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Conformational properties of glucosyl-thioglucosides and their *S*-oxides in solution

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ABSTRACT

A stereochemical study of a series of alkyl glucosyl-β-(1→6)-thioglucosides and their *S*-oxides by means of nuclear magnetic resonance and circular dichroism revealed that the populations around the thioglucosidic bond (ring I) as well as those of the interglycosidic linkage ω depend on the aglycone, the solvent and, in the *S*-oxides, on the absolute configuration of the sulfur atom. The results for the thio-disaccharides showed the strong influence of the solvent polarity on the conformational preferences of the interglycosidic bond. In polar solvents, the magnitudes of the rotamer populations, P_{gg} and P_{gt}, remained practically constant through the series, while in non-polar solvents a clear predominance of *gt* conformation was observed as well as the influence of the aglycone on the conformational equilibrium. The results for both (S_S)- and (R_S)-alkyl thiogentiobiosyl *S*-oxide series showed a clear predominance of the *gt* rotamer, P_{gt} always having a higher magnitude in the latter series than in the former. Both series exhibited linear correlations between interglycosidic P_{gg} and P_{gt} and Taft's steric parameter (E_S) for the alkyl group attached to the sulfinyl group, especially in non-polar solvents. The stereochemical study around the C1–S bond established that the flexibility around this linkage depends on aglycone size, solvent polarity, and the absolute configuration of the sulfur, derivatives of the S_S series showing higher flexibility in both polar and non-polar media. The conformational properties of these compounds in solution are explained in terms of stereoelectronic, steric, and solvent effects.

1. Introduction

Carbohydrates play important roles in biological systems. Protein/glycan recognition phenomena can be found in several events involved in cell–cell communication and system regulation such as: homeostasis,[1] immune response,[2] inflammation,[3] tumor metastasis,[4] bacterial colonization, and infection.[5] The success of protein/carbohydrate recognition in its early stage is highly sensitive to conformational requirements, where the glycan should display a suitable disposition. Therefore, the study of the conformational properties of carbohydrates is of key importance for a better understanding of these interactions.[6] The conformational flexibility of saccharides is described through torsion angles ψ (C1′–O6–C6–C5), ϕ (O5′–C1′–O6–C6), and ω (O5–C5–C6–O6). In particular, the flexibility around the C5–C6 bond is of key importance in oligosaccharides, which possess (1→6) glycosidic bonds in their structure. This type of linkage, particularly β-(1→6), confers a high degree of conformational freedom on the saccharide, thus these molecules present a higher entropy compared to saccharides with other glycosidic bond configurations.[7] The torsion angle ω can adopt any value between 0° and 360°. However, in practice we distinguish three staggered rotamers namely *gauche–gauche* (*gg*, $\omega = -60$), *gauche–trans* (*gt*, $\omega = 60$), and *trans–gauche* (*tg*, $\omega = 180$) as described in Figure 1.

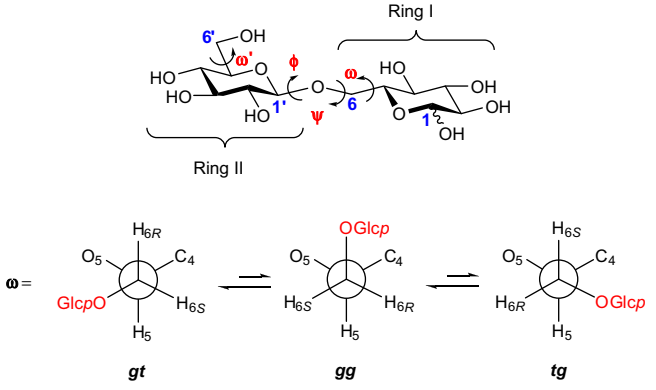

Figure 1. Rotamers around the interglycosidic C5–C6 bond in (1→6)-glucosyl-glucosides: *gauche–trans* (*gt*), *gauche–gauche* (*gg*), and *trans–gauche* (*tg*).[8]

Studies of the hydroxymethyl conformation in glycosides, free or connected to another sugar ring (torsion angle ω), have revealed

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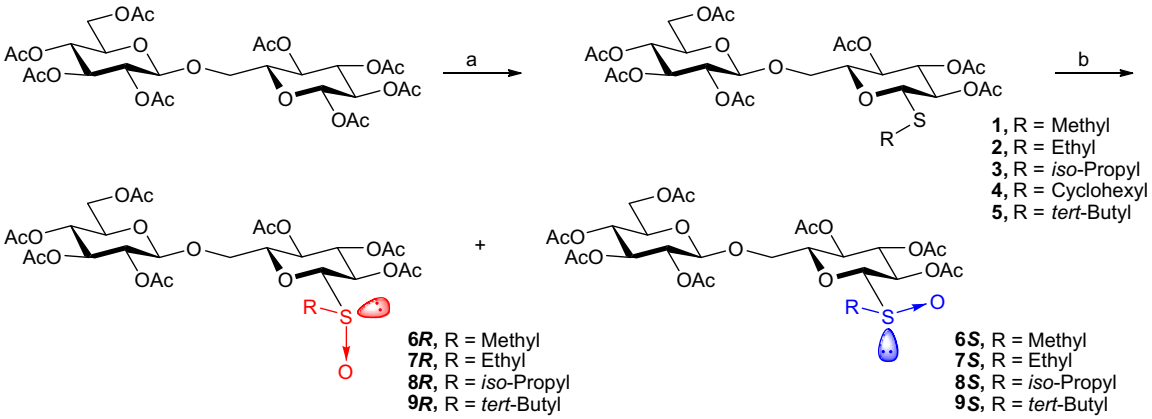

Scheme 1. Synthesis of glucosyl thioglucosides **1–5** and their *S*-oxides **6*R*–9*R*** and **6*S*–9*S***. Reagents and conditions: (a) compound **1**: $(NH_2)_2CS$, $BF_3{\cdot}Et_2O$, MeCN, reflux, then Et_3N, CH_3I; compounds **2–5**: R–SH, $BF_3{\cdot}Et_2O$, DCM, rt; (b) H_2O_2, Ac_2O, silica gel, DCM, rt.

that the populations of this group depend on the structure of the aglycone and its absolute configuration, the anomeric configuration, the glycosidic linkage type, and the nature of the solvent.[9] Furthermore, a conformational domino effect has been observed in alkyl disaccharides, where all the above factors present in glycosides were detected.[9h,i]

Stereoelectronic[10] and steric effects have been proposed to explain all these factors affecting the populations of the hydroxymethyl group in solution. Recently, a conformational study with alkyl glycosyl sulfoxides has allowed the stereoelectronic requirements involved in these populations to be studied.[11]

Conformational analysis of β-D-glucopyranosyl-(1→6)-D-glucose (gentiobiose) in aqueous solution[12] shows that rotamers *gg* and *gt* are the two main contributors to the conformational equilibrium around the interglycosidic bond, with populations of 34% and 66%, respectively. In contrast to monosaccharides, where the *gg* rotamer is the most populated, the hydroxymethyl group connecting the two sugar rings exhibits a preference for the *gt* population. Furthermore, it has been determined that the rotation around torsion angle ϕ is restricted due to the *exo*-anomeric effect,[10] while angle ψ has higher flexibility.[13]

Glycosyl sulfoxides have become important intermediates for the synthesis of bioactive molecules[14,15] and several of them show biological activity themselves, including antitumoral, anti-infective, and antidiabetic action.[14] Furthermore, the stereoelectronic interactions that cause the *exo*-anomeric effect have been proven to be involved in alkyl glycosyl sulfoxides, with the absolute configuration at the sulfur atom being of primary importance. Herein, we focus on the conformational properties around the glycosidic C1–S and interglycosidic C5–C6 bonds of a series of alkyl thiogentiobiosides and their corresponding sulfoxide series in solution, along with how the molecular characteristics of the (S_S)- and (R_S)-sulfoxide series affect these properties in various media.

2. Results and discussion

2.1. Synthesis and characterization

Alkyl β-thiogentiobiosides **2–5** were synthesized by treatment of β-Gentiobiose octaacetate with $BF_3{\cdot}Et_2O$ and the corresponding thiol (Scheme 1). This method is straightforward and economical, and achieves a high yield of thioglycosides.[16] The neighboring group participation of the acetyl group at C2 led to the stereoselective formation of β-thiodisaccharides. Nevertheless, long exposure of these to a Lewis acid may result in anomerization to an α-thioglycoside[17] and control of the reaction time is crucial for improved yield. This procedure was not employed in preparing compound **1**, due to the high volatility of methanethiol, but used in its place was that based on the S-alkylation of glycosyl thiouronium salts developed by Ibatullin.[18]

The anomeric configuration of thiogentiobiosides **1–5** was established by measuring the $^3J_{H1,H2}$ coupling constants (~9.8 Hz) and analysis of spatial couplings between H1, H3, and H5 from T-ROESY experiments. The anomeric configuration of the interglycosidic bond was corroborated in the same way ($J_{H1',H2'}$ ~8.0 Hz), and cross peaks between H1′, H3′, and H5′).

The pro-chiral protons H6*R* and H6*S* for both rings were identified and assigned as described in the literature.[19] Protons H6*R* and H6*S* on ring I are vicinal to the interglycosidic acetal function while H6*R*′ and H6*S*′ on ring II are vicinal to the ester. According to the data, the chemical shift relationship for protons on ring I is δH6*S* > δH6*R*, while for protons on ring II the opposite was established (δH6*R*′ > δH6*S*′). The coupling constant relationships with H5 were found to be $J_{H5,H6R} > J_{H5H6S}$, which was consistent with the previous chemical shift analysis.

The sulfur atom of the alkyl thiogentiobiosides was oxidized using the $H_2O_2/Ac_2O/SiO_2$ system,[20] which affords an epimeric mixture of (R_S)- and (S_S)-sulfinyl gentiobiosides **6–9** (Scheme 1). Due to the asymmetric induction of the sugar moiety, sulfoxides of (S_S)-configuration were the major product expected by oxidation of thiogentiobiosides.[21,22] Although the epimeric ratio (S_S) > (R_S) was observed in all the model compounds synthesized, we noticed that this relationship tends to remain similar as the bulk of the aglyconic alkyl group increases. Analysis of $^3J_{H1,H2}$ coupling constants and H1, H3, and H5 cross peaks in T-ROESY experiments provided evidence for retention of the anomeric configuration in both sugar residues after sulfur oxidation. Both (S_S)- and (R_S)-epimers can be isolated by normal phase chromatography on silica gel using ethyl acetate/hexane(s) systems as eluents. After separating the epimers, the spectroscopic characterization and assignment of the absolute sulfinyl configuration was crucial for the success of the present study. The absolute configuration of the sulfur was assigned by NMR and CD analyses according to the method developed in our group (Fig. 2).[23]

2.2. Conformational analysis of the hydroxymethyl groups in alkyl 1-thiogentiobiosides

The coupling constants $J_{H5,H6R}$ and $J_{H5,H6S}$ for both sugar units were obtained by first order analysis. The assignment and coupling constant measurements were carried out without difficulty due to the good separation of the chemical shifts for the H6 protons and their total correlation with the described spectroscopic character-

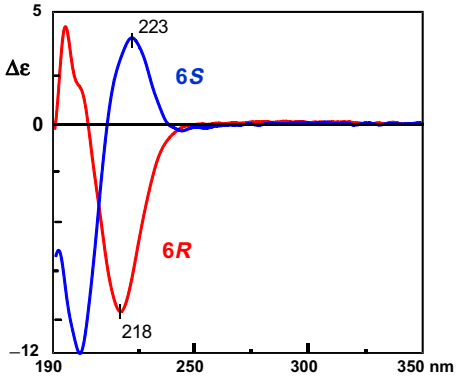

Figure 2. CD spectra of compounds **6*S*** and **6*R*** in CH_3CN.

