A High Yielding Chemical Synthesis of Sialyl Lewis x Tetrasaccharide and Lewis x Trisaccharide; Examples of Regio- and Stereodifferentiated Glycosylations

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Received June 22, 1998

Virtually complete regioselective galactosylation of the diol acceptor *p*-methoxyphenyl 6-*O*-benzyl-2-deoxy-2-tetrachlorophthalimido-*β*-D-glucopyranoside (**8**) with the donor phenyl 2,3,4-tri-*O*-acetyl-6-*O*-benzyl-1-thio-*β*-D-galactopyranoside (**11**) gave the lactosamine derivative **14**, which was fucosylated with the donor **15** to give the Le^x trisaccharide glycoside **2** after deprotection. Regioselective sialylation of the partially protected Le^x trisaccharide triol **24** with the sialyl donor **25** gave, after deprotection, the SLe^x tetrasaccharide glycoside **1**. The overall yields of **2** and **1** from the monosaccharide starting materials **8**, **11**, **15**, and **25** were 56% and 29%, respectively. In contrast to the virtually complete regio- and stereoselective galactosylation of **8**, fucosylation with the benzyl-protected donor **15** gave the corresponding 1→3- and 1→4-linked disaccharides in a ratio of 3.6:1 (highly stereo- but not regioselective glycosylation), whereas fucosylation with acetyl-protected donor **18** gave a 2.2:1 *β*/α-mixture of 4-O-linked disaccharides (highly regio- but not stereoselective glycosylation).

Introduction

The tetrasaccharide α-Neu*p*5NAc-(2→3)-*β*-D-Gal*p*-(1→4)-[α-L-Fuc*p*]-(1→3)-*β*-D-Glc*p*NAc (Sialyl Lewis x, SLe^x) has been identified as a ligand for the recruitment of leucocytes to endothelial cells in connection with inflammation[1] and has also been identified as a tumor-associated antigen.[2] The saccharide itself, as well as its dimer, has been obtained by chemical synthesis[3] and also by a combination of chemical and enzymatic synthesis.[4] We report an efficient chemical synthesis of the SLe^x glycoside **1** (Figure 1) in 29% total yield, starting from the simple monosaccharide building blocks **8**, **11**, **15**, and **25**. A slight deviation from the synthetic scheme yielded the Le^x trisaccharide **2** in 56% total yield. Other synthetic routes to Le^x trisaccharides have been reported.[5]

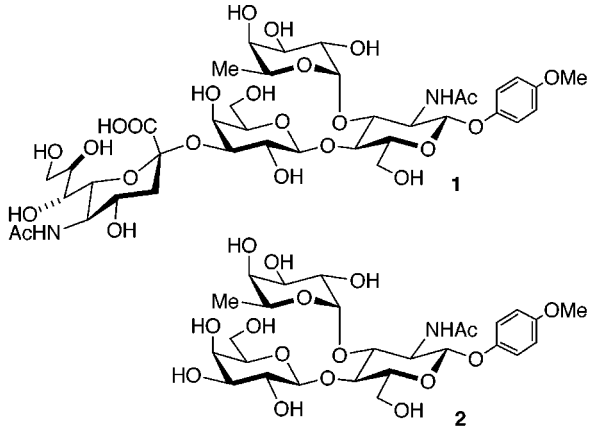

Figure 1. Structures of SLe^x tetrasaccharide and Le^x trisaccharide.

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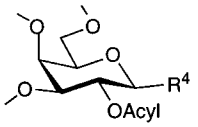
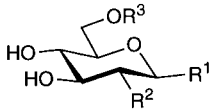
10.1021/jo981203x CCC: $15.00
Published on Web 11/24/1998

Table 1. Regioselective Galactosylation of Glucosamine Derivatives[a] Having HO-4 and HO-3 Unprotected

Donor: 

Acceptor: 

	acceptor			donor		
entry	R^1	R^2	R^3	R^4	promoter	O4/O3, yield (%)
1	O-TMSEt (**12**)	NPhth	Bn	SPh (**11**)	MSB, AgOTf	>87:1 (**13**, Scheme 2)
2	O-PMP (**8**)	NTCP	Bn	SPh (**11**)	MSB, AgOTf	>84:1 (**14**, Scheme 2)
3	O-Lactose deriv.	NHAc	Bn	SMe	MSB, AgOTf	36:45[26]
4	O-Allyl	NPhth	Bn	SMe	MeOTf	61:17[5d]
5	S-Et	NPhth	Bn	F	$SnCl_2$, AgOTf	45:25[5e]
6	O-Me	NPhth	Piv	F	$SnCl_2$, AgOTf	48:21[3k]
7	O-TBS	N_3	Bn	$OCNHCCl_3$	BF_3Et_2O	21:64[27]
8	O-$(CH_2)_8$COOMe	N_3	Ac	OAc	TMSOTf	24:42[4a]

[a] The acronyms used have the following meaning: TMSEt = 2-(trimethylsilyl)ethyl; MSB = methylsulfenyl bromide; PMP = *p*-methoxyphenyl; TCP = tetrachlorophthaloyl; Piv = pivaloyl; TBS = *tert*-butyldimethylsilyl.

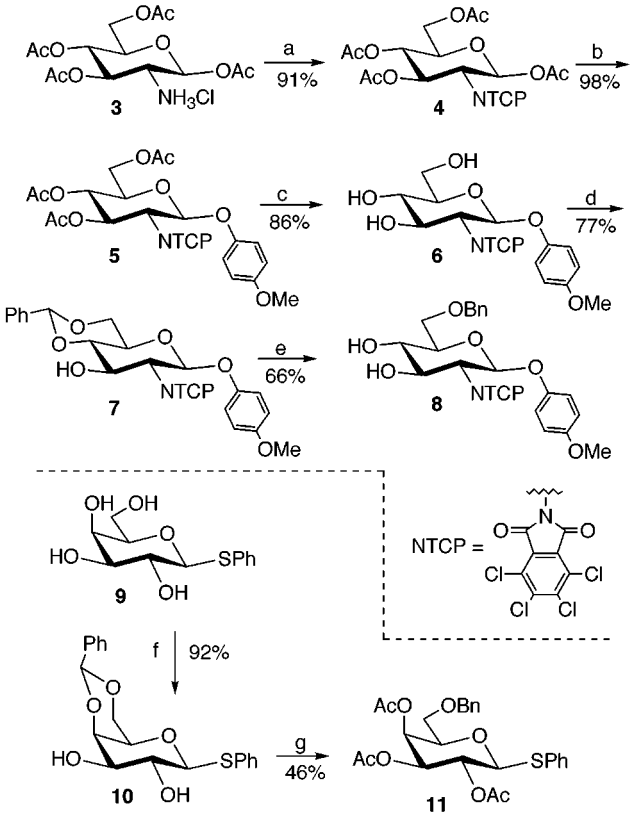
Results and Discussion

The published organochemical procedures for the synthesis of SLe^x tetrasaccharides rely on two initial strategies: (1) galactosylation or fucosylation of a protected glucosamine derivative, having only HO-4 or HO-3 unprotected, and (2) selective galactosylation or fucosylation of a glycoside acceptor, having HO-3 and HO-4 unprotected. The two methods require either a rather elaborate protection of the acceptor or good regioselectivity in the glycosylation of HO-4 or HO-3. As shown in Table 1, the HO-4/HO-3 selectivity was low for most of the published galactosylations (entries 3−8).

We wished to investigate additional combinations of protecting groups and activation methods to improve the HO-4/HO-3 regioselectivity in the first glycosylation step and thereby raise the overall yield of the SLe^x synthesis. The final synthetic protocol will be useful for the synthesis of additional SLe^x derivatives, such as deoxy analogues and spacer-arm glycosides for the preparation of various neoglycoconjugates.[6] It should be noted that the successful use of *N*-tetrachlorophthaloyl (NTCP)[7] protection was of crucial importance for the synthesis of the SLe^x-1‴→2′-lactam, presented in the following paper.[28]

I. Synthesis of Glycosylation Acceptor 8 and Donor 11. The known[8] glucosamine derivative **3** was treated with tetrachlorophthalic (TCP) anhydride in pyridine, followed by acetic anhydride, which gave the TCP-protected compound **4** (91%, Scheme 1). This was in our hands an improvement over the different published procedures for TCP protection of aminosugars.[7]

Scheme 1[a]



[a] Key: (a) $Cl_4C_6(CO)_2O$, pyridine, ∼22 °C, 10 H, then Ac_2O, 0 °C, 1 h; (b) *p*-MeO-C_6H_4OH, BF_3OEt_2, CH_2Cl_2, Ar, 20 °C, 11 h; (c) 0.018 M MeONa−MeOH, ∼22 °C, 12 min; (d) $C_6H_5CH(OMe)_2$, TsOH, MeCN, 1 h; (e) $NaBH_3CN$, THF, then HCl−OEt_2 (pH 2−3), 3 h; (f) $C_6H_5CH(OMe)_2$, TsOH, MeCN, 2 h; (g) BH_3NMe_3, $AlCl_3$, THF, 60 °C, 1 h.

p-Methoxyphenol was glycosylated with compound **4**, using boron trifluoride etherate (BF_3OEt_2) as promoter,[9] which gave the glycoside **5** in almost quantitative yield (98%) as the pure *β*-anomer. Initial attempts to de-*O*-acetylate **5** with methanolic sodium methoxide (MeONa/MeOH) were unsuccessful, due to the base-sensitive nature of the NTCP group.[10] However, short treatment

