Synthesis of C_{11} chain-extended analogues of *N*-acetylneuraminic acid

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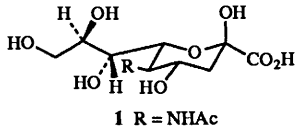
The synthesis of novel C_{11} chain-extended analogues of *N*-acetylneuraminic acid has been achieved from the *N*-acetyl-9-hydroxyneuraminic acid derivative 7 *via* a Swern oxidation/Wittig olefination sequence. In this way the novel α,β-unsaturated ester 12, the saturated ester 13 and the α,β-unsaturated aldehyde 14 of *N*-acetylneuraminic acid have been prepared in good overall yield.

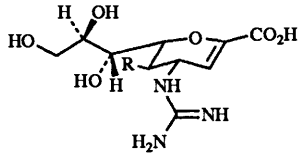
Introduction

N-Acetylneuraminic acid [sialic acid; Neu5Ac (**1**)] and related sialic acids are widely distributed in biological systems as the terminal sugars of oligosaccharide chains of a variety of glycoconjugates including glycoproteins and glycolipids.[1,2] A number of reports detail studies into the biological roles of sialic acids in such compounds, and especially their importance in cell-recognition phenomena.[1,3] As a consequence of these biological properties several groups have reported the chemical[4–6] or enzymic[7–9] synthesis of analogues of Neu5Ac as potential sialic acid-recognising protein inhibitors and probes for the elucidation of sialic acid metabolism. The structural variations reported to date involve modifications at every carbon of sialic acid, most notably 2,3-didehydro-2-deoxy (Neu5Ac2en) derivatives,[10,11] C-4[5,6,12] and C-5[8,13] modifications, and changes along the C-6 glycerol side chain including chain-shortened analogues.[5,9,12–14] Our own efforts towards the synthesis of structurally modified sialic acids have resulted in the preparation of the very potent influenza virus sialidase inhibitor 4-deoxy-4-guanidino-Neu5Ac2en **2**,[11] the 4-deoxy-4-guanidino-Neu5Ac derivative **3**[15] and 7-azido-7-deoxy-Neu5Ac **4**.[16]

Despite the vast number of structurally modified sialic acids reported in the literature in recent years,[4–16] including the C-2 homologated sialic acid analogue **5**,[17] and numerous publications describing the synthesis of chain-extended derivatives of other carbohydrates,[18] it appears that the preparation of C-6 chain-extended sialic acid analogues (*e.g.* **6**) has been somewhat neglected. Whilst this is perhaps due to the structural complexity already present in the C-6 glycerol side chain of Neu5Ac, we felt that such compounds would be valuable in allowing us to gain insight into the ability of enzymes involved in sialic acid metabolism to cope with the extra space requirements of C-6 chain-extended sialic acid analogues.



1 R = NHAc



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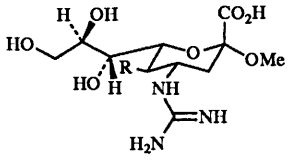

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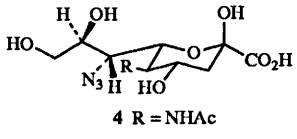
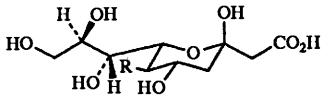


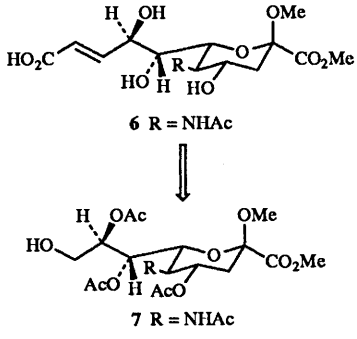
4 R = NHAc



5 R = NHAc

Results and discussion

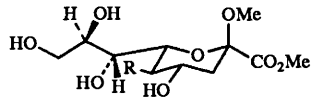
The synthesis of chain-extended carbohydrates has been achieved by many different approaches, although methods which commence from a given carbohydrate necessarily rely on some type of carbon–carbon bond-forming process at the position to be homologated.[18] For the synthesis of a chain-extended sialic acid analogue such as **6**, we felt that the best approach would involve a similar strategy wherein oxidation of the 9-hydroxy-Neu5Ac derivative **7** and subsequent Wittig olefination should furnish the desired chain-extended compounds (Scheme 1).



