Synthesis and Thermolysis of Enediynyl Ethyl Ethers as Precursors of Enyne−Ketenes

Anna Tarli and Kung K. Wang*

Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506-6045

Received July 28, 1997[⊗]

Enediynyl ethyl ethers **14**/**17** were synthesized by using the $Pd(PPh_3)_4$-catalyzed cross-coupling reactions between enynyl iodides **13**/**16** and (2-ethoxyethynyl)zinc chloride. Thermolysis of these enediynyl ethyl ethers in refluxing chlorobenzene (132 °C) promoted a retro-ene reaction to produce enyne−ketenes, which underwent the Moore cyclization reactions to form the biradicals having a phenyl radical center and a phenoxy radical center. The presence of two radical centers in the same molecule simultaneously provided many opportunities for intramolecular decay through disproportionation, radical−radical combination, and the formation of *o*-quinone methide.

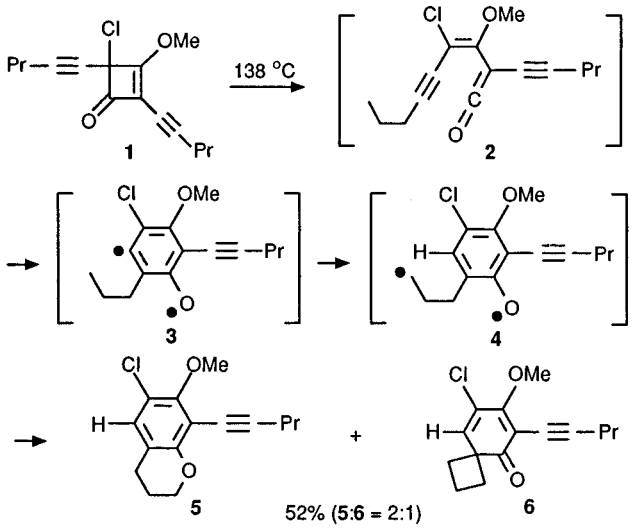
Introduction

The enyne−ketene derivatives have been generated as transient intermediates by the electrocyclic ring opening of 4-alkynylcyclobutenones at temperatures ranging from 80 to 138 °C.[1] Specifically, thermolysis of cyclobutenone **1** in refluxing *p*-xylene at 138 °C produced enyne−ketene **2**, which then underwent a Moore cyclization reaction to form biradical **3** having a reactive phenyl radical center and a phenoxy radical center (Scheme 1).[2] An intramolecular 1,5-hydrogen shift transformed **3** to a new biradical **4**, which in turn underwent an intramolecular radical−radical combination to give the chromanol **5** and the spiro ketone **6** (2:1) in 52% combined yield. Thermolysis of 3-azido-4-alkynyl-1,2-benzoquinones to induce the loss of N_2 and CO also provides an easy access to enyne−ketenes.[3]

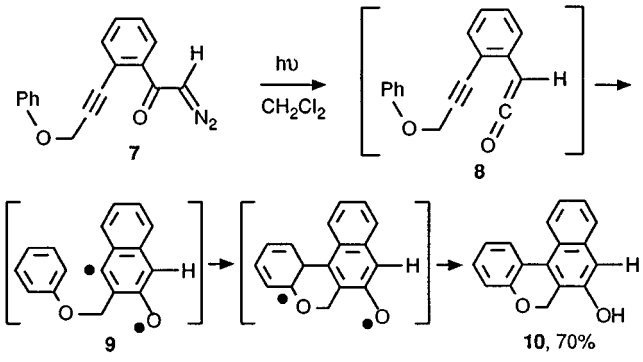
An alternative route to enyne−ketenes involves photolysis of enynyl α-diazo ketones to promote the Wolff rearrangement.[4] For example, irradiation of α-diazoacetophenone **7** in methylene chloride produced the naphthol **10** in 70% yield (Scheme 2).[4a,b] The transformation is believed to proceed through an initial photochemical Wolff rearrangement to form the benzoenyne−ketene **8**, which then cycloaromatizes to biradical **9**. Subsequent attack on the neighboring aromatic ring by the aryl radical followed by disproportionation leads to the naphthol **10**.

The ability to generate two reactive radical centers in the same molecule simultaneously by the Moore cyclization reaction of enyne−ketenes provides many synthetic opportunities. In addition to the intramolecular decaying routes outlined in Schemes 1 and 2, several other cascade sequences were also reported, leading to natural products[5] and unusual chemical structures not easily accessible by other methods.[1] Clearly, the chemistry of biradicals generated from the Moore cyclization of enyne−ketenes is a rich area for discovery of new and unusual reactions. We, therefore, developed a new and versatile pathway to enyne−ketenes to further enhance the availability of these reactive intermediates with diverse structural features for subsequent synthetic elaborations.

Scheme 1



Scheme 2



[⊗] Abstract published in *Advance ACS Abstracts,* November 15, 1997.

(1) (a) Moore, H. W.; Yerxa, B. R. *Chemtracts* **1992**, 273−313. (b) Wang, K. K. *Chem. Rev. (Washington, D.C.)* **1996**, *96*, 207−222. (c) Grissom, J. W.; Gunawardena, G. U.; Klingberg, D.; Huang, D. *Tetrahedron* **1996**, *52*, 6453−6518.

(2) Xu, S. L.; Moore, H. W. *J. Org. Chem.* **1992**, *57*, 326−338.

(3) (a) Chow, K.; Moore, H. W. *J. Org. Chem.* **1990**, *55*, 370−372. (b) Moore, H. W.; Chow, K.; Nguyen, N. V. *J. Org. Chem.* **1987**, *52*, 2530−2537. (c) Nguyen, N. V.; Chow, K.; Karlsson, J. O.; Doedens, R.; Moore, H. W. *J. Org. Chem.* **1986**, *51*, 419−420.

(4) (a) Padwa, A.; Austin, D. J.; Chiacchio, U.; Kassir, J. M.; Rescifina, A.; Xu, S. L. *Tetrahedron Lett.* **1991**, *32*, 5923−5926. (b) Padwa, A.; Chiacchio, U.; Fairfax, D. J.; Kassir, J. M.; Litrico, A.; Semones, M. A.; Xu, S. L. *J. Org. Chem.* **1993**, *58*, 6429−6437. (c) Nakatani, K.; Isoe, S.; Maekawa, S.; Saito, I. *Tetrahedron Lett.* **1994**, *35*, 605−608. (d) Nakatani, K.; Maekawa, S.; Tanabe, K.; Saito, I. *J. Am. Chem. Soc.* **1995**, *117*, 10635−10644.

(5) (a) Xiong, Y.; Moore, H. W. *J. Org. Chem.* **1996**, *61*, 9168−9177. (b) Perri, S. T.; Moore, H. W. *J. Am. Chem. Soc.* **1990**, *112*, 1897−1905. (c) Perri, S. T.; Dyke, H. J.; Moore, H. W. *J. Org. Chem.* **1989**, *54*, 2032−2034. (d) Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Am. Chem. Soc.* **1989**, *111*, 989−995.