Table 1
Chemical shifts for H1, C1, H6*R* and H6*S*, and $J_{H5,H6R}$ and $J_{H5,H6S}$ coupling constants for rings I and II of alkyl 1-thio-β-gentiobiosides **1–5** ($CDCl_3$)

Ring I							
No.	R	δH1	δC1	δH6*R*	δH6*S*	$J_{H5,H6R}$	$J_{H5,H6S}$
1	Me	4.37	82.9	3.57	3.88	6.8	2.2
2	Et	4.47	83.2	3.60	3.87	7.2	2.0
3	*i*-Pr	4.53	82.9	3.66	3.80	7.2	1.7
4	Cy	4.55	82.9	3.65	3.83	7.2	1.7
5	*t*-Bu	4.61	82.0	3.66	3.79	7.5	1.7
Ring II							
No.	R	δH1′	δC1′	δH6*R*′	δH6*S*′	$J_{H5',H6R'}$	$J_{H5',H6S'}$
1	Me	4.57	100.9	4.27	4.12	4.7	2.3
2	Et	4.58	100.7	4.28	4.13	4.8	2.3
3	*i*-Pr	4.56	100.5	4.24	4.13	4.9	2.4
4	Cy	4.60	100.6	4.27	4.13	4.9	2.4
5	*t*-Bu	4.58	100.3	4.26	4.11	5.0	2.3

Table 2
Calculated rotational populations P_{gg} and P_{gt} in different solvents for alkyl 1-thiogentiobiosides **1–5**

No.	C_6D_6		$CDCl_3$		$(CD_3)_2CO$		CD_3OD		CD_3CN	
	P_{gg}	P_{gt}	P_{gg}	P_{gt}	P_{gg}	P_{gt}	P_{gg}	P_{gt}	P_{gg}	P_{gt}
Ring I										
1	43	57	40	60	42	58	53	47	51	49
2	40	60	38	62	44	56	51	49	52	48
3	38	62	37	63	44	56	49	51	52	48
4	39	61	37	63	44	56	51	49	52	48
5	33	67	34	66	43	57	49	51	52	48
Ring II										
1	64	36	61	39	57	43	61	39	59	41
2	62	38	60	40	57	43	60	40	58	42
3	62	38	59	41	56	44	59	41	58	42
4	61	39	59	41	55	45	58	42	58	42
5	60	40	59	41	55	45	57	43	57	43

istics.[19] Selected NMR data for compounds **1–5** are presented in Table 1.

Analysis of the NMR data established that major changes occur in ring I, which holds the *S*-aglycone. The chemical shift for the anomeric proton on this ring showed a displacement to a low field with a difference of $\Delta\delta = 0.24$ ppm from compound **1** (R = methyl) to compound **5** (R = *tert*-butyl), establishing a trend that depends on the degree of substitution of the *S*-aglycone. The chemical shifts for H1′ on ring II remained approximately constant through the series with a value of 4.59 ppm, while the shift for the anomeric carbon showed a small displacement to high field with a difference of $\Delta\delta = 1$ ppm (ring I) or $\Delta\delta = 0.5$ ppm (ring II) from compound **1** (R = methyl) to compound **5** (R = *tert*-butyl).

Noteworthy results were obtained from the coupling constants $J_{H5,H6}$ on the saccharide ring bearing the *S*-alkyl moiety. As the degree of substitution of the *S*-aglycone increased, the $J_{H5,H6R}$ value increased. For methyl derivative **1**, the lowest $J_{H5,H6R}$ of 6.8 Hz was observed, whereas for compound **5**, which possesses the bulkiest aglycone, this value rose to 7.5 Hz. A similar but reduced tendency was also noted for $J_{H5',H6R'}$ on the second ring, with a $\Delta\delta = 0.3$ ppm between **1** and **5** compared to $\Delta\delta = 0.7$ ppm observed for $J_{H5,H6R}$. In contrast, $J_{H5,H6S}$ showed a decrease in magnitude from methyl derivative **1** ($J_{H5,H6S} = 2.2$ Hz) to *tert*-butyl thiogentiobioside **5** ($J_{H5,H6S} = 1.7$ Hz) while $J_{H5',H6S'}$ remains practically constant through the series.

The rotamer populations for the interglycosidic (ring I) and free (ring II) hydroxymethyl groups were calculated from the $^3J_{H5,H6}$ coupling constants, using the equation system proposed by Serianni.[24] These provide the most accurate representation for rotameric populations in solution among the different types of Karplus equations[25] and do not lead to negative values for the *tg* rotamer. Table 2 shows the calculated rotamer populations for compounds **1–5** in different solvents.

The collected data show the strong influence of solvent polarity on the conformational preferences of the interglycosidic bond. In the polar solvents methanol-d_4 and acetonitrile-d_3, rotamers *gg* and *gt* made a similar contribution to the conformational equilibrium. However, a slight preference for the *gt* conformation was observed in acetone-d_6. For the three polar solvents studied, magnitudes of P_{gg} and P_{gt} remained practically constant through the series; the full set of model compounds showed practically identical conformational preferences in the interglycosidic linkage for each polar solvent.

Different conformational behavior was observed for the interglycosidic bond in non-polar solvents (benzene-d_6 and chloroform-*d*), where there was a clear predominance of the *gt* conformation with an average P_{gt} value of 62%. Furthermore, in these solvents the influence of the aglycone over the conformational equilibrium was also observed as reflected in the P_{gg} and P_{gt} values along the series. An increase in the degree of substitution of the aglyconic alkyl group led to P_{gt} rising at the cost of P_{gg}.

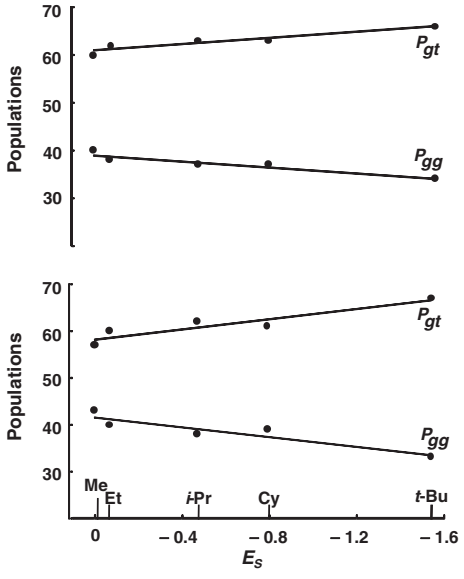

Figure 3. Rotamer populations P_{gg} and P_{gt} of the interglycosidic linkage (ring I) obtained in chloroform-*d* (above) and benzene-d_6 (below) versus E_S for thiogentiobiosides **1–5**.[28]

Methyl derivative **1** exhibited a P_{gt} of 57% for benzene-d_6, while P_{gt} increased to 67% for *tert*-butyl derivative **5**. For chloroform-*d* these values were 60% and 66%, respectively.

As previously determined by our group for both β-thioglycosides[26] and β-glycosyl sulfoxides,[11] good correlations between C5–C6 rotamer populations and Taft's steric parameters (E_S)[27] were also observed for thiogentiobiosides **1**–**5** in the different solvents used herein. Rotamer populations P_{gg} and P_{gt} obtained in non-polar solvents are represented as a function of E_S in Figure 3. For both benzene-d_6 and chloroform-*d*, a linear relationship between rotamer populations for *gg*/*gt* and E_S was established, the P_{gt} and P_{gg} values increased and decreased, respectively, as the absolute value of E_S increased.

The rotamer populations P_{gg} and P_{gt} obtained in polar solvents versus the corresponding Taft steric parameters are shown in Figure 4. In contrast to the flexibility observed in non-polar systems, the conformation around the C5–C6 bond through the series was confined, while the structure of the alkyl group did not seem to influence the interglycosidic conformation. However, different rotamer contributions were found, depending on the nature of the solvent. In acetonitrile, the *gg* rotamer was predominant at equilibrium, whereas in acetone it was *gt*. For these solvents, the P_{gg} and P_{gt} were practically identical for each compound throughout the series. In methanol, there was a slight trend in P_{gg} and P_{gt} values toward an increase in the absolute value of E_S, leading to an increase in the *gt* rotamer contribution. This behavior is similar but not as pronounced as that observed in non-polar solvents.

As occurred with thioglucosides,[26] the observed preferences around the hydroxymethyl group cannot be due to non-bonded interactions between this group and the *S*-aglycone, since this would induce an increase in the *gg* population as the size of the *S*-aglycone increases, instead of decreasing. According to Taft,[27] as the substituent becomes bulkier, the rotation around the *S*-glucosidic bond decreases, meaning that the population of the more stable rotamer *exo-syn* increases. Non-bonded interactions between the *S*-aglycone and the substituent at the 2-position are also likely, decreasing the *non-exo* rotamer and reducing the flexibility (Fig. 5).

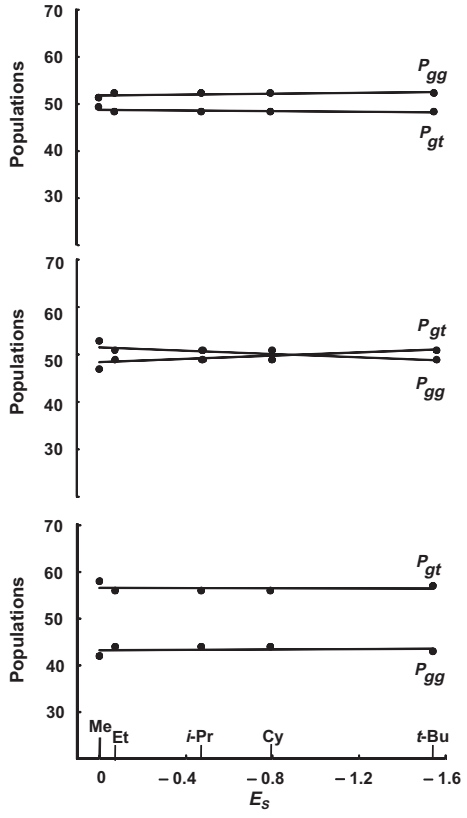

Figure 4. Rotamer populations *gg*/*gt* of the interglycosidic linkage (ring I) for compounds **1**–**5** versus Taft's parameter (E_S) in polar solvents: acetonitrile-d_3 (above), methanol-d_4 (center), and acetone-d_6 (below).[29]

A higher steric hindrance to motion as the substituent becomes bulkier leads to an increase in the more stable *exo-syn*, and therefore in the *exo*-anomeric effect. The participation of this effect is supported by the behavior of the chemical shift for the anomeric proton, since it is shielded along with the structural nature of the aliphatic alkyl group attached to the sulfur atom (Table 1). The shift runs from the methyl derivative **1** (4.37 ppm) to a primary alkyl group, such as ethyl **2** (4.48), to those with a secondary alkyl group: isopropyl **3** (4.56) and cyclohexyl **4** (4.56), and to the *tert*-butyl derivative **5** (4.62 ppm). As a result, the different values of the stereoelectronic $LP_S \rightarrow \sigma^*_{CO}$ interaction (the *exo*-anomeric effect) may express the rotational preferences of the hydroxymethyl group.

2.3. Conformational analysis of the hydroxymethyl groups in alkyl 1-thiogentiobioside *S*-oxides

As with thiogentiobiosides, the spin–spin coupling constants $J_{H5,H6R}$ and $J_{H5,H6S}$ for both rings were obtained by first-order analysis. For derivatives **6*S*–9*S***, signals of interest were well isolated in the ^{1}H NMR spectrum and the assignations were made following the data as described in the literature.[17] However, it was not possible to obtain the $J_{H5,H6}$ values for R_S sulfoxides in $CDCl_3$ due to the overlap of the H6*R* and H6*S* signals with H5 and H5′. However, chemical shifts for H6*R*′ and H6*S*′ appear well isolated in the ^{1}H NMR spectrum. Selected NMR data for the (S_S)- and (R_S)-sulfoxide series in $CDCl_3$ are presented in Tables 3 and 4 respectively.