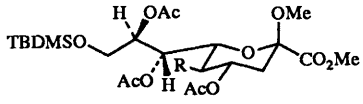
Scheme 1

Accordingly, selective monosilylation of methyl (methyl 5-acetamido-3,5-dideoxy-D-*glycero*-β-D-*galacto*-2-nonulopyranosid)onate [Neu5Ac1,β2Me$_2$ (**8**)][19] [*tert*-butyldimethylsilyl chloride–pyridine (TBDMSCl/py)] followed by acetylation (Ac$_2$O/py) provided the known[12] 9-*O*-silylated compound **9** in 90% overall yield from compound **8**. Careful desilylation of compound **9** (80% aq. HOAc; 50 °C; 20 min) furnished the desired 9-hydroxy-Neu5Ac derivative **7** in 81% yield. The conditions for this deprotection are quite critical, as higher temperatures or longer reaction times result in desilylation and concomitant acetate migration from the 8-position to the 9-position to give the 8-hydroxy-Neu5Ac derivative **10**. Others,[12] as well as ourselves,[20] have used this simple acetate migration

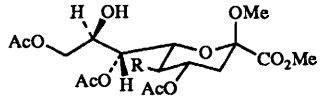
deliberately to prepare the 8-hydroxy derivative **10**. Indeed, even under the conditions described a small amount (~5% by ^{1}H NMR integration) of the isomeric alcohol **10** is formed and is extremely difficult to separate from compound **7** by column chromatography.



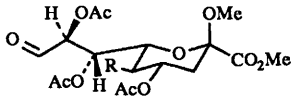
8 R = NHAc



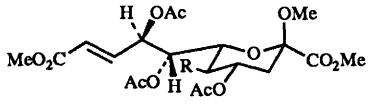
9 R = NHAc



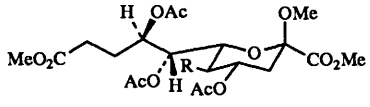
10 R = NHAc



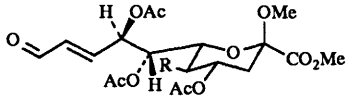
11 R = NHAc



12 R = NHAc



13 R = NHAc



14 R = NHAc

Swern oxidation of primary alcohol **7** provided the unstable 9-aldehyde derivative **11** of Neu5Ac in mediocre yield (42%). Since it appeared that this disappointing yield was primarily due to decomposition of the aldehyde **11** during isolation and purification, it was decided to perform the Wittig olefination on the crude 9-aldehyde of Neu5Ac. Thus, Swern oxidation of compound **7**, filtration of the total reaction product through a short column of silica gel, and then exposure of the partially purified aldehyde **11** in CH_2Cl_2 to methoxycarbonylmethylene(triphenyl)phosphorane at room temperature furnished the α,β-unsaturated ester **12** in 58% yield as a 1:1 mixture of inseparable geometrical isomers. Substituting the solvent CH_2Cl_2 for toluene in the Wittig olefination reaction gave the novel C_{11} chain-extended Neu5Ac derivative **12** in a much improved 71% yield (from **7**) as a 7:1 (*E*,*Z*) mixture of geometrical isomers. That the major component of this isomeric mixture was the *E* isomer was apparent from examination of the relevant coupling constants observed in the ^{1}H NMR spectrum of compound **12**. Thus, signals at δ 6.05 and 7.12 due to 10-H and 9-H, respectively, for the major isomer show a mutual coupling of 15.8 Hz, whereas the same protons in the minor isomer exhibit resonances at δ 5.95 (10-H) and 6.24 (9-H) with a mutual coupling of 11.6 Hz.

Importantly, the overall yield of the α,β-unsaturated ester **12** is 52% from the readily available Neu5Acl,β2Me$_2$ **8**, making this an attractive preparative route into these chain-extended analogues of Neu5Ac. Hydrogenation of enoate **12** (H_2/10% palladium on carbon) afforded the fully saturated C_{11} chain-extended Neu5Ac derivative **13** in 93% yield after chromatography and crystallisation.

In an attempt to introduce different functionality at the terminus of the C-6 side chain of Neu5Ac, Wittig condensation of the crude aldehyde **11**, prepared in the same way as described above, with (triphenylphosphoranylidene)acetaldehyde in toluene at room temperature gave the α,β-unsaturated aldehyde **14** in 55% yield from **7**. The lower yield in this instance is possibly due to two contributing factors. The aldehydic phosphorane used in this reaction is less reactive than its ester counterpart[21] and therefore required longer reaction times (40 h, compared with 15 h in the synthesis of compound **12**). Since the 9-aldehyde derivative **11** of Neu5Ac is relatively unstable the extended reaction time, and hence possible decomposition of compound **11**, may well have contributed to the lower yield of the α,β-unsaturated aldehyde **14**. Secondly, although the α,β-unsaturated aldehyde **14** is a relatively stable amorphous mass when pure, it appeared that some degree of decomposition occurred during the isolation and purification process.

