Synthesis of Thio-Linked Disaccharides by 1→2 Intramolecular Thioglycosyl Migration: Oxacarbenium versus Episulfonium Ion Intermediates

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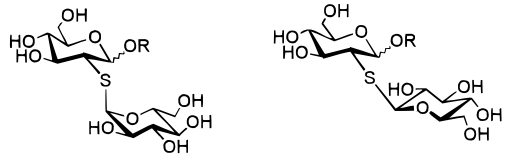
The conversion of 1,1′-thio-linked glucopyranosyl α-D-mannopyranosides to 1,2-thio-linked methyl sophorosides or methyl kojibiosides is described. The method involves the 1→2-migration of the thioglucopyranosyl portion of the nonreducing disaccharide with inversion of configuration at C-2 of the mannopyranose ring and concomitant formation of the methyl glucopyranoside. The thioglucosyl migration does not occur when electron-withdrawing benzoate protecting groups are present. The rearrangement occurs with retention of configuration in the migrating thioglucoside but the methyl glycoside is formed as a mixture of α- and β-isomers. This is attributed to a mechanism involving an oxacarbenium-ion intermediate rather than an episulfonium-ion intermediate. The relevance of this work to recent theoretical predictions concerning the relative stability of such intermediates is discussed.

Introduction

Carbohydrates play important roles in the critical molecular recognition events that initiate immunological responses to bacterial and viral infections.[1a,b] Cell surface carbohydrates are also important for the signaling and recognition processes that occur in inflammation and cancer metastasis.[1a,b] Carbohydrate mimetics[1c] may be applied in a variety of ways to investigate these processes. One such approach is to replace the oxygen atoms of carbohydrates with other heteroatoms that may give analogues with altered binding properties or increased stability toward enzyme degradation. As a means of investigating the binding of substrate analogues and inhibitors to glycosidase enzymes, we[2] and others[3] have prepared a variety of S-, Se-, or N-linked disaccharides. As a part of this program, the sulfur-linked analogues of kojibiosides and/or sophorosides were prepared by S-glycosylation of 2-thioglucosides using glucopyranose or 5-thio-glucopyranose trichloroacetimidate glycosyl donors (Chart 1).[4] Such an approach suffered from the formation of anomeric mixtures even when the glycosyl donor contained a participating ester group at the 2-position. An alternative synthetic route to this type of compound is the nucleophilic displacement of triflate leaving groups on the glycosyl acceptor by 1-thiolate glycosyl donors. This method has been extensively investigated by Driguez and co-workers,[3a] and by Defaye and Gelas[3b] for the synthesis of thio-linked oligosaccharides, but is occasionally of only limited utility due to side-product formation or poor product stereoselectivity. Recently, Hummel and Hindsgaul[3c] have developed a solid-phase variant in which hydroxyl protecting-groups on the β-thio-glycosyl donors are unnecessary and side products may be removed by simple filtration.[3c] As an alternative, and hopefully more selective, approach to 1,2-thio-linked disaccharides, we questioned whether a synthesis could be developed using a 1→2-thio migration as the key reaction.

Chart 1



Rearrangement of thioglycosides to give alkylated 2-thioglycosides through 1→2-thio migration is well-known in carbohydrate chemistry.[5] The reaction is postulated to proceed through formation of the transient episulfonium salt intermediate that results from the intramolecular displacement of a leaving group at C-2 by the neighboring nucleophilic sulfur atom at C-1

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(3) Driguez, H. In *Topics in Current Chemistry*; Driguez, H., Thiem, J., Eds.; Springer-Verlag: Berlin, 1997; Vol. 187, pp 85−116. (b) Defaye, J.; Gelas, J. In *Studies in Natural Product Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1991; Vol. 8, pp 315−357. (c) Hummel, G.; Hindsgaul, O. *Angew. Chem., Int. Ed. Engl.*, **1999**, *38*, 1782.

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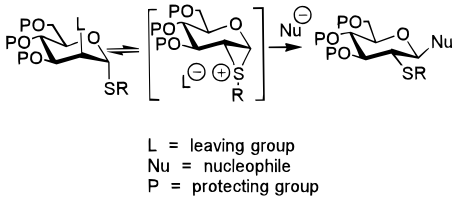
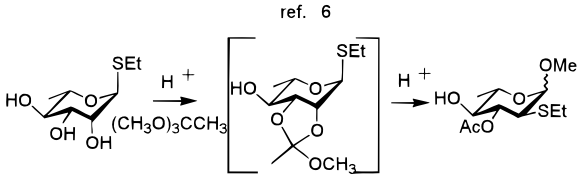
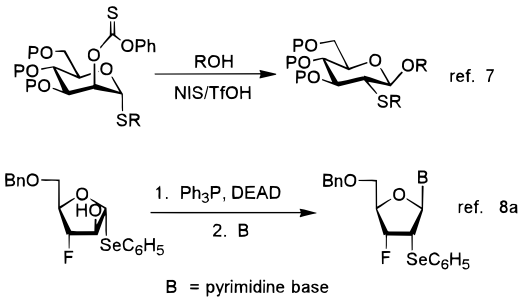
Scheme 1



Scheme 2



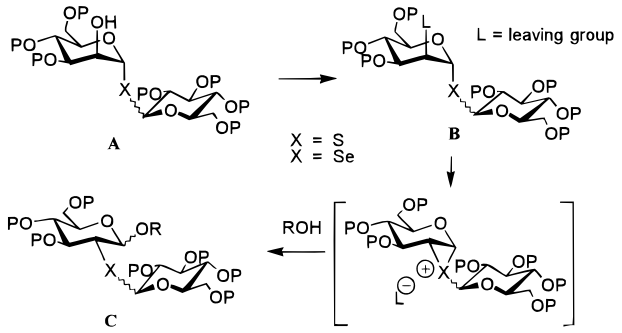
Scheme 3



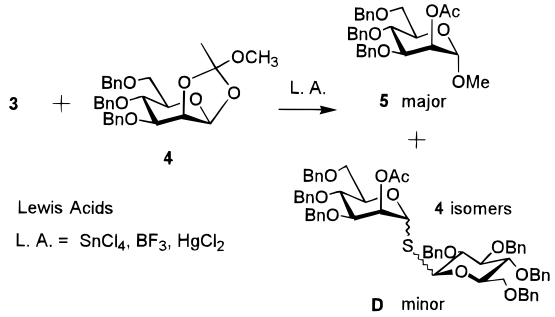
(Scheme 1). In certain cases, most recently noted during the preparation of α-L-rhamnopyranose thioglycosides with a 2,3-ortho ester protecting group,[6] when thioglycosides are used as glycosyl donors, rearrangement is an undesirable consequence of reactions that produce an electrophilic center at C-2 (Scheme 2). In other cases, the rearrangement has been used to advantage to control the stereochemistry in the synthesis of 2-deoxyglycosides.[7] Recently, the related 1→2-seleno migration has been used as a method to prepare 2-deoxy nucleosides from selenoglycosides[8] (Scheme 3). We reasoned that if the group R in Scheme 1 were a suitably protected glycosyl moiety, then rearrangement would result in a 1,2-thio-linked disaccharide by intramolecular glycosyl delivery, a concept closely linked to recent examples of intramolecular glycosylation using tethered glycosyl donor/acceptor pairs.[9]

We describe here our initial efforts at developing a synthesis of nonreducing thio- or seleno-linked mannopyranosyl-1,1′-glucopyranosyl disaccharides (**A**) and the subsequent methanolysis and rearrangement of appropriately protected and activated derivatives (**B**) to give methyl 2-*S(Se)*-glucopyranosyl-2-thio(seleno)glucopyranosides (**C**) by 1→2-thio(seleno) migration (Scheme 4). The results offer some insights into the intermediacy of oxacarbenium versus episulfonium ions in these types of rearrangements.

Scheme 4



Scheme 5



Results and Discussion

Two general approaches to mixed 1,1′-thio-linked disaccharides were investigated. By analogy to the known preparation of simple alkyl thioglycosides of α-D-mannopranose by thiolysis of 1,2-*O*-ortho esters,[10] the Lewis acid-catalyzed reaction of 2,3,4,6-tetra-*O*-benzyl-1-thio-D-glucopyranose (**3**)[11] with methyl 3,4,6-tri-*O*-benzyl-*β*-D-mannopyranose-1,2-orthoacetate (**4b**)[12] was initially investigated (Scheme 5). The thiol **3** was prepared from the glycosyl chloride **1**[13] via the isothiouronium salt **2** using the literature method.[11] Analysis of **3** by ^{1}H NMR spectroscopy indicated a 3:1 α/*β* mixture of 1-thiol isomers. For a variety of Lewis acid catalysts, the major product of the reaction of **3** with **4b** was the methyl glycoside **5**, a byproduct resulting from rearrangement of **4b** that has previously been observed[10] during thiolysis of ortho esters. The desired disaccharide was formed in very low yields as a mixture (**D**) of the four possible anomeric pairs.

A more successful approach was the SN_2 displacement of the α-glucopyranosyl chloride **1** by the 1-thio mannopyranose derivative **8.** Compound **8** was readily prepared in three steps from the known benzyl-protected mannopyranose ortho ester derivative **4b**.[12] Treatment of **4b** with HBr/HOAc afforded the glycosyl bromide **6** that, due to its unstable nature, was immediately reacted with thiourea to give the isothiouronium salt **7**. Hydrolysis of **7** with aqueous sodium metabisulfite solution produced the 1-thiol derivative **8**. Prolonged storage of **8** resulted in slow air oxidation to a disulfide, and thus, **8** was generally freshly prepared for each use. The reaction of

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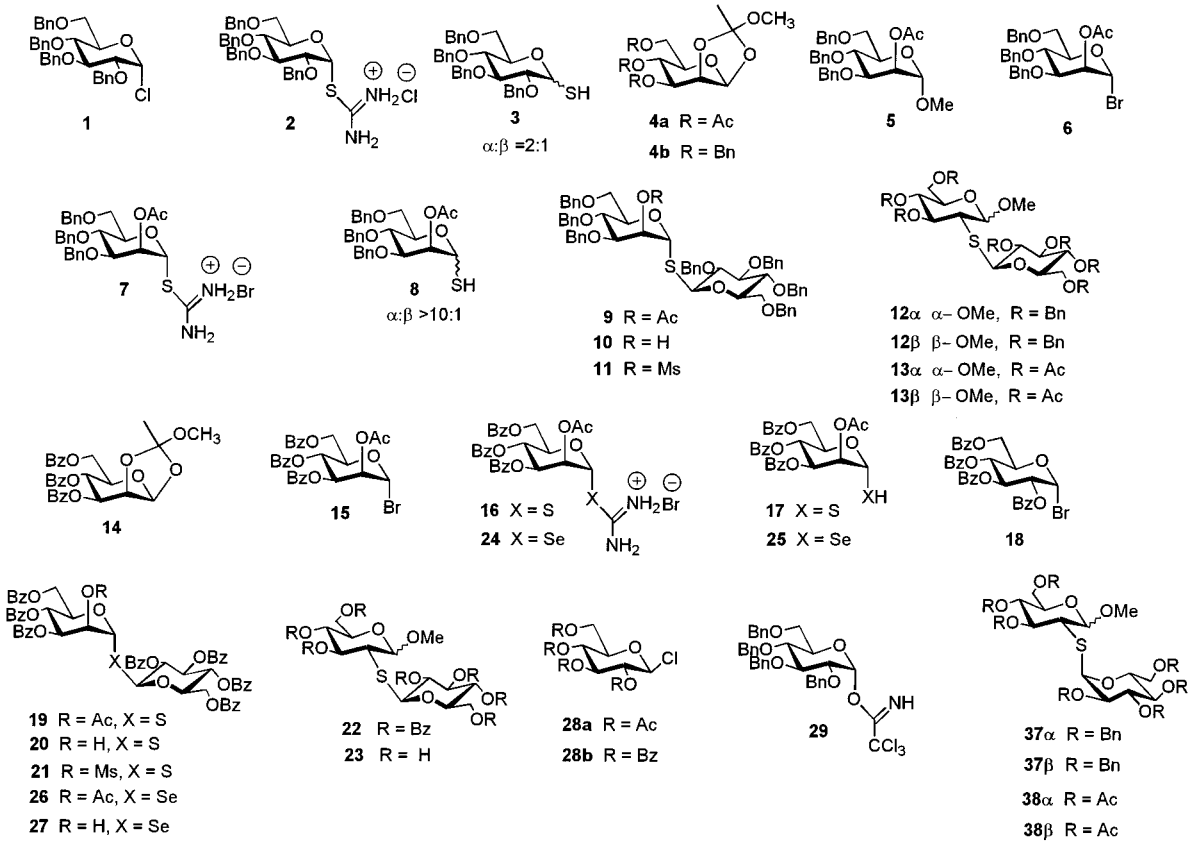
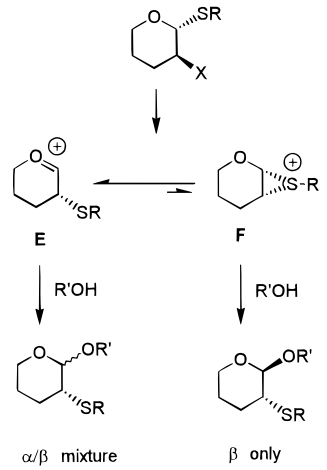
Chart 2



the thiol **8** with the chloride **1** proceeded with SN_2 inversion of anomeric configuration in the glucopyranose moiety to give mainly the α-D-manno-*β*-D-gluco 1,1-trehalose-type disaccharide **9**. This product was obtained with a diastereomeric purity of greater than 90%, which was reflective of the highly biased α/*β* equilibrium in the mannose 1-thiol **8** (~90% α). The acetate protecting group at O-2 of the manopyranose ring of **9** was removed by methanolysis and the resulting 2-OH group in **10** was converted to a suitable leaving group by mesylation to give **11**.

