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Note

Insulin-like and insulin-antagonistic carbohydrate derivatives. Synthesis of ω-substituted-alkyl 1-thio-α-D-mannopyranosides*

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As part of a research program concerned with the synthesis and biological evaluation of novel saccharide derivatives designed to affect cell-surface membranes selectively, we reported[3] that 6-aminohexyl 1-thio-α-D-mannopyranoside (α-AHTM) is capable of exerting insulin-like activity in rat adipocytes *in vitro* (*i.e.*, it can stimulate, in the absence of insulin, oxidation of D-glucose and lipogenesis from D-[^{14}C]glucose, and inhibit epinephrine- and cholera toxin-stimulated lipolysis[4]). The contribution of the sugar moiety of α-AHTM to the expression of full biological activity was demonstrated[3]. Systematic variations in the saccharide configuration, glycosidic linkage, aglycon moiety, and sugar substitution-pattern were subsequently investigated in order to delineate structure–activity relationships[3]. We have already described[1] the synthesis of aryl and aralkyl D-mannopyranosides and 1-thio-α-D-mannopyranosides for use in testing the effect of other aglycon spacer-arms on the biological activity. Replacement of the aliphatic stem with an aryl or aralkyl arm resulted in severe diminution of insulin-like activity relative to that[3] of α-AHTM. A second, structural parameter examined was the terminal, functional group on the aliphatic stem of α-AHTM. Negatively charged, neutral, and other reactive groups (such as benzyloxycarbonylamino, carboxyl, chloro, cyano, hydroxyl, mercapto, tosylamino, and tosyloxy) were introduced into the molecule in place of the primary amino group (positively charged at physiological pH) for comparison of insulin-like activity with that of α-AHTM. The present work describes the synthesis of these ω-substituted-alkyl 1-thio-α-D-mannopyranosides, which are also of interest as inhibitors of other, cell-surface receptors that recognize D-mannose derivatives, and as possible inducers and inhibitors of α-mannosidases‡.

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‡Analogously, substituted-alkyl 1-thio-β-D-galactopyranosides[5] have been found[6] to act either as inducers of the lactose operon of *Escherichia coli* or as inhibitors of β-D-galactosidase.

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The alkyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranosides were prepared by *S*-alkylation of 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranose[1,7] (**1**) with the appropriate, ω-substituted bromo- or iodo-alkane in the presence of potassium carbonate. Thiol **1** could be isolated, and subsequently alkylated, or, more conveniently, generated *in situ*, in the presence of the alkylating agent, by basic cleavage of the amidino group in 2-*S*-(tetra-*O*-acetyl-α-D-mannopyranosyl)-2-thiopseudourea hydrobromide[1,7]. In this way were prepared heptyl (**2**), 6-(benzyloxycarbonylamino)hexyl (**4**), 6-hydroxyhexyl (**6**), and 5-carboxypentyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranoside (**17**), and 6-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosylthio)-1-hexene (**19**). The *O*-deacetylated derivatives (**3**, **5**, 7, and **20**) were obtained by treatment of the corresponding tetraacetates with a catalytic amount of sodium methoxide. Saponification of **17** afforded the sodium salt of 5-carboxypentyl 1-thio-α-D-mannopyranoside (**18**).

A by-product of the condensation of thiol **1** with 6-iodo-1-hexanol was identified, on the basis of its n.m.r. and mass spectra, and microanalysis, as hexane-1,6-diyl bis(2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranoside) (**21**). Deacetylation of **21** gave hexane-1,6-diyl bis(1-thio-α-D-mannopyranoside) (**22**).