The preparation of the three chain-extended compounds **12**, **13** and **14**, in good overall isolated yield from a readily available precursor, represents the first reported synthesis of C_{11} analogues of *N*-acetylneuraminic acid. The application of this methodology to the synthesis of more complex sialic acid analogues is currently being investigated.

Experimental

General

Mps were determined on a Gallenkamp melting point apparatus and are uncorrected. ^{1}H and ^{13}C spectra were recorded using a Brüker AM-300 spectrometer unless indicated otherwise. *J*-Values are given in Hz. Two-dimensiona! correlation-shift spectroscopy experiments were recorded using the following parameters: DQF-COSY–16 scans, 512 slices, relaxation delay 4.0 s, 2 K data points transformed to 1 K × 1 K matrix, ssb 60° window, Qpol polynomial correction to fid prior to Fourier transformation; ^{1}H–^{13}C HMQC–48 scans, 256 slices, relaxation delay 2.5 s, 2K data points transformed to 1 K × 1 K matrix, ssb 90° window, Qpol polynomial correction to fid prior to Fourier transformation; ^{1}H–^{13}C HMBC–48 scans, 256 slices, relaxation delay 2.5 s, 2 K data points transformed to 1 K × 1 K matrix, ssb 90° window, Qpol polynomial correction to fid prior to Fourier transformation. Mass spectra were obtained using a JEOL JMS-DX 300 mass spectrometer. IR spectra were recorded on an Hitachi 270-30 spectrophotometer as KBr discs. Optical rotations were measured at 25 °C using a JASCO DIP-370 polarimeter. $[\alpha]_D$-values are given in units of 10^{-1} deg cm^2 g^{-1}. Microanalyses were performed by the Australian Microanalytical Service, Notting Hill, Victoria, or the Chemical and Microanalytical Service, Essendon, Victoria.

Methyl (methyl 5-acetamido-4,7,8-tri-*O*-acetyl-9-*O*-(*tert*-butyldimethylsilyl)-3,5-dideoxy-D-*glycero*-β-D-*galacto*-2-nonulopyranosid)onate 9

TBDMSCl (2.82 g, 18.7 mmol) was added to a solution of Neu5Acl,β2Me$_2$ **8** (3.50 g, 10.4 mmol) in pyridine (30 cm^3) at 0 °C under N_2. After stirring of the mixture for 3 h at room temperature, MeOH (3 cm^3) was added and the mixture was concentrated to a yellow syrup. The crude reaction mixture was then taken up in pyridine (30 cm^3)–Ac_2O (15 cm^3) and the mixture was stirred overnight at room temperature. After the addition of MeOH (~0.5 cm^3) the mixture was again concentrated to a yellow syrup, and purified by column chromatography on silica gel [EtOAc–hexane (3:1); R_f 0.4] and recrystallisation (Et_2O–hexane) gave the 9-O-*silyl com-*

pound **9** as needles (5.39 g, 90%), mp 112–115 °C (Found: C, 52.2; H, 7.7; N, 2.3. Calc. for $C_{25}H_{43}NO_{12}Si$: C, 52.0; H, 7.5; N, 2.4%); $[\alpha]_D$ −47.4 (*c* 2.13, $CHCl_3$); ν_{max}/cm^{-1} 1746, 1664, 1552, 1438, 1370, 1276, 1128 and 1166; $\delta_H(CDCl_3)$ −0.05 and −0.04 (2 × 3 H, 2 s, 2 × SiMe), 0.81 (9 H, s, SiBu^t), 1.86 (3 H, s, AcN), 1.99, 2.04 and 2.09 (3 × 3 H, 3 s, 3 × AcO), 2.41 (1 H, dd, $J_{3e,3a}$ 12.9, $J_{3e,4}$ 4.9, 3e-H), 3.23 (3 H, s, OMe), 3.64 (1 H, dd, $J_{9,9'}$ 11.4, $J_{9,8}$ 7.0, 9-H), 3.79 (3 H, s, CO_2Me), 3.94 (1 H; dd, $J_{6,5}$ 10.6, $J_{6,7}$ 1.8, 6-H), 4.03 (1 H, ddd, $J_{5,6} = J_{5,4} = J_{5,NH}$ 10.6, 5-H), 4.09 (1 H, dd, $J_{9',9}$ 11.4, $J_{9',8}$ 2.9, 9'-H), 5.08 (1 H, ddd, $J_{8,9}$ 7.0, $J_{8,7}$ 4.5, $J_{8,9'}$ 2.9, 8-H), 5.26 (1 H, ddd, $J_{4,3a} = J_{4,5}$ 10.6, $J_{4,3e}$ 4.9, 4-H), 5.35 (1 H, dd, $J_{7,8}$ 4.5, $J_{7,6}$ 1.8, 7-H) and 5.49 (1 H, d, $J_{NH,5}$ 10.6, NH); $\delta_C(CDCl_3)$ −5.5 and −5.4 (2 × SiMe), 18.1 (Si*C*Me$_3$) 20.8, 20.9 and 21.0 [3 × OC(O)*Me*], 23.0 [NC(O)*Me*], 25.7 (SiC*Me*$_3$), 37.3 (C-3), 49.2 (OMe), 51.1 (CO_2*Me*), 52.7 (C-5), 61.4 (C-9), 68.6, 68.9, 71.4 and 74.7 (C-4, - 6, -7 and -8), 98.9 (C-2), 167.4 (C-1) and 170.2, 170.3, 170.4 and 171.0 (3 × O*C*(O)Me and N*C*(O)Me); FAB MS *m/z* 578 ([M + 1]$^+$, 22%), 547 (32), 519 (28), 486 (100), 366 (32), 252 (39), 196 (93).

