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The Synthesis of Novel Mimics of the Sialyl Lewis X Determinant

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Abstract: Disaccharide mimics of the sialyl Lewis X (sLe^x) ligands have been prepared as potential antagonists of binding to the lectin domains of the E-selectin adhesion molecule. Versatile derivatives of sialic acid provide an entry to a series of simplified linker groups supporting the fucose and sialyl residues. The stereoselectivity of nucleophilic addition to the fucosyl ketone derivative **7** is determined by the conditions employed; basic and Lewis acid conditions give opposite results[1].

The selectins are a family of cell adhesion-receptor glycoproteins that are implicated in the adhesion of leucocytes to the vascular endothelium [2]. E-selectins mediate the adhesion of circulating neutrophils and monocytes to the cytokine stimulated endothelium of blood vessels, an essential early step in mounting an inflammatory response to an immunological challenge [3]. Blocking this interaction might represent a possible therapy for those pathological conditions in which neutrophil infiltration is excessive or misdirected; among others these include reperfusion injury, ARDS and Crohn's disease [4].

Figure 1

NeuNAcα (2→3)Gal ß(1→4)GlcNAc
Fuc(1→3)↵

NeuNAcα (2→3)Gal ß(1→3)GlcNAc
Fuc(1→3)↵

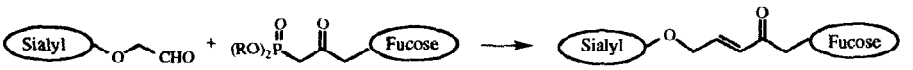
NeuNAcα (2→3)Gal ß(1→4)Glc
Fuc(1→3)↵

sialyl Lewis X (sLe^x) *sialyl Lewis A (sLe^a)* *3' -sialyl-3-fucosyl-lactose*

Recognition occurs by the interaction of the lectin domain of E-selectin with the glycosylated ligands on the inflammatory cell. It would appear that a key epitope [5,6] is formed by the fucose, sialic acid and by parts of the galactose residue since sLe^x [7], sLe^a [8] and 3'-sialyl-3-fucosyl lactose [5] (Figure 1) have all been shown to bind to E-selectin. We were interested in developing antagonists to the binding of ligands to the E-selectin and as part of this investigation we sought to probe the minimum structural components of sLe^x required for binding. As a starting point we chose to keep the functionalities presented to the receptor by the sialic acid and fucose residues and replace the galactose–N-acetylglucosamine unit with a synthetically much simpler linker group. A model of sLe^x derived from nmr data [9] and a comparison with tri- and tetrasaccharide structures in the Cambridge Data Base suggested a 6-carbon atom linker between the C-2 of the sialic acid and the C-4 of the fucose groups might act as a suitable unit. Our model indicated that equatorial substitution at the fucose would be optimal, both to

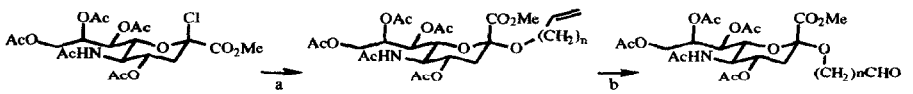
maintain the fucose residue in a chair-like conformation and also to ensure the 4-hydroxyl group is in an axial orientation where it is presumably more accessible to the receptor. A similar approach has recently been used to identify a triterpene glycoside, glycyrrhizin, as an inhibitor of selectin binding[10].

Figure 2



The synthetic strategy involved the addition of a fucosyl ketophosphonate to an aldehyde derivative of sialic acid (Figure 2). This allowed us to involve the very expensive sialic acid in as few synthetic steps as possible, as well as allowing some flexibility in the nature of the linker. For example the enone formed in the condensation can be reduced or hydroxylated as desired.

Scheme 1



3

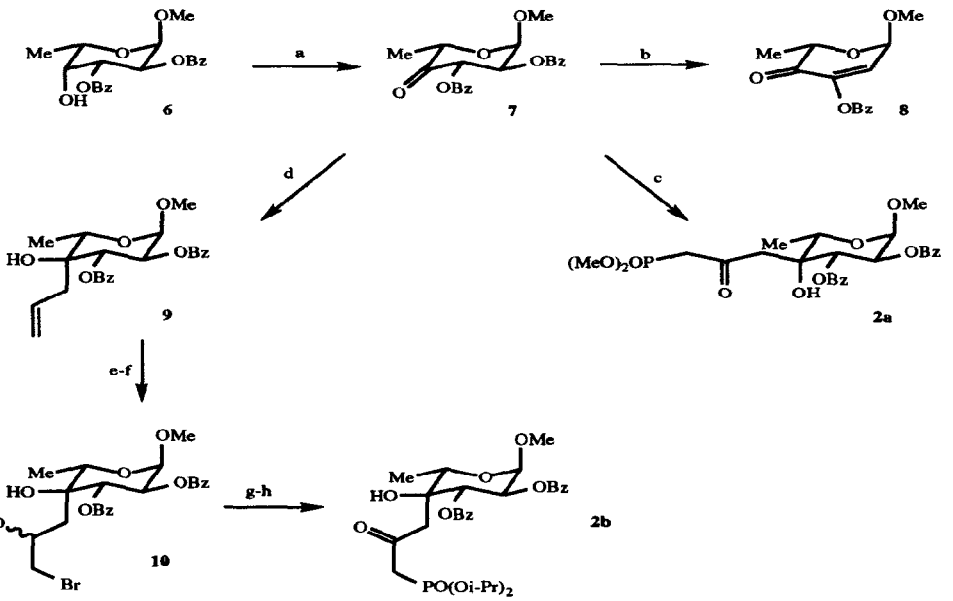
n = 1 1
n = 2 4
n = 3 5

Reagents for 1: a. Silver salicylate/CH_2=$CHCH_2OH$/4Å sieves 95% b. O_3/MeOH 0°C then Me_2S 60%

The aldehyde **1** was constructed in two steps from methyl tetra-O-acetyl α2-chloro-N-acetylneuramimidate[11] (Scheme 1). Reaction with allyl alcohol in the presence of silver salicylate [11] and powdered 4Å sieves gave the α-allyl glycoside **3** (n =1) in 95% yield. Ozonolysis in methanol at 0° followed by a dimethyl sulphide workup gave the sialic acid aldehyde **1** in 55% yield after chromatography on silica. Subsequent to our embarking on this work some further nmr studies on sLe^x using nOe measurements suggested that the 6-carbon linker may not be optimal [6]. To take account of this information the aldehydes **4** and **5** were prepared in a similar manner to that used for **1** by substituting the appropriate alcohols.

The fucose ketophosphonate **2a** was prepared from methyl 2,3-di-O-benzoyl-α-L-fucopyranoside **6** [12] (Scheme 2). Oxidation (pyridinium chlorochromate and 4Å sieves) gave the fucosyl ketone **7** in 80% yield. Elaboration of this ketone to the desired ketophosphonate proved difficult owing to its sensitivity towards base induced elimination of the 2-O-benzoyl group. For example reaction with ethyl triphenylphosphonium acetate in benzene gave enone **8** as the only identifiable product in 20% yield. We therefore decided to add a 3-carbon nucleophile to the *Si* face of ketone **7** under Lewis acid conditions and then develop this into an equatorial ketophosphonate group. However, although addition of allylsilane using $TiCl_4$[13] or $SnCl_4$ in dichloromethane at -78°C gave excellent yields of a homoallylic alcohol **9**, nOe experiments showed that attack had occurred exclusively from the face opposite to that required[14]. It would appear that the Lewis acid complex formed between the keto and methoxy groups is able to maintain the fucosyl ketone in a boat-like reactive conformation thereby leading to attack solely from the *Re* face in contrast to direct nucleophilic attack from the *Si* face (Figure 3).

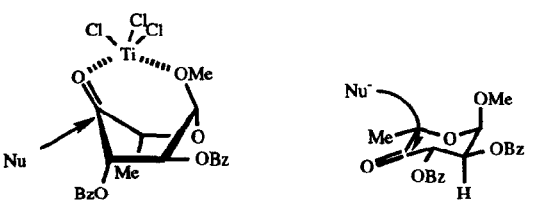
Scheme 2



a. PCC CH_2Cl_2 4Å sieves 12hr 80% b. Ph_3PCHCO_2Et C_6H_6 20% c. (1) $CH_3COCH_2PO(OMe)_2$, NaH-BuLi THF 0°C (2) $ClTi(O_i\text{-}Pr)_3$ -78°C (3) 7 -78°C 2hr 43% d. $CH_2{=}CHCH_2SiMe_3$ $TiCl_4$ CH_2Cl_2 -78°C 2hr 95% e. mCPBA CH_2Cl_2 48hr 92% f. Li_2NiBr_4 THF 2hr 98% g. PCC CH_2Cl_2 4Å sieve 12hr 78% h. $P(O_i\text{-}Pr)_3$ 80°C 2hr 39%.

Although we had obtained the wrong isomer it was decided to take this through to the axial ketophosphonate **2b** with the intention of inverting the C-4 centre at a later stage to give an equatorial derivative. Axial derivatives of **2b** would be of value in their own right both in providing structural comparisons against the equatorial isomers and also as controls in the biological evaluation.

Figure 3

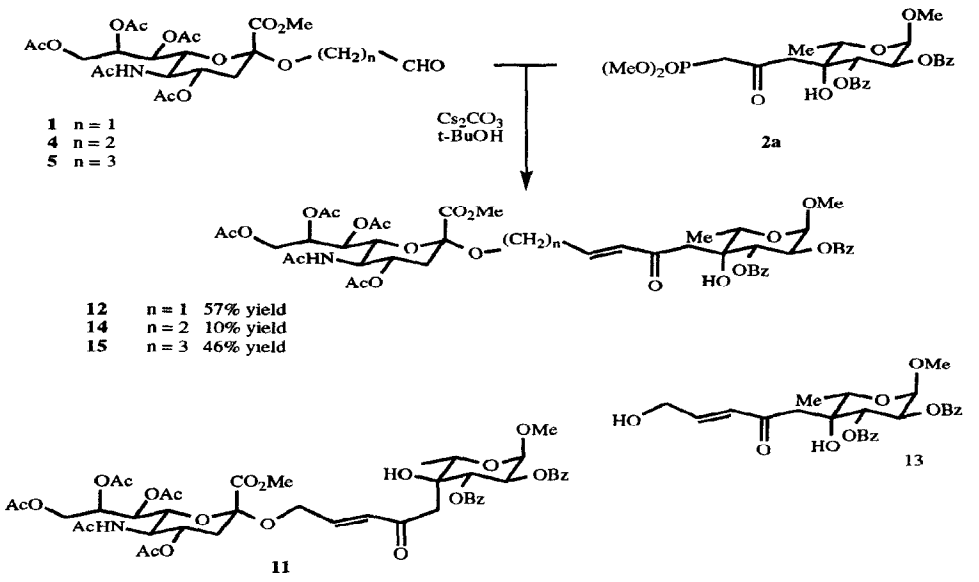


Epoxidation with mCPBA (92%), followed by treatment with Li_2NiBr_4 [15] was uneventful and gave a pair of diastereomeric bromohydrins **10** in 98% yield. Oxidation to the α-bromoketone with PCC and molecular sieves (78%) followed by an Arbusov reaction with triisopropylphosphite [16] at 80°C gave the ketophosphonate **2b** in 39% yield after chromatographic separation from the Perkow products. This compound reacted with the aldehyde **1** in t-butanol in the presence of Cs_2CO_3 to give the disaccharide **11**, the axial epimer of our desired target. Unfortunately, all attempts to invert the 4-hydroxy group, either in the alkene **9** or the ketophosphonate

2b, were unsuccessful so we went back to look at basic additions to the ketone **7**. Addition of the lithium dianion of dimethyl 2-oxopropylphosphonate[17] gave a 15% yield of the desired ketophosphonate **2a** with no contaminating axial by-product. The stereochemistry at C-4 was assigned from nOe enhancements of 3% and 5% observed from the axial H-3 and H-5 protons of the fucose ring to the protons of the methylene group between the ketone and C-4. No enhancement was observed between the CH_2 group and H-2 in contrast to that observed with **9**[14]. This result led us to examine the effects of reducing the basicity of the nucleophile by the addition of metal additives. In the presence of $CeCl_3$[18] the yield of **2a** rose to 29% but this was further improved by the use of $TiCl(Oi\text{-}Pr)_3$[19]. Thus the addition of one equivalent of the ketone **7** to two equivalents of the sodium-lithium dianion of dimethyl 2-oxopropylphosphonate in the presence of 1.2 equivalents of chlorotriisopropoxytitanium in THF at -78°C gave only the desired fucose ketophosphonate **2a** in 43% yield.

