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A Diastereoselective Route to Functionalised Epoxides by Reduction of Cyclic β-Ketosulphoxides

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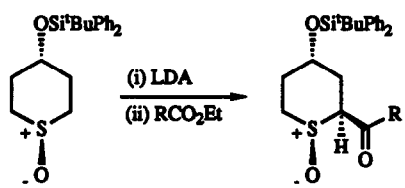
Abstract: A thiane oxide system **1**, bearing a protected hydroxyl group, undergoes stereoselective acylation to give a range of β-ketosulphoxides **2a–e**, which can then be reduced stereoselectively to give either of the corresponding hydroxysulphoxides **3** and **4**. Further manipulation of these compounds, involving thiane ring-opening, leads to a variety of functionalised epoxides.

The stereoselective reduction of β-ketosulphoxides, especially homochiral derivatives having an asymmetric sulphur centre, has been firmly established as a method of constructing chiral alcohols, with recent examples from the group of Solladié illustrating the utility of this approach in the total synthesis of a range of natural products.[1] Of key importance is the ability to select either diastereoisomeric hydroxysulphoxide from a particular ketosulphoxide, simply by the appropriate choice of reducing agent.[2] Subsequent removal of the sulphoxide auxiliary is then required, usually in a reductive step using Raney nickel. We demonstrate here that this type of approach can successfully be applied to certain cyclic β-ketosulphoxides, and show that the products can be further transformed into interestingly functionalised epoxides.

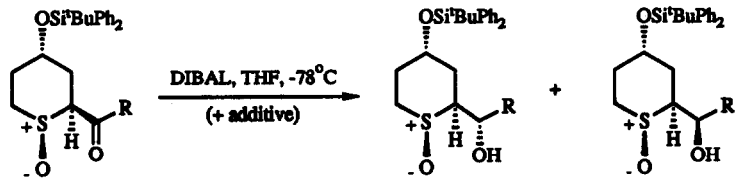
We have previously described the transformation of thiane oxide **1** into a number of substituted derivatives, including the β-ketosulphoxides **2a** and **2b**, via the intermediate sulphinyl carbanion, Scheme 1.[3]



R =	Me	^{t}Bu	Et	^{i}Pr	Ph
	(2a)	(2b)	(2c)	(2d)	(2e)
(%) =	73	82	86	52	81

Scheme 1

For our study of the reduction of these products we carried out a number of additional acylations to provide a range of β-ketosulphoxides **2a–2e** in good yield.[4] The stereochemistry of the ketosulphoxide products is as shown, with the acyl group being introduced *cis* to the sulphoxide oxygen. With these compounds in hand we examined their reduction using the protocols employed previously by Solladié to give the two diastereoisomeric hydroxysulphoxides **3** and **4**, Scheme 2.[2,5]



(2) (3) (4)

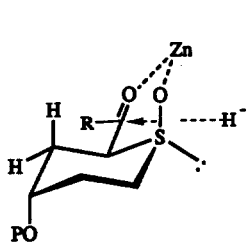
ketosulphoxide	R	additive	%	(3) : (4)
(2a)	Me	-	57	1 : 1.6
(2a)	Me	$ZnCl_2$	67	(4) only[a]
(2b)	^{t}Bu	-	88	(3) only[a]
(2b)	^{t}Bu	$ZnCl_2$	65	(4) only
(2c)	Et	-	72	1.9 : 1
(2c)	Et	$ZnCl_2$	75	(4) only
(2d)	^{i}Pr	-	50	(3) only
(2d)	^{i}Pr	$ZnCl_2$	60	(4) only
(2e)	Ph	-	-	-[b]
(2e)	Ph	$ZnCl_2$	74	(4) only

a - indicates other isomer not detected
b - reaction unsuccessful

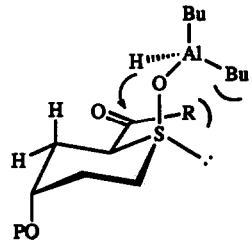
Scheme 2

Several points are worth noting from the results given in the table. Firstly, all the reductions employing $ZnCl_2$ in the reaction mixture proceeded to give only hydroxysulphoxide **4**. Secondly, the reactions involving the use of DIBAL alone give more mixed results, with **2b** and **2d** giving only **3**, whereas **2a** and **2c** give mixtures of isomers. In addition, we found that the reduction of **2e** with DIBAL alone did not give acceptable results, perhaps due to retro-aldol complications.

