Use of Cyclopropanes and Their Derivatives in Organic Synthesis

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Contents

I. Introduction

1. Overview

Under the influence of a variety of chemical reagents (e.g., electrophiles, nucleophiles, radicals) or external physical forces (e.g., heat, light), cyclopropane derivatives undergo a variety of ring-opening reactions. In contrast to normal paraffins, the chemistry of the cyclopropane C–C single bond resembles that of a carbon–carbon *double* bond. Relief of ring strain provides a potent thermodynamic driving force for these processes. Since numerous methodologies have been developed for the construction of three-membered carbocycles, the chemistry of cyclopropanes has emerged as a versatile tool in organic synthesis. In this section, the theoretical basis for the "unusual" reactivity and properties of cyclopropane is reviewed.

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2. Thermodynamic Considerations/Strain Energy

Formation of a cyclopropane ring requires that three $-CH_2-$ groups be accommodated into a cyclic arrangement with all C–C–C bond angles equal to 60°.[1,2] These bond angles are considerably less than the ideal 109.5° for sp^3-hybridized orbitals, resulting in significant angular (Bayer) strain. Further, cyclopropane suffers additional torsional (Pitzer) strain because the coplanar arrangement of the carbon atoms mandates that the C–H bonds be eclipsed. The relief of strain associated with ring opening is often invoked to rationalize the high reactivity of the cyclopropyl group.

However, the strain energies of cyclopropane and cyclobutane are similar: 27.5 and 26.5 kcal/mol, respectively.[3] This similarity is also revealed by considering the energy required for homolytic C–C cleavage, c-$(CH_2)_{n+2} \rightarrow {}^{\bullet}CH_2(CH_2)_nCH_2{}^{\bullet}$: 61 kcal/mol[4] for n = 1 and 62.5 kcal/mol for n = 2.[5] In contrast, whereas the chemistry of a cyclopropane ring resembles that of a carbon–carbon double bond (i.e., susceptible to electrophilic attack, easily oxidized, etc.), the chemistry of cyclobutane is unremarkable. Consequently, thermochemical considerations *alone* are insufficient to explain the unusual reactivity of cyclopropane.

3. Bonding in Cyclopropane

A. The Coulson–Moffitt Model

A popular description of bonding in cyclopropane, advanced by Coulson and Moffitt, imagines the construction of the cyclopropane ring from three sp^3-hybridized $-CH_2-$ groups (Figure 1).[6,7] As such, the sp^3 hybrids are pointed ca. 22° outward from the imaginary line connecting the nuclei, resulting in about 20% less effective overlap than the C–C bond of ethane. For this reason, the bonds are often referred to as "bent".[6-9]

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Henry Wong was born in Hong Kong in 1950. He graduated (B.Sc.) at the Chinese University of Hong Kong (1973) and obtained his Ph.D. (1976) from University College London (with the late Franz Sondheimer). After postdoctoral work (1976–1978) at Harvard University (with the late Robert B. Woodward), he returned to University College London as a Ramsay Memorial Fellow (1979–1980). From 1980 to 1982, he was an Associate Research Fellow at the Shanghai Institute of Organic Chemistry, Academia Sinica, China. He finally returned to Hong Kong as a Lecturer of the Hong Kong Polytechnic (1982–1983). He is currently a Senior Lecturer at the Chinese University of Hong Kong. His research interests include synthesis and study of nonnatural as well as natural products.

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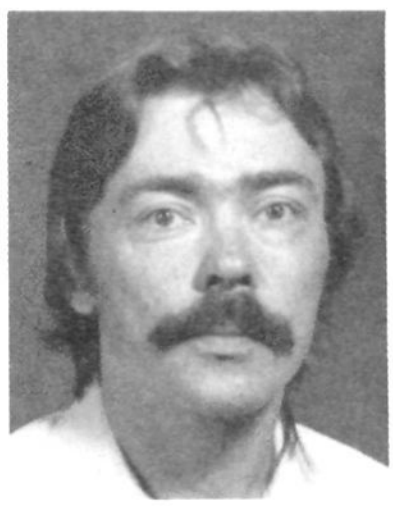


Tomas Hudlicky was born in 1949 and received his B.S. at Virginia Tech in 1973. He studied with Prof. E. Wenkert at Rice University, where he received his Ph.D. in 1977. After a postdoctoral fellowship with Prof. W. Oppolzer at the University of Geneva, he joined the faculty at Illinois Institute of Technology in Chicago. In 1982 he moved to Virginia Tech, where he now is Professor of Chemistry. He received the A. P. Sloan Fellowship in 1981 and the NIH Research Career Development Award in 1984. His research interests include the development of enantioselective synthetic methodology, the design of new reactions, total synthesis of natural products, and microbial transformations of achiral hydrocarbons and the use of their metabolites in chiral synthesis.

This diminished overlap is reckoned to be the source of the angular strain.

Other formulations of the Coulson–Moffitt model involve utilizing $sp^{2.3}$- and sp^5-hybridized orbitals to describe the carbon–hydrogen and carbon–carbon bonds, respectively. The greater p-character in the C–C σ-bonds is frequently invoked to explain the similarity of cyclopropane chemistry to that of olefins. Various physical properties (e.g., $J(^1H–^{13}C)$ and $J(^{13}C–^{13}C)$ NMR coupling constants) are adequately explained by this deviation from sp^3 hybridization.[10]

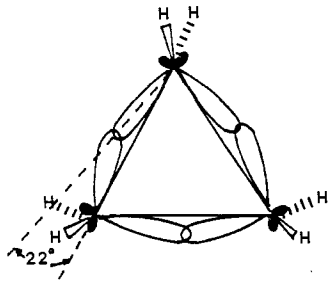


Figure 1. The Coulson–Moffitt model.

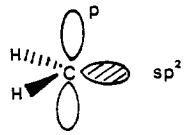


Figure 2.

B. The Walsh Model

The Walsh model[11–13] envisions cyclopropane as being constructed from three sp^2-hybridized $-CH_2-$'s (Figure 2), arranged such that the sp^2 hybrids are oriented radially toward the center of the cyclopropane ring. The molecular orbital diagram depicted in Figure 3 results from the use of this basis set.[14]

By this model, angular strain is also attributed to poor overlap. For example, the overlap of the orbitals comprising ψ_1 is diminished because the lobes of the sp^2 hybrids are oriented inward from the imaginary lines connecting the carbon atoms. Similarly, ψ_2 can be viewed as a distorted π-bond. (This distorted π-bond description of ψ_2 offers an intuitively appealing explanation of the reactivity of cyclopropane toward electrophilic reagents.)

C. The Notion of σ-Aromaticity

The classical approach to organic chemistry has been to treat σ-bonds as localized entities. However, as articulated by Dewar[15] in 1984, this assumption is often lacking. The concept of "σ-conjugation" provides an especially intriguing explanation of the physical and chemical properties of cyclopropane: the three C–C σ-bonds provide a cyclic array of 6 electrons; by the $4n + 2$ rule, cyclopropane is aromatic. In contrast, cyclobutane, with $4n$ electrons ($n = 1$), is antiaromatic.[15]

A slight modification of this approach, advocated by Cremer,[16] utilizes the Walsh basis set and the molecular orbital diagram depicted in Figure 3. σ-Aromaticity is postulated to arise from occupation of the "surface orbital", ψ_1, resulting in a three-center,two-electron bond.[16]

Several chemical and physical properties of cyclopropane, previously considered anomalous, are easily explained when σ-aromaticity is invoked. Some of these are highlighted below. For additional examples, the interested reader is directed to the original literature.[15,16]

1. Strain Energy. The strain energy of cyclopropane (27.5 kcal/mol)[3] is substantially lower than that calculated from the C–C–C bending force constant obtained from vibrational spectroscopy (104 kcal/mol);[15,17] part of the discrepancy is attributable to σ-aromaticity. (Note that the same calculation for cyclobutane *underestimates* the strain energy since eclipsing (Pitzer) interactions are not taken into account.[15])

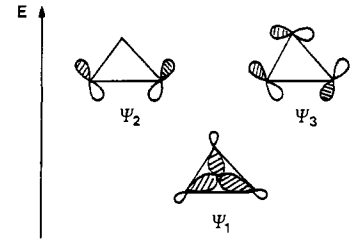


Figure 3. The Walsh model.

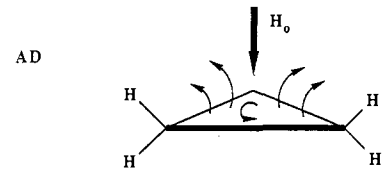
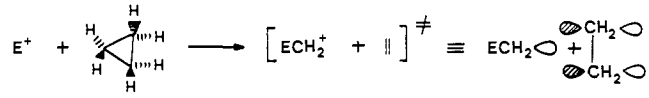


Figure 4. Ring-current effects in cyclopropane.

SCHEME I

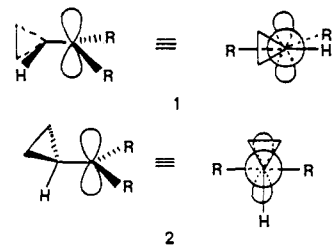


2. NMR Characteristics. Coupling constants (e.g., $J(^1H-^{13}C)$ and $J(^{13}C-^{13}C)$) are explicable by approximate sp^2 hybridization of carbon as explained by either the Coulson–Moffitt or Walsh models (vide supra). Ring-current effects provide a satisfactory explanation for the observed upfield shift of the protons of cyclopropane because its protons are shielded from the applied magnetic field (Figure 4).[15]

3. Reactivity of Cyclopropane toward Electrophiles. The high reactivity of cyclopropane toward electrophiles, frequently explained on the basis of a relief of strain, can be better understood on the basis of σ-aromaticity. For the reaction of $c\text{-}C_3H_6$ with an electrophile (Scheme I), aromaticity is maintained in the transition state (depicted in Scheme I as a methyl cation/ethylene π-complex for clarity).[15] Thus, the fact the cyclopropyl group remains essentially *intact* in the transition state accounts for its high reactivity. In contrast, the ring strain (thermodynamic) argument would suggest the cyclopropane ring is substantially broken in the transition state.

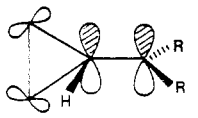
4. The Cyclopropyl Group as a Substituent

When attached to a π-system, a cyclopropyl ring can be characterized as a strong π-donor. The interaction of ψ_2 and ψ_3 (Figure 1) with the π system is maximal when the cyclopropyl ring adopts a bisected (1) rather than a symmetric (2) conformation with respect to the adjacent π-system.[18]



With the Walsh model, this conformational requirement is readily explained by considering the symmetry

of the orbitals involved in a system such as **3**.[18] The bisected conformation allows maximum overlap between the p-orbital on the cyclopropyl carbon and the adjacent π-system. In the symmetric conformation, these orbitals are orthogonal.



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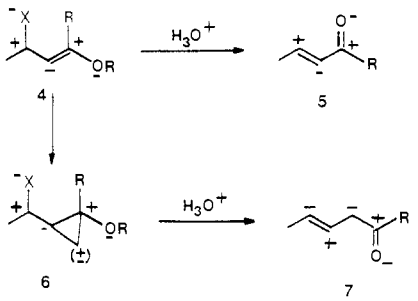
5. Perspective on Cyclopropanes in Synthesis

The utility of cyclopropanes in organic synthesis arises from the unique characteristics of the three-membered ring and the resemblance of its chemistry to that of a carbon–carbon double bond. Additionally, the incorporation of a cyclopropyl group provides an opportunity, upon reacting, for changes in either the consonant or the dissonant relationships within the carbon framework of the products. For example, hydrolysis of **4** provides enone **5** in which the consonant



relationship of charges has been retained. The incorporation of the odd carbon in the form of a cyclopropane in **6** allows for the cleavage to **7**, where the consonance (or dissonance) will be dictated solely on the basis of further *use* or will depend on additional functionalities surrounding the olefin.[19]

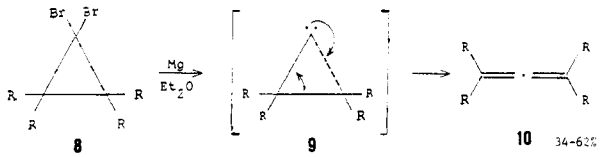
This quality becomes important during synthetic design as it allows the addition of only one carbon. The cyclopropane ring can thus be viewed as a "synthetic wedge tool", which is introduced *to disrupt* an existing charge parity or *to introduce* it in current or incipient operations.

Cyclopropanes and their derivatives have been used in virtually every synthetic sense that befits the utility of alkenes in synthesis. Their preparation is the subject of many reviews[20] and their applications in the preparation of organic compounds are extensive.[21] No attempt is made in this review to describe exhaustively every procedure or transformation. Rather the review should be viewed as a guide to the literature organized by the fundamental reaction types in which cyclopropanes participate. The coverage of the literature is complete through December 1987, and a comprehensive listing of reviews on aspects of cyclopropane chemistry is found in the reference section, irrespective of whether the reviews are mentioned explicitly in the text.[22]

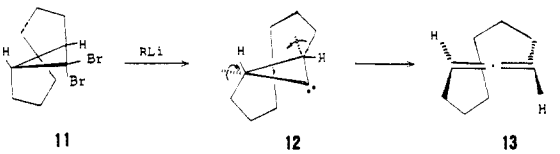
II. Thermal Ring Fission

1. Cyclopropyl Carbene Rearrangement

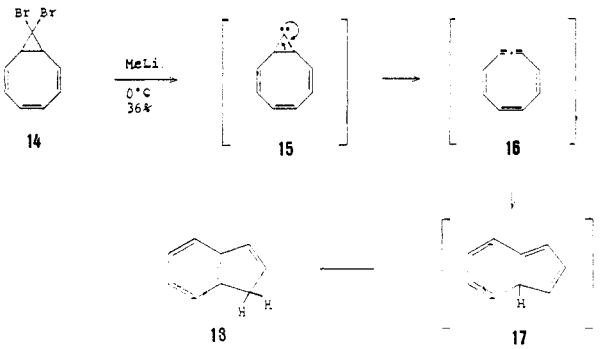
An intriguing rearrangement occurs when 1,1-dibromocyclopropanes are treated with magnesium. The product of this reaction is an allene,[23,24] which may arise from rearrangement of a cyclopropyl carbenoid.[9]



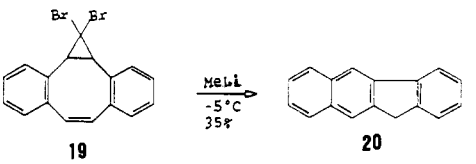
Alkyllithiums are also used to generate cyclopropyl carbenoids.[25] For example, treatment of dibromocyclopropane **11** with an alkyllithium yields intermediate **12**, which undergoes conrotatory ring opening to give allene **13** in an overall ring expansion.[26]



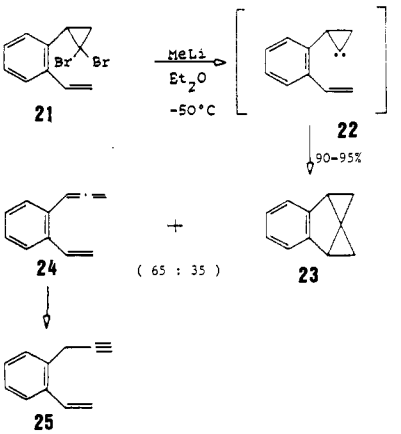
When other suitable functional groups are present in the molecule, the endocyclic allenes react further. Thus, dibromobicyclononatriene **14** reacts with methyllithium to form initially carbenoid **15**, which rearranges to the nine-membered cyclic polyene **16** and finally to bicyclic compound **17**. [1,5]-Sigmatropic rearrangement of **17** yields indene **18**.[27]



Through a similar series of events, **19** furnished the fused aromatic system **20**.[27]

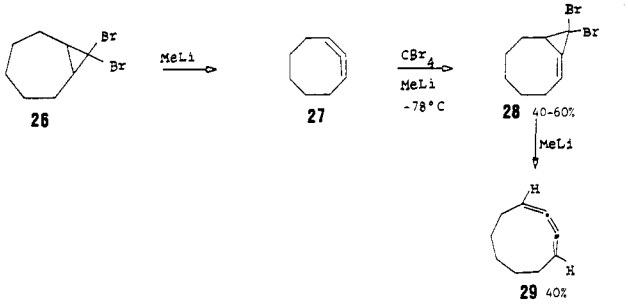


The cyclopropyl carbenoid can be trapped internally, as in the reaction of *o*-(2,2-dibromocyclopropyl)styrene (**21**) with methyllithium at −50 °C, which leads to a



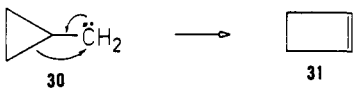
mixture of hydrocarbons, **23** and **24**, in 90–95% yield. At room temperature, the mixture of **23** and **24** is accompanied by a trace of alkyne **25**, formed by the base-induced isomerization of allene **24**.[28]

Dibromocyclopropane **26** can be converted to 1,2-cyclooctadiene (**27**) by reaction with methyllithium. Treatment of **27** with carbon tetrabromide and methyllithium at –78 °C generates methylenecyclopropane **28**, which is transformed into 1,2,3-cyclononatriene (**29**) by further treatment with methyllithium.[29] Various dibromovinylcyclopropanes have also been shown to lead to vinylcyclopropyl carbenes, which rearrange to either vinylallenes or cyclopentadienes.[30]

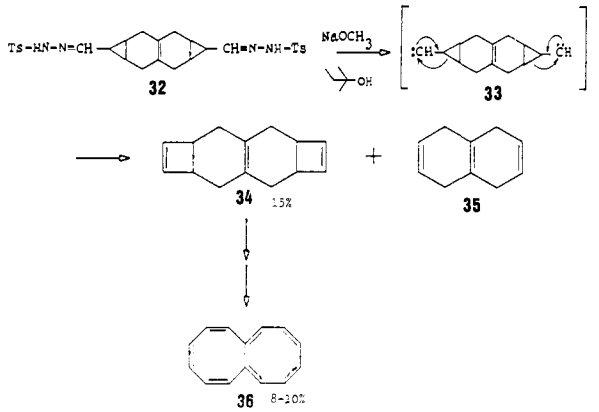


2. Cyclopropylmethyl Carbene Rearrangement

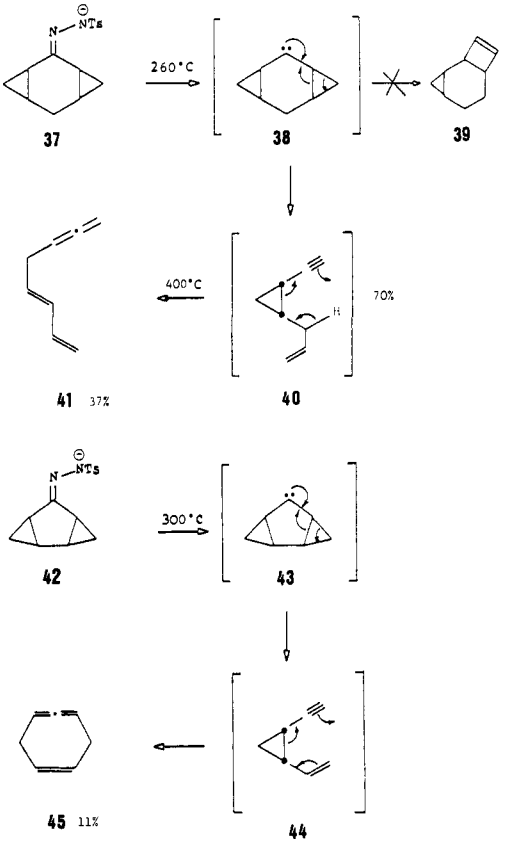
The generation of a carbene at a cyclopropylmethyl carbon results in a ring expansion through a 1,2-migration of the cyclopropyl C–C bond, resulting in formation of a cyclobutene.[31]



This strategy has been employed successfully in the synthesis of octalene **36**.[31] When ditosylhydrazone **32** and sodium methoxide in 3-ethyl-3-pentanol were heated at 140 °C, a mixture of **34**, **35**, and other compounds was obtained via the rearrangement of **33**. A 15% yield of **34** was realized, and this triene was then converted to octalene **36** though double electrocyclic ring opening of the cyclobutene rings.[32]

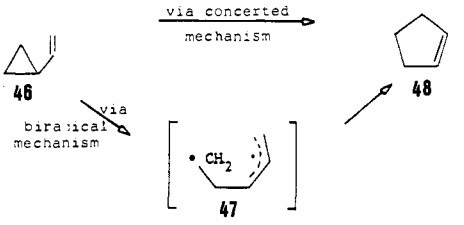


When the intermediate cyclopropylmethyl carbene is constrained so as to prevent rearrangement to cyclobutene, other rearrangements occur. For example, thermolysis of the anion of tosylhydrazone **37** at 260 °C furnished **40**. Because of the ring strain present in **38** and its potential ring-expanded product **39**, tricyclic carbene **38** rearranges with fission of one of the cyclopropyl rings to give **40** in 70% yield.[32] When the thermolysis temperature was raised to 400 °C, **40** underwent a homoene reaction to generate polyene **41** in 37% yield.[32] Similarly, treatment of **42** at 300 °C provided 11% of heptatriene **45**, presumably via a consecutive cyclopropyl carbene rearrangement in **43** and a homo-Cope rearrangement of vinylcyclopropane **44**.[33]



3. Vinylcyclopropane Rearrangement

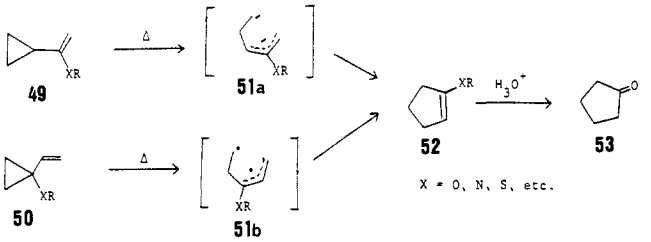
The chemical properties of cyclopropanes are greatly altered by conjugation with adjacent π-systems. Vinylcyclopropane undergoes unimolecular rearrangement to yield cyclopentene upon heating,[34,35] with an activation energy of 49.7 kcal/mol.[35,36] The mechanism[36,37] and stereochemistry[38] of this rearrangement have been discussed extensively. The majority of these rearrangements involve biradical intermediates.[36] although concerted processes have been proposed in several cases.[39,40] The versatility of this rearrangement has led to the development of several methodologies concerned with the preparation of functionalized cyclopentenes, and this subject has recently been reviewed.[45] The following examples show the utility of the vinylcyclopropane–cyclopentene rearrangement in the preparation of substituted or annulated cyclopentenes.