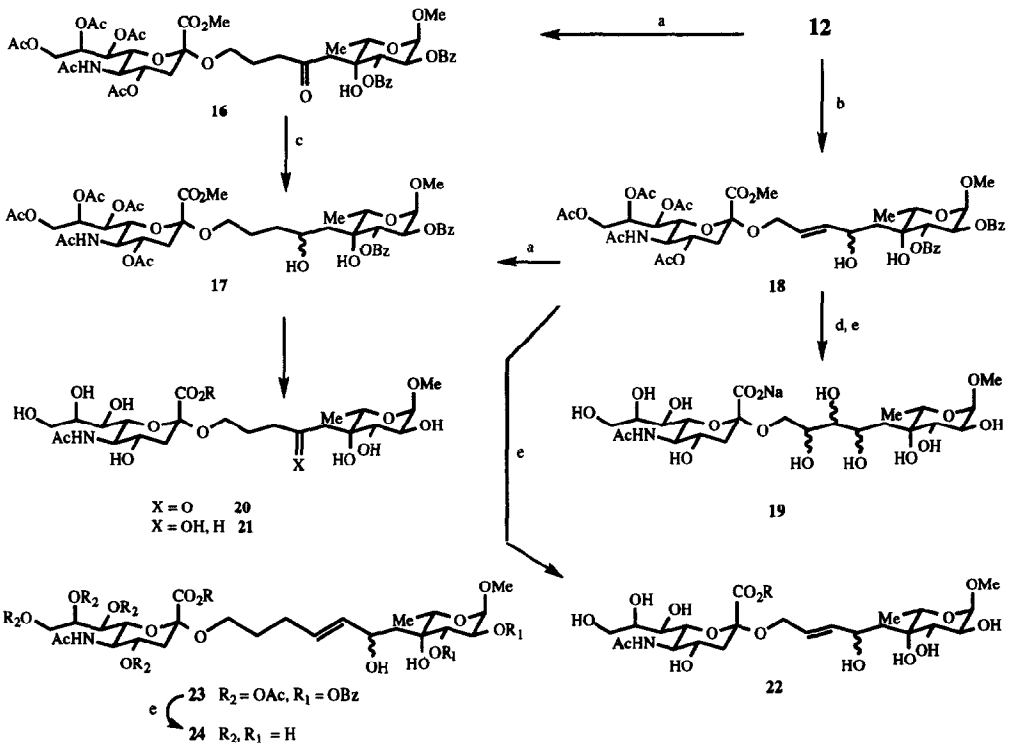
Owing to the base sensitive nature of both the sialic acid aldehyde **1** and the enone product **12** the Wadsworth-Emmons reaction proved to be unexpectedly demanding. Only one of the conditions we examined, Cs_2CO_3 in t-butanol [20], gave consistently satisfactory results [21]. The reaction of **1** with **2a** was relatively fast giving an optimal yield (57%) of the enone **12** after 2 hr at room temperature. Longer reaction times led to diminishing yields presumably as a result of hydrolysis of the sialic acid to give the enone alcohol **13**, which can be isolated as a by-product of the reaction. In contrast the reactions with the longer chain sialic acid aldehydes **4** and **5**, which are no longer activated towards nucleophilic attack by the α-ether oxygen, were much slower. The enone **15** is produced in a yield of 46% after 2 days at room temperature while only a 10% yield of the enone **14** has been achieved.

Scheme 3



Further elaboration of the enone **12** proved straightforward (Scheme 4). Catalytic hydrogenation gave the ketone **16** in quantitative yield and this was further reduced to the alcohols **17**. The enols **18** can be obtained by $NaBH_4$-$CeCl_3$ reduction of the enone **12** and these were then hydroxylated with OsO_4 to give, after removal of the O-acyl protecting groups and hydrolysis of the ester, a mixture of the four decols **19**. It was envisaged that the polyhydroxylated linker of the decols **19** might act as an unsophisticated mimic of parts of the functionality of the Gal–GlcNAc unit and so they were evaluated as mixtures in the biological assays. Removal of the acyl protecting groups (NaOMe-MeOH) from **16**, **17** and **18** and hydrolysis of the ester to the sodium salt gave the other desired final products **20-22**. The enone **15**, which incorporates the extended eight carbon linker, was treated in a similar manner to give the enols **23** from which the target compounds **24** were obtained following removal of the protecting groups.

Scheme 4



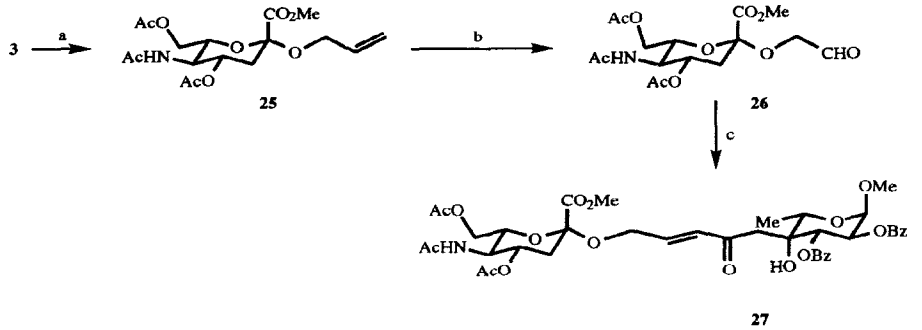
a. H_2 Pd/C MeOH 100% b. $NaBH_4$-$CeCl_3$ MeOH 77% c. $NaBH_4$ MeOH 100% d. OsO_4 t-BuOOH Et_4NOAc acetone 41% e. (1) NaOMe MeOH (2) NaOD D_2O for R = Me → Na

Sialic Acid modifications.

The cost of sialic acid along with its high functionalisation make this residue an attractive area for 'structural minimisation'. Also structure activity studies have indicated that much of the effect of this sugar is attributable to the charge carrying carboxylate function [8,22]. We wished to combine a simple analogue with our backbone linker chemistry so we chose to convert the C7-C9 glycerol sidechain to a smaller hydroxymethyl group. Periodate cleavage and borohydride reduction of the glycerol sidechain of the deprotected ether of **3** (n = 1) gave

the simplified derivative **25**. Following reprotection and ozonolysis the aldehyde **26** was prepared as above. Wadsworth-Emmons reaction with the ketophosphonate **2a** gave the enone **27** in yields similar to that obtained with the parent aldehyde **1** (Scheme 5). Further derivatives from this simplified series are being explored.

Scheme 5



a. (1) NaOMe MeOH (2) $NaIO_4$ $NaBH_4$ on Dowex (3) TMSCl MeOH (4) Ac_2O DMAP pyridine b. O_3 DMS c. Cs_2CO_3 **2a** t-BuOH

Both the methyl ester and the sodium carboxylate salt of the 6-carbon liked ketone **20** blocked the adhesion of an sLe^x myeloid cell line U937 to activated endothelial cell cultures at twenty five and thirty-fold higher concentrations than sLe^x. Derivatives with an extended linker such as **23** were not effective. Full biological details will be published elsewhere [23].

Acknowledgements

We wish to thank Dr E.Hodgkin for the modelling studies and Miss E.M.Morrice and Richard Todd for chemical support.

Experimental

All solvents and reagents used were Analar grade. Tetrahydrofuran was dried by heating under reflux in a still containing sodium metal and benzophenone for several hours under argon and was distilled immediately prior to use. Anhydrous dichloromethane was obtained from Aldrich. Solution transfers, where anhydrous conditions were required, were performed under argon using hypodermic syringes and cannulas. T.l.c. were performed on precoated silica gel plate 60-F254 plates (E. Merck, Darmstadt) and visualised by quenching of the fluorescence and (or) by charring after spraying with 5% anisaldehyde-5% sulphuric acid in ethanol. For "silica gel chromatography" 40-63μM silica gel 60 was used, and the ratio of compound to silica was typically 1:30. Solutions of crude products in organic solvents were dried over $MgSO_4$. The organic solvents were removed on a rotary evaporator equipped with a dry-ice acetone condenser at bath temperatures below 40°C under the vacuum of an oil pump. ^1H nmr spectra were recorded at 250 MHz on a Bruker AC-250. ^{13}C nmr spectra were recorded at 62.8 MHz.

The nmr assignments are annotated as follows; S stands for the sialic acid residue, F for the fucose residue and L for the linker joining the two sugars. The number following the letter represents the atom's position within each of the sugar residues. The numbering system for the linker runs away from the fucose residue, hence L-1 refers to the methylene adjacent to the 4-position of the fucose ring.

Methyl 2-allyl-5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-*D*-glycero-α-*D*-galacto-2-nonulosonate (3). A suspension of silver salicylate (0.46 g, 1.87 mmol), freshly activated powdered 4Å sieves (2.0 g) and methyl β-chloro-tetra-O-4,7,8,9-acetyl-N-acetyl-neuraminidate[9] (1.0 g, 1.87 mmol) was stirred in allyl alcohol (6.7 ml) at room temperature under argon for 5 hr. The crude mixture was filtered through a pad of celite with dichloromethane (2 x 50 ml) and evaporated. The residue was taken up in chloroform (100 ml), washed with 2M sodium bicarbonate solution (2 x 20 ml) and with 5% sodium thiosulphate solution (2 x 10 ml) then dried. Evaporation gave pure *O-allyl-neuraminidate* **3** as a white foam (0.97 g, 1.81 mmol, 93% yield); (Found: C, 51.68; H, 6.02; N, 2.74. $C_{23}H_{33}NO_{13}$ requires C, 51.97; H, 6.26; N, 2.63%.); ^{1}H nmr ($CDCl_3$) δ 5.83 (H, dddd, J = 10.5, 7. 5, and 5 Hz, allyl -CH=), 5.35 (H, m, S-8), 5.30 (H, dd, J = 8.5 and 1.8 Hz, S-7), 5.26 (H, dd, J = 17.0 and 1.5 Hz, =CH_2), 5.14 (H, d, J = 10 Hz, NHAc), 5.13 (H, dd, J = 10.5 and 1.5 Hz), 4.83 (H, m, S-4), 4.27 (H, dd, J = 12.5 and 2.7 Hz, S-9), 4.27 (H, m), 4.03-4.11 (3H, m), 3.84 (H, dd, J = 12.5 and 5.8 Hz, S-9), 3.76 (3H, s, methyl ester), 2.59 (H, dd, 12.0 and 4.8 Hz, S-3e), 1.86, 2.0, 2.02, 2.11, 2.13 (15H, 5 x s, NHAc and OAc); ^{13}C nmr ($CDCl_3$) δ 171.2, 170.9, 170.4, 170.3, 168.5 (S-1), 133.6, 117.4, 98.2 (S-2), 72.5 (S-6), 69.0, 68.5, 67.3, 66.0, 62.3, 49.3, 38.0, 23.1, 21.0, 20.7, 20.6, 20.6.

