Stereoselective sulfoxidation of α-mannopyranosyl thioglycosides: the *exo*-anomeric effect in action

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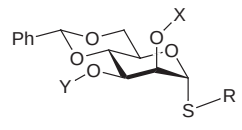
As a consequence of the *exo*-anomeric effect, and in contrast to their β-anomers, α-thioglycosides undergo stereoselective oxidation to give very predominantly the *R*-sulfoxides, as revealed by X-ray crystallography.

The sulfoxide method is a very powerful tool for the formation of glycosidic linkages to even very sterically hindered, unreactive glycosyl acceptors.[1–3] In most of the work described in the literature β-thioglycosides are oxidized to mixtures of sulfoxides,[3–5] which are used as such in the coupling reaction. In contrast, we have noted that a range of differentially protected α-mannopyranosyl thioglycosides are oxidized with excellent stereoselectivity to give essentially diastereomerically pure sulfoxides. These may then be employed productively in the efficient synthesis of β-mannopyranosides.[6–9] We now report the configuration of three α-mannopyranosyl sulfoxides, as determined by X-ray crystallography and chemical correlation, and discuss a possible reason for the stereoselectivity.

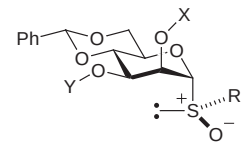
Initially, we noted that thioglycoside **1** was oxidized stereoselectively by magnesium monoperoxyphthalate (MMPP) in aqueous THF to give a single sulfoxide **8** in excellent yield, but were unable to assign configuration.[10] Similar results were obtained with MCPBA in CH_2Cl_2. Subsequently, the same phenomenon was observed with thioglycosides **2**–**7** and **15**–**17**, giving the corresponding sulfoxides **9**–**14** and **18**–**20**.[6–9,11,12] In view of the mechanism of the stereoselective β-mannosylation process,[9] in which the sulfoxide simply serves as a convenient precursor to the actual glycosylating species, the α-mannosyl triflate, the configuration at sulfur is of no consequence. However, curiosity dictated that we seek the origins of this unanticipated stereoselective sulfoxidation. Eventually, we were rewarded by the growth of single crystals of **20** (mp 109–111 °C) suitable for X-ray crystallographic analysis from EtOH solution. In due course the configuration at sulfur was revealed to be *R* (Fig. 1).

In an attempt to obtain an isomeric sulfoxide, **16** was oxidized with $NaIO_4$ and with Oxone, but in each case only **19** was obtained. It was therefore apparent that the stereoselectivity was not a function of the reagent and, for example, hydrogen bonding to the ring oxygen. We next submitted thioglycoside **21** to oxidation with MCPBA and again were rewarded by the formation of one major sulfoxide (> 10:1). Crystals suitable for X-ray analysis were again obtained (mp 190 °C, EtOH) and the structure consequently revealed to be **22** (Fig. 2), with the same configuration at sulfur as **20**. Again, a diverse range of oxidants provided the same major sulfoxide. Treatment of **22** with NaH and then BnBr in THF provided sulfoxide **10**, albeit in only 35% yield, so fixing its configuration at sulfur as *R*. Thus, we have established that three of the eleven sulfoxides in question have the same *R*-configuration and see no reason to doubt that the remainder follow the pattern.

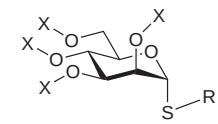
In view of the range of different oxidants and solvents employed, each giving the same result, we conclude that the stereoselectivity of the oxidation is dictated predominantly by



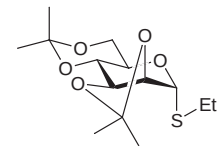
1 R = Et, X = TBDMS, Y = Bn
2 R = Et, X = TMS, Y = Bn
3 R = Et, X = Y = Bn
4 R = Ph, X = Y = Bn
5 R = Et, X = Y = allyl
6 R = Et, X = allyl, Y = Bn
7 R = Ph, X = Y = Me



