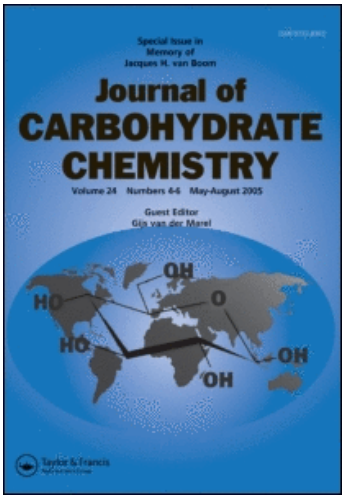

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SYNTHESIS OF 5-THIO-D-MANNOSE

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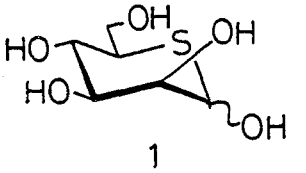
ABSTRACT

5-Thio-D-mannose (1), the first 5-thiosugar found recently in nature, was synthesized in 12 steps from D-mannose.

INTRODUCTION

D-Mannose, which has been shown to be recognized by the hepatic mannose receptor in the clearance of circulating glycoproteins,[1] is of potential relevance to the problems of drug targeting.[2] It is of interest to investigate the specificity of the D-mannose receptor for its 5-thio analog, because 5-thio-D-glucose shows an inhibition effect for some enzymes in the metabolism of carbohydrates.[3] 5-Thio-D-mannose (1) was recently isolated from the marine sponge Clathria pyramida as the only naturally occurring example to date of a 5-thiosugar.[4] Attention is also paid to the ecological role of this sugar in the organism. These things prompted us to prepare 1 in a large quantity.



1

A synthetic route to a 5-thiosugar has been already developed by Whistler et al.[5] That method involves conversion of a 5,6-epoxide into the corresponding 5,6-episulfide with inversion of configuration. The same method was applied to the synthesis of 1.

RESULTS AND DISCCUSSION

Methyl 2,3:5,6-di-O-isopropylidene-α-D-mannofuranoside (2), obtained in 73 % yield in 2 steps from D-mannose according to the method of Randall[6], was selected as the starting material. Selective hydrolysis of 2 with 80 % acetic acid gave methyl 2,3-O-isopropylidene-α-D-mannofuranoside (3, 93 % yield), which was converted into methyl 6-O-benzoyl-2,3-O-isopropylidene-α-D-mannofuranoside (4) in 72 % yield using benzoyl chloride (1.05 equiv), 4-dimethylaminopyridine and pyridine in dichloromethane at -28 ℃. Treatment of 4 with methanesulfonyl chloride in pyridine gave methyl 6-O-benzoyl-2,3-O-isopropylidene-5-O-methanesulfonyl-α-D-mannofuranoside (5) in 95 % yield. Attempted epoxidation by treatment of 5 with sodium methoxide gave

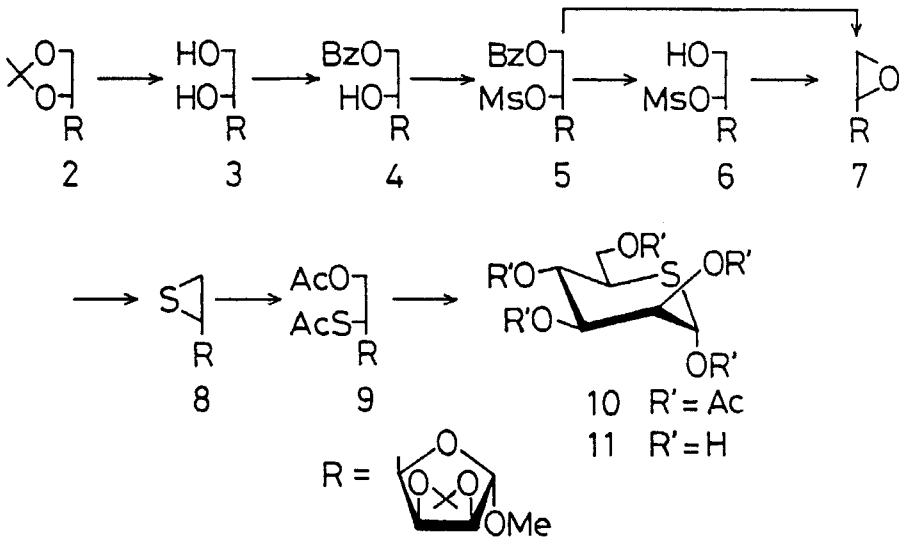


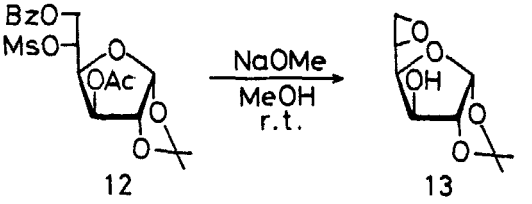
Table 1. ^{1}H NMR Data for Compounds 3-10[a].

