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LETTERS

Optically Active 2,3-Epoxy Sulfides As Precursors to 3-Hydroxy-1,2-Dithioethers and 3-Hydroxy-1-Alkenylthioethers

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Abstract: Procedures are reported for the conversion of 2,3-epoxysulfides to 3-hydroxy-1,2-dithioethers. Conventional nucleophilic ring opening using a thiolate gives a mixture of products resulting from ring opening at C-2 and C-3, with the latter predominating. With sodium thiolates in DMF a competing β-elimination process is observed to form 3-hydroxy-1-alkenylthioethers. Alternatively, Lewis acid induced thiiranium ion generation from a 2,3-epoxy sulfide, and nucleophilic ring opening with S-trimethylsilylthiophenol gives 3-hydroxy-1,2-dithioethers with full regio- and stereo-control.

The Sharpless asymmetric epoxidation, developed in the 1980's has proved itself to be amongst one of the most important asymmetric reactions available to synthetic chemists.[1] Its generality, and the versatility of the 2,3-epoxy alcohols it produces has lead to its widespread use in the synthesis of many different kinds of molecule. For some time, we have been interested in developing the chemistry of simple derivatives of 2,3-epoxy alcohols where the alcohol group is replaced by some other kind of heteroatom functionality.[2] In particular, we have shown that 2,3-epoxy amines are useful precursors to 3-trimethylsilyloxy-1,2-aziridinium ions which can be reacted efficiently with a variety of nucleophiles, and that 2,3-epoxy sulfides are precursors to 3-trimethylsilyloxy-1,2-thiiranium ions, which again can be trapped with a range of similar nucleophiles.[3] Alternatively, 2,3-epoxy sulfides can be oxidised stereoselectively to sulfoxides, or sulfones, and these can act as precursors for 2,3-dihydroxysulfoxides, or γ-hydroxy-α,β-unsaturated sulfoxides and sulfones.[2] In all these cases a high degree of stereochemical control is possible. We now wish to report further results in this area, in particular new reactions of 2,3-epoxy sulfides for the preparation of 3-hydroxy-1,2-dithioethers and 3-hydroxy-1-alkenylthioethers.

In conjunction with investigations into the stereoselectivity of the nucleophilic addition of thiolates to 3–hydroxy-1-alkenyl-sulfoxides and -sulfones,[4] we required access to various isomers of 3-hydroxy-1,2-dithioethers for regio- and stereo-chemical correlation. One of the simplest routes into these compounds is by nucleophilic ring opening of 2,3-epoxy sulfides using thiolate nucleophiles. A considerable amount of work has been published on nucleophilic ring opening of 2,3-epoxy alcohols and related compounds[5] however relatively little was known about the corresponding 2,3-epoxy sulfides. Our interest in this area was further aroused by the

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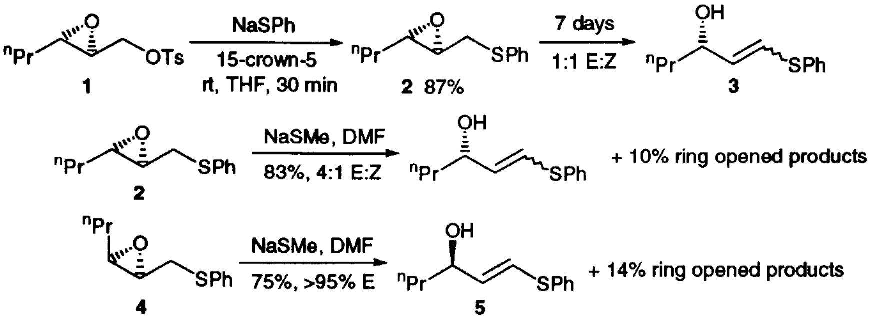
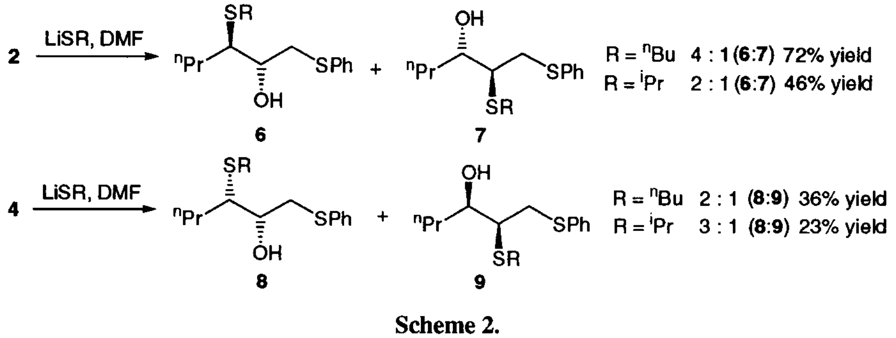
observation that prolonged reaction times during thioether formation using a sodium thiolate displacement of tosylate **1**, lead to significant byproducts, later identified as γ-hydroxy-α,β-unsaturated sulfides **3** (scheme 1).



