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Synthesis of methyl 4-acetamido-2,4-dideoxy-D-*glycero*-D-*galacto*-octopyranoside, a decarboxyneuraminic acid analogue*

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ABSTRACT

3,4-*O*-Isopropylidene-D-arabinose (**3**) was transformed by a Wittig reaction into (*E*/*Z*)-2,3,4-trideoxy-6,7-*O*-isopropylidene-D-*arabino*-oct-3-enose propane-1,3-diyl acetal (**5c**). The 8-benzoate (**7c**) of **5c** reacted with 3-chloroperoxybenzoic acid to give 3,4-anhydro-8-*O*-benzoyl-2-deoxy-6,7-*O*-isopropylidene-D-*glycero*-D-*gulo*-octose propane-1,3-diyl acetal (**9**). Treatment of the 5-trichloroacetimidate (**11**) of **9** with boron trifluoride etherate gave a 2-oxazoline **12**. Acid-catalysed opening of the oxazoline ring in **12** gave 8-*O*-benzoyl-2,4-dideoxy-6,7-*O*-isopropylidene-4-trichloroacetamido-D-*glycero*-D-*galacto*-octose propane-1,3-diyl acetal (**15**) which, with tributyltin hydride–azoisobutyronitrile yielded the 4-acetamido derivative **17**. Treatment of **17** with methanolic hydrogen chloride gave the title compound.

INTRODUCTION

Recent interest in sialyl transferases and sialidases has led to an extensive search for neuraminic acid derivatives that influence the activity of these enzymes[1–9]. The structural modifications are based mainly on neuraminic acid (**1**), which has limited availability from various natural sources[1]. Syntheses of neuraminic acid and its derivatives have been based on chain elongation of readily available C_6 sugars, to give C_9 species, then diastereospecific functionalisation[8–21]. However, the transformation of a 2-amino-2-deoxyglucose derivative into a 2-amino-2-deoxymannose derivative and the subsequent stereoselective conversion into a D-*glycero*-D-*galacto* C_9 species, which necessitates further modifications based on selective *O*-protection, is a stimulus to search for other approaches.

An alternative retrosynthesis strategy is based on a C_5 building block[21,22] which comprises the stereochemistry of the C-6,7,8 moiety of neuraminic acid and is shown in Scheme 1. Thus, a *cis*-selective Wittig reaction of a D-*arabino* derivative **C** and a *β*-nucleophilic propanone species **D** (where X is oxygen or its equivalent) provides the intermediate **B**. Diastereoselective epoxidation of **B** yields **A**, and an appropriate epoxide cleavage reaction then gives **1**. The application of this strategy for the synthesis of "decarboxyneuraminic acid" (**2**) is now reported. An *O*-benzyl protected decarboxyneuraminic acid analogue has been described by Walliman and Vasella[9].

* Dedicated to Professor Grant Buchanan on the occasion of his 65th birthday.
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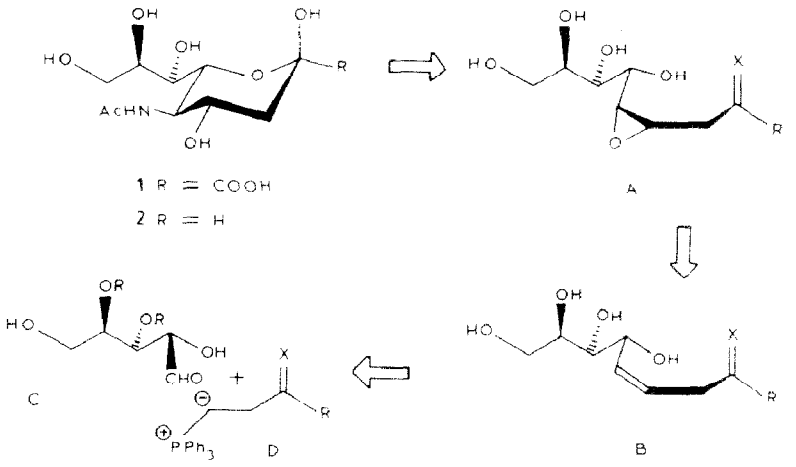


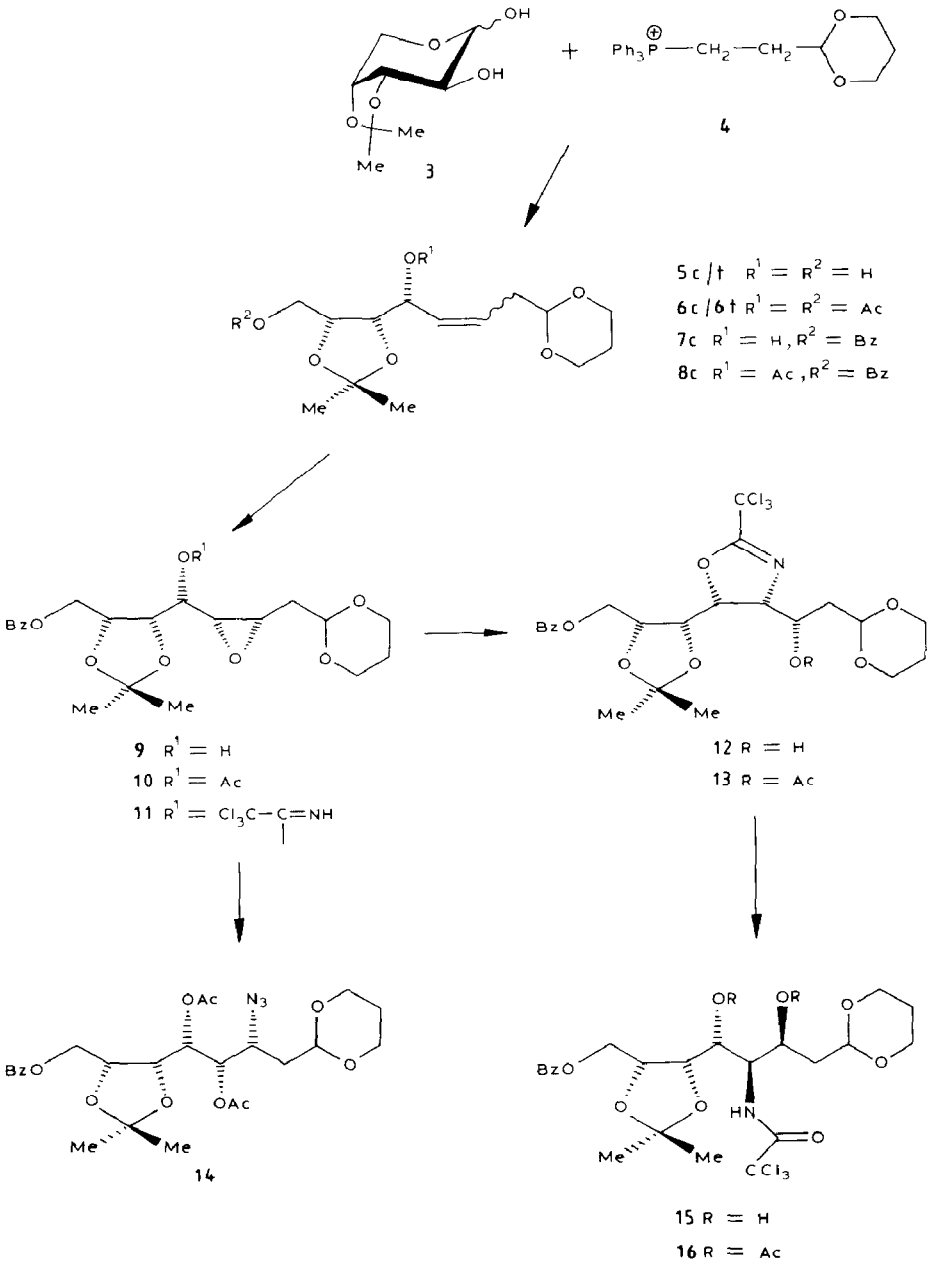
Scheme 1.

