Anionic Approaches to the Construction of Cyclopentanoids

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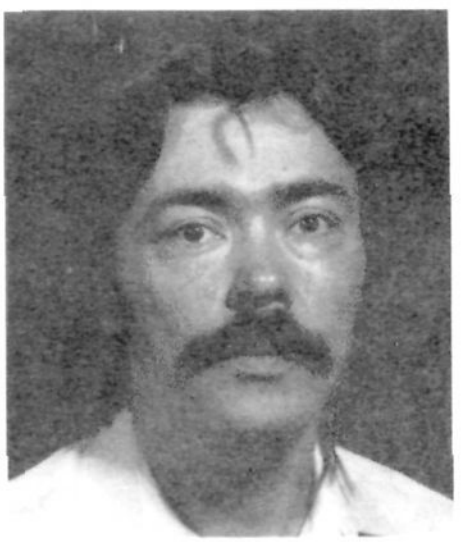

Tomas Hudlicky was born in 1949 and received his B.S. at Virginia Tech in 1973. He studied with Prof. E. Wenkert at Rice University, where he received his Ph.D. in 1977. After a postdoctoral fellowship with Prof. W. Oppolzer at the University of Geneva, he joined the faculty at Illinois Institute of 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.

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I. Introduction

The interest in synthetic methodology applicable to the preparation of cyclopentanoid compounds intensified in the mid-seventies as a direct consequence of the isolation and characterization of many new cyclopentanoid terpenes.[1,2] New synthetic strategies have been developed that would facilitate the preparation of fused cyclopentanoids, or polyquinanes, through inter- and intramolecular processes. Whereas the ultimate objective of this research, a process that would parallel the Diels–Alder reaction in scope and effectiveness, has not yet been accomplished, scores of annulation strategies[3] have evolved and many reviews on the subject have appeared.[4–18]

It is beyond the scope of this review to provide an exhaustive summary of the work in this area, but it is certainly possible to address the known methodology in the context of several general categories based on retrosynthetic disconnections. The most common disconnections involve either the [3 + 2] or the [4 + 1] strategies shown in Scheme I. These methods range from the use of purely anionic alkylative processes to softer organometallic reagents and radical cyclizations. The primary goal of this review is to summarize those methodologies derived from anionic reactions. Cationic, radical, organometallic, and other methodologies are mentioned in the section on miscellaneous methods with references to literature reviews provided as a guide.

The processes depicted in eq 1–6 need not involve single reaction steps. A number of effective multistep techniques have been developed; these are reviewed in the section on rearrangement strategies. The more

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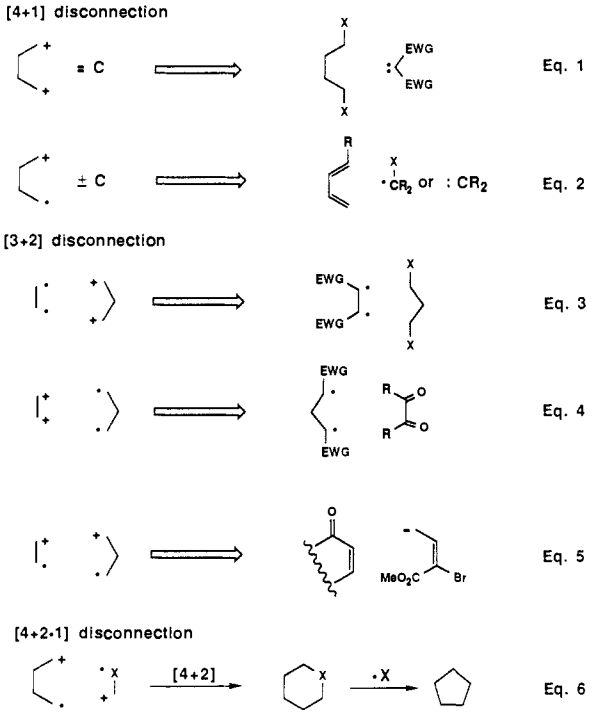
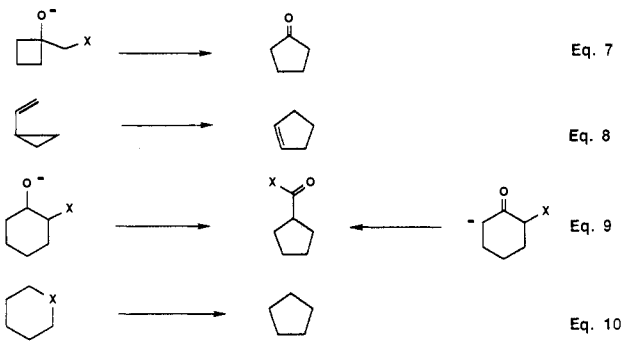
SCHEME I. Types of Disconnections in the Synthesis of Cyclopentanes

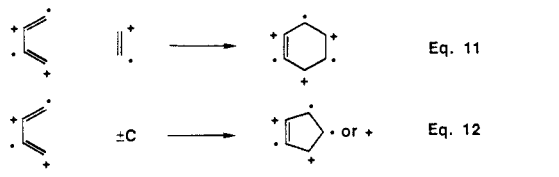


SCHEME II. Rearrangement Approaches to Cyclopentanoids



common protocols in this area include ring expansions (eq 7; see discussion in section V.3), the vinylcyclopropane rearrangement (eq 8; see section V.1), and ring contractions shown in eq 9 and 10 of Scheme II (see section V.4).

The number of diverse transformations and strategies necessary in the field of cyclopentanoid synthesis is a direct consequence of the charge dissymmetry of five-membered rings. As verbalized by Evans,[19] Seebach,[20] and Hudlicky,[16-18] the inherent synthetic dissonance present in any ring of an odd number of atoms makes the particular design of connective reagents difficult. The best example of this charge pairing is seen in a comparison of the Diels–Alder reaction (eq 11) with a hypothetical [4 + 1] annulation equivalent depicted in eq 12. The impossibility of designing a reagent that

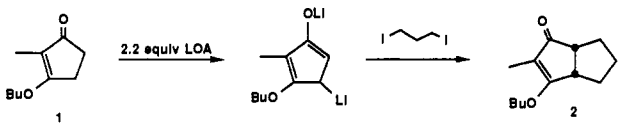


would parallel the behavior of dienophiles while maintaining the generality of the Diels–Alder process (as seen in tens of thousands of examples) is the main reason why the chemistry of cyclopentanoids in general is far more difficult than that of its six-membered counterparts. Several solutions to this problem have recently appeared, such as the two-step intramolecular cyclopropanation–rearrangement sequence of dienic diazo ketones[16,17,21] or the [4 + 2 − 1] atom-extrusion annulation strategy depicted in eq 6.[22] This review attempts to survey some of the general approaches to the solution of the charge parity problem and highlights recent developments from our own laboratory in the area of intermolecular [2 + 3] annulations of unsaturated carbonyl compounds.

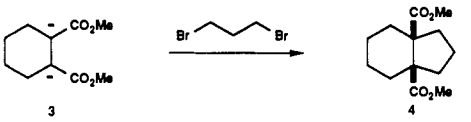
II. Alkylative Approaches

1. Dianion Intermediates

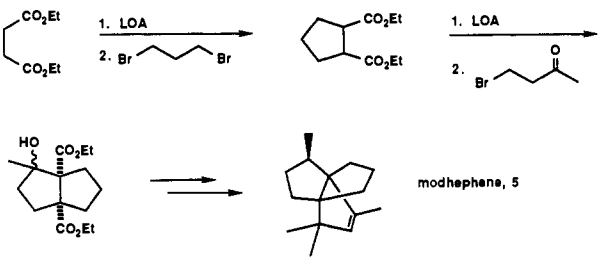
[*3 + 2*] *Methodology.* The dianion of cyclopentenones has been used in the construction of bicyclo[3.3.0]octenone systems. Koreeda has reported that the dianion of 3-isobutoxycyclopent-2-enones such as **1** is readily produced upon treatment with lithium diisopropylamide (LDA) (2.2 equiv, THF, −78 °C).[23] Quenching with 1,3-diiodopropane afforded *cis*-bicyclooctene **2** in >60% yield.



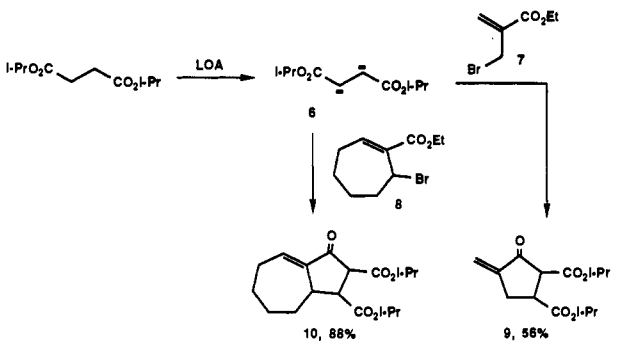
Garratt and co-workers have shown that treatment of vicinal diesters with LDA gives species that react as dianions and that can be alkylated with α,ω-dihalides and -ditosylates to afford bicyclo[4.*n*.0] systems.[24,25] With cyclohexane **3** the yield of the cis-fused hydrindan **4** was a respectable 71%. Mundy has used the same



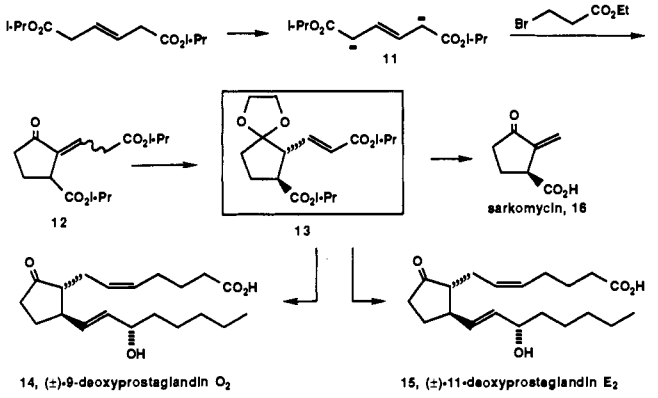
reaction to develop a general cyclopentane, cyclopentene, and cyclopentanone methodology[26] and applied it to a synthesis of modhephene (**5**). The key steps of the annulations are as follows.[26]



In a series of papers, Yamamoto reported direct coupling of various stabilized 1,2-dianions with electrophiles to form cyclopentanoids. For example, the reaction of the dianion of diisopropyl succinate (**6**) with α-(bromomethyl)acrylates **7** and **8** (2.1 equiv of LDA, THF, −78 °C) resulted in the efficient formation of cyclopentenones **9** and **10**, respectively.[27] Unfortunately, dianion **6** was unreactive toward other electro-

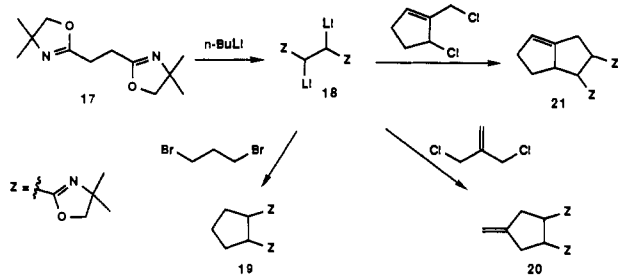


philes such as β-halopropionates. This problem was circumvented by employing the dianion of diisopropyl 3-hexenedioate (11).[28] Reaction of 11 with ethyl 3-



bromopropionate produced cyclopentenone 12 as a mixture of olefinic isomers, from which ketal 13 was isolated as the sole product in 52% overall yield. The ketal was subsequently transformed to a variety of primary prostaglandins such as 14 and 15 as well as to the antibiotic sarkomycin (16).

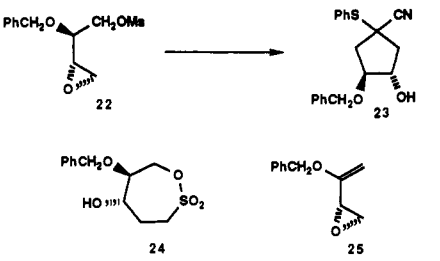
The extrapolation of this approach led to the investigation of the dianion of 2-oxazoline 17.[29] The dilithio



derivative 18 was prepared in high yield by metalation of 17 with *n*-BuLi (2 equiv, THF, −78 °C), and the resulting dianion was alkylated with a variety of electrophiles leading to the preparation of cyclopentanoids 19, 20, and 21. Alcoholysis of these compounds (H_2SO_4, EtOH) afforded the corresponding diesters in high yields.

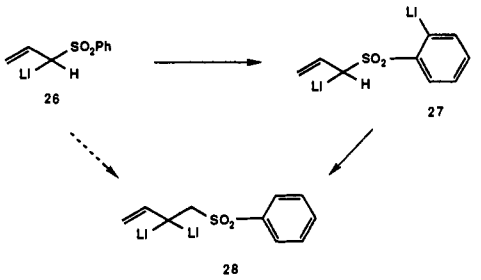
[*4 + 1*] *Methodology.* An example of an anionic [4 + 1] approach leading to chiral cyclopentanediols was presented by Gero and co-workers.[30] Treatment of epoxide 22, prepared from (*R,R*)-(+)-tartaric acid in six steps, with the anion derived from phenylthioacetonitrile ($PhSCH_2CN$, sodium hexamethyldisilazide (NaHMDS), toluene) gave the highly functionalized cyclopentane 23 in 70% yield.

