ogenous OH^- produces half-met$_o$ with one five- and one six-coordinate iron which are still hydroxo bridged. This is structurally equivalent to the deoxy site described in Scheme I. Thus there should be a very low Franck-Condon barrier for the one-electron interconversion between these forms of the hemerythrin active site.

Concluding Remarks

At this point a powerful excited-state spectroscopic methodology has been developed to probe non-heme Fe(II) active sites. It has provided important molecular level insight into the mechanism of the extradiol dioxygenases and the chemistry of hemerythrin, and it is defining structure/function correlations over the coupled binuclear non-heme iron proteins. Our research efforts are now evolving in a number of complementary directions. We are further developing this spectroscopic protocol and extending it to other non-heme Fe(II) enzymes and their interactions with substrate, small molecules, and cofactors of relevance to catalysis. Systems presently being studied include bleomycin, phenylalanine hydroxylase,[41] methane monooxygenase, ribonucleotide reductase, and acid phosphatase, the latter being active in catalysis in its mixed-valent state.[42] We are also extending our spectroscopic studies on non-heme ferrous enzymes to define oxygen analogues and intermediates. Many of these proteins form reversible complexes with NO. These $\{FeNO\}^7$ complexes have quite unusual spectral features, including an $S = {}^3/_2$ ground state.[43] These spectral features appear to relate to spin polarization effects,[44] and once understood they should allow one to probe for variations in electron delocalization over the $\{FeNO\}^7$ unit which would contribute to differences in O_2 activation by non-heme Fe(II) sites. Finally, in addition to the stable oxyhemerythrin site, oxygen intermediates have been reported for bleomycin[45] and ribonucleotide reductase.[33] Spectroscopic studies combined with self-consistent field-Xα-scattered wave calculations are presently being pursued on these and related systems to define electronic structure and how this is affected by geometric structural changes of relevance to catalysis.

This research has been supported by the NIH (GM40392 for the mononuclear non-heme iron enzyme studies) and the NSF (DMB-9019752 for the coupled binuclear non-heme iron protein studies). E.I.S. expresses his sincere appreciation to all his students and collaborators who are listed as coauthors in the literature cited for their commitment and major contributions to this science. We thank Sabine Pulver for her valuable assistance in the preparation of this manuscript.

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Charge as a Key Component in Reaction Design. The Invention of Cationic Cyclization Reactions of Importance in Synthesis

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It has been only within the last few decades that reactions of value in chemical synthesis have been created from scratch, rather than being discovered more or less by accident.[1,2] This Account will illustrate a feature of reaction design, the incorporation of a charged atom, that we have found to be particularly beneficial in the invention of new carbon-carbon bond-forming cyclization reactions. Our studies are founded on the observation that introduction of a charged atom into an array of atoms undergoing bond reorganization typically lowers the free energy of activation of the process. Thus, reactions of charged species typically occur under mild conditions where high selectivity in bond formation, a hallmark of useful reactions, is most probable.[3,4] The transformations that are the subject of this brief Account are depicted in Figure 1.

Larry E. Overman was born in Chicago, Illinois, in 1943. He obtained a B.A. degree from Earlham College in 1965 and completed his doctoral study in 1969 with Professor Howard W. Whitlock, Jr. at the University of Wisconsin. After working with Professor Ronald Breslow at Columbia University on an NIH postdoctoral fellowship, he joined the faculty at the University of California at Irvine in 1971. He is now Professor of Chemistry at Irvine and currently Chairman of the Department. Professor Overman's research interests focus on the invention of new reactions and strategies in organic synthesis and the total synthesis of complex target molecules.

(1) The state-of-the-art in organic synthesis has recently been reviewed in detail: *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vols. 1-9.

(2) For one leading chemist's account of reaction invention, see: Barton, D. H. R. *Aldrichchim. Acta* **1990**, *23*, 3.

(3) Selectivity of a variety of types is desired. Positional (regioselectivity) and stereochemical (stereoselectivity and enantioselectivity) orientation and functional group selectivity (chemoselectivity) are of paramount importance.

(4) For discussion of reaction temperature and selectivity relationships, see: (a) Seebach, D.; Hidber, A. *Chimia* **1983**, *37*, 449. Giese, B. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 125.

0001-4842/92/0125-0352$03.00/0

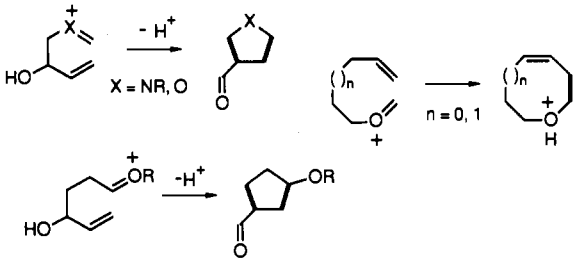


Figure 1. Cyclization reactions of charged intermediates. The new carbon–carbon bonds formed are in boldface print.

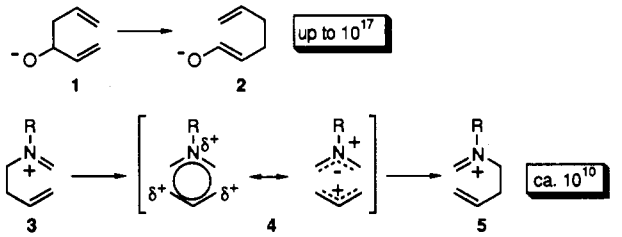
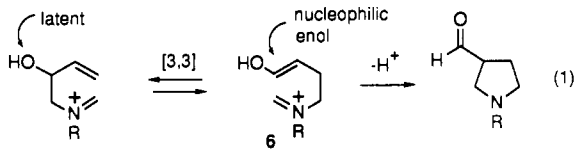


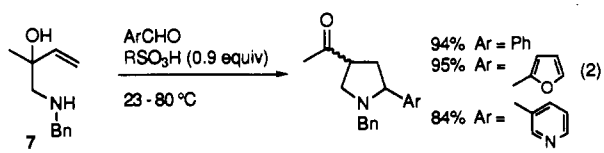
Figure 2. Examples of reactions dramatically accelerated by charge. (Rate acceleration relative to the Cope rearrangement of 1,5-hexatriene.)