Regarding the chemical shifts for the anomeric carbon bonded to a sulfinyl functionality, the δC1 in (R_S)-sulfoxides appeared at a higher field compared to its (S_S)-epimer. For instance, δC1 in methyl derivative **6*R*** was 87.4 ppm while in its (S_S)-epimer **6*S*** C1 appeared deshielded at 90.5 ppm. This relationship was observed in the four epimeric pairs. Comparison of δC1 along each epimeric series revealed a progressive displacement to higher fields as the degree of substitution of the alkyl group increases, that is, for the (S_S)-series, δC1 from methyl to *tert*-butyl derivative moved from 90.5 to 86.4 ppm while for the (R_S)-series, these values were 87.4–84.9 ppm, respectively.

The chemical shifts for C1′ showed practically no variations between the epimers and along the series, with an average chemical shift of 100.5 ppm. On the other hand, δH1 showed different behaviors depending on the epimeric series. In (R_S)-sulfoxides, it was possible to establish a trend where δH1 moves to a lower field as the degree of substitution of the aglycone increases (δH1 **6*R*** = 4.08 ppm; δH1 **9*R*** = 4.32 ppm). For the (S_S)-series, a similar trend was seen for derivatives **6*S***, **7*S***, and **8*S*** but moving to higher fields, (δH1 **6*S*** = 4.37; δH1 **8*S*** = 4.19 ppm); however, *tert*-butyl derivative **9*S*** escaped from this tendency (δH1 **9*S*** = 4.30 ppm).

A progressive rise in magnitude of $J_{H5,H6R}$ in the (S_S)-sulfoxides was observed as the degree of substitution of the aglycone increases (**6*S*** (Me) = 5.3 Hz; **9*S*** (*tert*-Bu) = 7.3 Hz), with a similar trend for $J_{H5',H6R'}$ on the second ring, but much less marked (**6*S*** = 4.8 Hz; **9*S*** = 5.1 Hz). From the analysis of (R_S)-sulfoxides in $CDCl_3$, there is only a slight trend of $J_{H5',H6R'}$ (**6*R*** = 5.0 Hz; **9*R*** = 5.4 Hz) through the series.

Hydroxymethyl rotamer populations for sulfoxides **6*S*–9*S*** and **6*R*–9*R*** were calculated from $J_{H5,H6R}$ and $J_{H5,H6S}$ values determined in different solvents using the Karplus-type set of equations proposed by Serianni.[24] Data obtained for the conformational proper-

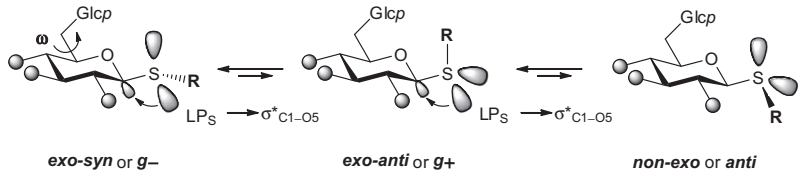

Figure 5. Molecular orbitals involved in the *exo*-anomeric effect for the three idealized staggered rotamers around the C1–S bond.[30]

Table 3
Chemical shifts for H1, C1, H6*R* and H6*S*, and $J_{H5,H6R}$ and $J_{H5,H6S}$ coupling constants for rings I and II of alkyl thiogentiobioside *S*-oxides **6*S*–9*S*** ($CDCl_3$)

Ring I							
No.	R	δC1	δH1	δH6*R*	δH6*S*	$J_{H5,H6R}$	$J_{H5,H6S}$
6*S*	Me	90.5	4.37	3.62	4.03	5.3	2.3
7*S*	Et	89.6	4.30	3.57	3.94	5.9	2.2
8*S*	*i*-Pr	88.2	4.19	3.56	3.86	6.6	2.1
9*S*	*t*-Bu	86.4	4.30	3.62	3.77	7.3	2.2
Ring II							
No.	R	δC1′	δH1′	δH6*R*′	δH6*S*′	$J_{H5,H6R'}$	$J_{H5,H6S'}$
6*S*	Me	100.5	4.56	4.28	4.15	4.8	2.3
7*S*	Et	100.5	4.51	4.25	4.11	4.8	2.2
8*S*	*i*-Pr	100.6	4.49	4.24	4.11	4.9	2.2
9*S*	*t*-Bu	100.6	4.51	4.25	4.12	5.1	2.3

Table 4
Chemical shifts for H1, C1, H6*R* and H6*S*, and $J_{H5,H6R}$ and $J_{H5,H6S}$ coupling constants for rings I and II of alkyl thiogentiobioside *S*-oxides **6*R*–9*R*** ($CDCl_3$)

Ring I							
No.	R	δC1	δH1	δH6*R*	δH6*S*	$J_{H5,H6R}$[a]	$J_{H5,H6S}$[a]
6*R*	Me	87.4	4.08	3.74	3.86	—	—
7*R*	Et	86.3	4.14	3.76	3.85	—	—
8*R*	*i*-Pr	85.2	4.28	3.80	3.80	—	—
9*R*	*t*-Bu	84.9	4.32	3.79	3.79	—	—
Ring II							
No.	R	δC1′	δH1′	δH6*R*′	δH6*S*′	$J_{H5,H6R'}$	$J_{H5,H6S'}$
6*R*	Me	100.5	4.56	4.27	4.14	5.0	2.1
7*R*	Et	100.5	4.56	4.28	4.14	5.1	2.3
8*R*	*i*-Pr	100.4	4.53	4.26	4.12	5.1	2.2
9*R*	*t*-Bu	100.4	4.55	4.26	4.11	5.4	2.2

[a] Values unobtainable due to signal overlap.

Table 5
Rotamer populations for the interglycosidic C5–C6 bond in different solvents for sulfoxides **6*S*–9*S***

No.	CD_2Cl_2		$CDCl_3$		$(CD_3)_2CO$		CD_3OD		CD_3CN	
	P_{gg}	P_{gt}	P_{gg}	P_{gt}	P_{gg}	P_{gt}	P_{gg}	P_{gt}	P_{gg}	P_{gt}
6*S*	51	49	55	45	45	55	61	39	50	50
7*S*	47	53	50	50	44	56	58	42	49	51
8*S*	44	56	44	56	41	59	53	47	49	51
9*S*	41	59	37	63	39	61	46	54	48	52

Table 6
Rotamer populations for the interglycosidic C5–C6 bond in different solvents for sulfoxides **6*R*–9*R***

No.	CD_2Cl_2		$(CD_3)_2CO$		CD_3OD		CD_3CN	
	P_{gg}	P_{gt}	P_{gg}	P_{gt}	P_{gg}	P_{gt}	P_{gg}	P_{gt}
6*R*	36	64	36	64	39	61	46	54
7*R*	34	66	35	65	37	63	43	57
8*R*	29	71	34	66	36	64	48	52
9*R*	—	—	35	65	35	65	47	53

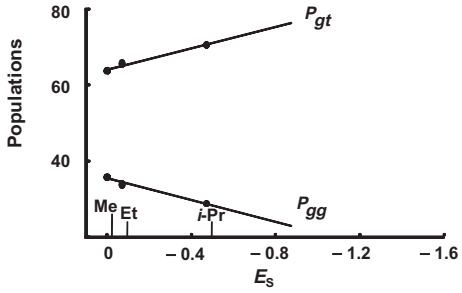

Figure 6. Rotational populations P_{gg} and P_{gt} of the interglycosidic linkage (ring I) obtained in dichloromethane-d_2 versus E_S for sulfoxides **6*R*–8*R***.[31]

ties around the C5–C6 bond (interglycosidic linkage) are displayed in Tables 5 and 6 for (S_S)- and (R_S)-series, respectively.

For the (S_S)-series, rotamer *gt* was predominant in the C5–C6 conformation, except for methyl derivative **6*S***, which showed a greater *gg* contribution in some solvents. The presence of rotamer *tg* was not detected, although a dependence of the P_{gg} and P_{gt} values on the nature of the aglycone was clear. As the degree of substitution of the alkyl group increased, P_{gt} rises and subsequently P_{gg} diminishes. This trend was found in the majority of the solvents studied; however in acetonitrile, the aglycone structure did not appear to influence the interglycosidic conformation and the ratio P_{gg}/P_{gt} ≈50:50% remained constant throughout the series.

The predominance of the *gt* rotamer was found in (R_S)-sulfoxides, which in most cases showed P_{gt} values higher than 60% (except for acetonitrile: P_{gt} ~54%). In addition, the (*R*)-sulfoxides presented higher *gt* contributions compared to their respective (*S*)-epimers.

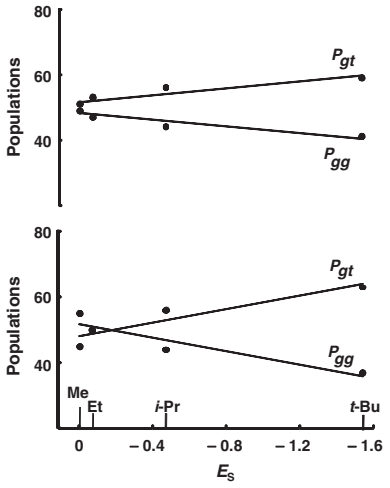

Figure 7. Rotational populations P_{gg} and P_{gt} of the interglycosidic linkage (ring I) obtained in dichloromethane-d_2 (above) and chloroform-*d* (below) versus E_S for sulfoxides **6*S*–9*S***.[32]

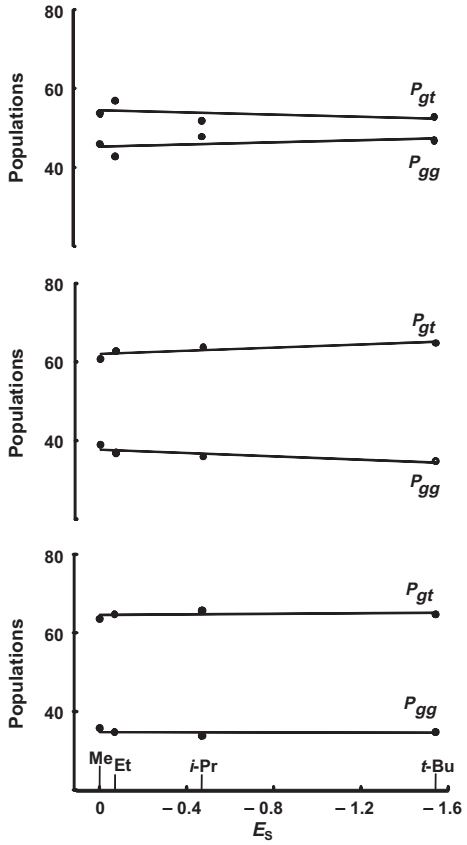

Figure 8. Rotational populations P_{gg} and P_{gt} of the interglycosidic linkage (ring I) obtained in acetonitrile-d_3 (above) methanol-d_3 (center), and acetone-d_6 (below) versus E_S for sulfoxides **6*R*–9*R***.[33]

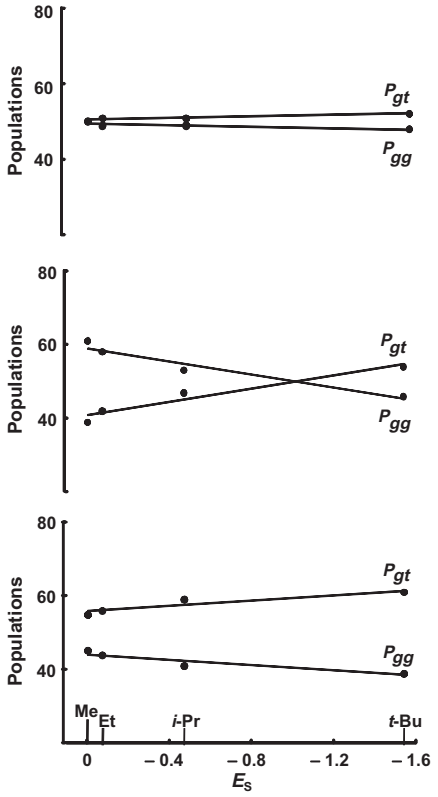

Figure 9. Rotational populations P_{gg} and P_{gt} of the interglycosidic linkage (ring I) obtained in acetonitrile-d_3 (above), methanol-d_3 (center), and acetone-d_6 (below) versus E_S for sulfoxides **6*S*–9*S***.[34]

The influence of the nature of the aglycone on C5–C6 conformation was also observed throughout the R_S series. In methanol and dichloromethane, the populations for *gg* and *gt* tended to decrease and increase, respectively, as the degree of substitution of the alkyl group increased; this trend was prominent in dichloromethane. Conversely, in acetone and acetonitrile, P_{gg} and P_{gt} tended to remain constant throughout the series.

