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Stereoselective Formation of Glycosyl Sulfoxides and Their Subsequent Equilibration: Ring Inversion of an α-Xylopyranosyl Sulfoxide Dependent on the Configuration at Sulfur

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Abstract: A series of four *S*-allyl D-thiopyranosides, α- and β-manno and xylo, were oxidized with MCPBA at low temperature to give seven of the eight possible sulfoxides, whose configuration at sulfur was determined either directly by X-ray crystallography or by correlation with closely related structures. For the axial thioglycosides oxidation leads very predominantly to the $(R)_S$-diastereomer in the xylo series and exclusively so in the manno series; the configuration at C2 is of little importance in determining the stereoselectivity of oxidation of axial thioglycopyranosides. In the equatorial series the configuration at C2 has a significant effect on the outcome of the reaction as, although both series favored the $(S)_S$-sulfoxide, selectivity was significantly higher in the case of the β-mannoside than of the β-xyloside. The two α-xylo sulfoxides have different conformations of the pyranoside ring with the $(R)_S$-isomer adopting the $^1C_4$ chair and the $(S)_S$-diastereomer the $^4C_1$. Each pair of diastereomeric sulfoxides was thermally equilibrated in C_6D_6 and in CD_3OD. In the mannose series the kinetic isomers are also thermodynamically preferred. In the xylose series, on the other hand, the nature of the thermodynamic isomer in both the α- and β-anomers is a function of solvent with a switch observed on going from C_6D_6 to CD_3OD. The results are rationalized in terms of the exo-anomeric effect, steric shielding provided by H3 and H5 in the axial series, the interaction of the C2−O2 and sulfoxide dipoles, and increased steric interactions on hydrogen bonding of the sulfoxides to CD_3OD.

Introduction

Since its introduction in 1989,[1] Kahne's sulfoxide glycosylation method has been shown to be one of the more powerful techniques available for the formation of glycosidic bonds. It enables coupling to a wide range of carbohydrates, including extremely complex and sensitive substrates[2−5] and does so under a standardized set of conditions.[6] The method has also been applied to solid-phase glycosylation, thereby enabling the preparation of oligosaccharide libraries.[7,8] The use of pyrimidine bases as nucleophiles in this chemistry permits the formation of nucleosides.[9,10] In the course of studies in this laboratory on the application of Kahne's method in the mannose series,[11,12] we made the unexpected observation that oxidation of an *S*-ethyl 4,6-*O*-benzylidene-protected α-mannothiopyranoside to the corresponding sulfoxide was highly stereoselective, giving, within the limits of detection, a single diastereomer.[13,14] The oxidation of equatorial thioglycosides, on the other hand is typically rather unselective and gives mixtures of both sulfoxides. Interestingly, equatorial thioglycosides have been converted to glycosyl sulfimides, by reaction with chloramine T, with excellent but as yet undetermined diastereoselectivity.[15,16]

Since the original observation that the axial thioglycoside **1** was converted with MCPBA to a single sulfoxide,[13] we have

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(14) The highly stereoselective oxidation of *S*-phenyl 3,4,6-tri-*O*-benzyl-α-D-thiomannopyranoside and of *S*-ethyl α-D-thioglucopyranoside was also reported, but the configuration at sulfur was not assigned. Stork, G.; La Clair, J. J. *J. Am. Chem. Soc.* **1996**, *118*, 247−248; Micheel, F.; Schmitz, H. *Ber. Deutsch. Chem. Ges.* **1939**, *72*, 992.
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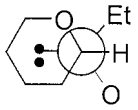
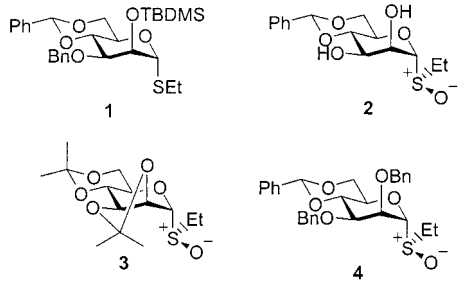
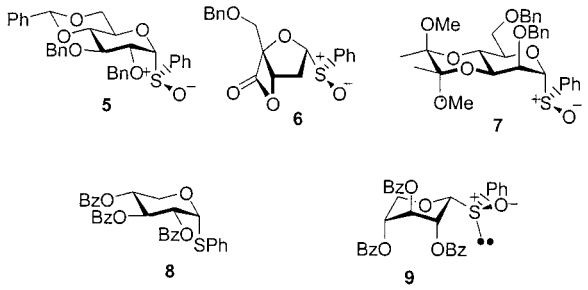


Figure 1. Crystallographically determined configuration and conformation of sulfoxides **2** and **3**.

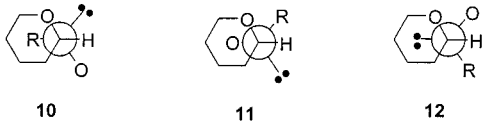
repeatedly observed that 4,6-*O*-benzylidene-protected axial thioglycosides are transformed by a range of common oxidizing agents with very high diastereoselectivity.[12,17−20] X-ray crystallographic analysis permitted the assignment of configuration as $(R)_S$ in sulfoxide **2** and in the related **3**.[21] Benzylation of sulfoxide **2** provided **4**, which was also obtained selectively by oxidation of the thioglycoside, and thus a third established example of the $(R)_S$ configuration at which point we considered the paradigm established and relented from our investigations of configuration.[21,22] The X-ray structures of **2** and **3** showed a common conformation about the C1−S(−O)R bond with the R group having a gauche relationship to the ring oxygen and the S−O and C1−O5 dipoles aligned antiparallel, as depicted in Figure 1. This in turn led us to postulate that the selectivity is a result of the exo-anomeric effect, which with an axial thioglycoside exposes the pro-*R* lone pair to solvent while shielding the pro-*S* one under the pyranose ring.[21] With equatorial thioglycosides both lone pairs are exposed and therefore mixtures of sulfoxides are obtained.



The high selectivity on oxidation is neither restricted to the mannose series, to pyranose rings, nor to 4,6-*O*-alkylidene-protected systems. Similarly high selectivity was observed with α-glucopyranosyl thioglycosides (e.g. **5**)[20] with a bicyclic furanoside (**6**),[10] and a bisacetal-protected system (**7**).[19] An especially interesting example is presented by the α-thioxyloside **8**, whose predominant conformation is the $^4C_1$ chair. On oxidation with MCPBA one very predominant sulfoxide was obtained but as the $^1C_4$ chair (**9**) as is evident from inspection of the ^{1}H NMR data.[17,18] We did not assign configuration rigorously in these latter cases but drew on an analogy with the above crystallographically established examples.



The axial $(S)_S$-isomer of the above $(R)_S$-sulfoxides is of interest for a number of reasons but especially because it may have interesting conformational effects on any pyranose system into which it is built. As we have noted above, the $(R)_S$-sulfoxide retains the gauche conformation of the exo-anomeric effect and opposes the S−O and C1−O5 dipoles. This conformation is best seen in the Newman projection (Figure 1). In the $(S)_S$-diastereomer none of the three staggered conformations (**10**−**12**) about the C1−S bond retains both of these favorable attributes. If the dipoles are antiparallel (**10**), then the aglycon suffers from an uncomfortably close 1,3-diaxial interaction with H3 and H5 of the pyranose ring; if (**11**) the exo-anomeric preferred conformation is retained, then it is the sulfoxide oxygen that suffers from the 1,3-diaxial interaction. When 1,3-diaxial interactions are avoided (**12**), there is a gauche relationship between the two dipoles. A knowledge of sulfoxide stereochemistry and conformation is also of considerable interest in the light of Vasella's lateral protonation model for glycosidase enzymes,[23,24] with the obvious implication being that the $(R)_S$-diastereomer should be the more active of the two in any sulfoxide-based inhibitor.



