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RING OPENING REACTIONS OF DELTACYCLENE EPOXIDES

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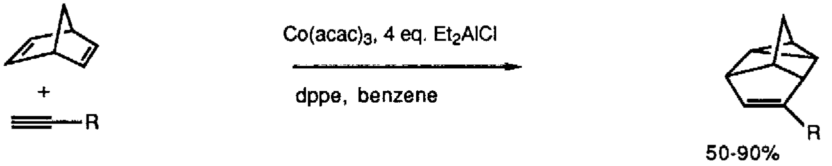
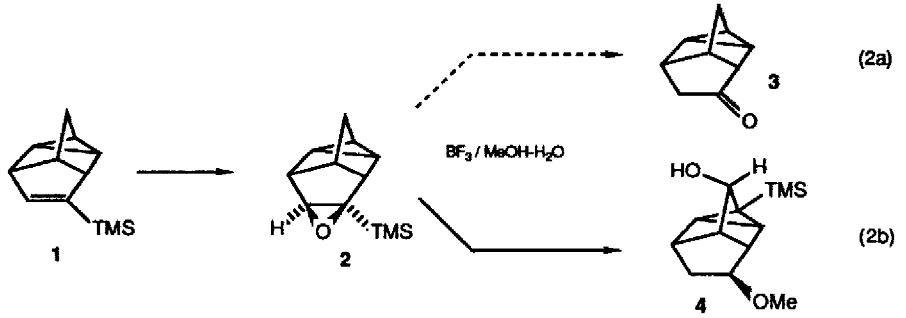
Abstract: A series of epoxides from reaction of substituted deltacyclenes with *meta*-chloroperbenzoic acid are reported. These compounds were found to react with $BF_3 \cdot Et_2O$ in $MeOH/H_2O$ to yield ring-opened products. Rearrangements were noted in some cases depending on the substitution pattern.

We have been interested in determining the utility of the homo-Diels Alder cycloaddition as a means of preparing natural and unnatural products.[2,3] This reaction is represented by the coupling of a substituted acetylene with norbornadiene(NBD) to yield a deltacyclene (eq. 1). We have recently shown that an activated cobalt complex is an effective catalyst for promoting this cycloaddition. The catalyst is prepared by *in situ* reduction of azeotropically dried $Co(acac)_3$ with Et_2AlCl in the presence of one equivalent of 1,2-bis(diphenylphosphino)ethane (dppe). Cycloaddition occurs readily between NBD and a wide range of acetylenes[2,4] including several sterically hindered acetylenes and alkyl acetylenes bearing remote oxygen functionality. In this letter we decribe the behavior of the epoxides derived from the deltacyclenes in the presence of $BF_3 \cdot Et_2O$.[5]

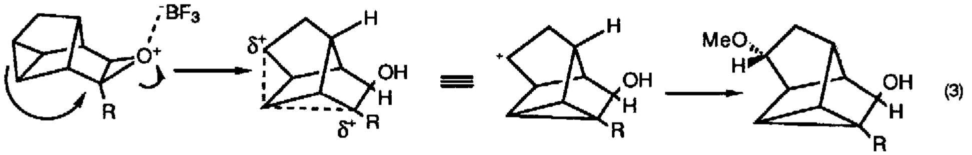


(1)

The cycloaddition product **1**, prepared by reaction of NBD with trimethylsilylacetylene (TMSA) in the presence of the cobalt catalyst, was reacted with MCPBA in a two phase mixture[6] to provide a single epoxide, **2**, in ca. 90% yield.[7] When epoxide **2** was treated with an aqueous methanolic solution of boron trifluoride etherate or perchloric acid, an oil was isolated in 60-75% yield. Acid catalyzed ring opening of epoxysilanes is known to yield ketones or dihydroxysilanes.[8] It was clear from the IR spectrum that ketone **3** had not been produced (eq. 2a). Analysis of the spectroscopic data (^1H NMR, COSY, HETCOR)[9] indicated that the presence of a methoxy, hydroxy and trimethylsilyl function each on a different carbon atom and thus simple ring opening followed by trapping had not taken place. Instead, the rearranged alcohol **4** was formed (eq. 2b). A single example of this type of rearrangement was observed by Coates.[10,11]



