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Study of the Endocyclic versus Exocyclic C−O Bond Cleavage Pathways of α- and β-Methyl Furanosides

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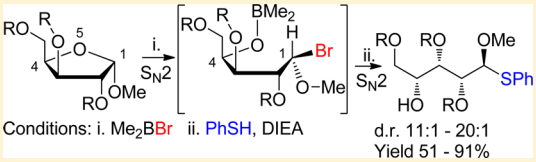
Supporting Information

ABSTRACT: The activation and ring-opening of methyl furanosides in the four natural sugar scaffolds (ribo, lyxo, arabino, and xylo) efficiently afforded acyclic thioacetals with high S_N2-like selectivity at the acetal center in the presence of Me_2BBr and thiophenol. The stereochemical outcome of these reactions provides important mechanistic insights into the activation pathway of five-membered semicyclic acetals. The thioacetal products should find applications in oligosaccharides synthesis and allow further development of acyclic strategies for the synthesis of novel nucleoside analogues.



INTRODUCTION

Carbohydrates are key structural elements of numerous biological molecules essential for life. Ribose or deoxyribose five-membered ring sugars constitute, for example, the backbones of DNA and RNA. The carbohydrate portion (glycans) of glycoproteins and lipoproteins is also crucial for a multitude of biological processes including cell-to-cell recognition, molecular trafficking, endocytosis, and signal transduction.[1] These features make them interesting targets for drugs against cancers and viral proliferation. The chemistry of carbohydrates has been developed and studied extensively, yet there is still an open question concerning the mechanism through which certain enzymatic or chemical reactions proceeds at the anomeric center.[2] This controversy originates from the unsymmetrical nature of the semicyclic acetal functionality of carbohydrates that allows for two plausible reaction pathways, namely the exocyclic and the endocyclic pathways (Figure 1).[3] The hydrolysis of glycosides would proceed through exocyclic C1−O1 bond cleavage after activation of the O1 oxygen group to form a cyclic oxocarbenium **A** (pathway A), whereas activation of the O5 oxygen would result in an endocyclic C1−O5 bond cleavage to generate acyclic oxocarbenium **B** (pathway B). Stereoelectronic assistance of antiperiplanar lone pair of electrons is proposed to facilitate both C−O bond cleavage modes.[4] Nucleophilic attack of a water molecule on the oxocarbenium intermediates leads, respectively, to the formation of cyclic and acyclic hemiacetals. The latter can cyclize back to the starting glycoside with probable anomerization. Alternatively, the loss of methanol could lead to the cyclic hemiacetal (lactol). As described herein, other nucleophiles allow trapping of the products from these two distinct pathways.

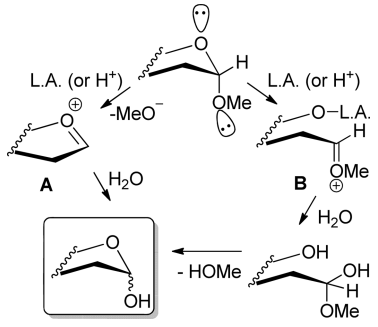


Figure 1. Exocyclic (A) versus endocyclic cleavage (B) pathways.

The preferred pathway for a given transformation at a semicyclic acetal center is not trivial to determine (Figure 1). The exocyclic cleavage is by far the most invoked reaction pathway and is supported by numerous kinetic studies,[4a,5] but experimental and computational studies performed on pyranosides and related compounds confirmed that the endocyclic cleavage pathway exists and cannot be ruled out.[5,6] Recently, evidence from bicyclic tetrahydropyranyl acetal hydrolysis reaction showed that, although the exocyclic pathway would be energetically favored over the endocyclic pathway for α-anomers, both pathways would compete for the hydrolysis of β-anomers.[2b] Other recent studies indicate that anomerization of α and β glycosides bearing a 2,3-cyclic protecting group proceeds by the endocyclic mechanism and that release of inner ring strain would promote this reaction pathway.[2a,7]

Furanosides have received much less attention than pyranosides regarding the endocyclic versus exocyclic question. Nevertheless, interesting kinetic studies performed on five-membered ring sugars indicated that they undergo hydrolysis with negative entropy of activation,[8] in clear contrast with the

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positive values found for pyranosides.[9] A first proposed mechanism that accounts for these activation parameters involves a bimolecular displacement of the protonated C1-methoxy group by water concerted with the cleavage of the exocyclic C−O bond (**C**, Figure 2).[8] Alternatively, the addition

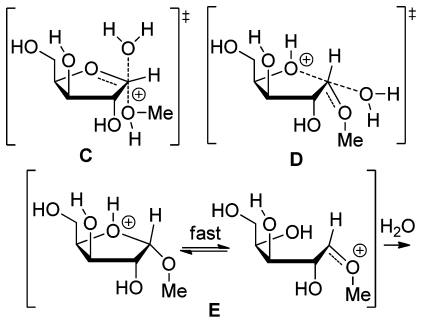

Figure 2. Suggested hydrolytic cleavage mechanisms for methyl furanosides.[8,10]

of water could occur through a bimolecular displacement concerted with the cleavage of the endocyclic C−O bond (**D**). Lastly, water was proposed to perform nucleophilic addition on rapidly equilibrating intermediates with oxocarbenium character (**E**, Figure 2).[8] Further mechanistic investigations and ^{18}O labeling studies of furanosides with electron-donating or electron-withdrawing aglycones gave support to the endocyclic cleavage pathway but did not allow discrimination between pathways involving transition state **D** or scenario **E** (Figure 2).[10] The configuration of the 5-membered ring substituents was also shown to have an important impact on rates of hydrolysis, which were consistently greater than for pyranosides.[8,10b−d]

In the context of developing new approaches for the synthesis of nucleoside analogues,[11] we decided to investigate ring-opening reactions with readily available methyl furanosides in the presence of Me_2BBr (Figure 3). Me_2BBr has been shown to efficiently activate acetal groups while carrying a bromide

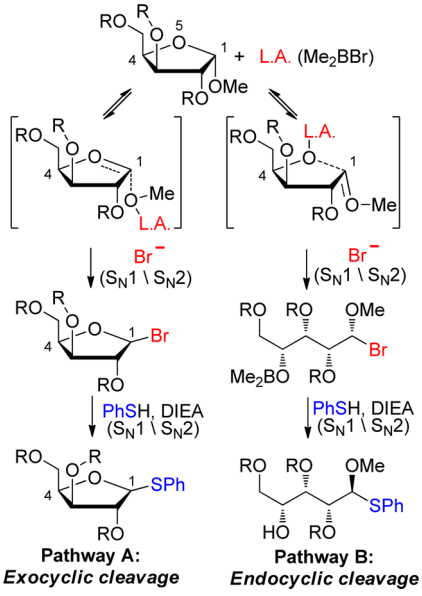

Figure 3. Exocyclic versus endocyclic cleavage with methyl lyxofuranoside (depicted with S_N2-like selectivity for pathway B).

anion nucleophile that can trap reactive intermediates at low temperatures before they can further react or equilibrate.[12] Addition of this Lewis acid to methyl furanosides would therefore generate acyclic and cyclic mixtures of bromoethers, which could react at low temperature with phenylthiol and a base (DIEA) to provide isolable thioacetals. The relative basicity of the O5 and O1 sites of activation and the presence of stabilizing or destabilizing stereoelectronic interactions brought by the different furanoside substituents in their preferred conformations are among the various factors likely to influence both modes of acetal cleavage and, thus, the observed mixtures of acyclic or cyclic thioacetals products. Substitution reactions at acetal centers have been proposed to occur through an array of mechanisms in the presence of a Lewis acid that range from fully S_N1 reactions involving oxocarbenium intermediates[4a,13] to S_N2-like displacements of contact ions pairs,[14] or alternatively, S_N2-like displacements with oxocarbenium character (exploded transition states[15]).[16] The configurations of the thioacetal moieties formed were therefore carefully determined in order to gain mechanistic insights.

In the present study, we show that a clear preference for the endocyclic cleavage is observed in the presence of Me_2BBr, giving access to acyclic thioacetals from the four natural methyl furanosides in high yields. Interestingly, the stereochemical outcome of the ring-opening reactions reveals that they proceed with S_N2-like selectivity, similar to what was hypothesized for hydrolysis reactions in aqueous media (**E**, Figure 2). We also show that the configuration of the furanosides clearly has an impact on both the reactivity and the preference for endocyclic versus exocyclic cleavage. The semicyclic or acyclic acetals obtained, which bear a thioether group that can be chemoselectively activated under mild conditions, are synthetically useful acyclic glycosyl donors for the development of strategies to generate nucleoside analogues and for the synthesis of new oligosaccharides and glycans.[11,16b]

RESULTS AND DISCUSSION

Endocyclic versus exocyclic acetal cleavage preference was investigated by performing nucleophilic substitution reactions in presence of Me_2BBr from the four benzylated α and β natural sugar scaffolds (Tables 1 and 2). After treatment of these furanosides with the Lewis acid in CH_2Cl_2 at −78 °C, DIEA and phenylthiol were added to generate thioacetals at low temperature. The relative stereochemistry of all acyclic thioacetals was determined by performing syn elimination of their corresponding sulfoxide to provide enol ethers with *E* or *Z* configurations allowing for unambiguous assignment of the parent thioacetal by ^1H NMR spectroscopy.

Activation of the ribo scaffold using the above conditions revealed that the anomeric configuration has a clear impact on the preferred cleavage pathway (entries 1 and 2, Table 1). Whereas the α-ribo anomer yielded preferentially cyclic thiophenyl ribofuranoside **2b**, the β-ribo anomer provided acyclic thioacetal **3b** in good yield. This reactivity pattern was intriguing, but even more surprising was the selective formation of only the 1,2-anti diastereoisomer **3b** (entry 2, Table 1). Acyclic thioacetals were formed from both the α- and β-xylo furanosides with, respectively, high 1,2-syn or good 1,2-trans selectivity at the acetal center (entries 3 and 4, Table 1). The observed selectivities of these reactions are clearly not consistent with an S_N1 mechanism and strongly suggested that the substitution reactions are occurring through two consecutive S_N2-like displacements. The lower diastereoselec-

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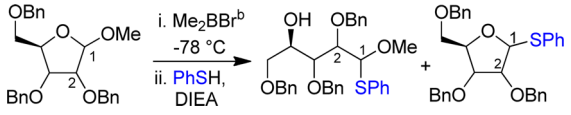
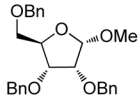
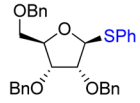
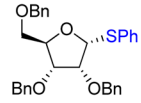
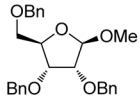
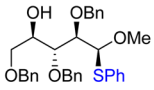
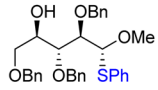
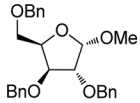
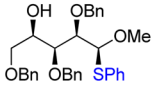
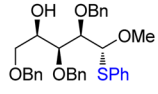
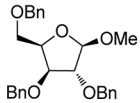
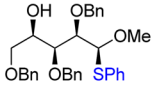
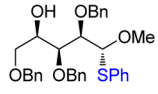
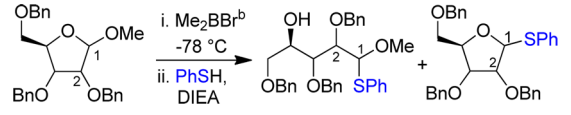
Table 1. Cleavage and Substitutions of α- and β-Methyl Furanosides (Ribo and Xylo Series)

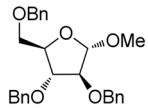
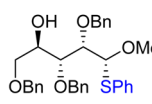
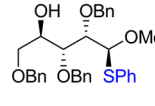
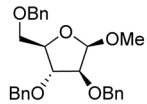
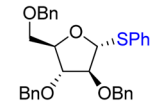
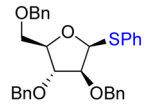
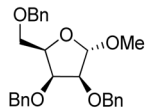
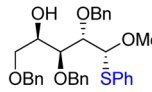
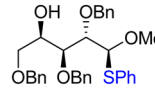
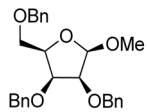
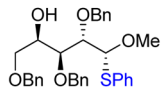
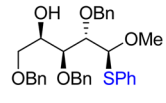


Entry	Substrate	Product Yield[a] (1,2-*syn* : 1,2-*anti*)
	 **1a** (α-*ribo*)	 **2a**  **2b**
1		79% (**2a**:**2b** = 1 : 4)
	 **1b** (β-*ribo*)	 **3a**  **3b**
2		83% (**3a**:**3b** = 1 : >20)
	 **4a** (α-*xylo*)	 **5a**  **5b**
3		51% (**5a**:**5b** = >20 : 1)
	 **4b** (β-*xylo*)	 **5a**  **5b**
4		91% (**10a**:**10b** = 1 : 8)

[a]Ratios were determined by ^{1}H NMR spectroscopic analysis of unpurified products. [b]Conditions: 2.0 equiv of Me_2BBr in CH_2Cl_2 at −78 °C. After the mixture was stirred for 30 min, 3.0 equiv of DIEA and 2.5 equiv of PhSH were added.

