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Published on Web 08/24/2009

2,3-Anhydrosugars in Glycoside Bond Synthesis: Mechanism of 2-Deoxy-2-thioaryl Glycoside Formation

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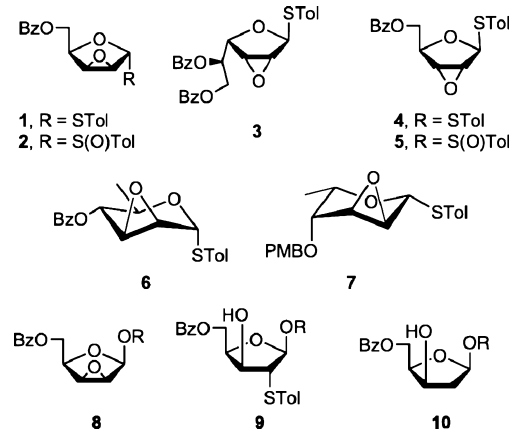
Abstract: A series of investigations probing the mechanism of the 2,3-anhydrosugar migration−glycosylation reaction were performed using a thioglycoside with the D-lyxo stereochemistry as the substrate. Among the work reported are the results of quantum mechanical calculations, NMR studies, the measurement of α-deuterium kinetic isotope effects, and the synthesis of a series of substrate analogues. All studies point to a consistent finding: that the reaction proceeds through an oxocarbenium ion intermediate, not an episulfonium ion as previously suggested. It is proposed that the high stereoselectivity of the reaction arises from a preferred "inside attack" of the nucleophile onto the oxocarbenium ion intermediate.

Introduction

Over the past several years we have published a series of papers demonstrating the utility of 2,3-anhydrosugar derivatives (e.g., **1**−**7**, Chart 1) in the synthesis of glycosidic bonds.[1−6] One reaction manifold available to these species is the assembly of 2,3-anhydosugar glycosides (e.g., **7**). Postglycosylation nucleophilic opening of the epoxide ring can lead to a diverse range of products including α-galactofuranosides,[4] β-arabinofuranosides,[5,6] and α-arabinofuranosides.[1,6] Another pathway, possible only for the 2,3-anhydrosugar thioglycosides (e.g., **1**), is the formation of 2-deoxy-2-thioaryl glycosides (**9**), which are useful precursors to 2-deoxy-glycosides (**10**).[2,3]

The formation of 2-deoxy-2-thioaryl glycosides occurs when thioglycosides such as **1**, **2**, and **4**−**6** are treated with an alcohol and a Lewis acid. The major, usually exclusive, product is the one in which the glycosidic bond is formed trans to the thioaryl group at C-2 (e.g., **9**). On the basis of this observation, and by analogy to other similar processes,[7−16] we proposed that the mechanism of this migration−glycosylation reaction proceeds via the pathway shown in Figure 1, pathway A.[2] Activation of the epoxide in **1** by the Lewis acid to generate **11** initiates the migration of the thioaryl group from C-1 to C-2 via an episulfonium ion intermediate **12** that, in turn, reacts with an alcohol to generate the glycoside **9** with a high degree of stereocontrol.

Chart 1



Episulfonium ions such as **12** have often been proposed[7−15,17] to be intermediates in glycosylations of this type, and their intermediacy provides a convenient explanation for the typically high stereoselectivity observed. There is little evidence, however, for their formation in these processes. Indeed, an increasing body of work, both experimental and computational, suggests that these glycosylations proceed through oxocarbenium ion species such as **13**, not episulfonium ions, **12**. For example, all reported computational efforts to identify stable α-oxygenated episulfonium ions have been unsuccessful and have suggested instead

(1) Cociorva, O. M.; Lowary, T. L. *Tetrahedron* **2004**, *60*, 1481–1489.
(2) Hou, D.; Lowary, T. L. *Org. Lett.* **2007**, *9*, 4487–4490.
(3) Hou, D.; Lowary, T. L. *J. Org. Chem.* **2009**, *74*, 2278–2289.
(4) Bai, Y.; Lowary, T. L. *J. Org. Chem.* **2006**, *71*, 9658–9671.
(5) Callam, C. S.; Gadikota, R. R.; Krein, D. M.; Lowary, T. L. *J. Am. Chem. Soc.* **2003**, *125*, 13112–13119.
(6) Gadikota, R. R.; Callam, C. S.; Wagner, T.; Del Fraino, B.; Lowary, T. L. *J. Am. Chem. Soc.* **2003**, *125*, 4155–4165.
(7) Auzanneau, F.-I.; Bundle, D. R. *Carbohydr. Res.* **1991**, *212*, 13–24.
(8) Zuurmond, H. M.; van der Klein, P. A. M.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron* **1993**, *49*, 6501–6514.
(9) Stick, R. V.; Tilbrook, D. M. G.; Williams, S. J. *Aust. J. Chem.* **1999**, *52*, 885–894.
(10) Bravo, F.; Viso, A.; Alcazar, E.; Molas, P.; Bo, C.; Castillon, S. *J. Org. Chem.* **2003**, *68*, 686–691.
(11) Poopeiko, N.; Fernandez, R.; Barrena, M. I.; Castillon, S.; Fornies-Camer, J.; Cardin, C. J. *J. Org. Chem.* **1999**, *64*, 1375–1379.
(12) Yang, Z.; Yu, B. *Carbohydr. Res.* **2001**, *333*, 105–114.
(13) Yu, B.; Yang, Z. *Org. Lett.* **2001**, *3*, 377–379.
(14) Lázár, L.; Bajza, I.; Jakab, Z.; Lipták, A. *Synlett* **2005**, 2242–2244.
(15) Sajtos, F.; Lázár, L.; Borbás, A.; Bajza, I.; Lipták, A. *Tetrahedron Lett.* **2005**, *46*, 5191–5194.
(16) Nicolaou, K. C.; Mitchell, H. J.; Fylaktakidou, K. C.; Suzuki, H.; Rodríguez, R. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1089–1093.
(17) Beaver, M.; Billings, S.; Woerpel, K. *Eur. J. Org. Chem.* **2008**, 771–781.

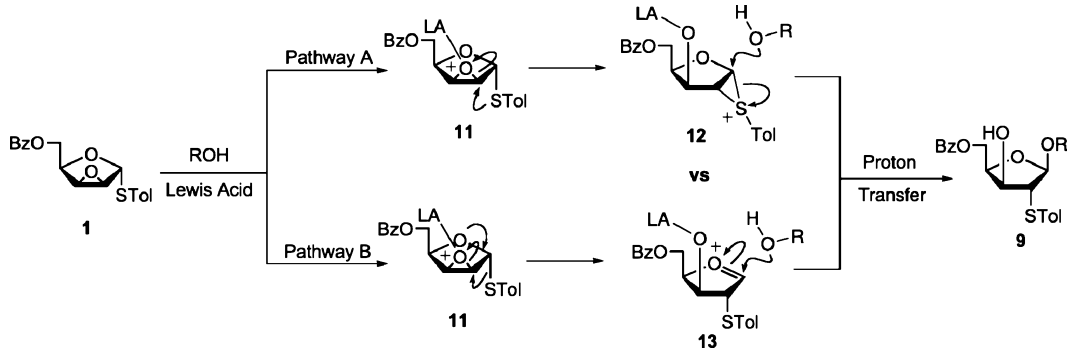


Figure 1. Possible mechanistic pathways for the formation of 2-deoxy-2-thioaryl-thioglycosides from 2,3-anhdyrosugar thioarylglycosides. Pathway A involves an episulfonium ion intermediate, whereas pathway B involves an oxocarbenium ion intermediate.

that the oxocarbenium ions are the true intermediates.[10,18−20] Other studies,[21,22] which report the formation of α/β mixtures of glycosides from these reactions, also support the formation of oxocarbenium ion intermediates, as these species would not be expected to react in a stereospecific manner. For a more detailed discussion of these processes, the reader is directed to an excellent recent review by Beaver et al.[17]

We describe here a series of studies with thioglycoside **1**, which are aimed at understanding the mechanism by which the migration−glycosylation shown in Figure 1 proceeds. In carrying out these investigations, a range of techniques was employed, including low-temperature ^{1}H NMR spectroscopy, computational studies, chemical synthesis, and the measurement of α-deuterium kinetic isotope effects. As discussed below in detail, the data obtained from all approaches point to the intermediacy of an oxocarbenium ion intermediate. Indeed, the isotopic labeling investigations reported here provide the first direct experimental evidence for the true nature of the reactive intermediate in this reaction.

Results and Discussion

Low-Temperature NMR Studies. In an earlier investigation[5] on the mechanism of 2,3-anhydrosugar glycoside formation from **1** and **4**, we used low-temperature NMR spectroscopy, as pioneered by Crich and Sun[23] and others,[24−27] to probe for reaction intermediates. Given our experience with these experiments, and recent investigations by Kim et al.[28] and Beaver et al.,[29] who had used NMR spectroscopy to detect the formation of sulfonium ion intermediates in other glycosylations, we hoped to exploit this technique to determine if a species such as **12** was formed in these reactions. In previous studies, glycosyl donors **14**[28] and **15**[29] were activated in the absence of an alcohol, and sulfonium ions **16** and **17**, respectively, were detected by NMR spectroscopy. These species could be characterized by

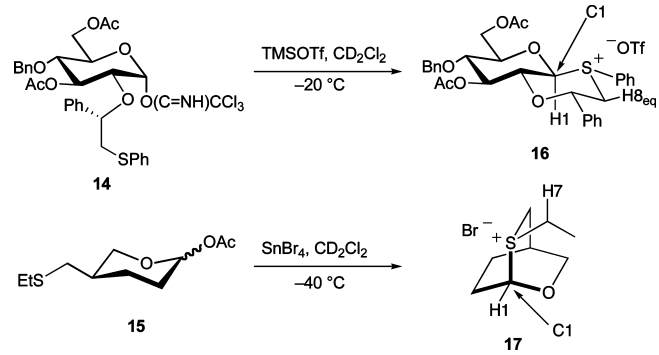


Figure 2. Sulfonium ions detected by Kim et al. (ref 28) and Beaver et al. (ref 29) using low-temperature NMR spectroscopy.

the expected shift of the anomeric proton (H1) to lower chemical shift compared to the parent glycosyl donors. Furthermore, an HMBC (heteronuclear multiple bond correlation) experiment correlated C1 and $H8_{eq}$ (sulfonium ion **16**) and C1 and H7 (sulfonium ion **17**) indicating that the SPh and SEt groups were connected to C1.

Mindful of these previous experimental studies, an NMR tube containing a solution of compound **1** in deuterated dichloromethane was cooled to −78 °C, and an ^{1}H NMR spectrum was recorded. The tube was then removed from the spectrometer, and TMSOTf was quickly added at −78 °C. After returning the sample to the spectrometer, the sample was warmed to room temperature in 10° increments over 2 h, and a spectrum was recorded at each temperature. Under these conditions no single intermediate showing an anomeric proton at higher chemical shift than the starting material, which based on earlier work[28−30] would be indicative of an episulfonium ion, was observed. Instead, a large number of different species were produced, the structures of which could not be determined. Upon bringing the spectrometer to room temperature, and allowing the tube to stand for several hours, the product was characterized as the hydrolyzed donor, due to absorption of atmospheric moisture.

In an attempt to gain an understanding of the ^{1}H NMR spectrum that would result from an episulfonium ion derived from **1**, we explored an alternate method of generating such a

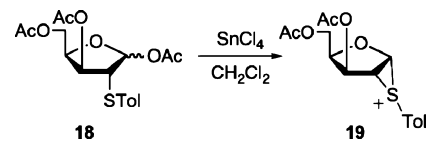


Figure 3. Alternate approach to generate an episulfonium ion.

(18) Dudley, T. J.; Smoliakova, I. P.; Hoffmann, M. R. *J. Org. Chem.* **1999**, *64*, 1247–1253.
(19) Smoliakova, I. P. *Curr. Org. Chem.* **2000**, *4*, 589–608.
(20) Jones, D. K.; Liotta, D. C. *Tetrahedron Lett.* **1993**, *34*, 7209–7212.
(21) Johnston, B. D.; Pinto, B. M. *J. Org. Chem.* **2000**, *65*, 4607–4617.
(22) Nicolaou, K.; Ladduwahetty, T.; Randall, J.; Chucholowski, A. *J. Am. Chem. Soc.* **1986**, *108*, 2466–2467.
(23) Crich, D.; Sun, S. X. *J. Am. Chem. Soc.* **1997**, *119*, 11217–11223.
(24) Boebel, T. A.; Gin, D. Y. *J. Org. Chem.* **2005**, *70*, 5818–5826.
(25) Garcia, B. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4269–4279.
(26) Honda, E.; Gin, D. Y. *J. Am. Chem. Soc.* **2002**, *124*, 7343–7352.
(27) Liu, J.; Gin, D. Y. *J. Am. Chem. Soc.* **2002**, *124*, 9789–9797.
(28) Kim, J.; Yang, H.; Park, J.; Boons, G.-J. *J. Am. Chem. Soc.* **2005**, *127*, 12090–12097.
(29) Beaver, M.; Billings, S.; Woerpel, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 2082–2086.

