# Sulfenate Intermediates in the Sulfoxide Glycosylation Reaction

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**Abstract:** The sulfoxide glycosylation reaction works remarkably well for many difficult glycosylations. We attribute this in part to the fact that an extremely reactive intermediate can be generated rapidly under mild conditions at low temperature. We find that anomeric sulfenates can be formed in the reaction and that these intermediates impede glycosylation at low temperature. A mechanism for sulfenate formation is proposed and a strategy for minimizing sulfenate formation is presented. The energetics and reactivity of anomeric sulfenates are also investigated. The mechanistic investigations described below have implications for other glycosylation reactions as well.

## Introduction

In a set of elegant papers published in the late 1960s, Mislow established that allylic sulfoxides interconvert rapidly with the corresponding allylic sulfenates through a [2,3]sigmatropic rearrangement.[1] This work explained many unusual features of allylic sulfoxides, such as why they racemize so rapidly when compared to other sulfoxides. It also provided a mechanistic basis for designing new synthetic transformations, the most important of which was the Evans method for synthesizing allylic alcohols from allylic sulfoxides by reducing the intermediate sulfenate.[2] Although Mislow had shown that the equilibrium favors the sulfoxide, the Evans reaction proceeds to completion because reduction of the sulfenate removes it from the equilibrium as soon as it forms.[3]

In this paper, we report that anomeric sulfoxides can rearrange to anomeric sulfenates. In contrast to the allylic sulfenates studied by Mislow and Evans, anomeric sulfenates are heavily favored in the sulfoxide−sulfenate equilibrium. A mechanism for sulfenate formation is proposed, and methods to minimize sulfenate formation are developed on the basis of the proposed mechanism.

## Results and Discussion

For the past several years the sulfoxide glycosylation reaction has been used to make oligosaccharides and other glycoconjugates both in solution and on solid phase supports.[4−37] We initially became interested in anomeric sulfoxides after noting that they can be activated at low temperature with triflic anhydride and that glycosylation takes place very rapidly even with relatively unreactive nucleophiles. A simple picture of the glycosylation reaction is shown in Scheme 1. The sulfoxide oxygen reacts with triflic anhydride to form a sulfonium species which ejects phenylsulfenyl triflate, producing an activated glycosyl donor. The activated glycosyl donor is then trapped by an alcohol to form a glycoside.

Over the past few years, however, various observations about the glycosylation reaction have made it clear that the reaction is much more complicated than Scheme 1 suggests. Unusual reactivity was first noted in our original communication: the activated sulfoxide appeared to be extremely reactive at −78 °C and yet stable at room temperature.[4] We have since observed reactions in which product starts to form at low temperature (−78 °C), then stops forming, and then starts again after the

(1) Bickart, P.; Carson, F. W.; Jacobus, J.; Miller, E. G.; Mislow, K. *J. Am. Chem. Soc*. **1968**, *90*, 4869.
(2) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res*. **1974**, *7*, 147.
(3) For a beautiful application combining both the Mislow rearrangement and the Evans rearrangement, see: Miller, J. G.; Kurz, W.; Untch, K. G.; Stork, G. *J. Am. Chem. Soc*. **1974**, *96*, 6774.
(4) Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc*. **1989**, *111*, 6881.
(5) Ikemoto, N.; Schreiber, S. L. *J. Am. Chem. Soc*. **1990**, *112*, 9657.
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(7) Chanteloup, L.; Beau, J.-M. *Tetrahedron Lett*. **1992**, *33*, 5347.
(8) Cheng, Y.; Ho, D. M.; Gottlieb, C. R.; Kahne, D. *J. Am. Chem. Soc*. **1992**, *114*, 7320.
(9) Ikemoto, N.; Schreiber, S. L. *J. Am. Chem. Soc*. **1992**, *114*, 2524.
(10) Sarkar, A. K.; Matta, K. L. *Carbohydr. Res*. **1992**, *233*, 245.
(11) Stork, G.; Kim, G. *J. Am. Chem. Soc*. **1992**, *114*, 1087.
(12) Andreotti, A. H. *J. Am. Chem. Soc*. **1993**, *115*, 3352.
(13) Raghavan, S.; Kahne, D. *J. Am. Chem. Soc*. **1993**, *115*, 1580.
(14) Wang, Y.; Zhang, H.; Voelter, W. *Z. Naturforsch*. **1993**, *48b*, 1143.
(15) Kim, S.-H.; Augeri, D.; Yang, D.; Kahne, D. *J. Am. Chem. Soc*. **1994**, *116*, 1766.
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(17) Sliedregt, L. A. J. M.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett*. **1994**, *35*, 4015.
(18) Wang, Y.; Zhang, H.; Voelter, W. *Z. Naturforsch*. **1994**, *50b*, 661.
(19) Yan, L.; Taylor, C. M.; Goodnow, R., Jr.; Kahne, D. *J. Am. Chem. Soc*. **1994**, *116*, 6953.
(20) Khiar, N.; Martin-Lomas, M. *J. Org. Chem*. **1995**, *60*, 7017.
(21) Wang, Y.; Zhang, H.; Voelter, W. *Chem. Lett*. **1995**, 273.
(22) Yan, L.; Kahne, D. *Synlett* **1995**, 523.
(23) Zhang, H.; Yali, W.; Voelter, W. *Tetrahedron Lett*. **1995**, *36*, 1243.
(24) Alonso, I.; Martin-Lomas, M. *Tetrahedron Lett*. **1996**, *37*, 1477.
(25) Boeckman, R. K., Jr.; Liu, Y. *J. Org. Chem*. **1996**, *61*, 7984.
(26) Broddefalk, J.; Bergquist, K.-E.; Kihlberg, J. *Tetrahedron Lett*. **1996**, *37*, 3011.
(27) Crich, D.; Sun, S. *J. Org. Chem*. **1996**, *61*, 4506.
(28) Crich, D.; Sun, S.; Brunckova, J. *J. Org. Chem*. **1996**, *61*, 605.
(29) Liang, R.; Yan, L.; Loebach, J.; Ge, M.; Uozumi, Y.; Sekanina, K.; Horan, N.; Gildersleeve, J.; Thompson, C.; Smith, A.; Biswas, K.; Still, W. C.; Kahne, D. *Science* **1996**, *274*, 1520−1522.
(30) Stork, G.; La Clair, J. J. *J. Am. Chem. Soc*. **1996**, *118*, 247.
(31) Yan, L.; Kahne, D. *J. Am. Chem. Soc*. **1996**, *118*, 9239.
(32) Crich, D.; Sun, S. *J. Am. Chem. Soc*. **1997**, *119*, 11217.
(33) Crich, D.; Sun, S. *J. Org. Chem*. **1997**, *62*, 1198.
(34) Ohnishi, Y.; Tachibana, K. *Bioorg. Med. Chem*. **1997**, *5*, 2251.
(35) Sofia, M. J.; Kakarla, R.; Kogan, N.; Dulina, R.; Hui, Y. W.; Hatzenbuhler, N. T.; Liu, D.; Chen, A.; Wagler, T. *Bioorg. Med. Chem. Lett*. **1997**, *7*, 2251.
(36) Zhang, H.; Wang, Y.; Thurmer, R.; Meisenbach, M.; Voelter, W. *Liebigs Ann./Recueil* **1997**, 1871.
(37) Crich, D.; Dai, Z. *Tetrahedron Lett*. **1998**, *39*, 1681.

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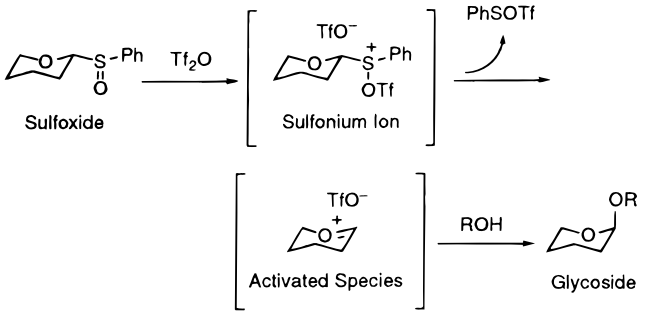
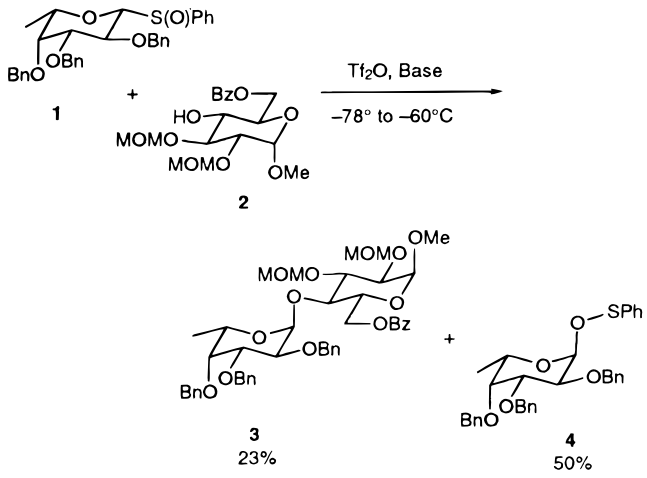
**Scheme 1.** Sulfoxide Activation and Glycosylation




**Scheme 2.** Identification of a Sulfenate




temperature has been raised. This behavior suggests that there are different reaction pathways that must be elucidated in order to better control the outcome of glycosylation.

