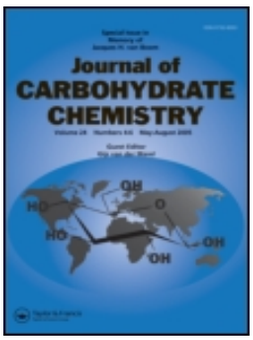

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Synthesis of *C*-Glycosyl Phosphate and Phosphonate, Analogues of *N*-Acetyl-α-D-Glucosamine 1-Phosphate[†]

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ABSTRACT

Synthesis of α-*C*-ethylene phosphate and phosphonate as well as α-*C*-methylene phosphate analogues of *N*-acetyl-α-D-glucosamine 1-phosphate is reported starting from the common perbenzylated 2-acetamido-2-deoxy-α-*C*-allyl glucoside. Anomerisation of the corresponding amino α-*C*-glucosyl aldehyde to the β-aldehyde was observed. Thus, both amino α- and β-*C*-glucosyl methanol were obtained after reduction.

Key Words: Glycosyl phosphate; α-*C*-glucosyl phosphate; α-*C*-glucosyl phosphonate; Amino *C*-glycosides.

INTRODUCTION

Glycosyl phosphates are essential precursors in the biosynthesis of the oligosaccharidic chains of glycoconjugates. The preparation of *C*-glycosyl phosphates and phosphonates as metabolically stable mimics of natural glycosyl phosphates is of great

[†]This paper is dedicated to Professor Gérard Descotes on the occasion of his 70th birthday.

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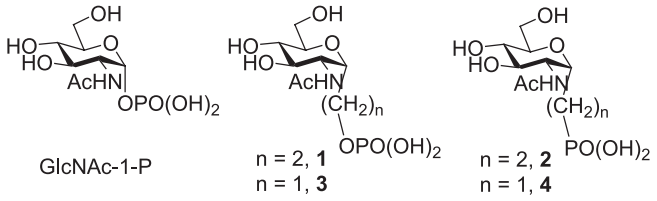

Figure 1. Structure of GlcNAc-1-P and target compounds **1–4**.

interest for the potential modulation of biological signals and metabolic activities.[1] Among the anomeric sugar phosphates, *N*-acetyl-α-D-glucosamine 1-phosphate (GlcNAc-1-P) is of particular interest. Besides being the key intermediate in the biosynthesis of *N*-linked glycoproteins, it is the metabolic precursor of the bacterial cell-wall components teichoic acid and mureine. Despite its important biological implication, only three synthetic analogues of GlcNAc-1-P have been reported. Nicotra and co-workers synthesised the phosphonate bio-isostere following a multi-step sequence.[2] The amino function was introduced at the end of the sequence to overcome the difficulty encountered during the preparation of the corresponding amino *C*-glycosyl halides and their subsequent conversion into phosphonate. Junker and Fessner prepared the diethyl 2-(3′,4′,6′-tri-*O*-acetyl-2′-deoxy-2′-trifluoroacetamido-α-D-glucopyranosyl)ethane phosphonate by radical promoted C—C bond formation between diethyl vinyl-phosphonate and the corresponding glycosyl bromide.[3] More recently, Schäfer and Thiem reported the synthesis of an α-*C*-methylene phosphate analogue of GlcNAc-1-P by using Kessler's dianion strategy to prepare the 1-*C*-α-carboxylic acid derivative of GlcNAc followed by transformation into the phosphate.[4]

In a previous communication,[5] we reported a concise synthesis of *C*-ethylene phosphate **1** and phosphonate **2** of GlcNAc-1-P (Figure 1). In this paper, we describe the detailed synthesis of compounds **1** and **2** starting from the amino α-*C*-allyl glucoside **5**, and our investigations into the accessibility of the known *C*-methylene phosphate and phosphonate analogues, **3**[4] and **4**[2] respectively, using the same starting material. These *C*-glycosyl phosphates and phosphonates may be considered as substrate analogues or inhibitors of GlcNAc-1-P uridyltransferase (Glm U)[6] and UDP-GlcNAc pyrophosphorylase.[7] They may also serve as precursors for the synthesis of potential inhibitors of *N*-acetylglycosaminyltransferases.[4]

RESULTS AND DISCUSSION

The stereoselective installation of a *C*-alkyl phosphate or phosphonate chain at the anomeric carbon atom of amino sugars with good stereocontrol is not a trivial task.[2] We decided to use the readily available amino α-*C*-glycoside **5**,[8] exhibiting the desired stereochemistry at the anomeric center, and to try to convert it into the target phosphates and phosphonates **1** to **4**. As shown in Scheme 1, the *C*-ethylene analogues **1** and **2** would be obtained via the intermediate alcohol **7**. On the other hand, the *C*-methylene analogues **3** and **4** can be synthesized from the *C*-glycoside **6**,[9] which is readily accessible by isomerisation of the double bond in **5**.

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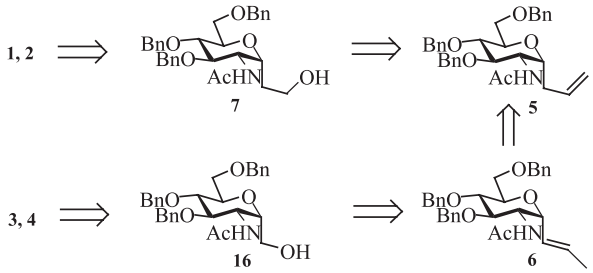
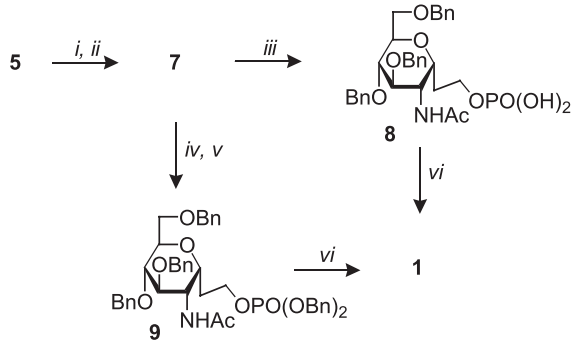


Scheme 1. Retrosynthesis of the target compounds **1–4**.