In this contribution we follow up on our earlier report of stereoselective thioglycoside oxidation with an investigation into the thermodynamic properties of eight sulfoxides as well as the kinetically selective reactions by which they are obtained. In undertaking the present investigation into the thermodynamic and conformational aspects of glycosyl sulfoxides we faced two primary problems. The first and most obvious of these was the need for a method to assign sulfoxide configuration. Although NMR methods for the assignment of sulfoxide configuration in glycosyl sulfoxides[25,26] are available, we have relied here on a combination of X-ray crystallography and of extrapolation

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(22) One apparent exception to the above series of highly selective oxidations is that of a fucopyranosyl thioglycoside, which was depicted as axial and gave two diastereomeric sulfoxides. We believe this to be a drawing error as the experimental part refers to the oxidation of a *β*-L-, and therefore equatorial, fucopyranoside; a fact with which the NMR data concur.[6] A second apparent exception, that of the low-temperature MCPBA oxidation of *S*-phenyl 2-*O*-TBDMS-4,6-*O*-benzylidene-3-*O*-*p*-methoxybenzyl- α-D-thiomannoside, a very close analogue of **2**, which was reported[5] to give two diastereoisomers, gave only one diastereoisomer in our hands. It is perhaps relevant to note that minor amounts of sulfone are often formed and that these are frequently surprisingly polar and therefore easily mistaken for a second sulfoxide.
(23) Heightman, T. D.; Vasella, A. T. *Angew. Chem., Int. Ed.* **1999**, *38*, 750−770.
(24) Varrot, A.; Schullein, M.; Pipelier, M.; Vasella, A.; Davies, G. J. *J. Am. Chem. Soc.* **1999**, *121*, 2621−2622.
(25) Buist, P. H.; Behrouzian, B.; MacIsaac, K. D.; Cassel, S.; Rollin, P.; Imberty, A.; Gautier, C.; Perez, S.; Genix, P. *Tetrahedron: Asymmetry* **1999**, *10*, 2881−2889. In this method the configuration at sulfur is deduced from the direction of very small chemical shift changes in the sulfoxide on introduction of (*S*)-α-methoxyphenylacetic acid. It has not yet been applied to axial glycosyl sulfoxides.
(26) Khiar, N. *Tetrahedron Lett.* **2000**, *41*, 9059−9063. This empirical method relies on the chemical shift difference between the two diastereotopic methylene hydrogens in ethyl (and presumably other alkyl) glycosyl sulfoxides. We have found several exceptions to this rule and therefore recommend that it should only be applied with considerable caution.

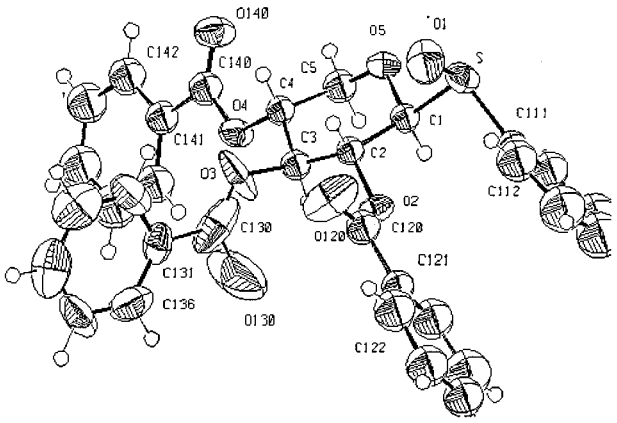
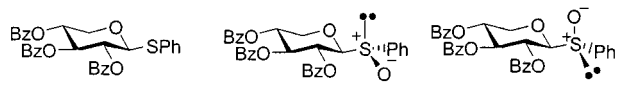


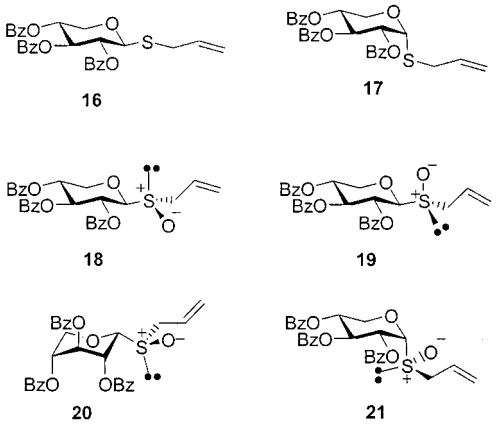
Figure 2. X-ray crystallographic structure of sulfoxide **14**.

from closely related molecules whose configuration was determined crystallographically. The second problem was one of how to achieve equilibration of the glycosyl sulfoxides. Photolytic equilibration, likely via radical pairs, was considered but found to be impractical owing to the preponderance of degradation products.[27,28] Eventually, the allyl sulfoxide/sulfenate equilibrium[29−31] was found to be satisfactory and reduced the problem to the relatively minor one of the synthesis of *S*-allyl thioglycosides and their oxidation.

Synthesis, Assignment of Configuration, and Kinetic Selectivity. As previously reported[17] oxidation of *S*-phenyl 2,3,4-tri-*O*-benzoyl-1-thio-β-D-xylopyranoside (**13**) with MCPBA at −78 °C in dichloromethane gave a 3/1 mixture of diastereomeric sulfoxides (**14**) and (**15**) which could be separated chromatographically. After recrystallization from ethanol the major isomer (**14**) was examined crystallographically, resulting in the assignment of configuration at sulfur as $(S)_S$ (Figure 2). This assignment, and the related observation by Martin-Lomas wherein oxidation of a β-*S*-phenyl thiogalactoside also gave the crystallographically determined $(S)_S$-sulfoxide as the major diastereomer[32] suggests that the sense, if not the degree of diastereoselectivity, is general for equatorial thioglycosides.[33]



A mixture of β-*S*-allyl 2,3,4-tri-*O*-benzoyl-1-thio-D-xylopyranosides (**16**) and the α-anomer (**17**) was synthesized by action of allyl mercaptan on tetrabenzoyl xylopyranose in the presence of BF_3 etherate and separated chromatographically. Shorter reaction times gave a higher proportion of the kinetic β-isomer, whereas prolonged exposure to the reaction conditions resulted in an enhancement of the thermodynamically more stable α-anomer. Both anomers existed in the $^4C_1$ chair conformation, as was the case with the corresponding *S*-phenyl thioxylosides, although it is noteworthy from the reduced $^3J_{H,H}$ couplings (Table 1) that another conformation, presumably the $^1C_4$ chair, is populated to a significant extent in **16**. Oxidation of the β-anomer **16** with MCPBA gave a 2.5/1 mixture) of sulfoxides (**18**) and (**19**), consistent with the oxidation of the β-*S*-phenyl system and of the Martin-Lomas β-*S*-phenyl thiogalactoside. Accordingly, the major diastereomer (**18**) was assigned the $(S)_S$ configuration. Both **18** and **19** are predominantly $^4C_1$ chairs but, again, it is apparent from analysis of the coupling constants (Table 1) that another conformation is populated to some extent, especially in **18**.



Oxidation of the α-*S*-allyl xylopyranoside (**17**) is considerably more interesting as, similar to its *S*-phenyl congenor (**8**), high selectivity for one diastereomer was observed, along with a complete change in conformation to the $^1C_4$ inverted chair. This substance (**20**) was assigned crystallographically as the $(R)_S$-sulfoxide (Figure 3), with the X-ray structure also revealing the ring conformation. The change in conformation on formation of the sulfoxide **20** holds in solution as well as in the crystal and is readily apparent from the magnitude of the $^3J_{H,H}$ couplings and from the $^4J_{H3,H5eq}$ w-coupling manifested by this sulfoxide (Table 1). The adoption of the $^1C_4$ conformation in peresterified β-xylopyranosyl glycosides and halides, leading to the placement of the electronegative group in the axial position where it benefits from the anomeric effect, is a common phenomenon.[34,35] The adoption of the $^1C_4$ chair conformation by α-xylopyranosides, thereby placing the anomeric substituent in an equatorial position, is less common and was first seen with positively charged anomeric substituents.[34,36,37] The possibility that the minor $^1C_4$ conformer of the thioglycoside **17** was undergoing oxidation more rapidly than the major $^4C_1$ conformer was considered improbable as this would entail oxidation of an equatorial thioglycoside and thus would be predicted to be considerably less stereoselective. Rather, it appeared likely that

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(28) Guo, Y.; Jenks, W. S. *J. Org. Chem.* **1997**, *62*, 857−864.
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(32) Khiar, N.; Alonso, I.; Rodriguez, N.; Fernandez-Mayorales, A.; Jimenez-Barbero, J.; Nieto, O.; Cano, F.; Foces-Foces, C.; Martin-Lomas, M. *Tetrahedron Lett.* **1997**, *38*, 8267−8270.
(33) The X-ray crystal structure of the $(R)_S$-sulfoxide of *S*-ethyl 4,6-*O*-benzylidene-2,3-di-*O*-acetyl-β-D-thioglucopyranoside has been published, but the paper does not indicate whether it was the major or the minor product of a relatively unselective (56:43) MCPBA oxidation of the thioglyoside.[25] A subsequent paper[26] seems to suggest it is the minor product which would conform with the oxidation of the *S*-phenyl β-thiogalactoside[32] of Martin-Lomas and the *S*-phenyl β-xyloside presented here.
(34) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: Berlin, 1983.
(35) For a detailed discussion of the conformation of "tetraaxial" β-xylopyranosides see Lichtenthaler, F. W.; Lindner, H. J. *Carbohydr. Res.* **1990**, *200*, 91−99.
(36) Vaino, A. R.; Chan, S. S. C.; Szarek, W. A.; Thatcher, G. R. J. *J. Org. Chem.* **1996**, *61*, 4514−4515.
(37) Vaino, A. R.; Szarek, W. A. *J. Org. Chem.* **2001**, *66*, 1097−1102.

