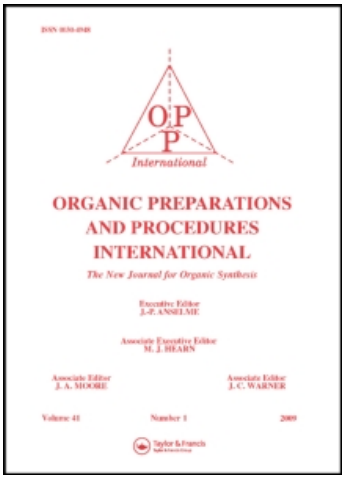

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BIOSYNTHETIC, BIOMIMETIC AND RELATED EPOXIDE CYCLIZATIONS. A REVIEW

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BIOSYNTHETIC, BIOMIMETIC AND RELATED EPOXIDE CYCLIZATIONS. A REVIEW

Stephen K. Taylor

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This review is dedicated to two Hope College alumni, E. E. van Tamelen, a pioneer in the field and Victor L. Heasley, who sparked my interest in research.

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BIOSYNTHETIC, BIOMIMETIC AND RELATED EPOXIDE CYCLIZATIONS. A REVIEW

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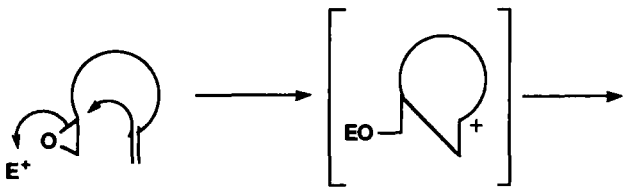
INTRODUCTION

Epoxy-ene cyclizations (Eq. 1) have been aggressively studied by several groups[1-9] since the early 1960's. However, these cyclizations were brought to prominence chiefly by van Tamelen and

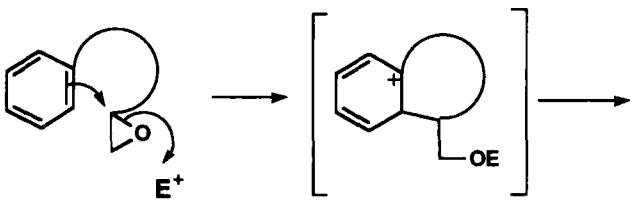


products (1)

E = Electrophile (positive or neutral)

coworkers.[3,4,10] A key example of such a reaction is the biosynthetic cyclization of 2,3-oxidosqualene to lanosterol (see below), which is fundamental to steroid biosynthesis.[3,4] The mechanism of this process is still under investigation.[11,12]

Epoxy-arene cyclizations (Eq. 2) have only recently been studied in any detail (see below).



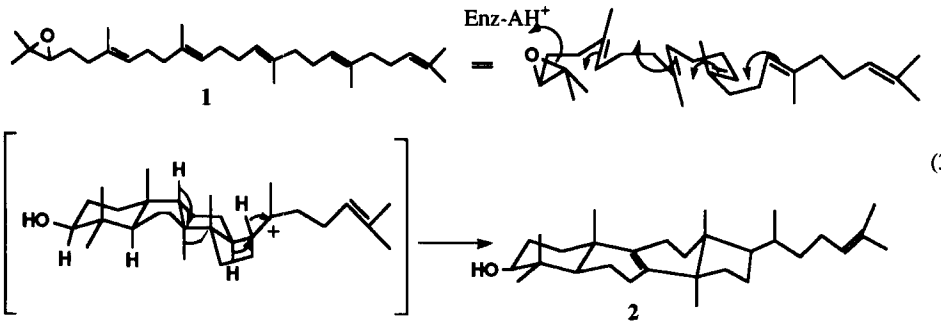
products (2)

We could only find two early reports[13,14] on this chemistry and they only dealt with it indirectly (e.g. as tests of whether oxidative alkenylbenzene cyclizations occurred *via* epoxides[13]). This manuscript summarizes the literature on both types of reactions since a 1975 article,[10] which reviewed the biomimetic epoxy-ene cyclizations to that date.

I. EPOXY-ENE CYCLIZATIONS

1. Enzymatic Cyclizations of 2,3-Oxidosqualene and Related Compounds

The biosynthesis of sterols is generally accepted to involve the cyclization of 2,3-oxidosqualene (**1**) to lanosterol (**2**; Eq. 3).[3,9] This is quite possibly the quintessential example of epoxide cyclization. In a single step, an acyclic epoxide with one stereogenic center is transformed into tetracycle **2**, which has seven stereogenic centers.

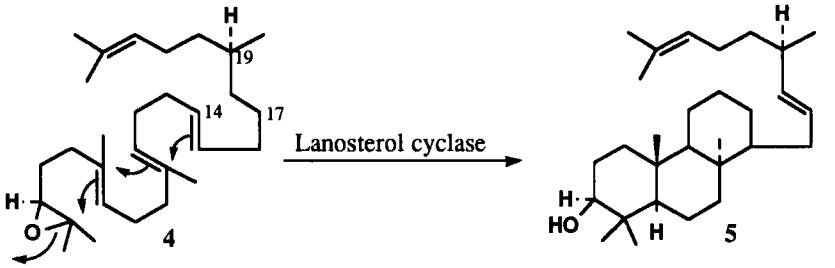


(3)

Both (R) and (S) enantiomers of 2,3-oxidosqualene have been investigated[15,16] and the (S) isomer has been shown to be the only precursor to lanosterol and other related 3ß-hydroxytriterpenes.[16] The enzyme squalene oxide cyclase,[3,4,10] microsomal extracts,[16] and Baker's yeast[17] have all been used to cyclize this and related compounds.[17]

Substrates other than **1** can be ring closed by the cyclase and the minimum structural requirement for cyclase activity is a 2-alkylundeca-2,6,10-triene-2,3-oxide backbone.[18-20] The C-6, C-10, and C-15 methyls and Δ^{14} and Δ^{18} double bonds are not necessary.[21] Suitably positioned heteroatoms which do not significantly alter the polyene backbone do not affect cyclase activity.[12,19]

Much of the cyclization chemistry can be accounted for on the basis of typical carbocation stability considerations.[20] Except for the formation of the C ring, the most stable carbocation is formed upon each ring-formation step. In the formation of the C ring, however, a disubstituted cation is formed to give a six-membered ring when a five-membered ring could form via a trisubstituted carbocation.[21,22] Studies involving 15'-nor-18,19-dihydro-2,3-oxidosqualene (Eq. 4) showed that a six-membered ring formed when the potential intermediates leading to either five- or six-membered ring



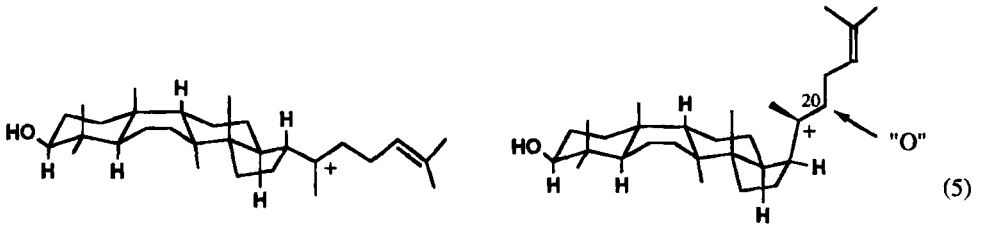
(4)

15'-Nor-18,19-dihydo-2,3-oxidosqualene

formation were both disubstituted.[21-23] This observation led to the conclusion that it is the confor-

mation imposed by lanosterol cyclase that causes six-membered ring formation.[21] A long-range proton transfer must occur in this reaction, and this suggests that the carbons involved are held closely by the enzyme.[21]

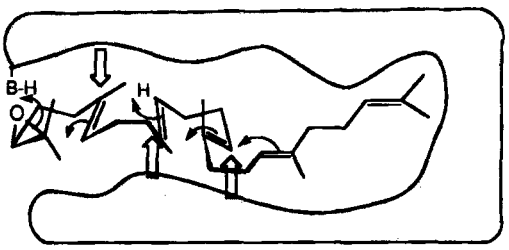
Another key point of lanosterol formation is that an enzyme-substrate complex at C-20 is not required for cyclization, but one was thought to protect the C-20 cation prior to the subsequent CH_3 and H migrations that lead to product.[18] This earlier theory proposed that for lanosterol formation, an alpha side-chain (Eq. 5) formed which underwent a rotation of 120° about the C17, C-20 bond prior to proton migration (from C17 to C-20) to achieve the required R configuration. Recently, however, Corey and coworkers[12] presented evidence that a ß-oriented side chain (Eq. 5) at C-17 is actually formed, which requires only a small rotation (<60°) about this axis to give the natural isomer. The conclusion was reached after Corey's group investigated a squalene oxide derivative that had an oxygen in place of the C-20. Cyclization of this compound with the microsomal protein from bakers' yeast produced a steroid with a ß-oriented acetyl group. This in essence trapped the cationic side chain in its original ß conformation. This evidence appears to alter a long-standing idea about covalent binding of the C20 to the cyclase in the biosynthesis.[12]



(5)

α-oriented side-chain β-oriented side-chain

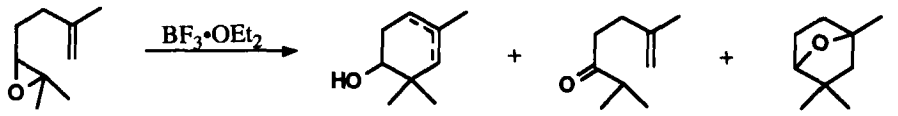
As summarized above, considerable work has been done (and reviewed[20]) on the modification of organic substrates to determine the substrate requirements for cyclase activity.[20-22] However, little is known about the the enzyme's role since it had not, until very recently, been purified (see below). In light of information gained from numerous polyene cyclizations, Johnson has proposed a model for the cyclization.[24] A proton is donated from an specific amino acid residue and the chair-boat-chair conformation required for the cyclization is dictated by the enzyme's topology. Negative point groups (indicated by arrows) stabilize the cationic or cation-like reactive species and accelerate the reaction. It can be further deduced[21] that a basic amino acid deprotonates the cyclization intermediate, as shown.



Mechanistic studies involving manipulation or modification of the cyclase enzyme have been less-studied, in part because the purification of it has been difficult.[25] Recently the enzyme was purified, and it was found to be inactivated by N-ethylmaleimide, indicating that a cysteine residue is essential for activity.[25] This and similar types of enzyme modification research should prove to be a rich area of investigation in the near future. Additional groups have purified the enzyme,[26-29] and claims exist that its structure determination [27]and the cloning of its gene are forthcoming.[27,29] The possibility of genetic engineering and the creation of new medicines and catalysts in this area promises to be an exciting field in the near future.

2. Nonenzymatic Biomimetic Cyclizations

Epoxy-ene cyclizations have been accomplished under nonenzymic conditions, chiefly by the utilization of Lewis-acid promoters (Eq. 6).[30,31] Generally, ring formation follows the pathway that will lead to the most stable cation (the relative propensity of 5-, 6-, and 7-membered rings will be discussed below).

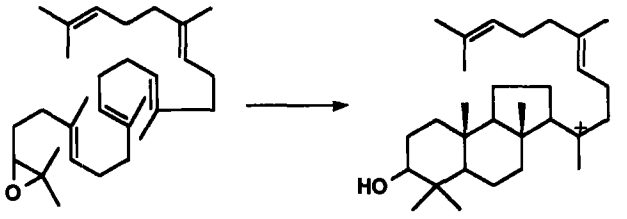


(6)

5 **6** 1.3 : **7** 1.2 : **8** 1.0

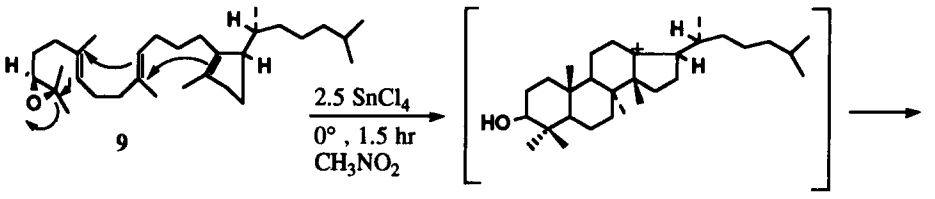
The reaction illustrated in Eq. 6 is a simple one. However, it is important to note that most of the biosynthetic cyclization behavior can be mimicked in related systems under nonenzymic conditions.[20,21] This is demonstrated in the following reactions as well as in earlier work, where numerous steroid compounds have been formed using these methods.[3-5] A notable exception is that treatment of **1** under acidic conditions[20] *in vivo* does not give lanosterol or any other tetracyclic products. The tricyclic products obtained were derived from the cation below (Eq. 7), which exemplifies the carbocation stability considerations mentioned above. Clearly the 6-membered C ring cannot be formed due the carbocation stability restriction.

