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Synthesis of new sugar amino acid derivatives of D-glucosamine

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Abstract

The synthesis of several new sugar amino acid derivatives of 2-acetamido-2-deoxy-D-glucose, bearing a *C*-glycosyl functionality as building blocks for the design and synthesis of natural glycoconjugates mimetics, is described. These compounds were prepared from the readily accessible per-benzylated amino *C*-allyl glucopyranosyl compounds, with TMSOTf/Ac_2O-mediated selective acetolysis of the 6-*O*-benzyl group as the key step. © 2003 Elsevier Science Ltd. All rights reserved.

Keywords: Sugar amino acids; 2-Acetamido-2-deoxy-D-glucose; Amino *C*-glycosyl compounds

1. Introduction

Amino sugars are widely distributed in biological systems.[1,2] Glycosides of 2-acetamido-2-deoxy-D-glucose are of particular importance because they are fundamental constituents of *N*-glycoproteins[2c] and mucin-type *O*-glycoproteins.[3] Recently, it has been shown that *O*-linked GlcNAc (*O*-GlcNAc) nucleoplasmic and cytoplasmic proteins[4] are implicated in signal transduction, transcription, translation, cancer, neuronal pathology and other biological process.[5] There is also evidence of a link between aberrant *O*-GlcNAc modification and diabetes.[5] Consequently, structural modification of GlcNAc and its conjugates would constitute useful glycomimetics of interest as inhibitors of GlcNAc processing enzymes.

C-Glycosyl compounds of GlcNAc[6] and α-GlcNAc thioconjugates[7] have recently been prepared as stable analogs of *O*-GlcNAc. It is known that *C*-glycosyl analogs of natural carbohydrates are good mimetics, resistant to glycosidase-catalyzed hydrolysis.[8] Moreover, efficient synthesis of functional amino *C*-glycosyl compounds is attractive for the generation of more complex carbohydrates. Of particular interest are sugar amino acids (SAAs), which have been successfully used in the design and synthesis of peptidomimetics, enzyme inhibitors, oligomers and polymers.[9] Several SAAs of D-glucosamine bearing the carboxylic acid functionality at either the C-1, C-3 or C-6 position of a pyranose backbone have been reported.[10] In this work, we report an easy preparation of several new SAAs derivatives of GlcNAc, containing a functional carbon chain at the anomeric position, with the amine and carboxylic function at either C-1 or C-6 position of the sugar moiety (Compounds **6**, **9**, **12**, **15** and **19**).

2. Results and discussion

Per-benzylated *C*-allyl glycosyl compounds are readily accessible[8] and can be easily converted into other functional groups (aldehyde, amine, carboxylic acid, hydroxyl group). Recently, Kobertz et al.[11] described a one-pot TMSOTf/Ac_2O mediated debenzylation/acetylation of the 6-*O*-benzyl group of per-benzylated glycosides. Application of this procedure to per-benzylated *C*-allyl glycosyl compounds should allow the further functionalization of these derivatives.[12] We then decided to use the per-benzylated amino α- and β-*C*-allyl glucopyranosyl compounds **1** and **16** as starting materials to prepare diversely functionalized amino *C*-glucosyl compounds.

The amino α-*C*-allyl glucosyl derivative **1** was prepared as described.[13] Acetolysis of the 6-*O*-benzyl group of **1** required 2 equiv of TMSOTf as catalyst instead of 1 equiv in the case of methyl tetra-*O*-benzyl-α-D-glucopyranoside[11] (Scheme 1). The resulting acetate

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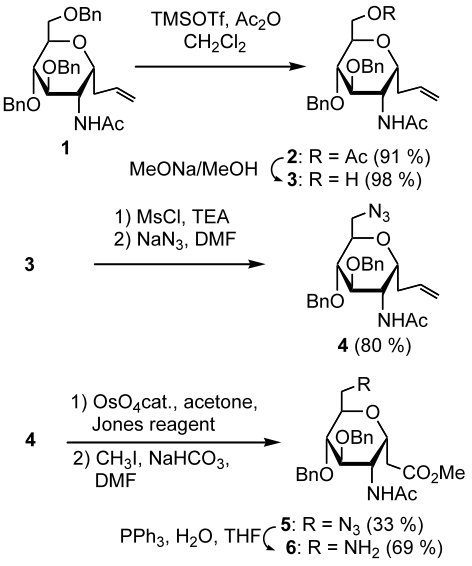
2 was deacetylated under Zemplén conditions to give the alcohol **3** which was transformed into azide **4** by displacement of the mesylate. The following oxidative conversion of alkene to carboxylic acid was more problematic. Oxidation with $KMnO_4$[14] led to a mixture of several compounds. The best result was achieved using a combination of OsO_4/Jones reagent.[15] The corresponding methyl ester **5** was obtained in 33% yield. Comparison of the δ values for H-1, H-2, NH, C-1 and C-2 with compounds with similar structure (see Table 1) clearly indicates the α configuration of **5**. Compared to the β isomers, the chemical shifts of the signals for H-1,[18] H-2 and NH are at lower field in the α isomer. However, a highfield shift for C-1 and C-2 for the α isomer is observed. Finally, compound **5** was reduced to the amine **6** using the Staudinger reaction.

Compounds **9** and **12** were prepared in a similar way (Scheme 2). Oxidation of primary alcohol function of **3** with Jones reagent followed by esterification furnished the SAA **9**. Oxidative cleavage (OsO_4/$NaIO_4$) of the double bond followed by reduction ($NaBH_4$) afforded the alcohol **10**. As before, the azide was introduced via a mesylate, then reduced to the amine **12**.

