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REGIO- AND STEREOSELECTIVE EPOXIDATION OF CHIRAL 1,4-CYCLOHEXADIENES

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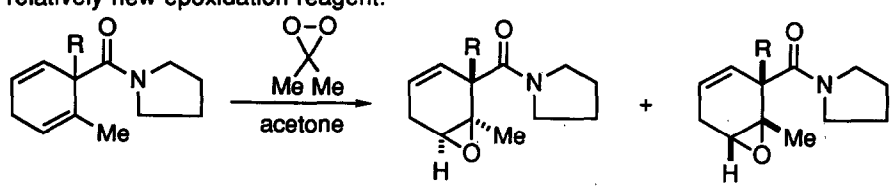
Abstract: The diastereoselectivities of epoxidations of diene amides **1b**, **7**, and **9** appear to depend on steric approach control with the involvement of amide conformers analogous to that observed by X-ray diffraction studies of epoxide **8** (Figure 1). This mechanistic framework should be useful for predicting the reactivity of diene amides related to **7** with other electrophilic reagents.

In connection with a project directed at the development of methods for asymmetric synthesis of chiral cyclohexanes,[1] we examined the epoxidation of 1,4-cyclohexadienes prepared from alkali metal in ammonia reduction and reduction-alkylation of 2-methyl- and 2-methoxybenzoic esters and benzamides. We selected dimethyldioxirane (DMDO)[2] as the reagent for study because of the anticipated sensitivity of products (e.g., **10**) to acid-catalyzed rearrangements. The chemistry described herein provides a useful method for the stereoselective preparation of 1,4-cyclohexadiene monoepoxides and also further defines the reactivity of DMDO. Reactivity data for DMDO are of interest because of the reported electrophilic,[3] nucleophilic,[4] and radical[5] character of this relatively new epoxidation reagent.



1a, R = H
b, R = Me

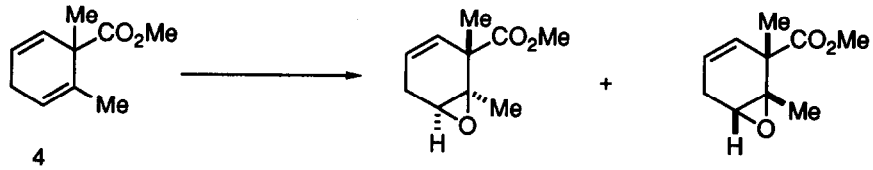
2a, 39%
b, 76%

3a, 27%
b

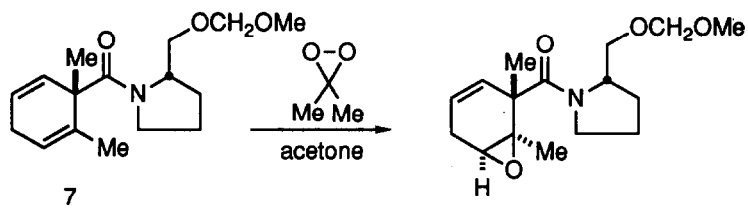
Reaction of diene amide **1a** in acetone and aqueous phosphate buffer solution (pH = 7.2) with DMDO gave a mixture of two epoxides, **2a** (39% isolated yield) and **3a** (27%). An ^1H NMR spectrum of the reaction mixture before flash chromatography on silica gel indicated that products resulting from allylic oxidation or epoxidation of the disubstituted double bond were not present. DMDO was generated in situ by addition of an aqueous solution of potassium peroxymonosulfate to the substrate at 0 °C. Excesses of potassium peroxymonosulfate (3 to 4 equiv) generated significant quantities of products of diepoxidation.

Epoxidation of diene amide **1b** occurred with higher stereoselectivity to give a mixture of **2b** and **3b** (7:1); flash chromatography on silica gel provided **2b** in 76% yield, but the minor isomer, **3b**, could not be obtained free of **2b**. It is noteworthy that m-chloroperbenzoic acid epoxidation of **1b** in CH_2Cl_2 gave a 7.3:1 mixture of **2b** and **3b**, from which **2b** was isolated in 78% yield.