An approach to forming the ring-size C ring is shown in Eq. 8, where the appropriate size C ring was achieved by using a preformed D ring.[20]



(7)

1



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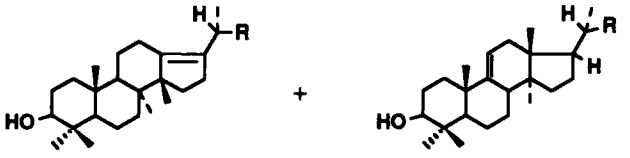
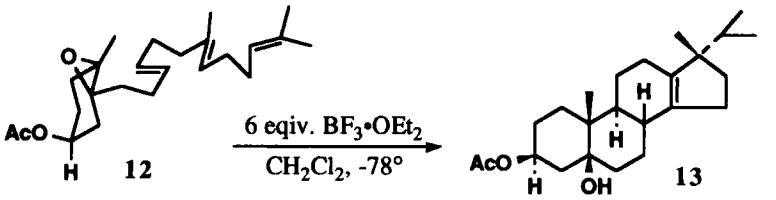


10
2%

11
3.5%

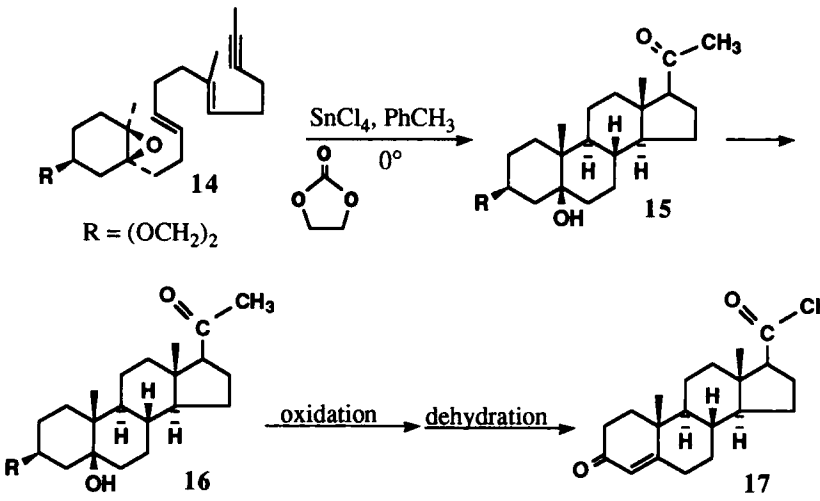
The first example of an authentic natural sterol synthesized by these methods was achieved by the reaction shown below.[32] The reaction product gave identical TLC, GC, MS, IR and proton NMR spectra as that of a compound produced by double bond isomerization and reduction of the natural product 20-methylpregna-4,20-diene-3-one.



(9)

25%

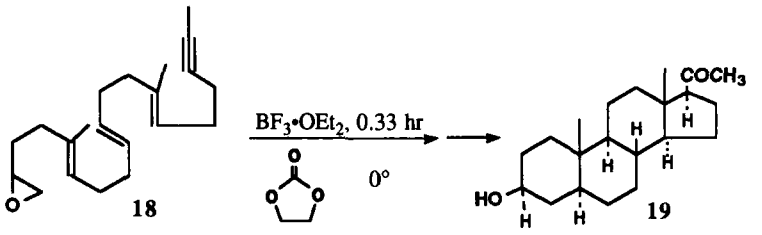
A similar reaction done using a methyl acetylene terminating group (Eq. 10) led to a well-known steroid, (±)-progesterone, in 44% yield.[33] The combination of a methyl acetylene terminator



(10)

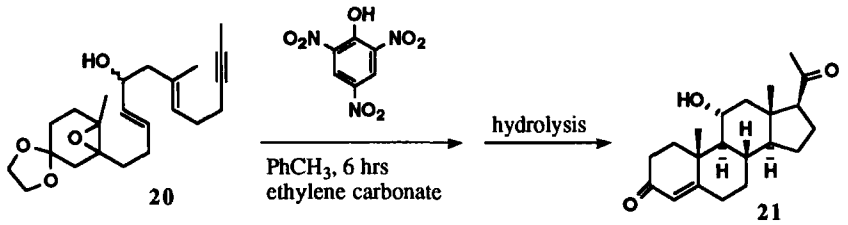
and a cyclohexene oxide was particularly effective as this reaction gave the highest yield of an isolated, pure nonaromatic steroid *via* these methods.

These biomimetic reactions are highly impressive, but the yields are generally low (2%, Eq. 11,[34] to 44%) and the product distributions are complex (Eq. 15 shows representative products). The low yield of allopregnanolone in Eq. 11 can be predicted on the basis of carbocation stabilities: product formation requires that the precursor epoxide ring open to give cationic character at a primary carbon, an unfavorable process. Despite the low yield, the reaction generates seven stereogenic centers, one more than the squalene oxide-lanosterol cyclization does. And, the centers all have the correct relative configuration of normal nonaromatic steroids.[2]



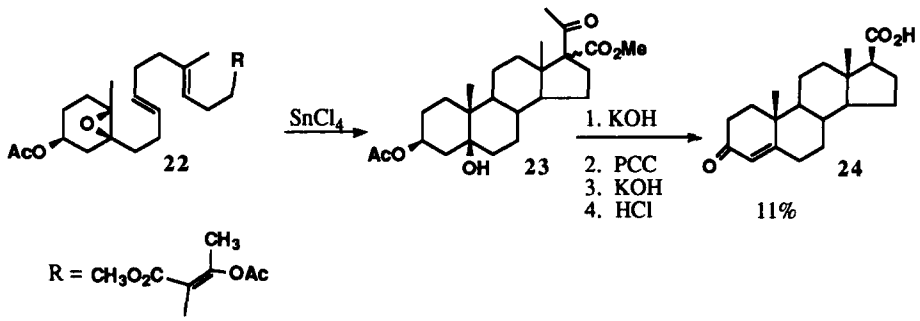
(11)

Quite generally, little comment is made regarding why one Lewis acid is more effective than another at promoting cyclization. The one that gives the highest yield is reported without much comment about why it does. The protonic acid phosphoric acid has been used[33,35] but not nearly as often as Lewis acids. In one unusual case,[35] picric acid was used to avoid the low yields that resulted from the use of $SnCl_4$ and BF_3•OEt_2.



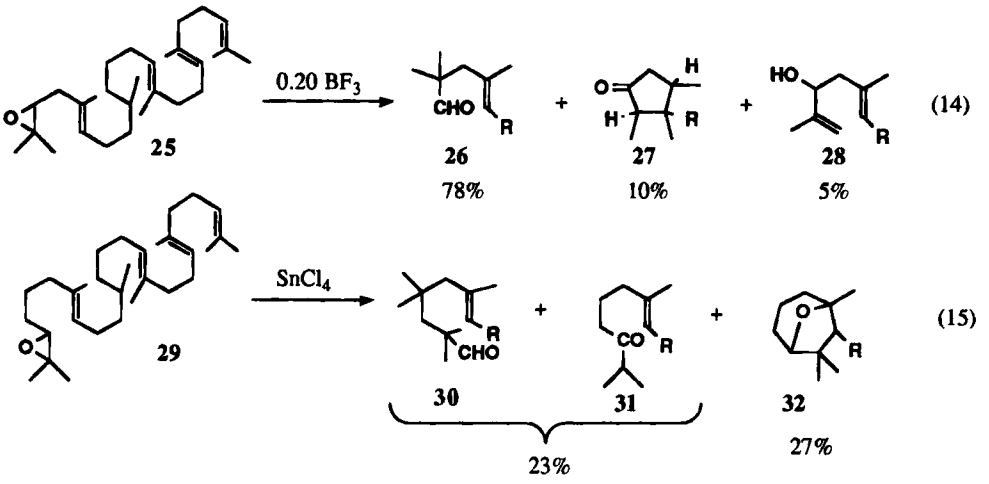
(12)

The use of a ß-keto ester enol acetate can function as an efficient terminator of cyclization. The total synthesis of (±)-androst-4-en-one-17-carboxylic acid has been achieved using these groups.[36]



(13)

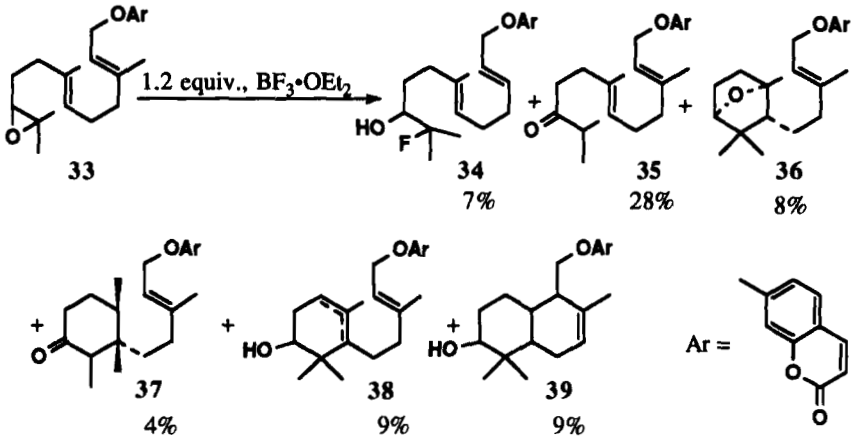
In an interesting set of experiments, van Tamelen and coworkers[37] investigated a compound that could cyclize to form a 5-membered ring at a tertiary epoxide position (Eq. 14). In the same study, he also investigated a compound that could form a 6-membered ring at a secondary epoxide position, or a 7-membered ring at a tertiary site (equation 15). The oxirane in Eq. 14 did not give any multi-ring products and only gave a low yield of monocyclization product. This is not surprising in light of the difficulty of forming 5-membered rings (see section IIa) *via* this process. Also, this cyclization is less likely since, by Baldwin's rules, it would be an endo process[38] (the first ring-formation step in these types of cyclizations is essentially concerted and Baldwin's rules can be applied; the application of Baldwin's rules to the subsequent ring-forming steps would be questionable). It is fascinating to consider the fact that nature does it the hard way in squalene oxide cyclization: it is an endo process!



The formation of a 6-membered ring would be an exo process in Eq. 15, whereas a 7-membered ring would occur by an endo cyclization. Here what little cyclization occurs gives a 7-membered ring. This is most likely due to the fact that the pathway forming this ether product involves a tertiary cation-like species. Also, 7-membered rings have been observed in several epoxide ring-forming reactions (see below). It is somewhat unfortunate that Baldwin's rules, despite their limitations, were not available before all these studies were done.

A problem with the work described above is that very few full reports with experimental details have been published,[31,39] and these describe earlier studies[40,41] on farnesiferol derivatives. Equation 16 shows one of these results[39] to give an idea of the many different types of products formed from these types of reactions.

Although the above mechanisms are usually shown as occurring in a single step, they are thought to be S_N2-like (concerted, with anchimeric assistance) only in the formation of the first ring, with the three remaining rings being formed by a series of steps involving conformationally rigid carbocationic intermediates.[18,19] This seems reasonable in light of kinetic work that shows only the first double bond accelerates the cyclization process.[19] A concerted process was invoked earlier,[7] but this



(16)

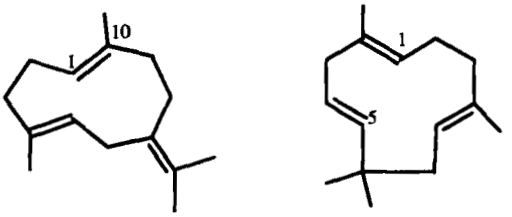
farnesiferol C synthesis

was proposed prior to the kinetic studies[19] and more recent work[19] proposes a stepwise mechanism.[42] It seems quite doubtful that more than two rings are formed in a concerted fashion.[42-46]

3. Medium-ring Epoxide Cyclizations

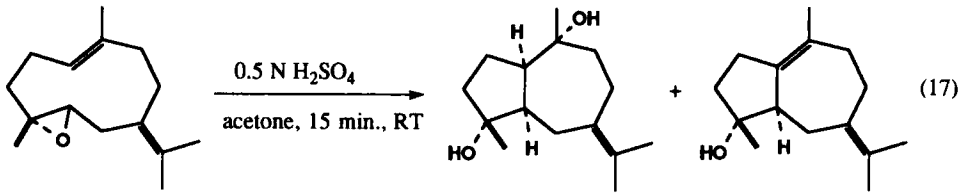
The chemistry of medium ring dienes and their epoxides is of particular interest because of the highly regio- and stereoselective reactions they exhibit.[47] Their reactions typically occur from a single conformation wherein one π-lobe of a double bond interacts transannularly with another double bond or epoxide position, making these reactants highly susceptible to attack by reagents. This chemistry, especially that of medium-ring 1,5-dienes, was reviewed earlier.[47,48]

The chemistry of many sesquiterpenoids has been shown to involve germacrene, **40**, (from plant sources) and humulene (**41**, principly from fungi). Taking cues from natural products, it was

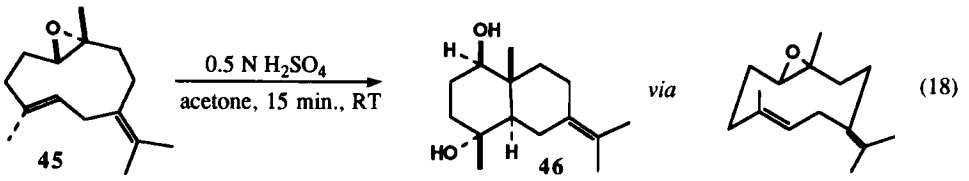


40 **41**

correctly anticipated that some sesquiterpenoids could arise from cyclizations of the epoxides[49,50] of these compounds. Indeed the biosynthesis of products directly from humulene requires that the $\Delta^{4,5}$ bond initially be protonated and then other steps would follow. However, since this bond is the least reactive of the three double bonds, biosynthesis from the epoxide, which has been prepared,[49] seems more likely. The reactions of two epoxides of germacrene have been investigated.[50] Epoxide **42**, the 4,5 isomer, cyclized to guaiane compounds **43** and **44**. Epoxide **45** cyclizes to selinane **46**. The 1,10 isomer cyclizes through the conformation shown, which is commonly the one 1,5- dienes react through.[47]

