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Synthesis of two analogues of the Sd^a determinant. Replacement of the sialic acid residue by a sulfate or a carboxymethyl group

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Abstract

Two analogues of the Sd^a determinant tetrasaccharide have been synthesized in order to investigate the physiological role of this carbohydrate moiety. These saccharides, having two different anionic substitutes for the sialic acid residue, are: β-D-Gal*p*NAc-(1 → 4)-3-*O*-SO_3H-β-D-Gal*p*-(1 → 4)-β-D-Glc*p*NAc-(1 → O)$(CH_2)_5NH_2$ and β-D-Gal*p*NAc-(1 → 4)-3-*O*-CH_2COOH-β-D-Gal*p*-(1 → 4)-β-D-Glc*p*NAc-(1 → O)$(CH_2)_5NH_2$. 5-Azidopentyl (2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1 → 4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside served as a general building block. The trisaccharides were obtained after prior selective derivatization of HO-3′ of the disaccharide derivative via a dibutyltin oxide mediated reaction, followed by coupling at HO-4′ with 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-galactopyranosyl trichloroacetimidate, and processing of the formed trisaccharide derivatives into their free forms. © 1997 Elsevier Science Ltd.

Keywords: Sd^a determinant, analogues; Tamm–Horsfall glycoprotein; Oligosaccharide, chemical synthesis

1. Introduction

The Sd^a determinant [1], α-Neu*p*5Ac-(2 → 3)-[β-D-Gal*p*NAc-(1 → 4)]-β-D-Gal*p*-(1 → 4)-β-D-Glc*p*NAc-(1 → R, occurring on human erythrocytes and detected in human tissues such as stomach, kidney, and colon [2,3], is typically found in N-glycans of the renal-specific human Tamm–Horsfall glycoprotein (TH-gp) [4]. TH-gp is a phosphatidylinositol-linked membrane protein that can be found in high concentrations in urine after cleavage from the membrane [5]. The physiological function of TH-gp is still unclear; however, several studies have indicated a role for TH-gp as a natural inhibitor of microbial infection of the urinary tract and urinary bladder. Both oligomannose and sialylated complex-type carbohydrate chains were reported to be involved in the inhibitory action of TH-gp against the adherence of *Escherichia coli* fimbriae to uroepithelial cells [6,7]. The carbohydrate chains of TH-gp have also been implicated in the binding of TH-gp to neu-

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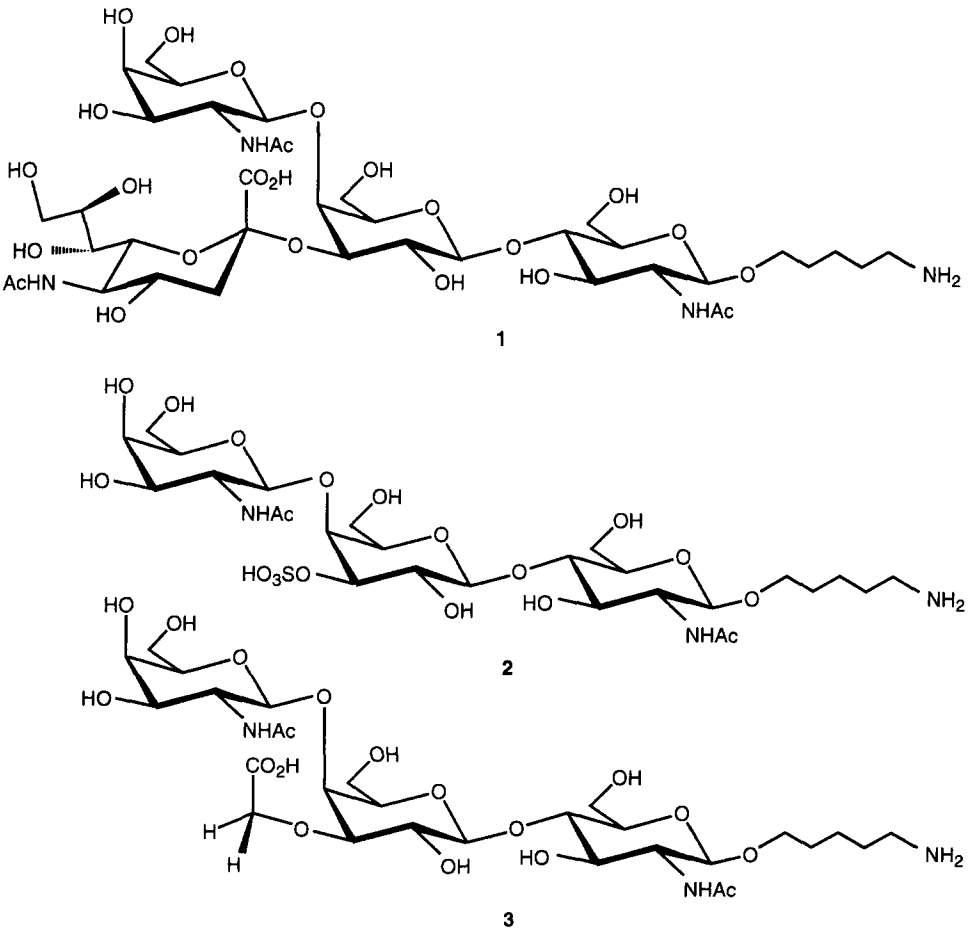
trophils [8] and in immunosuppressive properties displayed by TH-gp [9].

As part of the attempt to elucidate of the significance of the Sd^a determinant in these biological events, α-Neu*p*5Ac-(2 → 3)-[β-D-Gal*p*NAc-(1 → 4)]-β-D-Gal*p*-(1 → 4)-β-D-Glc*p*NAc-(1 → O)$(CH_2)_5NH_2$ (**1**) and two tetrasaccharide analogues of the Sd^a determinant, wherein GalNAc has been replaced by Gal or GlcNAc, have been synthesized [10]. Sulfate groups may in some biological systems serve as effective substitutes for sialic acid [11]. Moreover, the carboxymethyl group in analogues of sialyl Lewis X was shown to be useful for mimicking the negative charge of sialic acid [12]. Therefore, the syntheses of sulfate-analogue β-D-Gal*p*NAc-(1 → 4)-3-*O*-SO_3H-β-D-Gal*p*-(1 → 4)-β-D-Glc*p*NAc-(1 → O)$(CH_2)_5NH_2$ (**2**) and carboxymethyl-analogue β-D-Gal*p*NAc-(1 → 4)-3-*O*-CH_2COOH-β-D-Gal*p*-(1 → 4)-β-D-Glc*p*NAc-(1 → O)$(CH_2)_5NH_2$ (**3**) are deemed relevant and are described in this paper (see Scheme 1).