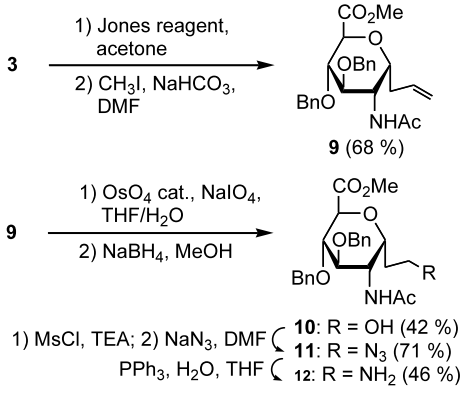
In order to get access to other derivatives, we decided to isomerize the terminal olefin of **1** (Scheme 3). The reaction was catalyzed by $PdCl_2$ in benzene under reflux.[19] Compound **13** was obtained as a mixture of two diastereoisomers (E/Z 21:4) in 71% yield. Selective acetolysis of **13** followed by deacetylation gave alcohol **14**, which was converted to the methyl ester **15** as for **9**.

The amino β-*C*-glucosyl compound **19** was generated by an analogous procedure (Scheme 4). The amino β-*C*-glucosyl compound **16**[13b,13c] was first protected as its benzyl ether **17**, followed by selective acetolysis, deacetylation, oxidation and esterification.

In summary, this work describes a convenient synthesis of several new sugar aminoacids derivatives of *N*-acetylglucosamine, by using the common starting materials. Compounds **9**, **15** and **19** which contain a C–C double bond, could be easily converted into other functional groups (amine, epoxide, carbonyl or hydroxyl groups etc). These multifunctional compounds could be used to increase the diversity of the SAA-



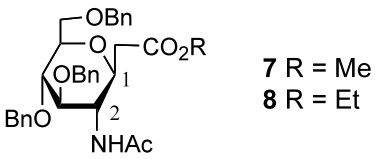
Scheme 1.

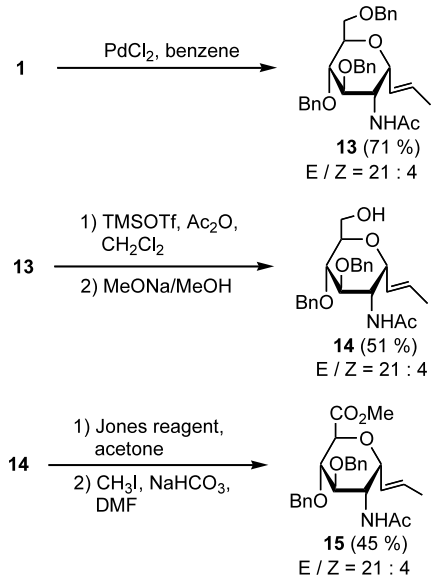


Scheme 2.

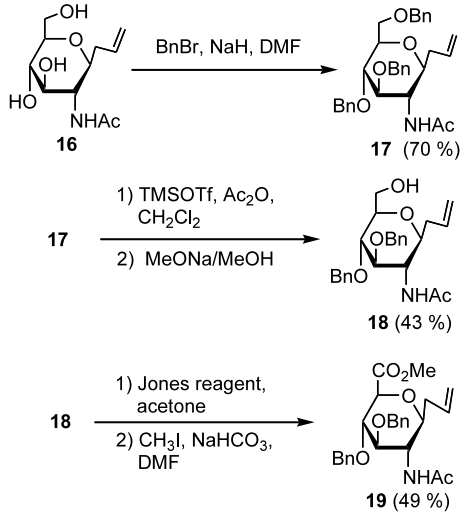
Table 1
NMR data for some amino *C*-D-glucopyranosyl compounds

Compound	Configuration	δ H-1	δ H-2	δ NH	δ C-1	δ C-2 (ppm)
5	α	4.45–4.48	4.27–4.31	6.61	65.0	46.9
7[16]	β	3.70	3.85	5.45	75.8	54.5
8[17]	β	3.63	3.85	5.00	76.7	55.2





Scheme 3.



Scheme 4.

building blocks and may find applications as potential glycomimetics, peptidomimetics or as building blocks for the synthesis of novel glycoconjugates.

3. Experimental

3.1. General procedures

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. Assignments were confirmed by $^1H/^1H$, $^1H/^{13}C$ correlations and Dept 135. Optical rotations were measured using a Perkin–Elmer 141 polarimeter and a 10-cm cell. Column chromatography was performed on E. Merck Silica Gel 60 (230–400 mesh). Analytical thin-layer chromatography was performed on E. Merck aluminum percolated 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. Dichloromethane was distilled over CaH_2. Microanalyses were performed at the Service de Microanalyse de l'Université Pierre et Marie Curie.

3.2. 3-(6′-*O*-Acetyl-2′-*N*-acetylamino-3′,4′-di-*O*-benzyl-2′-deoxy-α-D-glucopyranosyl)-1-propene (2)

