Synthesis of Functionalized Bicyclo[3.2.1]octanes and Their Multiple Uses in Organic Chemistry

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I. Introduction

Although the first bicyclo[3.2.1]octane skeleton was obtained at the beginning of this century by Komppa and Hirn,[1] the real development of its chemistry, from theoretical[2] and synthetic points of view, started around the mid-1960s with the publication of more practical syntheses. This structural moiety is the basic framework of numerous important biologically active natural compounds or their metabolites and has been the center of much interest worldwide. For example, the C/D ring system of gibberellins, an important class of tetracyclic diterpenes, is a functionalized [3.2.1] skeleton, which has attracted the attention of many research groups and has been the

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Jean Rodriguez was born in Cieza (Murcia), Spain, on June 25, 1958 and in 1959 his family emigrated to France. After completion of his diploma in chemistry at the University of Aix-Marseille III, France, he obtained his "Thèse de $3^{\text{ème}}$ cycle" in 1984. The same year, he entered the CNRS and completed his Ph.D. under the supervision of Professor B. Waegell at the same University in 1987. He was a postdoctoral Research Associate with Professor K. P. C. Vollhardt, University of California at Berkeley in 1988 and Associate Scientist at the same University during the summer 1993. He received his "Habilitation à Diriger des Recherches" from the University of Aix-Marseille III in 1992. He is currently Directeur de Recherches at the UMR 6516, at Marseille, and received the 1998 Société Française de Chimie-Acros prize in Organic Chemistry. His research interests include the development of new methodologies based on the selective functionalization of olefins and especially using new anionic domino reactions, and their applications to the stereoselective synthesis of bioactives compounds.

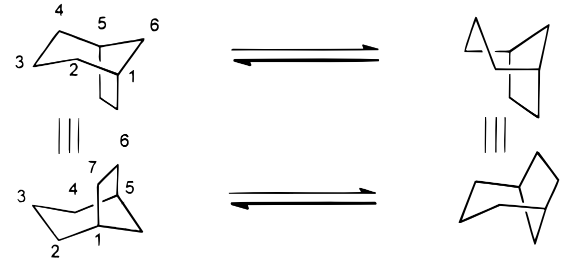
subject of an excellent and exhaustive review.[3] This bicyclic subunit is also included in many other bioactive sesqui- and diterpenes belonging, for example, to the kaurane, phyllocladane, stemodane, barbatane, beyerane, aphidicolane, zizane, cedrane, patchoulane, and ishwarane families as well as in more peculiar compounds such as quadrone, helmintosporal, copaborneol, sinularene, grayanotoxins, neolignans, sorokinianin,[4] and some highly substituted alkaloids.[5] Moreover, properly functionalized bicyclo[3.2.1]octanes have proved to be useful reactive intermediates in many interesting stereoselective transformations making these derivatives powerful building blocks in organic synthetic strategies directed toward the total synthesis of important natural products.

Several ingenious methods and also more conventional approaches for the stereoselective preparation of this valuable bicyclic nucleus have been developed. However, although three excellent reviews devoted to the related bicyclo[3.3.1]-[6] and bicyclo[4.2.1]nonanes[7] have been published, the chemistry of bicyclo[3.2.1]-octanes has not been reviewed to date.

In this article, we focus on the preparation of functionalized bicyclo[3.2.1]octanes and their synthetic uses. We hope that this review will prove useful in organic chemistry and will provide a valuable complement to the existing literature.[6,7]

II. Background

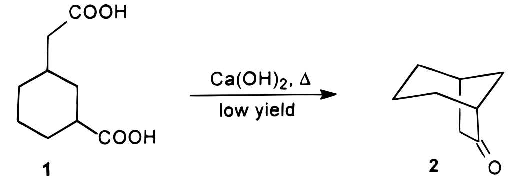
In sharp contrast with bicyclo[3.3.1]nonane[6] and bicyclo[4.2.1]nonane,[7] bicyclo[3.2.1]octane is a rather rigid molecule which can be regarded either as a six-membered ring **I** bearing a two-carbon bridge or as a seven-membered ring with a methylene bridge **II**. The conformational mobility of these structures is limited to a chair-boat interconversion, which is clearly in favor of **I** for obvious steric reasons[8] corroborated by calculated heats of formation.[9] On the basis of spectroscopic analysis[10] and exhaustive ^1H NMR studies[11] of funtionalized derivatives, it appears that the bicyclo[3.2.1]octane skeleton is essentially fixed in a chair-like six-membered ring form **I**.



I $\Delta H°_f = -33.03$ kcal mol^{-1}

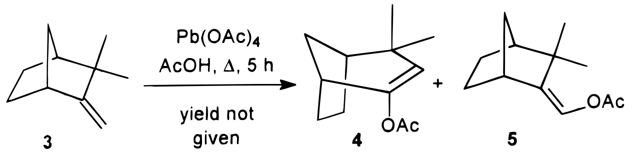
II $\Delta H°_f = -30.44$ kcal mol^{-1}

At the very beginning of this century, Komppa and Hirn[1] described the first preparation of bicyclo[3.2.1]-octan-7-one (**2**) by intramolecular cyclization and subsequent decarboxylation of hexahydrohomoisophthalic acid (**1**).



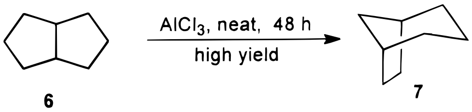
1 **2**

Two decades later, Lipp[12] identified the first ring expansion of a bicyclo[2.2.1] precursor during the fusion of ω-bromocamphene with KOH. This new ring enlargement was applied to camphene itself (**3**),[13] which reacts cleanly with $Pb(OAc)_4$ in AcOH to give enol acetate **4** as the major product together with camphene enol acetate **5**.

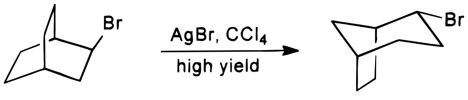


3 **4** **5**

The rearrangement of isomeric bicyclooctane substrates was first reported in 1936 by Barrett and Linstead[14] in the case of $AlCl_3$-induced isomerization of *cis*-bicyclo[3.3.0]octane (**6**) to **7**. Several years later, Doering and Farber[15] disclosed the transformation of 2-bromobicyclo[2.2.2]octane (**8**) to the corresponding [3.2.1] isomer **9** by reaction with AgBr.



6 **7**



8 **9**

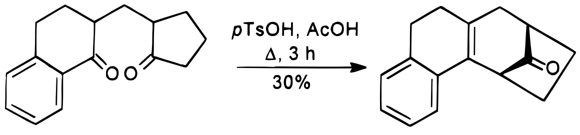
After these pioneering investigations, a growing interest in the bicyclo[3.2.1]octane ring system led to important developments making more complex structures available for the synthesis of natural compounds. Basically, the numerous methodologies developed over almost a century can be classified in four major groups, which will be developed in the different sections of this review, namely: (a) intramolecular C−C bond formations from properly functionalized precursors, (b) cycloadditions and other electrocyclizations, (c) ring expansion of bicyclo[2.2.1]heptanes, (d) rearrangement of polycyclic intermediates.

III. Intramolecular C–C Bond Formations

1. Aldol-Type Condensations

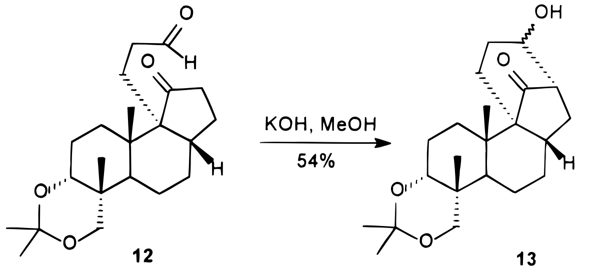
a. Ring Closures of the Three-Carbon Bridge

The aldol-type condensation of properly functionalized cyclopentanones provides a quite simple way to construct angular cyclic systems including the bicyclo[3.2.1]octane skeleton. One of the first examples, due to Julia and Varech,[16] is the acidic cyclization of **10** to the tetracyclic ketone **11** bearing a bicyclo[3.2.1]octane system.

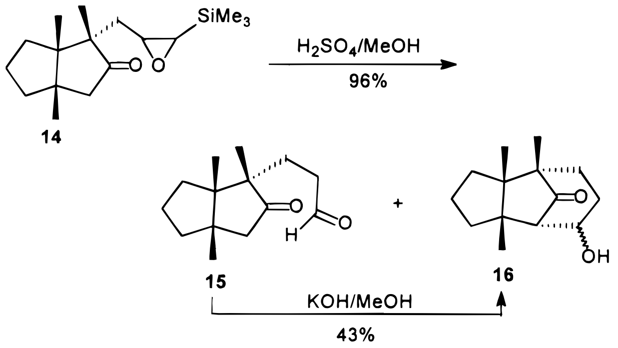


10 **11**

Acid- or base-induced cyclization of keto aldehydes has become a quite simple and general method for the formation of bicyclo[3.2.1]octanes, and is therefore extensively studied in gibberellin chemistry[3] and also applied successfully to several other total syntheses. For example, aphidicolin[17] is obtained from **12** through aldol **13** and a new route to gymnomitrol[18] involves aldolization of **15** or direct cyclization of epoxysilane **14** to give the same tricyclic structure **16** in 22% yield.

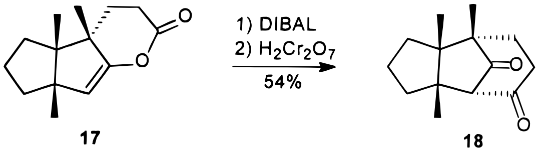


12 **13**



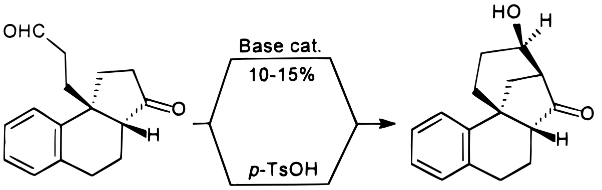
14 **15** **16**

Contemporaneously, in the course of the stereoselective synthesis of gymnomitrol, Coates and collaborators[19] used the same cyclization strategy starting with the tricyclic lactone **17**. Reduction with DIBAL afforded directly the corresponding bridged ketol intermediate **16**, which was further oxidized to **18** obtained in 54% overall yield.



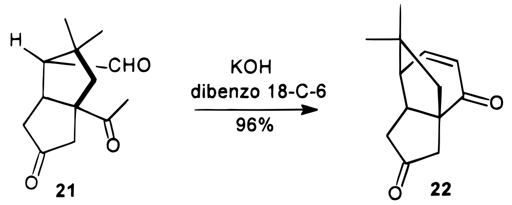
17 **18**

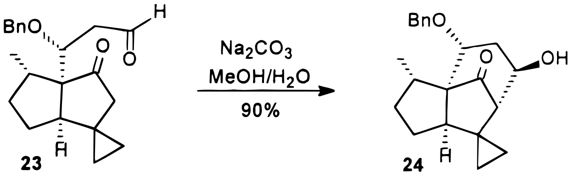
Very recently, Hegarty and Mann[20] showed that a variety of base-catalyzed aldolizations of tricyclic keto aldehyde **19** gave poor results in the construction of stemodin skeleton **20**. In contrast, reaction of **19** with a catalytic amount of pTsOH results in complete conversion and production of ketol **20** in 55% yield after equilibration.



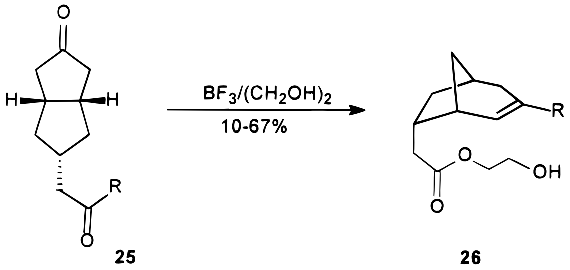
19 **20**

An aldol−dehydration sequence was proposed by Burke and collaborators[21] as a key step during the total synthesis of quadrone. The functionalized bicyclo[3.3.0]octane **21** treated with powdered KOH in the presence of dibenzo-18-crown-6 gave a 96% yield of the tricyclic diketone **22**, which represents the ABC rings of the natural product. More recently, this sequence was applied to an elegant synthesis of (−)-α-pipitzol[22] from the cyclization of cyclopropyl diquinane **23** to ketol **24** and also used in the steroid series.[23]

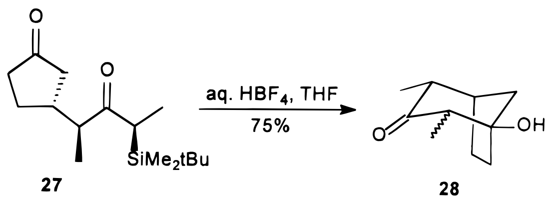




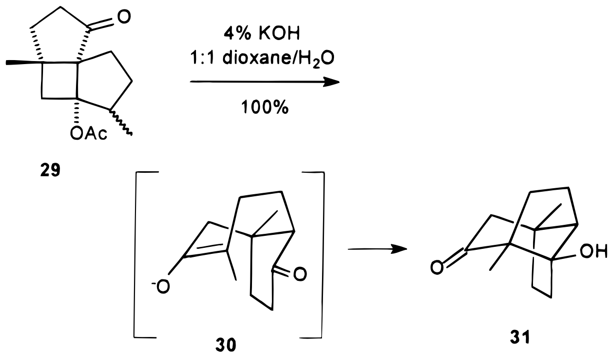
Alternatively, bicyclo[3.2.1]octenes **26** can be formed in moderate yields from bicyclo[3.3.0]octanones **25** after in situ fragmentation of the aldol intermediate generated under acetalization conditions.[24] An efficient asymmetric ring transformation is found when chiral cyclic 1,2-diols are used instead of glycol.[25]



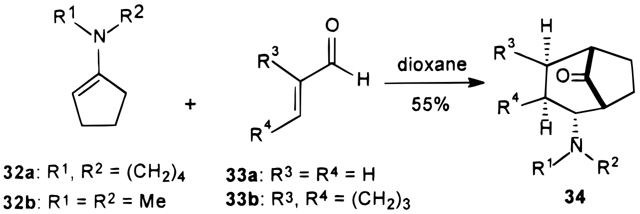
During the removal of the silicon substituent in **27**, Lohray and Zimbiniski[26] found an interesting regioselective intramolecular aldol reaction leading to **28** in good yield.



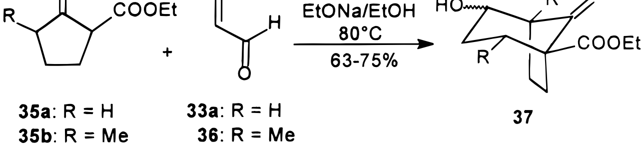
A powerful one-pot sequence was reported in 1985 by Seto and collaborators[27] for the construction of functionalized tricyclic skeletons as potential intermediates for the synthesis of terpenes. Retroaldolization of the cyclobutane derivative **29** promoted by KOH gave the bicyclic 1,5-diketone **30** which condensed intramolecularly to the desired hydroxytricyclic ketone **31** in quantitative yield.



Since 1,5-dicarbonyl intermediates constitute good candidates for carbocyclization reactions, the sequence based on Michael addition−intramolecular aldolization has attracted much interest for the construction of bicyclo[3.2.1]octanes. An old but efficient one-pot illustration of this approach is the well-known Stork−Landesman procedure,[28] which involves the condensation of cyclopentanone enamines **32** with α,*β*-unsaturated aldehydes **33** to give 2-aminosubstituted bicyclo[3.2.1]octan-8-ones such as **34**.

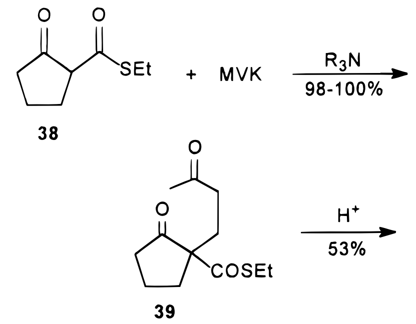


Alternatively α-activated cyclopentanones such as **35** also constitute good substrates for Michael additions leading to 1,5-dicarbonyls,[29] precursors of bicyclo[3.2.1]octanes. For example, hydroxy-substituted bicyclooctanones **37** can be obtained in one operation by a direct condensation of 2-carbethoxycyclopentanones **35** with α,*β*-unsaturated aldehydes **33a** and **36**.[30]

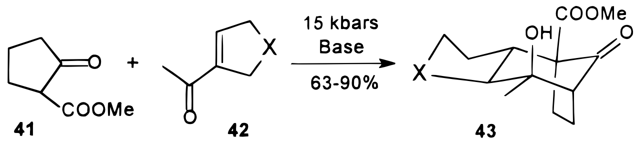


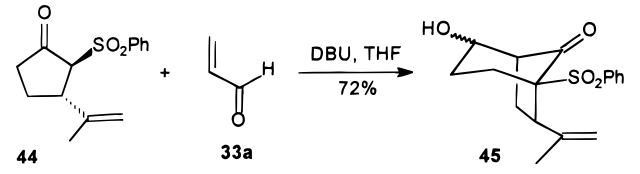
Similarly, it has been found that cyclopentanone **38** reacts smoothly with methyl vinyl ketone (MVK) in the presence of a tertiary amine to give high yields of Michael adduct **39** which undergoes H_2SO_4-induced cyclization to bridged system **40**.[31]

A detailed study[32] on the high-pressure-induced tandem Michael addition−intramolecular aldolization showed that the more common activated cyclopentanone **41** reacted with hindered cyclic or acyclic enones **42** to produce fair amounts of bridged cyclic

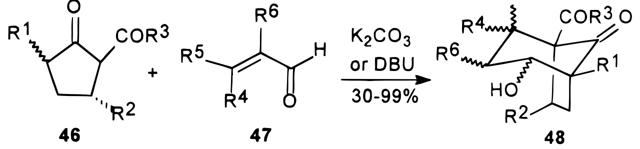


aldols **43**. More recently, Veselovskii and collaborators[33] proposed the same Michael–aldol sequence with phenylsulfonylcyclopentanone **44** and acrolein (**33a**) giving rise to functionalized bicyclo[3.2.1]octanone **45**.

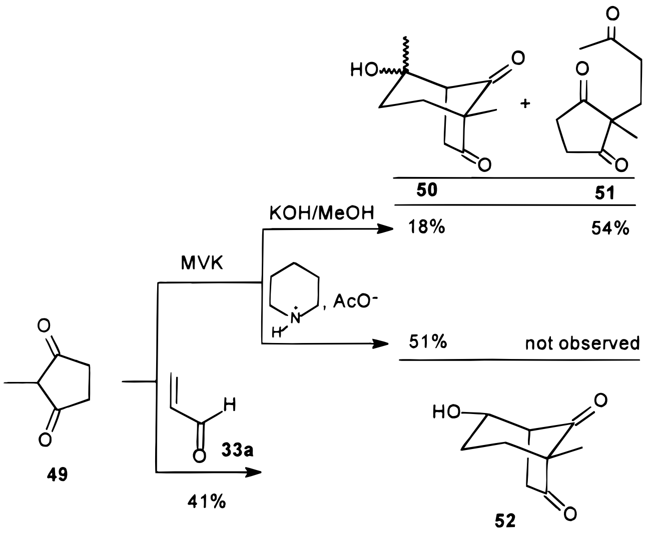




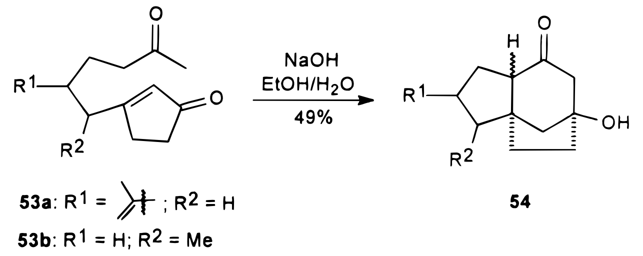
Our own work on this field[34] showed that highly functionalized and stereodefined 2-hydroxybicyclo[3.2.1]octan-8-ones **48** could be obtained very easily by a one-pot base-promoted tandem Michael addition–intramolecular aldolization of β-dicarbonyl derivatives **46** with α,β-unsaturated aldehydes **47**.



Enolate anions derived from 1,3-cyclopentadiones have also been used extensively for Michael additions, giving adducts susceptible to be cyclized to bridged derivatives. During experiments in steroid synthesis Whitehurst and collaborators[35] showed that the condensation of 2-methylcyclopentane-1,3-dione (**49**) with methyl vinyl ketone gave 4-hydroxy-1,4-dimethylbicyclo[3.2.1]octane-7,8-dione (**50**) as byproduct together with the expected Michael adduct **51**. Subsequent to this work, Hajos and Parrish[36] published an optimization of this cycloalkylation by using piperidinium acetate instead of KOH. These results were exploited more recently by Schick and collaborators[37] who studied the condensation of **49** with acrolein (**33a**) to give hydroxybicyclo[3.2.1]octanedione **52** in 41% yield.

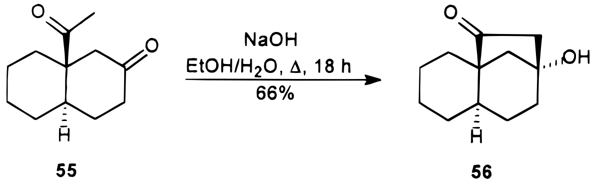


A practical application of the Michael–aldol carbocyclization was reported in 1978 by Posner and collaborators[38] who showed that monocyclic cyclopentenones **53** underwent a mild base-promoted double cyclization to form tricycles **54** in moderate yield.

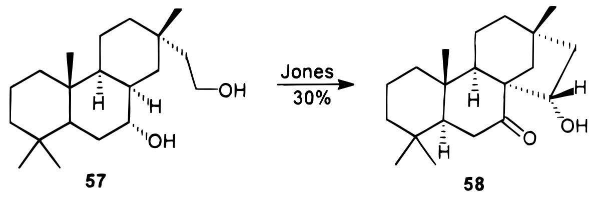


b. Ring Closures of the Two-Carbon Bridge

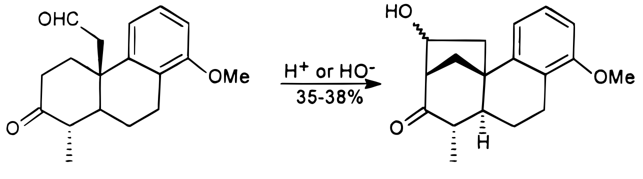
In 1962, Haworth and collaborators[39] showed the facile conversion of the decalone **55** into the bicyclic hydroxy ketone **56** by reaction with dilute NaOH solution.



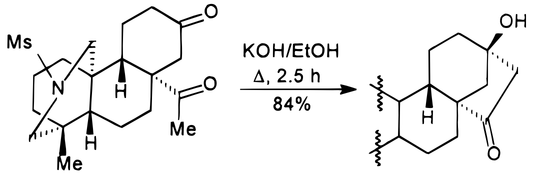
After this model study, the aldol approach involving the ethano ring closure from functionalized cyclohexanones has been successfully used in natural compound synthesis.[3] A partial synthesis of isohibaene[40] by chromic oxidation of diol **57** involved the aldolization of a keto aldehyde intermediate to give ketol **58**. Similarly, en route to complex diterpene



alkaloids of the atisine–garryine type, various advanced intermediates have been prepared by acid- or base-catalyzed cyclization of **59** to a mixture of epimeric alcohols **60**,[41] or by ring closure of methyl ketone **61** to **62**.[42]

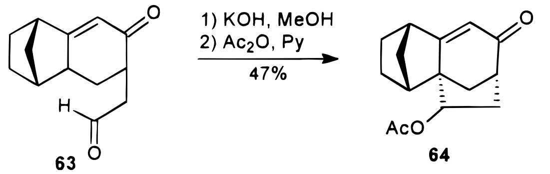


59 **60**

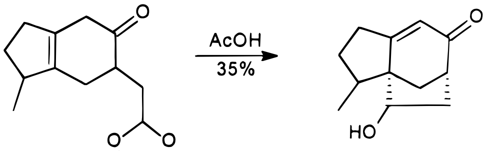


61 **62**

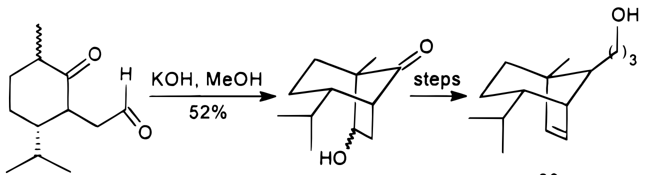
Engaged in studies toward the total synthesis of songorine, Wiesner and co-workers[43] proposed a method for the preparation of bridged terpenoids based on the intramolecular aldol condensation of keto aldehyde **63** to form the tetracyclic intermediate **64**. The same strategy was used to build up the tricyclic core of tricyclovetivene by acidic hydrolysis of **65** and subsequent cyclization to **66**. Similarly, conversion of **67** to **68** under basic conditions was used in the preparation of bicyclo[3.2.1]octene **69** precursor of (+)-sativene and (+)-cyclosativene[44] and very recently applied to the total synthesis of (+)-sorokinianin from *d*-carvone.[45]



63 **64**

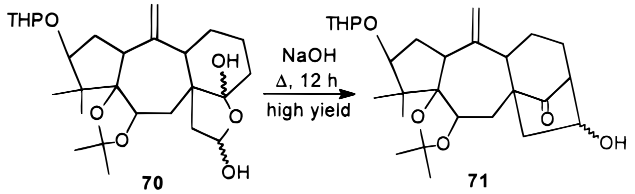


65 **66**



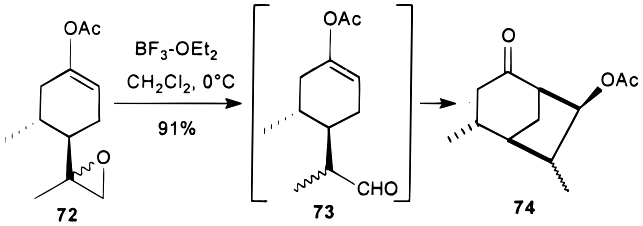
67 **68** **69**

In a partial synthesis of grayanotoxin,[46] the construction of the C/D rings is made by reaction of hemiacetal **70** with ethanolic NaOH giving rise to **71** as a mixture of epimers.



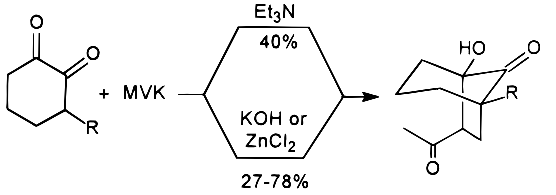
70 **71**

Also very interesting for the enantioselective construction of synthetically valuable bicyclo[3.2.1]octane systems is the recently reported one-pot transformation of epoxide **72** derived from (+)-nopinone.[47] Treatment of **72** with BF$_3$·OEt$_2$ initiates epoxide rearrangement to give the intermediate aldehydes **73**, which cyclize intramolecularly leading to the functionalized bicyclic ketones **74** in high yield.



72 **73** **74**

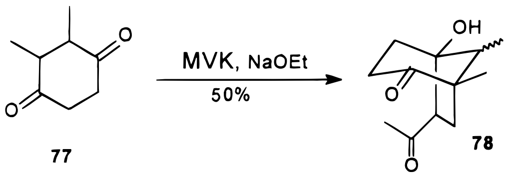
Cyclic 1,2-diones have seldom been employed in the Michael addition. However, during a study of the Robinson annulation with cycloalkanones, it was found that cyclohexane-1,2-dione (**75a**) reacted smoothly with methyl vinyl ketone in the presence of Et$_3$N to give the stable bicyclo hydroxy diketone **76a**.[48] A more detailed investigation of this annulation appeared 20 years later[49] and showed that KOH or ZnCl$_2$ could also be used to promote the condensative cyclization.



75a: R = H
75b: R = Me

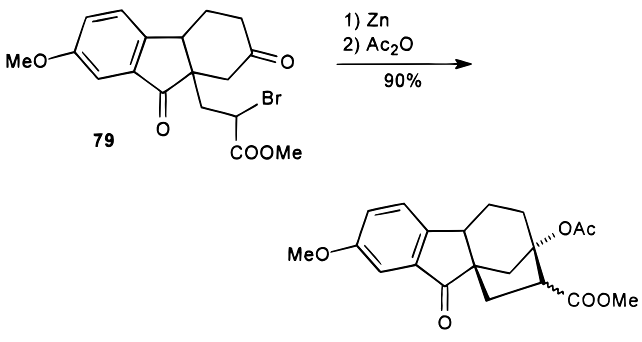
76a : R = H
76b : R = Me

A related reactivity was observed with 1,4-cyclohexanedione **77** en route to the total synthesis of eremophilane-type sesquiterpenes.[50] Bicyclic hydroxy ketone **78** was produced by reaction of **77** with methyl vinyl ketone under basic conditions.



77 **78**

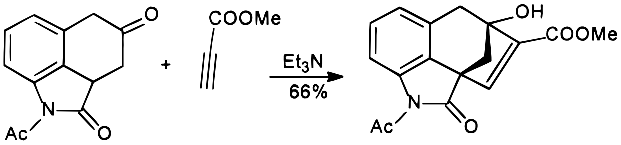
Also of interest is the Reformatsky reaction which was employed for direct access to the gibbane synthon **80** obtained in 90% yield from the reaction of bromo ester **79** with zinc followed by acetalyzation of the resulting aldol.[51]



79

80

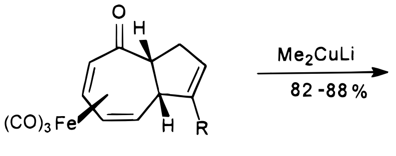
On the other hand, intramolecular aldol-type trapping of the enolate generated by reaction of cyclohexanone **81** with methyl propynoate (**82**) gave a 66% yield of the corresponding α,β-unsaturated tetracyclic ester **83** bearing a bridgehead hydroxy substituent.[52]



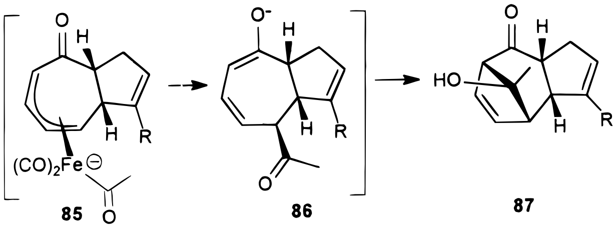
81 **82** **83**

c. Ring Closures of the One-Carbon Bridge

Highly reactive anionic acyl complexes can be formed by nucleophilic addition of simple lithio Grignard reagents to a coordinated carbonyl group of uncharged dienic-$Fe(CO)_3$ complexes.[53] This interesting behavior was extended to cuprates by Rosenblum and Watkins[54] for the construction of a tricyclic hydroxy ketone **87**, having a carbon skeleton closely related to β-patchoulene. Lithium dimethyl cuprate adds readily to the neutral diene−iron complexes **84** to give the reactive anionic acylmetals **85**. Migratory insertion of the acyl group with loss of the iron carbonyl, probably by Michael type addition, releases the dienolate ligands **86**, precursors of **87** via an intramolecular aldol condensation.

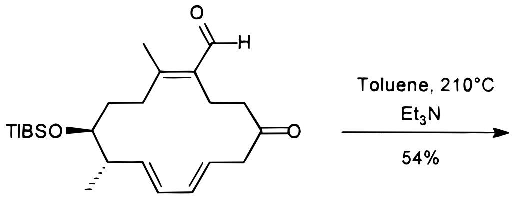


84a: R = H
84b: R = Me

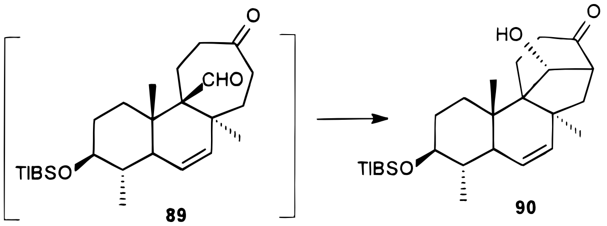


85 **86** **87**

Very recently, it has been found that the transannular Diels−Alder/intramolecular aldol tandem reaction constitutes a new powerful and stereocontrolled route to (+)-aphidicolin.[55] The transformation involves a cycloaddition of macrocycle **88** in the presence of Et_3N to give the key keto aldehyde **89** which is easily cyclized under the reaction conditions to the tetracyclic ketol **90**.



