Chiral Cyclopentane-Based Mimics of D-*myo*-Inositol 1,4,5-Trisphosphate from D-Glucose

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Two routes from D-glucose to chiral, ring-contracted analogs of the second messenger D-*myo*-inositol 1,4,5-trisphosphate are described. Methyl α-D-glucopyranoside was converted by an improved procedure into methyl 4,6-*O*-(*p*-methoxybenzylidene)-α-D-glucopyranoside (**6**) and thence into methyl 2-*O*-benzyl-3,4-bis-*O*-(*p*-methoxybenzyl)-α-D-*gluco*-hexodialdopyranoside (1,5) (**14**) in four steps. In the first ring-contraction method **14** was converted into methyl 2-*O*-benzyl-6,7-dideoxy-3,4-bis-*O*-(*p*-methoxybenzyl)-α-D-*gluco*-hept-6-enopyranoside (1,5) (**15**), which on sequential treatment with $Cp_2Zr(n\text{-}Bu)_2$ followed by $BF_3{\cdot}Et_2O$ afforded a mixture of (1*R*,2*S*,3*S*,4*R*,5*S*)-3-(benzyloxy)-4-hydroxy-1,2-bis[(*p*-methoxybenzyl)oxy]-5-vinylcyclopentane (**16**) and its 4*S*,5*R* diastereoisomer **17**. Removal of the *p*-methoxybenzyl groups of **16** and subsequent phosphorylation and deprotection afforded the first target compound, (1*R*,2*R*,3*S*,4*R*,5*S*)-3-hydroxy-1,2,4-tris(phosphonooxy)-5-vinylcyclopentane (**3**). In the second route, intermediate **14** was subjected to SmI_2-mediated ring contraction to give (1*R*,2*S*,3*S*,4*R*,5*S*)-3-(benzyloxy)-4-hydroxy-5-(hydroxymethyl)-1,2-bis[(*p*-methoxybenzyl)oxy]cyclopentane (**20**). Benzylation of **20** provided (1*R*,2*S*,3*S*,4*R*,5*S*)-3-(benzyloxy)-6-[(benzyloxy)methyl]-4-hydroxy-1,2-bis[(*p*-methoxybenzyl)oxy]cyclopentane (**22**) and (1*R*,2*S*,3*S*,4*R*,5*S*)-3,4-bis(benzyloxy)-5-(hydroxymethyl)-1,2-bis[(*p*-methoxybenzyl)oxy]cyclopentane (**21**), which were elaborated to the target trisphosphates (1*R*,2*R*,3*S*,4*R*,5*S*)-3-hydroxy-5-(hydroxymethyl)-1,2,4-tris(phosphonooxy)cyclopentane (**4**) and (1*R*,2*S*,3*R*,4*R*,5*S*)-1,2-dihydroxy-3,4-bis(phosphonooxy)-5-[(phosphonooxy)methyl]-cyclopentane (**5**), respectively. Both **3** and **4** mobilized intracellular Ca^{2+}, but **4** was only a few fold less potent than D-*myo*-inositol 1,4,5-trisphosphate, demonstrating that effective mimics can be designed that do not bear a six-membered ring.

Introduction

Many cell surface receptors on stimulation activate phospholipase C, liberating the second messenger D-*myo*-inositol 1,4,5-trisphosphate [Ins(1,4,5)P_3, **1**] (Figure 1). Ins(1,4,5)P_3 interacts with a family of intracellular receptor-operated Ca^{2+} channels to mobilize non-mitochondrial Ca^{2+} in many cell types,[1] and extensive biological investigations have followed the discovery of this signaling pathway in 1983.[2] Additionally, the chemical synthesis of structurally modified analogs of **1** has improved understanding of its structure−activity profiles with respect to its receptor and metabolizing enzymes.[3] In particular, a vicinal D-*threo* bisphosphate arrangement is essential for Ca^{2+}-releasing activity,[3,4] while the third phosphate and position 6 hydroxyl group provide enhanced affinity for the receptor.

Until recently, all reported approaches to structural modification of Ins(1,4,5)P_3 that produced agonists had concentrated upon modifications at phosphorus or hydroxyl group deletion, reorientation, alkylation, or replacement with isosteres and other groups in the *six-membered* cyclitol ring. The discovery of the naturally occurring, potently agonistic adenophostins A and B,[5] isolated from cultures of *Penicillium brevicompactum*, has more recently stimulated rational design and synthesis of Ins(1,4,5)P_3 mimics based on D-glucose or D-xylose.[6] Nevertheless, the 3,4-bisphosphate/2-hydroxyl arrangement, analogous to the 4,5-bisphosphate/6-hydroxyl triad in Ins(1,4,5)P_3, is contained within the six-membered pyranoside ring in all of these examples.

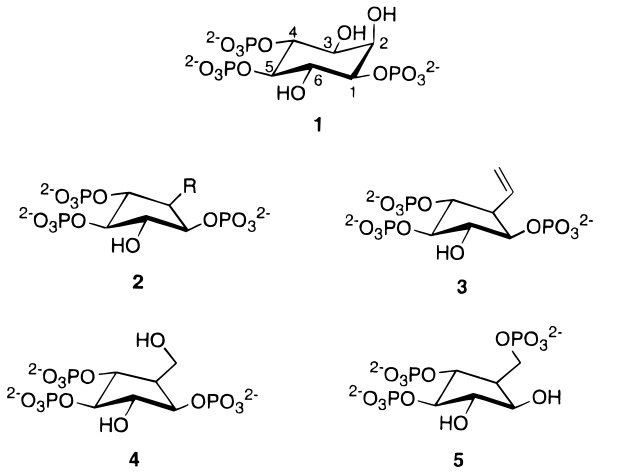

Figure 1. D-*myo*-Inositol 1,4,5-trisphosphate (**1**) and ring-contracted analogs.

Therefore, the requirement of a six-membered ring for activity has not been addressed. Since structure−activity

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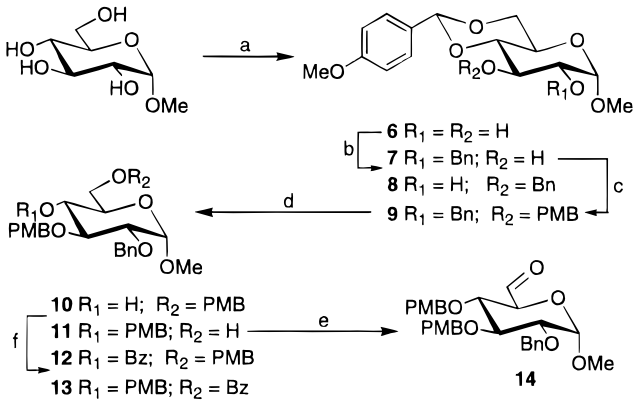
studies have demonstrated that positions 2 and 3, to some extent, of Ins(1,4,5)P_3 can be modified without significant loss of activity,[7] we reasoned that contracted structures such as **2**, in which the relative stereochemistry and substitution of positions equivalent to positions 4, 5, 6, and 1 of Ins(1,4,5)P_3 are broadly retained, might fulfill the recognition requirements of the Ins(1,4,5)P_3 receptor. We report here the preparation of two such compounds, (1*R*,2*R*,3*S*,4*R*,5*S*)-3-hydroxy-1,2,4-trisphosphono-5-vinylcyclopentane (**3**) and (1*R*,2*R*,3*S*,4*R*,5*S*)-3-hydroxy-5-(hydroxymethyl)-1,2,4-trisphosphocyclopentane (**4**), from D-glucose, using two recently described carbohydrate ring-contraction methods,[8,9] together with a related derivative (1*R*,2*S*,3*R*,4*R*,5*S*)-1,2-dihydroxy-3,4-bis(phosphonooxy)-5-[(phosphonooxy)methyl]cyclopentane (**5**), in which the third phosphate has been relocated. A preliminary account of the synthesis of **3** has appeared.[10]

Results and Discussion

The known[11] methyl 4,6-*O*-(*p*-methoxybenzylidene)-α-D-glucopyranoside (**6**) was prepared on a 0.7 mol scale by a slight modification of the literature method. Thus, methanol liberated from the acid-catalyzed reaction of methyl α-D-glucopyranoside with *p*-methoxybenzaldehyde dimethyl acetal in DMF was removed *via* an air condenser. Subsequent removal of the solvent and recrystallization afforded **6** in 84% yield without further manipulation. Stannylene-mediated benzylation of **6** gave the monobenzyl ethers **7** and **8** in a ratio of 4.4:1, and *p*-methoxybenzylation of the 2-benzyl derivative **7** under standard conditions provided fully protected **9** (Scheme 1).

Treatment of **9** with sodium cyanoborohydride and trimethylsilyl chloride in acetonitrile gave the chromatographically separable **10** and **11** in a ratio of *ca.* 1:1.7. The structures of **10** and **11** were established by comparison of the chemical shifts of their position 6 carbon atoms, as observed in the ^{13}C NMR spectra in $CDCl_3$. The C-6 of **10** resonates at lower field (69.2 ppm) than that of **11** (61.8 ppm) due to the α-effect of alkylation.[12] These assigned structures were confirmed by preparation of benzoates **12** and **13**. The ^1H NMR spectrum of **12** displayed a deshielded triplet at 5.28 ppm, corresponding to the position 4 methine; the position 6 methylene protons of **13** were deshielded to 4.46−4.97 ppm. The selectivity of *p*-methoxybenzylidene cleavage in this case was much poorer than that reported for the corresponding 2,3-di-*O*-benzyl glucoside;[11] however, exclusive formation of **11** was observed on treatment of **9** with $LiAlH_4$−$AlCl_3$ in refluxing THF.[13]

Scheme 1[a]



[a]Reagents and conditions: (a) *p*-methoxybenzaldehyde dimethyl acetal, *p*-toluenesulfonic acid, DMF, 70 °C, −MeOH; (b) (i) *n*-Bu_2SnO, *n*-Bu_4NI, CH_3CN, 4 Å molecular sieves, reflux; (ii) BnBr, reflux; (c) NaH, PMBCl, DMF, rt; (d) $LiAlH_4$, $AlCl_3$, THF, N_2, reflux; (e) (i) DMSO, $(COCl)_2$, CH_2Cl_2 then Et_3N, −60 °C; (f) BzCl, DMAP, pyridine; PMB = *p*-methoxybenzyl, Bn = benzyl; Bz = benzoyl.

