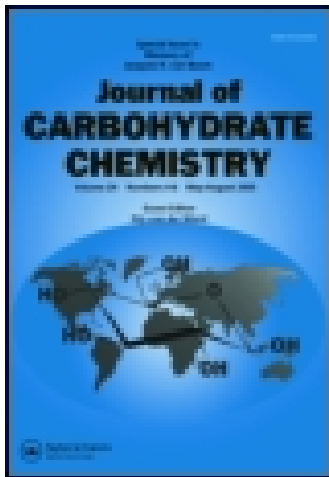


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SYNTHESIS OF SIALYL LEWIS X ANALOGUES 2¹

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ABSTRACT

Sialyl Lewis X (SLe^x analogues) containing β -L-fucopyranosyl residues with an alkyl [-(CH₂)₆-] (**1a**), a heteroalkyl [-(CH₂)₂-O-(CH₂)₃-] (**1b**) or a heterocycloalkyl [-2-cyclohexyl-O-(CH₂)₃-] (**2a**) moiety were synthesised by silver ion promoted glycosylation. Further analogues where sialic acid was replaced by a second β -L-fucopyranosyl (**3a**, **3b**) or hydrogensulphate unit (**4a**, **4b**) were also prepared.

INTRODUCTION

Adhesion to vascular endothelium has been recognised as a significant preliminary event in the extravasation of leucocytes during inflammation and of cancerous cells during metastasis. This adhesion is partly mediated by the selectins, a family of carbohydrate recognition proteins.^{3,4} E-selectin is an inducible glycoprotein expressed by endothelium during inflammation which promotes cell adhesion by its interaction with oligosaccharide ligands,⁵ principally the tetrasaccharide sialyl Lewis X (SLe^x).^{3,6} E-selectin binding to SLe^x was shown to be dependent on the fucose and sialic acid residues of the tetrasaccharide.^{6,7} It has been reported that a mixture of the trisaccharide Lewis X (Le^x) and Lewis X 3'-O-sulphate had a binding affinity for E-selectin similar to that of SLe^x

alone.⁸ Horie et al.⁹ claimed that compounds containing two fucose residues, separated by an amino-acid spacer had a considerable inhibitory effect on E-selectin binding. Inhibitors of E-selectin/SLe^X binding could be useful as anti-inflammatory or anti-metastatic agents.

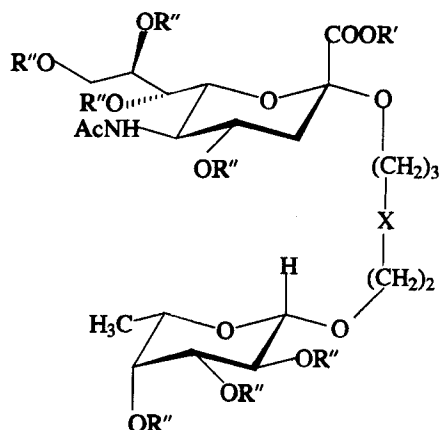
We have reported the synthesis of SLe^X and Le^X 3'-sulphate analogues, where the galactose and *N*-acetyl glucosamine units of SLe^X were replaced with alkyl or heteroalkyl spacers and the configuration at the glycosidic carbon of the fucose unit was α .¹ SLe^X analogues with β -fucosyl moieties have not been reported. To investigate further structure-activity relationships, SLe^X analogues containing β -L-fucosyl residues were synthesised with an alkyl [-(CH₂)₆-] (**1a**), a heteroalkyl [-(CH₂)₂-O-(CH₂)₃-] (**1b**) or a heterocycloalkyl [-2-cyclohexyl-O-(CH₂)₃-] (**2a**) spacer. Further analogues where the sialic acid unit was replaced with a second β -L-fucopyranosyl residue (**3a**, **3b**) or a hydrogensulphate moiety (**4a**, **4b**) were also prepared.

RESULTS AND DISCUSSION

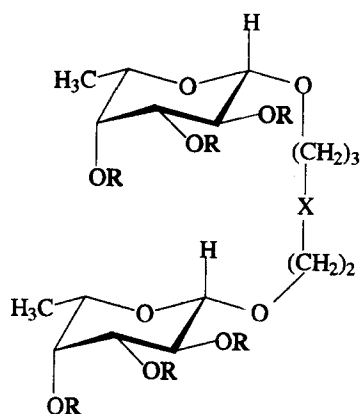
Synthesis of 1a: Monobenzylated diol **5**¹ was used as an acceptor in the synthesis of **1a**, **3a** and **4a**. β -Fucoside **4c** was synthesised by silver ion promoted glycosylation of the monobenzylated diol **5**, using fucopyranosyl chloride **6a**¹⁰ as a sugar donor. Benzyl deprotection of compound **4c** was carried out by hydrogenation (Pd/C), giving intermediate **4d**. Sialyl chloride **7**^{11,12} was reacted with **4d** in the presence of silver salicylate,¹³ yielding **1c**. Zemplen deprotection and base hydrolysis of **1c** resulted in the unprotected analogue **1a**.

Synthesis of 1b: 1,6-Hexanediol was used as an acceptor for the synthesis of compounds **1b**, **3b** and **4b**. Glycosylation of 1,6-hexanediol with **6a**, in the presence of silver salicylate, resulted in the mono-fucosylated product **4e** in high yield. α -Sialoside **1d** was prepared from fucoside **4e** and **7**, using silver salicylate as promotor. Zemplen hydrolysis followed by base hydrolysis of the protected glycoside **1d** resulted in the analogue **1b**.

