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Synthesis of the methyl thioglycosides of four stereoisomers and the 2-methoxy derivative of L-fucose ☆

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Abstract

The methyl 1-thioglycoside derivative of 2-*epi*-, 2,4-di-*epi*-, 3-*epi*-, 4-*epi*, and 2-*O*-methyl-L-fucopyranose have been prepared as glycosyl donors for the synthesis of sialyl Le^X ganglioside analogues containing modified α-L-fucopyranose residues.

Keywords: 1-Thioglycoside; L-Fucopyranose, methyl 1-thioglycoside derivatives; Selectins

1. Introduction

The selectins (E-, L- and P-selectin) are a family of cell-adhesion receptors that have been implicated in the initial interaction between leukocytes and vascular endothelium [2–5]. Binding of selectins to their carbohydrate ligands appears to be required for neutrophile extravasation, which plays a major role in lymphocyte recirculation and platelet adhesion. There is now general agreement [6–11] that all three selectins can recognize the sialyl Le^X determinant, α-Neu5Ac-(2 → 3)-β-D-Gal-(1 → 4)-[α-L-Fuc-(1 → 3)]-β-D-GlcNAc, and sialyl Le^A determinant, α-Neu5Ac-(2 → 3)-β-D-Gal-(1 → 3)-[α-L-Fuc-(1 → 4)]-β-D-GlcNAc, which are found as the terminal carbohydrate structure in both glycoproteins and glycolipids of cell membranes. Recently it has been shown [12] that sialyl Le^X analogues containing the C_7-Neu5Ac, C_8-Neu5Ac, 8-*epi*-Neu5Ac, and KDN (removal of the *N*-acetyl group of Neu5Ac) are recognized by three selectins in the same order as sialyl Le^X ganglioside. In addition, a sialyl Le^X analogue [12–15]

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containing sulfate in place of sialic acid has been recognized effectively by the selectins. For E-selectin, binding to sulfo-Le^X appears to be equivalent to binding to sLe^X, while for L- and P-selectin, binding to the sulfo structure shows characteristics distinct from sLe^X recognition. For deoxyfucose-containing sialyl Le^X analogues [12], E- and L-selectin require all three hydroxyl groups of the fucose residue for recognition, while P-selectin requires only the C-3 hydroxyl, indicating the importance of the fucose hydroxyl groups for selectin recognition. In view of these facts, it is of interest to clarify the more detailed structural features of the fucose residue in the sLe^X epitope required for recognition. As a part of our continuing studies on structure–activity correlations in the sialyl Le^X epitope, we describe here the synthesis of the protected methyl 1-thioglycosides of 2-*epi*-, 2,4-di-*epi*-, 3-*epi*-, 4-*epi*, and 2-*O*-methyl-L-fucopyranose, to be used as glycosyl donors in the synthesis of sialyl Le^X oligosaccharide and ganglioside analogues containing modified L-fucopyranoses.

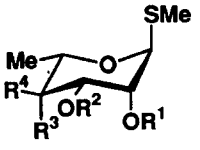
2. Results and discussion

For the synthesis of the target 1-thioglycosides, which were to be appropriately derivatized for use in α-glycoside synthesis, we employed methyl 1-thio-α-L-rhamnopyranoside [16] (**1**), 2-(trimethylsilyl)ethyl 2,4-di-*O*-benzoyl-β-L-fucopyranoside [17] (**6**), and methyl 1-thio-β-L-fucopyranoside [18] (**11**) for the starting materials. We then planned to undertake conversion of configuration at the appropriate hydroxyl center to afford the desired isomers, and convert the latter by appropriate protecting-group manipulation, or by thiomethylation and subsequent derivation, into the end products.

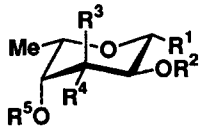
Partial *O*-benzoylation of **1** with benzoyl chloride at $-40°C$ gave methyl 2,3-di-*O*-benzoyl-1-thio-α-L-rhamnopyranoside (**2**) in 74% yield. This product, on 4-*O*-triflation and subsequent treatment with cesium acetate in the presence of 18-crown-6 in CH_3CN for 12 h at room temperature, was converted into methyl 4-*O*-acetyl-2,3-di-*O*-benzoyl-6-deoxy-1-thio-α-L-talopyranoside (**3**). Treatment of **3** with sodium methoxide in methanol, followed by *O*-benzylation with benzyl bromide in the presence of NaH in *N*,*N*-dimethylformamide, gave one of the desired 2-*epi* analogue derivatives of L-fucose, methyl 2,3,4-tri-*O*-benzyl-6-deoxy-1-thio-α-L-talopyranoside (**4**).

