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Stereoselective synthesis of glycobiosyl phosphatidylinositol, a part structure of the glycosyl-phosphatidylinositol (GPI) anchor of *Trypanosoma brucei* *

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ABSTRACT

O-α-D-Mannopyranosyl-(1 → 4)-*O*-2-amino-2-deoxy-α-D-glucopyranosyl-(1 → 6)-1D-*myo*-inositol 1-(1,2-di-*O*-myristoyl-*sn*-glycer-3-yl hydrogen phosphate), a part structure of the glycosyl-phosphatidylinositol (GPI) anchor of *Trypanosoma brucei*, was synthesised efficiently by the phosphonate approach. The glycobiosylinositol core was prepared in a stereocontrolled manner from 1D-2,3,4,5-tetra-*O*-benzyl-1-*O*-(4-methoxybenzyl)-*myo*-inositol, *tert*-butyldimethylsilyl 2-azido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside, and methyl 3,6-di-*O*-acetyl-2,6-di-*O*-benzyl-2-thio-α-D-mannopyranoside.

INTRODUCTION

The glycosyl-phosphatidylinositol (GPI) anchor[2], which attaches surface proteins to the cell membrane, has been found in various eukaryotes. Recently, it was suggested that the GPI anchor was involved in the signal transduction of insulin[3] and in Qa-2-mediated T-cell activation[4].

Ferguson et al.[5] elucidated the structures of the GPI anchor part of a variant surface glycoprotein (VSG) of the parasitic protozoan *Trypanosoma brucei*, and a typical structure may be depicted as **1**. Subsequently, the structures for the GPI anchors of rat-brain Thy-1 glycoprotein[6] and human erythrocyte acetylcholinesterase[7] were reported. These GPI anchors have a common structure composed of phosphatidylinositol, 2-amino-2-deoxyglucose, oligomannoside, and ethanolamine linked by a phosphodiester bond. Recently, syntheses have been reported of a glycopentaosyl core[8] of **1** and the non-reducing-end mannobiosyl structure[9], which was further linked to the peptide part via the phosphoethanolamine residue.

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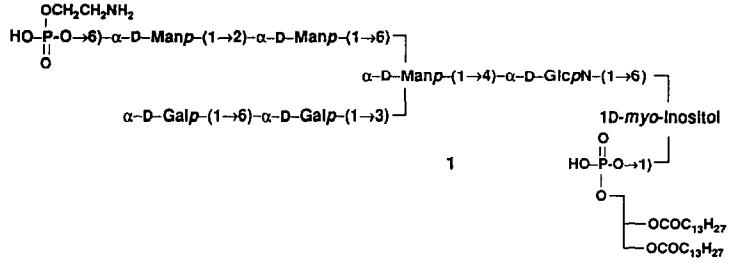
As part of studies[10] of the synthesis of GPI anchors, we now describe an efficient synthesis of the glycobiosyl phosphatidylinositol **2**, a part structure of **1**.

RESULTS AND DISCUSSION

In planning the synthesis of **2**, the phosphonate approach was chosen for the introduction of the phosphodiester function at O-1 of 1D-*myo*-inositol. The key intermediate **3** may be obtained from the D-mannose synthon **5**; the putative 2-amino-2-deoxy-D-glucose synthon **6**, which carries an azido group as the latent amino function; and the 1D-*myo*-inositol synthon **7**, which was designed not only for the synthesis of **2** but also for the total synthesis of **1**.



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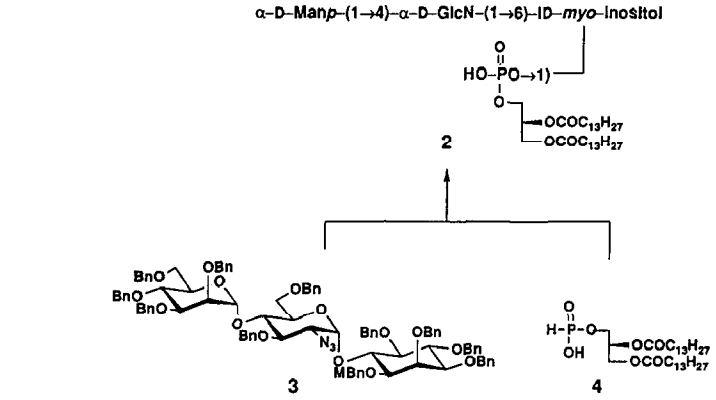
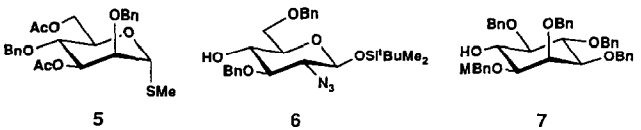


2

3 4

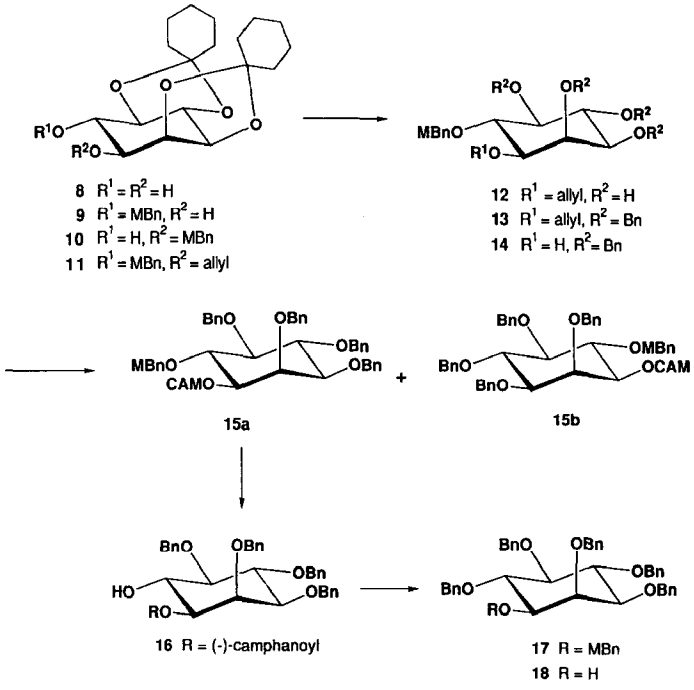


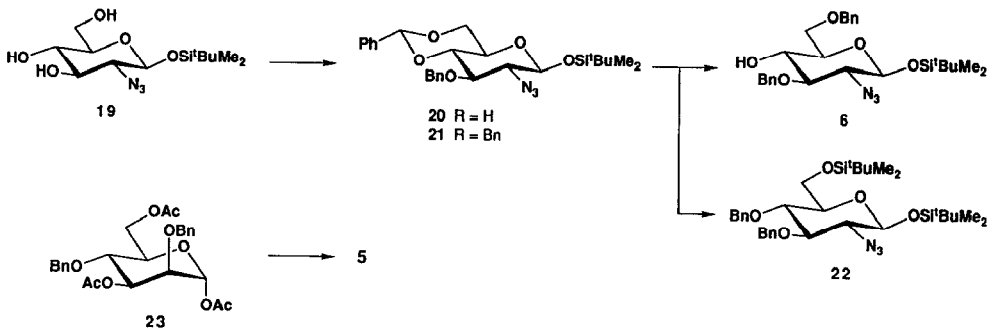
5 6 7

MBn = 4-methoxybenzyl

The synthon **7** was prepared as follows. 2,3:4,5-Di-*O*-cyclohexylidene-*myo*-inositol[11] (**8**) was treated with dibutyltin oxide, cesium fluoride, 4-methoxybenzyl chloride, and potassium iodide[12] to give 60% of the desired product **9** and 21% of **10**. The structure of **9** was confirmed by the ^{1}H NMR spectrum of the (−)-camphanoyl derivatives **15a** and **15b**, in which signals of H-1 were observed at 4.94 (dd, *J* 2.4 and 10.3 Hz) and 4.87 (dd, *J* 2.4 and 10.4 Hz), respectively. Allylation of **9** gave **11** (96%), acid hydrolysis of which followed by benzylation of the resulting tetraol **12** afforded **13** (68%). Treatment of **13** with potassium *tert*-butoxide in methyl sulfoxide and then with 0.1 M hydrogen chloride in aqueous acetone[13] removed the allyl group and gave racemic **14** that was resolved by treatment with (−)-camphanoyl chloride[14] to give 48% each of the desired ester **15a** and the diastereoisomer **15b**. The absolute structure of **15a** was confirmed by conversion into known[14] (+)-1D-1,2,3,4,5-penta-*O*-benzyl-*myo*-inositol (**18**). The synthon **7** was synthesised from **15a** in 83% overall yield in 4 steps with the following reagents: (*a*) ammonium cerium(IV) nitrate in 4:1 acetonitrile–water[15], (*b*) ethyl vinyl ether–*p*-toluenesulfonic acid in dichloromethane, (*c*) sodium hydroxide in methanol–tetrahydrofuran, and (*d*) 4-methoxybenzyl chloride–sodium hydride in *N*,*N*-dimethylformamide and then acetic acid in methanol.