Methyl 2-(2'-oxoethyl)-5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulosonate (1). **3** (0.42 g, 0.78 mmol) was ozonolysed in dichloromethane-methanol (50 ml, 10 ml) at 0°C for 2 hr. Methyl sulphide (2 ml) was added and the reaction mixture was stood for 8 hr at room temperature before evaporating. The residue was chromatographed on silica, eluant ethyl acetate to give the *aldehyde* **1** as a hygroscopic white foam (0.28 g, 0.52 mmol, 66% yield) (Found: C, 48.41; H, 5.83; N, 2.58. $C_{22}H_{31}NO_{14}$ 0.7 H_2O requires C, 48.39; H, 5.98; N, 2.56%.); ν_{max} (KBr) 1748, 1665, 1547, 1436, 1372, 1228,1129, 1040 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 9.58 (H, s, CHO), 5.62 (H, m), 5.28 (2H, m), 4.89 (H, m), 4.37-3.96 (6H, m), 3.77 (3H, s, OMe), 2.66 (H, dd, H-3e), 2.08 (6H, 2s, 2 x OAc), 2.05 (H, dd, H-3a), 1.98 (6H, 2s, 2 x OAc), 1.84 (3H, s, NHAc).

Methyl 2-(4'-oxobutan-1'-yl)-5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-*D*-glycero-α-*D*-galacto-2-nonulosonate (5). a) A suspension of methyl β-2-chloro-4,7,8,9-tetra-O-acetyl-N-acetyl-neuraminidate (375 mg, 0.74 mmol), silver salicylate (175 mg) and freshly activated powdered 4Å sieves (250 mg) was stirred in dry 4-penten-1-ol (7.6 ml) at room temperature in the dark. The slurry was filtered through celite and washed well with dichloromethane. The filtrate was evaporated *in vacuo*, then the residue was redissolved in dichloromethane (20 ml) and washed with 5% $NaHCO_3$ (aq), 5% sodium thiosulphate (aq), and water. Drying and evaporation gave the *alkene* as a white foam (330 mg, 0.59 mmol, 80% yield); ^{1}H nmr ($CDCl_3$) δ 1.8, 2.0, and 2.1 (15H, 5 x s, 4 x OAc, NHAc), 3.7 (3H, S-OMe), 4.9 (2H, m, CH_2=), 5.7 (H, m, -CH=); ^{13}C nmr ($CDCl_3$) δ 20.6, 20.7, and 20.9 (4 x AcO), 22.9 (NHAc), 29.8 and 29.9 (2 x CH_2), 37.9 (S-3), 46.2 (S-5), 52.4 (OMe), 62.3 (CH_2), 64.0 (S-9), 67.4 (S-4), 68.3 and 69.0 (S-7 and S-8), 72.3 (S-6), 98.6 (S-2), 114.7 (CH_2=), 137.8 (-CH=), 168.4, 170.0, 170.5, 170.7, 170.7 and170.8 (4 x OAc, NHAc and S-2).

b) The alkene (330 mg, 0.59 mmol) was ozonolysed as described for **3** to give after chromatography (silica - ethyl acetate) the desired *aldehyde* **5** as a white foam (210 mg, 63% yield); ^{1}H nmr ($CDCl_3$) δ 1.8 (5H, s, NHAc, CH_2), 2.0 (8H, 2 x s + m, 2 x OAc and CH_2), 2.1 (7H, 2 x s + m, 2 x OAc and S-3a), 2.5 (H, m, S-3e), 3.8 (5H, m, S-OMe and OCH_2), 4.1 (2H, m, S-9), 4.3 (H, dd), 4.8 (H, m), 5.3 (2H, m), 5.5 (H, d, NH), 9.7 (H, s, CHO).

Methyl 2-(3'-oxopropan-1'-yl)-5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-*D*-glycero-α-*D*-galacto-2-nonulosonate (4). This was prepared from **3** and 3-butene-1-ol in a manner similar to that described above to give the aldehyde **4** as an oil in 45% yield after column chromatography (EtOAc). It was used without further purification; ^{1}H nmr ($CDCl_3$) δ 1.8

(5H, m, NHAc), 1.95 (8H, s +m, OAc + S-3), 2.08 (6H, s, OAc), 2.55 (2H, m, CH_2CHO), 3.22 (H, dd, S-5), 3.62 (H, m), 3.75 (4H, s +m, OMe + S), 4.04 (4H, m, OCH_2+ S9), 4.29 (H, brd), 4.78 (H, m), 5.30 (2H, m), 5.65 (H, d, NH), 9.70 (H, d, J = 2Hz, CHO).

Methyl 2,3-di-O-benzoyl-4-oxo-β-L-fucopyranoside (7). A suspension of methyl 2,3-di-O-benzoyl-α-L-fucopyranoside[12] (10.1g, 26.2 mmol), pyridinium chlorochromate (25.4 g, 117.9 mmol) and dried powdered 4Å sieves (50 g) was mechanically stirred in degassed anhydrous dichloromethane (400 ml) under argon at room temperature for 18 hr. The supernatant was decanted from the solids and the solids were triturated with dichloromethane (5 x 50 ml). The combined dichloromethane layers were passed through a short silica column and evaporated to give pure *ketone* **7** as a colourless oil (8.01 g, 20.9 mmol, 80% yield) which solidified on standing; (Found: C, 65.38; H, 5.13. $C_{21}H_{20}O_7$ requires C, 65.62; H, 5.24%); ^{1}H nmr ($CDCl_3$) δ 8.05 (4H, 2d, OBz), 7.55 (2H, 2d, OBz), 7.5-7.35 (4H, 2t, OBz), 6.16 (H, d, H-3), 5.58 (H, d, H-2), 5.28 (H, d, H-1), 4.48 (H, q, H-5), 3.56 (3H, s, OCH_3), 1.41 (3H, d, H_3-6); ^{13}C nmr ($CDCl_3$) δ 197.7 (C-4), 165.5 (OCOPh), 133.5, 133.4, 130.0, 129.9, 129.0, 128.5, 128.5, 128.2 (2xOBz), 97.1 (C-1), 74.4, 72.8, 69.3, 56.2 (OCH_3), 13.8 (C-6).

Methyl 2,3-di-O-benzoyl-4-(3'-dimethylphosphono-2'-oxo-propan-1-yl)-6-deoxy-β-L-galactopyranoside (2a). Dimethyl 2-oxopropylphosphonate (0.42 g) was added to a stirred suspension of hexane-washed NaH (97 mg) in dry tetrahydrofuran (10 ml) at room temperature under argon. After 10 minutes n-butyl lithium (1.9 ml of a 1.35M solution in hexanes, 2.53 mmol) was added to the stirred white slurry at 0°C to give a deep yellow solution. After 30 minutes at 0°C, the solution was cooled to -78°C and chlorotriisopropoxytitanium (0.3 ml) was added from a warmed syringe. The dark brown solution was stirred for 5 minutes before a solution of ketone 7 (214 mg) in tetrahydrofuran (5 ml) was added by syringe. The reaction mixture was stirred at -78°C for 2hr then quenched with 2M HCl (aq) (5 ml) and extracted with ethyl acetate (2 x 50 ml). The combined organic layers were dried and evaporated to give an oil. Flash chromatography on silica using a gradient eluant (ethyl acetate then 5% methanol-ethyl acetate) gave the product contaminated with dimethyl 2-oxopropylphosphonate. This was removed by partial Kugelrohr distillation at 125°C and 0.9 mm Hg to afford pure *phosphonofucopyranoside* **2a** (125 mg 41% yield) as a light brown oil; ^{1}H nmr ($CDCl_3$) δ 7.99-7.87 (4H, 2d, 2 x OBz), 7.52-7.26 (6H, m, 2 x OBz), 5.82(H, d, J = 10.2 Hz, H-3), 5.49 (H, dd, J = 3.8 and 10.2 Hz, H-2), 5.14 (H, d, J = 3.8 Hz, H-1), 4.24 (H, q, J = 6.4 Hz, H-5), 4.10 (H, br s, OH), 3.71 (3H, d, J = 11.3 Hz, MeOP), 3.64 (3H, d, J = 11.3 Hz, MeOP), 3.41 (3H, s, F1-OMe), 3.10-2.99 (2H, dd, J = 5.5 and 22.6 Hz, $(MeO)_2OPCH_2CO$-), 2.86 (2H, s, $COCH_2$C-4), 1.30 (3H, d, J = 6.4 Hz); ^{13}C nmr ($CDCl_3$) δ 200.6 (-CO-), 166.2, 166.0 (2 x OCOPh), 133.3, 133.3, 129.8, 129.7, 129.3, 129.2, 128.4, 128.2 (2 x Ph), 97.0 (C-1), 75.1 (C-4), 72.9, 70.6, 67.8, 60.3 C1-OCH_3), 53.0, 52.9 ($P(OCH_3)_2$), 46.8 ($COCH_2$C-4), 43.58 and 41.6 (PCH_2CO), 13.5 (C-6); m/z calc for $C_{26}H_{31}O_{11}P$ [M+H] 551.16823; found 551.16787.

Methyl 2,3-di-O-benzoyl-4-(prop-2'-en-1'-yl)-6-deoxy-β-L-glucopyranoside (9). Allyl silane (4.45 g, 39 mmol) was added to a stirred solution of 7 (10.0 g, 26 mmol) and titanium tetrachloride (39 ml of a 1 M solution in dichloromethane, 39 mmol) in dichloromethane (120 ml) at -78°C under argon. The reaction mixture was held at -78°C until it solidified (20 min), then at -20°C for 3 hr, and then poured into $NaHCO_3$ (aq) (200 ml) and stirred until the aqueous layer became colourless. The organic layer was separated, washed with brine (100 ml), dried and evaporated *in vacuo* to give pure axial *homoallylic alcohol* **9** as a clear oil (9.0 g, 81% yield), (Found: C, 66.33; H, 6.05. $C_{24}H_{26}O_7$ 0.5 H_2O requires C, 66.19; H, 6.25%); ^{1}H nmr δ ($CDCl_3$) 8.0 (4H, 2 x d, OBz), 7.5 (2H, 2x t, OBz), 7.4 (4H, 2 x d, 2 x OBz), 6.08 (H, m, -CH=), 5.22 (H, d, F-3), 5.43 (H, dd, F-2), 5.29 and 5.15 (2H, m, CH_2=), 5.13 (H, d, F-1), 4.11 (H, q, F-5), 3.41 (3H, s, F-OMe), 3.18 (H, br s, OH), 2.8-2.56 (2H, 2 x dd, -CH_2), 1.38 (3H, d, F-OMe). NOE experiment ($CDCl_3$): irradiation of the allylic CH_2 resulted in an 11% enhancement at F-2, 6% at F-6 and 5% at the

olefinic CH_2 signals which is only consistent with an axial allylic substituent; ^{13}C nmr ($CDCl_3$) δ 167.3 (OCOPh), 166.0 (OCOPh), 133.8 (CH=), 133.4, 133.2, 129.9, 129.8, 129.2, 128.4, 128.3, 118.4 (CH_2=), 96.8 (F-1), 74.9 (F-4), 70.7, 70.0, 55.2 (F-OMe), 34.4 (allyl CH_2), 14.0 (F-6).