Steric effects of the amide group appear to be responsible for the stereoselectivity observed for **1b** (vide infra). The smaller methyl ester substituent is ineffective at stereodirection; epoxidation of **4** with DMDO gives **5** and **6** in a ratio of 1.6:1, although MCPBA gives somewhat better stereocontrol (3.3:1).



DMDO shows excellent diastereoselectivity for epoxidation of the (*S*)-prolinol derived benzamide **7**; the highly crystalline monoepoxide **8** was obtained in 68% yield. ^1H NMR spectra taken before chromatographic isolation indicated that **8** had formed with >13:1 diastereoselectivity. An X-ray determined molecular structure for **8** is shown in Figure 1. This determination provides an important confirmation of the stereoselectivity for reduction-methylation of chiral 2-methyl-benzamides, originally deduced by chemical interconversions and comparisons of optical rotations.[6]



The molecular structure shown in Figure 1 clearly demonstrates the importance of the amide group[7] in directing epoxidation to the distal face of the diene unit in **1b** and **7**.[8] Without angular methyl substitution (e.g., **1a**) poor diastereoselectivity is obtained because the more stable conformation of the amide linkage has the carbonyl group rotated by 180° about the bond to the cyclohexadiene ring (cf., Figure 1). This arrangement exposes both faces of the diene unit to attack by the epoxidation reagent. A methyl ester group with the more stable Z-geometry would be

expected to exert less control over the facial selectivity of the epoxidation reagent as was observed for the conversion of **4** to **5** and **6**.

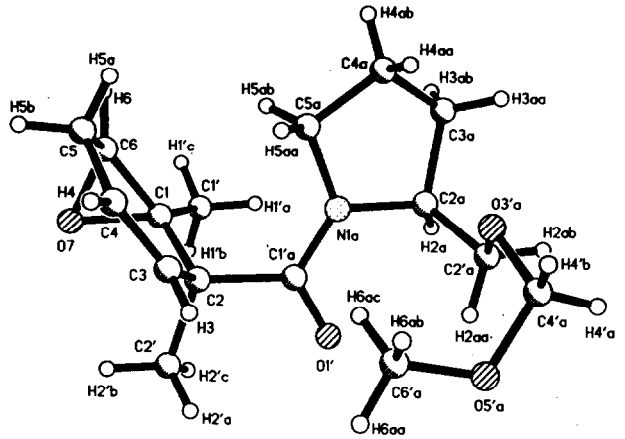
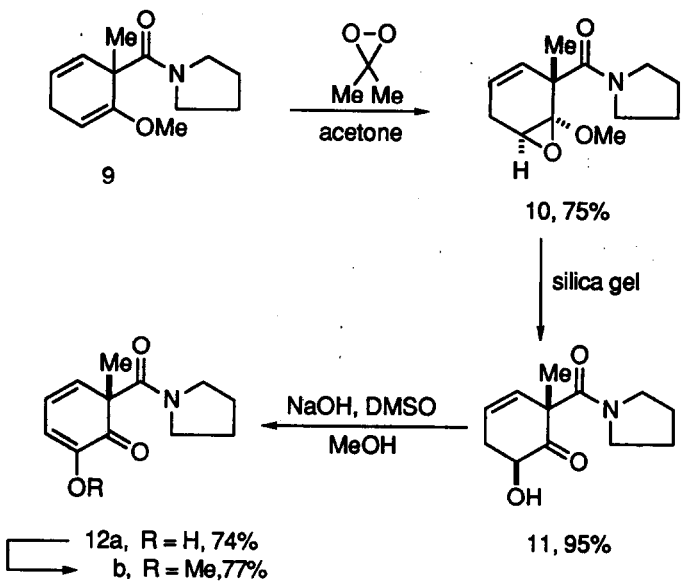


