Tetrahedron Letters, Vol. 33, No. 47, pp. 7237-7240, 1992
Printed in Great Britain

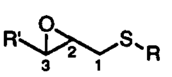
0040-4039/92 \$5.00 + .00
Pergamon Press Ltd

Stereoselective Synthesis of 2,3-Epoxy Sulphoxides.

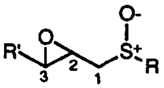
Christopher M. Rayner*, Man S. Sin and Andrew D. Westwell
School of Chemistry, University of Leeds, Leeds LS2 9JT, U.K..

Abstract: Methods for the diastereoselective preparation of various 2,3-epoxy sulphoxides are described using a double enantioselective oxidation approach. Direct comparisons of the selectivity and efficiency of the Davis and Kagan asymmetric sulphur oxidation procedures are given.

The ability of the Sharpless asymmetric epoxidation[1] to produce a wide variety of optically active 2,3-epoxy alcohols has lead to their exploitation as valuable synthetic intermediates.[2] The corresponding 2,3-epoxy sulphides (1), which may be readily prepared from epoxy alcohols, have however been little investigated and represent a new, readily available, optically active building block for use in synthesis.[3] As part of a general investigation in this area, we wished to have access to diastereomerically pure epoxysulphoxides (2) of known relative and absolute stereochemistry and we present here our studies in this area.

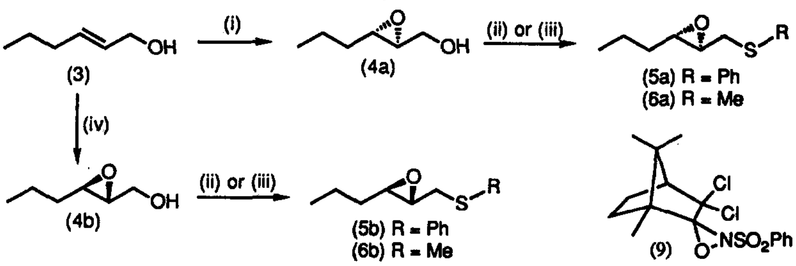


(1)



(2)

Our initial approach was to use a diastereoselective oxidation procedure where the sulphoxide chirality is controlled by the stereochemistry of the adjacent epoxide chiral centres. It soon became apparent however that only low diastereoselectivities could be obtained using this method. Instead we decided to adopt a double enantioselective approach exploiting the known enantioselectivity of the Sharpless epoxidation and also the recently developed methods for asymmetric sulphur oxidation of Kagan[4] and Davis.[5] This work also provided an ideal opportunity for a direct comparison of the selectivity and efficiency of the two sulphur oxidation systems which are the best chemical methods so far reported.[6] Although enzymatic methods can also give very high selectivities for asymmetric oxidation they often suffer from poor yields and so we chose not to investigate these to any degree.[7] We required S-phenyl and S-methyl epoxy thioethers (5) and (6) as substrates in both enantiomeric forms for our studies and their syntheses are shown in scheme 1.



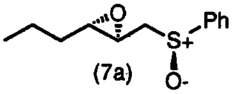
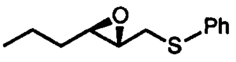
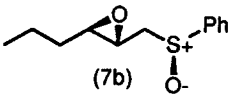
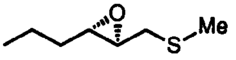
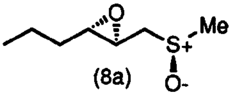
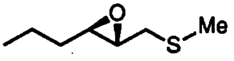
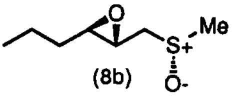
Reagents: i,Ti(O^{i}Pr)$_4$, CH$_2$Cl$_2$, ^{t}BuOOH, L-(+)-DET, 69% yield; ii, PhSSPh, PBu$_3$, pyridine; iii, MeSSMe, PBu$_3$, DMF; iv, Ti(O^{i}Pr)$_4$, CH$_2$Cl$_2$, ^{t}BuOOH, D-(-)-DET, 63% yield.

Scheme 1.

Asymmetric epoxidation of commercially available (3) using L-(+)-Diethyl tartrate (DET) as the chiral auxiliary[1] gave (4a)[>96%e.e.[#]]. Conversion to the phenyl thioether as previously reported[3] using phenyl disulphide and tributyl phosphine in pyridine was accomplished in 87% yield. In order to form the methyl thioether (6a), the use of methyl disulphide and tributyl phosphine effected clean conversion however it was necessary to use the more polar solvent N,N-dimethylformamide (DMF) for a reasonable reaction rate (65% yield). The analogous enantiomeric sulphides (5b) and (6b) [>96%e.e.[#]] were prepared in a similar way.