Simple refluxing of a buffered methanolic solution of **11** resulted in smooth 1,2-thioglycosyl migration with concomitant capture of the cationic reactive intermediate by methanol to produce quantitatively a 3:1 *β*/α mixture of the 2-thio-linked methyl sophorosides **12***β* and **12**α. The α- and *β*-isomers of **12** exhibited similar chromatographic mobilities and could not be completely separated; however, for analytical purposes, pure samples of each isomer were obtained from the chromatographic fractions. Encouragingly, the 1→2-thio migration had proceeded with complete retention of configuration at the anomeric center of the migrating 1-thioglucopyranose residue. However, contrary to our expectations, the methyl glucoside was formed with limited stereoselectivity. This may reflect the possibility that the reactive intermediate for 1,2-thio migration in pyranosides exists primarily as an oxacarbenium ion (**E**) rather than the alternative episulfonium ion **F** (Scheme 6).

Scheme 6



Oxacarbenium ions such as **E** are postulated to react with nonhindered alcohols to produce α/*β* glycoside mixtures in proportions partially governed by the relative steric hindrance to attack from either the α-or the *β*-face. These steric effects will be offset by a preference for formation of the α-isomer due to the kinetic consequences of the anomeric effect,[14] and the observed anomer ratio will reflect the balance of these two influences. On the other hand, an episulfonium ion such as **F** should be subject to backside nucleophilic attack at the more electrophilic C-1 position with opening of the three-membered ring to produce only the *β*-glycoside.

The fact that both α- and *β*-isomers of **12** were observed in the reaction of **11**, in which the experimental conditions were likely to produce kinetic rather than thermodynamic products, lends support to recent theoretical

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predictions. Calculations using both MNDO semiempirical[15] and high-level ab initio[16] methods have indicated that oxacarbenium ions are likely to be of lower energy than the alternative episulfonium ions, at least for simple ions in the gas-phase which could adopt either electronic state. The calculated geometry of these oxacarbenium ions closely mimics that found for oxacarbenium ions lacking a neighboring sulfur atom. The preferred formation of anti-type products from attack of nucleophiles at the carbon of the energetically preferred oxacarbenium ions was attributed to the steric and electronic effects of the neighboring thio-substituents rather than to any effects of the sulfur atom on the geometry of the intermediates.[16] Our experimental results also suggest that the oxacarbenium ion is the more reactive intermediate. In the present case, attack of methanol from the β-face of the more stable intermediate (the oxacarbenium ion corresponding to **E** in Scheme 6) will be favored due to the bulky 2-thio-linked glucoside substituent shielding the α-face. This preference must outweigh the alternative α-attack, favored by the anomeric effect, and leads to the observed 3:1 β/α ratio in the methyl glycoside **12**.

The benzyl protecting groups in the mixture of **12**α and **12**β were removed by Na/NH_3 reductive cleavage, and the OH groups were esterified to give the hepta-acetate derivatives **13**α and **13**β. These isomers were separated by fractional crystallization and were completely characterized. The spectroscopic data fully support the assigned structures and, in the case of **13**α**,** closely match with values that have been reported previously for the analogous allyl glycoside.[17]

To investigate whether the choice of protecting groups plays a role in the stereoselectivity of the 1→2-thio migration, we required a 1,1′-thiodisaccharide, corresponding to compound **11**, in which the benzyl ether protecting groups had been replaced by esters. A similar synthetic sequence to that used for the benzyl-protected disaccharide **9** was used to prepare a suitable disaccharide **19**. The acetate groups of the known ortho ester derivative **4a**[12] were removed by ammonolysis and replaced by benzoates to yield the tribenzoate **14**. Treatment with HBr/HOAc gave the sensitive mannopyranosyl bromide **15**. This was immediately reacted with thiourea to produce the α-isothiouronium salt **16**, by analogy to the literature preparation of the tetraacetyl derivative.[18] In situ generation of the thiol **17** and coupling with the glucopyranosyl bromide **18**[19] in a phase-transfer-catalyzed system[20] gave the 1,1′-thiodisaccharide **19** stereoselectively in excellent yield.

The acetate ester in **19** was unexpectedly resistant to selective methanolysis under either acid or base catalysis. Treatment of **19** with HCl/MeOH at room temperature, conditions that are recommended[21] for selective methanolysis of acetates in the presence of benzoates, resulted in little or no reaction, possibly due to the limited solubility of the starting material. When the reaction mixture was heated to reflux and made homogeneous by the addition of $CHCl_3$ as a cosolvent, methanolysis was extremely slow and not very selective. Termination of the reaction when ~20% of the starting material **19** remained was required in order to obtain a moderate yield of the 2′-OH product **20**. Mesylation of **20** proceeded uneventfully to provide **21**, the desired precursor for the 1→2-thio-migration reaction.

To our disappointment, however, refluxing a methanol solution of **21** in the presence of $NaHCO_3$, conditions that had produced a smooth 1→2-thio migration in **11**, resulted in none of the desired 1→2-thio migration product **22**. Extended reaction times, with the progress of the reaction followed by periodic TLC analysis, indicated only the slow production of a mixture of more polar products having one or more free OH groups resulting from partial, nonselective benzoate methanolysis. Interestingly, however, subjecting **21** to typical Zemplén deacylation conditions resulted not only in complete methanolysis of the benzoate esters but also in 1→2-thioglycosyl migration to produce the thio-linked methyl sophorosides **23**. The crude sophoroside mixture was characterized by acetylation to give the same two derivatives (heptacetates **13**α and **13**β) that had previously been obtained by acetylation of the crude methyl sophoroside mixture from **12**.

Evidently, the electron-withdrawing character of the benzoate protecting groups in **21** attenuates the nucleophilicity of the sulfur atom toward the adjacent mesylate and prevents the 1,2-thio migration from occurring. Alternatively, the attack of the 1-thio moiety could be sterically inhibited by the benzoyl protecting groups. During the Zemplén deacylation reaction, a point must be reached where a critical number of the electron-withdrawing benzoates have been removed such that the nucleophilicity of the sulfur atom has been restored or the rearrangement is no longer sterically inhibited, and the 1→2-thio migration takes place. It is not known precisely at which stage this occurs; however, the good yield of 1→2-thio migration products obtained from **21** indicates that this migration reaction occurs before any extensive methanolysis or displacement of the mesylate takes place.

As before, the anomeric configuration of the migrating thioglycoside was retained in the products; however, the methyl glycoside of **23** was formed as an anomeric mixture. The 3:2 β/α ratio for **13**, obtained after acetylation of **23**, was slightly different than in the previous case with the benzyl ethers; and varied somewhat when the methanolysis reaction of **21** was repeated under slightly different conditions of concentration and temperature. This may reflect the presence of a heterogeneous mixture of partially deacylated 1→2-migrating groups each having a different steric influence on methyl glycoside formation.

An attempt was made to apply the same reaction sequence to the preparation of 1,2-Se-linked disaccharides by 1→2-Se migration. Toward this end, the 1,1′-Se-linked disaccharide **26** was synthesized from the corresponding isoselenouronium salt **24** and the glycosyl bromide **18**. Compound **24** was prepared by the same methods used for the thio analogue **16**, except that selenourea was used in place of thiourea.[22]

While the hydrolysis reaction of **24** and the in situ reaction of the derived selenol **25** with **18** proceeded in acceptable yields to give **26**, the subsequent selective

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(19) Fletcher, H. G., Jr. *Methods Carbohydr. Chem.* **1963**, *2*, 226.
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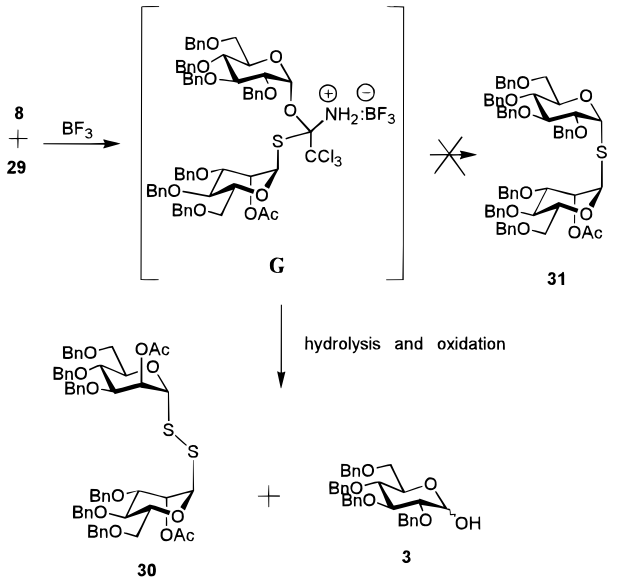
(22) Wagner, G.; Nuhn, P. *Arch. Pharm. (Weinheim)* **1964**, *297*, 461.

Scheme 7



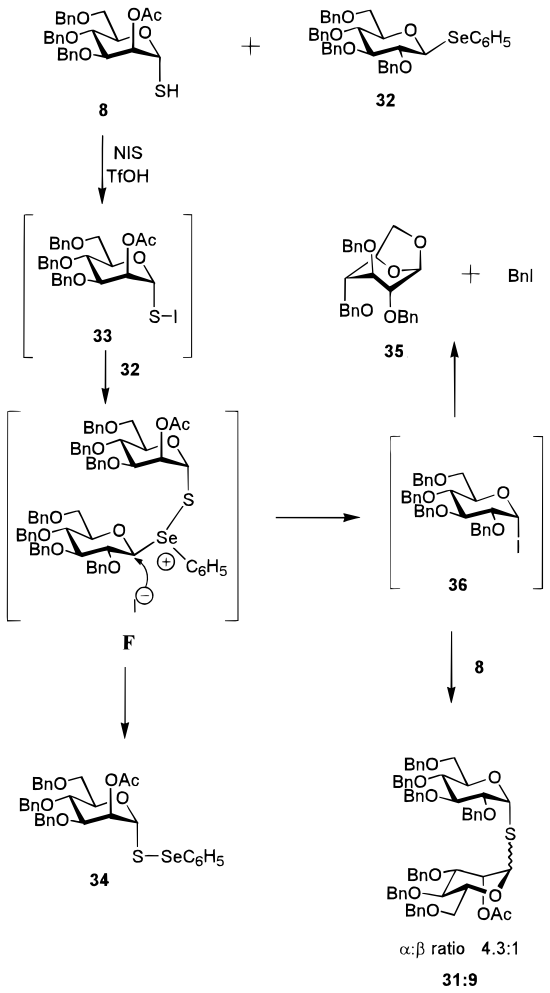
methanolysis reaction to produce **27** was even more problematic than in the case of the thio-linked compound **19.** Compound **26** could be recovered essentially unchanged from HCl/MeOH/CH_2Cl_2 solutions even under forcing conditions (80 °C, sealed tube). A variety of base-catalyzed methods were either not selective for removal of the acetate over the benzoate esters, or resulted in decomposition of **26** with formation of selenium metal. Failure to obtain **27** necessitated the abandonment of this route and hence the desired 1→2-seleno migration reaction.

Since the anomeric configuration of the migrating 1-thioglucoside in both **11** and **21** was retained, it appeared that 1,2-α-thio-linked kojibiosides should be similarly prepared if the required thio-linked α-mannose-1,1′-α-glucose could be selectively prepared. This proved to be more of a challenge than anticipated. Nucleophilic displacements of halides in the unstable *β*-glucopyranosyl series (**28a**[23] or **28b**[24]) by 1-thiolates, generated in situ from either of the thiols **8** or **17**, were unsuccessful. When the reactions were attempted in aqueous acetone, or under phase-transfer conditions, the sensitive halide derivatives were completely hydrolyzed to hemiacetal derivatives before thiolate displacement of the halides could occur. Reactions attempted under anhydrous conditions in DMF resulted in little or no reaction under mild conditions and led to decomposition of the 1-halogeno derivatives under more forcing conditions.

We thus turned our attention to the reaction of **8** with the trichloroacetimidate **29**, since literature precedent[25] suggested that, at least for simple alkanethiols, thioglycosides could be prepared from **29** with retention of configuration at the anomeric center. The reaction of the thiol **8** with the trichloroacetimidate **29**, catalyzed by BF_3 etherate, proceeded only sluggishly to give, after reflux of the reaction mixture, a low yield of a product identified as the 1,1′-thio-linked mannose disulfide **30** (Scheme 7).

