Anomeric effects of sulfones

Guangwu Chen, Richard W. Franck, Guangli Yang, and Michael Blumenstein

Abstract: The anomeric effect of the sulfone group in tetrahydropyrans has been determined. The value is >2 kcal mol^{-1}, which is larger than the *A*-value of a methyl group but less than the *A*-value of the sulfone in a tetrahydropyran. Hence, in an unsubstituted tetrahydropyranyl sulfone, the equatorial conformer predominates, whereas in a properly substituted methyltetrahydropyranyl sulfone, an axial sulfone is preferred over an axial methyl group.

Key words: sulfone, tetrahydropyran, anomeric effect.

Résumé : On a déterminé l'effet anomère du groupe sulfone dans les tétrahydropyranes. La valeur est supérieure à 2 kcal mol^{-1} et elle est nettement supérieure à la valeur de *A* d'un groupe méthyle, mais elle est inférieure à la valeur de *A* de la sulfone dans un tétrahydropyrane. Il en résulte que dans un tétrahydropyranylsulfone non substituée l'isomère équatorial prédomine alors que dans une méthyltétrahydropyranylsulfone substituée de façon appropriée la sulfone occupera la position axiale de façon préférentielle par rapport à un groupe méthyle axial.

Mots clés : sulfone, tétrahydropyrane, effet anomère.

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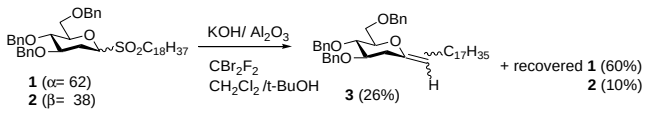
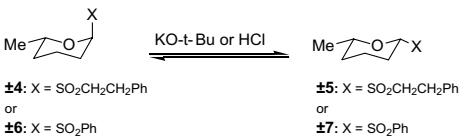
Introduction

The discovery and understanding of the anomeric effect in carbohydrate chemistry begins with Raymond Lemieux and John T. Edward (1). The original arguments rationalized the observation of a diminished equatorial preference of oxygen substituents at the anomeric carbon of carbohydrates in comparison to their equatorial preference in cyclohexanes; similar behavior of other electronegative substituents have since been observed and are included in the rationalization. The sulfone group is an often-prepared and well-known anomeric substituent, used as a starting material for the direct preparation of *C*-glycosides (2), through their lithiation and subsequent desulfonylation (3), via intermediate anomeric lithium (4) and samarium reagents (5) as well as the Ramberg–Bäcklund reaction (6). The sulfone has also been used, rather infrequently, as a leaving group for *O*-glycosylations (7). It was a surprise to us that the anomeric effect of sulfones had not been observed earlier (8). In this paper, experiments that show a large anomeric effect for sulfones are described.

Results and discussion

In our work on applying the Ramberg–Bäcklund reaction to carbohydrate anomeric sulfones, we observed that the α–β ratio of unreacted sulfones **1** and **2** recovered from the basic reaction mixture was not the same as the starting ratio, with the amount of α-isomer enhanced (eq. [1]). This observation could be explained in two ways: (*i*) the β-isomer was reactive whereas the α was not; and (or) (*ii*) the β-isomer was isomerizing to the α-isomer. These two explanations were easily verified. When pure α-isomer **1** was subjected to the Ramberg–Bäcklund conditions, no reaction was observed, consistent with the former explanation; however, when pure β-isomer **2** was subjected to the same conditions, the α-isomer was recovered along with Ramberg–Bäcklund product **3**. These reaction conditions were not an equilibration. The sulfones were, therefore, equilibrated with *t*-BuOK–benzene with no brominating agent present. The equilibrium ratio of β–α achieved in both directions was 57:43. This corresponds to an apparent *A*-value of 0.167 kcal mol^{-1} for the dodecyl sulfone group. Simpler tetrahydropyranyl phenyl sulfones **4**–**7** (eq. [2]) gave similar results (Table 1),





although a different *A*-value was recorded, presumably because of the absence of the electronegative substituents found in **1** and **2**. Tetrahydropyranyl phenethyl sulfones **4** and **5** failed to equilibrate under basic conditions. We assumed that proton exchange was not occurring at the anomeric carbon but at the α′-carbon of the phenethyl group. Thus, we turned to acid-catalyzed equilibration (Table 2). Both the phenyl and phenethyl sulfones gave similar *A*-values,

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Dedicated to the memory of Professor Raymond U. Lemieux.

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Table 1. Sulfone isomerizations via basic conditions.

