Design and Synthesis of Potential Inhibitors of Golgi Endo-α-mannosidase: 5-Thio-D-glucopyranosyl-α(1→3)-1-deoxymannojirimycin and Methyl 5-Thio-D-glucopyranosyl-α(1→3)-5-thio-α-D-mannopyranoside

Masayuki Izumi, Yoshitomo Suhara, and Yoshitaka Ichikawa*

Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205

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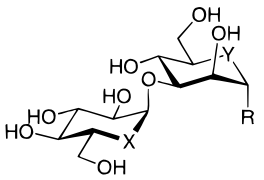
Introduction

At an early stage of the N-linked oligosaccharide biosynthetic pathway, a precursor oligosaccharyl moiety on a nascent polypeptide (**I**) is trimmed to an $Man_8GlcNAc_2$ oligosaccharide structure (**V**) by sequential exoglycosidase reactions in the endoplasmic reticulum (ER)[1,2] that are catalyzed by α-glucosidase I (**I** → **II**), α-glucosidase II (**II** → **III** → **IV**), and ER α-mannosidase I (**IV** → **V**) (Figure 1). It is then transported to the Golgi apparatus and is further processed to yield a $Man_5GlcNAc_2$ structure (**VI**), which leads to mature N-linked oligosaccharides. Each of these exoglycosidase reactions in the ER (**I** through **V**) is known to be blocked by specific inhibitors: castanospermine (CST) and 1-deoxynojirimycin (DNJ) inhibit α-glucosidase I and II, and 1-deoxymannojirimycin (DMJ) inhibits ER α-mannosidase I.[3] However, continual N-linked oligosaccharide formation is still observed in normal cells in the presence of these inhibitors[4] or in α-glucosidase-deficient mutant cells.[5]

The recently identified Golgi endo-α-mannosidase is an unusual enzyme that catalyzes the alternate pathway of N-linked oligosaccharide biosynthesis.[6,7] It cleaves glucosylated mannose (Glc_nMan) residues from the intermediate oligosaccharides (**I**, **II**, or **III**) and leaves the isomeric form of the $Man_8GlcNAc_2$ oligosaccharide structure (**VII**), which is then converted to the common intermediate (**VI**) by Golgi exomannosidases.[2,6,7] This Golgi endo-α-mannosidase has been found to be widely distributed among mammalian cells and is not blocked by commonly used exoglycosidase inhibitors such as CST, DNJ, and DMJ.[6,7] Extensive work by Spohr and Spiro has indicated that a disaccharide analogue Glc-α(1→3)-DMJ **1** can effectively inhibit the Golgi endo-α-mannosidase in vitro with a K_i of 1.5 μM.[8,9] This disaccharide analogue, however, is commonly subjected to hydrolysis by α-glucosidase II when used in cell culture experiments to liberate glucose and DMJ,[9] which are no longer effective against the Golgi endo-α-mannosidase. It is therefore highly desirable to develop an α-glucosidase II-resistant inhibitor of this endo-α-mannosidase in order to allow us to study not only the role of this novel enzyme but also the biological function of N-linked oligosaccharides.

Oligosaccharides containing 5-thio-pyranosyl linkages have been recently prepared and found to be resistant to hydrolysis by exoglycosidases, including α-glucosidase and α-fucosidase.[10−14] They have also been found to adopt a conformation similar to those of their normal 5-oxy-pyranosyl counterparts.[12] We therefore designed a disaccharide analogue of 5-thio-glucosyl-α(1→3)-DMJ **2** in which the α-glucosyl moiety of **1** is replaced by a 5-thio-glucose residue, with the expectation that **2** would not only be resistant to α-glucosidase II but also act as an inhibitor of endo-α-mannosidase. We also synthesized methyl 5-thio-glucosyl-α(1→3)-5-thio-mannoside **3** as another potential inhibitor of the Golgi endo-α-mannosidase and methyl 5-thio-glucosyl-α(1→3)-α-mannoside **4** as a reference compound for these 5-thio-glucosyl disaccharide analogues. In this paper, we describe the detailed synthesis of the disaccharide analogues (**2**, **3**, and **4**) and present a conformational analysis of these analogues with a molecular modeling program.



1 X=O, Y=NH, R=H
2 X=S, Y=NH, R=H
3 X=S, Y=S, R=OMe
4 X=S, Y=O, R=OMe

Results and Discussion

I. Synthesis of Methyl 3-*O*-(5-Thio-α-D-glucopyranosyl)-α-D-mannopyranoside 4. Recent investigation of the glycosylation of 5-thio-aldoses has revealed that the trichloroimidates[15] are effective glycosyl donors

* Corresponding author. Address: Department of Pharmacology and Molecular Sciences, The Johns Hopkins University School of Medicine, 725 North Wolfe St., Baltimore, MD, 21205. Tel: 410-614-2892. Fax: 410-955-3023. E-mail: yoshitaka_ichikawa@qmail.bs.jhu.edu.

