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Note

Fluorination of methyl 6-deoxy-1-thiohexopyranosides with diethylaminosulfur trifluoride (DAST), and the formation of unexpected products

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The selectin family, such as E-selectin (endotherial-leukocyto adhesion molecule-1), P-selectin (GMP-1), and L-selectin (leucocyte adhesion molecule-1), recognizes the sialyl Le^X determinant[1], α-Neu5Ac-(2 → 3)-β-D-Gal-(1 → 4)-[α-L-Fuc-(1 → 3)]-β-D-GlcNAc, which is found as the terminal carbohydrate structure in both glycolipids and glycoproteins. In the course of an investigation[2–4] on the structural requirements for the carbohydrate ligand of selectin recognition, we have demonstrated that both the fucose and sialic acid residues are required for full recognition. In order to clarify the structural requirement for the L-fucose moiety of the selectin recognition, we have designed a synthesis of the fluorinated 6-deoxyhexopyranose-containing the sialyl Le^X epitope. We report here fluorination of some methyl 6-deoxy-1-thiohexopyranoside derivatives.

We chose the readily available methyl 2,3,4-tri-*O*-acetyl-1-thio-β-L-fucopyranoside[3b] (**1**) and methyl 1-thio-α-L-rhamnopyranoside[5] (**5**) as the starting materials, and diethylaminosulfur trifluoride (DAST) as the fluorinating reagent. Although DAST is widely used to produce fluorinated carbohydrates in high yield, unpredictable products[6–8] are occasionally formed. Treatment of methyl 1-thio-β-L-fucopyranoside (**2**), prepared by *O*-deacetylation of methyl 2,3,4-tri-*O*-acetyl-1-thio-β-L-fucopyranoside[3b] (**1**), with 2,2-dimethoxypropane in *N*,*N*-dimethylformamide (DMF) in the presence of *p*-toluenesulfonic acid monohydrate gave methyl 3,4-*O*-isopropylidene-1-thio-β-L-fucopyranoside (**3**) in 90% yield **. The ^{1}H NMR spectrum revealed the presence of one isopropylidene and two methyl groups, H-2 as a doublet of doublets, and H-1 as a doublet, confirming the structure assigned. On treatment with DAST in dichloromethane for 1 h at 0°C, compound **3** afforded

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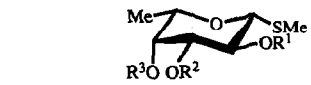
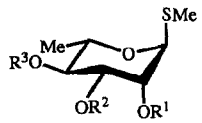
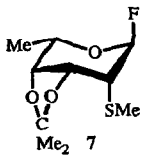
** Compounds **2** and **3** have been previously reported[9], although they were not fully characterized.



	R^1	R^2	R^3
1	Ac	Ac	Ac
2	H	H	H
3	H	isopropylidene	
4	Bz	Bz	H



	R^1	R^2	R^3
5	H	H	H
6	Bz	Bz	H



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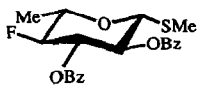

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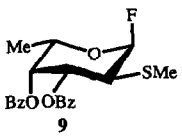

9

Fig. 1.

an unexpected glycosyl fluoride, 6-deoxy-3,4-*O*-isopropylidene-2-*S*-methyl-2-thio-α-L-talopyranoside (**7**) in 66% yield; the methylthio group at C-1 in **3** had migrated to C-2 and a fluorine atom became attached to C-1, analogous to behavior observed previously[6–8a]. The ^{1}H NMR spectrum of **7** exhibited the presence of one *C*-methyl group, one *S*-methyl group, an isopropylidene group, H-1 as a doublet of doublets at δ 5.68 ($J_{1,2}$ 6.6, $J_{1,F}$ 62.1 Hz), and H-2 as a multiplet, confirming the structure assigned.

