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RECENT DEVELOPMENTS IN THE SYNTHESIS, STRUCTURE AND CHEMISTRY OF BRIDGEHEAD ALKENES

KENNETH J. SHEA
Department of Chemistry, University of California, Irvine, CA 92717, U.S.A.

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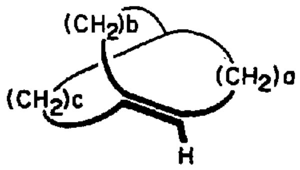
INTRODUCTION

Strain can be introduced in a molecule by distorting one or more chemical bonds from their "normal" bond lengths or bond angles. A substantial effort is directed towards the generation and study of strained organic molecules and comprehensive reviews are now available.[1,2]

Bridgehead alkenes represent a subclass of strained organic molecules that have been of keen interest to chemists for over fifty years. In the mid-1920s, Julius Bredt summarized the results of a study of the chemistry of naturally occurring bicyclic terpenes.[3] His conclusions, originally directed towards systems of the camphane and pinane series, ruled out the possibility of a double bond eminating from the bridgehead position. These findings, further elaborated and generalized by Bredt,[4] had an important influence on the development of many important classes of compounds that possess polycyclic skeletons. The guidelines that Bredt developed, although somewhat imprecisely defined, became known as Bredt's Rules.

The prohibition of bridgehead double bonds, of course, is not absolute. In bicyclic systems (1) where $S = a + b + c$ = large number, the double bond would exhibit properties quite similar to a normal trisubstituted C=C double bond. The practical limitations of Bredt's Rule were established by Prelog *et al.*[5] From a consideration of the stable, isolatable compounds derived from base catalyzed intramolecular aldol cyclization of a series of 2-carbomethoxy-2-(3-ketocycloalkanones), e.g. 2, it was concluded that Bredt's rule does not forbid a bridgehead double bond for the bicyclo[5.3.1] undecene ring system, e.g. 3. Because products derived from the bicyclo[4.3.1]decyl and smaller ring systems could not be isolated, it was assumed that these ring systems could not accommodate a bridgehead double bond.



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The literature up to 1950 was carefully summarized in a review by Fawcett.[6]

A breakthrough occurred in 1967 with the independent reports of Wiseman[7] and Marshall[8] of the synthesis of bicyclo[3.3.1]non-1-ene, an isolatable, although reactive, bridgehead alkene that contains a total of seven bridging atoms (S = 7). Many additional examples followed and several excellent reviews have since appeared.[9–12]

This review summarizes some of the more recent developments in the field in addition to drawing attention to certain aspects not treated in detail in previous reviews. Bridgehead alkenes, particularly the more highly strained members of the group, remain a challenging target for the synthetic organic chemist. The growing assortment of methods for the synthesis of compounds that contain bridgehead double bonds broadens the scope of this field by opening the possibility of utilizing these compounds as key intermediates in synthetic organic chemistry. Several applications of this type are noted in the last section of this review.

THERMODYNAMIC STABILITY AND STRUCTURE OF BRIDGEHEAD ALKENES

There have been several proposals that have attempted to relate the stability of a bridgehead alkene to the corresponding carbocyclic skeleton. Fawcett developed a quantitative expression of Bredt's rule which defined the S number as the sum of the number of atoms in the bridges of a bicyclic system, **1**, $S = a + b + c$.[6] Based upon the available data, Fawcett proposed that bridged bicyclic systems with $S = 9$ would be stable enough to permit isolation of the bridgehead alkene. An upper limit to the ring size for which the rule forbids such double bonds in isolatable compounds was placed at $S = 8$ while a lower limit at $S = 6$ was placed on transient reaction intermediates. Subsequent findings by Wiseman[7] and Marshall[8] necessitated a revision of these rules. To date the most successful scheme is that proposed by Wiseman which calls attention to the relationship between bridgehead alkenes and *trans*-cycloalkenes.[13] A bridgehead double bond in any bicyclic alkene is endocyclic to two rings (**1**); the double bond is *cis* in one ring (a–b) and *trans* in the other (a–c). Wiseman proposed that the strain of the bridgehead alkene is closely related to the strain of the corresponding *trans*-cycloalkene. Since *trans*-cyclooctene is the smallest *isolatable trans*-cycloalkene, bridgehead alkenes that incorporate this ring system should be isolatable, albeit highly reactive.

The Wiseman proposal permits a clear choice regarding the relative stability of certain isomeric bridgehead alkenes; thus both **4** and **5** (*trans*-cyclononene) are expected to be more stable than **6** (*trans*-cycloheptene). The proposal does not permit one to order the relative stabilities of isomers **4** and **5**, however.

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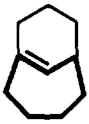

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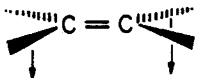

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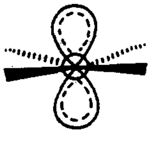
To understand the origin of the distortion (strain) in the bridgehead double bond it is instructive to consider first the structure and strain energy of *trans*-cyclooctene, a compound for which there is ample structural, thermochemical, and theoretical data.

The distortion imposed on a C=C double bond in a *trans*-cycloalkene is illustrated in the sequence **8**→**10**. The *trans*-linkage tends to twist the C=C double bond out of coplanarity (**8**→**9**), resulting in loss of overlap of the two p orbitals. In order to regain some of the p orbital overlap, it was suggested that the double bond carbons undergo a modest rehybridization (**9**–**10**), with incorporation of some s character into the p orbitals.[14–16] A consequence of this rehybridization is the pyrimadizalation of the carbons in the double bond (**10**).[10] There are two deformations which describe the double bond in



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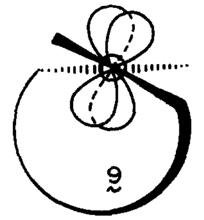

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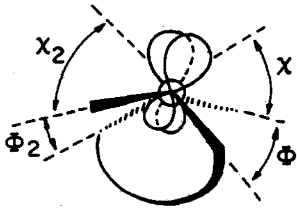

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trans-cycloalkenes, pure twisting or torsion Φ (deviation from coplanarity of the two p type orbitals) and out of plane bending (χ) which is a measure of the extent of rehybridization at the "sp^2" carbons. The independent geometric parameters that are necessary to define these non-planar distortions are shown in the figure. χ_1 and χ_2 are the angles formed by the single bonds eminating from the sp^2 carbons and measure the extent of out of plane deformations at each sp^2 center. Φ_1 and Φ_2 are the opposite C–C=C–C and C–C=C–C torsion angles. The angle of pure twisting (r) is defined as the average of these torsional angles; $(\Phi_1 + \Phi_2)/2$. A recent X-ray crystal structure of a *trans*-cyclooctene derivative demonstrates the extent of these distortions, **11**. The angle of pure twisting, τ, $(\Phi_1 + \Phi_2/2)$ is 18.5° and the two out of plane angles, χ_1 and χ_2, are 20° at C_1 and 28° at C_2 for *trans*-2-cyclooctenyl-3′,5′-dinitrobenzoate.[17] Thus, the average deviation of the C–C=C–C torsion angle from 180° (42.5°) is composed of two components, 18.5° of pure twisting and 24° of out of plane bending.

Force field calculations have been shown to satisfactorily reproduce the geometry and experimental strain energy of *trans*-cyclooctene.[16]

More recent calculations with bridgehead alkenes provide insight to the origin and magnitude of strain. These calculations establish more firmly the relationship between *trans*-cycloalkenes and bridgehead alkenes.[18] The strain energy of a bridgehead double bond (E_{oop}) is attributed to the sum of two deformation energies. This energy is associated with a twisting deformation E_Φ (a function of Φ_1 and Φ_2) and an out-of-plane bend E_χ (a function of χ_1 and χ_2). For example, in *trans*-cyclooctene the calculated deformation energies are $E_\Phi = 3.8$ and $E_\chi = 3.9$ kcal/mole. Thus, there is an almost equal contribution from each deformation made to the total deformation energy $E_{oop} = E_\Phi + E_\chi = 7.7$ kcal/mole.

Comparison of the calculated out-of-plane deformation energies (E_{oop}) for a number of bridgehead alkenes with E_{oop} of the corresponding *trans*-cycloalkene reveals a striking parallel.[18]

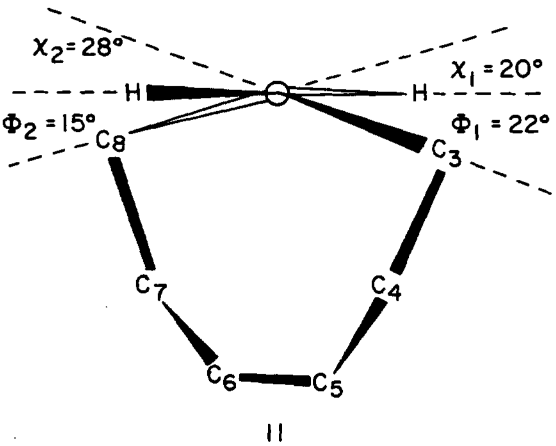

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Fig. 1. Torsion and out-of-plane bending angles (°) at the double bond (C_2=C_1 projection) of the 3,5-dinitrobenzoate ester of *trans*-cyclooctene-3-ol.

Based upon these observations the authors propose a quantitative reactivity criteria for bridgehead olefins. If one assumes the reactivity of such molecules can be expressed primarily in the non-planar deformation energy (E_{oop}) of the double bond (i.e. the sum of the deformation energies for pure twisting and out of plane bending) then room temperature chemical stability can be associated with those bridgehead alkenes possessing up to 15 kcal/mole of deformation energy per double bond. A larger calculated E_{oop} indicates chemical instability.

This rule is a quantitative expression of Wiseman's proposal since only bridgehead alkenes with *trans*-cyclooctene rings or larger fall within the stability limitations, the E_{oop} values of bridgehead alkenes containing *trans*-cycloheptene and *trans*-cyclohexene rings are higher than this limit by 2.4–9.0 and 16.8–25.5 kcal/mole, respectively.

These calculations predict an ordering of the relative stability of isomeric bridgehead alkenes. Interestingly, for pairs **12**, **13** and **14** the isomers with the double bond in the *shorter* bridge are calculated to be more stable. This same order of stability has been found in recent force field calculations by Burkert,[19] several results of which are given in Fig. 2. These calculations, together with recent experimental evidence, are contrary to conclusions arrived at in earlier work.[19,20]

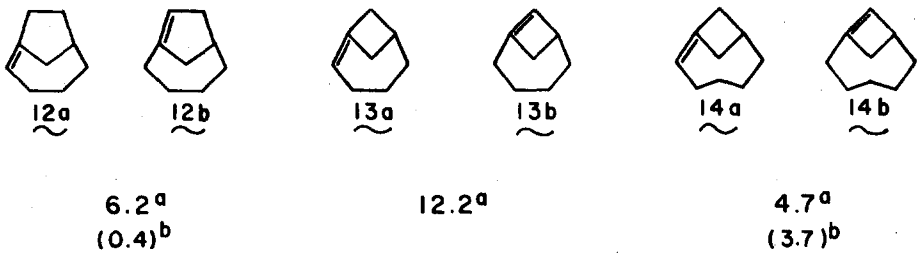

Fig. 2. Calculated potential energy differences (in kcal/mol) between isomeric bridgehead alkenes. In the above examples the compound with the bridgehead double bond in the smaller ring is the isomer calculated to be the most stable. [a]Ref. 18, [b]Ref. 19.

The individual C atoms in the bridgehead double bond are quite dissimilar. A consequence of the constraints imposed upon the bridgehead C atom is a greater pyramidal distortion (out-of-plane bending) at this site. It is quite possible that chemical reactivity, in particular the regiochemistry, can, at least in part, be attributed to the difference in hybridization between these two carbons. The bridgehead carbon is expected to be *less* nucleophilic than the second C atom of the double bond.

BRIDGEHEAD ADDITIONS AND ELIMINATIONS

All things being equal, the ease of formation of a bridgehead double bond or the facility with which reagents add to a bridgehead double bond is one measure of its kinetic and/or thermodynamic stability.

The rate and mechanism of hydration of strained bridgehead olefins **15** and **12b** were recently reported.[21] The kinetic isotope effects, $k_{H^+}/k_{D^+} = 2.5$ for **15** and 2.1 for **12b** are very similar to those observed for the addition of water to vinyl ethers. These results imply a rate determining proton transfer from catalyzing acid to the substrate. The reactions exhibit general acid catalysis which is also consistent with this finding. The second step in the reaction involves rapid hydration of the carbonium ion. The overall mechanism is completely analogous to the mechanism of hydration of simple unstrained olefins (eqn 1).

The strained double bond is higher in energy and considerably more reactive than a simple unstrained alkene, which is expected to result in an early transition state. A comparison of the rates of hydration of bridgehead alkenes **15** and **12a** with 2-methyl-2-butene permit a quantiative estimate of the rate acceleration provided by strain (Table 1). The 10^5-fold rate increase of **15** over 2-methyl-2-butene corresponds to a free energy difference of 7 kcal/mol. This value is less than the 12 kcal/mol strain in the bridgehead double bond[23] and implies that there is considerable strain present in the protonation transition state.

A comparative study of three isomeric bridgehead olefins **15**, **12** and **12b** towards addition of electrophilic reagents (H_2O, HOAc, HBr) has been used to evaluate the relative strain energies of the bridgehead double bonds.[22] Reaction of all three olefins with acetic acid took place without catalysis by mineral acid. Protonation is regiospecific and in all cases leads to the tertiary carbonium ion (eqn 1); the bridgehead acetates are the only products formed. Bridgehead alkene **15** is substantially more reactive than olefins **12a** and **12b**; addition of acetic acid is complete within minutes at room temperature. The relative rates of addition are given in Table 1.

Compounds **12a** and **12b** may be compared directly since they lead to the same carbonium ion. Since the transition state in endothermic carbenium ion formation should resemble the reaction intermediate, the difference in activation enthalpy $-\Delta\Delta H^{\ddagger}$) for protonation of **12a** and **12b** should be a reasonable

Table 1. Rates of electrophilic addition to strained bridgehead alkenes

REAGENT	 15	 12b	 12a		
H_3O^+ (25 °C)	1.24×10^5 (110)	1.12×10^3 (1)	---	(1)	REF 21
HOAc (25 °C)	275	(1)	3.95	---	REF 22

approximation of the ground state enthalpy differences between the two isomers. This analysis leads to the conclusion that **12a**, with the bridgehead double bond in the 4-atom bridge, is *more* strained than **12b** ($\Delta\Delta H^{\ddagger} = 0.6$ kcal/mole).

