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Chiral Base-mediated Rearrangement of *meso*-Cyclohexene Oxides to Allylic Alcohols

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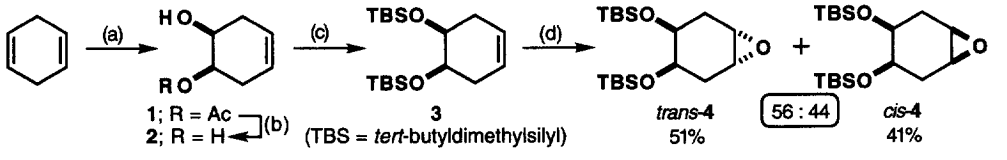
Abstract: Highly enantiomerically enriched allylic alcohols have been generated by rearranging single diastereomers of *meso*-cyclohexene oxides using a homochiral lithium amide base. PDC oxidation of each allylic alcohol product affords a different enantiomer of a synthetically useful cyclohexenone.

Asymmetric desymmetrisation of *meso* compounds is a particularly useful synthetic strategy and the success of enzymes for carrying out such reactions is well known.[1] More recently, non-enzymatic approaches have also emerged as useful methods[2] and one well studied area is the enantioselective desymmetrisation of *meso* cyclopentene oxides to allylic alcohols using chiral bases.[3] In contrast, chiral base-mediated rearrangement of substituted *meso* cyclohexene oxides has received scant attention and only one example has been reported: during work on the total synthesis of Laisol and Faranal, Mori used Asami's chiral base to rearrange a mixture of *trans* and *cis meso* cyclohexene oxides.[4] In this paper, we describe the synthesis of epoxides *trans*- and *cis*-**4** and their separate enantioselective rearrangement using Singh's[5,6] chiral base (*R*)-**7**.

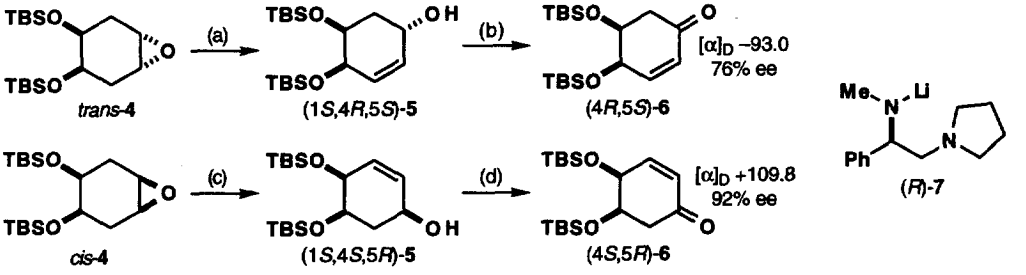


Reagents: (a) (i) KIO_3, I_2, AcOH, reflux, 3 h; (ii) KOAc, reflux, 3 h; (iii) water (48%); (b) Amberlite IRA(OH), 2:1 MeOH-THF, rt, 1 h (92%); (c) 2.4 eq TBSCl, 5 eq imidazole, CH_2Cl_2, rt, 16 h (97%); (d) *m*-CPBA, CH_2Cl_2, rt, 16 h (92%).

Our epoxide synthesis is outlined above. Using Krow's method,[7] 1,4-cyclohexadiene was converted into hydroxy acetate **1**[7] whose methanolysis to the known[7,8] water soluble diol **2** was best accomplished using commercially available (Aldrich) Amberlite IRA(OH).[8] Standard silylation generated the disilyl ether **3**.[9] Epoxidation of **3** proceeded with virtually no facial selectivity to give a 56:44 mixture of epoxides *trans*- and *cis*-**4** which were readily separable by chromatography. The relative stereochemistry of these epoxides was assigned by 500 MHz NOESY analysis.

Initially, epoxide *trans*-**4** was rearranged using 1.3 equivalents of Singh's chiral base (*R*)-**7** to give a 93% isolated yield of allylic alcohol **5** which had $[\alpha]_D$ –87.1 (*c.* 0.6 in $CHCl_3$). Conversion to its Mosher's esters[10] indicated that it had been generated with 76% ee. The major enantiomer was assigned as allylic alcohol (1*S*,4*R*,5*S*)-**5** by analysis of the ^1H NMR of the Mosher's esters.[11] This is the same sense (and a

similar degree) of asymmetric induction to that obtained by Singh when he used chiral base (*S*)-**7** to rearrange cyclohexene oxide itself.[5] In contrast, reaction of epoxide *cis*-**4** with chiral base (*R*)-**7** was much more sluggish and, after 20 hours, we isolated only a 38% yield of allylic alcohol **5** {$[\alpha]_D$ +20.4 (*c.* 0.6 in $CHCl_3$)}. It had 92% ee as shown by making the Mosher's esters and was identified as allylic alcohol (1*S*,4*S*,5*R*)-**5**.[11] In his study,[4] Mori also found that a related *cis* epoxide rearranged with higher enantioselectivity.



Reagents: (a) 1.3 eq chiral base (*R*)-**7**, THF, 0 °C → rt, 5 h (93%); (b) 1.3 eq PDC, CH_2Cl_2, rt, 3 h (78%); (c) 1.3 eq chiral base (*R*)-**7**, THF, 0 °C → rt, 20 h (38%); (d) 1.3 eq PDC, CH_2Cl_2, rt, 4 h (72%).

PDC oxidation[7] of each allylic alcohol afforded a different enantiomer of cyclohexenone **6**: (1*S*,4*R*,5*S*)-**5** gave (4*R*,5*S*)-**6** which had $[\alpha]_D$ −93.0 (*c.* 0.7 in $CHCl_3$) and (1*S*,4*S*,5*R*)-**5** gave (4*S*,5*R*)-**6** which had $[\alpha]_D$ +109.8 (*c.* 0.65 in $CHCl_3$). This further corroborated our stereochemical assignments of the allylic alcohols **5**. Enantiomerically pure enones like **6**, synthesised in four steps from (−)-quinic acid, have found widespread use in total synthesis.[12] However, to date, they have only been prepared in one enantiomeric form. Our route is similarly short (six steps from 1,4-cyclohexadiene) and allows acess to *both* enantiomers of enone **6** by rearranging either diastereomer of epoxide **4** with the same enantiomer of a chiral base or by rearranging a single diastereomer of epoxide **4** with either enantiomer of a chiral base.

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