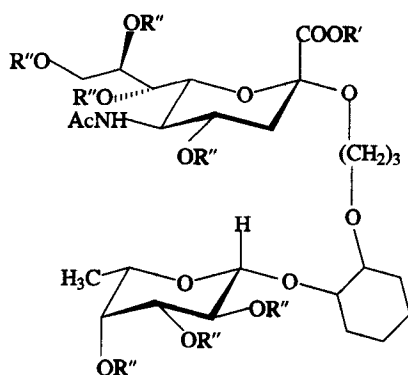
Synthesis of 2a: Spacer **8** was synthesised by conjugation of 3-benzoyloxypropyl tosylate¹ with *trans*-1,2-cyclohexanediol. β -Fucosylation of **8** with β -methylthio fucoside **6b**¹ resulted in glycoside **9a**, which was deprotected by hydrogenation in the presence of Pd/C to give **9b**. α -Sialylation of **9b** with **7** in the presence of silver salicylate resulted



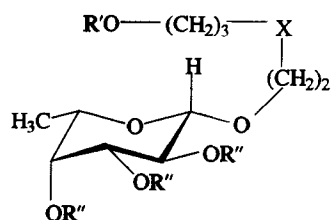
1	R'	R''	X
a	H	H	O
b	H	H	CH ₂
c	CH ₃	Ac	O
d	CH ₃	Ac	CH ₂



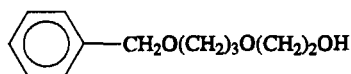
3	R	X
a	H	O
b	H	CH ₂
c	Ac	O
d	Ac	CH ₂



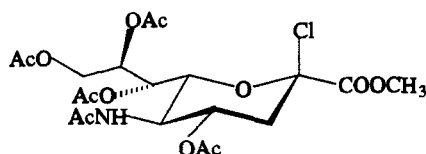
2	R'	R''
a	H	H
b	CH ₃	Ac



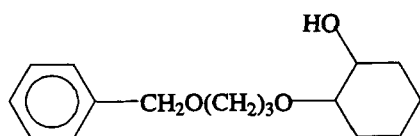
4	R'	R''	X
a	SO ₃ H	H	O
b	SO ₃ H	H	CH ₂
c	Bn	Ac	O
d	H	Ac	O
e	H	Ac	CH ₂
f	SO ₃ H	Ac	O
g	SO ₃ H	Ac	CH ₂



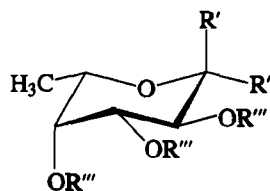
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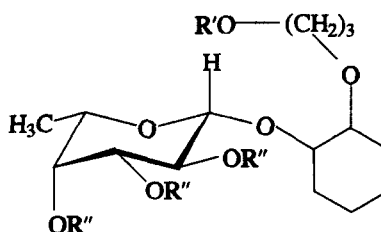
7



8



6	R'	R''	R'''
a	Cl	H	Ac
b	H	SCH ₃	Ac



9	R'	R''
a	Bn	Ac
b	H	Ac

in **2b** in high yield. Compound **2a** was obtained in almost quantitative yield from **2b** after Zemplan hydrolysis followed by aqueous-base hydrolysis.

Synthesis of 3a and 3b: Compound **3c** was obtained by reacting fucosylated alcohol **4d** with **6a** in a silver ion promoted reaction. Di- β -L-fucosylation of 1,6-hexanediol was achieved in a dimethyl(methylthio)sulphonium trifluoromethanesulphonate (DMTST)¹⁴ promoted glycosylation of 1,6-hexanediol with thiofucoside **6b**, yielding difucoside **3d**. Compound **3d** was also synthesised from glycoside **4e** and **6a**. Zemplan deprotection of **3c** and **3d** afforded the unprotected analogues **3a** and **3b**.

Synthesis of 4a and 4b: The acetyl protected fucosides **4d** and **4e** were reacted with chlorosulphonic acid, yielding compounds **4f** and **4g**, which were deprotected by Zemplan hydrolysis to give the sulphated products **4a** and **4b**.

EXPERIMENTAL

Purification was achieved by flash chromatography through Sorbsil C60-H40/60, using mobile phases as stated. Reaction progress was monitored by thin layer chromatography on Kieselgel 60 F₂₅₄ using mobile phases as stated. Visualisation was by UV light, iodine, or charring with sulphuric acid. The ion exchange resin used was Amberlite IR-120(H⁺). The solvents used in reaction mixtures were water-free. Reactions were carried out at room temperature unless otherwise stated. Solvents were evaporated under reduced pressure with a rotary evaporator.

¹H NMR spectra were obtained with a Bruker AM 500 instrument operating at a field of 500MHz. Chemical shifts are reported in ppm downfield from internal TMS. Mass spectra (FAB MS) were run with a VG Analytical ZAB-SE instrument using fast atom bombardment (FAB) techniques - 20kV Cs⁺ ion bombardment, with 2μL of appropriate matrix, either 3-nitrobenzyl alcohol or thioglycerol with NaI (MeOH) solution added when necessary to produce natriated species when no protonated molecular ions were observed. Accurate mass measurement (HRMS) was carried out on the same instrument at 10,000 reading power using CsI as a reference.

3-[2-(β-L-Fucopyranosyloxy)ethoxy]propyl 5-Acetamido-3,5-dideoxy-α-D-glycero-D-galacto-2-nonulopyranosonic acid (1a). **1c** (20 mg, 0.02 mmol) was dissolved in methanol (1.5 mL) and sodium methoxide (15 mg) was added. The reaction mixture was stirred at room temperature for 8 h then 0.35 mL water was added and the mixture was stirred for 16 h. The mixture was acidified to pH3 with Amberlite IR-120 (H⁺) ion exchange resin and filtered. The solution was concentrated and the residue was purified by chromatography using chloroform/methanol/water 5:6:2 v/v/v as the mobile phase to give **1a** (10 mg, 78%); R_f 0.36 (chloroform/methanol/water 5:6:2 v/v/v); ¹H NMR (D₂O) δ 4.20 (d, 1H, H-1_{fuc}, J_{1,2}=8.2 Hz), 3.27 (t, 1H, H-2_{fuc}), 2.56 (dd, 1H, H-3_{sia,eq}), 1.86 (m, 1H, H-2_{sia,ax}), 1.83 (s, 3H, NHAc), 1.27 (m, 2H, CH₂), 1.09 (d, 3H, H-6_{fuc}); FAB MS (glycerol+hexylamine matrix) *m/z* (%) 712 [M+2Na+hexylamine]⁺ (18), 659 [M+H+hexylamine]⁺ (45), 602 [M+2Na]⁺ (28), 580 [M+Na]⁺ (100); HRMS Calcd for C₂₂H₃₉NNaO₁₅: 580.2214. Found: 580.2223.

