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Cyclizations Wherein an Epoxide Acts as the Source of Initiation and Termination Steps. Evidence for an Early Transition State in Biomimetic Epoxide Cyclizations

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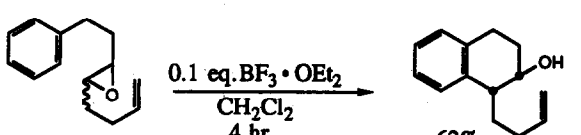
Abstract: Epoxides which can competitively cyclize to either a double bond or aromatic group undergo novel bicyclizations where an epoxide is the source of initiating and terminating groups. The results suggest that biomimetic epoxide cyclizations involve early transition states.

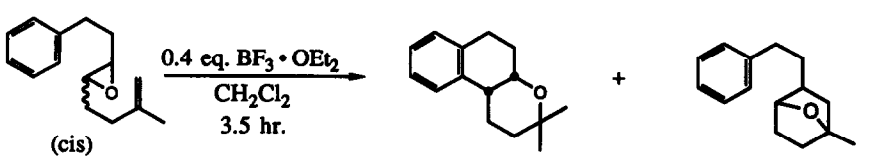
Polyene cyclizations using epoxides as cyclization initiators (epoxy-ene cyclizations) are important because these reactions are related to those involving the biosynthesis of steroids[1,2] and other important natural products.[1,2] These types of reactions have been reviewed recently.[2] A key point of discussion is whether the cyclizations are concerted or stepwise.[2,3]

Polyene cyclizations where a hydroxyl group serves as the terminating group are rare[2,4]: those where an epoxide serves as the initiator and a hydroxyl group serves as the terminator group are even rarer.[4c] We report epoxide bicyclizations where a single epoxide group is the source of both initiation and termination steps. The cyclizations form two rings in a clearly demonstrated stepwise fashion and the process provides evidence that biomimetic cyclizations involve an early transition state.

In earlier work[5] to determine the relative facility of epoxy-ene and epoxy-arene cyclizations, **1** was shown to cyclize to the aromatic position to stereoselectively give **2**. We decided to see if methyl substitution on the double bond (to give **3**) would cause the cyclization pathway to switch to the double bond since cyclization in this case would occur *via* a tertiary cation. Instead of predominant monocyclization to the double bond, we observed mainly a bicycliztion product wherein both functional groups reacted to give **4** (the minor product **5** did form by the former route).

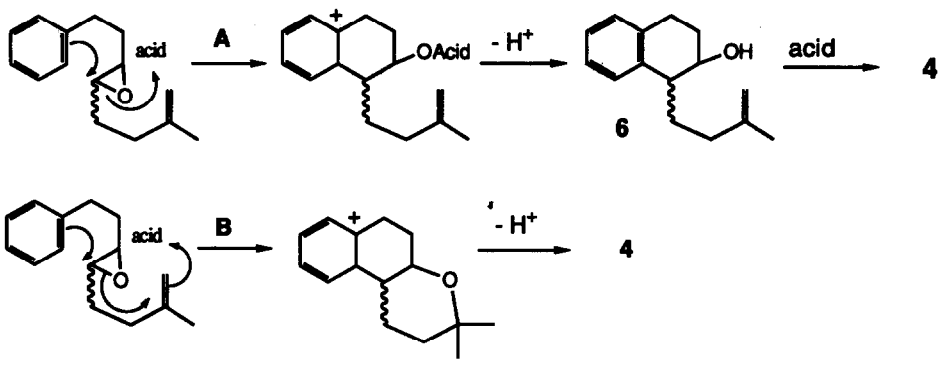


(cis) **1** → **2**, 62% (1)

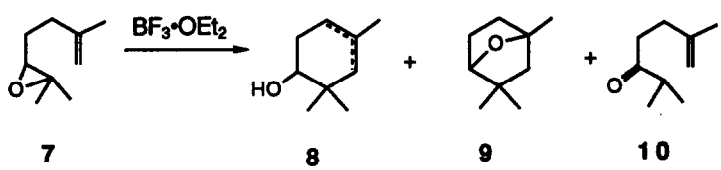


(cis) **3** → **4**, 53% + **5**, 17% (2)

There were two apparent pathways which could lead to **4**. One involved initial protonation to the double bond (pathway B) followed by oxygen bridging and aromatic cyclization.[6] Alternatively, the aromatic cyclization could occur followed by cyclization of the resulting alcohol to the double bond (pathway A). To test which



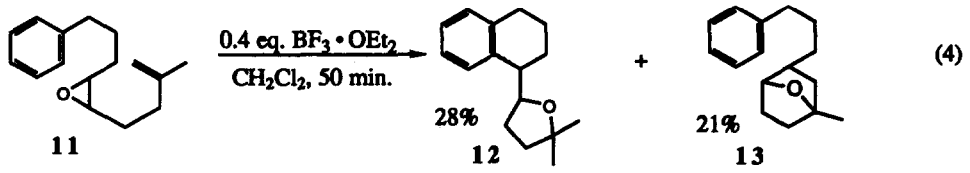
pathway occurred, we followed the reaction by proton NMR. The aromatic region clearly changed prior to any double bond changes, and this supported pathway A. We also prepared **6** independently[7] and subjected it to the reaction conditions. It quickly converted in >90% yield to **4**, also suggesting this reaction is a stepwise process occurring through pathway A. We also could detect **6** in significant quantities if we used the weak Lewis acid $SnCl_4$ or short reaction times using small quantities of BF_3•OEt_2 and short reaction times. The conversion of **6** to **4** using a relatively mild Lewis acid is noteworthy since cyclizations of this type normally utilize strong protonic acids.[2,4] We suspect that some biomimetic cyclizations may have involved this type of reaction, but it has not been demonstrated. To see if an early example involved this process, we repeated reaction 3[8,9] and then isolated and re-subjected product **8** to the reaction conditions to see if product **9** resulted. Under the reaction conditions, it did not form to any significant extent. Therefore, the hydroxyl group needs to be suitably positioned to cyclize to a substituted double bond under these mild conditions.