S0022-3263(97)01391-1 CCC: $14.00

Scheme 3

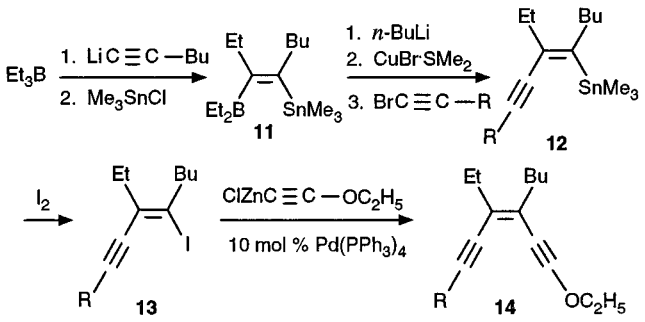


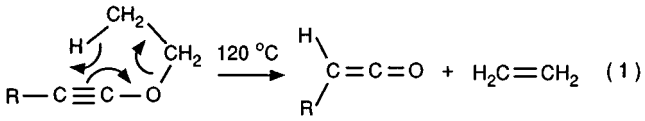
Table 1. Synthesis of Enynyl Iodides 13 and 16 and Enediynyl Ethyl Ethers 14 and 17

R^1	R	13/16	isolated yield, %	14/17	isolated yield,%
	Pr	**13a**	63	**14a**	21
	Bu	**13b**	73	**14b**	33
	CH_3OCH_2	**13c**	78	**14c**	35
	2-methylphenyl	**13d**	52	**14d**	49
	2-methoxyphenyl	**13e**	68	**14e**	30
Me	Me_2NCH_2	**16a**	52[a]	**17a**	58[b]
Pr	Me	**16b**	56	**17b**	23

[a] *Z*:*E* = 1.9:1. [b] *Z*:*E* = 1.8:1.

Results and Discussion

Thermolysis of alkynyl ethyl ethers at 120 °C to induce a retro-ene reaction with the elimination of ethylene had been shown to provide an easy and clean access to monoalkylketenes (eq 1).[6] We envisioned that enediynyl



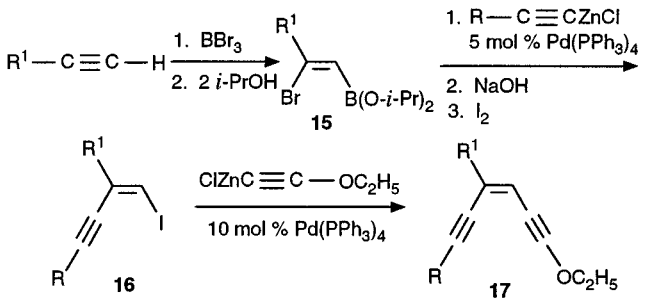
(1)

ethyl ethers could thus serve as precursors of enyne–ketenes. Our synthetic route to enediynyl ethyl ethers **14** is outlined in Scheme 3.

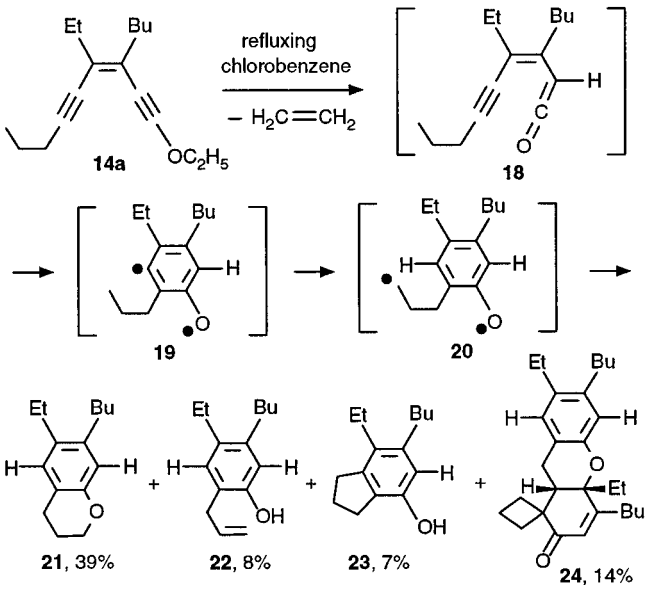
The enynyl iodides **13** were prepared from triethylborane in a single operation as reported previously.[7] Treatment of triethylborane with 1-lithio-1-hexyne followed by trimethyltin chloride produced the trimethyltin-substituted alkenylborane **11**. The transformation is stereoselective with the boron and the tin substituents cis to each other.[8] Sequential treatment of **11** generated in situ with *n*-butyllithium, $CuBr{\cdot}SMe_2$, 1-bromo-1-alkynes, and iodine furnished enynyl iodides **13** (Table 1). The subsequent $Pd(PPh_3)_4$-catalyzed cross coupling between **13** and (2-ethoxyethynyl)zinc chloride, derived from lithiation of the commercially available ethyl ethynyl ether with *n*-butyllithium followed by the addition of anhydrous zinc chloride, gave enediynyl ethyl ethers **14** having the *Z* geometry (Table 1). The corresponding *E* isomers were not detected.

A different pathway to enediynyl ethyl ethers **17** (Table 1) was also developed (Scheme 4). Bromoboration of

Scheme 4



Scheme 5



propyne and 1-pentyne with BBr_3 followed by treatment with 2-propanol as reported previously[9] furnished alkenyl boronic esters **15a** (*Z*:*E* = 4:1) and **15b**, respectively. The subsequent $Pd(PPh_3)_4$-catalyzed cross coupling with 1-alkynylzinc chlorides followed by iodination gave enynyl iodides **16a** (*Z*:*E* = 1.9:1) and **16b**. A second $Pd(PPh_3)_4$-catalyzed cross coupling with (2-ethoxyethynyl)zinc chloride then produced enediynyl ethyl ethers **17a** (*Z*:*E* = 1.8:1) and **17b**.

Enediynyl ethyl ethers **14** and **17** appeared to be very sensitive to silica gel and Florisil. Attempts to purify **14** and **17** by column chromatography using either silica gel or Florisil as the stationary phase resulted in their complete decomposition. Neutral alumina seemed to cause less decomposition and therefore was chosen as the stationary phase for column chromatography. Precautionary measures were taken to try to minimize decomposition of **14** and **17** by quickly passing them through a short neutral alumina column. Nevertheless, substantial amounts of decomposition still occurred which is partially responsible for the low efficiency of converting **13** and **16** to **14** and **17**, respectively.

When **14a** was subjected to heating in refluxing chlorobenzene at 132 °C, the chromanol **21** (39%) along with the phenols **22** (8%) and **23** (7%) as well as the spiro ketone **24** (14%) were isolated (Scheme 5). Apparently, an initial retro-ene reaction of **14a** produced enyneketene **18**, which then underwent a Moore cyclization to afford biradical **19**. An intramolecular 1,5-hydrogen shift then produced a new biradical **20**, which in turn under-

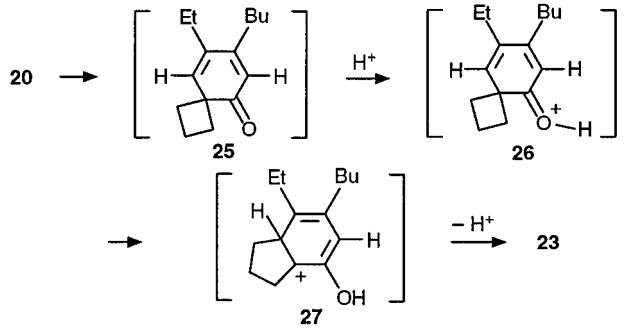
(6) (a) van Daalen, J. J.; Kraak, A.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1961**, *80*, 810–818. (b) Nieuwenhuis, J.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1958**, *77*, 761–768. (c) Liang, L.; Ramaseshan, M.; MaGee, D. I. *Tetrahedron* **1993**, *49*, 2159–2168. (d) Ficini, J. *Bull. Soc. Chim. Fr.* **1954**, 1367–1371.