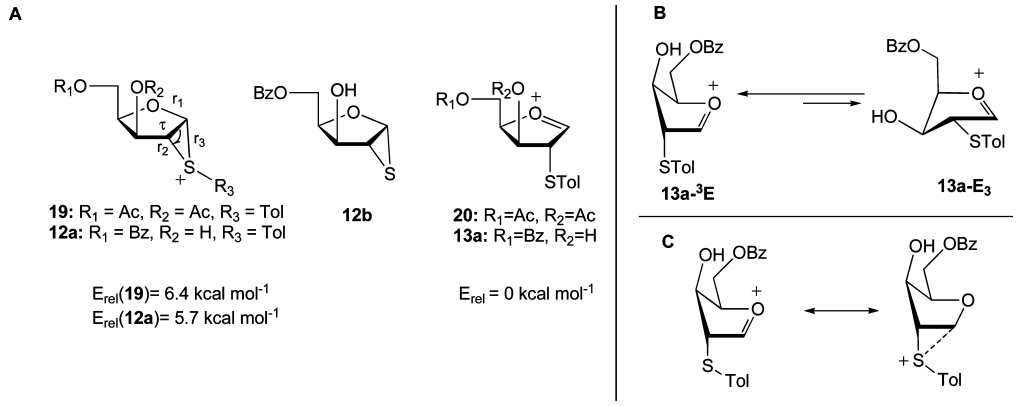


Figure 4. (A) Relative energy of episulfonium ions **19** and **12a**, and furanosyl oxocarbenium ions **20** and **13a**, as determined by B3LYP/6-311++G** DFT calculations. (B) Relative stabilities of two possible conformers of **13a**. (C) Resonance hybrid representation of **13a**.

species. We reasoned that this would be possible from compound **18**, upon activation with tin(IV) chloride as illustrated in Figure 3. Thus, **18** was synthesized (see the Supporting Information), and then low-temperature NMR experiments similar to those described for **1** were performed; however, the same results were obtained. These experiments thus suggest that a single episulfonium ion is not an intermediate in these reactions, but further confirmation required other approaches.

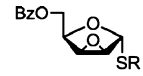
Density Functional Theory Calculations. Density functional theory (DFT) calculations have found increasing use in probing glycosylation mechanisms,[5,31−37] and we therefore applied this approach to this reaction. In this case, the oxocarbenium ion **20** (Figure 4A) was minimized at the HF/6-31G** and B3LYP/6-31+G** levels of theory. In an attempt to calculate the relative energy difference between **20** and episulfonium ion **19**, the latter was also minimized using the same conditions. All optimizations of **19** converged to an oxocarbenium ion as a minimum, and no three-membered episulfonium ion species was observed. The absence of this episulfonium ion structure can be attributed to the stabilization of the oxocarbenium ion. In the oxocarbenium ions observed, the lone pairs on the sulfur atom provide stabilization of the positive charge through orbital interactions with the π^* orbital of the C1=O$^+$ bond. Therefore, a structure in which the positive charge is delocalized between the sulfur atom and the oxygen in the ring may be more plausible than one involving a strained three-membered ring.[10]

All optimizations also gave the ^{3}E ring conformer as the energetically most stable species. After B3LYP/6-311++G** single-point energy calculations on the structures resulting from the optimization of **19** and **20**, no energy difference was observed between the two species, and the optimized geometries of each of these were virtually identical. The same calculations were also done on structures **12a** and **13a**, and these also resulted in convergence to the oxocarbenium ion in the ^{3}E ring form. Although **20** (and **13a**) can adopt one of two possible envelope conformers (E_3 and ^{3}E, Figure 4B), the latter is substantially more stable. Indeed, all attempts to optimize the E_3 conformer of **13a** led to its conversion to the ^{3}E conformation during geometry optimization.

Table 1. Selected Geometrical Parameters for Structures **19**, **20**, **12a**, and **13a**

	19	20	12a	13a
r_1	1.288	1.289	1.284	1.277
r_2	1.893	1.893	1.888	1.890
r_3	2.403	2.403	2.425	2.456
τ	90.8	90.8	92.1	93.5

Chart 2



21, R = Et
22, R = *t*-Bu
23, R = *p*-methoxyphenyl
24, R = *p*-nitrophenyl
25, R = *p*-methoxybenzyl

Our unsuccessful attempts to obtain an optimized episulfonium ion structure for the determination of the relative energy differences between **19** and **20** (as well as **12a** and **13a**) led us to explore constrained geometry optimizations on these structures. Previously, Bravo et al.[10] used DFT methods to determine the geometric and electronic structure of several cations (including episulfonium ions), which are potential intermediates in glycosylation reactions involving 2-thioalkyl/2-thioaryl glycosylating agents. In this computational study, optimized bond lengths involving the cationic species were reported, but a comparison of the different ring geometries (e.g., **13a-^{3}E** vs **13a-E$_3$**) was not described. From our above calculations, bond lengths were determined as presented in Table 1. In all cases, we observed that the C2−S bond (r_2, Figure 4) was significantly shorter than the C1−S bond length (r_3), consistent with a related study by Bravo et al.[10] As was also observed by Bravo et al., the C1−C2−S bond angle (τ) in these structures was ∼90°, substantially smaller than the ideal tetrahedral geometry. A possible rationale for this observation is that the bond angle adjusts to place the electron-rich sulfur closer to the electron-deficient C1=O$^+$ group, in turn stabilizing this intermediate. Thus, on the basis of these calculations, the intermediate **13a** cannot accurately be described as a "pure" oxocarbenium ion, nor can it be described as a "pure" episulfonium ion. Instead, it can be viewed as a resonance hybrid (Figure 4C), in which the left-hand structure in the figure is the major contributor.

(30) Dohn, D. R.; Casida, J. E. *Bioorg. Chem.* **1987**, *15*, 115–124.
(31) Zhu, X. M.; Kawatkar, S.; Rao, Y.; Boons, G.-J. *J. Am. Chem. Soc.* **2006**, *128*, 11948–11957.
(32) Berces, A.; Enright, G.; Nukada, T.; Whitfield, D. M. *J. Am. Chem. Soc.* **2001**, *123*, 5460–5464.
(33) Ionescu, A. R.; Berces, A.; Zgierski, M. Z.; Whitfield, D. M.; Nukada, T. *J. Phys. Chem. A* **2005**, *109*, 8096–8105.
(34) Kim, J. H.; Yang, H.; Khot, V.; Whitfield, D.; Boons, G.-J. *Eur. J. Org. Chem.* **2006**, 5007–5028.
(35) Yang, M. T.; Woerpel, K. A. *J. Org. Chem.* **2009**, *74*, 545–553.
(36) Whitfield, D. M.; Nukada, T. *Carbohydr. Res.* **2007**, *342*, 1291–1304.
(37) Whitfield, D. M. *Carbohydr. Res.* **2007**, *342*, 1726–1740.

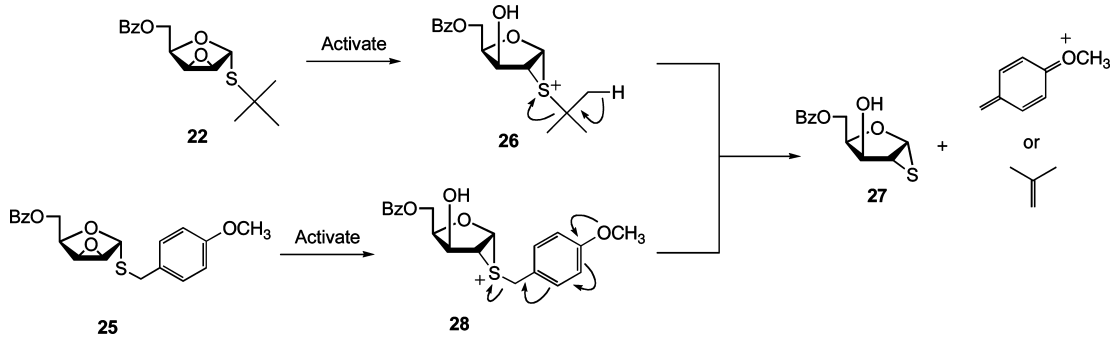


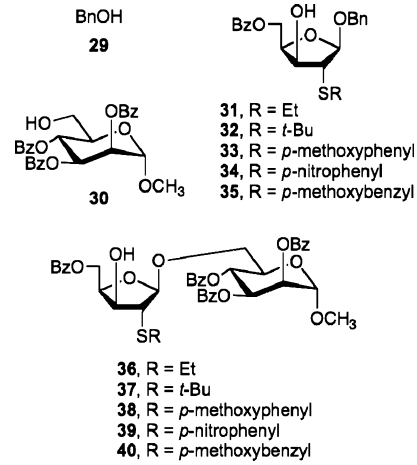
Figure 5. Proposed pathway leading to 1,2-thioanhydrosugar **27** from **22** or **25**.

In their earlier paper,[10] Bravo et al. also carried out calculations on the parent episulfide compound (e.g., **12b**) and showed that the two C−S bonds had similar bond lengths (1.871 Å for C2−S and 1.905 for C1−S). Consequently, a second set of geometry optimizations were performed at the B3LYP/6-31G** level of theory on **19** and **12a** where the C1−S and C2−S bonds were given fixed values corresponding to these optimal values.[10] These calculations all resulted in a minimized episulfonium ion structure, with no breakage of the C1−S bond, as was observed in the calculations in which these bonds were not fixed. Single-point energy calculations were then done on these optimized structures at the B3LYP/6-311++G** level of theory. Analysis of the newly acquired energy values for the episulfonium ions, and comparison to the energies of the oxocarbenium ions, shows that the oxocarbenium ions (**20** and **13a**) are more energetically stable than the corresponding episulfonium ions. More specifically, **20** is 6.4 kcal mol^{-1} more stable than **19**, and **13a** is 5.7 kcal mol^{-1} more stable than **12a**. Although this approach is admittedly artificial, it nevertheless allows us to estimate the energy difference between the oxocarbenium and episulfonium ion, the latter of which is unstable without the constraint. It should be noted that initial attempts at constrained optimizations, where the Bravo et al. optimal C−S bond lengths were not used, resulted in an increase in the energy of the system and a halt in the calculations. In addition, when the optimized episulfonium ion was allowed to fully minimize, without the bond length constraints described above, it minimized to the oxocarbeium ion.

These computational studies are consistent with the observations from the low-temperature NMR experiments, which failed to detect signals arising from an episulfonium ion. In contrast to the stable [2.2.2]-bridged bicyclic sulfonium ion **17** (Figure 2), we propose that the highly strained three-member ring is responsible for the relative instability of the episulfonium ion compared to the oxocarbenium ion. These calculations provide further evidence that the intermediate formed in these glycosylation is a 2-thiotolyl-oxocarbenium ion, not an episulfonium ion.

Effect of Different Aglycones. To explore further the nature of the intermediate in this glycosylation, and to elucidate the steric factors contributing to its stereoselectivity, we synthesized a panel of additional donors (**21**−**25**, Chart 2) for use in the reactions. We surmised that if the aglycone was smaller than an aryl group (e.g., an ethyl group as in **21**) there would be less steric repulsion on the α-face, leading to an increase in the amount of the 1,2-cis α-furanoside, should an oxocarbenium ion be the intermediate. To probe steric effects related to the aglycone in more detail, the *t*-butyl thioglycoside **22** was also synthesized. The ability of the aglycone to stabilize a positive charge on sulfur, as in an episulfonium ion, was to be probed through reactions comparing the electron-withdrawing *p*-nitrophenyl thioglycoside **23** and the electron-donating *p*-methoxyphenyl thioglycoside **24**.

Chart 3



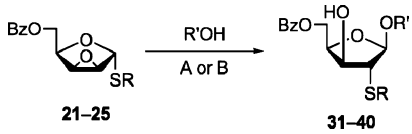
Furthermore, we envisioned that thioglycosides **22** and **25** could be used to probe the possible formation of an episulfonium ion as illustrated in Figure 5. If an intermediate such as **26** or **28** was produced, the loss of isobutylene (from **22**) or the *p*-methoxylbenzyl cation (from **25**) would lead to the formation of the 1,2-thioanhydrosugar (**27**). Formation of this byproduct would thus provide evidence for an episulfonium ion intermediate. An analogous approach has recently been used by Crich et al. to probe glycosylations proposed to proceed via neighboring group participation by acyl groups.[38]

Details on the synthesis of **21**−**25** can be found in the Supporting Information. Once prepared, each was used in glycosylations under the optimized conditions developed previously for benzyl alcohol (**29**, Chart 3) and methyl 2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside (**30**). All reactions proceeded smoothly and provided the desired 2-thioalkyl/aryl glycosides in good yield (Table 2).

