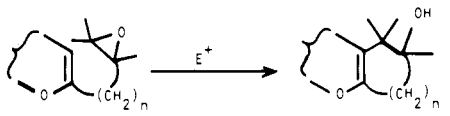
Lewis Acid Induced Cyclization of Vinyl Ether–Epoxides: a New Stereospecific Route to Carbocyclic Ketones and Ketolactones

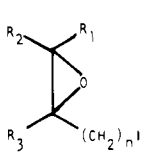
Sir:

Cationic olefin cyclizations have been the object of intense study in a number of laboratories since 1950.[1] These investigations have served to verify, in vitro, the Stork–Eschenmoser hypothesis[2] and resulted in the biomimetic synthesis of a variety of naturally occurring steroids and terpenes.[3,4] The epoxide,[5] among other groups,[6] has been utilized as the trigger for this type of cyclization reaction. However, the range of nucleophilic multiple bonds utilized has been much more limited. Only simple olefins,[7] acetylenes,[8] and chloro olefins[9] have been utilized thus far. Even though it has long been recognized that vinyl ethers are among the most nucleophilic of olefinic bonds,[10] the inaccessibility of suitable substrates has limited the exploration of the reactivity and potential synthetic utility of cyclization reactions of this functional group.[10] The use of a vinyl ether as the nucleophilic component offers the advantage of retaining useful functionality in the cyclization products. We describe now our studies which demonstrate the feasibility and utility of this class of cationic cyclization reactions (eq 1).

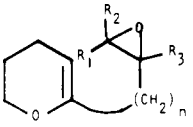


(1)

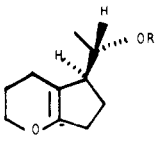
The requisite epoxy vinyl ethers were conveniently prepared by the general procedure described previously.[11] Treatment of 6-lithio-3,4-dihydro-2*H*-pyran with epoxy iodide **2**[12] in



(2) $R_1=R_3=H$, $R_2=CH_3$, $n=2$
(8) $R_1=R_2=CH_3$, $R_3=H$, $n=2$
(14) $R_1=R_2=H$, $R_3=CH_3$, $n=3$



(3) $R_1=R_3=H$, $R_2=CH_3$, $n=2$
(9) $R_1=R_2=CH_3$, $R_3=H$, $n=2$
(13) $R_1=R_2=H$, $R_3=CH_3$, $n=3$
(17) $R_1=R_2=CH_3$, $R_3=H$, $n=1$



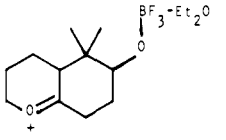
(4) R=H
(5) R=Ac

THF/HMPA (1 equiv)[13] at 0–25 °C (18 h) afforded a 42% (75%) yield of epoxydihydropyran **3**.[14]

We felt that cyclization of **3** would provide a good test of regiochemical tendencies, since the two modes of polarization of the epoxide lead to intermediates of comparable stability. Exposure of **3** to basic Al_2O_3 (activity I) at room temperature in hexane (24 h)[15] afforded, cleanly, a *single* hydroxydihydropyran (**4**)[14] in 90–100% yield. The reaction is entirely regio- and stereospecific as judged from spectral data.[16] Since **4** proved to be sensitive to common methods of purification, it was converted to the acetate **5** (Ac_2O/Py, 0 °C) for further characterization.[16] Treatment of **5** with 7.5% aqueous HCl/THF afforded hemiketal **6** exclusively. **6** was inert to oxidation under acidic conditions (CrO_3/acetone); however, treatment with Collins reagent[17] in CH_2Cl_2 afforded ketoaldehyde **7** (NMR δ 9.67 (t, 1 H), 4.5 (m, 1 H), 2.6–2.4 (m, 5 H), 1.15 (d, 3 H); IR 2900, 1740, 1370, 1245, 1035 cm^{-1})) which confirms the preceding structural assignments. The transformations to **7** also exemplify one of the useful applications of the above cyclization, the preparation of functionalized carbocyclic ketones. The stereospecificity of the process leads in this case to the creation of three contiguous asymmetric centers of definable relative configuration, including one in the acyclic side chain.