This reaction is particularly useful because vinylcyclopropanes are readily available and cyclopentenes are important structural units of natural products.[41] It

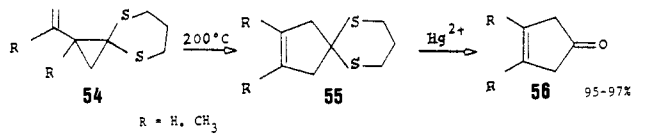
is not surprising that the vinylcyclopropane–cyclopentene rearrangement strategy has been employed extensively in the synthesis of complex natural products.[42]

This rearrangement is also useful because heteroatoms and other functional groups can be readily introduced at various positions in the starting vinylcyclopropane, resulting in the increased complexity of the cyclopentene obtained after rearrangement. For example, cyclopentanone **53** can be obtained via rearrangement of *either* vinylcyclopropane **49** *or* **50**.[37]

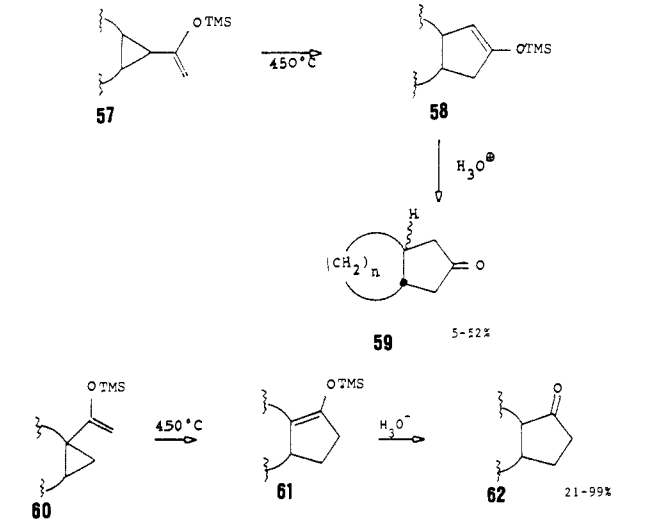


It is interesting to note that methoxy and dimethylamino groups on the cyclopropyl group of the vinylcyclopropane decrease the activation energies of rearrangement to 38.7 and 31.2 kcal/mol, respectively,[42] while the presence of these groups on the vinyl group has very little effect on the rate of rearrangement.[43] Other substituents on the cyclopropane moiety (trimethylsilyl, carbonyl, and imino groups) also have pronounced effects on the rate of the rearrangement as discussed below.

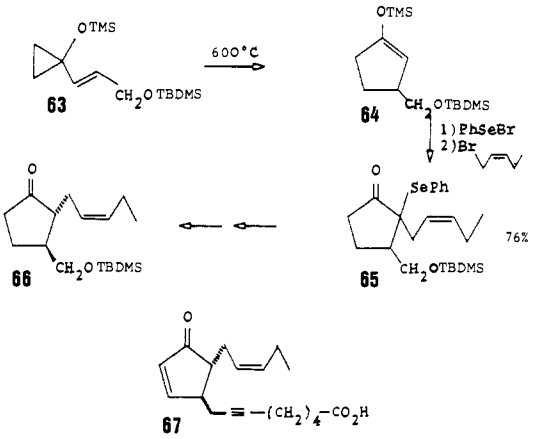
The methods for inducing the vinylcyclopropane–cyclopentene rearrangement range from photolysis or flash pyrolysis to subtle transition-metal catalysis.[41,44] Thermolysis of vinylcyclopropyl thioketal **54** at 200 °C leads to cyclopentene **55**. Thioketal **55** is converted to substituted cyclopent-3-enone **56** by treatment with mercury(II) solution.[46]



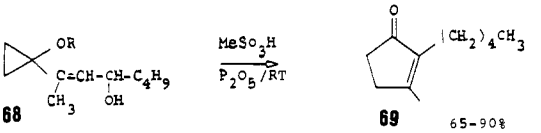
A cyclopentanone annulation methodology utilizing silyl enol ethers was developed by Monti.[47] For instance, bicyclic trimethylsilyl enol ethers **57** and **60** were heated at 450 °C to produce (after hydrolysis) **59** and **62**, respectively.[47]



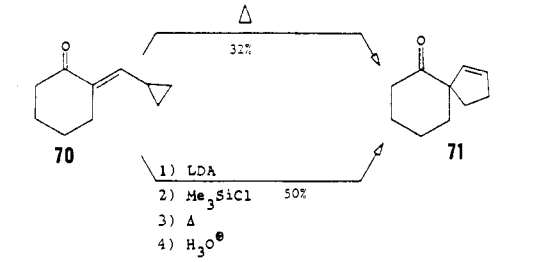
A similar strategy was employed by Salaün, who thermolyzed vinylcyclopropane **63** to furnish trimethylsilyl enol ether **64**.[48] This enol ether was treated with phenylselenium bromide and alkylated with *cis*-pent-2-enyl bromide to give **65** in 76% yield. This compound was converted to an important intermediate used in the synthesis of (±)-dicranenone A (**67**).[48]



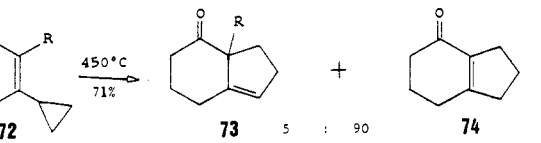
These examples[47,48] demonstrate that upon pyrolysis, (trimethylsilyl)oxy-substituted vinylcyclopropanes rearrange to ((trimethylsilyl)oxy)cyclopentenes, which can be hydrolyzed to cyclopentanones or subjected to further functionalization. Dihydrojasmone (**69**) was prepared by the acid-catalyzed rearrangement of vinylcyclopropane **68**,[49] although the mechanism of this reaction does not involve a true vinylcyclopropane–cyclopentene rearrangement.



Thermolysis of β-cyclopropyl enone **70** provides cyclopentene **71** in a facile entry to spirobicyclic systems.[50] Two procedures for converting **70** to **71** have been described: direct thermolysis of **70** to give a 32% yield of **71**, and the conversion of **70** to the corresponding trimethylsilyl enol ether, which rearranges to **71** in 50% overall yield after hydrolysis.[50]

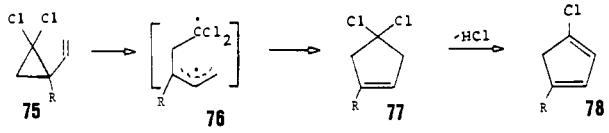


Thermolysis of vinylcyclopropane **72** at 450 °C yielded cyclopentene **73** or **74** (when R = H).[51]



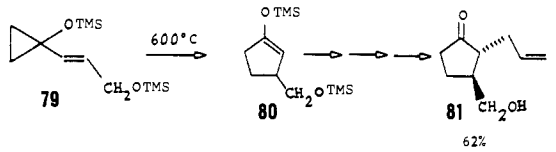
As discussed above in the mechanistic context, the substitution of heteroatoms on the vinylcyclopropane system has also been used extensively in synthetic procedures. Neureiter in his classical paper on the

discovery of the vinylcyclopropane–cyclopentene rearrangement reported that the pyrolysis of **75** yielded cyclopentadiene **78**, presumably via the loss of HCl from **77**.[34a]

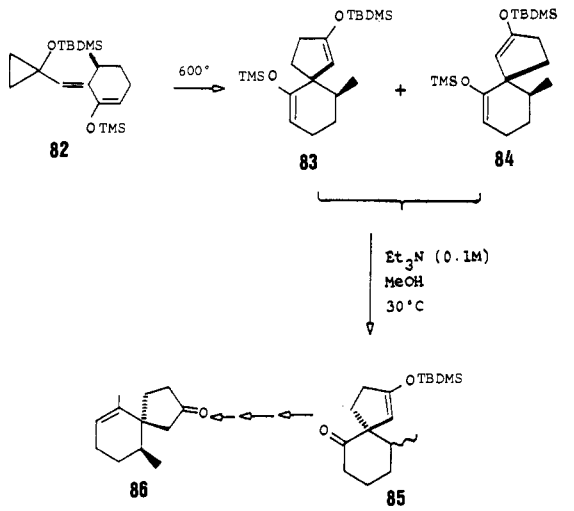


Flash pyrolysis of the trimethylsilyl ether **79** at 600 °C resulted in the isolation of **80**, which was transformed to prostaglandin precursor **81**.[52]

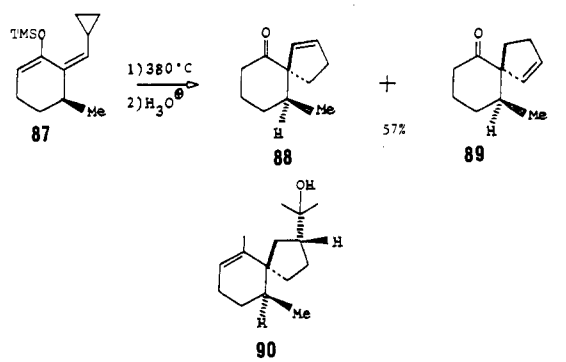
A trimethylsilyl ether accelerated vinylcyclopropane



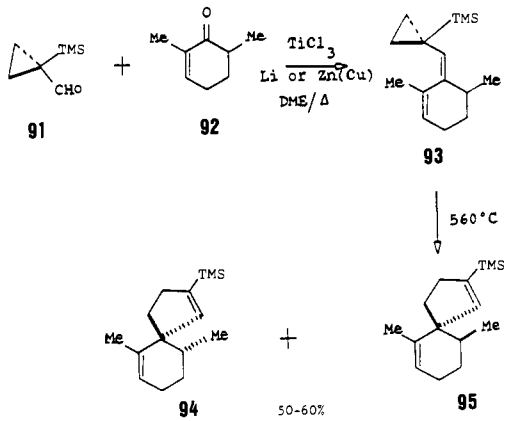
rearrangement was used in the synthesis of spirovetivane **86**. Flash thermolysis of **82** gave a 78:22 mixture of **83** and **84**. The product mixture was treated without purification with 0.1 M triethylamine in methanol to give the epimeric cyclohexanones **85**, which were transformed to **86**.[53] 2-(Cyclopropylmethylene)-



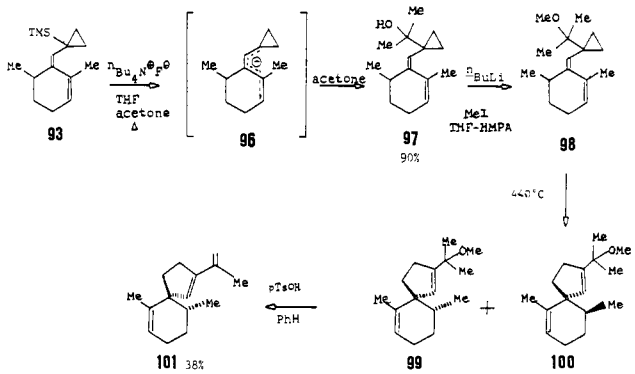
cycloalkenones such as **82** or **87** serve as convenient starting materials for a spiroannulation sequence. Thermolysis of silyl enol ether **87** at 380 °C, followed by acid hydrolysis of the crude thermolysate, afforded a 2.5:1 mixture of the two spiro enones **88** and **89** in a 57% yield.[54] The structural similarity of the spiroannulated compounds obtained in this manner to natural products such as hinesol (**90**) or vetispirene (**101**) prompted their synthesis through the use of silicon-substituted vinylcyclopropanes.



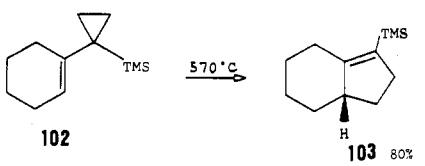
Reductive coupling of 1-(trimethylsilyl)cyclopropane-1-carboxaldehyde (**91**) and **92** in the presence of low-valent titanium provided **93** in 50–60% yield.[55] Thermolysis of **93** yielded a 4:1 mixture of spiro vinylsilanes **94** and **95**.[55]



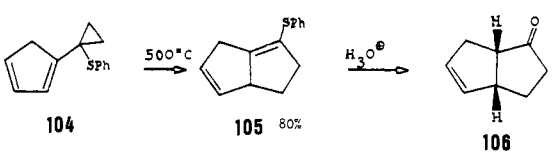
Alternatively, reaction of **93** with anhydrous tetra-*n*-butylammonium fluoride in THF–acetone solution at reflux temperature gave pentadienyl anion **96**, which was reacted with acetone to furnish alcohol **97** in 90% yield. Alcohol **97** was protected as its methyl ether **98**, which was thermolyzed at 440 °C to produce a separable mixture of **99** and **100** in the ratio of 5:1.[55] Treatment of **99** with *p*-toluenesulfonic acid in refluxing benzene yielded (±)-α-vetispirene (**101**) in 38% yield.[55]



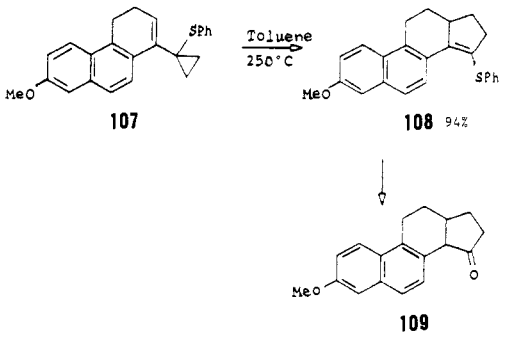
When vinylsilane **102** was passed through a quartz chip packed tube at 570 °C (30–40 Torr), silyl-substituted cyclopentene **103** was obtained in 80% yield.[56,57]



Sulfur-substituted vinylcyclopropanes furnish thioenol ethers of cyclopentanones upon thermolysis. Pyrolysis of **104** at 500 °C at 0.2 Torr led to vinyl sulfide **105** in 80% yield. Hydrolysis of **105** provided cyclopentanone **106** in 65% yield.[58] Similarly, thermolysis

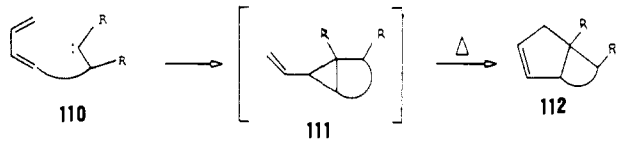


of **107** at 250 °C yielded **108** in 94% yield. The enol ether was then hydrolyzed to **109** in 73% yield.[59] Cyclopentene-annulated ring systems can be synthesized by intramolecular carbene addition to a 1,3-diene, which



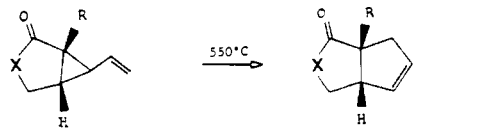
107 108 94% 109

involves a vinylcyclopropane intermediate. Application of this methodology can be illustrated by the following examples.



110 111 112

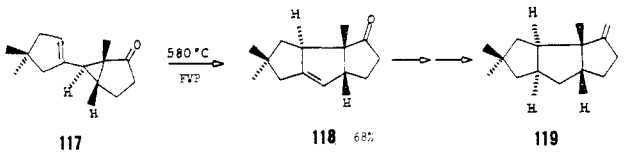
Pyrolytic conversion of **113a** and **113b** provided **114a**[44] and **114b**,[60] respectively. Similarly, lactone **115** was evaporated under vacuum at 580–600 °C through a Vycor tube to produce **116** in 28% yield.[61]



113a R = H
113b R = Me
115 R = CO_2Me

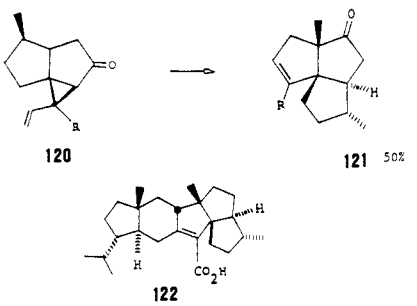
114a R = H 65%
114b R = Me 63%
116 R = CO_2Me 28%

Tricyclic compounds can also be prepared via the vinylcyclopropane–cyclopentene rearrangement. Thus **117** underwent flash vacuum pyrolysis at 580 °C (0.1 Torr) on Vycor glass conditioned with lead carbonate to give tricyclic ketone **118** in 68% yield. This material was converted to hirsutene (**119**).[62]



117 118 68% 119

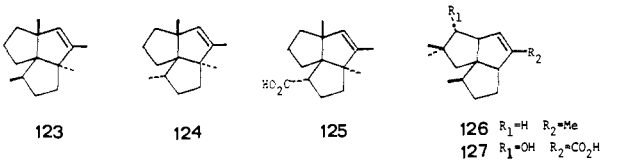
Another example of triquinane synthesis by this method is the formation of **121** in the flash pyrolysis of **120** over a $PbCO_3$-treated Vycor column.[63] This compound served as a potential intermediate in the total synthesis of retigeranic acid (**122**).[63]



120 121 50%

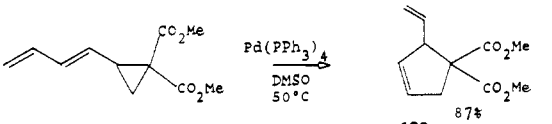
122

Several triquinane terpenes have been synthesized by this methodology since the publication of the last review.[41] These were epiisocomene (**123**),[65] isocomene (**124**),[66] isocomenic acid (**125**),[67] pentalenene (**126**),[68] and pentalenic acid (**127**).[69]



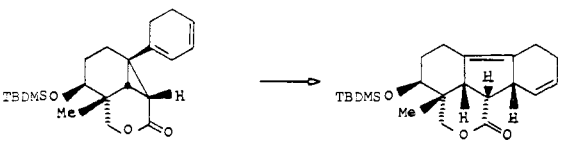
123 124 125 **126** R_1=H R_2=Me **127** R_1=OH R_2=CO_2H

Transition-metal-catalyzed rearrangements of vinylcyclopropanes have been utilized in synthesis and have been previously reviewed.[64] In the presence of a Pd(0) catalyst and under mild conditions, dienyl cyclopropanes activated by electron-withdrawing groups rearrange to cyclopentenes.[70] For example, when a DMSO solution of dienyl cyclopropane **128** was treated with $Pd(PPh_3)_4$ under an argon atmosphere at 50 °C, vinylcyclopentene **129** was formed.[70]



128 129

A critical step in Corey's total synthesis of the (±)-antheridium-inducing factor (A_{An}-2) of the fern *Anemia phyllitidis* involved a vinylcyclopropane–cyclopentene rearrangement.[71] Diethylaluminum chloride was used to promote rearrangement of **130** to **131** at 0 °C.[71]



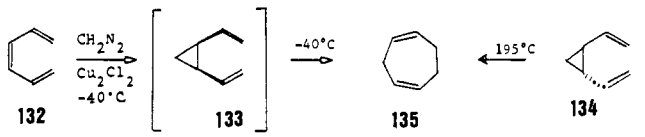
130 131 80%

Several other methods for inducing the vinylcyclopropane–cyclopentene rearrangement have recently become available. For example, trimethylsilyl iodide is used in a nucleophilic opening/alkylative reclosure sequence to provide annulated cyclopentenes in good yields (see later).[72] Other methods involve the anions of oxyvinylcyclopropanes[73] or the generation of their radical cations utilizing a stable aminium radical cation salt.[74] There have been isolated reports of Lewis acid catalyzed vinylcyclopropane–cyclopentene rearrangements involving substrates containing substituents that provide added stabilization to the incipient allylic cation intermediate.[75] In the case of carbanion-accelerated rearrangements of alkoxyvinylcyclopropanes, excellent stereoselectivity in the production of substituted cyclopentenols was observed, leading to speculation favoring a concerted mechanism for this particular rearrangement.[73]

Finally, in all of the documented vinylcyclopropane–cyclopentene rearrangements, the only significant competing process seems to be the 1,5-hydrogen shift (or retroene pathway) in any *cis*-alkylvinylcyclopropane. This process is controllable by careful temperature adjustment and is sometimes reversible.[60]

4. Divinylcyclopropane Rearrangement

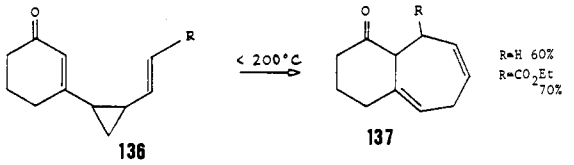
The preparation of seven-membered rings can be realized via thermal rearrangement of divinylcyclopropanes. Cyclopropanation of *cis*-hexatriene (**132**) with diazomethane in the presence of cuprous chloride at −40 °C resulted in the isolation of 1,4-cycloheptadiene (**135**).[36a,76] This result is in complete agreement with



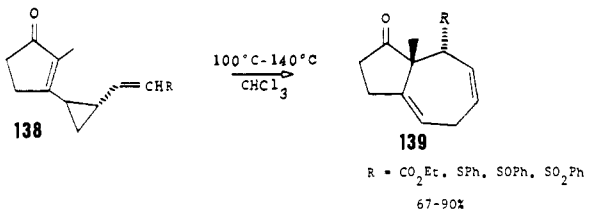
an earlier investigation in which the attempted preparation of *cis*-1,2-divinylcyclopropane unexpectedly yielded 1,4-cyclopentadiene (**135**).[77] It appears that the low activation energy for the Cope rearrangement of *cis*-1,2-divinylcyclopropane to 1,4-cycloheptadiene (**133** → **135**) allows this process to take place at lower temperatures. The mechanism of this isomerization has been proposed to be of a biradical nature.[36a,76]

In contrast, *trans*-1,2-divinylcyclopropane (**134**) is more stable and requires a temperature of 190 °C to isomerize to 1,4-cycloheptadiene.[36a,76] Allyl-stabilized biradicals are also the presumed intermediates in the trans → cis isomerization of divinylcyclopropanes.

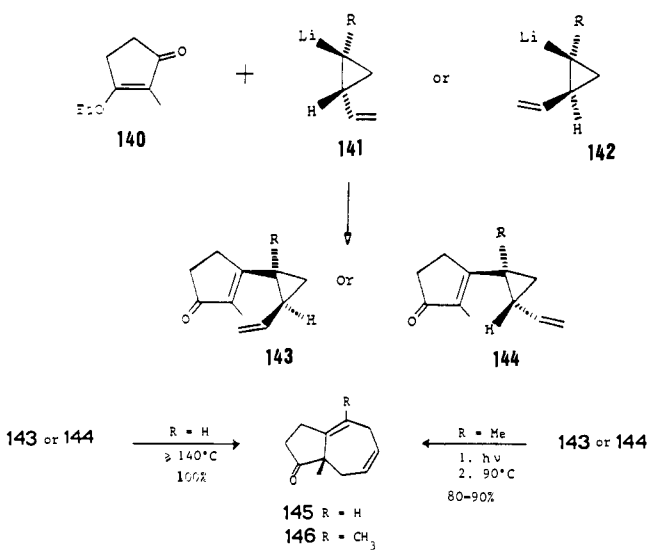
For example, thermolysis of **136** at 200 °C gives cycloheptadiene **137** in 60% (R = H) and 70% (R = CO_2Et) yield.[78,79]



Similarly, **138** undergoes rearrangement at 100–140 °C in $CHCl_3$ (sealed tube) to give hydroazulene **139** in 60% yield.[79] Bicyclo[5.3.0]decane and bicyclo[5.4.0]-undecane skeletons can be prepared via this procedure, and this technique has found application in several natural product syntheses.

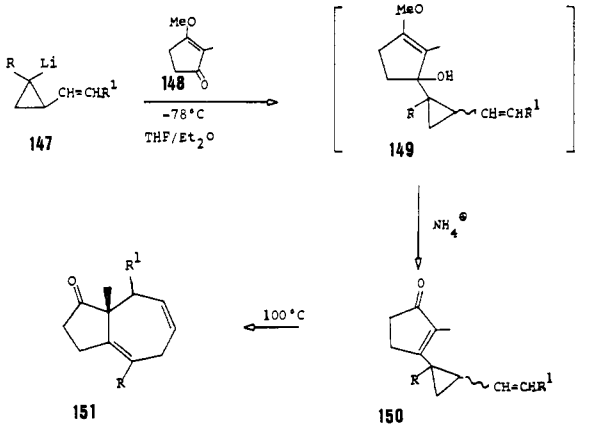


A general method for pseudoguaiane synthesis involving an internal divinylcyclopropane rearrangement has been developed. Cyclopentenone **140** was allowed to react with cyclopropyllithium **141** or **142** to give divinylcyclopropanes **143** or **144**, respectively. Ther-

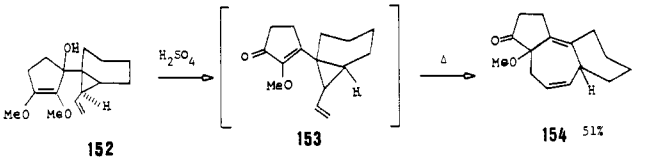


molysis of **143** or **144** at 140 °C produced cycloheptadiene **145** in nearly quantitative yield. When R = Me, photolysis followed by thermolysis of **143** or **144** at 98 °C gave cycloheptadiene **146** in 80–90% yield.[80–82] A pyrolysis temperature of 140 °C is required for the rearrangement of trans species **144**; the cis isomer **143** rearranges spontaneously upon its preparation.

