Cascade Radical Cyclizations via Biradicals Generated from Enediynes, Enyne-Allenes, and Enyne-Ketenes

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Contents

Kung K. Wang was born in Taiwan and received his B.S. degree from Tunghai University in 1972. After two years of compulsory military service, he joined the research group of Professor Herbert C. Brown at Purdue University and obtained his Ph.D. degree in 1979. He remained at Purdue for an additional two years before joining the faculty at West Virginia University. where he is now Professor of Chemistry. His research is in the area of designing and synthesizing multifunctional reagents substituted with combinations of boron, silicon, and tin appendages for synthetic applications.

I. Introduction

The Bergman cyclization of (*Z*)-3-hexene-1,5-diynes (enediynes) to 1,4-didehydrobenzene biradicals[1] and the Myers cyclization of (*Z*)-1,2,4-heptatrien-6-ynes (enyne-allenes) to α,3-didehydrotoluene biradicals[2] under thermal conditions provide easy entries to a variety of carbon biradicals. Similarly, the Moore cyclization of enyne-ketenes in which a ketene moiety replaces the allenic moiety of enyne-allenes leads to biradicals having an aryl and a phenoxy radical center.[3] The use of biradicals generated from enyne-ketenes for synthetic applications has been extensively investigated. In contrast, recent renewed interest in using the Bergman and the Myers cyclizations to generate carbon biradicals is due mainly to the discovery of several very potent antitumor antibiotics having the cyclic enediyne structures.[4] While much effort and the main emphasis of recent investigations have been focused on using these biradical-forming reactions for DNA cleavage, examples of using the resulting carbon biradicals for subsequent synthetic elaborations have begun to emerge.

It can be imagined that applications of a variety of reactions to the reactive radical sites of biradicals could provide new synthetic pathways for the construction of complex molecules. It is even more intriguing to imagine the various possibilities of having two radical centers in the same molecule simultaneously to induce synergetic and cooperative effects between them and thereby create new chemical transformations. Several such examples exploiting the interactions of radical centers in the same molecule for the construction of multicyclic systems and highly unusual chemical structures have recently been reported. These new synthetic opportunities are unique to the biradical-forming reactions not easily achievable by the more conventional radical-generating methods, such as the tin hydride method for producing radicals from the corresponding alkyl or aryl halides. Because of the highly reactive nature of the radical species, the first radical center generated by the tin hydride method from a dihalide will not have a long enough lifetime to wait for the second radical center to be generated.

Apart from the possibilities of interactions between the two radical centers in biradicals, the chemical reactivities of each individual radical generally resemble those of the corresponding monoradical. In the area of radical cyclization, the extremely high reaction rate in forming a five-membered ring by the 5-*exo* pathway of an aryl radical[5] was also found to be useful in trapping the aryl radical center of the biradicals generated from enediynes, enyne-allenes, and enyne-ketenes. The facile 1,5-hydrogen shift of an allylic hydrogen atom to the aryl radical center was also found to cause a serious competition with

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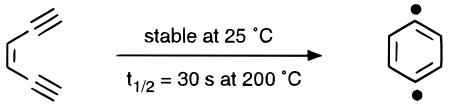
the 6-*exo* pathway in many cases for the construction of a six-membered ring.[6] With the recent rapid progress in radical chemistry and the establishment of basic principles of many radical reactions,[7] it is now possible to predict rationally the chemical behavior of these biradicals and to design cascade sequences that would lead to synthetically useful and structurally interesting molecules not easily accessible by other methods.

This review will focus mainly on cascade sequences involving an initial generation of biradicals from enediynes, enyne-allenes, and enyne-ketenes and the subsequent capturing of the resulting radical centers by intramolecular cyclization. The synthetic methods for preparation of the requisite enediynes, enyne-allenes, and enyne-ketenes will be discussed.

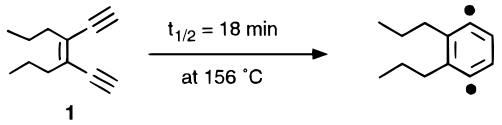
II. The Bergman Cyclization of Enediynes

In 1972, Bergman and Jones reported cycloaromatization of the parent (*Z*)-3-hexene-1,5-diyne to 1,4-didehydrobenzene biradical (eq 1).[1a] At 200 °C, the



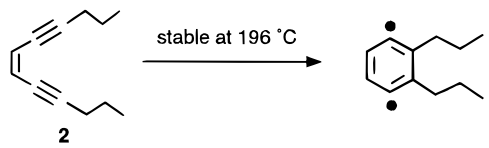
(1)

reaction was estimated to have a half-life of ~30 s. Since then a wealth of information concerning the effects of substitution patterns and structural features on the rate of cycloaromatization has become available.[8] A more careful measurement of the reaction rates of **1** allowed the determination of its activation energy (E_a) to be 27.4 ± 0.5 kcal/mol with a half-life of 18 min at 156 °C (eq 2).[1b,d] Placing



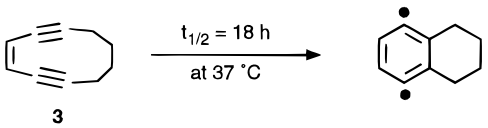
(2)

substituents at both ends of the enediyne system, such as **2**, reduces the rate of reaction, and **2** exhibits little propensity for cyclization at 196 °C (eq 3).[1b] By



(3)

tethering the two acetylenes into a 10-membered ring as shown in **3**, the activation energy is greatly reduced, and cycloaromatization of **3** occurs at 37 °C with a half-life of 18 h (eq 4).[8a] Incorporation of the



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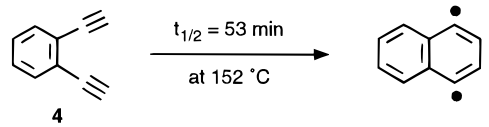
central carbon-carbon double bond of acyclic enediynes into a benzene ring has a minimal effect on the rate of the Bergman cyclization (eq 5).[8m] Aro-



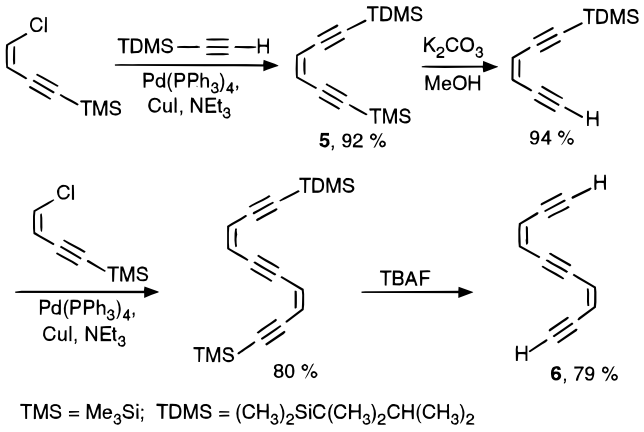
(5)

matic enediyne **4** was found to have a half-life of 53 min at 152 °C (E_a = 25.1 ± 0.8 kcal/mol).

A. Double Cycloaromatization

The extended enediyne system (*Z*,*Z*)-deca-3,7-diene-1,5,9-triyne (**6**) was synthesized by using two consecutive $Pd(PPh_3)_4$-catalyzed coupling reactions as outlined in Scheme 1.[9] Selective removal of the

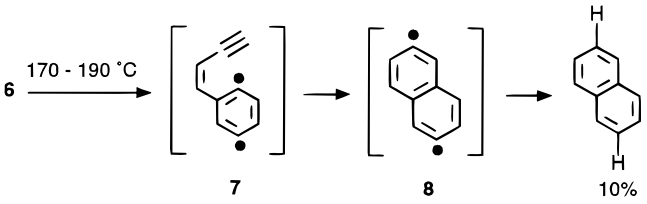
Scheme 1



trimethylsilyl group from **5** with potassium carbonate in methanol is also key to the success of the synthetic sequence.

Thermolysis of dilute solutions of **6** (<0.005 M, 170−190 °C) in a variety of solvents resulted in double cycloaromatization to furnish naphthalene in ca. 10% yield (Scheme 2). Various mechanistic and

Scheme 2



tracer experiments carried out on this thermolysis are consistent with the formation of didehydronaphthalene biradical **8** as a distinct intermediate most likely produced from an initial Bergman cyclization of **6** to form the 1,4-didehydrobenzene biradical **7** followed by a rapid radical cyclization.

Despite a low yield of converting **6** to naphthalene, the cascade sequence outlined in Scheme 2 nonetheless demonstrates the feasibility of trapping the radical center generated from an enediyne by an intramolecular cyclization reaction. The need to subject **6** to a high reaction temperature in order to promote cycloaromatization may be responsible for the low efficiency of conversion.

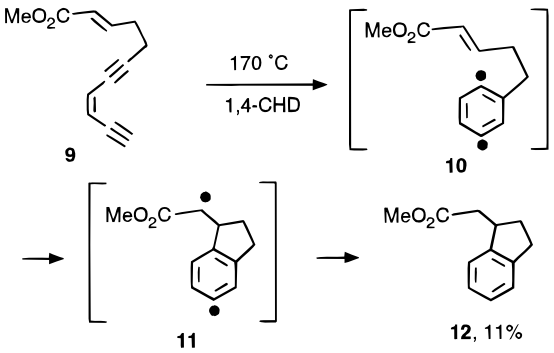
B. Olefins as Radical Acceptors for Tandem Radical Cyclizations

Enediynes substituted with one or two additional carbon−carbon double bonds as radical acceptors have been utilized for the tandem radical cyclizations. Grissom and co-workers have extensively studied the use of this strategy for the construction of multicyclic structures. Enediyne **9** and other structurally similar compounds were synthesized from (*Z*)-1,2-dichlo-

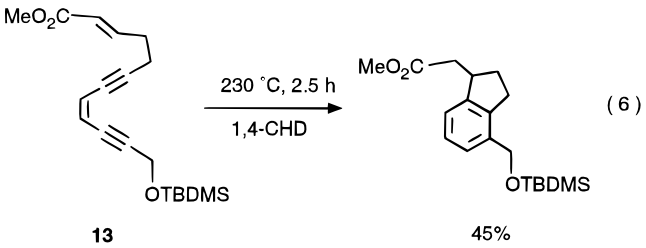
roethylene in four or five straightforward steps by using the $Pd(PPh_3)_4$-catalyzed cross coupling with terminal alkynes followed by manipulations to introduce the α,β-unsaturated ester moiety.[10]

Thermolysis of **9** in the presence of 1,4-cyclohexadiene (1,4-CHD) as a hydrogen-atom donor at 170 °C produced indan **12** in 11% yield (Scheme 3). An

Scheme 3

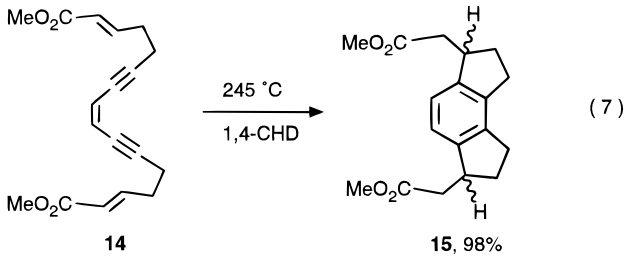


initial Bergman cyclization to **10** followed by a facile 5-*exo* cyclization to capture one of the aryl radicals gives the new biradical **11**, which then abstracts hydrogen atoms from 1,4-CHD to furnish **12**. The yield of the tandem cyclization sequence was improved when **13**, having substituents at both ends of the enediyne system, was thermolyzed at 230 °C (eq 6).[10] The higher temperature was needed due to



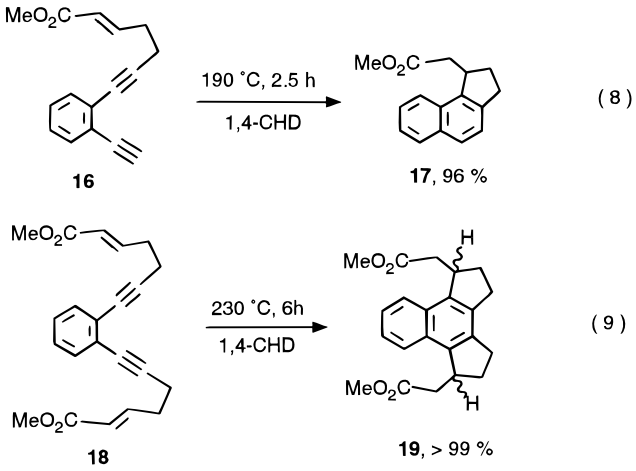
steric repulsions between the two substituents at both ends of the enediyne system.