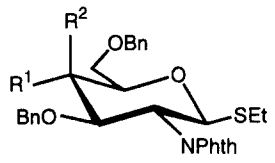
2. Results and discussion

Sulfate-analogue **2**.—The synthesis of **2** involved the regio-selective etherification of HO-3′ of 5-azidopentyl (2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1 → 4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside [10] (**4**) with the temporary protecting *p*-methoxybenzyl group via a dibutyltin oxide [13] mediated reaction, using *p*-methoxybenzyl chloride and tetrabutylammonium iodide in boiling toluene (→ **5**, 95%) [14] (see Scheme 2). The structure of **5** was confirmed by ^1H NMR analysis of the corresponding 4′-*O*-acetyl derivative **6**, which was obtained after acetylation of **5** with acetic anhydride–pyridine. A characteristic signal for **6** was found at δ 5.515 (dd, 1 H, $J_{3',4'}$ 3.0, $J_{4',5'} < 1$ Hz, H-4′), indicating the new ether bond to be at O-3′. In the first instance, for the synthesis of a suitable GalNAc donor for condensation with **5**, the use of ethyl 3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-

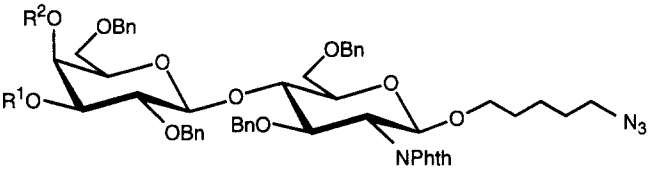


Scheme 1.

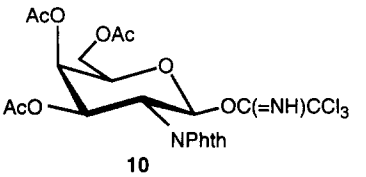
glucopyranoside [15] (**7**), already applied as a building block for the synthesis of lactosamine derivative **4** [10], was investigated as precursor. Reaction of **7** with trifluoromethanesulfonic anhydride [16] in dichloromethane–pyridine (→ **8**), and subsequent treatment with tetrabutylammonium acetate in *N,N*-dimethylformamide yielded the *galacto*-derivative **9** (91%). Coupling of **9** with **5** was unsuccessful using the promoter systems *N*-iodosuccinimide (NIS)-triflic acid (TfOH) [17] or methyl triflate [18]. Moreover, in these attempts to glycosylate **5**, the cleavage of the *p*-methoxybenzyl group was observed. Also the use



	R^1	R^2
7	OH	H
8	OTf	H
9	H	OAc



	R^1	R^2
4	H	H
5	pMBn	H
6	pMBn	Ac
17	CH_2COOMe	H
18	CH_2COOMe	Ac



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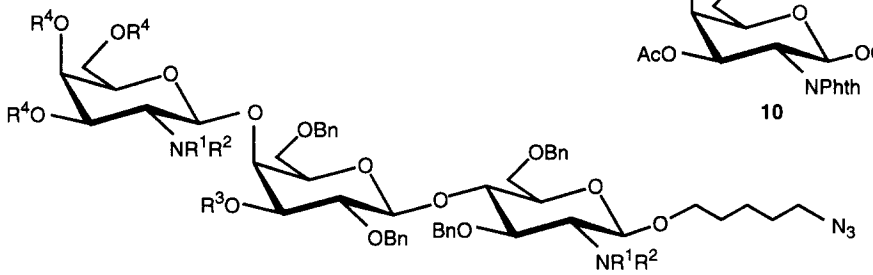
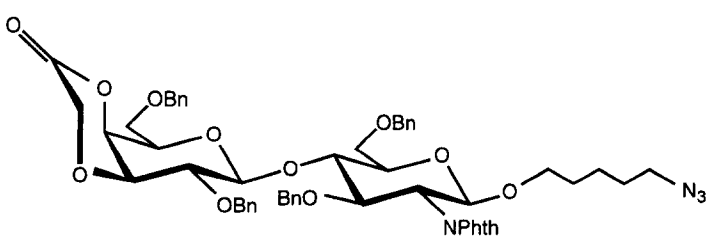


		R^1	R^2	R^3	R^4
5 + 10 →	**11**		Phth	pMBn	Ac
	12	H	Ac	pMBn	Ac
	13	H	Ac	H	Ac
	14	H	Ac	SO_3Na	Ac
	15	H	Ac	SO_3Na	H
17 + 10 →	**19**		Phth	CH_2COOMe	Ac
	20		Phth	CH_2COOH	Ac
	21	H	Ac	CH_2COOH	Ac
	22	H	Ac	CH_2COONa	H



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Scheme 2.

of dimethyl(thiomethyl)sulfonium tetrafluoroborate [19] as a promoter, applied successfully before in the presence of a *p*-methoxybenzyl group [20], failed. Therefore, in another approach 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-galactopyranosyl trichloroacetimidate [21] (**10**) was investigated as a donor. Condensation of **10** with **5** in toluene at −25 °C, using trimethylsilyl triflate as a catalyst, gave trisaccharide derivative **11** (64%). Dephthaloylation of **11**, using 1,2-diaminoethane [22] in *n*-butanol at 75 °C, followed by re-*N,O*-acetylation using acetic anhydride–pyridine resulted in the formation of **12** (93%), and subsequent de-*p*-methoxybenzylation, using ammonium cerium(IV) nitrate in acetonitrile–water, yielded **13** (74%). The sulfation of **13** was carried out with the sulfur trioxide–trimethylamine complex in anhydrous *N,N*-dimethylformamide at 55 °C and the formed product (**14**, 95%) was deacetylated (→ **15**, 95%), then hydrogenolyzed using palladium on carbon, to afford the target compound **2** (62%). For ^{1}H NMR data, see Table 1.