3-[2-(β-L-Fucopyranosyloxy)ethoxy]propyl 5-Acetamido-3,5-dideoxy-α-D-glycero-D-galacto-2-nonulopyranosonic acid (1b). **1a** (30 mg, 0.035 mmol) was

dissolved in methanol (3 mL) and sodium methoxide (15 mg) was added. The reaction mixture was stirred at 40 °C for 24 h then water (0.5 mL) was added. The solution was stirred at room temperature for 8 h then neutralised with Amberlite IR 120(H⁺) resin, filtered and concentrated. The residue was purified by flash chromatography using chloroform/methanol/water 5:6:2 v/v/v as the mobile phase to give **1b** (12 mg, 64%): *R*_f 0.38 (chloroform/methanol/water 5:6:2 v/v/v); ¹H NMR (D₂O) δ 4.22 (d, 1H, H-1_{fuc}, *J*_{1,2}=7.8 Hz), 3.30 (dd, 1H, H-2_{fuc}), 2.57 (dd, 1H, H-3_{sia,eq}), 1.90 (s, 1H, H-3_{sia,ax}), 1.83 (s, 3H, NHAc), 1.52-1.38 (m, 4H, 2 CH₂), 1.29 (bs, 4H, 2 CH₂), 1.08 (d, 3H, H-6_{fuc}); FAB MS *m/z* (%) 600 [M+2Na]⁺ (95), 578 [M+Na]⁺ (100), 556 [M+H]⁺ (13), 314 (32), 287 (33), 237 (49); HRMS Calcd for C₂₃H₄₁NNaO₁₄: 578.2424. Found: 578.2431.

Methyl {3-[2-(2,3,4-Tri-*O*-acetyl-β-L-fucopyranosyloxy)ethoxy]propyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-α-D-glycero-D-galacto-2-nonulopyranoside}onate (1c**).** Compounds **4d** (60 mg, 0.16 mmol) and **7** (88 mg, 0.17 mmol), with silver salicylate (63 mg, 0.26 mmol) were stirred in chloroform (1 mL) in the dark at room temperature for 24 h. The reaction mixture was diluted with chloroform (15 mL) and filtered. The filtrate was extracted with water (2 mL), saturated NaHCO₃ solution (2 mL) and with water (2 mL) again. The organic phase was dried over MgSO₄ and concentrated. The residue was purified by flash chromatography using hexane/ether/methanol/acetic acid 5:15:2:0.5 v/v/v/v as the mobile phase to give **1c** (75 mg, 57%): *R*_f 0.37 (hexane/ether/methanol/acetic acid 5:15:2:0.5 v/v/v/v); ¹H NMR (CDCl₃) δ 5.38 (m, 1H, H-8_{sia}), 5.33 (dd, 1H, H-7_{sia}), 5.23 (dd, 1H, H-4_{fuc}), 5.17 (dd, 2H, H-2_{fuc}, NH), 5.02 (dd, 1H, H-3_{fuc}), 4.83 (m, 1H, H-4_{sia}), 4.52 (s, 1H, H-1_{fuc}, *J*_{1,2}=9.1 Hz), 4.32 (dd, 1H, H-9'_{sia}), 4.13-4.02 (m, 2H, H-6_{sia}, H-9_{sia}), 3.93 (m, 1H, H-5_{fuc}), 3.81 (m, 1H, H-5_{sia}), 3.78 (s, 3H, OCH₃), 3.69 (m, 2H, CH₂O), 3.58 (t, 2H, CH₂O), 3.50 (t, 2H, CH₂O), 3.33 (m, 2H, CH₂O), 2.57 (dd, 1H, H-3_{sia,eq}), 1.93 (t, 1H, H-3_{sia,ax}), 2.17, 2.13, 2.07, 2.04, 2.03, 1.98, 1.89 (7s, 24H, 7 OAc, NHAc), 1.81 (m, 2H, CH₂), 1.22 (d, 3H, H-6_{fuc}); FAB MS *m/z* (%) 888 [M+Na]⁺ (100), 866 [M+H]⁺ (11), 635 (13), 415 (85), 273 (7); HRMS Calcd for C₃₇H₅₅NNaO₂₂: 888.3112. Found: 888.3102.

Methyl [6-(2,3,4-Tri-*O*-acetyl-β-L-fucopyranosyloxy)hexyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-α-D-glycero-D-galacto-2-nonulopyranoside]onate (1d**).** Compounds **4e** (600 mg, 1.53 mmol) and **7** (100 mg, 0.19 mmol), with silver salicylate (72 mg 0.29 mmol) were stirred in chloroform (10 mL) in the dark at room temperature