O-Benzylation of **1** in the same way afforded the 2,4-di-*epi*-analogue derivative of L-fucose (**5**) in 82% yield.

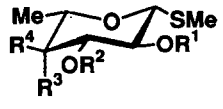
Methyl 2,3,4-tri-*O*-benzyl-6-deoxy-1-thio-β-L-glucopyranose (**10**), the 3-*epi*-analogue derivative of L-fucose, was prepared from **6** in good yield via inversion of the C-3 hydroxyl in **6** in essentially the same way as described for **3**; selective transformation [19] of the 2-(trimethylsilyl)ethyl group in **7** by an acetyl group using Ac_2O in the presence of boron trifluoride etherate in toluene for 5 h at room temperature, replacement [20] of the 1-acetoxy group in **8** with methylthio by stirring for 2.5 h at room temperature with trimethyl(methylthio)silane in dry CH_2Cl_2 in the presence of boron trifluoride etherate, and *O*-deacylation, followed by *O*-benzylation. Significant signals in the ^1H NMR spectrum of **10** were a one-proton doublet of doublets at δ 3.65 ($J_{1,2}$ 9.9, $J_{2,3}$ 2.9 Hz, H-2), a one-proton broad singlet at δ 3.74 (H-3), and a one-proton doublet of doublets at δ 3.21 ($J_{3,4}$ 1.5, $J_{4,5}$ 3.7 Hz, H-4), indicating the structure assigned.



	R^1	R^2	R^3	R^4
1	H	H	H	OH
2	Bz	Bz	H	OH
3	Bz	Bz	OAc	H
4	Bn	Bn	OBn	H
5	Bn	Bn	H	OBn



	R^1	R^2	R^3	R^4	R^5
6	OSE	Bz	H	OH	Bz
7	OSE	Bz	OAc	H	Bz
8	OAc	Bz	OAc	H	Bz
9	SMe	Bz	OAc	H	Bz
10	SMe	Bn	OBn	H	Bn



	R^1	R^2	R^3	R^4
11	H	H	OH	H
12	H	benzylidene		H
13	Bn	benzylidene		H
14	Bn	Bn	OH	H
15	Bn	Bn	H	OAc
16	Me	benzylidene		H
17	Me	Ac	OAc	H

SE = 2-(trimethylsilyl)ethyl
Bz = benzoyl
Bn = benzyl

Treatment of methyl 1-thio-β-L-fucopyranoside [18] (**11**) with benzaldehyde dimethyl acetal in *N*,*N*-dimethylformamide (DMF) in the presence of *p*-toluenesulfonic acid monohydrate gave the 3,4-*O*-benzylidene derivative (**12**) in 77% yield. This compound, on *O*-benzylation and subsequent reductive ring-opening of the benzylidene acetal in **14** with sodium cyanoborohydride–hydrogen chloride according to the method of Garegg et al. [21], afforded methyl 2,3-di-*O*-benzyl-1-thio-β-L-fucopyranoside (**14**) in 85% yield. Treatment of **14** with triflic anhydride in pyridine gave the 4-triflate, and this was converted by reaction with cesium acetate in the presence of 18-crown-6 in CH_3CN for 1 h at room temperature into methyl 4-*O*-acetyl-2,3-di-*O*-benzyl-6-deoxy-1-thio-β-L-glucopyranoside (**15**), the 4-*epi* analogue derivative of L-fucose, in 71% yield. Significant signals in the ^1H NMR spectrum of **15** were a one-proton broad triplet at δ 3.50 ($J_{1,2}$

9.3, $J_{2,3}$ 9.0 Hz, H-2), a one-proton triplet at δ 3.60 ($J_{3,4}$ 8.8 Hz, H-3) and a one-proton doublet of doublets at δ 4.80 ($J_{4,5}$ 11.0 Hz, H-4), indicating the structure assigned.

