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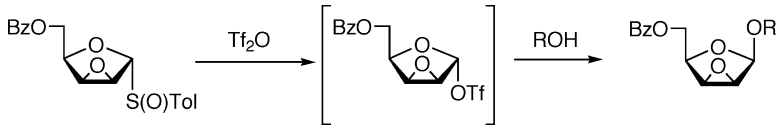

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2,3-Anhydrosugars in Glycoside Bond Synthesis. NMR and Computational Investigations into the Mechanism of Glycosylations with 2,3-Anhydrofuranosyl Glycosyl Sulfoxides

Christopher S. Callam, Rajendrakumar Reddy Gadikota, Douglas M. Krein, and Todd L. Lowary*,‡

Contribution from the Department of Chemistry, The Ohio State University, 100 West 18th Avenue, Columbus, Ohio 43210

Received March 3, 2003; E-mail: tlowary@ualberta.ca

Abstract: We report here the combined use of computational chemistry and low-temperature NMR spectroscopy to probe the mechanism of a highly stereoselective glycosylation reaction employing 2,3-anhydrofuranosyl glycosyl sulfoxides (**2** and **4**). The reaction involves a two-step process that is carried out in one pot. In the first step, the sulfoxide is reacted with triflic anhydride leading to the formation of a single intermediate. Using NMR spectroscopy, we have established the structure of this intermediate as a glycosyl triflate. In the second step, the acceptor alcohol is added to the reaction mixture, which leads to the highly stereocontrolled formation of the glycoside product. The structure of the major product is consistent with a pathway involving an S_N2-like displacement of the triflate by the alcohol. In the predominant intermediate that is formed, there is a trans relationship between the triflate group and epoxide. Therefore, in the glycoside product there is a cis relationship between the epoxide and the aglycone. In addition to providing insight into these reaction pathways, these investigations have also allowed us to identify conditions under which the glycosylations can be made to proceed with even greater stereoselectivity and in higher yield.

Introduction

In a previous paper,[1] we described new methodology for the synthesis of arabinofuranosyl-containing oligosaccharides in which one of the key steps was a stereocontrolled glycosylation reaction between an alcohol and a 2,3-anhydrosugar thioglycoside[2] or glycosyl sulfoxide[3] donor (**1**−**4**, Figure 1). The predominant, or frequently only, glycoside product of these reactions is the one in which the newly formed glycosidic bond is cis to the epoxide moiety (e.g., **5** and **6**). The extremely high stereocontrol observed in these reactions was intriguing, and we became interested in understanding the origin of this stereoselectivity. In this paper, we describe investigations that were carried out to probe the mechanisms by which the glycosylations with sulfoxides **2** and **4** proceed.

Results and Discussion

Preliminary Considerations. The activation protocol we initially developed for glycosylations with **2** and **4** involved first treatment of the sulfoxide (1.0 equiv) with triflic anhydride (Tf_2O, 1.2 equiv) in the presence of 2,6-di-*tert*-butyl-4-methyl pyridine (DTBMP, 4.0 equiv) at −78 °C in dichloromethane. After stirring for 10 min at this temperature, the alcohol (1.0 equiv) was added and the reaction mixture was warmed to room temperature prior to workup. Before continuing with detailed investigations into the mechanism of these glycosylations, we

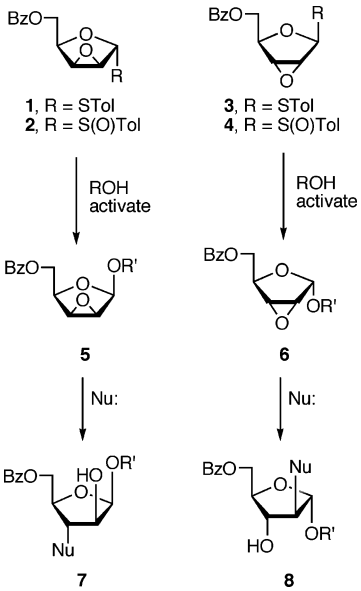

Figure 1. Synthesis of α and β-arabinofuranosides from glycosyl donors **1**−**4**.

‡ Present address: Department of Chemistry and Alberta Ingenuity Centre for Carbohydrate Science, The University of Alberta, Gunning-Lemieux Chemistry Centre, Edmonton, Alberta T6G 2G2, Canada.

(1) Gadikota, R. R.; Callam, C. S.; Wagner, T.; Del Fraino, B.; Lowary, T. L. *J. Am. Chem. Soc.* **2003**, *125*, 4155−4165.
(2) Garegg P. J. *Adv. Carbohydr. Chem. Biochem.* **1997**, *52*, 179.
(3) (a) Yan, L.; Kahne, D. *J. Am. Chem. Soc.* **1996**, *118*, 9239. (b) Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881.

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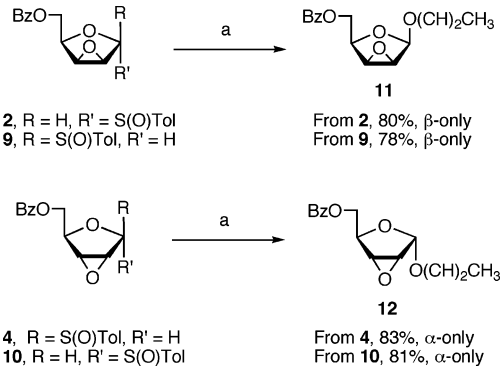


Figure 2. Reactions carried out to determine if the stereochemistry at the anomeric center in the donor influences the stereochemical outcome of the glycosylation reactions. Note that the yields are high and essentially identical regardless of the anomeric stereochemistry in the donor. Legend: (a) Tf_2O, DTBMP, CH_2Cl_2, −78 °C then *n*-octanol.[1]

viewed it important to determine (1) if the stereochemistry at the anomeric center in the donor influenced the stereochemistry of the product and (2) if the glycoside distribution was governed by the thermodynamic stability of the final products.

