Total synthesis, from D-xylose, of chiral, ring-contracted 1D-*myo*-inositol 1,4,5-trisphosphate and 1,3,4,5-tetrakisphosphate analogues with C-2 excised

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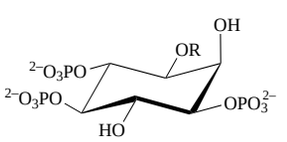
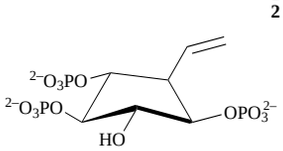
A route to chiral, cyclopentane-based congeners of the second messenger 1D-*myo*-inositol 1,4,5-trisphosphate and its enigmatic metabolite 1D-*myo*-inositol 1,3,4,5-tetrakisphosphate, starting from D-xylose, is described. Reaction of allyl α-D-xylopyranoside 7 with 2,2,3,3-tetramethoxybutane gave a 1 : 1 mixture of the 2,3- and 3,4-butanediacetal-protected derivatives 8 and 9. The latter was converted in four steps into 2-*O*-benzyl-3,4-bis-*O*-(*p*-methoxybenzyl)-D-xylopyranose 15, which on reduction with sodium borohydride gave 2-*O*-benzyl-3,4-bis-*O*-(*p*-methoxybenzyl)-D-xylitol 16. Swern oxidation followed by samarium(II) iodide-mediated pinacol coupling gave a 1 : 3 mixture of 1L-1,2,3,4/5-1-benzyloxy-2,3-dihydroxy-4,5-bis-(*p*-methoxybenzyloxy)cyclopentane 18 and 1L-1,2,4/3,5-3-benzyloxy-1,2-dihydroxy-4,5-bis-(*p*-methoxybenzyloxy)cyclopentane 19. The identity of the latter was confirmed by conversion into known compounds, and further elaboration gave the target compounds, 1D-1,2,4/3,5-cyclopentanepentaol 1,3,4-trisphosphate 5 and 1D-1,2,4/3,5-cyclopentanepentaol-1,2,3,4-tetrakisphosphate 6.

Introduction

1D-*myo*-Inositol 1,4,5-trisphosphate [Ins(1,4,5)P_3, **1**] is a second messenger responsible for increasing the intracellular Ca^{2+} concentration in stimulated cells. This results from its interaction with a tetrameric receptor situated in the lipid bilayer of the endoplasmic reticulum,[1] and various subtypes of the receptor have been reported.[2] Ins(1,4,5)P_3 is metabolised by two pathways: hydrolysis of the phosphate at position 5 by a low-affinity, high-capacity Ins(1,4,5)P_3 5-phosphatase giving Ins(1,4)P_2; or phosphorylation at position 3 by a high-affinity, low-capacity Ins(1,4,5)P_3 3-kinase giving Ins(1,3,4,5)P_4 **2**. The role of the latter has been controversial since its discovery in 1985,[3] and the recent isolation[4] and characterisation[5] of a highly selective Ins(1,3,4,5)P_4-binding protein, named GAP1^{IP4BP}, has stimulated renewed interest in this tetrakisphosphate.



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



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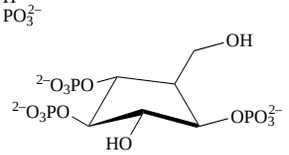

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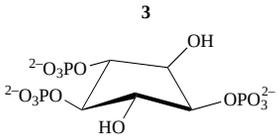

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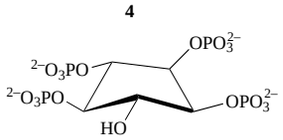

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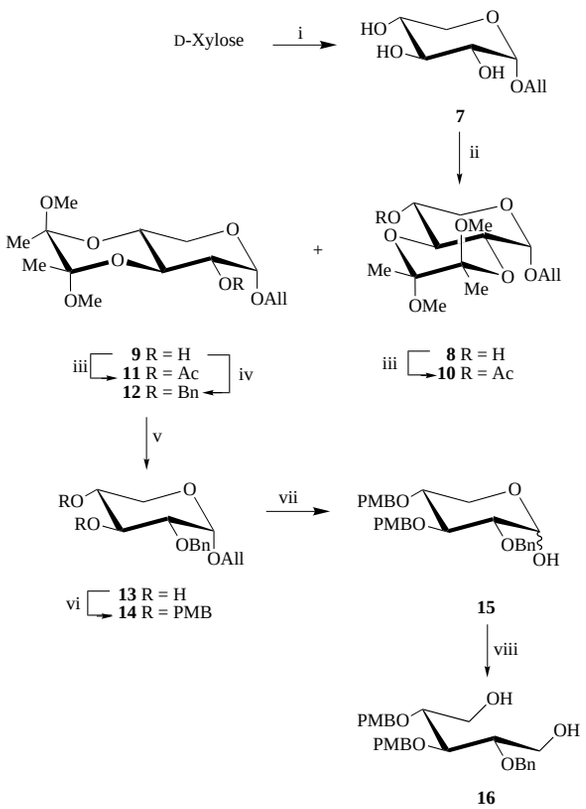
1D-*myo*-Inositol 1,4,5-trisphosphate **1**, 1D-*myo*-inositol 1,3,4,5-tetrakisphosphate **2** and ring-contracted structures

The intensive chemical synthesis of inositol polyphosphates and related compounds since 1986 has led to a good understanding of the structure-recognition parameters at the Ins(1,4,5)P_3 receptor: a D-*threo* vicinal bisphosphate is essential, while an equivalent to the position-6 hydroxy group and a third phosphate help to enhance potency.[6] In order to investigate how well the receptor will tolerate a smaller ring size, we wished to prepare a series of chiral cyclopentane derivatives in which the relative stereochemistry and substitution of positions equivalent to positions 4,5,6 and 1 of Ins(1,4,5)P_3 are retained. The first such compound, the vinylcyclopentane **3**, was found to be a weak full agonist;[7] the potency was found to be significantly increased when the hydrophobic vinyl substituent was replaced by hydroxymethyl, to give compound **4**.[8] However, in principle the most desirable trisphosphate in this series is compound **5**, which represents the ring-contracted Ins(1,4,5)P_3 derivative in which only the carbon atom at position 2 and its associated hydroxy group have been deleted. We reasoned that chiral compound **5** ought to be available by a route involving a samarium(II) iodide-mediated pinacol coupling[9,10] of a suitably protected D-*xylo*-pentodialdose such as compound **17** (Scheme 2). We report here the synthesis of compound **5**, together with the corresponding ring-contracted Ins(1,3,4,5)P_4 tetrakisphosphate **6**, from D-xylose.

Results and discussion

Fischer glycosidation of D-xylose with allyl alcohol in the presence of HCl gave a mixture of pyranosides from which the α-anomer **7** (Scheme 1) was isolated by crystallisation. Although uses of compound **7** have previously been reported,[11,12] it is characterised for the first time here. Stannylene-mediated benzylation[12,13] of compound **7** gave the required 2-*O*-benzyl derivative **13** in only poor yield (~25–30%) on a 10 g scale and consequently it was decided to explore the use of the recently described[14] butane-2,3-diacetal (BDA) protecting group with compound **7**, to complement other protecting strategies for xylopyranosides.[12,13,15,16] Acid-catalysed reaction of compound **7** with 2,2,3,3-tetramethoxybutane[14] in methanol gave, after 90 min, a 1 : 1 mixture of crystalline (**9**) and syrupy (**8**) products, which were separated by column chromatography in 93% yield (30 g scale); a prolonged reaction time did not alter the product ratio. The structures of products **9** and **8** were established by preparation of the corresponding acetates **11** and **10**, the ^{1}H



Scheme 1 *Reagents and conditions:* i, AllOH, HCl, reflux, 16 h (α-anomer by crystallisation, 28%); ii, $MeC(OMe)_2C(OMe)_2Me$, CSA, MeOH, $(MeO)_3CH$, reflux, 90 min (93%); iii, Ac_2O, pyridine, room temp., 2 h; iv, NaH, BnBr, DMF, 0 °C, 2 h; v, 95% aq. TFA–CH_2Cl_2 (1 : 1), room temp., 15 min (84% from **9**); vi, NaH, PMBCl, DMF, 60 °C, 2.5 h (74%); vii (*a*) Bu^{t}OK, DMSO, 50 °C, 3.5 h; (*b*) Me_2CO–1 M HCl (10 : 1), 50 °C, 30 min (87%); viii, $NaBH_4$, THF–water (3 : 2), room temp., 2 h (77%)

NMR spectra of which respectively revealed a deshielded doublet of doublets and a deshielded double doublet of doublets. With seed crystals available it was possible to isolate compound **9** from the reaction mixture in 20–25% yield by crystallisation and tens of grams of the required isomer were routinely isolated in this way. The lack of selectivity in protection of compound **7** with the BDA protecting group is consistent with experiments on methyl α-D-glucopyranoside, which also gave a 1 : 1 mixture of products,[14] but is in contrast with kinetic acetonation of methyl[15a] and benzyl[15b] β-D-xylopyranosides, which gave the 2,3-*O*-isopropylidene derivatives in greater than 70% yields. The unrequired isomer **8** was heated under reflux in methanol containing catalytic camphor-10-sulfonic acid (CSA) in an attempt to convert it into the 1 : 1 equilibrium mixture.[17] However, a long reaction time was necessary and after 7 days a mixture of **9**, **8**, **7** and a 1 : 1 anomeric mixture of methyl xylopyranosides was obtained in yields of 15, 14, 14 and 22%, respectively, making this an unsatisfactory method to procure further quantities of required regioisomer **9**.

