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INSULIN-LIKE, AND INSULIN-ANTAGONISTIC, CARBOHYDRATE DERIVATIVES. THE SYNTHESIS OF ARYL AND ARALKYL D-MANNOPYRANOSIDES AND 1-THIO-D-MANNOPYRANOSIDES*

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ABSTRACT

A number of novel, aryl and aralkyl D-mannopyranosides and 1-thio-D-mannopyranosides were synthesized for evaluation of insulin-like and insulin-antagonistic properties. The substituted-phenyl α-D-mannopyranosides were prepared by the general procedure of Helferich and Schmitz-Hillebrecht, the substituted-phenyl 1-thio-α-D-mannopyranosides by a method corresponding to the Michael synthesis of aromatic glycosides, and the aralkyl 1-thio-α-D-mannopyranosides by aralkylation of 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranose (**15**) and subsequent *O*-deacetylation. Compound **15** was obtained by basic cleavage of the amidino group in 2-*S*-(tetra-*O*-acetyl-α-D-mannopyranosyl)-2-thiopseudourea hydrobromide, the product of the reaction of tetra-*O*-acetyl-α-D-mannosyl bromide with thiourea. Benzyl 1-thio-β-D-mannopyranoside, obtained by reaction of the sodium salt of 1-thio-β-D-mannopyranose with α-bromotoluene, and benzyl 1-thio-α-L-mannopyranoside were also synthesized, in order to assess the stereospecificity of the biological activities measured.

INTRODUCTION

A research program in our laboratories has been concerned with the synthesis and biological evaluation of novel carbohydrate derivatives designed to affect cell-surface membranes selectively. The findings that (*a*) para-substituted-phenyl α-D-glycopyranosides can inhibit both the binding of insulin–Sepharose to its receptors on fat cells and insulin-stimulated utilization of D-glucose by these cells, with D-mannosides most frequently observed as more potent inhibitors than the corresponding D-glucosides or D-galactosides[4]; and (*b*) *p*-aminophenyl α-D-mannopyranoside (**1**) is capable of exerting insulin-like activity on rat adipocytes *in vitro*[3] (*i.e.*, can stimulate oxidation of D-glucose in the absence of insulin) prompted us to investigate analogous, low molecular-weight, substituted D-mannosides that might perturb the insulin receptor and give rise to insulin-like or insulin-antagonistic

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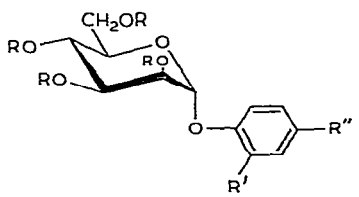
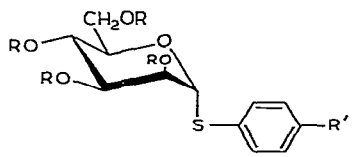
activity. We have previously reported[1,2] the synthesis of benzyl 1-thioglycosides of disaccharides of D-mannose, containing the more common, naturally occurring linkages, as potential affectors of fat-cell surface-membranes. The present work describes the synthesis of a number of novel, aryl and aralkyl D-mannopyranosides and 1-thio-D-mannopyranosides for measurement of insulin-like and insulin-antagonistic properties. In view of the interesting, insulin-mimicking activity observed with compound **1**, emphasis was placed on the preparation of aminoaryl and aminoalkaryl D-mannopyranosides. In order to assess the specificity of the biological activity, the compounds obtained in the present work were also submitted for testing in other available bioassays.

RESULTS AND DISCUSSION

The synthesis of *p*-aminophenyl α-D-mannopyranoside (**1**) has been reported[5]. Reductive formylation of **1** afforded the novel *p*-(dimethylamino)phenyl α-D-mannopyranoside (**2**). This compound did not display any insulin-like effects[6] at a concentration (10mM) at which **1** is significantly active[3], providing further evidence for the requirement of a primary amino group for biological activity*.

The other substituted-phenyl α-D-mannopyranosides were prepared by the general procedure of Helferich and Schmitz-Hillebrecht[8] for the synthesis of aromatic glycosides; this method is used for transforming 1,2-*trans*-glycosyl acetates into phenyl 1,2-*trans*-glycosides. Thus, heating of β-D-mannopyranose pentaacetate[9] in a melt with *p*-cyanophenol or *o*-cyanophenol in the presence of zinc chloride gave *p*-cyanophenyl and *o*-cyanophenyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (**3** and **6**, respectively). *O*-Deacetylation of **3** and **6** with a catalytic proportion of





1 R = R' = H, R'' = NH_2
2 R = R' = H, R'' = NMe_2
3 R = Ac, R' = H, R'' = CN
4 R = R' = H, R'' = CN
5 R = R' = H, R'' = CH_2NH_2
6 R = Ac, R' = CN, R'' = H
7 R = R'' = H, R' = CN
8 R = R'' = H, R' = CH_2NH_2

9 R = Ac, R' = OMe
10 R = H, R' = OMe
11 R = Ac, R' = NHAc
12 R = H, R' = NHAc
13 R = H, R' = NH_2

*A similar observation was made with the ω-aminoalkyl and ω-(dimethylamino)alkyl α-D-mannopyranosides[3]. For a study of the mechanism of insulin-like action exhibited by this class of saccharide derivatives, see ref. 7.

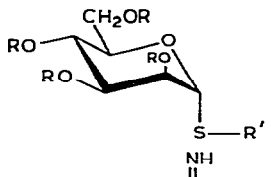
sodium methoxide afforded *p*-cyanophenyl and *o*-cyanophenyl α-D-mannopyranoside (**4** and **7**, respectively). Catalytic reduction of the cyano groups in **4** and **7** yielded *p*- and *o*-(aminomethyl)phenyl α-D-mannopyranoside (**5** and **8**, respectively)**. These two (D-mannosyloxy)aralkylamines exhibited only weak, insulin-like activity at a concentration of 100 μg/mL[3].

1-Thio-D-mannopyranosides were also investigated, as it was anticipated that they would be more resistant to enzymic hydrolysis than the corresponding *O*-linked derivatives and might therefore provide more-potent, insulin-like agents. 1-Thioglycopyranosides are also of interest as substrate-analog inhibitors of glycosidases[12,13]; competitive inhibitors of this type have been covalently attached to solid matrices, and the resulting adsorbents used for the purification of glycosidases[12,14] by affinity chromatography.