Before proceeding to a discussion of experimental studies, a few of the ways that a charged atom can facilitate a chemical transformation will be outlined in a qualitative fashion. Examples are drawn from the arena of sigmatropic rearrangements where rate acceleration by charge has been most widely studied.[5] (1) A charged atom can provide an enthalpic driving force. One example is the base-catalyzed oxy-Cope rearrangement (Figure 2, **1** → **2**) in which a localized alkoxide is partially converted into a delocalized enolate in the transition state.[6] (2) The charged atom can distort the reaction pathway of a concerted reaction toward a nonconcerted alternative having a lower free energy of activation. Much of the significant acceleration of the base-catalyzed oxy-Cope rearrangement has been attributed to this effect. Specifically, weakening of the allylic bond by the alkoxide substituent leads to bond cleavage far exceeding bond making in the transition state.[7] (3) Acceleration can result from charge being more delocalized in a transition state than in a starting material.[8,9] At least part of the rate acceleration of 2-azonia-[3,3]-sigmatropic rearrangements (cationic aza-Cope rearrangements; Figure 2, **3** → **5**), which take place at temperatures 100–200 °C lower than rearrangements of hydrocarbon counterparts, can be ascribed to delocalization of the positive charge onto the allyl fragment in transition state **4**.[10] (4) Empty and filled orbitals are powerful electron-withdrawing and electron-donating substituents; they can accelerate reactions in a variety of fashions loosely termed substituent effects.[11]

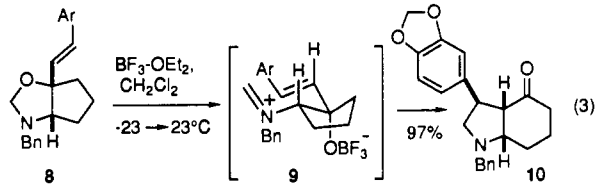
The Aza-Cope–Mannich Reaction. Synthesis of 3-Acylpyrrolidines. The combination of a Mannich reaction with the facile [3,3]-sigmatropic rearrangement of iminium cations results in a versatile synthesis of 3-acylpyrrolidines and other more complex ring systems containing this subunit (eq 1).[12] To be of use in synthesis, the cationic aza-Cope rearrangement needs to be irreversible. The "aza-Cope–Mannich" reaction (eq 1) was designed to achieve this aim by providing the opportunity for the "product" iminium ion sigmatropic isomer **6** to undergo highly exothermic Mannich cyclization.[13,14]



Most simply, this pyrrolidine synthesis involves the direct reaction of a homoallylic amine containing hydroxyl or alkoxyl substitution at the allylic site with an aldehyde in the presence of 1 equiv or less of acid (eq 2).[14] The mild conditions of this reaction (near ambient



temperature and neutral pH) are apparent in the high yields of the acylpyrrolidine synthesis with labile aldehydes such as furfural. Moreover, the reaction of amino alcohol **7** with aromatic aldehydes demonstrates the ability of the intramolecular Mannich reaction to "direct" the sigmatropic equilibrium by capturing the rearranged iminium ion sigmatropic isomer; in these cases the initially formed iminium ion would be stabilized by aryl conjugation. The aza-Cope–Mannich reaction can also be occasioned by reaction of 5-alkenyloxazolidines with acid.[15] A nice example, which illustrates both the use of a Lewis acid and the high stereoselectivity typically seen in this reaction, is presented in eq 3.[16]



(5) [3,3]-Sigmatropic rearrangements of several charged species are reviewed in the following: Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205.

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(8) For early suggestions of rate accelerations of this type in Cope rearrangements of cationic intermediates, see: Yates, P.; Eaton, P. E. *Tetrahedron Lett.* **1960**, 5. Cookson, R. C.; Hudec, J.; Williams, R. O. *Tetrahedron Lett.* **1960**, 29. Breslow, R.; Hoffman, J. M., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 2111.

(9) For general theoretical treatments, see: Carpenter, B. K. *Tetrahedron* **1978**, *34*, 1877. Wilcox, C. F., Jr.; Carpenter, B. K. *J. Am. Chem. Soc.* **1979**, *101*, 3897. Delbecq, F.; Anh, N. T. *Nouv. J. Chim.* **1983**, *7*, 505.

(10) For reviews, see: (a) Heimgartner, H.; Hansen, H.-J.; Schmid, H. In *Iminium Salts in Organic Chemistry*; Böhme, H., Viehe, H. G., Eds.; Wiley: New York, 1979; Part 2, pp 655–732. (b) Blechert, S. *Synthesis* **1989**, 71.

(11) For recent quantitative studies of substituent effects in [3,3]-sigmatropic rearrangements, see *inter alia*: (a) Burrows, C. J.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 6983, 6984. (b) Wilcox, C. S.; Babston, R. E. *J. Am. Chem. Soc.* **1986**, *108*, 6636. (c) Coates, R. M.; Rogers, B. D.; Hobbs, S. J.; Peck, D. R.; Curran, D. P. *J. Am. Chem. Soc.* **1987**, *109*, 1160. (d) Gajewski, J. J.; Jurayj, J.; Kimbrough, D. R.; Gande, M. E.; Ganem, B.; Carpenter, B. K. *J. Am. Chem. Soc.* **1987**, *109*, 1170.

(12) Reviewed briefly in the following: Overman, L. E.; Ricca, D. J. *Compr. Org. Synth.* **1991**, *2*, 1007.

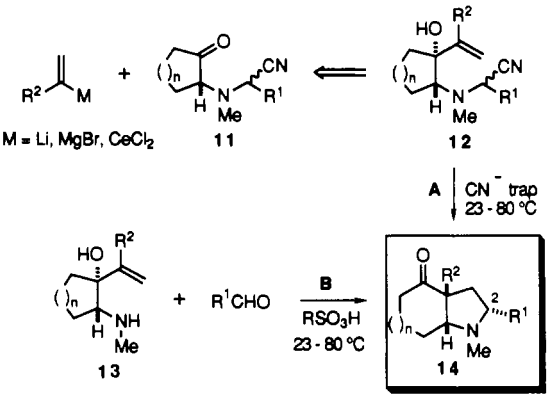
(13) Kakimoto, M.; Overman, L. E. *J. Am. Chem. Soc.* **1979**, *101*, 1310.

(14) Kakimoto, M.; Meier, G. P.; Okazaki, M.; Overman, L. E. *J. Am. Chem. Soc.* **1983**, *105*, 6622.

(15) Kakimoto, M.; Okawara, M.; Overman, L. E. *Tetrahedron Lett.* **1979**, *42*, 4041.

(16) Overman, L. E.; Shim, J. *J. Org. Chem.* **1991**, *56*, 5005.