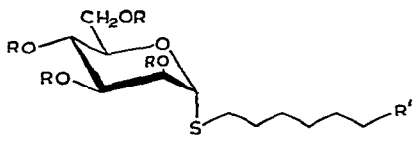
Two products were isolated from the reaction of the hexanol derivative **6** with *p*-toluenesulfonyl chloride in the presence of 4-(dimethylamino)pyridine. The major component (less mobile in t.l.c.) was identified as 6-(*p*-tolylsulfonyloxy)hexyl tetra-*O*-acetyl-1-thio-α-D-mannopyranoside (**8**), and the minor, as 6-chlorohexyl tetra-*O*-acetyl-1-thio-α-D-mannopyranoside (**10**). Zemplén deacetylation of **8** and **10** afforded 6-(*p*-tolylsulfonyloxy)hexyl and 6-chlorohexyl 1-thio-α-D-mannopyranoside (**9** and **11**, respectively).

Nucleophilic displacement of the tosyloxy group in **8** with cyanide or thioacetate anion in *N*,*N*-dimethylformamide gave the desired 6-cyanohexyl (**12**) and 6-(thioacetoxy)hexyl tetra-*O*-acetyl-1-thio-α-D-mannopyranoside (**14**), respectively. 6-Cyanohexyl 1-thio-α-D-mannopyranoside (**13**) was obtained by catalytic deacetylation of **12**. Treatment of **14** with an excess of sodium methoxide in methanol yielded the sodium salt (**15**) of 6-mercaptohexyl 1-thio-α-D-mannopyranoside.

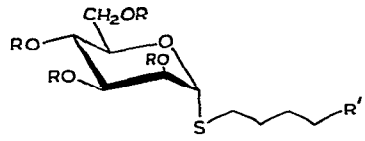
6-(*p*-Tolylsulfonylamino)hexyl 1-thio-α-D-mannopyranoside (**16**) was prepared by tosylation of α-AHTM[8] under Schotten–Baumann conditions.

The tetraacetates of the various ω-substituted-alkyl 1-thio-α-D-mannopyranosides exhibited the following characteristic, n.m.r.-spectral pattern in benzene-d_6: δ 1.64, 1.66, 1.68, and 1.75 (3-proton singlets, 4 OAc), 2.28 (multiplet, -SCH_2-), 4.23 (doublet of doublets, H-6′), 4.44 (doublet of doublets, H-6), 4.51 (multiplet, H-5), 5.29 (singlet, H-1), and 5.7–5.8 (complex multiplet, 3 H, H-2,3,4).

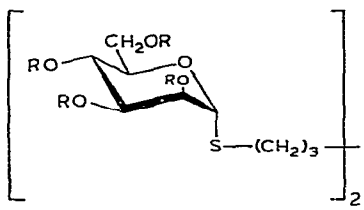
The ω-substituted-alkyl 1-thio-α-D-mannopyranosides did not display any insulin-like effects at a concentration (100 μg/mL) at which α-AHTM was significantly active (41% of the action of insulin at 25 μU/mL)[3]. This requirement of a primary amino group on the aliphatic stem of α-AHTM for biological activity later became readily understandable in light of its mechanism of insulin-like action[3,4].



2 R = Ac, R′ = Me
3 R = H, R′ = Me
4 R = Ac, R′ = NHZ
5 R = H, R′ = NHZ
6 R = Ac, R′ = OH
7 R = H, R′ = OH
8 R = Ac, R′ = OTs
9 R = H, R′ = OTs
10 R = Ac, R′ = Cl
11 R = H, R′ = Cl
12 R = Ac, R′ = CN
13 R = H, R′ = CN
14 R = Ac, R′ = SAc
15 R = H, R′ = SNa
16 R = H, R′ = NHTs



17 R = Ac, R′ = CH_2CO_2H
18 R = H, R′ = CH_2CO_2Na
19 R = Ac, R′ = $CH{=}CH_2$
20 R = H, R′ = $CH{=}CH_2$



21 R = Ac
22 R = H

However, several of the 1-thio-α-D-mannosides described herein [*e.g.*, 6-hydroxyhexyl 1-thio-α-D-mannopyranoside (**7**)] apparently retained their affinity for the insulin receptor. They were found to inhibit the binding of insulin–Sepharose to receptors on fat-cell surface-membranes in the affinity, buoyant-density assay and to antagonize insulin-stimulated oxidation of D-[^{14}C]glucose to $^{14}CO_2$ in rat adipocytes *in vitro*[9].