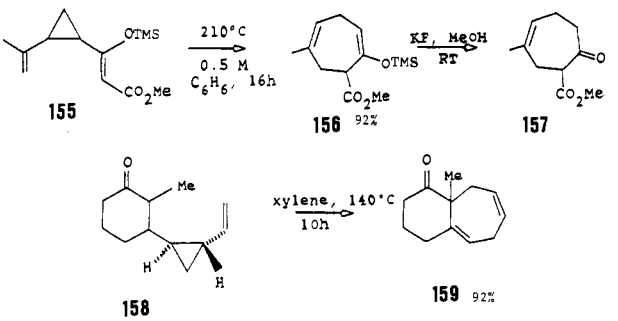
In another example, lithio reagent **147** was added to 2-methyl-3-methoxycyclopentenone (**148**) at −78 °C in THF–ether to give intermediate allylic alcohols **149**. Divinylcyclopropane systems **150** were formed after workup of the allylic alcohols with aqueous ammonium chloride. Thermolysis of divinylcyclopropane **150** at 100 °C provided the seven-membered-ring annulated hydroazulene **151**.[83]



Similarly, cyclopentene **152** formed divinylcyclopropane **153** on treatment with H_2SO_4. Thermolysis of **153** provided substituted cycloheptadiene **154**.[84]

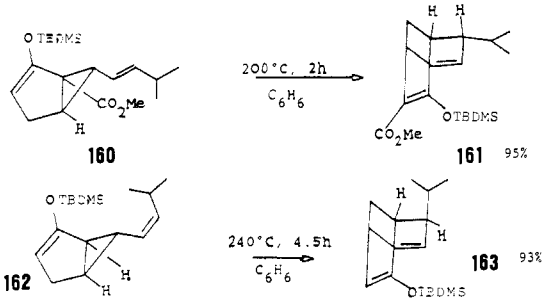


Vinylic substitution of the divinylcyclopropane system is tolerated and is subject to the same restrictions that apply to the vinylcyclopropane–cyclopentene rearrangement. I.e., cis-disubstituted vinyl groups retard the rate of rearrangement. Silyl enol ether **155** underwent seven-membered-ring annulation at 210 °C (0.5 M in benzene) to furnish 1,4-cycloheptadiene **156** in 92% yield. The enol ether in **156** was then hydrolyzed to give enone **157** in 95% yield.[85] Bicyclic dienone **159** was obtained in 92% yield on thermolysis of divinylcyclopropane **158** in refluxing xylene.[86]

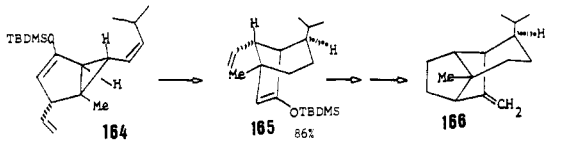


Thermal rearrangement of divinylcyclopropane systems has also been used to produce compounds containing the bicyclo[3.2.1]octane skeleton. For instance,

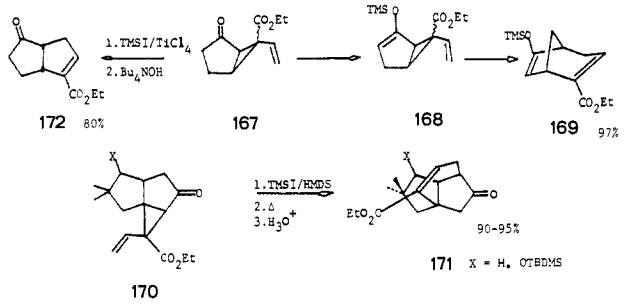
divinylcyclopropyl compound **160** was heated at 200 °C for 2 h in benzene to generate **161** in 95% yield.[87] For comparison, the cis isomer **162** was also thermolyzed at 240 °C for 4.5 h, furnishing **163** in 93% yield, thus indicating that the isomerization is stereoselective.[87]



The following example illustrates how this method was used in the synthesis of a racemic form of the marine sesquiterpene (±)-sinularene (**166**). Thermal isomerization of **164** furnished **165** in 86% yield.[88] The conversion of **165** to (±)-sinularene (**166**) has been achieved in several steps.[88]

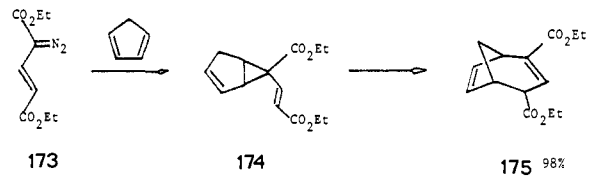


Most recently, the Cope rearrangement of divinylcyclopropanes has been exploited in the synthesis of some functionalized bicyclo[3.2.1]octane systems. Treatment of **167** with TMSI/HMDS at −78 °C pro-



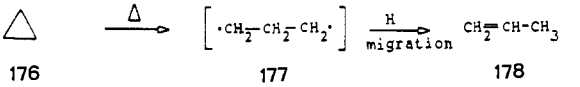
duced the intermediate silyl enol ethers **168**. The endo isomer of **168** rearranged to bicyclo[3.2.1]octane **169** between −78 °C and room temperature, while the exo isomer required pyrolysis at 450 °C to produce **169** in 97% yield.[72] Similarly, the tricyclic ketone **170** was converted to the bridged skeleton **171**.[68,69,72] In this context it should be noted that the silyl enol ethers of keto vinylcyclopropanes such as **167** also provide bicyclo[3.3.0]octanes **172** via the vinylcyclopropane–cyclopentene rearrangement. The endo/exo stereochemistry in **167** allows control over these operations.[68,69,72]

The addition of unsaturated diazo carbonyl compound **173** to a diene (e.g., cyclopentadiene) generated divinylcyclopropane **174**, which upon rearrangement furnished the annulated seven-membered-ring system **175**.[89,90] A mechanistic investigation of this process was reported.[90]



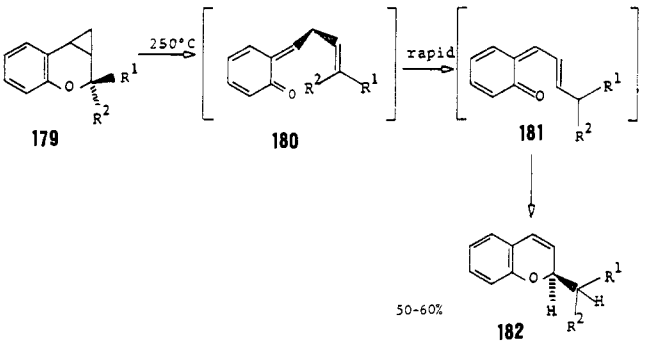
5. Miscellaneous Thermal Fission

The thermal isomerization of cyclopropane to propylene[91-93] has been discussed in detail.[36] The mechanism of the isomerization is thought to involve cleavage

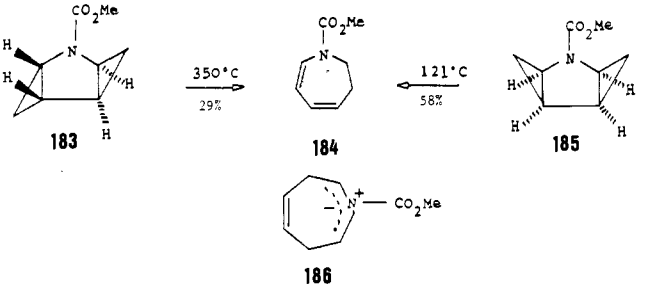


of the three-membered ring to the trimethylene biradical, which undergoes a subsequent hydrogen migration process to yield propylene.[86] The activation energy of this isomerization has been estimated to be 63.4 kcal/mol at 550–659 °C.[91]

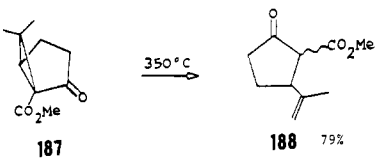
Synthetically, the cyclopropane to propylene isomerization is not generally useful because of the side reactions that accompany the isomerization, especially when other substituents are present.[36,93,94] In some special cases, however, this rearrangement provides products of practical use and in acceptable yields. Cyclic ether **179** undergoes rearrangement upon heating at 250 °C to provide **182**.[95] Higher temperature was



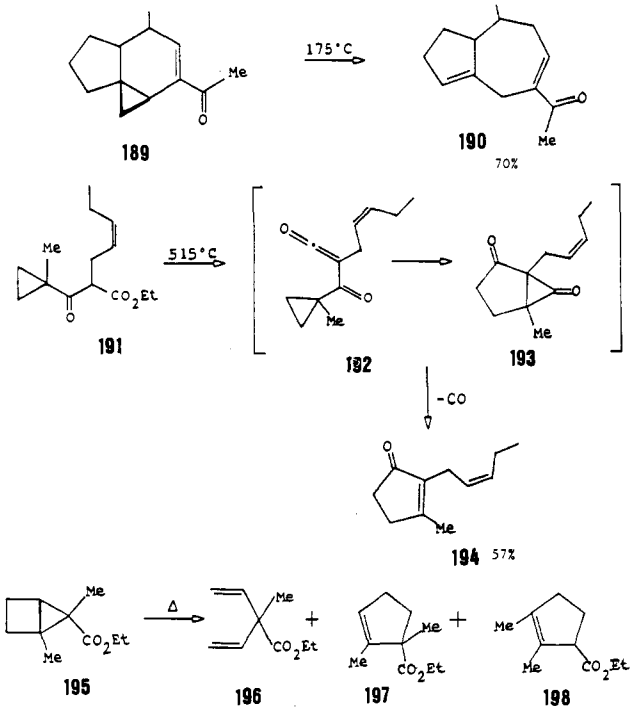
required for the conversion of anti-azotricyclic compound **183** to diene **184** than for syn compound **185**; rearrangement of **185** proceeds smoothly at 121 °C to give dihydroazepine **184**, whereas the rearrangement of **183** required 350 °C.[96] This difference in reactivity was rationalized in terms of the ease of the formation of the ylide intermediate **186**.[97] Passing a hexane solution of



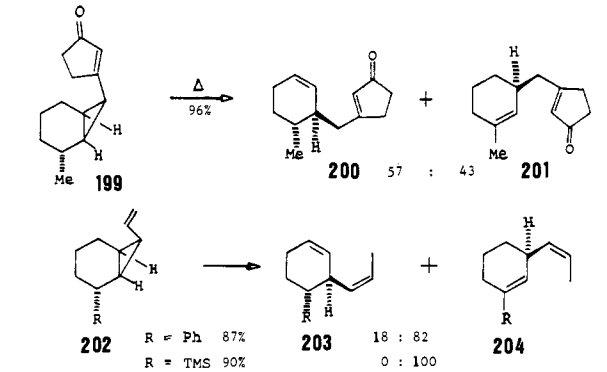
cyclopropyl ketone **187** through a column heated at 350 °C gave keto ester **188** in 79% yield via an ene-type process.[98] Thermolysis of methyl ketone **189** at 175 °C



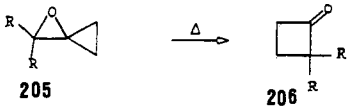
for 2 h yielded hydroazulene **190** in 70% yield.[99] Thermolysis of **191** at 515 °C gave **194** in 57% yield.[100] Pyrolysis of bicyclopentane **195** gave a high yield of the three isomeric esters **196**, **197**, and **198** in a ratio of 1:3:4.[101]



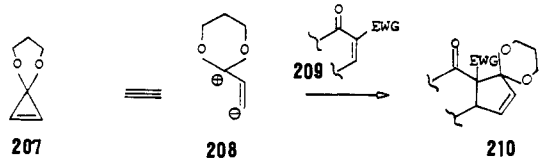
Homo-[1,5]-sigmatropic hydrogen migration was responsible for the rearrangement of **199** to a mixture of **200** and **201**.[102] Similarly, **202** upon thermolysis gave **203** and **204**.[102] This process occurs readily with *cis*-

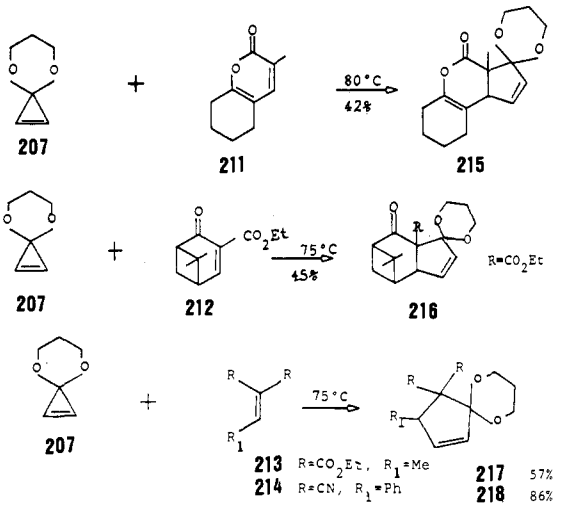


alkylvinylcyclopropanes and has been shown to be reversible.[60] The thermal rearrangement of oxaspiropentanes **205** to cyclobutanones **206** is well-known and its application has been reviewed elsewhere.[103]

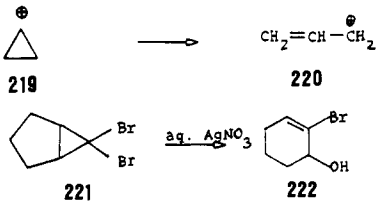


Thermal ring-opening cycloadditions of cyclopropyl derivatives with activated olefins have been reviewed.[104] The following examples illustrate thermal opening of cyclopropene rings and their subsequent cycloadditions with activated olefins.[105] Cyclopropenone ketal **207** was found to be an effective equivalent of 1,3-dipole **208** and undergoes [3 + 2] cycloaddition with activated olefins such as **209** to give five-membered rings of type **210**.[105] For instance, reactions of **207** with **211**, **212**, **213**, and **214** provide **215**, **216**, **217**, and **218**, respectively.[105]

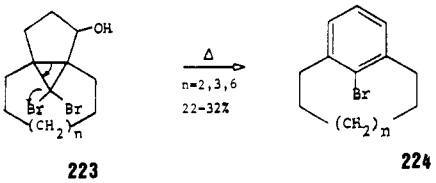




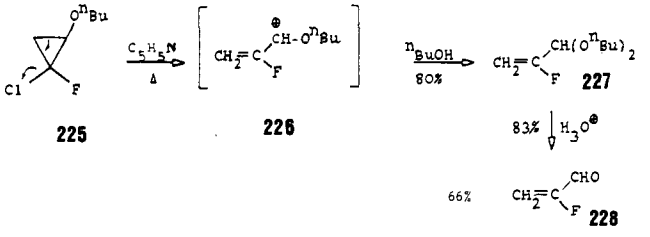
Cyclopropyl carbocations rearrange spontaneously to their corresponding allyl cations. The mechanism of this isomerization is concerted, and the stereochemistry can thus be predicted by orbital symmetry arguments.[106-108] This rearrangement has been extensively employed to effect ring expansions such as one involving dibromide **221**, which was converted to allylic alcohol **222**.[109] The synthesis of metacyclophanes **224**



was accomplished by thermolysis of the labile 2,2-dibromocyclopropyl carbinol **223**, which produced **224** upon ring expansion and elimination.[110]



It has recently been found that only the *Z* isomer of **225** (cis orientation of fluorine and alkoxy groups) underwent ring opening to allyl cation **226**, which could be trapped by 1-butanol, resulting in the isolation of acetal **227**.[111] Hydrolysis of **227** furnished 2-fluoroacrolein (**228**) in an overall yield of 66% from **225**.[111]

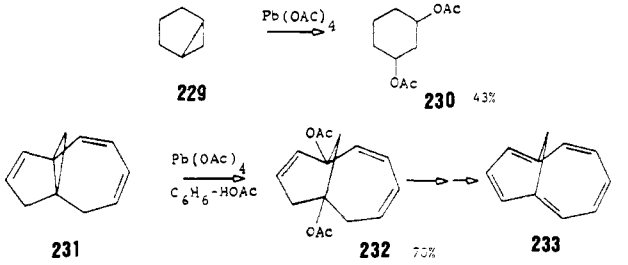


III. Oxidative and Reductive Ring Fission

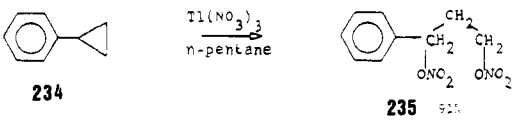
1. Oxidative Fission

Oxidative cleavage of cyclopropanes involves the breakage of a carbon–carbon bond of the cyclopropyl group, followed by the formation of two bonds of higher oxidation state. Steric and electronic effects of sub-

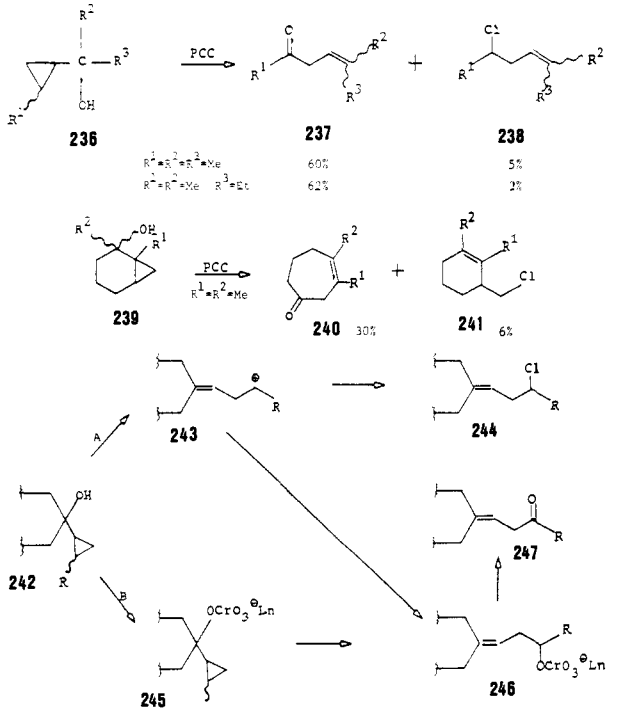
stituents on the ring, as well as the properties of the oxidizing agents, can facilitate regio- and stereospecific opening of the cyclopropane ring. For example, bicyclo[3.1.0]hexane (**229**) is cleaved by lead tetraacetate to provide diacetate **230**.[112] Similarly, Scott reported lead tetraacetate oxidation of the cyclopropane ring in **231** to diacetate **232**. Further transformations converted **232** to homoazulene **233**.[113] Cyclopropanes are



oxidized with thallium(III) nitrate in pentane to give nitrate esters. For example, on treatment with Tl-$(NO_3)_3$, cyclopropylbenzene **234** gave exclusively dinitrate ester **235** in 91% yield.[114]

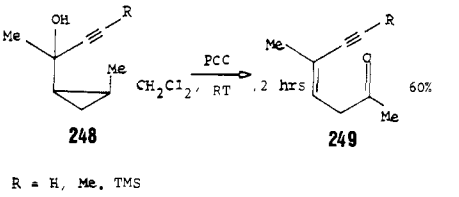


Oxidative rearrangement of *tert*-cyclopropylcarbinols gives β,γ-unsaturated ketones or halides. For example, carbinols **236** were cleaved by pyridinium chlorochromate to give a mixture of β,γ-unsaturated ketone **237** and homoallyl chloride **238**.[115] Similarly, **239** yielded **240** and **241**.[115] The proposed mechanism for the 1,4-carbonyl transposition is illustrated below:[115]



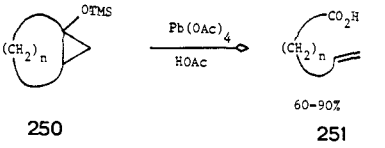
Recently, Holweger utilized this strategy to prepare β,γ-unsaturated ketone **249** in 60% yield.[116]

When a heteroatom is present on the cyclopropyl ring, the oxidation can proceed with the cleavage of two bonds to furnish olefins in a formal retro carbenoid addition. For example, $Pb(OAc)_4$ oxidation of silyl ethers such as **250** gives olefinic acids **251** in excellent



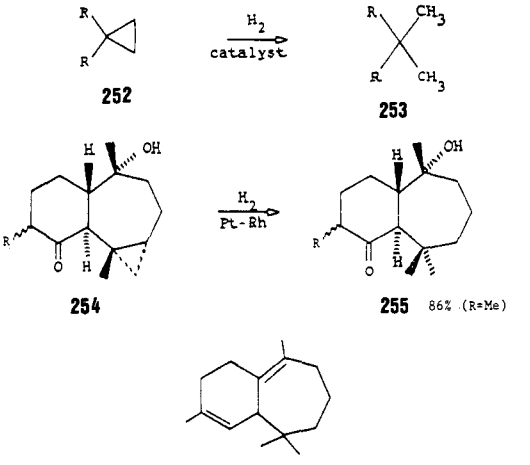
R = H, Me, TMS

yields. This procedure is quite general and has been used effectively to provide a homologous series of unsaturated acids.[117,118]

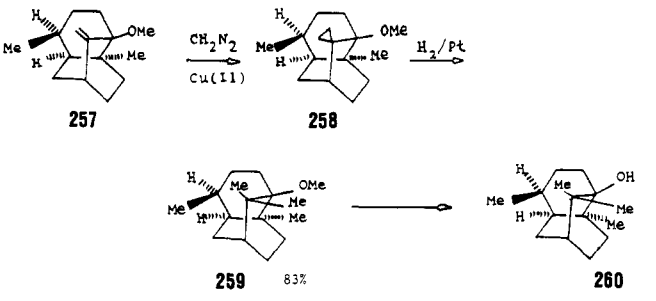


2. Reductive Fission

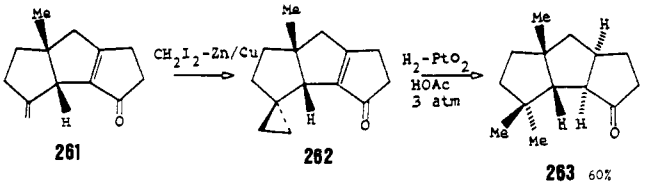
Cyclopropane can be cleaved at the least substituted bond by catalytic hydrogenation in a general synthesis of *gem*-dimethyl groups.[119-121] Hydrogenation of cyclopropane **254** over platinum–rhodium catalyst gave rise to ring opening and provided *gem*-dimethyl compound **255**, which served as a starting material for the synthesis of β-himachalene (**256**).[122]



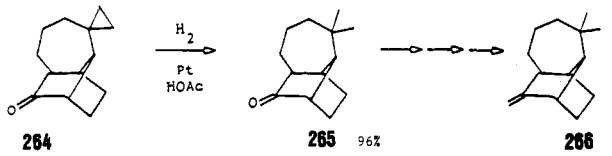
Cyclopropanation of the double bond in allyl ether **257** was achieved by treatment with diazomethane in the presence of a copper chelate and gave a 47% yield of cyclopropane **258**. The cyclopropane ring in **258** was catalytically hydrogenated to give (±)-patchouli alcohol methyl ether (**259**) in 83% yield. Ether **259** was then converted under mild conditions to (±)-patchouli alcohol (**260**).[123]



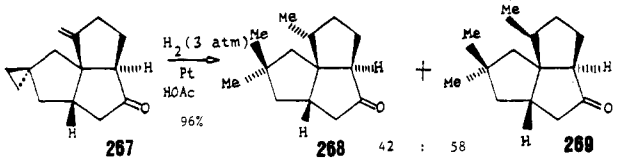
Simmons–Smith reaction of **261** produced cyclopropane **262** in 50% yield. This compound was catalytically hydrogenated over PtO_2 in acetic acid at 3 atm to generate 60% of ketone **263**.[124]



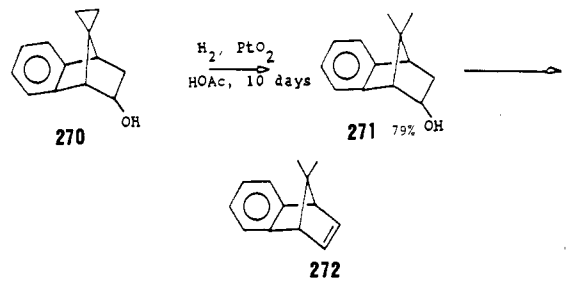
Cyclopropane **264** underwent regioselective hydrogenolysis over Pt in HOAc at room temperature to furnish a 96% yield of ketone **265**, which was converted to (±)-longifolene (**266**).[125]



Treatment of **267** with hydrogen in the presence of platinum effected both hydrogenolysis of the cyclopropane ring and hydrogenation of the double bond. A mixture of tricyclic ketones **268** and **269** in a ratio of 42:58 was produced in 96% yield.[126]

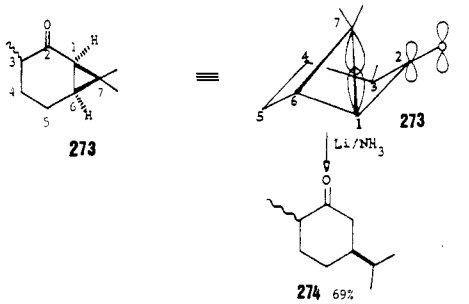


Hydrogenolysis of the spirocyclopropane ring in **270** was achieved in acetic acid solution with a platinum catalyst at ambient pressure. The major product (79%) of this reaction was the *gem*-dimethyl alcohol **271**, which was used to prepare 7,7-dimethylbenzonorbornene (9,9-dimethyl-1,4-methanonaphthalene) (**272**).[127]

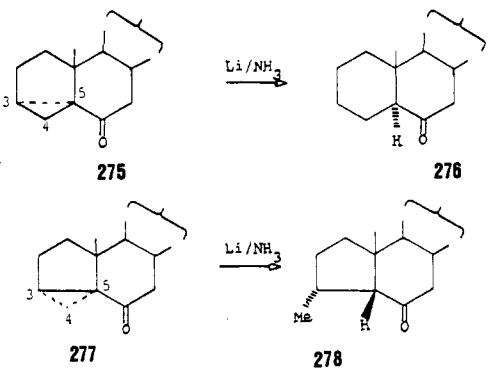


It should be reiterated that catalytic hydrogenation generally cleaves the least hindered bond of the three-membered ring, whereas the bond that breaks in a cyclopropyl ketone upon reduction by alkali metals in liquid ammonia is governed by stereoelectronic effects, specifically the magnitude of overlap between the cyclopropane C–C bond and the p-orbital of the carbonyl group.[128,129] The introduction of a *gem*-dimethyl group as well as ring enlargement can be realized by reductive fission of three-membered carbocycles. These transformations are both chemo- and stereospecific.

