Reaction of thiophenol with glucal epoxides: X-ray structure of 3,4,6-tri-*O*-*tert*-butyldimethylsilyl-1-*S*-phenyl-1-thio-α-D-glucopyranoside

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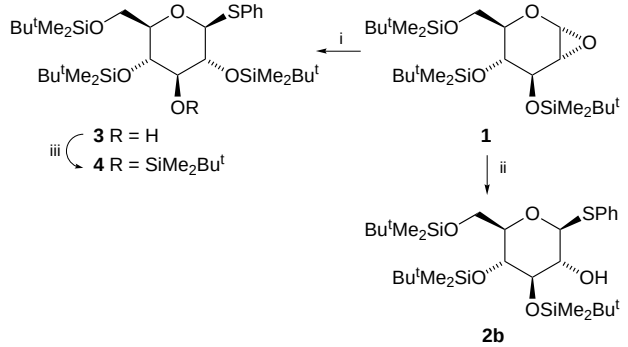
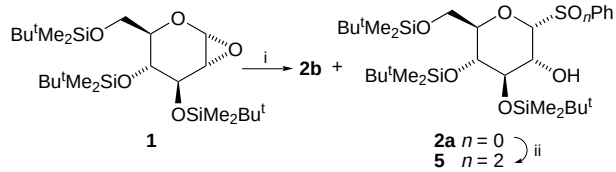
The reaction of the *tert*-butyldimethylsilyl protected glucal epoxide 1 with thiophenol under a variety of conditions gives three distinct adducts, including the α-phenylthioglycoside 2a, which exists both in solution and in the solid state in a $^1C_4$ conformation in which the C-2, C-3, C-4 and C-5 substituents are all axial.

1-Phenylthioglucosides have been widely used in glycosylation reactions. In the context of a project to develop nucleophilic glycosyl donors, we were interested in the development of effective routes to protected α- and β-phenylthioglucosides **2a** and **2b**. Our planned approach involved the reaction of the epoxide **1** (prepared by oxidation of the readily available glucal with dimethyldioxirane)[1] with phenylthiolate, a reaction which had been previously reported on the corresponding tribenzyl protected derivative by Spilling (using NaSPh)[2] and Danishefsky (using Bu_4NSPh).[3] Spilling obtained a low yield, and Danishefsky obtained a mixture of both α- and β-phenylthioglucosides. When the epoxide **1** was treated with lithium phenylthiolate (Scheme 1), the adduct **3** was cleanly obtained (72%), in which the initial product of ring-opening had undergone a silyl shift. However, treatment of the epoxide **1** with thiophenol in the presence of triethylamine did give the expected sulfide **2b** (85%). The structures of the two products were assigned on the basis of extensive two-dimensional NMR studies, including the preparation of acetylated derivatives. While conversion of the sulfide **2b** into the *tetra*-silylated derivative **4** (*tert*-butyldimethylsilyl trifluoromethanesulfonate, 2,6-lutidine, −78 °C to room temp., 16 h) proceeded reasonably efficiently (58%), the analogous reaction on **3** was very slow, and gave **4** in very poor yield (12%), testifying to the hindered nature of the C-3 hydroxy group.[4] We believe that the best explanation for these results is that the presence of two bulky protecting groups at C-3 and C-4 is unfavourable, and it is the relief of steric hindrance which is the driving force in the silyl migration.[5] In the ring-opening reaction in the presence of triethylamine, the triethylammonium cation presumably acts as a proton source, thus neutralising the C-2 alkoxide and thereby preventing silyl migration.



Scheme 1 *Reagents and conditions*: i, PhSLi (from PhSH and BuLi), 0 °C to room temp., THF, 16 h; ii, PhSH, NEt_3, 0 °C to room temp., 16 h, THF; iii, $Bu^tMe_2SiOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2, −78 °C to room temp., 16 h



Scheme 2 *Reagents and conditions*: i, PhSH, 0 °C to room temp., THF, 16 h; ii, MCPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 1.5 h

In order to explore this reaction further, we also examined the reaction of the epoxide **1** with thiophenol itself (Scheme 2). The major product from this reaction was the α-phenylthioglycoside **2a** (36%), together with a minor amount of the β-phenylthioglycoside **2b** (28%), already identified. Although the yields are not very high, the process has not been optimised, especially with respect to solvent. In this case, the reaction probably proceeds through the intermediacy of an oxonium ion, formed by ring opening of the epoxide, which is then selectively trapped from the α-face.