As in thioglycosides,[26] good correlations were observed between the rotamer populations in the different solvents and Taft's steric parameter (E_S).[27] For a better analysis and discussion of results, the data are presented according to solvent polarity.

Figure 6 shows *gg*/*gt* rotamer populations for sulfoxides **6*R*–8*R*** obtained in dichloromethane versus the E_S parameter corresponding to the aglyconic alkyl group. A good linear dependence on the rotamer populations and E_S was established, that is, as the absolute value of E_S increased, *gt* and *gg* contributions increased and decreased, respectively.

For sulfoxides **6*S*–9*S***, the calculated values for P_{gg} and P_{gt} in CD_2Cl_2 and $CDCl_3$ versus E_S are shown in Figure 7. In both solvents, there is a linear correlation between P_{gg} and P_{gt} values with E_S. The contributions of *gg* and *gt* rotamers decrease and increase, respectively, as the absolute value of Taft's parameter increases, with this tendency being more pronounced in $CDCl_3$.

In non-polar solvents, both (S_S)- and (R_S)-sulfoxides presented a linear correlation between *gg*/*gt* rotamer populations and Taft's parameter for the alkyl group of the aglycone. However, this dependence was more pronounced in the case of (R_S)-sulfoxides.

Figure 8 shows the relationship between *gg* and *gt* populations with E_S for sulfoxides **6*R*–9*R*** in polar solvents. The rotamer populations remain practically constant throughout the series for all polar solvents, and the *gt* rotamer is the most populated in all cases.

A correlation between P_{gg} and P_{gt} versus E_S for derivatives **6*S*–9*S*** in polar solvents is presented in Figure 9.

In this case, linear correlations between rotamer populations and E_S were also found. However, the (S_S)-series showed a different behavior depending on the solvent. Conformational equilibrium in acetonitrile was practically constant throughout the series and no dependence on E_S values could be established. The results obtained for acetone showed a slight dependence of the populations on E_S, where an increase in its absolute value led to an increased P_{gt} population and consequent drop in P_{gg}. This last trend was also observed, but more markedly, in methanol, where the contribution of P_{gt} gradually increased along the series, with it being the predominant conformer in sulfoxide **9*S***, which had the highest E_S value.

2.4. Conformational analysis around the C1–S linkage in alkyl 1-thiogentiobiosyl *S*-oxides

For a better analysis of the rotamers involved in this linkage, we decided to use a convenient nomenclature based on the orientation between the *R* alkyl group of the aglycone and the endocyclic oxygen atom O5 (Fig. 10). According to this, for the glycosidic bond we distinguish three staggered rotamers called *gauche plus* (*g*+), *gauche minus* (*g*−), and *anti*.

The stereoelectronic interactions between the lone pair of electrons in sulfur and the sigma antibonding orbital of the C1–O5 bond gave rise to the *exo*-anomeric effect in the glycosyl sulfoxides. Due to the presence of only one lone pair in glycosyl sulfoxides, the $LP_S \rightarrow \sigma^*_{C1-O5}$ hyperconjugation is determined by the absolute configuration of sulfur as well as the conformational preferences around the glycosidic bond. Therefore, both epimeric series present distinct intrinsic requirements for the *exo*-anomeric effect. For (S_S)-

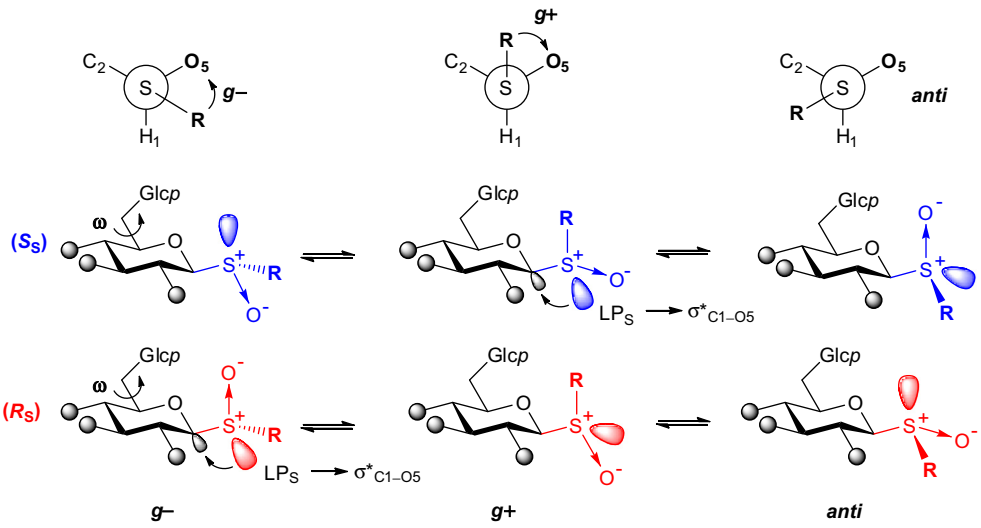

Figure 10. Rotamers around the C1–*S* linkage in alkyl β-gentiobiosyl sulfoxides and nomenclature used herein (upper line). S_S sulfoxides (center line, blue color). R_S sulfoxides (bottom line, red color).[30]

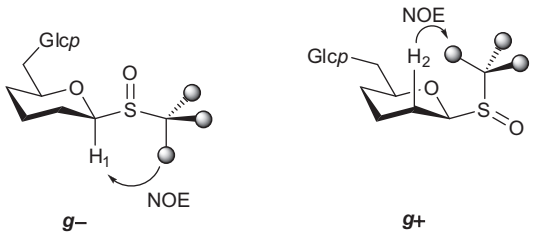

Figure 11. NOE for *g*– and *g*+ conformations in glycosyl sulfoxides.

sulfoxides, the conformer *g*+ fulfills the geometric and conformational requirements for the *exo*-anomeric effect, while in the (R_S)-series the *g*– rotamer satisfies the conditions.

In order to study the conformational properties around the C1–S bond, NOE experiments were carried out on methyl derivatives **6*R*** and **6*S*** and *tert*-butyl derivatives **9*R*** and **9*S***. NOE analysis is presented according to solvent polarity (Fig. 11).

2.4.1. Non-polar solvent (CD_2Cl_2)

Irradiation of the aglyconic methyl group on **6*R*** showed two NOE effects with H1 and H2, that with H2 being of lesser intensity. For *tert*-butyl derivative **9*R***, irradiation of the methyl groups showed an NOE effect only with H1. For the sulfoxide of the smaller aglycone, these results provide evidence that *g*+ and *g*– conformers are present in the equilibrium, with a greater contribution of *g*–. Meanwhile, for the sulfoxide of the bulkiest aglycone the observed NOE effect points to a conformation at C1–S anchored in *g*–. These results are supported by steric and stereoelectronic effects; the steric hindrance between H2 and voluminous aglycone disfavors the contribution of *g*+ to the equilibrium, with the *g*– conformer being more favored by steric effects. Moreover, for (R_S)-sulfoxides the *g*– conformer is stabilized by the stereoelectronic interaction $LP_S \rightarrow \sigma^*_{C1-O5}$, corresponding to the *exo*-anomeric effect. On the other hand, the presence of the *g*+ conformer on methyl derivative **6*R*** can be explained by the C1–O5 and S–O dipoles on the *g*+ conformer being in the *anti* disposition, generating a null resultant dipole, which is favored in low polarity solvents (Fig. 12). NOE experiments did not show the presence of the *anti* conformer.

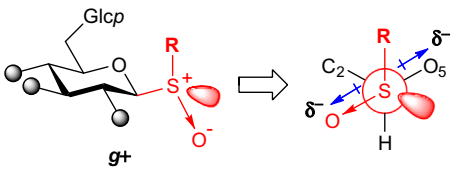

Figure 12. Alignment of C1–O5 and S–O dipoles for R_S sulfoxides on *g*+ conformation.

The irradiation of the aglyconic methyl group of sulfoxide **6*S*** showed an NOE with H1 and a second even more intense NOE with H2, indicating the presence of *g*– and *g*+ rotamers in the equilibrium, pointing to *g*+ as the most favored conformer. For *tert*-butyl derivative **9*S***, NOE was only observed with H1, revealing a conformation confined to *g*–. In the case of (S_S)-sulfoxides, the *g*+ conformation fulfills the requirements for the *exo*-anomeric effect. The high contribution of this rotamer to **6*S***, as implied by NOE experiments, could be explained by the stereoelectronic stabilization of *g*+ in addition to the low steric hindrance of the methyl group. Figure 13 summarizes these conformational properties.

2.4.2. Polar solvents

The NOE experiment for derivative **6*R*** in acetonitrile presented an intense effect between the methyl group and H1 and a small effect with H2, providing evidence of a conformational equilibrium where the *g*– rotamer predominates. For *tert*-butyl derivative **9*R***, an NOE was observed only with H1, supporting a conformation anchored in *g*–. NOE data in polar solvents indicated that rotamer *g*– is the main contributor to the glycosidic conformational equilibrium; this is valid even for methyl derivative **6*R***, which possesses the smallest aglycone. The restricted flexibility around C1–S of **6*R*** in polar media results from the stabilization of *g*– by both the stereoelectronic interaction $LP_S \rightarrow \sigma^*_{C1-O5}$ and the resulting net dipole formed between S–O and C1–O5 bonds, an alignment favored in polar systems (Fig. 14). The same stabilization occurs in *tert*-butyl derivative **9*R*** in addition to the steric hindrance between the bulky *tert*-butyl group and H2, which destabilizes the *g*+ conformation.

The 1D-NOE experiment for methyl sulfoxide **6*S*** in acetonitrile revealed effects with H1 and H2 of similar intensities, indicating a conformational equilibrium between *g*– and *g*+. For **9*S***, only an NOE with H1 was observed, hence the conformation was anchored in the *g*– rotamer.