Entry	Starting material	*T* (°C)	Time	Ratio (*trans*/*cis*)	$\Delta G°$ (kcal mol^{-1})
1	(±)-**6**	85	20 h	1:2.52	−0.658
			5 d	1:2.34	−0.605
2	(±)-**7**	85	20 h	1:5.65[a]	—
			5 d	1:2.52	−0.658
3	(±)-**5**	75	5 d	Only *cis*-isomer[b]	—
4	(±)-**4**/(±)-**5** (1:1.32)	75	5 d	1:1.28[b]	—

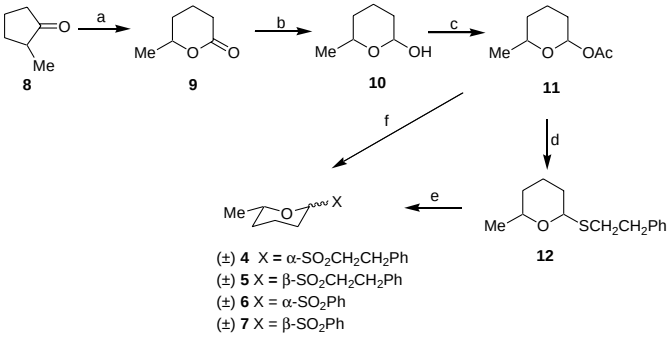
[a]No equilibrium obtained.
[b]No obvious isomerization detected.

Table 2. Sulfone isomerizations via acidic conditions.

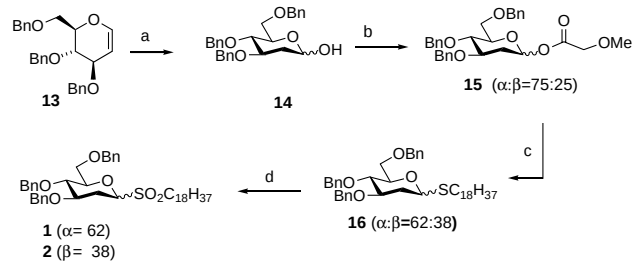
Entry	Starting material	Conditions	*T* (°C)	Time	Ratio (*trans*/*cis*)	$\Delta G°$ (kcal mol^{-1})
1	(±)-**4**	$CDCl_3$ (0.5 mL)	4	7 w	1:3.84	0.741
2	(±)-**4**/(±)-**5** (1:1.32)	$CDCl_3$ (1 mL), TMSCl (1.5 μL), *t*-BuOH (2 μL)	RT	2 w	1:3.62	0.762
3	(±)-**6**	$CDCl_3$ (0.5 mL)	4	3 w	1:1.27[a]	—
		$CDCl_3$ (1 mL), TMSCl (1.5 μL), *t*-BuOH (2 μL)	RT	2 w	1:3.18	0.685
4	(±)-**6**/(±)-**7** (1:2.52)	$CDCl_3$ (1 mL), TMSCl (12.5 μL), *t*-BuOH (10 μL)	RT	2 d	1:3.15	0.679

[a]No equilibrium obtained.

Scheme 1. Reagents and conditions: (*a*) MMPP, DMF, RT, 70%; (*b*) DiBAL, DCM, –78°C, 111% (raw yield); (*c*) Ac_2O, Et_3N, 4-DMAP, 0°C → RT, 73% (3 steps); (*d*) phenylethanethiol, K-10, benzene, RT, 78%; (*e*) MMPP, THF–H_2O–EtOH (4:4:1), 0°C, 1 h, 95%; (*f*) $NaSO_2Ph$, TFA, DCM, 78%.



Scheme 2. Reagents and conditions: (*a*) $Ph_3P·HBr$, H_2O, ether, 81% (*b*) $CH_3OCH_2CO_2H$, DCC, ether, 87% (*c*) $Yb(OTf)_3$, $C_{18}H_{37}SH$, CH_3CN, 60°C, 89% (*d*) MMPP, 95%.



and in the former case, the acid- and base-catalyzed isomer ratios were in good agreement.

The apparent size of the sulfone group was observed by a different method. Thus, *trans*-sulfones **4** and **6** were observed to exist in conformations where the sulfones were axial and the methyls were equatorial. Low-temperature NMR experiments (–110°C) did not succeed in producing spectra that displayed resolved peaks for each of the two possible chair conformers. Only a slight decreased in the $J_{5a,6a}$ value (10.6 Hz) for **6** compared with the value of isomer **7** (11.0 Hz), where the methyl is 100% equatorial, suggests the presence of the flipped-conformer of **6**.