88

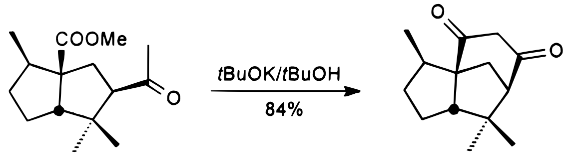


89 **90**

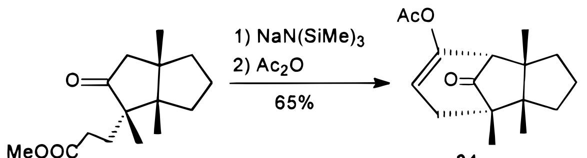
2. Claisen, Dieckmann, and Thorpe−Ziegler Cyclizations

a. Ring Closures of the Three-Carbon Bridge

Closely related to the aldolization approach are intramolecular Claisen-type carbocyclizations of properly functionalized precursors. Stork and Clarke[56] were the first to achieve the total synthesis of natural cedrenoid sesquiterpenes. Their approach to cedrol involved a base-catalyzed cyclization of bicyclic keto ester **91** to the tricyclic framework **92** of the natural product. Similarly, during a stereoselective synthesis of gymnomitrol and gymnomitrene, the properly functionalized keto ester **93** constitutes the precursor of the key tricyclic ketone **94** when treated with a strong base.[57]

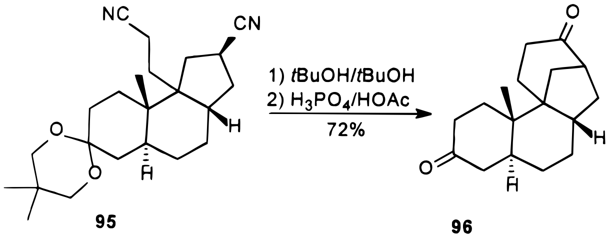


91 **92**



93 **94**

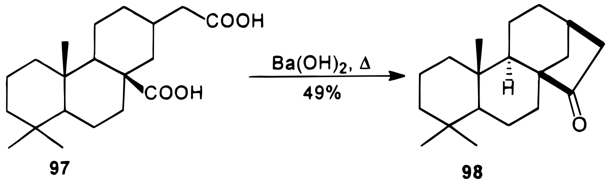
An example of intramolecular Thorpe−Ziegler carbocyclization of dinitrile **95** is also present in the literature and was reported by Piers's group[58] for the construction of tetracyclic stemodane framework **96**.



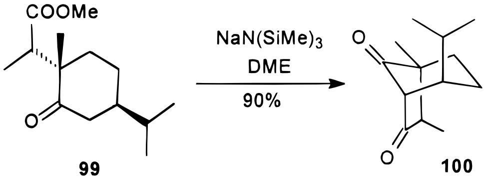
95 **96**

b. Ring Closures of the Two-Carbon Bridge

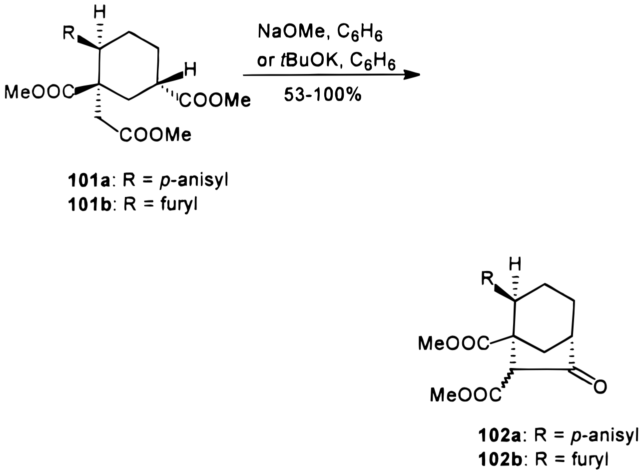
Since the pioneering work of Komppa and Hirn,[1] the construction of the bicyclo[3.2.1]octane skeleton by intramolecular condensations of carboxylic acid derivatives has also attracted great attention. For example, the direct pyrolysis of the barium salt of diacid **97** afforded tetracyclic ketone **98**, an intermediate in the synthesis of phyllocladene.[59]



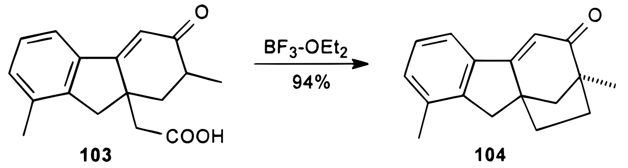
Following this cyclodehydration, new synthetic approaches based on Claisen-type, carbocyclizations appeared in the literature. The synthesis and the cyclization of chiral keto ester **99**, derived from (+)-carvomenthone, was extensively studied by Piers and collaborators.[60] Their strategy involves the formation of bicyclo[3.2.1]octane-1,3-dione **100** which serves as key starting synthon for the stereoselective total synthesis of copa and ylando sesquiterpenoids.



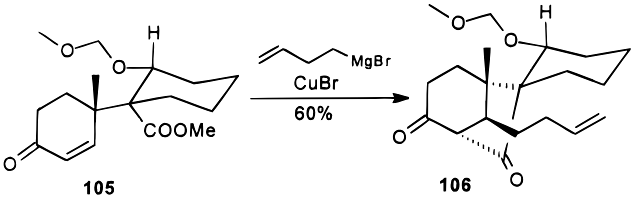
Condensations involving α,ω-diesters such as **101** were also developed and applied to the preparation of bicyclo[3.2.1]octanes **102**, precursors of the gibbane skeleton, or key intermediates in the synthesis of fujenoic acid.[61]



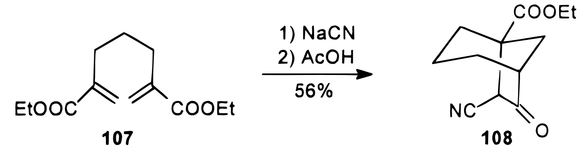
Reactive enol ether intermediates can also be trapped under dehydration conditions leading to bicyclo[3.2.1]octanones. The pioneering work of Loewenthal's group[62] directed toward the synthesis of compounds related to gibberellic acid showed the feasibility of such an electrophilic acylation in the case of keto acid **103** which was easily transformed, upon reaction with $BF_3 \cdot OEt_2$, to the tetracyclic ketone **104**, a precursor of gibberone. Adaptation of this strategy was proposed subsequently for the synthesis of *d*-phyllocladene and *Garrya veatchii* alkaloids.[63]

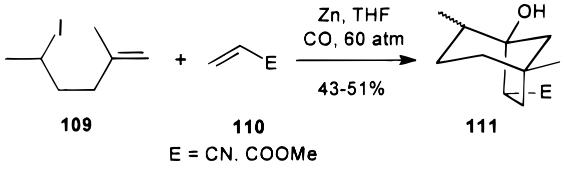


Pearson[64] showed that the copper-catalyzed conjugate addition of 4-butenylmagnesium bromide with properly functionalized cyclohexenone **105** occurred with intramolecular acylation of the intermediate enolate to give stereodefined bicyclo[3.2.1]octanedione **106** in good yield.



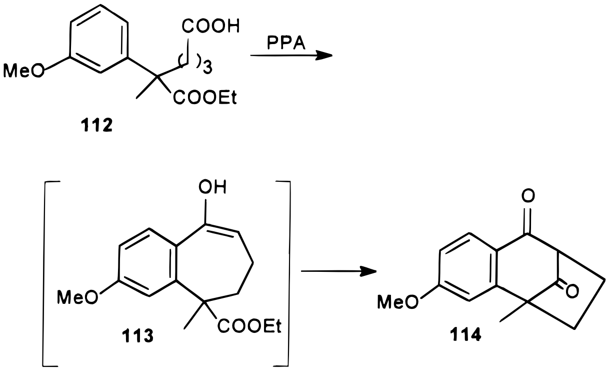
Finally, tandem annulations from totally acyclic precursors are still rare but synthetically attractive. For example, the cyanide ion mediated inter–intramolecular-Michael addition followed by Dieckmann-type ring closure allowed for the efficient one-pot preparation of **108** from the very simple acyclic dienic diester **107**.[65] Very recently, Sonoda and collaborators[66] showed the potential of a new three-component coupling approach starting with alk-4-enyl iodides. The zinc-initiated radical reduction/carbonylation/intramolecular addition to the double bond of **109** followed by in situ 1,4-addition to activated alkenes **110** results in the formation of a stabilized carbanion intermediate which adds to the internal carbonyl group to form the expected bridgehead hydroxy bicyclo[3.2.1]octane system **111** in fair yields and as a 1:1 mixture of isomers.





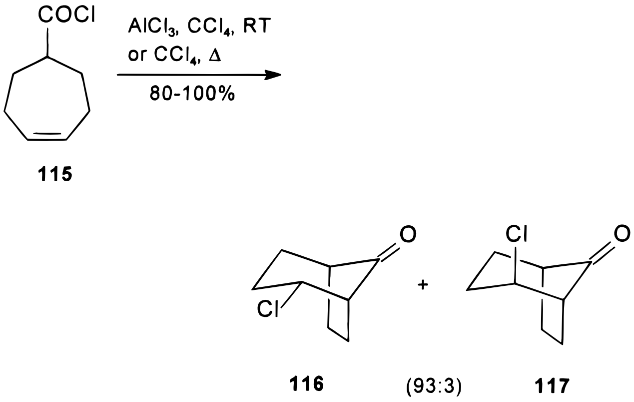
c. Ring Closure of the One-Carbon Bridge

A representative example of this mode of carbocyclization is the elegant one-pot construction of tricyclic diketone **114**, through **113**, by a tandem intramolecular acylation/Claisen ring closure observed by reaction of acid **112** with polyphosphoric acid (PPA).[67]

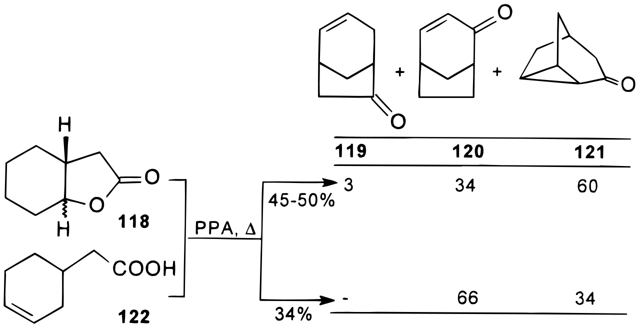


3. Acylation-Based Methods

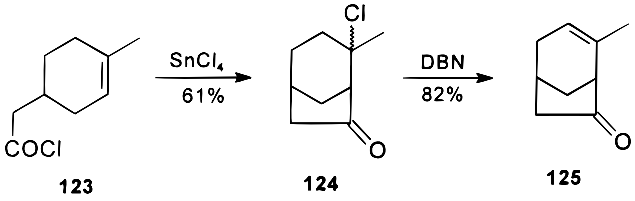
Acylations of properly functionalized precursors has seldom been employed[68] but give good results in some cases. For example, the direct acylation of isolated double bond was used by Kemp and Fickes[69] to determine the stereochemistry of the Friedel–Crafts reaction starting from cyclohept-4-ene-1-carboxylic acid chloride (**115**). A stereoselective cyclization in favor of 2-*endo*-chlorobicyclo[3.2.1]octan-8-one (**116**) was observed by reaction with $AlCl_3$ and a few years later, a detailed study of this cycloacylation showed that the same result was obtained thermally in the absence of Lewis acid.[70]



The observation by Ficini and Maujean[71] that lactones **118** gave bridged ketones **119**–**121** when heated in the presence of PPA allowed these investigators to propose the cyclodehydration of substituted cyclohexene **122** as a new potential entry for the preparation of functionalized bicyclo[3.2.1]octene.[72]

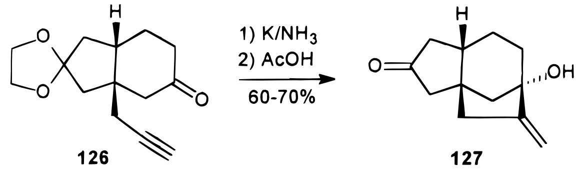


These results were exploited by Monti's group[73] who developed the intramolecular acylation of 4-methyl-2-cyclohexen-1-acetyl chloride (**123**) as a new regioselective synthetic route to valuable bicyclo[3.2.1]octane systems such as **124** and **125**.

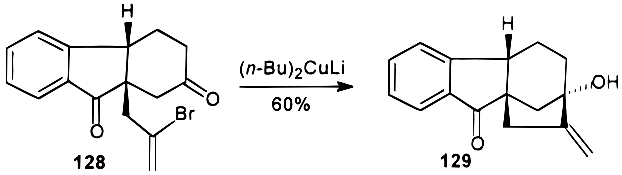


4. Reductive Cyclizations

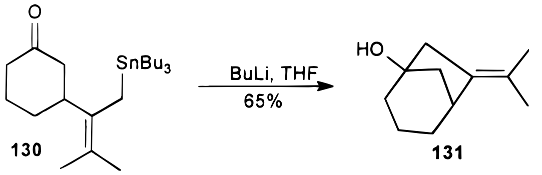
The reductive cyclization of functionalized carbonyl derivatives constitutes a quite direct method for the elaboration of bicyclic systems and has successfully been applied in the synthesis of natural compounds containing a bicyclo[3.2.1]octane nucleus by selective ring closure of the ethano bridge. Stork and collaborators[74,51b] have used the chemical reduction of γ-ethinyl ketone **126** for the construction of **127**, a significant tricyclic intermediate in the synthesis of gibberellic acid.

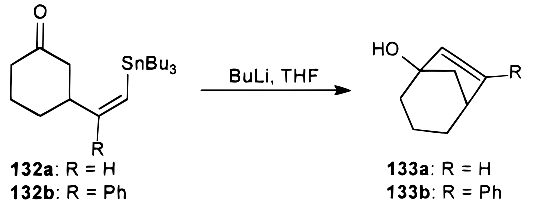


A related strategy based on the cyclization of vinyl halides to a carbonyl function was reported shortly after. While the Grignard reagent derived from **128**[75] failed to give any bridged compound, the corresponding cuprate gave the tricyclic methylene ketone **129** in 60% yield.[76] This methodology was also employed for a more direct access to ketone **127**[77] and used in a total synthesis of gibberellic acid.[78]

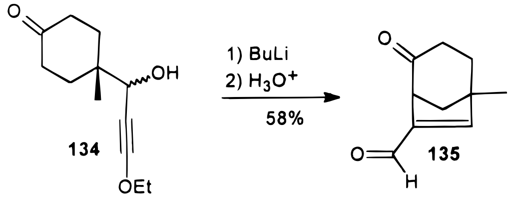


Other noncatalytic intramolecular ring formations involving the addition of an organolithium intermediate to an unsaturated function have been applied with success. A selective tin–lithium exchange is observed by Pulido and co-workers,[79] starting either with allyl- or vinylstannanes **130** or **132** which are smoothly cyclized to **131** and **133**, respectively.

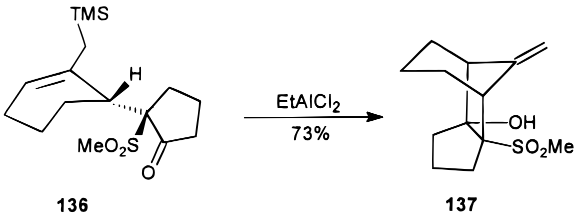




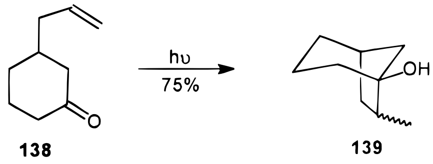
Alternatively, a new intramolecular carbolithiation reaction of alkoxyacetylenes allows the facile ring annulation of cyclohexanone **134** to produce, after hydrolysis, the corresponding bicyclo[3.2.1] keto aldehyde **135**, in 58%.[80]



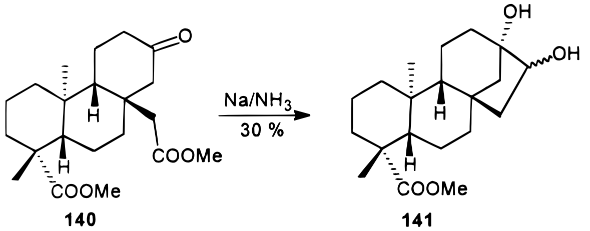
A closely related approach is the Lewis acid promoted annulation of allylsilanes developed by Trost and Coppola,[81] allowing the facile obtention of bridged methylene cyclopentanols. In an elegant approach to bicyclo[5.3.1]undecyl system of taxane, the cornerstone transformation involves the fragmentation of tricyclic hydroxy sulfone **137** obtained by Lewis acid initated intramolecular cyclization of allylsilane **136**.[82]



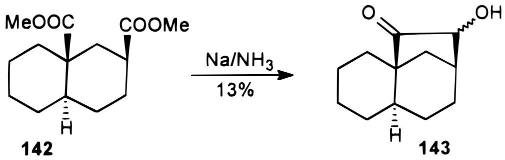
Photoreductive cyclization of δ,ϵ-unsaturated ketones was shown to be a powerful method for the synthesis of bicyclic cyclopentanols and could also be used for the formation of hydroxy bridgehead bicyclo[3.2.1]octanol **139** from the simple cyclohexanone **138**.[83]



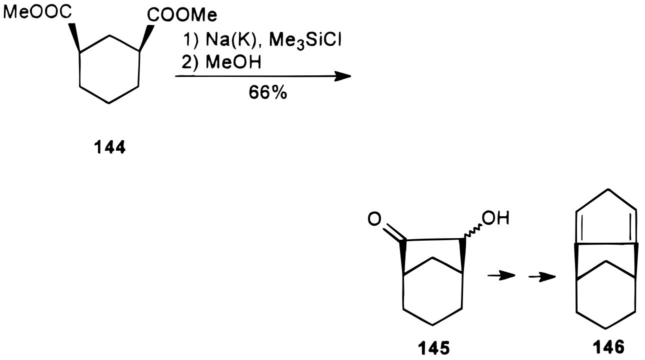
Other reductive cyclizations such as acyloin condensation and pinacolic reaction have also been applied successfully to natural product synthesis. For example the first preparation of steriol[84] was based on the reduction of keto diester **140** with sodium to give diols **141**, precursors of the natural target.



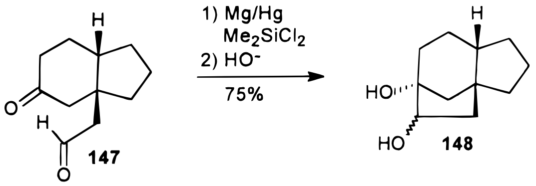
In 1961,[85] an approach based on the cyclization of diesters reported poor results during the transformation of **142** to **143** with sodium in liquid amonia.



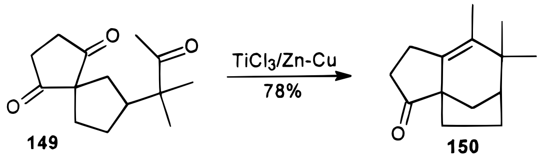
However, synthetically useful yields were obtained six years later by Russell's group[86] using sodium–potassium alloy. Very recently, Paquette and Hickey[87] have applied these acyloin cyclization conditions to **144** for the preparation of strained bicyclo[3.2.1] olefin **146**, through **145**, the latter obtained in 66% yield.



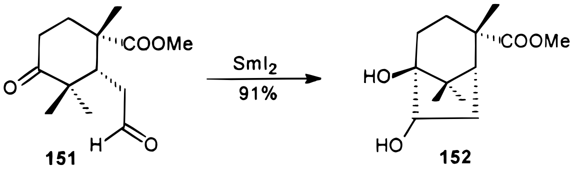
A more recent general route is the pinacolic reaction of keto aldehydes which has been extensively studied by Corey's group.[88−90] Model studies were conducted with bicyclic ketone **147** which underwent a facile reductive cyclization when exposed to a mixture of magnesium amalgam and dimethyldichlorosilane to furnish diols **148** after alkaline desilylation. A more detailed investigation showed the usefulness and the generality of a new Ti(II) reagent generated by reaction of $TiCl_4$ and amalgamated magnesium for the construction of the D-ring of gibberellins,[89] which was subsequently applied in the first total synthesis of gibberellic acid.[90]



McMurry coupling is also a powerful method to form carbon−carbon bonds from dicarbonyls and was used intramolecularly in the last step of the synthesis of (±)-isokhusimone **150** from triketone **149**.[91]



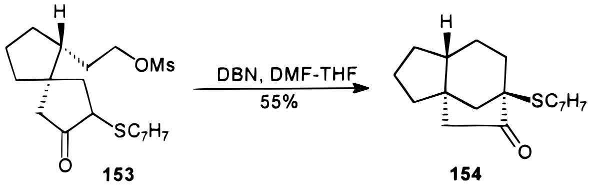
More recently, utilization of SmI$_2$-mediated reductive pinacol coupling of chiral keto aldehyde **151** was presented during an elegant synthesis of optically homogeneous bicyclo[3.2.1]octanone **152**, an A-ring bulding unit of taxoids.[92]



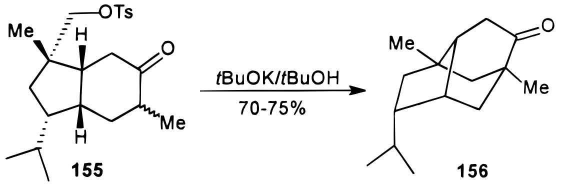
5. Alkylation-Based Methods

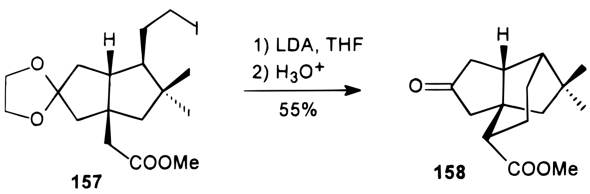
a. Ring Closures of the Three-Carbon Bridge

In the quest for new synthetic methods of general applicability, Trost and Latimer[93] developed an efficient stereocontrolled annulation of a bicyclo[3.2.1]octane onto a cycloalkanone. Their strategy involved a base-catalyzed cyclization of spiro ketone **153** to the expected tricyclic nucleus **154** bearing a synthetically useful bridgehead sulfur atom.

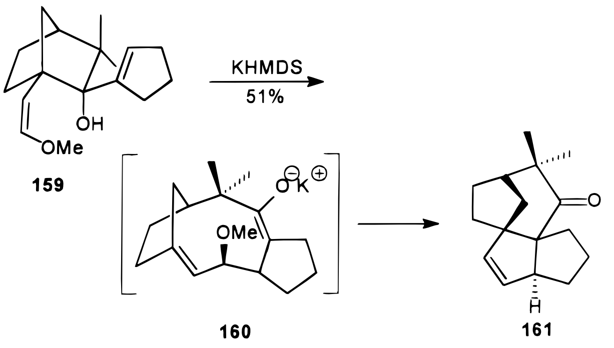


A total synthesis of 9-isocyanopupukeanane reported by Corey and collaborators[94] was based on a closely related approach, also used more recently by Chang's group,[95] which involved cyclization of keto esters **155** to give the desired tricyclic carbon skeleton **156**. Similarly, the ABC rings of quadrone, were built up through the cyclization of iododiquinane **157** to **158**.[96]



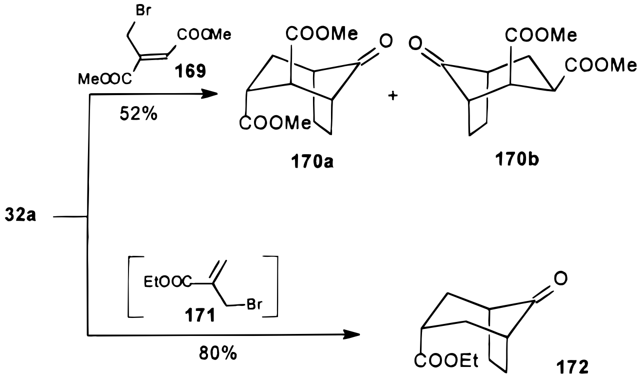


An interesting intramolecular S$_N$′ displacement of an allylic ether was reported by Paquette and coworkers[97] for the construction of complex tetracyclic ketone **161**. The enolate anion intermediate **160**, produced via [3,3] sigmatropic electron reorganization of hydroxydiene **159** is trapped by the allylic ether also generated by the rearrangement to give a 51% yield of **161**.

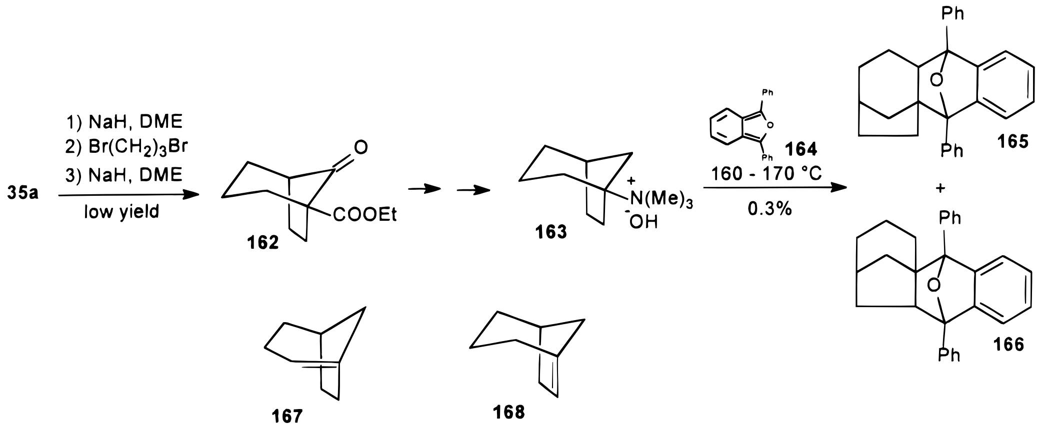


Another related method is the α,α′-dialkylation of carbonyl derivatives such as keto esters and more particularly cyclic enamines. For example, the preparation of strained bicyclo[3.2.1]oct-1-enes[98] was approached using the sequential cycloalkylation of 2-carbethoxycyclopentanone (**35a**) with 1,3-dibromopropane. The bicyclic ketone **162** was further transformed to the quaternary ammonium hydroxide **163** which upon pyrolysis in the presence of 1,3-diphenylisobenzofuran **164** gave a very low yield of Diels−Alder adducts **165** and **166** (Scheme 1). These results constitute the first experimental evidence of the transient formation of highly strained bridgehead alkenes **167** and **168**.

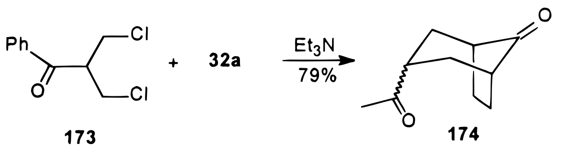
Synthetically more useful is the α,α′-annulation of cyclic ketones by tandem dialkylation of enamines. It was first reported in 1966 by Nelson and Lawton[99] in the case of dimethyl γ-bromomesaconate (**169**) and the pyrrolidine enamine of cyclopentanone (**32a**) which gave bicyclic keto diesters **170** in 52% yield. These authors found it beneficial to change bromo ester **169** for in situ generated α-(bromomethyl)acrylate (**171**) which was trapped by enamine **32a** to give the expected bicyclo[3.2.1]octanone **172** in 80% yield. The overall condensation generally follows a pathway including *C*-alkylation and proton transfer to re-form an enamine trapped by intramolecular Michael addition.



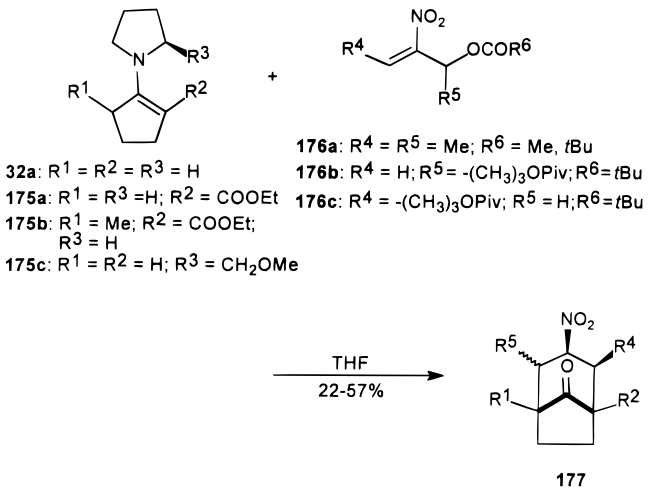
Scheme 1



After these pioneering studies, Stetter and collaborators[100] extended this original tandem cycloalkylation to 2,2-bis(chloromethyl)acetophenone (**173**) producing diketone **174** in good yield, which has been involved recently in the preparation of potential chiroptical triggers.[101]



These annulation techniques have been greatly improved by taking advantage of the reactivity of nitroallylic esters[102] and allylic sulfones[103] toward enamines. In 1990, Seebach's group[10] presented a new general and stereoselective [3+3] carbocyclization of enamines **32a** and **175** with allylic nitroacetates and pivalates **176** to give nitro ketones **177**. The method allows the formation of up to six new stereogenic centers with high diastereochemical control. Independently and almost simultaneously, Gravel and Lapierre[104] described closely related results using enamine **175a** and pivalates **176b** and **176c**. Interestingly, employing (*S*)-prolinol-derived enamine **175c** and nitroacetate **176a** resulted in the obtention of the corresponding bicyclic product in 40% yield and 90% ee.



32a: $R^1 = R^2 = R^3 = H$

175a: $R^1 = R^3 = H$; $R^2 = COOEt$

175b: $R^1 = Me$; $R^2 = COOEt$; $R^3 = H$

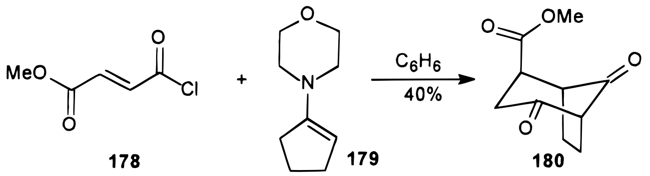
175c: $R^1 = R^2 = H$; $R^3 = CH_2OMe$

176a: $R^4 = R^5 = Me$; $R^6 = Me$, *t*Bu

176b: $R^4 = H$; $R^5 = -(CH_3)_3OPiv$; $R^6 = t$Bu

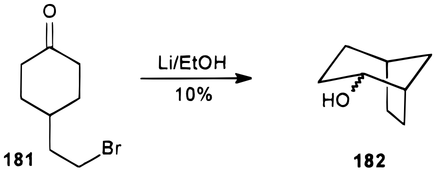
176c: $R^4 = -(CH_3)_3OPiv$; $R^5 = H$; $R^6 = t$Bu

Finally, in a recent publication, Butkus and Bielinyte[105] have shown that fumaric acid monomethyl ester chloride (**178**) constitutes a similar cycloannulating agent which enables the conversion of morpholine enamine **179** to bicyclic diketone **180**.

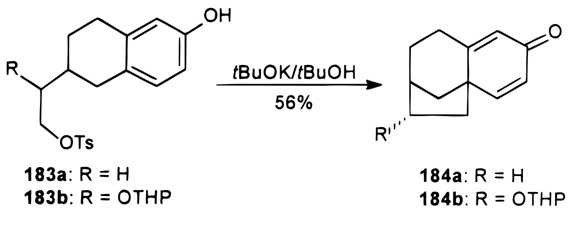


b. Ring Closures of the Two-Carbon Bridge

Newman and Yu[106] showed in 1952 that reaction of lithium with bromocyclohexanone **181** gave, albeit in low yield, bicyclo[3.2.1]octanol **182** instead of the expected [2.2.2] skeleton. After this first observation, nucleophilic intramolecular displacements leading to the formation of the two-carbon bridge have been successfuly exploited for synthetic purposes and some elegant syntheses of complex natural products were reported.