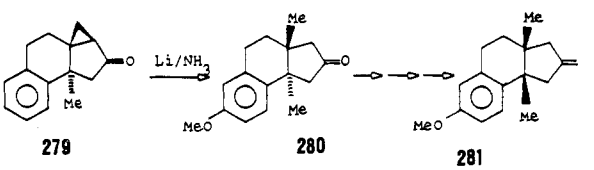
To illustrate the stereoelectronic control of this reduction, competition between various bonds in a cyclopropyl ketone such as **273** has been evaluated.[129] Because of geometric constraints, the overlap between the internal C_1–C_6 bond and the π-system of the carbonyl group is minimal, whereas the external C_1–C_7 is favorably aligned with the π-system, as illustrated in **273**. Consequently, reduction of **273** with lithium in liquid ammonia results in cleavage of the C_1–C_7 bond, yielding exclusively ketone **274**.[129]



The C_3–C_5 bond in **275** and the C_4–C_5 bond in **277** are better aligned with the π-system of the carbonyl. Under similar reductive conditions, only **276** and **278** were obtained from the reactions of **275** and **277**, respectively.[129,130] Cyclopropane **279** underwent reductive

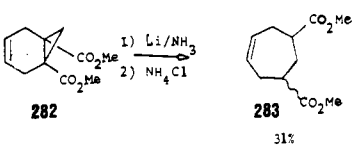


cleavage with Li/NH_3 to generate ketone **280**, which was an intermediate in the total synthesis of triterpenes of the lanostane cycloartane group, represented by **281**.[131,132]

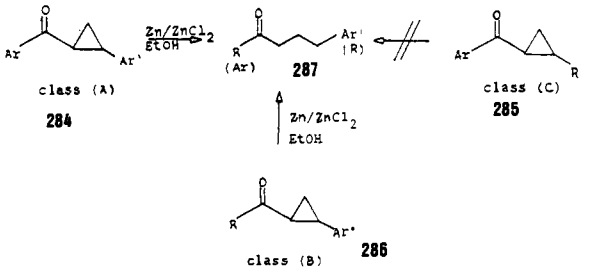


Because of the stereoelectronic control in the reductive fission of cyclopropyl ketones, only bond a in **279** is cleaved, despite the fact that cleavage of bonds b and c would provide more stable intermediates. It is therefore clear that the dissolving-metal reduction of cyclopropyl ketones proceeds under kinetic control.[131,132]

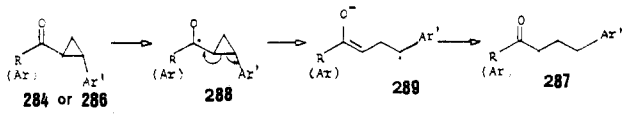
The cyclopropane ring in bicyclic compound **282** was cleaved reductively to **283**.[133] Aryl-substituted cyclo-



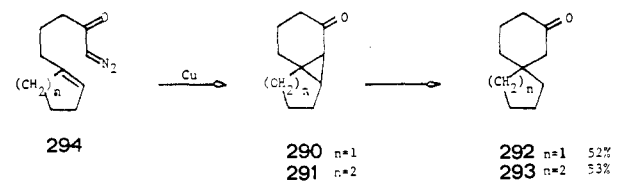
propyl ketones are cleaved to acyclic ketones by zinc or zinc chloride in refluxing ethanol.[134] Of the three classes of cyclopropyl ketones (**284**, **285**, and **286**), only



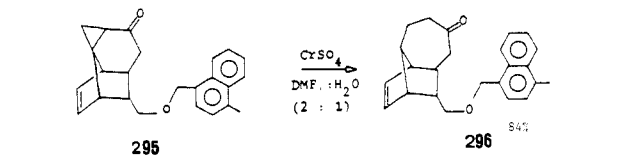
two can undergo reductive cleavage to acyclic ketones such as **287**.[134] The mechanism of this reaction is believed to involve the reduction of the carbonyl to ketyl anion **288** followed by rearrangement to **289**.[134]



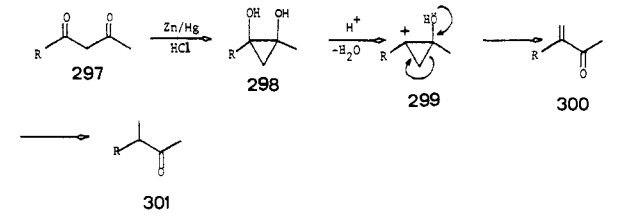
Reductive cleavage of cyclopropyl ketones **290** and **291** produced spiro ketones **292** and **293**, respectively, on treatment with lithium in ammonia/ether.[135] This method is perhaps one of the simplest procedures for the preparation of spirocyclic systems, as the starting substrates can be generated from olefinic diazo ketones **294**.[136]



Other methods of cyclopropane saturation are available. For example, exposure of ketone **295** to chromium(II) sulfate in DMF–H_2O (2:1), produced a longifolene-type skeleton **296** in 84% yield.[137]



Fission of an intermediate cyclopropane ring takes place during the Clemmensen reduction of 1,3-diketones. A mechanism for this rather complex process has been postulated and involves an intermediate cyclopropyl cation[138,139] formed from the pinacol-type coupling of the carbonyls.[140]



Reductive ring opening of cyclopropyl ketones has provided a useful method for the total synthesis of polycyclic natural products and has been successfully

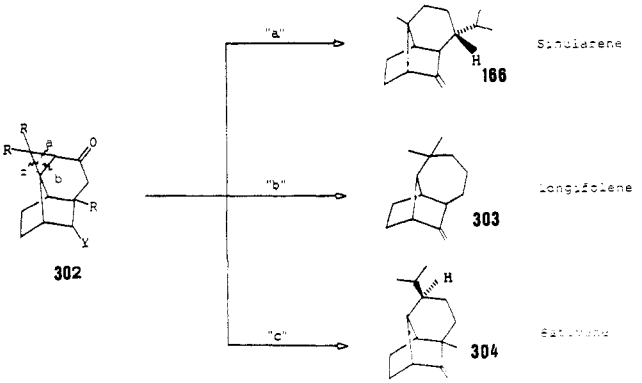
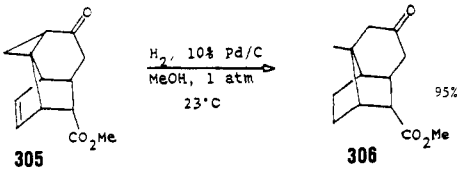


Figure 5.

employed in the stereocontrolled syntheses of (±)-hinesol, (±)-epihinesol, (−)-acorenone B, (±)-α-chamigrene, and (±)-sinularene.[137] After construction of the appropriate tetracyclic precursor, selective cyclopropane bond cleavage (a, b, or c) produced the desired tricyclic ring systems.[137] For instance, conjugated cyclopropyl ketone **305** was hydrogenated under mild conditions (23 °C, CH_3OH, 10% Pd/C) to give sinularene-type ketone **306** in 95% yield.[137]



IV. Electrophilic and Nucleophilic Ring Fission

1. Additions to Cyclopropanes

Simple fragmentation[141] of cyclopropane systems becomes possible when the ring is substituted with functionalities that provide an appropriate reinforcement of unidirectional electron flow (Figure 5). The weakest bond in the cyclopropane can be viewed as the electron pair which is absorbed into the incipient π-system or which leaves behind a cation. This special case of an E_1 or E_2 reaction, which is well-documented in the synthesis of alicyclic or cyclic compounds, is *further* reinforced in the case of cyclopropanes by the release of ring strain. Additionally, the reacting centers remain connected by the nonparticipating cyclopropane carbon. Depending on the functionalities present, such fragmentation of three-membered-ring carbocycles is an extremely useful method of construction of carbon skeletons resulting in changes in both the structure and the charge parity of products.

In direct analogy to the chemistry of alkenes, cyclopropanes are subject to addition reactions. The only operational difference is the presence of an extra carbon, the "synthetic wedge", which enhances the number of possible rearrangement pathways threefold compared to those available to alkenes. Depending on the substitution of cyclopropane with electron donors or acceptors, any of its three bonds are susceptible to cleavage (Figure 6). Note that either the nucleophile or the electrophile may (or may not) be connected to the cyclopropane (connection indicated by loops in Figure 6). Such connection distinguishes the reactive options of cyclopropanes from those of olefins equipped with similar donors or acceptors, as illustrated in Figure 7. In the case of enone **308**, the conceptual "cleavage" of the π-system by the combined effect of donor and acceptor groups leads only to a *resonance* form of itself. On the other hand, the analogous operation on cyclopropane **310** leads to a new compound by virtue of the connective properties of the extra carbon or "synthetic wedge". All of the ensuing discussion can be reduced to the simple mechanistic representation depicted in Figures 6 and 7. The reactions can generally proceed

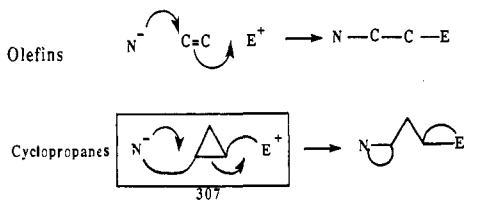


Figure 6.

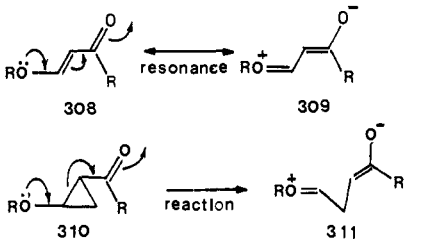
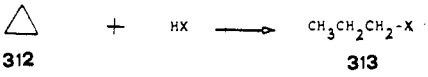


Figure 7.

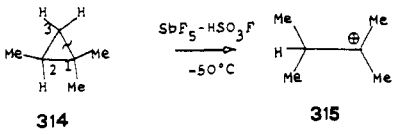
in either acidic or basic media and are organized in order of complexity with respect to the substitution patterns of the cyclopropane and the products.

2. Electrophilic Additions

As the cyclopropane ring behaves much like a carbon–carbon double bond, treatment of a three-membered ring with various electrophiles results in addition of the electrophile with concomitant fission of the ring.[39,142]

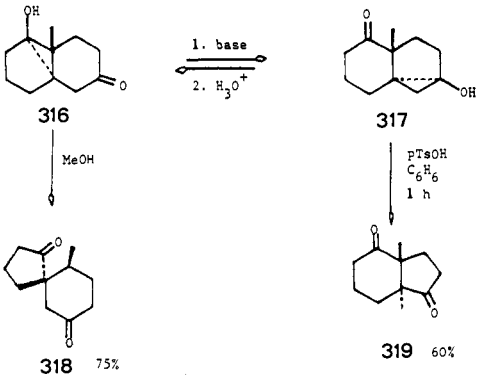


The electrophilic addition follows Markovnikov's rule for substituted cyclopropanes although exceptions have been reported. Addition of SbF_5–HSO_3F to 1,1,2-trimethylcyclopropane (**314**) at −50 °C gave clearly 2,3-dimethyl-2-butyl cation (**315**).[143] It appears that the protonation occurred at C-3, to generate the tertiary carbocation **315**.[143]

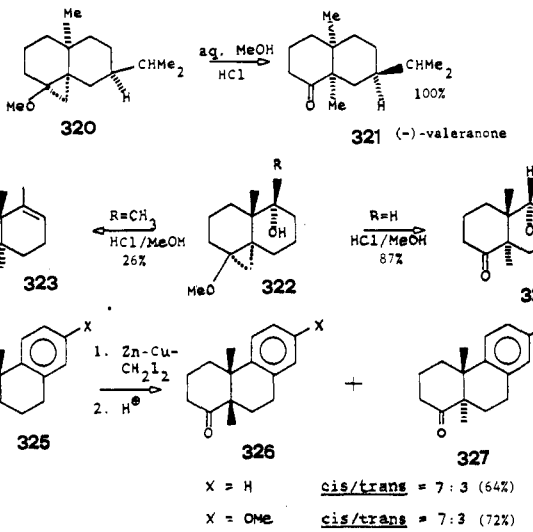


The accepted mechanism for the electrophilic addition to cyclopropane has been briefly reviewed.[144] The electrophile (e.g., H^+) adds to the carbon with the maximum number of protons, generating a cation at the most substituted carbon. The cation is subsequently trapped by its reaction with the nucleophile. As it is possible for the nucleophile to be situated within the same molecule, cleavage of appropriately substituted cyclopropanes would yield compounds containing "angular" methyl groups. The following examples demonstrate these generalizations.

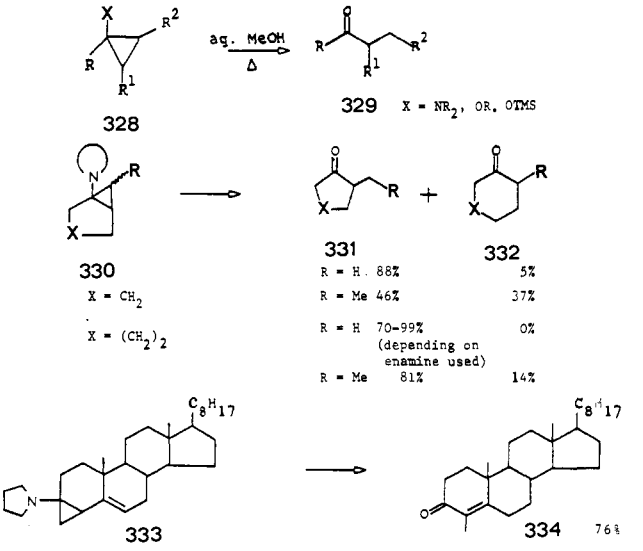
For example, cyclopropanol **317** gave, upon reaction with *p*-toluenesulfonic acid in refluxing benzene for 1 h, a 60% yield of angularly methylated indan **319**.[145] Those hydroxycyclopropanes containing suitably situated ketones can exist in equilibrium with their regioisomers. Thus **317** exists in equilibrium with **316**, which was transformed to a spiro compound **318** in >75% yield by reaction with methanol.[145]



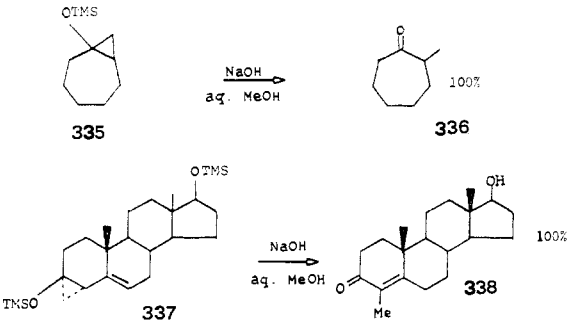
Other examples of introduction of angular methyl groups are shown below. Synthetically, the cyclopropanation of enol ethers followed by cyclopropane opening can be viewed as an alternative to regioselective methylation of ketones.[146–148]



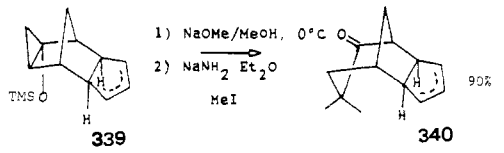
Alkyl and silyl enol ethers as well as enamines have also been used successfully in cyclopropanations leading to systems such as **328**. A wide variety of enamines have been transformed, via Simmons–Smith reaction and subsequent protonolysis, to α-methyl ketones in this fashion.[149] Treatment of trimethylsilyl ethers **335**



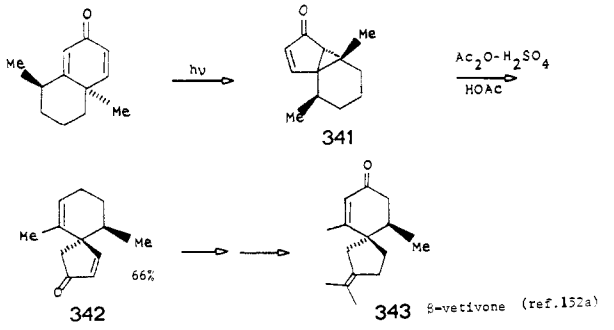
and **337** with NaOH in aqueous MeOH gave α-methylated ketones **336** and **338**, respectively, in quantitative yields.[150]



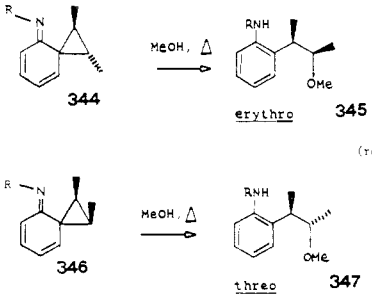
Similarly, trimethylsilyl cyclopropyl ether **339** upon treatment with sodium methoxide in methanol at 0 °C, followed by alkylation of the resulting ketone, provided geminally methylated ketone **340** in 90% yield.[151] The



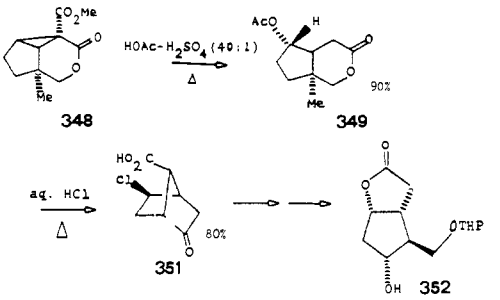
use of silyl ethers allows flexibility in the experimental conditions, as either strong acid, strong base, or nearly neutral fluoride ion catalysis can be employed. Activation of a cyclopropane by an electron-withdrawing group greatly accelerates the ring opening and protonation in analogy to such processes in activated olefins vs simple alkenes. The following examples involving keto cyclopropanes illustrate the utility of this chemistry.[152]



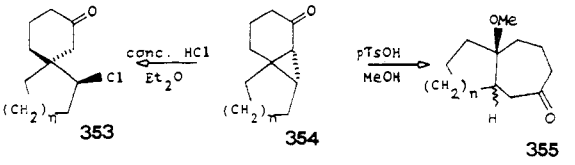
Stereospecific ring opening of *trans*- and *cis*-dimethylcyclopropyl imines **344** and **346** was achieved with inversion of configuration by treatment with methanol to afford erythro and threo products **345** and **347**, respectively.[152b] Stereospecific cleavage of the



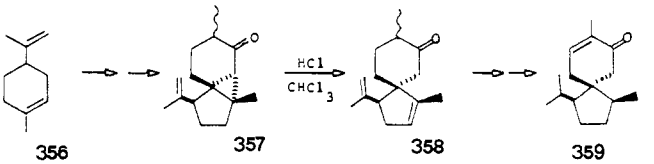
cyclopropyl ring in **348** occurred upon treatment with $HOAc–H_2SO_4$ (40:1) at 90 °C for 3 h, yielding acetate **349**, which served as a key intermediate in prostaglandin synthesis.[153] Optically active (+)-tricyclic acid **350** afforded chiral chloro acid **351** in 80% yield on exposure to aqueous HCl in another approach to prostaglandin precursor **352**.[154]



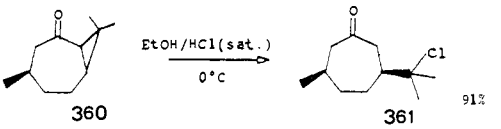
Different modes of ring opening can sometimes be elicited by modifying reaction conditions. Tricyclic ketone **354** was converted to either fused or spiro cyclic systems as shown below.[155]



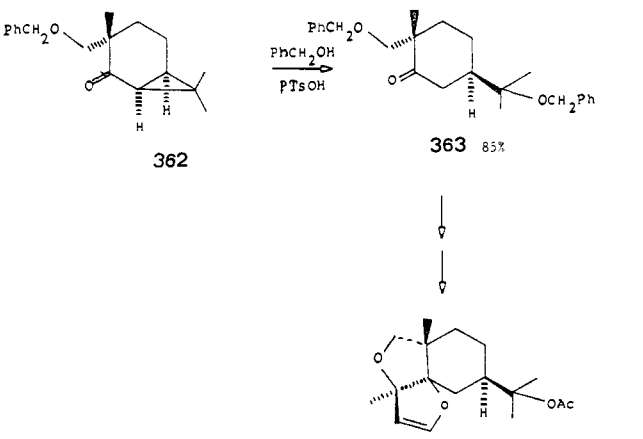
(–)-Acorenone (**359**) was prepared via the ring opening of **357** to **358**, starting from (*R*)-(+)-limonene (**356**).[155]



