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ENANTIOSELECTIVE OPENING OF SPIRO EPOXIDES DERIVED FROM *CIS* BICYCLO[3.3.0]OCTAN-3,7-DIONE USING CHIRAL LITHIUM AMIDE BASES

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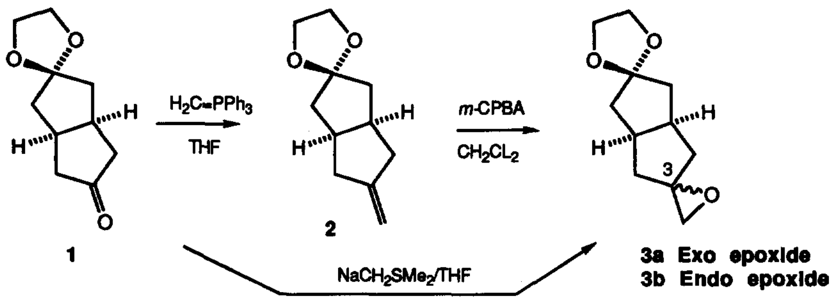
Abstract: *The monoketal derived from cis-bicyclo[3.3.0]octane-3,7-dione was converted to epoxides 3. The meso exo epoxide was cleaved via enantioselective deprotonation using chiral lithium amide bases to provide the synthetically useful alcohol 7 with up to 76%ee. The enantiomeric excess of the alcohol was determined by ^{1}H NMR chiral shift techniques.*

The mono ketal of *cis*-bicyclo[3.3.0]octane-3,7-dione **1** is an attractive starting material for the stereoselective synthesis of a broad range of polyfunctional compounds. Its functionality is quite flexible and either one or both rings can easily be cleaved, so that cyclopentane derivatives, 6-membered heterocycles or acyclic compounds can be formed. The *cis* ring junction of the molecule gives it a predisposition to react stereoselectively, and additional stereocentres are therefore readily introduced. There is also the potential for control of absolute as well as relative stereochemistry if the symmetry of the system can be broken in an enantioselective manner. We have been investigating ways in which chiral lithium amide bases can act as intermediaries in such processes. Enolization of the ketone is the most direct approach to breaking the symmetry of the system and this has already been achieved enantioselectively, providing the silyl enol ether of **1** in either enantiomeric form.[1,2] Chiral tertiary amines have also been used in enantioselective elimination reactions involving trifluoromethyl sulphonates derived from *cis*-bicyclo[3.3.0]octane-3,7-dione.[3]

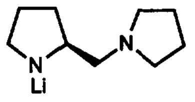
We have recently reported the conversion of the chiral silyl enol ether from **1** into other derivatives which are useful chiral synthons for natural products.[2,4] Asymmetric compounds, such as **7**, with a hydroxyalkyl chain in the 3-position of the bicyclic system were also required for our studies and in this communication we report that the *meso* epoxide **3a** can be transformed into alcohol **7** enantioselectively by treatment with chiral bases.

Epoxide **3** could be obtained from ketone **1** by reaction with methylene triphenyl phosphorane, to give alkene **2** (68%), followed by epoxidation with *m*-CPBA/NaHCO$_3$ to provide **3** (85%). The epoxide formed in this way at first appeared to be a single isomer by tlc, and ^{1}H NMR, but ^{13}C NMR revealed that it was in fact a mixture of *exo* and *endo* epoxides in a ratio of about 3:2 (see later).