As D-mannose is also recognized by other cell-surface receptors, the ability of the present compounds to inhibit rat-lung (alveolar) macrophage uptake[10] of radiolabelled, D-mannosylated bovine serum albumin (Man-BSA) was also investigated[11]. Previously described, synthetic aralkyl 1-thio-α-D-mannopyranosides[1] and benzyl 6-*O*-α-D-mannopyranosyl-1-thio-α-D-mannopyranoside[2b] had been found[1,11] to be inhibitors of this macrophage, glycoprotein-recognition system. 6-Hydroxyhexyl (**7**) and heptyl 1-thio-α-D-mannopyranoside (**3**) and the sodium salt (**18**) of 5-carboxypentyl 1-thio-α-D-mannopyranoside also inhibited uptake of Man-BSA (more potently than D-mannose), and exhibited kinetic behavior characteristic of competitive inhibition (K_I ~35 mM for compound **7**)[11].

EXPERIMENTAL

General methods. — Solutions were evaporated below 50° under diminished pressure. Melting points were determined with a Thomas–Hoover "Unimelt" apparatus and are uncorrected. Optical rotations were measured with either a Zeiss or a Perkin–Elmer Model 241 polarimeter. I.r. spectra were recorded with a Perkin–

Elmer Model 137 "Infracord" i.r. spectrometer. N.m.r. spectra were recorded at 300 MHz with a Varian SC-300 n.m.r. spectrometer. Chemical shifts are given on the δ scale. Spectra were measured at ambient temperature for solutions, as indicated, in benzene-d_6 or methanol-d_4, with tetramethylsilane ($\delta = 0.00$) as the internal standard. Spectra were analyzed on a first-order basis. T.l.c. was performed on plates (250 μm) of Silica Gel GF_{254} (Analtech), and indication was effected with ultraviolet light or a ceric sulfate (1%)–sulfuric acid (10%) spray. Column chromatography was conducted with Silica Gel No. 7734 (E. Merck; 70–230 mesh). Petroleum ether refers to a fraction having b.p. 35–60°.

*Heptyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-*D*-mannopyranoside* (**2**). — To a solution of thiol **1** (1.6 g, 4.4 mmol) and 1-bromoheptane (0.75 g, 4.2 mmol) in acetone (10 mL) was added a solution of potassium carbonate (0.55 g, 4.0 mmol) in water (5 mL), and the mixture was stirred for 1 h at room temperature and then concentrated. The aqueous residue was extracted with dichloromethane, and the extracts were combined, washed with water, dried (magnesium sulfate), and evaporated. The resulting syrup was chromatographed on a column of silica gel that was eluted with 10:1 dichloromethane–diethyl ether. Pure **2** was obtained as a solid that was recrystallized from ethanol; yield 0.91 g (45%); m.p. 82.5–84°, $[\alpha]_D^{27}$ +92° (*c* 1.2, chloroform); n.m.r. (benzene-d_6): δ 0.86 (t, CH_3).

Anal. Calc. for $C_{21}H_{34}O_9S$ (462.56): C, 54.53; H, 7.41; S, 6.93. Found: C, 54.78; H, 7.48; S, 6.99.

*Heptyl 1-thio-α-*D*-mannopyranoside* (**3**). — A mixture of **2** (300 mg, 0.65 mmol) with dry methanol (10 mL) was treated overnight at room temperature with 0.1M methanolic sodium methoxide (0.5 mL). The solution was made neutral with Bio-Rad AG 50W-X4 (H^+) ion-exchange resin, the suspension filtered, and the filtrate evaporated to a syrup that crystallized upon standing. Recrystallization from 2-propanol–diethyl ether afforded pure **3**; yield 185 mg (97%); m.p. 59–62°, $[\alpha]_D^{27}$ +189 ±0.6° (*c* 0.8, methanol).

