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USEFUL CHIRAL LACTONES DERIVED FROM *CIS*-BICYCLO[3.3.0]OCTAN-3,7-DIONE *VIA* ASYMMETRIC DEPROTONATION

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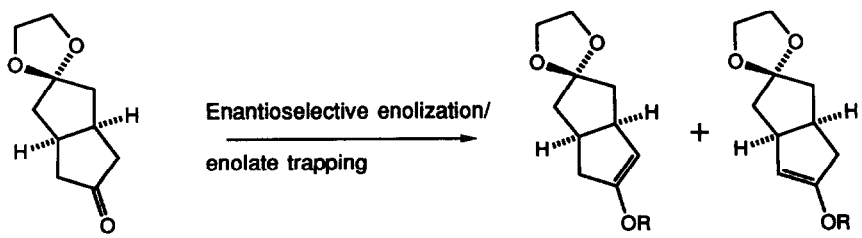
Abstract: *The monoketal derived from cis-bicyclo[3.3.0]octane-3,7-dione was deprotonated using chiral lithium amide bases and the enolates were trapped as either enol acetates or trimethylsilyl enol ethers. Oxidative cleavage of the enol derivatives provided useful bicyclic lactones, the ee's of which could be determined using NMR chiral shift techniques. The lactones are also potentially useful as intermediates for asymmetric synthesis.*

The mono ketal of *cis*-bicyclo[3.3.0]octane-3,7-dione **1** is a compound which has potential utility as a precursor for the synthesis of a broad range of natural products, and we have already developed synthetic routes to certain iridoids and alkaloids.[1] One of the main attractions of using the *meso* ketone **1** as a synthetic starting material is the possibility of breaking its symmetry in an asymmetrically controlled manner, thus providing access to advanced synthetic intermediates in either chiral form. As part of a wider study on the uses of chiral lithium amide bases for inducing asymmetry, we explored the asymmetric deprotonation of ketone **1**. Initially we tried enantioselective alkylation reactions, but the enantioselectivities were quite modest,[1] so we turned our attentions to enolate trapping.



1 **2a** **2b** **3a** **3b**

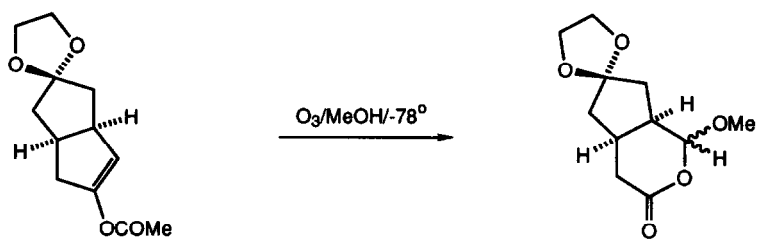
R = COMe **R = SiMe$_3$**

Scheme 1

Other workers have already reported the results of their study, whereby chiral silyl enol ethers were prepared by *in situ* trapping of enolates formed using chiral bases.[2] In this paper we report the conversion of the chiral enolate derivatives to useful, stable bicyclic lactones, the ee's of which can be determined by NMR shift techniques. We also compare the enantioselctivity of *in situ* silyl enol ether formation with that of enolate formation followed by sequential enol acetate formation.

One of our main objectives when working on the development of any asymmetric reaction is to devise a method for analysing the enantioselectivity of the process which does not rely on optical rotation measurements. These measurements are notoriously misleading and in work involving chiral bases the problem is particularly acute, because slight traces of base left in the product can cause large discrepancies in rotation values.[3,4] We could not find a chiral shift method for analysing the ee's of the enol acetates **2** or enol ethers **3** and we therefore looked for more stable derivatives which could be analysed in this way. At the same time we were investigating methods for cleaving the alkene bond of the enolate derivatives as part of our synthetic studies and the results from this work provided solutions to our problem.

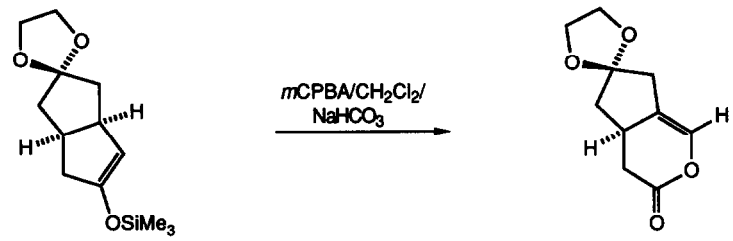
When the enol acetate **2** was ozonized in methanol, lactone **4** was obtained as the only major product (60% yield). It was an inseparable 3:1 mixture of diastereoisomers, assumed to be epimeric at the methoxyl group. The epimeric protons were well separated from one another, significantly down field from the other protons (δ5.05, d, J = 5Hz and δ5.15, d, J = 3Hz) and appeared to be ideal targets for chiral shift reagents. Europium reagents only caused signal broadening, but the addition of five equivalents of (R)-(-)-2,2,2-trifluoro-1-(9-anthryl) ethanol (TFAE) to the NMR solution produced the desired effect, causing each doublet to split. Thus, we were able to calculate the ee's of the enol acetates **2**, formed by enolization of ketone **1** using chiral bases, followed by reaction with acetic anhydride.[5,7]