Synthesis of **1** and **2** is shown in Schemes 2 and 3. The amino α-*C*-allyl glucopyranoside **5** was converted into **7** in 85% overall yield through a 2-step process (oxidative cleavage of the double bond with OsO_4 cat/$NaIO_4$, and reduction of the so obtained aldehyde). The phosphate moiety was introduced satisfactorily either by a one-step process (treatment of **7** with $POCl_3$) or by a two-step process (phosphorylation with $i Pr_2N(OBn)_2$ and subsequent oxidation with *m*CPBA). Deprotection of **8** and **9** by catalytic hydrogenolysis led to the desired *C*-glycopyranosyl phosphate **1** in excellent yield.

Synthesis of the phosphonate analogue **2** was achieved by conversion of alcohol **7** into the bromide **10** upon treatment with CBr_4/PPh_3 (Scheme 3). The Arbuzov reaction of **10** with $P(OEt)_3$ afforded **11** (85%) and a small portion of **12**, resulting from the intramolecular substitution of **10**. This side reaction was avoided when $P(OMe)_3$ was used in place of $P(OEt)_3$, thus allowing the use of a lower reflux temperature for the Arbuzov step. Finally, treatment of **11** and **13** with Me_3SiI (20 equiv) in CCl_4 led to the expected phosphonate **2**.

To obtain the *C*-methylene homologues **3** and **4**, we intended to use the *C*-glycoside **6**,[9] obtained by isomerisation of the double bond in **5** (Scheme 4). Thus, the alkene **6** was oxidatively cleaved using catalytic OsO_4 and $NaIO_4$ to provide the aldehyde **14**. However, this α-aldehyde was slowly and irreversibly isomerised to the β-anomer **15** after work-up. Attempted silica gel purification of **14** led to complete



Scheme 2. *i*. OsO_4, $NaIO_4$, THF/H_2O; *ii*. $NaBH_4$, CH_2Cl_2/MeOH, 85%; *iii*. $POCl_3$, THF, 88%; *iv*. $iPr_2NP(OBn)_2$, tetrazole, THF; *v*. *m*CPBA, 97%; *vi*. Pd/C, MeOH, AcOH cat. quant.

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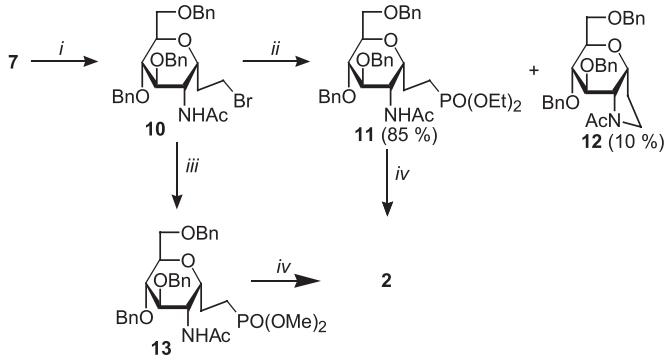
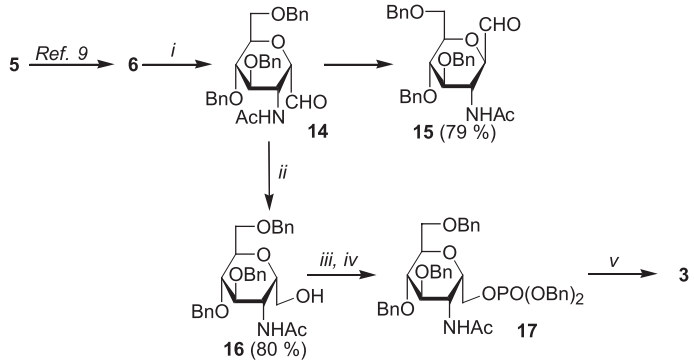


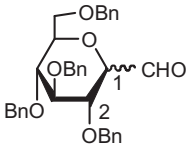
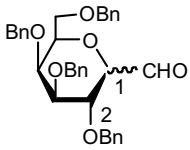
Scheme 3. *i*. CBr_4, PPh_3, CH_2Cl_2, RT, quant.; *ii*. $P(OEt)_3$, reflux; *iii*. $P(OMe)_3$, reflux, 90%; *iv*. TMSI, CCl_4, 0°C to RT, quant.

epimerisation, yielding the β-aldehyde **15** in 79% isolated yield. Assignment of the anomeric configuration of **14** and **15** was based on the observed $^3J_{1,2}$ coupling constants (3.1 Hz for **14** and 10.3 Hz for **15**), and confirmed by comparison of the δ values for CHO, H-1, H-2 and NH with those in related aldehydes[10,11] (see Table 1). Indeed, compared to those of the β-isomer, the chemical shifts of the signals for CHO, H-1, H-2 and NH in the α-isomer are shifted downfield. In addition the aldehyde proton appears as a singlet in the ^{1}H NMR spectrum of the α-anomer and as a doublet in the ^{1}H NMR spectrum of the β-anomer. Consequently, the crude α-aldehyde **14** was immediately converted to the alcohol **16**[4] in order to avoid epimerisation. Compound **16** was isolated in 80% overall yield from **6** (Scheme 4). Our method may be considered as an alternative approach to the preparation of **16** in 35% overall yield from 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-glucopyranose.[4] Treatment of **16** with $POCl_3$ failed to furnish the corresponding phosphate. Nevertheless, phosphorylation of the hydroxyl group in **16** with $i Pr_2NP(OBn)_2$ and subsequent oxidation with



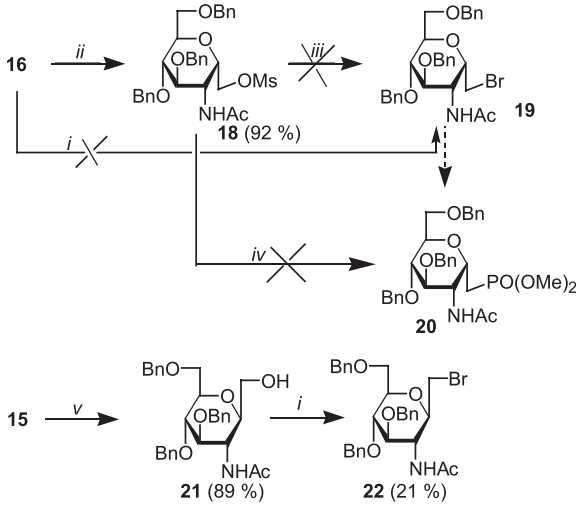
Scheme 4. *i*. OsO_4, $NaIO_4$, THF/H_2O, quant.; *ii*. $NaBH_4$, CH_2Cl_2/MeOH; *iii*. $iPr_2NP(OBn)_2$, tetrazole, THF; *iv*. *m*CPBA, 86%; *v*. Pd/C, MeOH, AcOH cat. quant.