Compound	H_1[b] ($J_{1,2}$)[c]	H_2 ($J_{2,3}$)	H_3 ($J_{3,4}$)	H_4 ($J_{4,5}$)	H_5 ($J_{5,6a}$, $J_{5,6b}$)	H_{6a}	H_{6b} ($J_{6a,6b}$)	Other signals
3[d]	4.87s (0)	4.54d (6.0)	4.82dd (3.2)	———	4.01-3.51m ———	———	———	1.74,1.87(2s,3H,Isp[e]),3.30(s,3H,OMe), 3.00,3.80(2bs,1H,OH)[f]
4[d]	4.91s (0)	4.56d (5.5)	4.86dd (3.7)	3.98dd (8.0)	4.30ddd (5.3, 3.0)	4.59dd (10.0)	4.65dd	1.34,1.50(2s,3H,Isp[e]),3.30(s,3H,OMe), 7.29-8.08(m,5H,OBz):3.08(bs,1H,OH)[f]
5	4.89s (0)	4.57d (6.2)	4.78dd (3.5)	4.20dd (8.0)	5.19ddd (5.6, 2.2)	4.57dd (12.5)	4.85dd	1.34,1.51(2s,3H,Isp[e]),3.11(s,3H,OMs), 3.24(s,3H,OMe),7.34-8.12(m,5H,OBz)
6[d]	4.88s (0)	4.56d (5.8)	4.74dd (3.5)	4.17dd (8.0)	4.87ddd (4.0, 2.8)	3.86dd (12.6)	4.09dd	1.32,1.48(2s,3H,Isp[e]),3.14(s,3H,OMs), 3.32(s,3H,OMe):2.70(t,1H,OH)[f]
7	4.95s (0)	4.55d (5.9)	4.72dd (3.6)	3.48dd (7.8)	3.20m (2.8, 4.6)	2.64dd (4.6)	2.90t	1.32,1.50(2s,3H,Isp[e]),3.34(s,3H,OMe)
8	4.89s (0)	4.54d (5.9)	4.70dd (3.4)	3.39dd (8.2)	3.19ddd (5.3, 5.8)	2.32dd (1.8)	2.62dd	1.34,1.50(2s,3H,Isp[e]),3.31(s,3H,OMe)
9	4.87s (0)	4.51d (5.5)	4.67dd (2.4)	4.40d (0)	——— 4.08-4.44m ———	———	———	1.29,1.48(2s,3H,Isp[e]),2.06(s,3H,OAc), 2.35(s,3H,SAc),3.29(s,3H,OMe)
10	5.80d (4.0)	5.33dd (3.0)	5.22dd (10.0)	5.45t (10.0)	3.54ddd (3.5, 5.8)	4.06dd (12.0)	4.30dd	2.02,2.06,2.10,2.18,2.20(5s,3H,OAc)

a. Mesured at 100MHz in $CDCl_3$. b. Chemical shifts in ppm from internal tetramethylsilane.
c. Coupling constants in Hz. d. After shaking with D_2O. e. Isopropylidene.
f. Without exchange with D_2O.

methyl 2,3-O-isopropylidene-5-O-methanesulfonyl-α-D-manno-furanoside (**6**) in 82 % yield and none of desired epoxide.

