Direct Stereoselective Synthesis of β-Thiomannosides

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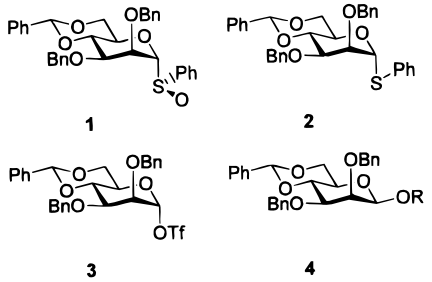
A highly diastereoselective synthesis of β-thiomannopyranosides is described in which *S*-phenyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-deoxy-1-thia-α-D-mannopyranoside *S*-oxide is treated with triflic anhydride and 2,6-di-*tert*-butyl-4-methylpyridine in CH_2Cl_2 at −78 °C leading to the formation of an intermediate α-mannosyl triflate. Addition of primary, secondary, or tertiary thiols then leads to the β-thiomannosides, by an S_N2-like displacement, in good yield and with excellent stereoselectivity. Deprotection is achieved either by Birch reduction or by Zemplen deacetylation, of the acetyl protected aglycons, followed by hydrogenolysis over Pearlman's catalyst. The assignment of configuration of the β-thiomannopyranosides is discussed in terms of the chemical shift of the mannose H5 resonance and the $^1J_{CH}$ of the mannose anomeric carbon.

Introduction

Recently, we have shown how Kahne's sulfoxide glycosylation method[1−3] can be adapted to permit the direct formation of the elusive β-mannopyranosides.[4−9] In this method, a mannosyl sulfoxide (**1**),[10−12] or the corresponding thiomannoside (**2**),[11,13] is activated at −78 °C with triflic anhydride or benzenesulfenyl triflate, respectively, with formation of an α-mannosyl triflate **3**.[14,15] Subsequent addition of an alcohol, primary, secondary, or tertiary, provokes an S_N2-like displacement resulting, overall, in the formation of the β-mannoside **4** in a highly stereoselective manner. A priori replacement of the alcohol as nucleophile by a thiol should lead to the formation of β-thiomannosides and, given the enhanced nucleophilicity of thiols over alcohols, do so with even greater β-selectivity. However, this extension of the original method is not necessarily as trivial as it appears at first sight. Activation of the sulfoxide **1** with triflic anhydride must lead to the formation of highly electrophilic sulfenic and/or sulfinic acid derivatives.[15,16] One of these, benzenesulfenyl triflate, was demonstrated to react quantitatively with **1** or **2** within in a matter of minutes at −78 °C, fortuitously, with formation of the key triflate intermediate **3**.[11,13,14] If such species are able to activate the thioglycoside or sulfoxide so rapidly, then it would seem likely they might compete effectively with the triflate **3** for capture of the thiol introduced as nucleophile. Moreover, early experiments by the Vernon and Overend groups showed that while displacement of halide from 2,3,4,6-tetra-*O*-methylglucopyranosyl chloride and 2,3,4,6-tetra-*O*-acetylglucopyranosyl bromide by thiolates was bimolecular and led cleanly to the β-thioglucosides, the corresponding reactions in the mannose series did not depend on thiolate concentration and gave complex reaction mixtures.[17,18] Finally, although thioglycosides are most commonly thought of in terms of convenient, shelf-stable glycosyl donors,[19] they also have significant potential as competitive inhibitors of oligosaccharide processing enzymes, which renders methods for their diastereoselective synthesis all the more important.[20,21]



Results and Discussion

Activation of the sulfoxide **1**,[22] in the presence of 2,6-di-(*tert*-butyl)-4-methylpyridine (DTBMP), with triflic anhydride at −78 °C followed by addition of 2 equiv of octane thiol (**5**) and gradual warming to 0 °C gave, after extraction and chromatography over silica gel, the β-thio-

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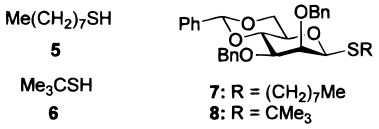
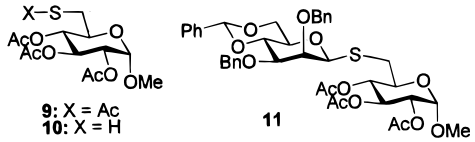
Table 1. Synthesis of β-Thiomannosides

entry	acceptor	product	% yield
1	**5**	**7**	74
2	**6**	**8**	77
3	**10**	**11**	69
4	**14**	**15**	61
5	**18**	**19**	63

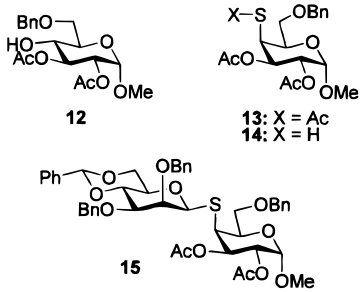
mannoside (**7**) in 74% isolated yield (Table 1, entry 1). Importantly, there was no indication of competing formation of the α-anomer in this reaction. Replacement of octane thiol by *tert*-butyl thiol (**6**) also gave an excellent yield of the corresponding, pure β-thiomannoside (**8**) (Table 1, entry 2). Our concerns about potential side reactions with byproducts from the activation were evidently unfounded, and we therefore turned to the synthesis, and application, of more appropriate primary and secondary carbohydrate-based thiols as nucleophiles.