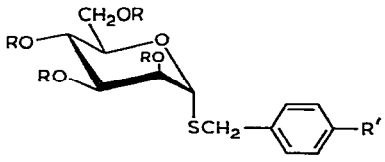
The substituted-phenyl 1-thio-α-D-mannopyranosides were prepared by a method corresponding to the Michael synthesis of aromatic *O*-glycosyl compounds, *i.e.*, by condensation of tetra-*O*-acetyl-α-D-mannopyranosyl bromide[15] with the appropriate arenethiol in the presence of aqueous sodium hydroxide; this procedure has been utilized by other workers for the synthesis of para-substituted-phenyl 1,2-*trans*-1-thio-D-glycopyranosides[16,17]. In this fashion were obtained *p*-methoxyphenyl and *p*-acetamidophenyl (the latter *via* acetylation of the *p*-aminophenyl derivative) 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranoside (**9** and **11**, respectively). Treatment of **9** and **11** with methanolic ammonia afforded *p*-methoxyphenyl and *p*-acetamidophenyl 1-thio-α-D-mannopyranoside (**10** and **12**, respectively). *p*-Aminophenyl 1-thio-α-D-mannopyranoside (**13**) was prepared by catalytic reduction of the nitro group in the known[17] *p*-nitrophenyl compound.

The aralkyl 1-thio-α-D-mannopyranosides were synthesized by *S*-aralkylation of 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranose (**15**) with the appropriate aralkyl bromide in the presence of potassium carbonate. The mercaptan **15** could be isolated and subsequently aralkylated, or, more conveniently, generated *in situ*, in the presence of the aralkylating agent, by basic cleavage of the amidino group in 2-*S*-(tetra-*O*-acetyl-α-D-mannopyranosyl)-2-thiopseudourea hydrobromide (**14**), the product of the reaction of tetra-*O*-acetyl-α-D-mannopyranosyl bromide[15] with thiourea in refluxing acetone. By this method were prepared benzyl (**16**), *p*-nitrobenzyl (**18**), *p*-cyanobenzyl (**23**), *p*-phenylbenzyl (**26**), and 2-phenylethyl (**28**) 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranoside. The unprotected derivatives (**17**, **19**, **24**, **27**, and **29**, respectively) were obtained by Zemplén deacetylation of the corresponding tetraacetates. Catalytic hydrogenation of **19** gave *p*-aminobenzyl 1-thio-α-D-mannopyranoside (**20**). *p*-Acetamidobenzyl 1-thio-α-D-mannopyranoside (**22**) was obtained by peracetylation of **20** and subsequent, selective *O*-deacetylation of the *N*-acetyltetra-*O*-acetyl compound **21**. Catalytic reduction of the cyano group in **24** yielded *p*-(aminomethyl)benzyl 1-thio-α-D-mannopyranoside (**25**). The D-mannosylthioaryl-

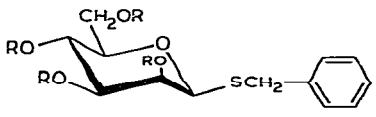
The β-D-glucoside analogs of **5 and **8** have been isolated from buckwheat seeds[10], and the α-L-rhamnoside analog of **8** from[11] the flowers of *Reseda odorata* L.



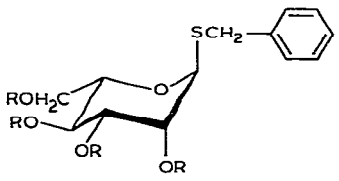
14 R = Ac,R′ = C(=NH)—NH_2 • HBr
15 R = Ac,R′ = H
28 R = Ac,R′ = CH_2CH_2Ph
29 R = H,R′ = CH_2CH_2Ph



16 R = Ac,R′ = H
17 R = R′ = H
18 R = Ac,R′ = NO_2
19 R = H,R′ = NO_2
20 R = H,R′ = NH_2
21 R = Ac,R′ = NHAc
22 R = H,R′ = NHAc
23 R = Ac,R′ = CN
24 R = H,R′ = CN
25 R = H,R′ = CH_2NH_2
26 R = Ac,R′ = Ph
27 R = H,R′ = Ph



30 R = Ac
31 R = H



32 R = Ac
33 R = H

amine **20** did not exhibit any insulin-like activity at 100 μg/mL, and the D-mannosyl-thioaralkylamine **25** showed only marginal activity at this concentration[3].

The β anomer and the enantiomer of **17** were also needed, for examination of the stereospecific nature of the biological activity. Benzyl 1-thio-β-D-mannopyranoside (**31**) was synthesized by reaction of the known[18] sodium salt of 1-thio-β-D-mannopyranose* with α-bromotoluene. Benzyl 1-thio-α-L-mannopyranoside (**33**) was prepared analogously to **17**, starting, however, with L-mannose. Compound **33** and its tetraacetate (**32**) were identical in all respects with **17** and **16**, respectively (m.p.; 300-MHz, n.m.r. spectrum; and t.l.c. mobility), and showed optical rotations of identical magnitude as, but opposite sign to, those of their enantiomeric counterparts.

Several of the aryl and aralkyl 1-thio-D-mannopyranosides were found to (*a*) inhibit the binding of insulin–Sepharose to receptors on fat-cell surface-membranes in the affinity, buoyant-density assay, (*b*) antagonize insulin-stimulated oxidation of

*This compound is obtained[18] by methanolysis of 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl ethylxanthate, which is isolated crystalline in low yield from the reaction of tetra-*O*-acetyl-α-D-mannopyranosyl bromide[15] with potassium ethylxanthate in refluxing acetone.

D-[^{14}C]glucose to $^{14}CO_2$ in rat adipocytes *in vitro*, and (*c*) inhibit insulin-stimulated uptake of D-glucose into rat diaphragm-muscle *in vitro*[4]. Among the more active compounds were benzyl 1-thio-α- and -β-D-mannopyranoside (**17** and **31**), and *p*-methoxyphenyl (**10**), *p*-nitrobenzyl (**19**), and *p*-aminobenzyl (**20**) 1-thio-α-D-mannopyranoside. Details of the insulin-like and insulin-antagonistic properties of these D-mannosides have been reported[3,4,7].

The aromatic D-mannosides were also tested for their ability to prevent *in vitro* penetration of hamster eggs by capacitated spermatozoa[19]. The most active compound tested proved to be *p*-nitrobenzyl 1-thio-α-D-mannopyranoside (**19**), which completely inhibited fertilization at a concentration of 1 mg/mL; dose–response behavior was observed. Also active in this system were *p*-acetamidophenyl (**12**), benzyl (**17**), and *p*-aminobenzyl (**20**) 1-thio-α-D-mannopyranoside (approximately half-inhibitory at 1 mg/mL); completely inactive at this concentration was *p*-methoxyphenyl 1-thio-α-D-mannopyranoside (**10**).