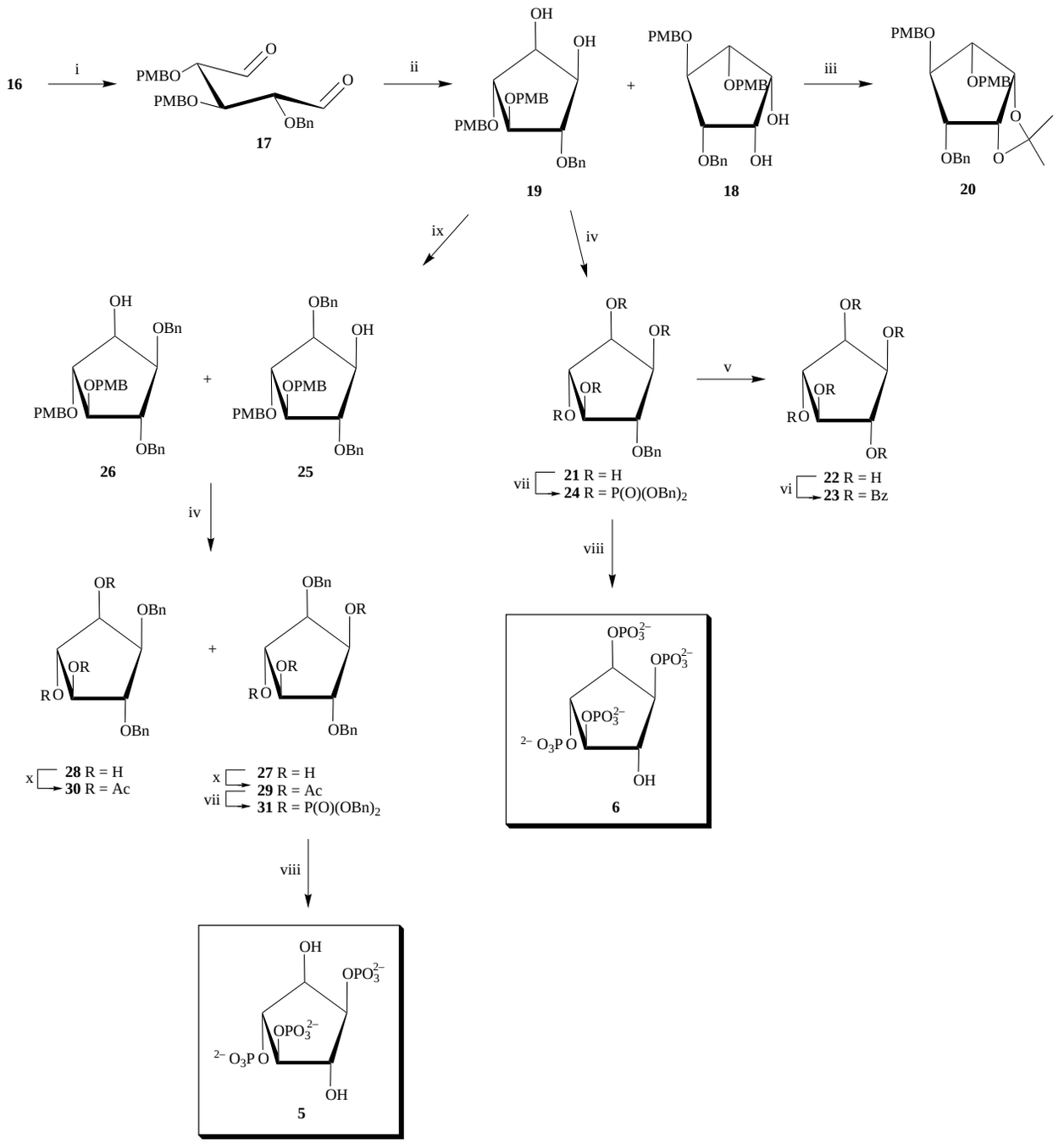
Benzylation of compound **9** with sodium hydride and benzyl bromide in dimethylformamide (DMF) gave the 2-*O*-benzyl derivative **12** and the BDA group was then removed with trifluoroacetic acid (TFA) to give compound **13** in 84% yield for the two steps. In contrast to allyl 2,6-di-*O*-benzyl-α-D-glucopyranoside, which was smoothly di-*O*-*p*-methoxybenzylated at room temp.,[18] a mixture of diol **13**, sodium hydride and *p*-methoxybenzyl chloride (PMBCl) in DMF required heating at 60 °C in order to give a good yield of fully protected compound **14**. It was felt necessary to replace the BDA group with *p*-methoxybenzyl ethers for two reasons. First, the presence of ketals next to an aldehyde group has been reported to cause side-reactions in the SmI_2–pinacol coupling, whereas ethers do not,[9] and, secondly, ethers adjacent to the aldehyde groups tend to direct *cis*-diol formation in the cyclitol products.[19]

Isomerisation of the allyl group of compound **14** with potassium *tert*-butoxide in dimethyl sulfoxide (DMSO)[20] followed by acidic hydrolysis of the resulting enol ethers gave xylopyranose **15** in 87% yield as a ~7 : 3 α : β anomeric mixture, as judged by NMR spectroscopy. Compound **15** is also a useful intermediate in the preparation of xylose-based analogues of the potent Ins(1,4,5)P_3 receptor agonist adenophostin A.[12,21] Reduction of compound **15** with sodium borohydride in tetrahydrofuran (THF)–water cleanly furnished xylitol **16** in 77% yield. The structure **16** was assigned on the basis of NMR spectroscopy: in the ^{1}H spectrum the two hydroxy protons presented as triplets which exchanged with D_2O; in the ^{13}C spectrum the methylene carbons resonated at δ_C 61.6, the three alkoxymethines resonated at δ_C 78.5, 78.9 and 79.0, and in both spectra signals characteristic of carbohydrate rings were absent.

Swern oxidation[22] of the xylitol **16** gave the required dialdose **17** (Scheme 2), which was azeotropically dried before being treated with an excess of samarium(II) iodide and 2-methylpropan-2-ol in THF[10] to give the products **18** and **19** in the ratio ~1 : 3. The identity of the major product **19** was established by chemical correlation with known compounds **22** and **23** and support for a five-membered-ring structure came from the ^{13}C NMR spectrum, which showed signals corresponding to alkoxymethine carbons at δ_C 85.3–86.3 and to hydroxymethine carbons at δ_C 73.9; signals arising from methylene carbons other than those of protecting groups were absent. The minor product **18** could not be separated from an impurity and was therefore characterised as its isopropylidene acetal **20**. Acidic hydrolysis of compound **19** gave tetraol **21**. Hydrogenation of monobenzyl ether **21** gave the known[23,24] 1,2,4/3,5-cyclopentanepentaol **22**, which on benzoylation gave the known[23] pentabenzoate **23**, thereby confirming the stereochemistry of diol **19** and derivatives and, since compound **18** contains a *cis*-diol (as deduced from the formation of an isopropylidene derivative), also indirectly confirming *its* stereochemistry too. The 1 : 3 product ratio for the pinacol coupling is consistent with the results of Perrin *et al.*[10] obtained from the symmetrical 2,3,4-tri-*O*-benzylpentodialdose, and the isolation exclusively of *cis*-diol products is also consistent with precedent.[9,10,19,25]

Tetraol **21** was phosphitylated with tetrazole-activated bis(benzyloxy)(diisopropylamino)phosphine[26] in methylene dichloride. Owing to the relatively poor solubility of tetraol **21** in this solvent, a long reaction time of 2 h was necessary. Oxidation of the intermediate tetrakisphosphite with *m*-chloroperbenzoic acid (MCPBA) gave fully protected compound **24**, which was deprotected by hydrogenation to furnish the target tetrakisphosphate **6**. Compound **6** was purified by ion-exchange chromatography, was isolated as its triethylammonium salt, and quantified by total phosphate assay.[27,28]

Attention now turned to preparation of the target trisphosphate **5**. Stannylene-mediated benzylation of *cis*-diol **19** with 1.1 mol equiv. of dibutyltin oxide and 1.2 mol equiv. of benzyl bromide gave a ~1 : 1 mixture of bisbenzyl ethers **25** and **26** in 87% yield. These isomers could not be separated, but upon acidic hydrolysis of the mixture the triols **27** and **28** were easily separated by column chromatography. The structures of triols **27** and **28** were assigned as follows: a sample of each was converted into its triacetate, giving compounds **29** and **30** respectively, and the ^{1}H NMR spectra of the latter were compared. The spectrum of compound **29** was non-first order and therefore not useful. However, the 2D ^{1}H chemical-shift-correlation (COSY) spectrum of compound **30** showed that the two most shielded ring methines (*i.e.* those geminal to benzyloxy substituents) at δ 3.97 and 4.07 coupled to each other, while one of the deshielded methine protons geminal to an acetate at δ 5.27 coupled only to the two other deshielded protons and was therefore assigned as the proton at position 3. These observations are consistent only with the structure **30**. Further evi-

