) to give crude hexenopyranoside **12** as a pale yellow oil; crystallisation from ethanol gave pure compound **12** (11.0 g, 62%), R_f 0.69 (hexane–ethyl acetate 2:3); mp 102–104 °C; [α]$_D$ −32 (*c* 1.0, $CHCl_3$) (Found: C, 70.8; H, 5.45. $C_{28}H_{26}O_7$ requires C, 70.86; H, 5.53%); δ_H($CDCl_3$; 270 MHz) 3.51 (3 H, s, OCH_3), 3.88 (1 H, dd, J 3.3 and 9.9, 2-H), 4.62 (1 H, t, $^4J_{4\text{-H},6\text{-H}} = {}^2J_{6\text{-H},6\text{-H}'} = 2.0$, 6-H), 4.64 and 4.66 (2 H, AB, J_{AB} 12.6, PhCH_2), 4.79 (1 H, t, $^4J_{4\text{-H},6\text{-H}'} = {}^2J_{6\text{-H},6\text{-H}'} = 2.0$, 6-H′), 4.85 (1 H, d, J 3.3, 1-H), 5.77 (1 H, dt, ^3J 9.7, ^4J 2.0, 4-H), 5.96 (1 H, t, J 9.7, 3-H), 7.20–7.54 (11 H, m, ArH) and 7.93–8.03 (4 H, m, *o*-H of benzoyl rings); δ_C($CDCl_3$; 67.8 MHz) 55.71 (OCH_3), 70.21 and 71.47 (CH), 73.08 (PhCH_2), 76.53 (CH), 97.34 (C-6), 98.86 (C-1), 127.94, 127.99, 128.26 and 128.41 (arom CH), 128.96 and 129.66 (2 × C-1 of benzoyl rings), 129.71 and 129.90 (arom CH), 132.96 and 133.37 (2 × C-4 of benzoyl rings), 137.46 (C-1 of benzyl ring), 150.30 (C-5) and 165.32 and 165.35 (2 × PhCO_2); m/z (FAB$^+$) 475 [(M + 1)$^+$, 5%], 105 (100); ν_{max}/cm^{-1} 1730 and 1670.

(2*S*,3*R*,4*S*,5*R*)-2,3-Dibenzoyloxy-4-benzyloxy-5-hydroxycyclohexanone 13 and (2*S*,3*R*,4*S*,5*S*)-2,3-dibenzoyloxy-4-benzyloxy-5-hydroxycyclohexanone 14

A solution of compound **12** (14.5 g, 30.6 mmol) in acetone–water (5:2) containing 1% acetic acid (300 cm^3) was stirred with mercury(II) trifluoroacetate (1.3 g, 3.1 mmol) for 30 h. The acetone was evaporated off and the residual gum was extracted with chloroform (3 × 200 cm^3). The combined organic extracts were washed successively with water (200 cm^3) and saturated aq. NaCl (200 cm^3), dried ($MgSO_4$), filtered and concentrated. The pale yellow oil thus obtained was subjected to flash chromatography (eluent hexane–ethyl acetate 7:3) to give compound **13** as a pale yellow oil (1.1 g, 8%); R_f 0.47 (ethyl acetate–hexane 3:2); $[\alpha]_D$ −33 (*c* 1.4, $CHCl_3$); δ_H($CDCl_3$; 270 MHz) 2.50–3.50 (1 H, br s, exch. D_2O, OH), 2.76 (1 H, ABX, $^2J_{AB}$ 14.5, $^3J_{5\text{-H},6\text{-H}^{ax}}$ 11.2, 6-H^{ax}), 2.96 (1 H, ABX, $^2J_{AB}$ 14.5, $^3J_{5\text{-H},6\text{-H}^{eq}}$ 5.2, 6-H^{eq}), 3.92–4.10 (2 H, m, 4- and 5-H), 4.74 and 4.85 (2 H, AB, J_{AB} 11.2, PhCH_2O), 5.71–5.80 (2 H, m, 2- and 3-H), 7.21–7.54 (11 H, m, ArH) and 7.97–8.03 (4 H, m, *o*-H of benzoyl rings); δ_C($CDCl_3$; 67.8 MHz) 43.96 (C-6), 68.16 and 71.96 (2 × CH), 75.33 (Ph*C*H_2), 77.58 and 83.05 (2 × CH), 128.11, 128.38, 128.44, 128.57 and 128.62 (arom CH), 129.10 (C-1 of benzoyl ring[s]), 129.75 and 130.00 (aromatic CH), 133.52 and 133.85 (2 × C-4 of benzoyl rings), 137.27 (C-1 of benzyl ring), 165.31 and 165.49 (2 × Ph*C*O_2) and 196.67 (C-1); *m*/*z* (FAB^+) 461 [(M + 1)$^+$, 5%], 105 (100).

