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## Base-Induced Rearrangements of Bicyclo[2.2.1] and Bicyclo[2.2.2]alkene-Derived Epoxides to Ketones and Alcohols

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Abstract: Previously unreported base-induced transformations of rigid bicycloalkene-derived epoxides (4, 8, and 16) are described, providing insight into the rearrangement mechanisms which operate following  $\alpha$ -lithiation in such systems. © 1997, Elsevier Science Ltd. All rights reserved.

Base-induced rearrangements of epoxides are attracting increasing interest.<sup>1,2</sup> Here we communicate our preliminary results concerning an examination of the  $\alpha$ -deprotonation-rearrangement chemistry of some rigid, bicycloalkene-derived epoxides. Our study builds on earlier work<sup>1</sup> to provide significant additional insight into the factors which influence product outcome in such systems.

Crandall originally reported the reaction of *exo*-norbornene oxide 1 with LiNEt<sub>2</sub> in refluxing benzene to give nortricyclanol 3 (55%, Eq. 1).<sup>1</sup> However, under similar conditions, Crandall and co-workers observed that *endo*-bornylene oxide gives a crude mixture (79%) of camphor, epicamphor and two tricyclanols [ketones: tricyclanols, 3:1 (1.5:1 at room temperature)].<sup>1</sup> In order to make a direct comparison of the effect of epoxide stereochemistry on product outcome, we individually treated *exo*-norbornene oxide 1 and *endo*-norbornene oxide 4<sup>3</sup> with LDA (2.5 equivs.) in Et<sub>2</sub>O at 0 °C for 16 h to give nortricyclanol 3 (90%, no norcamphor 7 observed) and a mixture of norcamphor 7 (55%) and nortricyclanol 3 (14%, 7:3, 4:1 by <sup>1</sup>H nmr analysis of the crude product mixture, Eq. 2) respectively.<sup>4</sup> We suggest that for lithiated *exo*-norbornene oxide 2 transannular C-H insertion proceeds readily as hydride migration is able to assist the breaking of the C-O bond (by attack at the C-O  $\sigma^*$  orbital). In contrast, lithiated *endo*-norbornene oxide 5 proceeds to carbene 6 which then partitions between (mainly) insertion into the adjacent LiOC-H bond to give the enolate of norcamphor 7 and transannular C-H insertion to give nortricyclanol 3.

We also examined the reaction of exo, exo-norbornadiene diepoxide 8<sup>5</sup> with LDA (2.5 equivs.) at 0 °C for 16 h which gave *meso*-nortricyclandiol 11<sup>6</sup> (56%, Eq. 3). In this case, as with *exo*-norbornene oxide 1, hydride migration may assist transannular C-H insertion from the presumed first-formed lithiated intermediate 9. However, rather than leading to a highly strained cyclopropyl containing spiro-epoxide, subsequent (or nearly concerted) rupture of the remaining epoxide ring could generate a cyclopropyl cation 10, which then undergoes reduction by LDA.



Crandall and co-workers also reported the rearrangement of bicyclo[2.2.2]octene oxide 12 to give mainly bicyclo[2.2.2]octanone 14 (Eq. 4).<sup>1</sup> This result indicates that, aside from epoxide stereochemistry, the propensity for transannular C-H insertion is very sensitive to the distance between the lithiated epoxide and transannular C-H bonds. However, we find that reaction of structurally related mono-epoxide 16<sup>7</sup> with LDA (2.5 equivs.) in Et<sub>2</sub>O at reflux for 16 h gives a mixture of ketone 17<sup>8</sup> (29%) and (mainly) alcohol 18<sup>9</sup> [55%, 17:18, 0.7:1 by <sup>1</sup>H nmr analysis of the crude product mixture (0.5:1 at -10 °C), Eq. 5]. The double bond in mono-epoxide 16 may promote C-H insertion by  $\pi$ - C-H  $\sigma$ \* orbital overlap in the lithiated epoxide (and/or at the carbene stage); bicyclo[2.2.2]octene oxide 12, which lacks such a promoting effect, proceeds entirely to carbene 13 which then partitions between (mainly) insertion into the adjacent LiOC-H bond resulting in the enolate of ketone 14, and transannular C-H insertion (exclusively<sup>1</sup> *cis* to OLi) to give alcohol 15 (Eq. 4).



In summary, in the LDA-induced transformations of bicycloalkene-derived epoxides (a) the first direct comparison of the effects of epoxide stereochemistry have been examined: in the norbornyl system the results are consistent with concerted transannular rearrangement under stereoelectronic control for *exo*-norbornene oxide 1, and rearrangement first to a carbene for *endo*-norbornene oxide 4; (b) with *exo,exo*-norbornadiene diepoxide 8 a novel rearrangement-concomitant reduction process has been observed; and (c) the presence of a double bond in bicyclo[2.2.2]octyl systems such as 16 results in transannular C-H insertion as the dominant reaction pathway.

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## REFERENCES AND NOTES

- 1. Crandall, J. K.; Apparu, M. Org. React. (N. Y.) 1983, 29, 345-443; Satoh, T. Chem. Rev. 1996, 96, 3303-3325.
- 2. Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. Tetrahedron 1996, 52, 14361-14384.
- 3. Zefirov, N. S.; Kasyan, L. I.; Gnedenkov, L. Y.; Shashkov, A. S. Cherepanova, E. G. Tetrahedron Lett. 1979, 949-950.
- 4. Isolated total yields of chromatographically homogeneous spectroscopically pure products are reported.
- 5. Murray, R. W.; Pillay, M. K.; Jeyaraman, R. J. Org. Chem. 1988, 53, 3007-3011.
- 6. Chizkov, A. O.; Zefirov, N. S.; Zyk, N. V.; Morrill, T. C. J. Org. Chem. 1987, 52, 5647-5655.
- Mono-epoxide 16 [cis:trans (epoxide to alkene), 94:6] was prepared from bicyclo[2.2.2]octadiene (Williams, R. V.; Chauhan, K.; Gadgil, V. J. J. Chem. Soc., Chem. Commun. 1994, 1739-1740) by epoxidation [MeCO<sub>3</sub>H (1.1 equivs.), Na<sub>2</sub>CO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to 25 °C, 16 h, 76%].
- 8. Evans, D. A.; Golob, A. M.; Mandel, N. S.; Mandel, G. S. J. Am. Chem. Soc. 1978, 100, 8170-8174.
- 9. The structure of alcohol 18 was determined by X-ray crystallographic analysis of the corresponding 3,5-dinitrobenzoate. Full details will be reported at a later date.

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