Table 1. NMR data for selected *C*-D-glycopyranosyl aldehydes.

Compound	Config.	δ CHO	H-1	δ H-2	δ NH (ppm)
14	α	9.84 (s)	4.03 ($J_{1,2}$ = 3.1 Hz)	4.35–4.55	6.47
15	β	9.45 (d)	3.56 ($J_{1,2}$ = 10.3 Hz)	3.90	5.23
	α[10]	9.98 (s)	4.40		
	β[10]	9.65 (d)	3.58–3.80		
	α[11]	9.88 (s)	4.32		
	β[11]	9.67 (d)	3.78		

*m*CPBA gave the phosphate **17** in 86% yield. Final hydrogenolysis of the benzyl protecting groups afforded **3** in quantitative yield.

Compound **4** has been prepared by Nicotra and colleagues through a multi-step sequence which required introduction of the amino function after installation of a phosphono group.[2] In order to provide an alternative approach, we tried to convert the α alcohol **16** into the bromide **19**. Unfortunately, all attempts (with PPh_3/CBr_4 or MsCl/pyr then LiBr) only resulted in the recovery of the starting material. Indeed, the bromide **19** formed in the reaction mixture decomposed during workup. Direct



Scheme 5. *i*. PPh_3, CBr_4, CH_2Cl_2; *ii*. MsCl, Pyr.; *iii*. LiBr, acetone; *iv*. $P(OMe)_3$, reflux; *v*. $NaBH_4$, $CHCl_2$/MeOH.

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treatment of mesylate **18** with trimethyl phosphite also failed to afford the desired phosphonate **20**.[12] On the contrary, treatment of the β-alcohol **21** (obtained by reduction of aldehyde **15** in 89% yield) with PPh_3 and CBr_4 furnished the expected bromide **22** in 21% isolated yield (Scheme 5).

In summary, the phosphate and phosphonate analogues of *N*-acetyl-α-D-glucosamine-1-phosphate **1** to **3** have been successfully synthesised from the common perbenzylated amino α-*C*-allyl glycoside **5**. In addition original preparations of α- and β-*C*-glycosyl methanol **16** and **21** by oxidation of α-*C*-methylvinyl glycoside **6**, and subsequent reduction, is reported. These compounds might be useful for the synthesis of potential inhibitors of glycosyltransferases and more generally of mimics of GlcNAc-1-P.

EXPERIMENTAL

General methods. Melting points were measured with a Thomas-Hoover apparatus. ^1H and ^{13}C NMR spectra were recorded on a Bruker AGH-250 spectrometer in $CDCl_3$ solution unless noted with tetramethylsilane (Me_4Si) as the internal standard. Assignments were confirmed by $^1H/^1H$, $^1H/^{13}C$ correlations and DEPT 135. Optical rotations were measured using a Perkin-Elmer 141 polarimeter. Column chromatography was performed on E. Merck Silica Gel 60 (230–400 mesh). Analytical thin-layer chromatography was performed on E. Merck aluminum precoated plates of Silica Gel 60F-254 with detection by UV and by spraying with 6 N H_2SO_4 and heating about 2 min at 300°C, or by spraying with a solution containing 10% H_2SO_4 (10 mL), $FeCl_3$ (0.1 g) and 6% orcinol in EtOH (1 mL) and then heating 10 min at 100°C. Dichloromethane was distilled over CaH_2. Tetrahydrofuran was distilled over Na and benzophenone. Microanalyses were performed at the Service de Microanalyse de l'Université Pierre et Marie Curie.

4-Acetamido-3,7-anhydro-5,6,8-tri-*O*-benzyl-2,4-dideoxy-D-*glycero*-D-*ido*-octitol (7). As described,[8] compound **5** was oxidized to the corresponding aldehyde (886 mg, 1.714 mmol) which was dissolved in MeOH (10 mL). $NaBH_4$ (130 mg, 3.428 mmol) was added, and the mixture was stirred for 1 h at rt. The solution was concentrated, dissolved in EtOAc (30 mL), washed with water, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (1/1 then 2/1 to 1/0 AcOEt/hexane) to afford **7** as a white solid (757 mg, 85%): mp 109–111°C, Rf 0.23 (AcOEt), $[\alpha]_D$ + 15.2 (*c* 1.0, CH_2Cl_2); IR (KBr) 3300, 1750, 1650, 1525 cm^{-1}. ^1H NMR: δ 1.61–1.64 (m, 1H, H-2), 1.73–1.76 (m, 1H, H-2′), 1.81 (s, 3H, Ac), 2.78 (broad s, 1H, OH), 3.40 (t, 1H, J = 1.5 Hz), 3.53 (dd, 1H, J_{gem} = 10.3, $J_{7,8}$ = 5.8 Hz, H-8), 3.67 (dd, 1H, J = 2.8, J = 1.7 Hz), 3.80 (t, 2H, J = 5.8 Hz, H-1), 4.04 (dd, 1H, J_{gem} = 10.3, $J_{7,8'}$ = 8.8 Hz, H-8′), 4.17–4.20 (m, 2H, H-3,4), 4.29 (ddd, 1H, $J_{7,8'}$ = 8.8, $J_{7,8}$ = 5.8, $J_{6,7}$ = 1.0 Hz, H-7), 4.40–4.64 (m, 6H, 3 × OCH_2), 6.91 (d, 1H, $J_{4,NH}$ = 9.8 Hz, NH), 7.18–7.35 (m, 15H, Ph); ^{13}C NMR: δ 23.7 (Ac), 32.7 (C-2), 48.5 (C-4), 60.7 (C-1), 67.2 (C-3), 67.4 (C-8), 72.3, 72.6 (CH_2), 73.6 (CH), 73.6 (CH_2), 74.4 (CH), 75.1 (C-7), 128.0–128.9 (Ph), 137.1, 137.3, 137.6 (C*ipso*), 170.0 (CO).