Scheme 1

Before proceeding with an enantioselective epoxide opening study, we wanted to find a good method for determining the ee of alcohol **7** which did not depend on optical rotation measurements. Epoxide **3** was therefore reacted with LDA in THF at 0°C for 24 h. to provide a racemic mixture of **7**. The reaction was clean, but only 58% of **7** was isolated together with recovered epoxide. We could not find an NMR chiral shift reagent which would resolve protons of the enantiomers of **7** but the methyl ether **8**, obtained quantitatively from **7**, proved to be a suitable substrate for analysis. Addition of 3-4 equivalents of (R)-(-)-2,2,2-trifluoro-1-(9-anthryl) ethanol (TFAE) to a 5mg sample of **8** in $CDCl_3$ caused complete resolution of the methoxyl singlets. Having established an analytical method for our target compound and taking into account the results of previous on epoxide opening studies[5a-d] we chose chiral bases **4**,[5d] **5**[6] and **6**[7] for an initial enantioselective epoxide cleavage study, with benzene THF and diethyl ether as solvents. The results of this study are presented in the Table.[8,9]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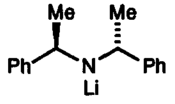
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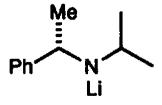
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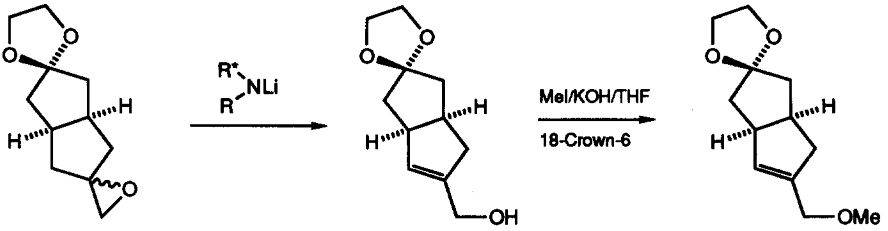
There are several interesting points worthy of note in these results. The choice of solvent is critical and in each case the highest yield was obtained using THF. For the mono basic bases **5** and **6** the highest enantioselectivity was also achieved using THF, whereas the bidentate base **4** was more enantioselective in benzene. An interesting reversal of the direction of selectivity was also observed when base **4** was used in benzene rather than THF or ether. The different reactivity of base **4** compared to the others is probably due to its ability to coordinate internally with the lithium atom in the transition state. In a previous study we noticed that benzene was a particularly good solvent with base **4** when a further coordination site was available in the substrate molecule.[5d] It is possible that the observed reversal of enantioselectivity in coordinating solvents is caused by a weakening of internal coordination between lithium and the tertiary amine nitrogen in base **4**. Since no secondary coordination site is available in bases **5** and **6**, solvents which can coordinate to the lithium atom in the transition state are preferred. An interesting general contrast between the opening of epoxide **3** and other epoxide cleavage reactions, is that the bidentate type proline derived base **4** is less effective than the methyl benzylamine derived base **5**.[5a-d] Indeed, C-2 symmetrical base **5** was used in the first reported enantioselective lithium amide mediated epoxide cleavage,[5a] but modest selectivity was observed and subsequently proline derived bases were found to be generally superior.[5b-d] However, the transition state for cleavage of spiro epoxides is probably quite different from that of other epoxides, and comparison of models indicates that it may actually be quite closely related to the transition state of enolization reactions.[11]



3a Exo epoxide
3b Endo epoxide

7

8

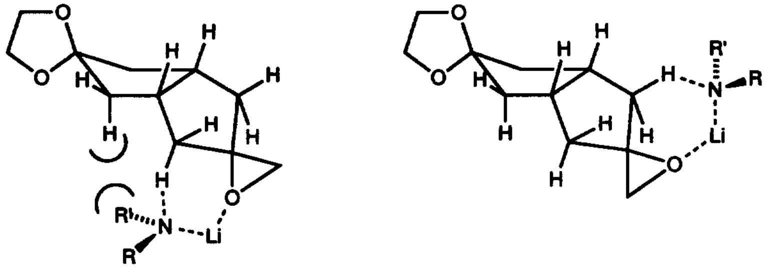
Scheme 2

Although the reactions were very clean, none of them went to completion and we thought the cause might be that the *endo* epoxide in the mixture does not react due to steric crowding around the concave face of the molecule (Figure). This explanation was substantiated when the a mixture of the epoxides recovered from several reactions was analysed by ^{13}C NMR and shown to be entirely one isomer. We had anticipated that methylene dimethylsulphonium ylide would react predominantly from the convex face of ketone **1** to give the *endo* epoxide selectively and in the event a 9:1 isomer mixture was obtained. The fact that the epoxide recovered from the cleavage reactions was the same as the major isomer from the ylide reaction allowed us to assign this as the *endo* epoxide with some certainty. Finally, the epoxide prepared from the sulphur ylide (9:1 *endo:exo*) was reacted with base **5** under the same conditions as before, except that the reaction was left for three days at 0°C. In this case the epoxide only reacted to the extent of about 15%. We therefore conclude that chiral bases differentiate quite cleanly between the *exo* and *endo* diastereoisomers of epoxide **3**, reacting selectively with the *exo* isomer and in an enantioselective manner.

