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On the Mechanism of Lithium Amide-Induced Rearrangements of 4-Substituted Cyclopentene Oxides to Cyclopentenols

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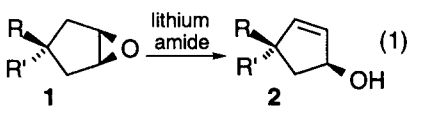
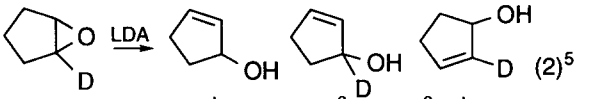
Abstract: The preparation and lithium amide-induced rearrangements of epoxides **4**, **10** (R = Bn, TBS) are described, providing insight into the rearrangement mechanisms which operate in such systems. © 1997 Elsevier Science Ltd.

Base-induced rearrangements of epoxides,[1] particularly enantioselective rearrangements of achiral epoxides,[2] are attracting increasing interest. The chiral base-induced rearrangements of 4-substituted cyclopentene oxides **1** to cyclopentenols **2** (which have application in the synthesis of prostaglandins, carbocyclic nucleosides and iridoids) have been intensively examined (Eq. 1).[2,3] A deuterium labelling study reported by Thummel and Rickborn in 1970 established that a *syn* β-elimination process operated in the rearrangements of 4-*t*-butylcyclohexene oxides to cyclohexenols using $LiNEt_2$ in ether-hexane,[4] and this has led to the adoption of this mechanism to aid in explanations for asymmetric induction in cyclopentene oxide systems with chiral lithium amides.[2] Morgan and Gajewski recently reported a deuterium labelling study with cyclohexene oxide which confirmed a β-elimination mechanism for this ring system.[5] However, their results with cyclopentene oxide indicated that cyclopentenol was formed *via* α-elimination using LDA in ether or benzene (Eq. 2). A knowledge of the mechanisms of base-induced rearrangements of epoxides is essential for understanding asymmetric induction processes (and the rational design of new chiral bases) in this area. Here we communicate our preliminary results concerning an examination of lithium amide-induced rearrangements of deuterium-labelled 4-substituted cyclopentene oxides.



1 **2** (1)

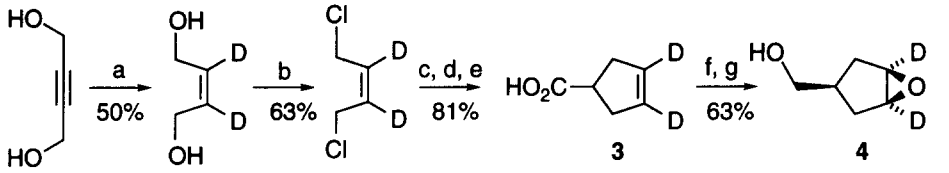


(2)[5]

	α only	α or β	β only
benzene	0.23	0.77	
ether	0.29	0.71	
HMPA		0.50	0.50

Our study focused on an examination of the mechanism(s) by which lithium amides react with epoxides **4** and **10** [R = Bn, *t*-butyldimethylsilyl (TBS)]) to generate the synthetically useful cyclopentenols **6**, **11** and **13** (Schemes 2 and 4).[2] The acid **3** was considered to be a potentially common precursor to both dideuterated epoxides **4** and **10**, and was prepared from *cis*-2,3-dideuterio-2-butene-1,4-diol[6] following established

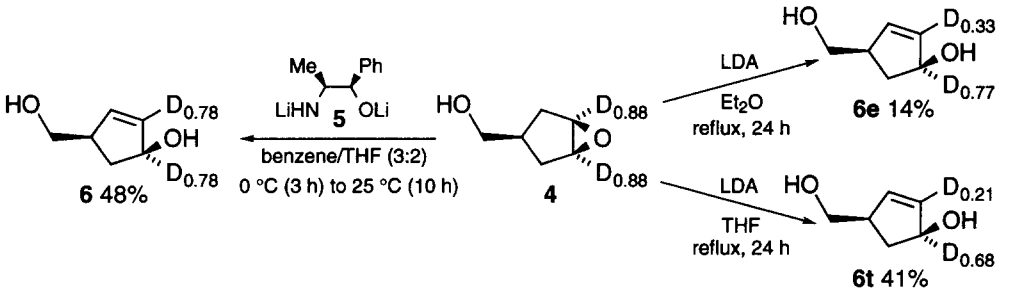
chemistry in the unlabelled series.[7,8] Subsequent reduction of the acid **3** followed by hydroxyl-directed epoxidation[9] gave the epoxide **4** (Scheme 1).