As detailed in the table, in all but one case, the reaction was exclusively selective for the β-isomer. In the one case in which it was not, the glycosylation between **21** and **30** (entry 6), the reaction still favored the β-glycoside to a large degree (α/β ratio of 1:13), as determined by ^{1}H NMR spectroscopy. Thus, it appears that the steric or electronic nature of the group on sulfur plays little, if any, role in the stereoselectivity of the reaction. In addition, the reactions involving **22** and **25** behaved the same

(38) Crich, D.; Hu, T.; Cai, F. *J. Org. Chem.* **2008**, *73*, 8942–8953.

Table 2. Reaction of Thioglycosides **21**−**25** with Alcohols **29** and **30**



entry	donor	acceptor	method[a]	product[b]	yield (%)[c]	β/α[d]
1	**21**	**29**	A	**31**	94	100:0
2	**22**	**29**	A	**32**	84	100:0
3	**23**	**29**	A	**33**	88	100:0
4	**24**	**29**	A	**34**	86	100:0
5	**25**	**29**	A	**35**	87	100:0
6	**21**	**30**	B	**36**	67	13:1
7	**22**	**30**	B	**37**	77	100:0
8	**23**	**30**	B	**38**	72	100:0
9	**24**	**30**	B	**39**	61	100:0
10	**25**	**30**	B	**40**	69	100:0

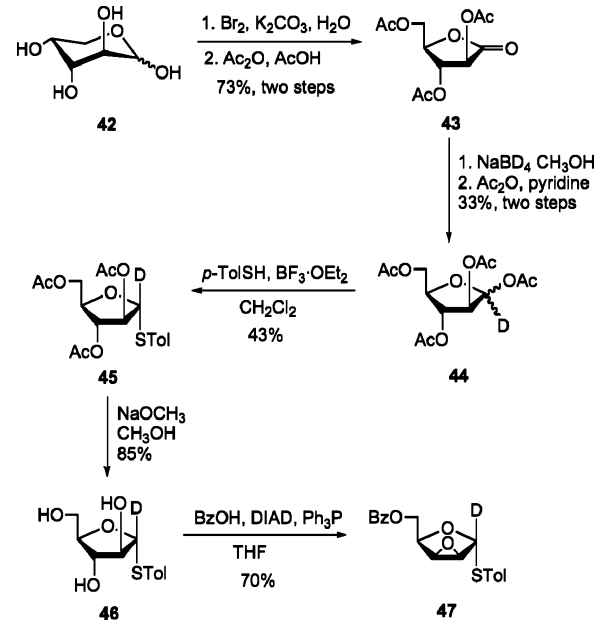
[a] Method A: 4 Å MS (10 equiv), CH_2Cl_2, reflux. Method B: $Cu(OTf)_2$ (1 equiv), 4 Å MS, CH_2Cl_2, rt. [b] See Chart 2 for structures of donors and Chart 3 for structures of products. [c] Isolated yield after chromatography. [d] Ratio determined by ^{1}H NMR spectroscopy after chromatography.

as the other donors, and the formation of product **27** was not observed. It should be mentioned that the results described here differ from earlier work by Viso et al. on a related glycosylation in which 2-hydroxy-thioglycosides were converted to 2-deoxy-2-thioaryl-nucleosides upon treatment under Mitsunobu conditions.[39] In that study, the stereoselectivity of the process was influenced by the nature of group on the sulfur. We are unsure as to the origin of this seemingly disparate behavior between our work and that of Viso et al., but presumably it results from the different reaction conditions and nucleophiles employed. When considered with the computational and NMR investigations described above, the results detailed in Table 1 point to a reaction governed by an S_N1 pathway involving an oxocarbenium ion intermediate, not one involving an episulfonium ion.

Kinetic Isotope Effect Studies. Recently, Crich and Chandrasekera[40] and El-Badri et al.[41] reported the use of α-deuterium kinetic isotope effects (α-DKIEs) in mechanistic investigations of their methodology for preparing β-mannopyranosides from either mannopyranosyl triflates or mannopyranosyl iodides, respectively. In these studies, the glycosyl triflate or iodide was generated and then treated with an alcohol; α-DKIEs values of 1.1−1.2 were measured. The magnitudes of these α-DKIEs indicate that the transition state in these reactions has substantial oxocarbenium ion character, and it was proposed that this displacement of the leaving group (i.e., the triflate or iodide) by the alcohol proceeded by way of an "exploded" S_N2 transition state.

The glycosylation under investigation here is more complicated in that two steps are involved: the generation of an electrophilic intermediate (e.g., either **12** or **13**, Figure 1) and its subsequent reaction with an alcohol. To probe further the mechanism of the reaction, in particular the nature of the transition state in the rate-determining step, we determined α-DKIEs using a substrate labeled with deuterium at C-1. The

Scheme 1



route used to prepare a suitable donor (**41**), which possesses >93% deuterium at the anomeric center, is summarized in Scheme 1.

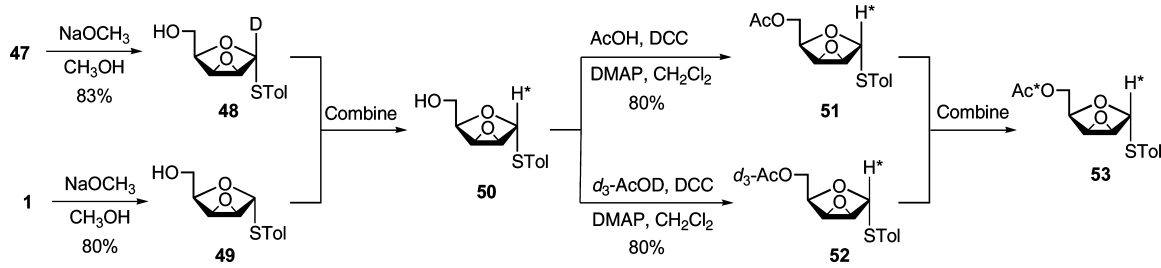
Initially, D-arabinose (**42**) was oxidized to the corresponding 1,4-lactone using aqueous bromine under basic conditions. The product was then acetylated with a catalytic amount of sulphuric acid and acetic anhydride in acetic acid at 50 °C to yield **43** in 73% overall yield.[42] The deuterium was introduced by reduction of **43** with sodium borodeuteride.[43] Subsequent acetylation of the resulting hemiacetal with a catalytic amount of DMAP and acetic anhydride in pyridine afforded compound **44** in 33% overall yield. The low yield for this process was due to the formation of the alditol, resulting from over reduction of the lactone by sodium borodeuteride. The α-thioglycoside **45** was obtained in 43% yield when **44** was treated with *p*-thiocresol and boron trifluoride etherate in dichloromethane at 0 °C. Deprotection of **45** was then achieved under standard conditions to provide **46** in 85% yield. Finally, treatment with diisopropylazodicarboxylate, triphenylphosphine, and benzoic acid provided **47** in 70% yield.

For the α-DKIE measurements, a 50:50 mixture of a substrate with and without a deuterium label at the anomeric carbon was required. Therefore, an equal amount of **48** and **49** (obtained by debenzoylation of **47** and **1**, respectively) was combined to give a mixture **50** containing ∼50% deuterium at C-1 (Scheme 2). In the following schemes, this material is indicated by H* at the anomeric center. Next, **50** was acetylated with acetic acid, or acetic acid-d_3, to yield either **51** or **52** (Scheme 3). Equal quantities of compound **51** and **52** were then mixed to give **53**, which was 50% enriched with deuterium at both C-1 and in the acetyl protecting group.

With **53** in hand, we measured α-DKIEs for two reactions, the glycosylation of benzyl alcohol (**29**, Scheme 3) and of methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (**30**). Each reaction was done in triplicate. In carrying out these experiments, donor **53** and approximately 50 mol % of internal standard 4,4,5,5-tetramethyl-2-(1-naphthyl)-1,3-dioxolane **54** were dis-

(39) Viso, A.; Poopeiko, N.; Castillón, S. *Tetrahedron Lett.* **2000**, *41*, 407–411.
(40) Crich, D.; Chandrasekera, N. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5386–5389.
(41) El-Badri, M. H.; Willenbring, D.; Tantillo, D. J.; Gervay-Hague, J. *J. Org. Chem.* **2007**, *72*, 4663–4672.
(42) Sun, R. C.; Okabe, M. *Org. Syn.* **1995**, *72*, 48–52.
(43) Bock, K.; Lundt, I.; Pedersen, C. *Carbohydr. Res.* **1981**, *90*, 7–16.

Scheme 2



Scheme 3

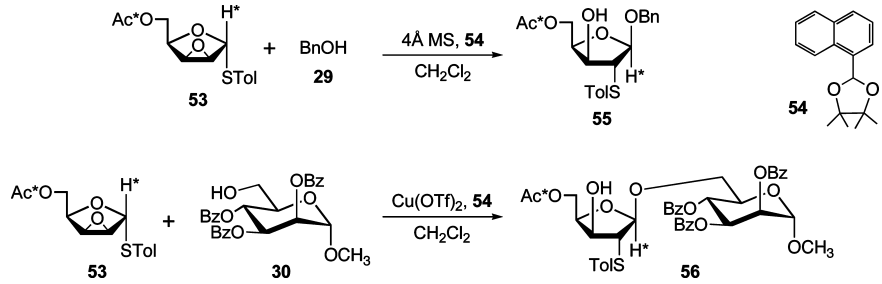


Table 3. α-DKIEs Measured for the Glycosylation of **29** with **53**[a]

reaction	KIE	*F*	*R*	R_0
1	1.14	0.720	3.283	3.524
2	1.23	0.794	3.261	3.585
3	1.23	0.735	3.239	3.610
average	1.20			

[a] F = yield of **55**. R = ratio of acetate peak/anomeric peak in **55**. R_0 = ratio of acetate peak/anomeric peak in **53**.

Table 4. α-DKIEs Measured for the Glycosylation of **30** with **53**[a]

reaction	KIE	*F*	*R*	R_0
1	1.12	0.595	3.267	3.50
2	1.20	0.635	3.222	3.610
3	1.18	0.653	3.250	3.585
average	1.17			

[a] F = yield of **56**. R = ratio of acetate peak/anomeric peak in **56**. R_0 = ratio of acetate peak/anomeric peak in **53**.

solved in chloroform-*d* and an ^{1}H NMR spectrum was recorded. The integration of acetate and the anomeric hydrogen peaks in **53** was measured against the methyl group signal of **54**. After removal of the chloroform-*d*, the residue was redissolved in dichloromethane, and to this solution was added the alcohol and the appropriate promotor (4 Å molecular sieves for **29**, copper(II) triflate for **30**). After completion of the reaction, the ^{1}H NMR spectrum of the crude reaction mixture revealed the percentage of reaction conversion through integration of the acetate methyl resonance against the methyl group signal of **54**. After flash chromatography, the ^{1}H NMR spectrum of the product 2-thiotolyl-2-deoxy-β-xylofuranoside (**55** or **56**) was recorded and the ratio of the acetate methyl resonance against the anomeric proton was integrated.

The α-DKIE for each glycosylation was determined according to eq 1, developed by Singleton and Thomas[44]

$$\mathrm{KIE} = \frac{\ln(1 - F)}{\ln[1 - (FR/R_0)]} \quad (1)$$

where F is the fractional conversion of donor **53** (the yield of **55** or **56**) and R and R_0 are the ratios of the anomeric protons integrations in the product and the starting donor, respectively, which correspond to the D/H ratios in **55** (or **56**) and **53**. The results of these calculations are shown in Tables 3 and 4; the average α-DKIEs were determined to be 1.20 and 1.17 for **29** and **30**, respectively.

These data are consistent with a rate-determining step in which the hybridization at C-1 changes from sp^3 to sp^2. Therefore, when considering the two pathways outlined in Figure 1, the formation of an electrophilic intermediate is clearly rate-limiting. Moreover, given the magnitude of the α-DKIEs this species must be the oxocarbenium ion **13** (pathway B), not an episulfonium ion. These data also suggest that the formation of **13** from **11**, which involves both opening of the protonated epoxide and 1,2-migration of the thioaryl group, is concerted (Figure 6) and that the transition state between the species occurs late in the reaction coordinate. It should be noted, however, that it is impossible to determine if the intermediate is the free oxocarbenium ion, or a structure such as **57**, which is intermediate between **13** and episulfonium ion **12**. In **57**, the positive charge of the oxocarbenium ion is stabilized to some degree by the valence electrons on sulfur, a situation proposed earlier in previous computational investigations[10] and also noted in the discussion of the DFT calculations described above.

Concerted transformations of this type have not been proposed for migration−glycosylation processes such as those under investigation here. However, examples of similar concerted processes do exist in the literature. For example, if one considers an episulfonium ion and a Lewis acid activated epoxide as valid models of each other (an admittedly crude approximation) the transformation shown in Figure 7 suggests a concerted process linking **11** and **13** is not unreasonable. The first, rate-limiting step in the conversion of episulfonium ion **58** into **60** has been proposed to be the concerted formation of cation **59**.[45,46] As

(44) Singleton, D.; Thomas, A. *J. Am. Chem. Soc.* **1995**, *117*, 9357–9358.