Table 1. Chemical Shifts and Coupling Constants[a] for the Xylopyranosides **16**−**21**[b]

	δH1	δH2	δH3	δH4	δH5eq	δH5ax	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5ax}$	$J_{4,5eq}$	$J_{5a,5b}$	others
16	4.99	5.42	5.75	5.26−5.32	4.61	3.73	6.3	6.3	6.9	6.0	4.2	12.3	
17	5.70	5.44	6.03	5.33−5.41	4.11	4.27	4.8	9.3	9.3	10.8	5.4	10.8	
18	4.83	5.13	5.88	5.33−5.38	4.52	3.90	6.3	6.3	6.3	4.2	6.0	12.6	
19	4.52	5.89	5.99	5.42−5.51	4.73	3.76−3.85	8.4	8.4	8.4	n.d.[c]	4.8	11.4	
20	4.84	5.61	5.20	5.88	4.15	4.38	2.1	<2.0	<2.0	<2.0	<2.0	13.2	$^4J_{3,5eq}$ 2.1
21	4.84	5.73	6.48	5.40−5.49	4.33	4.83	5.7	8.4	8.1	8.4	4.8	11.4	

[a] All coupling constants in Hertz. [b] All data for $CDCl_3$ solutions at ambient temperature. [c] n.d. = not determined due to poor resolution.

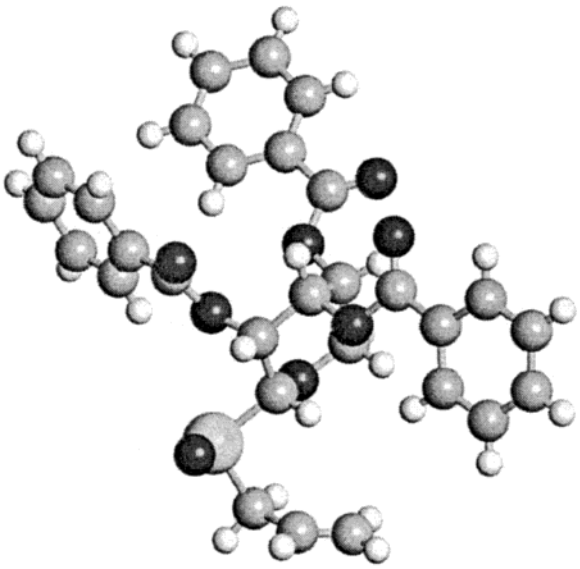
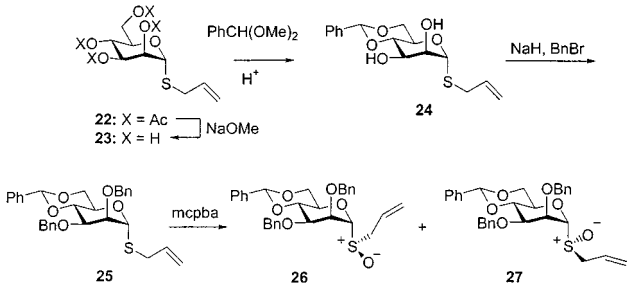


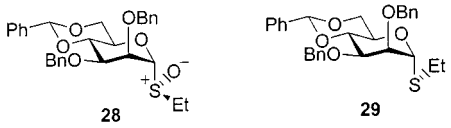
Figure 3. X-ray crystallographic structure of sulfoxide **20**.

Scheme 1

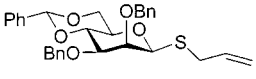


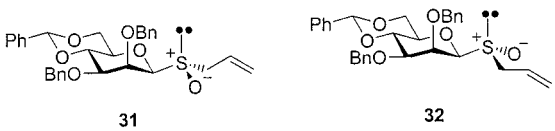
it was the major $^4C_1$ conformer that was being oxidized stereoselectively to the $(R)_S$-isomer, according to the model previously advanced for axial thioglycosides, followed by an inversion of conformation to accommodate the greater steric requirements of the sulfoxide group. The minor isomer (**21**) interestingly has the normal $^4C_1$ chair conformation.

In the mannopyranose series an α-*S*-allyl thioglycoside (**22**) was readily obtained by treatment of penta-*O*-acetyl mannopyranose with allyl mercaptan and BF_3. This could then be converted to the 4,6-*O*-benzylidene-protected derivative **25** by a standard set of reactions (Scheme 1). Oxidation of **25** with MCPBA in dichloromethane at −78 °C was completely selective, affording a single diastereomeric sulfoxide (**26**) to which we assign the $(R)_S$ configuration in accordance with the previous crystallographic studies. Owing to the high kinetic selectivity in the oxidation of the α-thiomannosides the isolation of significant quantities of the minor diastereoisomer was problematic. As noted previously, in the *S*-ethyl series several oxidants (mcpba, Oxone, MMPP, $NaIO_4$) were all extremely selective for the $(R)_S$-isomer. Subsequently, we have found that oxidation with *tert*-butyl hypochlorite in methanol/dichloromethane at −40 °C, according to Johnson,[38] is significantly less selective and provides a ratio of 2/1 of the $(R)_S/(S)_S$-isomers **4** and **28** from **29**. This change in selectivity obviously results from the different mechanism which does not involve direct oxygen transfer to the sulfide but, rather, chlorination followed by nucleophilic displacement. Unfortunately, even this method failed with the *S*-allyl thioglycosides, owing to the rapid cleavage of the allyl thioglycoside under the reaction conditions. A small amount of the $(S)_S$-diastereomer (**27**), sufficient for NMR purposes, was eventually obtained from the equilibration studies (vide infra).



The β-anomer (**30**), of **25**, was best obtained[39] by the triflic anhydride-mediated coupling of the α-*S*-ethyl sulfoxide **4** with freshly distilled allyl mercaptan.[40] Low-temperature oxidation of **30** with MCPBA provided a 7/1 mixture of two sulfoxides **31** and **32**, which could be separated by chromatography over silica gel. The major isomer (**31**) was assigned the *S*-configuration by analogy with that of the major diastereomer in the β-thioxyloside and β-thiogalactoside series, both of which are supported by crystallographic evidence (vide supra). Assuming that the equatorial thioglycosides are oxidized from the ground-state conformation about the glycosidic bond, namely that imposed by the exo-anomeric effect, then the reasons underlying the greater selectivity in the β-manno series than in the xylo series are obvious. The pro-*R* lone pair is shielded to a significantly greater extent in the manno series by the axial substituent at C2.





Thermodynamic Stereoselectivity. Both diastereomeric sulfoxides in the α- and β-xylo and β-manno- series were subjected

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(39) Crich, D.; Li, H. *J. Org. Chem.* **2000**, *56*, 801−805.
(40) The β-selective *S*-alkylation of 1-deoxy-1-thio mannopyranose derivatives was not satisfactory owing to difficulties in obtaining the requisite β-thiopyranose. Haque, M. B.; Roberts, B. P.; Tocher, D. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2881−2889.

Table 2. Kinetic and Thermodynamic Ratios[a]

		kinetic $(R)_S/(S)_S$ (mcpba, CH_2Cl_2, −78 °C)	thermodynamic $(R)_S/(S)_S$ (CD_3OD, 60 °C)	thermodynamic $(R)_S/(S)_S$ (C_6D_6, 60 °C)
19/**18**	β-xylo	0.4/1	1.5/1	0.7/1
20/**21**	α-xylo	1/0.1	2.5/1	0.5/1
32/**31**	β-manno	0.2/1	n.d.[b]	0.04/1
26/**27**	α-manno	1/0	2.6/1	3.1/1

[a] Determined by ^{1}H NMR integration of crude reaction mixtures. [b] n.d. = not determined.

to thermal equilibration in deuteriobenzene and deuteriomethanol at 60 °C (Table 2). In the α-manno series, owing to the very high kinetic selectivity, the minor diastereomer had first to be obtained from equilibration of the major isomer before it could be resubjected to the isomerization conditions. As expected from the mechanism of these sulfoxide isomerizations,[29] involving the reversible allyl sulfoxide sulfenate rearrangement with a reduction of polarity at the transition state, the equilibrations were more rapid in C_6D_6 than in CD_3OD. It is interesting to note in passing that no glycosylation occurred on equilibration in CD_3OD, suggesting that the *S*-glycosyl *O*-allyl sulfenate ester intermediates do not act as glycosyl donors unlike the related, regioisomeric *O*-glycosyl *S*-phenyl sulfenates reported by the Kahne group.[31] This might be due to an innate lower reactivity or may simply reflect their short lifetimes in an equilibrium that strongly favors the sulfoxide form.