We speculate that addition of the thiol **8** to the imine of **29** results in a relatively stable S,N acetal intermediate

Scheme 8



G (Scheme 7) that does not efficiently activate the glucose moiety for reaction with another mannose 1-thiol residue. The disulfide **30** may be formed through hydrolysis or oxidation of this intermediate, either during the lengthy reaction, or during the processing and purification. Evidently, this result points to a limitation in the use of normally reliable trichloroacetimidate glycosyl donors such as **29** for 1,1′-thioglycoside formation.

A final attempt to obtain the desired α′,α-linked mixed glycosyl sulfide **31** was at least partially successful. Selenoglycosides have recently emerged as useful glycosyl donors[26] that may be selectively activated under mild conditions in the presence of thioglycosides. We speculated that this selectivity might extend to the reaction of selenoglycosides with thiols to produce thioglycosides. The reaction between the thiol **8** and phenyl seleno-*β*-D-glucopyranoside **32**[27] with N-iodosuccinimide/triflic acid activation produced mainly phenylselenenyl 1-thiomannopyranoside **34** (60%), but also the desired α′,α isomer **31** in low yield, isolated as a mixture with the α′,*β* isomer **9** (Scheme 8). The ratio of **31**:**9** was 4.3:1, as estimated by integration of the ^{1}H NMR spectrum. A third product, isolated in a yield of 22%, was the known[28] 1,6-anhydro derivative **35**.

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The formation of **34** likely resulted from preferential reaction of the thiol **8** with NIS to produce the sulfenyl iodide **33**. This likely reacted with the selenoglycoside **32** to produce a reactive selenonium ion intermediate (**F**). Collapse of this intermediate would lead to **34** and the glycosyl iodide **36.** Either **36** reacted with the thiol **8** to give the desired 1,1′-thio-linked disaccharide, or alternatively, **36** was consumed by intramolecular attack of the 6-OBn group to produce **35** by nucleophilic debenzylation. [28]

Although **31** could not be obtained in a pure state, the mixture of **31** and **9** was carried through the deacetylation, mesylation and 1→2-thio migration sequence previously applied to pure **9**. This yielded a mixture of **37** and **11**. Analysis of the ^{1}H NMR spectrum of the crude product mixture showed that the 4:1 α/β ratio of the migrating thioglucoside was apparently maintained throughout the 1→2-thio migration step. At this stage, the minor components **11**α and **11**β were removed by chromatography and almost pure **37**β was obtained. The minor compound methyl α-kojibioside **37**α, generated during the thio-migration step, was also separated at this point and, although it was identified from the ^{1}H NMR spectra of relatively pure fractions, it could not be obtained entirely free of isomeric impurities. These fractions were therefore not carried on to produce the corresponding heptaacetate derivative **38**α. Compound **37**β was debenzylated and acetylated as before to produce methyl β-kojibioside heptaacetate **38**β as a pure crystalline compound. The ^{1}H and ^{13}C NMR spectra of the heptaacetate **38**β were in complete accord with the proposed structure and were very similar to those reported[17] for the corresponding allyl β-kojibioside.

Conclusions

In summary, a preliminary investigation of the synthesis of 1,2-thio-linked disaccharides by a 1→2-thioglycosyl migration reaction has shown that the method has potential. The rearrangement occurs with retention of anomeric configuration in the migrating thioglycoside. Electron-withdrawing protecting groups such as benzoate esters prevent the migration from occurring. The formation of anomeric mixtures at the reducing-end glycoside implicates oxacarbenium ions rather than episulfonium ions as the reactive intermediates in such reactions. This provides experimental evidence in support of theoretical predictions concerning the relative energies and reactivities of cationic intermediates that can exist in either oxacarbenium or episulfonium ion forms. The application of 1→2-thioglycosyl migration techniques for the efficient synthesis of 1,2-thio-linked disaccharides must await the development of better procedures for the stereoselective synthesis of mixed 1,1′-thio-linked, nonreducing disaccharides.

Experimental Section

For general experimental methods see ref 27. Optical rotations were measured at 22 ± 1 °C. ^{1}H and ^{13}C NMR spectra were recorded at 400.13 and 100.6 MHz for proton and carbon, respectively. All assignments were confirmed with the aid of two-dimensional ^{1}H, ^{1}H (COSYDFTP) or ^{1}H, ^{13}C (INVBTP) experiments using standard Bruker pulse programs. Primed locants in the NMR data for the 1,1′-disaccharides refer to the mannopyranose unit. MALDI mass spectra were obtained for samples dispersed in a 2,5-dihydroxybenzoic acid matrix using a PerSeptive Biosystems Voyager-DE instrument. Typically, other than mass peaks attributable to the matrix, the (M^+ + Na) ion was by far the most intense mass peak in each of the mass spectra. Exceptions are noted in the experimental by giving relative intensity values. In general, neither M^+ nor $M^+ + 1$ ions were observed.

2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranose-1-isothiouronium Chloride (2). A solution of the glycosyl chloride **1** (4.44 g, 7.94 mmol) in dry DMF (10 mL) was placed under an N_2 atmosphere. Thiourea (0.603 g, 0.828 mmol) and *n*-Bu_4NBr (0.01 g) were added, and the mixture was stirred at 80 °C for 2 h. The mixture was cooled and the DMF removed on high vacuum. The colorless, crystalline residue was recrystallized from acetone/CH_2Cl_2 to yield **2** (3.39 g, 67%): mp 166−167 °C; $[\alpha]_D$ +118 (*c* 5.4, $CHCl_3$) (lit.[11] for the bromide salt, mp 150−151 °C, $[\alpha]_D$ +159.7 (*c* 1.1, $CHCl_3$)); ^{1}H NMR ($CDCl_3$) δ 10.13 (2H, brs, NH_2), 8.71 (2H, brs, NH_2), 7.40−7.03 (m, 20H, Ar), 6.12 (d, 1H, $J_{1,2}$ = 5.4 Hz, H-1), 4.86, 4.73 (2d, each 1H, $J_{A,B}$ = 10.8 Hz, CH_2Ph), 4.77, 4.45 (2d, each 1H, $J_{A,B}$ = 10.8 Hz, CH_2Ph), 4.71, 4.65 (2d, each 1H, $J_{A,B}$ = 11.7 Hz, CH_2Ph), 4.49, 4.44 (2d, each 1H, $J_{A,B}$ = 12.1 Hz, CH_2Ph), 4.07 (ddd, 1H, $J_{4,5}$ = 10.0, $J_{5,6a}$ = 2.0, $J_{5,6b}$ = 6.5 Hz, H-5), 3.87 (dd, 1H, $J_{2,3}$ = 9.3 Hz, H-2), 3.70 (dd, 1H, $J_{3,4}$ = 9.0 Hz, H-3), 3.58 (dd, 1H, $J_{6a,6b}$ = 10.5 Hz, H-6a), 3.52−3.44 (m, 2H, H-4, H-6b); ^{13}C NMR ($CDCl_3$) δ 170.88 (*C*=NH_2), 138.03, 137.57, 137.08, 136.71 (4 × C-*ipso*, Ph), 128.61−127.76 (20C, Ph), 85.12 (C-1), 81.72 (C-3), 77.67 (C-5), 76.38, 75.81, 75.02, 73.50, 72.77 (2C) (4 × *C*H_2Ph, C-2, C-4), 68.08 (C-6); MALDI MS *m/e* 621.7 (100, M^+ − HCl + Na), 599.7 (88, M^+ − Cl). Anal. Calcd for $C_{35}H_{39}ClN_2O_5S$: C, 66.18; H, 6.19; N, 4.41. Found: C, 66.06; H, 6.15; N, 4.49.

2,3,4,6-Tetra-*O*-benzyl-1-thio-α/β-D-glucopyranose (3). The thiourea derivative **2** (1.27 g, 2.00 mmol) and $Na_2S_2O_5$ (450 mg, 2.37 mmol) were added to a stirred mixture of CH_2Cl_2 (15 mL) and water (7 mL). The mixture was refluxed for 1.5 h under N_2. After the mixture was cooled to room temperature, CH_2Cl_2 was added and the organic phase was separated and washed with water. Drying over $MgSO_4$ and solvent removal gave **3** as a colorless syrup (1.05 g, 94%) which slowly began to crystallize (mp 47−50 °C, lit.[11] mp 60−61 °C). Analysis by ^{1}H NMR indicated an anomeric mixture of 1-thiols (α/β, 2:1): MALDI MS *m/e* 595.7 (48, M^+ + K), 579.3 (100, M^+ + Na).

3α: ^{1}H NMR ($CDCl_3$) δ 5.74 (dd, 1H, $J_{1,2}$ = 5.1, $J_{1,SH}$ = 4.8 Hz, H-1), 4.97−4.45 (m, 8H, 4 × CH_2Ph), 4.21 (ddd, 1H, $J_{4,5}$ = 10.0, $J_{5,6a}$ = 3.3, $J_{5,6b}$ = 2.0 Hz, H-5), 3.89−3.60 (m, 5H, H-2, H-3, H-4, H-6a, and H-6b) 1.89 (d, 1H, SH).

3β: ^{1}H NMR ($CDCl_3$) δ 7.45−7.10 (m, 20H, Ar), 4.97−4.45 (m, 9H, 4 × CH_2Ph, H-1), 3.89−3.60 (m, 4H, H-3, H-4, H-6a, H-6b), 3.51−3.45 (m, 1H, H-5), 3.41−3.34 (m, 1H, H-2), 2.31 (d, 1H, $J_{1,SH}$ = 8.1 Hz, SH),

Typical Procedure for the Reaction of 3 with 4b using Lewis Acid Catalysis. The thiol **3** (0.810 g, 1.45 mmol) and the ortho ester **4b** (0.822 g, 1.62 mmol) were stirred with freshly activated, crushed 4 Å molecular sieves in dry acetonitrile (15 mL) for 15 min at room temperature. Mercuric bromide (0.607 g, 1.68 mmol) was added, and the mixture was stirred under N_2 at room temperature for 46 h. Dichloromethane was added, the solids were removed by filtration through Celite, and the filtrate was washed with saturated aqueous $NaHCO_3$ solution and dried over $MgSO_4$. Solvents were removed in vacuo, and the crude product mixture was separated by column chromatography on silica gel (toluene/EtOAc, 8:1). This yielded the pure methyl glycoside **5** as a colorless oil (0.487 g, 59%) in addition to slightly less-polar fractions that were shown by ^{1}H NMR to be impure mixtures of **5** with several isomeric 1,1′-thiodisaccharides **D** (Scheme 5). The major disaccharide components, compounds **9** and **31** (ratio **9**:**31** = 1:2), were estimated to have been formed in <5% yield. The thiol **3** had been mostly oxidized during processing to a mixture of disulfides found in the least-polar fractions. Similar results were obtained with the other Lewis acid catalysts (BF_3, $ZnCl_2$, and $SnCl_4$)

Compound **5**: $[\alpha]_D$ +31 (*c* 1.8, $CHCl_3$) (lit.[10b] +27.5 (*c* 1.30, $CHCl_3$)); ^{1}H NMR ($CDCl_3$): δ 7.4−7.1 (m, 15H, Ph), 5.36

(dd, 1H, $J_{1,2}$ = 1.8, $J_{2,3}$ = 3.3 Hz, H-2), 4.86, 4.47 (2d, each 1H, $J_{A,B}$ = 10.8 Hz, CH_2Ph), 4.73 (d, 1 H, H-1), 4.69, 4.52 (2d, each 1H, $J_{A,B}$ = 11.2 Hz, CH_2Ph), 4.68, 4.52 (2d, each 1H, $J_{A,B}$ = 12.1 Hz, CH_2Ph), 3.97 (dd, 1H, $J_{3,4}$ = 9.3 Hz, H-3), 3.87 (dd, 1H, $J_{4,5}$ = 9.3 Hz, H-4), 3.80 (dd, $J_{5,6a}$ = 4.2, $J_{6a,6b}$ = 10.2 Hz, H-6a), 3.79−3.68 (m, 2H, H-5 and H-6b), 3.36 (s, 3H, OCH_3), 2.17 (s, 3H, OAc); MALDI MS *m/e* 529.3 (M^+ + Na).