Mitsunobu[23,24] coupling of methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside with thioacetic acid gave the thiol ester **9** in 79% yield, which, on exposure to hydrazine hydrate, provided the primary thiol **10** in 71% yield. Coupling of this thiol with sulfoxide **1**, following activation by Tf_2O, provided the disaccharide **11** in 69% yield (Table 1).



A similar Mitsunobu reaction/selective deacetylation sequence applied to the glucoside **12**[25] provided the galacto-thioacetate **13** and the thiol **14**. Coupling of **14** with the sulfoxide **1** by the standard protocol afforded the β-thiomannoside **15** in 61% yield (Table 1).

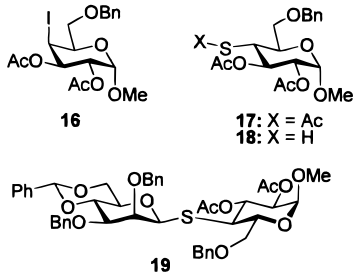


Reaction of **12** with triphenylphosphine and iodine in the presence of imidazole provided the galactoiodide **16**, which, on exposure to potassium thioacetate in DMF, afforded the glucothioacetate **17**. Treatment of **17** with hydrazine hydrate led to the thiol **18**, which was coupled with **1**, by the standard protocol, giving **19** in 63% yield (Table 1).

Table 2. Diagnostic NMR Data[a]

substance	anomeric configuration	solvent	δ H1	δ H5	$^1J_{C,H}$ (Hz)
7	β	$CDCl_3$	4.62	3.40	150.4
8	β	$CDCl_3$	4.73	3.43	149.3
11[a]	β	$CDCl_3$	4.73	3.38	153.7
15[a]	β	$CDCl_3$	4.52	3.25	153.7
19[a]	β	$CDCl_3$	4.71	3.37	151.6
21	β	MeOH-d_4	4.69	3.22	151.2
22	β	MeOH-d_4	4.80	3.25	149.5
2	α	$CDCl_3$	5.51	4.30	166.8
20	α	$CDCl_3$	5.35	4.25	165.7

[a] Data for the mannose system



In none of the above coupling reactions were we able to find evidence for the formation of the α-anomers in the ^1H and ^{13}C NMR spectra of the crude reaction mixtures, within the limits of detection, as determined by the absence of the characteristic downfield anomeric protons of authentic α-thiomannosides (Table 2). The coupling reactions were therefore very highly β-selective. The yields, while less than perfect, are good and sufficient for most practical purposes; several unidentified byproducts made up the mass balance.

The assignment of anomeric stereochemistry in the mannose series can be problematic owing to the similarity between the $^3J_{H1,H2}$ coupling constants in the α- and β-series. Evidently, for the β-anomer the stereochemistry may be established unambiguously by the observation of nuclear Overhauser interactions between the anomeric hydrogen and H3 and H5.[26] Indeed, noesy spectroscopy was used to confirm the configurations of **11**, **15**, **21** and **22**. The accepted method in the field, however, relies on the magnitude of the $^1J_{C,H}$ coupling between the anomeric carbon and its attached proton. In the *O*-glycosides, the α-anomer has a numeric value of around 173 Hz, while in the β-series 163 Hz is typical.[27] In addition, we have noted that in the 4,6-*O*-benzylidene-protected β-mannosides the mannose H5 occurs as an unusually upfield multiplet consistently resonating between δ 3.1 and 3.3 in $CDCl_3$ solution.[11] In the case of the β-thiomannosides prepared here we again observed the mannose H5 to resonate somewhat upfield in the region δ 3.25−3.43, in $CDCl_3$, as opposed to δ 4.25−4.35 the chemical shift of H5 in the authentic α-thiomannosides **2** and **20** (Table

(22) Sulfoxide **1** is a single diastereomer at sulfur,[11] most likely with configuration S_R.[12] The highly diastereoselective oxidation of the thioglycoside precursor is likely to be a consequence of the exo-anomeric effect which, in the β-series with the axial C−S bond, projects the *pro-S* lone pair underneath the pyranose ring and so renders it sterically inaccessible.[12] On the basis of the extensive work of Kahne with mixed diastereomeric sulfoxides in the β-series, it is unlikely that the configuration at sulfur is of consequence in the ensuing chemistry.[1−3]

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(26) The ^1H NMR spectra of all of the various thioglycosides presented here were sufficiently well-resolved as to enable full assignments to be made by the usual methods.