This result was quite unexpected because in the course of synthesis of 5-thio-D-glucose derivatives, treatment of the analogous glucose derivative **12** under the same conditions gave the epoxide **13** in 66 % yield.[7]



12 13

The difference of reactivity between **5** and **12** might be explained by the motional flexibility of the reaction site. ^{1}H NMR data from **5** ($J_{1,2}$ = 0, $J_{2,3}$ = 6.2, $J_{3,4}$ = 3.5, $J_{4,5}$ = 8.0 Hz) (Table 1.) and **12** ($J_{1,2}$ = 3.5, $J_{2,3}$ = 0, $J_{3,4}$ = 3.0, $J_{4,5}$ = 8.8 Hz)[7] indicate $^0T_1$ and $^2T_3$ twist conformations, respectively. As depicted in Figs. A and B, in the case of manno isomer **5** the reaction occurs in the cage (endocyclic region) of the 5-5 bicyclic system, while in the case of gluco isomer **12** in the more flexible exocyclic region. Thus, it is suggested that even the intramolecular substitution reaction on the carbon which is not directly attached to the bicyclic system may be sterically hindered by the endo-methyl group.

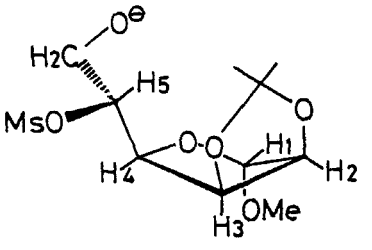


Fig. A manno $^0T_1$

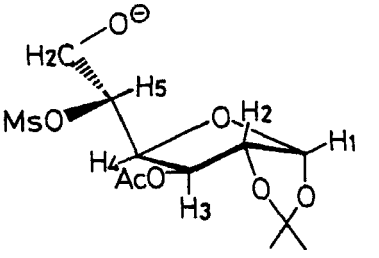


Fig. B gluco $^2T_3$

Further treatment of **6** with sodium methoxide under reflux gave methyl 5,6-anhydro-2,3-O-isopropylidene-β-L-gulofuranoside (**7**) in only 28 % yield. However, a much better result was obtained when compound **6** was treated with sodium hydride in N,N-dimethylformamide at room temperature to give **7** in 74 % yield. Furthermore, treatment of **6** with potassium tert-butoxide in tetrahydrofuran also gave **7** in 63 % yield. Compound **7** was converted into methyl 5,6-dideoxy-5,6-epithio-2,3-O-isopropylidene-α-D-mannofuranoside (**8**) in 81 % yield. In the ^{13}C NMR spectra of **8**, signals of C-5 and C-6 resonate at higher field compared with that of **7** (Table 2.). Acetolysis of **8** with potassium acetate, acetic acid and acetic anhydride gave methyl 6-O-acetyl-5-S-acetyl-2,3-O-isopropylidene-5-thio-α-D-mannofuranoside (**9**) in 96 % yield. Hydrolysis of **9** with 50 % acetic acid at 100 ℃ followed by acetylation gave 1,2,3,4,6-penta-O-acetyl-5-thio-α-D-mannopyranose (**11**) in 83 % yield. ^{13}C and ^{1}H NMR spectra of **10** and ^{13}C NMR spectra and the optical rotation of **11** are in accord with those reported.[4]

EXPERIMENTAL

General Procedures. Melting points were determined with a Yanagimoto micro melting-point apparatus and are uncorrected. Specific rotations were determined with a JASCO DIP-4 polarimeter. ^{1}H NMR spectra were recorded with a JEOL JNM-PS100 spectrometer, and ^{13}C NMR spectra were recorded with a JEOL JNM-FX90Q spectrometer. Column chromatography was performed on silica gel 60 (Merck) with the solvent system specified. Concentrations and evaporations were conducted in vacuo.

Methyl 2,3-O-Isopropylidene-α-D-mannofuranoside (3). A solution of **2** (9.53 g, 34.7 mmol) in aqueous acetic acid (80 %, 100 mL) was kept at room temperature for 24 h. The

Table 2. ^{13}C NMR Data for Compounds 7-11[a].

Compound	C_1[b]	C_2	C_3	C_4	C_5	C_6	Other signals
7	107.5	85.1	80.6	82.3	50.0	43.6	24.9, 26.1, 113.0 (Isp), 54.8 (OMe)
8	107.7	84.9	80.7	85.5	29.6	24.4	24.8, 26.1, 112.6 (Isp), 54.6 (OMe)
9	107.0	84.8	79.6	77.5	41.5	64.3	25.0, 26.0, 113.0 (Isp), 54.6 (OMe) 20.7, 170.5 (OAc), 30.7, 193.6 (SAc)
10	72.7	69.8	68.6	70.1	40.3	61.7	20.5, 20.9, 168.2, 169.5, (OAc)
11[c]	77.8	74.7	73.5	72.0	45.6	62.9	

a. Mesured at 22.5 MHz in $CDCl_3$.

b. Chemical shifts in ppm from internal tetramethylsilane.

c. In CD_3OD.

reaction mixture was concentrated and the residue was chromatographed on a silica gel column (hexane-acetone, 2:1 v/v) to give syrupy **3** (7.56 g, 93 %): bp 197-200 °C/ 0.5 mm, $[\alpha]_D^{24}$ +65.1° (c 0.99, chloroform).

