Synthesis of a Thio-Analogue of Lewis X by Regioselective Opening of Cyclic Sulfamidates

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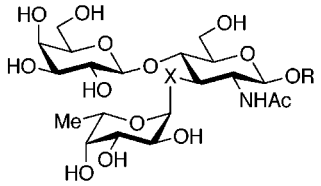
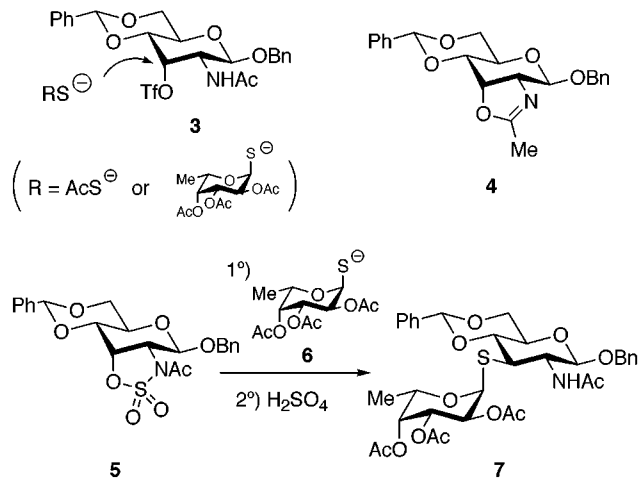
Lewis X (Le^x) trisaccharide **1** present at the termini of Le^x-bearing glycoconjugates plays a major role in biologically important functions. For instance, Le^x−Le^x interaction mediates cell−cell adhesion during embryogenesis.[1] The tetrasaccharide sialyl Le^x is involved in the acute inflammatory process[2] and has been found in tumor cells and carcinomas.[3] Besides, we have reported[4] that some oligosaccharides related to Le^x are inhibitors of neural cell division. Owing to the important biological interest of this trisaccharide, we planned to prepare the thiotrisaccharide **2** analogue of Le^x containing a sulfur atom linking the fucosyl and glucosaminyl moieties. Since thioglycosides have been proven to be resistant to glycosidase enzymes,[5] compound **2** will be more stable for in vivo experiments.



1 R = H, X = O
2 R = Bn, X = S

Several methods have been published[6] for the synthesis of thiooligosaccharides. Most of them involved S_N2-type substitutions of thiolate anions on glycosyl halides, or of 1-thio-donors on acceptors bearing good leaving groups. Applied to the formation of the 3-*S*-fucosyl linkage in **2**, both approaches require a nucleophilic displacement of a leaving group at C-3 of an allosamine derivative with a sulfur nucleophile (Scheme 1). However, the presence of the acetamido group at the adjacent C-2 position can lead to secondary reactions, such as the formation of oxazoline **4**. In fact, **4** was obtained[7] when the preparation of triflate **3** was attempted by triflation of the corresponding alcohol. To circumvent this problem, we have recently described[7a] the formation of cyclic sulfamidate **5** and its use[7b] in nucleophilic displacements to get 3-thio and 3-azido glucosamine derivatives. For instance, the treatment of **5** with fucose thiolate **6** furnished the thiodisaccharide **7** in good yield (Scheme 1). In the present work we report the application of this method to accomplish an efficient synthesis of **2**.

Scheme 1



For building the target molecule **2**, we first tried to use diol **8** (Scheme 2), obtained[7b] by acid hydrolysis of the benzylidene acetal in **7**, containing the thiofucosyl residue. Compound **8** was selectively acetylated at the C-6 hydroxyl to afford **9** (82%). Next, we attempted the galactosylation of **9** using trichloroacetimidate **11**. Both TMS-triflate and BF_3 etherate were used as promotors.[8] We observed rapid consumption of **11** but were unable to detect any glycosylation product. Similar results were obtained when the galactosylation was tried with bromide **12** and fluoride **13** in the presence of AgOTf[9] and BF_3 etherate[10] as promotors, respectively. To evaluate if the reactivity of 4-hydroxyl group of **9** could be influenced[11] by the nature of substituent at vicinal C-6 position, the *p*-methoxyphenyl derivative **10**, prepared from **8** in a Mitsunobu-type reaction (95%), was subjected to galactosylation. Again no glycosylation product was detected. The sulfoxide glycosylation method, which has been successfully used with unreactive alcohols,[12] was next tried. The reaction of **10** with sulfoxide **14** in the presence of Tf_2O (2 equiv) did not afford the desired glycoside; instead a new compound was formed which was identified[13] as the oxazine **15**. The formation of **15** could be explained by the initial triflation of the acetamido group of **10** followed by intramolecular triflate displacement by the 4-hydroxyl, as outlined in Scheme 3.[14]

At this point, we changed our strategy to assemble the target molecule **2**. The galactose and allosamine deriva-

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(13) See Supporting Information for details.