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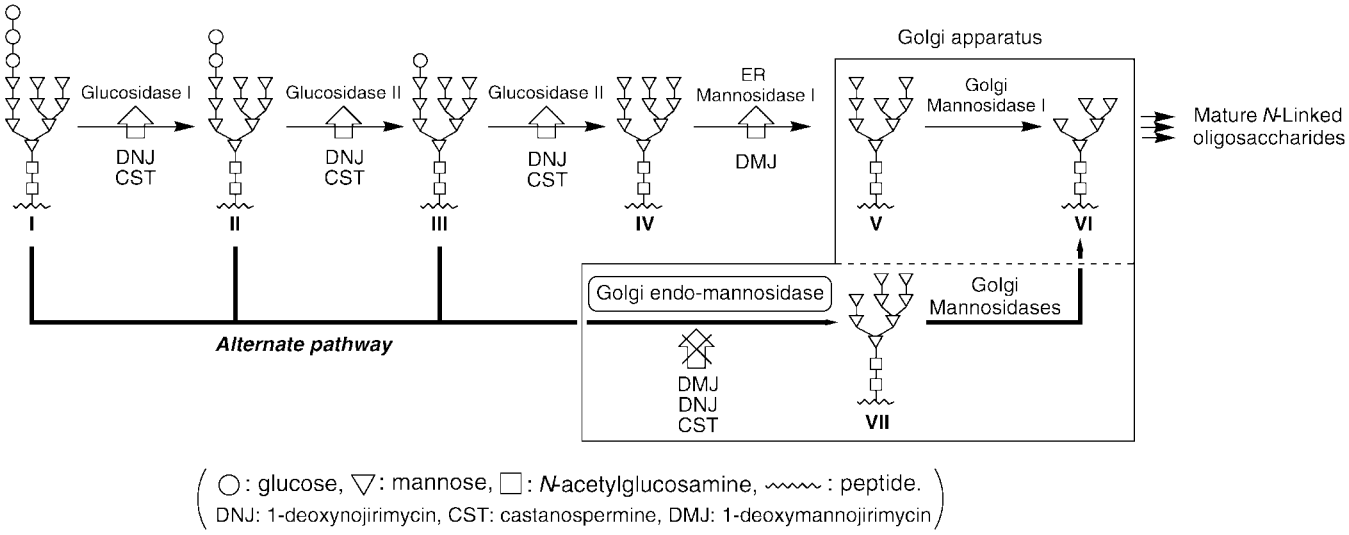
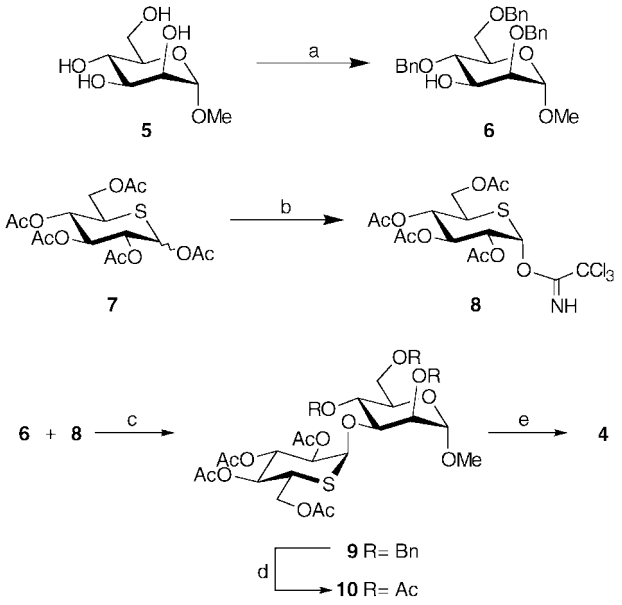


Figure 1. Two biosynthetic pathways of N-linked oligosaccharide.

in the synthesis of 5-thio-pyranosyl oligosaccharides.[11−14,16,17] It is interesting that these glycosylations were also found to form predominantly α-linkages, even though the 2-OH group of the donor was protected with an acetyl group that generally favors *β*-glycoside formation.[11,16] We therefore first examined our general synthetic protocol for the target disaccharide analogues: glycosylation (α-selectivity) and deprotection (O-debenzylation) with the synthesis of methyl 3-*O*-(5-thio-α-D-glucopyranosyl)-α-D-mannopyranoside **4**.

The acceptor mannose derivative, methyl 2,4,6-tri-*O*-benzyl-α-D-mannoside **6**,[18] was prepared in three steps from commercially available methyl α-D-mannoside **5** (Scheme 1). Stannylation of **5** with Bu_2SnO[19] in refluxing MeOH followed by alkylation with 4-methoxybenzyl chloride (MBnCl) in the presence of CsF in DMF gave a 3-*O*-MBn derivative. After benzylation of the remaining OH groups (NaH and BnBr), the MBn group was selectively removed with cerium ammonium nitrate (CAN) in aqueous acetonitrile to give the mannose acceptor **6**. The glycosyl donor trichloroacetimidate **8**[12] was prepared from 5-thio-D-glucose peracetate **7**[20] in the following manner: (i) removal of the anomeric acetate with NH_2NH_2·AcOH[21] (75% yield) and (ii) treatment of the resulting hemiacetal with CCl_3CN and DBU[22] (84% yield). The coupling reaction of **8** and **6** was performed in the presence of a catalytic amount of BF_3·OEt_2 in CH_2Cl_2 at −20 °C and gave a disaccharide analogue **9** in 22% yield. Hydrolysis of the donor imidate was a major side reaction. In the ^{1}H NMR spectrum of **9**, the anomeric proton (H-1′) appeared, as a doublet, at *δ* 5.06 with a small coupling constant of 2.8 Hz, confirming that the newly formed 5-thio-glucosidic linkage was an α-configuration.

Scheme 1[a]



[a] Reagents and conditions. (a) (i) Bu_2SnO/MeOH then MBnCl/CsF/DMF, (ii) NaH/BnBr/DMF, (iii) $(NH_4)_2Ce(NO_3)_6/CH_3CN-H_2O$ (55% overall); (b) (i) NH_2NH_2·AcOH/DMF/60 °C, (ii) CCl_3CN/DBU/CH_2Cl_2 (63%); (c) BF_3·OEt_2/MS4A/CH_2Cl_2/−20 °C (22%); (d) (i) H_2/$Pd(OH)_2$/MeOH, (ii) Ac_2O/pyridine (66%); (e) NaOMe/MeOH (quantitative).

Hydrogenation of a 5-thio-sugar-containing compound over a palladium catalyst (Pd−C) has been reported to be troublesome,[12] and in fact we observed incomplete hydrogenolytic cleavage of the benzyl groups of **9** over Pd−C. We then examined Perlman's catalyst ($Pd(OH)_2$) for O-debenzylation of **9**. Although the reaction was rather sluggish and it was necessary to renew the catalyst, all three benzyl groups were completely removed and the product **10** was isolated in 66% yield after O-acetylation. Finally, the acetyl groups of **10** were removed with methanolic NaOMe to give methyl 5-thio-D-glucopyranosyl-α(1→3)-α-D-mannopyranoside **4** in quantitative yield.