Carboxymethyl-analogue **3**.—For the synthesis of **3**, as a first step the regio-selective introduction of the methoxycarbonylmethyl group at HO-3′ of **4** [10] was carried out, using dibutyltin oxide and methyl bromoacetate. In the first instance the 3′,4′-lactonized disaccharide derivative **16** was formed almost exclusively (see Scheme 2), but the lactone ring could be opened easily by treatment with sodium methoxide in methanol, affording **17** (82%). The regio-selectivity of the reaction was proven by ^{1}H NMR analysis of the corresponding 4′-*O*-acetyl derivative **18**, which was obtained after acetylation of **17** with acetic anhydride–pyridine. Glycosylation of **17** with **10** in toluene at −35 °C, using trimethylsilyl triflate as a catalyst and applying the inversed addition procedure [23], afforded **19** (65%). Deprotection of **19**, using LiI [24] in anhydrous pyridine at 115 °C (→ **20**), followed by treatment with 1,2-diaminoethane in *n*-butanol, re-*N,O*-acetylation with acetic anhydride–pyridine (→ **21**), deacetylation (→ **22**), and finally catalytic hydrogenolysis, using palladium on carbon, afforded an overall yield of 24% the carboxymethyl-analogue **3**. For ^{1}H NMR data, see Table 1. The obtained moderate overall yield could partly be ascribed to the sluggish hydrogenolysis, which was probably caused by the presence of the 5-azidopentyl spacer. A similar observation was made by Spijker et al. [25] and Stahl et al. [26], who also reported moderate yields for the catalytic hydrogenolysis of azido-alkyl glycosides. It has to be noted that an inhibitory effect of aliphatic amines [27] on *O*-benzyl hydrogenolysis could have played a role too.

Compounds **2** and **3** are suitable for conjugation to a carrier by the presence of the 5-aminopentyl spacer, facilitating the planned evaluation of these com-

Table 1
500-MHz ^{1}H NMR data of trisaccharides **2** and **3**, as well as that of tetrasaccharide **1** [10] as a reference compound, having the general formula: β-D-Gal*p*NAc-(1 → 4)-[X]-β-D-Gal*p*-(1 → 4)-β-D-Glc*p*NAc-(1 → O)$(CH_2)_5NH_2$

Residue	Proton (*J*)	δ (ppm) / *J* (Hz)		
		1 X = α-Neu*p*5Ac-(2 → 3)	**2** X = 3-*O*-SO_3H	**3** X = 3-*O*-CH_2COOH
β-D-Glc*p*NAc	H-1 ($J_{1,2}$)	4.514 [a] (8.1)	4.518 [a] (8.0)	4.515 [a] (7.3)
	H-2 ($J_{2,3}$)	3.71	3.72	3.71
	NAc	2.031	2.033	2.031
β-D-Gal*p*	H-1 ($J_{1,2}$)	4.549 (8.0)	4.567 (7.8)	4.485 (7.3)
	H-2 ($J_{2,3}$)	3.356 (9.8)	3.508 (10.4)	3.465 (9.9)
	H-3 ($J_{3,4}$)	4.149 (2.8)	4.393 (2.9)	3.522 (2.3)
	H-4 ($J_{4,5}$)	4.113 (< 1)	4.405 (< 1)	4.299 (< 1)
β-D-Gal*p*NAc	H-1 ($J_{1,2}$)	4.731 (8.6)	4.618 (8.3)	4.570 (8.5)
	H-2 ($J_{2,3}$)	3.91	3.925 (11.0)	3.92
	H-3 ($J_{3,4}$)	3.68	3.750 (3.0)	3.70 (3.4)
	H-4 ($J_{4,5}$)	n.d. [b]	3.917 (< 1)	3.909 (< 1)
	NAc	2.014	2.081	2.054
Carboxymethyl	OCH_aH_bCOOH (^2J)	–	–	4.145 (−15.7)
	OCH_aH_bCOOH	–	–	4.069
5-Aminopentyl	$O(CH_2)_4CH_2NH_2$	2.951	2.968	2.972

[a] Virtual coupling to H-3.
[b] n.d.: not determined.

pounds in biochemical recognition assays with *E. coli* fimbriae and with human anti-Sd^a antibodies. Additionally, these compounds could be useful for the investigation of their possible immunoregulatory properties.

3. Experimental

General methods.—Reactions were monitored by TLC on Kieselgel 60 F_{254} (E. Merck), by detection with UV light and then charring with aq 50% H_2SO_4. Column chromatography was performed on Kieselgel 60 (E. Merck, 70–230 mesh), and size-exclusion chromatography on Sephadex LH-20. Solvents were evaporated under reduced pressure at 40 °C (water bath). Optical rotations were measured for solns in $CHCl_3$, unless otherwise stated, at 20 °C with a Perkin–Elmer 241 polarimeter, using a 10-cm 1-mL cell. The ^1H (300 MHz) and ^{13}C (APT, 75 MHz) NMR spectra were recorded at 27 °C with a Bruker AC-300 spectrometer or a Varian Gemini-300 instrument (^{13}C only). Two-dimensional double-quantum filtered ^1H–^1H correlation spectra (2D DQF ^1H–^1H COSY) were recorded using a Bruker AMX 500 apparatus (500 MHz) at 27 °C. Chemical shifts (δ) are given in ppm relative to the signal for internal Me_4Si (δ 0) for solns in $CDCl_3$, indirectly to CD_3OD (δ 3.30) for solns in CD_3OD, or by reference to acetone (δ 2.225) for solns in D_2O (pH ~ 8; pH meter reading has not been corrected for D isotope effect), for ^1H, and indirectly to $CDCl_3$ (δ 76.9) for solns in $CDCl_3$ or indirectly to CD_3OD (δ 49.0) for solns in CD_3OD, for ^{13}C. Fast-atom-bombardment mass spectrometry (FABMS) was performed on a JEOL JMS SX/SX 102A four-sector mass spectrometer, operated at 10 kV accelerating voltage, equipped with a JEOL MS-FAB 10 D FAB gun, operated at 10 mA emission current, producing a beam of 6-keV Xenon atoms. Elemental analyses were carried out by H. Kolbe Mikroanalytisches Laboratorium (Mülheim an der Ruhr, Germany).