Table 2. Cleavage and Substitutions of α- and β-Methyl Furanosides (Arabino and Lyxo Series)



Entry	Substrate	Product Yield[a] (1,2-*syn* : 1,2-*anti*)
	 **6a** (α-arabino)	 **7a**  **7b**
1		77% (**7a**:**7b** = 1 : >20)
	 **6b** (β-arabino)	 **8a**  **8b**
2		0
3[c]		37% (**8a**:**8b** = 1 : >20)
	 **9a** (α-*lyxo*)	 **10a**  **10b**
4		64% (**10a**:**10b** = 1 : 9)
	 **9b** (β-*lyxo*)	 **10a**  **10b**
5		71% (**10a**:**10b** = >20 : 1)

[a]Ratios were determined by ^{1}H NMR spectroscopic analysis of unpurified products. [b]Conditions: 2.0 equiv of Me_2BBr in CH_2Cl_2 at −78 °C. After the mixture was stirred for 30 min, 3.0 equiv of DIEA and 2.5 equiv of PhSH were added. [c]Reaction performed at −20 °C.

tivity noted for the formation **5b** from **4b** and the conversion of cyclic α-methyl ribofuranoside (**2a**,**b**) to thiofuranoside suggest that competing S_N1 like mechanism are at play at the ring cleavage or substitution steps.

Methyl furanosides in the arabino and lyxo scaffolds were next examined (Table 2). Acyclic thioacetals were selectively obtained over their cyclic counterparts from α-arabino-, α-lyxo, and β-lyxofuranosides (entries 1, 4, and 5, Table 2). The configuration at the anomeric carbon of the starting material was always conserved in the acyclic thioacetal products, consistent with predominant S_N2-like selectivity for both the ring-opening reaction and the subsequent displacement of acyclic bromoethers. β-Arabinofuranoside **6b** was the only methyl furanoside studied that remained unreacted at −78 °C in the presence of Me_2BBr followed by the addition of thiophenol (entry 2, Table 2). At higher temperature (−20 °C), α-thiofuranoside **8b** was formed, albeit in low yield (entry 3, Table 2). The lower S_N2-like selectivity (1:9) for the formation of **10b** from **9a** (entry 4, Table 2) also suggests that some product formation occurred through a competing S_N1 pathway.

Cleavage and Substitution of 2-Alkoxy THF-acetals. In order to investigate the individual contribution of the different ring substituents on selectivity and reactivity, different methoxy tetrahydrofurans were prepared and treated with Me_2BBr under the conditions previously described for the methyl furanosides substitutions (Tables 1 and 2). Our first model study involved semicyclic acetals with a C2-alkoxy group (Table 3). 1,2-*trans*-Acetal **11a** and 1,2-*cis*-acetal **11b** gave acyclic products **12a** and **12b** with high diastereoselectivies at —78 °C (entries 1 and 5, Table 3).

The high selectivity observed for the cleavage and substitution of 1,2-trans and 1,2-cis THF acetal is consistent with two consecutive S_N2-like displacements at the acetal center (Figure 4). S_N2-like acetal substitutions have been proposed to benefit from the rehybridization of the sp^3 lone pair of the oxygen into $2p_z$ orbital in the transition state (TS) with formation of a partial double bond. This lone pair participation would stabilize C−O bond breaking and C−Br bond forming

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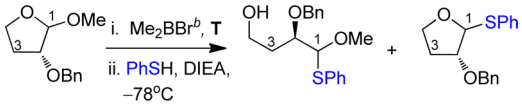
Table 3. Endocyclic versus Exocyclic Cleavage for C2-Benzyloxy Methyl THF-acetals



Entry	Substrate	T (°C)	Acyclic Yield (*d.r.*)[a]	Cyclic Yield (*d.r.*)[a]
	11a (1,2-trans) or **11b** (1,2-cis)		**12a**:**12b** 1,2-syn:1,2-anti	**13a**:**13b** 1,2-trans:1,2-cis
1	**11a**	–78	89% (1 : 11)	*not observed*
2	**11a**	0	78% (1 : 1.3)	10% (1.4 : 1)
3	**11a**	25	21% (1 : 1)	77% (1.3 : 1)
4[c]	**11a**	25	*not observed*	96% (1.3 : 1)
5	**11b**	–78	88% (10 : 1)	*not observed*

[a]Ratios were determined by ^{1}H NMR spectroscopic analysis of unpurified products. [b]Conditions: 2.0 equiv of Me_2BBr in CH_2Cl_2 at *T* (°C). After the mixture was stirred for 30 min, 3.0 equiv of DIEA and 2.5 equiv of PhSH were added at −78 °C. [c]The reaction was stirred 2h at 25 °C before the addition of PhSH and DIEA.

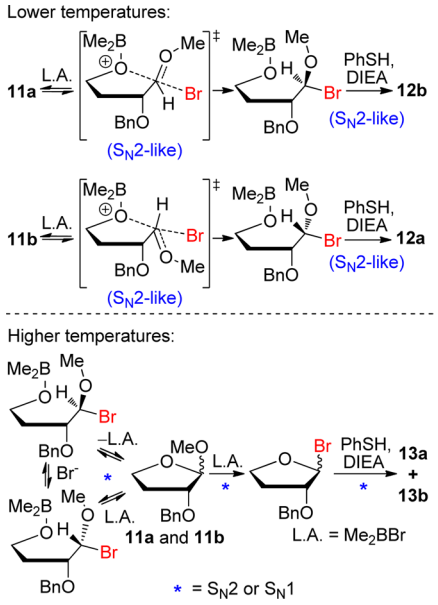


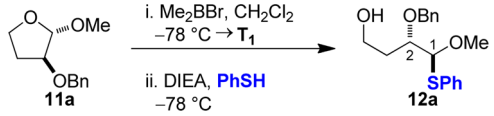
Figure 4. Impact of temperature on endo- versus exocyclic C−O bond cleavage pathways.

processes.[4a] The stereoelectronic assistance of the oxygen lone pair to reach the S_N2-like TS depicted at Figure 4 is also at the origin of the exoanomeric effect in the ground state.

The effect of temperature on the outcome of the formation of the bromoethers was next studied with C2-methoxy THF acetal by varying only the temperature at which the Me_2BBr was added (Table 3). The loss of S_N2-like selectivity at 0 °C for the reaction of **11a** with Me_2BBr suggests that at higher temperature an S_N1 mechanism pathway involving free oxocarbenium intermediates becomes competitive (entry 2, Table 3). Along with the equimolar mixture of **12a** and **12b** obtained, traces of cyclic products **13a** and **13b** were formed. These cyclic thiofuranosides were the major products at higher temperature and with prolonged stirring time in presence of the Lewis acid, prior to cooling the reaction at low temperature and addition thiophenol (entries 3 and 4, Table 3). Higher temperatures could therefore also promote a thermodynamic equilibration in favor of the cyclic bromoethers. The cyclic bromoether would then convert to thiofuranosides **13a** and **13b**, after the addition of thiophenol at −78 °C (Figure 4).

Acyclic bromoether intermediates could not be isolated or observed directly by ^{1}H NMR spectroscopy at low temperature, we therefore designed an experimental strategy to confirm that the displacement of these intermediates by phenylthiol was occurring through the proposed S_N2-like mechanism at −78 °C. This mechanism would infer that the observed ratios of thioacetals would originate from a corresponding ratio of acyclic bromoethers. By varying the ratio of bromoethers we should therefore vary similarly the ratio of the final hemithioacetals. As reported in entry 1 (Table 3), a ratio of 11 to 1 (1,2-anti:1,2-syn) was noted at −78 °C with the monosubstituted **11a** (solution **A**), while a 1.3:1 ratio (1,2-anti:1,2-syn) was obtained when the reaction was performed at 0 °C (solution **B**). In order to vary the ratio of bromoethers, known volumes of each solution (**B** in **A**) were combined before adding DIEA and phenylthiol at −78 °C (Table 4). Table 4

Table 4. Displacement of Anomeric Mixtures of Acyclic Bromoethers at −78 °C



	ratio of solution A and B			
entry	A^a (T_1 = −78 °C)	B^b (T_1 = 0 °C)	calcd dr **12a**:**12b**	obsd dr[c,d] **12a**:**12b**
1	1			11:1
2		1		1.3:1
3[d]	1	3	3.7:1	3:1
4[d]	1	1	6:1	6:1
5[d]	3	1	8.5:1	8:1
6[d]	6	1	9.6:1	10:1

[a]The reactions mixtures remained at −78 °C. [b]Me_2BBr was added at −78 °C; the temperature was then raised to 0 °C for 30 min and then lowered to −78 °C. [c]At −78 °C, prescribed volumes of solution **A** and **B** were mixed and then treated with DIEA and PhSH. [d]Ratios were determined by ^{1}H NMR spectroscopic analysis of the unpurified reaction mixtures.

summarizes the results obtained when various volumes for each experiment were combined and reacted with the thiophenol and DIEA. As reported in entries 3−6, an excellent correlation was observed between the calculated and experimental ratio of thioacetals, suggesting a direct relation between the bromoacetals obtained in the first step and in the final products.

Cleavage and Substitution of 2-Deoxy THF-acetals. The 2-deoxy systems studied did not exhibit any diastereoselectivity at the C1 center and the distribution of acyclic and cyclic products varied with different substitution patterns at C3 and C4 (Tables 5 and 6). Activation of THF acetals **14a** and

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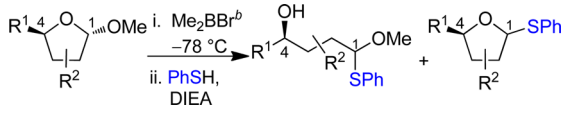
Table 5. Endocyclic versus Exocyclic Cleavage for C3- and C4-Alkyl THF Acetals



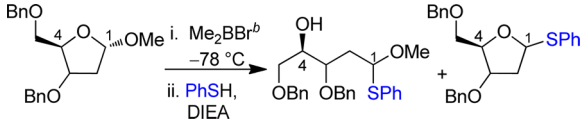
Entry		Yield (*d.r.*[a])	Yield (*d.r.*[a])
1	**14a** (1,3-trans)	**15a**:**15b** (1:1.3[c]) 93%	*not observed*
2	**14b** (1,3-cis)	**15a**:**15b**[c] (1.4:1[c]) 87%	*not observed*
3	**16a** (1,4-trans)	*not observed*	**18a**:**18b** (1:1) 82%
4	**16b** (1,4-cis)	**17a**:**17b** (1:1)[c] 64%	**18a**:**18b** (1:1) 18%

[a]Ratios were determined by ^{1}H NMR spectroscopic analysis of unpurified reaction mixtures. [b]Conditions: 2.0 equiv of Me_2BBr in CH_2Cl_2 at −78 °C. After the mixture was stirred for 30 min, 3.0 equiv of DIEA and 2.5 equiv of PhSH were added. [c]The relative configuration was not determined.

