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Involvement of the *S*-aglycon in the conformational preferences of thioglucosides

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Abstract—The conformational preferences of two series of alkyl β-D-thioglucopyranosides in solution were investigated by NMR and CD. The rotamer populations of the hydroxymethyl group were found to depend on the structural nature of the *S*-aglycon. The population of the *gt* rotamer increased and that of the *gg* rotamer decreased as the alkyl group attached to the S atom increased in size. These rotamer populations have a linear correlation with the Taft' steric parameters, the n_S–σ^*_{C-O} *exo*-anomeric interaction may express these rotational preferences. Comparative analysis of the hydroxymethyl populations between alkyl *O*- and *S*-glucosides revealed identical or slightly higher *gt* and smaller *gg* populations for the latter compounds.
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1. Introduction

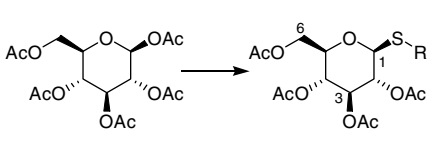
Thiosugars possess unique physicochemical and biological properties, as a consequence of geometric, conformational, and electronic differences from their oxygen analogs.[1] Thioglycosides are the most abundant family of naturally occurring thiosugars isolated from many different plant species. Replacement of the exocyclic oxygen atom with a sulfur atom increases their stability toward chemical and enzymatic action.[2] It also confers a high degree of flexibility around the interglycosidic linkage.[2] These compounds are therefore useful for a variety of purposes in bioorganic and medicinal chemistry research.

Our previous reports were centered on the understanding of the conformational preferences of the most important monosaccharides in nature: gluco-,[3] galacto-,[4] and mannopyranosides,[5] as well as disaccharides,[6] and on the glycomimetic *C*-glucopyranosides.[7] To extend the scope of our studies, we focused on thioglycosides, a common and attractive option for glycomimetic design.

2. Results

To carry out our conformational studies with alkyl β-thioglucosides, by means of nuclear magnetic resonance and circular dichroism, we have synthesized two series of model compounds. The first thioglucoside series possesses four acetyl groups, namely, alkyl 2,3,4,6-tetra-*O*-acetyl β-D-thioglucosides. The second possesses two acetyl and two chromophoric *p*-bromobenzoyl groups, namely, alkyl 2,3-di-*O*-acetyl-4,6-di-(*p*-bromobenzoyl) β-D-thioglucosides.

The model compounds **1a**, **3a**–**8a**, and **3b**–**8b** were synthesized according to method A,[8] namely, from penta-*O*-acetyl-β-D-(+)-glucopyranose (Scheme 1) or from



R
1a, acetyl
2a, methyl
3a, ethyl
4a, propyl
5a, benzyl
6a, isopropyl
7a, cyclohexyl
8a, *tert*-butyl

Scheme 1. Synthesis of the model thioglucosides **1a**–**8a**. Reagents and conditions: Method A: R-SH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt; Method B: (i) thiourea, $BF_3{\cdot}Et_2O$, CH_3CN, reflux, (ii) Et_3N, CH_3I or Ac_2O.

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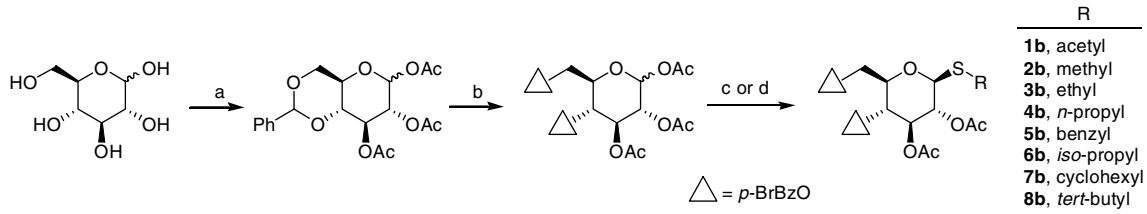


Scheme 2. Synthesis of model β-thioglucosides **1b**–**8b**. Reagents and conditions: (a) (i) $PhCH(OCH_3)_2$, *p*-TsOH, DMF, 50 °C, (ii) Ac_2O, Py; (b) (i) AcOH/H_2O (8:2), 60 °C, (ii) *p*-BrBzCl/Py, DMAP, 60 °C; (c) Method A: R-SH, $BF_3{\cdot}Et_2O$, CH_2Cl_2; (d) Method B: (i) $(NH_2)_2CS$, $BF_3{\cdot}Et_2O$, CH_3CN, 80 °C, (ii) Et_3N, CH_3I or Ac_2O, rt.

1,2,3-tris-*O*-acetyl-4,6-bis-*O*-(4-bromobenzoyl)-β-D-glucopyranose[9] (Scheme 2) by substitution of the anomeric acetyl group by a nucleophilic thiol. The *S*-acetyl derivative **1b** and methyl thioglucosides **2a** and **2b** were obtained by an alternative methodology (method B).[10] Thus, these compounds were obtained from the glucosyl thiouronium salt with acetic anhydride or methyl iodide, in accordance with Tiwari's procedure.[10]

The characterization of the β-thioglycosides was achieved by means of mono- (^1H and ^{13}C) and bi-dimensional (COSY-G, HMQC, and T-ROESY) NMR spectroscopy. The β anomeric configuration was determined by analyzing the J_{H1-H2} value (around 9.9 Hz), and confirming it in the T-ROESY experiments by observing cross-peaks between the anomeric proton H1 and H3, and between H1 and H5.

