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Stereochemical Properties of Glucosyl Sulfoxides in Solution

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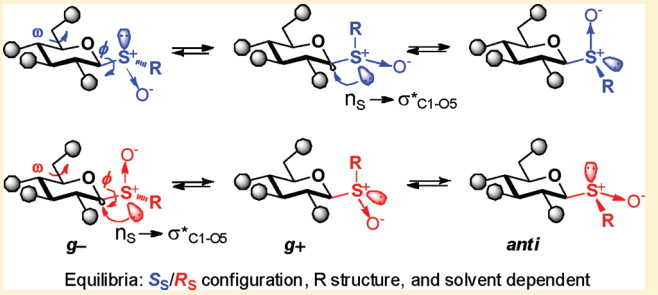
Supporting Information

ABSTRACT: A series of alkyl β-glucosyl sulfoxides were synthesized and characterized in order to study their stereochemical properties. The dependence of the aglycon, solvent and absolute configuration of the sulfinyl group on the conformational properties around the glucosidic and C5−C6 (hydroxymethyl group) bonds were studied. The results for R_S sulfoxides show linear correlations between the rotamer populations of the hydroxymethyl group and the corresponding Taft's steric parameter (E_S) of the alkyl group attached to the sulfinyl group in polar and apolar solvents, an increase in the absolute value of E_S leading to an increase in the *gt* population. In addition, NOE experiments reveal that as the bulkiness of the alkyl group increases the population of the *g*− rotamer increases, the latter stabilized by the *exo*-anomeric effect. These results are in complete agreement with the participation of the *exo*-anomeric effect in both conformational properties of R_S sulfoxides. Sulfoxides with the S_S configuration show different behavior to their R_S epimers; thus, an increase in the E_S value of the alkyl group leads to similar or lower *gt* populations in apolar solvents and to increases in *gt* in polar solvents. Their NOE studies reveal a conformational equilibrium (in polar and apolar solvents) between *g*− and *g*+, dependent on the size of the alkyl group R attached to the sulfinyl group. All these results for both epimers support the general hypothesis that the *exo*-anomeric effect modifies the conformation of the hydroxymethyl group, fulfills the stereoelectronic requirements, and shows dependence on the solvent.



INTRODUCTION

The conformational factors involved in carbohydrates are essential to understand their chemical or biological properties.[1] For instance, electronic interactions that have specific geometric (stereoelectronic) requirements are of prime importance to explain their conformational and anomeric properties.[2,3] Different stereoelectronic effects, the *exo*- and *endo*-anomeric effects,[3] are involved depending on the anomeric configuration (Figure 1), which account for the particular conformational properties.

In alkyl *S*- and *O*-β-D-glycosides the conformational preferences around the glycosidic linkage are described by the torsion angle C1′−X−C1−O5 (X = O, S), whose rotation gives rise to three staggered rotamers: *exo-syn*, *exo-anti*, and non-*exo*,[4] the *exo-syn* rotamer being the predominant (Figure 2).

The flexibility of the hydroxymethyl group around C5−C6 distinguishes three main rotamers called *gauche*−*gauche* (*gg*), *gauche*−*trans* (*gt*), and *trans*−*gauche* (*tg*) (Figure 3), the conformational preferences of this group being mainly influenced by[5] the absolute configuration of the stereocenter C4 of the sugar ring (the Hassel−Ottar effect),[6] the *gauche* effect, solvation effects,[7] the anomeric effect, and the nature of substituent groups, among other factors.

Many of the properties of these effects have been theoretically and experimentally elucidated over the years.[5−7,9−11] A recent

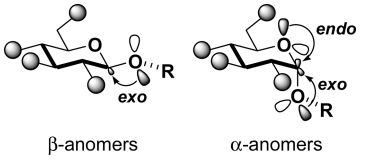


Figure 1. Alkyl β-D- and α-D-glucopyranosides showing the orbitals involved in the *exo*- and *endo*-anomeric effects.

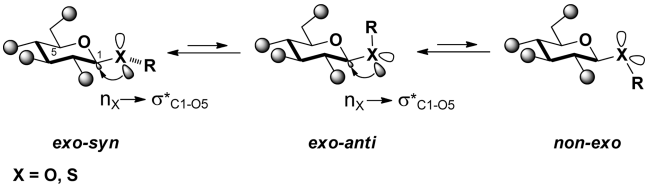


Figure 2. Three staggered rotamers around the glycosidic bond in glycosides.

long-range coupling study confirms that the magnitudes of long-range $^4J_{C1,H6R/S}$ and $^4J_{C3,H6R/S}$ depend mainly on the O5−C5−C6−O6 torsion angle and confirms that the rotamer

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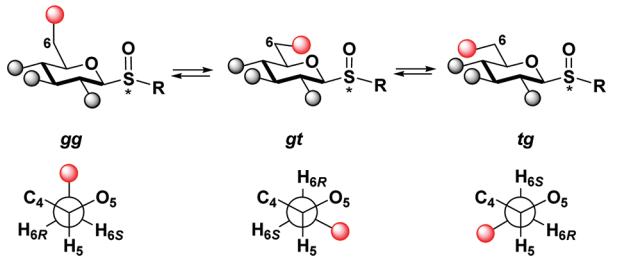

Figure 3. Rotamers around the C5−C6 bond in glucopyranosides: *gauche−gauche (gg), gauche−trans (gt),* and *trans−gauche (tg).*[8]

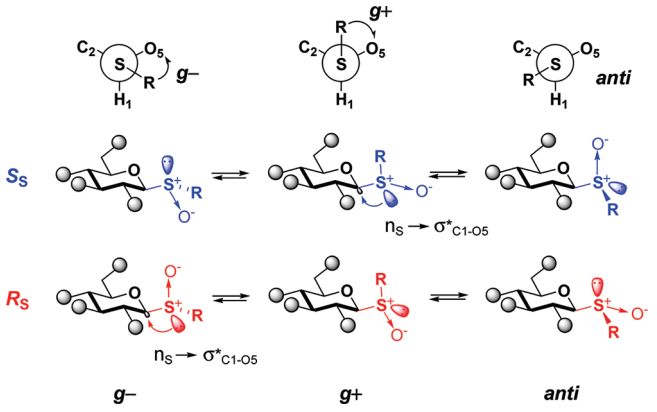

Figure 4. Rotamers around the glycosidic linkage in glucosyl sulfoxides and nomenclature used herein (upper line). S_S glucosyl sulfoxides (center line, blue color). R_S glucosyl sulfoxides (bottom line, red color).

distribution of the hydroxymethyl group depends on the anomeric configuration.[12] This conformational dependence was already revealed during our previous studies.[11] Nevertheless, a better knowledge of the conformational properties and dependences of this group is still needed, alkyl glycosyl sulfoxides being excellent compounds for this purpose. Glycosyl sulfoxides have become important intermediates for the synthesis of bioactive molecules[13,14] and several of them show biological activity themselves, including antitumoral, anti-infective, and antidiabetic actions.[14] The stereoelectronic interaction that gives origin to the *exo*-anomeric effect should also be present in alkyl glycosyl sulfoxides, since the sulfinyl sulfur atom has a lone electron pair able to interact with the antibonding σ orbital C1−O5. However, the effect would not be equally favored for R_S and S_S glycosyl sulfoxides because of the stereochemical characteristics of each series. Thus, the absolute configuration at the sulfur atom will allow a complementary analysis of the geometrical requirements of the contribution of n$\rightarrow\sigma^*$ donation to the conformer stability of the glucosidic linkage as well as the exocyclic hydroxymethyl group.

The absolute configuration of the sulfinyl group and the *exo*-anomeric effect in glucosyl sulfoxides has a strong influence on the conformational preferences around the glucosidic linkage. In the case of S_S sulfoxides, the *g*+ conformation is the one that must fulfill the spatial requirements for this stereoelectronic effect, whereas in R_S sulfoxides it must be the *g*− conformation (also called *exo*-anomeric conformation) (Figure 4).[15]

Recent theoretical and experimental work[16] has shown the influence of the $n_S \rightarrow \sigma^*_{C1-O5}$ overlap and the S−O C1−O5 dipole interaction on the conformational behavior of glycosyl sulfoxides in the gas phase and apolar media. The most stable configurations of α- and β-glycosyl sulfoxides are those where the aglycon is in the *g*− disposition and the lone pair of the sulfinyl group *anti* to the C1−O5 bond to establish the hyperconjugative interaction for the *exo*-anomeric effect (Figure 5). Therefore, the thermodynamic products and most stable configurations are S_S for α- and R_S for β-glycosyl sulfoxides.

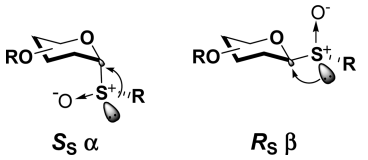

Figure 5. Most stable configuration for alkyl α-D- and β-D-glycopyranosides showing the orbitals involved in the *exo*-anomeric effect.[16]

Herein we report stereochemical results from a systematic study of a series of alkyl glucosyl sulfoxides on the basis of NMR and CD spectroscopic techniques in polar and apolar solvents. Correlations were observed between the absolute configuration of the sulfinyl group and the conformational properties of the glucosidic linkage (Figure 3) and hydroxymethyl group (Figure 4). The results clearly show the stereoelectronic requirements of the *exo*-anomeric effect over these two conformations.

RESULTS AND DISCUSSION

Synthesis and Characterization. The electrophilic oxidation of alkyl β-thioglucosides was carried out using H_2O_2/Ac_2O/silica gel in CH_2Cl_2 (Scheme 1) in good yields (80−95%).[17,18] The stereoselectivity of the oxidation was determined by the asymmetric induction of the glucosyl residue, which favored the formation of the sulfoxide with S_S configuration.[18−21] This methodology is one of the most useful for the synthesis of glucosyl sulfoxides, since it is fast, cheap, and simple.

The β anomeric configuration of the starting thioglucosides[22] was retained in the glucosyl sulfoxides, as determined by the $J_{H1,H2}$ coupling constant ($^3J \sim 9.8$ Hz) and by the cross peaks between H1, H5, and H3 in the T-ROESY experiments.