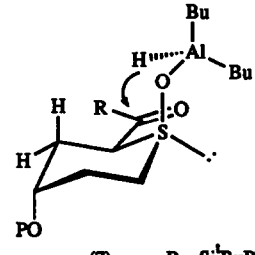
The results can reasonably be accommodated by the usual transition state models for this type of reduction, which involve either the least sterically hindered approach of the hydride reagent on a $ZnCl_2$-chelated ketosulphoxide, as represented by **5**, or intramolecular hydride delivery as in **6** and **7**.[2b,6]



(5)



(6)

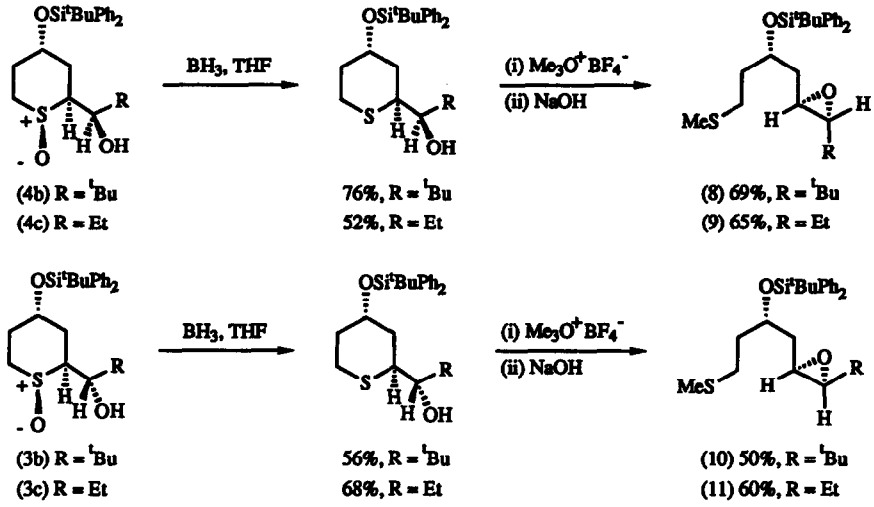


(7) P = Si^{t}BuPh$_2$

In the chelated form **5** the rearside hydride approach shown, which leads to **4**, is clearly less hindered than the alternative trajectory, which would involve substantial interaction with hydrogens on the thiane oxide ring. In addition, this mode of reduction may be assisted by a favourable interaction of the electrophilic $^{i}Bu_2AlH$ reagent with the sulphur lone pair.[2b]

In the reactions involving DIBAL alone we observed high levels of selectivity only with **2b** and **2d**, both of which have fairly bulky alkyl groups attached to the ketone. With the smaller methyl or ethyl ketones, **2a** and **2c**, very little selectivity was seen. The poor selectivity in the latter cases indicates that transition states approximated by **6** and **7** are close in energy. However, when the group R is relatively large, as is the case in **2b** and **2d**, the unfavourable interaction indicated in **6** involving the R group and one of the substituents on aluminium must dominate, leading to the exclusive formation of **3** via **7**.

Having developed a route to either **3** or **4**, we were interested in developing a method which would allow translation of the established stereochemistry into products lacking the thiane ring. One such procedure involves initial reduction of the sulphoxide group to the corresponding sulphide,[7] followed by treatment with $Me_3O^+BF_4^-$ and then base, to give the epoxide products shown in Scheme 3.[8]



Scheme 3

Two examples of each stereochemical series of hydroxysulphoxide **3** and **4** were taken through this sequence to give the *trans*-epoxide products **8** and **9** or the *cis*-compounds **10** and **11**.[9] The products are essentially protected forms of epoxides derived from *homoallylic* alcohols, which are not straightforward to prepare in stereoselective fashion. Furthermore, our stereoselective route to this type of epoxy alcohol derivative is quite versatile, and should allow the introduction of additional functionality, or substituents, by further substitution of the thiane oxide ring, or by manipulation of the thiomethyl group present in the final products.[10] Finally, it should be noted that the compounds described above are available in non-racemic form, since we have shown that enantioselective substitution of the thiane oxide **1** can be achieved by employing a homochiral lithium amide base for the deprotonation.[11]