There were a number of appealing features to this one-pot procedure: tartaric acid is a convenient starting material because both enantiomers are readily available,

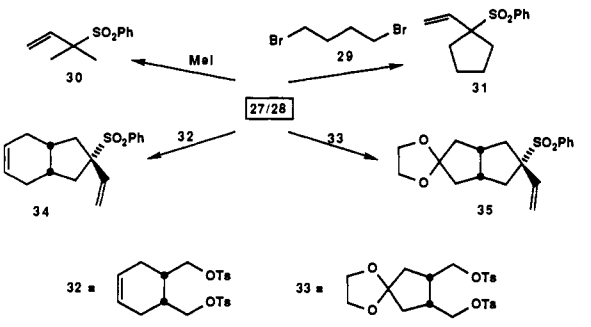


and it possesses C_2 symmetry.[31] This route thus leads to a short (seven steps) enantiodivergent approach to cyclopentanediols of type 23. There are, however, limitations to this procedure. Reaction of carbanions derived from $MeSCH_2CO_2Et$, $PhSCH_2SPh$, or $MeSCH_2SOMe$ with 22 led to exclusive formation of sultone 24, whereas changing the nature of the leaving group from the mesylate in 22 (e.g., to tosylate, chloride, or bromide) led to the product of elimination, vinyl epoxide 25.

Gais has reported the first synthesis of a 1,1-dilithioallyl phenyl sulfone (28).[32] These compounds are of interest not only for their synthetic potential but also for their structure in solution.[33] The second lithiation of 1-lithioallyl phenyl sulfone (26), at low temperature with 1 equiv of *n*-BuLi, leads to metalation in the position ortho to the sulfonyl group[34] to give 27 as the kinetic product with high selectivity. Upon warming,



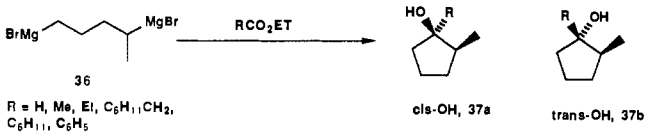
complete transmetalation to the thermodynamic product, 1,1-dilithioallyl phenyl sulfone (28), occurs. Dialkylation of 28 with methyl iodide gave 1,1-dimethyl sulfone 30 (80% yield, >98% regioselectivity). Cycloalkylation with a variety of α,ω-dibromoalkanes also proceeded well, as illustrated in the case of 1,4-dibromobutane (29), whose exposure to 28 led to cyclopentene 31 in 89% yield. Geminal cycloalkylation of 28 with ditosylates 32 and 33 led to cyclopentane-annulated systems 34 and 35 in high yields (77% and 82%, respectively) and high diastereoselectivity (70% and 90% de). The observation that mixtures of 27 and



28 can be used is noteworthy, as the alkylation usually requires higher temperatures (25–50 °C) which lead to complete equilibration to the thermodynamic dianion 28 prior to the ring closure. Interestingly, similar results

were obtained for the alkylation of pure 1,1′-dilithio compound **27**. Apparently, initial alkylation of **27** in the 1-position is followed by transmetalation and a second alkylation.[34]

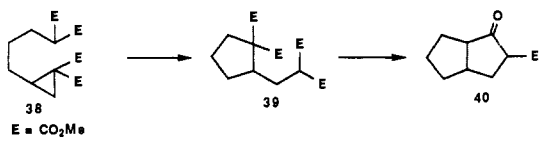
An alternate [4 + 1] route to cyclopentanols has been developed by Canonne.[35,36] In this instance the four-carbon fragment is a 1,4-dianion equivalent with the one-carbon fragment being the electrophile. This was accomplished by the reaction of 1,4-bis(bromomagnesio)pentane **36** with carboxylic esters. Several



conclusions were reached. First, cyclization was favored over the many possible intra- and intermolecular reactions. At normal concentrations no products arising from intramolecular reduction or enolization were observed. The annulation was also highly stereoselective, affording preferentially the *trans*-2-methyl-1-substituted cyclopentanols **37b**.

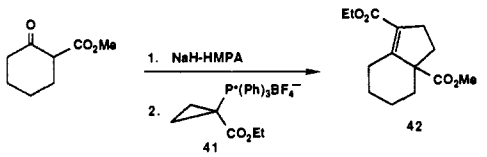
2. Activated Cyclopropanes

The construction of five-membered rings has also been accomplished through transpositions of activated cyclopropanes.[14,18,37,38] When the anion of cyclopropane **38** is generated (dimsylsodium, DMSO), cyclopentane **39** is formed in 84% yield through opening of the cyclopropane. Upon heating of the reaction mixture,



bicyclo[3.3.0]octanone **40** is formed in 71% yield, presumably through decarbomethoxylation of the Dieckmann product of **39**.[37] Such processes have also been exploited for non-carbon nucleophiles and have led to the synthesis of pyrrolizidine alkaloids, for example.[38] It should also be mentioned that the opening of activated cyclopropanes and vinylcyclopropanes with nucleophilic palladium species has been invoked in the transition-metal-catalyzed transformations of these compounds in favor of diradical mechanisms.[18] (See section V.2.)

Another approach resulting in an overall [3 + 2] annulation and involving nucleophilic cleavage of an activated cyclopropane is that of Fuchs.[39] Reaction of the cyclopropyl phosphonium salt **41** with an enolate results



in the ring opening of the cyclopropane with concomitant formation of a phosphonium ylide. An intramolecular Wittig reaction completes the cyclization. This technology was also found to be applicable to the synthesis of heterocyclic compounds and fused carbocyclic compounds. Table I shows a few examples of the versatility of this protocol.

TABLE I. Synthesis of Five-Membered-Ring Compounds by Wittig Annulation

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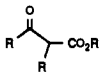
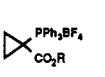
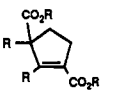
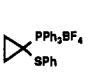
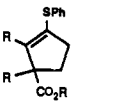
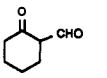
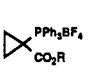
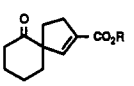
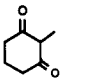
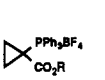
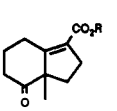
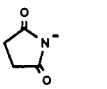
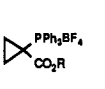
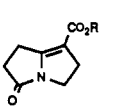
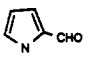
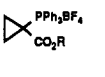
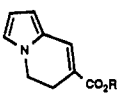
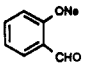
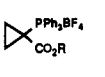
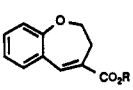
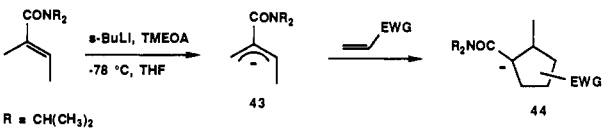
			39
			40
			41
			39
			42
			39
			39

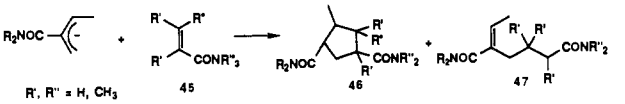
III. Approaches Based on the Michael Addition

1. Intermolecular Reactions

Beak and co-workers have reported a novel example of cyclopentane annulation that involves the Michael reaction of (2-carbamoylallyl)lithium reagents with electron-deficient olefins. These amide derivatives function as the 4π component in a formal [4π + 2π] [3 + 2] cyclization. The first example reported employed the organolithium reagent **43** derived from β'-metalation

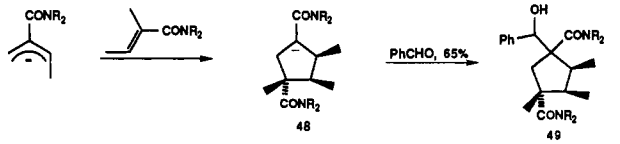


of secondary and tertiary α,β-unsaturated amides.[43,44] A similar approach has been reported by Kauffmann.[45-48] In a test of this procedure, lithiation of (*E*)-*N*,*N*-diisopropyl-2-methyl-2-butenamide followed by addition of acrylamides to the delocalized anion **43** afforded 2-methylcyclopentane-1,4-dicarboxamides **44** in yields ranging from 12% to 81%. Along with cyclopentanes, acyclic products were also formed, resulting from addition of the less substituted β'-carbon of **43** to the β-carbon of the acrylamide. The ratio of cyclic (**46**) to acyclic (**47**) products was typically in the range of 3:1. Electrophilic substitution of the cyclo-



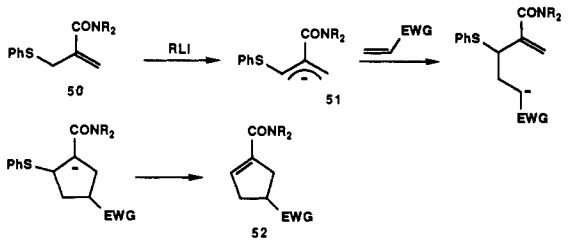
pentane enolate anions **48** formed in this sequence was accomplished in situ by the addition of benzaldehyde or methyl iodide to afford highly substituted cyclo-

pentanes of type **49**. Thus, in one pot, three new



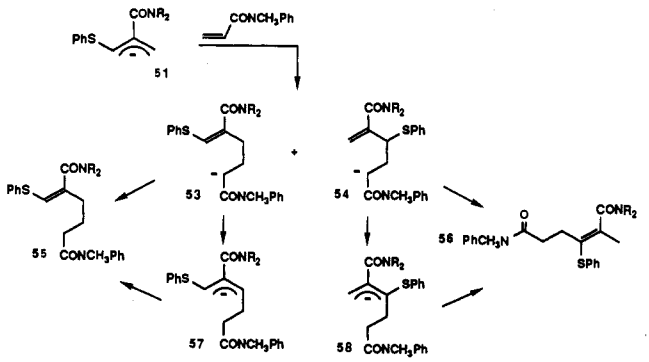
carbon–carbon bonds and three formal asymmetric centers were formed, illustrating the synthetic potential for cyclopentane formation via sequential [3 + 2] cyclization and electrophilic substitution of (2-carbamoylallyl)lithium reagents.

An improvement in this sequence was achieved by substituting a phenylthio group at the β'-position in acrylamides such as **50**.[49] It was believed that this

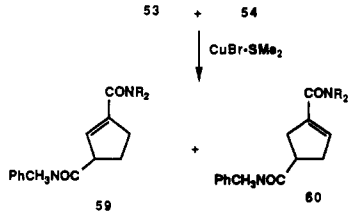


substitution would increase the reactivity of the reactant as well as the stability of the anion **51** in the metalation step, give regiocontrol of electrophilic addition in the second step, and provide a thermodynamic driving force in the final steps of this reaction by acting as a leaving group and leading to the formation of cyclopentene **52** in the overall [3 + 2] sequence.

When **51** was treated with *N*-methyl-*N*-phenylacrylamide, two acyclic amides, **55** and **56**, were formed in 21% and 9% yields, respectively. The formation of these products was believed to involve proton transfer of the initially formed adducts **53** and **54** to give **57** and **58** before quenching.

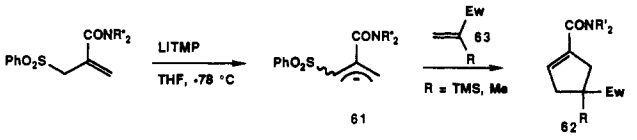


Cyclopentenes were formed, however, if lithiation and addition were followed by warming to room temperature in the presence of cuprous bromide and dimethyl sulfide. Cyclopentenes **59** and **60** were obtained as a



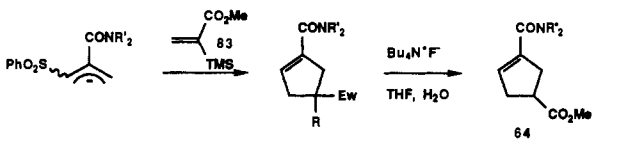
1:3 ratio in a combined yield of 39%. It is apparent from these results that some regioselectivity was observed in the electrophilic addition step and also that the pairing of an anionic [3 + 2] cyclization with an elimination step was feasible, even though the yields were only moderate.

These results were significantly improved when the phenylsulfonyl group was substituted for the phenylthio group.[50] When [1-(phenylsulfonyl)-2-carbamoylallyl]-lithium reagents such as **61** were added to a variety of

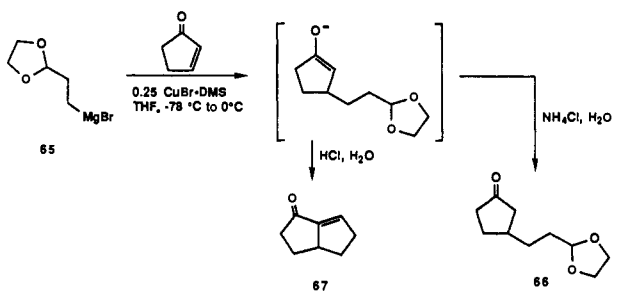


electron-deficient olefins, cyclopentenes were isolated in 89% to 22% yield. (A typical yield is about 60%.) In addition, complete stereospecificity was observed in the electrophilic addition step, and concise mechanistic details emerged as a result of this investigation.[50]

The reaction proved quite general for a number of electrophiles where the electron-withdrawing group was a ketone, ester, amide, nitrile, or sulfone. Also, α-substitution of the olefin increased the yields (>50%), possibly by protecting the carbonyl from undesired 1,2-addition and/or inhibiting polymerization of the 2π component. In the case of silylated unsaturated carbonyls **63** (R = TMS), the silicon group was removed by treatment with fluoride to afford 1,4-disubstituted cyclopentenes of type **64**.