(7) Wang, Z.; Wang, K. K. *J. Org. Chem.* **1994**, *59*, 4738–4742.

(8) Hooz, J.; Mortimer, R. *Tetrahedron Lett.* **1976**, 805–808. (b) Wrackmeyer, B.; Bihlmayer, C.; Schilling, M. *Chem. Ber.* **1983**, *116*, 3182–3191. (c) Zweifel, G.; Backlund, S. J. *J. Organomet. Chem.* **1978**, *156*, 158–170. (d) Wang, K. K.; Chu, K.-H. *J. Org. Chem.* **1984**, *49*, 5175–5178.

(9) Wang, K. K.; Wang, Z. *Tetrahedron Lett.* **1994**, *35*, 1829–1832.

Scheme 6



went radical−radical combination to give **21**, reminiscent of the formation of the chromanol **5** from **4**. Alternatively, a second intramolecular 1,5-hydrogen shift led to **22** as observed previously in a similar case.[2]

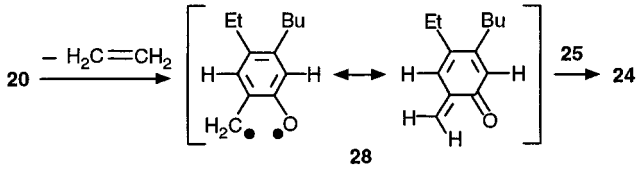
The formation of **23** could be accounted for by the pathway outlined in Scheme 6. Attack of the benzene ring by the primary radical in **20** for the radical−radical combination could give the spiro ketone **25** as observed in the formation of the spiro ketone **6** from **4**. Rearrangement of **25** to **23** is most likely catalyzed by an acid through an initial protonation to form **26**, ring expansion via 1,2-shift to afford **27**, and finally deprotonation to regain aromaticity to produce **23**.[10]

The structure assignment of **24** is consistent with its characteristic spectral data. The molecular ion (m/e = 408.3031, 58% relative intensity) was detected by using an HREI mass spectrometer. Signals at m/e = 218 (59%) and 191 (100%) due to the fragments derived from elimination of *o*-quinone methide **28** from the molecular ion and from the protonated **28**, respectively, were observed. An intense IR absorption at 1664 cm^{-1} indicates the presence of an α,β-unsaturated carbonyl group, which is corroborated with a ^{13}C NMR signal at 201.37 ppm. The ^{1}H NMR spectrum exhibits two singlets (6.75 and 6.65 ppm) in the aromatic region as expected and a triplet at 5.76 ppm with a small coupling constant (J = 1.5 Hz). The triplet signal can be attributed to the vinylic hydrogen attached to the α carbon of the α,β-unsaturated system with a long-range coupling to the allylic methylene hydrogens. In addition, four triplets due to the four methyl groups can be clearly discerned. The ^{13}C NMR spectrum shows 28 discrete signals with one from a carbonyl carbon, eight from the sp^2 carbons, and 19 from the sp^3 carbons. The APT experiment indicates that three of the sp^2 carbons are methine carbons. The signal at 79.76 ppm arises from the quaternary sp^3 carbon attached with an oxygen atom. The signal at 42.37 ppm is due to the sp^3 methine carbon. Furthermore, signals of the four methyl carbons were also observed.

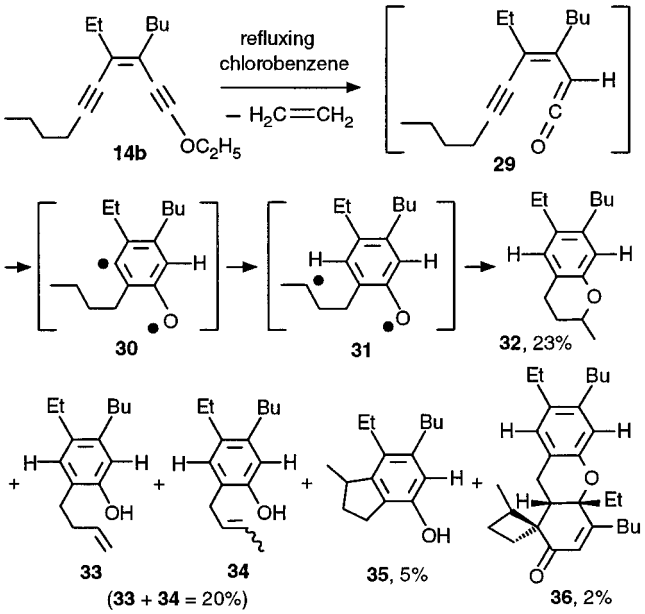
The formation of **24** suggests that a portion of the spiro ketone **25** was captured by the *o*-quinone methide **28** via a Diels−Alder reaction (Scheme 7). The *o*-quinone methide **28** could be produced from biradical **20** via the fragmentation process with the loss of a molecule of ethylene. The regiochemistry of the Diels−Alder reaction is consistent with what was observed previously in the trimerization of *o*-quinone methides.[11]

Similarly, thermolysis of **14b** in refluxing chlorobenzene also furnished the cycloaromatized adducts **32** to

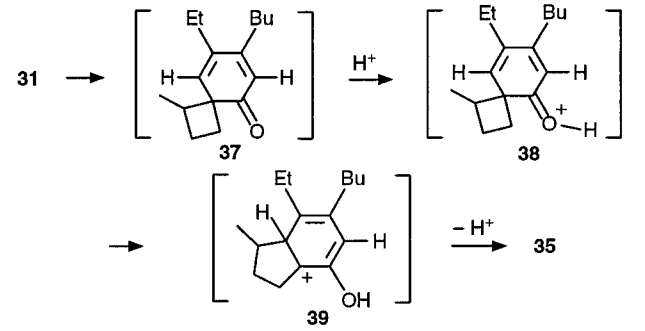
Scheme 7



Scheme 8



Scheme 9

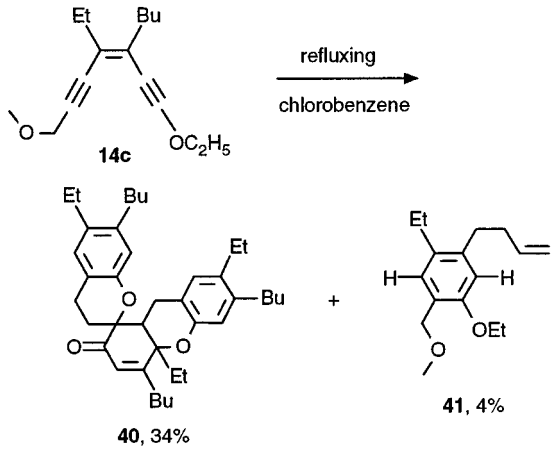


36 (Scheme 8). In comparison with **20**, the presence of an extra methyl group in **31** allows a new disproportionation to occur to afford **33**. In addition, both the *E* and the *Z* isomers of **34** (*E*:*Z* = 5:1) were produced (**33**:**34** = 1:1). The indan **35** is tentatively assigned the structure with the methyl group on the five-membered ring attached to the C-1 carbon instead of to the C-3 carbon. The structure assignment is based on the assumption that the methine carbon of the four-membered ring in **38** with more alkyl substituents would have a higher migratory aptitude toward the cationic center than that of the methylene carbon (Scheme 9).[10] The Diels−Alder reaction between **37** and *o*-quinone methide **28**, derived from **31** by elimination of a molecule of propylene, could produce the condensation adduct **36**. The stereochemistry of **36** is assigned based on the assumption that cycloaddition occurred from the less hindered side of **37** away from the methyl group on the four-membered ring.