Acknowledgements

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References

1. For some very recent examples, see G. Solladié and A. Almario, *Tetrahedron Lett.*, **1992**, *33*, 2477; G. Solladié, C. Ziani-Chérif, and F. Jesser, *Tetrahedron Lett.*, **1992**, *33*, 931; G. Solladié and C. Gerber, *Synlett*, **1992**, 449; G. Solladié, A. Almario, and F. Colobert, *Synlett*, **1992**, 167. For a review, see G. Solladié, *Pure and Appl. Chem.*, **1988**, *60*, 1699.
2. (a) G. Solladié, G. Demailly, and C. Greck, *Tetrahedron Lett.*, **1985**, *26*, 435; (b) M. C. Carreño, J. L. García Ruano, A. M. Martín, C. Pedregal, J. H. Rodriguez, A. Rubio, J. Sanchez, and G. Solladié, *J. Org. Chem.*, **1990**, *55*, 2120. See also H. Kosugi, H. Konta, and H. Uda, *J. Chem. Soc., Chem. Commun.*, **1985**, 211.
3. P. J. Cox, A. Persad, and N. S. Simpkins, *Synlett*, **1992**, 197.
4. Our initial assignment of the relative stereochemistry of the ketosulphoxides **2** is in error.[3] The stereochemistry shown for **2** is inferred from a single crystal X-ray structure determination of a derived hydroxysulphoxide **4b**, which clearly shows the relative configurations at all four asymmetric centres, as well as the unexpected conformation of these compounds having axial sulphoxide oxygen and silyloxy groups. Other data, including high field ^1H and ^{13}C NMR spectra, are fully in accord with the revised stereochemical assignments. Full details of this work, including stereochemical corrections will be published separately.
   Selected data: **2b** - δ_H (400 MHz, $CDCl_3$) 1.11 (9H, s), 1.21 (9H, s), 1.50 (1H, br.d, *J* 15, CH-3eq), 1.64 (1H, br.d, *J* 15, CH-5eq), 2.37 (1H, t, *J* 13.5, CH-5ax), 2.55 (1H, m, CH-3ax), 2.91 (1H, d, *J* 14, CH-6eq), 3.11 (1H, dt, *J* 13.5 and 3, CH-6ax), 4.26 (1H, br.s, CH-4eq), 4.42 (1H, dd, *J* 12 and 2.4 CH-2ax), 7.35–7.48 (6H, m) and 7.62–7.68 (4H, m); ν_{max} (film)/cm^{-1} 1704 (Found: C, 68.35; H, 8.20. $C_{26}H_{36}O_3SSi$ requires C, 68.42; H, 7.89%). **4b** - δ_H (270 MHz, $CDCl_3$) 0.83 (9H, s), 1.01 (9H, s), 1.46 (1H, br.d, *J* 14.5, CH-5eq), 1.74 (1H, br.d, *J* 15, CH-3eq), 2.14 (1H, br.t, *J* 13.5, CH-5ax), 2.29 (1H, t, *J* 14.5, CH-3ax), 2.72 (1H, br.d, *J* 14, CH-6eq), 3.00 (1H, dt, *J* 14 and 3, CH-6ax), 3.12 (1H, br.d, *J* 11, CH-2ax), 3.35 (1H, br.s, OH), 3.81 (1H, s, C*H*OH), 4.17 (1H, br.s, C*H*OSi), 7.24–7.36 (6H, m) and 7.52–7.56 (4H, m); ν_{max} (film)/cm^{-1} 3380 and 1069; *m/z* (FAB) 459 (M+1) (Found: C, 68.26; H, 8.34. $C_{26}H_{38}O_3SSi$ requires C, 68.12; H, 8.30%). **8** - δ_H (400 MHz, $CDCl_3$) 0.75 (9H, s), 0.99 (9H, s), 1.56 (2H, t, *J* 6, CH_2-4), 1.70 (2H, m, CH_2-2), 1.86 (3H, s), 2.16 (1H, d, *J* 2.3, CH-6), 2.36 (2H, m, CH_2-1), 2.72 (1H, dt, *J* 6 and 2.3, CH-5), 3.92 (1H, m, CH-3), 7.28–7.38 (6H, m) and 7.60–7.63 (4H, m); *m/z* (FAB) 457 (M+1).
5. For some related work on dithiane oxide systems, see P. C. Bulman Page and J. C. Prodger, *Synlett*, **1990**, 460.
6. Transition state representations **5–7** assume that the conformation assigned for ketosulphoxides **2** is maintained under the reaction conditions.[4]
7. D. R. Williams and J. G. Phillips, *Tetrahedron*, **1986**, *42*, 3013.
8. W. H. Pirkle and P. L. Rinaldi, *J. Org. Chem.*, **1978**, *43*, 3803; D. C. Farnum, T. Veysoglu, A. M. Cardé, and R. T. Cardé, *Tetrahedron Lett.*, **1977**, 4009; see also reference 2a.
9. The stereochemical assignments of the final epoxides follow from the known configuration of the intermediate hydroxysulphoxides, since the epoxide formation should be stereospecific. Coupling constants between the hydrogens attached to the epoxide ring are in accord with the expected values (**8**, 2.3; **9**, 2.2; **10**, 4.5; **11**, 4.3Hz).
10. For example, we have shown that the methylthio group in **8** can be reductively removed using Raney nickel.
11. P. J. Cox, A. Persad, and N. S. Simpkins, *Synlett*, **1992**, 194. We have now shown that ketosulphoxide **2b** can be accessed directly from **1** in 55% ee by using a homochiral lithium amide base for the deprotonation, and then quenching with $^tBuCO_2Et$. The non-racemic hydroxysulphoxide **4b** obtained by reduction of this material can be optically enriched by crystallisation (≥95% ee), and then converted to optically pure epoxide **8**.

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