Further elution gave *isomer* **14** (10.0 g, 71%); R_f 0.42 (ethyl acetate–hexane 3:2); mp 149–150 °C (from EtOH); $[\alpha]_D$ −61.5 (*c* 4.1, $CHCl_3$) (Found: C, 70.2; H, 5.2. $C_{27}H_{24}O_7$ requires C, 70.41; H, 5.26%); δ_H($CDCl_3$; 270 MHz) 2.68 (1 H, ABX, $^2J_{AB}$ 12, $^3J_{5\text{-H},6\text{-H}^{ax}}$ 3.7, 6-H^{ax}), 2.86 (1 H, ABX, $^2J_{AB}$ 12, $^3J_{5\text{-H},6\text{-H}^{eq}}$ 3.7, 6-H^{eq}), 3.17 (1 H, br s, exch. D_2O, OH), 4.09 (1 H, dd, *J* 2.5 and 10, 4-H), 4.45 (1 H, br m, 5-H), 4.60 and 4.74 (2 H, AB, J_{AB} 12, PhCH_2O), 5.67 (1 H, d, *J* 10, 2-H), 6.12 (1 H, t, *J* 10, 3-H), 7.15–7.58 (11 H, m, ArH) and 7.95–8.05 (4 H, m, *o*-H of benzoyl rings); δ_C($CDCl_3$; 67.8 MHz) 42.38 (C-6), 58.27, 65.81 and 71.75 (3 × CH), 72.39 (Ph*C*H_2), 79.06 (C-4), 127.94, 128.10, 128.30, 128.35 and 128.46 (arom CH), 128.75 and 129.37 (2 × C-1 of benzoyl rings), 129.71 and 129.95 (arom CH), 133.21 and 133.31 (2 × C-4 of benzoyl rings), 136.76 (C-1 of benzyl ring), 165.27 and 165.53 (2 × Ph*C*O_2) and 197.46 (C-1); *m*/*z* (FAB^+) 461 [(M + 1)$^+$, 20%], 105 (100).

(4*S*,5*R*,6*S*)-5,6-Dibenzoyloxy-4-benzyloxycyclohex-2-enone ethylene ketal 17 and (2*S*,3*R*,4*S*,5*S*)-2,3-dibenzoyloxy-4-benzyloxy-5-hydroxycyclohexanone ethylene ketal 16

A mixture of ketone **14** (5.2 g, 11.3 mmol), ethylene glycol (7.5 cm^3), 1,4-dioxane (50 cm^3), toluene (75 cm^3) and conc. H_2SO_4 (0.5 cm^3) was heated under reflux for 3.5 h with continuous azeotropic removal of water (Dean–Stark trap). TLC (ethyl acetate) indicated consumption of starting material (R_f 0.62) to give two products (R_f 0.79 and 0.48). Pyridine (2 cm^3) was added, the solution was cooled, and the solvents were evaporated off. The dark brown residue thus obtained was extracted with diethyl ether (250 cm^3) and the organic solution was washed successively with 5 mol dm^{-3} HCl (150 cm^3) and water (2 × 150 cm^3), dried ($MgSO_4$), filtered, and concentrated to give a pale yellow oil. Flash chromatography (eluent hexane–ethyl acetate 1:1) gave *enone ketal* **17** (1.8 g, 33%), mp 125–127 °C (from EtOH); $[\alpha]_D$ +14.8 (*c* 1.6, $CHCl_3$) (Found: C, 71.8; H, 5.4. $C_{29}H_{26}O_7$ requires C, 71.58; H, 5.39%); δ_H($CDCl_3$; 400 MHz) 3.89–4.12 (4 H, m, OCH_2CH_2O), 4.45 (1 H, dt, *J* 8.3 and 1.5, 4-H), 4.57 and 4.69 (2 H, AB, J_{AB} 11.9, PhCH_2O), 5.63 (1 H, d, *J* 11.2, 6-H), 5.75 (1 H, dd, $^4J_{4\text{-H},2\text{-H}}$ 1.5, $^3J_{3\text{-H},2\text{-H}}$ 10.3, 2-H), 5.97–6.01 (2 H, m, 3- and 5-H), 7.19–7.46 (11 H, m, ArH) and 7.86–7.96 (4 H, m, *o*-H of benzoyl rings); δ_C($CDCl_3$; 67.8 MHz) 66.15 and 66.51 (OCH_2CH_2O), 70.84 (Ph*C*H_2O), 72.75, 72.85 and 76.56 (C-4, -5 and -6), 106.02 (C-1), 127.73, 127.89, 128.18, 128.35 and 128.98 (C-2, -3 and arom CH), 129.24 (C-1 of benzoyl ring[s]), 129.69 and 129.77 (aromatic CH), 132.92 and 133.63 (2 × C-4 of benzoyl rings), 137.67 (C-1 of benzyl ring) and 165.60 (Ph*C*O_2); *m*/*z* (FAB^+) 487 [(M + 1)$^+$, 5%], 105 (100).