The synthon **6** was prepared from *tert*-butyldimethylsilyl 2-azido-2-deoxy-α-D-glucopyranoside[16] (**19**). Treatment of **19** with benzaldehyde dimethyl acetal in the presence of *p*-toluenesulfonic acid gave the 4,6-*O*-benzylidene derivative **20**,





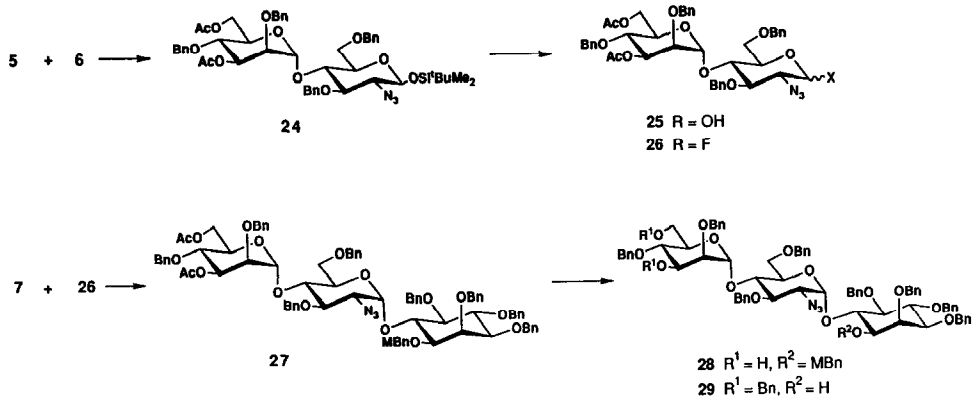
benzylation of which afforded **21** (73% from **19**). Reductive opening of the 4,6-*O*-benzylidene ring of **21**, using boron trimethylamine–aluminium chloride in tetrahydrofuran[17], yielded **6** and the regioisomer, which were separated easily by selective silylation of the latter to afford 83% of **6** and 13% of **22**.

The synthon **5** was obtained (85%) by reaction of 1,3,6-tri-*O*-acetyl-2,4-di*O*-benzyl-α-D-mannopyranose[18] (**23**) with methyl tributyltin sulfide[19] in the presence of tin(IV) chloride.

Compounds **5** and **6** were coupled in the presence of copper(II) bromide, tetrabutylammonium bromide, and silver triflate in nitromethane[20] to give the disaccharide derivative **24** (90%). The configuration at C-1′ in **24** was confirmed by the ^{13}C NMR spectrum, which contained a signal for C-1′ at 99.8 ppm ($^{1}J_{C,H}$ 167 Hz). Compound **24** was converted into the glycosyl donor **26** (89%, α,β-ratio 1:2) by desilylation with tetrabutylammonium fluoride and acetic acid in tetrahydrofuran[16], followed by fluorination with diethylaminosulfur trifluoride[21].

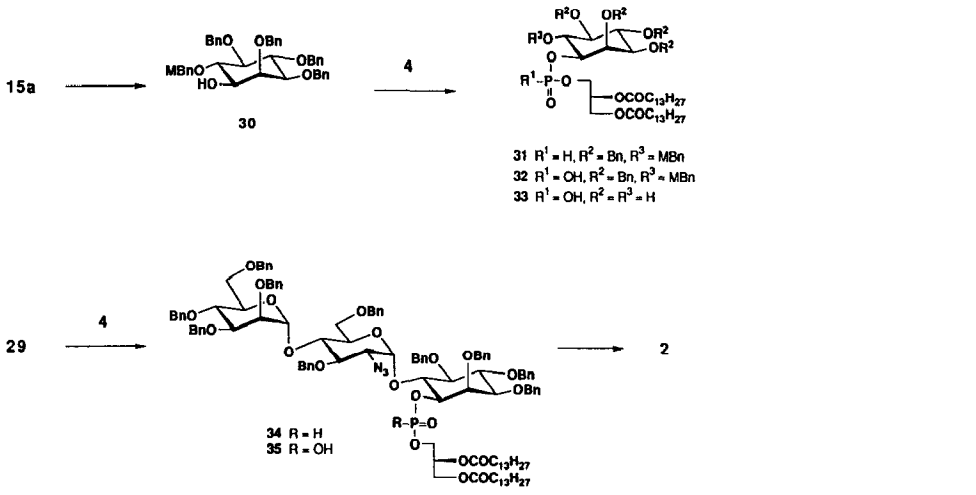
Crucial glycosylation of **7** with **26** in the presence of zirconocene dichloride and silver perchlorate in dry ether[22] gave a mixture (93%) of the desired α-linked product **27** and its β isomer in the ratio 3.7:1. The configurations at C-1″ for **27** and its β isomer were assigned from the ^{1}H NMR spectrum, which contained a signal for H-1′ at 5.60 ppm ($J_{1,2}$ 3.7 Hz) for **27** and at 4.97 ppm ($J_{1,2}$ 7.9 Hz) for its β isomer. Deacetylation of **27** afforded **28**, which was benzylated to give the key intermediate **3** (95% from **27**). The conversion of **3** into **29** (92%) was achieved, as described above, by reaction with ammonium cerium(IV) nitrate.

The synthesis of the phosphatidylinositol derivative **32** as a model for the introduction of the phosphodiester function at O-1 of 1D-*myo*-inositol was studied first. Saponification of **15a** gave **30**, which was coupled in the presence of pivaloyl chloride in pyridine[23] with 1,2-di-*O*-myristoyl-*sn*-glycerol 3-(hydrogen phosphonate) (**4**), prepared according to the method of Lindh and Stawinski[23], to afford the phosphonic diester **31** (80%) as a mixture of diastereomers. Oxidation of **31** with iodine then yielded the phosphoric diester **32** (71%), which was hydrogenolysed (Pd/C) to give quantitatively the phosphatidylinositol **33**.



The introduction of the phosphodiester moiety into **29** was performed in the above manner to afford **34** and then **35** (70% from **29**). The structure of **35** was confirmed by the presence in the ^{31}P NMR spectrum of a signal at -1.85 ppm. Hydrogenolysis (Pd/C) of **35** gave the target compound **2** (51%). The structure was confirmed by the ^{1}H and ^{31}P NMR spectra, and the FAB-mass spectrum, which contained the $[M^{+}+H]$ ion with m/z 1078 expected for **2**.

Compound **2** may be useful as a molecular probe for the elucidation of the physiological role of GPI anchors.



EXPERIMENTAL

General.—Melting points were determined with a Yanagimoto micro melting-point apparatus and are uncorrected. Optical rotations were determined with a Perkin–Elmer Model 241 MC polarimeter for solutions in $CHCl_3$ at 25°, unless noted otherwise. Column chromatography was performed on silica gel (Merck, 70–230 mesh). Flash-column chromatography was performed on Wako-gel C-300 (200–300 mesh). TLC and high-performance (HP) TLC were performed on Silica Gel 60 F_{254} (Merck). Molecular sieves were purchased from Nakarai Chemicals. The ^1H, ^{13}C and ^{31}P NMR spectra were recorded with a GNM-GSX-500, JEOL GX400, or FX90Q spectrometer for solutions in $CDCl_3$ (internal Me_4Si), unless noted otherwise. Values of $\delta_H(D_2O)$ are expressed in ppm downfield from the signal for Me_4Si by reference to internal ^{t}BuOH, (1.230). The ^{31}P resonances (δ_P) are referenced to external aq 85% H_3PO_4 unless noted otherwise.

(±)-2,3 : 4,5-Di-O-cyclohexylidene-6-O-(4-methoxybenzyl)-myo-*inositol* (**9**).—A mixture of **8**[11] (120 mg, 0.35 mmol) and Bu_2SnO (88 mg, 0.35 mmol) in toluene (5 mL) was stirred for 2 h under reflux with continuous azeotropic removal of water, then concentrated in vacuo. A mixture of the residue, CsF (69.2 mg, 0.45 mmol), 4-methoxybenzyl chloride (71 μL, 0.52 mmol), and KI (36 mg, 0.52 mmol) in *N,N*-dimethylformamide (3 mL) was stirred at 20° overnight, then diluted with EtOAc, washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. Preparative TLC (toluene–acetone, 9:1) of the residue gave **9** (97 mg, 60%) and **10** (33 mg, 21%).

Compound **9** had R_F 0.60. ^1H NMR data: δ 1.42–1.72 (m, 20 H, 10 CH_2), 2.58 (d, 1 H, *J* 1.2 Hz, OH), 3.54 (dd, 1 H, *J* 7.9 and 10.7 Hz, H-5), 3.805 (s, 3 H, OMe), 3.88 (dd, 1 H, *J* 1.8 and 7.9 Hz, H-6), 4.01 (dt, 1 H, *J* 3.7 and 1.8 Hz, H-1), 4.18 (dd, 1 H, *J* 7.6 and 10.7 Hz, H-4), 4.34 (t, 1 H, *J* 7.5 Hz, H-3), 4.43 (dd, 1 H, *J* 3.7 and 7.3 Hz, H-2), 4.60 (d, 1 H, *J* 11.6 Hz, C*H*$_2$Ar), 4.714 (d, H, *J* 11.3 Hz, C*H*$_2$Ar), 6.88 (d, 2 H, *J* 8.9 Hz, Ar*H*), 7.31 (d, 2 H, *J* 8.9 Hz, Ar*H*).

Anal. Calcd for $C_{26}H_{36}O_7$: C, 67.80; H, 7.88. Found: C, 67.71; H, 7.92.

Compound **10** had R_F 0.34. ^1H NMR data: δ 1.40–1.76 (m, 20 H), 2.60 (d, 1 H, *J* 2.1 Hz, OH), 3.30 (t, 1 H, *J* 9.8 Hz, H-5), 3.54 (dd, 1 H, *J* 4.6 and 7.0 Hz, H-1), 3.76 (dd, 1 H, *J* 8.6 and 10.1 Hz, H-4), 3.81 (s, 3 H, OMe), 4.06 (ddd, 1 H, *J* 2.1, 7.2, and 9.3 Hz, H-6), 4.20 (dd, 1 H, *J* 5.5 and 8.6 Hz, H-3), 4.38 (t, 1 H, *J* 4.9 Hz, H-2), 4.62 (d, 1 H, *J* 11.6 Hz, C*H*$_2$Ar), 4.72 (d, 1 H, *J* 11.6 Hz, C*H*$_2$Ar), 6.89 (d, 2 H, *J* 8.9 Hz, Ar*H*), 7.31 (d, 2 H, *J* 8.6 Hz, Ar*H*).

Anal. Calcd for $C_{26}H_{36}O_7 \cdot 0.33H_2O$: C, 66.93; H, 7.92. Found: C, 66.87; H, 7.83.