Benzyl 1-thio-α-D-mannopyranoside (**17**) was found[20] to be more potent than D-mannose as an inhibitor of rat-lung (alveolar), macrophage uptake[21] of radiolabeled D-mannosylated bovine serum albumin (Man-BSA) (K_I 6 mM). The enantiomer of **17**, benzyl 1-thio-α-L-mannopyranoside (**33**), was a much weaker inhibitor, providing additional evidence (stereospecificity) for receptor-mediated binding–uptake of glycoproteins and glycoconjugates by these macrophages. As anticipated[22], benzyl 6-*O*-α-D-mannopyranosyl-1-thio-α-D-mannopyranoside[2] was a better inhibitor (K_I 0.7 mM) than the monosaccharide derivative **17**, whereas *p*-nitrobenzyl (**19**) and *p*-aminobenzyl (**20**) 1-thio-α-D-mannopyranoside were less effective compounds[20]. It appears, therefore, that recognition by rat-lung macrophages involves both the sugar and the aglycon portions of the inhibitor molecule. Details of the biological experiments will be published elsewhere[20].

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 Perkin–Elmer Model 241 or a Zeiss polarimeter. 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 acetone-d_6, benzene-d_6, or methanol-d_4, with tetramethylsilane (δ = 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°.

p-(Dimethylamino)phenyl α-D-mannopyranoside (**2**). — To a solution of *p*-aminophenyl α-D-mannopyranoside[5] (**1**; 271 mg, 1.0 mmol) in methanol (15 mL)

were added glacial acetic acid (1.5 mL), 37% formaldehyde (0.8 mL), and Raney nickel (W. R. Grace No. 28; 150 mg). The mixture was shaken under hydrogen at 40 lb.in.$^{-2}$ for 2 h at room temperature, at which time t.l.c. (40:10:1 chloroform–methanol–water) indicated complete conversion into a faster-moving, ninhydrin-negative material. The mixture was filtered through Celite, and the filtrate was evaporated, and coevaporated several times with toluene (to remove traces of acetic acid). The resulting syrup was applied to a column of silica gel, and the product was eluted with 40:10:1 chloroform–methanol–water. Compound **2** was obtained as a solid that was recrystallized from 2-propanol; yield 254 mg (85%); m.p. 153–157°, $[\alpha]_D^{27}$ +127 ±0.9° (*c* 1, methanol); n.m.r. (methanol-d_4): δ 7.03 and 6.80 (2 m, -C_6H_4-), 5.32 (d, H-1), 3.98 (t, H-2), 3.88 (dd, H-3), 3.81–3.70 (m, 4 H, H-4,5,6,6′), and 2.84 (s, 6 H, NMe_2).

Anal. Calc. for $C_{14}H_{21}NO_6$ (299.33): C, 56.18; H, 7.07; N, 4.68. Found: C, 55.94; H, 7.22; N, 4.60.

p-*Cyanophenyl 2,3,4,6-tetra*-O-*acetyl*-α-D-*mannopyranoside* (**3**). — A mixture of β-D-mannopyranose pentaacetate[9] (4.0 g, 10.2 mmol), *p*-cyanophenol (4.0 g, 33.6 mmol), and freshly fused zinc chloride (0.1 g) was heated for 30 min at 160°. After allowing the mixture to cool to room temperature, benzene (60 mL) was added, and the organic solution was washed successively with cold water (2 × 60 mL), M aqueous sodium hydroxide (5 × 80 mL), and cold water (2 × 50 mL), dried (sodium sulfate), and evaporated. The resulting syrup crystallized from ethanol. Recrystallization from ethanol gave pure **3**; yield 2.2 g (48%); m.p. 162.5–164.5°, $[\alpha]_D^{27}$ +92.1 ±0.5° (*c* 1, chloroform); n.m.r. (benzene-d_6): δ 6.94 and 6.46 (2 d, -C_6H_4-), 5.75 (dd, $J_{2,3}$ 3.2, $J_{3,4}$ 10.3 Hz, H-3), 5.68 (t, $J_{4,5}$ 10 Hz, H-4), 5.59 (dd, $J_{1,2}$ 1.6 Hz, H-2), 5.04 (d, H-1), 4.20 (dd, $J_{5,6}$ 5.1, $J_{6,6'}$ 12.2 Hz, H-6), 4.00 (dd, $J_{5,6'}$ 2.2 Hz, H-6′), 3.78 (qd, H-5), and 1.74, 1.64, 1.63, and 1.62 (4 s, 12 H, 4 OAc).

Anal. Calc. for $C_{21}H_{23}NO_{10}$ (449.42): C, 56.12; H, 5.16; N, 3.12. Found: C, 56.15; H, 5.23; N, 2.87.

p-*Cyanophenyl* α-D-*mannopyranoside* (**4**). — To a solution of **3** (1.1 g, 2.4 mmol) in dry methanol (10 mL) was added a catalytic amount of sodium methoxide. The mixture was kept for 4 h at room temperature, made neutral with Bio-Rad AG-50W-X4 (H^+) ion-exchange resin, filtered, and evaporated to a crystalline solid. Recrystallization from methanol–diethyl ether afforded pure **4**; yield 0.67 g (97%); m.p. 182–183°, $[\alpha]_D^{27}$ +146 ±1.1° (*c* 0.9, methanol).

Anal. Calc. for $C_{13}H_{15}NO_6$ (281.27): C, 55.51; H, 5.38; N, 4.98. Found: C, 55.37; H, 5.29; N, 4.81.

p-(*Aminomethyl*)*phenyl* α-D-*mannopyranoside* (**5**). — A solution of **4** (500 mg, 1.8 mmol) in 18% (w/v) ammonia–methanol (11 mL) was shaken in the presence of Raney nickel (300 mg) under hydrogen at a pressure of 40 lb.in.$^{-2}$ for 6.5 h at room temperature. The catalyst was removed by filtration through Celite, the filtrate was evaporated to dryness, and the resulting residue was applied to a column of silica gel that was eluted with 5:5:1 chloroform–methanol–ammonium hydroxide (28.5%). The desired ninhydrin-positive product was obtained as a solid that was recrystallized

from methanol; yield 450 mg (84%); m.p. 175–177°, $[\alpha]_D^{27}$ +109 ±1.0° (*c* 1, water).