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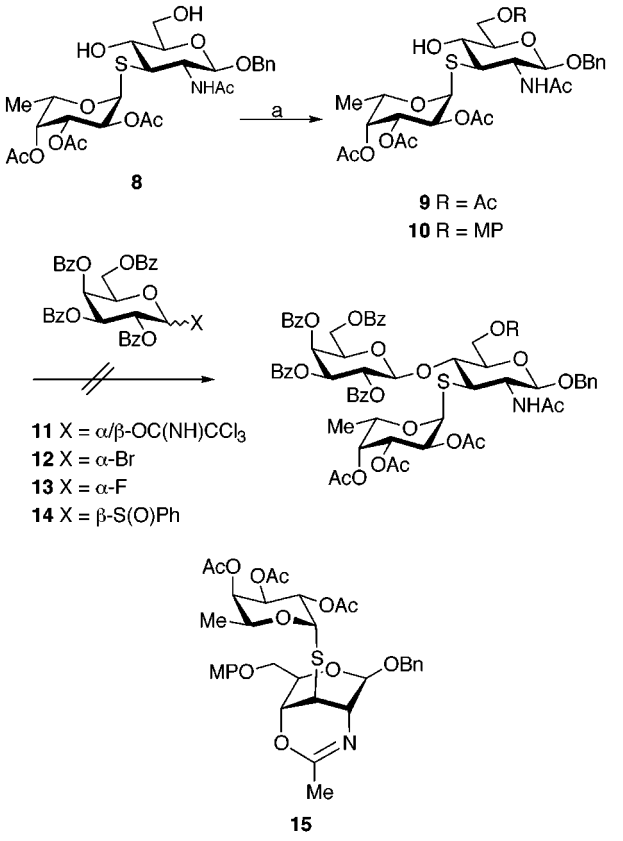
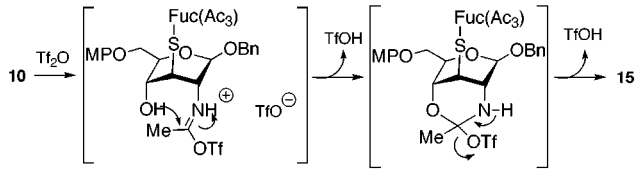
Scheme 2[a]



[a]Key : (a) **9:** AcCl, collidine, DCM, -78 °C, 82%.
10: *p*-methoxyphenol, Ph_3P, DIAD, THF, 70 °C , 95%.

Scheme 3



tives should be linked first to give a $\beta(1\rightarrow4)$ disaccharide, which after transformation into a cyclic sulfamidate and subsequent treatment with a fucose thiolate should furnish the desired thiotrisaccharide (Scheme 4). Thus, allylation of **16**, followed by acid hydrolysis of the benzylidene acetal, and selective benzoylation gave **19** through intermediates **17** and **18**. Glycosylation of **19** with donor **11** in the presence of TMSOTf for 8 h gave the desired disaccharide **21** but in low yield (26%), together with the orthodisaccharide **26** (29%) and recovered acceptor **19** (18%). Longer reaction times gave no improvement in the yield of **21**. A significant increase in yield, however, was obtained when the glycosylation was performed on the monosaccharide **20**. Disaccharide **22** was isolated in 63% yield together with orthodisaccharide **27** (8%) and recovered acceptor **20** (7%). In this case, the change of the substituent benzoyl group at O-6 of the acceptor by a *p*-methoxyphenyl group influenced appreciably the reactivity of the hydroxyl at C-4. The synthesis toward **2** was then continued using disaccharide **22**. Deallylation of **22** gave alcohol **23** which was transformed into the sulfamidate **24** using the two-step procedure,[15] i.e. reaction with thionyl chloride followed by oxidation. The regioselective opening of **24** with fucose 1-thiolate **6** took place smoothly and furnished thiotrisaccharide **25** in 77% yield. Two subsequent deprotection steps led to target trisaccharide **2**, which was characterized by applying various NMR techniques.

(14) An alternative mechanism could be envisaged through the initial triflation of the 4-hydroxyl of **10** followed by intramolecular triflate displacement by the acetamido group, proceeding with retention of the configuration at C-4 via a 3,4-episulfonium ion. However, the fact that oxazoline **4** was formed when alcohol **16** was treated with Tf_2O (ref 7) could support the mechanism depicted in Scheme 3.

Experimental Section

General Methods. Melting points are not corrected. TLC was performed using TLC plates GF_{254} with detection by charring with 5% H_2SO_4 in EtOH. Column chromatography was performed on silica gel (230−400 mesh) or sep-pack C18 cartridges. The eluent used is indicated and solvent ratios refer to volume. Solvents were distilled over drying agents: dimethylformamide (DMF), BaO; dichloromethane (DCM), CaH_2; tetrahydrofuran (THF), sodium/benzophenone ketyl; and pyridine (Py), BaO. ^{1}H NMR spectra were registered at 500, 400, 300, or 200 MHz. ^{13}C NMR spectra were obtained at 125, 75, or 50 MHz.

Benzyl *S*-(2,3,4-Tri-*O*-acetyl-α-L-fucopyranosyl)-(1→3)-2-acetamido-6-*O*-acetyl-2-deoxy-3-thio-*β*-D-glucopyranoside (9). To a stirred solution of **8**[7b] (155 mg, 0.26 mmol) in DCM (2 mL) under Ar at −78 °C were added collidine (68.7 μL, 0.52 mmol) and then acetyl chloride dropwise (22.2 μL, 0.31 mmol). After stirring for 3 h at −50 °C, the reaction mixture was diluted with DCM (25 mL), washed with sat. $NaHCO_3$ solution (25 mL), aq HCl 10% (25 mL), and brine (25 mL), dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (EtOAc−hexane 2:1) to yield **9** (139 mg, 82%) as a white solid: mp 102−105 °C; $[\alpha]_D$ −156.9° (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.35−7.27 (m, 5H), 5.74 (d, 1H, J = 5.0 Hz), 5.50 (d, 1H, J = 8.0 Hz), 5.28 (dd, 1H, J = 3.0 Hz, J = 1.2 Hz), 5.21−5.10 (m, 2H), 4.86 (d, 1H, J = 11.9 Hz), 4.80 (d, 1H, J = 7.7 Hz), 4.60−4.56 (m, 2H), 4.41−4.39 (m, 2H), 3.57 (m, 1H), 3.54−3.24 (m, 4H), 2.15 (s, 3H), 2.13 (s, 3H), 2.06 (s, 3H), 1.99 (s, 3H), 1.95 (s, 3H), 1.16 (d, 1H, J = 6.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.29, 170.36, 170.26, 169.77, 137.18, 128.46, 128.00, 99.90, 83.22, 78.69, 76.22, 70.76, 70.61, 69.59, 68.19, 68.02, 65.81, 63.64, 56.37, 52.24, 23.42, 20.87, 20.76, 20.59, 20.53, 15.92. Anal. Calcd for $C_{29}H_{39}NO_{13}S$: C, 54.28; H, 6.13; N, 2.18; S, 5.0. Found: C, 54.50; H, 6.10; N, 2.18; S, 4.78.