The authors go on to compare the relative strain energies for all three olefins using activation parameters for solvolysis of the bridgehead bromide of the corresponding alkene as a reference. Based upon this comparison and using the absolute value of strain of the double bond in **15** (12 kcal/mol),[23] the strain energy in bicyclo[4.2.1]-1(8)-nonene (**12b**) is estimated to be 8 kcal/mole compared with 9 kcal/mol in bicyclo[4.2.1]-1(2)-nonene (**12a**). Both olefins have similar double bond strain energies when compared with the parent *trans*-cyclooctene (9 kcal/mol).[24] Recent theoretical calculations are in agreement with the relative strain energies of bridgehead alkenes **12a** and **12b**.[18,19] There does not appear to be a simple relationship between the strain in the double bond and the substitution pattern of the bicyclic olefin. These results emphasize that the origins of ring strain in bicyclic molecules are subtle and caution should be exercised when predicting the relative strain in isomeric bridgehead alkenes.

An interesting comparison of the chemical reactivity of 1-methyl-*trans*-cyclooctene (**16**) and bicyclo[3.3.1]non-1-ene (**15**) has appeared.[25] Reactivity of **16** parallels more closely that of *trans*-cyclooctene than that of the bridgehead alkene. Thus in Diels–Alder and 1,3-dipolar cycloadditions, bridgehead olefin **15** is > 10 times more reactive than **16**. Only in electrophilic additions (H_3O^+, HOAc, Br_2) does **16** exhibit reactivity similar to **15** and not to *trans*-cyclooctene.

(1)

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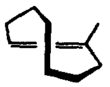

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The stereo- and regiochemistry of additions and eliminations from the bridgehead position have been the subject of several reports. A clear cut preference for *syn*-elimination has been established in the dehydrobromination of 3-bromo-tricyclo[5.3.1.$0^{3,8}$]undecane(3-bromohomoisotwistane **17**). In compound **17** the *exo*-H atom is rigidly held *cis* to the leaving 3-Br atom. Treatment of 2-*exo*-deuterio bromide (2-*exo*-^{2}H)-**17** with sodium amide in refluxing toluene yields the bridgehead alkene, tricyclo[5.3.1.$0^{3,8}$]undec-2-ene(4-homoisotwistene, **18**) containing only 0.3% of the 2-deuterio-olefin (2-^{2}H)-**18**. The low deuterium content in the bridgehead alkene product corresponds to a rate of *syn*-elimination 300 times larger than that of *anti*-elimination.[26]

This marked preference for *syn*-elimination prompted a study of the addition of a variety of reagents to 4-homoisotwist-2-ene (**18**). As expected, reactions are strongly *syn*-stereoselective.[27]

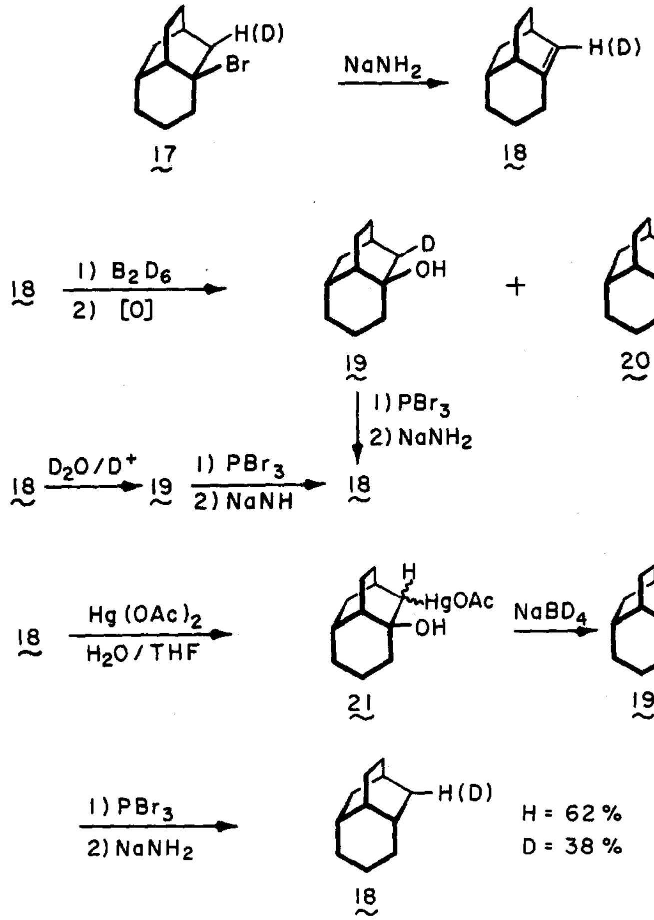
Hydroboration or deuterioboration of **18** proceeds with low regioselectivity resulting in mixtures of isomeric alcohols **19** and **20**. Stereospecificity, however, was high; the *endo* epimer of **20** was not obtained.

Acid catalyzed hydration (D_2O, D_2SO_4) of **18** yields exclusively the 2-deuterio-3-ol **19**, isotopic purity—86%. The bridgehead olefin (**18**) obtained from halogenation and elimination of this alcohol contains 0.6% [2-^{2}H]-18; this corresponds to almost complete *exo*–*syn*-addition of D_2O to the olefin.[28]

In contrast to hydration, the stereochemical findings of oxymercuration suggest comparable amounts of *syn* and *anti* addition of Hg^{2+} and nucleophile to the bridgehead double bond. This conclusion is based upon the extent of deuterium in the alkene (**18**) after a reductive deuteration, halogenation, and elimination sequence (eqn 2). Since only the 2-*exo*-position is eliminated upon dehydrohalogenation, the extent of retention of deuterium in the final olefin is used as a direct probe of the *syn* or *anti* addition mechanism.

To account for these results the authors are forced to propose that the *endo* face of alkene **18** is the sterically least hindered. They go on to suggest that electronic factors (i.e. greater electron density) are responsible for the previously observed *syn*–*exo* attack of diborane and water.

This analysis may be in error. An alternative explanation for the lack of stereospecificity in the mercuration reaction is the known lack of stereospecificity in the sodium borohydride (deuteride)



(2)

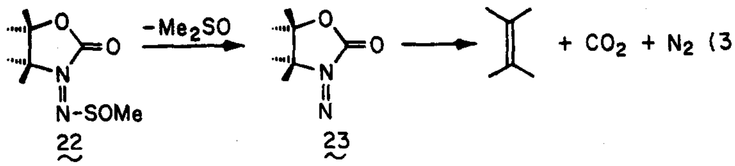
reductions of organomercury derivatives.[29] This reduction, believed to proceed by a free radical mechanism,[30] can incorporate deuterium from both *exo* and *endo* faces (lower selectivity in homolytic hydrogen transfer reactions). The deuterium incorporation in bridgehead alkene **18** need not, therefore, be a measure of the *syn,anti*-stereospecificity of the oxymercuration step.

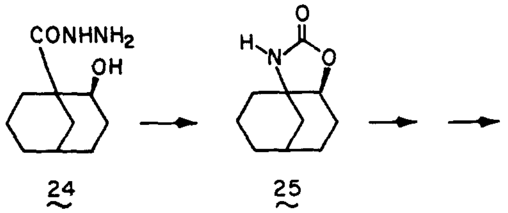
These regio and stereochemical preferences of bridgehead double bonds would appear to be consistent with the earlier investigations of Wiseman[13] and Marshall[31] who found high *syn*-stereospecificity in additions to the bridgehead double bond in bicyclo[3.3.1]non-1-ene. Low regiospecificity in hydroboration was also noted in these earlier studies.

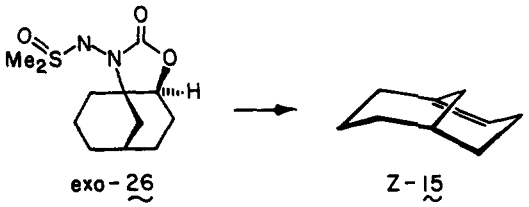
Thermal decomposition of N-sulfoximino-2-oxazolidones (**22**) yield Me_2SO, CO_2, N_2, and an olefin. The olefin is formed via a *syn* elimination from the sulfoxime, with probable involvement of a diazine intermediate **23** (eqn 3). This method proved to be highly effective for the synthesis of bicyclo[3.3.1]non-1-ene. In addition, the sulfoximine route permits a distinction between the relative ease of formation of the *E* and *Z* isomers of this bridgehead alkene.

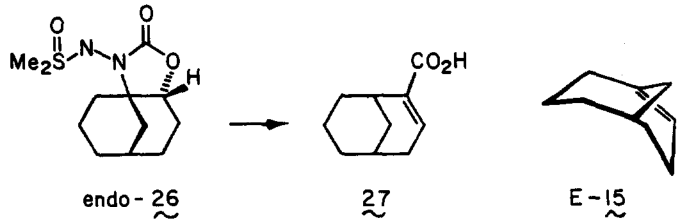
Isomeric *exo*-**26** and *endo*-**26** sulfoximines were prepared from the corresponding carbohydrazide (i.e. *exo*-**24**) via the oxazolidone (*exo*-**25**).

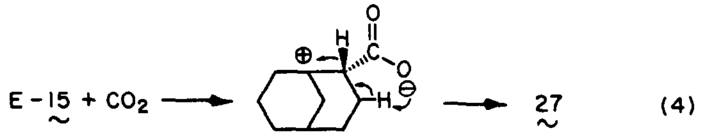
Syn elimination of sulfoximine *exo*-**26** should afford *Z*-**15** while *endo*-**26** is expected to yield the very highly strained *E*-**15**. In fact, elimination of *exo*-**26** proceeds smoothly at 120° to yield *Z*-**15** in 55% isolated yield. In contrast, bridgehead alkene is not observed upon heating *endo*-**26**; rather, at 150°, unsaturated acid **27** is recovered as the sole reaction product (50% yield). The difference in reactivity is attributed to the difference in strain of the isomeric alkenes (*E*-**15**–*Z*-**15**), estimated to be approximately 22 kcal/mol. It was suggested that unsaturated acid **27** arises by trapping with CO_2 of the very highly strained *E*-**15** (eqn 4). Regiospecific CO_2 trapping was attributed to the highly polar nature of severely distorted C=C double bonds. The case for involvement of bridgehead alkene *E*-**15** was forwarded without independent trapping experiments. The sulfoximine route nevertheless appears to be an attractive entry into highly strained carbon–carbon double bonds.











BRIDGEHEAD ENONES, ENOLIZATION AND RELATED PHENOMENA

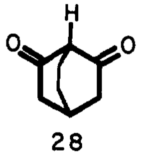
Bredt's rule nicely accounts for a number of chemical anomalies of bridged bicyclic systems. A specific example is the reluctance of bicyclic dione **28** to undergo enolization.[33] Ease of enolization tends to parallel the stability of the corresponding bridgehead alkene. Those enolates that involve transoid double bonds in *seven*-membered rings undergo exchange reluctantly, if at all. Many examples of this phenomenon can be found in the review by Fawcett.[6]

The remarkably easy bridgehead exchange in brendan-2-one (**29**) ($CH_3OD{\cdot}NaOCH_3$, 25°, 70 hr) stands in contrast to these results.[34] The corresponding anti-Bredt enolate (**30**) contains a transoid olefin in a 7-membered ring The mild conditions cannot be accounted for by increased s character of the C_3 carbon or by inductive stabilization of the carbanion by the carbonyl since no deuterium is incorporated at C_1.

The implication of this observation is that stabilization is available to the enolate anion even though the p orbitals must deviate substantially from coplanarity. The origin of this stabilization was attributed to the boat-like conformation since bicyclic ketone **32** and the bicyclic analog **33** did not incorporate deuterium (at the bridgehead position) under the reaction conditions. Thus, the bridgehead boat form markedly enhances enolate stability at C_3 but not at C_1; the stabilization is diminished considerably in a locked chair conformation. An explanation for this effect can be found by examination of the resulting enolate anions; in locked boat **29**, the *trans* double bond is constrained to a 7-membered ring whereas the locked chair in **32** contains the *trans* olefin to a 6-membered ring.

Further confirmation of this observation obtains from a very similar study of bicyclic ketones **34**, **35** and **36**. Virtually no deuterium was incorporated at the bridgehead position of bicyclic ketones **34** and **35**. In contrast, ketone **36** was found to be monodeuterated (95% d_1) at the bridgehead position (C*) under relatively mild conditions (2.0M NaOMe-MeOD, 33°, 22 hr). As in the case of **29**, the enhanced bridgehead acidity of **36** is ascribed to the locked boat conformation of the cyclohexanone ring.[35] For the conformationally flexible ketones **34** and **35**, the boat conformation represents an energy maximum; proton abstraction is expected to have a substantially higher activation energy.

Bicyclic amides with nitrogen at the bridgehead may exhibit stabilities that parallel carbocyclic bridgehead alkenes. Recent attempts to generate bicyclic carbamate **37** were unsuccessful,[36] a result that should be contrasted with the known stability of compounds such as **38**.



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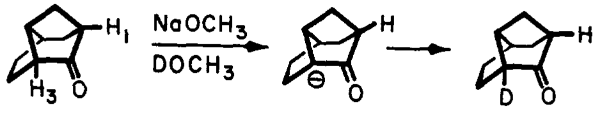

29 **30** **31-d**

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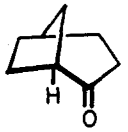

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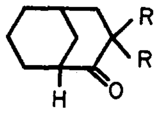

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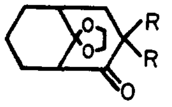

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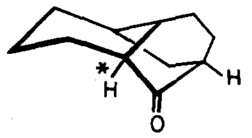

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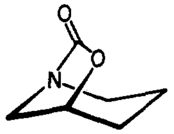

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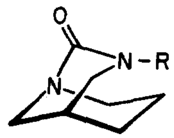
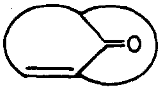


38

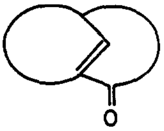
There are now many examples of compounds that contain a bridgehead double bond as part of a conjugated enone system. Permutations of bridgehead enones are illustrated by structures **39**–**42**. Geometrical constraints render coplanarity of the enone unit in structures **39** and **40** extremely difficult. The failure of representatives of these systems to undergo Michael addition and the absence of an enone chromophore can be attributed to this non-coplanarity.[10] The enone group in **41** and **42**, on the other hand, can achieve some degree of coplanarity without introduction of a substantial degree of additional strain. The principal distortion arises from twisting the C=C double bond which results in a geometry that might be expected for the photochemically excited states or the radical ions derived from these systems.[37]

Recent studies of two bridghead enones of the type illustrated by structures **41** and **42** serve to illustrate the spectrum of reactivity to be found in compounds of this type; each contains a bridgehead enone in a *trans*-cyclooctene ring.