By incorporating two α,β-unsaturated ester moieties for bis-radical cyclization, tricycle **15** as a 1:1 mixture of two diastereomers was obtained from **14** in 98% yield in a single operation (eq 7). The high



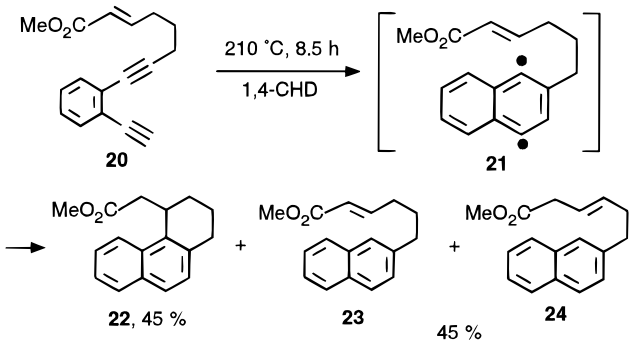
yield was attributed to the ability to quickly trap both of the highly reactive aryl radicals in the initially-formed 1,4-didehydrobenzene biradical by the two intramolecular carbon-carbon double bonds to form two α-carbomethoxy-stabilized radicals which were then quenched by 1,4-CHD.

The use of aromatic enediynes for tandem-radical cyclization is also possible and appears to be an efficient process. Thermal cyclization of **16**, readily prepared from 1,2-diiodobenzene, gave **17** in 96% yield (eq 8).[11] Similarly, bis-tandem cyclization of **18** furnished **19** in quantitative yield (eq 9).



A competition between the 6-*exo* cyclization and the 1,5-hydrogen shift of biradical **21**, derived from **20**, resulted in the formation of the tandem enediyne-radical cyclized product **22** and the simple enediyne trapped products **23** and **24** (Scheme 4). The slower

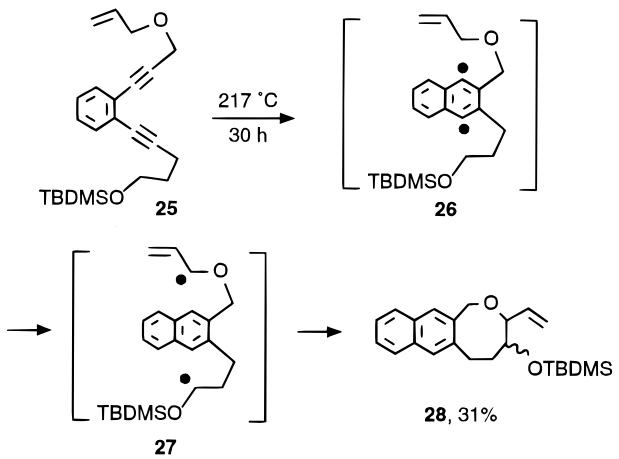
Scheme 4



rate of the 6-*exo* radical cyclization could also be responsible for the formation of **23** by allowing **21** to be quenched directly by 1,4-CHD. A 1:1 ratio of **22** to **23** and **24** (total combined yields 90%) at 0.5 M of 1,4-CHD was the best ratio that could be achieved.

The homolytic coupling of biradical **27**, generated from two 1,5-hydrogen shifts of **26**, gave **28** having an eight-membered ring (Scheme 5).[12]

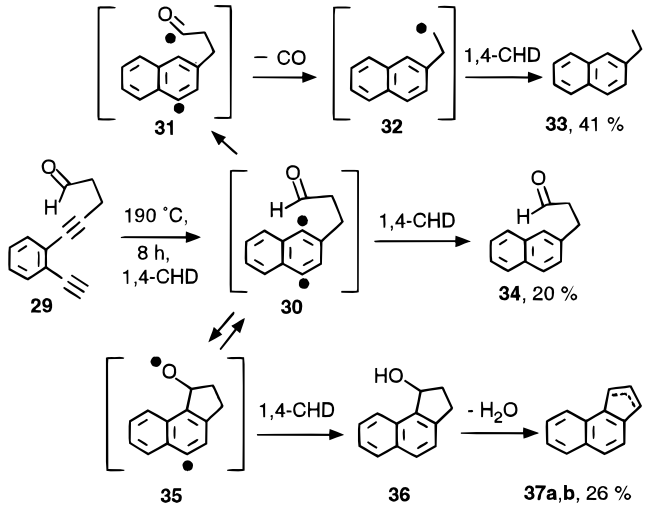
Scheme 5



C. Aldehydes and Ketones as Radical Acceptors for Tandem Radical Cyclizations

The tandem enediyne-radical cyclizations using aldehydes as radical acceptors generally produce a mixture of products due to the presence of several competing pathways for trapping the initially formed 1,4-didehydrobenzene biradicals. Thermolysis of **29** resulted in the formation of the simple enediyne cyclization products **33** (41%) and **34** (20%) as well as the tandem enediyne-radical cyclization products **37a** and **37b** (26%, 1:1 mixture of two regioisomers) (Scheme 6).[13] The expected tandem enediyne-radical

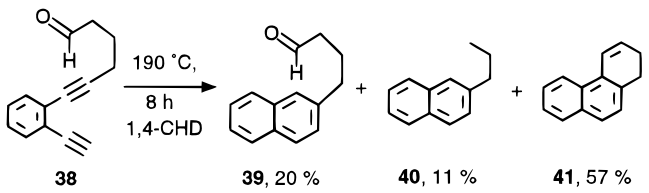
Scheme 6



cyclization product **36** was not directly observed, but is presumably converted to tricycles **37a** and **37b** via dehydration and double-bond isomerization due to the high reaction temperature. Aldehyde **34** could be formed directly from **30** by hydrogen-atom abstraction from 1,4-CHD as well as by an indirect pathway involving a 1,5-hydrogen shift to form **31** followed by hydrogen-atom abstraction from 1,4-CHD. Decarbonylation of **31** to **32** followed by hydrogen-atom abstraction from 1,4-CHD leads to β-ethylnaphthalene (**33**).

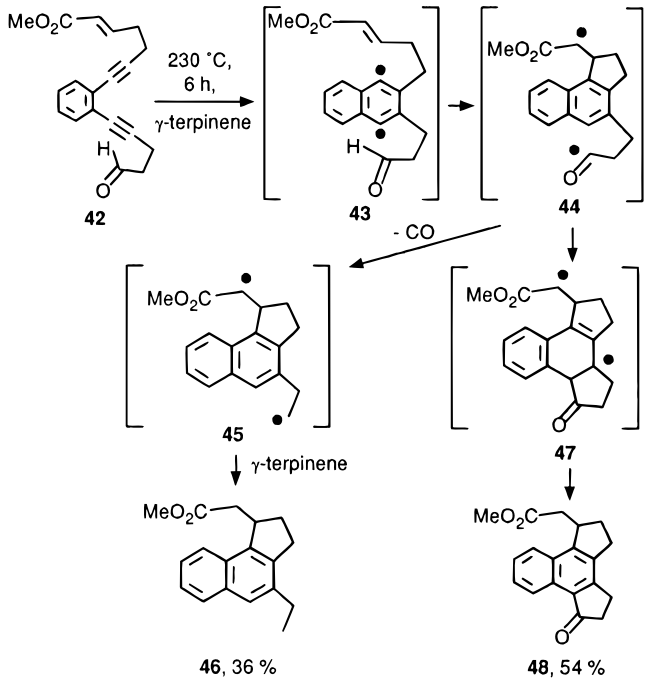
On the other hand, thermolysis of the homologous aldehyde **38** under the same conditions produced **41** from the tandem enediyne-radical cyclization as the major product (Scheme 7).[13]

Scheme 7



The tandem enediyne-radical cyclization of **42** substituted with an α,β-unsaturated ester acceptor and an aldehydic acceptor yields a mixture of products containing the tricycle **46** and the tetracycle **48** (Scheme 8).[12] While one of the aryl radicals of the initially formed biradical **43** is captured by the α,β-unsaturated ester, the other aryl radical undergoes a 1,5-hydrogen shift to give **44**. Biradical **44** either loses carbon monoxide to form **45**, which abstracts

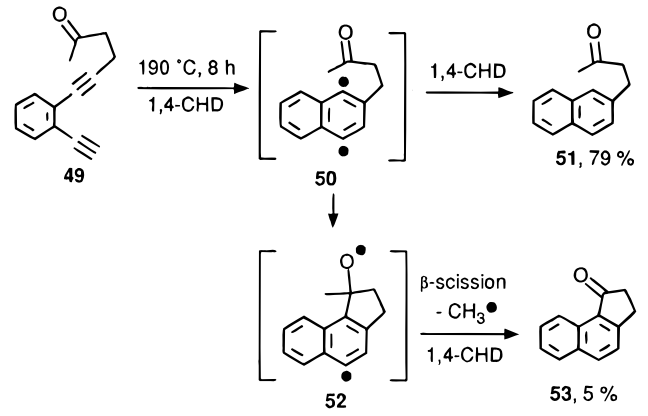
Scheme 8



hydrogen atoms from γ-terpinene to afford **46** or undergoes an intramolecular addition of the acyl radical to the aromatic ring followed by disproportionation to produce **48**. Interestingly, the product derived from intramolecular addition of the acyl radical to the aromatic ring was not observed in the case of **31** depicted in Scheme 6.

Thermolysis of **49** having a keto radical acceptor resulted in the formation of the simple enediyne cyclization product **51** in 79% yield along with a 5% yield of the tricyclic ketone **53** (Scheme 9).[14] Ketone

Scheme 9



53 arises from a radical cyclization of **50** to form **52**, which then undergoes a β-scission by losing a methyl radical.

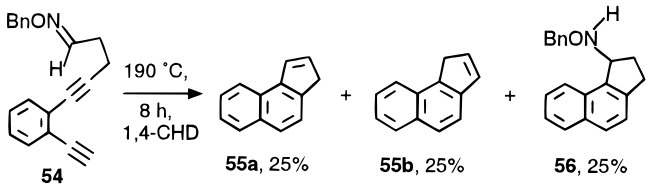
D. Oxime Ethers and Nitriles as Radical Acceptors for Tandem Radical Cyclizations

Enediynes having an oxime ether as the radical acceptor furnish the enediyne-radical cyclization products by either 5-*exo*- or 6-*exo*-radical cyclization in good yield.[13,14] The reactions are particularly useful in providing an alternative to the tandem 5-*exo* cyclization onto an aldehydic acceptor and the tan-

dem 6-*exo* cyclization onto an olefinic acceptor which encounter competitions from other undesirable pathways.

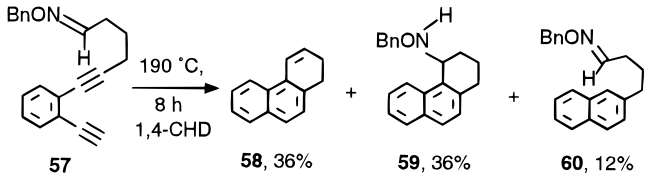
Unlike the formation of large amounts of the simple enediyne cyclization products from **29** having an aldehydic acceptor, subjecting **54** (*E*:*Z* = 1:1) to thermolysis under the same conditions produced only the enediyne-radical cyclization products consisting of hydrocarbons **55a** and **55b** (1:1 ratio) and *O*-benzylhydroxylamine **56**.[14] Hydrocarbons **55a** and **55b** were produced from elimination of a molecule of *O*-benzylhydroxylamine from **56** and double bond isomerization (Scheme 10).

Scheme 10



Employing oxime ether **57** (*E*:*Z* = 3:2) as the substrate furnished the tricyclic products **58** (36%) and **59** (36%) along with the simple enediyne cyclization product oxime ether **60** in 12% yield (Scheme 11).[14] In comparison with **20** (having an olefinic

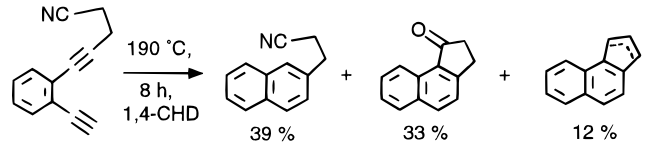
Scheme 11



acceptor) and **38** (having an aldehydic acceptor), the use of the oxime ether as the radical acceptor improves the ratio between the enediyne-radical cyclization products and the simple enediyne cyclization product to 6:1.

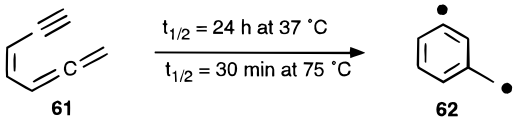
Several examples of using nitriles as the radical acceptor have also been investigated.[14] These reactions suffer from formation of mixtures of cyclization products (Scheme 12).