RESULTS AND DISCUSSION

The required 3,4-*O*-isopropylidene-D-arabinose (**3**) can be obtained directly from D-arabinose[23]. Wittig reaction of **3** in tetrahydrofuran with the phosphonium salt **4**[24], derived from *β*-bromopropionaldehyde, with potassium *tert*-butoxide as the base, provided the olefinic product **5** with high *cis*-selectivity (**5c**:**5t** = 9:1), as evidenced by *O*-acetylation of the crude product with acetic anhydride–pyridine and isolation of **6c** and **6t**. The configurational assignments are based on the ^{1}H-n.m.r. data (**6c** $J_{3,4}$ 11 Hz, **6t** $J_{3,4}$ 15.6 Hz). Immediate treatment of the crude **5c**,**5t** mixture with benzoyl cyanide–triethylamine selectively benzoylated the primary hydroxyl group, and the *cis*-isomer **7c** was isolated by chromatography. Acetylation of **7c** gave **8c**, the structure of which was indicated by the ^{1}H-n.m.r. data ($J_{3,4}$ 11 Hz).

Based on previous investigations of the epoxidation of allylic alcohols[25–27] and on the preferred conformation of **7c**, the required *threo*-selectivity (relative to the allylic hydroxyl group) should result by reaction with 3-chloroperoxybenzoic acid and, indeed, the desired epoxide **9** was obtained as the only product in high yield. Acetylation of **9** furnished **10**, the ^{1}H-n.m.r. data of which ($J_{3,4}$ 4.2, $J_{4,5}$ 8.5 Hz) were similar to those for the related *lyxo-cis*-epoxide systems[27,28]. Further proof of the structure of **9** was obtained by the subsequent transformations.

Treatment of **9** with sodium azide in dimethoxyethane–methoxyethanol[29–32] led, as expected[33], to the undesired 3-azido-3-deoxy derivative, identified as the 4,5-diacetate **14**. The required epoxide opening of **9** at C-4 was effected by a neighboring-group reaction that involved a 5-substituted derivative. Various appropriate N-containing reagents have been proposed[26,34,35] for generating a nucleophilic nitrogen and effecting regioselective *exo*-opening[36] of the epoxide moiety. Base-catalysed addition of trichloroacetonitrile to the epoxide **9** afforded the 5-trichloroacetimidate **11** in high yield. Treatment of **11** with boron trifluoride etherate caused regioselective cleavage of the

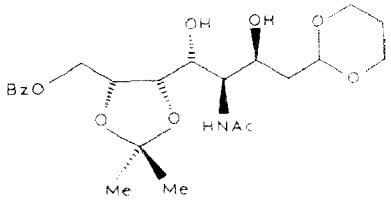


epoxide ring and gave the 2-oxazoline derivative **12** with the desired D-*glycero*-D-*galacto* configuration. Acetylation of **12** gave the 3-acetate **13** as indicated clearly by the ^{1}H-n.m.r. data. The *cis*-2-oxazoline structure of **12** and **13** was indicated by the typical[37] $J_{4,5}$ values of 9.5 and 9.7 Hz, respectively (*cf.* 5–6 Hz for *trans*-2-oxazolines). *p*-Toluenesulfonic acid-catalysed ring opening[38] of the oxazoline derivative **12** provided the trichloroacetamido-octose derivative **15**, which was converted into the 3,5-diacetate

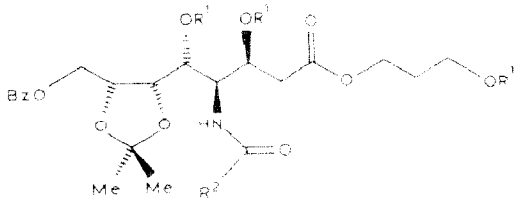
16. Treatment of **15** with tributyltin hydride–azoisobutyronitrile[39] gave the 4-acetamido-4-deoxy derivative **17** in high yield.

Reaction of **15** and **17** with ozone cleaved the cyclic acetals, as expected[40], to give the esters **18** and **20**, respectively, which were characterised as the triacetates **19** and **21**, respectively. The treatment of **15** with ozone also gave a minor by-product, which appeared to be the δ-lactone-derived ortho-ester (see Experimental).

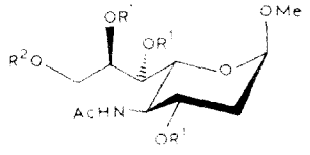
Treatment of **17** with methanolic hydrogen chloride at room temperature and acetylation of the product gave the methyl pyranoside derivative **22**. When the first reaction was performed at 60°, *O*-deacylation occurred and the target molecule methyl 4-acetamido-2,4-dideoxy-β-D-*glycero*-D-*galacto*-octopyranoside (**23**) was obtained. Acetylation of **23** gave the 3,6,7,8-tetra-*O*-acetyl derivative **24**. The ^{1}H-n.m.r. data of **22** and **24** accord with those found for the corresponding methyl glycosides of neuraminic acid[41]. The β configuration is derived from the coupling constants ($J_{3,4}$ 2.9, $J_{3,3ax}$ ~0 Hz).