Aldehyde **14** was smoothly prepared by Swern oxidation[14] of **11**. After column chromatography, the IR spectrum indicated absorption at 3400−3650 cm^{-1}, corresponding to OH stretching, in addition to the expected absorption at 1745 cm^{-1}, corresponding to C=O stretching. As azeotropic drying abolished the former band, it was assumed to arise from hydration of the aldehyde rather than from contamination by starting material. Although sufficiently stable to allow characterization, **14** gradually rehydrated on standing in air for several days and was therefore best prepared freshly. Hydration of related aldehydes has been reported.[15]

Wittig methylenation of **14** provided vinyl carbohydrate **15** (Scheme 2). The zirconium-mediated ring-contraction was carried out as described,[8] by treating **15** with Cp_2Zr-(*n*-$Bu)_2$ (prepared *in situ* from zirconocene dichloride and 2 equiv of *n*-butyllithium), followed by boron trifluoride etherate in THF. A complication was the gradual loss of *p*-methoxybenzyl protecting groups after the addition of boron trifluoride etherate. Nevertheless, the desired vinylcyclopentane **16** was obtained in 46% yield as a waxy solid, together with a small amount of the kinetically disfavored product **17**, which was crystalline. The relative stereochemistry of substituents for each of **16** and **17** was confirmed by phase-sensitive 2D-NOESY and NOE difference NMR spectroscopy, and the results of the latter experiments are summarized in Figure 2.

Acidic hydrolysis of the *p*-methoxybenzyl groups from **16** gave the triol **18**. Phosphitylation using bis(benzyloxy)(*N*,*N*-diisopropylamino)phosphine,[16] followed by oxidation of phosphites with *m*-CPBA, gave the fully protected trisphosphate **19**. ^{31}P NMR spectroscopy of the

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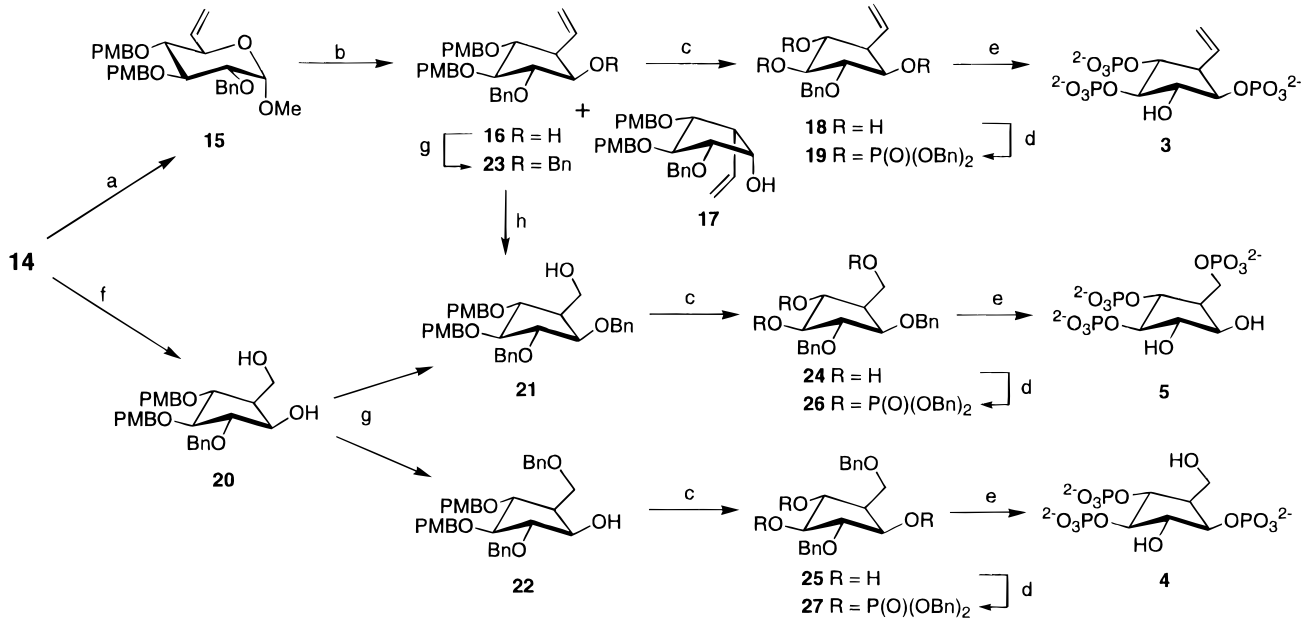
Scheme 2[a]



[a] Reagents and conditions: (a) CH_3PPh_3, *t*-BuOK, THF; (b) "Cp_2Zr"/THF then $BF_3{\cdot}Et_2O$, −78 °C to rt; (c) 1 M HCl/EtOH 1:2, reflux; (d) (i) *i*-$Pr_2NP(OBn)_2$, 1*H*-tetrazole, CH_2Cl_2, (ii) *m*-CPBA, −78 °C; (e) Na/NH_3, −78 °C; (f) SmI_2, THF, HMPA, *t*-BuOH, rt; (g) NaH, BnBr, DMF, 0 °C; (h) (i) OsO_4, $NaIO_4$, Et_2O-H_2O, rt, (ii) $NaBH_4$, MeOH, rt; Bn = benzyl, PMB = *p*-methoxybenzyl.

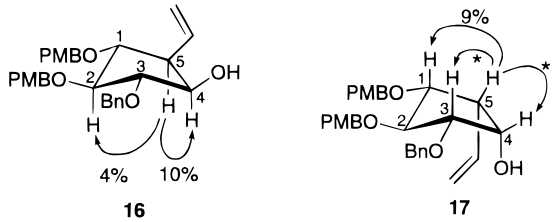


Figure 2. Results of NOE difference spectroscopy of diastereoisomers **16** and **17** (Bn = benzyl, PMB = *p*-methoxybenzyl). *Positive NOEs to H-3 and/or H-4 were observed for **17**, but could not be quantified due to overlap of these signals with one another and with OCH_3 of PMB groups.

intermediate trisphosphite triester showed an unusually high $^5J_{PP}$ coupling of 6.7 Hz [*cf.* 2.9 Hz and 3.4 Hz for precursors of Ins(4,5)P_2[17] and Ins(1,4,5)P_3[18] respectively], presumably reflecting the altered geometry of the P(III)−P(III) interaction in a five-membered ring; similar values were obtained for the other trisphosphites described in this paper. Deprotection using sodium in liquid ammonia[19] removed the benzyl ether and six benzyl esters, leaving the vinyl group intact. The logic of retaining this unusual feature in the target molecule was to produce a ring-contracted Ins(1,4,5)P_3 analog containing the essential recognition elements in the minimum number of synthetic steps, but with the potential for further modification. Purification by ion-exchange chromatography of the crude product on Q Sepharose fast flow resin gave the target trisphosphate **3**, which was isolated as the triethylammonium salt and quantified by total phosphate assay.[19]

Trisphosphate **3** was examined for Ca^{2+} mobilizing activity at the platelet Ins(1,4,5)P_3 receptor using fluorescence techniques and also using saponin-permeabilized platelets loaded with $^{45}Ca^{2+}$.[20] It was found to be a full agonist, although with an EC_{50} value 65-fold higher than that of Ins(1,4,5)P_3. These results demonstrated for the first time that *myo*-inositol 1,4,5-trisphosphate receptor-mediated Ca^{2+} mobilization does not necessarily require a cyclohexyl (or equivalent) structure.

At this stage it was impossible to say whether the considerably reduced potency of **3** relative to Ins(1,4,5)P_3 was related to the presence of the hydrophobic vinyl group or was a necessary consequence of the reduced ring size. In the five-membered ring, for example, the dihedral angle corresponding to O4−C4−C5−O5 of Ins(1,4,5)P_3 is larger than in Ins(1,4,5)P_3, and the relative position of the third phosphate group is slightly altered. However, noting that DL-3-*O*-ethyl-Ins(1,4,5)P_3 and DL-3-*O*-propyl-Ins(1,4,5)P_3[21] both have EC_{50} values of greater than 100 μM in SH-SY5Y neuroblastoma cells [*cf.* Ins(1,4,5)P_3 0.18 μM],[22] it seemed likely that replacement of the vinyl group of **3** with a more hydrophilic, hydroxyl-containing side chain might increase its potency. An obvious target was **4**, in which the vinyl group is replaced by hydroxymethyl, and a timely report by Sinaÿ and coworkers[9] offered a straightforward route from intermediate **14**.

Thus, treatment of **14** with samarium (II) iodide in THF in the presence of 2-methyl-2-propanol and HMPA gave two products that were separated by column chromatography and identified as the reduced starting material **11** (19%) and the derived **20** (37%). Benzylation of **20** at 0 °C with 1 equiv of NaH and 1.1 equiv of benzyl bromide in dry DMF gave a mixture of **21** and **22** in a ratio of 3:2, respectively. The structures of **21** and **22** were distinguished by comparison of chemical shifts of the methylene carbon atoms of the C-5 side chain in the

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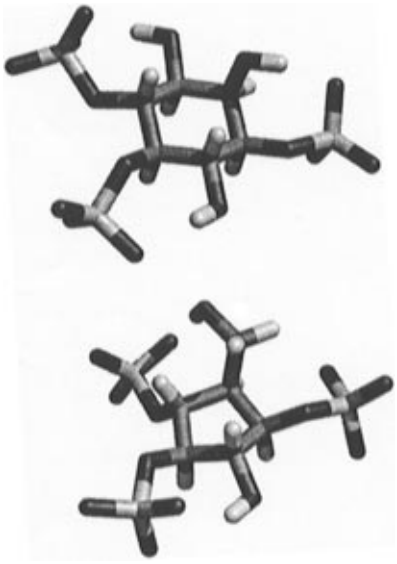

Figure 3. Energy-minimized structures of Ins(1,4,5)P_3 and ring-contracted analog **4**.

^{13}C NMR spectra, the α-effect of alkylation causing this signal in the spectrum of **22** to be deshielded relative to that of **21**.

Benzylation of the major product **16** of the zirconium-mediated contraction gave **23**, which on sequential treatment with OsO_4−$NaIO_4$ followed by $NaBH_4$[23] also afforded **21**, thereby confirming the stereochemistry of **20** and derivatives.