Methyl (methyl 5-acetamido-4,7,8-tri-*O*-acetyl-3,5-dideoxy-D-*glycero*-β-D-*galacto*-2-nonulopyranosid)onate 7

A solution of the 9-*O*-silyl ether **9** (2.20 g, 3.81 mmol) in 80% aq. acetic acid (30 cm^3) was stirred at 50 °C for 20 min before being concentrated under reduced pressure. Toluene (25 cm^3) was added and the mixture was concentrated to a syrup. Column chromatography on silica gel [EtOAc–MeOH (35:1)] gave unchanged 9-*O*-silyl ether **9** (R_f 0.8) (0.42 g) and the 9-hydroxy compound **7** (R_f 0.3) [1.16 g, 66%, 81% based on consumed substrate **9**] contaminated with small amounts (~ 5%) of the 8-hydroxy compound **10**. This material was used without further purification in the following reactions. For characterisation purposes, further column chromatography on silica gel [EtOAc–MeOH, (40:1)] gave the 8-*hydroxy compound* **10** (R_f 0.30) and the desired 9-*hydroxy compound* **7** (R_f 0.28). *Methyl* (*methyl* 5-*acetamido*-4,7,8-*tri*-O-*acetyl*-3,5-*dideoxy*-D-glycero-β-D-galacto-2-*nonulopyranosid*)*onate* **7** was obtained as plates, mp 82–86 °C (Found: C, 49.3; H, 6.45; N, 3.0. $C_{19}H_{29}NO_{12}$ requires C, 49.2; H, 6.3; N, 3.0%); $[\alpha]_D$ −45.3 (*c* 0.93, $CHCl_3$); ν_{max}/cm^{-1} 3500br, 1746, 1664, 1548, 1372, 1230 and 1032; $\delta_H(CDCl_3)$ 1.86 (1 H, dd, $J_{3a,3e}$ 12.8, $J_{3a,4}$ 11.3, 3a-H), 1.87 (3 H, s, AcN), 2.00, 2.06 and 2.18 (3 × 3 H, 3 s, 3 × AcO), 2.41 (1 H, dd, $J_{3e,3a}$ 12.8, $J_{3e,4}$ 4.9, 3e-H), 3.18 (3 H, s, OMe), 3.52 (1 H, dd, $J_{9,9'}$ 13.1, $J_{9,8}$ 2.0, 9-H), 3.79 (3 H, s, CO_2Me), 3.86 (1 H, dd, $J_{6,5}$ 10.3, $J_{6,7}$ 1.8, 6-H), 3.97 (1 H, dd, $J_{9',9}$ 13.1, $J_{9',8}$ 3.4, 9'-H), 4.16 (1 H, ddd, $J_{5,6} = J_{5,4} = J_{5,NH}$ 10.3, 5-H), 5.01 (1 H, ddd, $J_{8,7}$ 7.0, $J_{8,9'}$ 3.4, $J_{8,9}$ 2.0, 8-H), 5.21 (1 H, ddd, $J_{4,3a}$ 11.3, $J_{4,5}$ 10.3, $J_{4,3e}$ 4.9, 4-H), 5.24 (1 H, dd, $J_{7,8}$ 7.0, $J_{7,6}$ 1.8, 7-H) and 5.43 (1 H, d, $J_{NH,5}$ 10.3, NH); $\delta_C(CDCl_3)$ 20.8, 20.9 and 21.0 [3 × OC(O)*Me*], 23.0 [NC(O)*Me*], 37.3 (C-3), 49.2 (OMe), 51.1 (CO_2*Me*), 52.7 (C-5), 60.0 (C-9), 68.1, 68.8, 71.2 and 73.4 (C-4, -6, -7 and -8), 98.8 (C-2), 167.4 (C-1) and 170.3, 170.4, 171.0 and 171.8 [3 × O*C*(O)Me, N*C*(O)Me]; FAB MS *m/z* 464 ([M + 1]$^+$, 20%), 432 (34), 404 (21), 372 (100), 252 (24), 196 (43), 193 (48) and 126 (86).