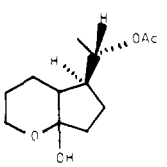
To determine if the cyclization was general, and confirm that regiospecificity is controlled by the usually cited factors related to carbonium ion stability, dihydropyran **9** was prepared as above from epoxy iodide **8**[12] in 53% yield.[14] We had observed during our studies of the cyclization of **3** that other Lewis acids were effective cyclization catalysts (BF_3·Et_2O, $SnCl_4$). In this case, exposure of **9** to BF_3·Et_2O (0.2 equiv) in CH_2Cl_2 (−25 °C, 5 min) afforded dihydropyran **10**[14] (40–50%) as the only detectable dihydropyran regioisomer. This result confirms the expectation that the regiochemistry of the cyclization can be controlled by alteration of the epoxide substitution pattern. The structure of **10** was evident from the NMR spectrum which exhibited two nonequivalent methyl resonances at δ 0.95 and 0.90 and the NMR of the derived acetate **11** (Ac_2O/Py/4-dimethylaminopyridine, 0 °C) which exhibited a triplet at δ 4.83 (-C*H*-OAc).

It is presumed that the intermediate in these processes is an oxonium ion such as **12.** Evidence for this pathway was obtained upon cyclization of epoxydihydropyran **13**[14] obtained as above from iodo epoxide **14**[12] (63%). In this case, it was assumed that regiospecific formation of the geminally substituted dihydropyran **15** would result. Indeed upon cyclization (BF_3·Et_2O/CH_2Cl_2, −25 °C, 5–10 min), **13** afforded **15** (50%),[14] along with a second substance characterized as the tricyclic ketal **16**[14] (25%). **16** presumably arises by intramo-



(12) (15)

lecular trapping of the intermediate oxonium ion by the side-chain hydroxyl. This process does not occur readily in **4** presumably owing to the increased strain in bridging a five-membered ring. A single steroisomer (**16**) is obtained and this substance has been assigned the trans ring junction stereochemistry on the basis of conformational constraints.[18] **16** was found to increase at the expense of **15** on longer exposure to the Lewis acid, and it was subsequently confirmed that **16** is obtained exclusively upon reexposure of **15** to the reaction conditions. An interesting variation of reactivity with catalyst was also encountered. Treatment of **15** with anhydrous $SnCl_4$ affords exclusively **16** in good yield (50%). Apparently $SnCl_4$



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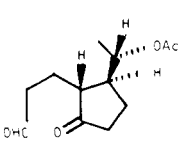

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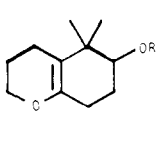
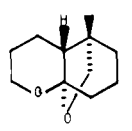


(10) R=H
(11) R=Ac



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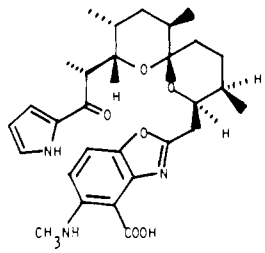
facilitates either direct collapse or subsequent addition across the vinyl ether double bond. The facile preparation of ketals such as **16** suggests applications to the ionophoric antibiotics.[19,20]

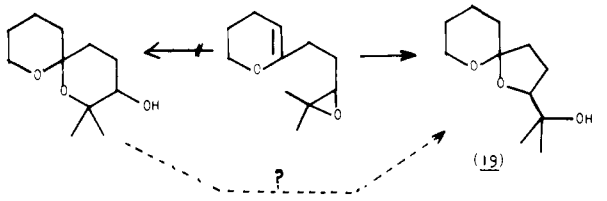
The cyclization is, however, limited by the need to obtain good orbital overlap in the transition state. Dihydropyran **17**, prepared from epoxy dimethylallyl bromide[12] (42%), in preliminary studies has failed to undergo cyclization under the usual conditions. This result may be another example of the disfavored nature of 5-endo-trig processes as defined by Baldwin.[21] We are currently exploring the scope and limitations of the cyclization process including applications to the synthesis of macrocycles and the prostaglandins.

The epoxydihydropyrans, such as **9**, exhibit an *entirely different mode of cyclization* upon exposure to aqueous acid.[22] This process provides another entry into the spirocyclic ketal ring systems found in the ionophoric antibiotics, such as A-23187 (**18**),[19,20] which we hope to exploit.