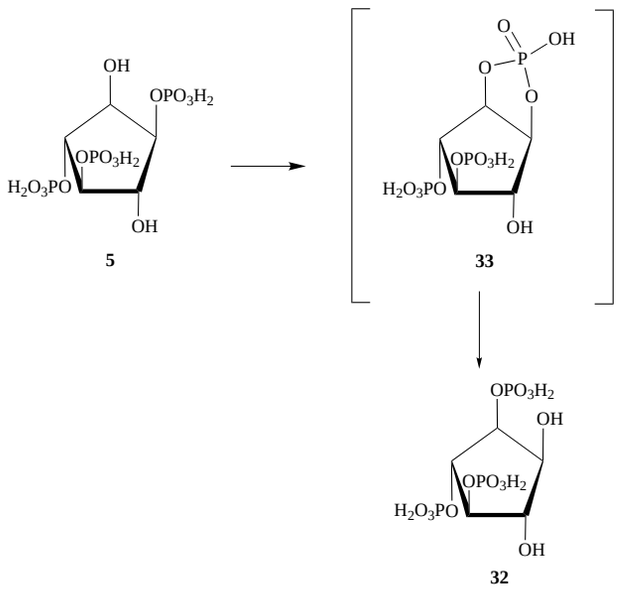


Scheme 2 *Reagents and conditions:* i (*a*) $(COCl)_2$, DMSO, CH_2Cl_2, N_2, −60 °C, 15 min; (*b*) Et_3N, room temp., 15 min; (*c*) toluene, reflux (Dean–Stark trap), 1 h; ii, SmI_2, Bu^{t}OH, N_2, −60 °C to room temp., 4 h (43% from **16**); iii, 2,2-dimethoxypropane–DMF, PTSA, room temp., 2 h; iv, 1 M HCl–EtOH (1:2), reflux, 2.5 h (76%); v, H_2, 10% Pd/C, MeOH–water (4:1), room temp., 40 h (79%); vi, BzCl, pyridine, room temp., 16 h; vii (*a*) $(BnO)_2PNPr^i_2$, 1*H*-tetrazole, CH_2Cl_2, room temp., 2 h; (*b*) MCPBA, 0 °C, 10 min; viii, H_2, 10% Pd/C, $NaHCO_3$, MeOH–water (4:1), room temp., 48 h; ix, Bu_2SnO, BnBr, Bu_4NBr, MeCN, 4 Å sieves, reflux, 24 h (87%); x, Ac_2O, pyridine, room temp., 2 h

dence came from considering the NMR spectrum of triol **27**: the most deshielded ring carbon atoms are the benzylated ones, due to the α-effect of alkylation;[29] the protons attached to these carbon atoms, as revealed in the 2D ^1H–^{13}C COSY spectrum, did not couple to each other, as revealed in the 2D ^1H–^1H COSY spectrum, an observation consistent with the proposed structure.

Phosphitylation and subsequent oxidation of triol **27** gave fully protected compound **31**. Hydrogenation of compound **31** gave the target trisphosphate **5**. However, both ^1H and ^{31}P NMR spectra clearly showed the presence of a trisphosphate impurity, presumably the migration product **32** of ring-opening of the cyclic intermediate **33** (Scheme 3); such a reaction is well precedented. The impurity comprised ~5–8% of the product, as judged by the integral ratios of duplicate signals in the ^1H NMR spectrum. Leaving the mixture of trisphosphates as their free acids in aqueous solution at ambient temperature gradually increased the proportion of minor product to ~30% over a period of three days, as judged by ^1H NMR spectroscopy, and to ~50% after 7–10 days. The acid-catalysed migration problem was overcome simply by including 3 mol equiv. of sodium hydrogen carbonate in the hydrogenation mixture;[30] in this case no migration occurred and pure compound **5** was purified by ion-exchange chromatography, isolated as its tris(triethylammonium) salt and quantified by total phosphate assay.[27,28] In some cases, however, the presence of sodium hydrogen carbonate appeared to slow the deprotection reaction.

The preparation of polyphosphates **5** and **6** represents further progress in our efforts to design inositol phosphate congeners that are structurally diverse from the parent compounds and these target compounds will be used to explore structure–activity aspects of binding to functional receptors and



Scheme 3 Phosphate migration on deprotection of compound **31**

metabolic enzymes. In the case of trisphosphate **5** a preliminary examination showed that when this compound was microinjected into *Xenopus* oocytes it was able to induce Ins(1,4,5)P_3-like oscillations indicative of release of Ca^{2+} stores, but a higher concentration was required relative to Ins(1,4,5)P_3. Full biological and physicochemical evaluation of polyphosphates **5** and **6** is in progress and will be reported elsewhere.

Experimental

Materials and methods

Chemicals were purchased from Aldrich, Sigma and Fluka. Light petroleum refers to the fraction with boiling range 40–60 °C. Methylene dichloride and 2-methylpropan-2-ol were dried over calcium hydride, distilled, and kept over 4 Å molecular sieves. DMF was distilled from barium oxide under reduced pressure and then stored over 4 Å molecular sieves. THF was dried by distillation from sodium in the presence of benzophenone ketyl. DMSO was purchased in anhydrous form.

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.*[31] and was carried out using Sorbsil C60 silica gel.

^{1}H and ^{13}C NMR spectra were recorded on JEOL JMN GX-270 or EX-400 NMR spectrometers. Unless otherwise stated, chemical shifts were measured in ppm relative to internal tetramethylsilane. ^{31}P NMR spectra were recorded on an EX-400 NMR spectrometer, and ^{31}P NMR chemical shifts were measured in ppm and denoted positive downfield from 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. FAB Mass spectra [*m*-nitrobenzyl alcohol (*m*NBA)] were recorded at the University of Bath Mass Spectrometry Service using a VG Analytical Autospec Mass Spectrometer. 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 by the Briggs phosphate test.[27,28]

Allyl α-D-xylopyranoside 7

Acetyl chloride (8.0 cm^3) was added dropwise to allyl alcohol (1200 cm^3) and the solution was stirred for 20 min at room temp., whereupon D-xylose (150 g, 1.0 mol) was added and the mixture was heated under reflux for 16 h. The resultant pale yellow solution was cooled to room temp. and was then stirred with an excess of Amberlite IR-45 (OH^-) for 1 h. The mixture was filtered and the filtrate was concentrated to give a viscous yellow syrup which solidified to a waxy solid on storage. This solid was dissolved in ethanol (1200 cm^3) and refrigerated at −20 °C. The *title compound* was collected as an amorphous solid over 3 crops (53.3 g, 28%); R_f 0.54 (ethyl acetate–propan-1-ol–water 9:4:2); mp 101–103 °C; $[\alpha]_D$ +149 (*c* 3.2, water) (Found: C, 50.7; H, 7.53. $C_8H_{14}O_5$ requires C, 50.5; H, 7.42%); δ_H(D_2O; 270 MHz; ref. int. HDO) 3.55–3.69 (5 H, m, 2-, 3- and 4-H, and 5-H_2), 4.01–4.24 (2 H, m, CH_2CH=CH_2), 4.92 (1 H, d, *J* 3.5, 1-H), 5.25 (1 H, d, *J* 10.3, CH_2CH=C$H_{cis}H_{trans}$), 5.35 (1 H, d, *J* 17.2, CH_2CH=$CH_{cis}H_{trans}$) and 5.98 (1 H, m, CH_2CH=CH_2); δ_C(D_2O; 100 MHz) 62.02 (C-5), 69.43 (*C*H_2CH=CH_2), 70.24 (C-4), 72.08 (C-2), 74.04 (C-3), 98.31 (C-1), 119.10 (CH_2CH=*C*H_2) and 134.39 (CH_2*C*H=CH_2); *m/z* (FAB^+) 133 [(M − C_3H_5O)$^+$, 100%]; (FAB^-) 189 [(M − 1)$^-$, 52%] and 343 [(M + NBA)$^-$, 100].

(1*R*,3*S*,4*S*,6*R*,9*S*,10*R*)-9-Allyloxy-10-hydroxy-3,4-dimethoxy-3,4-dimethyl-2,5,8-trioxabicyclo[4.4.0]decane 9 and (1*S*,3*R*,4*R*,6*R*,7*S*,10*R*)-7-allyloxy-10-hydroxy-3,4-dimethoxy-3,4-dimethyl-2,5,8-trioxabicyclo[4.4.0]decane 8

A solution of xylopyranoside **7** (30.0 g, 0.16 mol), 2,2,3,3-tetramethoxybutane[14] (38.0 cm^3, 0.19 mol), trimethyl orthoformate (69.0 cm^3, 0.63 mol) and CSA (1.8 g, 8.0 mmol) in methanol (500 cm^3) was heated under reflux for 90 min, when TLC (ethyl acetate) showed consumption of starting material (R_f 0.1) and TLC ($CHCl_3$–acetone 9:1) showed the presence of two products (R_f 0.43 and 0.24). Solid $NaHCO_3$ (2 g) was carefully added in portions and the suspension was cooled to room temp. The solvents were evaporated off and the residue was partitioned between diethyl ether (300 cm^3) and water (300 cm^3). The aqueous layer was back-extracted with diethyl ether (300 cm^3) and the combined organic fraction was dried ($MgSO_4$), filtered and concentrated. The syrup thus obtained was subjected to flash chromatography (eluent $CHCl_3$–acetone 20:1) to give *title compound* **9**, which crystallised as fine needles from light petroleum (22.1 g, 46%); mp 98–99 °C; $[\alpha]_D$ +285 (*c* 1.9, $CHCl_3$) (Found: C, 55.3; H, 8.05. $C_{14}H_{24}O_7$ requires C, 55.24; H, 7.95%); δ_H($CDCl_3$; 400 MHz) 1.30 and 1.35 (6 H, 2 s, 2 × Me), 2.06 (1 H, d, *J* 9.3, exch. D_2O, 10-OH), 3.27 and 3.31 (6 H, 2 s, 2 × OMe), 3.54–3.58 (1 H, ABX, $^2J_{AB}$ 9.8, ^3J 4.4, 7-H), 3.66–3.78 (3 H, m, 6-, 7- and 10-H), 3.86 (1 H, t, *J* 9.8, 1-H), 3.98–4.05 (1 H, m, C*H*HCH=CH_2), 4.21–4.25 (1 H, m, CH*H*CH=CH_2), 4.90 (1 H, d, *J* 3.9, 9-H), 5.22 (1 H, m, ^2J 1.0, ^3J 10.2, CH_2CH=C$H_{cis}H_{trans}$), 5.30 (1 H, m, ^2J 1.0, ^3J 17.6, CH_2CH= $CH_{cis}H_{trans}$) and 5.91 (1 H, m, CH_2CH=CH_2); δ_C($CDCl_3$; 100 MHz) 17.65 and 17.85 (2 × Me), 47.99 and 49.67 (2 × OMe), 60.02 (C-7), 66.18 (CH), 68.53 (*C*H_2CH=CH_2), 69.86 and 70.94 (2 × CH), 97.75 (C-9), 99.56 and 99.91 (C-3, -4), 118.12 (CH_2CH=*C*H_2) and 133.57 (CH_2*C*H=CH_2); *m/z* (FAB^+) 305 [(M + 1)$^+$, 8%], 273 [(M − OMe)$^+$, 40] and 101 (100).