8 R = Et, X = TBDMS, Y = Bn
9 R = Et, X = TMS, Y = Bn
10 R = Et, X = Y = Bn
11 R = Ph, X = Y = Bn
12 R = Et, X = Y = allyl
13 R = Et, X = allyl, Y = Bn
14 R = Ph, X = Y = Me



15 R = Et, X = Bn
16 R = Ph, X = Me



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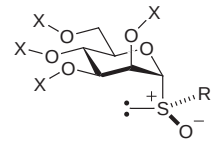
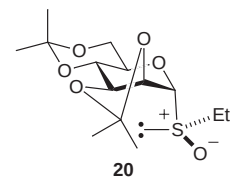


18 R = Et, X = Bn
19 R = Ph, X = Me



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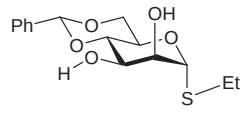

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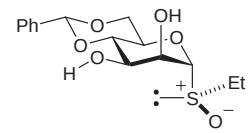

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steric effects[13] and the conformation imposed on the thioglycosides by the *exo*-anomeric effect.[14–16] Thus, as seen from the Newman projection in Fig 3, in the conformation imposed by the *exo*-anomeric effect the *pro-R* lone pair of the α-thioglycosides is exposed to attack. On the other hand oxidation of the *pro-S* lone pair would be substantially hindered by the pyranose ring, and especially by the axial hydrogens, H-3 and H-5. In the case of the β-thioglycosides, the two lone pairs are less sterically differentiated and mixtures of sulfoxides result.

Finally, we note that the two crystalline sulfoxides both adopt the same conformation (Fig. 1 and 2) about the C1–S bond, which roughly mirrors that imposed on the original thioglyco-

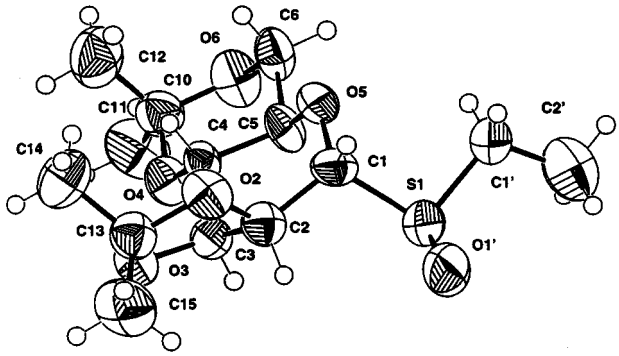


Fig. **1** Structure of **20** showing crystallographic numbering scheme adopted.

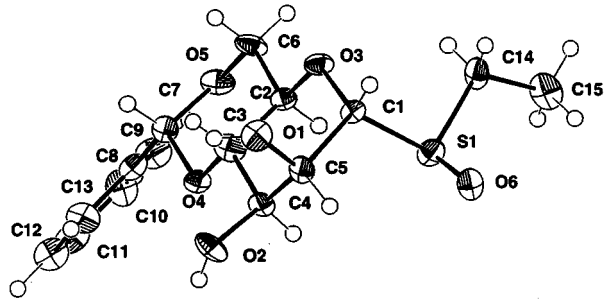
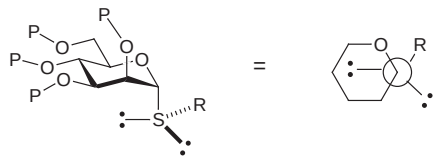


Fig. **2** Structure of **22** showing crystallographic numbering scheme adopted.