To a soln of 3-(2′-*N*-acetylamino-3′,4′,6′-tri-*O*-benzyl-2′-deoxy-α-D-glucopyranosyl)-1-propene (**1**)[13a] (515 mg, 1 mmol) in anhyd CH_2Cl_2 (4 mL) and Ac_2O (4 mL), was added a solution of TMSOTf (362 μL, 2 mmol) in CH_2Cl_2 (2 mL) at −40 °C under argon. After 1 h, the reaction was quenched with satd $NaHCO_3$. The aq layer was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic layers were washed with water, dried over $MgSO_4$, filtered, evaporated and purified by column chromatography (1:3 then 1:2 EtOAc–cyclohexane) to afford **2** as a white solid (427 mg, 91%): mp 136–139 °C; $[\alpha]_D$ +11.0 (*c* 1.0, CH_2Cl_2); R_f 0.38 (1:1 EtOAc–cyclohexane); IR (KBr) 3325, 3107, 3083, 3035, 1757, 1640 cm^{-1}. ^1H NMR: δ 7.33–7.16 (m, 10 H, Ph), 6.81–6.65 (m, 1 H, H-2), 6.42 (d, $J_{2',NH}$ 9.5 Hz, 1 H, NH), 5.06–4.95 (m, 2 H, H-1), 4.63 (dd, $J_{5',6''}$ 4.0, J_{gem} 11.8 Hz, 1 H, H-6″), 4.60 (d, J_{gem} 11.5 Hz, 1 H, OCHPh), 4.49 (d, J_{gem} 9.5 Hz, 1 H, OCHPh), 4.44 (d, J_{gem} 9.5 Hz, 1 H, OCHPh), 4.35 (d, J_{gem} 11.5 Hz, 1 H, OCHPh), 4.20–4.15 (m, 2 H, H-2′,5′), 4.04 (dd, $J_{5',6'}$ 4.8 Hz, 1 H, H-6′), 4.00–3.96 (m, 1 H, H-1′), 3.64–3.62 (m, 1 H, H-3′), 3.32 (m, 1 H, H-4′), 2.17–2.09 (m, 2 H, H-3), 1.99 (s, 3 H, Ac), 1.77 (s, 3 H, Ac). ^{13}C NMR: δ 170.8, 159.9 (CO), 137.5, 137.2 (C_{ipso}), 134.4 (C-2), 128.7, 128.3, 128.2, 127.9 (Ph), 117.2 (C-1), 74.3 (C-5′), 73.9 (C-3′), 73.5 (C-4′), 72.4, 72.0 (OCH_2), 67.4 (C-1′), 61.3 (C-6′), 47.3 (C-2′), 35.8 (C-3), 23.5, 21.0 (Me). Anal. Calcd for $C_{27}H_{33}NO_6$: C, 69.36; H, 7.11; N, 3.00. Found: C, 69.21; H, 7.09; N, 3.05.

3.3. 3-(2′-*N*-Acetylamino-3′,4′-di-*O*-benzyl-2′-deoxy-α-D-glucopyranosyl)-1-propene (3)

To a soln of **2** (271 mg, 0.580 mmol) in MeOH (10 mL) was added MeONa (1 M, 0.58 mL). After 20 h stirring at room temperature (rt), the reaction mixture was neutralized with 10% HCl at 0 °C and MeOH was removed under diminished pressure. The resulting residue was dissolved in CH_2Cl_2 (30 mL) and washed with water and brine. The organic layer was dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography (1:3 to 1:1 EtOAc–cyclohexane) afforded **3** as a white solid (241 mg, 98%): mp 127–131 °C; $[\alpha]_D$ +2.0 (*c* 1, CH_2Cl_2); R_f 0.27 (1:1

EtOAc–cyclohexane); IR (KBr) 3301, 3107, 3083, 3035, 1709, 1660 cm^{-1}. ^1H NMR: δ 7.32–7.18 (m, 10 H, Ph), 6.36 (d, $J_{2',NH}$ 9.8 Hz, 1 H, NH), 5.83–5.65 (m, 1 H, H-2), 5.08–4.99 (m, 2 H, H-1), 4.62 (d, J_{gem} 11.5 Hz, 1 H, OCHPh), 4.51 (d, J_{gem} 11.3 Hz, 1 H, OCHPh), 4.47 (d, J_{gem} 11.3 Hz, 1 H, OCHPh), 4.39 (d, J_{gem} 11.5 Hz, 1 H, OCHPh), 4.19–4.12 (m, 1 H, H-2′), 4.05–3.95 (m, 3 H, H-1′,5′,6″), 3.65–3.62 (m, 1 H, H-3′), 3.52–3.44 (m, 1 H, H-6′), 3.34–3.32 (m, 1 H, H-4′), 2.11–1.96 (m, 2 H, H-3), 1.96 (dd, $J_{6',OH}$ 3.0, $J_{6'',OH}$ 7.3 Hz, 1 H, OH), 1.77 (s, 3 H, Ac). ^{13}C NMR: δ 171.1 (CO), 137.6, 137.4 (C_{ipso}), 135.3 (C-2), 128.8, 128.4, 128.3, 128.0 (Ph), 117.9 (C-1), 76.9, 74.4, 74.0 (CH), 72.6, 72.3 (OCH_2), 67.6 (C-1′), 60.1 (C-6′), 48.0 (C-2′), 35.5 (C-3), 23.5 (Me). Anal. Calcd for $C_{25}H_{31}NO_5$: C, 70.57; H, 7.34; N, 3.29. Found: C, 70.76; H, 7.41; N, 3.19.

3.4. 3-(2′-*N*-Acetylamino-6′-azido-3′,4′-di-*O*-benzyl-2′,6′-dideoxy-α-D-glucopyranosyl)-1-propene (4)

Methanesulfonyl chloride (122 μL, 1.584 mmol) was added to a 0 °C soln of alcohol **3** (468 mg, 1.100 mmol) and TEA (282 μL, 2.024 mmol) in CH_2Cl_2 (4.8 mL). The ice bath was removed, and stirring was continued for 18 h before MeOH (63 μL) was added. The solution was concentrated, the residue dissolved in EtOAc (20 mL) and washed successively with water, $NaHCO_3$ 5% and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated to an oil, which was used directly without purification. The mesylate was dissolved in DMF (5 mL) and added to NaN_3 (367 mg, 5.654 mmol). The reaction was heated at 90 °C for 20 h. After evaporation, the residue was diluted in EtOAc (20 mL), washed successively with water, brine, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography (1:4 to 2:5 EtOAc–cyclohexane) to afford **4** as a white solid (394 mg, 80%): mp 146 °C; $[\alpha]_D$ +7.0 (*c* 1.0, CH_2Cl_2); R_f 0.17 (1:3 EtOAc–cyclohexane); IR (KBr) 3325, 3107, 3083, 3035, 2119, 1660 cm^{-1}. ^1H NMR: δ 7.32–7.17 (m, 10 H, Ph), 6.38 (d, $J_{2',NH}$ 9.8 Hz, 1 H, NH), 5.76–5.69 (m, 1 H, H-2), 5.05–4.96 (m, 2 H, H-1), 4.60 (d, J_{gem} 11.5 Hz, 1 H, OCHPh), 4.48 (d, J_{gem} 11.3 Hz, 1 H, OCHPh), 4.44 (d, J_{gem} 11.5 Hz, 1 H, OCHPh), 4.36 (d, J_{gem} 11.3 Hz, 1 H, OCHPh), 4.19–4.15 (m, 1 H, H-2′), 4.09–4.03 (m, 1 H, H-5′), 3.93–3.89 (m, 1 H, H-1′), 3.76 (dd, $J_{5',6''}$ 8.8, J_{gem} 13.0 Hz, 1 H, H-6″), 3.65–3.63 (m, 1 H, H-4′), 3.33–3.31 (m, 1 H, H-3′), 3.24 (dd, $J_{5',6'}$ 5.8 Hz, 1 H, H-6′), 2.23–2.08 (m, 2 H, H-3), 1.76 (s, 3 H, Ac). ^{13}C NMR: δ 170.2 (CO), 137.7, 137.4 (C_{ipso}), 134.3 (C-2), 129.1, 128.7, 128.6, 128.2 (Ph), 118.0 (C-1), 75.5 (C-5′), 74.5 (C-4′), 74.1 (C-3′), 72.8, 72.5 (OCH_2), 68.0 (C-1′), 49.8 (C-6′), 47.4 (C-2′), 35.9 (C-3), 23.7 (Me). Anal. Calcd for $C_{25}H_{30}N_4O_4$: C, 66.65; H, 6.71; N, 12.44. Found: C, 66.56; H, 6.79; N, 12.69.