One example of complex reactivity involves the reaction of sulfoxide **1** with alcohol **2** (Scheme 2). Although all of the sulfoxide was completely consumed at −78 °C, only a small amount of product was formed. As the reaction was warmed above −20 °C, more product was produced. If the reaction was quenched at low temperature, we could isolate a small amount of the desired disaccharide **3** (23%) along with a large quantity of an unknown compound. The physical properties of the unknown compound (NMR and mass spectra) suggested that it was the anomeric sulfenate **4**. This hypothesis was confirmed by independent synthesis of the anomeric sulfenate.

Anomeric phenylsulfenates have previously been found to decompose readily to lactols.[38,39] Although some of the sulfenate **4** formed in the course of the preceding glycosylation reaction probably decomposed during workup and purification, the purified yield of **4** was as high as 50% based on starting sulfoxide. The extensive formation of sulfenate led us to investigate how it forms and how it influences the course of the reaction.

**Possible Mechanisms for Sulfenate Formation.** The conversion of glycosyl sulfoxides to glycosyl sulfenates requires an activating agent (triflic anhydride) and occurs at low temperature. Therefore, we considered two mechanisms that seem to account for these features.

The first possible mechanism for glycosyl sulfenate formation involves the reaction of lactol present in the reaction mixture with phenylsulfenyl triflate, a highly electrophilic sulfenylating agent released during activation of the sulfoxide (see Scheme 3: Mechanism 1). Given the amount of sulfenate formed, this mechanism would require an efficient pathway for lactol formation under anhydrous conditions.

The second mechanism for sulfenate formation involves glycosylation of unreacted sulfoxide with the activated donor to form a sulfonium-linked disaccharide (see Scheme 3: Mechanism 2).[40] This sulfonium ion then ejects an anomeric sulfenate and regenerates the activated donor.

Mechanism 2 provides a catalytic cycle for the interconversion of sulfoxide and sulfenate. We reasoned that if such a cycle exists, then a catalytic amount of triflic anhydride and base should convert a diastereomerically pure sulfoxide to an equilibrium mixture of α and $\beta$ sulfenates and the four diastereomeric sulfoxides. To probe the existence of a catalytic cycle for the formation of sulfenate, we treated sulfoxide **1** with a catalytic amount of triflic anhydride in the presence of base at −78 °C. An anomeric mixture of lactols was isolated in 65% yield along with 25% of the sulfenate **4**, *but no sulfoxide could be detected*.

The complete consumption of sulfoxide **1** with catalytic triflic anhydride establishes a catalytic cycle, a result which is consistent with Mechanism 2.[41] However, instead of the expected mixture of sulfoxides and sulfenates, we isolated lactol as the major product. Because sulfenate **4** is known to decompose to lactol readily, it seemed possible that the lactol isolated from the reaction mixture came from the hydrolysis of sulfenate during work up and purification. If so, the principal species present in the reaction mixture at low temperature would be glycosyl sulfenate. To evaluate this possibility, we treated sulfoxide **1** with 0.34 equiv of triflic anhydride in the presence of base at −78 °C and monitored the $^1$H NMR spectrum. Comparison with spectra of the sulfoxide starting material, the lactols, and the pure sulfenate **4** at −78 °C indicated that all of the sulfoxide disappeared and that the sulfenate is the major species in the reaction mixture (see Figure 1).[42]

The experiments described above demonstrate that a catalytic cycle for conversion of sulfoxide **1** to sulfenate **4** exists and that this cycle is operative at −78 °C, the same temperature at which the glycosylation reaction is initiated. Although we cannot rule out the possibility that some sulfenate forms by Mechanism 1, we believe that the catalytic cycle shown in Mechanism 2 accounts for most of the sulfenate formed during the reaction of sulfoxide **1** with glycosyl acceptor **2**.

**Energetics of Sulfenate Formation.** An interesting implication of our mechanistic investigations is that the sulfenate **4** is thermodynamically favored over the sulfoxide **1** under conditions in which interconversion is possible. This implication was surprising since studies on the Mislow rearrangement and related synthetic transformations suggest that sulfoxides are usually favored over sulfenates at equilibrium in solution. We have compared the energetics of anomeric sulfoxides and anomeric sulfenates to simple sulfoxides and sulfenates to try and understand the apparent reversal in relative stabilities.

(38) The rapid decomposition to lactol can make the sulfenate difficult to observe by TLC.

(39) Fokt, I.; Szeja, W. *Carbohydr. Res.* **1991**, *222*, 271.

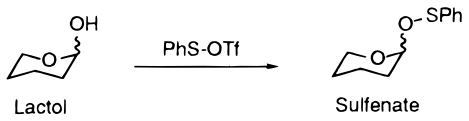
(40) Glycosylation of sulfoxides has been postulated previously, see: Narasaka, K.; Ichikawa, Y.; Kubota, H. *Chem. Lett.* **1987**, 2139.

(41) Crich has shown that PhSOTf can also activate sulfoxides and he proposes the formation of PhSOSPh as a byproduct (see ref 32). Formally another catalytic cycle exists where PhSOSPh reacts with the sulfoxide and $PhSO^-$ is ejected. Ejection of PhSOSPh regenerates the catalyst, and $PhSO^-$ is glycosylated to form sulfenate.

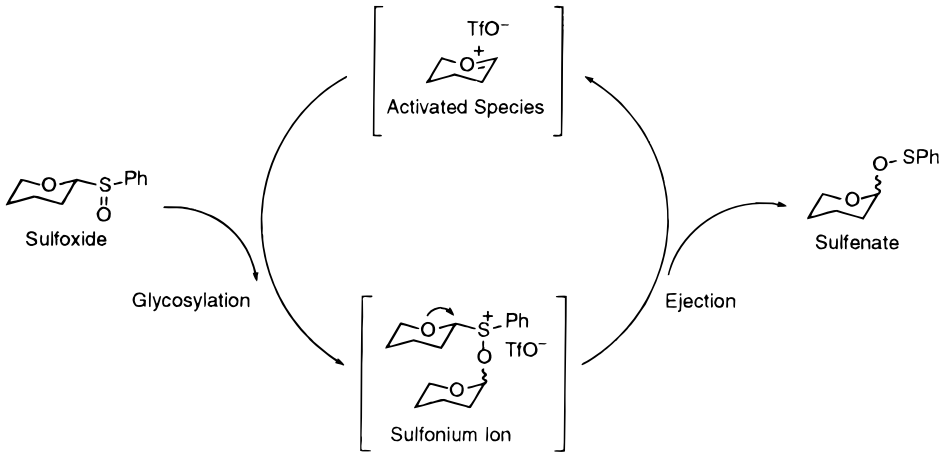
(42) The absence of methyl peaks below 1.0 ppm indicate that the other $\beta$-sulfoxide diastereomer and the α-sulfoxide are not present in the reaction. Small peaks at 5.25, 3.45, and 4.05 ppm are consistent with a minor amount of lactol.

**Scheme 3.** Proposed Mechanisms for Sulfenate Formation

***Mechanism 1.*** Sulfenylation of Lactol




***Mechanism 2.*** Glycosylation of the Sulfoxide



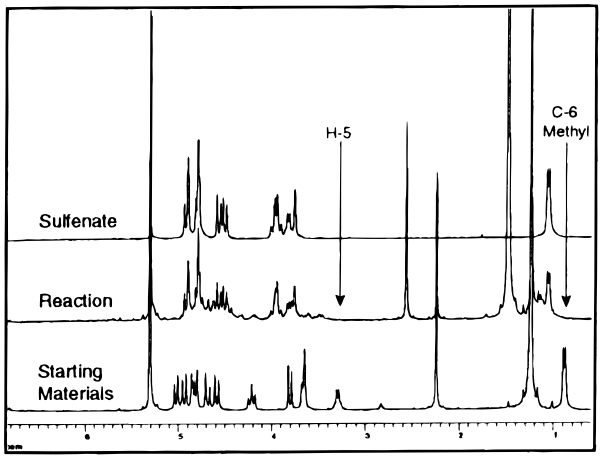




**Figure 1.** Low temperature NMR data.

A review of the literature confirms that sulfoxides are usually more stable than the corresponding sulfenates in solution.[43] In one typical example, Mislow found that allyl *p*-tolyl sulfoxide is favored by greater than 99% over allyl *p*-toluenesulfenate at equilibrium.[44] Interestingly, however, ab initio calculations by Wolfe have indicated that sulfenates are favored over sulfoxides in the gas phase. At the HF/6-31G*//HF/6-31G* level,[45] methyl methanesulfenate was found to be 11.3 kcal/mol more stable than dimethyl sulfoxide.[46] Our own calculations (Table 1) at higher levels of theory indicate that the gas-phase preference for MeS−OMe over DMSO is much less pronounced. At the MP4/6-31+G*//MP2/6-31+G* level, MeS−OMe is calculated to be only 3.3 kcal/mol more stable than DMSO. The experimental observation that sulfoxides are more stable than the corresponding sulfenates in solution is likely due to the preferential stabilization of the strong sulfoxide dipole by interaction with solvent. Solvation overwhelms the relatively small intrinsic preference for sulfenate and shifts the equilibrium to favor sulfoxide.