The ^1H NMR signals of the prochiral protons H6*S* and H6*R* were differentiated according to the data in the literature,[11] on the basis of their chemical shifts and coupling constants. In general, for D-glucopyranoside series, H6*R* proton signals appear at higher field than H6*S* signals (δ H6*S* > δ H6*R*), the reverse behavior being observed in acetate series where H6*S* appears at higher field than H6*R* (δ H6*R* > δ H6*S*). Furthermore, independently of the nature of the series, the $J_{H5,H6R}$ coupling constants have higher values than $J_{H5,H6S}$. Thus, for thioglycosides belonging to the acetyl series (**1a**–**8a**), δ H6*S* chemical shifts are between δ 4.08 and 4.14 and for δ H6*R* between δ 4.19 and 4.25 (Table 1), while for compounds **1b**–**8b**, corresponding to the dibenzoyl series, δ H6*S* values are between δ 4.48 and 4.53 and for δ H6*R* between δ 4.35 and 4.40 (Table 2). In addition, the coupling constant values of $J_{H5,H6R}$ and $J_{H5,H6S}$ followed the same behavior; thus for the acetyl series, $J_{H5,\ H6R}$ showed values between 4.5 and 6.0 Hz, while $J_{H5,\ H6S}$ was around 2.3 Hz; on the other hand, for the dibenzoyl series, $J_{H5,H6R}$ values were between 4.7 and 6.6 Hz and $J_{H5,H6S}$ around 3.2 Hz.

2.1. Conformational analysis

Rotation around the torsional angle ω (O5–C5–C6–O6) led to three staggered conformers: *gauche–gauche* (*gg*, $\omega = -60$), *gauche–trans* (*gt*, $\omega = 60$), and *trans–gauche* (*tg*, $\omega = 180$) (Fig. 1). The rotational behavior of the hydroxymethyl group can be determined by analyzing the $J_{H5,H6}$ coupling constants. Thus, an increase in the $J_{H5,H6R}$ constant around the C5–C6 bond (ω) was observed as the bulkiness of the *S*-aglycon increased. For the acetyl *S*-glucoside series, this coupling constant increased from 4.5 to

Table 1. NMR data, and calculated rotamer populations (%) around the C5–C6 bond for the model thioglucoside derivatives (acetyl series)

Entry	R	δ C1	δ H1	δ H6*R*	δ H6*S*	J_{H5-H6R}	J_{H5-H6S}	P_{gg}	P_{gt}	P_{tg}
1a	Acetyl	80.1	5.24	4.25	4.08	4.5	2.1	64	36	0
2a	Methyl	82.7	4.38	4.23	4.13	4.8	2.2	61	39	0
3a	Ethyl	83.5	4.48	4.24	4.13	4.9	2.2	60	40	0
4a	*n*-Propyl	83.7	4.47	4.23	4.12	5.0	2.2	59	41	0
5a	Benzyl	81.7	4.30	4.25	4.14	5.1	2.2	58	42	0
6a	*iso*-Propyl	83.4	4.58	4.23	4.12	5.2	2.3	56	44	0
7a	Cyclohexyl	83.2	4.59	4.22	4.12	5.3	2.4	55	45	0
8a	*tert*-Butyl	82.3	4.63	4.19	4.10	6.0	2.3	48	52	0

Table 2. NMR data, and calculated rotamer populations (%) around the C5–C6 bond for the model thioglucoside derivatives (dibenzoyl series)

Entry	R	δ C1	δ H1	δ H6*R*	δ H6*S*	J_{H5-H6R}	J_{H5-H6S}	P_{gg}	P_{gt}	P_{tg}
1b	Acetyl	80.4	5.36	4.35	4.48	4.8	3.0	58	37	5
2b	Methyl	83.1	4.50	4.39	4.53	4.7	3.4	56	35	9
3b	Ethyl	83.7	4.61	4.40	4.53	5.1	3.3	52	39	9
4b	*n*-Propyl	83.9	4.59	4.39	4.53	5.2	3.3	51	40	9
5b	Benzyl	82.1	4.39	4.40	4.52	5.0	3.2	54	38	8
6b	*iso*-Propyl	83.5	4.69	4.38	4.51	5.6	3.2	49	43	8
7b	Cyclohexyl	83.3	4.70	4.39	4.50	5.8	3.2	46	46	8
8b	*tert*-Butyl	82.5	4.74	4.37	4.49	6.6	2.9	39	56	5

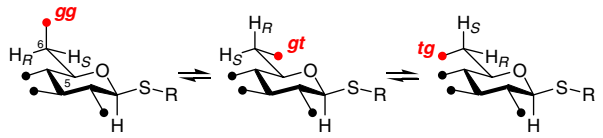
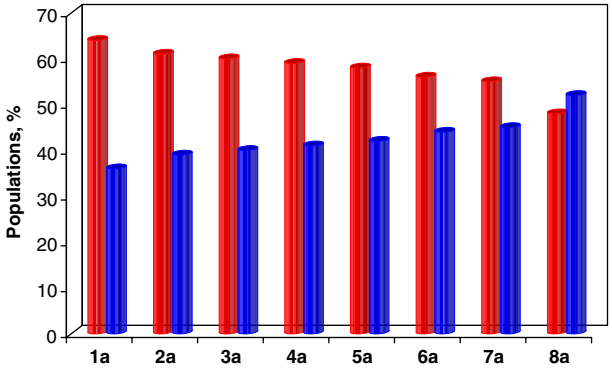