Anal. Calcd for $C_{10}H_{18}O_6$: C, 51.27; H, 7.75. Found: C, 51.25; H, 7.84.

Methyl 6-O-Benzoyl-2,3-O-isopropylidene-α-D-mannofuranoside (4). To a stirred solution of **3** (0.202 g, 0.86 mmol) in pyridine (0.42 mL) and dichloromethane (2 mL) was slowly added a solution of benzoyl chloride (0.10 mL, 0.90 mmol) in dichloromethane (2 mL) at -28 °C. After 10 min, the reaction mixture was mixed with water, and extracted with chloroform. The combined organic layer was washed successively with aqueous sodium hydrogencarbonate and water. After concentration of the solution, the residue was chromatographed on a silica gel column (hexane-ethyl acetate, 2:1 v/v) to give syrupy **4** (0.209 g, 72 %): $[\alpha]_D^{0}$ +54.2° (c 0.76, chloroform).

Anal. Calcd for $C_{17}H_{22}O_7$: C, 60.35; H, 6.55. Found: C, 60.58; H, 6.50.

Methyl 6-O-Benzoyl-2,3-O-isopropylidene-5-O-methanesulfonyl-α-D-mannofuranoside (5). To a stirred solution of **4** (0.335 g, 0.99 mmol) in pyridine (0.64 mL) and dichloromethane (3 mL) was slowly added a solution of methanesulfonyl chloride (0.46 mL, 5.95 mmol) in dichloromethane (3 mL) at 0 °C. After standing at room temperature for 20 h, the reaction mixture was mixed with water and extracted with chloroform. The combined organic layer was washed successively with aqueous sodium hydrogencarbonate and water. After concentration of the solution, the residue was chromatographed on a silica gel column (hexane-ethyl acetate, 3:1 v/v) to give syrupy **5** (0.393 g, 95 %): $[\alpha]_D^{21}$ +37.0°C (c 1.12, chloroform).

Anal. Calcd for $C_{18}H_{24}O_9S$: C, 51.91; H, 5.81; S, 7.70. Found: C, 52.25; H, 6.00; S, 7.53.

Methyl 2,3-O-Isopropylidene-5-O-methanesulfonyl-α-D-mannofuranoside (6). A solution of 5 (1.13 g, 2.71 mmol) in 0.01 M sodium methoxide-methanol (12 mL) was kept at room temperature overnight. The reaction mixture was neutralized with gaseous carbon dioxide and concentrated. The residue was dissolved in acetone and the solution was separated by filtration through celite and the filtrate concentrated. The residue was chromatographed on a silica gel column (hexane-ethyl acetate, 3:2 v/v) to give crystalline **6** (0.694 g, 82 %). Compound **6** was recrystalized from hexane-ethyl acetate: mp 127-128 °C, $[\alpha]_D^{25}$ +34.7° (c 1.02, chloroform).

Anal. Calcd for $C_{11}H_{20}O_8S$: C, 42.30; H, 6.45; S, 10.27. Found: C, 42.12; H, 6.47; S, 10.46.

Methyl 5,6-Anhydro-2,3-O-isopropylidene-β-L-gulofuranoside (7).

(i) With sodium methoxide: A solution of 5 (0.263 g, 0.364 mmol) in 0.03 M sodium methoxide-methanol (16 mL) was refluxed for 5 h. After cooling, the reaction mixture was neutralized with gaseous carbon dioxide and concentrated. The residue was dissolved in chloroform and washed with water. The organic layer was concentrated and chromatographed on a silica gel column (hexane-ethyl acetate, 4:1 v/v) to give crystalline **7** (0.022 g, 28 %).