Benzyl *S*-(2,3,4-Tri-*O*-acetyl-α-L-fucopyranosyl)-(1→3)-2-acetamido-2-deoxy-6-*O*-(*p*-methoxyphenyl)-3-thio-*β*-D-glucopyranoside (10). To a stirred solution of **8** (200 mg, 0.33 mmol), triphenylphosphine (131 mg, 0.5 mmol), and *p*-methoxyphenol (124 mg, 1 mmol) in THF (3 mL) at 70 °C under Ar was added dropwise diisopropyl azodicarboxylate (98.64 μL, 0.5 mmol), and the mixture was stirred at 70 °C for 3 h. After cooling, the solvent was evaporated under reduced pressure, and the residue purified by column chromatography (toluene−acetone 3:1) to give **10** (223 mg, 95%) as a white solid: mp 89−93 °C; $[\alpha]_D$ −140.3° (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.35−7.25 (m, 5H), 7.19−6.81 (m, 4H), 5.75 (d, 1H, J = 5.2 Hz), 5.68 (d, 1H, J = 8.3 Hz), 5.28 (dd, 1H, J = 2.8 Hz, J = 1.1 Hz), 5.21−5.10 (m, 2H), 4.84 (d, 1H, J = 11.9 Hz), 4.75 (d, 1H, J = 7.9 Hz), 4.62−4.55 (m, 2H), 4.30 (dd, 1H, J = 2.4 Hz, J = 10.6 Hz), 4.16 (dd, 1H, J = 5.5 Hz, J = 10.6 Hz), 3.76 (s, 3H), 3.69 (m, 1H), 3.59−3.49 (m, 2H), 3.34−3.26 (m, 2H), 2.15 (s, 3H), 2.05 (s, 3H), 1.99 (s, 3H), 1.93 (s, 3H) 1.16 (d, 1H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 170.40, 170.29, 170.22, 169.80, 152.89, 137.18, 128.39, 128.15, 127.89, 115.95, 114.54, 99.79, 83.40, 77.42, 70.53, 70.47, 70.18, 68.75, 68.14, 67.91, 65.68, 56.06, 55.65, 52.84, 20.71, 20.54, 20.48, 15.84. Anal. Calcd for $C_{34}H_{43}NO_{13}S$: C, 57.86; H, 6.14; N, 1.98; S, 4.54. Found: C, 57.58; H, 6.07; N, 2.02; S, 4.28.

Benzyl 2-Acetamido-3-*O*-allyl-4,6-*O*-benzylidene-2-deoxy-*β*-D-allopyranoside (17). Compound **16**[7b] (3 g, 7.52 mmol) was

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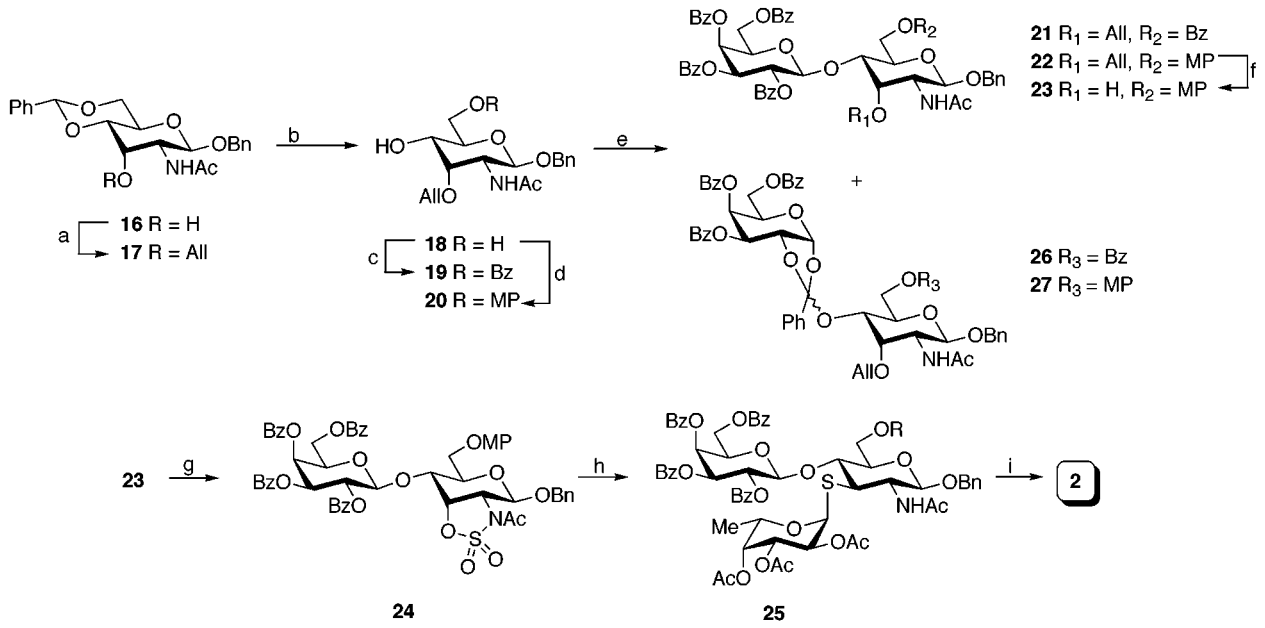
Scheme 4[a]