(±)-1-O-Allyl-2,3 : 4,5-di-O-cyclohexylidene-6-O-(4-methoxybenzyl)-myo-*inositol* (**11**).—To a stirred mixture of **9** (93 mg, 0.16 mmol) and NaH (55% in mineral oil; 14 mg, 0.32 mmol) was added allyl bromide (21 μL, 0.24 mmol) at 0°. The mixture was stirred at 20° for 3 h, then poured into ice–water, and extracted with Et_2O, and the extract was washed with H_2O and brine, dried ($MgSO_4$), and concentrated

in vacuo. Flash-column chromatography (toluene–EtOAc, 95:5) of the residue gave **11** (76 mg, 96%); R_F 0.42. ^{1}H NMR data: δ 1.39–1.75 (m, 20 H, 10 CH_2), 3.50 (dd, 1 H, *J* 7.9 and 10.7 Hz, H-5), 3.67 (t, 1 H, *J* 3.2 Hz, H-1), 3.81 (s, 3 H, OMe), 3.81 (dd, 1 H, *J* 2.7 and 7.6 Hz, H-6), 4.08–4.11 (m, 3 H), 4.31 (t, 1 H, *J* 7.3 Hz, H-3), 4.38 (dd, 1 H, *J* 3.7 and 7.0 Hz, H-2), 4.59 (d, 1 H, *J* 11.3 Hz, CH_2Ar), 4.69 (d, 1 H, *J* 11.3 Hz, CH_2Ar), 5.16 (m, 1 H), 5.27 (m, 1 H), 5.87 (m, 1 H), 6.88 (d, 2 H, *J* 8.9 Hz, Ar*H*), 7.30 (d, 2 H, *J* 8.5 Hz, Ar*H*).

Anal. Calcd for $C_{29}H_{40}O_7$: C, 69.57; H, 8.05. Found: C, 69.38; H, 8.02.

*(±)-1-*O*-Allyl-6-*O*-(4-methoxybenzyl)*-myo*-inositol* (**12**).—A solution of **11** (8.7 g, 17.4 mmol) in 0.1 M HCl–MeOH (100 mL) was stirred at 20° for 1 h, then concentrated in vacuo. Flash-column chromatography ($CHCl_3$–MeOH, 92:8) of the residue afforded **12** (4.18 g, 71%); R_F 0.25 (CH_3Cl–MeOH, 9:1). ^{1}H NMR data ($CDCl_3$–CD_3OD, 20:1): δ 3.32 (t, 1 H, *J* 9.3 Hz, H-4, H-5, or H-6), 3.34 (dd, 1 H, *J* 2.9 and 9.6 Hz, H-1 or H-3), 3.38 (dd, 1 H, *J* 2.9 and 9.6 Hz, H-1 or H-3), 3.71 (t, 1 H, *J* 9.5 Hz, H-4, H-5, or H-6), 3.74 (t, 1 H, *J* 9.6 Hz, H-4, H-5, or H-6), 3.81 (s, 3 H, OMe), 4.16 (m, 1 H, $CH_2CH{=}CH_2$), 4.18 (t, 1 H, *J* 2.9 Hz, H-2), 4.21 (m, 1 H, $CH_2CH{=}CH_2$), 4.68 (d, 1 H, *J* 10.7 Hz, CH_2Ar), 4.85 (d, 1 H, *J* 10.7 Hz, CH_2Ar), 5.22 (m, 1 H, $CH_2CH{=}CH_2$), 5.33 (m, 1 H, $CH_2CH{=}CH_2$), 5.96 (m, 1 H, $CH_2CH{=}CH_2$), 6.89 (d, 2 H, *J* 8.6 Hz, Ar*H*), 7.32 (d, 2 H, *J* 8.6 Hz, Ar*H*).

Anal. Calcd for $C_{17}H_{24}O_7$: C, 59.99; H, 7.11. Found: C, 59.71; H, 7.08.

*(±)-1-*O*-Allyl-2,3,4,5-tetra-*O*-benzyl-6-*O*-(4-methoxybenzyl)*-myo*-inositol* (**13**).—To a stirred mixture of **12** (4.18 g, 12.3 mmol) and NaH (55% in mineral oil; 3.2 g, 74 mmol) was added benzyl bromide (7.3 mL, 61.5 mmol) at 0°, and the mixture was stirred at 20° for 2 h. Work-up, as described for **11**, followed by flash-column chromatography (toluene–EtOAc, 95:5), gave **13** (8.27 g, 96%); R_F 0.56. ^{1}H NMR data: δ 3.24 (dd, 1 H, *J* 2.3 and 9.9 Hz, H-1 or H-3), 3.35 (dd, 1 H, *J* 2.3 and 9.9 Hz, H-1 or H-3), 3.43 (t, 1 H, *J* 9.3 Hz, H-4, H-5, or H-6), 3.78 (s, 3 H, OMe), 4.01 (t, 1 H, *J* 9.5 Hz, H-4, H-5, or H-6), 4.02 (t, 1 H, *J* 2.3 Hz, H-2), 4.06 (t, 1 H, *J* 9.5 Hz, H-4, H-5, or H-6), 4.08 (m, 1 H, $CH_2CH{=}CH_2$), 4.12 (m, 1 H, $CH_2CH{=}CH_2$), 4.60–4.91 (m, 10 H, 5 CH_2Ar), 5.18 (m, 1 H, $CH_2CH{=}CH_2$), 5.31 (m, 1 H, $CH_2CH{=}CH_2$), 5.92 (m, 1 H, $CH_2CH{=}CH_2$), 6.82 (d, 2 H, *J* 8.5 Hz, Ar*H*), 7.23–7.43 (m, 22 H, Ar*H*).

Anal. Calcd for $C_{45}H_{48}O_7 \cdot 0.05$toluene: C, 77.21 H, 6.91. Found: C, 76.83; H, 6.86.

*(±)-2,3,4,5-Tetra-*O*-benzyl-6-*O*-(4-methoxybenzyl)*-myo*-inositol* (**14**).—A mixture of **13** (8.1 g, 11.6 mmol) and KO^{t}Bu (13 g, 115 mmol) in Me_2SO (200 mL) was stirred at 60° for 1 h, then poured into ice–water, and extracted with EtOAc . The extract was washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. To the residue was added 1:9 M aq HCl–acetone (300 mL), and the mixture was heated under reflux for 10 min, then concentrated in vacuo. Flash-column chromatography (toluene–EtOAc, 95:5) of the residue gave **14** (7.45 g, quantitative); R_F 0.13. ^{1}H NMR data: δ 2.16 (d, 1 H, *J* 6.4 Hz, OH), 3.45 (dd, 1 H, *J* 2.4 and 9.8 Hz, H-3), 3.46 (t, 1 H, *J* 9.3 Hz, H-4, H-5, or H-6), 3.79 (s, 3 H,

OMe), 3.80 (t, 1 H, *J* 9.5 Hz, H-4, H-5, or H-6), 4.05 (t, 1 H, *J* 9.5 Hz, H-4, H-5, or H-6), 4.66–4.99 (m, 10 H, 5 C*H*$_2$Ar), 6.84 (d, 2 H, *J* 8.6 Hz, Ar*H*), 7.24–7.35 (m, 22 H, Ar*H*).

Anal. Calcd for $C_{42}H_{44}O_7$: C, 76.33; H, 6.71. Found: C, 76.10; H, 6.71.

*(±)-1*D*-2,3,4,5*-Tetra-O-*benzyl-1*-O-*[(−)-camphanoyl]-6*-O-*(4-methoxybenzyl)*-myo-*inositol* (**15a**).—A mixture of **14** (714 mg, 1.08 mmol), (−)-camphanoyl chloride (363 mg, 1.68 mmol), Et_3N (0.46 mL, 3.24 mmol), and 4-dimethylaminopyridine (38 mg, 0.31 mmol) in dichloroethane (19 mL) was stirred at 20° for 1 h, then washed with aq 5% $NaHCO_3$, aq 5% HCl, and brine, dried ($MgSO_4$), and concentrated in vacuo. Flash-column chromatography (Et_2O–CH_2Cl_2, 1:99) of the residue gave **15a** (421 mg, 48%) and **15b** (420 mg, 48%).

Compound **15a** had R_F 0.43; $[\alpha]_D$ + 9.5° (*c* 0.63). ^{1}H NMR data: δ 0.91 (s, 3 H, Me), 1.02 (s, 3 H, Me), 1.09 (s, 3 H, Me), 1.64–1.68 (m, 1 H), 1.83–1.91 (m, 2 H), 2.30–2.36 (m, 1 H), 3.55 (t, 1 H, *J* 9.2 Hz, H-5), 3.56 (dd, 3 H, *J* 2.2 and 9.3 Hz, H-3), 3.78 (s, 3 H, OMe), 4.09 (t, 1 H, *J* 9.5 Hz, H-4), 4.13 (t, 1 H, *J* 2.4 Hz, H-2), 4.16 (t, 1 H, *J* 9.3 Hz, H-6), 4.63–4.92 (m, 10 H, 5 C*H*$_2$Ar), 4.94 (dd, 1 H, *J* 2.4 and 10.3 Hz, H-1), 6.81 (d, 2 H, *J* 8.8 Hz, Ar*H*), 7.19 (d, 2 H, *J* 8.8 Hz, Ar*H*), 7.22–7.39 (m, 20 H, 4 Ph).

Anal. Calcd for $C_{52}H_{56}O_{10}$: C, 74.26; H, 6.71. Found: C, 74.19; H, 6.70.