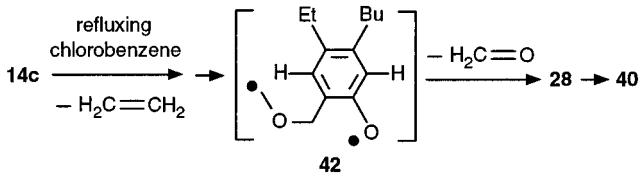
(10) (a) Baird, R.; Winstein, S. *J. Am. Chem. Soc.* **1962**, *84*, 788−792. (b) Wilds, A. L.; Djerassi, C. *J. Am. Chem. Soc.* **1946**, *68*, 1715−1719.

(11) (a) Merijan, A.; Shoulders, B. A.; Gardner, P. D. *J. Org. Chem.* **1963**, *28*, 2148−2149. (b) Westra, J. G.; Huysmans, W. G. B.; Mijs, W. J.; Gaur, H. A.; Vriend, J.; Smidt, J. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 1121−1133.

Scheme 10



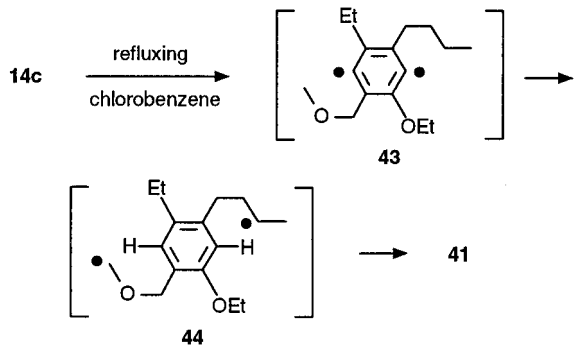
Scheme 11



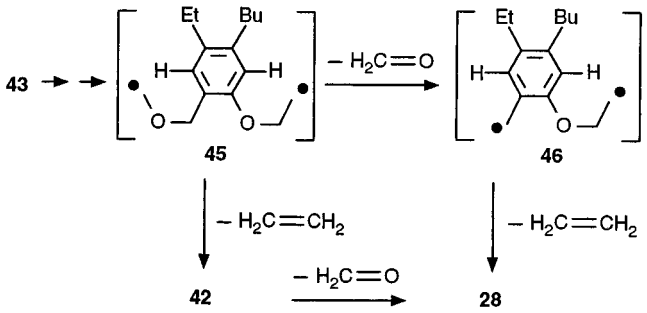
On heating in refluxing chlorobenzene, **14c** produced **40**, the trimer of *o*-quinone methide **28**, in 34% yield along with a small amount (4%) of **41** (Scheme 10). Interestingly, the anticipated 7-butyl-6-ethyl-4*H*-1,3-benzodioxin, which could be produced as in the cases of **21** and **32**, was not obtained. Apparently, the fragmentation process of biradical **42** to form **28** leading to the trimer **40** is more facile than those of **20** and **31**, presumably because the resulting carbon−oxygen double bond of formaldehyde is a stronger bond than the carbon−carbon double bond of ethylene and propylene (Scheme 11). A similar process with the elimination of a molecule of δ-lactone to form an *o*-quinone methide and subsequently the corresponding trimer was reported by Moore and co-workers.[12]

The formation of **41** is interesting and suggests that at least a small portion of **14c** proceeds through an initial Bergman cyclization reaction[13] to form the 1,4-didehydrobenzene biradical **43** (Scheme 12). Two intramolecular 1,5-hydrogen shifts of **43** could lead to **44**, which in turn could disproportionate to form **41** intramolecularly. The formation of **41** having a terminal carbon−carbon double bond indicates that only the hydrogen atoms on the methyl group attached to the secondary radical center could be reached by the other radical center for the intramolecular disproportionation. The absence of the adducts having an internal carbon−carbon double bond with either the *E* or the *Z* geometry by abstraction of a hydrogen atom from the methylene group adjacent to the secondary radical center in **44** also precludes the possibility of an intermolecular disproportionation.

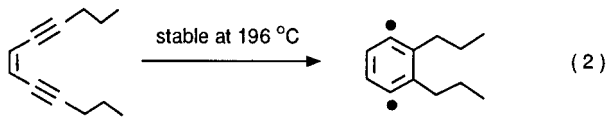
Scheme 12



Scheme 13



It is worth noting that the Bergman cyclizations of enediynes having alkyl substituents at both ends of the enediyne system require high reaction temperatures.[13b,d,f] For example, (*Z*)-6-dodecene-4,8-diyne was reported to exhibit little propensity for cyclization at 196 °C (eq 2).[13b,d]



(2)

It was therefore assumed at the outset that the Bergman cyclizations of the enediynyl ethyl ethers **14** and **17** would not be able to compete with the retro-ene reactions. The formation of **41** from an initial Bergman cyclization of **14c** suggests that the presence of an ethoxy group at one of the two acetylenic termini does not dramatically reduce the rate of cycloaromatization, and the Bergman cyclizations of **14** and **17** could occur with appreciable rates at 132 °C.

The possibility of an initial Bergman cyclization reaction in competition with the retro-ene reaction could also provide alternative pathways to biradicals **19**, **30**, and **42** and subsequent biradical species. For example, in the case of **14c**, two intramolecular 1,5-hydrogen shifts of biradical **43**, derived from an initial Bergman cyclization, could lead to a new biradical **45** (Scheme 13). Subsequent elimination of a molecule of ethylene from **45** could also lead to **42** having a more stable phenoxy radical center and consequently *o*-quinone methide **28**. Conversely, biradical **45** could first eliminate a molecule of formaldehyde to form **46** followed by a second elimination of ethylene to form **28**.

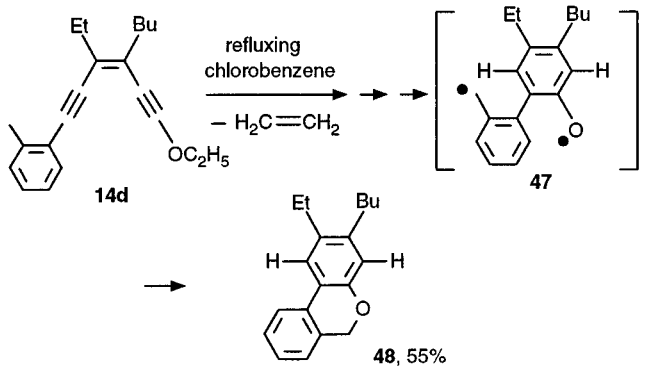
Thermolysis of **14d** produced **48** in 55% yield via a radical−radical combination of biradical **47** (Scheme 14). A similar cascade sequence was reported previously by Moore and co-workers.[14]

(12) (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*, 975−989. (b) Xiong, Y.; Xia, H.; Moore, H. W. *J. Org. Chem.* **1995**, *60*, 6460−6467.