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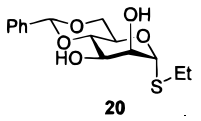
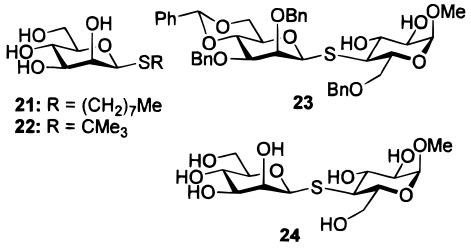
2). We suggest that, provided the pyranose is locked in



20

the $^4C_1$-chair system by the 4,6-*O*-benzylidene group, an H5 resonance in this region will be sufficient and diagnostic for the β-thiomannosides. However, we also investigated the $^1J_{C,H}$ coupling constants and find that, as with the *O*-glycosides, the numerical value is around 10−15 Hz smaller in the β- than in the α-series (Table 2). Both the α- and β-$^1J_{C,H}$ coupling constants are somewhat smaller than in the corresponding *O*-glycosides but a change of this nature is not unexpected given the replacement of the C−O by a C−S bond.[28]

Finally, deprotection of selected thioglycosides was explored. The simple *S*-alkyl substances **7** and **8** proved somewhat resistant to hydrogenolysis at ambient temperature and pressure over both Pd/C and $Pd(OH)_2$, and the use of more forcing conditions led to competing degradation. These compounds were therefore deprotected, following the example of Pinto and co-workers,[29] by Birch reduction, which gave **21** and **22** in excellent yield. A further example (**19**) was first exposed to catalytic sodium methoxide in methanol (Zemplen deacetylation), which provided **23** in 56% yield, followed by hydrogenolysis over Pearlman's catalyst leading to the isolation of **24** in 43% yield.



21: R = $(CH_2)_7Me$
22: R = CMe_3

23

24

Experimental Section

Unless otherwise stated, ^1H and ^{13}C NMR spectra were recorded as $CDCl_3$ solutions and have chemical shifts (δ) downfield from tetramethylsilane. Specific rotations are for $CHCl_3$ solutions unless otherwise stated. All solvents were dried and distilled by standard methods. All reactions were conducted under an atmosphere of dry N_2 or Ar. Microanalyses were carried out by Midwest Microlabs, Indianapolis.

Methyl 2,3,4-Tri-*O*-acetyl-6-acetylthio-α-D-glucopyranoside (9). Methyl 2,3,4-tri-*O*-acetyl-α-D-glucpyranoside (0.357 g, 1.11 mmol) and PPh_3 (0.443 g, 1.67 mmol, 1.5 equiv) were dissolved in THF (20 mL) at room temperature, and DEAD (0.200 g, 0.18 mL, 1.67 mmol, 1.5 equiv) was added dropwise. After 10 min, thioacetic acid (0.177 g, 0.17 mL, 2.22 mmol, 2.0 equiv) was added slowly, following which the reaction mixture was stirred overnight at room temperature. After consumption of the starting material, the reaction mixture was diluted with ethyl acetate and washed with saturated $NaHCO_3$ and water, and the water phase was extracted with ethyl acetate. The combined organic phase was washed with water and then brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/hexane 1/1) to give **9** (0.329 g, 0.87 mmol, 79%): $[\alpha]_D = +80.8°$ (*c*, 5.5); ^1H NMR δ 1.92 (s, 3 H), 1.98 (s, 3 H), 2.00 (s, 3 H), 2.27 (s, 3 H), 2.99 (dd, *J* = 14.2, 6.9 Hz, 1 H), 3.12 (dd, *J* = 14.2, 3.0 Hz, 1 H), 3.32 (s, 3 H), 3.84 (ddd, *J* = 9.9, 6.9, 3.0 Hz, 1 H), 4.70−4.83 (m, 2 H), 4.86 (t, *J* = 9.6 Hz, 1 H), 5.35 (t, *J* = 9.6 Hz, 1 H); ^{13}C NMR δ 20.7, 30.0, 30.4, 55.4, 68.2, 70.0, 70.9, 96.6, 169.9, 170.0, 170.1, 194.6. Anal. Calcd. for $C_{15}H_{22}O_9S \cdot 0.5H_2O$: C, 46.51; H, 5.98. Found: C, 46.55; H, 5.93.