To probe the first issue, we compared the products obtained upon glycosylation of *n*-octanol with **2** and **4** with those produced when donors with the opposite anomeric stereochemistry (**9** and **10**) were used (Figure 2). For the sulfoxides with the 2,3-anhydro-D-*lyxo* stereochemistry (**2** and **9**), the β-glycoside was obtained in essentially identical yield from either donor. Analogous results were obtained in the glycosylations with the 2,3-anhydro-D-*ribo* donors **4** and **10**; the α-glycoside was produced in nearly identical yield from either substrate. *Therefore, the stereochemistry at the anomeric center in the sulfoxide donor does not influence the product formed in these glycosylations*.[1]

To determine whether the product distribution was controlled by the relative stability of the products, the reactions shown in Figure 3 were carried out. On the basis of previous ab initio and density functional theory calculations on 2,3-anhydrosugar glycosides,[4] we made the assumption that the major products of these reactions (e.g., **11** and **12**) were *less* stable than the isomeric glycosides (e.g., **13** and **14**).[5] Proceeding under this assumption, we coupled glycosyl sulfoxide **2** with *n*-octanol in the presence of α-glycoside **13**.[4] Following the reaction, more than 90% of the added **13** could be recovered, together with an 82% yield of the expected product, **11**. If the products were formed as a consequence of the equilibration of α-glycoside **13** to β-glycoside **11**, significantly less **13** would have been isolated at the end of the reaction. When *n*-octanol was glycosylated with **6** in the presence of **14**, analogous results were obtained. *Therefore, under these conditions, the two glycosides do not equilibrate thus indicating that the observed product distribution is not due to thermodynamic control based on the relative stability of the two possible products.*

Armed with this information, we initiated more in-depth studies of the mechanism of these glycosylation reactions. Presented below is a detailed discussion of these investigations for the 2,3-anhydro-α-D-*lyxo*-sulfoxide, **2**. The same experiments were also carried out with the 2,3-anhydro-β-D-*ribo*-sulfoxide,

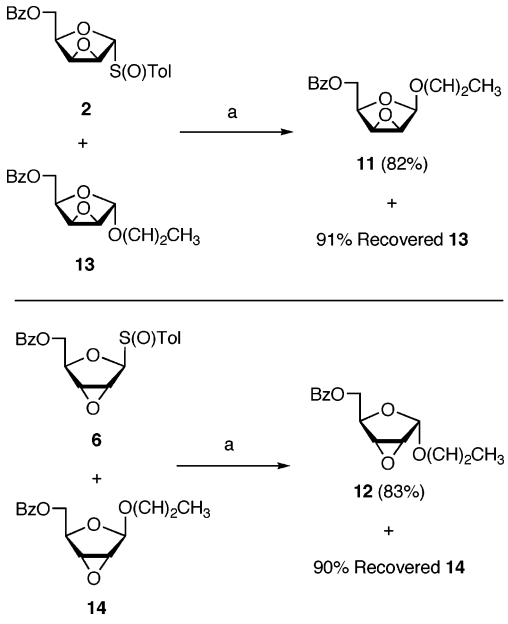


Figure 3. Reactions carried out to determine if the product glycosides equilibrate under the reaction conditions. Note that the glycoside added at the beginning of the reaction (e.g., **13**) is recovered in better than 90% at the end of the reaction, indicating that it does not isomerize to the major product of these reactions (e.g., **11**) under these conditions.

4, and the results were analogous to those obtained with **2**. Accordingly, a less detailed discussion is provided for the reactions involving **4**.

Proposed Mechanistic Pathway for Glycosylations with 2. The investigations outlined above clearly indicate that the stereocontrol observed in these glycosylations is neither the result of an S_N2 displacement of an activated sulfoxide leaving group nor determined by the stability of the final glycosides. Based on these observations and mindful of earlier work by Crich and co-workers on the mechanism of their stereoselective β-mannopyranoside synthesis,[6] we posited that these glycosylations proceed via the pathway outlined in Figure 4.

In the first step, Tf_2O is added to the sulfoxide in the presence of DTBMP, which leads to the formation of an ion pair (**16**) by way of the activated sulfoxide derivative **15**. In the absence of any other nucleophiles, **16** would be in equilibrium with glycosyl triflates **17** and **18**. It is expected that the α-triflate (**17**) would be the most stable of the three species (**16**, **17**, **18**) and would therefore predominate at equilibrium. In the second step, the alcohol is added to the reaction mixture, and an S_N2-like displacement of the triflate leaving group in **17** can be envisioned, leading to β-glycoside **19**. The stereocontrol of this process would therefore be determined by the relative concentration of **16**, **17**, and **18**, with the latter two species giving rise to products in a stereospecific fashion through displacement of the anomeric leaving group by the alcohol.[7] In contrast, if the reactive species were ion pair **16**, mixtures of glycosides would be expected.

In the glycosylations we have carried out to date with **2**,[1] the observed stereoselectivities suggest that if the reaction does

(4) Callam, C. S.; Gadikota, R. R.; Lowary, T. L. *J. Org. Chem.* **2001**, *66*, 4549.
(5) Even in the absence of high-level calculations, steric hindrance considerations can be used to predict that **13** would be more stable than **11** and that **14** would be more stable than **12**.
(6) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217.
(7) Other glycosylation reactions have been proposed to proceed via an S_N2-like displacement of a good leaving group (e.g., a halide) at the anomeric center: (a) Gervay, J.; Hadd, M. J. *J. Org. Chem.* **1997**, *62*, 6961. (b) Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056.

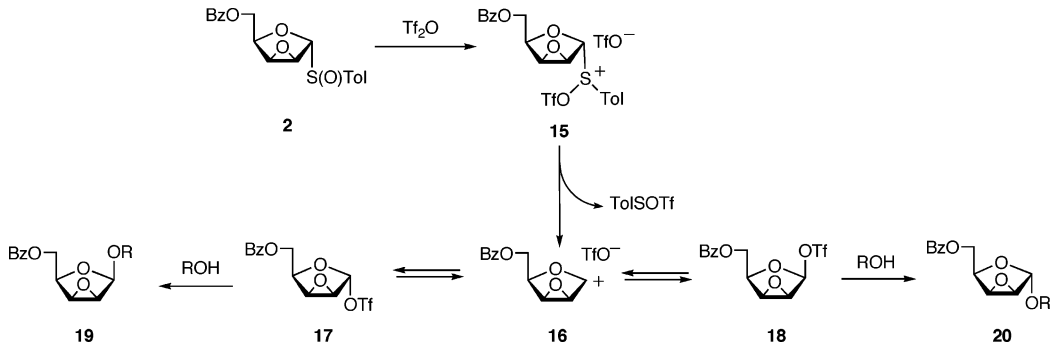


Figure 4. Proposed mechanistic pathway for glycosylation reactions employing sulfoxide **2**.

