Demonstration of a Common Concerted Mechanistic Pathway for the Acid-Catalyzed Cyclization of 5,6-Unsaturated Oxiranes in Chemical and Enzymatic Systems

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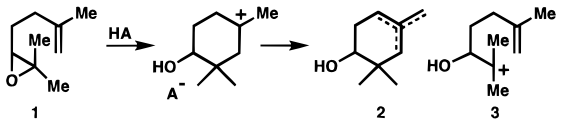
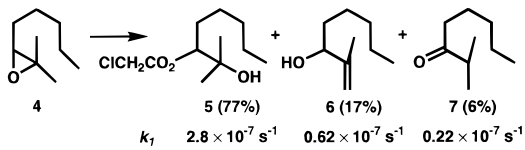
The acid catalyzed cyclization of chiral terminal epoxides of polyprenoids is an extremely powerful synthetic construction which is a key step in sterol and triterpene biosynthesis[1] and also an increasingly useful route for the enantioselective synthesis of a wide variety of polycyclic terpenoids.[2] Although it has recently been demonstrated that in sterol biosynthesis the oxirane cleavage and initial cyclization events are concerted,[1a] the relative timing of the oxirane cleavage and cyclization steps in nonenzymatic cyclization reactions of oxiranes has remained obscure. This paper describes the study of acid-catalyzed monocyclization processes such as **1** → **2** and provides compelling evidence that such reactions proceed via a pathway in which oxirane C−O cleavage and C−C bond formation are *concerted* rather than via discrete carbocations such as **3**.



1 2 3

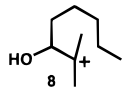
To evaluate the rate and nature of acid-catalyzed non-π-assisted reactions of **1**, the reaction of the saturated analogue **4** was investigated by GC and ^{1}H NMR analysis of kinetics and products. In $CDCl_3$ (or $CHCl_3$) as solvent at 25 °C with $ClCH_2COOH$ as catalyst[3] (0.1 M, 10 equiv), the reaction of **4** followed pseudo first-order kinetics and generated **5**−**7** as products in the indicated amounts and with the indicated dissected pseudo first-order rate constants for product formation. Kinetic measurements at several



4 5 (77%) 6 (17%) 7 (6%)

k_1 2.8×10^{-7} s^{-1} 0.62×10^{-7} s^{-1} 0.22×10^{-7} s^{-1}

different concentrations of $ClCH_2COOH$ showed very clearly that the reaction is *second order* in this acid catalyst, implying that at least **5** and **6** are probably formed by a process in which one molecule activates the oxirane function by hydrogen bonding and another attacks to form **5** by S_N2 displacement or **6** by E2 elimination. The pinacolic rearrangement product **7** arises via cation **8** in a reaction which is *first order* in $ClCH_2CO_2H$,[4] as shown by a study of the product ratio **7**/(**5** + **6**) as a function of acid concentration; no **7** can be detected when the cyclization is conducted at 0.5 M $ClCH_2CO_2H$. Thus, the pseudo-first-order



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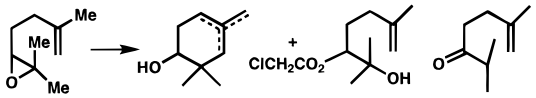
rate constant for the conversion of **4** to **8** is 0.22×10^{-7} s^{-1} at 0.1 M $ClCH_2CO_2H$ and 25 °C. Under these conditions, the substrate **1** reacts to form as the only products **2** and **9** in the amounts and at the rates shown (dissected pseudo-first-order rate constants). (The cyclized product **2** is a mixture of the three possible olefinic isomers, as shown.) None of the pinacolic rearrangement product **10** could be detected by GC analyses. Since

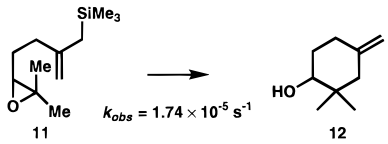


1 2 (52%) 9 (48%) 10 (0%)

k_1 3.3×10^{-7} s^{-1} 3.0×10^{-7} s^{-1}

the rate constant for cyclization of **1** (3.3×10^{-7} s^{-1}) is 15 times the rate constant for formation of the acyclic carbocation **8** from **4**, it follows that the transformation **1** → **2** occurs by a concerted pathway in which nucleophilic participation of the π-electrons of the double bond accelerate oxirane C−O cleavage and not by way of the discrete acyclic carbocation **3**. The absence of the pinacolic rearrangement product **10** in the acid-catalyzed cyclization of **1** also militates against the intermediacy of **3** in the cyclization of **1** to **2**.