Anal. Calc. for $C_{13}H_{19}NO_6 \cdot 0.5\ CH_3OH$: C, 53.81; H, 7.03; N, 4.65. Found: C, 53.96; H, 7.20; N, 4.58.

o-*Cyanophenyl 2,3,4,6-tetra*-O-*acetyl*-α-D-*mannopyranoside* (**6**). — A mixture of β-D-mannopyranose pentaacetate[9] (3.5 g, 9.0 mmol), *o*-cyanophenol (3.5 g, 29.4 mmol), and freshly fused zinc chloride (0.2 g) was heated for 1 h at 160°. After being cooled to room temperature, the dark-brown reaction-mixture solidified; it was broken up, dissolved in chloroform, and the solution washed with M aqueous sodium hydroxide. Undissolved material was removed by filtration through Celite, and the organic layer of the filtrate was successively washed with M aqueous sodium hydroxide (until colorless) and cold water (twice), dried (sodium sulfate), and evaporated. The residue was applied to a column of silica gel that was eluted with 3 : 1 ether–petroleum ether. The desired product was obtained as a crystalline solid that was recrystallized from ethanol; yield 0.9 g (22%); m.p. 164–165°, $[\alpha]_D^{27}$ +51.6 ±0.9° (*c* 1, chloroform); n.m.r. (benzene-d_6): δ 5.94 (dd, $J_{2,3}$ 3.2, $J_{3,4}$ 10.2 Hz, H-3), 5.80–5.73 (m, 2 H, H-2,4), 5.29 (d, $J_{1,2}$ 1.7 Hz, H-1), 4.28 (dd, $J_{5,6}$ 4.6, $J_{6,6'}$ 12.3 Hz, H-6), 4.09 (qd, $J_{4,5}$ 10 Hz, H-5), 4.04 (dd, $J_{5,6'}$ 2.1 Hz, H-6'), and 1.70, 1.68, 1.64, and 1.62 (4 s, 12 H, 4 OAc).

Anal. Calc. for $C_{21}H_{23}NO_{10}$ (449.42): C, 56.12; H, 5.16; N, 3.12. Found: C, 56.22; H, 5.16; N, 2.98.

o-*Cyanophenyl* α-D-*mannopyranoside* (**7**). — To a solution of **6** (0.45 g, 1.0 mmol) in dry methanol (5 mL) was added a catalytic amount of sodium methoxide. After being kept for 5 h at room temperature, the mixture was processed as for **4**. Crystallization of the resulting syrup from methanol–diethyl ether gave pure **7**; yield 0.25 g (89%); m.p. 156–157°, $[\alpha]_D^{27}$ +50.7 ±0.9° (*c* 1, methanol).

Anal. Calc. for $C_{13}H_{15}NO_6$ (281.27): C, 55.51; H, 5.38; N, 4.98. Found: C, 55.22; H, 5.31; N, 4.82.

o-(*Aminomethyl*)*phenyl* α-D-*mannopyranoside* (**8**). — A solution of **7** (210 mg, 0.75 mmol) in 10% (w/v) ammonia–methanol (10 mL) was shaken in the presence of Raney nickel (200 mg) under hydrogen at a pressure of 40 lb.in^{-2} for 7 h at room temperature. The mixture was filtered through Celite, the filtrate was evaporated, and the residue was applied to a column of silica gel that was initially eluted with 6:4:1 chloroform–methanol–water (to remove faster-moving materials) and then with 5:5:1 chloroform–methanol–ammonium hydroxide (28.5%), to afford pure **8** as a glass; yield 190 mg (86%); $[\alpha]_D^{27}$ +75.6 ±1.2° (*c* 0.8, water).

Anal. Calc. for $C_{13}H_{19}NO_6 \cdot 0.5\ H_2O$: C, 53.05; H, 6.85; N, 4.76. Found: C, 53.17; H, 6.86; N, 4.66.

p-(*Methoxyphenyl*) *2,3,4,6-tetra*-O-*acetyl-1-thio*-α-D-*mannopyranoside* (**9**). — To a solution of *p*-methoxybenzenethiol (2.9 g, 20.7 mmol) in M aqueous sodium hydroxide (28 mL) was added under a stream of nitrogen, with stirring, a solution of tetra-*O*-acetyl-α-D-mannosyl bromide[15] (5.9 g, 14.3 mmol) in acetone (35 mL). Stirring under nitrogen was continued for 2 h. The mixture was then concentrated, and the aqueous residue was extracted with dichloromethane. The extracts were combined, washed with water, dried (sodium sulfate), and evaporated. The residue

was treated overnight at room temperature with acetic anhydride (7 mL) and pyridine (11 mL). The excess reagents were removed by evaporation, and several coevaporations with toluene. The resulting syrup crystallized from ethanol; recrystallization from ethanol afforded pure **9**; yield 1.6 g (24%); m.p. 141–142°, $[\alpha]_D^{27}$ −75.7 ±0.5° (*c* 1, chloroform); n.m.r. (benzene-d_6): δ 7.58 and 6.72 (2 d, -C_6H_4-), 5.61 (t, $J_{3,4} = J_{4,5} = 10$ Hz, H-4), 5.05 (dd, $J_{2,3}$ 3.2 Hz, H-3), 4.77 (d, $J_{1,2}$ 2.4 Hz, H-1), 4.53 (dd, H-2), 4.29 (dd, $J_{5,6}$ 5.2, $J_{6,6'}$ 12.5 Hz, H-6), 4.02 (dd, $J_{5,6'}$ 2.4 Hz, H-6'), 3.24 (s, OMe), 3.09 (qd, H-5), 1.91 and 1.70 (2 s, 6 H, 2 OAc), and 1.67 (s, 6 H, 2 OAc).

Anal. Calc. for $C_{21}H_{26}O_{10}S$ (470.5): C, 53.61; H, 5.57; S, 6.82. Found: C, 53.82; H, 5.71; S, 6.68.

p-*Methoxyphenyl 1-thio*-α-D-*mannopyranoside* (**10**). — Deacetylation was accomplished by dissolving **9** (900 mg, 1.9 mmol) in methanol (20 mL) presaturated with ammonia at 0°, and keeping the solution overnight at 0°. Evaporation gave a syrup that crystallized from ethanol–petroleum ether, to afford pure **10**; yield 549 mg (95%); m.p. 136–138°, $[\alpha]_D^{27}$ +254 ±0.5° (*c* 1, methanol).