Table 1. Relative Energies of Triflates **17** and **18**

entry	compound	C_4–C_5 rotamer[a]	C_1–O_1 rotamer[b]	energy[c]	ΔE[d]
1	**17** (α)	gg	gg	3.4	5.2
	18 (β)	gg	gg	8.6	
2	**17** (α)	gg	gt	1.7	5.0
	18 (β)	gg	gt	6.7	
3	**17** (α)	gg	tg	1.6	4.3
	18 (β)	gg	tg	5.9	
4	**17** (α)	gt	gg	2.5	2.4
	18 (β)	gt	gg	4.9	
5	**17** (α)	gt	gt	0.3	4.7
	18 (β)	gt	gt	5.0	
6	**17** (α)	gt	tg	0.6	3.5
	18 (β)	gt	tg	4.1	
7	**17** (α)	tg	gg	2.2	1.3
	18 (β)	tg	gg	3.6	
8	**17** (α)	tg	gt	0.0	4.8
	18 (β)	tg	gt	4.8	
9	**17** (α)	tg	tg	0.1	3.9
	18 (β)	tg	tg	4.0	

[a] See Figure 5A for definitions. [b] See Figure 5B for definitions. [c] Relative B3LYP/6-31+G**//HF/6-31G* bottom-of-the-well energy in kcal/mol. [d] Energy difference of an α/β triflate pair for a given set of exocyclic orientations.

proceed as outlined in Figure 4, then **17** should be the only significant intermediate present prior to the addition of the alcohol. With this postulate formulated, we set out to obtain evidence for the formation of this species in these reactions. In our investigations, we used both computational chemistry and low-temperature NMR spectroscopy.

Relative Energies of Glycosyl Triflates 17/18 and Methyl Glycosides 21/22. If these glycosylations proceed via the pathway shown in Figure 4, the stereochemistry in the final glycoside product necessitates either (1) that the α-triflate **17** be formed in preference to the β-isomer **18** or (2) that a Curtin–Hammett-type kinetic scheme is operating in which a less stable α-triflate is also more reactive and the reaction is channeled through this intermediate. To shed light on these two possibilities, we have used ab initio and density functional theory calculations to determine the relative energies of **17** and **18** (Table 1). A total of 9 conformers for each triflate, differing in the orientation of certain exocyclic bonds, were investigated. All three possible staggered orientations about the C_4–C_5 and C_1–O_1 bonds were studied (see Figure 5 for rotamer definitions).[8] In all structures, upon minimization (HF/6-31G*) there was no significant rotation about these bonds. For each

(8) The trifluoromethyl group was placed anti to the C_1–O_1 bond. We also investigated a limited number of conformers that differed in the orientation about the O_1–S bond but found only very small differences in energy (~0.1 kcal/mol).

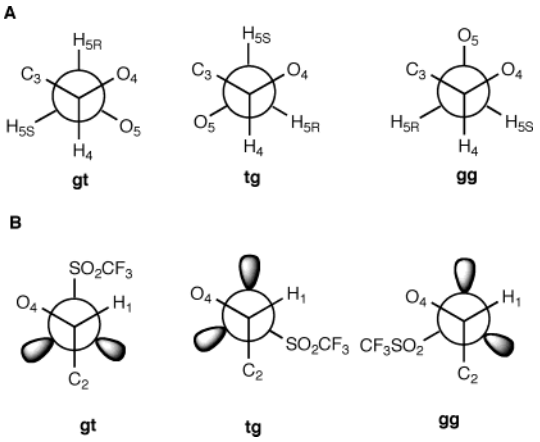


Figure 5. (A) Definition of staggered rotamers about the C_4–C_5 bond. (B) Definition of staggered rotamers about the C_1–O_1 bond.

optimized conformer, a single-point energy was calculated at the B3LYP/6-31+G** level of theory, and these energies are shown in Table 1. It is clear from these data that there is a substantial difference in energy (ΔE) between **17** and **18**. Although the exact ΔE is a function of the exocyclic group orientations, these values range between 1.3 and 5.2 kcal/mol, with the difference in most cases being 3.5 kcal/mol or larger. In the two cases (entries 4 and 7) where the ΔE is less than 3.0 kcal/mol, the triflate moiety is oriented under the ring (the C_1–O_1 conformer is "gg", Figure 5B) and, consequently, the lowest energy structure of the triflate pair has an energy more than 2.0 kcal/mol above the global minimum (entry 8α). Therefore, these structures are likely to be very minimally populated in the reaction mixture. These calculations suggest that, for the likely solution conformers of **17** and **18** (entries 5, 6, 8, and 9), the ΔE between them is 3.5–4.8 kcal/mol and a fully equilibrated mixture of **16**, **17**, and **18** would consist overwhelmingly of α-triflate **17**. The results of these calculations are inconsistent with the notion that these reactions proceed via a kinetic scheme in which the reaction is being channeled through a reactive, high-energy α-triflate intermediate.

We have also calculated the relative energies of the methyl glycosides (**21** and **22**, Chart 1) that would result from the S_N2 reaction of **17** and **18** with methanol (Table 2). As is true with the triflates, the energy difference between a given α/β pair is significant (2.6–3.7 kcal/mol), with the product in which the glycosidic bond is trans to the epoxide being the most stable. These calculations, together with others previously carried out on other 2,3-anhydrofuranosides,[4] support our previous assumption that the major products obtained from these reactions are

Chart 1

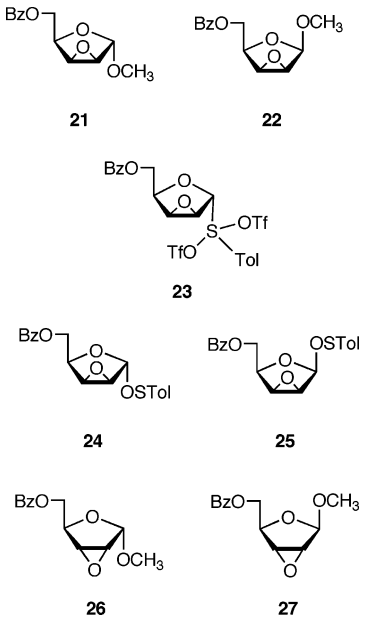


Table 2. Relative Energies of Methyl Glycosides **21** and **22**[a]

compound	C_4–C_5 rotamer[b]	energy[c]	ΔE[d]
21	gg	1.5	2.6
22	gg	4.0	
21	gt	1.2	2.7
22	gt	3.9	
21	tg	0.0	3.7
22	tg	3.7	

[a] C_1-O_1 bond was placed anti-periplanar to the C_1-C_2 bond. [b] See Figure 5A for definitions. [c] Relative B3LYP/6-31+G**//HF/6-31G* bottom-of-the-well energy in kcal/mol. [d] Energy difference of an α/β glycoside pair for a given set of exocyclic orientations.