Scheme 12



III. The Myers Cyclization of Enyne-Allenes

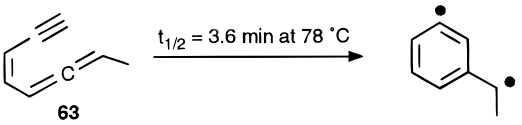
The Myers cyclization reaction of enyne-allenes to α,3-didehydrotoluenes provides a particularly attractive pathway to carbon biradicals for subsequent synthetic elaborations because the reaction occurs under mild thermal conditions and various synthetic routes to enyne-allenes with diverse chemical structures are becoming available.[2, 15−20] Simple acyclic enyne-allenes undergo facile Myers cyclizations at ambient or even subambient temperatures.[2] The parent (*Z*)-1,2,4-heptatrien-6-yne (**61**) cyclizes at 37 °C with a half-life of ca. 24 h (eq 10).[2a] At 75 °C, the



(10)

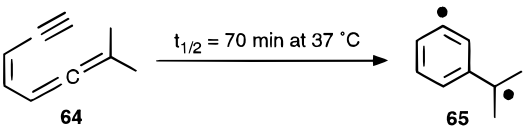
half-life of the reaction is reduced to 30 min. Compared to the Bergman cyclization of the parent enediyne, (*Z*)-3-hexene-1,5-diyne, which is calculated to be endothermic by 13 kcal/mol,[1,21] cycloaromatization of enyne-allene **61** is exothermic by 15 kcal/mol.[2,22] Even though biradical **62** has one less chemical bond than **61**, converting a π-bond of **61** to a σ-bond in **62**, along with gains from aromaticity and benzylic resonance, makes the process energetically favorable.[23]

Introduction of a methyl substituent at the terminus of the allenic moiety accelerates the reaction rate by approximately 6-fold, and **63** cyclizes with a half-life of ca. 3.6 min at 78 °C (eq 11).[2a] The formation



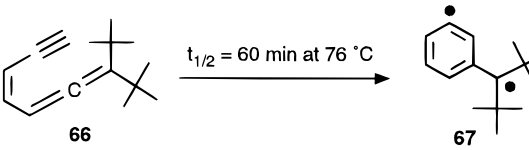
(11)

of a more stable secondary benzylic radical is apparently responsible for the rate enhancement. The presence of an additional methyl substituent appears to further increase the rate of cyclization, and **64** cyclizes to biradical **65** with a half-life of 70 min at 37 °C (eq 12).[24]



(12)

Enyne-allene **66**, having two sterically demanding *tert*-butyl groups, cyclizes at 76 °C with a half-life of 60 min (eq 13).[24] On thermolysis in refluxing ben-

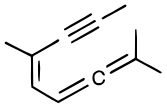


(13)

zene in the presence of an excess of 1,4-CHD, the reaction was essentially complete within 5 h, and α,α-di-*tert*-butyltoluene was isolated in 58% yield. The rate of cyclization of **66** is slower than that of **64**. However when compared to that of **61**, it is not significantly affected. Presumably, the small size of the hydrogen atom at the terminal position of the acetylenic moiety in **66** minimizes the steric interactions even with the *tert*-butyl group, and the formation of a more stable tertiary benzylic radical partially compensates for the steric interactions. It is worth noting that the benzylic radical center in **67** is an α,α-di-*tert*-butylbenzylic radical, which has been reported to be persistent in dilute solution at room temperature for several days.[25] For steric reasons, α,α-di-*tert*-butylbenzylic radical prefers a conformation with the p orbital of the radical center perpendicular to the π-bonds of the benzene ring, resulting

in the loss of 13 kcal/mol of the resonance energy. This preference also eliminates the possibility of twisting the terminal allenic carbon of **66** during the course of cyclization to allow at least a partial conjugation of the benzylic radical center with the benzene ring at the transition state in order to facilitate the rate of cyclization.[2a,23]

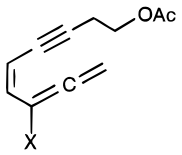
Placing an alkyl substituent at the terminus of the acetylenic moiety appears to reduce the rate of cyclization, presumably due to steric reasons. For example, **68** can be separated and purified by column



68

chromatography (silica gel) in 91% isolated yield at ambient temperature without formation of significant amount of the cycloaromatized product.[15] Enyne-allene **69** was estimated to have a half-life of 66 h at 37 °C.[2d] The higher thermal stability of enyne-allenes with a substituent at the acetylenic terminus is advantageous, allowing isolation, purification, and characterization of these molecules without special precaution.

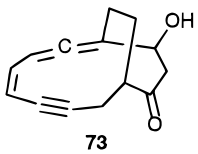
Interestingly, the presence of a substituent at C-3 position lowers the activation energy for cyclization. Enyne-allenes **70**, **71**, and **72** cyclize at 37 °C with respective half-lifes of 80, 100, and 16 min.[2d] The



69: X = H
70: X = P(O)Ph$_2$
71: X = Me
72: X = S(O)Ph

higher rates of cyclization were attributed to the preference of these enyne-allenes in adopting the s-cis conformation, which is required for cyclization in order to minimize steric interactions with the substituent at the C-3 position.

Surprisingly, incorporation of enyne-allene into a bicyclic [7.3.2] system as shown in **73** appears to decelerate the rate of cyclization.[26] The bicyclic enyne-allene **73** remained unchanged even after heating in CCl_4 for 5 h.

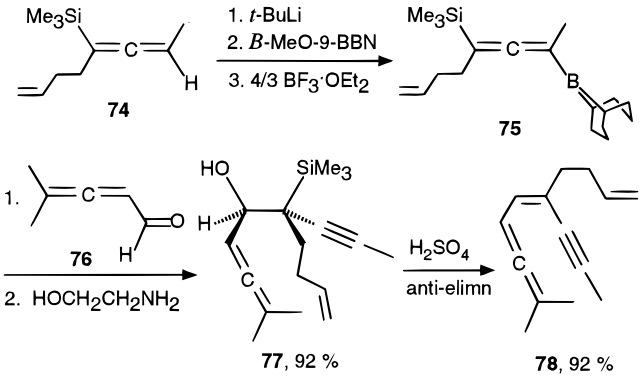


73

A. Formation of *o*-Quinodimethanes

The reaction sequence outlined in Scheme 13 provides a simple synthetic route to enyne-allene **78** having a 3-butenyl substituent suitable for tandem cycloaromatization and radical cyclization.[15] Allenylsilane **74** was lithiated with *tert*-butyllithium followed by treatment with *B*-methoxy-9-borabicyclo-[3.3.1]nonane (*B*-MeO-9-BBN) and $^4/_3BF_3{\cdot}OEt_2$ to produce allenylborane **75**. Subsequent condensation of **75** with the readily available conjugated allenic aldehyde **76** afforded, after treatment with 2-amino-ethanol, hydroxypropargylsilane **77** with high dia-

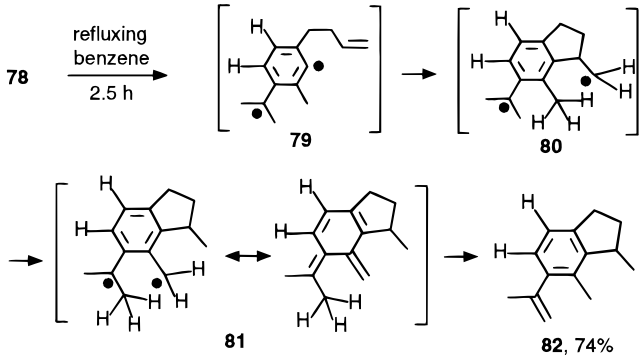
Scheme 13



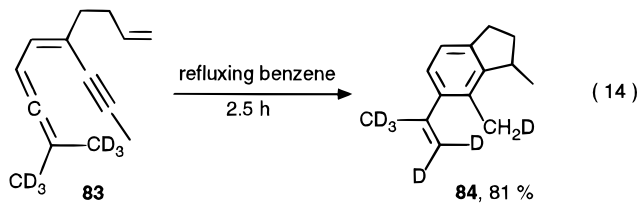
stereomeric purity (de = 92%) and in excellent yield. The ability to synthesize **77** with high diastereoselectivity is key to producing enyne-allene **78** with the desired *Z* geometry for the central carbon−carbon double bond. The H_2SO_4-induced anti elimination of hydroxytrimethylsilane from **77** gave **78** with high geometric purity (*Z*:*E* = 96:4).

Thermolysis of **78** in refluxing benzene furnished the indan derivative **82** in a single operation (Scheme 14). Apparently, the aryl radical in the initially

Scheme 14



formed biradical **79** is trapped by the carbon−carbon double bond intramolecularly in a typical 5-*exo* fashion to give **80**, which then decays to afford **82**. Because of the highly reactive nature of the radical species, the concentration of **80** has to be low during the course of the reaction, and it is therefore unlikely that a reaction mechanism involving exchange of hydrogen atoms among **80** intermolecularly could account for the formation of **82**. Instead, **80** decays through an intramolecular route with an initial 1,5-hydrogen shift to form *o*-quinodimethane **81** followed by a [1,5]-sigmatropic hydrogen shift to afford **82**. The preference for the reaction to proceed through such an internal decay route is supported by the formation of **84** when deuterated enyne-allene **83** was utilized. The migration of a deuterium atom to the benzylic position is consistent with the intramolecular pathway (eq 14).



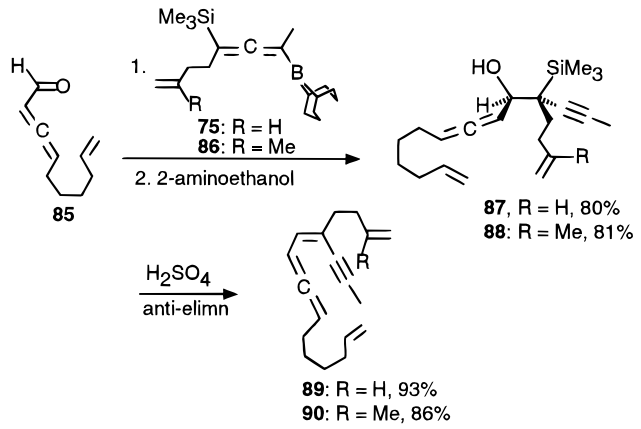
(14)

In comparison with examples reviewed so far, the existence of an intramolecular disproportionation route for biradical **80** avoids the need to include an external hydrogen-atom donor in order to terminate the cascade sequence. Undesirable premature quenching of the radical species by the hydrogen-atom donor along the cascade pathway is no longer a concern.

B. The Tetracyclic Steroidal Skeleton

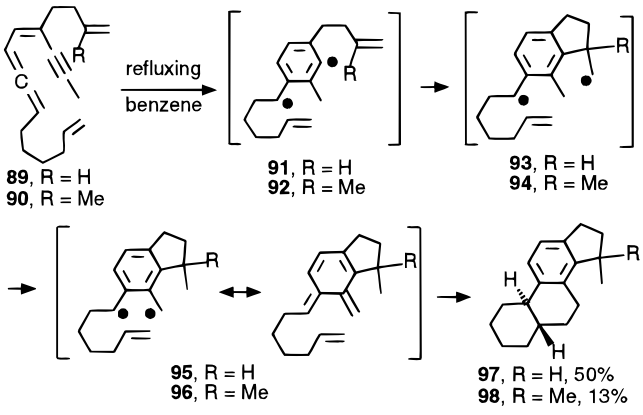
o-Quinodimethanes synthesized by the cascade sequence outlined in Scheme 14 have been successfully utilized for the construction of the tetracyclic steroidal skeleton.[16] Acyclic enyne-allene **89**, serving as a precursor to the steroidal skeleton, was likewise prepared by condensation of the conjugated allenic aldehyde **85** with γ-(trimethylsilyl)allenylborane **75** followed by treatment with 2-aminoethanol to afford **87** in 80% yield. The diastereoselectivity of the two newly formed asymmetric centers was again high (de = 94%). The subsequent H_2SO_4-induced Peterson olefination produced **89** in high geometric purity (*Z*:*E* = 96:4). Similarly, enyne-allene **90** (*Z*:*E* = 96:4) was prepared by using allenylborane **86** for condensation with **85** (Scheme 15).

Scheme 15



The thermally induced cascade radical cyclization of **89** to the fused 6,6,6,5-ring system was carried out in refluxing benzene for 2.5 h to furnish **97** having predominantly the trans ring junction (trans:cis = 92:8) (Scheme 16). Such a stereochemical outcome

Scheme 16



of the transformation from **95** to **97** is consistent with earlier reports of other closely related intramolecular Diels–Alder reactions of *o*-quinodimethanes.[27] Because the asymmetric center on the five-membered ring does not exert a significant influence on the facial selectivity of the intramolecular Diels–Alder reaction, a 1:1 mixture of two diastereomers for both the trans and the cis isomers was produced.