5-Azidopentyl (2,6-di-O-benzyl-3-O-p-methoxybenzyl-β-D-galactopyranosyl)-(1 → 4)-3,6-di-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**5**).—To a soln of 5-azidopentyl (2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1 → 4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside [10] (**4**; 1.09 g, 1.16 mmol) in dry MeOH (20 mL) was added dibutyltin oxide (456 mg, 1.83 mmol) and the mixture was stirred overnight at 60 °C under Ar. After cooling to room temperature, the mixture was concd and the residue dissolved in dry toluene (45 mL). Bu_4NI (175 mg, 0.47 mmol) and powdered 4 Å molecular sieves (0.5 g) were added and the mixture was stirred for 0.5 h at room temperature under Ar. Then, *p*-methoxybenzyl chloride (475 μL, 3.50 mmol) was added and the mixture was stirred for 4.5 h at 120 °C, when TLC (5:1 toluene–EtOAc) showed the disappearance of **4** (R_f 0.07) and the formation of **5** (R_f 0.43). After cooling to room temperature toluene (50 mL), MeOH (1 mL), and triethylamine (0.2 mL) were added and the stirring was continued for 15 min. After filtration through Celite and concn, column chromatography (5:1 toluene–EtOAc) of the residue afforded **5**, isolated as a colourless syrup (1.17 g, 95%); $[\alpha]_D$ +14° (*c* 1); NMR ($CDCl_3$): ^1H, δ 7.75–6.82 (m, 28 H, 4 Ph, $MeOC_6H_4CH_2O$ and Phth), 5.087 (d, 1 H, $J_{1,2}$ 8.3 Hz, H-1), 4.431 (d, 1 H, $J_{1',2'}$ 7.8 Hz, H-1'), 3.982 (bt, 1 H, H-4'), 3.798 (s, 3 H, CH_3OPhCH_2O), 2.452 (d, 1 H, $J_{HO,4'}$ 2.1 Hz, HO-4'); ^{13}C, δ 159.2, 129.8, 129.3 (2 C), and 113.7 (2 C) ($MeOC_6H_4CH_2O$), 102.8 (C-1'), 98.1 (C-1), 75.2, 74.3, 73.4, 72.9, 71.6, 68.8, 68.7, and 67.8 (C-6,6', 4 $PhCH_2O$, $MeOPhCH_2O$, and $OCH_2(CH_2)_4N_3$), 55.6 (C-2), 55.1 (CH_3OPhCH_2O), 50.9, 28.6, 28.1, and 22.9 [$OCH_2(CH_2)_4N_3$]. FAB$^+$MS ($C_{61}H_{66}N_4O_{13}$): *m/z* 1063 $[M+H]^+$.

Acetylation of a small amount of **5** with 1:1 acetic anhydride–pyridine, followed by co-concn with toluene (3 ×), EtOH (3 ×), and CH_2Cl_2 (3 ×), afforded **6**; ^1H NMR ($CDCl_3$): δ 7.80–6.80 (m, 28 H, 4 Ph, $MeOC_6H_4CH_2O$ and Phth), 5.515 (dd, 1 H, $J_{3',4'}$ 3.0, $J_{4',5'} < 1$ Hz, H-4'), 5.097 (d, 1 H, $J_{1,2}$ 8.3 Hz, H-1), 3.786 (s, 3 H, CH_3OPhCH_2O), 2.913 (m, 2 H, $O(CH_2)_4CH_2N_3$), 1.988 (s, 3 H, Ac).

Ethyl 4-O-acetyl-3,6-di-O-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-galactopyranoside (**9**).—To a soln of ethyl 3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside [15] (**7**; 1.09 g, 2.05 mmol) in dry pyridine (1.5 mL) and dry CH_2Cl_2 (75 mL), triflic anhydride (1.2 mL, 7.0 mmol) was added at 0 °C under Ar. The mixture was stirred for 30 min at 0 °C and 2 h at room temperature, when TLC (25:5 toluene–acetone) indicated the conversion of **7** into a new product (R_f 0.75) to be complete. The mixture was diluted with EtOAc (250 mL), washed with aq 5% $NaHCO_3$ (2 ×) and water, dried ($MgSO_4$), and concd. A soln of the residue and Bu_4NOAc (3.25 g, 10.8 mmol) in dry DMF (25 mL) was stirred for 16 h at room temperature under Ar, when TLC (97:3 CH_2Cl_2–acetone) showed the reaction to be complete. The mixture was diluted with EtOAc (250 mL) and washed with aq 5% NaCl (2 ×) and water. The

combined aq layers were extracted with EtOAc (2 ×) and the combined organic layers were dried ($MgSO_4$), and concd. Column chromatography (97:3 CH_2Cl_2–acetone) of the residue gave **9**, isolated as a foam (1.09 g, 91%); $[\alpha]_D$ +64° (*c* 1); R_f 0.55 (95:5 CH_2Cl_2–acetone); NMR ($CDCl_3$): ^1H, δ 7.87–7.60 and 7.40–6.85 (m, 14 H, 2 Ph and Phth), 5.708 (dd, 1 H, $J_{3,4}$ 3.3, $J_{4,5} < 1$ Hz, H-4), 5.294 (d, 1 H, $J_{1,2}$ 10.5 Hz, H-1), 4.457 (dd, 1 H, $J_{2,3}$ 10.6 Hz, H-2), 4.314 (dd, 1 H, H-3), 2.648 (m, 2 H, CH_3CH_2S), 2.135 (s, 3 H, Ac), 1.177 (t, 3 H, CH_3CH_2S); ^{13}C, δ 81.3 (C-1), 75.9, 73.4, and 65.9 (C-3,4,5), 73.3, 70.8, and 67.8 (C-6 and 2 $PhCH_2O$), 51.4 (C-2), 24.1 (CH_3CH_2S), 20.7 ($COCH_3$), 14.7 (CH_3CH_2S). Anal. Calcd for $C_{32}H_{33}NO_7S$: C, 66.76; H, 5.78. Found: C, 66.75; H, 5.87.