Unambiguous determination of the absolute configuration of the sulfinyl group is crucial in the present study. The major oxidation product of the ethyl β-thioglucosides with *m*-CPBA was reported to be the sulfoxide with S_S configuration.[20] This antecedent was not, however, sufficient to establish the absolute configuration of all our substrates, owing to the variability of the alkyl groups in our model compounds. Therefore, in order to determine the absolute configuration of the sulfinyl group in our sulfoxides, an in-depth stereochemical study was carried out by NMR and CD. The study pointed to CD as the preferential technique and showed clear advantages over NMR methods. Futhermore, a general rule for determining the absolute configuration of glycosyl sulfoxides by CD was established.[18]

Conformational Analysis of the Hydroxymethyl Group in Glucosyl Sulfoxides by NMR. The spin−spin coupling constants of the pyranoside ring protons were obtained by first-order analysis. The values of these coupling constants clearly demonstrated that all these compounds adopt the $^4C_1$ chair conformation. The NMR signals of the prochiral hydrogens H6*R* and H6*S* were assigned without difficulty, since their spectroscopic characteristics correlated totally with those described.[9] In some ^{1}H NMR spectra, the H6*R* and H6*S* signals overlapped, so the

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Scheme 1. Synthesis of Glucosyl Sulfoxides 1−7[17−20]

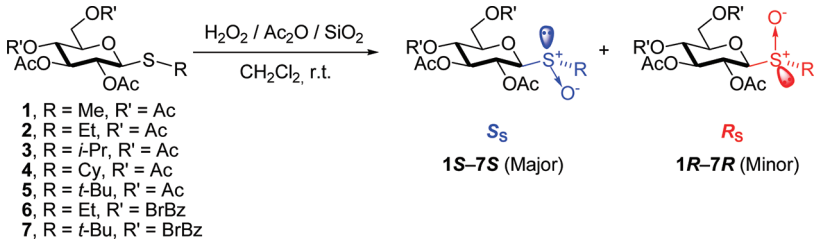


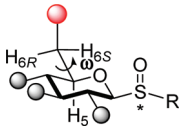
Table 1. Chemical Shifts for H1, C1, H6*R*, and H6*S*, and $J_{H5,H6R}$ and $J_{H5,H6S}$ Coupling Constants for the R_S Glucosyl Sulfoxides 1*R*−5*R* ($CDCl_3$)

no.	R	δ H1	δ C1	δ H6*R*	δ H6*S*	$J_{H5,H6R}$	$J_{H5,H6S}$
1*R*	methyl	4.15	87.4	4.26	4.23	5.0	2.8
2*R*	ethyl	4.19	86.6	4.25	4.25	5.2	2.8
3*R*	isopropyl	4.32	85.6	4.20	4.20	5.2	3.0
4*R*	cyclohexyl	4.32	85.3	4.21	4.21	5.0	3.7
5*R*	*tert*-butyl	4.35	85.4	4.15	4.20	6.7	2.7

Table 2. Chemical Shifts for H1, C1, H6*R*, and H6*S*, and $J_{H5,H6R}$ and $J_{H5,H6S}$ Coupling Constants for the S_S Glucosyl Sulfoxides 1*S*−5*S* ($CDCl_3$)

no.	R	δ H1	δ C1	δ H6*R*	δ H6*S*	$J_{H5,H6R}$	$J_{H5,H6S}$
1*S*	methyl	4.38	90.7	4.32	4.20	4.5	2.2
2*S*	ethyl	4.34	89.9	4.27	4.18	4.7	2.2
3*S*	isopropyl	4.22	88.6	4.21	4.16	4.9	2.2
4*S*	cyclohexyl	4.32	88.3	4.19	4.19	4.5	2.9
5*S*	*tert*-butyl	4.29	86.5	4.15	4.15	4.2	4.2

coupling constants $J_{H5,H6R}$ and $J_{H5,H6S}$ were measured from the H5 signal, which in most cases was isolated. Tables 1 and 2 show some NMR data for the *R* and *S* series of glucosyl sulfoxides, respectively.



Analysis of the collected data showed the sulfoxides from the two series behave very differently. The chemical shifts of the anomeric proton in the R_S sulfoxides provide evidence of a progressive deshielding throughout the series, specifically, as the degree of substitution of the *S*-aglycon increased. Nevertheless those of the anomeric proton for the S_S series fluctuated, showing no obvious trend. The chemical shift of the anomeric carbon for the R_S and S_S sulfoxides revealed a progressive shielding throughout both series, about 2 ppm for the R_S series and 4 ppm for S_S, this shift always being smaller for the R_S stereoisomer.

A similar pattern emerged for the $J_{H5,H6R}$ coupling constants. The methyl derivative **1*R*** showed a value of 5.0 Hz while for *tert*-butyl derivative **5R** it was higher, a value of 6.7 Hz. Contrary to this, that for the methyl **1*S*** was 4.5 Hz and for *tert*-butyl **5*S*** only

Table 3. Calculated Rotational Populations P_{gg}, P_{gt}, and P_{tg} in Different Solvents for the R_S Glucosyl Sulfoxides 1*R*−5*R*

	C_6D_6			$CDCl_3$			$(CD_3)_2CO$			CD_3OD			CD_3CN		
no.	P_{gg}	P_{gt}	P_{tg}	P_{gg}	P_{gt}	P_{tg}	P_{gg}	P_{gt}	P_{tg}	P_{gg}	P_{gt}	P_{tg}	P_{gg}	P_{gt}	P_{tg}
1*R*	61	39	0	57	40	3	53	47	0	58	42	0	53	47	0
2*R*	61	34	5	55	42	3	52	48	0	56	44	0	52	48	0
3*R*	55	45	0	54	42	4	49	51	0	54	46	0	50	50	0
4*R*	53	47	0	50	36	14	48	52	0				48	52	0
5*R*	41	57	2	40	57	3							42	58	0

Table 4. Calculated Rotational Populations P_{gg}, P_{gt}, and P_{tg} in Different Solvents for the S_S Glucosyl Sulfoxides 1*S*−5*S*

	C_6D_6			$CDCl_3$			$(CD_3)_2CO$			CD_3OD			CD_3CN		
no.	P_{gg}	P_{gt}	P_{tg}	P_{gg}	P_{gt}	P_{tg}	P_{gg}	P_{gt}	P_{tg}	P_{gg}	P_{gt}	P_{tg}	P_{gg}	P_{gt}	P_{tg}
1*S*	60	40	0	63	37	0	56	44	0	60	40	0	60	36	4
2*S*	59	41	0	61	39	0	55	45	0	59	41	0	59	41	0
3*S*	58	42	0	60	40	0	54	46	0	57	43	0	54	46	0
4*S*	59	41	0	61	35	4	51	49	0	56	44	0	55	45	0
5*S*	53	38	9	55	26	19	45	55	0	52	48	0	52	48	0

4.2 Hz. Furthermore, the magnitudes of the $J_{H5,H6R}$ coupling constants for R_S sulfoxides were always higher than those of their respective epimers S_S.

The rotamer populations of the hydroxymethyl groups (Tables 3 and 4) were calculated from the $^3J_{H5,H6}$ coupling constants. For this purpose, Serianni's equations[23] were used since they provide the most accurate representation among the different types of Karplus equations[24] of the rotameric populations in solution and leading to positive values for the *tg* population.

The study of the glucosyl sulfoxides in different apolar and polar solvents showed a strong influence on the rotational properties of the hydroxymethyl group, particularly for the more flexible ones, those with S_S configuration.[25] In apolar solvents, such as benzene and chloroform, sulfoxides **1*S*−5*S*** showed almost no variation in their populations. Nevertheless, this changed in polar solvents, where P_{gg} and P_{gt} decreased, their magnitudes increasing with the degree of substitution of the *S*-aglycon. On the other hand, glucosyl sulfoxides **1*R*−5*R*** showed this latter behavior in all solvents, although with different magnitudes. For the R_S sulfoxides, lower P_{gg} and higher P_{gt} than for the S_S epimers were obtained in all solvents.

For both sulfoxide series in all solvents there was a predominance of the *gg* rotamer. This was more pronounced in the case of

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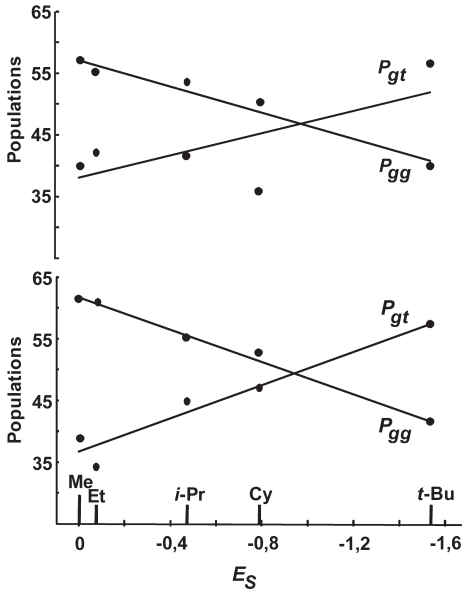

Figure 6. Rotational populations of *gg*/*gt* rotamers obtained in chloroform-*d* (above) and benzene-d_6 (below) versus corresponding E_S values for glucosyl sulfoxides **1*R*−5*R***.[27]

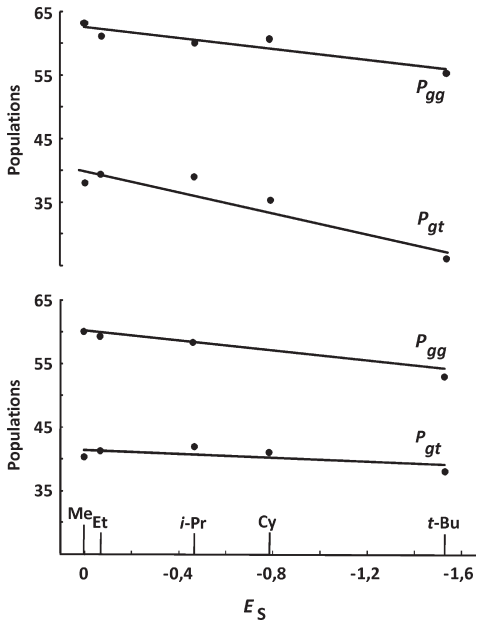

Figure 7. Rotational populations P_{gg} and P_{gt} obtained in chloroform-*d* (above) and benzene-d_6 (below) versus E_S for glucosyl sulfoxides **1*S*−5*S***.[28]

S_S sulfoxides, especially with apolar solvents (benzene and chloroform), where P_{gg} practically shows a constant value throughout the series with an approximated relation of P_{gg}/P_{gt} = 60:40%. It is interesting to observe small P_{tg} values only in a few cases, particularly in chloroform, where the derivatives **4*R*** and **5*S*** showed P_{tg} of 14 and 19%, respectively.