Further calculations show, however, that an oxygen substituent on the α carbon dramatically increases the energetic preference for sulfenate (Table 1). For example, while MeS−OMe is favored over DMSO by 2.2 kcal/mol at the MP2/6-31+G*//HF/6-31+G* level, MeS−$OCH_2$OMe is favored by 12.8 kcal/mol over methoxy−DMSO. A similar effect is seen when a fluorine is present on the α carbon (Table 1). The ability of either oxygen or fluorine substituents on the α carbon to increase the energetic difference between sulfoxide and sulfenate cannot be attributed to the inductive effect of an electron-withdrawing group because MeS−$OCH_2$CN and MeO−$SCH_2$-CN are only ∼3 kcal/mol more stable than cyano−DMSO (Table 1). Stereoelectronic stabilization of the sulfenate by oxygen or fluorine (i.e., an anomeric effect) may largely explain the increased energetic difference between sulfoxide and sulfenate.

Experimental evidence in the literature supports the results of our calculations.[47,48] For example, Maricich has found that phenyl methoxymethyl sulfoxide is quantitatively converted to the *S*-phenyl *O*-methoxymethyl sulfenate when heated to 35 °C for 2 days. We conclude that for compounds containing oxygen or fluorine in the α position, the energetic difference between sulfenate and sulfoxide is so large that favorable sulfoxide solvation cannot overcome the intrinsic preference for the sulfenate. Therefore, we predict that all anomeric sulfoxides will convert to the corresponding anomeric sulfenates given a suitable reaction pathway.

To test this hypothesis, we treated several structurally different anomeric sulfoxides with catalytic triflic anhydride and base (see Table 2). The temperature of the reaction mixtures was increased as necessary, and the disappearance of sulfoxide was

(43) Liebman, J. F.; Crawford, K. S. K.; Slayden, S. W. In *Thermochemistry of Organosulphur Compounds*; Liebman, J. F., Crawford, K. S. K., Slayden, S. W., Ed.; John Wiley and Sons: Chichester, 1993; pp 217−222.

(44) Tang, R.; Mislow, K. *J. Am. Chem. Soc.* **1970**, *92*, 2100.

(45) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; John Wiley & Sons: New York, 1986.

(46) Wolfe, S.; Schlegel, H. B. *Gazz. Chim. Ital.* **1990**, *120*, 285.

(47) Maricich, T. J.; Harrington, C. K. *J. Am. Chem. Soc.* **1972**, *94*, 5115.

(48) Banks, M. R.; Brown, A. R.; Cameron, D. K.; Gosney, I.; Cadogan, J. I. G. *J. Chem. Soc., Perkin Trans. 2* **1989**, 595.

**Table 1.** Computational Data[a] for Sulfoxides and Sulfenates

| computational level | $MeS(O)CH_2X$ (a.u.)[b] | $MeS-OCH_2X$ (a.u.)[b] | $MeO-SCH_2X$ (a.u.)[b] | difference[c] (kcal/mol) |
|---|---|---|---|---|
| X = H | | | | |
| HF/6-31+G*//HF/6-31+G* | −551.54509 | −551.56145 | | 10.3 |
| HF/6-31++G**//HF/6-31++G** | −551.55507 | −551.57106 | | 10.0 |
| MP2/6-31G*//HF/6-31G* | −552.11089 | −552.11895 | | 5.1 |
| MP2/6-31+G*//HF/6-31+G* | −552.12840 | −552.13186 | | 2.2 |
| MP2/6-31++G**//HF/6-31++G** | −552.17668 | −552.18057 | | 2.4 |
| MP2/6-31+G*//MP2/6-31+G* | −552.13005 | −552.13390 | | 2.4 |
| MP4/6-31+G*//MP2/6-31+G* | −552.19137 | −552.19664 | | 3.3 |
| X = F | | | | |
| HF/6-31+G*//HF/6-31+G* | −650.39222 (anti)[d] | −650.42980 (gau1)[d] | −650.41441 (gau1)[d] | 23.6 |
| MP2/6-31+G*//HF/6-31+G* | −651.14686 (anti) | −651.17219 (gau1) | −651.15891 (gau1) | 15.9 |
| X = OMe | | | | |
| HF/6-31+G*//HF/6-31+G* | −665.42139 (anti) | −665.45367 (gau1) | −665.44007 (gau1) | 20.2 |
| MP2/6-31+G*//HF/6-31+G* | −666.31414 (anti) | −666.33458 (gau1) | −666.32257 (gau1) | 12.8 |
| X = CN | | | | |
| HF/6-31+G*//HF/6-31+G* | −643.27284 (anti) | −643.29245 (gau1) | −643.29137 (gau1) | 12.3 |
| MP2/6-31+G*//HF/6-31+G* | −644.13262 (anti) | −644.13751 (gau1) | −644.13798 (gau1) | 3.4 |

[a] All but the MP4 calculations were performed by using the Spartan 4.0 package of programs (Wavefunction, Inc.), and its built-in default thresholds for wave function and gradient convergence were employed. The MP4 single-point calculations were performed by using Gaussian94. [b] 1 au = 627.503 kcal/mol. [c] Difference between the sulfoxide and the most stable of the sulfenate isomers; positive values favor the sulfenate. [d] The energies of only the most stable conformation of each sulfoxide or sulfenate are listed; pseudo-Newman projections of the possible conformations are illustrated below.

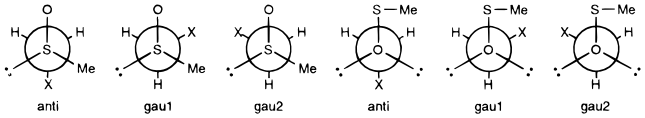
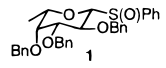
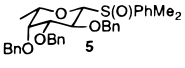
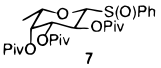
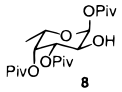
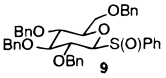
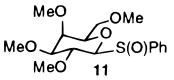
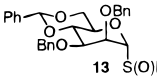



**Table 2.** Catalytic Conversion of Sulfoxides

| Entry | Sulfoxide | Temperature | Yield (α:β)[a] |
|---|---|---|---|
| 1) |  **1** | −78 °C | 25% Sulfenate **4**<br>65% Lactol |
| 2) |  **5** | −78 °C | 71% Sulfenates (**6a:6b** = 13:1)<br>21% Lactol |
| 3) |  **7** | −78 to −60 °C | 81%  **8** |
| 4) |  **9** | −78 to −60 °C | 15% Sulfenate **10** (all α)<br>66% Lactol |
| 5) |  **11** | −78 °C | 78% Sulfenates (**12a:12b** = 1:1)<br>10% Lactol |
| 6) |  **13** | −78 to −25 °C | 15% Sulfenate **14**[b]<br>61% Lactol |

[a] Yields and α:β are based on purified compounds. [b] It appears that two sulfenates are formed in equal amounts (based on analysis of mass spectroscopy, crude NMR, and TLC). Only one of the compounds (**14**) was stable enough to isolate and characterize. The stereochemistry of **14** was not assigned.

monitored. In every instance, the sulfoxides disappeared completely under the catalytic activation conditions; moreover, sulfenates were isolated in every case but one (see entry 3).[49] These results confirm that anomeric sulfoxides will convert to the corresponding sulfenates under appropriate conditions.

Nevertheless, sulfenates are not observed in every sulfoxide glycosylation reaction. This finding, combined with the fact that there are large differences in the temperature required to convert anomeric sulfoxides to sulfenates, suggests that there are significant differences in the kinetic accessibility of different anomeric sulfenates.

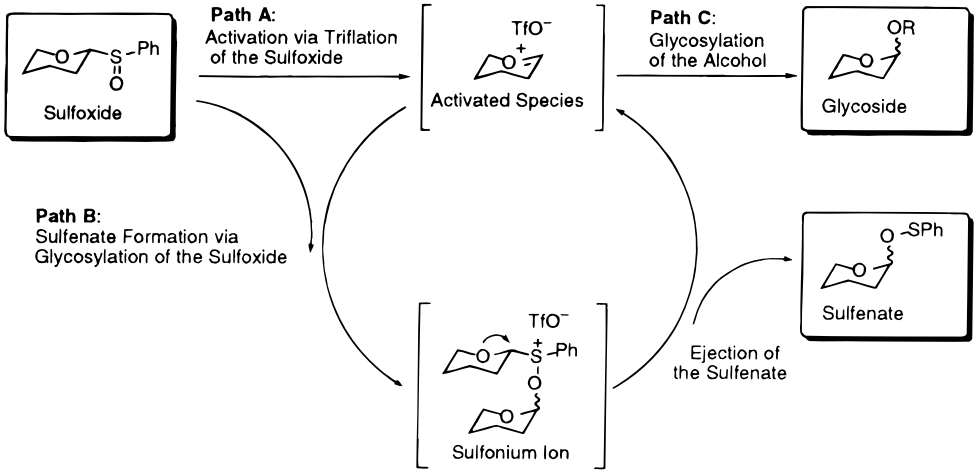
**Factors Influencing Sulfenate Formation.** The relative rates of several different processes presumably play a critical role in determining the extent of sulfenate formation (Scheme 4). The starting sulfoxide can either be triflated to form the activated species (Path A) or glycosylated to produce sulfenate (Path B). The amount of sulfenate formed will depend on the relative rates of triflation and sulfoxide glycosylation. As the activated species is produced, it can react with either the alcohol (Path C) or the sulfoxide (Path B). (In some cases, the activated species may also react with other nucleophiles in the reaction mixture to produce other intermediates. For example, Crich has evidence that anomeric triflates form in some glycosylation reactions and may be the reactive species. See below.)