2a/b **Scheme 2** **4**

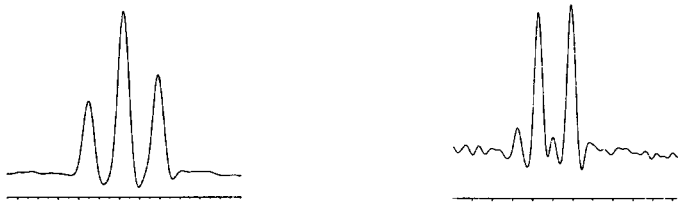
Silyl enol ether **3** was formed by *in situ* enolate trapping using a range of chiral bases and LDA for the racemic model.[6,7,8] Enol ether **3** is extremely labile (e.g. breaks down on pre-basified silica) and some chiral bases were difficult to remove completely. We therefore considered it unwise to measure the ee of **3** directly and we looked for a stable derivative which could be formed easily. Thus, enol ether **3** was treated with *m*-chloro peroxybenzoic acid, with the objective of forming a hydroxy ketone. To our surprise, unless the reaction was maintained

at low temperature, the major product was in fact enelactone **5**, with a distinctive enol ester proton which appeared as a sharp doublet at δ6.44 (J = 3.2Hz) in the ^{1}H NMR.[9]



3a/b **Scheme 3** **5**

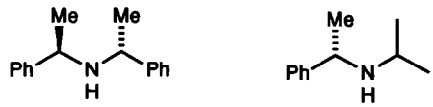
(R)-(-)-TFAE was again effective in splitting the downfield protons of the enantiomers.[7] At 300 MHz the enantiomeric protons of samples with low ee's were overlapped giving an apparent 'triplet' but the protons of mixtures with a reasonably high ee separated completely.



(a) Sample of 9% ee (approx.) (b) Sample of 72% ee

Figure - Resolution of enantiomeric protons using TFAE

We used a variety of chiral lithium amide bases in our studies, but of those we tried phenylethylamine derivatives proved to be the most effective. The reactions using bases **6**[10] and **7**[11] were used to compare the efficacy of enol acetate formation with that of silyl enol ether trapping and the results are apparent from the Table.



6 **7**

Derivative	Base	Yield%	Major enant.[12]	ee%
Enol acetate **2**	6	74†	**2b**	35
Enol acetate **2**	7	60†	**2a**	35
Enol ether **3**	6	90††	**3b**	48
Enol ether **3**	7	90††	**3a**	72

†Isolated yield (not optimized). ††Estimated yield taking into account secondary amine remaining after isolation.

Table

The enantioselectivity of the process is much higher when the enolate is trapped by *in situ* reaction with trimethylsilyl chloride, rather than by addition of acetic anhydride to the pre-formed enolate. It does appear that enolates can generally be formed from prochiral ketones with very high ee by enantioselective deprotonation, but racemization of the enolate is quite rapid.[3] This makes the internal TMS-Cl quench method the most efficient method so far developed for trapping chiral enolates. Our result for the sequence involving silyl enol ether formation using base **7** corresponds quite closely to that obtained by Koga *et al.* who estimated their ee as 71% by optical rotation measurements on the silyl enol ether **3**.

In conclusion, the lactones **4** and **5**, prepared enantioselectively from *meso* ketone **1**, have potential uses as intermediates for asymmetric synthesis and they are also useful probes for determining the enantioselectivity of deprotonation processes involving **1**, without relying on optical rotation measurements.

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References and notes:

1. 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
2. H. Izawa, R. Shirai, H. Kawasaki, H. Kim, and K. Koga, *Tetrahedron. Letters.,* **1989**, *30,* 7221
3. a) CM. Cain, R.P.C. Cousins, G. Coumbarides and N.S. Simpkins, *Tetrahedron,* **1989**, *46,* 523
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4. a) J.S. Sabol and R.J. Cregge, *Tetrahedron Letters,* **1989**, *30,* 3377; b) R. Hayes and T.W.Wallace, *Tetrahedron Letters,* **1990**, *31,* 3355; c) M. Asami, *Chemistry Letters.,* **1984**, 829
5. *Enol acetates:* Ketone **1** was added to a solution of the lithium amide base (2equ.) in THF at -78°C. After 30 Mins. acetic anhydride was added to the mixture and after a further 30 Mins. aqueous work-up was carried out.
6. *Silyl enol ethers:* Ketone **1** was added to a solution of the lithium amide base (2.4equ.) and TMS-Cl (5equ.), in THF at -78°C. After 1h. aqueous work-up was carried out.
7. All new compounds were characterized by a full range of spectral data, including 300 MHz ^{1}H NMR and HR MS. All chiral shift experiments were carried out at 300 MHz in $CDCl_3$, about 5mg of sample was used.
8. E.J. Corey and A. W. Gross, *J. Am. Chem. Soc.,* **1984**, *106,* 5754
9. α-Hydroxy ketones (3:1 epimeric mixture) were the major products if the reaction was maintained at -15°C.
10. C.G. Overburger, N.P. Marullo and R.G. Hiskey, *J. Am. Chem. Soc.,* **1961**, *83,* 1374
    Specific rotation of base **6** $[\alpha]_D^{23} = +157$
11. Prepared by reductive amination of (S)-(-)-phenylethylamine (Aldrich) using acetone and $NaBH_3CN$ in MeOH. Specific rotation of base **7** after distillation $[\alpha]_D^{23} = -61$ (c = 2.25 $CHCl_3$), cf. Ref. 3a, $[\alpha]_D^{23} = +61.4$ (c = 2.23 $CHCl_3$) for enantiomer.
12. Absolute configurations by comparison with Ref. 2.