For R_S sulfoxides, the conformational behavior around the C5−C6 bond depended on the structure of the *S*-aglycon, although for a particular aglycon it was independent of the solvent. Thus, an increase in the degree of substitution of R led to an increased *gt* population, similar to that observed with alkyl

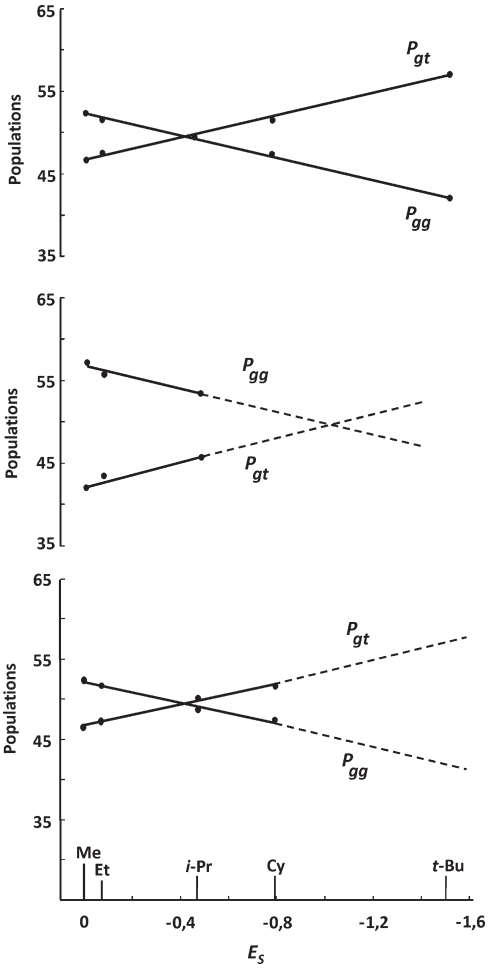

Figure 8. Rotational populations P_{gg} and P_{gt} in acetonitrile (above), methanol (center), and acetone (below) versus E_S for R_S glucosyl sulfoxides.[29]

thioglucosides.[22] The polarity of the solvent did not seem to affect the trend and magnitude, since in all cases a maximum of 57% was observed for the *gt* population.

Sulfoxides with S_S configuration showed similar rotational preferences in apolar solvents, where *gg* predominates whatever the structural nature of the aglycon. However, in polar solvents, such as acetone, methanol and acetonitrile, the *gg* and *gt* populations showed a tendency similar to their R_S epimers, where there was an influence of R on the rotation of the hydroxymethyl group.

As occurred with the alkyl β-D-thioglucosides,[22] good correlations between the hydroxymethyl rotational populations and Taft's steric parameters (E_S)[26] were found in different solvents. For a better analysis and comparison of results, these will be presented and discussed according to the polarity of solvents.

Figure 6 shows the relationship between the calculated rotational populations for R_S sulfoxides (**1*R*−5*R***) versus the E_S parameters of the corresponding substituent R in apolar solvents. The population of the *gt* and *gg* rotamers increased and decreased, respectively, as the absolute value E_S increased.

Regarding S_S glucosyl sulfoxides **1*S*−5*S*** in apolar solvents C_6D_6 and $CDCl_3$, Figure 7 shows the relationship between the calculated rotational populations and the E_S value of the corresponding aglycon (R). In both solvents, the *gt* populations were

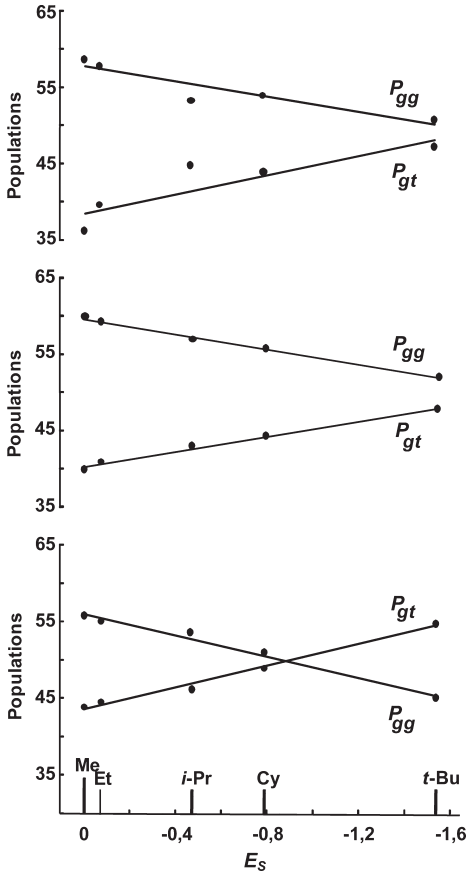

Figure 9. Rotational populations P_{gg} and P_{gt} in acetonitrile (above), methanol (center), and acetone (below) versus the corresponding E_S value of the alkyl group of the aglycon for S_S glucosyl sulfoxides.[30]

similar for sulfoxides **1*S***, **2*S***, and **3*S*** and decreased for the cyclohexyl **4*S*** and *tert*-butyl **5*S*** derivatives.

The general pattern exhibited by R_S sulfoxides, where the *gt* populations increased and *gg* decreased with the size of the aglycon, is no longer observed for the S_S epimers, where populations were similar or otherwise decreased.

We next consider the results of the conformational study of the hydroxymethyl group in polar solvents. Figure 8 shows the relationship of the *gg* and *gt* populations with Taft's steric parameter (E_S) for sulfoxides **1*R***−**5*R*** in acetone, methanol, and acetonitrile. The *gg* and *gt* populations show a good linear correlation with the E_S of the alkyl substituent of the aglycon. The *gt* rotamer population increases and that of the *gg* rotamer decreases as the degree of substitution of the aglycon increases. These results correspond with those for this stereoisomer in apolar solvents.

For S_S glucosyl sulfoxides, Figure 9 shows the correlation between the *gg* and *gt* rotational populations and Taft's steric parameter for the corresponding aglycon.

In acetone, methanol, and acetonitrile, in contrast with polar solvents, as the absolute value of E_S increased the *gg* population dropped and the *gt* population grew. This behavior is similar to that exhibited by the R_S epimers, although the populations are different: the R_S glucosyl sulfoxides showed smaller *gg* and higher *gt* populations than their corresponding S_S epimers.

Circular Dichroism Conformational Study. The rotational properties of the hydroxymethyl group of glucosyl sulfoxides were also studied by CD. First, the *O*-dibenzoyl derivatives **6*R***, **6*S***, **7*R***, and **7*S***, synthesized by oxidation of their respective precursor thioglycosides, were analyzed. The absolute configuration of the sulfinyl sulfur atom was established on the basis of the ^{1}H and ^{13}C NMR and CD data. Table 5 shows some NMR data for these sulfoxides.

Table 5. ^{1}H and ^{13}C NMR Data for the Glucosyl Sulfoxides 6*S*, 6*R*, 7*S*, and 7*R* ($CDCl_3$)

no.	R	abs conf	δ C1	δ H1	δ H6*R*	δ H6*S*	$J_{H5,H6R}$	$J_{H5,H6S}$
6*S*	ethyl	*S*	89.9	4.42	4.42	4.59	4.7	3.0
6*R*	ethyl	*R*	86.7	4.29	4.47	4.57	5.9	3.1
7*S*	*tert*-butyl	*S*	86.7	4.40	4.37	4.52	6.2	2.8
7*R*	*tert*-butyl	*R*	85.5	4.45	4.41	4.55	7.2	2.8

Table 6. Rotational Populations of *gg*, *gt*, and *tg* for the *O*-Dibenzoyl Glucosyl Sulfoxides 6*R*, 6*S*, 7*R*, and 7*S* in Chloroform and in Acetonitrile

		$CDCl_3$			CD_3CN		
no.	R	P_{gg}	P_{gt}	P_{tg}	P_{gg}	P_{gt}	P_{tg}
6*S*	ethyl	59	36	5	59	36	5
7*S*	*tert*-butyl	44	52	4	50	46	4
6*R*	ethyl	45	48	7	50	43	7
7*R*	*tert*-butyl	34	62	4	42	55	3

To compare NMR and CD data in the same solvent, the rotational populations of sulfoxides **6*R***, **6*S***, **7*R***, and **7*S*** were also calculated[23] in acetonitrile (Table 6).

The results showed the influence of the solvent on the conformation of the hydroxymethyl group in dibenzoyl derivatives (Table 6). An increase in solvent polarity led to a lower *gt* population, in favor of the *gg* rotamer. For these sulfoxides a small contribution of the *tg* rotamer was observed, remaining almost inalterable with the solvent.[31] The highest P_{gt} was for the *tert*-butyl derivative **7*R***, with 62 and 55% in $CDCl_3$ and CD_3CN, respectively. The ethyl derivatives showed smaller P_{gt} values than their respective *tert*-butyl analogues. Based on this, we established that the relationship between the bulkiness of the substituent and the conformation around C5−C6 can be extrapolated to these dibenzoyl derivatives.

Figure 10 shows the CD spectra obtained for glucosyl sulfoxides **6*R***, **6*S***, **7*R***, and **7*S***. The first Cotton effect, located to 251 nm, is consequence of the exciton coupling between the *O*-dibenzoyl chromophores.[32] The effect around 220 nm corresponds to the overlapping of the n→π transition of the sulfinyl group and the second Cotton effect of the exciton coupling.

In order to process the conformational data contained in these spectra, we focused on the intensities ($\Delta\varepsilon$) of the first Cotton effects.[33] According to the CD exciton chirality method,[32] the smaller intensity of the *tert*-butyl derivatives **7** must be due to a higher population of the *gt* rotamer (with a negative CD contribution) than their ethyl analogues **6**, and sulfoxides with R_S configuration have a greater contribution from the *gt* rotamer than their corresponding S_S epimers. These results are in complete agreement with those obtained by NMR (CD_3CN).