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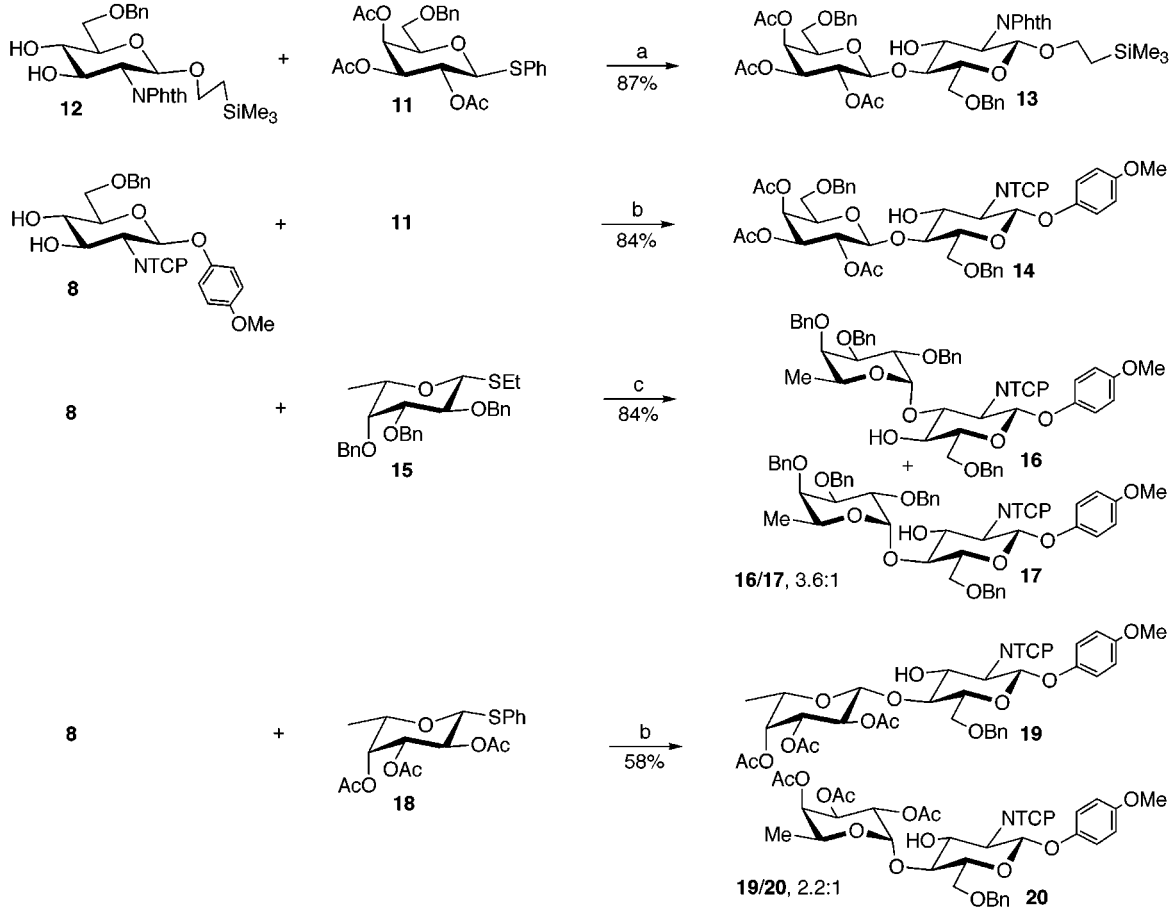
Scheme 2[a]



[a] Key: (a) AgOTf, MeCN, −70 °C, Ar, 5 min, then MeSBr, $ClCH_2CH_2Cl$, −70 °C, 1 h; (b) AgOTf, MeCN, −78 °C, Ar, 5 min, then MeSBr, $ClCH_2CH_2Cl$, −70 °C, 2 h; (c) AgOTf, MeCN, −45 °C, Ar, 5 min, then MeSBr, $ClCH_2CH_2Cl$, −70 °C, 1.5 h.

(<15 min) of **5** in a large volume of 0.018 M MeONa/MeOH solution effected de-O-acetylation (→**6**, 86%) while leaving the NTCP group virtually intact. These reaction conditions are probably close to being optimized. To the best of our knowledge, this is the first example of de-O-acetylation under basic conditions in the presence of an NTCP group. Attempted acid-catalyzed de-O-acetylation, using HCl in methanol, resulted in the formation of the methyl glycoside corresponding to **6** as the major product. The triol **6** was treated with α,α-dimethoxytoluene and *p*-toluenesulfonic acid (TsOH) to give the 4,6-*O*-benzylidene derivative **7** (77%). Reductive opening of the 4,6-*O*-benzylidene ring of **7** with sodium cyanoborohydride ($NaCNBH_3$) in ethereal hydrogen chloride solution[11] gave the diol acceptor **8** (66%).

Treatment of the known[12] thiophenyl galactoside **9** with α,α-dimethoxytoluene and TsOH gave the 4,6-*O*-benzylidene derivative **10**[13] (92%). Attempted reductive opening[11] of the 4,6-*O*-benzylidene ring with $NaCNBH_3$ was unsuccessful. Instead, reduction of **10** with trimethylaminoborane (BH_3NMe_3) and aluminum trichloride ($AlCl_3$),[14] followed by O-acetylation of the crude product with Ac_2O in pyridine, gave the glycosyl donor **11** (46%).

II. Regioselective Glycosylation of Diols. A number of papers have appeared where regioselective *β*-galactosylation of N-protected glucosamine derivatives were attempted. As shown in Table 1, mixtures of 1→3- and 1→4-linked disaccharides were obtained in all reported cases (entries 3−8). In contrast, and much to our surprise, *β*-galactosylation of the acceptors **8** and **12**[15] with the donor **11** under activation with methylsulfenyl bromide (MSB)[16] and silver trifluoromethanesulfonate (AgOTf) gave the 1→4-linked lactosamine derivatives **13** and **14** in 87 and 84% yield, respectively; the corresponding 1→3-linked compounds were not detected by TLC or NMR. On the other hand, fucosylation of **8** with the donor **15**[17] under the same reaction conditions as above gave a mixture of the 1→3- and 1→4-linked disaccharides **16** and **17** in 84% yield (Scheme 2). Here, the 1→3-linked compound **16** was formed in excess.

The dramatically different regioselectivities in *β*-D-galactosylation versus α-L-fucosylation of **8** constitute an example of regiodifferentiation (matched−mismatched

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glycosylation). A case of stereodifferentiation, leading to different α,β-mixtures depending on the structure of the glycosyl acceptors, was recently reported.[18] The observed regiodifferentiation prompted us to investigate the outcome of a glycosylation with the acetylated fucosyl donor **18**[19] (compound **18** is structurally similar to the enantiomer of the galactoside **11**). Glycosylation of **8** with **18**, under the same reaction conditions as with **11**, gave a mixture of **19** and **20** in 58% yield. As with **11**, **18** glycosylated **8** with virtually total regioselectivity, whereas the β/α stereoselectivity was only 2.2:1.

The varying regioselectivities shown in Table 1 and Scheme 2 seem to depend on a number of factors, such as the nature of the different protecting groups, and the nature and mode of activation of the donor. Additional glycosylations with other donors and acceptors, as well as modeling of transition states, are obviously needed in order to understand and predict the regio- and stereochemical outcome of these glycosylations.

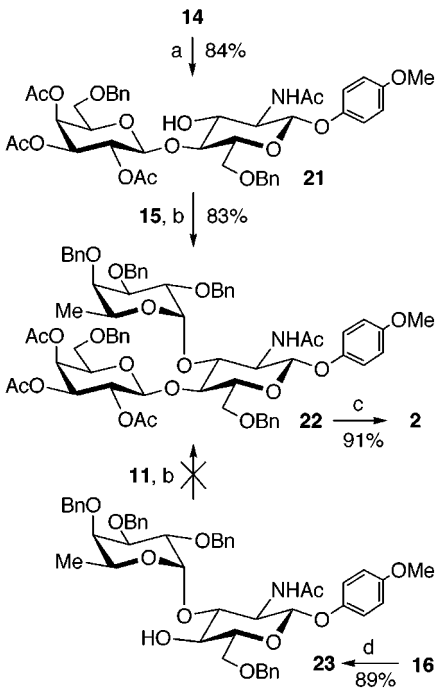
III. Synthesis of Le^x Trisaccharide 2 and SLe^x Tetrasaccharide 1. The NTCP-protected lactosamine derivative **14** was chosen as starting material for the final steps toward the Le^x and SLe^x saccharides, since it was easily obtained in pure form and in good yield (Scheme 2). Furthermore, the NTCP protection gave several options for manipulations later in the synthetic sequence.

Attempted fucosylation of HO-3 in **14**, using different fucosyl donors under various reaction conditions, was totally unsuccessful, despite the fact that others have managed to fucosylate the corresponding NPhth-protected lactosamine derivatives.[3k,5d,e] Equally unsuccessful was our attempted galactosylation of the fucose-containing disaccharide **23** using the galactosyl donor **11** (Scheme 3), although similar reactions have been performed by others[3b,c,j,m,5f] in modest to good yields.

To diminish the supposed steric hindrance in **14** against fucosylation, the large NTCP group (which had served its purpose to guide the regioselective galactosylation) was replaced by the much smaller NHAc group. Thus, treatment of **14** with 1,2-diaminoethane (Scheme 3),[7] followed by N-acetylation of the intermediate amine, gave the *N*-acetyllactosamine derivative **21** (88%). Similarly, compound **23** was obtained in 89% yield from **16**.