Methyl 2,3,4-Tri-*O*-acetyl-6-thio-α-D-glucopyranoside (10). 9 (0.329 g, 0.87 mmol) was dissolved in DMF (10 mL) at room temperature, and $N_2H_4 \cdot H_2O$ (0.019 g, 1.54 mmol, 1.77 equiv) was added slowly. After 5−10 min, CH_3CO_2H (0.0945 g, 1.54 mmol, 1.77 equiv) was added dropwise. After consumption of the starting material (∼20 min), the reaction mixture was diluted with ethyl acetate and washed with water, and the water phase was extracted with ethyl acetate. The combined organic phase was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/hexane 1/1) to give **10** as a glass (0.2098 g, 0.62 mmol, 72%): $[\alpha]_D = +128.2°$ (*c*, 3.1); ^1H NMR δ 1.74 (t, *J* = 8.4 Hz, 1 H), 2.00 (s, 3 H), 2.04 (s, 3 H), 2.07 (s, 3 H),2.58−2.70 (m, 2 H), 3.45 (s, 3 H), 3.87 (m, 1 H), 4.87 (dd, *J* = 10.2, 3.7 Hz, 1 H), 4.94 (d, *J* = 3.7 Hz, 1 H), 4.99 (t, *J* = 9.6 Hz, 1 H), 5.47 (t, *J* = 9.8 Hz, 1 H); ^{13}C NMR δ 20.8, 26.1, 55.5, 69.6, 70.1, 71.0, 71.3, 96.6, 169.9, 170.1, 170.2. Anal. Calcd for $C_{13}H_{20}O_8S$: C, 46.42; H, 5.99. Found: C, 46.10; H, 6.05.

Methyl 2,3-Di-*O*-acetyl-4-acetylthio-6-*O*-benzyl-α-D-galactopyranoside (13). The yellowish syrup **13** was prepared similarly to **9** in 54% yield: $[\alpha]_D = +71.7°$ (*c*, 1.3); ^1H NMR δ 1.94 (s, 3 H), 2.07 (s, 3 H), 2.34 (s, 3 H), 3.39 (s, 3 H), 3.45−3.67 (m, 2 H), 4.25−4.50 (m, 3 H), 4.56 (d, *J* = 12.1 Hz, 1 H), 4.88−5.05 (m, 2 H), 5.51 (dd, *J* = 10.0, 4.3 Hz, 1 H), 7.20−7.50 (m, 5 H); ^{13}C NMR δ 20.9, 21.0, 30.9, 47.4, 55.4, 67.9, 68.2, 69.8, 70.1, 73.5, 97.3, 127.7, 127.8, 128.5, 138.0, 169.9, 170.5, 194.0. Anal. Calcd for $C_{20}H_{26}O_8S$: C, 56.33; H, 6.14. Found: C, 56.13; H, 6.18.

Methyl 2,3-Di-*O*-acetyl-6-*O*-benzyl-4-thio-α-D-galactopyranoside (14). The preparation of **14** followed that of **10** and gave a 71% yield: $[\alpha]_D = +128.3°$ (*c*, 2.0); ^1H NMR δ 1.49 (d, *J* = 8.5 Hz, 1 H), 2.09 (s, 6 H), 3.37 (s, 3 H), 3.58−3.78 (m, 3 H), 4.32 (m, 1 H), 4.52 (d, *J* = 12.0 Hz, 1 H), 4.60 (d, *J* = 12.0 Hz, 1 H), 4.96 (d, *J* = 3.7 Hz, 1 H), 5.19 (dd, *J* = 10.6, 3.7 Hz, 1 H), 5.31 (dd, *J* = 10.6, 4.5 Hz, 1 H), 7.20−7.42 (m, 5 H); ^{13}C NMR δ 20.6, 20.7, 42.4, 55.1, 67.5, 68.3, 69.3, 70.0, 73.3, 97.0, 127.5, 127.6, 128.3, 137.8, 169.8, 170.1. Anal. Calcd for $C_{18}H_{24}O_7S$: C, 56.24; H, 6.29. Found: C, 56.09; H, 6.35.

Methyl 2,3-Di-*O*-acetyl-6-*O*-benzyl-4-iodo-α-D-galactopyranoside (16). 12 (1.725 g, 4.68 mmol), I_2 (3.563 g, 14.04 mmol, 3.0 equiv), PPh_3 (4.960 g, 18.72 mmol, 4.0 equiv), and imidazole (1.287 g, 18.72 mmol, 4.0 equiv) were added into THF (80 mL) at room temperature, and the ensuing mixture was stirred at 80 °C overnight. When the starting material disappeared, the reaction mixture was cooled to room temperature, diluted with toluene, and washed successively with saturated $NaHCO_3$, 5% sodium thiosulfate, and water. The water phase was extracted with ethyl acetate, and the combined organic phase was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/hexane 1/1) to give **16** as a white solid (2.014 g, 4.21 mmol, 90%): mp 44−46 °C; $[\alpha]_D = +118.8°$ (*c*, 1.7); ^1H NMR δ 2.08 (s, 3 H), 2.10 (s, 3 H), 3.39 (s, 3 H), 3.42−3.70 (m, 3 H), 4.49−4.63 (m, 3 H), 4.77 (dd, *J* = 4.1, 1.4 Hz, 1 H), 4.95 (d, *J* = 3.8 Hz, 1 H), 5.18 (dd, *J* = 10.4, 3.8 Hz, 1 H), 7.24−7.40 (m, 5 H); ^{13}C NMR δ 21.0, 21.1, 37.4, 55.5, 66.9, 68.5, 70.8, 73.8, 74.0, 97.3, 127.9, 128.0, 128.6, 137.9, 170.0, 170.3. Anal. Calcd for $C_{18}H_{23}O_7I$: C, 45.20; H, 4.85. Found: C, 44.96; H, 4.82.