Anal. Calcd for $C_{31}H_{37}NO_6$: C, 71.65; H, 7.18; N, 2.70. Found: C, 71.63; H, 7.13; N, 2.58.

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(4-Acetamido-3,7-anhydro-5,6,8-tri-*O*-benzyl-2,4-dideoxy-D-*glycero*-D-*ido*-octitol-1-yl) phosphate (8). $POCl_3$ (0.36 mL, 3.850 mmol) was added to a 0°C solution of **7** (200 mg, 0.385 mmol) in anhydrous THF (12 mL) under argon. After stirring for 20 h at rt, water (2 mL) was added and stirring was continued for 15 min. The solution was concentrated, the residue was dissolved in CH_2Cl_2 and washed twice with 1% aq HCl. The organic layer was concentrated and purified by eluting with MeOH on a resin Dowex H^+ (50WX8) column to afford **8** as a white solid (206 mg, 88%): mp 170–172°C, Rf 0.21 (8.5/0.5/1 CH_2Cl_2/MeOH/AcOH), $[\alpha]_D$ − 3.5 (*c* 1.0, CH_2Cl_2); IR (KBr) 3500, 3300, 1650, 1580 cm^{-1}. ^1H NMR: δ 1.70–1.95 (m, 2H, H-2), 1.84 (s, 3H, Ac), 3.54 (s, 1H), 3.65 (s, 1H), 3.71 (dd, 1H, J_{gem} = 10.0, $J_{7,8}$ = 6.6 Hz, H-8), 3.89 (dd, 1H, J_{gem} = 10.0, $J_{7,8'}$ = 7.0 Hz, H-8′), 4.00–4.30 (m, 5H), 4.38–4.67 (m, 6H, 3 × OCH_2), 6.88 (d, 1H, $J_{4,NH}$ = 9.3 Hz, NH), 7.23–7.35 (m, 15H, Ph), 8.45 (s, 2H, 2 × OH); ^{13}C NMR: δ 22.9 (Ac), 31.7 (C-2), 48.0 (C-4), 63.5 (C-1), 65.0 (C-3), 67.8 (C-8), 72.0, 72.1, 73.3 (CH_2), 73.7, 74.1 (C-5,6), 74.7 (C-7), 127.8–128.6 (Ph), 137.4, 137.6, 138.1 (C*ipso*), 171.5 (CO); ^{31}P NMR (202.46 MHz): δ 2.55.

Anal. Calcd for $C_{31}H_{38}NO_9P{\cdot}0.5\ H_2O$: C, 61.18; H, 6.46; N, 2.30. Found: C, 61.31; H, 6.70; N, 2.23.

Di-*O*-benzyl (4-acetamido-3,7-anhydro-5,6,8-tri-*O*-benzyl-2,4-dideoxy-D-*glycero*-D-*ido*-octitol-1-yl) phosphate (9). Tetrazole (81 mg, 1.155 mmol) and di-*O*-benzyl-di-*N,N*-isopropylphosphorodiamidite (194 μL, 0.578 mmol) were added to a solution of alcohol **7** (200 mg, 0.385 mmol) in anhydrous THF under argon. After stirring for 6 h at rt, *m*CPBA (332 mg, 1.925 mmol) was added, and srirring was continued for 2 h. The solution was diluted with CH_2Cl_2 (25 mL), washed successively with 10% aq Na_2SO_3, 10% aq $NaHCO_3$ and water, dried over $MgSO_4$, and concentrated. Purification by flash chromatography (1/1 to 1/0 AcOEt/hexane) afforded the title compound as a white solid (292 mg, 97%): mp 43–44°C, Rf 0.44 (AcOEt), $[\alpha]_D$ + 3.3 (*c* 1.86, CH_2Cl_2); IR (KBr) 3300, 1630, 1540 cm^{-1}. ^1H NMR: δ 1.75–1.90 (m, 2H, H-2), 1.87 (s, 3H, Ac), 3.63 (t, 1H, *J* = 1.5 Hz), 3.71 (t, 1H, *J* = 2.0 Hz), 3.75–3.85 (m, 2H, H-8,8′), 4.09–4.26 (m, 5H), 4.40–4.66 (m, 6H, 3 × OCH_2), 5.02 (d, 1H, $J_{C,P}$ = 8.3 Hz, POCH), 5.03 (d, 1H, $J_{C,P}$ = 8.3 Hz, POCH), 6.69 (d, 1H, $J_{4,NH}$ = 9.8 Hz, NH), 7.25–7.37 (m, 25H, Ph); ^{31}P NMR (202.46 MHz): δ − 0.15.

Anal. Calcd for $C_{45}H_{50}NO_9P$: C, 69.31; H, 6.46; N, 1.80. Found: C, 69.15; H, 6.66; N, 1.83.