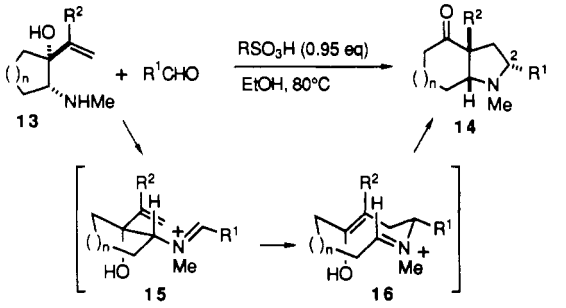
Scheme I
Representative Ring-Enlarging Pyrrolidine Annulations



method	n	R^1	R^2	yield
A (RSO_3H)	2	H	Ph	70%
A [$Cu(OCOCF_3)_2$]	2	H	Ph	91%
A ($AgNO_3$)	2	H	Ph	63%
A ($AgNO_3$)	2	H	H	64%
A ($AgNO_3$)	1	H	Ph	74%
B	1	Me	Ph	81%
A ($AgNO_3$)	0	H	Ph	78%
A ($AgNO_3$)	0	Me	Ph	66%

The rearrangement depicted in eq 3 is one example of a particularly useful variant of this heterocyclic synthesis in which pyrrolidine annulation is accompanied by one-carbon ring expansion of a starting carbocyclic ring. This ring-enlarging pyrrolidine annulation has been employed to construct a wide variety of ring systems, including the cis-fused hydroindoles, cyclopenta[*b*]pyrrolidines, and cyclohepta[*b*]pyrrolidines depicted in Scheme I.[17-19] The synthesis of **14** can be brought about either by direct reaction of a cyclic amino alcohol **13** with an aldehyde and acid or by loss of cyanide from the corresponding cyanoalkylamine **12**. This latter modification is particularly useful when the cyanoalkyl group is also employed to protect nitrogen during the construction of **12** from α-amino ketone (**11**) and alkenyl organometallic precursors.[17c,18b,20] The rearrangement of iminium ion intermediates derived from cyclobutylamine **12** (n = 0) at 50 °C contrasts dramatically with thermal rearrangements of neutral *trans*-divinylcyclobutanes; these latter rearrangements require elevated temperatures and proceed by diradical pathways to give predominantly products of 1,3-shift.[21] The facile iminium ion rearrangements in the "*trans*-divinylcyclobutane" series provide some of the best illustrations to date of the powerful activating effect of

Scheme II
Stereochemical Analysis of a Ring-Enlarging Pyrrolidine Annulation



the positively charged iminium ion functionality.

The ring-enlarging pyrrolidine annulation proceeds with selective (typically exclusive) formation of a single stereoisomer.[17c,18b,22] One of the most important attributes of this reaction, which markedly contributes to its utility in synthesis, is the ease with which the stereochemical outcome can be predicted. The stereochemistry of the major azacyclic product is determined by three factors: (1) the bias for the 2-azonia-[3,3]-sigmatropic rearrangement to proceed by a chair topography (for an (*E*)-alkene this preference is >3 kcal/mol);[23] (2) the preferential rearrangement of iminium ion stereoisomers that would have quasi equatorial substituents in the chair transition state;[17c,18b] and (3) the facility of intramolecular Mannich cyclizations. Thus, formation of the all-cis hydroindole **10** from **8** follows directly from the chair rearrangement topography depicted in **9** (eq 3). The incorporation of the alkene through formation of the two new carbon–carbon bonds in a suprafacial sense is a defining characteristic of this ring-forming reaction. The rearrangements outlined in Scheme I preferentially form the cis-fused bicyclic product having the 2-substituent on the more hindered concave face. This contrathermodynamic outcome signals kinetic control for the reorganization. The formation of **14** arises from preferred [3,3]-sigmatropic rearrangements of the (*E*)-iminium ion stereoisomer by a chair topography, **15** → **16** (Scheme II). The high selectivity observed also requires that intramolecular Mannich cyclization of **16** proceeds more rapidly than stereomutation of this *trans,trans*-azacycloalkadiene by either enol–keto or iminium ion–enamine tautomerization (Scheme II).[24]

The core functionality assembled by the aza-Cope–Mannich reaction is 3-acylpyrrolidine (**17**, Figure 3). In the language of antithetic synthesis analysis, the 3-acylpyrrolidine unit would be the retron that triggers application of the aza-Cope–Mannich transform.[25] The broad utility of this reaction for complex molecular synthesis has been verified by its use as the key strategic element of a wide variety of alkaloid total syntheses.[16,26-30] Representative examples are summarized in

(17) (a) Mendelson, L. T.; Overman, L. E. *J. Am. Chem. Soc.* **1981**, *103*, 5579. (b) Flippin, L. A.; Mendelson, L. T.; Overman, L. E. *Tetrahedron Lett.* **1982**, *23*, 2733. (c) Jacobsen, E. J.; Mendelson, L.; Overman, L. E. *J. Am. Chem. Soc.* **1983**, *105*, 6629.
(18) (a) Jacobsen, E. J.; Overman, L. E. *Tetrahedron Lett.* **1982**, *23*, 2737. (b) Doedens, R. J.; Jacobsen, E. J.; Overman, L. E. *J. Org. Chem.* **1983**, *48*, 3393.
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(21) Hammond, G. S.; DeBoer, C. D. *J. Am. Chem. Soc.* **1964**, *86*, 899. Berson, J. A.; Dervan, P. B.; Malherbe, R.; Jenkins, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 5937.
(22) Jacobsen, E. J.; Levin, J.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 4329.
(23) Doedens, R. J.; Meier, G. P.; Overman, L. E. *J. Org. Chem.* **1988**, *53*, 685.
(24) A complete stereochemical analysis of the aza-Cope–Mannich reaction can be found in refs 17c, 18b, and 22.
(25) Corey, E. J.; Chen, X.-M. *The Logic of Chemical Synthesis*; John Wiley & Sons: New York, 1989.
(26) Overman, L. E.; Sugai, S. *Helv. Chim. Acta* **1985**, *68*, 745.
(27) Fukaya, C.; Overman, L. E. *J. Am. Chem. Soc.* **1980**, *102*, 1454.
(28) Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Am. Chem. Soc.* **1991**, *113*, 2598.

Scheme III
Central Steps in the Aza-Cope–Mannich Synthesis of *Aspidosperma* Alkaloids