The evaluation of an anomeric effect for a substituent group requires a comparison of the apparent size of the group in an axial position in cyclohexane (where there can be no effect) to its apparent size in tetrahydropyran where an effect may be revealed. The *A*-value for CH_3 in cyclohexane is 1.8 kcal mol^{-1}, while that for SO_2CH_3 is 2.5 kcal mol^{-1} (9). Thus, in cyclohexane, sulfone is larger than methyl by 0.7 kcal mol^{-1}. From the equilibration and conformational data of the simple methyl tetrahydropyranyl sulfones we have studied, the sulfone appears to be smaller than methyl. We estimate that the apparent *A*-value for the sulfonyl group is 0.7 kcal mol^{-1}. If we assume that the sulfone *A*-value in tetrahydropyran, in the absence of an anomeric effect, should be equal to 2.5 kcal mol^{-1} (the same as the cyclohexane value) then the anomeric effect for the sulfone is $2.5_{predicted} - 0.7_{obsd} = 1.8$ kcal mol^{-1}. It is known, however, that the apparent size of axial groups in tetrahydropyran is larger than in cyclohexanes. We have proposed a correction factor of 1.5 in converting a cyclohexane *A*-value to that for a tetrahydropyran. This factor has been derived by comparison of the *A*-value of CH_3 (1.8) in cyclohexane to that of 2.7 at C-2 in tetrahydropyran (10). Hence the sulfone *A*-value could be as high as $2.5 \times 1.5 = 3.75$ kcal mol^{-1}, which leads to an anomeric effect of $3.75_{predicted} - 0.7_{obsd} = 3.05$ kcal mol^{-1}. In either case, the anomeric effect in favor of an axial sulfone is approximately 70% of the steric effect favoring the equatorial conformer. Hence, in the parent phenylsulfonyl tetrahydropyran itself, the group will appear to be equatorial. This is a different situation from the oxygen anomeric effect, which although a smaller force, overrides an equivalent or somewhat smaller steric effect. It is therefore possible to detect significant amounts of axial anomeric oxygen species in the parent tetrahydropyran under equilibrium

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circumstances. Clearly, in the one carbohydrate sulfone we have examined, the anomeric effect is even larger than in the simple cases. Further experiments on a family of carbohydrate sulfones are planned.

Experimental

General methods

^{1}H NMR spectra were recorded on GE QE 300, JEOL FX 400, and Varian 500 spectrometers. Chemical shifts are reported in ppm relative to internal tetramethylsilane (δ = 0.00), chloroform (δ = 7.26), methanol (δ = 3.31), or tetrahydrofuran (δ = 3.58). Coupling constants (*J*) are given in Hertz (Hz). Multiplicities are described by using the following abbreviations: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad. ^{13}C NMR spectra were recorded on GE QE 300 and JEOL FX 400 spectrometers. Chemical shifts are reported in ppm relative to internal standards chloroform (δ = 77.0), acetone (δ = 29.8), or tetrahydrofuran (δ = 67.6). Multiplicities refer to the resonance in the off-resonance spectra and were elucidated using the distortionless enhancement by polarization transfer (DEPT) spectral editing technique, with secondary pulses at 90° and 135°. Coupling constants ($^1J_{C,H}$) are described by using the following abbreviations: s = singlet (due to quaternary carbon); d = doublet (methine); t = triplet (methylene); q = quartet (methyl). Mass spectra were obtained on Agilent Techologies 1100 LC/MSD instrument using electrospray ionization (ESI) mode. Ion mass (*m*/*z*) signals are reported as values in atomic mass units followed, in parentheses, by peak intensities relative to the base peak (100%). Elution of all reactions were monitored by analytical thin layer chromatography (TLC) using silica gel 60 PF^{254} precoated plates (E. Merck), and spots were detected either by UV-absorption or by charring with H_2SO_4–4-methoxybenzaldehyde in methanol or ethanol — R_f values are also given under these conditions. Flash column chromatography was performed using E. Merck silica gel 60 (230–400 mesh). Unless otherwise stated, all commercially available chemicals were used without further purification, but some reagents were dried under vacuum before use. All reactions involving air- and (or) moisture-sensitive reagents were performed under nitrogen atmosphere with dry, freshly distilled solvents using standard syringe–cannula/septa techniques. All solvents were dried by usual methods and stored under nitrogen atmosphere in the dark in well-stoppered bottles. The synthesis of the starting sulfones, illustrated in Schemes 1 and 2, were routine and used known methods.

Oxidation of 2-methylcyclopentanone (8) for synthesis of lactone 9 (11)

To a solution of 2-methylcyclopentanone (8) (3.688 g, 37.6 mmol) in DMF (40 mL) was added MMPP (80%, 35 g, 56.6 mmol, 1.5 equiv). The slightly green suspension was stirred at RT overnight and became a white sticky mixture, whereupon TLC (PE–EE, 1:1) indicated that the oxidation was complete. The mixture was diluted with CH_2Cl_2 (40 mL) and washed with aqueous HCl (2 N, 2 × 30 mL). The combined organic phases were further washed with a saturated solution of $NaHCO_3$ (2 × 30 mL) and water (5 × 30 mL). After drying over Na_2SO_4, the solvent was evaporated under reduced pressure to afford a crude product, which was employed for the next step without further purification. Yield: 3.023 g (26.5 mmol, 70%); R_f = 0.48 (silica gel, PE–EE, 1:1); light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.47 (m, 1H, 5-H), 2.67–2.53 (m, 1H, 2-H), 2.52–2.38 (m, 1H, 2-H′), 1.92–1.45 (m, 4H, 2 × 3-H and 2 × 4-H), 1.40 (d, *J* = 6.2 Hz, 3H, 6-H).