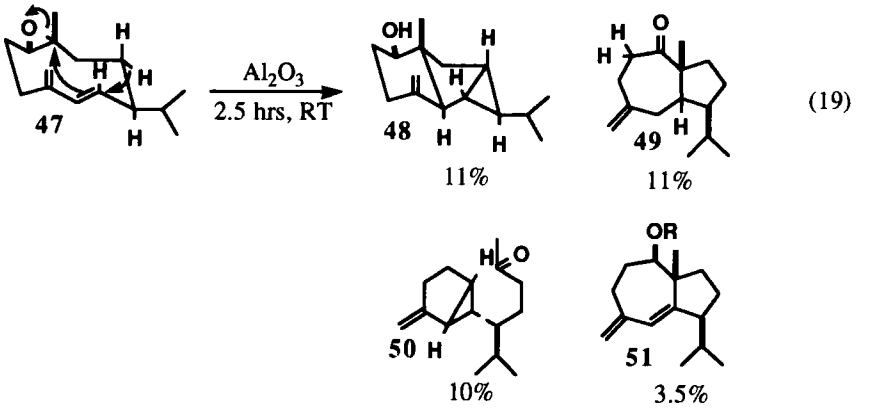


42 43 42% 44 22% (17)



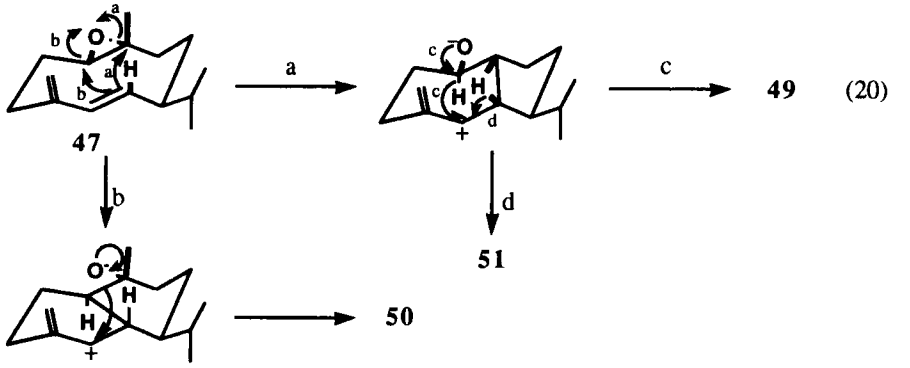
45 46 20% (18)

The reaction of **42** is interesting because it cyclizes to a 5-membered ring. Other than medium ring reactions, where transannular effects are significant, we have found only one other epoxy-ene cyclization where a 5-membered ring is formed (see below). The difficulty of forming this ring size has been demonstrated.[51,52] The epoxide also reacts at the least-substituted epoxide position, but this has been observed before,[13,29,52]



47 48 11% 49 11% (19)

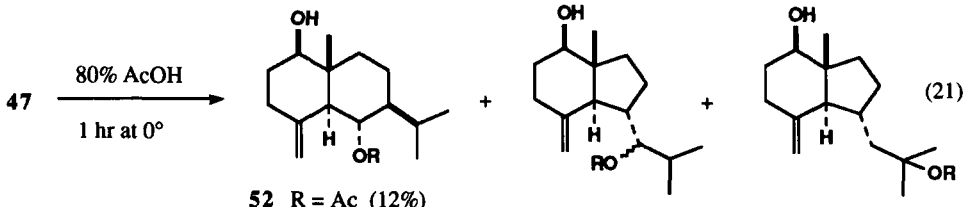
50 10% 51 3.5%



(20)

In two separate reports by the same group, the reactions of germacrene-D with basic alumina were reported to give the products below.[53,54] The mechanisms that account for the products (Eq. 20) suggest transannular H-migrations and bond formations are typically proposed.

Compound **47** gives different compounds when treated with $AlCl_3$ and aqueous acetic acid as shown in equations 21 and 22.[55] Clearly, a variety of ring systems can stereoselectively be obtained by just varying the acid promoter (Eqs.19-22). This can allow the synthesis of a large number of different products. However, the formation of a large number of compounds can be a serious disadvantage (e.g. six products are formed in Eq. 21). It is clear that the choice of the Lewis acid is critical in the formation of the desired compounds. Again, more should be reported on the results of varying the Lewis acid.



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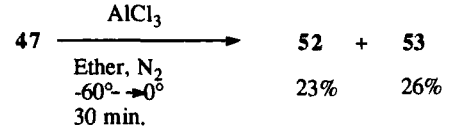
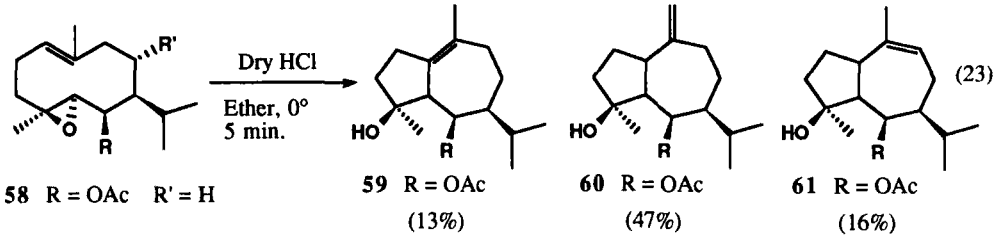


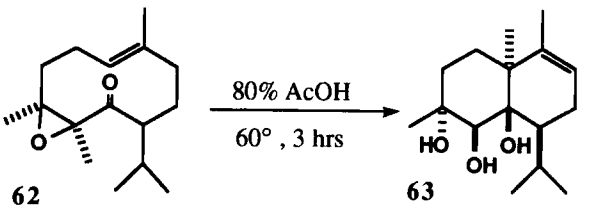
(22)

In contrast to the above results, the natural product **58**, an acetoxygermacrene, gives only guaiane products when cyclized with dry HCl.[56] The 5-membered ring results from epoxide ring-opening at the secondary position rather than the tertiary position. However, the double bond ring closure would involve a tertiary cation.

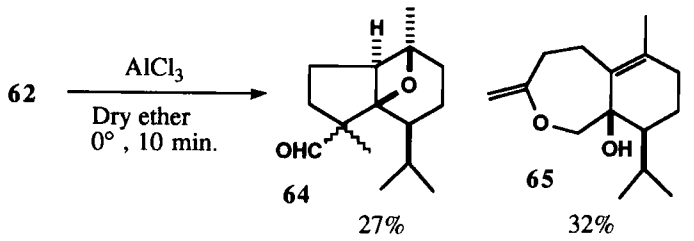


(23)

Epoxygermacrone (**62**) has been shown to give triol **63** on treatment with acetic acid.[57,58] It gives aldehyde **64** and ketone **65** treatment with $AlCl_3$.

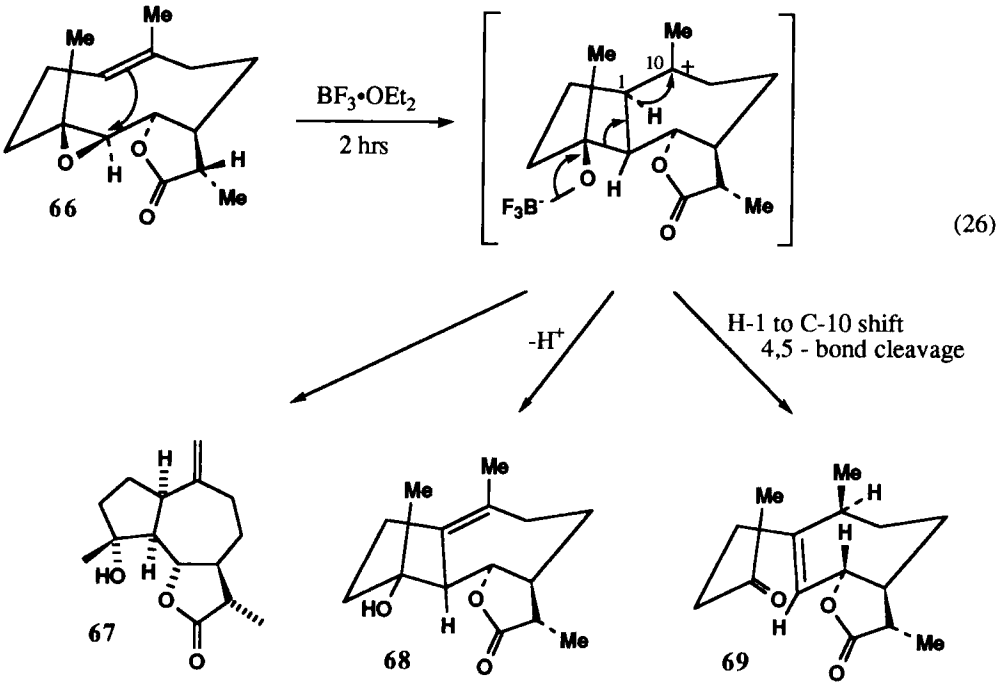


(24)



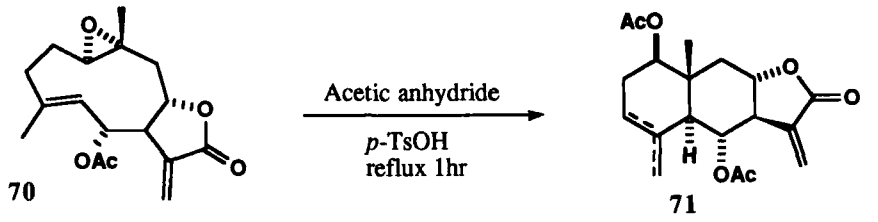
(25)

Dihydroparthenolide (**66**) has been investigated and reported to give guanolides **67** and **68** (a natural product)[59,60] when treated with BF_3•OEt_2. In a reinvestigation[61] a minor product was identified as the first xanthanolide (**69**, 2% yield)) prepared by biomimetic cyclization (Eq. 26 represents the total work of three groups and is not quantitized).



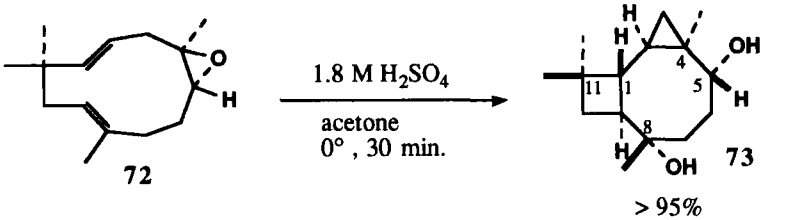
(26)

Pyrethrosin has been reported[62] to give a 1:1 mixture of the acetates below when treated with p-toluenesulfonic acid in acetic anhydride. This work is also a reinvestigation.[63,64]



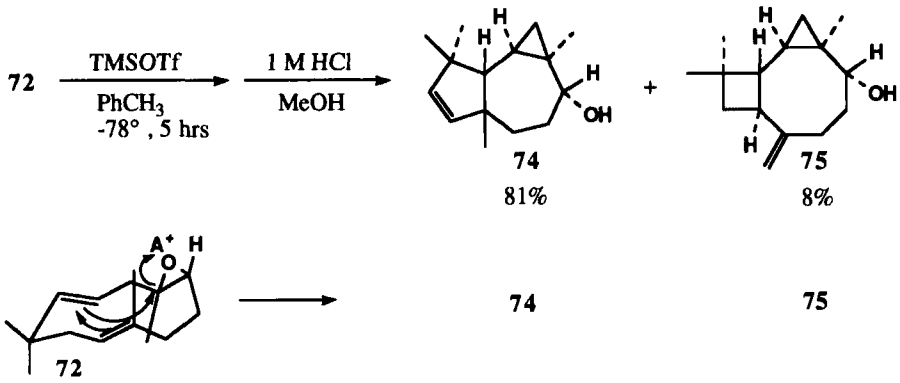
(27)

The three epoxides of humulene have been studied and their chemistry exemplifies the advantages and pitfalls of medium ring cyclization reactions. When the epoxide is formed[65] at the 1,2-position of humulene, the resulting epoxide can be cyclized in sulfuric acid to a single product in highest yield we have observed (Eq.28). An earlier report suggested that several products were formed[66] upon treating **72** with sulfuric acid. The former report repeated the earlier work[66] with a long reaction time and indeed found multiple products, which suggested that the additional products were formed due to secondary reactions. Thus, care should be taken to stop the reaction at the correct time to prevent secondary rearrangement products. The tricyclic product is an interesting ring system that would be difficult to achieve efficiently by other means.



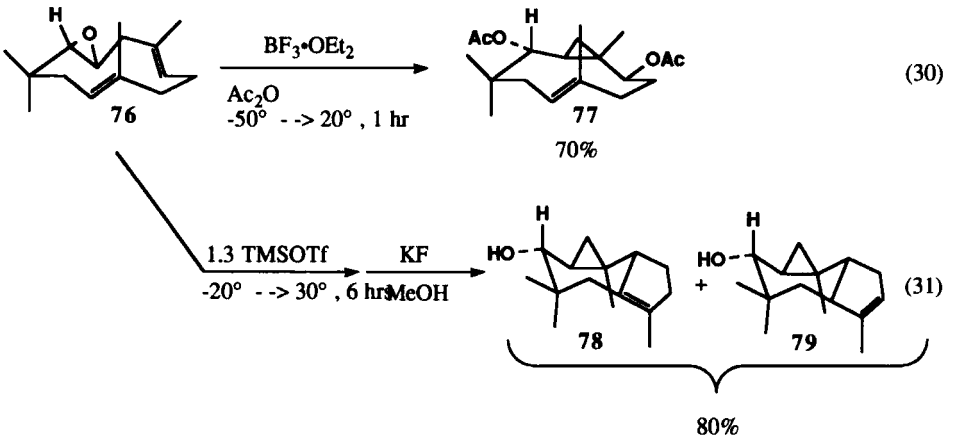
(28)

The same epoxide gives a different major product when treated with TMSOTf.[67] The conformation leading to the products is shown below.