Anal. Calc. for $C_{13}H_{18}O_6S$ (302.34): C, 51.64; H, 6.00; S, 10.60. Found: C, 51.37; H, 6.13; S, 10.57.

p-*Acetamidophenyl 2,3,4,6-tetra*-O-*acetyl-1-thio*-α-D-*mannopyranoside* (**11**). — To a solution of *p*-aminobenzenethiol (1.68 g, 13.4 mmol) in M aqueous sodium hydroxide (18.8 mL) was added under nitrogen, with stirring, a solution of tetra-*O*-acetyl-α-D-mannosyl bromide[15] (3.95 g, 9.6 mmol) in acetone (28 mL), and stirring was continued for 2 h at room temperature. The mixture was then concentrated, and the aqueous residue was extracted with dichloromethane. The extracts were combined, washed with water, dried (sodium sulfate), and evaporated. The residue was treated overnight at room temperature with acetic anhydride (6 mL) and pyridine (9 mL). The excess reagents were removed by evaporation, and several coevaporations with toluene. The residue was applied to a column of silica gel that was eluted with 25:1 dichloromethane–diethyl ether. The solid obtained upon evaporation of the appropriate fractions was recrystallized from methanol–water to afford pure **11**; yield 1.4 g (29%); m.p. 138–140°, $[\alpha]_D^{27}$ +97.5° (*c* 1, chloroform) {lit.[17] m.p. 139–141°, $[\alpha]_D$ +97.8° (*c* 0.81, chloroform)}.

p-*Acetamidophenyl 1-thio*-α-D-*mannopyranoside* (**12**). — Compound **11** (1.3 g, 2.6 mmol) was *O*-deacetylated with methanolic ammonia as described for the preparation of **10**. The residue was chromatographed on a column of silica gel, and elution was carried out with 7:1 chloroform–methanol, and then with 40:10:1 chloroform–methanol–water. Compound **12** was obtained as a chromatographically homogeneous syrup; yield 0.75 g (85%); $[\alpha]_D^{27}$ +162 ±1.1° (*c* 0.9, methanol); n.m.r. (methanol-d_4): δ 7.59–7.50 (m, -C_6H_4-), 5.36 (d, H-1), and 2.13 (s, 3 H, NHAc).

Anal. Calc. for $C_{14}H_{19}NO_6S \cdot 0.5\ H_2O$: C, 49.69; H, 5.96; N, 4.14; S, 9.47. Found: C, 49.52; H, 5.92; N, 4.22; S, 9.17.

p-*Aminophenyl 1-thio*-α-D-*mannopyranoside* (**13**). — A solution of *p*-nitrophenyl 1-thio-α-D-mannopyranoside[17] (300 mg, 0.9 mmol) in methanol (100 mL) was hydrogenated in the presence of 5% palladium-on-barium sulfate (200 mg) at a pressure of

40 lb.in.$^{-2}$ for 24 h at room temperature. The catalyst was removed by filtration through Celite, and the filtrate was evaporated. The product was purified by chromatography on plates (1.000 mm) of Silica Gel GF_{254} (Analtech) with 70:30:3 chloroform–methanol–water as the developer, and extraction with methanol. Evaporation of the extracts afforded pure, amorphous **13**; yield 207 mg (74%); $[\alpha]_D^{27}$ +267 ±0.5° (*c* 0.9, water).

Anal. Calc. for $C_{12}H_{17}NO_5S \cdot 0.5\ H_2O$: C, 48.64; H, 6.12; N, 4.73; S, 10.82. Found: C, 48.71; H, 6.09; N, 4.63; S, 10.58.

2-S-(2,3,4,6-Tetra-O-acetyl-α-D-mannopyranosyl)-2-thiopseudourea hydrobromide (**14**). — A solution of tetra-*O*-acetyl-α-D-mannosyl bromide[15] (78.8 g, 19.2 mmol) and thiourea (15 g, 19.7 mmol) in dry acetone (90 mL) was boiled under reflux for 2 h. The mixture was then cooled and evaporated, and the residue was partitioned between water (100 mL) and chloroform (70 mL). The aqueous layer was washed with chloroform (50 mL), and the product was allowed to crystallize from the aqueous layer overnight at 5°, to yield 52.6 g (54%) of **14**. An analytical sample was obtained by recrystallization from water; m.p. 125–128°, $[\alpha]_D^{27}$ +103 ±0.5° (*c* 1, acetone) {lit.[23] m.p. 131–133°, $[\alpha]_D^{20}$ +106.8° (*c* 1, methanol)}; n.m.r. (acetone-d_6): δ 6.47 (d, $J_{1,2}$ 1.5 Hz, H-1), 5.51 (dd, $J_{2,3}$ 3.7 Hz, H-2), 5.38 (t, $J_{3,4} = J_{4,5}$ = 10 Hz, H-4), 5.20 (dd, H-3), 4.54 (m, H-5), 4.34 (dd, $J_{5,6}$ 5.9, $J_{6,6'}$ 12.3 Hz, H-6), and 4.25 (dd, $J_{5,6'}$ 2.6 Hz, H-6').

Anal. Calc. for $C_{15}H_{23}BrN_2O_9S \cdot H_2O$: C, 35.65; H, 4.99; Br, 15.81; N, 5.54; S, 6.34. Found: C, 35.54; H, 5.03; Br, 15.90; N, 5.61; S, 6.40.

2,3,4,6-Tetra-O-acetyl-1-thio-α-D-mannopyranose (**15**). — A mixture of compound **14** (43 g, 85.1 mmol) in chloroform (85 mL) and water (70 mL) was treated with potassium pyrosulfite ($K_2S_2O_5$; 15 g) and boiled, in a nitrogen atmosphere, under reflux for 30 min. The mixture was cooled, and the organic layer was separated, washed once with cold water, dried (sodium sulfate), and evaporated to a syrup that could not be induced to crystallize; yield 26 g (84%). The compound (kept under nitrogen when stored) was used, without further purification, for the preparation of most of the aralkyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranosides described next.

Benzyl 2,3,4,6-tetra-O-acetyl-1-thio-α-D-mannopyranoside (**16**). — To a solution of the thiol **15** (1.6 g, 4.4 mmol) and α-bromotoluene (0.69 g, 4.0 mmol) in acetone (10 mL) was added, under nitrogen, a solution of potassium carbonate (0.55 g, 4.0 mmol) in water (5 mL). The mixture was stirred for 1 h at room temperature, and concentrated, the aqueous residue was extracted with dichloromethane, and the extracts were combined, washed with water, dried (magnesium sulfate), and evaporated. The residue was applied to a column of silica gel, and the product was eluted with 10:1 dichloromethane–diethyl ether. Recrystallization of the solid from ethanol gave pure **16**; yield 1.2 g (60%); m.p. 137–138.5°, $[\alpha]_D^{27}$ +154 ±0.9° (*c* 1, chloroform); n.m.r. (benzene-d_6): δ 5.77–5.64 (m, 3 H, H-2,3,4), 5.16 (d, $J_{1,2}$ 1.4 Hz, H-1), 4.44–4.38 (m, 2 H, H-5,6), 4.06 (dd, H-6'), 3.50 (d, 1 H, *J* 13.5 Hz, SC*H*Ph), 3.34 (d, 1 H, SC*H*Ph), and 1.72, 1.66, 1.64, and 1.48 (4 s, 12 H, 4 OAc).