Anal. Calc. for $C_{13}H_{26}O_5S$ (294.41): C, 53.03; H, 8.90; S, 10.89. Found: C, 52.78; H, 8.85; S, 10.82.

*6-(Benzyloxycarbonylamino)hexyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-*D*-mannopyranoside* (**4**). — To a solution of **1** (4.0 g, 11.0 mmol) and 6-(benzyloxycarbonylamino)-1-iodohexane[12] (3.9 g, 10.8 mmol) in acetone (20 mL) was added a solution of potassium carbonate (1.5 g, 10.9 mmol) in water (6 mL), and the mixture was stirred for 15 min at room temperature and then concentrated. The aqueous residue was extracted with dichloromethane, and the extract was washed with water, dried (sodium sulfate), and evaporated to a syrup that crystallized from aqueous ethanol. Two recrystallizations from the same solvent system afforded pure **4**; yield 5.9 g (90%); m.p. 82–82.7°, $[\alpha]_D^{27}$ +70.7 ±0.5° (*c* 1, chloroform); n.m.r. (benzene-d_6): δ 2.94 (q, $-CH_2N$) and 5.14 (s, 2 H, OCH_2Ph).

Anal. Calc. for $C_{28}H_{39}NO_{11}S$ (597.69): C, 56.27; H, 6.58; N, 2.34; S, 5.36. Found: C, 56.43; H, 6.47; N, 2.27; S, 5.61.

*6-(Benzyloxycarbonylamino)hexyl 1-thio-α-*D*-mannopyranoside* (**5**). — A mix-

ture of **4** (1.0 g, 1.7 mmol) with dry methanol (10 mL) was treated overnight at room temperature with 0.1M methanolic sodium methoxide (1 mL). Processing of the reaction mixture in the usual way yielded a syrup that crystallized upon standing. Recrystallization from ethyl acetate–diethyl ether afforded pure **5**; yield 683 mg (95%); m.p. 54.5–56.5°, $[\alpha]_D^{27}$ +118 ±0.5° (*c* 0.9, methanol).

Anal. Calc. for $C_{20}H_{31}NO_7S$ (429.54): C, 55.92; H, 7.28; N, 3.26; S, 7.47. Found: C, 55.81; H, 7.22; N, 3.07; S, 7.47.

6-Iodo-1-hexanol. — A solution of 6-chloro-1-hexanol (10 g, 73.2 mmol) in 2-butanone (30 mL) was boiled under reflux in the presence of potassium iodide (18 g, 108 mmol) for 48 h. The mixture was cooled, and filtered, and the filtrate was evaporated; the residue was partitioned between dichloromethane and water, and the organic layer successively washed with aqueous sodium thiosulfate solution (twice), and cold water (once), dried (sodium sulfate), and evaporated. The resulting oil was distilled under vacuum, to afford the desired iodide; yield 12.4 g (74%); b.p. 85–95°/2 mm Hg (ref. 13).

*6-Hydroxyhexyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-*D*-mannopyranoside* (**6**). — To a solution of **1** (7.8 g, 21.4 mmol) and 6-iodo-1-hexanol (4.9 g, 21.5 mmol) in acetone (50 mL) was added a solution of potassium carbonate (3.0 g, 21.7 mmol) in water (10 mL), and the mixture was stirred for 30 min at room temperature and then concentrated. The aqueous residue was extracted with dichloromethane, and the extract was washed with water, dried (sodium sulfate), and evaporated. The resulting syrup was chromatographed on a column of silica gel that was eluted with 10:1 chloroform–ethyl acetate. The fractions containing the faster-moving product were combined and evaporated, to give crystalline hexane-1,6-diyl bis(2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranoside) (**21**) (0.6 g); m.p. 95–98°, $[\alpha]_D^{27}$ +111 ±1° (*c* 0.9, chloroform).