(4-Acetamido-3,7-anhydro-2,4-dideoxy-D-*glycero*-D-*ido*-octitol-1-yl) phosphate (1). A solution of **8** or **9** (50 mg, 0.082 mmol) in MeOH (3 mL) was hydrogenated at atmospheric pressure in the presence of 10% palladium on charcoal (10 mg) for 24 h. The catalyst was filtered off, and the filtrate concentrated to give 29 mg (100%) of the title compound as a white solid: mp 198–200°C, Rf 0.64 (8/1 *i*PrOH/$AcONH_4$ 1 M), $[\alpha]_D$ + 5.2 (*c* 0.7, DMSO); IR (KBr) 3300, 1650, 1580 cm^{-1}. ^1H NMR (D_2O): δ 1.90 (dtd, 1H, J_{gem} = 14.7, $J_{1,2}$ = 7.7, $J_{2,3}$ = 3.5 Hz, H-2), 2.07 (s, 3H, Ac), 2.13 (dddd, 1H, J_{gem} = 14.7, $J_{1',2'}$ = 11.5, $J_{1,2'}$ = 5.3, $J_{2',3}$ = 9.1 Hz, H-2′), 3.46 (t, 1H, *J* = 9.1 Hz, H-6), 3.63 (ddd, 1H, $J_{6,7}$ = 9.1, $J_{7,8}$ = 5.0, $J_{7,8'}$ = 2.2 Hz, H-7), 3.76 (t, 1H, *J* = 9.1 Hz, H-5), 3.77 (dd, 1H, J_{gem} = 12.3, $J_{7,8}$ = 5.0 Hz, H-8), 3.89 (dd, 1H, J_{gem} = 12.3, $J_{7,8'}$ = 2.2 Hz, H-8′), 3.95–4.11 (m, 3H, H-1,1′,4), 4.27 (ddd, 1H, $J_{2',3}$ = 9.1, $J_{3,4}$ = 5.7, $J_{2,3}$ = 3.5 Hz, H-3); ^{13}C NMR

(D_2O): δ 22.5 (Ac), 26.2 (d, $J_{C,P}$ = 6.6 Hz, C-2), 53.7 (C-4), 61.6 (C-8), 63.0 (d, $J_{C,P}$ = 4.6 Hz, C-1), 71.0, 71.2, 71.3 (C-3,5,6), 73.5 (C-7), 175.1 (CO); ^{31}P NMR (202.46 MHz, D_2O): δ 2.82.

Anal. Calcd for $C_{10}H_{20}NO_9P{\cdot}1.5H_2O$: C, 33.71; H, 6.51; N, 3.93. Found: C, 33.80; H, 6.14; N, 3.80.

4-Acetamido-3,7-anhydro-5,6,8-tri-*O*-benzyl-1-bromo-1,2,4-trideoxy-D-*glycero*-D-*ido*-octitol (10). To a solution of alcohol **7** (200 mg, 0.385 mmol) in anhydrous CH_2Cl_2, were added PPh_3 (202 mg, 0.77 mmol) and CBr_4 (281 mg, 0.847 mmol) under an argon atmosphere. After stirring for 1 h at rt, the reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed twice with water. The organic layer was then dried ($MgSO_4$) and concentrated. Purification by column chromatography (1/1 AcOEt/hexane) afforded **10** as a white solid (224 mg, 100%): mp 101–102°C, Rf 0.61 (1/1 cyclohexane/AcOEt), $[\alpha]_D$ + 13.9 (*c* 1.0, CH_2Cl_2); IR (KBr) 3300, 1750, 1650, 1525 cm^{-1}. ^{1}H NMR: δ 1.78–2.05 (m, 2H, H-2), 1.79 (s, 3H, Ac), 3.49 (dd, 1H, $J_{1,2}$ = 7.6, $J_{1,2'}$ =5.8 Hz, H-1), 3.57 (t, 1H, *J* = 1.3 Hz, H-6), 3.64 (ddd, 1H, $J_{4,5}$ = 4.0, $J_{5,6}$ = 1.3, $J_{5,7}$ = 2.8 Hz, H-5), 3.77 (dd, 1H, J_{gem} = 10.0, $J_{7,8}$ = 7.0 Hz, H-8), 3.90 (dd, 1H, J_{gem} = 10.0, $J_{7',8}$ = 7.1 Hz, H-8′), 4.16–4.28 (m, 3H, H-3,4,7), 4.39–4.67 (m, 6H, 3 × OCH_2), 6.64 (d, 1H, $J_{4,NH}$ = 9.5 Hz, NH), 7.22–7.37 (m, 15H, Ph); ^{13}C NMR: δ 23.4 (Ac), 30.2 (C-2), 34.3 (C-1), 47.3 (C-4), 65.9 (C-3), 67.9 (C-8), 71.9, 72.1, 73.3 (CH_2), 73.5 (C-6), 74.2 (C-5), 75.2 (C-7), 127.6–129.7 (Ph), 137.3, 137.5, 138.1 (C*ipso*), 169.9 (CO).

Anal. Calcd for $C_{31}H_{36}BrNO_5$: C, 63.92; H, 6.23; N, 2.40. Found: C, 63.56; H, 6.21; N, 2.41.

Di-*O*-ethyl (4-acetamido-3,7-anhydro-5,6,8-tri-*O*-benzyl-1,2,4-trideoxy-D-*glycero*-D-*ido*-octitol-1-yl) phosphonate (11). A mixture of **10** (220 mg, 0.378 mmol) and triethyl phosphite (10 mL) was heated under reflux for 15 h, then concentrated in vacuo. Purification by column chromatography (0/1 to 1/9 acetone/AcOEt) afforded 205 mg (85%) of **11** (white solid) and 19 mg (10%) of pyrrolidine **12**. Compound **11**: mp 90–92°C, Rf 0.61 (1/1 AcOEt/hexane), $[\alpha]_D$ + 7.0 (*c* 1.0, CH_2Cl_2); IR (KBr) 3330, 1650, 1525 cm^{-1}. ^{1}H NMR: δ 1.23 (t, 6H, *J* = 7.0 Hz, 2 × CH_3), 1.30–1.85 (m, 4H, H-1,2), 1.78 (s, 3H, Ac), 3.53 (t, 1H, *J* = 1.5 Hz), 3.63 (m, 1H), 3.68 (dd, 1H, J_{gem} = 15.6, $J_{7,8}$ = 8.7 Hz, H-8), 3.79 (dd, 1H, J_{gem} = 15.6, $J_{7',8}$ = 6.9 Hz, H-8′), 3.81–3.86 (m, 1H, H-3), 3.99 (dt, 2H, *J* = 7.0, $J_{H,P}$ = 14.8 Hz, CH_2-OP), 4.00 (dt, 2H, *J* = 7.0, $J_{H,P}$ = 15.1 Hz, CH_2-OP), 4.08–4.19 (m, 2H, H-4,7), 4.37–4.58 (m, 6H, 3 × OCH_2), 6.45 (d, 1H, $J_{4,NH}$ = 9.6 Hz, NH), 7.23–7.36 (m, 15H, Ph); ^{13}C NMR: δ 16.3 (d, $J_{C,P}$ = 5.6 Hz, CH_3), 21.4 (d, $J_{C,P}$ = 142.5 Hz, C-1), 23.1 (Ac), 23.9 (C-2), 47.5 (C-4), 61.4 (d, $J_{C,P}$ = 6.1 Hz, CH_2-OP), 67.6 (C-8), 68.0 (d, $J_{C,P}$ = 17.4 Hz, C-3), 71.8, 72.1, 73.1 (CH_2), 73.3, 74.4, 74.6 (CH), 127.5–128.4 (Ph), 137.2, 137.4, 137.9 (C*ipso*), 169.7 (CO); ^{31}P NMR (202.46 MHz): δ 33.02.

