Sensitivity of $^1J_{C1-H1}$ Magnitudes to Anomeric Stereochemistry in 2,3-Anhydro-*O*-furanosides

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Received December 15, 2000

The magnitude of the one-bond coupling constant between C_1 and H_1 in 2,3-anhydro-*O*-furanosides has been shown to be sensitive to the stereochemistry at the anomeric center. A panel of 24 compounds was studied and in cases where the anomeric hydrogen is trans to the epoxide moiety, $^1J_{C1-H1} = 163-168$ Hz; and when this hydrogen is cis to the oxirane ring, $^1J_{C1-H1} = 171-174$ Hz. In contrast, for 2,3-anhydro-*S*-glycosides, the size of the $^1J_{C1-H1}$ is not sensitive to C_1 stereochemistry. Computational studies on all four methyl 2,3-anhydro-*O*-furanosides (**5**−**8**) demonstrated that $^1J_{C1-H1}$ was inversely proportional to the length of the C_1-H_1 bond. A previously reported equation, which relates C_1-H_1 bond distance and atomic charges to $^1J_{C1-H1}$ magnitudes, could be used to accurately predict the *J* values in the α-*lyxo* (**5**) and *β*-*ribo* (**8**) isomers. In contrast, with the *β*-*lyxo* (**6**) and α-*ribo* isomers (**7**), this equation underestimated the size of these coupling constants by 10−20 Hz.

Introduction

In 1969, Perlin and Casu reported[1] that the one-bond coupling constant between the anomeric carbon and its attached hydrogen ($^1J_{C1-H1}$) in α-D-glucose differed from that of *β*-D-glucose by 9 Hz. Since that time, the magnitude of this coupling constant in pyranosyl rings has become a reliable indicator of the stereochemistry at the anomeric center. In α-pyranosides, $^1J_{C1-H1}$ is approximately 170 Hz, and in the corresponding *β*-anomer, this coupling constant is smaller, about 160 Hz.[2] Although these trends are general for all pyranosides, this method is particularly useful for mannopyranosyl derivatives, because $^3J_{H1-H2}$ cannot be used to unambiguously distinguish the two anomers. More recent studies have demonstrated that $^1J_{C1-H1}$ magnitudes can also be used to differentiate 1,2-orthoesters of glucose and galactose from the isomeric glycosides.[3] In contrast, $^1J_{C1-H1}$ values in furanosides have been shown to be insensitive to anomeric stereochemistry,[4] due to conformational averaging of the *J*'s arising from all solution conformers of these flexible ring systems.

The factors that determine $^1J_{C-H}$ magnitudes in six-membered ring carbocyclic and heterocyclic compounds has been extensively studied.[2,5−9] When ring systems containing only first-row atoms are considered, $^1J_{C-H}$ magnitudes are inversely related to the length of the C−H bond and generally $^1J_{C-H(ax)}$ is smaller than $^1J_{C-H(eq)}$.

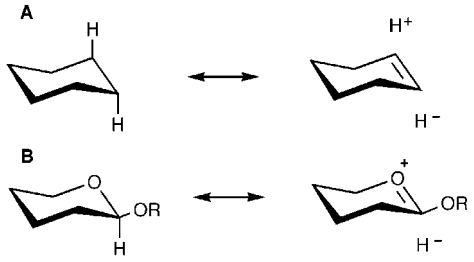

Figure 1. Selected hyperconjugative effects in cyclohexane (A) and a *β*-pyranoside (B).

For example, in cyclohexane the magnitude of $^1J_{C-H(ax)}$ is 122 Hz, while $^1J_{C-H(eq)}$ is 126 Hz.[8] Based on these *J*'s, it would be predicted that the axial C−H bond would be longer than its equatorial counterpart, and indeed this is true. The calculated (B3LYP/6-31+G**)[9] lengths of the axial and equatorial C−H bonds in cyclohexane are 1.1001 and 1.0972 Å, respectively. The increased bond lengths for the axial C−H bond can be attributed to $\sigma_{(C-Hax)} \rightarrow \sigma^*_{(C-Hax)}$ hyperconjugation (Figure 1A). A similar effect is observed at the anomeric center in pyranosides. When the C_1-H_1 bond is axial, it is placed antiperiplanar to one of the ring oxygen lone pairs. This maximizes $n_O \rightarrow \sigma^*_{C1-H1}$ hyperconjugation, which in turn lengthens the C_1-H_1 bond in the *β*-pyranosides, relative to the α-pyranosides (Figure 1B). Accordingly, $^1J_{C1-H1}$ is smaller in the *β*-pyranosides. This effect is often referred to as the Perlin Effect.[5] For six-membered ring heterocyclic compounds containing second row atoms, reverse Perlin effects are often seen, that is, there is not always an inverse relationship between $^1J_{C-H}$ and C−H bond length. This is particularly true for sulfur-containing molecules, and the most heavily investigated systems have been 1,3-dithianes and 1,3-oxathianes. In these rings it appears that these coupling constants are influenced by other factors in addition to the distance between the coupled atoms.[6,8,9]

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10.1021/jo001747a CCC: $20.00 © 2001 American Chemical Society
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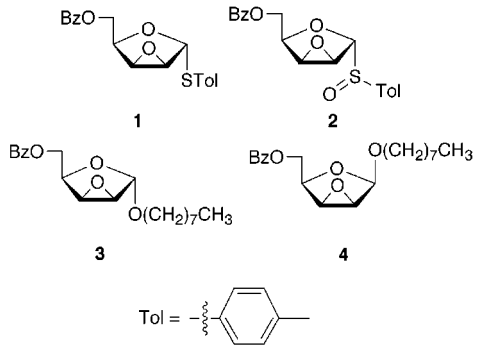
Chart 1



Recently, we have been exploring the ability of thioglycoside **1** and glycosyl sulfoxide **2** (Chart 1) to serve as glycosylating agents.[10] These compounds are efficient glycosyl donors. However, we were faced with the problem of unequivocally determining the stereochemistry at the anomeric center in the glycoside products (e.g., **3** and **4**). Unfortunately, two generally reliable[4] indicators of anomeric stereochemistry in furanosides, the chemical shift of the anomeric carbon and the magnitude of $^3J_{H1-H2}$, were very similar for both **3** and **4**. Furthermore, another possible determinant of C_1 stereochemistry, the chemical shift of the anomeric proton, was virtually identical in both **3** and **4**.

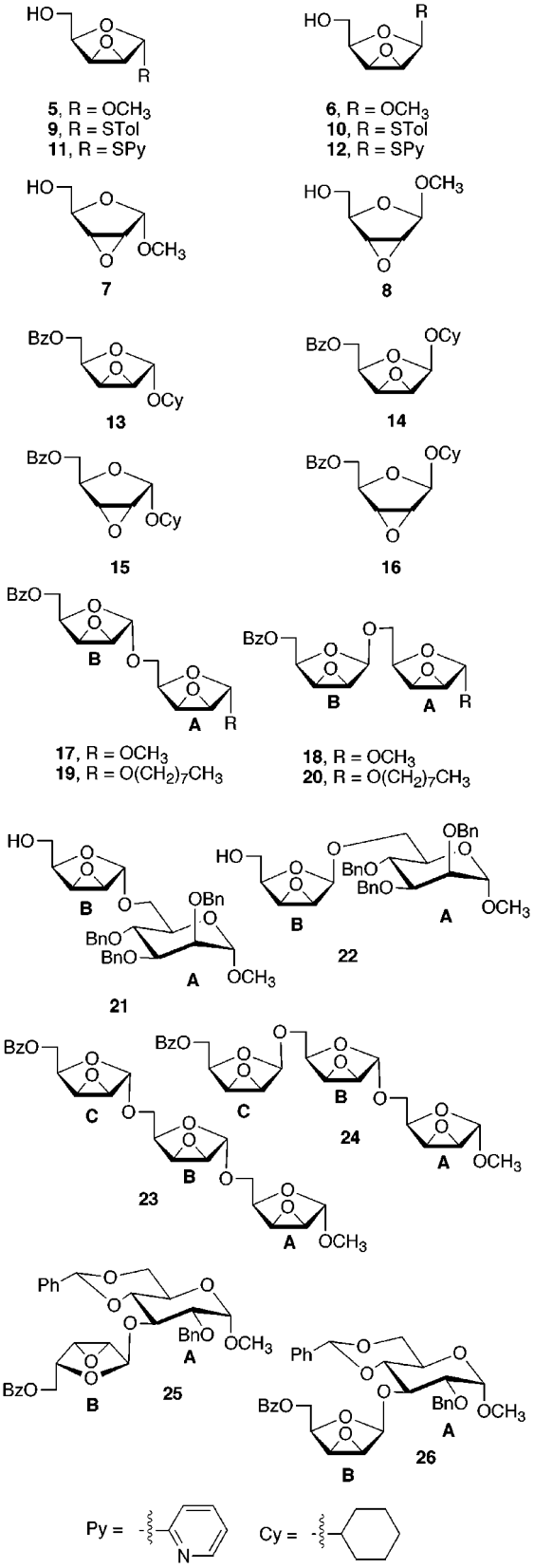
In this paper we report that the one-bond coupling constant between C_1 and H_1 in 2,3-*O*-anhydrofuranosides is diagnostic of the stereochemistry at the anomeric center. The studies described here extend work previously reported by Kim, Vyas, and Szarek[11] on ^{13}C NMR spectra of carbohydrates possessing epoxide functionality. In that study, $^1J_{C-H}$ in all four methyl 2,3-anhydrofuranosides (**5**−**8**, Chart 2) were measured. Surprisingly, however, no mention was made of the sensitivity of $^1J_{C1-H1}$ to the stereochemistry at the anomeric center. We report here the measurement of $^1J_{C1-H1}$ for a panel of mono- and oligosaccharides (Chart 2) and show that the trends observed in **5**−**8** are general for 2,3-anhydro-*O*-furanosides. Furthermore, through ab initio[12] and density functional theory (DFT) calculations,[13] we have determined bond lengths of **5**−**8** and have shown that there is an inverse relationship between C_1-H_1 bond distance and $^1J_{C1-H1}$.