Methyl (*methyl* 5-*acetamido*-4,7,9-*tri*-O-*acetyl*-3,5-*dideoxy*-D-glycero-β-D-galacto-2-*nonulopyranosid*)*onate* **10** was obtained as needles, mp 89–91 °C (Found: C, 47.4; H, 6.9; N, 2.8. $C_{19}H_{29}NO_{12}\cdot H_2O$ requires C, 47.4; H, 6.5; N, 2.9%); $[\alpha]_D$ −47.9 (*c* 0.92, $CHCl_3$); ν_{max}/cm^{-1} 3400br, 1760, 1664, 1548, 1440, 1374, 1318, 1254, 1166 and 1030; $\delta_H(CDCl_3)$ 1.80 (3 H, s, AcN), 2.01, 2.09 and 2.14 (3 × 3 H, 3 s, 3 × AcO), 2.43 (1 H, dd, $J_{3e,3a}$ 12.9, $J_{3e,4}$ 4.9, 3e-H), 3.32 (3 H, s, OMe), 3.81 (3 H, s, CO_2Me), 4.07–4.22 (5 H, m, 5-, 6-, 8-, 9- and 9'-H), 5.05 (1 H, d, $J_{7,8}$ 7.8, 7-H), 5.20 (1 H, ddd, $J_{4,3a} = J_{4,5}$ 11.6, $J_{4,3e}$ 4.9, 4-H) and 5.71 (1 H, d, $J_{NH,5}$ 9.3, NH); $\delta_C(CDCl_3)$ 20.8 and 20.9 [3 × OC(O)*Me*], 23.0 [NC(O)*Me*], 37.4 (C-3), 49.2 (OMe), 51.1 (CO_2*Me*), 52.7 (C-5), 66.0 (C-9), 68.4, 69.2, 69.6 and 70.6 (C-4, -6, -7 and -8), 98.7 (C-2), 167.6 (C-1) and 170.4, 170.8, 171.0 and 171.4 [3 × O*C*(O)Me, N*C*(O)Me]; FAB MS *m/z* 464 ([M + 1]$^+$, 51%), 432 (71), 372 (99), 210 (60) and 193 (100).

Methyl (methyl 5-acetamido-4,7,8-tri-*O*-acetyl-3,5-dideoxy-8-formyl-D-*glycero*-β-D-*galacto*-2-octulopyranosid)onate 11

DMSO (96 mm^3, 1.35 mmol) was added dropwise to a solution of oxalyl dichloride (75 mm^3, 0.86 mmol) in dry CH_2Cl_2 (2 cm^3) at −78 °C under N_2. A solution of the alcohol **7** (250 mg, 0.54 mmol) in dry CH_2Cl_2 (2 cm^3) was added after 5 min, and the mixture was stirred at −78 °C for 2 h. Et_3N (0.41 cm^3, 2.97 mmol) was added, the cooling bath was removed, and the mixture was allowed to warm to room temperature. The crude reaction mixture was poured onto water (10 cm^3), extracted with CH_2Cl_2 (3 × 10 cm^3), and the combined organic fractions were dried (Na_2SO_4), and concentrated under reduced pressure to afford an orange foam. Column chromatography on silica gel [EtOAc; R_f 0.25, followed by $CHCl_3$–MeOH (25:1); R_f 0.2] gave the 9-*aldehyde* **11** (104 mg, 42%) as an unstable amorphous mass, mp 65–70 °C $[\alpha]_D$ −37.6 (*c* 0.97, $CHCl_3$); ν_{max}/cm^{-1} 1752, 1664, 1544, 1438, 1370, 1232 and 1032; $\delta_H(CDCl_3)$ 1.90 (3 H, s, AcN), 2.02, 2.13 and 2.15 (3 × 3 H, 3 s, 3 × AcO), 2.46 (1 H, dd, $J_{3e,3a}$ 12.9, $J_{3e,4}$ 5.0, 3e-H), 3.23 (3 H, s, OMe), 3.82 (3 H, s, CO_2Me), 3.98 (1 H, dd, $J_{6,5}$ 10.3, $J_{6,7}$ 2.2, 6-H), 4.21 (1 H, ddd, $J_{5,6} = J_{5,4} = J_{5,NH}$ 10.3, 5-H), 5.28 (1 H, ddd, $J_{4,3a}$ 11.3, $J_{4,5}$ 10.3, $J_{4,3e}$ 5.0, 4-H), 5.30 (1 H, d, $J_{8,7}$ 5.1, 8-H), 5.44 (1 H, dd, $J_{7,8}$ 5.1, $J_{7,6}$ 2.2, 7-H), 5.62 (1 H, d, $J_{NH,5}$ 10.3, NH) and 9.67 (1 H, s, 9-H); $\delta_C(CDCl_3)$ 20.4, 20.7 and 20.8 [3 × OC(O)*Me*], 23.0 [NC(O)*Me*], 37.3 (C-3), 49.2 (OMe), 51.2 (CO_2*Me*), 52.8 (C-5), 68.3, 68.7, 71.5 and 72.2 (C-4, -6, -7 and -8), 99.0 (C-2), 167.1 (C-1), 169.7, 170.3, 170.4 and 171.1 [3 × O*C*(O)Me, N*C*(O)Me] and 194.6 (C-9); FAB MS *m/z* 461 (M$^+$, 25%), 443 ([M − H_2O]$^+$, 11), 429 ([M − MeOH]$^+$, 37), 401 ([M − CO_2Me]$^+$, 68), 369 (100), 328 (43), 296 (45), 208 (65), 196 (61) and 126 (90).