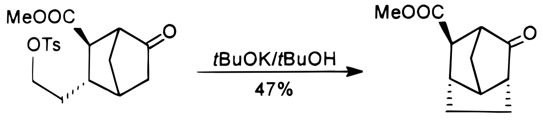
For example, an ingenious sequence involving a base-initiated cyclization of phenol tosylates **183** allowed the construction of tricyclic ketones **184** and constituted a important new entry into the synthesis of kaurene, garryine and atisine,[107] and hinesol.[108]



183a: R = H
183b: R = OTHP

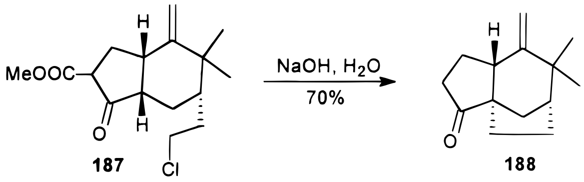
184a: R = H
184b: R = OTHP

Utilization of enolates generated from structurally advanced intermediates has been incorporated in numerous synthetic schemes and constitutes a decisive step for the construction of gibberellin framework[3] and other natural and unnatural derivatives. For example, the tricyclic keto ester **186**, incorporating a bicyclo[3.2.1]octane backbone, could be conveniently obtained, by intramolecular alkylation, from tosylate **185**.[109]

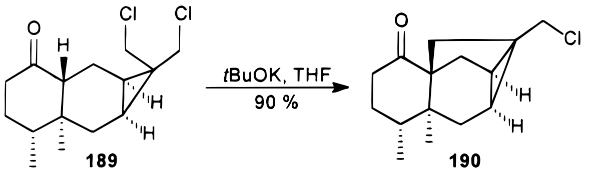


185 **186**

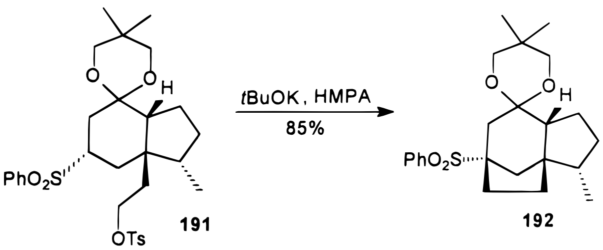
Subsequently, this intramolecular enolate displacement was employed successfully for the total synthesis of zizane sesquiterpenes.[110] These approaches are illustrated by the transformation of the enantiomerically pure chloroindanone **187** to (−)-khusimone **188**. Similarly, the first synthesis of ishwarone was completed by intramolecular alkylation of the enolate derived from tricyclic ketone **189** which gave a 90% yield of the expected tetracyclic intermediate **190**.[111] Also of interest is the intramolecular alkylation of the anion derived from bicyclic sulfone **191** which affords **192**, a precursor of zizaene.[112]



187 **188**

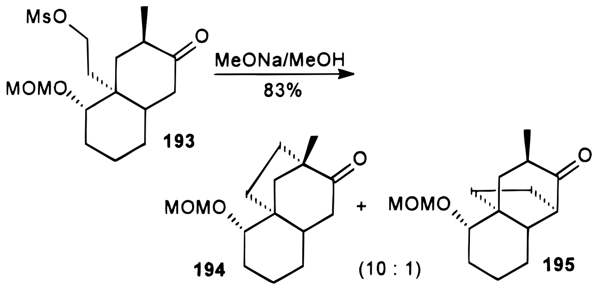


189 **190**

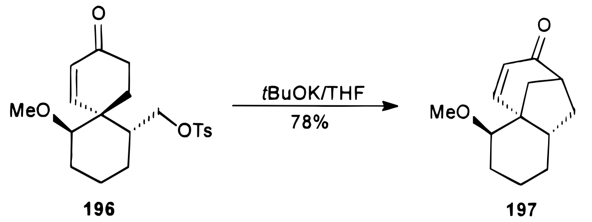


191 **192**

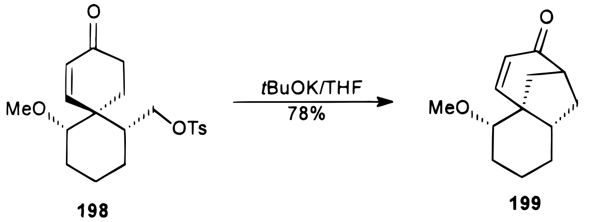
More recently, the intramolecular alkylation of keto mesylate **193** giving rise to the tricyclic BCD core of scopadulan diterpenes was reported by Ziegler and Wallace.[113] A highly regioselective enolate formation gives a 10:1 mixture of ketones **194** and **195** in 83% yield. A closely related approach is a facile access to aphidicolane and stemodane BCD ring systems **197** and **199** starting from spiro cyclohexenones **196** and **198**,[114] which was applied recently to the construction of phenolic analogues of aphidicolin.[115]



193 **194** **195**



196 **197**



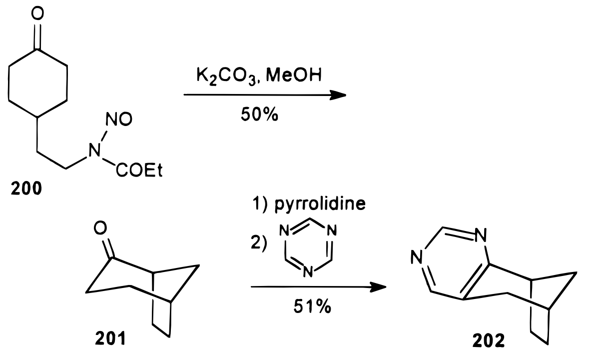
198 **199**

6. Carbenoid-Based Methods

Basically, carbenoid intermediates can react either by addition to an unsaturation or by insertion into a C−H bond. Well-known illustrations of the first reactivity are the Tiffeneau-like[116] ring enlargement or the tandem cyclopropanation/selective ring cleavage.

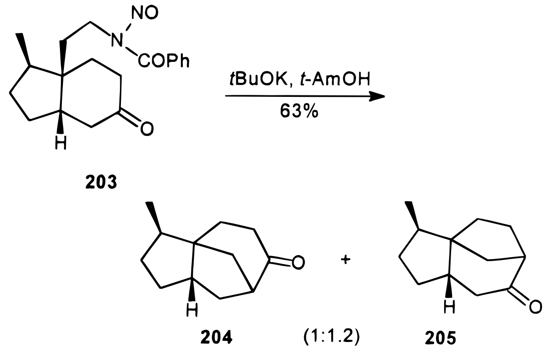
a. Tiffeneau-like Ring Enlargements

In 1963, Gutsche and collaborators[117] developed the ring enlargement approach to the construction of the bicyclo[3.2.1]octane skeleton. The base-catalyzed decomposition of *N*-nitroso amide **200** resulted in spontaneous cyclization and rearrangement to give the corresponding bicyclooctanone **201**, which was used to prepare the tricyclic pyrimidine **202**.[118]



200 **201** **202**

A few years later, this cyclization was exploited as the cornerstone of the synthesis of veatchine alkaloids[119] and more recently, the cyclorearrangement of homochiral hydroindanone **203** to a mixture of two isomeric ketones **204** and **205** in a 1:1.2 ratio, constituted the crucial step in the first total synthesis of (−)-prezizaene and (−)-prezizanol.[120]

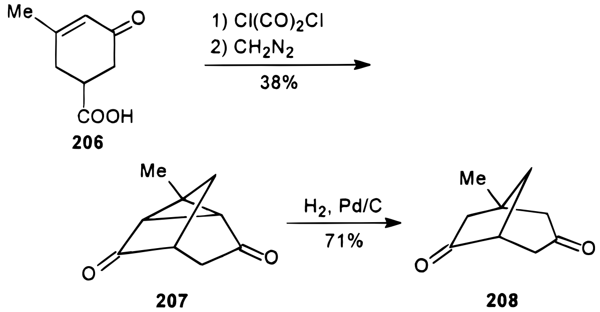


203

204 **205**

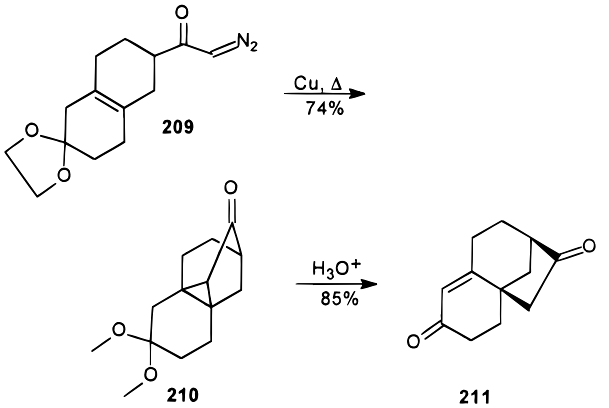
b. Tandem Cyclopropanation/Ring Cleavage

The intramolecular tandem cyclopropanation/selective ring cleavage of double bonds also constitutes a straightforward method with important synthetic developments. For example in 1965, Loewenthal and Becker[121] showed that internal addition of α-ketocarbene derived from cyclohexenone **206** gave tricyclic diketone **207** which upon catalytic hydrogenation furnished the bicyclo[3.2.1]octanedione **208** in 27% overall yield. Subsequently, Mander and co-workers[122] reported the acidic cleavage of tetracyclic ketone **210** obtained by intramolecular cyclopropanation of **209**, as a new entry to tricyclic structures such as **211**, found in numerous natural targets.



206

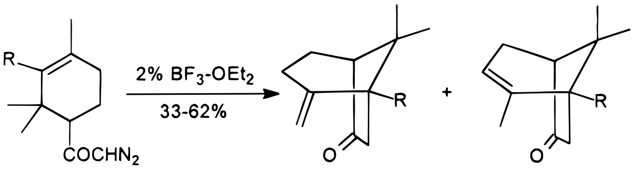
207 **208**



209

210 **211**

A few years later, it was found by Erman and Stone[123] that Lewis acids were able to catalyze intramolecular addition of diazo ketones to an isolated double bond, leading directly to bicyclo[3.2.1]-octenones without isolation of cyclopropyl intermediates. The key step in the elegant total synthesis of the α-patchoulane class of sesquiterpenes is representative of this new reactivity. The reaction of diazocyclohexenones **212** with $BF_3{\cdot}OEt_2$ afforded a mixture of bicyclic enones **213** and **214** in which the desired synthetic precursor **214b** prevailed largely.

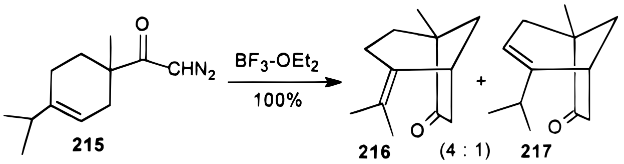


212a: R = H
212b: R = COOEt

213a: R = H
213b: R = COOEt

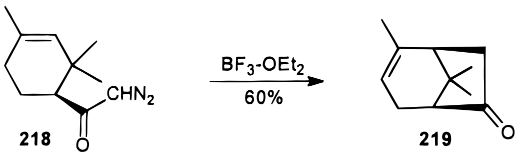
214a: R = H
214b: R = COOEt

A similar result was reported subsequently by Mander and co-workers[124] with the high yield, regioselective, $BF_3{\cdot}OEt_2$-induced cyclization of **215** to a 4:1 mixture of **216** and **217** used in the synthesis of (+)-14-norhelminthosporic acid derivatives.



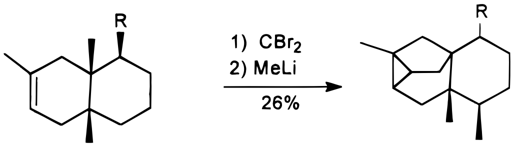
215 **216** **217**

Since these pioneering observations, intramolecular cyclization of unsaturated diazoketones has attracted considerable attention. Both aryl and isolated olefins were exploited by Mander's and Ghatak's groups during studies directed toward the development of new strategies for the construction of gibberellins[3] and stachane diterpenes.[125] Very recently, optically pure bicyclo[3.2.1]octanone **219**, a potential precursor of taxoids, was easily prepared from $BF_3{\cdot}OEt_2$-promoted cyclization of diazoketone **218**.[126]



218 **219**

A closely related strategy is the unique tandem dibromocarbene addition/selective C−H bond insertion reported by Cory and McLaren[127] in 1977 and successfully applied to the total synthesis of ishwarane **221a** and ishwarone **221b** from octalins **220a** and **220b**, respectively.

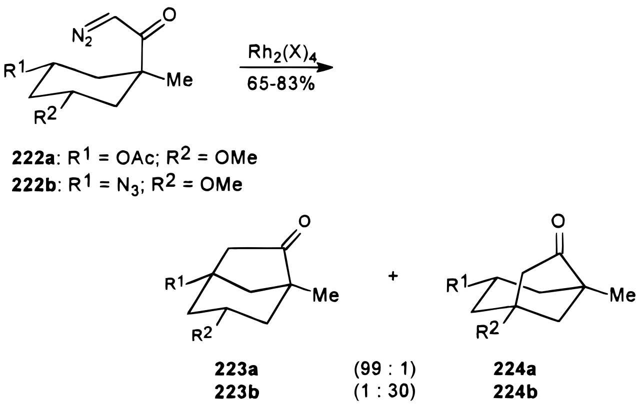


220a: R = H
220b: R = O=

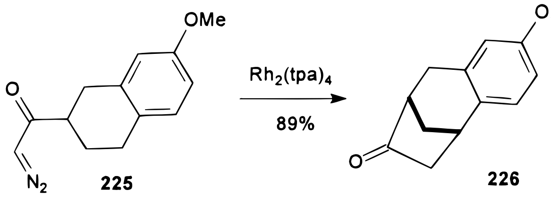
221a: R = H
221b: R = O=

c. C–H Insertions

A complete study from Adams and Wang[128] devoted to stereoelectronic effects in rhodium(II)-mediated carbenoid C−H insertion reactions appeared recently in the literature. These authors have shown that the method could be applied to the regioselective formation of bicyclo[3.2.1]octane frameworks depending on the substitution pattern. For example, diazocyclohexane **222a** gives almost exclusively bicyclooctanone **223a** while **222b** affords **224b** as the major compound under the same conditions. A rationalization of the observed regioselectivity is that electron-donating groups α to the C−H bond promote the insertion reaction.



A synthetic application of the regioselective C−H insertion concerns the recent studies developed by Mander and collaborators[129] devoted to the synthesis of galbulimima alkaloids incorporating a [3.2.1]octane nucleus. The model study[130] directed to the construction of the tricyclic ketone **226** showed the feasibility of the approach. The reaction proceeded in good yield when the diazo precursor **225** was treated with $Rh_2(tpa)_4$.

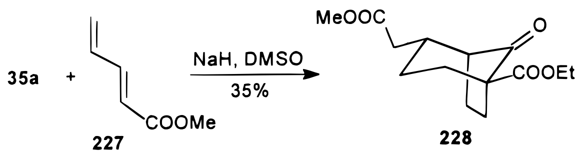


7. Michael Addition-Based Methods

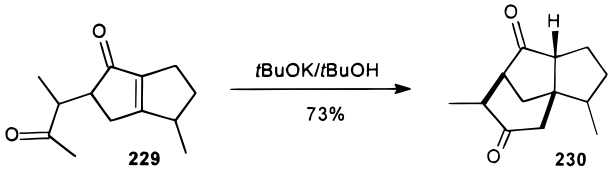
The Michael reaction is one of the most widely utilized approaches for C−C bond formation and finds numerous important applications for the construction of polycyclic ring systems.

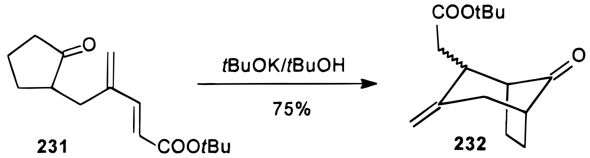
a. Ring Closures of the Three-Carbon Bridge

In 1968, Danishefsky and co-workers[131] reported a new route to functionalized bridged ring systems based on a tandem inter−intramolecular Michael addition. Carbethoxycyclopentanone (**35a**) gave 35% yield of bridgehead β-keto ester **228** by a route involving 1,6-conjugate addition to diene ester **227** followed by intramolecular Michael cyclization.

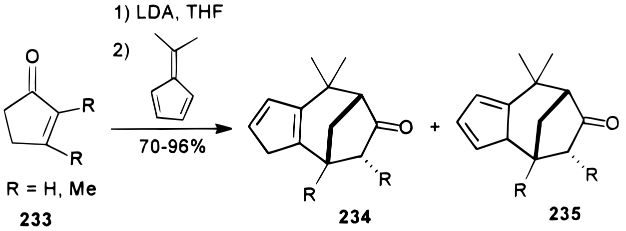


Also of synthetic interest is the facile construction of the bicyclo[3.2.1]octane nucleus found in cedrene by using an intramolecular Michael reaction of 1,4-diketone **229**, leading to the tricyclic carbon backbone **230** of the natural product.[132] More recently, intramolecular Michael carbocyclization of the dienic cyclopentanone **231**, proved to be a quite facile access to bridged bicyclic ketone **232**.[133]



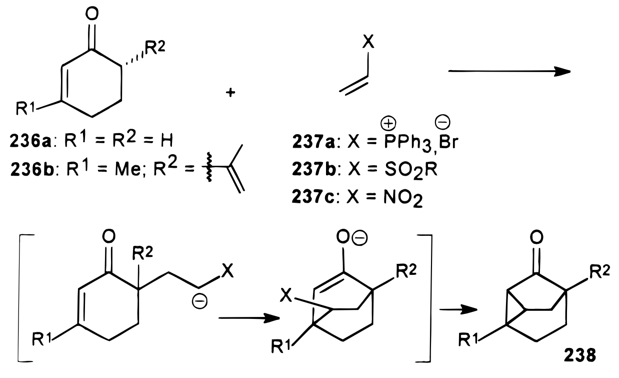


Double Michael reactions have found important synthetic applications[134] and very recently Hong[135] reported a sequential addition of dienolates derived from cyclopentanones **233** to fulvene for the rapid access to tricyclic structures **234** and **235** found in the isobarbatene family.

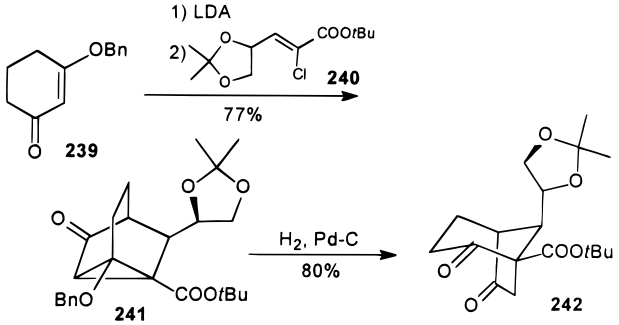


b. Ring Closures of the Two-Carbon Bridge

Bicycloannulation of 2-cyclohexenone (**236a**) based on the double Michael addition/substitution principle with acceptors such as vinylphosphonium bromides **237a**, vinyl sulfones **237b** and nitroolefins **237c**, found interesting synthetic applications as a result of extensive work from Cory's group.[136] This elegant method allows for the facile one-pot construction of [3.2.1.0^{2,7}] tricyclic carbon frameworks **238**, which can also be regarded as strained bicyclo[3.2.1]octane nuclei. Successfully applied to the stereoselective synthesis of trachyloban-19-oic acid, this strategy was used more recently as a divergent approach to patchouli sesquiterpenes from (−)-carvone (**236b**).

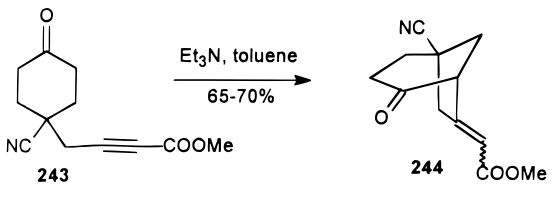


Acrylic esters bearing a halogen atom at the 2-position also served nicely as acceptors toward dienolates giving a similar stepwise bicycloannulation.[137] A recent example is the preparation of enantiomerically pure **242** from the selective cleavage of tricyclic intermediate **241** obtained by condensation of cyclohexenone **239** with chloro ester **240**.[138]



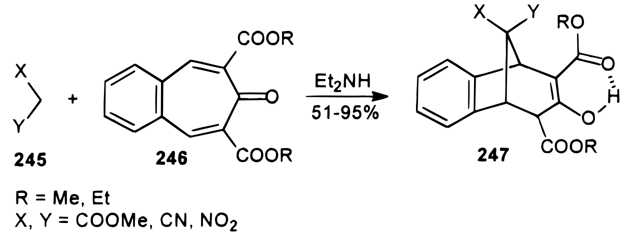
Besides these direct synthetic applications, the strained [3.2.1.0^{2,7}] tricyclic framework constitutes an easily accessible precursor of bicyclo[3.2.1]octanes by selective cleavage of cyclopropyl bonds (illustrative examples of this reactivity are shown in section III.6). This interesting behavior has led to the development of a powerful new method based on a sequential Michael–substitution–fragmentation reaction which will be presented in section VI of this review (see section VI.1).

As in the case of activated alkenes, 1,4-additions of carbanions to activated alkynes have found interesting applications. For example, the first fully stereocontrolled synthesis of (±)-hirsutic acid, reported by Trost and collaborators[139] involves, as its crucial step, an intramolecular Michael reaction of keto acetylenic ester **243**, leading to the key bicyclic intermediate **244** in good yield. A closely related result was reported more recently in the alkene series.[140]



c. Ring Closures of the One-Carbon Bridge

The double conjugate addition of activated methylene groups such as **245** to benzocycloheptadienone dicarboxylate **246** was reported and studied in detail by Föhlisch's group[141] as a pratical access to bicylo[3.2.1]octanes **247** by ring closure of the methano bridge.

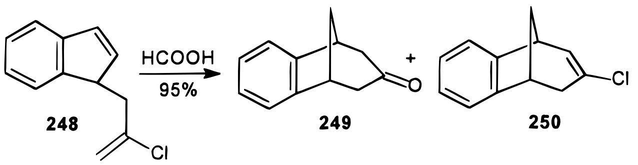


8. Carbocation-Based Methods

Carbocations are versatile reactive intermediates with a wide range of synthetic applications. Moreover, sequences involving cationic reactions are featured in the biosynthesis of important natural products and synthetic organic chemists have frequently used this type of biomimetic approach for the construction of complex polycyclic systems.

a. Ring Closures of the Three-Carbon Bridge

A synthetically valuable utilization of carbocations is intramolecular trapping by an olefin. This tandem cation–alkene cyclization was first reported by Lansbury and Nienhouse[142] as a new versatile synthesis of bridged cyclic ketones and has found numerous synthetic applications. The solvolytic cyclization of indene **248** proceeds in almost quantitative yield by closure of the propano bridge to give a 2:1 mixture of bicyclic ketone **249** and vinyl chloride **250**.

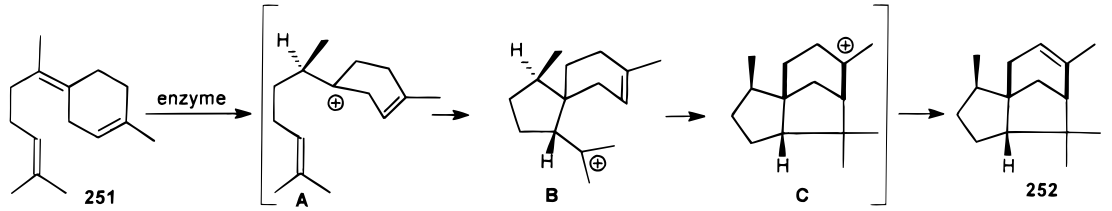


b. Ring Closures of the Two-Carbon Bridge

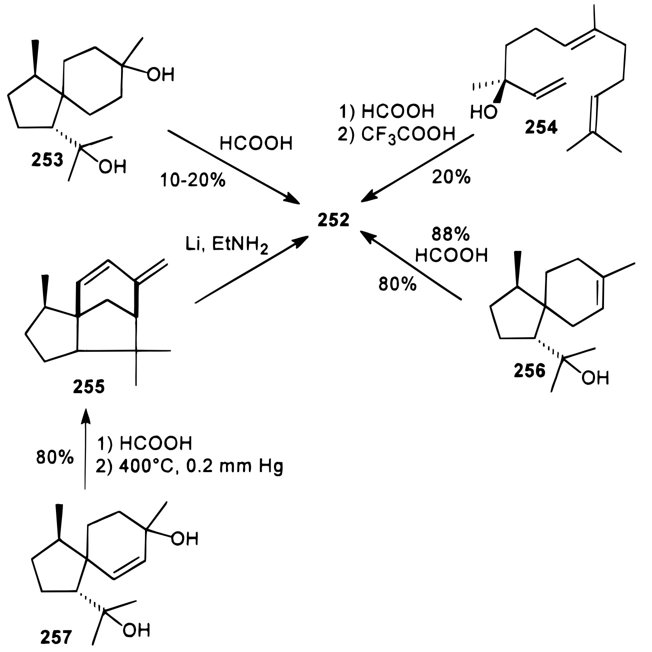
Examination of the proposed biosynthesis of cedrene (**252**, Scheme 2)[143] from bisabolene (**251**) through a cation–alkene carbocyclization sequence involving intermediates **A**–**C** has stimulated a broad synthetic interest from different research groups.

Two biogenetic-type syntheses of cedrene were reported in 1969 respectively from Corey's[144] and Lawton's[145] groups. Both approaches are based on the generation and the intramolecular cyclization of a spiro-carbocation intermediate of type **B**, giving the expected tricyclic skeleton. In the first synthesis, exposure of diol **253** to anhydrous formic acid produces a mixture of hydrocarbons from which pure **252** can be isolated, but with no more than 20% yield. A more efficient access involves spiro-enediol **257** which leads to **252**, through tricyclic diene **255** in 80% yield. Alternatively, Lawton[4] and a few years later Lansbury[146] developed original approaches to unsaturated alcohol **256** which cyclizes very efficiently to give cedrene **252** in 80% yield when dissolved in 88% formic acid. Finally, a chemical simulation of the biogenesis of cedrene **252** was demonstrated in

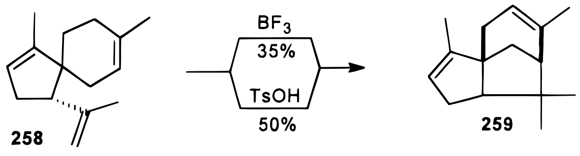
Scheme 2



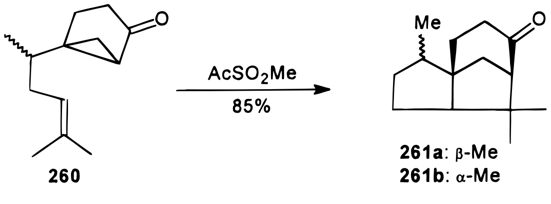
1972[147] by the acid-catalyzed biogenetic-like cyclization of nerolidol (**254**).



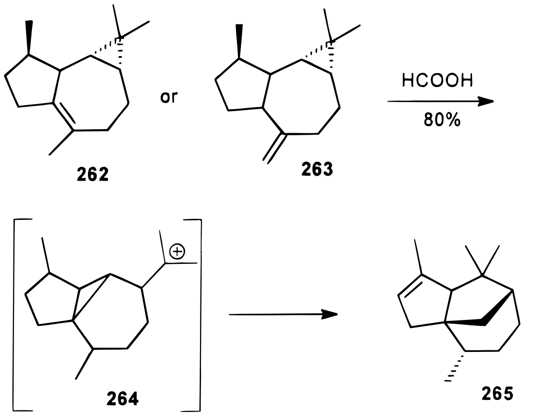
Subsequent to these pioneering studies, Demole and collaborators[148] reported the BF$_3$-catalyzed cyclization of β-acoratriene (**258**) to 2,8-cedradiene (**259**) in 35% yield which can be improved by using catalytic amount of *p*-TsOH.[149]



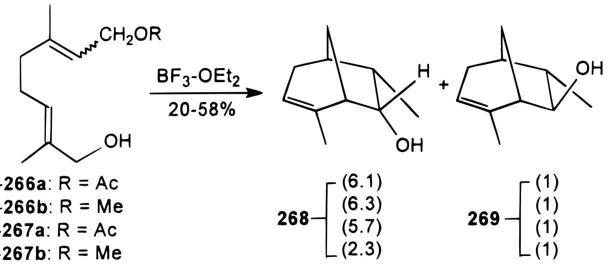
Further studies from Corey and Balanson[150] have shown the facile synchronous double annulation of the cyclopropyl ketones **260** to give a mixture of cedrone (**261a**) and epicedrone (**261b**) upon exposure to an excess of acetyl methanesulfonate.

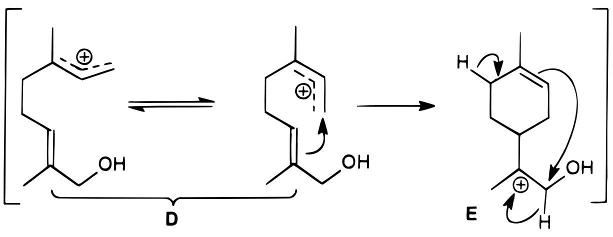


Very recently, it has been shown that ledene (**262**) and aromadendrene (**263**), when boiling in formic acid, cleanly rearranged to the tetracyclic olefin **265** in 80% yield[151] through a common tricyclo[5.3.0.0^{2,7}]decane cationic intermediate **264**.

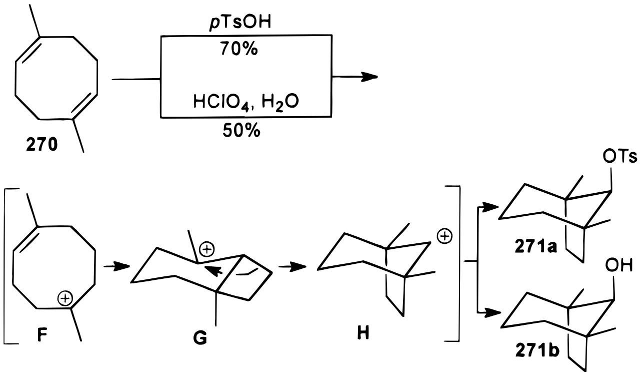


Another interesting cationic cascade bicyclization was reported more recently during a study directed toward chemical transformation of terpenoids.[152] Bicyclo[3.2.1]octanols **268** and **269** can be isolated in moderate yields from the reaction mixture of 10-hydroxygeraniol and 10-hydroxynerol derivatives **266** and **267** with BF$_3$·OEt$_2$. The transformation involves the cyclization of allylic cation intermediates **D** to the cyclohexenyl carbocation **E** which undegoes hydride shifts to yield the observed bicyclic derivatives.

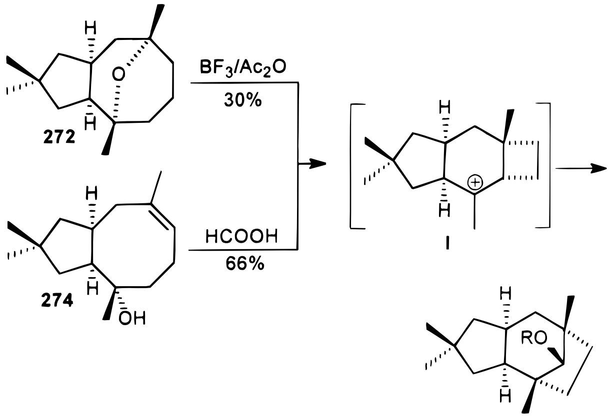




Transannular reactions with cationic rearrangements also abound in nature and have been studied as biomimetic routes to some natural and unnatural compounds. For example, it was shown that 1,5-dimethyl-1,5-cyclooctadiene (**270**) could be easily converted to bicyclo[3.2.1]octanol derivatives **271**, through the reactive cations **F**, **G**, and **H**, by reaction with *p*-TsOH or aqueous $HClO_4$, respectively.[153]

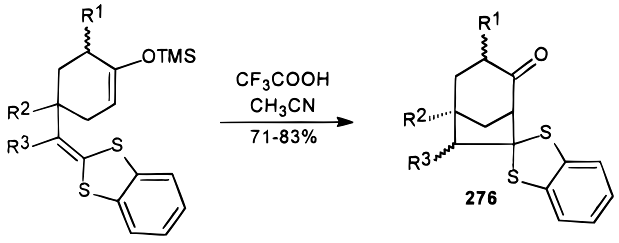


Similarly, treatment of tricyclic ether **272** by BF_3·OEt_2 in Ac_2O or formolysis of unsaturated alcohol **274** afforded respectively tricyclic derivatives **273** through a common protoilludyl cation **I** related to **G**.[154]



273a: R = Ac
273b: R = CHO

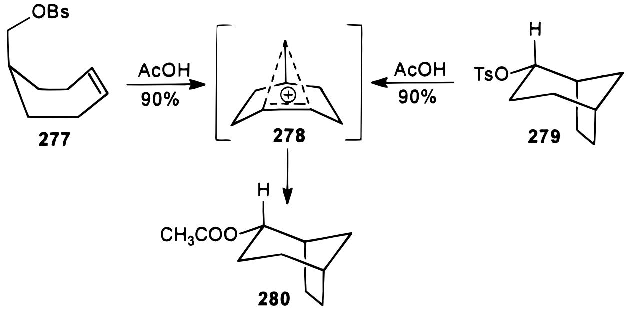
A more sophisticated but elegant approach to highly functionalized bicyclo[3.2.1]octane ring systems involving the intramolecular 1,3-benzodithiolium ion mediated cyclization onto enol ethers was reported by Rigby and Kotnis.[155] Exposure of the key ketene dithioacetals **275** to CF_3COOH resulted in the expected ring closure to provide the corresponding bicyclic products **276**. This new methodology is quite general and allows the construction of reasonably complex polycyclic systems even by using directly the free ketone instead of the corresponding silyl enol ether.