Results and Discussion

Synthesis of Substrates. Methyl glycosides **5**−**8** have been previously reported.[14] The other anhydrosugars shown in Chart 2 were synthesized as described below.

2,3-Anhydro-α-D-lyxofuranosides. Compound **3** was synthesized (Scheme 1) from octyl glycoside **27**[15] in 82% yield via a Mitsunobu reaction with benzoic acid, triphenylphosphine, and diisopropylazodicarboxylate (DIAD).

Chart 2



The preparation of **17**, **19**, **21**, and **25** is outlined in Scheme 2. Thioglycoside **29**[16] was reacted with alcohols **5**,[14] **28**, **30**,[17] and **31**,[18] to give **32**−**35** in 81−91% yield. Deprotection with sodium methoxide proceeded in 88−

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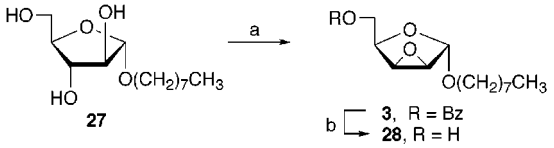
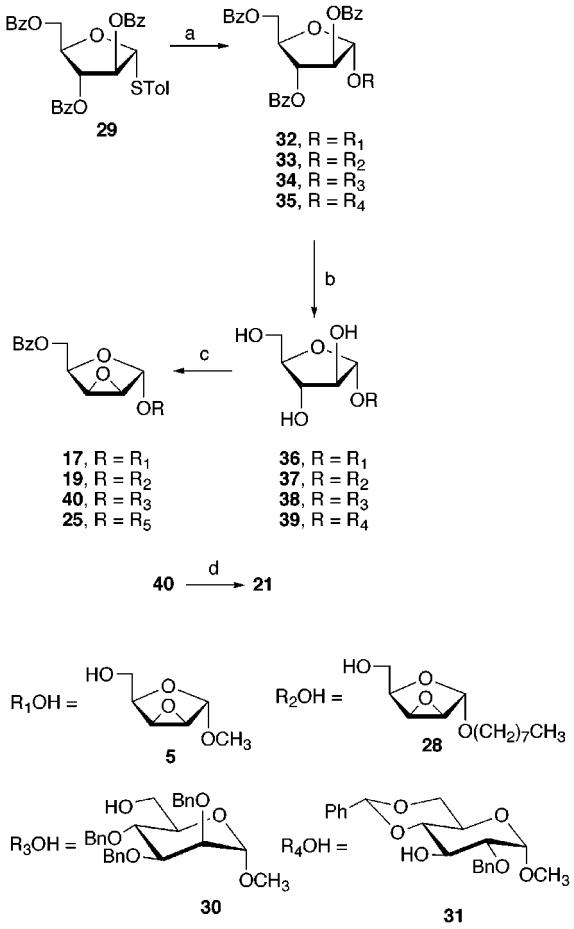
(15) Ramneantu, O.; Lowary, T. L., unpublished results.

Scheme 1



[a] BzOH, Ph_3P, DIAD, THF, 0 °C, 82%. [b] $NaOCH_3$, CH_3OH, rt, 91%.

Scheme 2

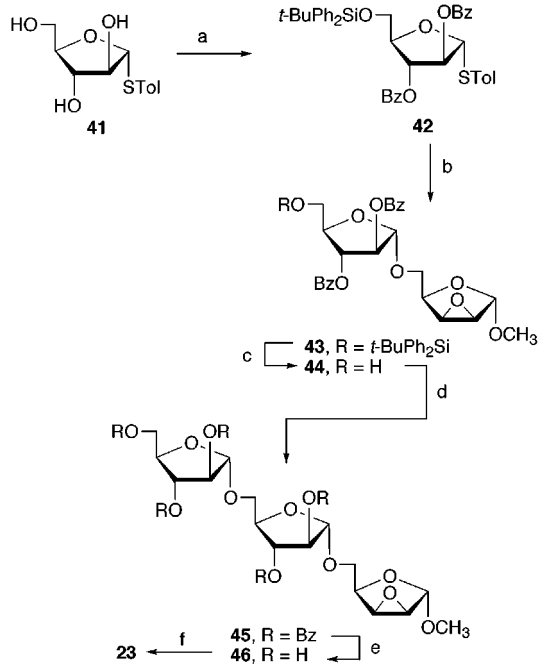


[a] **5**, **28**, **30** or **31**, NIS, AgOTf, CH_2Cl_2, 0 °C, 88% (**32**), 81% (**33**), 89% (**34**), 91% (**35**). [b] $NaOCH_3$, CH_3OH, rt, 97% (**36**), 90% (**37**), 89% (**38**), 88% (**39**). [c] BzOH, Ph_3P, DIAD, THF, 0 °C, 91% (**17**), 83% (**19**), 83% (**25**). [d] $NaOCH_3$, CH_3OH, rt, 73%, two steps from **38**.

97% yield, affording disaccharides **36**−**39**. Each of these was then converted, in 83−91% yield, to the corresponding anhydrosugars **17**, **19**, **25**, and **40** under the Mitsunobu protocol used for the synthesis of **3**. Reaction of **40** with sodium methoxide afforded **21**.

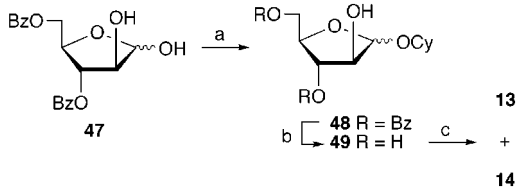
Trisaccharide **23** was prepared as detailed in Scheme 3. The known[19] thioglycoside **41** was converted in two steps and 88% yield to **42**, which was then coupled to **5**, affording disaccharide **43** (84% yield). The silyl group was removed with tetrabutylammonium fluoride to provide

Scheme 3



[a] *t*-$BuPh_2SiCl$, pyridine, 0 °C → rt; then BzCl, pyridine, 0 °C → rt, 88%. [b] **5**, NIS, AgOTf, CH_2CH_2, 0 °C, 84%. [c] *n*-Bu_4NF, THF, 0 °C, 81%. [d] **29**, NIS, AgOTf, CH_2Cl_2, 0 °C, 89%. [e] $NaOCH_3$, CH_3OH, rt, 90%. [f] BzOH, Ph_3P, DIAD, THF, 0 °C, 89%.