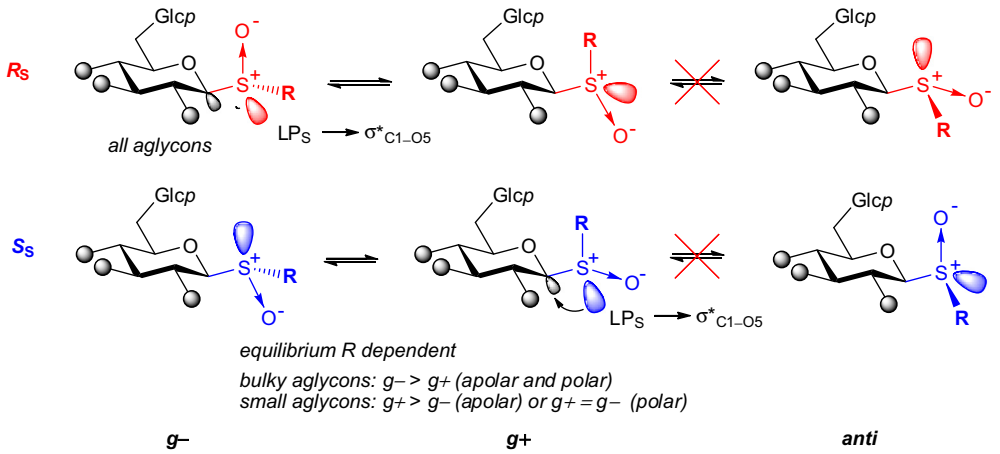

Figure 13. Conformations around the thioglucosidic linkage for R_S and S_S sulfoxides in solution.

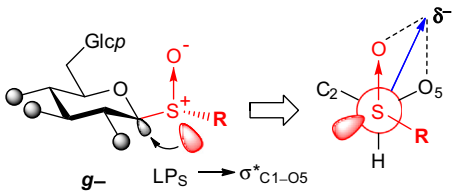

Figure 14. Alignment of C1–O5 and S–O dipoles for (R_S)-sulfoxides in the *g*– conformation.

Closer examination of the C1–S bond conformational equilibrium established that flexibility around this linkage depends on the aglycone size, the solvent polarity, and the absolute configuration of the sulfur. The methyl derivative of the (S_S)-series had a higher flexibility in both polar and non-polar media compared to its (R_S)-epimer. The rigidity of the methyl sulfoxide **6*R*** in both polar and non-polar media can be explained by the *exo*-anomeric effect, whereby the stereoelectronic interaction $LP_S \rightarrow \sigma^*_{C1-O5}$ would restrict free rotation around the thioglycosidic bond. For *tert*-butyl derivatives **9*S*** and **9*R***, the conformation is mainly directed by the steric hindrance between the *tert*-butyl group and H2. This interaction confines the glycosidic conformation to the *g*– rotamer (Fig. 13).

3. Conclusion

The alkyl β-thiogentiobiosides **1–5** and their corresponding (R_S)- and (S_S)-sulfinyl gentiobiosides, **6*R*–9*R*** and **6*S*–9*S***, respectively, were synthesized and characterized, and their conformational properties studied. Analysis of the hydroxymethyl groups in alkyl 1-thiogentiobiosides revealed that although both depend on the structural nature of the *S*-aglycone, the one connecting the two sugar rings is the more affected. The results showed the strong influence of the solvent polarity on the conformational preferences of the interglycosidic bond. While in polar solvents, the magnitudes of the rotamer populations, P_{gg} and P_{gt}, remained practically constant throughout the series; in non-polar solvents different conformational behavior was observed, with the *gt* rotamer being the most stable. Linear correlations between the increasing P_{gt} and the decreasing P_{gg} as well as the corresponding Taft's steric parameter (E_S) of the *S*-aglyconic alkyl group were observed in non-polar solvents.

The study performed with (S_S)- and (R_S)-alkyl thiogentiobiosyl *S*-oxides revealed the dominance of the *gt* rotamer, with P_{gt} always having a higher magnitude in the latter *S*-oxides than in the former. Both *S*-oxides exhibited linear correlations between the interglycosidic P_{gg} and P_{gt} and the corresponding Taft's steric parameters (E_S) of the alkyl group attached to the sulfinyl group, particularly in non-polar solvents, where increased *gt* and decreased *gg* populations were observed as the absolute value of E_S increased. Sulfoxides with an (R_S)-configuration exhibited better-defined correlations than the (S_S)-sulfoxides.

The results of the stereochemical studies on the C1–S revealed that in gentiobiosyl sulfoxides the $LP_S \rightarrow \sigma^*_{C1-O5}$ hyperconjugation is determined by the absolute configuration of the sulfur, in addition to the aglycone size and the nature of the solvent, with derivatives of the (S_S)-series showing a higher flexibility than their (R_S)-epimers. NOE analysis of the methyl and *tert*-butyl derivatives of both series in different media revealed that the conformational properties of gentiobiosyl sulfoxides in solution can be explained for each series on the basis of stereoelectronic and steric effects, as well as those of the solvent.

Considering these conformational results for the thioglycosidic linkage along with others obtained for the interglycosidic hydroxymethyl group, we established that for (R_S)-sulfoxides in non-polar media there is a correlation between the conformational properties of the interglycosidic C5–C6 bond and the *exo*-anomeric effect.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded at 400 or 500 MHz, and ^{13}C NMR at 75 MHz, VTU (variable temperature unit) 300.0 K. Chemical shifts are reported in parts per million. The residual solvent peak was used as an internal reference: for $CDCl_3$, 7.26 for proton and 77.0 ppm for the central peak of carbon NMR. Optical rotations were measured on a digital polarimeter in a 1 dm cell at 25 °C. UV and CD spectra were recorded in the range of 400–200 nm using 10 mm cells. For analytical thin-layer chromatography, silica gel ready-foils were used, developed with 254 nm UV light and/or spraying with $AcOH/H_2O/H_2SO_4$ (80:16:4) and heating at 150 °C. Flash column chromatography was performed using silica gel (60 Å). All reagents were from commercial sources (β-Gentiobiose were purchased from Sigma–Aldrich), and used without further purification. Solvents were dried and distilled before use. All reactions were performed under a dry nitrogen atmosphere. The compounds prepared were characterized on the basis of their one- (^{1}H and ^{13}C) and two-dimensional (COSY, HMQC, and T-ROESY) NMR spectra and HRMS, as well as by UV and CD spectroscopy for the case of sulfinyl derivatives.

4.2. General procedure for the synthesis of alkyl thiogentiobiosides

4.2.1. Method A[16]

Boron trifluoride etherate (0.1 equiv) was added via syringe to a stirred solution of β-D-gentiobiose octaacetate and the respective thiol (2.0 equiv) in dry dichloromethane (5.0 mL/mmol) at room temperature and under a nitrogen atmosphere. When TLC showed complete consumption of the starting material, the system was quenched by the addition of triethylamine and then diluted with dichloromethane. The organic fraction was washed with water and the aqueous layer re-extracted twice with a similar volume of dichloromethane. The organic layers were combined, dried over sodium sulfate and concentrated for purification by flash chromatography using silica gel and ethyl acetate/*n*-hexane systems as eluents.

4.2.2. Method B[18]

Boron trifluoride etherate (1.5 equiv) was added dropwise to a stirred solution of β-D-gentiobiose octaacetate and thiourea (2.0 equiv) in acetonitrile (5.0 mL/mmol) and the mixture refluxed at 80 °C. After total consumption of the starting material (as shown by TLC), the mixture was cooled to room temperature, after which triethylamine (3.0 equiv) and the respective alkyl halide (1.5 equiv) were added. The system was stirred for 3 h and the solvent was removed under reduced pressure. The crude was dissolved in dichloromethane and washed with water, dried over sodium sulfate, and concentrated for purification by flash chromatography over silica gel and ethyl acetate/*n*-hexane systems as eluents.

4.3. General procedure for the synthesis of alkyl thiogentiobiosyl *S*-oxides

To a suspension of the alkyl thiogentiobioside, acetic anhydride (1.3 equiv), and silica gel (200 mg/mmol) in dichloromethane, hydrogen peroxide (1.2 equiv from a 34% solution) was added dropwise. The reaction was vigorously stirred until total consumption of the starting material was evident from TLC. The solution was then diluted with dichloromethane and filtered to remove silica gel, washed with a saturated aqueous sodium bicarbonate solution and dried over magnesium sulfate. The solvent was removed under reduced pressure and the epimeric mixture purified by flash chromatography over silica gel with ethyl acetate/*n*-hexane systems as eluents.

4.4. Methyl 2,3,4-tri-*O*-acetyl-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside 1

Following the general procedure B, 300 mg (0.44 mmol) of gentiobiose octaacetate, 67 mg of thiourea, and 40 μL of CH_3I gave 202 mg (0.27 mmol, 62%) of gentiobiose thioglycoside **1**.[35] TLC R_f = 0.38 (*n*-hex/EtOAc 2:3); mp = 164 °C; $[\alpha]_D = -7.9$ (*c* 0.6, $CHCl_3$); HRMS calcd for $C_{27}H_{38}O_{17}NaS$ 689.1727 ($[M+Na]^+$), found: 689.1725; ^{1}H NMR (δ, $CDCl_3$) 5.20 (dd, *J* = 9.5, 9.5 Hz, H-3), 5.19 (dd, *J* = 9.5, 9.5 Hz, H-3′), 5.07 (dd, *J* = 9.8, 9.8 Hz, H-4′), 4.99 (dd, *J* = 9.5, 9.5 Hz, H-2), 4.97 (dd, *J* = 8.0, 9.8 Hz, H-2′), 4.89 (dd, *J* = 9.8, 9.8 Hz, H-4), 4.57 (d, *J* = 8.0 Hz, H-1′), 4.37 (d, *J* = 9.8 Hz, H-1), 4.27 (dd, *J* = 4.7, 12.4 Hz, H-6*R*′), 4.12 (dd, *J* = 2.3, 12.4 Hz, H-6*S*′), 3.88 (dd, *J* = 2.2, 11.2 Hz, H-6*S*), 3.69 (m, H-5, H-5′), 3.57 (dd, *J* = 6.8, 11.2 Hz, H-6*R*), 2.17 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (δ, $CDCl_3$) 170.7 (s), 170.2 (s), 170.1 (s), 169.6 (s), 169.5 (s), 169.5 (s), 169.4 (s), 100.9 (d, C-1′), 82.9 (d, C-1), 77.2 (d, C-5), 73.7 (d, C-3), 72.7 (d, C-3′), 71.9 (d, C-5′), 71.1 (d, C-2′), 69.2 (d, C-2), 68.9 (d, C-4), 68.4 (t, C-6), 68.3 (d, C-4′), 61.8 (t, C-6′), 20.7 (q), 20.7 (q), 20.7 (q), 20.6 (q), 20.6 (q), 20.6 (q), 20.5 (q), 11.5 (q). Anal. Calcd for $C_{27}H_{38}O_{17}S$: C, 48.64; H, 5.75; S, 4.81. Found: C, 48.18; H, 5.30; S, 4.64.

4.5. Ethyl 2,3,4-tri-*O*-acetyl-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside 2

Following the general procedure A, for β-thioglycosides synthesis, 268 mg (0.40 mmol) of gentiobiose octaacetate with 0.88 μL of ethylmercaptan gave 231 mg (0.34 mmol, 85%) of gentiobiose thioglycoside **2**.[36] TLC R_f = 0.40 (*n*-hex/EtOAc 2:3); mp = 200 °C; $[\alpha]_D = -20.0$ (*c* 0.6, $CHCl_3$); HRMS calcd for $C_{28}H_{40}O_{17}NaS$ 703.1884 ($[M+Na]^+$), found 703.1885; ^{1}H NMR (δ, $CDCl_3$): 5.21 (dd, *J* = 9.5, 9.5 Hz, H-3′), 5.19 (dd, *J* = 9.2, 9.2 Hz, H-3), 5.08 (dd, *J* = 9.7, 9.7 Hz, H-4), 4.99 (dd, *J* = 9.5, 9.5 Hz, H-2), 4.98 (dd, *J* = 9.7, 9.7 Hz, H-2′), 4.90 (dd, *J* = 9.8, 9.8 Hz, H-4′), 4.58 (d, *J* = 8.0 Hz, H-1′), 4.47 (d, *J* = 10.0 Hz, H-1), 4.28 (dd, *J* = 4.8, 12.3 Hz, H-6*R*′), 4.13 (dd, *J* = 2.3, 12.3 Hz, H-6*S*′), 3.87 (dd, *J* = 2.0, 10.9 Hz, H-6*S*), 3.69 (m, H5, H5′), 3.60 (dd, *J* = 7.2, 10.9 Hz, H-6*R*), 2.71 (m, 2H), 2.10 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H), 2.00 (s, 3H), 1.28 (dd, *J* = 7.5, 7.5 Hz, 3H); ^{13}C NMR (δ, $CDCl_3$) 170.5 (s), 170.2 (s), 170.1 (s), 169.6 (s), 169.4 (s), 169.4 (s), 169.3 (s), 100.7 (d, C-1′), 83.2 (d, C-1), 77.3 (d, C-5), 78.8 (d, C-3′), 72.8 (d, C-3), 71.9 (d, C-5′), 71.2 (d, C-2′), 69.9 (d, C-2), 69.2 (d, C-4′), 68.5 (t, C-6), 68.3 (d, C-4), 61.8 (t, C-6′), 24.1 (t), 20.7 (q), 20.7 (q), 20.7 (q), 20.6 (q), 20.6 (q), 20.6 (q), 20.6 (q), 14.9 (q). Anal. Calcd for $C_{28}H_{40}O_{17}S$: C, 49.41; H, 5.92; S, 4.71. Found: C, 49.90; H, 5.72; S, 4.42.