275a: $R^1 = R^2 = R^3 = H$
275b: $R^1 = R^3 = H$; $R^2 = Me$
275c: $R^1 = R^2 = H$; $R^3 = Me$
275d: $R^1 = Me$; $R^2 = R^3 = H$

c. Ring Closures of the One-Carbon Bridge

The first participation of a cationic intermediate in the construction of a bicyclo[3.2.1]octane skeleton was reported by Le Ny in 1960.[156] Acetolysis of brosylate **277** produced almost exclusively *endo*-bicyclo[3.2.1]oct-2-yl acetate (**280**) via the symmetrical bridged ion **278** which was also generated from *endo*-bicyclo[3.2.1]oct-2-yl tosylate **279**.[157]

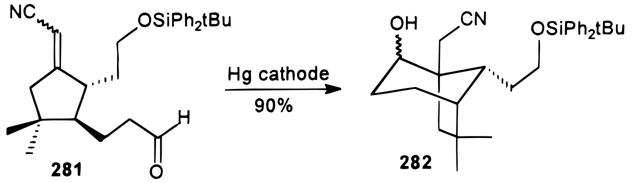


9. Free Radical-based Methods

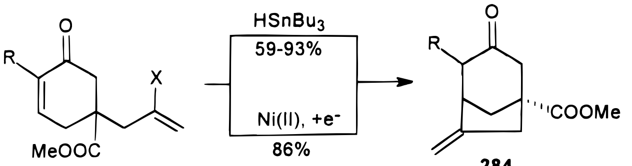
While free radicals have been well-recognized as versatile reactive intermediates for about 50 years, new reductive free radical annulation sequences of synthetic interest appeared only at the beginning of the 1980s with the pioneering work of Stork's and Beckwith's groups.[158] Besides the development of reductive radical carbocyclizations, the synthetic potential of oxidative methods have been developed more recently.

a. Reductive Methods

i. Ring Closures of the Three-Carbon Bridge. Although reductive radical carbocyclizations leading to bicyclo[3.2.1]octanes are essentially based on the formation of the ethano bridge, an elegant synthetic application of the three-carbon ring closure is Little's[159] approach to quadrone using the electroreductive ketyl–olefin cyclization of the elaborated precursor **281**. Functionalized key bicyclo[3.2.1] intermediates **282** are efficiently produced in 90% yield and transformed to quadrone in seven steps.



ii. Ring Closures of the Two-Carbon Bridge. Intramolecular addition of a vinyl radical to an activated double bond was extensively developed and successfully applied to the rapid construction of polycyclic derivatives by ring closure of the two-carbon ring. One of the first examples came from Marinovic and Ramanathan,[160] who proposed an intramolecular Michael addition of a radical to an α,β-unsaturated ketone moiety as a new carbocyclization method leading to bridged ring systems of synthetic interest. Their approach involves the formation of a vinyl radical by $HSnBu_3$-mediated homolysis of vinyl halides **283**, followed by regioselective exo cyclization to the activated double bond, leading to the expected bicyclo[3.2.1]octanone **284**. More recently, compound **284** was also obtained efficiently by using Ni(II) complex catalyzed electroreduction of **283** (R = H, X = Br).[161]

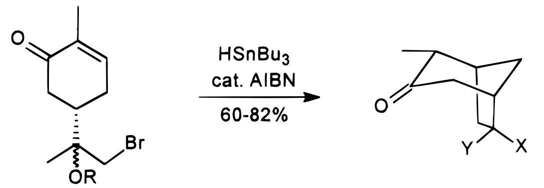


283

284

R = H, Me
X = Cl, Br, I

In the quest for a simple method for the construction of chiral bicyclo[3.2.1]octanes, Srikrishna and Hemamalini[162] have applied the intramolecular radical cyclization to α,β-unsaturated enones **285** derived from commercially available (*S*)-carvone. Upon reaction with $HSnBu_3$, these intermediates cleanly furnished a separable mixture of endo- and exo-bicyclic products **286** in good yields. Interestingly, the corresponding allylic alcohols also give good results when the reaction is performed at a lower concentration. Following this work, Berkowitz and Wilson[163] published a related approach based on the intramolecular vinyl radical addition to an allylic alcohol.

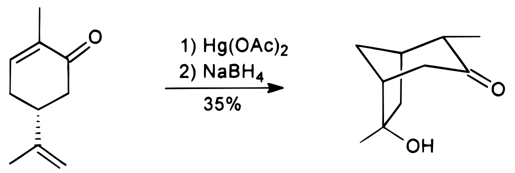


285

R = H, Me, Et, $PhCH_2$, Ac

286a: X = Me; Y = OR
286b: X = OR; Y = Me

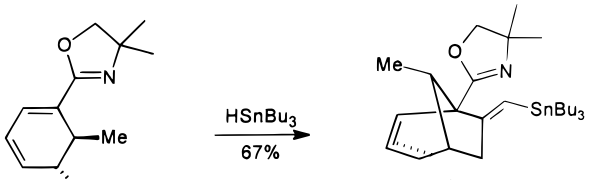
More recently,[164] an elegant asymmetric synthesis of (−)-hirsutene and (−)-3-hydroxyhirsutene involving the formation and the selective transformation of a chiral bicyclo[3.2.1]octanone was reported. Acetoxymercuration−demercuration of (*R*)−(−)-carvone (**287**) proceeds by a radical tandem cyclization to form **288** in 35% yield.



287

288

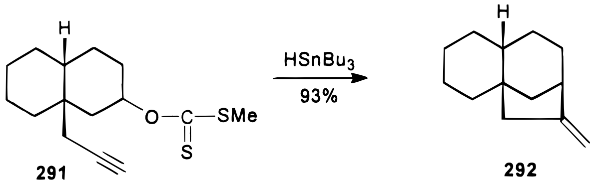
An intramolecular vinyl radical cyclization has also been proposed recently by Kuendig and Beruben[165] leading to tin containing bridged bicyclic compounds. The cyclization of **289** is initiated by a regioselective $HSnBu_3$ addition to the triple bond, giving a reactive radical intermediate, which adds to the more substituted double bond of the diene unit to form a mixture of bicyclic olefins **290** in a 65:35 ratio.



289

290

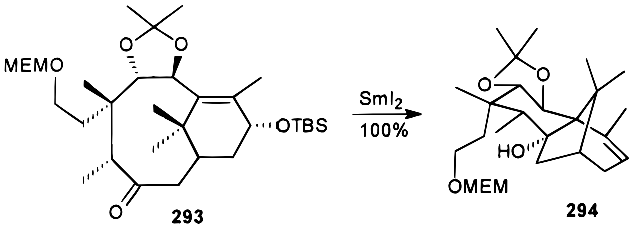
Very recently, Corey and Liu[166] have reported a new stereoselective synthetic route to the methylene bicyclo[3.2.1]octane **292**, a subunit of the kaurenoids and gibberellins. The method is based on the cyclohexyl radical addition to an unactivated triple bond by decomposition of xanthate **291** and has been applied to the enantioselective synthesis of neotripterifordin.[166b]



291

292

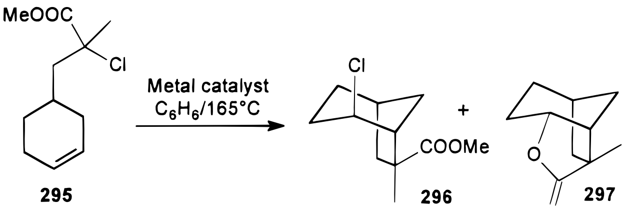
Unactivated olefinic ketones can also be cyclized efficiently to bridged bicyclic systems by SmI_2-induced intramolecular C−C bond formation. Thus, a 5-*exo*-ketyl-olefin cyclization of **293** was proposed by Holton and Williams[167] in 1988 for the elaboration of the highly functionalized tricyclic olefin **294** involved in the synthesis of taxusin. This radical ring closure, studied in more detail by Molander,[168] also constitutes the key step in a recent synthesis of (−)-grayanotoxin III.[169]



293

294

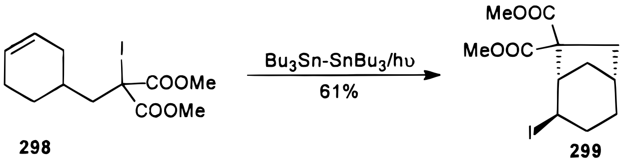
An intramolecular variant of Kharash radical cyclization catalyzed by various transition metal complexes constitutes a quite recent class of metal-templated radical reactions and has been applied to the construction of bridged carbocycles.[170] Fe(II), Ru(II) and Mo(I) are effective catalysts for the cyclization of cyclohexene **295** to a mixture of chloroester **296** and tricyclic lactone **297** in combined yields from 75% to 88%.



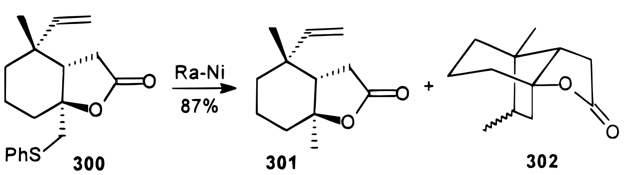
295

	296	**297**
$FeCl_2/3P(OEt)_3$	56%	32%
$RuCl_2(PPh_3)_3$	38%	37%
$[CpMo(CO)_3]_2$	57%	21%

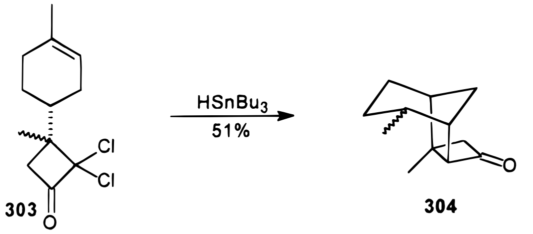
Alternatively, the atom-transfer cyclization reaction extensively studied by Curran and Chang[171] was also used successfully in the case of iodomalonate **298** to form, stereoselectively, the functionalized bicyclo[3.2.1]octane **299**, resulting from iodine abstraction by the less hindered face of the bicyclic system.



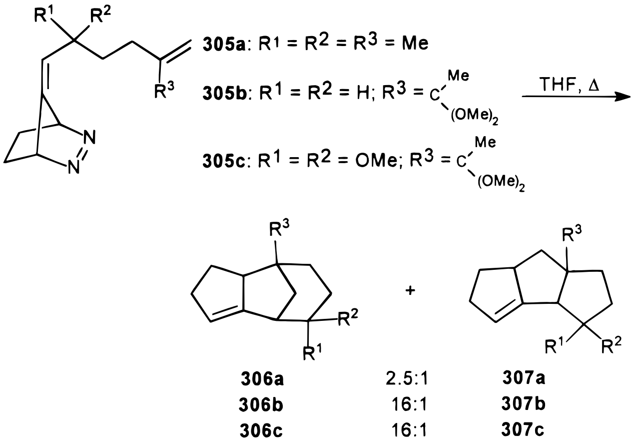
During a structural elucidation of novel lactone components isolated from the sex pheromone blend of male fruit flies, Battiste and collaborators[172] found an interesting cyclization leading to an unexpected functionalized bicyclo[3.2.1]octane. Desulfurization of *trans*-thio lactone **300** with Raney-Nickel produces (+)-anastrephin **301** as a minor product (13%) with isomeric saturated tricyclic lactones **302**. This result is in agreement with a radical cyclization to the proximate axial vinyl substituent in **300**.



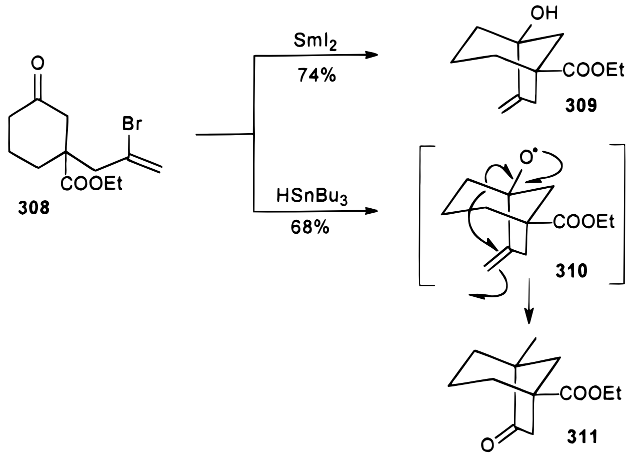
Dowd and collaborators[173] have used the free-radical annulation of dichlorocyclobutanones **303**, leading to useful fused tricyclic intermediates **304**.



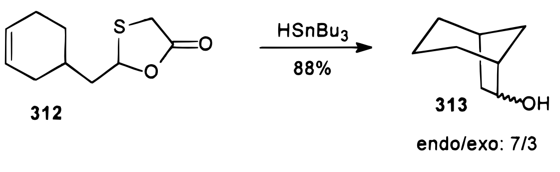
Since its discovery in 1966,[174] the trimethylenemethane diradical referred to as diyl and generated by low-temperature irradiation of 4-methylenepyrazoline, has found a quite recent synthetic development. More specifically, photochemical or thermal decomposition of bicyclic azo compounds such as **305** furnishes the corresponding cyclic diyls, which constitute powerful reactive intermediates.[175] Extensive studies from Little's group[176] have led to the development of the intramolecular trapping of diyls by a tethered double bond allowing direct access to fused or bridged polycyclic systems. For example, cycloaddition of diazene **305a** affords the bridged olefin **306a** as major product together with the linearly fused isomer **307a**. Further investigations have shown that both steric and electronic factors are responsible for the observed regioselectivity and that bridged bicyclic systems **306b**,**c** can be obtained almost exclusively by increasing steric effects.

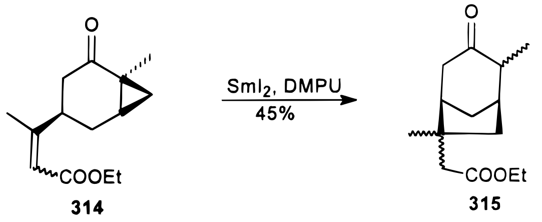


Radical cyclization to a carbonyl function was also efficiently used for the rapid construction of bicyclo[3.2.1]octane derivatives starting from simple monocyclic precursors.[177] For example, reduction of cyclohexanone **308** with SmI$_2$ leads to the expected bridged product **309**. However, with HSnBu$_3$, keto ester **311** is obtained, probably by a radical fragmentation–ring reconstitution sequence of radical intermediate **310**.



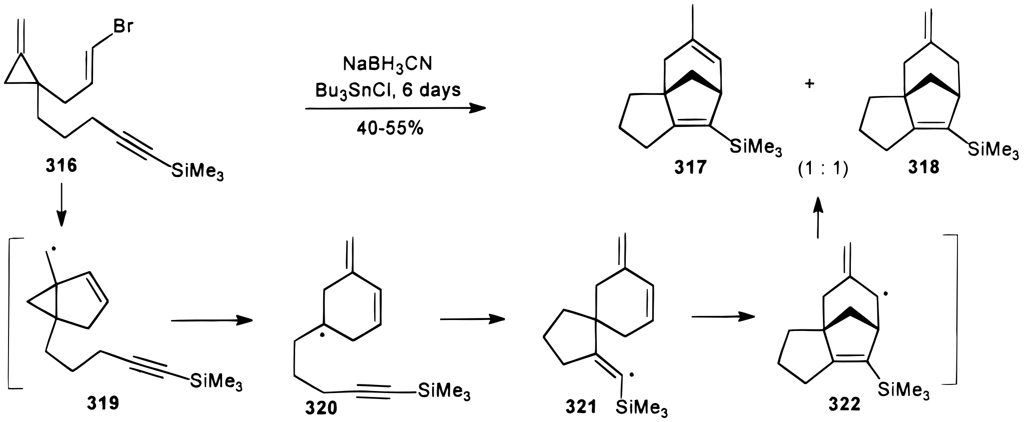
Other reductive radical carbocyclizations are involved in the construction of bicyclo[3.2.1]octane frameworks. Two interesting examples are the utilization of oxathiolanone **312** to form **313**[178] and the tandem radical ring opening–intramolecular cyclization of cyclopropyl intermediates **314** leading to **315** in acceptable yields.[179]





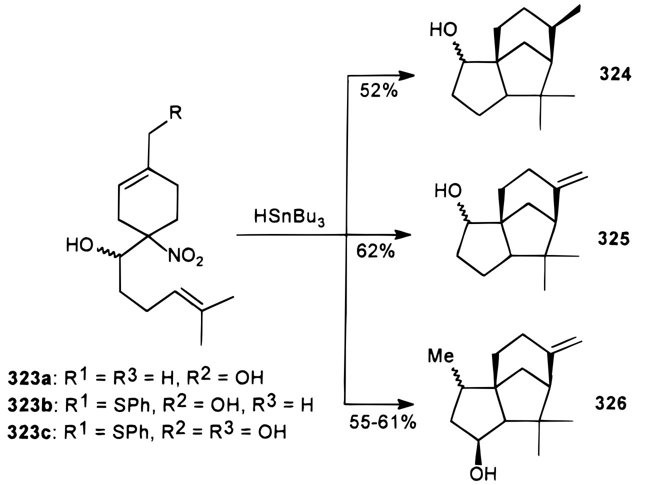
More reactive methylene cyclopropanes also constitute good candidates for cascade radical reactions.

Scheme 3

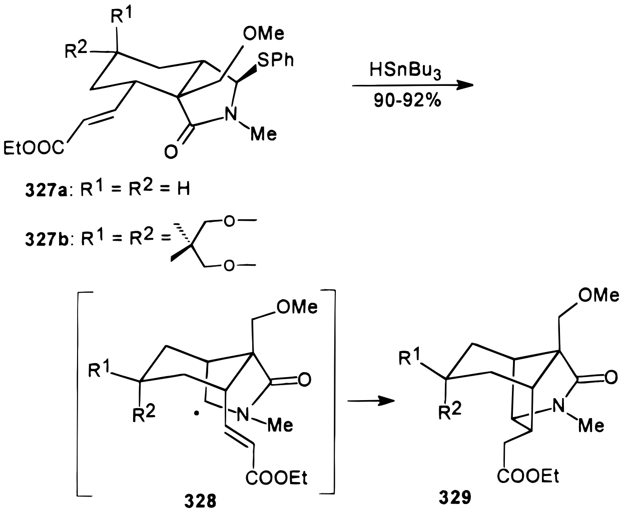


Recent work from Kilburn's group[180] showed the usefulness of such intermediates for the rapid assembly of polycyclic structures including a bicyclo[3.2.1]octane nucleus. Vinyl bromide **316** under Stork catalytic reductive conditions was very slowly consumed to give up to 55% yield of an 1:1 mixture of isomeric silyl dienes **317** and **318** (Scheme 3). The proposed mechanistic pathway involves the cyclization of the first formed vinyl radical to give **319** which rearranges to the methylene cyclohexenyl radical **320**. Intramolecular cyclization to the tethered alkyne followed by addition onto the intracyclic double bond from **321** produces the allyl radical **322**, which is then nonselectively reduced under the reaction conditions.

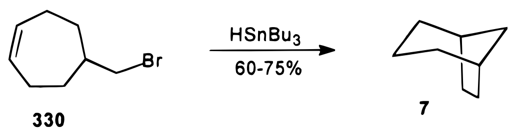
Utilization of a nitro group as precursor for radical intermediates is also well-established and has been applied recently by Chen's group[181] to the synthesis of natural compounds. Their strategy is based on the tandem radical cyclization of properly functionalized unsaturated nitrocyclohexenes **323**. Reduction of **323a** with $HSnBu_3$ gives the tricyclic alcohol **324** precursor of the Δ^2-cedrene skeleton. Similar treatment of **323b** bearing a thiophenyl substituent evolves by addition−elimination to form the *exo*-methylene derivative **325** implicated in the formal synthesis of α-cedrene. Finally, **326** obtained from cyclization of **323c** is used for the preparation of α- and *β*-biotol.



α-Acylamino radicals have found important synthetic applications since initial studies at the beginning of the 1980s. For example, extensive work from Hart and collaborators[182] has allowed a new entry into the construction of the bicyclo[3.2.1]octane substructure of gelsemine alkaloids. This approach involves an intramolecular Michael addition of α-acylamino radicals **328**, generated from α-thio lactams **327**, giving the required bridged heterocycles **329** in very good yields.



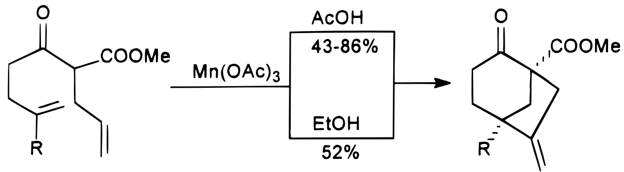
iii. Ring Closure of the One-Carbon Bridge. The simple cycloheptenylmethyl radical generated by $HSnBu_3$-promoted reduction of (bromomethyl)cycloheptene **330** is capable of cyclizing easily by addition to the isolated double bond leading to bicyclo[3.2.1]octane (**7**) in good yield.[183] Unfortunately, this efficient one-carbon ring closure found no further synthetic exploitation.



b. Oxidative Methods

Although reductive radical carbocyclizations from totally acyclic precursors for the construction of bridged bicyclic systems represent only side reactions,[184] oxidative methods, when used intramolecularly, have high synthetic values for the preparation of polycyclic systems.

Important work from Snider's group[185] contributed to the generalization of the Corey and Kang[186] Mn(III)-based oxidative tandem cyclizations for the construction of bridged polycyclic ring systems. Reaction of β-keto esters **331** with 2 equiv of $Mn(OAc)_3\cdot 2H_2O$ and 1 equiv of $Cu(OAc)_2\cdot H_2O$ in acetic acid gives an 86% yield of **332**, a fully functionalized CD ring system of gibberellic acid. Subsequently, a valuable solvent effect was observed which enables the cyclization of **331** (R = OMEM) to **332** (R = OMEM) in EtOH, when the use of AcOH failed to give any bridged compound. Further studies showed that the cascade carbocyclization could be performed with good asymmetric induction using chiral sulfoxides or 8-phenylmenthyl esters. Another synthetic advantage of this carbocyclization is the utilization of unsaturated nitriles, which give bicyclic diketones through the same radical cascade cyclization ending with the addition to the cyano group and subsequent hydrolysis.

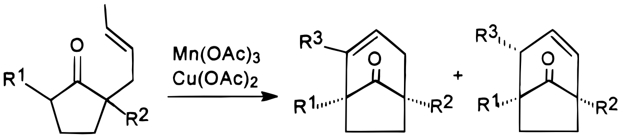


331 **332**

R = H, Me, $CH_2Si(Me)_3$, Cl, $OPO(OEt)_2$, OMEM

Following this important synthetic work, a detailed mechanistic investigation was published conjointly by the Curran and Snider groups.[187] Their results, based on a parallel study on Mn(III)-mediated oxidative cyclizations of unsaturated keto esters and atom-transfer cyclizations of the corresponding haloacetoacetates, support the conclusion that free radical intermediates, rather than Mn(III)-complexed radicals, are involved in the oxidative carbocyclization.

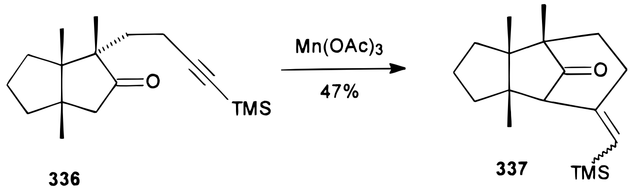
The Mn(III)-based oxidative free radical cyclization was extended to cyclopentanones α-substituted by an allylic or benzylic side chain.[188] For example, the precursors **333** are easily prepared by simple alkylation of the corresponding ketones and the cyclizations proceed smoothly to afford functionalized bicyclo[3.2.1]octenones **334** and **335**, in moderate to good yields.



333 **334** **335**

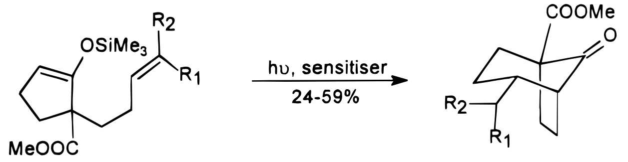
	yield (%)	
a: R^1 = H; R^2 = COOEt; R3 = H	75	15
b: R^1 = H; R^2 = COOEt; R^3 = Me	73	10
c: R^1 = Me; R^2 = COOEt; R^3 = H	41	9
d: R^1 = H; R^2 = $C_{12}H_{25}$; R^3 = H	44	7

A synthetic application based on the related oxidative cyclization of 5-hexynyl radicals has appeared recently in the literature.[189] Starting with α-substituted acetylenic ketone **336**, a seven-step synthesis of gymnomitrol is easily achieved from the key bridged tricyclic intermediate **337** obtained as a 1:1.4 diastereomeric mixture after standard cyclization in the presence of an excess of $Mn(OAc)_3$.



336 **337**

Another interesting oxidative cyclization deals with the photoinduced electron transfer (PET) of unsaturated silyl enol ethers **338** with subsequent capture of the radical intermediate to form bicyclooctanones **339** in moderate yields.[190]



338a: $R^1 = R^2$ = H
338b: $R^1 = R^2$ = Me

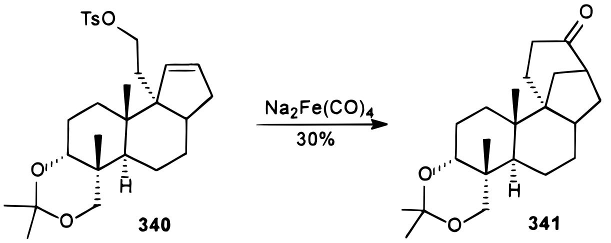
339

10. Organometallic-Based Methods

Organometallics constitute powerful tools in organic chemistry. Due to the high level of regio- and stereochemical control, transition metal promoted synthesis of complex natural and unnatural targets has found widespread development. Concerning the construction of bicyclo[3.2.1]octanes, the iron carbonyl chemistry and palladium carbocyclizations have attracted particular interest.

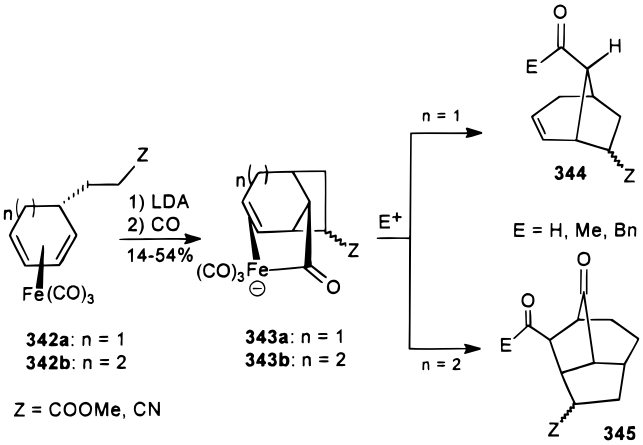
a. Iron Carbonyl Chemistry

i. Ring Closures of the Three-Carbon Bridge. Alkylative carbonylation of unsaturated tosylates is a well-known procedure for the construction of cyclic ketones[191] and an application to the elaboration of the bicyclic[3.2.1]octanone core **341** of aphidicoline from tetracyclic tosylate **340** was reported in 1979.[192]



340 **341**

ii. Ring Closures of the Two-Carbon Bridge. A new general strategy developed by Yeh and coworkers[193] is applied to the one-pot construction of functionalized bicyclo[3.2.1]octenes **344** by direct intramolecular alkylative carbonylation of (η^4-1,3-cyclohexadiene)$Fe(CO)_3$ complexes **342a** bearing a functionalized side chain. Quenching the reaction with various electrophiles allows the introduction of different functionalities at the methylene bridge. Mechanistically, the overall process is compatible with the regioselective formation of the σ,π-anionic intermediates which suffer carbonylation to the reactive acyl anions **343a**. Subsequent trapping of **343a** by an electrophile allows reductive elimination leading to the bridged bicyclic ligands **344**. Interestingly, starting with seven-membered ring iron complexes **342b**, the transformation leads to the one-pot construction of highly functionalized tricyclic stuctures **345**.[194] In this case the postulated anionic acyl iron carbonyl intermediates **343b** suffers alkylation followed by intramolecular alkene insertion into the iron−acyl bond and subsequent reductive elimination.



342a: n = 1
342b: n = 2

Z = COOMe, CN

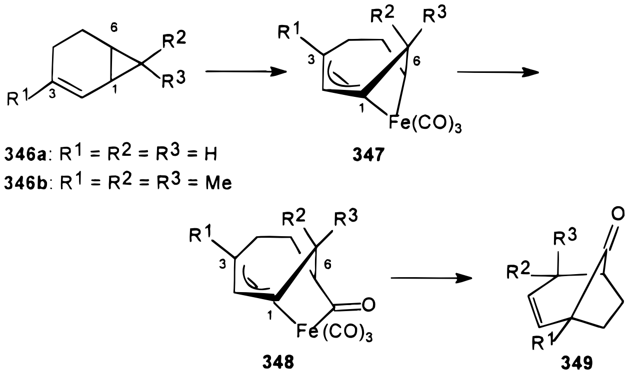
343a: n = 1
343b: n = 2

344

E = H, Me, Bn

345

iii. Ring Closures of the One-Carbon Bridge. In 1971, Moriarty and co-workers[195] reported the obtention of the first σ,π-bonded bicyclo[3.2.1]octene−Fe(CO)$_3$ complex by reaction of semibullvalene with Fe$_2$(CO)$_9$. One year later,[196] it was shown that other polycyclic structures incorporating a vinylcyclopropyl system underwent a similar rearrangement.[197] These σ-alkyl−π-allyl−iron complexes are rather stable molecules but can be easily carbonylated to give more reactive acyl intermediates, precursors, by reductive elimination, to various functionalized cyclic systems. An example of this reactivity is the transformation of bicyclo[4.1.0]hept-2-enes (**346**) to the seven-membered ring complexes **347** by selective cleavage of the C(1)−C(6) cyclopropyl bond. Carbonylation of **347** to **348** followed by regioselective reductive elimination, linked the acyl carbon to C(3) giving bicyclooctenone **349**.[198]



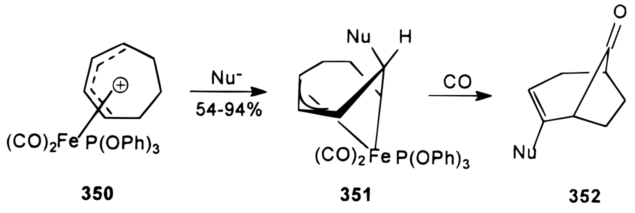
346a: R^1 = R^2 = R^3 = H
346b: R^1 = R^2 = R^3 = Me

347

348

349

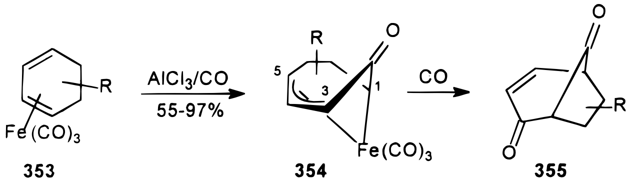
Another direct access to these reactive σ,π-bonded cycloheptene iron complexes is based on the regioselective nucleophilic hydride addition to η^5-cycloheptadienyl iron cations. Recently, Eilbracht and Hirschfelder[199] have shown that the regioselectivity of the nucleophilic addition can be affected by the replacement of one CO ligand by a weaker π-acceptor such as phosphine or a phosphite. For example, treatment of **350** with selected organometallic carbanions or NaCN resulted in the exclusive formation of **351** allowing for the preparation of various functionalized bridged bicyclic ketones **352** in good yield and with high selectivity.



350 **351** **352**

Nu = H, Me, Ph, Mesityl, 2-(OPh)-Ph, CN, Ph—C≡C, Bu—C≡C

AlCl$_3$-promoted carbonylative ring enlargement of tricarbonyl(cyclohexadiene)−iron **353** to keto−iron complexes **354** is also a well-established approach. The first report of this reactivity is due to Lewis' group[200] and concerns the facile preparation of bicyclo[3.2.1]oct-3-ene-2,8-dione (**355**, R = H). Generalization of this tandem double carbonylation to a series of functionalized 1,3-cyclohexadienes was reported, later, by Eilbracht and collaborators[201] as a new regioselective synthesis of bridged bicyclic ketones.

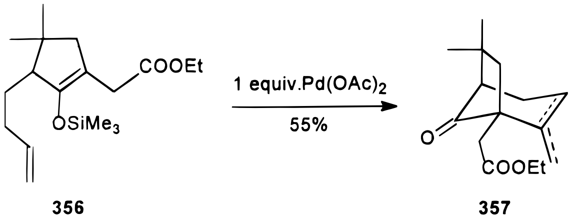


353 **354** **355**

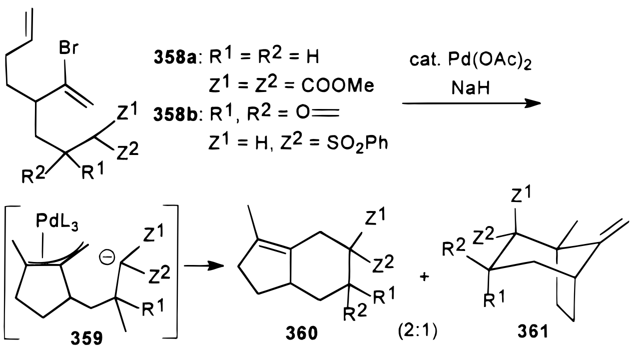
R	yield (%)
H	70
1-Methyl	22
1,4-Dimethyl	85
1-Methyl-5-isopropyl	87
6,6,7,7-Tetramethyl	67
7,7-Dimethyl	88
1,6,6-Trimethyl	84
1,4,6,6-Tetramethyl	97
1,3,6,6-Tetramethyl	69
3,4,6,6-Tetramethyl	81
3,4,7,7-Tetramethyl	77

b. Palladium Chemistry

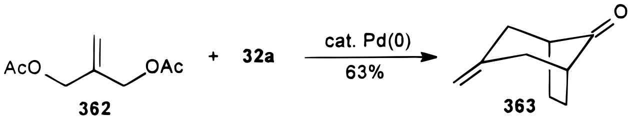
i. Ring Closures of the Three-Carbon Bridge. The stoichiometric reaction of silyl enol ethers with Pd(OAc)$_2$, initially studied by Ito and co-workers,[202] constitutes an important route to α,β-unsaturated carbonyl compounds. Further developments from Kende's group[203] have shown its successful application to the synthesis of bridged bicycloalkenones by cyclization of alkenyl substituted silyl enol ethers. Application to the formal synthesis of quadrone was made possible by starting from simple cyclopentene derivative **356** leading to a 8:1 mixture of olefinic isomers **357** in which the *exo*-methylene largely prevails.