[a]Key: (a) AllBr, NaH, DMF, 0 °C→ r.t., 98%; (b) camphorsulfonic acid, MeOH, 60 °C, 91%; (c) BzCl, DCM–Py (1:1), -20 °C, 91%; (d) *p*–methoxyphenol, Ph_3P, DIAD, THF, 70 °C, 90%; (e) **11**, TMSOTf, DCM, r.t., **21**, **26**: 26% and 29% respectively; **22**, **27**: 63% and 8% respectively; (f) 1. $[Ir(COD)(PMePh_2)_2]PF_6$, H_2, THF, r.t.; 2. H_2O, I_2, r.t., 82%; (g) 1. $SOCl_2$, Et_3N, DCM, 10 °C; 2. $NaIO_4$, $RuCl_3{\cdot}3H_2O$, CH_3CN, H_2O, CCl_4, 0 °C, 61%; (h) 1. **6**, NaH, DMF, 0 °C→ r.t.; 2. H_2O, H_2SO_4, THF, r.t., 77%; (i) 1. CAN, CH_3CN-H_2O (4:1), 0 °C; 2. NaOMe, MeOH, r.t., 86%.

suspended in DMF (40 mL), and NaH (270 mg, 11.27 mmol) was carefully added at 0 °C. The mixture was stirred at this temperature under Ar for 5 min, and then dropwise addition of allyl bromide (0.78 mL, 9.02 mmol) was made. The reaction mixture was stirred at room temperature for 1 h and cooled at 0 °C, and MeOH (5 mL) was added carefully. Solvents were evaporated, and the residue was purified by column chromatography (DCM−EtOAc 10:1) to give **17** (3.23 g, 98%) as a white solid: mp 225−228 °C; $[\alpha]_D$ −124.6° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.50−7.29 (m, 10H), 5.92−5.80 (m, 1H), 5.73 (d, 1H, J = 9.3 Hz), 5.51 (s, 1H), 5.31−5.15 (m, 2H), 4.92 (d, 1H, J = 12.4 Hz), 4.67 (d, 1H, J = 8.6 Hz), 4.58 (d, 1H, J = 12.4 Hz), 4.49−4.39 (m, 1H), 4.39 (dd, 1H, J = 4.9 Hz, J = 9.7 Hz), 4.24 (dt, 1H, J = 3.1 Hz, J = 8.9 Hz), 4.11−3.96 (m, 3H), 3.79 (t, 1H, J = 10.1 Hz), 3.73 (dd, 1H, J = 2.2 Hz, J = 9.4 Hz), 1.98 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.87, 138.11, 138.00, 135.22, 129.69, 128.96, 128.89, 128.29, 128.17, 126.71, 117.84, 102.58, 100.0, 80.70, 76.37, 74.08, 71.07, 69.79, 64.27, 52.58, 23.99. Anal. Calcd for $C_{25}H_{29}NO_6$: C, 68.32; H, 6.65; N, 3.19. Found: C, 68.64; H, 6.78; N, 3.25.

Benzyl 2-Acetamido-3-*O*-allyl-2-deoxy-*β*-D-allopyranoside (18). A mixture of **17** (2.84 g, 6.47 mmol) and camphorsulfonic acid (300.5 mg, 1.29 mmol) in MeOH (90 mL) was stirred at 60 °C for 1 h. After cooling at room temperature, the reaction mixture was neutralized with triethylamine (1 mL) and evaporated to dryness. Column chromatography (DCM−MeOH 15:1) of the residue gave **18** (2.07 g, 91%) as a white solid: mp 136−140 °C; $[\alpha]_D$ −87.7° (*c* 0.8, MeOH). ^{1}H NMR (CD_3OD) δ 7.54−7.42 (m, 5H), 6.24−6.11 (m, 1H), 5.46−5.31(m, 2H), 5.08 (d, 1H, J = 11.8 Hz), 4.97 (d, 1H, J = 8.3 Hz), 4.76 (d, 1H, J = 11.7 Hz), 4.55−4.48 (m, 1H), 4.34−4.27 (m, 1H), 4.09−3.81 (m, 6H), 2.15 (s, 3H); ^{13}C NMR (CD_3OD) δ 172.87, 139.20, 136.66, 129.34, 129.23, 128.96, 128.81, 128.59, 117.39, 99.85, 79.13, 76.17, 75.79, 71.57, 69.57, 63.09, 54.53, 22.60. Anal. Calcd for $C_{18}H_{25}NO_6$: C, 61.52; H, 7.17; N, 3.99. Found: C, 61.20; H, 7.13; N, 3.97.

Benzyl 2-Acetamido-3-*O*-allyl-6-*O*-benzoyl-2-deoxy-*β*-D-allopyranoside (19). To a solution of **18** (800 mg, 2.28 mmol) in DCM-Py 1:1 (22 mL) at −20 °C under Ar was added dropwise benzoyl chloride (0.32 mL, 2.73 mmol), and the reaction mixture was stirred at this temperature for 1 h. Then, the reaction mixture was quenched with MeOH (1 mL) and evaporated under reduced pressure. The residue was coevaporated with toluene (3 × 20 mL) and subjected to flash chromatography (hexane−acetone 3:2) to yield **19** (940 mg, 91%) as a white solid: mp 167−169 °C; $[\alpha]_D$ −103.2° (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.10−7.27 (m, 10H), 5.97−5.83 (m, 2H), 5.30−5.17 (m, 2H), 4.86 (d, 1H, J = 12.2 Hz), 4.70 (d, 1H, J = 7.3 Hz), 4.68 (dd, 1H, J = 4.8 Hz, J = 11.9 Hz), 4.61 (dd, 1H, J = 3.5 Hz, J = 11.9 Hz), 4.58 (d, 1H, J = 12.2 Hz), 4.31−4.24 (m, 1H), 4.19−4.11 (m, 2H), 4.06−4.00 (m, 2H), 3.78 (dd, 1H, J = 2.93 Hz, J = 8.3 Hz), 1.98 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.67, 166,84, 137.08, 134.48, 129.60, 129.41, 128.19, 128.08, 127.62, 127.51, 125.67, 117.01, 98.19, 76.91, 73.98, 72.71, 70.07, 67.96, 64.39, 52.13, 22.52. Anal. Calcd for $C_{25}H_{29}NO_7$: C, 65.92; H, 6.42; N, 3.07. Found: C, 66.13; H, 6.51; N, 3.09.