Unfortunately, very little is known about the relative rates of triflation, sulfoxide glycosylation, and alcohol glycosylation except that they appear to depend on the structure of the starting sulfoxide and alcohol (i.e., protecting groups, configuration of sugar, etc.). This makes it difficult to predict whether sulfenate formation will be a problem for any given glycosylation reaction and also makes it difficult to control sulfenate formation by making structural modifications.

An alternative strategy to control sulfenate formation is to vary the order of addition of the starting materials. To suppress sulfenate formation, we need to favor two processes: triflation of the sulfoxide and glycosylation of the alcohol. One way to accomplish this is to add the sulfoxide slowly to a solution of triflic anhydride, alcohol, and base. As the sulfoxide is added, there is a high concentration of triflic anhydride to activate the sulfoxide and a high concentration of alcohol to trap the activated species before more sulfoxide is added. By minimizing the amount of sulfoxide present during the addition period,

(49) The product in this case is a result of migration of the pivaloyl ester to the anomeric position. While the sulfenate could not be isolated, complete conversion of the sulfoxide under catalytic conditions could be explained by formation of a sulfenate followed by migration of the ester.

**Scheme 4.** Potential Pathways in the Reaction




the alcohol can compete more effectively for the activated species. We have found that even primary alcohols are not triflated at an appreciable rate under the reaction conditions, making this inverse addition method a viable option.

To determine how much the order of addition affects glycoside formation, we compared three different procedures for reacting sulfoxide **1** and acceptor **2**. Each reaction was initiated at −78 °C and quenched at −50 °C. In addition, the number of equivalents of triflic anhydride was held constant (1.8 equiv). Preactivation of sulfoxide **1** with triflic anhydride followed by addition of nucleophile **2** resulted in only 26% of disaccharide **3**. When the nucleophile and sulfoxide were premixed and then triflic anhydride was added, we obtained a 38% yield of **3**. Finally, when sulfoxide **1** was added slowly to a solution containing acceptor alcohol **2**, triflic anhydride, and base, we isolated 65% of disaccharide **3**. These results demonstrate that the order of addition can have a significant effect on the efficiency of glycoside formation, presumably by minimizing sulfenate formation.

**Reactivity of the Sulfenate.** One question that has not yet been addressed, however, pertains to the fate of the sulfenate. We have shown that extensive sulfenate formation impedes glycosylation at low temperatures. We have also observed that glycosylation reactions that stall following initiation at −78 °C can restart at higher temperatures. This raises the possibility that anomeric sulfenates can participate as glycosyl donors under the reaction conditions at higher temperatures.

To address this issue, we treated purified sulfenate **4** with nucleophile **1** in the presence of triflic anhydride and base. No reaction was observed between −78 °C and −20 °C; however, warming to 0 °C produced disaccharide **3** in a 50% isolated yield. Therefore, anomeric sulfenates can act as glycosyl donors at sufficiently high temperatures.[50−52] These results also indicate that there can be at least two pathways for glycoside formation in the sulfoxide reaction: glycosylation at low temperature through an activated glycosyl sulfoxide donor and glycosylation at warmer temperatures through a glycosyl sulfenate donor.

The identification of sulfenates in the reaction and the fact that they can act as glycosyl donors at warmer temperatures explains some unusual observations about the reaction. We noted earlier that the sulfoxide reaction can produce glycosyl donors that are extremely reactive at low temperatures as well as donors that are stable at higher temperatures.[53] A likely explanation is that two different intermediates are being observed, one that reacts at low temperature and another (a sulfenate) that is stable until much higher temperatures. Sulfenate formation also provides a simple explanation for the observation that in some glycosylation reactions, only a small amount of product is formed at low temperature even though all of the sulfoxide is consumed. Furthermore, it explains why raising the temperature of the reaction often results in additional product formation, presumably through activation of the sulfenate at higher temperatures.

**Other Intermediates in the Sulfoxide Reaction.** Recently, Crich has shown that for some glycosyl donors the stereochemical outcome of the sulfoxide glycosylation reaction depends on whether the alcohol is present during the activation step.[27,32] For example, premixing mannose sulfoxide **15** and an alcohol followed by addition of triflic anhydride produces the α glycoside, while preactivating the sulfoxide and then adding the alcohol produces the $\beta$ glycoside. The difference in stereochemical outcome indicates that the reactions are proceeding through two different intermediates. Crich has shown that one of these intermediates is an anomeric triflate and that reaction through the triflate leads to the $\beta$-linked product.[32] He proposes that the intermediate initially formed in the reaction can trap an alcohol directly to form the α glycoside or can be converted to a triflate which then reacts with an alcohol to produce the $\beta$ glycoside (see Scheme 5).

Taken together, our studies and Crich's studies demonstrate that the sulfoxide reaction is very complex. *At least three different intermediates can be produced: the initially formed reactive species, an anomeric triflate, and an anomeric sulfenate.* The relative proportion of each intermediate formed depends on the structures of the glycosyl donors and acceptors as well as on the order of addition of reagents. These intermediates affect the outcome of a glycosylation reaction in different ways. Thus, to achieve the desired outcome in a particular reaction, it is important to understand what the potential intermediates are, how they affect the reaction, and how to control the formation

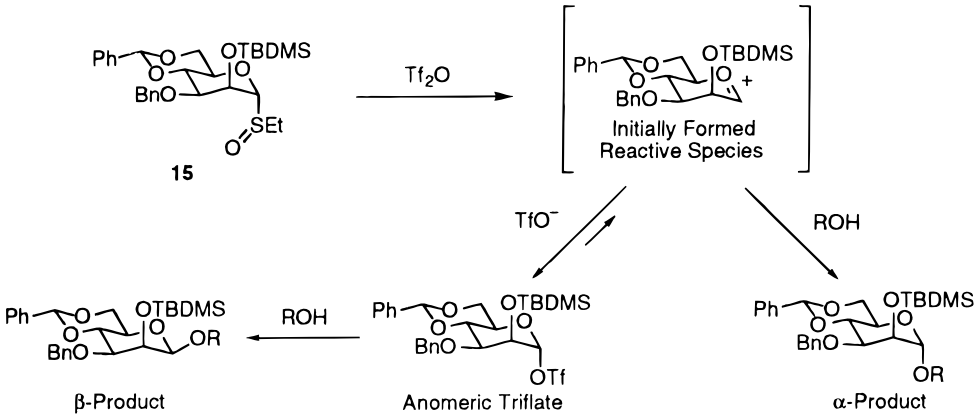
(50) For the attempted use of anomeric S−O sulfenates as glycosyl donors see Ferrier, R. J.; Furneaux, R. H.; Tyler, P. C. *Carbohydr. Res.* **1977**, *58*, 397.

(51) The exact mechanism for sulfenate activation is not clear. One possibility is that the sulfur atom is triflated to form a Swern-like intermediate. Gin has found that Swern intermediates are effective glycosyl donors, see: Garcia, B. A.; Poole, J. L.; Gin, D. Y. *J. Am. Chem. Soc.* **1997**, *119*, 7597.

(52) For the use of sulfenates as glycosyl acceptors, see: Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1987**, *28*, 2723, 4701.

(53) Crich has suggested that a single intermediate, an anomeric triflate, is both highly reactive at low temperatures and stable for prolonged times at higher temperatures (see ref 32).

**Scheme 5.** Crich's Mechanistic Proposal




of a specific intermediate in order to steer the reaction toward the desired product.

**Implications for Other Glycosylation Methods.** It is interesting to note that the order of addition can have a significant effect with other glycosylation methods as well. Schmidt recently reported that glycosylations of unreactive alcohols with glycosyl imidates are more efficient with inverse addition.[54] One possible explanation is that with unreactive alcohol acceptors, the activated species has an opportunity to glycosylate the starting imidate. If this happened, the resulting intermediate could break down to form the glycosyl trichloroacetamide, an unreactive byproduct. In fact, glycosyl trichloroacetamides are frequently observed as byproducts in the imidate reaction.[55,56] Furthermore, higher proportions of the glycosyl trichloroacetamide are observed with more unreactive alcohol acceptors.[57] These observations suggest that glycosylation of unreacted glycosyl donor is not unique to the sulfoxide reaction.

## Conclusions

The sulfoxide reaction generates a highly reactive glycosyl donor. In hindsight, it is not surprising that this activated glycosyl donor will glycosylate unreacted glycosyl sulfoxide. Interception of the activated donor by the sulfoxide leads to a much less reactive donor, an anomeric sulfenate. For many difficult glycosylations, reaction through the highly reactive donor is critical for the success of the glycosylation. When sulfenate formation impedes a reaction, inverse addition can be an effective strategy for improving the reaction.