Anal. Calc. for $C_{21}H_{26}O_9S$ (454.5): C, 55.50; H, 5.77; S, 7.05. Found: C, 55.30; H, 5.91; S, 7.26.

Benzyl 1-thio-α-D-mannopyranoside (**17**). — To a solution of **16** (300 mg, 0.7 mmol) in dry methanol (10 mL) was added 0.1M methanolic sodium methoxide (0.5 mL). The mixture was kept overnight at room temperature, made neutral with Bio-Rad AG-50W-X4 (H^+) ion-exchange resin, the suspension filtered, and the filtrate evaporated, to give **17** as a syrup that crystallized on standing; yield 183 mg (97%); m.p. 102–106.5°, $[\alpha]_D^{27}$ +342 ±1.8° (*c* 0.55, methanol).

Anal. Calc. for $C_{13}H_{18}O_5S$ (286.34): C, 54.53; H, 6.34; S, 11.20. Found: C, 54.58; H, 6.45; S, 10.98.

p-*Nitrobenzyl 2,3,4,6-tetra*-O-*acetyl-1-thio-α-D-mannopyranoside* (**18**). — This compound was prepared from thiol **15** (1.6 g, 4.4 mmol) and *p*-nitrobenzyl bromide (0.86 g, 4.0 mmol) by following the procedure described for **16**. The residue was chromatographed on a column of silica gel that was eluted with 10:1 dichloromethane–diethyl ether. The product was obtained as a crystalline solid that was recrystallized from ethanol; yield 1.1 g (50%); m.p. 136.5–137°, $[\alpha]_D^{27}$ +184 ±0.6° (*c* 0.9, chloroform) {lit.[23] m.p. 128–130°, $[\alpha]_D^{20}$ +160° (*c* 1, methanol)}; n.m.r. (benzene-d_6): δ 7.78 and 6.81 (2 d, -C_6H_4-), 5.74 (t, $J_{3,4} = J_{4,5} = 9.6$ Hz, H-4), 5.65 (dd, $J_{2,3}$ 3.1 Hz, H-3), 5.64 (m, H-2), 5.01 (broadened s, H-1), 4.36 (dd, $J_{5,6}$ 5.0, $J_{6,6'}$ 12 Hz, H-6), 4.30 (m, H-5), 4.12 (dd, $J_{5,6'}$ 2.0 Hz, H-6'), 3.24 (d, 1 H, SC*H*Ph), 3.04 (d, 1 H, SC*H*Ph), and 1.74, 1.68, 1.67, and 1.53 (4 s, 12 H, 4 OAc).

Anal. Calc. for $C_{21}H_{25}NO_{11}S$ (499.5): C, 50.50; H, 5.05; N, 2.80; S, 6.42. Found: C, 50.54; H, 5.10; N, 2.88; S, 6.42.

p-*Nitrobenzyl 1-thio-α-D-mannopyranoside* (**19**). — This compound was prepared from **18** (300 mg, 0.6 mmol) by following the procedure described for **17**. Processing of the mixture in the usual way gave a solid that was recrystallized twice from ethanol; yield 185 mg (93%); m.p. 139–141°, $[\alpha]_D^{27}$ +340 ±0.5° (*c* 1, methanol) {lit.[23] m.p. 150–152°, $[\alpha]_D^{20}$ +336° (*c* 1, methanol)}.

Anal. Calc. for $C_{13}H_{17}NO_7S$ (331.35): C, 47.12; H, 5.16; N, 4.22; S, 9.67. Found: C, 46.90; H, 5.10; N, 4.07; S, 9.87.

p-*Aminobenzyl 1-thio-α-D-mannopyranoside* (**20**). — A suspension of **19** (750 mg, 2.3 mmol) in methanol (200 mL) was hydrogenated in the presence of 5% palladium-on-barium sulfate (500 mg) at a pressure of 40 lb.in.$^{-2}$ for 4 h at room temperature. The mixture was filtered through Celite, and the filtrate was evaporated. Trituration of the resulting syrup with ethanol gave a solid that was recrystallized from aqueous methanol, to give pure **20**; yield 600 mg (88%); m.p. 194–195.5°, $[\alpha]_D^{27}$ +376 ±2.1° (*c* 0.47, methanol).

Anal. Calc. for $C_{13}H_{19}NO_5S$ (301.36): C, 51.81; H, 6.35; N, 4.65; S, 10.64. Found: C, 52.02; H, 6.36; N, 4.60; S, 10.55.

p-*Acetamidobenzyl 2,3,4,6-tetra*-O-*acetyl-1-thio-α-D-mannopyranoside* (**21**). — Compound **20** (300 mg, 1.0 mmol) was treated with acetic anhydride (4 mL) and pyridine (6 mL) overnight at room temperature. The excess reagents were removed by evaporation, followed by several coevaporations with toluene, and finally with carbon

tetrachloride. Crystallization of the resulting syrup was effected from ethanol–petroleum ether, to give pure **21**; yield 468 mg (92%); m.p. 140.8–141.8°, $[\alpha]_D^{27}$ +148 ±0.5° (*c* 1, chloroform); n.m.r. (benzene-d_6): δ 6.08 (broadened s, N*H*Ac), 5.76 (m, H-4), 5.73–5.68 (m, 2 H, H-2,3), 5.19 (broadened s, H-1), 4.42 (m, H-5), 4.40 (dd, $J_{5,6}$ 4.7 Hz, H-6), 4.11 (dd, H-6'), 3.49 (d, 1 H, SC*H*Ph), 3.33 (d, 1 H, SC*H*Ph), and 1.75, 1.68, 1.65, 1.50, and 1.45 (5 s, 15 H, 4 OAc and 1 NHAc).

Anal. Calc. for $C_{23}H_{29}NO_{10}S$ (511.55): C, 54.00; H, 5.71; N, 2.74; S, 6.27. Found: C, 54.06; H, 5.68; N, 2.79; S, 6.54.

p-*Acetamidobenzyl 1-thio*-α-D-*mannopyranoside* (**22**). — *O*-Deacetylation of **21** (600 mg, 1.2 mmol) with sodium methoxide in methanol, and processing in the usual way, gave a syrup that crystallized upon standing for several months; yield 383 mg (95%); m.p. 135–145°, $[\alpha]_D^{27}$ +339 ±0.5° (*c* 1, methanol); n.m.r. (methanol-d_4): 7.52 and 7.34 (2 d, -C_6H_4-), 5.06 (s, H-1), and 2.12 (s, 3 H, NHAc).