Scheme 4



[a] Cyclohexanol, *p*-TsOH, CH_2Cl_2, rt, 84%. [b] $NaOCH_3$, CH_3OH, rt, 93%. [c] BzOH, Ph_3P, DIAD, THF, 0 °C, 46% (**13**), 28% (**14**).

alcohol **44** (81%) which was then glycosylated with **29**. The resulting product, **45**, was debenzoylated to give **46** (80% yield from **44**). Triepoxide **23** was obtained in 89% yield from **46**, upon reaction with triphenylphosphine, DIAD, and benzoic acid.

Monosaccharide **13** was synthesized from the known[20] dibenzoate **47** as illustrated in Scheme 4. Treatment of **47** with cyclohexanol and *p*-toluenesulfonic acid afforded a mixture of cyclohexyl glycosides **48** in 84% yield. Deprotection with sodium methoxide afforded **49** (93% yield) which was subsequently converted to a mixture of **13** and **14** as described above for the other epoxides. Purification by chromatography provided pure **13** (46%) and **14** (28%).

2,3-Anhydro-α-D-ribofuranosides and 2,3-Anhydro-β-D-ribofuranosides. The synthesis of **15** and **16** (Scheme 5) began from the mixture of cyclohexyl glycosides **48**, which was mesylated and then reacted with sodium methoxide to afford epoxides **50** (58%) and **51** (24%). Treatment of each with benzoyl chloride in pyridine provided **15** and **16** in excellent yield.

2,3-Anhydro-β-D-lyxofuranosides. Compounds **4**, **18**, **20**, **22**, **24**, and **26** were obtained by glycosylation of the

(16) Prepared from methyl 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranoside by reaction with *p*-thiocresol and boron trifluoride etherate, see Experimental Section.

(17) Sondheimer, S. J.; Eby, R.; Schuerch, C. *Carbohydr. Res.* **1978**, *60*, 187.

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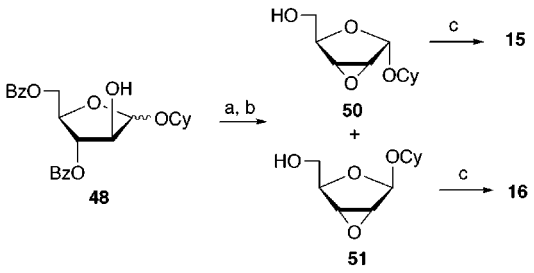
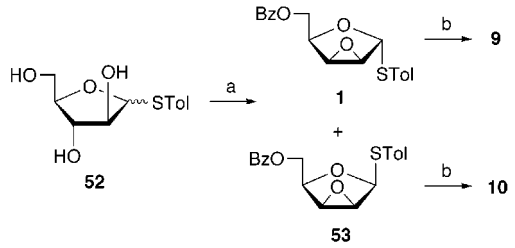
Scheme 5



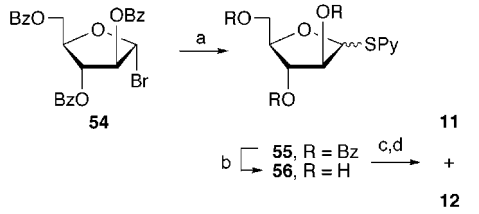
[a] MsCl, Et_3N, CH_2Cl_2, 0 °C. [b]$NaOCH_3$, CH_3OH, rt, 58% (**50**), 24% (**51**). [c]BzCl, pyridine, 0 °C → rt, 92% (**15**), 89% (**16**).

Scheme 6



[a] BzOH, Ph_3P, DIAD, THF, 0 °C, 73% (**1**), 12% (**53**). [b]$NaOCH_3$, CH_3OH, rt, 96% (**9**), 98% (**10**).

Scheme 7



[a] PySH, K_2CO_3, acetone:toluene 1:1, rt, 88%. [b]$NaOCH_3$, CH_3OH, rt, 95%. [c]BzOH, Ph_3P, DIAD, THF, 0 °C. [d]$NaOCH_3$, CH_3OH, rt, 56% (**11**), 25% (**12**) (two steps).

appropriate alcohol with thioglycoside **1** as previously reported.[10,21]

Thioglycosides. The synthesis of **9** and **10** was carried out as illustrated in Scheme 6. An anomeric mixture of thioglycosides **52**[19] was treated with benzoic acid under Mitsunobu conditions to afford an 85% yield of anhydrosugars **1** and **53** which could be easily separated by chromatography. Deprotection with sodium methoxide provided **9** and **10** in 96% and 98% yield, respectively.

Thioglycosides **11** and **12** were prepared as outlined in Scheme 7. Bromide **54**[22] was converted to a 3:1 α:β mixture of 2-pyridyl thioglycosides **55**, which was subsequently deprotected to provide **56** in 84% yield over the two steps. Reacting **56** with benzoic acid, triphenylphosphine, and DIAD, followed by deprotection provided **11** (56%) and **12** (25%).

Measurement of Coupling Constants. $^1J_{C1-H1}$ values in **3**−**26** were measured from the ^1H coupled 1-dimensional ^{13}C NMR spectrum[23] of each compound. The results are detailed in Table 1. In the *O*-glycoside series (**3**−**8**, **13**−**26**), the magnitude of the $^1J_{C1-H1}$ in the α-lyxo and α-*ribo* isomers (where the anomeric hydrogen is trans to the epoxide oxygen), is 163.1−168.0 Hz. In the α-*lyxo* and β-*ribo* isomers (anomeric hydrogen cis to the epoxide oxygen) the size of this coupling constant is larger, 171.5−174.3 Hz. Therefore, the magnitude of the $^1J_{C1-H1}$ can be used to determine the stereochemistry at the anomeric center in 2,3-anhydrofuranosyl *O*-glycosides. The conformational restraints placed on the furanose ring by the epoxide are presumably the reason that this coupling constant is sensitive to anomeric stereochemistry, whereas in conformationally unrestricted furanose rings, there is no such relationship. The parent furanose rings adopt multiple conformations in solution and hence the experimentally measured couplings represent an average of all conformers. In contrast, the epoxide moiety locks the furanose ring into a single conformation (see below). Interestingly, in the *S*-glycoside series there is no significant difference between the two anomers (compare **9** and **10**, and **11** and **12**).

Calculation of C_1-H_1 Bond Lengths in 5−8 and Correlation with $^1J_{C1-H1}$. To probe if the $^1J_{C1-H1}$ magnitude in these 2,3-anhydrosugars is inversely related to the C_1-H_1 bond length, we were interested in determining bond distances for some of the compounds for which we had experimental data. To date, no crystal structure data for any of the compounds listed in Chart 2 have been reported, and furthermore, only a few are crystalline solids. Accordingly, we chose to determine C_1-H_1 bond lengths by computational methods using both ab initio (HF/6-31G*)[12] and DFT (B3LYP/6-31G*)[13] calculations. In these investigations we have focused our attention on methyl glycosides **5**−**8**, and for each monosaccharide, all three possible C_4-C_5 rotamers (gg, gt, and tg, Figure 2) were considered.

All 12 conformers were optimized at both levels of theory described above, and then single point energies with the 6-31+G** basis set were calculated (Table 2). The energies of the HF- and B3LYP-optimized conformers are nearly identical. For **5**, **6**, and **8**, the lowest energy conformer was the one in which the C_4-C_5 bond adopted the tg rotamer. For **7**, the gg rotamer was the lowest energy conformer; however, the tg rotamer was of similar energy. When comparing an α/β pair (e.g., **5** and **6**, or **7** and **8**) the isomer with the methoxy group on the face of the furan ring opposite the epoxide oxygen is 1.5−4.5 kcal/mol more stable than the isomer where these groups are cis. This would be expected given that when the methoxy and epoxide moieties are on the same side of the ring there is increased steric crowding and also repulsion between the lone pair electrons on the oxygens.

The C_1-H_1 bond lengths in **5**−**8** determined from these calculations are shown in Table 3. The trends observed are consistent at both levels of theory; however, the B3LYP/6-31G* bond lengths are slightly (∼1.4%) longer than those calculated at the HF/6-31G* level of theory. This is to be expected given that electron−electron correlation is neglected at the HF level of theory.[12] The difference in bond lengths between the two levels of theory is similar to that previously reported for other furanose rings.[24] It is also interesting to note that for each

(21) Compounds **4** and **14** were also synthesized by subjecting the corresponding β-glycoside triol (e.g., octyl β-D-arabinofuranoside) to the sequence of reactions shown in Scheme 1.