14b with a benzyloxy group at C3 afforded acyclic products **15a** and **15b** in high yields (entries 1 and 2, Table 5). The 1,4-*trans* THF-acetal **16a** gave exclusively thiofuranosides **18a** and **18b**, whereas THF-acetal **16b** with a 1,4-cis configuration provided mainly acyclic thioacetals **17** in 64% yield, along with thiofuranosides **18** in 18% yield (entries 3 and 4, Table 5). Both acyclic and 1,4-substituted cyclic products were formed unselectively as 1:1 mixtures of diastereoisomers.

The endocyclic versus exocyclic cleavage preference was next examined with 2-deoxyfuranosides in the ribo and xylo series (Table 6). Thiofuranosides **21a**,**b** were the only products obtained from α-deoxyribofuranoside **19a**, while the β-deoxyribofuranoside **19b** exclusively afforded acyclic thioacetals **20a**,**b** (entries 1 and 2). Nucleophilic substitution of α-deoxyxylofuranoside **22a** gave thiofuranosides **24a**,**b** in 69% yield and acyclic thioacetals **23a**,**b** in 21% yield, whereas β-deoxyxylofuranoside **22b** only afforded acyclic thioacetals **23a**,**b** (entries 3 and 4, Table 6).

Table 6. Endocyclic versus Exocyclic Cleavage for 2-Deoxyribose and 2-Deoxyxylose



Entry		d.r.[a] (Yield)	d.r.[a] (Yield)
1[c]	**19a**	*not observed*	**21a**:**21b** (1:1) 86%
2[c]	**19b**	**20a**:**20b** (1.4:1)[d] 79%	*not observed*
3	**22a**	**23a**:**23b** (1.4:1)[d] 21%	**24a**:**24b** (1:3) 69%
4	**22b**	**23a**:**23b** (1.7:1)[d] 90%	*not observed*

[a]Ratios were determined by ^{1}H NMR spectroscopic analysis of unpurified products. [b]Conditions: 2.0 equiv of Me_2BBr in CH_2Cl_2 at −78 °C. After the mixture was stirred for 30 min, 3.0 equiv of DIEA and 2.5 equiv of PhSH were added. [c]Previously reported result by our group.[6d] [d]Relative stereochemistry was not determined.

S_N1 versus S_N2-like Pathways for the Cleavage of 2-Deoxy and 2-Alkoxy THF-acetals. The stereochemical outcome for 2-deoxy and 2-alkoxy THF-acetals indicates that these two families of substrates undergo endocyclic C−O bond cleavages through different mechanisms (Tables 1 and 6). The two successive displacement reactions involved could be influenced strongly by the presence of an electron-withdrawing group at C2. This reactivity trend could relate to the rate enhancement measured for hydrolysis reaction of 2-deoxypyranosides versus their corresponding pyranosides, which has been attributed to destabilization of oxocarbenium intermediates with an electron-withdrawing group at C2.[9,17] For the same reason, formation of acyclic bromoethers would occur through free 2-deoxy acyclic oxocarbeniums (Figure 5). Nucleophilic additions on these 2-deoxy species are expected to proceed with marginal diastereoselectivity,[13] consistent with the mixtures of thioacetals obtained after treatment of the reaction mixture with thiophenol. Conversely, in the presence of a C2-alkoxy group, free acyclic oxocarbenium formation would be

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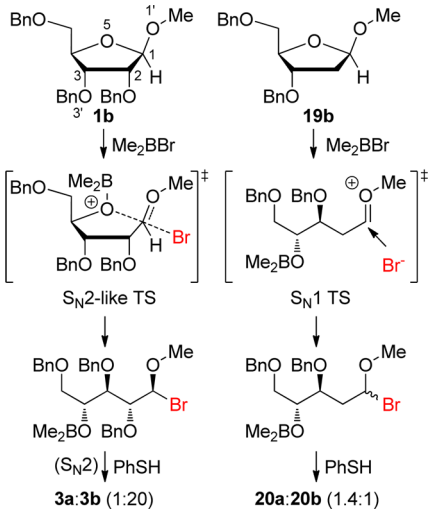

Figure 5. Endocyclic C−O bond cleavage mechanisms for ribo- and deoxyribofuranosides.

hampered and the S_N2-like pathway likely predominates to give acyclic thioacetals with high selectivity after two consecutive displacements (Figure 5).[18]

Endocyclic versus Exocyclic Cleavage. We can conclude from the present study that tetrahydrofuran derivatives have a strong propensity to furnish acyclic products in presence of Me_2BBr. These results are therefore suggestive that the exo anomeric effect (Figure 5) and the resulting stereoelectronic assistance of the exocyclic oxygen lone pairs is dominant in 5-membered rings. A noteworthy difference between C2-oxy and C2-deoxy systems was also observed in our study. The former showed a strong bias in fully substituted furanosides to cleave through the endocyclic pathway, with the notable α-ribofuranoside exception. α-Furanosides in the 2-deoxy series rather gave mainly cyclic products. This trend could be attributed in part to the greater ring strain energy released during the ring-opening reaction with more substituted systems. The conformational preference of the furanosides studied could represent another important factor influencing their reactivity by favoring the endo- or the exoanomeric effects, which would in turn modulate the relative basicity of the O1′ and O5 and the subsequent chemoselectivity of the activation by Me_2BBr. Furanosides generally undergo pseudorotation at the ground state through nonplanar envelope and twist conformers, which are influenced by different stereoelectronic effects, such as gauche interactions between vicinal alkoxy groups.[19]

At the transition-state level, the orientation of the ring substituents in low energy envelope conformation could allow stabilizing stereoelectronic effects influencing the formation of endocyclic or exocyclic oxonium intermediates (S_N1 or "exploded S_N2-like").[20] The preference for C2-endo TS **H** could provide a bias, for example, toward exocyclic cleavage of α-ribofuranoside **1a** (Figure 6) because the oxocarbenium intermediate displays a pseudoaxial C3-alkoxy group that provides electrostatic stabilization and a C2 carbon−hydrogen bond properly oriented for σ donation to the electron-poor anomeric center. These stabilizing stereoelectronic effects have been invoked in the context of C-glycosylation reactions of five-membered ring oxocarbenium intermediates.[20b] Conversely, the antiperiplanar orientation of C2-alkoxy group with the emerging exocyclic oxocarbenium species in TS **I** should not allow any significant stabilization by sigma donation and is

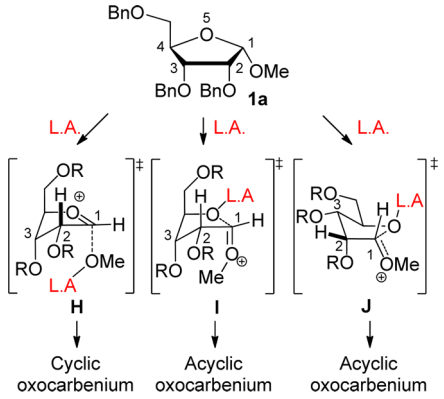

Figure 6. TS leading to cyclic or acyclic oxocarbenium intermediates from ribofuranoside **1a**.

likely destabilizing (Figure 6). The formation of acyclic bromoethers would therefore occur more readily through the other envelope conformation in TS **J**, where the orientation of the C2-hydrogen bond is correctly aligned to provide stabilization.

CONCLUSION

In summary, the present study unveils another facet of the reactivity of five-membered semicyclic acetals with a Lewis acid (Me_2BBr). These ring-opening reactions likely proceed predominantly through two consecutive S_N2-like nucleophilic displacements at the anomeric center to provide acyclic thioacetals. The presence of a C2-alkoxy group is necessary to maintain the high S_N2-like selectivity for the ring-opening reaction. The general preference for endocyclic cleavage pathway in the reactions studied could be attributed to the greater conformational flexibility of exocyclic C1−O1 bond, allowing more optimal antiperiplanar alignment for stereoelectronic assistance. The ring strain release for the opening of five-membered rings could also represent an important factor that enhances exocyclic cleavage in five-membered rings. The stereochemical outcome of the ring-opening reaction should allow for a broader general understanding of fundamental effect regarding the reactivity of methyl furanosides.

EXPERIMENTAL SECTION

General Comments. The characterization data for compounds **11a**, **11b**, **12a**, **12b**, **13a**, and **13b** was previously reported by our group.[15d] All reactions requiring anhydrous conditions were carried out under an atmosphere of nitrogen or argon in flame-dried glassware using standard syringe techniques. Dimethylboron bromide was used as a 2.0 M solution in dichloromethane and was synthesized by a known method.[21] ^{1}H NMR spectra were recorded on 400 and 500 MHz NMR spectrometers using $CDCl_3$ (δ = 7.26 ppm) as the internal reference. ^{13}C NMR spectra were recorded at 100 or 125 MHz using $CDCl_3$ (δ = 77.16 ppm) as the internal reference. Infrared spectra were recorded on a FT-IR spectrophotometer and signals are reported in cm^{-1}. Mass spectra were recorded either through electrospray ionization (ESI) or electron impact (EI) on an instrument operating at 70 eV, and FAB mass spectra were recorded with or without ionization. Optical rotations were recorded in dichloromethane unless otherwise noted (c in g of substrate/100 mL of solvent l = 1 dm).

General Experimental Method for the Formation of Acyclic and Cyclic Thioacetals from Methyl Furanosides (Procedure 1). To a cooled (−78 °C) solution of methyl α-D-ribofuranoside **1a**[22] (0.060 g, 0.14 mmol) in CH_2Cl_2 (2.4 mL, 0.06 M) was added dropwise a 2.0 M solution of dimethylboron bromide in CH_2Cl_2 (0.14 mL, 0.28 mmol). The reaction mixture was stirred at −78 °C for 30

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min before addition of *i*-Pr_2EtN (0.072 mL, 0.42 mmol) and benzenethiol (0.036 mL, 0.35 mmol). After the solution was cooled for 2 h at −78 °C, Ambersep 900 OH basic resin was added, and the reaction mixture was allowed to warm to ambient temperature over 15 min. The mixture was filtered and concentrated in vacuo. ^{1}H NMR spectroscopic analysis of the unpurified product indicated formation of a pair of diastereomers in a 1:4 (**2a**:**2b**; 1,2-*trans*:1,2-*cis*) ratio. The resulting yellowish oil was purified by flash chromatography (15:85 EtOAc/hexanes) to afford an inseparable mixture of **2** as a thick oil (0.055 g, 79%). ^{1}H NMR spectroscopic data obtained for **2a**,**b** correlate with previously reported data.[23]

*(1R,2R,3R,4R)-2,3,5-Tris(benzyloxy)-1-methoxy-1-(phenylthio)-pentan-4-ol (**3b**).* The representative procedure 1 was followed using methyl β-D-ribofuranoside **1b**[22] (0.050 g, 0.12 mmol), a 2.0 M solution of Me_2BBr in CH_2Cl_2 (0.12 mL, 0.24 mmol), PhSH (0.031 mL, 0.3 mmol), and *i*-Pr_2EtN (0.063 mL, 0.36 mmol) in CH_2Cl_2 (2 mL). The reaction was stirred 3 h at −78 °C and 90 min at 0 °C. ^{1}H NMR spectroscopic analysis of the unpurified product indicated formation of acyclic thioacetal **3b** as a single diastereoisomer. The resulting yellowish oil was purified by flash chromatography (20:80 EtOAc/hexanes) to afford **3b** as a thick oil (0.048 g, 83%): $[\alpha]^{25}_D$ −2.20 (*c* 0.92, CH_2Cl_2); R_f 0.24 (40:60 Et_2O/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 1.8, 7.6 Hz, 2H), 7.37−7.28 (m, 16H), 7.19−7.17 (m, 2H), 5.11 (d, *J* = 5.6 Hz, 1H), 4.90 (d, *J* = 11.3 Hz, 1H), 4.70 (d, *J* = 11.3 Hz, 1H), 4.55 (d, *J* = 11.9 Hz, 1H), 4.50 (d, *J* = 11.9 Hz, 1H), 4.41 (d, *J* = 11.4 Hz, 1H), 4.35 (d, *J* = 11.4 Hz, 1H), 4.22−4.18 (m, 1H), 4.04−4.01 (m, 2H) 3.66 (s, 1H), 3.65 (d, *J* = 1.4 Hz, 1H), 3.50 (s, 3H), 2.65 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 138.28, 138.23, 134.8, 132.6, 129.1, 128.5, 128.4, 128.4, 128.2, 128.0, 127.8, 127.7, 127.7, 127.6, 127.5, 92.6, 81.9, 79.3, 75.2, 73.4, 72.8, 71.4, 71.1, 56.9; IR (film) ν_{max} 3478, 3061, 3029, 2926, 2866, 1453, 1089; HRMS calcd for $C_{33}H_{36}NaO_5S^+$ (M + Na^+) 567.2176, found 567.2183 (+1.2 ppm).