Methyl 2,3-Di-*O*-acetyl-4-acetylthio-6-*O*-benzyl-α-D-glucopyranoside (17). 16 (1.478 g, 3.09 mmol) and potassium thioacetate (1.44 g, 12.4 mmol, 4.0 equiv) were dissolved in DMF (45 mL) at room temperature, and the reaction mixture was stirred at 90 °C for 2 h. After the starting material was consumed, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and washed with water. The

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water phase was extracted with ethyl acetate, and the combined organic phase was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/hexane 1/3−1/2) to give **17** (0.870 g, 2.04 mmol, 66%) as a yellowish syrup: $[\alpha]_D = +114.8°$ (*c*, 3.2); ^{1}H NMR δ 1.99 (s, 3 H), 2.05 (s, 3 H), 2.27 (s, 3 H), 3.45 (s, 3 H), 3.64 (m, 2 H), 3.75 (t, $J = 11.1$ Hz, 1 H), 3.92−4.03 (m, 1 H), 4.54 (AB quartet, $J = 13.4$, 12.3 Hz, 2 H), 4.91 (dd, $J = 9.9$, 3.6 Hz, 1 H), 4.99 (d, $J = 3.6$ Hz, 1 H), 5.46 (dd, $J = 11.1$, 9.9 Hz, 1 H), 7.21−7.42 (m, 5 H); ^{13}C NMR δ 20.7, 20.8, 30.7, 44.3, 55.4, 68.8, 69.5, 69.7, 72.3, 73.6, 97.0, 127.7, 127.8, 128.4, 138.0, 170.0, 170.2, 192.9. Anal. Calcd for $C_{20}H_{26}O_8S$: C, 56.33; H, 6.14. Found: C, 56.19; H, 6.22.

Methyl 2,3-Di-O-acetyl-6-*O*-benzyl-4-thio-α-D-glucopyranoside (18). The preparation of **18** followed that of **10** and gave a 65% yield: $[\alpha]_D = +94.2°$ (*c*, 1.6); ^{1}H NMR δ 1.37 (d, $J = 8.5$ Hz, 1 H), 2.05 (s, 3 H), 2.08 (s, 3 H), 3.08 (dd, $J = 20.1$, 10.4 Hz, 1 H), 3.39 (s, 3 H), 3.76 (dd, $J = 11.2$, 1.8 Hz, 2 H), 3.92 (m, 1 H), 4.53 (d, $J = 12.1$ Hz, 1 H), 4.66 (d, $J = 12.1$ Hz, 1 H), 4.85 (dd, $J = 10.0$, 3.6 Hz, 1 H), 4.97 (d, $J = 3.6$ Hz, 1 H), 5.28 (t, $J = 10.4$ Hz, 1 H), 7.22−7.40 (m, 5 H); ^{13}C NMR δ 20.7, 40.6, 55.5, 69.2, 72.2, 73.1, 73.8, 97.4, 128.0, 128.6, 138.1, 170.4. Anal. Calcd for $C_{18}H_{24}O_7S$: C, 56.24; H, 6.29. Found: C, 56.45; H, 6.39.

General Procedure for Coupling Reactions. Sulfoxide and DTBMP (2.0 equiv) were dissolved in CH_2Cl_2 (0.02−0.04 M in **1**), and Tf_2O (1.1 equiv) was added dropwise at −78 °C. After the mixture was stirred for 10−20 min, a CH_2Cl_2 solution of the thiol acceptor (2.0 equiv) was added slowly. The reaction mixture was then stirred for a further 2 h at −78 °C, then the temperature was increased to 0 °C over 1−2 h, and stirring was continued at 0 °C for another 0.5 h before the reaction was quenched with saturated $NaHCO_3$. The reaction mixture was diluted with ethyl acetate and washed with water, the aqueous phase was extracted with ethyl acetate, and the organic phases were combined and washed with water and brine, dried ($MgSO_4$), concentrated, and purified by flash chromatography on silica gel.