7 **8** **9** **10** (3)

To be sure that this reaction was not an isolated example, we treated **11** with 0.4 equivalents of BF_3•OEt_2 and found another bicyclization product (**12**) that appears to form by the same pathway. Products **12** and **13** account for 93% of the volatile product distribution.[10] To suppose that the five-membered ring of **12** forms by direct epoxide cyclization is not consistent with the paucity of examples of epoxy-ene cyclizations

that form this ring size or the structure of the product expected to occur by this route.



(4)

The fact that initial double bond cyclization does not predominate is surprising because this pathway could lead to a tertiary cation. The most direct explanation of this observation is that the transition state is early and therefore carbocation stability is not as important as expected. Since this reaction pathway is very similar to that of many biomimetic cyclizations (e.g. equation 3), this supports the idea that biomimetic cyclizations involve early transition states.

In a typical reaction, 71 mg (0.33 mmoles) of **3**[11] in 2 mL of dry methylene chloride was added dropwise under N_2 to 9 μL (0.073 mmoles) of $BF_3 \cdot OEt_2$ in 15 mL of dry methylene chloride. The solution was stirred at room temperature for 3.5 hr. and then it was washed with 5% $NaHCO_3$ and saturated NaCl and dried ($MgSO_4$). The products were purified directly by semipreparative HPLC using a 92:8 mixture of hexane:ethyl acetate (trace of EtOH). The yield of the reaction was determined by external standard using **4** that had been prepared independently. Compound **11** was treated similarly only the reaction time was 50 min. and yields were of isolated, pure compounds. Subsequent reactions were followed by GC and the existence of **6** was verified by GCMS comparison with the authentic sample.

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References and Notes

1. For reviews see: (a) van Tamelen, E. E. *Acc. Chem. Res.* **1968**, *1*, 111. (b) Johnson, W. S. *Bioorg. Chem.* **1976** *5*, 51. (c) Sutherland, J. K. *Chem. Soc. Rev.* **1980**, *9*, 265. (d) Goldsmith, D. *J. Forsch. Chem. Org. Natur.* **1971**,*29*, 363.

2. Taylor, S. K. *Org. Prep. Proc. Int.* **1992**, *24*, 245.

3. Bartlett, P. A. in *Asymmetric Synthesis*; . Morrison, J. D. ed.; Academic Press: New York, 1984; Vol. 3, Chapter 5.

4. (a) Snowden, R.L.; Eichenberger, J.-C.; Linder, S. M.; Sonnay, P.; Vial, C.; Schulte-Elte, K. H. *J. Org. Chem.* **1992**, *57*, 955. (b) Garst, M. E.; Cheung, Y.; Johnson, W. S. *J. Am. Chem. Soc.*, **1979**, *101*, 4404. (c) Sharpless, K. B. *J. Am. Chem. Soc.* **1970**, *92*, 6999.

5. Taylor, S. K.; Bischoff, D. S.; Blankespoor, C. L.; Deck, P. A.; Harvey, S. M.; Johnson, P. L.; Marolweski, A. E.; Mork, S. W.; Motry, D. G.; Van Eenenaam, R. *J. Org. Chem.* **1990**, *55*, 4202 and

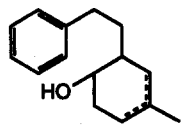
Correction, ibid., **1991**, *56*, 5736.

6. Certain aspects of the mechanism have been written as concerted for conciseness. However, the arrows do not necessarily indicate concerted processes.

7. Prepared from the reaction of the enolate of ß-tetralone and 5-bromo-2-methyl-pentene followed by reduction of the product with $LiAlH_4$.

8. Goldsmith, D. J. *J. Am. Chem. Soc.* **1962**, *84*, 3913 and Goldsmith, D. J.; Cheer, C. J. *J. Org. Chem.* **1965**, *30*, 2264.

9. Products **4** and **5** account for 81% of the volatile product distribution of equation 2. Products analogous to those represented by **8** (see below) in equation 3 account for another 9% as shown by GCMS and an NMR of the mixture of isomers. We were unable to separate these isomers, but they would be expected to accompany **5** based on the precendent reaction in equation 3. There may also be a small amount of product where the double bond has rearranged to the tertiary position.



10. The yields of these products were undoubtedly higher, but these are the yields of pure, isolated compounds. Impure chromatograph fractions containing these comounds were not counted in the yields.

11. The compounds **3** and **11** were prepared by m-CPBA epoxidation of aryldienes prepared by Wittig procedures reported earlier.[5] For example, the Wittig reagent used in the synthesis of **3** was prepared from the phosphonium salt of 1-bromo-3-phenylbenzene and it was combined with 4-methyl-4-pentenal. The resulting aryldiene was epoxidized, yielding two isomeric epoxides in a ratio of approximately 1:1. These isomers were separated by HPLC. Specific Wittig and epoxidation procedures are given in the aforementioned article.

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