Chloro ketone **43** reacted rapidly with methanolic NaOMe (15 min, 25°) to form ketone **45**. The reaction, which requires the presence of base, was attributed to the intervention of enone **44**, generated by dehydrochloronation, followed by conjugate addition of methanol.[38] In support of this proposal it was demonstrated that the intermediate enone **44** could be trapped if the elimination was carried out in the presence of added nucleophiles (X–H). The bridgehead enone could also be generated by decomposition (20°) of selinoxide **47**; again the enone could not be isolated but rather underwent addition of benzene–selenic acid, a biproduct in the elimination. Attempts to trap enone **44** as a cycloadduct (furan, butadiene, phenyl azide) were unsuccessful. These observations suggest enone **44** is an exceptionally reactive Michael acceptor but not particularly reactive in pericyclic reactions. Attempts to generate **44** under non-nucleophilic conditions, i.e. pyrolytic decomposition of the bridgehead acetate (**46**, X = OAc) resulted in fragmentation and molecular rearrangement.



39



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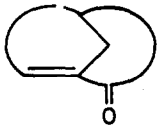
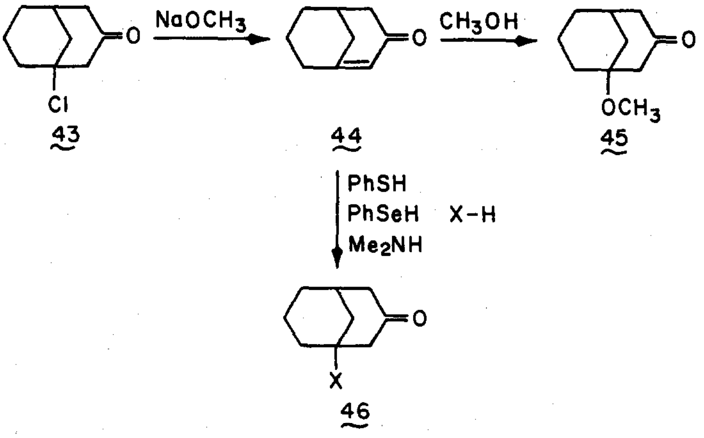
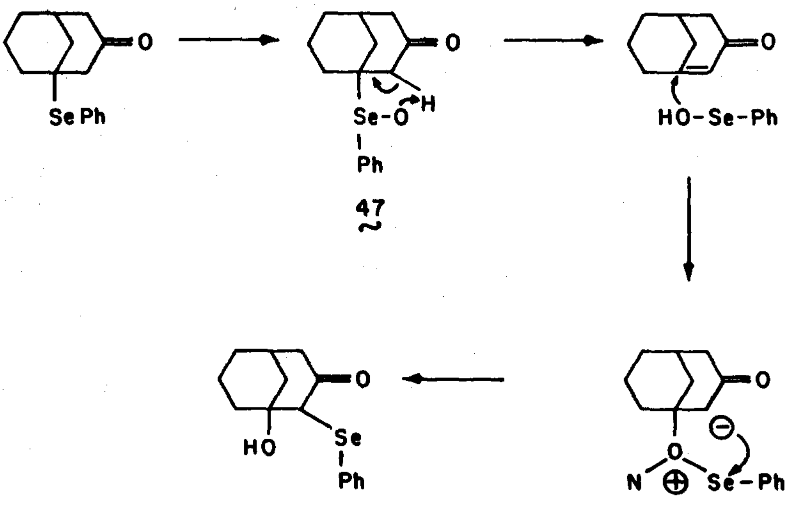


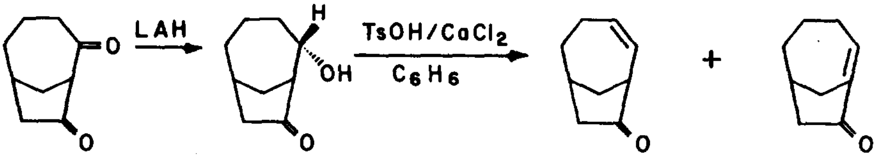
41

42

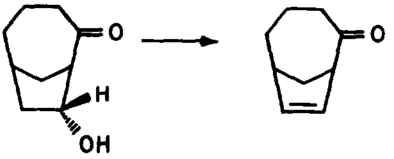




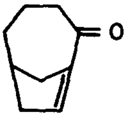
Bridgehead enone **50**, on the other hand, is a stable molecule.[39] It was formed in good yield by direct dehydration of the endo ketol **48** with *p*-toluenesulfonic acid and $CaCl_2$ in boiling benzene. Attempts to generate the isomeric enone **53** by a similar dehydration gave only polymeric products. A variety of alternate elimination procedures resulted in formation of the isomeric enone **52**. The greater resistance to formation of **53** when compared with **50** may be a reflection of their relative stabilities or reactivities. The apparent greater stability of the parent bridgehead alkene (**12b**) over isomer (**12a**) stands in contrast to this result. It should be noted however that the introduction of an additional sp^2 center into the bridgehead alkene may have a considerable influence on the strain of the molecule. The authors point out that oxoacid **54a** requires higher temperature for decarboxylation than the isomer **54b**.[40] The UV spectrum of enone **50** [λ_{max} 246 nm (ϵ4700)] indicates the double bond is still conjuaged with the CO group. This is further supported by the ready reaction of **50** with dimethylcuprate and diethylsodiomalonate to give conjugate addition products.



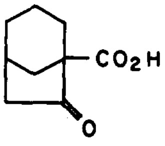
48 49 50



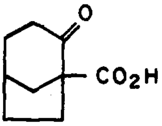
51 52



53



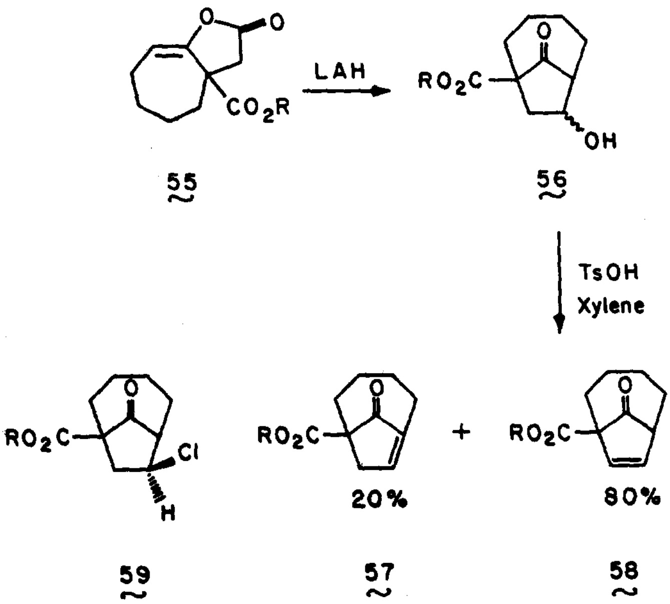
54a



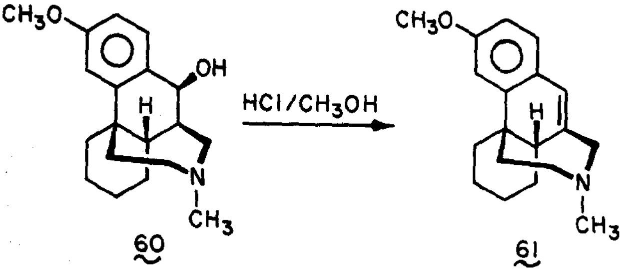
54b

Surprisingly, acid catalyzed dehydration has been shown to be effective for the preparation of an assortment of bridgehead alkenes. When an epimeric mixture of ketols **56**, obtained by reductive cyclization of enol lactone **55**, were dehydrated with *p*-toluenesulfonic acid in boiling xylene, two products were isolated. The minor component (<20%) was identified as bridgehead alkene **57**; the isomeric keto olefin (**58**) comprised the major reaction product. This same bridgehead enone was also obtained in 40% yield when the *exo*-chloride **59** was heated with collidine, presumably by *cis* elimination of HCl.[41] It can be concluded that the preparation of bridgehead alkenes that are part of medium ring systems may be accomplished in certain cases by more conventional means. For example, treatment of phenanthrol **60** with HCl in methanol gave bridgehead alkene **61**.[42] This species contains a relatively strain free bicyclo[4.3.1]dec-1(9)-ene ring with the bridgehead double bond conlained in a *trans*-cyclononene ring. In a closely related study the behavior or several derivatives of benzanonin-7β-ol (**62**) with HCl was reported.[43] It was demonstrated that the anti-Bredt olefin **63** is readily formed from the corresponding hydroxy or methoxy derivatives **62** and **64** by treatment with acid. The results suggest that compounds **62**, **63**, and **64** are in equilibrium. The failure to observe bridgehead alcohol is interesting; the usual site of protonation of bridgehead alkenes (formation of a bridgehead carbonium ion) is apparently less attractive than the benzylic ion involved in these addition-elimination reactions.

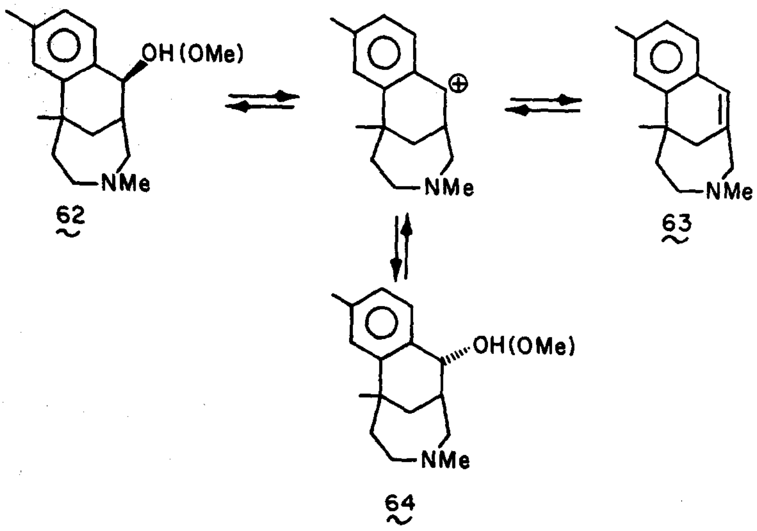
It is perhaps not surprising that this method was not successfully extended to the homologous alcohol **65** which, when treated with DCl, resulted in epimerization (**65**→**66**) but *no* incorporation of deuterium at the bridgehead position.[42]



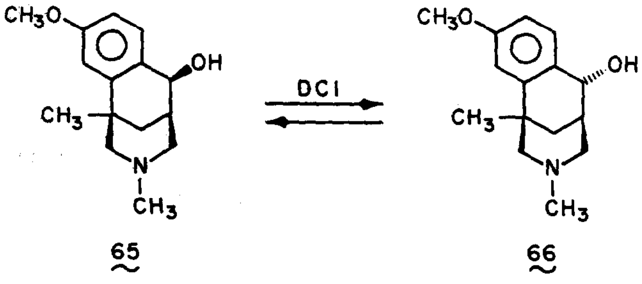
55 56 59 57 58



60 61



62 63 64



65 66

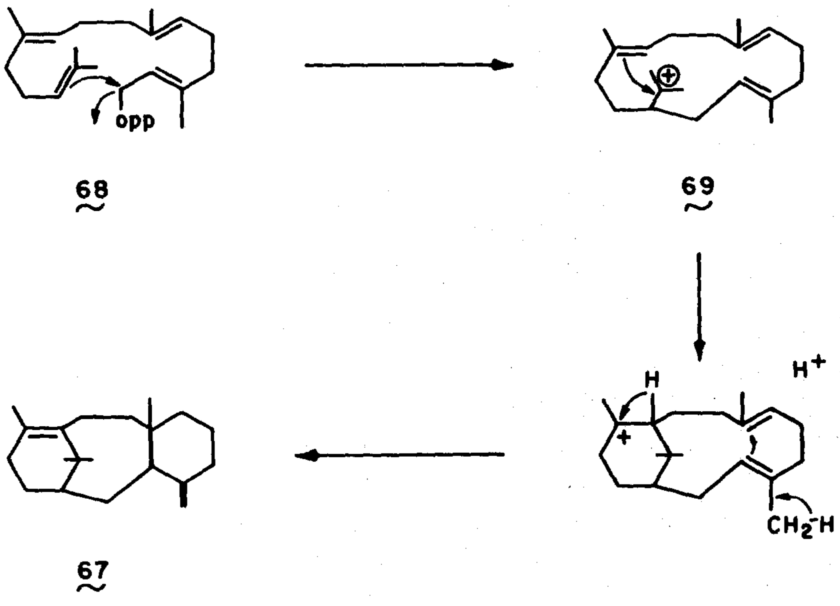
NATURALLY OCCURRING BRIDGEHEAD ALKENES

The bridgehead double bond has been found in several classes of naturally occurring terpenes. The double bonds in these molecules are not highly strained; however, their synthesis shares certain common objectives with the more highly strained analogs discussed in this review.