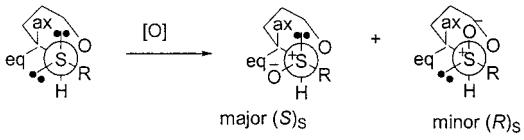
In deuteriobenzene in all cases but one the thermodynamic and kinetically preferred products in a given system were the same. Thus, oxidation of the β-xylopyranoside **16** gave a mixture of **18** and **19** enriched in **18**, either of which could be equilibrated to a similar mixture favoring **18**. Similarly in the β-manno series, oxidation of **30** gave preferentially **31** over **32**, and equilibration also resulted in a significant preference for **31**. In the α-manno series oxidation is extremely selective for the formation of **26**, equilibration of which provided a 10/1 mixture still favoring **26** over **27**. In C_6D_6, therefore, it is only in the α-xylo series that the kinetic and thermodynamic sulfoxides differ in configuration with the oxidation of **17** affording very preferentially **20**, whereas equilibration strongly favors **21**.

In deuteriomethanol however the pattern was different. As in C_6D_6 equilibration of the α-mannosides in CD_3OD strongly favored the kinetic $(R)_S$-isomer **27**. No equilibration of the β-manno series was conducted in CD_3OD because of the small amounts of material available. In CD_3OD in the β-xylo series, it is the $(R)_S$-isomer **19** that is favored under equilibrating conditions. In the α-xylo series the $(R)_S$-isomer (**20**), with its $^1C_4$ conformation, is the more stable sulfoxide in CD_3OD solution. Thus, in CD_3OD the situation was the exact reverse of that in C_6D_6 for both the α- and β-xylo series, whereas it was unchanged for the α-mannosyl sulfoxides.

Discussion

The kinetic selectivities are best rationalized by consideration of the exo-anomeric effect and the influence of the substituent at C2 on the carbohydrate ring. As originally proposed for the α-mannose series,[21] the exo-anomeric effect imposes the conformation depicted in Figure 1 on axial thioglycosides. This results in the pro-*R* lone pair being exposed and available for oxidation, whereas the pro-*S* lone pair is shielded under the ring. Any oxidation of the pro-*S* lone pair must bring the oxidant into a significant steric clash with H's 3 and 5 of the pyranose ring or result from a higher-energy conformation about the glycosidic bond. In a molecular orbital model of the exo-anomeric effect oxidation would occur on the more exposed lobe of the sulfur n_p-orbital.[41] A similar analysis of the β-thioglycosides is possible. Scheme 2 depicts an equatorial thioglycoside with the exo-anomeric effect conformation; both lone pairs are exposed, albeit to different degrees. Oxidation of the pro-*R* lone pair requires approach of the oxidant past the axial substituent at C2 and past the axial lone pair on the ring oxygen and is apparently less favored than attack on the pro-*S* lone pair which requires the oxidant to skirt the equatorial C2 substituent. In all established cases, it is the $(S)_S$-sulfoxide that is formed preferentially in the β-thioglycosides, even when the large group at C2 is equatorial as in the xylosides. One possible explanation for the favored formation of the $(S)_S$-sulfoxides in the β-xylo and related series, with the apparent preference for approach of the oxidant along the more hindered trajectory, invokes a destabilizing interaction between the axial lone pair on the ring oxygen and the incoming oxidant in the formation of the $(R)_S$-sulfoxide. Alternatively, it may be that the oxidation is best viewed in terms of the molecular orbital view of the exo-anomeric effect in which the more exposed lobe of the higher lying sulfur n_p-orbital undergoes electrophilic attack by the oxidant. In the β-manno series the substituent at C2 is axial and further hinders approach on the pro-*R* lone pair, leading to the enhanced selectivity for the $(S)_S$-sulfoxide over and above that seen here in the β-xylo series and previously with β-galactosides.[32,33]

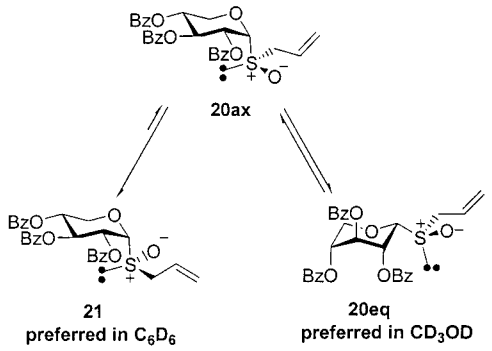
Scheme 2



The thermodynamics may be understood in terms of a combination of steric effects and dipolar repulsions between the S−O dipole on one hand and the endocyclic C1−O5 and exocyclic C2−O2 dipoles on the other. In C_6D_6 in the equatorial series (Scheme 2) the thermodymanically more stable $(S)_S$-sulfoxides can align the sulfoxide and endocyclic C−O dipoles antiparallel. In this manner the R group of the sulfoxide occupies the same space that it does in the exo-anomeric effect controlled thioglycoside. In the β-xylo series studied this conformation, and hence this configuration, is destabilized to some extent by the parallel nature of the sulfoxide and exocyclic, equatorial C2−O2 dipole which results in a relatively low thermodynamic selectivity in the xylo series. In the X-ray structures of the $(S)_S$-sulfoxides of the β-xyloside **14** (Figure 2), and in a computed structure of a related $(S)_S$-β-glucosyl sulfoxide,[25] this unfavorable dipolar interaction is relieved by adoption of a partially eclipsed glycosidic bond.[42] In the β-manno series, with the axial C2−O2 bond, this unfavorable interaction is not present, and the $(S)_S$-sulfoxide is more strongly favored. We anticipate that any eventual X-ray structures of $(S)_S$-β-mannosyl or β-

(41) For a detailed discussion of the pros and cons of the MO picture of the anomeric and exo-anomeric effects see: Juaristi, E.; Cuevas, G. *The Anomeric Effect*; CRC: Boca Raton, 1995.

Scheme 3



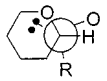
rhamnosyl sulfoxides will exhibit the fully staggered conformation depicted in Scheme 2.

In the α-manno series the S−O and endocyclic dipoles are almost perfectly antiparallel which results in the R group occupying the space it would in a typical exo-anomeric effect conformation (Figure 1) as demonstrated crystallographically with the *S*-ethyl sulfoxides **2** and **3**.

In C_6D_6 solution the α-xylo series is the anomaly. It conforms to the usual rule for selective formation of the $(R)_S$-sulfoxide under kinetic conditions, but the $(S)_S$-diastereomer is preferred on equilibration. Moreover, the kinetic isomer **20** adopts the inverted $^1C_4$ chair conformation. It is readily appreciated (Scheme 3) that in the $^4C_1$ conformation of the kinetic isomer (**20ax**) with the sulfoxide and endocyclic C1−O5 dipoles antiparallel, the sulfoxide and exocyclic C2−O2 dipoles are aligned and repel each other. The kinetic isomer therefore prefers the inverted $^1C_4$ conformation with the equatorial sulfoxide (**20eq**). In this inverted conformation the sulfoxide dipole sets itself antiparallel to the endocyclic C−O dipole and thus is not in conflict with the exocyclic C2−O2 dipole (Figure 3), that is, the situation is identical to that of the strongly favored $(S)_S$-sulfoxide (**31**) in the β-manno series.[43] In C_6D_6 solution the thermodynamically more stable $(S)_S$-α-sulfoxide retains the $^4C_1$ chair conformation **21** for which all of the staggered conformations about the glycosidic bond, **10**, **11** and **12**, are disfavored to some extent. We suggest that it approximates to an eclipsed conformation akin to **33** which minimizes dipolar repulsions and avoids any strong steric interactions with H3 and H5. A conformation of this type is especially envisaged because of the very downfield shift of H3 (δ 6.48) which indicates that H3 is exposed to the deshielding environment of the positive sulfur center rather than to a lone pair or sulfoxide oxygen. Sulfoxide **21** presumably does not undergo the ring flip as its $^1C_4$ sulfoxide would not benefit from the special circumstances of its isomer **20eq**, that is, it would be equivalent to the strongly disfavored β-manno sulfoxide **32**.

Under equilibrating conditions in CD_3OD additional steric factors come into play arising from hydrogen bonding of the sulfoxide group with the solvent. Thus, in the $(S)_S$-α-xyloside **21**, preferred in C_6D_6, the destabilizing 1,3-diaxial interactions are augmented in CD_3OD to the extent that the $(R)_S$-isomer **20** with its $^1C_4$ conformation and equatorial sulfoxide is now favored. In the equatorial series the $(S)_S$-sulfoxide is favored in C_6D_6 but the $(R)_S$-isomer in CD_3OD. Again we attribute this switch-over to the magnification of steric interactions arising from hydrogen bonding of the sulfoxide to the solvent. As noted above, the ideal conformation of the $(S)_S$-β-xylo-sulfoxide (**18**) with the antiparallel S−O and C1−O5 dipoles is destablized to some extent by the interaction of the sulfoxide dipole with the equatorial substituent at C-2 (Scheme 2) as reflected in the crystal structure of **14** (Figure 2). When the sulfoxide is hydrogen-bonded to the solvent, this interaction takes on a steric as well as a dipolar component, and the combination is sufficient to shift the equilibrium in favor of the $(R)_S$-isomer (**19**). For the α-mannosides the $(R)_S$-isomer is favored under equilibrating conditions in both C_6D_6 and CD_3OD as this isomer is best able to minimize dipolar and steric interactions. Although the β-mannosides were not investigated in CD_3OD, we expect that the $(S)_S$-isomer will be favored as in benzene as this isomer, with its close parallels to the $^1C_4$ $(R)_S$-α-xyloside, best accommodates all dipolar and steric interactions.