Methyl (methyl 5-acetamido-4,7,8-tri-*O*-acetyl-9,10-didehydro-3,5,9,10-tetradeoxy-10-methoxycarbonyl-D-*glycero*-β-D-*galacto*-2-deculopyranosid)onate 12

DMSO (535 mm^3, 7.54 mmol) was added dropwise to a solution of oxalyl dichloride (440 mm^3, 5.09 mmol) in dry CH_2Cl_2 (10 cm^3) at −78 °C under N_2. A solution of the alcohol **7** (1.40 g, 3.02 mmol) in dry CH_2Cl_2 (10 cm^3) was added after 5 min, and the mixture was stirred at −78 °C for 2 h. Et_3N (2.3 cm^3, 16.5 mmol) was added, the cooling bath was removed, and the mixture was allowed to warm to room temperature. The crude reaction mixture was filtered through a short column of silica gel (4 × 2 cm) with $CHCl_3$–MeOH (25:1) as eluent. The combined aldehyde-containing fractions were concentrated under reduced pressure to afford a pale yellow syrup, which was dissolved in toluene (25 cm^3), methoxycarbonylmethylene(triphenyl)phosphorane (1.73 g, 5.17 mmol) was added, and the mixture was stirred at room temperature for 15 h before being concentrated under reduced pressure. Column chromatography on silica gel [EtOAc; R_f 0.35, followed by $CHCl_3$–MeOH (25:1); R_f 0.30] gave the α,β-*unsaturated ester* **12** (1.11 g, 71%) as a mixture of geometrical isomers (*E*:*Z*, 7:1) as an amorphous mass, mp 74–76 °C (Found: C, 51.2; H, 6.4; N, 2.6. $C_{22}H_{31}NO_{13}$ requires C, 51.05; H, 6.0; N, 2.7%); $[\alpha]_D$ −41.8 (*c* 0.77, $CHCl_3$); ν_{max}/cm^{-1} 1750, 1666, 1548, 1438, 1372, 1274, 1234 and 1032; $\delta_H(CDCl_3)$ (*E*-isomer) 1.87 (3 H, s, AcN), 2.01 and 2.09 (9 H, 2 s, 3 × AcO), 2.45 (1 H, dd, $J_{3e,3a}$ 12.9, $J_{3e,4}$ 4.9, 3e-H), 3.24 (3 H, s, OMe), 3.76 (3 H, s, CO_2Me), 3.86 (3 H, s, CO_2Me), 3.94 (1 H, dd, $J_{6,5}$ 10.4, $J_{6,7}$ 2.3, 6-H), 4.17 (1 H, ddd, $J_{5,6} = J_{5,4} = J_{5,NH}$ 10.4, 5-H), 5.25 (1 H, ddd, $J_{4,3a}$ 11.4, $J_{4,5}$ 10.4, $J_{4,3e}$ 4.9, 4-H), 5.33 (1 H, dd, $J_{7,8}$ 4.6, $J_{7,6}$ 2.3, 7-H), 5.43 (1 H, d, $J_{NH,5}$ 10.4, NH), 5.61 (1 H, ddd, $J_{8,9}$ 5.4, $J_{8,7}$ 4.6, $J_{8,10}$ 1.6, 8-H), 6.05 (1 H, dd, $J_{10,9}$ 15.8, $J_{10,8}$ 1.6, 10-H) and 7.12 (1 H, dd, $J_{9,10}$ 15.8, $J_{9,8}$ 5.4, 9-H); (*Z*-isomer) 1.90 (3 H, s, AcN), 2.04 and 2.10 (9 H, 2 s, 3 × AcO), 2.42 (1 H, dd, $J_{3e,3a}$ 12.9, $J_{3e,4}$ 5.0, 3e-H), 3.16 (3 H,