The chemical transformation from **89** to **97** has been proposed to proceed through the reaction mechanism outlined in Scheme 16. It is most likely that the 5-*exo* ring closure to form **93** is the first event that occurs following cycloaromatization because aryl radicals are very reactive toward cyclization ($k_{5\text{-}exo}$ = ca. 5×10^8 s^{-1} at 50 °C).[5] It can also be anticipated that the subsequent 1,5-hydrogen shift to form **95** is several orders of magnitude faster than the possible intramolecular trapping of the benzylic radical center in **93** by the carbon–carbon double bond. Benzylic radicals have been shown to be very unreactive toward radical cyclization;[28] a slow rate to capture the benzylic radical in **93** by the 6-*exo* radical cyclization can be expected. Consequently, *o*-quinodimethane **95** is also an intermediate in the present case and is captured intramolecularly by the carbon–carbon double bond.

The use of enyne-allene **90** for cascade radical cyclization produced **98** in 13% yield. The low efficiency of conversion has been attributed to the presence of a methyl group at the internal position of a double bond which is known to reduce the rate of 5-*exo* cyclization significantly, making the undesirable 6-*endo* cyclization of **92** competitive.[29]

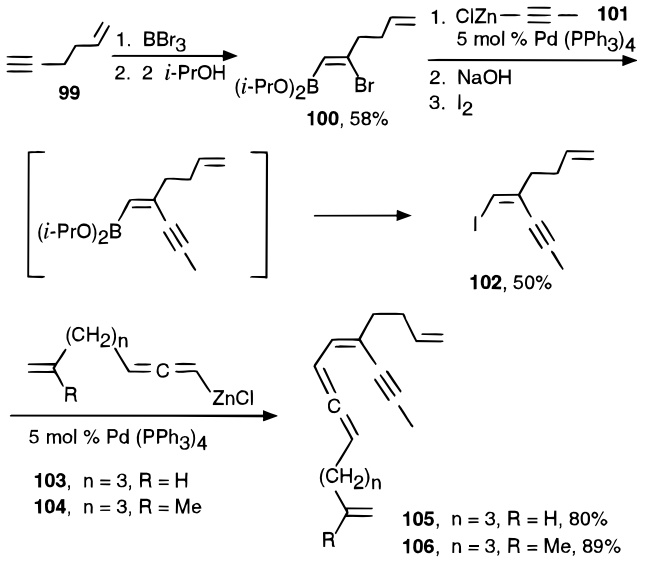
The synthetic strategy outlined in Scheme 16 represents a new example of a one-step 0 → ABCD ring construction of the tetracyclic steroidal skeleton having an aromatic C-ring. In comparison with the cationic polyolefinic cyclization[30] and the more recent transition metal-mediated reactions,[31] this strategy is unique in that cyclization is induced thermally and does not require an acid or a transition metal catalyst.

C. The Fused Tetracyclic 5,6,6,5-Ring System

The synthetic pathway outlined in Scheme 16 has been extended to the construction of the fused tetracyclic 5,6,6,5-ring system.[24a] This goal was achieved by simply reducing the length of the tether connecting the carbon–carbon double bond to the allenic moiety of the enyne-allene system by one carbon atom.

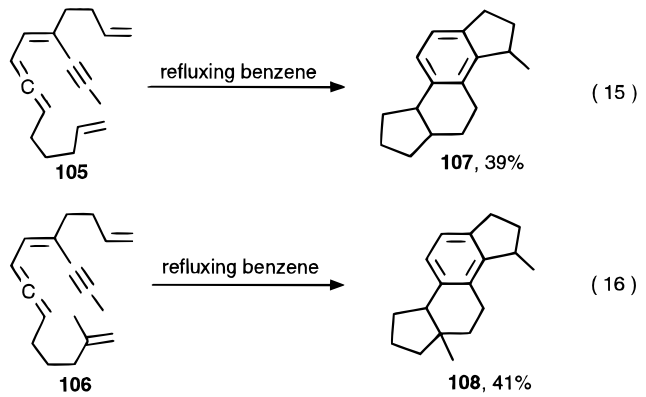
The prerequisite enyne-allenes **105** and **106** having a three-carbon tether were prepared by a convergent method outlined in Scheme 17.[17] Treatment of 1-hexen-5-yne (**99**) with BBr_3 followed by esterification with isopropyl alcohol furnished the corresponding (*Z*)-alkenylboronic ester **100** in 58% isolated yield. Conversion of **100** to enynyl iodide **102** was achieved by using the $Pd(PPh_3)_4$-catalyzed cross-coupling reaction with alkynylzinc chloride **101** followed by treatment with NaOH and iodine. A second $Pd(PPh_3)_4$-catalyzed cross-coupling reaction between **102** and allenylzinc chloride **103** (derived from treating 1,2,7-octatriene with *n*-butyllithium followed by anhydrous zinc chloride) proceeded smoothly to furnish enyne-allene **105** with high geometric purity (*Z*:*E* = 97:3).

Scheme 17



Similarly, enyne-allene **106** having a methyl substituent at the internal position of one of the additional double bonds was synthesized by cross coupling with allenylzinc chloride **104**.

Thermolysis of enyne-allene **105** was likewise conducted in refluxing benzene to furnish **107** having the fused 5,6,6,5-ring system in 39% yield (eq 15). The tetracyclic compound **107** was found to be a 3:3:2:2 mixture of all four possible diastereomers presumably because of a lack of facial selectivity as well as little preference for either *exo* or *endo* attack during the intramolecular Diels−Alder reaction to capture the corresponding *o*-quinodimethane at the last step of the cascade sequence. Placing a methyl substituent at the internal position of one of the additional carbon−carbon double bonds in **106** resulted in the formation of **108** substituted with an angular methyl group as a 1:1:7:9 mixture of four diastereomers in 41% yield (eq 16). The improved

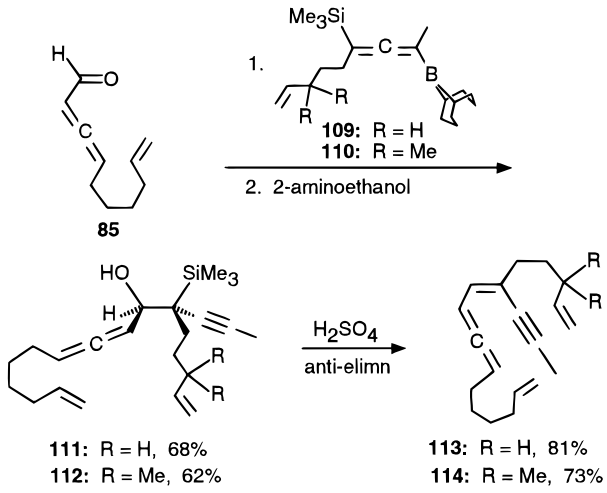


stereoselectivity is presumably due to a preference for either an *exo* or an *endo* attack during the intramolecular Diels−Alder reaction, producing either the cis or the trans ring junction (not determined) predominantly.

D. The Spiro Structures and the Fused Tetracyclic 6,6,6,6-Ring System

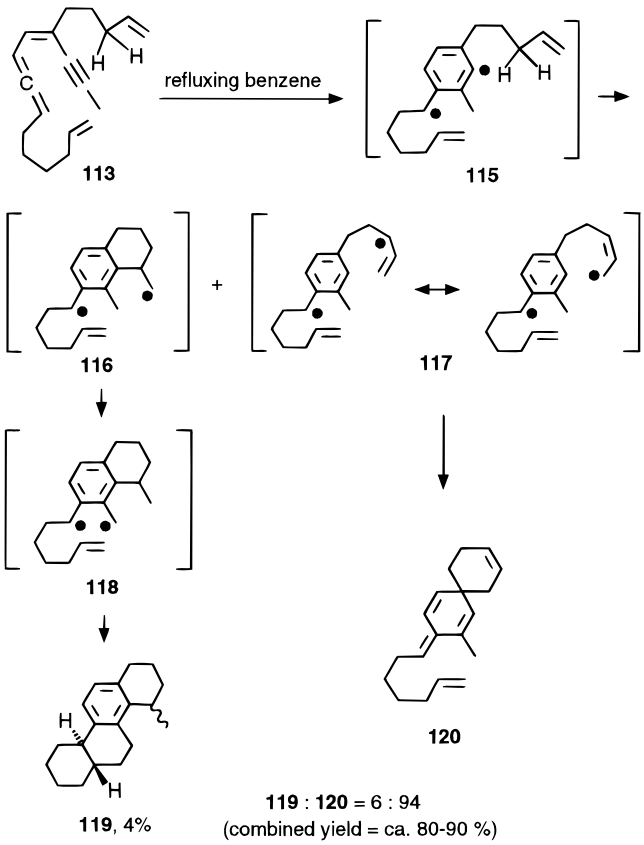
The possibility of constructing the fused 6,6,6,6-ring system by using enyne-allene **113** (having one of the tethers elongated by one carbon atom as compared to **89**) for the cascade radical cyclization has also been investigated.[24a] Enyne-allene **113** was synthesized by condensation of **85** with γ-(trimethylsilyl)allenylborane **109** followed by the H_2SO_4-induced Peterson olefination (Scheme 18).

Scheme 18



Thermolysis of **113** produced a small amount of the anticipated tetracyclic compound **119** (ca. 4% isolated yield, 1:1 mixture of two diastereomers) having the fused 6,6,6,6-ring system. However, the major product was the bicyclic spiro derivative **120** (not isolated, but observed by NMR) (**119**:**120** = 6:94) (Scheme 19).

Scheme 19

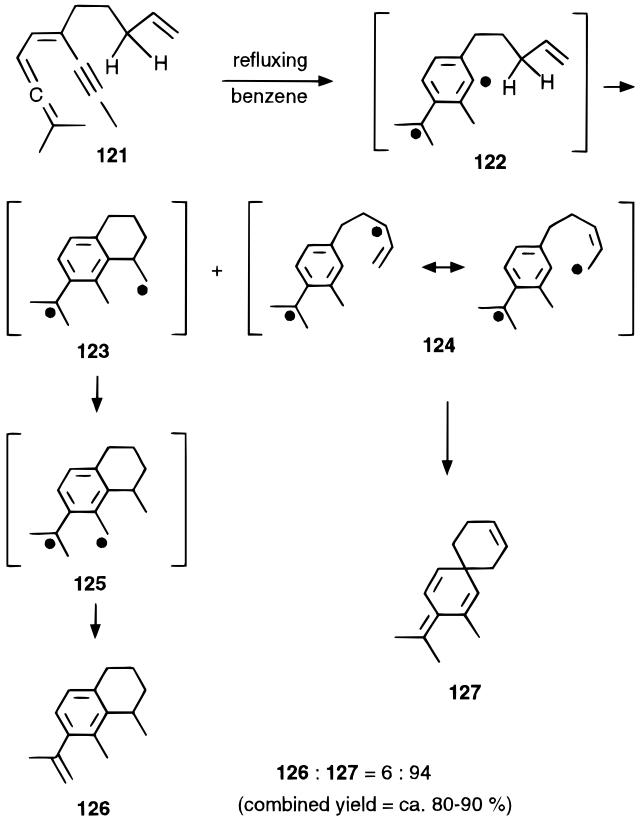


Apparently, instead of trapping the benzenoid radical in **115** by one of the intramolecular carbon−carbon

double bonds in a 6-*exo* fashion to afford biradical **116** leading to **119**, the majority of the reaction proceeds through a 1,5-hydrogen shift to furnish **117** containing an allylic radical. The subsequent attack on the *ipso* carbon of the benzene ring by the terminus of the allylic radical led to homolytic coupling that produced **120**. The chemical transformation from **113** to **119** and **120** is very efficient, producing a combined yield of ca. 80−90% as observed by the ^{1}H NMR.

While the cascade radical cyclization of **113** fails to produce the fused tetracycle **119** as the main product, it provides a new pathway to bicyclic spiro compounds. Indeed, thermolysis of **121** (which has one additional double bond attached to the enyne-allene system through a 3−carbon tether) produced the expected bicyclic derivative **127**, along with a minor amount of the tetrahydronaphthalene derivative **126** (**126**:**127** = 6:94, not separated, combined yield ca. 80−90% by the ^{1}H NMR) (Scheme 20).