5-Azidopentyl (3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-galactopyranosyl)-(1 → 4)-(2,6-di-O-benzyl-3-O-p-methoxybenzyl-β-D-galactopyranosyl)-(1 → 4)-3,6-di-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**11**).—To a soln of **5** (233 mg, 0.22 mmol) and 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-galactopyranosyl trichloroacetimidate [21] (**10**; 244 mg, 0.42 mmol) in dry toluene (10 mL) were added 3 Å molecular sieves (0.2 g), and the mixture was stirred for 45 min under Ar. The mixture was cooled to −35 °C and a soln of trimethylsilyl triflate (5.8 μL, 33 μmol) in dry CH_2Cl_2 (0.2 mL) was added. The mixture was stirred for 2.5 h, when TLC (3:2 toluene–EtOAc) showed the disappearance of **5** (R_f 0.73) and the formation of **11** (R_f 0.63). Pyridine (0.2 mL) was added, and the mixture was diluted with toluene (50 mL) and filtered. The filtrate was washed with aq 5% $NaHCO_3$ (2 ×) and water. The aq layers were combined and extracted with toluene (20 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concd. Column chromatography (96:4 CH_2Cl_2–acetone) of the residue on silica gel and subsequent column chromatography (1:1 CH_2Cl_2–MeOH) on Sephadex LH-20 afforded **11**, isolated as a colourless foam (208 mg, 64%); $[\alpha]_D$ −2° (*c* 1); R_f 0.29 (96:4 CH_2Cl_2–acetone); NMR ($CDCl_3$): ^1H, δ 7.97–6.80 (m, 32 H, 4 Ph, $MeOC_6H_4CH_2O$, and 2 Phth), 6.124 (dd, 1 H, $J_{2'',3''}$ 11.7, $J_{3'',4''}$ 3.5 Hz, H-3″), 5.491 (dd, 1 H, $J_{3'',4''}$ 3.6, $J_{4'',5''} < 1$ Hz, H-4″), 5.295 (d, 1 H, $J_{1'',2''}$ 8.4 Hz, H-1″), 5.091 (d, 1 H, $J_{1,2}$ 8.3 Hz, H-1), 3.803 (s, 3 H, CH_3OPhCH_2O), 2.111, 2.005, and 1.834 (3 s, each 3 H, 3 Ac); ^{13}C, δ 159.4, 130.0 (3 C), and 113.7 (2 C) ($MeOC_6H_4CH_2O$), 102.0 (C-1′), 99.4 (C-1″), 98.3 (C-1), 80.1, 79.9, 77.6, 75.3, 73.2, 70.3, 67.3, 66.4, 63.8, and 63.5 (C-3,4,5,2′,3′,4′,5′,3″,4″,5″), 74.8, 74.5, 73.1, 73.0, 72.4, 69.1, 68.8, 67.9, and 61.1 (C-6,6′,6″, 4 $PhCH_2O$, $MeOPhCH_2O$, and $OCH_2(CH_2)_4N_3$), 55.7 (C-2), 55.1 (CH_3OPhCH_2O), 51.3 (C-2″), 51.1, 28.6, 28.2, and 23.0 [$OCH_2(CH_2)_4N_3$]. Anal. Calcd for $C_{81}H_{85}N_5O_{22}$: C, 65.71; H, 5.79. Found: C, 65.76; H, 5.70.

5-Azidopentyl (2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-galactopyranosyl)-(1 → 4)-(2,6-di-O-benzyl-3-O-p-methoxybenzyl-β-D-galactopyranosyl)-(1 → 4)-2-acetamido-3,6-di-O-benzyl-2-deoxy-β-D-glucopyranoside (**12**).—A soln of **11** (194 mg, 131 μmol) and 1,2-diaminoethane (2.2 mL, 33 mmol) in *n*-butanol (8 mL) was stirred overnight at 75 °C under Ar. After cooling to room temperature the mixture was co-concd with toluene (3 ×). A soln of the residue in acetic anhydride (4.5 mL) and pyridine (2 mL) was stirred overnight at room temperature. After co-concn of the mixture with toluene (3 ×), EtOH (3 ×), and CH_2Cl_2 (3 ×), column chromatography (97:3 CH_2Cl_2–MeOH) of the residue afforded **12**, isolated as a colourless syrup (159 mg, 93%); $[\alpha]_D$ +4° (*c* 1); R_f 0.28 (9:1 CH_2Cl_2–MeOH); NMR ($CDCl_3$): ^1H, δ 7.40–6.91 (m, 24 H, 4 Ph and $MeOC_6H_4CH_2O$), 5.797 and 5.468 (2 bd, each 1 H, 2 NH), 5.289 (dd, 1 H, $J_{3'',4''}$ 2.9, $J_{4'',5''} < 1$ Hz, H-4″), 3.826 (s, 3 H, CH_3OPhCH_2O), 2.159, 2.000, 1.937, and 1.655 (4 s, 3,3,6,3 H, 5 Ac); ^{13}C, δ 170.3, 170.2, 170.1, 170.0, and 169.5 (5 $COCH_3$), 159.9, 129.8 (2 C), 129.4, and 114.3 (2 C) ($MeOC_6H_4CH_2O$), 103.0 (2 C) and 99.7 (C-1,1′,1″), 75.2, 74.0, 73.8, 73.3, 73.1, 68.9, 68.8 (2 C), and 61.1 (C-6,6′,6″, 4 $PhCH_2O$, $MeOPhCH_2O$, and $OCH_2(CH_2)_4N_3$), 51.3, 28.9, 28.5, and 23.2 [$OCH_2(CH_2)_4N_3$], 23.4 ($NHCOCH_3$). Anal. Calcd for $C_{69}H_{85}N_5O_{20}$: C, 63.53; H, 6.57. Found: C, 63.39; H, 6.57.

5-Azidopentyl (2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-galactopyranosyl)-(1 → 4)-(2,6-di-O-benzyl-β-D-galactopyranosyl)-(1 → 4)-2-acetamido-3,6-di-O-benzyl-2-deoxy-β-D-glucopyranoside (**13**).—To a soln of **12** (92 mg, 71 μmol) in acetonitrile (4.5 mL) and water (0.5 mL) was added ammonium cerium(IV) nitrate (116 mg, 212 μmol), and the mixture was stirred for 2 h at room temperature. TLC (97:3 CH_2Cl_2–MeOH) then showed the disappearance of **12** (R_f 0.33) and the formation of **13** (R_f 0.26). The mixture was diluted with CH_2Cl_2 (50 mL) and washed with aq 5% $NaHCO_3$ (3 ×). The aq layers were combined and extracted with CH_2Cl_2 (10 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concd. Column chromatography (77:23 CH_2Cl_2–acetone) of the residue afforded **13**, isolated