Anal. Calc. for $C_{15}H_{21}NO_6S$ (343.4): C, 52.47; H, 6.16; N, 4.08; S, 9.34. Found: C, 52.33; H, 6.38; N, 4.12; S, 9.21.

p-*Cyanobenzyl 2,3,4,6-tetra*-O-*acetyl-1-thio*-α-D-*mannopyranoside* (**23**). — To a solution of pseudothiourea derivative **14** (3.0 g, 5.9 mmol) in water (15 mL) were added potassium carbonate (0.94 g, 6.8 mmol), potassium pyrosulfite (1.3 g, 5.8 mmol), and a solution of *p*-cyanobenzyl bromide (1.16 g, 5.9 mmol) in acetone (15 mL). The mixture was stirred for 30 min at room temperature, concentrated, and the wet residue extracted with dichloromethane; the extracts were combined, washed with water, dried (sodium sulfate), and evaporated to a syrup that crystallized from ethanol–petroleum ether. Recrystallization from ethanol gave pure **23**; yield 2.6 g (91%); m.p. 92–92.5°, $[\alpha]_D^{27}$ +184 ±0.5° (*c* 1, chloroform); n.m.r. (benzene-d_6): δ 6.95 and 6.75 (2 d, -C_6H_4-), 5.73 (t, $J_{3,4} = J_{4,5}$ = 10 Hz, H-4), 5.63 (dd, $J_{2,3}$ 3.1 Hz, H-3), 5.61 (m, H-2), 4.98 (broadened s, H-1), 4.35 (dd, $J_{5,6}$ 5.0, $J_{6,6'}$ 12 Hz, H-6), 4.27 (qd, H-5), 4.08 (dd, $J_{5,6'}$ 2.1 Hz, H-6'), 3.21 (d, 1 H, SC*H*Ph), 3.02 (d, 1 H, SC*H*Ph), and 1.73, 1.67, 1.66, and 1.52 (4 s, 12 H, 4 OAc).

Anal. Calc. for $C_{22}H_{25}NO_9S$ (479.51): C, 55.11; H, 5.26; N, 2.92; S, 6.69. Found: C, 55.05; H, 5.29; N, 2.72; S, 6.73.

p-*Cyanobenzyl 1-thio*-α-D-*mannopyranoside* (**24**). — A mixture of **23** (1.8 g, 3.8 mmol) with dry methanol (15 mL) was treated with a catalytic amount of sodium methoxide for 5 h at room temperature. Processing in the usual way gave a crystalline solid that was recrystallized from methanol–ethyl acetate–diethyl ether; yield 1.1 g (94%); m.p. 145.5–147°, $[\alpha]_D^{27}$ +373 ±0.5° (*c* 1, methanol).

Anal. Calc. for $C_{14}H_{17}NO_5S$ (311.36): C, 54.01; H, 5.50; N, 4.50; S, 10.30. Found: C, 54.01; H, 5.38; N, 4.29; S, 10.30.

p-(*Aminomethyl*)*benzyl 1-thio*-α-D-*mannopyranoside* (**25**). — A solution of **24** (700 mg, 2.2 mmol) in 10% (w/v) ammonia–methanol (20 mL) was hydrogenated in the presence of Raney nickel (1 g) at a pressure of 40 lb.in.$^{-2}$ for 24 h at room temperature. The mixture was then filtered through Celite, the filtrate evaporated, and the residue applied to a column of silica gel. Elution with 5:5:1 chloroform–

methanol–ammonium hydroxide (28.5%) gave pure **25** as a syrup; yield 521 mg (72%); $[\alpha]_D^{27}$ +306° (*c* 0.9, methanol).

Anal. Calc. for $C_{14}H_{21}NO_5S \cdot 0.25\ H_2O$: C, 52.56; H, 6.77; N, 4.38; S, 10.02. Found: C, 52.52; H, 6.92; N, 4.26; S, 10.21.

p-*Phenylbenzyl 2,3,4,6-tetra*-O-*acetyl-1-thio*-α-D-*mannopyranoside* (**26**). — This compound was prepared from thiol **15** (2.0 g, 5.5 mmol) and *p*-phenylbenzyl bromide (1.3 g, 5.3 mmol) as for **16**. The product was obtained as a solid that was recrystallized twice from ethanol; yield 2.3 g (79%); m.p. 135–141° (softening), 141–142.3°, $[\alpha]_D^{27}$ +164 ±0.5° (*c* 1, chloroform); n.m.r. (benzene-d_6): δ 5.80–5.70 (m, 3 H, H-2,3,4), 5.24 (d, $J_{1,2}$ ~1.1 Hz, H-1), 4.44 (m, H-5), 4.42 (dd, $J_{5,6}$ 5.1 Hz, H-6), 4.13 (broadened d, H-6'), 3.56 (d, 1 H, SC*H*Ph), 3.39 (d, 1 H, SC*H*Ph), and 1.75, 1.68, 1.65, and 1.48 (4 s, 12 H, 4 OAc).

Anal. Calc. for $C_{27}H_{30}O_9S$ (530.6): C, 61.12; H, 5.70; S, 6.04. Found: C, 61.25; H, 5.63; S, 6.19.

p-*Phenylbenzyl 1-thio*-α-D-*mannopyranoside* (**27**). — Deacetylation of **26** (1.0 g, 1.9 mmol), and processing as described for the preparation of **17**, gave a syrup that crystallized from ethyl acetate–methanol; yield 622 mg (91%); m.p. 174.5–176°, $[\alpha]_D^{27}$ +333 ±0.5° (*c* 1, methanol).

Anal. Calc. for $C_{19}H_{22}O_5S$ (362.45): C, 62.96; H, 6.12; S, 8.85. Found: C, 63.28; H, 6.14; S, 8.90.