17



18 R^1 = H, R^2 = CCl_3
19 R^1 = Ac, R^2 = CCl_3
20 R^1 = H, R^2 = CH_3
21 R^1 = Ac, R^2 = CH_3



22 R^1 = Ac, R^2 = Bz
23 R^1 = R^2 = H
24 R^1 = R^2 = Ac

EXPERIMENTAL

General methods. — Melting points are uncorrected. Optical rotations were determined with a Perkin–Elmer 241 MC polarimeter for solutions in $CHCl_3$ at 20°, unless noted otherwise. ^{1}H-N.m.r. spectra were recorded on solutions in $CDCl_3$ (internal Me_4Si) with a Bruker WM 250 (or AC 250) Cryospec or a Jeol JNM-GX 400 instrument. R_f values refer to t.l.c. performed on Silica Gel 60 F_{254} (Merck). Column chromatography was performed under normal pressure with silica gel (Merck, 70–230 mesh ASTM and 230–400 mesh ASTM for flash-column chromatography) and under elevated pressure with LiChroprep Si 60 (Merck, 15–25 μm). The b.p. of the light

petroleum was 40–70°. The ozonolysis reactions were carried out with a Fischer ozoniser (model 501).

(Z)- (**6c**) *and* (E)-*5,8-Di*-O-*acetyl-2,3,4-trideoxy-6,7*-O-*isopropylidene*-D-arabino-*oct-3-enose propane-1,3-diyl acetal* (**6t**). — A 0.1M solution of potassium *tert*-butoxide in tetrahydrofuran (540 mL) was added to a stirred suspension of [2-(1,3-dioxan-2-yl)-ethyl]triphenylphosphonium bromide[24] (123.5 g, 270 mmol) in dry tetrahydrofuran (200 mL) to give an orange phosphorane. Stirring was continued at room temperature for 30 min and then a solution of **3**[23] (16 g, 90 mmol) in tetrahydrofuran (30 mL) was added. The mixture was stirred for 10 min, then poured into aqueous NH_4Cl, and extracted twice with ether. The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (ethyl acetate) of the residue provided a crude mixture (14.8 g, 57%) of **5c** and **5t**, R_F 0.29.

A solution of the crude mixture (350 mg, 1.2 mmol) in pyridine (15 mL) and acetic anhydride (15 mL) was stirred for 2 h at room temperature, then diluted with toluene (30 mL), and concentrated *in vacuo*. This procedure was repeated thrice. Column chromatography (2:1 light petroleum–ethyl acetate) of the residue under elevated pressure yielded **6c** (380 mg, 84.1%) and **6t** (40 mg, 8.9%).

Compound **6c** had $[\alpha]_D$ +25.5° (*c* 1), R_F 0.42. ^{1}H-N.m.r. data (400 MHz): δ 5.77–5.71 (dt, 1 H, $J_{3,4}$ 11 Hz, H-3), 5.57–5.47 (m, 2 H, H-4,5), 4.56–4.54 (dd, 1 H, $J_{1,2a} = J_{1,2b}$ = 5 Hz, H-1), 4.31–4.20, 4.07–4.00, 3.76–3.68 (3 m, 8 H, H-6,7,8a,8b and 2 OCH_2CH_2), 2.54–2.51 (m, 2 H, H-2a,2b), 2.11–1.97 (m, 7 H, 2 Ac and OCH_2CH_2), 1.47–1.22 (2 s, m, 7 H, 2 CH_3 and OCH_2CH_2).

Anal. Calc. for $C_{18}H_{28}O_8$: C, 58.06; H, 7.53. Found: C, 57.95; H, 7.62.

Compound **6t** had $[\alpha]_D$ −6.5° (*c* 1), R_F 0.34. ^{1}H-N.m.r. data (400 MHz): δ 5.90–5.82 (m, 1 H, H-3), 5.55–5.49 (dd, 1 H, $J_{3,4}$ 15.6, $J_{4,5}$ 7.5 Hz, H-4), 5.36–5.33 (dd, 1 H, $J_{5,6}$ 7.5 Hz, H-5), 4.53–4.51 (dd, 1 H, $J_{1,2a} = J_{1,2b}$ = 5.1 Hz, H-1), 4.30–4.22, 4.08–4.02, 3.74–3.68 (3 m, 8 H, H-6,7,8a,8b and 2 OCH_2CH_2), 2.37–2.30 (m, 2 H, H-2a,2b), 2.12–1.98 (m, 7 H, 2 Ac and OCH_2CH_2), 1.46, 1.34, 1.31–1.23 (2 s, m, 7 H, 2 CH_3 and OCH_2CH_2).

Anal. Found: C, 57.96; H, 7.64.

(E/Z)-*2,3,4-Trideoxy-6,7*-O-*isopropylidene*-D-arabino-*oct-3-enose propane-1,3-diyl acetal* (**5c**/**5t**). — A solution of the crude mixture **6c**/**6t** (446 mg, 1.2 mmol) in methanol (20 mL) containing sodium methoxide (0.02 mmol was kept for 1 h at room temperature, then neutralised with ion-exchange (H^+) resin, and concentrated. Column chromatography (ethyl acetate) of the residue gave oily **5c**/**5t** (350 mg, 99%), R_F 0.29. ^{1}H-N.m.r. data (400 MHz): δ 5.78–5.66 (m, 2 H, H-3,4), 4.58–4.50 (m, 2 H, H-1,6), 4.20–4.06 (m, 4 H, H-5,7,8a,8b), 3.76–3.68 (m, 4 H, 2 OCH_2), 3.45–3.32 (bs, 1 H, OH), 2.82–2.78 (bs, 1 H, OH), 2.58–2.51 (m, 1 H, H-2a), 2.42–2.36 (m, 1 H, H-2b), 2.08–1.99 (m, 1 H, OCH_2CH_2), 1.49–1.29 (m, 7 H, 2 CH_3 and OCH_2CH_2).

Anal. Calc. for $C_{14}H_{24}O_6$: C, 58.33; H, 8.33. Found: C, 58.20; H, 8.49.