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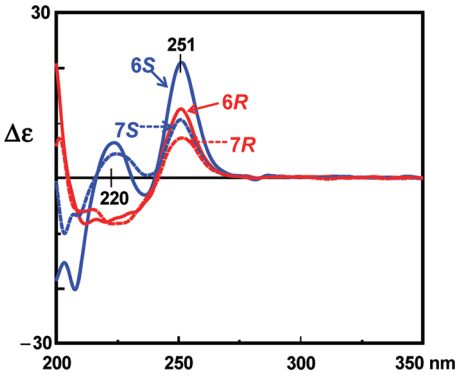

Figure 10. CD spectra of glucosyl sulfoxides **6*S***, **6*R***, **7*S***, and **7*R*** (CH_3CN).

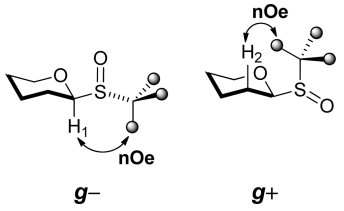

Figure 11. NOE effects for *g*− and *g*+ rotamers for R_S and S_S sulfoxides.

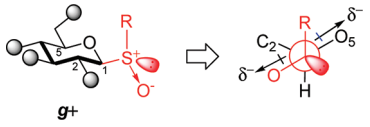

Figure 12. Disposition of the dipole moments of C1−O5 and S−O bonds for R_S sulfoxides in the *g*+ conformation.

Conformational Analysis around the Glucosidic Bond and the Exo-Anomeric Effect. A. Apolar Solvents. To study the conformation around the glycosidic linkage, NOE experiments (C_6D_6) were carried out. For sulfoxides **1*R***, **2*R***, and **5*R*** the nearest protons to the sulfinyl group on the aglycon were irradiated. NOE with H1 and H2 were observed for **1*R*** and **2*R*** (methyl and ethyl) and only with H1 in the case of sulfoxide **5*R***. The spectra obtained for the isopropyl and cyclohexyl sulfoxides **3*R*** and **4*R*** by irradiating the saccharidic H2 did not exhibit any NOE with the aglyconic proton because of the overlapping of the methine proton with H5. These results provide evidence that in sulfoxides having small aglycons, like **1*R*** and **2*R***, both rotamers *g*− and g+ contribute to the conformational equilibrium of the glucosidic linkage (Figure 11). As the size of the aglycon increases the rotational equilibrium moves toward *g*−, this being anchored in the case of bulky aglycons such as *tert*-butyl. In addition, the presence of *anti* populations were not detected by NOE experiments.[34]

The contribution of the *g*+ conformer to the equilibrium, observed in some sulfoxides, can be explained by the dipole moments of the C1−O5 and S−O bonds. For R_S sulfoxides, the *g*+ conformation has an *anti* disposition of these dipoles, which generates a null resulting dipole moment, so therefore this conformation would be favored in apolar solvents (Figure 12).

According to the NOE analysis, we established that the *g*− conformer is predominant in the conformational equilibrium

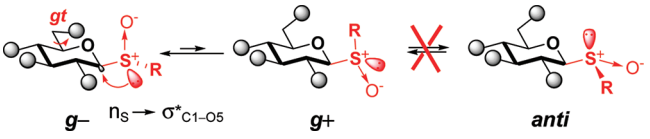

Figure 13. Conformational equilibrium around the glucosidic bond for R_S glucosyl sulfoxides in apolar solvents.

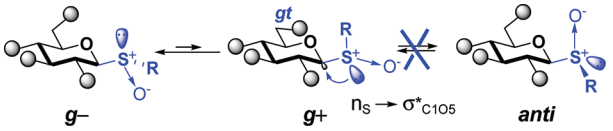

Figure 14. Conformational equilibrium around the glucosidic linkage for S_S sulfoxides in apolar solvents.

of R_S sulfoxides around the C1−S linkage (Figure 13). In these sulfoxides, the *g*− conformation fulfills the geometric requirements for the *exo*-anomeric effect.[3] Furthermore, as in β-thioglycosides, the rotational analysis of the hydroxymethyl group of R_S sulfoxides in apolar solvents (benzene and chloroform) showed a correlation with the *exo*-anomeric effect, where an increase in the intensity of this leads to an increased *gt* population.

NOE experiments were also carried out with S_S sulfoxides (C_6D_6). The analysis of these spectra established that the conformational equilibrium around the glucosidic linkage depends on the aglycon. For substrates having a small aglycon, **1*S*** (methyl) and **2*S*** (ethyl), NOE were observed with the anomeric H1 and H2 protons (Figure 11). This result may be associated with the presence of the *g*+ and *g*− conformers in the equilibrium. For the isopropyl and cyclohexyl derivatives **3*S*** and **4*S***, the main NOE observed is with the anomeric proton, the intensity with H2 diminishing with respect to H1. This suggests that for these latter sulfoxides there is a greater contribution from the *g*− conformer in the equilibrium. In the case of the *tert*-butyl sulfoxide **5*S***, the main NOE signal is with the anomeric proton H1, it being practically negligible with H2. This establishes that the glycosidic conformation for this sulfoxide is practically confined to the *g*− rotamer.

The results indicate that steric effects are of great importance in the stability of the *g*+ conformer. As the size of the substituent increases, a reduction in the relative intensity of NOE with H2 was observed, which means a loss in the contribution of *g*+ to the conformational equilibrium, where conformer *g*− becomes predominant.

The above-mentioned conformational analysis establishes that *g*− and g+ conformers contribute to the equilibrium and that their proportion depends on the steric nature of the substituent of the aglycon. On the other hand, the spectra did not show any signal indicating the presence of the *anti* rotamer (Figure 14).

The contribution of *g*+ to the conformational equilibrium is enhanced in sulfoxides having a small aglycon, in which the steric interactions with H2 are low. This conformer fulfills the geometrical requirements for the *exo*-anomeric effect. Furthermore, the rotational study of the hydroxymethyl group for sulfoxides **1*S***, **2*S***, and **3*S*** (benzene) showed P_{gt} of 40, 41, and 42%, respectively. However, the results for sulfoxides **4*S*** (cyclohexyl) and **5*S*** (*tert*-butyl) showed that the *g*− rotamer predominates in the glucosidic conformation, although without ruling out the presence of

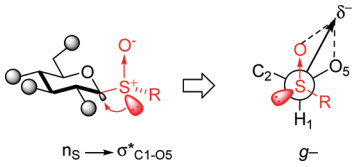

Figure 15. Net dipole moment for R_S sulfoxides in the *g*− conformation.

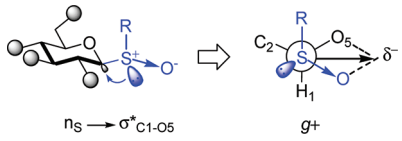

Figure 16. Net dipole moment for the C1−O5 and S−O bonds for the S_S sulfoxides in the *g*+ conformation.

g+. Conformer *g*− does not allow the corresponding orbital overlap for the *exo*-anomeric effect, so the tendency for the *gt* rotamer to increase is halted, due to the increased *g*− population. Similar P_{gt} to those of sulfoxides **1*S***−**3*S*** (Table 4) were thus obtained for compounds **4*S*** and **5*S***: 41 and 38%, respectively. Therefore, all these results are in agreement with those shown in Figures 6 and 7.

B. Polar solvents. NOE experiments were also carried out for the R_S glucosyl sulfoxides in acetonitrile-d_3. The methylene and methine protons of the sulfoxides having a primary or secondary aglycon were irradiated, whereas for the derivatives **1*R*** and **5*R*** the methyl groups were irradiated.

In all cases, a strong NOE with the H1 proton was found. Unlike what happens in benzene, NOEs with H2 were not observed in acetonitrile. This result allows us to rule out the presence of conformer *g*+ in the conformational equilibrium, *g*− being the major conformer. In consequence, a greater *gt* population should be expected in polar solvents that in apolar. This is seen on comparing Figure 6 (apolar solvent) and 8 (polar), especially for sulfoxides with small aglycons. The *g*− rotamer exhibits the C1−O5 and S−O dipole moments in a *gauche* arrangement, giving rise to a net dipole moment, this conformation therefore being favored in polar solvents (Figure 15). Furthermore, the *g*− conformation is stabilized by the *exo*-anomeric effect, so for R_S sulfoxides in polar solvents it can be inferred that the conformation equilibrium around the glucosidic linkage is anchored in the *g*− rotamer, as the NOE study indicates.

Considering the results obtained from the rotational analysis of the hydroxymethyl group, where an increase in the absolute value of E_S leads to a growth in the *gt* population, there is a clear correlation between the *exo*-anomeric effect and the rotational properties. The steric nature of the substituent R of the aglycon would modulate the intensity of the effect through a "steric protection" of the $n_S \rightarrow \sigma^*_{C1-O5}$ hyperconjugation, which would affect the populations of different rotamers probably by means of variations in the lengths of the C1−S and C1−O5 bonds.[3]

NOE experiments with S_S sulfoxides (CD_3CN) showed that those having a small aglycon, **1*S*** (methyl) and **2*S*** (ethyl), exhibit an intense spatial connection between irradiated protons (**1*S***: methyl group; **2*S***: methylene) with H1 and H2 protons. This result points to significant contributions of the *g*− and *g*+ conformers in the conformational equilibrium. Moreover, the *g*+ conformation (Figure 16), with the C1−O5 and S−O dipole moments in a *gauche* disposition, is favored in polar solvents. The stability of this conformer is also augmented by the *exo*-anomeric effect, since its lone electron pair is in the right disposition for hyperconjugation.

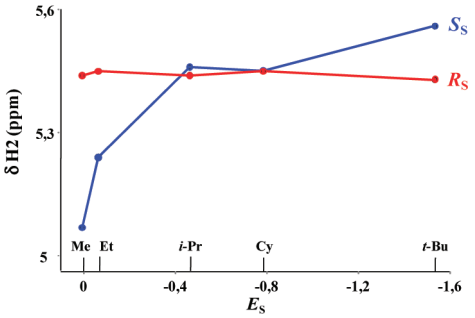

Figure 17. Chemical shift of H2 versus E_S for R_S and S_S glucosyl sulfoxides in $CDCl_3$.