for 24 h. The reaction mixture was diluted with chloroform (15 mL) and filtered. The filtrate was extracted with water (4 mL), saturated NaHCO_3 solution (4 mL) and water (4 mL). The organic phase was dried over MgSO_4 and concentrated. The residue was purified by flash chromatography using hexane/ether/methanol/acetic acid 5:15:2.5:0.5 v/v/v/v as the mobile phase to give **1d** (120 mg, 71%): R_f 0.42 (hexane/ether/methanol/acetic acid 5:15:2.5:0.5 v/v/v/v); ^1H NMR (CDCl_3) δ 5.37 (m, 1H, H-8_{sia}), 5.32 (dd, 1H, H-7_{sia}), 5.23 (dd, 1H, H-4_{fuc}), 5.17 (m, 2H, H-2_{fuc}, NH), 5.02 (dd, 1H, H-3_{fuc}), 4.83 (m, 1H, H-4_{sia}), 4.42 (d, 1H, H-1_{fuc}, $J_{1,2}=9.1$ Hz), 4.32 (dd, 1H, H-9'_{sia}), 4.08 (m, 2H, H-6_{sia}, H-9_{sia}), 3.90 (m, 2H, H-5_{fuc}, CH_2Oc), 3.81 (m, 1H, H-5_{sia}), 3.80 (s, 3H, OCH_3), 3.73 (m, 1H, CH_2Od), 3.46 (m, 1H, CH_2Ob), 3.21 (m, 1H, CH_2Oa), 2.57 (dd, 1H, H-3_{sia,eq}), 1.96 (dd, 1H, H-3_{sia,ax}), 2.35, 2.16, 2.13, 2.06, 2.03, 1.98, 1.90 (7s, 24H, 7 OAc , NHAc), 1.65-1.48 (m, 4H, 2 CH_2), 1.42-1.25 (m, 4H, 2 CH_2), 1.23 (d, 3H, H-6_{fuc}); FAB MS m/z (%) 886 [$\text{M}+\text{Na}$]⁺ (100), 415 (36), 273 (11); HRMS Calcd for $\text{C}_{38}\text{H}_{57}\text{NNaO}_{21}$: 886.3320. Found: 886.3315.

3-[2-(β -L-Fucopyranosyloxy)-*trans*-cyclohexyloxy]propyl 5-Acetamido-3,5-dideoxy- α -D-glycero-D-galacto-2-nonulopyranosic acid (2a). **2b** (222 mg, 0.24 mmol) was dissolved in methanol (16 mL) and sodium methoxide (156 mg, 2.89 mmol) was added. The reaction mixture was stirred at room temperature for 8 h, then water (2.6 mL) was added and it was stirred for a further 4 h at 40 °C. The solution was neutralised with Amberlite IR-120 (H^+) ion exchange resin, filtered and concentrated. The residue was purified by chromatography using chloroform/methanol/water 10:10:2 v/v/v as the mobile phase to give **2a** (133 mg, 91%): R_f 0.36 (chloroform/methanol/water 10:10:2 v/v/v); ^1H NMR (D_2O) δ 4.45 (2d, 1H, H-1_{fuc}, $J_{1,2}=9.8$ Hz), 2.58 (dd, 1H, H-3_{sia,eq}), 1.88 (s, 3H, NHAc), 1.68 (m, 2H, CH_2), 1.10 (d, 3H, H-6_{fuc}); FAB MS m/z (%) 656 [$\text{M}+2\text{Na}$]⁺ (17), 634 [$\text{M}+\text{Na}$]⁺ (5), 462 (24), 330 (100), 308 (37); HRMS Calcd for $\text{C}_{26}\text{H}_{45}\text{NNaO}_{15}$: 634.2686. Found: 634.2692.

Methyl {3-[2-(2,3,4-Tri-O-acetyl- β -L-fucopyranosyloxy)-*trans*-cyclohexyloxy]propyl 5-Acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy- α -D-glycero-D-galacto-2-nonulopyranoside}onate (2b). **9b** (114 mg, 0.25 mmol), **7** (130 mg, 0.25 mmol) and silver salicylate (94 mg, 0.38 mmol) were stirred in chloroform (10 mL) for 3 days. The reaction mixture was diluted with chloroform (15 mL) and filtered. The filtrate was extracted with saturated NaHCO_3 solution (4 mL) and water (4 mL). The

organic phase was dried over MgSO_4 , filtered and concentrated. The residue was purified by chromatography using hexane/ether/methanol/acetic acid 10:10:2:0.5 v/v/v/v as the mobile phase to give **2b** (163 mg, 71%): R_f 0.40 (hexane/ether/methanol/acetic acid 10:10:2:0.5 v/v/v/v); ^1H NMR (CDCl_3) δ 5.38 (m, 1H, H-8_{sia}), 5.34 (m, 1H, H-7_{sia}), 5.22 (dd, 1H, H-4_{fuc}), 5.15 (m, 1H, H-2_{fuc}), 5.10 (d, 1H, NH), 5.02 (2 dd, 1H, H-3_{fuc}), 4.84 (m, 1H, H-4_{sia}), 4.74, 4.59 (2d, 1H, H-1_{fuc} , $J_{1,2}=9.1$ Hz), 4.10 (m, 2H, H-6_{sia} , $\text{H-9}'_{\text{sia}}$), 3.79 (s, 3H, OCH_3), 3.35 (m, 1H, CHO), 2.58 (dd, 1H, $\text{H-3}_{\text{eq.sia}}$), 2.17, 2.13, 2.09, 2.08, 2.05, 2.00, 1.92 (7s, 24H, 7 OAc, NHAc), 1.96 (t, 1H, $\text{H-3}_{\text{ax.sia}}$), 1.80 (m, 2H, CH_2) 1.62-1.27 (m, 8H, 4 CH_2), 1.22 (d, 3H, H-6_{fuc}); FAB MS m/z (%) 942 $[\text{M}+\text{Na}]^+$ (100), 882 (7), 825 (5), 559 (10); HRMS Calcd for $\text{C}_{41}\text{H}_{61}\text{NNaO}_{22}$: 942.3582. Found: 942.3592.