Further elution gave the *ketal* **16** (3.1 g, 54%), mp 129–131 °C (from EtOH); $[\alpha]_D$ −57.4 (*c* 0.6, $CHCl_3$) (Found: C, 68.7; H, 5.8. $C_{29}H_{28}O_8$ requires C, 69.02; H, 5.60%); δ_H($CDCl_3$; 270 MHz) 1.96 (1 H, ABX, $^2J_{AB}$ 15, ^3J 3.3, 6-H^{ax}), 2.25 (1 H, ABX, $^2J_{AB}$ 15, ^3J 3.8, 6-H^{eq}), 3.24 (1 H, d, *J* 6.6, exch. D_2O, OH), 3.71 (1 H, dd, *J* 3.3 and 9.5, 4-H), 3.80–3.92 (2 H, m, O*C*H_2CH_2O), 4.06–4.16 (2 H, m, OCH_2CH_2O), 4.21 (1 H, br m, 5-H), 4.60 and 4.71 (2 H, AB, J_{AB} 12, PhCH_2O), 5.48 (1 H, d, *J* 9.5, 2-H), 6.01 (1 H, t, *J* 9.5, 3-H), 7.16–7.52 (11 H, m, ArH) and 7.88–7.97 (4 H, m, *o*-H of benzoyl rings); δ_C($CDCl_3$; 67.8 MHz) 36.63 (C-6), 65.40 (O*C*H_2CH_2O), 65.55 (CH), 66.72 (OCH_2*C*H_2O), 70.98 (CH), 71.88 (Ph*C*H_2O), 73.85 and 78.93 (2 × CH), 108.27 (C-1), 127.79 (C-1 of benzoyl ring), 127.83, 128.18, 128.30 and 128.35 (arom CH), 129.19 (C-1 of benzoyl ring[s]), 129.66 and 129.72 (arom CH), 132.87 and 133.16 (2 × C-4 of benzoyl rings), 137.31 (C-1 of benzyl ring) and 165.42 and 165.48 (2 × Ph*C*O_2); *m*/*z* (FAB^+) 505 [(M + 1)$^+$, 10%], 105 (100).

(2*S*,3*R*,4*S*,5*R*)-5-Acetoxy-2,3-dibenzoyloxy-4-benzyloxycyclohexanone ethylene ketal 18

(a) By inversion of triflate. To a solution of alcohol **16** (84 mg, 0.2 mmol) in dry methylene dichloride–dry pyridine (5:1; 3 cm^3) at −78 °C under nitrogen was added triflic anhydride (0.03 cm^3) dropwise. The solution was allowed to warm to room temperature and was stirred for 30 min, when TLC (ethyl acetate–hexane 3:2) indicated consumption of starting material (R_f 0.16) to give a product (R_f 0.56). The solvents were evaporated off. To the orange residue were added caesium acetate (200 mg, 1 mmol; dried *in vacuo* over P_2O_5 at 60 °C for 24 h) and dry DMF (3 cm^3). This mixture was stirred at room temperature for 3 h, when TLC (Et_2O) indicated presence of a major product (R_f 0.60) and a minor product (R_f 0.53). The solvent was evaporated off and the orange residue was extracted with ethyl acetate (50 cm^3). The organic extract was washed successively with saturated aq. NaCl (30 cm^3) and water (30 cm^3), dried ($MgSO_4$), filtered and concentrated. Flash chromatography (eluent hexane–ethyl acetate 7:3) gave enone ketal **17** (43 mg, 53%).