(18)

Treatment of **9** with 10% HCl/THF affords an ~2:1 mixture of two diastereomeric spirocyclic ketals **19** (NMR δ 3.67 (m, 3H), 2.36–1.33 (m, 11H), 1.27, 1.03 and 1.20, 1.08 (s, 6 H total)) in 60–70% yield. Two modes of closure were possible in principle, the first involving hydration of the vinyl ether and intramolecular cleavage of the epoxide (eq 2). The apparently observed pathway involves complete hydrolysis and reclosure to the presumably more stable system **19.** It is also, of course,

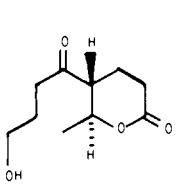


(2)

(19)

possible that the spiro 6,6 system undergoes conversion to the possibly more stable 6,5 system under the reaction conditions. Clearly, rapid assembly of these spirocyclic ketals is possible by suitable alteration of the cyclization conditions.

In terms of synthetic utility, the cyclization products themselves serve as valuable intermediates. Tetrahydrochromanes and related systems have previously been demonstrated to be cleaved oxidatively to ketolactones with MCPBA.[23] However, we have found this method to lack generality and to provide low yields of the desired ketolactones. We have extended early studies with singlet oxygen,[24] and the use of this reagent appears to be the method of choice for this cleavage. In spite of the enhanced possibility of competing ene processes in the more highly substituted vinyl ether,[25] treatment of **4** with $^1O_2$ (10–15 °C, CH_3CN/Rose Bengal) afforded the intermediate dioxetane.[26] No evidence of any hydroperoxide (resulting from ene processes) could be found by a sensitive peroxide test.[27] Decomposition of the dioxetane at 70 °C, however, did not give the desired medium-ring lactone but rather δ-lactone **20** resulting from intramolecular transesterification.[28] This problem could be circumvented by protection of the hydroxyl. Treatment of acetate **5** with singlet oxygen as above affords the desired ketooctalide **21** (mp 39–41 °C) in 56%



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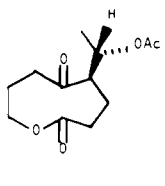

(21)

yield.[14] This cleavage method has proven to be general and yields of 50–70% have been obtained for several related examples.[29] The cyclization–cleavage sequence then provides a facile route to the difficultly accessible medium-ring lactones[30] with the possibility of inclusion of stereocenters when required. We are currently exploring the extension of this process to the larger rings required for an approach to the natural macrolides.[31]

Acknowledgment. We thank the National Institutes of Health for a research grant in partial support of this research (AI-12302). We also acknowledge the National Science Foundation for an instrument grant (CHE-76-07386) in support of the acquisition of a ^{13}C NMR spectrometer by the Department of Chemistry.

References and Notes

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(7) Among many examples: W. S. Johnson, T. Li, C. A. Harbert, W. R. Bartlett, T. R. Herrin, B. Staskun, and D. H. Rich, *J. Am. Chem. Soc.*, **92**, 4461 (1970).

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(10) A number of intermolecular Lewis acid catalyzed aldol and acylation processes have been described, for example: J. P. Dusza, J. P. Joseph, and S. Bernstein, *J. Am. Chem. Soc.*, **86**, 3908 (1964), and N. Cohen, *Acc. Chem. Res.*, **9**, 412 (1976), and references therein. Professor John McMurry of the University of California, Santa Cruz, has observed the cyclization of a related vinyl ether–epoxide (private communication).

(11) R. K. Boeckman, Jr., and K. J. Bruza, *Tetrahedron Lett.*, 4187 (1977).

(12) The epoxy bromides and iodides were prepared from the corresponding olefinic chloride or bromide by epoxidation (MCPBA/methylene chloride) followed by halide exchange (if required) with NaI in acetone.

(13) HMPA (Aldrich Chemical Co.) carefully dried over Na was used. Some other commercial samples were found to contain impurities (presumably secondary amines) which were not removed by the above purification tech-

nique and which markedly reduced the yields of the alkylation processes. Alkylation of ketone enolates and other substances with approximate pK_a of ≤ 24 were not markedly affected.