Anal. Calc. for $C_{34}H_{50}O_{18}S_2$ (810.89): C, 50.36; H, 6.22; S, 7.91. Found: C, 50.64; H, 6.17; S, 7.84.

The fractions containing the slower-moving product were combined and evaporated, to afford the title compound as a crystalline solid; yield 6.9 g (69%); m.p. 91–92°, $[\alpha]_D^{27}$ +93.6° ±0.5° (*c* 1, chloroform); n.m.r. (benzene-d_6): δ 3.34 (q, -CH_2OH).

Anal. Calc. for $C_{20}H_{32}O_{10}S$ (464.54): C, 51.71; H, 6.94; S, 6.90. Found: C, 51.57; H, 7.14; S, 7.11.

*6-Hydroxyhexyl 1-thio-α-*D*-mannopyranoside* (**7**). — To a solution of **6** (1.0 g, 2.2 mmol) in dry methanol (10 mL) was added a catalytic amount of sodium methoxide, and the mixture was kept overnight at room temperature and then processed in the usual way. The resulting syrup crystallized upon trituration with ethyl acetate–acetone; yield 630 mg (99%); m.p. 65–71°, $[\alpha]_D^{27}$ +150 ±0.5° (*c* 1, water).

Anal. Calc. for $C_{12}H_{24}O_6S$ (296.38): C, 48.63; H, 8.16; S, 10.82. Found: C, 48.56; H, 7.88; S, 10.67.

*Hexane-1,6-diyl bis(1-thio-α-*D*-mannopyranoside)* (**22**). — To a mixture of **21** (0.6 g, 0.74 mmol) with dry methanol (10 mL) was added a catalytic amount of

sodium methoxide, and the mixture was kept overnight at room temperature and then processed in the usual way. The resulting syrup crystallized upon vigorous scratching with a glass rod; yield 310 mg (88%); m.p. 120–122°, $[\alpha]_D^{27}$ +239 ±0.5° (*c* 1, methanol).

Anal. Calc. for $C_{18}H_{34}O_{10}S_2$ (474.59): C, 45.56; H, 7.22; S, 13.51. Found: C, 45.41; H, 7.09; S, 13.34.

*6-Chlorohexyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-*D*-mannopyranoside* (**10**) *and 6-(*p*-tolylsulfonyloxy)hexyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-*D*-mannopyranoside* (**8**). — To a solution of **6** (800 mg, 1.7 mmol) in dry dichloromethane (15 mL) were added 4-(dimethylamino)pyridine (252 mg, 2.1 mmol) and *p*-toluenesulfonyl chloride (394 mg, 2.1 mmol). The mixture was stirred, with exclusion of moisture, overnight at room temperature, and then diluted with dichloromethane (20 mL), and successively washed with M hydrochloric acid, saturated aqueous sodium hydrogencarbonate solution, and water, dried (sodium sulfate), and evaporated. The resulting syrup was dissolved in the minimal volume of dichloromethane, and the solution applied to a column of silica gel that was eluted with 2:1 diethyl ether–petroleum ether. The fractions containing the faster-moving product were combined and evaporated, to give chloride **10** as a solid that was recrystallized from ethanol–petroleum ether; yield 161 mg (19%); m.p. 85.4–86.4°, $[\alpha]_D^{27}$ +92.3 ±0.5° (*c* 0.9, chloroform); n.m.r. (benzene-d_6): δ 3.09 (t, -CH_2Cl).

Anal. Calc. for $C_{20}H_{31}ClO_9S$ (482.98): C, 49.74; H, 6.47; Cl, 7.34; S, 6.64. Found: C, 49.91; H, 6.50; Cl, 7.58; S, 6.88.