Further elution gave *acetate* **18** (11 mg, 12%), mp 217–222 °C (from ethyl acetate–hexane); $[\alpha]_D$ −32.2 (*c* 2.1, $CHCl_3$) (Found: C, 68.2; H, 5.4. $C_{31}H_{30}O_9$ requires C, 68.11; H, 5.54%); δ_H($CDCl_3$; 270 MHz) 1.84 (1 H, t, ^2J = ^3J = 12.5, 6-H^{ax}), 2.01 (3 H, s, $COCH_3$), 2.30 (1 H, dd, ^2J 12.5, ^3J 5.1, 6-H^{eq}), 3.82–3.92 (3 H, m, O*C*H_2CH_2O and 4-H), 4.07–4.12 (2 H, m, OCH_2CH_2O), 4.63 and 4.63 (2 H, AB, J_{AB} 11.6, PhCH_2O), 5.23 (1 H, ddd, *J* 12.5, 11.4 and 5.1, 5-H), 5.55 (1 H, d, *J* 10, 2-H), 5.81 (1 H, t, *J* 10, 3-H), 7.10–7.56 (11 H, m, ArH) and 7.86–8.04 (4 H, m, *o*-H of benzoyl rings); δ_C($CDCl_3$; 100 MHz) 21.03 (CH_3CO_2), 37.03 (C-6), 65.84 and 66.53 (OCH_2CH_2O), 71.14, 72.62 and 74.05 (C-2, -3 and -5), 74.56 (Ph*C*H_2O), 80.82 (C-4), 106.07 (C-1), 127.63, 127.87, 128.22, 128.25, 128.40, 129.17 and 129.55 (arom CH), 129.66 and 129.77 (2 × C-1 of benzoyl rings), 132.97 and 133.23 (2 × C-4 of benzoyl rings), 137.71 (C-1 of benzyl ring), 165.36 and 165.58 (2 × Ph*C*O_2) and 169.84 (CH_3CO_2); *m*/*z* (FAB^+) 547 [(M + 1)$^+$, 15%], 105 (100).

(b) By inversion of mesyl ester. A solution of compound **16** (848 mg, 1.7 mmol) in dry methylene dichloride–dry pyridine (2:1; 9 cm^3) was treated with mesyl chloride (0.15 cm^3, 1.9 mmol) at room temperature for 5 h, when TLC (ethyl acetate–hexane 3:2) indicated conversion of starting material into a product (R_f 0.58). The solvents were evaporated off and the residue was co-evaporated with toluene (3 × 50 cm^3). The residue was dissolved in ethyl acetate (150 cm^3) and this solution was washed with water (50 cm^3) to remove salts, then was dried ($MgSO_4$), filtered and evaporated to give a pale yellow solid. Dry toluene (40 cm^3), caesium acetate (3.2 g) and

18-crown-6 (444 mg, 1.7 mmol) were added and this mixture was heated under reflux for 4 days. Purification and flash chromatography as in method (a) gave compounds **17** (441 mg, 54%) and **18** (167 mg, 18%).