(29)

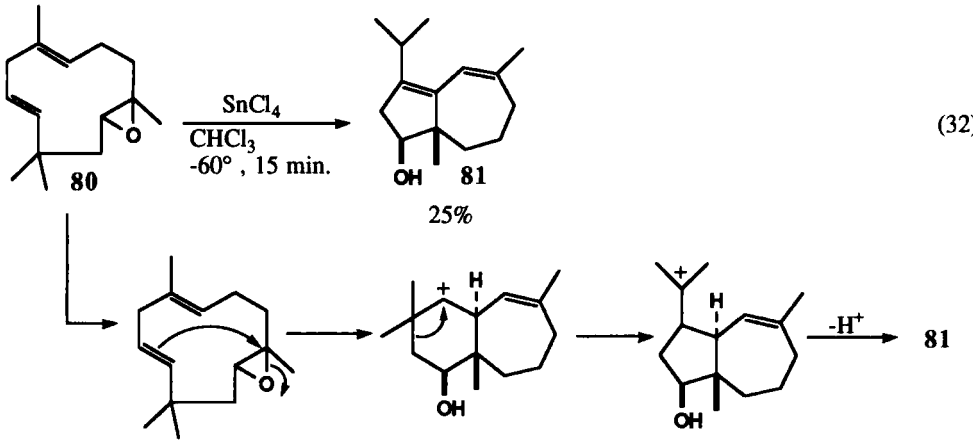
The 4,5-epoxidation product cleanly gives one bicyclic product when reacted with boron trifluoride etherate[68,69] (Eq. 30) and two tricyclic products with TMSOTf (Eq. 31).[68] The epoxide was synthesized by a novel method, namely partial deoxygenation of the humulene triepoxide with WCl_6/n-BuLi (direct epoxidation methods lead to reaction at the most-substituted double bond).[70]



(30)

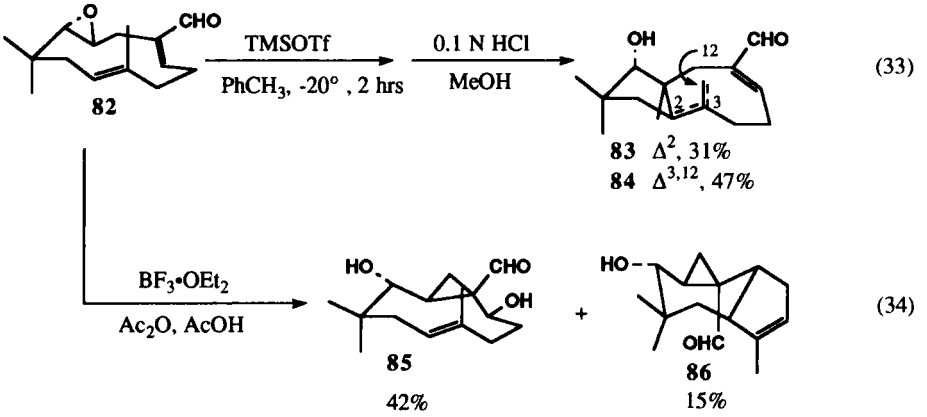
(31)

The 8,9-epoxidation (**80**) product cyclized to a single product which has the same skeletal structure as a constituent of peppermint oil (hydrocarbon products were also present).[71]



(32)

Shirahama's group used a typical Lewis acid and TMSOTf to induce different products (Eqs. 33-34) and ring systems[72] in the reaction of **82**. The aldehyde group on the humulene altered the

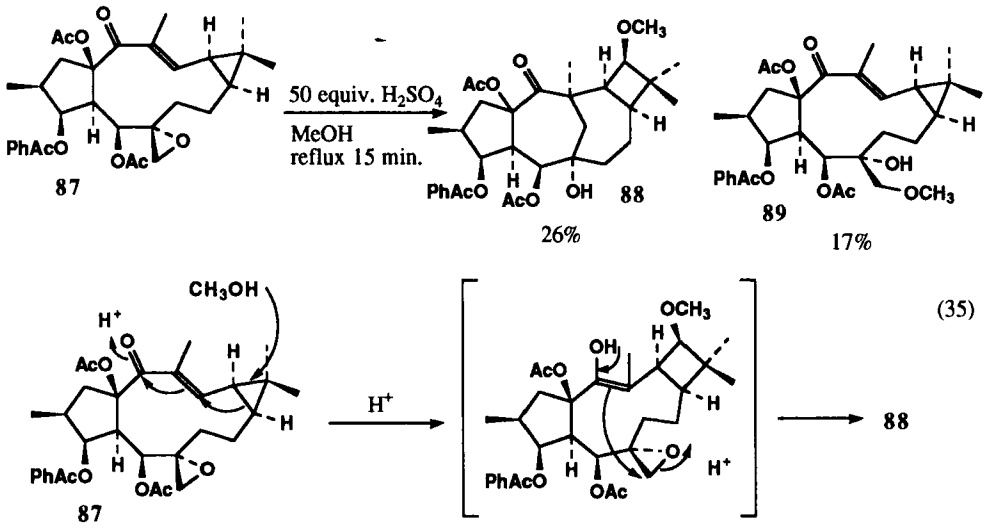


(33)

(34)

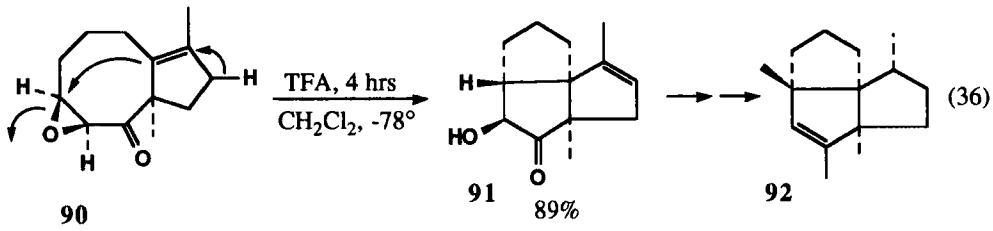
reaction pathway only slightly in the case of BF_3•OEt_2 but new ring structures were formed (relative to **76**) when the Lewis acid was TMSOTf.

The reaction of the natural product epoxylathyrol[73] with H_2SO_4 gives a novel product *via* ring expansion (3– 4-membered ring) and ring-formation processes (Eq. 35).



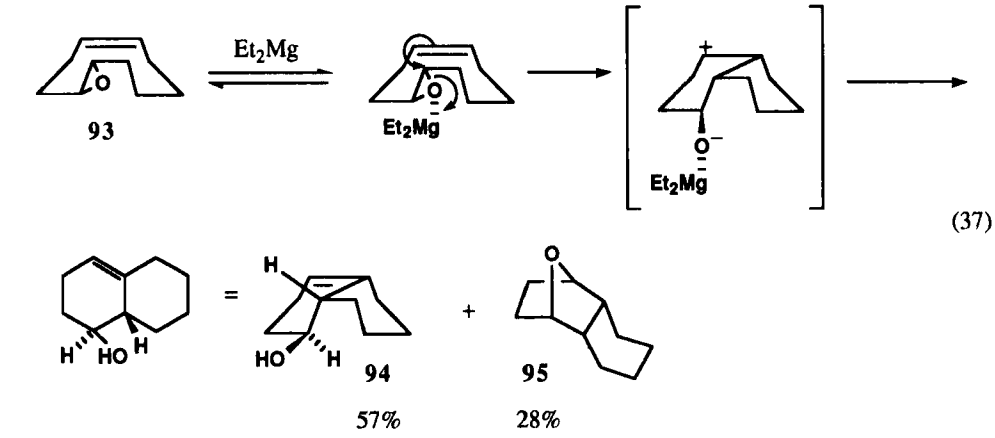
(35)

A non-natural product, epoxide **90**, was made and cyclized to a tricyclic compound[74] that was later transformed into isocomeme (**92**), a recently isolated sesquiterpene.



(36)

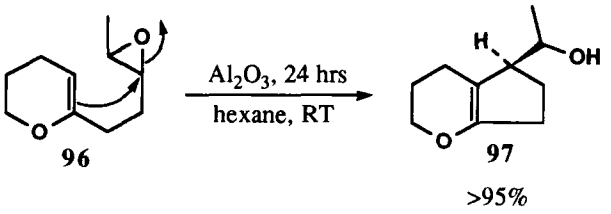
Another non-natural product was cyclized stereoselectively to a decalin ring system.[75] The



(37)

weak, basic Lewis acid Et_2Mg was used to minimize the number of products formed. When $BF_3{\cdot}OEt_2$ and $SnCl_4$ were used, numerous products were formed. This and other work suggests that the weakest Lewis acid that will do a given reaction should be used.

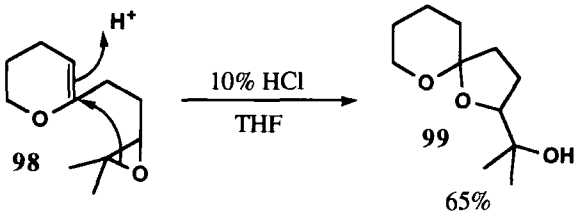
Certain epoxide reactions are different enough from the above epoxy-ene cyclizations to be included separately. One is the cyclization of the epoxy vinyl ether reaction below (Eq. 38).



(38)

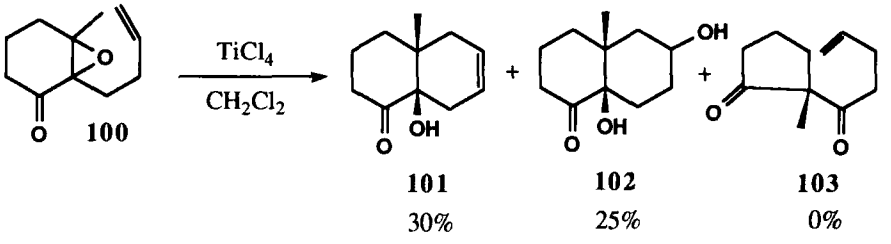
Here[76] a 5-membered ring forms: this is the only clearly established case of a non-medium ring cyclization giving a 5-membered ring. A comment was made about[76] the unusual nature of the reaction, but no explanation was given for it. Perhaps the reaction is essentially stepwise and does not require orbital overlap in the transition state. Certainly the heteroatom-stabilized carbocation that would form in the reaction would impart unique stability to the reaction pathway. Also, it was mentioned that **97** was sensitive to rearrangement and perhaps it is a rearrangement product (i.e. the 6-membered ring forms first and then gives **97**).

Another interesting reaction in the same work[76] is shown in Equation 39. It appears that the initial step in the reaction of **98** is the protonation of the double bond and then after that the epoxide oxygen attacks the stable cation to yield, after hydration, **99**. The sequence of protonation of the double bond and then epoxide ring opening is opposite to that of typical epoxy-ene cyclizations. Again the particular stability of the resonance-stabilized cation that results from protonation is probably responsible for this unusual reaction.



(39)

Sutherland[77-81] has done some interesting work with epoxy-enones (Eq. 40).[77] When $TiCl_4$



(40)

was used as the Lewis acid, only **101** was formed. When the solvent was ether and the weaker Lewis acid $ZnCl_2$ were used, the **101/103** ratio was 0.1. The ring contraction product is clearly favored by a weak Lewis acid. This may result because the weaker (and ether-coordinated) Lewis acid does not generate an electrophilic enough center to promote cyclization. Sutherland has extended his epoxy-enone work to systems that are similar to other epoxy-ene reactions above.[77-81]

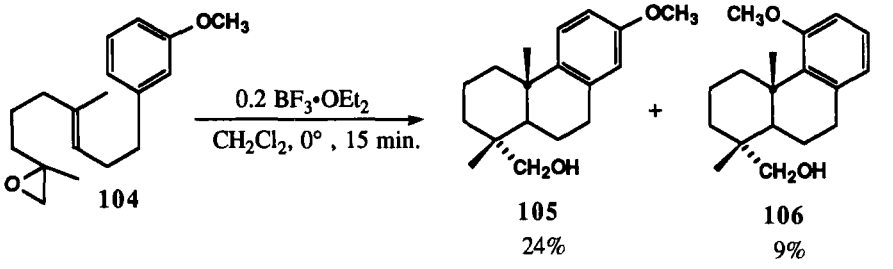
TABLE 1. Reactions Products of **100** when Treated with Lewis Acids

Lewis acid	Solvent	Ratio of **101/103***
$TiCl_4$	CH_2Cl_2	3.0
$AlCl_3$	"	0.3
$SnCl_4$	"	0.3
$ZnCl_2$	"	0.3
$ZnCl_2$	Et_2O	0.1

*No 102 was formed in these reactions

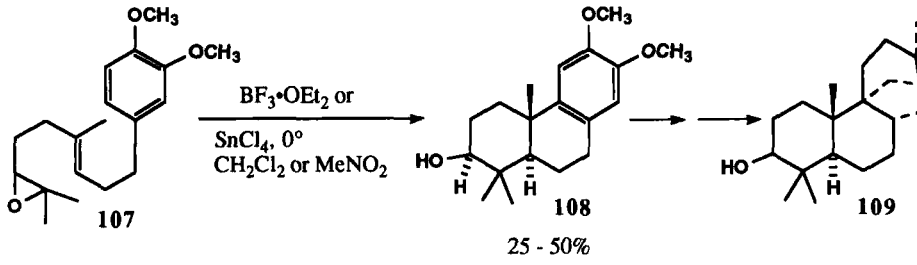
4. Epoxide Cyclizations with Non-double Bond Terminators