The fractions containing the slower-moving product were combined and evaporated, to afford tosylate **8**, which crystallized from ethanol; yield 700 mg (66%); m.p. 73.8–74.4°, $[\alpha]_D^{27}$ +104 ±1.2° (*c* 0.9, chloroform); n.m.r. (benzene-d_6): δ 1.85 (-PhCH_3) and 3.81 (t, -CH_2OTs).

Anal. Calc. for $C_{27}H_{38}O_{12}S_2$ (618.72): C, 52.41; H, 6.19; S, 10.36. Found: C, 52.46; H, 6.22; S, 10.04.

*6-Chlorohexyl 1-thio-α-*D*-mannopyranoside* (**11**). — To a solution of tetraacetate **10** (1.0 g, 2.1 mmol) in dry methanol (10 mL) was added a catalytic amount of sodium methoxide. The solution was kept overnight at room temperature and then processed in the usual way. The resulting syrup crystallized after vigorous scratching; recrystallization from ethyl acetate–diethyl ether gave pure **11**; yield 626 mg (96%); m.p. 64–89°, $[\alpha]_D^{27}$ +177 ±1.0° (*c* 1, methanol).

Anal. Calc. for $C_{12}H_{23}ClO_5S$ (314.82): C, 45.78; H, 7.36; Cl, 11.26; S, 10.18. Found: C, 45.96; H, 7.38; Cl, 11.13; S, 10.21.

*6-(*p*-Tolylsulfonyloxy)hexyl 1-thio-α-*D*-mannopyranoside* (**9**). — To a solution of **8** (150 mg, 0.24 mmol) in dry methanol (5 mL) was added a catalytic amount of sodium methoxide, and the mixture was kept overnight at 5° and then processed in the usual way. The resulting syrup crystallized upon standing. Recrystallization from acetone–diethyl ether gave pure **9**; yield 100 mg (92%); m.p. 99–101.5°, $[\alpha]_D^{27}$ +108 ±0.9° (*c* 1, methanol).

Anal. Calc. for $C_{19}H_{30}O_8S_2$ (450.57): C, 50.65; H, 6.71; S, 14.23. Found: C, 50.65; H, 6.64; S, 13.95.

*6-Cyanohexyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-*D*-mannopyranoside* (**12**). — A mixture of tosylate **8** (0.82 g, 1.3 mmol) and sodium cyanide (0.23 g, 4.7 mmol) in dry *N,N*-dimethylformamide (10 mL) was stirred, with exclusion of moisture, for 4 h at 45°. The mixture was then poured into ice–water (50 mL), the syrup extracted with dichloromethane (3 × 25 mL), and the extracts were combined, washed with ice–water, dried (sodium sulfate), and evaporated. As t.l.c. (2:1 ether–petroleum ether) indicated that partial deacetylation had taken place, the residue was treated with acetic anhydride and pyridine overnight at room temperature. The excess of reagents was removed by evaporation, followed by several coevaporations with toluene. The residue was applied to a column of silica gel that was eluted with 9:1 chloroform–ethyl acetate. The desired nitrile **12** was obtained as a syrup that crystallized from ethanol–petroleum ether; yield 0.53 g (84%); m.p. 88–89.2°, $[\alpha]_D^{27}$ +91.7 ±0.5° (*c* 1, chloroform).

Anal. Calc. for $C_{21}H_{31}NO_9S$ (473.55): C, 53.26; H, 6.60; N, 2.96; S, 6.77. Found: C, 53.24; H, 6.54; N, 2.95; S, 6.63.

*6-Cyanohexyl 1-thio-α-*D*-mannopyranoside* (**13**). — To a solution of **12** (1.0 g, 2.1 mmol) in dry methanol (10 mL) was added a catalytic amount of sodium methoxide. After being kept overnight at room temperature, the mixture was processed in the usual way, to give nitrile **13** as a syrup that crystallized from ethyl acetate–diethyl ether; yield 638 mg (99%); m.p. 82–83°, $[\alpha]_D^{27}$ +181 ±0.5° (*c* 1, methanol); ν_{max}^{Nujol} 2250 cm^{-1} (CN).