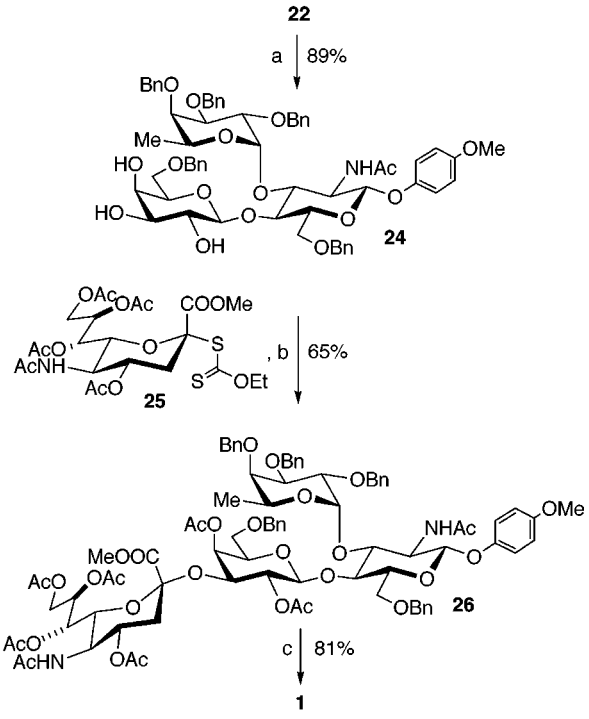
Fucosylation of HO-3 in **21** was then successfully performed by first treating the thiofucoside **15**[17] with bromine (Br_2, distilled from P_2O_5) to generate the corresponding fucosyl bromide[20] and then add the mixture to **21** in the presence of Bu_4NBr,[21] thus furnishing the Le^x trisaccharide derivative **22** (83%). Without distillation of Br_2, the yield of **22** dropped to approximately 60%. De-O-benzylation of **22**, followed by O-acetylation, gave the fully acetylated derivative of **2** for convenient structure determination. It was interesting to note that the $J_{1,2}$ coupling constants (glucosamine residue) of **22** and O-acetylated **2** were different (4.3 and 6.1 Hz, respectively), indicating the presence of steric strain in **22**, strong enough to perturb the GlcNAc ring. De-O-benzylation and de-O-acetylation of **22** gave the Le^x trisaccharide **2** (91%).

Scheme 3[a]



[a] Key: (a) $H_2NCH_2CH_2NH_2$, EtOH, 60 °C, 3 h, then Ac_2O, MeOH, H_2O, ~22 °C, 1 h; (b) Br_2, CH_2Cl_2, cyclohexene, then MS 4 Å, Bu_4NBr, CH_2Cl_2, DMF, ~22 °C, 20 h, then pyridine, 3 h; (c) H_2, Pd−C, AcOH, 4 h, then MeONa−MeOH, 1 h; (d) $H_2NCH_2CH_2NH_2$, EtOH, reflux, 3 h, then Ac_2O, pyridine, DMAP, ~22 °C, 16 h.

Scheme 4[a]



[a] Key: (a) MeONa−MeOH, ~22 °C, 1.5 h; (b) MS 3 Å, CH_2Cl_2, MeCN, Ar, −72 °C, 15 min, then AgOTf, MeCN, MeSBr, $ClCH_2CH_2Cl$, −72 °C, 2.5 h, then Ac_2O, pyridine, DMAP; (c) H_2, Pd−C, AcOH, 5 h, then MeONa−MeOH, 1 h, then aqueous 1 M NaOH, 1.5 h.

Removal of the *O*-acetyl groups of **22** (Scheme 4), using MeONa/MeOH, gave the triol acceptor **24** (89%). Sialylation of **24** with the sialyl donor **25**[22] under promotion

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of AgOTf and MSB[16] was completely regioselective, and the SLe^x tetrasaccharide derivative **26** was obtained pure (after O-acetylation of the unreacted hydroxyl groups in order to simplify the chromatographic purification) in 65% isolated yield. Such high regioselectivity has been demonstrated in other sialylations of galactose-based di- and triols.[22,23] The α-sialyl linkage was deduced from the coupling constant between the carbonyl carbon (C-1‴) and the axial proton in the 3‴-position[24] ($J_{C-1''':H-3'''ax}$ = 6.4 Hz). As for compound **22** above, **26** was also strained, which was witnessed by the abnormal coupling constant $J_{1,2}$ = 3.4 Hz. De-O-benzylation of **26**, followed by O-acetylation, gave a fully O-acetylated derivative of **1**, which had $J_{1,2}$ = 7.7 Hz, as expected for a relaxed pyranosidic GlcNAc ring.

Hydrogenolysis of the benzyl groups and methanolysis/hydrolysis of the esters of **26** gave the SLe^x glycoside **1** in 81% overall yield. The NMR data of **1** are in excellent agreement with those reported by Wong et al.[4e] for the corresponding allyl glycoside.

Experimental Section

The structures of all new compounds were confirmed by NMR analysis, including COSY, NOESY, HETCOR, and long-range HETCOR. NMR spectra were recorded with 400 and 500 MHz instruments. Chemical shifts are given in ppm downfield from the signal for Me_4Si, with reference to internal $CHCl_3$ or HDO. Melting points are uncorrected. Molecular sieves were activated for ∼5 min by heating at ∼500 °C under vacuum (oil pump). CH_2Cl_2 and MeCN were dried by distillation from CaH_2, THF was distilled from Na/benzophenone, DMF was dried over 4 Å molecular sieves and distilled, 1,2-diaminoethane was distilled, and bromine was distilled from P_2O_5. *p*-Methoxyphenol was recrystallized before use. Methylsulfenyl bromide (MSB)[16] was prepared in 1,2-dichloroethane to give a 4 M solution. The solution could be kept in a sealed glass ampule under Ar at −20 °C for several months.[15] Column chromatography was performed on SiO_2 (Matrex LC-gel; 60A, 35-70 MY, Grace) and TLC on Merck SiO_2 60 F_{256}. Compounds **3**,[8] **9**,[12] **12**,[15] **15**,[17] **18**,[19] and **25**[22] were prepared as described in the literature.

4-Methoxyphenyl (5-Acetamido-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonic acid)-(2→3)-(β-D-galactopyranosyl)-(1→4)-[α-L-fucopyranosyl]-(1→3)-(2-acetamido-2-deoxy-β-D-glucopyranoside) (1). Compound **26** (50 mg, 0.03 mmol) was dissolved in AcOH (1 mL), and Pd−C (10%, 50 mg) was added. The mixture was hydrogenated (H_2, 1 atm) for 5 h, filtered (Celite), and concentrated. The residue was dissolved in MeOH (3 mL), 1 M MeONa−MeOH (0.1 mL) was added, and the mixture was stirred for 1 h. Aqueous 1 M NaOH (0.2 mL) was added, and the mixture was stirred for 1.5 h. A 1:5 mixture of AcOH−H_2O (0.125 mL) was added, the reaction mixture was concentrated, and the residue was chromatographed (SiO_2, 60:35:5:0.1 CH_2Cl_2−MeOH−H_2O−AcOH) to give **1** (22.9 mg, 81%): $[\alpha]^{20}_D$ −25.5 (*c* 0.9 D_2O). ^{1}H NMR (D_2O) δ 6.80−6.95 (m, 4 H, OPMP), 5.01 (d, 1 H, *J* = 3.9 Hz, H-1″), 4.93 (d, 1 H, *J* = 8.5 Hz, H-1), 4.43 (d, 1 H, *J* = 7.8 Hz, H-1′), 4.04 (dd, 1 H, *J* = 10.1, 8.6 Hz, H-2), 3.97 (dd, 1 H, *J* = 9.7, 3.2 Hz, H-3′), 3.67 (s, 3 H, OMe), 3.41 (dd, 1 H, *J* = 9.6, 7.8 Hz, H-2′), 2.65 (dd, 1 H, *J* = 12.4, 4.6 Hz, H-3e‴), 1.91, 1.89 (s, 3H, 2 × NHAc), 1.67 (t, 1 H, *J* = 12.2 Hz, H-3a‴), 1.05 (d, 3 H, *J* = 6.6 Hz, H-6″); ^{13}C NMR ($CDCl_3$) δ 175.4, 174.9, 174.3, 155.2, 151.5, 118.7, 115.4, 102.0, 100.9, 100.0, 99.0, 76.0, 75.8, 75.3, 73.4, 73.3, 72.3, 72.2, 69.6, 68.7, 68.5, 68.1, 67.7, 63.0, 61.9, 59.9, 56.2, 56.1, 52.1, 40.1, 22.5, 22.4, 15.6; HRMS calcd for $C_{38}H_{58}O_{24}N_2Na$ (M + Na) 949.3277, found 949.3276.

4-Methoxyphenyl (β-D-Galactopyranosyl)-(1→4)-[α-L-fucopyranosyl]-(1→3)-(2-acetamido-2-deoxy-β-D-glucopyranoside) (2). Compound **22** (105 mg, 0.09 mmol) was dissolved in AcOH (2.5 mL, distilled from Ac_2O), and the mixture was hydrogenated (H_2, 1 atm, Pd−C, 10%, 100 mg) for 4 h, filtered through Celite, and concentrated. The residue was dissolved in MeOH (5 mL), 1 M NaOMe−MeOH (0.25 mL) was added, and the mixture was stirred for 1 h and then neutralized with Amberlite IR 120 H^+. The mixture was concentrated, and the residue was chromatographed (SiO_2, 65:30:5 CH_2Cl_2−MeOH−H_2O) to give **2** (50.0 mg, 91%): $[\alpha]^{20}_D$ −57.6 (*c* 0.6, H_2O); ^{1}H NMR (D_2O) δ 6.80−6.94 (m, 4 H, OPMP), 5.00 (d, 1 H, *J* = 4.0 Hz, H-1″), 4.92 (d, 1 H, *J* = 8.5 Hz, H-1), 4.60−4.75 (m, HDO, H-5″), 4.35 (d, 1 H, *J* = 7.8 Hz, H-1′), 4.02 (dd, 1 H, *J* = 9.9, 8.7 Hz, H-2), 3.75−3.95 (m, 4 H, H-3,4,4′,3″), 3.66 (s, 3 H, OMe), 3.50−3.62 (m, 9 H, H-5,6,3′,5′,6′,2″,4″), 3.37 (dd, 1 H, *J* = 9.8, 7.9 Hz, H-2′), 1.89 (s, 3 H, NHAc), 1.04 (d, 3 H, *J* = 6.6 Hz, H-6″); ^{13}C NMR ($CDCl_3$) δ 174.8, 155.2, 151.5, 118.6, 115.4, 102.2, 100.8, 99.0, 75.9, 75.3, 75.1, 73.4, 72.8, 72.2, 71.4, 69.5, 68.7, 68.0, 67.1, 61.9, 59.9, 56.1, 56.1, 22.5, 15.6; HRMS calcd for $C_{27}H_{41}O_{16}NNa$ (M + Na) 658.2323, found 658.2334.