(a) D_2 (1 atm.), Lindlar catalyst, py., 40 °C, 120 h; (b) $SOCl_2$, cat. py, –40 °C to 25 °C, 16 h; (c) $(MeO_2C)_2CH_2$, LiH, DMF, 25 °C, 72 h; (d) KOH, 80% aq. EtOH, 25 °C, 18 h; (e) 180 °C, 4 h; (f) $LiAlH_4$, Et_2O, 18 h, 25 °C, 12 h; (g) Bu^tOOH, cat. $VO(acac)_2$, CH_2Cl_2, 25 °C, 24 h.

Scheme 1

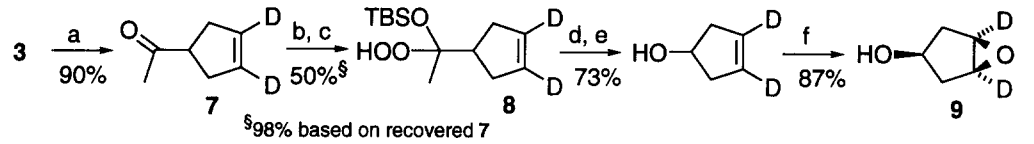
In accord with our earlier work[9] the epoxide **4** smoothly rearranged using dilithiated (1*R*,2*S*)-norephedrine **5** (3 equiv.) to give the alcohol **6** (Scheme 2). Analysis of the ^{1}H-nmr spectrum of alcohol **6** indicated a clean β-elimination mechanism. This information, when assessed in combination with our earlier study on rearrangements of quaternary-carbon containing symmetrical cyclopentene oxides using base **5** (Eq. 1, R = CH_2OH, R' = alkyl),[10] suggests that the β-elimination is a *syn* process. The slight loss of deuterium at both labelled positions in alcohol **6** also indicates partial reversible deprotonation at the α-position (reversible α-deprotonations have been observed in other deuterium labelling studies with epoxides and lithium amides).[1,11] Reaction of epoxide **4** with LDA (3 equiv.) in ether was noticeably slower than in the nondeuterated case, and required heating at reflux to give alcohol **6e** in poor yield. Significant, but not complete reduction of deuterium at the vinylic position in alcohol **6e** is consistent with rearrangement due to a mixture of α- and β-deprotonation; a similar result, but higher yielding, was observed from epoxide **4** and LDA (3 equiv.) in THF (**6t**, Scheme 2).[12]



Scheme 2

In order to examine the mechanism of the lithium amide-induced rearrangements of the epoxide **10** (R = Bn, TBS), the preparation of the precursor epoxyalcohol **9** from the ketone **7** (derived from the acid **3**, Scheme 3) was initially attempted *via* a one-pot epoxidation/Baeyer-Villiger protocol. However, all attempts to

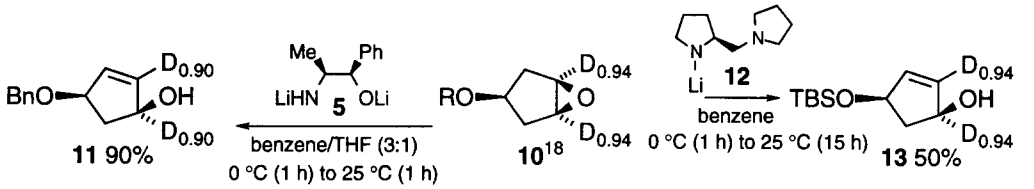
achieve this resulted in either no reaction, or only conversion to the corresponding epoxyketone, which was also separately unreactive to a variety of Baeyer-Villiger reaction conditions;[13] this lack of reactivity may be due to the electron withdrawing effect of the epoxide functional group. The desired transformation of ketone **7** into epoxyalcohol **9** was successfully carried out in a stepwise manner (Scheme 3). Proceeding *via* the α-silyloxyhydroperoxide **8**[14] is noteworthy in that this sequence achieves the equivalent of a Baeyer-Villiger reaction on the (unstrained) keto group in the presence of the double bond.