## Experimental Section

**General Methods.** NMR spectra were recorded on a JEOL GSX 270 or a JEOL GSX 500 Fourier transform NMR spectrometer. Proton chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) unless otherwise noted. Carbon chemical shifts are reported in parts per million (ppm) downfield from TMS using the solvent $CD_3COCD_3$ as an internal reference unless otherwise noted. Coupling constants (*J*) are reported in hertz (Hz). Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broadened (br). Mass spectra were obtained on a VG ZAB, VG 7070, HP 5989A (University of California, Riverside, Mass Spectrometry Facility), or a ZAB-SE (UIUC School of Chemical Sciences).

Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Flash column chromatography was performed using silica gel 60 (230−400 mesh) from EM Science/Bodman.

All reactions were carried out under argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise noted. All reagents were purchased from commercial suppliers and used without further purification unless otherwise noted.

**Methyl 6-*O*-Benzoyl-2,3-di-*O*-(methoxymethyl)-α-D-glucopyranoside (2).** To a stirred solution of methyl 4-*O*-benzyl-2,3-di-*O*-(methoxymethyl)-α-D-glucopyranoside[58] (1.1 g, 2.96 mmol) in methylene chloride (10 mL) was added triethylamine (3.4 mL, 24.5 mmol) and benzoyl chloride (1.4 mL, 12.0 mmol). The reaction was stirred at room temperature for approximately 30 min and then diluted with EtOAc (100 mL) and washed with 0.5 N aqueous HCl (100 mL), saturated aqueous $NaHCO_3$ (100 mL), and brine (100 mL). The aqueous layers were reextracted with EtOAc (100 mL), and the organics were combined, dried over $Na_2SO_4$, and then concentrated in vacuo. The crude product was taken up in ethanol (7 mL), and Pd/C-Degussa type (100 mg) was added. The reaction was stirred under an atmosphere of hydrogen for 12 h and then filtered through Celite and concentrated *in vacuo*. The product was purified by flash chromatography (gradient 33% to 50% EtOAc/petroleum ether) to afford **2** (0.70 g, 61%) as a colorless oil: $R_f$ = 0.25 (40% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 8.06 (d, $J$ = 7.2 Hz, 2H), 7.56 (t, $J$ = 7.2 Hz, 1H), 7.44 (t, $J$ = 7.2 Hz, 2H), 4.84 (d, $J$ = 3.6 Hz, 1H), 4.7−4.8 (m, 4H), 4.65 (dd, $J$ = 2.3, 11.9 Hz, 1H), 4.57 (dd, $J$ = 5.3, 11.9 Hz, 1H), 4.23 (br s, 1H), 3.91 (ddd, $J$ = 2.3, 5.3, 9.5 Hz, 1H), 3.71 (dd, $J$ = 9.5, 9.5 Hz, 1H), 3.61 (dd, $J$ = 3.6, 9.5 Hz, 1H), 3.50 (dd, $J$ = 9.5, 9.5 Hz, 1H), 3.46 (s, 3H), 3.45 (s, 3H), 3.39 (s, 3H); $^{13}$C NMR ($CD_3COCD_3$, 67.5 MHz) $\delta$ 167.0, 134.2, 131.5, 130.5, 129.7, 100.1, 98.8, 98.1, 81.0, 79.2, 71.4, 70.7, 65.2, 56.1, 55.7, 55.5; HRFABMS calcd for $C_{18}H_{27}O_9$ ($M + H^+$) 387.1655, found 387.1656.

**Methyl (2,3,4-Tri-*O*-benzyl-α-L-fucopyranosyl)-(1-4)-6-*O*-benzoyl-2,3-di-*O*-(methoxymethyl)-α-D-glycopyranoside (3).** The combined sulfoxide **1**[31] (127 mg, 0.234 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (146 mg, 0.711 mmol) were azeotroped three times with toluene (10 mL). To the residue in methylene chloride (7 mL) was added 4 Å molecular sieves (500 mg), and the resulting suspension was stirred at room temperature for 1 h. The suspension was cooled to −78 °C, and a solution of triflic anhydride (20 $\mu$L, 0.117 mmol) in methylene chloride (300 $\mu$L) was added over 1−2 min. The reaction was warmed to −60 °C, and then a solution of the alcohol **2** (40 mg, 0.104 mmol) in methylene chloride (4 mL) was added dropwise via syringe. After 15 min at −60 °C, the reaction was filtered into saturated aqueous $NaHCO_3$ (30 mL) and extracted with methylene chloride (3 × 20 mL). The organic layers were combined, dried over $Na_2SO_4$, and concentrated *in vacuo*. The products were purified by flash chromatography (gradient 8−70% EtOAc/petroleum ether) to afford the disaccharide **3** (19 mg, 23%), sulfenate **4** (63 mg, 50%), and unreacted alcohol **2** (24

(54) Schmidt, R. R.; Toepfer, A. *Tetrahedron Lett.* **1991**, *28*, 3353.
(55) Schmidt, R. R.; Effenberger, G. *Carbohydr. Res.* **1987**, *171*, 59.
(56) Nunomura, S.; Ogawa, T. *Tetrahedron Lett.* **1988**, *29*, 5681.
(57) Kobayashi, M.; Yamazaki, F.; Ito, Y.; Ogawa, T. *Carbohydr. Res.* **1990**, *201*, 51.
(58) Berkowitz, D. B.; Eggen, M.; Shen, Q.; Sloss, D. G. *J. Org. Chem.* **1993**, *58*, 6174.

mg, 60%). **Disaccharide 3**: $R_f = 0.3$ (30% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 8.03 (d, $J = 6.9$ Hz, 2H), 7.15−7.65 (m, 18 H), 5.03 (d, $J = 3.6$ Hz, 1H), 4.95 (d, $J = 11.5$ Hz, 1H), 4.6−4.9 (m, 11H), 4.52 (dd, $J = 4.3$,12.2 Hz, 1H), 4.25 (q, $J = 6.3$ Hz, 1H), 4.07 (dd, $J = 3.6$, 10.2 Hz, 1H), 3.8−4.0 (m, 3H), 3.74 (dd, $J = 9.3$, 9.3 Hz, 1H), 3.68 (br s, 1H), 3.53 (dd, $J = 3.6$, 9.3 Hz, 1H), 3.39 (s, 3H), 3.38 (s, 3H), 3.36 (s, 3H), 1.11 (d, $J = 6.3$ Hz, 3H); $^{13}$C NMR ($CD_3COCD_3$, 67.5 MHz) $\delta$ 166.6, 140.4, 140.2, 139.8, 130.3, 129.5, 129.2, 129.1, 129.05, 129.0, 128.7, 128.4, 128.3, 128.2, 128.16, 100.0, 99.9, 99.3, 98.4, 80.5, 80.2, 79.3, 79.0, 77.2, 77.1, 75.7, 74.5, 73.0, 69.9, 68.1, 64.7, 56.6, 55.5, 55.3, 17.1; HRFABMS calcd for $C_{45}H_{53}O_{13}$ ($M - H^-$) 801.3486, found 801.3499. **Sulfenate 4**: $R_f = 0.4$ (10% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 7.15−7.5 (m, 20 H), 5.01 (d, $J = 3.6$ Hz, 1H), 4.96 (d, $J = 11.6$ Hz, 1H), 4.87 (d, $J = 11.6$ Hz, 1H), 4.77 (t, $J = 11.3$ Hz, 2H), 4.62 (d, $J = 11.6$ Hz, 2H), 4.07 (dd, $J = 3.6$, 10.2 Hz, 1H), 3.97 (dd, $J = 2.6$, 10.2 Hz, 1H), 3.79 (q, $J = 6.6$ Hz, 1H), 3.65 (m, 1H), 1.03 (d, $J = 6.6$ Hz, 3H); $^{13}$C NMR ($CD_3COCD_3$, 67.5 MHz) $\delta$ 142.2, 140.7, 140.6, 140.3, 130.3, 129.7, 129.6, 129.5, 129.3, 129.2, 128.8, 128.7, 125.4, 106.9, 80.2, 79.4, 79.2, 76.3, 74.7, 73.7, 69.3, 29.6; HRDCIMS calcd for $C_{33}H_{38}NO_5S$ ($M + NH_4^+$) 560.2471, found 560.2471.

**General Procedure for the Catalytic Conversion of Sulfoxides.** The combined sulfoxide (0.20 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (0.40 mmol) were azeotroped three times with toluene (10 mL). The residue was taken up in methylene chloride (7 mL), and 4 Å molecular sieves (500 mg) was added. The resulting suspension was stirred at room temperature for 1 h and then cooled to −78 °C. Forty microliters of a triflic anhydride stock solution (10 $\mu$L triflic anhydride in 400 $\mu$L of methylene chloride; 40 $\mu$L of stock is approximately 0.006 mmol) was added over 1 min via syringe. The reaction was monitored by TLC and warmed if necessary until all of the sulfoxide completely disappeared. The reaction was filtered into saturated aqueous $NaHCO_3$ (30 mL) and extracted with methylene chloride (3 × 20 mL). The organic layers were combined, dried over $Na_2SO_4$, and concentrated *in vacuo*. The products were purified by flash chromatography.