6-Methyltetrahydropyran-2-ol (10) (12)

To a stirred solution of lactone **9** (230 mg, 2.0 mmol) in dry CH_2Cl_2 (15 mL) at –78°C was added a solution of *i*-Bu_2AlH in hexane (1.0 M, 4.0 mL, 4.0 mmol, 2.0 equiv). The mixture was allowed to stir for 2 h, at which time TLC indicated that the reduction was clean and complete. The reaction was quenched by careful addition of MeOH (5 mL) and warmed to ambient temperature, whereupon it was treated with a saturated aqueous solution of Rochelle's salt (15 mL) and was allowed to stir for about 2 h until the phases clearly separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 6 mL) and the combined organic phases were dried over Na_2SO_4. Evaporation of the solvents under reduced pressure afforded the crude lactol **10** in a *trans–cis* ratio of 1:1.7. Yield: 258 mg (2.2 mmol, >99%); R_f = 0.60 (silica gel, PE–EE, 1:1); brown yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.30 (br s, 1H, 2-H of *trans*), 4.72 (dd, *J* = 9.5, 2.2 Hz, 1H, 2-H of *cis*), 3.58 (dqd, *J* = 11.2, 6.2, 2.2 Hz, 1H, 6-H of *trans*), 3.88 (br s, 1H, OH of *cis*), 3.60 (dqd, *J* = 11.2, 6.2, 2.2 Hz, 1H, 6-H of *cis*), 3.25 (br s, 1H, OH of *trans*), 2.00–1.20 (m, 12H, 3 × CH_2 of *cis* and 3 × CH_2 of *trans*), 1.22 (d, *J* = 6.2 Hz, 3H, Me of *cis*), 1.13 (d, *J* = 6.2 Hz, 3H, Me of *trans*).

Acetylation of lactol 10

6-Methyltetrahydropyran-2-ol (**10**) (crude product, ca. 26.5 mmol) was dissolved under nitrogen in $DCM_{abs.}$ (60 mL). To this solution were added triethylamine (5.3 mL, 2 equiv) and acetic anhydride (7.2 mL, 2 equiv). After addition of a catalytic amount of 4-DMAP (64 mg, 0.02 equiv) the mixture was allowed to stir at RT for 1 h, whereupon TLC (PE–EE, 4:1) showed that the acetylation was complete. The mixture was concentrated in controlled vacuo to afford a crude product **11**, which, according to NMR, was so clean that further purification was not necessary. Yield: 4.311 g (27.3 mmol, 73% over 3 steps, *trans–cis* = 1:6.8); R_f = 0.78 (silica gel, PE–EE, 4:1); brown yellow oil with sweet odor. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.09 (br s, 1H, 2-H of *trans*), 5.61 (dd, *J* = 9.3, 2.3 Hz, 1H, 2-H of *cis*), 3.90 (dqd, *J* = 11.0, 6.3, 1.8 Hz, 1H, 6-H of *trans*), 3.63 (dqd, *J* = 11.0, 6.0, 2.2 Hz, 1H, 6-H of *cis*), 2.06 (s, 3H, CH_3CO of *cis*), 2.04 (s, 3H, CH_3CO of *trans*), 1.90–1.29 (m, 12H, 3 × CH_2 of *cis* and 3 × CH_2 of *trans*), 1.19 (d, *J* = 5.86 Hz, 3H, Me of *cis*), 1.10 (d, *J* = 6.2 Hz, 3H, Me of *trans*). ^{13}C NMR of *cis*-isomer (75 MHz, $CDCl_3$) δ: 169.1 (s, *C*OCH_3), 94.7 (d, O*C*HOAc), 73.2 (d, *C*HOCHOAc), 31.9, 29.7, 21.7 (3t, 3 × CH_2), 21.5, 21.2 (2q, CO*C*H_3 and CH_3).

Synthesis of thioglycoside 12 (13)

To a solution of lactol acetate **11** (1.824 g, 11.5 mmol) and benzeneethanethiol (1.547 mL, 1.0 equiv) in dry benzene (80 mL) was added montmorillonite K-10 (3 g). The mixture was stirred at RT for 2 h, whereupon TLC (PE–EE,

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20:1) showed that the thioglycosylation was complete. After filtration with suction, the solid residue was washed with DCM. The combined filtrates were evaporated in vacuo to afford a crude product, which was purified and partially separated by flash chromatography on silica gel (PE–EE, 20:1). Yield: 2.131 g (9.0 mmol, 78%).