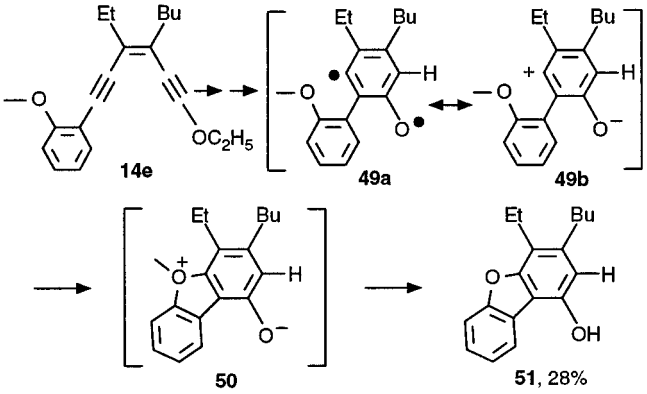
(13) (a) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660−661. (b) Lockhart, T. P.; Comita, P. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4082−4090. (c) Johnson, G. C.; Stofko, J. J., Jr.; Lockhart, T. P.; Brown, D. W.; Bergman, R. G. *J. Org. Chem.* **1979**, *44*, 4215−4218. (d) Lockhart, T. P.; Mallon, C. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1980**, *102*, 5976−5978. (e) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25−31. (f) Grissom, J. W.; Calkins, T. L.; McMillen, H. A. *J. Org. Chem.* **1993**, *58*, 6556−6558.

(14) Chow, K.; Nguyen, N. V.; Moore, H. W. *J. Org. Chem.* **1990**, *55*, 3876−3880.

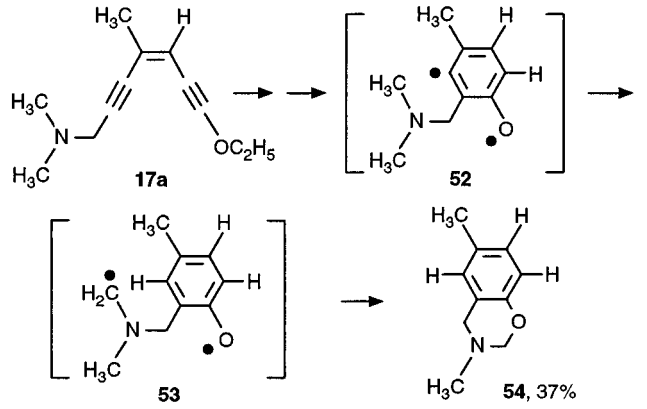
Scheme 14



Scheme 15



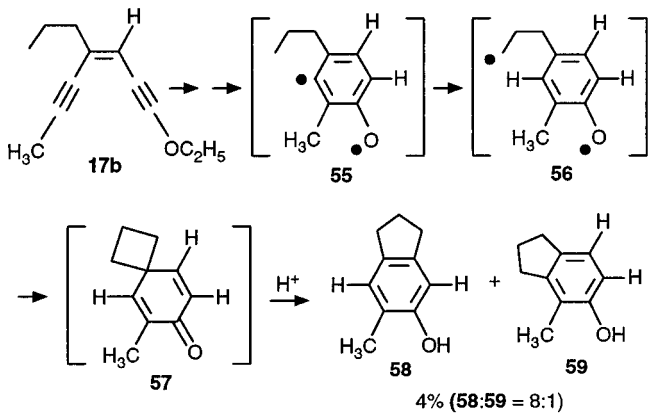
Scheme 16



Replacing the methyl group on the benzene ring of **14d** with a methoxy group dramatically changed the course of the reaction. The formation of **51** can be best accounted for by regarding the initially cycloaromatized intermediate **49** as the zwitterion **49b** instead of as the biradical **49a** (Scheme 15). Attack of the carbocationic center by the oxygen atom of the methoxy group would give the oxonium ion **50**, which then was converted to **51**. The dual chemical properties of the cycloaromatized intermediates derived from enyne−ketenes as biradicals and as zwitterions was first delineated by Moore and coworkers and provided insight into the electronic nature of these fascinating species.[12]

Enediynyl ethyl ether **17a** was converted to **54** in 37% yield (based on the *Z*-isomer) on heating in refluxing chlorobenzene (Scheme 16). Compared to **42**, the fragmentation process of biradical **53** appears to be slower, allowing the radical−radial combination to occur and thus producing **54**.

Scheme 17



Enediynyl ethyl ether **17b** differs from all of the previous cases in that the 1,5-hydrogen shift of the initially formed biradical **55** produces **56** having the new primary radical center located on the tether *para* to the phenoxy radical center (Scheme 17). The subsequent attack on the *ipso* carbon of the benzene ring by the primary radical would lead to the homolytic coupling adduct 6-methylspiro[3.5]nona-5,8-dien-7-one (**57**). The acid-catalyzed rearrangements of **57** could account for the formation of a mixture of **58** and **59** (8:1) in 4% yield.

It is worth noting that the spiro derivatives analogous to **57**, such as spiro[2.5]octa-4,7-dien-6-one,[15] spiro[4.5]-deca-6,9-dien-8-one,[15] and spiro[5.5]undeca-1,4-dien-3-one,[16] have been synthesized previously by intramolecular alkylation of the phenoxide ions through the participation of the benzene ring. However, spiro[3.5]-nona-5,8-dien-7-one is conspicuously missing, presumably because of difficulty in promoting intramolecular alkylation to form four-membered ring.[17] The formation of a carbon−carbon σ bond by the intramolecular homolytic coupling of biradical **56** provides the driving force that overcomes the formation of a strained four-membered ring and the disruption of aromaticity.

Conclusions

Thermolysis of enediynyl ethyl ethers provides a new pathway to enyne−ketenes for the Moore cyclization reactions to form the biradical species. A variety of intramolecular decay routes are available to these reactive intermediates, including the formation of chromanols, *o*-quinone methides, and spiro[3.5]nonadienones. Under certain reaction conditions, the chemical behavior of the resulting biradical can be best described in terms of the corresponding zwitterion. While we elected to use the commercially available ethyl ethynyl ether for coupling with enynyl iodides, several other alkyl alkynyl ethers, such as *tert*-butyl alkynyl ethers and isopropyl alkynyl ethers, had been shown to undergo the retro-ene reactions under milder thermal conditions.[6,18] For example, transformation of *tert*-butyl ethynyl ether to the parent ketene is essentially complete within 86 h at 30 °C.[18a] Such a mild thermal condition could make *tert*-

(15) (a) Winstein, S.; Baird, R. *J. Am. Chem. Soc.* **1957**, *79*, 756−757. (b) Baird, R.; Winstein, S. *J. Am. Chem. Soc.* **1963**, *85*, 567−578.
(16) Dreiding, A. S. *Helv. Chim. Acta* **1957**, *40*, 1812−1814.
(17) Knipe, A. C.; Stirling, C. J. M. *J. Chem. Soc. B* **1968**, 67−71.
(18) (a) Pericàs, M. A.; Serratosa, F.; Valentí, E. *Synthesis* **1985**, 1118−1120. (b) Moyano, A.; Pericàs, M. A.; Serratosa, F.; Valentí, E. *J. Org. Chem.* **1987**, *52*, 5532−5538. (c) Pericàs, M. A.; Serratosa, F.; Valentí, E. *Tetrahedron* **1987**, *43*, 2311−2316.