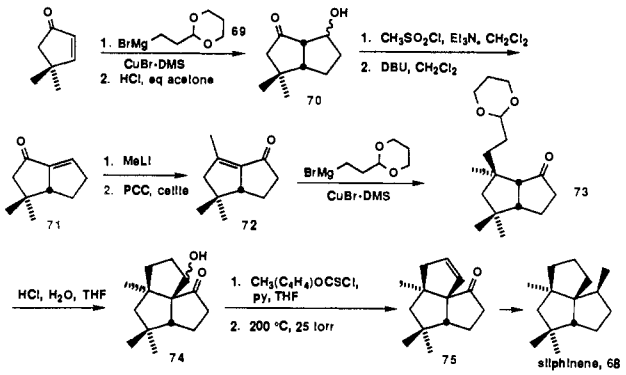


Helquist has developed a cyclopentene annulation based on the copper-catalyzed conjugate addition of acetal-containing Grignard reagents.[51,52] Addition of Grignard reagent **65** to cyclopenten-2-one (or a variety



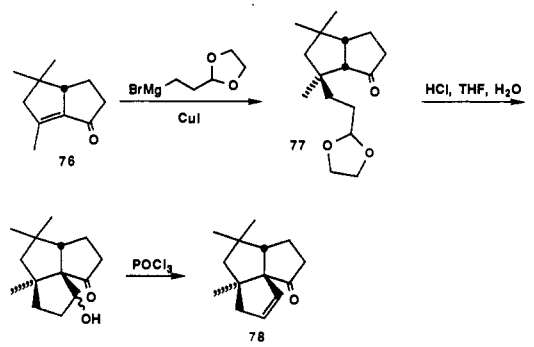
of other cyclic enones) in the presence of CuBr·DMS resulted in 1,4-addition with formation of keto acetal **66**, which can be isolated after the reaction is quenched with NH_4Cl. Treatment of the intermediate acetal with hydrochloric acid induced hydrolysis, intramolecular aldol condensation, and dehydration to afford bicyclic product **67**. Alternatively, the reaction could be quenched with hydrochloric acid to accomplish the entire multistep process in one-pot with overall yields ranging from 54% to 89%.

Paquette has used a related reaction sequence in a relatively short synthesis of (±)-silphinene (**68**);[53,54] the key iterative annulation steps are shown below. Reaction of 4,4-dimethylcyclopentenone with Grignard reagent **69**, derived from 2-(2-bromoethyl)-1,3-dioxane in the presence of CuBr·DMS, resulted in 1,4-addition, which after acid hydrolysis led to the intramolecular aldol product, keto alcohol **70**. The use of 1,3-propanediol avoided elimination products sometimes



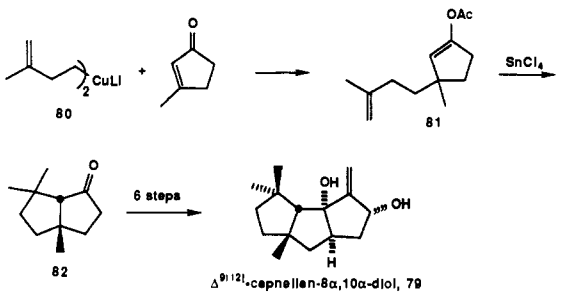
encountered with dioxolane derivatives such as **65**. Spontaneous dehydration of β-hydroxy ketones is not encountered in the bicyclo[3.3.0]octane systems but was accomplished by conversion of **70** to its mesylate followed by elimination with DBU to afford enone **71**. Alkylation followed by oxidation/allylic transposition set the stage for the second annulation sequence. Conjugate addition of reagent **69** to the transposed enone **72** followed by a second intramolecular aldol condensation resulted in highly stereocontrolled formation of two new carbon–carbon bonds from the β-face to give **74** exclusively. Dehydration of **74** under normal conditions could not be effected because of ready retroaldolization. However, condensation of **74** with 4-methylphenyl thiochloroformate gave the thiocarbonate ester, which after pyrolysis gave the tricyclic enone **75**. This material was converted to (±)-silphinene (**68**) in five steps.

In his synthesis of (±)-silphinene, Ito used a copper-catalyzed conjugate addition of an acetal-protected Grignard reagent.[55] The third ring was constructed by reacting bicyclic enone **76** with the Grignard reagent

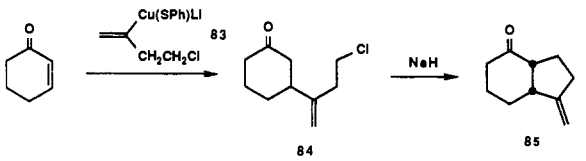


prepared from β-bromopropionaldehyde ethylene acetal in the presence of CuI. The resulting keto acetal, **77**, was deprotected and cyclized by treatment with acid and then dehydrated to afford tricyclic enone **78**, a key intermediate in Paquette's synthesis.[54]

Other organocopper reagents have been employed to effect Michael reactions leading to five-membered rings. In his synthesis of the marine natural product $\Delta^{9(12)}$-capnellene-8α,10α-diol (**79**), Pattenden employed the addition of a cuprate to a cyclopentenone to construct the A and B rings of the target molecule.[56] Addition of 3-methylcyclopent-2-enone to lithium bis(3-methylbut-3-enyl)cuprate (**80**) followed by quenching with acetic anhydride led to enol acetate **81** in 46% yield. Treatment of **81** with stannic chloride in wet methylene chloride gave bicyclooctanone **82** (63%). This compound was then converted to $\Delta^{9(12)}$-capnellene-8α,10α-diol (**79**) in six steps.

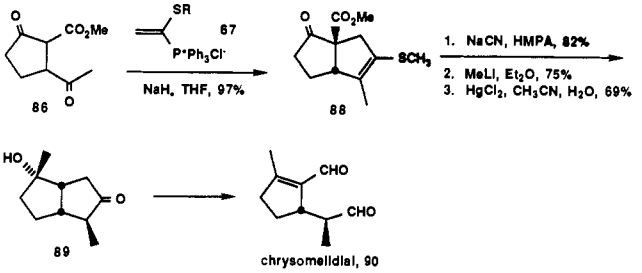


Piers exploited the conjugate addition of lithium (phenylthio)cuprates to cyclic enones in an efficient methylenecyclopentane annulation.[57] A typical example involves the preparation of bicyclic ketone **85** as shown.



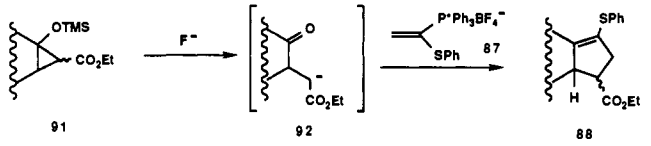
When cyclohexenone was treated with lithium (phenylthio)[2-(4-chlorobut-1-enyl)]cuprate, the conjugate addition product was obtained in 83% yield. Ring closure was effected by treating **84** with sodium hydride to afford **85** (75%). The overall transformation could be accomplished without isolation of the intermediate chloro ketones by adding 1.5 equiv of hexamethylphosphoramide prior to warming. Several other methylenecyclopentanes were obtained in overall yields of 55–60%.

Hewson has developed a procedure that involves Michael attack of an enolate on vinylphosphonium salts such as **87**.[58,59] The intermediate ylide then undergoes an intramolecular Wittig reaction to fused cyclopentenes such as **88** in an efficient one-pot process, illustrated below in a formal synthesis of chrysomelidial (**90**), the defense secretion of the chrysomelide bettle.



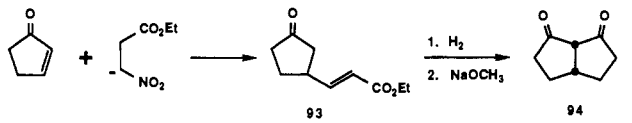
Treatment of diketo ester **86** with NaH followed by addition of vinylphosphonium chloride **87** led smoothly to bicyclo[3.3.0]octane **88** in 97% yield. Decarbomethoxylation followed by alkylation with MeLi and hydrolysis of the vinyl sulfide led to keto alcohol **89**, which has been previously converted to chrysomelidial.[60] The versatility of this procedure is illustrated in total syntheses of dihydrojasmone, dihydrojasmolone,[60] and prostaglandins PGD_1 methyl ester and 9-epi-PGD_1 methyl ester[61] and with formal syntheses of the antibiotics methylenomycins A and B.[60]

A related approach that used this strategy for the synthesis of cyclopentanoids has been reported by Marino.[62] Wittig reagent **87** was reacted with the ester enolate anion **92**, generated upon the fluoride-catalyzed opening of the donor/acceptor cyclopropane **91**. The intramolecular Wittig reaction then gave cyclopentenes of type **88** in an overall [3 + 2] annulation.



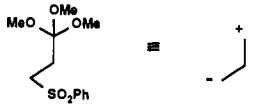
91 92 88

Stabilized carbanions are often used as nucleophiles in Michael additions. One straightforward example reported by Duthaler for the preparation of bicyclo-[3.3.0]octane-2,8-dione is shown below.[63] Addition of cyclopentenone to the anion of 3-nitropropionate gave the acrylate **93**, which after hydrogenation and intramolecular Claisen condensation afforded the bicyclo-[3.3.0]octanedione **94**.



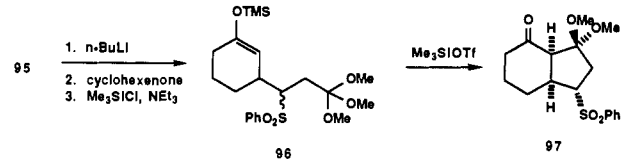
93 94

Ghosez has developed a 1,3-dipole equivalent, 3-(phenylsulfonyl)orthopropionate (**95**).[64] This reagent combines a potential carbanion center at C-3, stabilized by a phenylsulfonyl substituent, with the masked cationic character of an ortho ester function at C-1. Reaction of the anion of **95** (*n*-BuLi, 5 equiv of HMPA, THF) with cyclohexenone resulted in formation of an



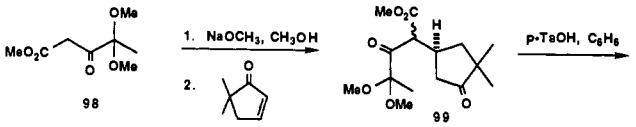
95

enolate anion, which was trapped as its trimethylsilyl ether **96**. Treatment of **96** with a catalytic amount of trimethylsilyl triflate smoothly effected cyclization to hydrindan **97**, which was obtained in 68% overall yield as a single diastereomer.

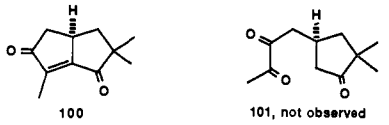


96 97

Danishefsky has also employed a 1,3-dipole equivalent in a synthesis of coriolin.[65,66] Reaction of the enolate anion of **98** with 5,5-dimethylcyclopentenone afforded **99** as a mixture of diastereomers. Decarbom-



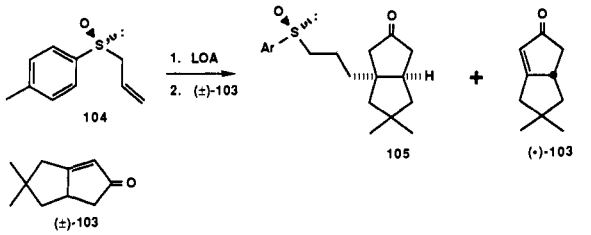
98 99



100 101, not observed

ethoxylation and cyclization with *p*-TsOH afforded enedione **100** in 50% overall yield. Interestingly, triketone **101**, a previously presumed intermediate in the reaction, was not isolated or observed, and it was therefore presumed not to be an intermediate in the annulation.

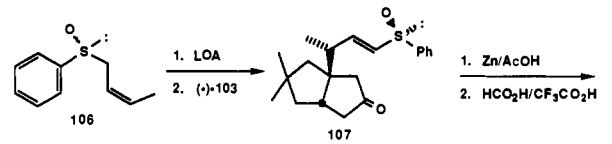
Hua has used chiral sulfinylallyl anions as Michael nucleophiles in the synthesis of (+)-pentalenene **102**.[67,68] A kinetic resolution of (±)-enone **103** was effected by reaction of the anion of (*S*)-allyl *p*-tolyl sulfoxide (**104**) (LDA, THF) with 2 equiv of (±)-**103**. The adduct **105** and (−)-(*S*)-**103** (45%) were obtained. Reaction of 2



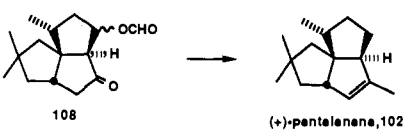
104 105 (+)-103

(±)-103

equiv of the anion derived from racemic *cis*-crotyl phenyl sulfoxide **106** with (−)-(*S*)-**3** afforded sulfoxide **107** (91% yield, 82% optical purity). The vinyl sulfoxide was reduced to a vinyl sulfide, which underwent hydrolysis followed by rapid intramolecular cyclization when treated with HCO_2H/CF_3CO_2H to give formate **108**. This compound was converted to (+)-pentelenene (**102**) in five steps.