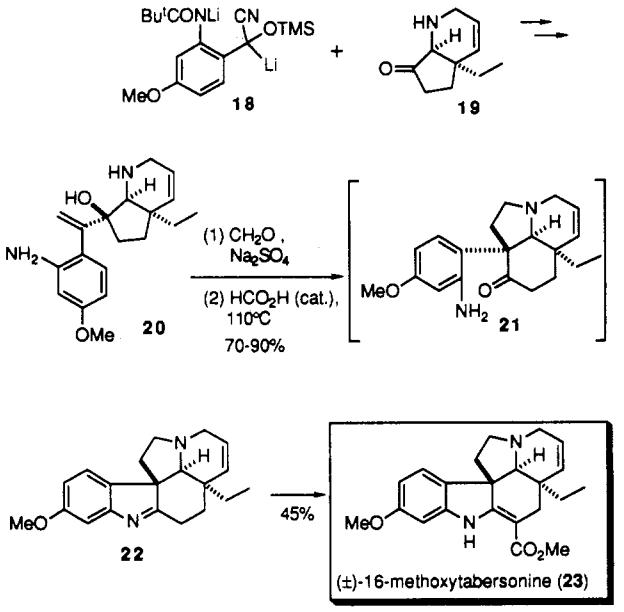
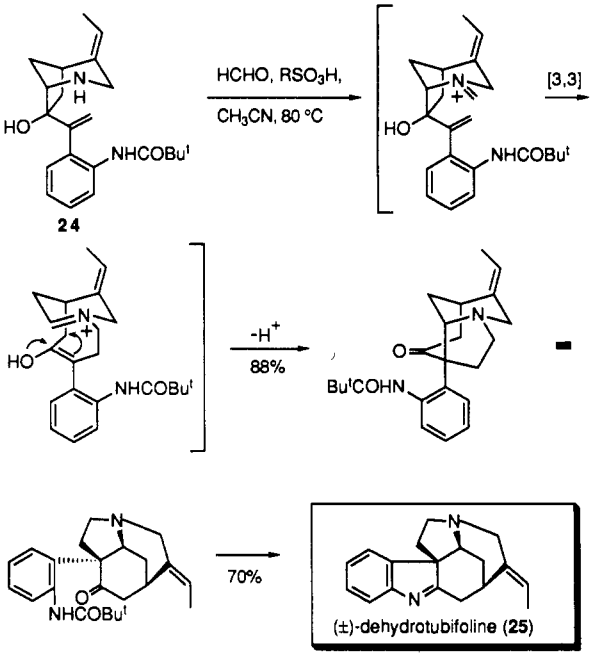


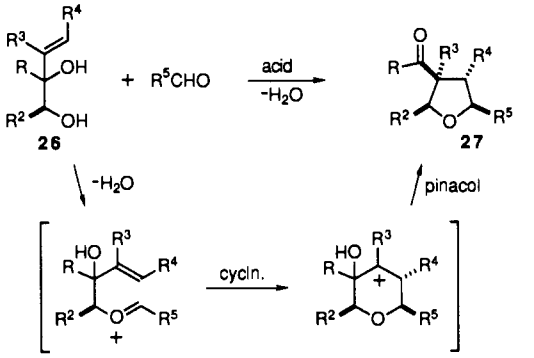
Figure 3, wherein the 3-acylpyrrolidine unit emanating from the aza-Cope–Mannich reaction is highlighted in boldface print.

The aza-Cope–Mannich reaction is notably powerful in simplifying alkaloid synthesis design when (a) the rearrangement solves stereochemical problems posed by the target structure and (b) the acyl group is exploited to further elaborate the aza-Cope–Mannich product. These features, as well as the characteristic mildness of this iminium ion reorganization, are well-illustrated in our early total synthesis of (±)-16-methoxytabersonine (**23**).[29] This *Aspidosperma* alkaloid is a useful precursor of vindoline,[31,32] a component of several dimeric indole alkaloids currently employed in cancer chemotherapy.[33] Notable enantioselective total syntheses of **23** have been accomplished recently by the Kuehne[31] and Magnus groups.[34] In our convergent synthesis of (±)-16-methoxytabersonine, the rearrangement substrate **20** was assembled from the reaction of the aromatic dianion **18** and the *cis*-pyrindinone **19** (Scheme III).[29] The central transformation, conversion of **20** to 16-methoxy-1,2,6,7-tetradehydroaspidospermidine (**22**), stereoselectively established the crucial quaternary carbon center and developed three of the five rings of the alkaloid target. This conversion was accomplished by treating **20** with paraformaldehyde and Na_2SO_4 to form the corresponding oxazolidine directly followed by heating this intermediate in toluene to provide **22** in 70–90% yield. The small amount of formic acid present in the formaldehyde is sufficient to catalyze both the aza-Cope–Mannich reaction and the subsequent dehydration of **21**. Formation of **21** with complete stereocontrol follows directly from the single chair rearrangement conformation available to the formaldiminium ion derivative of **20**.[29]

Scheme IV
Central Step in the Aza-Cope–Mannich Synthesis of *Strychnos* Alkaloids



Scheme V
Synthesis of 3-Acyltetrahydrofurans from Allylic Diols and Aldehydes (The Favored Prins Cyclization–Pinacol Rearrangement Pathway Is Illustrated)



Our recently developed approach to *Strychnos* alkaloids illustrates the viability of the aza-Cope–Mannich reaction when the homoallylic amine unit is embedded in a bridged bicyclic ring system.[30] The central step in the efficient total synthesis of our initial *Strychnos* target, (±)-dehydrotubifoline (**25**), is shown in Scheme IV.

Although I have chosen to highlight the total syntheses of two racemic alkaloids in this Account, preparation of the homoallylic amine rearrangement substrates **20** and **24** in nonracemic form would allow the alkaloid targets to be prepared asymmetrically. This approach for the asymmetric construction of alkaloids by aza-Cope–Mannich strategies was verified in an efficient total synthesis of (−)-crinine.[26]

Pinacol-Terminated Cationic Cyclizations. Synthesis of 3-Acyltetrahydrofurans. We recently described a general method for synthesizing substituted tetrahydrofurans from readily available allylic diol and carbonyl components (**26** → **27**, Scheme V).[35-37] The

(29) Burk, R.; Overman, L. E.; Sworin, M. *J. Org. Chem.* **1983**, *48*, 2685.
(30) Fevig, J. M.; Marquis, R. M., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5085.
(31) Bornmann, W. G.; Kuehne, M. E.; Mulamba, T.; Podhorez, D. E. *J. Org. Chem.* **1987**, *52*, 347.
(32) (a) Danieli, B.; Lesma, G.; Palmisano, G.; Riva, R. R. *J. Chem. Soc., Chem. Commun.* **1984**, 909. (b) Magnus, P.; Ladlow, M.; Cairns, P. M. *Tetrahedron Lett.* **1987**, *28*, 3307.
(33) Neuss, N.; Neuss, M. N. *Alkaloids (N.Y.)* **1990**, *37*, 229.
(34) Cardwell, K.; Hewitt, B.; Ladlow, M.; Magnus, P. *J. Am. Chem. Soc.* **1988**, *110*, 2242.