4.6. *iso*-Propyl 2,3,4-tri-*O*-acetyl-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside 3

Following the general procedure A, 633 mg (0.93 mmol) of gentiobiose octaacetate and 170 μL of *iso*-propyl mercaptan gave 497 mg (0.72 mmol, 77%) of gentiobiose thioglycoside **3**. TLC R_f = 0.42 (*n*-hex/EtOAc 2:3); mp = 204 °C; $[\alpha]_D = -20.5$ (*c* 0.4, $CHCl_3$); HRMS calcd for $C_{29}H_{42}O_{17}NaS$ 717.2040 ($[M+Na]^+$), found 717.2042; ^{1}H NMR (δ, $CDCl_3$) 5.19 (dd, *J* = 9.3, 9.3 Hz, H-3), 5.14 (dd, *J* = 9.3, 9.3 Hz, H-3′), 5.04 (dd, *J* = 9.6, 9.6 Hz, H-4′), 4.95 (dd, *J* = 9.3, 9.3 Hz, H-2′), 4.93 (dd, *J* = 9.4, 9.4 Hz, H-2), 4.86 (dd, *J* = 9.6, 9.6 Hz, H-4), 4.56 (d, *J* = 8.0 Hz, H-1′), 4.53 (d, *J* = 10.1 Hz, H-1), 4.24 (dd, *J* = 4.9, 12.4 Hz, H-6*R*′), 4.09 (dd, *J* = 2.4, 12.4 Hz, H-6*S*′), 3.80 (dd, *J* = 1.7, 11.0 Hz, H-6*S*), 3.67 (m, H-5, H-5′), 3.66 (dd, *J* = 7.2, 11.0 Hz, H-6*R*), 3.15 (m, 1H), 2.07 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 1.97 (s, 3H), 1.97 (s, 3H), 1.29 (d, *J* = 7.0 Hz, 3H), 1.27 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (δ, $CDCl_3$) 170.7 (s), 170.3 (s), 169.7 (s), 169.4 (s), 169.4 (s), 169.4 (s), 169.3 (s), 100.5 (d, C-1′), 82.9 (d, C-1), 77.2 (d, C-5), 73.7 (d, C-3), 72.7 (d, C-3′), 71.8 (d, C-5′), 71.0 (d, C-2′), 70.1 (d, C-2), 68.9 (d, C-4), 68.3 (t, C-6), 68.0 (d, C-4′), 61.7 (t, C-6′), 35.3 (d), 24.2 (q), 23.7 (q), 20.8 (q), 20.8 (q), 20.7 (q), 20.7 (q), 20.7 (q), 20.6 (q), 20.6 (q). Anal. Calcd for $C_{29}H_{42}O_{17}S$: C, 50.14; H, 6.09; S, 4.62. Found: C, 49.98; H, 5.75; S, 4.35.

4.7. Cyclohexyl 2,3,4-tri-*O*-acetyl-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside 4

Following the general procedure A, 527 mg (0.78 mmol) of gentiobiose octaacetate and 200 μL of cyclohexyl mercaptan gave 459 mg (0.63 mmol, 81%) of gentiobiose thioglycoside **4**. TLC R_f = 0.45 (*n*-hex/EtOAc 2:3); mp = 194 °C; $[\alpha]_D = -21.4$ (*c* 0.6, $CHCl_3$); HRMS calcd for $C_{32}H_{46}O_{17}NaS$ 757.2353 ($[M+Na]^+$), found 757.2353; ^{1}H NMR (δ, $CDCl_3$) 5.21 (dd, *J* = 9.2, 9.2 Hz, H-3), 5.19 (dd, *J* = 9.2, 9.2 Hz, H-3′), 5.07 (dd, *J* = 9.7, 9.7 Hz, H-4), 4.97 (dd, *J* = 8.3, 9.4 Hz, H-2′), 4.95 (dd, *J* = 9.6, 9.6 Hz, H-2), 4.89 (dd, *J* = 9.6, 9.6 Hz, H-4′), 4.60 (d, *J* = 8.0 Hz, H-1′), 4.55 (d, *J* = 9.9 Hz, H-1), 4.27 (dd, *J* = 4.9, 12.4 Hz, H-6*R*′), 4.13 (dd, *J* = 2.4, 12.4 Hz,

H-6S′), 3.83 (dd, J = 1.7, 10.9 Hz, H-6S), 3.67 (m, H-5, H-5′), 3.65 (dd, J = 7.2, 10.9 Hz, H-6R), 2.94 (m, 1H), 2.11 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H), 2.00 (s, 3H), 1.95 (m, 1H), 1.77 (m, 2H), 1.63 (m, 2H), 1.35 (m, 6H); ^{13}C NMR (δ, $CDCl_3$) 170.6 (s), 170.2 (s), 170.2 (s), 169.6 (s), 169.4 (s), 169.4 (s), 169.3 (s), 100.6 (d, C-1′), 82.9 (d, C-1), 77.4 (d, C-5), 73.9 (d, C-3), 72.8 (d, C-3′), 71.9 (d, C-5′), 71.1 (d, C-2′), 70.3 (d, C-2), 69.1 (d, C-4′), 68.4 (t, C-6), 68.3 (d, C-4), 61.8 (t, C-6′), 43.5 (d), 34.3 (t) 33.8 (t), 25.8 (t), 25.6 (t), 25.6 (t), 20.6 (q), 20.7 (q), 20.7 (q), 20.6 (q), 20.6 (q), 20.5 (q), 20.5 (q). Anal. Calcd for $C_{32}H_{46}O_{17}S$: C, 52.31; H, 6.31; S, 4.36. Found: C, 52.45; H, 6.05; S, 4.13.

4.8. *tert*-Butyl 2,3,4-tri-*O*-acetyl-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside 5

Following the general procedure A, 554 mg (0.82 mmol) of gentiobiose octaacetate and 220 μL of *tert*-butyl mercaptan gave 402 mg (0.57 mmol, 69%) of gentiobiose thioglycoside **5**. TLC R_f = 0.44 (*n*-hex/EtOAc 2:3); mp = 215 °C; $[\alpha]_D$ = −12.8 (*c* 0.5, $CHCl_3$); HRMS calcd for $C_{30}H_{44}O_{17}NaS$ 731.2197 ([M+Na]+), found 731.2197; ^{1}H NMR (δ, $CDCl_3$) 5.23 (dd, J = 9.4, 9.4 Hz, H-3), 5.15 (dd, J = 9.4, 9.4 Hz, H-3′), 5.05 (dd, J = 9.7, 9.7 Hz, H-4′), 4.96 (dd, J = 8.0, 9.5 Hz, H-2′), 4.93 (dd, J = 9.7, 9.7 Hz, H-2), 4.86 (dd, J = 9.7, 9.7 Hz, H-4), 4.61 (d, J = 10.1 Hz, H-1), 4.58 (d, J = 8.0 Hz, H-1′), 4.26 (dd, J = 5.0, 12.3 Hz, H-6R′), 4.11 (dd, J = 2.3, 12.3 Hz, H-6S′), 3.79 (dd, J = 1.7, 10.8 Hz, H-6S), 3.69 (m, H-5, H-5′), 3.66 (dd, J = 7.5, 10.8 Hz, H-6R), 2.16 (s, 3H), 2.09 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 2.02 (s, 3H), 2.02 (s, 3H), 1.99 (s, 3H), 1.36 (s, 9H). ^{13}C NMR (δ, $CDCl_3$) 170.6 (s), 170.2 (s), 170.2 (s), 169.6 (s), 169.4 (s), 169.3 (s), 169.2 (s), 100.3 (d, C-1′), 82.0 (d, C-1), 77.2 (d, C-5), 73.9 (d, C-3), 72.9 (d, C-3′), 71.9 (d, C-5′), 71.1 (d, C-2′), 70.2 (d, C-2), 69.0 (d, C-4), 68.3 (d, C-4′), 68.2 (d, C-6), 61.8 (t, C-6′), 44.2 (s), 31.5 (q, x 3), 20.8 (q), 20.7 (q), 20.7 (q), 20.6 (q), 20.6 (q), 20.5 (q), 20.5 (q). Anal. Calcd for $C_{30}H_{44}O_{17}S$: C, 50.84; H, 6.26; S, 4.52. Found: C, 51.03; H, 5.77; S, 4.28.

4.8.1. Sulfoxides 6*S* and 6*R*

Following the general method for the synthesis of glucosyl thioglucoside *S*-oxides, 156 mg (0.23 mmol) of thioglycoside **1** led to 144 mg (0.21 mmol, 91%) of the corresponding sulfoxide epimers (S_S/R_S = 2.5:1).

4.9. (S_S)-Methyl 2,3,4-tri-*O*-acetyl-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside *S*-oxide 6*S*

TLC R_f = 0.37 (MeOH/CH_2Cl_2 1:19); mp = 177 °C; $[\alpha]_D$ = −7.1 (*c* 0.3, $CHCl_3$); HRMS calcd for $C_{27}H_{38}O_{18}NaS$ 705.1677 ($[M+Na]^+$), found 705.1682; ^{1}H NMR (δ, $CDCl_3$) 5.31 (dd, J = 9.2, 9.2 Hz, H-3), 5.22 (dd, J = 9.5, 9.5 Hz, H-3′), 5.09 (dd, J = 9.7, 9.7 Hz, H-4′), 5.06 (dd, J = 9.7, 9.7 Hz, H-2), 5.03 (dd, J = 9.6, 9.6 Hz, H-4), 4.99 (dd, J = 7.8, 9.5 Hz, H-2′), 4.56 (d, J = 7.8 Hz, H-1′), 4.37 (d, J = 10.1 Hz, H-1), 4.28 (dd, J = 4.8, 12.3 Hz, H-6R′), 4.15 (dd, J = 2.3, 12.3 Hz, H-6S′), 4.03 (dd, J = 2.3, 11.2 Hz, H-6S), 3.81 (ddd, J = 2.3, 5.3, 9.9 Hz, H-5), 3.72 (ddd, J = 2.3, 4.8, 10.0 Hz, H-5′), 3.62 (dd, J = 5.3, 11.2 Hz, H-6R), 2.70 (s, 3H), 2.12 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (δ, $CDCl_3$) 170.6 (s), 170.2 (s), 170.0 (s), 169.7 (s), 169.5 (s), 169.4 (s), 169.3 (s), 100.5 (d, C-1′), 90.5 (d, C-1), 77.6 (d, C-5), 73.2 (d, C-3), 72.7 (d, C-3′), 71.9 (d, C-5′), 71.1 (d, C-2′), 68.3 (d, C-4′), 68.3 (d, C-2), 68.2 (d, C-4), 67.2 (t, C-6), 61.8 (t, C-6′), 33.1 (q), 20.7 (q), 20.7 (q), 20.6 (q), 20.6 (q), 20.6 (q), 20.5 (q), 20.5 (q); UV (CH_3CN) λ_{max} (ε) 210 nm (3500; CD (CH_3CN) λ_{ext} (Δε) 223 (4.4), 200 nm (−11.9). Anal. Calcd for $C_{27}H_{38}O_{18}S$: C, 47.50; H, 5.61; S, 4.70. Found: C, 47.16; H, 5.32; S, 4.26.

