

Number 11  
1993Control of Diastereoselectivity in the Nucleophilic Epoxidation of 1-Arylthio-1-nitroalkenes: Synthesis of Diastereoisomerically Pure  $\gamma$ -Hydroxy Threonine DerivativesRichard F. W. Jackson,<sup>\*a</sup> Joanna M. Kirk,<sup>a</sup> Nicholas J. Palmer,<sup>a</sup> David Waterson<sup>b</sup> and Martin J. Wythes<sup>c</sup><sup>a</sup> Department of Chemistry, Bedson Building, The University of Newcastle, Newcastle upon Tyne, UK NE1 7RU<sup>b</sup> Zeneca Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire, UK SK10 4TG<sup>c</sup> Pfizer Central Research, Sandwich, Kent, UK CT13 9NJ

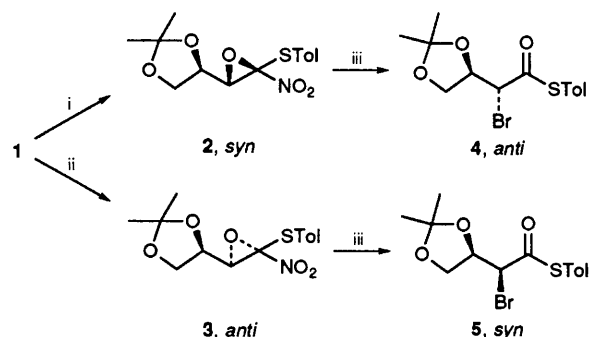
Epoxidation of the 1-nitro-1-(*p*-tolylthio)alkene **1** derived from *D*-isopropylidenglyceraldehyde with lithium *tert*-butyl peroxide affords the *syn* epoxide **2** with moderate selectivity, whereas epoxidation with potassium *tert*-butyl peroxide affords the *anti* diastereoisomer **3** preferentially; treatment of each of the epoxides **2** and **3** with amines, including ammonia, gives diastereoisomerically pure  $\alpha$ -amino thioesters with no trace of stereoisomeric contamination.

We have shown recently that 2-nitro-2-phenylthiooxiranes, prepared by nucleophilic epoxidation of 1-nitro-1-phenylthioalkenes, react with oxygen and halide nucleophiles to give  $\alpha$ -substituted *S*-phenyl thioesters under mild conditions.<sup>1</sup> Prompted by our recent investigations into the control of stereochemistry in nucleophilic epoxidation of  $\gamma$ -hydroxy  $\alpha,\beta$ -unsaturated sulfones by the allylic stereocentre,<sup>2</sup> we have investigated the stereoselectivity in nucleophilic epoxidation of the 1-nitro-1-(*p*-tolylthio)alkene **1**.

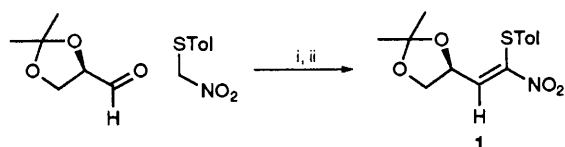
The alkene **1** was prepared from *D*-isopropylidenglyceraldehyde by condensation with (*p*-tolylthio)nitromethane (Scheme 1),<sup>3</sup> and appeared to be a single isomer (*Z*) as judged by <sup>1</sup>H NMR spectroscopy. Epoxidation of **1** with lithium *tert*-butyl peroxide gave a mixture of *syn* and *anti* epoxides **2** and **3** (ratio 5 : 1), from which the major *syn* isomer **2** could be obtained pure (60%) by crystallisation from light petroleum. An X-ray crystal structure analysis of the epoxide **2** established its structure unambiguously.<sup>4</sup> Epoxidation of **1** with potassium *tert*-butyl peroxide resulted in a reversal in diastereoselectivity, with the *anti* epoxide **3** now the major isomer (ratio of **2** to **3** 1 : 6.5). Column chromatography, followed by crystallisation of the minor component, afforded **3** as a pure diastereoisomer (63%). The two epoxides **2** and **3** were converted into the stereoisomeric *anti* and *syn*  $\alpha$ -bromo *S*-tolyl thioesters **4** (85%) and **5** (83%), respectively (Scheme 2). An X-ray crystal structure analysis<sup>4</sup> of the  $\alpha$ -bromo *S*-tolyl

thioester **4** confirmed that it possessed the *anti* configuration, and, therefore, that the epoxide ring-opening reaction had proceeded with inversion of configuration.