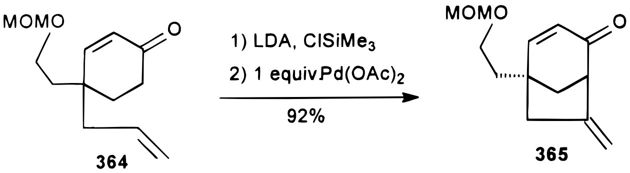
Recently reported for the construction of bicyclo[3.2.1] skeletons is the palladium-mediated tandem C−C bond formation based on nucleophilic substitution of π-allylpalladium complexes produced via the Heck reaction.[204] While mixtures of bridged and fused bicyclic compounds are usually obtained, this new approach presents the advantage of using totally acyclic precursors bearing the three different sites of reactivity. Vinyl bromides **358** are first cyclized to π-allyl intermediates **359**, which are trapped intramolecularly by the corresponding stabilized carbanions generated under the reaction conditions. In each case, poor regioselectivity of the nucleophilic substitution gives mixtures of the two possible bicyclic derivatives **360** and **361** in a ratio not exceeding 2:1.



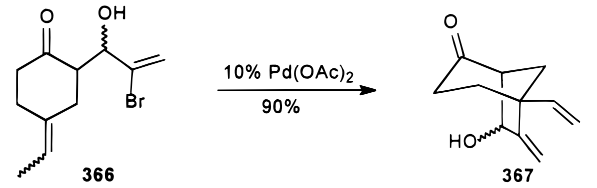
Finally, π-allylpalladium species derived from bifunctional electrophiles such 2-methylenepropane-1,3-diol diacetate (**362**) are important synthetic tools used successfully for catalytic annulation reactions. For example, Lu and Huang[205] have shown the facile palladium-catalyzed α,α'-dialkylation of cyclopentanone enamine **32a** with **362**, giving 63% yield of methylene bicycloalkanone **363**.



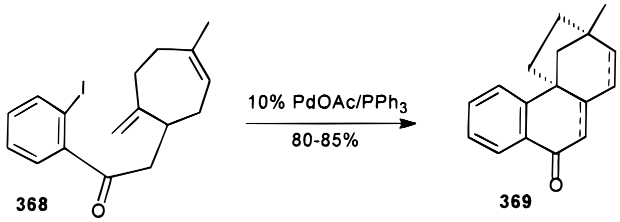
ii. Ring Closures of the Two-Carbon Ring. More recently, the Ito procedure was used as a new entry to C20 gibberellin synthesis from the bicyclic intermediate **365** obtained by cyclization of the functionalized trimethylsilyl enol ether derived from cyclohexenone **364**.[206]



The bicyclo[3.2.1]octane moiety **367**, which represents the CD rings of the natural aphidicolin, was also produced in a single step and 90% yield from easily accessible vinyl bromide **366**, using an intramolecular Heck reaction.[207]



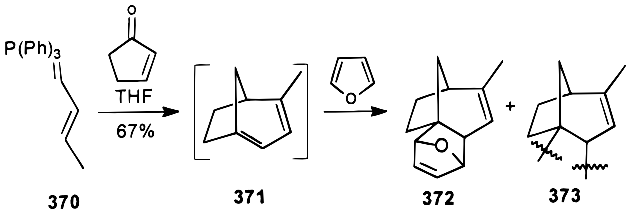
iii. Ring Closures of the One-Carbon Ring. Another efficient palladium-induced carbocyclization is the intramolecular Heck reaction which has been applied recently in the first synthesis of scopadulic acid.[208] The key bis-cyclization of dienyl iodide **368** to the tetracyclic core **369** was accomplished with a wide variety of palladium(0) catalysts in very good yield.



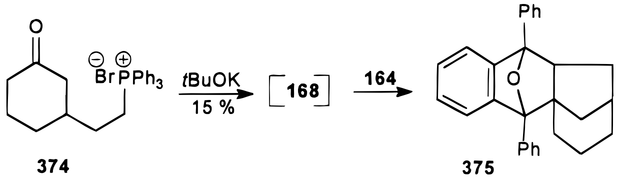
11. Miscellaneous Methods

a. Wittig Olefination

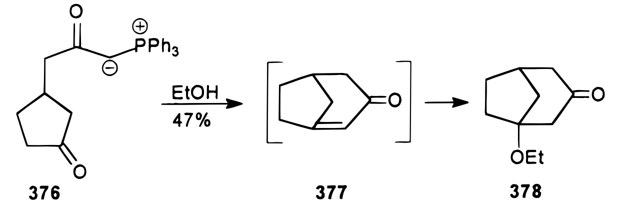
The intramolecular version of the Wittig reaction,[209] reported in 1962, has become a method of choice for the synthesis of annulated olefins. However, application to the construction of bridged alkenes appeared 11 years later with the work of Dauben's group[210] on the preparation of strained cycloalkenes. Reaction of cyclopent-2-enone with (*E*)-2-butenylidenetriphenylphosphorane (**370**) in refluxing THF containing an excess of furan gave the [4+2] cycloadduct **372**, in 37% yield together with 30% of dimeric bicyclo[3.2.1]octene **373**. These results account for the transient formation of highly strained bicyclo[3.2.1]octadiene **371**. Two years later, evidence for the formation of the unsubstituted bicyclo[3.2.1]oct-5-ene (**168**) was provided by the same group.[211] Thus,



trapping the product of the reaction of salt **374** and tBuOK, with diphenylisobenzofuran (**164**) leads to the isolation of tetracyclic ether **375** and therefore supports the existence of **168** as reactive intermediate.

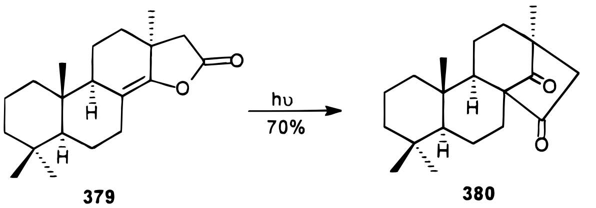


Further studies[212] have shown that bicycloalkenone **377**, bearing a double bond at the bridgehead position, can be generated from intramolecular cyclization of ylide **376**, trapped with ethanol and isolated as the bridgehead ether **378**.



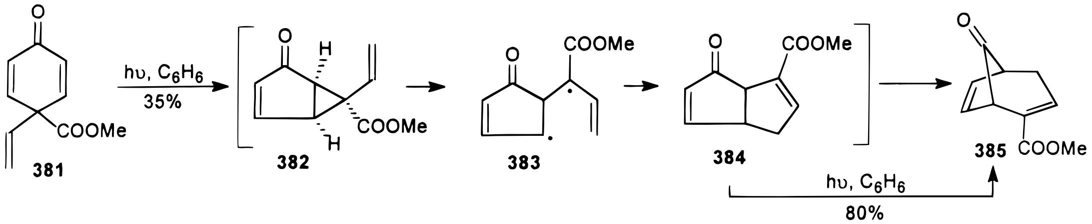
b. Photochemical Rearrangements

Although used only in few specific cases, the photochemically induced rearrangement of properly functionalized carbonyl derivatives can be applied to the construction of the bicyclo[3.2.1]octane framework. A synthetic example is the partial synthesis of hibaene[213] by photolysis of unsaturated lactone **379** to give **380** possessing the tetracyclic structure of the natural product.



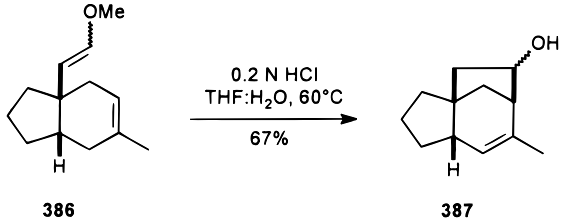
In 1974, Hart and Nitta[214] found that irradiation of vinylcyclohexadienone gave a bicyclo[3.2.1]octadienone in very good yield. A more recent investigation by Schultz and Green[215a] showed that, in the case of the conversion of **381** to **385** (Scheme 4), a thermal vinylcyclopropane to cyclopentene rearrangement (**382** to **384**) was unlikely and proposed a photochemical transformation by selective bond cleavage and reconstitution through the biradical intermediate **383**. Evidence for this pathway was provided by the independent preparation and irradiation of bicyclo[3.3.0]octadienone **384** to **385** in 80% yield.

Scheme 4



c. Prins Reaction

Very recently, an elegant anisatin model study based on the intramolecular Prins reaction was reported from Charonnat's group.[216] A simple hydrolysis of enol ethers **386** liberates the aldehydic function, which cyclizes in situ to form the tricyclic skeleton **387** as a 3:1 mixture of exo and endo isomer precusors of the required model.

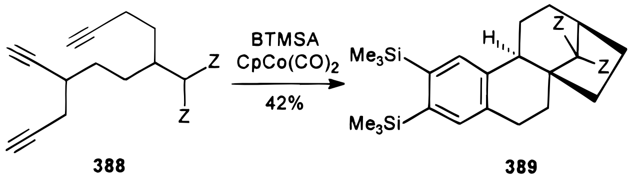


IV. Cycloadditions and Other Electrocyclizations

1. [4+2] Cycloadditions

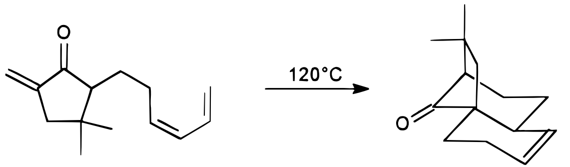
The Diels–Alder reaction is one of the most popular transformations used in organic synthesis but has found only limited application for the construction of the bicyclo[3.2.1] skeleton.

In 1979, Kametani and collaborators[217] proposed a new stereoselective total synthesis of tetracyclic diterpenes hibaol and dihydrohibaene based on the thermolysis of a properly functionalized benzocyclobutene. More recently, the facile intramolecular capture of *o*-quinodimethane intermediates was exploited by Malacria and co-workers[218] in an elegant one-pot sequence catalyzed by $CpCo(CO)_2$. Acyclic triyne **388** in the presence of bis(trimethylsilyl)acetylene (BTMSA) was converted stereoselectively to the tetracycle **389** of the phylocladane family by a cascade involving ene-type cycloisomerization, [2+2+2] cycloaddition, and intramolecular [4+2] Diels–Alder reaction. Further experimentation led to the reversal of the diastereoselectivity leading to the basic skeleton of kaurane diterpenes.

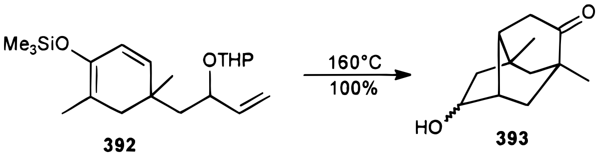


Z = COOMe, COMe

Two conceptually closely related routes to racemic quadrone, based on intramolecular Diels–Alder reaction, were reported independently by two different groups.[219] Both approaches involved the construction of bicyclo[3.2.1]octenone **391** by the stereoselective intramolecular cycloaddition of methylene cyclopentanone **390**. Similarly, after the work of Yamamoto and Sham[220] related to the total synthesis of 9-isocyanopupukeanone using the transformation of triene **392** to keto alcohol **393**, a successful preparation of 2- and 9-pupukeanone was also reported.[221]



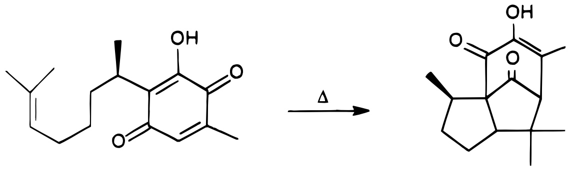
390 **391**



392 **393**

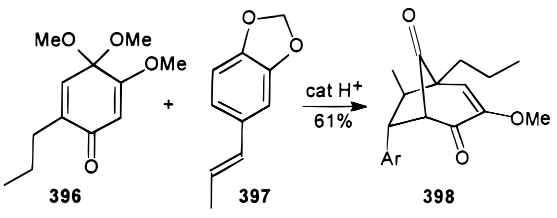
2. [5+2] Cycloadditions

Since the remarkable thermolysis of perezone (**394**) to isomeric α- and β-pipitzol (**395**) reported in 1965,[222] ionic [5π+2π] cycloadditions have attracted important interest for the synthesis of natural compounds.



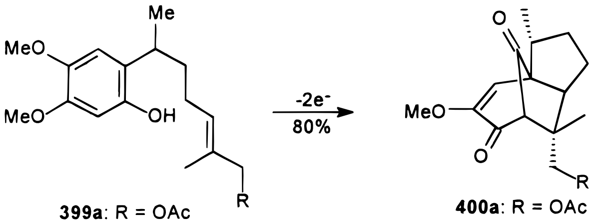
394 **395**

The first synthetic work in this field came from Büchi's group[223] who developed in connection with the synthesis of neolignans, gymnomitrol, and substituted tropolones, a new method for the preparation of bicyclo[3.2.1]octanes by acid-catalyzed addition of *p*-quinone monoketals to olefins. For example, quinone ketal **396** condenses with isosafrole **397** in the presence of a catalytic amount of 2,4,6-trinitrobenzenesulfonic acid to give functionalized bicyclooctane **398**. Unfortunately, modest yields associated with these cationic cycloadditions have been the main synthetic limitation of the transformation until very recently. This drawback can be overcome by using trimethylsilyl triflate in 3.0 M $LiClO_4$·EtOAc solution as promoter of the reactive cationic intermediate, giving yields up to 99%.[224]



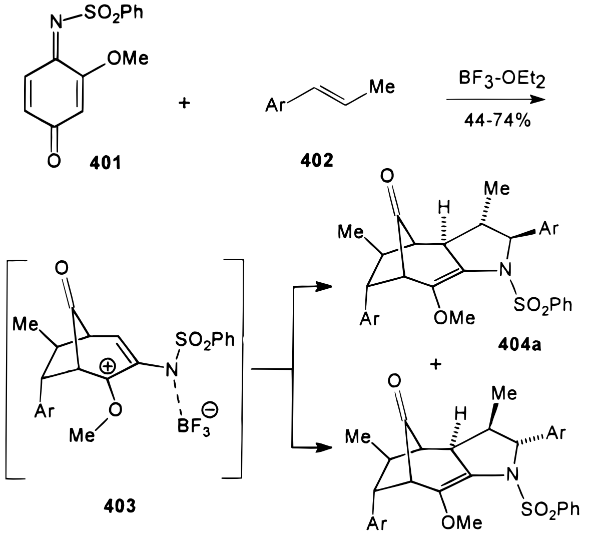
396 **397** **398**

After these pioneering studies, Yamamura[225] showed that a related bridged cyclopentadienyl [5+2] cycloaddition can also be efficiently generated by electrochemically from substituted phenols. Inter−intramolecular trapping of the resulting transient species have been applied to the synthesis of natural products. Illustrative examples are the syntheses of (±)-8,14-cedran oxide and (±)-silphinene which were prepared by simple chemical transformations of tricyclic diones **400a** and **400b**, obtained by electrolysis of the corresponding phenols **399**. Similarly, extensive studies from Engler's group[226] have led to the proposal of an efficient and versatile Lewis acid promoted [5+2] cycloaddition of styrenyl systems with 2-alkoxy-1,4-benzoquinones. Very recently, this methodology has been extended to the construction of highly functionalized and stereodefined bridged tricyclic systems by combining the [5+2] cycloaddition with a concomitant [3+2] or [3+3] cycloadditions.[227] The quinone monoimides **401** react with (*E*)-propenylbenzenes **402** in the presence of BF_3 to provide an alkoxy carbocation intermediate **403** which is trapped by a second propenylbenzene via a carbon−nitrogen bond formation to give the tricyclic heterocycles **404** in combined yields from 44% to 74%.

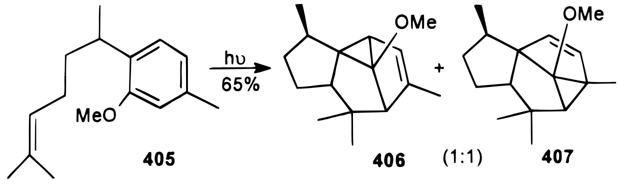


399a: R = OAc
399b: R = H

400a: R = OAc
400b: R = H



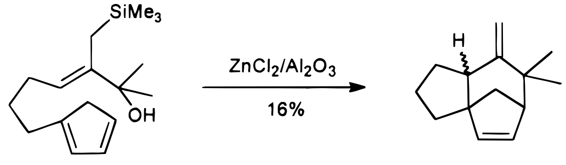
Arene−alkene photoadditions and especially the meta cycloaddition have gone through impressive developments in organic synthesis especially due to the important contribution from Wender's group.[228] A particularly elegant and direct access to a complex bicyclo[3.2.1] structure involves the concise synthesis of cedrene by irradiation of alkene **405** and subsequent selective transformations of cycloadducts **406** and **407**.



405 **406** **407**

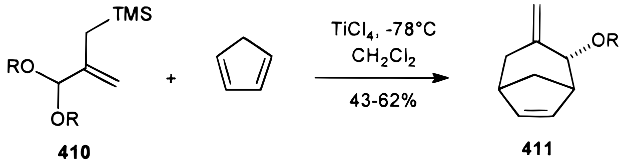
3. [4+3] Cycloadditions

Another direct access is the [4+3] cycloaddition of allyl cations with dienes, which has been studied in detail by Hoffmann[229] and proved to be a general and useful method for the construction of numerous bicyclo[3.2.1]octane systems. A short route to the zizaene class of sesquiterpenoids **409** from functionalized cyclopentadiene **408**, exploited the intramolecular version of this powerful [4+3] cycloaddition.[230]



408 **409**

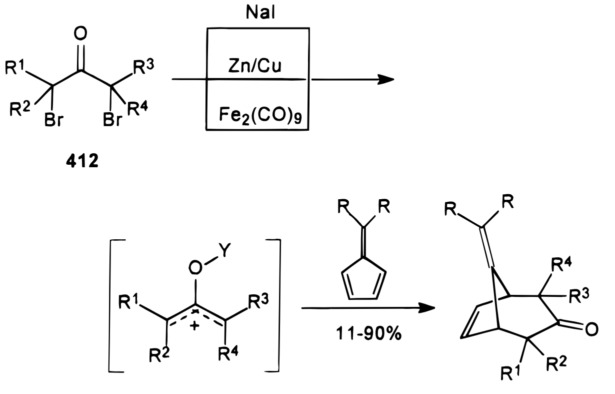
Very recently Harmata and Jones[231] reported an improved procedure for the generation of vinyl oxocarbeniums. This work represents one of the few utilizations of heteroatom-stabilized allylic cations in the [4+3] cycloaddition reaction. Functionalized allylsilanes **410** are conveniently prepared from commercially available materials and react smoothly at low temperature with cyclopentadiene in the presence of TiCl$_4$ to furnish the corresponding *exo*-methylene bicyclo[3.2.1]octenes **411** in fair yields.



410
R = Me, Et, *i*Pr

411

Among the variety of versatile cationic C-3 annulating agents, oxyallyl cations **413** derived from α,α′-dibromo ketones have attracted particular attention[232] since they are conveniently generated from simple precursors and readily add to cyclopentadienes or fulvenes[233] to produce bicyclo[3.2.1]octenones **414**. Dehalogenation of polybromo ketones **412** with Zn/Cu couple or NaI has been extensively studied by Cookson[234] and Hoffman groups[235] while the use of iron carbonyls was introduced by Noyori and Hayakawa,[236] who have also widely contributed to the development of this chemistry. Very recently, Lubineau and Bouchain[237] have shown the beneficial effect of water as solvent starting with α,α′-dibromo ketones or α-chloro ketones under various reductive conditions.



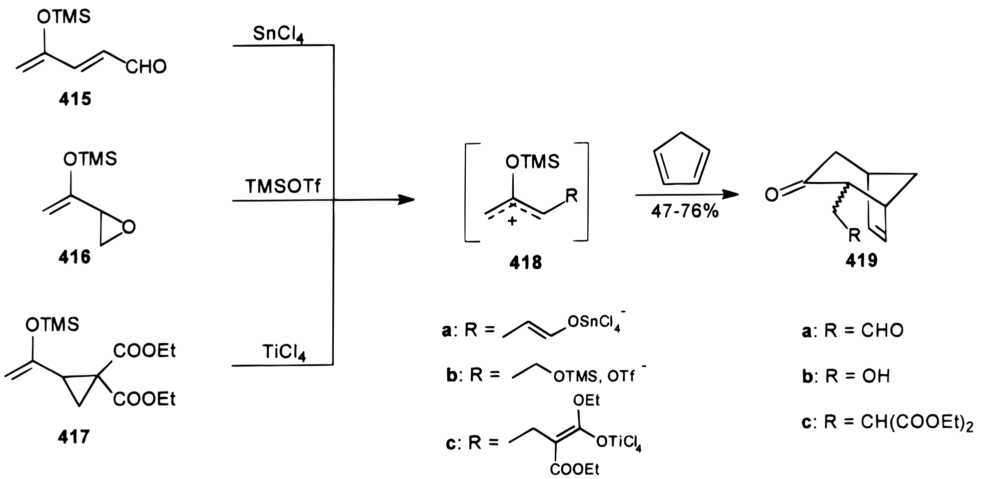
412

413
Y = Na, Cu, Fe

414
R = H, Me, OAc, OMe

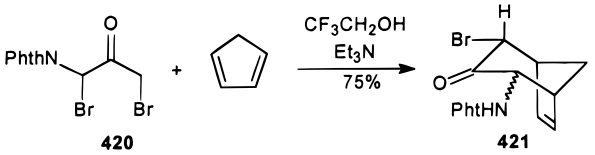
More specifically, functionalized oxyallyl cations are also easily accessible and can be utilized for the rapid assembly of substituted bicyclooctenones. For example, the reaction of silyl enol ethers **415**−**417** with Lewis acids gives the corresponding C-3 annulating intermediates **418** which can be trapped with cyclopentadiene to give mixtures of *exo*- and *endo*-bicyclic compounds **419** in moderate yields[238] (Scheme 5). While other oxygen- and halogen-substituted oxyallyl cations are known and used for synthetic purposes,[239] the first nitrogen derivative was reported

Scheme 5

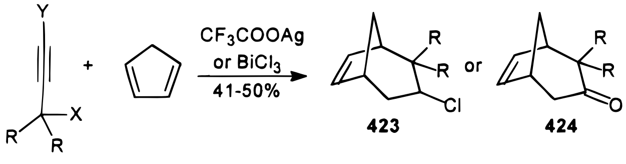


a: R = CHO
b: R = OH
c: R = CH(COOEt)$_2$

only very recently. Obtained through S_N1-like ionization from α,α′-phthalimidoyl dibromide **420**, it gave in the presence of cyclopentadiene, 75% yield of a 2:1 ratio of α-aminobicyclooctenones **421**.[240]



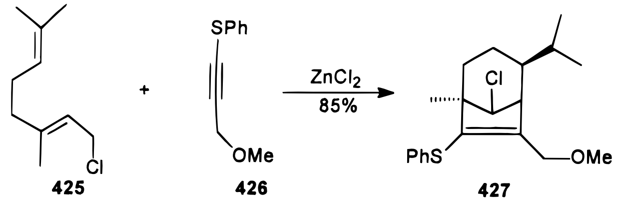
Another well-established alternative to functionalized bicyclo[3.2.1]octane systems is the [4+3] cycloaddition of allenyl cations. Mayr's studies[241] on the reactivity of propargylic halides have led to a new construction of bicyclic products such as **423** or **424** by reaction of alkynes **422** with cyclopentadiene in the presence of silver or bismuth salts.



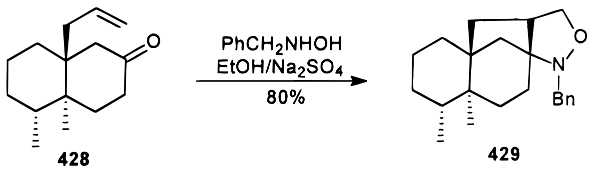
422a: X = Br, Y = R = H
422b: X= Cl, Y = H, R = Me
422c: X: Cl, Y = $SiMe_3$, R = Me_3

4. [3+2] Cycloadditions

While the [3+2] cycloaddition is one of the most attractive and logical approaches to five-membered rings[242] the extrapolation to the construction of bicyclo[3.2.1]octanes is still limited and only two different methods are reported. The first one is the [3+2] cycloaddition between allyl cations and substituted alkynes, which constitutes a quite general approach to halobicyclo[3.2.1]octenes such as **427** and was applied successfully to the total synthesis of 4-*epi*-helminthosporal from geranyl chloride **425** and thioacetylenic ether **426**.[243]

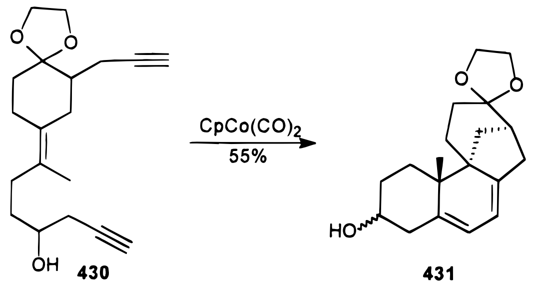


The exploitation of the intramolecular nitrone–olefin cycloaddition from easily accessible cycloalkanone **428** was reported by Funk and co-workers[244] in 1983 as a new general and facile bridged bicycloalkanes preparation. The first total synthesis of 7,12-secoishwaran-12-ol, a naturally occurring antifertility agent, from the tetracyclic isoxazolidine **429** well illustrates the synthetic potential of this method.

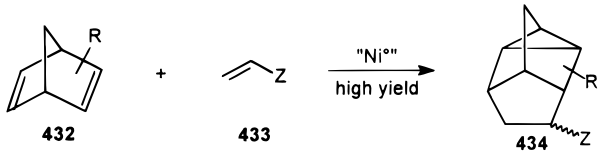


5. [2+2+2] Cycloadditions

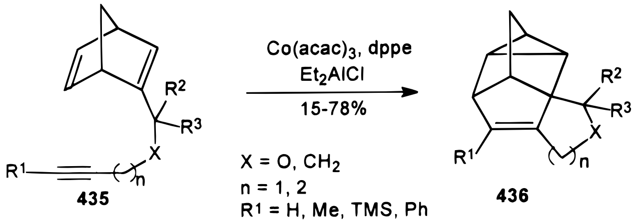
Also extensively studied and synthetically useful is the cobalt-catalyzed [2+2+2] cycloaddition of acetylenic precursors. More specifically, important contributions from Vollhardt's group[245] led to the proposal of an efficient one-step elaboration of the stemodane framework **431** via the stereoselective cyclization of monocyclic enediyne **430**.



The thermal [2+2+2] homo-Diels–Alder cycloaddition (HDA) of norbornadiene to electron-deficient olefins was disclosed in the late 1950s by two different groups.[246] This six-electron cyclization constitutes the most powerful tool for the preparation of rather strained tetracyclic compounds **434** and **436**, representative of the deltacyclane family and incorporating a bicyclo[3.2.1]octane substructure.[247] A more recent interest was paid to its metal-catalyzed version which is more efficient and can also be performed enantioselectively.[248] While low-valent nickel complexes are well-known to catalyze the intermolecular HDA reactions of bicyclo[2.2.1]heptadienes **432** with electron-deficient olefins **433**, cobalt catalysts gave good results with acetylenic dienophiles either inter- and intramolecularly, as shown by the facile cyclization of the tethered norbornadienes **435** to the pentacyclic framework **436**.[249]



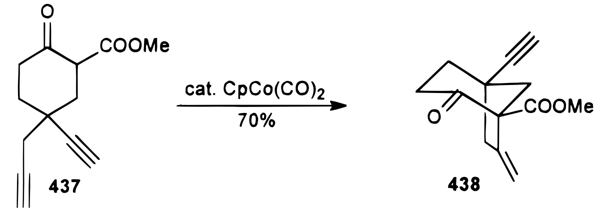
Z = COMe, CHO, CN
SO_2Ph, SOPh



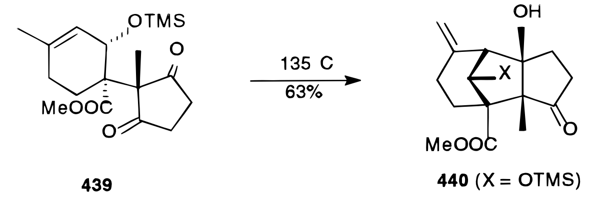
X = O, CH_2
n = 1, 2
R^1 = H, Me, TMS, Ph
R^2 , R^3 = H, Me

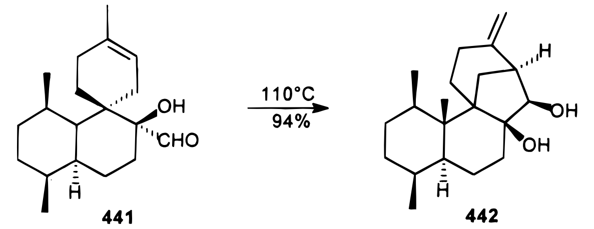
6. Ene-Type Cyclizations

Cobalt is also known to be a good catalyst for ene-type cycloisomerization of ϵ-acetylenic β-keto esters and was utilized successfully for the rapid assembly of methylene bicyclo[3.2.1]octanone **438** from the easily accessible precursor **437**.[250]



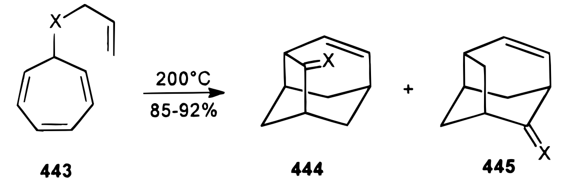
A very interesting and synthetically useful thermal ene reaction of **439** to form the functionalized tricyclic hydroxy diketone **440** constitutes the cornerstone of Trost's total synthesis of verrucarol.[251] Also of interest is the hydroxy-assisted intramolecular thermal ene reaction of spiro aldehyde **441** to the stemodane carbone backbone **442**.[252]



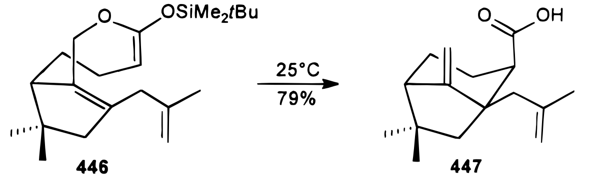


7. Sigmatropic Rearrangements

Sigmatropic rearrangements in cycloheptatrienes have been extensively studied from a mechanistic point of view, and an example of their synthetic potential is illustrated by the pyrolysis of allyl-substituted precursors such as **443**. The overall transformation, which involves sequential [1,5] hydrogen shift, [3,3] cycloisomerization, and intramolecular Diels–Alder reaction, produces the protoadamantane skeletons **444** and **445** in good yields.[253]



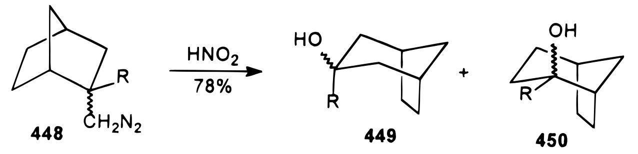
Finally, an alicyclic Claisen rearrangement applied to the construction of functionalized bridged bicycloalkene **447** from enol lactone **446** constitutes a new synthetic approach to quadrone.[254]



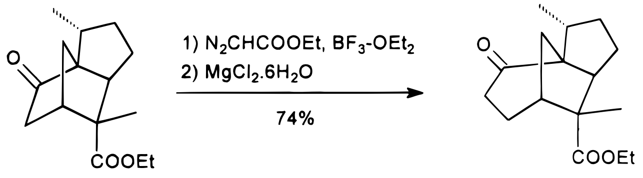
V. Ring Expansion of Bicyclo[2.2.1]heptanes

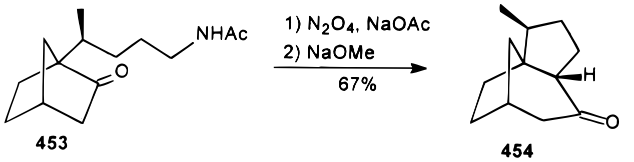
Since the pioneering work of Lipp[12] and Hückel[13] concerning the one-carbon ring expansion of camphene skeleton (vide supra), the preparation of bicyclo[3.2.1]octanes by homologation of bicylo[2.2.1]heptanes has attracted growing interest. Nowadays, this method constitutes an important approach which has been incorporated in some elegant synthetic strategies.