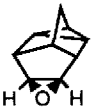
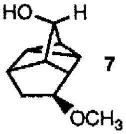
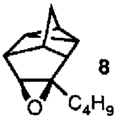
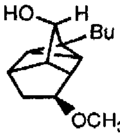
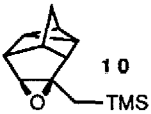
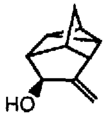
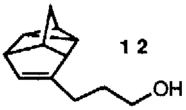
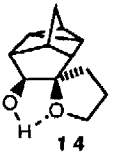
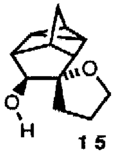
In order to probe the structural features necessary to observe rearrangement, a series of deltacyclene epoxides were prepared by the cycloaddition/epoxidation sequence and their behaviour in the presence of BF$_3$·Et$_2$O was examined (see Table). The unsubstituted epoxide **6** reacted to provide the hydroxyether **7** in 75% yield. A low yielding rearrangement has been reported upon treatment of **6** with HBr or HOAc.[10] Similarly, the alkyl substituted epoxide **8** rearranged to **9** in 80% yield. All three substrates appear to rearrange by the same mechanism through assistance by the cyclopropane bond (eq. 3). The site of ring opening in **8** is that carbon which is best able to bear a positive charge. In epoxysilane **2**, attack at the carbon bearing silicon is observed inspite of the stability of β-silyl cations. The regiochemistry of ring opening in epoxysilanes by other nucleophiles follows this same pattern.[12]



Rearrangement is not the only process possible in these systems. Cycloaddition of propargyltrimethylsilane with norbornadiene yielded a deltacyclene containing an allyl silane (eq. 1, R=CH$_2$TMS). Epoxidation under the usual conditions gave the desilylated allylic alcohol **11** along with the expected product **10**.[12, 13] Treatment with BF$_3$·Et$_2$O gave **11** as the only isolable product. In this instance, opening of the epoxide to generate a β-cation followed by attack of methanol at silicon with loss of the trimethylsilyl group is more facile than rearrangement.

Epoxidation of the TBDMS ether of **12** also gave a single stereoisomeric epoxide. However, standard conditions for the deprotection of the silylether (i.e. Bu$_4$NF or HF in aq. acetonitrile) yielded complex mixtures of products. Therefore, the silylether was first cleaved with Bu$_4$NF in THF and **12** was subjected to the usual epoxidation conditions. The corresponding epoxide was not observed. In the presence of the nucleophilic hydroxyl group and traces of acid, the epoxide had reacted to yield hydroxyfurans **13** and **14**. The stereochemistry at the spiro carbon was determined by an IR dilution study.[14] The major isomer has the two oxygen atoms in a 1,2-*syn* orientation which forms an intramolecular hydrogen bond. Participation of the cyclopropane bond blocks the endo face of the carbonium ion leading to net retention of configuration at C-8. The reactivity of the deltacyclane epoxides is clearly very high.

Table $BF_3 \cdot Et_2O$ Catalyzed Reaction of Deltacyclene Epoxides

Entry	Deltacyclene/Epoxide[1]	Time	Product[2]	Yield[3]
1	 6	1 h	 7	75%
2	 8	1 h	 9	80%
3	 1 0	12 h	 1 1	28%
4	 1 2	4 h	 1 4  1 5 5 : 1	78%[4]

1. Deltacyclenes prepared using method described in ref. 2., Epoxides prepared by reacting deltacyclene with MCPBA in CH_2Cl_2/0.5 M aq. $NaHCO_3$ ref.7. 2. $BF_3 \cdot Et_2O$ (8 eq.) was dissolved in MeOH (5 mL) and 4 drops of water were added. The epoxide (0.5 mmol) was added as a solution in MeOH (2 mL) and the reaction stirred at room temperature for the indicated time. 3. Yield after flash chromatography or distillation. 4. Epoxide was not isolated, see text.

The facility of the rearrangement appears to be very high with a variety of substituents on the epoxide. In those cases where an exceptional leaving group is present or there is an internal nucleophile the rearrangement reaction is unable to compete. Studies are presently underway to demonstrate the utility of this rearrangement in natural product synthesis, the results of which will be reported in due course.