(ii) With sodium hydride: To a stirred suspension of sodium hydride (55 %, 0.18 g, 3.7 mmol) in N,N-dimethylformamide (2 mL) was slowly added a solution of **6** (1.14 g, 3.65 mmol) in N,N-dimethylformamide (5 mL) and the reaction mixture was stirred at room temperature for 15 min. To the reaction mixture was added ice-cold water and the mixture was extracted with ether. The ether layer was washed with water. After removal of the solvent, the residue was chromatographed on a silica gel column (hexane-ethyl acetate, 4:1 v/v) to give crystalline **7** (0.585 g, 74 %).

(iii) With potassium tert-butoxide: A mixture of **6** (0.468 g 1.50 mmol) and potassium tert-butoxide (0.184 g, 1.65 mmol) in tetrahydrofuran (2.5 mL) was stirred at room temperature for 40 min. The reaction mixture was neutralized with gaseous carbon dioxide and diluted with water. After removal of tetrahydrofuran by evaporation, the water layer was extracted with chloroform. The extract was concentrated and the residue was chromatographed on a silica gel column (hexane-ethyl acetate, 4:1 v/v) to give crystalline **7** (0.203 g, 63 %).

Compound **7** was recrystallized from hexane: mp 66 °C, $[\alpha]_D^{20}$ +71.6° (c 0.79, chloroform).

Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.51; H, 7.44.

Methyl 5,6-Dideoxy-5,6-epithio-2,3-O-isopropylidene-α-D-mannofuranoside (8). A mixture of **7** (0.585 g, 2.70 mmol) and thiourea (0.58 g, 7.57 mmol) in methanol (10 mL) was stored at room temperature for 4 days. After concentration of the reaction mixture, the residue was dissolved in dichloromethane and the solution was separated by filtration through celite and concentrated. The residue was chromatographed on a silica gel column (hexane-ethyl acetate, 12:1 v/v) to give syrupy **8** (0.511 g, 81 %): $[\alpha]_D^{20}$ +37.0° (c 0.73, chloroform).

Anal. Calcd for $C_{10}H_{16}O_4S$: C, 51.70; H, 6.94; S, 13.80. Found: C, 51.54; H, 6.87; S, 13.38.

Methyl 6-O-Acetyl-5-S-acetyl-2,3-O-isopropylidene-5-thio-α-D-mannofuranoside (9). A mixture of **8** (0.309 g, 1.33 mmol) and potassium acetate (0.66 g, 6.73 mmol) in acetic acid (1.5 mL) and acetic anhydride (1.7 mL) was refluxed at 140 °C for 30 h. After cooling, the reaction mixture was concentrated. The residue was dissolved in dichloromethane and the solution was filtered through celite and concen-

trated. The residue was chromatogmaphed on a silica gel column (hexane-ethyl acetate, 6:1 v/v) to give crystalline **9** (0.403 g, 91 %). Compound **9** was recrystallized from petroleum ether: mp 60-61 °C, $[\alpha]_D^{21}$ +47.7° (c 0.94, chloroform).

Anal. Calcd for $C_{14}H_{22}O_7S$: C, 50.29; H, 6.63: S, 9.59. Fouund: C, 50.10; H, 6.80; S, 9.50.

1,2,3,4,6-Penta-O-acetyl-5-thio-α-D-mannopyranose (10). A solution of **9** (0.302 g, 0.90 mmol) in 50 % aqueous acetic acid (8 mL) was left at 100 °C for 38 h. After concentration, the residue was dissolved in water and the solution was washed with chroloform. The water layer was concentrated completely by coevaporation with toluene to give a syrup. The syrup was acetylated with acetic anhydride-pyridine in the usual manner to give, after column chromatography (hexane-ethyl acetate, 2:1 v/v), amorphous **10** (0.241 g, 66 %): mp 85-87 °C, $[\alpha]_D^{21}$ +83.1° (c 1.22, chloroform).

Anal. Calcd for $C_{16}H_{22}O_{10}S$: C, 47.29; H, 5.46; S,7.89. Found: C, 47.69; H, 5.54; S, 8.05.

5-Thio-α-D-mannopyranose (11). A solution of **10** (0.099 g, 0.24 mmol) in methanol-water-triethylamine (7:3:1, 15 mL) was left at room temperature for 7 h. After concentration, the residue was dissolved in water and the solution was washed with chloroform. The water layer was concentrated to give syrupy **11** (0.040 g, 83 %): $[\alpha]_D^{0}$ +49.7° (c 0.78, water). lit.[4] $[\alpha]_D$ +49.3° (c 0.75, water).

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