2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-1-thio-α-D-mannopyranose (8). A solution of 3,4,6-tri-*O*-benzyl-*β*-D-mannopyranose 1,2-(methyl orthoacetate) **4b**[12] (2.58 g, 5.09 mmol) in CH_2Cl_2 (40 mL) was stirred in an ice bath while HBr/HOAc (3.0 mL, 35 wt %) was added dropwise. After 15 min, the solution was washed with ice−water and cold saturated $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated to leave the unstable mannosyl bromide **6** as a pale yellow oil (2.88 g). The oil was dissolved in dry acetone (10 mL), and the solution was added to freshly activated 4 Å molecular sieves (2 g) and thiourea (388 mg, 5.10 mmol). The mixture was maintained at reflux temperature under a dry N_2 atmosphere for 2.5 h, cooled, and filtered through Celite. Solvent removal and trituration of the syrupy residue with hexanes gave **7** as a colorless amorphous powder (3.10 g). Attempted crystallization of this salt from a variety of mixed-solvent systems was unsuccessful. The crude product was dissolved in CH_2Cl_2 (40 mL), a solution of $Na_2S_2O_5$ (2.0 g) in water (20 mL) was added, and the mixture was heated at 40 °C for 45 min. After cooling, the CH_2Cl_2 layer was separated and washed with water and saturated aqueous sodium chloride solution. Drying over anhyd Na_2SO_4, filtration, and evaporation of the solvent gave the thiol **8** as a syrup (2.32 g, 89%): $[\alpha]_D$ +60.3 (*c* 2.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.4−7.1 (m, 15H, Ph), 5.59 (dd, 1 H, $J_{1,2}$ = 1.7 Hz, $J_{1,SH}$ = 7.2 Hz, H-1), 5.42 (dd, 1H, $J_{2,3}$ = 3.1 Hz, H-2), 4.84, 4.48 (2d, each 1H, $J_{A,B}$ = 10.7 Hz, CH_2Ph), 4.69, 4.54 (2d, each 1H, $J_{A,B}$ = 11.2 Hz, CH_2Ph), 4.66, 4.50 (2d, each 1H, $J_{A,B}$ = 12.1 Hz, CH_2Ph), 4.13 (ddd, 1H, $J_{4,5}$ = 9.3, $J_{5,6a}$ = 4.3, $J_{5,6b}$ = 1.9 Hz, H-5), 3.96 (dd, 1H, $J_{3,4}$ = 9.3 Hz, H-3), 3.91 (dd, 1H, H-4), 3.81 (dd, $J_{6a,6b}$ = 10.9 Hz, H-6a), 3.67 (dd, H-6b), 2.17 (d, 1H, SH), 2.16 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$) δ 170.32 (OAc, *C*═O), 138.15, 138.03, 137.50 (3 × C-*ipso*, Ph), 128.47−127.65 (15C, Ph), 77.38, 77.23 (C-1, C-3), 75.26 (*C*H_2Ph), 74.36 (C-4), 73.44 (C-5), 72.44 (*C*H_2-Ph), 71.92 (*C*H_2Ph), 71.36 (C-2), 68.59 (C-6), 21.10 (OAc); MALDI MS *m/e* 531.3 (M^+ + Na). Anal. Calcd for $C_{29}H_{32}O_6S$: C, 68.48; H, 6.34. Found: C, 68.52; H, 6.56.

2,3,4,6-Tetra-*O*-benzyl-*β*-D-glucopyranosyl 2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-1-thio-α-D-mannopyranoside (9). 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose (1.35 g, 2.50 mmol) was dissolved in CH_2Cl_2 (25 mL) containing a catalytic amount of DMF (0.20 mL). A solution of oxalyl chloride (0.85 mL, 9.7 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 10 min. The mixture was stirred at room temperature for 2 h and concentrated in vacuo to give the glycosyl chloride **1** quantitatively. To the chloride **1** was added a solution of the thiol **8** (1.13 g, 2.22 mmol) in acetone (20 mL). Solid *n*-Bu_4NBr (0.15 g, 0.46 mmol) and K_2CO_3 (1.0 g, 7.2 mmol) were added, and the heterogeneous mixture was refluxed under N_2 for 18 h. The mixture was cooled, the acetone was removed in vacuo, and the residue was partitioned between CH_2Cl_2 and water. The organic phase was washed with water, dried over anhyd $MgSO_4$, and concentrated to give a dark, red-brown oil. The oil was acetylated by treatment with acetic anhydride (3 mL), pyridine (7 mL), and a catalytic amount of 4-(dimethylamino)-pyridine for 4 h at 45 °C. The mixture was concentrated on high vacuum and coevaporated with toluene. Purification by silica gel chromatography (hexanes/EtOAc, 3:1) yielded **9** as a pale-yellow syrup (1.02 g, 45%). Analysis by ^{1}H NMR indicated a purity of >90% with minor amounts of anomeric isomers: $[\alpha]_D$ +47 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.4−7.1 (m, 35H, Ph), 5.67 (d, 1H, $J_{1',2'}$ = 1.5 Hz, H-1′), 5.53 (dd, 1H, $J_{2',3'}$ = 2.9 Hz, H-2′), 4.89, 4.85 (2d, each 1H, $J_{A,B}$ = 10.7 Hz, CH_2Ph), 4.89, 4.75 (2d, each 1H, $J_{A,B}$ = 10.3 Hz, CH_2Ph), 4.85, 4.46 (2d, each 1H, $J_{A,B}$ = 10.3 Hz, CH_2Ph), 4.80, 4.57 (2d, each 1H, $J_{A,B}$ = 10.8 Hz, CH_2Ph), 4.70, 4.52 (2d, each 1H, $J_{A,B}$ = 11.1 Hz, CH_2Ph), 4.58, 4.36 (2d, each 1H, $J_{A,B}$ = 12.0 Hz, CH_2Ph), 4.56, 4.49 (2d, each1 H, $J_{A,B}$ = 12.0 Hz, CH_2Ph), 4.46 (d, 1H, $J_{1,2}$ = 9.2 Hz, H-1), 4.14 (ddd, 1H, $J_{4',5'}$ = 9.5, $J_{5',6a'}$ = 3.5, $J_{5',6b'}$ = 1.8 Hz, H-5′), 3.98 (t, 1H, $J_{3'4'}$ = 9.5 Hz, H-4′), 3.92 (dd, 1H, H-3′), 3.74 (dd, 1H, $J_{6a',6b'}$ = 10.6 Hz, H-6a′), 3.68 (dd, 1H, $J_{3,4}$ = $J_{4,5}$ = 8.9 Hz, H-4), 3.68 (dd, 1H $J_{5,6a}$ = 3.1 Hz, $J_{6a,6b}$ = 11.5 Hz, H-6a), 3.64 (dd, 1H, $J_{5,6b}$ = 2.0 Hz, H-6b), 3.62 (dd, 1H, $J_{2,3}$ = 8.9 Hz, H-3), 3.58 (dd, 1H, H-6b′), 3.57 (t, 1H, H-2), 3.44 (ddd, 1H, H-5), 2.07 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$) δ 169.96 (OAc, *C*═O), 138.65, 138.53, 138.38, 138.23 (2C), 138.11, 137.75 (7 × C-*ipso*, Ph), 128.40−127.53 (35C, Ph), 86.66 (C-3), 84.22 (C-1), 81.84 (C-2), 81.49 (C-1′), 79.58 (C-5), 78.43 (C-3′), 77.63 (C-4), 75.53, 75.42, 75.13, 74.97 (*C*H_2Ph), 74.38 (C-4′), 73.59, 73.42 (*C*H_2Ph), 73.35 (C-5′), 71.86 (*C*H_2-Ph), 70.75 (C-2′), 68.87 (C-6′), 68.74 (C-6), 20.92 (OAc); MALDI MS *m/e* 1053.8 (M^+ + Na). Anal. Calcd for $C_{63}H_{66}O_{11}S$: C, 73.37; H, 6.45. Found: C, 73.06; H, 6.37.

2,3,4,6-Tetra-*O*-benzyl-*β*-D-glucopyranosyl 2-*O*-Methanesulfonyl-3,4,6-tri-*O*-benzyl-1-thio-α-D-mannopyranoside (11). A solution of the acetate **9** (1.96 g, 1.90 mmol) in CH_2Cl_2 (30 mL) was added to a NaOMe/MeOH solution (100 mL, 0.04 M), and the mixture was kept at room temperature for 4 h. The reaction mixture was neutralized by stirring with Rexyn 101 H^+ ion-exchange resin, filtered, and concentrated to give a syrup. Pure **10** was obtained by column chromatography (hexanes/EtOAc, 2:1) as a colorless glass (1.63 g, 89%): $[\alpha]_D$ +78 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.4−7.1 (m, 35H, Ph), 5.69 (d, 1H, $J_{1',2'}$ = 1.6 Hz, H-1′), 4.89, 4.75 (2d, each 1H, $J_{A,B}$ = 10.5 Hz, CH_2Ph), 4.88, 4.85 (2d, each 1H, $J_{A,B}$ = 11.1 Hz, CH_2Ph), 4.82, 4.49 (2d, each 1H, $J_{A,B}$ = 11.0 Hz, CH_2Ph), 4.80, 4.57 (2d, each 1H, $J_{A,B}$ = 10.9 Hz, CH_2Ph), 4.70, 4.66 (2d, each 1H, $J_{A,B}$ = 11.5 Hz, CH_2Ph), 4.54, 4.37 (2d, each 1H, $J_{A,B}$ = 12.1 Hz, CH_2Ph), 4.53, 4.49 (2d, each 1H, $J_{A,B}$ = 9.9 Hz, CH_2-Ph), 4.47 (d, 1H, $J_{1,2}$ = 9.5 Hz, H-1), 4.14 (dd, 1H, $J_{2',3'}$ = 3.1 Hz, H-2′), 4.14 (ddd, 1H, $J_{4',5'}$ = 9.6 Hz, $J_{5',6a'}$ 3.6, $J_{5',6b'}$ 2.0 Hz, H-5′), 3.97 (dd, 1H, $J_{3'4'}$ 9.1 Hz, H-4′), 3.84 (dd, 1H, H-3′), 3.68 (dd, 1H, $J_{6a',6b'}$ = 10.8 Hz, H-6a′), 3.67−3.59 (m, 4H, H-3, H-4, H-6a, H-6b), 3.58−3.53 (m, 1H, H-2), 3.54 (dd, 1H, H-6b′), 3.44 (m, 1H, H-5); ^{13}C NMR ($CDCl_3$) δ 138.54, 138.39, 138.09 (4C), 137.67 (7 × C-*ipso*, Ph), 128.55−127.59 (35C, Ph), 86.63 (C-3), 84.22 (C-1), 82.97 (C-1′), 81.73 (C-2), 80.06 (C-3′), 79.28 (C-5), 77.52 (C-4), 75.60, 75.34, 75.05, 74.99 (4 × *C*H_2Ph), 74.20 (C-4′), 73.37 (2C, 2 × *C*H_2Ph), 72.85 (C-5′), 72.04 (*C*H_2Ph), 70.35 (C-2′), 68.62 (C-6), 68.47 (C-6′); MALDI MS *m/e* 1011.6 (M^+ + Na).

The alcohol **10** (1.60 g, 1.62 mmol) was dissolved in CH_2Cl_2 (15 mL), pyridine (2.5 mL) and methanesulfonyl chloride (1.0 mL, 13 mmol) were added, and the reaction mixture was kept at room temperature for 3 h. The mixture was diluted with CH_2Cl_2 and stirred with saturated aqueous $NaHCO_3$ solution for 0.5 h to hydrolyze excess methanesulfonyl chloride. The organic phase was separated, washed with saturated aqueous $NaHCO_3$, and dried over $MgSO_4$. Solvent removal left a yellow oil that was purified by column chromatography (hexanes/EtOAc, 5:2) to yield **11** as a colorless waxy solid (1.54 g, 89%): $[\alpha]_D$ +43 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.4−7.1 (m, 35H, Ph), 5.82 (d, 1H, $J_{1',2'}$ = 1.9 Hz, H-1′), 5.20 (dd, 1H, $J_{2',3'}$ = 2.3 Hz, H-2′), 4.90, 4.85 (2d, each 1H, $J_{A,B}$ = 11.1 Hz, CH_2Ph), 4.89, 4.74 (2d, each 1H, $J_{A,B}$ = 10.3 Hz, CH_2Ph), 4.82, 4.48 (2d, each 1H, $J_{A,B}$ = 10.7 Hz, CH_2Ph), 4.81, 4.57 (2d, each 1H, $J_{A,B}$ = 10.8 Hz, CH_2Ph), 4.80, 4.62 (2d, each 1H, $J_{A,B}$ = 11.1 Hz, CH_2Ph), 4.56, 4.50 (2d, each 1H, $J_{A,B}$ = 12.1 Hz, CH_2Ph), 4.55, 4.39 (2d, each 1H, $J_{A,B}$ = 12.0 Hz, CH_2Ph), 4.47 (d, 1H, $J_{1,2}$ = 9.2 Hz, H-1), 4.10−4.04 (m, 1H, H-5′), 3.96−3.88 (m, 2H, H-3′, H-4′), 3.72 (dd, 1H, $J_{5',6a'}$ = 4.0, $J_{6a',6b'}$ = 11.0 Hz, H-6a′), 3.70−3.63 (m, 3H, H-4, H-6a, H-6b), 3.68 (dd, 1H, H-4), 3.64 (dd, 1H, $J_{2,3}$ = $J_{3,4}$ = 8.6 Hz, H-3), 3.58 (dd, 1H, H-2), 3.57 (dd, 1H, $J_{5',6b'}$ = 1.9 Hz, H-6b′), 3.47 (ddd, 1H, $J_{4,5}$ = 9.4, $J_{5,6a}$ = 3.4, $J_{5,6b}$ = 2.3 Hz, H-5), 2.92 (s, 3H, OSO_2-CH_3); ^{13}C NMR ($CDCl_3$) δ 139.0−137.0 (7 × C-*ipso*, Ph), 128.46−127.53 (35C, Ph), 86.60 (C-3), 83.77 (C-1), 81.46 (C-2), 80.88 (C-1′), 79.54 (C-5), 78.80 (C-2′), 77.85 (C-3′), 77.18 (C-4), 75.52, 75.35, 75.10, 74.94 (4 × *C*H_2Ph), 74.16 (C-4′), 74.06 (C-5′), 73.55, 73.45, 72.64 (3 × CH_2Ph), 68.94 (C-6), 68.56 (C-6′), 32.87 (OMs, CH_3); MALDI MS *m/e* 1089.3 (M^+ + Na). Anal. Calcd for $C_{62}H_{66}O_{12}S_2$: C, 69.79; H, 6.23. Found: C, 69.77; H, 6.22.