The earliest examples of naturally occurring bridgehead alkenes are members of the taxane group (**67**), tricyclic diterpenes that contain a novel bicyclo[5.3.1]-undec-1(10)-ene structural unit.[44,45] A suggested biogenetic pathway, given in Scheme 1, involves a cembrene-like intermediate (**69**) derived from cyclization of geranylgeranol (**68**).[46] Studies of the acid catalyzed cyclization of cembrene have not, as yet, produced the taxane ring structure.[47]

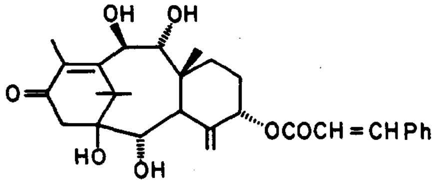
Many derivatives of taxane are now known, and are illustrated by the highly oxygenated species taxicin-1,O-cinnamoyl (**70**), where the bridgehead double bond is part of an α,β-unsaturated ketone,[48] and taxol (**71a**) a component of an extract isolated from the stems and bark of the western yew, *Taxus brevifolia*.[49]

Interest in taxane and its derivatives goes beyond the structural novelty of the bridgehead double bond since the report that taxol (**71a**) has potent antileukemic and tumor inhibitory properties,[49] the first compound possessing the taxane skeleton which has been demonstrated to have such activity. Since this report, the closely related cephalomannine (**71b**) which is cytotoxic and shows potent inhibition of PS leukaemia, has also been isolated.[50]



Certain derivatives of sesquiterpene dilactones of the germacrane type, illustrated by elephantin (**72a**) and elephantin (**72b**), also possess a bridgehead double bond;[51] the 1–10 *trans* double bond occurs in a 10-membered ring. A comparison of the X-ray crystal structures of elephantin (**72b**) with that of pregeijerene (**72c**), a 1,5,7-*trans,trans,cis*-monocyclicdecatriene, shows the lactone bridge produces a negligible distortion in the 1–10 double bond.[52] For example, the C-10-1-2-3 torsion angle in pregeijerene (**72c**) is 165.4°; a 11.2° twist is the major contributor to the distortion from 180°; there is only a slight departure from planar trigonal bonding at C-11-1-2 and C-10-1-2 of 3.4°. The situation is very similar in **72b**. The torsion angle at C-2-1-10-9 is 163°; displacement at C_{10} from the plane of C-1-9-15 is only 0.05 Å. It would appear that pyrimidalization of a bridgehead carbon occurs only at "significant" torsions of the bridgehead double bond.

Eremantholide A, a component of the aqueous alcohol extract from the Brazilian plant *Eremanthus elecagnus* was shown to possess significant inhibitory activity against cells derived from human carcinoma and has the novel structure shown in **73**. The highly interesting feature of Eremantholide A is the cyclodecadienone ring incorporating a bridgehead enol ether system. The two carbon–carbon double bonds C 2-4 and C 4-5 are orthogonal (88°) in the crystal, so there are no effects of extended conjugation of the unsaturated carbonyl.[53]



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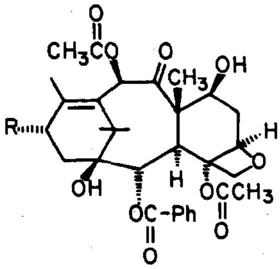
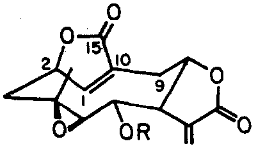


71

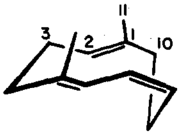
71 a, R = OC(O)CH(OH)CHPhNHC(O)Ph

71 b, R = OC(O)CH(OH)CHPhNHCOC(=CH(CH$_3$))CH$_3$

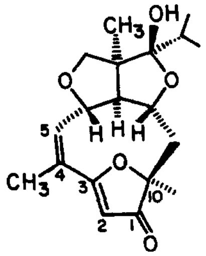


72

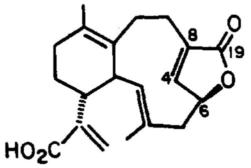
a, R = COC(CH$_3$)=CH$_2$
b, R = COCH=C(CH$_3$)$_2$



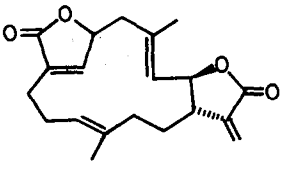
72c



73



74



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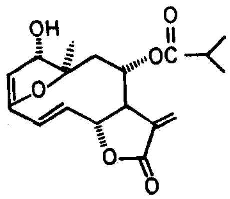
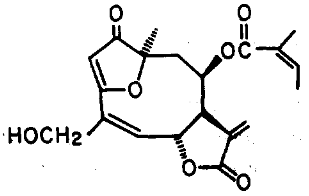
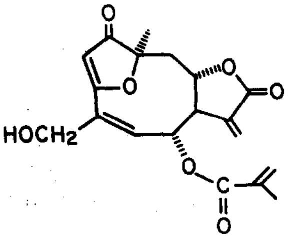


76



77



78

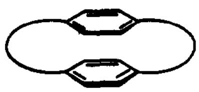
Ovalodiolic acid (**74**),[54] an acid cyclization product from the cembrene-type 14-membered ring diterpene Ovalodiolide (**75**),[55] contains a bridgehead α,β-unsaturated ester. There is an 8° torsion about C-6-7-8-19; distortion of the trisubstituted double bond is due to approximately equal contributions arising from twist around the double bond (Φ) and depature from planar trigonal geometry at C(8) (χ). Additional examples of bridgehead double bonds in 10-membered rings are ciliarin (**76**),[56] budlein-A (**77**),[57] and the closely related goyazenosolide (**78**).[58]

The macrocyclic diterpene dilactone Ovatodiolide (**75**), isolated from *Anisomeles ovata*, is a member of the cembrene class of diterpenoids. The bridgehead double bond is contained in a 14-membered ring. Torsion angles around the trisubstituted double bond lie close to the strain-free 180° values, and accordingly, the atoms in the individual moieties may be regarded as being coplanar.[55]

BRIDGEHEAD DIENES

Members of this group include cyclophanes (**79**, **80**)[2] and bridged annulenes (**81**, **82**).[2,59,60] The interplay between structure, stability, and aromaticity has been a lively area of chemical research and has been the subject of several reviews.[61,62] Systems that contain bridgehead dienes where aromatization is not an issue are less well known. A number of structural variants are possible; several of the more interesting types are shown below and include the bicyclic (**83a, b**) and tricyclic (**84a, b**) analogs of parallel and perpendicular conformations of *trans,trans*-cycloalkadienes.

In an extension of his earlier proposal, Wiseman suggested that a relationship may also exist between the stability of bridgehead dienes **83** and **84** and their monocyclic *trans,trans*-cycloalkadienyl counterparts.[63]



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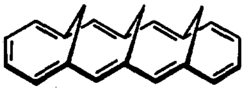
80



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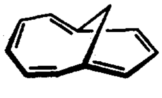
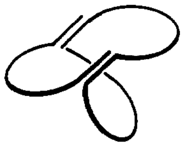
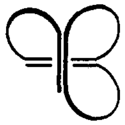


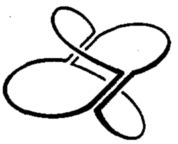
82



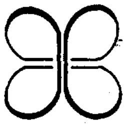
83a



83b



84a

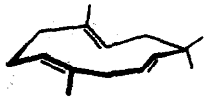


84b

Numerous examples of medium ring monocyclic *trans,trans*-cycloalkadienes can be found in natural product chemistry. These stable polyenes are exemplified by germacrene-A (**85**)[64] (*trans,trans*-1,5-cyclodecadiene ring) and humulene (**86**)[65] (*trans,trans,trans*-undecatriene ring).

To date, the smallest, isolatable, *trans,trans*-cycloalkadiene is **87**, *trans,trans*-1,5-cyclooctadiene.[66] The structure of this reactive diene has not been established; it is believed to be capable of existing in one or both conformations, i.e. the parallel (**87a**) or perpendicular (**87b**) forms.[16,66] These two structures may be considered as monocyclic progenitors of the bridgehead dienes **83** and **84**. The eight-membered ring may also represent a practical limit for an isolatable bridgehead diene.

85



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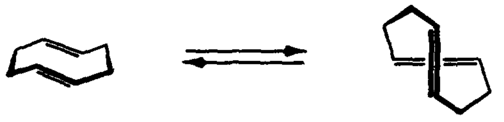
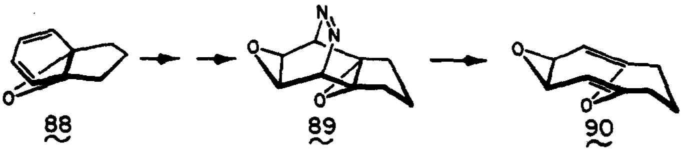
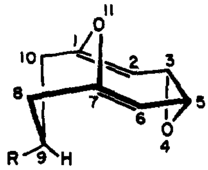


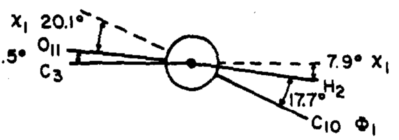
87a 87b

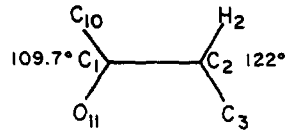


88 89 90



91



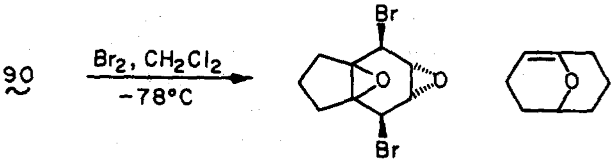


Recent examples of bridgehead dienes include the *syn*-oxipin oxide (90), prepared by nitrogen extrusion of diepoxide 89. The molecule contains an oxo-bridged *trans,trans*-1,5-cyclononadiene group locked in a parallel conformation.[67]

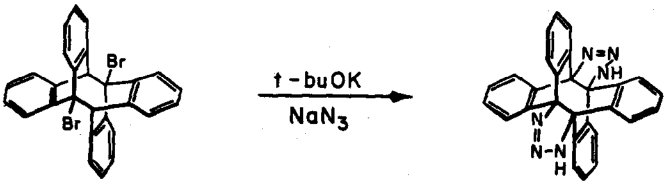
An X-ray crystal structure of the methoxy derivative (91) provides documentation of the distortion of the bridgehead double bond.[68] Both double bonds are twisted and the carbons, especially the bridgehead carbons, are pyramidalized. The degree of pyramidalization is 7.9° (C_2) and 20.1° (C_1). The torsional angle between the axis of the two π orbitals at C_1 and C_2 is 11.6°. The distortion at the bridgehead carbon becomes clear when the C_1–C_2 bond is viewed from above. The near-normal C_2 bond angles are to be contrasted with those of C_1, where, for example, the C_{10}–C_1–O_{11} bond angle is 109.7°.

The proximity of the two bridgehead double bonds, C_1–C_7 bond distance 2.176 ± 0.004 Å, manifests itself in both the chemical and spectroscopic properties of the molecule. Thus, bromination proceeds in a transannular fashion to produce the dibromoepoxide 92. The UV spectrum exhibits an absorption maximum ($\lambda_{max(EtOH)}$ 231 nm) that is substantially red-shifted from a model compound, 9-oxabicyclo[3.3.1]non-1-ene 93, which has an absorption at λ_{max} 190 nm.[69] The red-shift is consistent with a through space perturbation of the two bridgehead double bonds.[70]

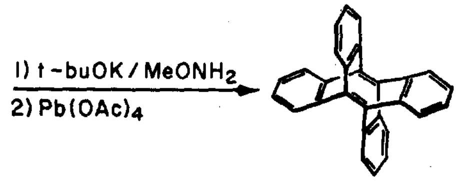
The first example of a molecule containing an ethano-bridged *trans*, *trans*-1,5-cyclooctadiene (parallel conformation) was reported in 1974. 9,9′,10,10′-tetradehydrodianthracene (96) was obtained by bis-dehydrobromination of the photodimer of 9-bromoanthracene (94). It was necessary to trap the bridgehead olefin with azide ion to avoid addition of t-butoxide to the bridgehead double bond. Conversion of bistriazoline 95 to the bis-N-aminotriazoline followed by oxidation regenerates bridgehead diene 96, a crystalline material stable to heat, air, and moisture. The molecule represents a symmetrically distorted double bond of the type shown in 96b. Pyramidalization at both bridgehead carbons amounts to 19.7°, very similar to the degree of pyramidalization in bridgehead diene (91). The distance between the bridgehead double bonds is 2.42 Å, significantly greater than the distance in 91 (2.176 Å). The stability of 96 is attributed to the absence of kinetically viable reaction pathways to isomeric or polymeric products.



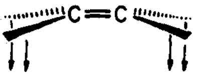
92 93



94 95



96



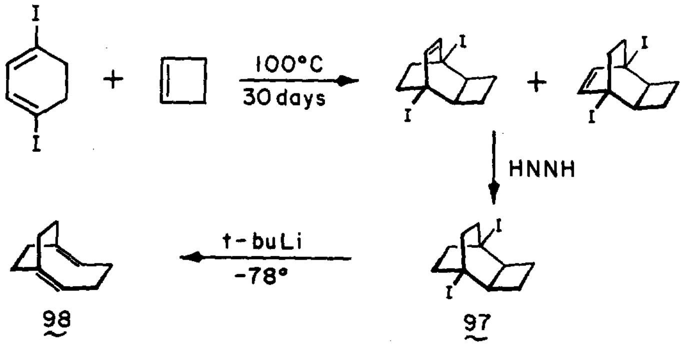
96b

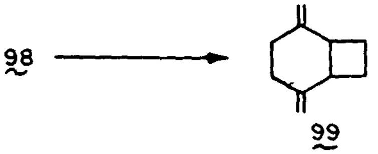
The stability of **96** is to be contrasted with the parent molecule in this series, bicyclo[4.2.2]deca-1,5-diene, **98**, an ethano-bridged derivate of *trans,trans*-1,5-cyclooctadiene locked in its meso or parallel conformation. The synthesis,[65] outlined below, relies upon a delicate, kinetically controlled deiodination of **97**. Bridgehead diene **98** is formed by almost exclusive cleavage of the cyclobutano bridge of **97**, rather than either of the ethano bridges, despite the greater thermodynamic stability of the product derived from the latter reaction. Bridgehead diene **98** is thermally labile and very sensitive to oxygen and has not yet been isolated in a pure state. Structure confirmation was obtained by characterization of the ozonolysis products (1,4-cyclohexanedione and succinic acid). Compound **98** undergoes a facile [3.3] sigmatropic rearrangement at 28° ($t_{1/2} = 5.2$ hr) to 1,5-dimethylene bicyclo[4.2.0]octane (**99**); an activation energy of 19.6 kcal/mol was calculated from the rate of isomerization at two temperatures. Compounds **87** and **98** exhibit comparable stabilities; the parallel between the stabilities of *trans,trans*-cycloalkadienes and their analogous bridgehead dienes appears to be a useful one.