Anal. Calc. for $C_{13}H_{23}NO_5S$ (305.39): C, 51.13; H, 7.59; N, 4.59; S, 10.50. Found: C, 50.91; H, 7.75; N, 4.42; S, 10.67.

*6-(*p*-Tolylsulfonylamino)hexyl 1-thio-α-*D*-mannopyranoside* (**16**). — To a solution of 6-aminohexyl 1-thio-α-D-mannopyranoside[8] (220 mg, 0.74 mmol) and sodium hydrogencarbonate (190 mg) in water (5 mL) was added dropwise at room temperature a solution of *p*-toluenesulfonyl chloride (191 mg, 1.0 mmol) in acetone (5 mL); a precipitate separated out that eventually redissolved. The mixture was stirred overnight at room temperature and then evaporated. The residue was extracted with methanol, insoluble material filtered off, and the filtrate evaporated to a syrup that was applied to a column of silica gel that was eluted with 4:1 chloroform–methanol. Evaporation of the appropriate fractions afforded the desired product as a syrup; yield 244 mg (73%); $[\alpha]_D^{27}$ +116° (*c* 1, methanol); n.m.r. (methanol-d_4): δ 2.43 (s, -PhCH_3), 2.60 (m, -SCH_2-), 2.82 (t, -CH_2NTs), 5.20 (d, H-1), 7.39 and 7.74 (2 d, -C$_6H_4$-).

Anal. Calc. for $C_{19}H_{31}NO_7S_2$ (449.59): C, 50.76; H, 6.95; N, 3.12; S, 14.26. Found: C, 50.63; H, 7.12; N, 2.90; S, 14.41.

*6-(Thioacetoxy)hexyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-*D*-mannopyranoside* (**14**).— A mixture of tosylate **8** (600 mg, 0.97 mmol) and potassium thioacetate (220 mg, 1.9 mmol) in dry *N,N*-dimethylformamide (8 mL) was stirred with exclusion of moisture for 2 h at 90°. The mixture was then cooled and concentrated, the residue

partitioned between dichloromethane and water, the organic layer evaporated, and the resulting syrup applied to a column of silica gel that was eluted initially with 1:1 and subsequently with 2:1 diethyl ether–petroleum ether. Thioacetate **14** crystallized, and was recrystallized, from ether-petroleum ether; yield 440 mg (87%); m.p. 65.5–67°, $[\alpha]_D^{27}$ +86.2 ±1.0° (*c* 1, chloroform); n.m.r. (benzene-d_6): δ 1.90 (3-proton singlet, SAc) and 2.74 (t, -CH_2SAc).

Anal. Calc. for $C_{22}H_{34}O_{10}S_2$ (522.63): C, 50.56; H, 6.56; S, 12.27. Found: C, 50.48; H, 6.84; S, 12.43.

*6-Mercaptohexyl 1-thio-α-*D*-mannopyranoside, sodium salt* (**15**). — To a solution of thioacetate **14** (194 mg, 0.37 mmol) in dry methanol (0.8 mL) was added M methanolic sodium methoxide (0.39 mL), and the mixture was stirred for 1 h at room temperature. The precipitated solid was filtered off, washed extensively with ethanol, and dried *in vacuo* at 50°; yield 65 mg (52%); m.p. 196–206° (dec.), $[\alpha]_D^{27}$ +128 ±1.2° (*c* 0.4, water).

Anal. Calc. for $C_{12}H_{23}NaO_5S_2 \cdot H_2O$: C, 40.89; H, 7.15; Na, 6.52; S, 18.19. Found: C, 41.05; H, 6.79; Na, 6.46; S, 18.08.