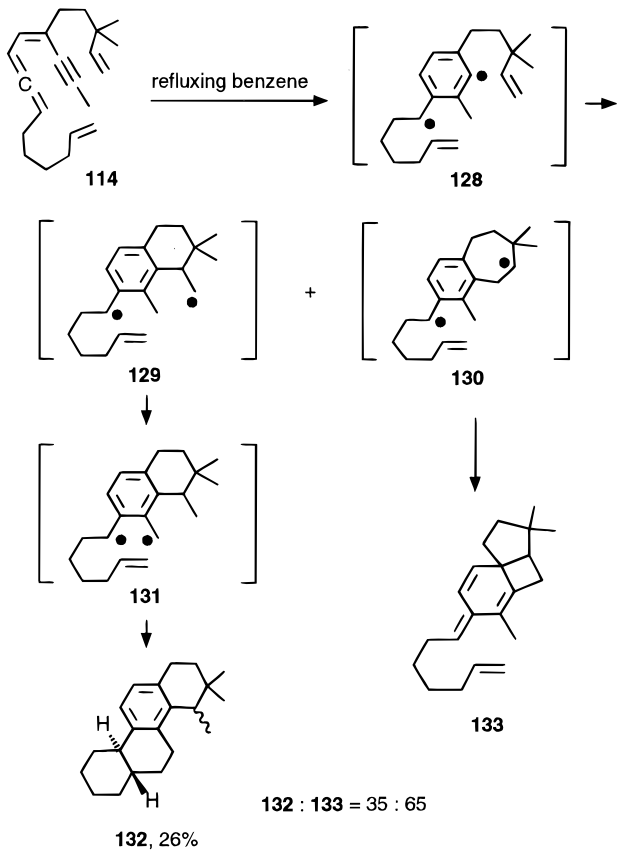
Scheme 20



Apparently, *o*-quinodimethane **125** derived from the 6-*exo* radical cyclization decayed through a 1,5-intramolecular hydrogen shift to produce **126** as observed previously for **81**.

An attempt has been made to try to eliminate the possibility of the 1,5-hydrogen shift from **115** to **117** in order to direct the cascade radical cyclization toward the 6-*exo* pathway leading to the fused 6,6,6,6-ring system. Enyne-allene **114**, having two methyl groups in place of the two allylic hydrogens in **113**, was synthesized for this purpose. After refluxing **114** in benzene, the anticipated tetracyclic adduct **132** was isolated in 26% yield (Scheme 21). However, **132** remained as the minor adduct and the tricyclic

Scheme 21



derivative **133** (not isolated, but observed by NMR) (**132**:**133** = 35:65), having an unusual structure, was produced predominantly. Undoubtedly, the tricyclic derivative **133** arises from a 7-*endo* ring closure of **128** to furnish **130**, leading to **133** by attack on the benzene ring by the homobenzylic radical center in **130** to accomplish homolytic coupling. It has been well established that the increased chain length of the 6-heptenyl radical permits the formation of greater amounts of the *endo* product.[29] The steric hinderance of the two geminal methyl groups in **128** may also be responsible for directing the radical cyclization toward the *endo* pathway.

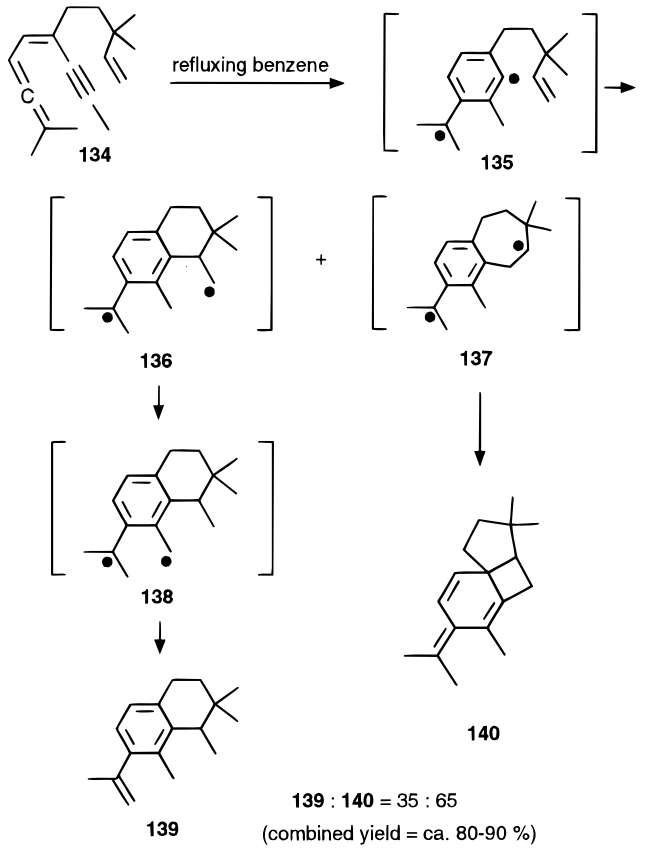
While tricycle **133** contains a strained chemical structure and does not possess aromaticity as in **132**, the transformation from **114** to **133** can still be expected to be highly exothermic. The overall transformation involves trading three π bonds for three σ bonds, a driving force of ca. 60 kcal/mol.

Acyclic enyne-allene **134** has also been synthesized as a simplified analogue of **114** (Scheme 22). On heating in refluxing benzene, **134** was converted to the bicyclic adduct **139** and the tricyclic derivative **140** as expected (**139**:**140** = 35:65, not separated, combined yield ca. 80−90% by the ^{1}H NMR).

E. Cascade Sequences Initiated by a Sigmatropic Rearrangement

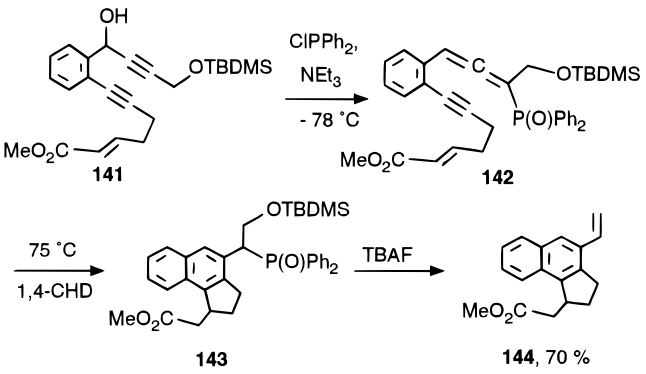
The use of a sigmatropic rearrangement to initiate cascade sequences of enyne-allenes has also been investigated. Enyne-allene **142** was synthesized via a [2,3]-sigmatropic rearrangement by treating the

Scheme 22



propargylic alcohol **141** with chlorodiphenylphosphine.[32] Thermolysis of **142** at 75 °C in the presence of 1,4-CHD produced the tandem radical cyclization product **143**, which was then subjected to a Horner−Wittig elimination to produce **144** in 70% overall yield (Scheme 23). In comparison with the tandem

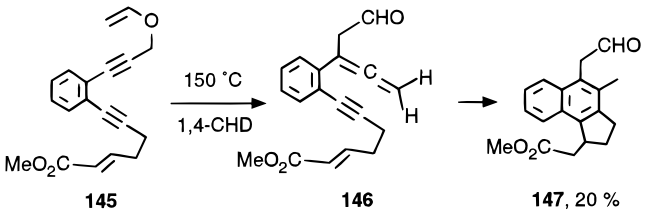
Scheme 23



radical cyclizations of enediynes which would require heating to 190 °C or higher, the mild thermal conditions employed in the present case would be more compatible with thermally sensitive functional groups.

A synthetic strategy involving the use of a [3,3]-sigmatropic rearrangement of propargyl vinyl ethers for the preparation of enyne-allenes for subsequent tandem radical cyclizations has also been established.[33] When **145** was subjected to heating at 150 °C, tricycle **147** was obtained in 20% yield (Scheme 24). An initial [3,3]-sigmatropic rearrangement to form **146** followed by a Myers cyclization, a 5-*exo*

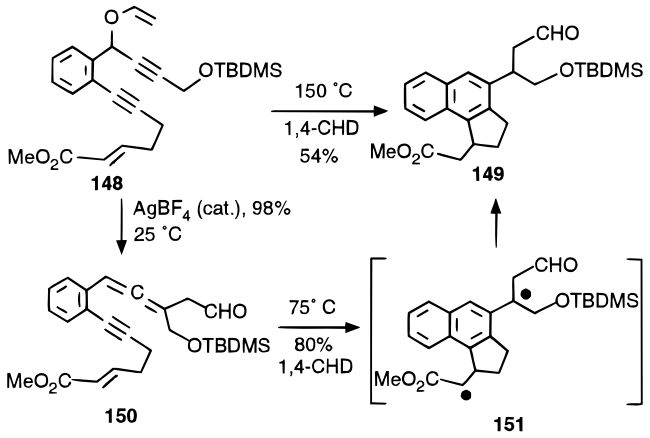
Scheme 24



cyclization of the resulting aryl radicals and a hydrogen-atom abstraction from 1,4-CHD could account for the formation of **147**.

Similarly, propargyl vinyl ether **148** was converted to **149** as a 1:1 mixture of diastereomers in 54% yield by thermolysis at 150 °C (Scheme 25).[33] Again, the

Scheme 25



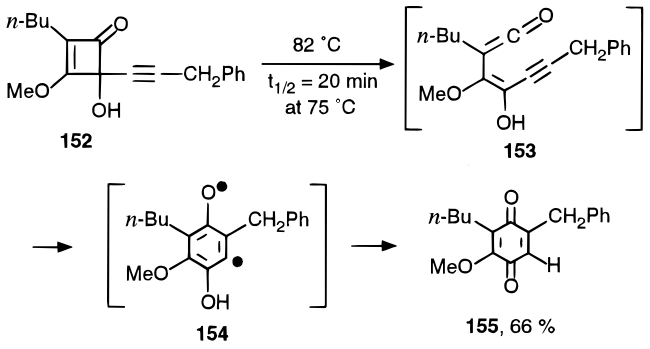
reaction proceeds through an initial [3,3]-sigmatropic rearrangement to trigger the cascade sequence. A higher yield in producing **149**, compared to **147**, has been attributed to the elimination of an unfavorable steric interaction between the substituent on the allenic carbon attached to the aryl ring and the *ortho* hydrogen of the aryl ring which causes the allene to rotate out of the plane defined by the aryl group, making cyclization less feasible. In addition, the presence of two alkyl substituents on the allenic carbon away from the aryl ring in **150** could also accelerate the rate of the Myers cyclization to **151** containing a more stable benzylic radical.

The enyne-allene intermediate **150** has been isolated in 98% yield by treating **148** with a catalytic amount of $AgBF_4$ at room temperature to induce a Lewis acid-catalyzed [3,3]-sigmatropic rearrangement. Thermolysis of **150** was conducted at 75 °C to afford **149** in 80% yield.

IV. The Moore Cyclization of Enyne-Ketenes

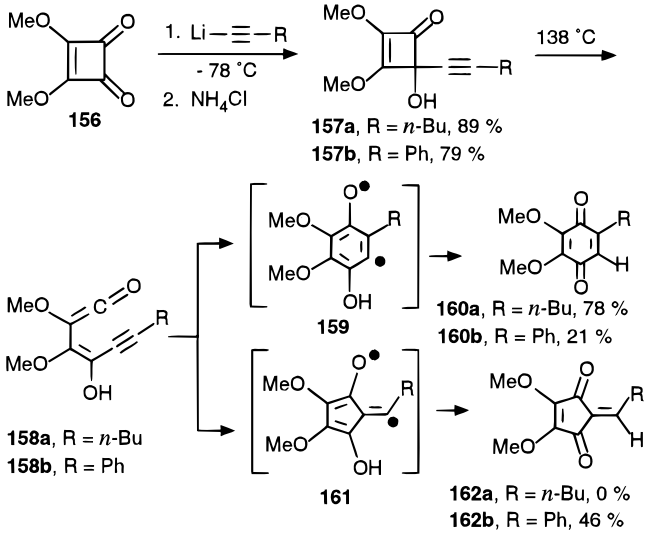
The Moore cyclization of enyne-ketenes is similar to that of enyne-allenes, producing biradicals containing an aryl and a phenoxy radical center.[3] While the intrinsic rate of the reaction has not yet been determined, thermolysis of 4-alkynylcyclobutenone **152** in acetonitrile at 82 °C afforded quinone **155** ($t_{1/2}$ = 20 min at 75 °C) in 66% yield (Scheme 26).[34] The reaction is believed to proceed through an electrocyclic ring opening of **152** to form enyne-ketene **153**, which then undergoes a Moore cyclization to form biradical **154** leading to **155**.