as a colourless syrup (62 mg, 74%); $[\alpha]_D$ −8° (*c* 1); NMR ($CDCl_3$): ^1H, δ 7.42–7.23 (m, 20 H, 4 Ph), 5.918 and 5.878 (2 bd, each 1 H, 2 NH), 5.309 (dd, 1 H, $J_{3'',4''}$ 3.3, $J_{4'',5''} < 1$ Hz, H-4''), 5.066 (dd, 1 H, $J_{2'',3''}$ 11.1 Hz, H-3''), 2.175, 1.974, 1.969, 1.948, and 1.876 (5 s, each 3 H, 5 Ac); ^{13}C, δ 102.7, 102.4, and 99.6 (C-1,1',1''), 80.6, 77.1, 76.7, 76.3, 75.1, 73.6, 73.5, 71.0, 70.5, and 66.5 (C-3,4,5,2',3',4',5',3'',4'',5''), 75.0, 73.8, 73.2, 73.1, 68.9 (2 C), 68.6, and 61.1(C-6,6',6'', 4 PhCH_2O, and O$CH_2(CH_2)_4N_3$), 55.5 and 51.3 (C-2,2''), 51.2, 28.8, 28.4, and 23.1 [O$CH_2(CH_2)_4N_3$], 23.4 (NHCOCH_3). Anal. Calcd for $C_{61}H_{77}N_5O_{19}$: C, 61.87; H, 6.55. Found: C, 62.36; H, 6.10.

5 - Azidopentyl (2 - acetamido - 2 - deoxy - β - D - galactopyranosyl)-(1 → 4)-(sodium 2,6-di-O-benzyl-β-D-galactopyranosyl 3-sulfate)-(1 → 4)-2-acetamido-3, 6 - di - O - benzyl - 2 - deoxy - β - D - glucopyranoside (**15**).—To a soln of **13** (54 mg, 46 μmol) in dry DMF (2.5 mL) was added sulfur trioxide–trimethylamine complex (346 mg, 2.49 mmol) and the mixture was stirred overnight at 55 °C under Ar. TLC (9:1 CH_2Cl_2–MeOH) then showed the disappearance of **13** and the formation of **14** (R_f 0.40). After cooling to room temperature, MeOH (0.2 mL) was added and stirring was continued for 5 min. The mixture was concd, and a soln of the residue in MeOH (10 mL) was stirred with Dowex-50 (Na^+) for 1 h. Then, the mixture was filtered and concd. Column chromatography (9:1 CH_2Cl_2–MeOH) of the residue afforded **14**, isolated as a white powder (56 mg, 95%); $[\alpha]_D$ +4° (*c* 1); NMR (CD_3OD): ^1H, δ 7.55–7.17 (m, 20 H, 4 Ph), 5.369 (dd, 1 H, $J_{3'',4''}$ 3.4, $J_{4'',5''} < 1$ Hz, H-4''), 2.139, 1.998, 1.968, and 1.935 (4 s, 3,6,3,3 H, 5 Ac); ^{13}C, δ 103.7, 103.5, and 102.8 (C-1,1',1''), 81.7, 81.4, 79.9, 78.2, 77.3, 76.3, 74.6, 72.2, 71.5, and 68.2 (C-3,4,5,2',3',4',5',3'',4'',5''), 76.5 (2 C), 74.3, 74.0, 71.0, 70.3, 69.3, and 62.7 (C-6,6',6'', 4 PhCH_2O, and O$CH_2(CH_2)_4N_3$), 56.4 and 51.9 (C-2,2''), 52.5, 30.1, 29.6, and 24.4 [O$CH_2(CH_2)_4N_3$], 23.5 and 23.0 (2 NHCOCH_3).

To a soln of **14** (49 mg, 38 μmol) in dry MeOH (4 mL) was added NaOMe till pH 9. The mixture was stirred overnight at room temperature, then neutralized with Dowex-50 (H^+), and filtered. To the filtrate was added Dowex-50 (Na^+), and the mixture was stirred for 45 min, then filtered and the soln was concentrated, affording **15** (42 mg, 95%) as a syrup; $[\alpha]_D$ +16° (*c* 1, MeOH); R_f 0.08 (85:15 CH_2Cl_2–MeOH); NMR (CD_3OD): ^1H, δ 7.53–7.19 (m, 20 H, 4 Ph), 2.049 and 1.934 (2 s, each 3 H, 2 NAc); ^{13}C, δ 174.4 and 173.2 (2 NH$COCH_3$), 104.4, 103.7, and 102.7 (C-1,1',1''), 81.8, 81.5, 79.8, 78.4, 77.1, 76.3, 76.1, 74.3, 74.1, and 69.4 (C-3,4,5,2',3',4',5',3'',4'',5''), 76.5, 76.0, 74.2, 74.0, 70.7, 70.3, 69.3, and 62.4 (C-6,6',6'', 4 PhCH_2O, and O$CH_2(CH_2)_4N_3$), 56.3 and 54.4 (C-2,2''), 52.5, 30.1, 29.6, and 24.4 [O$CH_2(CH_2)_4N_3$], 23.5 and 23.0 (2 NHCOCH_3). FAB$^-$MS ($C_{55}H_{70}N_5O_{19}NaS$): *m/z* 1136 $[M - Na]^-$.

5 - Aminopentyl (2 - acetamido - 2 - deoxy - β - D - galactopyranosyl)-(1 → 4)-(β-D-galactopyranosyl 3-sulfate) - (1 → 4) - 2 - acetamido - 2 - deoxy - β - D - glucopyranoside (**2**).—A soln of **15** (31 mg, 26 μmol) in 2-propanol (1.75 mL), water (0.75 mL), and HOAc (0.13 mL) was hydrogenolysed in the presence of 10% Pd–C (75 mg) for 17 h. The mixture was then filtered through Celite and concd. Column chromatography (5:10:3 CH_2Cl_2–MeOH–water) of the residue, followed by lyophilization from water, afforded **2**, isolated as a white powder (12.0 mg, 62%); $[\alpha]_D$ +16° (*c* 0.5, water); R_f 0.54 (5:10:3 CH_2Cl_2–MeOH–water); ^1H NMR (D_2O): see Table 1. FAB$^-$MS ($C_{27}H_{49}N_3O_{19}S$): *m/z* 750 $[M - H]^-$; FAB$^+$MS: *m/z* 752 $[M + H]^+$.