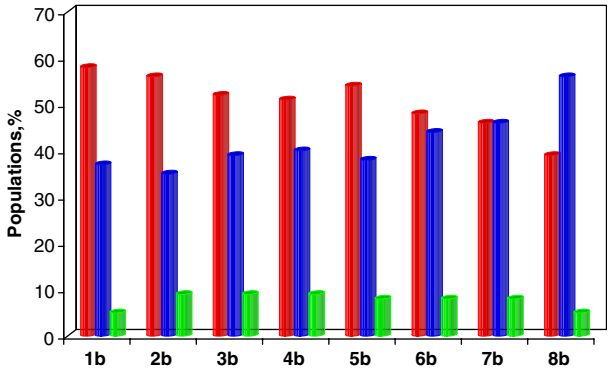
Figure 1. Hydroxymethyl rotamers in β-thioglucosides.

6.0 Hz, passing from compound **1a** to **8a**. Similarly, a gradual increase of $J_{H5,H6R}$ from 4.7 to 6.6 Hz was observed from **2b** to **8b** for the aliphatic alkyl *S*-glucosides (dibenzoyl series). Namely, from **2b** (4.7 Hz) to compounds with a linear aglycon: **3b** (5.1), and **4b** (5.2), to compounds with a branched aglycon: **6b** (5.6), **7b** (5.8), and **8b** (6.6 Hz). On the other hand, the $J_{H5,H6S}$ value remained more or less constant (around 2.3 Hz for the acetyl series and around 3.2 Hz for the dibenzoyl series).

The rotamer populations of the hydroxymethyl group can be calculated by applying the Serianni equations system,[12] using the experimental $J_{H5,H6R}$ and $J_{H5,H6S}$ coupling constants. Thus, the calculated populations for the acetyl and dibenzoyl series are summarized in Tables 1 and 2. They correlate with an increased *gt* population at the expense of the *gg*, the *tg* population remaining almost constant or nil, as seen in Graphs 1 and 2 for the acetyl and dibenzoyl thioglucoside series.



Graph 1. Calculated rotameric populations (%) (P_{gt}: blue; P_{gg}: red) for compounds **1a**–**8a** (acetyl series).



Graph 2. Calculated rotameric populations (%) (P_{gt}: blue; P_{gg}: red; P_{tg}: green) for compounds **1b**–**8b** (dibenzoyl series).

Both series exhibited almost identical *gt* populations, although slightly higher *gg* and nil *tg* populations were obtained for the acetyl series than for the dibenzoyl series (Tables 1 and 2). The increases in the rotational population of the *tg* rotamer in the latter series may be explained by a favorable π–π interaction between the two aromatic rings in this array.[13]

2.2. Circular dichroism analysis

Circular dichroism (CD) is a powerful technique that has mainly been used for determining the absolute configuration and conformation of a great number of compounds of both natural and synthetic origins. The development of the CD exciton chirality method[14] has made this technique even more useful. Its high sensitivity and simple spectral interpretation provide further conformational data. The exciton-coupled *p*-bromobenzoyl chromophores present in our model compounds **1b**–**8b** (dibenzoyl series) permit them to be analyzed by this method.

The CD spectra exhibited the exciton Cotton effects around 252 and 234 nm (Fig. 2). The amplitude of the split CD curves (*A* value)[15] gradually decreased from compound **1b** (22.4), **2b** (21.9), **3b** (21.6), **4b** (20.1), **6b** (19.6), **7b** (15.8), to **8b** (14.7).[16] The CD spectral differences between the model compounds arise from the pairwise interactions involving the chromophore at position 6, since no ring distortion has been observed for our model compounds. Therefore, these intensities are consistent with a gradually reduced positive contribution from the pairwise interaction between the chromophore at position 4 and that at position 6 in the *gg* spatial disposition and/or with a gradually higher negative contribution between these chromophores in the *gt* spatial disposition (Fig. 3).[14] These differences are in agreement with the above NMR results. In addition, while CD measurements were carried out in CH_3CN, NMR analyses were carried out in $CDCl_3$, so this conformational behavior is not solvent dependent.

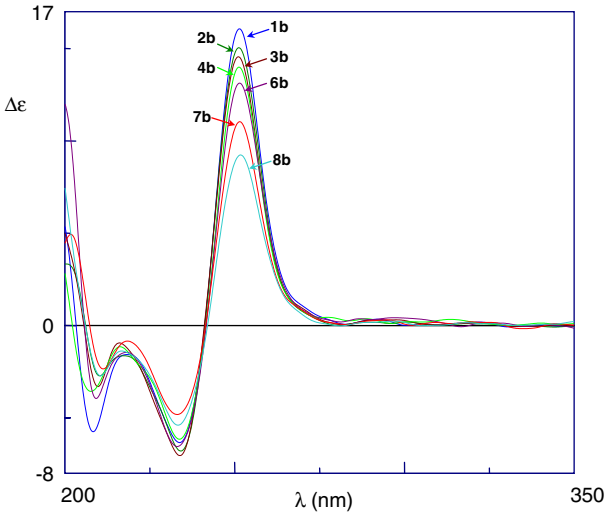


Figure 2. CD spectra of some model β-thioglucosides (CH_3CN).