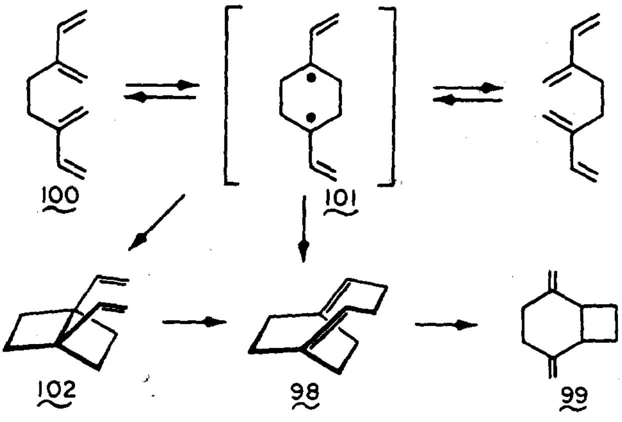
A more speculative report of bridgehead diene **98** arises from a study of the thermal behavior of tetraene **100**. This possibility stems from the observation that diene **99** is one of the reaction products obtained from thermolysis of tetraene **100** at 190°.[72] Tetraene **100**, among other things, is a 1,5-diene capable of undergoing a degenerate [3.3]sigmatropic rearrangement. A possible intermediate in this rearrangement, diyl **101**, can collapse to either bicyclic dienes **98** or **102**, all of which are related via [3.3]sigmatropic rearrangements of diene **99**, the product observed from this reaction. "Leakage" from a diradical manifold of the Cope rearrangement has recently been documented,[73] lending some credence to the above mechanism. However, because of an alternative and more direct mechanism, that is, 1,8-ring closure of tetraene **100** via diyl **103**, the proposed mechanism involving bridgehead diene **98** must remain at present only one of several possibilities.

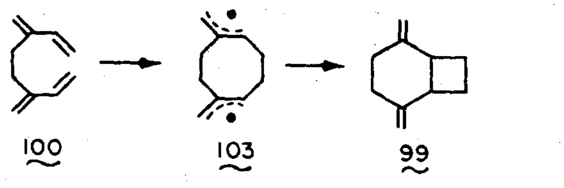
Pyrolysis of this same tetraene provides the first evidence, albeit circumstantial, for the isomeric bridgehead diene, **104**, an ethano bridged *trans,trans*-1,5-cyclooctadiene "locked" in the perpendicular conformation.[72] At 190°, tetraene **100** yields two bicyclic dienes, **105** and **106**, in addition to diene **99**. In an independent experimant, **106** was shown to be formed from **105**. The origin of these products can be understood in terms of an analogy of tetraene **100** to the dimerization of butadiene. Intermediate **105** is a divinylcyclobutane that arises from a formal intramolecular [2 + 2] cycloaddition of tetraene via one or both isomeric diyl intermediates (e.g. **107**). The rearrangement **105**→**106** involves a formal [3.3] sigmatropic shift of a stereodistyl *trans*-divinylcyclobutane.

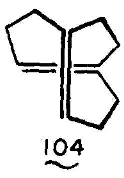
The two methylene groups can gain proximity via diradical **107**, which can close across carbons 1 and 8 (eqn 5) to yield bridgehead diene **104**. Compound **104** is not expected to survive the reaction conditions; rather it can undergo rearrangement to the thermodynamically more stable bicyclic diene **106**. Support of this proposal awaits a more detailed investigation of rearrangements of this type.





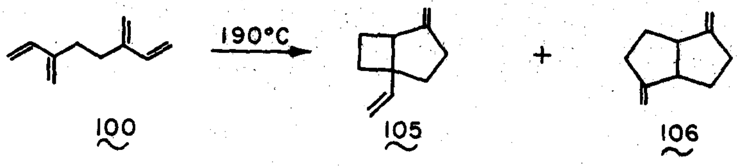




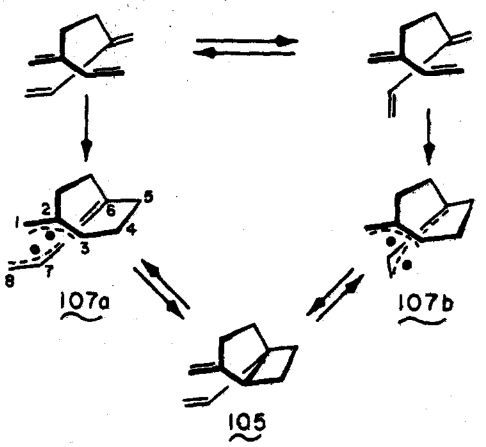


BETWEENANENES

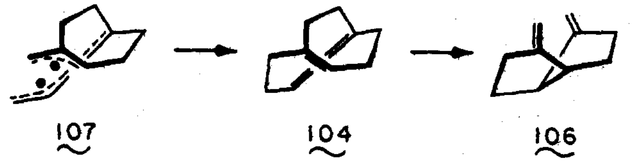
Betweenanenes are bicyclic hydrocarbons whose rings join the *trans* positions of a common double bond (**108**). These doubly bridged ethylenes have a unique geometric arrangement that requires the bridging chains to crisscross above and below the double bond. The failure of the *E*, *Z* system of nomenclature to distinguish between symmetrical members of this series, (i.e. **108**–**109**, n = n) prompted the novel name of betweenanene for isomers of **108**.[74] An alternative system of nomenclature has also been suggested which utilizes a "symmetry descriptor" to distinguish isomers **108** and **109**, for example



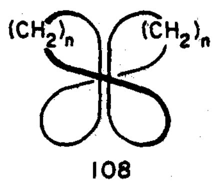
100 105 106



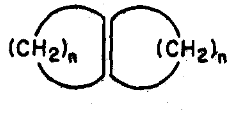
107a 107b 105



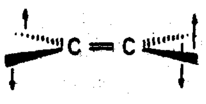
107 104 106 (5)



108



109

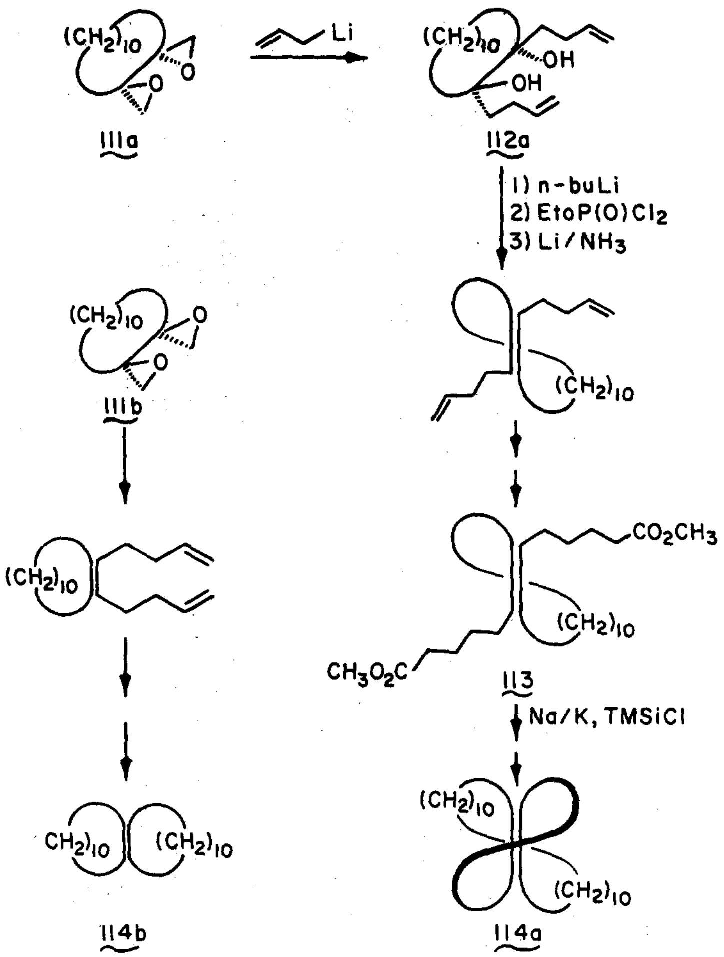


110

D_{2h}-bicyclo[8.8.0]octadec-1(10)-ene (**109**, n = 8) and D_2-bicyclo[8.8.0]octadec-1(10)-ene (**108**, n = 8).[75] The betweenanenes are a particularly interesting group of alkenes, the double bond is subejcted to a bizarre type of distortion, illustrated in **110**. In addition, the bridging chains sandwich the double bond, which should restrict the access of reagents.

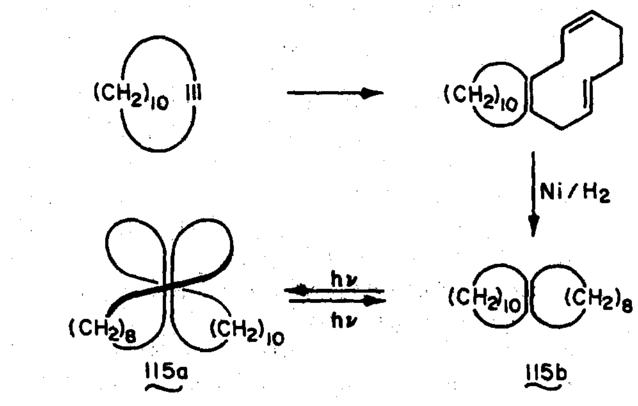
Marshall and Lewellyn were the first to report the synthesis of a betweenanene.[74] [10.10]Betweenanene (**114a**) and its *cis* isomer, bicyclo[10.10.0]docos-1(12)-ene (**114b**) were prepared by the methods outlined below. Starting materials were the isomeric bisepoxides **111a** and **111b** derived from cyclododecane-1,2-dione. *trans*-Bisepoxide (**111a**), when treated with allyl lithium, gave *trans*-diol **112a**. Conversion of this vicinal glycol to a tetrasubstituted olefin with overall *syn*-elimination of H_2O_2 was accomplished by reductive elimination (Li/NH_3) of the cyclic phosphoric amide. Elaboration of the two side chains precedes acyloin cyclization of diesters **113a**. Reduction of the enediol trimethylsilyl ether was accomplished in six steps to yield [10.10]betweenanene **114a**. A parallel sequence of reactions starting with bisepoxide **111b** yields the *cis* isomer **114b**.

Shortly thereafter, Nakazaki *et al.* reported their successful synthesis of [10.8]betweenanene (C_2-bicyclo[10.8.0]eicos-1(12)-ene) (**115a**).[76] Their strategy employs a photochemical isomerization of the



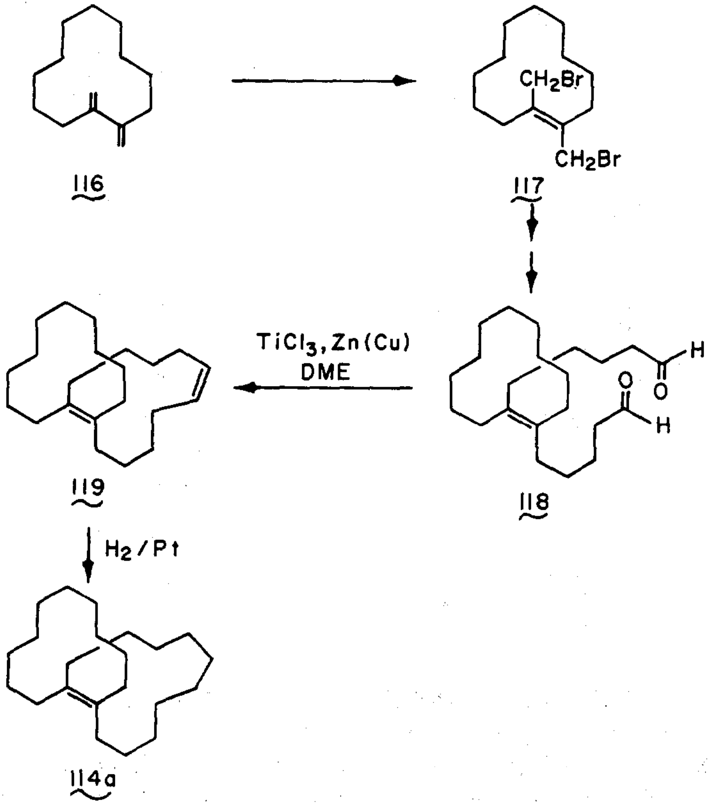
corresponding *cis* isomer (C$_{2v}$-bicyclo[10.8.0]eicos-1(12)-ene, **115b**). *cis* alkene **115b** was prepared by cooligomerization of cyclododecyne with 1,3-butadiene followed by partial hydrogenation. Direct photolysis of **115b** (low pressure Hg lamp, 3 hr) produces a 2:1 ratio of *trans* and *cis* isomers. The mixture is separated by taking advantage of the chemical inertness of the *trans* isomer (**115a**) towards dichlorocarbene addition; cyclopropanated *cis* isomer is readily separated from **115a** by column chromatography. Further illustrated of the difference in chemical reactivity obtains from catalytic hydrogenation (60°, EtOAc, HOAc, PtO$_2$, H$_2$); **115a** resisted hydrogenation while the *cis* isomer (**115a**) was saturated in 10 hr.