We believe that the stereochemical outcome of the epoxidation process can be rationalised on the basis of a reactive conformation in which the allylic hydrogen occupies the inside position (to minimise allylic strain),<sup>5</sup> and coordination by the  $\gamma$ -oxygen substituent directs attack by lithium *tert*-butyl peroxide to the same face (Fig. 1). In contrast, reaction with potassium *tert*-butyl peroxide is likely to be under stereoelectronic control, in which nucleophilic attack occurs *anti* to the allylic C–O bond (Fig. 2). Related diastereoselective additions to 1-nitro-1-phenylthioalkenes have been reported,<sup>6</sup> and attention has been drawn to the steric bulk of the nucleophile in controlling the stereochemical sense of such reactions.<sup>7</sup>



Scheme 2 Reagents and conditions: i, LiOOBu<sup>t</sup>, THF, –78 °C, 2 h; ii, KH–Bu<sup>t</sup>OOH, THF, –78 °C, 2 h; iii, MgBr<sub>2</sub>·Et<sub>2</sub>O, Et<sub>2</sub>O (1.2 equiv.), room temp., 2 h



Scheme 1 Reagents and conditions: i, KOBu<sup>t</sup>, Bu<sup>t</sup>OH–THF, 0 °C; ii, MeSO<sub>2</sub>Cl (3 equiv.), NEt<sub>3</sub> (3 equiv.), –78 °C to 0 °C, 54% overall yield<sup>†</sup>

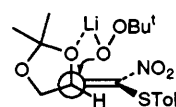
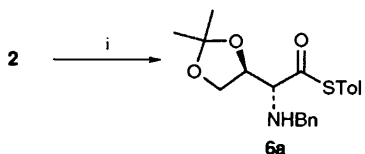
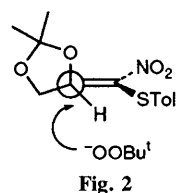
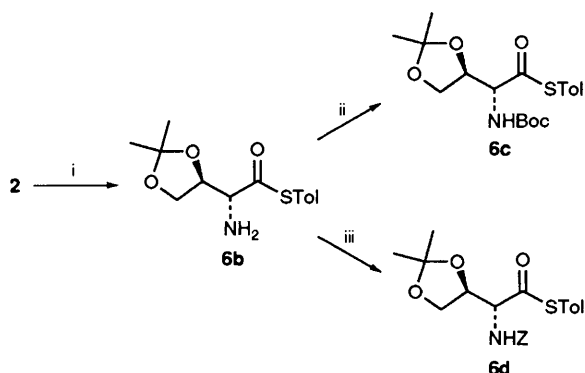
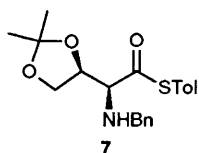


Fig. 1

<sup>†</sup> Abbreviations used: Tol = *p*-MeC<sub>6</sub>H<sub>4</sub>, Bn = PhCH<sub>2</sub>, Boc = Bu<sup>t</sup>OCO, Z = PhCH<sub>2</sub>OCO.

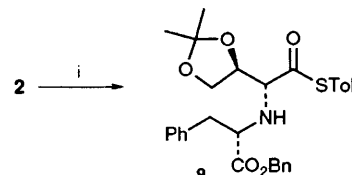
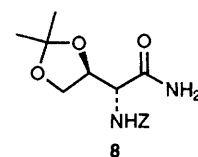


**Scheme 3** Reagents and conditions: i, BnNH<sub>2</sub> (2 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, room temp., 2 h



**Scheme 4** Reagents and conditions: i, NH<sub>3</sub> (d 880 aq., 5 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, room temp., 2 h; ii, Boc<sub>2</sub>O (10 equiv.), room temp., 2 h; iii, ZCl (10 equiv.), room temp., ½ h