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-(tetrachlorophthalimido)-β-D-glucopyranose (4). 1,3,4,6-Tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranose hydrochloride[8] (**3**, 10.0 g, 26.1 mmol) was dissolved in pyridine, and tetrachloropthalic anhydride (9.0 g, 31.5 mmol) was added. The mixture was stirred for 10 h and cooled to 0 °C, and Ac_2O was added. The mixture was stirred for 1 h and co-concentrated with toluene. The residue was chromatographed (SiO_2, 3:1 → 1:1 EtOAc−heptane), and the crude material was crystallized to give **4** (12.8 g, 80%). The mother liquid was concentrated, and an additional crop of crystals was obtained (3.7 g; total yield 91%): $[\alpha]^{20}_D$ +69.7 (*c* 0.9, $CHCl_3$); mp 169−171 °C; ^{1}H NMR ($CDCl_3$) δ 6.48 (d, 1 H, *J* = 8.8 Hz, H-1), 5.81 (dd, 1 H, *J* = 10.4, 9.0 Hz, H-3), 5.24 (dd, 1 H, *J* = 10.3, 9.1 Hz, H-4), 4.46 (dd, 1 H, *J* = 10.4, 8.8 Hz, H-2), 4.37 (dd, 1 H, *J* = 12.5, 4.5 Hz, H-6), 4.15 (dd, 1 H, *J* = 12.5, 2.1 Hz, H-6), 3.99 (ddd, 1 H, *J* = 10.2, 4.4, 2.1 Hz, H-5), 2.12, 2.06, 2.05, 1.92 (s, 3 H each, 4 × OAc); ^{13}C NMR ($CDCl_3$) δ 171.06, 170.95, 169.8, 169.1, 90.1, 73.1, 71.1, 68.3, 61.8, 54.8, 21.3, 21.2, 21.0, 20.9; HRMS calcd for $C_{22}H_{19}O_{11}NCl_4Na$ (M + Na) 635.9610, found 635.9608.

4-Methoxyphenyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-(tetrachlorophthalimido)-β-D-glucopyranoside (5). To a cold (0 °C) solution of **4** (10.0 g, 16.2 mmol) and 4-methoxyphenol (2.20 g, 18.0 mmol, recrystallized from ligroin) in dry CH_2Cl_2 (30 mL) was added BF_3OEt_2 (4.00 mL, 32.8 mmol) under Ar. The temperature was gradually raised to 20 °C during 2 h, and the mixture was stirred for 9 h, diluted with CH_2Cl_2 (100 mL), and washed with H_2O, saturated aqueous $NaHCO_3$, and H_2O. The organic phase was dried (Na_2SO_4) and concentrated. The residue was chromatographed (SiO_2, 2:1 EtOAc−heptane) to give **5** (10.8 g, 98%): $[\alpha]^{20}_D$ +63.3 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.75−6.90 (m, 4 H, OPMP), 5.86 (d, 1 H, *J* = 8.4 Hz, H-1), 5.78 (dd, 1 H, *J* = 10.5, 9.1 Hz, H-3), 5.27 (dd, 1 H, *J* = 10.1, 9.2 Hz, H-4), 4.57 (dd, 1 H, *J* = 10.5, 8.5 Hz, H-2), 4.37 (dd, 1 H, *J* = 12.2, 5.1 Hz, H-6), 4.17 (dd, 1 H, *J* = 12.2, 2.4 Hz, H-6), 3.93 (ddd, 1 H, *J* = 10.2, 5.0, 2.6 Hz, H-5), 3.75 (s, 3 H, OMe), 2.12, 2.06, 1.94 (s, 3 H each, 3 × OAc); ^{13}C NMR ($CDCl_3$) δ 171.05, 171.03, 169.8, 156.2, 150.5, 130.5, 127.3, 119.12, 119.10, 114.9, 97.3, 72.5, 71.3, 69.0, 62.3, 56.0, 55.7, 21.2, 21.0, 20.9; HRMS calcd for $C_{27}H_{23}O_{11}NCl_4Na$ (M + Na) 699.9928, found 699.9934.

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4-Methoxyphenyl 2-Deoxy-2-(tetrachlorophthalimido)-β-D-glucopyranoside (6). Compound **5** (10.5 g, 15.5 mmol) was dissolved in MeOH (1200 mL), and MeONa/MeOH (1 M, 20 mL) was added. The resulting MeONa concentration was thus 0.018 M, which was found to be crucial. The mixture was stirred for 12 min, and AcOH (100 mL) was added. The mixture was stirred for 10 min and co-concentrated twice with toluene. The residue was filtered through a silica column (1:1 toluene−acetone) to give crude **6** (7.40 g, 86%), which was immediately used in the next step without further purification.

4-Methoxyphenyl 4,6-*O*-Benzylidene-2-deoxy-2-(tetrachlorophthalimido)-β-D-glucopyranoside (7). Crude **6** (7.40 g, 13.4 mmol) was dissolved in MeCN (45 mL). α,α-Dimethoxytoluene (3.70 mL) and TsOH (20 mg) were added, and the mixture was stirred for 1 h. Et_3N (5 mL) was added, and the mixture was co-concentrated with toluene. The residue was chromatographed (SiO_2, 3:1 EtOAc−heptane), and the crude product was crystallized to give **7** (5.25 g, 61%). The mother liquid was concentrated, and an additional crop of crystals was obtained (1.39 g; total yield 77%): $[\alpha]^{20}_D$ +21.1 (*c* 0.9, $CHCl_3$); mp 165−167 °C; ^{1}H NMR ($CDCl_3$) δ 7.35−7.55 (m, 5 H, ArH), 6.75−6.90 (m, 4 H, OPMP), 5.80 (d, 1 H, *J* = 8.4 Hz, H-1), 5.60 (s, 1 H, ArCH), 4.67 (dd, 1 H, *J* = 10.2, 8.8 Hz, H-3), 4.51 (dd, 1 H, *J* = 10.6, 8.4 Hz, H-2), 4.42 (dd, 1 H, *J* = 10.3, 4.3 Hz, H-5), 3.85−3.90 (m, 1 H, H-6), 3.75 (s, 3 H, OMe), 3.69−3.74 (m, 2 H, H-4,6), 2.60−2.70 (m, 1 H, OH); ^{13}C NMR ($CDCl_3$) δ 156.1, 150.6, 137.2, 129.9, 128.8, 126.6, 118.8, 115.0, 102.4, 97.8, 82.3, 69.0, 68.7, 66.7, 57.4, 56.1; HRMS calcd for $C_{28}H_{21}O_8NCl_4Na$ (M + Na) 661.9919, found 661.9909.

4-Methoxyphenyl 6-*O*-Benzyl-2-deoxy-2-(tetrachlorophthalimido)-β-D-glucopyranoside (8). Compound **7** (1.74 g, 2.72 mmol) was dissolved in dry THF (30 mL), and molecular sieves (1.5 g, 3A, activated) and $NaBH_3CN$ (1.30 g, 20.8 mmol) were added. The mixture was stirred for 3 h at room temperature and cooled to 0 °C. An ice-cold saturated solution of HCl in Et_2O was added slowly until the pH (checked with a moist pH paper) reached 2−3. The mixture was stirred for 3 h, CH_2Cl_2 (200 mL) was added, and the mixture was filtered (Celite). The filtrate was washed successively with saturated aqueous $NaHCO_3$, H_2O, and brine and then concentrated. The residue was chromatographed (SiO_2, 2:1 heptane−EtOAc) to give **8** (1.16 g, 66%): $[\alpha]^{20}_D$ +14.0 (*c* 0.9 $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.30−7.40 (m, 5 H, ArH), 6.70−6.90 (m, 4 H, OPMP), 5.72 (m, virtual coupling similar to entry 19 in ref 25, H-1), 4.64, 4.57 (ABq, 1 H each, *J* = 11.9 Hz, OBn), 4.35−4.45 (m, 2 H, H-2,3), 3.74 (s, 3 H, OMe), 3.65−3.90 (m, 4 H, H-4,5,6), 3.23 (bs, 1 H, OH), 2.74 (bs, 1 H, OH); ^{13}C NMR ($CDCl_3$) δ 156.0, 150.8, 140.8, 137.8, 129.0, 128.5, 128.3, 119.0, 114.9, 97.4, 77.7, 74.5, 74.3, 74.0, 71.6, 70.8, 56.9, 56.0; HRMS calcd for $C_{28}H_{23}O_8NCl_4Na$ (M + Na) 664.0075, found 664.0070.

Phenyl 4,6-*O*-Benzylidene-1-thio-β-D-galactopyranoside (10). To a solution of phenylthio-β-D-galactopyranoside[12] (**9**, 7.10 g, 20.7 mmol) in MeCN (60 mL) were added α,α-dimethoxytoluene (5.10 mL) and TsOH (75 mg). The mixture was stirred for 2 h, Et_3N (2 mL) was added, and the solvent was removed. The residue was crystallized to give **10** (8.66 g, 92%): $[\alpha]^{20}_D$ −29.7 (*c* 1.3, $CHCl_3$); mp 164−165.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.25−7.50 (m, 10 H, ArH), 5.53 (s, 1 H, ArCH), 4.50 (m, 1 H, virtual coupling similar to entry 19 in ref 25, H-1), 4.40 (dd, 1 H, *J* = 12.5, 1.6 Hz, H-6), 4.22 (bd (1 H, *J* = 1.8 Hz, H-4), 4.04 (dd, 1 H, *J* = 12.5, 1.8 Hz, H-6), 3.68−3.75 (m, 2 H, H-2,3), 3.56 (dd, 1 H, *J* = 2.8, 1.5 Hz, H-5), 2.57−2.63 (m, 2 H, OH); ^{13}C NMR ($CDCl_3$) δ 137.2, 134.2, 129.8, 128.7, 126.9, 101.9, 87.4, 75.8, 74.2, 70.5, 69.7, 69.2; HRMS calcd for $C_{19}H_{20}O_5SNa$ (M + Na) 383.0929, found 383.0922.