II. Synthesis of 5-Thio-D-glucopyranosyl-α(1→3)-DMJ 2 (Scheme 2). To the best of our knowledge, this is the first synthesis of a disaccharide analogue composed

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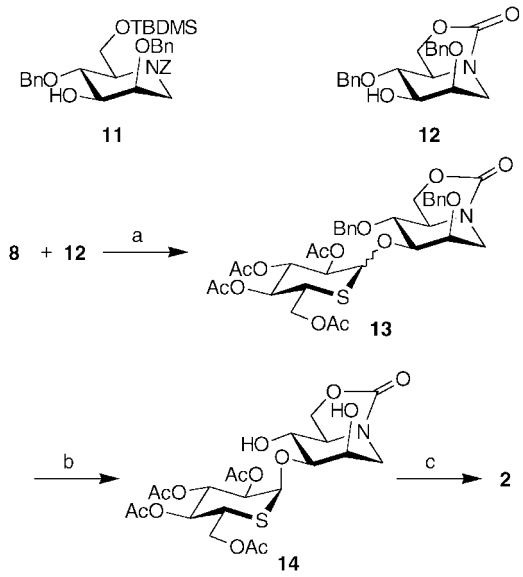
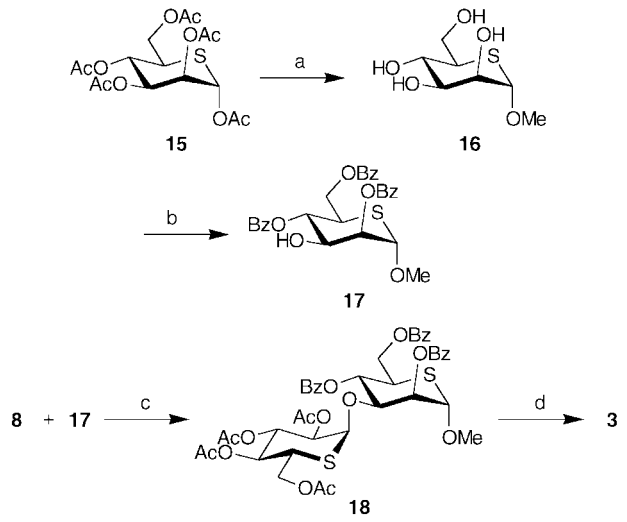
Scheme 2[a]



[a] Reagents and conditions: (a) TMSOTf/MS4A/CH_2Cl_2/−78 °C → rt., then Ac_2O/pyridine (59%); (b) H_2/$Pd(OH)_2$/MeOH (90%); (c) KOH/90% aqueous EtOH/65 °C (63%).

Scheme 3[a]



[a] Reagents and conditions: (a) HCl/MeOH (89%); (b) (i) Bu_2SnO/MeOH then MBnCl/Bu_4NI/CsF/DMF, (ii) BzCl/pyridine−CH_2Cl_2, (iii) $(NH_4)_2Ce(NO_3)_6$/CH_3CN−H_2O (30% overall); (c) TMSOTf/CH_2Cl_2/−78 °C → rt. (38%); (d) NaOMe/MeOH (quantitative).

of a 5-thio-sugar and an azasugar. As an acceptor, the following two DMJ derivatives[23] were examined: a 6-*O*-TBDMS derivative **11** and a 6-*O*,*N*-carbamate derivative **12**.[8b] Glycosylation of **11** with the imidate **8** in the presence of a catalytic amount of BF_3·OEt_2 at low temperature resulted in a complex mixture of products, presumably because the 6-*O*-silyl group could not tolerate the acidic conditions of this reaction. Under the same reaction conditions, the acid-stable carbamate derivative **12** also failed to give a coupling product. We then examined trimethylsilyl trifluoromethanesulfonate (TMSOTf) as an activator.[13] Addition of a catalytic amount of TMSOTf to a mixture of **8** and **12** in CH_2Cl_2 at −78 °C gave a disaccharide analogue **13** in 59% yield as a mixture of α- and *β*-anomers (5:1) judged by ^{1}H NMR. The α-anomer of **13**α was successfully isolated by silica gel chromatography after acetylation of the crude product of the glycosylation reaction in order to eliminate unreacted acceptor **12**, which was recovered in 42% yield as its 3-*O*-acetate. Anomeric configurations of the 5-thio-glucosidic linkages were determined by the ^{1}H NMR spectra. The H-1′ of **13**α was observed as a doublet, at *δ* 5.09 with a small coupling constant of 2.9 Hz, whereas the H-1′ of **13***β* appeared as a doublet at *δ* 4.57 with J = 8.8 Hz.

The benzyl groups of **13**α were removed over Perlman's catalyst ($Pd(OH)_2$) to give **14** in 90% yield. The acetyl and carbamate groups of **14** were simultaneously removed by treatment with KOH in 90% EtOH at 65 °C. The disaccharide analogue **2** was purified by silica gel chromatography (with 2-propanol−water−NH_4OH 7:2:1) and Sephadex G-25 chromatography (with water) and was isolated as an acetate salt in 63% yield. An attempt to isolate the product **2** as an HCl salt resulted in partial decomposition during the course of storage over a week, due to the instability of the 5-thio-sugar linkage to a mineral acid such as HCl.

III. Synthesis of Methyl 3-*O*-(5-Thio-α-D-glucopyranosyl)-5-thio-α-D-mannopyranoside 3 (Scheme 3). To our knowledge, this is the first reported synthesis of a 5-thio-sugar linked to another 5-thio-sugar. For the synthesis of **3**, we employed acyl groups for protection of the OH groups of the acceptor, because they would be more effectively removed by a simple treatment with NaOMe than would benzyl groups by repeated hydrogenation reactions. Treatment of a peracetylated 5-thio-D-mannose **15**[24] with methanolic HCl gave a methyl 5-thio-α-D-mannoside derivative **16**[25] in 89% yield. A series of treatments, (i) regioselective 4-methoxybenzylation of the 3-OH group, (ii) benzoylation of the 2,4,6-OH groups, and (iii) removal of the MBn group with CAN, gave the acceptor **17**. Glycosylation of **8** and **17** in the presence of TMSOTf produced stereoselectively an α-linked disaccharide analogue **18** in 38% yield, along with the unreacted acceptor **17** (69% yield in recovery). The stereochemistry of the newly formed 5-thio-glucosidic linkage was determined as an α-configuration by the ^{1}H NMR spectrum in which the H-1′ appeared as doublet at *δ* 4.94 with J = 3.0 Hz. Deprotection of **18** was accomplished by a single-step treatment with methanolic NaOMe to give **3** in quantitative yield.