Since these original reports, two new entires into the novel betweenanene system have appeared. The first involves a stereocontrolled route that begins with 1,2-dimethylenecyclododecane **116**. Bromination



affords *trans*-dibromide **117**. Bis alkylation and homologation eventually result in dialdehyde **118**. A key step, cyclization of **118**, was effected by McMurry's reagent ($TiCl_3$, Zn(Cu), DME) to afford [10.10]betweenadiene **119** in 40% yield. Catalytic hydrogenation completes the synthesis which represents a six-fold improvement in yield over the group's original route.[77]

The second route takes advantage of a rather unexpected acid catalyzed isomerization of *cis* and *trans* isomers. Thus **115b**, from 1,19-eicosadiene-6,15-dione (**120**) by the scheme outlined below, when treated with strong acid, results in an equilibrium mixture containing 70% of [8.10]betweenanene (**115a**). With [10.10]betweenanene (**114a**) and its precursor, bicyclo[10.10.0]docos-1(12)-ene (**114b**), the effect is even more dramatic; the betweenanene comprises more than 90% of the equilibrium mixture.[78]

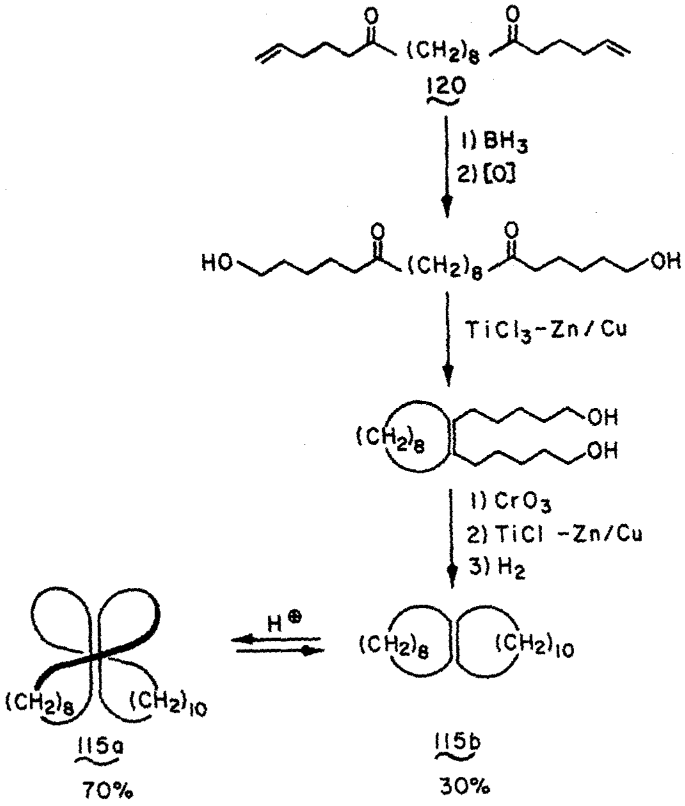


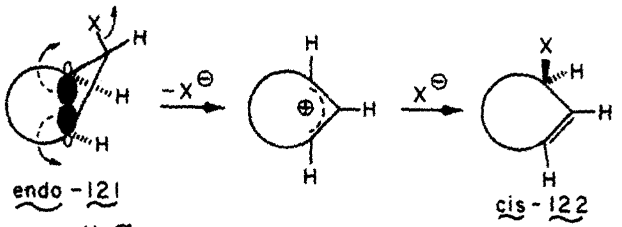
GENERATION OF BRIDGEHEAD ALKENES BY SOLVOLYSIS OF CYCLOPROPYL HALIDES

The cyclopropyl to allyl cation isomerization is a 2π electrocyclic ring opening. The reaction is stereospecific; loss of the anion occurs in concert with cleavage of the cyclopropane C–C bond. In bicyclic systems, the isomerization leads to ring expansion and formation of a cycloalkene. The stereochemical relationship between reactant and product is illustrated in eqns (6) and (7). Ring opening is disrotatory and occurs *anti* to the cyclopropyl leaving group. Thus *endo*-**121** results in formation of *cis*-**122** and *exo*-**123** yields *trans*-**124** via a *trans,trans*-allyl cation, providing the expanded ring can accommodate a *trans* double bond.

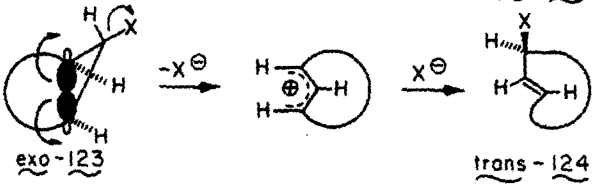
Tricyclic cyclopropanes, such as those illustrated in eqns (8) and (9), pose an interesting extension of this system. The cyclopropyl to allyl isomerization will lead to a bridgehead double bond. Imposition of the stereospecificity found in the bicyclic series results in the stereochemical relationships shown in the equations. (Brigehead alkenes will result regardless of whether orbital symmetry rules are obeyed.)

Werner *et al.* were the first to demonstrate the involvement of bridgehead alkenes in a reaction of this type.[80] They made the surprising observation that dichloro propellane **124** undergoes spontaneous decomposition (25°). Support for the proposed intermediate (**125**), a bridgehead alkene containing a *trans* cycloheptene ring, was obtained from analysis of the reaction products; these include a symmetrical dimer of **125** (X-ray crystal structure) and a Diels–Alder cycloaddition product, obtained when the decomposition of **124** was carried out in the presence of furan. The driving force for these arrangements

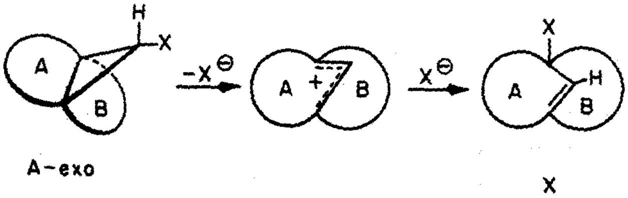

O
(CH2)8
O
120
1) BH3
2) [O]
HO
O
(CH2)8
O
OH
TiCl3-Zn/Cu
(CH2)8
OH
OH
1) CrO3
2) TiCl -Zn/Cu
3) H2
H⊕
(CH2)8
(CH2)10
115a
70%
(CH2)8
(CH2)10
115b
30%


X
H
H
H
endo-121
-X⊖
H
⊕
H
H
X⊖
X
H
H
H
cis-122

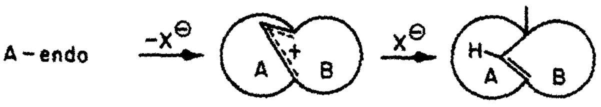
(6)


H
X
H
H
exo-123
-X⊖
H
⊕
H
H
X⊖
X
H
H
H
trans-124

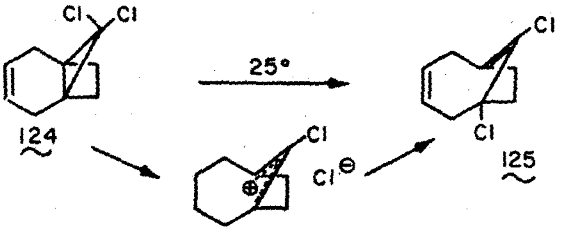
(7)


H
X
A
B
A-exo
-X⊖
A
+
B
X⊖
X
A
H
B

(8)


A-endo
-X⊖
A
+
B
X⊖
X
H
A
B

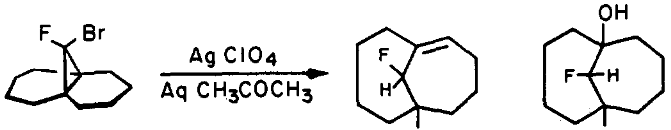
(9)


Cl
Cl
124
25°
Cl
Cl
125
Cl
⊕
Cl⊖

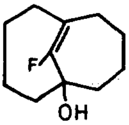
resides in the strain energy of the propellane skeleton, or, in part, from the stability of the halide salt in $Ag^{\oplus}$ catalyzed reactions.

Further support for this proposal comes from a follow-up ^{13}C labeling experiment[81] and a product study of a related transformation involving dihalopropellane **126**. Treatment of **126** with aqueous silver perchlorate results in formation of **127** and **128**. Both products can be derived from bridgehead alkene **129** or the carbocation derived from it (**130**).[82]

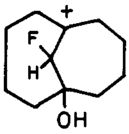
It has recently been suggested that solvolysis of a suitable propellane can provide an entry into a bridgehead olefin transoid in a 6-membered ring! This report is based upon the isolation of small quantities (*ca.* 2%) of products **132**, **133** and **134** from the silver assested solvolysis of dibromopropellane **131**. The origin of these products is attributed to bridgehead alkene **135**. The reliability of derived thermodynamic properties of bridgehead alkenes would be strengthened by additional evidence in support the involvement of **135**.



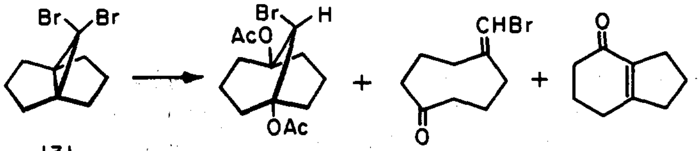
126 127 128



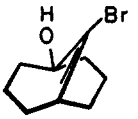
129



130

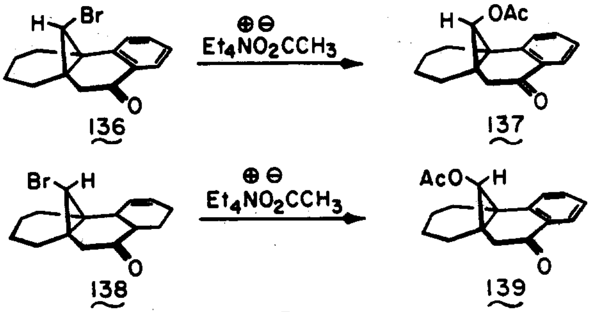


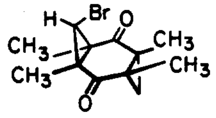
131 132 133 134



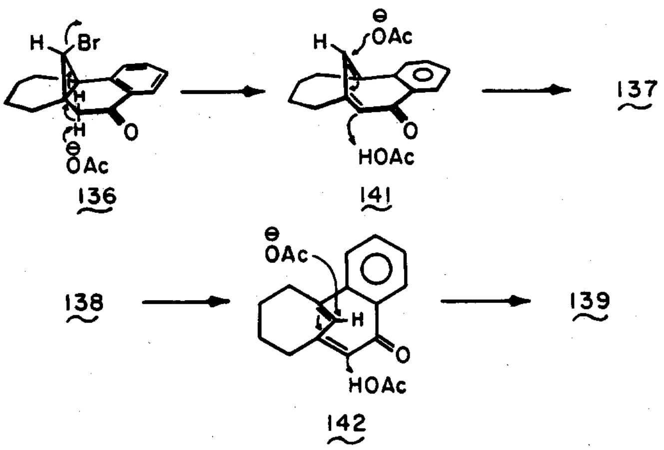
135

It appears that the cyclopropyl to allyl cation isomerization, or a closely related rearrangement, may provide an explanation for the interesting solvolysis results shown below. Under typical S_N2 conditions, *syn/anti* bromides **136** and **138** produce acetates **137** and **139**, respectively. The reactions are facile and give high yields at room temperature.[84] The stereospecificity and configuration were unambiguously established by X-ray crystal structures. These observations were cited as possible evidence for an S_N2 reaction with net *retention* of configuration, a proposal that has enjoyed some theoretical support[85] but has, as yet, eluded experimental verification.[86] A number of experimental facts necessitated a more critical examination of the results.[87a] First, the facility with which the substitutions occur stands in contrast to all previous substitutions on cyclopropanes. Furthermore, a closely related bicyclic halide, **140**, failed to undergo substitution even under forcing conditions. These observations prompted the intriguing suggestion that the substitution reaction is due to elimination of HBr with subsequent addition of HOAc. The proposed mechanism, which involves proton abstraction by acetate anion with concomitant cleavage of the propellane axis and ejection of bromide, produces a bridgehead diene. If the reactions occur in a stereospecific or concerted manner, as is implied in previous examples, then one



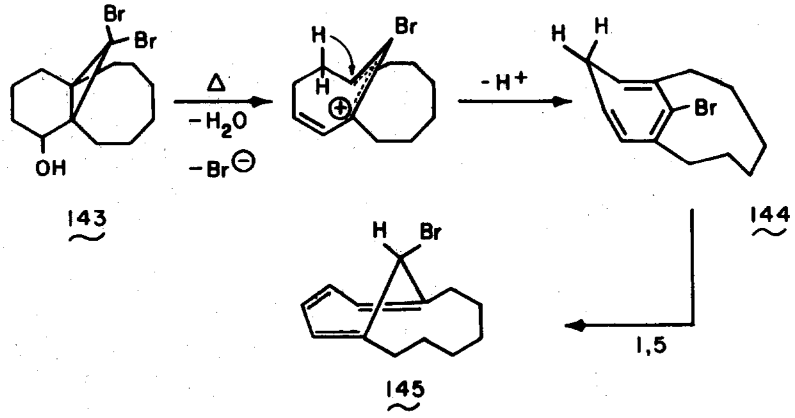


140



anticipates formation of an isomeric pair of bridgehead dienes **141** and **142** from bromides **136** and **138**, respectively. These highly strained bridgehead alkenes are disposed to permit attack by acetate on the same side of the one-carbon bridge as the bromide ion leaves; ring closure and reprotonation reforms the original ring system. Molecular models tend to confirm the predicted stereochemistry of attack by acetate as well as demonstrate that the double bridgehead system does not appear to be substantially more strained than an "ordinary" bridgehead alkene containing a *trans*-cycloheptene ring. Although the evidence for either mechanism is not firm, constraint must be exercised in interpreting these results in terms of an S_N2 mechanism with retention of stereochemistry. A more recent example of a substitution with retention on cyclopropane has been attributed to a partially opened cyclopropyl cation.[87b]

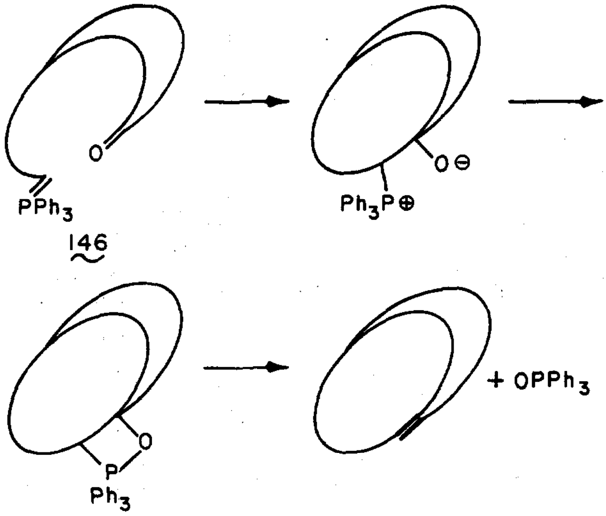
In a somewhat related case, thermolysis of 13,13-dibromotricyclo[6.4.1.$0^{1,8}$]triedecane **143** affords 13-bromobicyclo[6.4.1]trideca-8,10,12-triene (**145**) in 33% yield. It was assumed that thermal cleavage of