Methyl 3,4-di-*O*-acetyl-2-*O*-methyl-1-thio-β-L-fucopyranoside (**17**) was easily prepared from **11** in 81% yield by 2-*O*-methylation with CH_3I–Ag_2O in methanol and subsequent hydrolysis of the benzylidene group with aqueous 80% acetic acid, followed by *O*-acetylation.

3. Experimental

General methods.—Optical rotations were determined with a Union PM-201 polarimeter at 25°C, and IR spectra were recorded with a Jasco IRA-100 spectrophotometer. ^{1}H NMR spectra were recorded at 270 MHz with a Jeol JNM-GX 270 spectrometer. Preparative chromatography was performed on silica gel (Wako Chemical Co., 200 mesh) with the solvent systems specified. Concentrations were conducted in vacuo.

*Methyl 2,3-di-*O*-benzoyl-1-thio-α-*L*-rhamnopyranoside* (**2**).—To a solution of methyl 1-thio-α-L-rhamnopyranoside [16] (**1**, 1.1 g, 4.63 mmol) in pyridine (3.2 mL) and CH_2Cl_2 (2.6 mL), cooled to −40°C, was added a solution of benzoyl chloride (1.1 mL, 9.3 mmol) in CH_2Cl_2 (2.6 mL), and the mixture was stirred for 2 h at −30°C. A conventional workup gave the product, which was purified by column chromatography (1:2 EtOAc–hexane) on silica gel (60 g) to give **2** (1.37 g, 74%) as an amorphous mass: $[\alpha]_D$ −5.9° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.46 (d, 3 H, $J_{5,6}$ 6.0 Hz, H-6), 2.21 (s, 3 H, MeS), 3.96 (t, 1 H, $J_{3,4} = J_{4,5} = 9.7$ Hz, H-4), 4.22 (dd, 1 H, H-5), 5.29 (d, 1 H, $J_{1,2}$ 1.7 Hz, H-1), 5.48 (dd, 1 H, $J_{2,3}$ 3.3 Hz, H-3), 5.70 (dd, 1 H, H-2), and 7.26–8.09 (m, 10 H, 2 Ph). Anal. Calcd for $C_{21}H_{22}O_6S$ (402.5): C, 62.67; H, 5.51. Found: C, 62.51; H, 5.38.

*Methyl 4-*O*-acetyl-2,3-di-*O*-benzoyl-6-deoxy-1-thio-α-*L*-talopyranoside* (**3**).—To a solution of **2** (842 mg, 2.1 mmol) in pyridine (8.4 mL), cooled to 0°C, was added trifluoromethanesulfonic anhydride (1.1 mL, 6.3 mmol), and the mixture was stirred for 1.5 h at 0°C. After completion of the reaction, MeOH (1 mL) was added and the mixture was concentrated, then extracted with CH_2Cl_2. The extract was washed with 2 M HCl, M Na_2CO_3 and water, dried (Na_2SO_4), and concentrated. To a solution of the residue in CH_3CN (10 mL) were added cesium acetate (1.6 g, 8.3 mmol) and 18-crown-6 (2.8 g, 10.5 mmol), and the mixture was stirred for 12 h at room temperature and filtered. The filtrate was concentrated and then extracted with CH_2Cl_2. The extract was successively washed with 2 M HCl, M Na_2CO_3 and water, dried (Na_2SO_4), and concentrated. Column chromatography (1:4 EtOAc–hexane) of the residue on silica gel (60 g) gave **3** (413 mg, 44%) as crystals. Recrystallization from ether–hexane gave needles: mp 127–129°C; $[\alpha]_D$ −118.5° (*c* 1.0, $CHCl_3$): ^{1}H NMR ($CDCl_3$): δ 1.33 (d, 3 H, $J_{5,6}$ 6.4 Hz, H-6), 1.97 (s, 3 H, AcO), 2.13 (s, 3 H, MeS), 4.63 (dd, 1 H, $J_{4,5}$ 2.0 Hz, H-5), 5.42 (dd, 1 H, $J_{1,2}$ 1.1, $J_{2,3}$ 3.8 Hz, H-2), 5.44 (d, 1 H, H-1), 5.47 (t, 1 H, $J_{3,4}$ 3.8 Hz, H-3), 5.49 (br d, 1 H, H-4) and 7.17–8.17 (m, 10 H, 2 Ph). Anal. Calcd for $C_{23}H_{24}O_7S$ (445.5): C, 62.15; H, 5.44. Found: C, 62.00; H, 5.19.