Methyl 2,3-di-O-benzoyl-4-(3'-diisopropoxyphosphono-2'-oxoprop-1'-yl)-6-deoxy-β-L-glucopyranoside (2b). a) Excess technical grade (80% pure) *m*-chloroperoxybenzoic acid (15 g, 70 mmol) was added in 3 portions over 5 hr to a solution of **9** (9.21 g, 21.6 mmol) under reflux in dichloromethane (200 ml). The reaction mixture was cooled, stirred for 30 min with a saturated solution of sodium thiosulphate and sodium carbonate (200 ml), separated, and the organic layer was washed with brine and dried. Evaporation gave a 1:1 mixture of the desired epoxides *methyl 2,3-di-O-benzoyl-4-(2'(S and R),3'-epoxypropan-1'-yl)-6-deoxy-β-L-glucopyranoside* as an oil (8.77 g, 19.9 mmol, 92% yield), (Found: C, 63.05; H, 5.71. $C_{24}H_{26}O_8$. 0.8 H_2O requires C, 63,09; H, 6.09%); ν_{max} (film) 3464, 3061, 2934, 1723, 1279 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 8.01-7.92 (4H, m, OBz), 7.51-7.27 (6H, m, OBz), 5.78 and 5.74 (H, 2 x d, J = 10.6 and 10.6 Hz, F-3), 5.36 (H, dd, J = 3.9 and 10.6 Hz, F-2), 5.10 and 5.07 (H, 2 x d, J = 3.9 Hz, F-1), 4.09 (H, m, F-5), 3.66-3.55 (H, br m), 3.41 and 3.40 (3H, 2 x s, F-OMe), 3.37-3.28 (H, m, H-2'), 2.78 (H, m, H-3a'), 2.59 (H, m, H-3b'), 2.22-1.90 (2H, m, -CH_2-), 1.33 (3H, d, J = 6.6 Hz); ^{13}C nmr δ ($CDCl_3$) 165.9 (several lines), 134.5-128.3 (several lines OBz), 96.9, 77.0, 76.7, 75.5, 75.4, 70.5, 70.1, 70.0, 55.3, 49.2, 48.8, 47.8, 33.2, 32.7, 13.7, 13.5.

b) Nickel dibromide (6.97 g, 32 mmol) and lithium bromide (5.57 g, 64 mmol) were heated under reflux for 3 hr at 80°C in anhydrous tetrahydrofuran (100 ml) to afford a deep blue solution of Li_2NiBr_4 (32 mmol). The above epoxide mixture (8.8 g, 20 mmol) was added to this solution and heated under reflux at 80°C for 3 hr and then evaporated. The residue was taken up in ethyl acetate (200 ml) and citric acid (100 ml). The organic phase was separated, washed with brine, dried and evaporated to give the *bromohydrins, methyl 2,3-di-O-benzoyl-4-(3' bromo-2'[S and R]-hydroxypropan-1'-yl)-6-deoxy-β-L-glucopyranoside* **10** as a white foam (10.24 g, 19.6 mmol, 98% yield); ^{1}H nmr ($CDCl_3$) δ 8.1- 7.9 (4H, m, OBz), 7.47-7.27 (6H, m, OBz), 5.9 and 5.75 (H, 2 x d, F-3), 5.35 and 5.15 (H, 2 x dd, F-2), 5.08 (H, dd, F-1), 4.6 and 4.26 (2H, m, F-5 and H), 4.03 (H, m, CHOH), 3.45 (2H, m, CH_2Br), 3.40 (3H, s, F-OMe), 2.3-1.99 (2H, m, -CH_2-), 1.35 (3H, 2 x d, F-6); ^{13}C nmr ($CDCl_3$) δ 167.9, 166.8, 166.6, 166.0, 134.4, 133.1, 130.0, 129.8, 129.6, 129.3, 129.8, 128.4, 128.3, 128.1, 97.7, 77.7, 77.1, 76.6, 76.6, 75.9, 75.4, 75.1, 71.2, 71.0, 70.1, 69.8, 69.2, 67.9, 55.2, 53.4, 39.0, 38.3, 32.8, 32.2, 25.5, 13.9, 13.3.

c) The bromohydrin mixture **10** (0.5 g, 0.96 mmol) was stirred with two equivalents of pyridinium chlorochromate (412 mg, 1.91 mmol) and powdered 4Å sieves (0.5 g) in anhydrous dichloromethane (10 ml) for 15 hr under argon. The reaction mixture was concentrated, resuspended in ether and passed through a 5 cm pad of silica. The pad was flushed with additional portions of ether until no more compound was observed by tlc of the eluted fractions. Evaporation *in vacuo* gave the *methyl 2,3-di-O-benzoyl-4-(3' bromo-2'-oxo-prop-1'-yl)-6-deoxy-β-L-glucopyranoside* in about 90% purity as white foam (0.39 g, 78% yield); ^{1}H nmr ($CDCl_3$) δ 7.95 - 7.85 (4H, m, OBz), 7.53 - 7.27 (6H, m, OBz), 5.84 (H, d, J = 10.8 Hz, F-3), 5.24 (H, dd, J = 4.0 and 10.8 Hz, F-2), 5.09 (H, d, J = 4.0 Hz, F-1), 4.86 (H, s, OH), 4.10 (H, q, J = 6.3 Hz, F-5), 4.06 (2H, s, $BrCH_2$-), 3.41 (3H, s, F-OMe), 3.30 (H, d, J = 17.3 Hz, CO-CHaHb-COH), 2.97 (H, d, J = 17.3 Hz, CO-CHaHb-COH), 1.27 (3H, d, J = 6.3 Hz, F-6); ^{13}C nmr ($CDCl_3$) δ 203.4, 166.2, 166.0, 133.4, 129.8 (4 lines), 129.3, 129.1, 128.5 (4 lines), 96.8, 76.4, 75.5, 69.3, 68.7, 55.3, 36.6, 35.7, 13.9.

d) The α-bromoketone (1.28 g, 2.5 mmol) was heated at 80°C in triisopropylphosphite (10 ml) for 4 hr. The solvent was removed by kugelrohr distillation at 125°C and 1 mm Hg pressure to give a yellow oil. Flash chromatography using gradient elution; 20% ethyl acetate–hexane rising to neat ethyl acetate gave three products: *methyl 2,3-di-O-benzoyl-4-(2'-oxoprop-1'-yl)-6-deoxy-β-L-glucopyranoside* (0.10 g, 9% yield) Rf (ethyl acetate) 0.70; ^{1}H nmr ($CDCl_3$) δ 7.9-7.85 (4H, m, OBz), 7.5-7.27 (6H, m, OBz),

5.87 (H, d, F-3), 5.17 (H, dd, F-2), 5.08 (H, d, F-1), 4.09 (H, q, F-5), 4.43 (3H, s, F-OMe), 3.07 (H, d, CO-CHaHb-COH), 2.88 (H, d, CO-CHaHb-COH), 2.36 (3H, s, CH_3-CO-), 1.26 (3H, d, F-6); m/z 443 (M+H): *methyl 2,3-di-O-benzoyl-4-(2'-diisopropoxyphosphate-prop-3'-en-1'-yl)-6-deoxy-β-L-glucopyranoside* (0.28 g, 18% yield) Rf (ethyl acetate) 0.57; ^{1}H nmr ($CDCl_3$) δ 7.93 (2H, d, J = 7.1 Hz, OBz), 7.63 (2H, d, J = 7.3 Hz, OBz), 7.42-7.19 (6H, m, OBz), 5.78 (H, d, J = 10.9 Hz, F-3), 5.21 (H, dd, J = 4.0 and 10.9 Hz, F-2), 5.05 (H, d, J = 4.0 Hz, F-1), 4.96 and 4.79 (2H, 2 x s, $=CH_2$), 4.6-4.38 (4H, m, $P(-O-CH)_2$), 4.3 (H, br s, OH), 4.02 (H, q, F-5), 3.31 (3H, s, F-OMe), 2.86 (H, d, J = 15.2 Hz, CO-CHaHb-COH), 2.76 (H, d, J = 15.2 Hz, CO-CHaHb-COH), 1.25 (6H, d, J = 6.3 Hz, 2 x isopropyl CH_3), 1.17 (6H, d, J = 6.3 Hz, 2 x isopropyl CH_3), 1.02 (3H, d, J = 6.2 Hz, F-6); ^{13}C nmr ($CDCl_3$) δ 166.6 (OCOPh), 165.9 (OCOPh), 152.6 (J_{CP} = 32.3 Hz, =C-O-P), 133.1, 132.0, 129.8, 129.7, 129.6, 129.1, 128.2, 128.1, 102.1 (J_{CP} = 19.8 Hz, H_2C=C-O-P), 96.7 (F-1), 75.6 (F-4), 75.1, 73.4 (3 lines J_{CP} = 24.8 and 29.0 Hz, 2 x isopropyl O-CH), 70.9, 70.2, 55.1 (F-OMe), 34.1 (J_{CP} = 13.5 Hz, P-O-C-CH_2-COH), 23.5-23.1 (6 lines, 4 x isopropyl CH_3), 13.3 (F-6); m/z 607 (M+ H); and *methyl 2,3-di-O-benzoyl-4-(3'-diisopropoxyphosphono-2'-oxo-prop-1'-yl)-6-deoxy-β-L-glucopyranoside* **2b** as a white foam (0.49 g, 35% yield), m.p. 129-131° (ethyl acetate-hexane), Rf (ethyl acetate) 0.45; (Found: C, 58.45; H, 6.57. $C_{30}H_{39}O_{11}P$ 0.5H_2O requires C, 58.53; H, 6.54%); ^{1}H nmr ($CDCl_3$) δ 7.93-7.85 (4H, m, 2 x OBz), 7.5-7.25 (6H, m, 2 x OBz), 5.87 (H, d, F-3), 5.35 (H, br s, OH), 5.17 (H, dd, F-2), 5.09 (H, d, F-1), 4.75-4.55 (2H, m, 2 x isopropyl CHs), 4.06 (H, q, F-5), 3.39 (3H, s, F-OMe), 3.30-2.95 (4H, m, P-CH_2-$COCH_2$-), 1.30 (15H, 3 x d, F-6 and 4 x isopropyl CH_3s); ^{13}C nmr ($CDCl_3$) δ 203.2 (J_{CP} = 18Hz, ketone CO), 165.8, 165.7, 133.1, 129.8, 129.7, 129.6, 129.4, 129.0, 128.3, 96.6 (F-1), 76.2 (F-4), 75.6, 75.0, 74.6, 73.4, 71.8 (J_{CP} = Hz), 70.2, 69.6, 55.1, 46.6, 44.6, 40.9, 23.8, 13.8.