*(1S,2R,3S,4R)-2,3,5-Tris(benzyloxy)-1-methoxy-1-(phenylthio)-pentan-4-ol (**5a**).* The representative procedure 1 was followed using methyl α-D-xylofuranoside **4a**[22] (0.050 g, 0.12 mmol), a 2.0 M solution of Me_2BBr in CH_2Cl_2 (0.2 mL, 0.24 mmol), PhSH (0.031 mL, 0.30 mmol), and *i*-Pr_2EtN (0.063 mL, 0.36 mmol) in CH_2Cl_2 (2 mL). ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a pair of acyclic thioacetal diastereomers in a 20:1 (**5a**:**5b**; 1,2-*syn*:1,2-*anti*) ratio. ^{13}C and ^{1}H NMR data for the minor isomer **5b** correlate with the data obtained for the major isomer **5b** obtained from **4b** under the same reaction conditions. The resulting yellowish oil was purified by flash chromatography (20:80 EtOAc/hexanes) to afford **5a** as a thick oil (0.030 g, 51%): $[\alpha]^{25}_D$ +7.64 (*c* 0.72, CH_2Cl_2); R_f 0.18 (20:80 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57−7.55 (m, 2H), 7.39−7.29 (m, 18 H), 4.98 (d, *J* = 4.8 Hz, 1H), 4.92 (d, *J* = 11.1 Hz, 1H), 4.82 (d, *J* = 11.3 Hz, 1H), 4.71 (d, *J* = 11.1 Hz, 1H), 4.63 (d, *J* = 11.3 Hz, 1H), 4.52 (d, *J* = 11.9 Hz, 1H), 4.47 (d, *J* = 11.9 Hz, 1H), 4.06−4.02 (m, 2H), 3.99 (dd, *J* = 3.0, 5.7 Hz, 1H), 3.56−3.47 (m, 2H), 3.46 (s, 3H), 2.72 (d, *J* = 6.2 Hz, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 140.0, 139.8, 139.5, 136.4, 132.9, 129.7, 128.9, 128.82, 128.78, 128.5, 128.38, 128.36, 128.1, 128.0, 127.9, 127.8, 95.8, 83.4, 81.6, 76.5, 75.9, 74.6, 73.4, 72.0, 57.7; IR (film) ν_{max} 3450, 3031, 2927, 2861, 1450, 1072; HRMS calcd for $C_{33}H_{36}NaO_5S^+$ (M + Na^+) 567.2176, found 567.2165 (−1.9 ppm).

*(1R,2R,3S,4R)-2,3,5-Tris(benzyloxy)-1-methoxy-1-(phenylthio)-pentan-4-ol (**5b**).* The representative procedure 1 was followed using methyl β-D-xylofuranoside **4b**[22] (0.050 g, 0.12 mmol), a 2.0 M solution of Me_2BBr in CH_2Cl_2 (0.12 mL, 0.24 mmol), PhSH (0.031 mL, 0.30 mmol), and *i*-Pr_2EtN (0.063 mL, 0.36 mmol) in CH_2Cl_2 (2 mL). ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of acyclic thioacetals diastereomers in a 1:8 (**5a**:**5b** 1,2-*syn*:1,2-*anti*) ratio. ^{13}C and ^{1}H NMR data for the minor isomer correlate with ^{1}H and ^{13}C spectroscopicdata of isomer **5a** obtained from **4a**, under the same reaction conditions. The resulting yellowish oil was purified by flash chromatography (20:80 EtOAc/hexanes) to afford **5b** as a thick oil (0.054 g, 91%): $[\alpha]^{25}_D$ +31.7 (*c* 1.02, CH_2Cl_2); R_f 0.38 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52−7.50 (m, 2H), 7.37−7.26 (m, 18H), 5.02 (s, 1H), 4.86 (d, *J* = 11.0 Hz, 1H), 4.78 (d, *J* = 11.3 Hz, 1H), 4.72 (d, *J* = 11.0 Hz, 1H), 4.62 (d, *J* = 11.3 Hz, 1H), 4.49 (d, *J* = 11.9 Hz, 1H), 4.43 (d, *J* = 11.9 Hz, 1H), 4.01 (s, 2H), 3.93 (dd, *J* = 5.7, 11.4 Hz, 1H), 3.49 (s, 3H), 3.42−3.20 (m, 2H), 2.61 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 138.2, 138.0, 135.0, 133.0, 132.5, 129.1, 128.6, 128.50, 128.57, 128.39, 128.31, 127.89, 127.87, 127.8, 127.6, 93.0, 82.7, 79.2, 75.6, 75.2, 73.4, 71.3, 70.5, 56.9; IR (film) ν_{max} 3451, 3055, 3031, 2928, 2867, 1453, 1073; HRMS calcd for $C_{33}H_{36}NaO_5S^+$ (M + Na^+) 567.2176, found 567.2154 (−3.9 ppm).

*(1S,2S,3R,4R)-2,3,5-Tris(benzyloxy)-1-methoxy-1-(phenylthio)-pentan-4-ol (**7b**).* The representative procedure 1 was followed using methyl α-D-arabinofuranoside **6a**[22] (0.050 g, 0.12 mmol), a 2.0 M solution of Me_2BBr in CH_2Cl_2 (0.12 mL, 0.24 mmol), PhSH (0.031 mL, 0.30 mmol), and *i*-Pr_2EtN (0.063 mL, 0.36 mmol) in CH_2Cl_2 (2 mL). ^{1}H NMR spectroscopic analysis of the unpurified product indicated formation of acyclic thioacetal **7b** as a single diastereomer. The resulting yellowish oil was purified by flash chromatography (20:80 EtOAc/hexanes) to afford **7b** as a thick oil (0.045 g, 77%): $[\alpha]^{25}_D$ +28.5 (*c* 0.720, CH_2Cl_2); R_f 0.15 (20:80 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 1.9, 7.5 Hz, 2H), 7.35−7.20 (m, 18H), 4.93 (d, *J* = 6.5 Hz, 1H), 4.77 (d, *J* = 11.2 Hz, 1H), 4.58 (d, *J* = 11.2 Hz, 1H), 4.56 (s, 2H), 4.49 (d, *J* = 11.9 Hz, 1H), 4.45 (d, *J* = 11.9 Hz, 1H), 4.06 (dd, *J* = 3.4, *J* = 7.0 Hz, 1H), 3.92−3.91 (m, 1H), 3.86 (dd, *J* = 3.4, *J* = 6.5 Hz, 1H), 3.53 (d, *J* = 4.5 Hz, 2H), 3.50 (s, 3H), 2.62 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 138.2, 138.1, 133.7, 133.4, 129.0, 128.7, 128.5, 128.44, 128.40, 128.34, 128.30, 128.2, 128.0, 127.8, 127.8, 91.8, 80.8, 78.3, 75.0, 73.8, 73.5, 71.1, 70.5, 57.0; IR (film) ν_{max} 3480, 3066, 3031, 2921, 2861, 1453, 1069; HRMS calcd for $C_{33}H_{36}NaO_5S^+$ (M + Na^+) 567.2176, found 567.2192 (+2.8 ppm).

*(1S,2S,3R,4R)-2,3-Bis(benzyloxy)-4-(benzyloxymethyl)-1-(phenylthio)tetrahydrofuran (**8b**).* The representative procedure 1 was followed using methyl β-D-arabinofuranoside **6b**[22] (0.025 g, 0.06 mmol), a 2.0 M solution of Me_2BBr in CH_2Cl_2 (0.060 mL, 0.12 mmol), PhSH (0.015 mL, 0.15 mmol), and *i*-Pr_2EtN (0.031 mL, 0.18 mmol) in CH_2Cl_2 (1 mL). The reaction was stirred at −20 °C instead of −78 °C. ^{1}H NMR spectroscopic analysis of the unpurified product indicated formation of cyclic thioacetal **8b** as a single diastereoisomer. The resulting yellowish oil was purified by flash chromatography (20:80 EtOAc/hexanes) to afford **8b** as a thick oil (0.011 g, 37%). ^{1}H NMR spectroscopic data obtained for **8b** correlate with previously reported data.[24]

*(1S,2S,3S,4R)-2,3,5-Tris(benzyloxy)-1-methoxy-1-(phenylthio)-pentan-2-ol (**10b**).* The representative procedure 1 was followed using methyl α-D-lyxofuranoside **9a**[22] (0.060 g, 0.14 mmol), a 2.0 M solution of Me_2BBr in CH_2Cl_2 (0.14 mL, 0.28 mmol), PhSH (0.036 mL, 0.35 mmol), and *i*-Pr_2EtN (0.073 mL, 0.42 mmol) in CH_2Cl_2 (2.3 mL). The reaction mixture was stirred for 3 h at −78 °C and 90 min at 0 °C. ^{1}H NMR spectroscopic analysis of the unpurified product indicated formation of a pair of acyclic thioacetal diastereomers in a 1:9 (**10a**:**10b**; 1,2-*syn*/1,2-*anti*) ratio. ^{13}C and ^{1}H NMR spectroscopic data for the minor isomer **10a** correlate with the data obtained for the major isomer from **9b**, which were formed under the same reaction conditions. The resulting yellowish oil was purified by flash chromatography (20:80 EtOAc/hexanes) to afford **10b** as a thick oil (0.048 g, 64%): $[\alpha]^{25}_D$ −2.72 (*c* 1.03, CH_2Cl_2); R_f 0.32 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54−7.52 (m, 2H), 7.43 (d, *J* = 7.1 Hz, 2H), 7.39−7.28 (m, 14H), 7.24−7.22 (m, 2H), 5.06 (d, *J* = 3.6 Hz, 1H), 5.00 (d, *J* = 11.0 Hz, 1H), 4.80 (d, *J* = 10.9 Hz, 1H), 4.58 (d, *J* = 11.8 Hz, 1H), 4.53−4.46 (m, 3H), 4.20−4.15 (m, 2H), 3.97 (d, *J* = 7.3 Hz, 1H), 3.62−3.52 (m, 2H), 3.51 (s, 3H), 2.78 (d, *J* = 6.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.13, 138.12, 138.0, 135.4, 132.4, 129.2, 128.49, 128.45, 128.40, 128.2, 128.1, 128.0, 127.93, 127.91, 127.8, 127.4, 92.9, 82.3, 77.6, 75.9, 73.9, 73.4, 71.4, 69.5, 56.5; IR (film) ν_{max} 3480, 3030, 2934, 2861, 1453, 1212, 1073, 1026; HRMS calcd for $C_{33}H_{36}NaO_5S^+$ (M + Na^+) 567.2176, found 567.2160 (−2.8 ppm).