Diastereoisomers **21** and **22** were individually hydrolyzed to triols **24** and **25**, respectively. These were phosphitylated and oxidized to **26** and **27**, respectively, and deprotected to the target trisphosphates **5** and **4**, respectively, as described for precursors of **3**. Both **4** and **5** were purified by ion-exchange chromatography and isolated as their triethylammonium salts.

Trisphosphates **4** and **5** were examined for Ca^{2+} mobilizing activity in permeabilized Jurkat T-lymphocytes.[24] Preliminary results demonstrated an EC_{50} value for **4** only 2−4-fold higher than that of Ins(1,4,5)P_3 itself, showing that replacement of the hydrophobic vinyl substituent of **3** with hydroxymethyl results in a sharp increase in potency. Energy-minimized structures of **4** and Ins(1,4,5)P_3 (Figure 3) show clearly that the vicinal phosphate groups and secondary hydroxyl of **4** are well-placed to mimic the corresponding features in Ins(1,4,5)P_3. It is not yet clear whether the enhanced activity of **4** compared to **3** is due simply to the removal of the hydrophobic vinyl group, or whether the primary hydroxyl group engages in favorable interactions with the Ins(1,4,5)P_3 receptor binding site. Another possibility is that the hydroxymethyl group influences the orientation or ionization state of the adjacent phosphates by intramolecular hydrogen bonding. Interestingly, **5**, in which the relative arrangement of phosphate esters around the ring is not conserved, released little Ca^{2+} at the concentrations tested. Full biological results will be published elsewhere.

In conclusion, the Ca^{2+}-mobilizing ability of the prototype ring-contracted Ins(1,4,5)P_3 analog **3** demonstrated for the first time that a six-membered ring is not an absolute requirement for Ins(1,4,5)P_3 receptor agonists. A smaller ring polyphosphate that retained certain structural elements of Ins(1,4,5)P_3, namely three appropriately oriented phosphates and an equivalent to the 6-hydroxyl group, could still be recognized by the receptor. The enhanced potency of the hydroxymethyl analog **4** now shows that a cyclopentane-based structure can possess Ca^{2+}-mobilizing activity rivalling that of more conventional Ins(1,4,5)P_3 analogs based on six-membered rings. The utility of ring-contraction methodologies for the synthesis of other five-membered ring inositol phosphate analogs from carbohydrates is currently under investigation, while the detailed biology of this new class of second messenger mimics remains to be explored.

Experimental Section

Materials and Methods. Chemicals were purchased from Aldrich, Sigma, and Fluka. Dichloromethane was dried over phosphorus pentoxide, distilled, and kept over 4 Å molecular sieves. *N*,*N*-Dimethylformamide was distilled from barium oxide under reduced pressure and then stored over 4 Å sieves. Tetrahydrofuran (THF) was dried by passing through activated alumina to expel peroxide radicals, followed by distillation from sodium in the presence of benzophenone ketyl. 2-Methyl-2-propanol was distilled from calcium hydride. Hexamethylphosphoric triamide (HMPA) was stored over 4 Å sieves. Dimethyl sulfoxide (DMSO) and 1,4-dioxane were purchased in anhydrous form.

TLC was performed on precoated plates (Merck TLC aluminum sheets silica F_{254}, Art no. 5554) with detection by UV light or with methanolic phosphomolybdic acid followed by heating. Flash-column chromatography was performed on silica gel (Sorbsil C60).[25]

For ^{31}P NMR spectra δ values are denoted positive for shifts downfield from external aqueous 85% phosphoric acid. FAB-mass spectra were carried out using *m*-nitrobenzyl alcohol as the matrix. Melting points (uncorrected) were determined using a Kofler block. Optical rotations were measured at ambient temperature. Ion-exchange chromatography was performed on an LKB-Pharmacia medium pressure ion exchange chromatograph using DEAE Sepharose or Q Sepharose fast flow by elution with a gradient of triethylammonium hydrogencarbonate (TEAB) buffer. Quantitative analysis of phosphate was performed using a modification of the Briggs phosphate assay.[19,26]

(*N*,*N*-Diisopropylamino)dichlorophosphine was prepared by the method of Tanaka *et al.*[27] by adding 2 equiv of diisopropylamine to a solution of PCl_3 in dry ether at −78 °C. The crude product (δ_P 166.4) was purified by distillation under reduced pressure, and reaction with 2 equiv of benzyl alcohol in the presence of 2 equiv of triethylamine afforded bis(benzyloxy)(*N*,*N*-diisopropylamino)phosphine[28] (δ_P 145.24), which was purified by flash chromatography.

Molecular modeling calculations were performed on a Silicon Graphics Indigo R3000 workstation using the Insight II (Ver. 2.3.5) and Discover (Ver. 2.9.5) molecular modeling packages (Biosym Technologies, San Diego, USA). Energies were calculated using the AMBER force field. Structures for **4** and Ins(1,4,5)P_3 were first energy-minimized by steepest descent, and then partial charges were calculated for the fully-ionized structures using the AM1 semiempirical method as implemented in the MOPAC program (Ver. 6.0). The charged structures were then reminimized and finally optimized using the VAO9A minimizer.

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Methyl 4,6-*O*-(*p*-Methoxybenzylidene)-α-D-glucopyranoside (6). A 1 L flask containing methyl-α-D-glucopyranoside (131 g, 0.68 mol), *p*-methoxybenzaldehyde dimethyl acetal[11] (122 mL, 0.71 mol), *p*-toluenesulfonic acid (2 g), and DMF (500 mL) was fitted with an air condenser, attached to a water pump *via* a three-way tap, and evacuated. The system was stirred at 70 °C until MeOH ceased to condense (4 h). The solution was cooled, and the solvents were evaporated *in vacuo* to give a white residue. Crystallization from 2% w/v aqueous $NaHCO_3$ solution (11 L) gave the title compound as fine white needles (177 g, 84%): mp 202 °C (lit.[11] mp 194 °C); $[\alpha]_D$ = +88.4 (*c* 1.2, DMF) (lit.[11] $[\alpha]_D$ +97.4).

Methyl 2-*O*-Benzyl-4,6-*O*-(*p*-methoxybenzylidene)-α-D-glucopyranoside (7) and Methyl 3-*O*-Benzyl-4,6-*O*-(*p*-methoxybenzylidene)-α-D-glucopyranoside (8). A mixture of **6** (15.5 g, 49.7 mmol), dibutyltin oxide (13.6 g, 54.6 mmol), and tetrabutylammonium iodide (18.4 g, 49.8 mmol) was heated under reflux for 2 h in MeCN (600 mL) *via* a Soxhlet thimble containing 4 Å molecular sieves. The solution was cooled to room temperature and benzyl bromide (6.5 mL, 54.6 mmol) was added. The system was heated under reflux for a further 16 h and then cooled. Triethylamine (25 mL) was added, and stirring was continued for 3 h. The solvents were evaporated, and the orange residue was extracted with Et_2O (500 mL). The ethereal extract was vigorously stirred with saturated aqueous $NaHCO_3$ solution (200 mL) for 2 h, and the resulting suspension was filtered through Celite. The organic layer was collected, washed with H_2O (200 mL), dried ($MgSO_4$), filtered, and concentrated. The white residue thus obtained was subjected to flash chromatography (hexane/EtOAc 7:3) to give **7** (9.6 g, 48%): TLC (hexane/EtOAc 4:6) R_f = 0.53; mp 135−136.5 °C (from EtOH); $[\alpha]_D$ = +31.9 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.65 (d, J = 2.0 Hz, 1 H, D_2O ex , OH), 3.37 (s, 3 H, OCH_3), 3.44−3.49 (m, 2 H, C-2-H, C-4-H), 3.68 (t, J = 10 Hz, 1 H, 6-H_{ax}), 3.78 (s, 3 H, ArOCH_3), 3.77−3.80 (m, 1 H, C-5-H), 4.13 (td, J = 2.0 Hz, 9.7Hz, 1 H, D_2O shake gives t, C-3-H), 4.23 (dd, $^2J_{6-Heq,6-Hax}$ = 10 Hz, $^3J_{6-Heq,H-5}$ = 4.6 Hz, 1 H, C-6-H_{eq}), 4.60 (d, J = 3.4 Hz, 1 H, C-1-H), 4.69, 4.78 (AB, J_{AB} =12.2 Hz, 2 H, $C_6H_5CH_2O$), 5.47 (s, 1 H, C-7-H), 6.87 (d, J = 8.8 Hz, 2 H, C-3-H and C-5-H of *p*-methoxyphenyl ring), 7.25−7.42 (m, 7 H, aromatic CH); ^{13}C NMR ($CDCl_3$, 100.4 MHz) δ 55.3, 55.3 (2 × OCH_3), 62.0 (CH), 68.9 (C-6), 70.2 (CH), 73.2 ($C_6H_5CH_2O$), 73.3, 79.5 (CH), 98.5 (C-1), 101.9 (C-7), 113.6 (C-3 and C-5 of *p*-methoxyphenyl ring), 127.6, 127.6, 128.0, 128.1, 128.5 (aromatic CH), 129.6 (C-1 of *p*-methoxyphenyl ring), 137.9 (C-1 of benzyl ring), 160.1 (C-4 of *p*-methoxyphenyl ring); MS *m*/*z* (+ve ion FAB) 403 [(M + H)$^+$, 40]. Anal. Calcd for $C_{22}H_{26}O_7$, 65.64; H, 6.52. Found: C, 65.4; H, 6.47.