IV. Molecular Modeling. To examine our design of inhibitor **2**, we ran a Monte Carlo conformational search for **1** and **2** using the MacroModel molecular modeling program.[26] In molecular modeling studies, an AMBER* force field was used with the GB/SA water model, and the dielectric constant was given a value of 4.0 which has been utilized for conformational study of trisaccharides containing α(1→3) linkage by Imberty et al.[27] Every single conformer found within an energy window of 5 kcal/mol was subjected to a cluster analysis[27] with the XCluster program.[28] All ring atoms and an interglycosidic oxygen atom were used to divide all conformers into

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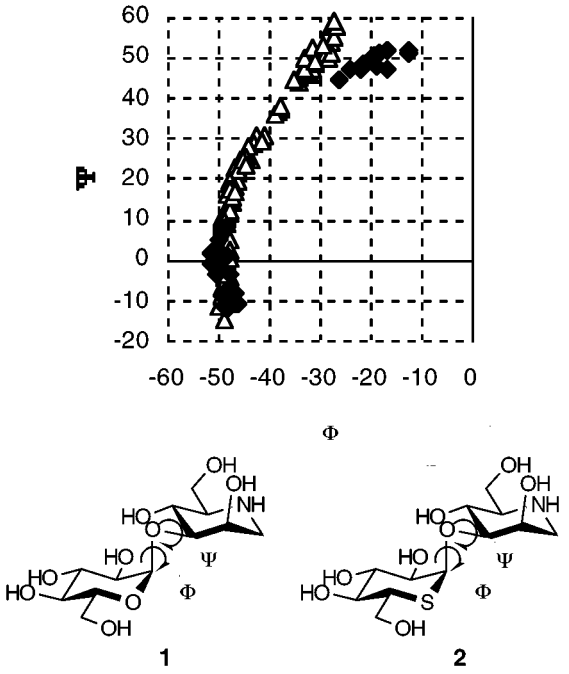

Figure 2. Plot of glycosidic torsions Φ (H1′−C1′−O3−C3) and Ψ (H3−C3−O3−C1′) of (△) **1** and (◆) **2**. All conformers found within an energy window of 5 kcal/mol were plotted.

Figure 3. Superimposition of representative structures of **1** (gray) and **2** (black).

a few clusters. Three clusters were found for **1**, and two were found for **2**. The largest cluster of each compound, 86.7% for **1** and 95.7% for **2**, included a global minimum (**1**, Φ/Ψ = −45°/25°; **2**, Φ/Ψ = −48°/−3°; Φ = H1′−C1′−O3−C3, Ψ = H3−C3−O3−C1′), and a conformer of **1** reported by Spohr et al.[8b] was also in that cluster. Glycosidic torsions Φ and Ψ of those clusters were similar to one another; however, the Ψ angle of **1** was more flexible than that of **2** (Figure 2). Superimposition[29] of each representative structure (**1**, Φ/Ψ = −48°/11°; **2**, Φ/Ψ = −50°/−3°) using essential functional groups for inhibitory activity[8c] suggested that **1** and **2** carry the same functional groups in similar positions (Figure 3) (rms = 0.265 Å).

In summary, three disaccharide analogues terminating in an α(1→3)-5-thio-D-glucosyl residue (**2**, **3**, and **4**) were synthesized. These are the first syntheses of a disaccharide analogue composed of a 5-thio-sugar → azasugar and 5-thio-sugar → 5-thio-sugar. α-Glycosylation of the imidate derivative of acetylated 5-thio-glucose **8** with various acceptors, including derivatives of mannose, 5-thio-mannose, and azasugar, was successfully accomplished in the presence of a catalytic amount of TMSOTf at low temperature. The analogues **2** and **3**, having DMJ and 5-thio-mannopyranoside at the reducing ends, respectively, were designed to be resistant to α-glucosidase II and to be potential inhibitors of an unusual Golgi endo-α-mannosidase that is responsible in the alternate pathway of N-linked oligosaccharide biosynthesis. A stable conformation of **2** was found to be similar to that of its O-glucosyl counterpart **1** on the basis of a conformational search and cluster analysis. Enzyme inhibition assays using these analogues are now in progress.

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Experimental Section

General Methods. NMR spectra were recorded on a Bruker AMX-300 spectrometer. Mass spectra were measured by the Mass Spectrometry Laboratory, University of Illinois at Urbana-Champaign (Urbana, IL). Column chromatography was performed with silica gel (60−200 mesh; Fisher Scientific). Flash column chromatography was performed with Baker silica gel (40 μm; J. T. Baker). Thin-layer chromatography (TLC) was carried out on plates precoated with silica gel 60 F254 (Merck, 5714).

Methyl 2,4,6-Tri-*O*-benzyl-α-D-mannopyranoside (6). A solution of methyl α-D-mannopyranoside **5** (1.0 g, 5.1 mmol) and Bu_2SnO (1.5 g, 6.0 mmol) in MeOH (9 mL) was refluxed for 3 h with vigorous stirring, then cooled and concentrated in vacuo. To a solution of the resulting white powder in DMF (10 mL) were added 4-methoxybenzyl chloride (1.0 mL, 7.4 mmol) and CsF (0.93 g, 6.1 mmol), and the mixture was stirred for 2 days at room temperature. The reaction mixture was concentrated in vacuo, and the residue was chromatographed on silica gel ($CHCl_3$-MeOH 15:1). Fractions containing methyl 3-*O*-(4-methoxybenzyl)-α-D-mannopyranoside were pooled and concentrated. To a cooled solution of the residual syrup in DMF (12 mL) was added NaH (60%; 1.06 g, 27 mmol) at 0 °C, and the mixture was stirred for 30 min. Benzyl bromide (3.4 mL, 29 mmol) was added dropwise to the cooled mixture, and the resulting mixture was stirred for an additional 1 h at room temperature. The reaction mixture was cooled, and MeOH was added carefully to the mixture in order to destroy the excess reagents; the mixture was then extracted with EtOAc. The combined extracts were washed with brine four times, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel (hexanes−EtOAc 8:1 → 7:1) to give methyl 2,4,6-tri-*O*-benzyl-3-*O*-(4-methoxybenzyl)-α-D-mannopyranoside (1.7 g) as a syrup.

A suspension of the 3-*O*-(4-methoxybenzyl) derivative (1.7 g, 2.9 mmol) and $(NH_4)_2Ce(NO_3)_6$ (3.1 g, 5.7 mmol) in CH_3CN−water (9:1, 14.4 mL) was stirred for 20 min at room temperature. The reaction mixture was diluted with $CHCl_3$, washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel (hexanes−EtOAc 5:1) to give **6** (1.3 g, 55% overall yield) as a syrup: ^{1}H NMR ($CDCl_3$) δ 7.37−7.21 (15H, m), 4.85 (1H, d, J = 11.0 Hz), 4.84 (1H, d, J = 1.5 Hz), 4.76 (1H, d, J = 11.7 Hz), 4.68 (1H, d, J = 12.1 Hz), 4.58−4.50 (3H, m), 4.00−3.93 (1H, m), 3.81−3.65 (5H, m), 3.35 (3H, s), 2.32 (1H, d, J = 9.6 Hz).