*(1R,2S,3S,4R)-2,3,5-Tris(benzyloxy)-1-methoxy-1-(phenylthio)-pentan-4-ol (**10a**).* The representative procedure 1 was followed using methyl β-D-lyxofuranoside **9b**[22] (0.017 g, 0.04 mmol), a 2.0 M solution

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of Me_2BBr in CH_2Cl_2 (0.04 mL, 0.08 mmol), PhSH (0.010 mL, 0.10 mmol), and *i*-Pr_2EtN (0.021 mL, 0.12 mmol) in CH_2Cl_2 (0.7 mL). ^1H NMR spectroscopic analysis of the unpurified product indicated the formation a pair of acyclic thioacetal diastereomers in a 20:1 (**10a**:**10b**; 1,2-*syn*/1,2-*anti*) ratio. ^{13}C and ^1H NMR data for the minor isomer **10b** correlate with the data obtained for the major isomer **9a** under the same reaction conditions. The resulting yellowish oil was purified by flash chromatography (20:80 EtOAc/hexanes) to afford **10a** as a thick oil (0.015 g, 71%): $[\alpha]^{25}_D$ −24.9 (*c* 1.03, CH_2Cl_2); R_f 0.41 (30:70 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.47−7.46 (m, 2H), 7.35−7.23 (m, 18H), 4.96 (d, *J* = 4.2 Hz, 1H), 4.79 (d, *J* = 11.1 Hz, 1H), 4.69 (d, *J* = 11.1 Hz, 1H), 4.59−4.46 (m, 4H), 4.15−4.13 (m, 1H), 4.08−4.06 (m, 1H), 3.95−3.94 (m, 1H), 3.55 (d, *J* = 5.8 Hz, 2H), 3.45 (s, 3H), 2.95 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 138.1, 138.04, 138.00, 135.47, 132.45, 129.2, 129.0, 128.4, 128.3, 128.09, 127.97, 127.92, 127.8, 127.4, 127.3, 94.1, 81.1, 78.3, 74.6, 73.8, 73.4, 71.3, 70.0, 57.2; IR (film) ν_{max} 3487, 3062, 3031, 2928, 2867, 1456, 1109; HRMS calcd for $C_{33}H_{36}NaO_5S^+$ (M + Na^+) 567.2176, found 567.2156 (−3.5 ppm).

*(±)-(2S,4R)-4-(Benzyloxy)-2-methoxytetrahydrofuran (**14a**) and (±)-(2R,4R)-4-(Benzyloxy)-2-methoxytetrahydrofuran (**14b**).* To a cooled (−78 °C) solution of 4-(benzyloxy)dihydrofuran-2(3*H*)-one[25] (2.0 g, 10 mmol) in dichloromethane (100 mL, 0.1 M) was added a 1.0 M solution of DIBAL-H in toluene (12.5 mL, 12.5 mmol). The resulting mixture was stirred for 2 h before addition of MeOH (33 mL, 0.3 M) and then treated with concentrated HCl (1 mL). The reaction mixture was stirred for 12 h at 25 °C before the organic layer was separated and the aqueous layer extracted three times with dichloromethane (100 mL). The combined organic layers were dried with anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The oily residue was purified by flash chromatography eluting with (30:70 EtOAc/hexanes) to afford a colorless liquid as pure **14a** (0.998 g, 46%) and pure **14b** (0.090 g, 4%) along with an anomeric mixture (0.140 g, 6%).

14a: R_f 0.43 (30:70 EtOAc/hexanes); ^1H NMR (500 MHz, DMSO) δ 7.36−7.27 (m, 5H), 4.96 (dd, *J* = 1.2, 5.9 Hz, 1H), 4.47 (d, *J* = 11.9 Hz, 1H), 4.41 (d, *J* = 11.9 Hz, 1H), 4.19−4.14 (m, 1H), 3.97 (dd, *J* = 6.2, 9.1 Hz, 1H), 3.67 (dd, *J* = 4.9, 9.2 Hz, 1H), 3.23 (s, 3H), 2.20 (ddd, *J* = 5.8, 7.9, 13.9 Hz, 1H), 1.85 (d, *J* = 14.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 128.6, 128.0, 127.8, 105.0, 76.9, 71.8, 71.6, 55.2, 39.0; IR (film) ν_{max} 2891, 1452, 1367, 1432, 1205, 1043; HRMS calcd for $C_{12}H_{16}NaO_3^+$ (M + Na^+) 231.0992, found 231.0993 (−0.44 ppm).

14b: R_f 0.45 (30:70 EtOAc/hexanes); ^1H NMR (500 MHz, DMSO) δ 7.36−7.27 (m, 5H), 5.09 (dd, *J* = 2.5, 5.4 Hz, 1H), 4.43 (s, 2H), 4.25 (dddd, *J* = 1.7, 3.0, 4.6, 6.3 Hz, 1H), 3.87 (d, *J* = 9.8 Hz, 1H), 3.75 (dd, *J* = 4.6, 9.9 Hz, 1H), 3.21 (s, 3H), 2.08 (ddd, *J* = 3.5, 4.9, 14.1 Hz, 1H), 2.01 (ddd, *J* = 2.5, 6.5, 14.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0, 128.4, 127.7, 105.1, 78.2, 71.2, 70.8, 55.0, 39.8; IR (film) ν_{max} 2910, 1452, 1346, 1207, 1108, 1043; HRMS calcd for $C_{12}H_{16}NaO_3^+$ (M + Na^+) 231.0992, found 231.0992.

*(±)-2-(Benzyloxy)-4-methoxy-4-(phenylthio)butan-1-ol (**15a,b**).* The representative procedure 1 was followed using **14a** (0.040 g, 0.19 mmol), a 2.0 M solution of Me_2BBr in CH_2Cl_2 (0.19 mL, 0.38 mmol), PhSH (0.048 mL, 0.48 mmol), and *i*-Pr_2EtN (0.099 mL, 0.57 mmol) in CH_2Cl_2 (1.9 mL). ^1H NMR spectroscopic analysis of the unpurified product indicated a pair of acyclic thioacetal diastereomers in a 1:1.25 (**15a**:**15b**)[26] ratio. The resulting yellowish oil was purified by flash chromatography (20:80 EtOAc/hexanes) to afford **15a,b** as a liquid in an inseparable diastereomeric mixture (0.057 g, 93%): R_f 0.15 (30:70 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.49−7.31 (m, 20H), 4.81 (t, *J* = 6.5 Hz, 1H, **15a**), 4.75 (dd, *J* = 3.6, 9.6 Hz, 1H, **15b**), 4.60 (d, *J* = 11.6 Hz, 1H), 4.57 (s, 2H), 4.52 (d, *J* = 11.6 Hz, 1H), 3.83−3.69 (m, 4H), 3.54 (dd, *J* = 6.0, 11.8 Hz, 1H), 3.51 (s, 3H, **15a**), 3.49−3.45 (m, 1H), 3.44 (s, 3H, **15b**), 2.18−2.11 (m, 2H), 2.01−1.96 (m, 2H), 1.88−1.83 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 138.3, 133.9, 132.7, 132.5, 129.0, 128.9, 128.68, 128.64, 128.05, 128.02, 128.00, 127.93, 127.90, 87.8, 87.0, 77.4, 76.8, 72.1, 71.9, 64.1, 63.9, 55.94, 55.92, 38.7, 37.4; IR (film) ν_{max} 3444, 2929, 2873, 1474, 1455, 1438, 1113, 1062; HRMS calcd for $C_{18}H_{22}NaO_3S^+$ (M + Na^+) 341.1182, found 341.1182 (+0.01 ppm).

*(2S,5S)-2-(Benzyloxymethyl)-5-methoxytetrahydrofuran (**16a**).* Compound **16a** was prepared following a Castillon procedure.[27] ^{13}C and ^1H NMR spectroscopic data for **16a** correlate with the previously reported data: $[\alpha]^{25}_D$ +81.4 (*c* 1.03, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) 7.39−7.28 (m, 5H), 5.09 (d, *J* = 5.1 Hz, 1H), 4.63 (d, *J* = 12.2 Hz, 1H), 4.59 (d, *J* = 12.2 Hz, 1H), 4.31 (qd, *J* = 5.1, 7.4 Hz, 1H), 3.54−3.58 (m, 2H), 3.38 (s, 3H), 2.12−1.98 (m, 2H), 1.90−1.85 (m, 1H), 1.71−1.65 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 128.4, 127.8, 105.6, 77.0, 73.5, 72.6, 54.8, 32.0, 26.0; HRMS calcd for $C_{13}H_{18}NaO_3^+$ (M + Na^+) 245.1148, found 245.1145 (−1.5 ppm).

*(2S,5R)-2-(Benzyloxymethyl)-5-methoxytetrahydrofuran (**16b**).* Compound **16b** was prepared following Castillon procedure.[27] ^{13}C and ^1H NMR spectroscopic data for **16b** correlate with the previously reported data: $[\alpha]^{25}_D$ +82.8 (*c* 1.14, CH_2Cl_2); R_f 0.26 (20:80; EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) 7.39−7.30 (m, 5H), 5.01 (d, *J* = 4.5 Hz, 1H), 4.64 (d, *J* = 12.2 Hz, 1H), 4.60 (d, *J* = 12.2 Hz, 1H), 4.34−4.28 (m, 1H), 3.55 (dd, *J* = 7.0, 9.8 Hz, 1H), 3.50 (dd, *J* = 4.8, 9.8 Hz, 1H), 3.33 (s, 3H), 2.03−1.89 (m, 3H), 1.79−1.71 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 128.4, 127.8, 127.7, 105.4, 79.2, 74.7, 73.4, 54.5, 32.8, 26.4; HRMS calcd for $C_{13}H_{18}NaO_3^+$ (M + Na^+) 245.1148, found: 245.1147 (−0.42 ppm).

*(2S)-1-(Benzyloxy)-5-methoxy-5-(phenylthio)pentan-2-ol (**17a,b**).* The representative procedure 1 was followed using **16b** (0.145 g, 0.65 mmol), a 2.0 M solution of Me_2BBr in CH_2Cl_2 (0.65 mL, 1.3 mmol), PhSH (0.17 mL, 1.6 mmol), and *i*-Pr_2EtN (0.34 mL, 1.9 mmol) in CH_2Cl_2 (6.5 mL). ^1H NMR spectroscopic analysis of the unpurified product indicated a pair of acyclic thioacetals diastereomers in a 1:1 (**17a**:**17b**) ratio and a pair of cyclic thiofuranoside diastereoisomers in a 1:1 (**18a**:**18b**) ratio. The resulting yellowish oil was purified by flash chromatography (25:75 EtOAc/hexanes) to afford the thiofuranoside **18** (0.035 g, 18%) and the acyclic thioacetal **17** as liquids in an inseparable diastereomeric mixture (0.139 g, 64%). **17a** and **17b** mixture: R_f 0.27 (40:60 EtOAc/hexanes); $[\alpha]^{25}_D$ 0.45 (*c* 1.11, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) 7.51−7.48 (m, 4H), 7.39−7.27 (m, 16H), 4.70−4.65 (m, 2H), 4.55 (s, 4H), 3.82−3.78 (m, 2H), 3.52−3.46 (m, 2H), 3.50 (s, 3H), 3.49 (s, 3H), 3.35−3.31 (m, 2H), 2.36 (bs, 2H), 2.02−1.93 (m, 2H), 1.90−1.82 (m, 2H), 1.70−1.58 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0, 133.8, 133.6, 133.2, 133.1, 128.8, 128.6, 127.9, 127.8, 127.7, 127.6, 90.93, 90.91, 74.55, 74.54, 73.47, 73.46, 70.1, 70.0, 55.7, 55.6, 32.1, 31.9, 29.9, 29.8; IR (film) ν_{max} 3451(bs), 3062, 3025, 2928, 2960, 1583, 1475, 1452, 1080, 1025; HRMS calcd for $C_{19}H_{24}NaO_3S^+$ (M + Na^+) 355.1338, found 355.1339 (+0.13 ppm).