Further elution gave **8** (2.2 g, 11%): TLC (hexane/EtOAc 4:6) R_f = 0.35; mp 176−178 °C (from EtOH); $[\alpha]_D$ = +76.2 (*c* 1.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.42 (d, J = 7.3 Hz, 1 H, D_2O ex, OH), 3.43 (s, 3 H, OCH_3), 3.58−3.84 (m, 8 H, C-2-H, C-3-H, C-4-H, C-5-H, C-6-H_{ax}, ArOCH_3), 4.34 (dd, $^3J_{6-Heq,H-5}$ = 3.8 Hz, $^2J_{6-Heq,6-Hax}$ = 9.3 Hz, 1 H, C-6-H_{eq}), 4.75−4.96 (m, AB, J_{AB} = 11.5 Hz, 3 H, $C_6H_5CH_2O$ overlapping with C-1-H), 5.51 (s, 1 H, C-7-H), 6.90 (d, J = 8.8 Hz, 2 H, C-3-H and C-5-H of *p*-methoxyphenyl ring), 7.24−7.42 (m, 7 H, aromatic CH); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 55.2 , 55.3 (2 × OCH_3), 62.5 (CH), 68.9 (C-6), 72.3 (CH), 74.7 ($C_6H_5CH_2O$), 78.8, 81.8 (CH), 99.8 (C-1), 101.2 (C-7), 113.5 (C-3 and C-5 of *p*-methoxyphenyl ring), 127.3, 127.6, 127.9, 128.3 (aromatic CH), 129.8 (C-1 of *p*-methoxyphenyl ring), 138.5 (C-1 of benzyl ring), 160.0 (C-4 of *p*-methoxyphenyl ring); MS *m*/*z* (+ve ion FAB) 403 [(M + H)$^+$, 30]. Anal. Calcd for $C_{22}H_{26}O_7$: C, 65.64; H, 6.52. Found: C, 65.5; H, 6.48.

Methyl 2-*O*-Benzyl-3-*O*-(*p*-methoxybenzyl)-4,6-*O*-(*p*-methoxybenzylidene)-α-D-glucopyranoside (9). A solution of **7** (9.6 g, 23.8 mmol) in dry DMF (50 mL) was sequentially treated with NaH (857mg of an 80% w/w dispersion in mineral oil, 28.6 mmol) and *p*-methoxybenzyl chloride (3.4 mL, 25.0 mmol). The mixture was stirred at room temperature for 3 h. Methanol (10 mL) was added, and stirring was continued for 1 h. The solvents were evaporated, and the residue was extracted with $CHCl_3$ (3 × 150 mL). The combined organic extracts were washed with H_2O (2 × 100 mL), dried ($MgSO_4$), filtered, and concentrated to give crude **9** (11.8 g). Crystallization from EtOH gave pure **9** (10.9 g, 87%): TLC (hexane/EtOAc 4:6) R_f = 0.60; mp 144−145 °C; $[\alpha]_D$ = −30.0 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.40 (s, 3 H, OCH_3), 3.50−3.59 (m, 2 H, C-2-H, C-4-H), 3.64−3.98 (m, 8 H, C-5-H, C-6-H_{ax}, 2 × ArOCH_3), 4.02 (t, J = 9.1Hz, 1 H, C-3-H), 4.39 (dd, $^3J_{6-Heq,H-5}$ = 4.3Hz, $^2J_{6-Heq,6-Hax}$ = 9.8Hz, 1 H, C-6-H_{eq}), 4.57 (d, J = 3.7Hz, 1 H, C-1-H), 4.67−4.88 (m, 4 H, 2 × ArCH_2O AB systems), 5.50 (s, 1 H, C-7-H), 6.82−6.92 (m, 4 H, 2 × C-3-H and C-5-H of *p*-substituted rings), 7.25−7.43 (m, 9 H, aromatic CH); ^{13}C NMR ($CDCl_3$, 100.4 MHz) δ 55.2, 55.3, 55.3 (3 × OCH_3), 62.3 (CH), 69.0 (C-6), 73.8, 75.0 (2 × ArCH_2O), 78.3, 79.2, 82.1 (CH), 99.3 (C-1), 101.2 (C-7), 113.6, 113.7 (2 × C-3 and C-5 of *p*-substituted rings), 127.3, 127.9, 128.1, 128.4, 129.7, 130.0 (aromatic CH), 130.9 (C-1 of *p*-substituted ring[s]), 138.2 (C-1 of benzyl ring), 159.2, 160.0 (2 × C-4 of *p*-substituted rings); MS *m*/*z* (+ve ion FAB) 523 [(M + H)$^+$, 10]. Anal. Calcd for $C_{30}H_{34}O_8$: C, 68.94; H, 6.56. Found: C, 68.9; H, 6.67.

Methyl 2-*O*-Benzyl-3,6-bis-*O*-(*p*-methoxybenzyl)-α-D-glucopyranoside (10) and Methyl 2-*O*-Benzyl-3,4-bis-*O*-(*p*-methoxybenzyl)-α-D-glucopyranoside (11). (*a*) A solution, kept at 0 °C, of trimethylsilyl chloride (12.5 mL, 98.4 mmol) in dry acetonitrile (15 mL) was added dropwise under N_2 to a vigorously stirred mixture of **9** (8.6 g, 16.4 mmol), sodium cyanoborohydride (6.2 g, 98.4 mmol), 3 Å molecular sieves, and dry acetonitrile (150 mL) at 0 °C. The suspension was allowed to warm to room temperature and was stirred under N_2 for 3.5 h, when TLC (hexane/EtOAc 2:3) indicated conversion of starting material (R_f = 0.62) into a minor product (R_f = 0.51) and a major product (R_f = 0.28). The suspension was filtered through Celite into ice-cold saturated aqueous $NaHCO_3$ solution (300 mL), and the residue was washed with acetonitrile. The aqueous layer was extracted with Et_2O (2 × 200 mL), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (250 mL), dried ($MgSO_4$), filtered, and concentrated. The yellow residue thus obtained was subjected to flash chromatography (eluent hexane/EtOAc 7:3) to give **10** as a colorless oil (2.4 g, 28%): $[\alpha]_D$ = +12.6 (*c* 2.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$; 270 MHz) δ 2.36 (br s, 1 H, D_2Oex, OH), 3.38 (s, 3 H, OCH_3), 3.48−3.79 (m, 6 H, C-2-H, C-3-H, C-4-H, C-5-H, C-6-H, C-6-H′), 3.78, 3.79 (2 s, 6 H, 2 × OCH_3), 4.43−4.93 (m, 7 H, C-1-H, 3 × ArCH_2O AB systems), 6.83−6.90 (m, 4 H, C-3-H and C-5-H of PMB rings), 7.22−7.36 (m, 9 H, aromatic CH); ^{13}C NMR ($CDCl_3$; 67.8 MHz) δ 55.1, 55.2 (2 × OCH_3), 69.2 (C-6), 69.8, 70.7 (C-4, C-5), 73.1, 73.2, 75.0 (3 × ArCH_2O), 79.5, 81.0 (C-2, C-3), 98.1 (C-1), 113.7, 113.9 (2 × C-3 and C-5 of PMB rings), 127.8, 128.0, 128.4, 129.2, 129.6 (aromatic CH), 130.0, 130.9 (2 × C-1 of PMB rings), 138.0 (C-1 of benzyl ring), 159.1, 159.3 (2 × C-4 of PMB rings); MS *m*/*z* (−ve ion FAB) 523 [(M − H)$^-$, 70], 677 [(M + NBA)$^-$, 80]. Anal. Calcd for $C_{30}H_{36}O_8$: C, 68.67; H, 6.92. Found: C, 68.9; H, 6.91.

A sample of **10** was converted into its syrupy 4-*O*-benzoyl ester **12** with benzoyl chloride in pyridine: $[\alpha]_D$ = −12.1 (*c* 2.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$; 270 MHz) δ 3.43 (s, 3 H, OCH_3), 3.42−3.54 (m, 2 H, C-6-H, C-6-H′), 3.62−3.67 (m, 4 H, OCH_3, C-2-H), 3.70 (s, 3 H, OCH_3), 3.94 (ddd, J =3.5, 9.2, 9.8 Hz, 1 H, C-5-H), 4.03 (t, J = 9.5 Hz, 1 H, C-3-H), 4.37, 4.41 (AB, J_{AB} = 13.1 Hz, 2 H, ArCH_2O), 4.53−4.85 (m, 5 H, C-1-H, 2 × ArCH_2O AB systems) 5.28 (t, 1 H, J = 9.7 Hz, C-4-H), 6.59 (d, J = 8.6 Hz, 2 H, C-3-H and C-5-H of PMB ring), 6.71 (d, J = 8.6 Hz, 2 H, C-3-H and C-5-H of PMB ring), 7.04 (d, J = 8.6 Hz, 2 H, C-2-H and C-6-H of PMB ring), 7.15 (d, J = 8.6Hz, 2 H, C-2-H and C-6-H of PMB ring), 7.25−7.56 (m, 8 H, aromatic CH), 7.90−7.94 (m, 2 H, C-2-H and C-6-H of benzoyl ring); MS *m*/*z* (+ve ion FAB) 628 [(M + H)$^+$, 10].

Further elution (eluent hexane/EtOAc 2:3) gave **11** as a pale yellow oil that solidified to a waxy solid (mp 50−51.5 °C) on standing (4.1 g, 48%): $[\alpha]_D$ = +7.5 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$; 400 MHz) δ 1.85 (br s, 1 H, D_2Oex, OH), 3.35 (s, 3 H, OCH_3), 3.45−3.50 (m, 2 H, C-2-H, C-4-H), 3.59−3.76 (m, 3 H, C-5-H, C-6-H, C-6-H′), 3.78, 3.79 (2 s, 6 H, 2 × ArOCH_3), 3.97 (t, 1 H, J = 9.3 Hz, C-3-H), 4.55−4.99 (m, 7 H, C-1-H, 3 × ArCH_2O AB systems), 6.84−6.88 (m, 4 H, 2 × C-3-H and C-5-H of PMB rings), 7.20−7.38 (m, 9 H, aromatic CH); ^{13}C

NMR ($CDCl_3$; 67.8 MHz) δ 55.1, 55.2 (2 × OCH_3), 61.8 (C-6), 70.6 (C-5), 73.4, 74.6, 75.4 (3 × ArCH_2O), 77.5, 80.0, 81.7 (C-2, C-3, C-4), 98.1 (C-1), 113.8, 113.8 (2 × C-3 and C-5 of PMB rings), 127.8, 128.0, 128.4, 129.6, 129.6 (aromatic CH), 130.3, 130.9 (2 × C-1 of PMB rings), 138.1 (C-1 of benzyl ring), 159.1, 159.3 (2 × C-4 of PMB rings); MS *m/z* (−ve ion FAB) 677 [(M + NBA)$^-$, 60]. Anal. Calcd for $C_{30}H_{36}O_8$: C, 68.67; H, 6.92. Found: C, 68.6; H, 7.05.