(45) Lucchini, V.; Modena, G.; Pasquato, L. *J. Am. Chem. Soc.* **1988**, *110*, 6900–6901.

(46) Lucchini, V.; Modena, G.; Pasquato, L. *J. Am. Chem. Soc.* **1991**, *113*, 6600–6607.

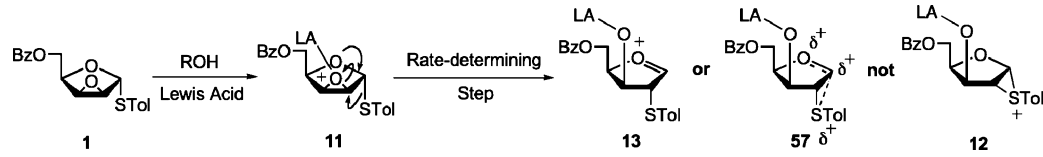


Figure 6. Proposed pathway leading from **11** to oxocarbenium ion **13** or a related intermediates **57**; although all the data reported in this paper suggests that episulfonium ion **12** is not produced in these reactions, it is shown for purposes of comparison.

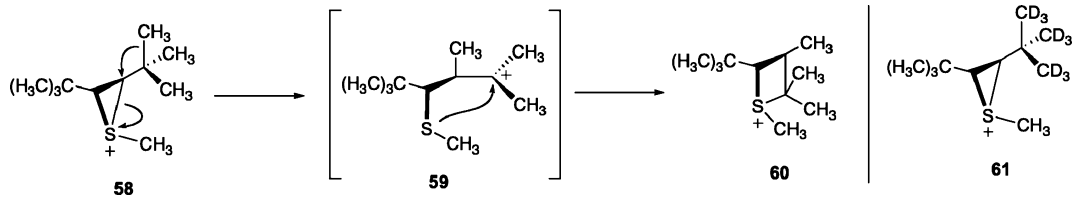


Figure 7. Proposed mechanism for the conversion of **57** to **59**, via concerted formation of **58** (refs 45 and 46).

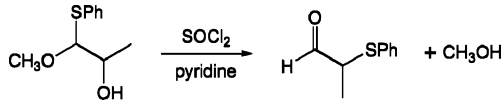


Figure 8. De Groot rearrangement (refs 48 and 49).

part of the mechanistic investigations on the formation of **60** from **58**, substrates in which the methyl groups were deuterated (e.g., **61**) were synthesized, and a k_H/k_D of 1.27 was measured.[46] The magnitude of this α-DKIE is in agreement with a concerted process possessing a transition state with substantial positive charge.

The similarity between this α-DKIE and those measured for the reactions of **1** support a concerted process in the formation of **13** from **11**. Furthermore, inspection of 2,3-anhydrosugar thioglycosides for which X-ray crystallographic data is available[47] indicates that in these rigid species the C−S bond is aligned in a near-perfect antiperiplanar orientation with both the C2−O_{ep} bond, as well as the region of space expected to be occupied by one of the ring oxygen lone pairs. Such an arrangement would facilitate a concerted 1,2-shift concomitant with epoxide ring-opening leading to **13**.

Notwithstanding the example described in the previous paragraphs, there is a paucity of α-DKIE data on analogous reactions with which the data in Tables 3 and 4 can be compared. For example, none of the migration−glycosylation processes reported previously have been subjected to such analysis, nor have similar transformations outside the glycosylation area, such as the de Groot rearrangement (Figure 8)[48,49] and related variants.[50] However, α-DKIEs obtained for the acid-catalyzed opening of epoxides can prove instructive. In a study published in 1980,[51] Hanzlik and Westkaemper measured the effect of isotopic substitution on the methanolysis of *p*-nitrostryene epoxide under acidic conditions. These studies demonstrated that deuterium labeling of the "reacting" carbon (analogous to C-1 in **12**, Figure 6) showed an estimated α-DKIE of 1.19 and on that basis proposed that the reaction proceeded through a late transition state, comparable to a structure of the type **57**. Thus, the magnitude of the α-DKIE measured for reactions of **1** is consistent with the process outlined in Figure 6. It should be appreciated that our measurements do not rule out the fast formation of an episulfonium ion followed by a rate-determining rearrangement to the oxocarbenium ion, as has been suggested previously.[20] However, with regard to the stereocontrol of the glycosylation reaction under investigation here, this mechanistic difference is immaterial.

It should also be mentioned that this isotope effect clearly rules out attack of the oxygen on the electrophile as the rate-determining step. In the case of rate-limiting S_N1 attack of the alcohol on **13** one would expect an inverse α-DKIE because the C-1 hybridization would change from sp^2 to sp^3. Similarly, were the S_N2 attack of the alcohol on an episulfonium ion such as **12** rate-limiting an inverse α-DKIEs would also be expected, as has been calculated for the methanolysis of protonated epoxides proceeding via tight S_N2-like transition states.[51]

Explanation for Glycosylation Selectivity. All of the data presented above suggests that the glycosylation−migration reaction of **1** proceeds via concerted rate-determining formation of oxocarbenium ion intermediate **13**. No evidence, from either experimental or computational studies, could be obtained for the formation of an episulfonium ion intermediate. It should be noted, however, that the computational studies do suggest that some stabilization of the positive charge by the sulfur atom is possible via a structure similar to **57** (Figure 6). A model rationalizing the observed highly favored β-face approach of the acceptor is presented in Figure 9. The furanosyl oxocarbenium ion, in which the bond linking C-1 and O-5 has significant double-bond character can adopt two possible conformations, **62** and **63**, the E_3 and ^3E conformers, respectively. The computational studies described above have indicated that the most stable conformation of this oxocarbenium ion is the ^3E conformer **63**. This is presumably due to not only favorable stereoelectronic and electrostatic effects[35,52] between the substituents at C-2 and C-3 and the positively charged ring oxygen in **63** but also due to unfavorable steric interactions between the benzoyloxymethyl group at C-4 and H-2 in **62**. We propose that based on Woerpel's "inside attack" model,[53,54] that nucleophilic attack from the top face of the ring should be favored, giving the 1,2-trans glycoside as the major product. Formation of the 1,2-cis product would require attack of the alcohol on

(47) Gallucci, J. C.; Gadikota, R. R.; Lowary, T. L. *Acta Crystallogr., Sect. C* **2000**, *56*, E365–E365.
(48) Jansen, B. J. M.; Peperzak, R. M.; Degroot, A. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 549–553.
(49) Jansen, B. J. M.; Peperzak, R. M.; Degroot, A. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 489–494.
(50) Sromek, A.; Gevorgyan, V. *Top. Curr. Chem.* **2007**, *274*, 77–124.
(51) Hanzlik, R.; Westkaemper, R. *J. Am. Chem. Soc.* **1980**, *102*, 2464–2467.
(52) Wolfe, S. *Acc. Chem. Res.* **1972**, *5*, 102–111.

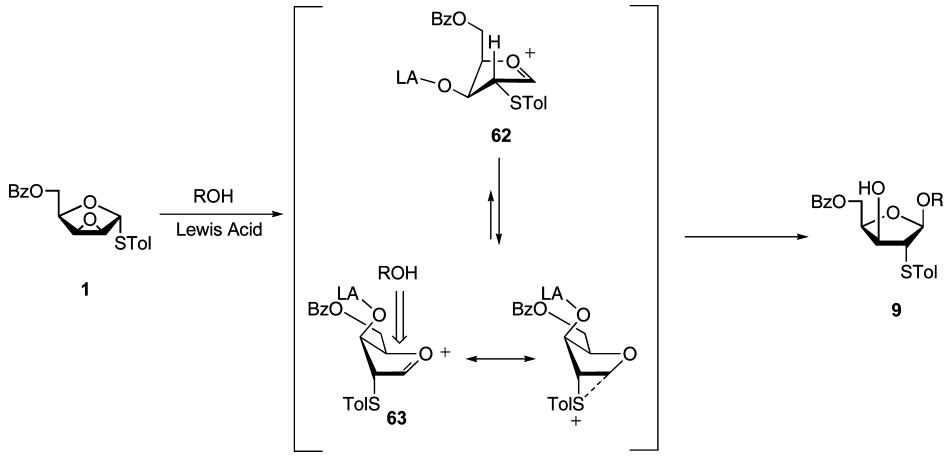


Figure 9. Proposed model for stereoselectivity in migration/glycosylation reactions with **1**.

the bottom face of the less populated conformer **62** or attack cis to the bulky thiotolyl group in the dominant conformer **63**.

In conclusion, a series of experiments probing the mechanism of the 2,3-anhydrosugar migration−glycosylation reaction were performed on thioglycoside **1**. All of the data support the pathway shown in Figure 9, which involves the rate-determining generation of an oxocarbenium ion intermediate that reacts in a stereoselective manner with an alcohol nucleophile. Particularly compelling evidence comes from the measured α-DKIEs (magnitudes of 1.17−1.20), which provide, for the first time, a direct measure of a rate-limiting transition state in migration−glycosylations of this type. Thus, although the formation of an episulfonium intermediate provides a convenient explanation for the observed stereospecificity of these reactions, we propose instead that the stereochemical outcome of the reaction results from "inside attack"[53,54] of the nucleophile onto the lowest energy conformer of the oxocarbenium ion.

Although these investigations have been performed only for thioglycoside **1**, in light of previous studies described above, we consider it likely that similar reactions of thiofuranoside **4** and pyranosides **6** and **7** also proceed via a similar pathway. More generally, the results reported here, when considered together with those reported previously by other groups,[10,18−22] may suggest that all glycosylations[7−17] involving potential equilibration of glycosyl 1,2-episulfonium and 2-thioalkyl/aryl oxocarbenium ions, involve the latter intermediates. Further support for this assertion is of course necessary, and the measurement of α-DKIEs for similar processes will no doubt provide essential insight into the mechanisms of these reactions.

Experimental Section

Benzyl 5-*O*-Benzoyl-2-deoxy-2-ethylthio-*β*-D-xylofuranoside (31). To a solution of benzyl alcohol (**29**, 51 mg, 0.47 mmol) and **21** (88 mg, 0.31 mmol) in CH_2Cl_2 (15 mL) was added 4 Å molecular sieves (1.50 g). The mixture was heated at reflux until TLC showed completion of the reaction. The reaction mixture was concentrated to a crude residue that was purified by chromatography (5:1 hexane−EtOAc) to afford **31** (114 mg, 94%) as a colorless oil: R_f 0.62 (2:1 hexane−EtOAc); $[\alpha]_D$ −24.1 (*c*, 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.11−8.07 (m, 2H, Ar), 7.59−7.53 (m, 1H, Ar), 7.46−7.41 (m, 2H, Ar), 7.38−7.29 (m, 5H, Ar), 5.16 (s, 1H, H-1), 4.84 (d, 1H, J = 11.6 Hz, $PhCH_2$), 4.72−4.67 (m, 2H, H-4, H-5a), 4.59−4.53 (m, 2H, H-5b, $PhCH_2$), 4.27 (dd, 1H, $J_{3,OH}$ = 10.6 Hz, $J_{3,4}$ = 3.5 Hz, H-3), 3.40 (s, 1H, H-2), 3.20 (d, 1H, $J_{3,OH}$ = 10.6 Hz, OH), 2.65 (q, 2H, J = 7.3 Hz, $C\underline{H}_2CH_3$), 1.30 (t, 3H, J = 7.3 Hz, $CH_2C\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.4 (<u>C</u>=O), 136.8 (Ar), 133.1 (2 × Ar), 130.0 (Ar), 129.8 (2 × Ar), 128.6 (2 × Ar), 128.4 (2 × Ar), 128.2 (2 × Ar), 107.0 (C-1), 81.1 (C-4), 76.6 (C-3), 69.8 ($PhCH_2$), 64.5 (C-5), 55.2 (C-2), 26.2 ($\underline{C}H_2CH_3$), 14.7 ($CH_2\underline{C}H_3$). HRMS (ESI) calcd for (M + Na) $C_{21}H_{24}O_5S$: 411.1237. Found: 411.1242.