*(2S,5R)-2-(Benzyloxymethyl)-5-(phenylthio)tetrahydrofuran (**18a**) and (2S,5S)-2-(Benzyloxymethyl)-5-(phenylthio)-tetrahydrofuran (**18b**).* The representative procedure 1 was followed using **16a** (0.130 g, 0.58 mmol), a 2.0 M solution of Me_2BBr in CH_2Cl_2 (0.6 mL, 1.17 mmol), PhSH (0.148 mL, 1.45 mmol), and *i*-Pr_2EtN (0.303 mL, 1.74 mmol) in CH_2Cl_2 (5.8 mL). ^1H NMR spectroscopic analysis of the unpurified product indicated a pair of cyclic thioacetal diastereomers in a 1:1.1 (**18a**:**18b**) ratio. The resulting yellowish oil was purified by flash chromatography (5:95 EtOAc/hexanes) to afford **18a,b** (0.142 g, 82%) .

18a: R_f 0.50 (40:60 EtOAc/hexanes); $[\alpha]^{25}_D$ 237.9 (c 1.03, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) 7.55−7.53 (m, 2H), 7.37−7.24 (m, 8H), 5.61 (dd, *J* = 3.9, 6.8 Hz, 1H), 4.62 (d, *J* = 12.2 Hz, 1H), 4.59 (d, *J* = 12.2 Hz, 1H), 4.37−4.32 (m, 1H), 3.70 (dd, *J* = 6.4, 10.0 Hz, 1H), 3.58 (dd, *J* = 5.1, 10.0 Hz, 1H), 2.42−2.34 (m, 1H), 2.16−2.06 (m, 2H), 1.90 (ddd, *J* = 8.7, 12.8, 15.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 135.4,131.4, 128.9, 128.4, 127.8, 127.6, 127.0, 87.4, 80.4, 73.54, 73.52, 33.0, 28.2; IR (film) ν_{max} 3062, 3025, 2934, 2861, 1583, 1479, 1440, 1052, 1024; HRMS calcd for $C_{18}H_{20}NaO_2S^+$ (M + Na^+) 323.1076, found 323.1078 (+08 ppm).

18b: R_f 0.57 (40:60 EtOAc/hexanes); $[\alpha]^{25}_D$ 221.8 (*c* 1.13, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) 7.56−7.54 (m, 2H), 7.38−7.23 (m, 8H), 5.74 (dd, *J* = 4.1, 7.1 Hz, 1H), 4.61 (s, 2H), 4.46 (tt, *J* = 4.6, 7.3 Hz, 1H), 3.61 (dq, *J* = 4.6, 10.4 Hz, 2H), 2.45 (dddd, *J* = 5.7, 7.0, 9.9, 13.0 Hz, 1H), 2.15−2.07 (m, 1H), 2.03 (dddd, *J* = 4.1, 6.3,

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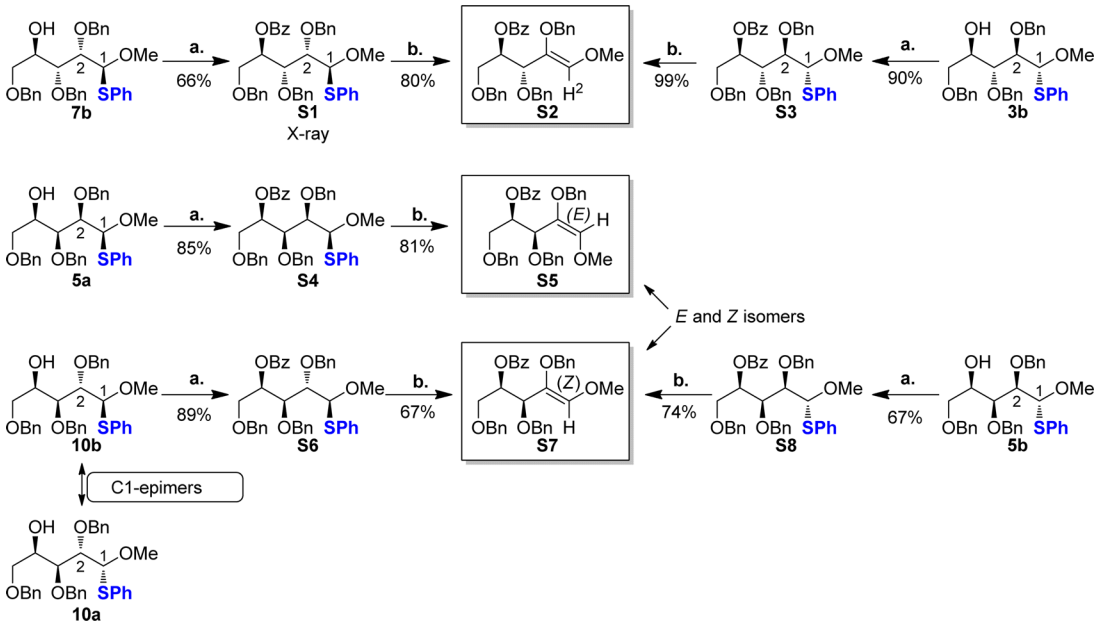

Figure 7. Stereochemical proof of structure for acyclic thioacetals **3b**, **5a**, **5b**, **7b**, **10a**, and **10b**.

8.6, 12.9 Hz, 1H), 1.80 (dddd, J = 6.4, 7.4, 9.3, 11.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 135.8, 131.2, 128.9, 128.5, 127.8, 127.7, 126.9, 87.7, 77.8, 73.4, 71.8, 32.8, 27.4; IR (film) ν_{max} 3062, 3025, 2940, 2863, 1583, 1479, 1450, 1069, 1024; HRMS calcd for $C_{18}H_{20}NaO_2S^+$ (M + Na^+) 323.1076, found 323.1072 (−1.0 ppm).

*(2R,3S)-1,3-Bis(benzyloxy)-5-methoxy-5-(phenylthio)pentan-2-ol (**20a,b**).* The representative procedure 1 was followed using **19b**[28] (0.050 g, 0.15 mmol), a 2.0 M solution of Me_2BBr in CH_2Cl_2 (0.15 mL, 0.30 mmol), PhSH (0.039 mL, 0.38 mmol), and *i*-Pr_2EtN (0.079 mL, 0.46 mmol) in CH_2Cl_2 (2.5 mL). ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of acyclic thioacetal diastereomers in a 1.3:1 (**20a**:**20b**)[26] ratio. The resulting yellowish oil was purified by flash chromatography (5:95 EtOAc/CH_2Cl_2) to afford **20a** (0.034 g, 52%) with **20b** (0.018 g, 27%) as liquids.

20a: R_f 0.41 (10:90 EtOAc/CH_2Cl_2); $[\alpha]^{25}_D$ −48.8 (*c* 0.60, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48−7.46 (m, 2H), 7.38−7.28 (m, 13H), 4.82 (dd, J = 3.3, 10.0 Hz, 1H), 4.62 (d, J = 11.4 Hz, 1H), 4.52 (d, J = 1.9 Hz, 2H), 4.50 (d, J = 11.5 Hz, 1H), 3.91 (qd, J = 4.3, 8.6 Hz, 1H), 3.73 (ddd, J = 3.4, 4.5, 9.5 Hz, 1H), 3.55−3.50 (m, 2H), 3.38 (s, 3H), 2.40 (d, J = 4.0 Hz, 1H), 2.10−2.04 (m, 1H), 1.97 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 138.0, 133.8, 133.2, 128.9, 128.6, 128.1, 128.0, 127.94, 127.91, 127.7, 87.2, 73.6, 72.9, 72.2, 70.9, 55.6, 38.1; IR (film) ν_{max} 3463 (bs), 3068, 3031, 2922, 2867, 1450, 1067; HRMS calcd for $C_{26}H_{30}NaO_4S^+$ (M + Na^+) 461.1757, found: 461.1764 (+1.5 ppm).

20b: R_f 0.28 (10:90 EtOAc/CH_2Cl_2); $[\alpha]^{25}_D$ +2.67 (c 0.30, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (dd, J = 3.0, 6.5 Hz, 2H), 7.39−7.26 (m, 13H), 4.87 (t, J = 6.5 Hz, 1H), 4.56−4.51 (m, 4H), 3.91−3.87 (m, 1H), 3.81−3.78 (m, 1H), 3.52 (s, 3H), 3.51−3.47 (m, 2H), 2.62 (d, J = 3.8 Hz, 1H), 2.13 (td, J = 6.7, 13.7 Hz, 1H), 2.01 (ddd, J = 4.0, 6.6, 14.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 138.0, 134.0, 132.6, 128.9, 128.57, 128.56, 128.06, 128.00, 127.9, 127.8, 127.8, 87.8, 77.4, 73.6, 72.4, 71.7, 70.9, 56.0, 36.2; IR (film) ν_{max} 3475 (bs), 3068, 3037, 2928, 2867, 1456, 1091; HRMS calcd for $C_{26}H_{30}NaO_4S^+$ (M + Na^+) 461.1757, found 461.1765 (+1.6 ppm).

*(2R,3R)-1,3-Bis(benzyloxy)-5-methoxy-5-(phenylthio)pentan-2-ol (**23a,b**) and (2R,3R)-3-(Benzyloxy)-2-(benzyloxymethyl)-5-(phenylthio)tetrahydrofuran[29] (**24a,b**).* The representative procedure 1 was followed using known compound **22a**[30] (0.119 g, 0.36 mmol), a 2.0 M solution of Me_2BBr in CH_2Cl_2 (0.36 mL, 0.72 mmol), PhSH (0.093 mL, 0.91 mmol), and *i*-Pr_2EtN (0.188 mL, 1.1 mmol) in CH_2Cl_2 (3.6 mL). ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of cyclic thioacetal diastereomers in a 1:3 (**24a**:**24b**) ratio with the corresponding acyclic thioacetals in a 1.4:1 (**23a**:**23b**)[26] ratio. The resulting yellowish oil was purified by flash chromatography (20:80 EtOAc/hexanes) to afford thiofuranoside **24a** (0.022 g, 15%), thiofuranoside **24b** (0.079 g, 54%), and an inseparable mixture of acyclic thioacetal **23a,b** (0.034 g, 21%). Compound **24a,b** was previously reported in the literature, but without complete characterization data, which are therefore provided herein.

23a,b: R_f 0.24 (30:70; EtOAc/hexanes); $[\alpha]^{25}_D$ +0.48 (*c* 0.099, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46−7.44 (m, 4H), 7.36−7.26 (m, 26H), 4.78−4.74 (m, 2H), 4.58−4.46 (m, 8H), 3.86−3.73 (m, 4H), 3.51−3.43 (m, 4H), 3.46 (s, 3H, **23a**), 3.40 (s, 3H, **23b**), 2.46 (d, J = 5.3 Hz, 1H, **23a**), 2.34 (d, J = 6.1 Hz, 1H, **23b**), 2.10 (ddd, J = 3.7, 9.0, 14.3 Hz, 1H, **23b**), 2.05 (t, J = 6.2 Hz, 2H, **23a**), 2.00−1.95 (m, 1H, **23b**); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 138.3, 138.1, 138.0, 134.0, 133.8, 132.9, 132.6, 128.94, 128.91, 128.6, 128.5, 128.08, 128.07, 127.96, 127.95, 127.92, 127.91, 127.88, 127.87, 127.78; IR (film) ν_{max} 3445, 3062, 3031, 2926, 2867, 1454, 1096, 1070, 1026; HRMS calcd for $C_{26}H_{30}O_4NaS$ (M + Na+) 461.1757, found 461.1755 (−0.36 ppm).