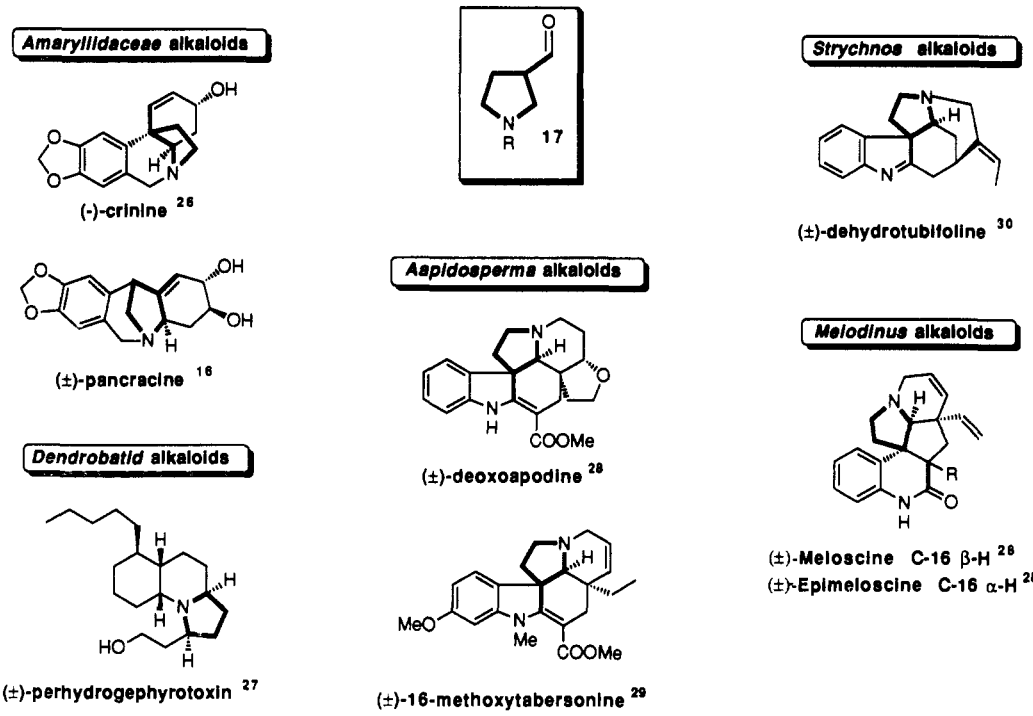


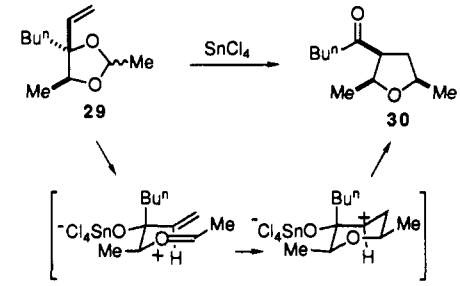
Figure 3. Representative alkaloid syntheses accomplished using the aza-Cope–Mannich rearrangement as the key step. The 3-acylpyrrolidine subunit is shown in boldface print.

design of this reaction followed directly from our earlier development of the aza-Cope–Mannich rearrangement.[38] Unexpectedly, mechanistic studies demonstrated that this synthesis of 3-acyltetrahydrofurans did not take place as conceptualized in our initial design (by sequential 2-oxonia-[3,3]-sigmatropic rearrangement–aldol cyclization), but rather it took place by the Prins cyclization–pinacol rearrangement reaction sequence illustrated in Scheme V.[36,37] In many ways this mechanistic outcome was fortunate, since it provided the stimulus for our more general development of pinacol-terminated cationic cyclization reactions (vide infra).

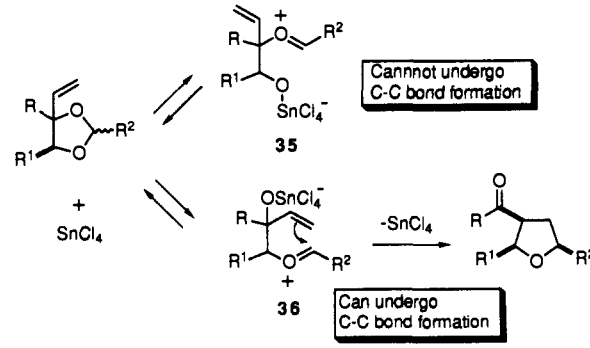
Representative examples of this new, highly stereocontrolled synthesis of tetrahydrofurans and related oxacycles are shown in Figure 4.[35-37,39,40a,b] The rearrangement can be triggered by treating an acetal intermediate with 1–3 equiv of a Lewis acid at low temperature ($SnCl_4$ is generally preferred). Alternatively, with many aldehydes the direct acid-promoted condensation of the allylic diol with an aldehyde is more convenient.[40a,b,41] Only three steps are typically required for assembly of the substituted tetrahydrofuran from commercially available starting materials.

Other characteristics of this tetrahydrofuran synthesis are illustrated in the examples shown in Figure 4. High

Scheme VI
Stereochemical Analysis of the Acyltetrahydrofuran Synthesis



Scheme VII
Stereoelectronic Considerations



cis stereoselectivity (at least 20:1)[36] is observed in the preparation of tetrahydrofurans containing side chains at carbons 2 and 5, and the kinetic product also has a cis relationship of these side chains to the 3-acyl substituent. In most cases both the syn and anti diol stereoisomers afford the same tetrahydrofuran product (e.g., **28** or **29** → **30**). Thus, a mixture of four stereoisomeric acetals can evolve to a single tetrahydrofuran (**31** → **32**). When the allylic diol is nonracemic, tetrahydrofuran products of high enantiomeric purity are obtained ((5*S*)-**33** → **34**).[39] The stereochemical outcome

(35) Hopkins, M. H.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 4748.
(36) Hopkins, M. H.; Overman, L. E.; Rishton, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 5354.
(37) For a brief review of our early work in this area, see: Overman, L. E. In *Selectivities in Lewis Acid-Promoted Reactions*; NATO ASSI Series 289; Schinzer, D., Ed.; Kluwer Academic: Dordrecht, The Netherlands, 1989; pp 1–20.
(38) Detailed mechanistic investigations of this synthesis of 3-acylpyrrolidines strongly support a mechanism involving 2-azonia-[3,3]-sigmatropic rearrangement followed by Mannich cyclization.[22]
(39) Overman, L. E.; Rishton, G. M. *Org. Synth.*, in press.
(40) Unpublished results of (a) G. M. Rishton (b) D. MacMillan, (c) T. Gahman, (d) S. Inoue, and (e) M. Bratz and W. Bullock.
(41) Brown, M. J.; Harrison, T.; Herrinton, P. M.; Hopkins, M. H.; Hutchinson, K. D.; Mishra, P.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5365.