Benzyl 5-*O*-Benzoyl-2-*t*-butylthio-2-deoxy-*β*-D-xylofuranoside (32). Benzyl alcohol (**29**, 35 mg, 0.33 mmol) and **22** (67 mg, 0.22 mmol) were coupled in CH_2Cl_2 (15 mL) using 4 Å molecular sieves (1.0 g) as described for the preparation of **31**. Chromatography (5:1 hexane−EtOAc) of the crude product gave **32** (75 mg, 84%) as a colorless oil: R_f 0.81 (2:1 hexane−EtOAc); $[\alpha]_D$ −18.9 (*c*, 0.1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.11−8.07 (m, 2H, Ar), 7.59−7.53 (m, 1H, Ar), 7.46−7.41 (m, 2H, Ar), 7.38−7.28 (m, 5H), 5.19 (s, 1H, H-1), 4.82 (d, 1H, J = 11.6 Hz, $PhCH_2$), 4.71−4.63 (dd, 1H, $J_{5a,5b}$ = 11.9 Hz, $J_{4,5a}$ = 7.7 Hz, H-5a), 4.60−4.51 (m, 3H, $PhCH_2$, H-4, H-5b), 4.28 (dd, 1H, $J_{3,OH}$ = 11.2 Hz, $J_{3,4}$ = 2.7 Hz, H-3), 3.33 (s, 1H, H-2), 3.25 (d, 1H, $J_{3,OH}$ = 11.2 Hz, OH), 1.39 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.4 (<u>C</u>=O), 136.9 (Ar), 133.01 (Ar), 133.03 (Ar), 129.8 (Ar × 2), 128.6 (Ar × 2), 128.3 (Ar × 2), 128.2 (Ar × 2), 128.1 (Ar), 108.5 (C-1), 81.1 (C-4), 78.3 (C-3), 69.8 ($Ph\underline{C}H_2$), 64.5 (C-5), 52.9 (C-2), 44.2 ($S\underline{C}(CH_3)_3$), 31.2 ($SC(\underline{C}H_3)_3$). HRMS (ESI) calcd for (M + Na) $C_{23}H_{28}O_5S$: 439.1550. Found: 439.1548.

Benzyl 5-*O*-Benzoyl-2-deoxy-2-*p*-methoxyphenylthio-*β*-D-xylofuranoside (33). Benzyl alcohol (**29**, 48 mg, 0.45 mmol) and **23** (80 mg, 0.22 mmol) were coupled in CH_2Cl_2 (15 mL) with 4 Å molecular sieves (1.5 g) as described for the preparation of **31**. The mixture was heated at reflux until TLC showed completion of the reaction. Chromatography (5:1 hexane−EtOAc) of the crude product gave **33** (92 mg, 88%) as a colorless oil: R_f 0.65 (2:1 hexane−EtOAc); $[\alpha]_D$ −21.6 (*c*, 0.4, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.11−8.07 (m, 2H, Ar), 7.60−7.54 (m, 1H, Ar), 7.47−7.25 (m, 9H, Ar), 6.88−6.84 (m, 2H, Ar), 5.16 (s, 1H, H-1), 4.81 (d, 1H, J = 11.6 Hz, $PhCH_2$), 4.78−4.73 (m, 1H, H-4), 4.69 (dd, 1H, $J_{5a,5b}$ = 11.9 Hz, $J_{4,5a}$ = 4.5 Hz, H-5a), 4.56 (dd, 1H, $J_{5a,5b}$ = 11.9 Hz, $J_{4,5b}$ = 7.4 Hz, H-5b), 4.52 (d, 1H, J = 11.6 Hz, $PhCH_2$), 4.25 (dd, 1H, $J_{3,OH}$ = 11.2 Hz, $J_{3,4}$ = 4.3 Hz, H-3), 3.81 (s, 3H, OCH_3), 3.70 (s, 1H, H-2), 3.14 (d, 1H, $J_{3,OH}$ = 11.2 Hz, OH); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.4 (<u>C</u>=O), 160.0 (Ar), 136.8 (Ar), 134.8 (2 × Ar), 133.1 (Ar), 130.0 (Ar), 129.8 (2 × Ar), 128.6 (2 × Ar), 128.4 (2 × Ar), 128.1 (2 × Ar), 128.0 (Ar), 123.1 (Ar), 115.0 (2 × Ar), 106.2 (C-1), 81.2 (C-4), 75.8 (C-3), 69.8 ($Ph\underline{C}H_2$), 64.5 (C-5), 59.1 ($O\underline{C}H_3$), 55.4 (C-2). HRMS (ESI) calcd for (M + Na) $C_{26}H_{26}O_6S$: 489.1342. Found: 489.1345.

(53) Smith, D. M.; Tran, M. B.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 14149–14152.
(54) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208–12209.

Benzyl 5-*O*-Benzoyl-2-deoxy-2-*p*-nitrophenylthio-β-D-xylofuranoside (34). Benzyl alcohol (**29**, 28 mg, 0.26 mmol) and **24** (64 mg, 0.17 mmol) were coupled in CH_2Cl_2 (15 mL) with 4 Å molecular sieves (1.0 g) as described for the preparation of **31**. Chromatography (5:1 hexane−EtOAc) of the crude product gave **34** (71 mg, 86%) as a colorless oil: R_f 0.68 (2:1 hexane−EtOAc); $[\alpha]_D$ −3.0 (*c*, 0.3, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.15−8.05 (m, 4H, Ar), 7.60−7.55 (m, 1H, Ar), 7.46−7.42 (m, 2H, Ar), 7.39−7.30 (m, 7H, Ar), 5.19 (s, 1H, H-1), 4.86 (d, 1H, J = 11.6 Hz, $PhCH_2$), 4.75−4.70 (m, 2H, H-4, H-5a), 4.61−4.56 (m, 2H, H-5b, $PhCH_2$), 4.34 (dd, 1H, $J_{3,OH}$ = 10.9 Hz, $J_{3,4}$ = 5.1 Hz, H-3), 3.99 (s, 1H, H-2), 3.30 (d, 1H, $J_{3,OH}$ = 10.9 Hz, OH); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.4 (C=O), 145.8 (Ar), 144.1 (Ar), 136.3 (Ar), 133.2 (2 × Ar), 129.78 (Ar), 129.75 (2 × Ar), 128.7 (2 × Ar), 128.43 (2 × Ar), 128.36 (2 × Ar), 127.3 (2 × Ar), 124.3 (2 × Ar), 105.6 (C-1), 81.2 (C-4), 75.8 (C-3), 70.2 ($PhCH_2$), 63.9 (C-5), 56.0 (C-2). HRMS (ESI) calcd for $(M + Na)^+$ $C_{25}H_{23}NO_7S$: 504.1088. Found: 504.1081.

Benzyl 5-*O*-Benzoyl-2-deoxy-2-*p*-methoxybenzylthio-β-D-xylofuranoside (35). Benzyl alcohol (**29**, 22 mg, 0.20 mmol) and **25** (50 mg, 0.13 mmol) were coupled in CH_2Cl_2 (15 mL) with 4 Å molecular sieves (0.75 g). Chromatography (4:1 hexane−EtOAc) of the crude product gave **35** (56 mg, 87%) as a colorless oil: R_f 0.67 (2:1 hexane−EtOAc); $[\alpha]_D$ −21.9 (*c*, 0.1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.09−8.05 (m, 2H, Ar), 7.58−7.55 (m, 1H, Ar), 7.45−7.41 (m, 2H, Ar), 7.37−7.28 (m, 5H, Ar), 7.22−7.19 (m, 2H, Ar), 6.87−6.83 (m, 2H, Ar), 5.05 (s, 1H, H-1), 4.77 (d, 1H, J = 11.6 Hz, $PhCH_2$), 4.68−4.63 (m, 2H, H-4, H-5a), 4.53 (dd, 1H, $J_{5a,5b}$ = 11.7 Hz, $J_{4,5b}$ = 8.3 Hz, H-5b), 4.46 (d, 1H, J = 11.6 Hz, $PhCH_2$), 4.19 (d, 1H, $J_{3,OH}$ = 11.1 Hz, $J_{3,4}$ = 4.3 Hz, H-3), 3.80 (s, 3H, OCH_3), 3.77 (s, 2H, $ArCH_2S$), 3.26 (s, 1H, H-2), 3.07 (d, 1H, $J_{3,OH}$ = 11.1 Hz, OH); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.4 (C=O), 159.0 (Ar), 136.8 (Ar), 133.0 (Ar), 130.02 (2 × Ar), 129.99 (Ar), 129.7 (2 × Ar), 129.1 (Ar), 128.6 (2 × Ar), 128.4 (2 × Ar), 128.2 (2 × Ar), 128.1 (Ar), 114.1 (2 × Ar), 106.7 (C-1), 81.2 (C-4), 76.3 (C-3), 69.8 ($PhCH_2$), 64.4 (C-5), 55.3 (OCH_3), 54.9 (C-2), 36.0 (CH_2S). HRMS (ESI) calcd for (M + Na) $C_{27}H_{28}O_6S$: 503.1499. Found: 503.1496.

Methyl 5-*O*-Benzoyl-2-deoxy-2-ethylthio-β-D-xylofuranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside (36). To a solution of **30** (128 mg, 0.25 mmol) and **21** (71 mg, 0.25 mmol) in CH_2Cl_2 (15 mL) was added 4 Å molecular sieves (200 mg). After the mixture was stirred at room temperature for 30 min, $Cu(OTf)_2$ (92 mg, 0.25 mmol) was added and the solution was stirred for an additional 2 h. After neutralization with triethylamine, the reaction mixture was concentrated to a crude residue that was purified by chromatography (4:1 hexane−EtOAc) to afford **36** (133 mg, 67%) as a colorless oil: R_f 0.56 (2:1 hexane−EtOAc); $[\alpha]_D$ −77.9 (*c*, 0.7, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.13−8.09 (m, 2H, Ar), 8.05−8.02 (m, 2H, Ar), 7.96−7.94 (m, 2H, Ar), 7.83−7.80 (m, 2H, Ar), 7.63−7.35 (m, 10H, Ar), 7.28−7.24 (m, 2H, Ar), 5.94 (dd, 1H, $J_{4,5}$ = $J_{3,4}$ = 10.1 Hz, H-4), 5.85 (dd, 1H, $J_{3,4}$ = 10.1 Hz, $J_{2,3}$ = 3.3 Hz, H-3), 5.70 (dd, 1H, $J_{2,3}$ = 3.3 Hz, $J_{1,2}$ = 1.6 Hz, H-2), 5.13 (s, 1H, H-1′), 4.99 (d, 1H, $J_{1,2}$ = 1.6 Hz, H-1), 4.70−4.59 (m, 3H, H-4′, H-5a′, H-5b′), 4.28−4.20 (m, 2H, H-5, H-3′), 4.13 (dd, 1H, $J_{6a,6b}$ = 10.9 Hz, $J_{5,6a}$ = 2.2 Hz, H-6a), 3.62 (dd, 1H, $J_{6a,6b}$ = 10.9 Hz, $J_{5,6b}$ = 3.6 Hz, H-6b), 3.57 (d, 1H, $J_{3',OH}$ = 12.0 Hz, OH), 3.55 (s, 3H, OCH_3), 3.46 (s, 1H, H-2′), 2.69 (q, 2H, J = 7.3 Hz, CH_2CH_3), 1.33 (t, 3H, J = 7.3 Hz, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.3 (C=O), 165.44 (2 × C=O), 165.42 (C=O), 133.44 (Ar), 133.43 (Ar), 133.1 (Ar), 133.0 (Ar), 130.0 (2 × Ar), 129.8 (2 × Ar), 129.73 (2 × Ar), 129.72 (2 × Ar), 129.3 (Ar), 129.2 (Ar), 129.0 (2 × Ar), 128.52 (2 × Ar), 128.46 (2 × Ar), 128.3 (2 × Ar), 128.2 (2 × Ar), 107.3 (C-1′), 98.9 (C-1), 81.5 (C-4′), 76.6 (C-3′), 70.2 (C-3), 70.1 (C-2), 69.3 (C-5), 66.8 (C-4), 64.6 (C-5′), 64.5 (C-6), 55.7 (OCH_3), 55.4 (C-2′), 26.3 (CH_2CH_3), 14.7 (CH_2CH_3). HRMS (ESI) calcd for (M + Na) $C_{42}H_{42}O_{13}S$: 809.2238. Found: 809.2225.