**Catalytic Conversion of 2,3,4-Tri-*O*-benzyl-1-(phenylsulfinyl)-α-L-fucopyranose (1).** Catalytic conversion of sulfoxide **1** afforded 25% of 2,3,4-tri-*O*-benzyl-1-(phenylsulfenyl)-α-L-fucopyranose (**4**) and 65% of an anomeric mixture of lactols.

**Synthesis and Catalytic Conversion of 2,3,4-Tri-*O*-benzyl-1-(2,6-dimethylphenylsulfinyl)-*β*-L-fucopyranoside (5a,b).** To a solution of 1,2,3,4-tetra-*O*-acetyl-L-fucopyranoside (7.8 g, 23.5 mmol) in methylene chloride (60 mL) was added 2,6-dimethylthiophenol (4.7 mL, 35.3 mmol). The reaction was cooled to at −72 °C, and boron trifluoride etherate (5.8 mL, 47.2 mmol) was added dropwise via syringe. The reaction was warmed slowly to 0 °C and stirred at 0 °C overnight. Saturated aqueous $NaHCO_3$ (50 mL) was added, and the reaction was stirred vigorously for 15 min. The organic layer was then separated, dried over $Na_2SO_4$, and concentrated *in vacuo*. The product was purified by flash chromatography (10% acetone/petroleum ether) to afford 2,6-dimethylphenyl 2,3,4-tri-*O*-acetyl-1-thio-*β*-L-fucopyranoside (7.7 g, 80%): $R_f = 0.25$ (15% acetone/petroleum ether); $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 7.13 (m, 3H), 5.31 (dd, $J = 10.2$, 10.2 Hz, 1H), 5.22 (d, $J = 3.6$ Hz, 1H), 4.99 (dd, $J = 3.6$, 10.2 Hz, 1H), 4.38 (d, $J = 10.2$ Hz, 1H), 3.62 (q, $J = 6.6$ Hz, 1H), 2.55 (s, 6H), 2.20 (s, 3H), 2.13 (s, 3H), 1.99 (s, 3H), 1.14 (d, $J = 6.6$ Hz, 3H); $^{13}$C NMR ($CD_3COCD_3$, 67.5 MHz) $\delta$ 171.6, 170.7, 170.5, 145.4, 132.9, 130.7, 129.7, 89.7, 73.8, 73.5, 71.9, 69.4, 23.2, 21.4, 21.2, 17.1; HRFABMS calcd for $C_{20}H_{26}O_7SNa$ ($M + Na^+$) 433.1297, found 433.1313.

To the above sulfide (3.0 g, 7.32 mmol) in methanol (25 mL) was added sodium methoxide (100 mg). The resulting solution was stirred at room temperature overnight and then neutralized with Amberlite IR-120 (plus) acidic resin. The resin was filtered and rinsed several times with methanol (3 × 30 mL). The combined filtrate was concentrated *in vacuo* and used without further purification.

To the crude tetraol (~7.32 mmol) in THF (20 mL) was added benzyl bromide (5.2 mL, 43.9 mmol). The reaction was cooled to 0 °C, and NaH (925 mg of 95% dispersion, 36.6 mmol) was added. Tetrabutylammonium iodide (1.0 g) and DMF (10 mL) were added, and the reaction was allowed to warm to room temperature. The reaction was quenched by slow addition of $H_2O$ (10 mL) and then diluted with EtOAc (100 mL), extracted with $H_2O$ (50 mL) and brine (50 mL), dried over $Na_2SO_4$, and concentrated *in vacuo*. The product was purified by flash chromatography (50% methylene chloride/petroleum ether) to afford 2,6-dimethylphenyl 2,3,4-tri-*O*-benzyl-1-thio-*β*-L-fucopyranoside (3.0 g, 74%): $R_f = 0.3$ (5% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 7.0−7.5 (m, 18H), 5.06 (d, $J = 10.5$ Hz, 1H), 4.98 (d, $J = 11.9$ Hz, 1H), 4.88 (d, $J = 10.5$ Hz, 1H), 4.72 (m, 3H), 4.27 (d, $J = 9.6$ Hz, 1H), 3.87 (dd, $J = 9.6$, 9.6 Hz, 1H), 3.57 (d, $J = 2.6$ Hz, 1H), 3.50 (dd, $J = 2.6$, 9.6 Hz, 1H), 3.26 (q, $J = 6.3$ Hz, 1H), 2.56 (s, 6H), 1.07 (d, $J = 6.3$ Hz, 3H); $^{13}$C NMR ($CD_3COCD_3$, 67.5 MHz) $\delta$ 145.0, 140.3, 140.0, 139.9, 133.3, 129.7, 129.2, 129.0, 128.95, 128.9, 128.8, 128.5, 128.3, 128.25, 128.2, 90.9, 85.5, 79.5, 78.0, 76.2, 75.7, 74.7, 73.2, 22.9, 17.5; HRFABMS calcd for $C_{35}H_{37}O_4S$ ($M - H^-$) 553.2413, found 553.2438.

To the above sulfide (500 mg, 0.903 mmol) in methylene chloride (10 mL) at −42 °C was added 3-chloroperoxybenzoic acid (272 mg of 65% dispersion, 1.02 mmol). The reaction was allowed to warm to −5 °C and then cooled to −30 °C, and dimethyl sulfide (100 $\mu$L) was added. The reaction was diluted with methylene chloride (50 mL) and extracted with saturated aqueous $NaHCO_3$ (50 mL). The organic layer was dried over $Na_2SO_4$ and concentrated *in vacuo*. The products were purified by flash chromatography (5:4:1 methylene chloride/petroleum ether/EtOAc) to afford a mixture of 2,3,4-tri-*O*-benzyl-1-(2,6-dimethylphenylsulfinyl)-*β*-L-fucopyranosides **5** (430 mg, 84%). More polar diastereomer: $R_f = 0.3$ (5:4:1 methylene chloride/petroleum ether/EtOAc); $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 7.1−7.5 (m, 16H), 7.01 (d, $J = 7.6$ Hz, 2H), 5.09 (d, $J = 9.9$ Hz, 1H), 4.99 (d, $J = 11.9$ Hz, 1H), 4.87 (d, $J = 9.9$ Hz, 1H), 4.70 (m, 3H), 4.35 (dd, $J = 9.1$, 9.1 Hz, 1H), 3.69 (dd, $J = 2.4$, 9.1 Hz, 1H), 3.59 (d, $J = 2.4$ Hz, 1H), 3.44 (q, $J = 6.3$ Hz, 1H), 2.57 (s, 6H), 1.01 (d, $J = 6.3$ Hz, 3H); $^{13}$C NMR ($CD_3COCD_3$, 67.5 MHz) $\delta$ 140.9, 140.7, 140.5, 140.2, 132.1, 130.8, 129.7, 129.6, 129.5, 129.3, 129.1, 129.0, 128.9, 128.7, 128.6, 94.4, 85.8, 78.3, 77.7, 76.0, 75.9, 75.7, 73.4, 20.6, 17.7; HRDCIMS calcd for $C_{35}H_{42}NO_5S$ ($M + NH_4^+$) 588.2784, found 588.2804. Less polar diastereomer: $R_f = 0.35$ (5:4:1 methylene chloride/petroleum ether/ EtOAc); $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 7.1−7.5 (m, 18H), 6.98 (d, $J = 7.6$ Hz, 2H), 5.0 (m, 3H), 4.75 (m, 3H), 4.53 (dd, $J = 9.6$, 9.6 Hz, 1H), 4.06 (d, $J = 9.6$ Hz, 1H), 3.68 (dd, $J = 2.6$, 9.6 Hz, 1H), 3.62 (m, 1H), 3.42 (q, $J = 6.3$ Hz, 1H), 2.55 (s, 6H), 1.10 (d, $J = 6.3$ Hz, 3H); $^{13}$C NMR ($CD_3COCD_3$, 67.5 MHz) $\delta$ 140.8, 140.3, 140.2, 137.2, 131.6, 131.1, 129.8, 129.6, 129.5, 129.3, 129.2, 129.1, 129.0, 128.9, 128.8, 94.4, 85.8, 78.2, 76.9, 76.5, 76.2, 75.1, 73.4, 20.4, 17.8; HRDCIMS calcd for $C_{35}H_{39}O_5S$ ($M + H^+$) 571.2518, found 571.2528.