Aryl-terminated cyclizations were demonstrated by Goldsmith[82] in 1969 (Eq. 41; the isomeric cis epoxide gave similar products only with cis-fused rings). The aromatic ring-terminator is



(41)

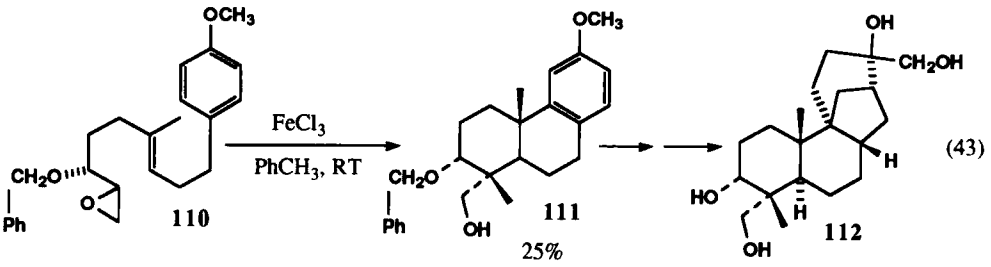
effective[79,81] and gives reasonable yields in light of the number of transformations achieved in a single step. Nasipuri[2,83,84] and van Tamelen[85,86] have studied similar systems, and racemic maritimol, used in venereal disease treatment, has been synthesized[85] by these methods (Eq. 42). Racemic aphidicolin



(42)

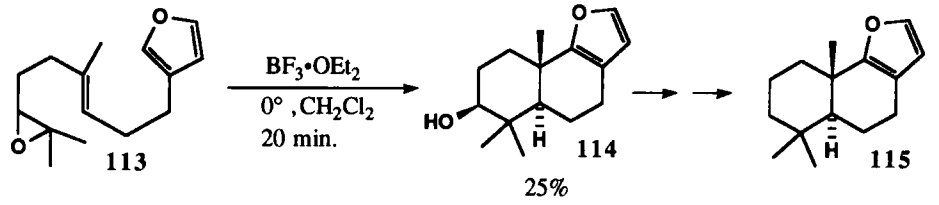
has also been made by epoxy-ene cyclization[86] which is terminated by an aromatic group (Eq. 43).

Note that the aromatic is activated by a methoxy group in all these cases.



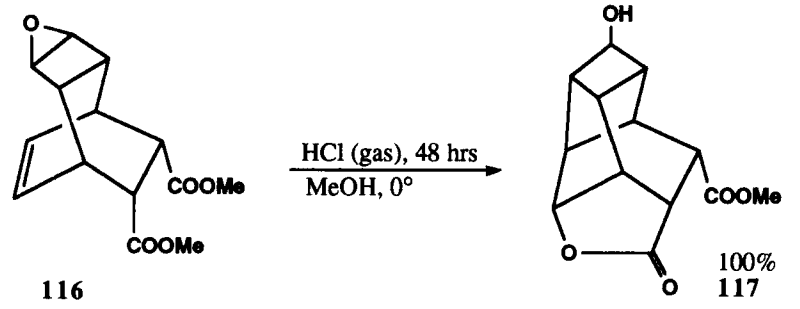
(43)

Nasipuri[2,83] and Das achieved a biomimetic synthesis of pallescensin (**115**) by utilizing a novel furan-terminated cyclization (Eq. 44). The yield of the natural product, however, was higher (84%) when the precursor to the epoxide (the diene) was cyclized with the same Lewis acid. It should be noted however, that weak Lewis acids are used in newer epoxide cyclization work[87] (see below) with furans to avoid degrading them. Use of ZnI_2 and $Ti(O\text{-}i\text{-}Pr)_3Cl$ led to 62 and 65% yields of **114**, respectively.



(44)

Bridged bicyclic compounds have been investigated[88-91] and an example of an ester-terminated reaction that leads directly to a lactone is shown in Eq. 45.

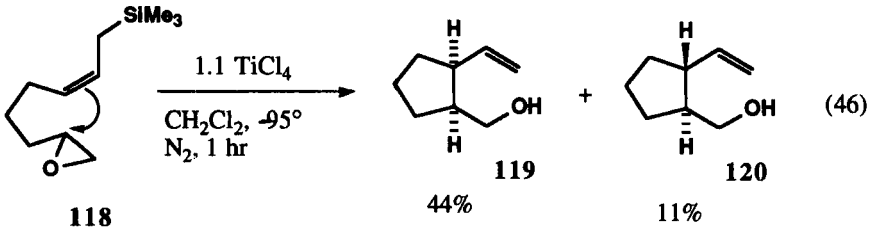


(45)

5. Epoxysilane Cyclizations

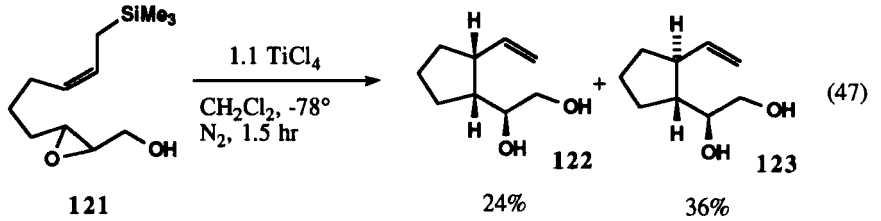
Silicon has a remarkable ability to stabilize positive charge at a ß position.[92] This unique characteristic has been utilized to do highly regio- and stereoselective cyclization reactions. A suitably arranged Si atom can not only stabilize positive charge, but the removal of it during the cyclization process (by typical methods such as treatment with F^-) makes a participating double bond more nucleophilic (see Eq. 49).[93]

As mentioned above, 5-membered rings are hard to form by epoxide cyclizations. However,



(46)

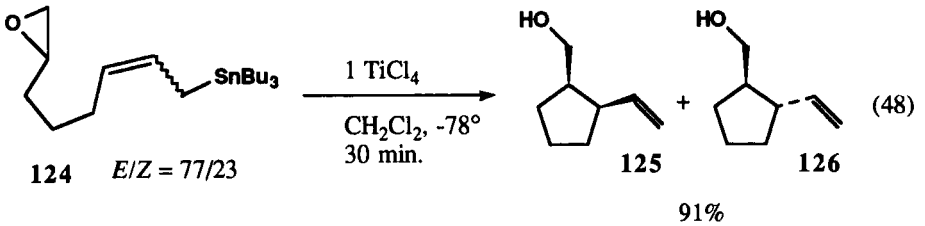
epoxysilanes do form these rings in good yields (Eq. 46).[94-96] The conditions required are mild (-95°) and the reaction times are short. Suitable Sharpless epoxides[94] (i.e. optically active epoxides



(47)

formed from allylic alcohols) also are cyclized in good yields (Eq. 47). This is an important reaction since optically active epoxides are readily available by the Sharpless method, and they can be used in these reactions. However, note that the stereoselectivity of ring-formation is not as clean (cis epoxide leads to only a 4:1 ratio of cis:trans product in Eq. 46 and a 6:1 ratio in Eq. 47) as that of many reactions cited herein. It is encouraging that the selectivity in the Sharpless-type epoxide in Eq. 47 is better than that shown in Eq. 46. The low selectivity can be explained by the fact that the reaction is less concerted due to the difficulty of colinear attack in the transition state.[51] However, clearly this is the method of choice for the formation of 5-membered rings by epoxide cyclization. Also, it should be noted that the trans double bond isomers of **118** and **119** would probably have given higher yields and better selectivity since this has been observed in other studies comparing the reactions of cis and trans isomers (see below).

A tin analog of **118** cyclizes in even better yield (Eq. 48).[97,98] The stereoselectivity is not excellent, but the reactions involve a trans double bond isomer, which is again expected to give a higher yield than the corresponding cis isomers. The study also reported a thorough comparison of the results of using different Lewis acids (Table 1).[97]



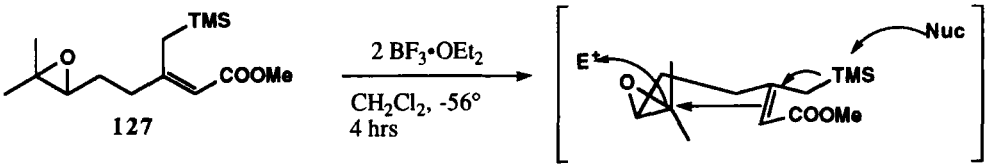
(48)

TABLE 2. Reactions of **124** (*E*/*Z* = 77/23) with different Lewis acids

Lewis acid	Temp. (°C)	Yield (%)	**125**	**126**
$TiCl_4$	-78	100	74	26
$TiCl_4$	-20	90	63	36
$SnCl_4$	-78	21	11	89
TMSOTf	-78	81	74	26

The $SnCl_4$ reaction entry in Table 1 is misleading since this reaction gave many undesirable side products presumed to be due to exchange between tributyl and trichlorostannyl groups and different reaction pathways induced by this promoter.[97]

Six-membered rings have been formed in high yields by epoxysilane cyclizations.[99-101] Eq. 49 shows how removal of the Si group during the cyclization can be viewed as making the participating double bond more nucleophilic.[99] In contrast to 5-membered ring formation, the 6-membered ring formation was implied to be completely stereoselective and this is reasonable. The product (**128**) was transformed into the natural product karahana ether **130** using conventional reactions.



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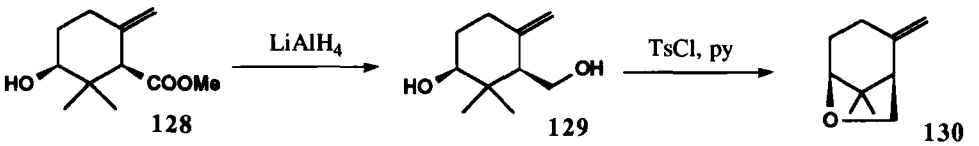
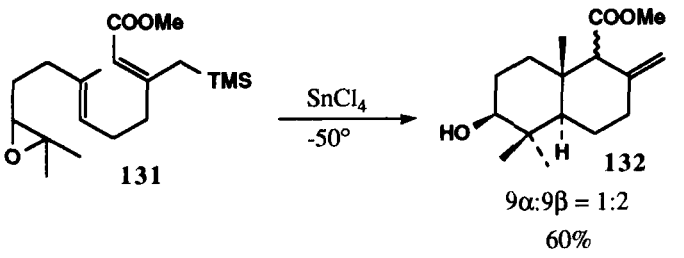


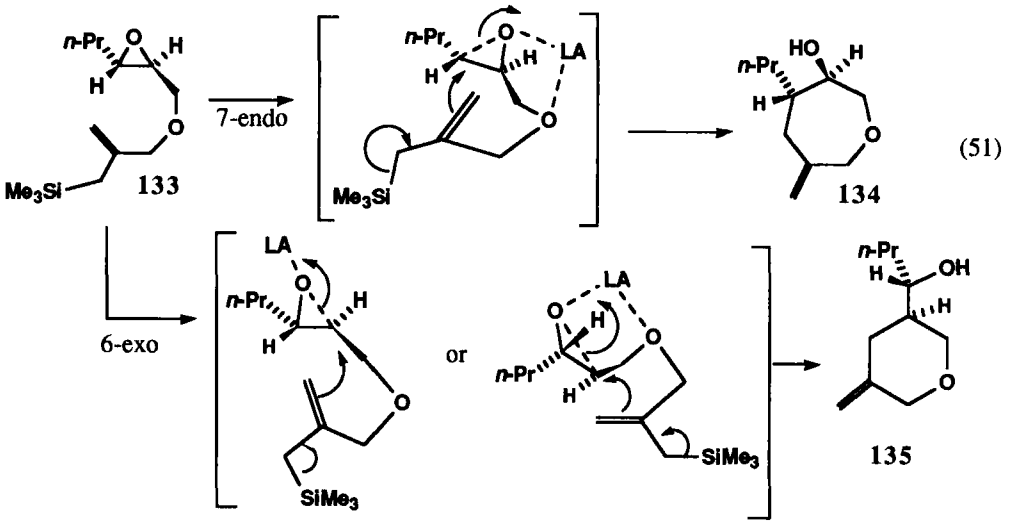
The bicyclization reaction[99] in Eq. 50 allows one to illustrate the influence of the Si atom



(50)

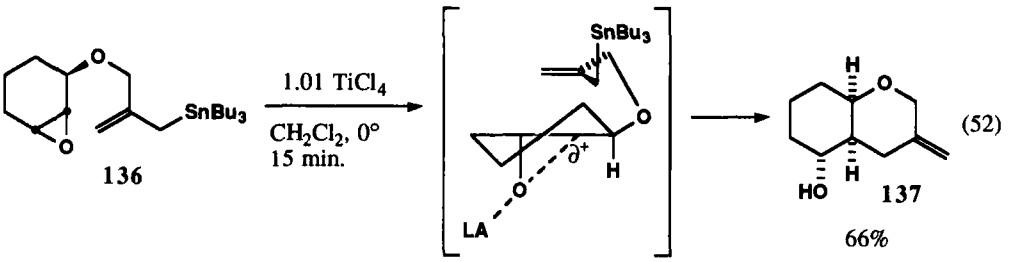
directly. The analog without the Si group has been studied, and it gives a more complex product distribution (7 products) and a lower yield (10-28%) of the isomeric alkenes.[99] Here the Si atom clearly shows advantageous directing and activating effects.