Methyl 5-*O*-Benzoyl-2-*t*-butylthio-2-deoxy-β-D-xylofuranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside (37). Alcohol **30** (130 mg, 0.26 mmol) and **22** (79 mg, 0.26 mmol) were coupled in CH_2Cl_2 (15 mL) containing 4 Å molecular sieves (200 mg) with $Cu(OTf)_2$ (93 mg, 0.26 mmol) as described for the preparation of **36**. Chromatography (4:1 hexane−EtOAc) of the crude product gave **37** (162 mg, 77%) as a colorless oil: R_f 0.52 (2:1 hexane−EtOAc); $[\alpha]_D$ −62.6 (*c*, 0.5, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$, δ_H) 8.13−8.11 (m, 2H, Ar), 8.05−8.02 (m, 2H, Ar), 7.96−7.93 (m, 2H, Ar), 7.83−7.80 (m, 2H, Ar), 7.62−7.58 (m, 1H, Ar), 7.56−7.47 (m, 4H, Ar), 7.44−7.34 (m, 5H, Ar), 7.27−7.24 (m, 2H, Ar), 5.96 (dd, 1H, $J_{4,5}$ = $J_{3,4}$ = 10.0 Hz, H-4), 5.85 (dd, 1H, $J_{3,4}$ = 10.0 Hz, $J_{2,3}$ = 3.3 Hz, H-3), 5.71 (dd, 1H, $J_{2,3}$ = 3.3 Hz, $J_{1,2}$ = 1.8 Hz, H-2), 5.15 (s, 1H, H-1′), 4.99 (s, 1H, H-1), 4.67−4.55 (m, 3H, H-4′, H-5a′, H-5b′), 4.28 (dd, 1H, $J_{3',OH}$ = 11.9 Hz, $J_{3',4'}$ = 4.1 Hz, H-3′), 4.23 (ddd, 1H, $J_{4,5}$ = 10.0 Hz, $J_{5,6a}$ = $J_{5,6b}$ = 3.4 Hz, H-5), 4.11 (dd, 1H, $J_{6a,6b}$ = 10.5 Hz, $J_{5,6a}$ = 3.4 Hz, H-6a), 3.64 (d, 1H, $J_{3',OH}$ = 11.9 Hz, OH), 3.62 (dd, 1H, $J_{6a,6b}$ = 10.5 Hz, $J_{5,6b}$ = 3.4 Hz, H-6b), 3.55 (s, 3H, OCH_3), 3.39 (s, 1H, H-2′); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.3 (C=O), 165.4 (2 × C=O), 165.4 (C=O), 133.44 (Ar), 133.39 (Ar), 133.1 (Ar), 132.9 (Ar), 130.07 (Ar), 130.05 (2 × Ar), 129.74 (2 × Ar), 129.72 (2 × Ar), 129.3 (Ar), 129.2 (Ar), 129.1 (Ar), 128.6 (2 × Ar), 128.5 (2 × Ar), 128.41 (2 × Ar), 128.35 (2 × Ar), 128.2 (2 × Ar), 108.7 (C-1′), 98.9 (C-1), 81.5 (C-4′), 78.4 (C-3′), 70.2 (C-3), 70.1 (C-2), 69.4 (C-5), 66.7 (C-4), 64.7 (C-5′), 64.5 (C-6), 55.7 (OCH_3), 53.0 (C-2′), 44.2 ($SC(CH_3)_3$), 31.1 ($SC(CH_3)_3$). HRMS (ESI) calcd for (M + Na) $C_{44}H_{46}O_{13}S$: 837.2551. Found: 837.2544.

Methyl 5-*O*-Benzoyl-2-deoxy-2-*p*-methoxyphenylthio-β-D-xylofuranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside (38). Alcohol **30** (148 mg, 0.29 mmol) and **23** (105 mg, 0.29 mmol) were coupled in CH_2Cl_2 (15 mL) containing 4 Å molecular sieves (250 mg) using $Cu(OTf)_2$ (106 mg, 0.29 mmol) as described for the preparation of **36**. Chromatography (4:1 hexane−EtOAc) of the crude product gave **38** (182 mg, 72%) as a colorless oil: R_f 0.43 (2:1 hexane−EtOAc); $[\alpha]_D$ −56.0 (*c*, 0.49, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.10−8.03 (m, 4H, Ar), 7.96−7.92 (m, 2H, Ar), 7.83−7.80 (m, 2H, Ar), 7.60−7.47 (m, 3H, Ar), 7.46−7.34 (m, 8H, Ar), 7.28−7.24 (m, 3H, Ar), 6.90−6.86 (m, 2H, Ar), 5.93 (dd, 1H, $J_{4,5}$ = $J_{3,4}$ = 10.0 Hz, H-4), 5.85 (dd, 1H, $J_{3,4}$ = 10.0 Hz, $J_{2,3}$ = 3.3 Hz, H-3), 5.70 (dd, 1H, $J_{2,3}$ = 3.3 Hz, $J_{1,2}$ = 1.8 Hz, H-2), 5.15 (s, 1H, H-1′), 4.96 (d, 1H, $J_{1,2}$ = 1.8 Hz, H-1), 4.80−4.75 (m, 1H, H-4′), 4.68−4.60 (m, 2H, H-5a′, H-5b′), 4.27−4.18 (m, 2H, H-3′, H-5), 4.11 (dd, 1H, $J_{6a,6b}$ = 10.9 Hz, $J_{5,6a}$ = 2.4 Hz, H-6a), 3.82 (s, 3H, $ArOCH_3$), 3.78 (s, 1H, H-2′), 3.61 (dd, 1H, $J_{6a,6b}$ = 10.9 Hz, $J_{5,6b}$ = 3.9 Hz, H-6b), 3.52 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.3 (C=O), 165.4 (3 × C=O), 159.9 (Ar), 134.7 (2 × Ar), 133.41 (Ar), 133.40 (Ar), 133.1 (Ar), 133.0 (Ar), 130.1 (Ar), 130.0 (2 × Ar), 129.8 (2 × Ar), 129.7 (2 × Ar), 129.3 (Ar), 129.2 (Ar), 129.0 (Ar), 128.52 (2 × Ar), 128.45 (2 × Ar), 128.31 (2 × Ar), 128.28 (2 × Ar), 128.2 (2 × Ar), 123.3 (Ar), 115.0 (2 × Ar), 106.4 (C-1′), 98.8 (C-1), 81.6 (C-4′), 75.9 (C-3′), 70.12 (C-3), 70.08 (C-2), 69.3 (C-5), 66.8 (C-4), 64.7 (C-5′), 64.4 (C-6), 59.1 (C-2′), 55.7 ($ArOCH_3$), 55.4 (OCH_3). HRMS (ESI) calcd for (M + Na) $C_{47}H_{44}O_{14}S$: 887.2344. Found: 887.2350.

Methyl 5-*O*-Benzoyl-2-deoxy-2-*p*-nitrophenylthio-β-D-xylofuranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside (39). Alcohol **30** (143 mg, 0.28 mmol) and **24** (105 mg, 0.28 mmol) were coupled in CH_2Cl_2 (15 mL) containing 4 Å molecular sieves (250 mg) with $Cu(OTf)_2$ (102 mg, 0.28 mmol) as described for the synthesis of **36**. Chromatography (4:1 hexane−EtOAc) of the crude product gave **39** (152 mg, 61%) as a colorless oil: R_f 0.49 (2:1, hexane−EtOAc); $[\alpha]_D$ −56.4 (*c*, 0.8, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.20−8.16 (m, 2H, Ar), 8.14−8.11 (m, 2H, Ar), 8.06−8.02 (m, 2H, Ar), 7.99−7.96 (m, 2H, Ar), 7.84−7.81 (m, 2H, Ar), 7.66−7.61 (m, 1H, Ar), 7.58−7.37 (m, 11H, Ar), 7.30−7.25 (m, 2H, Ar), 6.05 (dd, 1H, $J_{4,5}$ = $J_{3,4}$ = 10.1 Hz, H-4), 5.89 (dd, 1H, $J_{3,4}$ = 10.1 Hz, $J_{2,3}$ = 3.3 Hz, H-3), 5.72 (dd, 1H, $J_{2,3}$ = 3.3 Hz, $J_{1,2}$ = 1.8 Hz, H-2), 5.20 (s, 1H, H-1′), 5.03 (d, 1H, $J_{1,2}$

= 1.8 Hz, H-1), 4.76−4.66 (m, 3H, H-4′, H-5a′, H-5b′), 4.34 (dd, 1H, $J_{3',OH}$ = 11.9 Hz, $J_{3',4'}$ = 4.4 Hz, H-3′), 4.24 (ddd, 1H, $J_{4,5}$ = 10.1 Hz, $J_{5,6a}$ = $J_{5,6b}$ = 2.7 Hz, H-5), 4.20 (dd, 1H, $J_{6a,6b}$ = 10.7 Hz, $J_{5,6a}$ = 2.7 Hz, H-6a), 4.09 (s, 1H, H-2′), 3.78 (d, 1H, $J_{3',OH}$ = 11.9 Hz, OH), 3.62 (dd, 1H, $J_{6a,6b}$ = 10.7 Hz, $J_{5,6b}$ = 2.7 Hz, H-6b), 3.56 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.3 (C=O), 165.6 (C=O), 165.43 (C=O), 165.40 (C=O), 145.8 (Ar), 144.2 (Ar), 133.6 (Ar), 133.5 (Ar), 133.2 (Ar), 133.1 (Ar), 130.0 (2 × Ar), 129.9 (Ar), 129.8 (2 × Ar), 129.7 (4 × Ar), 129.4 (Ar), 129.1 (Ar), 128.9 (Ar), 128.57 (2 × Ar), 128.55 (2 × Ar), 128.4 (2 × Ar), 128.3 (2 × Ar), 127.1 (2 × Ar), 124.4 (2 × Ar), 105.8 (C-1′), 99.0 (C-1), 81.8 (C-4′), 75.8 (C-3′), 70.2 (C-2), 70.0 (C-3), 69.0 (C-5), 66.6 (C-4), 64.22 (C-5′), 64.17 (C-6), 56.0 (C-2′), 55.8 (OCH_3). HRMS (ESI) calcd for $(M + Na)^+$ $C_{46}H_{41}NO_{15}S$: 902.2089. Found: 902.2094.

Methyl 5-*O*-Benzoyl-2-deoxy-2-*p*-methoxybenzylthio-β-D-xylofuranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside (40). Alcohol **30** (129 mg, 0.25 mmol) and **25** (95 mg, 0.25 mmol) were coupled in CH_2Cl_2 (15 mL) containing 4 Å molecular sieves (250 mg) with $Cu(OTf)_2$ (92 mg, 0.25 mmol) as described for the synthesis of **36**. Chromatography (4:1 hexane−EtOAc) of the crude product gave **40** (155 mg, 69%) as a colorless oil: R_f 0.47 (2:1 hexane−EtOAc); $[\alpha]_D$ −67.5 (*c*, 0.8, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.08−8.01 (m, 4H, Ar), 7.99−7.95 (m, 2H, Ar), 7.84−7.80 (m, 2H, Ar), 7.61−7.50 (m, 3H, Ar), 7.45−7.35 (m, 7H, Ar), 7.30−7.24 (m, 4H, Ar), 6.84−6.80 (m, 2H, Ar), 5.96 (dd, 1H, $J_{4,5}$ = $J_{3,4}$ = 10.0 Hz, H-4), 5.85 (dd, 1H, $J_{3,4}$ = 10.0 Hz, $J_{2,3}$ = 3.3 Hz, H-3), 5.71 (dd, 1H, $J_{2,3}$ = 3.3 Hz, $J_{1,2}$ = 1.8 Hz, H-2), 5.06 (s, 1H, H-1′), 4.96 (d, 1H, $J_{1,2}$ = 1.8 Hz, H-1), 4.66−4.57 (m, 3H, H-4′, H-5a′, H-5b′), 4.22−4.14 (m, 2H, H-5, H-3′), 4.09 (dd, 1H, $J_{6a,6b}$ = 10.9 Hz, $J_{5,6a}$ = 2.6 Hz, H-6a), 3.86 (d, 1H, *J* = 13.4 Hz, $ArCH_2S$), 3.82 (d, 1H, *J* = 13.4 Hz, $ArCH_2S$), 3.70 (s, 3H, $ArOCH_3$), 3.57 (dd, 1H, $J_{6a,6b}$ = 10.9 Hz, $J_{5,6b}$ = 3.6 Hz, H-6b), 3.52 (s, 3H, OCH_3), 3.50 (d, 1H, $J_{3',OH}$ = 8.1 Hz, OH), 3.40 (s, 1H, H-2′); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.3 (C=O), 165.45 (C=O), 165.41 (C=O), 165.40 (C=O), 158.9 (Ar), 133.44 (Ar), 133.41 (Ar), 133.1 (Ar), 133.0 (Ar), 130.1 (2 × Ar), 130.04 (Ar), 129.98 (2 × Ar), 129.88 (2 × Ar), 129.8 (2 × Ar), 129.7 (2 × Ar), 129.3 (Ar), 129.2 (Ar), 129.0 (Ar), 128.6 (Ar), 128.51 (2 × Ar), 128.48 (2 × Ar), 128.4 (2 × Ar), 128.2 (2 × Ar), 114.1 (2 × Ar), 107.2 (C-1′), 98.8 (C-1), 81.7 (C-4′), 76.3 (C-3′), 70.12 (C-3), 70.06 (C-2), 69.3 (C-5), 66.7 (C-4), 64.5 (C-6), 64.4 (C-5′), 55.7 (OCH_3), 55.3 ($ArOCH_3$), 55.1 (C-2′), 36.2 ($ArCH_2S$). HRMS (ESI) calcd for (M + Na) $C_{48}H_{46}O_{14}S$: 901.2501. Found: 901.2501.