butyl enediynyl ethers[19] suitable for serving as precursors to produce biradicals for DNA cleavage.[4c−d,20]

Experimental Section

All reactions were conducted in over-dried (120 °C) glassware under a nitrogen atmosphere. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from benzophenone ketyl prior to use. Methyl 2-propynyl ether, 3-(dimethylamino)-1-propyne, 2-iodotoluene, 2-iodoanisole, 2.5 M solution of *n*-butyllithium in hexanes, 1.0 M solution of triethylborane in THF, 1.0 M solution of trimethyltin chloride in THF, CuBr·SMe_2, $Pd(PPh_3)_4$, BBr_3, and anhydrous chlorobenzene were purchased from Aldrich Chemical Co., and were used as received. Propyne, 1-pentyne, 1-hexyne, and ethyl ethynyl ether (50 wt % in hexanes) were purchased from Farchan Laboratory Inc., and were used without further purification. (2-Methylphenyl)acetylene was prepared by the $Pd(PPh_3)_4$-catalyzed cross coupling of 2-iodotoluene with (trimethylsilyl)-acetylene followed by desilylation with K_2CO_3 in a 2:1 mixture of methanol and Et_2O. (2-Methoxyphenyl)acetylene was likewise synthesized from 2-iodoanisole. 1-Bromo-1-pentyne, 1-bromo-1-hexyne, and 1-bromo-3-methoxy-1-propyne were prepared by treatment of the corresponding 1-alkynes with *n*-butyllithium followed by bromine.[21] 1-Bromo-2-(2-methylphenyl)acetylene and 1-bromo-2-(2-methoxyphenyl)acetylene were synthesized by bromination of (2-methylphenyl)acetylene and (2-methoxyphenyl)acetylene with potassium hypobromite.[21] Enynyl iodide **13b** was prepared as reported previously.[7] Silica gel (70−230 mesh) and neutral alumina (Brockman activity 1, 80−200 mesh) for column chromatography were purchased from Aldrich and Fisher, respectively. ^1H (270 MHZ) and ^{13}C (67.9 MHZ) NMR spectra were recorded in $CDCl_3$ using $CHCl_3$ (^1H δ 7.26) and $CDCl_3$ (^{13}C δ 77.00) as internal standard.

(*Z*)-6-Ethyl-7-iodo-6-undecen-4-yne (13a). The following procedure for the preparation of **13a** is representative. To 0.99 mL of 1-hexyne (0.706 g, 8.60 mmol) in 9 mL of THF at 0 °C was added 3.4 mL of a 2.5 M solution of *n*-butyllithium (8.6 mmol) in hexanes. After 15 min, triethylborane (8.6 mL, 1.0 M in THF, 8.6 mmol) was slowly introduced, and the reaction mixture was then allowed to warm to rt. After additional 1 h, 8.6 mL of a 1.0 M solution of trimethyltin chloride (8.6 mmol) in THF was added. The reaction mixture was stirred at rt for 1 h before it was cooled to −78 °C followed by treatment with 3.4 mL of a 2.5 M solution of *n*-butyllithium (8.6 mmol) in hexanes. After 15 min, the reaction mixture was transferred via cannula to a second flask containing 1.77 g of CuBr·SMe_2 (8.60 mmol) in 17 mL of THF maintained at −78 °C. After 1 h at −78 °C, 1-bromo-1-pentyne (1.76 g, 12.0 mmol) in 3 mL of Et_2O was introduced dropwise, and the reaction mixture was stirred at −78 °C for 1 h before it was allowed to warm slowly to rt. The reaction mixture was treated with 8.6 mL of a 6 N NaOH solution and 8.6 mL of a 30% H_2O_2 solution. After 1 h at rt, the organic layer was separated, washed with water, dried over $MgSO_4$, and concentrated to give the corresponding crude enynylstannane derivative **12a**. A solution of I_2 (2.18 g, 8.60 mmol) in 17 mL of Et_2O was added to the crude enynylstannane derivative in 35 mL of Et_2O. The resulting mixture was stirred at rt for 1 h followed by the addition of a saturated $Na_2S_2O_3$ solution to destroy excess I_2. An additional 70 mL of water and 90 mL of Et_2O were added, and the organic layer was then separated, washed with a saturated NaCl solution, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel/hexanes) to furnish 1.65 g of **13a** (63%) as a yellow liquid: IR (neat) 2215, 1462 cm^{-1}; ^1H δ 2.56 (2 H, t, J = 7.4 Hz), 2.34 (2 H, t, J = 6.9 Hz), 2.26 (2 H, q, J = 7.5 Hz), 1.67−1.43 (4 H, m), 1.31 (2 H, sextet, J = 7.5 Hz), 1.10 (3 H, t, J = 7.5 Hz), 1.04 (3 H, t, J = 7.3 Hz), 0.91 (3 H, t, J = 7.2 Hz); ^{13}C δ 132.65, 110.89, 93.42, 85.34, 40.27, 31.79, 26.66, 22.06, 21.69, 21.53, 13.96, 13.66, 13.55; MS *m/e* 304 (M^+), 177, 135; HRMS calcd for $C_{13}H_{21}I$ 304.0688, found 304.0687.

(*Z*)-3-Butyl-1-ethoxy-4-ethyl-3-nonene-1,5-diyne (14a). The following procedure for the preparation of **14a** is representative. A solution of 0.304 g of **13a** (1.00 mmol) and 0.120 g of $Pd(PPh_3)_4$ (0.104 mmol) in 2.5 mL of THF was degassed by three cycles of freeze−thaw and stirred at rt for 30 min. In a second flask, 0.420 g of a solution of ethyl ethynyl ether (50 wt %, 3.00 mmol) in hexanes was dissolved in 6.0 mL of THF and then treated with 1.2 mL of a 2.5 M solution of *n*-butyllithium (3.0 mmol) in hexanes at 0 °C followed by the addition of a degassed solution of anhydrous zinc chloride (0.50 g, 3.6 mmol) in 7.2 mL of THF. After 5 min, the reaction mixture containing **13a** was transferred via cannula to the second reaction flask followed by the addition of 1 mL of HMPA. The resulting solution was stirred at rt for 12 h followed by the addition of 0.1 mL of a 30% H_2O_2 solution to oxidize triphenylphosphine to triphenylphosphine oxide for the purpose of facilitating the purification of **14a**. The resulting solution was stirred for 15 min followed by the addition of 20 mL of water and 40 mL of hexanes. The organic layer was separated, dried over $MgSO_4$, and concentrated. The residue was quickly passed through a short column containing 20 g of neutral alumina (2.0 cm in diameter and 7.5 cm in length/hexanes) at 0 °C by applying a slight pressure on the top of the column to afford 0.052 g of **14a** (21%) as a yellow oil: IR (neat) 2245, 1115, 1009 cm^{-1}; ^1H δ 4.15 (2 H, q, J = 7.1 Hz), 2.36 (2 H, t, J = 6.9 Hz), 2.18 (2 H, q, J = 7.5 Hz), 2.15 (2 H, t, J = 7.5 Hz), 1.58 (2 H, sextet, J = 7.2 Hz), 1.47 (2 H, quintet, J = 7 Hz), 1.42 (3 H, t, J = 7.1 Hz), 1.31 (2 H, sextet, J = 7.4 Hz), 1.06 (3 H, t, J = 7.5 Hz), 1.02 (3 H, t, J = 7.4 Hz), 0.89 (3 H, t, J = 7.2 Hz); ^{13}C δ 127.32, 126.73, 102.32, 92.92, 82.09, 74.73, 41.86, 32.24, 30.90, 25.32, 22.42 (2 carbons), 21.72, 14.34, 13.99, 13.56, 13.38; MS *m/e* 246 (M^+), 218, 217, 203, 189, 175, 161; HRMS calcd for $C_{17}H_{26}O$ 246.1984, found 246.1973. The yield of this coupling reaction was slightly improved to 25% by using 5% of bis(dibenzylideneacetone)-palladium with 10% of bis(1,3-diphenylphosphino)propane to catalyze cross coupling between **13a** and 2 equiv of 2-ethoxyethynylzinc chloride. In this case, it was not necessary to use H_2O_2 to facilitate purification.