(Z)-*8*-O-*Benzoyl-2,3,4-trideoxy-6,7*-O-*isopropylidene*-D-arabino-*oct-3-enose propane-1,3-diyl acetal* (**7c**). — To a solution of crude **5c**/**5t** (8.6 g, 30 mmol) in dry

acetonitrile (80 mL) and triethylamine (20 mL) at −20° was added benzoyl cyanide (4.6 g, 35 mmol). The mixture was stirred for 2 h at −20°, then poured into saturated aqueous NH_4Cl, and extracted thrice with dichloromethane. The combined extracts were dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography (1:1 light petroleum–ethyl acetate) of the residue gave **7c** (11.05 g, 94%) as a pale-yellow oil, b.p. 210°/0.065 Torr, $[\alpha]_D$ −15° (*c* 1), R_f 0.21. ^{1}H-N.m.r. data (400 MHz): δ 8.10, 7.50, 7.38 (3 m, 5 H, Ph), 5.71–5.68 (m, 2 H, H-3,4), 4.60–4.23 (m, 6 H, H-1,5,6,7,8a,8b) 4.10–4.00, 3.89–3.79 (2 m, 4 H, 2 OCH_2CH_2), 3.08 (d, 1 H, *J* 3 Hz, OH), 2.55–2.31 (m, 2 H, H-2a,2b), 2.06–1.97 (m, 1 H, OCH_2CH_2), 1.55–1.23 (m, 7 H, 2 CH_3 and OCH_2CH_2).

Anal. Calc. for $C_{21}H_{28}O_7$: C, 64.29; H, 7.14. Found: C, 64.10; H, 7.30.

(Z)-5-O-Acetyl-8-O-benzoyl-2,3,4-trideoxy-6,7-O-isopropylidene-D-arabino-*oct-3-enose propane-1,3-diyl acetal* (**8c**). This compound, synthesised (97%) from **7c** as described for **6c**, had R_f 0.7 (1:1 light petroleum–ethyl acetate). ^{1}H-N.m.r. data (400 MHz): δ 8.06–8.04, 7.55–7.51, 7.43–7.39 (3 m, 5 H, Ph), 5.81–5.70 (m, 2 H, H-3,5), 5.56–5.53 (dd, 1 H, $J_{3,4}$ 11, $J_{4,5}$ 9.3 Hz, H-4), 4.54–4.30 (m, 5 H, H-1,6,7,8a,8b), 4.04–4.00, 3.72–3.66 (2 m, 4 H, 2 OCH_2CH_2), 2.61–2.48 (m, 2 H, H-2a,2b), 2.05–1.94 (m, 4 H, Ac and OCH_2CH_2), 1.47, 1.35, 1.27–1.24 (2 s, m, 7 H, 2 CH_3 and OCH_2CH_2).

Anal. Calc. for $C_{23}H_{30}O_8$: C, 63.59; H, 6.92. Found: C, 63.50; H, 6.90.

3,4-Anhydro-8-O-benzoyl-2-deoxy-6,7-O-isopropylidene-D-glycero-D-gulo-*octose propane-1,3-diyl acetal* (**9**). A solution of **7c** (12.5 g, 42 mmol) in dry dichloromethane (150 mL) at 0° was treated with dry 3-chloroperoxybenzoic acid (9 g, 50 mmol). After 20 min, a white precipitate had formed, and stirring was continued for 12 h at 0°. The mixture was poured into aqueous $NaHCO_3$ and extracted twice with dichloromethane (300 mL). The combined extracts were dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography (1:1 light petroleum–ethyl acetate) of the residue yielded **9** (11 g, 84%), m.p. 104–106° (from ethyl acetate), $[\alpha]_D$ −2.8° (*c* 1), R_f 0.27. ^{1}H-N.m.r. data (400 MHz): δ 8.04–8.02, 7.56–7.52, 7.43–7.40 (3 m, 5 H, Ph), 4.71–4.68 (dd, 1 H, $J_{1,2a}$ 3.4, $J_{1,2b}$ 6.1 Hz, H-1), 4.64–4.53 (m, 3 H, H-7,8a,8b), 4.38–4.36 (dd, 1 H, $J_{5,6}$ 1.7, $J_{6,7}$ 7 Hz, H-6), 4.08–4.05, 3.76–3.71 (2 m, 5 H, H-5 and 2 OCH_2CH_2), 3.25–3.20 (m, 1 H, H-3), 3.16–3.13 (dd, 1 H, $J_{3,4}$ 4.2, $J_{4,5}$ 6.9 Hz, H-4), 2.33–2.31 (d, 1 H, $J_{5,OH}$ 8.1 Hz, OH), 2.04–1.98 (m, 2 H, H-2a and OCH_2CH_2), 1.89–1.84 (m, 1 H, H-2b), 1.54, 1.38 (2 s, 6 H, 2 CH_3), 1.33–1.30 (m, 1 H, OCH_2CH_2).

Anal. Calc. for $C_{21}H_{28}O_8$: C, 61.77; H, 6.86. Found: C, 61.75; H, 6.99.

5-O-Acetyl-3,4-anhydro-8-O-benzoyl-2-deoxy-6,7-O-isopropylidene-D-glycero-D-gulo-*octose propane-1,3-diyl acetal* (**10**). Synthesised (98%) from **9** as described for **6c**, **10** had $[\alpha]_D$ +13° (*c* 1), R_f 0.6 (1:1 light petroleum–ethyl acetate). ^{1}H-N.m.r. data (400 MHz): δ 8.03–8.01, 7.56–7.52, 7.43–7.41 (3 m, 5 H, Ph), 5.11–5.08 (dd, 1 H, $J_{4,5}$ 8.5, $J_{5,6}$ 2.2 Hz, H-5), 4.71–4.69 (dd, 1 H, $J_{1,2a}$ 3.2, $J_{1,2b}$ 5.9 Hz, H-1), 4.54–4.49 (m, 1 H, H-7), 4.47–4.45 (dd, 1 H, $J_{6,7}$ 6.5 Hz, H-6), 4.40–4.38 (m, 2 H, H-8a,8b), 4.07–4.04, 3.76–3.68 (2 m, 4 H, 2 OCH_2CH_2), 3.33–3.30 (dd, 1 H, $J_{3,4}$ 4.2 Hz, H-4), 3.26–3.22 (m, 1 H, H-3), 2.12, 2.08–1.89 (s, m, 6 H, Ac, H-2a,2b, and OCH_2CH_2), 1.55, 1.37 (2 s, 6 H, 2 CH_3), 1.33–1.30 (m, 1 H, OCH_2CH_2).

Anal. Calc. for $C_{23}H_{30}O_9$: C, 61.33; H, 6.67. Found: C, 61.30; H, 6.74.