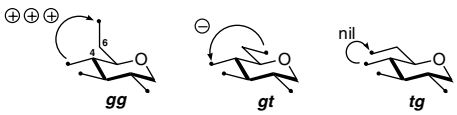


Figure 3. 4/6 Pairwise interaction involving the chromophore at the 6 position in each of the three stable rotamers (*gg*, *gt*, and *tg*).

2.3. Origin of the conformational preferences of the hydroxymethyl group

The observed preferences cannot be due to non-bonded interactions between the hydroxymethyl group and the *S*-aglycon, since this would induce an increase in the *gg* population as the size of the *S*-aglycon increases instead of decreasing. However, a good correlation between the hydroxymethyl rotational populations around the C5–C6 bond and Taft's steric parameters (E_S) was observed for both series (Figs. 4 and 5).[17,18] Furthermore, plots of the populations versus corresponding σ_α values (polarizability parameter) showed no good linear relationships ($R^2 = 0.54$).[19]

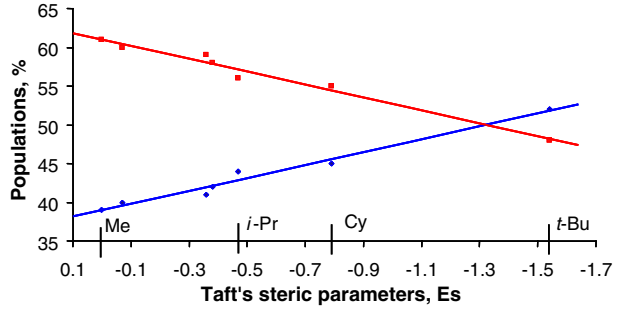


Figure 4. Rotational populations of *gg*/*gt* rotamers (red/blue) versus corresponding E_S values (acetyl series).[20]

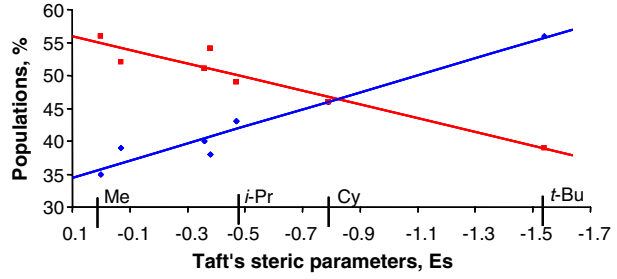


Figure 5. Rotational populations of *gg*/*gt* rotamers (red/blue) versus corresponding E_S values (dibenzoyl series).[21]

The E_S values are composite terms, derived from both potential energy steric effects (steric strains) and kinetic energy steric effects (steric hindrances to motion). According to Taft,[17] introduction of a straight-chain alkyl group in place of the standard hydrogen substituent raises the activation energy due to steric hindrance. Therefore, as the substituent becomes bulkier, rotation around the *S*-glucosidic bond decreases and the more stable rotamer, the *exo-syn,* increases its population.[22] Non-bonded interactions between the *S*-aglycon and the substituent at position 2 are also likely to exist,[23] decreasing the non-*exo* rotamer and reducing flexibility (Fig. 6).

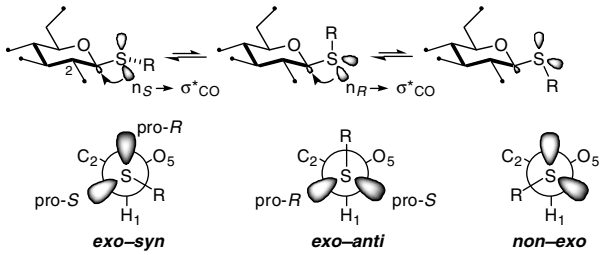


Figure 6. Molecular orbitals involved in the *exo*-anomeric effect for the three idealized staggered rotamers around the C1–S bond.

The higher antiperiplanar disposition population of the *pro-S* electron pair against the endocyclic oxygen, as the *exo-syn* rotamer population increases, should lead to a stronger *exo*-anomeric effect.[24,25] So, different values of this effect should modify the bond lengths around the anomeric carbon, as occurred in *O*-glycosides,[26] and express in this way the conformational preferences of the hydroxymethyl group.

The participation of the *exo*-anomeric 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. From the methyl derivative **2a** (4.38 ppm) to compounds with a primary alkyl group, such as ethyl **3a** and propyl **4a** (around 4.48 ppm), to those with a secondary alkyl group: isopropyl **6a** and cyclohexyl **7a** (around 4.58), and to the *tert*-butyl derivative **8a** (4.63 ppm). The same behavior occurred for H-1 in the dibenzoyl series, from 4.50 for **2b** to 4.74 ppm for **8b** ($\Delta\delta = 0.24$ ppm).