(*Z*)-(2-Bromo-1-propenyl)diisopropoxyborane (15a). To a solution of 25.1 g of BBr_3 (9.5 mL, 100 mmol) in 50 mL of dry pentane under a nitrogen atmosphere at −78 °C was added 2.8 L of gaseous propyne. After 1 h at −78 °C, the reaction mixture was allowed to warm to rt. After an additional 2 h, the reaction mixture was transferred via cannula into a second flask containing a mixture of 50 mL of 2-propanol and 50 mL of pentane at −10 °C. After 30 min at −10 °C, the top layer was separated, and the bottom layer was extracted with cold pentane (3 × 20 mL). The top layer and the pentane extracts were combined and concentrated. The residue was then distilled at reduced pressure (40−43 °C, 0.10 Torr) to afford 20.1 g of **15a** (81%, *Z*:*E* = 4:1) as a colorless liquid: IR (neat) 1381, 1324, 1117 cm^{-1}; ^1H δ 5.93, (1 H, q, J = 1.2 Hz), 4.40 (2 H, septet, J = 6.1 Hz), 2.34 (3 H, d, J = 1 Hz), 1.16 (12 H, d, J = 6.1 Hz); ^{13}C δ 132.95, 125 (br), 66.47, 31.91, 24.46; MS *m/e* 235/233 (M^+ − 15), 169, 149, 147. A minor set of signals due to the presence of the *E*-isomer were also observed: ^1H δ 5.89 (1 H, q, J = 1 Hz), 4.29 (2 H, septet, J = 6.1 Hz), 2.51 (3 H, d, J = 1 Hz), 1.14 (6 H, d, J = 6 Hz).

(*Z*)- and (*E*)-5-(Dimethylamino)-1-iodo-2-methyl-1-penten-3-yne (16a). A solution of 2.49 g of **15a** (10.0 mmol), 0.600 g of $Pd(PPh_3)_4$ (0.519 mmol), and 30 mL of THF was degassed by three cycles of freeze−thaw and kept under a nitrogen atmosphere at rt for 45 min. In a second flask, 3-(dimethylamino)-1-propynylzinc chloride was prepared by treatment of a degassed solution of 1.00 g of 3-(dimethylamino)-1-propyne (1.3 mL, 12.0 mmol) in 10 mL of THF with 4.4 mL of a 2.5 M solution of *n*-butyllithium (11.0 mmol) in hexanes for 5 min followed by the addition of a degassed solution of 1.6 g of anhydrous $ZnCl_2$ (12 mmol) in 14 mL of THF. The solution of 3-(dimethylamino)-1-propynylzinc chloride was then trans-

(19) For an example of *tert*-butyl enediynyl ether, see: Hu, J. M.S. Thesis supervised by Dr. Plato A. Magriotis, Department of Chemistry, West Virginia University, August 1993.

(20) Sullivan, R. W.; Coghlan, V. M.; Munk, S. A.; Reed, M. W.; Moore, H. W. *J. Org. Chem.* **1994**, *59*, 2276−2278.

(21) Brandsma, L. *Preparative Acetylenic Chemistry* 2nd ed.; Elsevier: Amsterdam, 1988; pp 149−151.

ferred via cannula to the flask containing **15a** at rt. After 5 min, the reaction mixture was heated to reflux for 2 h before it was allowed to cool to 0 °C followed by sequential treatment with 14 mL of a 6 N NaOH solution and 7.60 g of iodine (30.0 mmol) in 40 mL of Et_2O. After 1 h of stirring at rt, a saturated $Na_2S_2O_3$ solution was introduced to reduce excess iodine. An additional 60 mL of Et_2O was added and the organic layer was then separated. The aqueous layer was extracted with Et_2O (3 × 40 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (neutral alumina/50% diethyl ether in hexanes) to furnish 1.28 g of **16a** (52%, *Z*:*E* = 1.9:1) as an orange oil: IR (neat) 2207, 1029 cm^{-1}; ^1H δ (*Z*-isomer) 6.35 (1 H, q, *J* = 1.4 Hz), 3.45 (2 H, s), 2.37 (6 H, s), 1.99 (3 H, d, *J* = 1.6 Hz); (*E*-isomer) 6.62 (1 H, q, *J* = 1.2 Hz), 3.33 (2 H, s), 2.29 (6 H, s), 1.97 (3 H, d, *J* = 1.2 Hz); ^{13}C δ (*Z*-isomer) 131.88, 90.64, 87.76, 82.95, 48.48, 44.10, 24.95; (*E*-isomer) 129.26, 86.76, 85.21, 84.62, 48.39, 44.15, 24.86; MS *m*/*e* 249 (M^+), 122, 107.

Thermolysis of Enediynyl Ethyl Ether 14a. The following procedure is representative for the thermolysis of enediynyl ethyl ethers. Enediynyl ethyl ether **14a** (0.056 g, 0.227 mmol) was dissolved in 114 mL of anhydrous chlorobenzene, and the resulting solution was degassed by three cycles of freeze−thaw and then heated to reflux. After 3 h, the solution was cooled to rt, and chlorobenzene was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel/8%-50% of diethyl ether in hexanes) to afford 0.0194 g of the chromanol **21** (39%), 0.0041 g of the phenol **22** (8%), 0.0034 g of the bicyclic phenol **23** (7%), and 0.0063 g of the Diels−Alder adduct **24** (14%).

7-Butyl-3,4-dihydro-6-ethyl-2*H*-1-benzopyran (21): yellow oil; IR (neat) 1625, 1574, 1498, 1102 cm^{-1}; ^1H δ 6.82 (1 H, s), 6.60 (1 H, s), 4.15 (2 H, t, *J* = 5.1 Hz), 2.74 (2 H, t, *J* = 6.4 Hz), 2.55 (2 H, q, *J* = 7.5 Hz), 2.52 (2 H, t, *J* = 7.8 Hz), 1.98 (2 H, m), 1.63−1.48 (2 H, m), 1.39 (2 H, sextet, *J* = 7.2 Hz), 1.18 (3 H, t, *J* = 7.5 Hz), 0.93 (3 H, t, *J* = 7.2 Hz); ^{13}C δ 152.67, 139.62, 133.61, 129.39, 119.39, 116.77, 66.36, 33.27, 32.00, 24.68, 24.51, 22.76, 22.66, 15.62, 14.01; MS *m*/*e* 218 (M^+), 203, 176, 175, 161; HRMS calcd for $C_{15}H_{22}O$ 218.1671, found 218.1676.