Chelation control has been invoked to explain some interesting regiochemical results[93] in the cyclization of **133**, which contains an oxygen capable of participating in complexation. Two products (Eq. 51) could form, one *via* chelation control to give **134**. The second product (**135**) would occur through a pathway wherein chelation is not possible. BF_3•OEt_2 is not a chelating-type Lewis acid, and treatment of **133** with it gave nearly equal amounts of **134** and **135** (1.2:1). However $TiCl_4$, a chelating Lewis acid, gave only **135** in 95% yield. This pathway appears to be a clear case of chelation control. Analogous epoxystannanes gave good yields but low selectivity (86% yield of **134** and **135** in a 1:1.1 ratio). This was attributed to an early transition state that was less discriminatory toward incipient positive charge.



(51)

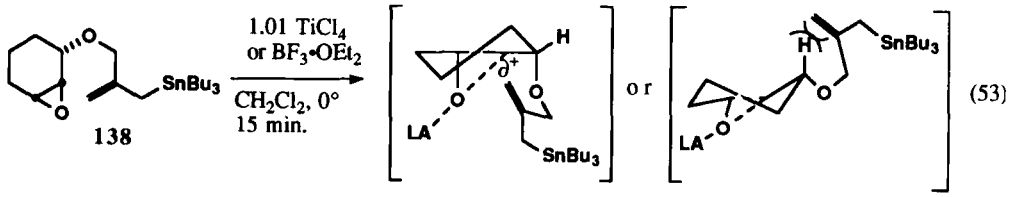
Another dramatic example of the effects of chelation occurs in the same article.[93] Compound **136** cleanly cyclized to **137** in 66% yield. And as Eq. 52 shows, the double bond can readily adopt a



(52)

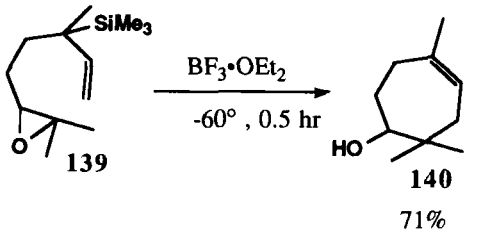
colinear geometry to the epoxide as it ring opens. But the isomeric **138** cannot adopt the required colinear geometry from either of the conformations it could react from (Eq. 53). In this case, no cyclization product is observed. Chelation effects have been postulated in simpler cases.[102-103]

Karahanaenol (**140**) has been made by the cyclization of the epoxysilane **139**.[104] The



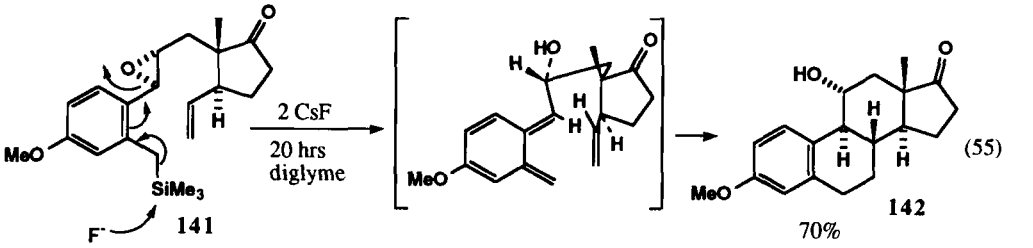
(53)

epoxide was synthesized from geraniol, and it was suggested that some 7-membered ring monoterpenes may be biosynthesized by an analogous process.



(54)

A novel synthesis of steroids has involved these types of precursors.[105] Although it is not purely the type of reaction discussed herein, Eq. 55 shows how an epoxysilane is ring opened by fluoride ion, and then the resulting intermediate undergoes a Diels-Alder reaction. The use of CsF is a particularly mild, effective desilylation procedure.

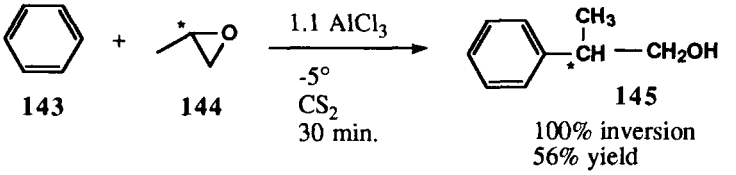


(55)

II EPOXY-ARENE CYCLIZATIONS

1. Epoxide Cyclizations to Benzene-type Aromatics

The intermolecular Friedel-Crafts reaction of optically active propylene oxide with benzene was shown to be 100% stereospecific[106] (Eq. 56). This surprising result suggests that intramolecular

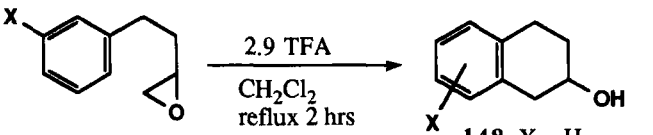


(56)

epoxide Friedel-Crafts reactions, or epoxy-arene cyclizations, might offer highly stereoselective ring-formation reactions. We were initially discouraged from trying these reactions by fellow chemists

because they believed the disruption of the aromatic character in the transition state would lead to low yields. Also, they felt that the epoxide is a good nucleophile and attack of the epoxide oxygen on the incipient positive charge in the reactive species would lead to dimerization, trimerization etc. However, dilute conditions, which are typically used in all of the reactions in this article, minimize this problem. And the supposed problem of breaking up the aromatic character has a very positive side, as will be discussed below.

The early reports on epoxy-arene cyclizations were not encouraging. Davidson and Norman[13] found that **146** gave 1% of cyclization product when treated with TFA. However, the methoxy-



146, X = H
147, X = CH_3O

148 X = H
149 X = 6 - MeO
150 X = 8 - MeO

(57)

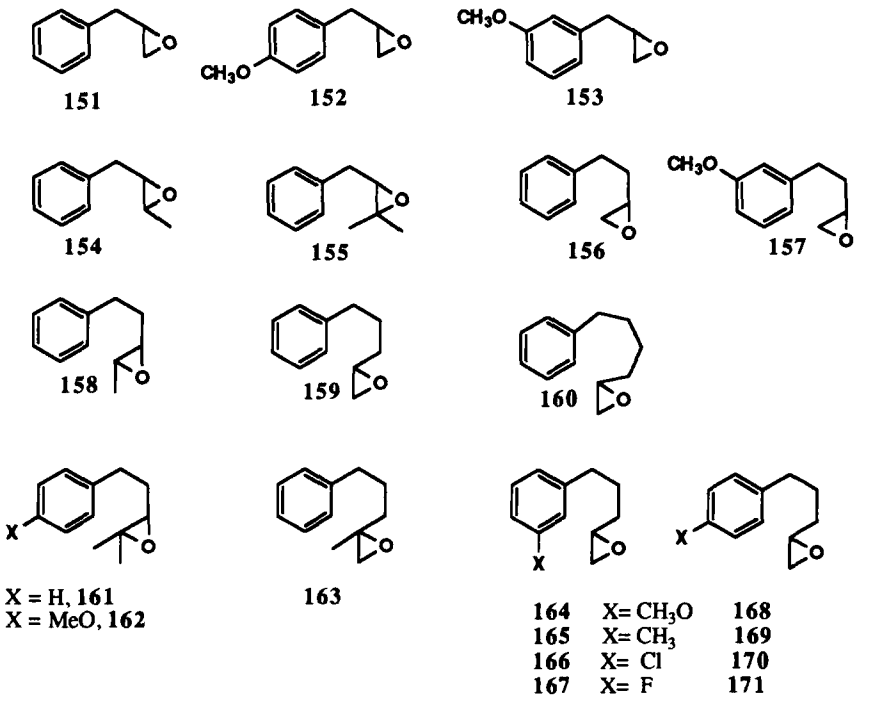
activated **147** was reported to give 18% of **149** (the other 82% was diol that involved simple aqueous ring-opening of the epoxide). We reinvestigated the reaction[52] and found similar results, except that **150** (an expected ortho alkylation product) was also present. The highest yield we observed was 34% (**149**:**150** = 23:77) using $SnCl_4/CH_2Cl_2$. Note that the cyclization involved ring opening at the primary epoxide position to give a 6-membered ring rather than ring opening at the secondary position to give a 5-membered ring.

Julia and Labia[14] investigated epoxides that had tertiary carbons and also observed low yields of cyclization product. We reinvestigated this work, confirmed it and studied additional epoxides (see below). However, it is important to note that the major thrust of both Davidson and Norman's[13] and Julia's and Labia's[14] work was on oxidative cyclizations of arylalkenes (e.g. Davidson and Norman wanted to see if the oxidative cyclizations of 4-phenyl-1-butene occurred *via* 1,2-epoxy-4-phenylbutane).

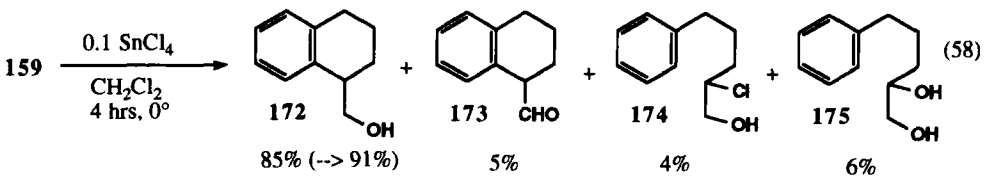
Our approach to developing this area was to make a series of epoxides which could cyclize to 4-, 5-, 6-, and 7-membered rings at primary, secondary and tertiary epoxide positions (Chart 1).[52,107,108] For example compounds **151-153** could form 4-membered rings at secondary epoxide positions or they could form 5-membered rings at primary epoxide positions. Compound **154** could form a 4- or 5-membered ring at secondary epoxide positions. **155** might form a 5-membered ring at a tertiary position or a 4-membered ring at a secondary position. The same reasoning can be applied to compounds **156-163**, where rings of various sizes can form competitively.

The results of Eq. 57 point out an interesting fact: preference for 6-membered ring formation (over 5) is important enough to override the normal preference for ring opening at the most substituted carbon. We never observed 4- or 5-membered ring formation in compounds **151-158**. This suggests a strong stereoelectronic effect in these types of reactions. For these reactions, diols (from hydration of the epoxide during aqueous workup) and carbonyl compounds (formed from typical hydride[109] shifts) formed.[13,52]

Chart 1



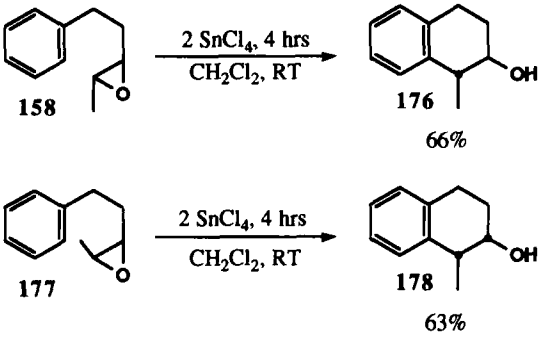
Six-membered ring formation is facile: **159** cyclizes in as high as 91% GC yield.[52,107] The



(58)

side products shown are representative and will not always be drawn in subsequent schemes for conciseness.

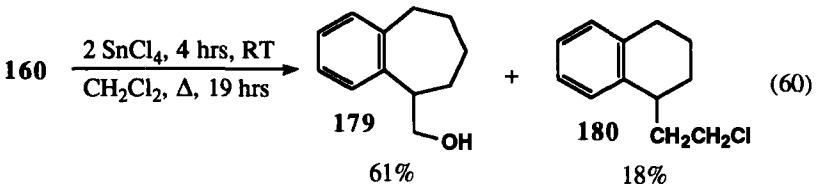
The reaction to give 6-membered rings can be stereospecific as shown in Eq. 59. Here the yields are lower than for **159** and this can be predicted from Baldwin's[38] rules: the former reaction is



(59)

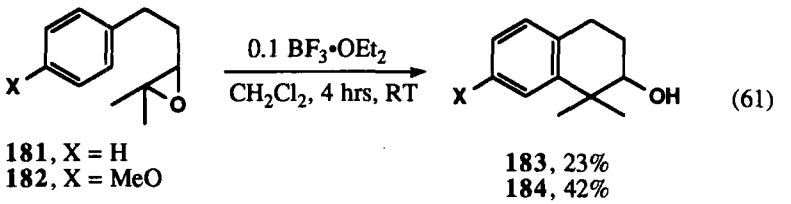
exo whereas the latter reactions are *endo*. Indeed the yields and cyclization preferences are predicted by these rules, with the exception that *exo* 5-membered ring formation is less facile than *endo* 6-membered ring formation (see above).[107]

Seven-membered rings can also be formed in reasonable yields[52] although there is some tendency toward rearrangement (**180**). However, the reactions done in this early paper[52] did not recognize that catalytic quantities of Lewis acid and short reaction times[107] can be used. Had the reaction been done under these mild conditions, rearrangement might not have occurred.



(60)

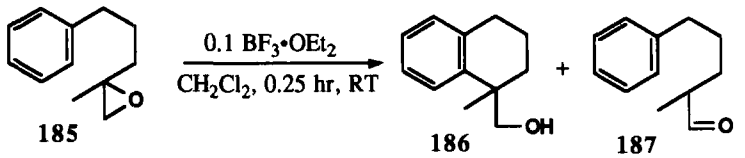
Tertiary epoxides form rings in modest yields.[14,107] The highest yield obtained from these compounds was 53% in the case of of the *exo* cyclization of **185**.[108] For these compounds, there is a



181, X = H
182, X = MeO

183, 23%
184, 42%

(61)



53% 35%

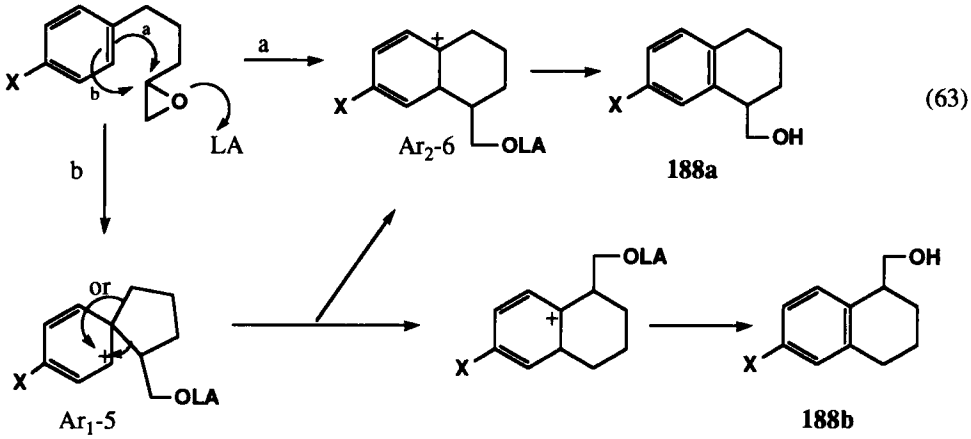
(62)

marked tendency toward rearrangement to carbonyl compounds (e. g. **187**).