3-[2-(β -L-Fucopyranosyloxy)ethoxy]propyl β -L-Fucopyranoside (3a). **3c** (40 mg, 0.06 mmol) was dissolved in methanol (3 mL) and sodium methoxide (30 mg, 0.5 mmol) was added. The reaction mixture was stirred at 40 °C for 24 h. The solution was neutralised with Amberlite IR-120(H^+), filtered and concentrated. The residue was purified by chromatography using chloroform/methanol/water 6:5:2 v/v/v as the mobile phase to give **3a** (20 mg, 83%): R_f 0.42 (chloroform/methanol/water 6:5:2 v/v/v); ^1H NMR (D_2O) δ 4.20 (d, 2H, H-1 , $\text{H-1}'$, $J_{1,2}=J_{1',2'}=8.7$ Hz), 3.69 (m, 2H, CH_2O), 3.61 (m, 2H, H-5 , $\text{H-5}'$), 3.57 (d, 2H, H-4 , $\text{H-4}'$), 3.50 (m, 2H, CH_2O), 3.46 (dd, 2H, H-3 , $\text{H-3}'$), 3.42 (m, 4H, 2 CH_2O), 3.26 (dd, 2H, H-2 , $\text{H-2}'$), 1.45 (m, 2H, CH_2), 1.08 (d, 6H, H-6 , $\text{H-6}'$); FAB MS m/z (%) 452 $[\text{M}+\text{K}]^+$ (46), 435 $[\text{M}+\text{Na}]^+$ (100); HRMS Calcd for $\text{C}_{17}\text{H}_{32}\text{NaO}_{11}$: 435.1841. Found: 435.1834.

6-(β -L-Fucopyranosyloxy)hexyl β -L-Fucopyranoside (3b). Compound **3d** (40 mg, 0.06 mmol) was dissolved in methanol (3 mL) and sodium methoxide (30 mg) was added. The reaction mixture was stirred at 40 °C for 24 h, neutralised with Amberlite IR-120 (H^+) ion exchange resin, filtered and concentrated. The residue was purified by chromatography using chloroform/methanol/water 6:5:2 v/v/v as the mobile phase to give **3b** (20 mg, 83%): R_f 0.44 (chloroform/methanol/water 6:5:2 v/v/v); ^1H NMR (D_2O) δ 4.22 (d, 2H, H-1 , $\text{H-1}'$, $J_{1,2}=J_{1',2'}=8.87$ Hz), 3.72 (m, 2H, CH_2O), 3.63 (m, 2H, H-5 , $\text{H-5}'$), 3.58 (d, 2H, H-4 , $\text{H-4}'$), 3.49 (m, 2H, CH_2O), 3.48 (dd, 2H, H-3 , $\text{H-3}'$), 3.29 (dd, 2H, H-2 , $\text{H-2}'$), 1.47 (m, 4H, 2 CH_2), 1.23 (m, 4H, 2 CH_2), 1.09 (d, 6H, H-6 , $\text{H-6}'$); FAB MS m/z (%) 450 $[\text{M}+\text{K}]^+$ (50), 433 $[\text{M}+\text{Na}]^+$ (100); HRMS Calcd for $\text{C}_{18}\text{H}_{34}\text{NaO}_{10}$: 433.2048. Found: 433.2056.

3-[2-(2,3,4-Tri-*O*-acetyl- β -L-fucopyranosyloxy)ethoxy]propyl 2,3,4-Tri-*O*-acetyl- β -L-fucopyranoside (3c). Compounds **6a** (80 mg, 0.25 mmol) and **4d** (196 mg, 0.5 mmol), with silver salicylate (92 mg, 0.38 mmol) in chloroform (5 mL) were stirred in the dark at room temperature for 24 h. The suspension was diluted with chloroform (15 mL), filtered and extracted with water (3 mL), saturated NaHCO₃ solution (3 mL) and with water (3 mL) again. The organic phase was dried over MgSO₄ and concentrated. The residue was purified by chromatography using ethyl acetate/methanol 10:0.5 v/v as the mobile phase to give **3c** (120 mg, 73%): R_f 0.62 (ethyl acetate/methanol 10:0.5 v/v); ¹H NMR (CDCl₃) δ 5.17 (dd, 2H, H-4, H-4'), 5.13 (dd, 2H, H-2, H-2'), 4.98 (dd, 2H, H-3, H-3'), 4.47 (d, 2H, H-1, H-1', J_{1,2}=J_{1',2'}=8.7 Hz), 3.92 (m, 2H, CH₂O), 3.66 (m, 2H, CH₂O), 3.58 (m, 4H, 2 CH₂O), 2.12, 2.03, 1.94 (3s, 18H, 6 OAc), 1.75 (m, 2H, CH₂), 1.17 (d, 6H, H-6, H-6'); FAB MS *m/z* (%) 687 [M+Na]⁺ (53), 133 (100); HRMS Calcd for C₂₉H₄₄NaO₁₇: 687.2475. Found: 687.2479.