3.5. Methyl (2′-*N*-acetylamino-6′-azido-3′,4′-di-*O*-benzyl-2′,6′-dideoxy-α-D-glucopyranosyl) ethanoate (5)

To a soln of **4** (71 mg, 0.158 mmol) in acetone (1 mL) was added a 4 (wt)% soln of OsO_4 in *t*BuOH (63 μL) and Jones reagent (1 M, 0.79 mL). After stirring 20 h at rt, the mixture was concentrated, dissolved in EtOAc (10 mL) and washed successively with water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated to an oil, which was dissolved in DMF (0.5 mL). Sodium hydrogenocarbonate (20 mg, 0.238 mmol) was added to the solution, followed by methyl iodide (20 μL, 0.321 mmol). After 20 h, the mixture was concentrated and diluted in EtOAc. The organic solution was washed successively with water, brine, dried over $MgSO_4$, filtered, concentrated and purified by preparative TLC with 1:1 EtOAc–cyclohexane as eluent to afford **5** (25 mg, 33%): mp 128 °C; $[\alpha]_D$ +6.5 (*c* 1.2, CH_2Cl_2); R_f 0.25 (1:1 EtOAc–cyclohexane); IR (KBr) 2119, 1757, 1685 cm^{-1}. ^1H NMR: δ 7.36–7.25 (m, 10 H, Ph), 6.61 (d, $J_{2',NH}$ 9.5 Hz, 1 H, NH), 4.70 (d, J_{gem} 11.5 Hz, 1 H, OCHPh), 4.56 (d, J_{gem} 11.3 Hz, 1 H, OCHPh), 4.50 (d, J_{gem} 11.5 Hz, 1 H, OCHPh), 4.48–4.45 (m, 1 H, H-1′), 4.41 (d, J_{gem} 11.3 Hz, 1 H, OCHPh), 4.31–4.27 (m, 1 H, H-2′), 4.12 (t, *J* 7.0 Hz, 1 H, H-5′), 3.83 (dd, $J_{5',6''}$ 8.0, J_{gem} 12.8 Hz, 1 H, H-6″), 3.73–3.70 (m, 1 H, H-3′), 3.68 (s, 3 H, OMe), 3.43 (dd, $J_{5',6'}$ 6.5 Hz, 1 H, H-6′), 3.42–3.41 (m, 1 H, H-4′), 2.48–2.45 (m, 2 H, H-2), 1.82 (s, 3 H, Ac). ^{13}C NMR: δ 171.3, 170.0 (CO), 137.2, 137.0 (C_{ipso}), 128.8, 128.4, 128.3, 127.9 (Ph), 75.3 (C-5′), 73.8 (C-3′), 73.4 (C-4′), 72.4, 72.2 (OCH_2), 65.0 (C-1′), 52.0 (OMe), 49.5 (C-6′), 46.9 (C-2′), 36.7 (C-2), 23.3 (Me). Anal. Calcd for $C_{25}H_{30}N_4O_6$: C, 62.23; H, 6.27; N, 11.61. Found: C, 62.36; H, 6.34; N, 11.81.

3.6. Methyl (2′-*N*-acetylamino-6′-amino-3′,4′-di-*O*-benzyl-2′,6′-dideoxy-α-D-glucopyranosyl) ethanoate (6)

To a soln of **5** (40 mg, 0.083 mmol) in THF (1 mL), was added Ph_3P (24 mg, 0.091 mmol) and water (16 μL, 0.889 mmol). The mixture was stirred at rt for 20 h. After concentration, the residue was purified by preparative TLC with 1:9 MeOH–CH_2Cl_2 as eluent to afford **6** as a white solid (27 mg, 69%): mp 116 °C; $[\alpha]_D$ +17.6 (*c* 0.5, CH_2Cl_2); R_f 0.38 (1:9 MeOH–CH_2Cl_2); IR (KBr) 3421, 3324, 3300, 1757, 1685, 1660 cm^{-1}. ^1H NMR: δ 7.38–7.22 (m, 10 H, Ph), 6.69 (d, $J_{2',NH}$ 9.5 Hz, 1 H, NH), 4.66 (d, J_{gem} 11.8 Hz, 1 H, OCHPh), 4.57 (d, J_{gem} 11.5 Hz, 1 H, OCHPh), 4.48 (d, J_{gem} 11.8 Hz, 1 H, OCHPh), 4.44–4.41 (m, 1 H, H-1′), 4.39 (d, J_{gem} 11.5 Hz, 1 H, OCHPh), 4.37–4.30 (m, 1 H, H-2′), 4.07–4.01 (m, 1 H, H-5′), 3.67 (s, 3 H, OMe), 3.66–3.64 (m, 1 H, H-3′), 3.33–3.32 (m, 1 H, H-4′), 2.61–2.46 (m, 4 H, H-2,6′), 2.41 (s, 2 H, NH_2), 1.83 (s, 3 H, Ac). ^{13}C NMR: δ 172.6, 170.3 (CO), 137.7, 137.6 (C_{ipso}), 129.0,

