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ENANTIOSELECTIVE PROTONATION OF A PROCHIRAL BICYCLOBUTANE BRIDGED ENOLATE ANION

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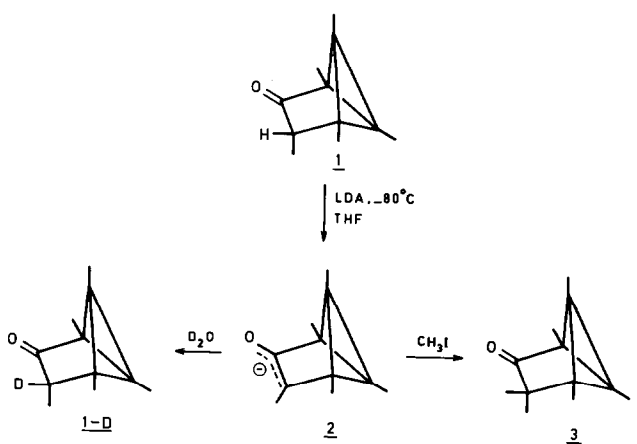
Abstract: Protonation of bicyclobutane bridged enolate anion 2, formed from ketone 1 and lithium (S,S)-α,α'-dimethyldibenzylamide, has yielded optically active ketone 1 (e.e. 48%).

Syntheses and properties of functionalized 2,4-ethano bridged bicyclobutanes have been published in recent years[1] and reports concerning carbenes[2], radicals[3] and cations[4] generated on a position α to the bicyclobutane have appeared. In this preliminary publication we wish to report the formation of anion 2 from racemic ketone 1 using a chiral lithium amide, and the subsequent enantioselective quenching of 2 to regenerate 1 with an enantiomeric excess of 48%.

Anion formation of ketone 1 proved to be difficult because treating an ethereal solution of 1 with a solution of NaOD/D_2O (40%) in the presence of a catalytic amount of tetra (n-butyl) ammonium hydrogen sulfate[5] did not lead to hydrogen-deuterium exchange (20°C, 8 hrs). This may be due to a number of factors, such as steric hindrance or increased strain energy. However, treatment



of ketone 1 with a sixfold excess of lithium diisopropyl amide (LDA) in THF at temperatures below -70°C and quenching with D_2O afforded mixtures of 1 and 1-D in ratios depending on the reaction temperature[6] (Table) (yield ∿70%). Reaction of anion 2 with methyl iodide yielded the permethylated ketone 3[7] (yield 82%).

Inspired by a recent finding[8] of enantioselective protonation we have attempted to prepare optically active ketone 1 by protonating anion 2 with chiral proton donors such as R(-)-mandelic acid, (-)-ephedrine and (-)-menthol, but no optical activity was observed in the product[9]. However, the use of a chiral amide[8,10], viz. lithium (S,S)-α,α'-dimethyldibenzylamide[11], for generating

Table. Formation (1 + LDA) and quenching (D_2O) of anion 2.

Temp. (°C)	Reaction time (hr)	Product ratio[a] 1-D/1
-100	2	0.9 : 1.0
- 90	1	1.0 : 1.0
- 85	3	1.5 : 1.0
- 85	1	1.4 : 1.0
- 75	3	2.9 : 1.0
- 75	2	2.9 : 1.0

a) according to ^{1}H-NMR spectroscopic measurements.

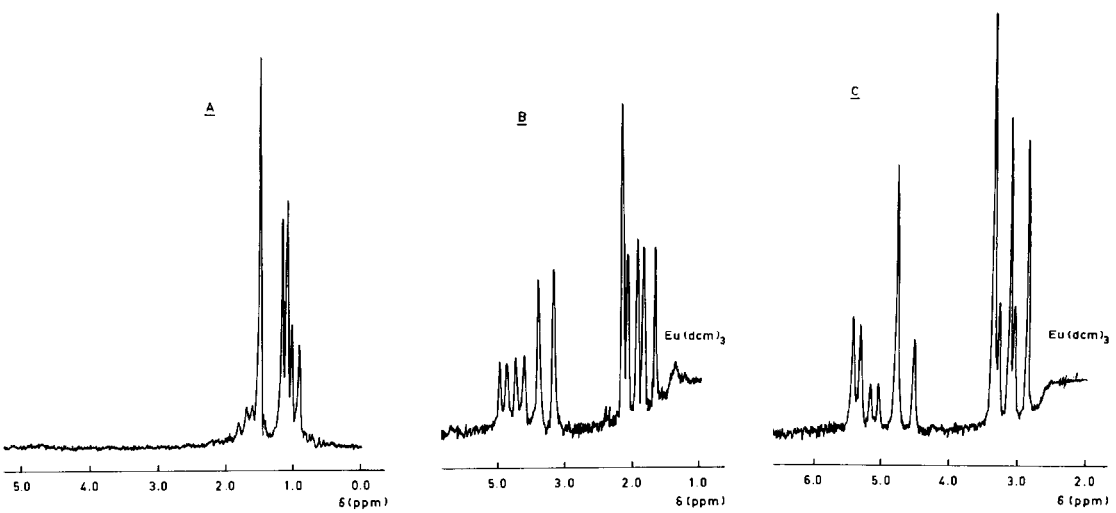
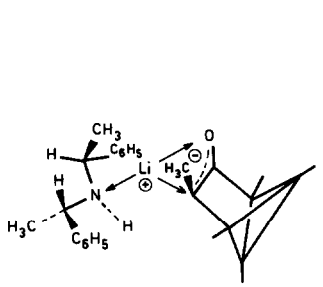