Scheme 1

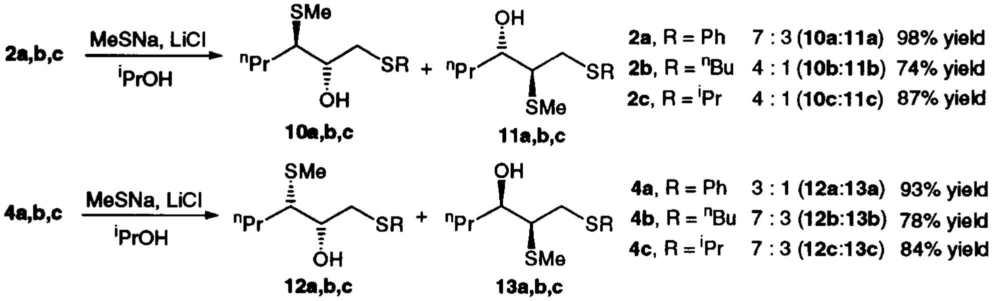
For example after 7 days, **3** was the sole identifiable product but a 1:1 mixture of *E*- and *Z*-isomers. Better selectivity and faster reaction rates could be obtained by using purified 2,3-epoxysulfide precursors, changing solvent to DMF (4:1 *E*:*Z*), and using NaSMe as base. Using the Z-epoxide precursor **4** gave *E*-**3** as the major product in 75% yield. Takano and coworkers have reported[6] a similar transformation, however much more strongly basic conditions were employed (ⁿBuLi, THF, HMPA). Our much simpler procedure reported here avoids the use of toxic HMPA, and occurs under milder conditions which may be more compatible with sensitive functionality in more complex substrates.

Although interesting, these results indicated that nucleophilic ring opening of 2,3-epoxysulfides was not necessarily as straightforward as envisaged. Fortunately changing to the lithium salt of the thiolate nucleophile had a significant effect on the outcome of the reaction (scheme 2). No sign of any elimination product was observed in these cases, and the major products resulted from attack at C-3, which was similar to that observed for ring opening reactions of 2,3-epoxy alcohols with nucleophiles.[5]



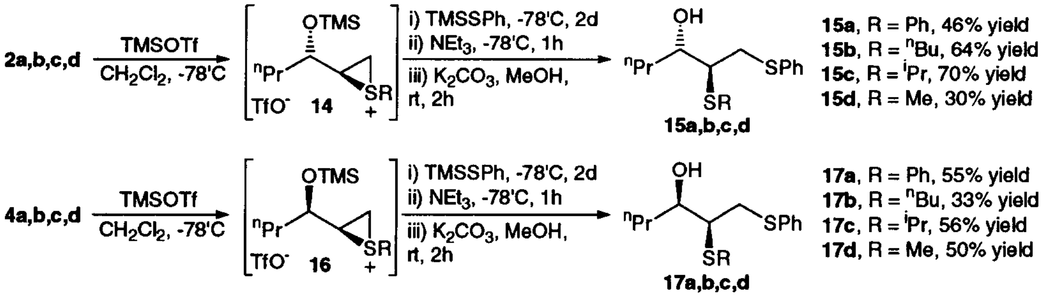
Scheme 2.