(22) Fletcher, H. G., Jr. *Methods Carbohydr. Chem.* **1963**, *2*, 228.
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Table 1. $^1J_{C1,H1}$ in 2,3-Anhydrofuranosides 3−26[a]

	ring A		ring B		ring C	
compound	H_1-O_{ep} orientation[b]	$^1J_{C1-H1}$[c]	H_1-O_{ep} orientation[b]	$^1J_{C1-H1}$[c]	H_1-O_{ep} orientation[b]	$^1J_{C1-H1}$[c]
3	cis	172.4	−	−	−	−
4	trans	164.1	−	−	−	−
5	cis	172.8	−	−	−	−
6	trans	166.5	−	−	−	−
7	trans	167.8	−	−	−	−
8	cis	173.5	−	−	−	−
9	cis	172.3	−	−	−	−
10	trans	171.5	−	−	−	−
11	cis	166.6	−	−	−	−
12	trans	166.3	−	−	−	−
13	cis	172.5	−	−	−	−
14	trans	163.1	−	−	−	−
15	trans	164.5	−	−	−	−
16	cis	172.5	−	−	−	−
17	cis	172.7	cis	173.8	−	−
18	cis	172.8	trans	165.9	−	−
19	cis	174.0	cis	172.5	−	−
20	cis	172.3	trans	166.3	−	−
21	−	168.4[d]	cis	174.2	−	−
22	−	166.2[d]	trans	166.0	−	−
23	cis	173.2	cis	174.1	cis	173.8
24	cis	173.7	cis	174.3	trans	166.9
25	−	163.7[e]	cis	173.6	−	−
26	−	163.5[e]	trans	168.0	−	−

[a] See Charts 1 and 2 for structures. [b] Relative orientation of anomeric hydrogen (H_1) and the epoxide oxygen (O_{ep}). [c] In Hz. [d] α-Mannopyranosyl residue. [e] α-Glucopyranosyl residue.

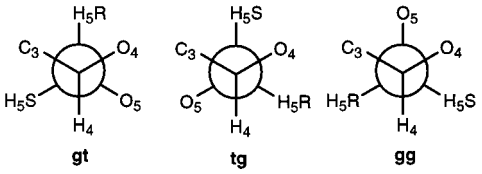

Figure 2. Definition of gauche−gauche (gg), gauche−trans (gt), and trans-gauche (tg) rotamers about the C_4-C_5 bond.

Table 2. Relative Energies of 5−8[a]

compound	B3LYP/6-31+G** //HF/6-31G*	B3LYP/6-31+G** //B3LYP/6-31G*
5-gg	4.5	4.5
5-gt	1.7	1.7
5-tg	0.0	0.0
6-gg	9.0	9.0
6-gt	5.7	5.7
6-tg	3.9	4.0
7-gg	4.5	4.5
7-gt	6.9	6.9
7-tg	4.7	4.7
8-gg	2.9	3.0
8-gt	2.5	2.5
8-tg	0.6	0.6

[a] Bottom of the well energies in kcal/mol at the specified level of theory.

ring system, the C_1-H_1 bond length calculated for the gt and tg rotamers are very similar, if not identical, while that for the gg conformer is significantly different. As is clear from the data in Table 3, for a given anomeric pair of 2,3-anhydrosugar methyl glycosides (e.g., **5** and **6**), the C_1-H_1 bond is longer in the anomer in which H_1 is trans to the epoxide, which is also the isomer that has the smaller $^1J_{C1-H1}$ (Table 1). Thus, there is an inverse relationship between C_{1-H1} bond length and $^1J_{C1-H1}$ in these compounds. In contrast to pyranose systems, the anomer with the longer bond length is not the same in both families of compounds. In the *ribo*-family, the α-isomer has the longest C_1-H_1 bond, whereas in the *lyxo*-series, the C_1-H_1 distance is greater in the β-anomer.

Other Conformational Features of 5−8. The preferred conformation of the five-membered ring in 2,3-anhydrofuranosides has been the topic of some discussion,[11,25] and our calculations shed light on this issue. The epoxide ring in **5**−**8** necessitates that the furan ring can only adopt either the E_O or ^OE conformer. In all four compounds, the preferred conformation is a "boat", that is, the oxygen of the furanose ring is on the same side of the molecule as the epoxide (Figure 3). These structures are consistent with a previous report[26] in which the conformation of 2′,3′-anhydronucleoside derivatives was probed through X-ray crystallography, ^{1}H NMR spectroscopy, and molecular mechanics calculations.

In the case of the *lyxo* isomers, **5** and **6**, the five-membered ring adopts an ^OE conformation, which would be expected to be favorable because the sterically demanding hydroxymethyl group at C_4 is oriented in a pseudoequatorial orientation. On the other hand, the furanoid ring in the *ribo* isomers, **7** and **8**, is in the E_O conformation. In this conformation, the C_4 hydroxymethyl group is placed in a pseudoaxial orientation, which, a priori, would be expected to be unfavorable. However, the furanose ring in **7** and **8** is less highly puckered than in **5** and **6**. It appears, therefore, that in the methyl 2,3-anhydro-*O*-ribofuranosides, the ring flattens appreciably to minimize unfavorable transannular steric interactions involving the hydroxymethyl group at C_4. All four ring systems are appreciably less puckered than conformationally free furanose rings.[27] In addition to the expected flattening induced by the epoxide moiety, electron repulsion between the lone pairs of the furan, glycosidic, and

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Table 3. Calculated C_1-H_1 Bond Lengths and $^1J_{C1,H1}$ in Methyl 2,3-Anhydrofuranosides 5−8

compound[a]	H_1-O_{ep} orientation[b]	level of theory	C_1-H_1 distance[c]	calculated $^1J_{C1,H1}$[d]	experimental[e] $^1J_{C1,H1}$
5-gg	cis	HF/6-31G*	1.0836	173.5	
5-gt	cis	HF/6-31G*	1.0841	171.4	172.8
5-tg	cis	HF/6-31G*	1.0841	171.4	
6-gg	trans	HF/6-31G*	1.0920	142.9	
6-gt	trans	HF/6-31G*	1.0910	146.6	166.5
6-tg	trans	HF/6-31G*	1.0907	147.6	
7-gg	trans	HF/6-31G*	1.0874	158.3	
7-gt	trans	HF/6-31G*	1.0906	147.6	167.8
7-tg	trans	HF/6-31G*	1.0901	149.3	
8-gg	cis	HF/6-31G*	1.0852	167.7	
8-gt	cis	HF/6-31G*	1.0839	172.2	173.5
8-tg	cis	HF/6-31G*	1.0838	172.5	
5-gg	cis	B3LYP/6-31G*	1.0989	116.1	
5-gt	cis	B3LYP/6-31G*	1.0994	114.2	172.8
5-tg	cis	B3LYP/6-31G*	1.0994	114.2	
6-gg	trans	B3LYP/6-31G*	1.1082	84.7	
6-gt	trans	B3LYP/6-31G*	1.1070	88.8	166.5
6-tg	trans	B3LYP/6-31G*	1.1065	90.4	
7-gg	trans	B3LYP/6-31G*	1.1038	99.9	
7-gt	trans	B3LYP/6-31G*	1.1061	91.5	167.8
7-tg	trans	B3LYP/6-31G*	1.1055	93.4	
8-gg	cis	B3LYP/6-31G*	1.1007	110.0	
8-gt	cis	B3LYP/6-31G*	1.0991	114.9	173.5
8-tg	cis	B3LYP/6-31G*	1.0989	115.6	

[a] See Figure 2 for definitions of the gg, gt, and tg rotamers about the C_4-C_5 bond. [b] Relative orientation of anomeric hydrogen (H_1) and the epoxide. [c] In angstroms. [d] In hertz, coupling constants calculated using eq 1. [e] From Table 1.