(6*S*)-6-Benzoyloxy-4-benzyloxycyclohex-4-ene-1,3-dione 1-ethylene ketal 20

Oxalyl chloride (1.7 cm^3 of a 2 mol dm^{-3} solution in methylene dichloride, 3.4 mmol) was added to a 100 cm^3 three-necked flask at −50 to −60 °C [CO_2(s)–$CHCl_3$-bath] under nitrogen. Dry DMSO (0.44 cm^3, 6.2 mmol) was added dropwise over a period of 5 min. After 5 min, a solution of alcohol **16** (1.6 g, 3.1 mmol) in dry methylene dichloride was added dropwise. The system was stirred at −50 to −60 °C for 20 min, when triethylamine (1.7 cm^3, 12.5 mmol) was added dropwise. The mixture was allowed to warm to room temperature over a period of 20 min, then the solvents were evaporated off. The residue was extracted with methylene dichloride (150 cm^3) and the organic extract was washed with water (150 cm^3), dried ($MgSO_4$), filtered and concentrated. The yellow oil thus obtained was purified by flash chromatography (eluent hexane–ethyl acetate 7:3) to give the *title compound* **20** (1.2 g, 99%), which was crystallised as fine needles from EtOH; R_f 0.59 (ethyl acetate–hexane 3:2); mp 96–97 °C; $[\alpha]_D$ +125.3 (*c* 2.2, $CHCl_3$) (Found: C, 69.4; H, 5.3. $C_{22}H_{20}O_6$ requires C, 69.45; H, 5.30%); δ_H($CDCl_3$; 400 MHz) 2.81 (1 H, ABX, $^2J_{AB}$ 16.1, ^4J 1.0, 2-H), 3.19 (1 H, AB, $^2J_{AB}$ 16.1, 2-H), 3.96–4.11 (4 H, m, OCH_2-CH_2O), 4.87 (2 H, s, PhCH_2O), 5.84 (1 H, ABX, $^3J_{AB}$ 5.4, ^4J 1.0, 6-H), 5.90 (1 H, AB, $^3J_{AB}$ 5.4, 5-H), 7.26–7.62 (8 H, m, ArH) and 8.01–8.06 (2 H, m, *o*-H of benzoyl ring); δ_C($CDCl_3$; 100 MHz) 46.05 (C-2), 65.73 and 65.82 (OCH_2CH_2O), 69.95 (C-6), 70.21 (PhCH_2O), 107.13 (C-1), 110.99 (C-5), 127.63, 128.24, 128.35, 128.55, 128.62 and 128.80 (arom CH), 129.55 (C-1 of benzoyl ring), 129.70 (arom CH), 133.47 (C-4 of benzoyl ring), 135.24 (C-1 of benzyl ring), 152.50 (C-4), 165.78 (PhCO_2) and 189.85 (C-3); *m*/*z* (FAB^+) 381 [$(M + 1)^+$, 10%], 91 (100).

(4*S*,5*R*,6*R*)-4,5-Dibenzoyloxy-6-benzyloxycyclohexane-1,3-dione 3-ethylene ketal 19

A mixture of alcohol **16** (1.0 g, 2.0 mmol), PCC (5.0 g, 23.2 mmol), powdered molecular sieves and dry methylene dichloride (15 cm^3) was stirred at room temperature for 6 h, when TLC (ethyl acetate) indicated conversion of starting material (R_f 0.2) into a product (R_f 0.67). Diethyl ether (250 cm^3) was added to the dark brown suspension and the mixture was filtered through Celite. The filtrate was washed successively with water (200 cm^3) and saturated aq. NaCl (200 cm^3), dried ($MgSO_4$), filtered and concentrated. Crystallisation from ethanol gave the *title compound* **19** (526 mg) and further quantities (total 620 mg, 62%) were isolated by flash chromatography of the mother liquors (eluent hexane–ethyl acetate 1:1); mp 185–187 °C; $[\alpha]_D$ −34.0 (*c* 1.9, $CHCl_3$) (Found: C, 69.1; H, 5.2. $C_{29}H_{26}O_8$ requires C, 69.30; H, 5.22%); δ_H($CDCl_3$; 40 MHz) 2.77 and 2.95 (2 H, AB, J_{AB} 14.5, 2-H_2), 3.84–3.94 (2 H, m, OCH_2CH_2O), 4.03–4.12 (2 H, m, OCH_2CH_2O), 4.31 (1 H, m, 6-H), 4.55 (1 H, d, *J* 12.2, PhC*H*HO), 4.93 (1 H, d, *J* 12.7, PhCH*H*O), 5.88–5.90 (2 H, m, 4- and 5-H), 7.08–7.52 (11 H, m, ArH) and 7.87–7.96 (4 H, m, *o*-H of benzoyl rings); δ_C 48.10 (C-2), 66.22 and 66.48 (OCH_2CH_2O), 71.50 (CH), 72.65 (PhCH_2O), 73.85 (CH), 81.98 (C-6), 105.77 (C-3), 127.79, 128.00, 128.22 and 128.43 (arom CH), 128.86 and 129.27 (2 × C-1 of benzoyl rings), 129.74, 133.06 and 133.36 (2 × C-4 of benzoyl rings), 136.86 (C-1 of benzyl rings), 165.13 and 165.34 (2 × PhCO_2) and 199.69 (C-1); *m*/*z*: (FAB^+) 503 [$(M + 1)^+$, 90%], 105 (100).