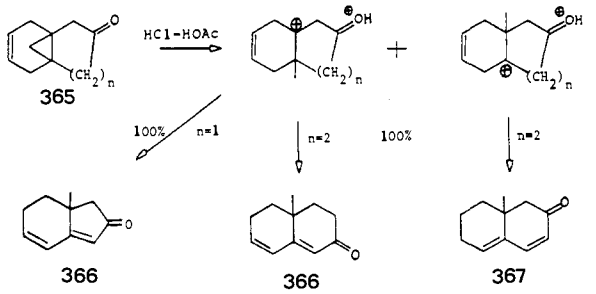
The normal factors governing the trapping of alkyl cations with nucleophiles (S_N1 or S_N2), as opposed to elimination of adjacent protons (E_1 or E_2), operate in keto cyclopropanes as well. Thus, protonation of a cyclopropane can generate a cation stable enough to be trapped by the conjugate base of the original Lewis acid–base pair. The following example illustrates the



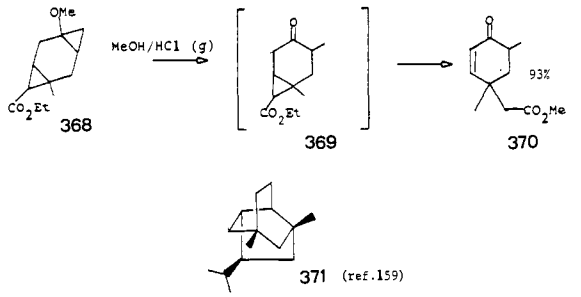
phenomenon and indicates its utility in the design and execution of synthesis of natural products such as (–)-phytuberin (**364**).[156,157]



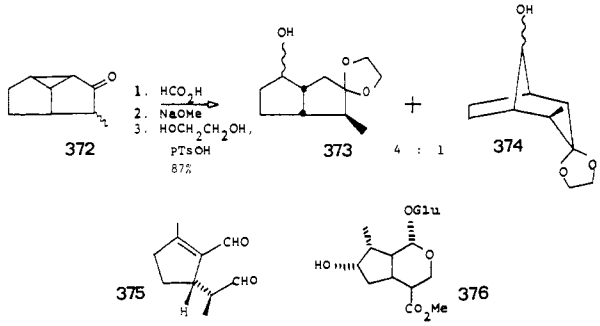
Tricyclo[4.3.1.$0^{1,6}$]dec-3-en-8-one or tricyclo[4.4.1.$0^{1,6}$]undec-8-en-3-one **365** was treated with hydrochloric acid in acetic acid to give two isomeric ketones, **366** and **367**, quantitatively.[158]



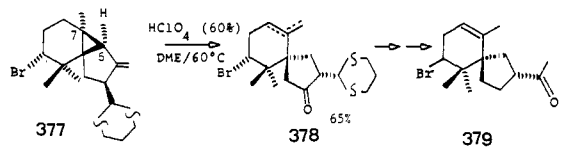
Reaction of tricyclic ester **368** with methanolic HCl produced cyclohexenone derivative **370** in 93% yield. This substance was transformed to (+)-9-pupukeanone (**371**).[159] The regiocontrol in the opening of keto cyclopropanes was used in general approaches to syntheses of natural products such as the monoterpenes chrysomelidial (**375**)[160] and loganin (**376**).[161]



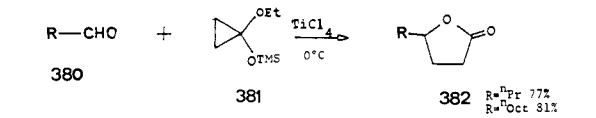
Treatment of **372** with 9% formic acid at 70–80 °C for 30 min followed by methanolysis and ketalization gave 87% of **373** and **374** in a 4:1 ratio.[160,164] The former substance was converted to chrysomelidial (**375**) and loganin (**376**).

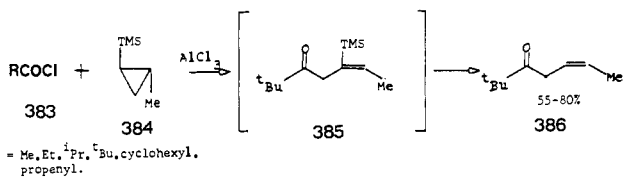


(±)-Spirolaurenone (**379**), an antifungal sesquiterpene isolated from the red algae *Laurencia glandulifera*, was synthesized by a sequence in which the key step was the cyclopropane opening of **377**.[162] The acid-catalyzed opening produced a mixture of exo and endo olefins.

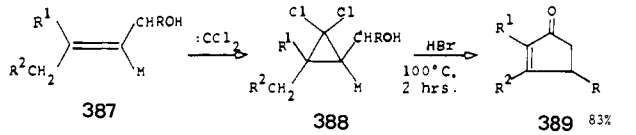


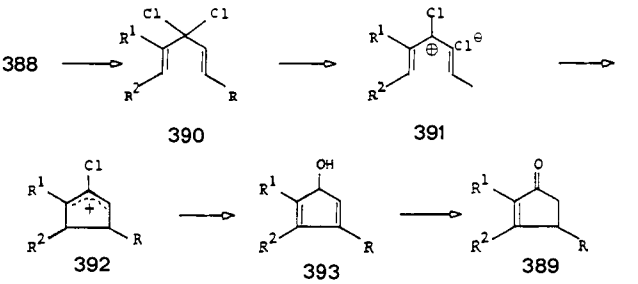
The presence of more than one heteroatom greatly enhances the tendency of cyclopropanes to undergo electrophilic addition. For example, reaction of 1-ethoxy-1-(trimethylsiloxy)cyclopropane (**381**) with aliphatic aldehydes **380** in the presence of $TiCl_4$ gave γ-lactones **382** in high yields.[163] The mechanism is believed to involve electrophilic attack of titanium chloride on the cyclopropane.[163] Reaction of 1-(trimethylsilyl)-2-methylcyclopropane (**384**) with acid chlorides **383** in the presence of $AlCl_3$ in methylene chloride afforded β,γ-unsaturated ketones **386** regio- and stereospecifically.[164]



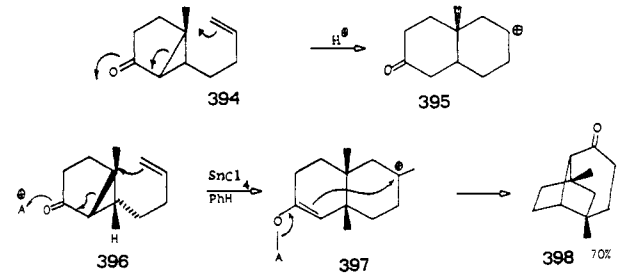


A synthetic method for cyclopentannulation was reported by Hiyama et al.[165] It is based upon one-carbon homologation of allylic alcohols such as **387** with dichlorocarbene to provide **388**. Treatment of alcohol **388** with 47% hydrobromic acid at 100 °C gave **389** in 83% yield.[165] The mechanism of the cyclopentenone formation can be rationalized by invoking a Nazarov-type process involving thermal conrotatory ring closure of **391** to produce the cyclopentenyl cation. Deprotonation followed by hydrolysis of the resulting chloro diene gives **389**.



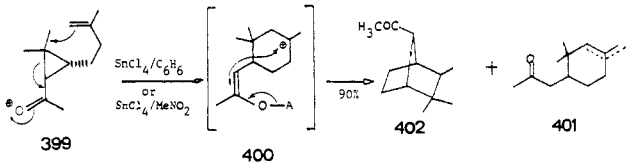


When an acylcyclopropane contains an internal, suitably situated nucleophile, the possibility of multiple C–C bond formation presents itself. For example, acylcyclopropane **394** undergoes acid-catalyzed reaction with a suitably disposed olefinic center leading to the formation of a new ring such as **395**.[166] Similarly, treatment of *endo*-bicyclo[3.1.0]hexanone **396** with stannic chloride in benzene afforded tricycle **398** in 70% yield. The cationic intermediate was trapped by the enol generated through acylcyclopropane opening.[167]

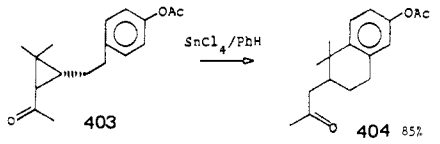


Similar treatment of the nonrigid acylcyclopropane **399** resulted in a >90% yield of a 80:20 mixture of **401** and **402**.[168] In contrast, reaction of **399** with 10 equiv of stannic chloride in CH_3NO_2 (25 °C) for 30 min afforded a 20:80 mixture.[168]

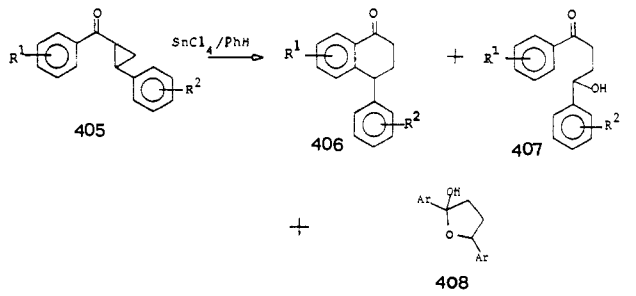
An example involving the annulation of an aromatic ring involves treatment of arene acylcyclopropane **403**



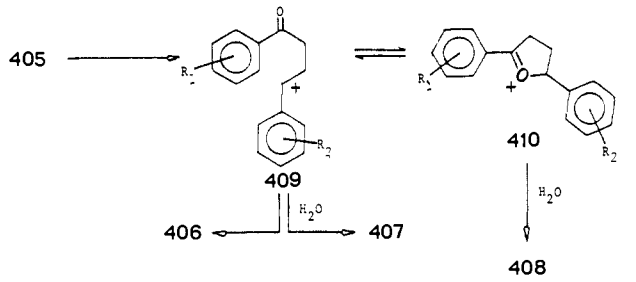
with stannic chloride in benzene, yielding **404** in 85% yield.[168] Cyclization of the activated arylaroylcyclo-



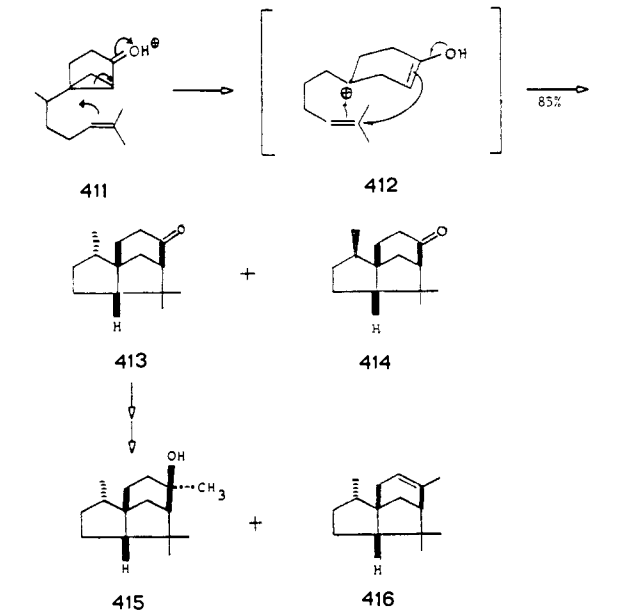
propane **405** was achieved with stannic chloride in benzene at room temperature and afforded mainly tetralone **406**.[169] The mechanism of the above trans-



formation involves the formation of benzyl carbocation **409** as illustrated below:[169]

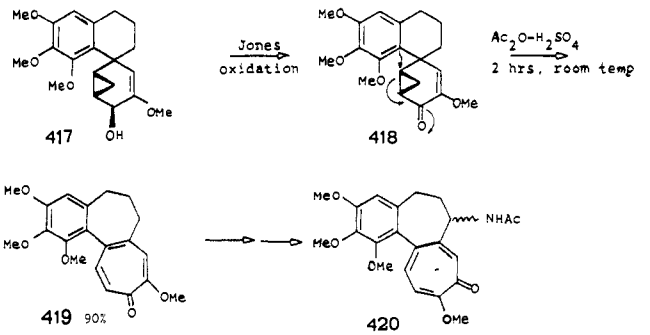


Two elegant examples involving this type of rearrangement are provided by the total syntheses of cedrene and coldicine.[171] Treatment of a mixture of two diastereomeric forms of **411** with acetyl methanesulfonate in methylene chloride at −40 °C for 12 h



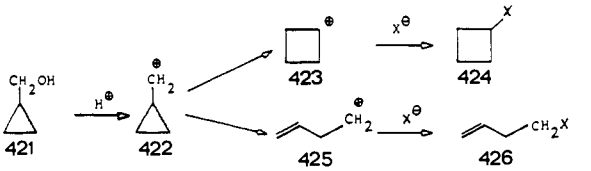
followed by aqueous workup afforded **413** and **414** in an 85% combined yield.[170] Tricyclic ketone **413** was converted to (±)-cedrol (**415**) and (±)-cedrene (**416**).[170]

The alkaloid (±)-colchicine (**420**) was synthesized by Tobinaga in a sequence where the key step involved cyclopropyl intermediate **418**, which was treated with Ac_2O–H_2SO_4 (2:1) for 2 h at room temperature to give **419** in a one-pot operation involving cyclopropane ring cleavage, aryl migration, and dehydrogenation.[171]



3. Cyclopropylcarbinyl Cation and Related Rearrangements

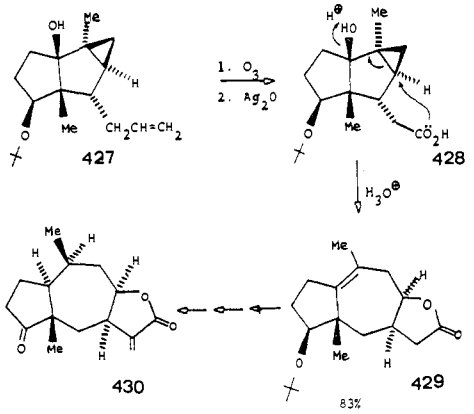
The cyclopropylcarbinyl cation system provides an intriguing example of the number of rearrangements possible for small-ring compounds.[39] It is well-known that the intermediates of this rearrangement are either the cyclobutyl cation **423** or the allylcarbinyl cation **425**.



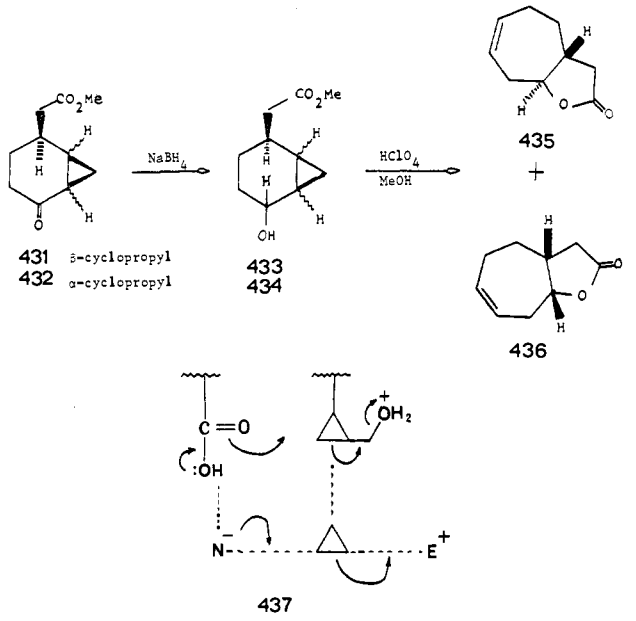
Relief of ring strain and the formation of more stable carbocations are perhaps responsible for the conversion of cyclopropylcarbinyl cation **422** to cyclobutyl cation **423**. On the other hand, **422** will also undergo ring fission to furnish allylcarbinyl cation **425**. The application of these isomerizations is of particular value to organic synthesis.

The chemistry of this rearrangement has been extensively studied, from both a theoretical and a practical point of view.[144,172,173] It appears that some degree of control over the two avenues of rearrangement is available; both cyclobutanes and allylic systems can be synthesized in this fashion. Thus, ring-expansion methodology, 1,4-dicarbonyl compounds, γ-unsaturated carbonyl compounds, and their derivatives are all available through the exploitation of this rearrangement. Wenkert[172] and Trost[173] utilized this rearrangement extensively in the synthesis of terpenoids and cyclobutanones, respectively. Selected examples below illustrate the generality of this process.

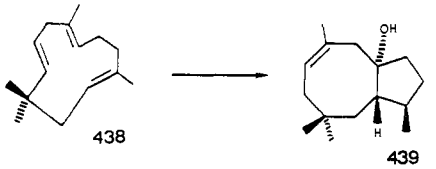
Ozonolysis of the allyl-substituted tricyclic substrate **427** followed by treatment with silver oxide afforded acid **428**. Hydroazulene lactone **429** was obtained from **428** upon reaction with aqueous perchloric acid in an overall yield of 80%. This strategy constituted the key step in the total synthesis of confertin (**430**).[174]



Similarly, reduction of a mixture of ketones **431** and **432** with sodium borohydride led to the epimeric alcohols **433** and **434**, respectively. This mixture, upon treatment with aqueous perchloric acid in methanol, afforded an 85:15 mixture of the trans and cis lactones **435** and **436**.[175] The reactions of the cyclopropylcarbinyl systems in the two aforementioned examples seem to involve the assistance of an internal nucleophile with concomitant ejection of water and cyclopropane bond imigration as shown in **437**. An interesting biomimetic

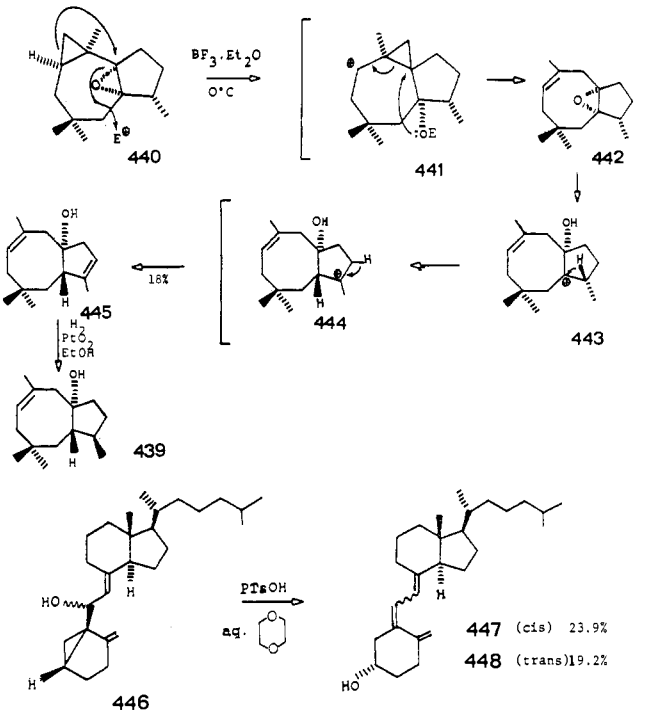


mechanism involving cyclopropylcarbinyl system **441** was proposed to explain the conversion of humulene (**438**) to dactylol (**439**).[176] When cyclopropane **440** was

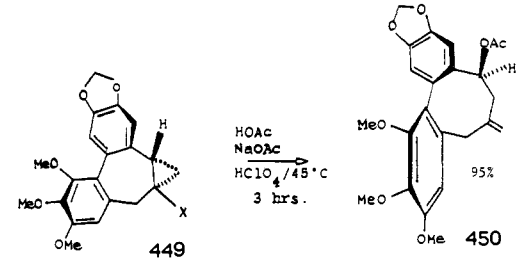


treated with BF_3-Et_2O at 0 °C, product **445** was produced. This result can be ascribed to opening of cyclopropylcarbinyl cation **441** followed by the epoxide opening, transannular cyclization, and a hydride transfer (**443** → **444** → **445**). Selective hydrogenation of **445** yielded dactylol (**439**).[177] Solvolysis of **446** in the presence of *p*-toluenesulfonic acid in aqueous dioxane at 55 °C afforded vitamin D_3 (**447**) and its trans isomer **448**.[178]

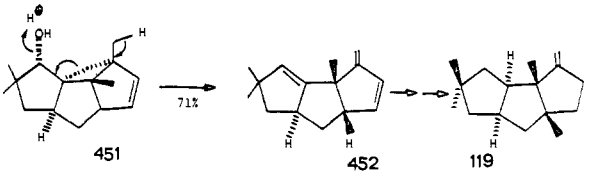
Reaction of cyclopropylcarbinol **449** in acetate buffer



at 45 °C for 3 h gave **450** in 95% yield. Acetate **450** was transformed to (±)-steganone, an antileukemic bisbenzocyclooctadiene lignan.[179] Two examples of cy-

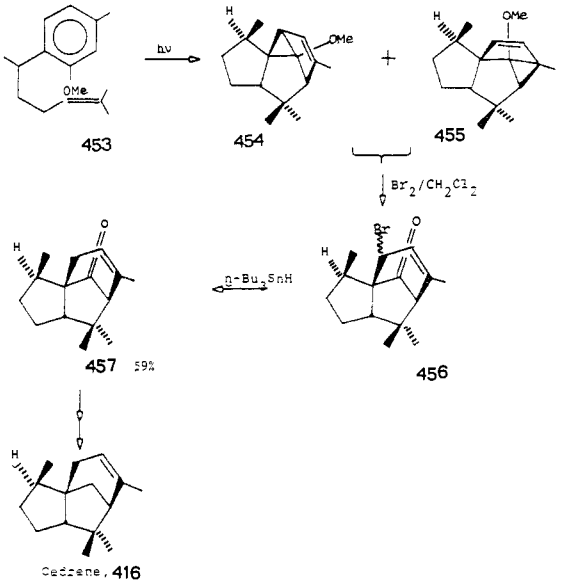


clopropylcarbinyl systems were used by Wender in the synthesis of hirsutene and cedrene.[180] Tetracyclic alcohol **451**, prepared by photolysis of the corresponding arene–olefin cyclization, underwent rearrangement with anhydrous 10-camphorsulfonic acid in benzene at room temperature, producing cleanly triene **452** in 71% yield. This triquinane was transformed to (±)-hirsutene (**119**).[181]

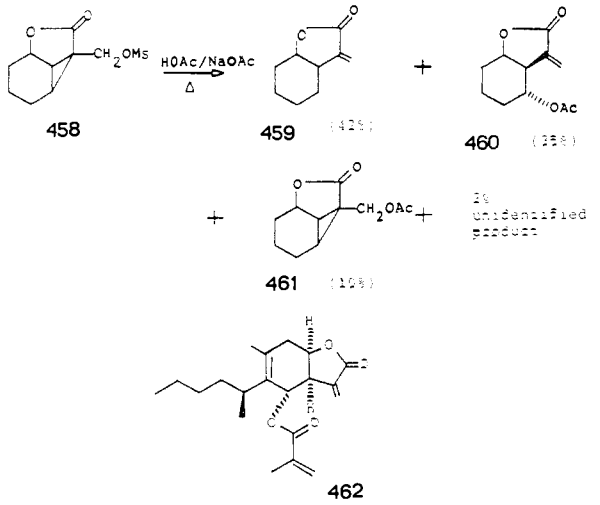


Similarly, a mixture of **454** and **455**, prepared from arene–olefin cycloaddition of **453**, was treated with bromine (1 equiv in CH_2Cl_2). Electrophilic attack on the double bond induced cleavage of the cyclopropane ring with the assistance of the methoxy group and afforded only 10α- and 10β-bromocedren-11-one **456**. The bromides were treated immediately with tri-*n*-butyltin hydride to give **457** in 59% overall yield. Wolff–Kishner reduction of this compound provided (±)-α-cedrene (**416**).[182]

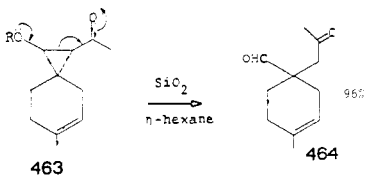
When cyclopropyl lactone **458** was exposed to refluxing glacial acetic acid containing 1.2 equiv of sodium acetate, three substances, **459**–**461**, and an unidentified