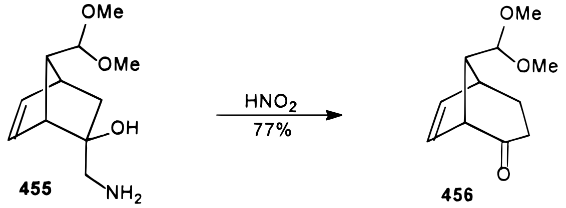
In 1938,[255] it was shown that the deamination of aminomethyl norbornanes **448** with nitrous acid gave bicyclo[3.2.1]octanols **449** and **450**. This observation was subsequently studied in more detail[256] and can be closely related to the diazomethane-mediated ring expansion of norcamphor derivatives.[257] Total syntheses of natural products of the cedrane family[258] have been successfully achieved by using this basic approach. A recent example is the stereoselective preparation of cedranediol[259] from bicyclic ketone **452** obtained by ring expansion of bicyclo[2.2.1]octanone **451**. The intramolecular version of this transformation which leads to **454** from **453** constitutes the key step in a total synthesis of (±)-zizaene.[260] Another elegant synthetic exploitation of this concept appeared recently with the facile deamination of **455** to form **456**, a new versatile building block.[261,262]



(R = H, Me)

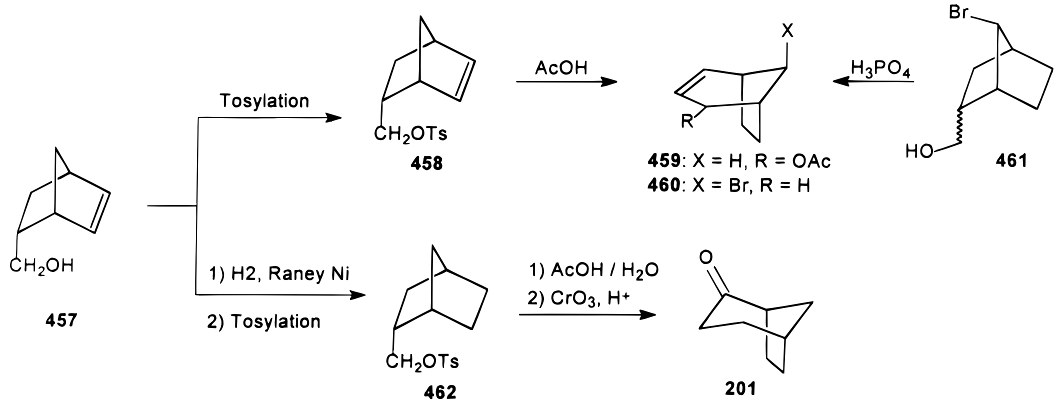




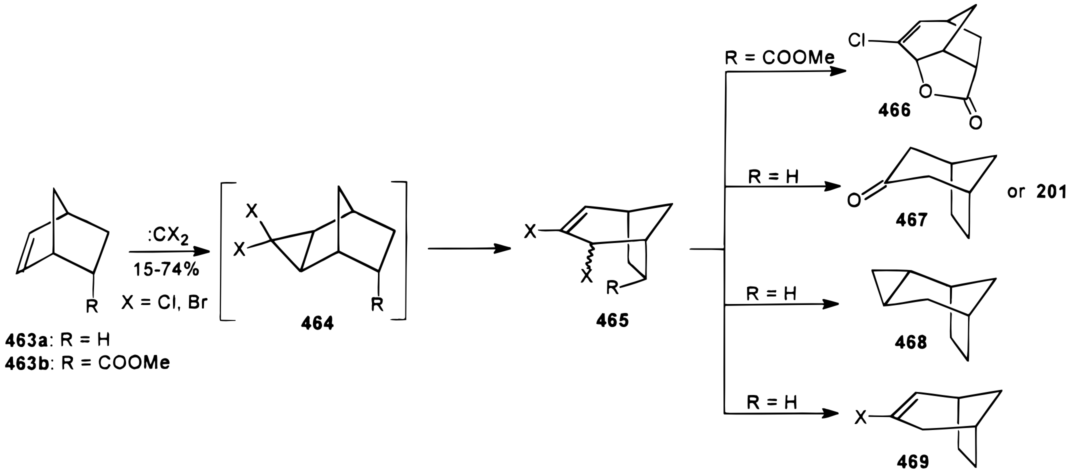


Owing to the practical availability of functionalized bicyclo[2.2.1]heptanes by Diels–Alder cycloaddition, the solvolytic one-carbon ring-enlargement method found real development at the beginning of the 1960s.[263] The acetolysis of tosylate **458**, derived from commercially available 2-(hydroxymethyl)bicyclo-[2.2.1]hept-5-ene (**457**) gives mainly the ring-expanded acetate **459**.[264] Similarly, the reaction of bromo alcohols **461** with phosphoric acid is used for the synthesis of *syn*-8-bromobicyclo[3.2.1]oct-2-ene

Scheme 6

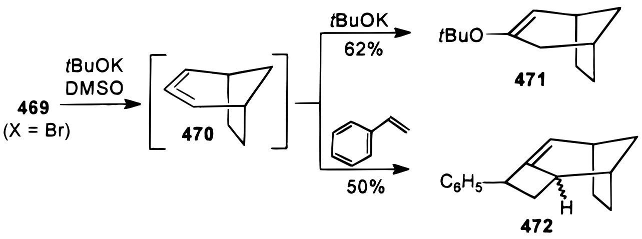


Scheme 7

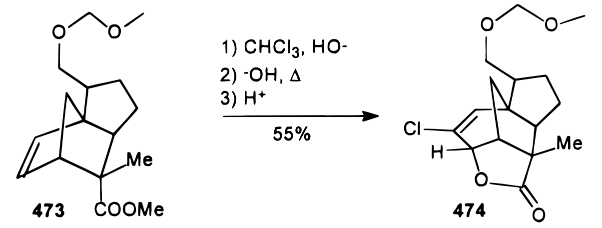


(**460**)[265] (Scheme 6). Application to the high yield, regioselective preparation of bicyclooctanone **201** from **462** was reported contemporaneously.[266]

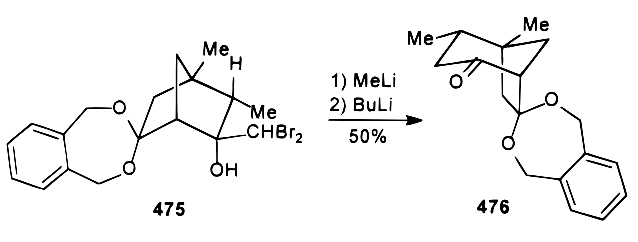
Shortly after its discovery, the rearrangement of *gem*-dihalocyclopropanes observed with strained cyclic olefins was extrapolated to the norbornane series, independently and in the same year, by five different groups.[267] This tandem addition–ring expansion is efficient with norbonenes **463** or norbornadiene[268] and has been used quite often as a simple and inexpensive preparative method for the construction of useful functionalized bicyclo[3.2.1]octanes. Spontaneous rearrangement of cyclopropyl intermediates **464** gives the corresponding dihalo bicyclic olefins **465** which can be selectively manipulated to give either lactone **466**, bicyclooctanones **467** or **201**, tricyclo[4.2 × $10^{2,4}$]nonane **468**[269] or vinyl halides **469**[270] (Scheme 7). The latter (X = Br) has been used to prove the transient existence of the highly strained bicyclic allene **470** trapped as either enol ether **471** or as its styrene [2+2] cycloadduct **472**.[271]



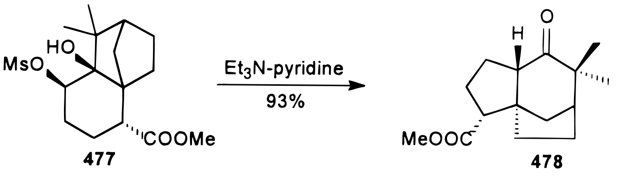
Finally, the cornerstone transformation in a total synthesis of cedranediol is the regiospecific ring enlargement of tricyclic olefin **473** to give the properly functionalized carbon framework **474**.[272]



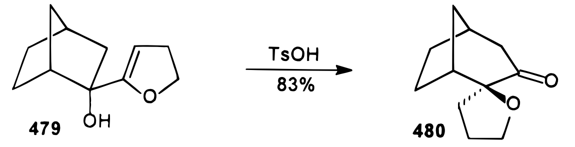
The 1,2-rearrangement of halohydrins introduced by Sisti,[273] was recently included in a synthetic strategy directed toward the synthesis of glycinoeclepin A from monoprotected bicyclooctanedione **476**, easily obtained in 50% yield by transposition of hydroxy dibromide **475**.[274] Similarly, pinacol-type

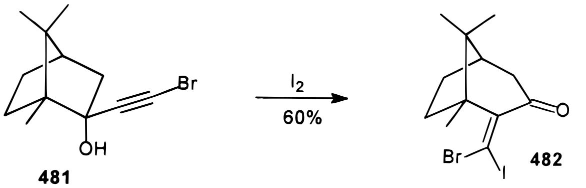


fragmentation of tricyclic mesylate **477** furnished the expected rearranged carbon skeleton **478**, involved in the total synthesis of various zizane sesquiterpenes.[275]

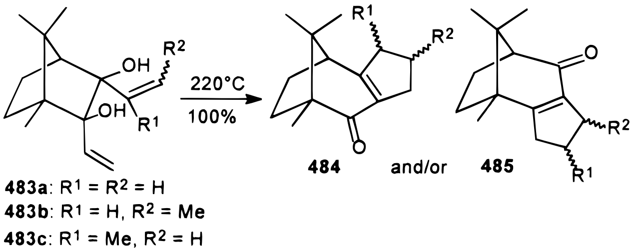


More recently reported are the electrophilic ring expansions of related norbornanol systems such as the oxonium-promoted pinacol-like rearrangement of bridged bicyclic alcohol **479** to **480**[276] or the iodine-induced homologation of camphor derivative **481** to the unsaturated ketone **482**.[277]

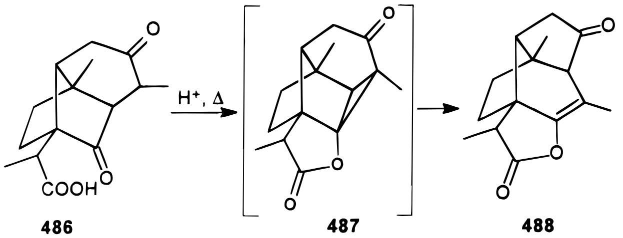




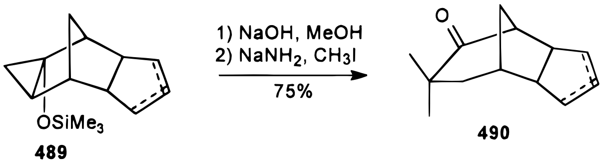
Tandem thermal Cope rearrangement–intramolecular cyclodehydration of 2,3-divinyl-2,3-norbornanediols **483** was proposed by Conia and Lireverend[278] as a new entry to tricyclic enones **484** and **485**, and applied to a concise synthesis of β-patchoulene.



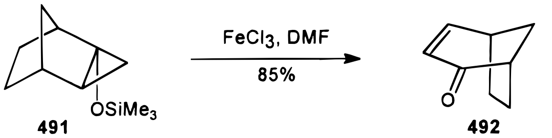
After the somewhat intricate transformation of santonic acid (**486**) to parasantonide (**488**), formulated to proceed by a tandem intramolecular aldol condensation–retroaldol cleavage[279] through cyclopropyl intermediate **487**, the related homoenolization



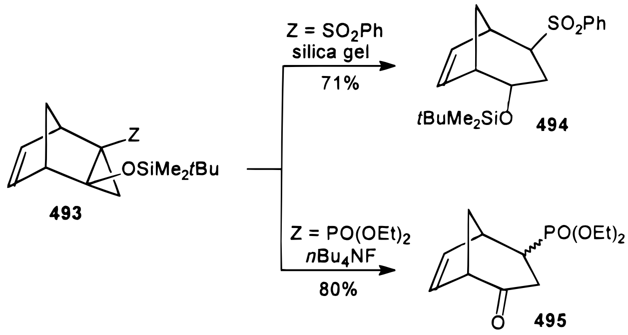
of cyclopropoxide analogues became a quite general method. More particularly, extensive work from Stother's group[280] has strongly contributed to the development of this approach toward natural product synthesis. An illustrative example is the simple route to hirsutene by rearrangement of **489** to **490** precusor of the natural product.



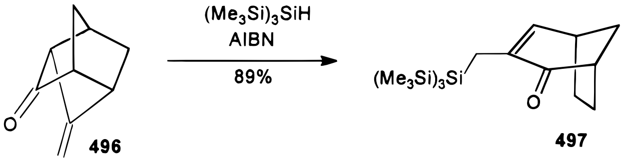
More recently, Ogasawara and Kawamura[281] proposed an elegant stereo- and enantiocontrolled synthesis of (+)-juvabione and (+)-epijuvabione from (+)-norcamphor. Cyclopropanol intermediate **491**, easily obtained by cyclopropanation of norcamphor trimethylsilyl enol ether, on treatment with FeCl$_3$ afforded directly (+)-bicyclo[3.2.1]oct-3-en-2-one (**492**), which constitutes the key intermediate of the syntheses.



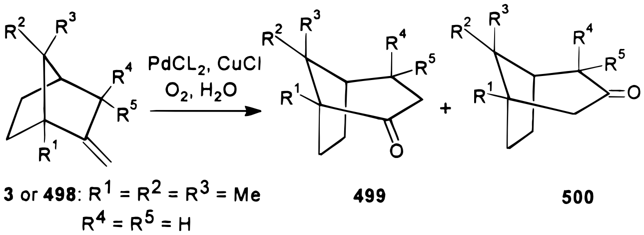
Also of interest is the high reactivity of donor-/acceptor-substituted cyclopropanes **493** which are smoothly transformed to functionalized bicyclo[3.2.1]octanes **494** or **495** by selective cleavage of the internal cyclopropyl bond.[282] This specific reactivity, referred to as the corner attack, has been extensively studied by Coxon's group which has published a series of interesting papers dealing with the regio- and stereoselectivity of the cleavage by acids, mercuric acetate, and bromine.[283]



Recently, tris[(trimethylsilyl)silyl] radical mediated fragmentation of strained bicyclo[2.2.1] derivative **496** was shown to give the unexpected bicyclo[3.2.1]octenone **497** in 89% yield through a pathway involving a cascade of radical addition and fragmentation reactions.[284]



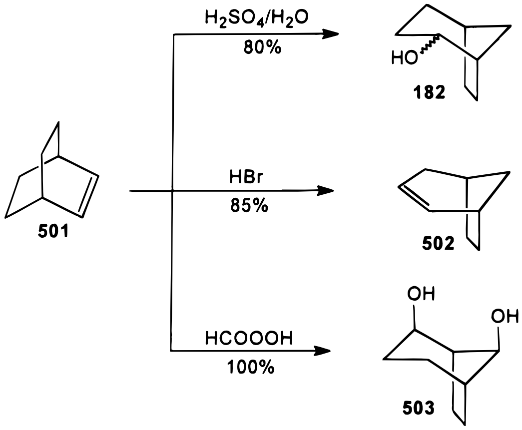
Finally, in contrast to the photochemistry of methylenenorbornenes, which usually gives a mixture of photoproducts including bicyclo[3.2.1] structures,[285] the palladium(II)-catalyzed ring expansion of camphene (**3**) and methylenecamphor **498** proceeds more selectively leading to a 3:1 mixture of the corresponding bicycloalkanones **499** and **500**.[286]



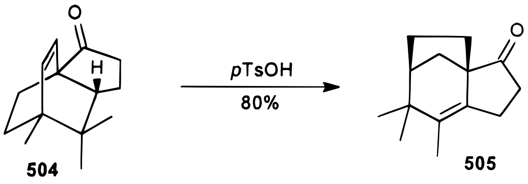
VI. Rearrangement of Polycyclic Intermediates

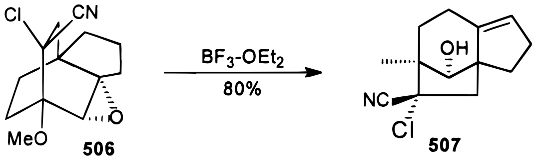
1. Isomerization of Bicyclo[2.2.2]octanes

Following the first rearrangement of a bicyclo[2.2.2]octane to a bicyclo[3.2.1]octane framework,[15] this facile skeletal reorganization met with considerable interest during the 1950s and 1960s. Elegant synthetic strategies have incorporated this efficient isomerization. Direct acid-mediated ring interconversion of bicyclo[2.2.2]octene (**501**) was found to give, depending on the reaction conditions, the bicyclooctanol **182**[106] or the bicyclo[3.2.1]octene **502**,[287] while performic acid oxidation furnished diol **503** in quantitative yield, a transformation also effective with dibenzobicyclo[2.2.2]octadiene.[288] Similarly, the deamination of bicyclic amines,[289] Hell–Volhard–Zelinsky bromination of bicyclo[2.2.2]octane-2-carboxylic acid,[290] ionic chlorination,[291] and also radical addition of HBr[292] to unsaturated [2.2.2] bridged precursor proceed with isomerization to the corresponding functionalized bicyclo[3.2.1]octane derivatives.

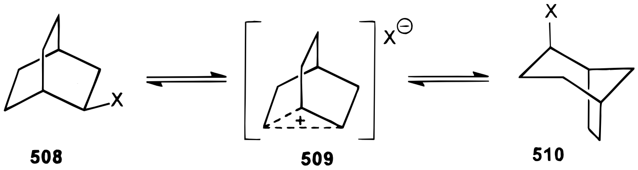


Synthetic examples of the acid-promoted rearrangement of bicyclo[2.2.2]octenes are represented by the high yield obtention of isokhusimone **505** from reaction of tricyclic ketone **504** with *p*-TsOH[293] and the BF_3·OEt_2 induced isomerization of epoxide **506**to the tricyclic skeleton **507**,[294] which was applied to the synthesis of gymnomitrol and isogymnomitrol.[295]

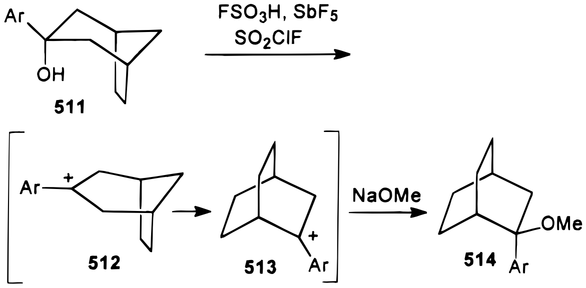




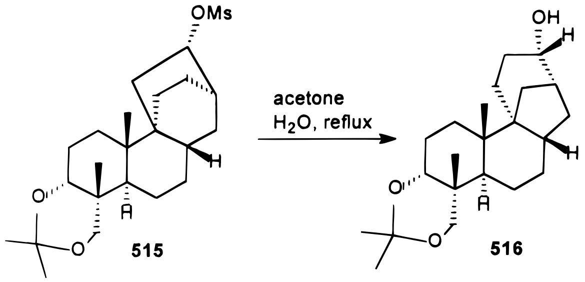
These useful cationic isomerizations have been extensively studied and earlier solvolytic observations in the bicyclo[2.2.2]oct-2-yl series **508** have shown the intervention of a nonclassical cation **509** to explain the observed isomerization **508** ↔ **510**.[296]



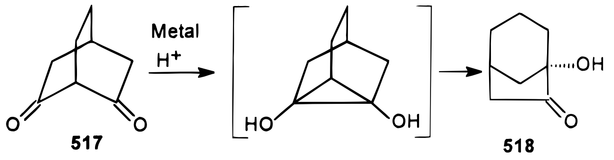
In contrast, more recent investigations by Kelly's group have provided evidence for stable cations **512** and **513** during ionizations of 3-*exo*-arylbicyclo[3.2.1]octan-3-ols **511**, leading to bicyclo[2.2.2] **514**.[297] A synthetic application of this Wagner–Meerwein-type rearrangement was reported by Vogel and Gabioud[298] for the preparation of a new tetrakis(methylene)bicyclo[3.2.1]octane system used in a study of the Diels–Alder reaction with tetracyanoethylene.



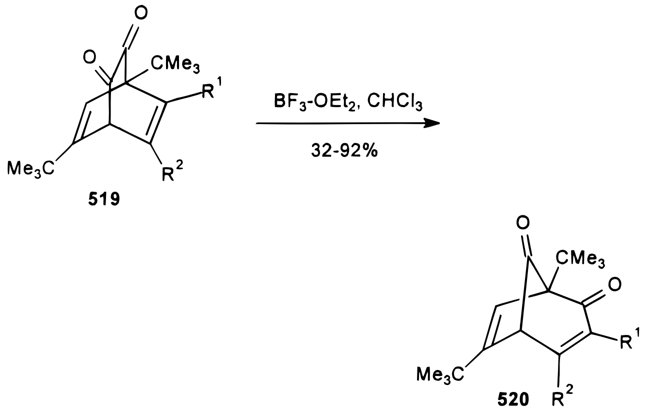
Since carbocationic rearrangements abound in nature, the solvolytic isomerization of bicyclo[2.2.2]octyl intermediate constitutes a potential biogenetic-type methodology, which was applied successfully to the total synthesis of complex diterpenoids.[299] An illustration is the solvolysis of mesylate **515**, leading to **516**, the basic skeleton of aphidicolin.[300]



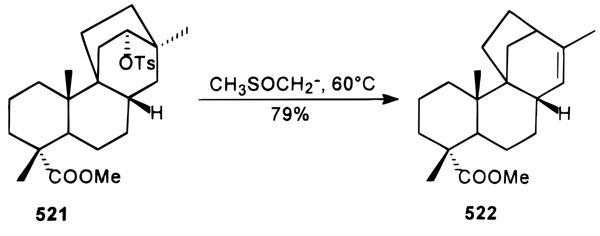
Closely related to these carbocationic rearrangements is the intramolecular pinacol condensation of bicyclo[2.2.2]octanediones of type **517**, giving hydroxy bridgehead bicyclic octanones **518** which was applied to the total syntheses of steriol and epiallogibberic acid.[301]

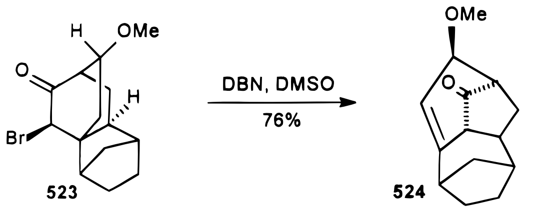


A recent extrapolation to the rearrangement of 1,2-diones promoted by BF$_3$·OEt$_2$ was proposed by Nair's group.[302] These authors showed the facile synthesis of bicyclo[3.2.1]octene-2,8-diones **520** starting from readily available bicyclo[2.2.2]octene-7,8-diones **519**.

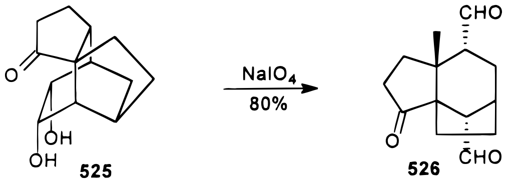


Also of great synthetic value is the base-promoted fragmentation of properly functionalized bicyclooctyl intermediates. Tosylate **521** reacted with methylsulfinyl carbanion leading to the tetracyclic olefin **522** involved in the stemarin synthesis[303] and the bromo ketone **523** on treatment with DBN in DMSO, easily rearranged to **524** having the tetracyclic structure found in chasmanine and napelline alkaloids.[304]

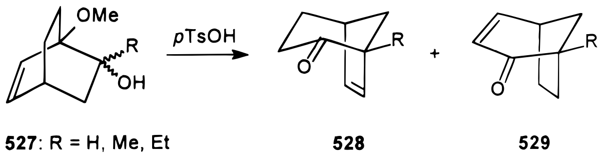




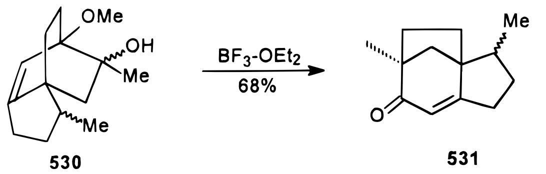
More recently, an oxidative C−C bond cleavage of tricyclic diol **525** to the bicyclic dialdehyde **526** was proposed as a rapid entry into the core of gibberellic acid and zizaene.[305]



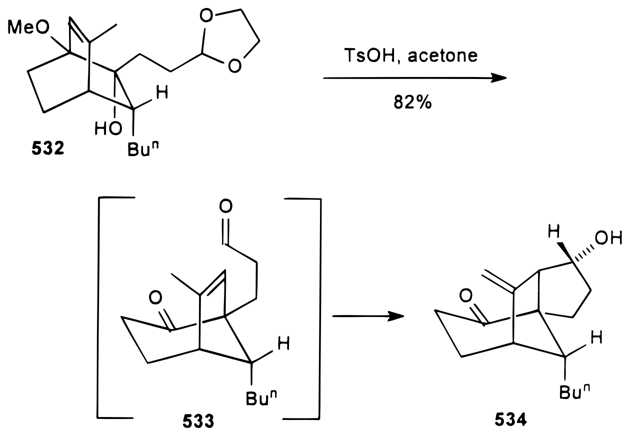
A straightforward route to bicyclo[2.2.2]octenes involves the Diels−Alder reaction of 1,3-cyclohexadienes and ketene equivalents. However due to the practical difficulties of preparing functionalized 1,3-cyclohexadienes, cycloadditions of readily available dihydroanisole derivatives emerged as a method of choice for the preparation of synthetic valuable methoxy bridgehead bicyclo[2.2.2]octenes. A detailed study from Roger's group[306] disclosed the synthesis and the acid-catalyzed rearrangement of a series of 1-methoxybicyclo[2.2.2]oct-5-enes **527** as a new powerful entry into bridgehead substituted bicyclo[3.2.1]-octenes **528** and **529**. Interestingly, it was found that the *exo*-alcohols and their derivatives led almost exclusively to **528**, while enones **529** were obtained from the corresponding *endo* precursors.



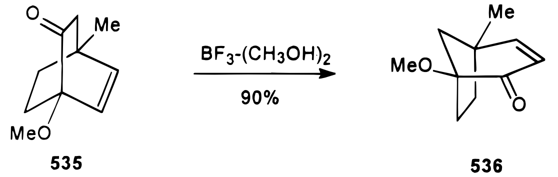
Following this pioneering study, growing interest has been paid to this rearrangement which has found numerous synthetic applications. In particular, subsequent exploitation by Monti and co-workers[307] has strongly contributed to the development of this method for the construction of natural compounds as shown by the synthesis of stachenone, quadrone, and the gibberellin skeleton. More recently, utilization of this strategy has concerned the concise total synthesis of quadrone, and terrecyclic acid A.[308] The important contribution from Rao's group,[309] directed toward the synthesis of natural products, is illustrated by the facile conversion of **530** to **531**, a precursor of two new sesquiterpenes and more recently used as a novel synthesis of tricyclo[5.3.1.0^{1,5}] skeletons.[310] This pinacol-type rearrangement was applied elegantly to a formal synthesis of perhydrohistrionicotoxin by Kim and collaborators.[311] Treatment of acetal **532** with TsOH in refluxing acetone gave the rearranged bicyclo[3.2.1] aldehyde intermediate **533** which was transformed in situ to the desired tricyclic structure **534** in 92% overall yield via an intramolecular ene reaction.



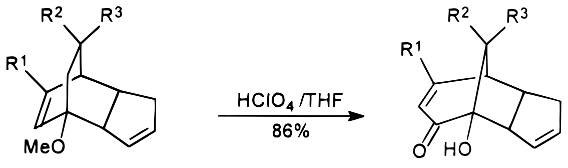
In 1989, Uyehara and collaborators[312] reported a very interesting and useful sequential rearrangement approach to bridgehead substitution of 1-methoxybicyclo[2.2.2]oct-5-en-2-ones based on the isomeriza-



tion of methoxy functionalized [2.2.2]octene **535** into the thermally more stable methoxy bridgehead bicyclo[3.2.1]octenone **536**.



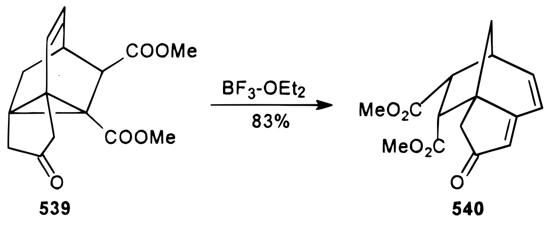
In a very recent study, Singh and Jagadish[313] have exploited the $HClO_4$-mediated rearrangement of endo-annulated bicyclo[2.2.2]octenones **537** as a new route to synthetically valuable functionalized tricyclo-[5.3.1.0^{2,6}] intermediates **538**.