Anal. Calcd for $C_{35}H_{46}NO_8P$: C, 65.71; H, 7.25; N, 2.19. Found: C, 65.31; H, 7.12; N, 2.08.

Di-*O*-methyl (4-acetamido-3,7-anhydro-5,6,8-tri-*O*-benzyl-1,2,4-trideoxy-D-*glycero*-D-*ido*-octitol-1-yl) phosphonate (13). Compound **13** was prepared from **10** and trimethyl phosphite as described for **12**. Yield 90%, mp 51–52°C, Rf 0.12

(AcOEt), $[\alpha]_D$ + 9.7 (*c* 0.95, CH_2Cl_2). ^{1}H NMR: δ 1.61–1.90 (m, 4H, H-1,2), 1.82 (s, 3H, Ac), 3.56 (s, 1H), 3.65 (m, 1H), 3.70 (dd, 1H, J_{gem} = 10.0, $J_{7,8}$ = 6.8 Hz, H-8), 3.75 (d, 6H, $J_{H,P}$ = 10.8 Hz, 2 × CH_3-OP), 3.82 (dd, 1H, J_{gem} = 10.0, $J_{7',8}$ = 7.0 Hz, H-8′), 3.90 (m, 1H, H-3), 4.10–4.22 (m, 2H, H-4,7), 4.41–4.63 (m, 6H, 3 × OCH_2), 6.48 (d, 1H, $J_{4,NH}$ = 9.5 Hz, NH), 7.21–7.35 (m, 15H, Ph); ^{13}C NMR: δ 21.0 (d, $J_{C,P}$ = 142.3 Hz, C-1), 23.6 (Ac), 24.3 (d, $J_{C,P}$ = 4.0 Hz, C-2), 48.0 (C-4), 68.1 (C-8), 68.6 (d, $J_{C,P}$ = 17.3 Hz, C-3), 72.4, 72.6, 73.6 (CH_2), 73.6, 75.0 (CH), 127.5–128.4 (Ph), 137.2, 137.5, 137.9 (C*ipso*), 169.7 (CO); ^{31}P NMR (202.46 MHz): δ 35.9.

Anal. Calcd for $C_{33}H_{42}NO_8P$: C, 64.80; H, 6.92; N, 2.29. Found: C, 64.43; H, 7.13; N, 2.09.

(4-Acetamido-3,7-anhydro-1,2,4-trideoxy-D-*glycero*-D-*ido*-octitol-1-yl) phosphonate (2). To a solution of **11** (180 mg, 0.281 mmol) in anhydrous CCl_4 (7 mL) at 0°C under an argon atmosphere, was added TMSI (0.801 mL, 5.62 mmol). After stirring for 1 h at rt, water (5 mL) was added and stirring continued during 30 min. The mixture was then separated. The aqueous layer was washed twice with Et_2O and concentrated to afford **11** as a solid which was recrystallized from THF (88 mg, 100%): mp 132–134°C (THF), Rf 0.79 (8/1 *i*PrOH/$AcONH_4$ 1 M), $[\alpha]_D$ + 55.8 (*c* 0.87, H_2O). ^{1}H NMR (D_2O): δ 1.50–1.80 (m, 2H, H-1), 1.65–1.90 (m, 2H, H-2), 1.92 (s, 3H, Ac), 3.38 (t, 1H, *J* = 9.0 Hz, H-6), 3.48 (ddd, 1H, $J_{6,7}$ = 9.0, $J_{7,8}$ = 5.0, $J_{7,8'}$ = 1.8 Hz, H-7), 3.68 (dd, 1H, J_{gem} = 12.0, $J_{7,8}$ = 5.0 Hz, H-8), 3.71 (t, 1H, *J* = 9.0 Hz, H-5), 3.84 (dd, 1H, J_{gem} = 12.0, $J_{7,8'}$ = 1.8 Hz, H-8′), 3.95 (dd, 1H, $J_{3,4}$ = 5.6, $J_{4,5}$ = 9.0 Hz, H-4), 3.95–4.08 (m, 1H, H-3); ^{13}C NMR (D_2O): δ 20.6 (C-2), 23.2 (Ac), 24.9 (d, $J_{C,P}$ = 134.5, C-1), 54.6 (C-4), 62.3 (C-8), 71.8, 72.2 (C-5,6), 73.6 (C-7), 75.6 (C-3), 175.1 (CO); ^{31}P NMR (202.46 MHz, D_2O): δ 32.04.

Anal. Calcd for $C_{10}H_{20}NO_8P$: C, 38.34; H, 6.44; N, 4.47. Found: C, 38.60; H, 6.66; N, 4.31.