*Methyl 2,3,4-tri-*O*-benzyl-6-deoxy-1-thio-α-*L*-talopyranoside* (**4**).—To a solution of **3** (280 mg, 0.63 mmol) in MeOH (6 mL) was added NaOMe (20 mg), and the mixture

was stirred for 3 h at room temperature then neutralized with Amberlite IR-120 (H^+) resin. The solution was concentrated, and the residue was dissolved in dry DMF (10 mL). To the stirred solution was added NaH in oil suspension (100 mg, 2.85 mmol, 60% NaH by weight), the mixture was stirred for 30 min at 0°C, and then benzyl bromide (0.3 mL, 2.85 mmol) was added. The stirring was continued for 2 h at room temperature, and MeOH (0.5 mL) was added. The mixture was concentrated to a syrup, then extracted with CH_2Cl_2. The extract was washed with water, dried (Na_2SO_4) and concentrated. Column chromatography (1:5 EtOAc–hexane) of the residue on silica gel (60 g) gave **4** (187 mg, 64%), as an amorphous mass: $[\alpha]_D$ −70.0° (*c* 1.9, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.31 (d, 3 H, $J_{5,6}$ 6.6 Hz, H-6), 2.09 (s, 3 H, MeS), 3.60 (br d, 1 H, $J_{3,4}$ ~ 2 Hz), 4.13 (m, 1 H, $J_{4,5}$ 2.0 Hz, H-5), 4.48, 4.53, 4.64, 4.77, 4.84, 4.96 (6 d, 6 H, 3 CH_2Ph), 5.32 (d, 1 H, $J_{1,2}$ 1.8 Hz, H-1), and 7.24-7.40 (m, 15 H, 3 Ph). Anal. Calcd for $C_{28}H_{32}O_4S$ (464.6): C, 72.38; H, 6.94. Found: C, 72.20; H, 6.87.

*Methyl 2,3,4-tri-*O*-benzyl-1-thio-α-*L*-rhamnopyranoside* (**5**).—To a solution of **1** (1.0 g, 5.15 mmol) in dry DMF (10 mL) was added NaH in oil suspension (900 mg, 23 mmol, 60% NaH by weight), the mixture was stirred for 30 min at 0°C, and benzyl bromide (2.8 mL, 23 mmol) was then added. The stirring was continued for 3 h at room temperature. After completion of the reaction, MeOH (1 mL) was added to the mixture, and it was concentrated. Column chromatography (1:5 EtOAc–hexane) of the residue on silica gel (100 g) gave **5** (1.96 g, 82%) as an amorphous mass: $[\alpha]_D$ −67.6° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.34 (d, 3 H, $J_{5,6}$ 6.2 Hz, H-6), 2.07 (s, 3 H, MeS), 3.64 (t, 1 H, $J_{4,5}$ 9.2, $J_{3,4}$ 10.8 Hz, H-4), 3.80 (dd, 1 H, $J_{2,3}$ 3.1 Hz, H-3), 3.83 (d, 1 H, H-2), 3.99 (dd, 1 H, H-5), 4.52–4.97 (6 d, 6 H, 3 CH_2Ph), 5.15 (s, 1 H, H-1), and 7.05–7.81 (m, 15 H, 3 Ph). Anal. Calcd for $C_{28}H_{32}O_4S$ (464.6): C, 72.38; H, 6.94. Found: C, 72.21; H, 6.81.