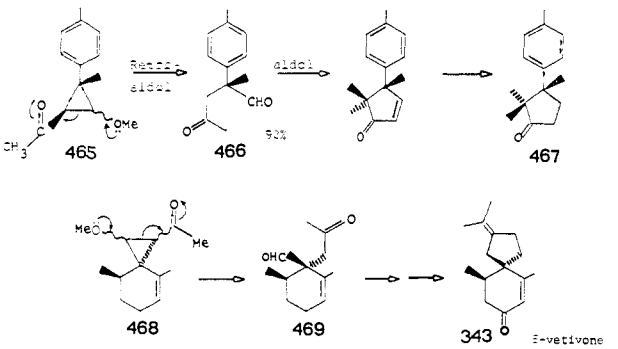


product were isolated.[183] This synthetic strategy was further employed in the synthesis of eriolanin (**462**).[184]

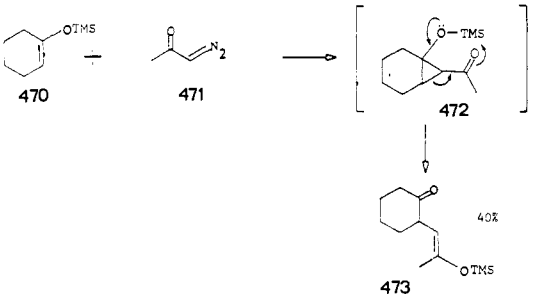


The synthesis of 1,4-dicarbonyl compounds via tandem cyclopropanation–cyclopropylcarbinyl rearrangement has been applied to the preparation of many natural products. Wenkert and others have extensively used this sequence.[172,185,186] Most recently, this rearrangement has been used in the synthesis of natural products, as in Wenkert's isocomene[185] and Marino's pentalenolactone[186] syntheses. Chromatography of ketone **463** on silica gel promoted the retro-aldol reaction and afforded aldehyde **464** in 96% yield.[187] Similar strategy has been used in synthesis of (±)-α-cuparenone **467** and β-vetivone (**343**).[188] In these syntheses, the copper-mediated carbenoid addition of α-diazo ketones and esters to enol acetates led to acetoxycyclopropyl carbonyl compounds, which upon hydrolysis underwent subsequent retro-aldol ring opening to 1,4-dicarbonyl compounds.[136,189] More recently, the enol acetates were replaced with silyl enol ethers, which have been found receptive of carbenoids. For example,

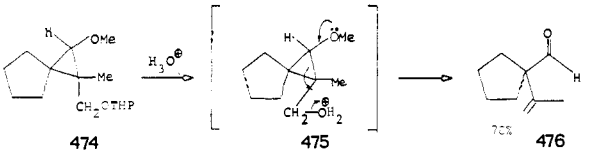




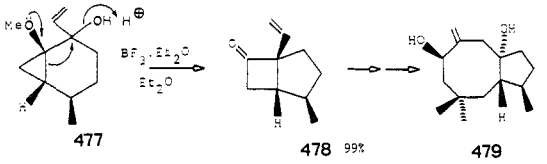
reaction of diazoacetone with **470**, in the presence of cupric acetylacetonate afforded **472**, which underwent subsequent silatropic retro-aldol rearrangement to a masked 1,4-dicarbonyl compound **473**.[190] Treatment



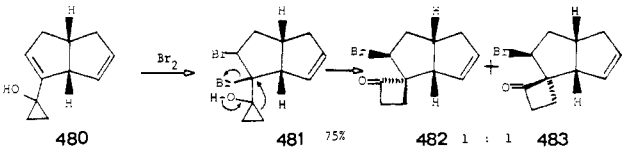
of spiro compound **474** with HCl in aqueous acetone effected the cleavage of the cyclopropane ring with concomitant formation of the isopropenyl moiety to give **476** via intermediate **475**.[191]



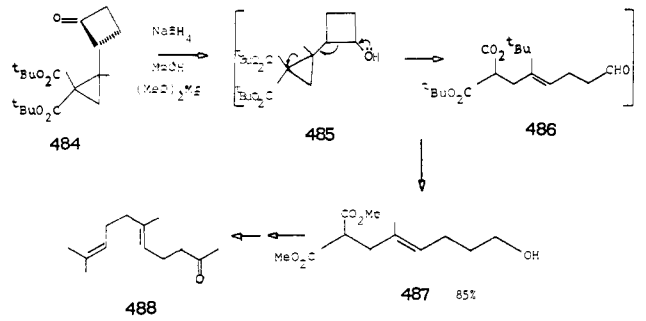
Formation of cyclobutanone **478** was achieved through treatment of norcaranol **477** with 1 equiv of $BF_3{\cdot}Et_2O$.[192] This compound was an important intermediate in the synthesis of (±)-poitediol (**479**), an unusual sesquiterpene diol isolated from the red seaweed *Laurencia poitei*.[192]



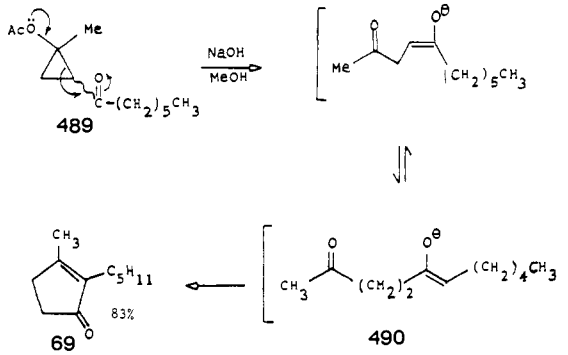
Treatment of vinylcyclopropyl alcohol **480** with bromine afforded an equimolar mixture of spiro ketones **482** and **483**.[193] The mechanism of the ring expansion may involve intermediate dibromide **481** or a bromonium ion.[193]



Treatment of 2-cyclopropylbutanone **484** with a methanolic solution of sodium borohydride and magnesium methoxide at 0 °C, followed by reflux for 40 h, led to an 85% yield of diester **487**. This compound is an important precursor to many acyclic terpene units

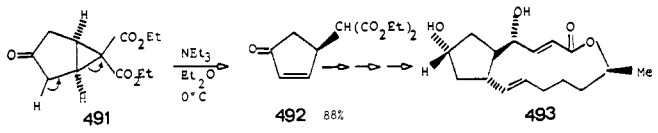


such as (*E*)-geranylacetone **488**.[194] A solution of **489** and sodium hydroxide in methanol gave dihydrojasmone (**69**) in 83% yield through intermediate **490**.[188]

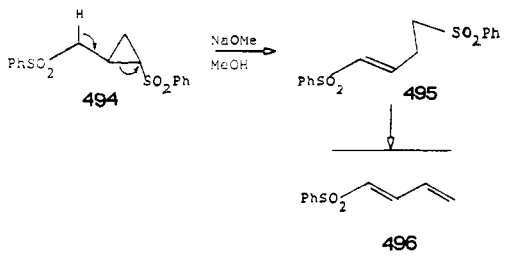


The advantage of a suitably masked cyclopropylcarbinyl system lies in the fact that both acid- and base-catalyzed rearrangements can be effected. The choice depends on the use of acetates or silyl ethers (base deprotection) or allyl ethers (acid catalysis).

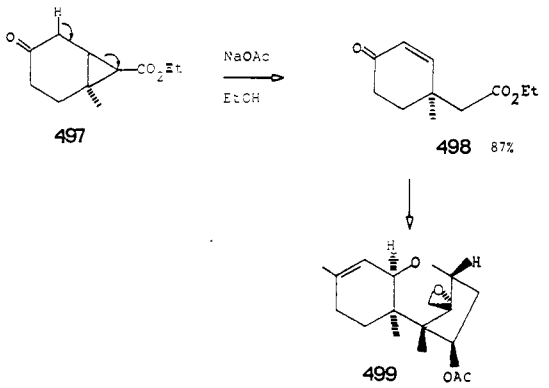
Activated cyclopropanes also undergo cleavage under basic conditions. This reaction can be compared mechanistically to either additions to enones (resulting in overall substitution) or to elimination (E_1cb or E_2) of β-halocarbonyl groups. In the case of cyclopropanes, the bond that would normally break on departure of a leaving group is either channeled into the π-system of an electron-withdrawing substituent or it becomes a new π-system. The following examples illustrate the utility of the base-induced cyclopropylcarbinyl rearrangement. Treatment of ketone **491** with Et_3N generated a useful precursor **492** for the synthesis of brefeldin A (**493**).[195]



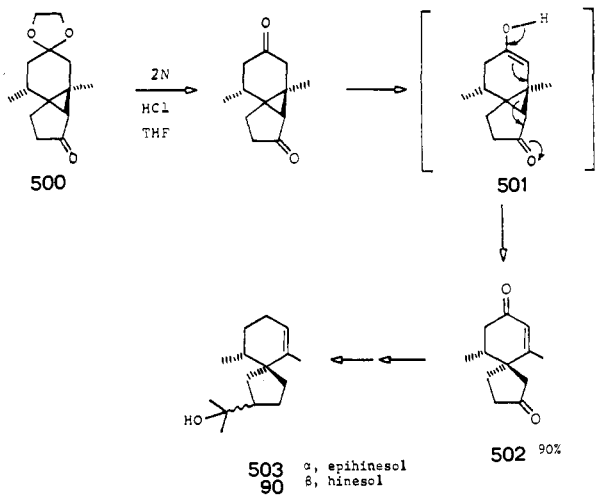
Treatment of cyclopropyl sulfone **494** with ethanolic sodium ethoxide gave **495**, which was converted to diene **496** upon elimination of $PhSO_2H$.[196]



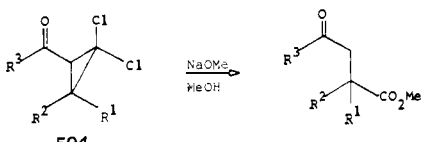
The total synthesis of a phytotoxic trichothecane group sesquiterpene, (±)-trichodermin (**499**), featured the ring opening of **497** by sodium acetate in ethanol to give **498**.[197,198] The conversion of **497** to **498** exemplifies an extremely useful methodology: the equivalent of a selective γ-alkylation of an enone. The enone is deconjugated by the normal kinetic protonation of its dienolate, the β,γ-unsaturated site is cyclopropanated, and the cyclopropane is opened to provide the γ-alkylated enone selectively.



Treatment of cyclic ketal ketone **500** with 2 N HCl in THF gave spiro enedione **502** via enol intermediate **501**. Cyclopropane **501** was then converted to (±)-hinesol (**90**) and (±)-epihinesol (**503**).[199] Treatment of



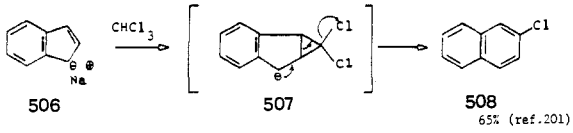
gem-dichlorocyclopropanes **504** with sodium methoxide in methanol afforded ketones **505** in high yields.[200]



R^1	R^2	R^3	yield of **505**, %
H	$-(CH_2)_3-$		>94
Me	$-(CH_2)_3-$		>94
H	$-(CH_2)_4-$		>94
H	$-(CH_2)_5-$		>94
Me	Me	Me	83
$-(CH_2)_5-$		H	75

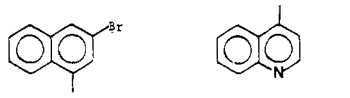
Reaction of indenylsodium (**506**) with chloroform results in the formation of 2-chloronaphthalene (65% yield), presumably via rearrangement of **507**.[201]

This type of reaction has been used extensively in the preparation of aromatics such as **509**.[202] This methodology has been extended to synthesis of heterocyclic



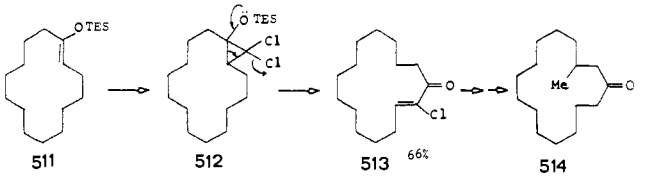
506 507 508 65% (ref.201)

compounds such as **510**,[203] obtained by cyclopropanation and ring expansion of 3-methylindole.[203]



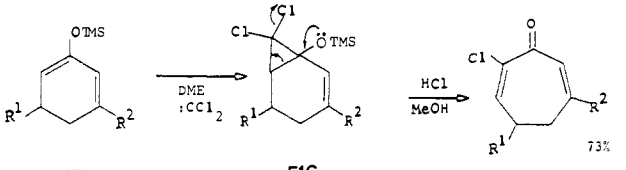
509 44% (ref.202) 510 (ref.203)

Muscone (**514**) was synthesized via cyclopropanation of triethylsilyl enol ether **511** followed by treatment with 1 N HCl in THF at room temperature for 1 h. Ketone **513** was isolated in 66% yield and was readily converted into (±)-muscone (**514**).[204] Dichlorocarbene



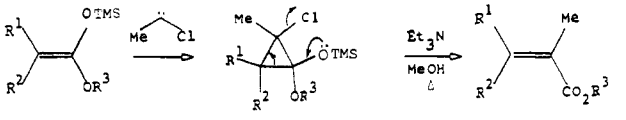
511 512 513 66% 514

addition and hydrolysis of dienyl silyl ether **515** gave **516**, which upon treatment with acid rearranged to α-chloro dienone **517** in 73% yield.[205] Trimethylsilyl



515 516 517

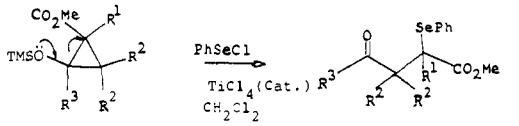
enol ether **518** underwent cycloaddition with chloromethylcarbene to give, after rearrangement of cycloadduct **519**, α-unsaturated ester **520**.[206]



518 519 520

R¹	R²	R³	yield of **520**, %	*E*/*Z*
H	H	CH_2Ph	91	
Me	H	Et	88	68/32
Et	H	Et	94	60/40
^{n}Am	H	Et	95	64/36
^{t}Bu	H	Me	83	83/17
Ph	H	Me	75	61/39
Me	Me	Et	91	
	$-(CH_2)_4-$	Me	89	
Ph	Ph	Me	32	
^{s}Bu	H	Me	94	60/40

A recent report described the ring opening of trimethylsilyl ether **521** and the trapping of the intermediate with phenylselenium chloride to provide **522**.[207] This reaction was used extensively in the preparation of various γ-keto esters.[208]

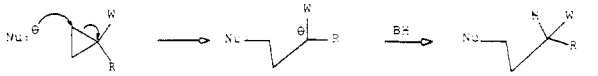


521 522

R¹	R²	R³	yield of **522**, %
H	Me	H	69
H	Me	Me	88
H	^{t}Bu	H	85
Me	^{t}Bu	H	82

4. Nucleophilic Addition

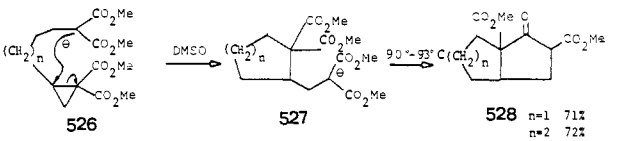
Cleavage of three-membered carbocycles by nucleophiles is possible only when an electron-withdrawing group (W) is present on the ring.[209] This methodology



523 524 525

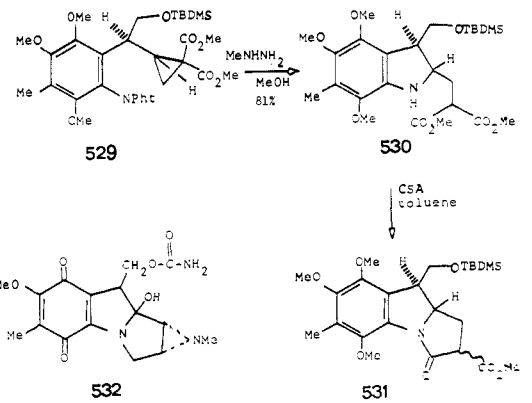
has been widely applied in organic synthesis and is known as the homologous (or 1,5) version of the classical Michael addition.[210] The following examples demonstrate how this type of reaction has been applied intramolecularly in the preparation of some fused-ring compounds. Central to the approaches to cyclic compounds is the initial nucleophilic attack of an enolate, alkoxide, or amine on an activated cyclopropane, with subsequent intramolecular ring closure.

Anions **526** reacted readily at room temperature in DMSO via an intramolecular nucleophilic addition to the cyclopropyl group, yielding **527**. When **527** was heated, a 70% yield of the bicyclic ketones **528** was obtained.[211] Cyclopropane **529** was subjected to hy-



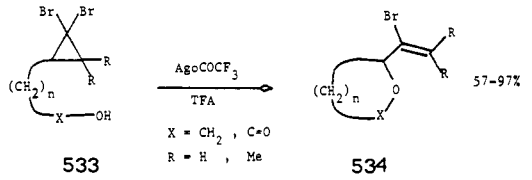
526 527 528 n=1 71% n=2 72%

drazinolysis to give an 81% yield of **530**. Heating **530** in the presence of camphorsulfonic acid yielded 50% of lactam ester **531**, which was used in the total synthesis of mitomycin B (**532**).[212]



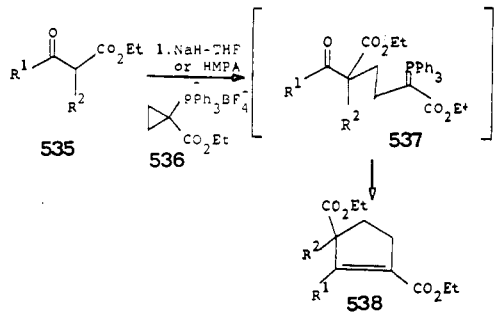
529 530 532 531

The cationic π-cyclization constitutes an important method for the synthesis of an alicyclic and heterocyclic compounds, e.g., **534**. Lactones, tetrahydrofurans, and tetrahydropyrans can be synthesized by this method.[213]



533 534

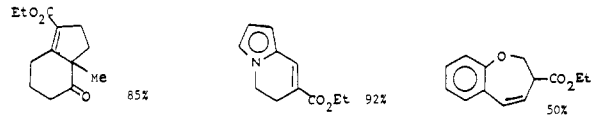
Nucleophilic addition to an activated cyclopropane can also be accomplished *inter*molecularly, although the process requires more activation than its intramolecular counterpart.[209] For example, β-keto ester **535** (as its sodium enolate) adds to cyclopropane **536** to produce the phosphorane intermediate **537**, which rearranges to cyclopentene diester **538**.[214]



535 536 537 538

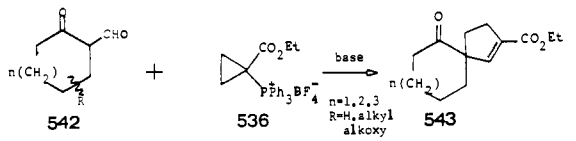
R^1	R^2	yield of **538**, %
CH_3	H	95
Ph	H	90
CH_3	CH_3	88

The following examples illustrate the utility of phosphonium salt **536** as a cycloalkenylation reagent. The initiating nucleophile need not be the carbon of an enolate anion as in the reactions leading to **538** and **539**; amines and alkoxides also participate in the ring opening of **536**, providing entry into heterocyclic systems **540** and **541**.[214] A general synthesis of spirocycles

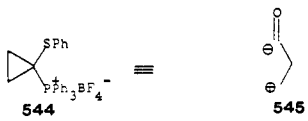


539 540 541

543 was accomplished by reactions of **536** with β-keto esters or symmetrical 1,3-dicarbonyl systems such as **542**.[215] A new compound, (1-(phenylthio)cyclopropyl)triphenylphosphonium tetrafluoroborate (**544**), equivalent to the acyl synthon **545**, has been reported.[216]

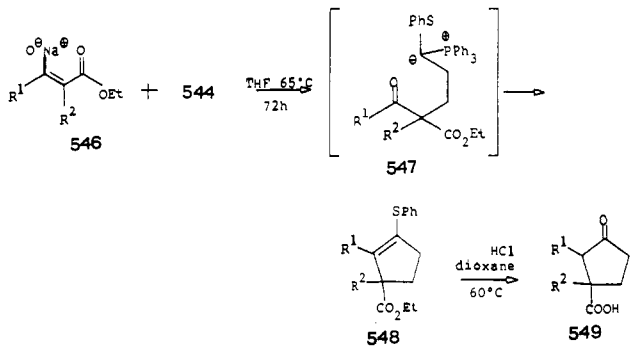


542 536 543



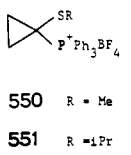
544 545

Sodium enolates of β-keto esters **546** were added to **544** to give intermediate phosphonium ylides **547**, whose intramolecular Wittig reaction gave rise to vinyl sulfides **548** in good yields. Hydrolysis in 20% HCl–dioxane in 60 °C produced keto acids **549**.[216] Variations in the thioether functionality have also been investigated. Sodium enolates of β-keto ester **546** were added to **544**, **550**, or **551** to give, after acidic hydrolysis of intermediate thioenol ethers, cyclopentanone carboxylic acids **549** in 80% overall yield.[217]



546 547 548 549

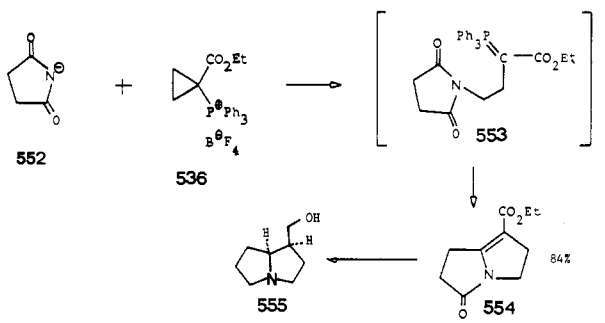
R^1	R^2	yield of **549**, %
CH_3	H	75
CH_3	CH_2Ph	80
Ph	H	75



550 R = Me

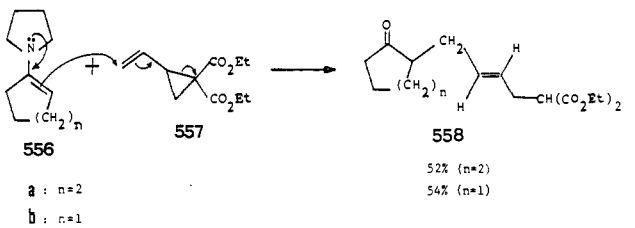
551 R = iPr

Treatment of phosphorus ylide **536** with succinimide anion (**552**) yields an intermediate **553**, which rearranges to bicyclic N-bridgehead lactam **554** in 84% yield.[217] This lactam constituted an intermediate in a brief synthesis of isoretronecanol (**555**).[218]



552 536 553 555 554

The reaction of enamines **556a** and **556b** with vinylcyclopropyl diester **557** in *p*-cumene at reflux, followed by mild acid hydrolysis, gave ketones **558a** and **558b** in 52% and 54% yield, respectively.[219] This reaction constitutes a vinylogous equivalent of the opening of activated cyclopropanes with carbon nucleophiles.