128.6, 128.4, 128.1, 128.0 (Ph), 78.2, 74.5, 74.3 (C-3′,4′,5′), 72.7, 72.6 (OCH_2), 63.5 (C-1′), 52.3 (OMe), 47.7 (C-2′), 40.1 (C-6′), 36.9 (C-2), 23.7 (Me). Anal. Calcd for $C_{25}H_{32}N_2O_6$: C, 65.77; H, 7.06; N, 6.14. Found: C, 65.89; H, 7.09; N, 6.03.

3.7. Methyl 5-*N*-acetylamino-2,6-anhydro-3,4-di-*O*-benzyl-8,9-didehydro-5,7,8,9-tetradeoxy-D-*glycero*-L-*gluco*-nonuronate (9)

To a soln of alcohol **3** (84 mg, 0.2 mmol) in acetone (5 mL), was added Jones reagent (1 M, 0.6 mL, 0.6 mmol). The mixture was stirred 48 h at rt. After concentration, the residue was dissolved in EtOAc (10 mL), washed successively with water, $Na_2S_2O_3$ 5%, HCl 5%, brine, dried over $MgSO_4$, filtered and concentrated. The corresponding acid was then esterified as for **5**. Purification by preparative TLC with 3:2 EtOAc–cyclohexane as eluent afforded **9** as an oil (62 mg, 68%): $[\alpha]_D$ +38 (*c* 0.5, CH_2Cl_2); R_f 0.60 (2:1 EtOAc–cyclohexane); IR (KBr) 3421, 3083, 3035, 1757, 1685 cm^{-1}. ^1H NMR: δ 7.30–7.14 (m, 10 H, Ph), 6.59 (d, $J_{2',NH}$ 10.0 Hz, 1 H, NH), 5.92–5.76 (m, 1 H, H-8), 5.13–4.98 (m, 2 H, H-9), 4.63 (d, J_{gem} 11.3 Hz, 1 H, OCHPh), 4.52 (d, J_{gem} 11.3 Hz, 1 H, OCHPh), 4.44 (d, J_{gem} 11.3 Hz, 1 H, OCHPh), 4.51–4.38 (m, 2 H, H-2,6), 4.39 (d, J_{gem} 11.3 Hz, 1 H, OCHPh), 4.20–4.15 (m, 1 H, H-5), 4.09–4.07 (m, 1 H), 3.64 (t, *J* 3.0 Hz, 1 H), 3.50 (s, 3 H, OMe), 2.23–2.13 (m, 2 H, H-7), 1.76 (s, 3 H, Ac). ^{13}C NMR: δ 170.0, 169.9 (CO), 137.4, 137.1 (C_{ipso}), 134.4 (C-8), 128.8, 128.5, 128.0, 127.9, 127.5 (Ph), 117.2 (C-9), 74.5, 74.1, 73.1 (CH), 72.3, 71.8 (OCH_2), 69.7 (C-6), 52.1 (OMe), 47.3 (C-5), 36.0 (C-7), 23.4 (Me). Anal. Calcd for $C_{26}H_{31}NO_6$: C, 68.86; H, 6.89; N, 3.09. Found: C, 68.66; H, 6.77; N, 3.02.

3.8. Methyl 5-*N*-acetylamino-2,6-anhydro-3,4-di-*O*-benzyl-5,7-dideoxy-D-*glycero*-L-*gluco*-octuronate (10)

Osmium tetraoxyde (4% soln in *t*BuOH, 93 μL) and $NaIO_4$ (146 mg, 0.684 mmol) were added to a soln of **9** (155 mg, 0.342 mmol) in a mixture of THF–water (2:1, 1.5 mL). After 20 h stirring at rt, the mixture was concentrated, diluted in EtOAc (30 mL), washed with water, $Na_2S_2O_3$ 5%, brine, dried over $MgSO_4$, filtered and concentrated to an oil which was dissolved in MeOH (1 mL). Sodium borohydride (26 mg, 0.684 mmol) was added and the mixture was stirred for 20 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 preparative TLC with 2:1 EtOAc–cyclohexane as eluent to afford **10** (66 mg, 42%) as an oil: $[\alpha]_D$ +63.3 (*c* 0.3, CH_2Cl_2); R_f 0.67 (EtOAc); IR (KBr) 3397, 3083, 1757, 1685 cm^{-1}. ^1H NMR: δ 7.33–7.15 (m, 10 H, Ph), 6.65 (d, $J_{2',NH}$ 9.3 Hz, 1 H, NH), 4.65 (d, J_{gem} 11.3 Hz, 1 H, OCHPh), 4.53 (d, J_{gem} 11.8 Hz, 1 H, OCHPh), 4.51–4.40 (m, 2 H, H-2,6), 4.47 (d, J_{gem} 11.3 Hz, 1 H, OCHPh), 4.41 (d, J_{gem} 11.8 Hz, 1 H, OCHPh), 4.18–4.11 (m, 1 H, H-5), 4.09–4.07 (m, 1 H), 3.76–3.73 (m, 2 H, H-8), 3.67–3.64 (m, 1 H), 3.54 (s, 3 H, OMe), 3.01 (s, 1 H, OH), 1.78 (s, 3 H, Ac), 1.66–1.59 (m, 2 H, H-7). ^{13}C NMR: δ 170.7, 170.3 (CO), 137.6, 137.2 (C_{ipso}), 129.1, 128.8, 128.3, 128.2, 127.7 (Ph), 74.7, 74.3, 73.1 (CH), 72.7, 72.1 (OCH_2), 68.9 (CH), 60.1 (C-8), 52.7 (OMe), 48.3 (C-5), 33.8 (C-7), 23.7 (Me). Anal. Calcd for $C_{25}H_{31}NO_7$: C, 65.63; H, 6.83; N, 3.06. Found: C, 65.50; H, 6.89; N, 3.12.