*2-(Trimethylsilyl)ethyl 3-*O*-acetyl-2,4-di-*O*-benzoyl-6-deoxy-β-*L*-gulopyranoside* (**7**). —To a solution of 2-(trimethylsilyl)ethyl 2,4-di-*O*-benzoyl-β-L-fucopyranoside [17] (**6**; 1.0 g, 2.12 mmol) in pyridine (5 mL), cooled to 0°C, was added trifluoromethanesulfonic anhydride (0.7 mL, 4.14 mmol). The mixture was then stirred for 1 h at 0°C, and MeOH (0.5 mL) was added. The mixture was concentrated and extracted with CH_2Cl_2. The extract was washed with 2 M HCl, M Na_2CO_3 and water, dried (Na_2SO_4) and concentrated. To a solution of the residue in CH_3CN (7 mL) were added CsOAc (1.3 g, 8.5 mmol) and 18-crown-6 (1.8 g, 8.5 mmol), and the mixture was stirred for 4 h at room temperature. The precipitate was filtered off and washed with hexane. The filtrate and washings were combined and concentrated. Column chromatography (1:6 EtOAc–hexane) of the residue on silica gel (100 g) gave **7** (940 mg, 86%), as an amorphous mass: $[\alpha]_D$ −0.2° (*c* 0.6, $CHCl_3$); IR: ν 1760 and 1220 (ester), 860 and 840 (Me_3Si), and 710 cm^{-1} (Ph); ^1H NMR ($CDCl_3$): δ 0.98 (m, 2 H, $Me_3SiCH_2CH_2$), 1.34 (d, 3 H, $J_{5,6}$ 6.6 Hz, H-6), 2.17 (s, 3 H, AcO), 3.66 and 4.12 (m, 2 H, $Me_3SiCH_2CH_2$), 4.34 (m, 1 H, H-5), 5.02 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1), 5.23 (dd, 1 H, $J_{3,4}$ 1.8, $J_{4,5}$ 4.2 Hz, H-4), 5.40 (dd, 1 H, $J_{2,3}$ 3.5 Hz, H-2), 5.68 (br t, 1 H, H-3), and 7.29–8.19 (m, 10 H, 2 Ph). Anal. Calcd for $C_{27}H_{34}O_8Si$ (514.7): C, 63.01; H, 6.66. Found: C, 62.72; H, 6.39.

*1,3-Di-*O*-acetyl-2,4-di-*O*-benzoyl-6-deoxy-β-*L*-gulopyranose* (**8**).—To a solution of **7** (1.36 g, 2.64 mmol) in toluene (22 mL) were added $BF_3 \cdot OEt_2$ (0.19 mL) and acetic anhydride (2 mL), and the mixture was stirred for 5 h at room temperature, and

concentrated then extracted with CH_2Cl_2. The extract was successively washed with M Na_2CO_3 and water, dried (Na_2SO_4) and concentrated. Column chromatography (1:4 EtOAc–hexane) of the residue on silica gel (70 g) gave **8** (980 mg, 81%) as crystals. Recrystallization from ethyl acetate–hexane gave needles: mp 137°C; $[\alpha]_D$ −103.0° (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.21 (d, 3 H, $J_{5,6}$ 6.6 Hz, H-6), 2.10, 2.15 (2 s, 6 H, 2 AcO), 4.45 (m, 1 H, H-5), 5.21 (dd, 1 H, $J_{2,3}$ 3.5, $J_{3,4}$ 1.7 Hz, H-4), 5.70 (br t, 1 H, H-3), 6.28 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1), and 7.41–8.17 (m, 10 H, 2 Ph). Anal. Calcd for $C_{24}H_{24}O_9$ (456.5): C, 63.15; H, 5.30. Found: C, 63.14; H, 5.19.

*Methyl 3-*O*-acetyl-2,4-di-*O*-benzoyl-6-deoxy-1-thio-β-*L*-gulopyranoside* (**9**).—To a solution of **8** (680 mg, 1.49 mmol) in dry CH_2Cl_2 (14 mL) were added Me_3SiSMe (0.5 mL, 3.73 mmol) and $BF_3 \cdot OEt_2$ (0.2 mL), and the mixture was stirred for 2.5 h at room temperature, then extracted with CH_2Cl_2. The extract was successively washed with M Na_2CO_3 and water, dried (Na_2SO_4) and concentrated. Column chromatography (1:4 EtOAc–hexane) of the residue on silica gel (60 g) gave **9** (580 mg, 87%) as crystals. Recrystallization from EtOAc–hexane gave needles: mp 126°C; $[\alpha]_D$ −103.0° (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.30 (d, 3 H, $J_{5,6}$ 6.4 Hz, H-6), 2.19, 2.27 (2 s, 6 H, AcO, MeS), 4.30 (m, 1 H, H-5), 4.98 (d, 1 H, $J_{1,2}$ 10.3 Hz, H-1), 5.21 (dd, 1 H, $J_{3,4}$ 3.7, $J_{4,5}$ 1.5 Hz, H-4), 5.52 (dd, 1 H, $J_{2,3}$ 3.3 Hz, H-2), 5.64 (br t, 1 H, H-3), and 7.26–8.14 (m, 10 H, 2 Ph). Anal. Calcd for $C_{23}H_{24}O_7S$ (444.5): C, 62.15; H, 5.44. Found: C, 62.01; H, 5.37.