*3,4-Anhydro-8-*O*-benzoyl-2-deoxy-6,7-*O*-isopropylidene-5-*O*-trichloroacetamido-*D*-glycero-*D*-gulo-octose propane-1,3-diyl acetal* (**11**). — To a solution of **9** (9.4 g, 23 mmol) in dry dichloromethane (70 mL) was added trichloroacetonitrile (3.5 mL, 35 mmol) followed with vigorous stirring by potassium hydride (70 mg, 3 mmol) to give a brown mixture. More potassium hydride (35 mg, 1.5 mmol) was added, stirring was continued for 10 h, and the mixture was diluted with dichloromethane (50 mL), filtered through Celite, and concentrated *in vacuo*. Column chromatography (3:1 light petroleum–ethyl acetate) of the residue gave **11** (10.9 g, 86%), $[\alpha]_D$ +2.2° (*c* 1), R_F 0.44. ^{1}H-N.m.r. data (400 MHz): δ 8.57 (s, 1 H, NH), 8.08–8.01, 7.55–7.01, 7.42–7.38 (3 m, 5 H, Ph), 5.37–5.34 (d, 1 H, $J_{4,5}$ 8.5 Hz, H-5), 4.73–4.71 (dd, 1 H, $J_{1,2a}$ 3.2, $J_{1,2b}$ 5.9 Hz, H-1), 4.59–4.40 (m, 4 H, H-6,7,8a,8b), 4.11–4.05, 3.77–3.68 (2 m, 4 H, 2 OCH_2CH_2), 3.48–3.45 (dd, 1 H, $J_{3,4}$ 4.2 Hz, H-4), 3.26–3.22 (m, 1 H, H-3), 2.10–1.93 (m, 3 H, H-2a,2b and OCH_2CH_2), 1.60, 1.38 (2 s, 6 H, 2 CH_3), 1.36–1.29 (m, 1 H, OCH_2CH_2).

Anal. Calc. for $C_{23}H_{28}Cl_3NO_8$: C, 49.79; H, 5.07; N, 2.54. Found: C, 50.08; H, 5.22; N, 2.53.

cis-*5-[(1*R*,2*R*)-3-Benzoyloxy-1,2-(dimethylmethylenedioxy)propyl]-4-[(1*S*]-2-(1,3-dioxan-2-yl)-1-hydroxyethyl]-2-trichloromethyl-2-oxazoline* (**12**). — To a solution of **11** (10 g, 18.1 mmol) in dry dichloromethane (100 mL) at 0° were added two drops of boron trifluoride etherate. After 20 min, t.l.c. showed the complete disappearance of **11**. The mixture was poured into aqueous $NaHCO_3$, and the organic layer was dried ($MgSO_4$) and concentrated. Column chromatography (2:1 light petroleum–ethyl acetate) of the residue gave **12** (8.7 g, 87%), m.p. 146–147° (from ether), $[\alpha]_D$ +47° (*c* 1), R_F 0.21. ^{1}H-N.m.r. data (400 MHz): δ 8.04 7.95, 7.55–7.48, 7.41–7.35 (3 m, 5 H, Ph), 5.02–4.99 (dd, 1 H, $J_{4,5}$ 9.7, $J_{5,6}$ 3.8 Hz, H-5), 4.81–4.76 (dd, 1 H, $J_{1,2a}$ 3.6, $J_{1,2b}$ 6.1 Hz, H-1), 4.74–4.71 (dd, 1 H, $J_{6,7}$ 6.2 Hz, H-6), 4.65–4.61 (ddd, 1 H, $J_{7,8b}$ 6.2, $J_{7,8a}$ 8 Hz, H-7), 4.57–4.52 (dd, 1 H, $J_{8a,8b}$ 12.3 Hz, H-8a), 4.41–4.36 (dd, 1 H, H-8b), 4.30–4.26 (dd, 1 H, $J_{3,4}$ 3.66 Hz, H-4), 4.25–4.20 (m, 1 H, H-3), 4.10–4.05, 3.94–3.84 (2 m, 4 H, 2 OCH_2CH_2), 3.40 (bs, 1 H, OH), 2.10–1.97 (m, 2 H, H-2a and OCH_2CH_2), 1.82–1.75 (ddd, 1 H, $J_{2a,2b}$ 14 Hz, H-2b), 1.60, 1.38 (2 s, 6 H, 2 CH_3), 1.35–1.28 (m, 1 H, OCH_2CH_2).

Anal. Calc. for $C_{23}H_{28}Cl_3NO_8$: C, 49.79; H, 5.07; N, 2.54. Found: C, 50.02; H, 5.18; N, 2.50.

cis-*4-[(1*S*)-1-Acetoxy-2-(1,3-dioxan-2-yl)ethyl]-5-[(1*R*,2*R*)-3-benzoyloxy-1,2-(dimethylmethylenedioxy)propyl]-2-trichloromethyl-2-oxazoline* (**13**). — Synthesised (98%) from **12** as described for **6c**, **13** had $[\alpha]_D$ +36° (*c* 1), R_F 0.38 (2:1 light petroleum–ethyl acetate). ^{1}H-N.m.r. data (400 MHz): δ 8.03–8.01, 7.58–7.54, 7.46–7.42 (3 m, 5 H, Ph), 5.35–5.31 (ddd, 1 H, H-3), 5.05–5.00 (dd, 1 H, $J_{4,5}$ 9.5, $J_{5,6}$ 5.8 Hz, H-5), 4.69–4.60 (2 m, 3 H, H-1,4,7), 4.53–4.49 (dd, 1 H, $J_{7,8a}$ 5.1, $J_{8a,8b}$ 12 Hz, H-8a), 4.44–4.41 (dd, 1 H, $J_{6,7}$ 5.8 Hz, H-6), 4.37–4.33 (dd, 1 H, $J_{7,8b}$ 5.6 Hz, H-8b), 4.10–4.03, 3.76–3.66 (2 m, 4 H, 2 OCH_2CH_2), 2.14–1.97 (m, 6 H, H-2a,2b, OCH_2CH_2, and Ac), 1.50, 1.36 (2 s, 6 H, 2 CH_3), 1.34–1.29 (m, 1 H, OCH_2CH_2).

Anal. Calc. for $C_{25}H_{30}Cl_3NO_9$: C, 50.48; H, 5.05; N, 2.35. Found: C, 50.35; H, 5.08; N, 2.03.