From the data in the above studies, it is clear that ring formation propensities follow the order 6>7>5. Also, ring formation yields in epoxy-arene cyclizations are greatest at secondary positions and next best at tertiary positions: They are lowest at primary positions and have only been observed at activated aromatics.

Two characteristics of the reports described in this review concerned us. First, most of the publications were preliminary communications with only partial experimental descriptions. Second, there were not enough kinetic and physical organic studies done. We therefore did kinetic studies on **159** and **164-167**. A linear free energy plot[107] of the data yielded a ρ of -0.91. This reflects a small aromatic substituent effect in the reaction and suggests that arenium ion formation is not highly important in the rate-determining step. A straight line plot was obtained using σ_p^+ values and this suggests the

mechanism may resemble an Ar_1-5 mechanism more than the Ar_2-6 alternative[109] (Eq. 63). However, there were only traces of the rearrangement products (**188b**) that usually form *via* an Ar_1-5 intermediate[109] and therefore we do not favor either mechanistic extreme. Also, if the Ar_1-5 mechanism is the



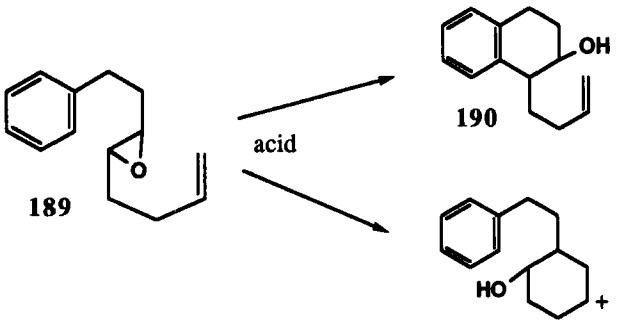
(63)

only operative pathway, a para-methoxy substituent would activate the ring and a meta one would deactivate the reaction. Yet both meta and para methoxy groups accelerate the reaction.[111] This may suggest the pathway will be altered somewhat based on electron demand (i.e. it will take the path that provides the most stable reactive species). Though the picture is far from complete, the presence of some kinetic work should help lead to a better understanding in the future.

Workup of Friedel-Crafts reactions is often involved. For example, if $AlCl_3$ is used as the catalyst, acidic workup (to dissolve amphoteric aluminum salts), basic neutralization and drying are generally necessary. A novel approach was introduced to avoid these operations and also to facilitate monitoring the reactions. An HPLC column was packed with Nafion®H, a Teflon®-like polymeric superacid. In preliminary studies, epoxide **159** was pumped through the column[112] and it gave a 60% yield of **172** (Eq. 58). No workup was was necessary: the compound was merely collected in a vial as it exited from the HPLC detector. A student was able to do and analyze as many as ten reactions in one day on this system whereas only one reaction/analysis could be done per day by conventional techniques. Also, an analytical column was placed between the reactor column and the HPLC detector and then the reactants and products could be separated for monitoring the reaction progress. Initially, poor yields were obtained. However, when trichlorofluoromethane, methylene chloride and TFE were cosolvents, yields increased to good levels (presumably the fluorine-containing solvents, particularly TFE, dissolve the compounds off the fluorine-rich polymer). Further work has been done on several epoxides and it will be reported soon.

Our kinetic studies convinced us that our epoxy-arene cyclizations might be fast enough to compete with epoxy-ene ones (despite the fact that the aromatic character is broken up in the transition state). For example, the reaction of **159** with 0.1 equivalents of $SnCl_4$ (dilute conditions) at -5 °C was essentially over in 20 minutes.

To determine if these reactions could compete with epoxy-ene reactions, we made a series of compounds like **189** which could competitively cyclize to aromatic or double positions. We then treated them with Lewis acids to see which process was most facile.[113]

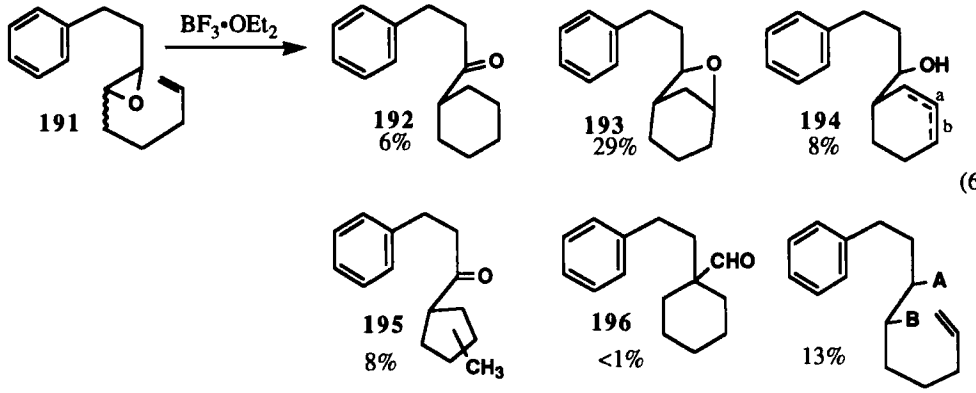


(64)

We also wanted to see if Baldwin's rules could be used to predict which process would occur (e.g. would an *exo* aromatic cyclization occur in preference to an *endo* double bond one; see **198** wherein this is the case).

Epoxide **189** did the surprising thing: it cyclized in 72% yield to the aromatic group. The product composition was very clean. In addition to **190,** only about 1% of a carbonyl compound could be detected by capillary GC. Here neither cyclization pathway would be favored according to Baldwin's rules, if applicable, since both processes would be *endo.*

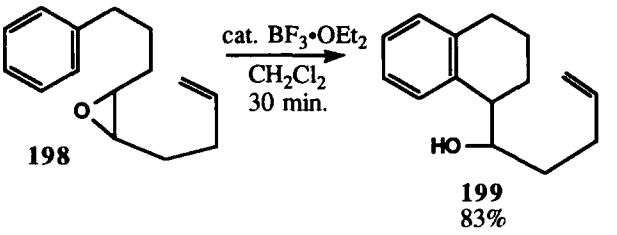
For **191**, relative to **189**, an extra methylene group has been added between the epoxide and the double bond. This makes the double bond process *exo* whereas the aromatic cyclization remains *endo.* The alkene wins in this case (Eq. 65). However, note the numerous products that form.



(65)

197a, A= OH; B= F
197b, A= F; B= OH
197c, A= B = OH

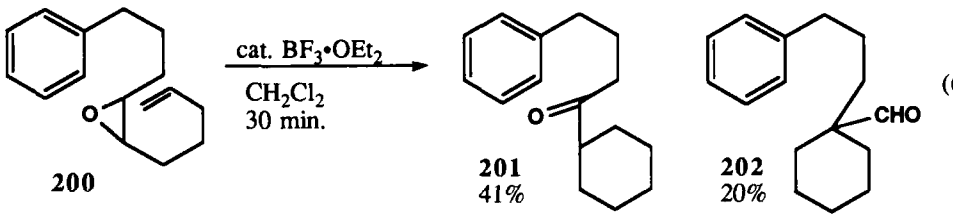
In **198**, the aromatic cyclization would be *exo* and the double bond *endo.* Here again the *exo* process occurs and only one compound predominates (75-83% yield of **199**).



198 199 83% (66)

At first, it puzzled us that essentially one product formed when epoxy-arene cyclization occurred, whereas many products formed when epoxy-ene cyclization did. But in retrospect, it is not surprising. The reactive species formed when the double bond reacts would resemble the cation shown in Eq. 64. Several hydride shifts and proton eliminations (and oxygen bridging to form an ether, as in Eq. 8) are nearly isoenergetic and therefore can and do happen. Only one process is likely to occur when aromatic cyclization occurs: the resulting arenium ion would lose a proton to rearomatize the ring. This is undoubtedly responsible for the product selectivity and it is the up side to aromatic cyclization.

Both cyclization processes of **200** would be *exo*. Based on the result in Eq. 64, we expected aromatic cyclization to predominate. However, double bond reaction did (there were 1-2% quantities



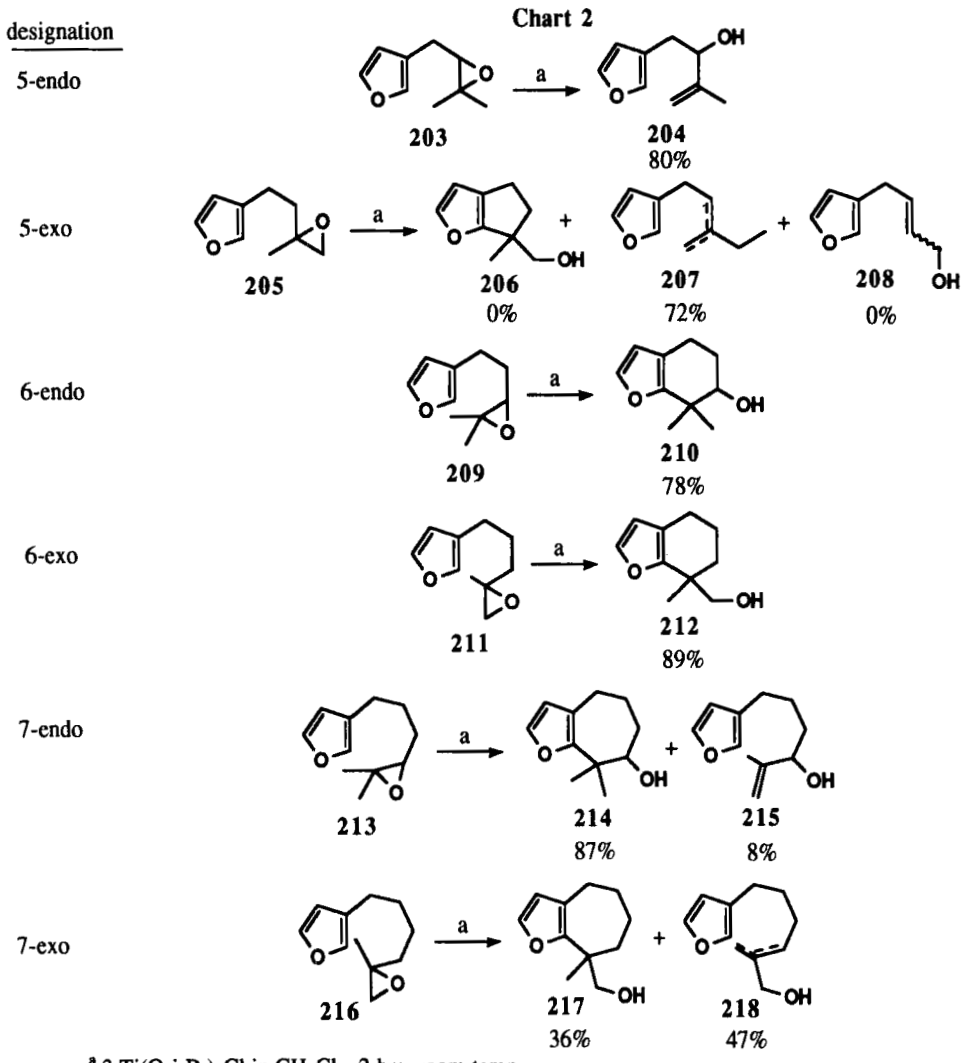
200 201 41% 202 20% (67)

of several compounds but they were not identified). We suspect that the results in Eq. 67 reflect the inherently greater reactivity of the double bond since both pathways can easily attain the geometry required for ring formation. No good explanation currently exists for the predominance of epoxy-arene cyclization in Eq. 64. But it is interesting that the larger aryl group cyclizes when the required geometry is more difficult to achieve.