Scheme 26



The electrocyclic ring opening of 4-alkynylcyclobutenones at temperatures ranging from 80 °C to 138 °C provides a versatile route to a variety of enyne-ketenes.[3] 4-Alkynylcyclobutenones can be readily prepared by treating cyclobutenediones with 1-lithio-1-alkynes.[35] Specifically, treatment of dimethyl squarate (**156**) with 1-lithio-1-hexyne followed by quenching of the reaction mixture with ammonium chloride furnished cyclobutenone **157a**, which upon thermolysis in refluxing *p*-xylene at 138 °C produced the 1,4-benzoquinone **160a** as the sole product (Scheme 27). The reaction is considered to

Scheme 27

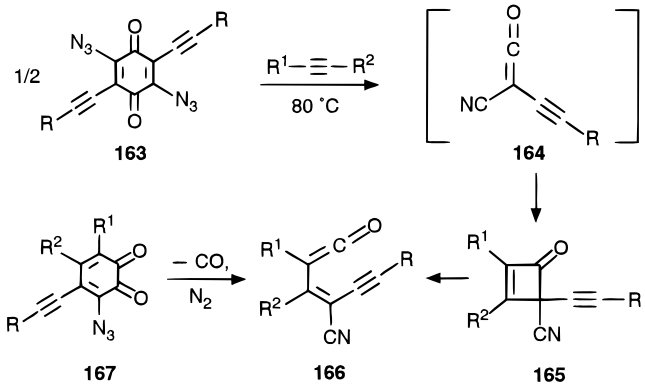


proceed through a stereoselective ring opening of **157a** in which the electron-donating hydroxyl group rotates outward to give enyne-ketene **158a** having the *Z* geometry.[35a,36] Subsequent cycloaromatization to biradical **159** followed by an intermolecular hydrogen-atom transfer process results in the formation of **160a**.[34,37]

When the R group is phenyl (**157b**), the enyne-ketene **158b** also undergoes a competing ring closure to form the five-membered ring biradical **161** in which the phenyl group stabilizes the adjacent radical site. As a result, a mixture of **160b** and **162b** was produced from **157b**.

Alkynylcyanoketenes **164**, generated in situ by thermolysis of 2,5-diazido-3,6-dialkynyl-1,4-benzoquinones **163**, have also been employed for [2 + 2] cycloadditions with alkynes to produce the corresponding 4-alkynylcyclobutenones **165** which open to enyne-ketenes **166** having a 4-cyano substituent (Scheme 28).[38] Similarly, thermolysis of 3-azido-4-

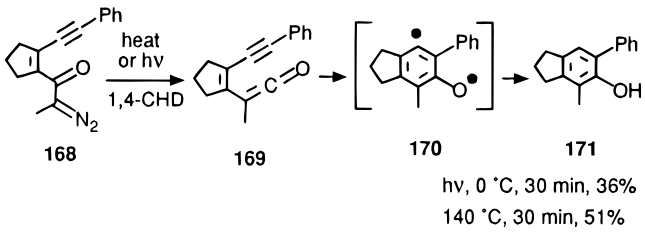
Scheme 28



alkynyl-1,2-benzoquinones **167** to induce the loss of N_2 and CO provides a direct pathway to **166**.[38,39]

An alternative pathway to enyne-ketenes involves photolysis of enynyl α-diazo ketones. Irradiation of **168** in the presence of 1,4-CHD at 0 °C for 30 min produced **171** in 36% yield (Scheme 29).[40] The

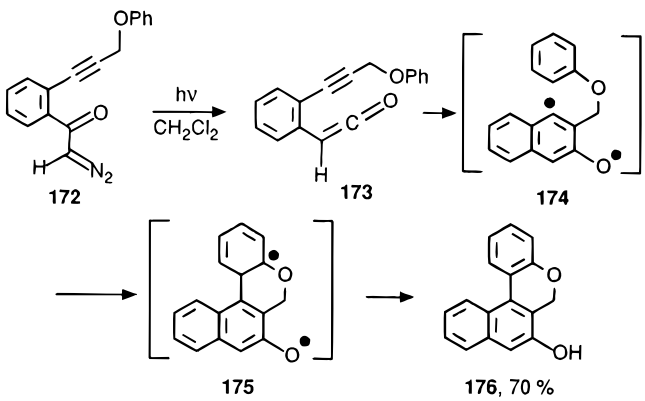
Scheme 29



reaction has been proposed to proceed through a photoinduced Wolff rearrangement to produce enyne-ketene **169** followed by a Moore cyclization to form biradical **170**, which then abstracts hydrogen atoms from 1,4-CHD to furnish phenol **171**. Transformation from **168** to **171** has also been induced thermally at 140 °C.

The Wolff rearrangement has also been utilized to prepare enyne-ketenes having the central carbon—carbon double bond incorporated in a benzene ring.[41] Irradiation of α-diazoacetophenone **172** in methylene chloride produced naphthol **176** in 70% yield (Scheme 30). The rearrangement proceeds through an initial

Scheme 30



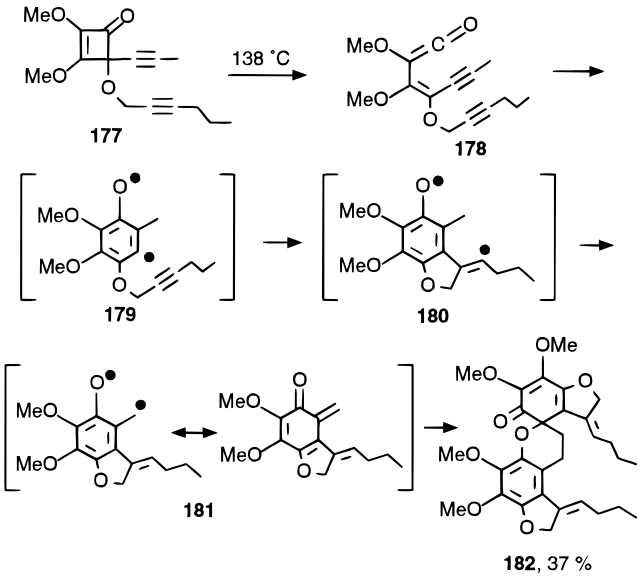
photochemical Wolff rearrangement to form the aromatic enyne-ketene **173**, which then cycloaroma-

tizes to biradical **174**. Subsequent attack on the neighboring aromatic ring by the aryl radical followed by disproportionation leads to naphthol **176**.

A. Formation of *o*-Quinone Methides

An example illustrating the cascade radical cyclization of enyne-ketene **178** to *o*-quinone methide **181** followed by dimerization to form **182** is outlined in Scheme 31.[42] The reaction pathway involves an

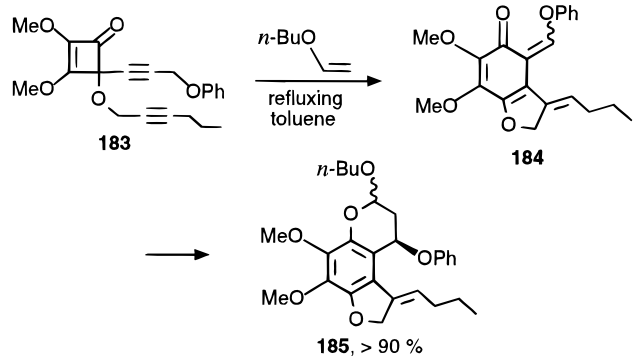
Scheme 31



electrocyclic ring opening of **177** to enyne-ketene **178**, which then undergoes a Moore cyclization to form biradical **179**. The aryl radical in **179** then undergoes a 5-*exo* cyclization to form the new biradical **180**. A subsequent 1,5-hydrogen shift furnishes **181**, which then dimerizes to form **182**. This reaction mechanism is reminiscent of the formation of *o*-quinodimethane **81** from enyne-allene **78**.

An analogous example using the same cascade sequence to produce *o*-quinone methide **184** for the subsequent hetero-Diels–Alder reaction is outlined in Scheme 32.[42] *o*-Quinone methide **184**, derived

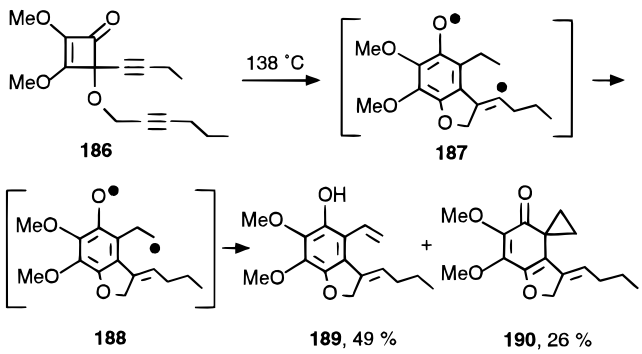
Scheme 32



from **183**, is captured by butoxyethylene to give chromanol **185** as a 2:1 mixture of diastereomers in greater than 90% yield.

Interestingly, by starting from **186**, which has the 4-alkynyl substituent elongated by one carbon atom as compared to **177**, the fate of biradical **187** is different (Scheme 33). Instead of the expected 1,5-

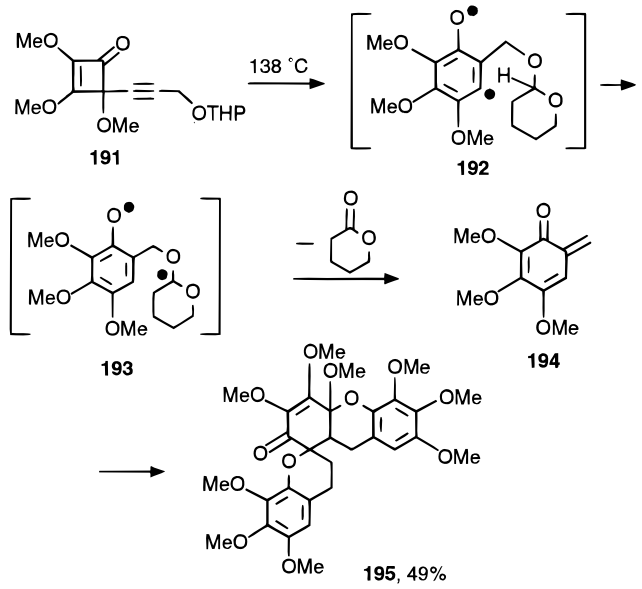
Scheme 33



hydrogen transfer to give the corresponding *o*-quinone methide, the 1,6-hydrogen shift predominates to afford the new biradical **188**, which then disproportionates to form methylenebenzofuran **189** as well as undergoes an intramolecular radical–radical combination to give the spiro compound **190**. It is interesting to note that a direct coupling of the two radical centers in **188** to form a second furan ring was not observed.

A reaction pathway to *o*-quinone methides involving a fragmentation process has also been reported.[35a] Specifically, biradical **192** produced from **191** undergoes a 1,5-hydrogen shift to form **193** (Scheme 34).

Scheme 34

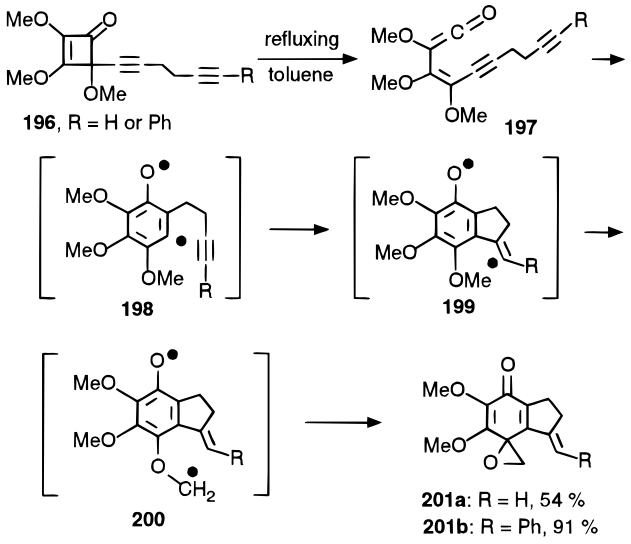


Biradical **193** then loses a molecule of δ-lactone to give *o*-quinone methide **194**, which yields a trimer with the structure tentatively assigned as depicted in **195**.

B. The Spiro Structures and the Annelated Quinones

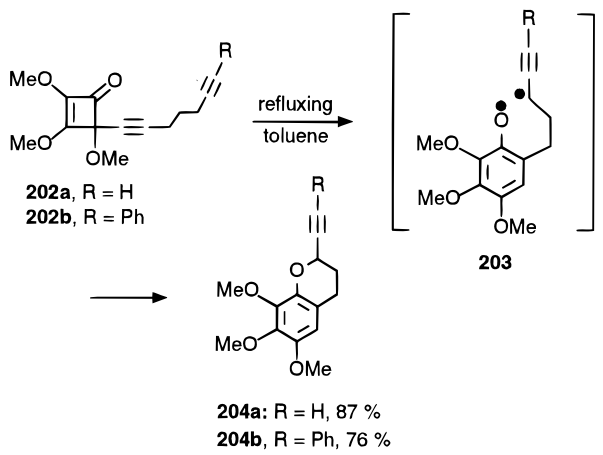
The intramolecular radical–radical combination to form spiro compounds has also been observed when 4-(1,5-dialkynyl)-4-methoxycyclobutenones **196** were subjected to thermolysis in refluxing toluene (Scheme 35).[37] The annelated spiro epoxides **201** were isolated in 54% and 91% yield. Apparently, the vinyl radical in **199** abstracts a hydrogen atom for the adjacent methoxy group to give **200** which leads directly to **201**.

