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Stereoselective Syntheses of Protected *D*-Threonine and *L-allo*-Threonine

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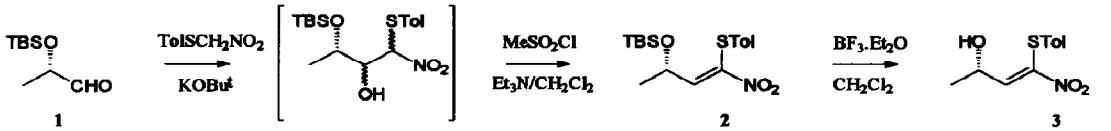
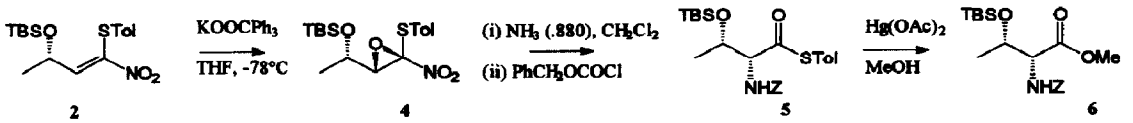
Abstract: Syntheses of both protected *D*-threonine and *L-allo*-threonine are described, in which reagent controlled stereoselective epoxidation of a common intermediate is the key step.

The stereoselective synthesis of β-hydroxy-α-amino acids has been extensively studied, and several excellent methods for their preparation have been established.[1] We have recently reported an approach to the synthesis of β,γ-dihydroxy amino acids, in which the key step is stereoselective nucleophilic epoxidation of 1-arylthio-1-nitroalkenes, using either lithium or potassium *t*-butylperoxide.[2] This method has the virtue that either stereoisomeric product may be obtained by appropriate choice of reagent, and we now wished to test it in the simplest case, the stereoselective synthesis of protected threonine and *allo*-threonine.

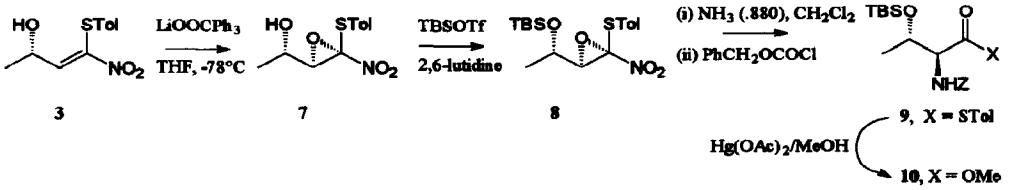
Preparation of the required 1-(4-tolylthio)-1-nitroalkene **2** was achieved (40 %) by condensation of 4-tolylthionitromethane with the known[3] protected lactaldehyde derivative **1** using a potassium *t*-butoxide promoted nitro aldol condensation, followed by elimination.[4] The *t*-butyldimethylsilyloxy group was chosen for its poor coordination ability (which should be ideal for potassium *t*-butylperoxide *anti*-epoxidation), and for its ease of removal using acid conditions to give the free alcohol **3** (which in turn should be an ideal precursor for lithium *t*-butylperoxide epoxidation). In the event, treatment of the silyl ether **2** with boron trifluoride etherate[5] gave the required alkene **3** (73 %).



Nucleophilic epoxidation of the *t*-butyldimethylsilyl protected alkene **2** with potassium triphenylmethylperoxide[6] (which we have found to give better *anti*-stereoselectivity than potassium *t*-butylperoxide, in the epoxidation of arylthionitroalkenes), gave a mixture of two stereoisomeric oxiranes in a ratio of 20:1 (combined yield 82 %), as determined by ^{1}H NMR. At this stage it was not possible to assign unambiguously the stereochemistry of the major isomer, although we presumed that it was the *anti*-epoxide **4** by analogy with our previous work.[2] Treatment of this epoxide with aqueous ammonia (.880) according to our previous procedures,[2] followed by cooling to 0 °C and addition of benzyl chloroformate, gave the *Z*-protected threonine derivative **5** (82 % overall from **4**). Treatment of this thioester with mercury (II) acetate in methanol gave the methyl ester **6** (86 %), which was identified as protected *D*-threonine by comparison of its ^{1}H NMR with authentic data in the literature.[7] The measured optical rotation for **6** also compared favourably with the literature value.[8] Since the ring-opening reaction with ammonia proceeds with inversion of configuration,[2] this confirms that the initial epoxidation process did occur to give the *anti* epoxide **4**.



Having established an effective route to protected *D*-threonine, we then investigated the nucleophilic epoxidation of the free hydroxy alkene **3**. Reaction with lithium *t*-butylperoxide gave cleanly a single stereoisomeric epoxide (65 %), to which we have assigned *syn*-stereochemistry **7** on the basis of our previous work.[2] This assignment of stereochemistry was shown to be correct by protection of the free hydroxyl group using *t*-butyldimethylsilyl triflate and 2,6-lutidine[9] to give the *syn*-epoxide **8** (83 %), which was clearly distinguishable from the *anti*-epoxide **4** that we had already prepared. Treatment of the *syn*-epoxide **8** with aqueous ammonia (0.880), followed by addition of benzyl chloroformate, gave the Z-protected *L-allo*-threonine thioester **9** (65 %). Treatment of **9** with mercury (II) acetate in methanol (65 %) gave fully protected *L-allo*-threonine methyl ester **10**,[10] which exhibited different spectroscopic properties from the protected *D*-threonine derivative **6**. Since both **6** and **10** are derived from a common precursor **2**, and there is no evidence for the racemisation in the conversion of this precursor into **6**, the enantiomeric purity of **10** is assured.



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8. For compound **6**, $[\alpha]_D$ = +9.0° (c 1 in $CHCl_3$); the literature[7] rotation for *ent*-**6** is $[\alpha]_D$ = -7.31° (c 3.55 in $CHCl_3$).
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10. For compound **10**, $[\alpha]_D$ = +27.3° (c 0.55 in CH_2Cl_2).

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