P = protecting group or H

Fig. **3**

sides by the *exo*-anomeric effect. However, in this instance, it seems likely that this is more a consequence of minimization of repulsion between the C1–O5 and S–O dipoles.[17]

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Notes and references

1 R. Liang, L. Yan, J. Loebach, M. Ge, Y. Uozumi, K. Sekanina, N. Horan, J. Gildersleeve, C. Thompson, A. Smith, K. Biswas, W. C. Still and D. Kahne, *Science*, 1996, **274**, 1520.
2 D. Kahne, S. Walker, Y. Cheng and D. V. Engen, *J. Am. Chem. Soc*., 1989, **111**, 6881.
3 L. Yan and D. Kahne, *J. Am. Chem. Soc*., 1996, **118**, 9239.
4 R. Kakarla, R. G. Dulina, N. T. Hatzenbuhler, Y. W. Hui and M. J. Sofia, *J. Org. Chem*., 1996, **61**, 8347.
5 However, we note that the two unprotected β-galactosyl phenyl sulfoxides are hydrolyzed at different rates by aqueous TfOH, presumably due to differential intramolecular hydrogen bonding interactions: N. Khiar, I. Alonso, N. Rodriguez, A. Fernandez-Mayorales, J. Jimenez-Barbero, O. Nieto, F. Cano, C. Foces-Foces and M. Martin-Lomas, *Tetrahedron Lett*., 1997, **38**, 8267.
6 D. Crich and S. Sun, *Tetrahedron*, 1998, **54**, 8321.
7 D. Crich and S. Sun, *J. Org. Chem*., 1996, **61**, 4506.
8 D. Crich and S. Sun, *J. Org. Chem*., 1997, **62**, 1198.
9 D. Crich and S. Sun, *J. Am. Chem. Soc*., 1997, **119**, 11217.
10 D. Crich, S. Sun and J. Brunckova, *J. Org. Chem*., 1996, **61**, 605.
11 D. Crich and Z. Dai, *Tetrahedron Lett*., 1998, **53**, 1681.
12 A further, unassigned example of diastereoselective sulfoxidation of an α-mannosyl thioglycoside: G. Stork and J. J. La Clair, *J. Am. Chem. Soc*., 1996, **118**, 247.
13 C. R. Johnson and D. McCants, *J. Am. Chem. Soc*., 1965, **87**, 1109.
14 E. Juaristi and G. Cuevas, *The Anomeric Effect*, CRC Press, Boca Raton, 1995.
15 P. Deslongchamps, *Stereoelectronic Effects in Organic Chemistry*, Pergamon, Oxford, 1983.
16 A. J. Kirby, *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer-Verlag, Berlin, 1983.
17 *Crystal data* for **20**: $C_{14}H_{24}O_6S$, M = 320.39, monoclinic, a = 11.282(7), b = 9.766(10), c = 15.555(12) Å, β = 99.73(6)°, V = 1689(2) Å^3; $P2_1$, Z = 4 (two independent molecules per asymmetric unit), μ = 0.22 mm^{-1}. Of 3381 reflections measured at room temperature, 3163 independent reflections were used in refinement on F^2. Final agreement factors for 390 least-squares parameters for 1887 data with $I > 2\sigma(I)$ (with values for all independent reflections in parentheses): R = 0.0412 (0.0830), R_w = 0.0984 (0.1217), GOF = 1.032 (1.131). For **22**: $C_{15}H_{20}O_6S$, M = 328.37, monoclinic, a = 5.1509(2), b = 12.9187(4), c = 11.4762(5), β = 95.554(2)°, V = 760.07(8) Å^3, $P2_1$, Z = 2. μ = 0.24 mm^{-1}. Of 2613 reflections measured at T = 173 K, there were 1718 independent reflections used in refinement against F^2 with 1551 having $I > 2\sigma(I)$. Final agreement factors for 199 least-squares parameters (with values for all independent reflections in parentheses): R = 0.0864 (0.1039), $wR2$ = 0.2847 (0.2582), GOF = 2.415 (2.414). CCDC 182/1088. The crystallographic data is available as a .cif file: see http://www.rsc.org/suppdata/cc/1998/2763/

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