With these sulphide substrates in hand we initially investigated their oxidation reactions under the conditions developed by Davis et. al. using (-) α,α-dichlorocamphorsulphonyloxaziridine (9).[5] These oxidations are summarised in table 1.[8]

<u>TABLE 1. Davis Oxidation of 2,3-Epoxy Sulphides.</u>

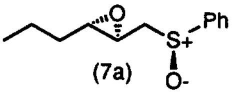
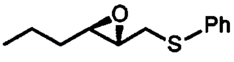
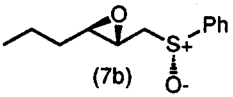
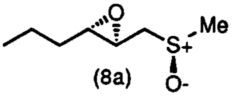
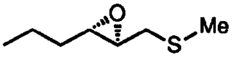
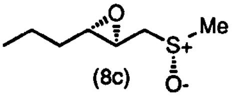
Substrate	Major product	Ratio (temperature, yield)
 (5a)	 (7a)	13 : 1 (0, 65) 6.3 : 1 (25, 65)
 (5b)	 (7b)	7.0 : 1 (0, 59) 2.0 : 1 (25, 61)
 (6a)	 (8a)	1.5 : 1 (25, 38) 1.5 : 1 (0, 85)
 (6b)	 (8b)	1.3 : 1 (25, 31) 1.3 : 1 (0, 65) 3.3 : 1 (-40[†], 31)

Notes: all reactions were carried out in CCl$_4$, under nitrogen at the stated temperatures (°C) until complete by TLC analysis. Ratios were determined by ^{1}H and/or ^{13}C NMR (inverse gated decoupling after doping with Cr(acac)$_3$).† Reaction run in CHCl$_3$.

Some interesting points on the selectivity of the oxidation are apparent from the results obtained. Most obviously, this oxidation method showed good selectivity for the phenyl epoxy sulphide substrates, but gave disappointing selectivity in the case of the methyl thioethers. As would be expected there is a distinct temperature effect, superior selectivities being observed at lower temperatures (below 0°C the rate of reaction was too long to be practical for phenyl thioethers). Interestingly, better selectivity is observed when the system is matched such that the oxygen is delivered on the opposite side of the molecule to the epoxide, possibly a result of reduced steric hindrance / electronic repulsion between substrate and reagent. Finally, oxidation of the methyl thioether proceeds with low selectivity, however the same (enantiomeric) diastereomer is obtained as the major product irrespective of the absolute configuration of the substrate. The reagent is thus acting as a diastereoselective rather than enantioselective oxidant albeit with poor selectivity. The product methyl sulphoxides (8a,b,c) proved to be rather sensitive materials to handle giving variable yields, and were inseparable by chromatography. This is in sharp contrast to the phenyl sulphoxides which were relatively easy to manipulate and could be separated by column chromatography on silica gel.[3]

We next decided to investigate the oxidation procedure developed by Kagan et. al.[4], which uses a modified Sharpless oxidation system for asymmetric sulphur oxidation.These results are shown in table 2.

TABLE 2. Kagan Oxidation of 2,3-Epoxy Sulphides.

Substrate	Major product	Ratio (temperature, yield)
 (5a)	 (7a)	1.8 : 1 (-40, 86)
 (5b)	 (7b)	1.4 : 1 (-40, 90)
 (6a)	 (8a)	5.1 : 1 (-40, 61)
 (6a)	 (8c)	4.6 : 1 (-40†, 72)

Notes: all reactions were carried out under nitrogen at the stated temperature (°C) using Ti(O^{i}Pr)$_4$, H_2O (1 equiv.), L-(+)-DET and cumene hydroperoxide in CH_2Cl_2 unless otherwise stated.† Reaction carried out using D-(-)-DET rather than L-(+)-DET. Ratios were determined by ^1H and/or ^{13}C NMR (inverse gated decoupling after doping with Cr(acac)$_3$).

Again some very interesting results are obtained from these reactions. Most gratifying is that this system is successful for the S-methyl thioethers which previously gave very poor results using the Davis oxidation. Thus for our systems the Davis and the Kagan oxidations nicely complement each other, the Davis oxidation being particularly successful for the S-phenyl thioethers and the Kagan oxidation for S-methyl thioethers. Again slightly better selectivity is observed when the system is matched such that the oxygen is delivered on the opposite side of the substrate to the epoxide. In the cases of (5a) and (5b) where low selectivity is observed the same (enantiomeric) diastereomer is produced. Thus as with the Davis oxidation of the S-methyl thioethers, with poor substrates the Kagan system is now acting as a diastereoselective oxidant with low selectivity. Even with more successful substrates there is still a general tendency with both the Davis and the Kagan systems for such selectivity to be favoured although it is not sufficient to override the enantioselective preference of the external reagent. This diastereoselectivity may have a number of possible causes, the most obvious being steric or electronic repulsion of the oxidising agent by the epoxide oxygen as shown for (6b) in figure 1.[9] Although this is a relatively small effect, it is interesting that it is observed for both the Kagan and Davis oxidising systems.