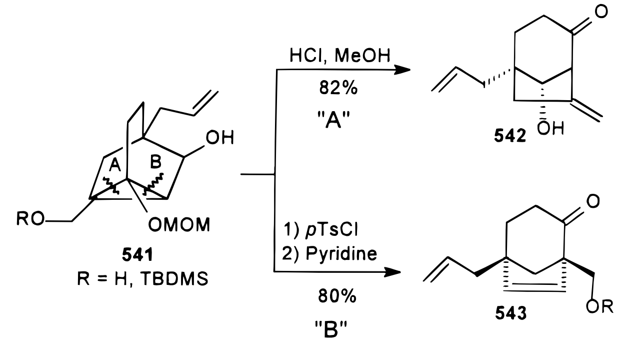
537a: R^1 = R^3 = H, R^2 = Me
537b: R^1 = H, R^2 = R^3 = Me
537c: R^1 = R^2 = R^3 = Me
537d: R^1 = R^2 = R^3 = H

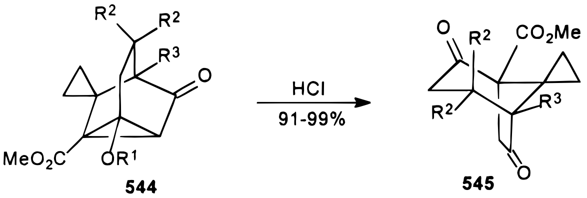
538

The readily available [3.2.1.0^{2,7}] tricyclic framework can be regarded as a highly strained bicyclo[2.2.2]-octane system which, upon selective C−C bond cleavage, can afford synthetically valuable bicyclo[3.2.1]-octanes. For example, the methanohydroazulene **540** is easily accessible through the stereoselective rearrangement of tetracyclic ketone **539**.[314]



Similarly, the bicycloannulation of cyclic dienolates with various Michael acceptors (see section III.7.b) has been recently exploited to prepare highly functionalized tricyclo[3.2.1.0^{2,7}]octanols **541**, precursors of kaurane or stachane-type bicyclo[3.2.1]octane systems **542** and **543**. This annulation sequence has been previously applied to the total synthesis of helminthosporal.[315] Direct acid cleavage of the A bond gave **542** selectively, while **543** is obtained exclusively from the corresponding tosylate by rupture of the B bond. Contemporaneously, a general access to spiroannulated bicyclic intermediates **545** from easily accessible tetracyclic ketones **544** was also reported.[316]

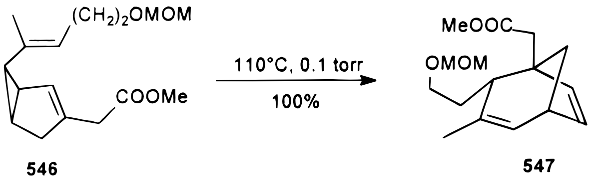




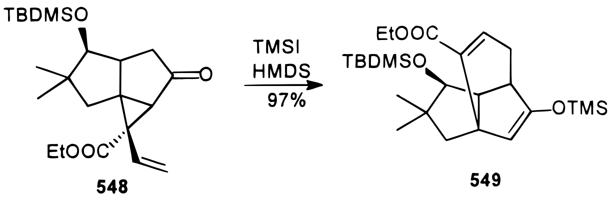
R^1 = Me, Et, *i*Pr, *n*Bu, allyl, (+)-menthyl
R^2 = H, Me
R^3 = H, allyl

2. From Cyclopropane-Containing Intermediates

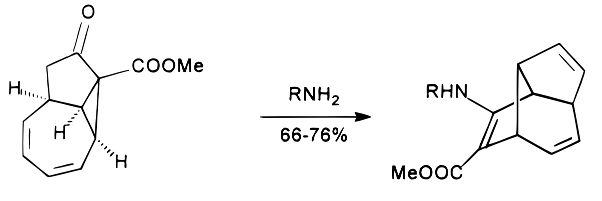
In the 1960s, it was shown that valence isomerization of highly reactive vinylcyclopropanes readily occurred to give bicyclo[3.2.1]octane systems.[317] After these pioneering observations, the [3.3] sigmatropic rearrangement of divinylcyclopropane systems became a powerful access to functionalized bicyclo[3.2.1]-octadienes which have found interesting synthetic applications, particularly from Piers's group.[318] For example, heating compound **546** at 110 °C under reduced pressure generated a quantitative yield of **547**, a precursor of prezizanol and prezizaene sesquiterpenes.[319]



Nucleophilic ring opening constitutes a versatile alternative to pyrolytic transformations, which was successfully used for the construction of complex bicyclo[3.2.1] derivatives such as **549**, easily obtained by reaction of ketone **548** with iodotrimethylsilane.[320]



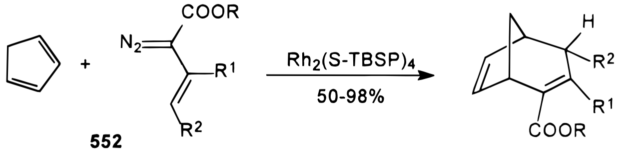
Quite similarly, reaction of tricyclic keto ester **550** with benzylamine or aniline provides the rearranged product **551** with respective yields of 66% and 76%.[321]



550

551: R = Ph, CH_2Ph

To overcome the difficulties in preparing stereoselectively the *cis*-divinylcyclopropane precursors, Davies proposed a powerful tandem cyclopropanation/Cope rearrangement process as a simple solution to this problem. An interesting review[322] on the topic appeared recently and well-illustrated the efficiency of this new approach. Subsequently it was demonstrated that asymmetric synthesis of bicyclo[3.2.1]octa-2,6-dienes **553** could be achieved by rhodium(II) (*S*)-*N*-[*p*-(*tert*-butyl)phenylsulfonyl]prolinate [Rh_2(*S*-TBSP)$_4$] catalyzed decomposition of vinyldiazomethanes **552** in the presence of cyclopentadiene.[323]



552

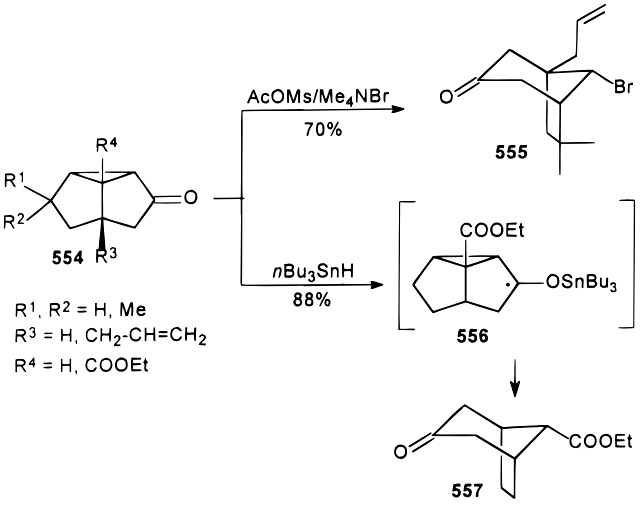
R = Me, Et, tBu

R^1 = H, Me, OTBDMS

R^2 = H, vinyl, Me, Ph, COOEt

553 (ee: 5-91%)

While the C2−C8 bond of the cyclopropane ring in tricyclo[3.3.0.0^{2,8}]octan-3-ones was generally found to cleave more easily than the C1−C2 bond,[324] few examples of the latter process have been reported. An elegant total synthesis of quadrone was elaborated through the fragmentation of **554** to the key bicyclic ketone **555** obtained in 70% upon reaction with bromide ion.[325] More recently, it was shown that reduction of strained tricyclic ketones **554** with nBu_3SnH gave a good yield of keto ester **557** via *O*-stannyl ketyl intermediate **556**.[326]



554

R^1, R^2 = H, Me

R^3 = H, CH_2-CH=CH_2

R^4 = H, COOEt

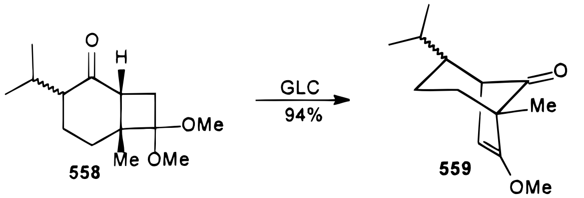
555

556

557

3. From Cyclobutane-Containing Intermediates

While the thermal cleavage of cyclobutene intermediates has found limited use for the construction of bicyclo[3.2.1]octanes,[327] solvolytic rearrangements of strained cyclobutanes constitute a rather general approach with interesting synthetic developments. For instance, the well-known Cargill-type[328] rearrangement of cyclobutyl carbinyl ketones has been exploited for the convergent synthesis of sativene, copacamphene, sativenediol, and helminthosporal from bicyclo[3.2.1]oct-6-en-8-ones **559**, easily obtained when dimethoxy ketals **558** were submitted to GLC conditions.[329] More recently, a Lewis acid catalyzed version, starting from heterosubstituted cyclobutenes **560**, was reported as a general access to highly functionalized bicyclic ketones **561**.[330]



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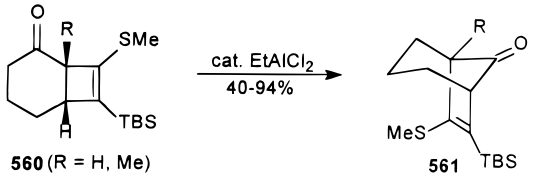
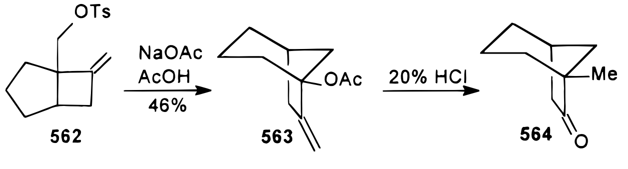
559



560 (R = H, Me)

561

The interesting tandem rearrangement of methylene cyclobutane **562** to acetoxy bridgehead olefin **563** or methyl bridgehead ketones **564**, first reported by Ziegler and Kloek,[331] was successfully applied to the total synthesis of steriol, isosteriol,[332] phyllacladene, and isophyllocladene[333] and more recently used for the stereoselective construction of *trans*-6/6-fused tricyclic structure **566** by reaction of mesylate **565** with $MeAlCl_2$.[334] A closely related solvolytic approach was exploited for the preparation of (−)-hibaene.[335]



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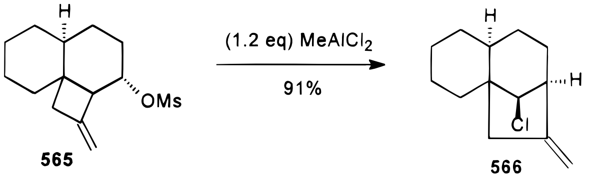
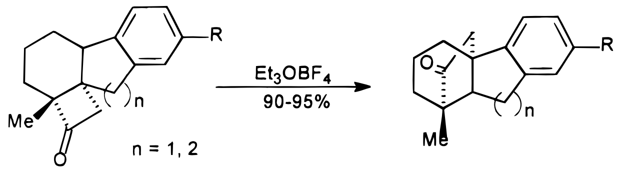


565

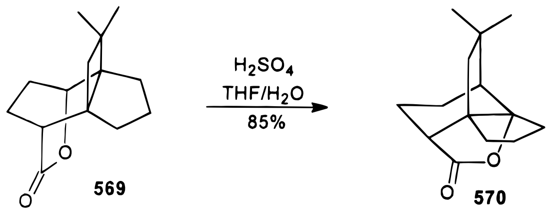
566

Alternatively, on treatment with triethyloxonium fluoroborate, the angularly fused cyclobutanones **567** suffered a stereoselective transformation to give the bridged tetracyclic ketones **568**, intermediates to diterpene alkaloids and C_{20} gibberellins.[336]



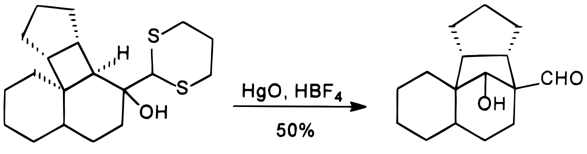
567: R = Me, OMe **568**

Cationic rearrangements of saturated analogues also represent an important synthetic tool used by Corey and Nozoe[337] in the direct synthesis of α-caryophyllene alcohol and subsequently applied by Yoshii and collaborators[338] in an elegant short-step entry to (±)-quadrone. A more recent extrapolation of these rearrangements to the [4.3.2]propellane lactone **569** constitutes the cornerstone of Smith's[339] synthetic strategy for the preparation of both enantiomers of quadrone from the rearranged tetracyclic lactone **570**.



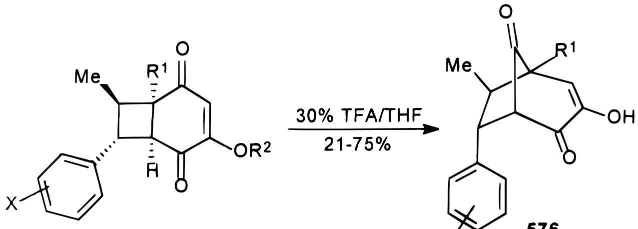
569 **570**

The reactivity of other polyclic α-substituted cyclobutanes such as **571** was used to access the synthetically valuable hydroxy substituted bicyclo[3.2.1] intermediate **572**.[340]



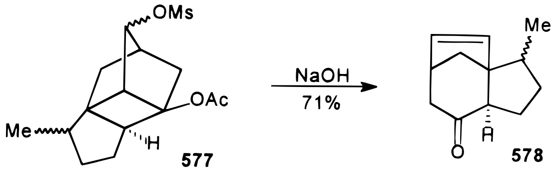
571 **572**

Similarly, the recent contribution from Engler's group,[341] directed toward the synthesis of burchellin and guianin neolignans, showed the facile acidic transformation of cyclobutanes **573**−**575** to the synthetically useful triketones **576**.



573: $R^1 = R^2 = Me$
574: R^1 = allyl, $R^2 = Me$
575: R^1 = allyl, $R^2 = Bn$
576

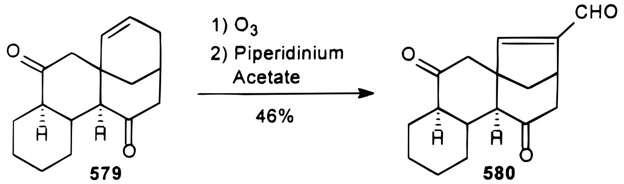
Besides solvolytic ring reorganizations, properly functionalized cyclobutanol intermediates can also be efficiently fragmented via a retro-aldol-type process. This method coupled with the intramolecular de Mayo cycloaddition was developed and judiciously utilized by Pattenden's group.[342] For instance, the selective fragmentation of tricyclo[3.2.1.$0^{3,6}$]octanes **577** appeared to be a general entry to bicyclo[3.2.1]-octane ring systems **578**, which was applied to the total synthesis of zizaene. Subsequently, Seto and coworkers[27] have used a similar approach for an expeditious preparation of daucene starting from **29** (vide supra).



577 **578**

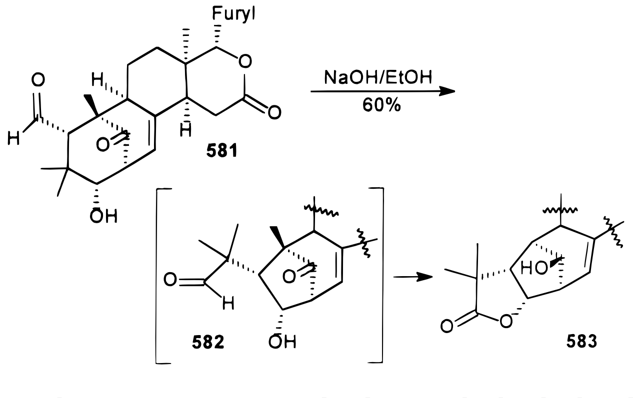
4. From Bridged Bicyclononane Precursors

The tandem ring cleavage and reconstitution sequence and the direct skeletal rearrangement approach constitute the two main methods used for the one-carbon atom contraction of bicyclo[3.3.1]nonanes. Corey and Nozoe[343] reported first the sequential oxidative cleavage−aldol condensation of unsaturated intermediates which was applied to the total synthesis of helminthosporal and gibberellic acid.[344] More recently, en route to the kaurane framework, a new exploitation of this methodology was proposed by Kraus and collaborators.[345] Ozonolysis of tetracyclic olefin **579** followed by cyclization of the resulting dialdehyde gave the [3.2.1] unit **580** found in corymbol diterpene.



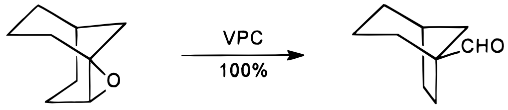
579 **580**

Also of interest is the remarkable formation of hydroxybicyclo[3.2.1]octane **583** by the base-mediated ring contraction of keto aldehyde **581** derived from naturally occurring swietenine.[346] The overall transformation evolved through a retro-aldol ring opening leading to **582** which suffered an intramolecular Cannizaro reaction followed by lactonization.



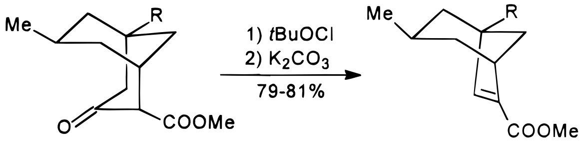
581 **582** **583**

A direct ring regression leading to the bridgehead aldehyde **585** was observed during purification of epoxide **584** by vapor-phase chromatography.[347] More



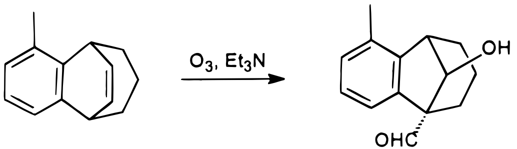
584 **585**

recently, the well-known Büchi[348] ring contraction, based on tandem dehydrochlorination–decarbonylation of chloro β-keto esters, was extrapolated to the bicyclo[3.3.1]nonane series **586** and proved to be a powerful entry to functionalized building blocks such as **587**.



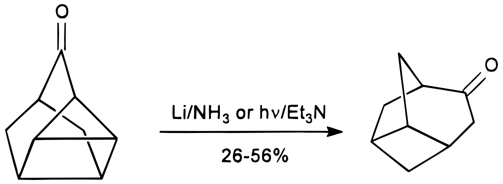
586 R = OH; -CH$_2$-CH=CH$_2$ **587**

Oxidative cleavage-induced one-carbon ring contraction of bicyclo[3.2.2]nonene **588** gave tricyclic aldol **589** which upon further modification served for the preparation of an intermediate involved in the total synthesis of laurenene.[349]



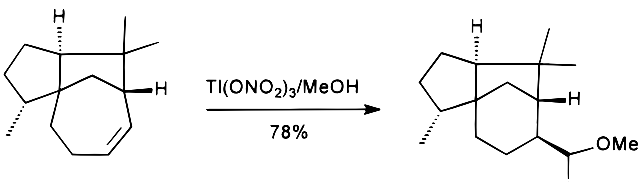
588 **589**

The novel tricyclononanone **591** was obtained recently by reductive cleavage of **590** with lithium in liquid ammonia or via photochemically induced electron transfer.[350]



590 **591**

An interesting ring contraction of a bicyclo[4.2.1]nonene was recently developed by Rigby's group[351] and successfuly applied for the synthesis of β-cedrene from the tricyclic acetal **592** obtained by reaction of olefin **593** with $Tl(ONO_2)_3$.



592 **593**

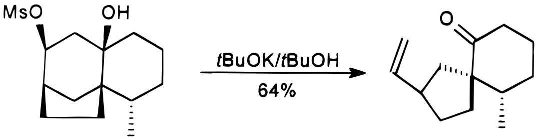
VII. Reactivity

Bicyclo[3.2.1]octanes constitute powerful building blocks with specific reactivities and have also proved to be useful intermediates in many fragmentations and rearrangements leading to nonbridged carbocycles or providing important tools for the construction of natural and unnatural bioactive products.

1. Fragmentations Leading to Nonbridged Carbocycles

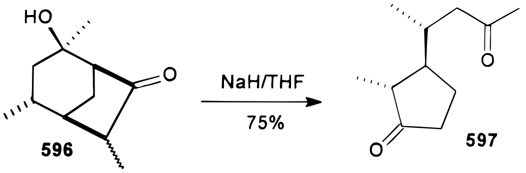
a. Five-Membered Rings

The fragmentation of bicyclo[3.2.1]octanes to cyclopentanes was observed more than 30 years ago during solvolytic studies of bridged bicyclic tosylates.[352] Since that date, important synthetic exploitations of such transformations have been proposed by many research groups. One of the first was the work of Marshall and Brady[108] who have included a Grob-type fragmentation as key step in a total synthesis of (±)-hinesol. The properly functionalized bicyclo[3.2.1]octanol **594**, underwent a ring fragmentation to the spiro framework **595** of the natural product.



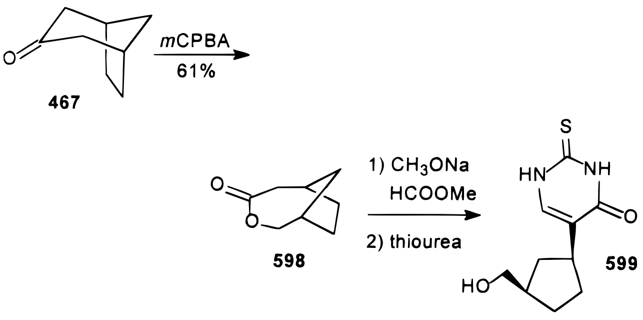
594 **595**

Also very interesting for the enantioselective construction of synthetic valuable cyclopentanoids is the recently reported[47] transformation of optically active bicyclic hydroxy ketones **596** obtained from (+)-nopinone. Exposure of **596** with NaH proceeded smoothly in retro-aldol reaction followed by epimerization of the ring methyl group providing a new route to cyclopentanone **597** having the absolute configuration found in the steroid D ring.



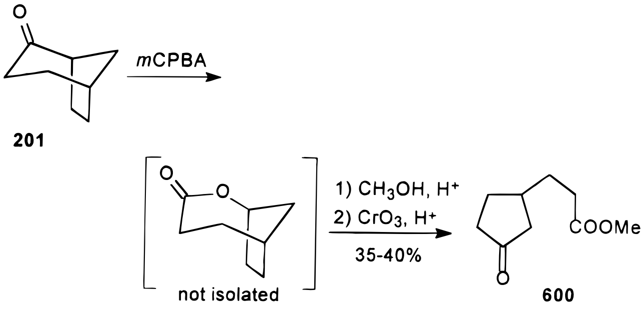
596 **597**

Oxidative degradation of bridged bicyclic ketones also constitutes a direct entry to cyclopentanoids. For example, Playtis and Fissekis[353] were the first to exploit Baeyer–Villiger oxidation of ketone **467** for the preparation of pseudonucleoside analogues such as **599**, after subsequent transformations of the resulting bicyclic lactone **598**.

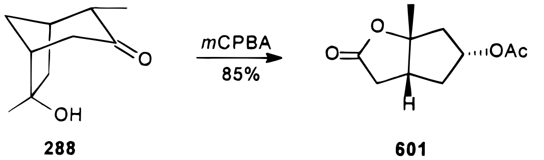


467 **598** **599**

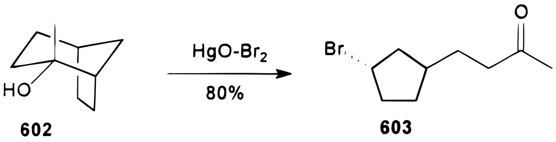
Contemporaneously, Eaton and collaborators[266] proposed the transformation of bicyclooctanone **201**, based on a regioselective Bayer–Villiger oxidation followed by methanolysis and Jones oxidation of the hydroxy ester intermediate, leading to the functionalized cyclopentanone **600** involved in the synthesis of peristylane.



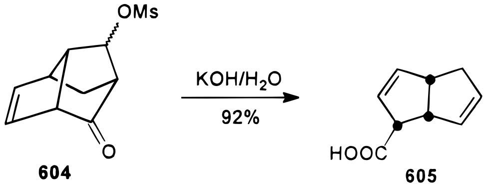
More recently,[164] an elegant asymmetric synthesis of (−)-hirsutene and (−)-3-hydroxyhirsutene from chiral bicyclo[3.2.1]octanone **288** was reported. Hydroxy ketone **288**, easily obtained from (*R*)−(−)-carvone is oxidatively rearranged to (+)-bicyclic lactone **601** precursor of the natural products by using standard modifications.



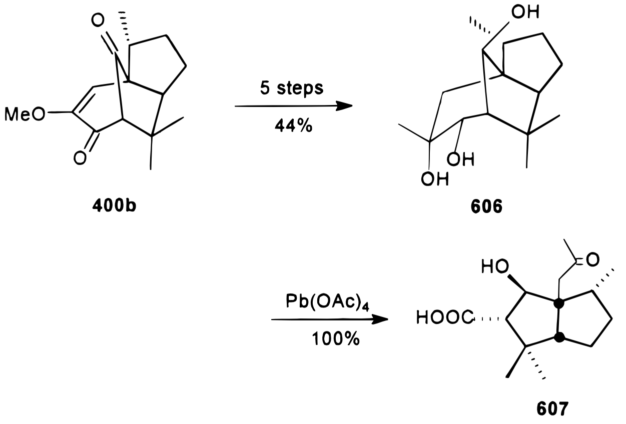
Alternatively, oxidation of alcohol **602** by HgO·Br$_2$ was found to give a β-fragmentation through the thermal decomposition of the intermediate hypobromite leading exclusively to the functionalized sensitive bromocyclopentane **603** in 80% yield.[354]



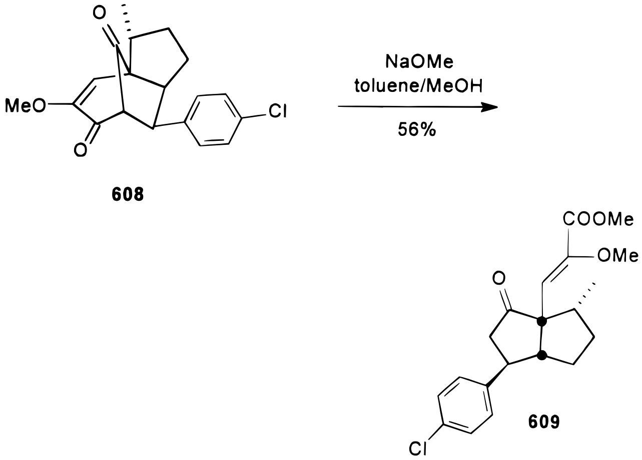
Skeletal rearrangements from bridged bicyclo[3.2.1]-octanes to the entropically disfavored[355] isomeric bicyclo[3.3.0]octanes were observed during solvolytic studies[356] or via β-enolization of bicyclooctanones,[357] but have been applied only recently for natural product synthesis. For example, a facile base-promoted fragmentation of 1,3-dioxygenated bicyclo[3.2.1] derivatives **604** appeared quite recently for the preparation of diquinane **605**, involved in the synthesis of verbenalol.[261]



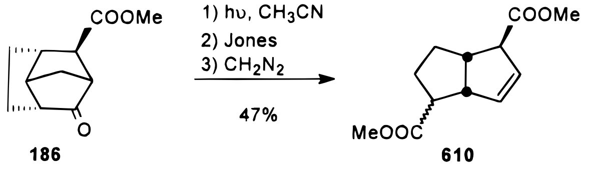
Yamamura and collaborators[225a] have developed the selective cleavage of highly functionalized bridged intermediates for the rapid construction of diquinanes as key building blocks for the synthesis of triquinane-type sesquiterpenes. For example silphinene was obtained through a sequence involving the oxidative cleavage of triol **606** elaborated by standard manipulations of dienone **400b**. Reaction of **606** with Pb(OAc)$_4$ gave the functionalized diquinane **607** precursor of the natural product.



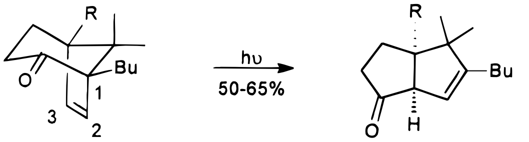
Two years later, the same group[225b] studied the behavior of **608** toward a chemoselective retro-Claisen reaction promoted by NaOMe which was found to give the bicyclo[3.3.0]octanone **609** in 56% yield as only one diastereomer.



Also of interest are photochemical transformations of properly functionalized substrates. One of the first synthetic applications concerns the irradiation of the tricyclic keto ester **186** which gave, after Jones oxidation of the intermediate aldehyde followed by esterification, the bicyclo[3.3.0] diester **610**, a key structural intermediate in the total synthesis of the naturally occurring iridoid glucoside, forsythide.[109]



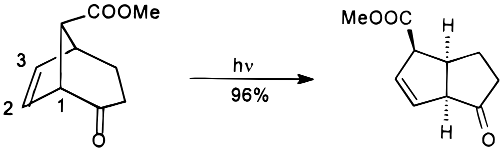
Similarly, Yamamoto's group[358] also used the regioselective photochemical [1,3]-acyl migration of various bicyclo[3.2.1]oct-6-en-2-ones **611** to bicyclic ketones **612** as a new entry to the total synthesis of $\Delta^{9(12)}$-capnellenes.



611
R = H, Me

612

Another elegant synthetic exploitation of this photochemical rearrangement appeared more recently with the facile transformation of **613** to synthetically useful diquinane **614** involved in the synthesis of mussaenoside and 8-epiloganin aglycons.[262]



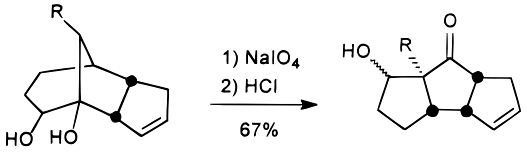
613

614

More recently, a Lewis acid catalyzed carbocyclic reorganization of highly functionalized bicyclic alcohols **615** was reported. $BF_3\cdot OEt_2$ was found to catalyze the rearrangement and bicyclopentenones **616** were obtained when $R^1 = H$ after quenching the reaction with a mixture of $CuCl_2\cdot H_2O$ and p-TsOH·H_2O. The transformation evolves through cationic intermediates with the selective migration of the C4–C5 bond to give good yields of **616** (Scheme 8). On the other hand, introduction of a methyl substituent at C1 (**615b**, $R^1 = Me$) results in an alternative mode of rearrangement leading to bicyclic dienes **617** by the selective migration of the C1–C2 bond.[359]

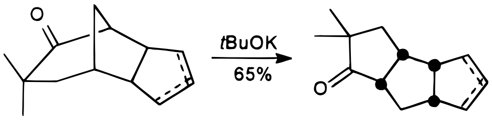
More complex cyclopentanoids such as triquinanes can also be conveniently obtained starting from properly functionalized bridged tricyclic substrates. In a very recent study, Singh and Jagadish[313] have exploited the tandem oxidative cleavage–intramolecular aldolization from tricyclic diol **618** as a new route to functionalized *cis*:*syn*:*cis*-tricyclopentanoids **619** obtained as a 1:1 mixture of hydroxy epimers.

Extensive work by Stother's group[360] concerning the homoenolization has strongly contributed to the development of this approach toward natural products synthesis. An illustrative example is the simple route to hirsutene by rearrangement of **490**, to lineary fused tricyclopentanone **620** precursor of the natural product.



618

619a: R = H
619b: R = Me

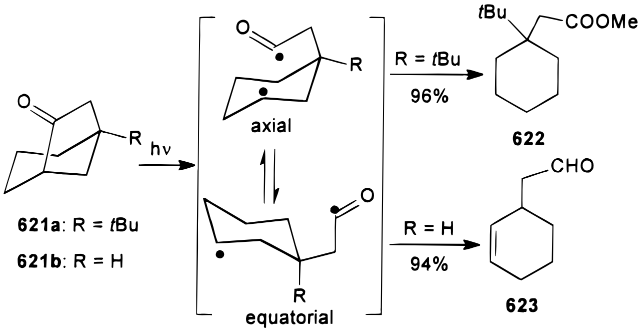


490

620

b. Six-Membered Rings

A detailed study of the photochemistry of substituted bicyclo[3.2.1]octan-6-ones leading to functionalized six-membered rings showed two different pathways controlled by conformational inversion of biradical intermediates.[361] For example, photolysis of *tert*-butyl bridgehead octanone **621a** gave almost exclusively the corresponding ester **622** obtained by trapping the ketene intermediate arising from disproportionation of the transient axial biradical. Contrarily, the unsubstituted bridged ketone **621b** evolved through the equatorial biradical after a conformational equilibrium to give the expected unsaturated aldehyde **623** with 93% yield.



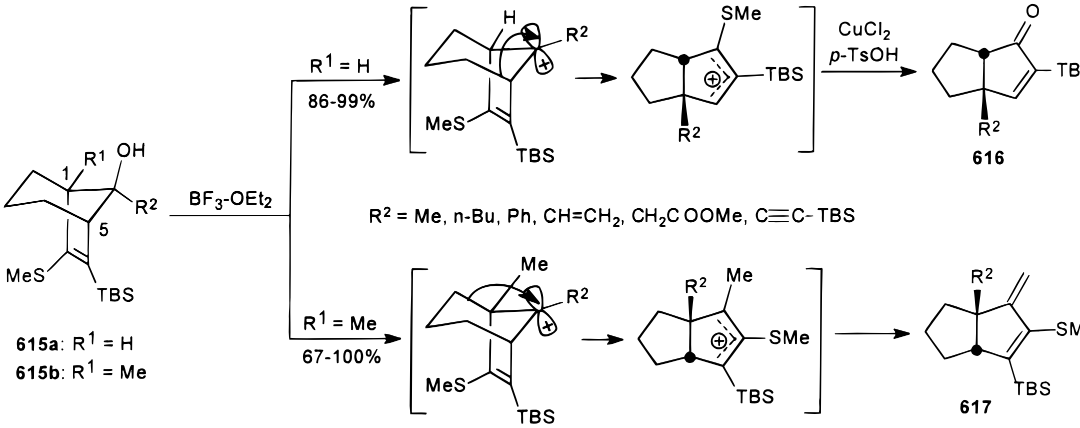
621a: R = *t*Bu
621b: R = H

622

623

The high synthetic potential of some bicyclooctanones was demonstrated by Monti and collab-

Scheme 8



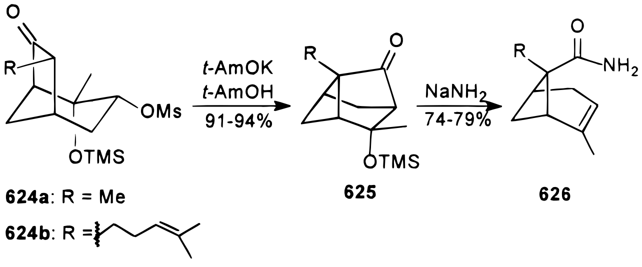
615a: R^1 = H
615b: R^1 = Me

616

R^2 = Me, n-Bu, Ph, CH=CH$_2$, CH$_2$COOMe, C≡C-TBS

617

orators[73b−d] and successfully applied to the stereoselective synthesis of natural compounds. For example, intramolecular alkylation of ketotosylate **624** delivered the strained tricyclic ketone **625** which suffered a fragmentation by reaction with $NaNH_2$ affording the bicyclo[3.1.1]heptane skeleton **626** of α-*cis*-bergamotene and α-pinene. Similarly, a Wharton-type



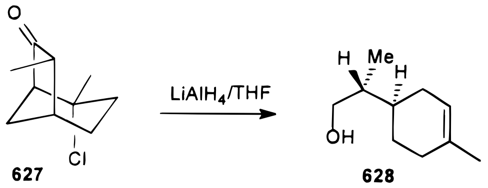
624a: R = Me

624b: R =

625

626

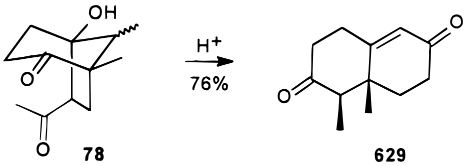
fragmentation of bicyclo[3.2.1]octane **627** was proposed as a key step in the stereoselective preparation of **628**, a juvabione synthesis relay.