So far, we have demonstrated the rotational population dependence of the hydroxymethyl group in alkyl gluco-,[3] galacto-,[4] and mannopyranosides,[5] *C*-glycosides,[7] and herein β-thioglucosides on the structural nature of the aglycon, its absolute configuration and anomeric configuration. This behavior is explained by the different values of the *exo*-anomeric effect in *O*-glycosides,[3–5] and herein with *S*-glucosides too, and by the *exo*-deoxoanomeric effect in

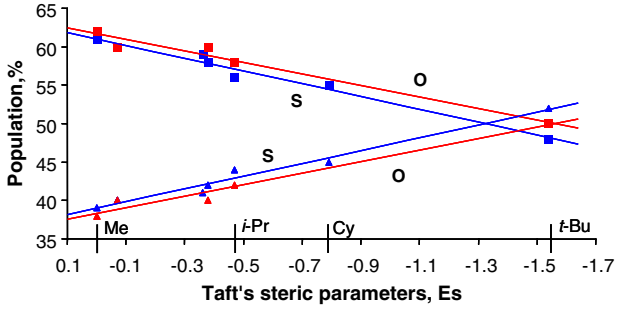


Figure 7. Rotational populations of *gg*/*gt* rotamers (■/▲) for alkyl *O*- (red) and *S*-glucosides (blue) versus corresponding E_S values (acetyl series).[20,28]

C-glycosides.[7] Furthermore, as the size of the aglycon increased, the population of the *gt* rotamer was observed to increase in all cases. Comparing rotamer populations of alkyl *O*-[27] and *S*-glucosides revealed (Fig. 7) analogous or slightly higher *gt* (blue triangle) and lower *gg* (blue square) populations for the latter, both types of compounds showing similar slopes and deviations. Therefore, these data point to similar *exo*-anomeric effects for the *S*- and *O*-glucosides. The C(sp^3)–S bond (1.81 Å) being longer than C(sp^3)–O (1.41 Å) does not favor a stereoelectronic n_S–σ^*_{CO} interaction, however, the similar electronegativity between C and S, and the stronger nucleophilicity of the lone electron pair of the sulfur atom compared to the oxygen atom could counteract the greater bond length.

3. Conclusions

Two series of alkyl β-D-thioglucopyranosides were synthesized and their conformational preferences in solution investigated by NMR and CD. Analysis of the ^{1}H NMR coupling constant values and CD spectral data revealed that the rotamer populations of the hydroxymethyl group were dependent on the structural nature of the *S*-aglycon. It was also observed that as the size of the alkyl group attached to the *S* atom increased, the population of the *gt* rotamer increased, at the expense of the *gg* rotamer. In addition, a linear correlation was found between the Taft steric parameters and the hydroxymethyl rotamer populations. A higher steric hindrance to motion as the substituent becomes bulkier is derived from Taft's analysis; this should lead to an increased population of the more stable rotamer, the *exo-syn*. The stereoelectronic n_S–σ^*_{CO} interaction (the *exo*-anomeric effect) may express the rotational preferences of the hydroxymethyl group.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C NMR at 100 MHz, VTU 300.0 K. Chemical shifts are reported in ppm. The residual solvent peak ($CDCl_3$) was used as internal reference, 7.26 for proton and 77.0 for carbon NMR. Optical rotations were measured on a digital spectropolarimeter in a 1 dm cell. UV and CD spectra were recorded in the range 350–200 nm using 10 mm cells. The concentrations of the CD samples were ascertained from the UV spectra, using the experimentally determined ε values at 250 nm: di-(*p*-bromobenzoate) ε 38,200.

For analytical thin-layer chromatography, silica gel readyfoils were used and 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 60 Å silica gel. All reagents were obtained from commercial sources and used without further purification. Solvents were dried and distilled before use. All reactions were performed under a dry nitrogen atmosphere.

4.2. General procedures for the synthesis of β-D-thioglucopyranosides

Method A:[8] Boron trifluoride etherate (0.1 equiv) was added dropwise to a stirred solution of the sugar donor β-D-glucose pentaacetate or 1,2,3-tris-*O*-acetyl-4,6-bis-*O*-(4-bromobenzoyl)-β-D-glucopyranose[9] and the respective thiol (2 equiv) in dry dichloromethane (5 mL/mmol) at room temperature and under N_2 atmosphere. The reaction progress was followed by TLC. When the starting compound was consumed it was quenched by addition of Et_3N and diluted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The products were purified by chromatography using silica gel and solutions of *n*-hexane/ethyl acetate in various proportions as eluents.

Method B:[10] Boron trifluoride etherate (1.5 equiv) was added dropwise to a stirred solution of the glycosyl donor (1 equiv) and thiourea (2 equiv) in CH_3CN (5 mL/mmol), and the mixture refluxed at 80 °C. After full consumption of the sugar, the reaction mixture was cooled to room temperature and Et_3N (3 equiv) and acetic anhydride (1.5 equiv) or the corresponding alkyl halide (1.5 equiv) were added. The mixture was stirred for 3 h and the solvent removed under reduced pressure. The resultant syrup was diluted with CH_2Cl_2 and washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the crude over silica gel and *n*-hexane/ethyl acetate afforded the respective thioglycoside.