s, OMe), 3.75 (3 H, s, CO_2Me), 3.81 (3 H, s, CO_2Me), 3.87 (1 H, dd, $J_{6,5}$ 10.4, $J_{6,7}$ 2.6, 6-H), 4.20 (1 H, ddd, $J_{5,6} = J_{5,4} = J_{5,NH}$ 10.4, 5-H), 5.23 (1 H, ddd, $J_{4,3a}$ 11.4, $J_{4,5}$ 10.4, $J_{4,3e}$ 5.0, 4-H), 5.38 (1 H, dd, $J_{7,8}$ 5.8, $J_{7,6}$ 2.6, 7-H), 5.43 (1 H, d, $J_{NH,5}$ 10.4, NH), 5.95 (1 H, dd, $J_{10,9}$ 11.6, $J_{10,8}$ 1.0, 10-H), 6.24 (1 H, dd, $J_{9,10}$ 11.6, $J_{9,8}$ 8.8, 9-H) and 6.56 (1 H, ddd, $J_{8,9}$ 8.8, $J_{8,7}$ 5.8, $J_{8,10}$ 1.0, 8-H); $\delta_C(CDCl_3)$ (*E* isomer) 20.7 and 20.8 [3 × OC(O)*Me*], 23.0 [NC(O)*Me*], 37.3 (C-3), 49.4 (OMe), 50.9 (CO_2Me), 51.5 (CO_2Me), 52.5 (C-5), 68.7, 69.0, 70.6 and 72.3 (C-4, -6, -7 and -8), 98.8 (C-2), 123.2 (C-10), 140.8 (C-9), 166.0 (C-11), 167.2 (C-1) and 169.9, 170.3, 170.4 and 171.0 [3 × O*C*(O)Me, N*C*(O)Me]; FAB MS *m/z* 518 ($[M + 1]^+$, 7%), 486 ($[M - MeOH]^+$, 10), 458 (12), 426 (72), 196 (100), 139 (31) and 126 (76).

Methyl (methyl 5-acetamido-4,7,8-tri-*O*-acetyl-3,5,9,10-tetradeoxy-10-methoxycarbonyl-D-*glycero*-β-D-*galacto*-2-deculopyranosid)onate 13

A solution of the α,β-unsaturated ester **12** (0.45 g, 0.87 mmol) in EtOH (10 cm^3) containing 10% palladium on carbon (45 mg) was stirred under an atmosphere of hydrogen for 15 h at room temperature before being filtered through Celite; the filter was washed with EtOH (3 × 10 cm^3), and the combined EtOH fractions were concentrated under reduced pressure. Column chromatography on silica gel (EtOAc; R_f 0.38) and crystallisation (Et_2O–hexane) gave the *saturated ester* **13** (0.42 g, 93%) as needles; mp 118–121 °C (Found: C, 51.0; H, 6.4; N, 2.75. $C_{22}H_{33}NO_{13}$ requires C, 50.85; H, 6.4; N, 2.7%); $[\alpha]_D$ −17.1 (*c* 0.94, $CHCl_3$); ν_{max}/cm^{-1} 1742, 1720, 1680, 1544, 1436, 1368, 1272, 1230, 1166 and 1032; $\delta_H(CDCl_3)$ 1.86 (3 H, s, AcN), 2.00, 2.03 and 2.14 (3 × 3 H, 3 s, 3 × AcO), 2.33–2.45 (5 H, m, 3e-, 9-, 9′-, 10- and 10′-H), 10-H_2), 3.25 (3 H, s, OMe), 3.63 (3 H, s, CO_2Me), 3.79 (3 H, s, CO_2Me), 3.91 (1 H, dd, $J_{6,5}$ 10.4, $J_{6,7}$ 2.3, 6-H), 4.12 (1 H, ddd, $J_{5,6} = J_{5,4} = J_{5,NH}$ 10.4, 5-H), 4.98–5.04 (1 H, m, 8-H), 5.22 (1 H, ddd, $J_{4,3a}$ 11.2, $J_{4,5}$ 10.4, $J_{4,3e}$ 4.9, 4-H), 5.29 (1 H, dd, $J_{7,8}$ 3.0, $J_{7,6}$ 2.3, 7-H) and 5.48 (1 H, d, $J_{NH,5}$ 10.4, NH); $\delta_C(CDCl_3)$ 20.7 and 20.8 [3 × OC(O)*Me*], 22.8 [NC(O)*Me*], 24.4 (C-9), 29.9 (C-10), 37.1 (C-3), 49.0 (OMe), 51.1 (CO_2Me), 51.4 (CO_2Me), 52.5 (C-5), 68.9, 69.5, 71.8 and 73.6 (C-4, -6, -7 and -8), 98.7 (C-2), 167.1 (C-1), 170.2, 170.4, 170.9 and 171.0 [3 × O*C*(O)Me, N*C*(O)Me] and 173.2 (C-11); FAB MS *m/z* 520 ($[M + 1]^+$, 11%), 488 ($[M - MeOH]^+$, 11), 460 (14), 428 (100), 308 (17), 266 (27), 196 (90) and 126 (74).