4.10. (R_S)-Methyl 2,3,4-tri-*O*-acetyl-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside *S*-oxide 6*R*

TLC R_f = 0.35 (MeOH/CH_2Cl_2 1:19); mp = 230 °C; $[\alpha]_D$ = −50.8 (*c* 0.4, $CHCl_3$); HRMS calcd for $C_{27}H_{38}O_{18}NaS$ 705.1677 ($[M+Na]^+$), found 705.1685; ^{1}H NMR (δ, $CDCl_3$) 5.39 (dd, J = 9.4, 9.4 Hz, H-2), 5.35 (dd, J = 9.1, 9.1 Hz, H-3), 5.19 (dd, J = 9.5, 9.5 Hz, H-3′), 5.07 (dd, J = 9.7, 9.7 Hz, H-4′), 4.98 (dd, J = 8.1, 9.6 Hz, H-2′), 4.97 (dd, J = 9.7, 9.7 Hz, H-4), 4.56 (d, J = 8.1 Hz, H-1′), 4.27 (dd, J = 5.0, 12.3 Hz, H-6R′), 4.14 (dd, J = 2.1, 12.3 Hz, H-6S′), 4.08 (d, J = 9.6 Hz, H-1), 3.86 (m, H-6S, H-5), 3.74 (dd, J = 7.5, 11.0 Hz, H-6R), 3.70 (ddd, J = 2.1, 5.0, 10.0 Hz, H-5′), 2.68 (s, 3H), 2.10 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (δ, $CDCl_3$) 170.5 (s), 170.1 (s), 169.4 (s), 169.4 (s), 169.4 (s), 169.2 (s), 168.9 (s), 100.5 (d, C-1′), 87.4 (d, C-1), 78.1 (d, C-5), 73.6 (d, C-3), 72.7 (d, C-3′), 72.0 (d, C-5′), 71.2 (d, C-2′), 68.4 (d, C-4), 68.2 (d, C-4′), 68.1 (t, C-6), 66.9 (d, C-2), 61.7 (t, C-6′), 33.3 (q), 20.7 (q), 20.5 (q), 20.5 (q), 20.5 (q), 20.5 (q), 20.5 (q), 20.5 (q); UV (CH_3CN) λ_{max} (ε) 210 nm 3500; CD (CH_3CN) λ_{ext} (Δε) 218 (−8.6), 194 nm (4.4). Anal. Calcd for $C_{27}H_{38}O_{18}S$: C, 47.50; H, 5.61; S, 4.70. Found: C, 47.13; H, 5.28; S, 4.24.

4.10.1. Sulfoxides 7*S* and 7*R*

Following the general procedure for the synthesis of glucosyl thioglucoside *S*-oxides, 155 mg (0.23 mmol) of thioglycoside **2** gave 131 mg (0.19 mmol, 83%) of the corresponding sulfoxide epimers (S_S/R_S = 2:1).

4.11. (S_S)-Ethyl 2,3,4-tri-*O*-acetyl-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside *S*-oxide 7*S*

TLC R_f = 0.40 (MeOH/CH_2Cl_2 1:19); mp = 178 °C; $[\alpha]_D$ = −25.0 (*c* 0.7, $CHCl_3$); HRMS calcd for $C_{28}H_{40}O_{18}NaS$ 719.1833 ($[M+Na]^+$), found 719.1841; ^{1}H NMR (δ, $CDCl_3$) 5.27 (dd, J = 9.1, 9.1 Hz, H-3), 5.21 (dd, J = 9.5, 9.5 Hz, H-2), 5.18 (dd, J = 9.5, 9.5 Hz, H-3′), 5.06 (dd, J = 9.7, 9.7 Hz, H-4′), 4.96 (dd, J = 7.9, 9.4 Hz, H-2′), 4.96 (dd, J = 9.5, 9.5 Hz, H-4), 4.51 (d, J = 7.9 Hz, H-1′), 4.30 (d, J = 9.6 Hz, H-1), 4.25 (dd, J = 4.8, 12.3 Hz, H-6R′), 4.11 (dd, J = 2.2, 12.3 Hz, H-6S′), 3.94 (dd, J = 2.2, 11.1 Hz, H-6S), 3.77 (ddd, J = 2.2, 5.9, 9.9 Hz, H-5), 3.69 (ddd, J = 2.2, 4.8, 9.9 Hz, H-5′), 3.57 (dd, J = 5.9, 11.1 Hz, H-6R), 2.89 (m, 2H), 2.09 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H), 1.37 (dd, J = 7.5, 7.5 Hz, 3H); ^{13}C NMR (δ, $CDCl_3$) 170.5 (s), 170.1 (s), 169.9 (s), 169.6 (s), 169.4 (s), 169.3 (s), 169.3 (s), 100.5 (d, C-1′), 89.6 (d, C-1), 77.6 (d, C-5), 73.2 (d, C-3), 72.7 (d, C-3′), 71.9 (d, C-5′), 70.9 (d, C-2′), 68.4 (d, C-2), 68.3 (d, C-4′), 68.2 (d, C-4), 67.4 (t, C-6), 61.8 (t, C-6′), 41.6 (t), 20.7 (q), 20.6 (q), 20.6 (q), 20.6 (q), 20.5 (q), 20.5 (q), 20.5 (q), 6.5 (q); UV (CH_3CN) λ_{max} (ε) 210 nm (3500); CD (CH_3CN) λ_{ext} (Δε) 227 (8.4), 201 nm (−17.9). Anal. Calcd for $C_{28}H_{40}O_{18}S$: C, 48.27; H, 5.59; S, 4.60. Found: C, 48.53; H, 5.59; S, 4.31.

4.12. (R_S)-Ethyl 2,3,4-tri-*O*-acetyl-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside *S*-oxide 7*R*

TLC R_f = 0.38 (MeOH/CH_2Cl_2 1:19); mp = 221 °C; $[\alpha]_D$ = −46.1 (*c* 0.2, $CHCl_3$); HRMS calcd for $C_{28}H_{40}O_{18}NaS$ 719.1833 ($[M+Na]^+$), found 719.1836; ^{1}H NMR (δ, $CDCl_3$) 5.43 (dd, J = 9.5, 9.5 Hz, H-2), 5.36 (dd, J = 9.2, 9.2 Hz, H-3), 5.20 (dd, J = 9.5, 9.5 Hz, H-3′), 5.07 (dd, J = 9.7, 9.7 Hz, H-4′), 4.99 (dd, J = 8.0, 9.6 Hz, H-2′), 4.97 (dd, J = 9.5, 9.5 Hz, H-4), 4.56 (d, J = 8.0 Hz, H-1′), 4.28 (dd, J = 5.1, 12.3 Hz, H-6R′), 4.14 (dd, J = 2.3, 12.3 Hz, H-6S′), 4.14 (d, J = 9.8 Hz, H-1), 3.85 (m, H-5, H6S), 3.76 (dd, J = 8.6, 11.2 Hz, H-6R), 3.71 (ddd, J = 2.3, 5.1, 9.9 Hz, H-5′), 3.12 (m, 1H), 2.80 (m, 1H), 2.11 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.05 (s,

3H), 2.04 (s, 3H), 2.01 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (δ, $CDCl_3$) 170.5 (s), 170.3 (s), 170.1 (s), 169.4 (s), 169.4 (s), 169.2 (s), 168.8 (s), 100.5 (d, C-1′), 86.3 (d, C-1), 78.3 (d, C-5), 73.7 (d, C-3), 72.7 (d, C-3′) 72.0 (d, C-5), 71.1 (d, C-2′), 68.4 (d, C-4), 68.2 (d, C-4′), 68.2 (t, C-6), 66.9 (d, C-2), 61.8 (t, C-6′), 41.3 (t), 20.7 (s), 20.6 (s), 20.5 (s), 20.5 (s), 20.5 (s), 20.5 (s), 20.5 (s), 7.4 (s); UV (CH_3CN) λ_{max} (ε 210 nm (3500 ; CD (CH_3CN) λ_{ext} (Δε) 220 (−10.8), 196 nm (3.2). Anal. Calcd for $C_{28}H_{40}O_{18}S$: C, 48.27; H, 5.59; S, 4.60. Found: C, 48.37; H, 5.64; S, 4.24.

4.12.1. Sulfoxides 8*S* and 8*R*

Following the general procedure for the synthesis of glucosyl thioglucoside *S*-oxides, 398 mg (0.57 mmol) of thioglycoside **3** led to 372 mg (0.52 mmol, 91%) of the corresponding sulfoxide epimers (S_S/R_S = 1.6:1).

4.13. (S_S)-Isopropyl 2,3,4-tri-*O*-acetyl-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside *S*-oxide 8*S*

TLC R_f = 0.41 (MeOH/CH_2Cl_2 1:19); mp = 139 °C; $[\alpha]_D$ = −1.7 (*c* 1.1, $CHCl_3$); HRMS calcd for $C_{29}H_{42}O_{18}NaS$ 733.1990 ([M+Na]$^+$), found 733.1990; ^{1}H NMR (δ, $CDCl_3$) 5.40 (dd, *J* = 9.5, 9.5 Hz, H-2), 5.26 (dd, *J* = 9.2, 9.2 Hz, H-3), 5.17 (dd, *J* = 9.5, 9.5 Hz, H-3′), 5.03 (dd, *J* = 9.6, 9.6 Hz, H-4′), 4.94 (dd, *J* = 8.0, 9.5 Hz, H-2′), 4.92 (dd, *J* = 9.7, 9.7 Hz, H-4), 4.49 (d, *J* = 8.0 Hz, H-1′), 4.24 (dd, *J* = 4.9, 12.3 Hz, H-6*R*′), 4.19 (d, *J* = 9.7 Hz, H-1), 4.11 (dd, *J* = 2.2, 12.3 Hz, H-6*S*′), 3.86 (dd, *J* = 2.1, 11.2 Hz, H-6*S*), 3.76 (ddd, *J* = 2.1, 6.6, 9.3 Hz, H-5), 3.67 (ddd, *J* = 2.2, 4.9, 10.0 Hz, H-5′), 3.56 (dd, *J* = 6.6, 11.2 Hz, H-6*R*), 3.09 (m, 1H), 2.07 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.98 (s, 3H), 1.32 (d, *J* = 7.1 Hz, 3H), 1.28 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (δ, $CDCl_3$) 170.5 (s), 170.1 (s), 170.0 (s), 169.5 (s), 169.4 (s), 169.4 (s), 169.2 (s), 100.6 (d, C-1′), 88.2 (d, C-1), 77.8 (d, C-5), 73.3 (d, C-3), 72.7 (d, C-3′), 72.0 (d, C-5′), 70.9 (d, C-2′), 68.8 (d, C-2), 68.3 d, C-4, 68.2 (d, C-4′), 67.7 (t, C-6), 61.8 (t, C-6′), 47.7 (d), 20.7 (q), 20.7 (q), 20.6 (q), 20.6 (q), 20.6 (q), 20.5 (q), 20.5 (q), 16.9 (q), 13.1 (q); UV (CH_3CN) λ_{max} (ε 210 nm (3500; CD (CH_3CN) λ_{ext} (Δε) 229 (7.6), 203 nm (−6.4). Anal. Calcd for $C_{29}H_{42}O_{18}S$: C, 49.01; H, 5.96; S, 4.51. Found: C, 49.21; H, 5.72; S, 4.08.