3.9. Methyl 5-*N*-acetylamino-2,6-anhydro-8-azido-3,4-di-*O*-benzyl-5,7,8-trideoxy-D-*glycero*-L-*gluco*-octuronate (11)

Alcohol **10** was transformed to the azide **11** as described for **4**. The product was purified by preparative TLC with 1:1 EtOAc–cyclohexane as eluent to afford **11** (71%) as an oil: $[\alpha]_D$ +30 (*c* 0.3, CH_2Cl_2); R_f 0.72 (EtOAc); IR (KBr) 3421, 2119, 1757, 1685 cm^{-1}. ^1H NMR: δ 7.31–7.15 (m, 10 H, Ph), 6.65 (d, $J_{2',NH}$ 10.0 Hz, 1 H, NH), 4.65 (d, J_{gem} 11.3 Hz, 1 H, OCHPh), 4.45 (d, J_{gem} 11.3 Hz, 1 H, OCHPh), 4.41–4.38 (m, 4 H, H-2,6, 2 × OCHPh), 4.15–4.09 (m, 3 H), 3.63 (t, *J* 3.0 Hz, 1 H), 3.53 (s, 3 H, OMe), 3.46–3.39 (m, 2 H, H-8), 1.76 (s, 3 H, Ac), 1.73–1.56 (m, 2 H, H-7). ^{13}C NMR: δ 170.2 (CO), 137.6, 137.2 (C_{ipso}), 129.1, 128.8, 128.3, 128.2, 127.8 (Ph), 74.8, 74.2, 73.2 (CH), 72.7, 72.1 (OCH_2), 68.0 (C-6), 52.5 (OMe), 48.4 (C-8), 48.0 (C-5), 31.6 (C-7), 23.7 (Ac). Anal. Calcd for $C_{25}H_{30}N_4O_6$: C, 62.23; H, 6.27; N, 11.61. Found: C, 62.39; H, 6.18; N, 11.80.

3.10. Methyl 5-*N*-acetylamino-8-amino-2,6-anhydro-3,4-di-*O*-benzyl-5,7,8-trideoxy-D-*glycero*-L-*gluco*-octuronate (12)

The azide **11** was reduced to the amine **12** as described for **6**. Purification by preparative TLC with 1:9 MeOH–CH_2Cl_2 as eluent afforded **12** as an oil in 46% yield: $[\alpha]_D$ +42.5 (*c* 0.4, CH_2Cl_2); R_f 0.25 (1:19 MeOH–CH_2Cl_2); IR (KBr) 3421, 3035, 1757, 1733, 1685 cm^{-1}. ^1H NMR: δ 7.38–7.23 (m, 10 H, Ph), 6.76 (d, $J_{2',NH}$ 9.8 Hz, 1 H, NH), 4.72 (d, J_{gem} 11.3 Hz, 1 H, OCHPh), 4.59 (d, J_{gem} 11.3 Hz, 1 H, OCHPh), 4.55 (d, J_{gem} 11.5 Hz, 1 H, OCHPh), 4.48 (d, J_{gem} 11.5 Hz, 1 H, OCHPh), 4.61–4.45 (m, 2 H, H-2,6), 4.22–4.13 (m, 3 H), 3.72 (t, *J* 3.0 Hz, 1 H), 3.60 (s, 3 H, OMe), 3.45 (s, 2 H, NH_2), 3.04–2.96 (m, 2 H, H-8), 1.86 (s, 3 H, Ac), 1.80–1.52 (m, 2 H, H-7). ^{13}C NMR: δ 170.6, 170.4 (CO), 137.6, 137.2 (C_{ipso}), 129.1, 128.8, 128.3, 128.2, 127.8 (Ph), 74.5, 74.1, 73.1 (CH), 72.6, 72.2 (OCH_2), 68.8 (CH), 52.7 (OMe), 48.2 (C-5), 38.6 (C-8), 30.1 (C-7), 23.7 (Me). Anal. Calcd for $C_{25}H_{32}N_2O_6$: C, 65.77; H, 7.06; N, 6.14. Found: C, 65.66; H, 7.00; N, 6.21.

3.11. (*E*)-1-(2′-*N*-Acetylamino-3′,4′,6′-tri-*O*-benzyl-2′-deoxy-α-D-glucopyranosyl)-1-propene (13)

To a soln of **1** (500 mg, 0.971 mmol) in benzene (5 mL), was added $PdCl_2$ (50 mg, 0.282 mmol). The mixture was heated at reflux for 23 h, then concentrated. Purification by column chromatography (1:3 to 2:1 EtOAc–hexane) afforded **13** (356 mg, 71%) as a mixture of two diastereoisomers ($E/Z = 21:4$): mp 98–100 °C; $[\alpha]_D$ + 27.0 (*c* 1.2, CH_2Cl_2); R_f 0.36 (1:1 EtOAc–cyclohexane); IR (KBr) 3325, 3060, 3035, 1733 cm^{-1}. ^1H NMR of the major isomer *E*: δ 7.27–7.15 (m, 15 H, Ph), 6.12 (d, $J_{2',NH}$ 9.5 Hz, 1 H, NH), 5.70 (qd, $J_{1,2}$ 15.4, $J_{2,3}$ 6.5 Hz, 1 H, H-2), 5.33 (ddq, $J_{1,1'}$ 6.3, $J_{1,3}$ 1.6 Hz, 1 H, H-1), 4.59–4.33 (m, 6 H, 3 × OCH_2Ph), 4.35–4.33 (m, 1 H, H-1′), 4.15–4.10 (m, 2 H), 3.77–3.51 (m, 4 H), 1.74 (s, 3 H, Ac), 1.61 (m, 3 H, H-3). ^{13}C NMR of the major isomer *E*: δ 168.2 (CO), 136.6, 136.2, 136.0 (C_{ipso}), 128.5 (CH=), 127.0, 126.8, 126.4, 126.3, 126.1, 125.2 (Ph), 125.2 (CH=), 73.7, 73.2, 72.4 (CH), 67.9 (CH), 66.4 (C-6′), 47.3 (C-2′), 21.7, 16.5 (Me). Anal. Calcd for $C_{32}H_{37}NO_5$: C, 74.53; H, 7.23; N, 2.71. Found: C, 74.46; H, 7.11; N, 2.69.