2,3,5-Tri-*O*-acetyl-D-arabino-1,4-lactone (43). D-Arabinose (**42**, 15 g, 0.10 mmol) was dissolved in water (40 mL) and K_2CO_3 (17 g, 0.12 mmol) was added in portions. After the clear aqueous solution was cooled to 0 °C, Br_2 (6.0 mL, 0.11 mmol) was added dropwise. The resulting orange solution was warmed to room temperature and stirred for 18 h. The reaction mixture was quenched by the addition of 88% formic acid (2.0 mL), and the solution was concentrated. After addition of HOAc (20 mL), the reaction mixture was concentrated again to remove any residual water. The yellowish semisolid residue was redissolved in HOAc (20 mL) and cooled to 0 °C before Ac_2O (90 mL) and concentrated H_2SO_4 (1 mL) were added. After the reaction mixture was stirred at 50 °C for 18 h, it was cooled to 0 °C and water (100 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layer was washed with saturated aqueous $NaHCO_3$ solution (2 × 100 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by chromatography (4:1 hexane−EtOAc) to afford **43** (20 g, 73%) as an oil. $[\alpha]_D$ +24.6 (*c*, 0.6, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$, δ_H) 5.57 (d, 1H, $J_{2,3}$ = 6.9 Hz, H-2), 5.46 (dd, 1H, $J_{2,3}$ = $J_{3,4}$ = 6.9 Hz, H-3), 4.57−4.53 (m, 1H, H-4), 4.67 (dd, 1H, $J_{5a,5b}$ = 12.6 Hz, $J_{4,5a}$ = 2.9 Hz, H-5a), 4.27 (dd, 1H, $J_{5a,5b}$ = 12.6 Hz, $J_{4,5b}$ = 5.0 Hz, H-5b), 2.18 (s, 3H, CH_3CO), 2.12 (s, 3H, CH_3CO), 2.11 (s, 3H, CH_3CO); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 170.2 (C=O), 169.8 (C=O), 169.4 (C=O), 168.2 (C=O), 77.4 (C-4), 72.6 (C-3), 72.2 (C-2), 62.1 (C-5), 20.6 (CH_3CO), 20.5 (CH_3CO), 20.3 (CH_3CO). HRMS (ESI) calcd for (M + Na) $C_{11}H_{14}O_8$: 297.0581. Found: 297.0583.

1,2,3,5-Tetra-*O*-acetyl-D-[1-D]-arabinofuranose (44). A solution of **43** (3.9 g, 14.22 mmol) in CH_3OH (50 mL) was cooled to 0 °C and stirred with Amberlite IR-120 (H^+) resin (10 g). Sodium borodeuteride ($NaBD_4$, 0.60 g, 14.22 mmol) was added in portion. The reaction mixture was stirred for an additional 30 min at 0 °C before the resin was filtered and then washed with CH_3OH. The filtrate was concentrated to a crude residue that was purified by chromatography (2:1 hexane−EtOAc) to afford 2,3,5-tri-*O*-acetyl-D-[1-^{2}H]-arabinofuranose (1.5 g, 38%) as a colorless oil. This oil (1.5 g, 5.41 mmol) was redissolved in pyridine (10 mL). To this solution was added Ac_2O (1.02 mL, 10.82 mmol) and DMAP (75 mg, 0.27 mmol). The reaction mixture was stirred at room temperature for 16 h, the pyridine was evaporated at 50 °C, and the crude product was purified by chromatography (2:1 hexane−EtOAc) to obtain **44** (1.51 g, 87%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 5.62 (dd, 0.67H, $J_{3,4}$ = 9.2 Hz, J_{23} = 2.1 Hz, H-3), 5.28 (d, 0.67H, $J_{2,3}$ = 2.3 Hz, H-2), 5.25 (ddd, 0.67H, $J_{3,4}$ = $J_{4,5b}$ = 4.7 Hz, $J_{4,5a}$ = 2.6 Hz, H-4), 5.21 (d, 0.33H, $J_{2',3'}$ = 1.7 Hz, H-2′), 5.05 (dd, 0.33H, $J_{3',4'}$ = 4.7 Hz, $J_{2',3'}$ = 1.7 Hz, H-3′), 4.42−4.32 (m, 0.67H, H-5a′ and H-4′), 4.30 (dd, 0.67H, $J_{4,5a}$ = 2.6 Hz, $J_{5a,5b}$ = 12.6 Hz, H-5a), 4.27−4.17 (m, 0.67H, H-5b′), 4.16 (dd, 0.67H, $J_{4,5b}$ = 4.7 Hz, $J_{5a,5b}$ = 12.6 Hz, H-5b), 2.15−2.05 (m, 12H, $O(CO)CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 170.5−169.2 (6 × C=O), 167.5 (C=O β-Ac), 82.3 (C-4′), 80.5 (C-2′), 76.8 (C-3′), 69.6 (C-2), 68.6 (C-3), 68.1 (C-4), 63.0 (C-5′), 61.6 (C-5), 21.0−20.3 (8 × CH_3). HRMS (ESI) calculated for (M + Na) $C_{13}H_{17}DO_9$: 342.0906. Found: 342.0908.

Tolyl 2,3,5-Tri-*O*-acetyl-1-thio-α-D-[1-D]-arabinofuranoside (45). To a solution of compound **44** (3.0 g, 9.40 mmol) and *p*-thiocresol (1.4 g, 11.28 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added BF_3·OEt_2 (3.54 mL, 28.19 mmol) dropwise over 10 min. The reaction mixture was stirred for 3 h at 0 °C, and then the reaction was quenched by the addition of a saturated aqueous $NaHCO_3$ solution. The organic layer was separated, dried with Na_2SO_4, filtered, and concentrated to a crude residue that was purified by chromatography (4:1 hexane−EtOAc) to yield **45** (1.55 g, 43%) as a colorless oil: R_f (2:1 hexane−EtOAc); $[\alpha]_D$ +149.2 (*c*, 0.3, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.42−7.38 (m, 2H, Ar), 7.15−7.11 (m, 2H, Ar), 5.26 (d, 1H, $J_{2,3}$ = 2.2 Hz, H-2), 5.07 (dd, 1H, $J_{3,4}$ = 5.5 Hz, $J_{2,3}$ = 2.2 Hz, H-3), 4.47 (ddd, 1H, $J_{3,4}$ = $J_{4,5b}$ = 5.5 Hz, $J_{4,5a}$ = 3.8 Hz, H-4), 4.39 (dd, 1H, $J_{5a,5b}$ = 12.0 Hz, $J_{4,5a}$ = 3.8 Hz, H-5a), 4.28 (dd, 1H, $J_{5a,5b}$ = 12.0 Hz, $J_{4,5b}$ = 5.5 Hz, H-5b), 2.33 (s, 3H, tolyl CH_3), 2.12 (s, 3H, CH_3CO), 2.10 (s, 3H, CH_3CO), 2.09 (s, 3H, CH_3CO); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 170.5 (C=O), 170.0 (C=O), 169.6 (C=O), 138.1 (Ar), 132.7 (2 × Ar), 129.8 (2 × Ar), 129.5 (Ar), 81.4 (C-2), 79.9 (C-4), 77.2 (C-3), 62.8 (C-5), 21.1 (tolyl CH_3), 20.8 (CH_3CO), 20.7 (2 × CH_3CO). HRMS (ESI) calcd for (M + Na) $C_{18}H_{21}DO_7S$: 406.1041. Found: 406.1039.

Tolyl 1-Thio-α-D-[1-D]-arabinofuranoside (46). To a solution of compound **45** (1.55 g, 4.04 mmol) in 1:1 CH_2Cl_2−CH_3OH (60 mL) was added 1 M $NaOCH_3$ in CH_3OH (5 mL). After stirring for 16 h at room temperature, the reaction mixture was neutralized with Amberlite IR-120 H^+ resin, filtered, and concentrated. The resulting oil was purified by chromatography (10:1, CH_2Cl_2−CH_3OH) to afford **46** (0.88 g, 85%) as a white solid: R_f 0.34 (10:1, CH_2Cl_2−CH_3OH); $[\alpha]_D$ +208.0 (*c*, 0.2, CH_2Cl_2); ^{1}H NMR (500 MHz, CD_3OD, δ_H) 7.42−7.39 (m, 2H, Ar), 7.13−7.09 (m, 2H, Ar), 4.00−3.89 (m, 3H, H-2, H-3, H-4), 3.75 (dd, 1H, $J_{5a,5b}$ = 12.2 Hz, $J_{4,5a}$ = 2.7 Hz, H-5a), 3.63 (dd, 1H, $J_{5a,5b}$ = 12.2 Hz, $J_{4,5b}$ = 4.6 Hz, H-5b), 2.30 (s, 3H, tolyl CH_3); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 138.7 (Ar), 133.4 (2 × Ar), 132.4 (Ar), 130.6 (2 × Ar), 84.3 (C-4), 83.3 (C-2), 77.7 (C-3), 62.5 (C-5), 21.1 (tolyl CH_3). HRMS (ESI) calcd for (M + Na) $C_{12}H_{15}DO_4S$: 280.0724. Found: 280.0726.

Tolyl 2,3-Anhydro-5-*O*-benzoyl-1-thio-α-D-[1-D]-lyxofuranoside (47). Compound **46** (0.88 g, 3.42 mmol), benzoic acid (0.63 g, 5.13 mmol), and triphenylphosphine (5.48 g, 10.26 mmol) were dissolved in THF (50 mL) at 0 °C. Diisopropylazodicarboxylate (2.09 mL, 10.6 mmol) was added dropwise over a period of 10 min. After complete addition of the reagent, the reaction mixture was warmed to room temperature and was stirred for 45 min. The solution was subsequently concentrated to a crude oil that was purified by chromatography (8:1 hexane−EtOAc) to obtain **47** (0.82 g, 70%) as a white amorphous solid: R_f 0.81 (2:1 hexane−EtOAc); $[\alpha]_D$ +155.3 (*c*, 0.1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.10−8.06 (m, 2H, Ar), 7.60−7.55 (m, 1H, Ar), 7.48−7.41 (m, 4H, Ar), 7.15−7.12 (m, 2H, Ar), 4.56 (dd, 1H, $J_{5a,5b}$ = 11.3 Hz, $J_{4,5a}$ = 5.7 Hz, H-5a), 4.50 (dd, 1H, $J_{5a,5b}$ = 11.3 Hz, $J_{4,5b}$ = 6.0 Hz, H-5b), 4.29 (dd, 1H, $J_{4,5b}$ = 6.0 Hz, $J_{4,5a}$ = 5.7 Hz, H-4), 3.94 (d, 1H, $J_{2,3}$ = 2.8 Hz, H-2), 3.84 (d, 1H, $J_{2,3}$ = 2.8 Hz, H-3), 2.35 (s, 3H, tolyl C$\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.2 (C$\underline{=}$O), 138.4 (Ar), 133.4 (2 × Ar), 133.2 (2 × Ar), 129.9 (2 × Ar), 129.8 (2 × Ar), 128.6 (Ar), 128.4 (2 × Ar), 74.2 (C-4), 62.4 (C-5), 57.6 (C-2), 55.7 (C-3), 21.1 (tolyl $\underline{C}H_3$). HRMS (ESI) calcd for (M + Na) $C_{19}H_{17}DO_4S$: 366.0881. Found: 366.0878.

Tolyl 2,3-Anhydro-1-thio-α-D-[1-D]-lyxofuranoside (48). To a solution of **47** (1.02 g, 2.97 mmol) in 1:1 CH_2Cl_2−CH_3OH (80 mL) was added 1 M $NaOCH_3$ in CH_3OH (4 mL). After stirring for 2 h at room temperature, the reaction mixture was neutralized with Amberlite IR-120 H^+ resin, filtered, and concentrated. The resulting oil was purified by chromatography (4:1 hexane−EtOAc) to afford **48** (0.59 g, 83%) as a white solid: R_f 0.34 (2:1 hexane−EtOAc); $[\alpha]_D$ +128.7 (*c*, 0.2, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.45−7.41 (m, 2H, Ar), 7.16−7.12 (m, 2H, Ar), 4.07 (ddd, 1H, $J_{4,5a}$ = $J_{4,5b}$ = 5.0 Hz, $J_{3,4}$ = 0.6 Hz, H-4), 3.91 (d, 1H, $J_{2,3}$ = 2.8 Hz, H-2), 3.90−3.85 (m, 2H, H-5a, H-5b), 3.77 (dd, 1H, $J_{2,3}$ = 2.8 Hz, $J_{3,4}$ = 0.6 Hz, H-3), 2.34 (s, 3H, tolyl CH_3), 1.88 (br, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.4 (Ar), 133.4 (2 × Ar), 129.9 (2 × Ar), 128.6 (Ar), 76.4 (C-4), 61.5 (C-5), 57.1 (C-2), 55.7 (C-3), 21.1 (tolyl $\underline{C}H_3$). HRMS (ESI) calcd for (M + Na) $C_{12}H_{13}DO_3S$: 262.0619. Found: 262.0619.