Phenyl 2,3,4-Tri-*O*-acetyl-6-*O*-benzyl-1-thio-β-D-galactopyranoside (11). To a solution of **10**[13] (13.71 g, 38 mmol) in dry THF (100 mL) was added BH_3NMe_3 (11.0 g). The mixture was cooled to 0 °C, and $AlCl_3$ (22.8 g) was added during 20 min. The mixture was stirred for 30 min at room temperature and 60 min at 60 °C, and CH_2Cl_2 (500 mL) was added. The mixture was washed with aqueous H_2SO_4 (0 °C, 1 M), H_2O, and saturated aqueous $NaHCO_3$. The water phase was extracted with EtOAc. The combined organic phase was dried (Na_2SO_4) and concentrated. The crude material was dissolved in pyridine (100 mL), and Ac_2O (90 mL) was added. The mixture was stirred for 20 h and co-concentrated with toluene. The residue was chromatographed (SiO_2, 1:10 → 2:1 EtOAc−heptane) to give **11** (8.5 g, 46%): $[\alpha]^{20}_D$ −22.2 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.25−7.50 (m, 10 H, ArH), 5.50 (dd, 1 H, *J* = 3.3, 0.9 Hz, H-4), 5.25 (t, 1 H, *J* = 10.0 Hz, H-2), 5.07 (dd, 1 H, *J* = 9.9, 3.3 Hz, H-3), 4.75 (d, 1 H, *J* = 10.0 Hz, H-1), 4.47, 4.56 (ABq, 1 H each, *J* = 11.9 Hz, OBn), 3.91 (dt, 1 H, *J* = 6.3, 1.0 Hz, H-5), 3.52, 3.62 (dABq, 1 H each, *J* = 9.7, 6.3 Hz, H-6), 2.10, 2.05, 1.99 (s, 3 H each, 3 × OAc); ^{13}C NMR ($CDCl_3$) δ 170.6, 170.5, 170.0, 138.0, 133.4, 132.5, 129.4, 128.9, 128.33, 128.29, 87.2, 76.5, 74.0, 72.6, 68.2, 68.1, 67.9, 21.3, 21.09, 21.06; HRMS calcd for $C_{25}H_{28}O_8SNa$ (M + Na) 511.1403, found 511.1412.

4-(Trimethylsilyl)ethyl (2,3,4-Tri-*O*-acetyl-6-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-(6-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside) (13). To a solution of **11** (763 mg, 1.56 mmol) and **12**[15] (600 mg, 1.20 mmol) in CH_2Cl_2 (12.0 mL) at −70 °C under Ar was added a solution of AgOTf (920 mg, 3.58 mmol) in MeCN (5.0 mL). After 5 min, a 4 M solution of methylsulfenyl bromide[16] (MSB) in 1,2-dichloroethane (0.75 mL) was added during 15 min. The mixture was stirred for 1 h, isopropylamine (1.0 mL) was added, and the stirring was continued at −70 °C for 1.5 h. The mixture was concentrated, and the residue was chromatographed (SiO_2, 3:1 → 1:1 heptane-EtOAc) to give **13** (964 mg, 87%): $[\alpha]^{20}_D$ −5.1 (*c* 0.8 $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.15−7.55 (m, 14 H, ArH), 5.38 (d, 1 H, *J* = 2.8 Hz, H-4′), 5.20 (d, 1 H, *J* = 8.4 Hz, H-1), 5.19 (dd, 1 H, *J* = 10.3, 8.0 Hz, H-2′), 4.94 (dd, 1 H, *J* = 10.5, 3.5 Hz, H-3′), 4.55, 4.75 (ABq, 1 H each, *J* = 12.1 Hz, OBn), 4.51, d, 1 H, *J* = 8.0 Hz, H-1), 4.45−4.50 (m, 1 H, H-3), 4.32, 4.43 (ABq, 1 H each, *J* = 11.8 Hz, OBn), 4.20 (dd, 1 H, *J* = 10.8, 8.5 Hz, H-2), 3.95 (dt, 1 H, *J* = 10.0, 5.6 Hz, OCH_2CH$_2$SiMe$_3$), 3.85 (t, 1 H, *J* = 6.9 Hz, H-5′), 3.65−3.75 (m, 4 H, H-4,5,6), 3.50−3.55 (m, 1 H, OCH_2CH$_2$SiMe$_3$), 3.52 (dd, 1 H, *J* = 9.5, 7.3 Hz, H-6′), 3.40 (dd, 1 H, *J* = 9.5, 5.7 Hz, H-6′), 2.04, 2.00, 1.95 (s, 3 H each, 3 × OAc), 0.77, 0.86 (ddABq, 1 H each, *J* = 14.0, 10.2, 6.8 Hz, OCH$_2$CH_2SiMe$_3$), −0.12 (s, 3 H, SiMe$_3$); ^{13}C NMR ($CDCl_3$) δ 170.5, 170.4, 169.7, 138.6, 137.4, 134.3, 132.3, 128.9, 128.8, 128.3, 128.3, 128.2, 128.2, 101.7, 98.2, 82.3, 74.7, 74.1, 74.0, 72.7, 71.4, 70.3, 69.4, 68.5, 67.8, 67.6, 67.3, 56.5, 21.2, 21.0, 21.0, 18.1, −1.1; HRMS calcd for $C_{45}H_{55}O_{15}NSiNa$ (M + Na) 900.3239, found 900.3245.

A sample of **13** was acetylated; a ^{1}H NMR signal appeared at δ 5.65 (dd, 1 H, *J* = 10.9, 8.9 Hz, H-3).

4-Methoxyphenyl (2,3,4-Tri-*O*-acetyl-6-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-(6-*O*-benzyl-2-deoxy-2-(tetrachlorophthalimido)-β-D-glucopyranoside) (14). To a solution of **11** (266 mg, 0.54 mmol) and **8** (250 mg, 0.39 mmol) in CH_2Cl_2 (3.5 mL) at −78 °C under Ar was added a solution of AgOTf (300 mg, 1.16 mmol) in MeCN (1.75 mL). After 5 min, a 4 M solution of methylsulfenyl bromide[16] (MSB) in 1,2-dichloroethane (0.245 mL) was added during 10 min. The mixture was stirred for 2 h, isopropylamine (0.3 mL) was added, and the stirring was continued at −78 °C for 1 h. The mixture was concentrated, and the residue was chromatographed (SiO_2, 3:1 → 2:1 heptane−EtOAc) to give **14** (329 mg, 84%): $[\alpha]^{20}_D$ +15.4 (*c* 0.9 $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.15−7.40 (m, 10 H, ArH), 6.70−6.90 (m, 4 H, OPMP), 5.63 (d, 1 H, *J* = 8.4 Hz, H-1), 5.39 (d, 1 H, *J* = 3.4 Hz, H-4′), 5.20 (dd, 1 H, *J* = 10.5, 7.9 Hz, H-2′), 4.97 (dd, 1 H, *J* = 10.4, 3.5 Hz, H-3′), 4.70, 4.53 (ABq, 1 H each, *J* = 11.7 Hz, OBn), 4.55 (d, 1 H, *J* = 8.3 Hz, H-1′), 4.50−4.55 (m, 1 H, H-3), 4.49, 4.37 (ABq, 1 H each, *J* = 11.9 Hz, OBn), 4.44 (dd, 1 H, *J* = 10.8, 8.4 Hz, H-2), 4.36 (d, 1 H, *J* = 2.1 Hz, OH), 3.90−3.95 (m, 1 H, H-5′), 3.74 (s, 3 H, OMe), 3.70−3.80 (m, 4 H, H-4,5,6), 3.55 (dd, 1 H, *J* = 9.6, 7.7 Hz, H-6′), 3.46 (dd, 1 H, *J* = 9.6, 5.0 Hz, H-6′), 2.09,

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2.01, 1.99 (s, 3 H each, 3 × OAc); ^{13}C NMR ($CDCl_3$) δ 170.6, 170.4, 169.7, 155.9, 150.9, 138.4, 137.4, 128.9, 128.7, 128.3, 128.2, 128.1, 127.8, 119.0, 114.9, 101.7, 97.4, 82.0, 74.9, 74.1, 73.9, 72.8, 71.3, 69.9, 69.4, 68.3, 67.7, 56.8, 56.0, 21.1, 21.04, 20.98; HRMS calcd for $C_{47}H_{45}O_{16}NCl_4Na$ (M + Na) 1042.1390, found 1042.1396.

A sample of **14** was acetylated; a ^{1}H NMR signal appeared at δ 5.67 (dd, 1 H, J = 10.5, 8.7 Hz, H-3).

4-Methoxyphenyl (2,3,4-Tri-*O*-benzyl-α-L-fucopyranosyl)-(1→3)-(6-*O*-benzyl-2-deoxy-2-(tetrachlorophthalimido)-β-D-glucopyranoside) (16) and 4-Methoxyphenyl (2,3,4-Tri-*O*-benzyl-α-L-fucopyranosyl)-(1→4)-(6-*O*-benzyl-2-deoxy-2-(tetrachlorophthalimido)-β-D-glucopyranoside) (17). To a mixture of **8** (100 mg, 0.16 mmol), ethyl 2,3,4-tri-*O*-benzyl-1-thio-α-L-fucopyranoside[17] (**15**, 147 mg, 0.31 mmol), and AgOTf (100 mg, 0.39 mmol) was added CH_2Cl_2 (2.0 mL). The solution was cooled to −45 °C under Ar. After 5 min, a 4 M solution of methylsulfenyl bromide[16] (MSB) in 1,2-dichloroethane (0.081 mL) was added during 20 min. The mixture was stirred for 1.5 h, isopropylamine (0.2 mL) was added, and the stirring was continued for 1 h at −45 °C. The mixture was filtered through a short column (SiO_2, 1:1 heptane−EtOAc), concentrated, and chromatographed (SiO_2, 8:1 heptane−acetone) to give **16** (107 mg 65%) and **17** (30 mg, 18%). Compound **16**: $[\alpha]^{20}_D$ +18.6 (*c* 0.9 $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.15−7.50 (m, 20 H, ArH), 6.70−6.95 (m, 4 H, OPMP), 5.83 (d, 1 H, J = 8.5 Hz, H-1), 4.91 (bd, 1 H, J = 1.9 Hz, H-1′), 4.73, 4.82 (ABq, 1 H each, J = 11.8 Hz, OBn), 4.61, 4.65 (ABq, 1 H, J = 12.1 Hz, OBn), 4.60, 4.95 (ABq, 1 H each, J = 11.4 Hz, OBn), 4.51 (dd, 1 H, J = 10.8, 8.6 Hz, H-2), 4.47 (d, 1 H, J = 1.4 Hz, H-4′), 4.18 (dd (1 H, J = 10.7, 8.0 Hz, H-3), 4.11, 4.36 (ABq, 1 H each, J = 13.0 Hz, OBn), 4.16 (q, 1 H, J = 6.0 Hz, H-5′), 3.90−3.95 (m, 2 H, H-6,2′), 3.74 (s, 3 H, OMe), 3.55−3.80 (m, 4 H, H-4,5,6,3′), 1.15 (d, 3 H, J = 6.5 Hz, H-6′); ^{13}C NMR ($CDCl_3$) δ 164.4, 163.4, 155.9, 150.9, 140.3, 140.3, 138.9, 138.8, 138.6, 138.0, 129.9, 129.6, 128.9, 128.8, 128.7, 128.7, 128.6, 128.3, 128.2, 128.1, 128.0, 127.8, 126.2, 127.2, 119.0, 114.9, 100.4, 97.2, 83.7, 78.9, 78.3, 75.8, 75.4, 74.1, 73.9, 73.5, 71.4, 69.4, 69.1, 56.0, 55.6, 16.9; HRMS calcd for $C_{55}H_{51}O_{12}NCl_4Na$ (M + Na) 1080.2063, found 1080.2050.