Compound **15b** had R_F 0.30; $[\alpha]_D$ −13° (*c* 1.64). ^{1}H NMR data: δ 0.88 (s, 3 H, Me), 0.98 (s, 3 H, Me), 1.09 (s, 3 H, Me), 1.64–1.69 (m, 1 H), 1.84–1.96 (m, 2 H), 2.27–2.32 (m, 1 H), 3.55 (t, 1 H, *J* 9.3 Hz, H-5), 3.57 (dd, 1 H, *J* 2.1 and 9.8 Hz, H-3), 3.77 (s, 3 H, OMe), 4.10 (t, 1 H, *J* 9.6 Hz, H-4), 4.16 (dd, 1 H, *J* 9.3 and 10.1 Hz, H-6), 4.22 (t, 1 H, *J* 2.1 Hz, H-2), 4.63–4.84 (m, 7 H, 3.5 C*H*$_2$Ar), 4.87 (dd, 1 H, *J* 2.4 and 10.4 Hz, H-1), 4.89–4.98 (m, 3 H, 1.5 C*H*$_2$Ar), 6.81 (d, 2 H, *J* 8.9 Hz, Ar*H*), 7.18 (d, 2 H, *J* 8.5 Hz, Ar*H*), 7.21–7.37 (m, 20 H, 4 Ph).

Anal. Calcd for $C_{52}H_{56}O_{10}$: C, 74.26; H, 6.71. Found: C, 74.18; H, 6.71.

*(+)-1*D*-2,3,4,5-Tetra*-O-*benzyl-1*-O-*[(−)-camphanoyl]*-myo-*inositol* (**16**).—A mixture of **15a** (395 mg, 0.47 mmol) and ammonium cerium(IV) nitrate (1.03 g, 1.88 mmol) in MeCN (12 mL) and H_2O (3 mL) was stirred at 0° for 1 h, then extracted with EtOAc. The extract was washed with aq $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. Flash-column chromatography (toluene–EtOAc, 9:1) of the residue gave **16** (339 mg, quantitative); R_F 0.15; $[\alpha]_D$ +1.5° (*c* 0.33). ^{1}H NMR data: δ 0.95 (s, 3 H, Me), 1.01 (s, 3 H, Me), 1.10 (s, 3 H, Me), 1.65–1.70 (m, 1 H), 1.85–1.91 (m, 1 H), 1.96–2.01 (m, 1 H), 2.27 (d, 1 H, *J* 3.1 Hz, OH), 2.32–2.37 (m, 1 H), 3.39 (t, 1 H, *J* 9.2 Hz), 3.57 (dd, 1 H, *J* 2.3 and 9.9 Hz, H-3), 4.07 (t, 1 H, *J* 9.5 Hz), 4.12 (t, 1 H, *J* 2.4 Hz, H-2), 4.15 (dt, 1 H, *J* 3.1 and 9.8 Hz, H-6), 4.64–5.00 (m, 8 H, C*H*$_2$Ph), 4.91 (dd, 1 H, *J* 2.6 and 10.2 Hz, H-1), 7.26–7.35 (m, 20 H, 4 Ph).

Anal. Calcd for $C_{44}H_{48}O_9 \cdot 0.2H_2O$: C, 72.95; H, 6.73. Found: C, 72.89; H, 6.74.

*(+)-1*D*-2,3,4,5-Tetra*-O-*benzyl-1*-O-*(4-methoxybenzyl)*-myo-*inositol* (**7**).—A mixture of **16** (36 mg, 0.05 mmol), ethyl vinyl ether (48 μL, 0.5 mmol), and *p*-TsOH (0.2 mg, 1 μmol) in CH_2Cl_2 (1 mL) was stirred at 20° for 1 h, then washed with aq

$NaHCO_3$ and brine, dried (K_2CO_3), and concentrated in vacuo. A mixture of the residue and NaOH (10 mg, 0.25 mmol) in tetrahydrofuran (0.5 mL) and MeOH (1 mL) was stirred at 20° overnight, then diluted with EtOAc, washed with H_2O and brine, dried (K_2CO_3), and concentrated in vacuo. A mixture of the residue, NaH (55% in mineral oil; 3.9 mg, 0.08 mmol), and 4-methoxybenzyl chloride (8 μL, 0.06 mmol) in *N,N*-dimethylformamide (1 mL) was stirred at 20° for 1 h. After work-up, as described for **11**, a mixture of the residue and AcOH (0.1 mL) in MeOH (2 mL) was stirred at 20° for 1 h, then diluted with EtOAc, washed with H_2O, aq $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated in vacuo. Preparative TLC (toluene–EtOAc, 9:1) of the residue gave **7** (25.9 mg, 83%); R_F 0.28; mp 77–77.5°; $[\alpha]_D$ + 8.8° (*c* 2.59). ^{1}H NMR data: δ 2.47 (s, 1 H, OH), 3.16 (dd, 1 H, *J* 2.2 and 10.0 Hz, H-3), 3.36 (t, 1 H, *J* 9.3 Hz, H-5), 3.37 (dd, 1 H, *J* 2.4 and 9.8 Hz, H-1), 3.81 (s, 3 H, OMe), 4.02 (t, 1 H, *J* 2.3 Hz, H-2), 4.05 (t, 1 H, *J* 9.5 Hz, H-4), 4.15 (bt, 1 H, *J* 9.5 Hz, H-6), 4.42–4.92 (m, 10 H, CH_2Ar), 6.85–6.87 (m, 2 H, Ar*H*), 7.20–7.39 (m, 22 H, Ar*H*).

Anal. Calcd for $C_{42}H_{44}O_7$: C, 76.33; H, 6.71. Found: C, 76.14; H, 6.70.

*(+)-1*D*-2,3,4,5,6-Penta*-O*-benzyl-1*-O*-(4-methoxybenzyl)*-myo*-inositol* (**17**).—Benzylation of **5** (21 mg, 32 μmol), as described for **13**, with preparative TLC (toluene–EtOAc, 95:5) of the product, gave **17** (24 mg, quantitative); R_F 0.48; $[\alpha]_D$ +0.6° (*c* 0.55). ^{1}H NMR data: δ 3.33 (dd, 1 H, *J* 2.1 and 5.5 Hz, H-1 or H-3), 3.35 (dd, 1 H, *J* 2.4 and 5.5 Hz, H-1 or H-3), 3.47 (t, 1 H, *J* 9.3 Hz, H-4, H-5, or H-6), 3.81 (s, 3 H, OMe), 4.00 (t, 1 H, *J* 2.3 Hz, H-2), 4.06 (t, 1 H, J 9.5 Hz, H-4, H-5, or H-6), 4.08 (t, 1 H, *J* 9.5 Hz, H-4, H-5, or H-6), 6.83–7.41 (m, 29 H, Ar*H*).

Anal. Calcd for $C_{49}H_{50}O_7 \cdot 0.1CHCl_3$: C, 78.37; H, 6.62. Found: C, 77.59; H, 6.67.

*(+)-1*D*-2,3,4,5,6-Penta*-O*-benzyl*-myo*-inositol* (**18**).—Treatment of **17** (22 mg, 29 μmol) with ammonium cerium(IV) nitrate (32 mg, 59 μmol) in aq 9% MeCN, as described for **16**, followed by flash-column chromatography (toluene–EtOAc, 95:5) gave **18** (15.5 mg, 85%); R_F 0.29; $[\alpha]_D$ + 11° (*c* 0.66). ^{1}H NMR data: δ 3.46 (dd, 1 H, *J* 2.4 and 9.8 Hz, H-1 or H-3), 3.48 (t, 1 H, *J* 9.2 Hz, H-4, H-5, or H-6), 3.48 (dd, 1 H, *J* 2.8 and 9.8 Hz, H-1 or H-3), 3.81 (t, 1 H, *J* 9.6 Hz, H-4, H-5, or H-6), 4.03 (t, 1 H, *J* 2.8 Hz, H-2), 4.06 (t, 1 H, *J* 9.6 Hz, H-4, H-5, or H-6), 7.26–7.36 (m, 25 H, 5 Ph).

tert-*Butyldimethylsilyl 2-azido-4,6-*O*-benzylidene-2-deoxy-β-*D*-glucopyranoside* (**20**).—A mixture of **19**[16] (24.6 g, 77.2 mmol), Benzaldehyde dimethyl acetal (31.4 mL, 208 mmol), and *p*-TsOH (0.38 g, 2 mmol) in MeCN (700 mL) was stirred at 20° overnight, then neutralised with Et_3N, and concentrated in vacuo. The residue was extracted with EtOAc, and the extract was washed with aq $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. Flash-column chromatography (toluene–EtOAc–Et_3N, 90:10:1) of the residue gave **20** (29.2 g, 93%), R_F 0.51 (toluene–EtOAc, 9:1); $[\alpha]_D$ −40° (*c* 0.40). ^{1}H NMR data: δ 0.16 (s, 3 H, Me), 0.18 (s, 3 H, Me), 0.94 (s, 9 H, ^{t}Bu), 2.65 (s, 1 H, OH), 3.32 (dd, 1 H, *J* 7.6 and 9.5 Hz, H-2), 3.41 (ddd, 1 H, *J* 4.9, 9.2, and 10.1 Hz, H-5), 3.56 (t, 1 H, *J* 9.2 Hz, H-4),

3.63 (dt, 1 H, *J* 1.2 and 9.5 Hz, H-3), 3.78 (t, 1 H, *J* 10.2 Hz, H-6a), 4.29 (dd, 1 H, *J* 5.0 and 10.5 Hz, H-6b), 4.65 (d, 1 H, *J* 7.16 Hz, H-1), 5.53 (s, 1 H, C*H*Ar), 7.16–7.49 (m, 5 H, Ph).