trans-Isomer: R_f = 0.46 (silica gel, PE–EE, 20:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35–7.15 (m, 5H, Ph), 5.37 (d, *J* = 5.1 Hz, 1H, 2-H), 4.19 (dqd, *J* = 11.0, 6.2, 2.2 Hz, 1H, 6-H), 2.98–2.75 (m, 4H, CH_2CH_2Ph), 2.00–1.22 (m, 6H, 2 × 3-H, 2 × 4-H, and 2 × 5-H), 1.17 (d, *J* = 6.2 Hz, 3H, Me). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 140.7 (s, Ph-C1), 128.4, 128.2 (2d, Ph-C2,6 and Ph-C3,5), 126.1 (d, Ph-C4), 81.9 (d, O*C*HOCH$_2$CH$_2$Ph), 64.8 (d, *C*HOCHOCH$_2$CH$_2$Ph), 36.7, 33.3, 32.0, 30.3, 19.6 (5t, 5 × CH_2), 21.7 (q, CH_3).

cis-Isomer: R_f = 0.40 (silica gel, PE–EE, 20:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.30–7.14 (m, 5H, Ph), 4.47 (dd, *J* = 11.0, 2.2 Hz, 1H, 2-H), 3.46 (dqd, *J* = 11.0, 6.2, 1.8 Hz, 1H, 6-H), 3.02–2.84 (m, 4H, CH_2CH_2Ph), 1.92–1.10 (m, 6H, 2 × 3-H, 2 × 4-H, and 2 × 5-H), 1.22 (d, *J* = 6.2 Hz, 3H, Me). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 140.8 (s, Ph-C1), 128.4, 128.3 (2d, Ph-C2,6 and Ph-C3,5), 126.1 (d, Ph-C4), 82.6 (d, O*C*HOCH$_2$CH$_2$Ph), 75.0 (d, *C*HOCHOCH$_2$CH$_2$Ph), 36.8, 32.6, 31.8, 31.5, 24.4 (5t, 5 × CH_2), 22.1 (q, CH_3). ES-MS *m*/*z* (%): 254.2 (100) $[M + NH_4]^+$; 498.2 (25) $[2M + NH_4]^+$; 263.1 (70) $[M + Na]^+$; 503.2 (18) $[2M + Na]^+$.

Oxidation of thioglycoside for syntheses of anomeric sulfones (±)-4 and (±)-5 (14)

The isomeric mixture of thioglycosides (±)-**12** (1.076 g, 4.0 mmol) was dissolved in a mixed solvent (54 mL, THF–H_2O–EtOH, 4:4:1) and to it at 0°C was added MMPP (7.9 g, 2.5 equiv). The mixture was allowed to stir at 0°C for 1 h, at which time TLC (PE–EE, 6:1) indicated the completion of the oxidation. The mixture was neutralized with a saturated solution of $NaHCO_3$ (30 mL). The aqueous phase was extracted with DCM (3 × 20 mL). The combined organic phases were dried over Na_2SO_4. Evaporation of the solvent in vacuo afforded a crude product, which was subsequently purified by flash chromatography (PE–EE, 8:1 to 5:1) to afford the pure title phenylethylsulfone of both (±)-**4** (*trans*) and (±)-**5** (*cis*) in a ratio of 2:3. Yield: 1.16 g (4.32 mmol, 95%). Pure *trans*-sulfide (60 mg, 0.254 mmol) was oxidized according to the same procedure. After work-up and flash chromatography pure *trans*-anomeric sulfone (±)-**4** was obtained (yield: 64 mg, 0.239 mmol, 94%) without observing any isomerization at the anomeric position under the oxidation conditions.

(±)-**4**: R_f = 0.40 (silica gel, PE–EE, 6:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.42–7.22 (m, 5H, Ph), 4.73 (dd, *J* = 6.2, 2.2 Hz, 1H, 2-H), 4.48 (dqd, *J* = 10.4, 6.2, 2.2 Hz, 1H, 6-H), 3.40–3.12 (2m, 4H, CH_2CH_2Ph), 2.15–1.21 (m, 6H, 2 × 3-H, 2 × 4-H, and 2 × 5-H), 1.23 (d, *J* = 6.2 Hz, 3H, Me). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 140.7 (s, Ph-C1), 128.0, 127.6 (2d, Ph-C2,6 and Ph-C3,5), 126.1 (d, Ph-C4), 86.3 (d, O*C*HSO$_2$CH$_2$CH$_2$Ph), 68.9 (d, *C*HOCHSO$_2$CH$_2$CH$_2$Ph), 50.7 (t, SO$_2$*C*H$_2$CH$_2$Ph), 30.9, 27.2, 20.1, 17.8 (4t, 4 × CH_2), 20.9 (q, CH_3). ES-MS *m*/*z* (%): 286.2 (100) $[M + NH_4]^+$; 554.2 (9) $[2M + NH_4]^+$; 291.1 (38) $[M + Na]^+$; 559.2 (8) $[2M + Na]^+$.