3.12. (*E*)-1-(2′-*N*-Acetylamino-3′,4′-di-*O*-benzyl-2′-deoxy-α-D-glucopyranosyl)-1-propene (14)

Compound **13** was acetolyzed as described for **1** and deacetylated as described for **2**. Purification by column chromatography (1:1 to 2:1 EtOAc–cyclohexane) afforded **14** (white solid, 51%) as a mixture of two diastereoisomers ($E/Z = 21:4$): mp 140 °C; $[\alpha]_D$ + 35.0 (*c* 1.0, CH_2Cl_2); R_f 0.31 (2:1 EtOAc–cyclohexane); IR (KBr) 3300, 3083, 3035, 1733, 1660 cm^{-1}. ^1H NMR of the major isomer *E*: δ 7.29–7.17 (m, 10 H, Ph), 5.99 (d, $J_{2',NH}$ 9.0 Hz, 1 H, NH), 5.69 (qd, $J_{1,2}$ 15.0, $J_{2,3}$ 6.8 Hz, 1 H, H-2), 5.38 (ddq, $J_{1,1'}$ 6.8, $J_{1,3'}$ 1.0 Hz, 1 H, H-1), 4.63–4.50 (m, 4 H, 2 × OCH_2Ph), 4.43–4.40 (m, 1 H, H-1′), 4.15–4.08 (m, 1 H, H-2′), 3.94–3.83 (m, 2 H, H-5′,6″), 3.63–3.58 (m, 2 H, H-3′,6′), 3.43 (t, $J_{3',4'} = J_{4',5'} = 4.0$ Hz, 1 H, H-4′), 2.60 (s, 1 H, OH), 1.72 (s, 3 H, Ac), 1.60 (d, $J_{2,3}$ 6.3 Hz, 3 H, H-3). ^{13}C NMR of the major isomer *E*: δ 170.4 (CO), 138.2, 137.9 (C_{ipso}), 131.3 (CH=), 129.0, 128.5, 128.3 (Ph), 126.5 (CH=), 76.2 (C-5′), 76.1 (C-3′), 75.6 (C-4′), 73.4, 73.3 (OCH_2), 70.5 (C-1′), 61.1 (C-6′), 50.0 (C-2′), 23.7, 18.5 (Me). Anal. Calcd for $C_{25}H_{31}NO_5$: C, 70.57; H, 7.34; N, 3.29. Found: C, 70.45; H, 7.31; N, 3.37.

3.13. Methyl (*E*)-5-*N*-acetylamino-2,6-anhydro-3,4-di-*O*-benzyl-7,8-didehydro-5,7,8,9-tetradeoxy-D-*glycero*-L-*gluco*-nonuronate (15)

The alcohol **14** was oxidized and esterified as described for **9** to afford, after purification by preparative TLC with 1:1 EtOAc–cyclohexane as eluent, the ester **15** (oil, 45%) as a mixture of two diastereoisomers ($E/Z = 21:4$): $[\alpha]_D$ + 38.2 (*c* 1.1, CH_2Cl_2); R_f 0.72 (EtOAc); IR (KBr) 3445, 3348, 1757, 1685 cm^{-1}. ^1H NMR of the major isomer *E*: δ 7.33–7.15 (m, 10 H, Ph), 6.55 (d, $J_{2',NH}$ 10.0 Hz, 1 H, NH), 5.81 (qd, $J_{7,8}$ 15.3, $J_{8,9}$ 6.5 Hz, 1 H, H-8), 5.35 (ddq, $J_{6,7}$ 6.5, $J_{7,9}$ 1.5 Hz, 1 H, H-7), 4.82–4.80 (m, 1 H, H-6), 4.68–4.38 (m, 5 H, H-2, 2 × OCH_2Ph), 4.21–4.17 (m, 1 H, H-5), 4.08–4.07 (m, 1 H, H-4), 3.67 (t, $J_{2,3} = J_{3,4} = 3.0$ Hz, 1 H, H-3), 3.51 (s, 3 H, OMe), 1.75 (s, 3 H, Ac), 1.62 (d, 3 H, H-9). ^{13}C NMR of the major isomer *E*: δ 170.4, 170.1 (CO), 137.7, 137.4 (C_{ipso}), 130.4 (C-8), 129.1, 128.8, 128.7, 128.2, 127.8 (Ph), 127.4 (C-7), 74.6 (C-4), 74.4 (C-2), 73.1 (C-3), 72.6, 72.1 (OCH_2), 70.9 (C-6), 52.5 (OMe), 48.3 (C-5), 23.7 (Ac), 18.5 (C-9). Anal. Calcd for $C_{26}H_{31}NO_6$: C, 68.86; H, 6.89; N, 3.09. Found: C, 68.69; H, 6.95; N, 3.16.