***S*-Octyl 2,3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-mannopyranoside (7):** yield 74%; yellowish syrup; $[\alpha]_D = -43.7°$ (*c*, 0.8); ^{1}H NMR δ 0.88 (t, $J = 6.9$ Hz, 3 H), 1.20−1.44 (m, 10 H), 1.58 (m, 2 H), 2.67 (t, $J = 7.3$ Hz, 2 H), 3.40 (m, 1 H), 3.72 (dd, $J = 9.9$, 3.2 Hz, 1 H), 3.91 (t, $J = 10.4$ Hz, 1 H), 4.00 (d, $J = 3.2$ Hz, 1 H), 4.27 (m, 2 H), 4.62 (s, 1 H), 4.72 (d, $J = 12.4$ Hz, 1 H), 4.78−4.95 (m, 2 H), 5.02 (d, $J = 11.3$ Hz, 1 H), 5.63 (s, 1 H), 7.20−7.60 (m, 15 H); ^{13}C NMR δ 14.3, 22.9, 29.0, 29.4, 30.2, 32.0, 32.1, 68.7, 72.1, 73.2, 75.9, 78.8, 79.0, 80.0, 86.5, 101.6, 126.3, 127.8, 127.9, 128.3, 128.4, 128.6, 128.8, 129.1, 137.8, 138.3, 138.6. Anal. Calcd for $C_{35}H_{44}O_5S$: C, 72.88; H, 7.69. Found: C, 72.77; H, 7.74.

***S*-*tert*-Butyl 2,3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-mannopyranoside (8):** yield 77%; yellowish syrup; $[\alpha]_D = -48.6°$ (*c*, 4.1); ^{1}H NMR δ 1.36 (s, 9 H), 3.43 (m, 1 H), 3.76 (dd, $J = 9.8$, 3.1 Hz, 1 H), 3.90 (t, $J = 10.3$ Hz, 1 H), 4.01(d, $J = 2.1$ Hz, 1 H), 4.18−4.32 (m, 2 H), 4.68−4.78 (m, 2 H), 4.80 (d, $J = 11.1$ Hz, 1 H), 4.86 (d, $J = 12.5$ Hz, 1 H), 5.01 (d, $J = 11.1$ Hz, 1 H), 5.62 (s, 1 H), 7.25−7.55(m, 15 H); ^{13}C NMR δ 31.8, 43.5, 68.8, 71.9, 73.1, 76.1, 79.0, 80.0, 80.2, 83.7, 101.6, 126.3, 127.7, 127.8, 128.3, 128.4, 128.6, 128.7, 129.1, 129.4, 129.5, 131.8, 135.6, 137.8, 138.4, 138.7. Anal. Calcd for $C_{31}H_{36}O_5S\cdot H_2O$: C, 69.12; H, 7.11. Found: C, 69.11; H, 6.80.

Methyl 2,3,4-tri-*O*-acetyl-6-*S*-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranosyl)-6-thio-α-D-glucopyranoside (11): yield 69%; glass; $[\alpha]_D = +32.0°$ (*c*, 0.6); ^{1}H NMR δ 2.00 (s, 3 H), 2.02 (s, 3 H), 2.08 (s, 3 H), 2.72−2.82 (m, 2 H), 3.35 (s, 3 H), 3.31−3.47 (m, 1 H), 3.71 (dd, $J = 9.8$, 3.0 Hz, 1 H), 3.84−3.96 (m, 2 H), 3.98 (d, $J = 2.6$ Hz, 1 H), 4.20−4.34 (m, 2 H), 4.71 (m, 2 H), 4.77 (d, $J = 11.2$ Hz, 1 H), 4.83−4.98 (m, 4 H), 5.02 (d, $J = 11.2$ Hz, 1 H), 5.43 (t, $J = 9.4$ Hz, 1 H), 5.62 (s, 1 H), 7.21−7.56 (m, 15 H); ^{13}C NMR δ 20.9, 21.0, 32.8, 55.6, 68.6, 69.9, 70.2, 71.2, 72.1, 72.2, 73.5, 75.9, 78.7, 79.0, 80.1, 87.0, 96.7, 101.7, 126.3, 127.9, 128.0, 128.3, 128.4, 128.6, 128.9, 129.1, 137.8, 138.2, 138.6, 170.1, 170.2, 170.4. Anal. Calcd for $C_{40}H_{46}O_{13}S$: C, 62.65; H, 6.05. Found: C, 62.62; H, 6.09.