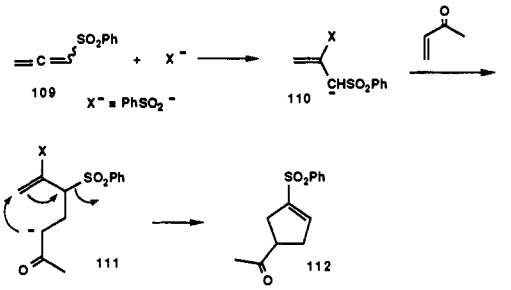


106 107



108 (+)-pentalenene,102

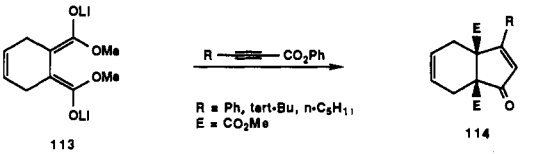
Padwa has developed a synthesis of cyclopentenyl sulfones via a cyclization–elimination reaction of (phenylsulfonyl)allene (**109**).[69] This approach involved



109 $X^- = PhSO_2^-$ 110 111 112

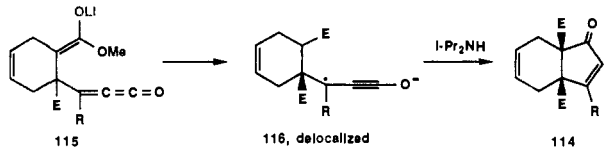
treating (phenylsulfonyl)allene with an activated alkene in the presence of a nucleophile. Generation of carbanion **110** by reaction of the nucleophile with **109** followed by Michael addition with the olefin led to carbanion **111**. This intermediate then underwent cyclization followed by elimination to provide a five-membered ring. When allene **109**, sodium benzenesulfinate, and methyl vinyl ketone were allowed to react, cycloadduct **112** was obtained in 73% yield.

Corey has reported a one-step annulation sequence for the synthesis of ring-fused cyclopetenones.[70] Reaction of the dilithio derivative of *cis*-4-cyclohexene-1,2-dicarboxylate **113** (2.2 equiv of LDA, 3 equiv of HMPA, THF) with 3-substituted propiolic phenyl esters generated cyclopentenones of type **114**. The re-



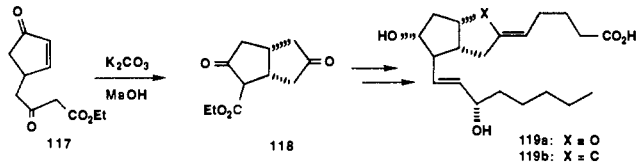
113 114

action is believed to proceed by initial conjugate addition of the dilithio reagent to the propiolic ester with loss of phenoxide leading to diketene **115**. Diketene **115** is not geometrically suited for ring closure because the distance between the electrophilic ketene carbonyl and the nucleophilic enolate α-carbon is too great. It was proposed that the cyclization of **115** to **114** may take place after electron transfer to afford a species such as **116**. Proton transfer from diisopropylamine to **116** would then give **114**.

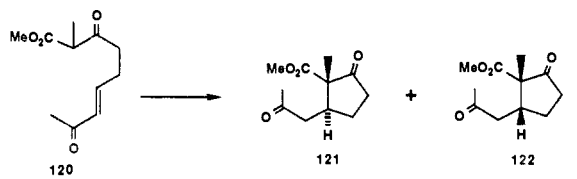


2. Intramolecular Michael Additions

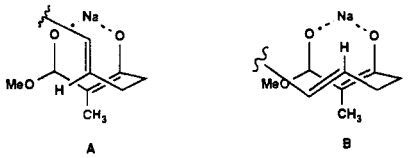
Intramolecular Michael additions have found widespread use in cyclopentane annulation. Barco has reported the preparation of a carbocyclic analogue (**119**) of the prostaglandin PGI_2.[71] Treatment of diketo ester **117** with potassium carbonate led quantitatively to Michael product **118**, which was subsequently converted to **119**.



Stork has also studied the reaction in which a β-keto ester undergoes intramolecular addition to an unsaturated system.[72-74] Cyclization of **120** was found to be quite nonselective in polar media and led to mixtures of **121** and **122** in which the cis:trans ratio varied from 1:1 (*t*-BuOK, *t*-BuOH) to 3:1 (NaOMe, MeOH). In

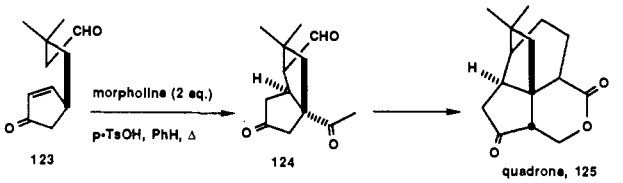


sharp contrast, it was found that the cyclic metal chelate of **120** (catalytic NaH, benzene) gave a 90% yield of the trans product **121**. None of the cis isomer was detected. It was proposed that the high stereoselection was the result of the orientation of the acceptor chain being away from the chelate ring, stabilizing transition state B leading to **122**. Similar selectivity has been



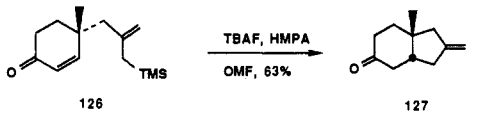
observed with the enolate anions of zirconium. Furthermore, an important distinction was made between two classes of intramolecular Michael reactions. For the case where the electrophilic unsaturation is in a ring, the reaction usually proceeds to afford cis-fused bicyclic products. With the electrophilic unsaturation not a part of the ring, trans-fused bicyclic systems result.[75,76]

As part of a study directed toward a synthesis of the novel antitumor sesquiterpene quadrone (**125**), Burke has made use of an intramolecular Michael addition in the construction of the key bicyclo[3.3.0]octane derivative **124**.[77] Treatment of cyclopentenone **123** with 2



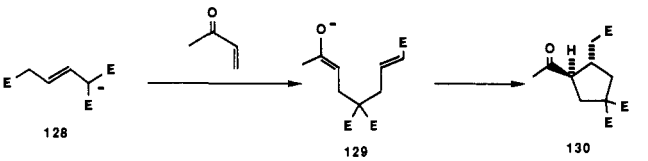
equiv of morpholine and a catalytic amount of *p*-TsOH in refluxing benzene led in 92% yield to **124**. Remarkably, other possible intramolecular condensation pathways were suppressed by simple adjustment of reaction conditions.

Majetich has reported an intramolecular conjugate addition of an allylic anion, generated from an allylsilane, with various Michael acceptors.[78,79] Acyclic allylsilanes such as **126** yielded cyclopentanes of type **127**



in the presence of Michael acceptors (α,β-unsaturated esters or nitriles). This new method of carbocyclization has a number of advantages. Generation of the allyl anion is carried out under very mild conditions, and the high chemoselectivity of the allylic anion enables highly functionalized substrates to be studied. Remarkable selectivity has also been observed with regard to closures of five- vs seven-membered rings and six- vs eight-membered rings. This methodology has been widely applied to the synthesis of carbocyclic natural products and has been recently summarized.[80]

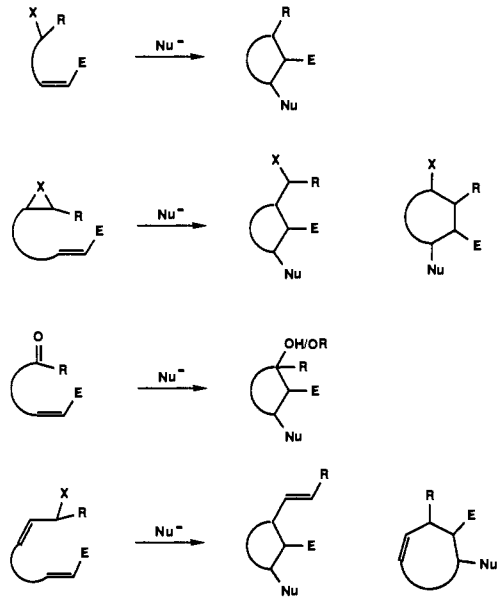
Bunce has reported a one-pot tandem Michael reaction sequence for the construction of five-membered rings.[81] Design of the reagent for this sequence required that both the Michael donor and the acceptor be positioned in the same molecule. To prevent intramolecular condensation at undesired locations, it was necessary to separate these two subunits by fewer than three carbons so that developing ring strain deters cyclization. Consideration of these criteria led to investigation of the reactions of compound **128**. Intermo-



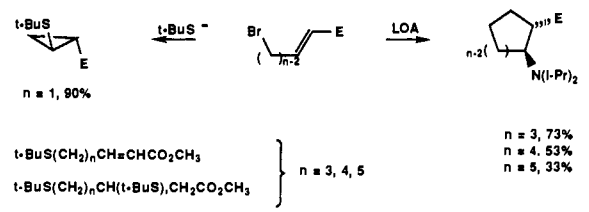
lecular conjugate addition of the anion of **128** to an acceptor molecule initially generated an enolate anion **129**. Intramolecular capture of this intermediate by the built-in α,β-unsaturated ester then led to the formation of cyclopentane **130**. Both cyclic and acyclic enones were studied. Yields ranged from 65% to 83%. Evaluation of other carbanion-stabilizing functionalities (CN, COR) on the Michael donor moiety generally gave poorer results than the malonate-derived reagents.

An interesting strategy employing an intramolecular Michael addition has been termed the MIRC reaction (Michael-initiated ring closure) by Little.[82] This general

SCHEME III. Variations of the MIRC Technology



SCHEME IV. Three- versus Five-Membered-Ring Closures

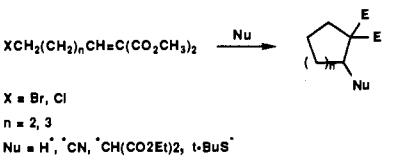


set of transformations is initiated by conjugate addition to an α,β-unsaturated ester or ketone to produce an enolate, which subsequently undergoes ring closure. Four possible variations of this reaction are shown in Scheme III. The reaction is related to Cook's method involving the Michael addition of carbon-centered nucleophiles to esters of the type $X(CH_2)_nCH{=}CHCOC(PPh_3)CO_2Et$.[83] Initially, sulfur and nitrogen nucleophiles were used to initiate the MIRC reaction for the construction of β-heteroatom-substituted cycloalkyl esters. Cyclopropanes, pentanes, hexanes, and heptanes have been made. The dependence of the reaction path (MIRC vs S_N2) depends strongly on the choice of nucleophile.

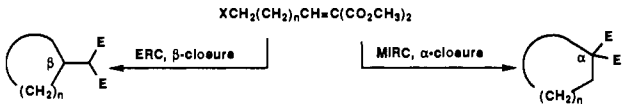
With lithium alkylthiolates as nucleophiles, products arising from S_N2 and bisaddition (S_N2 plus Michael) usually predominate, except for the case of cyclopropane formation (n = 1), as in Scheme IV. Using LDA as a nucleophile leads to MIRC products in the cyclopentane (n = 3, 73%), hexane (n = 4, 53%), and heptane (n = 5, 33%) series.

As noted by Little, however, the variation of reaction pathway with nucleophile presented a practical limitation upon the scope of the MIRC reaction. This was particularly true if one wished to use a large variety of nucleophiles in order to exploit the carbon–nucleophile bond in the product by modifying it in a synthetically useful fashion.[84] It was found that by using doubly activated substrates (i.e., 1,1-diesters instead of monoesters) five- and six-membered rings were formed in fair to excellent yields (46–94%), even when employing nucleophiles that did not afford MIRC products when monoactivated systems were used (Scheme V). Nucleophiles included L-Selectride, KCN, $NaCH(CO_2C$-

SCHEME V. MIRC with Doubly Activated Acceptors



SCHEME VI. α-Carbon versus β-Carbon Closures



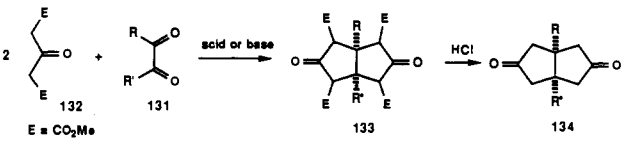
$H_3)_2$, and t-BuSNa or t-BuSLi. Significantly, by this modification it proved possible to couple a conjugate addition to a ring-closure reaction while employing a variety of nucleophiles.