Methyl (methyl 5-acetamido-4,7,8-tri-*O*-acetyl-9,10-didehydro-3,5,9,10-tetradeoxy-10-formyl-D-*glycero*-β-D-*galacto*-2-deculopyranosid)onate 14

DMSO (96 mm^3, 1.35 mmol) was added dropwise to a solution of oxalyl dichloride (75 mm^3, 0.86 mmol) in dry CH_2Cl_2 (3 cm^3) at −78 °C under N_2. A solution of the alcohol **7** (250 mg, 0.54 mmol) in dry CH_2Cl_2 (2 cm^3) was added after 5 min, and the mixture was stirred at −78 °C for 2 h. Et_3N (0.41 cm^3, 2.97 mmol) was added, the cooling bath was removed, and the mixture was allowed to warm to room temperature. The crude reaction mixture was filtered through a short column of silica gel (4 × 2 cm) with $CHCl_3$–MeOH (25:1) as eluent. The combined aldehyde-containing fractions were concentrated under reduced pressure to afford a pale yellow syrup, which was dissolved in toluene (5 cm^3), (triphenylphosphoranylidene)acetaldehyde (245 mg, 0.81 mmol) was added, and the mixture was stirred at room temperature for 40 h before being concentrated under reduced pressure. Column chromatography on silica gel [EtOAc; R_f 0.4, followed by $CHCl_3$–MeOH (25:1); R_f 0.35] gave the α,β-*unsaturated aldehyde* **14** (145 mg, 55%) as an amorphous mass, mp 80–84 °C (Found: C, 49.7; H, 5.8; N, 2.5. $C_{21}H_{29}NO_{12}\cdot H_2O$ requires C, 49.9; H, 6.2; N, 2.8%); $[\alpha]_D$ −37.7 (*c* 0.94, $CHCl_3$); ν_{max}/cm^{-1} 1748, 1692, 1664, 1546, 1372, 1232 and 1036; $\delta_H(CDCl_3)$ 1.88 (3 H, s, AcN), 2.02, 2.10 and 2.11 (3 × 3 H, 3 s, 3 × AcO), 2.48 (1 H, dd, $J_{3e,3a}$ 13.0, $J_{3e,4}$ 4.9, 3e-H), 3.24 (3 H, s, OMe), 3.83 (3 H, s, CO_2Me), 3.99 (1 H, dd, $J_{6,5}$ 10.4, $J_{6,7}$ 2.2, 6-H), 4.19 (1 H, ddd, $J_{5,6} = J_{5,4} = J_{5,NH}$ 10.4, 5-H), 5.26 (1 H, ddd, $J_{4,3a}$ 11.2, $J_{4,5}$ 10.4, $J_{4,3e}$ 4.9, 4-H), 5.36–5.42 (2 H, m, 7-H and NH), 5.67–5.71 (1 H, m, 8-H), 6.28 (1 H, ddd, $J_{10,9}$ 15.8, $J_{10,11}$ 7.8, $J_{10,8}$ 1.4, 10-H), 7.14 (1 H, dd, $J_{9,10}$ 15.8, $J_{9,8}$ 5.0, 9-H) and 9.61 (1 H, d, $J_{11,10}$ 7.8, 11-H); $\delta_C(CDCl_3)$ 20.7 and 20.8 [3 × OC(O)*Me*], 23.0 [NC(O)*Me*], 37.2 (C-3), 49.2 (OMe), 51.2 (CO_2Me), 52.7 (C-5), 68.7, 69.5, 71.8 and 72.7 (C-4, -6, -7 and -8), 98.9 (C-2), 133.3 (C-10), 150.4 (C-9), 167.0 (C-1), 170.0, 170.2 and 171.0 [3 × O*C*(O)Me, N*C*(O)Me] and 193.2 (C-11); FAB MS *m/z* 487 (M^+, 9%), 485 (23), 469 ($[M - H_2O]^+$, 5), 455 ($[M - MeOH]^+$, 12), 425 (13), 395 (47), 369 (21), 196 (100) and 126 (94).

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