Base	**Solvent**	**Yield%**[a)]	**Major enant.**[11]	**ee%**[b)]
LDA	THF	58	-	0[c)]
4	THF	58	d-(+)	21
4	Benzene	35	l-(-)	58
4	Et_2O	50	d-(+)	23[c)]
5	THF	50	d-(+)	76
5	Benzene	40	d-(+)	21[c)]
5	Et_2O	56	d-(+)	23[c)]
6	THF	55	l-(-)	42[c)]
6	Benzene	0	-	-
6	Et_2O	53	l-(-)	20

[a)] Isolated yield, chromatographically pure (not optimized). [b)] Determined by chiral shift reagent on methyl ether **8**.
[c)] Reactions carried out at 0°C.[12]

Table - Reaction of chiral bases with epoxide 3 (3:2 *exo:endo*)



Endo epoxide

Exo epoxide

Figure

In conclusion, we have shown that chiral lithium amide bases cleave *meso* spiro epoxide **3a** with a high degree of enantioselectivity providing the useful chiral allylic alcohol **7**, the ee of which we have determined using chiral shift techniques. It is significant that phenylethylamine derived base **5** was found to be effective, because it is cheap and easy to prepare in either enantiomeric form, allowing either enantiomer of **7** to be prepared. In future work we intend to broaden our studies to include a wider range of spiro epoxides and bases and in the long term we hope that our results will help in formulating a predictive model for matching substates with bases for highly enantioselective in deprotonation reactions.

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References and notes:

1. H. Izawa, R. Shirai, H. Kawasaki, H. Kim, and K. Koga, *Tetrahedron. Letters.*, **1989**, *30*, 7221
2. J. Leonard, J.D. Hewitt, D. Ouali, S.J. Simpson and R.F. Newton, *Tetrahedron Asymmetry*, in press
3. H. Kashihara, H. Suemume, T. Kawahara and K. Sakai, *Tetrahedron Letters*, **1987** *28*, 6489
4. a) S.K. Rahman, Ph.D. Thesis, University of Salford **1988**; b) J. Leonard, D. Ouali and S.K. Rahman, *Tetrahedron Letters*, **1990**, *31*, 739
5. a) J.K. Whitesell and S.W. Felman, *J. Org. Chem.*, **1980** *45*, 755; b) M. Asami, *Chemistry Lett.*, **1984**, 829; c) M. Asami, *Bull. Chem. Soc. Jpn.*, **1990** *63*, 721; d) S.K. Hendrie and J. Leonard, *Tetrahedron*, **1987**, *43*, 3289
6. C.G. Overburger, N.P. Marullo and R.G. Hiskey, *J. Am. Chem. Soc.*, **1961**, *83*, 1374
   Specific rotation of base **5** $[\alpha]_D^{23}$ = +157
7. Prepared by reductive amination of (S)-(-)-phenylethylamine (Aldrich) using acetone and $NaBH_3CN$ in MeOH.
   Specific rotation of base **6** after crystallization of the HCl salt, followed by distillation of the free base - $[\alpha]_D^{23}$ = -64 (c = 2.25 $CHCl_3$), cf. Ref. 10, $[\alpha]_D^{23}$ = +61.4 (c = 2.23 $CHCl_3$) for enantiomer.
8. General procedure for enantioselective epoxide opening reactions:
   Butyl lithium (2.3 mmol) was added to a solution of the chiral amine (2.4 mmol) in the solvent (10 ml) at 0°C. After 30 mins. the mixture was cooled to -10°C and a solution of epoxide 3 (1 mmol) in solvent (1 ml) was added. When tlc analysis indicated that no more epoxide was being converted to more polar product, the mixture was diluted with ether and washed with dil. HCl, and sat. $NaHCO_3$ then dried with Na_2SO_4. After solvent evaporation, alcohol 7 was isolated by flash chromatography on silica.
9. All new compounds were characterized by a full range of spectral data, including 300 MHz ^1H NMR and HR MS. All chiral shift experiments were carried out at 300 MHz in $CDCl_3$, 5mg of sample was used + 3-4 eq. of (R)-(-)-TFAE.
10. CM. Cain, R.P.C. Cousins, G. Coumbarides and N.S. Simpkins, *Tetrahedron*, **1989**, *46*, 523
11. The absolute stereochemistry has not yet been confirmed, but we have tentatively assigned the d-(+) enantiomer as 7, by comparing simple transition state molecular models for this reaction and for enolization reactions of ketone 1.
12. There was a slight but distinct increase in enantioselectivity when the reaction temperature was reduced from 0°C to -10°C.

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