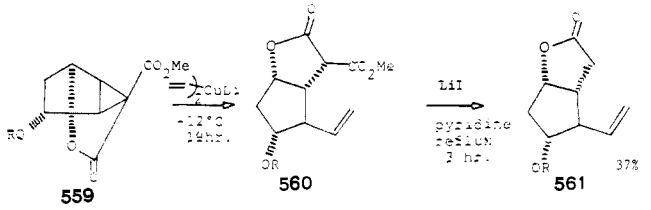


556 557 558

a : n=2 52% (n=2)

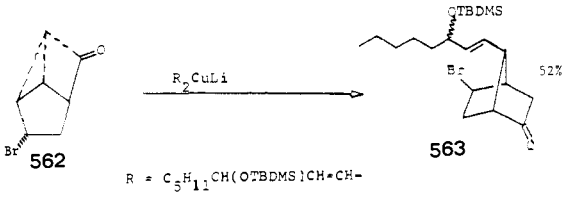
b : n=1 54% (n=1)

The reaction of cyclopropyl ketones with organomagnesium and organocopper reagents is well documented.[220] The success of such ring-opening reactions, analogous to 1,4-addition of cuprates to enones, depends on the choice of the organometallic reagent. The following examples offer a glance at the predictable use of these additions in synthesis. Reaction of tricyclic lactone ester **559** with divinylcopper lithium gave lactone ester **560**, which was decarboethoxylated with lithium iodide to produce lactone **561** in 37% yield.[221]



559 560 561

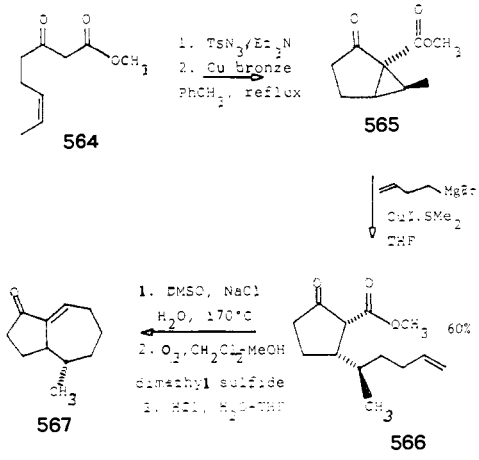
Strained tricyclic ketone **562** reacted efficiently with cuprate reagent to afford the norbornanone **562** in 52% yield. This compound served as a precursor to several prostaglandins.[222,223] It is important to note that the stereochemistry of **562** dictates that of **563** because the cuprate reagent attacks from the least hindered side.



562 563

Compounds such as **562** are easily accessible through the reactions of diazo ketones with olefins.[41,136,222,223]

The following example depicts the construction of a bicyclo[3.1.0]hexane system by using a tandem diazo ketone addition to double bond[136] and the facile cleavage of the strained fused ring system to the desired carbon skeleton. Cyclopropanation of **564** afforded cyclopropyl ketone **565** in 57% yield. Cuprous iodide mediated homoconjugated addition of the Grignard reagent to **565** in THF gave **566** in 60% yield. Decarbomethoxylation, ozonolysis, and aldol condensation then gave enone **567** in 35% yield.[224]

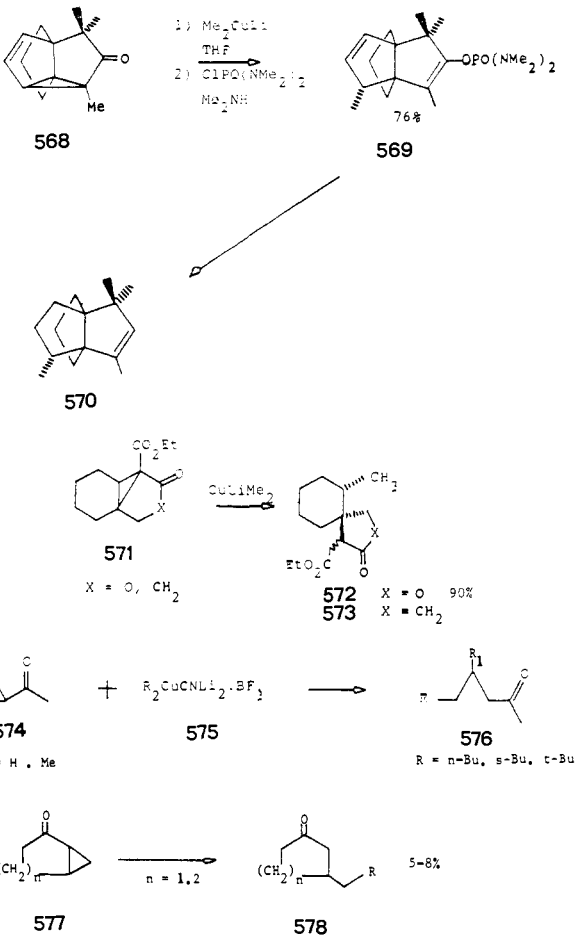


564 565 567 566

Cyclopropane **568** reacted with 5 equiv of Me_2CuLi stereoselectively to furnish phosphorodiamidate **569** in 76% yield. The phosphonate enol moiety in **569** was then reduced in 93% yield, and the intermediate diolefin was selectively hydrogenated to modhephene (**570**) in quantitative yield.[225] Other examples of cuprate additions to activated cyclopropanes include the preparation of **572** and **573**.[226]

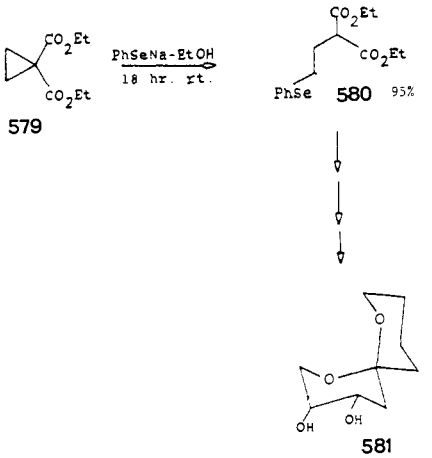
Cyclopropyl ketones such as **574** undergo 1,5-addition at the less substituted carbon with the complex reagent $R_2CuCNLi_2 \cdot BF_3$ (**575**) in moderate to good yields.[227] With fused cyclopropyl ketones such as **577**, the yields are considerably diminished.[227]

A recent paper by Bertz and Cook[228] discusses several mechanisms that may be operative during the additions of cuprates to activated cyclopropanes. A point of interest that triggered this investigation was the observed difference in reactivity between the propellane intermediates in Cook's synthesis of modhephene.[229] The examples of cuprate additions to cyclopropanes are too numerous to list here, but an appropriate survey of relevant additional examples is available in the reference section.[230-235]

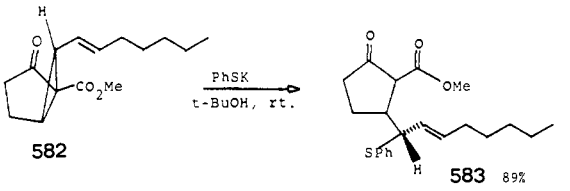


568 569 570 571 572 573 574 575 576 577 578

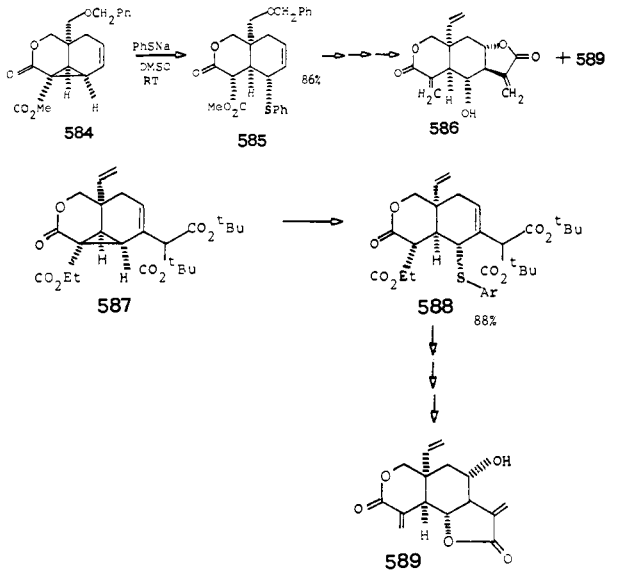
Sulfur and selenium nucleophiles also cleave activated cyclopropanes, thus providing convenient departure points for further functionalizations at the side of addition. During the synthesis of talaromycin B (**581**), the reaction of cyclopropane diester **579** with PhSeNa–EtOH afforded alkyl diester **580** in 95% yield.[236] Similarly, the PhS^-K^+-induced ring-opening reaction of **582** produced the 2,3-disubstituted cyclopentanone **583** in 89% yield.[237] Similar treatment of **584** with PhSNa



579 580 581

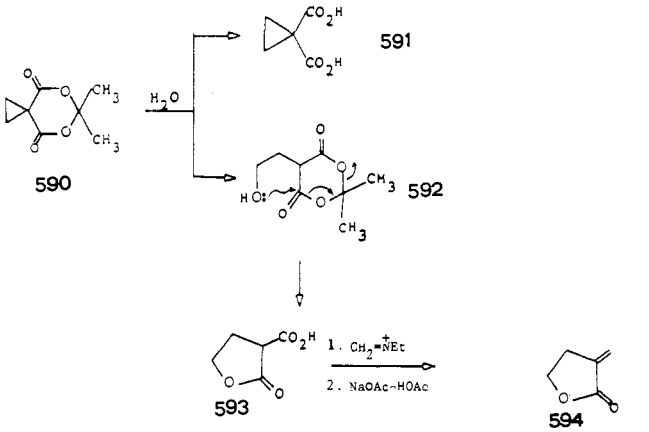


yielded **585**, which was converted to (±)-vernolepin (**589**) and (±)-vernomenin (**586**).[238]

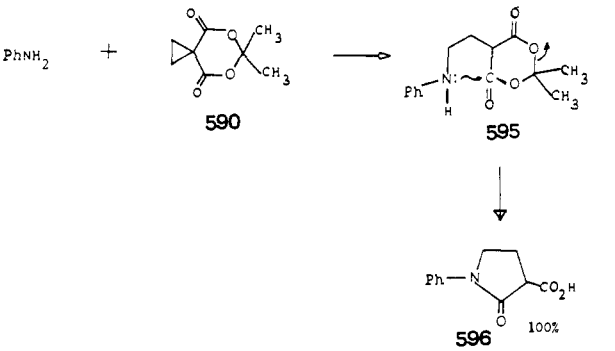


In another approach to vernolepin, opening of the cyclopropane ring in **587** was achieved efficiently by sodium *p*-methoxythiophenolate in THF to afford **588** in 88% yield.[239] Again, release of ring strain played an important role in the building of the extensively substituted bicyclic system. Nitrogen and oxygen nucleophiles have also been used in cyclopropane ring-opening reactions, usually for the purposes of modifying the skeleton or the functionalities of the starting substrates.

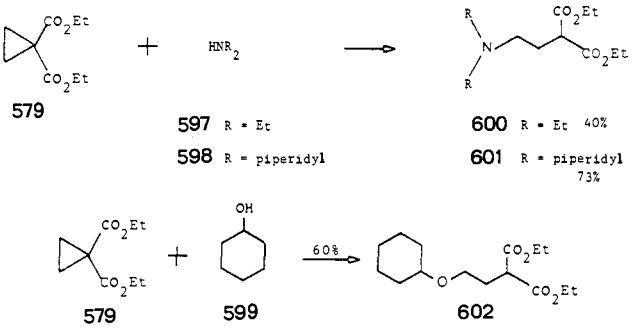
When **590** was heated with 2:1 acetone–water, a 9:1 mixture of 3-carboxybutyrolactone (**592**) and cyclopropane-1,1-dicarboxylic acid (**591**) were obtained. This technology provided synthons such as **593** for conversion to α-methylene lactones **594**.[240] Similarly, a



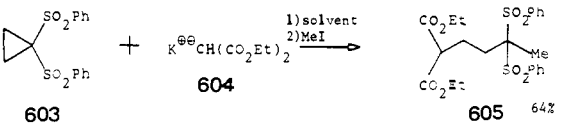
quantitative yield of lactam acid **596** was obtained from treatment of **590** with aniline. A likely pathway involved the formation of the intermediate **595**.[240] Ring-opening addition of amines such as **597** and **598** or alcohols such as **599** to diethyl cyclopropane-1,1-



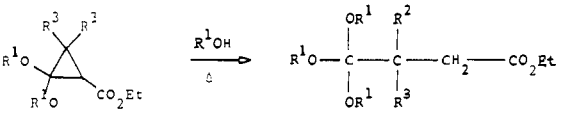
dicarboxylate (**579**) led to 1,1,3-trisubstituted propanes **600**, **601**, and **602**, respectively.[241] Amine nucleophiles



therefore react in direct analogy to the reaction of cyclopropanes such as 1,1-bis(phenylsulfonyl)cyclopropane (**603**) with the anions of malonic ester, which provided **605** in 64% yield.[242] Recently, it has been



reported that the alcoholysis of cyclopropane **606** yields 4,4,4-trialkoxybutanoic ester **607**.[243]

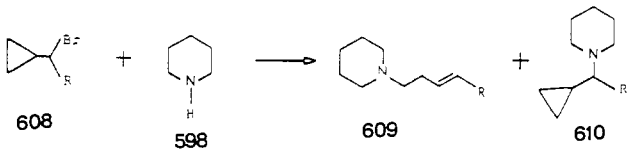


R^1	R^2	R^3	yield of **607**, %
Me	H	H	73
Et	H	H	70
Me	Me	H	72
Et	Me	H	76
Me	Et	H	78
Me	Ph	H	67
Me	Me	Me	66
Me	$-(CH_2)_4-$		50

Other variations of the nucleophile-induced ring opening of cyclopropanes involve replacing the activating electron-withdrawing group with $-CR_2X$, where X is a leaving group. Departure of X^- will lead to the formation of olefins situated 1,3 to the position of nucleophilic opening and is functionally equivalent to a cyclopropylcarbinyl rearrangement.

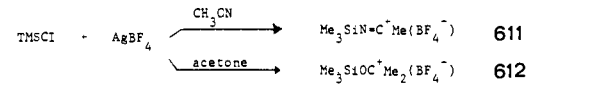
Reaction of piperidine with 1-bromo-1-cyclopropylalkanes **608** afforded mixtures of products **609** and **610**. Excellent yields of the homoallylic substitution product **609** were achieved when the bromide-bearing carbon was sufficiently sterically hindered.[244]

Halides are often used in the nucleophilic opening of activated cyclopropanes.[245] A stoichiometric combina-



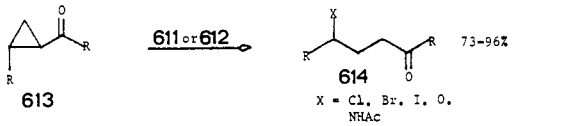
608 598 609 610

tion of trimethylsilyl chloride and silver tetrafluoroborate in acetonitrile or acetone solution yielded two useful reagents **611** and **612**, which were used to convert cyclopropyl carbinols or ketones into homoallyl and γ-substituted ketone derivatives, respectively.[246]



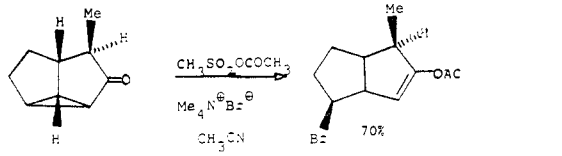
611 **612**

The presence of sodium halides in the reaction mixture resulted in the formation of the corresponding alkyl halides. The presence of water resulted in formation of alcohols (X = OH), while the use of anhydrous **611** in the absence of any additives, followed by aqueous workup, led to acetamides (X = NHAc).[246] Tricyclic



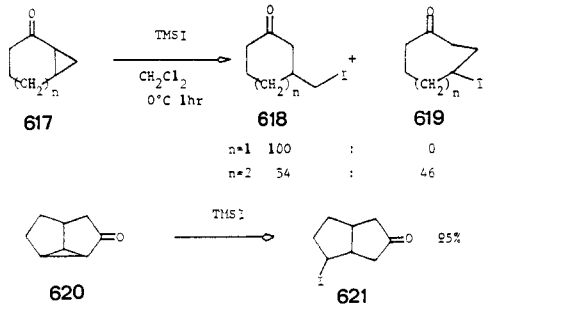
613 **614** 73–96%

ketone **615** was transformed to **616** in a solution of acetyl methanesulfonate, tetramethylammonium bromide, and acetonitrile.[247] Miller has used trimethylsilyl



615 **616** 70%

iodide in a procedure that provided iodo ketones **618**, **619**, and **621** in excellent yields.[248] Iwata reported the



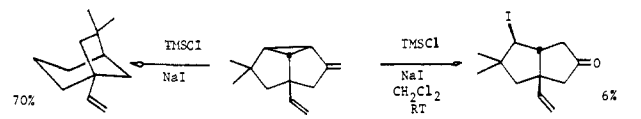
617 **618** **619**

n=1 100 : 0

n=2 54 : 46

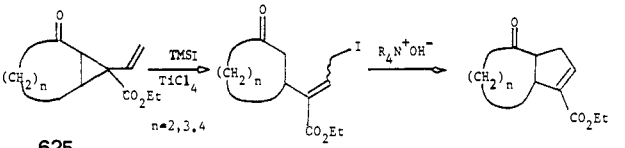
620 **621** 95%

cleavage of ketone **622** to a bridged bicyclo[3.2.1] system **623** in preference to bicyclo[3.3.0]octane **624** with TMSI generated in situ.[249]



623 **622** **624** 70% 6%

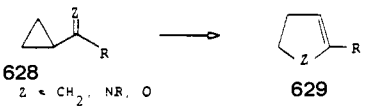
Recently, this methodology has also been found useful in the cyclopentene annulation procedure. Vinylcyclopropanes **625** have been treated with TMSI or TMSI/$TiCl_4$ to yield, through the allylic S_N2' opening, iodides **626**, which were cyclized to cyclopentene-annulated systems **627**. Overall, this transformation is equivalent to the vinylcyclopropane–cyclopentene rearrangement.[72] Most recently, a report of the nucleophilic cleavage of cyclopropanes under the conditions of asymmetric induction appeared. Vitamin B_{12s} has been used as the agent of nucleophilic opening of activated cyclopropanes to give moderate induction (24–33% ee) at the site of ring opening.[250] Chiral cyclopropyl ketones yielded optically active bromomethylene compounds with trimethylsilyl bromide.[251]



625 **626** **627**

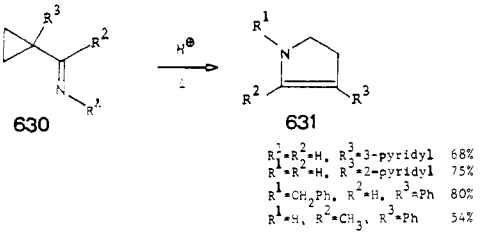
5. Imine–Cyclopropane and Carbonyl–Cyclopropane Rearrangement

Under appropriate conditions, cyclopropanes in conjugation with an unsaturated functional group can undergo the rearrangement (i.e., **628**–**629**) depicted below. The thermal isomerization of vinylcyclopropane to cyclopentene (Z = CH_2) has been discussed. Although these rearrangements represent a heterocyclic variant of the vinylcyclopropane–cyclopentene rearrangement, they need to be treated separately because the mechanistic details can involve not only thermolysis but also protonation of the cyclopropyl ketone followed by either external or internal trapping of the cation. Although no review of these rearrangements is available in the context of the vinylcyclopropane–cyclopentene formalism, the number of examples in the literature certainly warrants one.[252] When Z = NR, the resultant dihydropyrrole system can be manipulated to achieve the synthesis of alkaloids. Alternatively, when Z = O and R = OR′, hydrolysis leads to the isolation of γ-lactone.



628 Z = CH_2, NR, O **629**

The following examples depict the application of imine–cyclopropane and carbonyl–cyclopropane rearrangement in organic synthesis. The acid-catalyzed thermal rearrangement of cyclopropylimines **630** has been reported as a general method for the synthesis of Δ^2-pyrrolines **631**, which are useful intermediates in alkaloid synthesis.[253]



630 **631**

R^1=R^2=H, R^3=3-pyridyl 68%

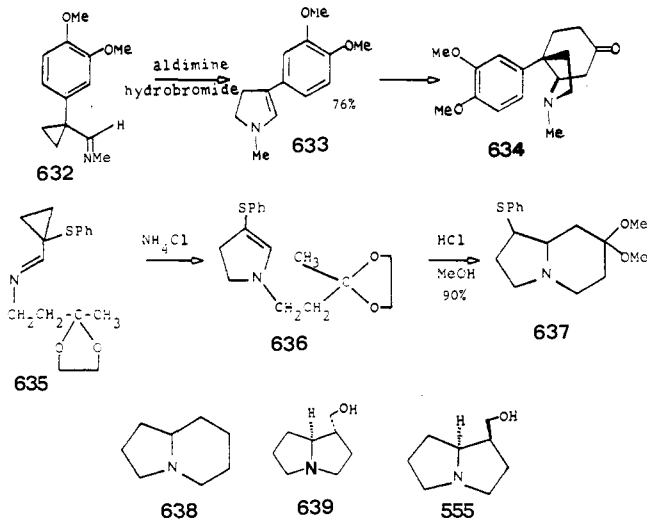
R^1=R^2=H, R^3=2-pyridyl 75%

R^1=CH_2Ph, R^2=H, R^3=Ph 80%

R^1=H, R^2=CH_3, R^3=Ph 54%

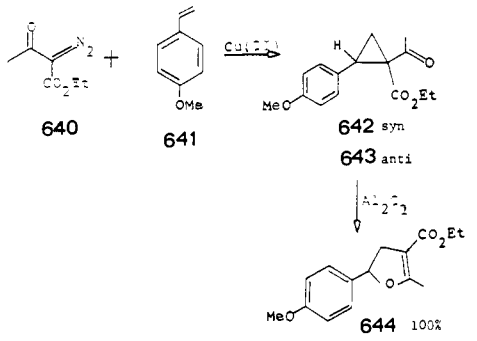
The applications of this reaction have been reviewed.[254] An example of this strategy was in the total synthesis of (±)-mesembrine (**634**).[255]

Rearrangement of the cyclopropylimine **635** afforded pyrroline **636** in 80% yield. Treatment of **636** with methanolic HCl induced cyclization to indolizidine **637** in 90% yield.[256] (±)-δ-Coniceine **638** was prepared via this route.[256]

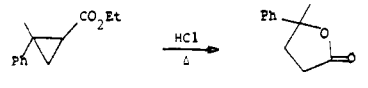


Similarly, the total synthesis of (±)-isoretronecanol (**555**) and trachelanthimidine (**639**) was executed in an analogous manner.[256] It is interesting to note that the parent system, cyclopropylimine, was known since 1929, long before vinylcyclopropane was even isolated.[257]

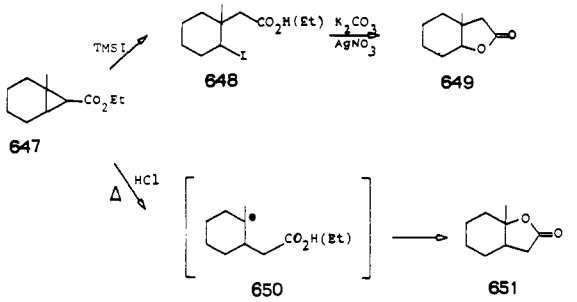
Replacement of nitrogen by oxygen provides an opportunity for a similar rearrangement leading to furanoid derivatives. A syn–anti mixture of cyclopropyl β-keto esters **642** and **643** in 1.9:1 ratio was prepared in 30% yield from the Cu(II)-catalyzed thermolysis of the diazo compound **640** and *p*-methoxystyrene (**641**). Alumina promoted the rearrangement of **642** and **643** to **644** in nearly quantitative yield.[258]



Cyclopropyl esters capable of giving stable carbocations upon protonation yield butyrolactones upon heating with acid. Application of this strategy to the cyclopropyl ester **645** afforded an 80% yield of **646**.[259]