The above conclusions were confirmed in a study of the cyclization of **11**, the trimethylsilyl analogue of **1**. In $CDCl_3$ (or $CHCl_3$) at 25 °C using 0.1 M $ClCH_2CO_2H$ (10 equiv) as catalyst, the unsaturated epoxide **11** was converted completely to monocyclic product **12** at a pseudo-first-order rate constant of 174×10^{-7} s^{-1}, indicating powerful nucleophilic assistance by the double bond and a concerted oxirane cleavage−cyclization pathway. The



11 $k_{obs} = 1.74 \times 10^{-5}$ s^{-1} 12

relative rates of cyclization and acyclic carbocation formation in this case must be greater than 800. Examination of literature data on the addition of fully formed carbocations to olefinic substrates

(1) (a) Corey, E. J.; Cheng, H.; Baker, C. H.; Matsuda, S. P. T.; Li, D.; Song, X. *J. Am. Chem. Soc.* **1997**, *119*, 1277. (b) Corey, E. J.; Cheng, H.; Baker, C. H.; Matsuda, S. P. T.; Li, D.; Song, X. *J. Am. Chem. Soc.* **1997**, *119*, 1289. (c) For a recent review, see: Abe, I.; Rohmer, M.; Prestwich, G. D. *Chem. Rev.* **1993**, *93*, 2189.

(2) (a) Corey, E. J.; Roberts, B. E. *Tetrahedron Lett.* **1997**, *38*, 8921. (b) Corey, E. J.; Liu, K. *J. Am. Chem. Soc.* **1997**, *119*, 9929. (c) Corey, E. J.; Luo, G.; Lin, L. S. *J. Am. Chem. Soc.* **1997**, *119*, 9927. (d) Corey, E. J.; Wood, H. B., Jr. *J. Am. Chem. Soc.* **1996**, *118*, 11982. (e) Corey, E. J.; Lin, S. *J. Am. Chem. Soc.* **1996**, *118*, 8765. (f) Corey, E. J.; Lee, J.; Liu, D. R. *Tetrahedron Lett.* **1994**, *35*, 9149. (g) Corey, E. J.; Lee, J. *J. Am. Chem. Soc.* **1993**, *115*, 8873.

(3) Chloroacetic acid was selected for the kinetic and product studies as a mimic of D-456, the essential protic source in lanosterol synthase[1a,1b] and also because it afforded a convenient rate of reaction at 25 °C. The rate of reaction of substrate **1** using acetic acid as catalyst was in comparison very slow at 25 °C, as is consistent with the known acidities (e.g., in H_2O at 25 °C pK_a values are 4.75 and 2.92 for CH_3CO_2H and $ClCH_2CO_2H$). Each of the products of $ClCH_2CO_2H$-catalyzed reactions of oxiranes described in this paper are primary products which remain unchanged under the reaction conditions. Although it is conceivable that the pinacolic product **7** arises by a process in which oxirane cleavage and hydrogen shift are concerted, such a mechanism seems very improbable for stereoelectronic reasons. In addition, were it to occur, the rate of tertiary cation formation would have to be even slower and all arguments made herein would still apply.

(4) The finding that the kinetics for the disappearance of **4** show a second-order dependence on $[ClCH_2CO_2H]$ is not inconsistent with a first-order dependence on $[ClCH_2CO_2H]$ for the formation of the pinacolic product **7** from **4**, since the pathway **4** → **7** represents only 6% of the total reaction; i.e., our experimental data do not allow a distinction between order 2 and 1.94 in $[ClCH_2CO_2H]$.

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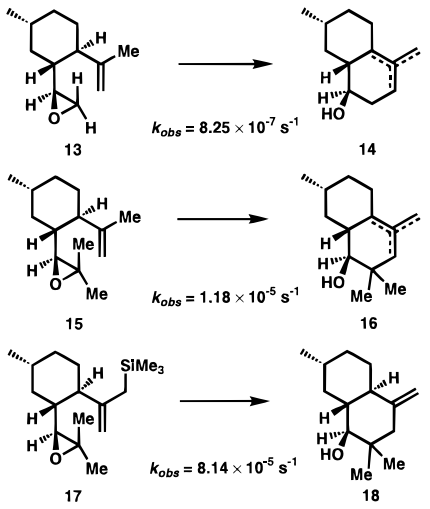
Scheme 1

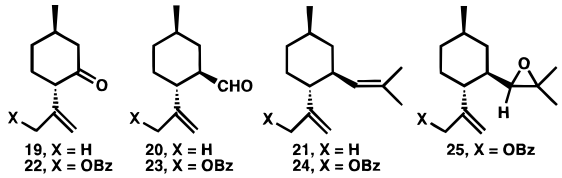


indicates roughly 10^3-fold Me_3Si rate enhancement, considerably greater than the value of 53 which is calculated from the above data for concerted cyclization of **11** relative to **1**.[5]