Unfortunately, yields were still only modest. It is known that nucleophilic ring opening of epoxides is catalysed by protic solvents and metal salts, including LiCl.[7] Using this combination, a further improvement in reaction yield was observed, again with a strong preference for attack at C-3 (scheme 3). In this case, a variety of 2,3-epoxy sulfide substrates were investigated for ring opening using sodium methanethiolate. For alkylsulfides **2a,b** and **4a,b**, the size of the alkyl group appeared to have little effect on the regioselectivity of the reaction. However, the S-phenyl thioethers gave significantly different selectivities, depending on the initial epoxide geometry. In the case of the *E*-**2a**, reduced C-3 attack is observed whereas the opposite is observed for *Z*-**4a**.



Scheme 3

Although we had now established optimised conditions for nucleophilic ring opening, the formation of mixtures of regioisomers, which were in some cases very difficult to separate, and the predominance of the product resulting from opening at C-3, was unhelpful in our future studies. We thus investigated one further method of ring opening, that is, by Lewis acid induced thiiranium ion formation, with subsequent ring opening with a thiolate nucleophile or its equivalent. This mirrors our previous work, which utilised nitrogen nucleophiles.[3] Importantly, our previous work had established this to be a regio- and stereo-specific process for a range of substrates, including most of those described above. Thus treatment of a 2,3-epoxysulfide with trimethylsilyltriflate at -78°C gives a thiiranium ion **14**, which undergoes regiospecific ring opening at C-1 with S-trimethylsilylthiophenol. As predicted, the products were single stereo- and regioisomers, being produced in moderate to good overall yield for the 3 step process, *viz.* thiiranium ion generation, nucleophilic trapping, and desilylation (scheme 4).[8]



Scheme 4.

Note that now the nucleophilic sulfur reagent is introduced at C-1, and that a single regioisomer is produced rather than the mixtures observed from conventional nucleophilic ring opening of a 2,3-epoxy sulfide. This method also allows access to both diastereomeric products **15** and **17**, with full stereochemical control. This allows unambiguous assignments of regio- and stereochemistry and will play a crucial role in our subsequent studies of thiolate addition to 3-hydroxy-1-alkenyl sulfoxides and sulfones, the results of which will be reported in due course.

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References and notes.