(a) MeLi (2 equiv.), Et_2O, 0 °C to 25 °C, 4 h; (b) LDA, TBSOTf, THF, HMPA, −78 °C to 0 °C, 1 h; (c) H_2O_2 (2*M* in Et_2O), Et_2O, cat. TFA, 25 °C,14 h; (d) $(Bz)_2O$, DMAP, hexane, 25 °C, 4 h, then reflux, 4 h; (e) K_2CO_3, MeOH; (f) MCPBA, CH_2Cl_2, 0 °C, 2 h.

Scheme 3

Following Milne and Murphy's work with the unlabelled system,[15] the epoxide **10** (R = Bn, easily prepared from **9**)[15] on treatment with dilithiated (1*R*,2*S*)-norephedrine **5** (3 equiv.) gave the alcohol **11**. The ^1H nmr spectrum of alcohol **11** indicated a clean β-elimination process (Scheme 4). β-Elimination was also observed using the epoxide **10** (R = TBS, prepared from **9**)[16] with lithium (*S*)-2-[(pyrrolidin-1-yl)methyl]pyrrolidide **12**[16] (1.5 equiv.) in benzene, which gave alcohol **13**.[17]



Scheme 4

The mode of reactivity (α- or β-deprotonation) of an epoxide with a base is significantly influenced by the conformations accessible to the epoxide under the reaction conditions.[1] Calculations indicate that cyclopentene oxide does not easily adopt a conformation suitable for *syn* β-elimination.[5] Our study shows that *cis* 4-substituted cyclopentene oxides such as **4** and **10** generally rearrange to allylic alcohols *via* a β-elimination mechanism (although our results with LDA and epoxide **4** suggest that the nature of the base also influences the site of deprotonation). A possible explanation for the switch in mechanistic pathway followed for epoxides **4** and **10** compared with cyclopentene oxide is that the 4-substituent in the former cases results in the 'chair cyclohexane' conformation being favoured (with a suitable geometry for *syn* β-elimination), rather than the 'boat cyclohexane' conformation favoured for cyclopentene oxide. Coordination of the base to both oxygen atoms in epoxides **4** and **10**[16] may also encourage β-elimination.

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11. Identical deuterium levels at the vinylic and allylic positions in alcohol **6** suggest no detectable enantioselectivity in this reversible α-deprotonation process (8% *ee* was observed in the rearrangement of *exo*-norbornene oxide to nortricyclanol using base **5**: Hodgson, D. M.; Wisedale, R. *Tetrahedron: Asymmetry* **1996**, *7*, 1275-1276).
12. In ether, the isolated yield of alcohol **6e** does not strictly rule out mainly (or exclusively) β-deprotonation operating in combination with a secondary deuterium isotope effect; the result in THF is more convincing that some of alcohol **6t** arises *via* α-deprotonation.
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15. Milne, D.; Murphy, P. J. *J. Chem. Soc., Chem. Commun.* **1993**, 884-886; *corrigendum*, **1994**, 675. We find treatment of unlabelled epoxide **10** (R = Bn) using dilithiated (1*R*,2*S*)-norephedrine **5** (3 equiv.) in benzene/THF (3:1) at 0 °C gives unlabelled alcohol (+)-**11**. PCC oxidation[16] of unlabelled alcohol (+)-**11** gives (4*R*)-4-(benzyloxy)-2-cyclopentenone {$[\alpha]_D^{23}$ +21.9 (*c* 0.9 in $CHCl_3$), lit. (Torii, S.; Inokuchi, T.; Oi, R.; Kondo, K.; Kobayashi, T. *J. Org. Chem.* **1986**, *51*, 254-256) $[\alpha]_D^{6}$ +42 (*c* 0.9 in $CHCl_3$)}. Our results therefore indicate that the predominant sense of asymmetric induction indicated in Milne and Murphy's work should be reversed.
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17. Reaction of epoxide **10** (R = Bn or TBS) with LDA (3 equiv.) in THF (–70 °C, 3 h) gave similar results (R = Bn: 95% yield, $D_{0.85}$ at both vinylic and carbinol carbons; R = TBS: 90% yield, $D_{0.90}$ at both vinylic and carbinol carbons).
18. The slight difference in deuterium levels in epoxides **4** and **10**, reflect different runs in the formation of *cis*-2,3-dideuterio-2-butene-1,4-diol.

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