Methyl 5-acetamido-2-[5"-(methyl 2',3'-di-*O*-benzoyl-6'-deoxy-β-L-glucopyranoside-4'-yl)-4"-oxo-pent-2"-en-1-yl]-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-*D*-glycero-α-*D*-galacto-2-nonulosonate (11). A suspension of caesium carbonate (180 mg, 0.55 mmol), **1** (300 mg, 0.537 mmol) and **2b** (300 mg, 0.495 mmol) were stirred in 2-methylpropan-2-ol (7 ml) at between 25°C and 30°C to give an intense yellow solution. The reaction was quenched after 100 minutes with 2M HCl (aq) (0.5 ml) and azeotroped to dryness with toluene. The residue was flash chromatographed on silica (45 g) using 80% ethyl acetate-hexane to give first recovered **2b**, then secondly *enone* **11** as a white foam (180 mg, 38% yield), m.p. 107-110° (ethyl acetate - hexane); (Found: C, 56.46; H, 5.81; N, 1.41. $C_{46}H_{55}NO_{21}$ 1.0 H_2O requires C, 56.61; H; 5.89; N, 1.43%); ^{1}H nmr ($CDCl_3$) δ 7.94 (2H, d, J = 8.1 Hz, OBz), 7.88 (2H, d, J = 8.0 Hz, OBz), 7.48 (2H, t, J = 7.3 Hz, OBz), 7.37-7.27 (2H, m, OBz), 6.89 (H, dt, J = 3.6 and 15.8 Hz, L-4), 6.48 (H, d, J = 15.8 Hz), 6.01 (H, s), 5.87 (H, d, J = 10.6 Hz, F-3), 5.41-5.31 (2H, m), 5.15 (H, dd, J = 10.6 and 4.0 Hz, F-2), 5.14 (H, m), 5.09 (H, d, J = 4.0 Hz, F-1), 4.92 (H, m, S-4), 4.55 (H, br d, J = 16.9 Hz), 4.29 (H, dd, J = 2.2 and 12.5 Hz), 4.16-4.03 (5H, m, F-5, 1 x S-9, 1 x L-5, S-6, S-5), 3.78 (3H, s, S-OMe), 3.40 (3H, s, F-OMe), 3.12 and 3.02 (2H, 2 x d, J = 16.8 Hz, L-1), 2.68 (H, dd, J = 4.6 and 12.9 Hz, S-3e), 2.16, 2.13, 2 x 2.04 (12H, 4 x s, 4 x OAc), 2.10 (H, dd, S-3a), 1.90 (3H, s, NHAc), 1.22 (3H, d, J = 7.0 Hz, F-6); ^{13}C nmr ($CDCl_3$) δ 202.0 (L-2, ketone), 171.1, 170.8, 170.6, 170.2, 170.0, 168.0, 166.0, 165.6, 143.7, 133.2, 132.9, 129.8, 129.7, 129.6, 129.3, 129.1, 128.3, 128.2, 98.4 (S-2), 96.7 (F-1), 76.9, 74.8, 72.6, 71.0, 69.4, 68.9, 68.2, 67.2, 63.4, 62.4, 60.4, 55.2 (F-OMe), 52.8 (S-OMe), 49.3 (S-5), 37.9 (S-3), 35.6 (L-1), 23.1 (NHAc), 21.1, 20.9, 20.8, 20.7, 14.1 (F-6).

Wadsworth Emmons reaction between aldehyde (1) and ketophosphonate (2a). A suspension of caesium carbonate (180 mg, 0.65 mmol), **1** (300 mg, 0.55 mmol) and **2a** (300 mg, 0.56 mmol) was stirred in 2-methylpropan-2-ol (10 ml) for 2 hr at 30°C. The yellow solution was quenched with 2M H_3PO_4 (aq) (1 ml) and evaporated *in vacuo*. The residue was taken up in dichloromethane (80 ml), washed with sodium bicarbonate solution (20 ml) and water (20 ml), dried and concentrated. The crude reaction mixture was flash chromatographed on silica using ethyl acetate to afford *methyl 5-acetamido-2-[5"-(methyl 2',3'-di-O-*

benzoyl-6'-deoxy-β-L-galactopyranoside-4'-yl)-4"-oxo-pent-2"-en-1"-yl]-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulosonate **12** as a yellow oil (320 mg, 0.33 mmol, 60% yield). (Found: C, 56.76; H, 5.97; N, 1.41. $C_{46}H_{55}NO_{21}$ $0.6H_2O$ requires C, 57.03; H, 5.85; N, 1.44%); ^{1}H nmr ($CDCl_3$) δ 7.9 (4H, m, OBz), 7.5-7.3 (6H, m, OBz), 6.57 (H, dt, L-4), 6.15 (H, d, L-3), 5.82 (H, d, F-3), 5.50 (H, dd, F-2), 5.3 (2H, m, S-7, S-8), 5.15 (H, d, F-1), 4.85 (2H, m, S-4, NH), 4.33-3.85 (6H, m, 2 x L-5, 2 x S-9, F-5, S-6), 3.77 (H, br s, OH), 3.75 (3H, s, F-OMe), 2.85 (H, d, L-1), 2.65 (H, d, L-1'), 2.57 (H, dd, S3e), 2.15 (6H, 2 x s, 2 x OAc), 2.10 (H, m, S3a), 2.05 (6H, 2 x s, 2 x OAc), 1.90 (3H, s, NHAc), 1.30 (3H, d, F-6); ^{13}C nmr ($CDCl_3$) δ 199.3 (L-2), 170.8, 170.5, 170.2, 170.0, 169.9, 167.9, 166.0, 165.9, (4 x OAc, NHAc, 2 x OBz, S-1), 143.4 (L-4), 2 x 133.1, 129.7, 129.4, 129.4, 128.2, 128.2 (2 x OBz), 128.3 (L-3), 98.3 (S-2), 97.0 (F-1), 75.9 (F-4), 73.1 (F-3), 72.5 (F-5), 70.8 (F-2), 68.8 (S-4), 68.6 (S-6), 68.3 (S-8), 67.2 (S-7), 63.2 (S-9), 62.4 (L-5), 55.4 (F-OMe), 52.8 (S-OMe), 49.3 (S-5), 42.2 (L-1), 37.7 (S-3), 23.0 (NHAc), 21.0, 20.7, 20.7, 20.6 (4 x OAc), 13.9 (F-6). The allylic alcohol *methyl 2,3-di-O-benzoyl-4-[5'-hydroxy-2'-oxo-pent-3'-en-1'-yl]-6-deoxy-β-L-galactopyranoside* **13** was also isolated as an oil (21 mg); ^{1}H nmr ($CDCl_3$) δ 8.0-7.88 (4H, m, 2 x OBz), 7.53-7.27 (6H, m, 2 x OBz), 6.67 (H, dt, J = 15.8 and 3.8 Hz, L4), 6.15 (H, dt, J = 15.8 and 1.9 Hz, L3), 5.82 (H, d, J = 10.3 Hz, F3), 5.47 (H, dd, J = 10.3 and 3.8 Hz, F2), 5.18 (H, d, J = 3.8 Hz), 4.90 (H, br s, OH), 4.12 (3H, m, L5, F5), 3.41 (3H, s, F1-OMe), 2.85 (H, d, J = 15.6 Hz, L1), 2.57 (H, d, J = 15.6 Hz, L1'), 1.33 (3H, d, J = 6.4 Hz, F6).

Methyl 5-acetamido-2-[7"-(methyl 2',3'-di-O-benzoyl-6'-deoxy-β-L-galactopyranoside-4-yl)-6"-oxo-hept-4"-en-1"-yl]-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulosonate (15). Caesium carbonate (72 mg, 0.21 mmol) was added to a stirred solution of **2a** (100 mg, 0.18 mmol) and **5** (102 mg, 0.18 mmol) in t-butanol (12 ml) at room temperature. After 18 hr the reaction mixture was quenched with several drops of 6M HCl (aq) and toluene was added. The solvents were removed *in vacuo* to give an off-white foam. Chromatography on silica, eluant ethyl acetate, gave *enone* **15** as a white foam (70 mg, 71 μmol, 48% yield); ^{1}H nmr δ ($CDCl_3$) 1.3 (3H, d, F-6), 1.45 (2H, m, L-6), 1.8 (3H, s, NHAc), 2.0 (6H, 2 x s, OAc), 2.1 (6H, 2 x s, OAc), 2.48 (H, d, L-1), 2.52 (2H, m, L-5), 2.84 (H, d, L-1'), 3.12 (H, m), 3.4 (3H, s, F-OMe), 3.6-3.8 (3H, m), 4.05 (5H, m, 2 x L-7, 2 x S-9, F-5), 4.26 (H, d, S-6), 4.81 (H, m), 5.12 (H, brd), 5.32 (2H, m, S-4, NH), 5.40 (H, dd, F-2), 5.61 (H, d, F-3), 5.8 (H, d, L-3), 6.7 (H, dt, L-4), 7.0-7.5 (6H, m, OBz), 7.86 (4H, m, OBz); ^{13}C nmr δ ($CDCl_3$) 13.9 (F-6), 20.7, 20.8, 21.0, 23.1 (NHAc), 27.5, 28.7, 38.0 (S-3), 41.1, 49.3 (S-5), 52.6 (S-OMe), 55.4 (F-OMe), 62.3 (L-7), 63.7 (S-9), 67.3, 68.4, 68.9, 69.0, 71.0, 72.4, 73.2, 97.0 (F-1), 98.6 (S-2), 128-130, 132.9, 133 (L-4), 149.7 (L-3), 165.9, 168.3, 170.0, 170.3, 170.6, 170.9, 200.2 (L-2); m/z (FAB) 1008 (M + Na), 952, 925, 414.

Methyl 5-acetamido-2-[5"-(methyl 2',3'-di-O-benzoyl-6'-deoxy-β-L-galactopyranoside-4'-yl)-4"-oxo-pent-1"-yl]-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulosonate (16). **12** (70 mg, 7.31 x 10^{-5}mol) was stirred with 10% palladium on charcoal (5 mg) in methanol (5 ml) at room temperature under 1 atm of hydrogen gas. After 16 hr the reaction mixture was filtered through a pad of celite and concentrated to afford the *ketone* **16** as a yellow foam (68 mg, 98%); ^{1}H nmr ($CDCl_3$) δ 7.97-7.87 (4H, 2 x d, OBz), 7.52-7.27 (6H, m, OBz), 5.76 (H, d, J = 10.3 Hz, F-3), 5.51 (H, dd, J = 10.3 and 3.6 Hz, F-2), 5.35-5.23 (3H, m, S-7, S-8, OH), 5.14 (H, d, J = 3.6 Hz, F-1), 4.86 (H, br s, NH), 4.82 (H, m, S-4), 4.30 (H, dd, J = 1.9 and 12.2 Hz), 4.15-4.02 (3H, m, S-9', S-6, F-5), 3.79 (3H, s, S-OMe), 3.59 (H, m, L-5), 3.41 (3H, s, F-OMe), 3.13 (H, m, L-5'), 2.63 (2H, 4 lines, J = 10.3 Hz, L-1, L-1'), 2.50 (H, dd, J = 4.6 and 12.9 Hz, S-3e), 2.42 (2H, q, J = 7.3 Hz, L-3), 2.13 (3H, s, OAc), 2.12 (3H, s, OAc), 2.07 (H, S-3a), 2.02 (3H, s, NHAc), 1.5 (2H, m, L-4), 1.29 (3H, d, J = 6.3 Hz, F-6); ^{13}C nmr ($CDCl_3$) δ 210.5 (L-2), 170.9-165.9 (8 lines, 4 x OAc, 2 x OBz, CO_2Me, NHAc), 133.3, 133.0, 129.8, 129.7, 129.3, 129.1, 128.4, 128.2 (2 x OBz), 98.6, (S-2), 97.1 (F-1), 75.6 (F-4), 73.4 (F-3), 72.5 (F-5), 70.6 (F-2), 69.1, 68.6, 68.3, 67.3 (S-4, S-6, S-7, S-8), 63.5 (S-9), 62.4 (L-5), 55.5 (F-OMe), 52.6 (S-OMe), 49.3 (S-5), 44.5 (L-1), 40.7 (L-3), 37.9 (S-3), 23.1 (NHAc), 22.1 (L-4), 21.0, 20.8, 20.8, 20.7 (4 x OAc), 13.8 (F-6); m/z 982 (M + Na), 901, 474, 414.