Methyl 3,4,6-Tri-*O*-benzyl-2-*S*-(2,3,4,6-tetra-*O*-benzyl-*β*-D-glucopyranosyl)-2-thio-α/*β*-D-glucopyranoside (12α

and 12*β*). The mesylate **11** (1.42 g, 1.33 mol) and $NaHCO_3$ (2.0 g) were added to MeOH (100 mL), and the mixture was stirred at reflux for 26 h. The reaction mixture was cooled, and the MeOH was removed on the rotary evaporator. The residue was partitioned between EtOAc and water. The organic phase was washed with water and saturated aqueous NaCl solution and dried over $MgSO_4$. The solvent was removed to yield a colorless syrup (1.36 g, 100%). Analysis of the mixture by ^{1}H NMR showed an anomeric methyl glycoside mixture with a 3:1 ratio of **12***β*:**12**α. The mixture was subjected to column chromatography (hexanes:EtOAc, 3:1) to obtain analytical samples of the two products. Complete separation could not be achieved.

The minor, less-polar, **12**α-isomer (R_f 0.31) was isolated as a colorless syrup: $[\alpha]_D$ +24 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.4−7.1 (m, 35H, Ph), 5.00, 4.78 (2d, each 1H, $J_{A,B}$ = 10.2 Hz, CH_2Ph), 4.95, 4.74 (2d, each 1H, $J_{A,B}$ = 10.6 Hz, CH_2Ph), 4.92 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 4.87, 4.78 (2d, each 1H, $J_{A,B}$ = 10.9 Hz, CH_2Ph), 4.85, 4.52 (2d, each 1H, $J_{A,B}$ = 10.9 Hz, CH_2Ph), 4.82 (d, 1H, $J_{1',2'}$ = 9.9 Hz, H-1′), 4.78, 4.54 (2d, each 1H, $J_{A,B}$ = 10.6 Hz, CH_2Ph), 4.64, 4.53 (2d, each 1H, $J_{A,B}$ = 12.1 Hz, CH_2Ph), 4.61, 4.50 (2d, each 1H, $J_{A,B}$ = 12.1 Hz, CH_2Ph), 3.98 (dd, 1H, $J_{2,3}$ = 10.9, $J_{3,4}$ = 8.8 Hz, H-3), 3.83 (ddd, 1H, $J_{4,5}$ = 10.1, $J_{5,6a}$ = 3.8, $J_{5,6b}$ = 1.9 Hz, H-5), 3.77 (dd, 1H, $J_{6a,6b}$ = 10.5 Hz, H-6a), 3.71 (dd, 1H, $J_{6a',6b'}$ = 12.5 Hz, H-6a′), 3.68 (dd, 1H, H-6b), 3.67 (dd, 1H, H-6b′), 3.67 (dd, 1H, H-4), 3.63 (dd, 1H, H-4′), 3.49 (dd, 1H, $J_{2',3'}$ = $J_{3',4'}$ = 9.0 Hz, H-3′), 3.38 (s, 3H, OCH_3), 3.37 (dd, 1H, H-2′), 3.33 (ddd, 1H, $J_{4',5'}$ = 9.6, $J_{5',6a'}$ = 2.5, $J_{5',6b'}$ = 3.7 Hz, H-5′), 3.24 (dd, 1H, H-2); ^{13}C NMR ($CDCl_3$) δ 138.45, 138.31, 138.25, 138.16, 138.14 (2C), 137.95 (7 × C-*ipso*, Ph), 128.37−127.49, (35C, Ph), 101.18 (C-1), 86.57 (C-3′), 85.70 (C-1′), 83.27 (C-3), 82.36 (C-2′), 79.24 (C-4), 78.75 (C-5′), 77.84 (C-4′), 76.11, 75.77, 75.51, 74.96 (2C), 73.55, 73.46, (7 × *C*H_2Ph), 70.71 (C-5), 68.83 (C-6′), 68.67 (C-6), 55.31 (OCH_3), 48.90 (C-2); MALDI MS *m/e* 1025.8 (M^+ + Na). Anal. Calcd for $C_{62}H_{66}O_{10}S$: C, 74.23; H, 6.63. Found: C, 74.06; H, 6.58.

The major, more-polar, **12***β*-isomer (R_f 0.24) was isolated as a colorless amorphous solid: $[\alpha]_D$ +8.3 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.4−7.1 (m, 35H, Ph), 4.99, 4.79 (2d, each 1H, $J_{A,B}$ = 10.5 Hz, CH_2Ph), 4.94, 4.72 (2d, each 1H, $J_{A,B}$ = 10.5 Hz, CH_2Ph), 4.88 (d, 1H, $J_{1',2'}$ = 9.8 Hz, H-1′), 4.86, 4.77 (2d, each 1H, $J_{A,B}$ = 11.7 Hz, CH_2Ph), 4.78, 4.54 (2d, each 1H, $J_{A,B}$ = 10.9 Hz, CH_2Ph), 4.77, 4.52 (2d, each 1H, $J_{A,B}$ = 11.0 Hz, CH_2-Ph), 4.62, 4.54 (2d, each 1H, $J_{A,B}$ = 12.2 Hz, CH_2Ph), 4.58, 4.51 (2d, each 1H, $J_{A,B}$ = 12.3 Hz, CH_2Ph), 4.38 (d, 1H, $J_{1,2}$ = 8.7 Hz, H-1), 3.73 (dd, 1H, $J_{6a,6b}$ = 10.6 Hz, H-6a), 3.71 (dd, 1H, $J_{6a',6b'}$ = 11.0 Hz, H-6a′), 3.69 (dd, 1H, $J_{2,3}$ = 10.4, $J_{3,4}$ = 9.7 Hz, H-3), 3.68 (dd, 1H, H-6b), 3.64 (dd, 1H, H-6b′), 3.59 (dd, 1H, H-4′), 3.58 (dd, 1H, H-4), 3.53 (dd, 1H, $J_{2',3'}$ = $J_{3',4'}$ = 8.6 Hz, H-3′), 3.51 (s, 3H, OCH_3), 3.48 (ddd, 1H, $J_{4,5}$ = 9.6, $J_{5,6a}$ = 2.4, $J_{5,6b}$ = 4.3 Hz, H-5), 3.42 (dd, 1H, H-2′), 3.39 (ddd, 1H, $J_{4',5'}$ = 9.1, $J_{5',6a'}$ = 2.1, $J_{5',6b'}$ = 4.8 Hz, H-5′), 3.20 (dd, 1H, H-2); ^{13}C NMR ($CDCl_3$) δ 138.50−138.07 (7 × C-*ipso*, Ph), 128.37−127.48, (35C, Ph), 102.85 (C-1), 86.64 (C-3′), 85.11 (C-3), 84.29 (C-1′), 82.53 (C-2′), 79.27 (C-4′), 78.99 (C-5′), 77.91 (C-4), 75.89, 75.70, 75.38, 74.98 (2C), (5 × *C*H_2Ph), 74.85 (C-5), 73.54, 73.50, (2 × *C*H_2Ph), 69.10, 68.93 (C-6, C-6′), 55.43 (OCH_3), 50.35 (C-2); MALDI MS *m/e* 1025.8 (M^+ + Na). Anal. Calcd for $C_{62}H_{66}O_{10}S$: C, 74.23; H, 6.63. Found: C, 74.32; H, 6.60.

Methyl 3,4,6-Tri-*O*-acetyl-2-*S*-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)-2-thio-α/*β*-D-glucopyranoside (13α and 13*β*). A solution of **12**α/**12***β* (1.05 g, 1.05 mmol) in dry THF (25 mL) was added to liquid NH_3 (∼60 mL) in a −50 °C bath. The cooling bath was removed, and small pieces of Na were added over 0.5 h during which time approximately half of the NH_3 was allowed to evaporate. When the solution remained a dark-blue color for 15 min, the color was discharged by the dropwise addition of MeOH (0.5 mL) and the remaining NH_3 was evaporated by gentle warming in a water bath. Solvents were removed in vacuo, and the crude orange-brown residue was acetylated by treatment with pyridine (20 mL) and acetic anhydride (12 mL) for 4 h at room temperature. The reaction mixture was concentrated in vacuo to give a syrup that was then dissolved in CH_2Cl_2. The solution was washed with saturated $NaHCO_3$ solution and water, dried ($MgSO_4$), and concentrated to give a red-brown oil. Analysis by TLC indicated a complex mixture of several components. Separation by column chromatography (hexanes/EtOAc, 2:3) gave a mixture of **13**α and **13***β* (α/*β*, 1:1.9; 116 mg; 23%). ^{1}H NMR analysis of several faster running impurities indicated the presence of mostly acetylated monosaccharide deivatives, the result of cleavage of the dissacharide **12** during the debenzylation reaction. Pure samples of the isomers **13**α and **13***β* were obtained by fractional crystallization from Et_2O/hexanes.

Compound **13**α: mp 166−168 °C; $[\alpha]_D$ +25 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.43 (dd, 1H, $J_{2,3}$ = 11.2, $J_{3,4}$ = 9.3 Hz, H-3), 5.14 (dd, 1H, $J_{2',3'}$ = $J_{3'4'}$ = 9.3 Hz, H-3′), 5.07 (dd, 1H, $J_{4',5'}$ = 9.7 Hz, H-4′), 4.99 (dd, 1H, $J_{4,5}$ = 9.8 Hz, H-4), 4.91 (d, 1H, $J_{1,2}$ = 3.4 Hz, H-1), 4.90 (dd, 1H, $J_{1',2'}$ = 10.3 Hz, H-2′), 4.68 (d, 1H, H-1′), 4.32 (dd, 1H, $J_{5,6a}$ = 4.4, $J_{6a,6b}$ = 12.3 Hz, H-6a), 4.28 (dd, 1H, $J_{5',6a'}$ = 4.9, $J_{6a',6b'}$ 12.4 Hz, H-6a′), 4.13 (dd, 1H, $J_{5',6b'}$ = 2.2 Hz, H-6b′), 4.06 (dd, 1H, $J_{5,6b}$ = 2.2 Hz, H-6b), 4.02 (ddd, 1H, H-5), 3.68 (ddd, 1H, H-5′), 3.38 (s, 3H, OCH_3), 3.11 (dd, 1H, H-2), 2.10, 2.09, 2.08, 2.03, 2.02, 2.01, 1.99 (7s, each 3H, 7 × OAc, CH_3); ^{13}C NMR ($CDCl_3$) δ 170.57 (2C), 170.17, 169.91, 169.70, 169.31, 169.18 (7 × OAc, *C*═O), 100.45 (C-1), 84.49 (C-1′), 75.99 (C-5′), 73.78 (C-3′), 73.08 (C-3), 70.15 (C-2′), 69.49 (C-4), 68.17 (C-4′), 67.70 (C-5), 61.99 (2C), (C-6, C-6′), 55.77 (OCH_3), 47.90 (C-2), 20.81−20.45 (7 × OAc, CH_3); MALDI MS *m/e* 689.3 (M^+ + Na). Anal. Calcd for $C_{27}H_{38}O_{17}S$: C, 48.65; H, 5.75. Found: C, 48.51, H, 5.68.