3-Acetamido-2,6-anhydro-4,5,7-tri-*O*-benzyl-3-deoxy-*aldehydo*-D-*glycero*-D-*ido*-heptopyranose (14) and 3-acetamido-2,6-anhydro-4,5,7-tri-*O*-benzyl-3-deoxy-*aldehydo*-D-*glycero*-D-*gulo*-heptopyranose (15). To a solution of alkene **6**[9] (255 mg, 0.495 mmol) in a mixture of THF/H_2O (2/1, 2 mL), were added OsO_4 (4% solution in *t*-BuOH, 124 μL) and $NaIO_4$ (529 mg, 2.475 mmol). After stirring for 20 h at rt, the mixture was concentrated, diluted in CH_2Cl_2, washed with water, 5% aq $Na_2S_2O_3$ and brine, dried over $MgSO_4$, filtered and concentrated to give the aldehyde **14** as an oil (244 mg, 98%). Purification by column chromatography (AcOEt) epimerised the α-aldehyde **14** to the β-aldehyde **15** which was isolated as an oil (197 mg, 79%).

Compound **14**: Rf 0.50 (AcOEt). ^{1}H NMR: δ 1.75 (s, 3H, Ac), 3.50–3.75 (m, 4H), 4.11 (td, 1H, *J* = 3.4, *J* = 6.0 Hz, H-6), 4.03 (d, 1H, $J_{2,3}$ = 3.1 Hz, H-2), 4.35–4.55 (m, 7H, H-3, 3 × OCH_2), 6.47 (d, 1H, $J_{3,NH}$ = 9.5 Hz, NH), 7.19–7.36 (m, 15H, Ph), 9.84 (s, 1H, H-1); ^{13}C NMR: δ 23.0 (Ac), 46.6 (C-3), 67.1 (C-7), 72.6, 72.8, 73.2 (CH_2), 73.9, 75.1, 75.4 (CH), 127.7–128.5 (Ph), 137.1, 137.3, 137.7 (C*ipso*), 170.0, 199.5 (CO).

Compound **15**: Rf 0.50 (AcOEt). ^{1}H NMR: δ 1.68 (s, 3H, Ac), 3.43–3.48 (m, 1H), 3.56 (dd, 1H, $J_{1,2}$ = 2.5, $J_{2,3}$ = 10.3 Hz, H-2), 3.60–3.67 (m, 4H), 3.90 (ddd, 1H, $J_{2,3}$ = 10.3 Hz, $J_{3,NH}$ = 8.3, $J_{3,4}$ = 8.1 Hz, H-3), 4.45–4.60 (m, 4H, 2 × OCH_2), 4.72 (d, 1H, J_{gem} = 9.6 Hz, CH-O), 4.80 (d, 1H, J_{gem} = 9.6 Hz, CH-O), 5.23 (d, 1H,

$J_{3,NH}$ = 8.3 Hz, NH), 7.10–7.30 (m, 15H, Ph), 9.45 (d, 1H, $J_{1,2}$ = 2.5 Hz, H-1); ^{13}C NMR: δ 22.1 (Ac), 50.0 (C-3), 67.5 (C-7), 72.5, 73.5, 73.9 (CH_2), 78.6, 79.3, 82.3, 82.4 (CH), 128.2–129.1 (Ph), 136.6, 136.9 (C*ipso*), 170.6, 197.5 (CO).

Anal. Calcd for $C_{30}H_{33}NO_6$: C, 71.55; H, 6.60; N, 2.78. Found: C, 71.39; H, 6.71; N, 2.88.

3-Acetamido-2,6-anhydro-4,5,7-tri-*O*-benzyl-3-deoxy-D-*glycero*-D-*ido*-heptitol (16).[4] $NaBH_4$ (30 mg, 0.789 mmol) was added to a solution of **14** (206 mg, 4 mmol) in a mixture of MeOH/CH_2Cl_2 (1/1, 2 mL), and the mixture was stirred for 20 h at rt. The solution was concentrated, dissolved in AcOEt, washed with water, dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography (2/1 to 1/0 AcOEt/cyclohexane) afforded **16** (165 mg, 80%) as a white solid: mp 90°C, R_f 0.55 (AcOEt), $[\alpha]_D$ + 20.7 (*c* 1.1, CH_2Cl_2), + 19.2 (*c* 1.0, acetone), Lit.[4] mp 89–91°C, $[\alpha]_D$ + 20.1 (*c* 1.22, acetone); IR (KBr) 3421, 3324, 3107, 3059, 3035, 1685, 1660 cm^{-1}.

Di-*O*-benzyl (3-acetamido-2,6-anhydro-4,5,7-tri-*O*-benzyl-3-deoxy-D-*glycero*-D-*ido*-heptitol-1-yl) phosphate (17). Compound **17** was prepared from **16** as described for **9**. Purification by flash chromatography (1/1 to 1/0 AcOEt/hexane) afforded the title compound as an oil (86%): Rf 0.66 (AcOEt), $[\alpha]_D$ + 0.0, $[\alpha]_{Hg\ (546)}$ − 0.44, $[\alpha]_{Hg\ (365)}$ − 11.3 (*c* 1.13, CH_2Cl_2); IR (KBr) 3300, 1650, 1525 cm^{-1}. ^{1}H NMR: δ 1.77 (s, 3H, Ac), 3.60 (m, 1H), 3.66 (t, 1H, *J* = 3.1 Hz), 3.72–3.76 (m, 2H, H-8,8′), 4.01–4.07 (m, 2H, H-1), 4.17 (ddd, 1H, *J* = 7.4, J = 5.3, *J* = 2.2 Hz, H-2), 4.22–4.27 (m, 2H, H-3,6), 4.40–4.61 (m, 6H, 3 × OCH_2), 4.95–5.08 (m, 4H, 2 × $POCH_2$), 6.54 (d, 1H, *J* = 9.5 Hz, NH), 7.19–7.34 (m, 25H, Ph); ^{13}C NMR: δ 23.3 (Ac), 46.0 (C-3), 67.7 (C-7), 67.8 (d, $J_{C,P}$ = 7.0 Hz, C-2), 67.9 (d, $J_{C,P}$ = 4.0 Hz, C-1), 69.3 (d, $J_{C,P}$ = 5.0 Hz, CH_2OP), 72.5, 72.7, 73.7 (CH_2), 73.8, 74.8 (C-4,5), 75.5 (C-6), 127.7–128.6 (Ph), 136.0 (d, $J_{C,P}$ = 4.5 Hz, C*ipso* Ph-OP), 137.4, 137.5, 138.1 (C*ipso*), 169.9 (CO); ^{31}P NMR (202.46 MHz): δ 0.01.