*Methyl 2,3,4-tri-*O*-benzyl-6-deoxy-1-thio-β-*L*-gulopyranoside* (**10**).—To a solution of **9** (810 mg, 1.82 mmol) in MeOH (10 mL) was added NaOMe (20 mg), and the mixture was stirred for 3 h at room temperature. A workup similar to that described for **4** gave the *O*-deacylated compound. *O*-Benzylation (DMF (10 mL), NaH in oil suspension (660 mg, 16.4 mmol; 60% NaH by weight) and benzyl bromide (1.3 mL, 11 mmol) for 3 h at room temperature) and processing as described for **4** gave **10** (680 mg, 81%) as an amorphous mass: $[\alpha]_D$ +24.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.18 (d, 3 H, $J_{5,6}$ 6.6 Hz, H-6), 2.18 (s, 3 H, MeS), 3.21 (dd, 1 H, $J_{3,4}$ 1.5, $J_{4,5}$ 3.7 Hz, H-4), 3.65 (dd, 1 H, $J_{1,2}$ 9.9, $J_{2,3}$ 2.9 Hz, H-2), 3.74 (1 H, H-3), 3.96 (m, 1 H, $J_{4,5}$ 1.5 Hz, H-5), 4.36–4.71 (6 d, 6 H, 3 C*H*$_2$Ph), 4.87 (d, 1 H, H-1), and 7.15–7.36 (m, 15 H, 3 Ph). Anal. Calcd for $C_{28}H_{32}O_4S$ (464.6): C, 72.38; H, 6.94. Found: C, 72.16; H, 6.69.

*Methyl 3,4-*O*-benzylidene-1-thio-β-*L*-fucopyranoside* (**12**).—To a solution of methyl 1-thio-β-L-fucopyranoside [18] (**11**; 2.0 g, 10.3 mmol) in dry DMF (20 mL) were added benzaldehyde dimethyl acetal (3.1 mL, 20.6 mmol) and *p*-toluenesulfonic acid monohydrate (30 mg), and the mixture was stirred for 20 h at room temperature. Conventional workup gave **12** (2.24 g, 77%) as an amorphous mass, which consisted of two asymmetric molecules at the benzylidene acetal carbon atom. Column chromatography (1:4 EtOAc–hexane) of the mixture on silica gel (20 g) gave the endo form 1.02 g (35%) and the exo form 1.22 g (42%), respectively. The endo form had $[\alpha]_D$ −38.2° (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.43 (d, 3 H, $J_{5,6}$ 6.6 Hz, H-6), 2.22 (s, 3 H, MeS), 3.75 (dd, 1 H, $J_{1,2}$ 10.1, $J_{2,3}$ 7.2 Hz, H-2), 3.86 (m, 1 H, $J_{4,5}$ 2.0 Hz, H-5), 4.01 (dd, 1 H, $J_{3,4}$ 5.3 Hz, H-4), 4.19 (d, 1 H, H-1), 4.37 (dd, 1 H, H-3), 6.19 (s, 1 H, C*H*Ph), and 7.35–7.47 (m, 5 H, Ph). Anal. Calcd for $C_{14}H_{18}O_4S$ (282.4): C, 59.55; H, 6.43. Found: C, 59.54; H, 6.28. The exo form had $[\alpha]_D$ −4.7° (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.50 (d, 3 H, $J_{5,6}$ 6.6 Hz, H-6), 2.17 (s, 3 H, MeS), 3.58 (dd, 1 H, $J_{1,2}$ 10.2, $J_{2,3}$ 6.6 Hz,

H-2), 3.98 (m, 1 H, $J_{4,5}$ 2.2 Hz, H-5), 4.13 (dd, 1 H, $J_{3,4}$ 5.9 Hz, H-4), 4.19 (d, 1 H, H-1), 4.20 (dd, 1 H, H-3), 5.97 (s, 1 H, C*H*Ph), and 7.26–7.54 (m, 5 H, Ph). Found: C, 59.53; H, 6.32.