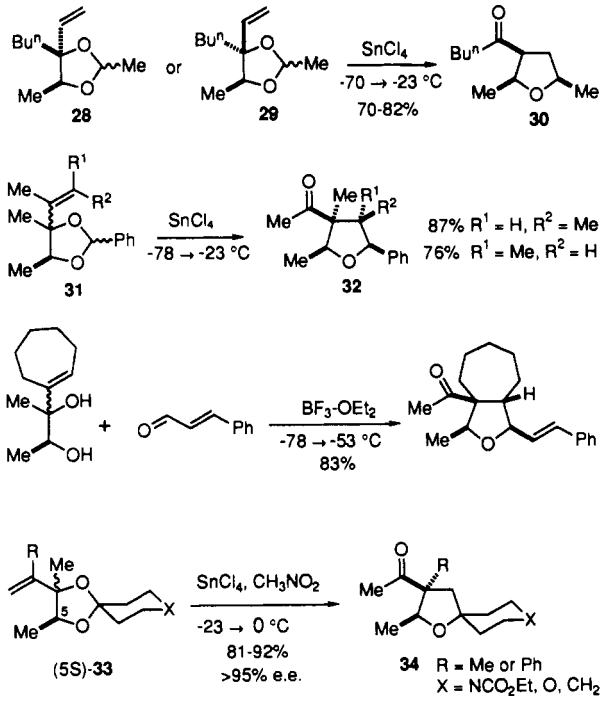
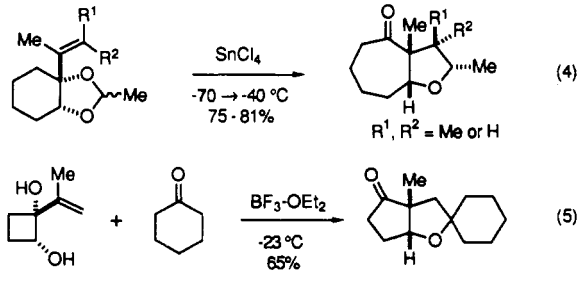


Figure 4. Preparation of representative 3-acyltetrahydrofurans. Unless noted otherwise, the solvent was CH_2Cl_2.

of this new tetrahydrofuran synthesis follows directly from a preference for chair topographies in both the cyclization and pinacol rearrangement steps.[36,41] This stereochemical analysis for the formation of tetrahydrofuran **30** from acetal **29** is outlined in Scheme VI.

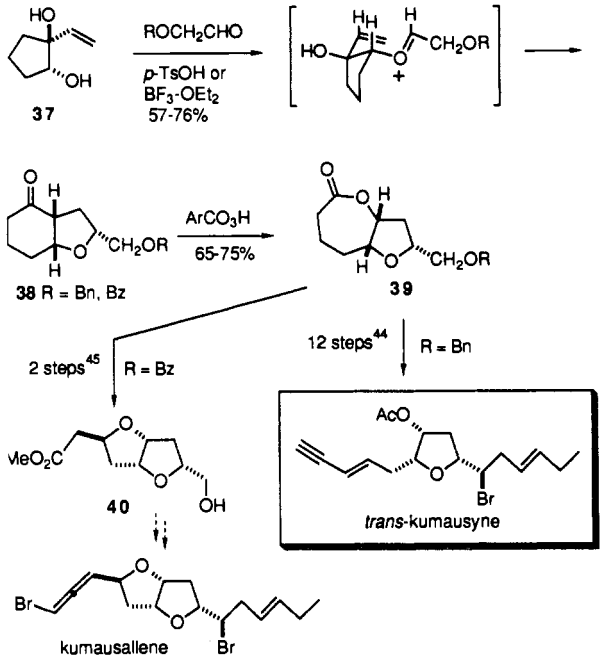
Stereoelectronic requirements of ring formation were important in the design of this convenient tetrahydrofuran synthesis (Scheme VII).[42] Thus, although two α-alkoxycarbenium ions (**35** and **36**) are readily accessible from acid-promoted ring opening of a 4-alkenyl-1,3-dioxolane, only **36** has sufficiently good overlap between the carbenium ion carbon and the alkene to undergo carbon–carbon bond formation. Prins cyclization of **35** is not expected to be a competing process, since it would involve a highly disfavored 5-endo trigonal cyclization.[42] As a result, there is no need to differentiate the two oxygens (e.g., by selective protection of the allylic oxygen), a feature that notably contributes to the power of this new tetrahydrofuran synthesis.

A useful ring-enlarging tetrahydrofuran annulation results when the starting allylic diol is a 1-alkenylcycloalkane-1,2-diol. The examples shown in eqs 4 and 5 exemplify the high stereocontrol realized in this reaction; in each case only a single oxacycle is formed.[41] The stereochemical outcome has been analyzed in detail and again derives from a preference for chair topographies in both the cyclization and rearrangement steps.[41]

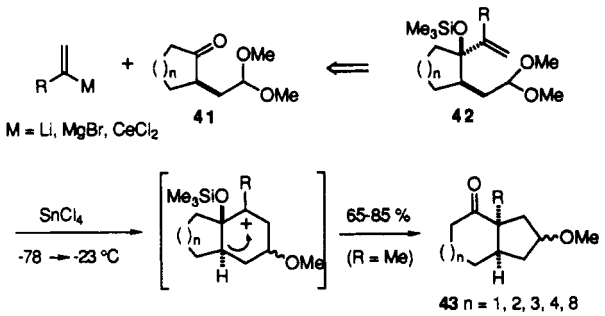


(42) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, *734*, 736.

Scheme VIII
General Strategy for the Synthesis of *Laurencia* Nonisoprenoid Sesquiterpenes from *cis*-Hydrobenzofuranones



Scheme IX
Ring-Enlarging Cyclopentane Annulations

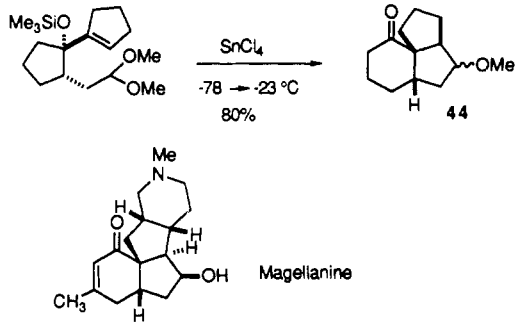


We recently delineated a general strategy for the synthesis of halogenated tetrahydrofuranoid lipids,[43] the central feature of which was the quick assembly of *cis*-hydrobenzofuranones **38** by ring-enlarging tetrahydrofuran annulations of *trans*-cyclopentanediol **37** (Scheme VIII).[44] Use of the 1*S*,2*R* enantiomer of **37** in this reaction affords **38** with complete retention of absolute chirality. The bicyclic lactone **39**, available from **38** by Baeyer–Villiger oxidation, is an excellent platform for the synthesis of this family of natural products. The conversion of **39** to *trans*-kumausyne has been described,[44] as has the synthesis of the dioxobicyclo[3.3.0]octane **40**, a potential precursor of kumausallene.[45]

Pinacol-Terminated Cationic Cyclizations. Ring-Enlarging Cyclopentane Annulations. A related cyclization–pinacol sequence has been developed for the preparation of carbocycles (Scheme IX).[46] This

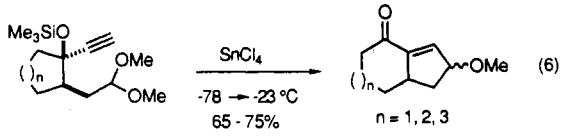
(43) For reviews, see: Faulkner, D. J. *Nat. Prod. Rep.* **1984**, *1*, 251, 551; **1986**, *3*, 1; **1987**, *4*, 539; **1988**, *5*, 613; **1990**, *7*, 269; **1991**, *8*, 97.
(44) Brown, M. J.; Harrison, T.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5378.
(45) Hutchinson, K. D. Ph.D. Dissertation, University of California—Irvine, Irvine, CA, 1991.
(46) Hirst, G. C.; Howard, P. N.; Overman, L. E. *J. Am. Chem. Soc.* **1989**, *111*, 1514.