6-(2,3,4-Tri-*O*-acetyl- β -L-fucopyranosyloxy)hexyl 2,3,4-Tri-*O*-acetyl- β -L-fucopyranoside (3d). **Method A:** Compounds **4e** (360 mg, 0.92 mmol) and **6a** (100 mg, 0.32 mmol) were dissolved in chloroform (1 mL). Silver salicylate (120 mg, 0.48 mmol) was added and the reaction mixture was stirred in the dark at room temperature for 24 h. The suspension was diluted with chloroform (20 mL), filtered and extracted with water (3 mL), saturated NaHCO₃ solution (3 mL) and with water (3 mL) again. The organic phase was dried over MgSO₄ and concentrated. The residue was purified by chromatography using hexane/ether/methanol/acetic acid 15:15:2.5:0.5 v/v/v/v as the mobile phase to give **3d** (120 mg, 71%). **Method B:** **6b** (263 mg, 0.79 mmol), 1,6-hexanediol (46 mg, 0.39 mmol), molecular sieves 4Å (4.0 g) and DMTST (480 mg, 1.86 mmol) were stirred in dichloromethane (5 mL) for 30 minutes. Triethylamine (0.5 mL) was added and the mixture was diluted with dichloromethane (15 mL). The mixture was filtered and the filtrate was extracted with saturated NaHCO₃ solution (3 mL), and washed with water (4 mL). The solution was dried over MgSO₄ and concentrated. The residue was purified by chromatography with ethyl acetate/methanol 10:0.25 v/v as the mobile phase, to give **3d** (217 mg, 83%): R_f 0.58 (ethyl acetate/methanol 10:0.25 v/v); ¹H NMR (CDCl₃) δ 5.21 (d, 2H, H-4, H-4'), 5.14 (dd, 2H, H-2, H-2'), 5.00 (dd, 2H, H-3, H-3'), 4.40 (d, 2H, H-1, H-1', J_{1,2}=J_{1',2'}=9.2 Hz), 3.87 (m, 2H, CH₂O), 3.78 (m, 2H, H-5, H-5'), 3.43 (m, 2H, CH₂O), 2.14, 2.01, 1.96 (3s, 18H, 6 OAc), 1.55 (m, 4H, 2 CH₂); FAB MS

m/z (%) 685 $[M+Na]^+$ (53), 133 (100); HRMS Calcd for $C_{30}H_{46}NaO_{16}$: 685.2682. Found: 685.2692.

2-(3-Hydroxypropoxy)ethyl β -L-Fucopyranoside Hydrogensulfate (4a).

Compound **4f** (150 mg, 0.31 mmol) was dissolved in methanol (5 mL) and sodium methoxide (40 mg, 0.74 mmol) was added. The reaction mixture was stirred for 2 h at room temperature then neutralised with ion exchange resin. The solution was filtered, concentrated, and the residue was purified by chromatography using ethyl acetate/methanol/water 10:5:3 v/v/v as the mobile phase to give **4a** (93 mg, 85%): R_f 0.43 (ethyl acetate/methanol/water 10:5:3 v/v/v); 1H NMR (D_2O) δ 4.26 (d, 1H, H-1, $J_{1,2}$ = 7.63 Hz), 3.99 (t, 2H, CH_2O), 3.87 (m, 1H, CH_2Oa), 3.68 (m, 1H, CH_2Ob), 3.66 (m, 1H, H-5), 3.58 (d, 1H, H-4), 3.52 (m, 4H, 2 CH_2O), 3.49 (dd, 1H, H-3), 3.35 (dd, 1H, H-2), 1.83 (m, 2H, CH_2), 1.11 (d, 3H, H-6); FAB MS m/z (%) 391 $[M+2Na]^+$ (48); HRMS Calcd for $C_{11}H_{22}Na_2O_{10}S$: 391.0649. Found: 391.0641.

6-Hydroxyhexyl β -L-Fucopyranoside 6-Hydrogensulfate (4b). 4g (40 mg, 0.085

mmol) was dissolved in methanol (3 mL) and sodium methoxide (40 mg, 0.74 mmol) was added. The reaction mixture was stirred for 2 h at room temperature and neutralised with ion exchange resin. The solution was concentrated and the residue was purified by chromatography using ethyl acetate/methanol/water 10:5:3 v/v/v as the mobile phase to give **4b** (22 mg, 72%): R_f 0.46 (ethyl acetate/methanol/water 10:5:3 v/v/v); 1H NMR (D_2O) δ 4.22 (d, 1H, H-1, $J_{1,2}$ = 7.88 Hz), 3.92 (t, 2H, CH_2O), 3.73 (m, 1H, CH_2Oa), 3.62 (m, 1H, H-5), 3.58 (d, 1H, H-4), 3.51 (m, 1H, CH_2Ob), 3.47 (dd, 1H, H-3), 3.30 (dd, 1H, H-2), 1.56-1.47 (m, 4H, 2 CH_2), 1.30-1.20 (m, 4H, 2 CH_2), 1.10 (d, 3H, H-6); FAB MS m/z (%) 389 $[M+2Na]^+$ (26); HRMS Calcd for $C_{12}H_{24}Na_2O_9S$: 389.0857. Found: 389.0863.

2-(3-Benzoyloxypropoxy)ethyl 2,3,4-Tri-O-acetyl- β -L-fucopyranoside (4c).

Compounds **5** (750 mg, 3.57 mmol), and **6a** (1.0 g, 3.24 mmol), with silver salicylate (1.18 g, 4.86 mmol) were stirred in chloroform (10 mL) in darkness at room temperature for 10 h. The mixture was filtered and the filtrate was extracted with saturated $NaHCO_3$ (2 mL) and water (2 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography using chloroform/ether 10:2 v/v as the mobile phase to give **4c** (1.14 g, 73.5%): R_f 0.51 (chloroform/ether 10:2 v/v); 1H NMR ($CDCl_3$) δ 7.27-7.18 (m, 5H, 5 Ar-H), 5.13 (dd, 1H, H-4), 5.10 (dd, 1H, H-2), 4.91 (dd, 1H, H-3), 4.48 (d, 1H, H-1, $J_{1,2}$ = 7.9 Hz), 4.45 (s, 2H, CH_2Ar), 3.87 (m, 1H,

CH₂Oa), 3.69 (m, 1H, H-5), 3.62 (m, 1H, CH₂Ob), 3.50-3.45 (m, 6H, 3 CH₂O), 2.10, 1.96, 1.92 (3s, 9H, 3 OAc), 1.82 (m, 2H, CH₂), 1.14 (d, 3H, H-6); FAB MS *m/z* (%) 505 [M+Na]⁺ (100), 273 (42), 91 (51); HRMS Calcd for C₂₄H₃₄NaO₁₀: 505.2059. Found: 505.2038.