Methyl 2,3-di-*O*-acetyl-6-*O*-benzyl-4-*S*-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranosyl)-4-thio-α-D-galactopyranoside (15): yield 61%; glass; $[\alpha]_D = +32.6°$, (*c*, 0.3); ^{1}H NMR δ 1.91 (s, 3 H), 2.10 (s, 3 H), 3.24 (m, 1 H), 3.40 (s, 3 H), 3.59 (dd, $J = 9.7$, 3.0 Hz, 2 H), 3.71 (dd, $J = 10.5$, 4.3 Hz, 1 H), 3.80 (m, 2 H), 3.99 (d, $J = 2.6$ Hz, 1 H), 4.12 (dd, $J = 10.5$, 4.9 Hz, 1 H), 4.22 (t, $J = 9.5$ Hz, 1 H), 4.34 (m, 1 H), 4.52 (m, 1 H), 4.52 (d, $J = 12.1$ Hz, 1 H), 4.59 (d, $J = 12.1$ Hz, 1 H), 4.70 (d, $J = 12.4$ Hz, 1 H), 4.83 (d, $J = 10.9$ Hz, 1 H), 4.86 (d, $J = 12.4$ Hz, 1 H) 4.98 (d, $J = 3.8$ Hz, 1 H), 5.03 (d, $J = 10.9$ Hz, 1 H), 5.19 (dd, $J = 10.6$, 3.8 Hz, 1 H), 5.44 (dd, $J = 10.6$, 4.1 Hz, 1 H), 5.59 (s, 1 H), 7.18−7.52 (m, 20 H); ^{13}C NMR δ 21.0, 21.1, 48.9, 55.4, 68.4, 69.2, 69.7, 70.9, 71.3, 72.3, 73.3, 73.5, 76.3, 77.4, 78.8, 78.9, 79.6, 86.5, 97.2, 101.6, 126.2, 127.6, 127.8, 127.9, 128.0, 128.6, 128.7, 129.1, 137.6, 138.0, 138.4, 169.9, 170.6. Anal. Calcd for $C_{45}H_{50}O_{12}S\cdot 1.5H_2O$: C, 64.19; H, 6.34. Found: C, 64.22; H, 6.08.

Methyl 2,3-di-*O*-acetyl-6-*O*-benzyl-4-*S*-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranosyl)-4-thio-α-D-glucopyranoside (19): 63% yield; $[\alpha]_D = +4.1°$ (*c*, 0.5); ^{1}H NMR δ 1.99 (s, 3 H), 2.08 (s, 3 H), 3.03 (t, $J = 10.7$ Hz, 1 H), 3.39 (s, 3 H), 3.30−3.52 (m, 1 H), 3.74 (dd, $J = 9.9$, 3.0 Hz, 1 H), 3.78−3.92 (m, 3 H), 3.93 (d, $J = 2.2$ Hz, 1 H), 4.04 (dd, $J = 10.7$, 3.7 Hz, 1 H), 4.11−4.28 (m, 2 H), 4.54 (d, $J = 12.0$ Hz, 1 H), 4.60 (d, $J = 12.0$ Hz, 1 H), 4.73 (m, 2 H), 4.80−5.00 (m, 5 H), 5.47 (t, $J = 10.7$ Hz, 1 H), 5.59 (s, 1 H), 7.19−7.58 (m, 20 H); ^{13}C NMR δ 20.9, 45.6, 55.4, 67.7, 68.5, 69.3, 70.5, 71.7, 72.3, 73.5, 73.6, 75.7, 78.4, 78.6, 80.4, 83.4, 97.2, 101.6, 126.2, 127.6, 127.7, 127.9, 128.2, 128.3, 128.5, 129.1, 137.6, 137.9, 138.3, 170.3, 170.5. Anal. Calcd for $C_{45}H_{50}O_{12}S\cdot 0.5H_2O$: C, 65.60; H, 6.24. Found: C, 65.47; H, 6.13.

***S*-Octyl 1-Thio-α-D-mannopyranoside (21).** Thioglycoside **7** (40.7 mg) was dissolved in THF (2 mL), and liquid ammonia (7 mL) was condensed into the flask. Sodium (∼30 mg) was then added until a persistent blue color was obtained. Solid NH_4Cl (∼0.1 g) was then added, and the solvents were allowed to evaporate under air. The crude reaction mixture was purified by chromatography on silica gel (eluent: EtOAc/hexane 1/1 then $CHCl_3$/MeOH 12/1) to give the title compound (18 mg, 83%) as a colorless oil: $[\alpha]_D = -43.5°$ (*c*, 0.17, MeOH); ^{1}H NMR δ (MeOH-d_4) 0.88 (t, $J = 6.6$ Hz, 3 H), 1.20−1.48 (m, 10 H), 1.62 (m, 2 H), 2.70 (td, $J = 7.3$, 3.3 Hz, 2 H), 3.22 (m, 1 H), 3.45 (dd, $J = 9.4$, 3.3 Hz, 1 H), 3.56 (t, $J = 9.5$ Hz, 1 H), 3.69 (dd, $J = 11.9$, 5.5 Hz, 1H), 3.80−3.95 (m, 2 H), 4.69 (s, 1 H); ^{13}C NMR δ (MeOH-d_4) 14.6, 23.9, 30.1, 30.5 (2 C's), 31.3, 32.3, 33.2, 63.1, 68.5, 74.2, 76.5, 82.5, 86.4; FABHRMS *m*/*z* 331.1556 (calcd for $C_{14}H_{28}O_5SNa$ 331.1555, $M^+ + Na$).