A sample of **16** was acetylated; a ^{1}H NMR signal appeared at δ 5.04 (dd, 1 H, J = 10.1, 8.4 Hz, H-4).

Compound **17**: $[\alpha]^{20}_D$ −8.8 (*c* 1.1 $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.20−7.45 (m, 20 H, ArH), 6.70−6.95 (m, 4 H, OPMP), 5.67 (d, 1 H, J = 8.3 Hz, H-1), 4.97 (d, 1 H, J = 3.9 Hz, H-1′), 4.76, 4.86 (ABq, 1 H each, J = 11.8 Hz, OBn), 4.67, 4.82 (ABq, 1 H each, J = 11.5 Hz, OBn), 4.63, 4.98 (ABq, 1 H each, J = 11.4 Hz, OBn), 4.30−4.45 (m, 4 H, H-2,3, OBn), 4.09 (dd, 1 H, J = 10.2, 3.8 Hz, H-2′), 4.03 (q, 1 H, J = 6.5 Hz, H-5′), 3.99 (d, 1 H, J = 9.6 Hz, H-6), 3.88 (dd, 1 H, J = 10.2, 2.7 Hz, H-3′), 3.70−3.80 (m, 2 H, H-5,6), 3.74 (s, 3 H, OMe), 3.67 (bd, 1 H, J = 1.6 Hz, H-4′), 3.54 (dd, 1 H, J = 9.5, 8.3 Hz, H-4), 1.10 (d, 3 H, J = 6.5 Hz, H-6′); ^{13}C NMR ($CDCl_3$) δ 155.8, 151.0, 138.9, 138.7, 138.7, 129.0, 128.90, 128.86, 128.8, 128.74, 128.73, 128.70, 128.67, 128.64, 128.56, 128.33, 128.27, 128.21, 128.1, 128.0, 127.83, 127.81, 119.01, 118.95, 114.9, 100.9, 97.2, 83.1, 79.2, 76.1, 75.5, 75.2, 74.2, 73.6, 73.5, 70.7, 68.7, 56.9, 56.0, 17.1; HRMS calcd for $C_{55}H_{51}O_{12}NCl_4Na$ (M + Na) 1080.2063, found 1080.2050.

A sample of **17** was acetylated; a ^{1}H NMR signal appeared at δ 5.72 (dd, 1 H, J = 10.5, 8.4 Hz, H-3).

4-Methoxyphenyl (2,3,4-Tri-*O*-acetyl-β-L-fucopyranosyl)-(1→4)-(6-*O*-benzyl-2-deoxy-2-(tetrachlorophthalimido)-β-D-glucopyranoside) (19) and 4-Methoxyphenyl (2,3,4-Tri-*O*-acetyl-α-L-fucopyranosyl)-(1→4)-(6-*O*-benzyl-2-deoxy-2-(tetrachlorophthalimido)-β-D-glucopyranoside) (20). To a solution of **8** (100 mg, 0.16 mmol) and **18**[19] (83 mg, 0.22 mmol) in CH_2Cl_2 (1.4 mL) at −78 °C was added a solution of AgOTf (120 mg, 3.58 mmol) in MeCN (0.7 mL). A solution of methylsulfenyl bromide[16] (MSB) in 1,2-dichloroethane (0.098 mL, 4 M) was added during 10 min. The mixture was stirred for 1.5 h at −78 °C, isopropylamine (0.1 mL) was added, and the stirring was continued at −78 °C for 1 h. The mixture was filtered through a short column (SiO_2, 1:1 heptane−EtOAc), concentrated, and chromatographed (SiO_2, 3:1 → 2:1 heptane−EtOAc) to give an unseparable mixture of **19** and **20** (75 mg, 58%, **19**:**20** 2.2:1). The mixture was conventionally acetylated (pyridine−Ac_2O−DMAP), and the product was purified by chromatography (SiO_2, 2:1 heptane−EtOAc) to give a mixture of acetylated **19** and **20**. Selected data for acetylated **19**: ^{1}H NMR ($CDCl_3$) δ 5.89 (d, 1 H, J = 8.4 Hz, H-1), 5.66 (dd, 1 H, J = 10.5, 8.6 Hz, H-3), 4.64 (d, 1 H, J = 8.0 Hz, H-1′), 3.73 (s, 3 H, OMe), 2.20, 2.01, 1.97, 1.94 (4 s, OAc), 1.17 (d, 3 H, J = 6.4 Hz, H-6′); ^{13}C NMR ($CDCl_3$) δ 171.09, 171.07, 170.7, 169.9, 156.0, 150.7, 138.9, 138.5, 128.7, 128.0, 127.9, 101.7, 96.8, 75.4, 75.1, 74.0, 73.8, 16.3. Selected data for acetylated **20**: ^{1}H NMR ($CDCl_3$) δ 5.88 (d, 1 H, J = 8.5 Hz, H-1), 5.76 (dd, 1 H, J = 10.4, 8.7 Hz, H-3), 5.21 (d, 1 H, J = 3.5 Hz, H-1′), 3.74 (s, 3 H, OMe), 2.10, 2.07, 2.06, 1.96 (4 s, OAc), 1.26 (d, 3 H, J = 6.6 Hz, H-6′); ^{13}C NMR ($CDCl_3$) δ 171.3, 170.6, 170.4, 169.8, 156.0, 150.8, 140.9, 128.8, 128.1, 127.9, 107.0, 97.0, 75.13, 75.12, 74.0, 73.7, 16.6; HRMS of the **19**/**20** mixture calcd for $C_{40}H_{39}O_{15}NCl_4Na$ (M + Na) 936.0972, found 936.0961.

4-Methoxyphenyl (2,3,4-Tri-*O*-acetyl-6-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-(2-acetamido-6-*O*-benzyl-2-deoxy-β-D-glucopyranoside) (21). Compound **14** (100 mg, 0.10 mmol) was dissolved in dry EtOH (3 mL), and 1,2-diaminoethane[7] (0.030 mL, 0.5 mmol) was added. The mixture was heated at 60 °C for 3 h and concentrated. The residue was dissolved in MeOH−H_2O−Ac_2O (2.5, 0.5, 0.75 mL), stirred for 1 h, and then concentrated and chromatographed (SiO_2, 2:1 CH_2Cl_2−acetone) to give **21** (69 mg, 88%): $[\alpha]^{20}_D$ −15.8 (*c* 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.48 (d, 1 H, J = 8.8 Hz, H-1), 7.25−7.50 (m, 10 H, ArH), 6.75−7.00 (m, 4 H, OPMP), 5.97 (d, 1 H, J = 7.5 Hz, NH), 5.40 (d, 1 H, J = 8.3 Hz, H-1), 5.24 (d, 1 H, J = 2.9 Hz, H-4′), 5.16 (dd, 1 H, J = 10.4, 8.0 Hz, H-2′), 4.99 (dd, 1 H, J = 10.4, 3.4 Hz, H-3′), 4.63, 4.50 (ABq, 1 H each, J = 12.2 Hz, OBn), 4.61 (d, 1 H, J = 8.4 Hz, H-1′), 4.56, 4.40 (ABq, 1 H each, J = 11.9 Hz, OBn), 4.34 (d, 1 H, J = 2.0 Hz, OH), 4.28 (bt, 1 H, J = 7.7 Hz, H-3), 3.76 (s, 3 H, OMe), 3.35−3.90 (m, 8 H, H-2,4,5,6,5′,6′), 2.07, 2.02, 2.01, 1.99 (s, 3 H each, 3 × OAc, NHAc); ^{13}C NMR ($CDCl_3$) δ 171.0, 170.54, 170.53, 169.7, 155.8, 151.7, 138.5, 137.6, 128.99, 128.86, 128.5, 128.4, 128.3, 128.2, 128.1, 119.1, 114.9, 101.6, 99.6, 81.8, 74.4, 74.1, 73.9, 72.7, 71.6, 71.3, 69.7, 68.6, 68.0, 67.7, 57.9, 56.1, 24.1, 21.2, 21.1, 21.0; HRMS calcd for $C_{41}H_{49}O_{15}NNa$ (M + Na) 818.3000, found 818.2996.

