

## Synthesis of Chiral $\alpha$ -Alkoxyketones *via* Allene Oxides

Michael Shipman,\*# and Heidi R. Thorpe

Department of Chemistry, Loughborough University, Loughborough, Leics., LE11 3TU, U.K.

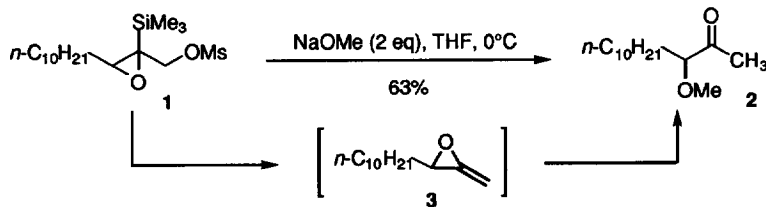
Ian R. Clemens

Glaxo Wellcome Research & Development Ltd, Glaxo Wellcome Medicines Research Centre, Stevenage, Herts, SG1 2NY, U.K.

**Abstract:** Treatment of enantiomerically enriched epoxy mesylates 7-9 with potassium alkoxides under carefully controlled reaction conditions (18-crown-6, THF,  $-78^{\circ}\text{C}$ ) provide the corresponding  $\alpha$ -alkoxyketones 10-13 without significant racemisation. The reactions are shown to proceed with net stereochemical inversion at the epoxide centre. © 1997, Elsevier Science Ltd. All rights reserved.

Allene oxides are highly strained molecules which have been shown to undergo a variety of novel chemical transformations.<sup>1</sup> Despite the considerable synthetic utility of these compounds, little work has emerged on the development of asymmetric methods based upon homochiral allene oxides. Kabat has described asymmetric routes to  $\alpha$ -fluoroketones<sup>2</sup> and  $\gamma$ -hydroxy- $\beta$ -keto phosphonates<sup>3</sup> which are postulated to involve chiral, nonracemic allene oxides. More direct evidence for the existence of homochiral allene oxides has recently been provided by Konioko *et al* who successfully isolated enantiomerically enriched (*S*)-(-)-1-*tert*-butyl allene oxide.<sup>4</sup>

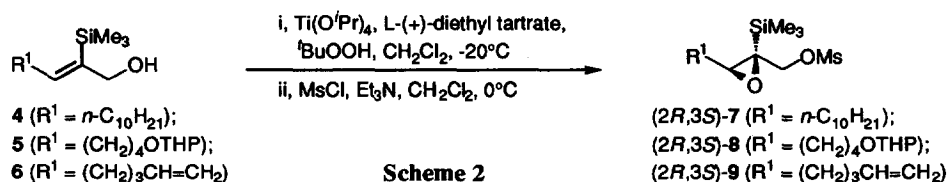
Our interest in this area began with the observation that epoxy mesylates can be converted to the corresponding  $\alpha$ -alkoxyketones upon treatment with sodium alkoxides.<sup>5</sup> For example, treatment of epoxy mesylate **1** with sodium methoxide gives  $\alpha$ -methoxyketone **2** in 63% yield (Scheme 1). We were able to obtain indirect evidence that these reactions proceed *via* an allene oxide intermediate *eg* **3**. We reasoned that if the epoxy mesylates could be made in enantiomerically enriched form, this chemistry may provide a novel route to chiral, nonracemic  $\alpha$ -alkoxyketones by way of homochiral allene oxides. In this Letter, we describe our preliminary observations on this process and present reaction conditions which enable enantiomerically enriched  $\alpha$ -alkoxyketones to be prepared using this chemistry.



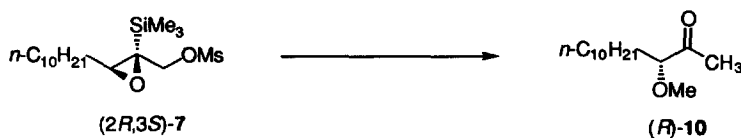
Scheme 1

\* Present Address: Department of Chemistry, University of Exeter, Exeter, Devon, EX4 4QD, U.K.

The enantiomerically enriched epoxy mesylate precursors **7-9** used in this study were readily prepared using literature methods. Thus, allylic alcohols **4-6** were converted to the corresponding chiral epoxy alcohols in moderate yields (54-41%) using the Sharpless asymmetric epoxidation protocol (Scheme 2).<sup>7</sup> Conversion of these materials to the corresponding MTPA esters established that they had been produced with high levels of asymmetric induction (83-85%*ee*). These epoxides were assigned the (2*R*,3*S*)-stereochemistry on the basis of literature precedent.<sup>8</sup> Mesylation of the epoxy alcohols furnished the desired chiral precursors **7-9** which were used without further purification.