Catalytic conversion of sulfoxide **5** afforded 66% of 2,3,4-tri-*O*-benzyl-1-(2,6-dimethylphenylsulfenyl)-α-L-fucopyranose (**6a**), 5% of 2,3,4-tri-*O*-benzyl-1-(2,6-dimethylphenylsulfenyl)-*β*-L-fucopyranose (**6b**), and 21% of an anomeric mixture of lactols. **Sulfenate 6a**: $R_f = 0.5$ (10% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 7.0−7.5 (m, 18H), 4.95 (d, $J = 3.6$ Hz, 1H), 4.89 (d, $J = 11.5$ Hz, 1H), 4.83 (d, $J = 11.7$ Hz, 1H), 4.69 (d, $J = 11.7$ Hz, 1H), 4.66 (d, $J = 12.2$ Hz, 1H), 4.57 (d, $J = 11.5$ Hz, 1H), 4.52 (d, $J = 12.2$ Hz, 1H), 3.96 (dd, $J = 3.6$, 10.2 Hz, 1H), 3.80 (dd, $J = 2.4$, 10.2 Hz, 1H), 3.50 (d, $J = 2.4$ Hz, 1H), 3.26 (q, $J = 6.6$ Hz, 1H), 2.57 (s, 6H), 0.62 (d, $J = 6.6$ Hz, 3H); $^{13}$C NMR ($CD_2Cl_2$, 67.5 MHz) $\delta$ 143.4, 139.5, 139.4, 139.2, 136.9, 131.4, 128.9, 128.8, 128.7, 128.65, 128.6, 128.3, 128.0, 104.7, 79.2, 78.8, 77.5, 75.5, 73.5, 73.4, 68.0, 22.0, 16.3; HRDCIMS calcd for $C_{35}H_{42}NO_5S$ ($M + NH_4^+$) 588.2784, found 588.2795. **Sulfenate 6b**: $R_f = 0.4$ (10% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 7.0−7.5 (m, 18H), 4.95 (d, $J = 11.5$ Hz, 1H), 4.65 (m, 5H), 4.39 (d, $J = 7.6$ Hz, 1H), 3.76 (dd, $J = 7.6$, 9.5 Hz, 1H), 3.47 (m, 3H), 2.59 (s, 6H), 1.19 (d, $J = 6.3$ Hz, 3H); $^{13}$C NMR ($CD_3COCD_3$, 67.5 MHz) $\delta$ 144.5, 140.8, 140.5, 137.5, 132.7, 129.6, 129.5, 129.4, 129.3, 129.1, 129.0, 128.7, 128.6, 109.2, 84.0, 81.0, 78.4, 76.2, 75,9, 73.9, 72.3, 22.6, 17.6; HRDCIMS calcd for $C_{35}H_{42}NO_5S$ ($M + NH_4^+$) 588.2784, found 588.2783.

**Catalytic Conversion of 2,3,4-Tri-*O*-pivaloyl-1-(phenylsulfinyl)-α-L-fucopyranose (7).** Catalytic conversion of sulfoxide **7**[29] afforded 81% of 1,3,4-tri-*O*-pivaloyl-α-L-fucopyranose (**8**): $R_f = 0.33$ (20% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 6.24 (d, $J = 3.6$ Hz, 1H), 5.30 (d, $J = 3.3$ Hz, 1H), 5.24 (dd, $J = 3.3$, 10.6 Hz,

1H), 4.25 (m, 2H), 1.88 (d, $J$ = 8.2 Hz, 1H), 1.28 (s, 18H), 1.20 (s, 9H), 1.13 (d, $J$ = 6.6 Hz, 3H); $^{13}$C NMR ($CD_3COCD_3$, 67.5 MHz) $\delta$ 178.4, 178.2, 177.7, 93.8, 72.4, 72.0, 68.7, 67.0, 40.4, 40.2, 39.9, 28.1, 28.0, 27.9, 16.9; HRFABMS calcd for $C_{21}H_{36}O_8Na$ (M + $Na^+$) 439.2308, found 439.2319.

**Catalytic Conversion of 2,3,4,6-Tetra-*O*-benzyl-1-(phenylsulfinyl)-α-D-glucopyranose (9).** Catalytic conversion of sulfoxide **9**[4] afforded 15% of 2,3,4,6-tetra-*O*-benzyl-1-(phenylsulfenyl)-α-D-glucopyranose (**10**) and 66% of an anomeric mixture of lactols. **Sulfenate 10**: $R_f$ = 0.5 (10% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 7.55 (m, 2H), 7.2−7.4 (m, 21H), 7.13 (m, 2H), 5.00 (d, $J$ = 3.6 Hz, 1H), 4.97 (d, $J$ = 12.2 Hz, 1H), 4.82 (d, $J$ = 10.9 Hz, 1H), 4.80 (d, $J$ = 10.9 Hz, 1H), 4.70 (d, $J$ = 11.9 Hz, 1H), 4.59 (m, 2H), 4.46 (d, $J$ = 10.9 Hz, 1H), 4.43 (d, $J$ = 12.2 Hz, 1H), 4.00 (dd, $J$ = 9.2, 9.2 Hz, 1H), 4.7 (m, 3H), 3.57 (dd, $J$ = 3.6, 9.2 Hz, 1H), 3.39 (m, 1H); $^{13}$C NMR ($CD_3COCD_3$, 67.5 MHz) $\delta$ 141.6, 140.6, 140.2, 140.1, 139.9, 132.4, 130.4, 129.7, 129.65, 129.6, 129.3, 129.2, 129.0, 128.8, 128.7, 128.6, 126.4, 105.9, 82.8, 82.1, 79.1, 76.5, 76.1, 74.45, 74.4, 73.4, 70.0; HRFABMS calcd for $C_{40}H_{40}O_6NaS$ (M + $Na^+$) 671.2443, found 671.2456.

**Synthesis and Catalytic Conversion of 2,3,4,6-Tetra-*O*-methyl-1-(phenylsulfinyl)-β-D-galactopyranoside (11).** To a solution of phenyl 1-thio-β-D-galactopyranoside[59] (4.0 g, 14.7 mmol) in DMF (80 mL) at 0 °C was add NaH (3.0 g of a 95% dispersion, 118 mmol). Methyl iodide (5.5 mL, 88 mmol) was added via syringe over 5 min. The reaction was warmed to room temperature and stirred overnight. Methanol (5 mL) was added slowly over 15 min, and the reaction was diluted with EtOAc (100 mL), extracted with $H_2O$ (100 mL), and brine (100 mL), dried over $Na_2SO_4$, and concentrated *in vacuo*. The product was purified by flash chromatography (25% EtOAc/petroleum ether) to afford of phenyl 2,3,4,5-tetra-*O*-methyl-1-thio-β-D-galactopyranoside (4.0 g, 83%): $R_f$ = 0.3 (33% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 7.55 (d, $J$ = 7.6 Hz, 2H), 7.25 (m, 3H), 4.50 (d, $J$ = 9.4 Hz, 1H), 3.70 (d, $J$ = 3.0 Hz, 1H), 3.59 (s, 3H), 3.56 (s, 3H), 3.45−3.65 (m, 3H), 3.53 (s, 3H), 3.41 (dd, $J$ = 9.4, 9.4 Hz, 1H), 3.37 (s, 3H), 3.20 (dd, $J$ = 3.0, 9.4 Hz, 1H); $^{13}$C NMR ($CD_3COCD_3$, 67.5 MHz) $\delta$ 136.6, 131.9, 130.2, 128.0, 88.4, 87.3, 80.6, 78.1, 76.7, 72.4, 61.7, 61.5, 59.7, 58.7; HRFABMS calcd for $C_{16}H_{24}O_5NaS$ (M + $Na^+$) 351.1242, found 351.1239.

To the above sulfide (353 mg, 1.08 mmol) in methylene chloride (10 mL) at −42 °C was added 3-chloroperoxybenzoic acid (314 mg of 65% dispersion, 1.18 mmol). The reaction was warmed slowly to −10 °C and then cooled to −30 °C, and dimethyl sulfide (100 μL) was added. The reaction mixture was diluted with methylene chloride (30 mL), extracted with saturated aqueous $NaHCO_3$ (30 mL), dried over $Na_2SO_4$, and concentrated *in vacuo*. The products were purified by flash chromatography (25% acetone/petroleum ether) to afford a mixture of sulfoxides **11** (319 mg, 86%). Less polar diastereomer: $R_f$ = 0.25 (25% acetone/petroleum ether); $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 7.68 (m, 2H), 7.49 (m, 3H), 4.19 (d, $J$ = 8.9 Hz, 1H), 3.84 (dd, $J$ = 8.9, 8.9 Hz, 1H), 3.65 (d, $J$ = 2.6 Hz, 1H), 3.56 (m, 3H), 3.50 (s, 3H), 3.48 (s, 3H), 3.46 (s, 3H), 3.37 (s, 3H), 3.30 (dd, $J$ = 2.6, 8.9 Hz, 1H);); $^{13}$C NMR ($CD_3COCD_3$, 67.5 MHz) $\delta$ 144.1, 131.5, 129.9, 125.6, 98.5, 87.3, 78.9, 76.1, 75.0, 72.4, 61.6, 60.5, 59.6, 58.3; HRDCIMS calcd for $C_{16}H_{25}O_6S$ (M + $H^+$) 345.1372, found 345.1363. More polar diastereomer: $R_f$ = 0.22 (25% acetone/petroleum ether); $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 7.63 (m, 2H), 7.48 (m, 3H), 4.01 (dd, $J$ = 9.5, 9.5 Hz, 1H), 3.80 (s, 3H), 3.78 (d, $J$ = 9.5 Hz, 1H), 3.71 (d, $J$ = 2.6 Hz, 1H), 3.65 (m, 1H), 3.63 (s, 3H), 3.61 (s, 3H), 3.40 (m, 3H), 3.27 (s, 3H); $^{13}$C NMR ($CD_3COCD_3$, 67.5 MHz) $\delta$ 142.6, 131.7, 130.0, 126.5, 94.8, 87.4, 79.7, 76.6, 76.3, 71.9, 61.8, 61.6, 59.5, 58.6; HRDCIMS calcd for $C_{16}H_{25}O_6S$ (M + $H^+$) 345.1372, found 345.1382.