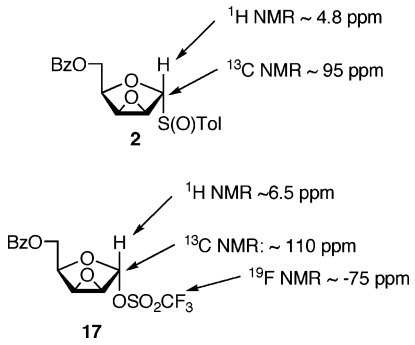


Figure 6. Expected chemical shifts for selected atoms in **2** and **17**. ^1H and ^{13}C chemical shifts are referenced to TMS (δ_H, δ_C 0.0 ppm). ^{19}F chemical shifts are referenced to external trifluroacetic acid (δ_F 0.0 ppm).

those that are the least thermodynamically stable of the two possible glycosides.

Detection of Triflate Intermediates Generated from 2 by Low-Temperature NMR. Having gained some support for the pathway proposed in Figure 4 from our computational investigations, we next sought to gain experimental support for the formation of glycosyl triflate intermediates in these reactions. We chose to probe for the presence of these intermediates by low-temperature NMR spectroscopy as previously described by Crich and co-workers.[6] As illustrated in Figure 6, differentiation of the glycosyl triflates (**17**) from the sulfoxides (**2**) can be straightforwardly done through the use of ^1H, ^{13}C, and ^{19}F NMR

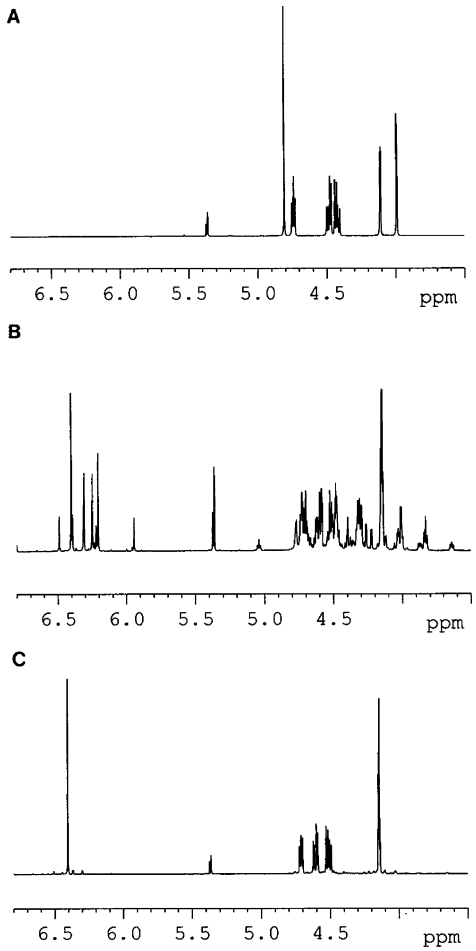


Figure 7. Partial ^1H NMR spectra of reactions involving **2**. (A) The reaction mixture prior to addition of Tf_2O; the singlet at 4.81 ppm is the anomeric hydrogen of **2**. The spectrum was recorded at −78 °C. (B) The reaction mixture approximately 3 min after adding Tf_2O; note the appearance of a number of species with ^1H resonances in the region between 6.0 and 6.5 ppm. The spectrum was recorded at −78 °C. (**C**) The reaction mixture 60 min after the addition of Tf_2O; the singlet at 6.40 ppm is the anomeric hydrogen of the proposed triflate intermediate. The spectrum was recorded at −40 °C.

spectroscopy. Furthermore, distinguishing between the triflate intermediates and ion pair **16** can be done using ^{13}C NMR spectroscopy, as C-1 in the oxonium ion would be expected to have a chemical shift well above 200 ppm.[9]

We first monitored these reactions using ^1H NMR spectroscopy. Initially, a solution of **2**[10] and DTBMP in CD_2Cl_2 was cooled to −78 °C, and a spectrum was recorded. The region of this spectrum between 3.5 and 6.8 ppm is shown in Figure 7A. The tube was then removed from the spectrometer and kept at −78 °C, and Tf_2O was added. Working quickly, we then returned the sample to the cooled spectrometer, and another spectrum was recorded, which is provided in Figure 7B. Approximately 3 min elapsed from the time the Tf_2O was added until this spectrum was obtained.

A comparison of the spectra in Figure 7A and B indicates that, as expected, the signal for the anomeric hydrogen in the sulfoxide (the singlet at ~4.8 ppm) has disappeared. However, instead of a single peak appearing in the region between 6.0

(9) Olah, G. A.; Parker, D. G.; Yoneda, N. *J. Org. Chem.* **1977**, *42*, 32.
(10) A single sulfoxide stereoisomer was used in these investigations. Previous work (ref 1) demonstrated that the stereochemistry at this center had no effect upon the product ratio.