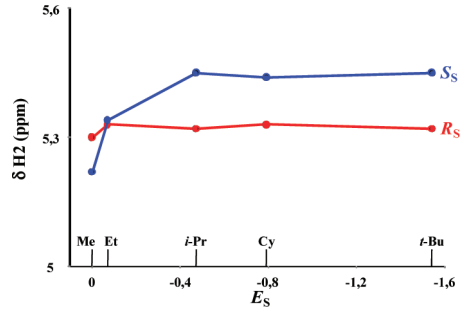

Figure 18. Chemical shift of H2 versus E_S for R_S and S_S glucosyl sulfoxides in CD_3CN.

For sulfoxides **3*S*** (isopropyl) and **4*S*** (cyclohexyl), the main NOE was with the anomeric proton, although a smaller NOE with H2 was also observed. This establishes that in these sulfoxides having a secondary aglycon the equilibrium between *g*+ and *g*− is displaced toward the *g*− conformer. For sulfoxide **5*S***, we can see that the *tert*-butyl group has a NOE exclusively with H1, which indicates that for this compound the glucosidic bond is exclusively in the *g*− conformation.

Figures 17 and 18 show the chemical shifts of H2 for the different alkyl R_S and S_S glucosyl sulfoxides in chloroform and acetonitrile, respectively. Striking changes are seen for S_S sulfoxides, depending on the aglycon and the solvent, while values for R_S sulfoxides were practically constant.

According to previous work with ethyl glycosyl sulfoxides,[19] the chemical shifts of H2 have to appear at lower fields in sulfoxides with R_S absolute configuration than in those of S_S because of the *syn* disposition between the sulfinylic oxygen and the H2 in R_S sulfoxides. However, this criterion is not general. Thus, in the present study we found that the H2 chemical shift depends on the nature of the aglycon (R) and the solvent. In $CDCl_3$, the methyl and ethyl sulfoxides complied with this pattern; however, H2 showed a similar chemical shift in both isopropyl and cyclohexyl sulfoxide series and for the *tert*-butyl derivative H2 a lower field appeared in the case of the S_S-configured sulfoxide.

On the basis of the results obtained from the NOE study, sulfoxides exhibit different conformational behavior around the glucosidic linkage, according to the size of its aglycon, the

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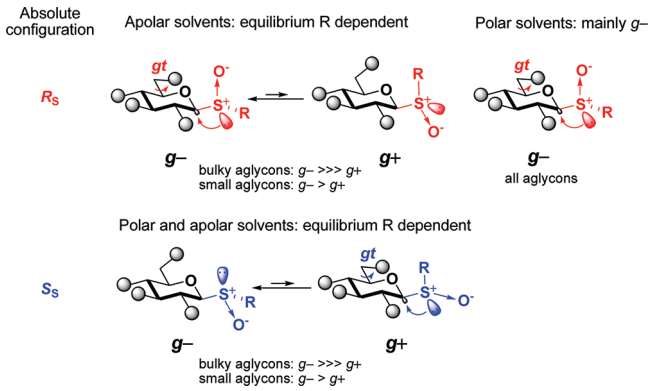

Figure 19. Conformations of the glucosidic linkage for R_S and S_S sulfoxides in polar and apolar solvents.

structural nature of the solvent, and the absolute configuration at the sulfur atom (Figure 19). For sulfoxides with an R_S configuration, the conformation of the glucosidic linkage in polar solvents is mainly confined to the *g*− conformer, independently of the size of R, while for S_S sulfoxides there is a conformational equilibrium between *g*− and *g*+. Such equilibrium was also noted for these S_S sulfoxides in apolar solvents and found to be dependent on the alkyl group, small groups like methyl and ethyl presenting a higher contribution from the g+ conformer. This would explain the shielding of H2 in these S_S sulfoxides (Figures 17 and 18) due to the *syn* disposition between the R (Me, Et) group and H2. On the other hand, R_S sulfoxides showed no variation in δ H2, as a result of the conformational rigidity of their glucosidic linkages. Nevertheless, NOE experiments with R_S sulfoxides having small aglycons in the apolar solvent C_6D_6 revealed a higher degree of conformational flexibility around the glucosidic linkage and explain the slight changes observed in δ H2 in this solvent. All these observations are shown in Figure 19.

We hope that the stereochemical properties of glucosyl sulfoxides in solution describe herein, namely, the effect of sulfoxide configuration and conformation on the rotational population of the C5−C6 bond, provide a better understanding of the manner in which the aglycon interacts with the hydroxymethyl group and how the reactivity of glycosides can be affected by the populations of the *gg*, *gt*, and *tg* rotamers.[35]

CONCLUSIONS

Analysis of the synthesized glucosyl sulfoxides showed that the conformational behavior around both the C5−C6 (hydroxymethyl) and C1−O1 (glucosidic) bonds are determined by the absolute configuration of the sulfinyl group, as well as the nature of the solvent and the structural nature of the aglycon. For R_S sulfoxides the following characteristics were observed: (i) higher *gt* populations of the hydroxymethyl group than for their corresponding S_S epimers; (ii) a greater degree of substitution of the aglycon leads to increased *gt* and decreased *gg* populations; (iii) a linear relationship between the rotamer populations of the hydroxymethyl group and the corresponding Taft's steric parameter (E_S) of the alkyl group attached to the sulfinyl group; (iv) a mostly *g*− conformation around the glucosidic linkage in polar solvents, accompanied by a dependency on the size of the aglycon in apolar solvents—for small aglycons a *g*−/g+ equilibrium displaced toward *g*−, and for larger aglycons an anchored *g*− conformation.

The corresponding study with S_S glucosyl sulfoxides found the following: (i) The conformation around the C5−C6 bond was highly susceptible to the polarity of the solvent. In apolar solvents the structure of aglycon did not show any effect on the conformation of the hydroxymethyl group. However, in polar solvents the rotational behavior was analogous to that shown by their R_S epimers, namely: an increase in the degree of substitution of the aglycon led to increases in the *gt* population. (ii) Small aglycons (methyl and ethyl) showed a greater degree of flexibility around the glucosidic linkage than their R_S epimers, and in both polar and apolar solvents, there was an equilibrium between *g*− and *g*+ rotamer conformation. Nevertheless, this moved toward *g*− as the size of aglycon increased, due to steric interactions.

A relationship between the stereoelectronic *exo*-anomeric effect and the rotational properties of the hydroxymethyl group can be inferred from both types of glucosyl sulfoxides. For the R_S stereoisomers, in polar and apolar solvents, the population of the *gt* and *gg* rotamers increased and decreased, respectively, as the absolute value of the Taft's parameter (E_S) of the alkyl group attached to the sulfinyl group increased (Figures 6 and 8) and in accordance with the main rotamer around the glucosidic linkage, the *g*−, which possesses the appropiate orbital requirements to facilitate the *exo*-anomeric effect. For S_S sulfoxides, however, the population of the predominant *g*− rotamer is solvent dependent and explains the noncorrelation between the structure of the aglycon and the hydroxymethyl group populations in apolar solvents, as for this conformation there is no orbital overlapping for the *exo*-anomeric effect (Figure 7). Finally, the higher *g*+ population in polar solvents, complying with the right spatial requirements for the *exo*-anomeric effect, led to similar behavior in the R_S stereoisomers, although of a smaller magnitude (Figure 9), due to the equilibrium between the *g*− and *g*+ rotamers.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of Glucopyranosyl Sulfoxides.[17] To a solution of the thioglucoside, Ac_2O (1.3 equiv), and silica gel (200 mg/mmol) in CH_2Cl_2 (5 mL/mmol) was slowly added H_2O_2 (1.2 equiv from a 34% aqueous solution). The reaction was stirred until completion (TLC). The mixture was then diluted with CH_2Cl_2, filtered to remove the silica gel, washed with saturated $NaHCO_3$ solution, and dried over $MgSO_4$. Excess solvent was removed under reduced pressure and the mixture of epimers purified by silica gel column chromatography (*n*-hexane/EtOAc mixtures). Compounds **6*S***, **6*R***, **7*S***, and **7*R*** were purified by silica gel preparative TLC (*n*-hex/EtOAc 1:1).

Sulfoxides 1*S* and 1*R*. Following the general procedure for the synthesis of glucopyranosyl sulfoxides, 841 mg (2.2 mmol) of methyl 2,3,4,6-tetra-*O*-acetyl 1-thio-β-D-glucopyranoside led to 827 mg (2.1 mmol, 95%) of sulfoxide **1** as an epimeric mixture (S_S/R_S = 3:1).

(S_S) Methyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside *S*-oxide (1*S*): TLC R_f = 0.34 ($MeOH/CH_2Cl_2$ 1:19); mp =126−127 °C; $[\alpha]_D$ = −12 (*c* 0.9, $CHCl_3$); HRMS calcd for $C_{15}H_{22}O_{10}NaS$ 417.0831 ($[M + Na]^+$), found 417.0831; ^1H NMR (δ, $CDCl_3$) 5.31 (dd, *J* = 9.3, 9.3 Hz, H-3), 5.10 (dd, *J* = 9.5, 9.5 Hz, H-4), 5.07 (dd, *J* = 9.6, 9.6 Hz, H-2), 4.38 (d, *J* = 10.2 Hz, H-1), 4.32 (dd, *J* = 4.5, 12.8 Hz, H-6*R*), 4.20 (dd, *J* = 2.2, 12.8 Hz, H-6*S*), 3.84 (ddd, *J* = 2.2, 4.5, 10.1 Hz, H-5), 2.68 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (δ, $CDCl_3$) 170.4 (s), 169.9 (s), 169.7 (s), 169.3 (s), 90.7 (d, C-1), 76.8 (d, C-5), 73.1 (d, C-3), 68.2 (d, C-2), 67.6 (d, C-4), 61.3 (t, C-6), 32.8 (q), 20.6 (q), 20.5 (q), 20.5 (q), 20.5 (q); UV (CH_3CN) λ_{max} (ε) 200 nm (3500); CD (CH_3CN) λ_{ext} ($\Delta\varepsilon$) 222 (6.4),

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200 nm (−14.3). Anal. Calcd for $C_{15}H_{22}O_{10}S$: C, 45.68; H, 5.62; S, 8.13. Found: C, 45.71; H, 5.64.