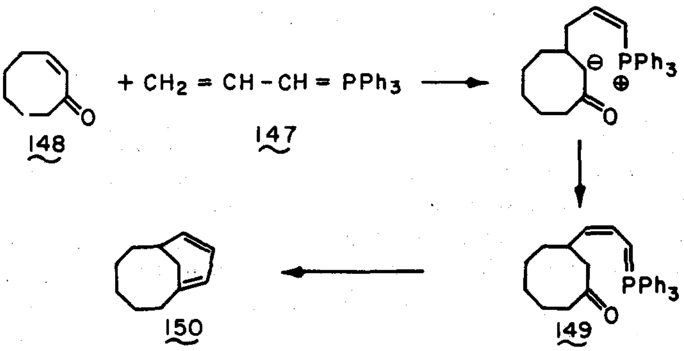


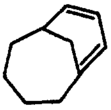
the cyclopropane ring under dehydration and dehydrobromination conditions gives initially an unstable bromocycloheptatriene **144** which is transformed to the more stable isomer **145** by a suprafacial 1,5-sigmatropic shift of hydrogen.[88]

BRIDGEHEAD ALKENES VIA WITTIG OLEFINATION

Intramolecular Wittig olefination provides a versatile and high yield synthetic entry into bridgehead alkenes. The general scheme, outlined below, involves generation of keto ylid **146** which undergoes intramolecular cyclization. The success of this reaction arises from the fact that the bridgehead double







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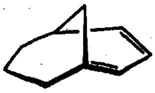
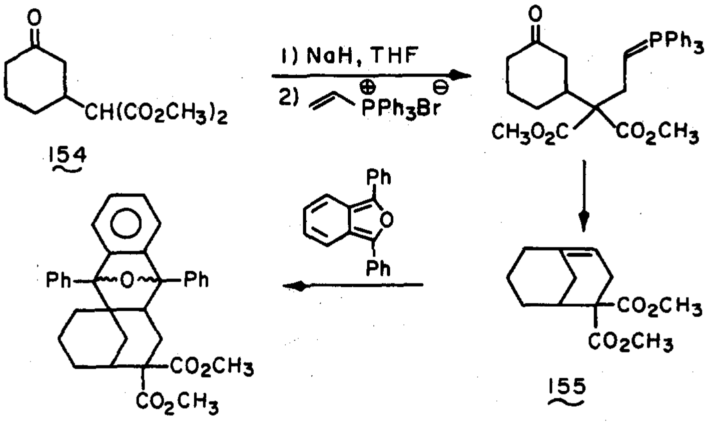


152

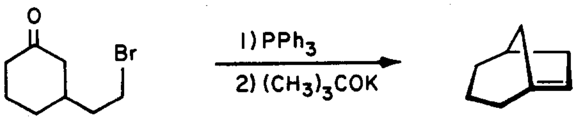
153



bond is not introduced until the second step, a reaction that proceeds concomitantly with elimination of triphenylphosphine oxide. The remarkable aspect of this reaction is the ease with which highly strained bridgehead alkenes can be prepared under relatively mild conditions. The first examples of this reaction utilized conjugate addition of allyl ylide **147** with a cyclic α,β-unsaturated ketone (**148**) to prepare the keto ylid **149** Spontaneous cyclization results in formation of diene **150** in 72% yield.[89] In a similar manner, bridgehead alkenes **151** and **152** were prepared, also in reasonable yield (>50%); diene **152** was too reactive to permit isolation and underwent spontaneous dimerization under the reaction conditions. Quite remarkably, this method permits generation of very highly strained bridgehead alkenes, such as bicyclo[3.2.1]octa-1,3-diene (**153**-*trans*-cycloheptene ring), which was characterized as a dimer and as the [4+2]cycloadduct with furan.

Keto ylide **146** can also be formed by deprotonation of a preformed ketophosphonium salt. The scope of this reaction was extended to allow greater flexibility in the construction of the alkene bridge. Thus, 4,4-biscarbomethoxybicyclo[3.3.1]non-1-ene (**155**) was generated and trapped as a stereoisomeric mixture of diphenylisobenzofuran adducts from the enolate anion of **154** and triphenylvinylphosphonium bromide.[90] In a similar manner, the highly strained bicyclo[3.2.1]oct-1(17)-ene (**157**) was produced from bromoketone (**156**) in 15% yield (diphenylisobenzofuran adduct). Although attempts to extend the synthesis to bicyclo[2.2.1]hept-1-ene (**158**) (a *trans*-cyclohexane) were unsuccessful,[90] the method has found considerable application in the synthesis of a variety of isomeric bridgehead alkenes and strained bicyclic olefins, illustrated by compounds **159–162**.[91,92] Ready access to these compounds permits a more thorough investigation of the chemical properties of bridgehead double bonds. A case in point is bridgehead alkene **162**, which can be trapped by added dienes, such as diphenylisobenzofuran, but also undergoes a rather novel dimerization reaction to the cyclopropyl hydrocarbon (**163**).[92]

A further application was found in the synthesis of the first optically active "anti-Bredt" compound, (−)-(5S)-bicyclo[3.3.1]non-1-ene (**165**) prepared from (−)-(1R,3S)-*cis*-3-hydroxycyclohexanecarboxylic acid (**164**).[93] The absolute rotation $[\alpha]_{D,abs}$ for **165** was calculated to be −720° (CHCl$_3$), based upon the estimated optical purity of the starting material. The authors call attention to the comparison between this value and the reported value $[\alpha]_{D,abs}$ −458° (neat) of (−)-(R)-*trans*-cyclooctene.[94]



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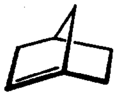

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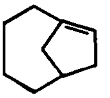

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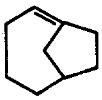

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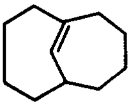

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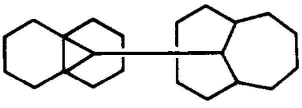

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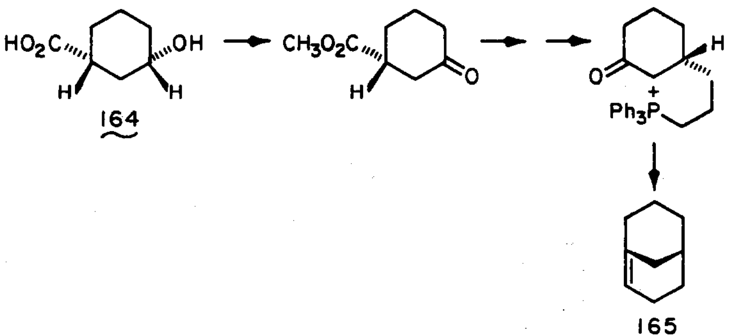
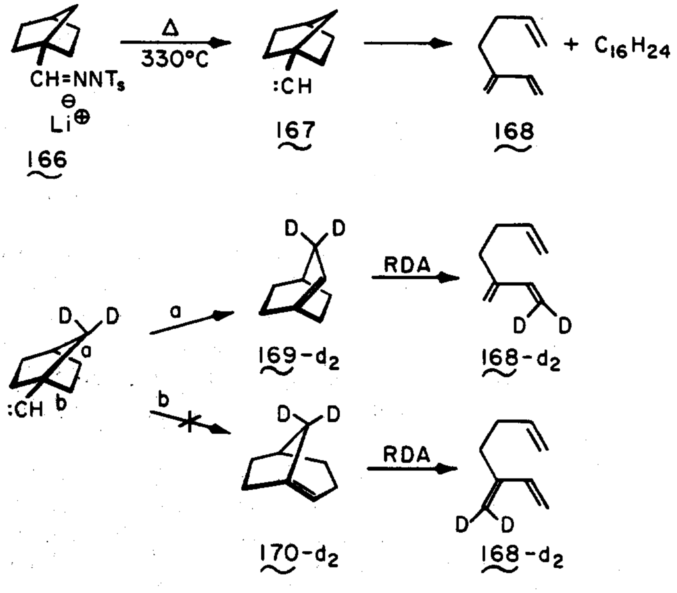


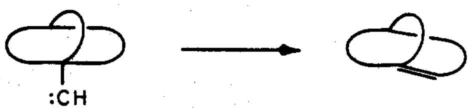
165

BRIDGEHEAD ALKENES AND THE DIELS-ALDER REACTION

Jones and Wolf noted that generation of carbene **167** via thermal decomposition of lithium tosylhydrazone **166** results in formation of 3-methylene-1,6-heptadiene (**168**) along with dimeric material ($C_{16}H_{24}$).[95] To account for these products it was suggested that carbene **167** undergoes ring expansion by either the short bridge (Path a), or long bridge (Path b), to bridgehead alkenes **169** or **170**. These highly strained species, which may be generated initially in a vibrationally excited state, can undergo spontaneous retro Diels–Alder reaction (RDA) to acyclic triene **168**. Dimeric products presumably arise from bimolecular encounters of bridgehead alkenes. Interestingly, the deuterium labeling experiment (Scheme 1) establishes the dominant reaction pathway (>85%) proceeds via migration of the short bridge (Path a) to yield the more highly strained bridgehead alkene **169**, bicyclo[2.2.2]oct-1-ene. Dimer formation in this case suggests the retro Diels–Alder reaction is not spontaneous; rather, bridgehead alkene survives long enough to suffer bimolecular collisions. Owing to the high chemical reactivity of alkyl carbenes, this route (eqn 10) must be regarded as one of the more attractive entries into very highly strained bridgehead alkenes. Indeed, this approach has resulted in the successful generation of 3-homoadamantene (**171**)[96] (the carbene route is only one of several methods that have been employed to generate this highly reactive bicyclic *trans*-cycloheptene)[97] and adamantene (**172**) itself from 3-noradamantylcarbene.[98]

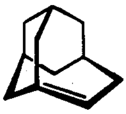


Scheme 1.



(10)

A more recent example of a retro Diels–Alder reaction of this type comes from a study of the flash thermolysis of trimethylsilyl ester (**173**).[99] Despite the substantial body of evidence implicating bridgehead enols in the decarboxylation of bicyclic β-keto acids, isolation of these intermediates is frustrated by their rapid proton tautomerism to bicyclic ketones. Although these authors do not provide *direct* evidence for bridgehead enols, the case is strengthened by documenting an additional reaction manifold of the intermediate. At temperatures between 600–750°, trimethylsilylketoester **173** gives rise to enol ethers **175** and **176**. These products are further characterized by conversion to ketones **177** and **178**. The rationale for these products is outlined in the Scheme. Decarboxylative transfer of the trimethylsilyl group results in formation of bridgehead enol ether **174** which, under the reaction conditions, undergoes retro Diels–Alder reaction to enol ether **175** or isomerization, presumably during work-up, to give enol ether **176**. At elevated temperatures product mixtures are richer in enol ether **175** and secondary retro-ene decomposition products derived from **175**.



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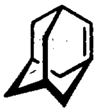

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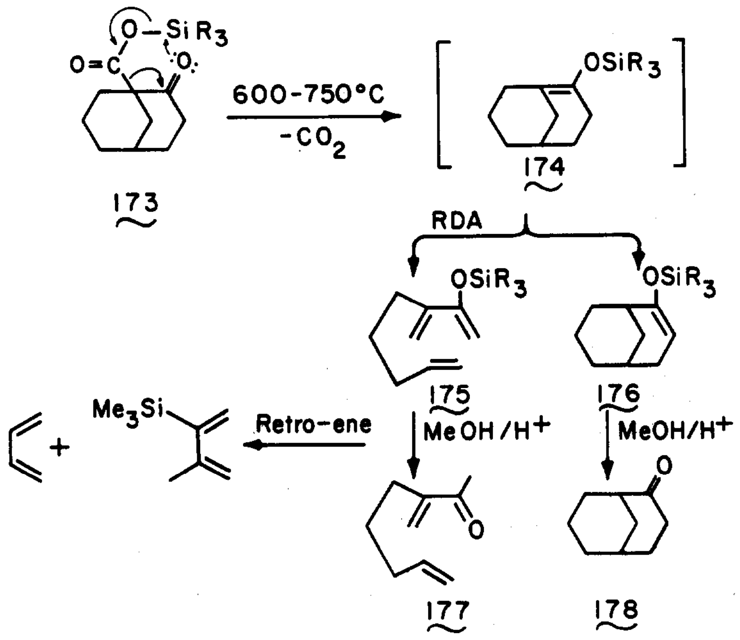


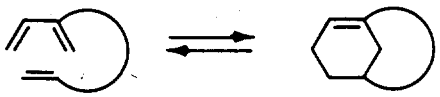
Chemical intuition regarding the reverse reaction, that is, *formation* of strained bridgehead alknees by an intramolecular Diels–Alder cycloaddition (eqn 11), may be prejudiced because of the strain energy associated with a bridgehead double bond. In fact, this reaction is an extremely effective one for the synthesis of a wide variety of bridgehead alkenes.

The first instance this reaction occurred during a study of the thermal rearrangement of tetraene **100**. Gas phase pyrolysis (400°, 7s), produces, among other products, two bicyclic dienes, **179** and **180**, one of which contains a highly strained bridgehead double bond.[100] 2,5-Bismethylenebicyclo[2.2.2]octane (**180**) was later found to be a secondary reaction product, derived from the primary thermolysis product, bridgehead alkene **179**. This rearrangement can occur by either a stepwise or a concerted reaction. The primary thermolysis product, **179**, arises by an intramolecular Diels–Alder cycloaddition (eqn 12); the bridgehead alkene, under certain conditions, accounts for as much as 6% of the thermolysis products.

The utility of the intramolecular Diels–Alder cycloaddition was established by a survey of the thermal behavior of trienes **181a, b, c**. At temperatures between 400–500° and contact times of 5–15 sec all trienes result in formation of substantial quantities of bridgehead alkenes. The reactions are "clean"; conversions are shown below.[100,101]

When the number of atoms that bridge the diene and dienophile exceeds three, i.e. **181b, c**, several regioisomeric transition states become accessible; these are illustrated in eqn (13) and (14). In all cases, the reactions were found to be highly (>98%) regiospecific; cycloaddition results in formation of the **meta** regioisomer.