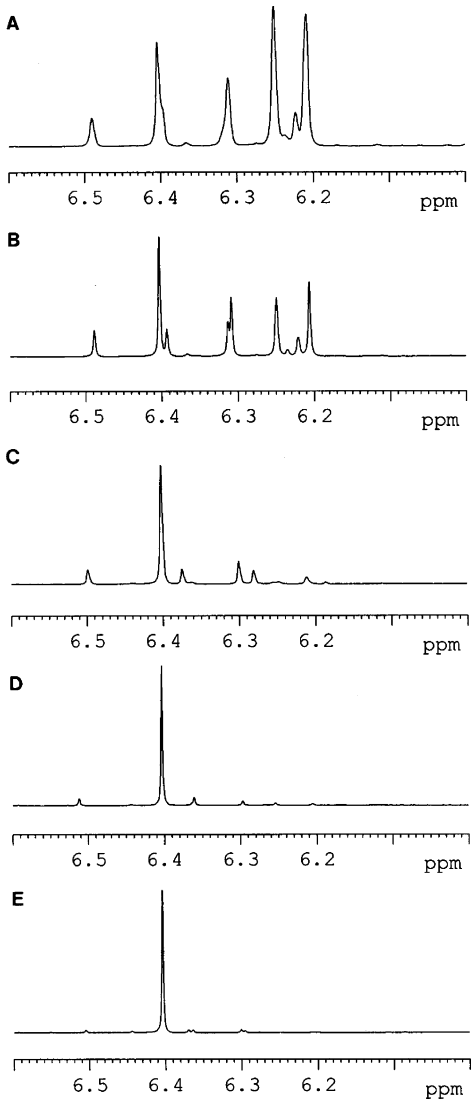


Figure 8. Partial ^{1}H NMR spectra of reactions involving **2**. Equilibration of reaction intermediates over time. (A) 1 min after Tf_2O addition (−78 °C). (B) 10 min after Tf_2O addition (−78 °C). (C) 20 min after Tf_2O addition (−60 °C). (D) 40 min after Tf_2O addition (−40 °C). (E) 60 min after Tf_2O addition (−40 °C).

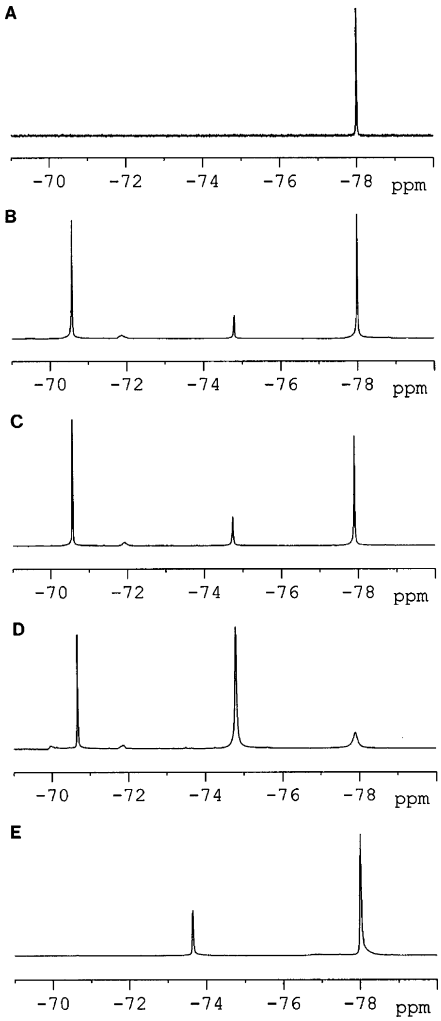


Figure 9. Partial ^{19}F NMR spectra of reactions involving **2**. Equilibration of reaction intermediates over time. Peak assignments were as follows: −70.6 ppm, OTf−; −74.8 ppm, proposed triflate intermediate; −78.0 ppm, Tf_2O; −73.9 ppm, CH_3OTf. (A) 1 min after Tf_2O addition (−78 °C). (B) 10 min after Tf_2O addition (−78 °C). (C) 20 min after Tf_2O addition (−60 °C). (D) 40 min after Tf_2O addition (−40 °C). (E) After addition of methanol (60 min after the addition of Tf_2O, −40 °C).

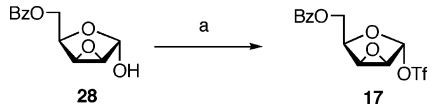
and 6.5 ppm, a number of peaks are present, thus indicating the formation of multiple species.[11] This was an initially disappointing result, which suggested that the reaction manifold was far more complex than we had anticipated. We were, however, pleased to discover that all of the intermediates equilibrated into a single species (Figure 7C) over time. These changes in the reaction mixture are shown in Figure 8, which depicts the region between 6.0 and 6.6 ppm for ^{1}H NMR spectra measured over an 80-min period. Although the equilibration of the intermediates into a single species occurred at −78 °C, warming the temperature to −60 and then −40 °C accelerated this process. This species, which we propose is triflate **17**, is stable at −40 °C for more than 80 min.

The chemical shift of the anomeric hydrogen of this intermediate is consistent with it being a glycosyl triflate.[4] Further support was obtained by ^{13}C NMR spectroscopic experiments, which were carried out exactly as described above for the ^{1}H experiments. A shift in the anomeric carbon from 96.3 to 109.2 ppm, which is characteristic of a glycosyl triflate intermediate,[6] was observed (see Figure S1 in the Supporting Information). Finally, the results of our ^{19}F NMR spectroscopic investigations were also consistent with the intermediate being a glycosyl triflate (Figure 9). Over time, the signal for Tf_2O (−70.5 ppm) and TfO− (−78 ppm) decreased at the expense of a signal at −74.8 ppm, which we attribute to the glycosyl triflate. Upon addition of methanol to the NMR tube, this peak and the one for the Tf_2O disappeared and were replaced by signals for methyl triflate and TfO−.

These experiments demonstrate that, under these conditions, a single intermediate is formed in these reactions and we propose that this species is a glycosyl triflate. However, a critical issue was the stereochemistry at the anomeric center. As reported earlier by us,[4] the only NMR spectroscopic parameter that can be used to unambiguously assign anomeric stereochemistry in 2,3-anhydrosugar glycosides is the magnitude of the $^1J_{C-1,H-1}$. In our previous investigations, we showed that in glycosides with H_1 trans to the epoxide moiety that $^1J_{C-1,H-1} = 163-168$ Hz; when this hydrogen is cis to the oxirane ring, $^1J_{C-1,H-1} =$

(11) Following the progress of these reactions is facilitated by the fact that the resonance for the anomeric hydrogen in 2,3-anhydrofuranosides appears as a singlet, regardless of anomeric stereochemistry.