The final question is simply why is **21** more stable in C_6D_6 than **20eq** with its favored sulfoxide conformation and configuration? The answer must quite simply be that **21** benefits from both the anomeric effect and the equatorial disposition of its other three substituents and that these two effects combined outweigh any advantages present in the favored conformation about the glycosidic bond in **20eq**. This small advantage is easily overridden in CD_3OD when increased 1,3-diaxial interactions arising from solvation of the sulfoxide cause a shift in favor of **20eq**.



33

Experimental Section

General. Unless otherwise stated ^1H and ^{13}C NMR spectra were recorded as $CDCl_3$ solutions at 300 and 75 MHz, respectively, with chemical shifts in ppm downfield from tetramethylsilane. Specific rotations are for $CHCl_3$ solutions. IR spectra were recorded as casts on NaCl plates. Commercial MCPBA was purified by extraction.[44] All solvents were dried and distilled by standard means. FAB and ESI HRMS were conducted by the University of Minnesota mass spectroscopy laboratory and the UIC Research Resources Center, respectively. Microanalyses were carried out by Midwest Microlabs, Indianapolis.

***S*-Ethyl 4,6-*O*-Benzylidene-1-thio-α-D-mannopyranoside $(R)_S$-Oxide (2).** *S*-Ethyl 4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside (0.281 g, 0.90 mmol) was dissolved in CH_2Cl_2 (44 mL), and placed in an ice/H_2O bath. MCPBA (0.202 g, 1 equiv), dissolved in CH_2Cl_2 (4 mL), was added slowly dropwise, and the resulting solution left to stir for 50 min at 0 °C. The reaction was quenched with saturated $NaHCO_3$ (4 mL), and following separation of the organic and aqueous layers, the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The pooled organic phases were washed with brine (25 mL), dried (Na_2SO_4), and concentrated under vacuum, leaving a white solid (0.274 g, 93%). Mp 190 °C; $[\alpha]_D = +62°$ ($c = 0.5$, MeOH); ^1H NMR δ 7.45−7.49 (m, 2H), 7.36−7.39 (m, 3H), 5.58 (s, 1H), 4.72 (s, 1H), 4.66 (d, $J = 3.0$ Hz, 1H), 4.21−4.27 (m, 2H), 4.06−4.09 (m, 1H), 3.73−3.77 (m, 2H),

(42) Note that, if the exo-anomeric effect is the interaction of a lone pair of the glycosidic sulfur (oxygen in a normal *O*-glycoside) with the σ* orbital of the endocyclic C1−O5 bond, the effect per se does not exist in conformations such as that in Figure 1, formulas **10** and **12**, and the major sulfoxide of Scheme 2. It cannot be said, therefore, that in a partially eclipsed conformation the exo-anomeric effect is disrupted for such sulfoxides.

(43) The inversion could be seen as a manifestation of the reverse anomeric effect,[34] but as this effect has been largely discredited[36,37] this is seen as unlikely.

(44) Schwartz, N. N.; Blumbergs, J. H. *J. Org. Chem.* **1964**, *29*, 1976.

2.96−3.01 (m, 1H), 2.71−2.78 (m, 1H), 2.20−2.80 (br s, 2H), 1.40 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR δ 136.9, 129.5, 129.1, 128.5, 126.4, 102.5, 93.2, 69.3, 68.6, 68.3, 67.1, 44.0, 6.0; IR 1041 cm^{-1}; ESIHRMS Calcd for $C_{15}H_{20}O_6NaS$ $[M + Na]^+$: 351.0888, found: 351.0878.

***S*-Allyl 2,3,4-Tri-*O*-benzoyl-1-thio-β-D-xylopyranoside (16).** 1,2,3,4-Tetra-*O*-benzoyl-β-D-xylopyranoside (1.026 g, 1.81 mmol) was dissolved in CH_2Cl_2 (6.0 mL) under argon. Freshly distilled allyl mercaptan (225 μL, 3.53 mmol) was added, followed by the slow dropwise addition of BF_3·OEt_2 (300 μL, 2.4 mmol). The reaction mixture was stirred for 1.5 h at 25 °C, after which it was quenched with saturated $NaHCO_3$ (3 mL). The resulting aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the pooled organic extracts were then washed with brine (20 mL), dried (Na_2SO_4), and concentrated. Crystallization from hexanes/EtOAc at 4 °C removed the majority of the minor α-anomer, after which purification of the mother liquor on a silica gel column (eluent: $CHCl_3$) afforded **16** as an oil (0.299 g, 31%). $[\alpha]^{25}_D = -3.0$ ($c = 1.0$); ^{1}H NMR δ 7.97−8.03 (m, 6H), 7.49−7.56 (m, 3H), 7.32−7.41 (m, 6H), 5.73−5.88 (m, 1H), 5.75 (t, $J = 6.9$ Hz, 1H), 5.42 (t, $J = 6.3$ Hz, 1H), 5.26−5.32 (m, 1H), 5.19 (d, $J = 17.1$ Hz, 1H), 5.16 (d, $J = 10.0$ Hz, 1H), 4.99 (d, $J = 6.3$ Hz, 1H), 4.61 (dd, $J = 12.3$ and 4.2 Hz, 1H), 3.73 (dd, $J = 12.3$ and 6.0 Hz, 1H), 3.40 (dd, $J = 13.5$ and 8.4 Hz, 1H), 3.27 (dd, $J = 13.2$ and 6.0 Hz, 1H); ^{13}C NMR δ 165.7, 165.4, 165.3, 133.6, 133.5, 133.5, 130.1, 130.0, 129.4, 129.1, 128.5, 128.5, 118.3, 81.4, 70.7, 70.3, 69.1, 63.6, 33.6; ESIHRMS Calcd for $C_{27}H_{30}NO_7S$ $(M + NH_4)^+$: 536.1743, found: 536.1746.

***S*-Allyl 2,3,4-Tri-*O*-benzoyl-1-thio-α-D-xylopyranoside (17).** 1,2,3,4-Tetra-*O*-benzoyl-β-D-xylopyranoside (0.600 g, 1.06 mmol) and allyl mercaptan (0.20 mL, 8.5 mmol) were dissolved in CH_2Cl_2 (4.0 mL), BF_3·OEt_2 (0.13 mL, 1.06 mmol) was added dropwise, and the reaction mixture was stirred under argon for 72 h. The reaction mixture was diluted with saturated $NaHCO_3$ (10 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The pooled organic phases were washed with brine (15 mL) and then dried ($MgSO_4$) and concentrated. The isolated product was purified by repeated chromatography on silica gel column (eluent: $CHCl_3$/hexanes, 10/1) to afford pure **17** as a white solid (84 mg, 16%), along with the β-anomer (**16**) (64 mg, 11%). Mp 162 °C; $[\alpha]^{25}_D = 8.0$ ($c = 2.0$); ^{1}H NMR δ 7.82−8.02 (m, 5H), 7.29−7.56 (m, 10H), 6.03 (t, $J = 9.3$ Hz, 1H), 5.67−5.81 (m, 1H), 5.70 (d, $J = 4.8$ Hz, 1H), 5.44 (dd, $J = 9.3$ and 4.8 Hz, 1H), 5.33−5.41 (m, 1H), 5.10−5.19 (m, 2H), 4.27 (t, $J = 10.8$ Hz, 1H), 4.11 (dd, $J = 10.8$ and 5.4 Hz, 1H), 3.26 (dd, $J = 13.5$ and 8.4 Hz, 1H), 3.16 (dd, $J = 13.5$ and 5.7 Hz, 1H); ^{13}C NMR δ 165.7, 165.6, 165.5, 133.6, 133.5, 133.4, 133.1, 130.14, 130.0, 129.9, 129.9, 129.3, 129.2, 129.1, 128.6, 128.6, 128.5, 118.3, 81.3, 71.3, 70.2, 69.9, 60.2, 32.6. Anal. Calcd for $C_{29}H_{26}O_7S$: C, 66.61; H, 5.05. Found: C, 66.68; H, 5.13.