2-(3-Hydroxypropoxy)ethyl 2,3,4-Tri-*O*-acetyl-β-L-fucopyranoside (4d).

Compound **4c** (210 mg, 0.43 mmol) was dissolved in methanol (7 mL) and hydrogenated at room temperature using Pd/C 10% (70 mg). The mixture was filtered and the solvent was evaporated. The residue was purified by chromatography using ethyl acetate/methanol 10:0.5 v/v as the mobile phase to give **4d** (157 mg, 92%): R_f 0.53 (ethyl acetate/methanol 10:0.5 v/v); ¹H NMR (CDCl₃) δ 5.18 (dd, 1H, H-4), 5.15 (dd, 1H, H-2), 4.97 (dd, 1H, H-3), 4.48 (d, 1H, H-1, J_{1,2}=8.6 Hz), 3.96 (m, 1H, CH₂Oa), 3.78 (m, 1H, H-5), 3.71 (t, 2H, CH₂O), 3.66 (m, 1H, CH₂Ob), 3.60 (m, 4H, 2 CH₂O), 2.13, 2.03, 1.94 (3s, 9H, 3 OAc), 1.78 (m, 2H, CH₂), 1.19 (d, 3H, H-6); FAB MS *m/z* (%) 415 [M+Na]⁺ (100), 393 [M+H]⁺ (6), 273 (27); HRMS Calcd for C₁₇H₂₈NaO₁₀: 415.1580. Found: 415.1591.

6-Hydroxyhexyl 2,3,4-Tri-*O*-acetyl-β-L-fucopyranoside (4e). Compound **6a** (0.84 g, 2.72 mmol) and 1,6-hexanediol (0.6 g, 5.45 mmol) were dissolved in chloroform (3 mL). Silver salicylate (1.0 g, 4.08 mmol) was added and the reaction mixture was stirred in the dark at room temperature for 24 h. The suspension was diluted with chloroform (15 mL), filtered, and extracted with water (2 mL), then with saturated NaHCO₃ solution (2 mL), and with water (2 mL) again. The organic phase was dried over MgSO₄ and concentrated. The residue was purified by flash chromatography using ethyl acetate/methanol 10:0.5 v/v as the mobile phase to give **4e** (880 mg, 83%): R_f 0.52 (ethyl acetate/methanol 10:0.5 v/v); ¹H NMR (CDCl₃) δ 5.22 (dd, 1H, H-4), 5.17 (dd, 1H, H-2), 5.00 (dd, 1H, H-3), 4.41 (d, 1H, H-1, J_{1,2}=7.9 Hz), 3.88 (m, 1H, H-5), 3.77 (m, 1H, CH₂Oa), 3.62 (t, 2H, CH₂O), 3.44 (m, 1H, CH₂Ob), 2.15, 2.02, 1.96 (3s, 9H, 3 OAc), 1.56 (m, 4H, 2 CH₂), 1.37 (m, 4H, 2 CH₂), 1.20 (d, 3H, H-6); FAB MS *m/z* (%) 413 [M+Na]⁺ (100), 391 [M+H]⁺ (6), 273 (52); HRMS Calcd for C₁₈H₃₀NaO₉: 413.1787. Found: 413.1780.

2-(3-Hydroxypropoxy)ethyl 2,3,4-Tri-*O*-acetyl-β-L-fucopyranoside Hydrogensulfate (4f). Pyridine (10 mL) was cooled to 0 °C and chlorosulfonic acid (590 mg, 5.00 mmol) and **4d** (200 mg, 0.50 mmol) were added. The reaction mixture was stirred at 0 °C for 3 h then methanol (0.2 mL) was added. The reaction mixture was

concentrated and toluene (3 mL) was distilled off. The crude product was purified by chromatography using ethyl acetate/methanol 10:3 v/v as the mobile phase, to give **4f** (175 mg, 73%): R_f 0.36 (ethyl acetate/methanol 10:3 v/v); ^1H NMR (CDCl_3) δ 5.22 (d, 1H, H-4), 5.14 (t, 1H, H-2), 5.05 (dd, 1H, H-3), 4.56(d, 1H, H-1, $J_{1,2}=7.83$ Hz), 4.17 (t, 2H, CH_2O), 3.93 (m, 1H, CH_2Oa), 3.85 (m, 1H, H-5), 3.74 (m, 1H, CH_2Ob), 3.57 (m, 4H, 2 CH_2), 2.19, 2.07, 1.98 (3s, 9H, 3 OAc), 1.94 (m, 2H, CH_2), 1.21 (d, 3H, H-6); FAB MS m/z (%) 517 $[\text{M}+2\text{Na}]^+$ (25), 415 (7); HRMS Calcd for $\text{C}_{17}\text{H}_{28}\text{Na}_2\text{O}_{13}\text{S}$: 517.0966. Found: 517.0968.

6-Hydroxyhexyl 2,3,4-Tri-*O*-acetyl- β -L-fucopyranoside 6-Hydrogensulfate (4g).

Pyridine (2 mL) was cooled to 0 °C and chlorosulfonic acid (180 mg, 1.50 mmol) and **4e** (60 mg, 0.15 mmol) were added. The reaction mixture was stirred at 0 °C for 3 h then methanol (0.2 mL) was added. The mixture was concentrated and toluene (3 mL) was distilled from the residue. The crude product was purified by chromatography twice using ethyl acetate/methanol 10:3 v/v firstly, and dichloromethane/methanol 10:2 v/v secondly as the mobile phase to give **4g** (57 mg, 81%): R_f 0.38 (ethyl acetate/methanol 10:3 v/v); ^1H NMR (CDCl_3) δ 5.22 (d, 1H, H-4), 5.11 (dd, 1H, H-2), 5.03 (dd, 1H, H-3), 4.44 (d, 1H, H-1, $J_{1,2}=7.9$ Hz), 4.02 (t, 2H, CH_2O), 3.87 (m, 1H, CH_2Oa), 3.82 (m, 1H, H-5), 3.45 (m, 1H, CH_2Ob), 2.18, 2.08, 2.02 (3s, 9H, 3 OAc), 1.72-1.50 (m, 4H, 2 CH_2), 1.38-1.23 (m, 4H, 2 CH_2), 1.20 (d, 3H, H-6); FAB MS m/z (%) 515 $[\text{M}+2\text{Na}]^+$ (100), 413 (35), 307 (35); HRMS Calcd for $\text{C}_{18}\text{H}_{30}\text{Na}_2\text{O}_{12}\text{S}$: 515.1173. Found: 515.1166.