Methyl 2-O-benzyl-3,4-O-benzylidene-1-thio-β-L-fucopyranoside (**13**).—To a solution of **12** (endo form; 4.3 g, 15.2 mmol) in dry DMF (25 mL), cooled to 0°C, was added NaH in oil suspension (900 mg, 22.8 mmol, 60% NaH by weight), and the mixture was stirred for 30 min. Benzyl bromide (2.7 mL, 22.8 mmol) was added, and the mixture was stirred for 12 h at room temperature. A workup similar to that described for **4** gave **13** (5.32 g, 94%) as crystals. Recrystallization from ether–hexane gave needles: mp 58–59°C; $[\alpha]_D$ +13.7° (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.40 (d, 3 H, $J_{5,6}$ 6.6 Hz, H-6), 2.21 (s, 3 H, MeS), 3.57 (dd, 1 H, $J_{1,2}$ 9.5, $J_{2,3}$ 6.6 Hz, H-2), 3.77 (m, 1 H, $J_{4,5}$ 1.8 Hz, H-5), 4.06 (dd, 1 H, $J_{3,4}$ 5.7 Hz, H-4), 4.34 (d, 1 H, H-1), 4.52 (br t, 1 H, H-3), 4.82, 4.92 (2 d, 2 H, CH_2Ph), 6.02 (s, 1 H, C*H*Ph), and 7.28–7.47 (m, 10 H, 2 Ph). Anal. Calcd for $C_{21}H_{24}O_4S$ (372.5): C, 67.72; H, 6.49. Found: C, 67.65; H, 6.24.

Methyl 2,3-di-O-benzyl-1-thio-β-L-fucopyranoside (**14**).—To solution of **13** (257 mg, 0.7 mmol) in dry tetrahydrofuran (3 mL) was added 4 Å molecular sieves (4A-MS; 450 mg), and the mixture was stirred for 3 h at room temperature. Sodium cyanoborohydride (650 mg, 10.4 mmol) was gradually added. After the reagent had dissolved, hydrogen chloride in ether was added at room temperature until the evolution of gas ceased. (Caution: HCN is produced.) TLC indicated that the reaction was complete after 5 min. The mixture was diluted with CH_2Cl_2 (50 mL) and water (10 mL), filtered, washed with M Na_2CO_3 and water, dried (Na_2SO_4) and concentrated. Column chromatography (1:5 EtOAc–hexane) of the residue on silica gel (60 g) gave **14** (232 mg, 90%) as crystals. Recrystallization from ether–hexane gave needles: mp 127–128°C; $[\alpha]_D$ −0.3° (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.34 (d, 3 H, $J_{5,6}$ 6.4 Hz, H-6), 2.21 (s, 3 H, MeS), 3.65 (t, 1 H, $J_{1,2}$ 9.3, $J_{2,3}$ 9.2 Hz, H-2), 3.80 (d, 1 H, $J_{3,4}$ 2.8 Hz, H-4), 4.29 (d, 1 H, H-1), 4.71–4.89 (4 d, 4 H, 2 CH_2Ph), and 7.24–7.42 (m, 10 H, 2 Ph). Anal. Calcd for $C_{21}H_{26}O_4S$ (374.5): C, 67.35; H, 7.00. Found: C, 67.09; H, 6.72.