Benzyl 2-Acetamido-3-*O*-allyl-2-deoxy-6-*O*-(*p*-methoxyphenyl)-*β*-D-allopyranoside (20). To a mixture of **18** (823 mg, 2.34 mmol), triphenylphosphine (1.22 g, 4.68 mmol), and *p*-methoxyphenol (581 mg, 4.68 mmol) in THF (23.4 mL) at 70 °C under Ar was added dropwise diisopropyl azodicarboxylate (0.92 mL, 4.68 mmol), and the mixture was stirred at this temperature for 1 h. After cooling, the solvent was evaporated under reduced pressure and the residue purified by column chromatography (EtOAc) to give **20** (964 mg, 90%) as a white solid: mp 167−169 °C; $[\alpha]_D$ −83.7° (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.38−7.26 (m, 5H), 6.81 (s, 4H), 6.04 (d, 1H, J = 8.3 Hz), 5.96−5.83 (m, 1H), 5.29−5.18 (m, 2H), 4.84 (d, 1H, J = 12.1 Hz), 4.76 (d, 1H, J = 6.3 Hz), 4.59 (d, 1H, J = 12.1 Hz), 4.29−4.22 (m, 1H), 4.20−4.09 (m, 5H), 4.03 (t, 1H, J = 3.3 Hz), 3.95 (dt, 1H, J = 6.2 Hz, J = 3.2 Hz), 2.48 (d, 1H, J = 6.2 Hz), 1.99 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.70, 153.74, 152.78, 137.18, 134.44, 128.11, 127.64, 127.52, 117.06, 115.59, 114.40, 98.45, 75.91, 73.89, 73.43, 70.11, 68.73, 68.02, 55.48, 51.81, 22.59. Anal. Calcd for $C_{25}H_{31}NO_7$: C, 65.63; H, 6.83; N, 3.06. Found: C, 65.71; H, 7.02; N, 3.18.

Benzyl *O*-(2,3,4,6-Tetra-*O*-benzoyl-*β*-D-galactopyranosyl)-(1→4)-2-acetamido-3-*O*-allyl-6-*O*-benzoyl-2-deoxy-*β*-D-allopyranoside (21). A mixture of **19** (30 mg, 0.066 mmol) and 2,3,4,6-tetra-*O*-benzoyl-α/*β*-D-galactopyranosyl trichloroacetimidate (73 mg, 0.099 mmol) and 4 Å molecular sieves (ca. 30 mg) in DCM (1.5 mL) under Ar was stirred at room temperature for 30 min. Then, a solution of trimethylsilyl triflate in DCM (0.1 M, 99 μL, 0.0099 mmol) was added dropwise at room temperature, and the reaction mixture was stirred under Ar. After 1 h, more trimethylsilyl triflate (0.1 M in DCM, 66 μL, 0.066 mmol) was added and the reaction was stirred for 9 h. Triethylamine was added, and the mixture was filtered through Celite and

concentrated. The residue was purified by column chromatography (hexane−EtOAc 2:1→EtOAc) to give **26** (19 mg, 29%), **21** (17 mg, 26%) and recovered **19** (5 mg, 18%).

26: ^{1}H NMR ($CDCl_3$) δ 8.00−7.17 (m, 30H), 6.04 (d, 1H, J = 5.0 Hz), 5.81−5.67 (m, 2H), 5.79 (dd, 1H, J = 1.7 Hz, J = 3.6 Hz), 5.08 (m, 1H), 5.04−4.97 (m, 2H), 4.77 (d, 1H, J = 12.3 Hz), 4.73 (dd, 1H, J = 6.8 Hz, J = 5.0 Hz),4.59 (d, 1H, J = 7.3 Hz), 4.49 (m, 3H), 4.33 (dd, 1H, J = 8.5 Hz, J = 13.5 Hz), 4.22 (m, 1H), 4.14−4.07 (m, 3H), 4.05−3.98 (m, 2H), 3.95−3.89 (m, 2H), 1.97 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.52, 166.28, 165.87, 165.12, 164.93, 138.03, 137.45, 134.59, 133.58, 133.34, 133.14, 132.93, 130.18, 129.85, 129.78, 128.73, 129.66, 129.37, 129.02, 128.87, 128.59, 128.34, 127.7, 125.53, 117.16, 98.85, 98.55, 77.32, 74.26, 73.40, 71.55, 70.22, 70.15, 69.09, 66.59, 63.58, 51.62, 23.45.

21: $[\alpha]_D$ +23.3° (c 0.63, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.94−7.14 (m, 30H), 5.93 (m, 1H), 5.90 (dd, 1H, J = 3.3 Hz, J = 0.9 Hz), 5.75 (dd, 1H, J = 7.9 Hz, J = 10.4 Hz), 5.70 (bs, 1H, NH), 5.46 (dd, 1H, J = 3.3 Hz, J = 10.4 Hz), 5.26−5.14 (m, 2H), 4.89 (d, 1H, J = 7.7 Hz), 4.72 (d, 1H, J = 12.3 Hz), 4.55−4.43 (m, 3H), 4.41−4.34 (m, 3H), 4.22−4.11 (m, 5H), 4.00 (m, 1H), 3.93 (dd, 1H, J = 2.3 Hz, J = 9.1 Hz), 1.90 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.33, 165.81, 156.66, 165.51, 165.43, 165.32, 165.21, 137.48, 135.05, 133.42, 133.16, 128.77, 129.70, 129.56, 129.04, 128.63, 128.47, 128.31, 127.68, 117.22, 102.43, 98.79, 77.48, 74.02, 71.54, 71.44, 70.77, 70.04, 69.81, 68.99, 67.87, 65.03, 63.23, 54.85, 23.40. Anal. Calcd for $C_{59}H_{55}NO_{16}$: C, 68.53; H, 5.36; N, 1.35. Found: C, 68.81; H, 5.40; N, 1.41.