3.14. 3-(2′-*N*-Acetylamino-3′,4′,6′-tri-*O*-benzyl-2′-deoxy-β-D-glucopyranosyl)-1-propene (17)

A soln of 3-(2′-*N*-acetylamino-2′-deoxy-β-D-glucopyranosyl)-1-propene (**16**) [13b,13c] (488 mg, 0.200 mmol) in anhyd DMF (10 mL) was added dropwise to a suspension of NaH (1.3 equiv/OH) in DMF (2 mL) at 0 °C. Benzyl bromide (0.75 mL, 0.623 mmol) was added dropwise after 30 min of further stirring at 0 °C and the mixture stirred for additional 16 h at rt. Methanol (2 mL) was then added and the mixture was concentrated under diminished pressure. The residue was dissolved in EtOAc (30 mL), washed with water, brine, dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (1:1 EtOAc–hexane) gave **17** (700 mg, 70%) as a white solid: mp 128 °C; $[\alpha]_D$ + 10.0 (*c* 1, CH_2Cl_2); R_f 0.54 (2:1 EtOAc–hexane); IR (KBr) 3325, 3107, 3083, 3035, 1660, 1612 cm^{-1}. ^1H NMR: δ 7.28–7.13 (m, 15 H, Ph), 5.90–5.72 (m, 1 H, H-2), 5.12–4.93 (m, 2 H, H-1), 4.87 (d, $J_{2',NH}$ 9.8 Hz, 1 H, NH), 4.76 (t, J_{gem} 12.0 Hz, 2 H, OCH_2Ph), 4.59–4.51 (m, 4 H, 2 × OCH_2Ph), 3.70–3.55 (m, 5 H), 3.38–3.22 (m, 2 H), 2.23–2.10 (m, 2 H, H-3), 1.73 (s, 3 H, Ac). ^{13}C NMR: δ 170.0 (CO), 138.4, 138.3, 138.0 (C_{ipso}), 134.7 (C-2), 128.5, 128.4, 128.3, 128.2, 128.0, 127.8, 127.7, 127.5 (Ph), 116.8 (C-1), 83.0, 79.1, 78.9, 78.4 (CH), 74.8, 74.3, 73.4 (OCH_2Ph), 68.9 (C-6′), 54.9 (C-2′), 36.5 (C-3), 23.5 (Ac). Anal. Calcd for $C_{32}H_{37}NO_5$: C, 74.53; H, 7.23; N, 2.71. Found: C, 74.46; H, 7.12; N, 2.79.

3.15. 3-(2′-*N*-Acetylamino-3′,4′-di-*O*-benzyl-2′-deoxy-β-D-glucopyranosyl)-1-propene (18)

Compound **17** was acetolyzed as described for **1** and deacetylated as described for **2**. Purification by column chromatography (1:1 to 2:1 EtOAc–cyclohexane) af-

forded **18** as a white solid (43%): mp 158–160 °C; $[\alpha]_D$ −1.8 (*c* 1, CH_2Cl_2); R_f 0.35 (2:1 EtOAc–cyclohexane). ^{1}H NMR: δ 7.26–7.20 (m, 10 H, Ph), 5.85–5.68 (m, 1 H, H-2), 5.57 (d, $J_{2',NH}$ 8.8 Hz, 1 H, NH), 5.02–4.95 (m, 2 H, H-1), 4.77 (d, J_{gem} 10.8 Hz, 1 H, OCHPh), 4.74 (d, J_{gem} 12.5 Hz, 1 H, OCHPh), 4.61 (d, J_{gem} 11.5 Hz, 1 H, OCHPh), 4.59 (d, J_{gem} 10.8 Hz, 1 H, OCHPh), 3.81–3.47 (m, 5 H), 3.37–3.28 (m, 2 H, H-1′ + CH), 2.27–2.10 (m, 3 H, H-3, OH), 1.76 (s, 3 H, Ac). ^{13}C NMR: δ 170.4 (CO), 138.5, 138.0 (C_{ipso}), 134.5 (C-2), 128.6, 128.3, 128.1, 128.0, 127.9 (Ph), 117.1 (C-1), 83.1, 79.1, 78.9, 78.2 (CH), 75.0, 74.6 (OCH_2), 62.2 (C-6′), 54.9 (C-2′), 36.5 (C-3), 23.5 (Me). Anal. Calcd for $C_{25}H_{31}NO_5$: C, 70.57; H, 7.34; N, 3.29. Found: C, 70.73; H, 7.45; N, 3.40.

3.16. Methyl 5-*N*-acetylamino-2,6-anhydro-3,4-di-*O*-benzyl-8,9-didehydro-5,7,8,9-tetradeoxy-L-*glycero*-L-*gluco*-nonuronate (19)

Ester **19** was prepared as described for **9**. Purification by preparative TLC with 3:2 EtOAc–cyclohexane as eluent afforded **19** as a white solid (49%): mp 146 °C; $[\alpha]_D$ −1.0 (*c* 0.8, CH_2Cl_2); R_f 0.53 (3:2 EtOAc–cyclohexane). ^{1}H NMR: δ 7.27–7.20 (m, 10 H, Ph), 5.84–5.68 (m, 1 H, H-8), 5.09 (d, $J_{2',NH}$ 7.5 Hz, 1 H, NH), 5.01–4.94 (m, 2 H, H-9), 4.79 (d, J_{gem} 11.5 Hz, 1 H, OCHPh), 4.71 (d, J_{gem} 11.0 Hz, 1 H, OCHPh), 4.57 (d, J_{gem} 11.8 Hz, 1 H, OCHPh), 4.54 (d, J_{gem} 10.8 Hz, 1 H, OCHPh), 3.85–3.62 (m, 4 H), 3.66 (s, 3 H, OMe), 3.47–3.37 (m, 1 H, H-6), 2.27–2.15 (m, 2 H, H-7), 1.73 (s, 3 H, Ac). ^{13}C NMR: δ 170.2, 169.4 (CO), 138.3, 137.8 (C_{ipso}), 134.2 (C-8), 128.7, 128.6, 128.4, 128.2, 128.1 (Ph), 117.3 (C-9), 81.8, 80.7, 78.9, 78.4 (C-2,3,4,6), 75.0, 74.6 (OCH_2), 54.9, 52.6 (C-5, OMe), 36.5 (C-7), 23.6 (Me). Anal. Calcd for $C_{26}H_{31}NO_6$: C, 68.86; H, 6.89; N, 3.09. Found: C, 68.99; H, 6.74; N, 2.99.

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