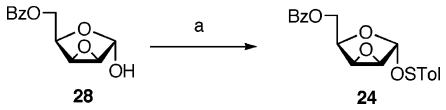
Scheme 1 [a]



28 17

[a] Tf_2O, DTBMP, CD_2Cl_2, −78 °C.

Scheme 2 [a]



28 24

[a] *p*-TolSCl, pyridine, CD_2Cl_2, −78 °C.

171−174 Hz.[2] Although this intermediate is not a glycoside, we nevertheless measured the magnitude of this coupling constant in the hope that it would provide information about the anomeric stereochemistry. For the species giving rise to the ^{1}H NMR spectrum shown in Figure 7C, the $^1J_{C-1,H-1}$ is 197.2 Hz.[12] As would be expected[13] for carbohydrate derivatives with a strongly electron withdrawing group at the anomeric center, the $^1J_{C-1,H-1}$ magnitude is substantially larger than those measured from the corresponding glycosides. Unfortunately, this factor complicated the definitive assignment of the anomeric stereochemistry in the proposed glycosyl triflate intermediate, as we had no appropriate standards with which to compare this number.

We therefore proceeded to synthesize an authentic sample of **17**. First, pure α-lactol **28** was prepared[14] and then treated with triflic anhydride and DTBMP in CD_2Cl_2 (Scheme 1). A single product was formed in this reaction, and its ^{1}H NMR spectrum was identical to that obtained of the species produced upon reaction of sulfoxide **2** with Tf_2O. Lactol **28** is 2.3−2.8 kcal/mol more stable than its corresponding *β*-isomer (depending upon the C_4-C_5 bond orientation, Table S3).[15] Given this energy difference, we view complete anomerization of **28** to its *β*-isomer under these triflation conditions as very unlikely; therefore, we assign the anomeric stereochemistry in this triflate and the one produced in these glycosylation reactions as α.

Being confident in our assignment of **17** as an α-glycosyl triflate, we turned out attention to a final important issue: probing the identity of the intermediates formed in the early stages of the reaction, which eventually equilibrate to **17**. From the spectra shown in Figure 7B, it appears that as many as 9 different compounds are initially present. Presumably, one of these compounds is the *β*-triflate **18**, while another may be the activated sulfoxide intermediate **15** (Figure 4). The sulfurane **23** (Chart 1), which can be formed by the reaction of **15** with TfO−, is also another possible intermediate. As for the identity of the other species, it is possible that various rotamers about the C_1-O_1 and C_1-S bonds in the various intermediates are present, which only slowly equilibrate to **17** at the low temperatures used in these reactions.

Another possibility is that glycosyl sulfenates (e.g., **24** and **25**, Chart 1) are being formed. In previous investigations by Kahne and co-workers,[16] it was demonstrated that sulfenate intermediates are formed in some glycosylations with glycosyl sulfoxides. These sulfenates were shown to be unreactive at low temperatures (−78 °C) but do act as glycosylating agents when the reaction mixture is warmed to −20 °C.[16] To determine if these other intermediates are glycosyl sulfenates, we synthesized an authentic sample of **24** as indicated in Scheme 2.[17] Reaction of **28** with *p*-TolSCl[18] and pyridine in an NMR tube afforded a single glycosyl sulfenate, **24** (see ^{1}H NMR spectrum in Supporting Information). The ^{1}H NMR spectrum of this mixture showed a resonance at 5.57 ppm, which is characteristic of the anomeric hydrogen in glycosyl sulfenates.[17] This peak, however, does not correspond to any of the intermediates formed in the early stages of the reaction of **2** with triflic anhydride. We therefore conclude that glycosyl sulfenates are not formed as intermediates in these reactions.

Detection of Triflate Intermediates Generated from 4 by Low-Temperature NMR. With an understanding of the mechanistic pathway operating for glycosylations with sulfoxide **2**, we next carried out a similar series of investigations with glycosyl sulfoxide **4**, which possesses the 2,3-anhydro-D-*ribo* stereochemistry. The results of these studies were exactly analogous to those obtained with **2** and support the mechanistic pathway outlined in Figure 10. This pathway involves the formation of a *β*-triflate intermediate (**31**) that is then displaced in an S_N2-like manner upon addition of the alcohol, providing the α-glycoside **33** as the major product.

As would be expected based on the results described above for **2**, our calculations demonstrated that triflate **31** is more stable than **32** and that methyl glycoside **27** (Chart 1) is more stable than **26**. In our NMR studies on glycosylations involving **4**, the only major difference compared to **2** is that the equilibration of the initially formed intermediates to a single glycosyl triflate is slower for **4**. In the interest of space, the results of these investigations (relative energies of triflates and methyl glycosides, NMR spectra) are included in the Supporting Information.[19]

Improvement of the Reaction Stereoselectivity Based on these Mechanistic Investigations. In addition to providing us with insight into the mechanism of these reactions, these investigations have also allowed us to improve our synthetic methodology. The conditions we developed initially for carrying out these reactions involved treatment of the sulfoxide at −78 °C with Tf_2O and then stirring the mixture for 10 minutes at this temperature before the addition of the alcohol. The NMR spectra provided in Figures 7 and 8 clearly show that the equilibration of all of the intermediates is not complete after only 10 min at −78 °C. Under these conditions, it would be expected that the stereoselectivity would be reduced as a consequence of the reaction of the acceptor alcohol with an intermediate (e.g., **18**) other than the predominant triflate that eventually forms (e.g., **17**). We reasoned that it might be possible to improve further the stereoselectivity of this reaction by modification of the protocol used. Indeed, this was found to be the case. We have changed the protocol such that, after the

(12) Measured from the ^{1}H-coupled ^{13}C spectrum.
(13) Bock, K.; Pedersen, C. *J. Chem. Soc., Perkin Trans. 2* **1974**, 293.
(14) Lactol **28** was prepared, as a single isomer, by the hydrolysis of thioglycoside **1** using *N*-iodosuccinimide and silver triflate (see Experimental Section). The $^1J_{C-1,H-1}$ value for this species is 175.6 Hz, which is consistent with the proposed α-stereochemistry (see ref 4).
(15) These energy differences were obtained from B3LYP/6-31+G**//HF/6-31+G* calculations on **28** and the corresponding *β*-anomer (see Table S3).
(16) (a) Kahne, D.; Gildersleeve, J.; Pascal, R. A. *J. Am. Chem. Soc.* **1998**, *120*, 5961. (b) Kahne, D.; Gildersleeve, J.; Smith, A.; Sakurai, K.; Raghavan, S. *J. Am. Chem. Soc.* **1999**, *121*, 6176.
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(19) For **4**, we have not synthesized authentic samples of the corresponding triflate or sulfenate species.