Benzyl *O*-(2,3,4,6-Tetra-*O*-benzoyl-*β*-D-galactopyranosyl)-(1→4)-2-acetamido-3-*O*-allyl-2-deoxy-6-*O*-(*p*-methoxyphenyl)-*β*-D-allopyranoside (22). A mixture of **20** (720 mg, 1.57 mmol) and 2,3,4,6-tetra-*O*-benzoyl-α/*β*-D-galactopyranosyl trichloroacetimidate (1.74 g, 2.36 mmol) and 4 Å molecular sieves (ca. 300 mg) in DCM (40 mL) under Ar was stirred at room temperature for 30 min. Then, a solution of trimethylsilyl triflate in DCM (0.1 M, 2.36 mL, 0.236 mmol) was added dropwise at room temperature, and the reaction mixture was stirred under Ar. After 1 h, more trimethylsilyl triflate (0.1 M in DCM, 1.57 mL, 0.157 mmol) was added, and the reaction was stirred for 9 h. Triethylamine was added, and the mixture was filtered through Celite and concentrated. The residue was purified by column chromatography (hexane−EtOAc 2:1→EtOAc) to give **27** (130.4 mg, 8%), **22** (1.03 g, 63%), and recovered **20** (50.4 mg, 7%).

27: ^{1}H NMR ($CDCl_3$) δ 7.97−7.25 (m, 25H), 6.83−6.76 (m, 4H), 6.31 (d, 1H, J = 5.0 Hz), 6.03 (bs, 1H, NH), 5.99−5.75 (m, 1H), 5.72 (dd, 1H, J = 3.7 Hz, J = 1.6 Hz), 5.25 (m, 1H), 5.17−4.93 (m, 2H), 4.87 (dd, 1H, J = 5.0 Hz, J = 6.7 Hz), 4.81 (d, 1H, J = 12.1 Hz), 4.72 (d, 1H, J = 6.6 Hz), 4.64−4.51 (m, 2H), 4.45−4.18 (m, 6H), 4.12−4.00 (m, 4H), 3.75 (s, 3H), 1.92 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.61, 165.88, 165.16, 164.96, 153.97, 152.92, 138.19, 137.50, 134.56, 133.58, 133.35, 133.14, 129.83, 129.73, 129.39, 129.01, 128.87, 128.60, 128.51, 128.35, 127.70, 125.49, 121.14, 117.02, 115.71, 114.57, 99.05, 98.50, 74.33, 72.94, 72.71, 71.57, 70.88, 70.14, 70.03, 69.07, 68.34, 66.58, 66.35, 62.06, 55.67, 51.26, 23.4.

22: mp 89−92 °C; $[\alpha]_D$ +33.1° (c 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.03−7.21 (m, 25H), 6.76−6.59 (m, 4H), 6.10−5.92 (m, 1H), 5.98 (d, 1H, J = 2.7 Hz), 5.81 (dd, 1H, J = 10.4 Hz, J = 7.8 Hz), 5.54 (dd, 1H, J = 10.4 Hz, J = 3.2 Hz), 5.37−5.23 (m, 2H), 4.98 (d, 1H, J = 7.9 Hz), 4.80 (d, 1H, J = 12.3 Hz), 4.66−4.58 (m, 1H), 4.63 (d, 1H, J = 7.4 Hz), 4.52 (d, 1H, J = 12.3 Hz), 4.50 (dd, 1H, J = 6.4 Hz, J = 11.3 Hz), 4.34 (t, 1H, J = 6.4 Hz), 4.30−4.22 (m, 4H), 4.17 (dd, 1H, J = 2.3 Hz, J = 8.5 Hz), 4.11−4.03 (m, 1H), 3.96 (dd, 1H, J = 2.7 Hz, J = 10.4 Hz), 3.84 (dd, 1H, J = 10.4 Hz, J = 3.9 Hz), 3.79 (s, 3H), 2.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.33, 165.94, 165.37, 165.19, 165.10, 153.95, 152.63, 137.59, 135.05, 133.55, 133.29, 129.79, 129.66, 129.16, 129.01, 128.81, 128.60, 128.43, 128.26, 127.77, 127.59, 117.16, 115.65, 114.55, 102.2, 99.05, 73.64, 71.83, 71.46, 69.95, 67.48, 61.88, 55.68, 51.26, 23.38. Anal. Calcd for $C_{59}H_{59}NO_{16}$: C, 68.4; H, 5.55; N, 1.35. Found: 68.78; H, 5.47; N, 1.40.