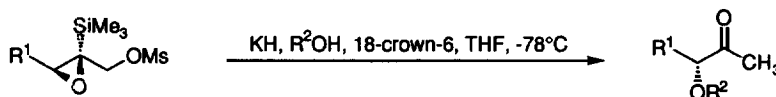
At the outset of this work, we were uncertain whether the strongly basic reaction conditions required for the conversion of the epoxy mesylates into the corresponding  $\alpha$ -alkoxyketones would facilitate product racemisation. Indeed, our initial attempts at effecting the stereocontrolled conversion of epoxy mesylate **7** into  $\alpha$ -methoxyketone **10** were unsuccessful. Treatment of enantiomerically enriched (2*R*,3*S*)-**7** (84%*ee*) with sodium methoxide, freshly prepared from sodium hydride and methanol, furnished *racemic* **10** in 63% yield. A series of experiments were then undertaken to establish if racemisation could be prevented by modifying the reaction conditions (Table 1). Sodium methoxide at low temperature was insufficiently reactive to facilitate rearrangement and the starting mesylate was recovered unchanged (Entry 2). While the use of potassium methoxide, freshly prepared from potassium hydride and methanol, at 0°C facilitated product racemisation, this alkoxide was sufficiently reactive to produce a modest yield of the desired ketone at low temperature (Entries 3 & 4). <sup>1</sup>H NMR analysis with (+)-Eu(hfc)<sub>3</sub> revealed that this material had been produced with little racemisation. Further experimentation established that addition of 18-crown-6 improved the yield of ketone **10** without diminishing the stereoselectivity of the process (Entry 5). Interestingly, an excess of potassium methoxide can be employed in this reaction without significant product racemisation (Entry 6).



Entry	Reaction Conditions	Yield <sup>†</sup>	% <i>ee</i> <sup>§</sup>
1	NaOMe (2 eq), THF, 0°C to rt,	63%	0%
2	NaOMe (2 eq), THF, -78°C	no reaction	-
3	KOMe (2 eq), THF, 0°C to rt	54%	0%
4	KOMe (2 eq), THF, -78°C	26%	80%
5	KOMe (2 eq), 18-crown-6 (2 eq), THF, -78°C	52%	80%
6	KOMe (3 eq), 18-crown-6 (3 eq), THF -78°C	not determined	80%

**Table 1.** <sup>†</sup> Yield of isolated material after column chromatography. <sup>§</sup> Determined by <sup>1</sup>H NMR analysis in the presence of (+)-Eu(hfc)<sub>3</sub> using racemic material for comparison purposes.

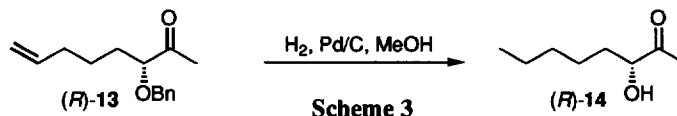
Further studies reveal that these modified reaction conditions are quite general providing access to a variety of chiral  $\alpha$ -alkoxyketones in moderate yields (Table 2). Significantly, in each case, the enantiomeric purity of the product closely reflects that of the starting epoxide. While the reaction tolerates functionality in the epoxy mesylate (Entries 3 & 4), we have found that only relatively unhindered potassium alkoxides can be used. Thus, potassium *iso*-propoxide, freshly prepared from *iso*-propanol and potassium hydride, does not yield any of the desired  $\alpha$ -*iso*-propoxy substituted ketone but simply triggers decomposition of the starting epoxide.



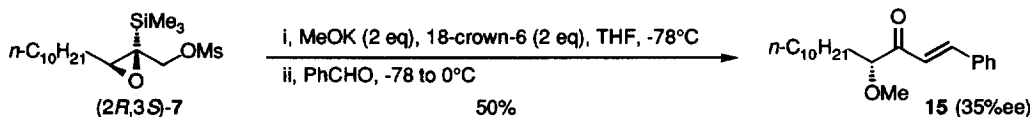
Entry	Precursor	R <sup>1</sup>	R <sup>2</sup> OH	Product <sup>†</sup>	% ee <sup>‡</sup>
1	7	<i>n</i> -C <sub>10</sub> H <sub>21</sub>	MeOH	<b>10</b> (52%)	80% (84%)
2	7	<i>n</i> -C <sub>10</sub> H <sub>21</sub>	1-Naphthalenemethanol	<b>11</b> (57%)	79% (84%)
3	8	-(CH <sub>2</sub> ) <sub>4</sub> OTHP	1-Naphthalenemethanol	<b>12</b> (53%)	83% (83%)
4	9	-(CH <sub>2</sub> ) <sub>3</sub> CH=CH <sub>2</sub>	PhCH <sub>2</sub> OH	<b>13</b> (52%)	83% (85%)