***S*-Allyl 2,3,4-Tri-*O*-benzoyl-1-thio-β-D-xylopyranoside (S)$_S$-Oxide (18) and *S*-Allyl 2,3,4-Tri-*O*-benzoyl-1-thio-β-D-xylopyranoside (R)$_S$-Oxide (19).** MCPBA (100%, 0.0912 g, 0.53 mmol) in CH_2Cl_2 (0.85 mL) and added dropwise at −78 °C to a stirred solution of **16** (0.274 g, 0.53 mmol) in CH_2Cl_2 (6.7 mL). The reaction was left to stir for 2 h and then was gradually warmed to 2 °C and quenched with saturated $NaHCO_3$ (2 mL). The resulting aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and after pooling, the organic extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. Chromatography on silica gel (eluent: $CHCl_3$/EtOAc/hexanes, 3/1/1) gave **18** (213 mg, 75%) and **19** (67.3 mg, 24%). (**18**): mp 80−82 °C; $[\alpha]^{25}_D = -43$ ($c = 1.0$); ^{1}H NMR δ 7.95−8.03 (m, 5H), 7.31−7.43 (m, 10H), 5.96−6.10 (m, 1H), 5.88 (t, $J = 6.3$ Hz, 1H), 5.73 (t, $J = 6.3$ Hz, 1H), 5.47−5.67 (m, 2H), 5.33−5.38 (m, 1H), 4.83 (d, $J = 6.3$ Hz, 1H), 4.52 (dd, $J = 12.6$ and 4.2 Hz, 1H), 3.90 (dd, $J = 12.6$, 6.6 Hz, 1H), 3.80 (m, 1H), 3.68 (dd, $J = 13.5$ and 4.2 Hz, 1H); ^{13}C NMR δ 165.6, 165.4, 133.8, 133.8, 130.2, 130.1, 130.1 129.9, 128.7, 128.6, 125.6, 124.6, 90.1, 69.8, 68.0, 67.2, 65.7, 52.6; IR υ 1722, 1602, 1583, 1451, 1314, 1278, 1259, 1148, 1106, 1093, 1068, 1025, 708 cm^{-1}; FABHRMS Calcd for $C_{29}H_{26}NaO_8S$ $(M + Na)^+$: 557.1246, found: 557.1255. (**19**): mp 60−62 °C; $[\alpha]^{25}_D = -4.9$ ($c = 1.0$); ^{1}H NMR δ 7.80−7.92 (m, 5H), 7.32−7.57 (m, 10H), 5.99 (t, $J = 8.4$ Hz, 1H), 5.89 (t, $J = 8.4$ Hz, 1H), 5.74−5.85 (m, 1H), 5.42−5.51 (m, 3H), 4.73 (dd, $J = 11.4$ and 4.8 Hz, 1H), 4.52 (d, $J = 8.4$ Hz, 1H), 3.76−3.85 (m, 3H); ^{13}C NMR δ 165.8, 165.5, 164.9, 133.7, 133.7, 133.6, 130.3, 130.0, 130.0, 130.0, 128.9, 129.0, 128.8, 128.8, 128.6, 128.6, 128.4, 125.7, 124.5, 87.1, 72.4, 69.3, 67.2, 67.0, 52.3; IR υ 1727, 1660, 1583, 1451, 1316, 1281, 1256, 1177, 1094, 1068, 1027, 707 cm^{-1}; FABHRMS Calcd for $C_{29}H_{26}NaO_8S$ $(M + Na)^+$ 557.1246, found: 557.1259.

***S*-Allyl 2,3,4-Tri-*O*-benzoyl-1-thio-α-D-xylopyranoside (R)$_S$-Oxide (20).** MCPBA (100%, 18.7 mg, 0.108 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise at −78 °C to a stirred solution of **17** (58 mg, 0.107 mmol) in CH_2Cl_2 (1.5 mL). After stirring at −78 °C for 2 h, the reaction mixture was allowed to warm to 0 °C and quenched with saturated $NaHCO_3$ (1 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the pooled organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The crude product was then purified by prep TLC (eluent: hexanes/EtOAc, 1/1) to give **20** (37.4 mg, 65%). Mp 171−174 °C; $[\alpha]^{25}_D = -82$ ($c = 0.44$); ^{1}H NMR δ 8.19 (d, $J = 8.4$ Hz, 2H), 8.07 (dd, $J = 8.4$ and 1.2 Hz, 2H), 7.80 (dd, $J = 8.4$ and 0.9 Hz, 2H), 7.61−7.67 (m, 2H), 7.39−7.53 (m, 5H), 7.06 (t, $J = 8.1$ Hz, 2H), 5.95−6.15 (m, 1H), 5.88 (m, 1H), 5.61 (br s, 1H), 5.55 (d, $J = 9.9$ Hz, 1H), 5.48 (d, $J = 16.8$ Hz, 1H), 5.20 (d, $J = 1.8$ Hz, 1H), 4.84 (d, $J = 2.1$ Hz, 1H), 4.38 (d, $J = 13.2$ Hz, 1H), 4.15 (dd, $J = 13.2$ and 2.1 Hz, 1H), 3.84 (dd, $J = 13.8$ and 6.9 Hz, 1H), 3.53 (dd, $J = 13.8$ and 8.4 Hz, 1H); ^{13}C NMR δ 165.5, 165.0, 164.1, 134.1, 133.7, 133.5, 130.4, 130.1, 130.0, 129.3, 129.0, 128.8, 128.7, 128.6, 128.3, 125.6, 124.2, 88.5, 67.5, 66.7, 66.1, 65.7, 52.9; FABHRMS Calcd for $C_{29}H_{26}NaO_8S$ $(M + Na)^+$: 557.1246, found: 557.1259.

***S*-Allyl 2,3,4-Tri-*O*-benzoyl-1-thio-α-D-xylopyranoside (S)$_S$-Oxide (21).** Sulfoxide **20** (6.0 mg) in C_6D_6 (0.5 mL) was heated to 60 °C in an NMR tube with periodic monitoring by ^{1}H NMR spectroscopy. After 3 days the contents were separated via prep TLC (eluent: hexanes/EtOAc, 1/1) and then column chromatography on silica gel (eluent: hexanes/EtOAc, 2/1) leading to the isolation of **21** (2.8 mg, 47%).

^{1}H NMR δ 8.07 (d, $J = 9.0$ Hz, 2H), 7.96 (d, $J = 8.7$ Hz, 4H), 7.31−7.57 (m, 9H), 6.48 (t, $J = 8.4$ Hz, 1H), 5.79−5.93 (m, 1H), 5.73 (dd, $J = 8.4$ and 5.4 Hz, 1H), 5.45 (m, 1H), 5.42 (d, $J = 18.3$ Hz, 1H), 5.39 (d, $J = 9.9$ Hz, 1H), 4.80−4.87 (m, 2H), 4.33 (dd, $J = 11.1$ and 4.8 Hz, 1H), 3.86 (dd, $J = 12.9$ and 8.1 Hz, 1H), 3.75 (dd, $J = 12.6$ and 7.2 Hz, 1H); ^{13}C NMR δ 134.1, 133.6, 133.5, 130.4, 130.1, 130.0, 129.9, 129.0, 128.8, 128.6, 128.6, 125.7, 124.3, 85.6, 70.2, 69.3, 69.0, 66.7, 52.3; IR υ 1720, 1451, 1278, 1256, 1091, 1067, 1027, 699 cm^{-1}; FABHRMS Calcd for $C_{29}H_{26}NaO_8S$ $(M + Na)^+$: 557.1246; found: 557.1268.

***S*-Allyl 2,3,4,6-Tetra-*O*-acetyl-1-thio-α-D-mannopyranoside (22).** D-Mannose pentaacetate (4.07 g, 10.5 mmol) in CH_2Cl_2 (14.7 mL) was stirred with allyl mercaptan (1.71 mL, 21.4 mmol) and BF_3·OEt_2 (2.2 mL, 18.1 mmol) for 3 days at room temperature and then treated with saturated $NaHCO_3$, extracted with CH_2Cl_2 (3 × 50 mL), washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated. The resulting red oil was purified on a silica gel column (eluent: hexanes/EtOAc, 2/1), yielding **22** as a white crystalline solid (1.37 g, 32%). Mp 65−67 °C; $[\alpha]^{25}_D = 67$ ($c = 1.0$); ^{1}H NMR δ 5.70−5.84 (m, 1H), 5.25−5.35 (m, 3H), 5.11−5.19 (m, 3H), 4.27−4.40 (m, 2H), 4.08 (dd, $J = 10.2$ and 1.8 Hz, 1H), 3.11−3.26 (m, 2H), 2.15 (s, 3H), 2.09 (s, 3H), 2.03 (s, 3H), 1.97 (s, 3H); ^{13}C NMR δ 170.7, 170.0, 169.9, 169.8, 132.6, 118.8, 80.9, 71.1, 69.8, 69.1, 66.4, 62.6, 33.3, 21.0, 20.9, 20.8, 20.8; ESIHRMS Calcd for $C_{17}H_{28}NO_9S$ $(M + NH_4)^+$: 422.1485, found: 422.1496.