Compound **13***β*: mp 168−171 °C; $[\alpha]_D$ −8.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.15 (dd, 1H, $J_{2',3'}$ = $J_{3'4'}$ = 9.2 Hz, H-3′), 5.08 (dd, 1H, $J_{4',5'}$ = 9.7 Hz, H-4′), 5.05 (dd, 1H, $J_{2,3}$ 10.8, $J_{3,4}$ = 9.8 Hz, H-3), 4.98 (dd, 1H, $J_{1',2'}$ = 10.1 Hz, H-2′), 4.98 (dd, 1H, $J_{4,5}$ = 9.4 Hz, H-4), 4.75 (d, 1H, H-1′), 4.36 (d, 1H, $J_{1,2}$ = 8.6 Hz H-1), 4.30 (dd, 1H, $J_{5,6a}$ = 4.6, $J_{6a,6b}$ = 12.3 Hz, H-6a), 4.26 (dd, 1H, $J_{5',6a'}$ = 4.8, $J_{6'a,6b'}$ = 12.4 Hz, H-6a′), 4.13 (dd, 1H, $J_{5',6b'}$ = 2.4 Hz, H-6b′), 4.12 (dd, 1H, $J_{5,6b}$ = 2.3 Hz, H-6b), 3.68 (ddd, 1H, H-5′), 3.67 (ddd, 1H, H-5), 3.56 (s, 3H, OCH_3), 3.06 (dd, 1H, H-2), 2.08 (s, 6H, 2 × OAc, CH_3), 2.06, 2.05, 2.02, 2.01, 1.99 (5s, each 3H, 5 × OAc, CH_3); ^{13}C NMR ($CDCl_3$) δ 170.57−169.07 (7 × OAc, *C*═O), 103.69 (C-1), 83.65 (C-1′), 76.17 (C-5′), 73.91 (C-3′), 72.98 (C-3), 71.67 (C-5), 71.39 (C-2′), 69.43 (C-4), 68.15 (C-4′), 62.13 (C-6), 62.05 (C-6′), 57.25 (OCH_3), 49.77 (C-2), 20.71−20.56 (7 × OAc, CH_3); MALDI MS *m/e* 689.5 (M^+ + Na). Anal. Calcd for $C_{27}H_{38}O_{17}S$: C, 48.65; H, 5.75. Found: C, 48.57, H, 5.74.

3,4,6-Tri-*O*-benzoyl-[(*R*/*S*)-1,2-*O*-(1-methoxyethylidene]-*β*-D-mannopyranose (14). The ortho ester **4a**[12] (38.7 g, 107 mmol) was dissolved in MeOH (200 mL). The solution was saturated with NH_3 gas and kept at room temperature for 1.5 h. The solvent was removed to yield the intermediate deacylated triol as a pale-brown syrup. The syrup was dissolved in pyridine (200 mL) and stirred with ice-bath cooling while benzoyl chloride (55.0 mL, 474 mmol) was added dropwise. The cooling bath was removed, and the mixture was stirred at room temperature for 2 h. The reaction flask was re-cooled in an ice bath and small pieces of ice were added in order to hydrolyze excess benzoyl chloride. Dichloromethane (500 mL) was added, and the solution was washed with saturated aqueous $NaHCO_3$ solution. The organic phase was separated and concentrated by rotary evaporation, first at water-aspirator pressure and then with high vacuum to remove pyridine. This yielded crude **14** as a red-brown solid. The solid was dissolved in warm CH_2Cl_2 (∼100 mL) and filtered and the filtrate diluted with warm MeOH (∼250 mL) and cooled slowly. The crystalline solid (50.6 g) was collected by filtration and washed with cold MeOH. The mother liquors were concentrated, and the residue was purified by column chromatography to yield additional pure crystalline product (1.87 g). Compound **14** was obtained as a mixture of 1,2-ortho ester diastereomers, in 89% yield; *R*/*S* = 13:1 by ^{1}H NMR: mp 155−157 °C; $[\alpha]_D$ −22.8 (*c* 2.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) *R* isomer δ 8.1−7.3 (m, 15H, Ph), 5.92 (dd, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.7 Hz, H-4), 5.67 (d, 1H, $J_{1,2}$ = 2.6 Hz, H-1), 5.56 (dd, 1H, $J_{2,3}$ = 4.0 Hz, H-3), 4.86 (dd, 1H, H-2), 4.62 (dd, 1H, $J_{5,6a}$ = 3.2 Hz, $J_{6a,6b}$ = 12.1 Hz, H-6a), 4.46 (dd, 1H, $J_{5,6b}$ = 4.7 Hz, H-6b), 4.07 (ddd, 1H, H-5), 3.26 (s, 3H, OCH_3), 1.77 (s, 3H, ortho ester

CH_3); *S* isomer δ 8.1−7.3 (m, 15H, Ph), 6.04 (dd, 1H, $J_{3,4} = J_{4,5} = 9.9$ Hz, H-4), 5.61 (dd, 1H, $J_{2,3} = 4.2$ Hz, H-3), 5.43 (d, 1H, $J_{1,2} = 2.5$ Hz, H-1), 4.72 (dd, 1H, $J_{5,6a} = 2.7$ Hz, $J_{6a,6b} = 12.2$ Hz, H-6a), 4.63 (dd, 1H, H-2), 4.41 (dd, 1H, $J_{5,6b} = 3.9$ Hz, H-6b), 4.07 (ddd, 1H, H-5), 3.42 (s, 3H, OCH_3), 1.50 (s, 3H, ortho ester CH_3); ^{13}C NMR ($CDCl_3$) *R* isomer δ 166.07, 165.96, 165.24 (3 × OBz, *C*═O), 133.39−124.50 (18C, Ph), 124.5 (ortho ester C) 97.75 (C-1), 76.75 (C-2), 71.78 (C-5), 71.47 (C-3), 66.59 (C-4), 63.30 (C-6), 49.88 (OCH_3), 24.25 (ortho ester *C*H_3); MALDI MS *m/e* 571.2 (M^+ + Na). Anal. Calcd for $C_{30}H_{28}O_{10}$: C, 65.69; H, 5.14. Found: C, 65.81; H, 5.14.

2-*O*-Acetyl-3,4,6-tri-*O*-benzoyl-α-D-mannopyranose-1-isothiouronium Bromide (16). The ortho ester **14** (5.49 g, 10.0 mmol) was dissolved in CH_2Cl_2 (60 mL). The solution was cooled in an ice bath and stirred while a solution of HBr/HOAc (35 wt %, 5 mL) was added dropwise. After 30 min, the mixture was diluted with CH_2Cl_2 and washed with ice-cold water and cold saturated $NaHCO_3$ solution. The organic phase was dried over $MgSO_4$ and evaporated to give crude bromide **15** as a colorless syrup in quantitative yield: ^{1}H NMR ($CDCl_3$) δ 8.08−7.88 (3m, 6H, 3 × OBz *ortho* H's), 7.59−7.33 (m, 9H, 3 × OBz, *meta* and *para* H's), 6.43 (d, 1 H, $J_{1,2} = 1.3$ Hz, H-1), 6.16 (dd, 1H, $J_{2,3} = 3.3$, $J_{3,4} = 10.2$ Hz, H-3), 6.03 (dd, 1H, $J_{4,5} = 10.1$ Hz, H-4), 5.68 (dd, 1H, H-2), 4.66 (dd, 1H, $J_{5,6a} = 2.6$, $J_{6a,6b} = 12.2$ Hz, H-6a), 4.59 (ddd, 1H, $J_{5,6b} = 4.5$ Hz, H-5), 4.49 (dd, 1H, H-6b), 2.13 (s, 3H, OAc). The sensitive bromide **15** was immediately dissolved in dry acetonitrile (20 mL) and refluxed with thiourea (803 mg, 10.5 mmol) under N_2 for 4 h. The mixture was cooled and the solvent removed in vacuo to leave a colorless foam. This was triturated with Et_2O to produce an easily filtered solid. Filtration and washing of the filter cake with anhyd Et_2O gave the crude thiourea derivative **16** as a dry, powdery, amorphous solid containing some thiourea hydrobromide (6.65 g, >90%, ~90% α-isomer). Attempts to crystallize this material from a variety of solvent systems were not successful: ^{1}H NMR ($CDCl_3$) δ 9.62 (2H, brs, NH_2), 8.62 (2H, brs, NH_2), 8.01−7.82 (m, 6H, 3 × OBz, *ortho* H's), 7.59−7.25 (m, 9H, 3 × OBz, *meta* and *para* H's), 6.50 (brs, 1 H, H-1), 5.94 (dd, 1H, $J_{3,4} = J_{4,5} = 10.0$ Hz, H-4), 5.69 (dd, 1H, $J_{1,2} = 1.2$, $J_{2,3} = 3.6$ Hz, H-2), 5.54 (dd, 1H, H-3), 4.83 (ddd, 1H, $J_{5,6a} = 2.4$, $J_{5,6b} = 5.6$ Hz, H-5), 4.73 (dd, 1H, $J_{6a,6b} = 12.8$ Hz, H-6a), 4.48 (dd, 1H, H-6b), 1.91 (s, 3H, OAc, CH_3); ^{13}C NMR ($CDCl_3$) δ 169.50 (*C*═NH_2), 169.22 (OAc, *C*═O), 166.06, 165.53, 165.31 (3 × OBz, *C*═O), 133.72, 133.63, 133.49 (3 × OBz, C_{para}), 129.93−128.50 (15C, Ph), 82.68 (C-1), 72.13 (C-5), 70.09 (C-3), 69.06 (C-2), 65.98 (C-4), 62.53 (C-6), 20.33 (OAc, CH_3); MALDI MS *m/e* 615.2 (19, M^+ − HBr + Na), 593.1 (16, M^+ − Br), 517.1 (100, $M^+ - CH_4N_2BrS$).

2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl 2-*O*-Acetyl-3,4,6-tri-*O*-benzoyl-1-thio-α-D-mannopyranoside (19). 2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranosyl bromide **18**[19] (165 mg, 0.250 mmol) and the isothiouronium salt **16** (136 mg, 0.202 mmol) were dissolved in EtOAc (4 mL) and added to a solution of *n*-Bu_4NHSO_4 (102 mg, 0.300 mmol) in saturated aqueous $NaHCO_3$ (2.0 mL). The mixture was stirred rapidly at room temperature for 48 h during which time the product **19** slowly began to crystallize. The mixture was diluted with CH_2Cl_2 and washed with water. The organic phase was dried over $MgSO_4$ and concentrated to a solid. Purification by silica gel chromatography (hexanes/EtOAc, 2:1) yielded **19** as a colorless crystalline solid (194 mg, 85%). An analytical sample was obtained by recrystallization from CH_2Cl_2: mp 207−208 °C; $[\alpha]_D$ +40 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.13−7.78 (7m, 14H, 7 × OBz, *ortho* H's), 7.58−7.25 (m, 21H, 7 × OBz, *meta* and *para* H's), 6.04 (dd, 1H, $J_{3',4'} = J_{4',5'} = 10.0$ Hz, H-4′), 5.88 (dd, 1H, $J_{2,3} = J_{3,4} = 9.5$ Hz, H-3), 5.82 (d, 1H, $J_{1',2'} = 1.5$ Hz, H-1′), 5.74 (dd, 1H, $J_{4,5} = 9.9$ Hz, H-4), 5.71 (dd, 1H, $J_{1,2} = 9.9$ Hz, H-2), 5.61 (dd, 1H, $J_{2',3'} = 3.2$ Hz, H-3′), 5.53 (dd, 1H, H-2′), 5.08 (d, 1H, H-1), 4.71 (dd, 1H, $J_{5',6a'} = 2.9$, $J_{6a',6b'} = 12.3$ Hz, H-6a′), 4.69 (dd, 1H, $J_{5,6a} = 2.8$, $J_{6a,6b} = 12.4$ Hz, H-6a), 4.62 (ddd, 1H, $J_{5',6b'} = 3.0$ Hz, H-5′), 4.48 (dd, 1H, H-6b′), 4.40 (dd, 1H, $J_{5,6b} = 4.3$ Hz, H-6b), 4.19 (ddd, 1H, H-5), 2.02 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$) δ 169.38 (OAc, *C*═O), 165.97 (2C), 165.78, 165.34, 165.25, 165.06, 165.00 (7 × OBz, *C*═O), 133.40−132.93 (7 × OBz, C_{para}), 130.12−128.30 (35C, Ph), 82.94 (C-1), 81.22 (C-1′), 76.85 (C-5), 74.21 (C-3), 71.54 (C-2), 71.29 (C-2′), 70.66 (C-5′), 70.14(C-3′), 69.12 (C-4), 66.75 (C-4′), 62.69 (2C, C-6, C-6′), 20.48 (OAc, CH_3); MALDI MS *m/e* 1151.3 (M^+ + Na). Anal. Calcd for $C_{63}H_{52}O_{18}S$: C, 67.01; H, 4.64. Found: C, 66.96; H, 4.68.