627

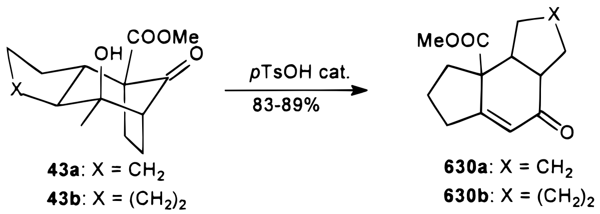
628

En route to the total synthesis of eremophilane type sesquiterpenes,[50] bicyclic hydroxy ketone **78** was easily transformed upon acidic treatment to decalone **629**, a key intermediate of the synthesis. This acidic retro-aldol−Robinson annulation sequence proved to be quite general and was applied to a variety of bridged intermediates such as **43** to form fused polycyclic derivatives **630**.[32]



78

629



43a: X = CH_2

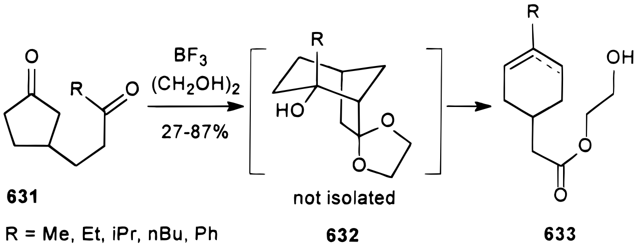
43b: X = $(CH_2)_2$

630a: X = CH_2

630b: X = $(CH_2)_2$

Sakai's group[362] found that under acetalization conditions, β-substituted cyclopentanones **631** undergo a facile ring transformation leading to functionalized six-membered rings **633** through the fragmentation of nonisolable bicyclic ketals intermediates **632**.

Finally, the construction of the calcitriol A ring precusor **636** from optically pure bicyclo[3.2.1]octenone **634** involved a regioselective Baeyer−Villiger oxidation followed by epoxidation to form **635** and subsequent translactonization to the desired bicyclic lactone **636**.[363]

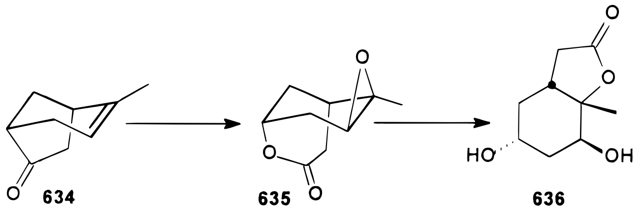


631

R = Me, Et, iPr, nBu, Ph

632

633



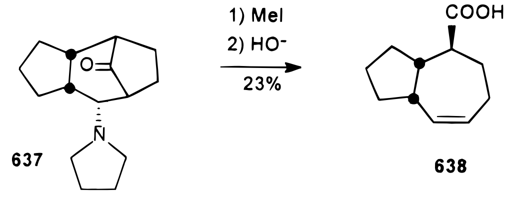
634

635

636

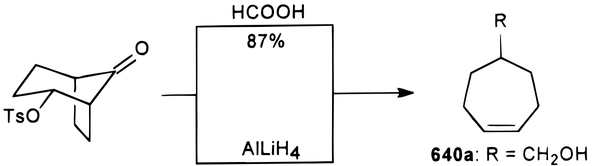
c. Seven-Membered Rings

The specific fragmentation of 2-amino-substituted bicyclo[3.2.1]octan-8-ones such as **637** known as Stork−Landesman procedure[28a] constitutes an old but efficient approach to cycloheptene carboxylic acids also useful for the preparation of functionalized perhydroazulenes **638**.[28b,c] A related fragmentation of tosylate **639** was observed upon solvolysis or reductive cleavage leading to the formation of functionalized cycloheptenes **640**.[364]



637

638

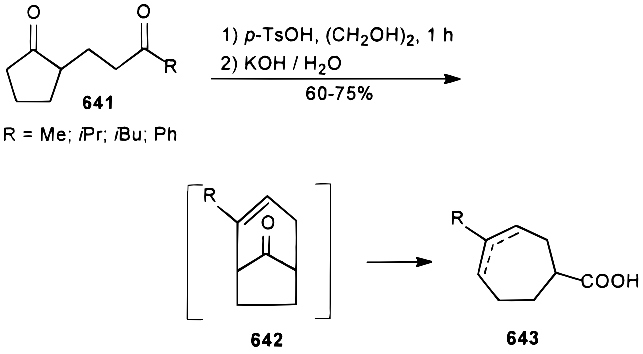


639

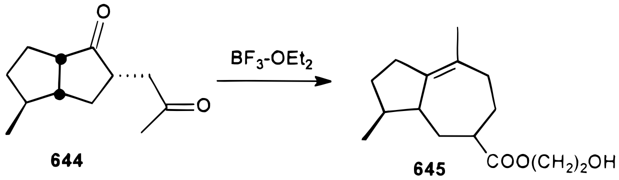
640a: R = CH_2OH

640b: R = COOH

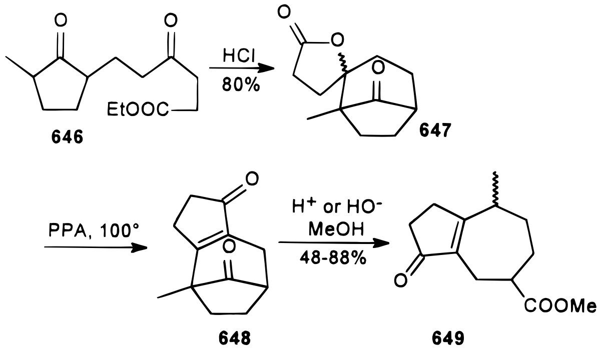
Following the pioneering work of Stork and Landesman, a strategy for the synthesis of seven-membered rings involving the tandem aldol formation-selective bridge scission of functionalized bicyclic intermediates has been extensively studied and reviewed by Buchanan in 1969[6a] and was first reported by Dauben and McFarland in 1960.[365] An illustration of this simple synthetic method is the facile one-pot preparation of functionalized seven-membered rings **643** from easily accessible 1,5-dicarbonyl substrates **641** under acetalization conditions which involves nonisolable bicyclo[3.2.1]octenones **642**.[366] More recently, Sakai's group[367] has adapted this powerful methodology to the synthesis of bulnesol starting from bicyclic cyclopentanone **644** which was successfully transformed to the desired hydrohazulene skeleton **645**



upon reaction with ethylene glycol in the presence of a large excess of $BF_3{\cdot}OEt_2$.

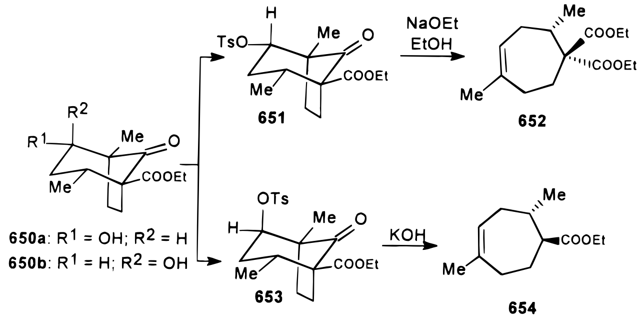


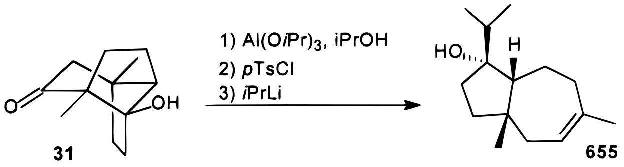
Starting from more elaborated diketones, functionalized hydroazulenes are also available, making this method useful for natural products synthesis as illustrated by a short total synthesis of racemic guaiol.[368] The overall sequence from ketone **646** involves aldol cyclization with subsequent intramolecular transesterification of the intermediate to give lactone **647** which is converted to **648**, precursor of the desired hydroazulene framework **649** which was converted to the natural product by standard transformations.



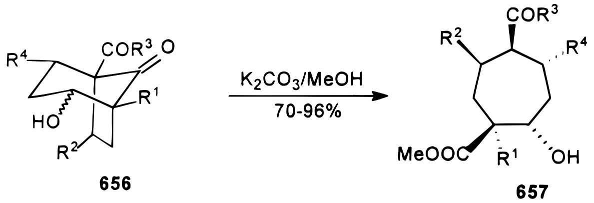
Another related and remarkable access to cycloheptenes involves the Grob-type fragmentation of bridged bicyclic tosylates also developed by Buchanan and collaborators.[30a,c] For example, hydroxy-substituted bicyclooctanones **650a** and **650b** were separated and transformed to the tosylates **651** and **653** which react with the same facility under fragmentation conditions but follow different pathways. When heated with NaOEt in EtOH **651** gives mainly the expected *gem*-diester **652** while **653** furnishes **654** through a retro-Dieckmann reaction followed by a *syn*-decarboxylative elimination of the tosyl and the carboxy groups.

A new entry to the total synthesis of daucene[27a] involved a related fragmentation of 1,3-hydroxy tosylate intermediate derived from **31** to give the new hydroazulene derivatives **655**, potential synthetic intermediates of some carotane- and dolastane-type terpenes.

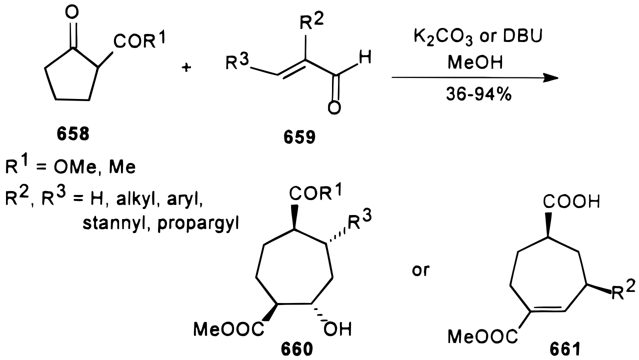




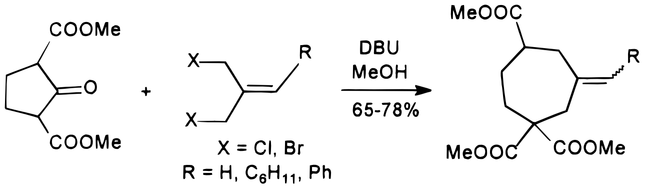
Recent studies from our group on the reactivity of aldols **656** showed a facile and stereoselective fragmentation promoted by K_2CO_3 in MeOH leading to functionalized cycloheptanols **657** in good yields.[34b]



This peculiar reactivity is at the origin of a new one-pot stereoselective two-carbon ring expansion[369] of cyclopentanones **658** with α,β-unsaturated aldehydes **659** through a cascade Michael addition–regioselective aldol cyclization–reverse Dieckmann ring cleavage (MARDi).[370] Highly substituted and stereodefined cycloheptanols **660** or cycloheptenes **661** are produced in good yields by using K_2CO_3 or DBU as promoters for the fragmentation.

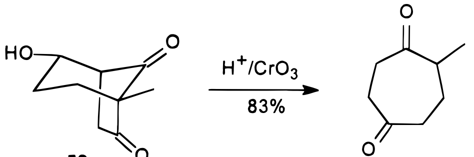


Similarly, a one-pot formation–in situ fragmentation of alkylidene bicyclo[3.2.1]octane derivatives was also recently reported[371] as a new facile anionic domino reaction for the preparation of functionalized cycloheptanes bearing an exocyclic unsaturation. Chemoselective α,α'-dialkylation of diactivated cyclopentanone **662** with 1,3-dihalides **663** takes place in MeOH under simple basic reaction conditions to give the bridged bicyclooctanone intermediates which suffered a retro-Dieckmann cleavage leading to the expected seven-membered rings **664** as mixtures of *E* and *Z* isomers in good overall yields.



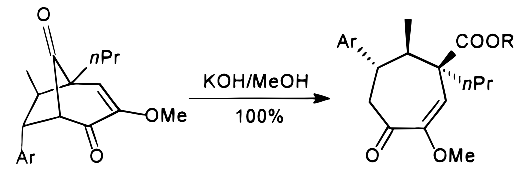
662 **663** **664**

Also of high synthetic value is the related retro-Claisen cleavage of 1,3-bicyclic diketones disclosed by Grob and Hostynek in 1963[372] and exploited more recently by Schick and collaborators[37] to produce 5-methylcycloheptane-1,4-dione (**665**). Oxidation of hydroxybicyclo[3.2.1]octanedione **52** gave a 83% yield of **665** after hydrolytic ring opening of the trione intermediate followed by in situ decarboxylation.

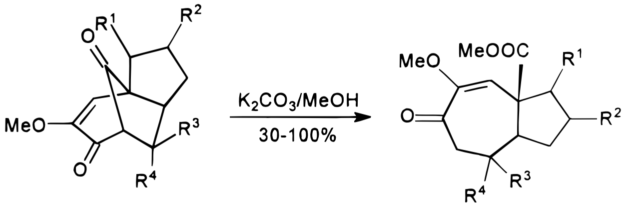


52 **665**

Similarly, base-induced retro-Claisen ring fragmentation of highly functionalized bicyclic intermediates furnishes cycloheptenone **666**, precursor of a substituted tropolone related to colchinine alkaloid.[223] This simple approach to seven-membered rings was then used as a general entry to highly functionalized *trans*-hydroazulenes **668** when coupled with Büchi type fragmentation of tricyclic intermediates **667**.[225c]



398 **666**

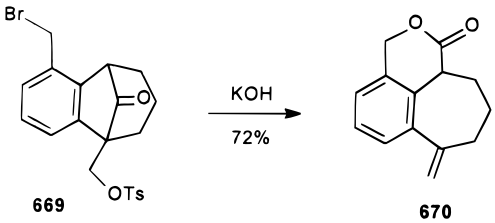


667 **668**

R^1 = H, Me; R^2 = H, OBn

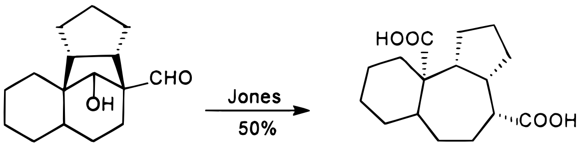
R^3 = H, CH_2-OBn; R^4 = H, CH_2-OBn, Ph, *p*-Ph-NO_2, *o*-Ph(OMe)$_2$

A related KOH-promoted Grob-type fragmentation of keto tosylate **669** gives a carboxylate anion intermediate which undergoes in situ heterocyclization to the tricyclic lactone **670** involved in the total synthesis of laurenene.[349]



669 **670**

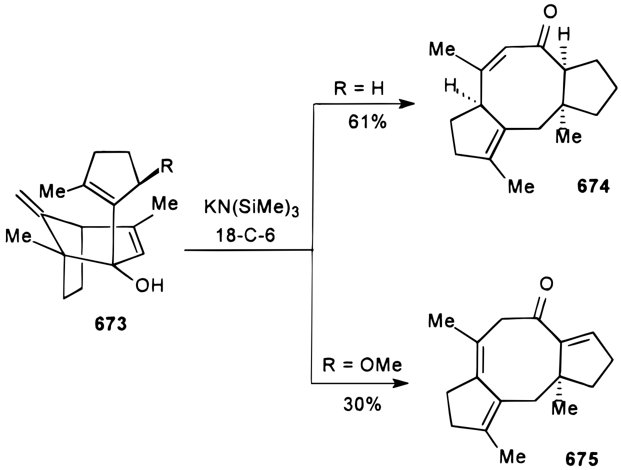
The reactivity of other polyclic bridgehead derivatives such as **671** has been used in a tandem process combining Jones oxidation and retro-aldol cleavage. This powerful technology allowed the stereocontrolled construction of angularly functionalized trans-fused cycloheptanoids such as **672**.[340a]



671 **672**

d. Eight-Membered Rings

While synthetically very interesting this type of ring reorganization is still rare and to our knowledge only one example is to be found in the literatrure. Paquette and co-workers[373] have prepared the methylene-bridged bicyclic alcohol **673**, involved in the construction of the dicyclopenta[*a*,*d*]cyclooctene core of ceroplastin terpenes through an easy anionic oxy-Cope rearrangement to produce the required fused systems **674** and **675** with high stereochemical discrimination.

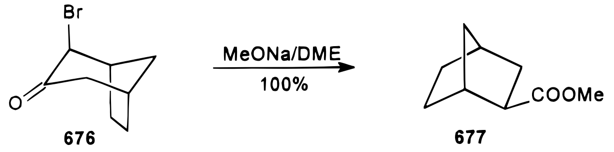


673 **674** **675**

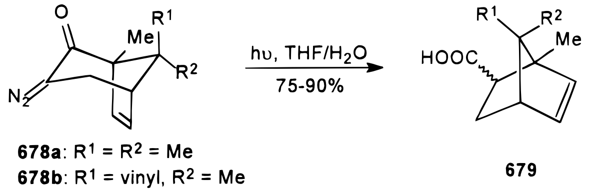
2. Isomerizations to Other Bridged Bicyclic Systems

a. Bicyclo[2.2.1]heptanes

If the ring enlargement of bicyclo[2.2.1]heptane constitutes a well-established method to access the bicyclo[3.2.1]octane skeleton, the reverse transformation, which has received much less attention, is also a viable synthetic process. For example, Favorskii ring contraction of *β*-bromobicyclooctanone **676** gives a quantitative yield of the corresponding bicyclo[2.2.1]heptane **677**.[374] More recently, the total synthesis of



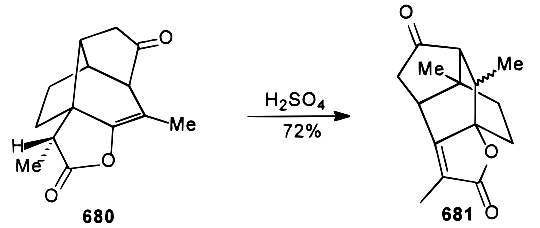
(±)-camphorenone, based on Wolf rearrangement of α-diazo ketones **678** to bicyclic carboxylic acids **679**, was reported by Uyehara and co-workers.[375]



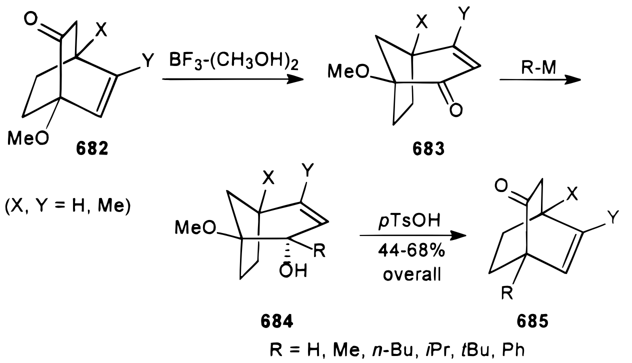
678a: $R^1 = R^2 = Me$
678b: R^1 = vinyl, $R^2 = Me$

b. Bicyclo[2.2.2]octanes

The reverse transformation, namely [3.2.1] → [2.2.2] has been known for a long time, but apart from the transformation of parasantonide (**680**) to a mixture of α- and β-metasantonins (**681**),[376] synthetic exploitation has emerged only recently.[377]



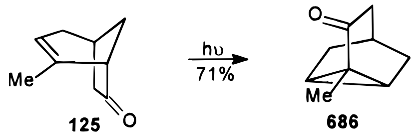
In 1989, Uyehara and collaborators[312] reported a very interesting and useful sequential rearrangement approach to bridgehead substitution of 1-methoxybicyclo[2.2.2]oct-5-en-2-ones. The method is based on the known isomerization of methoxy-functionalized bicyclo[2.2.2]octenes **682** into bicyclo[3.2.1]octenones **683**. Selective 1,2-alkylation of these intermediates with various nucleophiles gave the corresponding allylic alcohols **684**, which underwent a reverse ring reorganization to form a new bicyclo[2.2.2]octene **685** substituted at the bridgehead position. The first total



R = H, Me, *n*-Bu, *i*Pr, *t*Bu, Ph

synthesis of a novel sesquiterpenoid nakafuran[378] and a recent synthetic route to khusiol[379] well-illustrate the synthetic potential of this unique sequential transformation which has been extended recently to the formal substitution of both bridgeheads of a bicyclo[3.2.1]octenone.[380]

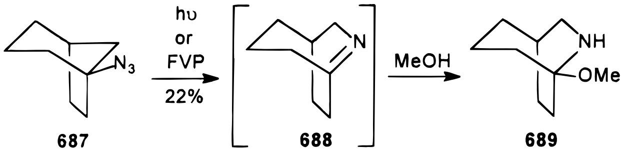
The strained tricyclic core of some important terpenes was easily constructed by photochemical rearrangement of **125** which produced a functionalized tricyclic cyclopropyl ketone **686**, a precursor used for the total synthesis of α-santalene and teresantalic acid.[73d]



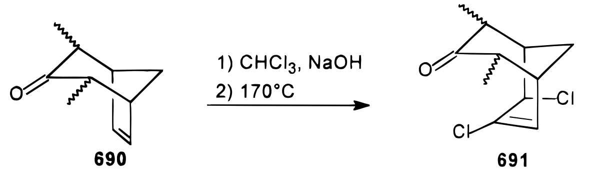
c. Other Bicyclo[n.m.1] Systems

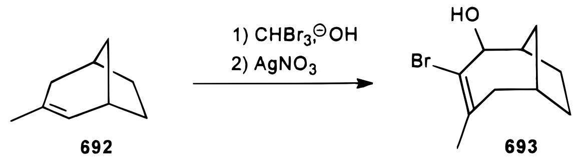
Starting from properly functionalized bicyclo[3.2.1] derivatives several selective ring expansions of the methano, the ethano, and the propano bridges have been developed.

An example of the less common atom insertion into the methano bridge is the thermal or photochemical decomposition of bridgehead azide **687** in MeOH, [381] which allows the isolation of **689** formed by addition of MeOH to the transient bridgehead imine **688** resulting from regioselective nitrogen insertion.



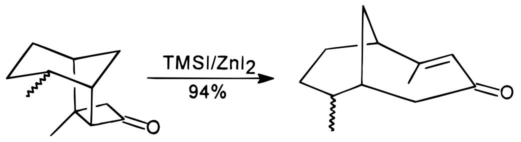
The one-carbon ring expansion of bicyclo[3.2.1] olefins **690** using the dichlorocarbene addition followed by fragmentation gave the expected dichlorobicyclo[3.3.1]nonanes **691**, precursors of functionalized barbaralanes.[382] Similarly, homologation of the six-membered ring unit of bicyclo[3.2.1]octene **692** was used for the preparation of various allylic alcohols of the bicyclo[4.2.1]nonane series such as **693**.[383]





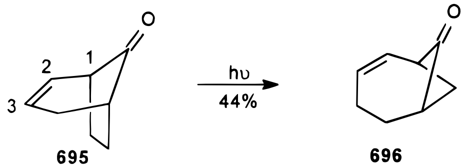
Dowd and collaborators[173] have used the reactivity of the useful fused tricyclic intermediates **304** which upon reaction with TMSI/ZnI_2 suffered a two-carbon ring expansion to form bridged bicyclo[4.3.1]dodecenones **694**.

Another unusual and interesting ring isomerization of bicyclo[3.2.1]octenones[384] was reported during ultraviolet irradiation of ketone **695**, which was easily transformed to bridged bicyclo[4.1.1]octenone **696** in 44% yield by photochemically assisted [1,3]-



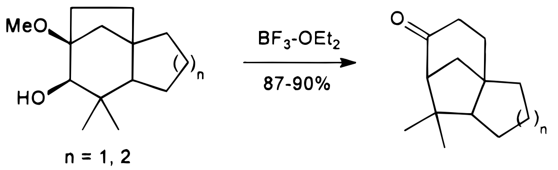
304 **694**

acyl migration resulting in a formal simultaneous ring expansion of the propano bridge and ring contraction of the ethano bridge.



695 **696**

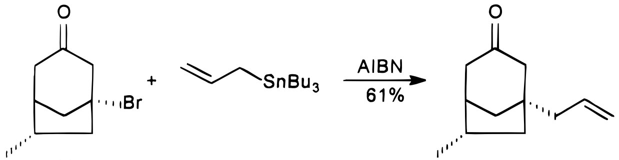
Finally, a novel ring reorganization of dihydroxy-substituted bicyclo[3.2.1]octanes to the isomeric bicyclo[3.2.1] ketones was recently reported and applied to the total syntheses of 2-norcedrene and funebrene analogues. Thus, treatment of methoxy bridgehead diols **697** with BF_3·OEt_2 in refluxing benzene gave the rearranged ketones **698** in very good yields.[385]



n = 1, 2
697 **698**

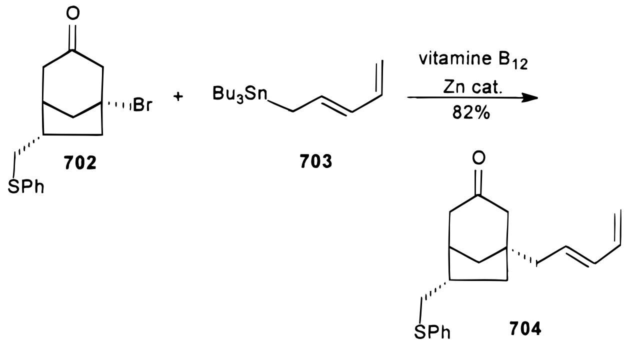
3. Selective Functionalizations of Bicyclo[3.2.1]octanes

While bridgehead carbocations are well-known and have been synthetically employed for a long time,[386] the use of the parent radical intermediates in synthesis is more recent. Fourteen years after Büchi's agarofuran synthesis,[387] based on an intramolecular bridgehead radical addition to an acetylene, Kraus and co-workers[388] studied the preparation and the reactivity of some bicyclo[3.2.1]octane bridgehead radicals. Their first report in this field concerns the substitution of bromide **699** with allyltributyltin (**700**) to give 61% yield of the corresponding allylated bicyclo[3.2.1]octanone **701**.

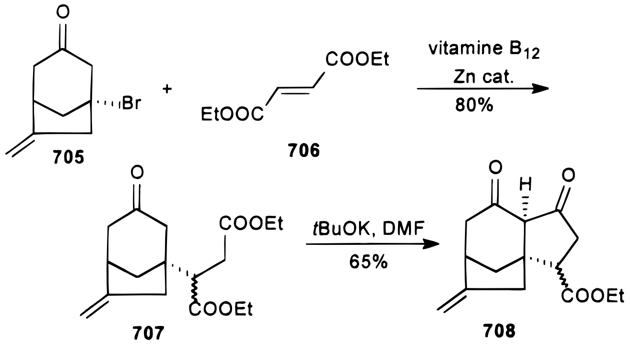


699 **700** **701**

Subsequently an elegant approach to the skeleton of leucothol A was elaborated from diene **704** obtained in 82% yield by vitamin B12−zinc catalyzed allylation of **702** with 2,4-pentadienyltributyltin (**703**). Similarly, organocobalt generated radical from keto bromide **705** adds to diethyl fumarate (**706**) to form, in 80% yield, **707**, a precursor of tricyclic diketone **708** which bears functionalities suitable for the synthesis of some gibberellins.

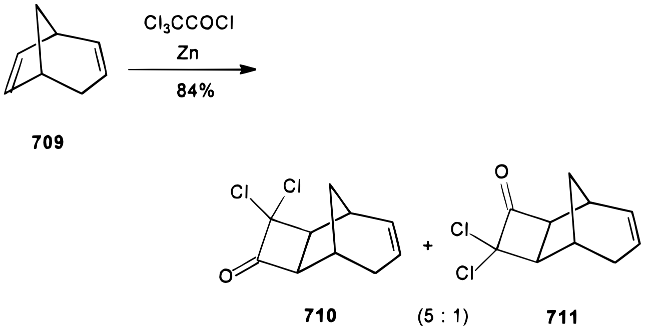


702 **703** **704**



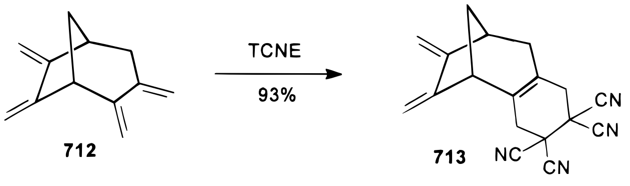
705 **706** **707** **708**

Unsaturated bicyclo[3.2.1] derivatives such as bicyclooctadienes constitute interesting substrates from a theoretical point of view [2a,b,d,389] but have also been used as synthetic tools in organic chemistry, especially in cycloaddition reactions.[390] For example, dichloroketene adds chemoselectively to the cyclopentene moiety of **709** to give the two regioisomers **710** and **711** in a ratio of 5:1.[391]



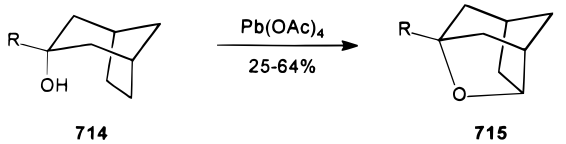
709 **710** **711**

Another interesting chemoselectivity during Diels−Alder reaction of tetrakis(methylene)bicyclo[3.2.1]-octane **712** with tetracyanoethylene (TCNE) was reported by Vogel and Gabioud[298] who have shown a higher reactivity of the 1,3-diene unit borne by the six-membered ring moiety, giving rise to **713** in 93%.



712 **713**

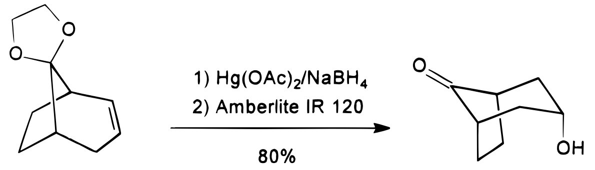
A selective transannular functionalization of hydroxy bicyclo[3.2.1]octene **714**, leading to the corresponding tricyclofurane **715**, can be promoted either by decomposition of the corresponding hypobromite[392] or by direct oxidation with $Pb(OAc)_4$, a method which was also effective in the cedrane skeleton.[393]



714
R = H, Me

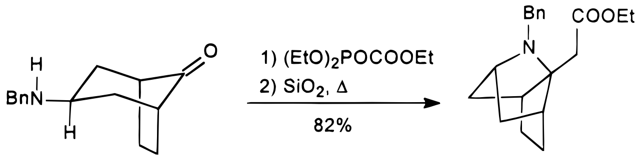
715

A synthetically useful hydroxy ketone **717** was obtained regio- and stereoselectively by oxymercuration−demercuration of bicyclo[3.2.1]octene **716**[394] and subsequently used for the preparation of a related aminobicyclic ketone **718** involved in a study of a transannular aza-Michael addition, leading to the bicyclo[4.2.1.0^{3,7}]nonane **719**.[395]



716

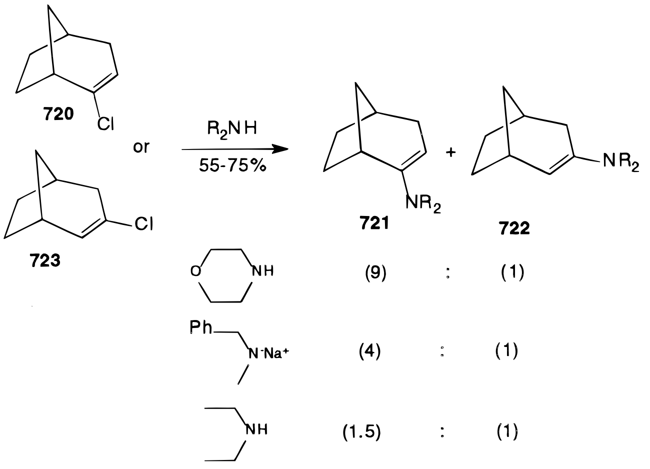
717



718

719

Finally, other functionalized bicyclo[3.2.1]octenes such as 2- or 3-halo derivatives have been involved in reactions with nucleopholic bases to give substitution products.[271,396] For example, 2- and 3-chlorobicyclo-[3.2.1]octenes **720** and **723** react with secondary amines to afford a mixture of the **721** and **722** in a ratio depending on the nature of the base used.[397]



VIII. Conclusion

The critical selection of the diverse methodologies developed over almost one century clearly shows that the bicyclo[3.2.1]octane system is still a challenging target. The high synthetic potential of this structural entity, found in important natural and unnatural compounds, is well-illustrated by numerous examples in which this bicyclic carbon framework is also a valuable reactive intermediate playing a significant role in many synthetic pathways.

Future development of new synthetic transformations will enlarge the chemistry of this target as recently shown by the first example of the utilization of ring-closing metathesis for the construction of bridged cycloalkenes including the [3.2.1] skeleton,[398] the enantioselective intramolecular cyclization of prochiral cyclohexanones,[399] and new applications of the Prins reaction[400] or of the Mn(III)-based oxidative free radical cyclization,[401] which appeared while this review was in revision.

We are currently engaged in efforts to develop new anionic domino reactions for the stereoselective synthesis of polycyclic systems presenting high synthetic value.[399]

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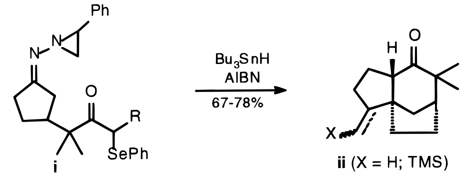

i **ii** (X = H; TMS)

R = $CH_2CH{=}CH_2$; $CH_2CH_2{-}C{\equiv}C{-}TMS$

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