A sample of compound **9** was converted to its crystalline *acetate* **11** with acetic anhydride in pyridine; mp 73 °C (from light petroleum 60–80 °C); $[\alpha]_D$ +252 (*c* 0.7, $CHCl_3$) (Found: C, 55.5; H, 7.63. $C_{16}H_{26}O_8$ requires C, 55.47; H, 7.57%); δ_H($CDCl_3$; 270 MHz) 1.29 and 1.30 (6 H, 2 s, 2 × Me), 2.10 (3 H, s, $MeCO_2$), 3.27 and 3.29 (6 H, 2 s, 2 × OMe), 3.56 (1 H, dd, *J* 5.3 and 10.0, 7-H), 3.70 (1 H, t, *J* 10.5, 1-H), 3.82 (1 H, ddd, *J* 5.3, 9.4 and 10.5, 6-H), 3.92–4.00 (1 H, m, C*H*HCH=CH_2), 4.09–4.20 (2 H, m, 7-H′, CH*H*CH=CH_2), 4.77 (1 H, dd, *J* 3.8 and 10.5, 10-H), 5.08 (1 H, d, *J* 3.8, 9-H), 5.19 (1 H, m, ^2J 1.0, ^3J 10.3, CH_2CH=C$H_{cis}H_{trans}$), 5.28 (1 H, m, ^2J 1.0, ^3J 17.2,

$CH_2CH{=}CH_{cis}H_{trans}$) and 5.88 (1 H, m, $CH_2CH{=}CH_2$); *m*/*z* (FAB^+) 315 [$(M - OMe)^+$, 60%] and 101 (100).

Further elution gave *compound* **8** as a pale yellow syrup (23.0 g, 47%); $[\alpha]_D$ −59.1 (*c* 1.85, $CHCl_3$) (Found: C, 54.8; H, 7.92. $C_{14}H_{24}O_7$ requires C, 55.24; H, 7.95%); δ_H($CDCl_3$; 400 MHz) 1.32 and 1.33 (6 H, 2 s, 2 × Me), 2.62 (1 H, br s, OH), 3.25 and 3.29 (6 H, 2 s, 2 × OMe), 3.58 (1 H, t, $^2J = {}^3J = 10.7$, 9-H^{ax}), 3.67–3.71 (2 H, m, 6-H, 9-H^{eq}), 3.84 (1 H, ddd, *J* 5.9, 9.8 and 10.7, 10-H), 3.99 (1 H, t, *J* 9.8, 1-H), 4.09–4.14 (1 H, m, C*H*HCH=CH_2), 4.18–4.21 (1 H, m, CH*H*CH=CH_2), 4.84 (1 H, d, *J* 3.4, 7-H), 5.20 (1 H, m, ^2J 1.5, ^3J 10.2, $CH_2CH{=}C{H_{cis}}H_{trans}$), 5.33 (1 H, m, ^2J 1.5, ^3J 17.1, $CH_2CH{=}CH_{cis}H_{trans}$) and 5.92 (1 H, m, $CH_2CH{=}CH_2$); δ_C($CDCl_3$; 100 MHz) 17.67 and 17.94 (2 × Me), 47.84 and 47.93 (2 × OMe), 62.00 (C-9), 68.00 (CH), 68.05 ($CH_2CH{=}CH_2$), 68.14 and 69.95 (2 × CH), 95.67 (C-7), 99.45 and 99.90 (C-3, -4), 117.85 ($CH_2CH{=}CH_2$) and 134.01 ($CH_2CH{=}CH_2$); *m*/*z* (FAB^+) 305 [$(M + 1)^+$, 10%], 273 [$(M - OMe)^+$, 50] and 101 (100).

A sample of compound **8** was converted to its syrupy *acetate* **10** with acetic anhydride in pyridine; R_f 0.6 ($CHCl_3$–acetone 9 : 1); $[\alpha]_D$ −61.8 (*c* 1.2, $CHCl_3$) (Found: C, 55.4; H, 7.54. $C_{16}H_{26}O_8$ requires C, 55.47; H, 7.57%); δ_H($CDCl_3$; 400 MHz) 1.27 and 1.32 (6 H, 2 s, 2 × Me), 2.06 (3 H, s, $MeCO_2$), 3.25 and 3.27 (6 H, 2 s, 2 × OMe), 3.50 (1 H, t, *J* 10.7, 1-H), 3.76–3.82 (2 H, m, 6-, 9-H), 4.08–4.21 (3 H, m, $CH_2CH{=}CH_2$, 9-H′), 4.84 (1 H, d, *J* 3.4, 7-H), 4.92 (1 H, ddd, *J* 5.9, 9.8 and 10.7, 10-H), 5.22 (1 H, m, ^2J 1.5, ^3J 10.3, $CH_2CH{=}C{H_{cis}}H_{trans}$), 5.34 (1 H, m, ^2J 1.5, ^3J 17.1, $CH_2CH{=}CH_{cis}H_{trans}$) and 5.94 (1 H, m, $CH_2CH{=}CH_2$); *m*/*z* (FAB^+) 347 [$(M + 1)^+$, 10%], 315 [$(M - OMe)^+$, 60] and 101 (100).

Equilibration of compound 8

A solution of butanediacetal **8** (7.10 g, 23.3 mmol) in methanol (250 cm^3) containing CSA (250 mg) was heated under reflux for 1 week. The solution was cooled and solid $NaHCO_3$ (1 g) was added. Stirring was continued for 10 min, then the suspension was filtered and the filtrate was concentrated. The orange syrup thus obtained was partitioned between diethyl ether (200 cm^3) and water (200 cm^3). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give an orange syrup, which was subjected to flash chromatography (eluent $CHCl_3$–acetone 20 : 1) to give regioisomer **9** (1.09 g, 15%); mp 98–99 °C; mixed mp 97–99 °C.

Further elution gave starting material (1.02 g, 14% recovery). A series of faint shadow spots less mobile than starting material **8** were not isolated.

The aqueous layer was concentrated and ethanol (3 × 250 cm^3) was evaporated off from the residue. The resultant cloudy syrup was subjected to flash chromatography (eluent ethyl acetate–methanol 9 : 1) to give allyl glycoside **7** (613 mg, 14%); mp 99–103 °C.

Further elution gave a syrupy product, which was shown by ^{1}H NMR spectroscopy to be a ~1 : 1 anomeric mixture of methyl D-xylopyranosides (846 mg, 22%); selected δ_H($CDCl_3$; 270 MHz) 3.36 and 3.50 (2 s, OMe of α and β anomers), 4.28 (0.5 H, d, *J* 7.9, 1-H^β) and 4.74 (0.5 H, d, *J* 3.3, 1-H^α). The α and β superscripts denote signals arising from the α and β anomers respectively.

(1*R*,3*S*,4*S*,6*R*,9*S*,10*R*)-9-Allyloxy-10-benzyloxy-3,4-dimethoxy-3,4-dimethyl-2,5,8-trioxabicyclo[4.4.0]decane 12

A solution of alcohol **9** (21.0 g, 68.9 mmol) in dry DMF (400 cm^3) was stirred with sodium hydride [3.2 g of a 60% (w/w) dispersion in mineral oil, 75.7 mmol] and benzyl bromide (9.0 cm^3, 75.7 mmol) at 0 °C for 2 h, when TLC ($CHCl_3$–acetone 9 : 1) showed consumption of starting material (R_f 0.3) to give a product (R_f 0.65). Methanol (50 cm^3) was added and the mixture was stirred for a further 15 min. The solvents were evaporated off and the residue was partitioned between diethyl ether (400 cm^3) and water (400 cm^3). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give 27.9 g of a pale yellow syrup, which was used directly in the next step. A portion was subjected to flash chromatography (eluent $CHCl_3$–acetone 20 : 1) to give an analytically pure sample of *compound* **12** as a syrup; $[\alpha]_D$ +159 (*c* 5.3, $CHCl_3$) (Found: C, 64.2; H, 7.65. $C_{21}H_{30}O_7$ requires C, 63.93; H, 7.67%); δ_H($CDCl_3$; 400 MHz) 1.30 and 1.35 (6 H, 2 s, 2 × Me), 3.27 and 3.32 (6 H, 2 s, 2 × OMe), 3.47–3.55 (2 H, m, 7-, 10-H), 3.68 (1 H, t, $^2J = {}^3J = 10.7$, 7-H′), 3.75 (1 H, ddd, *J* 4.9, 9.3 and 10.7, 6-H), 4.00 (1 H, m, C*H*HCH=CH_2), 4.11–4.18 (2 H, m, CH*H*-CH=CH_2, 1-H), 4.66 (1 H, AB, J_{AB} 12.5, PhC*H*HO), 4.76 (1 H, d, *J* 3.4, 9-H), 4.86 (1 H, AB, J_{AB} 12.5, PhCH*H*O), 5.20 (1 H, m, ^3J 10.7, $CH_2CH{=}C{H_{cis}}H_{trans}$), 5.30 (1 H, m, ^2J 1.5, ^3J 17.1, CH_2-$CH{=}CH_{cis}H_{trans}$), 5.91 (1 H, m, $CH_2CH{=}CH_2$) and 7.26–7.37 (5 H, m, PhH); δ_C($CDCl_3$; 100 MHz) 17.67 and 18.00 (2 × Me), 47.95 and 48.06 (2 × OMe), 59.53 (C-7), 66.70 (CH), 68.11 ($CH_2CH{=}CH_2$), 70.19 (CH), 73.35 (PhCH_2O), 76.55 (C-10), 96.54 (C-9), 99.56 and 99.71 (C-3, -4), 118.05 ($CH_2CH{=}CH_2$), 127.54, 127.65 and 128.27 (Ph), 133.85 ($CH_2CH{=}CH_2$) and 138.79 (*ipso*-C); *m*/*z* (FAB^+) 395 [$(M + 1)^+$, 4%], 363 [$(M - OMe)^+$, 85] and 91 (100).