This work was extended by contrasting the behavior of diesters when subjected to either hydride-initiated ring closure (a MIRC reaction) or electrochemically initiated closure as shown in Scheme VI.[85] The former leads to closure involving the α-carbon atom of the enolate as reported above, while the electrochemical route, termed electroreductive cyclization (ERC), afforded a ring with one fewer carbon atom in the cycle, resulting from the closure from the β- rather than the α-carbon (Scheme VI). The two methods complement each other nicely—substrates that lead to five- or six-membered rings with the MIRC protocol afford four- or five-membered rings with the ERC method. For further applications of this methodology consult a recent review.[14]

IV. Condensation Reactions

1. Weiss–Cook Reaction

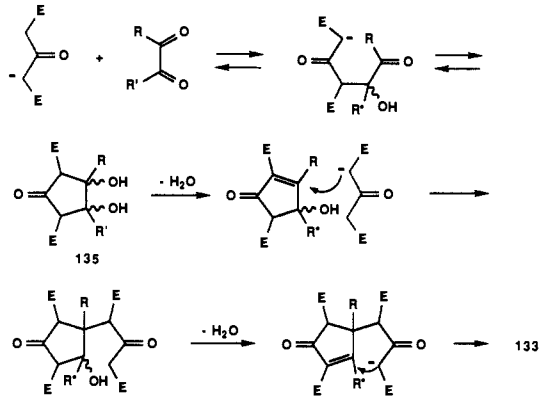
The Weiss–Cook reaction has been employed in the construction of a number of polyquinanes. The reaction of 1,2-dicarbonyl compounds **131** with two molecules of dimethyl 3-ketoglutarate (**132**) gives in high yields *cis*-bicyclo[3.3.0]octane-3,7-diones such as **133**, whose



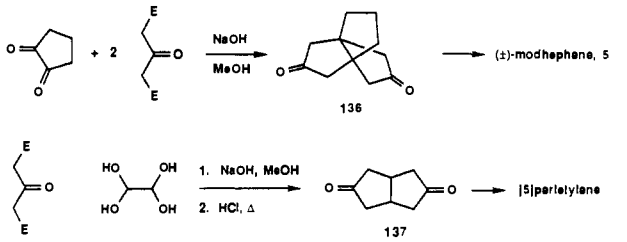
decarbomethoxylation to diquinanes **134** occurs upon heating with acid.[86–88] The generality of the reaction in terms of the wide range of substituents tolerated, combined with the ease of construction of the diquinane skeleton, has made this reaction sequence a popular method for the synthesis of a number of polyquinanes.[89]

This reaction proceeds under either acidic or basic catalysis, although basic conditions are generally used. The proposed mechanism is believed to involve initial condensation of dimethyl 3-ketoglutarate with a 1,2-dicarbonyl substrate to afford diol **135** (Scheme VII), which after dehydration, undergoes sequential Michael attack, dehydration, and Michael attack to afford diquinane nucleus **133**.[90–93] It has been established that steric factors present in the 1,2-diketone play the dominant role in determining the success of the reaction, as opposed to the electronic effects of the R groups of the 1,2-dione.

SCHEME VII. The Weiss-Cook Reaction



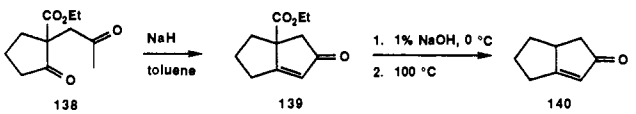
A key step in Cook's synthesis of modhephene (**5**) involved the Weiss–Cook reaction in the preparation of a [3.3.3]propellane intermediate **136**.[94] Eaton and Woodward have used the Weiss–Cook sequence to prepare bicyclo[3.3.0]octane-3,7-dione (**137**).[95,96] This compound was used by Eaton in a preparation of [5]-peristylene.[95]



2. Intramolecular Aldol Reaction

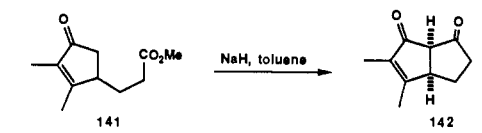
A well-established method for the synthesis of cyclopentenones is the intramolecular aldol condensation of 1,4-diketones, or related condensations of 1,4-dicarbonyl systems. The diketones are generally constructed by carbon–carbon bond-forming reactions of diketone enolate anions or imine anions with C-3 synthons (i.e., $CH_3COCH_2^+$). Most of these sequences require three distinct steps: (1) alkylation, (2) hydrolysis or oxidation, and (3) an intramolecular aldol or related condensation.

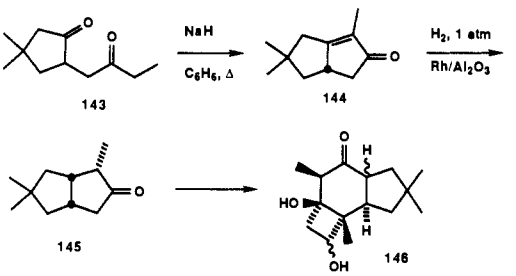
The bicyclic enone **140** was synthesized by Hart via an intramolecular aldol condensation.[97] Surprisingly, this simple enone had previously eluded synthesis by means of other approaches.[98,99] The aldol step proceeds in 55% yield when diketone **138** is treated with sodium hydride in refluxing toluene. Mild hydrolysis of **139** followed by decarboxylation affords enone **140** in 38% overall yield from **138**.



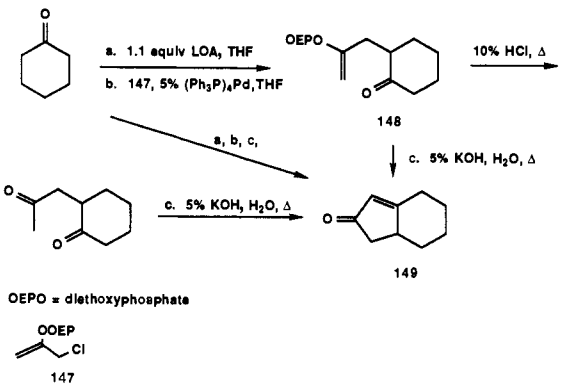
As part of studies directed toward the synthesis of pentalenolactone, Schlessinger prepared dione **142** by employing an intramolecular aldol condensation.[98] Reaction of keto ester **141**, prepared from 2-methylcyclopentane-1,3-dione in four steps, with sodium hydride in toluene resulted in rapid cyclization to give the dione in 70% yield.

Bicyclic ketone **145** has been used in a synthesis of the protoilludane skeleton **146**.[99,100] Magnusson reported that diketone **143** underwent an intramolecular aldol condensation when treated with sodium hydride in refluxing benzene to give enone **144**. Hydrogenation afforded the desired bicyclic ketone.

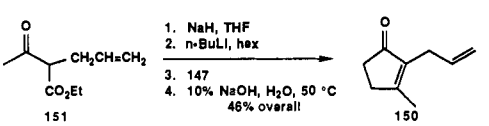




Welch has developed a reagent for one-pot cyclopentenone annulation in a synthesis of desoxyallethrolone, *cis*-jasmone, and methylenomycin.[101] The reagent that was used, 3-chloro-2-[(diethoxyphosphoryl)oxy]-1-propene (**147**) serves the function of a masked bromoacetone equivalent. The reaction is illustrated in the preparation of bicyclic enone **149** from cyclohexanone. Generation of the enolate of cyclohexanone followed by the addition of **147** afforded the alkylation product **148** in 91% yield. Hydrolysis of the enol phosphate **148** (10% HCl) followed by intramolecular aldol condensation (5% KOH, H_2O) then gave the bicyclic enone **149** in 88% yield. If, after alkylation, enol phosphate **148** was treated with 5% NaOH in refluxing $EtOH/H_2O$, concomitant hydrolysis and intramolecular aldol condensation resulted. Alternatively, the overall transformation could be obtained in one pot as shown below, where the yield of **149** from cyclohexanone was 79%.

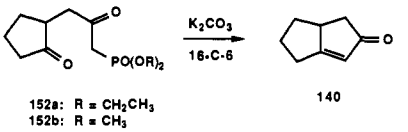


The synthesis of desoxyallethrone **150** incorporates this methodology. Generating the dianion of **151** with NaH followed by the addition of 1 equiv of *n*-BuLi and subsequent alkylation with **147** produced, after treatment with 10% aqueous NaOH at 50 °C, desoxyallethrolone **150** in 46% overall yield. Further examples of aldol and related methodology can be found in several recent reviews.[4,8,14]

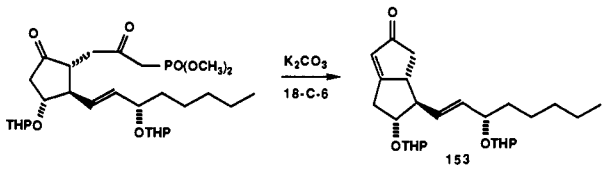


3. Intramolecular Wittig Reaction

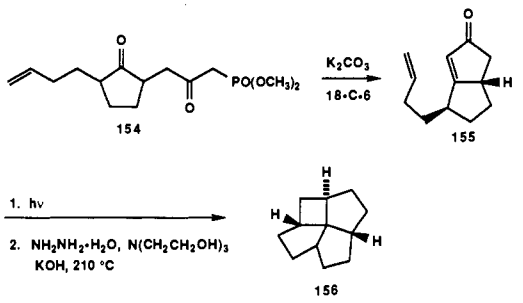
Aristoff has reported the synthesis of bicyclic enone **140** via an intramolecular Wadsworth–Emmons reaction.[102] Treatment of ketone **152b** with 1 equiv of potassium carbonate and 3 equiv of 18-crown-6 (18-C-6) in benzene gave octenone **140** in 59% yield. Previously,



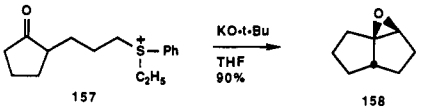
it had been reported that treatment of **152a** with sodium hydride in hot dimethoxyethane gave only a "tarry mass" instead of the expected enone **140**.[103] Apparently, the former conditions are mild enough not to destroy the ketone, yet basic enough for the formation of the β-ketophosphonate of **152b**. This mild procedure has been used in the synthesis of the prostacyclin analogue 6α-carbaprostaglandin I_2 (**153**).[104]



Dauben has used an intramolecular Wadsworth–Emmons approach in the first synthesis of [4.5.5.5]fenestrane (**156**).[105] Treatment of **154** with potassium carbonate and 18-crown-6 resulted in the formation of enone **155** in 92% yield. Notable was the epimerization of the butenyl side chain to the more stable exo configuration without the migration of the cyclopentenone double bond. Intramolecular photocyclization gave [4.5.5.5]fenestrone, which was subjected to Wolff–Kischner reduction to afford [4.5.5.5]fenestrane in 59% yield from **154**.

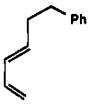
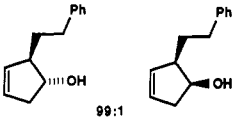
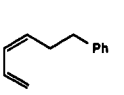
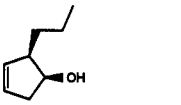
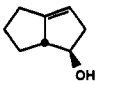
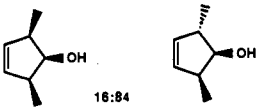
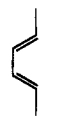
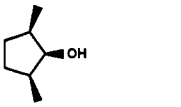


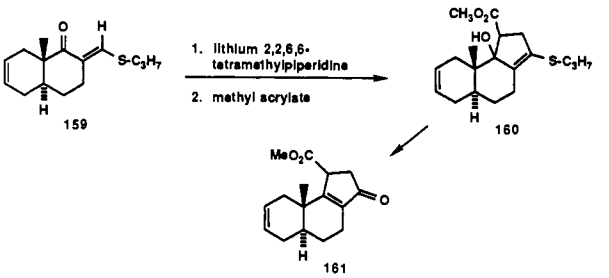
The intramolecular addition of sulfur ylides has also been employed in annulation.[106,107] Reaction of sulfonium salts **157** with potassium *tert*-butoxide led to cyclopentane epoxides **158** in good overall yields.



Allyl anion mediated annulations have also been reported.[108] An example is the reaction of the anion of α-thiomethylene **159** with a Michael acceptor to give alcohol **160** as the cycloaddition product. Cyclopentenones are produced upon dehydration and hydrolysis in what amounts to an anionic [3 + 2] cycloaddition.

TABLE II. Alkoxide-Accelerated Rearrangement of Vinylcyclopropanes[111,112]

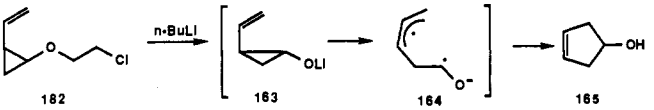
diene	cyclopentene	%
		77-82
		78
		70
		30-37
		74



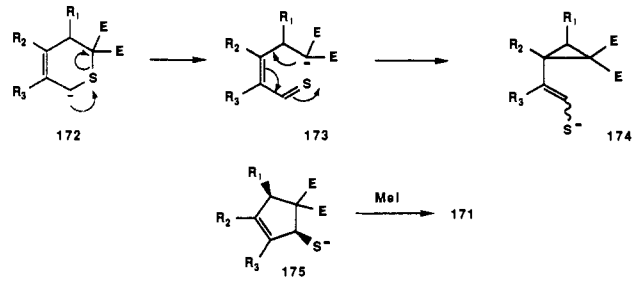
V. Rearrangements

1. Vinylcyclopropane Rearrangement

The vinylcyclopropane rearrangement is a convenient method of preparation of functionalized cyclopentenes.[15-18,109,110] While most such rearrangements proceed through diradical intermediates, some involve anionic intermediates both during the preparation of the vinylcyclopropanes and their subsequent rearrangement. Danheiser reported the synthesis of β-chloroethyl ethers of vinylcyclopropanols **162** and their rearrangement to cyclopentenols **165** by treatment with *n*-BuLi proceeding at room temperature.[111] The rearrangement was thought to proceed through the initially generated alkoxide **163**, which unraveled to anion diradical **164**. The closure of anion diradical **164** was found to be stereospecific,[112] and the rearrangement was

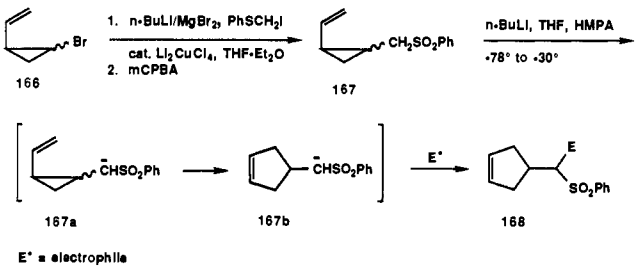


SCHEME VIII. Atom-Extrusion Approach to Cyclopentenes



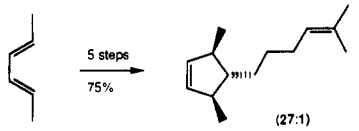
judged to be one of the few vinylcyclopropane–cyclopentene rearrangements proceeding either via a concerted mechanism or through intermediate **164**. Some examples are shown in Table II and indicate an unusually high stereoselectivity for this type of rearrangement.