*6-(2,3,4,6-Tetra-*O*-acetyl-α-*D*-mannopyranosylthio)-1-hexene* (**19**). — To a solution of 2-*S*-(tetra-*O*-acetyl-α-D-mannopyranosyl)-2-thiopseudourea hydrobromide monohydrate[1,7] (2 g, 4.0 mmol), potassium carbonate (0.55 g, 4.0 mmol), and potassium pyrosulfite ($K_2S_2O_5$; 1 g, 4.5 mmol) in water (10 mL) was added a solution of 6-bromo-1-hexene (0.64 g, 3.9 mmol) in acetone (10 mL). The mixture was stirred for 3 h at room temperature, and concentrated, the aqueous residue was partitioned between dichloromethane and water, and the organic layer dried (sodium sulfate), and evaporated. The resulting syrup was applied to a column of silica gel that was eluted with 9:1 chloroform–ethyl acetate. Evaporation of the appropriate fractions gave a solid that was twice recrystallized from ethanol–petroleum ether; yield 1.4 g (79%); m.p. 61.5–62.3°, $[\alpha]_D^{27}$ +97.6 ±1.0° (*c* 0.9, chloroform).

Anal. Calc. for $C_{20}H_{30}O_9S$ (446.52): C, 53.80; H, 6.77; S, 7.18. Found: C, 53.84; H, 6.88; S, 7.15.

*6-(α-*D*-Mannopyranosylthio)-1-hexene* (**20**). — A solution of tetraacetate **19** (0.5 g, 1.1 mmol) in dry methanol (10 mL) was treated with a catalytic amount of sodium methoxide overnight at room temperature. Usual processing of the reaction mixture then gave the desired product as a syrup that could not be induced to crystallize; yield 0.29 g (93%); $[\alpha]_D^{27}$ +197° (*c* 0.8, methanol).

Anal. Calc. for $C_{12}H_{22}O_5S \cdot 0.25\ H_2O$: C, 50.95; H, 8.02; S, 11.33. Found: C, 51.04; H, 7.76; S, 11.63.

*5-Carboxypentyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-*D*-mannopyranoside* (**17**). — To a solution of 2-*S*-(tetra-*O*-acetyl-α-D-mannopyranosyl)-2-thiopseudourea hydrobromide monohydrate[1,7] (2 g, 4.0 mmol), potassium carbonate (1.1 g, 8.0 mmol), and potassium pyrosulfite (1 g, 4.5 mmol) in water (10 mL) was added a solution of 6-bromohexanoic acid (0.77 g, 3.9 mmol) in acetone (10 mL). The mixture was stirred for 3 h at room temperature, made neutral with M hydrochloric acid, and concentrated. The aqueous residue was partitioned between dichloromethane and

water, and the organic layer washed with ice–water, dried (sodium sulfate), and evaporated to a solid. Two recrystallizations from ethanol–petroleum ether gave pure **17**; yield 1.8 g (95%); m.p. 101.5–102°, $[\alpha]_D^{27}$ +89 ±1.0° (*c* 1, chloroform); n.m.r. (benzene-d_6): δ 2.01 (t, -CH_2CO_2H).

Anal. Calc. for $C_{20}H_{30}O_{11}S$ (478.52): C, 50.20; H, 6.32; S, 6.70. Found: C, 50.41; H, 6.15; S, 6.80.

5-Carboxypentyl 1-thio-α-D-mannopyranoside, sodium salt (**18**). — To a solution of **17** (500 mg, 1.0 mmol) in methanol (8 mL) was added 2M aqueous sodium hydroxide (3.8 mL), and the mixture was stirred for 45 min at 40°, and cooled. The product was precipitated by adding ethanol (20 mL), and stirring for 30 min at 0°. The solid was filtered off, and extensively washed successively with ethanol and methanol; yield 347 mg (quantitative); m.p. 275–279° (dec.), $[\alpha]_D^{27}$ +146 ±0.5° (*c* 1, water).

Anal. Calc. for $C_{12}H_{21}NaO_7S$ (332.35): C, 43.37; H, 6.37; Na, 6.91; S, 9.65. Found: C, 43.06; H, 6.25; Na, 6.78; S, 9.42.

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