2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl 3,4,6-Tri-*O*-benzoyl-1-thio-α-D-mannopyranoside (20). A solution of HCl/MeOH was prepared by adding acetyl chloride (1.2 mL, 1.8 mmol) to MeOH (30 mL) with ice-bath cooling. Chloroform (30 mL) and the acetate **19** (1.13 g, 1.00 mmol) were added, and the mixture was stirred at reflux. Periodic analysis by TLC (toluene/EtOAc, 3:1) indicated formation of the desired product as a slightly more polar component along with minor amounts of even more polar compounds due to the slower hydrolysis of the benzoate esters. The reaction was terminated after 10.5 h when ~20% of the starting material remained. The mixture was cooled and diluted with $CHCl_3$. The organic phase was washed with saturated aqueous $NaHCO_3$ solution and water. The solution was dried over $MgSO_4$ and concentrated to a syrup. Column chromatography (toluene/EtOAc, 5:1) yielded recovered **19** (146 mg, 13%) and **20** (523 mg, 48%) as a colorless amorphous solid: $[\alpha]_D$ +78 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.13−7.78 (7m, 14H, 7 × OBz, *ortho* H's), 7.58−7.25 (m, 21H, 7 × OBz, *meta* and *para* H's), 6.05 (dd, 1H, $J_{3',4'} = J_{4',5'} = 9.8$ Hz, H-4′), 5.90 (dd, 1H, $J_{2,3} = J_{3,4} = 9.5$ Hz, H-3), 5.76 (d, 1H, $J_{1',2'} = 2.0$ Hz, H-1′), 5.73 (dd, 1H, $J_{4,5} = 10.0$ Hz, H-4), 5.70 (dd, 1H, $J_{1,2} = 9.9$ Hz, H-2), 5.50 (dd, 1H, $J_{2',3'} = 3.0$ Hz, H-3′), 5.10 (d, 1H, H-1), 4.72−4.62 (m, 3H, H-5, H-6a, H-6a′), 4.51 (dd, 1H, $J_{5',6b'} = 3.3$, $J_{6'a,6b'} = 12.0$ Hz, H-6b′), 4.42 (dd, 1H, $J_{5,6b} = 4.6$, $J_{6a,6b} = 12.3$ Hz, H-6b), 4.37 (dd, 1H, H-2′), 4.20 (ddd, 1H, $J_{5,6a} = 2.8$ Hz, H-5), 2.46 (bs, 1H, O*H*); ^{13}C NMR ($CDCl_3$) δ 166.08 (2C), 165.79, 165.42, 165.33, 165.09, 164.94 (7 × OBz, *C*═O), 133.42−132.87 (7 × OBz, C_{para}), 130.02−128.28 (35C, Ph), 83.47 (C-1′), 82.98 (C-1), 76.90 (C-5), 74.22 (C-3), 72.59 (C-3′), 71.69 (C-2), 70.55 (C-2′), 70.50 (C-5′), 69.20 (C-4), 66.82 (C-4′), 62.75 (2C, C-6, C-6′); MALDI MS *m/e* 1109.5 (M^+ + Na). Anal. Calcd for $C_{61}H_{50}O_{17}S$: C, 67.40; H, 4.64. Found: C, 67.61; H, 4.76.

2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl 2-*O*-Methanesulfonyl-3,4,6-tri-*O*-benzoyl-1-thio-α-D-mannopyranoside (21). The alcohol **20** (809 mg, 0.744 mmol) was dissolved in pyridine (12 mL), and methanesulfonyl chloride (2.0 mL, 26 mmol) was added. The reaction mixture was kept at room temperature for 1.5 h. Volatile material was removed by application of high vacuum, and the residue was diluted with CH_2Cl_2. The solution was washed with saturated aqueous $NaHCO_3$ solution, 2 M aqueous HCl solution, and saturated aqueous $NaHCO_3$ solution and dried over $MgSO_4$. Solvent removal left a pale-orange oil that was crystallized from CH_2Cl_2/hexanes to yield **21** as a colorless crystalline solid (746 mg, 86%): mp 203−204 °C; $[\alpha]_D$ +33 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.08−7.78 (m, 14H, 7 × OBz, *ortho* H's), 7.58−7.25 (m, 21H, 7 × OBz, *meta*,*para* H's), 6.02 (d, 1H, $J_{1',2'} = 1.8$ Hz, H-1′), 6.00 (dd, 1H, $J_{3',4'} = J_{4',5'} = 10.0$ Hz, H-4′), 5.90 (dd, 1H, $J_{2,3} = J_{3,4} = 9.5$ Hz, H-3), 5.74 (dd, 1H, $J_{4,5} = 9.8$ Hz, H-4), 5.72 (dd, 1H, $J_{1,2} = 9.9$ Hz, H-2), 5.59 (dd, 1H, $J_{2',3'} = 3.1$ Hz, H-3′), 5.31 (dd, 1H, H-2′), 5.10 (d, 1H, H-1), 4.69 (dd, 1H, $J_{5',6a'} = 3.0$, $J_{6'a,6b'} = 12.3$ Hz, H-6a′), 4.68 (dd, 1H, $J_{5,6a} = 2.7$, $J_{6a,6b} = 12.4$ Hz, H-6a), 4.58 (ddd, 1H, $J_{5',6b'} = 3.1$ Hz, H-5′), 4.48 (dd, 1H, H-6b′), 4.45 (dd, 1H, $J_{5,6b} = 4.6$ Hz, H-6b), 4.22 (ddd, 1H, H-5), 2.85 (s, 3H, OMs, CH_3); ^{13}C NMR ($CDCl_3$) δ 165.98 (2C), 165.74, 165.43, 165.16, 165.05, 165.01 (7 × OBz, *C*═O), 133.53, 133.44 (2C), 133.38, 133.22, 133.04, 132.96 (7 × OBz, C_{para}), 129.95−128.28 (35C, Ph), 82.82 (C-1), 81.41 (C-1′), 77.59 (C-2′), 77.09 (C-5), 74.16 (C-3), 71.44 (C-2), 70.91 (C-5′), 69.92 (C-3′), 69.07 (C-4), 66.20 (C-4′), 62.69 (C-6′), 62.57 (C-6), 38.50 (OMs, CH_3); MALDI MS *m/e* 1187.7 (M^+ + Na). Anal. Calcd for $C_{62}H_{52}O_{19}S_2$: C, 63.91; H, 4.50. Found: C, 64.08, H, 4.44.

Procedure for 1→2-Thio Migration Reaction for Compound 21. The mesylate **21** (282 mg, 0.242 mmol) was added to a 0.05 M NaOMe/MeOH solution (22 mL), and the mixture was refluxed under N_2 for 2 h. After being cooled to room temperature, the basic solution was neutralized by dropwise addition of HOAc (pH ~6) and concentrated to give a pale-yellow, cloudy residue. The crude mixture of methyl

sophorosides **23** was acetylated by treatment with acetic anhydride (4 mL), pyridine (5 mL), and DMAP (50 mg) for 1 h at room temperature. The mixture was poured onto crushed ice (~20 g) and stirred until the ice melted. The mixture was extracted twice with CH_2Cl_2, and the combined extracts were washed with cold, saturated $NaHCO_3$, cold, aqueous 5% HCl, and again with $NaHCO_3$. Drying over $MgSO_4$ and solvent removal gave a mixture of **13**α and **13**β (142 mg, 88%). Analysis of the crude reaction mixture by ^{1}H NMR indicated the ratio of **13**β/**13**α was 3:2. Pure samples of each isomer were obtained by chromatography on silica gel (hexanes:EtOAc, 1:1) and both isomers exhibited identical spectra to the samples of **13**β and **13**α that were obtained previously from **12**β/**12**α.

2-*O*-Acetyl-3,4,6-tri-*O*-benzoyl-α-D-mannopyranose-1-isoselenouronium Bromide (24). The ortho ester **14** (2.74 g, 5.00 mmol) was dissolved in CH_2Cl_2 (40 mL). The solution was cooled in an ice bath and stirred while a solution of HBr/HOAc (35 wt %, 3.0 mL) was added dropwise. After 30 min, the mixture was diluted with CH_2Cl_2 and washed with ice-cold water and cold saturated $NaHCO_3$ solution. The organic phase was dried over $MgSO_4$ and evaporated to give crude bromide **15** in quantitative yield (2.98 g). The bromide was immediately dissolved in dry acetonitrile (19 mL) and refluxed with selenourea (602 mg, 5.06 mmol) under N_2 for 1.5 h. The mixture was cooled and the solvent removed in vacuo to leave a gummy yellow residue. This was triturated with Et_2O to produce a yellow, powdery solid. Filtration and washing of the filter cake with anhyd Et_2O gave the crude selenourea derivative **24** as a dry amorphous solid (3.12 g, >80%, ~90% α-isomer) containing some selenourea hydrobromide. Efforts to crystallize this material from a variety of solvent systems were not successful. An attempt to purify the mixture by column chromatography on silica gel (CH_2Cl_2/MeOH, 12:1) resulted in decomposition: ^{1}H NMR ($CDCl_3$) δ 9.77 (2H, brs, NH_2), 8.69 (2H, brs, NH_2), 8.01−7.80 (m, 6H, 3 × OBz, *ortho* H's), 7.59−7.25 (m, 9H, 3 × OBz, *meta* and *para* H's), 6.68 (brs, 1 H, H-1), 5.96 (dd, 1H, $J_{3,4} = J_{4,5} = 9.9$ Hz, H-4), 5.73 (dd, 1H, $J_{1,2} = 1.3$, $J_{2,3} = 3.3$ Hz, H-2), 5.53 (dd, 1H, H-3), 4.79 (ddd, 1H, $J_{5,6a} = 2.2$, $J_{5,6b} = 5.6$ Hz, H-5), 4.75 (dd, 1H, $J_{6a,6b} = 12.4$ Hz, H-6a), 4.49 (dd, 1H, H-6b), 1.96 (s, 3H, OAc); MALDI MS *m/e* 641.1 (8, $M^+ - Br$), 633.2 (5, $M^+ - HBr + Na$), 571.2 (100, $M^+ - CH_4N_2Se$).

2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl 2-*O*-Acetyl-3,4,6-tri-*O*-benzoyl-1-seleno-α-D-mannopyranoside (26). 2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranosyl bromide **18**[19] (329 mg, 0.499 mmol) and the isoselenouronium salt **24** (364 mg, 0.505 mmol) were dissolved in acetone (5 mL) and added to a solution of K_2CO_3 (152 mg, 1.10 mmol) and $Na_2S_2O_5$ (114 mg, 0.526 mmol) in water (2 mL). The mixture was stirred rapidly at room temperature for 2 h. The mixture was diluted with EtOAc and washed with water and saturated aqueous NaCl solution. The organic phase was dried over $MgSO_4$ and concentrated to give a solid. Purification by silica gel chromatography (hexanes/EtOAc, 8:5) yielded **26** as a colorless crystalline solid (432 mg, 73%). An analytical sample was obtained by recrystallization from hexanes/EtOAc: mp 196 °C; $[\alpha]_D$ +36 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.11−7.78 (7m, 14H, 7 × OBz, *ortho* H's), 7.58−7.23 (m, 21H, 7 × OBz, *meta* and *para* H's), 6.22 (d, 1H, $J_{1',2'} = 1.2$ Hz, H-1′), 6.05 (dd, 1H, $J_{3',4'} = J_{4',5'} = 10.0$ Hz, H-4′), 5.86 (dd, 1H, $J_{2,3} = J_{3,4} = 9.4$ Hz, H-3), 5.78 (dd, 1H, $J_{1,2} = 9.7$ Hz, H-2), 5.76 (dd, 1H, $J_{4,5} = 9.5$ Hz, H-4), 5.63 (dd, 1H, $J_{2',3'} = 3.2$ Hz, H-3′), 5.58 (dd, 1H, H-2′), 5.30 (d, 1H, H-1), 4.78−4.71 (m, 1H, H-6a′), 4.66 (dd, 1H, $J_{5,6a} = 2.8$, $J_{6a,6b} = 12.4$ Hz, H-6a), 4.56−4.48 (m, 2H, H-5′ and H6b′), 4.42 (dd, 1H, $J_{5,6b} = 4.4$ Hz, H-6b), 4.18 (ddd, 1H, H-5), 1.97 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$) δ 169.43 (OAc, *C*═O), 166.02, 165.97, 165.80, 165.33 (2C), 165.09, 165.05 (7 × OBz, *C*═O), 133.39−132.94 (7 × OBz, C_{para}), 130.18−128.29 (35C, Ph), 77.84 (C-1′), 77.74 (C-5), 77.58 (C-1), 74.16 (C-3), 72.35 (C-5′), 72.28 (C-2), 72.08 (C-2′), 70.74 (C-3′), 69.24 (C-4), 66.74 (C-4′), 62.79 (2C, C-6, C-6′), 20.47 (OAc, CH_3); MALDI MS *m/e* 1199.2 (M^+ + Na). Anal. Calcd for $C_{63}H_{52}O_{18}Se$: C, 64.34; H, 4.46. Found: C, 64.52; H, 4.42.