4-Methoxyphenyl (2,3,4-Tri-*O*-acetyl-6-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-[2,3,4-Tri-*O*-benzyl-α-L-fucopyranosyl]-(1→3)-(2-acetamido-6-*O*-benzyl-2-deoxy-β-D-glucopyranoside) (22). Ethyl 2,3,4-tri-*O*-benzyl-1-thio-α-L-fucopyranoside[17] (**15**, 200 mg, 0.42 mmol) was dissolved in dry CH_2Cl_2 (1.5 mL), and freshly distilled Br_2 (0.020 mL in 0.250 mL CH_2Cl_2) was added. The mixture was stirred for 15 min, and cyclohexene was added until the color of Br_2 disappeared. The mixture was then added to a mixture of **21** (164 mg, 0.21 mmol), molecular sieves (4A, 750 mg), Bu_4NBr (120 mg), and 5:3 CH_2Cl_2−DMF (1.6 mL). The mixture was stirred for 20 h, pyridine (0.2 mL) was added, and the stirring was continued for 3 h. The mixture was filtered (Celite) and co-concentrated with toluene. The residue was chromatographed (SiO_2, 2:1 heptane−EtOAc) to give **22** (211 mg, 83%): $[\alpha]^{20}_D$ −56.6 (*c* 1.1 $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.15−7.45 (m, 25 H, ArH), 6.70−6.90 (m, 4 H, OPMP), 6.24 (d, 1 H, J = 8.4 Hz, NH), 5.46 (d, 1 H, J = 3.5 Hz, H-4′), 5.32 (d, 1 H, J = 4.3 Hz, H-1), 5.14 (d, 1 H, J = 3.7 Hz, H-1″), 5.10 (dd, 1 H J = 10.5, 7.9 Hz, H-2′), 4.97, 4.67 (ABq, 1 H each, J = 11.8 Hz, OBn), 4.99 (dd, 1 H, J = 10.6, 7.2 Hz, H-3′), 4.81, 4.77 (ABq, 1 H each, J = 11.8 Hz, OBn), 4.79, 4.68 (ABq, 1 H each, J = 12.0 Hz, OBn), 4.51 (d, 1 H, J = 7.8 Hz, H-1′), 4.50, 4.34 (ABq, 1 H each, J = 12.3 Hz, OBn), 4.35, 4.30 (ABq, 1 H each, J = 12.0 Hz, OBn), 4.05−4.20 (m, 2 H, H-2,2″), 4.05 (q, 1 H, J = 6.4 Hz, H-5″), 3.98 (t, 1 H, J = 4.8 Hz, H-3″), 3.93 (dd, 1 H, J = 10.0, 6.4 Hz, H-6), 3.84 (dd, 1 H, J = 10.1, 2.7 Hz, H-3), 3.50−3.80 (m, 6 H, H-4,5,6,5′,6′,4″), 3.76 (s, 3 H, OMe), 3.43 (dd, 1 H, J = 9.1, 8.0 Hz, H-6′), 2.04, 1.99, 1.97, 1.92 (s, 3 H each, 3 × OAc, NHAc), 1.06 (d, 3 H, J = 6.5 Hz, H-6″); ^{13}C NMR ($CDCl_3$) δ 170.6, 170.5, 170.4, 155.3, 151.6, 139.23, 139.17, 138.4, 137.8, 129.0, 128.88, 128.86, 128.6, 128.4, 128.32, 128.27, 128.1, 128.02,

128.00, 127.99, 127.8, 118.5, 114.8, 100.0, 98.8, 97.5, 79.7, 77.8, 77.3, 75.0, 74.5, 73.9, 73.7, 73.6, 73.4, 73.1, 72.4, 71.0, 69.7, 69.5, 67.7, 67.3, 67.2, 56.1, 23.6, 21.3, 21.1, 21.0, 17.1; HRMS calcd for $C_{68}H_{77}O_{19}NNa$ (M + Na) 1234.4987, found 1234.4987.

A sample of **22** was de-O-benzylated (H_2, Pd−C, AcOH) and then O-acetylated to give the fully acetylated derivative of **2**: ^{1}H NMR ($CDCl_3$) δ 6.75−6.95 (m, 4 H, OPMP), 5.81 (d, 1 H, J = 8.6 Hz, NH), 5.49 (d, 1 H, J = 4.0 Hz, H-1″), 5.44 (d, 1 H, J = 2.7 Hz, H-4′), 5.39 (d, 1 H, J = 2.6 Hz, H-4″), 5.25 (dd, 1 H, J = 11.0, 3.4 Hz, H-3″), 5.14 (dd, 1 H, J = 10.5, 8.0 Hz, H-2′), 5.12 (d, 1 H, J = 6.1 Hz, H-1), 5.08 (dd, 1 H, J = 10.9, 3.9 Hz, H-2″), 5.04 (dd, 1 H, J = 10.4, 3.5 Hz, H-3′), 4.72 (q, 1 H, J = 6.6 Hz, H-5″), 4.60 (dd, 1 H, J = 11.7, 3.8 Hz, H-6), 4.49 (d, 1 H, J = 8.0 Hz, H-1′), 4.46 (dd, 1 H, J = 11.4, 6.3 Hz, H-6′), 4.30 (dd, 1 H, J = 11.5, 7.6 Hz, H-6′), 4.25 (dd, 1 H, J = 11.8, 5.8 Hz, H-6), 4.17 (t, 1 H, J = 7.4 Hz, H-3), 4.07 (q, 1 H, J = 7.2 Hz, H-2), 3.90−4.00 (m, 2 H, H-4,5′), 3.77 (s, 3 H, OMe), 3.75−3.80 (m, 1 H, H-5), 2.22, 2.17, 2.10, 2.09, 2.08, 2.04, 2.00, 1.99 (s, 27 H, OAc, NHAc), 1.22 (d, 3 H, J = 6.6 Hz, H-6″).

4-Methoxyphenyl (2,3,4-Tri-*O*-benzyl-α-L-fucopyranosyl)-(1→3)-(2-acetamido-6-*O*-benzyl-2-deoxy-β-D-glucopyranoside) (23). Compound **16** (70 mg, 0.066 mmol) was dissolved in dry EtOH (7 mL), and 1,2-diaminoethane[7] (0.200 mL, 3.0 mmol) was added. The mixture was refluxed for 3 h and concentrated. The residue was filtered through a short column (SiO_2, 20:1 toluene−EtOH), and the eluate was concentrated. The residue was dissolved in pyridine (5 mL), and Ac_2O (4 mL) and DMAP (∼3 mg) were added. The mixture was stirred overnight and then co-concentrated with toluene. The residue was dissolved in MeOH (10 mL), and 1 M MeONa/MeOH (0.5 mL) was added. The mixture was stirred for 4 h, filtered on a short column (SiO_2, 5:1 CH_2Cl_2−EtOH), and chromatographed (SiO_2, 20:1 CH_2Cl_2−EtOH) to give **23** (50 mg, 89%): $[\alpha]^{20}_D$ −44.3 (*c* 0.9 $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.25−7.45 (m, 20 H, Ar), 6.75−7.00 (m, 4 H, OPMP), 5.61 (d, 1 H, J = 7.3 Hz, NH), 5.32 (d, 1 H, J = 8.4 Hz, H-1), 4.99−5.02 (m, 1 H, H-1′), 4.77, 4.83 (ABq, 1 H each, J = 11.6 Hz, OBn), 4.67, 4.87 (ABq, 1 H each, J = 11.7 Hz, OBn), 4.65, 4.98 (ABq, 1 H each, J = 11.4 Hz, OBn), 4.58, 4.62 (ABq, 1 H each, J = 12.1 Hz, OBn), 4.23 (bs, 1 H, OH), 4.12−4.17 (m, 1 H, H-5′), 4.11 (dd, 1 H, J = 10.1, 3.5 Hz, H-2′), 3.97 (dd, 1 H, J = 10.0, 2.4 Hz, H-3′), 3.91−3.97 (m, 1 H, H-3), 3.89 (dd, 1 H, J = 10.9, 2.0 Hz, H6), 3.76 (s, 3 H, OMe), 3.50−3.75 (m, 5 H, H-2,4,5,6,4′), 1.62 (s, 3 H, NHAc), 1.18 (d, 3 H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 171.4, 155.7, 151.9, 138.9, 138.7, 129.0, 128.9, 128.8, 128.73, 128.72, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 119.2, 114.9, 100.0, 99.8, 84.5, 76.4, 75.53, 75.45, 74.6, 73.9, 73.3, 70.9, 69.9, 68.6, 56.6, 56.1, 23.6, 17.1; HRMS calcd for $C_{49}H_{55}O_{11}NNa$ (M + Na) 856.3674, found 856.3672.

A sample of **23** was de-O-benzylated (H_2, Pd/C, AcOH) and then O-acetylated to give the fully acetylated derivative: ^{1}H NMR ($CDCl_3$) δ 6.79−6.98 (m, 4 H, OPMP), 5.89 (d, 1 H, J = 7.6 Hz, NH), 5.47 (d, 1 H, J = 7.8 Hz, H-1), 5.35 (dd, 1 H, J = 11.3, 3.5 Hz, H-3′), 5.30 (d, 1 H, J = 3.4 Hz, H-1′), 5.27 (dd, 1 H, J = 3.3, 1.3 Hz, H-4′), 5.13 (dd, 1 H, J = 11.1, 3.5 Hz, H-2′), 5.02 (t, 1 H, J = 9.0 Hz, H-4), 4.52 (t, 1 H, J = 9.3 Hz, H-3), 4.23 (dd, 1 H, J = 12.2, 5.9 Hz, H-6), 4.18 (q, 1 H, J = 6.8 Hz, H-5′), 4.10 (dd, 1 H, J = 11.8, 2.9 Hz, H-6), 3.77 (s, 3 H, OMe), 3.70−3.76 (m, 1 H, H-5), 3.47 (q, 1 H, J = 9.4 Hz, H-2), 2.17, 2.12, 2.09, 2.07, 2.01, 2.00 (s, 3 H each, 5 × OAc, NHAc), 1.10 (d, 3 H, J = 6.5 Hz, H-6′).