1. J.G. Hill, M.G. Finn and K.B. Sharpless, *Asymmetric Synthesis*, ed. J.D. Morrison, Academic Press, New York. 1985, Vol. 5; A. Pfenninger, *Synthesis*, 1986, 89; B.E. Rossiter, *Asymmetric Synthesis*, ed. J.D. Morrison, Academic Press, New York, 1985, Vol. 5. R.A. Johnson and K.B. Sharpless, in *Comprehensive Organic Synthesis*, ed. B.M. Trost, Pergamon Press, Oxford, 1991, vol. 7, chap. 3.2, pp. 389-436; see also ref 2.
2. A.D. Westwell, M. Thornton-Pett and C.M. Rayner, *J. Chem. Soc., Perkin Trans. 1*, 1995, 847.
3. C.M. Rayner, *Synlett*, 1997, 11. For related work see: H. Hayakawa, N. Okada and M. Miyashita, *Tetrahedron Lett.*, 1999, **40**, 3191 and references cited therein.
4. I. Forristal, K.R. Lawson and C.M. Rayner, unpublished results.
5. M.Caron, P.R. Carlier and K.B. Sharpless, *J. Org. Chem.*, 1988, **53**, 5185; K.S. Kirschenbaum and K.B. Sharpless, *Chemistry Lett.*, 1987, 11; C.H. Behrens, S.Y. Ko, K.B. Sharpless and F.J. Walker, *J. Org. Chem.*, 1985, **50**, 5687; C.H. Behrens and K.B. Sharpless, *J. Org. Chem.*, 1985, **50**, 5696; M. Caron and K.B. Sharpless, *J. Org. Chem.*, 1985, **50**, 1557.
6. S. Takano, Y. Sugihara and K. Ogasawara, *Synlett*, 1992, 668; *idem*, *Tetrahedron Lett.*, 1993, **34**, 845; *idem*, *Tetrahedron Asymmetry*, 1993, **4**, 1795.
7. P.C.B. Page, C.M. Rayner and I.O. Sutherland, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1375.
8. Selected NMR data, δ_H(400 MHz; $\mathrm{CDCl_3}$), **15a**: 0.90 (3H, t, *J* 7.1, $\mathrm{CH_2CH_2C}H_3$), 1.26-1.54 (4H, m, $\mathrm{C}H_2\mathrm{C}H_2\mathrm{CH_3}$), 2.26 (1H, d, *J* 6.5, OH), 3.17-3.26 (2H, m, $\mathrm{C}H_2\mathrm{SPh}$), 3.32-3.38 (1H, m, C*H*SPh), 3.89-3.93 (1H, m, C*H*OH), 7.17-7.40 (10H, m, ArH); **15b**: 0.89 (3H, t, *J* 7.3, $\mathrm{S(CH_2)_3C}H_3$), 0.92 (3H, t, *J* 7.1, $\mathrm{CH_2CH_2C}H_3$), 1.25-1.57 (8H, m, $\mathrm{C}H_2\mathrm{C}H_2\mathrm{CH_3}$ and $\mathrm{SCH_2C}H_2\mathrm{C}H_2\mathrm{CH_3}$), 2.29 (1H, d, *J* 7.0, OH), 2.47-2.60 (2H, m, $\mathrm{SC}H_2\mathrm{CH_2CH_2CH_3}$), 2.89-2.94 (1H, m, $\mathrm{C}H\mathrm{S(CH_2)_3CH_3}$), 3.15 (1H, dd, *J* 13.8 and 7.4, one of $\mathrm{CHOHC}H_2$), 3.22 (1H, dd, *J* 13.8 and 7.5, remaining $\mathrm{CHOHC}H_2$), 3.85-3.91 (1H, m, C*H*OH), 7.26-7.40 (5H, m, ArH); **15c**: 0.91 (3H, t, *J* 7.2, $\mathrm{CH_2CH_2C}H_3$), 1.21 (3H, d, *J* 6.7, one of $\mathrm{CH(C}H_3)_2$), 1.24 (3H, d, *J* 6.7, remaining $\mathrm{CH(C}H_3)_2$), 1.26-1.57 (4H, m, $\mathrm{C}H_2\mathrm{C}H_2\mathrm{CH_3}$), 2.36 (1H, d, *J* 7.6, OH), 2.94 (1H, septet, *J* 6.7, $\mathrm{C}H\mathrm{(CH_3)_2}$), 2.94-2.99 (1H, m, $\mathrm{C}H\mathrm{SCH(CH_3)_2}$), 3.17 (2H, d, *J* 7.4, $\mathrm{CHOHC}H_2$), 3.87-3.93 (1H, m, C*H*OH), 7.17-7.39 (5H, m, ArH); **15d**: 0.93 (3H, t, *J* 7.1, $\mathrm{CH_2C}H_3$), 1.25-1.57 (4H, m, $\mathrm{C}H_2\mathrm{C}H_2$), 2.14 (3H, s, $\mathrm{SCH_3}$), 2.26 (1H, d, *J* 6.4, OH), 2.82-2.87 (1H, m, $\mathrm{C}H\mathrm{SCH_3}$), 3.15 (1H, dd, *J* 13.5 and 7.5, one of $\mathrm{C}H_2\mathrm{SPh}$), 3.24 (1H, dd, *J* 13.5 and 6.6, remaining $\mathrm{C}H_2\mathrm{SPh}$), 3.85-3.91 (1H, m, C*H*OH), 7.16-7.40 (5H, m, ArH); **17a**: 0.91 (3H, t, J 6.7, $\mathrm{CH_2CH_3}$), 1.25-1.74 (4H, m, $\mathrm{CH_2CH_2}$), 1.95 (1H, d, J 6.5, OH), 3.14-3.18 (1H, m, CHSPh), 3.22 (1H, dd, J 4.9 and 13.7, one of $\mathrm{CH_2SC_6H_5}$), 3.33 (1H, dd, J 9.4 and 13.7, remaining $\mathrm{CH_2SC_6H_5}$), 4.09-4.15 (1H, m, CHOH), 7.16-7.40 (10H, m, ArH); **17b**: 0.88 (3H, t, *J* 7.3, $\mathrm{S(CH_2)_3C}H_3$), 0.93 (3H, t, *J* 7.3, $\mathrm{CH_2CH_2C}H_3$), 1.25-1.60 (8H, m, $\mathrm{C}H_2\mathrm{C}H_2\mathrm{CH_3}$ and $\mathrm{SCH_2C}H_2\mathrm{C}H_2\mathrm{CH_3}$), 2.03 (1H, d, *J* 6.9, OH), 2.48-2.57 (2H, m, $\mathrm{SC}H_2\mathrm{CH_2CH_2CH_3}$), 2.66-2.73 (1H, m, $\mathrm{C}H\mathrm{S(CH_2)_3CH_3}$), 3.23 (1H, dd, *J* 13.5 and 6.0, one of $\mathrm{CHOHC}H_2$), 3.31 (1H, dd, *J* 13.5 and 8.4, remaining $\mathrm{CHOHC}H_2$), 3.90-3.96 (1H, m, C*H*OH), 7.15-7.40 (5H, m, ArH); **17c**: 0.93 (3H, t, *J* 7.2, $\mathrm{CH_2CH_2C}H_3$), 1.18 (3H, d, *J* 6.7, one of $\mathrm{CH(C}H_3)_2$), 1.23 (3H, d, *J* 6.7, remaining $\mathrm{CH(C}H_3)_2$), 1.25-1.64 (4H, m, $\mathrm{C}H_2\mathrm{C}H_2\mathrm{CH_3}$), 1.97 (1H, br, OH), 2.70-2.75 (1H, m, $\mathrm{C}H\mathrm{SCH(CH_3)_2}$), 2.92 (1H, septet, *J* 6.7, $\mathrm{C}H\mathrm{(CH_3)_2}$), 3.22 (1H, dd, *J* 13.5 and 5.6, one of $\mathrm{CHOHC}H_2$), 3.31 (1H, dd, *J* 13.5 and 8.7, remaining $\mathrm{CHOHC}H_2$), 3.93-3.97 (1H, m, C*H*OH), 7.18-7.39 (5H, m, ArH); **17d**: 0.93 (3H, t, *J* 7.2, $\mathrm{CH_2C}H_3$), 1.30-1.63 (4H, m, $\mathrm{C}H_2\mathrm{C}H_2$), 2.10 (1H, d, *J* 6.4, OH), 2.13 (3H, s, $\mathrm{SCH_3}$), 2.63-2.68 (1H, m, C*H*SMe), 3.23 (1H, dd, *J* 13.4 and 6.4, one of $\mathrm{C}H_2\mathrm{SPh}$), 3.30 (1H, dd, *J* 13.4 and 8.0, remaining $\mathrm{C}H_2\mathrm{SPh}$), 3.89-3.95 (1H, m, C*H*OH), 7.18-7.39 (5H, m, ArH).