Benzyl *O*-(2,3,4,6-Tetra-*O*-benzoyl-*β*-D-galactopyranosyl)-(1→4)-2-acetamido-2-deoxy-6-*O*-(*p*-methoxyphenyl)-*β*-D-allopyranoside (23). A solution of **22** (671 mg, 0.65 mmol) and $[Ir(COD)(PMePh_2)_2]PF_6$ (3 mg) in dry THF (8 mL) was degassed and placed under H_2 atmosphere until the color of the solution turned from pale red to pale green. Then, H_2 was replaced by Ar, and the reaction was stirred for 2 h at room temperature. Water (2.8 mL) and I_2 (174.5 mg, 0.68 mmol) were added, and the mixture was stirred for 3 h. DCM (30 mL) was added, and the crude was washed with $Na_2S_2O_3$ 10% (2 × 30 mL) and then with water (30 mL), dried (Na_2SO_4), and concentrated. Column chromatography (hexane−EtOAc 1:1) of the residue gave **23** (529 mg, 82%). Mp 103−106 °C; $[\alpha]_D$ +42.2° (c 2.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.99−7.12 (m, 25H), 6.57−6.40 (m, 4H), 5.92 (d, 1H, J = 3.4 Hz), 5.84 (d, 1H, J = 9.5 Hz), 5.72 (dd, 1H, J = 7.9 Hz, J = 10.5 Hz), 5.50 (dd, 1H, J = 3.5 Hz, J = 10.5 Hz), 4.88 (d, 1H, J = 7.9 Hz), 4.73 (d, 1H, J = 12.3 Hz), 4.57 (d, 1H, J = 7.8 Hz), 4.51 (dd, 1H, J = 4.6 Hz, J = 11.6 Hz), 4.46 (d, 1H, J = 12.4 Hz), 4.39 (dd, 1H, J = 5.4 Hz, J = 11.5 Hz), 4.30 (m, 2H), 4.19 (m, 1H), 3.95−3.85 (m, 3H), 3.74 (dd, 1H, J = 3.9 Hz, J = 10.4 Hz), 3.67 (s, 3H), 1.80 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.45, 166.04, 165.44, 165.36, 165.28, 153.85, 152.76, 137.58, 133.67, 133.41, 133.32, 129.94, 129.68, 129.62, 129.18, 128.91, 128.64, 128.44, 128.27, 127,68, 127.57, 115.61, 114.48, 101.66, 98.34, 77.48, 72.13, 71.25, 69.97, 69.49, 68.87, 68.08, 67.63, 62.34, 55.65, 51.05, 23.34. Anal. Calcd for $C_{56}H_{53}NO_{16}$: C, 67.53; H, 5.36; N, 1.41. Found: C, 67.84; H, 5.33; N, 1.46.

Benzyl *O*-(2,3,4,6-Tetra-*O*-benzoyl-*β*-D-galactopyranosyl)-(1→4)-2-acetamido-2-deoxy-6-*O*-*p*-methoxyphenyl-*β*-D-allopyranosyl 2,3-Sulfamidate (24). Compound **23** (200 mg, 0.2 mmol) was dissolved in THF (2 mL) under Ar at 10 °C. Pyridine (40 μL, 0.48 mmol) and thionyl chloride (18 μL, 0.24 mmol) were added dropwise, and the reaction mixture was stirred under Ar at 10 °C for 1 h. Then, more pyridine (20 μL, 0.24 mmol) and thionyl chloride (18 μL, 0.24 mmol) were added, and the reaction was continued for 30 min. After this time, the mixture was diluted with DCM (30 mL) and washed with ice−water (30 mL), and the aqueous phase was extracted with DCM (3 × 20 mL). The combined organics were dried (Na_2SO_4) and concentrated. The residue was dissolved in a mixture of CCl_4 (0.4 mL), acetonitrile (0.4 mL), and water (0.4 mL), sodium periodate (92.8 mg, 0.4 mmol) and $RuCl_3 \cdot H_2O$ (1 mg) were added, and the reaction was stirred at 0 °C for 1 h. The mixture was filtered through a pad of Celite; the filtrate was diluted with DCM (30 mL), washed with water (30 mL), dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (hexane−EtOAc 2:1) to give **24** (130 mg, 61%). mp 105−108 °C; $[\alpha]_D$ +39.5° (c 0.9, $CHCl_3$); IR (KBr) 1380, 1180 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.09−7.17 (m, 25H), 6.73−6.58 (m, 4H), 5.93 (d, 1H, J = 2.7 Hz), 5.78 (dd, 1H, J = 10.3 Hz, J = 7.9 Hz), 5.48 (m, 2H), 4.95 (d, 1H, J = 7.8 Hz), 4.84 (d, 1H, J = 5.4 Hz), 4.82 (d, 1H, J = 12.1 Hz), 4.66 (dd, 1H, J = 11.3 Hz, J = 7.2 Hz), 4.53−4.42 (m, 4H), 4.34 (t, 1H, J = 6.8 Hz), 4.08 (m, 1H), 3.98 (d, 1H, J = 10.5 Hz), 3.84 (dd, 1H, J = 10.7 Hz, J = 3.7 Hz), 3.77 (s, 3H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 166.0, 165.89, 165.62, 165.42, 164.74, 154.28, 152.16, 136.30, 133.72, 133.52, 133.33, 129.69, 129.62, 129.59, 128.71, 128.57, 128.46, 128.41, 128.25, 128.06, 127.76, 115.48, 114.69, 102.89, 98.27, 79.93, 72.07, 71.77, 71.42, 70.99, 70.31, 69.30, 67.73, 66.78, 62.03, 58.93, 55.68, 22.30. Anal. Calcd for $C_{56}H_{51}NO_{18}S$: C, 63.57; H, 4.86; N, 1.32; S, 3.03. Found: C, 63.87; H, 4.90; N, 1.37; S, 3.30.