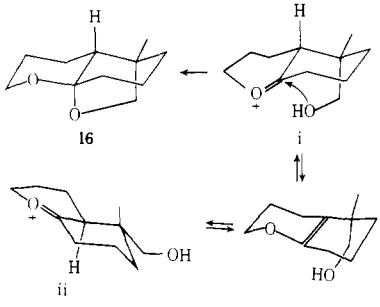
(14) All new compounds exhibited consistent spectral data (IR, NMR (^1H, ^{13}C)) and correct combustion or exact mass analytical data. Yields cited are for distilled or carefully chromatographically purified materials. Yields have not been optimized and in several cases crude materials of acceptable purity are obtained directly without purification (yields in parentheses, losses occur upon purification). Selected spectral data: **3**, ^1H NMR δ 4.55 (t, 1H), 3.97 (t, 2H), 2.75 (m, 2H), 2.3–1.4 (m, 8H), 1.3 (d, 3H); **5**, ^1H NMR δ 4.73 (m, 1H), 4.02 (t, 2H), 2.4–1.6 (m, 8H), 2.1 (s, 3H), 1.04 (d, 3H); **9**, ^1H NMR δ 4.55 (t, 1H), 3.97 (t, 2H), 2.73 (t, 1H), 2.35–1.42 (m, 8H), 1.31 (s, 3H), 1.27 (s, 3H); **10**, ^1H NMR δ 3.90 (t, 2H), 3.52 (t, 1H), 2.25–1.35 (m, 9H), 1.05 (s, 3H), 1.00 (s, 3H); **13**, ^1H NMR δ 4.50 (t, 1H), 3.98 (t, 2H), 2.60 (s, 2H), 2.25–1.4 (m, 10H), 1.35 (s, 3H); **15** characterized as the acetate, ^1H NMR δ 3.95 (m, 4H), 2.1 (s, 3H), 2.25–1.20 (m, 10H), 1.03 (s, 3H); **16**, ^1H NMR δ 3.6 (m, 4H), 2.17–1.06 (m, 12H), 0.88 (s, 3H), and IR 2900, 1450, 1375 cm^{-1}; **21**, ^1H NMR δ 5.37 (m, 1H), 4.82 (m, 1H), 3.86 (m, 2H), 2.13 (s, 3H), 1.12 (d, 3H).

(15) Agitated magnetic stirring for 8 h followed by standing for 16 h. This heterogeneous reaction was found to depend on the activity of the Al_2O_3 utilized.

(16) The ^{13}C NMR spectrum of **3** exhibited only 10 resonances, with no doubling characteristic of a diastereomeric mixture, particularly at the carbons bearing the side chain and hydroxyl.

(17) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

(18) The structure of **16** follows from consideration of the possible conformations available to the intermediate oxonium ions i and ii. Only i is capable of



cyclization and only the trans ring junction can result since the sp^2 nature of the ring junction carbon bearing the positive charge permits the adjacent hydrogen to occupy only an axial environment if effective overlap of the adjacent oxygen lone pairs is to occur.

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(21) J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 734 (1976), and references therein; (b) cf. ref 1j.

(22) For a related cyclization of an epoxy ketone under acidic conditions, see W. K. Anderson and T. Veysoglu, *J. Org. Chem.*, **38**, 2267 (1973); under basic conditions, see T. Masamune, M. Ono, S. Sato, and A. Murai, *Tetrahedron Lett.*, 371 (1978).

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(24) (a) A. P. Schaap and P. D. Bartlett, *J. Am. Chem. Soc.*, **92**, 6055 (1970); (b) P. D. Bartlett, G. D. Mendenhall, and A. P. Schaap, *Ann. N.Y. Acad. Sci.* **171**, 79 (1970).

(25) It was observed that even in CH_3CN the ratio of dioxetane to ene modes is only 85:15 for dihydropyran[24] and it is the generally observed trend for more highly substituted olefins to prefer the ene pathway; cf. W. Fenical, D. R. Kearns, and P. Radlick, *J. Am. Chem. Soc.*, **91**, 3396 (1969).

(26) Singlet oxygen was generated by irradiation of the solution (CH_3CN) containing Rose Bengal at 10–15 °C with a sodium vapor lamp through a filter with a cut-off at ≤ 500 nm. The presence of the dioxetane was confirmed by the observation of chemiluminescence upon heating.