2-Phenylethyl 2,3,4,6-tetra-O-*acetyl-1-thio*-α-D-*mannopyranoside* (**28**). — To a solution of thiol **15** (2.0 g, 5.5 mmol) in acetone (10 mL) were added (2-bromoethyl)-benzene (1.0 g, 5.4 mmol) and a solution of potassium carbonate (0.75 g, 5.4 mmol) in water (3 mL). The mixture was stirred for 30 min at room temperature, and concentrated; the wet residue was partitioned between dichloromethane and water, and the organic layer dried (sodium sulfate), and evaporated to a solid; yield 1.8 g (70%); m.p. 85.5–86.8°, $[\alpha]_D^{27}$ +96 ±0.5° (*c* 0.9, chloroform); n.m.r. (benzene-d_6): δ 5.77–5.67 (m, 3 H, H-2,3,4), 5.20 (broadened s, H-1), 4.44 (m, H-5), 4.40 (dd, $J_{5,6}$ 5.2 Hz, H-6), 4.18 (broadened d, H-6'), 2.71–2.44 (m, 4 H, -CH_2CH_2-), and 1.69 and 1.65 (6-proton singlets, 4 OAc).

Anal. Calc. for $C_{22}H_{28}O_9S$ (468.52): C, 56.40; H, 6.02; S, 6.84. Found: C, 56.27; H, 5.89; S, 6.58.

2-Phenylethyl 1-thio-α-D-*mannopyranoside* (**29**). — Compound **28** (1.0 g, 2.1 mmol) was deacetylated with methanolic sodium methoxide, and the product was processed in the usual way. The resulting syrup crystallized from acetone–diethyl ether; yield 615 mg (96%); m.p. 88.5–89.2°, $[\alpha]_D^{27}$ +198 ±0.5° (*c* 0.9, methanol).

Anal. Calc. for $C_{14}H_{20}O_5S$ (300.37): C, 55.98; H, 6.71; S, 10.67. Found: C, 55.82; H, 6.71; S, 10.42.

Benzyl 2,3,4,6-tetra-O-*acetyl-1-thio*-β-D-*mannopyranoside* (**30**). — To a solution of the sodium salt[18] (1.0 g, 4.6 mmol) of 1-thio-β-D-mannopyranose in 40% aqueous ethanol (25 mL) was added α-bromotoluene (0.78 g, 4.6 mmol). The mixture was heated for 30 min at 50°, cooled, and evaporated, and the residue was treated with acetic anhydride (4 mL) and pyridine (6 mL) overnight at room temperature. The

excess reagents were removed by evaporation, and several coevaporations with toluene. The residue was taken up in dichloromethane, and the solution washed twice with cold water, and evaporated to a syrup that was applied to a column of silica gel and eluted with 9:1 chloroform–ethyl acetate. The desired compound was obtained as a solid that was recrystallized from ethanol–petroleum ether; yield 1.8 g (86%); m.p. 102–103°, $[\alpha]_D^{27}$ −159 ±0.9° (*c* 1.1, chloroform); n.m.r. (benzene-d_6): δ 5.64 (m, H-2), 5.60 (t, $J_{3,4} = J_{4,5} = 10$ Hz, H-4), 5.02 (dd, $J_{2,3}$ 3.3 Hz, H-3), 4.31 (dd, $J_{5,6}$ 5.2, $J_{6,6'}$ 12.3 Hz, H-6), 4.17 (broadened s, H-1), 4.12 (dd, $J_{5,6'}$ 1.9 Hz, H-6'), 3.73 (d, 1 H, *J* 13.2 Hz, SC*H*Ph), 3.52 (d, 1 H, SC*H*Ph), 3.16 (qd, H-5), and 1.71, 1.70, 1.68, and 1.64 (4 s, 12 H, 4 OAc).

Anal. Calc. for $C_{21}H_{26}O_9S$ (454.5): C, 55.50; H, 5.77; S, 7.05. Found: C, 55.72; H, 5.77; S, 7.18.

*Benzyl 1-thio-β-*D*-mannopyranoside* (**31**). — To a mixture of **30** (1.0 g, 2.2 mmol) with dry methanol (15 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 afford a syrup that crystallized spontaneously. Recrystallization from methanol–diethyl ether gave pure **31**; yield 580 mg (92%); m.p. 131.5–132.5°, $[\alpha]_D^{27}$ −229 ±0.9° (*c* 1, methanol).

Anal. Calc. for $C_{13}H_{18}O_5S$ (286.34): C, 54.53; H, 6.34; S, 11.20. Found: C, 54.57; H, 6.59; S, 11.27.

*Benzyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-*L*-mannopyranoside* (**32**). — To a solution of acetic anhydride (17 mL) in pyridine (22 mL), cooled to 0°, was added L-mannose (2 g) portionwise, with stirring. The mixture was stirred for 2 h at 0°, and the resulting solution was kept for 48 h at 5°, poured into ice–water, and extracted with dichloromethane; the extracts were combined, and evaporated, and traces of pyridine and acetic acid were removed by several coevaporations with toluene. The syrup obtained was dissolved in dichloromethane (25 mL) and treated with 31% hydrogen bromide in acetic acid (12 mL) for 3 h at room temperature. The mixture was then diluted with dichloromethane (20 mL), washed three times with ice–water, dried (sodium sulfate), and evaporated, to afford tetra-*O*-acetyl-α-L-mannopyranosyl bromide (5 g) as a chromatographically homogeneous syrup. A solution of the bromide and thiourea (1 g) in dry acetone (15 mL) was boiled under reflux for 3 h, cooled, and evaporated; the residue was dissolved in water (15 mL) and the solution washed twice with diether ether. To the aqueous layer were added potassium carbonate (1.15 g), potassium pyrosulfite (1.3 g), and a solution of α-bromotoluene (1 mL) in acetone (15 mL). The mixture was stirred for 2 h at room temperature, concentrated, and extracted with dichloromethane (3 × 25 mL), and the extracts were combined, washed with water, and evaporated. The residue was applied to a column of silica gel that was eluted with 30:1 chloroform–ethyl acetate. Pure **32** was obtained as a solid that was recrystallized from ethanol; yield 1.8 g; m.p. 136–137.5°, $[\alpha]_D^{27}$ −159° (*c* 1, chloroform); the 300-MHz, n.m.r. spectrum of **32** in benzene-d_6 was identical with that of **16**.

Anal. Found: C, 55.37; H, 5.73; S, 7.20.

*Benzyl 1-thio-α-*L*-mannopyranoside* (**33**). — To a solution of **32** (600 mg) in

dry methanol (20 mL) was added a catalytic amount of sodium methoxide. The mixture was kept overnight at room temperature, and processed in the usual way, to afford pure **33** as a syrup that crystallized upon standing. A quantitative yield was obtained; m.p. 104–107.5°, $[\alpha]_D^{27}$ −347° (*c* 0.5, methanol).

Anal. Calc. for $C_{13}H_{18}O_5S$ (286.34): C, 54.53; H, 6.34; S, 11.20. Found: C, 54.60; H, 6.36; S, 11.04.

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