24a: R_f 0.40 (30:70 EtOAc/hexanes); $[\alpha]^{25}_D$ −170.8 (c 1.16, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 7.2 Hz, 2H), 7.37−7.23 (m, 13H), 5.57 (dd, J = 4.3, 7.9 Hz, 1H), 4.67 (d, J = 4.5 Hz, 1H), 4.65 (d, J = 4.4 Hz, 1H), 4.60 (d, J = 12.0 Hz, 1H), 4.49 (d, J = 12.1 Hz, 1H), 4.27 (td, J = 5.1, 6.7 Hz, 1H), 4.22 (dt, J = 2.8, 5.3 Hz, 1H), 3.94 (dd, J = 5.1, 10.2 Hz, 1H), 3.88 (dd, J = 6.6, 10.2 Hz, 1H), 2.56 (ddd, J = 5.7, 7.8, 13.7 Hz, 1H), 2.32 (ddd, J = 2.9, 4.2, 14.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 138.1, 136.4, 130.9, 128.9, 128.5, 128.4, 127.9, 127.8, 127.69, 128.66, 126.8, 86.2, 82.6, 77.6, 73.6, 71.5, 69.6, 38.9; IR (film) ν_{max} 3062, 3029, 2864, 1453, 1094, 1064; HRMS calcd for $C_{25}H_{26}NaO_3S^+$ (M + Na^+) 429.1495, found 429.1493 (−0.38 ppm).

24b: R_f 0.45 (30:70 EtOAc/hexanes); $[\alpha]^{25}_D$ +132.7 (c 0.95, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 7.2 Hz, 2H), 7.36−7.23 (m, 13H), 5.79 (t, J = 6.8 Hz, 1H), 4.64 (d, J = 11.9 Hz, 1H), 4.60 (d, J = 12.1 Hz, 1H), 4.57 (d, J = 11.9 Hz, 1H), 4.47 (d, J = 12.1 Hz, 1H), 4.38 (dt, J = 3.8, 5.9 Hz, 1H), 4.20−4.19 (m, 1H), 3.90 (dd, J = 6.0, 10.1 Hz, 1H), 3.79 (dd, J = 5.9, 10.1 Hz, 1H), 2.61 (ddd, J = 1.4, 7.1, 14.2 Hz, 1H), 2.13−2.08 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 138.1, 135.4, 131.3, 128.9, 128.6, 128.5, 127.88, 127.84, 127.7, 127.6, 127.1, 85.8, 80.4, 78.2, 73.6, 71.6, 68.0, 39.2; IR (film) ν_{max} 3062, 3031, 2922, 2864, 1453, 1093, 1060; HRMS calcd for $C_{25}H_{26}NaO_3S^+$ (M + Na^+) 429.1495, found 429.1489 (−1.2 ppm).

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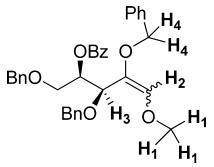
Synthesis of Olefins and Proof of Structures. The relative stereochemistry of thioacetals **3b**, **5a**, **5b**, **7b**, **10a**, and **10b** was determined by ^{1}H NMR correlations of the corresponding *Z*- or *E*-olefin, obtained after a two step oxidation−*syn*-elimination sequence (Figure 7 and Table 7).[31] Thioacetal **S1** was confirmed by X-ray crystallographic analysis. Detailed analysis of the *E*- and *Z*-configurations of analogous olefins was reported previously by our group.[15d]

Table 7. Chemical Shift (δ ppm) Correlation for Olefins S5 and S7



	H_1	H_2	H_3	H_4
S5 (*E*)	3.45 (s)	6.01 (s)	4.88 (d)	4.75(d)
				4.65 (d)
S7 (*Z*)	3.59 (s)	5.68 (s)	3.94 (d)	5.14(d)
				5.03 (d)
	$\delta Z > \delta E$	$\delta Z < \delta E$	$\delta Z < \delta E$	$\delta Z > \delta E$

General Experimental Method for the Preparation of Benzoates from Alcohols 3b, 5a, 5b, 7b, and 10b with (Procedure 2). To a cooled (0 °C) solution of thioacetal **7b** (0.030 g, 0.06 mmol) in CH_2Cl_2 (0.6 mL, 0.1 M) was added 4-(dimethylamino)pyridine (0.037 g, 0.30 mmol) with benzoyl chloride (0.021 mL, 0.18 mmol). The reaction mixture was maintained at 0 °C for 2 h before addition of a saturated solution of sodium bicarbonate. The organic layer was separated, and the aqueous layer was extracted (3×) with EtOAc. The combined organic layers were dried on anhydrous magnesium sulfate, filtered, and concentrated in vacuo. ^{1}H NMR spectroscopic analysis of the unpurified product indicated **S1** as a pair of diastereomers in a 1:18 (1,2-*syn*:1,2-*anti*) ratio. The resulting yellowish oil was purified by flash chromatography (5:95 acetone/hexanes) to afford **S1** (0.025 g, 66%) as a white crystal. Slow evaporation of a EtOAc/hexanes solution afforded a suitable crystal for X-ray analysis (CIF, Supporting Information).

*(1S,2S,3R,4R)-2,3,5-Tris(benzyloxy)-1-methoxy-1-(phenylthio)-pentan-4-yl benzoate (**S1**):* mp = 88.7 °C; $[\alpha]^{25}_D$ +28.5 (*c* 0.72, CH_2Cl_2); R_f 0.35 (20:80 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.3 Hz, 2H), 7.58 (dd, *J* = 7.4 Hz, 1H), 7.54 (d, *J* = 7.1 Hz, 2H), 7.41 (dd, *J* = 7.8 Hz, 2H), 7.36−7.19 (m, 18H), 5.39 (td, *J* = 4.1, 5.9 Hz, 1H), 4.95 (d, *J* = 6.9 Hz, 1H), 4.84 (d, *J* = 11.5 Hz, 1H), 4.81 (d, *J* = 11.5 Hz, 1H), 4.77 (d, *J* = 10.6 Hz, 1H), 4.60 (dd, *J* = 4.0, 6.1 Hz, 1H), 4.55 (d, *J* = 12.1 Hz, 1H), 4.48 (d, *J* = 12.1 Hz, 1H), 4.45 (d, *J* = 10.6 Hz, 1H), 4.00 (dd, *J* = 3.5, 10.9 Hz, 1H), 3.89−3.84 (m, 2H), 3.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 138.5, 138.2, 134.0, 133.1, 130.1, 129.8, 129.0, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.90, 127.82, 127.79, 127.71, 127.70, 127.6, 91.9, 81.0, 78.7, 75.7, 75.1, 73.4, 73.3, 68.1, 57.0; IR (film) ν_{max} 3068, 3031, 2928, 2879, 1718, 1462, 1270, 1109, 1069, 1109, 1069; HRMS calcd for $C_{40}H_{40}NaO_6S^+$ (M + Na^+) 671.2443, found 671.2458 (+2.2 ppm).

General Experimental Method for the *syn*-Elimination via Sulfoxides (Procedure 3). To a cooled (0 °C) solution of benzoylated thioacetal **S1** (0.055 g, 0.08 mmol) in CH_2Cl_2 (0.7 mL, 0.14 M) was added *m*-chloroperbenzoic acid (0.018 g, 0.08 mmol, 77% w/w in H_2O). The reaction mixture was maintained at 0 °C for 30 min before addition of saturated solution of sodium bicarbonate. The organic layer was separated, and the aqueous layer was extracted (3×) with EtOAc. The combined organic layers were dried on anhydrous magnesium sulfate, filtered, and concentrated in vacuo. To a solution of the oily residue in toluene (0.7 mL, 0.2 M) was added sodium bicarbonate (0.018 g, 0.12 mmol). The reaction mixture was reflux at 110 °C for 2 h before cooling at ambient temperature. Water was then added, the layers were separated, and the aqueous layer was extracted (3×) with EtOAc. The combined organic layers were dried on anhydrous magnesium sulfate, filtered, and concentrated in vacuo. ^{1}H NMR spectroscopic analysis of the unpurified product indicated **S2** as a single diastereoisomer. The resulting yellowish oil was purified by flash chromatography (10:90 EtOAc/hexanes) to afford **S2** (0.037 g, 80%) as an oil. **S2** (0.051 g, 99%) was also generated following representative procedure 3 from thioacetal **S3** (0.061 g, 0.094 mmol), *m*-CPBA (0.020 g, 0.094 mmol), $NaHCO_3$ (0.012 g, 0.14 mmol) in CH_2Cl_2 (0.7 mL), and toluene (0.6 mL).

*(3R,4R,Z)-2,3,5-Tris(benzyloxy)-1-methoxypent-2-en-4-yl benzoate (**S2**):* $[\alpha]^{25}_D$ +8.00 (*c* 1.25, CH_2Cl_2); R_f 0.58 (20:80 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.6 Hz, 2H), 7.59 (dd, *J* = 7.9, 15.4 Hz, 1H), 7.45 (dd, *J* = 7.7 Hz, 2H), 7.41 (d, *J* = 7.1 Hz, 2H), 7.33−7.26 (m, 13H), 5.73 (s, 1H), 5.56 (td, *J* = 3.8, 7.4 Hz, 1H), 5.10 (d, *J* = 11.7 Hz, 1H), 5.04 (d, *J* = 11.7 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.59 (d, *J* = 12.2 Hz, 1H), 4.50 (d, *J* = 12.2 Hz, 1H), 4.38 (d, *J* = 12.0 Hz, 1H), 4.04 (d, *J* = 7.3 Hz, 1H), 3.97 (d, *J* = 3.8 Hz, 2H), 3.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 138.5, 138.4, 138.3, 136.7, 135.2, 133.5, 132.9, 130.7, 129.9, 128.4, 128.34, 128.27, 127.9, 127.8, 127.7, 127.6, 127.6, 127.5, 73.3, 73.2, 73.1, 70.4, 68.7, 60.5; IR (film) ν_{max} 3037, 2928, 2861, 1719, 1452, 1272, 1109, 1030; HRMS calcd for $C_{34}H_{34}NaO_6^+$ (M + Na^+) 561.2248, found 561.2244 (−0.7 ppm).

*(1R,2R,3R,4R)-2,3,5-Tris(benzyloxy)-1-methoxy-1-(phenylthio)-pentan-4-yl benzoate (**S3**).* The representative procedure 2 was followed using thioacetal **3b** (0.260 g, 0.5 mmol), 4-DMAP (0.305 g, 2.5 mmol), and BzCl (0.17 mL, 1.5 mmol) in CH_2Cl_2 (5 mL). The resulting yellowish oil was purified by flash chromatography (20:80 Et_2O/hexanes) to afford **S3** as a thick oil (0.293 g, 90%): $[\alpha]^{25}_D$ +2.6 (*c* 1.5, CH_2Cl_2); R_f 0.21 (10% Et_2O/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.6 Hz, 2H), 7.60 (dd, *J* = 7.4 Hz, 1H), 7.53 (d, *J* = 2.0 Hz, 1H), 7.53−7.51 (m, 1H), 7.47 (dd, *J* = 7.7 Hz, 2H), 7.42−7.41 (m, 2H), 7.36−7.28 (m, 16H), 5.89−5.86 (m, 1H), 5.09 (d, *J* = 4.3 Hz, 1H), 4.97 (d, *J* = 11.1 Hz, 1H), 4.80 (d, *J* = 11.1 Hz, 1H), 4.73 (d, *J* = 11.3 Hz, 1H), 4.58 (d, *J* = 12.2 Hz, 1H), 4.50 (dd, *J* = 12.1 Hz, 2H), 4.30 (dd, *J* = 3.3, 6.3 Hz, 1H), 4.09 (dd, *J* = 4.6, 6.1 Hz, 1H), 3.97−3.90 (m, 2H), 3.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 138.3, 138.2, 138.1, 135.2, 133.1, 132.5, 130.4, 129.8, 129.1, 128.51, 128.47, 128.41, 128.37, 128.2, 128.0, 127.8, 127.7, 127.6, 127.4, 92.7, 81.8, 79.1, 75.0, 73.5, 73.4, 73.1, 68.8, 56.8; IR (film) ν_{max} 3478, 3061, 3029, 2926, 2866, 1453, 1089; HRMS calcd for $C_{40}H_{40}NaO_6S^+$ (M + Na^+) 671.2438, found 671.2462 (+3.6 ppm).