Tolyl 2,3-Anhydro-5-*O*-(acetyl-D_3)-1-thio-α-D-(50%-1-D)-lyxofuranoside (52). Thioglycoside **50** (a 1:1 mixture of **48** and **49**, 315 mg, 1.32 mmol), DMAP (243 mg, 1.98 mmol), and dicyclohexylcarbodiimide (546 mg, 2.65 mmol) were dissolved in CH_2Cl_2 (20 mL) at room temperature. CD_3CO_2D (125 mg, 1.98 mmol) was added dropwise, and after complete addition, the reaction mixture was stirred for 2 h. The solution was subsequently filtered, and the filtrate was concentrated to a crude oil that was purified by chromatography (5:1 hexane−EtOAc) to obtain **52** (301 mg, 80%). R_f 0.49 (2:1 hexane−EtOAc); $[\alpha]_D$ +211.2 (*c*, 0.3, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.44−7.40 (m, 2H, Ar), 7.15−7.12 (m, 2H, Ar), 5.49 (s, 0.5H, H-1), 4.31 (dd, 1H, $J_{5a,5b}$ = 11.4 Hz, $J_{4,5a}$ = 5.9 Hz, H-5a), 4.23 (dd, 1H, $J_{5a,5b}$ = 11.4 Hz, $J_{4,5b}$ = 5.8 Hz, H-5b), 4.13 (ddd, 1H, $J_{4,5a}$ = 5.9 Hz, $J_{4,5b}$ = 5.8 Hz, $J_{3,4}$ = 0.7 Hz, H-4), 3.91 (d, 1H, $J_{2,3}$ = 2.9 Hz, H-2), 3.75 (dd, 1H, $J_{2,3}$ = 2.9 Hz, $J_{3,4}$ = 0.7 Hz, H-3), 2.34 (s, 3H, tolyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 170.6 (C$\underline{=}$O), 138.4 (Ar), 133.3 (2 × Ar), 129.9 (2 × Ar), 128.6 (Ar), 87.1 (C-1), 74.2 (C-4), 62.0 (C-5), 57.6 (C-2), 55.6 (C-3), 21.1 (tolyl $\underline{C}H_3$). HRMS (ESI) calcd for (M + Na) $C_{14}H_{13}D_3O_4S$, 306.0850; $C_{14}H_{12}D_4O_4S$, 307.0913. Found: 306.0849, 307.0913.

Benzyl 5-*O*-(50% Acetyl-D_3)-2-deoxy-2-*p*-thiotolyl-β-D-(50% 1-D)-xylofuranoside (55). Thioglycoside **53** (a 1:1 mixture of **51** and **52**, 52 mg, 0.19 mmol) and 4,4,5,5-tetramethyl-2-(1-naphthyl)-1,3-dioxolane (**54**, 24 mg, 0.09 mmol) were dissolved in $CDCl_3$, and the ^{1}H NMR spectrum was recorded. After removal of $CDCl_3$, the resulting mixture was redissolved in CH_2Cl_2 (20 mL) with benzyl alcohol (**29**, 30 mg, 0.28 mmol) and 4 Å molecular sieves (800 mg). The mixture was heated at reflux for 1.5 h before it was filtered. The filtrate was concentrated, and the ^{1}H NMR spectrum was recorded. The crude residue was then purified by chromatography (5:1 hexane−EtOAc) to afford **55**, and the ^{1}H NMR spectrum was recorded. R_f 0.49 (3:1 hexane−EtOAc); $[\alpha]_D$ −40.1 (*c*, 0.2, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.38−7.27 (m, 7H, Ar), 7.14−7.11 (m, 2H, Ar), 5.15 (s, 0.5H, H-1), 4.80 (d, 1H, *J* = 11.6 Hz, $PhCH_2$), 4.63−4.59 (m, 1H, H-4), 4.51 (d, 1H, *J* = 11.6 Hz, $PhCH_2$), 4.45 (dd, 1H, $J_{5a,5b}$ = 11.9 Hz, $J_{4,5a}$ = 4.4 Hz, H-5a), 4.30 (dd, 1H, $J_{5a,5b}$ = 11.9 Hz, $J_{4,5b}$ = 7.6 Hz, H-5b), 4.19 (dd, 1H, $J_{3,OH}$ = 11.2 Hz, $J_{3,4}$ = 4.3 Hz, H-3), 3.76 (s, 1H, H-2), 3.08 (d, 1H, $J_{3,OH}$ = 11.2 Hz, OH), 2.34 (s, 3H, tolyl CH_3), 2.11 (s, 1.5H, CH_3CO); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 170.9 (C$\underline{=}$O), 137.9 (Ar), 136.7 (Ar), 131.7 (2 × Ar), 130.1 (2 × Ar), 129.4 (Ar), 128.6 (2 × Ar), 128.1 (3 × Ar), 106.2 (C-1), 81.1 (C-4), 75.8 (C-3), 69.8 ($Ph\underline{C}H_2$), 64.1 (C-5), 58.1 (C-2), 21.1 (tolyl $\underline{C}H_3$), 21.0 ($\underline{C}H_3CO$). HRMS (ESI) calcd for $(M + Na)^+$ $C_{21}H_{24}O_5S$, 411.1237; $C_{21}H_{23}DO_5S$, 412.1299; $C_{21}H_{21}D_3O_5S$, 414.1425; $C_{21}H_{20}D_4O_5S$, 415.1488. Found: 411.1238, 412.1300, 414.1426, 415.1487, respectively.

Methyl 5-*O*-(50% Acetyl-D_3)-2-deoxy-2-*p*-thiotolyl-β-D-(50% 1-D)-xylofuranosyl)-(1→6)-2,3,4-tri-*O*-benzoyl-β-D-mannopyranoside (56). Thioglycoside **53** (a 1:1 mixture of **51** and **52**, 81 mg, 0.29 mmol) and 4,4,5,5-tetramethyl-2-(1-naphthyl)-1,3-dioxolane **54** (37 mg, 0.14 mmol) were dissolved in $CDCl_3$, and the ^{1}H NMR spectrum was recorded. After removal of $CDCl_3$, the resulting mixture was redissolved in CH_2Cl_2 (20 mL) with acceptor **30** (145 mg, 0.29 mmol) and 4 Å molecular sieves (250 mg). After the mixture was stirred at room temperature for 30 min, $Cu(OTf)_2$ (104 mg, 0.29 mmol) was added, and the mixture was stirred for 5 h. The mixture was then filtered, the filtrate was concentrated, and the ^{1}H NMR spectrum was recorded. After neutralization with triethylamine, the crude residue was then purified by chromatography (2:1, hexane−EtOAc) to afford **56** and the ^{1}H NMR spectrum was recorded. R_f 0.24 (3:1 hexane−EtOAc); $[\alpha]_D$ −70.5 (*c*, 0.3, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.12−8.08 (m, 2H, Ar), 7.98−7.94 (m, 2H, Ar), 7.83−7.80 (m, 2H, Ar), 7.61−7.57 (m, 1H, Ar), 7.54−7.50 (m, 1H, Ar), 7.47−7.33 (m, 7H, Ar), 7.27−7.24 (m, 2H, Ar), 7.15−7.12 (m, 2H, Ar), 5.94 (dd, 1H, $J_{4,5}$ = $J_{3,4}$ = 10.1 Hz, H-4), 5.85 (dd, 1H, $J_{3,4}$ = 10.1 Hz, $J_{2,3}$ = 3.3 Hz, H-3), 5.70 (dd, 1H, $J_{2,3}$ = 3.3 Hz, $J_{1,2}$ = 1.8 Hz, H-2), 5.15 (s, 0.5H, H-1′), 4.95 (d, 1H, $J_{1,2}$ = 1.8 Hz, H-1), 4.65−4.60 (m, 1H, H-4′), 4.44−4.35 (m, 2H, H-5a′, H-5b′), 4.22−4.17 (m, 2H, H-5, H-3′), 4.08 (dd, 1H, $J_{6a,6b}$ = 10.9 Hz, $J_{5,6a}$ = 2.6 Hz, H-6a), 3.84 (s, 1H, H-2′), 3.64 (dd, 1H, $J_{6a,6b}$ = 10.9 Hz, $J_{5,6b}$ = 3.7 Hz, H-6b), 3.54 (d, 1H, $J_{3',OH}$ = 11.9 Hz, OH), 3.51 (s, 3H, OCH_3), 2.35 (s, 3H, tolyl CH_3), 2.06 (s, 1.5H, CH_3CO); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 170.7 (C$\underline{=}$O), 165.4 (3 × C$\underline{=}$O), 137.7 (Ar), 133.44 (Ar), 133.42 (Ar), 133.1 (Ar), 131.5 (2 × Ar), 130.1 (2 × Ar), 130.0 (2 × Ar), 129.8 (2 × Ar), 129.7 (2 × Ar), 129.6 (Ar), 129.3 (Ar), 129.2 (Ar), 129.1 (Ar), 128.53 (2 × Ar), 128.47 (2 × Ar), 128.2 (2 × Ar), 106.4 (C-1′), 98.8 (C-1), 81.4 (C-4′), 75.8 (C-3′), 70.11 (C-2), 70.05 (C-3), 69.3 (C-5), 66.7 (C-4), 64.3 (C-5′), 64.1 (C-6), 58.1 (C-2′), 55.7 (OCH_3), 21.1 (tolyl $\underline{C}H_3$), 20.9 ($\underline{C}H_3CO$). HRMS (ESI) calcd for $(M + Na)^+$ $C_{42}H_{42}O_{13}S$, 809.2238; $C_{42}H_{41}DO_{13}S$, 810.2301; $C_{42}H_{39}D_3O_{13}S$, 812.2427; $C_{42}H_{38}D_4O_{13}S$, 813.2489. Found: 809.2237, 810.2305, 812.2430, 813.2493, respectively.

NMR Experiments Carried Out To Probe Formation of Episulfonium Ion Intermediates. An NMR tube containing a solution of compound **1** (25 mg, 0.07 mmol) in CD_2Cl_2 (1 mL) was cooled to −78 °C, and a spectrum was recorded at 400 MHz. The tube was then removed from the spectrometer, and TMSOTf (13 μL, 0.07 mmol) was quickly added at −78 °C. After returning the sample to the spectrometer, the sample was warmed to room temperature in 10° increments over 2 h, and a spectrum was recorded at each temperature. A similar series of experiments was carried out using **18** (25 mg, 0.07 mmol) in CD_2Cl_2 (1 mL) and $SnCl_4$ (8 μL, 0.07 mmol).

Calculation of Kinetic Isotope Effects. The procedure used was analogous to that reported earlier by El-Badri et al.[41] The ^{1}H NMR spectra of the mixture of donor **53** and internal standard **54**, the crude reaction mixture, and the product 2-thiotolyl-2-deoxy-β-xylofuranoside (**55** or **56**) were recorded in $CDCl_3$ at 500 MHz.

For each of spectra, the protons of the acetate group on O5, the anomeric, and the internal standard protons were integrated on an expanded region of the desired peak. The α-DKIE for each glycosylation was determined using eq 1[44] (KIE = ln(1 − *F*)/ln[1 − (*FR*/*R*$_0$)]), where *F* is the fractional conversion of donor **53** (the yield of **55** or **56**) and *R* and *R*$_0$ are the ratios of the anomeric protons integrations in the product and the starting donor, respectively. These ratios correspond to the D/H ratios in **55** (or **56**) and **53**.

Gas-Phase ab Initio Geometry Optimizations. Ab initio molecular orbital and density functional theory calculations were performed using Gaussian 03.[55] Episulfonium ions **19** and **12a** and oxocarbenium ions **20** and **13a** were studied at the Hartree−Fock (HF) and density functional theory (B3LYP) levels with the 6-31G** basis set. An initial geometry optimization was done on each structure with no geometrical restraints. On each of the resulting geometries, a single-point energy calculation was done using the B3LYP/6-311++G** level of theory. Two additional calculations at the same level of theory were also done on the ^{3}E and E$_3$ ring conformers of **13a** to investigate ring conformation. The constrained geometry optimizations were conducted at the B3LYP/6-31G** level of theory on structures **12a** and **19** while keeping the C1−S bond and the C2−S bond fixed at 1.901 and 1.871 Å, respectively. Single-point energies of these geometries were subsequently calculated at the B3LYP/6-311++G** level.

(55) Frisch, M. J.; et al. Gaussian 03, version C.02, 2004; Gaussian, Inc.: Wallingford, CT.

Acknowledgment. This work was supported by the Natural Sciences and Engineering Research Council of Canada and The Alberta Ingenuity Centre for Carbohydrate Science. We thank Professors Keith Woerpel (University of California, Irvine), Rik Tykwinski (University of Alberta), and Andrew Bennet (Simon Fraser University) for helpful discussions.

Supporting Information Available: Details on the synthesis of compounds not described in the main text, ^{1}H and ^{13}C NMR spectra for new compounds, and complete ref 55. This material is available free of charge via the Internet at http://pubs.acs.org.

JA9029945