Anal. Calcd for $C_{44}H_{48}NO_9P$: C, 69.01; H, 6.32; N, 1.83. Found: C, 68.64; H, 6.41; N, 1.72.

(3-Acetamido-2,6-anhydro-3-deoxy-D-*glycero*-D-*ido*-heptitol-1-yl) phosphate (3).[4] Compound **17** was deprotected as described for **9** to afford **3** as a white solid (100%): mp 120–124°C, $[\alpha]_D$ + 31.7 (*c* 0.7, H_2O), Litt.[4] $[\alpha]_D$ + 29 (*c* 0.5, H_2O). ^{31}P NMR (202.46 MHz, D_2O): δ 2.72.

3-Acetamido-2,6-anhydro-4,5,7-tri-*O*-benzyl-3-deoxy-1-*O*-methylsulfonyl-D-*glycero*-D-*ido*-heptitol (18). To a solution of **16** (70 mg, 0.139 mol) in dry pyridine, was added methanesulfonyl chloride (22 μL, 0.278 mmol) dropwise. After 1 h, CH_2Cl_2 was added and the mixture was washed twice with 5% aq HCl and once with water, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (AcOEt) afforded the title compound as a white solid (92%): mp 57–58°C, Rf 0.60 (AcOEt), $[\alpha]_D$ + 9.4 (*c* 0.85, CH_2Cl_2); IR (KBr) 3300, 1650, 1525 cm^{-1}. ^{1}H NMR: δ 1.85 (s, 3H, Ac), 3.01 (s, 3H, Ms), 3.58–3.59 (m, 1H), 3.68 (dd, 1H, J_{gem} = 10.0, $J_{6,7}$ = 6.5 Hz, H-7), 3.63–3.67 (m, 1H), 3.92 (dd, 1H, J_{gem} = 10.0, $J_{6,7'}$ = 7.5 Hz, H-7′), 4.20–4.25 (m, 3H, H-1,2), 4.30–4.40 (m, 2H, H-3,6), 4.40–4.65 (m, 6H, 3 × OCH_2), 6.70 (d, 1H, $J_{3,NH}$ = 9.0 Hz, NH), 7.20–7.40 (m, 15H, Ph); ^{13}C NMR:

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δ 23.7 (Ac), 38.1 (Ms), 46.1 (C-3), 67.2 (C-2), 67.7 (C-7), 70.9 (C-1), 72.4, 72.6 (CH_2), 73.3 (CH), 73.8 (CH_2), 74.1 (CH), 75.7 (C-6), 127.6–128.7 (Ph), 137.0, 137.2, 137.9 (C*ipso*), 169.9 (CO).

Anal. Calcd for $C_{31}H_{37}NO_8S$: C, 63.79; H, 6.39; N, 2.40. Found: C, 63.73; H, 6.61; N, 2.46.

3-Acetamido-2,6-anhydro-4,5,7-tri-*O*-benzyl-3-deoxy-D-*glycero*-D-*gulo*-heptitol (21). Compound **21** was prepared from **15** as described for **16**. Yield 89%, mp 142–143°C, Rf 0.19 (AcOEt), $[\alpha]_D$ + 23.1 (*c* 1.16, CH_2Cl_2). ^{1}H NMR: δ 1.74 (s, 3H, Ac), 3.11 (dd, 1H, $J_{3,4}$ = 10.0, $J_{4,5}$ = 2.5 Hz, H-4), 3.43–3.71 (m, 7H), 3.86 (td, 1H, $J_{2,3}$ = $J_{3,4}$ = 10.0, $J_{3,NH}$ = 8.0 Hz, H-3), 4.52–4.90 (m, 6H, 3 × OCH_2), 4.94 (d, 1H, $J_{3,NH}$ = 8.0 Hz, NH), 7.19–7.42 (m, 15H, Ph); ^{13}C NMR: δ 23.2 (Ac), 50.9 (C-3), 61.9, 69.2 (C-1,7), 73.6, 74.2, 75.1 (CH_2), 79.1, 79.2 (CH), 79.9 (C-4), 82.0 (CH), 127.8–128.9 (Ph), 137.8, 138.0, 138.4 (C*ipso*), 171.8 (CO).

Anal. Calcd for $C_{30}H_{35}NO_6$: C, 71.27; H, 6.98; N, 2.77. Found: C, 71.55; H, 7.01; N, 2.68.

3-Acetamido-2,6-anhydro-4,5,7-tri-*O*-benzyl-1-bromo-4,5,7-tri-*O*-benzyl-1,3-dideoxy-D-*glycero*-D-*gulo*-heptitol (22). Compound **22** was prepared from **21** as described for **10**. Purification by flash chromatography (1/1 AcOEt/cyclohexane) afforded the title compound as a white solid (21%): mp 177–178°C, Rf 0.76 (AcOEt), $[\alpha]_D$ + 16.0 (*c* 1.0, CH_2Cl_2). ^{1}H NMR: δ 1.74 (s, 3H, Ac), 3.32–3.47 (m, 3H, CH + H-1), 3.52–3.71 (m, 6H), 4.50–4.82 (m, 6H, 3 × OCH_2), 5.02 (d, 1H, $J_{3,NH}$ = 7.0 Hz, NH), 7.13–7.32 (m, 15H, Ph); ^{13}C NMR: δ 23.6 (Ac), 33.4 (C-1), 54.7 (C-3), 68.8 (C-7), 73.6, 74.7, 75.0 (CH_2), 78.2, 78.9, 79.4, 82.2 (CH), 127.7–128.8 (Ph), 138.1, 138.4, 138.5 (C*ipso*), 170.8 (CO).

Anal. Calcd for $C_{30}H_{34}BrNO_6$: C, 61.86; H, 5.53; N, 2.40. Found: C, 61.58; H, 5.66; N, 2.60.

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