A sample of **11** was converted to its 6-*O*-benzoyl ester **13** with benzoyl chloride in pyridine: TLC (hexane/EtOAc 2:3) R_f = 0.64; mp 120.5 °C (from 2-propanol); $[\alpha]_D$ = +86.2 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$; 270 MHz) δ 3.38 (s, 3 H, OCH_3), 3.54−3.62 (m, 2 H, C-2-H, C-4-H), 3.72, 3.81 (2 s, 6 H, 2 × $ArOCH_3$), 3.92 (dq, *J* = 2, 9.6 Hz, 1 H, C-5-H), 4.03 (t, *J* = 9.2 Hz, 1 H, C-3-H), 4.46−4.97 (m, 9 H, 3 × ArCH_2O AB systems, C-1-H, C-6-H, C-6-H′), 6.80 (d, *J* = 8.6 Hz, 2 H, C-3-H and C-5-H of PMB ring), 6.89 (d, *J* = 8.6 Hz, 2 H, C-3-H and C-5-H of PMB ring), 7.17−8.14 (m, 14 H, aromatic CH); MS *m/z* (+ve ion FAB) 628 [M$^+$, 5]. Anal. Calcd for $C_{37}H_{40}O_9$: C, 70.68; H, 6.41. Found: C, 70.9; H, 6.30.

(b) To a solution of **9** (5.7 g, 10.9 mmol) in freshly distilled, dry THF (200 mL) was added $LiAlH_4$ (2 g) in one portion. The mixture was gradually brought to refluxing temperature. After 1 h, $AlCl_3$ (6 g) was carefully added in portions over 30 min. The mixture was stirred under reflux for a further 2 h and then cooled to 0 °C. Excess $LiAlH_4$ was destroyed by careful addition of EtOAc (20 mL), and $Al(OH)_3$ was precipitated by addition of water (30 mL). The system was extracted with Et_2O (300 mL), and the combined organic extracts were washed with H_2O (200 mL), dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (eluent hexane/EtOAc 7:3) of the concentrate gave exclusively **11** (4.2 g, 73%).

Methyl 2-*O*-Benzyl-3,4-bis-*O*-(*p*-methoxybenzyl)-α-D-*gluco*-hexodialdopyranoside (1,5) (14). Dry DMSO (0.33 mL) was added dropwise to a 2 M solution of oxalyl chloride in CH_2Cl_2 (1.25 mL, 2.5 mmol) at −60 °C under N_2. After 5 min, a solution of **11** (1.2 g, 2.3 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 5 min. The mixture was stirred at −60 °C for 20 min when Et_3N (1.2 mL, 9.2 mmol) was added. After a further 10 min, the mixture was allowed to warm to room temperature. The solvents were evaporated, and the residue was subjected to flash chromatography (eluent EtOAc/hexane 3:2) to give the crude product, which showed OH stretching at ν_{max} 3480 cm^{-1} in the IR spectrum. The product was dissolved in toluene (150 mL) and heated under reflux for 3 h with continuous azeotropic removal of water (Dean−Stark trap). The solution was cooled and concentrated to give the pure title compound as a pale yellow oil (1.0 g, 84%): TLC (EtOAc) R_f = 0.62 with streaking; $[\alpha]_D$ = +19.6 (*c* 4.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$; 400 MHz) δ 3.36 (s, 3 H, OCH_3), 3.47 (dd, *J* = 3.4, 9.3 Hz, 1 H, C-2-H), 3.53 (t, *J* = 8.8, 10.3 Hz, 1 H, C-4-H), 3.79, 3.80 (2 s, 6 H, 2 × $ArOCH_3$), 4.05 (t, *J* = 9.3 Hz, 1 H, C-3-H), 4.13 (d, *J* = 10.3 Hz, 1 H, C-5-H), 4.53−4.93 (m, 7 H, 3 × ArCH_2O AB systems, C-1-H), 6.85−6.89 (m, 4 H, C-3-H and C-5-H of PMB rings), 7.15−7.36 (m, 9 H, aromatic CH), 9.62 (s, 1 H, C-6-H); ^{13}C NMR ($CDCl_3$; 100.4 MHz) δ 55.3, 55.7 (2 × OCH_3), 73.6 (ArCH_2O), 74.3 (C-5), 74.7, 75.6 (2 × ArCH_2O), 77.5, 79.3, 81.5 (C-2, C-3, C-4), 98.4 (C-1), 113.9 (C-3 and C-5 of PMB rings), 128.1, 128.2, 128.5, 128.6, 129.0, 129.6, 129.7, 129.8 (aromatic CH), 129.9, 130.6 (2 × C-1 of PMB rings), 137.9 (C-1 of benzyl ring), 159.3, 159.5 (2 × C-4 of PMB rings), 197.6 (C-6); MS *m/z* (−ve ion FAB) 677 [(M + NBA)$^-$, 60]; IR (liquid film) ν_{max} 1745 cm^{-1}. Anal. Calcd for $C_{30}H_{34}O_8$: C, 68.94; H, 6.56. Found: C, 68.7; H, 6.63.

Methyl 2-*O*-Benzyl-6,7-dideoxy-3,4-bis-*O*-(*p*-methoxybenzyl)-α-D-*gluco*-hept-6-enopyranoside (1,5) (15). A dry 100 mL flask was charged with methyltriphenylphosphonium bromide (3.70 g, 10.4 mmol), previously dried *in vacuo* at 60 °C. Dry THF (10 mL) was added and the suspension was cooled to −10 °C, with stirring, under N_2. Potassium *tert*-butoxide (9.8 mL of a 1.0 M solution in dry THF) was added, and the yellow suspension was allowed to reach room temperature. After being stirred for a further 10 min, the suspension was cooled to −10 °C and a solution of **14** (2.60 g, 4.98 mmol) in dry THF (5 mL) was added. The color darkened to deep orange almost immediately, the mixture was allowed to warm to room temperature with stirring for an additional 1 h, and then the solvent was evaporated to give a brown oil. Purification by flash chromatography (EtOAc/pentane 1:3) gave **15** as a waxy solid (2.23 g, 86%): $[\alpha]_D$ = −23 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.21 (dd, *J* = 9.3, 9.2 Hz, 1 H, C-4-H), 3.37 (s, 3 H, OCH_3), 3.50 (dd *J* = 9.7, 3.2 Hz, 1 H, C-2-H), 3.79, 3.80 (2 s, 6H, 2 × $ArOCH_3$), 3.96 (dd, *J* = 9.5, 9.2 Hz, 1 H, C-3-H), 4.02 (dd, *J* = 9.3, 6.8 Hz, 1 H, C-5-H), 4.51−4.90 (m, 6 H, 3 × ArCH_2O AB systems), 4.58 (d, *J* = 3.2 Hz, 1 H, C-1-H), 5.26 (br d, *J* = 10.1 Hz, 1 H, C-7-H, *cis*), 5.40 (br d, *J* = 17.2 Hz, 1 H, C-7-H, *trans*), 5.88 (ddd, *J* = 17.2, 10.1 Hz, 6.8 Hz, 1H, C-6-H), 6.83−7.36 (m, 13 H, aromatic CH); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 55.1, 55.3 (OCH_3), 71.4 (CH), 73.4, 74.8, 75.5 (ArCH_2O), 79.8, 81.4, 82.0 (CH), 98.1 (C-1), 113.8, 113.8 (2 × C-3 and C-5 of PMB rings), 118.0 (C-7), 127.8, 128.1, 128.4, 129.6, 129.6 (aromatic *C*H), 130.4, 131.1 (2 × C-1 of PMB rings), 135.3 (C-6), 138.2 (C-1 of benzyl ring), 159.2, 159.3 (2 × C-4 of PMB rings); MS *m/z* (+ve ion FAB) 519 [(M − H)$^+$, 2.0)], 121 [$(CH_2C_6H_4OCH_3)^+$, 100], 91 [$(C_7H_7)^+$ 20]; MS *m/z* (−ve ion FAB) 673 [(M + NBA)$^-$, 25], 399 [(M − $CH_2C_6H_4OCH_3)^-$, 100]. Anal. Calcd for $C_{31}H_{36}O_7$: C, 71.52; H, 6.97. Found: C, 71.5; H, 7.07.

(1*R*,2*S*,3*S*,4*R*,5*S*)-3-(Benzyloxy)-4-hydroxy-1,2-bis[(*p*-methoxybenzyl)oxy]-5-vinylcyclopentane (16) and (1*R*,2*S*,3*S*,4*S*,5*R*)-3-(Benzyloxy)-4-hydroxy-1,2-bis[(*p*-methoxybenzyl)oxy]-5-vinylcyclopentane (17). Zirconocene dichloride (672 mg, 2.30 mmol) was placed into a dry 100 mL flask under N_2, followed by THF (10 mL). The suspension was cooled to −78 °C, and *n*-BuLi (1.84 mL of a 2.5 M solution in hexane, 4.60 mmol) was added. The mixture was stirred at −78 °C for 1 h, and then a solution of the vinyl carbohydrate **15** (1.00 g, 1.92 mmol) in THF (8 mL) was added. The clear yellow solution was allowed to reach room temperature, and stirring was continued for 3 h, during which time it gradually darkened to reddish orange. The solution was cooled to 0 °C, and a solution of boron trifluoride etherate (0.45 mL, 3.7 mmol) in THF (5 mL) was added. Stirring was continued at room temperature, and TLC (CH_2Cl_2/EtOAc 10:1) showed conversion of starting material (R_f = 0.72) to a major product (R_f = 0.56) within 30 min. After 45 min, TLC showed that PMB groups were being lost. HCl (1 M, 50 mL) was added and the mixture extracted with CH_2Cl_2 (2 × 50 mL). The organic extracts were combined, washed with brine (100 mL), dried ($MgSO_4$), and concentrated to give a yellow oil, which was purified by column chromatography (CH_2Cl_2/Me_2CO 30:1) to give the major diastereoisomer **16** (433 mg, 46%) as a waxy solid. A small amount of the minor diastereoisomer **17** was also isolated (∼30 mg, 3%).