Hydrolysis of the protected ketone (16). **16** (50 mg, 5.21 x 10^{-5}mol) was stirred with 1 equivalent (5.2 x 10^{-5}mol) of sodium methoxide in anhydrous methanol (4 ml) under argon for 14 hr. The reaction mixture was neutralised with 1 drop of hydrochloric acid then concentrated and flash chromatographed on silica using a gradient elution of 10% increasing to 50% methanol in ethyl acetate. *Methyl 5-acetamido-2-[5''-(methyl 6'-deoxy-β-L-galactopyranoside-4'-yl)-4''-oxo-pent-2''-en-1''-yl]-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulosonate* **20** (R = Me) was obtained as a light yellow oil (20 mg, 66% yield); ^{1}H nmr (D_2O) δ 4.84 (H, d, F-1), 4.07 (H, q, J = 6.4 Hz, F-5), 3.83 (3H, s, S-OMe), 3.82-3.39 (11H, m, F-2, F-3, S-4, S-5, S-6, S-7, S-8, 2 x S-9, 2 x L-5), 3.36 (3H, s, F-OMe), 2.87 (H, d, J = 16.4 Hz, L-1), 2.66-2.59 (4H, m, L-1', 2 x L-3, S-3e), 1.99 (3H, s, NHAc), 1.87-1.70 (3H, m, 2 x L-4, S-3a), 1.12 (3H, d, J = 6.4 Hz, F-6); ^{13}C nmr (D_2O) δ 213.5 (L-2), 175.2 (S-1), 178.4 (NHAc), 99.5 (S-2), 99.4 (F-1), 76.0 (F-4), 73.1 (S-8), 71.3 (F-2), 70.9 (F-3), 69.2 (S-7), 68.5 (S-6), 68.1 (F-5), 67.4 (S-4), 64.1 (L-5), 63.3 (S-9), 55.3 (F-OMe), 53.6 (S-OMe), 52.0 (S-5), 45.5 (L-1), 40.6 (L-3), 39.4 (S-3), 23.2 (L-4), 22.3 (NHAc), 13.0 (F-6); m/z calc for $C_{24}H_{41}NO_{15}$ [M + Na] 606.23739; found 606.23763.

(**20** R = Me)(15 mg, 25.6 μmol) was dissolved in D_2O (0.6 ml) containing one equivalent of sodium deuteroxide (26 μmol). Saponification as judged by ^{1}H nmr was complete after 18 hr. The solution was concentrated to give *sodium 5-acetamido-2-[5''-(methyl 6'-deoxy-β-L-galactopyranoside-4'-yl)-4''-oxo-pent-2''-en-1''-yl]-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulosonate* (**20** R = Na) as a clear glass (17 mg, quantitative yield); ^{1}H nmr (D_2O) δ 4.8 (H, d, F-1), 4.08 (H, q, F-5), 3.9-3.39 (10H, m), 3.35 (3H, s, FOMe), 2.68 (H, dd, S-3e), 2.04 (3H, s, NHAc), 1.8-1.3 (5H, m, 2 x L-1, 2 x L-3, 2 x L-4, S-3a), 1.18 (3H, d, F-6); ^{13}C nmr (D_2O) δ 181.3, 175.4, 173.8, 100.8, 99.5, 76, 74.6, 72.8, 72.0, 69.3, 68.5, 68.3, 64.0, 62.9, 55.3, 52.3, 49.0, 40.7, 23.6, 23.2, 22.3, 13.1.

Methyl 5-acetamido-2-[5''-(methyl 2',3'-di-O-benzoyl-6'-deoxy-β-L-galactopyranoside-4'-yl)-4''-(R and S)-hydroxy-pent-2''-en-1''-yl]-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulosonate (18). Sodium borohydride (26 mg, 0.69 mmol) was added bit by bit to a stirred solution of **12** (220 mg, 0.23 mmol) and $CeCl_3.7H_2O$ (85 mg, 0.345 mmol) in methanol (5 ml) at room temperature. After 1 hr the reaction mixture was quenched with 2M H_3PO_4 (aq) (3ml) and concentrated *in vacuo*. The residue was partitioned between dichloromethane (50 ml) and 2M HCl (aq) (50 ml) and then the organic layer was dried and evaporated to afford the *enols* **18** as a white foam (170 mg, 0.17 mmol, 77% yield). The ratio of epimers at L-2 is approximately 3:2 by ^{1}H nmr. ^{1}H nmr ($CDCl_3$) δ 8.00-7.87 (4H, m, OBz), 7.47-7.27 (6H, m, OBz), 5.90 (1/2H, d), 5.75 (1/2H, d), 5.64-5.24 (6H, m), 5.13 (H, m, F-1), 4.81 (H, m), 4.51-3.93 (9H, m), 3.85-3.72 (H,m), 3.71 and 3.65 (3H, 2 x s, S-OMe), 3.39 (3H, s, FOMe), 2.54 (H, S-3e), 2.09, 2.03-1.99 and 1.92 (13H, 8 x s, 4 x OAc, S-3a), 1.84 (3H, 2 x s, NHAc), 1.77-1.6 (H, m, L-1), 1.37-1.29 (H, m, L-1'), 1.25 and 1.22 (3H, 2 x d, F-6); ^{13}C nmr ($CDCl_3$) δ 171.0, 170.9, 170.2, 168.4, 166.0, 135.2, 134.9, 133.0, 129.7, 129.3, 128.6, 126.0, 98.4 (2 lines S-2), 97.0 (F-1), 75.3, 73.9, 72.6, 72.3, 71.3, 70.9, 69.3, 69.1, 68.5, 67.5, 64.6, 62.9 (CH_2), 62.4 (CH_2), 55.4, 52.8, 49.1, 40.0 (CH_2), 37.8 (CH_2), 23.2, 21.1, 20.9, 20.8, 14.1, 13.8.

Methyl 5-acetamido-2-[5''-(methyl 6'-deoxy-β-L-galactopyranoside-4'-yl)-4''-(R and S)-hydroxy-pent-2''-en-1''-yl]-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulosonate (22). **18** (92 mg, 0.09mmol) was stirred with two equivalents of sodium methoxide (0.18 mmol) in methanol (5 ml) at room temperature under argon. After 16 hr the reaction mixture was neutralised with Dowex H+ resin and preabsorbed onto silica (0.5 g). Flash chromatography on silica using a gradient elution of 10% rising to 50% methanol-ethyl acetate gave the *dissaccharide* **22** (R = Me) as a white solid (32 mg, 57% yield). The ratio of epimers is approximately 2:1. ^{1}H nmr (CD_3OD) δ 5.69 (2H, m, L-3, L-4), 4.78 (3H, m), 4.60 (H, d, F-1), 4.28-4.22 (2H, m), 3.93 (2H, m), 3.80 (3H, s, S-OMe), 3.82-3.45 (7H, m), 3 33 (3H, s, F-OMe), 2.65 (H, dd, J = 4.3 and 12.7 Hz, S-3e),

1.97 (3H, s, NHAc), 1.89-1.66 (2H, m, S-3a, L-1), 1.56-1.46 (H, m, S-1'), 1.15 and 1.14 (3H, 2 x d, J = 6.3 Hz, F-6); ^{13}C nmr (CD_3OD) δ 175.2 (S-1), 171.0, 137.5 and 137.3 (L-3), 126.9 and 126.7 (L-4), 101.1 (F-1), 100.1 (S-2), 76.3 (F-4), 75.0, 73.7, 72.8, 72.4, 71.0, 70.2, 69.9, 69.7, 69.0, 68.5, 68.4, 65.4 (2 lines L-5), 64.7 (S-9), 55.6 (S-OMe), 53.8 and 53.5 (S-5 and F-OMe), 43.3 and 42.5 (L-1), 41.7 (S-3), 22.7 (NHAc), 14.3 and 14.0 (F-6).

Sodium 5-acetamido-2-[5"-(methyl 6'-deoxy-β-L-galactopyranoside-4'-yl)-4"-(R and S)-hydroxy-pent-2"-en-1"-yl]-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulosonate (22, R =Na). **22** (R = Me) (17 mg, 29 μmol) was stirred with two equivalents of NaOD (58.1 μmol) in D_2O (0.5 ml) for 20 hr. The reaction mixture was concentrated *in vacuo* to give the desired *sodium carboxylate salts* **23** (17 mg, quantitative yield); ^{1}H nmr (D_2O) δ 5.74 (2H, m, L-3, L-4), 4.9-4.7 (water peak obscuring F-1), 4.27 (2H, m), 4.05-3.90 (2H, m), 3.82-3.49 (9H, m), 3.34 (3H, s, F-OMe), 3.29 (4H, m), 2.66 (H, m), 1.98 (3H, s, NHAc), 1.98-1.89 (H, m, S-3a), 1.82-1.55 (2H, m, L1), 1.16 and 1.14 (3H, 2 x d, F-6); ^{13}C nmr (D_2O) δ 175.3 (S-1), 170.4 (NHAc), 136.6 and 136.4 (L-3), 126.5 and 126.1 (L-4), 99.3 (F-1 and S-2), 75.7 and 75.5 (F-4), 73.3, 73.0, 72.0, 71.4, 70.9, 70.7, 69.4, 68.6, 68.0, 67.6, 67.4, 65.0 (2 lines L-5), 63.4 and 62.9 (S-9), 55.3 (F-OMe), 53.7, 52.0, 49.2, 40.7 (S-3), 40.3 and 39.6 (L-1), 22.4 and 22.3 (NHAc), 13.2 and 12.9 (F-6).

Methyl 5-acetamido-2-[5"-(methyl 2',3'-di-O-benzoyl-6'-deoxy-β-L-galactopyranoside-4'-yl)-4"-(R and S)-hydroxy-pent-1"-yl]-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulosonate (17). **18** (81 mg, 0.085 mmol) was stirred with 10% palladium on charcoal catalyst (10 mg) in methanol (5 ml) for 3 hr. The reaction mixture was filtered through celite using methanol (50 ml) and then evaporated to give the *saturated alcohols* **17** as a white foam (82 mg, 100% yield); ^{1}H nmr δ ($CDCl_3$) 8.01-7.86 (4H, m), 7.46-7.26 (6H, m), 5.92 and 5.73 (H, 2 x d, J = 10.3 Hz and 10.2 Hz, F-3), 5.51-5.25 (4H, m), 5.14 (H, F-1), 4.82 (H, m), 4.32-3.6 (11H, m), 3.36 (3H, 2 x s, F-OMe), 3.23 (H, m), 2.51 (H, m, S-3e), 2.11-1.84 (15H, 4 x OAc and NHAc), 1.80-1.30 (10H, m); ^{13}C nmr δ ($CDCl_3$) 171.0-166.1 (7 lines), 133.3 (2 lines), 129.7, 129.3 128.4, 128.4, 128.2, 98.6 (2 lines, S-2), 97.0 (F-1), 75.3, 74.2, 72.4, 71.3 and 71.1, 69.5-67.4 (6 lines), 65.0, 62.7, 62.6, 55.4 (2 lines), 52.6, 49.2, 41.3, 40.1, 37.9, 35.5, 35.3, 25.5, 23.1, 21.0-20.8 (multiple lines), 13.7 and 13.5.