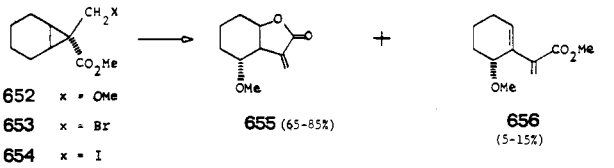


On reaction with trimethylsilyl iodide, **647** yielded lactone **649**, whereas HCl-catalyzed lactone formation allowed the reversal of regiospecificity to provide **651**.[259]

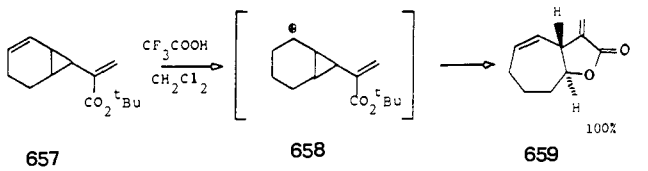


Formation of **649** is attributed to the cleavage of **647** by TMSI to give iodide **648**, which upon treatment with basic Ag^+ gives **649**. On the other hand, protonation of **647** to carbocation **650** is invoked to rationalize the formation of **651**.[259]

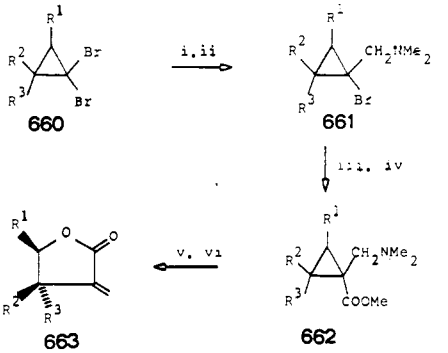
Solvolysis of methoxy ester **652** with $LiClO_4$ in dioxane provided α-methylene lactone **655** contaminated with 25% of diene ester **656**. Bromo ester **653** and iodo ester **654** underwent $AgClO_4$ induced rearrangement to give 65–85% of α-methylene lactone **655**, contaminated with 5–15% of the diene byproduct.[260]



Treatment of propenoate **657** with 10% trifluoroacetic acid in methylene chloride led to cation **658**, which underwent ring expansion to **659**. The α-methylene lactone system (**659**) was formed quantitatively.[261]



A new method for constructing the α-methylene-γ-butyrolactone moiety under neutral, anhydrous conditions was reported.[262] The starting amino ester **662** was prepared from amino bromide **661**, which was previously produced from *gem*-dibromocyclopropane **660**. When **662** was treated with trimethylsilyl iodide and the crude products were distilled, α-methylene-γ-butyrolactones **663** were obtained with higher regio- and stereoselectivity.[262]

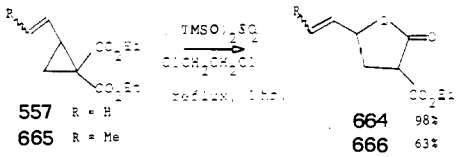


			% yield		
R^1	R^2	R^3	**661**	**662**	**663**
Ph	H	H	59	73	62
^{n}hex	H	H	71	60	58
$-(CH_2)_4-$		H	61	61	64
^{n}hex	^{n}hex	H			67
^{n}hex	H	^{n}hex			73

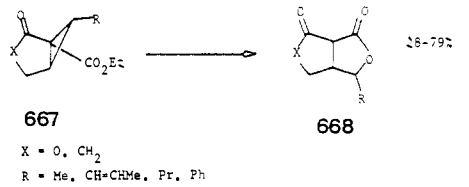
(i) *n*-BuLi, −95 °C, THF, (ii) $CH_2{=}NMe_2{}^+I^-$, (iii) *n*-BuLi or *t*-BuLi, −78 °C, THF, (iv) $(MeO)_2C{=}O$, (v) Me_3SiI, (vi) distillation.

When a 1,2-dichloroethane solution of 2-vinylcyclopropane-1,1-dicarboxylate (**557**) was heated to reflux in the presence of bis(trimethylsilyl) sulfone, γ-butyrolactone **664** was produced in 98% yield.[263] The acceleration of this particular rearrangement can be attrib-

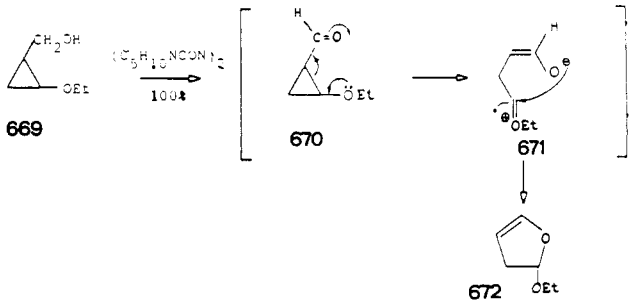
uted to the formation of an allylic cation, which stabilizes the intermediate by ~11 kcal/mol. Alkyl-sub-



stituted cyclopropanes **667** gave rise to lactones **668** under identical conditions.[263] This methodology has been applied to several activated cyclopropanes with excellent results. Oxidation of alcohol **669** with azo-



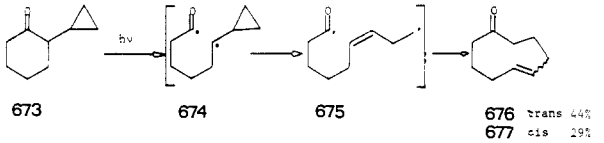
α,α'-bis[piperidine-1-carbaldehyde] led to aldehyde **670**, which rearranged spontaneously to the intermediate open-chained ion **671**. This intermediate recyclized to form dihydrofuran **672** in almost quantitative yield.[264]



V. Miscellaneous Ring Fission

1. Fission Caused by Irradiation

The photochemistry of three-membered-ring compounds has been the topic of several previous reviews.[41,265] The only example discussed here involves 2-cyclopropylcyclohexanone (**673**), which upon irradiation gave a mixture of *trans*- and *cis*-cyclonon-4-enones **676** and **677** as major products.[266] The mechanism presumably involves photochemically induced α-cleavage, followed by rearrangement of the resulting cyclopropylcarbinyl radical **674** and collapse of diradical **675**.

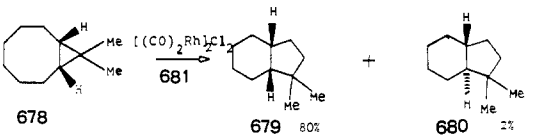


Additional examples of cyclopropane ring isomerization to olefins have been reported.[267-269] The photochemistry of vinylcyclopropanes has been reviewed.[41]

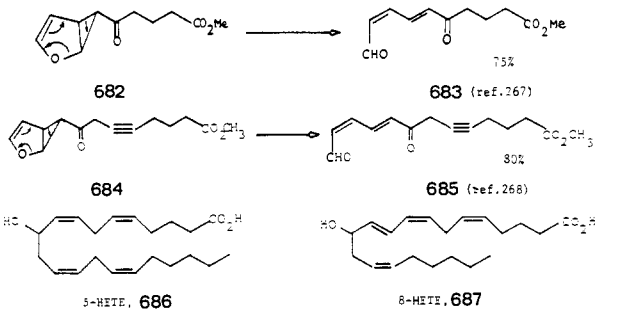
2. Transition-Metal-Mediated Ring Fission

Some aspects of transition-metal-catalyzed ring opening of cyclopropanes have been reviewed.[41,64] Transition metals can promote the cleavage of cyclopropane derivatives; however, the structures of the resulting products are sometimes unexpected. It is not always possible to provide reasonable and acceptable mechanisms for such reactions. Cyclopropane derivatives exhibit unusually low oxidation potentials, suggesting electron transfer may be involved in many of these reactions.[270] The following examples illustrate the diversity of this process.

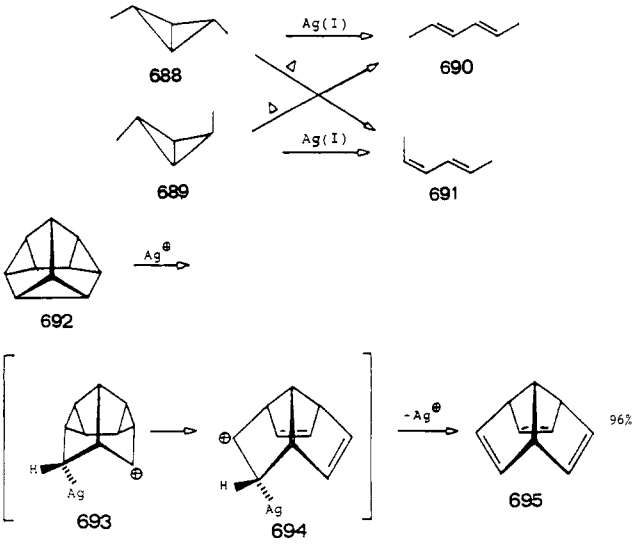
Heating **678** at 190 °C for 30 min in the presence of a catalytic amount of **681** gave a mixture consisting of 80% *cis*-dihydroindene **679** and 2% *trans*-dihydroindene **680**.[271]



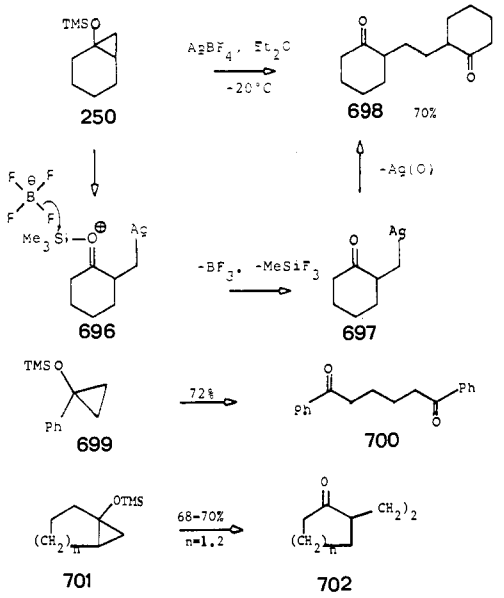
The rearrangement of acylcyclopropyl ethers such as **682**[272] and **684**[273] to keto dienes has been reported. These substrates were formed by the $[Rh(OAc)_2]_2$-catalyzed cyclopropanations of furans, although it is not clear whether the rearrangements were solely the result of the action of the rhodium catalyst used in the decomposition of diazo ketones or whether these rearrangements proceeded via thermal or acid-catalyzed mechanisms.[258,273] The dienes obtained in this fashion were not stereochemically homogeneous, although the cis,trans isomers were the major products. These compounds were further transformed to 5-HETE (**686**),[272] 8-HETE (**687**),[273] and other compounds of this type such as 12-HETE,[274] (±)-12-HETE,[274] and (–)-HETE.[274]



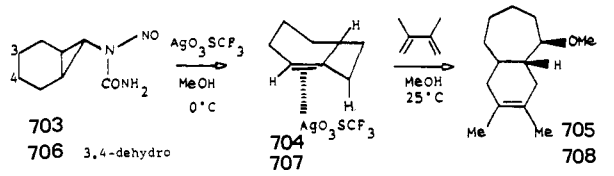
When treated with silver perchlorate in benzene, *exo,exo*- and *endo,exo*-2,4-dimethylbicyclobutanes **688** and **689** rearrange stereospecifically to *trans,trans*- and *cis,trans*-2,2-hexadienes **690** and **691**, respectively.[275] Treatment of **692** with $AgClO_4$ in benzene-d_6 affords triquinacene **695** in 96% yield.[276]



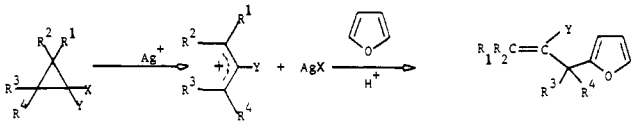
The addition of siloxycyclopropane to a suspension of silver tetrafluoroborate in anhydrous ether (at −20 °C under N_2) afforded diketone **698** in 70% yield. It is believed that **696** and **697** are intermediates in this reaction. Other examples of the reaction of siloxycyclopropanes with $AgBF_4$ are shown below.[277] Silver



trifluoromethanesulfonate (triflate) was utilized for the transformation of **703** to **705**. Analogously, **706** was converted to **708** in 65% yield.[278]



Allyl cations **710**, generated from electrocyclic ring opening of the corresponding cyclopropyl halide with silver perchlorate in THF/ether, were trapped with furan and afforded 2-allylfuran derivatives **711** in fair to good yields as shown.[279] β-Alkoxycyclopropane-



709							
R^1	R^2	R^3	R^4	X	Y	conditions	yield of 711, %
Me	Me	Me	Me	Br	Br	rt, 1 h	40
Me	Me	Me	H	Br	Br	rt, 1 h	76
Me	Me	H	H	Br	Br	reflux, 6 h	73
Ph	Me	H	H	Br	Br	reflux, 6 h	73
Ph	H	H	H	Br	Br	reflux, 6 h	61
^{n}Pr	H	H	H	Br	Br	reflux, 6 h	54
Me	Me	Me	Me	Cl	Cl	reflux, 6 h	60
Ph	H	H	H	Br	H	reflux, 6 h	37

carboxylate ester **712** can be selectively transformed to vinyl ether **713** with various transition-metal catalysts. The product yields obtained with different catalysts are shown.[280] When **714** was treated with zinc chloride followed by successive addition of a catalytic amount of CuBr·Me_2S complex, hexamethylphosphoric triamide (HMPA), and the unsaturated carbonyl compound,

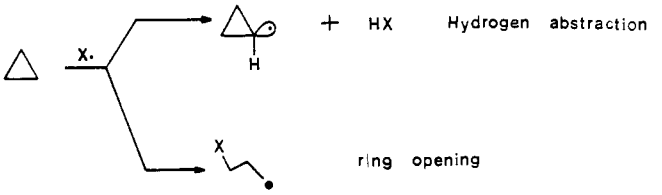


Figure 8.

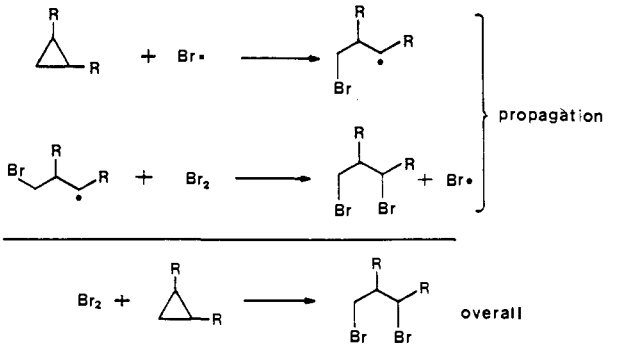
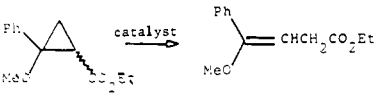
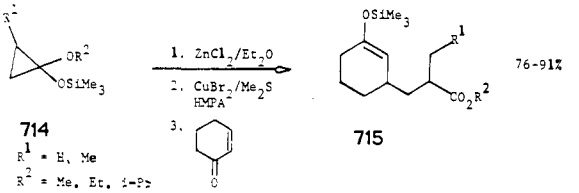


Figure 9.



catalyst	yield, %
$PtCl_2$·2PhCN	98
$[Rh(CO_2)Cl]_2$	98
Cu bronze	97

ester **715** was produced, and the results are shown below.[281] Recently, a chloropalladation of vinylcyclopropanes has been reported and the kinetics of the process studied.[282]



3. Free Radical Reactions of Cyclopropanes

For the reaction of a radical X• with a cyclopropane, two competing pathways are possible: hydrogen abstraction or ring opening (Figure 8).[284]

Generally, hydrogen abstraction is observed only for extremely reactive radicals (Cl•,[283] *t*-BuO•,[283] and imidyl[283,285]), whereas ring opening is observed for less reactive radicals (I•, Br•[286,287]). This difference can be accounted for by considering the unusually high bond dissociation energy of a cyclopropyl C–H bond (106 kcal/mol).[288]

The free radical bromination of alkylcyclopropanes has been studied in detail. The products of the reaction arise from the formal 1,3-addition of Br_2. An S_H2 process, wherein Br• attacks the least hindered carbon, to yield the most stable radical, has been proposed (Figure 9).[286] Products of hydrogen abstraction (e.g., the corresponding cyclopropyl bromides) have not been reported.

A recent report suggests that cyclopropyl bromides can be synthesized from cyclopropanes by means of

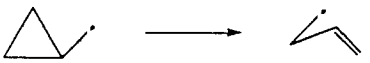
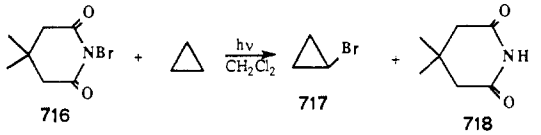


Figure 10.

imidyl radical chemistry. For example, the photoinitiated reaction of cyclopropane with 3,3-dimethyl-*N*-bromoglutarimide (**716**) yields cyclopropyl bromide in excellent yield. In this reaction, imidyl radical rather than bromine atom is the chain-propagating species.[285]

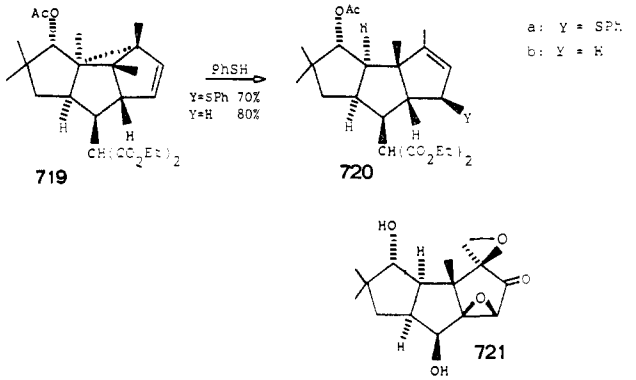


716 717 718

4. Rearrangement of the Cyclopropylcarbinyl Radical

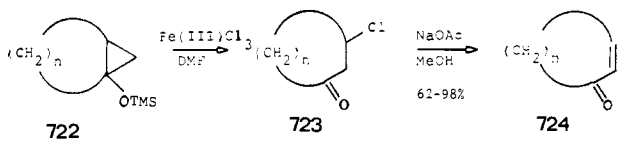
As in the case of the cation, the cyclopropylcarbinyl radical undergoes facile unimolecular rearrangement (Figure 10). The rate constant for this process is $>10^8$ s^{-1}.[289] The following examples illustrate the use of this radical-based methodology in organic synthesis.

Ring opening of tetracyclic acetate **719** was achieved by heating with 1 equiv of thiophenol at 100 °C. Addition of PhS• to the double bond, followed by ring opening and trapping by PhSH produced **720a** in 70% yield.[290] Reductive desulfurization produced **720b** in 80% yield. **720b** proved to be an important precursor to (±)-coriolin (**721**) and other oxygen-rich natural products.[290] Treatment of trimethylsilyl ethers **722** (*n*



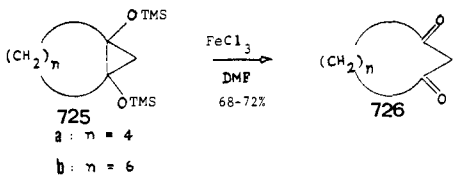
719 720 721

= 3–10) with $FeCl_3$ in DMF followed by base-induced elimination provided 2-cycloalkenones **724**.[291] Simi-



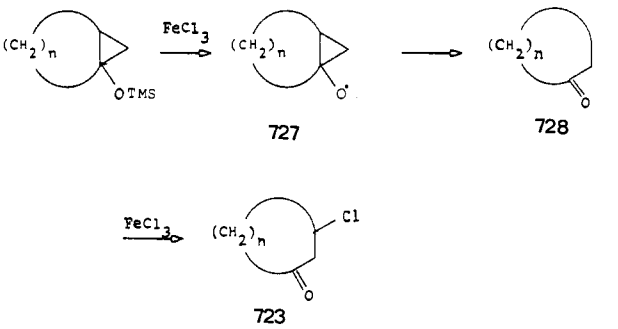
722 723 724

larly, bis(trimethylsiloxy)bicyclo[*n*.1.0]alkanes **725** were transformed to cycloalkane-1,3-diones **726** by action of $FeCl_3$ in DMF.[291]



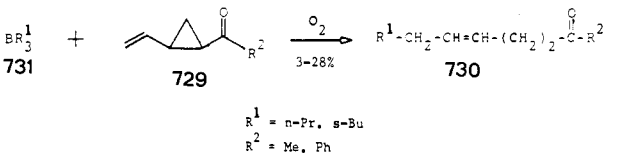
725 a: n = 4 b: n = 6 726

The mechanism of the regioselective ring opening is believed to involve alkoxy radical intermediate **727**, which undergoes homolytic scission of the carbon–carbon bond (β-scission). Abstraction of chlorine by ring-opened radical **728** yields 3-chlorocycloalkanone **723**.[291] Oxygen-induced reaction of organoborane



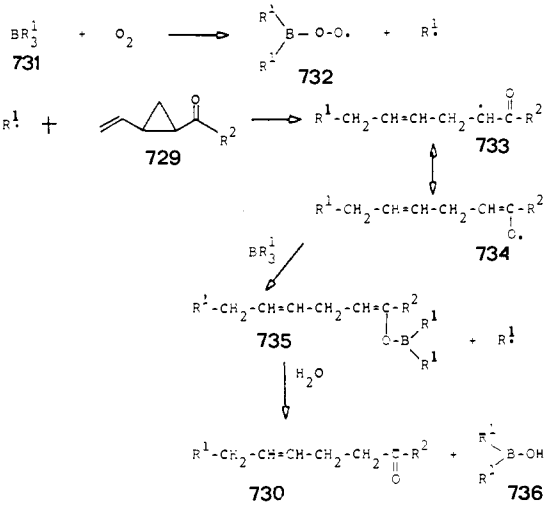
727 728 723

reagents **731** with 1-acyl-2-vinylcyclopropanes **729** produced 1,6-adducts, which were subsequently hydrolyzed to the corresponding γ,δ-unsaturated ketones **730**.[292] Since the reaction was inhibited by O_2, a free



731 729 730

radical chain mechanism was proposed for this transformation:[292]



731 732 729 733 734 735 730 736

VI. Summary

As the syntheses of cyclopropane derivatives can be accomplished by several highly efficient procedures, these derivatives have emerged as important intermediates for the construction of relatively complex molecules. Perhaps more importantly, asymmetric cyclopropanation can be realized in a number of ways. Hence, chiral complex molecules can be obtained via appropriate transformations of these chiral cyclopropane derivatives. This latter aspect has only recently begun to be addressed in detail. Although we have presented several possibilities for the molecular manipulation of three-membered carbocycles, the potential of cyclopropanes has by no means been fully exploited. The underlying theme of this review has been the comparison of the chemistry of alkenes with that of cyclopropanes. The direct result of extrapolating such comparison to synthetic design of complex

molecules has been the explosive growth of new synthetic methodologies. One of the more important aspects of cyclopropane chemistry is the fact that newly established methods that rely on transformation of cyclopropanes are frequently adopted to oxiranes and aziridines in efforts to provide for methodologies in the domain of heterocyclic synthesis. We anticipate that more new strategies will be discovered in the future.

VII. Acknowledgment

We thank Miss Sau Ling Chim and Ms. Wanda Ritter for typing the manuscript and Mr. Kim Fah Liew for drawing all the structural formulas. Special thanks go to Dr. Josie Reed for editorial comments.

Registry No. Cyclopropane, 75-19-4.

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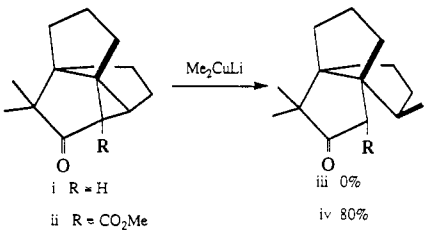

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