Major Diastereoisomer (16): TLC (CH_2Cl_2/acetone 30:1) R_f = 0.32; $[\alpha]_D$ = +9 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.99 (d, *J* = 4.22 Hz, D_2O ex, 1 H, C-4-OH), 2.86 (ddd, *J* = 7.8, 7.8, 6.2 Hz, 1 H, C-5-H), 3.77, 3.78 (2s, 6H, 2 × OCH_3), 3.77 (obscured by OCH_3, 1 H, C-3-H), 3.93−4.01 (m, 2 H, C-1-H and C-2-H), 4.11 (m, D_2O ex gives dd, *J* = 6.0, 3.1 Hz, 1 H, C-4-H), 4.45−4.65 (m, 6 H, 3 × Ar*C*HO AB systems), 5.23 (br d, *J* = 17.2 Hz, 1 H, =CH_2, *trans*), 5.25 (br d, *J* = 10.6 Hz, 1 H, =CH_2, *cis*), 5.91 (ddd, *J* = 17.2, 10.8, 8.0 Hz, 1 H, CH=), 6.83−6.87 (m, 4 H, C-3-H and C-5-H of PMB rings), 7.20−7.25 (m, 4 H, C-2-H and C-6-H of PMB rings), 7.28−7.35 (m, 5 H, C_6H_5); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 51.0 (C-5), 55.2 (2 × OCH_3), 71.6 (OCH_2Ar), 71.6 (2 × OCH_2Ar), 75.4, 84.5, 87.2, 87.9 (C-1, C-2, C-3, C-4), 113.7, 113.7 (C-3 and C-5 of PMB rings), 118.8 (=CH_2), 127.7, 127.7, 128.4, 129.4, 129.5 (aromatic *C*H), 130.1, 130.4 (2 × C-1 of PMB rings), 134.7 (CH=), 138.1 (C-1 of benzyl ring), 159 2, 159.1 (C-4 of PMB rings); MS *m/z* (+ve ion FAB) 489 [(M − H)$^+$, 1.2)], 369 [(M − $CH_2C_6H_4OCH_3)^+$, 6.0), 121 [$(CH_2C_6H_4OCH_3)^+$, 100]; MS *m/z* (−ve ion FAB) 643 [(M + NBA)$^-$, 100]. Anal. Calcd for $C_{30}H_{34}O_6$: C, 73.45; H, 6.99. Found: C, 73.2; H, 7.05.

Minor Diastereoisomer (17): TLC (CH_2Cl_2/acetone 30:1) R_f = 0.36; mp 83−85 °C (from EtOH); $[\alpha]_D$ = −26 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.53 (d, *J* = 8.3 Hz, 1 H, D_2O ex, C-4-OH), 2.71 (ddd, *J* = 8.3, 7.8, 7.8 Hz, 1 H, C-5-H), 3.66 (dd *J* = 7.8, 4.4 Hz, 1 H, C-1-H), 3.79, 3.80 (2s, 6 H, 2 × OCH_3), 3.79−3.87 (m, partly obscured by OCH_3, 2 H, C-3-H and C-4-H), 3.94 (dd, *J* = 4.3, 2.44 Hz, 1 H, C-2-H), 4.43−4.69

(m, 6 H, 3 × ArCH_2O AB systems), 5.16 (br d, J = 10.3 Hz, 1 H, =CH_2, *cis*), 5.23 (br d, J = 17.1 Hz, =CH_2, 1 H, *trans*), 5.84 (ddd, J = 17.1, 10.3 7.8 Hz, 1 H, CH=), 6.85−6.89 (m, 4 H, C-3-H and C-5-H of PMB rings), 7.31−7.37 (m, 4 H, C-2-H and C-6-H of PMB rings), 7.31−7.37 (m, 5 H, aromatic CH); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 53.7 (C-5), 55.2 (2 × OCH_3), 71.5, 71.6, 71.8 (OCH_2Ar), 73.8, 81.8, 85.2, 86.1 (C-1, C-2, C-3, C-4), 113.7, 113.8 (C-3 and C-5 of PMB rings), 117.1 (=CH_2), 127.8, 127.9, 128.4, 129.4, 129.4 (aromatic *C*H), 129.9, 130.2 (2 × C-1 of PMB rings), 137.6 (C-1 of benzyl ring), 137.8 (CH=), 159.1, 159.3 (C-4 of PMB rings); MS m/z (+ve ion FAB) 489 [(M − H)$^+$, 1.0)], 369 [(M − $CH_2C_6H_4OCH_3$)$^+$, 5.0), 121 [($CH_2C_6H_4$-OCH_3)$^+$, 100]; 91 [(C_7H_7)$^+$, 10]. Anal. Calcd for $C_{30}H_{34}O_6$: C, 73.45; H, 6.99. Found: C, 73.6; H, 7.02.

(1*R*,2*S*,3*S*,4*R*,5*R*)-3-(Benzyloxy)-1,2,4-trihydroxy-5-vinylcyclopentane (18). To a solution of **16** (175 mg, 0.357 mmol) in EtOH (40 mL) was added 1 M HCl (20 mL). The solution was refluxed for 3 h, and then the solvents were removed by evaporation *in vacuo*. The residue was taken up in EtOAc (50 mL) and washed with saturated $NaHCO_3$ solution and brine (25 mL of each). The combined aqueous layers were reextracted with EtOAc (50 mL), and the combined organic layers were then dried ($MgSO_4$) and concentrated to give a yellow oil. Purification by column chromatography ($CHCl_3$/MeOH 5:1) gave the triol **18** as a waxy solid: mp 64−66 °C (78 mg, 87%); $[\alpha]_D$ = +53 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.55 (ddd, J = 9.3, 7.8, 7.3 Hz, 1 H, C-5-H), 2.79 (br s, 1 H, D_2O ex, OH), 2.92 (br s, D_2O ex, 1 H, OH), 3.65 (dd J = 5.4, 2.0 Hz, 1 H, C-3-H), 3.88 (br dd, 1 H, D_2O ex gives dd, J = 7.3, 5.4 Hz, C-2-H), 3.95−4.00 (br m, 2 H, sharpens on D_2O ex, C-1-H and C-4-H), 4.10 (br s, 1 H, D_2O ex, OH), 4.54, 4.58 (AB, J_{AB} = 11.7 Hz, 2 H, O$CH_2C_6H_5$), 5.20 (dd, J = 17.1, 1.6 Hz, 1H, =CH_2, *trans*), 5.23 (dd, J = 10.3, 1.6 Hz, 1 H, =CH_2, *cis*), 5.82 (ddd, J = 17.1, 10.3, 7.8 Hz, 1 H, CH=), 7.22−7.32 (m, 5 H, C_6H_5); ^{13}C NMR ($CDCl_3$, 100.4 MHz) δ 51.5 (C-5), 71.8 (O$CH_2C_6H_5$), 74.7, 76.7, 81.5, 89.1 (C-1, C-2, C-3, C-4), 119.6 (=CH_2), 127.9, 127.9, 128.5 (aromatic *C*H), 133.77 (*C*H=), 137.8 (C-1 of benzyl ring); MS m/z (+ve ion FAB) 501 [(2M + H)$^+$, 2.0], 249 [(M − H)$^+$, 5.0)], 149 (30), 91 [(C_7H_7)$^+$, 100]; MS m/z (−ve ion FAB) 403 [(M + NBA)$^-$, 100], 249 [(M − H)$^-$, 50)], 149 (50). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.9; H, 7.44.

(1*R*,2*R*,3*S*,4*R*,5*S*)-3-(Benzyloxy)-1,2,4-tris[[bis(benzyloxy)phosphoryl]oxy]-5-vinylcyclopentane (19). To a solution of bis(benzyloxy)(*N*,*N*-diisopropylamino)phosphine (670 mg, 1.94 mmol) in CH_2Cl_2 (2 mL) was added 1*H*-tetrazole (200 mg, 2.85 mmol). The mixture was stirred at room temperature for 10 min, and then the triol **18** (80 mg, 0.320 mmol) was added. The mixture was stirred for a further 1 h, after which a 90 MHz ^{31}P NMR spectrum showed signals around 139 ppm (a singlet and an AB quartet with J = 6.7 Hz) corresponding to the trisphosphite triester. The mixture was cooled to −78 °C, and *m*-CPBA (517 mg, 3.00 mmol) was added. The mixture was warmed to room temperature, with stirring, and then diluted with EtOAc (50 mL). The solution was washed with 10% w/v Na_2SO_3 solution, 1 M HCl, saturated $NaHCO_3$, and brine (50 mL of each), dried ($MgSO_4$), and concentrated to give an oil. Purification by column chromatography ($CHCl_3$/acetone 10:1) gave the trisphosphate triester **19** as a colorless oil (271 mg, 82%): $[\alpha]_D$ = +3.5 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.02 (m, 1 H), 4.20 (br s, 1 H), 4.50 (AB, J_{AB} = 11.2Hz, 1 H), 4.68 (br dd, J = 7.8, 4.9 Hz, 1 H), 4.87−5.08 (m, 14 H), 5.18 (d, J = 10.3, 1.5 Hz, 1 H), 5.26 (d, J = 17.1, 1.5 Hz, 1 H), 5.86 (ddd, J = 17.1, 10.3, 8.3 Hz, 1 H), 7.17−7.33 (m, 35 H); ^{13}C NMR ($CDCl_3$, 100.4 MHz) δ 50.9 (C-5), 69.2, 69.4, 69.5, 69.6, 72.0 (7 × O$CH_2C_6H_5$), 81.2, 84.1, 85.6, 86.2 (C-1, C-2, C-3, C-4), 120.7 (=CH_2), 127.4, 127.5, 127.7, 127.9, 128.0, 128.1, 128.2, 128.3, 128.5 128.9 (aromatic *C*H), 131.4 (*C*H=), 135.4, 135.5, 135.5, 135.6, 135.7, 135.8, 137.3 (7 × C-1 of benzyl ring); ^{31}P NMR ($CDCl_3$, 161.7 MHz) δ −1.97, −2.12, −2.34; MS m/z (+ve ion FAB) 1031 [(M + H)$^+$, 2.5)], 149 (20), 91 [(C_7H_7)$^+$, 100]; MS m/z (−ve ion FAB) 938 (14), 277 [($C_6H_5O)_2PO_2^-$, 100]. Anal. Calcd for $C_{56}H_{57}O_{13}P_3$: C, 65.24; H, 5.57. Found: C, 65.0; H, 5.60.