Conceptually similar is the anion-accelerated opening of vinyl cyclopropyl sulfones such as **167**, reported to occur at low temperature. The alkylation of vinyl-

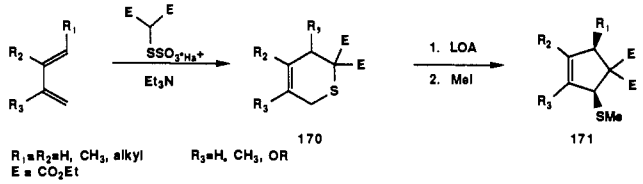


E⁺ = electrophile

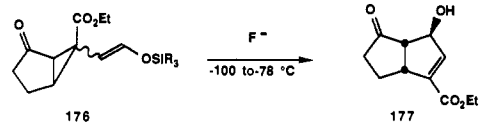
cyclopropyl bromides **166** with $PhSCH_2I$ followed by oxidation to sulfone **167** and treatment with *n*-BuLi gave the rearranged anion **167b**, which was trapped by a variety of electrophiles to afford functionalized cyclopentenes of type **168**. This rearrangement is stereospecific and proceeds under milder conditions than the aforementioned vinylcyclopropanol rearrangement. For example, (*E*,*E*)-2,4-hexadiene was converted in five steps to the trisubstituted cyclopentene **169** with excellent stereoselectivity.[113]



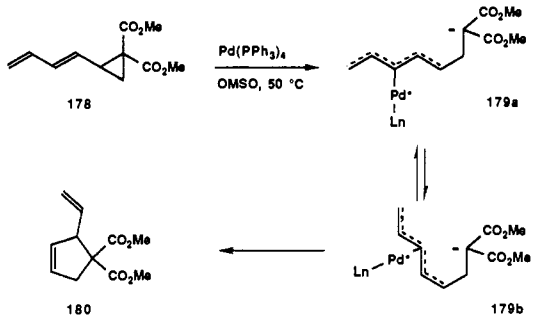
Larsen reported an interesting atom-extrusion approach to cyclopentenes that relies on an anionic sigmatropic process and is also stereospecific. A hetero-Diels–Alder reaction of dienes with diethyl (thiosulfato)malonate (generated in situ) gave thiopyrans of type **170**, which were subjected to the base-induced ring contraction to yield cyclopentenes **171** in high yields and with excellent stereoselectivity.[22] The mechanism ad-



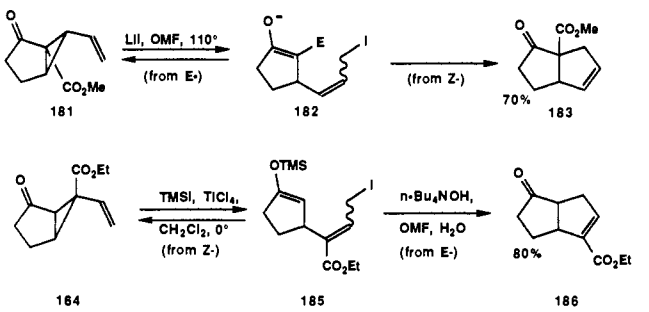
vanced for this reaction is depicted in Scheme VIII and appears to involve a [1,2]-sigmatropic migration (Wittig rearrangement). The acceleration provided by the thioenolate anion terminated vinylcyclopropane **174** may be governed by the same principles that operate in the recently discovered fluoride-catalyzed rearrangement of silyl ethers of type **176**.[114] The details of this rearrangement are discussed in section V.2 in the context of α-halocrotonate annulations.



The vinylcyclopropane rearrangement of appropriately activated cyclopropanes is known to occur also via a nucleophilic opening followed by alkylative reclosure. The palladium-catalyzed reorganization of vinylcyclopropane **178** is thought to involve the zwitterionic

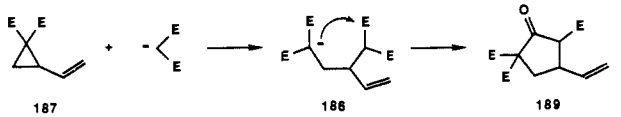


species **179**, which undergoes the ring closure from the preferred W-conformation to vinylcyclopentene **180**.[13,15,18,115] This reaction requires both the dienyl group and the electron-withdrawing group(s) and fails with simple vinylcyclopropanes. Nucleophilic opening of vinylcyclopropanes **181** with LiI[116] or vinylcyclo-



propanes **184** with (TMS)I in the presence of $TiCl_4$[16,18,117] led to cyclopentenes **183** and **184**, respectively. In both cases only the (*Z*)-**182** and (*E*)-**185** undergo the desired closure in the second step to cyclopentenes; both isomers are recycled to the starting vinylcyclopropanes though the kinetically preferred three-membered-ring closures.[16-18,118]

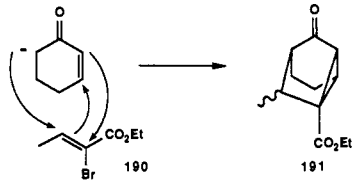
A reaction of malonates or bis(phenylsulfonyl)methanes with vinylcyclopropanes leads sometimes to cyclopentanone formation through further Dieckmann-type reaction of the ring-opened intermediates, generated through a nonvinylogous attack of the nucleophile on the cyclopropane, as illustrated in the case of **187**.[119]



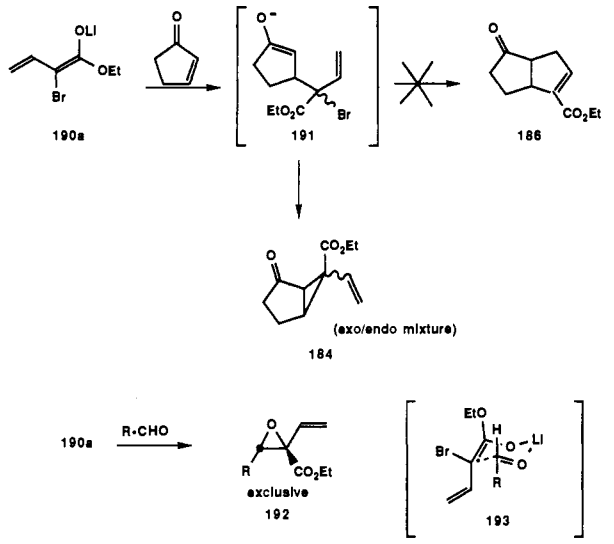
Further examples of the above reactions can be found in several recent reviews[13-18] and leading references.[117,118]

2. Annulations with α-Halocrotonates

Hagiwara reported the use of reagent **190** in bisannulation protocols involving the double conjugate reaction scheme shown below.[120] The interaction of the



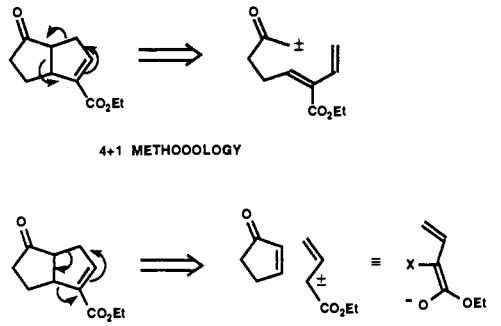
kinetic enolate anion of cyclohexenone with the Michael acceptor in **190** defined the order of bond-forming sequences and therefore the regiochemistry of the products. When the order of acid–base operations is reversed and the dienolate of **190**, **190a**, is generated and



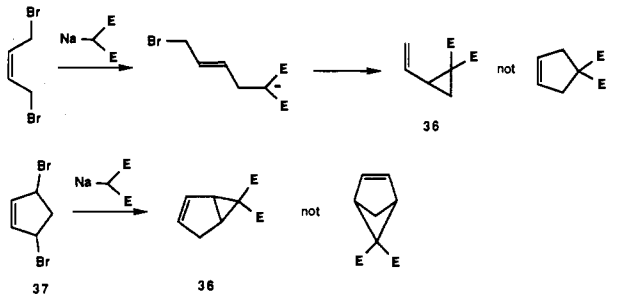
added to enones,[118,121] aldehydes,[122] or acrylates,[121] vinylcyclopropanes or vinyloxiranes are formed in excellent yields.[118] The process is not stereoselective as the vinylcyclopropanes are generated as more or less random mixtures of exo and endo stereoisomers. By contrast, the addition of **190a** to aldehydes produced exclusively the syn vinyloxiranes **192**, apparently through the aldol-like transition state **193**.[122] A plausible intermediate in the vinylcyclopropanation sequence above is the conjugate adduct **191**, although trapping experiments proved unsuccessful. The question of enolate-geometry relationships to the exo:endo ratio is being investigated. From low-temperature ^1H and ^{13}C NMR studies, it appears that both (*E*)- and (*Z*)-dienolate anions are present in the reactions. No explanation is available for the stereoselectivity (and thus the probable in situ equilibration of one dienolate anion) in the case of additions to aldehydes.[123]

There are many examples of preparation of vinylcyclopropanes by this type of methodology, and these fall into four major categories of the Michael-initiated ring-closure methodology (MIRC), developed by Little[82] and discussed earlier. Because the closure of enolate anion **191** to cyclopentene **186** would be a disfavored 5-endo-trig process, it can be expected that transformations depicted for the MIRC type reactions (Scheme III, section III.2) will not lead to formation of cyclopentanoids when there is a choice. (One exception is the Beak annulation of amides, discussed in section

SCHEME IX. Disconnective Modes of Cyclopentene Annulation



III.1.[49,50]) For example, the alkylation of malonate with 2-butenyl dibromide leads to vinylcyclopropane **194** through kinetic ring closure.[124] Similarly, sterically



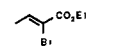
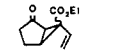
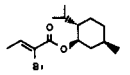
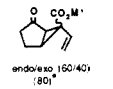
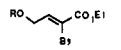
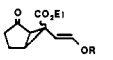
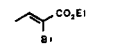
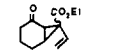
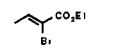
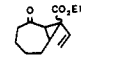
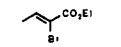
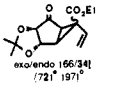
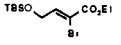
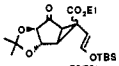
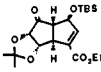
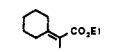
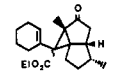
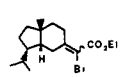
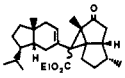
constrained dibromide **195** gives **196** and not the product of a direct S_N2 displacement.[125] The vinylcyclopropanes thus generated can then be used in the rearrangement schemes described earlier. An excellent review that summarizes the preparation of activated vinylcyclopropanes and cyclopropanes is available.[14]

The intermolecular [2 + 3] annulation of enones depicted in Scheme IX evolved from the intramolecular [4 + 1] annulation of dienic diazo ketone and is based on the disconnective reasoning illustrated below. The application of the intramolecular process to many syntheses of triquinane terpenes has recently been reviewed.[17,21] The [2 + 3] version of this process has accomplished the next step in the evolution of a *general synthetic methodology* of five-membered-ring synthesis. It is more efficient as a result of its *convergent* nature; it proceeds under milder conditions than the [4 + 1] process, and it tolerates a higher degree of functionalization.