Treatment of methyl 2,3-di-*O*-benzoyl-1-thio-β-L-fucopyranoside (**4**, prepared by 2,3-di-*O*-benzoylation of compound **2**) with DAST gave the desired 4-fluoro compound, methyl 2,3-di-*O*-benzoyl-4,6,dideoxy-4-fluoro-1-thio-β-L-glucopyranoside (**8**) in 45% yield. The ^{1}H NMR spectrum of **8** exhibited signals for H-5 at δ 3.81 ($J_{4,5}$ 9.4, $J_{5,6}$ 6.0, and $J_{5,F}$ 2.7 Hz), H-4 at δ 4.35 ($J_{3,4} = J_{4,5} = 9.4$, $J_{4,F}$ 50.3 Hz), H-3 at δ 5.76 ($J_{2,3} = J_{3,4} = 9.4$, $J_{3,F}$ 13.3 Hz), H-2 at δ 5.44 ($J_{1,2}$ 9.8 Hz), and H-1 at δ 4.61, consistent with the assignment of the 4-fluoro-β-L-glucopyranose

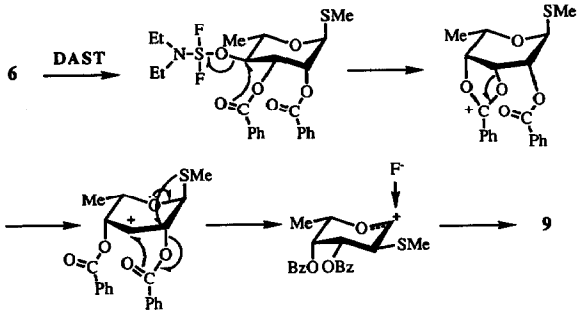

Fig. 2.

configuration. In contrast, when treated with DAST under the same conditions, methyl 2,3-di-*O*-benzoyl-1-thio-α-L-rhamnopyranoside [derived from methyl 1-thio-α-L-rhamnopyranoside[5] (**5**) by selective benzoylation] gave the unpredicted 1-fluoro compound **9** in 42% yield. In the ^{1}H NMR spectrum of **9**, H-1 appeared as a doublet of doublets at δ 5.94 ($J_{1,F}$ 51.3, $J_{1,2}$, 2.4 Hz) and H-2 as a multiplet at δ 3.29 ($J_{2,3}$ 11.7, $J_{2,F}$ 30.2 Hz), indicating the 1-fluoro substituent to be *cis* to the *S*-methyl group on C-2.

As regards the mechanism of formation of **9**, as proposed in the scheme, the oxygen atom of the hydroxyl group at C-4 replaces a fluorine atom of DAST, with loss of hydrogen fluoride, to form the sulfoxo group, and the intermediate may then be converted via orthoester formation with inversion of configuration at the C-4. Successive, intramolecular rearrangements of the benzoyl and *S*-methyl groups, and then 1-fluorination from the β-side, would give methyl 3,4-di-*O*-benzoyl-2-*S*-methyl-2-thio-α-L-fucopyranosyl fluoride (**9**).

EXPERIMENTAL

General methods.—Melting points are uncorrected. Optical rotations were determined with a Union PM-201 polarimeter at 25°C. ^{1}H NMR spectra were recorded with a Jeol JNM-GX 270 spectrometer. Preparative chromatography was performed on silica gel (Wako Co., 200 mesh) with the solvents specified. Concentrations were conducted in vacuo.

Methyl 1-thio-β-L-fucopyranoside (**2**).—To a solution of methyl 2,3,4-tri-*O*-acetyl-1-thio-β-L-fucopyranoside[3b] (**1**; 2.4 g, 7.5 mmol) in MeOH (15 mL) was added NaOMe (30 mg), and the mixture was treated with Amberlite IR-120 (H^+) resin to remove the base. The solution was concentrated to give a crystalline product. Recrystallization from EtOH–Et_2O gave **2** (1.4 g, 96%) as needles; mp 103–105; $[\alpha]_D$ +21.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR (CD_3OD); δ 1.34 (d, 3 H, $J_{5,6}$ 6.4 Hz, *Me*CH), 2.26 (s, 3 H, MeS), 3.56 (dd, 1 H, $J_{2,3}$ 9.2, $J_{3,4}$ 2.4 Hz, H-3), 3.63 (t, 1 H, $J_{1,2} = J_{2,3} = 9.2$ Hz, H-2), 3.74 (q, 1 H, H-5), 3.75 (d, 1 H, $J_{3,4}$ 2.6 Hz, H-4), and

4.28 (d, 1 H, H-1). Anal. Calcd for $C_7H_{14}O_4S$ (194.3): C, 43.28; H, 7.26. Found: C, 43.26; H, 7.47.