Methyl 4-O-acetyl-2,3-di-O-benzyl-6-deoxy-1-thio-β-L-glucopyranoside (**15**).—To a solution of **14** (54 mg, 0.14 mmol) in pyridine (0.5 mL), cooled to 0°C, was added trifluoromethanesulfonic anhydride (48 μL, 0.28 mmol), and the mixture was stirred for 1 h at 0°C, then MeOH (0.1 mL) was added. The mixture was concentrated and extracted with CH_2Cl_2. The extract was washed with 2 M HCl, M Na_2CO_3, and water, dried (Na_2SO_4) and concentrated. To a solution of the residue in CH_3CN (2 mL) were added CsOAc (111 mg, 0.56 mmol) and 18-crown-6 (152 mg, 0.56 mmol), and the mixture was stirred for 1 h at room temperature. Processing as described for **3** gave **15** (42.3 mg, 71%) as crystals. Recrystallization from ether–hexane gave needles: mp 83–85°C; $[\alpha]_D$ +13.3° (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.20 (d, 3 H, $J_{5,6}$ 6.2 Hz, H-6), 1.94 (s, 3 H, AcO), 2.22 (s, 3 H, MeS), 3.43 (dd, 1 H, $J_{4,5}$ 11.0 Hz, H-5), 3.50 (br t, 1 H, $J_{1,2}$ 9.3, $J_{2,3}$ 9.0 Hz, H-2), 3.60 (t, 1 H, $J_{3,4}$ 8.8 Hz, H-3), 4.35 (d, 1 H, H-1), 4.63–4.92 (4 d, 4 H, 2 CH_2Ph), 4.81 (dd, 1 H, H-4), and 7.25–7.39 (m, 10 H, 2 Ph). Anal. Calcd for $C_{23}H_{28}O_5S$ (416.5): C, 66.32; H, 6.78. Found: C, 66.19; H, 6.55.

Methyl 3,4-O-benzylidene-2-O-methyl-1-thio-β-L-fucopyranoside (**16**).—To a solution of **12** (endo form; 830 mg, 2.94 mmol) in MeOH (30 mL), cooled to 0°C, were

added CH_3I (0.37 mL, 6.9 mmol) and Ag_2O (820 mg, 3.53 mmol), and the mixture was stirred for 12 h at room temperature in the dark. The precipitate was then collected and washed with CH_2Cl_2. The combined filtrate and washings was concentrated. Column chromatography (1:3 EtOAc–hexane) of the residue on silica gel (100 g) gave **16** (700 mg, 80.5%) as crystals. Recrystallization from ether–hexane gave needles: mp 63–64°C; $[\alpha]_D$ +9.4° (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.42 (d, 3 H, $J_{5,6}$ 6.6 Hz, H-6), 2.25 (s, 3 H, MeS), 3.35 (dd, 1 H, $J_{1,2}$9.5, $J_{2,3}$ 6.4 Hz, H-2), 3.64 (s, 3 H, MeO), 3.78 (m, 1 H, $J_{4,5}$ 2.0 Hz, H-5), 4.06 (dd, 1 H, $J_{3,4}$ 5.7 Hz, H-4), 4.27 (d, 1 H, H-1), 4.43 (br t, 1 H, H-3), 6.16 (s, 1 H, C*H*Ph), and 7.36–7.48 (m, 5 H, Ph). Anal. Calcd for $C_{15}H_{20}O_4S$ (296.4): C, 60.79; H, 6.80. Found: C, 60.73; H, 6.51.

*Methyl 3,4-di-*O*-acetyl-2-*O*-methyl-1-thio-β-*L*-fucopyranoside* (**17**).—A solution of **16** (69 mg, 0.23 mmol) in 80% aq AcOH (5 mL) was stirred for 5 h at 50°C and concentrated. The residue was acetylated with acetic anhydride (0.5 mL) in pyridine (2 mL). The product was purified by chromatography on a column of silica gel (20 g) with 1:2 EtOAc–hexane to give **17** (68 mg, quant) as crystals. Recrystallization from ether–hexane gave needles: mp 80–82°C; $[\alpha]_D$ +8.0° (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.20 (d, 3 H, $J_{5,6}$ 6.4 Hz, H-6), 2.04, 2.17 (2 s, 6 H, 2 AcO), 2.26 (s, 3 H, MeS), 3.36 (t, 1 H, $J_{1,2} = J_{2,3} = 9.7$ Hz, H-2), 3.54 (s, 3 H, MeO), 3.78 (m, 1 H, H-5), 4.34 (d, 1 H, H-1), 4.93 (dd, 1 H, $J_{3,4}$ 3.5 Hz, H-3), and 5.25 (dd, 1 H, H-4). Anal. Calcd for $C_{12}H_{20}O_6S$ (292.4): C, 49.30; H, 6.90. Found: C, 49.28; H, 6.93.

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