Anal. Calcd for $C_{19}H_{29}N_3O_5Si$: C, 56.00; H, 7.17; N, 10.31. Found: C, 56.13; H, 7.21; N, 9.95.

tert-*Butyldimethylsilyl 2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-β-*D*-glucopyranoside* (**21**).—Benzylation of **20** (29.0 g, 71.2 mmol), as described for **13**, flash-column chromatography (toluene–hexane, 7:3) of the product, and recrystallization from hexane gave **21** (27.8 g, 79%); R_F 0.72 (toluene–EtOAc, 39:1); mp 100–101°; $[\alpha]_D$ – 85° (*c* 0.91). ^{1}H NMR data: δ 0.15 (s, 3 H, Me), 0.16 (s, 3 H, Me), 0.94 (s, 9 H, ^{t}Bu), 3.36 (dd, 1 H, *J* 7.6 and 9.5 Hz, H-2), 3.38 (ddd, 1 H, *J* 4.9, 9.5, and 10.4 Hz, H-5), 3.51 (t, 1 H, *J* 9.5 Hz, H-3 or H-4), 3.71 (t, 1 H, *J* 9.5 Hz, H-3 or H-4), 3.79 (t, 1 H, *J* 10.4 Hz, H-6a), 4.29 (dd, 1 H, *J* 4.9 and 10.4 Hz, H-6b), 4.58 (d, 1 H, *J* 7.6 Hz, H-1), 4.79 (d, 1 H, *J* 11.6 Hz, CH_2Ph), 4.90 (d, 1 H, *J* 11.3 Hz, CH_2Ph), 5.56 (s, 1 H, C*H*Ph), 7.25–7.48 (m, 10 H, 2 Ph).

Anal. Calcd for $C_{26}H_{35}N_3O_5Si$: C, 62.75; H, 7.09; N, 8.44. Found: C, 62.74; H, 7.09; N, 8.34.

tert-*Butyldimethylsilyl 2-azido-3,6-di-*O*-benzyl-2-deoxy-β-*D*-glucopyranoside* (**6**).—To a stirred mixture of **21** (27.7 g, 55.7 mmol), boron–triethylamine complex (55.9 g, 779 mmol), and powdered molecular sieves 4A (MS4A) (30 g) was added aluminum chloride (104.1 g, 78 mmol) at 0°. The mixture was stirred at 20° overnight, then extracted with EtOAc, and the extract was washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. Flash-column chromatography (toluene–EtOAc, 39:1) of the residue gave a mixture of **6** and **22** (30.6 g). A solution of the mixture, imidazole (2 g, 30 mmol), and *tert*-butyldimethylsilyl chloride (4.5 g, 30 mmol) in *N*,*N*-dimethylformamide (300 mL) was stirred at 20° for 1 h, then extracted with EtOAc, and the extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Flash-column chromatography (toluene–EtOAc, 49:1) of the residue gave **6** (23.2 g, 84%) and **22** (4.30 g, 13%).

Compound **6** had R_F 0.37 (toluene–EtOAc, 95:5); $[\alpha]_D$ – 32° (*c* 0.42). ^{1}H NMR data: δ 0.16 (s, 6 H, 2 Me), 0.94 (s, 9 H, ^{t}Bu), 2.62 (d, 1 H, *J* 2.2 Hz, OH), 3.21 (dd, 1 H, *J* 8.7 and 9.9 Hz, H-3), 3.31 (dd, 1 H, *J* 7.7 and 9.9 Hz, H-2), 3.42 (dt, 1 H, *J* 9.5 and 4.9 Hz, H-5), 3.64 (ddd, 1 H, *J* 2.2, 8.8, and 9.5 Hz, H-4), 3.71 (d, 2 H, *J* 4.9 Hz, H-6a,6b), 4.53 (d, 1 H, *J* 7.6 Hz, H-1), 4.55 (d, 1 H, *J* 11.7 Hz, 0.5 CH_2Ph), 4.59 (d, 1 H, *J* 12.2 Hz, 0.5 CH_2Ph), 4.76 (d, 1 H, *J* 11.5 Hz, 0.5 CH_2Ph), 4.91 (d, 1 H, *J* 11.5 Hz, 0.5 CH_2Ph), 7.26–7.40 (m, 10 H, 2 Ph).

Anal. Calcd for $C_{26}H_{37}N_3O_5Si$: C, 62.50; H, 7.46; N, 8.41. Found: C, 62.19; H, 7.48; N, 8.23.

Compound **22** had R_F 0.83; $[\alpha]_D$ – 23° (*c* 2.52). ^{1}H NMR data: δ 0.05 (s, 3 H, Me), 0.06 (s, 3 H, Me), 0.15 (s, 3 H, Me), 0.15 (s, 3 H, Me), 0.89 (s, 9 H, ^{t}Bu), 0.93 (s, 9 H, ^{t}Bu), 3.24 (ddd, 1 H, *J* 2.2, 3.3 and 9.5 Hz, H-5), 3.29 (dd, 1 H, *J* 7.5 and 10.1 Hz, H-2), 3.80–3.81 (m, 2 H, H-6a,6b), 4.49 (d, 1 H, *J* 7.7 Hz, H-1), 4.66–4.88 (m, 4 H, 2 CH_2Ph), 7.25–7.38 (m, 10 H, 2 Ph).

Anal. Calcd for $C_{32}H_{51}N_3O_5Si_2$: C, 62.60; H, 8.37; N, 6.85. Found: C, 62.34; H, 8.39; N, 6.75.

*Methyl 3,6-di-*O*-acetyl-2,6-di-*O*-benzyl-1-thio-α-*D*-mannopyranoside* (**5**).—To a stirred mixture of **23**[18] (9.72 g, 20 mmol) and methyl tributyltin sulfide (6.8 mL, 22 mmol) in dichloroethane (200 mL) was added tin(IV) chloride (2.6 mL, 22 mmol) at 0°. The mixture was stirred at 0° for 3 h, then washed with aq $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. Flash-column chromatography (toluene–EtOAc, 9:1) of the residue gave **5** (8.06 g, 85%); R_F 0.62 (toluene–EtOAc, 3:1); $[\alpha]_D$ + 53° (*c* 0.35). NMR data: ^1H, δ 1.97 (s, 3 H), 2.06 (s, 3 H), 2.12 (s, 3 H), 3.96 (t, 1 H, *J* 9.5 Hz, H-4), 3.97 (dd, 1 H, *J* 1.8 and 3.4 Hz, H-2), 4.21 (dt, 1 H, *J* 3.7 and 9.8 Hz, H-5), 4.33 (d, 2 H, *J* 3.7 Hz, H-6a,6b), 4.51 (d, 1 H, *J* 12.2 Hz, 0.5 CH_2Ph), 4.58 (d, 1 H, *J* 12.2 Hz, 0.5 CH_2Ph), 4.68 (d, 1 H, *J* 12.2 Hz, 0.5 CH_2Ph), 4.70 (d, 1 H, *J* 11.3 Hz, 0.5 CH_2Ph), 5.18 (dd, 1 H, *J* 3.4 and 9.5 Hz, H-3), 5.24 (d, 1 H, *J* 1.5 Hz, H-1), 7.26–7.35 (m, 10 H, 2 Ph); ^{13}C, δ 83.0 ($J_{C\text{-}1,H\text{-}1}$ 167.2 Hz, C-1).

Anal. Calcd for $C_{25}H_{30}O_7S$: C, 63.28; H , 6.37. Found: C, 63.01; H, 6. 42.

tert-*Butyldimethylsilyl-2-azido-3,6-di-*O*-benzyl-2-deoxy-4-*O*-(3,6-di-*O*-acetyl-2,4-di-*O*-benzyl-α-*D*-mannopyranosyl)-β-*D*-glucopyranoside* (**24**).—A mixture of **6** (49.9 mg, 0.1 mmol), **5** (71.1 mg, 0.15 mmol), silver trifluoromethanesulfonate (69 mg, 0.27 mmol), tetrabutylammonium bromide (12 mg, 0.038 mmol), $CuBr_2$ (60 mg, 0.27 mmol), and MS4A (200 mg) in nitromethane (2 mL) was stirred at 20° for 2 h, then neutralised with Et_3N, and filtered through Celite. The filtrate was diluted with EtOAc, washed with aq $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. Flash-column chromatography (toluene–EtOAc, 95:5) of the residue gave **24** (92 mg, 90%); R_F 0.46 (toluene–EtOAc, 9:1); $[\alpha]_D$ + 5.4° (*c* 0.35). NMR data: ^1H, δ 0.17 (s, 3 H, Me), 0.18 (s, 3 H, Me), 0.94 (s, 9 H, ^{t}Bu), 1.96 (s, 3 H, Ac), 1.98 (s, 3 H, Ac), 3.34–3.39 (m, 2 H), 3.46 (ddd, 1 H, *J* 1.8, 5.2, and 9.8 Hz, H-5), 3.69 (dd, 1 H, *J* 5.3 and 11.1 Hz, H-6), 3.75 (t, 1 H, *J* 2.6 Hz, H-2′), 3.88 (t, 1 H, *J* 9.7 Hz, H-4′), 4.06 (d, 1 H, *J* 12.2 Hz, 0.5 CH_2Ph), 4.16 (d, 1 H, J 11.9 Hz, 0.5 CH_2Ph), 4.16 (dd, 1 H, *J* 2.0 and 11.8 Hz, H-6′a), 4.20 (dd, 1 H, *J* 4.1 and 12.1 Hz, H-6′b), 4.53 (d, 1 H, *J* 12.2 Hz, 0.5 CH_2Ph), 4.54 (d, 1 H, *J* 11.3 Hz, 0.5 CH_2Ph), 4.55 (d, 1 H, *J* 6.1 Hz, H-1), 4.60 (d, 1 H, *J* 12.2 Hz, 0.5 CH_2Ph), 4.66 (d, 2 H, *J* 11.3 Hz, CH_2Ph), 5.02 (d, 1 H, *J* 11.6 Hz, 0.5 CH_2Ph), 5.21 (dd, 1 H, *J* 2.9 and 8.1 Hz, H-3′), 5.24 (d, 1 H, *J* 2.4 Hz, H-1′), 7.09–7.36 (m, 20 H, 4 Ph); ^{13}C, δ 97.2 ($^1J_{C,H}$ 162.3 Hz, C-1), 99.8 ($^1J_{CH}$ 167.2 Hz, C-1′).

Anal. Calcd for $C_{50}H_{63}N_3O_{12}Si \cdot 0.2$toluene: C, 65.35; H, 6.89; N, 4.45. Found: C, 65.64; H, 6.89; N, 4.46.