5-Butyl-4-ethyl-2-(2-propenyl)phenol (22): ^1H δ 6.87 (1 H, s), 6.62 (1 H, s), 6.02 (1 H, ddt, *J* = 17.0, 10.1, and 6.4 Hz), 5.17 (1 H, dq, *J* = 17 and 1.7 Hz), 5.14 (1 H, dq, *J* = 10 and 1.6 Hz), 4.77 (1 H, br OH), 3.37 (2 H, dt, *J* = 6.4 and 1 Hz), 2.55 (2 H, q, *J* = 7.5 Hz), 2.53 (2 H, t, *J* = 7.8 Hz), 1.6−1.48 (2 H, m), 1.39 (2 H, sextet, *J* = 7.2 Hz), 1.17 (3 H, t, *J* = 7.6 Hz), 0.93 (3 H, t, *J* = 7.1 Hz); ^{13}C δ 152.00, 140.25, 136.91, 134.33, 130.32, 122.40, 116.42, 116.28, 35.13, 33.35, 32.07, 24.82, 22.87, 15.76, 14.10; MS *m*/*e* 218 (M^+), 203, 189, 175, 161, 147.

6-Butyl-2,3-dihydro-7-ethyl-1*H*-inden-4-ol (23): ^1H δ 6.48 (1 H, s), 2.89 (2 H, t, *J* = 7.5 Hz), 2.83 (2 H, t, *J* = 7.5 Hz), 2.55 (2 H, q, *J* = 7.7 Hz), 2.54 (2 H, t, *J* = 7.7 Hz), 2.10 (2 H, quintet, *J* = 7.5 Hz), 1.6−1.5 (2 H, m), 1.45−1.3 (2 H, m), 1.09 (3 H, t, *J* = 7.5 Hz), 0.94 (3 H, t, *J* = 7.1 Hz); ^{13}C δ 149.53, 145.10, 140.26, 130.32, 126.51, 113.79, 34.05, 32.05, 31.84, 28.76, 24.90, 22.86, 22.59, 14.81, 14.04; MS *m*/*e* 218 (M^+), 203, 189, 175, 161, 147.

The Diels−Alder Adduct 24: IR (neat) 1664, 800 cm^{-1}; ^1H δ 6.75 (1 H, s), 6.65 (1 H, s), 5.76 (1 H, t, *J* = 1.5 Hz), 2.9−1.8 (17 H, m), 1.66−1.2 (8 H, m), 1.15 (3 H, t, *J* = 7.5 Hz), 1.10 (3 H, t, *J* = 7.3 Hz), 0.93 (3 H, t, *J* = 7.3 Hz), 0.81 (3 H, t, *J* = 7 Hz); ^{13}C δ 201.37, 169.57, 151.54, 139.95, 133.85, 128.42 (CH), 124.35 (CH), 118.13, 116.41 (CH), 79.76, 51.75, 42.37 (CH), 33.51, 33.20, 32.75, 32.05, 29.88, 29.21, 28.92, 24.61, 24.34, 22.74, 22.41, 16.06, 15.45 (CH_3), 14.02 (CH_3), 13.82 (CH_3), 7.85 (CH_3); MS *m*/*e* 408 (M^+), 380, 218, 217, 203, 191, 190, 189, 175, 161; HRMS calcd for $C_{28}H_{40}O_2$ 408.3028, found 408.3031.

Thermolysis of Enediynyl Ethyl Ether 14c. The same procedure was repeated as described for the thermolysis of **14a** except that 0.133 g of **14c** (0.535 mmol) was used to afford 0.034 g of the trimer **40** (34%) and 0.005 g of **41** (4%).

The Trimer 40: viscous yellow oil; IR (neat) 1680, 1098 cm^{-1}; ^1H δ 6.81 (1 H, s), 6.79 (1 H, s), 6.74 (1 H, s), 6.63 (1 H, s), 5.91 (1 H, t, *J* = 1 Hz), 3.03−2.87 (2 H, m), 2.82−2.68 (3 H, m), 2.6−2.48 (10 H, m), 2.45−2.35 (1 H, m), 2.35−2.27 (1 H, m), 2.25−2.14 (1 H, m), 1.91 (1 H, dq, *J* = 14.6 and 7.0 Hz), 1.62−1.46 (6 H, m), 1.45−1.28 (6 H, m), 1.18 (3 H, t, *J* = 7.5 Hz), 1.15 (3 H, t, *J* = 7.5 Hz), 1.11 (3 H, t, *J* = 7.3 Hz), 0.95 (3 H, t, *J* = 7.3 Hz), 0.93 (3 H, t, *J* = 7.1 Hz), 0.85 (3 H, t, *J* = 7.1 Hz); ^{13}C δ 196.19, 169.25, 151.11, 151.04, 139.96, 139.85, 134.07, 133.94, 128.34 (CH), 128.31 (CH), 123.85 (CH), 118.81, 118.09, 117.07 (CH), 115.99 (CH), 80.83, 80.25, 40.64 (CH), 33.54, 33.24, 33.16, 32.07, 32.05, 29.99, 29.50, 28.89, 24.67 (2 carbons), 24.65, 22.74, 22.72, 22.43, 21.43, 15.48 (2 methyls), 14.04 (CH_3), 13.99 (CH_3), 13.81 (CH_3), 8.05 (CH_3); MS *m*/*e* 570 (M^+), 541, 483, 468, 423, 392, 380; HRMS calcd for $C_{39}H_{54}O_3$ 570.4073, found 570.4081.

1-(3-Butenyl)-5-ethoxy-2-ethyl-4-(methoxymethyl)benzene (41): ^1H δ 7.13 (1 H, s), 6.66 (1 H, s), 5.89 (1 H, ddt, *J* = 17.1, 10.4, and 6.5 Hz), 5.07 (1 H, dq, *J* = 17.2 and 1.7 Hz), 4.99 (1 H, ddt, *J* = 10.1, 1.8, and 1 Hz), 4.47 (2 H, s), 4.03 (2 H, q, *J* = 7.0 Hz), 3.43 (3 H, s), 2.68 (2 H, t, *J* = 7.7 Hz), 2.59 (2 H, q, *J* = 7.5 Hz), 2.32 (2 H, q, *J* = 7.6 Hz), 1.40 (3 H, t, *J* = 6.9 Hz), 1.19 (3 H, t, *J* = 7.5 Hz); ^{13}C δ 154.59, 139.69, 138.27, 133.64, 129.32, 124.33, 114.78, 112.48, 69.39, 63.80, 58.36, 35.36, 32.28, 24.83, 15.73, 14.98; MS *m*/*e* 248 (M^+), 233, 219, 217, 207, 175, 147.

Acknowledgment. The financial support of the National Science Foundation (CHE-9618676) is gratefully acknowledged. We thank Mr. Chongsheng Shi for preparing compounds **15a**, **15b**, and **16b**.

Supporting Information Available: Experimental procedures and spectroscopic data for **13c**−**e**, **14b**−**e**, **15b**, **16b**, **17a**,**b**, **32**−**36**, **48**, **51**, **54**, **58**, and **59** and ^1H and ^{13}C NMR spectra of **13a**,**c**−**e**, **14a**−**e**, **15a**,**b**, **16a**,**b**, **17a**,**b**, **21**−**24**, **32**−**34**, **40**, **41**, **48**, **51**, **54**, **58**, and **59** (61 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO971391B