Methyl 3,4-O-isopropylidene-1-thio-β-L-fucopyranoside (**3**).—To a solution of **2** (2.0 g, 10.3 mmol) in DMF (10 mL) were added 2,2-dimethoxypropane (2.5 mL) and *p*-toluenesulfonic acid monohydrate (50 mg), and the mixture was stirred for 5 h at 60°C, and then neutralized with Amberlite IR-410 (HO^-) resin. The solution was concentrated. Column chromatography (1:1 EtOAc–hexane) of the residue on silica gel (100 g) afforded **3** (2.2 g, 90%). Recrystallization from ether gave needles; mp 63–65°C; $[\alpha]_D$ −47.5° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.37, 1.54 (2 s, 6 H, Me_2C), 1.41 (d, 3 H, $J_{5,6}$ 6.6 Hz, MeC), 2.21 (s, 3 H, MeS), 3.57 (dd, 1 H, $J_{1,2}$ 10.2, $J_{2,3}$ 6.7 Hz, H-2), and 4.14 (d, 1 H, H-1). Anal. Calcd for $C_{10}H_{18}O_4S$ (234.3): C, 51.26; H, 7.74. Found: C, 51.23; H, 7.49.

Methyl 2,3-di-O-benzoyl-1-thio-β-L-fucopyranoside (**4**).—To a solution of **2** (2.5 g, 12.9 mmol) in dry pyridine (9 mL) and dry CH_2Cl_2 (18 mL) was added dropwise a solution of BzCl (3.1 mL, 27 mmol) in dry CH_2Cl_2 (7.5 mL) at −40°C, and the mixture was stirred for 30 min at −40°C. Methanol (1 mL) was added and the mixture was concentrated, then extracted with CH_2Cl_2. The extract was successively washed with 2 M HCl and H_2O, dried (Na_2SO_4), and concentrated. Column chromatography (1:3 EtOAc–hexane) of the residue on silica gel (50 g) gave **4** (3.4 g, 66%) as a syrup; $[\alpha]_D$ −96.2° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.41 (d, 3H, $J_{5,6}$ 6.4 Hz, MeC)), 2.24 (s, 3 H, MeS), 3.93 (q, 1 H, H-5), 4.14 (br d, 1 H, $J_{3,4}$ 3.1 Hz, H-4), 4.59 (d, 1 H, $J_{1,2}$ 9.9 Hz, H-1), 5.36 (dd, 1 H, $J_{2,3}$ 10.1 Hz, H-3), 5.80 (t, 1 H, $J_{1,2} = J_{2,3} = 10.0$ Hz, H-2), and 7.31–8.07 (m, 10 H, 2 Ph). Anal. Calcd for $C_{21}H_{22}O_6S$ (402.5): C, 62.67; H, 5.51. Found: C, 62.53; H, 5.68.

Methyl 2,3-di-O-benzoyl-1-thio-α-L-rhamnopyranoside (**6**).—To a solution of methyl 1-thio-α-L-rhamnopyranoside[5] (**5**; 900 mg, 4.6 mmol) in dry pyridine (3.2 mL) and CH_2Cl_2 (6.4 mL) was added dropwise a solution of BzCl (1.1 mL, 92 mmol) in dry CH_2Cl_2 (2.6 mL) at −40°C, and the mixture was stirred for 30 min at −40°C. Methanol (3 mL) was added to the mixture, which was concentrated and then extracted with CH_2Cl_2. The extract was successively washed with 2 M HCl and H_2O, dried (Na_2SO_4), and then concentrated. Column chromatography (1:3 EtOAc–hexane) of the residue on silica gel (100 g) gave **6** (1.4 g, 75%) as an amorphous mass; $[\alpha]_D$ −5.9° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.46 (d, 3 H, $J_{5,6}$ 6.2 Hz, MeC)), 2.21 (s, 3 H, MeS), 3.96 (t, 1 H, $J_{3,4} = J_{4,5} = 9.6$ Hz, H-4), 4.22 (q, 1 H, H-5), 5.29 (d, 1 H, $J_{1,2}$ 1.6 Hz, H-1), 5.48 (dd, 1 H, $J_{2,3}$ 3.4 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, 62.68; H, 5.62.