4.3. 2,3-Di-*O*-Acetyl-1-*S*-acetyl-4,6-bis-*O*-(4-bromobenzoyl)-1-thio-β-D-glucopyranose 1b

TLC $R_f = 0.35$ (*n*-hexane/EtOAc 7:3); $[\alpha]_D = +50.4$ (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.85–7.76 (m, 4H), 7.57–7.52 (m, 4H), 5.49 (dd, $J = 9.3$ and 9.3 Hz, H-3), 5.41 (dd, $J = 9.7$ and 9.7 Hz, H-4), 5.36 (d, $J = 10.5$ Hz, H-1), 5.21 (dd, $J = 9.1$ and 10.5 Hz, H-2), 4.48 (dd, $J = 3.0$ and 12.3 Hz, H-6*S*), 4.35 (dd, $J = 4.8$ and 12.3 Hz, H-6*R*), 4.11 (ddd, $J = 3.0$, 4.8 and 9.8 Hz, H-5), 2.39 (s, 3H), 2.04 (s, 3H), 1.92 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 191.9 (s), 169.9 (s), 169.4 (s), 165.3 (s), 164.4 (s), 132.0-127.4, 80.4 (d, C-1), 76.2 (d, C-5), 73.6 (d, C-3), 69.3 (d, C-4), 68.9 (d, C-2), 62.9 (t, C-6), 30.8 (q), 20.6 (q), 20.5 (q). UV (CH_3CN) λ_{max} 244 nm; CD (CH_3CN) λ_{ext} nm ($\Delta\varepsilon$) 251 (16.1), 233 (−6.3).

4.4. Methyl 2,3-di-*O*-acetyl-4,6-bis-*O*-(4-bromobenzoyl)-1-thio-β-D-glucopyranoside 2b

TLC $R_f = 0.35$ (*n*-hexane/EtOAc 3:1); $[\alpha]_D = +6.0$ (*c* 0.8, $CHCl_3$); HRMS (FAB): Calcd for $C_{25}H_{24}O_9\ ^{79}Br_2SCs$ ($[M+Cs]^+$): 790.8562, found: 790.8583; ^{1}H NMR ($CDCl_3$) δ 7.83–7.77 (m, 4H), 7.56–7.51 (m, 4H), 5.45 (dd, $J = 9.3$ and 9.3 Hz, H-3), 5.39 (dd, $J = 9.4$ and 9.4 Hz, H-4), 5.15 (dd, $J = 9.5$ and 9.5 Hz, H-2), 4.53 (dd, $J = 3.4$ and 12.6 Hz, H-6*S*), 4.50 (d, $J = 10.0$ Hz, H-1), 4.40 (dd, $J = 4.8$ and 12.6 Hz, H-6*R*), 4.00 (ddd, $J = 3.4$, 4.8 and 9.3 Hz, H-5), 2.17 (s, 3H), 2.08 (s, 3H), 1.90 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.0 (s), 169.5 (s), 165.3 (s), 164.4 (s), 131.9-127.4, 83.0 (d, C-1), 75.7 (d, C-5), 73.4 (d, C-3),

69.6 (d, C-4), 69.0 (d, C-2). 63.2 (t, C-6), 20.7 (q), 20.5 (q), 11.3 (q); UV (CH_3CN) λ_{max} 245 nm; CD (CH_3CN) λ_{ext} nm ($\Delta\varepsilon$) 251 (15.1), 234 (−6.8).

4.5. Ethyl 2,3-di-*O*-acetyl-4,6-bis-*O*-(4-bromobenzoyl)-1-thio-β-D-glucopyranoside 3b

TLC $R_f = 0.42$ (*n*-hexane/EtOAc 3:1); $[\alpha]_D = +1.7$ (*c* 1.0, $CHCl_3$); HRMS (FAB): Calcd for $C_{26}H_{26}O_9\ ^{79}Br_2SCs$ ($[M+Cs]^+$): 804.8719, found: 804.8711; ^1H NMR ($CDCl_3$) δ 7.82–7.77 (m, 4H), 7.55–7.51 (m, 4H), 5.44 (dd, $J = 9.2$ and 9.2 Hz, H-3), 5.39 (dd, $J = 9.5$ and 9.5 Hz, H-4), 5.12 (dd, $J = 9.5$ and 9.5 Hz, H-2), 4.61 (d, $J = 10.0$ Hz, H-1), 4.52 (dd, $J = 3.3$ and 12.2 Hz, H-6*S*), 4.39 (dd, $J = 5.1$ and 12.2 Hz, H-6*R*), 3.98 (ddd, $J = 3.3$, 5.1 and 8.9 Hz, H-5), 2.78–2.63 (m, 2H), 2.07 (s, 3H), 1.90 (s, 3H), 1.26 (dd, $J = 7.4$ and 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.1 (s), 169.4 (s), 165.3 (s), 164.4 (s), 131.1-127.5, 83.7 (d, C-1), 75.7 (d, C-5), 73.5(d, C-3), 69.9 (d, C-2), 69.8 (d, C-4), 63.4 (t, C-6), 24.2 (t), 20.7 (q), 20.5 (q), 14.9 (q); UV (CH_3CN) λ_{max} 245 nm; CD (CH_3CN) λ_{ext} nm ($\Delta\varepsilon$) 251 (14.6), 234 (−7.0).