In our initial study on ring-opening reactions of 2-nitro-2-phenylthiooxiranes,<sup>1</sup> we had not investigated the possibility of using nitrogen nucleophiles, and we now report that a variety of primary amines, including ammonia, react with the oxiranes **2** and **3** under mild conditions to give the corresponding  $\alpha$ -amino *S*-tolyl thioesters **6** and **7** in a completely stereospecific manner. For example, treatment of **2** with benzylamine in dichloromethane gave the diastereomerically pure  $\gamma$ -hydroxy threonine derivative **6a** (88%) (Scheme 3).<sup>8,9</sup> Reaction of the stereoisomer **3** under the same conditions gave **7** (80%). More usefully, treatment of **2** with ammonia (880, aqueous solution) in dichloromethane gave the free *anti*  $\alpha$ -amino *S*-tolyl thioester **6b**, which could be isolated either as the *tert*-butoxycarbonyl derivative **6c** (67%) or the benzyloxycarbonyl derivative **6d** (69%), by addition either of *tert*-butyl pyrocarbonate or benzyloxycarbonyl chloride, respectively, after TLC had indicated complete consumption of the oxirane **2** (Scheme 4). The stereochemistry of the *Z*-protected derivative **6d** was confirmed by an X-ray crystal structure analysis,<sup>4</sup> and also by conversion to



**Scheme 5** Reagents and conditions: i, (*S*)-PhCH<sub>2</sub>CH(NH<sub>2</sub>)CO<sub>2</sub>Bn (2 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, room temp., 24 h

the corresponding amide **8** (by extended treatment with ammonia) followed by comparison of <sup>1</sup>H NMR data for this compound with those in the literature.<sup>9</sup> It is noteworthy that reaction of the *S*-tolyl thioester to give a primary amide is significantly slower than the original ring opening of the 2-nitro-2-(tolylthio)oxirane group, testifying to its very high reactivity towards nucleophiles.

As a final example, reaction of oxirane **2** with phenylalanine benzyl ester gave the secondary amine **9** (80%) as a single stereoisomer as judged by <sup>1</sup>H NMR spectroscopy (Scheme 5). This result not only illustrates a novel route to enzyme inhibitors, but also confirms that no significant racemisation had occurred in the formation of the 1-nitro-1-(*p*-tolylthio)-alkene **1**.

We thank the SERC for a CASE award (N. J. P.) and a Quota award (J. M. K.), Professor W. Clegg and Dr M. R. J. Elsegood for determining the X-ray crystal structures and Pfizer Central Research and Zeneca Pharmaceuticals for support.

Received, 17th March 1993; Com. 3/01559I

## References

- M. Ashwell, R. F. W. Jackson and J. M. Kirk, *Tetrahedron*, 1990, **46**, 7429.
- R. F. W. Jackson, S. P. Standen and W. Clegg, *Tetrahedron Lett.*, 1991, **32**, 5393.
- M. Miyashita, T. Kumazawa and A. Yoshikoshi, *J. Org. Chem.*, 1980, **45**, 2945; A. G. M. Barrett, G. G. Graboski and M. A. Russell, *J. Org. Chem.*, 1986, **51**, 1012; A. G. M. Barrett, *Chem. Soc. Rev.*, 1991, **20**, 95.
- W. Clegg and M. R. J. Elsegood, unpublished results; full details of the X-ray structure analyses will be published elsewhere.
- R. W. Hoffmann, *Chem. Rev.*, 1989, **89**, 1841.
- A. G. M. Barrett and S. A. Lebold, *J. Org. Chem.*, 1990, **55**, 3853.
- A. G. M. Barrett, P. D. Weipert, D. Dhanak, R. K. Husa and S. A. Lebold, *J. Am. Chem. Soc.*, 1991, **113**, 9820.
- For recent approaches to the synthesis of  $\gamma$ -hydroxythreonine derivatives, see: S. Saito, N. Bunya, M. Inaba, T. Moriwake and S. Torii, *Tetrahedron Lett.*, 1985, **26**, 5309; M. Hirama, H. Hioki and S. Itô, *Tetrahedron Lett.*, 1988, **29**, 3125; M. Bols and I. Lundt, *Acta Chem. Scand., Ser. B*, 1988, **42**, 67; C. Palomo, F. Cabré and J. M. Ontoria, *Tetrahedron Lett.*, 1992, **33**, 4819; and ref. 9.
- S. Cardani, A. Bernardi, L. Colombo, C. Gennari, C. Scolastico and I. Venturini, *Tetrahedron*, 1988, **44**, 5563.