Scheme X
Model Study for the Synthesis of Magellanine



synthesis begins with a ketone and involves the introduction of a two-carbon acetal side chain, followed by the reaction of the keto acetal **41** with a vinyl organometallic. Lewis acid promoted rearrangement of the silyl ether derivative **42** then accomplishes ring-enlarging cyclopentane annulation to yield the bicyclic keto ether **43**. Although our investigations of this chemistry are still in a germinal stage, the high utility of this unusual mode of carbocycle construction is already apparent. The examples summarized in Scheme IX illustrate the synthesis of bicyclics in which the ketonic ring is 6-, 7-, 8-, 9-, or 13-membered.[40c,d,46] In all cases only the cis-fused carbocyclic product was formed.

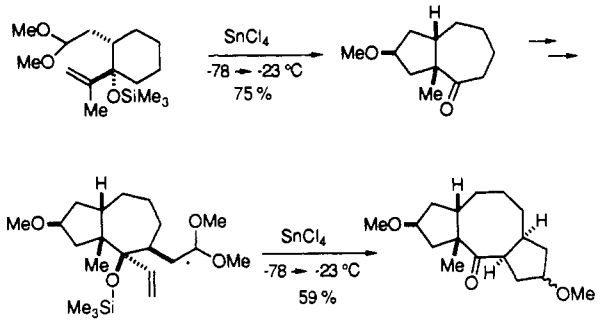
Additional examples of this carbocycle construction are shown in eq 6 and Scheme X. As in the pyrrolidine and tetrahydrofuran syntheses developed earlier, the stereochemical outcome is readily rationalized (more importantly, anticipated) from a chair preference for the Prins cyclization and pinacol rearrangement steps.[37] The stereoselective construction of the tricyclo[7.3.0^{1,9}.0^{1,6}]dodecane **44** in only five steps from cyclopentanone is significant, since this angularly fused tricycle constitutes three of the four rings and the proper oxidation of *Lycopodium* alkaloids of the magellanine family (Scheme X).[47] In light of the considerable instability of vinyl cations,[48] the success of related transformations of substrates containing the terminal alkyne unit is notable (eq 6).[49]



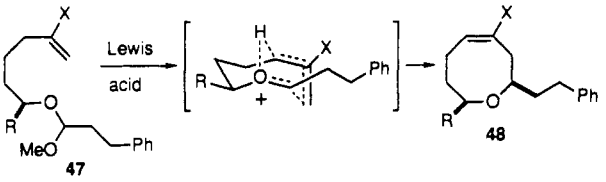
Since the products of cyclization–pinacol rearrangement contain a ketone, the annulation sequence of Scheme IX can be carried out in an iterative fashion to form two five-membered rings and accomplish a net two-carbon ring expansion of the starting ketone.[46] The rapid assembly of the dicyclopenta[*a*,*d*]cyclooctane ring system found in several biologically important sesterterpenes and diterpenes, such as the fusicoccins and ophiobolins,[50] outlines this concept (Scheme XI).[46]

Many extensions of this new carbocycle synthesis are readily envisaged. For example, if the acetal is tethered to the ketonic ring by two carbons, a ring-enlarging

Scheme XI
Synthesis of Dicyclopentacyclooctanes by Iterative Ring-Enlarging Cyclopentane Annulations



Scheme XII
Formation of Δ⁴-Oxocenes from Lewis Acid Promoted Cyclizations of 5-Hexenyl Acetals



X	reaction conditions	Δ⁴-oxocene, yield
H	$EtAlCl_2$, CH_2Cl_2, -60 °C	11% (R = H)
$SiMe_3$	$SnCl_4$, CH_2Cl_2, -60 → -20 °C	31% (R = Me)
SPh	BF_3-OEt_2, t-BuOMe, -78 → -30 °C	78% (R = Me)

cyclohexane annulation will result.[40d] The studies described in this and the previous section, together with those of Trost[51] and Sworin,[52] clearly establish the power of reaction designs that employ pinacol rearrangements to terminate cationic cyclizations.

Intramolecular Ene Cyclizations. Synthesis of Eight-Membered Cyclic Ethers. Although discovered initially during another investigation,[53] the preparation of Δ⁴-oxocenes from Lewis acid promoted cyclizations of 5-hexenyl acetals fits properly within the theme of this Account. The interconversion of 1,7-octadiene and *cis*-cyclooctene has been known since the 1950s.[54] However, this reaction is of little significance for the synthesis of eight-membered carbocycles as a result of its unfavorable equilibrium and harsh reaction conditions (Figure 5). In dramatic contrast, our recent investigations demonstrate the considerable utility of related cyclizations of unsaturated α-alkoxycarbenium ions.[55-57] Of particular note, this cationic cyclization

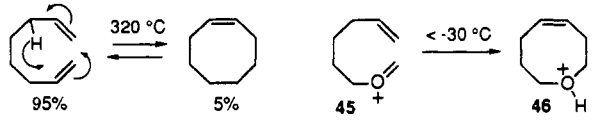
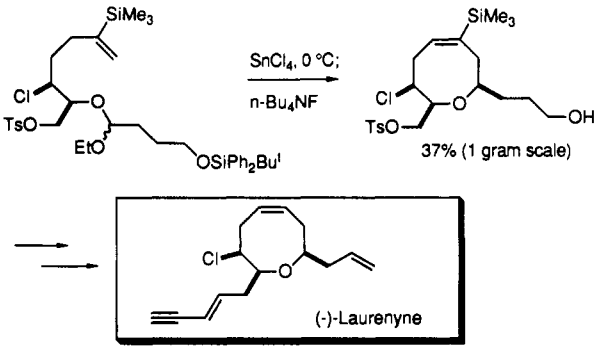


Figure 5. Effect of charge on intramolecular ene cyclizations.