Figure. ^{1}H NMR spectra: A: racemic ketone 1; B: racemic ketone 1 with $Eu(dcm)_3$; C: optically active ketone 1 ($[\alpha]_D^{20} = -73.6°$) with $Eu(dcm)_3$.

anion 2, followed by the reaction with H_2O led to optically active ketone 1, $[\alpha]_D^{20} = -73.6^o$ (c = 2.1, ethanol)[12]. By using the chiral shift reagent Eu(dcm)$_3$[13] it was found that the asymmetric induction had occurred with an e.e. of 48%[14] (See ^{1}H-NMR spectra in Figure).

It is likely that the intermolecular transfer of chirality is due to a multi coordination[15] of the lithium atom involving diastereomeric complexes of type 4 and 5. Because of the interference of two methyl groups in 5 during rotation around the N-Li bond the former complex (4) is slightly favored. An equilibrium between both complexes is shifted to 4 and by consequence protonation yields an excess of one of the enantiomers. We are at present actively engaged in extending this principle of asymmetric induction to other substrates as well as to other reactions involving carbanions.



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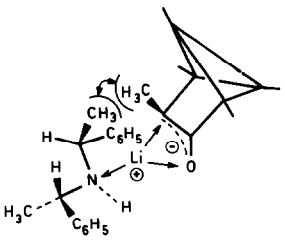

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References and Notes

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4. C. Giordano, R.F. Heldeweg and H. Hogeveen, J. Am. Chem. Soc. 99, 5181 (1977); R.F. Heldeweg, H. Hogeveen and L. Zwart, Tetrahedron Lett. 2535 (1977).
5. W.P. Weber and G.W. Gokel: "Phase Transfer Catalysis in Organic Synthesis", Springer-Verlag, Heidelberg, 1977.
6. At temperatures above -70^o rearrangement of the tricyclic skeleton was observed.
7. Spectroscopic data for 3. I.R. 1730 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 0.81 (s, 6H), 1.02 (broad s, 6H), 1.41 (s, 6H); ^{13}C NMR ($CDCl_3$): 3.1 ($2CH_3$), 4.3 (CH_3), 5.7 (CH_3), 19.8 ($2CH_3$), 28.2 (2C), 43.2 (C), 44.4 (C), 50.6 (C), 221.8 (C=O) ppm; MS exact mass at m/e 178.135 (calc. for $C_{12}H_{18}O$ 178.136).

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9. In the case of (-)-menthol we were unable to separate the reaction mixture obtained, and the results remain inconclusive.

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11. The chiral amine, used as precursor for the amide was prepared as described by C.G. Overberger, N.P. Marullo and R.G. Hiskey, J. Am. Chem. Soc. 83, 1374 (1961). These authors asssumed (-)-1-phenylethylamine to have the R configuration; however, according to J.J.C. Gros and S. Bourcier ("Absolute Configurations", Volume 4 of "Stereochemistry, Fundamentals and Methods", Ed. H.B. Kagan, Thieme, Stuttgart, 1977) (-)-1-phenylethylamine has the S configuration. The obtained α,α'-dimethyldibenzylamine (S,S + 14% R,S) exhibited a rotation of $[\alpha]_D^{20} = -120^o$ (c = 1.8, ethanol). It was easily converted into the lithium salt by treatment with one equiv. of n-butyllithium at -40^oC (30 min.).

12. 260 mg (1.6 mmol) of 1 in 5 mL THF was added under a nitrogen atmosphere to 6.4 mmol of lithium (S,S)-α,α'-dimethyldibenzylamide in 35 ml THF/n-hexane (6:1 v/v) at -90^oC and stirred for 2 hrs at -75^oC. Quenching with water and work-up (pentane/water extraction) afforded a mixture of 1 and (S,S)-α,α'-dimethyldibenzylamine. Repeated short path distillation (40^oC/ 0.03 mm) afforded 165 mgr (60%) of optically active ketone 1, the absolute configuration of which is unknown.

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14. This is a minimum value because the amide used still contained about 14% of the meso-isomer and moreover the anion 2 may not have been completely formed (See text and Table).

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