4-Methoxyphenyl (6-*O*-Benzyl-β-D-galactopyranosyl)-(1→4)-[2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl]-(1→3)-(2-acetamido-6-*O*-benzyl-2-deoxy-β-D-glucopyranoside) (24). To a solution of compound **22** (210 mg, 0.17 mmol) in MeOH (10 mL) was added 1 M MeONa−MeOH (0.5 mL). The mixture was stirred for 1.5 h, quenched by addition of AcOH (0.5 mL), and co-concentrated with toluene. The residue was chromatographed (SiO_2, 20:1 CH_2Cl_2−EtOH) to give **24** (167 mg, 89%): $[\alpha]^{20}_D$ −52.4 (*c* 1.3 $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.20−7.40 (m, 25 H, ArH), 6.75−6.95 (m, 4 H, OPMP), 6.09 (d, 1 H, J = 7.2 Hz, NH), 5.26 (d, 1 H, J = 7.4 Hz, H-1), 5.17 (d, 1 H, J = 3.5 Hz, H-1″), 4.72, 4.76 (ABq, 1 H each, J = 11.5 Hz, OBn), 4.67, 4.93 (ABq, 1 H each, J = 11.4 Hz, OBn), 4.60, 4.94 (ABq, 1 H each, J = 11.5 Hz, OBn), 4.54 (d, 1 H, J = 7.4 Hz, H-1′), 4.51, 4.61 (ABq, 1 H each, J = 12.2 Hz, OBn), 4.47, 4.50 (ABq, 1 H each, J = 12.2 Hz, OBn), 4.32 (t, 1 H, J = 8.8 Hz, H-3), 4.27 (q, 1 H, J = 6.5 Hz, H-5″), 4.00−4.15 (m, 2 H, H-4,2″), 3.85−3.95 (m, 4 H, H-6,3″, OH), 3.76 (s, 3 H, OMe), 3.45−3.75 (m, 9 H, H-2,5,2′,3′,5′,6′,4″), 2.74 (bs, 1 H, OH), 2.65 (bs, 1 H, OH), 1.14 (d, 3 H, J = 6.5 Hz, H-6″), 1.67 (s, 3 H, NHAc); ^{13}C NMR ($CDCl_3$) δ 170.9, 155.7, 151.8, 139.0, 138.9, 138.7, 138.4, 138.2, 129.1, 128.92, 128.90, 128.8, 128.7, 128.6, 128.5, 128.4, 128.2, 128.12, 128.05, 128.0, 127.7, 119.4, 114.8, 101.1, 100.1, 98.2, 80.0, 77.9, 77.7, 77.3, 75.4, 75.2, 75.0, 74.7, 73.8, 73.4, 72.8, 69.4, 69.3, 68.7, 67.7, 56.1, 23.7, 17.3; HRMS calcd for $C_{62}H_{71}O_{16}NNa$ (M + Na) 1108.4671, found 1108.4652.

4-Methoxyphenyl (Methyl(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosyl)onate)-(2→3)-(4-*O*-acetyl-6-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-[2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl]-(1→3)-(2-acetamido-6-*O*-benzyl-2-deoxy-β-D-glucopyranoside) (26). To a mixture of compound **24** (144 mg, 0.132 mmol), the sialyl donor **25**[22] (160 mg, 0.264 mmol), and activated molecular sieves (3A, 90 mg) were added CH_2Cl_2 (1.08 mL) and MeCN (0.90 mL). The mixture was stirred for 15 min at room temperature and for 15 min at −72 °C under Ar. A solution of AgOTf (90 mg) in MeCN (0.90 mL) was added, and the mixture was left for 5 min. A 4 M solution of methylsulfenyl bromide[16] (MSB) in 1,2-dichloroethane (0.083 mL) was added during 30 min. The mixture was stirred for 2.5 h, diisopropylamine (0.180 mL) was added, and the mixture was stirred for another 1.5 h. The reaction mixture was filtered through a short column (SiO_2, 20:1 CH_2Cl_2−EtOH). The crude product was acetylated (Ac_2O−pyridine) and co-concentrated with toluene, and the residue was chromatographed (SiO_2, 3:1 → 2:1 toluene−acetone) to give **26** (141 mg, 65%): $[\alpha]^{20}_D$ −36.0 (*c* 1.3 $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.10−7.43 (m, 25 H, ArH), 6.70−6.92 (m, 4 H, OPMP), 6.46 (d, 1 H, J = 9.1 Hz, NH), 5.60 (ddd, 1 H, J = 8.9, 6.0, 2.7 Hz, H-8‴), 5.37 (dd, 1 H, J = 8.9, 2.7 Hz, H-7‴), 5.25 (d, 1 H, J = 3.4 Hz, H-1), 5.19 (d, 1 H, J = 3.6 Hz, H-1″), 5.09 (d, 1 H, J = 3.8 Hz, H-4′), 5.07 (d, 1 H, J = 6.2 Hz, NH), 4.99 (dd 1 H, J = 10.2, 7.9, H-2′), 4.87−4.95 (m, 1 H, H-4‴), 4.77, 4.82 (ABq, 1 H each, J = 11.4 Hz, OBn), 4.72 (d, 1 H, J = 8.0 Hz, H-1′), 4.67, 4.79 (ABq, 1 H each, J = 11.8 Hz, OBn), 4.66 (dd, 1 H, J = 10.2, 3.6 Hz, H-3′), 4.63, 4.95 (ABq, 1 H each, J = 11.8 Hz, OBn), 4.37, 4.47 (ABq, 1 H each, J = 11.8 Hz, OBn), 4.30−4.40 (m, 2 H, H-2,9‴), 4.15, 4.32 (ABq, 1 H each, J = 12.0 Hz, OBn), 3.95−4.12 (m, 7 H, H-3,4,5,6,2″,5‴,9‴), 3.87, (s, 3 H, OMe), 3.77−3.86 (m, 3 H, H-5′,3″,5″), 3.75 (s, 3 H, OMe), 3.69 (q, 1 H, J = 4.1 Hz, H-6), 3.65 (dd, 1 H, J = 10.6, 2.6 Hz, H-6‴), 3.47 (dd, 1 H, J = 9.4, 5.5 Hz, H-6′), 3.35−3.45 (m, 2 H, H-6′,4″), 2.60 (dd, 1 H, J = 12.6, 4.5 Hz, H-3‴), 2.20, 2.13, 2.09, 2.03, 2.02, 2.00, 1.95, 1.87 (s, 3 H each, 6 × OAc, 2 × NHAc), 1.75 (t, 1 H, J = 12.6 Hz, H-3‴), 0.98 (d, 3 H, J = 10.5 Hz, H-6″); ^{13}C NMR ($CDCl_3$) δ 170.9, 170.7, 170.5, 170.4, 170.3, 170.0, 169.7, 167.9 (C-1‴, $J_{C-1''';H-3'''ax}$ 6.4 Hz),[24] 154.7, 151.3, 139.0, 138.73, 138.68, 138.4, 137.7, 128.40, 128.37, 128.34, 128.31, 128.19, 128.15, 127.9, 127.71, 127.66, 127.6, 127.44, 127.43, 127.37, 127.3, 127.1, 117.8, 114.4, 99.1, 98.3, 96.9, 96.8, 90.5, 78.9, 74.6, 73.8, 73.4, 73.00 72.8, 72.73, 72.68, 72.1, 71.9, 71.1, 70.2, 70.0, 69.3, 67.9, 67.6, 67.3, 67.0, 62.5, 60.0, 55.6, 53.2, 49.2, 37.6, 23.2, 23.1, 21.4, 20.9, 20.8, 20.6, 16.5; HRMS calcd for $C_{86}H_{102}O_{30}N_2Na$ (M + Na) 1665.6415, found 1665.6438.

A sample of **26** was de-O-benzylated (H_2, Pd/C, AcOH) and then O-acetylated to give the fully acetylated derivative of **1**: ^{1}H NMR ($CDCl_3$) δ 6.75−6.95 (m, 4 H, OPMP), 6.67 (d, 1 H, J = 9.0 Hz, NH), 5.55 (dt, 1 H, J = 9.5, 3.3 Hz, H-8‴), 5.47 (d, 1 H, J = 4.5 Hz, H-1″), 5.45 (dd, 1 H, J = 9.5, 2.8 Hz, H-7‴), 5.35 (d, 1 H, J = 2.8 Hz, H-4″), 5.25 (dd, 1 H, J = 10.9, 3.3 Hz, H-3″), 5.09 (d, 1 H, J = 10.3 Hz, NH‴), 5.07 (d, 1 H, J = 7.7 Hz, H-1), 5.04 (dd, 1 H, J = 10.6, 3.7 Hz, H-2″), 4.97 (d, 1 H, J = 3.7 Hz, H-4′), 4.85−4.95 (m, 3 H, H-2′,5″,4‴), 4.74 (d, 1 H, J = 8.1 Hz, H-1′), 4.70 (dd, 1 H, J = 11.8, 2.8 Hz, H-6), 4.58 (dd, 1 H, J = 10.2, 3.5 Hz, H-3′), 4.37 (dd, 1 H, J = 11.5. 7.0 Hz, H-6′), 4.31 (dd, 1 H, J = 12.9, 2.7 Hz, H-9‴), 4.23 (dd, 1 H, J = 11.6, 6.8 Hz, H-6′), 4.17 (dd, 1 H, J = 12.0, 5.7 Hz, H-6), 4.13 (d, 1 H, J = 9.1 Hz, H-3), 4.10 (dd, 1 H, J = 12.9, 9.0 Hz, H-9‴), 4.00−4.09 (m, 2 H, H-2,5‴), 3.97 (t, 1 H, J = 8.1 Hz, H-4), 3.90 (t, 1 H, J = 7.0 Hz, H-5′), 3.87 (s, 3 H, OMe),

3.77 (s, 3 H, OMe), 3.70−3.75 (m, 1 H, H-5), 3.65 (dd, 1 H, J = 10.7, 2.8 Hz, H-6‴), 2.60 (dd, 1 h, J = 12.8, 4.8 Hz, H-3e‴), 2.24, 2.17, 2.16, 2.15, 2.12, 2.10, 2.08, 2.06, 2.06, 2.01, 2.00, 1.98, 1.87 (s, 3 H each, 11 × OAc, 2 × NHAc), 1.68 (t, 1 H, J = 12.4 Hz, H-3a‴), 1.20 (d, 3 H, J = 6.5 Hz, H-6″).

Acknowledgment. This work was supported by the Swedish Natural Science Research Council.

Supporting Information Available: ^{1}H NMR spectra for all title compounds described in the Experimental Section (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO981203X