(R_S)-Methyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside *S*-oxide (1*R*): TLC R_f = 0.32 (MeOH/CH_2Cl_2 1:19); mp = 172−173 °C; $[\alpha]_D$ = −66 (*c* 0.9, $CHCl_3$); MS (FAB) calcd for $C_{15}H_{22}O_{10}NaS$ 417.0831 ($[M + Na]^+$), found 417.0833; ^1H NMR (δ, $CDCl_3$) 5.44 (dd, *J* = 9.6, 9.6 Hz, H-2), 5.36 (dd, *J* = 9.3, 9.3 Hz, H-3), 5.14 (dd, *J* = 9.7, 9.7 Hz, H-4), 4.26 (dd, *J* = 5.0, 12.5 Hz, H-6*R*), 4.23 (dd, *J* = 2.8, 12.5 Hz, H-6*S*), 4.15 (d, *J* = 9.9 Hz, H-1), 3.82 (ddd, *J* = 2.8, 5.0, 10.1 Hz, H-5), 2.69 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (δ, $CDCl_3$) 170.5 (s), 170.4 (s), 169.2 (s), 168.9 (s), 87.4 (d, C-1), 76.8 (d, C-5), 73.7 (d, C-3), 67.8 (d, C-4), 66.8 (d, C-2), 61.8 (t, C-6), 33.1 (q), 20.7 (q), 20.6 (q), 20.5 (q), 20.5 (q); UV (CH_3CN) λ_{max} (ε) 200 nm (3500); CD (CH_3CN) λ_{ext} ($\Delta\varepsilon$) 217.4 (−9.1), 198.4 nm (3.1). Anal. Calcd for $C_{15}H_{22}O_{10}S$: C, 45.68; H, 5.62; S, 8.13. Found: C, 45.70; H, 5.66.

Sulfoxides 2*S* and 2*R*. Following the general procedure for the synthesis of glucopyranosyl sulfoxides, 630 mg (1.6 mmol) of the ethyl 2,3,4,6-tetra-*O*-acetyl 1-thio-β-D-glucopyranoside gives 570 mg (1.4 mmol, 87%) of the corresponding epimeric mixture of sulfoxides (S_S/R_S = 2:1).

(S_S)-Ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside *S*-oxide (2*S*): TLC R_f = 0.36 (MeOH/CH_2Cl_2 1:19); mp = 123−124 °C; $[\alpha]_D$ = −34 (*c* 1.6, $CHCl_3$); HRMS calcd for $C_{16}H_{24}O_{10}NaS$ 431.0988 ($[M + Na]^+$), found 431.0992; ^1H NMR (δ, $CDCl_3$) 5.30 (dd, *J* = 9.2, 9.2 Hz, H-3), 5.24 (dd, *J* = 9.5, 9.5 Hz, H-2), 5.09 (dd, *J* = 9.6, 9.6 Hz, H-4), 4.34 (d, *J* = 9.8 Hz, H-1), 4.27 (dd, *J* = 4.7, 12.6 Hz, H-6*R*), 4.18 (dd, *J* = 2.2, 12.6 Hz, H-6*S*), 3.80 (ddd, *J* = 2.2, 4.7, 10.1 Hz, H-5), 2.96−2.85 (m, 2H), 2.08 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 1.38 (dd, *J* = 7.6, 7.6 Hz, 3H); ^{13}C NMR (δ, $CDCl_3$) 170.4 (s), 169.9 (s), 169.6 (s), 169.3 (s), 89.9 (d, C-1), 76.8 (d, C-5), 73.2 (d, C-3), 68.4 (d, C-2), 67.6 (d, C-4), 61.4 (t, C-6), 41.3 (t), 20.6 (q), 20.5 (q), 20.5 (q), 20.4 (q), 6.5 (q); UV (CH_3CN) λ_{max} (ε) 203 nm (3500); CD (CH_3CN) λ_{ext} ($\Delta\varepsilon$) 226 (7.1), 200 nm (−13.9). Anal. Calcd for $C_{16}H_{24}O_{10}S$: C, 47.05; H, 5.92; S, 7.85. Found: C, 47.31; H, 6.07; S, 7.53.

(R_S)-Ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside *S*-oxide (2*R*): TLC R_f = 0.34 (MeOH/CH_2Cl_2 1:19); mp = 160−161 °C; $[\alpha]_D$ = −51 (*c* 0.4, $CHCl_3$); HRMS calcd for $C_{16}H_{24}O_{10}NaS$ 431.0988 ($[M + Na]^+$), found 431.0989; ^1H NMR (δ, $CDCl_3$) 5.45 (dd, *J* = 9.6, 9.6 Hz, H-2), 5.36 (dd, *J* = 9.4, 9.4 Hz, H-3), 5.13 (dd, *J* = 9.7, 9.7 Hz, H-4), 4.25 (m, H-6*S*, H-6*R*), 4.19 (d, *J* = 10.4 Hz, H-1), 3.80 (ddd, *J* = 2.8, 5.2, 10.1 Hz, H-5), 3.13 (m, 1H), 2.81 (m, 1H), 2.08 (s. 3H), 2.06 (s. 3H), 2.04 (s. 3H), 2.03 (s. 3H), 1.34 (dd, *J* = 7.5, 7.5 Hz, 3H); ^{13}C NMR (δ, $CDCl_3$) 170.5 (s), 170.4 (s), 169.2 (s), 168.5 (s), 86.6 (d, C-1), 76.9 (d, C-5), 73.8 (d, C-3), 67.8 (d, C-4), 66.9 (d, C-2), 61.9 (t, C-6), 41.2 (t), 20.7 (q), 20.6 (q), 20.5 (q), 20.5 (q), 7.3 (q); UV (CH_3CN) λ_{max} (ε) 203 nm (3500); CD (CH_3CN) λ_{ext} ($\Delta\varepsilon$) 220 (−11.0), 197 nm (4.0). Anal. Calcd. for $C_{16}H_{24}O_{10}S$: C, 47.05; H, 5.92; S, 7.85. Found: C, 47.39; H, 6.12; S, 7.76.

Sulfoxides 3*S* and 3*R*. Following the general procedure for the synthesis of glucopyranosyl sulfoxides, 1.3 g (3.3 mmol) of the isopropyl 2,3,4,6-tetra-*O*-acetyl 1-thio-β-D-glucopyranoside led to 1.3 g (3.1 mmol, 94%) of the corresponding sulfoxide epimers (S_S/R_S = 1.4:1).

(S_S)-Isopropyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside *S*-oxide (3*S*): TLC R_f = 0.40 (MeOH/CH_2Cl_2 1:19); mp = 122−123 °C; $[\alpha]_D$ = −10 (*c* 1.4, $CHCl_3$); HRMS calcd for $C_{17}H_{26}O_{10}NaS$ 445.1144 ($[M + Na]^+$), found 445.1140; ^1H NMR (δ, $CDCl_3$) 5.46 (dd, *J* = 9.5, 9.5 Hz, H-2), 5.29 (dd, *J* = 9.3, 9.3 Hz, H-3), 5.08 (dd, *J* = 9.4, 9.4 Hz, H-4), 4.22 (d, *J* = 9.8 Hz, H-1), 4.21 (dd, *J* = 4.9, 12.6 Hz, H-6*R*), 4.16 (dd, *J* = 2.2, 12.6 Hz, H-6*S*), 3.77 (ddd, *J* = 2.2, 4.9, 10.1 Hz, H-5), 3.12 (m, 1H), 2.08 (s. 3H), 2.06 (s. 3H), 2.04 (s. 3H), 2.02 (s. 3H), 1.34 (d, *J* = 7.0 Hz, 3H), 1.30 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (δ, $CDCl_3$) 170.4 (s), 170.1 (s), 169.6 (s), 169.3 (s), 88.6 (d, C-1), 76.8 (d, C-5), 73.2 (d, C-3), 68.8 (d, C-2), 67.7 (d, C-4), 61.6 (t, C-6), 47.7 (d), 20.7 (q), 20.6 (q), 20.6 (q), 20.5 (q), 16.9 (q), 13.2 (q); UV (CH_3CN) λ_{max} (ε) 203 nm (3500); CD (CH_3CN) λ_{ext} ($\Delta\varepsilon$) 230 (9.1), 200 nm (−13.1). Anal. Calcd. for $C_{17}H_{26}O_{10}S$: C, 48.33; H, 6.20; S, 7.59. Found: C, 48.57; H, 6.36; S, 7.20.

(R_S)-Isopropyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside *S*-oxide (3*R*): TLC R_f = 0.38 (MeOH/CH_2Cl_2 1:19); mp = 153−154 °C; $[\alpha]_D$ = −57 (*c* 1.0, $CHCl_3$); HRMS calcd for $C_{17}H_{26}O_{10}NaS$ 445.1144 ($[M + Na]^+$), found 445.1147; ^1H NMR (δ, $CDCl_3$) 5.44 (dd, *J* = 9.5, 9.5 Hz, H-2), 5.36 (dd, *J* = 9.2, 9.2 Hz, H-3), 5.11 (dd, *J* = 9.6, 9.6 Hz, H-4), 4.32 (d, *J* = 9.8 Hz, H-1), 4.25−4.17 (m, H-6*S*, H-6*R*), 3.78 (ddd, *J* = 3.0, 5.2, 10.0 Hz, H-5), 3.39 (m, 1H), 2.09 (s. 3H), 2.07 (s. 3H), 2.02 (s. 3H), 2.01 (s. 3H), 1.42 (d, *J* = 7.0, 3H), 1.16 (d, *J* = 7.0, 3H); ^{13}C NMR (δ, $CDCl_3$) 170.5 (s), 169.1 (s), 169.1 (s), 168.6 (s), 85.6 (d, C-1), 77.1 (d, C-5), 73.8 (d, C-3), 67.9 (d, C-4), 67.0 (d, C-2), 62.1 (t, C-6), 47.3 (d), 20.6 (q), 20.6 (q), 20.5 (q), 20.4 (q), 16.6 (q), 15.6 (q); UV (CH_3CN) λ_{max} (ε) 205 nm (3500); CD (CH_3CN) λ_{ext} ($\Delta\varepsilon$) 221 (−9.6), 197 nm (1.9). Anal. Calcd for $C_{17}H_{26}O_{10}S$: C, 48.33; H, 6.20; S, 7.59. Found: C, 48.38; H, 6.32; S, 7.36.