**Table 2.** <sup>†</sup> Yield of isolated material after column chromatography given in parenthesis. <sup>‡</sup> Enantiomeric purity of the starting material given in parenthesis. The enantiomeric excesses of the products were determined by <sup>1</sup>H NMR analysis in the presence of (+)-Eu(hfc)<sub>3</sub> (Entries 1 & 4) or by chiral HPLC analysis (Entries 2 & 3).

We envisaged that these reactions proceed with stereochemical inversion at the epoxide centre. Palladium catalysed hydrogenation of  $\alpha$ -benzyloxyketone **13** resulted in the simultaneous removal of the benzyl ether and the alkene double bond furnishing  $\alpha$ -hydroxyketone **14** (Scheme 3). The optical rotation of this material was found to be of opposite sign to the known (*S*)-enantiomer confirming that  $\alpha$ -benzyloxyketone **13** possessed the (*R*)-configuration.<sup>9</sup> This result confirms that these alkoxide triggered reactions proceed with net stereochemical inversion at C-3.



In an effort to further extend the scope of this reaction, we reasoned that it may be possible to introduce electrophiles into the reaction mixture and effect further bond forming processes using the potassium enolate, which we speculated must be formed in the reaction mixture prior to work-up. To test this hypothesis, mesylate (*2R,3S*)-**7** (84% ee) was reacted with two equivalents of potassium methoxide, then benzaldehyde was added to the reaction mixture and the solution allowed to warm to 0°C. Gratifyingly, this reaction gave enone **15** in 50% yield *via* a one-pot, three component coupling (Scheme 4). Unfortunately, partial racemisation of the product was observed under these reaction conditions and further studies are required before this type of process will be of value in asymmetric synthesis.



**Scheme 4**

In summary, the results presented herein provide a novel entry into a variety of enantiomerically enriched  $\alpha$ -alkoxyketones. Additional work to explore the mechanism and scope of these reactions is ongoing and will be disclosed in due course.

**Acknowledgements.** We are grateful to the EPSRC for a CASE award (to HRT), The Royal Society and Glaxo Group Research Ltd for their generous financial support. We are indebted to Dr J.A. Ballantine and his staff at the EPSRC Mass Spectrometry Service for high resolution mass spectra and Dr D.S. Ennis at Smithkline Beecham Pharmaceuticals, Tonbridge for assistance with some of the optical rotations.

#### REFERENCES & NOTES

1. For reviews on the chemistry of allene oxides, see (a) Chan, T. H.; Ong, B. S. *Tetrahedron* **1980**, *36*, 2269; (b) L'Abbe, G.; *Angew. Chem., Int. Ed. Engl.*, **1980**, *19*, 276; (c) Stang, P.J.; *The Chemistry of Functional Groups, Supplement E: The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Analogues*; Patai, S., Ed.; Wiley: New York, 1983; pp 859; (d) Smadja, W.; *Chem. Rev.*, **1983**, *83*, 263.
2. Kabat, M. M. *Tetrahedron: Asymmetry* **1993**, *4*, 1417.
3. Kabat, M. M. *Tetrahedron Lett.* **1993**, *34*, 8543.
4. Konoike, T.; Hayashi, T.; Yoshitaka, A. *Tetrahedron: Asymmetry* **1994**, *5*, 1559.
5. Clemens, I. R.; Shipman, M.; Thorpe, H. R. *Synlett* **1995**, 1065.
6. The synthesis of these allylic alcohols has been described, see reference 5.
7. Gao, Y.; Hansen, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
8. Takeda, Y.; Matsumoto, T.; Sato, F. *J. Org. Chem.* **1986**, *51*, 4728.
9. The optical rotation of (*R*)-**13** was  $[\alpha]_D = -40^\circ$  (*c* 0.03, CHCl<sub>3</sub>). Literature value for the corresponding (*S*)-enantiomer (90%ee),  $[\alpha]_D = +92^\circ$  (*c* 0.03, CHCl<sub>3</sub>). See Bel-Rhlid, R.; Fauve, A.; Veschambre, H. *J. Org. Chem.*, **1989**, *54*, 3221.

(Received in UK 29 November 1996; accepted 13 December 1996)