Allyl 2-*O*-benzyl-α-D-xylopyranoside 13

The syrup from the previous step (27.9 g) was dissolved in methylene dichloride (100 cm^3) and 95% (v/v) TFA in water (100 cm^3) was added. The solution was stored at room temp. for 15 min, then the solvents were evaporated off. The residue was dissolved in diethyl ether (400 cm^3) and the solution was washed with saturated aq. $NaHCO_3$ (2 × 400 cm^3). The combined aqueous washings were back-extracted with diethyl ether (200 cm^3) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The concentrate was subjected to flash chromatography (eluent hexane–ethyl acetate 1 : 3, then ethyl acetate) to give the *title compound* as a pale yellow syrup (16.2 g, 84% from **9**); $[\alpha]_D$ +113 (*c* 2.3, $CHCl_3$) (Found: C, 63.9; H, 7.22. $C_{15}H_{20}O_5$ requires C, 64.26; H, 7.20%); δ_H($CDCl_3$; 270 MHz) 3.31 (1 H, dd, *J* 3.4 and 9.5, 2-H), 3.44–3.62 (5 H, m, simplifies to 3 H on D_2O exch., 2 × OH, 4-H and 5-H_2), 3.85–3.94 (2 H, br m, sharpens on D_2O exch., C*H*HCH=CH_2, 3-H), 4.11–4.18 (1 H, m, CH*H*CH=CH_2), 4.63 and 4.64 (2 H, AB, J_{AB} 12.0, PhCH_2O), 4.75 (1 H, d, *J* 3.5, 1-H), 5.20 (1 H, m, ^2J 1.5, ^3J 10.3, $CH_2CH{=}C{H_{cis}}H_{trans}$), 5.31 (1 H, m, ^2J 1.5, ^3J 17.2, $CH_2CH{=}$ $CH_{cis}H_{trans}$), 5.91 (1 H, m, $CH_2CH{=}CH_2$) and 7.30–7.35 (5 H, m, Ph); δ_C($CDCl_3$; 67.8 MHz) 61.42 (C-5), 68.20 ($CH_2CH{=}CH_2$), 70.00 (C-4), 72.80 (PhCH_2O), 73.19 (C-3), 79.34 (C-2), 95.42 (C-1), 117.87 ($CH_2CH{=}CH_2$), 128.04, 128.12 and 128.51 (Ph CH), 133.76 ($CH_2CH{=}CH_2$) and 137.92 (*ipso*-C); *m*/*z* (FAB^-) 279 [$(M - 1)^-$, 58%] and 433 [$(M + NBA)^-$, 100].

Allyl 2-*O*-benzyl-3,4-bis-*O*-(*p*-methoxybenzyl)-α-D-xylopyranoside 14

A solution of diol **13** (16.2 g, 57.7 mmol) in dry DMF (400 cm^3) was stirred with sodium hydride [6.0 g of a 60% (w/w) dispersion in mineral oil, 144 mmol] and PMBCl (16.4 cm^3, 121 mmol) at 60 °C for 2.5 h, when TLC (ethyl acetate–hexane 3 : 2) showed conversion of starting material (R_f 0.15) into a product (R_f 0.7). The mixture was cooled to room temp., methanol (50 cm^3) was added, and stirring was continued for 15 min. The solvents were evaporated off and the dark brown residue was extracted with methylene dichloride (3 × 300 cm^3). The combined organic extracts were washed successively with water (300 cm^3) and saturated aq. NaCl (500 cm^3), dried ($MgSO_4$), filtered and concentrated. Flash chromatography of the concentrate (eluent hexane–ethyl acetate 9 : 1, then 3 : 1) gave the *title compound* as a pale yellow syrup (22.2 g, 74%); $[\alpha]_D$ +30.9 (*c* 1.4, $CHCl_3$) (Found: C, 71.8; H, 6.93. $C_{31}H_{36}O_7$ requires C, 71.50; H, 6.97%); δ_H($CDCl_3$; 400 MHz) 3.44 (1 H, dd, *J* 3.4, 9.3, 2-H), 3.51–3.55 (3 H, m, 4-H and 5-H_2), 3.79 and 3.80 (6 H, 2 s, 2 × OMe), 3.87–3.91 (1 H, br m, 3-H), 3.95–4.00 (1 H, m, C*H*HCH=CH_2), 4.12–4.17 (1 H, m, CH*H*CH=CH_2), 4.54 and

4.68 (2 H, AB, J_{AB} 11.2, ArCH_2O), 4.64 and 4.77 (2 H, AB, J_{AB} 12.2, ArCH_2O), 4.71 (1 H, d, *J* 3.4, 1-H), 4.79 and 4.84 (2 H, AB, J_{AB} 10.3, ArCH_2O), 5.21 (1 H, m, ^3J 10.3, $CH_2CH{=}CH_{cis}$-H_{trans}), 5.31 (1 H, m, ^2J 1.5, ^3J 17.1, $CH_2CH{=}CH_{cis}H_{trans}$), 5.91 (1 H, m, $CH_2CH{=}CH_2$), 6.85–6.87 (4 H, m, *ortho*-H of PMB rings) and 7.23–7.36 (9 H, Ar); δ_C($CDCl_3$; 100 MHz) 55.25 (2 × OMe), 60.13 (C-5), 68.01 ($CH_2CH{=}CH_2$), 73.21, 73.32 and 75.48 (3 × ArCH_2O), 77.85 (C-4), 79.66 (C-2), 81.20 (C-3), 95.70 (C-1), 113.75 and 113.83 (2 × *ortho*-C of PMB rings), 118.03 ($CH_2CH{=}CH_2$), 127.78, 128.00, 128.09, 128.38, 129.42 and 129.66 (Ar CH), 130.50 and 131.18 (2 × *ipso*-C of PMB rings), 133.81 ($CH_2CH{=}CH_2$), 138.35 (*ipso*-C of phenyl ring) and 159.16 and 159.29 (2 × *para*-C of PMB rings); *m/z* (FAB^+) 520 [$(M + 1)^+$, 12%] and 121 (100).

2-*O*-Benzyl-3,4-bis-*O*-(*p*-methoxybenzyl)-D-xylopyranose 15

A solution of glycoside **14** (10.2 g, 19.6 mmol) in dry DMSO (150 cm^3) was stirred with freshly sublimed potassium *tert*-butoxide (4.4 g, 39.2 mmol) at 50 °C for 3.5 h. The dark brown mixture was cooled to room temp. and poured into water (250 cm^3). The resultant mixture was extracted with 200 cm^3 portions of diethyl ether until TLC showed no further PMB-containing material to be present in the aqueous layer. The combined organic extracts were washed with saturated aq. KCl (300 cm^3), dried ($MgSO_4$), filtered, and concentrated to give a yellow syrup (10.8 g). This syrup was dissolved in acetone (250 cm^3) and heated to 50 °C. Aq. HCl (1 mol dm^{-3}; 25 cm^3) was added and stirring was continued at 50 °C for 30 min, when TLC (ethyl acetate–hexane 3:2) showed conversion of the prop-1-enyl ethers (R_f 0.65) into a product (R_f 0.45). Solid $NaHCO_3$ (5.2 g) was added and the suspension was allowed to cool to room temp. The acetone was evaporated off and the gummy residue was partitioned between diethyl ether (250 cm^3) and water (250 cm^3). The aqueous layer was back-extracted with diethyl ether (250 cm^3) and the combined organic fraction was dried ($MgSO_4$), filtered and concentrated. The orange syrup thus obtained was subjected to flash chromatography (eluent hexane–ethyl acetate 4:1, then 1:1) to give the *title compound* as a pale yellow oil which solidified to an off-white solid on storage (8.20 g, 87% from **14**); mp 88–90 °C (from diethyl ether–light petroleum); $[a]_D$ +13.8 (*c* 1.6, $CHCl_3$, 1 h) (Found: C, 69.95; H, 6.76. $C_{28}H_{32}O_7$ requires C, 69.97; H, 6.72%); δ_H($CDCl_3$; 400 MHz) 3.02 (0.7 H, d, *J* 3.1, exch. D_2O, OH^{α}), 3.21–3.30 (0.6 H, m, 2- and 4-H^{β}), 3.34 (0.3 H, d, *J* 5.5, exch. D_2O, OH^{β}), 3.45 (0.7 H, dd, *J* 3.7 and 8.9, 2-H^{α}), 3.48–3.92 (3.7 H, m, 3-H, 4-H^{α} and 5-H_2), 3.80 and 3.82 (6 H, 2 s, 2 × OMe), 4.54–4.89 (6.3 H, m, 3 × ArCH_2O, 1-H^{β}), 5.09 (0.7 H, dd, *J* 3.1 and 3.7, simplifies to d, *J* 3.7 on D_2O exch., 1-H^{α}), 6.83–6.87 (4 H, m, *ortho*-H of PMB rings) and 7.23–7.34 (9 H, m, ArH); δ_C($CDCl_3$; 100 MHz) 55.27 (OMe), 60.37 (C-5^{α}), 63.75 (C-5^{β}), 72.88, 72.93, 73.37, 74.74, 75.14 and 75.18 (ArCH_2O), 77.18, 79.46 and 80.18 (C-2–C-5^{α}), 82.35 and 82.88 (C-2^{β} and -3^{β}), 91.44 (C-1^{α}), 97.71 (C-1^{β}), 113.77, 113.83 and 113.86 (*ortho*-C of PMB rings), 127.71, 127.96, 128.00, 128.38, 128.47, 129.41, 129.46, 129.64 and 129.86 (Ar), 130.21, 130.36, 130.69 and 130.83 (*ipso*-C of PMB rings), 137.87 (*ipso*-C^{α} of benzyl ring), 138.40 (*ipso*-C^{β} of benzyl ring), 159.20, 159.29 and 159.33 (*para*-C of PMB rings). The α and β superscripts denote signals arising from the α and β anomers respectively; *m/z* (FAB^-) 633 [$(M + NBA)^+$, 100%].