*2-Azido-3,6-di-*O*-benzyl-2-deoxy-4-*O*-(3,6-di-*O*-acetyl-2,4-di-*O*-benzyl-α-*D*-mannopyranosyl)-*D*-glucopyranose* (**25**). – A mixture of **24** (77 mg, 0.083 mmol), AcOH (43 μL, 0.78 mmol), M Bu_4NF in tetrahydrofuran (0.33 mL), and tetrahydrofuran (3 mL) was stirred at 20° overnight, then extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Flash-column chromatography (toluene–EtOAc, 4:1) of the residue gave **25** (60 mg, 89%) as a

2:1 α,β-mixture; R_F 0.22. ^{1}H NMR data: δ 5.24 (dd, 0.59 H, J 2.9 and 8.7 Hz, H-3′), 5.34 (t, 0.59 H, J 3. 5 Hz, H-1α).

Anal. Calcd for $C_{44}H_{49}N_3O_{12}$: C, 65.01; H, 6.08; N, 5.18. Found: C, 65.06; H, 6.18; N, 5.05.

*2-Azido-3,6-di-*O*-benzyl-2-deoxy-4-*O*-(3,6-di-*O*-acetyl-2,4-di-*O*-benzyl-α-*D*-mannopyranosyl)-*D*-glucopyranosyl fluoride* (**26**).—A mixture of **25** (375 mg, 0.46 mmol) and Et_2NSF_3 (73 μL, 0.55 mmol) in dichloroethane (10 mL) was stirred at −23° for 0.5 h, then poured into ice–water, and extracted with $CHCl_3$. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Flash-column chromatography (toluene–EtOAc, 9:1) of the residue gave **26** (375 mg, quantitative) as a 1:2 α,β-mixture; R_F 0.44. ^{1}H NMR data: δ 5.11 (dd, 0.66 H, J 7.0 and 52.4 Hz, H-1β), 5.25 (dd, 0.34 H, J 3.3, 8.4 Hz, H-3′), 5.68 (dd, 0.34 H, J 2.2 and 52.8 Hz, H-1α).

Anal. Calcd for $C_{44}H_{48}FN_3O_{11}$: C, 64.93; H, 5.95; N, 5.16. Found: C, 64.91; H, 6.00; N, 5.06.

*O-(3,6-Di-*O*-acetyl-2,4-di-*O*-benzyl-α-*D*-mannopyranosyl)-(1 → 4)-*O*-(2-azido-3,6-di-*O*-benzyl-2-deoxy-α-*D*-glucopyranosyl)-(1 → 6)-1*D*-2,3,4,5-tetra-*O*-benzyl-1-*O*-(4-methoxybenzyl)*-myo-*inositol* (**27**).—A mixture of **26** (596 mg, 0.63 mmol), **7** (300 mg, 0.45 mmol), Cp_2ZrCl_2 (857 mg, 2.93 mmol), $AgClO_4$ (608 mg, 2.93 mmol), and MS4A (1 g) in Et_2O (15 mL) was stirred at 0° overnight, then neutralised with Et_3N, and filtered through Celite. The filtrate was washed with aq $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. Flash-column chromatography (toluene–acetone, 95:5) of the residue gave **27** (480 mg, 73%) and the β isomer (130 mg, 20%).

Compound **27** had R_F 0.60; $[\alpha]_D$ + 49° (c 0.60). NMR data: ^{1}H, δ 1.92 (s, 3 H, Ac), 1.96 (s, 3 H, Ac), 3.19 (dd, 1 H, J 3.7 and 10.4 Hz, H-2′), 3.26 (dd, 1 H, J 2.1 and 10.1 Hz, H-1 or H-3), 3.36 (dd, 1 H, J 2.3 and 9.9 Hz, H-1 or H-3), 3.62 (s, 3 H, OMe), 3.73 (dt, 1 H, J 9.8 and 3.2 Hz, H-5′), 3.79 (t, 1 H, J 2.6 Hz, H-2″), 3.98 (bs, 1 H, H-2), 3.99 (d, 1 H, J 12.8 Hz, 0.5 CH_2Ph), 4.08 (d, 1 H, J 10.7 Hz, 0.5 CH_2Ph), 4.37 (bd, 1 H, J 9.8 Hz, H-5″), 4.39–5.06 (m, 16 H, 8 CH_2Ph), 5.19 (d, 1 H, J 2.1 Hz, H-1″), 5.29 (dd, 1 H, J 3.1 and 9.5 Hz, H-3″), 5.60 (d, 1 H, J 3.7 Hz, H-1′), 6.84 (d, 2 H, J 8.6 Hz, ArH), 7.07–7.36 (m, 42 H, ArH); ^{13}C, δ 97.6 ($^1J_{C,H}$ 177.0 Hz, C-1′), 100.3 ($^1J_{C,H}$ 172.1 Hz, C-1″).

Anal. Calcd for $C_{86}H_{91}N_3O_{18}$: C, 71.00; H, 6.31; N, 2.89. Found: C, 70.70; H, 6.31; N, 2.73.

The β isomer had R_F 0.67; $[\alpha]_D$ + 6.7° (c 0.82). NMR data: ^{1}H, δ 1.94 (s, 3 H, Ac), 1.95 (s, 3 H, Ac), 3.36 (dd, 1 H, J 2.3 and 9.9 Hz, H-1 or H-3), 3.37 (dd, 1 H, J 8.1 and 9.9 Hz, H-2′), 3.41 (dd, 1 H, J 2.1 and 9.8 Hz, H-1 or H-3), 3.62 (dd, 1 H, J 5.0 and 12.4 Hz, H-6′a), 3.75 (t, 1 H, J 2.8 Hz, H-2″), 3.83 (s, 3 H, OMe), 3.89 (ddd, 1 H, J 1.8, 4.6, and 9.8 Hz, H-5″), 4.00 (bs, 1 H, H-2), 4.07 (d, 1 H, J 11.6 Hz, 0.5 CH_2Ph), 4.15 (dd, 1 H, J 4.9 and 11.9 Hz, H-6″a), 4.16 (d, 1 H, J 11.9 Hz, 0.5 CH_2Ph), 4.21 (dd, 1 H, J 1.8 and 11.9 Hz, H-6″b), 4.34 (d, 1 H, J 11.9 Hz, 0.5 CH_2Ph), 4.45–4.85 (m, 13 H, 6.5 CH_2Ph), 4.97 (d, 1 H, J 7.9 Hz, H-1′), 4.98 (d,

1 H, *J* 11.3 Hz, 0.5 CH_2Ph), 5.01 (d, 1 H, *J* 11.3 Hz, 0.5 CH_2Ph), 5.20 (d, 1 H, *J* 2.1 Hz, H-1″), 5.22 (dd, 1 H, *J* 2.9 and 8.4 Hz, H-3″), 6.91 (d, 2 H, *J* 8.9 Hz, Ar*H*), 7.09–7.36 (m, 42 H, Ar*H*); ^{13}C, δ 99.9 ($^1J_{C,H}$ 171.6 Hz, C-1″), 101.5 ($^1J_{C,H}$ 165.9 Hz, C-1′).

Anal. Calcd for $C_{86}H_{91}N_3O_{18}$: C, 71.00; H, 6.31; N, 2.89. Found: C, 71.28; H, 6.45; N, 2.53.

O-*(2,4-Di*-O-*benzyl-α*-D-*mannopyranosyl)-(1 → 4)*-O-*(2-azido-3,6-di*-O-*benzyl-2-deoxy-α*-D-*glucopyranosyl)-(1 → 6)-1*D-*2,3,4,5-tetra*-O-*benzyl-1*-O-*(4-methoxybenzyl)*-myo-*inositol* (**28**).—A mixture of **27** (480 mg, 0.33 mmol), 28% NaOMe in MeOH (0.13 mL), tetrahydrofuran (5 mL), and MeOH (10 mL) was stirred at 20° for 5 h, then neutralised with Amberlyst 15 (H^+) resin, filtered, and concentrated in vacuo. Flash-column chromatography (toluene–EtOAc, 9:1) of the residue gave **28** (452 mg, quantitative); R_F 0.18; $[\alpha]_D$ + 54° (*c* 5.55). NMR data: ^{1}H, δ 3.22 (dd, 1 H, *J* 3.7 and 9.8 Hz, H-2′), 3.44 (dd, 1 H, *J* 2.4 and 11.6 Hz, H-6′a), 3.66 (s, 3 H, OMe), 3.99 (d, 1 H, *J* 11.3 Hz, 0.5 CH_2Ph), 4.13 (d, 1 H, *J* 11.6 Hz, 0.5 CH_2Ph), 4.26 (bd, 1 H, *J* 9.8 Hz, H-5″), 4.39–5.08 (m, 16 H, 8 CH_2Ph), 5.29 (d, 1 H, *J* 1.5 Hz, H-1″), 5.61 (d, 1 H, *J* 3.7 Hz, H-1′), 6.81–7.39 (m, 44 H, Ar*H*).

Anal. Calcd for $C_{82}H_{87}N_3O_{16}$: C, 71.86; H, 6.40; N, 3.07. Found: C, 72.04; H, 6.48; N, 2.80.

O-*(2,3,4,6-Tetra*-O-*benzyl-α*-D-*mannopyranosyl)-(1 → 4)*-O-*(2-azido-3,6-di*-O-*benzyl-2-deoxy-α*-D-*glucopyranosyl)-(1 → 6)-1*D-*2,3,4,5-tetra*-O-*benzyl-1*-O-*(4-methoxybenzyl)*-myo-*inositol* (**3**).—A mixture of **28** (113 mg, 0.082 mmol), BnBr (0.038 mL), and NaH (60% in mineral oil, 13 mg, 0.33 mmol) in tetrahydrofuran (5 mL) was stirred at 60° for 7 h, then poured into ice–water, and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Flash-column chromatography (toluene–EtOAc, 95:5) of the residue gave **3** (127 mg, quantitative); R_F 0.80 (toluene–EtOAc, 9:1); $[\alpha]_D$ +40° (*c* 0.75). ^{1}H NMR data: δ 3.56 (s, 3 H, OMe), 4.19–5.05 (m, 22 H, 11 CH_2Ph), 5.34 (d, 1 H, *J* 2.1 Hz, H-1″), 5.63 (d, 1 H, *J* 3.6 Hz, H-1′), 6.80 (d, 2 H, *J* 8.5 Hz, Ar*H*), 7.13–7.37 (m, 52 H, Ar*H*).