Figure 1. Molecular Structure of **8**

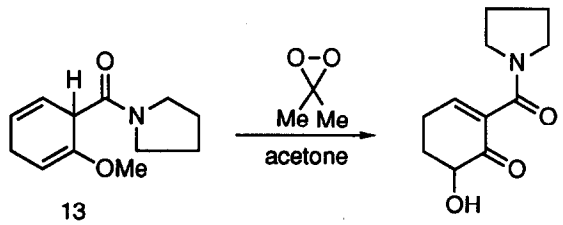
Enol ether **9** also is epoxidized with excellent diastereoselectivity (Scheme I).[9] On treatment with silica gel, **10** rearranges to **11** in nearly quantitative yield. The relative configuration in **11** is tentatively assigned as shown on the basis of a presumed acid-catalyzed mechanism for the opening of epoxide **10**. Hydroxyketone **11** is converted to 2-hydroxy-2,4-cyclohexadien-1-one

Scheme I



12a by the utilization of Grieco's method for oxidation of α-hydroxyketones.[10] Methylation of **12a** (NaH, THF, MeI) provides **12b**, thus demonstrating a new option for preparation of this important class of cyclohexadienones.[11]

Application of the epoxidation methodology to enol ether **13** resulted in the isolation of 6-hydroxy-2-cyclohexen-1-one **14**. Substrates such as **14** containing a chiral amide linkage should be of value in asymmetric conjugation additions.[12,13]



13 14, 77%

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References and Notes

1. Schultz, A. G. *Acc. Chem. Res.* **1990**, *23*, 207.
2. (a) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205. (b) Murry, R. W.; Rajadhyksha, S. N.; Mohan, L. *J. Org. Chem.* **1989**, *54*, 5783.
3. Cicala, G.; Curci, R.; Fiorentino, M.; Laricchivta, O. *J. Org. Chem.* **1982**, *47*, 2670.
4. Adam, W.; Hadjiarapoglov, L.; Nestler, B. *Tetrahedron Lett.* **1990**, *31*, 331.
5. (a) Murray, R. W.; Jeyaraman, R.; Mohan, L. *J. Am. Chem. Soc.* **1986**, *108*, 2470. (b) Baumstark, A. L.; Beeson, M.; Vasquez, P. C. *Tetrahedron Lett.* **1989**, *30*, 5567.
6. Schultz, A. G.; Macielag, M.; Sundararaman, P.; Taveras, A. G.; Welch, M. *J. Am. Chem. Soc.* **1988**, *110*, 7828.
7. An orientation of the carbonyl group identical to that in **8** with the dipole pointing away from the cyclohexadiene ring has been observed from X-ray crystallographic studies of 2,5-cyclohexadien-1-ones with 4-carboxamido and methyl ester substitution; see: (a) Schultz, A. G.; Taveras, A. G.; Taylor, R. E.; Tham, F. S.; Kullnig, R. K. (manuscript submitted for review). (b) Schultz, A. G.; Harrington, R. E. *J. Org. Chem.* **1991**, *56*, 6391.
8. Theoretical calculations have shown that there is no difference in energy between spiro and planar transition structures for transfer of oxygen from dioxirane to ethylene; see: Bach, R. D.; Owensby, A. L.; Andrés, J. L.; Schlegel, H. B. *J. Am. Chem. Soc.* **1991**, *113*, 7031.
9. For prior examples of epoxidation of enol alkyl ethers and silyl enol ethers with dimethyldioxirane, see: (a) Baertschi, S. W.; Raney, K. D.; Stone, M. P.; Harris, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 7929. (b) Troisi, L.; Cassidei, L.; Lopez, L.; Mello, R.; Curci, R. *Tetrahedron Lett.* **1989**, *30*, 259. (c) Chenault, H. K.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 4249.
10. Grieco, P. A.; Ferriño, S.; Vidari, G.; Huffman, J. C. *J. Org. Chem.* **1981**, *46*, 1022.
11. (a) Schultz, A. G.; Dittami, J. P.; Lavieri, F. P.; Salowey, C.; Sundararaman, P.; Szymula, M. B. *J. Org. Chem.* **1984**, *49*, 4429. (b) Schultz, A. G.; Puig, S. *J. Org. Chem.* **1985**, *50*, 915.
12. Schultz, A. G.; Harrington, R. E. *J. Am. Chem. Soc.* **1991**, *113*, 4926.
13. Satisfactory combustion analyses were obtained for all new compounds reported, except **3b** and **14**.

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