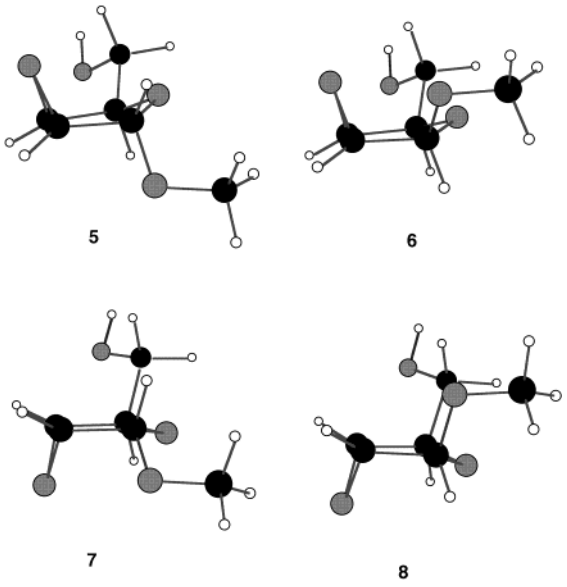

Figure 3. Representative examples of HF/6-31G* optimized conformers of **5**−**8**; note the relatively flat furan ring.

epoxide oxygens would also be expected to further force the ring into a more planar conformation. The pseudorotational phase angles and puckering amplitudes for all of the conformers listed in Table 3 can be found in the Supporting Information (Table S1).

Prediction of $^1J_{C1-H1}$ Magnitudes by an Empirical Relationship. Armed with the bond length data presented in Table 3, we next explored how well the $^1J_{C1-H1}$ magnitudes could be predicted using a previously reported[5] relationship (eq 1) that correlates $^1J_{C1-H1}$ with C_1-H_1 bond length (r, in Å) and the atomic charge on the carbon and hydrogen atoms, q_C and q_H, respectively. In the original report,[5] the bond lengths were determined by HF/6-31G* optimization of model compounds, and the atomic charges were obtained by Mulliken population analysis.[28] The use of model compounds was necessary given that the computational resources available at the time made such calculations on monosaccharides a formidable challenge.

$$^1J_{C1-H1} = -3432 + 182.2q_Cq_H + 3889/r \qquad (1)$$

Using eq 1, we have calculated $^1J_{C1-H1}$ for all three possible C_4-C_5 rotamers of **5**−**8** (Table 3).[29] The most noticeable observation is that when the B3LYP/6-31G* bond lengths are used, the coupling constants are dramatically underestimated. This is to be expected because eq 1 was developed by correlating experimental $^1J_{C,H}$ data with bond lengths calculated by the HF/6-31G* method. Accordingly, when the "longer" B3LYP/6-31G* bond distances are used, it would be expected that the J values would be underestimated.

When the HF/6-31G* bond lengths are used, better agreement between the calculated (Table 3) and experimental (Table 1) coupling constant magnitudes is seen. In particular, for those isomers in which the anomeric hydrogen is cis to the epoxide (**5** and **8**) the agreement is excellent. For example, in **5**, the experimental value is 172.8 Hz, whereas the calculated values are 171.4 or 173.4 Hz, depending upon the C_4-C_5 rotamer. Although the correlation between calculated and experimental J values for **5** and **8** is excellent, for **6** and **7**, there is a 10−20 Hz discrepancy. In an effort to improve the accuracy of these predictions, we also carried out a series of calculations in which atomic charges measured from NBO analysis[30] were used in place of those from the Mulliken population analysis. This resulted in only

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(28) (a) Mulliken, R. S. *J. Chem. Phys.* **1955**, *23*, 1833. (b) Mulliken, R. S. *J. Chem. Phys.* **1955**, *23*, 1841. (c) Mulliken, R. S. *J. Chem. Phys.* **1955**, *23*, 2338. (d) Mulliken, R. S. *J. Chem. Phys.* **1955**, *23*, 2343.

(29) The required bond lengths were taken from the optimized geometries of **5**−**8** at both levels of theory. Atomic charges were determined by Mulliken population analysis.

Table 4. Calculated C_1-H_1 Bond Lengths and $^1J_{C1,H1}$ in Methyl Pyranosides 58−65

compound[a]	C_1-H_1 distance[b]	calculated $^1J_{C1,H1}$[c]	experimental[d] $^1J_{C1,H1}$
58	1.0869	158.7	170
59	1.0923	141.5	158
60	1.0915	144.1	161
61	1.0866	159.7	179
62-gg	1.0868	159.4	
62-gt	1.0873	157.6	170
62-tg	1.0869	159.2	
63-gg	1.0927	140.0	
63-gt	1.0917	143.8	159
63-tg	1.0921	141.5	
64-gg	1.0866	160.0	
64-gt	1.0868	159.3	170
64-tg	1.0869	159.2	
65-gg	1.0920	142.3	
65-gt	1.0915	144.5	159[e]
65-tg	1.0911	144.7	

[a] See Figure 2 for definitions of the gg, gt, and tg rotamers about the C_4-C_5 bond. [b] In angstroms; measured from HF/6-31G* optimized geometries. [c] In hertz, calculated using eq 1. [d] From ref 2. [e] Value taken from ref 31.

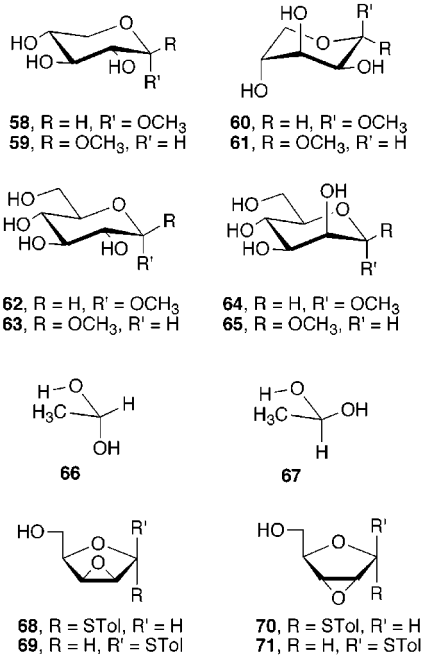
marginal improvement (see Table S2 in the Supporting Information).

We were curious as to whether this discrepancy between the predicted and experimentally measured coupling constants was unique to these rings systems. Consequently, bond lengths obtained from the HF/6-31G* optimization of methyl pyranosides **58**−**65** were used in conjunction with eq 1 to predict $^1J_{C1-H1}$ magnitudes in these glycosides. The results of these calculations are shown in Table 4, together with the experimentally measured couplings.[2,31] From these data it is clear that for **58**−**65** (and likely other pyranose glycosides) that eq 1 underestimates the $^1J_{C1-H1}$ magnitudes by approximately 10−20 Hz relative to the experimental values.

In the initial report describing eq 1, two different conformers of acetaldehyde hydrate, **66** and **67**, were used as model compounds for an α- and *β*-glycoside, respectively. The calculated C−H bond lengths were 1.0837 Å (**66**) and 1.08906 Å (**67**), which are shorter than those determined for **58**−**65** (Table 4). In light of this information, it is not surprising that this equation underestimates these $^1J_{C1-H1}$ magnitudes. It can also be concluded that (1) the underestimation of these couplings for **6** and **7** is not unique to these anhydrosugars; (2) the good correlation between the calculated and experimental values observed for **5** and **8** is fortuitous; and (3) eq 1 should be updated through the calculation of C_1-H_1 bond lengths in a range of carbohydrate derivatives.

Relationship between $^1J_{C1-H1}$ and C_1-H_1 Bond Length in Thioglycosides. As mentioned above, the magnitude of $^1J_{C1-H1}$ in thioglycosides **9**−**12** is not sensitive to the stereochemistry at the anomeric center. This prompted us to determine the C_1-H_1 bond lengths in **68**−**71** (Chart 3) at the B3LYP/6-31G* level of theory. These calculations demonstrated that the trend observed in **5**−**8**, i.e., that the C_1-H_1 bond was longer in the *β-lyxo* and α-*ribo* isomers, was also present in these thioglycosides (see Supporting Information, Table S3). However,

Chart 3



the difference is smaller, 0.0045−0.006 Å in the *O*-glycosides vs 0.0055−0.008 Å in the *S*-glycosides. The lack of correlation between C_1-H_1 bond length and $^1J_{C1-H1}$ in these thioglycosides is consistent with previous studies[8,9] on 1,2-oxathiane (**72**, Figure 4). In **72**, the C_2-H_{2ax} bond is longer than the C_2-H_{2eq} bond, but $^1J_{C2-H2eq} = {}^1J_{C2-H2zx}$. As in the case of the sulfur-containing heterocycles studied to date (1,3-oxathiane, 1,2-dithiane), it appears that in thioglycosides **9**−**12**, the factors that influence one bond C−H coupling constants is an interplay of a number of factors including, but not limited to the C−H bond length (e.g, orbital hybridization, atom electronegativities.)