***S*-Allyl 1-Thio-α-D-mannopyranoside (23).** To a solution of **22** (1.209 g, 3.25 mmol) in distilled MeOH (11.7 mL) was added sodium (0.073 g, 3.04 mmol), followed by stirring for 2 h. The pH of the mixture was adjusted to neutrality with amberlyst 15 ion-exchange resin and then dried (Na_2SO_4) and concentrated to yield **23** as a glass (0.536 g, 76%); $[\alpha]^{25}_D = 19$ ($c = 1.0$); ^{1}H NMR (CD_3OD) δ 5.76−5.90 (m,

1H), 5.08−5.21 (m, 3H), 3.61−3.91 (m, 6H) 3.29 (dd, J = 13.8 and 8.4 Hz, 1H), 3.15 (dd, J = 13.5 and 5.1 Hz, 1H); ^{13}C NMR (CD_3OD) δ 138.2, 118.0, 84.9, 75.2, 73.8, 73.6, 69.1, 62.9, 33.9; ESIHRMS Calcd for $C_9H_{16}NaO_5S$ $(M + Na)^+$: 259.0616, found: 259.0611.

***S*-Allyl 4,6-*O*-Benzylidene-1-thio-α-D-mannopyranoside (24).** Benzaldehyde dimethyl acetal (BDA) (172 μL 1.15 mmol) was added dropwise at 0 °C to a stirred solution of **23** (0.271 g, 1.15 mmol) and camphorsulfonic acid (CSA) (27 mg, 0.12 mmol) in freshly distilled THF (5.4 mL). After stirring for 20 min at 0 °C and 20 min at room temperature the reaction mixture was heated to reflux for 1 h and then concentrated to remove MeOH, replenished with solvent, and concentrated again. The reaction was repeated with **23** (0.2036 g, 0.86 mmol), BDA (129 μL, 0.86 mmol), and CSA (0.0211 g, 0.091 mmol). The crude products from both preparations were combined and purified on a silica gel column (eluent: hexanes/EtOAc, 2/1→1/3), to give **24** as a white solid (0.307 g, 47%). Mp 150−153 °C; $[\alpha]^{25}_D = 51$ (c = 1.5); ^{1}H NMR δ 7.46−7.51 (m, 2H), 7.36−7.40 (m, 3H), 5.76−5.81 (m, 1H), 5.67 (s, 1H), 5.29 (s, 1H), 5.17 (d, J = 17.4 Hz, 1H), 5.16 (d, J = 9.3 Hz, 1H), 3.81−4.28 (m, 6H), 3.25 (dd, J = 13.8 and 8.7 Hz, 1H), 3.15 (dd, J = 13.8 and 3.1 Hz, 1H), 2.55−2.95 (br s, 2H); ^{13}C NMR δ 137.2, 133.1, 129.4, 128.5, 126.4, 118.4, 102.5, 83.2, 79.3, 72.4, 69.4, 68.8, 63.7, 33.2; ESIHRMS Calcd for $C_{16}H_{20}NaO_5S$ $(M + Na)^+$: 347.0929, found: 347.0919.

***S*-Allyl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside (25).** Sodium hydride (0.0794 g, 1.82 mmol) was slowly added portionwise at 0 °C to a solution of benzyl bromide (165 μL, 1.42 mmol) and thioglycoside **24** (0.145 g, 0.45 mmol) in THF (2.9 mL) followed by stirring at room temperature for 4.5 h and then heating to reflux for 5 h. The reaction mixture was concentrated and then redissolved in EtOAc (20 mL), washed with water (10 mL) and brine (10 mL), and dried ($MgSO_4$). The crude product was concentrated and purified on a silica gel column (eluent: hexanes/EtOAc, 10/1), to give **25** as a clear oil (0.165 g, 73%). $[\alpha]^{25}_D = 68$ (c = 0.5); ^{1}H NMR δ 7.49−7.53 (m, 2H), 7.29−7.40 (m, 13H), 5.67−5.80 (m, 1H), 5.64 (s, 1H), 5.24 (d, J = 0.9 Hz, 1H), 5.13 (d, J = 16.2 Hz, 1H), 5.12 (d, J = 10.8 Hz, 1H), 4.77 (d, J = 12.0 Hz, 1H), 4.73 (s, 2H), 4.61 (d, J = 12.0 Hz, 1H), 4.12−4.32 (m, 3H), 3.86−3.93 (m, 3H), 3.20 (dd, J = 13.2 and 8.4 Hz, 1H), 3.09 (dd, J = 13.8 and 6.0 Hz, 1H); ^{13}C NMR δ 138.5, 138.0, 137.8, 129.0, 128.6, 128.5, 128.3, 128.1, 128.0, 127.8, 127.7, 126.2, 126.1, 118.2, 101.6, 82.3, 79.4, 78.1, 76.7, 73.3, 73.2, 73.1, 68.8, 65.0, 33.5; FABHRMS Calcd for $C_{30}H_{33}O_5S$ $(M + H)^+$: 505.2048; found: 505.2009.

***S*-Allyl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside R_S-Oxide (26).** MCPBA (100%, 5.9 mg, 0.034 mmol) in CH_2Cl_2 (1.0 mL) and added dropwise at −78 °C to a stirred solution of thioglycoside **25** (17.3 mg, 0.034 mmol) in CH_2Cl_2 (1.5 mL). After stirring for 2 h, the reaction mixture was allowed to warm to −30 °C and then quenched with saturated $NaHCO_3$ (1 mL). CH_2Cl_2 (10 mL) and saturated $NaHCO_3$ (5 mL) were added to dilute the mixture, and the aqueous phase was then extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were pooled and washed with brine (15 mL), dried (Na_2SO_4), and concentrated, to give **26** as a glass (18.4 mg, 100%). $[\alpha]^{25}_D = -20$ (c = 0.1); ^{1}H NMR δ 7.29−7.49 (m, 15H), 5.81−5.95 (m, 1H), 5.63 (s, 1H)), 5.49 (d, J = 9.6 Hz, 1H), 5.40 (dd, J = 17.1 and 1.2 Hz, 1H), 4.83 (d, J = 11.7 Hz, 1H), 4.80 (d, J = 11.7 Hz, 1H), 4.72 (d, J = 1.2 Hz, 1H), 4.70 (d, J = 11.7 Hz, 1H), 4.67 (d, J = 12.0 Hz, 1H), 4.48 (dd, J = 3.3 and 1.5 Hz, 1H), 4.34 (t, J = 9.5 Hz, 1H), 4.20 (dd, J = 9.6 and 4.2 Hz, 1H), 4.10 (dd, J = 9.9 and 3.6 Hz, 1H), 3.80 (t, J = 9.9 Hz, 1H), 3.73 (dd, J = 8.7 and 3.9 Hz, 1H), 3.66 (dd, J = 10.2 and 6.6 Hz, 1H), 3.32 (dd, J = 13.8 and 8.1 Hz, 1H); ^{13}C NMR δ 138.2, 137.7, 137.3, 129.2, 128.6, 128.5, 128.4, 128.1, 127.8, 126.1, 124.8, 124.6, 101.7, 91.9, 78.0, 77.6, 76.3, 74.2, 73.3, 73.1, 70.3, 68.3, 53.6; IR υ 1124, 1092, 1069, 1033, 1028, 1005, 993 cm^{-1}; ESIHRMS Calcd for $C_{30}H_{32}NaO_6S$ $(M + Na)^+$: 543.1817, found: 543.1843.

***S*-Allyl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside $(S)_S$-Oxide (27).** Equilibration of **26** (2.4 mg) in CD_3OD for three weeks at 60 °C gave a mixture of **26** and **27**. Separation by chromatography on silica gel (eluent: $CHCl_3$/hexanes/methanol, 25/9/1) gave **26** (0.6 mg, 25%) and **27** (0.3 mg, 12%). ^{1}H NMR (500 MHz) δ 7.10−7.54 (m, 15H), 5.71−5.77 (m, 1H), 5.62 (s, 1H), 5.31−5.36 (m, 2H), 4.92−4.62 (m, 5H), 4.35−4.41 (m, 3H), 4.23 (dd, J = 4.5 and 1.2 Hz, 1H), 3.70−3.90 (m, 2H), 3.62 (m, 1H), 3.52−3.57 (dd, J = 9.0 and 4.5 Hz, 1H); ^{13} C NMR (125 MHz) δ 138.6, 137.9, 137.4, 129.0, 128.7, 128.5, 128.3, 128.2, 127.8, 126.3, 125.5, 124.4, 101.9, 88.8, 79.0, 78.7, 74.0, 73.3, 70.6, 68.7, 53.0.