Scheme 35



When the tether connecting the two alkynyl groups at the 4-position of the starting 4-methoxycyclobutenones was elongated by one carbon atom as shown in **202** (Scheme 36), a 1,5-hydrogen shift of the

Scheme 36

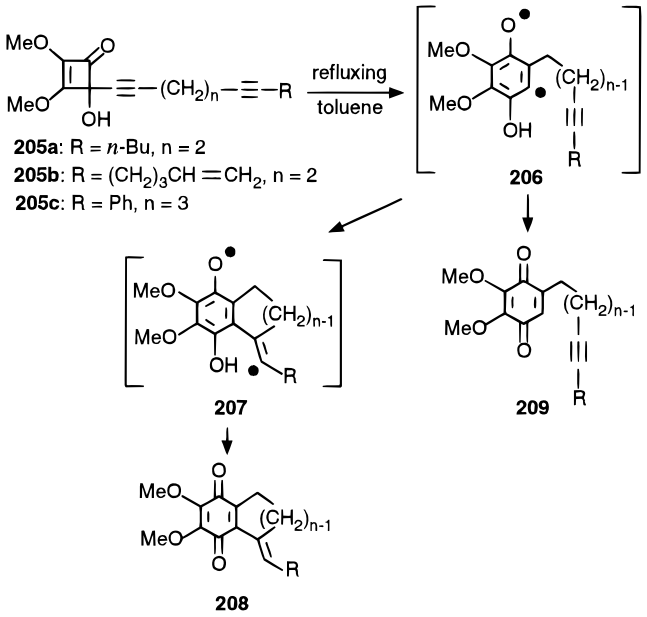


initially formed biradicals became the preferred pathway, leading to propargyl radicals **203**. The subsequent ring closure then gave the chromanols **204a** (87%) and **204b** (76%). It is worth noting that biradicals **203**, unlike **188**, did not undergo disproportionation or ring close to the spiro compounds having a four-membered ring.

Replacing the 4-methoxy group in **196** with a hydroxyl group precludes the possibility of forming spiro epoxides. Instead, under high dilution (3.86×10^{-3} M) the cascade sequence starting from **205a** is terminated by a 1,5-hydrogen transfer from the adjacent hydroxyl group to the vinyl radical in **207**, producing annelated quinone **208a** (80% yield) along with a small amount of nonannelated quinone **209a** in 3.5% yield (Scheme 37). Similar results were also observed with **205b** and **205c**.

Formation of the annelated quinone **208c** in 63% yield (**209c**, not detected) from **205c** under high dilution (2.5×10^{-3} M) indicates a preference for a rare 6-*exo* cyclization to form **207c** over the 1,5-hydrogen transfer from the propargylic position. A facile 1,5-hydrogen transfer from the adjacent hydroxyl group to **207c** then terminates the cascade

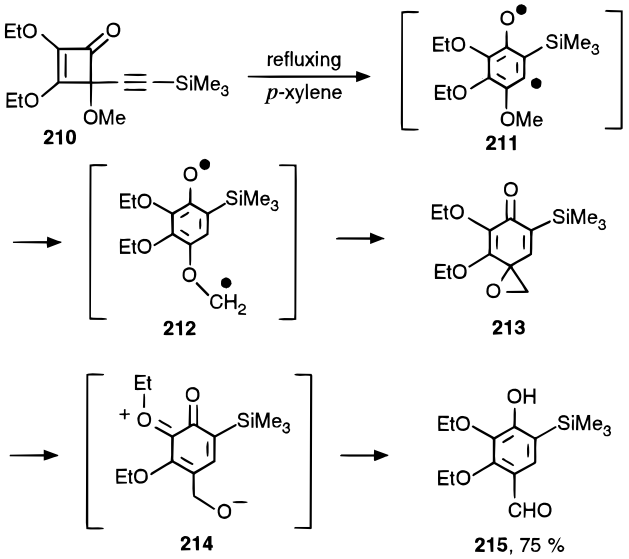
Scheme 37



sequence. This result is in sharp contrast to the behavior of **202b** where a preference for the 1,5-hydrogen shift was observed, leading to the chromanol **204b**. A higher steric hinderance for 6-*exo* cyclization in the case of **202b** may be responsible for directing the reaction toward 1,5-hydrogen transfer. The possible reversibility of the potential 6-*exo* cyclization of **202b** due to a slower subsequent 1,6-hydrogen transfer from the adjacent methoxy group could also ultimately cause the formation of the chromanol **204b**.

Spiro epoxide **213** can also be synthesized from cyclobutenone **210** (Scheme 38).[35a,39d,34] Ring expan-

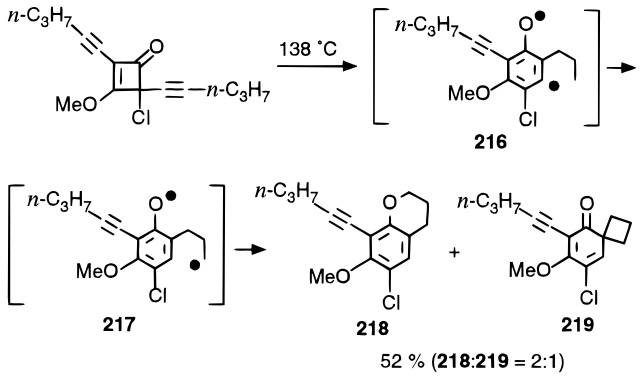
Scheme 38



sion of **210** to biradical **211** followed by a 1,4-hydrogen transfer from the adjacent methoxy group produced **212**, which underwent radical−radical combination to furnish spiro epoxide **213**. Under the reaction condition, **213** was slowly transformed to the highly functionalized aromatic aldehyde **215** in 75% yield. The formation of **215** is rationalized as arising via the zwitterionic intermediate **214**, which then tautomerizes to **215**.[35a]

The presence of a propyl substituent in biradical **216** provides an opportunity for a 1,5-hydrogen transfer, leading to the new biradical **217** (Scheme 39).[43] Intramolecular radical−radical combination then gives the observed products **218** and **219** in a 2:1 ratio. For comparison, it is of interest to note that a similar radical−radical combination to form chromanol **204** also occurs with biradical **203**. Formation of the spiro compound **219** having a four-membered ring resembles the homolytic coupling of **188** to form **190** outlined in Scheme 33.

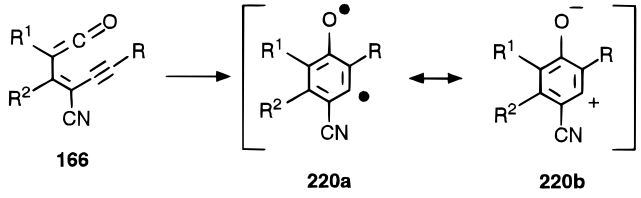
Scheme 39



C. Biradicals versus Zwitterions

The cascade sequences of enyne-ketenes reviewed so far are consistent with a reaction mechanism involving an initial Moore cyclization to a biradical species. The characteristics of the radical reactions have also been observed with enyne-ketenes having a 4-cyano substituent as shown in **166** (Scheme 40).

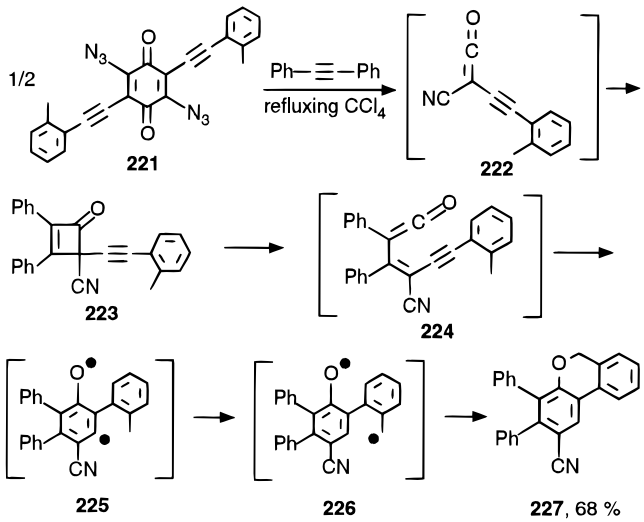
Scheme 40



Interestingly, under certain reaction conditions the chemical behavior of **166** can be best described in terms of a zwitterionic intermediate **220b**. Such dual chemical properties as biradical and zwitterion have been beautifully delineated by Moore and co-workers and provide insight into the electronic state of these fascinating intermediates.[3]

The biradical pathway outlined in Scheme 41 could adequately account for the formation of **227** from thermolysis of **221** in the presence of diphenylacetylene.[38] The reaction involves a [2 + 2] cycloaddition of diphenylacetylene with alkynylcyanoketene **222**, generated in situ from thermolysis of **221**, to give cyclobutenone **223**. Under the reaction condition, electrocyclic ring opening of **223** then leads to enyne-ketene **224**. Cycloaromatization of **224** to biradical **225** followed by a 1,5-hydrogen shift leads to **226**, providing a pathway for subsequent radical−radical combination to give **227**. It is of interest to note that, unlike cyclobutenone **157b** (with a 4-hydroxyl substituent and a radical-stabilizing phenyl group at the terminus of the alkynyl moiety) which prefers the pathway leading to the five-membered ring biradical

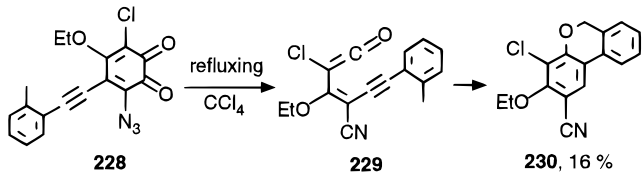
Scheme 41



161, the presence of a 4-cyano group in **224** redirects the electrocyclic ring closure toward the formation of the 6-membered ring biradical **225**.

In an analogous study, enyne-ketene **229** having a 4-cyano substituent was generated by subjecting **228** to thermolysis in refluxing CCl_4 to induce the loss of N_2 and CO (Scheme 42).[39c] A cascade cycliza-

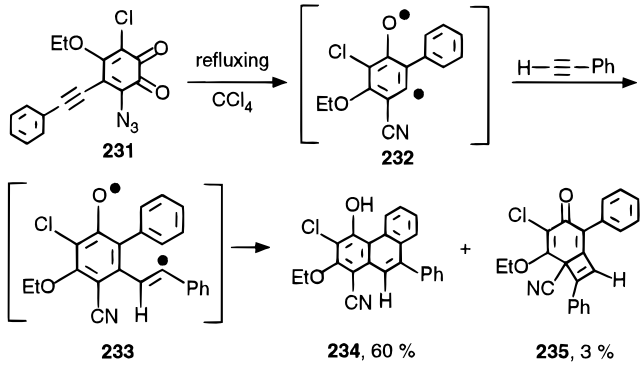
Scheme 42



tion via biradical intermediates likewise could account for the formation of **230**.

Biradical **232** (without a methyl substituent) provides an opportunity for the addition of the aryl radical in **232** to phenylacetylene, giving rise to the new biradical **233** (Scheme 43).[38] Subsequent in-

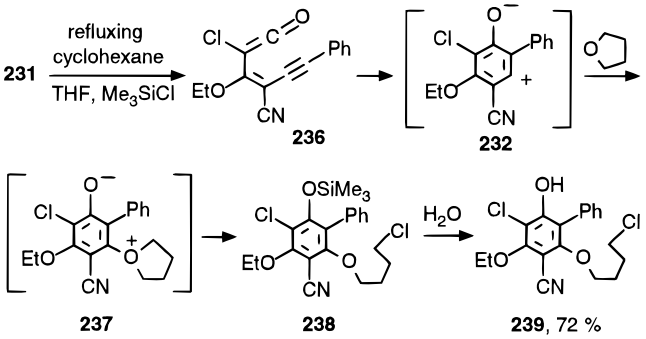
Scheme 43



tramolecular arylation leads to phenanthrene **234** in 60% yield along with 3% of the bicyclo[4.2.0]-octatrienone **235** via a different pathway involving radical−radical combination.