2,3,4,6-Tetra-*O*-acetyl-5-thio-α-D-glucopyranosyl Trichloroacetimidate (8). A solution of 1,2,3,4,6-penta-*O*-acetyl-5-thio-D-glucopyranose **7** (900 mg, 2.2 mmol) and NH_2NH_2·AcOH (350 mg, 3.8 mmol) in DMF was stirred for 3 h at 60 °C, and the reaction mixture was cooled. The mixture was diluted with EtOAc, washed with brine 3 times, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel (hexanes−EtOAc 12:7) to give 2,3,4,6-tetra-*O*-acetyl-5-thio-D-glucopyranose (600 mg, 75%) as a syrup. To a cooled solution of the product (600 mg, 1.5 mmol) and CCl_3CN (2.2 mL, 22 mmol) was added DBU (32 μL, 0.21 mmol) at 0 °C, and the mixture was stirred overnight. The reaction mixture was directly applied to a silica gel chromatography (hexanes−EtOAc 2:1) to give **8** (700 mg, 84%) as an amorphous powder: ^{1}H NMR ($CDCl_3$) δ 8.70 (1H, brs), 6.36 (1H, d, J = 3.0 Hz), 5.57 (1H, t, J = 9.9 Hz), 5.38 (1H, dd, J = 3.3, 10.1 Hz), 4.39 (1H, dd, J = 4.8, 12.2 Hz), 4.08 (1H, dd, J = 2.9, 12.2 Hz), 3.67−3.62 (1H, m), 2.07, 2.05, 2.02, 2.00 (3H×4, each s).

Methyl 3-*O*-(2,3,4,6-Tetra-*O*-acetyl-5-thio-α-D-glucopyranosyl)-2,4,6-tri-*O*-benzyl-α-D-mannopyranoside (9). A suspension of the trichloroacetimidate **8** (263 mg, 0.518 mmol), the acceptor mannoside **6** (201 mg, 0.432 mmol), and activated

molecular sieves 4A (1.6 g) in anhydrous CH_2Cl_2 was stirred under Ar for 1 h at room temperature and cooled to −20 °C. $BF_3{\cdot}OEt_2$ (4.2 μL) was added to this cooled mixture, and the resulting mixture was stirred for 1 h at −20 °C. The reaction mixture was neutralized with Et_3N and filtered through a Celite pad, and the filtrate was concentrated. The residue was purified by flash column chromatography (hexanes−EtOAc 2:1) to give **9** (93 mg, 22%) as a syrup: ^{1}H NMR ($CDCl_3$) δ 7.43−7.16 (15H, m), 5.63 (1H, t, *J* = 9.9 Hz), 5.27 (1H, dd, *J* = 9.5, 10.8 Hz), 5.18 (1H, dd, *J* = 2.9, 10.3 Hz), 5.06 (1H, d, *J* = 2.8 Hz), 4.93 (1H, d, *J* = 11.5 Hz), 4.86 (1H, d, *J* = 1.7 Hz), 4.81 (1H, d, *J* = 12.1 Hz), 4.74−4.50 (4H, m), 4.16−4.00 (4H, m), 3.77−3.68 (4H, m), 3.43 (1H, ddd, *J* = 3.3, 4.3, 10.9 Hz), 3.38 (3H, s), 2.02, 2.00, 1.99, 1.60 (3H×4, each s); ^{13}C NMR ($CDCl_3$) δ 170.4, 170.1, 169.6, 169.4, 138.5, 138.2, 138.1, 129.9, 128.7, 128.6, 128.4, 128.2, 127.8, 127.6, 127.5, 127.4, 127.3, 127.0, 126.9, 97.7, 81.0, 80.8, 76.6, 74.6, 74.5, 74.4, 73.4, 72.1, 71.7, 71.6, 70.8, 69.0, 61.0, 54.9, 39.0, 20.5, 20.2; HRFABMS calcd for $C_{42}H_{49}O_{14}S$ $(M - H)^+$ 809.2843, found 809.2840.

Methyl 3-*O*-(2,3,4,6-Tetra-*O*-acetyl-5-thio-α-D-glucopyranosyl)-2,4,6-tri-*O*-acetyl-α-D-mannopyranoside (10). A suspension of **9** (93 mg, 0.12 mmol) and 20% $Pd(OH)_2$ on carbon (Perlman's catalyst; 60 mg) in MeOH was stirred under H_2 atmosphere overnight at room temperature. The mixture was filtered through a Celite pad, and the filtrate was concentrated. The residue was hydrogenated under the same conditions three more times until the TLC experiment (hexanes−EtOAc 1:4) indicated that all the benzyl groups were removed. The residue was acetylated with Ac_2O and pyridine and purified by flash column chromatography (hexanes−EtOAc 1:1) to give **10** (50 mg, 66%) as a syrup: ^{1}H NMR ($CDCl_3$) δ 5.38−5.22, (4H, m), 5.01−4.97 (2H, m), 4.71 (1H, s), 4.39 (1H, dd, *J* = 4.8, 12.1 Hz), 4.29 (1H, dd, *J* = 3.6, 9.6 Hz), 4.22 (1H, dd, *J* = 5.5, 12.2 Hz), 4.08 (1H, dd, *J* = 2.7, 12.3 Hz), 4.06 (1H, dd, *J* = 3.0, 12.1 Hz), 3.86 (1H, ddd, *J* = 2.7, 5.4, 10.0 Hz), 3.63 (1H, ddd, *J* = 3.2, 4.5, 10.4 Hz), 3.41 (3H, s), 2.24, 2.11, 2.07, 2.05, 2.04, 2.03, 1.98 (3H×7, each s); ^{13}C NMR ($CDCl_3$) δ 170.6, 170.5, 169.7, 169.4, 98.7, 80.3, 74.8, 73.0, 71.7, 70.3, 69.9, 68.4, 62.5, 61.1, 55.2, 38.7, 20.8, 20.76, 20.72, 20.6, 20.5; HRFABMS calcd for $C_{27}H_{39}O_{17}S$ $(M + H)^+$ 667.1908, found 667.1905.