4.6. Propyl 2,3-di-*O*-acetyl-4,6-bis-*O*-(4-bromobenzoyl)-1-thio-β-D-glucopyranoside 4b

TLC $R_f = 0.47$ (*n*-hexane/EtOAc 3:1); $[\alpha]_D = +1.9$ (*c* 0.1, $CHCl_3$); HRMS (FAB): Calcd for $C_{27}H_{28}O_9NaS^{79}Br^{81}Br$ ($[M+Na]^+$): 710.9698, found: 710.9704; ^1H NMR ($CDCl_3$) δ 7.82–7.77 (m, 4H), 7.56–7.51 (m, 4H), 5.44 (dd, $J = 9.2$ and 9.2 Hz, H-3), 5.38 (dd, $J = 9.5$ and 9.5 Hz, H-4), 5.11 (dd, $J = 9.5$ and 9.5 Hz, H-2), 4.59 (d, $J = 10.0$ Hz, H-1), 4.52 (dd, $J = 3.2$ and 12.2 Hz, H-6*S*), 4.39 (dd, $J = 5.2$ and 12.2 Hz, H-6*R*), 3.97 (ddd, $J = 3.2$, 5.2 and 9.0 Hz, H-5), 2.75–2.57 (m, 2H), 2.07 (s, 3H), 1.90 (s, 3H), 1.67–1.57 (m, 2H), 0.94 (dd, $J = 7.3$ and 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.1 (s), 169.4 (s), 165.3 (s), 164.4 (s), 131.9–127.5, 83.9 (d, C-1), 75.7 (d, C-5), 73.5(d, C-3), 69.9 (d, C-2), 69.8 (d, C-4), 63.3 (t, C-6), 32.2 (t), 23.2 (t), 20.7 (q), 20.5 (q), 13.4 (q); UV (CH_3CN) λ_{max} 245 nm; CD (CH_3CN) λ_{ext} nm ($\Delta\varepsilon$) 251 (13.8), 234 (−6.3); Anal. Calcd for $C_{27}H_{28}Br_2O_9S$: C, 47.11; H, 4.10; S, 4.66. Found: C, 47.42; H, 3.84; S, 4.32.

4.7. Benzyl 2,3-di-*O*-acetyl-4,6-bis-*O*-(4-bromobenzoyl)-1-thio-β-D-glucopyranoside 5b

TLC $R_f = 0.38$ (*n*-hexane/EtOAc 3:1); $[\alpha]_D = -49.8$ (*c* 0.8, $CHCl_3$); HRMS (FAB): Calcd for $C_{31}H_{28}O_9NaSBr_2$ ($[M+Na]^+$): 756.9718, found: 756.9733.; ^1H NMR ($CDCl_3$) δ 7.86–7.76 (m, 4H), 7.56–7.52 (m, 4H), 7.52–7.26 (m, 5H), 5.38–5.35 (m, H-3 and H-4), 5.15 (dd, $J = 9.6$ and 9.6 Hz, H-2), 4.52 (dd, $J = 3.2$ and 12.2 Hz, H-6*S*), 4.40 (dd, $J = 5.0$ and 12.2 Hz, H-6*R*), 4.39 (d, $J = 9.9$ Hz, H-1), 3.93 (d, $J = 13.0$ Hz, 1H), 3.87 (m, H-5), 3.83 (d, $J = 13.0$ Hz, 1H), 2.03 (s, 3H), 1.89 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.0 (s), 169.4 (s), 165.3 (s), 164.4 (s), 136.7–127.4, 82.1 (d, C-1), 75.7 (d, C-5), 73.4 (d, C-3), 69.8 (d, C-4), 69.8 (d, C-2), 63.4 (t, C-6), 33.8 (t), 20.7 (q), 20.5 (q); UV (CH_3CN) λ_{max} 245 nm; CD (CH_3CN) λ_{ext} nm ($\Delta\varepsilon$) 252 (12.9), 234 (−8.5), 211 (−8.9); Anal. Calcd for $C_{31}H_{28}Br_2O_9S$: C, 50.56; H, 3.83; S, 4.35. Found: C, 50.54; H, 3.98; S, 4.34.

4.8. Isopropyl 2,3-di-*O*-acetyl-4,6-bis-*O*-(4-bromo-benzoyl)-1-thio-β-D-glucopyranoside 6b

TLC $R_f = 0.40$ (*n*-hexane/EtOAc 3:1); $[\alpha]_D = -6.3$ (*c* 0.7, $CHCl_3$); HRMS (FAB): Calcd for $C_{27}H_{28}O_9NaSBr_2$ ($[M+Na]^+$): 708.9718, found: 708.9684; ^1H NMR ($CDCl_3$) δ 7.82–7.77 (m, 4H), 7.56–7.50 (m, 4H), 5.45 (dd, $J = 9.4$ and 9.4 Hz, H-3), 5.37 (dd, $J = 9.7$ and 9.7 Hz, H-4), 5.08 (dd, $J = 9.4$ and 9.4 Hz, H-2), 4.69 (d, $J = 10.1$ Hz, H-1), 4.51 (dd, $J = 3.2$ and 12.1 Hz, H-6*S*), 4.38 (dd, $J = 5.6$ and 12.1 Hz, H-6*R*), 3.98 (ddd, $J = 3.2$, 5.6 and 9.3 Hz, H-5), 3.17 (m, 1H), 2.07 (s, 3H), 1.90 (s, 3H), 1.29 (d, $J = 6.7$ Hz, 3H), 1.27 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.1 (s), 169.4 (s), 165.3 (s), 164.4 (s), 132.0-127.5, 83.5 (d, C-1), 75.6 (d, C-5), 73.5(d, C-3), 70.2 (d, C-2), 69.9 (d, C-4), 63.5 (t, C-6), 35.7 (d), 24.0 (q), 23.8 (q), 20.7 (q), 20.5 (q); UV (CH_3CN) λ_{max} 245 nm; CD (CH_3CN) λ_{ext} nm ($\Delta\varepsilon$) 251 (13.1), 233 (−6.5); Anal. Calcd for $C_{27}H_{28}Br_2O_9S$: C, 47.11; H, 4.10; S, 4.66. Found: C, 47.11; H, 4.18; S, 4.46.