Anal. Calcd for $C_{96}H_{99}N_3O_{16}$: C, 74.35; H, 6.43; N, 2.71. Found: C, 74.64; H, 6.46; N, 2.76.

O-*(2,3,4,6-Tetra*-O-*benzyl-α*-D-*mannopyranosyl)-(1 → 4)*-O-*(2-azido-3,6-di*-O-*benzyl-2-deoxy-α*-D-*glucopyranosyl)-(1 → 6)-1*D-*2,3,4,5-tetra*-O-*benzyl*-myo-*inositol* (**29**).—Treatment of **3** (30 mg, 0.019 mmol) with ammonium cerium(IV) nitrate (53 mg, 0.096 mmol) in MeCN (2 mL) and H_2O (0.2 mL), as described for **16**, with preparative TLC (toluene–EtOAc, 5:1) of the product, gave **29** (24.8 mg, 92%); R_F 0.43 (hexane–EtOAc, 4:1); $[\alpha]_D$ + 37° (*c* 0.63). ^{1}H NMR data: δ 2.94 (bd, 1 H, *J* 7.6 Hz, OH), 3.30 (dd, 1 H, *J* 4.0 and 10.1 Hz, H-2′), 4.16–5.02 (m, 20 H, 10 CH_2Ph), 5.23 (d, 1 H, *J* 1.8 Hz, H-1″), 5.40 (d, 1 H, *J* 3.7 Hz, H-1′), 7.13–7.33 (m, 50 H, 10 Ph).

Anal. Calcd for $C_{88}H_{91}N_3O_{15}$: C, 73.88; H, 6.41; N, 2.94. Found: C, 73.72; H, 6.40; N, 2.95.

(+)-1D-2,3,4,5-Tetra-O-*benzyl-6*-O-*(4-methoxybenzyl)*-myo-*inositol* (**30**).—A mixture of **15a** (500 mg, 0.55 mmol) and NaOH (120 mg, 3 mmol) in MeOH (5 mL) and tetrahydrofuran (3 mL) was stirred at 20° for 4.5 h, then extracted with EtOAc. The extract was washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. Flash-column chromatography (toluene–EtOAc, 9:1) of the residue gave **30** (380 mg, 97%); R_F 0.20; $[\alpha]_D$ + 12° (*c* 0.71). ^1H NMR data: δ 3.45 (dd, 1 H, *J* 2.4 and 9.8 Hz, H-1 or H-3), 3.46 (t, 1 H, *J* 9.3 Hz, H-4, H-5, or H-6), 3.78 (s, 3 H, OMe), 3.80 (t, 1 H, *J* 9.5 Hz, H-4, H-5, or H-6), 4.02 (t, 1 H, *J* 2.4 Hz, H-2), 4.05 (t, 1 H, *J* 9.5 Hz, H-4, H-5, or H-6), 4.66–4.99 (m, 10 H, 5 C*H*$_2$Ar), 6.84 (d, 2 H, *J* 8.6 Hz, Ar*H*), 7.24–7.35 (m, 22 H, Ar*H*).

Anal. Calcd for $C_{42}H_{44}O_7$: C, 76.33; H, 6.71. Found: C, 76.14; H, 6.75.

1,2-Di-O-*myristoyl*-sn-*glycerol 3-(hydrogen phosphonate)* (**4**).—To a stirred solution of imidazole (1.7 g, 24.5 mmol) in toluene (20 mL) was added dropwise a solution of PCl_3 (0.47 mL, 5.4 mmol) in toluene (5 mL) at 0°, then a solution of Et_3N (1.95 mL, 14 mmol) in toluene (5 mL). Stirring was continued for 10 min, a solution of 1,2-*O*-myristoyl-*sn*-glycerol (922 mg, 1.8 mmol) in toluene (20 mL) was added dropwise during 50 min at −5°, the mixture was stirred for 1 h, and the reaction was quenched by the addition of aq 20% pyridine (100 mL). After 15 min, the mixture was extracted with $CHCl_3$, and the extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Flash-column chromatography ($CHCl_3$–MeOH–H_2O, 100:10:1) of the residue gave **4** (365 mg, 35%). The Na salt of **4** had R_F 0.22; $[\alpha]_D$ + 4.6° (*c* 0.63, $CHCl_3$–MeOH, 9:1). NMR data ($CDCl_3$–CD_3OD, 10:1): ^1H, δ 0.88 (t, 6 H, *J* 7.0 Hz, 2 CH_2CH_3), 1.26 (m, 40 H), 1.58 (m, 4 H), 3.90 (m, 2 H), 4.18 (dd, 1 H, *J* 6.7 and 11.9 Hz, Glo H-1a), 4.39 (dd, 1 H, *J* 2.8 and 12.2 Hz, Glo H-1b), 5.22 (m, 1 H, Glo H-2), 6.70 (d, 1 H, *J* 629 Hz, P*H*); ^{31}P, δ 6.85 (d, $^1J_{P,H}$ 631 Hz).

Anal. Calcd for $C_{31}H_{60}NaO_7P$: C, 62.18; H, 10.10. Found: C, 62.17; H, 10.19.

1D-2,3,4,5-Tetra-O-*benzyl-6*-O-*(4-methoxybenzyl)*-myo-*inositol* 1-*(1,2-di*-O-*myristoyl*-sn-*glycer-3-yl phosphonate)* (**31**).—A mixture of **30** (26 mg, 0.04 mmol), **4** (46 mg, 0.08 mmol), and pivaloyl chloride (0.03 mL, 0.24 mmol) in pyridine (1 mL) was stirred at 20° for 5 h, then quenched with H_2O, and extracted with EtOAc. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Preparative TLC (toluene–EtOAc, 9:1) of the residue gave **31** (39.1 mg, 80%); R_F 0.38 and 0.41. NMR data: ^1H, δ 0.88 (m, 6 H), 3.78 and 3.79 (2 s, 3 H, OMe); ^{31}P, δ 9.79 (dd, $^1J_{P,H}$ 727, $^3J_{P,H}$ 8.8 Hz), 8.54 (dd, $^1J_{P,H}$ 721, $^3J_{P,H}$ 8.8 Hz).

Anal. Calcd for $C_{73}H_{103}O_{13}P \cdot H_2O$: C, 70.84; H, 8.55. Found: C, 70.62; H, 8.66.

(−)-1D-2,3,4,5-Tetra-O-*benzyl-6*-O-*(4-methoxybenzyl)*-myo-*inositol 1-(1,2-di*-O-*myristoyl*-sn-*glycer-3-yl triethylammonium phosphate)* (**32**).—A mixture of **31** (24 mg, 0.02 mmol) and iodine (10 mg, 0.04 mmol) in aq 2% pyridine (1 mL) was stirred for 20 min at 20°, then diluted with $CHCl_3$, washed with M $Et_3HN \cdot HCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo. Preparative TLC ($CHCl_3$–MeOH–Et_3N, 95:4:1) of the residue gave **32** (19 mg, 71%), R_F 0.48 (MeOH–$CHCl_3$–Et_3N, 5:93:2), $[\alpha]_D$ −10° (*c* 1.50). NMR data: ^1H, δ 0.88 (t, 6 H, *J* 7.1

Hz, 2 CH_2CH_3), 1.10–1.53 (m, 51 H), 2.17–2.21 (m, 4 H), 2.90–2.95 (m, 6 H), 3.49 (dd, 1 H, *J* 2.1 and 10.0 Hz, H-3), 3.74 (s, 3 H, OMe), 4.16 (ddd, 1 H, *J* 2.1, 9.7, and 11.0 Hz, H-1), 4.55 (bs, 1 H, H-2), 4.60–4.97 (m, 10 H, 5 CH_2Ar), 5.19 (m, 1 H), 6.78 (d, 2 H, *J* 8.7 Hz, Ar*H*), 7.20–7.43 (m, 22 H, Ar*H*); ^{31}P, δ −0.775.

Anal. Calcd for $C_{73}H_{103}O_{14}P \cdot 0.66Et_3N$: C, 70.97; H, 8.74; N, 0.72. Found: C, 71.03; H, 8.72; N, 0.40.

*(+)-1*D-myo-*Inositol 1-(1,2-di-*O*-myristoyl-*sn*-glycer-3-yl hydrogen phosphate)* (**33**).—A mixture of **32** (40 mg, 0.03 mmol) and 20% $Pd(OH)_2/C$ in $CHCl_3$ (3.6 mL) and MeOH (1.2 mL) was stirred under H_2 at 20° for 40 min, then filtered through Celite. 4 M NH_4OH was added to the filtrate which was concentrated in vacuo. Chromatography of the residue on SiO_2 ($CHCl_3$–MeOH–4 M NH_4OH, 9:6:1) and then on LH20 ($CHCl_3$–MeOH–H_2O, 60:30:4) gave **33** (28 mg, quantitative); R_F 0.64 ($CHCl_3$–MeOH–4 M NH_4OH, 9:7:2); $[\alpha]_D$ + 13° (*c* 0.41, $CHCl_3$–MeOH, 5:1). NMR data (Me_2SO-d_6): ^1H, δ 0.85 (t, 6 H, *J* 6.9 Hz, 2 CH_2CH_3), 1.18 (t, 9 H, *J* 7.3 Hz, 3 Me), 1.24 (m, 40 H), 2.26 (m, 4 H), 2.91 (bt, 1 H, *J* 8.9 Hz, H-5), 3.08 (q, 6 H, *J* 6.9 Hz, 3 NCH_2CH_3), 4.08 (dd, 1 H, *J* 7.0 and 11.9 Hz, Glo H-1a), 4.28 (dd, 1 H, *J* 2.9 and 12.1 Hz, Glo H-1b), 5.08 (m, 1 H, Glo H-2); ^{31}P, δ 1.87 (s).