6-Deoxy-3,4-O-isopropylidene-2-S-methyl-2-thio-α-L-talopyranosyl fluoride (**7**).—To a solution of **3** (50 mg, 0.21 mmol) in dry CH_2Cl_2 (2 mL) was added DAST (70 μL), and the mixture was stirred for 1 h at 0°C. Methanol (0.5 mL) was added to the mixture, which was then concentrated. Column chromatography (1:5 EtOAc–hexane) of the residue on silica gel (10 g) gave **7** (33.5 mg, 66%) as a syrup; $[\alpha]_D$ −44.5° (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.30 (d, 3 H, $J_{5,6}$ 6.4 Hz, MeC), 1.35,

1.46 (2 s, 6 H, Me_2C), 2.29 (s, 3 H, MeS), 2.81 (ddd, 1 H, $J_{1,2}$ 6.6, $J_{2,3}$ 2.5 $J_{2,F}$ 18.2 Hz, H-2), 3.94 (br q, 1 H, H-5), 4.15 (d, 1 H, $J_{3,4}$ 7.7 Hz, H-4), 4.61 (ddd, 1 H, $J_{3,F}$ 4.2 Hz, H-3), and 5.68 (dd, 1 H, $J_{1,F}$, 62.1 Hz, H-1). Anal. Calcd for $C_{10}H_{17}FO_3S$ (236.3): C, 50.83; H, 7.25. Found: C, 50.98; H, 7.36.

Methyl 2,3-di-O-benzoyl-4,6-dideoxy-4-fluoro-1-thio-β-L-glucopyranoside (**8**).—To a solution of **4** (100 mg, 0.25 mmol) in dry CH_2Cl_2 (2 mL) was added DAST (82 μL, 0.63 mmol) at 0°C, and the mixture was stirred for 2 h at 0°C. Methanol (0.5 mL) was added to the mixture which was then concentrated. Column chromatography (1:6 EtOAc–hexane) of the residue on silica gel (20 g) afforded **8** (45 mg, 46%) as an amorphous mass; $[\alpha]_D$ −50.8° (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.47 (dd, 3 H, $J_{5,6}$ 6.0, $J_{F,6}$ 1.3 Hz, MeC), 2.22 (s, 3 H, MeS), 3.81 (ddd, 1 H, $J_{4,5}$ 9.4, $J_{5,F}$ 2.7 Hz, H-5), 4.35 (dt, 1 H, $J_{3,4} = J_{4,5} = 9.4$, $J_{4,F}$ 50.3 Hz, H-4), 4.61 (d, 1 H, $J_{1,2}$ 9.8 Hz, H-1), and 5.44 (near t, 1 H, $J_{1,2} = J_{2,3} = 9.8$ Hz, H-2), 5.76 (dt, 1 H, $J_{3,F}$ 13.3 Hz, H-3), and 7.38–8.01 (m, 10 H, 2 Ph). Anal. Calcd for $C_{21}H_{21}FO_5S$ (404.5): C, 62.36; H, 5.23. Found: C, 62.33; H, 5.05.

3,4-Di-O-benzoyl-2-S-methyl-2-thio-α-L-fucopyranosyl fluoride (**9**).—To a solution of **6** (60 mg, 0.14 mmol) in dry CH_2Cl_2 (1.4 mL) was added DAST (50 μL, 0.38 mmol) at 0°C, and the mixture was stirred for 1 h at 0°C. A similar work up as described for **7** gave **9** (25 mg, 42%) as an amorphous mass; $[\alpha]_D$ −241.1° (*c* 0.84, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.29 (d, 3 H, $J_{5,6}$ 6.7 Hz, MeC), 2.16 (s, 3 H, MeS), 3.29 (ddd, 1 H, $J_{1,2}$ 2.4, $J_{2,3}$ 11.7, $J_{2,F}$ 30.2 Hz, H-2), 4.53 (q, 1 H, H-5), 5.71 (m, 2 H, H-3,4), 5.94 (dd, 1 H, $J_{1,F}$ 51.3 Hz, H-1), and 7.30–8.06 (m, 10 H, 2 Ph). Anal. Calcd for $C_{21}H_{21}FO_5S$ (404.5): C, 62.36; H, 5.23. Found: C, 62.49; H, 5.18.

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