5-Azidopentyl (2,6-di-O-benzyl-3-O-methoxycarbonylmethyl-β-D-galactopyranosyl)-(1 → 4)-3,6-di-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**17**).—To a soln of **4** [10] (359 mg, 0.38 mmol) in dry MeOH (5 mL) was added dibutyltin oxide (155 mg, 0.62 mmol), and the mixture was stirred overnight at 60 °C under Ar. After cooling to room temperature, the mixture was concd and the residue was dissolved in dry toluene (10 mL). Bu_4NI (152 mg, 0.41 mmol) and powdered 4 Å molecular sieves (0.3 g) were added, and the mixture was stirred for 1 h at room temperature. Then, methyl bromoacetate (218 μL, 2.30 mmol) was added and the mixture was stirred for 3.5 h at 80 °C, when TLC (5:1 toluene–EtOAc) showed the formation of a major product with R_f 0.36, namely, the 3',4'-lactonized disaccharide **16**. After cooling to room temperature, the mixture was filtered through Celite and concd. Column chromatography (7:3 hexane–EtOAc) of a small amount of the residue afforded the 3',4'-lactonized disaccharide **16**; NMR ($CDCl_3$): ^1H, δ 7.85–6.82 (m, 24 H, 4 Ph and Phth), 5.119 (d, 1 H, $J_{1,2}$ 8.3 Hz, H-1), 4.488 (d, 1 H, $J_{1',2'}$ 7.6 Hz, H-1'), 4.176 and 3.692 (2 d, each 1 H, $^2J_{a,b}$ −18.0 Hz, OCH_aH_bCOO); ^{13}C, δ 166.8 (OCH_2COO), 103.0 (C-1'), 98.2 (C-1), 78.7, 77.0, 74.9, 73.8, 73.6, 72.0, and 71.5 (C-3,4,5,2',3',4',5'), 74.4, 74.3, 73.4, 73.1, 68.9, 67.7, 66.3, and 60.2 (C-6,6', 4 PhCH_2O, O$CH_2(CH_2)_4N_3$, and OCH_2COO), 55.6 (C-2), 51.0, 28.6, 28.2, and 22.9 [O$CH_2(CH_2)_4N_3$].

To a soln of crude **16** in dry MeOH (10 mL) was added NaOMe till pH 9, and the mixture was stirred for 0.5 h. TLC (5:1 toluene–EtOAc) then showed the formation of **17** (R_f 0.18) and the mixture was neutralized with Dowex-50 (H^+), filtered, and concd. Column chromatography (96:4 CH_2Cl_2–acetone) of the residue afforded **17**, isolated as a colourless syrup (318 mg, 82%); $[\alpha]_D$ +9° (*c* 1); R_f 0.32 (96:4 CH_2Cl_2–acetone); NMR ($CDCl_3$): ^{1}H, δ 7.85–6.82 (m, 24 H, 4 Ph and Phth), 5.095 (d, 1 H, $J_{1,2}$ 8.3 Hz, H-1), 4.422 (d, 1 H, $J_{1',2'}$ 7.7 Hz, H-1'), 4.396 and 4.163 (2 d, each 1 H, $^2J_{a,b}$ −16.9 Hz, OCH_aH_bCOOMe), 3.746 (s, 3 H, OCH_2COOCH_3); ^{13}C, δ 171.7 (*C*OOMe), 102.6 (C-1'), 98.0 (C-1), 83.7, 79.1, 78.1, 76.9, 75.0, 72.7, and 66.7 (C-3,4,5,2',3',4',5'), 75.1, 74.3, 73.3, 72.9, 70.3, 68.7, 68.0, and 67.7 (C-6,6', 4 Ph*C*H_2O, $OCH_2(CH_2)_4N_3$, and OCH_2COOMe), 55.5 (C-2), 51.8 (OCH_2COOCH_3), 50.8, 28.5, 28.0, and 22.8 [$OCH_2(CH_2)_4N_3$]. FAB$^+$MS ($C_{56}H_{62}N_4O_{14}$): *m/z* 1015 $[M + H]^+$.

Acetylation of a small amount of **17** with 1:1 acetic anhydride–pyridine, followed by co-concn with toluene (3 ×), EtOH (3 ×), and CH_2Cl_2 (3 ×), afforded **18**; ^{1}H NMR ($CDCl_3$): δ 7.80–6.85 (m, 24 H, 4 Ph and Phth), 5.450 (dd, 1 H, $J_{3',4'}$ 3.2, $J_{4',5'} < 1$ Hz, H-4'), 5.101 (d, 1 H, $J_{1,2}$ 8.3 Hz, H-1), 3.713 (s, 3 H, OCH_2COOCH_3), 2.917 (m, 2 H, $O(CH_2)_4CH_2N_3$), 1.995 (s, 3 H, Ac).

5-Azidopentyl (3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-galactopyranosyl)-(1 → 4)-(2,6-di-O-benzyl-3-O-methoxycarbonylmethyl-β-D-galactopyranosyl)-(1 → 4)-3,6-di-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**19**).—A soln of **17** (194 mg, 0.19 mmol) in dry toluene (7 mL), containing 3 Å molecular sieves (0.2 g), was stirred for 1 h under Ar. The mixture was cooled to −35 °C and a soln of trimethylsilyl triflate (5.2 μL, 29 μmol) in dry CH_2Cl_2 (0.1 mL) was added. To this mixture was added dropwise a soln of 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-galactopyranosyl trichloroacetimidate [21] (**10**; 224 mg, 0.39 mmol) in dry toluene (5 mL), and the mixture was stirred for 1 h. Then TLC (3:1 toluene–EtOAc) showed the disappearance of **17** (R_f 0.33) and the formation of **19** (R_f 0.20), and the mixture was neutralized with pyridine, diluted with toluene (50 mL), and filtered. The filtrate was washed with aq 5% $NaHCO_3$ (2 ×) and water. The aq layers were combined and extracted with toluene (25 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concd. Column chromatography (95:5 CH_2Cl_2–acetone) of the residue afforded **19**, isolated as a colourless syrup (179 mg, 65%); $[\alpha]_D$ −25° (*c* 1); R_f 0.32 (95:5 CH_2Cl_2–acetone); NMR ($CDCl_3$): ^{1}H, δ 7.95–6.95 (m, 28 H, 4 Ph and 2 Phth), 6.076 (dd, 1 H, $J_{2'',3''}$ 11.4, $J_{3'',4''}$ 3.5 Hz, H-3''), 5.535 (d, 1 H, $J_{1'',2''}$ 8.5 Hz, H-1''), 5.489 (d, 1 H, $J_{4'',5''} < 1$ Hz, H-4''), 5.105 (d, 1 H, $J_{1,2}$ 8.3 Hz, H-1), 3.752 (s, 3 H, OCH_2COOCH_3), 2.146, 2.025, and 1.828 (3 s, each 3 H, 3 Ac); ^{13}C, δ 101.7 and 99.3 (C-1',1''), 98.2 (C-1), 81.9, 80.7, 77.2, 76.6, 76.2, 75.1, 73.5, 70.1, 67.2, and 66.4 (C-3,4,5,2',3',4',5',3'',4'',5''), 74.6, 74.4, 73.1, 73.0, 70.3, 69.2, 68.7, 67.6, and 61.0 (C-6,6',6'', 4 PhCH_2O, $OCH_2(CH_2)_4N_3$, and OCH_2COOMe), 55.6 (C-2), 51.6 and 51.1 (C-2'', OCH_2COOCH_3), 50.9, 28.5, 28.1, and 22.8 [$OCH_2(CH_2)_4N_3$]. Anal. Calcd for $C_{76}H_{81}N_5O_{23}$: C, 63.72; H, 5.70. Found: C, 63.58; H, 5.66.