(±)-**5**: R_f = 0.26 (silica gel, PE–EE, 6:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45–7.25 (m, 5H, Ph), 4.25 (dd, 1H, *J* = 11.4, 2.2 Hz, 2-H), 3.52–3.42 (m, 2H, 6-H and SO$_2$C*H*H), 3.32 (m, 1H, SO$_2$CH*H*), 3.18 (m, 2H, CH_2Ph), 2.10–1.28 (m, 6H, 2 × 3-H, 2 × 4-H, and 2 × 5-H), 1.26 (d, *J* = 6.3 Hz, 3H, Me). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 140.8 (s, Ph-C1), 128.7, 128.5 (2d, Ph-C2,6 and Ph-C3,5), 126.9 (d, Ph-C4), 90.3 (d, O*C*HSO$_2$CH$_2$CH$_2$Ph), 76.1 (d, *C*HOCHSO$_2$CH$_2$CH$_2$Ph), 50.0 (SO$_2$*C*H$_2$CH$_2$Ph), 27.8 (SO$_2$CH$_2$*C*H$_2$Ph), 32.2, 22.3, 21.9 (3t, 3 × CH_2), 21.8 (q, CH_3). ES-MS *m*/*z* (%): 286.2 (100) $[M + NH_4]^+$; 554.2 (9) $[2M + NH_4]^+$; 559.2 (23) $[2M + Na]^+$; 291.1 (100) $[M + Na]^+$; 559.2 (26) $[2M + Na]^+$.

Preparation of phenylsulfone (±)-6 and (±)-7 (15)

Lactol acetate **11** (50 mg, 0.32 mmol) was dissolved in dry DCM (15 mL) and to it was added sodium benzenesulfinate (109 mg, 0.66 mmol, 2 equiv). After addition of trifluoroacetic acid (0.1 mL, 4 equiv) the mixture was allowed to stir for 4 h at RT, whereupon TLC (PE–EE, 4:1) indicated the completion of the reaction. The mixture was diluted with DCM (15 mL) and then decanted into a saturated solution of $NaHCO_3$ (30 mL). The organic phase was washed once with water (20 mL) and dried over Na_2SO_4. Evaporation of the solvent in vacuo gave a crude product, which was subsequently purified by flash chromatography (PE–EE, 4:1) to afford each pure title phenylsulfone (±)-**6** and (±)-**7** Yield: 59 mg (0.246 mmol, 78%, *trans*-(±)-**6**–*cis*-(±)-**7** = 2:1, separable).

(±)-**6**: R_f = 0.30 (silica gel, PE–EE, 6:1); amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.90–7.40 (m, 5H, Ph), 4.38 (dd, *J* = 6.6, 1.5 Hz, 1H, 2-H), 3.45 (dqd, *J* = 10.6, 6.2, 2.3 Hz, 1H, 6-H), 2.10–1.29 (m, 6H, 2 × 3-H, 2 × 4-H, and 2 × 5-H), 1.19 (d, *J* = 6.2 Hz, 3H, Me). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 133.6 (s, Ph-C1), 129.0, 128.6 (2d, Ph-C2,6 and Ph-C3,5), 128.8 (d, Ph-C4), 92.1 (d, O*C*HSO$_2$Ph), 69.6 (d, *C*HOCHSO$_2$Ph), 32.2, 23.6, 18.6 (3t, 3 × CH_2), 21.6 (q, CH_3).

(±)-**7**: amorphous solid; R_f = 0.22 (silica gel, PE–EE, 6:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.90–7.40 (m, 5H, Ph), 4.73 (dd, *J* = 11.0, 2.2 Hz, 1H, 2-H), 4.60 (dqd, *J* = 11.0, 6.2, 2.2 Hz, 1H, 6-H), 2.20–1.29 (m, 6H, 2 × 3-H, 2 × 4-H, and 2 × 5-H), 1.13 (d, *J* = 6.2 Hz, 3H, Me). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 133.5 (s, Ph-C1), 129.6, 128.7 (2d, Ph-C2,6 and Ph-C3,5), 128.8 (d, Ph-C4), 90.6 (d, O*C*HSO$_2$Ph), 74.5 (d, *C*HOCHSO$_2$Ph), 31.8, 22.5, 21.9 (3t, 3 × CH_2), 21.6 (q, CH_3). ES-MS *m*/*z* (%): 258.2 (100) $[M + NH_4]^+$; 498.2 (25) $[2M + NH_4]^+$; 263.1 (70) $[M + Na]^+$; 503.2 (18) $[2M + Na]^+$.

Isomerization

Initially, isomerization was carried out under basic conditions. Molecules *trans*-(±)-**6** and *cis*-(±)-**7** were separately dissolved in dry benzene (2 mL). After addition of *t*-BuOK (10 mg) the solution was isomerized by heating at reflux for 5 days, whereupon the equilibrium was achieved according to the NMR analysis. isomerizations with compounds (±)-**4** and (±)-**5** were done under the similar conditions (*t*-BuOK); however, no isomerization was detected after heating at reflux for 5 days by NMR analysis. (Table 1).