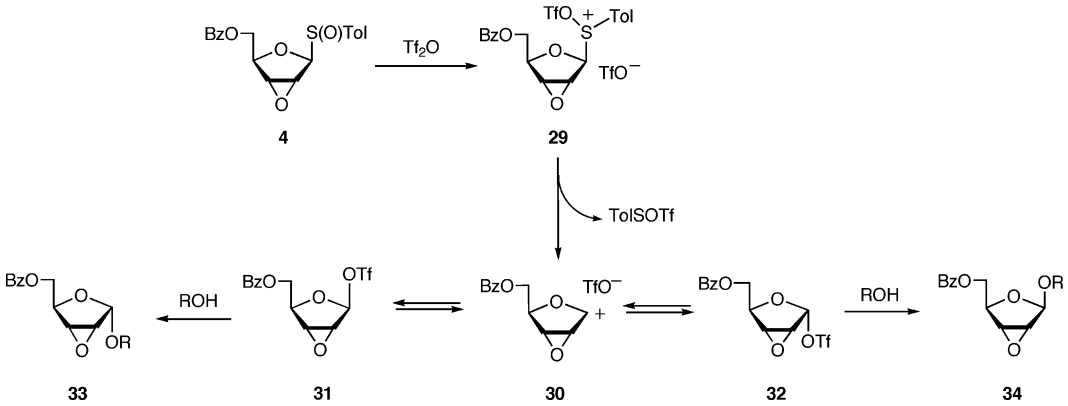

Figure 10. Proposed mechanistic pathway for glycosylation reactions employing sulfoxide **4**.

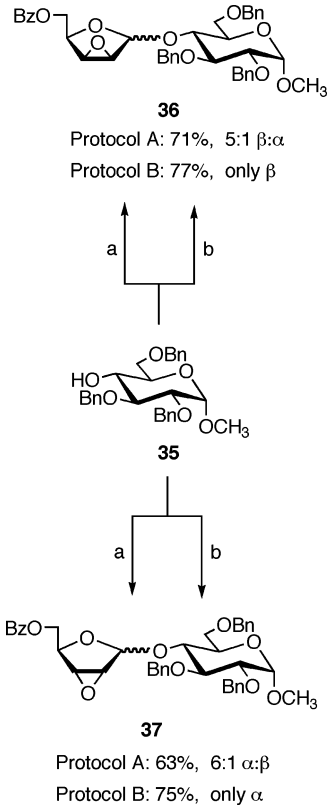

Figure 11. Stereoselectivities and yields of the glycosylation of **35** with **2** and **4** under initial and modified conditions. Note that the modified protocol affords the glycoside in higher yields and with better stereoselectivity. Legend: (a) **2** or **4**, Tf_2O, DTBMP, CH_2Cl_2, −78 °C, 10 min, then **35**, −78 °C → rt. (b) **2** or **4**, Tf_2O, DTBMP, CH_2Cl_2, −78 °C, 10 min then −40 °C for 20 min then **35**, −40 °C → rt.

addition of the Tf_2O to the sulfoxide at −78 °C, the reaction mixture is stirred for 10 min and then warmed to −40 °C. After stirring at −40 °C for 20 min, the alcohol is added and the reaction mixture is brought to room temperature and then worked up. Shown in Figure 11 are some examples[1] comparing both activation protocols, which demonstrate that this modification increases both the yield and stereoselectivity of these glycosylations. Additional examples can be found in our earlier paper.[1]

Conclusions

In conclusion, we have used a combination of computational chemistry and low-temperature NMR spectroscopy to probe the mechanism of a highly stereoselective glycosylation reaction involving 2,3-anhdyrofuranosyl glycosyl sulfoxides. We propose that, under the conditions in which these reactions are carried out, a single glycosyl triflate intermediate is formed and this species then reacts with the acceptor alcohol via an S_N2-like reaction affording products with a high degree of stereocontrol. The predominant formation of a triflate intermediate in which there is a trans relationship between the triflate group and epoxide oxygen leads to glycoside products in which there is a cis relationship between the epoxide and the aglycone. It is important to note that we cannot absolutely rule out the possibility that these reactions proceed by the trapping of an oxonium ion/ion pair species such as **16**. We did not, however, detect the presence of an oxonium ion intermediate by NMR spectroscopy. Moreover, if a species such as **16** were the intermediate undergoing reaction with the alcohol, we would expect that the stereoselectivity of these reactions would be lower. In this regard, we also note that in some glycosylations the stereocontrol is not total.[1] It is plausible that in these cases the erosion of stereocontrol arises from the reaction of the acceptor alcohol with both the predominant triflate species and the oxonium ion (or minor triflate species). A similar erosion would also be expected if the major triflate species was in rapid equilibrium with the oxonium ion and minor triflate species. Not only have these investigations provided insight into these reaction pathways but they have also allowed us to identify conditions under which the reactions can be made to proceed with even greater stereoselectivity and in higher yield.

Experimental Section

Synthetic Chemistry. General methods.[1]

A. Probing the interconversion of Glycosides 11 and 13 under the Reaction Conditions. Sulfoxide **2** (180 mg, 0.5 mmol), DTBMP (410 mg, 2.0 mmol), and 4-Å molecular sieves (0.1 g) were dried for 3 h under vacuum in the presence of P_2O_5. To this mixture was added CH_2Cl_2 (10 mL) and a solution of **13**[2] (177 mg, 0.5 mmol) in CH_2Cl_2 (1 mL), and the reaction mixture was cooled to −78 °C. Triflic anhydride (105 μL, 0.6 mmol) was added, and the mixture was allowed to stir for 10 min. The solution was warmed to −40 °C and was stirred for 20 min, followed by the dropwise addition of a solution of octanol (94 μL, 0.6 mmol) in CH_2Cl_2 (1.0 mL) over 5 min. After 15 min, the reaction mixture turned dark brown/green, and a saturated solution of $NaHCO_3$ was added. The solution was then allowed to warm to room temperature, filtered through Celite, dried (Na_2SO_4), filtered, and concentrated to yield a crude oil that was purified by chromatography (10:1, hexane:EtOAc) to provide **11**[1] (143 mg, 82%) and recovered

13[2] (151 mg, 91%) as oils. The R_f values for **11** and **13** (10:1, hexane:EtOAc) are 0.30 and 0.40, respectively.