On the other hand when benzoquinone **231** was decomposed in refluxing cyclohexane containing an excess of tetrahydrofuran and Me_3SiCl, the highly functionalized phenol **239** was obtained in 72% isolated yield (Scheme 44).[39c] The formation of **239** can be best accounted for by regarding the initially

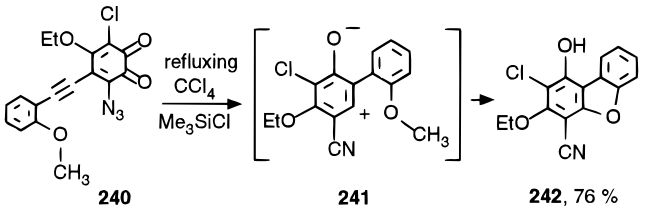
Scheme 44



cycloaromatized intermediate **232** as a zwitterion. Attack on the carbocationic center by THF to form the oxonium ion **237** followed by a sequence of events involving silylation of the phenoxide ion, opening of the oxonium ion by attach of the released chloride ion and final hydrolytic desilylation provide a pathway to **239**.

Additional experimental results supporting the zwitterion pathway have also been observed under other reaction conditions.[39c] Transformation from **240** to **242** outlined in Scheme 45 again serves as an

Scheme 45



excellent example of a reaction pathway involving dipolar intermediates rather than biradical species.[39c]

V. Conclusions

The chemistry of biradicals generated from thermal rearrangements discussed in this review is a rich area for discovery of new and unusual reactions. Clearly, the development of this field is still in its infancy and many discoveries still lie ahead. The use of these biradicals for the synthesis of complex natural products is virtually unexplored.[44] While interesting examples employing Bergman cyclization for the preparation of polyphenylenes, polynaphthalenes, and oligo(acenes) have been reported,[45] applications of the biradical-forming reactions to materials synthesis have yet to be systematically investigated. Moreover, the feasibility of generating persistent radicals by these thermal processes has barely been demonstrated. Designing suitable systems as precursors to tetraradicals, hexaradicals, and potentially high-spin polyradicals[46] remains an area for one to imagine.

VI. Acknowledgments

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VII. References and Notes

(1) (1) (a) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660. (b) Lockhart, T. P.; Comita, P. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4082. (c) Johnson, G. C.; Stofko, J. J., Jr.; Lockhart, T. P.; Brown, D. W.; Bergman, R. G. *J. Org. Chem.* **1979**, *44*, 4215. (d) Lockhart, T. P.; Mallon, C. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1980**, *102*, 5976. (e) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25.

(2) (a) Myers, A. G.; Kuo, E. Y.; Finney, N. S. *J. Am. Chem. Soc.* **1989**, *111*, 8057. (b) Myers, A. G.; Dragovich, P. S. *J. Am. Chem. Soc.* **1989**, *111*, 9130. (c) Nagata, R.; Yamanaka, H.; Okazaki, E.; Saito, I. *Tetrahedron Lett.* **1989**, *30*, 4995. (d) Nagata, R.; Yamanaka, H.; Murahashi, E.; Saito, I. *Tetrahedron Lett.* **1990**, *31*, 2907. (e) Nicolaou, K. C.; Maligres, P.; Shin, J.; de Leon, E.; Rideout, D. *J. Am. Chem. Soc.* **1990**, *112*, 7825.

(3) For an excellent review, see: Moore, H. W.; Yerxa, B. R. *Chemtracts* **1992**, 273.

(4) For excellent reviews, see: (a) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387. (b) Maier, M. E. *Synlett* **1995**, 13.

(5) Abeywickrema, A. N.; Beckwith, A. L. J. *J. Chem. Soc., Chem. Commun.* **1986**, 464.

(6) Curran, D. P.; Kim, D.; Liu, H. T.; Shen, W. *J. Am. Chem. Soc.* **1988**, *110*, 5900.

(7) (a) Curran, D. P. *Synthesis* **1988**, 417, 489. (b) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (c) For a series of papers on selectivity and synthetic applications of radical reactions in a *Tetrahedron Symposium-in-Print* edited by B. Giese, see: *Tetrahedron* **1985**, *41*, 3887. (d) Borden, W. T., Ed. *Diradicals*; Wiley-Interscience: New York, 1982. (e) For a series of papers on biradicals in a *Tetrahedron Symposium-in-Print* edited by J. Michl, see: *Tetrahedron* **1982**, *38*, 737.

(8) (a) Nicolaou, K. C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E. J.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4866. (b) Nicolaou, K. C.; Ogawa, Y.; Zuccarello, G.; Kataoka, H. *J. Am. Chem. Soc.* **1988**, *110*, 7247. (c) Wender, P. A.; McKinney, J. A.; Mukai, C. *J. Am. Chem. Soc.* **1990**, *112*, 5369. (d) Magnus, P.; Carter, P. *J. Am. Chem. Soc.* **1988**, *110*, 1626. (e) Magnus, P.; Lewis, R. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 6921. (f) Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 5367. (g) Wong, H. N. C.; Sondheimer, F. *Tetrahedron Lett.* **1980**, *21*, 217. (h) Boger, D. L.; Zhou, J. *J. Org. Chem.* **1993**, *58*, 3018. (i) Singh, R.; Just, G. *Tetrahedron Lett.* **1990**, *31*, 185. (j) Semmelhack, M. F.; Neu, T.; Foubelo, F. *Tetrahedron Lett.* **1992**, *33*, 3277. (k) Nicolaou, K. C.; Liu, A.; Zeng, Z.; McComb, S. *J. Am. Chem. Soc.* **1992**, *114*, 9279. (l) Grissom, J. W.; Calkins, T. L. *J. Org. Chem.* **1993**, *58*, 5422. (m) Grissom, J. W.; Calkins, T. L.; McMillen, H. A.; Jiang, Y. *J. Org. Chem.* **1994**, *59*, 5833.

(9) Bharucha, K. N.; Marsh, R. M.; Minto, R. E.; Bergman, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 3120.

(10) Grissom, J. W.; Calkins, T. L.; McMillen, H. A. *J. Org. Chem.* **1993**, *58*, 6556.

(11) (a) Grissom, J. W.; Calkins, T. L.; Egan, M. *J. Am. Chem. Soc.* **1993**, *115*, 11744. (b) Grissom, J. W.; Calkins, T. L. *Tetrahedron Lett.* **1992**, *33*, 2315.

(12) Grissom, J. W.; Calkins, T. L.; Huang, D.; McMillen, H. *Tetrahedron* **1994**, *50*, 4635.

(13) Grissom, J. W.; Klingberg, D. *J. Org. Chem.* **1993**, *58*, 6559.

(14) Grissom, J. W.; Klingberg, D.; Meyenburg, S.; Stallman, B. L. *J. Org. Chem.* **1994**, *59*, 7876.

(15) Andemichael, Y. W.; Gu, Y. G.; Wang, K. K. *J. Org. Chem.* **1992**, *57*, 794.

(16) Andemichael, Y. W.; Huang, Y.; Wang, K. K. *J. Org. Chem.* **1993**, *58*, 1651.

(17) Wang, K. K.; Wang, Z. *Tetrahedron Lett.* **1994**, *35*, 1829.

(18) Wang, Z.; Wang, K. K. *J. Org. Chem.* **1994**, *59*, 4738.

(19) Ezcurra, J. E.; Pham, C.; Moore, H. W. *J. Org. Chem.* **1992**, *57*, 4787.

(20) Fujiwara, K.; Kurisaki, A.; Hirama, M. *Tetrahedron Lett.* **1990**, *31*, 4329.

(21) Wenthold, P G.; Squires, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 6401.

(22) (a) Wenthold, P G.; Wierschke, S. G.; Nash, J. J.; Squires, R. R. *J. Am. Chem. Soc.* **1993**, *115*, 12611. (b) Wenthold, P G.; Wierschke, S. G.; Nash, J. J.; Squires, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 7378. (c) Logan, C. F.; Ma, J. C.; Chen, P. *J. Am. Chem. Soc.* **1994**, *116*, 2137.

(23) Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1991**, *113*, 1907.

(24) (a) Wang, Z. Ph.D. Thesis, Department of Chemistry, West Virginia University, March 1995. (b) Wang, K. K.; Wang, Z.; Sattsangi, P. D. *J. Org. Chem.*, in press.

(25) Schreiner, K.; Berndt, A. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 144.

(26) Maier, M. E.; Langenbacher, D. *Synlett* **1994**, 713.

(27) (a) Funk, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1976**, *98*, 6755. (b) Oppolzer, W.; Roberts, D. A.; Bird, T. G. *Helv. Chim. Acta* **1979**, *62*, 2017. (c) Ito, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 863. (d) Nicolaou, K. C.; Barnette, W. E.; Ma, P. *J. Org. Chem.* **1980**, *45*, 1463.

(28) (a) Franz, J. A.; Alnajjar, M. S.; Barrows, R. D.; Kaisaki, D. L.; Camaioni, D. M.; Suleman, N. K. *J. Org. Chem.* **1986**, *51*, 1446. (b) Franz, J. A.; Barrows, R. D.; Camaioni, D. M. *J. Am. Chem. Soc.* **1984**, *106*, 3964.

(29) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925.

(30) (a) Johnson, W. S.; Chen, Y.-Q.; Kellogg, M. S. *J. Am. Chem. Soc.* **1983**, *105*, 6653. (b) van Tamelen, E. E.; Leiden, T. M. *J. Am. Chem. Soc.* **1982**, *104*, 2061. (c) Bartlett, P. A. In *Asymmetric Synthesis*; Morrision, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 341.
(31) (a) Lecker, S. H.; Nguyen, N. H.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1986**, *108*, 856. (b) Zhang, Y.; Wu, G.-z; Agnel, G.; Negishi, E.-i. *J. Am. Chem. Soc.* **1990**, *112*, 8590. (c) Bao, J.; Dragisich, V.; Wenglowsky, S.; Wulff, W. D. *J. Am. Chem. Soc.* **1991**, *113*, 9873.
(32) Grissom, J. W.; Slattery, B. J. *Tetrahedron Lett.* **1994**, *35*, 5137.
(33) Grissom, J. W.; Huang, D. *J. Org. Chem.* **1994**, *59*, 5114.
(34) Sullivan, R. W.; Coghlan, V. M.; Munk, S. A.; Reed, M. W.; Moore, H. W. *J. Org. Chem.* **1994**, *59*, 2276.
(35) (a) Foland, L. D.; Karlsson, J. O.; Perri, S. T.; Schwabe, R.; Xu, S. L.; Patil, S.; Moore, H. W. *J. Am. Chem. Soc.* **1989**, *111*, 975. (b) Reed, M. W.; Pollart, D. J.; Perri, S. T.; Foland, L. D.; Moore, H. W. *J. Org. Chem.* **1988**, *53*, 2477. (c) Liebeskind, L. S.; Fengl, R. W.; Wirtz, K. R.; Shawe, T. T. *J. Org. Chem.* **1988**, *53*, 2482. (d) Liebeskind, L. S.; Foster, B. S. *J. Am. Chem. Soc.* **1990**, *112*, 8612.
(36) Perri, S. T.; Foland, L. D.; Moore, H. W. *Tetrahedron Lett.* **1988**, *29*, 3529.
(37) Xia, H.; Moore, H. W. *J. Org. Chem.* **1992**, *57*, 3765.
(38) Chow, K.; Nguyen, N. V.; Moore, H. W. *J. Org. Chem.* **1990**, *55*, 3876.
(39) (a) Nguyen, N. V.; Chow, K.; Karlsson, J. O.; Doedens, R.; Moore, H. W. *J. Org. Chem.* **1986**, *51*, 419. (b) Dorsey, D. A; King, S. M.; Moore, H. W. *J. Org. Chem.* **1986**, *51*, 2814. (c) Moore, H. W.; Chow, K.; Nguyen, N. V. *J. Org. Chem.* **1987**, *52*, 2530. (d) Chow, K.; Moore, H. W. *J. Org. Chem.* **1990**, *55*, 370.
(40) Nakatani, K.; Isoe, S.; Maekawa, S.; Saito, I. *Tetrahedron Lett.* **1994**, *35*, 605.
(41) Padwa, A.; Austin, D. J.; Chiacchio, U.; Kassir, J. M.; Rescifina, A.; Xu, S. L. *Tetrahedron Lett.* **1991**, *32*, 5923.
(42) Xu, S. L.; Taing, M.; Moore, H. W. *J. Org. Chem.* **1991**, *56*, 6104.
(43) Xu, S. L.; Moore, H. W. *J. Org. Chem.* **1992**, *57*, 326.
(44) (a) Perri, S. T.; Dyke, H. J.; Moore, H. W. *J. Org. Chem.* **1989**, *54*, 2034. (b) Perri, S. T.; Moore, H. W. *J. Am. Chem. Soc.* **1990**, *112*, 1897. (c) Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Am. Chem. Soc.* **1989**, *111*, 989.
(45) (a) John, J. A.; Tour, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 5011. (b) Grubbs, R. H.; Kratz, D. *Chem. Ber.* **1993**, *126*, 149.
(46) Rajca, A. *Chem. Rev.* **1994**, *94*, 871.

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