***trans*-2-(3-Benzoyloxypropoxy)cyclohexanol (8).** 3-Benzoyloxypropyl 4-toluenesulphonate (3.87 g, 12.09 mmol), *trans*-1,2-cyclohexanediol (6.3 g, 55.2 mmol), and potassium hydroxide (1.5 g, 26.78 mmol) in xylene (16 mL) were stirred at 120-130 °C for 3 h. The reaction mixture was allowed to cool and benzene (46 mL) was added. The suspension was extracted with water (21 mL) and the organic phase was dried over MgSO_4 and concentrated. The residue was purified by chromatography using hexane/ethyl acetate 1:1 v/v as the mobile phase to give **8** (2.08 g, 65.2%): R_f 0.5 (hexane/ethyl acetate 1:1 v/v); ^1H NMR (CDCl_3) δ 7.31-7.16 (m, 5H, 5 Ar-H), 4.46 (s, 2H, CH_2Ar), 3.67 (m, 1H, CHO), 3.52 (m, 2H, CH_2O), 3.42 (m, 1H, CHO), 3.31 (m, 1H, CH_2Oa), 2.93 (m, 1H, CH_2Ob), 2.01-2.89 (m, 2H, CH_2), 1.81 (m, 2H, CH_2), 1.63 (m, 2H, CH_2), 1.22-0.97 (m, 4H, 2 CH_2); FAB MS m/z (%) 282 $[\text{M}+\text{NH}_3+\text{H}]^+$ (63), 265 $[\text{M}+\text{H}]^+$ (100), 91 (6); HRMS Calcd for $\text{C}_{16}\text{H}_{25}\text{O}_3$: 265.1804. Found: 265.1811.

***trans*-2-(3-Benzoyloxypropoxy)cyclohexyl 2,3,4-Tri-*O*-acetyl- β -L-fucopyranoside (9a).** Compounds **8** (260 mg, 0.98 mmol) and **6b** (430 mg, 1.28 mmol), molecular sieves 4Å (5.0 g) and DMTST (525 mg, 2.95 mmol) in dichloromethane (10 mL) were stirred for 1 h. Triethylamine (1 mL) was added, and the mixture was diluted with dichloromethane (15 mL) and filtered. The filtrate was extracted with saturated NaHCO₃ solution (3 mL), washed with water (3 mL), dried over MgSO₄ and concentrated. The residue was purified by chromatography with hexane/ether/methanol 5:7:0.5 v/v/v as the mobile phase to give **9a** (400 mg, 76%): *R*_f 0.38 (hexane/ether/methanol 5:7:0.5 v/v/v); ¹H NMR (CDCl₃) δ 7.35-7.23 (m, 5H, 5 Ar-H), 5.20 (m, 1H, H-4), 5.16 (t, 1H, H-2), 4.97 (dd, 1H, H-3), 4.75, 4.52 (2d, 1H, H-1, *J*_{1,2}=7.98 Hz), 4.48 (s, 2H, CH₂Ar), 3.73 (m, 1H, H-5), 3.60 (2t, 4H, 2 CH₂O), 3.33 (m, 1H, CHO), 3.12 (m, 1H, CHO), 2.18, 2.13, 2.03, 1.98, 1.96 (5s, 9H, 3 OAc), 1.84 (m, 2H, CH₂), 1.76-1.35 (m, 8H, 4 CH₂), 1.19 (d, 3H, H-6); FAB MS *m/z* (%) 559 [M+Na]⁺ (100), 273 (20), 153 (23), 111 (19); HRMS Calcd for C₂₈H₄₀NaO₁₀: 559.2518. Found: 559.2514.

***trans*-2-(3-Hydroxypropoxy)cyclohexyl 2,3,4-Tri-*O*-acetyl- β -L-fucopyranoside (9b).** Compound **9a** (357 mg, 0.66 mmol) and Pd/C 10% (500mg) catalyst were stirred in methanol (5 mL) under hydrogen for 2 days. The catalyst was filtered off and the filtrate was concentrated. The residue was purified by chromatography with hexane/ether/methanol 3:7:1 v/v/v as the mobile phase to give **9b** (282 mg, 95%): *R*_f 0.43 (hexane/ether/methanol 3:7:1 v/v/v); ¹H NMR (CDCl₃) δ 5.20 (dd, 1H, H-4), 5.15 (m, 1H, H-2), 5.00 (dd, 1H, H-3), 4.73, 4.51 (2d, 1H, H-1, *J*_{1,2}=7.96 Hz), 3.76, 3.65 (2t, 4H, 2 CH₂O), 3.59, 3.51 (2m, 1H, CHO), 3.22, 3.16 (2m, 1H, CHO), 2.18, 2.16, 2.06, 2.04, 1.97 (5s, 9H, 3 OAc), 1.78 (m, 2H, CH₂), 1.22, 1.19 (2d, 3H, H-6); FAB MS *m/z* (%) 469 [M+Na]⁺ (45), 447 [M+H]⁺ (10), 273 (100); HRMS Calcd for C₂₁H₃₄NaO₁₀: 469.2049. Found: 469.2040.

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