4.14. (R_S)-Isopropyl 2,3,4-tri-*O*-acetyl-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-glucopyranosyl)-1-thio-β-glucopyranoside *S*-oxide 8*R*

TLC R_f = 0.40 (MeOH/CH_2Cl_2 1:19); mp = 221 °C; $[\alpha]_D$ = −50.0 (*c* 0.5, $CHCl_3$); HRMS calcd for $C_{29}H_{42}O_{18}NaS$ 733.1990 ([M+Na]$^+$), found 733.2001; ^{1}H NMR (δ, $CDCl_3$) 5.42 (dd, *J* = 9.6, 9.6 Hz, H-2), 5.36 (dd, *J* = 9.3, 9.3 Hz, H-3), 5.18 (dd, *J* = 9.6, 9.6 Hz, H-3′), 5.05 (dd, *J* = 9.7, 9.7 Hz, H-4′), 4.98 (dd, *J* = 8.0, 9.6 Hz, H-2′), 4.94 (dd, *J* = 9.5, 9.5 Hz, H-4), 4.53 (d, *J* = 8.1 Hz, H-1′), 4.28 (d, *J* = 9.8 Hz, H-1), 4.26 (dd, *J* = 5.1, 12.1 Hz, H-6*R*′), 4.12 (dd, *J* = 2.2, 12.1 Hz, H-6*S*′), 3.80 (m, H-6*R*, H-6*S* and H-5), 3.69 (ddd, *J* = 2.2, 5.1, 10.0 Hz, H-5′), 3.36 (m, 1H), 2.10 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 2.03 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H), 1.43 (d, *J* = 7.0 Hz, 3H), 1.16 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (δ, $CDCl_3$) 170.5 (s), 170.4 (s), 170.1 (s), 169.5 (s), 169.5 (s), 169.4 (s), 169.1 (s), 100.4 (d, C-1′), 85.2 (d, C-1), 78.4 (d, C-5), 73.8 (d, C-3), 72.8 (d, C-3′), 72.0 (d, C-5′), 71.3 (d, C-2′), 68.5 (d, C-4), 68.2 (d, C-4′), 68.2 (t, C-6), 67.0 (t, C-2), 61.8 (t, C-6′), 47.2 (d), 20.7 (q), 20.7 (q), 20.6 (q), 20.6 (q), 20.5 (q), 20.5 (q), 20.5 (q), 16.7 (q), 15.5 (q); UV (CH_3CN) λ_{max} (ε 210 nm (3500; CD (CH_3CN) λ_{ext} (Δε) 222 (−9.4), 198 nm (2.9). Anal. Calcd for $C_{29}H_{42}O_{18}S$: C, 49.01; H, 5.96; S, 4.51. Found: C, 49.27; H, 5.38; S, 4.02.

4.14.1. Sulfoxides 9*S* and 9*R*

Following the general procedure for the synthesis of glucosyl thioglucoside *S*-oxides, 309 mg (0.44 mmol) of thioglycoside **5** led to 264 mg (0.37 mmol, 84%) of the corresponding sulfoxide epimers (S_S/R_S = 1.4:1).

4.15. (S_S)-*tert*-Butyl 2,3,4-tri-*O*-acetyl-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside *S*-oxide 9*S*

TLC R_f = 0.48 (MeOH/CH_2Cl_2 1:19); mp = 197 °C; $[\alpha]_D$ = +8.3 (*c* 0.6, $CHCl_3$); HRMS calcd for $C_{30}H_{44}O_{18}NaS$ 747.2146 ([M+Na]$^+$), found 747.2158; ^{1}H NMR (δ, $CDCl_3$) 5.51 (dd, *J* = 9.3, 9.3 Hz, H-2), 5.24 (dd, *J* = 9.1, 9.1 Hz, H-3), 5.16 (dd, *J* = 9.5, 9.5 Hz, H-3′), 5.03 (dd, *J* = 9.7, 9.7 Hz, H-4′), 4.94 (dd, *J* = 8.0, 9.4 Hz, H-2′), 4.91 (dd, *J* = 9.9, 9.9 Hz, H-4), 4.51 (d, *J* = 8.0 Hz, H-1′), 4.30 (d, *J* = 9.6 Hz, H-1), 4.25 (dd, *J* = 5.1, 13.3 Hz, H-6*R*′), 4.12 (dd, *J* = 2.2, 13.3 Hz, H-6*S*′), 3.77 (m, H-5, H-6*S*), 3.68 (ddd, *J* = 2.2, 5.1, 10.0 Hz, H-5′), 3.62 (dd, *J* = 7.3, 12.0 Hz, H-6*R*), 2.10 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (δ, $CDCl_3$) 170.5 (s), 170.2 (s), 170.1 (s), 169.4 (s), 169.4 (s), 169.3 (s), 169.1 (s), 100.6 (d, C-1′), 86.4 (d, C-1), 77.6 (d, C-5), 73.7 (d, C-3), 72.8 (d, C-3′), 72.1 (d, C-5), 71.0 (d, C-2′), 68.8 (d, C-2), 68.3 (d, C-4), 68.2 (d, C-4′), 68.1 (t, C-6), 61.8 (t, C-6′), 55.7 (s), 23.1 (q, x 3C), 20.7 (q), 20.7 (q), 20.7 (q), 20.6 (q), 20.6 (q), 20.5 (q), 20.5 (q); UV (CH_3CN) λ_{max} (ε 210 nm (3500; CD (CH_3CN) λ_{ext} (Δε) 230 (7.9), 203 nm (−6.8). Anal. Calcd for $C_{30}H_{44}O_{18}S$: C, 49.72; H, 6.12; S, 4.42. Found: C, 49.76; H, 6.10; S, 3.97.

4.16. (R_S)-*tert*-Butyl 2,3,4-tri-*O*-acetyl-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside *S*-oxide 9*R*

TLC R_f = 0.47 (MeOH/CH_2Cl_2 1:19); mp = 190 °C; $[\alpha]_D$ = −51.1 (*c* 0.4, $CHCl_3$); HRMS calcd for $C_{30}H_{44}O_{18}NaS$ 747.2146 ([M+Na]$^+$), found 747.2150; ^{1}H NMR (δ, $CDCl_3$) 5.40 (dd, *J* = 9.1, 9.1 Hz, H-2), 5.30 (dd, *J* = 9.3, 9.3 Hz, H-3), 5.16 (dd, *J* = 9.4, 9.4 Hz, H-3′), 5.03 (dd, *J* = 9.7, 9.7 Hz, H-4′), 4.94 (dd, *J* = 8.0, 9.3 Hz, H-2′), 4.92 (dd, *J* = 9.5, 9.5 Hz, H-4), 4.55 (d, *J* = 8.0 Hz, H-1′), 4.32 (d, *J* = 10.0 Hz, H-1), 4.26 (dd, *J* = 5.4, 12.3 Hz, H-6*R*′), 4.11 (dd, *J* = 2.2, 12.3 Hz, H-6*S*′), 3.79 (m, H-5, H-6*R*, H-6*S*), 3.69 (ddd, *J* = 2.2, 5.4, 10.0 Hz, H-5′), 2.10 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (δ, $CDCl_3$) 170.5 (s), 170.4 (s), 170.3 (s), 170.1 (s), 169.4 (s), 169.2 (s), 168.7 (s), 100.4 (d, C-1′), 84.9 (d, C-1), 78.2 (d, C-5), 73.7 (d, C-3), 72.9 (d, C-3′), 72.0 (d, C-5), 71.2 (d, C-2′), 68.4 (d, C-4), 68.2 (t, C-6), 68.2 (d, C-4′), 67.4 (d, C-2), 61.8 (t, C-6′), 55.9 (s), 24.1 (q x 3C), 20.7 (q), 20.6 (q), 20.5 (q), 20.5 (q), 20.5 (q), 20.5 (q), 20.5 (q); UV (CH_3CN) λ_{max} (ε 210 nm (3500; CD (CH_3CN) λ_{ext} (Δε) 224 (−8.2), 204 nm (8.4). Anal. Calcd for $C_{30}H_{44}O_{18}S$: C, 49.72; H, 6.12; S, 4.42. Found: C, 49.31; H, 5.72; S, 3.87.

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28. *Regression line equations for compounds* ***1–5***. Chloroform: $P_{gg} = 3.3\ E_S + 39.1$ ($R^2 = 0.89$); $P_{gt} = -3.3\ E_S + 60.9$ ($R^2 = 0.89$). Benzene: $P_{gg} = 5.4\ E_S + 41.7$ ($R^2 = 0.86$); $P_{gt} = -5.4\ E_S + 58.3$ ($R^2 = 0.86$).
29. *Regression line equations for compounds* ***1–5***. Acetonitrile: $P_{gg} = -0.36\ E_S + 51.6$ ($R^2 = 0.26$); $P_{gt} = 0.36\ E_S + 48.4$ ($R^2 = 0.26$). Methanol: $P_{gg} = 1.8\ E_S + 51.6$ ($R^2 = 0.47$); $P_{gt} = -1.8\ E_S + 48.4$ ($R^2 = 0.47$). Acetone: $P_{gg} = 0.12\ E_S + 43.3$; $P_{gt} = -0.12\ E_S + 56.7$.
30. The classical nomenclature (*exo-syn, exo-anti, non-exo*) is not suitable for glycosyl sulfoxides, since they only have a nonbonded electron pair. Therefore, a nomenclature based on the disposition of the *R* substituent with respect to the endocyclic oxygen O5 was used, as shown in Figure 10. In addition, we herein differentiate (S_S)- and (R_S)-sulfoxides with blue and red colors, respectively.
31. *Regression line equations for compounds* ***6R–8R***: $P_{gg} = 14.1\ E_S + 35.5$ ($R^2 = 0.98$); $P_{gt} = -14.1\ E_S + 64.5$ ($R^2 = 0.98$).
32. *Regression line equations for compounds* ***6S–9S***: Dichloromethane: $P_{gg} = 10.3\ E_S + 51.8$ ($R^2 = 0.88$); $P_{gt} = -10.3\ E_S + 48.2$ ($R^2 = 0.88$); Chloroform: $P_{gg} = 5.3\ E_S + 48.5$ ($R^2 = 0.78$); $P_{gt} = -5.3\ E_S + 51.5$ ($R^2 = 0.78$).
33. *Regression line equations for compounds* ***6R–9R***: Acetonitrile: $P_{gg} = -1.5 + 45.2$ ($R^2 = 0.24$); $P_{gt} = 1.5\ E_S + 54.8$ ($R^2 = 0.24$); Methanol: $P_{gg} = 2.0\ E_S + 37.8$ ($R^2 = 0.69$); $P_{gt} = -2.0\ E_S + 62.2$ ($R^2 = 0.69$); Acetone $P_{gg} = 0.3\ E_S + 35.2$ ($R^2 = 0.07$); $P_{gt} = -0.3\ E_S + 64.8$ ($R^2 = 0.07$).
34. *Regression line equations for compounds* ***6S–9S***: Acetonitrile: $P_{gg} = 1.0\ E_S + 49.5$ ($R^2 = 0.78$); $P_{gt} = -1.0\ E_S + 50.5$ ($R^2 = 0.78$); methanol: $P_{gg} = 8.9\ E_S + 59.148$ ($R^2 = 0.94$); $P_{gt} = -8.9\ E_S + 40.9$ ($R^2 = 0.94$); acetone: $P_{gg} = 3.6\ E_S + 44.1$ ($R^2 = 0.87$); $P_{gt} = -3.6\ E_S + 55.9$ ($R^2 = 0.87$).
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