(47) MacLean, D. B. *Alkaloids (N.Y.)* **1985**, *26*, 241.
(48) Stang, P. J.; Rappoport, Z.; Hanack, M.; Subramanian, L. R. *Vinyl Cations*; Academic Press: New York, 1979.
(49) Johnson, T.; Overman, L. E. *Tetrahedron Lett.* **1991**, *32*, 7361.
(50) Cordell, G. A. *Phytochemistry* **1974**, *13*, 2343. Hansen, J. R. *Nat. Prod. Rep.* **1986**, *3*, 123.
(51) Trost, B. M.; Lee, D. C. *J. Am. Chem. Soc.* **1988**, *110*, 6556.
(52) Sworin, M.; Neumann, W. L. *J. Org. Chem.* **1988**, *53*, 4894.
(53) Overman, L. E. *Lect. Heterocycl. Chem.* **1985**, *8*, 59.
(54) Blomquist, A. T.; Taussig, P. R. *J. Am. Chem. Soc.* **1957**, *79*, 3505. Roth, W. R. *Chimia* **1966**, *20*, 229.
(55) (a) Blumenkopf, T. A.; Bratz, M.; Castañeda, A.; Look, G. C.; Overman, L. E.; Rodriguez, D.; Thompson, A. S. *J. Am. Chem. Soc.* **1990**, *112*, 4386. (b) Blumenkopf, T. A.; Castañeda, A.; Overman, L. E.; Thompson, A. S. *J. Am. Chem. Soc.* **1986**, *108*, 3516.

Scheme XIII
Cyclization Step in the Total Synthesis of (−)-Laurenyne



(**45** → **46**) occurs at temperatures more than 300 °C *lower* than the hydrocarbon counterpart (Figure 5).

The three examples shown in Scheme XII highlight some of the features of this direct synthesis of unsaturated eight-membered-ring ethers. The yield of Δ^4-oxocene increases as the vinylic substituent is varied from H to $SiMe_3$ to SPh; notably high yields (75–80%) are obtained in vinyl sulfide–acetal cyclizations carried out under non-high-dilution conditions (0.05 M). That demanding medium rings can be prepared in this way by the direct cyclization of simple acyclic precursors that are not biased toward coiled conformations is remarkable. Although beyond the scope of this overview, detailed investigations of cyclizations in the terminal alkene and vinylsilane series reveal that the lower yields of Δ^4-oxocenes obtained in these cases do not result from competing bimolecular processes, but rather from competitive cyclization in an alternate sense to form 2-oxocanyl cations.[55a]

Hallmarks of this synthesis of unsaturated eight-membered cyclic ethers are the formation of only the Δ^4 regioisomer and the high selectivity (>25:1) realized for forming the cis isomer **48** of the 2,8-disubstituted Δ^4-oxocene (Scheme XII). Several lines of evidence implicate a concerted ene cyclization mechanism for $SnCl_4$-promoted cyclizations of 5-(trimethylsilyl)-5-hexenyl acetals.[57] As depicted in Scheme XII, ene cyclization of the (*E*)-oxocarbenium ion derived from acetal **47** is fully consistent with the observed regio- and stereochemical outcome.

An oxonium ene cyclization was the central step in the first practical synthetic entry to the oxocene metabolites of the algae genus *Laurencia*.[56] Laurenyne is representative of this large class of unsaturated eight-membered-ring ethers that contains cis-oriented side chains at carbons 2 and 8.[43] The pivotal cyclization step in the synthesis of (−)-laurenyne is shown in Scheme XIII. This step forms the eight-membered ring with complete regiochemical and stereochemical fidelity, introduces the Δ^4 unsaturation, and appends the two side chains. Ongoing studies in our laboratories are examining the likelihood that related acetal cyclizations that employ vinyl sulfide nucleophiles will provide more efficient entry to this demanding natural products class.[40e]

(56) Overman, L. E.; Thompson, A. S. *J. Am. Chem. Soc.* **1988**, *110*, 2248.
(57) Blumenkopf, T. A.; Look, G. C.; Overman, L. E. *J. Am. Chem. Soc.* **1990**, *112*, 4399.

Conclusions and Prospects. The investigations summarized in this brief Account confirm that the rearrangement of charged intermediates is a fertile arena for the invention of reactions of value in organic synthesis. A defining characteristic of the carbon–carbon bond-forming cyclization reactions highlighted here is the marked increase in molecular complexity that is achieved. The capacity of charged atoms to reduce the activation free energy of molecular reorganizations contributes to the high stereochemical and regiochemical selectivity that distinguishes these ring construction methods. Particularly powerful is the class of cyclization reactions that couple ring annulation with the expansion of a starting ring. These latter transformations broaden the range of potential precursors of a specific target structure to include progenitor ring systems of smaller sizes. Last, but certainly not least, the cyclization reactions developed in this program are experimentally straightforward. The "low-tech" nature of this chemistry, whose initiation typically requires only generation of a solvated charged intermediate, is unquestionably one of its greatest virtues.

The progress in synthetic organic chemistry during the past 30 years has been breathtaking. A wide variety of selective reagents and synthetic strategies have emerged that allow impressively complex target molecules to be constructed.[58] Nonetheless, the science of synthetic organic chemistry is remarkably immature when confronted with the challenge of preparing, in an economic manner, even relatively simple target molecules. For example, many currently investigated drug candidates contain only a few rings and/or stereocenters, yet their synthesis in a practical fashion presents formidable challenges.[59] As organic chemists strive in the future to develop truly practical sequences for assembling increasingly complex target molecules, reactions that form molecular networks in a selective fashion using simple (inexpensive) reagents and low-tech reaction conditions will assume growing importance.

I am particularly grateful to the colleagues cited in the references for their collaboration and inspiration. The investigations in this area have been supported since their inception by grants from the National Institutes of Neurological Diseases and Stroke, most recently by a Jacob Javits Distinguished Investigator Award. Partial support from the National Science Foundation is also gratefully acknowledged. Support for postdoctoral collaborators from the National Institutes of Health, the American Cancer Society, the National Science and Engineering Council of Canada, the Alexander von Humboldt Foundation, the Ministry of Education, Science, and Culture of Japan, the Swiss National Science Foundation, and the Sankyo Chemical Co. is warmly appreciated.

(58) Kishi's total synthesis of palytoxin is a definitive example: Armstrong, R. W.; Beau, J.-M.; Cheon, S. H.; Christ, W. J.; Fujioka, H.; Ham, W.-H.; Hawkins, L. D.; Jin, H.; Kang, S. H.; Kishi, Y.; Martinelli, M. J.; McWhorter, W. W., Jr.; Mizuno, M.; Nakata, M.; Stutz, A. E.; Talamas, F. X.; Taniguchi, M.; Tino, J. A.; Ueda, K.; Uenishi, J.; White, J. B.; Yonaga, M. *J. Am. Chem. Soc.* **1989**, *111*, 7525.
(59) Lednicer, D.; Mitscher, L. A.; Georg, G. I. *The Organic Chemistry of Drug Synthesis*; Wiley: New York, 1990; Vol. 4 and earlier volumes in this series.