*4,5-Di-*O*-acetyl-3-azido-8-*O*-benzoyl-2,3-dideoxy-6,7-*O*-isopropylidene-*D*-glyce-*

ro-D-ido-*octose propane-1,3-diyl acetal* (**14**). — To a solution of **9** (1 g, 2.45 mmol) in 1,2-dimethoxyethane (10 mL), methoxyethanol (20 mL), and water (20 mL) were added sodium azide (0.65 g, 10 mmol) and ammonium chloride (0.55 g, 10 mmol). The mixture was boiled under reflux for 10 h, then cooled to room temperature, and concentrated. The residue was acetylated, as described above for the preparation of **6c**, to give amorphous **14** (1.05 g, 80%), $[\alpha]_D$ −8.9° (*c* 1), R_f 0.45 (3:1 light petroleum–ethyl acetate). ^{1}H-N.m.r. data (250 MHz): δ 8.06–7.98, 7.58–7.52, 7.49–7.37 (3 m, 5 H, Ph), 5.48–5.46 (dd, 1 H, $J_{4,5}$ 5.7, $J_{5,6}$ 3.7 Hz, H-5), 5.28–5.25 (dd, 1 H, $J_{3,4}$ 4.2 Hz, H-4), 4.64–4.44 (dd, 1 H, $J_{1,2a}$ 5.1, $J_{1,2b}$ 5.1 Hz, H-1), 4.51–4.31 (m, 4 H, H-6,7,8a,8b), 4.11–4.00, 3.82–3.68 (2 m, 5 H, 2 OCH_2CH$_3$ and H-3), 2.18–1.81 (m, 9 H, H-2a,2b, OCH$_2$CH_3 and 2 Ac), 1.48, 1.33–1.28 (2 s, m, 7 H, OCH$_2$CH_3 and 2 CH$_3$).

Anal. Calc. for $C_{25}H_{33}N_3O_{10}$: C, 56.07; H, 6.17; N, 7.85. Found: C, 55.97; H, 6.19; N, 7.19.

8-O-Benzoyl-2,4-dideoxy-6,7-O-isopropylidene-4-trichloroacetamido-D-glycero-D-galacto-*octose propane-1,3-diyl acetal* (**15**). — A solution of **12** (6.8 g, 12.3 mmol) in pyridine (50 mL) and water (12.5 mL) containing *p*-toluenesulphonic acid monohydrate (750 mg, 3.9 mmol) was kept for 12 h at 80°. Aqueous sodium hydrogen carbonate (70 mL) was added, the mixture was stirred for 1 h, and the solvents were evaporated. The residue was extracted three times with dichloromethane (50 mL), and the combined extracts were dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography (1:1 light petroleum–ethyl acetate) of the residue yielded **15** (6.38 g, 91%), $[\alpha]_D$ −4.1° (*c* 1), R_f 0.41. ^{1}H-N.m.r. data (400 MHz): δ 8.04–8.01, 7.56–7.51, 7.47–7.39 (3 m, 5 H, Ph), 7.32–7.29 (d, 1 H, $J_{4,NH}$ 11 Hz, NH), 4.82–4.79 (dd, 1 H, $J_{1,2a}$ 3.2, $J_{1,2b}$ 5.5 Hz, H-1), 4.64–4.48 (m, 4 H, H-4,7,8a,8b), 4.33–4.31 (d, 1 H, $J_{4,5}$ 5.8 Hz, H-6), 4.14–4.07 (m, 2 H, OCH_2CH$_3$), 3.93–3.86 (m, 2 H, H-3,5), 3.82–3.71 (m, 2 H, OCH_2CH$_3$), 3.66 (bs, 1 H, OH), 2.75–2.72 (d, 1 H, OH), 2.13–2.02 (m, 1 H, OCH$_2$CH_2), 1.87–1.79, 1.74–1.69 (2 m, 2 H, H-2a,2b), 1.52, 1.41–1.35 (2 s, m, 7 H, 2 CH$_3$ and OCH$_2$CH_3).

Anal. Calc. for $C_{23}H_{30}Cl_3NO_9$: C, 49.39; H, 5.26; N, 2.45. Found: C, 48.31; H, 5.34; N, 2.35.

3,5-Di-O-acetyl-8-O-benzoyl-2,4-dideoxy-6,7-O-isopropylidene-4-trichloroacetamido-D-glycero-D-galacto-*octose propane-1,3-diyl acetal* (**16**). — Synthesised (98%) from **15** as described for **6c**. **16** had m.p. 40–56° (from ether), $[\alpha]_D$ −42° (*c* 1), R_f 0.57 (1:2 light petroleum–ethyl acetate). ^{1}H-N.m.r. data (400 MHz): δ 8.03–8.01 (m, 2 H, Ph), 7.66–7.64 (d, 1 H, $J_{4,NH}$ 10 Hz, NH), 7.57–7.54, 7.45–7.41 (2 m, 3 H, Ph), 5.35–5.33 (m, 1 H, H-3), 5.18–5.16 (d, 1 H, $J_{4,5}$ 4.9 Hz, H-5), 4.63–4.60 (dd, 1 H, $J_{1,2a}$ 4.8, $J_{1,2b}$ 4.8 Hz, H-1), 4.56–4.50 (m, 3 H, H-4,6,7), 4.42–4.38, 4.31–4.28 (2 m, 2 H, H-8a,8b), 4.10–4.03, 3.76–3.69 (2 m, 4 H, 2 OCH_2CH$_3$), 2.10–1.90 (2 s, m, 9 H, H-2a,2b, OCH$_2$CH_3, and 2 Ac), 1.54, 1.38 (2 s, 6 H, 2 CH$_3$), 1.31–1.28 (m, 1 H, OCH$_2$CH_3).

Anal. Calc. for $C_{27}H_{34}Cl_3NO_{11}$: C, 49.51; H, 5.20; N, 2.14. Found: C, 49.56; H, 5.24; N, 2.11.

4-Acetamido-8-O-benzoyl-2,4-dideoxy-6,7-O-isopropylidene-D-glycero-D-galacto-*octose propane-1,3-diyl acetal* (**17**). — To a solution of **15** (5 g, 8.2 mmol) in dry benzene was added tributyltin hydride (7.14 mL, 27 mmol) and azoisobutyronitrile (70

mg, 0.42 mmol). The mixture was boiled under reflux for 1 h, cooled to room temperature, poured into aqueous $NaHCO_3$, and extracted thrice with dichloromethane. The combined extracts were dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography (1:2 toluene–acetone) of the residue gave amorphous **17** (3.4 g, 89%), $[\alpha]_D$ +15° (*c* 1), R_F 0.47. ^{1}H-N.m.r. data (400 MHz): δ 8.04–8.02, 7.55–7.51, 7.43–7.39 (3 m, 5 H, Ph), 6.17–6.14 (d, 1 H, $J_{4,NH}$ 9.5 Hz, NH), 4.81–4.98 (dd, 1 H, $J_{1,2a}$ 3.6, $J_{1,2b}$ 5.6 Hz, H-1), 4.67–4.61, 4.55–4.43 (2 m, 4 H, H-4,7,8a,8b), 4.30–4.28 (m, 1 H, H-6), 4.14–4.06 (m, 2 H, OCH_2CH_2), 3.93–3.89 (dd, 1 H, $J_{4,5}$ 8, $J_{5,6}$ 8 Hz, H-5), 3.83–3.71 (m, 3 H, H-3 and OCH_2CH_2), 3.58 (bs, 1 H, OH), 2.88–2.86 (d, 1 H, *J* 9 Hz, OH), 2.11–2.0 (s, m, 4 H, Ac and OCH_2CH_2), 1.82–1.75, 1.72–1.65 (2 m, 2 H, H-2a,2b), 1.51, 1.39–1.33 (2 s, 6 H, 2 CH_3 and OCH_2CH_2).