B. Probing the Interconversion of Glycosides 12 and 14 under the Reaction Conditions. The experiments done with **11** and **13** were also carried out with **12** and **14**, using the protocol described above. Following the reaction and workup, the products were purified by chromatography (10:1, hexane:EtOAc) to provide **12**[1] (83%) and recovered **14**[1] (90%) as oils. The R_f values for **12** and **14** (10:1, hexane:EtOAc) are 0.45 and 0.27, respectively.

C. 5-*O*-Benzoyl-2,3-anhydro-α-D-lyxofuranose (28). To a solution of **1**[1] (1.1 g, 3.22 mmol) in CH_3CN/H_2O (5:1, 15 mL) at 0 °C was added NIS (0.86 g, 3.85 mmol). The solution was allowed to stir for 10 min followed by the addition of AgOTf (21 mg, 0.38 mmol). After the solution was stirred for 10 min, triethylamine (2 mL) was added and the solution was diluted with CH_2Cl_2 and filtered through Celite. The filtrate was washed with a saturated aqueous $Na_2S_2O_3$ solution, water, and brine. The organic layer was dried, filtered, and concentrated, and the residue was purified by chromatography (hexanes/EtOAc, 4:1) yielding **28** (0.68 g, 90%) as a white solid: R_f 0.14 (hexanes/EtOAc, 2:1); ^{1}H NMR (500 MHz, CD_2Cl_2, δ_H) 8.06 (d, 2 H, $J = 7.2$ Hz), 7.57 (t, 1 H, $J = 7.5$, 7.5 Hz), 7.44 (dd, 2 H, 7.5, 7.5 Hz), 5.32 (d, 1 H, $J = 4.1$ Hz), 4.37−4.27 (m, 3 H), 3.67 (d, 1 H, $J = 2.8$ Hz), 3.56 (d, 1 H, $J = 2.8$ Hz), 3.30 (br d, 1 H, $J = 4.0$ Hz); ^{13}C NMR (125 Hz, CD_2Cl_2, δ_C) 166.2, 133.1, 129.6, 129.4, 128.3, 95.6, 73.9, 62.9, 56.7, 54.1. $^1J_{C-1,H-1} = 175.6$. HRMS (ESI) calcd for ($M + Na^+$) $C_{12}H_{12}O_5$ 259.0582, found 259.0571.

Computational Methods. Ab initio molecular orbital[20] and density functional theory (DFT)[21] calculations were performed using Gaussian 98.[22] The optimized geometries were calculated at the HF/6-31G* level of theory,[20] and single-point energies of these optimized geometries were calculated at the B3LYP/6-31+G** level of theory[23] (Tables 1 and S1). To obtain a better understanding of the potential energy surface of the glycosyl triflates, all possible combinations of anomers and rotamers about the C_4-C_5 bond and the C_1-O_1 bonds were explored (a total of 18 conformers; see Tables 1 and S1). The optimization process did not lead to significant changes in rotamer orientation. For the methyl glycosides (Tables 2 and S2), only the rotamers about only the C_4-C_5 bond were explored; the C_1-O_1 bond in these molecules was placed in the position favored by the *exo*-anomeric effect,[24] and no significant change in the orientation about this bond was seen upon optimization.

NMR Experiments. All NMR experiments were performed in duplicate in 5-mm NMR tubes dried under a stream of argon and stoppered with septa under a positive pressure of argon. The ^{1}H and ^{13}C spectra were recorded at 500 and 125 MHz, respectively; the ^{19}F NMR spectra were recorded at 235 MHz. Chemical shifts are in ppm and are referenced to the solvent for ^{1}H and ^{13}C spectra (^{1}H, $CHDCl_2$, δ_H 5.32 ppm; ^{13}C, CD_2Cl_2, δ_C 53.8 ppm). ^{19}F spectra were referenced to external trifluoroacetic acid (δ_F 0.00 ppm).

A. Following the Formation of Intermediates Produced from 2 and 4 by NMR Spectroscopy. The sulfoxide (60 mg, 0.17 mmol) and DTBMP (40 mg, 0.20 mmol) were dissolved in CD_2Cl_2 (1.1 mL) in an NMR tube, and a spectrum was recorded at −78 °C. The tube was removed and kept at −78 °C, and then Tf_2O (23 μL, 1.8 mmol) was added. The tube was then quickly returned to the cooled spectrometer, and spectra were taken over 60 min, while warming the probe from −78 to −40 °C.

B. Synthesis of an Authentic Sample of 17. A solution of **28** (36 mg, 0.15 mmol) and DTBMP (62 mg, 0.30 mmol) in CD_2Cl_2 (1.0 mL) was cooled to −78 °C in a 5-mm NMR tube. To this solution was added Tf_2O (26 μL, 0.17 mmol). The solution stirred for 20 min at −78 °C and was vortexed periodically to allow for efficient mixing. The ^{1}H spectrum of the product (obtained at −78 °C) matched that of the intermediate formed upon treatment of sulfoxide donor **2** with Tf_2O.

C. Synthesis of an Authentic Sample of Sulfenate 24. To a solution of lactol **28** (40 mg, 0.17 mmol) and DTBMP (40 mg, 0.20 mmol) in CD_2Cl_2 (1.1 mL) in an NMR tube cooled to −78 °C was added *p*-TolSCl[16] (14 μL, 0.18 mmol). The progress of the reaction was monitored by ^{1}H spectroscopy while warming from −78 °C to −40 °C over the course of 60 min. After a single product was formed, the probe was again cooled to −78 °C and the spectrum provided in the Supporting Information was recorded.

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Supporting Information Available: Results of computational and NMR investigations involving sulfoxide **4** (relative energies of triflates and methyl glycosides, NMR spectra), Cartesian coordinates of all optimized geometries, NMR spectra of sulfenate **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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