Methyl 3-*O*-(5-Thio-α-D-glucopyranosyl)-α-D-mannopyranoside (4). A solution of **10** (50 mg, 75 μmol) in MeOH (1.4 mL) and 30% NaOMe in MeOH (24 μL) was allowed to stand overnight at room temperature. The mixture was neutralized with Dowex 50W-X8 $[H^+]$ resin, and the resin was filtered off. The filtrate was concentrated, and the residue was purified on a column of Sephadex G-25 with water. The fractions containing **4** were pooled and concentrated. The residue was lyophilized from water to give **4** (28 mg, quantitative yield) as an amorphous powder: ^{1}H NMR (D_2O) δ 5.16 (1H, d, *J* = 2.7 Hz), 4.77 (1H, brs), 4.19 (1H, dd, *J* = 3.3, 9.5 Hz), 3.98−3.62 (9H, m), 3.44 (3H, s), 3.18−3.11 (1H, m); ^{13}C NMR (D_2O) δ 101.6, 84.6, 78.4, 76.4, 74.7, 74.3, 73.6, 70.7, 67.4, 61.6, 60.8, 55.6, 44.1; HRFABMS calcd for $C_{13}H_{25}O_{10}S$ $(M + H)^+$ 373.1168, found 373.1169.

3-*O*-(2,3,4,6-Tetra-*O*-acetyl-5-thio-α/β-D-glucopyranosyl)-2,4-di-*O*-benzyl-*N*,6-*O*-carbonyl-1,5-dideoxy-1,5-imino-D-mannitol (13). A suspension of **8** (354 mg, 0.695 mmol), 2,4-di-*O*-benzyl-*N*,6-*O*-carbonyl-1,5-dideoxy-1,5-imino-D-mannitol (**12**) (499 mg, 1.35 mmol), and activated molecular sieves 4A (2 g) in anhydrous CH_2Cl_2 (7.9 mL) was stirred for 1 h at room temperature and cooled to −78 °C. TMSOTf (20 μL) was added dropwise to the cooled suspension, and the reaction mixture was gradually warmed to 0 °C in a period of 2 h and stirred for an additional 1 h at room temperature. Pyridine (2 mL) and Ac_2O (1.5 mL) were added to the mixture, and the resulting reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with $CHCl_3$ and filtered through a Celite pad. MeOH was added to the filtrate, and the resulting solution was concentrated. The remaining solvent was coevaporated with toluene several times. The residue was purified by flash column chromatography (hexanes−EtOAc 1:1 → 1:2) to give first the acetylated acceptor 3-*O*-acetyl-2,4-di-*O*-benzyl-*N*,6-*O*-carbonyl-1,5-dideoxy-1,5-imino-D-mannitol (232 mg, 42%), second the α-anomer of **13** (244 mg, 49%) as a white solid, and finally the β-anomer of **13** (49 mg, 10%) as a syrup; **13**α (α-anomer): ^{1}H NMR ($CDCl_3$) δ 7.41−7.27 (10H, m), 5.62 (1H, t, *J* = 9.9 Hz), 5.27 (1H, dd, *J* = 9.6, 10.8 Hz), 5.20 (1H, dd, *J* = 2.9, 10.4 Hz), 5.09 (1H, d, *J* = 2.9 Hz), 4.99 (1H, d, *J* = 12.1 Hz), 4.87 (1H, d, *J* = 11.9 Hz), 4.62 (1H, d, *J* = 12.1 Hz), 4.41 (1H, d, *J* = 11.9 Hz), 4.23 (1H, dd, *J* = 2.5, 14.4 Hz), 4.21 (1H, t, *J* = 8.6 Hz), 4.11 (1H, dd, *J* = 4.7, 12.4 Hz), 4.07 (1H, brs), 3.94 (1H, t, *J* = 9.3 Hz), 3.76 (1H, dd, *J* = 3.7, 9.0 Hz), 3.73 (1H, dd, *J* = 2.8, 13.3 Hz), 3.69 (1H, dd, *J* = 2.5, 9.7 Hz), 3.55 (1H, dt, *J* = 3.7, 8.5 Hz), 3.21 (1H, dt, *J* = 3.8, 10.9 Hz), 2.88 (1H, d, *J* = 14.5 Hz), 2.05, 2.01, 1.99, 1.74 (3H×4, each s); ^{13}C NMR ($CDCl_3$) δ 170.4, 169.9, 169.5, 169.3, 157.7, 137.9, 137.5, 128.7, 128.6, 128.1, 127.69, 127.67, 127.5, 83.9, 81.4, 76.4, 75.0, 74.5, 73.9, 71.9, 70.5, 70.4, 65.6, 60.8, 57.5, 40.9, 39.0, 20.8, 20.6, 20.5, 20.4; HRFABMS calcd for $C_{35}H_{42}NO_{13}S$ $(M + H)^+$ 716.2377, found 716.2374. **13**β (β-anomer): ^{1}H NMR ($CDCl_3$) δ 7.44−7.28 (10H, m), 5.45 (1H, t, *J* = 9.1 Hz), 5.30 (1H, dd, *J* = 9.6, 10.5 Hz), 5.08 (1H, t, *J* = 9.4 Hz), 4.91 (1H, d, *J* = 11.6 Hz), 4.79 (1H, d, *J* = 11.9 Hz), 4.57 (1H, d, *J* = 8.8 Hz), 4.50 (1H, d, *J* = 11.6 Hz), 4.45 (1H, d, *J* = 11.9 Hz), 4.31−4.22 (3H, m), 4.09 (1H, dd, *J* = 3.5, 11.9 Hz), 3.90 (1H, brs), 3.87−3.82 (2H, m), 3.72 (1H, t, *J* = 9.1 Hz), 3.55−3.48 (1H, m), 2.97−2.91 (1H, m), 2.82 (1H, d, *J* = 14.6 Hz), 2.06, 2.04, 2.02, 1.91 (3H×4, each s); ^{13}C NMR ($CDCl_3$) δ 170.4, 169.7, 169.3, 169.2, 157.7, 138.0, 136.9, 128.7, 128.6, 128.5, 128.44, 128.41, 128.3, 128.2, 128.1, 128.0, 127.7, 127.5, 80.7, 77.3, 75.2, 75.0, 74.4, 72.9, 71.8, 70.4, 69.4, 65.7, 61.5, 57.0, 41.0, 40.5, 20.6, 20.5; HRFABMS calcd for $C_{35}H_{42}NO_{13}S$ $(M + H)^+$ 716.2377, found 716.2380.