The crucial vinylcyclopropane–cyclopentene rearrangement has been accomplished under a variety of nonpyrolytic conditions, for example, the (TMS)I/$TiCl_4$ opening and reclosure of vinylcyclopropanes of type **184**.[117] Most recently, the enol ether terminated vinylcyclopropanes were generated and rearranged to annulated cyclopentenes under the conditions of fluoride or Lewis acid catalysis. The mechanism as well as the apparent stereoselectivity of this process is being actively investigated.[114]

Tables III and IV show the diverse nature of vinylcyclopropanes that are available by the extension and modification of Hagiwara's reagent. Both carbon and oxygen substituents are tolerated without any changes in the α/γ regioselectivity in the incipient addition of the delocalized enolate anions to electrophilic acceptors. The corresponding cyclopentenes are generated by processes ranging from flash vacuum pyrolysis (FVP) to low-temperature rearrangements that are apparently

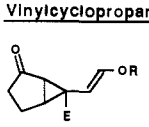
TABLE III. Pyrolytic Transformations of Vinylcyclopropanes[118]

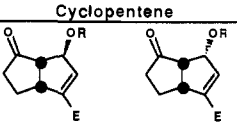
Enone	Bromocrotonate	Vinylcyclopropane	Cyclopentene
		 exo/endo 157/43] (67)[a] 196)[b]	 (43)[a] 550°)[c]
		 endo/exo 160/40] (80)[a]	SM 550°)[d]
	 R=TBS	 exo/endo 144/56] 138)[a] 165)[b]	 endo/exo (72/28) 152)[a] 525°)[c]
	R=COC$_6$H$_4$OPh-p	exo/endo 170/30] 140)[a] 178)[b]	endo/exo 99/1] 128)[a] 525°)[c]
		 exo/endo 168/32] 190)[a] 193)[b]	 (19)[a] 600°)[c]
		 exo/endo 163/37] 183)[a] 184)[b]	 (21)[a] 600°)[c]
		 exo/endo 166/34] (72)[a] 197)[b]	 151)[a] 550°)[c]
		 exo/endo 172/28] 136)[a] 146)[b]	 (75)[a] 525°)[c]
		 exo/endo 116/82] 140)[a]	—
		 exo/endo 140/60] 156)[a] 179)[b]	 +  150)[a] (74)[b] 585°)[c]

[a] Isolated yield. [b] GC yield. [c] Exo/endo refers to the orientation of the vinyl group. [d] Temperature of pyrolysis. [e] Unoptimized isolated yield.

subject to anion acceleration. Table III shows the results of pyrolytic transformation. The stereoselectivity in the thermal rearrangements leading to substituted cyclopentenes appears to be governed by the endo effect[126] and leads for the most part to endo functionalization. Similar stereochemical consequences have been observed in the related vinylaziridine–pyrroline rearrangement, which leads to C-2-functionalized pyrrolizidines.[16,127] Table IV shows studies of fluoride, iodide, and Lewis acid mediated rearrangements. The exact nature of the mechanism operating in these transformation is unknown at the moment. The mild conditions, however, bode well for an eventual one-pot sequence performed at temperatures around −100 °C with complete control of stereochemistry, as shown in Scheme X.[114] The fascinating feature of this type of vinylcyclopropane rearrangement lies in the control of the C-2-stereochemistry. Whereas the fluoride-catalyzed rearrangement leads to predominantly the exo configuration (perhaps through the equilibration of aldol products),[128] the Lewis acid mediated transformations afford almost exclusively the endo isomer. The α,β-unsaturated aldehyde (Table IV) has been determined not to be an intermediate in the reaction.[114] The details of this reaction sequence, which contains the mildest conditions for a vinylcyclopropane–cyclopentene rearrangement to date, are currently under investigation in our laboratories.

TABLE IV. Stereoselectivity of Thermolytic versus Low-Temperature Rearrangements of Enol Ether Terminated Vinylcyclopropanes



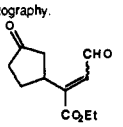


R	Method	Ratio[c]
TBS	A	0 : 100
MEM	A	27 : 73
SEM	A	25 : 75
TBDPS[a]		—
TIPS[a]		—
TBS	B	80 : 20
TBS	C	60 : 40
TBS	D[b]	0 : 100
TBS	E	25 : 75

TBS = t-butyldimethylsilyl
MEM = 2-methoxyethoxymethyl
SEM = 2-(trimethylsilyl)ethoxymethyl
TBDPS = /-butyldiphenylsilyl
TIPS = tri-/-propylsilyl

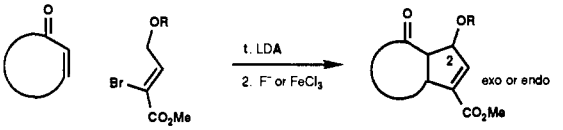
A = 550 °C, FVP (flash vacuum pyrolysis)
B = Bu_4NF (5 eq)
C = TMSI, CH_2Cl_2, HMDS, -78 °C
D = $FeCl_3$, CH_2Cl_2
E = $ZnBr_2$, CH_2Cl_2

Note: a) Only products arising from decomposition were observed. b) Aldehyde i was isolated from $FeCl_3$-catalyzed reactions and was shown not to be a reaction intermediate. c) Determined by ^1H NMR or by capillary gas chromatography.



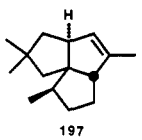
i

SCHEME X. Oxocyclopentene Annulation of Enones

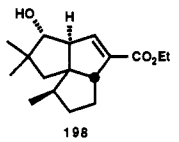


mations afford almost exclusively the endo isomer. The α,β-unsaturated aldehyde (Table IV) has been determined not to be an intermediate in the reaction.[114] The details of this reaction sequence, which contains the mildest conditions for a vinylcyclopropane–cyclopentene rearrangement to date, are currently under investigation in our laboratories.

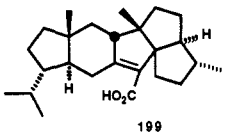
The utility of the [2 + 3] annulation protocol has been expressed in the efficient syntheses of several natural products: pentalenene (**197**),[129] pentalenic acid (**198**),[21,129] retigeranic acid (**199**),[118,130] specionin (**200**),[131] and ipomeamarone (**201**).[131] The overall sequence depicted in Scheme X is likely to find wide applicability to the synthesis of highly oxygenated cyclopentanoid natural products.



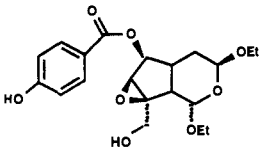
197



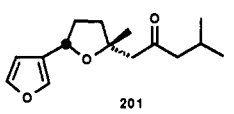
198



199



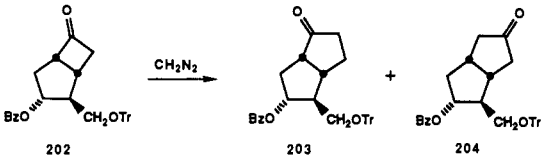
200



201

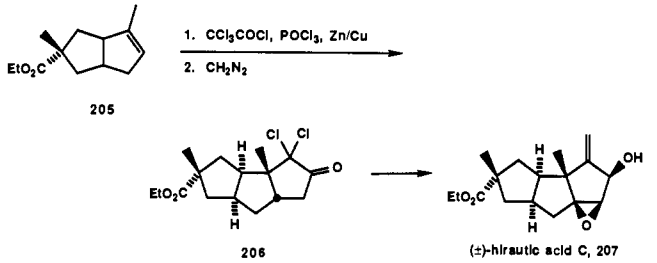
3. Ring Expansions

A popular method for the construction of cyclopentanones remains the ring expansion of cyclobutanones.[11,132,133] Reaction of cyclobutanones with diazomethane leads to ring homologation, but with simple alkyl-substituted ketones, regioselectivity is often lacking, as in the case of **202**, whose reaction led to a mixture of **203** and **204**.[134]



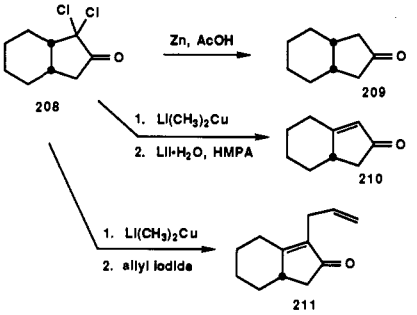
202 203 204

Better results are obtained with α,α-dichlorocyclobutanones. With diazomethane, these compounds undergo exclusive migration of the nonchlorinated carbon, as illustrated in a key step of Greene's synthesis of (±)-hirsutic acid C (**207**).[135] In addition to controlling



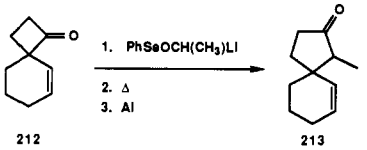
205 206 (±)-hirsutic acid C, 207

bond migration, dichloro substitution allows for elaboration of the initially formed dichlorocyclopentanones.[136] The reactive tendencies of hydrindanone **208** were examined in some detail by Greene. Reduction, reductive elimination, or alkylation afforded cyclopentanone **209**, cyclopentenone **210**, or alkylated cyclopentanone **211**. Annulations of this type can also be performed in an iterative manner and have been applied widely to the synthesis of triquinane terpenes.[1,16]



208 209 210 211

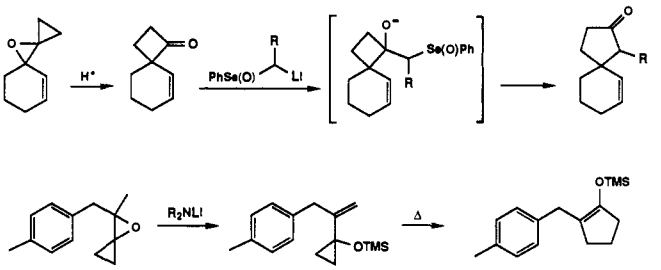
Gadwood reported a regiospecific alkylative ring expansion of 2,2-disubstituted cyclobutanones via α-lithio selenoxides.[137] When spirononenone **212** was treated



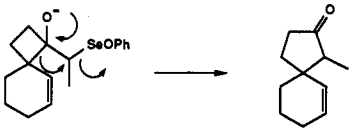
212 213

with 1-lithioethyl phenyl selenoxide followed by treatment of the crude reaction mixture with aluminum amalgam, the homologated product was obtained in 71% yield. Exclusive migration of the more highly substituted carbon had occurred. The mechanism of the ring expansion was proposed to be a pinacol-like

SCHEME XI. Cyclopentanoid Synthesis via Ring Expansion of Oxaspirocyclopentanes



rearrangement of the initial adduct **214**, in which the more highly substituted carbon migrates preferentially.

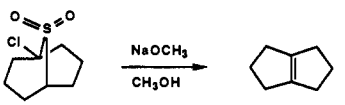


214 215

The chemistry of oxaspirocyclopentanes, their ring expansions to cyclobutanones, or their annulations to butenolides or cyclopentanes have been developed by Trost, Salaun, and others.[10,12,133,138,139] The major reactive pathways are shown in Scheme XI.

4. Ring Contractions

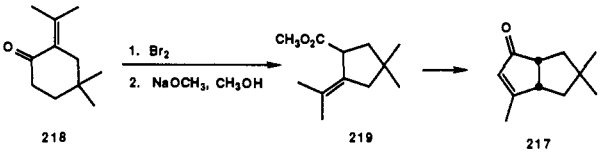
Anion-induced ring contraction to cyclopentanones is rarer than the corresponding expansions from cyclobutanones. One example is the Ramburg–Backlund elimination reaction of α-halo sulfones, shown below.[140]



215 216

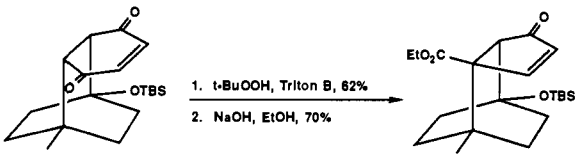
This reaction presented one of the first alkene syntheses in which the position of the double bond was clearly defined, and although still valuable, especially in the synthesis of strained compounds, it has lost some of its importance since the introduction of alternative stereo- and regioselective olefin syntheses.

Ring contraction via the Favorskii rearrangement continues to be utilized. Paquette has employed this reaction, originally developed by Wolinsky,[141] in the construction of bicyclo[3.3.0]octenone **217**, a useful synthon in triquinane synthesis.[142]



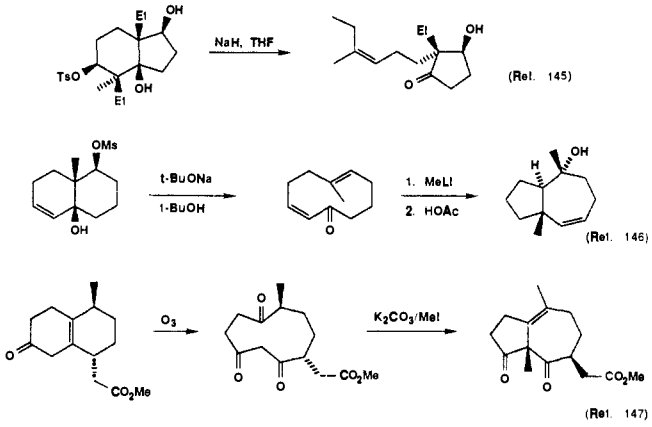
218 219 217

A similar rearrangement was also used by Still in a synthesis of (±)-trichodermol.[143] The Favorskii-like ring contraction of cyclohexanedione **220** proceeded regiospecifically to afford cyclopentenone **221** in 57% overall yield.



220 221

SCHEME XII. Fragmentation Strategies in Cyclopentane Synthesis



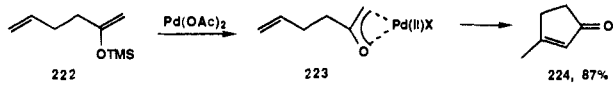
A commonly used strategy in the earlier carbocyclic terpene syntheses relied on the simultaneous ring contraction and ring expansion of bicyclic systems.[144] Although usually carried out under solvolytic (i.e., acid-catalyzed cationic conditions),[144] some fragmentations of alcohols induced with base are known. Such fragmentations depend on stereoelectronic effects and on orbital overlap of the departing σ-bond with the developing bond, and some involve several distinct steps,[146,147] as the examples in Scheme XII demonstrate,

VI. Miscellaneous Methods

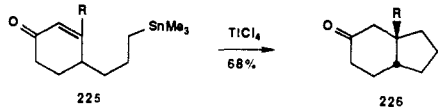
In this section, a short overview of other nonanionic but commonly used approaches to cyclopentanoid construction is presented. No attempt has been made at an exhaustive review; only representative examples are shown. The interested reader should instead refer to the reviews cited here as a guide to the specific topics.