2-*O*-Benzyl-3,4-bis-*O*-(*p*-methoxybenzyl)-D-xylitol 16

Sodium borohydride (5.1 g, 136 mmol) was added in portions over a period of 20 min to a solution of pyranose **15** (16.3 g, 33.9 mmol) in THF–water (3:2; 500 cm^3) and the mixture was stirred at room temp. for 2 h, when TLC (ethyl acetate) showed consumption of starting material (R_f 0.65) to give a product (R_f 0.4). The THF was evaporated off and the gummy aqueous residue was extracted with diethyl ether (3 × 200 cm^3). The combined organic extracts were washed with aq. HCl (1 mol dm^{-3}; 200 cm^3), dried ($MgSO_4$), filtered and concentrated. The concentrate was purified by flash chromatography (eluent hexane–ethyl acetate 1:1) to give the *title compound* as a solid (12.6 g, 77%); mp 60–62 °C; $[a]_D$ −2.6 (*c* 3.1, $CHCl_3$) (Found: C, 69.4; H, 7.13. $C_{28}H_{34}O_7$ requires C, 69.68; H, 7.1%); δ_H($CDCl_3$; 400 MHz) 2.18 (1 H, t, *J* 6.2, exch. D_2O, CH_2OH), 2.23 (1 H, t, *J* 6.2, exch. D_2O, CH_2OH), 3.56–3.78 (7 H, m, 1-H_2, 2-, 3- and 4-H, and 5-H_2), 3.80 (6 H, s, 2 × OMe), 4.56 and 4.56 (2 H, AB, J_{AB} 11.6, ArCH_2O), 4.60–4.66 (4 H, m, 2 × overlapping ArCH_2O AB systems), 6.84–6.87 (4 H, m, *ortho*-H of PMB rings) and 7.22–7.35 (9 H, m, ArH); δ_C($CDCl_3$; 100 MHz) 55.29 (2 × OMe), 61.58 (C-1, -5), 72.37, 72.75 and 74.05 (3 × ArCH_2O), 78.47, 78.93 and 78.99 (C-2–C-4), 113.92 (*ortho*-C of PMB rings), 127.93, 128.03, 128.51 and 129.72 (Ar CH), 129.96 and 130.03 (2 × *ipso*-C of PMB rings), 130.16 (Ar), 138.00 (*ipso*-C of phenyl ring) and 159.42 and 159.47 (2 × *para*-C of PMB rings); *m/z* (FAB^-) 635 [$(M + NBA)^-$, 100%].

1L-1,2,3,4/5-1-Benzyloxy-2,3-dihydroxy-4,5-bis(*p*-methoxybenzyloxy)cyclopentane 18 and 1L-1,2,4/3,5-3-benzyloxy-1,2-dihydroxy-4,5-bis(*p*-methoxybenzyloxy)cyclopentane 19

A dry solution of DMSO (8.5 cm^3, 120 mmol) in methylene dichloride (8 cm^3) was added dropwise to a 2 mol dm^{-3} solution of oxalyl dichloride in methylene dichloride (30.0 cm^3, 60.0 mmol) under N_2 at −60 °C. After 5 min, a solution of the xylitol **16** (11.6 g, 24.0 mmol) in dry methylene dichloride (50 cm^3) was added dropwise over a period of 5 min and stirring was continued at −60 °C for 15 min, whereupon triethylamine (TEA) (33.0 cm^3, 240 mmol) was added. The suspension was warmed to room temp. Methylene dichloride (200 cm^3) was added and the solution was washed successively with water (200 cm^3) and brine (200 cm^3), dried ($MgSO_4$), filtered and concentrated. The orange syrup thus obtained was dissolved in toluene (500 cm^3) and the solution was heated under reflux with continuous azeotropic removal of water (Dean–Stark trap) for 1 h. The solution was cooled under a stream of N_2 and concentrated. The orange/brown syrup thus obtained was dissolved in freshly distilled, dry THF (100 cm^3) and added dropwise during 20 min to a 0.1 mol dm^{-3} solution of samarium(II) iodide in THF (600 cm^3, 60.0 mmol) containing freshly distilled, dry 2-methylpropan-2-ol (6.8 cm^3, 72.0 mmol) at −60 °C under a stream of N_2. The blue/black mixture was stirred for 1 h at −60 °C and for 3 h at room temp., then was poured into aq. HCl (1 mol dm^{-3}; 800 cm^3). The resulting emulsion was extracted with diethyl ether (2 × 500 cm^{-3}). The combined organic extracts were washed with 5% (w/v) aq. $Na_2S_2O_3$ (600 cm^3), dried ($MgSO_4$), filtered and concentrated. Flash chromatography (eluent $CHCl_3$–acetone 10:1) gave many mobile PMB-containing shadow spots (not isolated).

Further elution gave title compound **18** as an orange syrup (~1.40 g, 12%), which could not be separated from an impurity. A sample of this syrup (450 mg) was stirred at room temp. with 2,2-dimethoxypropane–DMF (1:2; 30 cm^3) containing toluene-*p*-sulfonic acid (PTSA) (10 mg) for 2 h; neutralisation with TEA (10 cm^3) followed by concentration and column chromatography (eluent $CHCl_3$–acetone 10:1) gave *isopropylidene acetal* **20** as a pale yellow syrup; R_f 0.73 ($CHCl_3$–acetone 5:1); $[a]_D$ 0.0 (*c* 2.0, $CHCl_3$) (Found: C, 71.1; H, 6.97. $C_{31}H_{36}O_7$ requires C, 71.50; H, 6.97%); δ_H($CDCl_3$; 400 MHz) 1.29 and 1.45 (6 H, 2 s, 2 × Me), 3.70 (1 H, m, CH), 3.79 and 3.80 (6 H, 2 s, 2 × OMe), 4.04–4.12 (2 H, m, 2 × CH), 4.38–4.84 (8 H, m, 2 × CH, 3 × ArCH_2O AB systems), 6.84–6.88 (4 H, m, *ortho*-H of PMB rings) and 7.24–7.41 (9 H, m, ArH); *m/z* (FAB^+) 520 (M^+, 22%), 519 ($[M - 1]^+$, 82), 399 ($[M - PMB]^+$, 12) and 121 (100).

Further elution gave *compound* **19** as a waxy solid (3.55 g, 31% from **16**); R_f 0.13 ($CHCl_3$–acetone 10:1); $[a]_D$ +2.6 (*c* 2.7, $CHCl_3$) (Found: C, 69.8; H, 6.77. $C_{28}H_{32}O_7$ requires C, 69.97; H, 6.72%); δ_H($CDCl_3$; 400 MHz) 2.59 (2 H, br s, 2 × OH), 3.78

and 3.79 (6 H, 2 s, 2 × OMe), 3.83–3.87 (3 H, m, 3 × CH), 4.01 (2 H, br s, 2 × CH), 4.50 (2 H, s, ArCH_2O), 4.56 (2 H, s, ArCH_2O), 4.63 (2 H, s, ArCH_2O), 6.84–6.89 (4 H, m, *ortho*-H of PMB rings) and 7.20–7.36 (9 H, m, ArH); δ_C($CDCl_3$; 100 MHz) 55.27 (2 × OMe), 71.56, 71.73 and 72.04 (3 × ArCH_2O), 73.88 (C-1, -2), 85.26, 85.90 and 86.25 (C-3–C-5), 113.75 and 113.84 (*ortho*-C of PMB rings), 127.79, 127.91, 128.42 and 129.61 (Ar), 130.05 and 130.08 (2 × *ipso*-C of PMB rings), 138.06 (*ipso*-C of benzyl ring) and 159.23 and 159.31 (2 × *para*-C of PMB rings); *m/z* (FAB^+) 359 [$(M - PMB)^+$, 80%] and 121 (100); (FAB^-) 479 [$(M - 1)^-$, 80%] and 633 [$(M + NBA)^-$, 100].

1L-1,2,4/3,5-3-Benzyloxy-1,2,4,5-tetrahydroxycyclopentane 21

Aq. HCl (1 mol dm^{-3}; 50 cm^3) was added to a solution of compound **19** (1.50 g, 3.1 mmol) in ethanol (100 cm^3) and the solution was heated under reflux for 2.5 h, when TLC (ethyl acetate) showed consumption of starting material (R_f 0.55) to give a product (R_f 0.02–0.05). The solution was cooled, concentrated, and toluene (2 × 200 cm^3) and then ethanol (200 cm^3) were added and then evaporated from the residue. The brown syrup thus obtained was subjected to flash chromatography (loading solvent methylene dichloride; eluent ethyl acetate–methanol 9 : 1) to give the *title compound* as a solid (592 mg, 76%); R_f 0.33 (ethyl acetate–methanol 4 : 1); mp 92–93 °C; $[a]_D$ +14.5 (*c* 3.5, MeOH) (Found: C, 60.2; H, 6.72. $C_{12}H_{16}O_5$ requires C, 59.98; H, 6.72%); δ_H(D_2O; 270 MHz; ref. int. HDO) 3.71–3.81 (4 H, m, 4 × CH), 4.00 (1 H, m, CH), 4.65 and 4.71 (2 H, AB, J_{AB} 13.5, PhCH_2O) and 7.38–7.41 (5 H, m, Ph); δ_C(D_2O; 67 MHz) 71.71 (CH), 71.79 (Ph*C*H_2O), 72.78, 77.13 and 78.20 (3 × CH), 87.16 (C-3), 128.02, 128.24 and 128.36 (Ph) and 136.68 (*ipso*-C); *m/z* (FAB^-) 239 [$(M - 1)^-$, 53%] and 393 [$(M + NBA)^-$, 100].