Anal. Calc. for $C_{23}H_{33}NO_9$: C, 59.10; H, 7.07; N, 3.00. Found: C, 59.24; H, 7.22; N, 2.93.

*3-Hydroxypropyl 8-*O*-benzoyl-2,4-dideoxy-6,7-*O*-isopropylidene-4-trichloroacetamido-*D*-glycero-*D*-galacto-octonate* (**18**). — A solution of **15** (0.4 g, 0.7 mmol) was ozonolysed in dry ethyl acetate (40 mL) at −40°. After 5 min, t.l.c. showed no remaining **15**. Excess of ozone was removed by flushing with nitrogen. The mixture was brought to room temperature, and concentrated *in vacuo*. Column chromatography (1:2 light petroleum–ethyl acetate) of the residue under elevated pressure yielded amorphous **18** (312 mg, 76%), $[\alpha]_D$ −21.5° (*c* 1), R_F 0.27, and a by-product (31 mg, 7%), R_F 0.37.

18. ^{1}H-N.m.r. data (400 MHz): δ 8.04–8.01, 7.56–7.52, 7.43–7.39 (3 m, 5 H, Ph), 7.30 (bs, 1 H, NH), 4.72–4.52 (4 m, 4 H, H-6,7,8a,8b), 4.33–4.28 (m, 2 H, $CH_2CH_2CH_2OH$), 4.26–4.22 (m, 1 H, H-4), 3.96–3.92 (m, 2 H, H-3,5), 3.75–3.68 (m, 3 H, $CH_2CH_2CH_2OH$ and OH), 2.88 (bs, 1 H, OH), 2.58–2.45 (m, 2 H, H-2a,2b), 1.90–1.83 (m, 2 H, $CH_2CH_2CH_2OH$), 1.60 (bs, 1 H, OH), 1.53, 1.38 (2 s, 6 H, 2 CH_3).

Anal. Calc. for $C_{23}H_{30}Cl_3NO_{10}$: C, 47.06; H, 5.12; N, 2.39. Found: C, 46.50; H, 5.10; N, 2.51.

By-product. ^{1}H-N.m.r. data (400 MHz): δ 8.05–8.01, 7.56–7.52, 7.44–7.38 (3 m, 5 H, Ph), 6.69 (bs, 1 H, NH), 4.79–4.74 (dd, 1 H, $J_{7,8a}$ 7.6, $J_{8a,8b}$ 13.1 Hz, H-8), 4.63–4.58 (m, 2 H, H-7,8b), 4.35–4.29 (m, 2 H, H-4,6), 4.26–4.18 (m, 1 H, H-3), 4.08–3.99 (dd, 1 H, $J_{4,5} = J_{5,6}$ = 9.6 Hz, H-5), 3.96–3.89 (m, 2 H, OCH_2CH_2), 3.84–3.75 (m, 2 H, OCH_2CH_2), 2.41–2.34 (dd, 1 H, $J_{2a,3}$ 4.8, $J_{2a,2b}$ 12.4 Hz, H-2a), 2.19–2.02 (m, 2 H, OCH_2CHCH_2O and OH), 1.72–1.67 (dd, 1 H, $J_{2b,3}$ 12.4 Hz, H-2b), 1.58–1.47 (m, 4 H, OCH_2CHCH_2O and CH_3), 1.40 (s, 3 H, CH_3).

Anal. Calc. for $C_{23}H_{28}Cl_3NO_9$: C, 48.56; H, 4.93; N, 2.46. Found: C, 48.53; H, 5.28; N, 2.43.

*3-Acetoxypropyl 3,5-di-*O*-acetyl-8-*O*-benzoyl-2,4-dideoxy-6,7-*O*-isopropylidene-4-trichloroacetamido-*D*-glycero-*D*-galacto-octonate* (**19**). — Synthesised (99%) from **18** as described for **6c**, **19** had $[\alpha]_D$ −34.5° (*c* 1), R_F 0.37 (1:1 light petroleum–ethyl acetate). ^{1}H-N.m.r. data (400 MHz). δ 8.03–7.99 (m, 2 H, Ph), 7.70–7.68 (d, 1 H, $J_{4,NH}$ 9.8 Hz, NH), 7.57–7.54, 7.44–7.40 (2 m, 3 H, Ph), 5.50–5.45 (m, 1 H, H-3), 5.15–5.13 (d, 1 H, $J_{4,5}$ 4.1 Hz, H-5), 4.62–4.51 (m, 3 H, H-6,8a,8b), 4.41–4.30 (m, 2 H, H-4,7), 4.21–4.07 (m, 4 H, $CH_2CH_2CH_2OAc$), 2.73–2.68 (m, 2 H, H-2a,2b), 2.11–2.04 (3 s, 9 H, 3 Ac), 2.01–1.92 (m, 2 H, $CH_2CH_2CH_2OH$), 1.54, 1.37 (2 s, 6 H, 2 CH_3).

Anal. Calc. for $C_{29}H_{36}Cl_3NO_{13}$: C, 48.85; H, 5.05; N, 1.97. Found: C, 48.89; H, 5.35; N, 2.38.

*3-Hydroxypropyl 4-acetamido-8-O-benzoyl-2,4-dideoxy-6,7-O-isopropylidene-*D-glycero-D-galacto-*octonate* (**20**). — Synthesised (74%) from **17** as described for **18**, **20** had R_f 0.31 (1:2 toluene–acetone). ^{1}H-N.m.r. data (400 MHz): δ 8.04–8.01, 7.55–7.52, 7.43–7.39 (3 m, 5 H, Ph), 6.29–6.27 (d, 1 H, $J_{4,NH}$ 9.5 Hz, NH), 4.72–4.61 (m, 2 H, H-3,8), 4.52–4.45 (m, 2 H, H-6,8a), 4.32–4.18 (2 m, 3 H, H-7 and $CH_2CH_2CH_2OH$), 4.03–3.98 (m, 1 H, H-4), 3.85–3.68 (m, 4 H, H-5, OH, and $CH_2CH_2CH_2OH$), 3.10–3.00 (bs, 1 H, OH), 2.55–2.49 (dd, 1 H, $J_{2a,2b}$ 16.4, $J_{2a,3}$ 9 Hz, H-2a), 2.46–2.41 (dd, 1 H, $J_{2b,3}$ 4.6 Hz, H-2b), 2.04 (s, 3 H, NAc), 1.88–1.63 (m, 3 H, OH and $CH_2CH_2CH_2OH$), 1.52, 1.38 (2 s, 6 H, 2 CH_3).