Attempted Reaction of 8 with the Trichloroacetimidate 29. The thiol **8** (2.21 g, 4.34 mmol) and trichloroacetimidate **29**[25] (3.19 g, 4.66 mmol) were dissolved in CH_2Cl_2 (35 mL) and stirred with freshly activated, crushed 4 Å molecular sieves (1.0 g). Boron trifluoride/diethyl etherate (0.1 mL) was added, and the mixture was stirred under N_2 at room temperature for 24 h. Analysis by TLC indicated that little if any reaction had occurred. More BF_3 etherate (0.2 mL) was added, and after a further 24 h at room temperature, analysis by TLC again showed only minimal change. The mixture was then refluxed for 21 h. At this point, TLC analysis indicated formation of a small amount of a product of intermediate polarity between the thiol **8** and the trichloroacetimidate **29** but little if any material with the R_f value of compound **31**. The mixture was cooled to room temperature and diluted with CH_2Cl_2 and filtered through Celite 454. The filtrate was washed with saturated aqueous $NaHCO_3$ solution, and water and dried over $MgSO_4$. Solvent removal gave a yellow oil. Attempted purification of this material by column chromatography on silica gel (hexanes/EtOAc, 3:1) resulted in streaking due to decomposition of one or more components of the mixture. The only compound isolated in a pure state was the disulfide **30**, a colorless glass (0.42 g, 19%): ^{1}H NMR ($CDCl_3$) δ 7.4−7.1 (m, 30H, Ph), 5.56 (dd, 2H, $J_{2,3} = 3.2$ Hz, 2 × H-2), 5.34 (d, 2H, $J_{1,2} = 1.7$ Hz, 2 × H-1), 4.85, 4.49 (2d, each 2H, $J_{A,B} = 10.7$ Hz, 2 × CH_2Ph), 4.68, 4.52 (2d, each 2H, $J_{A,B} = 11.1$ Hz, 2 × CH_2Ph), 4.68, 4.48 (2d, each 2H, $J_{A,B} = 12.1$ Hz, 2 × CH_2Ph), 4.13−3.94 (m, 4H, 2 × H-3, 2 × H-4), 3.91−3.82 (m, 4H, 2 × H-5 and 2 × H-6a), 3.71 (dd, 2H, $J_{6a,6b} = 11.2$ Hz, 2 × H-6b), 2.12 (s, 6H, 2 × OAc, CH_3); ^{13}C NMR ($CDCl_3$) δ 170.04 (2 × OAc, *C*═O), 138.32, 138.22, 137.54 (each 2C, 6 × C-*ipso*, Ph), 128.47−127.65 (30C, Ph), 88.93 (2 × C-1), 77.99 (2 × C-3), 75.16 (2 × *C*H_2Ph), 74.06, 73.94 (each 2C, 2 × C-4 and 2 × C-5), 73.48 (2 × *C*H_2Ph), 71.99 (2 × *C*H_2Ph), 69.41 (2 × C-2), 68.60 (2 × C-6), 21.10 (2 × OAc, *C*H_3); MALDI MS *m/e* 1037.4 (M^+ + Na).

2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl 2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-1-thio-α-D-mannopyranoside (31) and Phenylselenenyl 2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-1-thio-α-D-mannopyranoside (34). Phenyl 2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **32**[27] (701 mg, 1.03 mmol) and the thiol **8** (526 mg, 1.03 mmol) were dissolved in CH_2Cl_2 (8 mL) and stirred with freshly activated crushed 4 Å molecular sieves for 10 min at room temperature. *N*-Iodosuccinimide (236 mg, 1.05 mmol) and triflic acid (2 μL) were added. The mixture was stirred at room temperature for 2.5 h. The purple solution was diluted with CH_2Cl_2 and filtered through Celite 454. The filtrate was washed with 10% aqueous $Na_2S_2O_3$ solution and water. The yellow solution was dried over anhyd $MgSO_4$ and concentrated to give a yellow oil that darkened on standing. Purification of the crude mixture by chromatography on two successive silica gel columns (first with hexanes/EtOAc, 3:1 and then with ether/hexanes, 1:1) yielded three fractions in addition to diphenyl diselenide. The least polar material was the selenenyl-sulfide **34** that was obtained as a pale-yellow syrup (302 mg, 44%). Next to elute was a mixture of the 1,1′-disaccharides **31** and **9** (365 mg, 34%) as a colorless syrup. Analysis by ^{1}H NMR indicated a **31**:**9** ratio of 4.3:1. Finally, the 1,6-anhydro compound **35** (103 mg, 23%) was obtained as a colorless syrup which slowly crystallized. An analytically pure sample was obtained by recrystallization from EtOH: mp 90−91 °C; $[\alpha]_D$ −25 (*c* 1.0, $CHCl_3$) (lit.[28] mp 88−89 °C; $[\alpha]_D$ −30.9 (*c* 1.0, $CHCl_3$)).

Compound **31**: ^{1}H NMR ($CDCl_3$) δ 7.4−7.1 (m, 35H, Ph), 5.64 (d, 1H, $J_{1,2} = 5.2$ Hz, H-1), 5.44 (d, 1H, $J_{1',2'} = 1.4$ Hz, H-1′), 5.38 (dd, 1H, $J_{2',3'} = 2.9$ Hz, H-2′), 4.91, 4.75 (2d, each 1H, $J_{A,B} = 10.8$ Hz, CH_2Ph), 4.88, 4.50 (2d, each 1H, $J_{A,B} = 11.0$ Hz, CH_2Ph), 4.81, 4.47 (2d, each 1H, $J_{A,B} = 10.8$ Hz, CH_2-Ph), 4.67, 4.52 (2d, each 1H, $J_{A,B} = 11.1$ Hz, CH_2Ph), 4.67, 4.50 (2d, each 1H, $J_{A,B} = 12.6$ Hz, CH_2Ph), 4.63, 4.48 (2d, each 1H, $J_{A,B} = 12.1$ Hz, CH_2Ph), 4.61, 4.43 (2d, each 1H, $J_{A,B} = 12.0$ Hz, CH_2Ph), 4.24 (ddd, 1H, $J_{4',5'} = 9.3$, $J_{5',6a'} = 4.6$, $J_{5',6b'} = 1.9$ Hz, H-5′), 4.12 (ddd, 1H, $J_{4,5} = 9.2$ Hz, H-5), 3.94 (dd, 1H, $J_{3',4'} = 9.2$ Hz, H-3′), 3.90 (dd, 1H, H-4′), 3.83 (dd, 1H, $J_{2,3} = 9.4$ Hz, H-2), 3.81 (dd, 1H $J_{5,6a} = 3.2$, $J_{6a,6b} = 10.8$ Hz, H-6a), 3.78

(dd, 1H, $J_{6'a,6b'} = 10.8$ Hz, H-6a′), 3.77 (dd, 1H, $J_{3,4} = 9.1$ Hz, H-3), 3.71 (dd, 1H, H-4), 3.67 (dd, 1H, H-6b′), 3.65 (dd, 1H, $J_{5,6b} = 1.9$ Hz, H-6b), 2.12 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$) δ 170.20 (OAc, *C*═O), 138.61, 138.43, 138.25, 138.09, 137.98, 137.64, 137.50 (7 × C_{ipso}, Ph), 128.40−127.54 (35C, Ph), 82.58 (C-3), 81.84 (C-1), 79.20 (C-1′), 78.78, 78.74 (C-2 and C-3′), 77.08 (C-4), 75.68, 75.04, 75.00 (3 × *C*H_2Ph), 74.55 (C-4′), 73.46(2C) (2 × *C*H_2Ph), 72.92 (C-5′), 72.14, 71.89 (2 × *C*H_2-Ph), 71.51 (C-5), 70.82 (C-2′), 68.96 (C-6′), 68.26 (C-6), 21.04 (OAc, *C*H_3).

Compound **34**: $[\alpha]_D$ +44 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.7−7.0 (m, 20H, Ph), 5.53 (dd, 1H, $J_{1,2} = 1.7$, $J_{2,3} = 3.2$ Hz, H-2), 5.48 (d, 1H, H-1), 4.80, 4.43 (2d, each 1H, $J_{A,B} = 10.6$ Hz, C*H*$_2$Ph), 4.63, 4.41 (2d, each 1H, $J_{A,B} = 12.1$ Hz, C*H*$_2$Ph), 4.57, 4.42 (2d, each 1H, $J_{A,B} = 11.2$ Hz, C*H*$_2$Ph), 3.97 (dd, 1H, $J_{3,4} = 9.4$, $J_{4,5} = 9.7$ Hz, H-4), 3.89 (dd, 1H, H-3), 3.77 (ddd, 1H, $J_{5,6a} = 3.3$, $J_{5,6b} = 1.8$ Hz, H-5), 3.64 (dd, 1H, $J_{6a,6b} = 11.0$ Hz, H-6a), 3.20 (dd, 1H, H-6b), 2.11 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$): δ 170.16 (OAc, *C*═O), 138.26−127.58 (24C, Ph), 88.85 (C-1), 78.01 (C-3), 75.25 (*C*H_2Ph), 74.22 (C-4), 73.44 (C-5), 73.33 (*C*H_2Ph), 71.82 (*C*H_2Ph), 69.96 (C-2), 68.01(C-6), 21.03 (OAc); MALDI MS *m/e* 687.2 (M^+ + Na).

Methyl Tri-*O*-acetyl-2-*S*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-2-thio-*β*-D-glucopyranoside 38*β*. The 4.3:1 mixture of **31** and **9** (322 mg, 0.312 mmol) was deacetylated, mesylated, and subjected to the same 1→2-thioglycosyl migration conditions previously described for pure **9**. This yielded a 4:1 mixture of **37** and **11**, each of which had been formed as an approximately 1:3 α/*β* isomeric mixture of methyl glycosides. From this mixture, pure **37***β* was isolated by column chromatography (toluene/EtOAc, 10:1) as a colorless glass (77 mg, 25% for three steps): ^{1}H NMR ($CDCl_3$) δ 7.40−7.05 (m, 35H, Ph), 5.94 (d, 1H, $J_{1',2'} = 4.7$ Hz, H-1′), 4.94, 4.76 (2d, each 1H, $J_{A,B} = 10.9$ Hz, C*H*$_2$Ph), 4.86, 4.81 (2d, each 1H, $J_{A,B} = 10.1$ Hz, C*H*$_2$Ph), 4.82, 4.55 (2d, each 1H, $J_{A,B} = 10.1$ Hz, C*H*$_2$Ph), 4.81, 4.58 (2d, each 1H, $J_{A,B} = 11.6$ Hz, C*H*$_2$Ph), 4.77, 4.42 (2d, each 1H, $J_{A,B} = 10.9$ Hz, C*H*$_2$Ph), 4.65, 4.57 (2d, each 1H, $J_{A,B} = 12.2$ Hz, C*H*$_2$Ph), 4.54, 4.27 (2d, each 1H, $J_{A,B} = 12.2$ Hz, C*H*$_2$Ph), 4.37 (d, 1H, $J_{1,2} = 8.9$ Hz, H-1), 4.19 (ddd, 1H, $J_{4',5'} = 10.0$, $J_{5',6a'} = 3.1$, $J_{5',6b'} = 2.1$ Hz, H-5′), 3.90−3.82 (m, 2H, H-2′, H-3′), 3.78−3.71 (m, 2H, H-6a, H-6b), 3.68−3.63 (m, 1H, H-4′), 3.60 (dd, 1H, $J_{3,4} = 8.7$, $J_{4,5} = 9.8$ Hz, H-4), 3.57 (s, 3H, OCH_3), 3.47 (ddd, 1H, $J_{5,6a} = 2.5$, $J_{5,6b} = 4.0$ Hz, H-5), 3.40 (dd, 1H, $J_{6a',6b'} = 11.2$ Hz, H-6a′), 3.36 (dd, 1H, $J_{2,3} = 11.3$, H-3), 3.34 (dd, 1H, H-6b′), 2.95 (dd, 1H, H-2).

Treatment of the benzyl-protected methyl kojibioside **37***β* with sodium in liquid ammonia/THF and acetylation of the crude debenzylated product as described for the preparation of **13** yielded acetylated methyl kojibioside **38***β* as a crystalline solid (44 mg, 86%) after purification by column chromatography (toluene/EtOAc, 10:1). An analytically pure sample was obtained by recrystallization from EtOH: mp 167−168 °C; $[\alpha]_D$ +130° (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.04 (d, 1H, $J_{1',2'} = 5.9$ Hz, H-1′), 5.32 (dd, 1H, $J_{2',3'} = 10.0$, $J_{3'4'} = 9.5$ Hz, H-3′), 5.02 (dd, 1H, H-2′), 5.00−4.94 (m, 2H, H-3, H-4), 4.99 (dd, 1H, $J_{4',5'} = 10.3$ Hz, H-4′), 4.37 (d, 1H, $J_{1,2} = 8.8$ Hz, H-1), 4.33 (ddd, 1H, $J_{5',6a'} = 5.2$, $J_{5',6b'} = 2.6$ Hz, H-5′), 4.30 (dd, 1H, $J_{5,6a} = 4.5$, $J_{6a,6b} = 12.2$ Hz, H-6a), 4.22 (dd, 1H, $J_{6a',6b'} = 12.3$ Hz, H-6a′), 4.17 (dd, 1H, H-6b′), 4.11 (dd, 1H, $J_{5,6b} = 2.3$ Hz, H-6b), 3.68−3.63 (m, 1H, H-5), 3.51 (s, 3H, OCH_3), 2.99−2.91 (m, 1H, H-2), 2.15−2.00 (7s, each 3H, 7 × OAc, CH_3); ^{13}C NMR ($CDCl_3$) δ 170.60−169.42 (7 × OAc, *C*═O), 105.72 (C-1), 80.93 (C-1′), 71.61 (C-5), 71.12 (C-3), 70.45 (C-2′), 70.33 (C-3′), 69.61 (C-4), 68.64 (C-4′), 68.22 (C-5′), 61.97 (C-6), 61.87 (C-6′), 57.50 (OCH_3), 46.53 (C-2), 20.65−20.50 (7 × OAc, *C*H_3); MALDI MS *m/e* 689.3 (M^+ + Na). Anal. Calcd for $C_{27}H_{38}O_{17}S$: C, 48.65; H, 5.75. Found: C, 48.90, H, 5.72.

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