Determination of stereochemistry of diol 19 and derivatives

A dispersion of 10% Pd/C (495 mg) in water (10 cm^3) was added to a solution of tetraol **21** (500 mg, 2.07 mmol) in methanol (40 cm^3) and the mixture was hydrogenated at 40–50 psi at room temp. for 40 h. The suspension was filtered and the residue was well washed with water (20 cm^3). The combined filtrate and washings were concentrated to give a pale yellow oil (246 mg, 79%). Trituration with ethanol gave crystalline 1,2,4/3,5-cyclopentanepentaol **22**, mp 147–149 °C [lit.,[23] 149–150 °C; lit.,[24] 149.5–150.5 °C]. A sample was benzoylated with benzoyl chloride in pyridine to give pentabenzoate **23**, mp 176–177.5 °C (from EtOH) [lit.,[23] 172–173 °C].

1L-1,2,4/3,5-3-Benzyloxy-1,2,4,5-tetrakis[bis(benzyloxy)-phosphoryloxy]cyclopentane 24

A mixture of bis(benzyloxy)(diisopropylamino)phosphine[26] (551 mg, 1.59 mmol), 1*H*-tetrazole (167 mg, 2.39 mmol) and dry methylene dichloride (3 cm^3) was vigorously stirred at room temp. for 20 min, whereupon tetraol **21** (48 mg, 199 μmol) was added. The suspension was stirred for a further 2 h, when TLC (ethyl acetate–methanol 4 : 1) showed consumption of starting material (R_f 0.4) to give a product (R_f 0.65), and ^{31}P NMR spectroscopy showed a complex pattern of phosphite peaks at δ_P 139.00–140.05, together with a little unchanged phosphitylating reagent-tetrazolide intermediate (δ_P 127.4). The suspension was cooled to 0 °C and MCPBA (550 mg, 3.19 mmol) was added. The suspension was allowed to warm to room temp. and was then stirred for 15 min. The clear solution was diluted with ethyl acetate (50 cm^3) and this solution was washed successively with 10% (w/v) aq. $Na_2S_2O_3$ (50 cm^3), saturated aq. $NaHCO_3$ solution (2 × 50 cm^3) and saturated aq. NaCl (50 cm^3), dried, filtered and concentrated. The concentrate was purified by flash chromatography (eluent $CHCl_3$–acetone 20 : 1) to give the *title compound* as a pale yellow syrup (163 mg, 64%); R_f 0.45 ($CHCl_3$–acetone 5 : 1); $[a]_D$ +7.5 (*c* 2.7, $CHCl_3$) [Found: M^+, 1281.3484. $C_{68}H_{69}O_{17}P_4$ (*M* + H) requires *m/z*, 1281.3485]; δ_H($CDCl_3$; 400 MHz) 4.26 (1 H, br m, 5-H), 4.50 and 4.53 (2 H, AB, J_{AB} 11.6, PhCH_2O), 4.83–5.08 (19 H, m, 8 × PhCH_2O, 3 × CH), 5.22 (1 H, ddd, *J* 4.3, 7.3 and 7.9, CH) and 7.16–7.27 (45 H, m, Ph); δ_C($CDCl_3$; 100 MHz) 69.51, 69.57, 69.62, 69.68, 69.73 and 69.81 (Ph*C*H_2O of benzyl esters), 72.29 (Ph*C*H_2O of benzyl ether), 82.68, 82.75, 83.25, 83.28 and 83.99 (C-1–C-5), 127.85, 127.94, 127.98, 128.05, 128.33, 128.51, 128.71 and 128.82 (Ph), 135.44, 135.51 and 135.59 (*ipso*-C of benzyl ester rings) and 136.98 (*ipso*-C of benzyl ether ring); δ_P($CDCl_3$; 162 MHz) −2.30, −2.08, −2.06 and −1.95 (4 s); *m/z* (FAB^+) 1281 [$(M + 1)^+$, 68%] and 91 (100).

1D-1,2,4/3,5-Cyclopentanepentaol 1,2,3,4-tetrakisphosphate 6

Sodium hydrogen carbonate (45 mg, 534 μmol) and a suspension of 10% Pd/C (190 mg) in water (5 cm^3) were added to a solution of compound **24** (163 mg, 127 μmol) in methanol (20 cm^3) and the mixture was hydrogenated at 40–45 psi at room temp. for 48 h to give compound **6** essentially quantitatively, as judged by NMR analysis. The suspension was filtered and the residue was well washed with water. The combined filtrate and washings were concentrated to remove methanol, and portions of the resultant solution were purified by ion-exchange chromatography, eluting with a gradient of TEAB (0–1 mol dm^{-3}), pH 7.5. The triethylammonium salt of compound **6** eluted between 800 and 900 mmol dm^{-3} buffer. Fractions containing compound **6**, as judged by total phosphate assay,[27,28] were combined and concentrated to give a residue, to which methanol (2 × 200 cm^3) was added and then evaporated to give *compound* **6** as its *triethylammonium salt*; $[a]_D$ −23 (*c* 0.9 calc. for free acid, TEAB, pH ~8) (Found: M^-, 468.9085. $C_5H_{13}O_{17}P_4$ [*M* − H] requires *m/z*, 468.9103); δ_H(D_2O; pH ~4; 400 MHz; ref. int. HDO) 4.15 (1 H, t, *J* 6.0, 5-H), 4.27 (1 H, ddd, *J* 4.3, 4.6 and 8.9, $CHOPO_3$), 4.39 (1 H, br ddd, $CHOPO_3$) and 4.49–4.56 (2 H, m, 2 × $CHOPO_3$); δ_P(D_2O; pH ~4; 162 MHz) (^1H-coupled) −0.48 (1 P, d, *J* 9.9), −0.40 (1 P, d, *J* 9.0), −0.27 (1 P, d, *J* 8.6) and −0.15 (1 P, d, *J* 9.4); *m/z* 469 [$(M - 1)^-$, 100%].

Stannylene-mediated benzylation of diol 19

A mixture of the cyclopentane **19** (1.79 g, 3.73 mmol), dibutyltin oxide (1.02 g, 4.10 mmol), tetrabutylammonium bromide (1.20 g, 3.73 mmol), benzyl bromide (0.53 cm^3, 4.5 mmol) and acetonitrile (150 cm^3) was heated under reflux for 24 h *via* a Soxhlet thimble containing 4 Å molecular sieves, when TLC ($CHCl_3$–acetone 10 : 1) indicated consumption of starting material (R_f 0.05) to give a product (R_f 0.6). The mixture was cooled and the solvent was evaporated off. The residue was dissolved in diethyl ether (250 cm^3) and this solution was vigorously stirred with saturated aq. $NaHCO_3$ (150 cm^3) for 1 h. The resulting suspension was filtered through Celite and the residue was well washed with diethyl ether. The combined organic extract and washings were dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluent $CHCl_3$–acetone 20 : 1) gave a waxy solid (1.84 g, 87%) which ran as a single spot on TLC in the following systems: methylene dichloride–acetone (30 : 1) (R_f 0.6); ethyl acetate–hexane (4 : 1) (R_f 0.65); diethyl ether (R_f 0.55); diethyl ether–light petroleum (4 : 1) (R_f 0.4); methylene dichloride–methanol (30 : 1) (R_f 0.24–0.38), but which was shown by ^{13}C NMR spectroscopy to be a ~1 : 1 mixture of *bisbenzyl ethers* **25** and **26** (Found: C, 73.7; H, 6.73. $C_{35}H_{38}O_7$ requires C, 73.65; H, 6.72%); δ_C($CDCl_3$; 100 MHz) 55.29 (OMe), 71.52, 71.58, 71.84, 72.15 and 72.29 (Ph*C*H_2O), 72.97 and 73.02 (*C*HOH), 81.18, 84.44, 84.82, 85.37, 86.28 and 86.65 (alkylated ring CH), 113.73 and 113.79 (*ortho*-C of PMB rings), 127.65, 127.72, 127.83, 127.93, 128.05, 128.36, 128.57, 129.44, 129.55 and 129.59 (Ar), 130.17 and 130.25 (*ipso*-C of PMB rings), 137.51, 138.13 and 138.22 (*ipso*-C of benzyl rings) and 159.20 and 159.23 (*para*-C of PMB rings); *m/z* (FAB^+) 570 (M^+, 12%), 449 [$(M - PMB)^+$, 90] and 121 (100).