Sulfoxides 4*S* and 4*R*. Following the general procedure for the synthesis of glucopyranosyl sulfoxides, 1.2 g (2.7 mmol) of cyclohexyl 2,3,4,6-tetra-*O*-acetyl 1-thio-β-D-glucopyranoside gives 1.0 g (2.3 mmol, 84%) of the epimeric mixture of the corresponding sulfoxides (S_S/R_S = 1.2:1).

(S_S)-Cyclohexyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside *S*-oxide (4*S*): TLC R_f = 0.59 (MeOH/CH_2Cl_2 1:19); mp =138 °C; $[\alpha]_D$ = −22 (*c* 1.4, $CHCl_3$); HRMS calcd for $C_{20}H_{30}O_{10}NaS$ 485.1457 ($[M + Na]^+$), found 485.1458; ^1H NMR (δ, $CDCl_3$) 5.45 (dd, *J* = 9.5, 9.5 Hz, H-2), 5.29 (dd, *J* = 9.3, 9.3 Hz, H-3), 5.08 (dd, *J* = 9.6, 9.6 Hz, H-4), 4.32 (d, *J* = 9.9 Hz, H-1), 4.19−4.18 (m, H-6*S*, H-6*R*), 3.77 (ddd, *J* = 2.9, 4.5, 10.0 Hz, H-5), 2.93 (m, 1H), 2.07 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 1.94−1.88 (m, 4H), 1.72−1.50 (m, 4H), 1.42−1.35 (m, 2H); ^{13}C NMR (δ, $CDCl_3$) 170.4 (s), 170.1 (s), 169.6 (s), 169.3 (s), 88.3 (d, C-1), 76.5 (d, C-5), 73.3 (d, C-3), 68.7 (d, C-2), 67.7 (d, C-4), 61.7 (t, C-6), 55.9 (d), 26.8 (t), 25.5 (t), 25.3 (t), 25.2 (t). 25.2 (t), 20.6 (q), 20.6 (q), 20.5 (q), 20.4 (q); UV (CH_3CN) λ_{max} (ε) 205 nm (3500); CD (CH_3CN) λ_{ext} ($\Delta\varepsilon$) 231 (8.0), 202 nm (−12.4). Anal. Calcd for $C_{20}H_{30}O_{10}S$: C, 51.94; H, 6.54; S, 6.93. Found: C, 51.99; H, 6.65; S, 6.74.

(R_S)-Cyclohexyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside *S*-oxide (4*R*): TLC R_f = 0.58 (MeOH/CH_2Cl_2 1:19); mp =143 °C; $[\alpha]_D$ = −55 (*c* 1.2, $CHCl_3$); HRMS calcd for $C_{20}H_{30}O_{10}NaS$ 485.1457 ($[M + Na]^+$), found 485.1463; ^1H NMR (δ, $CDCl_3$) 5.45 (dd, *J* = 9.6, 9.6 Hz, H-2), 5.36 (dd, *J* = 9.3, 9.3 Hz, H-3), 5.10 (dd, *J* = 9.7, 9.7 Hz, H-4), 4.32 (d, *J* = 9.9 Hz, H-1), 4.22−4.18 (m, H-6*S*, H-6*R*), 3.78 (ddd, *J* = 3.7, 5.0, 10.0 Hz, H-5), 3.26 (m, 1H), 2.27 (m, 1H), 2.25 (m, 1H), 2.07 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 1.94−1.84 (m, 2H), 1.73−1.65 (m, 4H), 1.53−1.32 (m, 4H); ^{13}C NMR (δ, $CDCl_3$) 170.4 (s), 170.3 (s), 169.1 (s), 168.6 (s), 85.3 (d, C-1), 77.1 (d, C-5), 73.9 (d, C-3), 67.9 (d, C-4), 66.8 (d, C-2), 62.3 (t, C-6), 55.3 (d), 26.6 (t), 25.8 (t), 25.4 (t), 25.2 (t), 25.2 (t), 20.6 (q), 20.5 (q), 20.5 (q), 20.4 (q); UV (CH_3CN) λ_{max} (ε) 205 nm (3500); CD (CH_3CN) λ_{ext} ($\Delta\varepsilon$) 222 (−8.3), 194 nm (1.2). Anal. Calcd for $C_{20}H_{30}O_{10}S$: C, 51.94; H, 6.54; S, 6.93. Found: C, 51.99; H, 6.65; S, 6.74.

Sulfoxides 5*S* and 5*R*. Following the general procedure for the synthesis of glucopyranosyl sulfoxides, 1.4 g (3.4 mmol) of *tert*-butyl 2,3,4,6-tetra-*O*-acetyl 1-thio-β-D-glucopyranoside provides 1.3 g (3.0 mmol, 88%) of the epimeric mixture of the corresponding sulfoxides (S_S/R_S = 1.3:1).

(S_S)-*tert*-Butyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside *S*-oxide (5*S*): TLC R_f = 0.57 (MeOH/CH_2Cl_2 1:19); mp = 134 °C; $[\alpha]_D$ = +37 (*c* 1.0, $CHCl_3$); HRMS calcd for $C_{18}H_{28}O_{10}NaS$

459.1301 ([M + Na]$^+$), found 459.1302; ^{1}H NMR (δ, $CDCl_3$) 5.56 (dd, J = 9.3, 9.3 Hz, H-2), 5.27 (dd, J = 9.1, 9.1 Hz, H-3), 5.07 (dd, J = 9.7, 9.7 Hz, H-4), 4.29 (d, J = 9.7 Hz, H-1), 4.15 (d, J = 4.2 Hz, H-6*R*, H-6*S*), 3.74 (ddd, J = 4.2, 4.2, 10.1 Hz, H-5), 2.06 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (δ, $CDCl_3$) 170.3 (s), 170.2 (s), 169.3 (s), 169.3 (s), 86.5 (d, C-1), 76.4 (d, C-5), 73.6 (d, C-3), 68.8 (d, C-2), 67.8 (d, C-4), 61.9 (t, C-6), 55.8 (s), 23.0 (q, 3Cs), 20.7 (q), 20.6 (q), 20.5 (q), 20.5 (q); UV (CH_3CN) λ_{max} (ε) 206 nm (3500); CD (CH_3CN) λ_{ext} ($\Delta\varepsilon$) 229 (8.9), 203 nm (−6.4). Anal. Calcd for $C_{18}H_{28}O_{10}S$: C, 49.53; H, 6.47; S, 7.35. Found: C, 49.70; H, 6.41; S, 7.02.

(*R*$_S$) *tert*-Butyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside *S*-oxide (5*R*): TLC R_f = 0.56 (MeOH/CH_2Cl_2 1:19); mp = 140 °C; $[\alpha]_D$ = −59 (*c* 1.0, $CHCl_3$); HRMS calcd for $C_{18}H_{28}O_{10}NaS$ 459.1301 ([M + Na]$^+$), found 459.1305; ^{1}H NMR (δ, $CDCl_3$) 5.43 (dd, J = 9.7, 9.7 Hz, H-2), 5.32 (dd, J = 9.3, 9.3 Hz, H-3), 5.06 (dd, J = 9.7, 9.7 Hz, H-4), 4.35 (d, J = 10.1 Hz, H-1), 4.20 (dd, J = 2.7, 12.4 Hz, H-6*S*), 4.15 (dd, J = 6.7, 12.4 Hz, H-6*R*), 3.78 (ddd, J = 2.7, 6.7, 9.8 Hz, H-5), 2.06 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (δ, $CDCl_3$) 170.4 (s), 170.3 (s), 169.2 (s), 168.7 (s), 85.4 (d, C-1), 76.7 (d, C-5), 73.7 (d, C-3), 68.0 (d, C-4), 67.4 (d, C-2), 62.5 (t, C-6), 56.1 (s), 24.9 (q, × 3Cs), 20.5 (q), 20.5 (q), 20.5 (q), 20.5 (q); UV (CH_3CN) λ_{max} (ε) 200 nm (3500); CD (CH_3CN) λ_{ext} ($\Delta\varepsilon$) 223 (−8.5), 203 nm (−7.3). Anal. Calcd for $C_{18}H_{28}O_{10}S$: C, 49.53; H, 6.47; S, 7.35. Found: C, 49.55; H, 6.66; S, 7.23.

Sulfoxides 6*S* and 6*R*. Following the general procedure for the synthesis of glucopyranosyl sulfoxides, 216 mg (0.32 mmol) of ethyl 2,3-di-*O*-acetyl-4,6-bis-*O*-(4-bromobenzoyl)-1-thio-β-D-glucopyranoside gives 183 mg (0.27 mmol, 84%) of the corresponding sulfoxide epimeric mixture (S_S/R_S = 1.7:1).

(*S*$_S$) Ethyl 2,3-di-*O*-acetyl-4,6-bis-*O*-(4-bromobenzoyl)-1-thio-β-D-glucopyranoside *S*-oxide (6*S*): TLC R_f = 0.30 (*n*-hex/EtOAc 1:4); mp = 184 °C; $[\alpha]_D$ = −3 (*c* 0.5, $CHCl_3$); HRMS calcd for $C_{26}H_{26}O_{10}{}^{79}Br_2NaS$ 710.9511 ([M + Na]$^+$), found 710.9531; ^{1}H NMR (δ, $CDCl_3$) 7.82 (m, 4H), 7.57 (m, 4H), 5.54 (dd, J = 9.3, 9.3 Hz, H-3), 5.43 (dd, J = 9.7, 9.7 Hz, H-4), 5.37 (dd, J = 9.5, 9.5 Hz, H-2), 4.59 (dd, J = 3.0, 12.4 Hz, H-6*S*), 4.42 (dd, J = 4.7, 12.4 Hz, H-6*R*), 4.42 (d, J = 10.0 Hz, H-1), 4.08 (ddd, J = 2.0, 4.7, 9.8 Hz, H-6*R*), 2.91 (m, 2H), 2.09 (s, 3H), 1.93 (s, 3H), 1.36 (dd, J = 7.5 y 7.5 Hz, 3H); ^{13}C NMR (δ, $CDCl_3$) 169.9 (s), 169.7 (s), 165.1 (s), 164.4 (s), 132.0 (d, × 2C), 131.8 (d, × 2C), 131.3 (d, × 2C), 131.1 (d, × 2C), 129.3 (s), 128.6 (s), 128.1 (s), 127.2 (s), 89.9 (d, C-1), 77.1 (d, C-5), 72.8 (d, C-3), 69.0 (d, C-2), 68.5 (d, C-4), 62.5 (t, C-6), 41.5 (t), 20.6 (q), 20.4 (q), 6.4 (q); UV (CH_3CN) λ_{max} (ε) 245 nm (38200); CD (CH_3CN) λ_{ext} ($\Delta\varepsilon$) 251 (20.9), 236 (−3.1), 223 (6.4), 207 nm (−20.2). Anal. Calcd for $C_{26}H_{26}Br_2O_{10}S$: C, 45.23; H, 3.80; S, 4.64. Found: C, 45.21; H, 3.90; S, 4.70.