Interestingly, after *trans*-isomer (±)-**4** was stored in $CDCl_3$ in the refrigerator for 3 weeks isomerization was observed,

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although equilibrium was not reached. Similarly *trans*-isomer (±)-**6** was isomerized and reached equilibrium after storing in deuterated chloroform in a refrigerator for 7 weeks. Compound (±)-**6** was also stored in THF-d_6 in the refrigerator for 10 weeks; however, according to the NMR analysis, no isomerization was detected.

Acidic isomerization was preformed in NMR tubes at RT by treatment with small amounts of TMSCl and *t*-BuOH. The equilibrium ratios are given in Table 2.

2-Deoxyglucose series

In our synthesis, benzylated thioglycoside **16** was made from benzylated 2-deoxyglucose derivative **15** via the Inanaga–Yb(OTf)$_3$ method (16). Sulfide **16** was oxidized using MMPP to form sulfone **1**,**2** in good yield.

Tri-*O*-benzyl-2-deoxyglucose (14)

To a mixture of **13** (2.083 g, 5 mmol) and THF (15 mL) was added $Ph_3P{\cdot}HBr$ (0.0858 g, 0.25 mmol). The solution was stirred at RT for 10 min, then H_2O was added (0.135 mL, 0.017mol). This mixture was stirred at RT for 3 h. The mixture was treated with saturated $NaHCO_3$ solution (5 mL) and H_2O (10 mL) and extracted with EtOAc (3 × 20 mL). The organic phase was washed by brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on a column of 100 g silica gel (eluted with 30% EtOAc–petroleum ether) to afford 1.78 g of **14** (81%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.20–7.30 (m, 15H), 5.41 (d, J = 2.3 Hz, 1H), 4.90 (dd, J = 6.4, 3.0 Hz, 1H), 4.80 (m, 6H), 4.05 (m, 1H), 3.60 (m, 2H), 2.85 (s, 1H, OH), 2.32 (m, 1H), 1.70 (m, 1H).

Tri-*O*-benzyl-2-deoxy-1-*O*-methoxyacetylglucose (15)

To a mixture of 2-deoxyglucose **14** (0.194 mL, 2.53 mmol) and ether (20 mL) was added DCC (0.522 g, 2.53 mmol). The mixture was stirred at RT for 10 min, then methoxyacetic acid (1.10 g, 2.3 mmol) was added, followed by 4-pyrrolidinopyridine (0.034 g, 0.23 mmol). After standing overnight, the solution was filtered to remove the solid phase, and then it was washed with brine (50 mL). The aqueous phase was extracted with ether (3 × 20 mL), dried over Na_2SO_4, and concentrated. The residue was chromatographed on a column of 50 g of silica gel (eluted with 20% EtOAc–petroleum ether) to afford 0.110 g of **15** as a colorless oil (87%, α:β = 3:1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.20–7.30 (m, 15H), 6.30 (d, J = 2.7 Hz, 1H), 5.77 (dd, J = 10.5, 2.7 Hz, 1H), 4.88 (m, 1H), 4.60 (m, 6H), 3.98 (s, 2H), 3.41 (s, 3H, OMe), 2.35 (m, 1H), 1.85 (m, 1H).

Thioglycoside (16)

A solution of **15** (0.358 g, 0.707 mmol) and octadecyl mercaptan (0.263 g, 0.919 mmol) in dry acetonitrile (10 mL) was warmed to 53°C (bath temp) under nitrogen, and to this mixture was added a solution of Yb(OTf)$_3$ in acetonitrile (5 mmol L^{-1}, 0.71 mL, 0.5 mol%). After stirring for 2 h, the reaction was quenched with saturated $NaHCO_3$ solution (10 mL), and extracted by CH_2Cl_2 (3 × 20 mL). The organic phase was washed by H_2O, dried over Na_2SO_4, and concentrated. The residue was chromatographed on a column of 20 g of silica gel (eluted with 10% EtOAc–petroleum ether) to afford 0.442 g of **16** (89%, α:β = 8:5) as a white solid. Anal. calcd for $C_{45}H_{66}O_4S$: C 76.87, H 9.46, S 4.56; found: C 76.59, H 9.15, S 4.68.

α-Isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.20–7.30 (m, 15H), 4.91–4.53 (m, 6H), 4.52–4.47 (dd, J = 1.5, 11.7 Hz, 1H), 3.78–3.63 (m, 3H), 3.53–3.40 (m, 2H), 2.70 (m, 2H), 2.34 (m, 1H), 1.75 (m, 1H), 1.60 (m, 2H), 1.20 (s, 30H), 0.88 (t, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 139.22, 139.15, 138.80, 129.03, 128.94, 128.50, 128.46, 128.35, 128.23, 81.34, 79.31, 78.85, 75.63, 74.17, 72.55, 71.72, 69.72, 36.75, 36.74, 31.79, 30.51, 30.36, 30.16, 30.03, 29.75, 23.51, 14.94.