Benzyl *S*-(2,3,4-Tri-*O*-acetyl-α-L-fucopyranosyl)-(1→3)-[*O*-(2,3,4,6-tetra-*O*-benzoyl-*β*-D-galactopyranosyl)-(1→4)]-2-acetamido-2-deoxy-6-*O*-(*p*-methoxyphenyl)-3-thio-*β*-D-glucopyranoside (25). To a solution of 2,3,4-tri-*O*-acetyl-1-thio-α-L-fucopyranose[16] (41 mg, 0.133 mmol) in DMF (0.4 mL) was added NaH (3.5 mg, 0.146 mmol) at 0 °C under Ar, and the mixture was stirred for 5 min at this temperature. Then, a solution of **24** (70 mg, 0.066 mmol) in dry DMF (0.4 mL) was added slowly at 0 °C. After stirring for 30 min at room temperature, the solvent was evaporated under reduced pressure. The residue was treated with a mixture of THF−H_2SO_4−H_2O (300:3:1, 0.4 mL) at room temperature for 30 min. The reaction mixture was diluted with DCM (30 mL), washed with sat. $NaHCO_3$ solution (20 mL) and water (20 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (hexane−EtOAc 1:1) to yield **25** (65 mg, 77%). Mp 111−114 °C; $[\alpha]_D$ −52.5° (c 0.83, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.05−7.20 (m, 25H), 6.84−6.66 (m, 4H), 6.37 (d, 1H, J = 9.0 Hz), 5.96 (d, 1H, J = 3.5 Hz), 5.75 (d, 1H, J = 5.6 Hz), 5.69 (dd,

(16) Hashimoto, H.; Shimada, K.; Horito, S. *Tetrahedron: Asymmetry* **1994**, *5*, 2351−2366.

1H, J = 7.9 Hz, J = 10.5 Hz), 5.56 (dd, 1H, J = 10.5 Hz, J = 3.5 Hz), 5.23 (dd, 1H, J = 5.6 Hz, J = 10.7 Hz), 5.09 (d, 1H, J = 3.2 Hz), 5.04 (dd, 1H, J = 10.6 Hz, J = 3.2 Hz), 4.85 (d, 1H, J = 7.9 Hz), 4.77 (dd 1H, J = 6.3 Hz, J = 11.2 Hz), 4.64 (d, 1H, J = 12.1 Hz), 4.51−4.34 (m, 4H), 4.28−4.24 (m, 3H), 4.14 (t, 1H, J = 5.1 Hz), 4.03 (dd, 1H, J = 4.0 Hz, J = 9.8 Hz), 3.79 (m, 1H), 3.77 (s, 3H), 3.30 (t, 1H, J = 5.1 Hz), 2.13 (s, 3H), 2.10 (s, 3H), 2.04 (s, 3H), 1.94 (s, 3H), 1.05 (d, 1H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 170.46, 170.25, 169.95, 169.66, 165.87, 165.75, 165.61, 165.33, 154.33, 151.94, 137.21, 133.70, 133.36, 129.78, 129.73, 129.25, 129.04, 128.83, 128.75, 128.65, 128.49, 128.35, 128.28, 127.67, 127.39, 115.23, 114.91, 100.35, 99.97, 84.41, 77.20, 75.72, 75.58, 71.73, 71.01, 70.92, 70.52, 69.94, 68.42, 67.83, 67.61, 65.25, 61.38, 55.73, 54.27, 44.67, 23.27, 20.87, 20.64, 15.94. Anal. Calcd for $C_{68}H_{69}NO_{22}S$: C, 63.59; H, 5.42; N, 1.09; S, 2.50. Found C, 63.31; H, 5.48; N, 1.12; S, 2.76.

Benzyl *S*-(α-L-Fucopyranosyl)-(1→3)-[*O*-(*β*-D-galactopyranosyl)-(1→4)]-2-acetamido-2-deoxy-3-thio-*β*-D-glucopyranoside (2). To an ice cold solution of **25** (38 mg, 0.029 mmol) in CH_3CN-H_2O 4:1 (0.4 mL) was added ceric ammonium nitrate (38.1 mg, 0.069 mmol), and the reaction mixture was stirred for 30 min at 0 °C. After this time, the mixture was diluted with DCM (10 mL) and partitioned between brine (10 mL) and DCM, and the aqueous phase was extracted with DCM (3 × 10 mL). The combined organics were washed with water (10 mL), dried (Na_2SO_4), and concentrated. The residue was suspended in MeOH (1 mL) and treated with NaOMe (0.1 M, 1 mL) for 3 h at room temperature. Then, the mixture was neutralized with Amberlite IR-120 (H^+), filtered, and concentrated. The residue was purified by reverse-phase column chromatography, using CH_3CN-H_2O 5% as eluent to give **2** (16 mg, 86%): mp 167−170 °C; $[\alpha]_D$ −123.6° (*c* 0.48, MeOH); ^{1}H NMR (D_2O) δ 7.27−7.16 (m, 5H, Ar), 5.30 (d, 1H, J = 5.6 Hz), 4.69 (d, 1H, J = 9.8 Hz), 4.48 (d, 1H, J = 12.2 Hz), 4.43 (m, 1H), 4.31 (d, 2H, J = 7.9 Hz), 3.83 (dd, 1H, J = 2.3 Hz, J = 12.3 Hz), 3.79 (dd, 1H, J = 5.6 Hz, J = 10.4 Hz), 3.73−3.41 (m, 14H), 3.33 (dd, 1H, J = 7.7 Hz, J = 9.9 Hz), 2.69 (t, 1H, J = 10.8 Hz), 1.72 (s, 3H), 0.98 (d, 1H, J = 6.4 Hz); ^{13}C NMR (CD_3OD) δ 173.22, 139.16, 129.32, 128.85, 128.67, 103.56, 102.75, 86.81, 80.19, 76.38, 74.99, 73.53, 72.92, 72.28, 71.44, 70.13, 69.81, 68.64, 62.55, 62.34, 57.87, 23.01, 16.82. Anal. Calcd for $C_{27}H_{41}NO_{14}S$: C, 51.02; H, 6.50; N, 2.20; S, 5.04. Found: C, 51.31; H, 6.28; N, 2.27; S, 5.28.

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Supporting Information Available: Copies of NMR spectra for compound **15** (6 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 ordering information.

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