3-*O*-(2,3,4,6-Tetra-*O*-acetyl-5-thio-α-D-glucopyranosyl)-*N*,6-*O*-carbonyl-1,5-dideoxy-1,5-imino-D-mannitol (14). A suspension of **13**α (177 mg, 0.248 mmol) and 20% $Pd(OH)_2$ on carbon (160 mg) in MeOH (7 mL) was stirred under H_2 atmosphere overnight at room temperature. The mixture was filtered through a Celite pad, and the filtrate was concentrated. The residue was purified by flash column chromatography ($CHCl_3$−MeOH 19:1) to give **14** (120 mg, 90%) as a syrup: ^{1}H NMR ($CDCl_3$) δ 5.53 (1H, t, *J* = 9.4 Hz), 5.31 (1H, dd, *J* = 9.6, 10.8 Hz), 5.15−5.11 (2H, m), 4.45−4.35 (4H, m), 4.11 (1H, dd, *J* = 3.4, 12.1 Hz), 4.07 (1H, dd, *J* = 3.0, 11.0 Hz), 3.99 (1H, dd, *J* = 2.3, 14.5 Hz), 3.72 (1H, dt, *J* = 4.0, 10.8 Hz), 3.56 (1H, ddd, *J* = 3.8, 7.8, 9.4 Hz), 3.47−3.43 (2H, m), 3.29 (1H, brs), 3.09 (1H, dd, *J* = 1.4, 14.5 Hz), 2.07, 2.06, 2.04, 2.02 (3H×4, each s); ^{13}C NMR ($CDCl_3$) δ 170.8, 170.0, 169.9, 169.5, 158.4, 84.8, 81.0, 75.1, 72.1, 70.8, 68.3, 67.4, 65.6, 61.3, 58.0, 45.7, 39.1, 20.6, 20.5; HRFABMS calcd for $C_{21}H_{30}NO_{13}S$ $(M + H)^+$ 536.1438, found 536.1438.

3-*O*-(5-Thio-α-D-glucopyranosyl)-1,5-dideoxy-1,5-imino-D-mannitol (2). A solution of **14** (95.2 mg, 0.178 mmol) and KOH (227 mg, 4.0 mmol) in 90% aqueous EtOH (4.6 mL) was stirred for 4 h at 65 °C, and the mixture was cooled to 0 °C. The cooled mixture was carefully neutralized to pH 7 with 1 M acetic acid, and the resulting solution was concentrated. The residue was chromatographed on silica gel (2-propanol−water−NH_4OH 7:2:1) and subsequently with Sephadex G-25 (water) to **2** (44.7 mg, 63%) as an acetic acid salt after being lyophilized from water for 4 days: ^{1}H NMR (D_2O) δ 5.18 (1H, d, *J* = 2.8 Hz), 4.53 (1H, brs), 4.11 (1H, t, *J* = 10.0 Hz), 4.01 (1H, dd, *J* = 3.1, 12.6 Hz), 3.95 (1H, dd, *J* = 2.9, 9.8 Hz), 3.93−3.90 (3H, m), 3.85 (1H, dd, *J* = 3.0, 9.6 Hz), 3.77 (1H, dd, *J* = 8.7, 9.6 Hz), 3.65 (1H, dd, *J* = 8.7, 10.4 Hz), 3.42 (1H, dd, *J* = 2.9, 13.6 Hz), 3.30 (1H, d, *J* = 13.6 Hz), 3.24−3.12 (2H, m), 1.93 (3H, s); ^{13}C NMR (D_2O) δ 84.5, 80.1, 76.3, 74.6, 74.3, 66.8, 66.5, 61.2, 60.9, 58.9, 48.3, 44.2; HRFABMS calcd for $C_{12}H_{24}NO_8S$ $(M - AcO)^+$ 342.1223, found 342.1222.

Methyl 5-Thio-α-D-mannopyranoside (16). A solution of 1,2,3,4,6-penta-*O*-acetyl-5-thio-α-D-mannopyranose **15** (3.03 g, 7.46 mmol) in methanolic HCl prepared from AcCl (6 mL) and ice-cooled MeOH (60 mL) was stirred overnight at room temperature in a tightly capped flask. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$ and concentrated to give a solid. The solid was suspended in hot EtOH (200 mL), and the insoluble material was filtered off. The filtrate was concentrated, and the residue was chromatographed on silica gel ($CHCl_3$−MeOH 9:1 → 4:1) to give **16** (1.4 g, 89%) as a syrup. Spectral data of its tetraacetate were consistent with those reported.[24]

Methyl 2,4,6-Tri-*O*-benzoyl-5-thio-α-D-mannopyranoside (17). A suspension of **16** (1.4 g, 6.66 mmol) and Bu_2SnO (2.0 g, 8.0 mmol) in MeOH (12 mL) was refluxed for 3 h, cooled, and concentrated. A mixture of the residue, 4-methoxybenzyl chlo-

ride (1.3 mL, 9.6 mmol), Bu_4NI (840 mg, 2.3 mmol), and CsF (1.2 g, 7.9 mmol), was stirred overnight at room temperature. The reaction mixture was diluted with CH_3CN (100 mL), and insoluble material was filtered off by a Celite pad. The filtrate was concentrated, and the residue was chromatographed on silica gel ($CHCl_3$-MeOH 30:1 → 4:1). Fractions containing 3-*O*-(4-methoxybenzyl) derivative were pooled and concentrated to give a syrup which contained a substantial amount of tetrabutylammonium salt. The starting material **16** (800 mg, 57%) was also recovered from the column.

A solution of the syrup containing 3-*O*-(4-methoxybenzyl) derivative and BzCl (1 mL) in pyridine (4 mL) and CH_2Cl_2 (4 mL) was stirred for 2 h at room temperature, and a portion of ice was added to the reaction mixture in order to decompose the excess reagent. The mixture was diluted with CH_2Cl_2 and was subsequently washed with 1 M HCl and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel (hexanes−EOAc 3:1) to give methyl 2,4,6-tri-*O*-benzoyl-3-*O*-(4-methoxybenzyl)-5-thio-α-D-mannopyranoside as a syrup.

A suspension of the syrup and $(NH_4)_2Ce(NO_3)_6$ (2.0 g, 3.65 mmol) in CH_3CN−water (9:1, 9 mL) was stirred for 30 min at room temperature. The mixture was diluted with $CHCl_3$ and was washed twice with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (hexanes−EtOAc 4:1 → 3:1) to give **17** (454 mg, 30% based on the consumed **16**) as a syrup: ^{1}H NMR ($CDCl_3$) δ 8.13−8.04 (6H, m), 7.63−7.39 (9H, m), 5.90 (1H, d, J = 10.3 Hz), 5.60 (1H, dd, J = 3.1, 3.8 Hz), 4.76 (1H, d, J = 3.8 Hz), 4.64 (1H, dd, J = 3.5, 11.8 Hz), 4.53 (1H, dd, J = 4.9, 11.8 Hz), 4.30 (1H, brs), 3.75 (1H, ddd, J = 3.5, 4.9, 10.3 Hz), 3.52 (3H, s), 2.33 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 166.8, 166.0, 165.7, 133.5, 133.4, 133.1, 129.9, 129.8, 129.6, 129.3, 129.2, 128.8, 128.5, 128.4, 128.3, 128.0, 83.0, 74.6, 73.1, 70.1, 62.4, 56.3, 39.5; HRFABMS calcd for $C_{28}H_{27}O_8S$ $(M + H)^+$ 523.1427, found 523.1428.