(1*R*,2*R*,3*S*,4*R*,5*S*)-3-Hydroxy-1,2,4-tris(phosphonooxy)-5-vinylcyclopentane (3). Ammonia (~100 mL) was condensed into a three-neck flask at −78 °C. An excess of sodium was added to dry the liquid NH_3, and the deep blue solution was stirred at −78 °C for 30 min. A small volume of the dry NH_3 (~30 mL) was then distilled into a second three-neck flask and kept at −78 °C. Sodium was added until the solution remained blue-black for 10 min. A solution of **19** (80 mg, 78 μmol) in dry dioxane (2 mL) was added to the vigorously-stirring Na/NH_3 mixture. After 60−90 s the reaction was carefully quenched with MeOH, followed by deionized water. Ammonia and solvents were then removed by evaporation *in vacuo*. The residue was dissolved in deionized water (500 mL) and purified by ion-exchange chromatography on Q Sepharose fast flow resin, eluting with a gradient of triethylammonium bicarbonate buffer (0−1 M), pH 8.0. The glassy triethylammonium salt of **3** eluted between 300 and 400 mM. Fractions containing **3**, as judged by Briggs phosphate assay,[19] were combined and concentrated to give a residue from which MeOH was evaporated three times to give glassy **3** as its triethylammonium salt (yield 45 μmol, 58%): $[\alpha]_D$ = −8, $[\alpha]_{436}$ = −28 (*c* 0.36, TEAB buffer pH 7.8, calcd for free acid); high resolution −ve FAB: m/z 398.963 (M$^-$) calcd for $C_7H_{14}O_{13}P_3^-$, 398.965; ^{1}H NMR (D_2O, 400 MHz, pH 3.2) δ 2.76 (ddd, J = 8.9, 7.9, 7.9 Hz, 1 H, C-5-H), 3.98 (t, J = 3.7, 3.7 Hz, 1 H, C-3-H), 4.14−4.21 (m, 2 H, C-2-H, C-4-H), 4.37 (ddd, J = 8.9, 8.9, 5.2 Hz, 1 H, C-1-H), 5.07 (br d, J = 10.4 Hz, 1 H, =CH_2, *cis*), 5.12 (br d, J = 17.4 Hz, 1 H, =CH_2, *trans*), 5.75 (ddd, J = 17.4, 10.4, 7.9 Hz, 1 H, C*H*=); ^{31}P NMR (D_2O, 161.7 MHz, pH 3.2, ^{1}H-coupled) δ 1.62 (d, J_{HP} = 9.0 Hz, 1 P), 1.86 (d, J_{HP} = 8.8 Hz, 1 P), 2.20 (d, J_{HP} = 9.0 Hz, 1 P); MS m/z (+ve ion FAB) 102 [($C_2H_5)_3NH^+$, 100]; MS m/z (−ve ion FAB) 798 [2M$^-$, 10], 399 [M$^-$, 100].

(1*R*,2*S*,3*S*,4*R*,5*S*)-3-(Benzyloxy)-4-hydroxy-5-(hydroxymethyl)-1,2-bis[(*p*-methoxybenzyl)oxy]cyclopentane (20). To a 0.1 M solution of SmI_2 in THF (100 mL, 10 mmol) under N_2 were added HMPA (5 mL) and freshly distilled, dry *t*-BuOH (0.4 mL, 4.3 mmol). A solution of **14** (926 mg, 1.8 mmol) in freshly distilled, dry THF (20 mL) was then added dropwise over 15 min, and the blue-black mixture was stirred under a stream of N_2 for an additional 1 h. HCl (1 M, 100 mL) was added, and the mixture was extracted with Et_2O (3 × 150 mL). The combined organic extracts were washed with 5% w/v aqueous $Na_2S_2O_3$ solution (100 mL) and H_2O (100 mL), dried ($MgSO_4$), filtered, and concentrated. The residual orange oil was subjected to flash chromatography (eluent hexane/EtOAc 3:2) to give **11** (175 mg, 19%).

Further elution with EtOAc gave **20** as a pale yellow oil (321 mg, 37%): TLC (EtOAc) R_f = 0.49; $[\alpha]_D$ = +19.5 (*c* 4.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$; 400 MHz) δ 2.24 (m, 1 H), 2.50−3.40 (br s, 2 H, 2 × OH), 3.72−3.77 (m, 7 H), 3.78−3.83 (m, 2 H), 3.90 (t, J = 5.4 Hz, 1 H), 3.97 (t, J = 5.9 Hz, 1 H), 4.24 (dd, J = 3.9, 6.8 Hz, 1 H), 4.47−4.65 (m, 6 H), 6.83−6.86 (m, 4 H), 7.20−7.33 (m, 9 H); ^{13}C NMR ($CDCl_3$; 100 MHz) δ 46.7 (C-5), 55.2 (OCH_3), 60.9 (*C*H_2OH), 71.7, 71.8 (3 × Ar*C*H_2O), 75.2, 81.7, 87.4, 87.9 (C-1, C-2, C-3, C-4), 113.7 (C-3 and C-5 of PMB rings), 127.7, 127.8, 128.4, 129.4, 129.5 (aromatic CH), 130.1, 130.3 (2 × C-1 of PMB rings), 138.1 (C-1 of benzyl ring), 159.1, 159.2 (2 × C-4 of PMB rings); MS m/z (−ve ion FAB) 493 [(M − H)$^-$, 50]. Anal. Calcd for $C_{29}H_{34}O_7$: C, 70.41; H, 6.93. Found: C, 70.5; H, 6.57.

(1*R*,2*S*,3*S*,4*R*,5*S*)-3-(Benzyloxy)-5-[(benzyloxy)methyl]-4-hydroxy-1,2-bis[(*p*-methoxybenzyl)oxy]cyclopentane (22) and (1*R*,2*S*,3*S*,4*R*,5*S*)-3,4-Bis(benzyloxy)-5-(hydroxymethyl)-1,2-bis[(*p*-methoxybenzyl)oxy]cyclopentane (21). A solution of **20** (200 mg, 0.4 mmol) in dry DMF (3 mL) at 0 °C was sequentially treated with NaH (17mg of a 60% w/w dispersion in mineral oil, 0.4 mmol) and benzyl bromide (0.05 mL, 0.45 mmol). The mixture was stirred at 0 °C for 1 h, when TLC (EtOAc/hexane 3:2) indicated two products (R_f = 0.58 and 0.49) and unreacted starting material (R_f = 0.15). Methanol (1 mL) was added, and the solution was stirred for an additional 5 min. The solvents were evaporated, and the residue was extracted with $CHCl_3$ (100 mL). The organic solution was washed with H_2O (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated. The syrupy residue was subjected to flash chromatography (eluent $CHCl_3$/acetone 30:1) to give **22** as a pale yellow oil (67 mg, 28%): $[\alpha]_D$ = +30.4

(*c* 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$; 400 MHz) δ 2.31 (m, J = 4.9, 9.3 Hz, 1 H, C-5-H), 3.32 (d, J = 3.4 Hz, 1 H, OH), 3.72−3.78 (m, 2 H, CH_2OCH_2Ph), 3.77−3.81 (m, 7 H, 2 × OCH_3, C-3-H), 3.90 (t, J = 5.9 Hz, 1 H, C-2-H), 4.06 (dd, J = 5.9, 9.3 Hz, 1 H, C-1-H), 4.25 (br m, 1 H, C-4-H), 4.40−4.70 (m, 8 H, 4 × ArCH_2O AB systems), 6.81−6.87 (m, 4 H, C-2-H and C-5-H of PMB rings), 7.15−7.37 (m, 14 H, aromatic CH); ^{13}C NMR ($CDCl_3$; 100.4 MHz) δ 45.4 (C-5), 55.3 (OCH_3), 68.0 (CH_2OCH_2-Ph), 71.7, 71.8, 72.0, 73.5 (4 × ArCH_2O), 75.1, 81.3, 88.0 (4 × CH), 113.7 (C-2 and C-5 of PMB rings), 127.6, 127.8, 127.8, 127.9, 128.4, 128.4, 128.5, 129.5, 129.6 (aromatic CH), 130.4, 130.6 (2 × C-1 of PMB rings), 137.5, 138.2 (2 × C-1 of benzyl rings), 159.2, 159.2 (2 × C-4 of PMB rings); MS *m*/*z* (+ve ion FAB) 463 [(M − PMB)$^+$, 65]. Anal. Calcd for $C_{36}H_{40}O_7$: C, 73.94; H, 6.90. Found: C, 73.8; H, 7.00.

Further elution gave **21** as a pale yellow oil (98 mg, 41%): $[\alpha]_D$ = +27.9 (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$; 400 MHz) δ 2.33 (m, J = 5.9 Hz, 1 H, C-5), 2.57 (br m, 1 H, ex D_2O, OH), 3.77, 3.78 (2 s, 6 H, 2 × OCH_3), 3.82−3.87 (m, 2 H, CH_2OH), 3.88−3.91 (br m, 1 H, C-3-H), 3.95 (t, J = 5.9 Hz, 1 H, C-2-H), 4.00−4.03 (br m, 1 H, C-1-H), 4.12 (dd, J = 5.9, 8.8 Hz, 1 H, 4-H), 4.46−4.66 (m, 8 H, 4 × ArCH_2O AB systems), 6.84−6.87 (m, 4 H, C-3-H and C-5-H of PMB rings), 7.23−7.35 (m, 14 H, aromatic CH); ^{13}C NMR ($CDCl_3$; 100.4 MHz) δ 46.8 (C-5), 55.3 (OCH_3), 61.0 (CH_2OH), 71.8, 71.9, 72.2 (4 × ArCH_2O), 82.2, 82.4, 85.8, 88.4 (C-1, C-2, C-3, C-4), 113.8 (C-3 and C-5 of PMB rings), 127.6, 127.7, 128.0, 128.4, 128.5, 128.6, 129.4, 129.5, 129.6 (aromatic CH), 130.3, 130.5 (2 × C-1 of PMB rings), 137.6, 138.0 (2 × C-1 of benzyl rings), 159.2, 159.2 (2 × C-4 of PMB rings); MS *m*/*z* (+ve ion FAB) 463 [(M − PMB)$^+$, 15]. Anal. Calcd for $C_{36}H_{40}O_7$: C, 73.94; H, 6.90. Found: C, 73.7; H, 6.92.

Further elution with EtOAc gave starting material **20** (50 mg, 25% recovery).