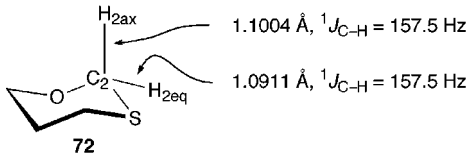


Figure 4. C_2-H_{2ax} and C_2-H_{2eq} bond lengths and the associated $^1J_{C-H}$ in 1,3-oxathiane. B3LYP/6-31+G** bond lengths were taken from ref 9 and $^1J_{C-H}$ from ref 8.

Conclusions

In conclusion we have shown that the $^1J_{C1-H1}$ in 2,3-anhydro-*O*-furanosides is sensitive to the stereochemistry at the anomeric center and that the magnitude of the coupling constant is inversely related to the C_1-H_1 bond length. We have also shown that a previously reported equation (eq 1) relating C_1-H_1 bond length to $^1J_{C1-H1}$ magnitudes underestimates these coupling in many cases. Circumventing this problem requires that this relationship be reparametrized, and such investigations are currently in progress.

Experimental Section

General. Solvents were distilled from the appropriate drying agents before use. Unless stated otherwise, all reactions were carried out under a positive pressure of argon and were

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(31) Podlasek, C. A.; Wu, J.; Stripe, W. A.; Bondo, P. B.; Serianni, A. S. *J. Am. Chem. Soc.* **1995**, *117*, 8625.

monitored by TLC on silica gel 60 F_{254} (0.25 mm, E. Merck). Spots were detected under UV light or by charring with 10% H_2SO_4 in ethanol. Solvents were evaporated under reduced pressure and below 40 °C (bath). Organic solutions of crude products were dried over anhydrous Na_2SO_4. Column chromatography was performed on silica gel 60 (40−60 μM). The ratio between silica gel and crude product ranged from 100 to 50:1 (w/w). Optical rotations were measured at 21 ± 2 °C. Melting points are uncorrected. ^{1}H NMR spectra were recorded at 400 or 500 MHz, and chemical shifts are referenced to either TMS (0.0, $CDCl_3$), CD_3OD (3.31, CD_3OD), or external dioxane (3.75, D_2O). ^{13}C NMR spectra were recorded at 100 or 125 MHz, and ^{13}C chemical shifts are referenced to $CDCl_3$ (77.00, $CDCl_3$), CD_3OD (49.15, CD_3OD), or external dioxane (68.11, D_2O). Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA. Electrospray mass spectra were recorded on samples suspended in THF or CH_3OH. Physical data (^{1}H NMR, ^{13}C NMR, MS, optical rotation, and elemental analysis) for all new compounds is included in the Supporting Information.

***n*-Octyl 2,3-Anhydro-5-*O*-benzoyl-α-D-lyxofuranoside (3).** To a solution of **27**[15] (1.0 g, 3.8 mmol), triphenylphosphine (2.5 g, 9.5 mmol), and benzoic acid (0.7 g, 5.7 mmol) in THF was added DIAD (1.9 mL, 9.5 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature for 30 min. The solution was concentrated to an oil which was purified by column chromatography (hexanes/EtOAc, 6:1) to yield **3** as a colorless oil (1.08 g, 82%).

***n*-Octyl 2,3-Anhydro-α-D-lyxofuranoside (28).** To a solution of **3** (1.08 g, 3.1 mmol) in CH_3OH (25 mL) was added 0.1 M $NaOCH_3$ in CH_3OH (3 mL). After stirring for 4 h at room temperature, the reaction mixture was neutralized with prewashed Amberlite IR-120 H^+ resin, filtered, and concentrated. The resulting syrup was chromatographed (hexanes/EtOAc, 2:1) to obtain **28** (0.68 g, 91%) as a colorless liquid.

***p*-Tolyl 2,3,5-Tri-*O*-benzoyl-1-thio-α-D-arabinofuranoside (29).** To a solution of methyl 2,3,5 tri-*O*-benzoyl-α-D-arabinofuranoside[22] (10 g, 21.0 mmol) in CH_2Cl_2 (50 mL) was added $BF_3{\cdot}Et_2O$ (7.9 mL, 63.0 mmol) at 0 °C under an argon atmosphere. The solution was allowed to stir for 10 min, and then *p*-thiocresol (2.60 g, 21.0 mmol) was added. The reaction mixture was stirred for 5 h, diluted with CH_2Cl_2, and then poured into a cold saturated $NaHCO_3$ solution. The layers were separated, and organic layer was washed successively with a saturated $NaHCO_3$ solution and water and then dried and concentrated. Upon addition of methanol to the resulting oil, the product crystallized. Recrystallization from methanol gave **29** (9.6 g, 81%) as a white solid.

Synthesis of 32−35. All alcohols and donors were predried under vacuum in the presence of P_2O_5 for 4 h prior to use. To a solution of the alcohol (**5**,[14] **28**, **30**,[17] **31**[18]) (0.8 mmol) and donor **29**[16] (1.0 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added powdered 4 Å molecular sieves (0.5 g). The reaction mixture was stirred for 20 min at 0 °C, and then *N*-iodosuccinimide (1.0 mmol) and silver triflate (0.25 mmol) were added. After stirring for 30 min, triethylamine was added. The reaction mixture was diluted with CH_2Cl_2 and filtered through Celite. The filtrate was washed with a saturated solution of sodium thiosulfate, water, and brine. The organic layer was subsequently dried, filtered, and concentrated. The resulting crude oil was purified by chromatography to give disaccharides **32**−**35**.

Methyl 5-*O*-(2,3,5-Tri-*O*-benzoyl-α-D-arabinofuranosyl)-2,3-anhydro-α-D-lyxofuranoside (32). Chromatography (hexanes/EtOAc, 5:1) provided **32** (1.79 g, 88%) as a colorless syrup.

***n*-Octyl 5-*O*-(2,3,5-Tri-*O*-benzoyl-α-D-arabinofuranosyl)-2,3-anhydro-α-D-lyxofuranoside (33).** Chromatography (hexanes/EtOAc, 6:1) provided **33** (1.19 g, 81%) as a colorless syrup.

Methyl 6-*O*-(2,3,5-Tri-*O*-benzoyl-α-D-arabinofuranosyl)-2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (34). Chromatography (hexanes/EtOAc, 5:1) provided **34** (1.35 g, 89%) as a colorless syrup.

Methyl 3-*O*-(2,3,5-Tri-*O*-benzoyl-α-D-arabinofuranosyl)-4,6-*O*-benzylidene-3-*O*-benzyl-α-D-glucopyranoside (35). Chromatography (hexanes/EtOAc, 4:1) provided **35** (1.21 g, 91%) as a white solid.

Synthesis of 36−39. A solution of the each disaccharide **32**−**35** (0.6 mmol) in CH_2Cl_2 (10 mL) and CH_3OH (10 mL) was treated with a catalytic amount of 1 M $NaOCH_3$ in CH_3OH (2 mL) solution at room temperature. After stirring for 6 h the reaction mixture was neutralized with dry ice and concentrated. The crude product was purified by chromatography to yield compounds **36**−**39**.

Methyl 5-*O*-(α-D-Arabinofuranosyl)-2,3-anhydro-α-D-lyxofuranoside (36). Chromatography ($CHCl_3$:CH_3OH, 10:1) provided **36** (686 mg, 97%) as a colorless syrup.

***n*-Octyl 5-*O*-(α-D-Arabinofuranosyl)-2,3-anhydro-α-D-lyxofuranoside (37).** Chromatography (hexanes/EtOAc, 1:1) provided **37** (492 mg, 90%) as a colorless syrup.

Methyl 6-*O*-(α-D-Arabinofuranosyl)-2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (38). Chromatography (hexanes/EtOAc, 1:1) provided **38** (771 mg, 89%) as a colorless syrup.

Methyl 3-*O*-(α-D-Arabinofuranosyl)-4,6-*O*-benzylidene-2-*O*-benzyl-α-D-glucopyranoside (39). Chromatography ($CHCl_3$/CH_3OH, 15:1) provided **39** (541 mg, 88%) as a white solid.