The adduct **2a** was crystalline, and we were able to confirm its structure by X-ray diffraction, as indicated in Fig. 1.† We were surprised to discover a $^1C_4$ conformation in the crystalline state, in which the four substituents at C-2, C-3, C-4 and C-5 are in axial positions, with the phenylthio group equatorial. The other notable feature is that there is a hydrogen bond between the C-2 hydroxy proton and O-1, which may help to stabilise the $^1C_4$ conformation. The $^1C_4$ conformation does appear to be very rare, although it has been observed in the case of a bis(*tert*-butyldiphenylsilyl) α-aryl *C*-olivoside, in which three substituents, rather than four, are in an axial position.[6] Analysis of the ^1H NMR spectrum of **2a** suggested that, in $CDCl_3$ at least, the solution conformation was very similar to that in the solid

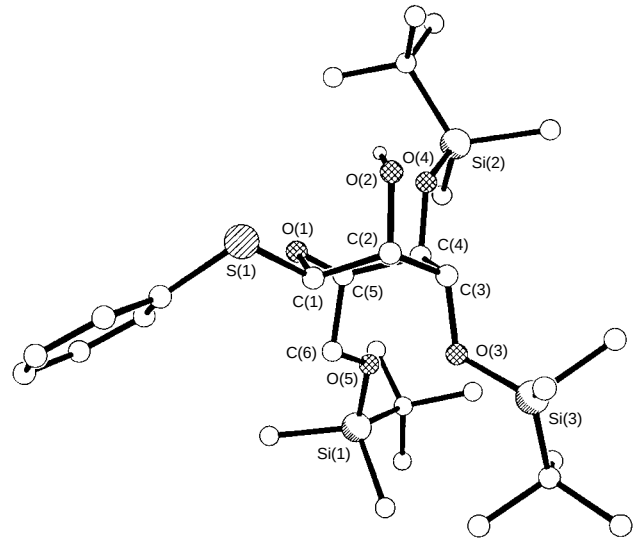


Fig. 1 The conformation of **2a** in the crystal structure. Hydrogen atoms, other than the hydroxy proton, and minor disorder components are omitted for clarity.

state, with very small vicinal coupling constants around the ring, and significant long-range (*W*) coupling between H-2 and H-4, and between H-3 and H-5 (indicating that each of these protons was in an equatorial position). The corresponding sulfone **5**, prepared by oxidation of the sulfide **2a**, exhibited almost identical coupling constants and is therefore probably also in the same conformation in solution.

The '*A* value' of the phenylthio group (4.60–5.19 kJ mol^{-1})[7] is not sufficiently large to force the other substituents axial, so the most obvious explanation is that the adjacent *tert*-butyldimethylsilyloxy groups at C-3 and C-4 are more sterically encumbered when they are diequatorial than when they are diaxial.‡ Eliel's important report on the '*A* values' of silyloxy groups, which clearly showed (rather counter-intuitively) that a *tert*-butyldimethylsilyloxy group had a *smaller* '*A* value' than a trimethylsilyloxy group,[8] provides strong support for this idea. The ease with which the *tert*-butyldimethylsilyl group at C-3 of **2b** migrates to C-2 is probably another manifestation of this same phenomenon.

It is clear that the pronounced conformational effects of *tert*-butyldimethylsilyl ethers may have useful consequences in control of reaction stereoselectivity.

We thank the EPSRC for a CASE award (C. L. W.) and for equipment grants, Rhône-Poulenc Rorer for support and Drs B. Porter, A. J. Ratcliffe and M. Podmore (RPR) for helpful discussions. R. F. W. J. also thanks the Nuffield Foundation for a One Year Science Research Fellowship.

Footnotes and References

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† *Crystal data* for **2a**: $C_{30}H_{58}O_5SSi_3$, M_r = 615.1, orthorhombic, $P2_12_12_1$, a = 27.1719(17), b = 10.9754(7), c = 12.3479(8) Å, V = 3682.4(4) Å^3, Z = 4, D_c = 1.109 g cm $^{-3}$, μ = 0.22 mm^{-1} (Mo-Kα, λ = 0.71073 Å), T = 160 K. Measurements were made on a Siemens SMART CCD area detector diffractometer. Data were collected by narrow-frame ω rotation. 19 575 reflections, $2\theta \leqslant 50°$, 6467 unique reflections, R_{int} = 0.091, semi-empirical absorption correction, transmission 0.84–0.97. Structure solution was by direct methods, refinement on F^2 for all data, with anisotropic displacement parameters, riding H atoms (with rotational freedom for methyl and hydroxy hydrogen atoms), and two-fold disorder for one silyl group. $R_w = [\Sigma w(F_o^2 - F_c^2)/\Sigma w(F_o^2)^2]^{\frac{1}{2}} = 0.223$ for all data, conventional $R = 0.101$ for F values of 5551 reflections with $F_o^2 > 2\sigma(F_o^2)$, goodness of fit 1.129, absolute configuration indicated by refinement of enantiopole parameter (ref. 9) to −0.3(2), residual electron density within ± 0.61 e Å^{-3}. The indicated absolute configuration was consistent with the known absolute configuration of the starting material. The quality of data collection and structure refinement are limited by the deformed nature of the crystals (apparently slightly bent, giving distorted reflections) and the structural disorder. Programs were standard Siemens control and integration software, Siemens SHELXTL, and local programs. CCDC 182/580.

‡ This suggestion was first made by Suzuki (ref. 6). This type of behaviour has been noted before in the case of glycals (ref. 10), and in β-lactams derived from glycals by cycloaddition (ref. 11). It has also been suggested as an influence on reactivity, but without direct evidence (ref. 4.).

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Received in Liverpool, UK, 27th June 1997; 7/04534D