***S*-Ethyl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside $(S)_S$-Oxide (28).** *tert*-Butyl hypochlorite (24 μL)[45] was added in 4-μL amounts over a 2-h period at −78 ° to stirred solution of **29**[12] (0.110 g, 0.22 mmol) in CH_2Cl_2 (1.1 mL) and MeOH (1.1 mL) which had been shielded from the light. The reaction mixture was then allowed to warm to −20 °C, was quenched with 10% aqueous Na_2CO_3 (6 mL), and diluted with CH_2Cl_2 (40 mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 20 mL), and then dried ($MgSO_4$), and concentrated. Chromatography on silica gel (eluent: hexanes/EtOAc, 2/1→1/1) gave 89.5 mg of a mixture enriched in **28** of which 32.1 mg was further separated on a silica gel column (eluent: $CHCl_3$/MeOH, 50/1) to give the pure S_S-isomer (3.8 mg, 3%). $[\alpha]^{25}_D = 120$ (c = 0.1); ^{1}H NMR (400 MHz) δ 7.26−7.47 (m, 2H), 7.20−7.40 (m, 13 H), 5.62 (s, 1H), 4.90 (d, J = 11.9 Hz, 1H), 4.84 (d, J = 12.0 Hz, 1H), 4.69 (d, J = 11.9 Hz, 1H), 4.66 (d, J = 12.0 Hz, 1H), 4.40−4.50 (m, 1H), 4.29−4.37 (m, 4H), 4.15 (s, 1H), 3.75 (t, J = 10.1 Hz, 1H), 2.76−2.82 (m, 1H), 2.64−2.68 (m, 1H), 1.24 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz) δ 137.6, 129.2, 128.8, 128.6, 128.4, 128.2, 127.9, 126.4, 102.0, 90.1, 78.9, 76.6, 74.2, 70.5, 68.8, 42.6, 7.3; IR υ 1100, 1051, 1023, 970 cm^{-1}; ESIHRMS Calcd for $C_{29}H_{32}NaO_6S$ $(M + Na)^+$: 531.1817, found: 531.1835.

***S*-Allyl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-mannopyranoside (30).** Triflic anhydride (38.5 μL, 0.24 mmol) was added dropwise at −78 °C to a solution of **4**[12] (0.102 g, 0.21 mmol) and 2,4,6 tri-*tert*-butyl pyrimidine[46] (0.103 g, 0.42 mmol) in CH_2Cl_2 (3.0 mL). After stirring for 20 min freshly distilled allyl mercaptan (60 μL, 0.60 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise followed by stirring at −78 °C for 3 h. After warming up to −25 °C, the reaction was quenched with saturated $NaHCO_3$ (2 mL) and then further diluted with saturated $NaHCO_3$ (4 mL) and CH_2Cl_2 (30 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), and the pooled organic extracts were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. Chromatography on silica gel column (eluent: hexanes/EtOAc, 5/1) afforded **30** as an oil (37.2 mg, 35%). $[\alpha]^{25}_D = -33$ (c = 0.2); ^{1}H NMR δ 7.29−7.53 (m, 15H), 5.74−5.88 (m, 1H), 5.64 (s, 1H), 5.12 (d, J = 10.2 Hz, 1H), 5.10 (d, J = 17.1 Hz, 1H), 5.03 (d, J = 11.1 Hz, 1H), 4.87 (d, J = 12.6 Hz, 1H), 4.82 (d, J = 11.7 Hz, 1H), 4.73 (d, J = 12.3 Hz, 1H), 4.58 (s, 1H), 4.30 (d, J = 9.9 Hz, 1H), 4.28 (dd, J = 10.2 and 3.3 Hz, 1H), 4.00 (d, J = 3.3 Hz, 1H), 3.83 (t, J = 10.5 Hz, 1H), 3.78 (dd, J = 9.9 and 3.3 Hz, 1H) 3.42−3.35 (m, 2H), 3.26 (dd, J = 13.5 and 5.7 Hz, 1H); ^{13}C NMR δ 138.6, 138.2, 137.7, 134.0, 129.0, 128.8, 128.5, 128.3, 127.8, 127.7, 126.2, 117.73, 101.6, 83.9, 80.1, 79.0, 78.5, 75.8, 73.2, 71.9, 68.6, 33.9; FABHRMS Calcd $C_{30}H_{32}O_6S$ M^+: 504.1970, found: 504.1950.

***S*-Allyl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-mannopyranoside *S*-Oxide $(S)_S$ (31)- and $(R)_S$ (32)-Isomers.** A solution of **30** (14.4 mg, 0.028 mmol) in CH_2Cl_2 (1.0 mL) was stirred at −78 °C and titrated with MCPBA (100%, 5.6 mg, 0.033 mmol) in CH_2Cl_2 (1.0 mL) until the reaction was judged to be complete by TLC (eluting solvent: hexanes/EtOAc, 1/1). The reaction mixture was further stirred for 2 h at −78 °C and then quenched at −69 °C with saturated $NaHCO_3$ (1

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mL). The mixture was then diluted with CH_2Cl_2 (10 mL) and $NaHCO_3$ (2 mL), and the resulting aqueous layer was twice extracted with CH_2Cl_2 (10 mL). The organic extracts were pooled, washed with brine (10 mL), dried ($MgSO_4$), concentrated, and fractionated on a silica gel column (eluent: $CHCl_3$/EtOAc/hexanes, 3/1/1) to give the $(S)_S$-isomer **31** (7.7 mg, 54%) and the $(R)_S$-isomer **32** (1.2 mg, 8%). **31**: $[\alpha] = -50$ ($c = 0.5$); ^{1}H NMR δ 7.30−7.52 (m, 15H), 5.90−6.04 (m, 1H), 5.63 (s, 1H), 5.49 (d, $J = 9.9$ Hz, 1H), 5.38 (dd, $J = 17.7$ and 0.9 Hz, 1H), 5.11 (d, $J = 10.5$ Hz, 1H), 4.83 (d, $J = 10.5$ Hz, 1H), 4.82 (d, $J = 12.3$ Hz, 1H), 4.78 (d, $J = 12.3$ Hz, 1H), 4.47 (dd, $J = 1.2$ and 3.0 Hz, 1H), 4.22−4.33 (m, 3H), 3.86 (t, $J = 11.1$ Hz, 1H), 3.77 (dd, $J = 9.3$ and 3.0 Hz, 1H), 3.71 (dd, $J = 13.2$ and 6.3 Hz, 1H), 3.41−3.50 (m, 1H), 3.35 (dd, $J = 13.5$ and 8.4 Hz, 1H); ^{13}C NMR δ 138.1, 138.0, 137.4, 129.2, 128.8, 124.0, 101.8, 91.7, 78.9, 78.6, 76.3, 73.4, 72.9, 68.2, 52.3; IR υ 1095, 1043 cm^{-1}; FABHRMS Calcd for $C_{30}H_{33}O_6S$ $(M + H)^+$: 521.1998, found: 521.1954. **32**: ^{1}H NMR δ 7.29−7.51 (m, 15H), 5.74−5.88 (m, 1H), 5.66 (s, 1H), 5.33 (d, $J = 10.2$ Hz, 1H), 5.16 (d, $J = 16.5$ Hz, 1H), 5.07 (d, $J = 11.4$ Hz, 1H), 4.93 (d, $J = 12.6$ Hz, 1H), 4.84 (d, $J = 11.7$ Hz, 1H), 4.76 (d, $J = 11.7$ Hz, 1H), 4.34−4.41 (m, 3H), 4.27 (d, $J = 1.8$ Hz, 1H), 3.93 (t, $J = 10.5$ Hz, 1H), 3.75 (dd, $J = 10.2$ and 3.3 Hz, 1H), 3.47−3.56 (m, 1H), 3.31 (dd, $J = 13.5$ and 6.9 Hz, 1H), 3.22 (dd, $J = 13.5$ and 8.1 Hz, 1H); ^{13}C NMR δ 128.7, 128.6, 128.4, 128.3, 128.0, 127.8, 126.5, 126.2, 123.4, 101.8, 91.3, 80.0, 78.9, 74.7, 73.6, 73.5, 73.3, 68.3; IR υ 1095, 1056, 1027; HRMS Calcd for $C_{30}H_{32}NaO_8S$ $(M + Na)^+$: 543.1817, found: 543.1847.

General Protocol for Equilbration Experiments. The sulfoxides (2−5 mg) were dissolved in either C_6D_6 or CD_3OD (0.5 mL) in an NMR tube and heated at 60 °C in an oil bath with periodic monitoring by ^{1}H- or ^{13}C NMR analysis until equilibrium was attained.

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Supporting Information Available: Listings of the positional and thermal parameters for **14** and **20** with bond distances and angles for the non-hydrogen atoms (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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