1L-1,2,4/3,5-1,3-Bisbenzyloxy-2,4,5-trihydroxycyclopentane 27 and 1D-1,2,4/3,5-1,5-bisbenzyloxy-2,3,4-trihydroxycyclopentane 28

Aq. HCl (1 mol dm^{-3}; 40 cm^3) was added to a solution of the mixture of bisbenzyl ethers **25** and **26** (1.63 g, 2.86 mmol) in ethanol (80 cm^3) and the solution was heated under reflux for 2 h, when TLC ($CHCl_3$–acetone 10 : 1) showed consumption of starting material (R_f 0.5) to give a product (R_f 0). The solution was cooled, the solvents were evaporated off, and ethanol (2 × 150 cm^3) was added to and evaporated from the residue. The syrup thus obtained was subjected to flash chromatography (eluent $CHCl_3$–acetone 8 : 1, then 3 : 1) to give *triol* **27** as a syrup which crystallised on storage (400 mg, 42%); R_f 0.3 ($CHCl_3$–acetone 1 : 1); mp 92–93 °C; $[\alpha]_D$ +29.7 (*c* 1.1, $CHCl_3$) (Found: M^+, 331.1533. $C_{19}H_{23}O_5$ [M + H] requires *m/z*, 331.1545); δ_H($CDCl_3$; 400 MHz) 2.93 (3 H, br s, 3 × OH), 3.67 (1 H, dd, *J* 2.9 and 5.9, 1- or 3-H), 3.73 (1 H, t, *J* 7.3, 3- or 1-H), 3.79 (1 H, dd, *J* 5.9 and 7.3, 4- or 5-H), 3.99 (1 H, dd, *J* 2.9 and 5.9, 2-H), 4.04 (1 H, t, *J* 7.3, 5- or 4-H), 4.58 and 4.65 (2 H, AB, J_{AB} 11.7, PhCH_2O), 4.59 and 4.64 (2 H, AB, J_{AB} 11.7, PhCH_2O) and 7.25–7.34 (10 H, m, Ph); δ_C($CDCl_3$; 100 MHz) 71.93 (Ph*C*H_2O), 72.02 (C-2), 72.75 (Ph*C*H_2O), 78.62 and 78.86 (C-4, -5), 81.14 and 87.71 (C-1, -3), 127.83, 127.96, 128.09, 128.25, 128.47, 128.53 and 128.67 (Ph) and 137.29 and 137.78 (2 × *ipso*-C); *m/z* (FAB^-) 329 [$(M - 1)^-$, 30%] and 483 [$(M - NBA)^-$, 100].

A sample of compound **27** was converted into *triacetate* **29** with acetic anhydride in pyridine; R_f 0.6 ($CHCl_3$–acetone 10 : 1); $[\alpha]_D$ +15.4 (*c* 3.4, $CHCl_3$) (Found: C, 65.9; H, 6.13. $C_{25}H_{28}O_8$ requires C, 65.76; H, 6.19%); δ_H($CDCl_3$; 400 MHz) 2.04, 2.05 and 2.09 (9 H, 3 s, 3 × $MeCO_2$), 4.01–4.06 (2 H, m, 1-, 3-H), 4.53–4.65 (4 H, m, 2 × overlapping PhCH_2O AB systems), 5.11–5.14 (2 H, m, 2- and 4-, 5-H), 5.22 (1 H, dd, *J* 4.9 and 5.4, 5- or 4-H) and 7.25–7.35 (10 H, m, Ph); *m/z* (FAB^+) 457 [$(M + 1)^+$, 30%] and 91 (100).

Further elution (eluent $CHCl_3$–acetone 2 : 1) gave *triol* **28** as a solid (320 mg, 34%); R_f 0.2 ($CHCl_3$–acetone 1 : 1); mp 85–87 °C; $[\alpha]_D$ 0.0 (*c* 1.2, $CHCl_3$) (Found: C, 68.7; H, 6.61. $C_{19}H_{22}O_5$ requires C, 69.06; H, 6.72%); δ_H($CDCl_3$; 400 MHz) 3.75–3.88 (7 H, m, 3 × OH, 4 × CH), 3.93 (1 H, t, *J* 7.3, CH), 4.49 (1 H, AB, J_{AB} 11.6, PhC*H*HO), 4.51 (2 H, s, PhCH_2O), 4.58 (1 H, AB, J_{AB} 11.6, PhCH*H*O) and 7.21–7.28 (10 H, m, Ph); δ_C($CDCl_3$; 100 MHz) 71.89 and 72.24 (2 × Ph*C*H_2O), 73.74, 78.80, 79.99, 80.14 and 86.17 (C-1–C-5), 127.69, 127.80, 127.96, 128.07, 128.18, 128.36 and 128.49 (Ph) and 137.38 and 137.95 (2 × *ipso*-C); *m/z* (FAB^+) 331 [$(M + 1)^+$, 30%] and 91 (100).

A sample of triol **28** was converted into *triacetate* **30** by treatment with acetic anhydride in pyridine; R_f 0.55 ($CHCl_3$–acetone 10 : 1); $[\alpha]_D$ +15.2 (*c* 2.0, $CHCl_3$) (Found: C, 65.7; H, 6.24. $C_{25}H_{28}O_8$ requires C, 65.76; H, 6.19%); δ_H($CDCl_3$; 400 MHz) 2.05, 2.07 and 2.09 (9 H, 3 s, 3 × $MeCO_2$), 3.97 (1 H, dd, *J* 4.9 and 5.4, 1- or 5-H), 4.07 (1 H, t, *J* 5.4, 5- or 1-H), 4.52 and 4.56 (2 H, AB, J_{AB} 11.7, PhCH_2O), 4.62 (2 H, s, PhCH_2O), 5.13 (1 H, t, *J* 4.9, 2- or 4-H), 5.21 (1 H, dd, *J* 4.9 and 5.4, 4- or 2-H), 5.27 (1 H, t, *J* 4.9, 3-H) and 7.25–7.36 (10 H, m, Ph); *m/z* (FAB^+) 457 [$(M + 1)^+$, 26%] and 91 (100).

1L-1,2,4/3,5-1,3-Bisbenzyloxy-2,4,5-tris[bis(benzyloxy)phosphoryloxy]cyclopentane 31

A mixture of bis(benzyloxy)(diisopropylamino)phosphine[26] (960 mg, 2.78 mmol) 1*H*-tetrazole (292 mg, 4.17 mmol) and dry methylene dichloride (4 cm^3) was vigorously stirred at room temp. for 15 min, whereupon triol **27** (153 mg, 464 μmol) was added and stirring was continued for 1 h. The mixture was cooled to 0 °C and MCPBA (960 mg, 5.56 mmol) was added. The mixture was stirred at room temp. for 10 min, then was diluted with ethyl acetate (100 cm^3). The solution was washed successively with 10% (w/v) aq. $Na_2S_2O_3$ (50 cm^3), saturated aq. $NaHCO_3$ (2 × 50 cm^3) and saturated aq. NaCl (50 cm^3), dried, filtered and concentrated. The concentrate was purified by flash chromatography (eluent $CHCl_3$–acetone 20 : 1) to give the *title compound* as an oil (440 mg, 85%); $[\alpha]_D$ +6.6 (*c* 2.0, $CHCl_3$) (Found: C, 66.2; H, 5.72. $C_{61}H_{61}O_{14}P_3$ requires C, 65.93; H, 5.54%); δ_H($CDCl_3$; 400 MHz) 4.12–4.20 (2 H, m, 1- and 3-H), 4.49–4.67 (4 H, m, PhC*H*HO, 2-, 4- and 5-H), 4.81–5.07 (15 H, m, 15 × PhC*H*HO) and 7.19–7.26 (40 H, m, Ph); δ_C($CDCl_3$; 100 MHz) 69.46, 69.51 and 69.64 (Ph*C*H_2O of benzyl esters), 72.26 and 72.29 (Ph*C*H_2O of benzyl ethers), 76.85, 80.03 and 83.19 [with C–P coupling], 83.70 [with C–P coupling], 84.36 (C-1–C-5), 127.78, 127.85, 128.02, 128.31, 128.38, 128.49 and 128.69 (Ph), 135.50, 135.57, 135.62 and 135.70 (*ipso*-C of benzyl ester rings) and 137.18 (*ipso*-C of benzyl ether ring[s]); δ_P($CDCl_3$; 162 MHz) −2.27, −2.13 and −1.87 (3 s); *m/z* ($FAB)^+$ 1111 [$(M + 1)^+$, 60%] and 91 (100).

1D-1,2,4/3,5-Cyclopentanepentaol 1,3,4-trisphosphate 5

Sodium hydrogen carbonate (40 mg, 466 μmol) and a suspension of 10% Pd/C (166 mg) in water (5 cm^3) were added to a solution of compound **31** (167 mg, 150 μmol) in methanol (20 cm^3) and the mixture was hydrogenated at 40 psi at room temp. for 48 h to give compound **5** essentially quantitatively, as judged by NMR analysis. The suspension was filtered and the filtrate was well washed with water. The combined filtrate and washings were partially evaporated to remove methanol and portions of the resulting solution were purified by ion-exchange chromatography on Q Sepharose fast-flow resin, eluting with a gradient of TEAB buffer (0–1 mol dm^{-3}), pH 7.5. The triethylammonium salt of compound **5** was eluted between 580 and 670 mmol dm^{-3} buffer. Fractions containing compound **5**, as judged by total phosphate assay,[27,28] were combined and concentrated to give a residue from which methanol (2 × 200 cm^3) was evaporated to give *title trisphosphate* **5** as its *tris*(*triethylammonium*) *salt*; $[\alpha]_D$ −26.2 (*c* 2.0 calc. for free acid, TEAB, pH ~8) (Found: M^-, 388.9456. $C_5H_{12}O_{14}P_3$ $[M - H]^-$ requires *m/z*, 388.9440); δ_H(D_2O, pH ~4, 400 MHz; ref. int. HDO) 3.98–4.02 (2 H, m, 2 × CH), 4.08–4.15 (2 H, m, 2 × CH) and 4.20 (1 H, ddd, J_{HP} 8.8, *J* 4.0, 4.3, $CHOPO_3$); δ_C(D_2O; pH ~4; 100 MHz) 74.30 (C-2 or -5), 78.40 ($^3J_{CP}$ 5.5, C-5 or -2) and 79.12, 83.35 and 84.08 (C-1, -3 and -4 [with C–P coupling]); δ_P(D_2O; pH ~7; 162 MHz) (^{1}H-coupled) 0.79 (1 P, d, *J* 9.7), 1.16 (1 P, d, *J* 8.8) and 1.79 (1 P, d, *J* 7.3); *m/z* (FAB^-) 389 [$(M - 1)^-$, 100%].

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