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(30) For one recent approach to this problem, see T. Wakamatsu, K. Akasaka, and Y. Ban, *Tetrahedron Lett.*, 2751, 2755 (1977).

(31) For a recent review, see K. C. Nicolaou, *Tetrahedron*, **33**, 683 (1977).

(32) Fellow of the Alfred P. Sloan Foundation (1976–1980); recipient of a Career Development Award (CA-00273) from the National Cancer Institute of the National Institutes of Health (1976–1981).

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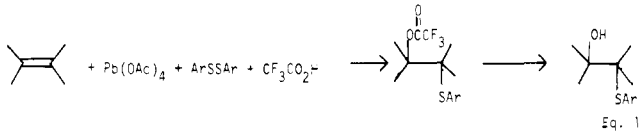
Hydroxysulfenylation of Olefins. An Olefin Cleavage with Functional Group Differentiation

Sir:

We report that combination of a lead (+4) salt and a disulfide provides a convenient general approach to hydroxysulfenylation of olefins.[1,2] The importance of vicinal oxygen and sulfur substitution stems from the great flexibility for structural elaboration.[3] Among such reactions is the ability to cleave the C–C bond bearing these substituents.[4] The combination of the hydroxysulfenylation with an improved cleavage of a β-hydroxylsulfide allows an olefin cleavage with differentiation of regiochemistry and functional groups. The application of this latter reaction toward a precursor of (±)-verrucarinic acid, a portion of the macrocyclic chain of verrucarin A,[5] is reported. An unusual conversion of a hydroxysulfide to an epoxide which can represent a net epoxidation from the sterically hindered face of an olefin is also noted.

Lead tetraacetate (1.0–1.5 equiv) and diphenyl disulfide (1.0–1.5 equiv) in the presence of 8–15 equiv of trifluoroacetic acid (generating a lead (+4) trifluoroacetate in situ)[6] in methylene chloride at 0 or −40 °C form a blue solution which rapidly turns yellow. Addition of 1 equiv of an olefin at this stage leads to smooth and rapid reaction at 0 or −40 °C to produce initially the β-trifluoroacetoxysulfide which upon basic workup generates the thiohydrin as summarized in eq 1 and



Eq. 1

Table I.[7] The chemoselectivity as well as the electrophilic nature of the reaction is illustrated by the case of carvone (Table I, entry 11) in which only the isolated double bond reacts.

The regiochemistry is dependent upon the temperature, the olefin, and the disulfide. Thus, with 1-methylcyclohexene, the regioselectivity increases from 4:1 to 27:1 of **3:4** by dropping the temperature of the reaction from 0 to −40 °C. In the case of cholesteryl benzoate, an ~1:1 mixture of the regio- and stereoisomers **10** and **11** is obtained even at −40 °C. Increasing the steric hindrance of the sulfenylating agent by switching to di-*o*-anisyl disulfide improved the selectivity to 1:3. That this enhanced regiochemistry represents a steric and not an electronic effect is evidenced by the nearly 1:1 ratio obtained with di-*p*-anisyl disulfide.[8]

The stereochemistry has been proven for a few cases and assumed for the remaining examples. In the case of the additions to cyclopentene, cyclohexene, and 4-*tert*-butylcyclohexene, the adducts are identical with authentic samples of the trans isomers available by independent methods. In the case of steroid **9** the protons at C(2) and C(3) are broadened singlets at δ 4.06 and 3.45, indicative of these protons being equatorial.

The mechanism of the reaction is obscure. It does involve transfer of an equivalent of ArS^+.[9] Thus, unsaturated acids (Table I, entry 8 and 14) lead to sulfenyllactonization. The ease of this procedure and the avoidance of handling benzenesulfenyl chloride give this method some advantage over a recently reported version of this reaction.[10] The stereo- and regiochemistry are also in accord with initial complexation of an ArS^+ species to the least hindered side of an olefin to generate the equivalent of an episulfonium ion followed by nucleophilic opening with trifluoroacetate. In this regard, the cholesteryl system is of great interest since the isomer ratio is dependent upon the initial complexation. The bulkier *o*-anisyl reagent leads to reaction via preferential β side attack and thus accounts for the enhanced selectivity.

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