(1*R*,2*S*,3*S*,4*R*,5*S*)-3,4-Bis(benzyloxy)-1,2-bis[(*p*-methoxybenzyl)oxy]-5-vinylcyclopentane (23). Compound **16** (27.4 mg, 60 μmol) was benzylated with NaH and benzyl bromide in DMF as described for **20** to give **23**: TLC ($CHCl_3$/acetone 10:1) R_f = 0.7; $[\alpha]_D$ = +3.4 (*c* 1.6, $CHCl_3$); ^1H NMR ($CDCl_3$; 400 MHz) δ 2.87 (m, 1 H, C-5-H), 3.78, 3.79 (2 s, 6 H, OCH_3), 3.86−4.01 (m, 4 H, C-1-H, C-2-H, C-3-H, C-4-H), 4.47−4.59 (m, 8 H, 4 × ArCH_2O AB systems), 5.17 (dd, J = 1.8, 10.4 Hz, 1 H, =CH_2, *cis*), 5.23 (dd, J = 1.0, 17.2 Hz, 1 H, =CH_2, *trans*), 6.07 (ddd, J = 9.1, 10.3, 17.3 Hz, 1 H, CH=), 6.83−6.87 (m, 4 H, C-3-H and C-5-H of PMB rings), 7.21−7.37 (m, 16 H, aromatic CH); ^{13}C NMR ($CDCl_3$; 67.8 MHz) δ 50.0 (C-5), 54.6 (2 × OCH_3), 70.9, 71.1, 71.3 (4 × ArCH_2), 81.9, 84.9, 85.1, 87.4 (C-1, C-2, C-3, C-4), 113.1 (C-3 and C-5 of PMB rings), 117.0 (=CH_2), 127.1, 127.7, 128.8, 128.9 (aromatic CH), 129.9, 130.0 (2 × C-1 of PMB rings), 135.2 (CH=), 137.7 (C-1 of benzyl ring[s]), 158.6 (C-4 of benzyl ring[s]); MS *m*/*z* (+ve ion FAB) 580 [(M$^+$), 15], 459 [(M − PMB)$^+$, 70].

Determination of the Stereochemistry of 20 and Derivatives. A solution of **23** (30 mg, 52 μmol) in Et_2O (5 mL) was added to a saturated aqueous solution of $NaIO_4$ (5 mL) containing OsO_4 (4 mg, 17 μmol), and this mixture was stirred at room temperature for 24 h. The mixture was diluted with Et_2O (15 mL) and H_2O (15 mL), and the organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was redissolved in MeOH (5 mL), and $NaBH_4$ (6mg) was added. After 30 min the mixture was concentrated, and the residue was partitioned between Et_2O (50 mL) and H_2O (20 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated, and the residue was purified by flash chromatography ($CHCl_3$/acetone 20:1) to give **21** (9 mg, 30%). The ^1H NMR spectra of this sample, a sample prepared by the SmI_2 route, and a 1:1 mixture of the two were indistinguishable.

(1*R*,2*S*,3*S*,4*R*,5*R*)-3-(Benzyloxy)-5-[(benzyloxy)methyl]-1,2,4-trihydroxycyclopentane (25). Compound **25** was prepared from **22** using an analogous procedure to that described for **18**: TLC (EtOAc) R_f = 0.31; $[\alpha]_D$ = +30.0 (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$; 400 MHz) δ 2.16−2.23 (br m, 1 H), 3.14 (br s, 1 H), 3.43 (br s, 1 H), 3.61 (dd, J = 3.4, 6.1 Hz, 1 H), 3.67−3.74 (m, 3 H, CH_2OCH_2Ph), 3.82 (br t, J = 6.5 Hz, 1 H), 3.95 (br dd, J = 7.6 Hz, 1 H), 4.14−4.18 (br m, 1 H), 4.46, 4.48 (AB, J_{AB} = 11.9 Hz, 2 H, PhCH_2O), 4.60, 4.67 (AB, J_{AB} = 11.6 Hz, 2 H, PhCH_2O), 7.23−7.35 (m, 10 H); ^{13}C NMR ($CDCl_3$; 100.4 MHz) δ 45.9 (C-5), 68.1 (CH_2OCH_2Ph), 72.0, 73.5 (2 × PhCH_2O), 74.5, 76.0, 81.0 (C-1, C-2, C-4), 89.2 (C-3), 127.8, 127.9, 128.0, 128.4, 128.6 (aromatic CH), 137.5, 138.0 (2 × C-1 of benzyl rings); MS *m*/*z* (+ve ion FAB) 345 [(M + H)$^+$, 15]; MS *m*/*z* (−ve ion FAB) 343 [(M − 1)$^-$, 38], 497 [(M + NBA)$^-$, 98].

(1*R*,2*R*,3*S*,4*R*,5*S*)-3-Hydroxy-5-(hydroxymethyl)-1,2,4-tris(phosphonooxy)cyclopentane (4). Triol **25** was phosphitylated and oxidized as described for **18**. After workup and column chromatography the ^{31}P NMR spectrum of **27** showed three peaks at δ_P −2.47, −2.16, and −2.08 ppm, but the ^1H NMR spectrum indicated the presence of minor impurities. This crude product was deprotected as described for **19** and purified by ion-exchange chromatography on Q Sepharose fast flow resin, eluting with a gradient of triethylammonium bicarbonate buffer (0−1 M), pH 7.3. The triethylammonium salt of **4** eluted between 610−640 mM buffer: $[\alpha]_D$ = −11.0 (*c* 0.4 calcd for free acid, TEAB, pH 8.6); high resolution −ve FAB *m*/*z* 402.962 (M − H)$^-$, calcd for $C_6H_{12}O_{14}P_3^-$ 402.960; ^1H NMR (D_2O, pH *ca.* 4, 400 MHz) δ 2.29 (br quintet, J = 7.3 Hz, 1 H, C-5-H), 3.65 (ABX, $^2J_{AB}$ = 12 Hz, ^3J = 6 Hz, 1 H, C*H*HOH), 3.71 (ABX, $^2J_{AB}$ = 12 Hz, ^3J = 7.3 Hz, 1 H, CH*H*OH), 3.94 (t, J = 4.6 Hz, 1 H, C-3-H), 4.16−4.31 (m, 3 H, C-1-H, C-2-H, C-4-H); ^{31}P NMR (D_2O, pH *ca.* 4, 161.7 MHz) δ 0.36 (d, J_{HP} = 9.3 Hz, 1 P), 0.49 (d, J_{HP} = 8.8 Hz, 1 P), 0.66 (d, J_{HP} = 9.2 Hz, 1 P); MS *m*/*z* (−ve ion FAB) 403 [(M − H)$^-$, 100].

(1*R*,2*S*,3*S*,4*R*,5*R*)-1,2-Bis(benzyloxy)-3,4-dihydroxy-5-(hydroxymethyl)cyclopentane (24). Compound **24** was prepared from **21** using an analogous procedure to that described for **18**: R_f = 0.2 (EtOAc); ^1H NMR ($CDCl_3$; 270 MHz) δ 2.08 (br m, 1 H, C-5-H), 2.50 (br s, 1 H, OH), 3.17 (br s, 1 H, OH), 3.78−3.97 (m, 5 H), 4.16 (t, J = 9 Hz, 1 H), 4.34 (br s, 1 H, OH), 4.39, 4.53 (AB, J_{AB} = 11.7 Hz, 2 H, PhCH_2O), 4.60, 4.73 (AB, J_{AB} = 11.7 Hz, 2 H, PhCH_2O), 7.22−7.33 (m, 10 H, aromatic CH); ^{13}C NMR ($CDCl_3$; 67.8 MHz) δ 46.9 (C-5), 60.1 (CH_2OH), 71.8, 71.8 (2 × PhCH_2O), 75.4, 82.0, 82.0, 87.3 (C-1, C-2, C-3, C-4), 127.7, 127.8, 127.9, 128.0, 128.4, 128.5 (aromatic CH), 137.5, 138.1 (2 × C-1 of phenyl rings); MS *m*/*z* (+ve ion FAB) 345 [(M + H)$^+$, 15%]; MS *m*/*z* (−ve ion FAB) 497 [(M + NBA)$^-$, 95].

(1*R*,2*S*,3*R*,4*R*,5*S*)-1,2-Bis(benzyloxy)-3,4-bis[[bis(benzyloxy)phosphoryl]oxy]-5-[[bis(benzyloxy)phosphoryl]oxy]methyl]cyclopentane (26). Compound **24** was phosphitylated and oxidized as described for **18** to give **26**: $[\alpha]_D$ = +7.0 (*c* 4.9, $CHCl_3$); ^1H NMR ($CDCl_3$; 270 MHz) δ 2.65 (q, J = 4.5 Hz, 1 H), 3.89 (m, 1 H), 4.04 (br s, 1 H), 4.28−4.59 (m, 6 H), 4.83−5.02 (m, 14 H), 7.19−7.37 (m, 20H); ^{31}P NMR ($CDCl_3$; 161.7 MHz) δ −5.09 (sextet, J_{HP} = 7.5 Hz, 1 P), −4.38 (sextet, J_{HP} = 8.1 Hz, 1 P), −3.89 (septet, J_{HP} = 7.8 Hz, 1 P); MS *m*/*z* (+ve ion FAB) 1125 [(M + H)$^+$, 80].

(1*R*,2*S*,3*R*,4*R*,5*S*)-1,2-Dihydroxy-3,4-bis(phosphonooxy)-5-[(phosphonooxy)methyl]cyclopentane (5). Compound **26** was deprotected as described for **19** and purified by ion-exchange chromatography on Q Sepharose fast flow resin, eluting with a gradient of triethylammonium bicarbonate buffer (0−1 M, pH 7.5). The triethylammonium salt of **5** eluted between 560−600 mM buffer: $[\alpha]_D$ = +8.3 (*c* 0.36 calcd for free acid, TEAB, pH 8.6); high resolution −ve FAB *m*/*z* 402.961 (M − H)$^-$, calcd for $C_6H_{12}O_{14}P_3^-$ 402.960; ^1H NMR (D_2O, pH *ca.* 4, 400 MHz) δ 2.34 (br m, 1 H), 3.82−3.86 (m, 1 H), 3.95−4.03 (m, 4 H), 4.17−4.21 (br m, 1 H), 4.29−4.33 (m, 1 H); ^{31}P NMR (D_2O, pH *ca.* 4, 161.7 MHz) δ −0.36 (d, J_{HP} = 9.3 Hz, 1 P), 0.31 (d, J_{HP} = 8.8 Hz, 1 P), 0.66 (t, J_{HP} = 6.1 Hz, 1 P); MS *m*/*z* (−ve ion FAB) 403 [(M − H)$^-$, 100].

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