Anal. Calcd for $C_{73}H_{103}O_{14}P \cdot Et_3N \cdot 0.5H_2O$; C, 59.69; H, 10.14; N, 1.62. Found: C, 59.39; H, 10.05; N, 1.63.

O-*(2,3,4,6-Tetra-*O*-benzyl-α-*D*-mannopyranosyl)-(1 → 4)-*O*-(2-azido-3,6-di-*O*-benzyl-2-deoxy-α-*D*-glucopyranosyl)-(1 → 6)-1*D*-2,3,4,5-tetra-*O*-benzyl-*myo*-inositol 1-(1,2-di-*O*-myristoyl-*sn*-glycer-3-yl phosphonate)* (**34**).—Coupling of **29** (32 mg, 0.022 mmol) with **4** (26 mg, 0.044 mmol), as described for **31**, and preparative TLC (toluene–EtOAc, 95:5) of the product gave **34** (34.4 mg, 79%); R_F 0.41 and 0.45. NMR data: ^1H, δ 0.88 (m, 6 H), 3.25 (dd, 1 H, *J* 3.5 and 9.9 Hz, H-2′), 5.26 and 5.28 (2 d, 1 H, *J* 2.0 Hz, H-1″), 5.60 (d, 1 H, *J* 3.7 Hz, H-1′), 7.16–7.34 (m, 50 H, 10 Ph); ^{31}P, δ 8.36 (dd, $^1J_{P,H}$ 723, $^3J_{P,H}$ 9.8 Hz), 9.18 (dd, $^1J_{P,H}$ 719, $^3J_{P,H}$ 8.8 Hz).

Anal. Calcd for $C_{119}H_{150}N_3O_{21}P$: C, 71.84; H, 7.60; N, 2.11. Found: C, 71.93; H, 7.68; N, 2.24.

O-*(2,3,4,6-Tetra-*O*-benzyl-α-*D*-mannopyranosyl)-(1 → 4)-*O*-(2-azido-3,6-di-*O*-benzyl-2-deoxy-α-*D*-glucopyranosyl)-(1 → 6)-1*D*-2,3,4,5-tetra-*O*-benzyl-*myo*-inositol 1-(1,2-di-*O*-myristoyl-*sn*-glycer-3-yl hydrogen phosphate)* (**35**).—Oxidation of **34** (30 mg, 0.015 mmol) with iodine (7.6 mg, 0.03 mmol), as described for **32**, with preparative TLC ($CHCl_3$–MeOH, 95:5) of the product, gave **35** (26.8 mg, 89%); R_F 0.24 ($CHCl_3$–MeOH, 97:3); $[\alpha]_D$ + 19° (*c* 2.1). NMR data: ^1H, δ 0.88 (t, 6 H, *J* 7.0 Hz, 2 Me), 1.24 (m, 40 H), 1.54 (m, 4 H), 2.21 (t, 4 H, *J* 7.5 Hz, 2 $COCH_2$), 3.31 (dd, 1 H, *J* 3.7 and 10.4 Hz, H-2′), 3.71 (bs, 1 H, H-2), 5.20 (d, 1 H, *J* 1.6 Hz, H-1″), 5.21 (m, 1 H, Glo H-2), 5.42 (d, 1 H, *J* 3.7 Hz, H-1′), 7.13–7.37 (m, 50 H, 10 Ph); ^{31}P, δ −1.85 (s). Mass spectrum: *m/z* 2026 ($M^+ + Na$).

Anal. Calcd for $C_{119}H_{150}N_3O_{22}P \cdot H_2O$: C, 70.63; H, 7.57; N, 2.08. Found: C, 70.76; H, 7.61; N, 2.00.

O-*α*-D-*Mannopyranosyl-(1 → 4)-*O*-2-amino-2-deoxy-α-*D*-glucopyranosyl-(1 → 6)-*

*1*D-myo-*inositol 1-(1,2-di*-O-*myristoyl*-sn-*glycer-3-yl sodium phosphate)* (**2**).—A mixture of **35** (19 mg, 9.4 μL) and 20% $Pd(OH)_2/C$ (30 mg) in $CHCl_3$ (1.2 mL), MeOH (0.6 mL), and H_2O (0.08 mL) was stirred under H_2 at 20° for 2 h, then filtered through Celite, and concentrated in vacuo. A mixture of the residue and Amberlite IRC50 (Na^+) resin in 9:7:2 $CHCl_3$–MeOH–H_2O (5 mL) was stirred for 2 h, then filtered, and concentrated in vacuo. Chromatography of the residue on LH20 ($CHCl_3$–MeOH–H_2O, 9:7:2) gave **2** (5.1 mg, 51%); R_F 0.43 ($CHCl_3$–MeOH–4 M NH_4OH, 9:7:2); $[\alpha]_D$ + 64° (*c* 0.37, $CHCl_3$–MeOH–H_2O, 9:7:2). NMR data (Me_2SO-d_6–D_2O, 49:1): ^1H, δ 0.86 (t, 6 H, *J* 6.9 Hz, 2 Me), 2.81 (dd, 1 H, *J* 3.1 and 10.4 Hz, H-2′), 4.05 (t, 1 H, *J* 2.4 Hz, H-2), 4.10 (dd, 1 H, *J* 7.3 and 11.9 Hz, Glo H-1a), 4.20 (ddd, 1 H, *J* 2.6, 7.8, and 10.5 Hz, H-1), 4.31 (dd, 1 H, *J* 3.1 and 11.9 Hz, Glo H-1b), 5.09 (m, 1 H, Glo H-2), 5.23 (d, 1 H, *J* 1.5 Hz, H-1″), 5.27 (d, 1 H, *J* 3.4 Hz, H-1″); ^{31}P, δ 0.284 (s). Mass spectrum: *m/z* 1078 ($M^+ + H$).

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REFERENCES

1 Y. Ito, S. Nunomura, S. Shibayama and T. Ogawa, *J. Org. Chem.*, 57 (1992) 1821–1831.
2 M.A.J. Ferguson and A.F. Willimas, *Annu. Rev. Biochem.*, 57 (1988) 285–320.
3 A.R. Saltiel, J.A. Fox, P. Sherline, and P. Cuatrecasas, *Science*, 233 (1986) 967–972.
4 P.J. Robinson, M. Millrain, J. Antoniou, E. Simpson, and A.L. Mellor, *Nature (London)*, 342 (1989) 85–87.
5 M.A.J. Ferguson, S.W. Homans, R.A. Dwek, and T.W. Rademacher, *Science*, 239 (1988) 753–759.
6 S.W. Homans, M.A.J. Ferguson, R.A. Dwek, T.W. Rademacher, R. Anand, and A.F. Williams, *Nature (London)*, 333 (1988) 269–272.
7 W.L. Roberts, S. Santikarn, V.N. Reinhold, and T.L. Rosenberry, *J. Biol. Chem.*, 263 (1988) 18776–18784.
8 D.R. Mootoo, P. Konradsson, and B. Fraser-Reid, *J. Am. Chem. Soc.*, 111 (1989) 8540–8542.
9 R. Verduyn, J.J.A. Beliën, C.M. Dreef-Tromp, G.A. van der Marel, and J.H. van Boom, *Tetrahedron Lett.*, 32 (1991) 6637–6640.
10 C. Murakata and T. Ogawa, *Tetrahedron Lett.*, 31 (1990) 2439–2442; 32 (1991) 101–104, 671–674.
11 P.J. Garegg, T. Iversen, R. Johansson, and B. Lindberg, *Carbohydr. Res.*, 130 (1984) 322–326.
12 N. Nagashima and M. Ohno, *Chem. Lett.*, (1987) 141–144; K.-L. Yu and B. Fraser-Reid, *Tetrahedron Lett.*, 29 (1988) 979–982.
13 J. Gigg and R. Gigg, *J. Chem. Soc., C*, (1966) 82–86.
14 D.C. Billington, R. Baker, J.J. Kulagowski, and I.M. Mawer, *J. Chem. Soc., Chem. Commun.*, (1987) 314–316.
15 R. Johansson and B. Samuelsson, *J. Chem. Soc., Chem. Commun.*, (1984) 201–202; T. Fukuyama, A.A. Laird, and L.M. Hotchkiss, *Tetrahedron Lett.*, 26 (1985) 6291–6292.
16 W. Kinzy and R.R. Schmidt, *Liebigs Ann. Chem.*, (1985) 1537–1545.
17 M. Ek, P.J. Garegg, H. Hultberg, and S. Oscarson, *J. Carbohydr. Chem.*, 2 (1983) 305–311.

18 T. Ogawa and K. Sasajima, *Tetrahedron*, 37 (1981) 2787–2792.
19 T. Ogawa and M. Matsui, *Carbohydr. Res.*, 54 (1977) c17–c21.
20 S. Sato, M. Mori, Y. Ito, and T. Ogawa, *Carbohydr. Res.*, 155 (1986) c6–c10.
21 Wm. Rosenbrook, Jr., D.A. Riley, and P.A. Lartey, *Tetrahedron Lett.*, 26 (1985) 3–4; G.H. Posner and S.R. Haines, *ibid.*, 26 (1985) 5–8.
22 T. Matsumoto, H. Maeta, K. Suzuki, and G. Tsuchihashi, *Tetrahedron Lett.*, 29 (1988) 3567–3570.
23 I. Lindh and J. Stawinski, *J. Org. Chem.*, 54 (1989) 1338–1342; T.M. Slaghek, A.A.M. Maas, J.P. Kamerling, and J.F.G. Vliegenthart, *Carbohydr. Res.*, 211 (1991) 25–39.