*3-Acetoxypropyl 4-acetamido-3,5-di-O-acetyl-8-O-benzoyl-2,4-dideoxy-6,7-O-isopropylidene-*D-glycero-D-galacto-*octonate* (**21**). — Synthesised (98%) from **20** as described for **6c**, **21** had $[\alpha]_D$ −5.1° (*c* 1), R_f 0.7 (1:2 toluene–acetone). ^{1}H-N.m.r. data (400 MHz): δ 8.04–7.99, 7.58–7.54, 7.45–7.35 (3 m, 5 H, Ph), 6.12–6.09 (d, 1 H, $J_{4,NH}$ 10 Hz, NH), 5.41–5.37 (ddd, 1 H, $J_{2a,3}$ 6.6, $J_{2b,3}$ 6.6, $J_{3,4}$ 2.5 Hz, H-3), 5.06–5.03 (dd, 1 H, $J_{4,5}$ 7.2, $J_{5,6}$ 3.5 Hz, H-5), 4.65–4.60 (ddd, 1 H, $J_{4,NH}$ 10 Hz, H-4), 4.51–4.47 (dd, 1 H, $J_{7,8a}$ 4.2, $J_{8a,8b}$ 11.4 Hz, H-8a), 4.41–4.37 (m, 1 H, H-7), 4.36–4.33 (dd, 1 H, $J_{6,7}$ 6.4 Hz, H-6), 4.29–4.24 (dd, 1 H, $J_{7,8b}$ 6.5 Hz, H-8b), 4.15–4.10 (m, 4 H, $CH_2CH_2CH_2OAc$), 2.56–2.48 (m, 2 H, H-2a,2b), 2.09–1.91 (4 s, 1 m, 14 H, $CH_2CH_2CH_2OAc$, 3 Ac, and NAc), 1.51, 1.34 (2 s, 6 H, 2 CH_3).

Anal. Calc. for $C_{29}H_{39}NO_{13}$: C, 57.14; H, 6.41; N, 2.30. Found: C, 56.89; H, 6.57; N, 2.17.

*Methyl 4-acetamido-3,6,7-tri-O-acetyl-8-O-benzoyl-2,4-dideoxy-β-*D-glycero-D-galacto-*octopyranoside* (**22**). — A solution of **17** (0.5 g, 1.1 mmol) in saturated dry methanolic hydrogen chloride (50 mL) was stirred for 12 h at room temperature, then neutralised with ion-exchange (HO^-) resin, filtered, and concentrated *in vacuo*. The residue was acetylated, as described for **6c**, to give amorphous **22** (375 mg, 69%), $[\alpha]_D$ −27.5° (*c* 1), R_f 0.62 (1:1 toluene–acetone). ^{1}H-N.m.r. data (400 MHz): δ 8.02–7.99, 7.55–7.51, 7.42–7.39 (3 m, 5 H, Ph), 5.43–5.41 (dd, 1 H, $J_{5,6}$ 1.7, $J_{6,7}$ 6.4 Hz, H-6), 5.40–5.36 (ddd, 1 H, $J_{7,8b}$ 6.4, $J_{7,8a}$ 2.8 Hz, H-7), 5.28–5.25 (d, 1 H, $J_{4,NH}$ 10 Hz, NH), 5.22–5.16 (ddd, 1 H, $J_{2a,3}$ 11.7, $J_{2eq,3}$ 4.9, $J_{3,4}$ 10.3 Hz, H-3), 4.89–4.88 (d, 1 H, $J_{1,2ax}$ 2.9, $J_{1,2eq}$ 0 Hz, H-1), 4.86–4.82 (dd, 1 H, $J_{8a,8b}$ 12.4 Hz, H-8), 4.23–4.19 (dd, 1 H, H-8b), 4.11–4.02 (ddd, 1 H, $J_{4,5}$ 10.4, $J_{4,NH}$ 10 Hz, H-4), 3.95–3.92 (dd, 1 H, $J_{5,6}$ 1.7 Hz, H-5), 3.31 (s, 3 H, Me), 2.19–1.84 (4 s, 2 m, 14 H, H-2*ax*,2*eq*, NAc, and 3 Ac).

Anal. Calc. for $C_{24}H_{31}NO_{13}\cdot H_2O$: C, 54.65; H, 6.26; N, 2.66. Found: C, 54.73; H, 6.16; N, 2.65.

*Methyl 4-acetamido-2,4-dideoxy-β-*D-glycero-D-galacto-*octopyranoside* (**23**) *and its 3,6,7,8-tetra-acetate* (**24**). — A solution of **17** (0.4 g, 0.9 mmol) in dry saturated methanolic hydrogen chloride was stirred for 15 h at 60°, then neutralised with ion-exchange (HO^-) resin, filtered, and concentrated *in vacuo* to give crude **23**, R_f 0.15 (1:1 toluene–acetone). Acetylation of **23**, as described for **6c**, gave amorphous **24** (265 mg, 61%), $[\alpha]_D$ −5.8° (*c* 1), R_f 0.57 (1:1 toluene–acetone). ^{1}H-N.m.r. data (400 MHz): δ

5.34–5.32 (dd, 1 H, $J_{5,6}$ 1.9, $J_{6,7}$ 6.3 Hz, H-6), 5.27–5.12 (m, 3 H, NH and H-3,7), 4.88–4.87 (d, 1 H, $J_{1,2ax}$ 2.9, $J_{1,2eq}$ 0 Hz, H-1), 4.50–4.46 (dd, 1 H, $J_{7,8a}$ 2.8, $J_{8a,8b}$ 12.5 Hz, H-8a), 4.10–4.03 (m, 2 H, H-4,8b), 3.92–3.88 (dd, 1 H, $J_{4,5}$ 10.4 Hz, H-5), 3.29 (s, 3 H, Me), 2.15–1.81 (4 s, 2 m, 17 H, H-2*ax*,2*eq*, NAc, and 4 Ac).

Anal. Calc. for $C_{19}H_{29}NO_{11}\cdot 0.5H_2O$: C, 50.10; H, 6.37; N, 3.07. Found: C, 49.73; H, 6.38; N, 3.10.

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