5-Azidopentyl (3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-galactopyranosyl)-(1 → 4)-(2,6-di-O-benzyl-3-O-carboxymethyl-β-D-galactopyranosyl)-(1 → 4)-3,6-di-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**20**).—A soln of **19** (112 mg, 78 μmol) and LiI [24] (160 mg, 1.20 mmol) in dry pyridine (6 mL) was stirred in the dark overnight at 115 °C under Ar. The reaction was followed on TLC (95:5 CH_2Cl_2–MeOH), showing that after one night the reaction was not complete. More LiI (300 mg, 2.24 mmol) was added and the mixture was stirred for an additional 32 h, when TLC showed the reaction to be complete. After cooling to room temperature the mixture was co-concd with toluene (2 ×), and the residue was dissolved in CH_2Cl_2 (50 mL), washed with M HCl (2 ×) and water (3 ×), dried (Na_2SO_4), filtered, and concd. Column chromatography (94:6 CH_2Cl_2–MeOH) of the residue afforded **20**, isolated as a light yellow glass (82 mg, 75%); $[\alpha]_D$ −24° (*c* 1); R_f 0.27 (95:5 CH_2Cl_2–MeOH); ^{1}H NMR (CD_3OD): δ 7.95–6.95 (m, 28 H, 4 Ph and 2 Phth), 6.036 (dd, 1 H, $J_{2'',3''}$ 11.7, $J_{3'',4''}$ 3.6 Hz, H-3''), 5.616 (d, 1 H, $J_{1'',2''}$ 8.6 Hz, H-1''), 5.474 (d, 1 H, $J_{4'',5''} < 1$ Hz, H-4''), 5.106 (d, 1 H, $J_{1,2}$ 8.5 Hz, H-1), 2.925 (m, 2 H, $O(CH_2)_4CH_2N_3$), 2.088, 2.005, and 1.789 (3 s, each 3 H, 3 Ac). FAB$^+$MS ($C_{75}H_{79}N_5O_{23}$): *m/z* 1419 $[M + H]^+$.

5-Azidopentyl (2-acetamido-2-deoxy-β-D-galactopyranosyl)-(1 → 4)-(2,6-di-O-benzyl-3-O-carboxymethyl-β-D-galactopyranosyl)-(1 → 4)-2-acetamido-3,6-di-O-benzyl-2-deoxy-β-D-glucopyranoside sodium salt (**22**).—A soln of **20** (82 mg, 58 μmol) and 1,2-diaminoethane (1.93 mL, 28.9 mmol) in *n*-butanol (8 mL) was stirred overnight at 90 °C under Ar. After cooling to room temperature

the mixture was co-concd with toluene (3 ×) and CH_2Cl_2 (3 ×). A soln of the residue in acetic anhydride (6 mL) and pyridine (3 mL) was stirred overnight at room temperature, then the mixture was co-concd with toluene (3 ×) and CH_2Cl_2 (3 ×). To a soln of the residue in dry MeOH (1 mL) NaOMe was added up to pH 9. After stirring for 4 h at room temperature, TLC (85:15 CH_2Cl_2–MeOH) indicated the reaction to be complete (R_f (**22**) 0.13). Size-exclusion column chromatography (1:1 CH_2Cl_2–MeOH) of the mixture on Sephadex LH-20, followed by column chromatography (8:3 CH_2Cl_2–MeOH) of the crude product on silica gave **22**, isolated as a white foam (44 mg, 66%); $[\alpha]_D$ +3° (*c* 1, MeOH); NMR (CD_3OD): ^1H, δ 7.40–7.15 (m, 20 H, 4 Ph), 2.046 and 1.915 (2 s, each 3 H, 2 Ac); ^{13}C, δ 177.9 (*C*OONa), 174.4 and 173.1 (2 *C*OCH$_3$), 104.4, 103.9, and 102.7 (C-1,1′,1″), 56.3 and 54.6 (C-2,2″), 52.5, 30.1, 29.6, and 24.4 [$OCH_2(CH_2)_4N_3$], 23.4 and 23.0 (2 NHCO*C*H$_3$). FAB$^+$MS ($C_{57}H_{72}N_5O_{18}Na$): *m/z* 1139 $[M + H]^+$.

5 - Aminopentyl (2 - acetamido - 2 - deoxy - β - D - galactopyranosyl)-(1 → 4)-(3-O-carboxymethyl-β-D-galactopyranosyl)-(1 → 4)-2-acetamido-2-deoxy-β-D-glucopyranoside (**3**).—A soln of **22** (22 mg, 19 μmol) in 2-propanol (1 mL), water (1 mL), and HOAc (0.12 mL) was hydrogenolysed in the presence of 10% Pd–C (60 mg) for 16 h. The mixture was filtered through Celite and concd. Column chromatography (5:10:3 CH_2Cl_2–MeOH–water) of the residue, followed by lyophilization from water, afforded **3**, isolated as a white powder (6.6 mg, 48%); $[\alpha]_D$ +2° (*c* 0.5, water); R_f 0.29 (5:10:3 CH_2Cl_2–MeOH–water); ^1H NMR (D_2O): see Table 1. FAB$^-$MS ($C_{29}H_{51}N_3O_{18}$): *m/z* 728 $[M - H]^-$; FAB$^+$MS: *m/z* 730 $[M + H]^+$.

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