Reduction of ketone 19 with (*R*)-alpine hydride

To a solution of ketone **19** (150 mg, 0.3 mmol) in THF (5 cm^3) at −78 °C was added (*R*)-alpine hydride (1.2 cm^3 of a 0.5 mol dm^{-3} solution in THF, 0.6 mmol) and the system was kept at −78 °C for 1 h. After dropwise addition of 1 mol dm^{-3} HCl (0.5 cm^3), the mixture was evaporated to dryness. The residue was extracted with chloroform (50 cm^3) and the organic extract was washed with water (50 cm^3), dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (eluent hexane–ethyl acetate 2:3) gave exclusively alcohol **16** (129 mg, 88%), mp and mixed mp 128–130 °C.

D-1,6-Di-*O*-benzoyl-5-*O*-benzyl-3-deoxy-*myo*-inositol 22 and L-1,2-di-*O*-benzoyl-3-*O*-benzyl-5-deoxy-*scyllo*-inositol 21

To a solution of compound **13** (533 mg, 1.2 mmol) in 1,4-dioxane (15 cm^3) was added sodium borohydride (132 mg, 3.5 mmol). This mixture was stirred at room temperature for 1 h, when TLC (ethyl acetate) indicated consumption of starting material (R_f 0.65) to give a minor product (R_f 0.52) and a major product (R_f 0.44). After dropwise addition of 1 mol dm^{-3} HCl (0.5 cm^3), the system was evaporated to dryness. The residue was extracted with chloroform (2 × 50 cm^3) and the combined organic extracts were washed with water (50 cm^3), dried ($MgSO_4$), filtered and concentrated. The residue was subjected to flash chromatography (eluent hexane–ethyl acetate 1:1) to give compound **22** as a waxy solid (115 mg, 22%); $[\alpha]_H$ −61.1 (*c* 2.0, $CHCl_3$); δ_H($CDCl_3$; 400 MHz) 1.69 (1 H, ddd, ^2J 14.0, ^3J 11.9 and 2.4, 3-H^{ax}), 2.34 (1 H, dt, ^2J 14.0, ^3J 4.3, 3-H^{eq}), 2.43 and 2.53 (2 H, 2 br s, exch. D_2O, 2 × OH), 3.62 (1 H, t, *J* 9.5, 5-H), 4.24 (1 H, ddd, *J* 4.9, 9.2 and 11.9, 4-H), 4.36 (1 H, br m, 2-H), 4.66 and 4.75 (2 H, AB, J_{AB} 11.3, PhCH_2O), 5.26 (1 H, dd, *J* 2.8 and 10.1, 1-H), 5.99 (1 H, t, *J* 9.8, 6-H), 7.16–7.50 (11 H, m, ArH), and 7.91–8.07 (4 H, m, *o*-H of benzoyl rings); *m*/*z* (FAB^+) 463 [$(M + 1)^+$, 80%], 57 (100).