(*R*$_S$) Ethyl 2,3-di-*O*-acetyl-4,6-bis-*O*-(4-bromobenzoyl)-1-thio-β-D-glucopyranoside *S*-oxide (6*R*): TLC R_f = 0.29 (*n*-hex/EtOAc 1:4); mp =204 °C; $[\alpha]_D$ = −17 (*c* 0.3, $CHCl_3$); HRMS calcd for $C_{26}H_{26}O_{10}{}^{79}Br_2NaS$ 710.9511 ([M + Na]$^+$), found 710.9520; ^{1}H NMR (δ, $CDCl_3$) 7.85−7.80 (m, 4H), 7.59−7.55 (m, 4H), 5.59 (dd, J = 9.0, 9.0 Hz, H-3), 5.54 (dd, J = 9.3, 9.3 Hz, H-2), 5.43 (dd, J = 9.3, 9.3 Hz, H-4), 4.57 (dd, J = 3.1, 12.3 Hz, H-6*S*), 4.47 (dd, J = 5.9, 12.3 Hz, H-6*R*), 4.29 (d, J = 9.4 Hz, H-1), 4.10 (ddd, J = 3.1, 5.9, 9.5 Hz, H-5), 3.13 (m, 1H), 2.82 (m, 1H), 2.08 (s, 3H), 1.93 (s, 3H), 1.29 (dd, J = 7.5, 7.5, 3H); ^{13}C NMR (δ, $CDCl_3$) 170.3 (s), 168.8 (s), 165.2 (s), 164.3 (s), 132.0 (d, × 2C), 131.8 (d, × 2C), 131.3 (d, × 2C), 131.1 (d, × 2C), 129.2 (s), 128.6 (s), 128.1 (s), 127.3 (s), 86.7 (d, C-1), 76.7 (d, C-5), 73.4 (d, C-3), 69.3 (d, C-4), 66.9 (d, C-2), 63.3 (t, C-6), 41.3 (t), 20.6 (q), 20.5 (q), 7.3 (q); UV (CH_3CN) λ_{max} (ε) 245 nm (38200); CD (CH_3CN) λ_{ext} ($\Delta\varepsilon$) 251 (12.5), 220 (−8.1), 212 nm (−8.4). Anal. Calcd for $C_{26}H_{26}Br_2O_{10}S$: C, 45.23; H, 3.80; S, 4.64. Found: C, 45.24; H, 3.88; S, 4.73.

Sulfoxides 7*S* and 7*R*. Following the general procedure for the synthesis of glucopyranosyl sulfoxides, 263 mg (0.37 mmol) of the *tert*-butyl 2,3-di-*O*-acetyl-4,6-bis-*O*-(4-bromobenzoyl)-1-thio-β-D-glucopyranoside gives 187 mg (0.26 mmol, 71%) of the corresponding sulfoxide mixture (S_S/R_S = 3:1).

(*S*$_S$) *tert*-Butyl 2,3-di-*O*-acetyl-4,6-bis-*O*-(4-bromobenzoyl)-1-thio-β-D-glucopyranoside *S*-oxide (7*S*): TLC R_f = 0.52 (*n*-hex/EtOAc 1:4); mp =153 °C; $[\alpha]_D$ = +12 (*c* 0.7, $CHCl_3$); HRMS calcd for $C_{28}H_{30}O_{10}{}^{79}Br_2NaS$ 738.9824 ([M + Na]$^+$), found 738.9828; ^{1}H NMR (δ, $CDCl_3$) 7.85−7.80 (m, 4H), 7.60−7.56 (m, 4H), 5.67 (dd, J = 9.3, 9.3 Hz, H-2), 5.51 (dd, J = 9.2, 9.2 Hz, H-3), 5.39 (dd, J = 9.6, 9.6 Hz, H-4), 4.52 (dd, J = 2.8, 12.4 Hz, H-6*S*), 4.40 (d, J = 9.6 Hz, H-1), 4.37 (dd, J = 6.2, 12.4 Hz, H-6*R*), 4.05 (ddd, J = 2.8, 6.2, 9.6 Hz, H-5), 2.06 (s, 3H), 1.95 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (δ, $CDCl_3$) 170.1 (s), 169.4 (s), 165.1 (s), 164.4 (s), 133.7 (s), 132.0 (d, × 2C), 131.8 (d, × 2C), 131.3 (d, × 2C), 131.1 (d, × 2C), 130.2 (s), 129.8 (s), 128.3 (s), 86.7 (d, C-1), 76.5 (d, C-5), 73.3 (d, C-3), 69.0 (d, C-2), 68.9 (d, C-4), 63.0 (t, C-6), 55.9 (s), 23.1 (q, × 3C), 20.7 (q), 20.5 (q); UV (CH_3CN) λ_{max} (ε) 245 nm (38200); CD (CH_3CN) λ_{ext} ($\Delta\varepsilon$) 251 (10.6), 224 (4.4), 209 (−7.0), 203 nm (−10.2). Anal. Calcd for $C_{28}H_{30}Br_2O_{10}S$: C, 46.81; H, 4.21; S, 4.46. Found: C, 46.86; H, 4.32; S, 4.50.

(*R*$_S$) *tert*-Butyl 2,3-di-*O*-acetyl-4,6-bis-*O*-(4-bromobenzoyl)-1-thio-β-D-glucopyranoside *S*-oxide (7*R*): TLC R_f = 0.51 (*n*-hex/EtOAc 1:4); mp = 156 °C; $[\alpha]_D$ = −41 (*c* 0.2, $CHCl_3$); HRMS calcd for $C_{28}H_{30}O_{10}{}^{79}Br_2NaS$ 738.9824 ([M + Na]$^+$), found 738.9841; ^{1}H NMR (δ, $CDCl_3$) 7.80−7.78 (m, 4H), 7.58−7.52 (m, 4H), 5.56−5.50 (m, H-3, H-2), 5.36 (dd, J = 9.6, 9.6 Hz, H-4), 4.55 (dd, J = 2.8, 12.3 Hz, H-6*S*), 4.45 (d, J = 9.6 Hz, H-1), 4.41 (dd, J = 7.2, 12.3 Hz, H-6*R*), 4.11 (ddd, J = 2.8, 7.2, 9.6 Hz, H-5), 2.09 (s, 3H), 1.93 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (δ, $CDCl_3$) 170.4 (s), 168.7 (s), 165.2 (s), 164.4 (s), 132.0 (d), 131.8 (d), 131.3 (d), 131.1 (d), 129.2 (s), 128.6 (s), 128.0 (s), 127.3 (s), 85.5 (d, C-1), 76.7 (d, C-5), 73.4 (d, C-3), 69.3 (d, C-4), 67.4 (d, C-2), 63.7 (t, C-6), 56.2 (s), 24.2 (q, 3Cs), 20.6 (q), 20.5 (q); UV (CH_3CN) λ_{max} (ε) 245 nm (38200); CD (CH_3CN) λ_{ext} ($\Delta\varepsilon$) 251 (7.3), 223 (−8.3), 211 nm (−6.1). Anal. Calcd for $C_{28}H_{30}Br_2O_{10}S$: C, 46.81; H, 4.21; S, 4.46. Found: C, 46.92; H, 4.33; S, 4.55.

■ ASSOCIATED CONTENT

Supporting Information. NOE experiments, NMR and CD tables, as well as ^{1}H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(28) Regression line equations for S_S sulfoxides. Benzene: $P_{gg} = 3.9_S + 60.1$ ($R^2 = 0.81$); $P_{gt} = 1.5E_S + 41.3$ ($R^2 = 0.41$). Chloroform: $P_{gg} = 4.3E_S + 62.5$ ($R^2 = 0.83$); $P_{gt} = 7.9E_S + 39.9$ ($R^2 = 0.78$).

(29) Regression line equations for R_S sulfoxides. Acetone: $P_{gg} = 6.3E_S + 52.6$ ($R^2 = 0.96$); $P_{gt} = 6.3_S + 47.4$ ($R^2 = 0.96$). Methanol: $P_{gg} = 7.3E_S + 57.3$ ($R^2 = 0.86$); $P_{gt} = 7.3E_S + 42.7$ ($R^2 = 0.86$). Acetonitrile: $P_{gg} = 6.9E_S + 52.9$ ($R^2 = 0.99$); $P_{gt} = 6.9E_S + 47.0$ ($R^2 = 0.99$).

(30) Regression line equations for S_S sulfoxides. Acetone: $P_{gg} = 6.9E_S + 56.2$ ($R^2 = 0.97$); $P_{gt} = 6.9E_S + 43.8$ ($R^2 = 0.97$). Methanol: $P_{gg} = 4.9E_S + 59.6$ ($R^2 = 0.99$); $P_{gt} = 4.9E_S + 40.4$ ($R^2 = 0.99$). Acetonitrile: $P_{gg} = 4.9E_S + 58.8$ ($R^2 = 0.82$); $P_{gt} = 6.3E_S + 39.7$ ($R^2 = 0.70$).

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(33) The amplitude (*A* value) of split CD Cotton effects is defined as $A = \Delta\varepsilon_1 - \Delta\varepsilon_2$ where $\Delta\varepsilon_1$ and $\Delta\varepsilon_2$ are intensities of the first and second Cotton effects, respectively. Occasionally, the presence of a background ellipticity alters the intensity of the Cotton effects at short wavelengths. For this reason, the intensities of the second Cotton effects and the amplitudes (*A* values) of the CD spectra of our model compounds may not be precise; the intensities of the first Cotton effects are thus more accurate for comparative analysis.

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