Synthesis of 17, 19, 21, and 25. Each disaccharide **36**−**39** (0.4 mmol), triphenylphosphine (1.0 mmol), and benzoic acid (0.6 mmol) was dissolved in THF (20 mL), and the solution was cooled to 0 °C. DIAD (1.0 mmol) was added dropwise to the solution over a 10 min period, and the reaction was then stirred for an additional 1 h while allowing to warm to room temperature. The solution was then concentrated, and the residue was purified by chromatography to give the products in 73−91% yield.

Methyl 5-*O*-(2,3-Anhydro-5-*O*-benzoyl-α-D-lyxofuranosyl)-2,3-anhydro-α-D-lyxofuranoside (17). Chromatography (hexanes/EtOAc, 7:1) provided **17** (771 mg, 91%) as a white solid.

***n*-Octyl 5-*O*-(2,3-Anhydro-5-*O*-benzoyl-α-D-lyxofuranosyl)-2,3-anhydro-α-D-lyxofuranoside (19).** Chromatography (hexanes/EtOAc, 5:1) provided **19** (412 mg, 83%) as a white solid.

Methyl 6-*O*-(2,3-Anhydro-α-D-lyxofuranosyl)-2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (21). It was impossible to completely purify **40** due to the presence of DIAD-based impurities which were inseparable by chromatography. Therefore, the crude product obtained after an initial chromatographic purification (hexanes/EtOAc, 4:1) was deprotected with 0.1 M $NaOCH_3$ in CH_3OH as described for the synthesis of **36**. Chromatography (hexanes/EtOAc, 6:1) yielded **21** (585 mg, 73%) as a clear syrup.

Methyl 3-*O*-(2,3-Anhydro-α-D-lyxofuranosyl)-4,6-*O*-benzylidene-3-*O*-benzyl-α-D-glucopyranoside (25). Chromatography (hexanes/EtOAc, 6:1) afforded **25** (391 mg, 83%) as a white solid.

***p*-Cresyl 5-*O*-*tert*-Butyldiphenylsilyl-2,3-di-*O*-benzoyl-1-thio-α-D-arabinofuranoside (42).** To a stirred solution of **41**[19] (1.05 g, 4.1 mmol) in pyridine (10 mL) was added tertbutylchlorodiphenylsilane (1.35 g, 4.9 mmol) at 0 °C. The reaction mixture was allowed to stir for 5 h while warming to room temperature. The solution was recooled to 0 °C, and benzoyl chloride (1.2 mL, 10.2 mmol) was added. The reaction mixture was allowed to stir overnight while warming to room temperature, and then CH_3OH was added. The mixture was diluted with CH_2Cl_2 and washed successively with a saturated solution of $NaHCO_3$ and water. The organic layer was dried and concentrated, and the resulting residue was purified by chromatography (hexanes/EtOAc, 8:1) to give **42** (2.52 g, 88%) as a colorless syrup.

Methyl 5-*O*-[5-*O*-*tert*-Butyldiphenylsilyl-2,3-di-*O*-benzoyl-α-D-arabinofuranosyl]-2,3-anhydro-α-D-lyxofuranoside (43). To a solution of alcohol **5**[14] (0.70 g, 4.8 mmol) and donor **42** (3.36 g, 4.8 mmol) in CH_2Cl_2 (30 mL) was added powdered 4 Å molecular sieves (1.0 g). The reaction mixture was stirred for 20 min at 0 °C, and then *N*-iodosuccinimide (1.07 g, 4.80 mmol) and silver triflate (0.38 g, 1.4 mmol) were added. After 15 min, triethylamine was added. The reaction mixture was diluted with CH_2Cl_2 and filtered through Celite.

The filtrate was concentrated, and the resulting syrup was chromatographed (hexanes/EtOAc, 8:1) to give **43** (2.91 g, 84%) as a colorless syrup.

Methyl 5-*O*-[2,3-Di-*O*-benzoyl-α-D-arabinofuranosyl]-2,3-anhydro-α-D-lyxofuranoside (44). To a solution of disaccharide **43** (2.85 g, 3.9 mmol) in THF (30 mL) was added TBAF (1.13 g, 4.3 mmol) at 0 °C under argon atmosphere. The reaction mixture was allowed to stir for 1 h and then concentrated to a syrup which was purified by chromatography (hexanes/EtOAc, 4:1) providing **44** (1.55 g, 81%) as a clear syrup.

Methyl 5-*O*-[5-*O*-(2,3,5-Tri-*O*-benzoyl-α-D-arabinofuranosyl)-2,3-di-*O*-benzoyl-α-D-arabinofuranosyl]-2,3-anhydro-α-D-lyxofuranoside (45). Reaction of alcohol **44** (1.5 g, 3.0 mmol) and donor **29** (2.27 g, 4.0 mmol) as described for the synthesis of **32**, followed by chromatography (hexanes/EtOAc, 4:1) provided **45** (2.56 g, 89%) as a white solid.

Methyl 5-*O*-[5-*O*-(α-D-Arabinofuranosyl)-α-D-arabinofuranosyl]-2,3-anhydro-α-D-lyxofuranoside (46). Trisaccharide **46** was prepared from **45** (2.5 g, 2.68 mmol) as described for the preparation of **36**. Chromatography ($CHCl_3$/CH_3OH, 10:1) provided **46** (990 mg, 90%) as a colorless syrup.

Methyl 5-*O*-[5-*O*-(2,3-Anhydro-5-*O*-benzoyl-α-D-lyxofuranosyl)-2,3-anhydro-α-D-lyxofuranosyl)-2,3-anhydro-α-D-lyxofuranoside (23). Trisaccharide **23** was synthesized from **46** (700 mg, 1.7 mmol) as described for the preparation of **17**. Chromatography (hexanes/EtOAc, 3:1) afforded **23** (720 mg, 89%) as a white solid.

Cyclohexyl 3,5-Di-*O*-benzoyl-α/*β*-D-arabinofuranoside (48). To a solution of diol **47**[20] (1.0 g, 2.8 mmol) and cyclohexanol (1.1 g, 12 mmol) in CH_2Cl_2 (20 mL) was added *p*-TsOH (50 mg, 0.23 mmol). After stirring for 6 h, the solution was diluted with CH_2Cl_2 (30 mL), washed with saturated $NaHCO_3$ solution and water, and dried. The solution was filtered and concentrated to an oil which was purified by chromatography (hexanes/EtOAc, 3:1) to yield **48** (1.02 g, 84%) as a white solid.

Cyclohexyl α/*β*-D-Arabinofuranoside (49). To a solution of **48** (1.0 g, 2.27 mmol) in CH_3OH (20 mL) was added 0.1 M $NaOCH_3$ in CH_3OH (0.5 mL). After stirring for 6 h at room temperature, the reaction mixture was neutralized with Amberlite IR-120 H^+ resin, filtered, and concentrated. The residue was purified by chromatography (10:1, $CHCl_3$, CH_3OH) to give **49** (484 mg, 93%) as a colorless syrup.

Cyclohexyl 2,3-Anhydro-5-*O*-benzoyl-α-D-lyxofuranoside (13) and Cyclohexyl 2,3-Anhydro-5-*O*-benzoyl-*β*-D-lyxofuranoside (14). Epoxides **13** and **14** was synthesized from **49** (468 mg, 2.0 mmol) as described for the preparation of **17**. Chromatography (hexanes/EtOAc, 8:1 → hexanes/EtOAc, 6:1) provided **13** (280 mg, 46%) and **14** (180 mg, 28%) as white crystalline solids.

Cyclohexyl 2,3-Anhydro-α-D-ribofuranoside (50) and Cyclohexyl 2,3-Anhydro-*β*-D-ribofuranoside (51). To a solution of **48** (1.20 g, 2.7 mmol) in CH_2Cl_2 (25 mL) and triethylamine (1.51 mL, 11 mmol) at 0 °C was added methanesulfonyl chloride (0.32 mL, 2.9 mmol). The reaction mixture was stirred for 30 min and then cold water added. The reaction mixture was diluted with CH_2Cl_2, and the organic layer was washed with a saturated solution of $NaHCO_3$ and then water. After drying the organic layer was filtered and concentrated to a syrup. The resulting residue was redissolved in CH_3OH, and 1 M $NaOCH_3$ in CH_3OH (2 mL) was added. The solution was stirred overnight, neutralized with Amberlite IR-120 H^+ resin, filtered, and concentrated. The residue was purified by column chromatography (hexanes/EtOAc, 5:1) to give **50** (311 mg, 58%) as a white solid and **51** (132 mg, 24%) as a colorless syrup.