Methyl 3-*O*-(2,3,4,6-Tetra-*O*-acetyl-5-thio-α-D-glucopyranosyl)-2,4,6-tri-*O*-benzoyl-5-thio-α-D-mannopyranoside (18). A suspension of **8** (148 mg, 0.291 mmol), **17** (287 mg, 0.55 mmol), and activated molecular sieves 4A (800 mg) in anhydrous CH_2Cl_2 (3.3 mL) was stirred for 1 h at room temperature under Ar atmosphere and cooled to −78 °C. TMSOTf (8.2 μL) was added dropwise to the cooled mixture, and the mixture was gradually warmed to 0 °C in a period of 1.5 h. The reaction mixture was neutralized with Et_3N and filtered through a Celite pad. The filtrate was concentrated, and the residue was purified by flash column chromatography (hexanes−EtOAc 3:1 → 2:1 → 3:2 → 1:1) to give first the recovered acceptor **17** (198 mg, 69% recovered) and then **18** (96 mg, 38% based on **8**) as a syrup: ^{1}H NMR ($CDCl_3$) δ 8.20−7.99 (6H, m), 7.66−7.35 (9H, m), 6.05 (1H, t, J = 10.0 Hz), 5.87 (1H, t, J = 3.9 Hz), 5.28 (1H, t, J = 9.7 Hz), 5.17 (1H, dd, J = 9.5, 10.5 Hz), 5.03 (1H, dd, J = 3.0, 10.1 Hz), 4.94 (1H, d, J = 3.0 Hz), 4.77 (1H, d, J = 4.0 Hz), 4.58 (1H, dd, J = 4.0, 11.9 Hz), 4.48−4.41 (2H, m), 4.20 (1H, dd, J = 4.0, 11.9 Hz), 3.76−3.71 (2H, m), 3.60−3.53 (1H, m), 3.53 (3H, s), 2.01, 1.93, 1.83, 1.27 (3H×4, each s); ^{13}C NMR ($CDCl_3$) δ 170.4, 169.8, 169.5, 168.8, 166.0, 165.7, 165.0, 133.6, 133.4, 133.0, 130.0, 129.9, 129.7, 129.5, 129.4, 129.3, 128.7, 128.5, 128.3, 82.9, 81.1, 77.3, 74.0, 72.5, 71.8, 71.5, 70.7, 62.5, 60.7, 56.3, 39.6, 38.9, 20.5, 20.3, 19.6; HRFABMS calcd for $C_{42}H_{45}O_{16}S_2$ $(M + H)^+$ 869.2149, found 869.2140.

Methyl 3-*O*-(5-Thio-α-D-glucopyranosyl)-5-thio-α-D-mannopyranoside (3). A solution of **18** (94 mg, 0.108 mmol) in MeOH (2 mL) and 30% NaOMe in MeOH (34 μL) was stirred overnight at room temperature, and the mixture was neutralized with Dowex 50W-X8 [H^+]. The resin was filtered off, and the filtrate was concentrated. The residue was chromatographed with Sephadex G-25 (water) and lyophilized from water to give **3** (42 mg, quantitative yield) as a foam: ^{1}H NMR (D_2O) δ 5.11 (1H, d, J = 2.6 Hz), 4.59 (1H, d, J = 3.8 Hz), 4.47 (1H, t, J = 3.4 Hz), 4.03 (1H, t, J = 10.1 Hz), 3.99−3.81 (6H, m), 3.78 (1H, t, J = 9.9 Hz), 3.66 (1H, dd, J = 8.9, 10.4 Hz), 3.50 (3H, s), 3.18 (1H, ddd, J = 4.0, 5.3, 10.4 Hz), 3.16−3.09 (1H, m); ^{13}C NMR (D_2O) δ 86.7, 85.1, 80.6, 76.5, 74.7, 74.3, 72.7, 70.3, 61.1, 60.9, 56.7, 44.7, 44.2; HRFABMS calcd for $C_{13}H_{25}O_9S_2$ $(M + H)^+$ 389.0940, found 389.0938.

Molecular Modeling. All calculations were performed on a Silicon Graphics INDY R5000 workstation using MacroModel ver.5.5 software. Initial structures, built within MacroModel, were subjected to conjugate gradient energy minimization with the AMBER* force field and the GB/SA water model, and dielectric constant was set at 4.0.[27] The Monte Carlo (MC) approach was used for the global conformational search. Six-membered rings were left at their stable $^4C_1$ chair conformation, and all other torsion angles were randomly modified at each MC step. MC steps (2000) were carried out for all compounds, and after each MC step, resultant geometry was minimized using 2000 gradient conjugate steps; all conformers found within 50 kJ/mol of a global minimum were stored. For each compound, this 2000 step MC search was run 3 times with SEED option to make sure all conformers were found. All conformers were next subjected to further conjugate gradient energy minimization using the energy-convergence criterion of 0.001 kJ/Å·mol. As a result, a global minimum of each compound was found several times. Within 5 kcal/mol of the global minimum, 92 unique conformers were found for compound **1** and 37 unique conformers were found for compound **2**.

Cluster analyses of these conformers were carried out using XCluster ver.1.3 software. All ring atoms and an interglycosidic oxygen atom were used for the analysis by means of Arms method. A clustering level which had the largest minimum separation ratio was picked for threshold. Three clusters were found for **1** and two for **2**. A representative structure of each cluster which resembles the average geometry for each cluster was selected by the program. As for relative importance of each cluster, their population was calculated using a Boltzmann type of distribution with the smallest free-energy conformer in the cluster. Superimposition of representative structure was carried out using MacroModel. Atoms essential for inhibitory activity, O-2, N-5, C-6, O-3′, O-4′, and C-6′, were used for rigid superimposition, and rms deviation of superimposed atoms was calculated.

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Supporting Information Available: Characteristics of clusters of compounds **1** and **2**, ^{1}H NMR spectra of compounds **2**−**4**, **6**, **8**−**10**, **13**, **14**, **17**, and **18** and ^{13}C NMR spectra of compounds **2**−**4**, **9**, **10**, **13**, **14**, **17**, and **18** (23 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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