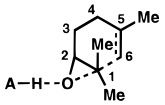
We have also carried out product and kinetic studies with the substrates **13**, **15**, and **17** which are converted to the corresponding cyclization products **14**, **16**, and **18** with the indicated pseudo-first-order rate constants (0.1 M $ClCH_2CO_2H$ in $CDCl_3$ at 25 °C) (Scheme 1). Products **14** and **16** were a mixture of three position isomeric olefins resulting from the three possible modes of proton loss from the intermediate bicyclic carbocation. The rates of reaction of **13**, **15**, and **17** relative to formation of carbocation **8** from **4** provide a measure of the driving force for cyclization: 38 for **13**, 540 for **15**, and 3700 for **17**. The greater driving force for **15** → **16** (540) than for **1** → **2** (15) is readily understood as a consequence of a favorable conformational restriction of **15**, relative to **1**, i.e., a less negative $\Delta S^{\ddagger}$ for **15** than for **1**. The smaller driving force for **13** → **14** relative to **15** → **16** clearly indicates that acid-catalyzed cleavage of the oxirane ring is more difficult in the former case since that involves generation of a partial positive charge at a primary rather than tertiary carbon. In addition, although the trimethylsilyl group in **17** provides additional driving force for cyclization (3700) relative to **15** (540), the difference is only a factor of 7, far from what might have been predicted.[5] Although surprising at first glance, this small acceleration may be due to substantial steric repulsion involving the Me_3Si group during the cyclization of **17** as well as to an early transition state with regard to C−C bond formation.[6]

Parallel studies of substrates **1**, **4**, **13**, and **15** using Cl_3CCO_2H as acid catalyst instead of $ClCH_2CO_2H$ under standard conditions ($CDCl_3$, 25 °C) afforded comparable results, although the individual rate constants were greater, as expected from the greater acidity of Cl_3CCO_2H. The Cl_3CCO_2H induced cyclizations of **4**, **13**, and **15** were each concerted with oxirane C−O cleavage, since rate accelerations due to nucleophilic participation of the olefinic π-electrons were observed in each case.

As described in the Supporting Information, substrate **15** was synthesized from (2*S*,5*R*)−(−)-isopulegone (**19**) via aldehyde **20** and diene **21** (by selective epoxidation of **21**); substrate **13** was synthesized from **20**; and substrate **17** was synthesized from **19** via **22**−**25**.



In conclusion, the results reported herein demonstrate that in the acid-catalyzed cyclization of 5,6-unsaturated oxiranes to form a six-membered ring, the oxirane cleavage and cyclization events are concerted. The cyclization reaction is accelerated by the olefinic linkage in proportion to its π-nucleophilicity. Taken together the experimental data define transition state **26** for the cyclization of **1** in which there is partial positive charge at C(1) and C(5) (considerably less at the latter than the former) and partial cleavage of the O−C(1) bond and partial formation of the C(1)−C(6) bond.[7] Additional driving force results when the



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unsaturated oxirane is conformationally constrained to favor the geometry required for concerted cyclization. Although our studies were carried out with protic acid catalysts, it is most likely that the concerted mechanistic pathway also dominates with Lewis acid catalysts such as $MeAlCl_2$ and Me_2AlCl, which are the optimum reagents (in CH_2Cl_2) for synthetic applications.[2,8] Indeed, one reason for the success of these acid-induced cyclizations of unsaturated epoxides in synthesis is that the acid-coordinated oxirane has sufficient lifetime to allow proper positioning of the nucleophilic double bond and sufficient electrophilic reactivity to induce C−C bond formation.[2] The concertedness of the reaction obviates the intermediacy of an initiating carbocation and associated side reactions such as pinacolic rearrangement and proton loss. In addition, the present results make it understandable that, for enzymatic cyclizations such as the conversion of 2,3-oxidosqualene to lanosterol, optimal folding of the substrate by the enzyme should accelerate cyclization (as well as control stereochemistry) and permit a modestly acidic group such as D456 of lanosterol synthase to serve as an effective activator.[1a] Finally, it is now abundantly clear that further advances in the development of cationic cyclization processes for synthesis will depend on the control of the level of activation in the initiation step and also of substrate conformation.

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Supporting Information Available: Experimental procedures, spectroscopic data for synthetic intermediates and kinetic data (40 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(5) Mayr, H.; Patz, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938.

(6) Examination of HGS stereochemical models for the cyclization of **17** in the conformation allowing maximum delocalization of the C−$SiMe_3$ σ-electrons toward the developing carbocation in the transition state reveals a major steric repulsion between the Me_3Si group and a nearby CH_2 of the preexisting ring.

(7) For a recent theoretical study of transition states for cation-olefin cyclization, see: Jenson, C.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1997**, *119*, 10846.

(8) It is also relevant that these conditions also disfavor S_N2-type oxirane cleavage, since both the catalyst and medium are nonnucleophilic.