Cyclohexyl 2,3-Anhydro-5-*O*-benzoyl-α-D-ribofuranoside (15). To a solution of **50** (250 mg, 1.2 mmol) in pyridine (2 mL) at 0 °C was added benzoyl chloride (0.2 mL, 1.8 mmol) dropwise, and the reaction mixture was stirred for 30 min at room temperature. The reaction was then diluted with CH_2Cl_2 and then washed with chilled 5% HCl, a saturated solution of $NaHCO_3$, and water. The organic layer was dried, filtered, and concentrated. Chromatography (hexanes/EtOAc, 6:1) provided **15** (342 mg, 92%) as a white solid.

Cyclohexyl 2,3-Anhydro-5-*O*-benzoyl-*β*-D-ribofuranoside (16). Benzoate **16** was synthesized from **51** (100 mg, 0.46 mmol) as described for the preparation of **15**. Chromatography (hexanes/EtOAc, 6:1) provided **16** (132 mg, 89%) as a clear syrup.

***p*-Tolyl 2,3-Anhydro-5-*O*-benzoyl-1-thio-α-D-lyxofuranoside (1) and *p*-Tolyl 2,3-Anhydro-5-*O*-benzoyl-1-thio-*β*-D-lyxofuranoside (53).** Compound **52**[19] (2.0 g, 7.81 mmol), triphenylphosphine (5.2 g, 19.8 mmol), and benzoic acid (1.42 g, 11.6 mmol) were dissolved in THF (50 mL), and the solution was cooled to 0 °C. DIAD (3.86 mL, 19.5 mmol) was added dropwise over 10 min. After complete addition, the reaction mixture was allowed to warm to room temperature and was stirred for 45 min. The solution was subsequently evaporated to yield an which, upon trituration with cold diethyl ether, precipitated triphenylphosphine oxide. The solid was filtered off, and the filtrate was concentrated to an oil which was purified by chromatography (hexanes/EtOAc, 5:1), providing **1** (1.95 g, 73%) and **53** (310 mg, 12%) as white crystalline solids.

***p*-Tolyl 2,3-Anhydro-1-thio-α-D-lyxofuranoside (9).** To a solution of **1** (1.0 g, 2.92 mmol) in CH_3OH (20 mL) and CH_2Cl_2 (5 mL) was added 0.1 M $NaOCH_3$ in CH_3OH (4 mL). After stirring for 8 h at room temperature, the reaction mixture was neutralized with Amberlite IR-120 H^+ resin, filtered, and concentrated to an oil which was purified by chromatography (hexanes/EtOAc, 2:1) to yield **9** (670 mg, 96%) as a white solid.

***p*-Tolyl 2,3-Anhydro-1-thio-*β*-D-lyxofuranoside (10).** Thioglycoside **10** was synthesized from **53** (300 mg, 0.88 mmol) as described for the preparation of **9**. Chromatography (hexanes/EtOAc, 2:1) provided **10** (204 mg, 98%) as a colorless syrup.

2-Pyridyl 2,3,5-Tri-*O*-benzoyl-1-thio-α/*β*-D-arabinofuranoside (55). To a mixture of 2-mercaptopyridine (1.29 g, 11.7 mmol) and potassium carbonate (2.01 g, 14.6 mmol) in acetone (30 mL) was added **54**[22] (5.11 g, 9.75 mmol) in toluene (30 mL). The reaction mixture was stirred overnight. The resulting salts were filtered through Celite, and the filtrate was concentrated. Chromatography (hexanes/EtOAc, 4:1) afforded **55** (4.74 g, 88%) as a white foam.

2-Pyridyl 1-Thio-α/*β*-D-arabinofuranoside (56). To a solution of **55** (4.32 g, 8.3 mmol) in CH_3OH (40 mL) and CH_2Cl_2 (20 mL) was added 0.1 M $NaOCH_3$ in CH_3OH (4 mL). After stirring for 6 h at room temperature, the reaction mixture was neutralized with Amberlite IR-120 H^+ resin, filtered, and concentrated. The residue was purified by column chromatography ($CHCl_3$/CH_3OH, 10:1) to give **56** (1.91 g, 95%) as a colorless syrup.

2-Pyridyl 2,3-Anhydro-1-thio-α-D-lyxofuranoside (11) and 2-Pyridyl 2,3-Anhydro-1-thio-*β*-D-lyxofuranoside (12). Compound **56** (1.5 g, 6.7 mmol), triphenylphosphine (4.0 g, 15.4 mmol), and benzoic acid (1.12 g, 9.2 mmol) were dissolved in THF (50 mL), and the solution was cooled to 0 °C. DIAD (3.86 mL, 19.5 mmol) was added dropwise over 10 min. After complete addition, the reaction mixture was allowed to warm to room temperature and was stirred for 45 min. The solution was subsequently evaporated to yield a crude oil which, upon trituration with cold diethyl ether, precipitated triphenylphosphine oxide. The solid was filtered off, and the filtrate was concentrated. The resulting oil was dissolved in CH_3OH (40 mL) and dichloromethane (20 mL), and then 0.1 M $NaOCH_3$ in CH_3OH (4 mL) was added. After stirring for 6 h at room temperature, the reaction mixture was neutralized with Amberlite IR-120 H^+ resin, filtered, and concentrated. The residue was purified by chromatography (EtOAc/hexanes, 2:1) to give **11** (770 mg, 56%) and **12** (350 mg, 25%) as colorless syrups.

Measurement of $^1J_{C1-H1}$. The $^1J_{C1-H1}$ were measured from the ^{1}H-coupled ^{13}C NMR spectra[23] of **3**−**26**, that were recorded at 125 MHz on samples dissolved in $CDCl_3$.

Computational Investigations. Ab initio molecular orbital and DFT calculations were conducted using Gaussian

98.[32] For each of compounds **5**−**8**, all three possible staggered C_4-C_5 rotamers (Figure 2) were considered: gauche−gauche (gg), gauche−trans (gt), or trans-gauche (tg). Optimizations were carried out using both Hartree−Fock (HF)[12] and density functional theory (B3LYP)[13] calculations with the 6-31G* basis set. In all optimizations, the orientation about the C_1-O_1 bond was initially chosen to maximize the *exo*-anomeric effect[33] (the methyl group was placed trans to the C_1-C_2 bond). The orientation about the C_5-O_5 bond was initially set with the hydrogen of the hydroxyl group oriented trans to the C_4-C_5 bond. During the optimizations, no significant changes were seen in the orientations about these two bonds, or about the C_4-C_5 bond. In all calculations, the initial furan ring geometry was ^{O}E. For the conformers of **7** and **8**, this ring minimized to E_O, but for **5** and **6** it remained ^{O}E. To ensure that the ^{O}E conformer was not a local minima for **5** and **6**, we also began these calculations with furan ring in the E_O conformation; however, upon optimization, these conformers minimized to ^{O}E. An identical approach was used in the optimization of thioglycosides **68**−**71**. The Cartesian coordinates for the optimized conformers are given in the Supporting Information. Single-point energy calculations were carried out at the B3LYP level of theory with the 6-31+G** basis set; these energies can be found in the Supporting Information. Atomic charges were determined by Mulliken population[28] and NBO[30] analysis.

Acknowledgment. This work was supported by the National Institutes of Health (AI44045), the National Science Foundation (CHE-9875163), and the OSU Spectroscopy Institute. We also acknowledge support from the Ohio Supercomputer Center where some of the calculations were performed. We thank Justin B. Houseknecht for technical assistance and Dr. Christopher M. Hadad (The Ohio State University) for help with the computational work and for helpful discussions.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for **3**, **4**, and **9**−**26**. Characterization data for all new compounds. Cartesian coordinates, pseudorotational phase angles and puckering amplitudes for the HF/6-31G* and B3LYP/6-31G*-optimized geometries of **5**−**8**, tables of relevant structural parameters in **5**−**8** and **68**−**71**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO001747A

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