Further elution gave compound **21** (376 mg, 70%), mp 82–87 °C (from ethyl acetate–hexane); $[\alpha]_D$ −65.0 (*c* 1.4, $CHCl_3$) (Found: C, 70.1; H, 5.7. $C_{27}H_{26}O_7$ requires C, 70.10; H, 5.67%); δ_H($CDCl_3$; 400 MHz) 1.65 (1 H, q, ^2J = ^3J = 11.9, 5-H^{ax}), 2.34 (1 H, dt, ^2J 12.8, ^3J 4.6, 5-H^{eq}), 2.51 and 2.60 (2 H, 2 br s, exch. D_2O, 2 × OH), 3.58 (1 H, t, *J* 9.3, 3-H), 3.71 (1 H, br m, simplifies to ddd on D_2O exch., *J* 4.6, 9.2 and 11.6, 4-H), 3.85 (1 H, br m, simplifies to ddd on D_2O exch., *J* 4.6, 9.5 and 11.8, 6-H), 4.53 and 4.64 (2 H, AB, J_{AB} 11.2, PhCH_2O), 5.25 (1 H, t, *J* 9.8, 1-H), 5.47 (1 H, t, *J* 9.8, 2-H), 7.06–7.43 (11 H, m, ArH) and 7.82–7.87 (4 H, m, *o*-H of benzoyl rings); δ_C($CDCl_3$; 100 MHz) 36.66 (C-5), 68.15, 68.44 and 72.94 (3 × CH), 75.19 (PhCH_2), 77.55 and 83.77 (2 × CH), 128.02, 128.33, 128.39 and 128.54 (arom CH), 128.99 and 129.29 (2 × C-1 of benzoyl rings), 129.62 and 129.82 (arom CH), 133.22 and 133.33 (2 × C-4) of benzoyl rings), 137.50 (C-1 of benzyl ring) and 165.66 and 166.96 (2 × PhCO_2); *m*/*z* (FAB^+) 463 [$(M + 1)^+$, 30%], 91 (100).

L-1-*O*-Benzyl-3-deoxy-*scyllo*-inositol 23

To a solution of compound **21** (370 mg, 0.8 mmol) in methanol (25 cm^3) was added sodium hydroxide (128 mg, 3.2 mmol) and this mixture was heated under reflux for 90 min when TLC (ethyl acetate–MeOH 4:1) indicated conversion of starting material (R_f 0.82) into a product (R_f 0.43). The solution was cooled and concentrated. The residue was purified by flash chromatography (eluent ethyl acetate–MeOH 9:1) to give the title compound **23** as a solid (174 mg, 86%), mp 119–121 °C; $[\alpha]_D$ −3.3 (*c* 1.2, $CHCl_3$); δ_H(D_2O; ref. int. D_2O; 400 MHz) 1.47 (1 H, q, ^2J = $^3J_{3\text{-}H^{ax},2\text{-}H}$ = $^3J_{3\text{-}H^{ax},4\text{-}H}$ = 12.2, 3-H^{ax}), 2.17 (1 H, dt, ^2J 12.2, ^3J 4.6, 3-H^{eq}), 3.22–3.34 (3 H, m, 1-, 5- and 6-H), 3.50 (1 H, ddd, *J* 4.6, 9.7 and 12.2, 2- or 4-H), 3.63 (1 H, br m, 4- or 2-H), 4.82 (2 H, s, PhCH_2O), 7.35–7.65 (5 H, m, ArH); δ_C(D_2O; 67.8 MHz) 35.66 (C-3), 67.07, 67.14 and 72.63 (inositol CH), 73.70 (PhCH_2O), 75.68 and 84.02 (inositol CH), 127.14, 127.47, 127.64 and 128.31 (arom CH) and 136.43 (C-1 of benzyl ring); *m*/*z* (FAB^+) 255 [$(M + 1)^+$, 10%], 73 (100); (FAB^-) 253 [$(M - 1)^-$, 30%] and 407 [$(M + NBA)^-$, 30%], 188 (100).

L-1-*O*-Benzyl-3-deoxy-2,4,5,6-tetrakis[bis(*p*-chlorobenzyl)-phospho]-*scyllo*-inositol 24