At 428°, bridgehead alkene **182a** exists in equilibrium with triene **181a**. The equilibrium constant was used in conjunction with available thermodynamic data to obtain an estimate of the enthalpy, entropy, and free energy of reaction. These are shown below. The surprising result is the fact that cycloaddition is strongly exothermic, despite 22 kcal/mole of strain energy in the product.[101,102] At the high temperatures necessary to bring about cycloaddition at a convenient rate, the unfavorable entropy term neutralizes the reaction exothermicity. The influence of intramolecularity on the thermodynamics of the Diels–Alder reaction is given in Table 1.



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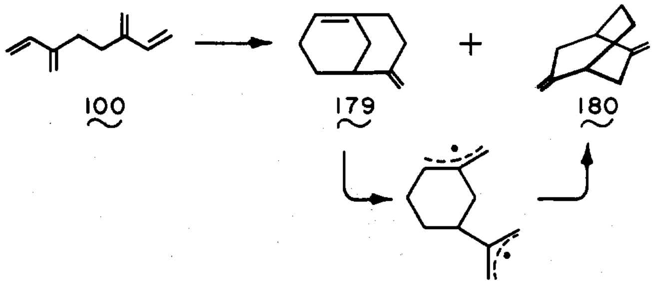
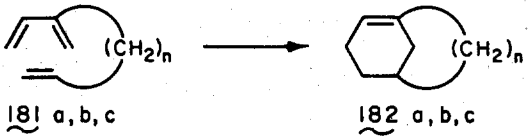
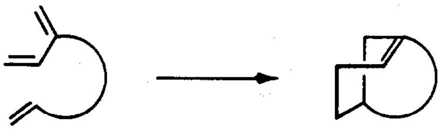


(12)

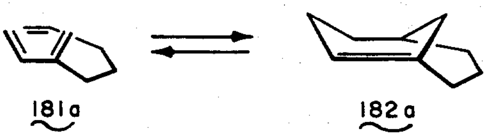


	% Conversion	Temperature
a n = 3	24	424
n = 4	55	441
n = 5	27	510



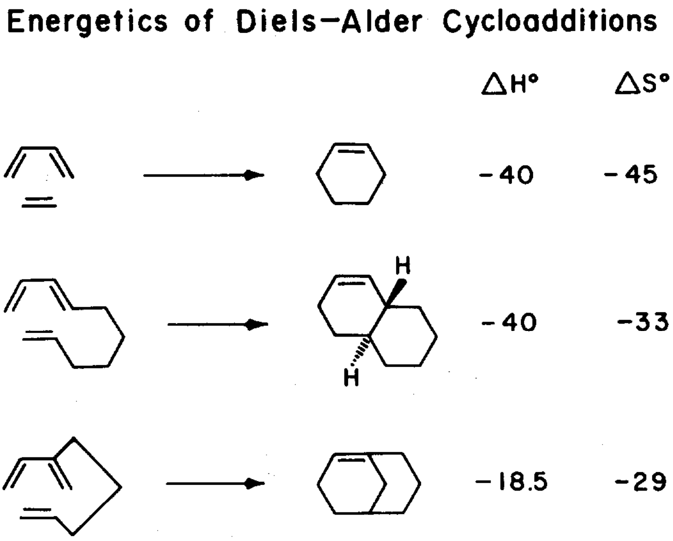
meta (13)

para (14)



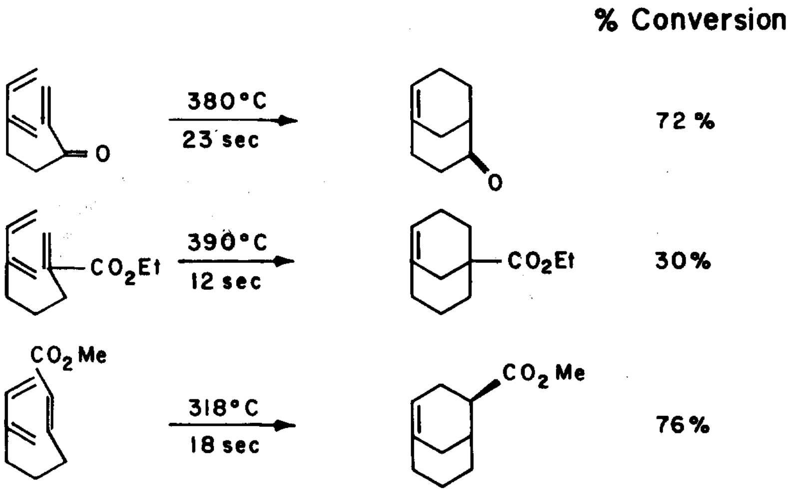
ΔH°_{rexn} - 18 kcal/mol

ΔS°_{rexn} - 29 eu



The synthetic utility of the intramolecular Diels–Alder route to bridgehead alkenes can be substantially improved by activation of the dienophile.[101,102] Thus, when electron withdrawing substituents are placed in conjugation with the dienophile, the temperatures necessary to effect cycloaddition are reduced and the yields of bridgehead alkenes are increased. This strategy has the added attraction of permitting the incorporation of a number of functional groups in the bridgehead alkene molecule, some of which are not compatible with existing methods for the preparation of bridgehead alkenes. A summary of the bridgehead alkenes prepared by this route is given in Tables 2 and 3.

Table 2. Gas phase pyrolysis

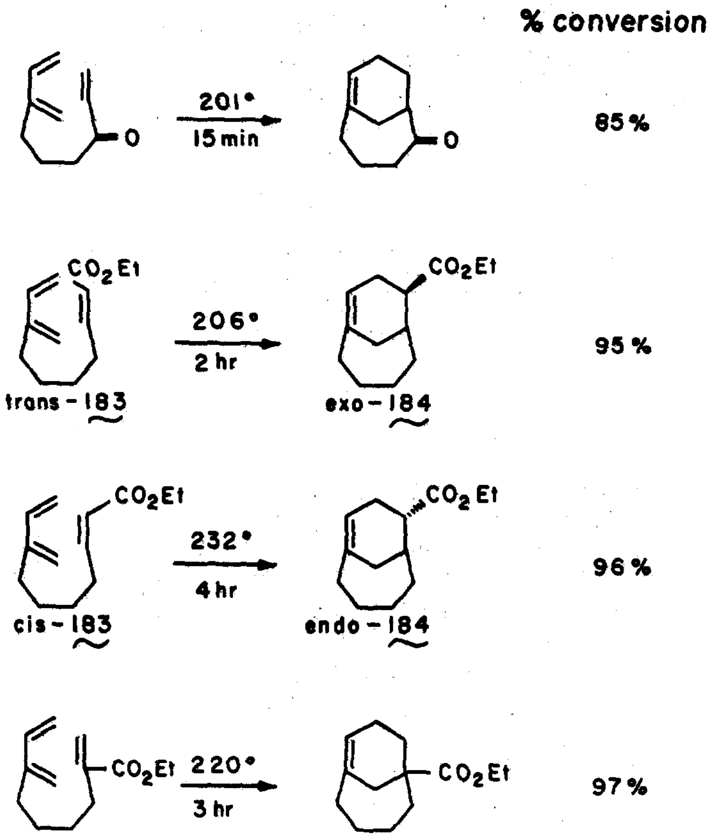


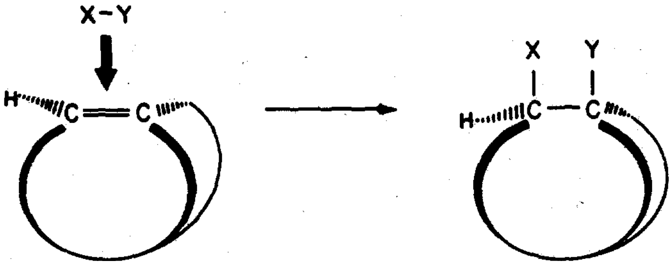
The more highly strained bicyclo[3.3.1]non-1-enes are best prepared in the gas phase flow pyrolysis apparatus while the less strained bicyclo[4.3.1]dec-1(10)-enes can be obtained in gold to excellent yield by conventional solution phase techniques (0.1 M, xylene). Preliminary results indicate the cycloaddition is stereo- as well as regiospecific. Thus, the *exo* and *endo* bridgehead esters (**184**) are formed from the triene esters *trans*-**183** and *cis*-**183**, respectively.[102]

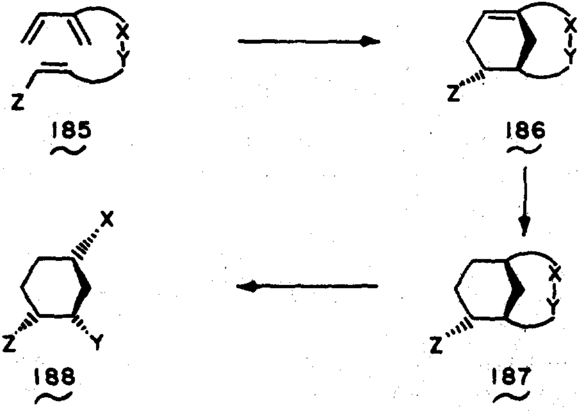
CONCLUSIONS

Bridgehead alkenes can be prepared by a variety of synthetic techniques. Their availability will permit a more thorough investigation of the properties of strained C=C double bonds. Indeed, ready access to these compounds, including highly functionalized derivatives, may signal a new era in bridgehead alkene chemistry, especially for their potential in preparative organic chemistry.

Table 3. Solution phase pyrolysis



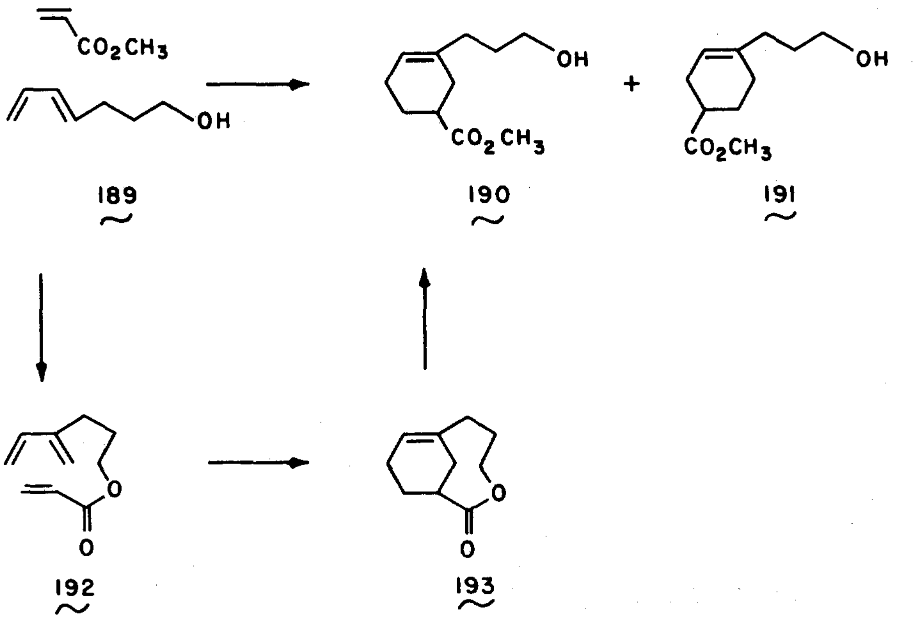




From a synthetic standpoint, there are two particularly noteworthy aspects of the chemical reactivity of bridgehead alkenes. First, the bridgehead double bond, because of its strain, is a reactive C=C double bond. It will add a variety of reagents under relatively mild conditions. Second, only one face of the strained C=C double bond is accessible to attacking reagents (eqn 15); addition occurs in a stereospecific *syn* manner.

One illustration of the synthetic potential of bridgehead alkenes is shown in the scheme. The approach utilizes the Diels–Alder entry into the bicyclo[3.n.1]bridgehead alkene skeleton. Cyclization of triene **185** yields bridgehead alkene **186**. Addition of a reagent, e.g. H_2, across the double bond (*syn* addition) gives **187**. Cleavage of the bond (X–Y) generates a trisubstituted cyclohexane (**188**) with control over three asymmetric centers.

Two examples serve to illustrate this approach. Conventional bimolecular Diel–Alder cycloaddition of methyl acrylate and dienol **189** results in formation of an inseparable mixture of regioadducts, **190** and **191**. Alternatively, transesterification produces trieneester **192** which undergoes intramolecular Diels–Alder cycloaddition to bridgehead lactone **193**. Hydrolysis and diazomethane esterification give pure **190**, free from regioisomer **191**. If bridgehead lactone **193** is catalytically reduced, hydrolyzed, and esterified, pure *cis*-1,3-cyclohexane derivative **195** is formed. Catalytic reduction of **190** gives, as expected, an epimeric mixture. In a similar manner, cis,cis-1,2,4-trisubstituted cyclohexane (**197**) is obtained via bridgehead lactone **196** (eqn 16).



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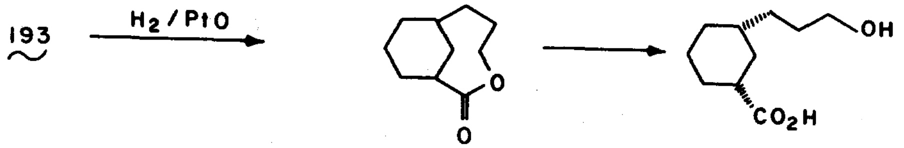

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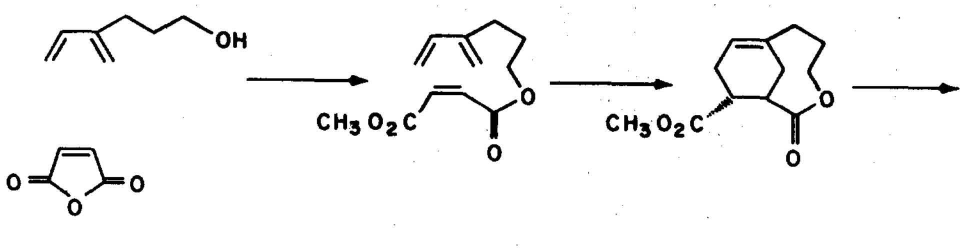

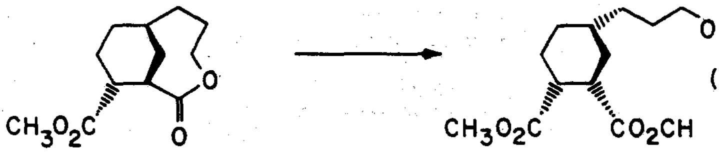

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