5-Acetamido-2-[5"-(methyl 6'-deoxy-β-L-galactopyranoside-4'-yl)-4"-(R and S)-hydroxy-pent-1"-yl]-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulosonic acid (21). **17** (66 mg, 0.07 mmol) was stirred with two equivalents of sodium methoxide (0.14 mmol) in methanol (4 ml). After 14 hr the reaction mixture was neutralised with 2M HCl (aq) (0.1 ml) and azeotroped to dryness with toluene. The residue was taken up in methanol, preabsorbed onto silica and flash chromatographed on silica using a gradient elution of 10% methanol-ethyl acetate rising to neat methanol. The carboxylic acids (**21**, R = H) were obtained as a white solid (38 mg, 66.5 μmol, 96% yield); ^{1}H nmr (D_2O) δ 4.9-4.8 (H_2O peak), 4.62 (H, m), 4.03 (H, q, J = 6.9 Hz, F-5), 3.99-3.40 (13H, m), 3.31 (3H, s, F-OMe), 3.27 (3H, m), 2.78 (H, dd, J = 3.6 and 12.5 Hz, S-3e), 1.98 (3H, s, NHAc), 1.82-1.35 (7H, m), 1.16 and 1.14 (3H, 2 x d, J = 6.9 Hz, F-6); ^{13}C nmr (CD_3OD) δ 175.5, 174.8 (2 lines), 101.8 (S-2), 101.1 and 101.0 (F-1), 76.6, 76.4, 74.3, 73.9, 72.9, 72.4, 71.0, 70.3, 69.7, 69.5, 69.3, 69.1, 67.4, 65.1 and 64.6 (L-5), 64.3 (S-9), 55.6 and 55.5 (F-OMe), 54.2 (S-5), 43.3, 42.8 and 42.6 (S3 and L-1), 36.7 and 36.3 (L-3), 26.8 and 26.7 (L-4), 22.7 (NHAc), 14.3 and 14.0 (F-6).

Reaction of the enols (18) with osmium tetroxide. A solution of osmium tetroxide (2.5% by weight) in t-butanol (25 μl, 1.6 mmol) was added to a solution of **18** (95 mg, 99 μmol), t-butyl hydroperoxide (70% in H_2O) (22 μl, 60 μmol) and tetraethyl ammonium acetate tetrahydrate (7 mg, 24.8 μmol) in acetone (4 ml) and the mixture was stirred for 60 hr at room temperature. Water (5 ml), sodium bisulphite (0.5 g) and ethyl acetate (20 ml) were added, and stirring was continued for 20 min

before the layers were separated. The aqueous phase extracted with ethyl acetate (20 ml) and the combined organic layers were dried and evaporated to afford a yellow oil. Flash chromatography on silica using ethyl acetate gave an inseparable mixture of the diastereomeric *triols methyl 5-acetamido-2-[5"-(methyl 2',3'-di-O-benzoyl-6'-deoxy-β-L-galactopyranoside-4'-yl)-2",3",4"-trihydroxy-pent-1"-yl]-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulosonate* (4 epimers synthesised (2'R, 3'R, 4'S), (2'S, 3'R, 4'S), (2'R, 3'S, 4'R) and (2'S, 3'S, 4'R)) as a white solid (40 mg, 40 μmol); ^{1}H nmr ($CDCl_3$) δ 8.0-7.82 (4H, m, OBz), 7.48-7.28 (6H, m, OBz), 6.00-5.78 (H, m), 5.62-5.09 (4H, m), 4.86 (H, m), 4.35-3.6 (14H, m) 3.34 (3H, 3 x s, F-OMe), 2.6-2.55 (H, m, S-3e), 2.15-1.87 (15H, several singlets, 4 x OAc, NHAc), 1.4-1.3 (5H, m).

Sodium 5-acetamido-2-[5"-(methyl 6'-deoxy-β-L-galactopyranoside-4'-yl)-2",3",4"-trihydroxy-pent-1"-yl]-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulosonate (19). 4 epimers synthesised (2"R, 3"R, 4"S), (2"S, 3"R, 4"S), (2"R, 3"S, 4"R), and (2"S, 3"S, 4"R). The acylated triols (40 mg, 40 μmol) were taken up in dry methanol (4 ml) containing one equivalent of sodium methoxide (40 μmol). After 24 hr at room temperature, the reaction mixture was evaporated and the residue flash chromatographed on silica using a gradient elution of 20% rising to 50% methanol in ethyl acetate. The desired *triol carboxylic acid sodium salts* **19** were obtained as an oil (10 mg); ^{1}H nmr δ (D_2O) 4.9 (H, m, F-1), 4.1-3.4 (14H, m), 3.30 (3H, 3 lines, F-OMe), 2.6 (H, m, S-3e), 1.97 (3H, s, NHAc), 1.85 (H, m), 1.7-1.5 (2H, L-1), 1.15 (3H, m, F-6); ^{13}C nmr δ (D_2O) 175.3, 174.0, 101.0, 100.8, 99.5, 99.46, 76.1, 75.8, 74.8-74.0 (5 lines), 73.0, 72.3-71.8 (3 lines), 69.8, 69.4, 69.2, 68.5, 68.0, 67.5, 66.7, 66.4, 63.0, 61.2, 55.2, 53.4, 52.6, 49.1, 40.9 (2 lines), 39.7, 39.2, 37.7, 22.3, 14.4, 13.4, 13.0.

Methyl 5-acetamido-2-[7"-(methyl 2',3'-di-O-benzoyl-6'-deoxy-β-L-galactopyranoside-4-yl)-6"-(R and S) hydroxy-hept-4"-en-1"-yl]-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulosonate (24). **15** (50 mg, 50.8 μmol) and cerium trichloride (19 mg, 76.1 μmol) were stirred for 15 min in ethanol (5 ml) then sodium borohydride (6 mg, 152 μmol) was added. After 20 min more sodium borohydride (100 mg) was added and the reaction mixture was stirred for 5 minutes before quenching with 2M HCl (aq). The solvent was removed *in vacuo* and the residue taken up in ethyl acetate (50 ml), washed with 2M HCl (50 ml), dried and the solvent evaporated to give the *alcohols* **24** as a yellow oil (50 mg). The epimer ratio (a:b) was 3:7; ^{1}H nmr δ ($CDCl_3$) 7.97-7.87 (4H, m, 2 x OBz), 7.46-7.27 (6H, m, 2 x OBz), 5.945 (3/10H, d, J = 10.4 Hz, F_a-3), 5.68 (7/10H, d, J = 9.5 Hz, F_b-3), 5.4-5.3 (6H, m, F-2, S-7, S-8, S-4, L-3, L-4), 5.16 (H, d, J = 4.3 Hz, F-1), 4.5-3.70 (14H, m), 3.41 (3H, s, F-OMe), 2.6 (H, m, S-3e), 2.1-2.0 (15H, m, 4 x OAc and NHAc), 2.0-1.35 (7H, m), 1.27 and 1.24 (3H, 2 x d, J = 7.0 Hz); m/z 1010 (M +Na), 414.

Methyl 5-acetamido-2-[7"-(methyl 6'-deoxy-β-L-galactopyranoside-4'-yl)-6"-(R and S) hydroxy-hept-4"-en-1"-yl]-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulosonate (25). **24** (50 mg) was treated with two equivalents of sodium methoxide (110 μmol) in dry methanol (4 ml) at room temperature for 20 hr. The solution was preabsorbed and flash chromatographed on silica using a gradient elution of 20% rising to 50% methanol-ethyl acetate to give the *methyl esters* **25** as a yellow oil (19 mg, 31 μmol, 62% yield from **15**): ^{1}H nmr δ (CD_3OD) 5.67-5.37 (2H, m, L-3, L-4), 4.58 (H, d, F-1), 4.32-4.20 (H, m, S-5), 3.94 (H, q, F-5), 3.87-3.28 (15H, m including 3 singlets at 3.68, 3.33 and 3.31: these are S-OMe and 2 x F-OMe), 2.64 (H, dd, J = 4.6 and 12.8 Hz, S-3e), 2.05-1.43 (10H, m including s at 1.97, NHAc, S-3a, 2 x L-1, 2 x L-5, 2 x L-6), 1.16 and 1.13 (3H, 2 x d, F-6); ^{13}C nmr δ (CD_3OD) 175.2, 171.2, 135.3, 131.3, 130.9, 101.2, 101.1, 100.6, 76.2, 74.9, 73.6, 72.5, 71.1, 70.2, 69.6, 69.3, 69.0, 68.5, 64.7, 64.4, 55.5, 53.8, 53.4, 43.5, 41.7, 30.2, 29 4, 22.6, 22.6, 14.2, 13.9.

Sodium 5-acetamido-2-[7"-(methyl 6'-deoxy-β-L-galactopyranoside-4-yl)-6"-(R and S) hydroxy-hept-4"-en-1"-yl]-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulosonate (25 R = Na). **25** (R = Me) was hydrolysed using two

equivalents of NaOD in D_2O affording the *sodium carboxylate salts* **25** as an oil (19 mg, 31 μmol, quantitative yield); ^{1}H nmr δ (D_2O) 5.50-5.46 (2H, m, L-3, L-4), 4.92 (H, m, F-1), 4.19 (H, m), 3.98 (H, m), 3.82 (H, m), 3.82-3.35 (12H, m), 3.30 (3H, s, F-OMe), 2.67 (H, m, S-3e), 2.08-2.02 (3H, m), 1.98 (3H, s, NHAc), 1.64-1.59 (4H, m), 1.17 and 1.14 (3H, 2 x d, 6.6 and 6.6 Hz, F-6); ^{13}C nmr δ (D_2O) 175.3, 175.3, 173.8, 170.5, 133.1, 132.9, 132.4, 132.3, 100.9 (S-2), 99.4 and 99.3 (F-1), 75.6 (2 lines, F-4), 73.1, 72.8, 72.0, 70.9, 70.6, 69.4, 69.3, 68.5, 68.4, 67.9, 67.4, 64.6, 63.3, 62.8, 55.2, 52.2, 49.1(S-5), 40.7(S-3), 40.5 and 39.5 (L-1), 28.6 and 28.1 (both 2 lines, L-5 and L-6), 22.3 (NHAc), 13.1 and 12.8 (F-6).