β-Isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.35–7.21 (m, 15H), 5.45 (d, J = 5.1 Hz, 1H), 4.92–4.49 (m, 6H), 4.19 (m, 1H), 3.95 (m, 1H), 3.83 (dd, J = 3.67, 11.0 Hz, 1H), 3.66 (m, 2H), 2.53 (m, 2H), 2.30 (dd, J = 4.76, 13.19 Hz, 1H), 2.08 (m, 1H), 1.59 (m, 2H), 1.35 (s, 30H), 0.91 (t, 3H).

Sulfone 2

A solution of MMPP (0.227 g, 0.45 mmol) in H_2O (2 mL) was added to a solution of **16** (β-isomer, 0.112 g, 0.159 mmol) in EtOH (2 mL) and THF (2 mL), and the mixture was kept at 55°C for 2 h. The mixture was concentrated to dryness in vacuo. The residue was treated with saturated $NaHCO_3$ solution (10 mL), and extracted with EtOAc (3 × 15 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by chromatography on silica gel (eluted with 25% EtOAc–petroleum ether) to afford pure sulfone **2** (β-isomer) as a white solid 0.11 g (95%). MS calcd. for $C_{45}H_{66}O_6S$: 734; found: 757 ([M + Na]$^+$). When the identical reaction was carried out with the (isomer of **16** as starting material, the α-sulfone **1** was afforded.

α-Isomer: mp 58–60°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.20–7.30 (m, 15H), 4.84 (dd, J = 7.0, 3.3 Hz, 1H, H-1), 4.80–4.45 (m, 6H, OCH_2Ph), 4.37 (m, 1H, H-5), 4.20 (m, 1H, H-3), 3.68 (d, J = 3.3 Hz, 2H, H-6), 3.58 (dd, J = 7.2, 9.3 Hz, 1H, H-4), 3.06 (t, 2H), 2.82 (m, 1H, H-2e), 2.06 (m, 1H, H-2a), 1.30 (s, 30H), 0.90 (t, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 138.78, 138.71, 138.53, 129.10, 129.02, 128.97, 128.44, 128.37, 128.308, 86.67, 77.53, 76.59, 75.62, 74.76, 74.06, 72.76, 69.73, 50.51, 32.73, 30.50, 30.32, 30.16, 30.08, 29.84, 29.39, 26.31, 23.50, 22.44, 14.93.

β-Isomer: mp 87–88°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.34–7.20 (m, 15H), 4.95–4.50 (m, 6H, OCH_2Ph), 4.30 (dd, J = 11.0, 3.0 Hz, 1H, H-1), 3.76–3.51 (m, 5H), 3.60 (t, 2H), 2.65 (m, 1H, H-2e), 1.88 (m, 1H, H-a), 1.27 (s, 30H), 0.88 (t, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 137.60, 137.55, 137.32, 128.04, 127.92, 127.60, 127.38, 127.29, 127.19, 127.13, 96.90, 86.78, 79.70, 78.99, 76.78, 74.80, 72.89, 71.02, 68.60, 48.86, 31.47, 29.23, 29.06, 28.89, 28.83, 28.59, 28.15, 27.42, 22.22, 20.75, 13.64.

Isomerization of the α,β isomers of 1 and 2

To a solution of β-sulfone **2** (12 mg, 0.016 mmol) in benzene (1 mL) and *t*-BuOH (0.2 mL) was added *t*-BuOK (10 mg, 0.107 mmol). The reaction mixture was refluxed at 70°C for 24 h. The mixture was diluted by dichloromethane, filtered, and dried in vacuo. The α:β ratio (36:64) was determined by the H-1 peak in ^{1}H NMR.

To a solution of α-sulfone **1** (12 mg, 0.016 mmol) in benzene (1 mL) and *t*-BuOH (0.2 mL) was added *t*-BuOK (10 mg, 0.107 mmol). The reaction mixture was refluxed at

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70°C for 24 h. The mixture was diluted by dichloromethane, filtered, and dried in vacuo. The α:β ratio (53:47) was determined by ^{1}H NMR analysis.

To a solution of sulfone **1**,**2** (α:β = 3:1) (20 mg, 0.027 mmol) in THF (5 mL), *t*-BuOH (1 mL), and KOH–Al_2O_3 (20 mg, 50% (by weight), 0.107 mmol) was added crown ether-18 (0.2 equiv). The reaction mixture was heated at reflux (52°C) for one week. The mixture was diluted by dichloromethane, filtered, and dried in vacuo. The α:β ratio (42:58) was determined by the H-1 peak in ^{1}H NMR.

Pure α-sulfone **1** was treated under the above conditions. The α:β ratio (44:56) was determined by ^{1}H NMR.

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