Catalytic conversion of sulfoxide **11** afforded 39% of 2,3,4,6-tetra-*O*-methyl-1-(phenylsulfenyl)-α-D-galactopyranose (**12a**), 40% of 2,3,4,6-tetra-*O*-methyl-1-(phenylsulfenyl)-β-D-galactopyranose (**12b**), and 10% of an anomeric mixture of lactols. **Sulfenate 12a**: $R_f$ = 0.28 (15% acetone/petroleum ether); $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 7.51 (d, $J$ = 7.3 Hz, 2H), 7.38 (t, $J$ = 7.3 Hz, 2H), 7.25 (m, 1H), 5.09 (d, $J$ = 3.3 Hz, 1H), 3.77 (m, 2H), 3.60 (dd, $J$ = 3.3, 8.9 Hz, 1H), 3.55 (s, 3H), 3.52 (s, 3H), 3.47 (m, 2H), 3.43 (s, 3H), 3.34 (s, 3H), 3.24 (dd, $J$ = 5.3, 8.9 Hz, 1H); $^{13}$C NMR ($CD_3COCD_3$, 67.5 MHz) $\delta$ 142.2, 130.4, 128.3, 125.9, 106.8, 81.3, 80.2, 77.5, 72.1, 71.8, 61.9, 59.9, 59.7, 58.8; HRDCIMS calcd for $C_{16}H_{25}O_6S$ (M + $H^+$) 345.1372, found 345.1377. **Sulfenate 12b**: $R_f$ = 0.25 (15% acetone/petroleum ether); $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 7.40 (m, 4H), 7.20 (m, 1H), 4.41 (d, $J$ = 7.9 Hz, 1H), 3.64 (m, 2H), 3.60 (s, 3H), 3.57 (s, 3H), 3.53 (m, 1H), 3.50 (s, 3H), 3.40 (m, 2H), 3.39 (s, 3H), 3.12 (dd, $J$ = 3.3, 9.9 Hz, 1H);$^{13}$C NMR ($CD_3COCD_3$, 67.5 MHz) $\delta$ 142.2, 130.3, 128.1, 125.3, 110.7, 85.5, 82.8, 76.4, 75.1, 72.1, 61.7, 61.6, 59.6, 58.9; HRFABMS calcd for $C_{16}H_{24}O_6NaS$ (M + $Na^+$) 367.1191, found 367.1205.

**Catalytic Conversion of 2,3-di-*O*-benzyl-4,6-benzylidene-1-(phenylsulfinyl)-α-D-mannopyranose (13).** Catalytic conversion of sulfoxide **13**[33] afforded 15% of 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-(phenylsulfenyl)-β-D-mannopyranose (**14**) and 61% of an anomeric mixture of lactols. **Sulfenate 14**: $R_f$ = 0.33 (15% acetone/petroleum ether); $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 7.2−7.6 (m, 20H), 5.60 (s, 1H), 4.96 (d, $J$ = 12.0 Hz, 1H), 4.88 (d, $J$ = 12.0 Hz, 1H), 4.73 (d, $J$ = 12.2 Hz, 1H), 4.59 (d, $J$ = 12.2 Hz, 1H), 4.57 (s, 1H), 4.34 (dd, $J$ = 4.9, 10.5 Hz, 1H), 4.21 (dd, $J$ = 9.6, 9.6 Hz, 1H), 3.92 (m, 2H), 3.57 (dd, $J$ = 3.0, 9.6 Hz, 1H), 3.34 (ddd, $J$ = 4.9, 9.6, 9.6 Hz, 1H); $^{13}$C NMR ($CD_3COCD_3$, 67.5 MHz) $\delta$ 141.8, 140.6, 140.5, 139.7, 130.5, 130.0, 129.6, 129.5, 129.4, 128.8, 128.7, 128.6, 127.7, 125.9, 108.8, 102.7, 79.8, 79.7, 79.0, 76.6, 73.4, 69.6, 69.2; HRFABMS calcd for $C_{33}H_{33}O_6S$ (M + $H^+$) 557.1998, found 557.1999.

**Glycosylation Using Sulfenate (4) as the Glycosyl Donor.** Sulfenate **4** (34 mg, 0.063 mmol), alcohol **2** (25 mg, 0.065 mmol), and 2,6-di-*tert*-butyl-4-methylpyridine (91 mg, 0.44 mmol) were azeotroped three times with toluene (10 mL). Methylene chloride (5 mL) was added followed by 4 Å molecular sieves (500 mg). The resulting suspension was stirred at room temperature for 1 h and then cooled to −78 °C. A solution of triflic anhydride (21 μL, 0.125 mmol) in methylene chloride (350 μL) was added over 1−2 min. The reaction was warmed slowly and monitored by TLC for the disappearance of sulfenate **4** and the formation of disaccharide **3**. After 15 min at 0 °C, the reaction was filtered into saturated aqueous $NaHCO_3$ (30 mL) and extracted with methylene chloride (3 × 20 mL). The organic layers were combined, dried over $Na_2SO_4$, and concentrated *in vacuo*. The product was purified by flash chromatography (33% EtOAc/petroleum ether) to afford disaccharide **3** (26 mg, 50%).

**Comparison of Glycosylation Procedures. (A) Preactivation.** The combined sulfoxide **1** (82 mg, 0.151 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (224 mg, 1.09 mmol) was azeotroped three times with toluene (10 mL). To the residue in methylene chloride (5 mL) was added 4 Å molecular sieves (500 mg), and the resulting suspension was stirred at room temperature for 1 h. The suspension was cooled to −78 °C, and a solution of triflic anhydride (46 μL, 0.272 mmol) in methylene chloride (350 μL) was added over 1−2 min. A solution of alcohol **2** (26 mg, 0.067 mmol) in methylene chloride (3 mL) was added dropwise via syinge. The reaction was warmed to −50 °C, and after 15 min at −50 °C, the reaction was filtered into saturated aqueous $NaHCO_3$ (30 mL) and extracted with methylene chloride (3 × 20 mL). The organic layers were combined, dried over $Na_2SO_4$, and concentrated *in vacuo*. The product was purified by flash chromatography (33% EtOAc/petroleum ether) to afford disaccharide **3** (14 mg, 26%).

**(B) Premix.** The combined sulfoxide **1** (80 mg, 0.148 mmol), alcohol **2** (25 mg, 0.065 mmol), and 2,6-di-*tert*-butyl-4-methylpyridine (223 mg, 1.09 mmol) was azeotroped three times with toluene (10 mL). To the residue in methylene chloride (8 mL) was added 4 Å molecular sieves (500 mg), and the resulting suspension was stirred at room temperature for 1 h. The suspension was cooled to −78 °C, and a solution of triflic anhydride (45 μL, 0.267 mmol) in methylene chloride (350 μL) was added over 1−2 min. The reaction was warmed to −50 °C, and after 15 min at −50 °C, the reaction was filtered into saturated aqueous $NaHCO_3$ (30 mL) and extracted with methylene chloride (3 × 20 mL). The organic layers were combined, dried over $Na_2SO_4$, and concentrated *in vacuo*. The product was purified by flash

(59) Ferrier, R. J.; Furneaux, R. H. *Methods in Carbohydrate Chemistry*; Academic Press: New York, 1980; Vol. VII.

chromatography (33% EtOAc/petroleum ether) to afford disaccharide **3** (20 mg, 38%).

**(C) Inverse Addition.** The combined alcohol **2** (25 mg, 0.065 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (220 mg, 1.07 mmol) was azeotroped three times with toluene (10 mL). To the residue in methylene chloride (5 mL) was added 4 Å molecular sieves (500 mg), and the resulting suspension was stirred at room temperature for 1 h. The suspension was cooled to −78 °C, and a solution of triflic anhydride (45 $\mu$L, 0.267 mmol) in methylene chloride (350 $\mu$L) was added over 1−2 min. A solution of sulfoxide **2** (80 mg, 0.148 mmol) in methylene chloride (3 mL) was added via syringe over 10−15 min. The reaction was warmed to −50 °C, and after 15 min at −50 °C, the reaction was filtered into saturated aqueous $NaHCO_3$ (30 mL) and extracted with methylene chloride (3 × 20 mL). The organic layers were combined, dried over $Na_2SO_4$, and concentrated *in vacuo*. The product was purified by flash chromatography (33% EtOAc/petroleum ether) to afford disaccharide **3** (34 mg, 65%).

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**Supporting Information Available:** $^1$H NMR spectra for **2**−**6**, **8**, **10**−**12**, and **14**, and low-temperature $^1$H NMR spectra for the sulfoxides (both diastereomers of **1** and the α sulfoxide), sulfenate **4**, and lactols (2,3,4-tri-*O*-benzyl-L-fucopyranose), and a table with the calculated energies of all conformations of substituted sulfoxides and sulfenates examined (23 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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