1. Organometallic Reagents

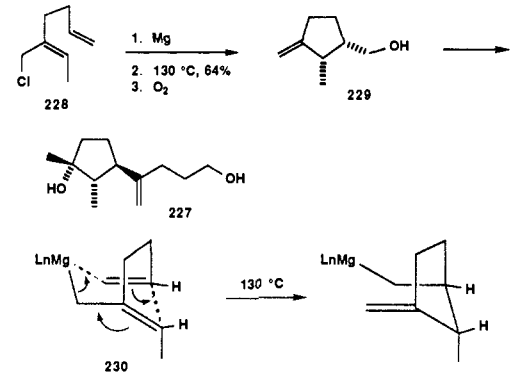
Saegusa has reported a Pd(II)-promoted intramolecular cyclization of silyl enol ethers of alkenyl methyl ketones to cyclic α,β-unsaturated ketones.[148] The authors proposed that oxo(π-allyl)palladium(II) complexes such as **223** may be involved as key intermediates.



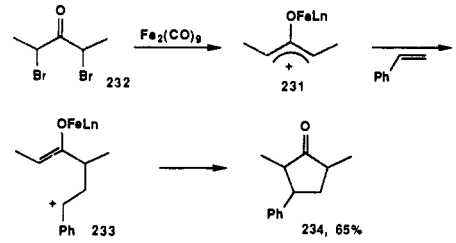
MacDonald has developed a method for effecting intramolecular conjugate addition to 2-cyclohexenones of unactivated carbon nucleophiles through the use of novel alkyltin(IV) chemistry.[149] This method of carbocyclization illustrated the use of the carbon–tin σ-bond as a latent carbanionic nucleophile. Crucial to the success of the reaction is activation of the enone with a Lewis acid to develop a β-electrophilic site to react with a proximal carbon–tin σ-bond.



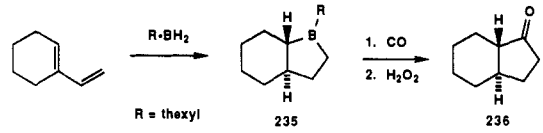
A key step in the first total synthesis of (±)-chokol-A (**227**) as reported by Oppolzer was a type I magnesium ene reaction.[150,151] The high regioselectivity and stereoselectivity of the cyclization product **229** are consistent with a concerted reaction involving transition state **230**.



Noyori has reported that reactive oxalyl–Fe(II) intermediates add across aryl-substituted olefins in a [3 + 2] cyclopentannulation strategy.[152] The oxalyl–Fe(II) intermediates **231** are generated from secondary or tertiary α,α'-dibromo ketones and iron carbonyls.

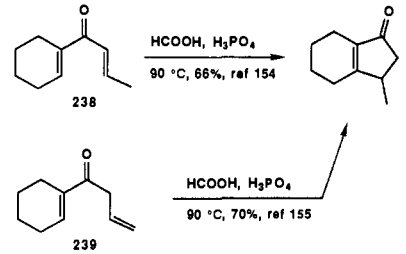


Carbonylation of thexylboracyclane **235** with carbon monoxide, followed by oxidation with hydrogen peroxide, provides bicyclic ketone **236** having a kinetic transfused ring junction that, in the case of most fused cyclopentanones, equilibrates to the energetically more favorable cis disposition.[153] The thexylboracyclane is simply derived from the corresponding 1,3-diene and thexylborane. The principal limitation of this method is the high pressure (1000 psi) required for the carbonylation.

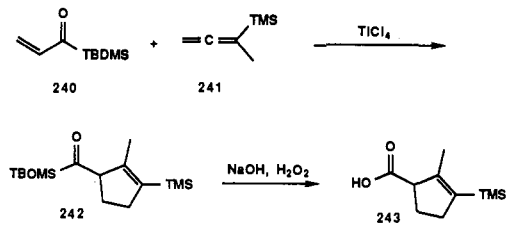


2. Cationic Processes

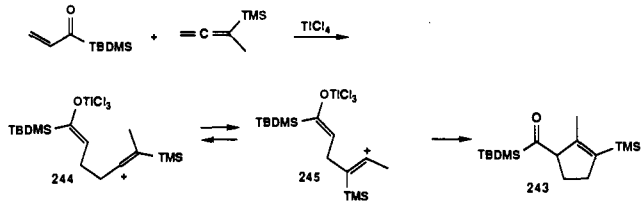
The Nazarov cyclization is the acid-induced ring-closure reaction of allyl vinyl and divinyl ketones to form substituted cyclopentenones such as **237**.[6,4,8,154,155] This cyclization is an attractive protocol because of its simple operation and the ready availability of starting materials.



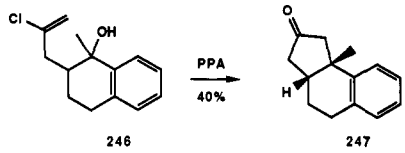
α,β-Unsaturated acylsilanes combine with allenylsilanes in a [3 + 2] annulation route to five-membered rings.[156] The reaction occurs in the presence of $TiCl_4$



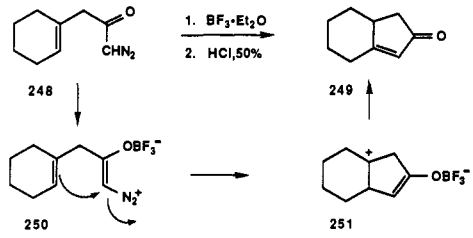
at −78 °C to form trimethylsilyl-cyclopentene annulated products in good yields. Treatment of the annulation products with 10% aqueous NaOH and 30% aqueous H_2O_2 effects their smooth conversion to the corresponding carboxylic acids. α,β-Unsaturated acylsilanes can thus be regarded as allenophilic carboxylic acid equivalents in this [3 + 2] annulation, A possible mechanism involves regiospecific electrophilic addition at C-3 of the allenylsilane to provide a vinyl cation, which can undergo a 1,2-TMS shift followed by closure to afford cyclopentenones.



Lansbury has developed an intramolecular cyclization of β-chloroallyl groups with electrophilic centers.[157] Cyclization of **246** proceeded to ketone **247** in 40% yield when treated with poly(phosphoric acid).

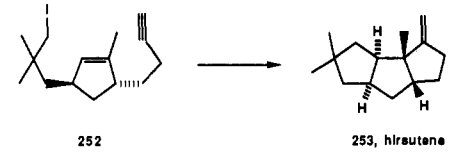


Smith has exploited the Lewis acid promoted decomposition of α-diazo ketones for the annulation of cyclopentenones.[158] It was demonstrated that the α-diazo ketone functionality represented an effective initiator of olefinic cationic cyclization, It was proposed that the reaction proceeded via initial complexation of the Lewis acid with the ketone oxygen to afford intermediate **250**. Subsequent loss of nitrogen and cyclization lead to a stabilized tertiary carbocation, which upon elimination of a proton and hydrolysis gave conjugated cyclopentenones.



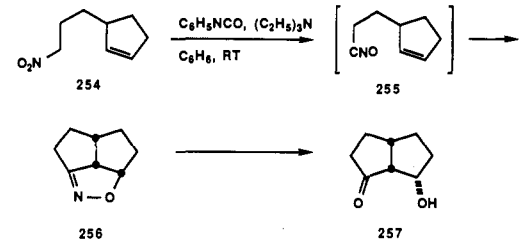
3. Radical Cyclizations

One of the most versatile methods for the construction of cyclopentanoids is free radical cyclization. An excellent review of this and other applications of free radicals in organic synthesis has recently become available.[7,159] A dramatic example of how complex polyquinane skeletons can be built is illustrated by the tandem radical cyclization of iodide **252** to hirsutene (**253**) as reported by Curran.[159]

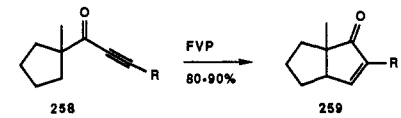


4. Thermal and Photochemical Routes

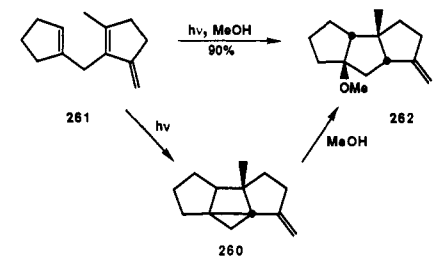
Intramolecular thermal cycloadditions of nitrile oxides to carbon–carbon double bonds have led to fused cyclopentanones.[160] This [3 + 2] dipolar cycloaddition proceeds to a tricyclic isoxazoline **256**, which after reduction to an imine alcohol with Raney nickel in glacial acetic acid is hydrolyzed to β-ketol **257**.



Gas-phase pyrolysis of substituted 1-pentyn-3-ones has led to 2-cyclopentenones.[161] The reaction is believed to proceed via C–H insertion of a vinylidene resulting from a 1,2-alkyl migration from the alkyne.



An intramolecular photochemical [2 + 2] cycloaddition of dicyclopentenes followed by trapping of the strained cyclopropane intermediate **260** afforded the linear fused polycyclic system **262** in excellent yield.[162] Unfortunately, this general photochemical cycloaddition is not applicable to systems derived from the fusion of six- and five-membered rings.



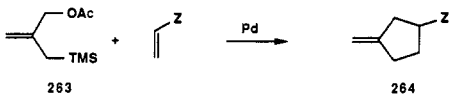
Photochemical ring contractions of cyclohexadienones are well-known[144] and have been used in the synthesis of hydrazulene natural products. The ene reaction strategy as applied to the construction of carbocyclic and heterocyclic natural products by Oppolzer constitutes also a powerful method of synthesis of cyclopentanoids.[163] The vinylcyclopropane–cyclopentene rearrangement has been widely used in synthesis by Hudlicky, Piers, Trost, Danheiser, Paquette, and others.[15-18] (Sections V.1 and V.2 described only anion-based processes.)

5. Trimethylenemethane and Equivalents

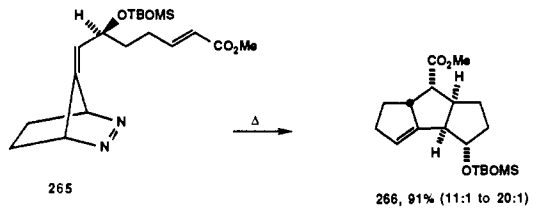
Trimethylenemethane (TMM) and its equivalents have been extensively used in [3 + 2] cycloaddition

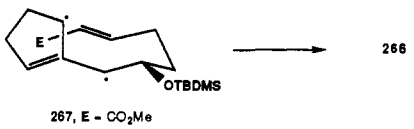
approaches to five-membered rings. Several such equivalents exist; these have been recently reviewed by Trost.[9] Some of the most versatile are 1,3-bifunctional conjunctive reagents such as compound **263**. Reaction

of **263** with activated olefins in the presence of catalytic Pd leads to methylenecyclopentanes in moderate to good yields. Suitable activators include esters, nitriles, sulfones, and ketones.



Rapid construction of the triquinane nucleus by means of an intramolecular 1,3-diyl trapping reaction has been developed by Little.[164] Diazenes are employed as TMM precursors in this reaction. The intramolecular 1,3-diyl trapping reaction is a kinetically controlled process, allowing for rational control of the stereochemical outcome of the reaction by examination of the possible transition states involved. The low-energy transition state leading to **266** is shown below.





VII. Summary

This review has attempted to summarize those methods of synthesis of cyclopentanoids that utilize anionic processes. Such a summary cannot be exhaustive because of the tremendous amount of literature on the subject. It must also, at times, diverge from purely anionic processes to the description of other methods because of discussion of target molecules or multistep sequences, The last section on miscellaneous transformations is intended to bridge this gap and to provide a brief guide to the nonanionic processes. Wherever possible recent reviews are provided as a guide to the general literature.

The efforts of our own research group in the area of cyclopentene annulations via the sequential Michael addition/internal alkylation of α-halocrotonates to enones are highlighted in sections V.1 and V.2 and include some new and unpublished material pertaining to cyclopentanoid construction via anion-accelerated vinylcyclopropane rearrangement. This [2 + 3] annulation methodology has rapidly evolved into a powerful technique of synthesis not only in the carbocyclic field but also in the heterocyclic field and was also found to be applicable to the synthesis of pyrrolines and dihydrofurans. The current discussion sets this method into the context of the general category of reactions based on anionic processes.

VIII. Acknowledgments

The authors acknowledge Dr. Josephine W. Reed for proofing and editing the manuscript and Ms. Vera Good for assistance with typing. Our co-workers, whose names appear in the cited references, are thanked for their spirited effort in developing the cyclopentene methodology described in this review.

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(3) The literature contains both the terms *annelation* and *annulation* as descriptors of ring-forming processes. The use of the former term should be discouraged as its connotation points to the act of "strengthening", which is not always the case in fused-ring construction. Most dictionaries do not contain the former term at all as a noun. The Webster dictionary defines these terms in the following way. *Annelation*: from L. anellus = ring or from anneal = strengthen. At best this word has been erroneously coined since it has no correct connotation of a process. *Annulation*: from L. annularis = an act of ring formation, to furnish with rings. Obviously, from a synthetic standpoint this word should be used to describe ring-forming methodologies. The former terminology should be laid to rest as its use leads to confusion in the literature and to doubling the search effort in retrieval of data connected with annulation strategies.
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