***S*-*tert*-Butyl 1-Thio-β-D-mannopyranoside (22).** Deprotection of **8** with Na in liquid NH_3 analogously to the procedure described above for **21** gave **22** in 80% yield as a colorless oil: $[\alpha]_D = -79.0°$ (*c*, 0.3, MeOH); ^{1}H NMR (MeOH-d_4) δ 1.36 (s, 9 H), 3.25 (m, 1 H), 3.50 (dd, $J = 9.4$, 3.3 Hz, 1 H), 3.58 (t, $J = 9.4$ Hz, 1 H), 3.68 (dd, $J = 11.9$, 5.3 Hz, 1 H), 3.75−3.90 (m, 2 H), 4.80 (d, $J = 0.8$ Hz, 1 H); ^{13}C NMR (MeOH-d_4) δ 32.2, 63.1, 68.4, 72.5, 75.2, 76.6, 82.1, 83.7; FABHRMS *m*/*z* 275.0931 (calcd for $C_{10}H_{20}O_5SNa$ 275.0929, $M^+ + Na$).

Methyl 6-*O*-Benzyl-4-*S*-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranosyl)-4-thio-α-D-glucopyranoside (23). Diacetate **19** (200 mg) was dissolved in freshly distilled MeOH (20 mL) and transferred to a solution of sodium (0.5 mg) in dry MeOH (10 mL). The resulting reaction mixture was stirred at room temperature until TLC indicated completion, after which Dowex 50 cation-exchange resin was added to neutralize the solution to pH 7. The reaction mixture was then filtered, evaporated, and purified by chromatography on silica gel (eluent: EtOAc/hexane 3/1) to give the title compound as an oil (101.3 mg, 57%): $[\alpha]_D = +35.8°$ (*c*, 0.9); ^{1}H NMR ($CDCl_3$) δ 2.27 (d, $J = 7.2$ Hz, 1 H), 2.94 (t, $J = 10.4$ Hz, 1 H), 3.34 (m, 1 H), 3.42 (s, 3 H), 3.59 (dd, $J = 9.8$, 3.0 Hz, 2 H), 3.62−3.75 (m, 3 H), 3.79 (d, $J = 2.0$ Hz, 1 H), 3.83−3.94 (m, 2 H), 4.16−4.34 (m, 2 H), 4.37 (d, $J = 12.1$ Hz, 1 H), 4.54 (s, 1 H), 4.62−4.78 (m, 4 H), 4.85 (d, $J = 3.6$ Hz, 1 H), 4.91 (d, $J = 12.2$ Hz,

1 H), 4.99 (d, J = 11.1 Hz, 1 H), 5.59 (s, 1 H), 7.20−7.54 (m, 20 H); ^{13}C NMR ($CDCl_3$) δ 51.0, 52.4, 55.8, 68.2, 69.5, 70.2, 71.8, 73.1 (2 C's), 73.7 (2 C's), 76.0, 78.5, 80.0, 87.0, 99.6, 101.6, 126.2, 127.8, 128.0, 128.1, 128.4, 128.6, 129.1, 137.5, 137.7, 138.2, 138.5. Anal. Calcd for $C_{41}H_{46}O_{10}S\cdot 0.75H_2O$: C, 66.10; H, 6.43. Found: C, 66.06; H, 6.35.

Methyl 4-*S*-(β-D-Mannopyranosyl)-4-thio-α-D-glucopyranoside (24). Compound **23** (63 mg) was dissolved in anhydrous EtOH (20 mL), treated with $Pd(OH)_2$ (60 mg), and stirred under H_2 at atmospheric pressure for 2 days. Filtration and concentration gave disaccharide **24** as a colorless oil (13.8 mg, 43%): $[\alpha]_D$ = +43.2 (*c* 0.4, MeOH); ^{1}H NMR (MeOH-d_4, 400 MHz) δ 2.75 (t, J = 10.8 Hz, 1 H), 3.20 (m, 1 H), 3.34 (s, 3 H), 3.40 (td, J = 9.5, 3.5 Hz, 2 H), 3.47 (d, J = 9.6 Hz, 1 H), 3.50−3.65 (m, 3 H), 3.79 (m, 2 H), 3.89 (d, J = 3.2 Hz, 1 H), 3.96 (dd, J = 11.8, 1.8 Hz, 1 H), 4.66 (d, J = 3.6 Hz, 1 H), 4.77 (s, 1 H); ^{13}C NMR (CD_3OD) δ 55.8, 63.1, 63.3, 68.5, 72.4, 73.6, 74.5, 74.8, 76.4, 82.9, 84.1, 101.4, 102.7. Anal. Calcd for $C_{13}H_{24}O_{10}S$: C, 41.93; H, 6.50. Found: C, 41.61; H, 6.73.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for **21** and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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