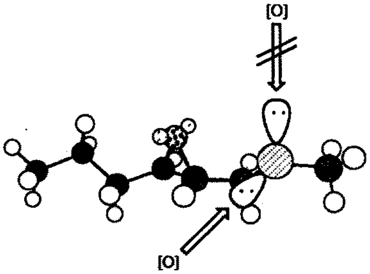


Figure 1.

In conclusion, we have shown that for a series of epoxy sulphides, the best so far reported chemical methods for the asymmetric sulphur oxidation provide complimentary selectivity depending on the substrate. For the S-phenyl epoxythioethers the Davis oxidation procedure is the method of choice whereas for the S-methyl epoxythioethers the Kagan procedure is superior. We now have access to all possible diastereomers of the S-phenyl and S-methyl epoxy sulphoxides with known relative and absolute stereochemistry and further investigations into their chemistry are currently underway.[10]

Acknowledgements: We wish to thank SERC for a studentship (ADW), the Nuffield Foundation for an award under its Scheme for Newly Appointed Science Lecturers (CMR) and an Undergraduate Research Bursary (MSS) and the University of Leeds and ICI for financial support.

References.

1. Sharpless, K.B.; Exon, C.M.; Regenye, R. *Org. Synth.*, **1984**, *63*, 66; Katsuki,T.; Sharpless, K.B. *J. Amer. Chem. Soc.*, **1980**, *102*, 5974; Hill, J.G.; Finn, M.G.; Sharpless, K.B. *Asymmetric Synthesis*, Morrison, J.D. Ed.; Academic Press: New York. 1985; Vol. 5.
2. a)Pfenninger, A. *Synthesis*, **1986**, 89; b) Rossiter, B.E. *Asymmetric Synthesis*, Morrison, J.D. Ed.; Academic Press: New York. 1985; Vol. 5. See also Page, P.C.B.; Rayner, C.M.; Sutherland, I.O. *J. Chem. Soc., Perkin Trans.* 1, **1990**, 1375 and references cited therein.
3. Rayner, C.M.; Westwell, A.D. *Tetrahedron Lett.*, **1992**, *33*, 2409.
4. a) Kagan, H.B.; Rebiere, F. *Synlett*, **1990**, 643; b) Zhao, S.H.; Samuel, O.; Kagan, H.B. *Org. Synth.*, **1989**, *68*, 49.
5. Davis, F.A.; Reddy, R.T.; Weissmiller, M.C. *J. Amer. Chem. Soc.*, **1989**, *111*, 5964; Davis, F.A.; Reddy, R.T.; Han, W.; Carroll, P.J. *J. Amer. Chem. Soc.*, **1992**, *114*, 1428.
6. There is a recent report of studies of enantioselective vinyl sulphide oxidation using various asymmetric oxidation procedures, see Rossi, C.; Fauvre, A.; Madesclaire, M.; Roche, D.; Davis, F.A.; Reddy, R.T. *Tetrahedron Asymm.*, **1992**, *3*, 629.
7. Holland, H.L. *Chem. Rev.*, **1988**, *88*, 473.
8. The stereochemical assignments and ^{1}H NMR data of the 2,3-epoxy phenylsulphoxides (7a) and (7b) have been discussed previously in refence 3. Assignments for the 2,3-epoxy methylsulphoxides (8a) and (8c) are based on the known enantioselectivity of the Kagan oxidation system described in reference 4a. ^{1}H NMR ($CDCl_3$, 400MHz); (8a) and (8b) δ 0.95 (3H, t, J 7.1Hz, $\underline{CH_3}$-CH_2), 1.40-1.65 (4H, m, CH_2CH_2), 2.66 (3H, s, CH_3S), 2.68 (1H, dd, J 13.1, 8.2Hz, one of CH_2-1), 2.87 (1H, dt, J 1.2, 4.7Hz, CH-3), 3.05 (1H, ddd, J 8.2, 3.6, 1.2Hz, CH-2), 3.15 (1H, dd, J 3.6, 13.1Hz, remaining CH_2-1); (8c) δ 0.97 (3H, t, J 7.2Hz, $CH_2\underline{CH_3}$), 1.45-1.65 (4H, m, CH_2CH_2), 2.70 (3H, s, CH_3S), 2.72 (1H, dd, J 6.9, 14.0Hz, one of CH_2-1), 2.91 (1H, dt, J 2.2, 5.5Hz, CH-3), 3.11 (1H, dd, J 3.7, 14.0Hz, remaining CH_2-1), 3.26 (1H, ddd, J 6.9, 3.7, 2.2Hz, CH-2).
9. The structure in figure 1 was minimised using Chem3D Plus™ and sulphur lone pairs (somewhat exaggerated for clarity) added manually using Chemdraw™.
10. All new compounds were characterised by ^{1}H and ^{13}C NMR, IR, and mass spectra, and gave satisfactory elemental analysis and/or accurate mass spectra.

Enantiomeric excesses were determined by ^{1}H NMR using $Eu(hfc)_3$ on the corresponding acetate.

(Received in UK 10 July 1992)