*(1S,2R,3S,4R)-2,3,5-Tris(benzyloxy)-1-methoxy-1-(phenylthio)-pentan-4-yl Benzoate (**S4**).* The representative procedure 2 was followed using thioacetal **5a** (0.165 g, 0.25 mmol), 4-DMAP (0.153 g, 1.25 mmol), and BzCl (0.087 mL, 0.75 mmol) in CH_2Cl_2 (2.5 mL). The resulting yellowish oil was purified by flash chromatography (10:90 acetone/hexanes) to afford **S4** as a thick oil (0.178 g, 85%): $[\alpha]^{25}_D$ −6.67 (*c* 1.20, CH_2Cl_2); R_f 0.23 (20% acetone/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 7.5 Hz, 2H), 7.64−7.59 (m, 3H), 7.50 (dd, *J* = 7.7 Hz, 2H), 7.42−7.28 (m, 18H), 5.71 (dd, *J* = 5.4, 9.9 Hz, 1H), 5.08 (d, *J* = 6.1 Hz, 1H), 5.02 (d, *J* = 11.0 Hz, 1H), 4.85 (d, *J* = 11.5 Hz, 1H), 4.82 (d, *J* = 11.5 Hz, 1H), 4.74 (d, *J* = 11.0 Hz, 1H), 4.53 (d, *J* = 12.2 Hz, 1H), 4.46 (d, *J* = 12.1 Hz, 1H), 4.40 (dd, *J* = 5.2 Hz, 1H), 4.00−3.98 (m, 1H), 3.83 (dd, *J* = 4.1, 10.7 Hz, 1H), 3.71 (dd, *J* = 5.5, 10.7 Hz, 1H), 3.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 138.5, 138.3, 138.0, 134.7, 133.1, 132.4, 130.1, 129.8, 129.0, 128.45, 128.42, 128.38, 128.31, 128.2, 127.9, 127.7, 127.66, 127.62, 127.2, 92.7, 79.5, 78.0, 75.2, 73.9, 73.52, 73.06, 68.6, 56.3; IR (film) ν_{max} 3062, 3035, 2879, 1724, 1462, 1273, 1097, 738, 702; HRMS calcd for $C_{40}H_{40}NaO_6S^+$ (M + Na^+) 671.2438, found 671.2461 (+3.4 ppm).

*(3S,4R,E)-2,3,5-Tris(benzyloxy)-1-methoxypent-2-en-4-yl Benzoate (**S5**).* The representative procedure 3 was followed using thioacetal **S4** (0.050 g, 0.09 mmol), *m*-CPBA (0.020 g, 0.09 mmol), $NaHCO_3$ (0.011 g, 0.14 mmol) in CH_2Cl_2 (0.6 mL), and toluene (0.5 mL). ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of **S5** as a single diastereoisomer. The resulting yellowish oil was purified by flash chromatography (30:70 EtOAc/hexanes) to afford **S5** as a thick oil (0.034 g, 81%): $[\alpha]^{25}_D$ −18.5 (*c* 1.00, CH_2Cl_2); R_f 0.34 (40:60 EtOAc/hexanes); ^{1}H NMR (500 MHz,

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$CDCl_3$) δ 8.05 (d, J = 7.2 Hz, 2H), 7.55 (dd, J = 7.4 Hz, 1H), 7.42 (dd, J = 7.7 Hz, 2H), 7.32−7.21 (m, 15H), 6.01 (s, 1H), 5.78−5.75 (m, 1H), 4.88 (d, J = 7.9 Hz, 1H), 4.75 (d, J = 11.6 Hz, 1H), 4.64 (dd, J = 10.3, 11.7 Hz, 2H), 4.56 (d, J = 12.2 Hz, 1H), 4.46 (d, J = 12.3 Hz, 2H), 3.80 (dd, J = 3.0, 11.1 Hz, 1H), 3.73 (dd, J = 5.8, 11.2 Hz, 1H), 3.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 140.4, 138.8, 138.4, 137.3, 134.3, 132.8, 130.8, 130.0, 128.5, 128.31, 128.26, 128.17, 128.0, 127.9, 127.7, 127.5, 127.42, 127.38, 73.7, 73.2, 72.6, 71.4, 70.6, 69.2, 60.5; IR (film) ν_{max} 3062, 2928, 2873, 1730, 1444, 1273, 1201, 1115, 1067; HRMS calcd for $C_{34}H_{34}NaO_6^+$ (M + Na^+) 561.2248, found 561.2249 (+0.18 ppm).

*(1S,2S,3S,4R)-2,3,5-Tris(benzyloxy)-1-methoxy-1-(phenylthio)-pentan-4-yl Benzoate (**S6**).* The representative procedure 2 was followed using thioacetal **10b** (0.050 g, 0.09 mmol), 4-DMAP (0.055 g, 0.45 mmol), and BzCl (0.031 mL, 0.27 mmol) in CH_2Cl_2 (1 mL). The resulting yellowish oil was purified by flash chromatography (20:80 EtOAc/hexanes) to afford **S6** as a thick oil (0.057 g, 89%): $[\alpha]^{25}_D$ +19.5 (c 1.15, CH_2Cl_2); R_f 0.44 (20:80 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, J = 8.1 Hz, 2H), 7.59 (dd, J = 7.4 Hz, 1H), 7.49 (d, J = 6.9 Hz, 2H), 7.45 (dd, J = 7.8 Hz, 2H), 7.39 (d, J = 7.4 Hz, 2H), 7.33−7.27 (m, 16H), 5.74 (dt, J = 2.2, 6.1 Hz, 1H), 5.18 (d, J = 3.0 Hz, 1H), 4.89 (d, J = 10.4 Hz, 1H), 4.69−4.53 (m, 5H), 4.22 (dd, J = 2.0, 7.6 Hz, 1H), 4.07 (dd, J = 2.9, 7.7 Hz, 1H), 3.86−3.78 (m, 2H), 3.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 138.4, 138.02, 138.00, 135.7, 133.1, 133.0, 132.1, 130.3, 123.0, 129.1, 129.0, 128.48, 128.46, 128.43, 128.3, 127.88, 127.80, 127.75, 127.70, 127.2, 92.4, 82.2, 77.2, 75.6, 74.3, 73.3, 72.2, 68.2, 56.5; IR (film) ν_{max} 3062, 3031, 2922, 2861, 1718, 1453, 1269, 1109, 1026; HRMS calcd for $C_{40}H_{40}NaO_6S^+$ (M + Na^+) 671.2438, found 671.2418 (−2.9 ppm).

*(3S,4R,Z)-2,3,5-Tris(benzyloxy)-1-methoxypent-2-en-4-yl Benzoate (**S7**).* The representative procedure 3 was followed using thioacetal **S6** (0.050 g, 0.09 mmol), *m*-CPBA (0.020 g, 0.09 mmol), $NaHCO_3$ (0.011 g, 0.14 mmol) in CH_2Cl_2 (0.6 mL), and toluene (0.5 mL) and was stirred 16 h at 110 °C. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of **S5**:**S7** (*E*:*Z*) as a pair of diastereomers in a 1:5 ratio. The resulting yellowish oil was purified by flash chromatography (30:70 EtOAc/hexanes) to afford **S7** as a thick oil (0.024 g, 67%). Representative procedure 3 was also followed using benzoylated thioacetals **S4**:**S8** (dr 1:13) (0.050 g, 0.08 mmol), *m*-CPBA (0.018 g, 0.08 mmol), $NaHCO_3$ (0.011 g, 0.12 mmol) in CH_2Cl_2 (0.6 mL), and toluene (0.5 mL). ^{1}H NMR spectroscopic analysis of the unpurified product indicated **S5**:**S7** (*E*:*Z*) as a pair of diastereomers in a 1:13 ratio. The resulting yellowish oil was purified by flash chromatography (30:70 EtOAc/hexanes) to afford **S7** as a thick oil (0.031 g, 74%): $[\alpha]^{25}_D$ −38.9 (c 0.66, CH_2Cl_2); R_f 0.33 (20:80 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, J = 7.3 Hz, 2H), 7.59 (dd, J = 7.4 Hz, 1H), 7.45 (dd, J = 7.8, 15.7 Hz, 4H), 7.36−7.25 (m, 13H), 5.68−5.67 (m, 2H), 5.14 (d, J = 11.5 Hz, 1H), 5.03 (d, J = 11.5 Hz, 1H), 4.60 (d, J = 12.4 Hz, 1H), 4.55 (d, J = 12.2 Hz, 1H), 4.45 (d, J = 12.2 Hz, 1H), 4.36 (d, J = 12.4 Hz, 1H), 3.94 (d, J = 7.3 Hz, 1H), 3.79 (dd, J = 3.2, 11.0 Hz, 1H), 3.72 (dd, J = 5.4, 11.0 Hz, 1H), 3.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 138.3, 138.2, 135.72, 135.68, 132.9, 132.8, 130.6, 130.0, 128.5, 128.38, 128.35, 128.33, 128.2, 127.82, 127.77, 127.68, 127.59, 127.52, 77.4, 73.8, 73.6, 73.2, 70.0, 69.0, 60.6; IR (film) ν_{max} 3062, 3031, 2940, 2867, 1719, 1452, 1273, 1108, 1067, 1029; HRMS calcd for $C_{34}H_{34}NaO_6^+$ (M + Na^+) 561.2248, found 561.2232 (−2.8 ppm).

*(1R,2R,3S,4R)-2,3,5-Tris(Benzyloxy)-1-methoxy-1-(phenylthio)-pentan-4-yl Benzoate (**S8**).* The representative procedure 2 was followed using thioacetals **5a**:**5b** (dr 1:13) (0.050 g, 0.098 mmol), 4-DMAP (0.059 g, 0.49 mmol), and BzCl (0.034 mL, 1.5 mmol) in CH_2Cl_2 (1 mL). ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of **S4**:**S8** as a pair of diastereomers in a 1:13 (1,2-*syn*:1,2-*anti*) ratio. The resulting yellowish oil was purified by flash chromatography (20:80 Et_2O/hexanes) to afford **S8** as a thick oil (0.052 g, 81%): $[\alpha]^{25}_D$ −33.5 (c 1.12, CH_2Cl_2); R_f 0.41 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, J = 7.8 Hz, 2H), 7.61 (dd, J = 7.3 Hz, 1H), 7.48 (dd, J = 7.7 Hz, 2H), 7.40 (d, J = 7.1 Hz, 2H), 7.31−7.24 (m, 15H), 7.16−7.09 (m, 3H), 5.56 (dd, J = 5.1, 9.8 Hz, 1H), 4.99 (d, J = 5.3 Hz, 1H), 4.88 (d, J = 10.9 Hz, 1H), 4.81 (d, J = 11.3 Hz, 1H), 4.76 (d, J = 11.2 Hz, 1H), 4.67 (d, J = 10.9 Hz, 1H), 4.47−4.41 (m, 3H), 3.88 (dd, J = 5.2 Hz, 1H), 3.74 (dd, J = 4.0, 10.7 Hz, 1H), 3.60 (dd, J = 5.9, 10.7 Hz, 1H), 3.51 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 138.3, 138.2, 138.0, 133.8, 133.2, 133.1, 132.4, 130.1, 129.9, 128.8, 128.47, 128.38, 128.37, 128.31, 128.1, 127.71, 127.65, 127.63, 127.5, 92.4, 81.1, 78.1, 75.2, 75.1, 73.3, 73.1, 68.4, 56.9; IR (film) ν_{max} 3068, 3031, 2940, 2855, 1719, 1596, 1452, 1270, 1069, 1026; HRMS calcd for $C_{40}H_{40}NaO_6S^+$ (M + Na^+) 671.2443, found 671.2425 (−2.7 ppm).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H NMR and ^{13}C NMR spectra are available for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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