A mixture of 1*H*-tetrazole (139 mg, 1.98 mmol), dry methylene dichloride (5 cm^3) and bis(*p*-chlorobenzyloxy)diisopropylamino)phosphine[48] [$(PCBO)_2PNPr^i_2$] (546 mg, 1.32 mmol) was stirred at room temperature for 20 min, whereupon the tetraol **23** (42 mg, 0.17 mmol) was added and the mixture was stirred for a further 30 min. TLC (ethyl acetate) indicated conversion of starting material (R_f 0.04) into a product (R_f 0.71–0.83). The mixture was cooled to −78 °C and MCPBA (900 mg) was added. The solution was allowed to warm to room temperature and after 10 min TLC (ethyl acetate–hexane 3:2) showed a new product (R_f 0.10). The solution was extracted with diethyl ether (100 cm^3) and the organic extract was washed successively with 10% (w/v) aq. $Na_2S_2O_3$, 1 mol dm^{-3} HCl, saturated aq. $NaHCO_3$ and saturated aq. NaCl (each 50 cm^3). The organic solution was dried ($MgSO_4$), filtered, and concentrated. Purification of the residue by flash chromatography (eluent hexane–ethyl acetate 7:3, then 1:1) gave the *title compound* **24** as a waxy solid (140 mg, 54%); $[\alpha]_D$ −4.5 (*c* 5.3, $CHCl_3$) (Found: C, 52.9; H, 3.95. $C_{69}H_{62}Cl_8O_{17}P_4$ requires C, 52.87; H, 3.99%); δ_H($CDCl_3$: 400 MHz) 1.81 (1 H, q, $^2J = {}^3J = 11.9$, 3-H^{ax}), 2.88 (1 H, ddd, ^2J 11.9, ^3J 4.6 and 4.8, 3-H^{eq}), 3.61 (1 H, t, *J* 8.9, 1-H), 4.29–4.61 (4 H, m, 2-, 4-, 5- and 6-H), 4.70–5.01 (18 H, m, 9 × ArCH_2O AB systems) and 6.85–7.30 (37 H, m, ArH); δ_C($CDCl_3$; 100 MHz) 34.77 (C-3), 69.45, 69.50, 69.54, 69.58, 69.63, 69.70, 69.76 and 69.85 (8 × ArCH_2O), 73.40 and 75.10 (2 × CH), 75.41 (PhCH_2O), 78.10, 79.73 and 81.94 (3 × CH), 127.15, 127.73, 128.39, 129.12, 129.45, 129.52, 129.60, 129.69, 129.76, 129.94, 129.98, 130.02, 130.07, 130.16 and 130.16 (arom CH), 134.53, 134.61, 134.66, 134.74, 137.77, 134.86, 134.90, 134.94, 135.19, 135.27, 135.34, 135.39, 135.50, 135.54 and 135.63 (C-1 and -4 of 8 × *p*-chlorobenzylphospho rings) and 138.50 (C-1 of benzyl ring); δ_P($CDCl_3$; 162 MHz) −2.25, −1.78, −1.73 and −1.70 (4 s); *m*/*z* (FAB^+) 1567 (20%), 1569 (50%), 1571 (68%), 1573 (45%), 1575 (18%) and 1577 (6%) [all $(M + 1)^+$], 125 (100).

D-2-Deoxy-*myo*-inositol 1,3,4,5-tetrakisphosphate 3

Ammonia was condensed into a three-necked flask at −78 °C. An excess of sodium was added to dry the ammonia, a quantity (~30 cm^3) of which was then distilled into a second three-necked flask and kept at −78 °C. Sodium was added until the solution remained blue–black for 10 min. A solution of compound **24** (71 mg, 45 μmol) in dry 1,4-dioxane (1.5 cm^3) was added and the mixture was stirred for 2 min. The reaction was quenched with methanol (1 cm^3), followed by water (1 cm^3). The solvents were evaporated off and the residue was dissolved in de-ionised water (400 cm^3) and purified by ion-exchange chromatography on Q Sepharose Fast Flow, with a gradient of triethylammonium hydrogen carbonate (TEAB) buffer (0–1 mol dm^{-3}), pH 9.0 as eluent. The triethylammonium salt of the title compound eluted between 250–280 mmol dm^{-3} buffer; $[\alpha]_D$ 0.0 (*c* 0.3, calc. for free acid, TEAB, pH 7.5); δ_H(D_2O; pH ~6; 400 MHz) 1.55 (1 H, q, $^2J = {}^3J = 11.6$, 2-H^{ax}), 2.37 (1 H, br m, 2-H^{eq}), 3.44 (1 H, t, *J* 9.2, 6-H) and 3.84–3.95 (4 H, m, 1-, 3-, 4- and 5-H); δ_P(D_2O; pH ~6; 400 MHz) (^{1}H-coupled) −0.27 (d, J_{HP} 7.7), 0.05 (d, J_{HP} 8.2), 0.72 (d, J_{HP} 8.2) and 0.83 (d, J_{HP} 9.0); *m*/*z* (FAB^-) 483 [$(M - 1)^-$, 100%] (Found: M^-, 482.926. $C_6H_{16}O_{17}P_4$ [$M - H$]$^-$ requires *m*/*z*, 482.926).

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