2. Epoxide Cyclizations to Non-benzene-type Aromatics

Epoxide cyclizations that occur directly to furan[87] (rather than epoxy-ene cyclizations that are terminated by furan as in Eq. 44) and pyrrole have been studied by Tanis[114] and coworkers. In thorough studies, several epoxides were investigated and the validity of Baldwin's rules in predicting the relative ease of their ring closures was tested. Chart 2 summarizes the results and gives the Baldwin's rules designations. Although several Lewis acids were tested, $Ti(O\text{-}i\text{-}Pr)_3Cl$ gave the best yields in almost all cases. This hybrid Lewis acid [3 $Ti(O\text{-}i\text{-}Pr)_4$ + $TiCl_4$] was utilized to absorb protic acid, moderate Lewis acidity and minimize furan side-reactions. With BF_3•OEt_2, Et_2AlCl, $EtAlCl_2$, alumina and $Ti(O\text{-}i\text{-}Pr)_3Cl$ no 5-membered ring formation was observed whether the cyclization was *exo* or *endo*.[87] However, **206** was produced in 25% yield (along with 44% **207**) when $ZnCl_2$ was used as the

Chart 2



[a] 3 $Ti(O\text{-}i\text{-}Pr)_3Cl$ in CH_2Cl_2, 2 hrs, room temp

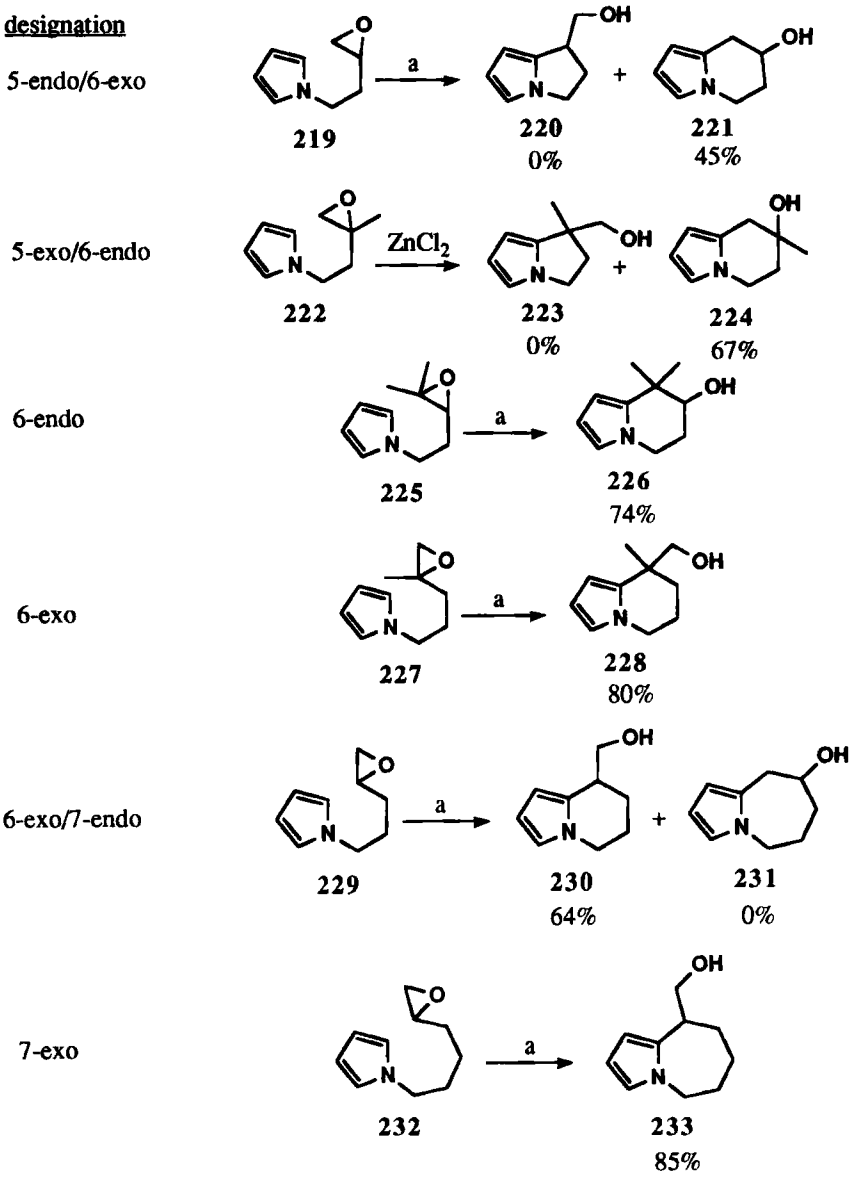
Lewis acid. This is an apparent exception to the paucity of epoxide 5-membered ring formation examples, but it is peculiar that none of the other Lewis acids yielded this product. It is conceivable that ZnI_2 formed an iodohydrin which then cyclized after I^- loss. This possibility was not tested.

The 6-endo and 6-exo cyclization yields (78 and 89%, respectively) in Chart 2 showed that the *exo* process is more facile. This is similar to our results (Eqs.58 and 59). It is interesting that the 7-endo cyclization gave a higher yield than the 7-exo process. The Baldwin's rule designations are clearly useful for predicting the relative ease of 6-membered ring formation. But the rules for 7-membered ring formation are not expected to be as valuable since the longer side chains involved can more easily attain the required colinear attack.

The epoxy-pyrrole results[114] are summarized in Chart 3. The results are similar to those of

the furan work with two exceptions. First, epoxide **219** gives ring formation at the least substituted carbon (this has been observed before in activated aromatics; see Eq.57). This can be attributed to two factors: the preference for 6-membered ring formation and the strong nucleophilicity of the pyrrole ring. Second, a similar anti-Markovnikov pathway was observed for **229**, as yields of **230** and **231**

Chart 3

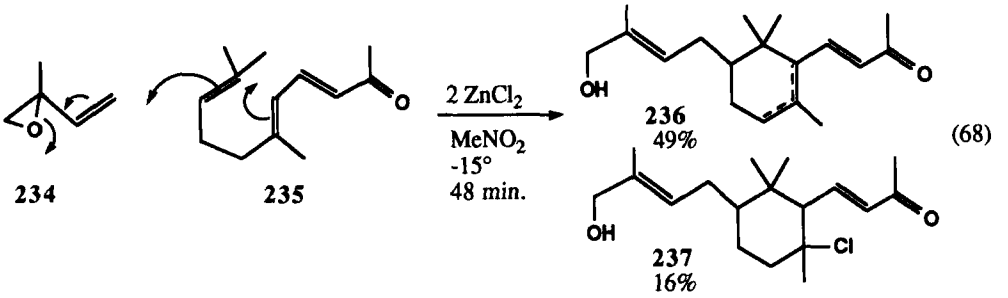


[a] 3 $Ti(O\text{-}i\text{-}Pr)_3Cl$ in CH_2Cl_2, 0°, 15 min.

were 37% and 48%, respectively. Again the nucleophilicity was probably responsible for this behavior. Again, care must be taken to avoid acid-induced pyrrole ring reactions. The pyrrole cyclizations

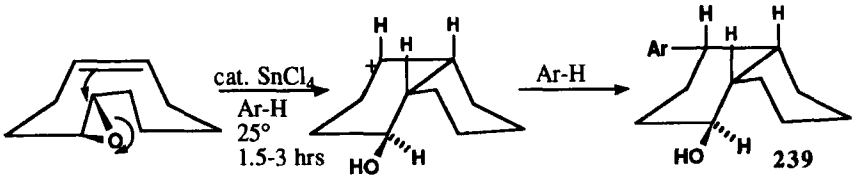
are potentially useful in alkaloid synthesis.[114]

Before proceeding to the next section, it is worthwhile pointing out examples of intermolecular variants of the chemistry described herein. Ferezou and Julia[115] ring opened an acyclic epoxide and it then coupled intermolecularly to a dienone; this intermediate then cyclized (Eq. 68). This is a novel example of an epoxide initiating a ring closure in an intermolecular fashion. This chemistry was used to make carotenoids.



(68)

In another study, epoxide cyclization was promoted in the usual fashion, but the resulting cation was used in an intermolecular Friedel-Crafts reaction.[116] This Friedel-Crafts reaction was highly stereoselective for the isomer shown (**239**). These two examples represent a little-studied area and perhaps more research along these lines should be attempted.

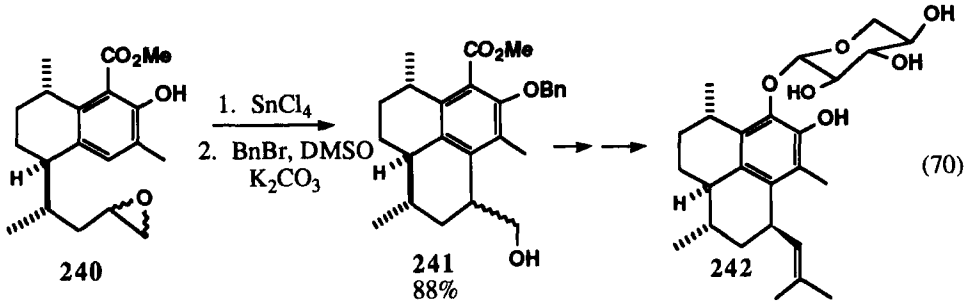


(69)

Ar= Ph (70%), tolyl (75%), EtPh (50%), furanyl (48%), thiophenyl (30%), etc.

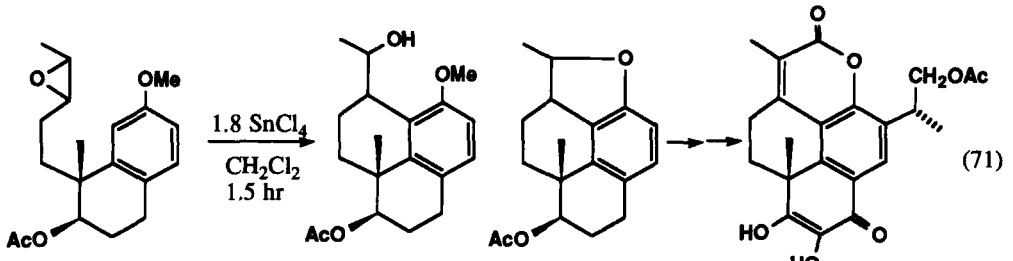
3. Natural Products from Epoxy-arene Cyclizations

Epoxy-ene cyclizations have been exploited in natural products synthesis. Since the epoxy-arene reactions are relatively new,[52,87,107,108,114] they have not been used significantly in this regard. However, some natural products have been made utilizing this chemistry as a key step.



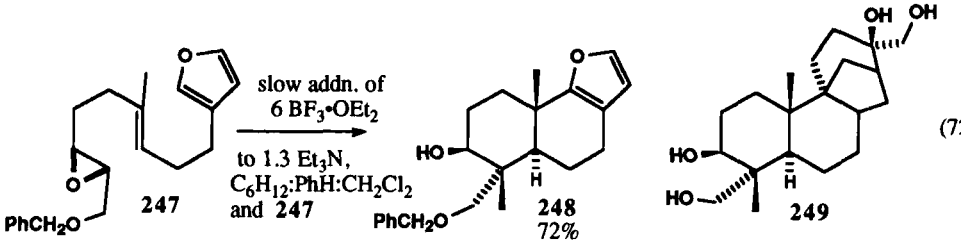
(70)

Pseudopterosin A (**242**), a potent antiinflamatory and analgesic, has been made[117] using the cyclization of **240** as a key step. The ring-formation step and the benzylation occurred in 88% overall yield, which verifies our contention that these reactions can go in high yields. Note that the reaction is a favored 6-exo process. A ring similar ring formation reaction was used to form the major portion of ring skeleton of edulone A (**246**).[118] The product **245** is interesting in that it is probably formed from **244** by attack of the methoxy group on the acid-complexed hydroxyl group (or a similar process). We have observed this same reaction in meta-methoxy-substituted aryl cyclizations.[119]



243 → **244** 58% + **245** 38% → **246** (71)

Tanis[120,121] has used a furan-terminated epoxy-ene reaction to synthesize (+)-aphidicolin (**249**). A key part of this synthesis is that the epoxide cyclization (**247** to **248**) was completely stereoselective. The optically active epoxide was made using the Sharpless epoxidation procedure and it exemplifies the potential of this procedure in making natural products of high optical purity.



247 → **248** 72% → **249** (72)

Conclusions

Epoxy-ene and epoxy-arene reactions undergo surprisingly selective reactions. The epoxy-ene reactions have been elegantly exploited in organic synthesis, whereas the potential of epoxy-arene cyclizations in synthesis has just begun to be explored. The epoxy-arene cyclizations can compete surprisingly well kinetically with epoxy-ene cyclizations, but this is highly dependent on stereoelectronic factors. This stereoelectronic influence is strong enough to even produce reactions at the least-substituted carbon (which is not expected based on electronic effects alone).

Epoxy-arene cyclizations have a selectivity advantage due to the fact that they generally do not suffer the multiple hydride shifts and proton eliminations that epoxy-ene reactions do. The arenium ion resulting from arene cyclizations will simply eliminate the ring proton that will lead to rearomatization of the ring.

Epoxysilane cyclizations offer some unique advantages that have not been fully exploited. The Si atom imparts selectivity not seen in carbogens. This area looks very promising.

More physical organic studies need to be done in these areas. In particular, it should be determined why various Lewis acids work best in these reactions. Our kinetic work on epoxy-arene reactions raised some questions which should be answered.[107] A complex is formed between benzene and ethylene oxide in dilute, neutral solution.[122] This complex may influence results of epoxy-arene cyclizations, since it might line up the aromatic and the epoxide in the conformation required for cyclization. The influence of this complex in these reactions should be tested.

Several epoxy-silane[123-126] cyclizations and an epoxyneocembrene[127] cyclization came to our attention since this review was submitted.

Acknowledgments.- We thank Research Corporation, the Petroleum Research Fund (administered by the American Chemical Society) and the National Science Foundation for early support of this work. The National Institutes of Health (GM 44318-01) is gratefully acknowledged for current support involving the influence of Lewis acids on the reactions of epoxides. The National Science Foundation has also provided current support for students through the REU program (CHE-8807450). The student coauthors (see references 52, 107, 108, 112, 113 and 116) are especially thanked for their hard work in these pursuits. Yvonne N. Grassl is appreciated for doing many of the equations herein.

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23. At one time, it was believed that a five-membered ring was formed first followed by a rearrangement to a six-membered ring [see E. E. van Tamelen, K.B.Sharpless, R.Hanzlik, R. B. Clayton, A. L. Burlingame, and P. Wszolek, *J. Am. Chem. Soc.*, **89**, 7150 (1967)]. This idea has some current support[11] but it has been questioned by van Tamelen and others.[21]

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