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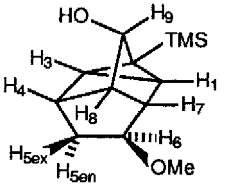
References and Notes

1. NSERC(Canada) University Research Fellow 1987-1992.
2. Lautens, M.; Crudden, C.M. submitted for publication.

3. This reaction has been studied extensively a) Cookson, R.C.; Dance, J.; Hudec, J. *J. Chem. Soc.***1964**, 5416. b) Schrauzer, G.N.; Eichler, S. *Chem. Ber.* **1962**, 95, 2764. c) Blomquist, A.T.; Meinwald, Y.C. *J. Am. Chem. Soc.* **1959**, 81, 667. d) Schrauzer, G.N. *Adv. Catal.* **1968**, 18, 373 and references therein.
4. The first use of this catalyst system to promote the homo Diels Alder reaction was reported by; a) Lyons, J.E.; Myers, H.K. Schneider, A. *J. Chem. Soc., Chem. Comm.* **1978**, 636. b) *idem, ibid*, 638; *idem*, "Transition Metal Mediated Organic Synthesis" *Ann. N.Y. Acad. Sci.* **1980**, 333, 273. Slocum, D.W.; Hughes, O.R. Eds. The yields reported in their work are all <45%. By azeotropically drying the Co(acac)$_3$, we have expanded the scope of this reaction and obtained synthetically useful yields (60-95%), ref. 2.
5. The only related studies we are aware of are those carried out by Coates in a reaction of deltacylcene epoxide with acetic acid, see ref. 10.
6. Anderson, W. K.; Veysoglu, T. *J. Org. Chem.*, **1973**, 38, 2267.
7. Satisfactory NMR, IR, and mass spectra and/or combustion analyses were obtained for all new compounds. The epoxides were characterized spectroscopically but due to their high sensitivity to toward silica gel they were used directly in the next step without further purification.
8. a) Stork, G.; Colvin, E. *J. Am Chem. Soc.* **1971**, 93, 2080. b) Stork, G.; Jung, M.E. *J. Am Chem. Soc.* **1974**, 96, 3682. c) Boeckman Jr., R. K.; Bruza, K.J. *J. Org. Chem.* **1979**, 44, 4781.
9. ^{13}C NMR (off resonance decoupled): 83.2(CH), 80.9(CH), 56.3(CH$_3$), 46.9(CH), 45.1(CH), 40.7(CH), 36.6(CH$_2$), 20.9(CH), 19.4(C), 19.3(CH), -1.8(CH$_3$); ^{1}H NMR: 4.10 (1H, H$_9$, d, J=6.3 Hz), 3.49 (1H, H$_6$, dd, J=2.5, 6.5 Hz), 3.23 (3H, OMe, s), 2.46 (1H, H$_4$, m), 2.20 (1H, H$_7$, m), 2.09 (1H, H$_{5ex}$ dd, J=6.5, 13.1 Hz), 1.94 (1H, H$_8$, m), 1.53 (1H, H$_{5en}$, dt, J=2.5, 13.1Hz), 1.05 (1H, H$_3$, d, J=5.5Hz), 0.83 (1H, H$_1$, d, J=5.5Hz), 0.02 (9H, s).



10. Coates, R.M.; Kirkpatrick, J.L. *J. Am Chem. Soc.* **1968**, 90, 4162, Coates, R.M.; Kirkpatrick, J.L. *ibid*, **1970**, 92, 4883.
11. Freeman has observed a degenerate rearrangement in the deuteration of deltacyclene, see Freeman, P.K.; Balls, D.M. *Tetrahedron Lett.* **1967**, 437.
12. Colvin, E. "Silicon in Organic Synthesis", pg. 89, Butterworths, London (1981)
13. The poor yield in this example reflects the instability of the epoxysilane toward the reaction and work-up conditions.
14. The major isomer, **14** , had an IR stretch (O-H) at 3475 cm^{-1} which was unaffected by 10-fold dilution. The minor isomer, **15**, had two stretches at 3628 and 3455 cm^{-1} when run as a concentrated solution in CCl$_4$. Upon dilution a single stretch at 3628 cm^{-1} was observed.

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