Preparation of the sialic acid mimic (25). a) The sialic acid ester **3** (7g, 13 mmol) in methanol (100 ml) was added under argon to a solution of sodium methoxide in methanol (33 ml of a 0.1M soln). The solution was stirred for 3 hr by when the reaction was adjudged complete by tlc ($CHCl_3$-MeOH, 9:1). Dowex resin (H^+ form) was added to neutralise the solution which was filtered and evaporated to leave a yellow solid (3.74 g, 76%).

b-d) Sodium borohydride (50 g) in water (200 ml) was mixed with Amberlite IRA 400 anion exchange resin (Cl^- form) (100 g). The slurry was stirred for 1 hr the solution then decanted and replaced with a fresh portion of the borohydride solution. After 30 min the slurry was filtered, washed thoroughly with water and stored at room temperature as a damp slurry. A second portion of Amberlite resin was added to sodium periodate in water (600 ml of a 0.5M solution). The resin was stirred gently for 1 hr and then the solution was removed by decanting and a fresh solution of sodium periodate added. This process was repeated once more and then the resin was filtered and washed thoroughly with water. The two resins (40 g of each) were washed with methanol and then added portionwise with stirring to a solution of the deacetylated sialic acid derivative (1.74 g) in dry methanol (200 ml) under argon. Stirring was continued for 90 min when tlc indicated the reaction was complete. The solution was filtered, washed with methanol (2 x 100 ml) and the solvent evaporated. Chromatography on silica (hexane-methanol, 1:1 to 100% methanol) gave the required sidechain modified sialic acid derivative acid (0.68 g). The total product was reesterified by stirring overnight in methanol with chlorotrimethylsilane. Removal of the solvent gave the ester as a brown oil which was redissolved in pyridine (3 ml). Dimethylaminopyridine (15 mg) and acetic anhydride (1.5 ml) were added and the mixture stirred under argon overnight. The solution was then diluted with dichloromethane (80 ml) and washed with 1M hydrochloric acid (2 x 50 ml), water, sodium bicarbonate soln, brine and dried. Evaporation of the solvent left a brown oil which after chromatography (hexane: ethyl acetate, 1:1) gave the desired *ester , methyl 5-acetamido-2-allyl-4,7-di-O-acetyl-3,5-dideoxy–β-L-arabino-2-heptulopyranosonate* **25** as a yellow oil; ^{1}H nmr ($CDCl_3$) δ 1.86 (3H, s, NHAc), 1.96 (6H, s, OAc), 2.06 (H, m, 'S'-3a), 2.62 (H, dd, 'S'-3e), 3.78 (3H, s, OMe), 3.9-4.4 (7H, m, OCH_2 x 2 +), 5.02 (H, m, CHO), 5.14 (H, dd, =CHaHb), 5.24 (H, brd, =CHaHb), 5.75 (H, d, NH), 5.85 (H, m, CH=CH_2); ^{13}C nmr ($CDCl_3$) δ 20.89, 20.9, 22.8, 38.7, 51.2 (C-5), 53.7, 64.6, 66.2, 71.5, 73.5 (C-6), 101.5 (C-2), 116.7, 136.2, 172.2, 172.9, 173.6, 174.9.

Ozonolysis of alkene (25). A slow stream of ozone was passed through a solution of the methyl ester **25** (0.3 g) in dichloromethane-methanol (5:1, 25 ml) at -5°C for 2 hr by when tlc indicated that the starting material had been consumed. Dimethylsulphide (2 ml) was added and the reaction mixture was allowed to stand overnight. The solvent was removed to leave the *aldehyde, methyl 5-acetamido-2-(2-oxoethyl)-4,7-di-O-acetyl-3,5-dideoxy–β-L-arabino-2-heptulopyranosonate* **26** (205 mg, 68%) as a yellow oil which was used in the coupling step without further purification; ^{1}H nmr ($CDCl_3$) δ 1.85 (3H, s, NHAc), 1.96 (6H, s, OAc), 2.06 (H, m, 'S'-3a), 2.46 (H, dd, 'S'-3e), 2.58 (H, dd, CHaHbCHO), 2.58 (H, dd, CHaHbCHO), 3.72 (3H, s, OMe), 3.95-4.3 (5H, m, OCH_2), 4.94 (H, m), 5.25 (H, m), 5.75 (H, m), 9.62 (H, m, CHO); ^{13}C nmr ($CDCl_3$) δ 20.83, 20.85, 23.0, 37.0, 50.3 (C-5), 52.7, 63.4, 68.8, 71.5, 73.6 (C-6), 98.3 (C-2), 168.6, 170.3, 171.1, 171.7, 199.9.

Wadsworth Emmons reaction of aldehyde (26). The aldehyde **26** (185 mg), ketophosphonate **2a** (185 mg) and caesium

carbonate (140 mg) were stirred together at room temperature in 2-methyl-2-propanol (6 ml) for 2.5 hr. Phosphoric acid (1 ml, 2M soln) was added and the solution evaporated to dryness. The residue was redissolved in dichloromethane (50 ml) and washed with sodium bicarbonate solution, brine and dried. Evaporation of the solvent gave a colourless oil which after chromatography (hexane-ethyl acetate, 3:1) gave the desired *methyl 5-acetamido-2-[5"-(methyl 2',3'-dibenzoyl-6'-deoxy-β-L-galactopyranoside-4'-yl)-4"-oxo-pent-2"-en-1"-yl]-4,7-di-O-acetyl-3,5-dideoxy-β-L-arabino-2-heptulopyranosonate* **27** as an oil (100 mg); ^{1}H nmr ($CDCl_3$) δ 1.36 (3H, d, F-Me), 1.98 (3H, s, NAc), 2.03 (3H, s, OAc), 2.10 (3H, s, OAc), 2.48 (H, m, 'S'-3e), 2.60 (H, d, L-1), 2.64 (H, m), 2.82 (H, d, L'-1), 3.42 (3H, s, F-OMe), 3.79 (3H, s, CO_2Me), 3.83 (2H, m), 4.03-4.35 (7H, m), 4.92 (H, ddd, 'S'-5), 5.18 (H, d, F-1), 5.55 (2H, m, NH + F-2), 5.82 (H, d, J =11 Hz, F-3), 6.13 (H,brd, J = 16.5Hz, L-3), 6.55 (H, dt, J = 16.5 Hz L-4), 7.25- 7.55 (6H, m, OBz), 7.85-7.95 (4H, m, OBz); ^{13}C nmr ($CDCl_3$) δ 13.9, 20.9 (2 x OAc), 23.2, 37.1, 42.3, 50.4, 52.9, 55.5, 62.7, 63.3, 68.7, 70.9, 73.8, 76.1 (F-4), 97.1 (F-1), 98.2, ('S'-2), 128.3, 128.8, 129.7, 133.2, 143.5 (L-4), 165.6, 165.8, 168.4, 170.5, 171.0, 171.2; m/z 836.3 (M + Na), 814.3 (M + H), 782.3, 754.3, 521.2.

References

1. A preliminary account of this work has appeared; N.M. Allanson; A.H. Davidson and F.M. Martin, *Tetrahedron Lett.* 1993, **24**, 3945.
2. (a) Springer, T.A., *Nature* 1990, **346**, 425. (b) Osborn, L., *Cell* 1990, **62**, 3. (c) Parekh, R.B.; Edge, C.J., *Tibtech* 1994, **12**, 339.
3. Stoolman, L.M., *Cell* 1989, **56**, 907.
4. McEver, R.P., *Thrombosis and Haemostasis* 1991, **65**, 223.
5. Tyrrell, D.; James,P.; Rao,N.; Foxall, C.; Abbas, S.; Dasgupta, F.; Nashed, M.; Hasegawa, A.; Kiso, M.; Asa, D.; Kidd, J.; Brandley, B.K., *Proc. Natl. Acad. Sci. USA* 1991, **88**, 10372.
6. (a) Ball, G.E.; O'Neill, R.A.; Schultz, J.E.; Lowe, J.B.; Weston, B.W.; Nagy, J.O.; Brown, E.G.; Hobbs, C.J.; Bednarski, M.D., *J. Am. Chem. Soc.* 1992, **114**, 5449. (b) Lin, Y-C.; Hummel, C.W.; Huang, D-H.; Ichikawa, Y.; Nicolaou, K.C.; Wong, C-H., *J. Am. Chem. Soc.* 1992, **114**, 5452.
7. (a) Lowe, J.B.; Stoolman, L.M; Nair, R.P.; Larsen, R.D.; Berhend, T.L.; Marks, R.M., *Cell* 1990, **63**, 475. (b) Phillips, M.L.; Nudelman, E.; Gaeta. F.C.A.; Perez, M.; Singhal, A.K.; Hakomori, S-I.; Paulson, J.C., *Science* 1990, **250**, 1130. (c) Walz, G.; Aruffo, A.; Kolanus, W.; Bevilacqua, M.; Seed, B., *Science* 1990, **250**, 1132.
8. (a) Berg, E.L.; Robinson, M.K.; Mansson, O.; Butcher, E.C.; Magnani, J.L., *J. Biol. Chem.* 1991, **266**, 14869. (b) Takada, A.; Ohmori, K.; Takahashi, N.; Tsuyuoka, K.; Yago, A.; Zenita, K.; Hasegawa, A.; Kannagi, R., *Biochem. Biophys. Res. Comm.* 1991, **179**, 713.
9. (a) Sabeson, S.; Bock, K; Lemieux, R.U., *Can. J. Chem.* 1984, **62**, 1034. (b) Thorgersen, H.; Lemieux, R.U.; Bock, K.; Meyer, B., *Can. J. Chem.* 1980, **60**, 44.
10. Narasinga Rao, B.N.; Anderson, M.B.; Musser, J.H.; Gilbert, J.H.; Schaefer, M.E.; Foxall, C.; Brandley, B.K., *J. Biol. Chem.* 1994, **269**, 19663.
11. Roy, R.; Lafferiere, C.A., *Can. J. Chem.* 1990, **68**, 2045.
12. Lindhorst, T.K.; Thiem, J., *Carbohydr. Res.* 1991, **209**, 119.
13. Hosomi, A.; Sakurai, H., *Tetrahedron Lett.* 1976, **17**, 1295.
14. A nOe enhancement of 11% was observed between the H-2 ring proton and the allylic CH_2 group.
15. Turner, J.V., *Tet Lett.* 1984, **25**, 2061.
16. Karanewsky, D.S.; Badia, M.C.; Ciosek, C.P.; Robl, J.A.; Sofia, M.J.; Simpkins, L.M.; DeLange, B; Harrity, T.W.; Biller, S.A.; Gordon, E.M., *J. Med. Chem.* 1990, **33**, 2956.
17. Grieco, P.A.; Pogonowski, C.S., *J. Am. Chem. Soc.* 1973, **95**, 3071.
18. Paquette, L.A.; Combrink, K.D.; Elmore, S.W.; Rogers, R.D., *J. Am. Chem. Soc.* 1991, **113**, 1335.
19. Reetz, M.T.; Steinbach, R.; Westermann, J.; Peter, R., *Angew. Chem. Int. Ed. Eng.* 1980, **19**, 1011.
20. Blackwell, C.M.; Davidson, A.H.; Launchbury, S.B.; Lewis, C.N.; Morrice, E.M.; Reeve, M.M.; Roffey, J.A.R.; Tipping, A.S.; Todd, R.S., *J. Org. Chem.* 1992, **57**, 1935.
21. Other conditions explored include: DIPEA or DBU, LiBr, MeCN; LiHMDS, THF or Et_2O, -78 → 0°; NaHMDS, THF, -78 → 0°; K_2CO_3, 18C-6, DCM; Cs_2CO_3, iPrOH; $LiOH.H_2O$; Et_2O; $MgBr_2$, NEt_3.
22. Brandley, B.K.; Kiso, M.; Abbas, S.; Nikrad, P.; Srivasatava, O.; Foxall, C.; Oda, Y.; Hasegawa, A., *Glycobiology* 1993, **178**, 623.
23. A brief summary of biological results and protocols appears in patent WO 94/17084.

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