4.9. Cyclohexyl 2,3-di-*O*-acetyl-4,6-bis-*O*-(4-bromobenzoyl)-1-thio-β-D-glucopyranoside 7b

TLC $R_f = 0.45$ (*n*-hexane/EtOAc 3:1); $[\alpha]_D = +3.9$ (*c* 0.9, $CHCl_3$); HRMS (FAB): Calcd for $C_{30}H_{32}O_9NaS^{81}Br_2$ ($[M+Na]^+$): 752.9991, found: 752.9957; ^1H NMR ($CDCl_3$) δ 7.82–7.77 (m, 4H), 7.55–7.50 (m, 4H), 5.44 (dd, $J = 9.4$ and 9.4 Hz, H-3), 5.35 (dd, $J = 9.7$ and 9.7 Hz, H-4), 5.07 (dd, $J = 9.5$ and 9.5 Hz, H-2), 4.70 (d, $J = 10.1$ Hz, H-1), 4.50 (dd, $J = 3.2$ and 12.2 Hz, H-6*S*), 4.39 (dd, $J = 5.8$ and 12.2 Hz, H-6*R*), 3.98 (ddd, $J = 3.2$, 5.8 and 9.4 Hz, H-5), 2.90 (m, 1H), 2.06 (s, 3H), 2.03–1.91 (m, 2H), 1.89 (s, 3H), 1.69–1.56 (m, 4H), 1.45–1.13 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 170.0 (s), 169.3 (s), 165.2 (s), 164.4 (s), 131.9–127.5, 83.3 (d, C-1), 75.6 (d, C-5), 73.5(d, C-3), 70.2 (d, C-2), 69.9 (d, C-4), 63.5 (t, C-6), 43.9 (d), 34.1 (t), 33.9 (t), 26.0 (t), 25.9 (t), 25.5 (t), 20.7 (q), 20.5 (q); UV (CH_3CN) λ_{max} 245 nm; CD (CH_3CN) λ_{ext} nm ($\Delta\varepsilon$) 251 (11.0), 233 (−4.8); Anal. Calcd for $C_{30}H_{32}Br_2O_9S$: C, 49.46; H, 4.43; S, 4.40. Found: C, 49.44; H, 4.60; S, 4.43.

4.10. *tert*-Butyl 2,3-di-*O*-acetyl-4,6-bis-*O*-(4-bromo-benzoyl)-1-thio-β-D-glucopyranoside 8b

TLC $R_f = 0.42$ (*n*-hexane/EtOAc 3:1); $[\alpha]_D = -13.7$ (*c* 0.6, $CHCl_3$); HRMS (FAB): Calcd for $C_{28}H_{30}O_9NaSBr_2$ ($[M+Na]^+$): 722.9875, found: 722.9841; ^1H NMR ($CDCl_3$) δ 7.81–7.78 (m, 4H), 7.57–7.52 (m, 4H), 5.48 (dd, $J = 9.4$ and 9.4 Hz, H-3), 5.32 (dd, $J = 9.5$ and 9.5 Hz, H-4), 5.03 (dd, $J = 9.7$ and 9.7 Hz, H-2), 4.74 (d, $J = 10.2$ Hz, H-1), 4.49 (dd, $J = 2.9$ and 12.2 Hz, H-6*S*), 4.37 (dd, $J = 6.6$ and 12.2 Hz, H-6*R*), 4.01 (ddd, $J = 2.9$, 6.6 and 9.7 Hz, H-5), 2.05 (s, 3H), 1.90 (s, 3H), 1.35 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 170.1 (s), 169.3 (s), 165.3 (s), 164.5 (s), 132.0–127.5, 82.5 (d, C-1), 75.6 (d, C-5), 73.6 (d, C-3), 70.2 (d, C-2), 69.9 (d, C-4), 63.8 (t, C-6), 44.3 (s), 31.4 (q × 3Cs), 20.8 (q), 20.5 (q); UV (CH_3CN) λ_{max} 245 nm; CD (CH_3CN) λ_{ext} nm ($\Delta\varepsilon$) 252 (9.2), 233 (−5.5); Anal. Calcd

for $C_{28}H_{30}Br_2O_9S$: C, 47.88; H, 4.30; S, 4.57. Found: C, 47.89; H, 4.62; S, 4.35.

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28. Regression line equations for the *O*-glucopyranosides: $P_{gg} = 7.4568E_S + 61.669$; $R^2 = 0.9677$; $P_{gt} = -7.4568E_S + 38.331$; $R^2 = 0.9677$.